STUDIES ON THE CATALYTIC REACTIONS OF 3-DIAZOOXINDOLES: SYNTHESIS OF 3-FUNCTIONALIZED INDOLES, INDOLE INCORPORATED MACROCYCLES AND SPIRO-INDOLOFUROBENZOPYRANS

Thesis submitted to the Bharathidasan University, Tiruchirappalli in partial fulfillment of the requirements for the award of the degree of

Doctor of Philosophy
in
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by

A. PRABU

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Under the guidance of
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Tiruchirappalli - 620 024
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June 2022

Dedicated to my family members & friends

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A. PRABU

ABBREVIATIONS

ABq	AB quartet
ABqd	AB quartet of doublet
Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
Ar	Aryl
ATR	Attenuated Total Reflectance
Bn	Benzyl
br	Broad
Bu	Butyl
Calcd	Calculated
CBTF	Sodium 4-((4-(cyanoethynyl)benzoyl)oxy)-2,3,5,6-tetrafluorobenzenesulfonate
CCDC	Cambridge Crystallographic Data Centre
CTAB	Cetyltrimethylammonium bromide
d	Doublet
DABCO	1,4-Diazabicyclo(2.2.2)-octane
DBN	1,5-Diazabicyclo(4.3.0)-non-5-ene
DBU	Diaza-1,8-bicyclo(5.4.0)-undecene
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublet
DEPT	Distortionless enhancement by polarization transfer
DG	Directing group
DIPEA	*N,N*-Diisopropylethylamine
DMAD	Dimethyl acetylenedicarboxylate
DMB	Dimethylbutane
DMF	*N, N*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMU	Dimethylurea
equiv	Equivalent
ESI	Electron spray ionization
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram
HFIP	Hexafluoroisopropyl alcohol
HRMS	High resolution mass spectroscopy

Hz	Hertz
IPA	Isopropyl alcohol
IR	Infra-red
J	Coupling constant
LED	Light-emitting diode
M	Molar
m	*Meta*
MA	Methyl acrylate
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minute(s)
mL	Milliliter(s)
mol	Mole(s)
mp	Melting point
MS	Molecular sieves
NFSI	N-Fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance
NPM	*N*-Phenyl maleimide
o	*Ortho*
p	*Para*
PG	Protecting group
Ph	Phenyl
ppm	Parts per million
p-TSA	*para*-Toluenesulfonic acid
rt	Room temperature
s	Singlet
SPA	Spiro-phosphoric acid
TBAB	Tetrabutylamonium bromide
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TBHP	Tert-Butyl hydroperoxide
temp	Temperature
tert	Tertiary
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethyl silane

CONTENTS

CHAPTER - I

INTRODUCTION & BACKGROUND

Synthetic organic chemistry is the "art" of constructing complex molecular structures of organic compounds by combining smaller, easily accessible (commercially available) compounds. This science has found applications in the production of organic compounds of commercial interest, the construction of new, potentially bioactive molecules derived from rational design, the challenge of synthesizing very complex natural products, and the development of new methods and strategies to make this science more efficient.

The efficient synthesis of complex scaffolds, which frequently contain complex ring systems and/or a large number of stereocenters, will be a major challenge for synthetic organic chemists. Synthetic analysis and planning are obligated for the synthesis of a complex organic compound; the most efficient method is retrosynthetic analysis, which is based on proper disconnections that virtually generate smaller fragments, which are then disconnected until commercially available compounds are reached. Each reaction in the synthetic scheme only affected the required functional group, leaving others unaffected and thus requiring to be protected. The development and application of efficient methodologies capable of forming multiple bonds with precise chemo-, regio-, and stereocontrol could be beneficial in addressing this issue. Because the most target molecules are chiral, stereoselectivity is also important in the synthetic strategy. To perform stereoselective synthesis, various approaches have been developed.

Several chemical transformations demonstrate elegant and innovative methodologies that have had a significant impact on organic chemistry by simplifying previously multifaceted or excessive step count transformations. Examples include Diels-Alder and Ugi reactions, which use simple starting materials to converge to a product or

asymmetric reactions such as the Sharpless epoxidation and dihydroxylation reactions or the asymmetric aldol reactions, all of which allow the preparation of complex molecules.

To simplify and accelerate the synthetic procedures, tandem or cascade reactions are a chemical process that consists of at least two consecutive reactions in which each subsequent reaction occurs solely as a result of the chemical functionality formed in the previous step. Cascade reactions have been developed rather than using limited linear reaction sequences for the construction of complex molecules.[1-4] These processes form multiple bonds in a single operation, frequently resulting in the formation of functionalized polycyclic structures with some degree of chemo-, regio- or stereochemical control and more importantly, they can be used in asymmetric synthesis.[5-7] This technique paved the way for the development of combinatorial synthesis, a method for producing a large number of organic compounds based on the combinatorial arrangement of different building blocks in products.

There is currently an effort to make synthetic chemistry more environmentally friendly. All of these studies make organic synthesis more efficient, cost-effective, and safe. Cascade, domino, tandem, and/or one-pot reactions have been extensively studied since the mid-1980s, and several reviews published on this synthetic methods[8-10] attest to their importance and utility. Synthetic organic chemistry revolves around the formation of carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds. These transformations have been accomplished through a variety of methods. The usual synthetic procedure involves the reaction of two activated carbon species, which couple to form a new carbon-carbon bond.[11] One efficient way to accomplish this transformation is to use carbenes or carbenoid substrates, which are best accomplished by using transition

metal-stabilized carbenes or carbenoids generated through metal-catalyzed decomposition. Carbenes have piqued the interest of chemists for decades, primarily as a tool for studying bonding and hybridization until the mid-1970s. Because of the highly reactive nature of the substrate, much of their implementation was restricted. The discovery that various transition metals such as Cu, Rh, Mo and Ru could be used to mediate carbene reactivity allowed the 'carbene' to be used without some undesirable side reactions. Since the mid-1960s, there has been an increase in the number of transition metal-catalyzed carbene/carbenoid type transformations, which is most likely due to the improved reactivity of the constantly evolving pool of catalysts. Metallocarbenoids have become more useful in reactions such as cyclopropanation of olefin, cycloaddition with diploarophile and X-H insertion.

Carbenes: Since 1960s, there have been several significant developments in the discovery and use of carbenes in organic synthesis, and this highly reactive carbene species has become an important mechanistic tool for the study of bonds and carbon structure as well as a synthetic tool in various C-C and C-X bond-forming reactions. Doering, Winstein, and Woodward invented the term "carbine." The study of carbenes, like the terminology used to describe them, has evolved. The parent carbene, methylene, is referred to as a "free carbene," and this terminology is used when discussing simple divalent carbon species (Figure 1). Free carbenes can be produced in two ways: 1) through photolysis or thermolysis of suitable carbene precursors such as ketenes or compounds containing a diazo-group, and 2) through 1,1-elimination of HX from R^2CHX compounds.[12-17] The multiplicity of free carbenes is generally unpredictable[18] and singlet and triplet states have been observed experimentally using matrix isolation techniques.[19] Due to their high reactivity and low selectivity, free carbenes have limited synthetic utility in organic chemistry.[20]

History, structure and reactivity of carbenes: Carbenes are neutral bivalent carbon intermediates with two substituents covalently bound to carbon and the two remaining electrons distributed between two non-bonding orbitals. If the two electrons are spin paired **1**, a singlet carbene is formed, and if the electrons' spins are parallel, a triplet carbene **2** is formed (Figure 1). Methylene ($:CH_2$) has a triplet ground state, whereas fluorocarbene (HFC:) and difluorocarbene ($F_2C:$) have a singlet ground state.[21] These electronic structures were predicted using both experimental evidence and *ab initio* calculations. A *sp* triplet **3** structure is proposed[15,22,23] as an alternative structure to the excited singlet and the triplet carbene (Figure 1).

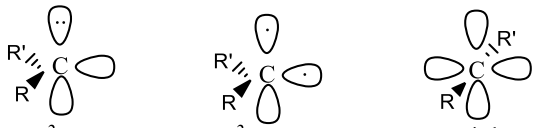


Figure 1. Electronic structure of carbene

A singlet state carbene has a *p*-orbital with two non-bonding spin paired electrons and an empty orthogonal sp^2 orbital, where the fully occupied *p*-orbital is anionic and the empty sp^2-orbital is cationic. Singlet (electrophilic) carbenes are commonly associated with reactions like cyclopropanation, insertion, and ylide formation. The electron-withdrawing/donating ability of the groups attached adjacent to the carbene carbon strongly influences the electrophilic/nucleophilic character of the singlet carbene. Substituents that donate electrons in nature (doubly bonded heteroatoms like O and N) make the carbene carbon nucleophilic.

Reactive, unstable carbenes include those in which the divalent carbon is singly-bound to a heteroatom or bonded to substituents that are less capable of maintaining resonance, such as alkyl groups. These "destabilizing" substituents make the divalent carbon more electrophilic and thus reactive.

The triplet state is a biradical with unpaired electrons in both orthogonal sp^2 and *p*-orbitals. This type of carbene participates in hydrogen abstraction/recombination

reactions.[24] It is necessary to be able to determine the multiplicity of the ground state of the carbene during generation to control the reaction's outcome.

Following the discovery that transition metals can catalyze the decomposition of diazo-containing species,[25,26] the term carbenoid was coined to describe the "carbene-like" structure of the reacting species, in which a metal stabilizes the carbene carbon.[27]

Towards this end, the detailed literature reports for diazocarbonyl compounds and their reactions will be covered in this section with the following sub-sections.

1.1. Chemistry of diazocarbonyl compounds

1.2. Reactions of diazocarbonyl compounds

1.1. Chemistry of diazocarbonyl compounds

Carbenoids derived from early transition metals like W, Mo, Cr, and Fe are typically stable, isolable compounds **5** that are relatively unreactive in various synthetic methods.[28,29] Reactive carbenoids **6** are typically derived from late transition metals such as Rh, Ru, Cu, and Pd, which exist primarily as transient species in catalytic processes. Reactive carbenoids are more useful in organic synthesis than stable carbenoids (Figure 2).[30] The interaction of the metal with the carbene significantly reduces reactivity while increasing the selectivity of the carbene. Furthermore, these species are almost exclusively generated in the singlet state and behave similarly to dipolar intermediates.[31]

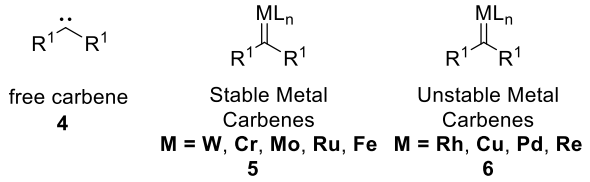


Figure 2 Metallo-carbenoids

Transition metal catalysts: Synthetic utility of carbenoid chemistry has been the development of highly efficient transition metal catalysts for diazo decomposition reactions with Cu and Rh being the most important metal atoms used.[32,33] The

preferential use of Rh and Cu catalysts is due, in large part, to their ability to substitute a wide range of ligands, which has resulted in the development of a diverse range of catalysts. This arsenal of catalysts has enabled the diazo-decomposition reaction to be fine-tuned on both a steric and an electronic level. In diazo-decomposition reactions, chemo- and stereoselectivity can be controlled by modifying the diazo compound (chiral auxiliaries), metal-ligand differentiation,[34] or both.[35]

The nucleophilic diazo-containing carbon attacks a vacant electrophilic coordination site of the metal catalyst in these reactions, which are generally considered catalytic in metal. Three potential electrophilic addition sites to the metal catalyst are provided by the electron-rich diazocarbonyl compounds (Figure 3).

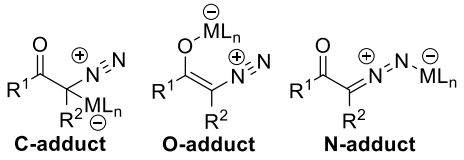
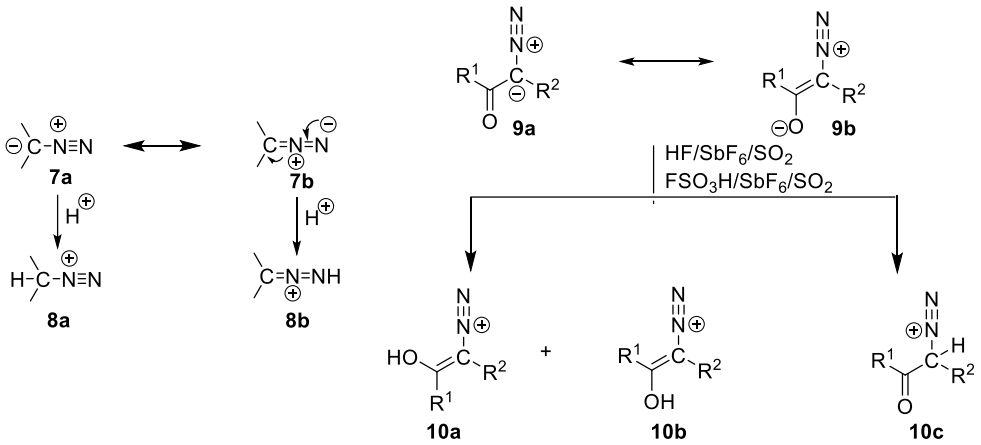


Figure 3



Scheme 1. Protonation of diazo compounds

The diazo-carbon and the terminal nitrogen atom **7a**,**b** are two obvious sites for protonation in simple diazoalkanes. In the case of unsubstituted non-carbonyl substrates, it was determined that C-protonation **8a** is the thermodynamically preferred process, whereas N-protonation **8b** appears to be the kinetically preferred process (Scheme 1). At low temperature (-60 to -80 °C), super acids (e.g. HF-SbF_5-SO_2 or

FSO_3H-SbF_5-SO_2) produce the *O*-protonated enoldiazonium ions **10a** (*cis*) and **10b** (*trans*) in the series containing diazocarbonyl substitution **9a**,**b** (*trans*).

Under these conditions, neither C- nor N-protonated species were found. C-protonation does occur in aqueous acidic conditions, however, and H/D exchange studies show that it is reversible. Using the hard/soft Lewis acid/base principles,[36] protonations should occur preferentially at the 'harder' Lewis basic site, whereas electrophilic addition of soft Lewis acids (e.g., $Cu^{+2/+1}$ / Ru^{+2} / Rh^{+2} etc.) should occur preferentially at the 'softer' Lewis basic site. Overall, only an electrophilic metal catalyst attack on carbon is expected to be productive in the formation of metallo-carbenoid species.

Copper catalysts: The first useful transition metal catalysts used for diazo compounds were heterogeneous Cu-catalysts, such as copper-bronze and copper(II) sulphate. Homogenous Cu-catalysts were developed in 1960's as alternatives to heterogeneous catalysts owing to ambiguities with the actual active catalytic species observed in the catalytic reactions. The introduction of catalysts such as copper(II) chloride and copper(II) trifluoromethanesulfonate advanced the fundamental understanding of copper catalysis in carbene transformations when diazo compounds were found to reduce Cu(II) to Cu(I). Following this discovery, it was determined that the active catalytic species was Cu(I) rather than Cu(II).[37] Because of the air sensitivity of Cu(I) catalysts, copper(II) complexes are preferred for the reactions of diazo compounds. Typically, two bidentate ligands are bound to the metal in the case of copper(II) pre-catalysts. The catalytic sequence is thought to consist of a Cu(II) to Cu(I) reduction followed by the dissociation of one of the two bidentate ligands during diazo-decomposition.[32] Several copper catalysts have been developed for diazo compounds, including chiral ligands for asymmetric reactions (Figure 4).

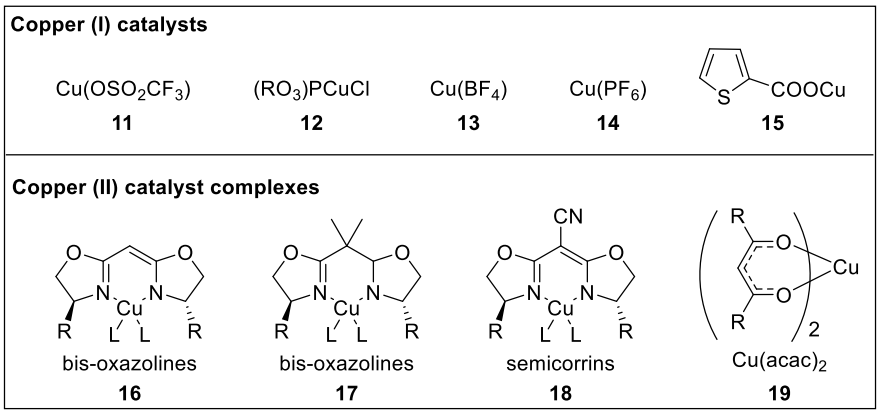


Figure 4. Typical copper catalysts for diazo-decomposition

Rhodium catalysts: Teyssie and co-workers introduced dirhodium(II) tetraacetate[38] ($Rh_2(OAc)_4$), which was prepared and characterized in 1960s, as an effective catalyst for diazo-decomposition in 1973. Since its discovery, rhodium(II) acetate has been the most commonly used catalyst for metal carbene transformations. In general, rhodium(II) catalysts offer more control over chemoselectivity than copper-based counterparts.

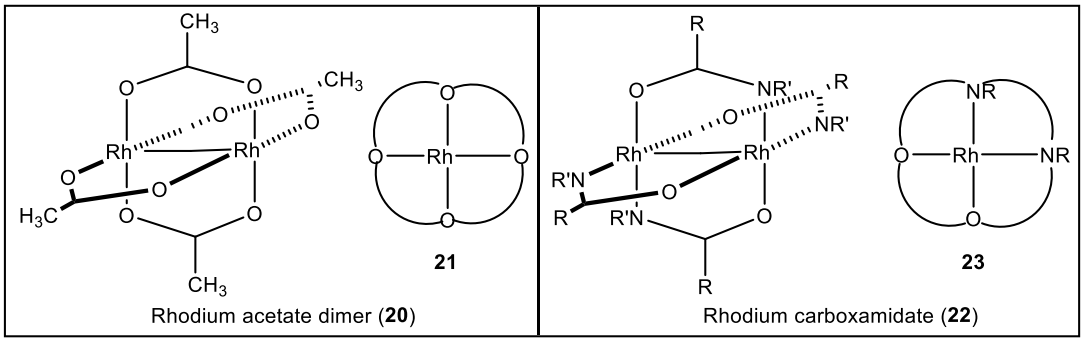


Figure 5. Structures of rhodium(II) carboxylates/carboxamidates

The wide range of ligands available, such as carboxamidate ligands and bridging carboxylate, allows for electronic and steric fine-tuning and selectivity amplification. Except for diazomethane-based reactions, these catalysts are generally useful for most diazo-decomposition reactions. Rhodium has three common oxidation states: +1, +2, and +3; but Rh^{+2} being the most common oxidation state in rhodium carbenoid

chemistry. Rh(II) dimerizes easily and complexes of carboxamidates and bridging carboxylates form a paddlewheel structure around the Rh-Rh bond axis (Figure 5).

α-Diazocarbonyl compounds: The overall structure of the diazo-substrate is important in addition to the importance assigned to the catalyst's electronics and steric nature. The reactivity of the diazo center toward the catalyst can be altered by adding or removing electron-drawing or -donating ligands to the diazo center.[39] Electron withdrawing groups to the diazo-center stabilize the diazo-substrate, making it easier to prepare. Alternatively, the presence of an electron-donating substituent to the diazo-center increasing reactivity reduces thermal stability, and thus complicates the preparation of these diazo-derivatives. α-Diazocarbonyl compounds are the favoured structural motif for diazo decomposition reactions, due to their ease of preparation and ability to restrict reactivity *via* $Rh_2(II)L_4$ ligand modification. Those diazo compounds with two neighbouring electron-withdrawing groups are more stable than those with a single electron-withdrawing group. The diazo-stability moiety decreases as the attached group's electron-withdrawing capacity increases, with diazoesters being more stable than diazoketones and diazoamides being more stable than diazoesters.[32] The thermal stability of substituted diazocarbonyl compounds follows the general profile depicted in Figure 6.[40]

The preparation of diazocarbonyl compounds is still an active research area that has made significant progress in recent years. Improving safety is still the primary

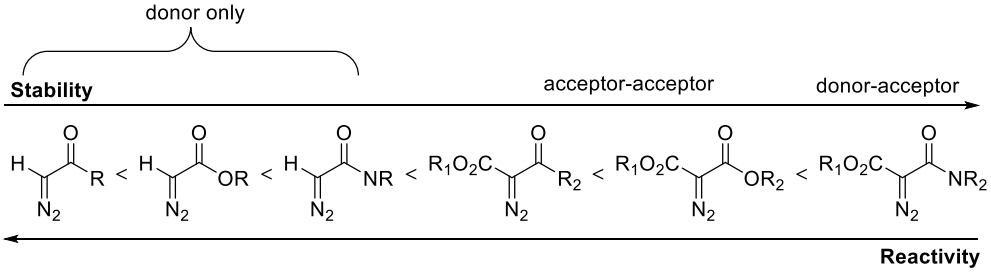


Figure 6. Relative stabilities of α-diazocarbonyl compounds

motivation for diazomethane acylation and diazo transfer strategies[41] (Figure 7). As an alternative to the Arndt-Eistert methodology, a diazomethane-free route has been developed. The most significant advances in the safer preparation and application of diazomethane have been made in the field of flow chemistry. Commercial equipment based on tube-in-tube technology has recently and successfully been used to prepare a wide range of diazocarbonyl compounds on a gram scale, and it is expected that the chemistry community will use it more widely in the future. While flow chemistry has been used in the diazo transfer methodology, the majority of the work has focused on the progress of novel sulfonyl azide reagents with enhanced stability.

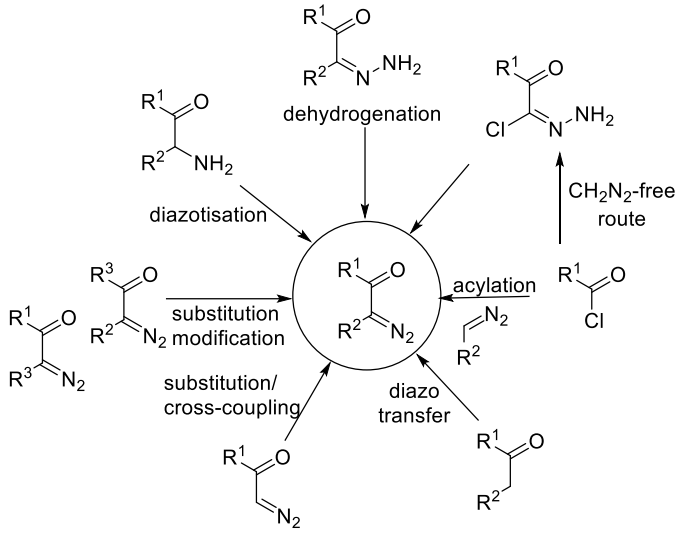
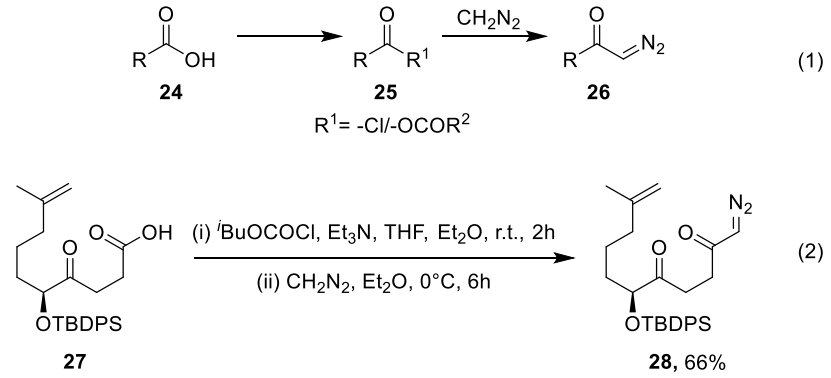


Figure 7. Scope of transformations of diazocarbonyl compounds

Since Curtius first reported the diazotization of α-diazocarbonyl compound from a natural amino acid in 1883,[42a] various methodologies have been developed, and there are some well-established methods for the preparation of various types of diazocarbonyl compounds for this day. The two most common methods for preparing diazocarbonyl compounds are acylation of diazomethane with an anhydride or acyl halide and diazo transfer from an azide reagent to the carbon nearby to a carbonyl group. Despite the dangers of diazomethane, the first method is still the most important for producing acyclic terminal-diazoketones. Arndt and Eistert synthesized

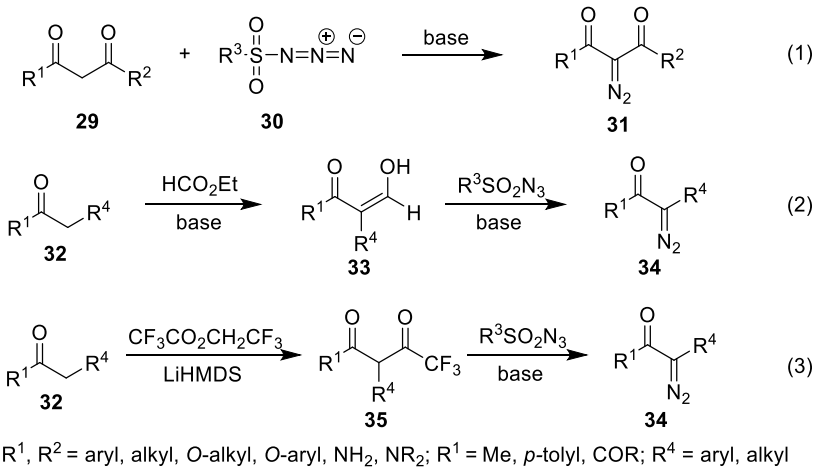
diazoketones **26** by acylation of diazomethane in the late 1920s (Scheme 3, equation 1).[42b] This reaction requires the addition of an acid chloride **25** (R^1 = Cl) solution to an etheral diazomethane solution. To avoid the formation of chloromethyl ketone, an excess of diazomethane is usually essential to utilize the hydrogen chloride produced as a by-product in the reaction sequence. In the presence of acid-sensitive substrates, mixed anhydrides **25** (R^1 = $OCOR^2$) are used as diazoketone precursors. By reacting carboxylic acids with chloroformates (e.g., methyl, ethyl, or isobutyl chloroformate), followed by treating the intermediate (mixed anhydride) with diazomethane, it is now possible to generate diazoketones *in situ*. For example, diazoketone **28**, a key intermediate in the asymmetric synthesis of (–)-indicol, was prepared after activation of the acid **27** *via* mixed anhydride formation with isobutyl chloroformate (Scheme 3, equation 2).[42c]



Scheme 3. (1) General scheme for the preparation of diazoketone. (2) Synthesis of diazoketone **28**, a key intermediate in the asymmetric total synthesis of (-)-indicol

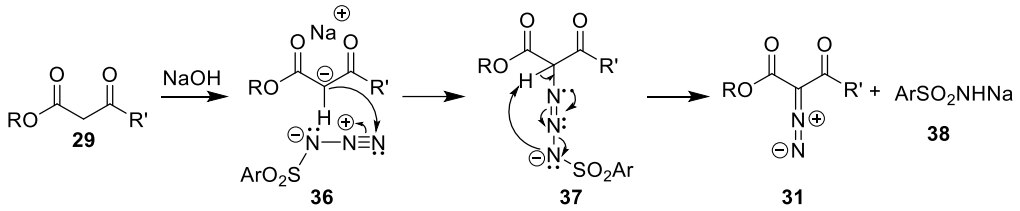
Diazo transfer is the preferred method for producing cyclic α-diazocarbonyl compounds. This methodology has also been used in many acyclic systems that are not accessible *via* acyl-transfer processes. Dimroth first described this concept in 1910,[43a] and Regitz extensively researched it in 1967.[43b] In the presence of an adequately strong base to deprotonate the active methylene compounds, diazo transfer reactions of active methylene compounds **29** typically use *p*-sulfonyl azide **30** as a diazo transfer reagent

(Scheme 4, eq 1). Thus, after being exposed to tosyl azide with triethylamine as the base, -diketones, -ketoamides, -ketoesters and malonic esters are easily converted into 2-diazo-1,3-dicarbonyl products **31** (Scheme 4, eq 2). However, because simple ketones **32**, such as methyl ketones, do not usually react directly with sulfonyl azides, they must be activated *via* formylation (Claisen condensation of the ketone with ethyl formate). In a process known as the deformylating diazo transfer, the resulting α-formyl ketones **33** suffered the actual diazo transfer to yield the corresponding -diazoketones **34**. When the substrate is a base-sensitive, such as α,β-enone, the deformylating diazo transfer usually yields a low yield, but Doyle and Danheiser discovered that activating the carbonyl compound **32** with trifluoroacetyl group results in a higher yield (Scheme 4, eq 3).[43c,d]



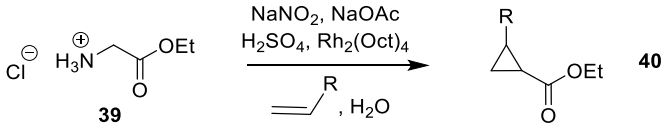
Scheme 4. (1) Regitz diazo transfer (2) Deformylating diazo transfer (3) Detrifluoroacetylating diazo transfer

In most cases, the mechanism for transferring a diazo group onto active methylene compounds (Scheme 5) involves an intermediate triazine **37**. The azide reacts with the carbanion **36** to form triazine **37**, which spontaneously decomposes with a simultaneous proton shift to form the diazo moiety **31** and sulfonamide **38**.



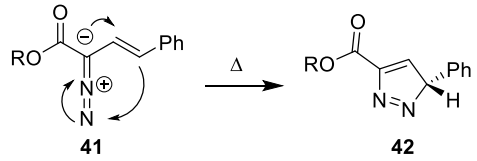
Scheme 5. Mechanism of diazo-transfer onto active methylene compound

Charette and co-workers have reported[44] the preparation of ethyl diazoacetate (EDA) from glycine ethyl ester hydrochloride **39** and shown the subsquent cyclopropanation **40** (Scheme 6). When $NaNO_2$ solution was added to glycine ethyl ester hydrochloride with $Rh_2(Oct)_4$ and olefin substrate (3 Equiv), EDA was formed and consumed simultaneously. The reaction was carried out on a gram scale and yields were greater than 70%. This protocol has not yet been extended to other types of diazo-substrates.



Scheme 6. Charette's *in situ* preparation of EDA and subsequent cyclopropanation

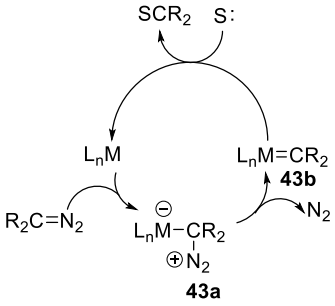
Davies classified diazo compounds with an olefin group attached 'α' to the diazo moiety as a push-pull diazo-system,[45] based on electron flow in the substrate. The vinyldiazo compounds **41** are quite reactive and thermally unstable, quickly decomposing at ambient temperature *via* electrocyclization process (1,3-dipolar cycloaddition) to the thermally stable 3*H*-pyrazole **42**. (Scheme 7).[46] Substitution at the diazo-carbon has a significant impact on the rate of cyclization, with electron-drawing groups stabilizing and electron-donating groups increasing the rate of cyclization.[47] Moreover, the introduction of a 2nd electron-withdrawing group only at the vinyl terminus improves stability to the point where these compounds can be stored indefinitely at ambient temperature.[48]



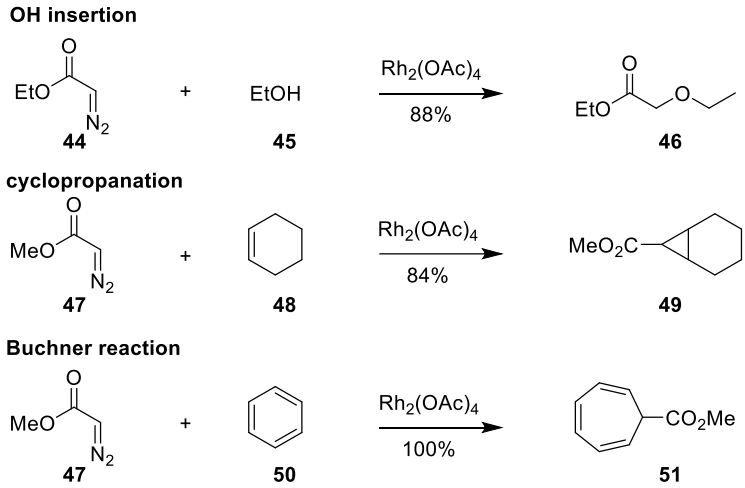
Scheme 7. Electrocyclization of vinyldiazo esters

1.2. Reactions of diazocarbonyl compounds

Reactions of metallocarbenes/carbenoids: The metallo-carbenoid intermediate has several reaction pathways at its disposal. The catalyst used for diazo-decomposition as well as the substrates accessible to the resulting carbenoids, both influence the specific pathway. Yates and co-workers recommended that the reaction of transition metal catalysts[27] with diazocarbonyl compounds produced electrophilic carbene species **43a**. The transition metals' catalytic activity is dependent on coordinative unsaturation at the metal center, which allows them to react as electrophiles with diazocarbonyl compounds. The electrophilic addition of the metal catalyst to the diazocarbon generates dinitrogen extrusion, resulting in the metal-stabilized carbine **43b**. The carbenoid entity is moved to an electron-rich substrate, bringing the catalytic cycle to a close (Scheme 8).



Scheme 8

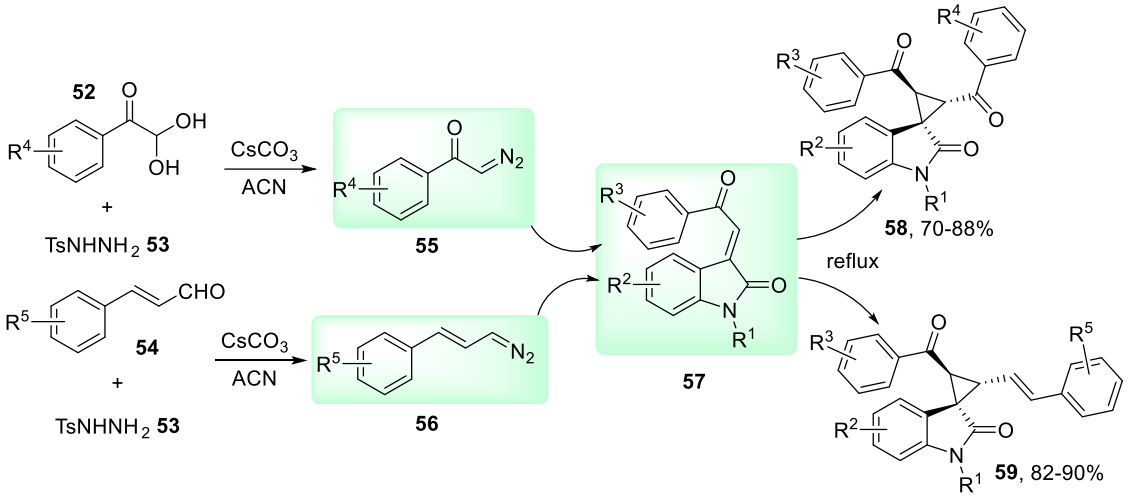


Scheme 9

Teyssie and co-workers' pioneering work in 1970 reported the utility of diazo compounds, particularly through Rh(II) catalysts (Scheme 9). Their research expanded the scope of catalysts yielding a vast library of effective transformations ranging from

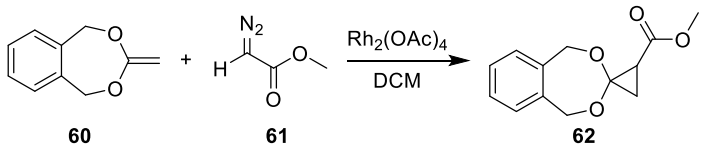
O-H[49] and X-H[50] insertion to cyclopropanation of olefins[51] or addition to aromatic compounds.[52]

Cyclopropanation: An efficient diastereoselective cyclopropanation of 3-alkylidene oxindoles **57** with *in situ* generated diazocarbonyl compounds **55**/**56** under metal-free, thermal conditions was established[53] to generate 3-spirocyclopropyl-2-oxindoles **58**/**59**. The method is applicable to a wide range of substrates and employs readily available starting materials (Scheme 10).



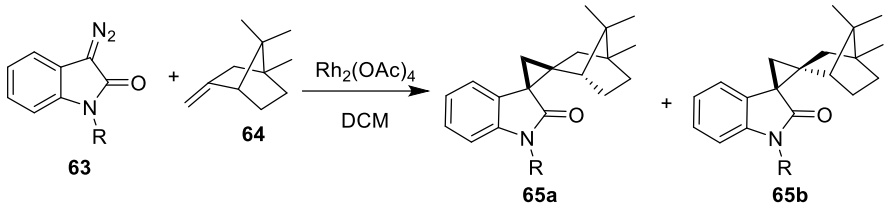
Scheme 10

Down and co-workers have studied the reaction of methyldiazo acetate **61** and diazoacetonitrile with cyclic ketene acetal **60** producing the mono-spiro cyclopropyl derivatives **62** which are known to be highly unstable (Scheme 11).[54]



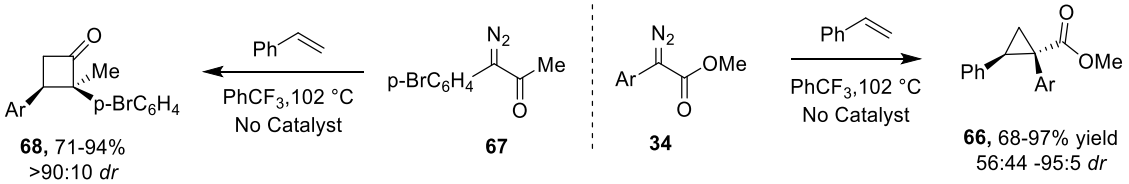
Scheme 11

The cyclopropanation reaction of diazoamides **63** with a series of cyclic alkenes **64** *via* rhodium carbenoid was performed by our research group (Scheme 12).[55] The rhodium carbenoid underwent cyclopropanation with 1,7,7-trimethyl-3-methylenebicyclo[2.2.1]



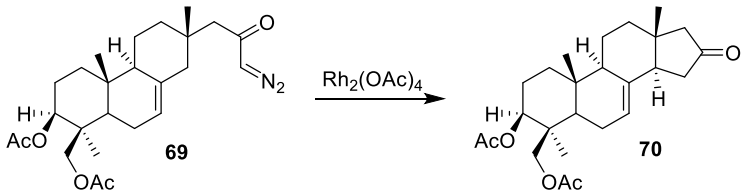
Scheme 12

heptane **64** to yield the corresponding products **65** in good yield under mild conditions. Davies and co-workers[56] reported that thermally stimulated cycloaddition of donor/acceptor carbenes provided cyclopropanation **66** from aryldiazoacetates **34a** in the absence of a transition metal catalyst in high-yield (Scheme 14). Moreover, the reaction is highly diastereoselective when the aryl group contains a lot of electrons. Under similar reaction conditions, decomposition of aryldiazoketones **67** led to the formation of cyclobutanones **68** in good yields with diastereocontrol *via* ketene intermediate. According to kinetic studies of thermal reactions, acceptor groups stabilize diazo compounds (Scheme 13).



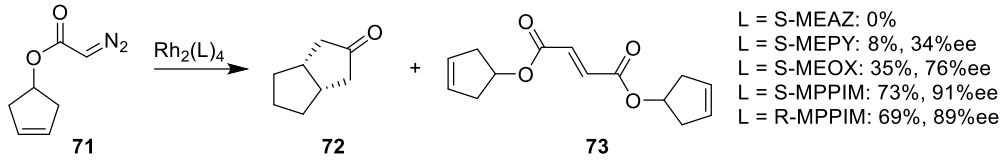
Scheme 13

Insertion reactions; C-H Insertion: Wenkert's preparation of the steroid skeletal system **70** from diazoketone **69** using $Rh_2(OAc)_4$ as a catalyst *via* C-H insertion[57] reaction in organic synthesis was reported in 59% yield (Scheme 14).



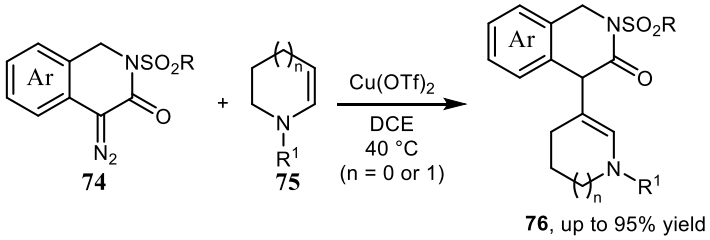
Scheme 14

Doyle's achiral catalysts produced better yields of intramolecular C-H insertion products with good chiral induction. The conversion of diazoacetate **71** to lactone **72** was accomplished in the presence of oxazolidinone or imidazolidinone catalyst in moderate to good yield using high enantioselectivity. The use of Rh_2(R-MPPIM)$_4$ furnished the opposite antipode of **72** (1*R*,5*S*).[58] In this case of $Rh_2(OAc)_4$ catalyst failed to deliver the racemic C-H insertion product, whereas the Rh_2(S-MEPY)$_4$ and Rh_2(S-MEAZ)$_4$ catalysts produced dimer **73** as the major product or a low yield of the C-H insertion product (Scheme 15).



Scheme 15

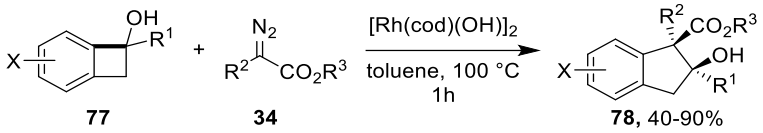
Wang and co-workers[59] reported a specific C–H bond insertion of Cu-carbenes from 4-diazo-1,4-dihydroisoquinolin-3-ones **74** into C(sp^2)–H bonds of N-sulfonyl enamides **75** yielding a sequence of 4-(1,4,5,6-tetrahydropyridin-3-yl)-1,4-dihydroisoquinolin-3(2*H*)-one **76** in excellent yields (Scheme 16).



Scheme 16

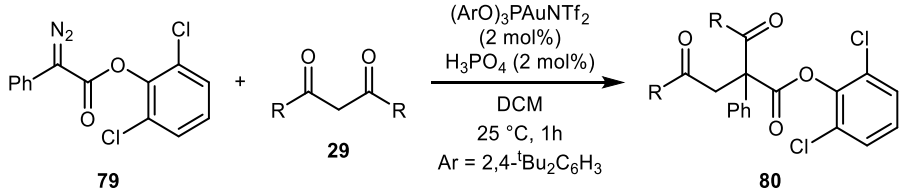
C-C Insertion reactions: Carbene insertion into the C-C bonds is uncommon in comparison to C-H insertion and cyclopropanation reactions, which are most frequently seen in intramolecular ring expansion reactions involving various carbene precursors. Thermal or photolytic activation is more common in such types of reactions than transition metal activation. Wang and co-workers reported a formal carbene[60] insertion

into the C-C bond of benzocyclobutenols **77** with diazoesters **34** in the presence of Rh(I). The product indanol compounds **78** were obtained (Scheme 17).



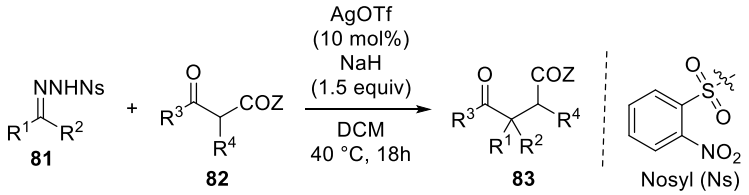
Scheme 17

A gold catalysed[61] formal C–C bond insertion reaction of diazoesters **79** with 1,3-diketones **29**, which delivered an efficient access to C–C bond insertion polycarbonyl compounds **80** with a quaternary carbon (Scheme 18). The presence of H_3PO_4 in the reaction mixture increases the yield of the polycarbonyl compounds **80**.

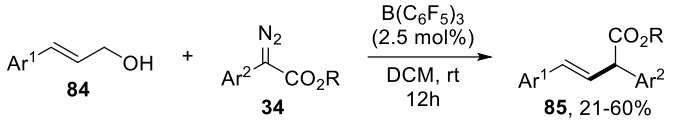


Scheme 18

Bi and co-workers have reported[62] the Ag(I)-catalyzed formal carbene insertion into 1,3-dicarbonyls **82** with N-nosylhydrazones **81** serving as diazo surrogates. Through the selective cleavage of the C-C(=O) σ-bond of acyclic 1,3-dicarbonyls **82**, two new C-C bonds were formed at the carbene carbon center, allowing the high yield preparation of various synthetically useful polysubstituted γ-diketones **83** (Scheme 19). $B(C_6F_5)_3$ Catalyzed[63] C–C bond functionalization of arylallyl alcohols **84** with diazo ester **34** has been developed *via* C-C bond scission. This method can also be used to homologize allyl alcohols **84** to homoallyl alcohols (Scheme 20).

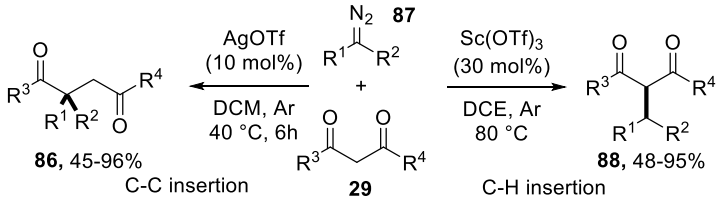


Scheme 19



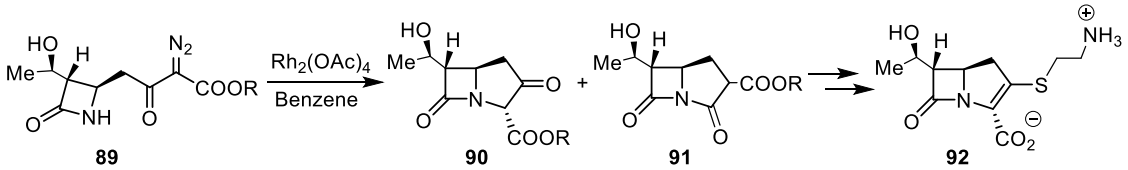
Scheme 20

Bi and co-workers have demonstrated[64] the reaction of 1,3-dicarbonyl compounds **29** with diazo compounds **87**, a catalyst control in net C-H insertion *vs* C-C insertion reactions. In the presence of AgOTf, diazocarbonyl compound **87** was inserted into 1,3-dicarbonyl compounds **29** C(=O)-C bond to yield 1,4-dicarbonyl product **86** with all-carbon α-quaternary center. The reaction path changed to formal C-H insertion when $Sc(OTf)_3$ was used as the catalyst to yield 2-alkylated 1,3-dicarbonyl compounds **88** (Scheme 21).



Scheme 21

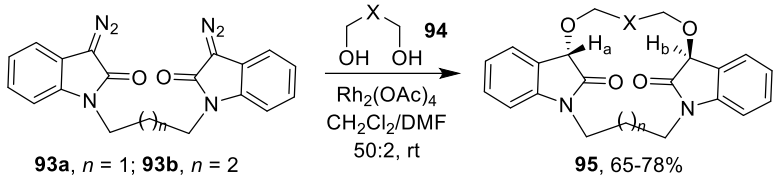
N-H Insertion reactions: The C-H insertion reactions were much more common in organic synthesis than polar X-H bond insertion. Merck demonstrated[65] the preparation of carbapenems, (-)-thienamycin **92** *via* rhodium-catalyzed intramolecular N-H insertion of β-lactams **89** (Scheme 22). The reaction pathway yielded a 9:1 ratio of imide **90** to lactam **91**.



Scheme 22

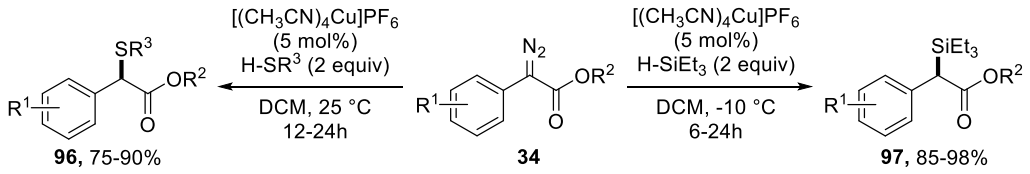
O-H Insertion reactions: Several recent studies have been published on the use of transition metal catalysis to insert carbenoids into the O-H bond of alcohol or heteroatom-H bond. Our research group reported an intermolecular double O–H

insertion reaction[66] of diazoamides **93** and dihydroxy compounds **94** in the presence of rhodium(II) acetate as a catalyst, which resulted in the synthesis of bis-(3-oxy-1,3-dihydro-2*H*-indol-2-one) systems **95**. This double O-H insertion reaction protocol was used to successfully synthesize several C_2-symmetric macrocycles with complete diastereoselectivity of oxindole units (Scheme 23).



Scheme 23

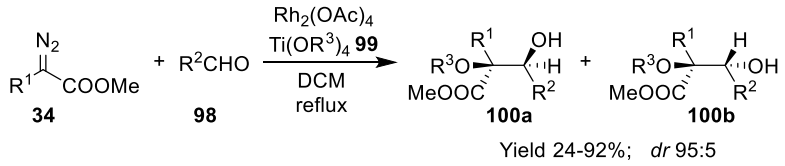
S-H and Si-H Insertion reactions: Ollevier and co-workers reported[67] an efficient copper-catalyzed carbenoid insertion reaction of diazoesters **34** into S–H and Si–H bonds. A wide range of thioesters **96** and silylesters **97** were obtained in high yield using 5 mol% of copper(I) salt as a catalyst (Scheme 24).



Scheme 24

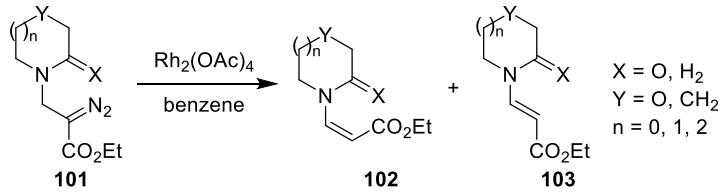
Addition reaction: Synergistic catalysis, in which the electrophile and nucleophile are simultaneously activated by two different catalysts, has emerged as a potent strategy in organic synthesis. This novel concept has resulted in the attainment of organic transformations that were previously inaccessible to single specific catalytic systems. The strategy of dual-metal catalysis was first used in the three-component reactions of diazoacetates, alcohols and aldehydes. The combination of Ti(O^{t}Bu) and $Rh_2(OAc)_4$ allowed the incorporation of reactive electrophiles with aldehydes **98**. The *R*-

alkoxyhydroxy ester **100** was obtained in moderate to good yield when a less sterically hindered titanium(IV) alkoxide **99** was used as a reagent (Scheme 25).[68]



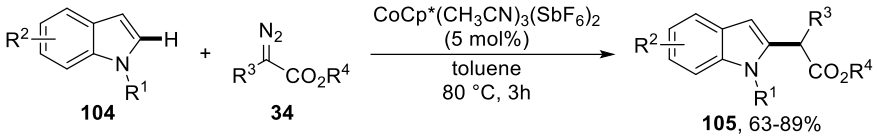
Scheme 25

Elimination reactions: Highly competitive reactions namely 1,2-hydride or 1,2-alkyl shifts could occur during the transformation of diazocarbonyl substances having β-hydrogen atoms. Previous work from our group revealed[69] the reaction of cyclic diazoamides/diazoamines **101** with a catalytic amount of rhodium(II) acetate to yield the corresponding cyclic enamides/enamines **102**/**103** (Scheme 26). Surprisingly, cyclic diazoamines resulted in stereoselectively Z-enamines as a single isomer.



Scheme 26

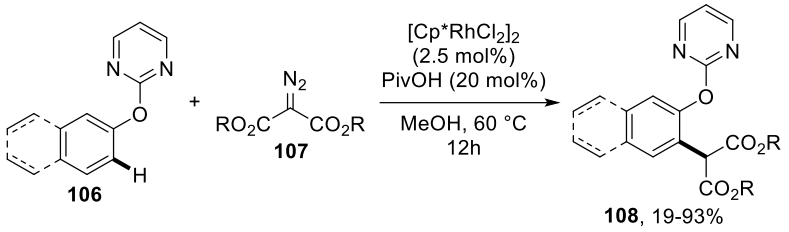
C-H Alkylation reactions: Anbarasan and co-workers[70] were successful in developing Cp*Co(III)-catalyzed highly selective C2-alkylation of indoles **104** with donor-acceptor carbenes. This method sustains a broad range of functional indoles **104** and D/A carbenes while producing C2-alkylation products **105** in good to excellent yields (Scheme 27).



Scheme 27

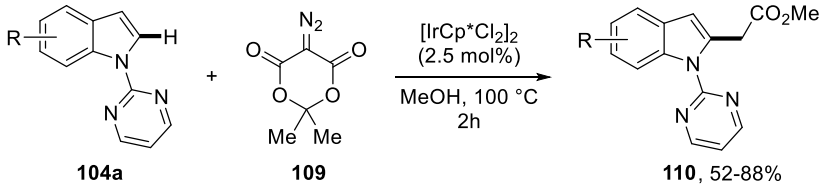
Swamy and co-workers[71] have described the *ortho*-alkylation of phenoxy derivatives **106** with diazo esters **107** *via* Rh(III) catalysis utilizing 2-phenoxypyrimidines /

pyridines **108** as substrates (Scheme 28). The reaction was renewed for *bis*-alkylation of *para*-substituted phenoxypyrimidines **106** to use more diazo compound with N_2 gas as the only by-product.



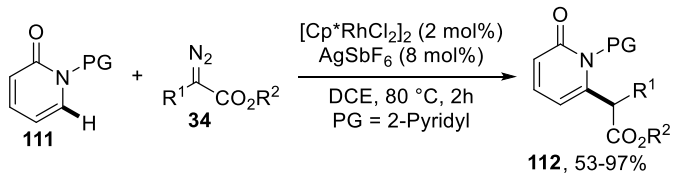
Scheme 28

Wei Yi and co-workers have disclosed[72] the synthesis of 2-acetate-substituted indoles **110** *via* Ir(III)-catalyzed carbenoid insertion and C(sp^2)-H alkylation of indoles **104a** with diazotized Meldrum's acid **109** (Scheme 29).



Scheme 29

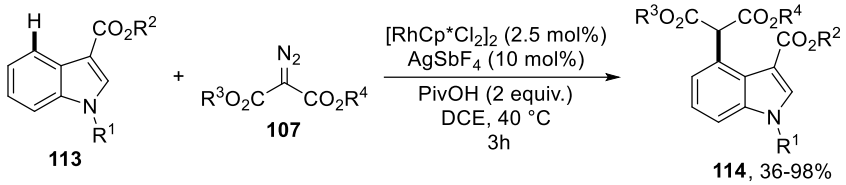
Rh(III)-catalyzed C-6 alkylation of 2-pyridones **111** with diazo compounds **34** was reported under mild reaction conditions. The pyridyl substituent connected to the nitrogen center of the pyridone ring **112** triggers regioselectivity in this reaction.[73] Remarkably, the reaction tolerates a wide range of functional groups and has been successfully applied to the production of biologically active heterocycles (Scheme 30).



Scheme 30

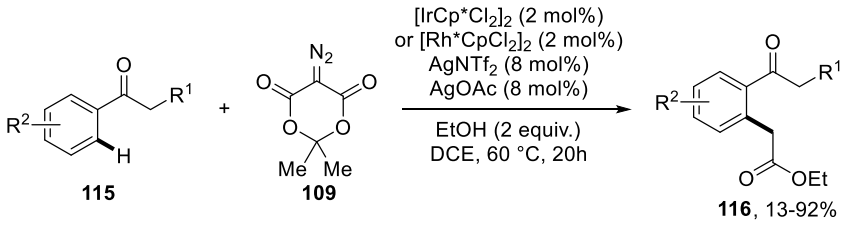
The direct functionalization on indole has received a lot of attention in recent years. Selective C2-H and C3-H functionalization have received considerable attention. However, because of their poor reactivity, functionalization at C4-H position is the

most difficult. Li and co-workers have invented[74] a method for C4 alkylation of indoles **114** using carbene as a precursor. They demonstrated efficient site-selective Rh(III) catalyzed C4-alkylation of indoles **113** using diazo esters **107** as a coupling partner (Scheme 31).



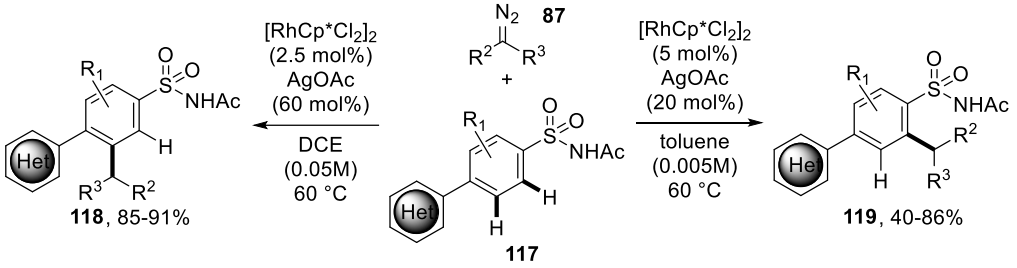
Scheme 31

Kim and co-workers have reported[75] the selective synthesis of ethyl 2-[2,3,4-trimethoxy-6-(1-octanoyl)phenyl]acetates **116** *via* Ir(III)- or Rh(III)-catalyzed redox-neutral C-H alkylation of acetophenones **115** using Meldrum's diazo compounds **109**. This synthetic transformation yields a wide variety of *ortho*-alkylated acetophenones **116** with high site-selectivity or functional group suitability (Scheme 32).



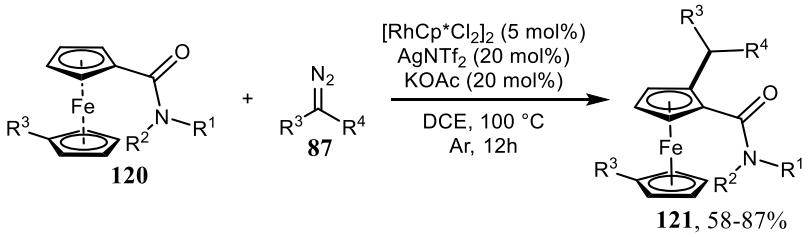
Scheme 32

The limitations of arene C-H functionalization of aryl sulfonamides **117** bearing strongly coordinating N-heterocycles were further investigated.[76] Notably, they overcome the limitations by employing solvents with varying polarities and additive concentrations. Under the Rh(III)-catalyst, a mixture of less polar solvent and low concentrated additive generated the *ortho*-position comparative to the sulfonamide group with extremely good site-selectivity. In comparison, a chlorinated solvent with a mixture of additive and Rh(III) catalyst provided product with high selectivity when compared to N-heterocycle-oriented *ortho*-functionalization (Scheme 33).



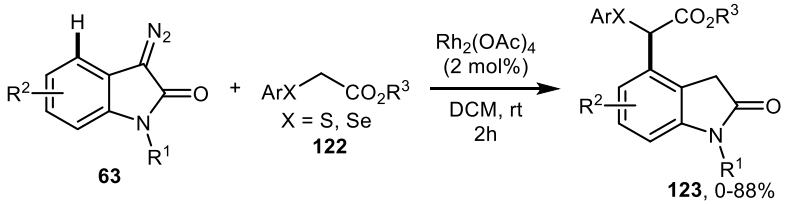
Scheme 33

Sun and co-workers have reported[77] the *ortho*-alkylation of ferrocenes **120** *via* Rh(III) catalyzed C-H functionalization. In this method, they illustrated a Rh(III)-catalyzed direct *ortho* C-H alkylation of ferrocenes **120** with diazo malanoates **87** under the effect of a loosely coordinating group. This protocol described a method for obtaining diverse ferrocene derivatives employing carboxamides, resulting in high yield of alkylated ferrocenes **121** (Scheme 34).



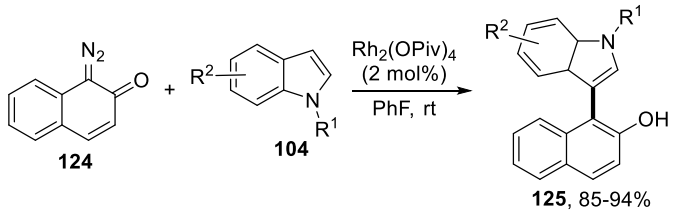
Scheme 34

An efficient Rh(II)-catalyzed[78] Sommelet-Hauser rearrangement of 3-diazoindolin-2-ones **63** with α-thioesters/α-selenoester **122** has been achieved for the synthesis of C4-thioalkylated/-selenoalkylated oxindoles **123**. The progressed reaction dealt with the selective C-H alkylation of C4-position of 3-diazoindolin-2-ones **63** *via* generation of S-ylide/Se-ylide and [2,3]-sigmatropic rearrangement and delivered the diverse C4-thioalkylated/-selenoalkylated oxindoles **123** in good to excellent yield (Scheme 35).



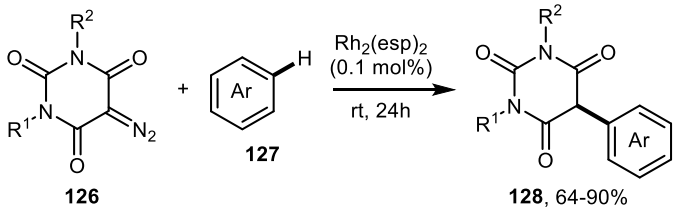
Scheme 35

Arylation reactions: A $Rh_2(OPiv)_4$-catalyzed[79] cross-coupling reaction has been used to establish the regioselective direct 3-arylation of indoles **104** with 1-diazonaphthalen-2-(1*H*)-ones **124**. This protocol delivered a diversity of novel 3-naphthylindoles **125** in high yield. The direct coupling of furan, pyrrole or benzofuran with 1-diazonaphthalen-2-(1*H*)-ones **124** was demonstrated to provide 2- / 3-arylated heterocycles (Scheme 36).



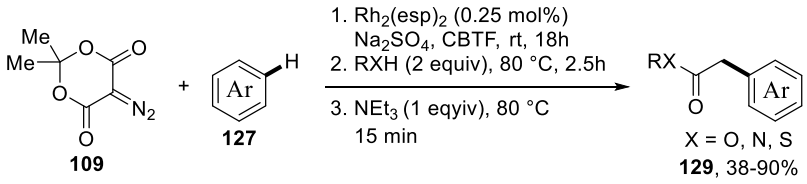
Scheme 36

Lam and co-workers have described[80] the direct arylation of 5-diazobarbituric acids **126** with arenes **127** in the presence of rhodium(II) complex as acatalyst, permitting easy access to 5-aryl barbituric acids **128**. Free NH groups are allowed on barbituric acid **126** with no complications caused by NH insertion processes. In a short period, this method was used to produce a strong matrix metalloproteinase inhibitor (Scheme 37).



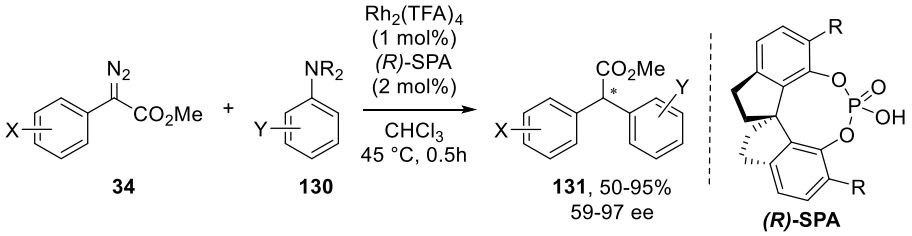
Scheme 37

The one-pot arylation of a Meldrum's acid-cultivated[81] diazo reagent **109** with electron-rich arenes **127** led to the formation of arylacetic acid amides, esters and thioesters **129**. An anticancer compound was efficiently synthesized using the methodology (Scheme 38).



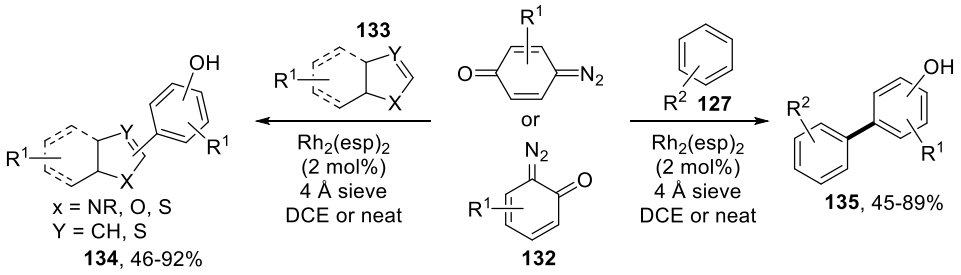
Scheme 38

An achiral $Rh_2(TFA)_4$ complex and a chiral spirophosphoric acid [*(R)*-SPA] were used to succeed in an asymmetric arylation of diazo compounds **34** with aniline derivatives **130**. α-Diarylacetates **131** were prepared in high yields with high enantioselectivity.[82] Initial mechanistic studies proposed that the arylation reaction occurred in a stepwise manner, starting with Rh-mediated arene C-H insertion and ending with a stereo-centre generating 1,2-H shift (Scheme 39).

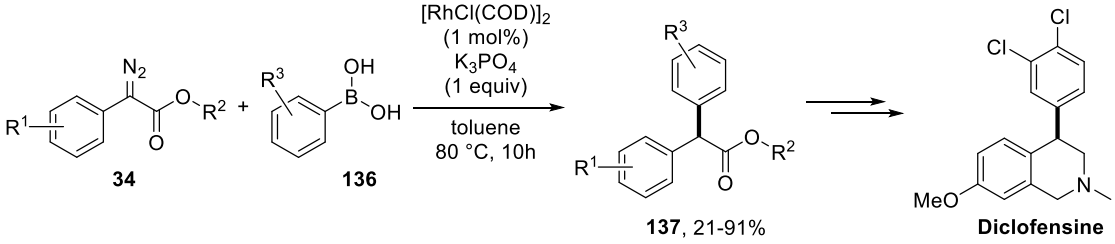


Scheme 39

Zhou, Che and co-workers have demonstrated[83] an efficient synthesis of biaryls **134**/**135** *via* aromatic C-H arylation with diazo quinones **132** catalyzed by Rh(II). The novel biaryl **134**/**135** synthesis could be produced under mild and neutral conditions or without directing group chelating agent assistance. The reaction gave a range of functionality and applied to a wide range of aromatics (Scheme 40).



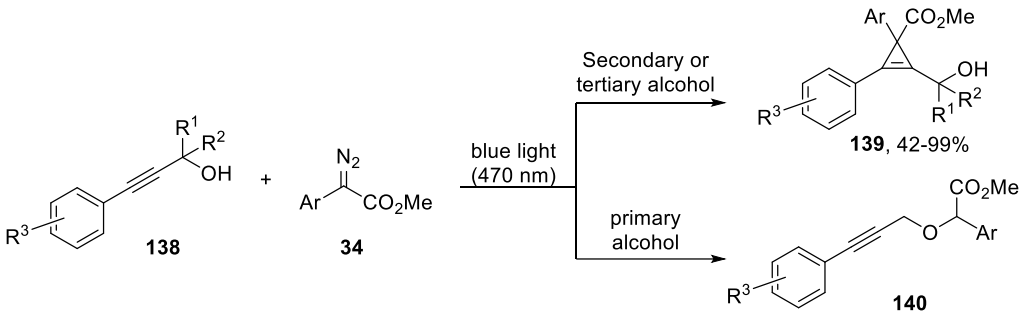
Scheme 40



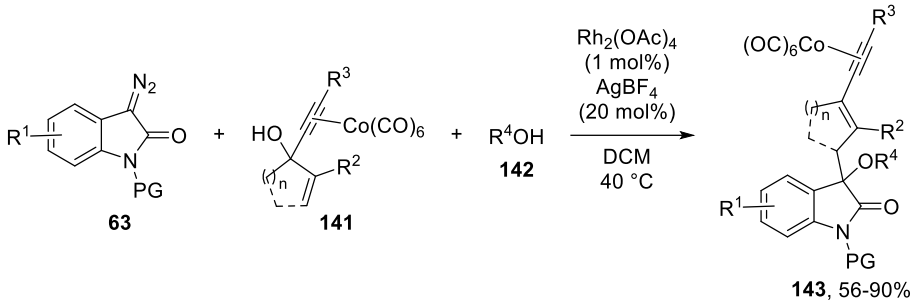
Scheme 41

Anbarasan and co-workers have demonstrated[84] the Rh-catalyzed two-component reaction of α-diazoesters **34** with arylboronic acids **136**. This reaction provided the way for the synthesis of diarylacetates **137** (Scheme 41).

Reactions of diazocarbonyl compounds with propargylic alcohols: Koenigs and co-workers have reported[85] the use of blue light (470 nm) in photochemical carbene transfer reactions of D/A diazoalkanes **34** under mild reaction conditions with propargylic alcohols **138**, which gave access to cyclopropenes **139** and O-H insertion product **140** in comparison to previous metal-catalyzed carbene transfer reactions (Scheme 42).



Scheme 42

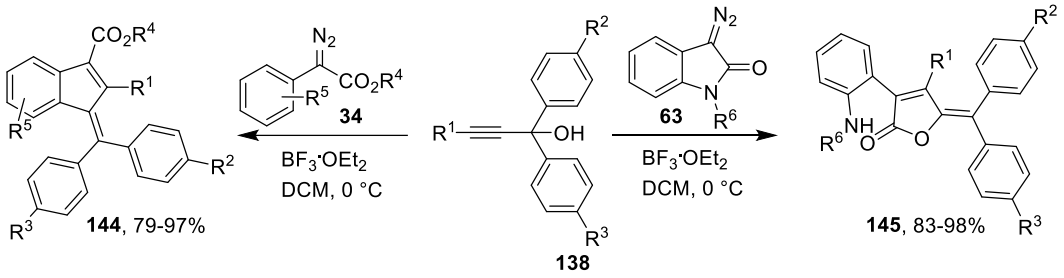


Scheme 43

A multi-component reaction of diazo compounds **63** with propargylic alcohol-$Co_2(CO)_6$ complexes **141** and alcohols **142** in the presence of Rh(II)/Ag(I) catalyst has been described, which denotes the first trapping procedure of oxonium ylides with carbocations through the S_N1/S_N1' type route.[86] This transformation enables the efficient synthesis of $Co_2(CO)_6$-complexed 3,3-disubstituted oxindoles **143**. The 3,3-

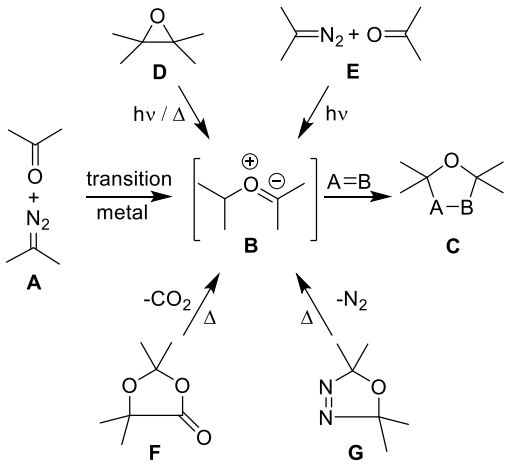
disubstituted oxindoles **143** with ene-alkynyl group and controlled spiro-oxindole-vinyldihydropyrans were obtained in further derivatization of the product, which was initiated by the deprivation of the di-cobalt species (Scheme 43).

Our group has shown[87] that $BF_3{\cdot}OEt_2$ catalyzed the synthesis of fully substituted indenes **144** and furanones **145** from diazocarbonyl compounds **34/63** and propargylic alcohols **138**. This methodology provides indene **144** and furanone **145** systems from α-diazocarbonyl compounds with clean, quick and yielding, making it a promising applicant for industrial uses (Scheme 44).



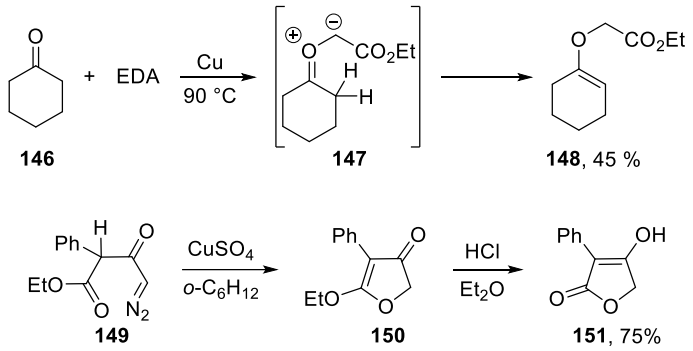
Scheme 44

Reactions of carbonyl ylides from diazocarbonyl compounds: Carbonyl ylides, like nitrogen and sulfur ylides, can be formed by the interaction of metal carbene intermediate and carbonyl compounds. There are several methods for producing carbonyl ylides described in the literature (Scheme 45).[88] The most general methods include photolysis or thermolysis of epoxides (D) with electron-withdrawing substituents, thermal extrusions of nitrogen from 1,3,4-oxadiazolines (G),[89] extrusions of carbon dioxide from 1,3-dioxolan-4-ones (F)[90] and photolysis of diazocarbonyl compounds in noble gas matrixes (E)[91], and others. Among these, the addition of a metallo-carbenoid



Scheme 45

obtained from a diazo precursor onto the oxygen atom of a carbonyl group is the simplest route to transient carbonyl ylides (A). The intermolecular or intramolecular transition metal catalytic route to carbonyl ylides from diazocarbonyl compounds is a simple process. Intramolecular carbonyl ylide formation and reactions have been studied more thoroughly than intermolecular carbonyl ylides, as there appear to be very few examples of intermolecular carbonyl ylide formation and reactions. The transient carbonyl ylides (B) produced by the catalytic route could be easily trapped inter- or intramolecularly with π-bonds *via* a variety of 1,3-dipolar cycloaddition reactions, yielding oxygen-containing polycyclic systems (C).

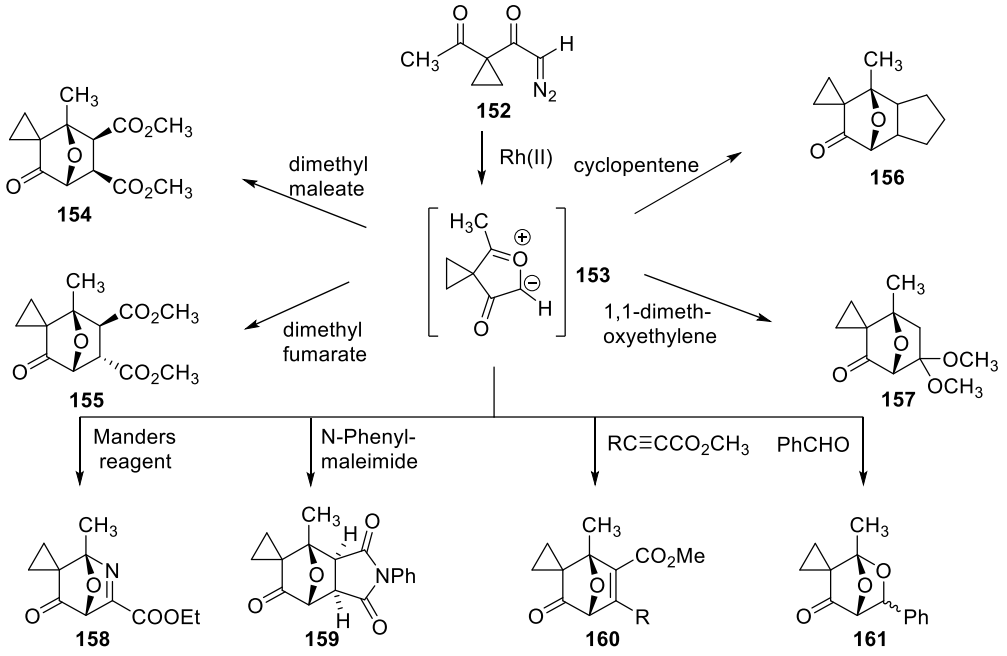


Scheme 46

Reactions of carbonyl ylides: Carbonyl ylides are dipolar reactions with a high degree of versatility in their chemical reactions. The most basic examples of carbonyl ylide formation in diazo compound catalytic reactions conducted in the absence of dipolarophiles demonstrate that intermolecular proton transfer is a common route to stable products (Scheme 46),[92] this transformation was used to produce 3(2*H*)-furanones **151**[93] in high-yield. Moreover, because copper salts were used in these early examples, diazo decomposition needed a comparatively high temperature. The use of Rh(II) catalysts, which initiate diazo decomposition to occur under much milder conditions, might have allowed this methodology to be extended beyond proton transfer transformation to the more general synthetic applications.[94] Carbonyl ylides

161 have been reported to produce oxa-bridged compounds through reactions with dipolarophiles such as Manders reagent, methyl vinyl ketone, methyl acrylate, methyl propargyl, and ether propargyl chloride.[95] Reaction of the cyclopropyl substituted five-membered-ring carbonyl ylides **153** (Scheme 47) generated from α-diazo ketones **152**, with numerous dipolarophiles has been reported.[96]

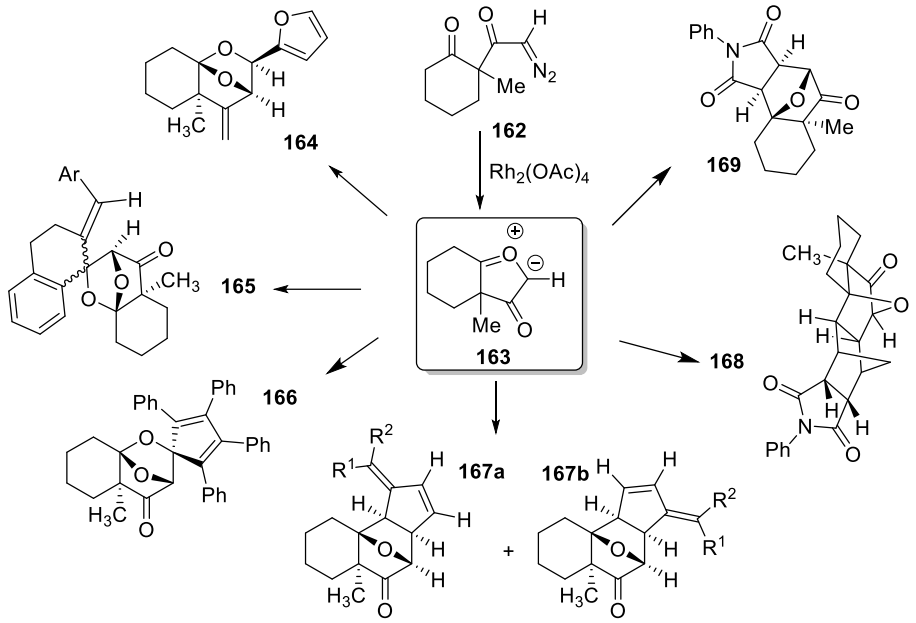
Reactions of bicyclic carbonyl ylides **163** with interesting substrates such as tosylimines[97] norbornenes,[96c] fulvenes, and stereoselective studies with several carbonyl compounds such as aryl aldehydes, -unsaturated aldehydes, and 2,3,4,5-tetraphenylcyclopenta-2,4-dienone[98] have been reported from our laboratory. The reaction of ylides **163** and arylidenetetralones in the presence of $Rh_2(OAc)_4$ resulted in



Scheme 47

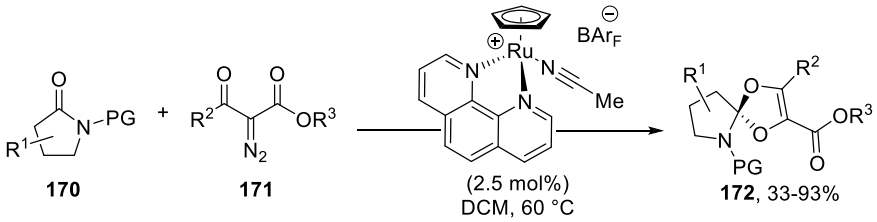
the spiro-dioxa ring systems **165** with high regio- and chemoselectivity.[99] The product **165** was derived as a diastereomeric ratio (dr = 2:3) without C=C bond addition product formation. The 1,3-dipolar cycloaddition reactions of the bicyclic 5-membered ylides

163 were shown from the diazocarbonyl compound **162** in the presence of $Rh_2(OAc)_4$ as a catalyst (Scheme 48).



Scheme 48

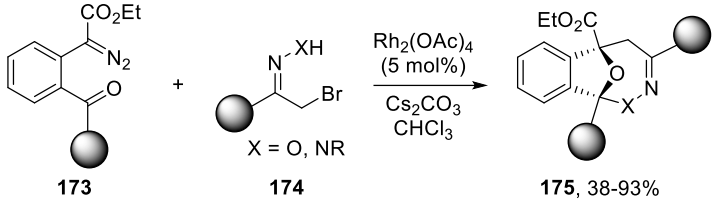
Lacour and co-workers have reported[100] that the reactions of pyrrolidinones **170** with Ru(II)-catalyzed metal carbenes derived from α-diazo-β-ketoesters **171** resulted in the synthesis of spirocyclic amide acetals **172.** The composition of the sensitive products is induced by a 1:1 combination of 1,10-phenanthroline and $[CpRu(MeCN)_3][BArF]$. DFT calculations could provide a complete characterization of this carbonyl ylides mediated process (Scheme 49).



Scheme 49

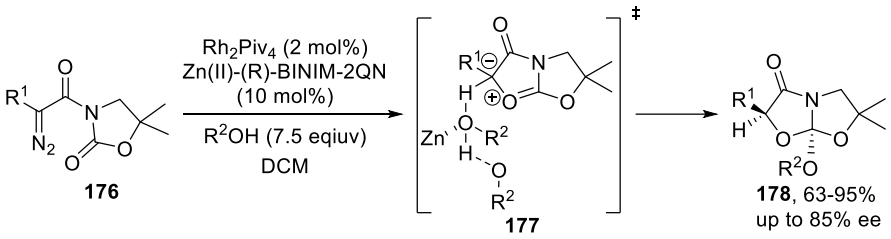
Constructing a suitable strategy for synthesizing novel diazocine compounds **175** is important since their use has been restricted due to the difficulty of synthesizing them. Zhan, Han and co-workers have described[101] an *in situ* catalytic [4+3]-cycloaddition reaction of azoalkenes **173** with carbonyl ylides. The Rh(II)-catalyzed tandem reaction

exhibited excellent atom and step economy, allowing for the first time access to oxa-bridged diazocines **175** (Scheme 50).



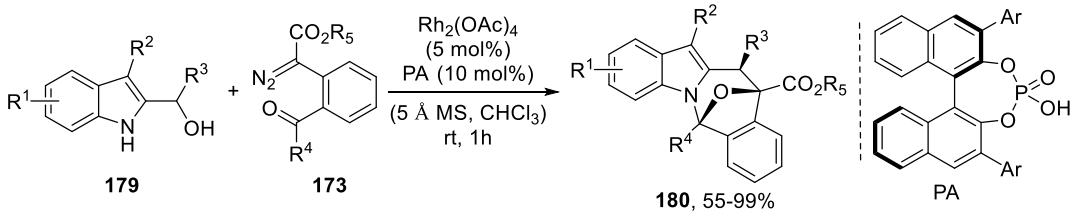
Scheme 50

The use of a dual catalytic system in chiral Lewis acid Rh/Zn asymmetric alcohol addition reactions to cyclic carbonyl ylides **177**, produced from N-(diazocarbonyl)-2-oxazolidinones **176**, was reported.[102] The innovative heterocycles **178** have been synthesized in high yield by constructing a chiral quaternary heteroatom inserted carbon center (Scheme 51).



Scheme 51

Schneider and co-workers have described[103] the stereoselective [3+3]-cycloannulation of carbonyl ylides through indolyl-2-methides **179** to yield oxa-bridged azepino[1,2-a]indoles **180** in a single synthetic step. All transient intermediates are produced in single catalytic cycles by cooperative Rh(II) and chiral phosphoric acid (PA) catalysis. The products including three chiral centers were achieved with superior stereoselectivity (Scheme 52).



Scheme 52

According to the literature review presented here, recent advances in the chemistry of diazocarbonyl substances and metallo-carbenoides showed the synthesis of a range of molecules with selectivity is viable. Furthermore, there have been ongoing efforts to synthesize a wide range of heterocycles. Highly substituted spiro-heterocyclic moiety has been reported as the most common structural units in a variety of naturally occurring bioactive compounds. Thus, a part of the work presented in this thesis was undertaken with a broad view to exploring Lewis acid, Brønsted acid and transition metal-catalyzed reactions of 3-diazooxindoles (diazoamides) to synthesize various 3-functionalized indoles, indole incorporated macrocycles and spiro-indolofurobenzopyrans.

The detailed literature reports on reactions of diazocarbonyl compounds with enones and synthesis of 3-alkylated oxindoles (Chapter 2); reactions of diazocarbonyl compounds with aldehydes and synthesis of 3-aryloxindoles (Chapter 3); reactions of diazocarbonyl compounds with indoles and synthesis of 2,3′-biindoles (Chapter 4.1), synthesis of indole incorporated macrocycles (Chapter 4.2); synthesis of 3*H*-indoles derivatives (Chapter 5); synthesis of spiro-indoloheterocycles *via* [3+2]-cycloaddition (Chapter 6) will be discussed in the respective chapter of this Thesis.

CHAPTER - II

AN UNEXPECTED SYNTHESIS OF 3-ALKYLATED OXINDOLES AND SPIRO-INDOLOOXIRANES

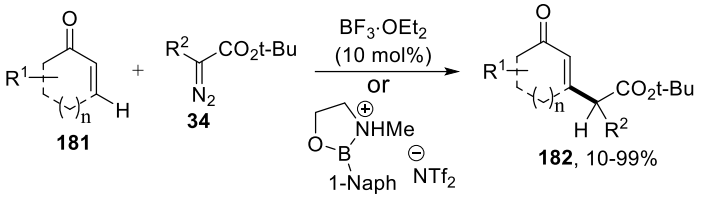
The cleavage of C–C bonds has been one of the most difficult subjects in organic chemistry.[104] For the past two decades, the functionalization of the C–C single bond,[105] double bond,[106] and triple bond[107] has been investigated. In particular, the metal-catalyzed cleavage reactions of C=C double bonds have been established as a powerful tool in organic transformations. The cleavage reactions of the C=C double bond have been reported *via* oxidative cleavage using transition metal catalysts,[108] photochemical methods[109] or oxidants[110] (ozonolysis, the Lemieux–Johnson protocol, mCPBA, PCC, TEMPO or aryl-γ^3-iodane-based) in combination with peroxides, peracids or other oxidizing reagents. The chemoselective cleavage of the C=C double bond is one of the most interesting and highly challenging themes in target-oriented synthesis. A few metal-mediated (Cu, Fe, Ru or Pd) chemoselective cleavage reactions of C=C double bond of α,β-enones have also been reported.[111] As a result, no report was made on the development of Lewis acid-catalyzed chemoselective cleavage of C=C of the,-unsaturated carbonyl compound.

The detailed literature reports for diazocarbonyl compounds, α,β-unsaturated carbonyl compounds and their reactions will be covered in the following sub-sections:

2.1.1. Reaction of diazocarbonyl compounds with enones
2.1.2. Transition metal-catalysed C=C cleavage reactions of enones
2.1.3. Synthesis of spiro-indolooxiranes

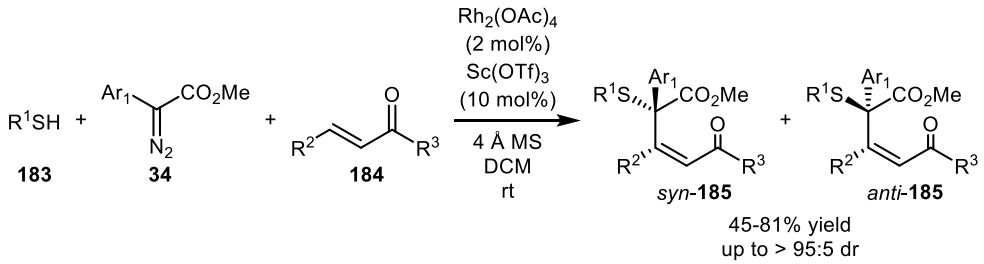
2.1.1. Reaction of diazocarbonyl compounds with enones

C-H Insertion reactions: Ryu and co-workers reported[112] that the reaction of diazoacetates **34** using $BF_3{\cdot}OEt_2$ or an oxazaborolidinium ion as a catalyst yielded functionalized cyclic enones **182** from simple cyclic enones **181** in a single step with high yield (Scheme 53).



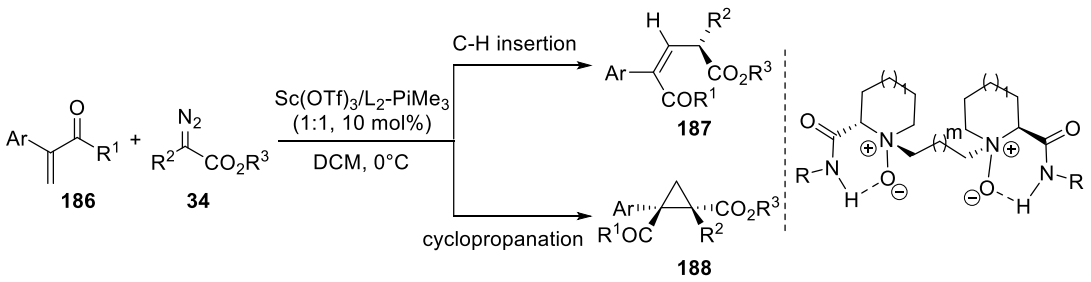
Scheme 53

Rh(II)/Sc(III) co-catalyzed[113] three-component reaction of diazo compounds **34** with thiophenols **183** and enones **184** was used to develop a simple method to synthesize γ-sulphur functionalized ketones **185**. In this method, various γ-sulfur-substituted ketones **185** were obtained in high yield with better diastereoselectivity (Scheme 54).



Scheme 54

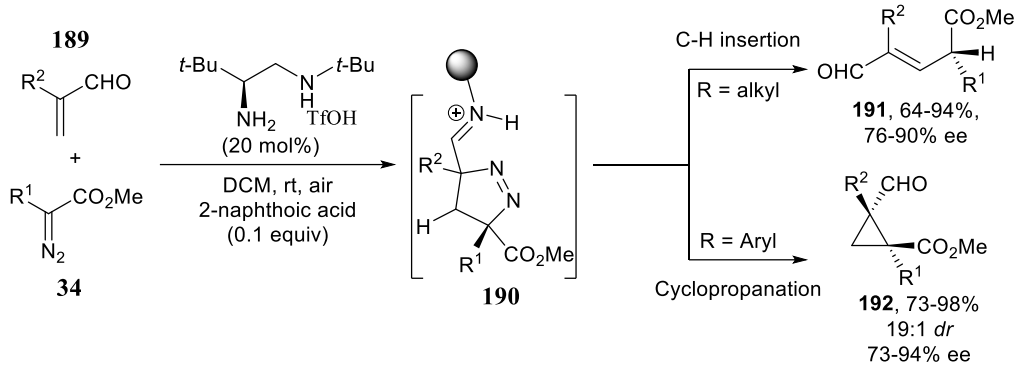
Feng and co-workers demonstrated[114] the asymmetric reaction of α-alkyl diazo compounds **34** and α-unsaturated ketones **186** in the presence of *N,N'*-dioxide-scandium(III) complex as a catalyst clearly showed the importance of favouring the cyclopropanation products **188** over β-hydride shift products **187**. Several *tetra*-substituted cyclopropanes **188** and *E*-enones **187** were synthesized in high yield with good enantioselectivity (Scheme 55).



Scheme 55

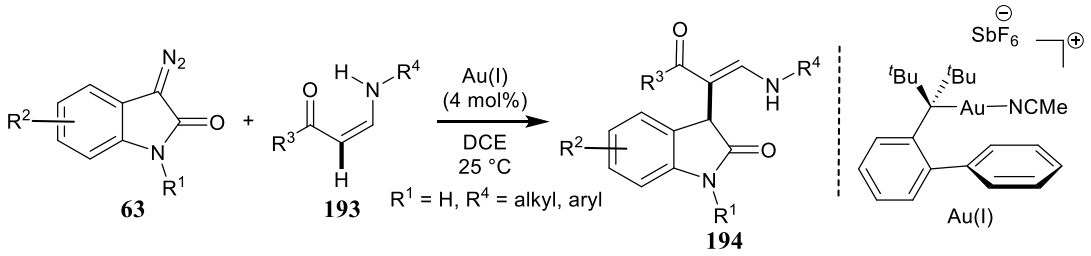
An amino-derived catalyzed[115] coupling of α-diazoesters **34** with α-substituted acrylaldehydes **189** resulted in chemoselective C-H insertion products **191** or

cyclopropanation products **192** depending on alpha-substituents of diazoester **34**. The absence of metal or Lewis acid co-catalyst, a diamine catalyst, obtained from L-*tert*-leucine, allowed both cyclopropanation and C-H insertion routes in better yields and excellent enantioselectivity at ambient temperature (Scheme 56).



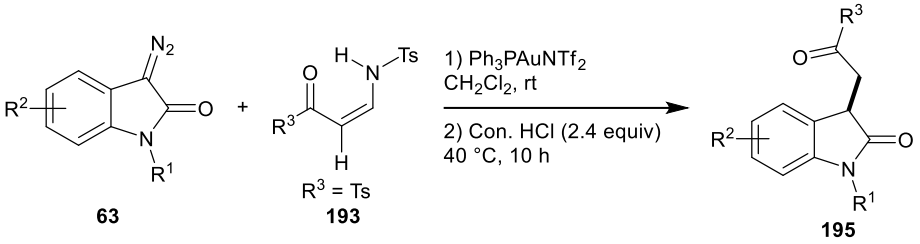
Scheme 56

Li and co-workers have developed[116] an efficient cascade Au(I)-catalyzed reaction of diazoamides **63** with enaminones **193** for the synthesis of 3-alkylated oxindoles **194** under mild reaction conditions. The Au(I)-catalyzed reaction of enaminones **193** with diazoamides **63** provided chemo- and diastereoselective C(sp^2)–H functionalized products (Scheme 57).



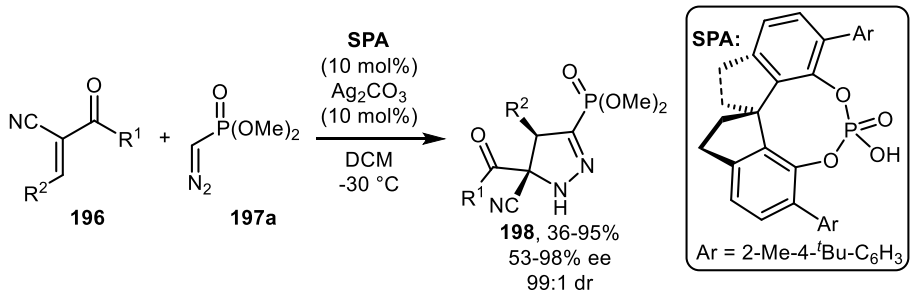
Scheme 57

Li and co-workers have also demonstrated[117] gold(I)/Brønsted acid consecutive catalyzed synthesis of 3-alkylated oxindoles **195** under mild reaction conditions. The Au(I)-catalyzed chemoselective C(sp^2)–H functionalization of tosyl group substituted enaminones **193** and the Brønsted acid-facilitated sequential cleavage of the C–C double bond was completely incorporated (Scheme 58).

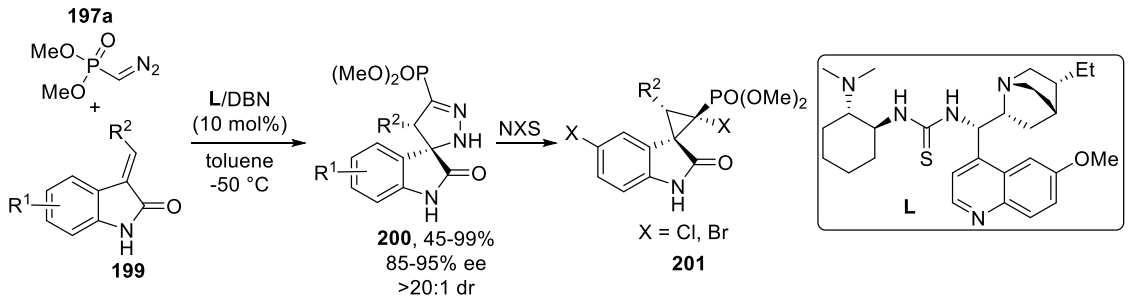


Scheme 58

1,3-Dipolar cycloaddition reactions: An efficient method to construct the functionalized chiral nonspiro-phosphonylpyrazolines **198** has been developed with superior stereoselectivity using chiral silver phosphate catalyst.[118] In this method, generation of an asymmetric [3+2]-cycloaddition reaction using Seyferth-Gilbert reagent **197a** and unsaturated ketones **196** with an added nitrile was demonstrated. A collection of nonspiro-chiral phosphonylpyrazolines from this method has been accessed (Scheme 59).



Scheme 59

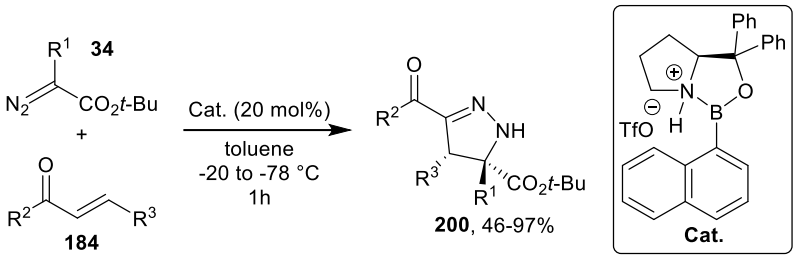


Scheme 60

Peng and co-workers have developed[119] a new approach to obtain enantio-enriched spirocyclic cyclopropanes **201** *via* a 1,3-dipolar cycloaddition of dimethyl (diazomethyl)phosphonate **197a** and 3-arylideneoxindoles **199**, preceded by ring

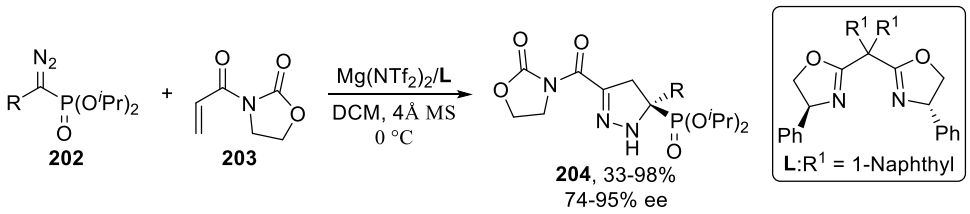
contraction induced by NCS or NBS. Ring contraction can be used to convert the chiral 3,3′-spiro-phosphonylpyrazoline oxindoles **200** into spiro-phosphonylcyclopropane oxindoles **201** (Scheme 60).

Ryu and co-workers investigated[120] α-substituted diazoacetates **34** and acyclic, α-substituted ketones **184** with chiral oxazaborolidinium ions to obtain highly enantioselective [3+2]-cycloaddition products **200**. Functionalized 2-pyrazolines **200** were synthesised in excellent yield with good enantioselectivity (Scheme 61).



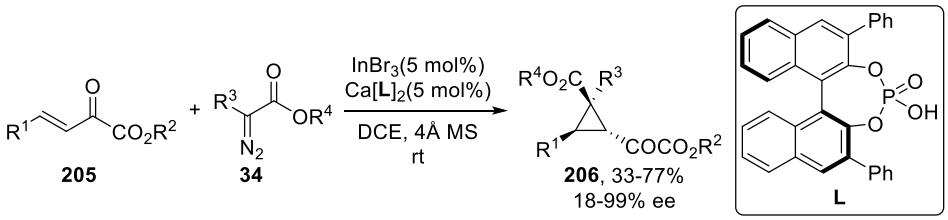
Scheme 61

A chiral Mg(II) complex has been used to catalyze a productive asymmetric [3+2]-cycloaddition reaction between 3-acryloyl-2-oxazolidinone **203** and α-substituted diazophosphonates **202**.[121] This reaction produced the product in good yield and superior stereoselectivity of the resulting chiral 5,5-disubstituted 1*H*-pyrazoline-5-phosphonates **204** (Scheme 62).



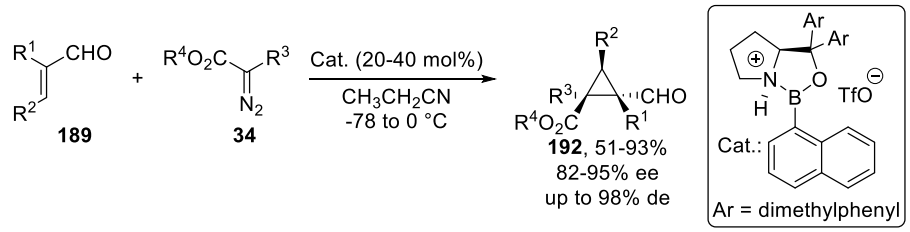
Scheme 62

Cyclopropanation reactions: Lv, Luo and co-workers have explored[122] an enantioselective cyclopropanation of diazoesters **34** with β,γ-unsaturated α-ketoesters **205** by chiral calcium phosphate complexes and $InBr_3$. The process proceeded through Michael addition followed by cyclization route, yielding highly substituted chiral cyclopropanes **206** as a single diastereoisomer (Scheme 63).



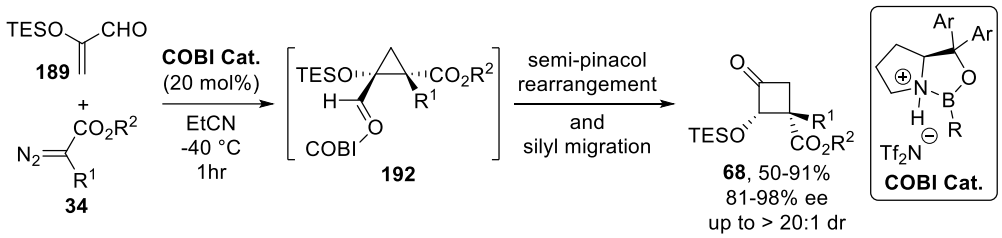
Scheme 63

Ryu and co-workers have developed[123] Michael-initiated cyclopropanation of aryl and alkyl diazoacetates **34** with α,β-substituted aldehydes **189** yielding highly substituted chiral cyclopropane derivatives **192** using (S)-oxazaborolidinium ion as a catalyst. This method produced high yields of tetrasubstituted cyclopropanes **192** with incredible enantioselectivity (Scheme 64).



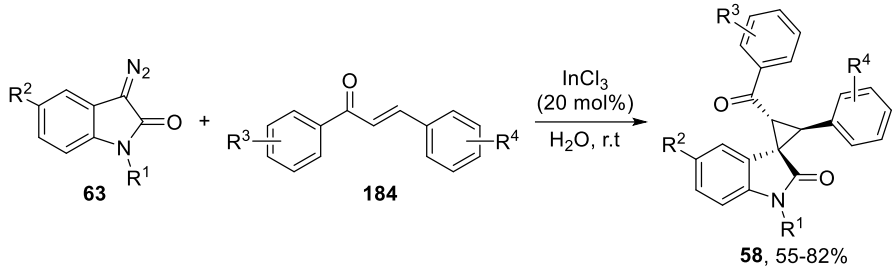
Scheme 64

A chiral COBI-catalyzed[124] asymmetric synthesis of cyclobutanones **68** from α-alkyl or α-aryl diazoesters **34** and α-silyloxyacroleins **189** has been developed. Through two-stage cyclopropanation/semipinacol rearrangement in the presence of a COBI catalyst, several α-silyloxycyclobutanones **68a** with a chiral β-quaternary centre were synthesized in excellent yield with high enantio- and diastereoselectivity (Scheme 65).



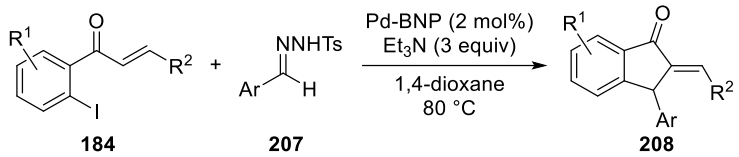
Scheme 65

Our research group has demonstrated[125] the highly diastereoselective method for synthesizing a series of spiro[cyclopropane-1,3-oxindoles] **58** from diazoamides **63** and chalcones **184** in water utilizing $InCl_3$ as a catalyst (Scheme 66).



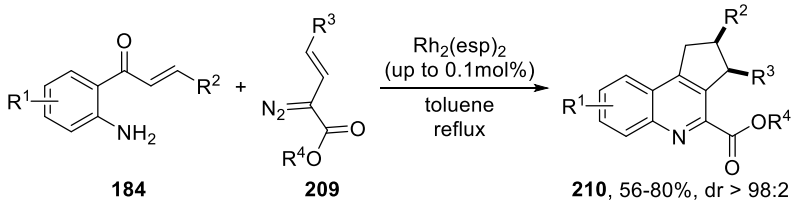
Scheme 66

Indanones **208** have been synthesized[126] *via* the palladium nanoparticle (Pd-BNP)-catalyzed coupling of 2-iodophenyl enones **184** and benzaldehyde hydrazones **207**, which involves the formation of arylpalladium carbenes intermediates, subsequent migration and ring closure. This ligand-free approach demonstrated a broad substrates and good yield with excellent *E*-selectivity (Scheme 67).



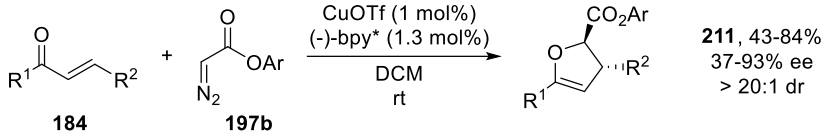
Scheme 67

Quinolines **210** have been synthesized[127] *via* mechanistically complex reaction of vinyl diazocarbonyl compounds **209** and *o*-aminochalcones **184** in which the carbene complex adduct adds to the carbonyl group to divinylindoline intermediate, which then produced oxy-Cope rearrangement product followed by an aldol process to yield the functionalized quinolones **210** (Scheme 68).



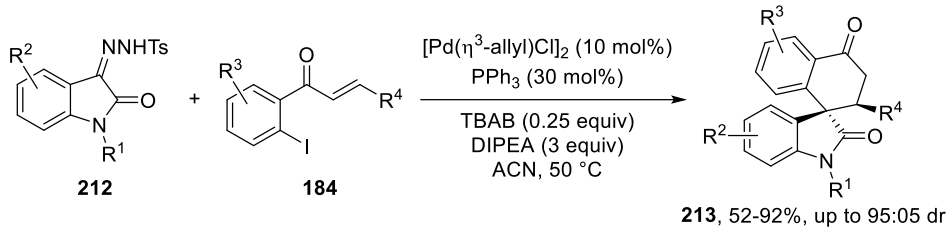
Scheme 68

Fu and co-workers described[128] the first enantio- and diastereoselective Cu(II)-catalyzed [4+1]-cycloaddition of enones **184** with diazo compounds **197b** to obtain highly substituted 2,3-dihydrofurans **211** using a chiral bipyridine ligand (Scheme 69).



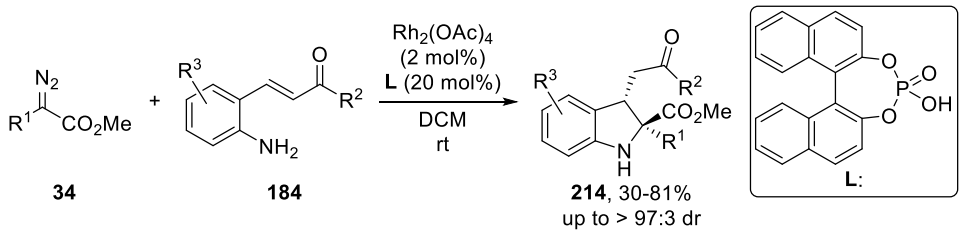
Scheme 69

Sekar and co-workers have investigated[129] the Pd-catalyzed diastereoselective synthesis of α-tetralone-fused spirooxindoles **213**. The Pd-catalyzed domino reaction starts with carbene relocating insertion then moves on to *6-endo-trig* mode of conjugate addition from widely accessible isatin-derived tosylhydrazones **212** and 2′-iodochalcones **184**. The protocol's adaptability was demonstrated by its broad substrate scope, high functional group tolerance in good yield (Scheme 70).



Scheme 70

Hu and co-workers extended[130] the Rh(II)/ Brønsted acid co-catalyzed formal [4+1]-annulation approach of amine-substituted enones **184** and diazoacetates **34** to yield 2,2,3-trisubstituted indoline derivatives **214** with high diastereoselectivity (Scheme 71).

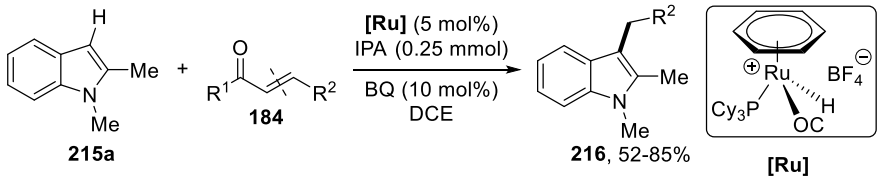


Scheme 71

2.1.2. Transition metal-catalyzed C=C cleavage reactions of enones

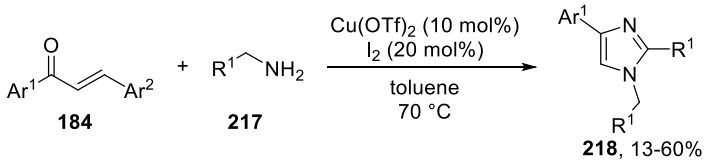
Yi and co-workers have demonstrated[111a] a new catalytic chelate assistance procedure for regioselective C_α–C_β bond cleavage of unsaturated carbonyl compounds. They discovered that the coupling reaction of indoles **215a** with α,β-unsaturated

aldehydes/ketones **184** provided the intermediate of coupling products, which then underwent the regioselective C=C cleavage reaction assisted by both indole **215a** and ketone **184** chelate directing groups (Scheme 72).



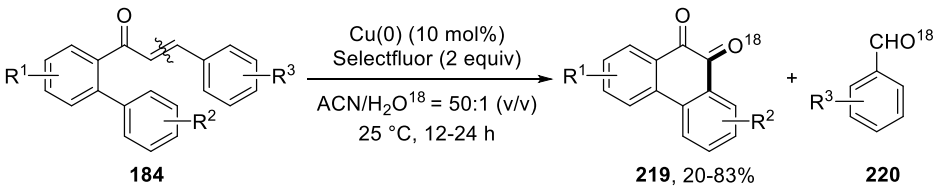
Scheme 72

The $Cu(OTf)_2/I_2$-catalyzed[111b] unfamiliar C-C bond cleavage of chalcones **184** and benzylamines **217** resulted in the formation of 1,2,4-trisubstituted-(1*H*)-imidazoles **218**. The β-portion was removed from the reaction following the cleavage of α,β-unsaturated C=C bond. The reaction controls a variety of functional groups furnishing products in moderate to good yields (Scheme 73).



Scheme 73

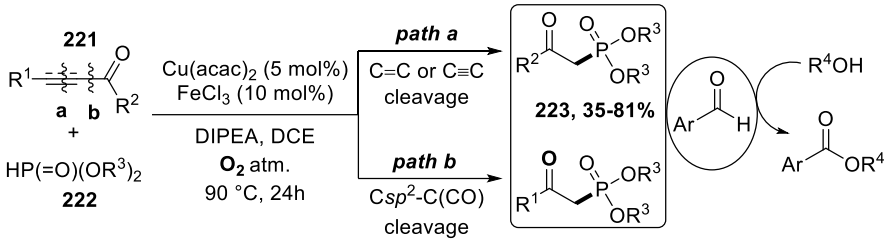
Liu and co-workers have explored[111c] a broad and quick procedure for the synthesis of 9,10-phenanthraquinone derivatives **219** using a Cu(0)/Selectfluor system-promoted oxidative C-C bond cleavage/annulation of *o*-aryl chalcones **184**. A number of substituted 9,10-phenanthraquinones **219** were investigated (Scheme 74).



Scheme 74

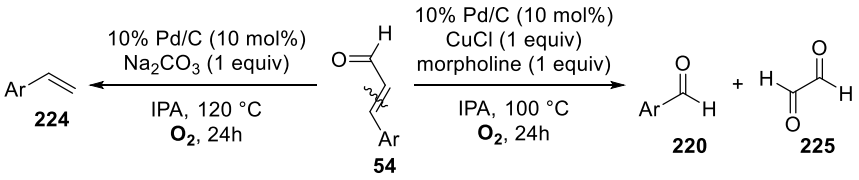
Song and co-workers have reported[111d] the alkyne C-C bond cleavage with concurrent phosphorylation under aerobic conditions using a combination of Cu/Fe catalysts

(Scheme 75). The scope of α,β-unsaturated ketones **221** included substrates with double/triple bonds. The remaining snippet of the cleaved molecule was oxidized to provide the corresponding aldehyde.



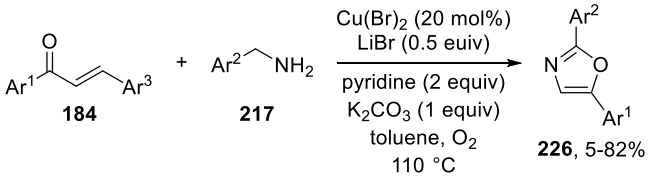
Scheme 75

Pd/C Catalyzed[111e] method for regioselectively altering the cleavage sites of C–C bonds in cinnamaldehyde derivatives **54** *via* a slight change in reaction conditions in isopropanol under O_2 atmosphere has been provided. Styrene derivatives **224** could be formed selectively by adding Na_2CO_3 in conjunction with the dissociation of carbon monoxide, whereas benzaldehyde derivatives **220** could be formed by adding CuCl and morpholine in place of Na_2CO_3 (Scheme 76).



Scheme 76

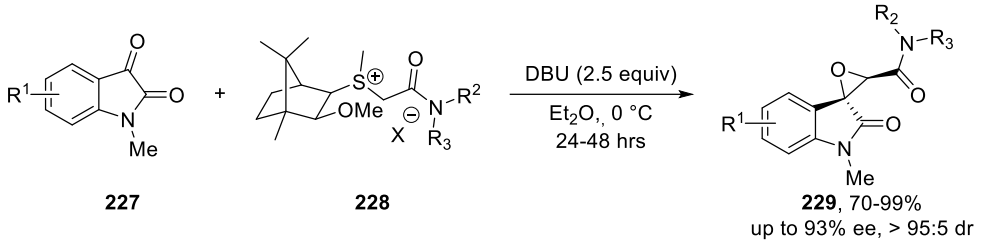
Cheng and co-workers revealed[111f] that Cu(II)-catalyzed oxidative cyclization of chalcone **184** with benzylic amine **217** resulted in moderate to good yield of 2,5-diaryl oxazoles **226**. The procedure involved O_2 as a clean oxidant and the key step is the oxidative cleavage of the C=C bond (Scheme 77).



Scheme 77

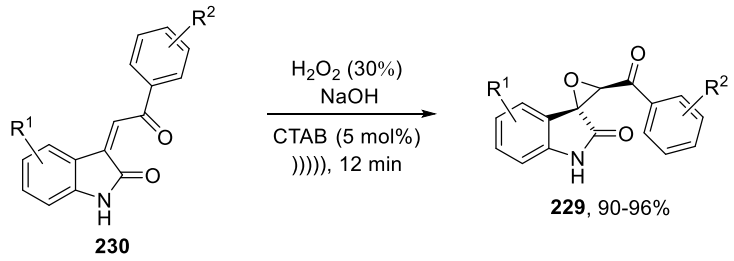
2.1.3. Synthesis of spiro-indolooxiranes

Asymmetric synthesis of epoxyoxindoles **229** from isatins **227** has been developed[131] using chiral sulfur ylides **228**, generated from camphor-derived sulfonium salts. This reaction provided efficient privileged access to enantio-enriched spiro-epoxyoxindoles **229** under mild reaction conditions with high enantio- and diastereoselectivity (Scheme 78).



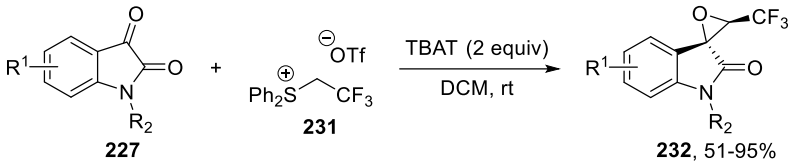
Scheme 78

Under ultrasound irradiation, 3-aroylmethylene indole-2-ones **230** were epoxidized[132] with aqueous hydrogen peroxide (H_2O_2 30%) using cetyltrimethylammonium bromide (CTAB) as a phase transfer catalyst to yield spiro[indole-3,2'-oxiranes] **229** in good yield (Scheme 79).



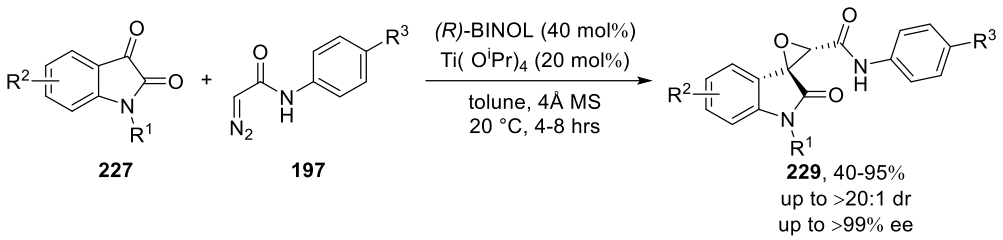
Scheme 79

Zhai and co-workers have demonstrated[133] that the Corey-Chaykovsky reaction of N-alkyl isatins **227** with sulfur ylides to successfully prepare CF_3-containing spiro-epoxyoxindoles **232** with excellent diastereoselectivity. These spiro-epoxyoxindoles **232** were further derivatized using a Lewis acid reaction or photochemical promoted allylation (Scheme 80).



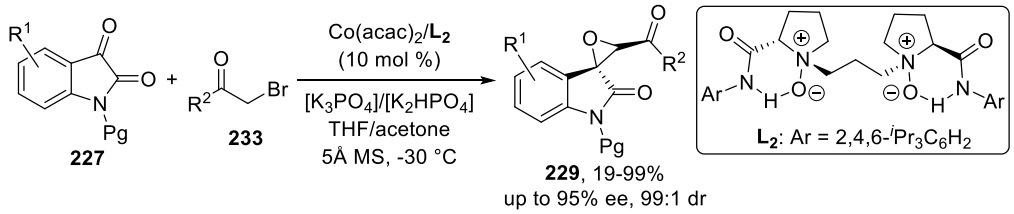
Scheme 80

A chiral Ti(O^iPr)$_4$/BINOL complex was used as a catalyst in an efficient asymmetric Darzens reaction of N-protected isatins **227** with diazoacetamides **197**.[134] This reaction is a simple method for producing spiro-epoxyoxindoles **229**. A gram-scale reaction with excellent enantioselectivity and stereoselectivity was also succeeded in 95% yield (Scheme 81).



Scheme 81

Feng and co-workers have synthesized[135] spirooxindoles **229** using the Darzens reaction, which was catalyzed by Co-complexes. Consequently, *N*-protected isatins **227** reacted with α-bromoketones **233** *via* Michael-intramolecular *O*-alkylation sequence to produce spiro-oxindole epoxides **229** in high yields, excellent stereoselectivity and good functional group acceptance (Scheme 82).



Scheme 82

Scope and objectives: Based on the above literature, the coupling reactions of diazocarbonyl compounds with α,β-unsaturated carbonyls provided competitive C-H insertion products, pyrazole derivatives obtained *via* [3+2]-cycloaddition to the olefin moiety leading to 1,3-dipolar cycloaddition, cyclopropanation of olefin and construction of various heterocycles and carbocycles are possible when subjected to different catalysts. The characterization of catalytic tools is critical for facilitating enantio-selective but also chemo-selective control in diazocarbonyl compound transformation. Various metals (Ag, Au, Mg and Ca) and boron catalysts, chiral ligands could promote C-H insertion, 1,3-dipolar cycloaddition and cyclopropanation with different substrates. Rh, Cu and Pd-derived catalysts could promote the synthesis of heterocycles and carbocycles. These methods provide a mixture of products. However, these are a few reported C=C double bond cleavage reactions that suffer from the need for expensive catalysts and require a large number of combined reagents, harsh reaction conditions or multi-step synthesis. No reports are available for transition metal-free chemoselective cleavage of C=C bond of α,β-enones. Therefore, the objectives of the present work are mainly focused on the metal-free synthesis of 3-alkylated oxindoles from diazoamides and chalcones *via* C=C double bond cleavage.

The objectives of the present work are the following:

- To study the reaction of diazoamides and chalcones in the presence of Lewis acids.
- To develop transition metal-free method to synthesize 3-alkylated oxindoles.
- Utilize this protocol for synthesizing spiro-indolooxiranes.

RESULTS AND DISCUSSION

2.2.1. Lewis acid catalyzed synthesis of 3-alkylated oxindoles

Oxindoles and their variants, particularly 3-functionalized oxindoles, are naturally and pharmacologically beneficial scaffolds with numerous biological properties relevant to medicinal chemistry. Many of these oxindoles have potent biological activities[136] with high efficacy, such as anti-bacterial, anti-leukemia, anti-cancer, anti-malarial, anti-tumor, anti-HIV, anti-diabetic, anti-oxidant, kinase is inhibitory, AChE inhibitory, anti-leishmanial, β3 adrenergic receptor agonistic, phosphatase inhibitory, analgesic, spermicidal, vasopressin antagonists, progesterone antagonists, neuroprotective, hormone secretagogue, and receptor antagonist (Figure 8). The traditional C-3 alkylation of oxindoles with alkyl halides has serious limitations and the formation of dialkylated products involve less regioselectivity, the formation of salt wastes, and the use of toxic reagents.

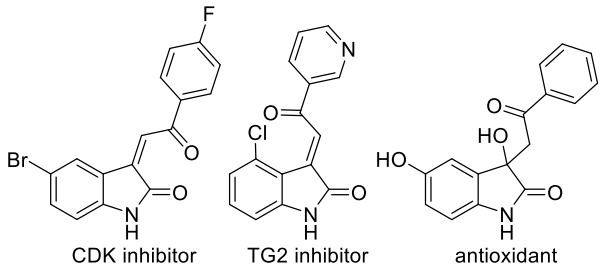


Figure 8

Chalcone, an easily available α,β-unsaturated ketone, is a well-known precursor in organic synthesis with a wide spectrum of medicinal applications.[137] An α,β-unsaturated compounds play a critical role in organic synthesis. They contain two types of functional moieties: C=C unsaturated bonds and carbonyl groups. As a special C=C cleavage reaction, α,β-unsaturated ketone has been rarely explored by transition metal-catalyzed reactions. However, these are a few reported C=C double bond cleavage reactions that suffer from the need for expensive catalysts and require a large number of

combined reagents, harsh reaction conditions or multi-step synthesis.

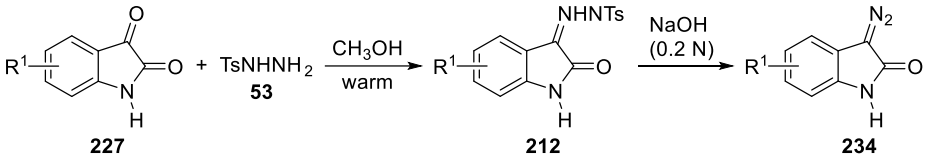
Highly diastereoselective synthesis of spiro-indolocyclopropanes was reported[125] by us from diazoamides **63** and chalcones **184** in the presence of $InCl_3$ as a catalyst in water. However, a similar reaction in the presence of $BF_3{\cdot}OEt_2$ in chloroform provided a new product instead of the expected cyclopropane formation with a change in the Lewis acid and solvent system. To the best of our knowledge, no reports are available for transition metal-free chemoselective cleavage of the C=C bond of α,β-enones. As a continuation of our interest in exploring the chemistry of diazoamides,[87,138] we herein report an efficient general approach for the synthesis of the unexpected 3-alkylated oxindoles **195** obtained from diazoamides **63** and α,β-unsaturated carbonyl compounds **184** in the presence of $BF_3{\cdot}OEt_2$ as a catalyst under mild conditions *via* chemoselective cleavage of the C(sp^2)–C(CO) bond. In this chapter, comprehensive research and discussion on the synthesis of 3-alkylated oxindoles will be presented. The present investigations are described in the following three sub-sections.

2.2.1. Synthesis of diazoamides and chalcones
2.2.2. Synthesis of 3-alkylated oxindoles
2.2.3. Synthesis of spiro-indolooxiranes

Synthesis of diazoamides and chalcones

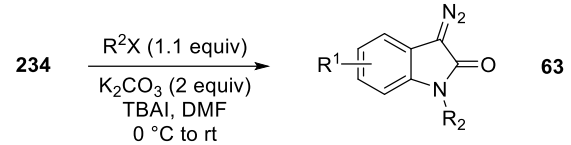
Synthesis of N-substituted 3-diazo-2-oxindoles **(63):** In general, diazoamides have usually been prepared using Bamford Steven's reaction.[139] The cyclic diazoamides, 3-diazoindol-2-ones **234**, were chosen and prepared using Bamford Steven's reaction from isatin **227**. The condensation of isatin **227** and *p*-toluene sulphonylhydrazide **53** in warm methanol provided the corresponding hydrazones **212** as a yellow crystalline solid. Notably, the condensation of hydrazones took place only with the isatin C-3 carbonyl group and not with the amide carbonyl group at C-2 position. The treatment of

hydrazones with 0.2N NaOH solution over a week yielded 3-diazoindol-2-ones **234** as blood red crystals. The NH unit of the synthesized diazooxindoles was alkylated in the presence of K_2CO_3 in DMF with various alkylating agents (Scheme 83). In general, the diazo compounds were identified using a common strong IR band of approximately 2100 cm^{-1} (Table 1).



Scheme 83

Table 1. Synthesis of cyclic diazoamides **63**



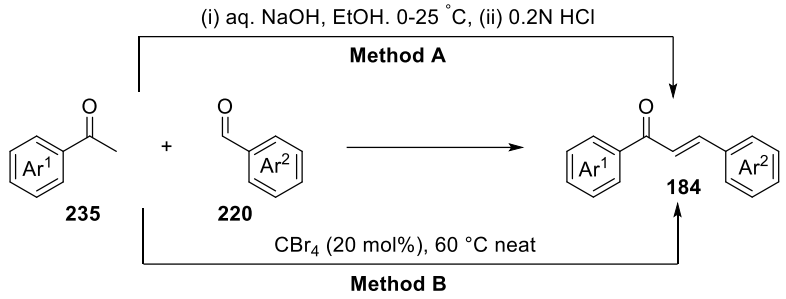
Entry	Diazoamides	R^1	R^2	Yield[a] (%)	IR ($\nu_{max,}$ cm^{-1})
1	**63a**	H	Bn	90	2109
2	**63b**	H	Me	85	2130
3	**63c**[b]	H	Et	80	2118
4	**63d**	H	propargyl	84	2097
5	**63e**	H	benzoyl	40	2115
6	**63f**	5-F	Me	91	2110
7	**63g**	4-Br	Me	80	2119
8	**63h/63i**	5-Cl	Me or Bn	85 or 88	2101/2113
9	**63j**	5-I	Me	65	2130
10	**63k/63l**	5-Me	Bn or Me	79	2095
11	**63m**	5-MeO	Bn	76	2135
12	**63n**	6-MeO	Bn	70	2116

[a]Isolated yield. [b]Liquid.

Synthesis of chalcones **184**

Method A: Chalcones **184** were synthesized[140a] through NaOH-catalyzed Claisen-Schmidt condensation reactions involving acetophenones **235** and substituted aldehydes **220** (Table 2). In a 100 mL round-bottomed flask equipped with a magnetic stirrer, a mixture of aldehyde **220** (0.01 mol) and acetophenone **235** (0.01 mol) was dissolved in 10 mL ethanol. The reaction mixture was then treated with 10 mL NaOH solution (1g

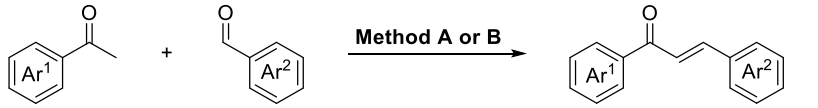
in 10 mL H_2O) dropwise for 5 minutes on vigorous stirring for 30 minutes when the solution became turbid and the reaction temperature was kept between 20-25 °C.



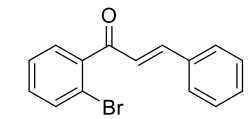
Scheme 84

***Method B*:** Acetophenone **235** (1 equiv), aldehyde **220** (4 equiv) and CBr_4 (2 equiv) were combined in an oven-dried and kept at 60 °C under neat conditions. After completion of the reaction, it was quenched with sodium bisulfite solution and extracted with ethyl acetate (Scheme 84).[140b] The bis-chalcones **238** were synthesized from method **A** where terephthalaldehyde (1 equiv) and acetophenone (2 equiv)

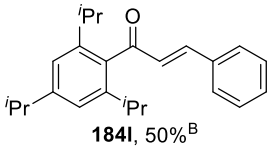
Table 2. Synthesis of chalcones **184**



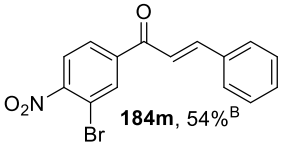
184a, Ar^1 = H, 95%
184b, Ar^1 = 4-Me, 95%
184c, Ar^1 = 4-OMe, 98%
184d, Ar^1 = 4-Ph, 90%
184e, Ar^1 = 4-OH, 86%
184f, Ar^1 = 4-F, 92%
184g, Ar^1 = 4-Cl, 89%
184h, Ar^1 = 4-Br, 90%
184i, Ar^1 = 4-CN, 76%
184j, Ar^1 = 4-NO_2, 64%



184k, 65%

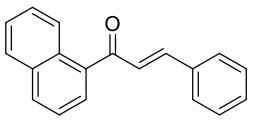


184l, 50%[B]

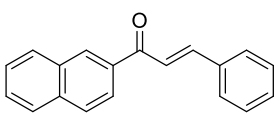


184m, 54%[B]

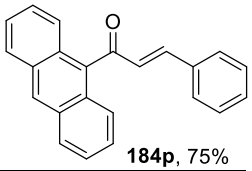
184q, Ar^2 = 4-Me 94%
184r, Ar^2 = 4-OMe, 92%
184s, Ar^2 = 4-Ph, 91%
184t, Ar^2 = 4-OH, 90%
184w, Ar^2 = 3-F, 80%
184x, Ar^2 = 4-Cl, 96%
184y, Ar^2 = 4-Br, 94%
184z, Ar^2 = 4-NO_2, 78%
184aa, Ar^2 = 4-CN, 64%



184n, 85%



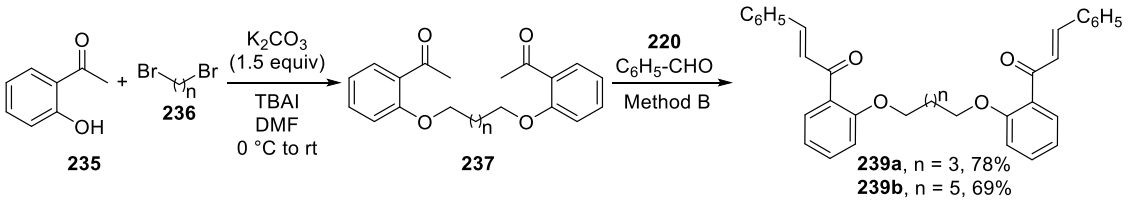
184o, 81%



184p, 75%

[a]Isolated yield.

derivatives as starting materials. The next type of bis-chalcones **239** has been synthesized using method **B** where bis-*O*-alkylated acetophenone derivatives as starting materials (Scheme 85).



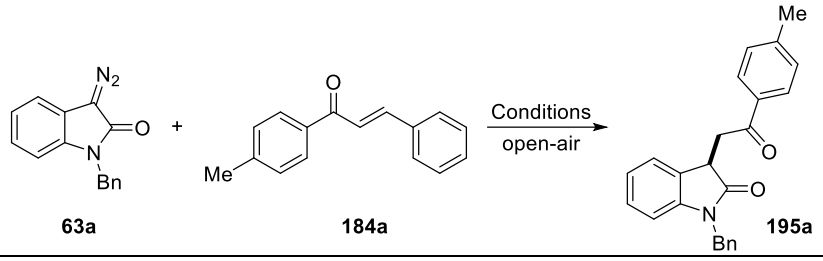
Scheme 85

Synthesis of 3-alkylated oxindoles

In order to study the cleavage of C=C bond, the reaction of diazoamide **63a** with chalcone **184a** as an appropriate reaction partner in the presence of a Lewis acid catalyst was chosen. An initial study on the feasibility of using a solution containing diazoamide **63a** (1.0 mmol) and chalcone **184a** (1.0 mmol) in the presence of 10 mol% of $FeCl_3$ at 0 °C under an open-air atmosphere in dichloromethane (DCM) for 5 minutes afforded the unexpected and interesting 3-alkylated oxindole **195a** in 40% yield (Table 3, entry 1). Product **195a** was characterized on the basis of spectral data (IR, NMR, and HRMS). In the ^{1}H-NMR spectrum (Figure 9), singlets appeared in the range of δ 2.40 and 4.97 ppm which indicated the CH_3 and NCH_2 protons, respectively. The newly formed CH and CH_2 protons appeared as a doublet of doublets at 3.44, 3.86 and 4.16 ppm. The remaining aromatic protons appeared around 6.72 - 7.90 ppm. In the ^{13}C-NMR spectrum (Figure 10), the amide and keto carbonyl carbons showed peaks at δ 177.9 and 196.5 ppm. The newly generated CH and CH_2 carbons appeared at 41.3 and 40.0 ppm. The CH_3 and NCH_2 carbons appeared at 21.7 and 44.0 ppm. Because of the presence of symmetry in the part of the molecule, ^{13}C-NMR contains fewer carbon signals than expected. The high-resolution mass spectrum showed the required

molecular ion peak at 356.1644 m/z. Benzoic acid was obtained as the by-product, based on ^{1}H-NMR studies. It was confirmed that the β-portion of the chalcone has been eliminated from the reaction, indicating that the reaction may be proceeding through the chemoselective C=C bond cleavage of chalcones. Furthermore, the reaction was also performed in the presence of $AlCl_3$ or $SnCl_4$ but this did not improve the yield of product **195a** (Table 3, entries 2 and 3). There was no product formation when the reaction was carried out in DCM using $InCl_3$ as a catalyst (Table 3, entry 4). Among the catalysts screened, $FeCl_3$ provided the best yield of the desired product **195a**. The reaction was also performed with various triflates, In $(OTf)_3$, Yb$(OTf)_3$, and Sc$(OTf)_3$, but did not result the desired product **195a** (Table 3, entries 5-7). Then various boron catalysts, such as $B(C_6F_5)_3$, $BF_3{\cdot}OEt_2$, Tr(BF_4) and Trop(BF_4), were screened (Table 3, entries 8-11) but no desired product was obtained in the presence of $B(C_6F_5)_3$ (Table 3, entry 8). To our delight, when the non-metal Lewis acid $BF_3{\cdot}OEt_2$ was efficiently employed in the reaction between **63a** and **184a** to afford **195a** in moderate yield (58%; entry 9). However, the reaction with Tr(BF_4) or Trop(BF_4) afforded **195a** in 32 and 45% yields, respectively (Table 3, entries 10 and 11). Brønsted acids, such as TfOH and *p*-TSA, were also catalysts in this transformation, but yielded the desired product **195a** in lower yield (Table 3, entries 12 and 13). Among the catalysts, $BF_3{\cdot}OEt_2$ was found to be better. Next, the screening of several solvents, *viz*., dichloroethane (DCE), chloroform, dioxane, toluene, and dimethylformamide (DMF) at 0 °C (Table 3, entries 14–18) revealed that commercial chloroform was the best to provide **195a** in 73% yield. The reaction was carried out at 30 °C to afford the 3-alkylated oxindole **195a** in 45% yield (Table 3, entry 19). The yield of product **195a** did not improve when the reaction was carried out at -10 °C or when the amount of the catalyst used was changed

Table 3. Optimization of reaction conditions for the formation of **195a**.[a]



63a **184a** **195a**

Entry	Catalyst	Solvent	Temp [°C]	t [min]	Yield[b] (%) of **195a**
1	$FeCl_3$	DCM	0	5	40
2	$AlCl_3$	DCM	0	5	21
3	$SnCl_4$	DCM	0	5	29
4	$InCl_3$	DCM	0	5	nr[c]
5	$In(OTf)_3$	DCM	0	180	nr[c]
6	$Yb(OTf)_3$	DCM	0	180	nd[d]
7	$Sc(OTf)_3$	DCM	0	180	nd[d]
8[e]	$B(C_6F_5)_3$	$CHCl_3$	0	5	nd[d]
9	$BF_3{\cdot}OEt_2$	DCM	0	5	58
10	$Tr(BF_4)$	$CHCl_3$	0	5	32
11	$Trop(BF_4)$	$CHCl_3$	0	5	45
12	TfOH	DCM	0	5	38
13	*p*-TSA	DCM	0	5	27
14	$BF_3{\cdot}OEt_2$	DCE	0	30	47
15	**$BF_3{\cdot}OEt_2$**	**$CHCl_3$**	**0**	**5**	**73**
16	$BF_3{\cdot}OEt_2$	Dioxane	0	240	nr[c]
17	$BF_3{\cdot}OEt_2$	PhMe	0	5	30
18	$BF_3{\cdot}OEt_2$	DMF	0	180	nr[c]
19	$BF_3{\cdot}OEt_2$	$CHCl_3$	30	30	45
20	$BF_3{\cdot}OEt_2$	$CHCl_3$	-10	5	49
21[f/g]	$BF_3{\cdot}OEt_2$	$CHCl_3$	0	5	33/70
22[h/i]	$BF_3{\cdot}OEt_2$	$CHCl_3$	0	5	nr[c]
23[j]	$BF_3{\cdot}OEt_2$	$CHCl_3$	0	5	13
24	-	$CHCl_3$	0	120	nr[c]

[a]Reaction conditions: The reaction was carried out by adding 10 mol% of Lewis acid to a solution of diazoamide **63a** (1.0 mmol) and chalcone **184a** (1.0 mmol) in commercial solvent under an open-air atmosphere at 0 °C. [b]Isolated yield. [c]No reaction. [d]No desired product. [e]Reaction was carried out under argon atmosphere. [f/g]5 or 20 mol% of catalyst used. [h/i]Reactions were carried out under argon or oxygen atmosphere in dry $CHCl_3$. [j]Addition of 10μL of water.

(Table 3, entries 20 and 21). Remarkably, the desired product **195a** did not form when the reaction was performed under an argon or oxygen atmosphere in dry chloroform (Table 3, entry 22). The addition of water (10 μL) to the reaction mixture in the presence of 10 mol% of $BF_3{\cdot}OEt_2$ provided **195a** in 13% yield only (Table 3, entry 23). Entries 22 and 23 clearly indicate that the presence of moisture plays a vital role in this

transformation. No reaction took place in the absence of a catalyst (Table 3, entry 24). Thus, the optimized reaction conditions for the formation of **195a** were found to be 10 mol% of $BF_3 \cdot OEt_2$ in commercial chloroform at 0 °C under an open-air atmosphere, as shown in Table 1, entry 15.

With the optimized reaction conditions in hand, the substrate scope of the reaction was examined. The scope of Ar^1 ring of chalcones (Table 4) was explored. To this end, a series of highly substituted Ar^1 rings of chalcones were synthesized to react with diazoamides. The reactions of diazoamides with chalcones bearing electron-donating methyl and methoxy groups at 4-position of Ar^1 ring provided the corresponding 3-alkylated oxindoles **195a-d** in 68–73% yield. There was some effect of the substituent located on the amide nitrogen of the diazoamide. Moreover, the unsubstituted diazoamide failed to afford the 3-alkylated oxindole **195e** and the starting materials were recovered. The bulky 4-phenyl substituted chalcone provided the desired product **195f** in moderate yield. Importantly, the sterically demanding 2,4,6-triisopropyl substituted chalcone furnished product **195g** in 57% yield. However, the chalcone having the hydroxy substituents did not deliver the product **195h**. Electron-withdrawing substituents (F, Cl and Br) on Ar^1 ring of chalcones were well tolerated and afforded the corresponding products **195i-l** and the halogen atom present in the resulting products could be used for further transformations. Moreover, a strong electron-withdrawing group, such as $-NO_2$, was also well-tolerated to deliver the desired products **195m,n** in comparable yields. Chalcones having the CN substituent did not produce the desired product **195o**. The reaction utilizing the naphthalene or anthracene system also gave the corresponding 3-alkylated oxindoles **195x-z** in moderate yields.

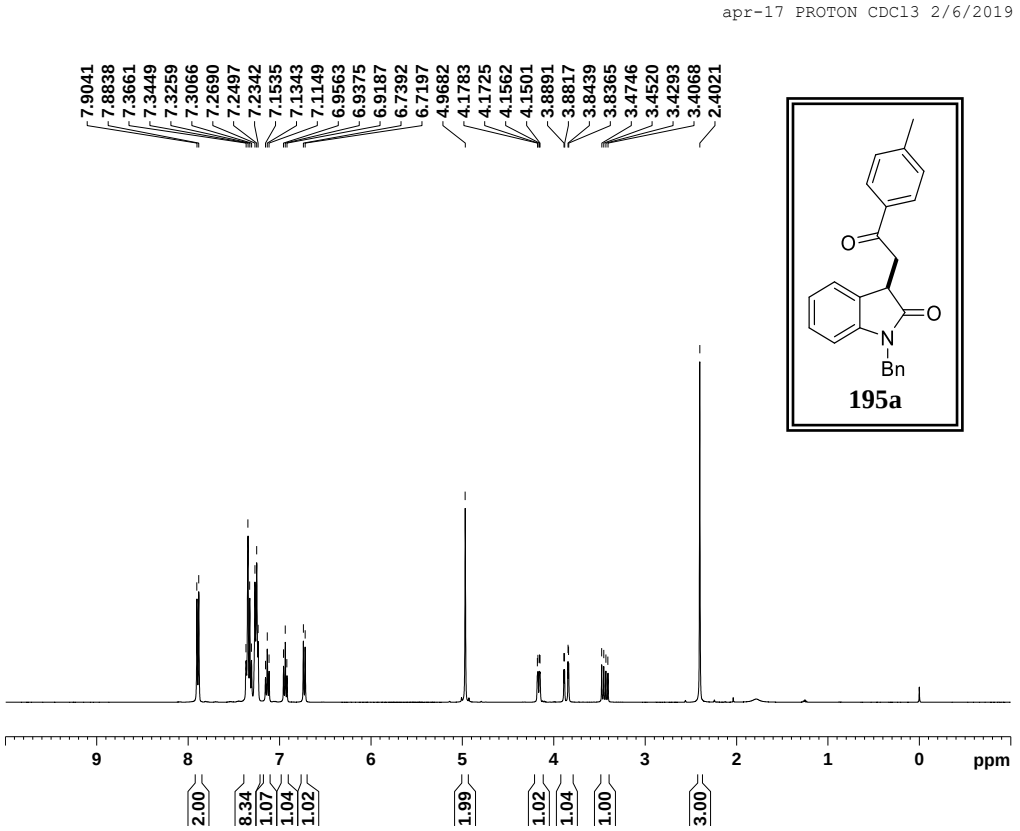


Figure 9. ^{1}H-NMR (δ) spectrum of **195a**

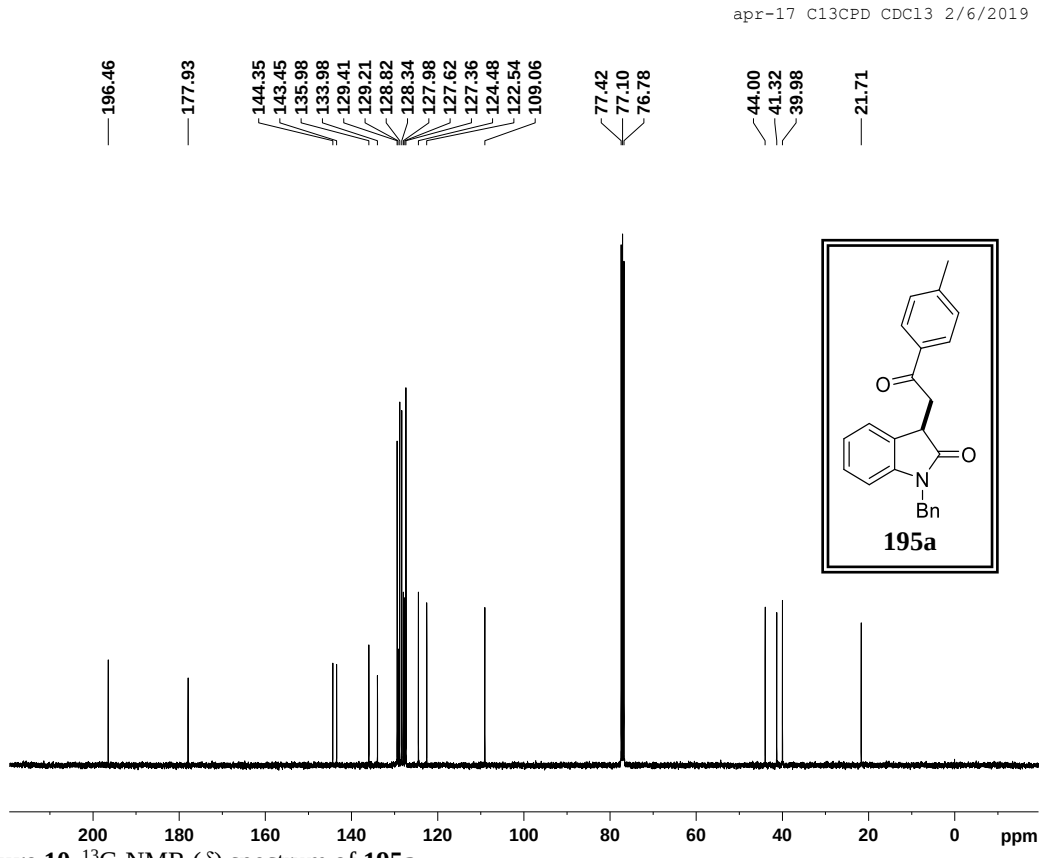
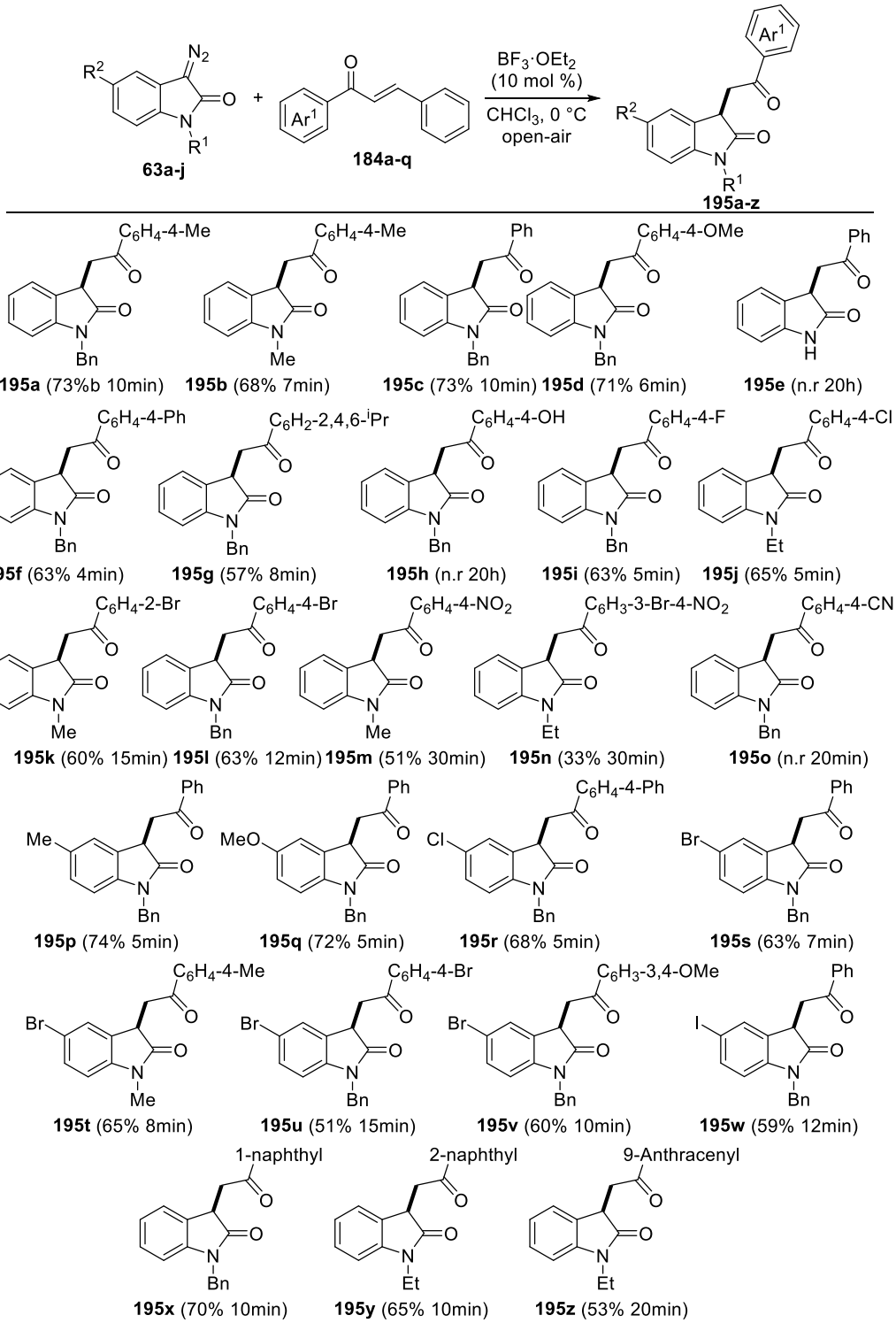


Figure 10. ^{13}C-NMR (δ) spectrum of **195a**

Table 4. Synthesis of 3-alkylated oxindoles **195**, reactivity of Ar^1 ring[a]



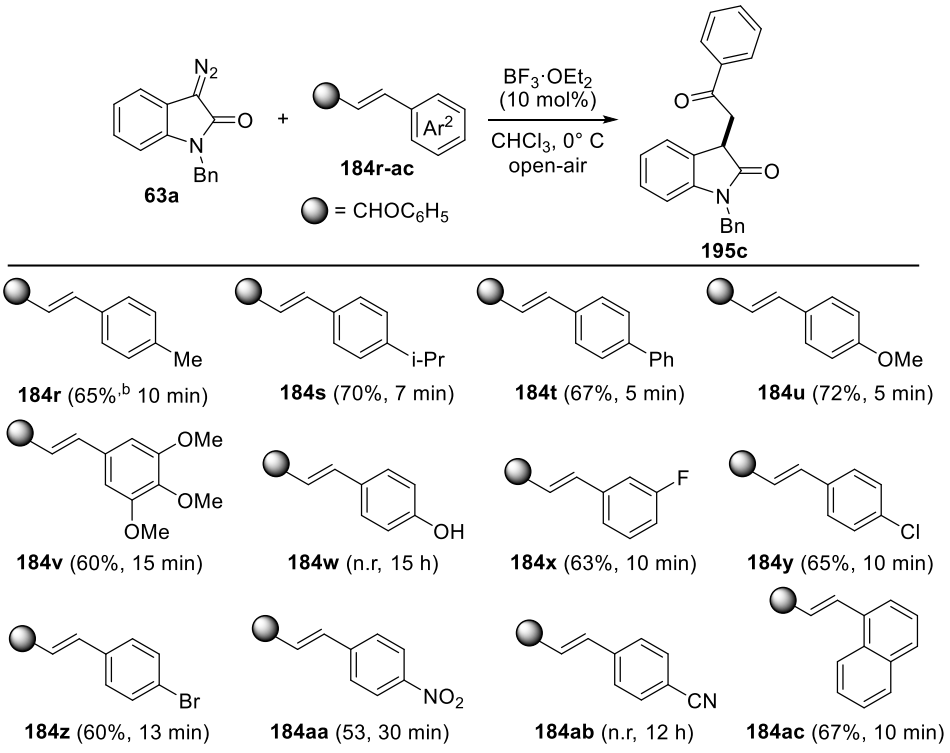
[a]Reaction conditions: equimolar amount of **63** and **184**, $BF_3{\cdot}OEt_2$ (10 mol%), $CHCl_3$ (2 mL), 0 °C.
[b]Isolated yield.

Next, the Ar^2 ring of chalcone was also examined (Table 5). A series of Ar^2 substituted chalcones was suitable for use in this reaction to give product **195c** in moderate to good

yield. Electron-donating substituents at the 3-, 4- and 5-positions of Ar^2 afforded the corresponding product **195c** in moderate to good yields. The hydroxy substituent on Ar^2 of chalcone did not deliver the expected product **195c**. On the other hand, substrates with electron-withdrawing groups like F, Cl, Br, and NO_2 on the aryl ring of Ar^2 provided the desired product **195c** in moderate yield. Next, the effect of the substituent on diazoamides **63** was examined. Electron-rich diazoamides gave the desired products **195p** and **195q** in good yields. Halo-substituted diazoamides were also found to be suitable substrates to deliver the 3-alkylated oxindoles **195r-195w** in moderate yields (Table 4).

In order to further explore the scope of this methodology, reactions with other diazocarbonyl compounds were tested. The reaction of ethyl diazoacetate under the optimized conditions failed to deliver the product. The reaction with methyl phenyl

Table 5. Synthesis of 3-alkylated oxindole **195c**, reactivity of Ar^2 ring[a]

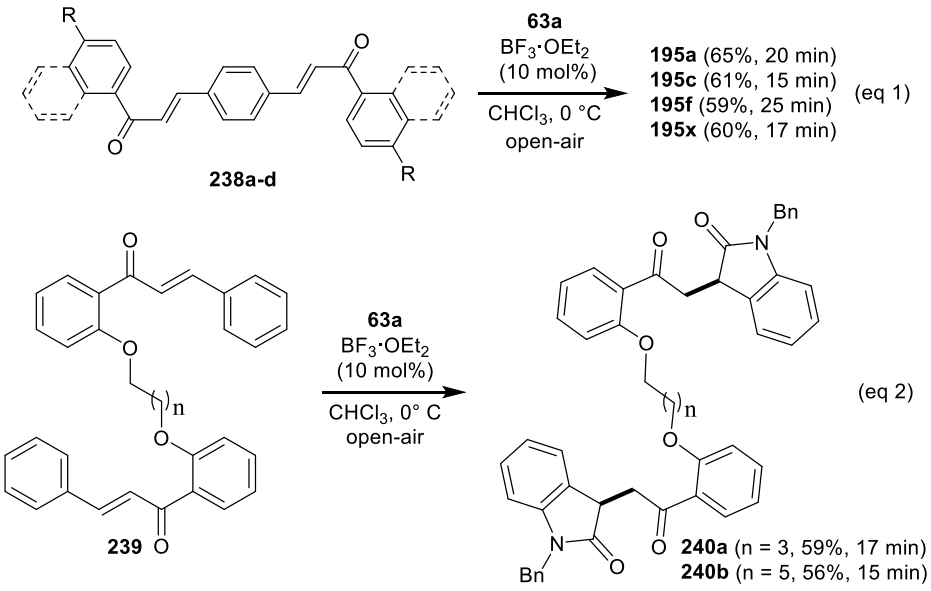


[a]Reaction conditions: equimolar amount of **63a** and **184**, $BF_3{\cdot}OEt_2$ (10 mol%), $CHCl_3$ (2 mL), 0 °C. [b]Isolated yield.

diazoacetate and 2-diazo-1-tetralone afforded the corresponding cyclopropane **195aa** and a complex mixture, respectively.

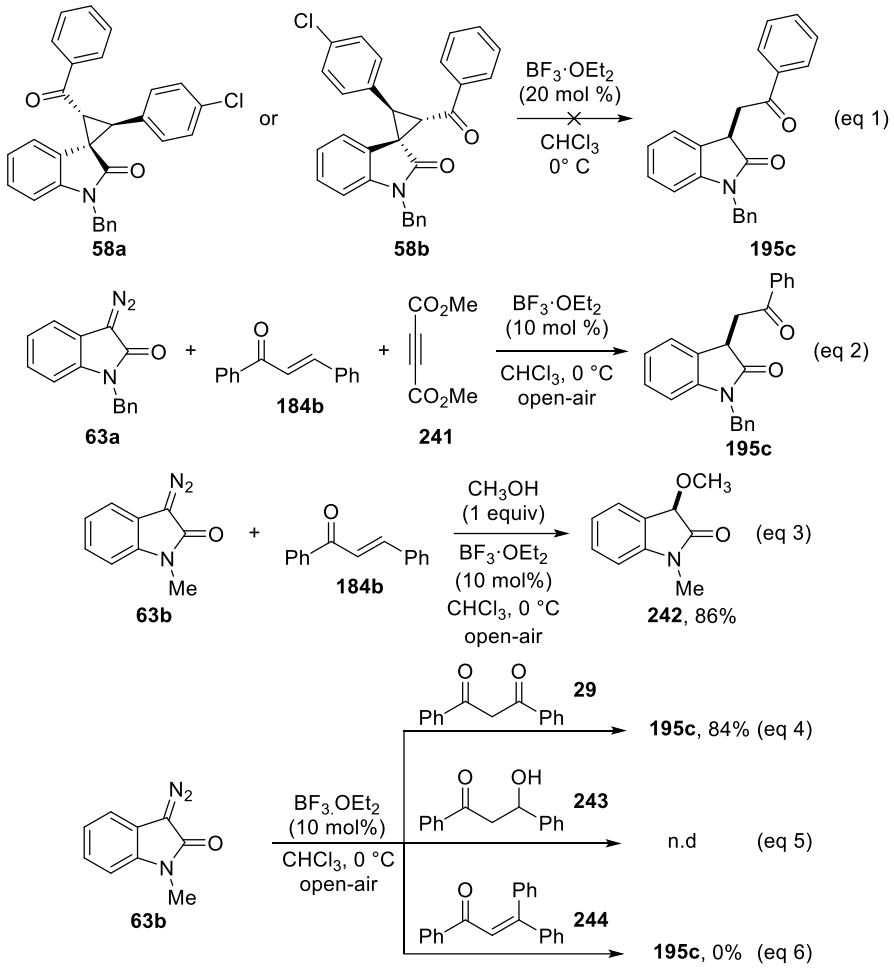
The efficiency of this methodology was further extended[141] to demonstrate the cleavage process of the two C=C double bonds by utilizing bis-chalcones **238**. Bis-chalcones (1 equiv) **238a-d** were allowed to react with diazoamide **63a** (2 equiv) under the optimized conditions and the reaction proceeded through the cleavage of two C=C double bonds furnishing products **195a**, **195c**, **195f** and **195x** in moderate yields (Scheme 86, eq 1). The scope of the process was extended for other bis-chalcones **239** in a similar manner. The reaction of bis-chalcones **239a,b** (1 equiv) with two equiv of diazoamide **63a** under the optimized conditions led to the formation of *bis*-3-alkylated oxindoles **240a,b** (Scheme 86, eq 2).

To gain crucial insight into the mechanism of this chemoselective C=C double bond cleavage of α,β-enones, a few control experiments were carried out to verify the reaction pathway. In line with the literature,[142] $BF_3{\cdot}OEt_2$ was found to activate the chalcone **184a** based on NMR titration experiments. Cyclopropane may be



Scheme 86. Effect of reactivity of *bis*-chalcones

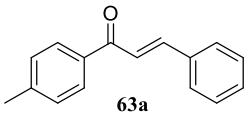
considered[122-125] as an intermediate for these reactions. Hence, spirocyclopropane **58a**[125] and its diastereomer **58b**[143] were synthesized based on the literature method. The reaction of spirocyclopropanes **58a** and **58b** in the presence of 20 mol% of $BF_3 \cdot OEt_2$ in chloroform at 0 °C to room temperature did not provide the desired product **195c** and the starting materials were recovered (Scheme 87, eq 1). Next, we investigated the multicomponent reaction of diazoamide **63b** with chalcone **184a** in the presence of dimethyl acetylenedicarboxylate (DMAD) under the optimized conditions and **195b** was obtained in 68% yield and the unreacted DMAD was recovered (96%, Scheme 87, eq 2). These results indicate that the reaction did not proceed *via* spirocyclopropane as an intermediate. Based on the literature,[112-117] C–H insertion may also be a possible intermediate for these reactions. Diazoamide **63a** was reacted with acetophenone instead of chalcone under the optimized conditions and product **195c** was not obtained, which indicates that acetophenone is not an intermediate in this transformation. The reaction was carried out in the presence of 1 equivalent of methanol to provide 3-methoxyindolin-2-one **242**[144] (86% of the isolated yield based on diazoamide **63b**) indicating that chalcone was not involved in the reaction (Scheme 87, eq 3). The reaction was carried out with 1,3-diphenylpropane-1,3-dione **29** instead of chalcone under the optimization conditions to provide the desired product **195c** in 84% yield (Scheme 87, eq 4). However, when the reaction was performed with 3-hydroxy-1,3-diphenylpropan-1-one **243** instead of chalcone under the optimization conditions, the desired product **195c** was not formed (Scheme 87, eq 5). The reaction with 3-phenyl substituted chalcone **244** instead of chalcone failed to deliver the desired product **195c**, with the starting material chalcone being recovered (Scheme 87, eq 6), indicating the possible hydroxylation at β-position on the chalcone.



Scheme 87. Control experiments

NMR-Titration and studies experiments

The ^{13}C NMR titration experiments were performed to investigate the interactions of chalcone **63a** and the results revealed the presence of binding with $BF_3{\cdot}OEt_2$ (Figure 11). Next, the ^{1}H-NMR experiments were performed at different time intervals to follow the reaction between diazoamide **63a** and chalcone **184a** in the presence of $BF_3{\cdot}OEt_2$ to afford product **195a** with the by-product of benzoic acid determined using D_2O exchange experiment as shown in Figure 12. In order to determine the presence of benzoic acid as a by-product during the formation of product **195a**, NMR experiments at different time interval were recorded between benzaldehyde and $BF_3{\cdot}OEt_2$ in $CDCl_3$ as shown in Figure 13. The disappearance of aldehyde at 10.20 ppm with the



63a

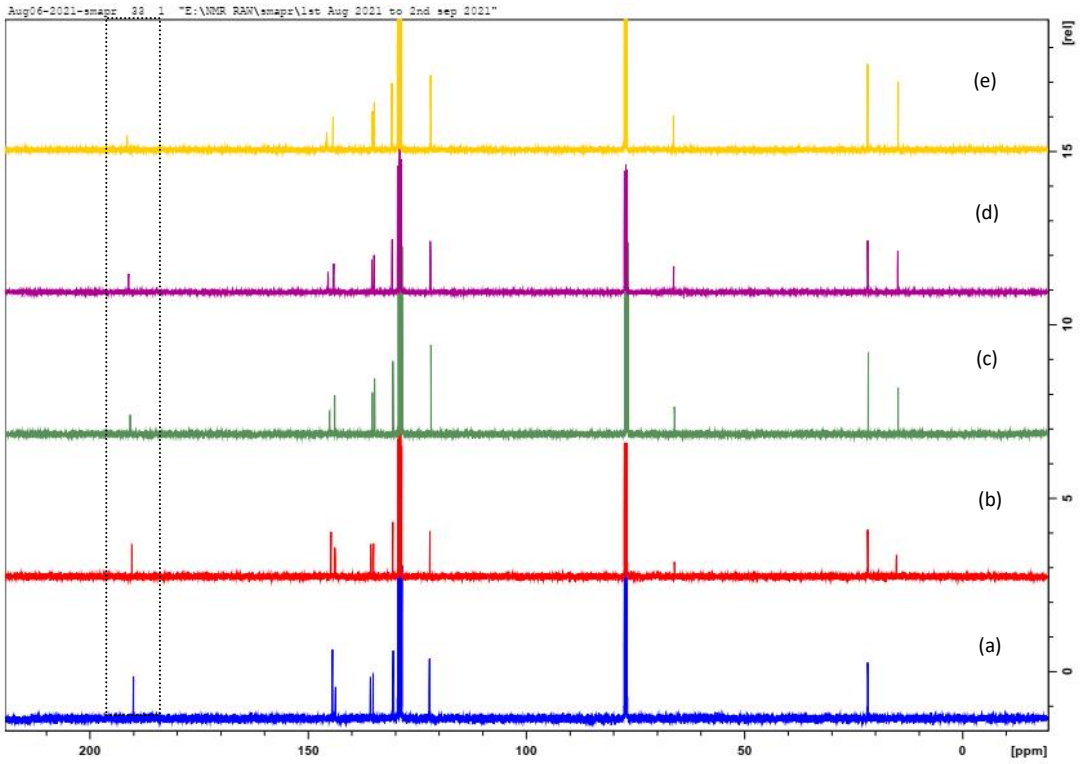


Figure 11. ^{13}C-NMR spectra of chalcone **63a** signals in $CDCl_3$

(a) Chalcone **63a** only.
(b) Chalcone **63a** (20 mg) with $BF_3{\cdot}OEt_2$ (4 µL)
(c) Chalcone **63a** (20 mg) with $BF_3{\cdot}OEt_2$ (6 µL)
(d) Chalcone **63a** (20 mg) with $BF_3{\cdot}OEt_2$ (8 µL)
(e) Chalcone **63a** (20 mg) with $BF_3{\cdot}OEt_2$ (10 µL)

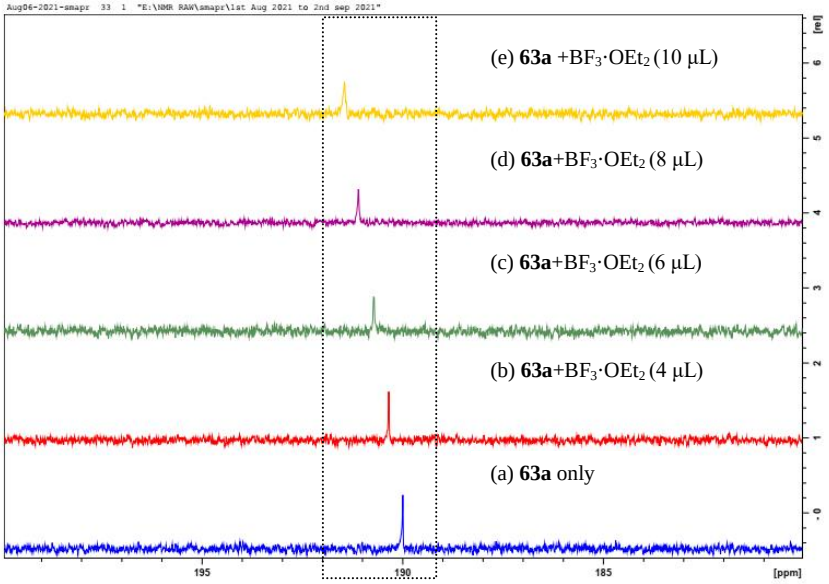


Figure 11a. Expansion and shift for carbonyl peak around 190 ppm

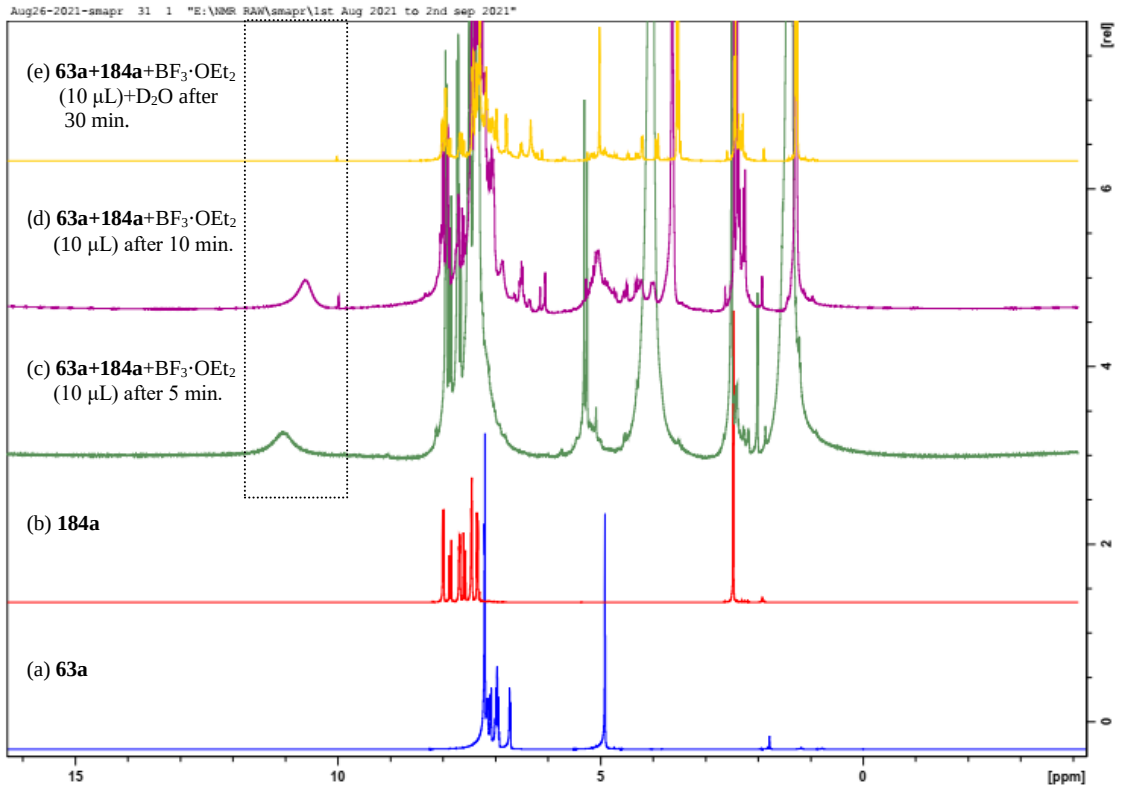


Figure 12. ^{1}H-NMR spectra of reaction mixture **195a** signals in $CDCl_3$

(a) Diazoamide **63a** (10 mg)
(b) Chalcone **184a** (10 mg)
(c) A mixture of diazoamide **63a** (10 mg), chalcone **184a** (10 mg), $BF_3{\cdot}OEt_2$ (10 µL) after 5 minutes
(d) A mixture of diazoamide **63a** (10 mg), chalcone **184a** (10 mg), $BF_3{\cdot}OEt_2$ (10 µL) after 10 minutes
(e) A mixture of diazoamide **63a** (10 mg), chalcone **184a** (10 mg), $BF_3{\cdot}OEt_2$ (10 µL) and 1 drop of D_2O after 30 minutes

appearance of benzoic acid as a broad singlet at 11.32 ppm was observed and confirmed with D_2O exchange experiments.

Product **195a** can be regarded to be formed from 3-alkylated oxindole *via* the formal C=C cleavage of a double bond in the presence of a Lewis acid as a catalyst. On the basis of the literature precedent, the control experiments and NMR studies, a plausible mechanism is shown in Scheme 88. The adduct of water and the boron reagent[142a] could potentially act as a reagent with chalcone **184** to generate boron-based enolate **A**. The nucleophilic attack of enolate **B** on the diazonium ion led to the formation of intermediate **C**. The retro-aldol reaction of **C** affords product **195** and aryl aldehyde

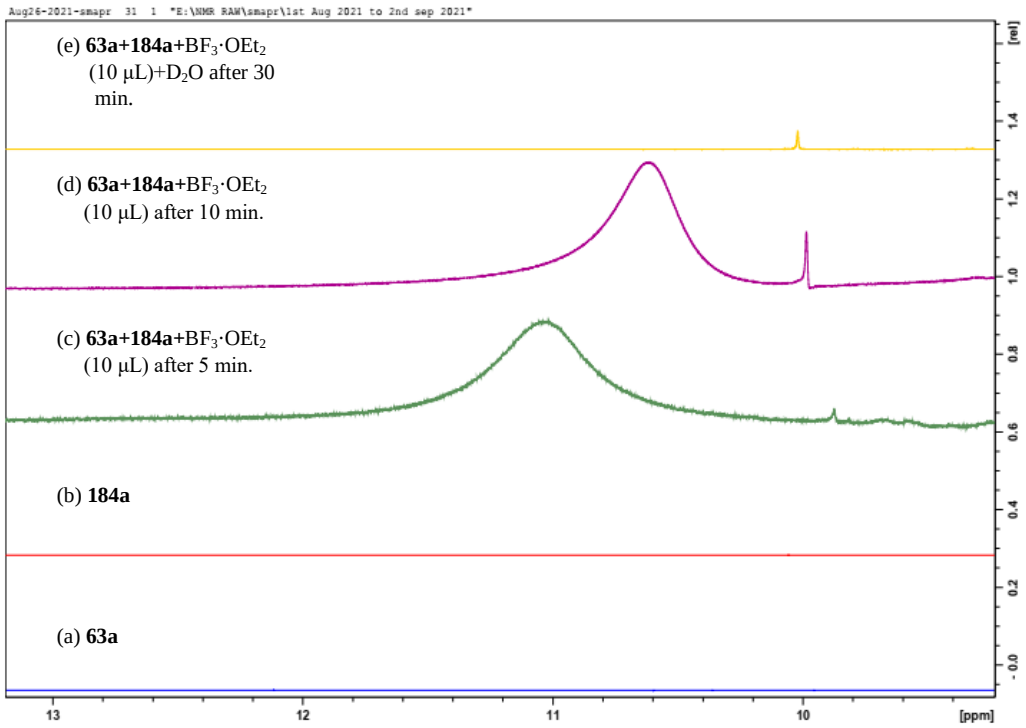


Figure 12a. Expansion for carboxylic acid peak

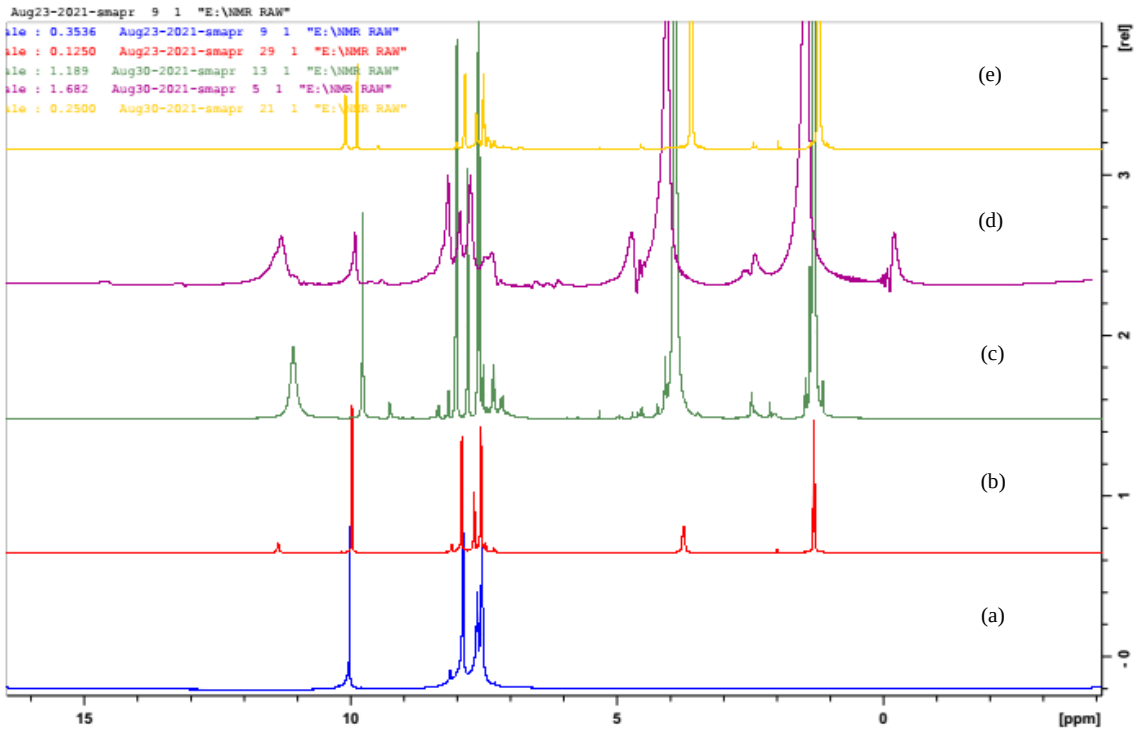
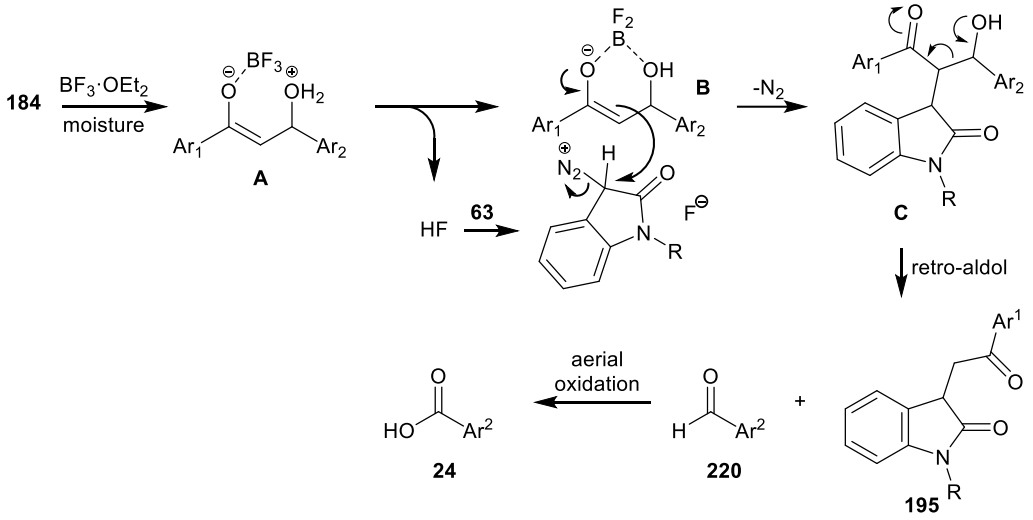


Figure 13. ^{1}H-NMR spectra of benzaldehyde signals in $CDCl_3$

(a) Benzaldehyde only.
(b) Benzaldehyde (20 mg) with BF_3·OEt_2 (5 µL) after 5 minutes.
(c) Benzaldehyde (20 mg) with BF_3·OEt_2 (5 µL) after 10 minutes.
(d) Benzaldehyde (20 mg) with BF_3·OEt_2 (5 µL) after 20 minutes.
(e) A mixture of benzaldehyde, BF_3·OEt_2 (5 µL) and 1 drop of D_2O after 30 minutes.

220. The aerial oxidation of aryl aldehyde **220** in the presence of $BF_3{\cdot}OEt_2$ provided the corresponding carboxylic acid **24** as shown by NMR studies.



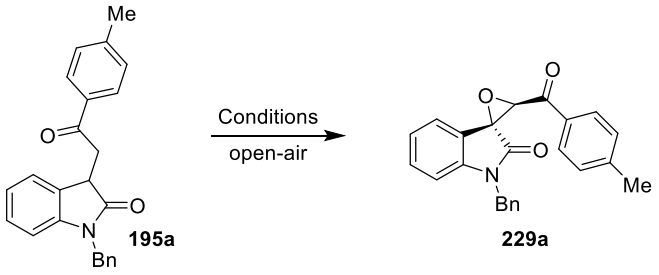
Scheme 88. Plausible mechanism for **195**

2.2.2. Synthesis of spiro-indolooxiranes

Further to develop the synthesis of spiro-indolooxiranes, the required 3-alkylated oxindole **195a** was synthesized from diazoamide. The reaction of 3-alkylated oxindole **195a** was initially studied with triethylamine (TEA) in the presence of various catalysts and solvents, the results were summarized in Table 6. Our initial investigation began with the epoxide formation of 3-alkylated oxindole **195a** dissolved in 4 mL of toluene at room temperature for 13h in the presence of 10 mol% of $NiBr_2$ and 1.0 equiv of trimethylamine, the desired spiro-indolooxirane **229a** was isolated in 35% yield (Table 6, entry 1). The ^{1}H-NMR spectrum of product **229a** exhibited three characteristic peaks such as two singlets at δ 5.01 and 5.02 ppm indicating the NCH_2/OCH protons of an oxindole ring system. A singlet at 2.40 ppm is indicated the CH_3 protons (Figure 14). ^{13}C-NMR spectral analyses of product **229a** showed peaks for a NCH_2 carbon at 44.5 ppm, CH_3 carbon at 21.9 ppm, quaternary carbon at 60.9 ppm, OCH carbon at 64.0 ppm, amide and keto-carbonyl groups appeared at δ 170.5 and 190.2 ppm, which clearly indicates the formation of product **229a** (Figure 15). Moreover, $FeCl_3$ didn't

improve the yield of product **229a** (Table 6, entry 2). In order to optimize the reaction conditions, various copper catalysts, such as $CuCl_2$, CuBr, or CuI, were examined; however, CuI enhanced the yield of product **229a** (Table 6, entry 5). Then, various bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), and 1,4-diazabicyclo[2.2.2]octane (DABCO) were utilized to optimize. Among the bases screened, DMAP was optimal to give spiro-indolooxirane **229a** in 68% yield (Table 6, entry 7). Successively, the screening of solvents (Table 6, entries 9–12) revealed that acetone was the best choice in terms of isolated yield of product **229a**. The above reaction was carried out at 50 °C to furnish product **229a** in 44% yield (Table 6, entry 13). The reaction was carried out under an argon atmosphere however, the desired product **229a** was not formed (Table 6, entry14). Thus, the optimized

Table 6. Optimization of reaction conditions of spiro-indolooxiranes **229a**.[a]



Entry	Catalyst	Base	Solvent	Temp. (°C)	Yield[b] %
1	$NiBr_2$	TEA	PhMe	rt	35
2	$FeCl_3$	TEA	PhMe	rt	22
3	$CuCl_2$	TEA	PhMe	rt	30
4	CuBr	TEA	PhMe	rt	46
5	CuI	TEA	PhMe	rt	61
6	CuI	DBU	PhMe	rt	20
7	CuI	DMAP	PhMe	rt	68
8	CuI	DABCO	PhMe	rt	nr[c]
9	CuI	DMAP	THF	rt	39
10	CuI	DMAP	DMF	rt	15
11	**CuI**	**DMAP**	**Acetone**	**rt**	**91**
12	CuI	DMAP	DCM	rt	nr[c]
13	CuI	DMAP	Acetone	50	44
14[d]	CuI	DMAP	Acetone	rt	nr[c]

[a]Reaction conditions: 10 mol% catalyst, **195a** (0.13 mmol, 1.0 equiv), base (0.13 mmol, 1.0 equiv), solvent (4.0 mL), at room temperature, for 15 h under an open-air atmosphere. [b]Isolated yield. [c]The reaction was conducted at 50 °C. [d]The reaction is carried out under an argon atmosphere.

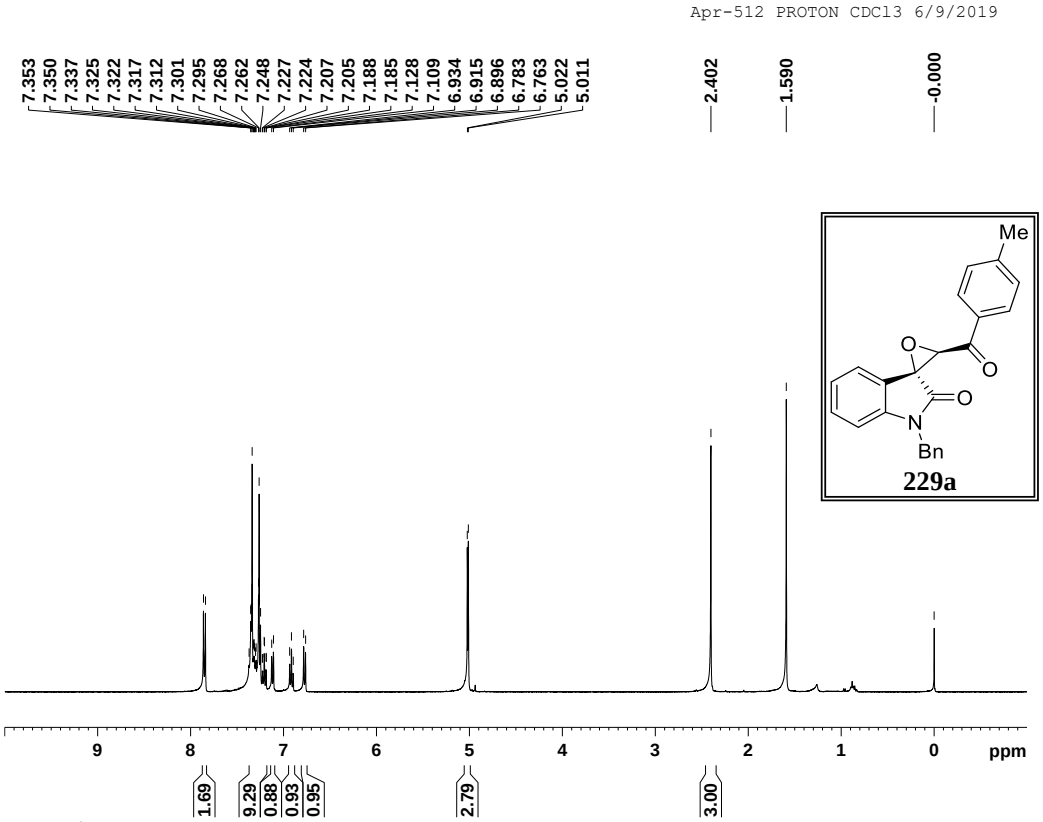


Figure 14. ^{1}H NMR (δ) spectrum of **229a**

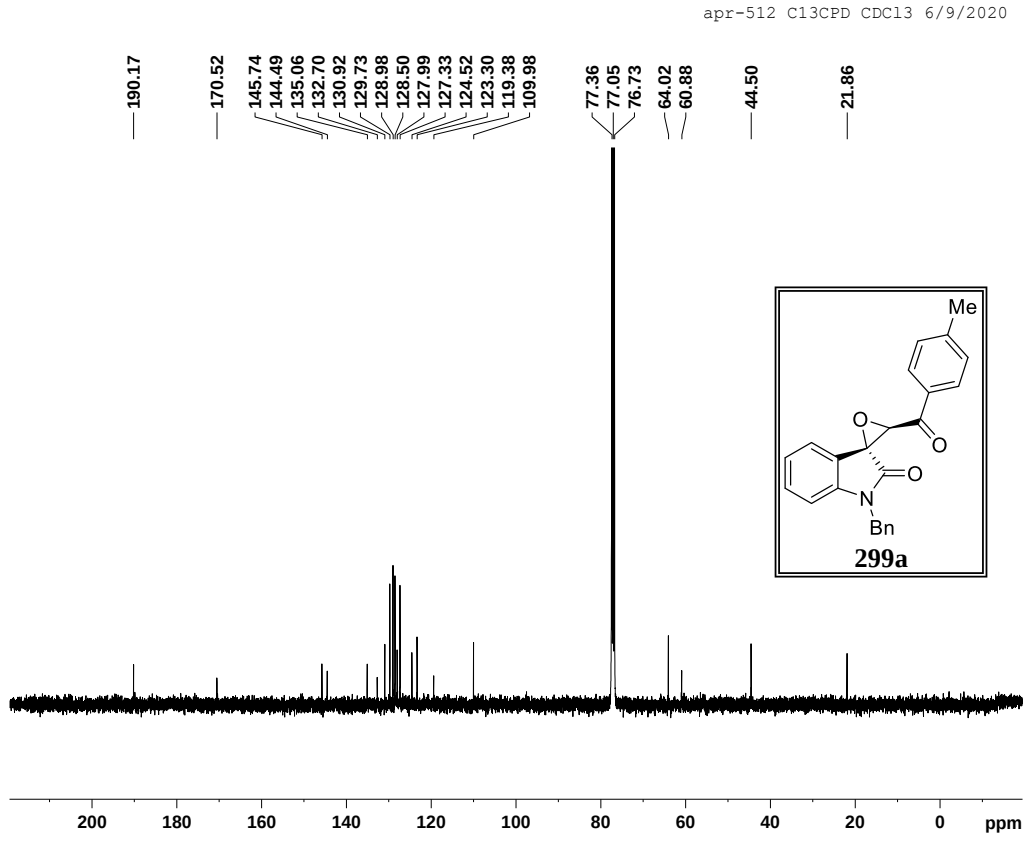
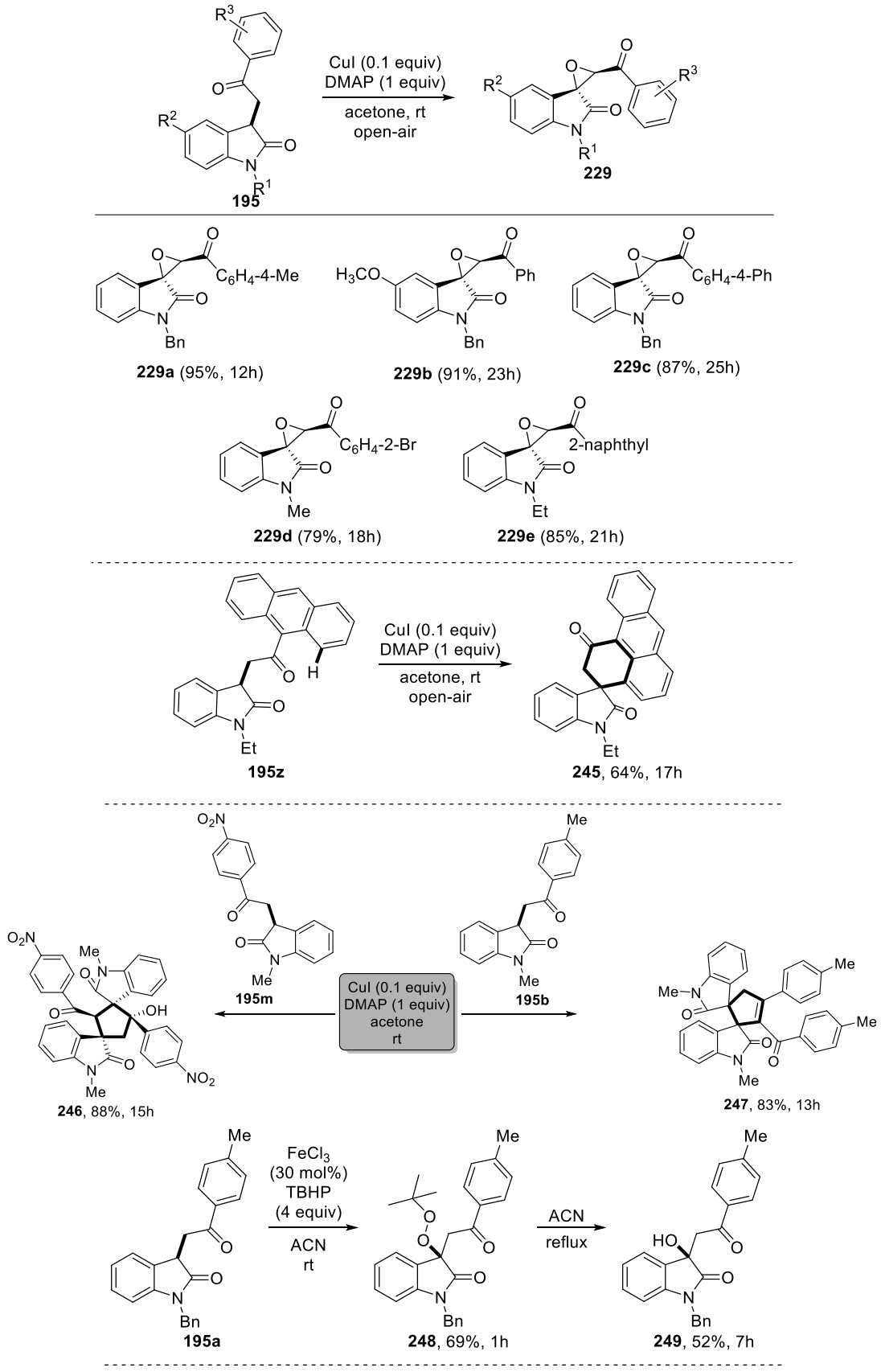


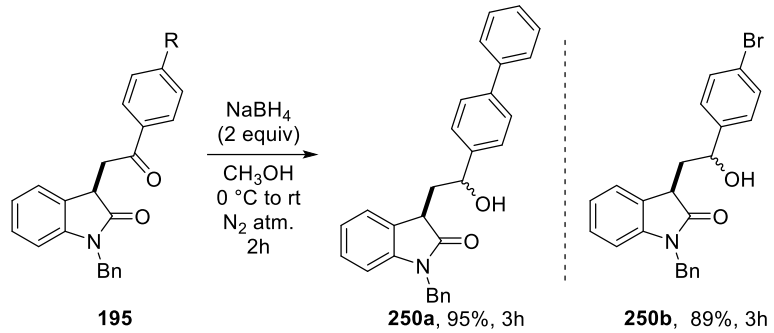
Figure 15. ^{13}C NMR (δ) spectrum of **229a**

reaction conditions for the formation of product **229a** were found to be 10 mol% of CuI and DMAP in acetone at room temperature as indicated in Table 6, entry 11. Based on the optimized conditions at hand, the scope of the 3-alkylated oxindoles **195** has been initiated in the presence of CuI/DMAP at room temperature under an open-air atmosphere to afford spiroindolooxiranes **229a-229e** in 79-95% yields. The stereochemistry of the product was tentatively assigned as a trans-isomer based on the literature.[131,132,134,135]

Interestingly, the formation of spiro[benzo[de]anthracene-3,3'-indoline]-1,2'(2*H*)-dione **245** was also observed from **195z**. Surprisingly 1,2 and 1,3-dispiro-indolopentanes **246** and **247** were observed under similar conditions when **195b** and **195m** (Scheme 89). The treatment of **395a** with *tert*-butyl hydroperoxide (TBHP) in the presence of $FeCl_3$ in acetonitrile was performed to afford **248**[145] incorporating the peroxide functionality. Subsequent heating of **248** in acetonitrile at 80 °C produced 3-hydroxy-3-alkylated oxindole **249**. 3,3-Disubstituted oxindoles[146] are important skeletal structures commonly found in both naturally occurring alkaloids and potent bioactive compounds. The functionalization of the ketone into alcohol using $NaBH_4$ was intended to produce racemic alcohols **250a** and **250b** in excellent yields.

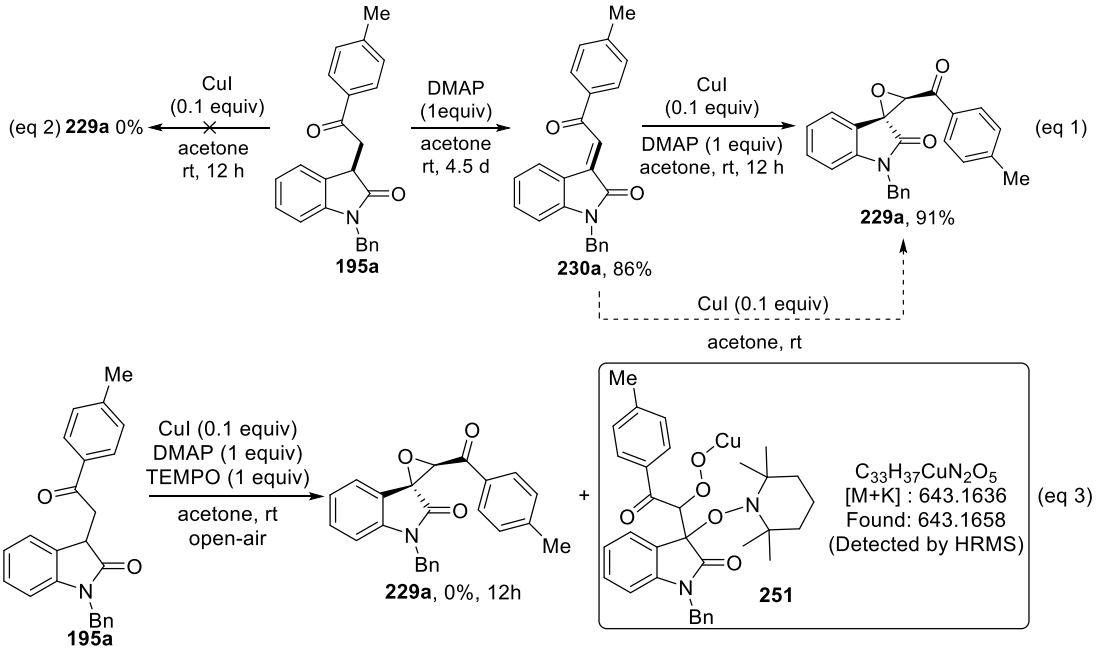
To understand the reaction mechanism of this epoxidation transformation, a few control experiments were performed. When the reaction was carried out with 3-alkylated oxindole **195a** at room temperature in the presence of DMAP, the formation of oxindole-derived α,β-unsaturated enamide **230a** was successfully isolated in 86% yield. The oxindole-derived α,β-unsaturated enamide **230a** was converted into spiro-indolooxirane **229a** (Scheme 90, (eq 1)). Similarly, the reaction with CuI didn't give the product, but the subsequent addition of 1 equiv of DMAP delivered the desired


CuI (0.1 equiv)
DMAP (1 equiv)
acetone, rt
open-air
195
229
229a (95%, 12h)
229b (91%, 23h)
229c (87%, 25h)
229d (79%, 18h)
229e (85%, 21h)
195z
245, 64%, 17h
195m
195b
CuI (0.1 equiv)
DMAP (1 equiv)
acetone
rt
246, 88%, 15h
247, 83%, 13h
FeCl3
(30 mol%)
TBHP
(4 equiv)
ACN
rt
ACN
reflux
195a
248, 69%, 1h
249, 52%, 7h



Scheme 89. Synthetic applicability of the current protocol

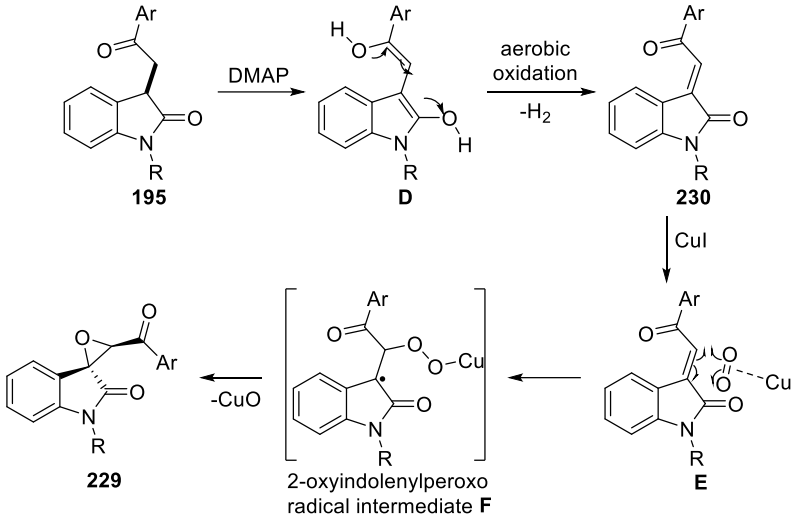
product **229a** (Scheme 90, eq 2). In order to study the mechanistic pathway for the reaction, we examined the reaction between 3-alkylated oxindole **195a** (1 equiv) and CuI (0.1 equiv) in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and did not afford the desired product **229a** (Scheme 90, (eq 3)). This suggests a radical pathway in this transformation.



Scheme 90. Control experiments for **229a**

A plausible mechanism for the formation of spiro-indolooxiranes **229** from 3-alkylated oxindoles **195** is depicted in Scheme 91. Under mild basic conditions, protons at the CH_{α} and CH_{β} position of **195** are amenable for oxidation to provide an intermediate **230**. Copper-bound dioxygen is able to activate superoxide to insert into the α,β-

unsaturated enamide **230** forming 2-oxyindolenylperoxo radical intermediate **F**, which triggers the O-O bond cleavage reaction leading to spiro-indolooxiranes **229**.



Scheme 91. Plausible reaction mechanism for **229**

General information

Using a capillary melting point apparatus, melting points were determined and not corrected. The solid compounds were crystallized using ethyl acetate and hexane as solvents. IR spectra were done using the ATR technique on a Bruker Alpha FT-IR spectrophotometer. All compounds were thoroughly characterized. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz using $CDCl_3$ as an internal standard in ppm (δ) and are reported as follows: chemical shift (ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet), ABq = AB quartet and coupling constants (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded in $CDCl_3$ at 100 MHz. Chemical shifts are reported in delta (δ)) units, parts per million (ppm) relative to the triplet center, which for $CDCl_3$ is 77.7 ppm. ^{13}C-NMR and DEPT experiments were used to determine carbon types. The residual solvent signals were used as references, and the chemical shifts were converted to the TMS scale ($CDCl_3$: H = 7.26 ppm, C = 77.7 ppm). On a Thermo Exactive Orbitrap mass spectrometer, high-resolution mass analyses were carried out using the electrospray ionization (ESI) technique. All solvents are commercial-grade (LR) and have not been distilled. Thin-layer chromatography was performed on silica or alumina plates, and components were observed under iodine/UV light at 254 nm. On silica gel, column chromatography was performed (100-200 mesh). All reactions were carried out in oven-dried glassware under nitrogen positive pressure with magnetic stirring. Acetophenone, aldehyde, and $BF_3{\cdot}OEt_2$ were purchased from M/s Aldrich or M/s Alfa Aesar and used according to the instructions.

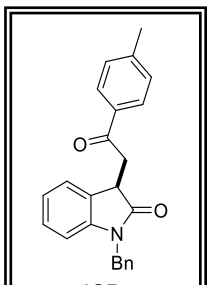
Caution: *In general, diazocarbonyl compounds should be considered toxic and potentially explosive. Even though no explosive properties of the diazocarbonyl compounds used in this study were discovered, it is strongly advised that they be handled with extreme caution in a well-ventilated fume hood.*

Experimental Section

General experimental procedure for the synthesis of alkylated oxindoles 195

To a solution of diazoamide **63** (1.0 equiv) and chalcone **184** (1.0 equiv) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere and monitored by TLC until the disappearance of the diazoamide. After the appropriate period, the reaction mixture was diluted with $CHCl_3$ (10 mL) and water (15 mL). The organic phase was separated and the aqueous layer was washed with $CHCl_3$ (10 mL). The concentration of the combined organic layers under reduced pressure afforded the crude product, which was purified by column chromatography using silica gel to afford the corresponding product **195**.

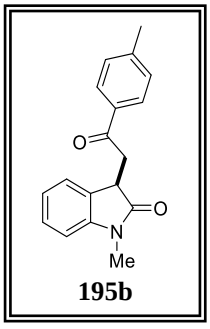
Synthesis of 1-benzyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195a): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*)-1-(4-methylphenyl)-3-phenylprop-2-en-1-one (**184a**, 90 mg, 0.40 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195a** (103 mg, 73%) as a colourless crystalline solid according to general procedure. R_f = 0.39 (EtOAc/hexane = 1:4, v/v); mp 146-147 °C; IR (neat): ν_{max} 2922, 1708, 1684, 1607, 1462, 1354, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.40 (s, 3H, CH_3), 3.44 (dd, J_1 = 18 Hz, J_2 = 9 Hz, 1H, CH), 3.86 (dd, J_1 = 18.1 Hz, J_2 = 2.9 Hz, 1H, CH), 4.16 (dd, J_1 = 8.8 Hz, J_2 =



195a

2.3 Hz,1H, CH), 4.97 (s, 2H, CH_2), 6.73 (d, *J* = 7.6 Hz, 1H, ArH), 6.92-6.96 (m, 1H, ArH), 7.12-7.15 (m, 1H, ArH), 7.23-7.37 (m, 8H, ArH), 7.89 (d, *J* = 8 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.7, 40.0, 41.3, 44.0, 109.1, 122.5, 124.5, 127.4, 127.6, 128.0, 128.3, 128.8, 129.2, 129.4, 134.0, 135.0, 143,5, 144.4, 177.9, 196.5 ppm; HRMS (ESI) Calculated for $C_{24}H_{21}NO_2$ $(M+H)^+$: 356.1651 found: 356.1644.

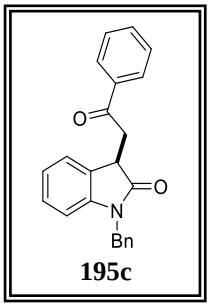
Synthesis of 1-methyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195b): To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and (2*E*)-1-(4-methylphenyl)-3-phenylprop-2-en-1-one (**184a**, 128, 0.58 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195b** (110 mg, 68%) as a colourless crystalline solid according to general procedure. R_f = 0.25 (EtOAc/hexane = 1:4, v/v); mp 198-199 °C; IR (neat): ν_{max} 2923, 1704, 1606, 1467, 1345, 1263, 1090, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.40 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.36 (dd, J_1 = 18 Hz, J_2 = 9.2 Hz, 1H, CH), 3.80 (dd, J_1 = 18 Hz, J_2 = 2.8 Hz, 1H, CH), 4.07 (d, *J* = 9.2 Hz, 1H, CH), 6.85 (d, *J* = 7.6 Hz, 1H, ArH), 6.98 (t, *J* = 7.6 Hz, 1H, ArH), 7.25-7.29 (m,4H, ArH), 7.87 (d, J = 8 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.7, 26.4, 40.0, 41.2, 108.0, 122.5, 124.5, 128.1, 128.3, 129.2, 129.4, 133.9, 144.3, 144.4, 177.9, 196.6 ppm; HRMS (ESI) Calculated for $C_{18}H_{17}NO_2$ $(M+H)^+$: 280.1338 found: 280.1333.



195b

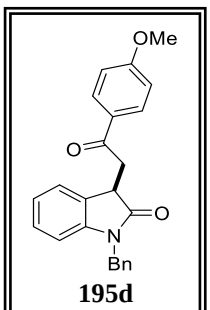
Synthesis of 1-benzyl-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-indol-2-one (195c)[147]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*)-1,3-diphenylprop-2-en-1-one (**184b**, 83 mg, 40 mmol) in $CHCl_3$

(5 mL) was added 10 mol% of $BF_3 \cdot OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195c** (99 mg, 73%) as a colourless crystalline solid according to general procedure. R_f = 0.34 (EtOAc/hexane = 1:4, v/v); mp 162-163 °C; IR (neat): ν_{max} 3057, 2914, 1702, 1605, 1356, 1216, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.47 (dd, J_1 = 27.2 Hz, J_2 = 9.0 Hz, 1H, CH), 3.89 (dd, J_1 = 18.4 Hz, J_2 = 3.2 Hz, 1H, CH), 4.17 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H, CH), 4.97 (s, 2H, CH_2), 6.74 (d, J = 7.6 Hz, 1H, ArH), 6.95 (t, J = 7.6 Hz, 1H, ArH), 7.14 (t, J = 7.6 Hz, 1H, ArH), 7.25-7.38 (m, 6H, ArH) 7.45-7.49 (m, 2H, ArH), 7.56-7.59 (m, 1H, ArH), 7.98-8.01 (m, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 40.1, 41.3, 44.0, 109.1, 122.6, 124.4, 127.4, 127.7, 128.1, 128.2, 128.8, 128.9, 129.1, 133.5, 136.0, 136.4, 143.5, 177.9, 196.9 ppm; HRMS (ESI) Calculated for $C_{23}H_{19}NO_2$ $(M+H)^+$: 342.1494 found: 342.1485.



195c

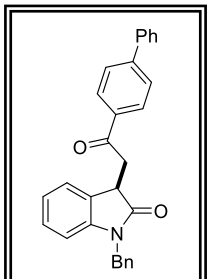
Synthesis of 1-benzyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195d)[148]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (**184c**, 95 mg, 0.40 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3 \cdot OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195d** (105 mg, 71%) as a colourless crystalline solid according to general procedure. R_f = 0.18 (EtOAc/hexane = 1:4, v/v); mp 166-167 °C; IR (neat): ν_{max} 2924, 1705, 1674, 1595, 1359, 1165 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.42 (dd, J_1 = 18.0 Hz, J_2 = 9.0 Hz, 1H, CH), 3.82 (d, J = 2.8 Hz, 1H, CH), 3.87 (s, 3H, CH_3), 4.17 (d, J = 7.6 Hz, 1H, CH), 4.97 (s, 2H, CH_2), 6.73 (d, J = 7.6 Hz, 1H, ArH), 6.93-6.97 (m, 3H, ArH), 7.14 (t,



195d

J = 7.6 Hz, 1H, ArH), 7.24-7.37 (m, 6H, ArH), 7.98 (d, J = 8.8 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 39.7, 41.4, 44.0, 55.5, 109.0, 113.9, 122.5, 124.5, 127.4, 127.6, 128.0, 129.3, 129.5, 130.5, 136.0, 143.4, 163.8, 178.0, 195.3 ppm; HRMS (ESI) Calculated for $C_{24}H_{21}NO_3$ $(M+H)^+$: 372.1600 found: 372.1594.

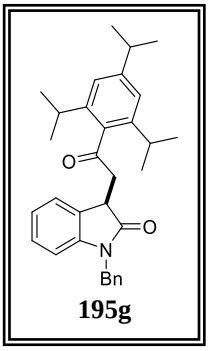
Synthesis of 3-[2-([1,1'-biphenyl]-4-yl)-2-oxoethyl]-1-benzyl-1,3-dihydro-2*H*-indol-2-one (195f)[149]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (*2E)*-1-([1,1'-biphenyl]-4-yl)-3-phenylprop-2-en-1-one (**184d**, 114 mg, 0.40 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195f** (105 mg, 63%) as a colourless crystalline solid according to general procedure. R_f = 0.30 (EtOAc/hexane = 1:4, v/v); mp 161-162 °C; IR (neat): ν_{max} 2921, 1707, 1605, 1481, 1353, 1273, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.43 (dd, J_1 = 18.1 Hz, J_2 = 9.0 Hz, 1H, CH), 3.85 (dd, J_1 = 18.1 Hz, J_2 = 3.0 Hz, 1H, CH), 4.12 (dd, J_1 = 8.8 Hz, J_2 = 2.5 Hz, 1H, CH), 4.91 (s, 2H, CH_2), 6.67 (d, *J* = 7.6 Hz, 1H, ArH), 6.89 (t, *J* = 7.6 Hz, 1H, ArH), 7.08 (t, *J* = 7.6 Hz, 1H, ArH), 7.17-7.41 (m, 9H, ArH), 7.54-7.63 (m, 4H), 8.00 (d, J = 8.4 Hz, 2H, ArH)) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 40.1, 41.3, 44.0, 109.1, 122.6, 124.5, 127.3, 127.7, 128.1, 128.4, 128.8, 129.0, 129.1, 135.1, 135.9, 139.8, 143.5, 146.2, 177.9, 196.5 ppm; HRMS (ESI) Calculated for $C_{29}H_{23}NO_2$ $(M+Na)^+$: 440.1626 found: 440.1621.



195f

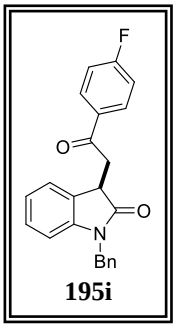
Synthesis of 1-benzyl-3-[2-oxo-2-(2,4,6-trimethylphenyl)ethyl]-1,3-dihydro-2*H*-indol-2-one (195g): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*)-3-phenyl-1-(2,4,6-triisopropylphenyl)prop-2-en-1-one (**184e**, 134 mg, 0.40 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$.

The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195g** (106 mg, 57%) as a colourless amorphous solid according to general procedure. R_f = 0.51 (EtOAc/hexane = 1.5:3.5, v/v); mp 116-117 °C; IR (neat): ν_{max} 2961, 1706, 1610, 1461, 1354, 1211, 1008, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.06-1.16 (m, 18H, CH_3), 2.56-2.65 (m, 2H, CH_2), 2.76-2.83 (m, 1H, CH), 3.14 (dd, J_1 = 19.0 Hz, J_2 = 8.2 Hz, 1H, CH), 3.50 (dd, J_1 = 18.6 Hz, J_2 = 3.0 Hz, 1H, CH), 3.97-3.99 (m, 1H, CH), 4.87 (ABq, $\Delta\delta_{AB}$ = 0.08, J = 15.7 Hz, 2H, CH_2), 6.66 (d, J = 7.6 Hz, 1H,ArH), 6.91-6.94 (m, 3H, ArH), 7.06-7.28 (m, 7H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 24.0, 30.8, 34.4, 41.1, 44.0, 47.3, 109.2, 121.2, 122.3, 124.1. 127.4, 127.6, 128.1, 128.8, 136.0, 136.5, 143.7, 143.9, 149.9, 177.5, 207.5 ppm; HRMS (ESI) Calculated for $C_{32}H_{37}NO_2$ $(M+H)^+$: 468.2903 found: 468.2897.



195g

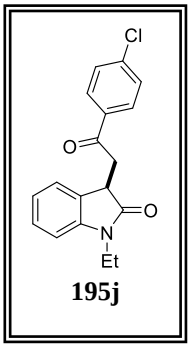
Synthesis of 1-benzyl-3-[2-(4-fluorophenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195i): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (**184f**, 90 mg, 0.40 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to furnish product **195i** (90 mg, 63%) as a colourless crystalline solid according to general procedure. R_f = 0.24 (EtOAc/hexane = 1:4, v/v); mp 127-128 °C; IR (neat): ν_{max} 2918, 1699, 1601, 1354, 1221, 1160, 841, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.45 (dd, J_1 = 18.2 Hz, J_2 = 8.8 Hz, 1H, CH), 3.86 (dd, J_1 = 18.2 Hz, J_2 = 3.1 Hz, 1H, CH), 4.16 (dd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, 1H, CH), 4.98 (s, 2H, CH_2), 6.75 (d, J = 7.6 Hz, 1H, ArH), 6.96 (t, J = 7.6 Hz, 1H, ArH), 7.13-7.18 (m, 3H, ArH), 7.23-7.37 (m, 6H, ArH), 8.01-8.05 (m, 2H, ArH) ppm;



195i

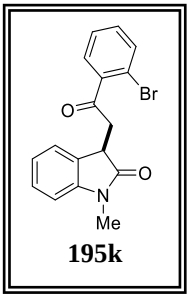
^{13}C NMR ($CDCl_3$, 100 MHz) δ = 40.0, 41.3, 44.0, 109.1, 115.9 (d, J = 22 Hz), 122.6, 124.4, 127.4, 127.8, 128.1, 128.8, 129.0, 130.9 (d, J = 10 Hz), 132.8 (d, J = 2 Hz), 135.9, 143.5, 166 (d, J = 254 Hz), 177.7, 195.3 ppm; HRMS (ESI) Calculated for $C_{23}H_{18}FNO_2$ $(M+H)^+$: 360.1400 found: 360.1390.

Synthesis of 3-[2-(4-chlorophenyl)-2-oxoethyl]-1-ethyl-1,3-dihydro-2*H*-indol-2-one (195j): To a solution of 3-diazo-1-ethyl-1,3-dihydro-2*H*-indol-2-one (**63c**, 100 mg, 0.53 mmol) and (2*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (**184g**, 130 mg, 0.53 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195j** (109 mg, 65%) as a colourless amorphous solid according to general procedure. R_f = 0.32 (EtOAc/hexane = 1:4, v/v); mp 151-152 °C; IR (neat): ν_{max} 2920, 1705, 1609, 1487, 1356, 1219, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.31 (t, J = 7.6 Hz, 3H, CH_3), 3.36 (dd, J_1 = 18.4 Hz, J_2 = 9.2 Hz, 1H, CH), 3.76-3.85 (m, 3H, CH_2/CH), 4.04 (dd, J_1 = 9 Hz, J_2 = 2.9 Hz, 1H, CH), 6.88 (d, J = 7.6 Hz, 1H, ArH), 6.96-7.00 (m, 1H, ArH), 7.23-7.29 (m, 2H, ArH), 7.43-7.45 (m, 2H, ArH), 7.91 (d, J = 8.8 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.7, 34.9, 40.0, 41.2, 108.2, 122.3, 124.5, 128.1, 129.0, 129.2, 129.6, 134.7, 139.9, 143.4, 177.1, 195.8 ppm; HRMS (ESI) Calculated for $C_{18}H_{16}{}^{35}ClNO_2$ $(M+H)^+$: 314.0948 found: 314.0931.



195j

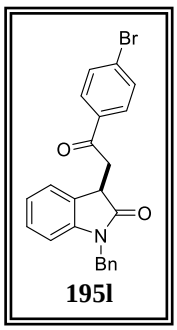
Synthesis of 3-[2-(2-bromophenyl)-2-oxoethyl]-1-methyl-1,3-dihydro-2*H*-indol-2-one (195k): To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and (2*E*)-1-(2-bromophenyl)-3-phenylprop-2-en-1-one (**184h**, 115 mg, 0.58 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture



195k

was stirred at 0 °C under an open-air atmosphere to afford product **195k** (120 mg, 60%) as a colourless crystalline solid according to general procedure. R_f = 0.40 (EtOAc/hexane = 1:4, v/v); mp 184-185 °C; IR (neat): ν_{max} 3056, 2922, 1693, 1609, 1353, 1215, 1104, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.30 (s, 3H, CH_3), 3.50 (dd, J_1 = 18.4 Hz, J_2 = 8.8 Hz, 1H, CH), 3.91 (dd, J_1 = 18.4 Hz, J_2 = 3.2 Hz, 1H, CH), 4.10 (dd, J_1 = 18.4 Hz, J_2 = 3.2 Hz, 1H, CH), 6.90-7.05 (m, 2H, ArH), 7.26-7.34 (m, 2H, ArH), 7.73 (t, J = 8 Hz, 1H, ArH), 8.32-8.47 (m, 2H, ArH), 8.81-8.82 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.5, 40.2, 41.0, 108.3, 122.6, 123.1, 124.2, 127.7, 128.4, 128.6, 130.1, 133.7, 137.5, 144.4, 148.5, 177.3, 195.09 ppm; HRMS (ESI) Calculated for $C_{17}H_{14}{}^{79}BrNO_2$ $(M+H)^+$: 344.0286 found: 344.0282.

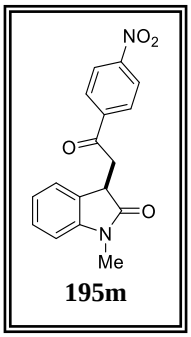
Synthesis of 1-benzyl-3-[2-(4-bromophenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195l)[148]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (**184i**, 115 mg, 0.40 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195l** (106 mg, 63%) as a colourless crystalline solid according to general procedure. R_f = 0.46 (EtOAc/hexane = 1:4, v/v); mp 132-133 °C; IR (neat): ν_{max} 2922, 1693, 1609, 1353, 1215, 1104, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.44 (dd, J_1 = 18 Hz, J_2 = 8.8 Hz, 1H, CH), 3.85 (dd, J_1 = 18 Hz, J_2 = 3 Hz, 1H, CH), 4.15 (dd, J_1 = 8.4 Hz, J_2 = 2,4 Hz, 1H, CH), 4.97 (s, 2H, CH_2), 6.75 (d, J = 7.6 Hz, 1H, ArH), 6.96 (t, J = 7.6 Hz, 1H, ArH), 7.14-7.37 (m, 7H, ArH), 7.62 (d, J = 8.4 Hz, 2H, ArH), 7.86 (d, J = 8.8 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 40.0, 41.2, 44.0, 109.2, 122.6, 124.3, 127.4, 127.7, 128.1,



195l

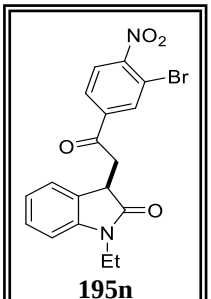
128.78, 128.84, 129.7, 132.1, 135.0, 135.9, 143.5, 177.7, 195.9 ppm; HRMS (ESI) Calculated for $C_{23}H_{18}{}^{79}BrNO_2$ $(M-H)^+$: 418.0448 found: 418.0451.

Synthesis of 1-methyl-3-[2-(4-nitrophenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195m): To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and (2*E*)-1-(4-nitrophenyl)-3-phenylprop-2-en-1-one (**184j**, 101 mg, 0.58 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195m** (91 mg, 51%) as a colourless crystalline solid according to general procedure. R_f = 0.18 (EtOAc/hexane = 1.5:3.5, v/v); mp 131-132 °C; IR (neat): ν_{max} 2928, 1696, 1610, 1468, 1347, 1215, 1091, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.13 (s, 3H, CH_3), 3.24 (dd, J_1 = 18.4 Hz, J_2 = 8.8 Hz, 1H, CH), 3.62 (dd, J_1 = 18.4 Hz, J_2 = 3.6 Hz, 1H, CH), 3.97 (dd, J_1 = 8.7 Hz, J_2 = 3.4 Hz, 1H, CH), 6.91-6.95 (m, 1H, ArH), 7.17-7.35 (m, 5H, ArH), 7.48-7.50 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.5, 41.4, 43.7, 108.2, 118.4, 122.6, 124.5, 127.6, 128.3, 128.6, 128.9, 132.0, 133.9, 140.6, 144.3, 177.2, 200.9 ppm; HRMS (ESI) Calculated for $C_{17}H_{14}N_2O_4$ $(M+H)^+$: 311.1032 found: 311.1043.



195m

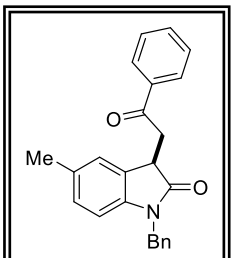
Synthesis of 3-[2-(3-bromo-4-nitrophenyl)-2-oxoethyl]-1-ethyl-1,3-dihydro-2*H*-indol-2-one (195n): To a solution of 3-diazo-1-ethyl-1,3-dihydro-2*H*-indol-2-one (**63c**, 100 mg, 0.53 mmol) and (2*E*)-1-(3-bromo-4-nitrophenyl)-3-phenylprop-2-en-1-one (**184k**, 176 mg, 0.53 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195n** (71 mg, 33%) as a colourless crystalline solid according to general procedure. R_f = 0.15 (EtOAc/hexane = 1.5:3.5, v/v); mp 201-202 °C; IR (neat): ν_{max} 2929,



195n

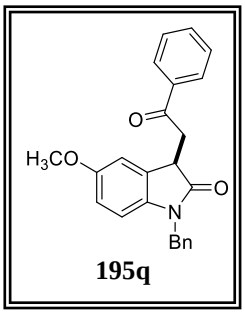
1695, 1604, 1535, 1353, 1217, 1029,738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.32 (t, J = 7.2 Hz, 3H, CH_3), 3.41 (dd, J_1 = 18.4 Hz, J_2 = 8.4 Hz, 1H, CH), 3.78-3.85 (m, 3H, CH_2/CH), 4.03 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H, CH), 6.90 (d, J = 7.6 Hz, 1H, ArH), 7.00 (t, J = 7.6 Hz, 1H, ArH), 7.21-7.31 (m, 2H, ArH), 7.88 (d, J = 7.9 Hz, 1H, ArH), 7.98-8.01 (m, 1H, ArH), 8.4 (d, J = 1.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.6, 35.0, 40.1, 41.0, 108.4, 120.2, 122.5, 124.3, 125.1, 128.4, 128.6, 131.9, 135.8, 136.2, 143.5, 150.1, 176.7, 194.1 ppm; HRMS (ESI) Calculated for $C_{18}H_{15}{}^{79}BrN_2O_4$ $(M+H)^+$: 403.0293 found: 403.0285.

Synthesis of 1-benzyl-5-methyl-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-indol-2-one (195p)[147]: To a solution of 1-benzyl-3-diazo-5-methyl-1,3-dihydro-2*H*-indol-2-one (**63d**, 100 mg, 0.38 mmol) and (2*E*)-1,3-diphenylprop-2-en-1-one (**184b**, 176 mg, 0.38 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to obtain product **195p** (100 mg, 74%) as a colourless crystalline solid according to general procedure. R_f = 0.39 (EtOAc/hexane = 1:4, v/v); mp 161-162 °C; IR (neat): ν_{max} 2913, 1698, 1599, 1493, 1445, 1353, 1185, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.29 (s, 3H, CH_3), 3.53 (dd, J_1 = 18.2 Hz, J_2 = 9 Hz, 1H, CH), 3.95 (dd, J_1 = 18.2 Hz, J_2 = 3.0 Hz, 1H, CH), 4.20-4.22 (m, 1H, CH), 5.02 (s, 2H, CH_2), 6.68 (d, J = 8 Hz, 1H, ArH), 7.00 (d, J = 8 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 7.30-7.65 (m, 8H, ArH), 8.07 (d J = 8 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.1, 40.2, 41.3, 44.0, 108.9, 125.28, 125.33, 127.4, 127.6, 128.3, 128.76, 128.82, 129.2, 132.2, 133.5, 136.0, 136.4, 141.0, 177.8, 197.0 ppm; HRMS (ESI) Calculated for $C_{24}H_{21}NO_2$ $(M+H)^+$: 356.1651 found: 356.1646.



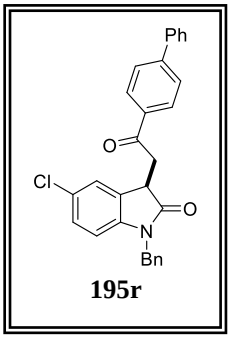
195p

Synthesis of 1-benzyl-5-methoxy-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-indol-2-one (195q): To a solution of 1-benzyl-3-diazo-5-methoxy-1,3-dihydro-2*H*-indol-2-one (**63e**, 100 mg, 0.36 mmol) and (2*E*)-1,3-diphenylprop-2-en-1-one (**184b**, 75 mg, 0.36 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to yield product **195q** (96 mg, 72%) as a colourless crystalline solid according to general procedure. R_f = 0.18 (EtOAc/hexane = 1:4, v/v); mp 173-174 °C; IR (neat): ν_{max} 2923, 1701, 1599, 1445, 1363, 1187, 1147, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.52 (dd, J_1 = 18.2 Hz, J_2 = 9.0 Hz,1H, CH), 3.74 (s, 3H, CH_3), 3.94 (dd, J_1 = 18.2 Hz, J_2 = 2.8 Hz, 1H, CH), 4.19-4.21 (m, 1H, CH), 5.00 (s, 2H, CH_2), 6.66-6.73 (m, 2H, ArH), 6.95 (s, 1H, ArH), 7.30-7.40 (m, 5H, ArH), 7.52 (t, J = 7.6 Hz, 2H, ArH), 7.61-7.65 (m, 1H, ArH), 8.05 (d, J = 7.2 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 40.2, 41.7, 44.1, 55.8, 109.4, 112.0, 112.3, 127.3, 127.6, 128.2, 128.75, 128.82, 130.5, 133.5, 136.0, 136.3, 136.9, 155.9, 177.5, 196.9 ppm; HRMS (ESI) Calculated for $C_{24}H_{21}NO_3$ $(M+H)^+$: 372.1600 found: 372.1623.



195q

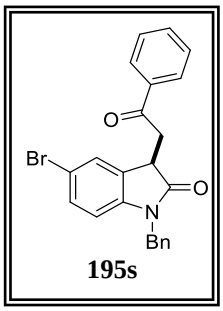
Synthesis of 3-[2-([1,1'-biphenyl]-4-yl)-2-oxoethyl]-5-chloro-1-benzyl-1,3-dihydro-2*H*-indol-2-one (195r): To a solution of 1-benzyl-5-chloro-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63f**, 100 mg, 0.35 mmol) and (2*E*)-1-([1,1'-biphenyl]-4-yl)-3-phenylprop-2-en-1-one (**184d**, 100 mg, 0.35 mmol) in $CHCl_3$ (10 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to furnish product **195r** (108 mg, 68%) as a colourless crystalline solid according to general procedure. R_f = 0.26 (EtOAc/hexane = 1.5:.3.5, v/v); mp 178-179



195r

°C; IR (neat): ν_{max} 2919, 1707, 1681, 1601, 1483, 1352, 1263, 805 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.49-3.57 (m, 1H, CH), 3.94 (dd, J_1 = 18.4 Hz, J_2 = 2.8 Hz, 1H, CH), 4.15 (d, J = 5.6 Hz, 1H, CH), 4.97 (s, 2H, CH_2), 6.33-6.65 (m, 1H, ArH), 7.12 (d, J = 6.8 Hz, 1H, ArH), 7.25-7.49 (m, 9H, ArH), 7.62-7.71 (m, 4H, ArH), 8.05-8.08 (m, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 39.9, 41.2, 44.1, 110.0, 124.9, 127.30, 127.33, 127.4, 127.8, 127.95, 128.01, 128.4, 128.8, 128.9, 129.0, 130.8, 134.8, 135.5, 139.8, 142.1, 146.4, 177.3, 196.1 ppm; HRMS (ESI) Calculated for $C_{29}H_{22}{}^{35}ClNO_2$ $(M+Na)^+$: 474.1237 found: 474.1244.

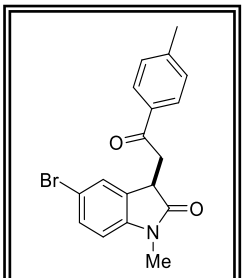
Synthesis of 1-benzyl-5-bromo-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-indol-2-one (195s): To a solution of 1-benzyl-5-bromo-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63g**, 100 mg, 0.30 mmol) and (2*E*)-1,3-diphenylprop-2-en-1-one (**184b**, 56 mg, 0.30 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to obtain product **195s** (81 mg, 63%) as a colourless crystalline solid according to general procedure. R_f = 0.46 (EtOAc/hexane = 1:4, v/v); mp 162-163 °C; IR (neat): ν_{max} 2917, 1707, 1602, 1483, 1350, 1289, 1217, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.55 (dd, J_1 = 18.4 Hz, J_2 = 8.8 Hz, 1H, CH), 3.95 (dd, J_1 = 18.4 Hz, J_2 = 2.4 Hz, 1H, CH), 4.18 (d, J = 8 Hz, 1H, CH), 5.00 (s, 2H, CH_2), 6.64 (d, J = 8.4 Hz, 1H, ArH), 7.30-7.66 (m, 10H, ArH), 8.04 (d, J = 7.6 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 39.9, 41.2, 44.1, 110.5, 115.3, 127.3, 127.6, 127.8, 128.3, 128.8, 128.9, 130.9, 131.1, 133.7, 135.4, 136.1, 142.5, 177.2, 196.5 ppm; HRMS (ESI) Calculated for $C_{23}H_{18}{}^{79}BrNO_2$ $(M+Na)^+$: 442.0420 found: 442.0419.



195s

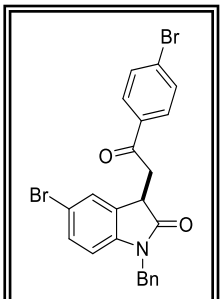
Synthesis of 5-bromo-1-methyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195t): To a solution of 5-bromo-3-diazo-1-methyl-1,3-dihydro-2*H*-indol-

2-one (**63h**, 100mg, 0.40 mmol) and (2*E*)-1-(4-methylphenyl)-3-phenylprop-2-en-1-one (**184a**, 89 mg, 0.40 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195t** (93mg, 65%) as a colourless crystalline solid according to general procedure. R_f = 0.35 (EtOAc/hexane = 1:4, v/v); mp 153-154 °C; IR (neat): ν_{max} 2917, 1711, 1606, 1483, 1345, 1098, 806 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.42 (s, 3H, CH_3), 3.25 (s, 3H, CH3), 3.39 (dd, J_1 = 18.4 Hz, J_2 = 8.8 Hz, 1H, CH), 3.82 (dd, J_1 = 18.3 Hz, J_2 = 2.9 Hz, 1H, CH), 4.03-4.05 (m, 1H, CH), 6.73 (d, J = 8.4 Hz, 1H, ArH), 7.27-7.41 (m, 4H, ArH), 7.87 (d, J = 8.4 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.7, 26.5, 39.8, 41.2, 109.4, 115.2, 127.7, 128.3, 129.4, 130.9, 131.2, 133.7, 143.4, 144.6, 177.2, 196.2 ppm; HRMS (ESI) Calculated for $C_{18}H_{16}{}^{79}BrNO_2$ $(M+H)^+$: 358.0443 found: 358.0437.



195t

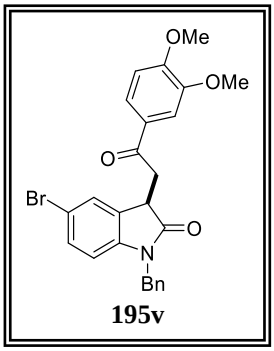
Synthesis of 1-benzyl-5-bromo-3-[2-(4-bromophenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195u): To a solution of 1-benzyl-5-bromo-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63g**, 100 mg, 0.30 mmol) and (2*E*)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (**184i**, 137 mg, 0.30 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to furnish product **195u** (76mg, 51%) as a colourless crystalline solid according to general procedure. R_f = 0.54 (EtOAc/hexane = 1:4, v/v); mp 148-149 °C; IR (neat): ν_{max} 2920, 1710, 1586, 1482, 1348, 1169, 809 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.39 (dd, J_1 = 18.4 Hz, J_2 = 8.4 Hz, 1H, CH), 3.77 (dd, J_1 = 18.4 Hz, J_2 = 3.2 Hz, 1H, CH), 4.00-4.02 (m, 1H, CH), 4.87 (ABq, $\Delta\delta_{AB}$ = 0.02, J = 15.8 Hz, 2H, CH_2), 6.51 (d, J = 8.4 Hz,



195u

1H, ArH), 7.16-7.28 (m, 7H, ArH), 7.54 (d, *J* = 8.4 Hz, 2H, ArH), 7.77 (d, *J* = 8.4 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 39.8, 41.2, 44.1, 110.6, 115.4, 127.3, 127.5, 127.8, 128.9, 129.0, 129.7, 130.9, 131.0, 132.1, 134.8, 135.4, 142.5, 177.0, 195.5 ppm; HRMS (ESI) Calculated for $C_{23}H_{17}{}^{79}Br^{81}BrNO_2$ $(M+H)^+$: 499.9684 found: 499.9683.

Synthesis of 5-bromo-3-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]-1-benzyl-1,3-dihydro-2*H*-indol-2-one (195v): To a solution of 1-benzyl-5-bromo-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63g**, 100 mg, 0.30 mmol) and (2*E*)-1-(3,4-dimethoxyphenyl)-3-phenylprop-2-en-1-one (**184l**, 137 mg, 0.30 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195v** (86mg, 60%) as a colourless amorphous solid according to general procedure.

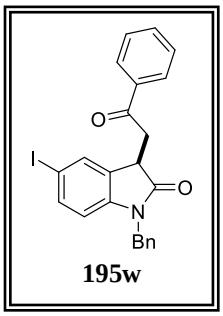


195v

R_f = 0.11 (EtOAc/hexane = 1.5:3.5, v/v); mp 123-124 °C; IR (neat): ν_{max} 2943, 1710, 1670, 1487, 1343, 1273, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.64 (dd, J_1 = 19 Hz, J_2 = 8.1 Hz, 1H, CH), 3.83 (s, 3H, CH_3), 3.92-3.98 (m, 4H, CH_3/CH), 4.11 (dd, J_1 = 7.6 Hz, J_2 = 2.8 Hz, 1H, CH), 5.00 (ABq, $\Delta\delta_{AB}$ = 0.08, *J* = 15.7 Hz, 2H, CH_2), 6.62 (d, *J* = 8 Hz, 1H, ArH), 6.96 (d, *J* = 8.8 Hz, 1H, ArH), 7.09-7.12 (m, 1H, ArH), 7.28-7.42 (m, 8H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 41.8, 44.0, 44.8, 55.86, 55.92, 110.4, 113.2, 113.8, 115.2, 121.4, 126.7, 127.3, 127.7, 128.9, 130.6, 131.5, 135.6. 142.6, 153.5, 153.8, 177.5, 197.5 ppm; HRMS (ESI) Calculated for $C_{25}H_{22}{}^{79}BrNO_4$ $(M+H)^+$: 480.0810 found: 480.0805.

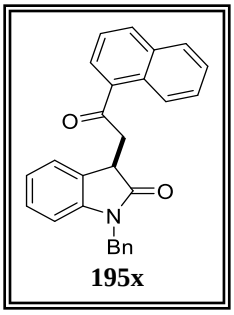
Synthesis of 1-benzyl-5-iodo-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-indol-2-one (195w): To a solution of 1-benzyl-3-diazo-5-iodo-1,3-dihydro-2*H*-indol-2-one (**63i**, 100 mg, 0.27 mmol) and (2*E*)-1,3-diphenylprop-2-en-1-one (**184b**, 56 mg, 0.27 mmol)

in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195w** (74 mg, 59%) as a colourless crystalline solid according to general procedure. R_f = 0.43 (EtOAc/hexane = 1:4, v/v); mp 196-197 °C; IR (neat): ν_{max} 2918, 1705, 1598, 1483, 1351, 1215, 1175, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.56 (dd, J_1 = 18.4 Hz, J_2 = 8.4 Hz, 1H, CH), 3.94 (dd, J_1 = 18.4 Hz, J_2 = 2.8 Hz, 1H, CH), 4.15-4.17 (m, 1H, CH), 5.00 (s, 2H, CH_2), 6.55 (d, J = 8 Hz, 1H, ArH), 7.30-7.67 (m, 10H, ArH), 8.04 (d, J = 7.6 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 39.9, 41.0, 44.0, 85.3, 111.1, 127.3, 127.8, 128.3, 128.8, 128.9, 131.5, 133.1, 133.7, 135.5, 136.1, 136.9, 143.3, 177.0, 196.4 ppm; HRMS (ESI) Calculated for $C_{23}H_{18}INO_2$ $(M+H)^+$: 468.0460 found: 468.0464.



195w

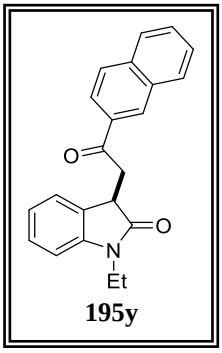
Synthesis of 1-benzyl-3-[2-(naphthalen-1-yl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195x): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*)-1-(naphthalen-1-yl)-3-phenylprop-2-en-1-one (**184m**, 163 mg, 0.40 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to yield product **195x** (110 mg, 70%) as a colourless crystalline solid according to general procedure. R_f = 0.44 (EtOAc/hexane = 1.5:3.5, v/v); mp 161-162 °C; IR (neat): ν_{max} 2919, 1703, 1608, 1355, 1217, 1170, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.53 (dd, J_1 = 18 Hz, J_2 = 8.8 Hz, 1H, CH), 3.92-3.98 (m, 1H, CH), 4.24 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H, CH), 5.03 (s, 2H, CH_2), 6.79 (d, J = 7.6 Hz, 1H, ArH), 7.00 (t, J = 7.6 Hz, 1H, ArH), 7.20 (t, J = 7.6 Hz, 1H, ArH), 7.29-7.65 (m, 11H, ArH), 8.04-8.06 (m, 2H, ArH), ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 40.1, 41.3, 44.0, 109.1, 122.6, 124.4, 127.4,



195x

127.6, 128.0, 128.2, 128.75. 128.84, 129.1,133.5, 135.9, 136.4, 143.5, 177.9, 196.9 ppm; HRMS (ESI) Calculated for $C_{27}H_{21}NO_2$ $(M+H)^+$: 392.1651 found: 392.1653.

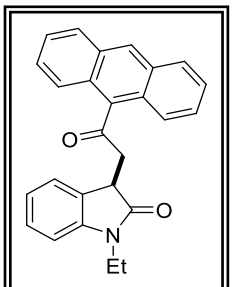
Synthesis of 1-ethyl-3-[2-(naphthalen-2-yl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (195y): To a solution of 3-diazo-1-ethyl-1,3-dihydro-2*H*-indol-2-one (**63c**, 100 mg, 0.53 mmol) and (2*E*)-1-(naphthalen-2-yl)-3-phenylprop-2-en-1-one (**184n**, 137 mg, 0.53 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to afford product **195y** (113mg, 65%) as a colourless amorphous solid according to general procedure. R_f = 0.39 (EtOAc/hexane = 1:4, v/v); mp 111-112 °C; IR (neat): ν_{max} 2978, 1699, 1609, 1462, 1358, 1227, 1133, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.27 (t, J = 7.2 Hz, 3H, CH), 3.48 (dd, J_1 = 17.9 Hz, J_2 = 8.7 Hz, 1H, CH), 3.75-3.88 (m, 3H, CH/CH_2), 4.13 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H, CH), 6.84 (d, J = 7.6 Hz, 1H, ArH), 7.00 (t, J = 7.6 Hz, 1H, ArH), 7.24-7.59 (m, 5H, ArH), 7.83-7.96 (m, 3H, ArH), 8.61 (d, J = 8.4 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.7, 34.9, 41.8, 43.1, 108.3, 122.4, 124.4, 124.5, 125.8, 126.6, 128.07, 128.12, 128.2, 128.5, 129.3, 130.1, 133.1, 134.0, 135.1, 143.5, 177.2, 201.0 ppm; HRMS (ESI) Calculated for $C_{22}H_{19}NO_2$ $(M+H)^+$: 330.1494 found: 330.1486.



195y

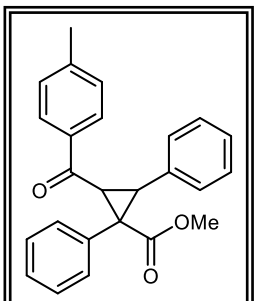
Synthesis of 3-[2-(anthracen-9-yl)-2-oxoethyl]-1-ethyl-1,3-dihydro-2*H*-indol-2-one (195z): To a solution of 3-diazo-1-ethyl-1,3-dihydro-2*H*-indol-2-one (**63c**, 100 mg, 0.53 mmol) and (2*E*)-1-(anthracen-9-yl)-3-phenylprop-2-en-1-one (**184o**,163 mg, 0.53 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to yield product **195z** (106 mg, 53%) as a colourless amorphous solid according to general procedure. R_f = 0.41 (EtOAc/hexane =

1.5:3.5, v/v); mp 121-122 °C; IR (neat): ν_{max} 2979, 1702, 1609, 1462, 1366, 1273, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.34, (t, J = 7.2 Hz, 3H, CH_3), 3.66 (dd, J_1 = 19.6 Hz, J_2 = 7.4 Hz, 1H, CH), 3.77-3.96 (m, 3H, CH/CH_2) 4.07 (dd, J_1 = 7.2 Hz, J_2 = 3.2 Hz, 1H, CH), 6.95 (d, J = 7.6 Hz, 1H, ArH), 7.16 (t, J = 7.6 Hz, 1H, ArH), 7.36 (t, J = 7.6 Hz, 1H, ArH) 7.44-7.53 (m, 5H, ArH), 7.78-7.80 (m, 2H, ArH), 7.98-8.01 (m, 2H, ArH), 8.46 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.5, 35.0, 41.3, 46.7, 108.5, 122.30, 122.33, 124.1, 124.2, 125.6, 126.98, 127.03, 128.3, 128.8, 129.0, 131.0, 134.9, 144.0, 177.0, 207.0 ppm; HRMS (ESI) Calculated for $C_{26}H_{21}NO_2$ $(M+H)^+$: 380.1651 found: 380.1629.



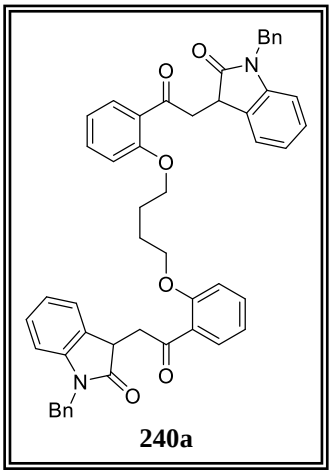
195z

Synthesis of methyl 2-(4-methylbenzoyl)-1,3-diphenylcyclopropane-1-carboxylate (195aa)[150]: To a solution of methyl 2-diazo-2-phenylacetate (**63k**, 100 mg, 0.57 mmol) and (2*E*)-1-(4-methylphenyl)-3-phenylprop-2-en-1-one (**184a,** 126 mg, 0.57 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to furnish product **195aa** (44 mg, 21%) as a colourless amorphous solid according to general procedure. R_f = 0.8 (EtOAc/hexane = 0.5:4.5, v/v); mp 157-158 °C; IR (neat): ν_{max} 2951, 1715, 1670, 1445, 1263, 1180, 716 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.49 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 4.03 (d, J = 7.2 Hz, 1H, CH), 4.45 (d, J = 7.2 Hz, 1H, CH), 7.29-7.43 (m, 12H, ArH), 8.06 (d, J = 8 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.8, 35.2, 35.4, 48.7, 52.7, 127.3, 127.9, 128.3, 128.4, 128.6, 128.8, 129.5, 130.1, 134.8, 135.3, 135.5, 144.2, 170.0, 193.5 ppm; HRMS (ESI) Calculated for $C_{25}H_{23}O_3$ $(M+H)^+$: 371.1647 found: 371.1607.



195aa

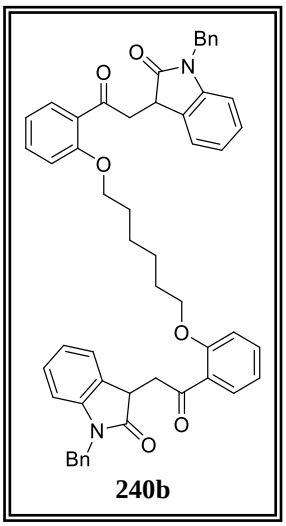
Synthesis of 3,3'-(butane-1,4-diylbis(oxy)bis(2,1-phenylene)bis(2-oxoethane-2,1-diyl)bis(1-benzylindolin-2-one) (240a): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*,2'*E*)-1,1'-((butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(3-phenylprop-2-en-1-one) (**239a**, 101 mg, 0.20 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under an open-air atmosphere to obtain product **240a** (182 mg, 59%) as a colourless crystalline solid according to general procedure. R_f = 0.28 (EtOAc/hexane = 1.5:3.5, v/v); mp 187-188 °C; IR (neat): ν_{max} 2927, 1707, 1672, 1599, 1454, 1356, 1291, 1236, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.73 (s, 1H, CH), 2.31-2.34 (m, 1H, CH), 3.44 (dd, J_1 = 18.4 Hz, J_2 = 9.2 Hz, 1H, CH), 3.90 (dd, J_1 = 18.4 Hz, J_2 = 3.2 Hz, 1H, CH), 4.12-4.28 (m, 3H, CH_2), 4.86-4.92 (m, 2H, CH_2), 6.69 (d, J = 7.6 Hz, 1H, ArH), 6.88-6.99 (m, 3H, ArH), 7.08-7.13 (m, 1H, ArH), 7.22-7.42 (m, 7H, ArH), 7.75 (d, J = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.2, 41.7, 43.9, 45.3, 65.1, 109.0, 112.6, 121.0, 122.5, 124.4, 127.3, 127.5, 127.6, 127.9, 128.8, 129.3, 130.5, 134.1, 136.0, 143.4, 157.9, 177.9, 198.7 ppm (we observed half number of signals due to the C_2 symmetry); HRMS (ESI) Calculated for $C_{50}H_{44}N_2O_6$ $(M+K)^+$: 807.2863 found: 807.2852.



240a

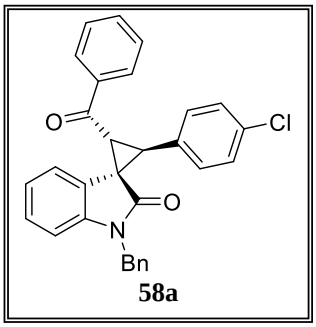
Synthesis of (hexane-1,6-diylbis(oxy)bis(2,1-phenylene)bis(2-oxoethane-2,1-diyl)bis(1-benzylindolin-2-one) (240b): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*,2'*E*)-1,1'-((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))bis(3-phenylprop-2-en-1-one) (**239b**, 106 mg, 0.2 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was

stirred at 0 °C under an open-air atmosphere to afford product **240b** (179 mg, 56%) as a colourless crystalline solid according to general procedure. R_f = 0.30 (EtOAc/hexane = 1.5:3.5, v/v); mp 210-211 °C; IR (neat): ν_{max} 2931, 1709, 1671, 1602, 1457, 1356, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.50 (s, 2H, CH_2), 1.83 (s, 2H, CH_2), 3.54-3.60 (m, 1H, CH_2), 3.90-3.60 (m, 4H, CH_2), 4.88-5.02 (m, 2H, CH_2), 6.69-6.71 (m, 1H, ArH), 6.92-6.99 (m, 3H, ArH), 7.09-7.13 (m, 1H, ArH), 7.21-7.30 (m, 6H, ArH), 7.41-7.45 (m, 1H, ArH), 7.77 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.1, 29.1, 42.0, 44.0, 45.3, 68.5, 109.1, 112.4, 120.6, 122.6, 124.3, 127.2, 127.6, 127.8, 128.8, 129.6, 130.4, 130.7, 134.1, 135.8, 143.3, 158.6, 178.4, 198.5 ppm (we observed half number of signals due to the C_2 symmetry); HRMS (ESI) Calculated for $C_{52}H_{48}N_2O_6$ $(M+H)^+$: 797.3591 found: 797.3588.



240b

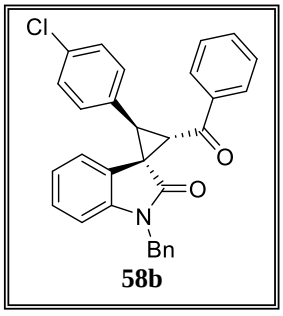
Synthesis of 2-benzoyl-3-(4-chlorophenyl)-1'-ethylspiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (58a): To a solution of $InCl_3$ (20 mol%) in 6:2 mL water and THF were added 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and (2*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (**184g**, 97 mg, 0.40 mmol) under an open-air atmosphere. The reaction mixture was stirred at ambient temperature for 24 h and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatographic purification (Hexane/EtOAc) to afford the desired cyclopropane product product **58a** (154 mg, 83%) as a colourless crystalline solid. R_f = 0.31 (EtOAc/hexane = 1:4, v/v); mp 225-226 °C; IR (neat): ν_{max} 3057, 1708, 1673, 1606,



58a

1357, 1179, 1091, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.13 (d, J = 8 Hz, 1H, CH), 4.31 (d, J = 8.4 Hz, 1H, CH), 4.93 (ABq, $\Delta\delta_{AB}$ = 0.06, J = 15.6 Hz, 2H, CH_2), 6.76 (d, J = 7.6 Hz, 1H, ArH), 6.94 (t, J = 7.6 Hz, 1H, ArH), 7.11 (t, J = 7.6 Hz, 1H, ArH), 7.21-7.41 (m, 12H, ArH), 7.51-7.55 (m, 1H, ArH), 7.93 (d, J = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 38.6, 41.4, 44.1, 109.2, 122.0, 122.6, 125.7, 127.3, 127.7, 128.4, 128.5, 128.8, 128.9, 130.7, 131.9, 133.5, 133.9, 136.0, 136.9, 142.9, 172.0, 192.7 ppm; HRMS (ESI) Calculated for $C_{30}H_{22}{}^{35}ClNO_2$ $(M+H)^+$: 464.1417 found: 464.1412.

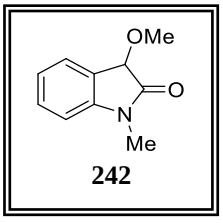
Synthesis of 2-benzoyl-3-(4-chlorophenyl)-1'-methylspiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (58b): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**) (100 mg, 0.40 mmol) and dimethyl phosphite (40 µL, 0.44 mmol) in 2.0 mL THF was added to a flame-dried round bottom flask equipped with a magnetic stirring bar under argon. The solution was cooled to -30 °C and 0.5 M KHMDS in toluene (110 µL, 0.48 mmol, 1.2 equiv) was added dropwise, then a solution of (2*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (**184g**, 97 mg, 0.40 mmol) in 1.0 mL THF was added dropwise. The reaction was allowed to proceed at the same temperature and was monitored by TLC. α,β-Unsaturated ketone was fully consumed and the reaction mixture quenched with saturated aqueous ammonium chloride. After being warmed to ambient temperature, the mixture was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatographic purification (Hexane/EtOAc) to afford the desired cyclopropane product **58b** (132 mg, 71%) as a colourless crystalline solid. R_f = 0.31 (EtOAc/hexane = 1:4, v/v); mp 196-197 °C; IR (neat): ν_{max} 2922, 1706,



58b

1605, 1459, 1353, 1175, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.67 (d, J = 8.4 Hz, 1H, CH), 4.22 (d, J = 8.0 Hz, 1H, CH), 4.59 (d, J = 15.6 Hz, 1H, CH), 5.19 (d, J = 15.6 Hz, 1H, CH), 6.18 (d, J = 7.6 Hz, 1H, ArH), 6.79-6.85 (m, 2H, ArH), 7.02 (d, J = 6.8 Hz, 1H, ArH), 7.02-7.39 (m, 11H, ArH), 7.78 (d, J = 8.4 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 37.5, 39.3, 41.7, 44.0, 109.3, 121.3, 122.1, 125.2, 127.3, 127.7, 127.8, 128.0, 128.7, 129.2, 129.8, 129.9, 133.5, 134.8, 135.8, 139.9, 143.2, 172.5, 190.7 ppm; HRMS (ESI) Calculated for $C_{30}H_{22}{}^{35}ClNO_2$ $(M+H)^+$: 464.1417 found: 464.1410.

Synthesis of 3-methoxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (242)[151]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol), (2*E*)-1-(4-methylphenyl)-3-phenylprop-2-en-1-one (**184a**, 90 mg, 0.58 mmol) and methanol (23 μL, 0.58 mmol) in $CHCl_3$ (5 mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C temperature to yield product **242** (88 mg, 86%) as a light yellow amorphous solid. R_f = 0.46 (EtOAc/hexane = 1.5:3.5, v/v); mp 131-132 °C; IR (neat): ν_{max} 2927, 1705, 1612, 1467, 1350, 1019, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.19 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 4.86 (s, 1H, CH), 6.82 (d, J = 7.8 Hz, 1H, ArH), 7.10 (t, J = 7.6 Hz, 1H, ArH), 7.32-7.36 (m, 1H, ArH), 7.38-7.42 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.0, 56.1, 76.7, 108.4, 122.9, 125.3, 130.0 144.3, 174.3 ppm.



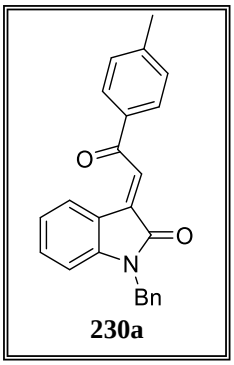
242

General experimental procedure for the synthesis of spiro-indolooxiranes 229

A mixture of DMAP (1.0 equiv) and copper iodide (0.1 equiv) in 4 mL acetone was stirred at room temperature for 5 minutes. Then, 3-alkylated oxindole (**195**, 1.0 equiv) was added to the reaction mixture and stirred for 15-24 h. The mixture was then quenched with water and extracted with ethyl acetate (3×10 mL). The concentration of

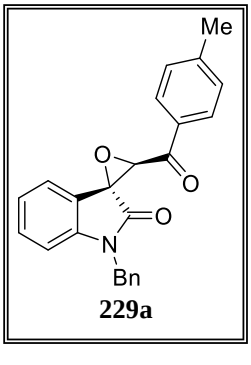
the combined organic layers under reduced pressure afforded the crude product, which was purified by column chromatography using silica gel to afford the corresponding product **229**.

Synthesis of (3*E*)-1-benzyl-3-[2-(4-methylphenyl)-2-oxoethylidene]-1,3-dihydro-*2H*-indol-2-one (230a): To a solution of DMAP (0.14 mmol) in acetone (4 mL) was added 1-benzyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (**195a**, 50 mg, 0.14 mmol) the reaction mixture was stirred at room temperature to afford product **230a** (42 mg, 86%) as a colourless amorphous solid according to general procedure. R_f = 0.46 (EtOAc/hexane = 1:4, v/v); mp 141-142 °C; IR (neat): ν_{max} 2922, 1701, 1659, 1596, 1482, 1345, 1228, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.33 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 6.64 (d, *J* = 8 Hz, 1H, ArH), 7.11 (d. *J* = 8 Hz, 1H, ArH), 7.30-7.37 (m, 6H, ArH), 7.57-7.61 (m, 2H, ArH), 7.67-6.68 (m, 1H, ArH), 7.98 (s, 1H, ArH), 8.16-8.19 (m, 3H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.1, 44.0, 109.03, 120.3, 126.4, 127.3, 127.7, 128.3, 128.85, 128.92, 132.4, 133.0, 133.8, 135.6, 136.8, 137.7, 143.0, 168.2, 191.3 ppm; HRMS (ESI) Calculated for $C_{24}H_{19}NO_2$ $(M+H)^+$: 354.1494 found: 354.1504.



230a

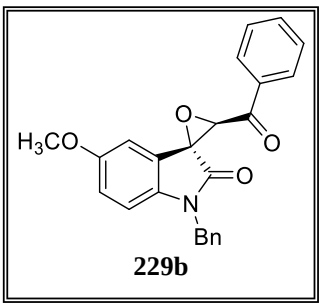
Synthesis of 1-benzyl-3'-(4-methylbenzoyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (229a): To a solution of DMAP (17 mg, 0.14 mmol) and copper iodide (3 mg, 0.014 mmol) in acetone (4 mL) was added 1-benzyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (**195a**, 50 mg, 0.14 mmol). The reaction mixture was stirred at room temperature to afford product **229a** (49 mg, 95%) as a colourless crystalline solid according to general procedure. R_f = 0.35 (EtOAc/hexane =



229a

1:4, v/v); mp 198-199-174 °C; IR (neat): ν_{max} 2923, 1701, 1599, 1445, 1363, 1187, 1147, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.40 (s, 3H, CH_3), 5.02 (d, J = 4.4 Hz, 3H, NCH_2/OCH), 6.77 (d, J = 8 Hz, 1H, ArH), 6.92 (t, J = 7.6 Hz, 1H, ArH), 7.12 (d, J = 7.6 Hz, 1H, ArH), 7.19-7.37 (m, 10H, ArH), 7.85 (d, J = 8.4 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.9, 44.5, 60.9, 64.0, 110.0, 119.4, 123.3, 124.5, 127.3, 128.0, 128.5, 129.0, 129.7, 130.9, 132.7, 135.1, 144.5, 145.7, 170.5, 190.2 ppm; HRMS (ESI) Calculated for $C_{24}H_{19}NO_3$ $(M+H)^+$: 370.1443 found: 370.1437.

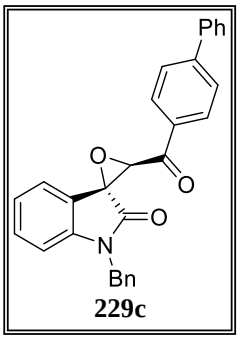
Synthesis of 3'-benzoyl-1-benzyl-5-methoxyspiro[indole-3,2'-oxiran]-2(1*H*)-one (229b): To a solution of DMAP (16 mg, 0.13 mmol) and copper iodide (3 mg, 0.013 mmol) in acetone (4 mL) was added 1-benzyl-5-methoxy-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-indol-2-one (**195q**, 50 mg, 0.13 mmol). The reaction mixture was stirred at room temperature to afford product **229b** (47 mg, 91%) as a colourless amorphous solid according to general procedure. R_f = 0.23 (EtOAc/hexane = 1:4, v/v); mp 148-149 °C; IR (neat): ν_{max} 2923, 1701, 1599, 1445, 1363, 1187, 1147, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.57 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 4.97 (s, 1H, CH), 6.59-6.67 (m, 3H, ArH), 7.19-7.56 (m, 8H, ArH), 7.88 (d, J = 7.6 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.6, 55.7, 61.2, 64.01, 110.7, 110.8, 116.4, 120.4, 127.3, 128.0, 128.4, 129.0, 129.1, 134.5, 135.15, 135.19, 137.7, 156.2, 170.2, 190.70 ppm; HRMS (ESI) Calculated for $C_{24}H_{19}NO_4$ $(M+H)^+$: 386.1392 found: 386.1386.



229b

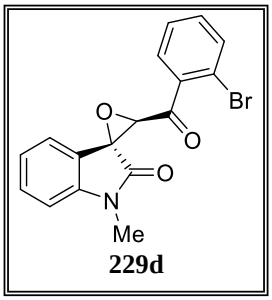
Synthesis of 3'-([1,1'-biphenyl]-4-carbonyl)-1-benzylspiro[indole-3,2'-oxiran]-2(1*H*)-one (229c): To a solution of DMAP (15 mg, 0.12 mmol) and copper iodide (3 mg, 0.012 mmol) in acetone (4 mL) was added 3-[2-([1,1'-biphenyl]-4-yl)-2-oxoethyl]-

1-benzyl-1,3-dihydro-2*H*-indol-2-one (**195f**, 50 mg, 0.12 mmol). The reaction mixture was stirred at room temperature to afford product **229c** (45 mg, 87%) as a colourless crystalline solid according to general procedure. R_f = 0.37 (EtOAc/hexane = 1:4, v/v); mp 210-211 °C; IR (neat): ν_{max} 2923, 1701, 1599, 1445, 1363, 1187, 1147, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.07 (s, 2H, CH_2), 5.12 (s, 1H, CH), 6.96 (d, *J* = 0.8 Hz, 1H, ArH), 6.98-7.00 (m, 1H, ArH), 7.19-7.21 (m, 1H, ArH), 7.25-7.29 (m, 1H, ArH), 7.33-7.53 (m, 7H, ArH), 7.63-7.74 (m, 5H, ArH), 8.07 (d, *J* = 8.4 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.5, 61.0, 64.1, 110.0, 119.4, 123.3, 124.6, 127.3, 127.4, 127.6, 128.0, 128.6, 129.0, 129.1, 131.0, 133.8, 135.1, 139.4, 144.6, 147.3, 170.5, 190.2 ppm; HRMS (ESI) Calculated for $C_{29}H_{21}NO_3$ $(M+Na)^+$: 454.1419 found: 454.1414.



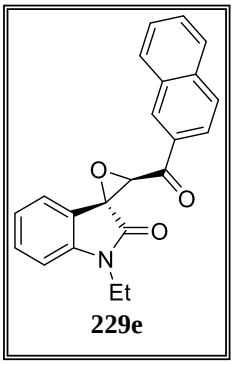
229c

Synthesis of 3'-(2-bromobenzoyl)-1-methylspiro[indole-3,2'-oxiran]-2(1*H*)-one (229d): To a solution of DMAP (18 mg, 0.16 mmol) and copper iodide (3 mg, 0.016 mmol) in acetone (4 mL) was added 3-[2-(2-bromophenyl)-2-oxoethyl]-1-methyl-1,3-dihydro-2*H*-indol-2-one (**195k**, 50 mg, 0.16 mmol). The reaction mixture was stirred at room temperature to afford product **229d** (42 mg, 79%) as a colourless crystalline solid according to general procedure. R_f = 0.31 (EtOAc/hexane = 1:4, v/v); mp 167-169 °C; IR (neat): ν_{max} 2923, 1701, 1599, 1445, 1363, 1187, 1147, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.22 (s, 3H, CH_3), 4.81 (s, 1H, CH), 6.81-6.85 (m, 1H, ArH), 6.96 (t, *J* = 7.6 Hz, 1H, ArH), 7.24-7.34 (m, 4H, ArH), 7.48-7.53 (m, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.9, 62.7, 65.4, 109.0, 119.3, 120.5, 123.3, 124.8, 127.9, 131.0, 131.2, 133.7, 134.2, 137.8, 145.5, 170.1, 193.2 ppm; HRMS (ESI) Calculated for $C_{17}H_{12}{}^{79}BrNO_3$ $(M+H)^+$: 358.0079 found: 358.0083.



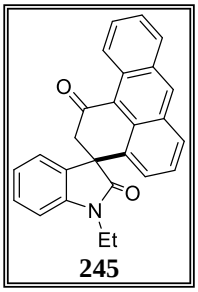
229d

Synthesis of 1-ethyl-3'-(naphthalene-2-carbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (229e): To a solution of DMAP (18 mg, 0.15 mmol) and copper iodide (3 mg, 0.015 mmol) in acetone (4 mL) was added 1-ethyl-3-[2-(naphthalen-2-yl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (**195y**, 50 mg, 0.15 mmol). The reaction mixture was stirred at room temperature to afford product **229e** (44 mg, 85%) as a colourless amorphous solid according to general procedure. R_f = 0.38 (EtOAc/hexane = 1:4, v/v); mp 135-136 °C; IR (neat): ν_{max} 2923, 1701, 1599, 1445, 1363, 1187, 1147, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.40 (t, J = 7.2 Hz, 3H, CH_3), 3.82-3.98 (m, 2H, CH_2), 4.99 (s, 1H, CH), 6.95-6.99 (m, 2H, ArH), 7.26-8.10 (m, 8H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.8, 35.6, 61.6, 65.0, 109.2, 119.6, 123.1, 124.4, 124.8, 125.5, 127.0, 128.7, 129.0, 130.1, 130.3, 131.1, 131.9, 134.0, 134.8, 144.6, 169.9, 193.2 ppm; HRMS (ESI) Calculated for $C_{22}H_{17}NO_3$ $(M+H)^+$: 344.1287 found: 344.1286.



229e

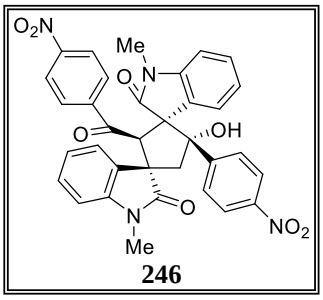
Synthesis of 1'-ethylspiro[benzo[de]anthracene-3,3'-indoline]-1,2'(2*H*)-dione (245): To a solution of DMAP (1.0 mmol) and copper iodide (0.1 mmol) in acetone (4 mL) was added 3-(2-(anthracen-9-yl)-2-oxoethyl)-1-ethylindolin-2-one (**195z,** 50 mg, 0.16 mmol). The reaction mixture was stirred at room temperature to obtain product **245** (124mg, 71%) as a white solid according to general procedure. R_f = 0.23 (EtOAc/hexane = 1:4, v/v); mp 215-216 °C; IR (neat): ν_{max} 2923, 1727, 1612, 1463, 1361, 1106, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.41 (s, J = 7.2 Hz, 3H, CH_3), 3.22 (d, J = 14 Hz, CH), 3.58 (d, J = 14 Hz, CH), 3.86-3.95 (m, 2H, CH_2), 6.99-7.12 (m, 5H, ArH), 7.30-7.43 (m, 2H, ArH), 7.61-7.80 (m, 3H, ArH), 8.02-8.12 (m, 2H, ArH),



245

8.94 (s, 1H, ArH), 9.69 (d, *J* = 8.8 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.8, 35.1, 47.9, 55.1, 108.9, 123.1, 123.82, 123.84, 125.3, 125.4, 126.2, 126.8, 128.7, 128.85, 128.89, 129.9, 130.1, 131.2, 131.8, 132.8, 133.1, 133.7, 135.5, 141.8, 176.9, 198.0 ppm; HRMS (ESI) Calculated for $C_{26}H_{19}NO_2$ $(M+H)^+$: 378.1494 found: 378.1481.

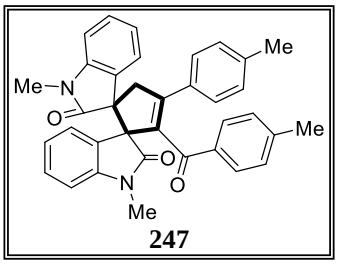
Synthesis of 4'-hydroxy-1,1''-dimethyl-2'-(4-nitrobenzoyl)-4'-(4-nitrophenyl) dispiro[indoline-3,1'-cyclopentane-3',3''-indoline]-2,2''-dione (246): To a solution of DMAP (1.0 mmol) and copper iodide (0.1 mmol) in acetone (4 mL) was added 1-methyl-3-(2-(4-nitrophenyl)-2-oxoethyl)indolin-2-one (**195m**, 50mg, 0.17 mmol). The reaction mixture was stirred at room temperature to afford product **246** (124mg, 71%) as a white solid according to general procedure. R_f = 0.23 (EtOAc/hexane = 1:4, v/v); mp 240-241 °C; IR (neat): ν_{max} 3300, 2930, 1695, 1612, 1531, 1475, 1351, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.56 (d, *J* = 14 Hz, 1H, CH), 2.98 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 4.41 (d, *J* = 7 Hz, 1H, CH), 5.23 (s, 1CH, OH), 6.36 (d, *J* = 7.6 Hz, 1H, ArH), 6.68 (d, *J* = 8 Hz, 1H, ArH), 7.051-7.05-7.51 (m, 14H, ArH), 7.39-7.97 (m, 9H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.0, 26.9, 45.6, 54.1, 64.6, 66.9, 83.8, 107.8, 107.9, 121.4, 121.9, 122.4, 122.7, 124.7, 125.2, 125.9, 126.6, 126.9, 128.2, 128.9, 129.1, 129.48, 129.58, 132.0, 132.4, 138.3, 140.0, 142.3, 144.0, 147.5, 147.6, 176.0, 183.1, 194.3 ppm; HRMS (ESI) Calculated for $C_{34}H_{26}N_4O_8$ $(M+H)^+$: 619.1829 found: 619.1857.



246

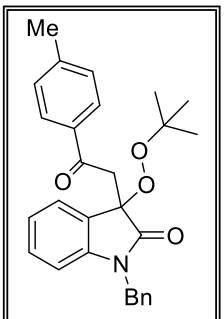
Synthesis of 1,1''-dimethyl-3'-(4-methylbenzoyl)-4'-(*p*-tolyl)dispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-2,2''-dione (247): To a solution of DMAP (1.0 mmol) and copper iodide (0.1 mmol) in acetone (4 mL) was added 1-methyl-3-(2-oxo-

2-(p-tolyl)ethyl)indolin-2-one (**195b**, 50mg, 0.14 mmol). The reaction mixture was stirred at room temperature to yield product **247** (124mg, 71%) as a white solid according to general procedure. R_f = 0.23 (EtOAc/hexane = 1:4, v/v); mp 220-221 °C; IR (neat): ν_{max} 2926, 1709, 1642, 1609, 1421, 1348, 1094, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.10 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 3.28 (d, *J* = 16.8 Hz, 1H, CH), 3.77 (d, *J* = 16.8 Hz, 1H, CH), 6.44-6.63 (m, 3H, ArH), 6.80-7.17 (m, 10H, ArH), 7.53 (d, *J* = 7.2 Hz, 1H, ArH), 7.75 (d, *J* = 8 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.3, 21.7, 25.8, 26.3, 44.3, 58.6, 69.5, 107.7, 107.8, 122.2, 122.6, 124.5, 124.9, 125.7, 126.5, 128.6, 128.8, 128.94, 128.96, 128.98, 129.86, 132.3, 134.7, 135.6, 138.7, 143.2, 143.8, 144.7, 152.8, 175.6, 178.1, 194.6 ppm; HRMS (ESI) Calculated for $C_{36}H_{30}N_2O_3$ $(M+H)^+$: 539.2325 found: 539.2315.



247

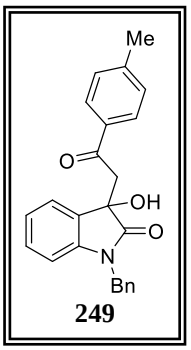
Synthesis of 3-*tert*-butoxy-1-benzyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (248): To a solution of $FeCl_3$ (7 mg, 0.04 mmol) and TBHP (55 μL, 0.56 mmol) in acetonitrile (2 mL) was added 1-benzyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-*2H*-indol-2-one (**195a**, 50 mg, 0.14 mmol) and the reaction mixture was stirred at room temperature to afford product **248** (41 mg, 69%) as a colourless liquid according to general procedure. R_f = 0.38 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 2923, 1730, 1684, 1611, 1465, 1358, 1181, 1007, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.04 (s, 9H, $C(CH_3)_3$, 2.32 (s, 3H, CH_3), 3.71-3.91 (m, 2H, CH_2), 4.66 (d, *J* = 16 Hz, 1H, NCH), 5.26 (d, *J* = 16 Hz, 1H, NCH), 6.55 (d, *J* = 8 Hz, 1H, ArH), 6.85-6.89 (m, 1H, ArH), 7.07-7.33 (m, 10H,



248

ArH), 7.73 (d, *J* = 8.4 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.7, 26.4, 42.5, 43.9, 80.7, 82.4, 109.2, 122.0, 124.1, 127.1, 128.3, 128.6, 129.2, 129.7, 134.0, 135.9, 144.3, 144.5, 174.0, 194.2 ppm; HRMS (ESI) Calculated for $C_{28}H_{29}NO_3$ $(M+H)^+$: 444.2175 found: 444.2168.

Synthesis of 1-benzyl-3-hydroxy-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (249): To a solution of 3-tert-butoxy-1-benzyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1,3-dihydro-*2H*-indol-2-one (**248**, 30 mg, 0.07 mmol) in acetonitrile (5 mL) was stirred under reflux conditions for 6 h to obtain product **249** (14 mg, 52%) as a colourless crystalline solid. R_f = 0.13 (EtOAc/hexane = 1.5:3.5, v/v); mp 161-162 °C; IR (neat): ν_{max} 3364, 3059, 1680, 1608, 1349, 1174, 1000, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.44 (s, 3H, CH_3), 3.63 (d, *J* = 17.2 Hz, 1H of CH_2), 3.91 (d, *J* = 17.2 Hz, 1H of CH_2), 4.98 (ABq, $\Delta\delta_{AB}$ = 0.06, *J* = 15.6 Hz, 2H, CH_2), 6.76 (d, *J* = 7.2 Hz, 1H, ArH), 7.01-7.04 (m, 1H, ArH), 7.20-7.45 (m, 9H, ArH), 7.84 (d, *J* = 7.6 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.7, 44.0, 44.5, 74.6, 109.7, 123.1, 124.0, 127.3, 127.7, 128.4, 128.9, 129.4, 129.8, 130.2, 134.0, 135.6, 142.9, 144.8, 176.7, 197.8 ppm; HRMS (ESI) Calculated for $C_{24}H_{21}NO_3$ $(M+H)^+$: 372.1600 found: 372.1604.

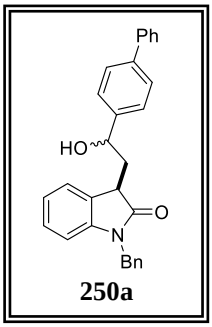


249

General experimental procedure for the synthesis of alcohol 250

A mixture of 3-alkylated oxindoles **195** (4.0 mmol) in dry MeOH (15 mL) was added $NaBH_4$ (8.0 mmol) slowly at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to stir for 5 h at room temperature and the solvent was evaporated. The mixture was then quenched with water and extracted with ethyl acetate (3×10 mL). The concentration of the combined organic layers under reduced pressure afforded the crude product and purified by chromatography to afford the corresponding alcohol **250**.

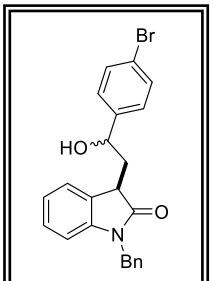
Synthesis of 3-[2-([1,1'-biphenyl]-4-yl)-2-hydroxyethyl]-1-benzyl-1,3-dihydro-2*H*-indol-2-one (250a): To the stirred solution of 3-[2-([1,1'-biphenyl]-4-yl)-2-oxoethyl]-1-benzyl-1,3-dihydro-*2H*-indol-2-one (**195f**, 50 mg, 0.12 mmol) in dry MeOH (40 mL) was added $NaBH_4$ (14 mg, 0.36 mmol) slowly at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to stir for 2 h at 0 °C to obtain the corresponding alcohol **250a** (47 mg, 95%) as a colourless crystalline solid. R_f = 0.15 (EtOAc/hexane = 1.5:3.5, v/v); mp 171-172 °C; IR (neat): ν_{max} 3380, 2991, 1689, 1610, 1485, 1359, 1070, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.17-2.29 (m, 2H, CH_2), 2.44-2.50 (m, 1H, CH), 3.63-3.77 (m, 1H, CH), 4.83-4.85 (m, 2H, CH_2), 5.14-5.17 (m, 1H, CH), 6.64-6.68 (m, 1H, ArH), 6.91-6.98 (m, 1H, ArH), 7.05-7.12 (m, 1H, ArH), 7.17-7.28 (m, 6H, ArH), 7.35 (t, J = 7.6 Hz, 2H, ArH), 7.44-7.52 (m, 6H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 39.3, 40.7, 42.6, 43.96, 43.98, 45.1, 71.1, 73.5, 109.3, 109.4, 122.8, 122.9, 123.7, 124.0, 126.1, 126.5, 127.11, 127.14, 127.25, 127.31, 127.37, 127.39, 127.7, 127.8, 128.0, 128.2, 128.8, 128.9, 130.0, 135.6, 135.7, 140.3, 140.6, 140.9, 141.0, 143.0, 143.2, 143.3, 143.5, 179.2 ppm; HRMS (ESI) Calculated for $C_{29}H_{25}NO_2$ $(M+Na)^+$: 442.1783 found: 442.1783.



250a

Synthesis of 1-benzyl-3-[2-(4-bromophenyl)-2-hydroxyethyl]-1,3-dihydro-*2H*-indol-2-one (250b): To the stirred solution of 1-benzyl-3-[2-(4-bromophenyl)-2-oxoethyl]-1,3-dihydro-*2H*-indol-2-one (**195l**, 50 mg, 0.12 mmol) in dry MeOH (40 mL) was added $NaBH_4$ (14 mg, 0.36 mmol) slowly at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to stir for 5 h at room temperature to afford the corresponding alcohol **250b** (44 mg, 89%) as a colourless crystalline solid. R_f = 0.12 (EtOAc/hexane = 1.5:3.5 v/v); mp 167-168 °C; IR (neat): ν_{max} 3401, 2923, 1691, 1611,

1485, 1364, 1071, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.16-2.34 (m, 2H, CH), 2.47-2.54 (m, 1H, CH), 3.70 (dd, J_1 = 9.6 Hz, J_2 = 3.6 Hz, 1H, CH), 3.84 (dd, J_1 = 9.2 Hz, J_2 = 4.8 Hz, 1H, CH), 4.32 (d, J = 6.4 Hz, 1H, CH), 4.95-5.01 (m, 2H, CH_2), 5.20 (d. J = 6.8 Hz, 1H, CH), 6.77-6.81 (m, 1H, ArH), 7.04-7.39 (m, 10H, ArH), 7.51-7.54 (m, 2H, ArH), ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 39.1, 40.7, 42.4, 43.97, 44.0145.2, 7.07, 73.3, 109.4, 109.5, 121.1, 121.3, 122.9, 123.0, 123.6, 123.9, 127.4, 127.5, 127.76, 127.84, 128.1, 128.3, 128.6, 128.8, 128.87, 128.92, 131.5, 131.6, 135.5, 135.6, 142.9, 143.17, 143.22, 143.5, 179.1, 179.2 ppm; HRMS (ESI) Calculated for $C_{23}H_{20}{}^{81}BrNO_2$ $(M+H)^+$: 424.0735 found: 424.0764.



250b

CHAPTER - III

SYNTHESIS OF SUBSTITUTED 3-ARYLOXINDOLES FROM DIAZOAMIDES

Over the last few decades, the chemistry of diazocarbonyl compounds has also been extensively studied and a variety of viable reactions such as C-H insertion, heteroatom-H insertion,[152] cyclopropanation,[153] addition,[154] polymerization,[155] nucleophilic olefination,[156] and others have been developed.[157] The reaction of diazo compounds with aldehydes has been established[158] as a valuable method for the synthesis of various ketones, homologated aldehydes and epoxides. Figure 16 shows that the reactions of diazoalkanes and involve[158] three different approaches: (a) C–H insertion (1,2-H shift), (b) C–C insertion (1,2-C shift), or (c) an electrocyclization reaction *via* two-step mechanism involving carbonyl 1,2-addition of the diazo compounds, followed by a 1,2-(H or C) shift. Figure 16 represents a mechanistic proposal for diazo compound addition reactions to aldehydes: When the diazo functional group is added to the aldehyde, the negatively charged carbon nearby to the diazo functional group can act as a nucleophile, and a tetrahedral diazonium alkoxide intermediate is formed. There are

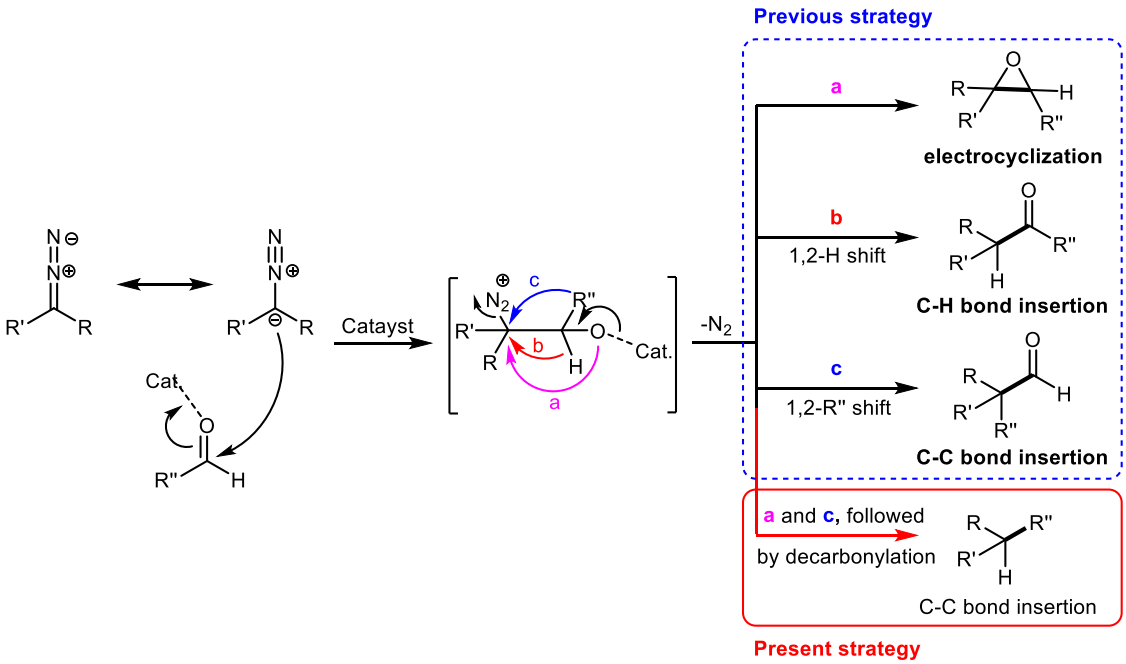


Figure 16. Reactions of diazo compounds with aldehydes

three possible outcomes: (a) a formal C-H insertion (1,2-H shift), (b) a formal C-C insertion (1,2-C shift) or (c) epoxide formation with sequential N_2 extrusion. Several protocols have been established to construct selective C-H or C-C bond insertions, the majority of which depended on Lewis acid catalysis. The Lewis acid catalyst's function is to enhance the aldehyde. However, the 1,2-carbon shift has been scarcely reported in involving the diazo functionality.

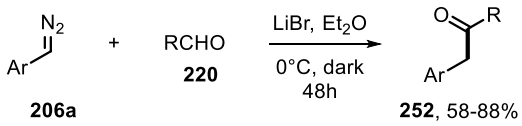
The detailed literature reports for diazocarbonyl compounds, aldehydes and its reactions will be covered in the following sub-sections.

3.1.1. Reactions of diazocarbonyl compounds with aldehydes

3.1.2. Synthesis of 3-aryloxindoles

3.1.1. Reactions of diazocarbonyl compounds with aldehydes

Lithium bromide catalyzed[159] C-H insertion reaction of aldehydes **202** with aryl diazomethanes **206a** in the presence of tenfold excess of lithium bromide in diethyl ether afforded C-H insertion products **252** (Scheme 92).

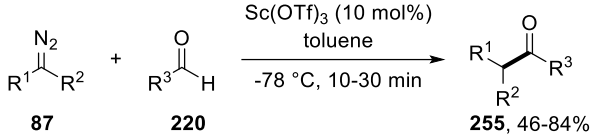


Scheme 92

Xu and co-workers have developed[160] a mild synthesis of β-ketonitriles **254** by effectively affecting a specific 1,2-H shift in the $BF_3{\cdot}OEt_2$-catalyzed reactions of aromatic aldehydes **220** with diazoacetonitrile **253**. With this method, a series of structurally diverse β-ketonitriles **254** was readily synthesized in 48–87 % yield (Scheme 93).

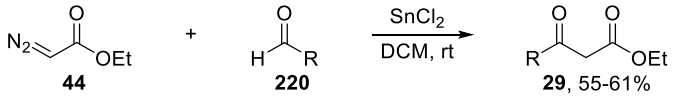
Scheme 93

Kingsbury and co-workers have reported[161] a reliable protocol for the formal incorporation of non-stabilized diazo compounds **87** into aldehydes **220**. The substituted aldehyde **220** reacted with diazo compounds **87** in the presence of $Sc(OTf)_3$ to afford the unsymmetrical ketones **255** *via* C-H insertion reaction (Scheme 94).



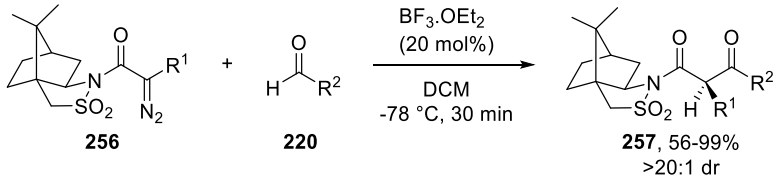
Scheme 94

Roskamp and co-workers have explored[162] the reaction of ethyl diazoacetate **44** with aldehydes **220** yielding β-ketoesters **29** with moderate to good yields. This method is efficiently useful to prepare β-ketoesters **29** from diazoacetate **197c** in the presence of $SnCl_2$ as a catalyst (Scheme 95).

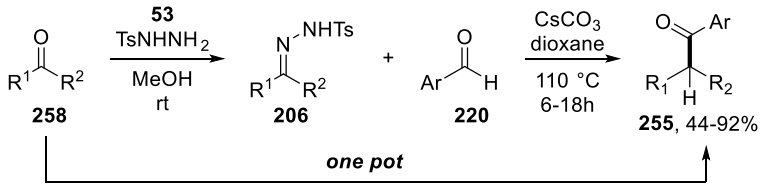


Scheme 95

An asymmetric redox C-C bond insertion reaction between α-diazocarbonyl compounds **256** and aldehydes **220** has been developed[163] as a useful and general procedure for the creation of α-alkyl-β-keto imides **257** acquiring tertiary stereogenic center (Scheme 96).



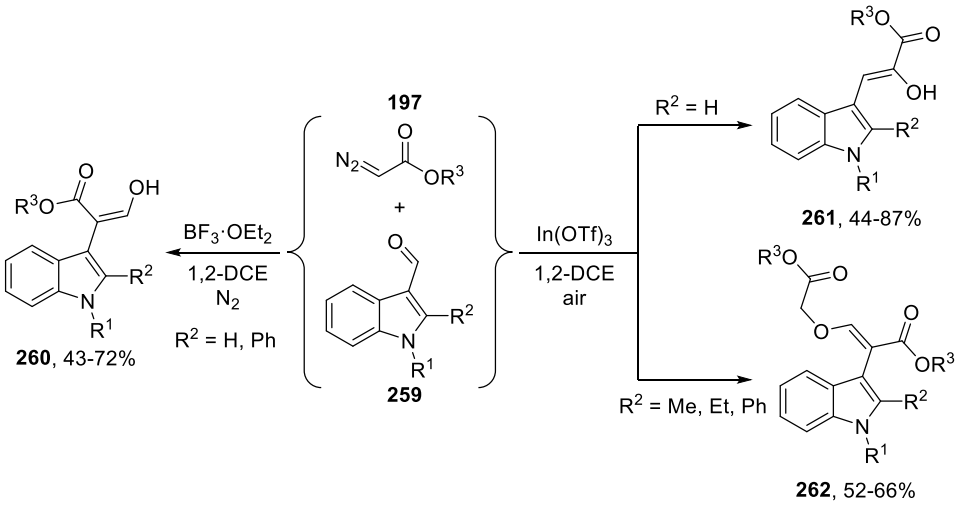
Scheme 96



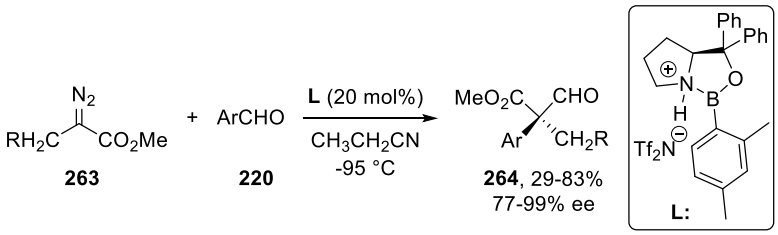
Scheme 97

Allwood and co-workers have reported[164] a method to obtain aromatic ketones **255** from the reaction of aromatic aldehydes **220** with tosylhydrazones **53** in fair to good yield for a wide range of substrates (Scheme 97).

An effective method for the direct transformation of 3-formylindoles **259** with diazo esters **197** catalyzed by $BF_3{\cdot}OEt_2$ and $In(OTf)_3$ has been reported[165] for the synthesis of various and functionalized indolyl acrylates **260-262**. By using a catalyst and substituent controlled, regio- and stereoselective sequence reaction, this one-pot methodology yielded (*Z*)-3-hydroxy-2-indolyl acrylates **260,** (*Z*)-*α*-hydroxy-β-indolyl acrylates **261** and (*E*)-β-(2-alkoxy-2-oxoethoxy)-indolyl acrylates **262** (Scheme 98).



Scheme 98

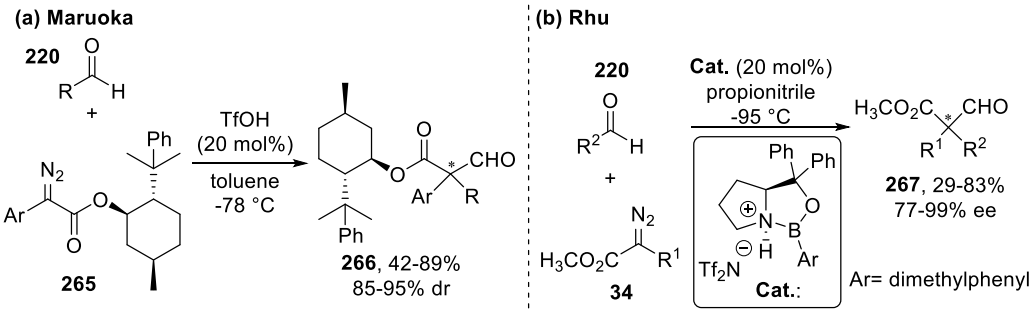


Scheme 99

Rhu and co-workers have described[166] an enantioselective method to synthesize all-carbon quaternary functionalized acyclic systems **264** *via* (S)-oxazaborolidinium ion promoted formal C-C insertion reactions of diazoesters **263** into aryl aldehydes **220**

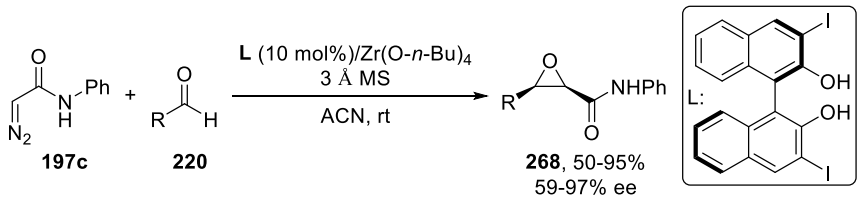
bonds. In the presence of chiral boron Lewis acid-catalyzed, the reaction proceeded with better yield, excellent regioselectivity and enantioselectivity (Scheme 99).

Maruoka, Rhu and co-workers have successfully reported[167] the asymmetric formal C-C bond insertion reaction into aldehydes **220** with the stereoselective formal insertion of aryldiazoacetates **34/265** into aromatic/unsaturated aldehydes **220** by TfOH or oxazaborolidinium ion catalyst (Scheme 100). The α-quaternary-β-ester aldehydes **266/267** were isolated in good yields with high diastereoselectivity for the majority of substrates.

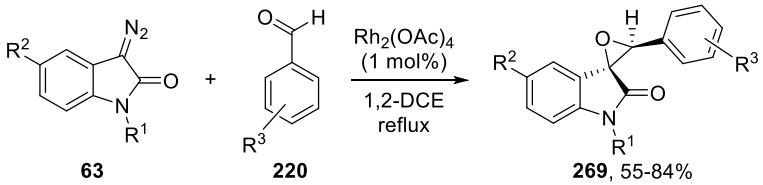


Scheme 100

An asymmetric Darzens reaction[168] of diazo-N,N-dimethylacetamide **19c** with aldehydes **220** catalysed by stable chiral zirconium derived Lewis acid catalyst was demonstrated from tetrabutoxyzirconium and 3,3'-diiodobinaphthol to furnish *cis*-glycidic amides **268** in good yields with excellent enantioselectivity (Scheme 101).



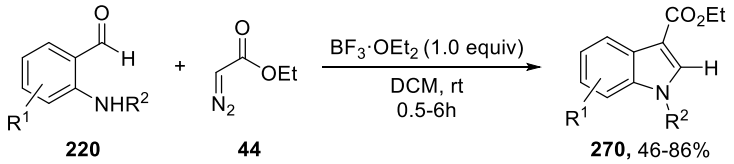
Scheme 101



Scheme 102

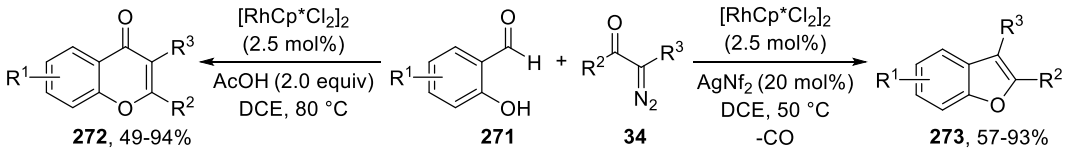
Our group has explored[169] the synthesis of intermolecular stereoselective epoxides **269** from the reaction of cyclic diazoamides **63** with aryl aldehydes **220** catalyzed by rhodium(II) acetate. A range of spiro-indolooxiranes **269** has been synthesized using the described method. This method yielded bis-spiro-indolooxiranes when aryl dialdehydes were used as starting materials (Scheme 102).

Fournier and co-workers have investigated[170] an efficient method for 3-ethoxycarbonylindoles **270**. The indole ring system was easily achieved by adding ethyl diazoacetate **44** to 2-aminobenzaldehydes **220**. This enabled the synthesis of various indole scaffolds from readily available anthranilic acids and 2-aminobenzaldehydes (Scheme 103).



Scheme 103

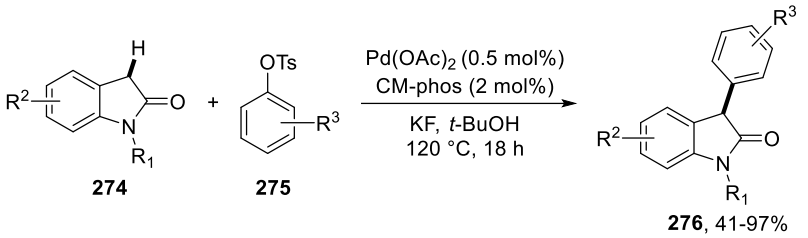
Lin, Yao and co-workers have described[171] a controllable Rh/Ag-catalyzed cyclization of α-diazocarbonyl compounds **34** with salicylaldehydes **271**, resulting in the different synthesis of chromones **272** and benzofurans **273**. Benzofurans **273** were obtained *via* C–H activation, decarbonylation, annulation process, whereas AcOH produced chromones **272** *via* C–H activation and annulation route. The reaction was demonstrated for the tolerance of functional groups and scalable (Scheme 104).



Scheme 104

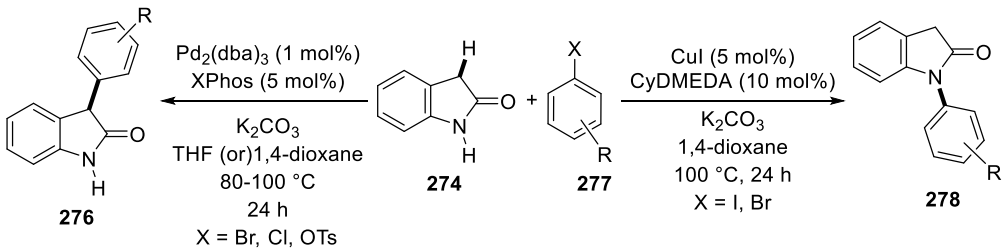
3.1.2. Synthesis of 3-aryloxindoles

Kwong and co-workers have reported[172] the $Pd(OAc)_2$-catalyzed selective 3-arylation of 2-oxindoles **274** with aryl tosylates **275**. The resulted 3-arylated oxindoles **276** could be achieved in good yield using the Pd/CM-phos catalyst system (Scheme 105).



Scheme 105

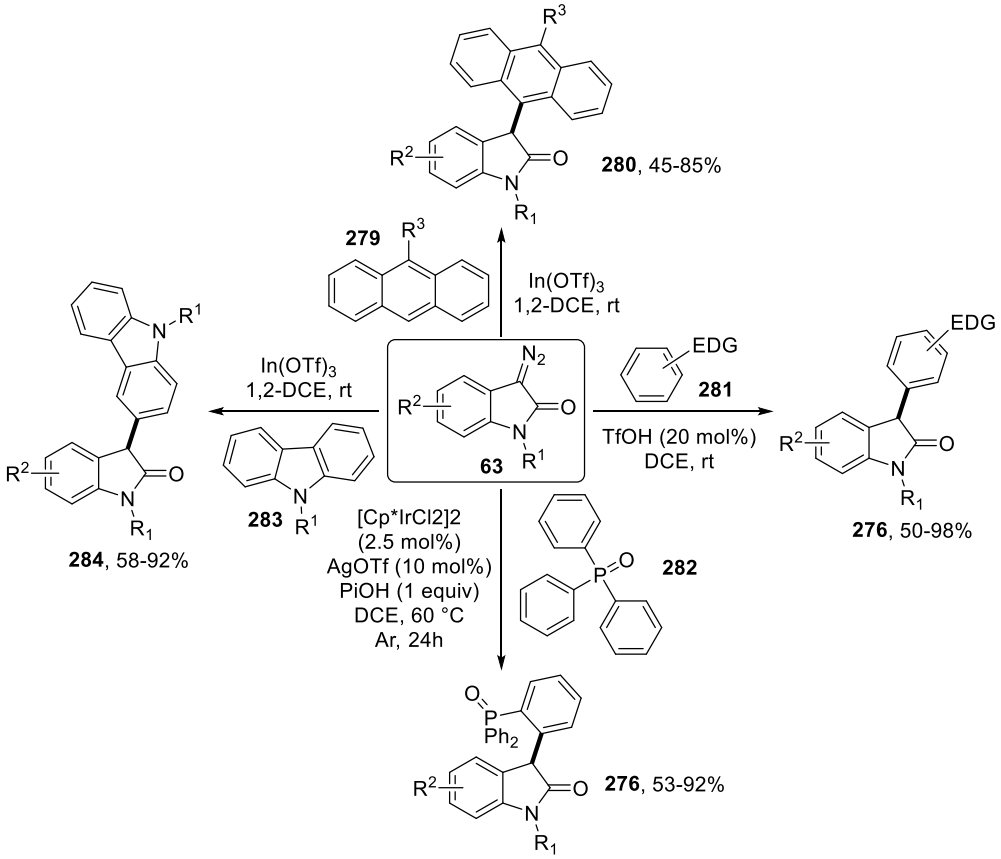
Buchwald and co-workers have discovered[173] the Cu and Pd-catalyzed cross-coupling reactions for the selective N- and C-arylation of oxindoles **274**. An orthogonal chemoselectivity was obtained in cross-coupling reactions of unprotected oxindoles **274** with aryl halides **277** in the presence of Cu and Pd-based catalyst systems. A Pd-based catalyst method for arylated oxindoles **276** with chemoselectivity at 3-position, whereas a Cu-based catalyst method arylated solely at the N-position (Scheme 106).



Scheme 106

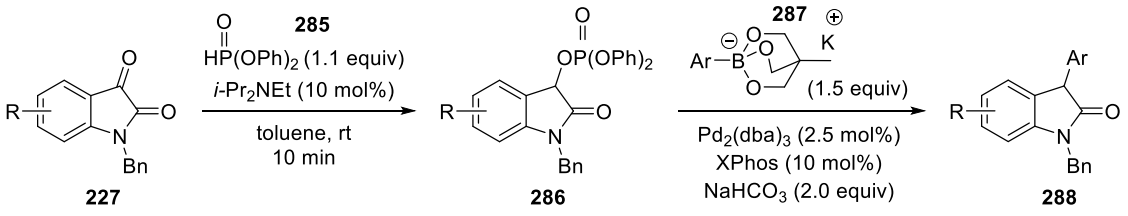
Hu and co-workers have performed[174a] the insertion reaction to C-H bonds of electron-rich arenes **281** with diazoamides **63**. Lee and co-workers reported[174b] the $In(OTf)_3$-catalyzed direct arylation reaction of diazoamides **63** with anthracenes **279** or carbazoles **283** to yield 3-anthracenyloxindoles **280** and 3-carbazolyloxindoles **284**. Yang and co-workers demonstrated[174c] the Ir(III)/Ag-catalyzed direct C–H insertion of

triphenylphosphine oxide **282** with diazoamides **63** to furnish a variety of 3-(2-(diphenylphosphoryl)phenyl)indolin-2-ones **276** (Scheme 107).



Scheme 107

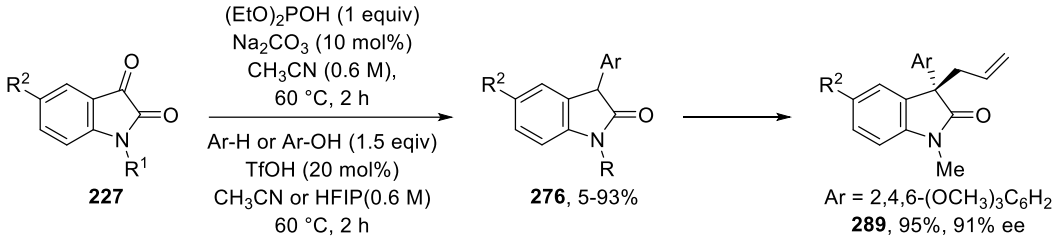
An efficient synthesis of 3-aryloxindoles **276** from isatin derivatives **227** has been developed.[175] The method entails forming an oxindole **286** with a phosphate moiety **285** at C-3 position through the [1,2]-phospha-Brook rearrangement caused by Pd-catalyzed cross-coupling with aryl boron salts **287** (Scheme 108).



Scheme 108

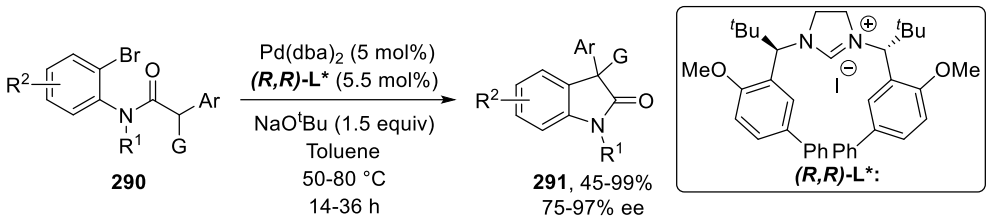
3-Aryloxindoles **276** were obtained[176] from isatin **227** *via* a two-step mechanism involving a phospha-Brook rearrangement followed by Friedel-Crafts alkylation in a

single-step process. Furthermore, the use of arylated products **276** was demonstrated in asymmetric allylation and then protonation *via* decarboxylation (Scheme 109).



Scheme 109

Kundig and co-workers have reported[177] the $Pd(dba)_2$-catalyzed asymmetric intramolecular 3-arylation of amide enolates **290** resulting chiral 3-alkoxy/3-aminooxindoles **291** in high yield with good enantioselectivity when a new five-membered chiral N-heterocyclic complex ligand was used (Scheme 110).



Scheme 110

Aromatic compounds having multiple C-H bonds make site-selective functionalization of C-H bonds a challenging task. Site-selective functionalization of C-H bonds is a most attractive strategy as it tolerates efficient and reliable getting into target molecules. During the past few years, *ortho/meta* or *para* site-selective C-H activation of the aromatic compound was effectively demonstrated using a catalyst, steric, electronic, and directing group effects.[178] Directing groups play a vital role in C-H activation reactions which offers site-selective functionalization through chelation assistance for *ortho*-functionalization. However, C-H bond direct *meta*-selective functionalization is still a challenging task in synthetic pathway.

Salicylaldehyde derivatives have been employed as versatile building blocks for the preparation of chromones and benzofurans *via* hydroxyl-directed aldehyde C(sp^2)-H annulation and activation of aldehydic C(sp^2)-H bond functionalization has gained considerable attention (Figure 17).[179] C-H-activation of the aryl ring system of salicylaldehyde derivatives is not yet been reported.

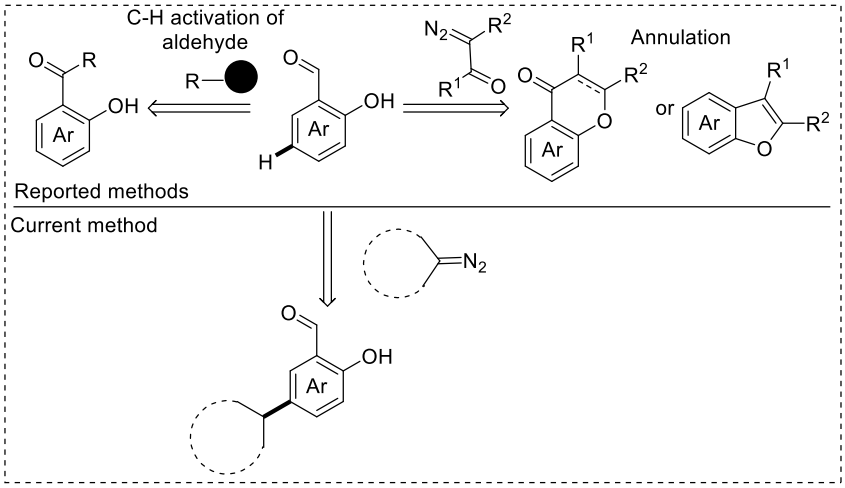


Figure 17. Functionalization of salicylaldehydes

Scope and objectives: Based on the above literature, one-pot reactions of diazocarbonyl compounds with aryl aldehydes provided a competitive synthesis of ketones (C-H insertion, 1,2-H shift), homologated aldehydes (C-C insertion, 1,2-C shift), epoxide products (electrocyclization) and construction of various heterocycles when subjected to nature of the diazo compound and substituent of the starting metrical. There have been several effective approaches for formal insertion reactions using stabilized diazo compounds in the literature. On the other hand, non-stabilized diazoalkanes have received less attention. C-H Insertion and 1,2-H shift yielded products for a wide range of aldehydes in the presence of Lewis acid as a catalyst. In comparison to formal C-C insertion reactions into aldehydes, formal C-H insertions have significantly known in the literature. 3-Aryloxindoles are ubiquitous subunits found in a broad range of natural products and biologically active molecules and show antiviral, anti-bacterial and anti-carcinogenic properties. Therefore, the objectives of the present work are mainly focused on the metal-free synthesis of 3-aryloxindoles from diazoamides and aryl aldehydes *via* decarbonylation.

The objectives of the present work are the following:

- To study the involvement of diazoamides and aryl aldehydes or chelating aldehydes in the presence of Lewis acids.
- To develop an unprecedented transition metal-free one-pot method for the synthesis of 3-aryloxindoles.
- To utilize the electron-withdrawing nature of aryl aldehydes act as an arylation reagent for the synthesis of 3-aryloxindoles.

RESULTS AND DISCUSSION

3.2. Lewis acid catalyzed synthesis of 3-arylated oxindoles

Oxindole unit is a significant core structure in several medicinal molecules and natural naturally occurring substances. 3-Aryloxindoles are synthetically interesting as they have found various applications in biology and pharmaceutical chemistry[180] (Figure. 18). These molecules have shown to have potent bioactivity in drug discovery, for instance, as a neuroprotective agent,[181] as a potent growth hormone secretagogue,[182] an anti-cancer agent[183] and a nootropic drug.[184] 3-Aryloxindoles are mostly used as precursors for the synthesis of 3,3-disubstituted oxindole or indoline derivatives, which form the core of a large number of natural products and pharmaceutical agents.[174a,185] The synthesis of 3-aryloxindoles has been known via Grignard reagents with isatin,[186] palladium-catalyzed intramolecular cyclizations of 3-aryl acetanilides,[177] palladium-catalyzed reactions of oxindoles with aryl boron reagents,[172,173,187] Ni, Fe(III), Ir(III) or Sc(III)-catalyzed 3-arylation of 2-oxindoles[188] and the TfOH-catalyzed[174a] reaction of 3-diazooxindoles. Among these methods, most substrates scope of electron-donating groups is better tolerated than electron-withdrawing groups. These methodologies

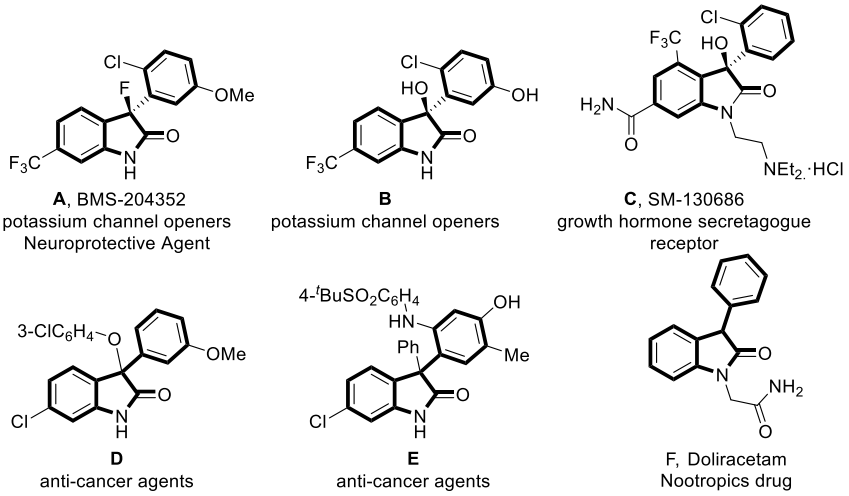


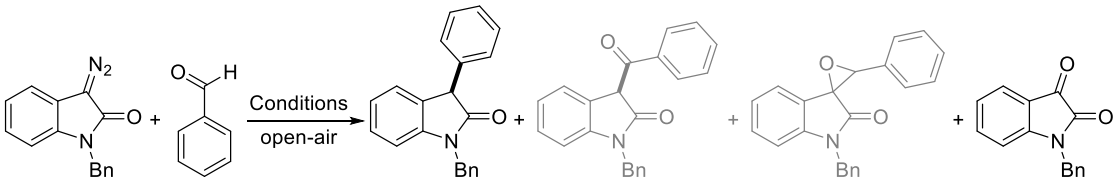
Figure 18. 3-Aryloxindole motif in bioactive molecules and natural products

require the use of air-sensitive and expensive transition-metal reagents, arylating agents (aryl halides, tosylates, arylboronic acids, arylboroxines and electron-rich arenes), additives, harsh reaction conditions, an inert atmosphere or multistep synthesis. The main focus of this chapter is an atom-economical tandem reaction that can provide a wide variety of different substituted 3-aryloxindoles **276** from diazoamides **63** and aryl aldehydes **220** in the presence of 20 mol% of $BF_3.OEt_2$ at 0 °C under an open-air atmosphere.

To establish the arylation methodology, diazoamide **63a** and benzaldehyde **220a** were selected as model substrates. Initial studies on the reaction of **63a** (1 equiv) and **220a** (1.1 equiv) in the presence of 20 mol% of $Sc(OTf)_3$ under an open-air atmosphere in dichloromethane (DCM) at room temperature for 2h showed that 3-aryloxindole **276a** was obtained in 56% yield (Table 7, entry 1), which is quite different from our earlier[169] work on the synthesis of spiro-indolooxiranes *via* the reaction of diazoamides and aryl aldehydes in the presence of rhodium acetate as a catalyst (Scheme 1). Product **276a** was characterized based on spectral data (NMR & HRMS) and the absence of aldehyde group was observed. In ^{1}H-NMR spectrum (Figure 19), the singlet, ABq peaks appeared at δ 4.80 and 5.04 ppm which indicated the newly generated CH proton and NCH_2 protons. The remaining aromatic protons appeared at 6.88 to 7.44 ppm. In ^{13}C-NMR spectrum (Figure 20), the amide carbonyl carbon showed a peak at δ = 176.2 ppm. The newly generated CH carbon appeared at 52.2 and 44.0 ppm indicating the NCH_2 carbon. Because of the presence of symmetry in the part of the molecule, ^{13}C-NMR contains fewer carbon signals than expected. The high-resolution mass spectrum showed the required molecular ion peak at 300.1383 m/z. The arylation product **276a** was obtained possibly *via* 1,2-aryl migration with high selectivity followed by

decarbonylation, as depicted in Fig. 16. No other competitive reactions *via* 1,2-H shift or epoxide was observed. We screened the reaction conditions by changing the catalyst, solvent, temperature, time, etc. To optimize the reaction conditions, various Lewis acids such as $In(OTf)_3$, $AlCl_3$, $FeCl_3$ and $SnCl_4$ were investigated (Table 7, entries 2–5). No superior results were obtained when the reaction was performed in the presence of $TiCl_4$ or silica gel (Table 7, entries 6 and 7). $TiCl_4$ provided isatin **227a** in 80% yield.

Table 7. Optimization of reaction conditions for the formation of **276a**[a]



63a **220a** *via* 1,2-Aryl shift **276a** *via* 1,2-H shift Not detected *via* electrocyclization Not detected **227a**

Entry	Catalyst (20 mol%)	Solvent	T (°C)	t (h)	Yield [%][b] **276a/227a**
1	$Sc(OTf)_3$	DCM	rt	2	56/0
2	$In(OTf)_3$	DCM	rt	2	42/0
3	$AlCl_3$	DCM	rt	2	15/0
4	$FeCl_3$	DCM	rt	2	48/0
5	$SnCl_4$	DCM	rt	2	18/0
6	$TiCl_4$	DCM	rt	2	0/80
7	Silica gel	DCM	rt	10	nr[c]
8	$BF_3{\cdot}OEt_2$	DCM	rt	2	74/0
9	$B(C_6F_5)_3$	DCM	rt	2	nd[d]
10	$Tr(BF_4)$	DCM	rt	2	37/0
11	*p*-TSA	DCM	rt	2	41/0
12	TfOH	DCM	rt	2	59/0
13	Con.HCl	DCM	rt	2	43/11
14	$BF_3{\cdot}OEt_2$	$CHCl_3$	rt	2	59/0
15	$BF_3{\cdot}OEt_2$	ACN	rt	2	23/0
16	$BF_3{\cdot}OEt_2$	Benzene	rt	2	35/0
17	$BF_3{\cdot}OEt_2$	Toluene	rt	2	19/0
18	$BF_3{\cdot}OEt_2$	DCM	rt	0.5	75/0
19	$BF_3{\cdot}OEt_2$	DCE	reflux	2	30/0
20	**$BF_3{\cdot}OEt_2$**	**DCM**	**0**	**0.5**	**88/0**
21[e]	$BF_3{\cdot}OEt_2$	DCM	0	0.5	87/0
22	$BF_3{\cdot}OEt_2$	DCM	-20	0.5	47/0
23	$BF_3{\cdot}OEt_2$	DCM	0	0.5	46/0[f] or 81/0[g]
24	-	DCM	0	24	nr[c]

[a]Reaction conditions: The reaction was carried out by adding 20 mol% of catalyst to a solution of diazoamide **63a** (0.40 mmol) and aldehyde **220a** (0.44 mmol) under an open-air atmosphere at 0 °C. [b]Isolated product. [c]No reaction. [d]No desired product. [e]Reactions were carried out under an oxygen or argon atmosphere in dry DCM. [f]10 mol% of $BF_3{\cdot}OEt_2$. [g]30 mol% of $BF_3{\cdot}OEt_2$.

Various boron catalysts, such as $BF_3{\cdot}OEt_2$, $B(C_6F_5)_3$ and $Tr(BF_4)$, were examined (Table 7, entries 8-10); among them, $BF_3{\cdot}OEt_2$ was efficiently used for the reaction between **63a** and **220a** to afford product **276a** in a remarkable yield (Table 7, entry 8). Interestingly, Brønsted acids such as *p*-TSA or TfOH could promote this reaction but in moderate yield (Table 7, entries 11 and 12). The target product **276a** was obtained in 43% yield along with 11% of isatin **227a** as a by-product when con. HCl was used as a catalyst (Table 7, entry 13). DCM was found to be the best solvent compared to other solvents, namely; chloroform, acetonitrile, benzene or toluene (Table 7, entries 14–17). Shorter reaction duration provided a better yield of product **276a** (Table 7, entry 18). The yield of product **276a** did not improve even at reflux conditions. (Table 7, entry 19); however, the yield was improved at 0 °C (Table 7, entry 20). The reaction was performed under an oxygen or argon atmosphere in dry DCM to furnish **276a** in 87% yield (Table 7, entry 21). Upon further reducing the temperature to -20 °C, the yield of product **276a** was reduced (Table 7, entry 22). Reducing or increasing the amount of the catalyst did not explicitly improve the yield of the product **276a** (Table 7, entry 23). No reaction took place in the absence of a catalyst (Table 7, entry 24). Hence, the optimized reaction conditions for the formation of **276a** were found to be 20 mol% of $BF_3{\cdot}OEt_2$ in DCM at 0 °C under an open-air atmosphere (Table 7, entry 20). It is worth noting that the reaction is tolerant in an open-air atmosphere. The generality and scope of this interesting protocol for accessing 3-aryloxindoles was investigated. With the optimized reaction conditions in hand, we next examined the scope of $BF_3{\cdot}OEt_2$ catalyzed arylation reactions with a wide range of electron-donating or electron-withdrawing aryl aldehydes. Based on the literature, the major issue identified was the presence of functional-group tolerance or strong electron-withdrawing substituents

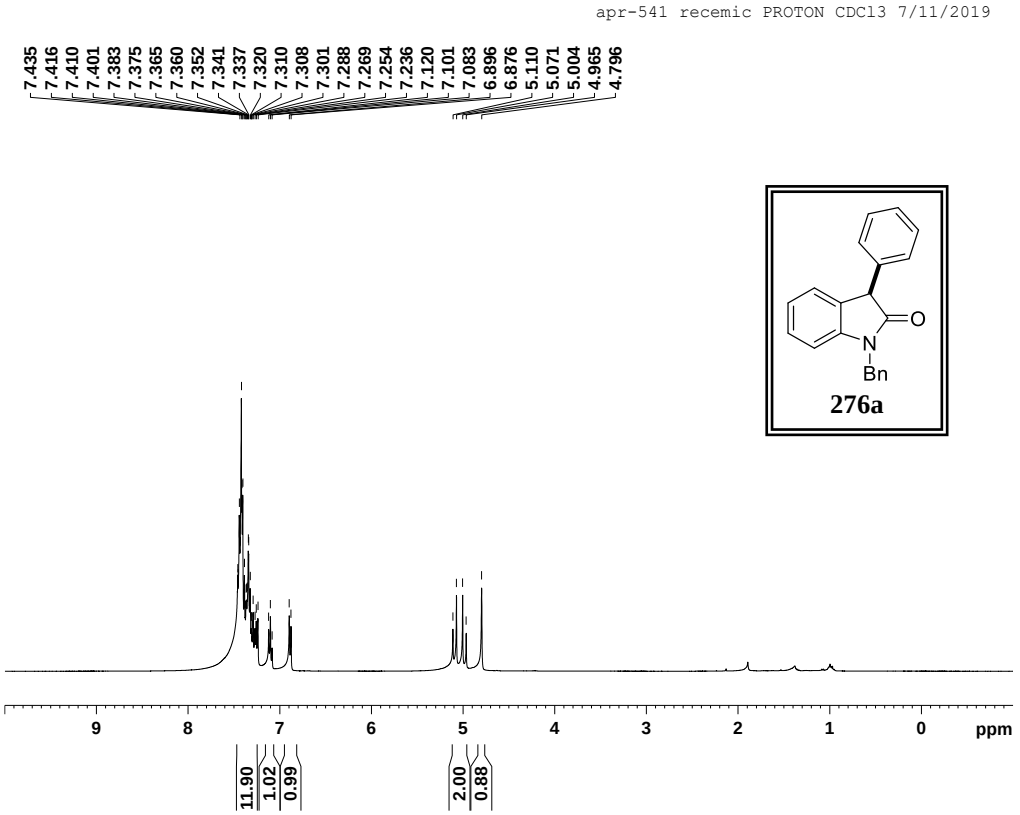


Figure 19. ^{1}H NMR (δ) spectrum of **276a**

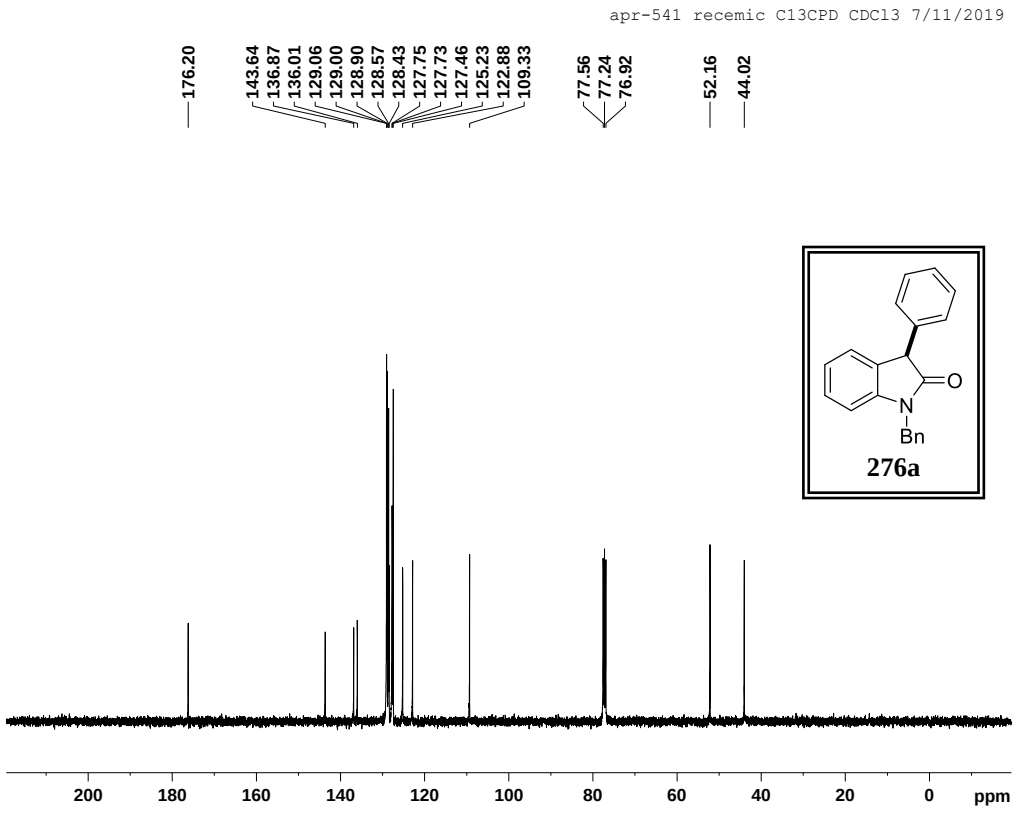
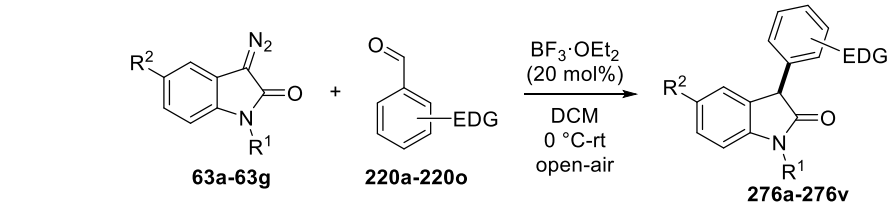
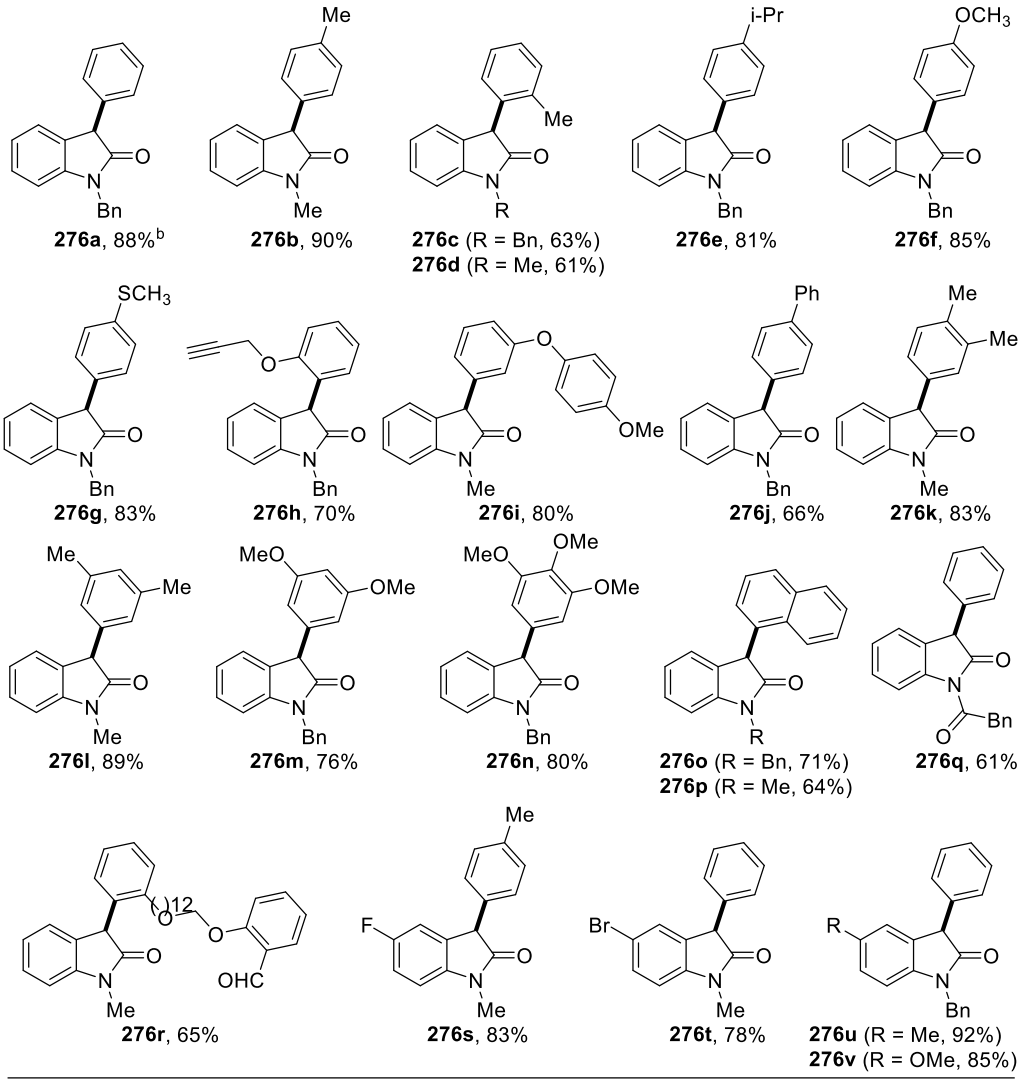


Figure 20. ^{13}C NMR (δ) spectrum of **276a**

in the reported methods. The substituent effect on the diversity of aryl aldehydes was employed in this transformation. Next, the reaction afforded various 3-aryloxindoles **276b-v** from diazoamides **63a-g** and electron-donating aryl aldehydes **220a–o** *via* 1,2-aryl migration followed by decarbonylation, as shown in Table 8. The reaction of 4-methylbenzaldehyde provided **276b** in 90% yield. The reaction with 2-methylbenzaldehyde furnished **276c** and **276d** in moderate yields and *ortho*-CH_3 appeared[189] as a broad singlet instead of a sharp singlet, probably due to steric and electronic effects. The reaction with 4-isopropylbenzaldehyde gave the corresponding product **276e** in good yield. A similar reaction with 4-methoxybenzaldehyde and 4-(methylthio)benzaldehyde yielded the desired products **276f** and **276g** in good yield, respectively. The presence of sterically hindered *O*-propargylated salicylaldehyde afforded the corresponding 3-aryloxindole **276h** in a moderate yield. Product **276i** was obtained in a good yield when 3-(4-methoxyphenoxy)benzaldehyde was used. The reaction with biphenyl-4-carbaldehyde provided the desired product **276j** in a moderate yield. The reaction with disubstituted benzaldehydes, 3,4-dimethylbenzaldehyde, 3,5-dimethylbenzaldehyde or 3,5-dimethoxybenzaldehyde afforded products **276k-m** in good yields, respectively. When trisubstituted 3,4,5-trimethoxybenzaldehyde was used, product **276n** was obtained in good yield. The reaction employing 1-naphthaldehyde also gave the corresponding 3-aryloxindoles **276o**,**p** in moderate yields. No reaction occurred when 9-anthracenecarboxaldehyde, 1-methyl-1*H*-indole-3-carbaldehyde or cinnamaldehyde was used. To satisfy our curiosity, reactions with aliphatic aldehydes were also investigated. Towards this end, propionaldehyde, pivaldehyde or cyclohexanecarboxaldehyde was utilized in these reactions, but in vain. Subsequently, N-benzoyl substituted diazoamide **63c** smoothly furnished the desired product **276q** in

Table 8. Synthesis of 3-aryloxindoles **276a-v** having Ar-EDG modification[a,b]



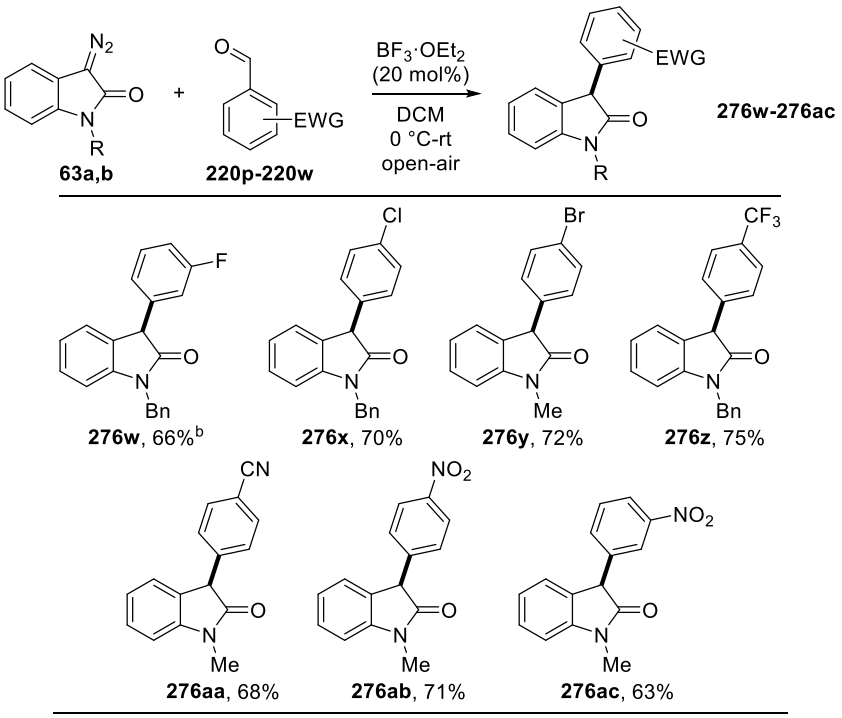


[a]Reaction conditions: Equimolar amount of **63** and **220**, $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2 (5 mL), 0 °C. [b]Isolated yield based on **63**

61% yield. Furthermore, diazoamide **63b** (1 equiv) was reacted with *bis*-arylaldehyde **220o** (0.5 equiv) to furnish *mono*-3-aryloxindole **276r** in 65% yield. Besides, the effect of the substituents of diazoamides **63** was examined. Halo-substituted diazoamides **63d** and **276e** were also found to be feasible substrates to obtain 3-aryloxindoles **276s,t** in good yields. Electron-donating diazoamides **63f,g** gave the desired products **276u,v**.

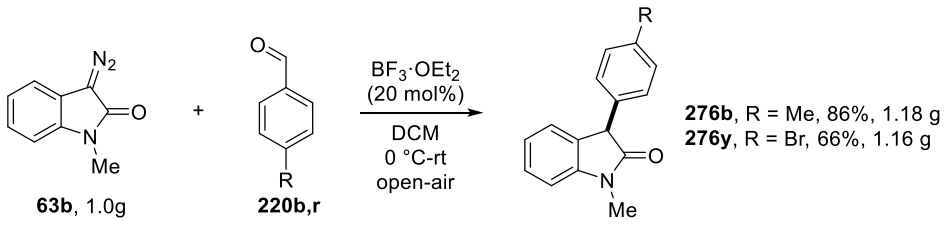
The electron-deficient arenes generally performed[157a,174-177,180,187b,190] poorly than electron-rich arenes due to steric and electronic factors on the aryl ring system. Thus, electron-withdrawing substituents on arenes are rarely reported in the presence of expensive metal catalysts, stoichiometric amounts of reagents or harsh conditions. The present protocol is effective for both electron-donating and -withdrawing aryl aldehydes. Aryl aldehydes having trifluoro, nitrile or nitro substituents are viable substrates for this transformation (Table 9). 3-Fluorobenzaldehyde was also used in this reaction to afford the corresponding product **276w**. 4-Chloro- or Bromo-benzaldehyde was also tolerated to furnish the corresponding products **276x,y** in moderate yields. 4-(Trifluoromethyl)benzaldehyde having a strong deactivating CF_3 group at *para*-position was also well-tolerated to produce the expected product **276z** in 75% yield. The strong electron-withdrawing CN or NO_2 substituent on benzaldehyde was also examined to obtain the desired products **276aa-ac** in moderate yields.

Table 9. Synthesis of 3-aryloxindoles **276w-276ac** having Ar-EWG modification[a,b]

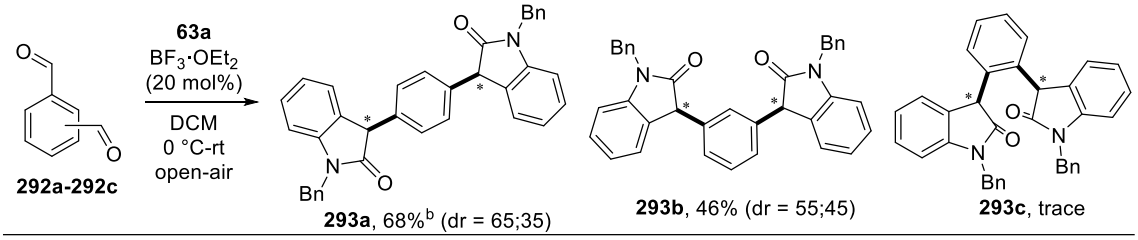


[a]Reaction conditions: Equimolar amount of **63** and **220**, $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2 (5 mL), 0 °C. [b]Isolated yield based on **63**.

To reveal the reliability and practicality of the present decarbonylative arylation methodology, gram-scale experiments were carried out with diazoamide **63b** and 4-methylbenzaldehyde under the optimized conditions to afford the corresponding product **276b** in moderate yield (Scheme 111). To improve the yield, a solution of **63b** was introduced[191] through a syringe pump with a flow rate (5 mLh^{-1}) to afford **276b** in 86% yield. Similarly, 3-aryloxindole **276y** was also prepared. Of note, the gram-scale synthesis required the controlled addition of diazoamide to improve the yield.



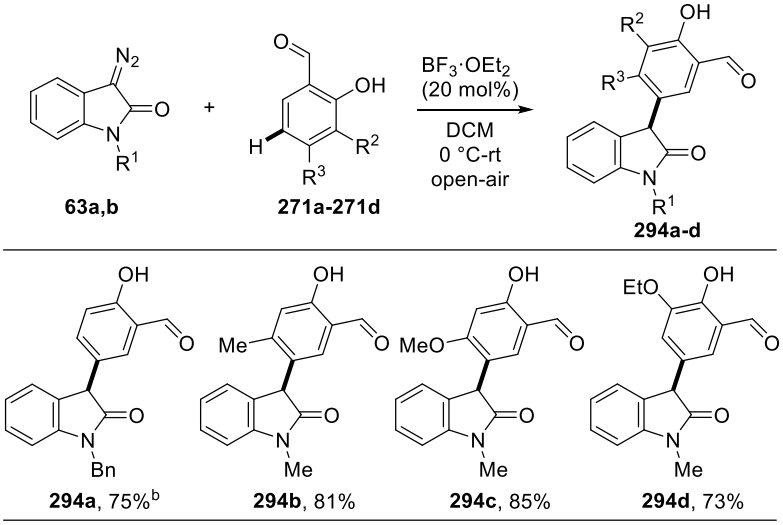
Scheme 111. Gram scale preparation of 3-aryloxindoles **276b** and **276y**



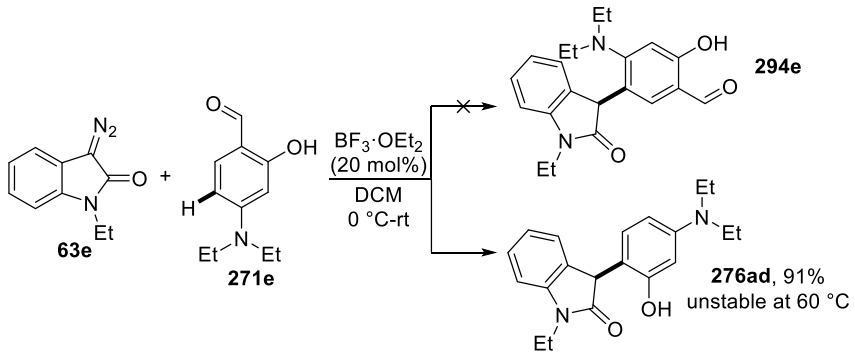
[a]Reaction conditions: **63a** (0.40 mmol), **292** (0.20 mmol), $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2 (5 mL), 0 °C. [b]Isolated yield based on **292**. [c]Based on ^{1}H-NMR.

Scheme 112. Synthesis of *bis*-3-aryloxindoles **293a-c**.[a,b]

The scope of this process was further similarly extended to *bis*-3-arylaldehydes **292a-292c**. Towards this end, terephthalaldehyde **292a** was reacted with 2 equiv of diazoamide **63a** in the presence of 20 mol% of $BF_3{\cdot}OEt_2$ as a catalyst to furnish the corresponding *bis*-3-aryloxindole **293a** in 68% yield as a mixture of diastereomers in the ratio of 65:35. Similarly, isophthalaldehyde **292b** was used as the substrate to give the corresponding *bis*-3-aryloxindole **293b** in 46% yield as a mixture of diastereomers in the ratio of 55:45. The sterically demanding *o*-phthalaldehyde **292c** provided **293c** in a trace amount (Scheme 112).



[a]Reaction conditions: Equimolar amount of **63** and **271**, $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2 (5 mL), 0 °C. [b]Isolated yield based on **63**.

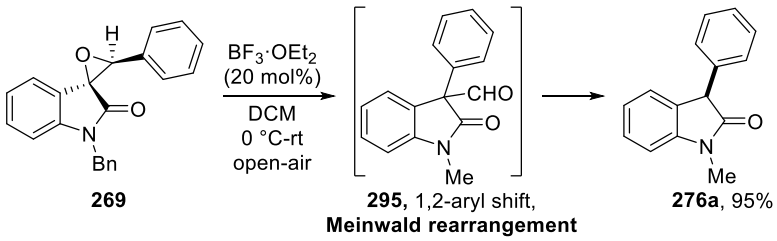


Scheme 113. Synthesis of 3-aryloxindoles **294** and effect of hydroxy substituent.[a,b]

Further investigation of salicylaldehydes **271a-d** with diazoamides **63a,b** was carried out as shown in Scheme 113. The reactions proceeded smoothly to afford *meta* to the aldehyde **271** or *para* to the hydroxy site-selective C-H functionalization products **294a-d** in a chemo- and regioselective manner. Notably, no other competitive reactions of annulation, the epoxide or O-H insertion reaction, were observed.[179] The hydroxy group plays a vital role in the formation of this site-selective C–H functionalization product **294**, which may be due to the presence of intramolecular hydrogen bonding in salicylaldehyde. Product **294a** was characterized based on spectral data (NMR & HRMS). In ^{1}H-NMR spectrum (Figure 21), the singlets appeared at 9.88 and 11.05 ppm which indicated the CHO and OH protons, δ 4.75 ppm indicates the newly generated

CH proton. The remaining aromatic protons appeared in the range of 6.72 to 7.90 ppm. In ^{13}C-NMR spectrum (Figure 22), the amide and aldehyde carbonyl carbons appeared at δ = 175.8 and 196.5 ppm. The newly generated CH appeared at 50.1 ppm and the NCH_2 carbon at 44.1 ppm. However, *O*-propargyl salicylaldehyde provided the corresponding decarbonylative arylation product **276h** instead of the C-H functionalization product **294**.

To further understand the mechanism of arylation process, a control experiment was carried out as shown in Scheme 114. When spiro-indolooxirane[169] **269** was subjected to the reaction conditions, 3-aryloxindole **276a** was obtained in 95% yield *via* the 1,2-aryl shift of **295** followed by decarbonylation, whereas the corresponding product was not observed *via* the 1,2-H shift. This experiment indicates the possibility of the formation of an epoxide intermediate *via* Meinwald rearrangement.



269 **295,** 1,2-aryl shift, **Meinwald rearrangement** **276a**, 95%

Scheme 114. Meinwald rearrangement reaction of epoxide **269**

^{1}H-NMR experiments for the reaction of **63a** and **220a**: To find out the insight into the mechanism, an experiment was planned in a NMR tube. Towards this, an equimolar amount of diazoamide **63a** and benzaldehyde **220a** was dissolved in $CDCl_3$ and the ^{1}H-NMR spectrum was recorded at different time intervals. Initially, -NCH_2 and –CHO protons appeared as a singlet at 5.07 and 10.06 ppm, [Figure 23(i)]. A new aldehyde peak was observed at 9.85 ppm after the addition of 10 μL of $BF_3{\cdot}OEt_2$ into the NMR tube [Figure 23(ii), (iii)]. Then, the peak at 9.85 ppm disappeared after the addition of 10 μL of water into the NMR tube and the formation of a singlet at 4.77 ppm

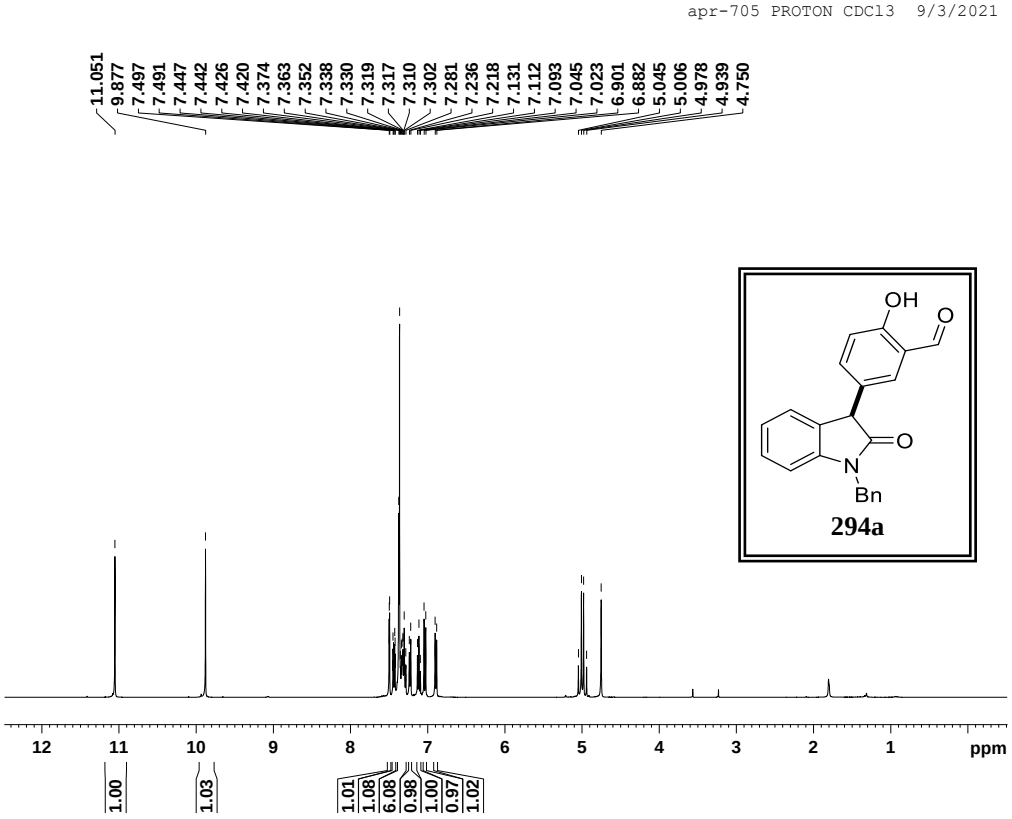


Figure 21. ^{1}H NMR (δ) spectrum of **294a**

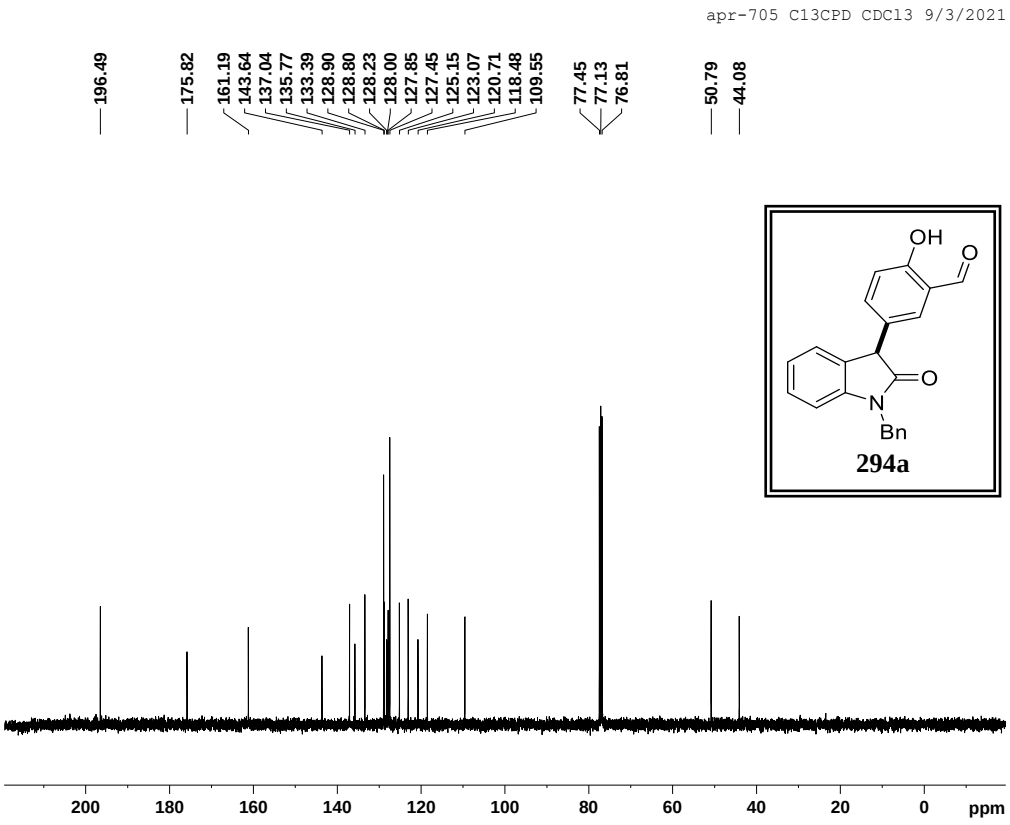
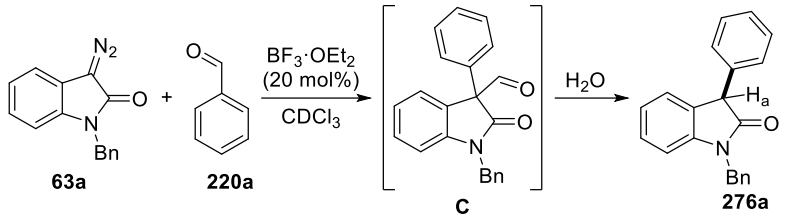
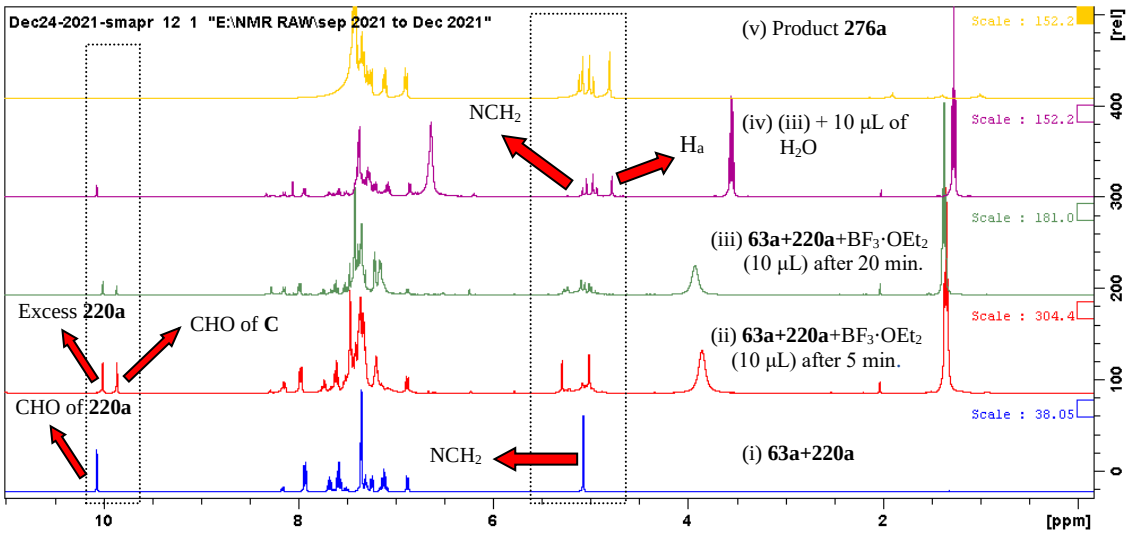
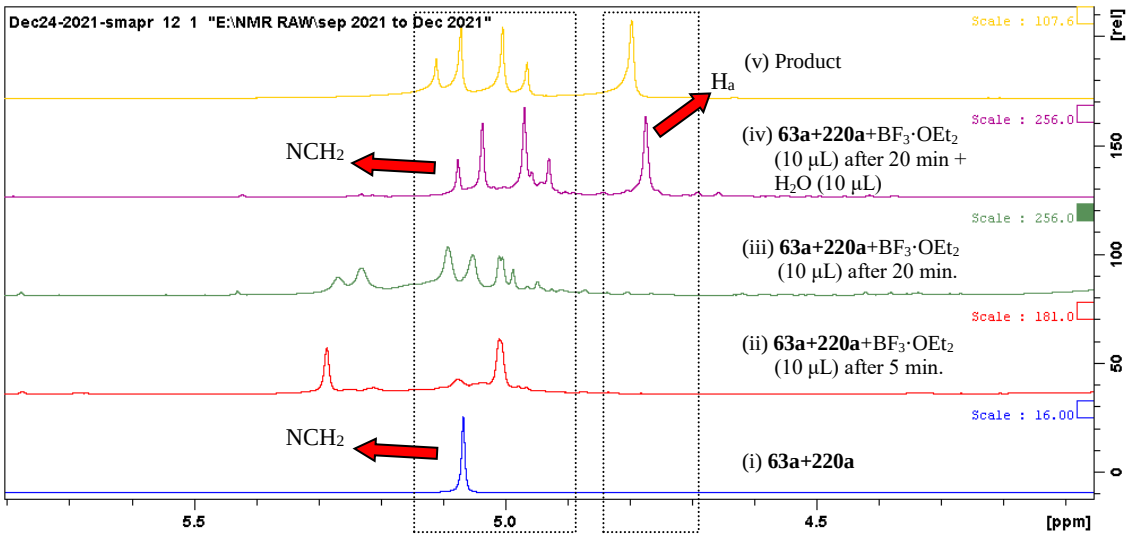


Figure 22. ^{13}C NMR (δ) spectrum of **294a**



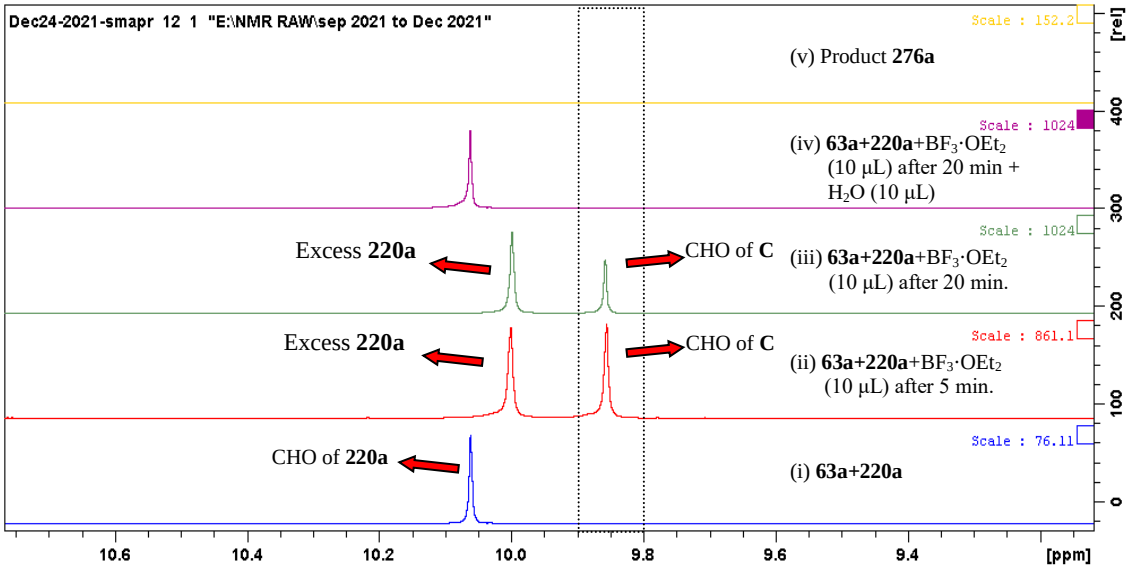




Expansion for NCH_2 peak

[Figure 23(iv)] that is responsible for H_a proton of **276a**.

NMR experiments for the reaction of epoxide **269:** To find out the insight into the mechanism, an experiment was planned in a NMR tube. Towards this, spiro-indolooxirane **269** was dissolved in $CDCl_3$ and the ^{1}H-NMR spectrum was recorded at different time intervals. Initially, NCH_2 and CH protons appeared as an AB quartet and



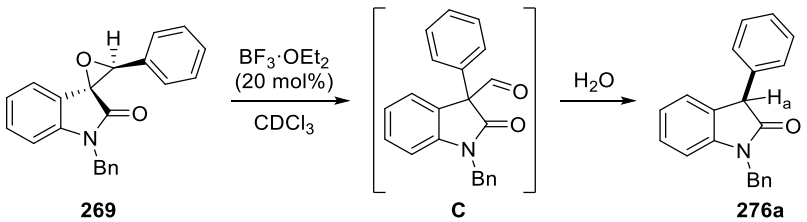
Expansion for aldehyde peak

Figure 23. ^{1}H-NMR spectra of reaction mixture **276a** signals in $CDCl_3$

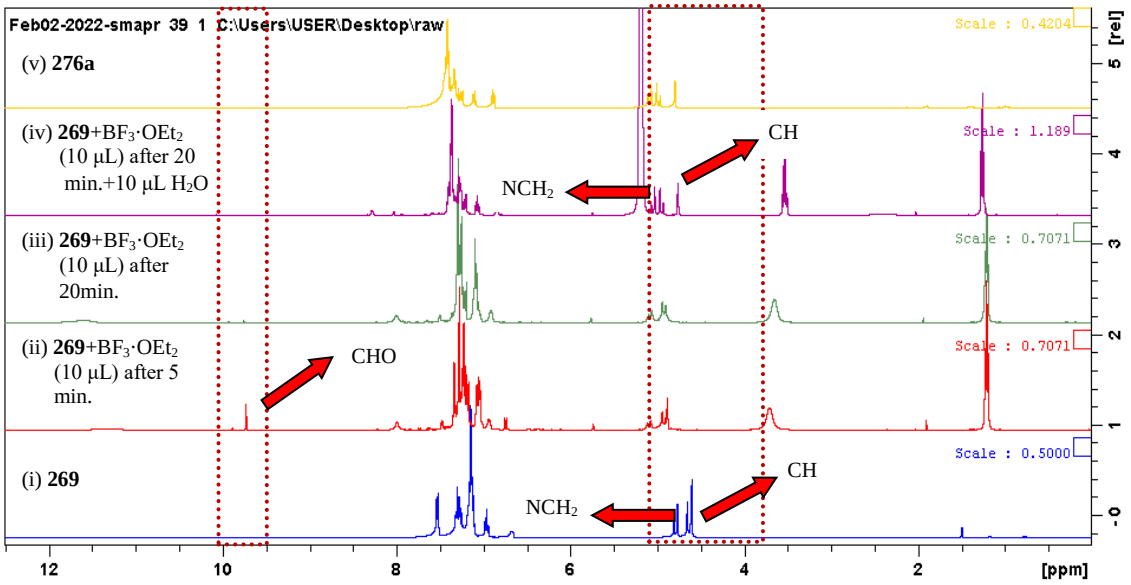
(i) A mixture of diazoamide **63a** (10 mg) and benzaldehyde **220a** (5 mg)
(ii) A mixture of diazoamide **63a** (10 mg), benzaldehyde **220a** (5 mg), $BF_3{\cdot}OEt_2$ (10 µL) after 5 min
(iii) A mixture of diazoamide **63a** (10 mg), benzaldehyde **220a** (5 mg), $BF_3{\cdot}OEt_2$ (10 µL) after 20 min
(iv) A mixture of diazoamide **63a** (10 mg), benzaldehyde **220a** (5 mg), $BF_3{\cdot}OEt_2$ (10 µL), H_2O (10 µL)
(v) Isolated product **276a**

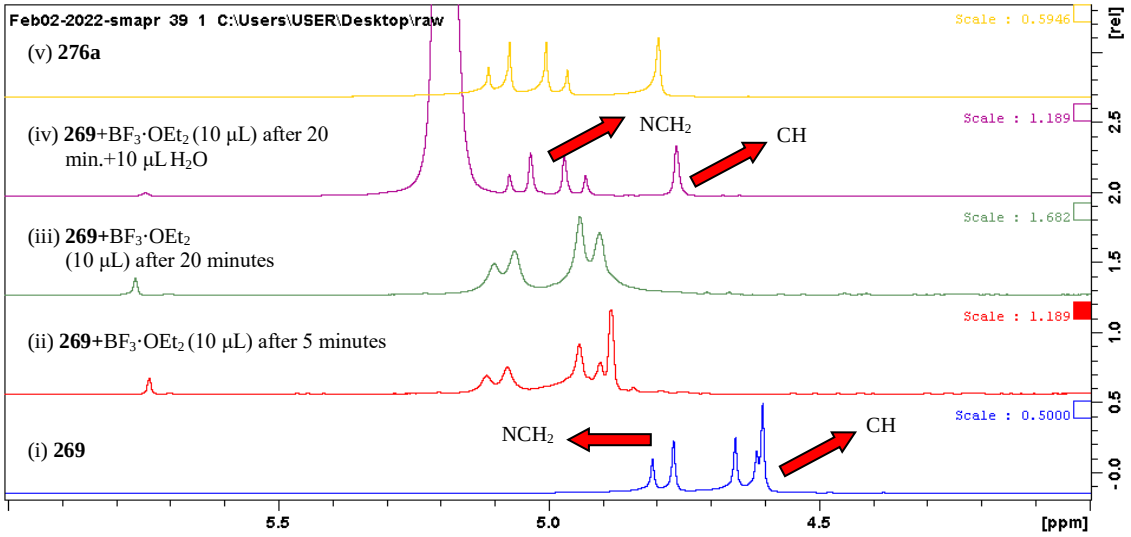
a singlet at 4.71 and 4.60 ppm, respectively [Figure 24(i)]. A new aldehyde peak was observed at 9.73 ppm after the addition of 10 µL of $BF_3{\cdot}OEt_2$ into the NMR tube [Figure 24(ii), (iii)]. Then, the peak at 9.73 ppm disappeared after the addition of 10 µL of water into the NMR tube and the formation of a singlet at 4.78 ppm [Figure 24(iv)] that is responsible for H_a proton of **276a**.

A plausible mechanism for **276** was proposed as shown in Scheme 115 based on the above results, control experiments and ^{1}H-NMR experiments. In the presence of $BF_3{\cdot}OEt_2$, the nucleophilic attack on diazoamide **63** by aryl aldehyde **220** may produce

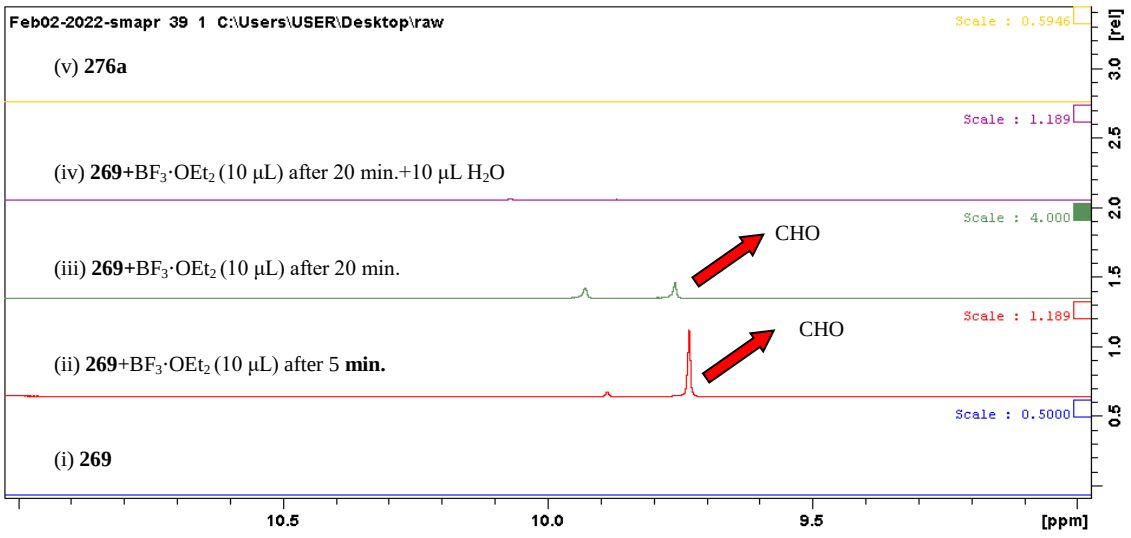


269 **C** **276a**





Expansion for NCH_2 peak



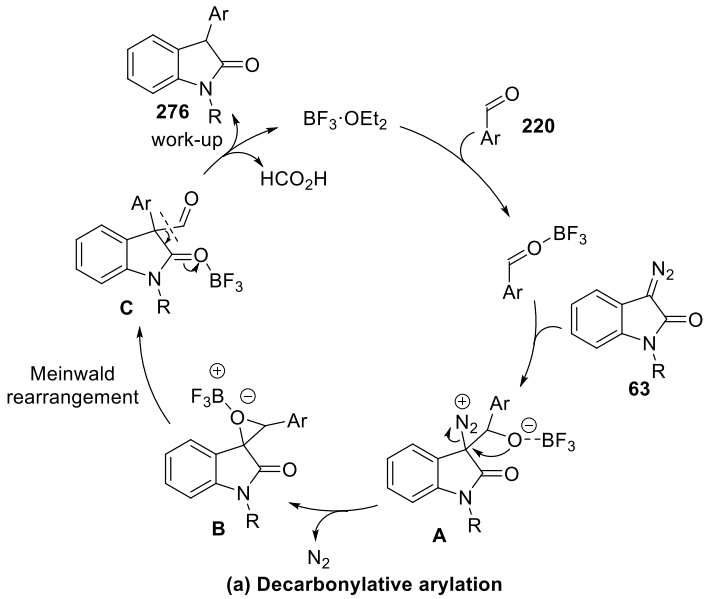
Expansion for aldehyde peak

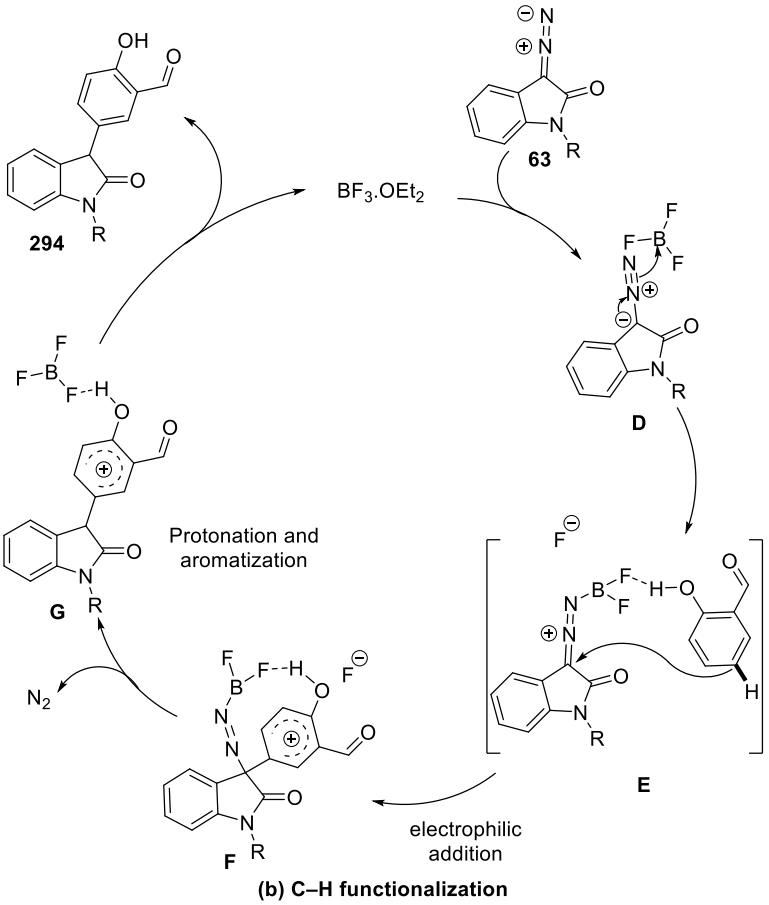
Figure 24. ^{1}H-NMR spectra of reaction mixture **276a** signals in $CDCl_3$

(i) Epoxide **269**
(ii) A mixture of epoxide **269** (20 mg) and $BF_3{\cdot}OEt_2$ (10 μL) after 5 minutes
(iii) A mixture of epoxide **269** (20 mg) and $BF_3{\cdot}OEt_2$ (10 μL) after 20 minutes
(iv) A mixture of epoxide **269** (20 mg) and $BF_3{\cdot}OEt_2$ (10 μL) after 20 minutes and H_2O (10 μL)
(v) Isolated product **276a**

an intermediate **A**. Subsequently, intermediate **A** may provide spiro-indolooxiranes **B** with the elimination of nitrogen. Meinwald rearrangement of **B** may provide **C** which on decarbonylation furnishing the desired product **276**.

In this case of salicylaldehyde, the phenolic nature of the hydroxyl group has a good nucleophilic character rather than of the aldehyde functional group. In this case, $BF_3{\cdot}OEt_2$ activates the diazoamide **63** to generate the intermediate **D** followed by a nucleophilic attack by the OH group of salicylaldehyde leading to the form of the boron complex **E**. The electrophilic addition at *meta*-position of aldehyde or *para*-position of OH group on the salicylaldehyde leads to the formation of hydrogen bonding between OH and F on the catalyst in intermediate **F**.[192] Consequently, protonation and aromatization proceed sequentially leading to the formation of 3-aryloxindole **294**. Similarly, the product **276ad** may be formed in Scheme 115.





Scheme 115. Plausible reaction mechanism for the formation of **276** and **294**

General information

All reactions were carried out in oven-dried glassware under nitrogen positive pressure with magnetic stirring. Aldehyde and $BF_3 \cdot OEt_2$ were purchased from M/s Aldrich or M/s Alfa Aesar and used according to the instructions.

Experimental Section

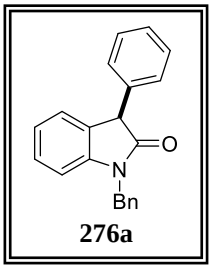
General experimental procedure for the synthesis of 3-aryloxindoles (276, 293, 294): An oven-dried single-neck round-bottom flask (50 mL) containing a solution diazoamides (**63**, 1 equiv) and appropriate aldehydes (**220**, **271** or **292**, 0.5-1 equiv) in dichloromethane (DCM, 5 mL) under an open-air atmosphere and the reaction mixture was stirred at 0 °C. After 10 minutes, 20 mol% of $BF_3 \cdot OEt_2$ was transferred using a 100 μL pipette to the reaction mixture. The reaction mixture was stirred and monitored using TLC until the disappearance of the diazoamide. After the appropriate period, the reaction mixture was allowed to room temperature and then DCM (20 mL) and water (20 mL) were added. The organic phase was separated and the aqueous layer was washed with DCM (20 mL). The combined organic layers were washed with brine solution and dried over sodium sulphate. The concentration of the combined organic layers under reduced pressure afforded the crude product, which was purified by column chromatography using silica gel to afford the corresponding products **276**, **293** and **294**.

General experimental procedure for 276a under inert atmosphere: An oven-dried double-neck round bottom flask (50 mL) was put under a vacuum and flushed with an argon atmosphere for two times. Diazoamide **63a** (1 equiv) and benzaldehyde (**220a**, 1.1 equiv) were dissolved in 5 mL of dry DCM and added to the reaction mixture into

the round-bottom flask. After 10 minutes, 20 mol% was transferred using a 100 μL pipette to the reaction mixture. The reaction mixture was stirred and monitored using TLC until the disappearance of the diazoamide **63a**. After the appropriate period, the reaction mixture was allowed to room temperature and then DCM (20 mL) and water (20 mL) were added. The organic phase was separated and the aqueous layer was washed with DCM (20 mL). The combined organic layers were washed with brine solution and dried over sodium sulphate. The concentration of the combined organic layers under reduced pressure afforded the crude product, which was purified by column chromatography using silica gel to afford the corresponding product **276a**.

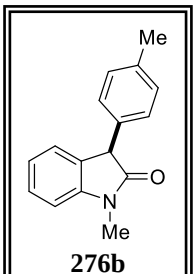
General experimental procedure for gram-scale experiments for 276b and 276y: An oven-dried double-neck round bottom flask (100 mL) containing a solution of the appropriate aldehyde **220** (1.1 equiv) in dichloromethane (DCM, 5 mL) under an open-air atmosphere and the reaction mixture was stirred at 0 °C. After 10 minutes, 20 mol% of $BF_3 \cdot OEt_2$ was transferred using a 100 μL pipette to the reaction mixture. Then added a solution of diazoamide **63** (1 equiv) in DCM (10 mL) using a syringe pump with the rate of addition 5 mL/h. The reaction mixture was stirred and monitored using TLC until the disappearance of the diazoamide. After the appropriate period, the reaction mixture was allowed to room temperature and then DCM (40 mL) and water (40 mL) were added. The organic phase was separated and the aqueous layer was washed with DCM (20 mL). The combined organic layers were washed with brine solution and dried over sodium sulphate. The concentration of the combined organic layers under reduced pressure afforded the crude product, which was purified by column chromatography using silica gel to afford the corresponding products **276b** and **276y**.

Synthesis of 1-benzyl-3-phenyl-1,3-dihydro-2*H*-indol-2-one (276a)[189]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and benzaldehyde (**220a**, 47 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276a** (106 mg, 88%) as a white solid according to general procedure. R_f = 0.46 (EtOAc/hexane = 1:4, v/v); mp 114-115 °C; IR (neat): ν_{max} 3033, 1707, 1607, 1485, 1347, 1187, 744746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.80 (s, 1H, CH), (ABq, $\Delta\delta_{AB}$ = 0.10, J = 15.6 Hz, 2H, CH_2), 6.89 (d, J = 8 Hz, 1H, ArH), 7.08-7.12 (m, 1H, ArH), 7.24-7.46 (m, 12H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.0, 52.2, 109.3, 122.9, 125.2, 127.5, 127.7, 127.8, 128.4, 128.6, 128.9, 129.0, 129.1, 136.0, 136.9, 143.6, 176.2 ppm; HRMS (ESI) Calculated for $C_{21}H_{17}NO$ $(M+H)^+$: 300.1388 found: 300.1383.



276a

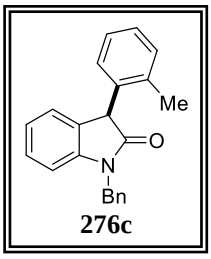
Synthesis of 1-methyl-3-(4-methylphenyl)-1,3-dihydro-2*H*-indol-2-one (276b)[189]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 4-methylbenzaldehyde (**220b**, 70 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276b** (124 mg, 90%) as a white solid according to general procedure. R_f = 0.41 (EtOAc/hexane = 1:4, v/v); mp 92-93 °C; IR (neat): ν_{max} 2920, 1703, 1601, 1485, 1350, 1015, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.31 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 4.56 (s, 1H, CH), 6.88 (d, J = 7.6 Hz ,1H, ArH), 7.02-7.16 (m, 6H ArH), 7.31 (t, J = 7.6 Hz ,1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ =



276b

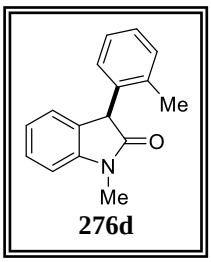
21.2, 26.5, 51.7, 108.2, 122.7, 125.0, 128.3, 128.4, 129.1, 129.6, 133.7, 137.3, 144.5, 176.2 ppm; HRMS (ESI) Calculated for $C_{16}H_{15}NO(M+H)^+$: 238.1232 found: 238.1260.

Synthesis of 1-benzyl-3-(2-methylphenyl)-1,3-dihydro-2*H*-indol-2-one (276c)[193]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 2-methylbenzaldehyde (**220c**, 53 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276c** (79 mg, 63%) as a white solid according to general procedure. R_f = 0.5 (EtOAc/hexane = 1:4, v/v); mp 86-87 °C; IR (neat): ν_{max} 2923, 1711, 1610, 1487, 1350, 1187, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.49 (br s, 3H, CH_3), 4.96 (s, 3H, CH_2/CH), 6.79- 7.34 (m, 13H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.0, 44.0, 109.1, 122.8, 124.7, 126.4, 127.6, 127.7, 128.2, 128.8, 129.3, 131.1, 135.5, 136.0, 137.3, 143.5, 176.3 ppm; HRMS (ESI) Calculated for $C_{22}H_{19}NO(M+H)^+$: 314.1545 found: 314.1548.



276c

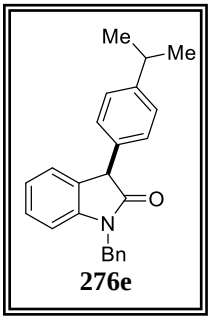
Synthesis of 1-methyl-3-(2-methylphenyl)-1,3-dihydro-2*H*-indol-2-one (276d)[187a]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 1-methylbenzaldehyde (**220c**, 70 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276d** (84 mg, 61%) as a white solid according to general procedure. R_f = 0.38 (EtOAc/hexane = 1:4, v/v); mp 131-132 °C; IR (neat): ν_{max} 2992, 1683, 1607, 1466, 1252, 1088, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.33 (br s, 3H, CH_3), 3.19 (s, 3H, CH_3), 4.76 (s, 1H, CH), 6.81-6.85 (m, 1H, ArH), 6.93-7.26 (m, 7H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 19.8, 26.5, 108.1, 122.8, 124.6, 126.4,



276d

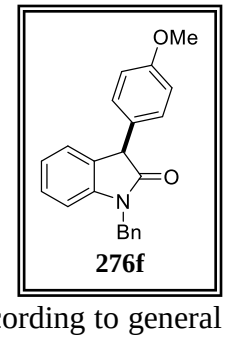
127.7, 128.3, 129.3, 131.0, 135.5, 137.2, 144.4, 176.2 ppm; HRMS (ESI) Calculated for $C_{16}H_{15}NO(M+H)^+$: 238.1232 found: 238.1234.

Synthesis of 1-benzyl-3-[4-(propan-2-yl)phenyl]-1,3-dihydro-2*H*-indol-2-one (276e): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 4-isopropylbenzaldehyde (**220d**, 65 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276e** (110 mg, 81%) as a white solid according to general procedure. R_f = 0.52 (EtOAc/hexane = 1:4, v/v); mp 146-147 °C; IR (neat): ν_{max} 2922, 1706, 1607, 1488, 1353, 1018, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.23 (d, J = 7.2 Hz, 6H, $2CH_3$), 2.84-2.94 (m, 1H, CH), 4.68 (s, 1H, CH), 4.94 (ABq, $\Delta\delta_{AB}$ = 0.10, J = 16 Hz, 2H, CH_2), 6.77 (d, J = 7.6, 1H, ArH), 7.00 (t, J = 7.5 Hz, 1H, ArH), 7.13-7.21 (m, 6H, ArH), 7.24-7.32 (m, 5H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.99, 24.02, 33.9, 44.0, 51.8, 109.2, 122.8, 125.2, 127.1, 127.4, 127.7, 128.3, 128.4, 128.8, 129.1, 134.0, 136.0, 143.6, 148.2, 176.4 ppm; HRMS (ESI) Calculated for $C_{24}H_{23}NO(M+H)^+$: 342.1858 found: 342.1862.



276e

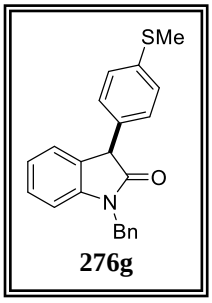
Synthesis of 1-benzyl-3-(4-methoxyphenyl)-1,3-dihydro-2*H*-indol-2-one (276f)[174a]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 4-methoxybenzaldehyde (**220e**, 60 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276f** (112 mg, 85%) as a white solid according to general procedure. R_f = 0.3 (EtOAc/hexane = 1:4, v/v); mp 108-109 °C; IR (neat): ν_{max} 2924, 1708, 1606, 1489, 1353, 1098, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.79 (s, 3H,



276f

CH_3), 4.65 (s, 1H, CH), 4.93 (ABq, $\Delta\delta_{AB}$ = 0.09, J = 15.6 Hz, 2H, CH_2), 6.77 (d, J = 8 Hz, 1H, ArH), 6.87 (d, J = 8.8 Hz, 2H, ArH), 7.01 (t, J = 7.6 Hz, 1H, ArH), 7.13-7.21 (m, 4H, ArH), 7.24-7.31 (m, 5H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.0, 51.3, 55.4, 109.2, 114.5, 122.8, 125.1, 127.4, 127.7, 128.3, 128.79, 128.83, 129.2, 129.5, 136.0, 143.6, 159.1, 176.5 ppm; HRMS (ESI) Calculated for $C_{22}H_{19}NO_2(M+H)^+$: 330.1494 found: 330.1485.

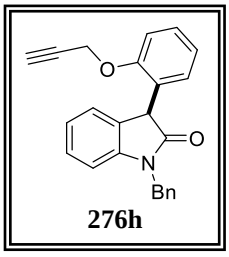
Synthesis of 1-benzyl-3-[4-(methylsulfanyl)phenyl]-1,3-dihydro-2*H*-indol-2-one (276g): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 4-(methylthio)benzaldehyde (**220f**, 67 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276g** (115 mg, 83%) as a white solid according to general procedure. R_f = 0.33 (EtOAc/hexane = 1:4, v/v); mp 123-124 °C; IR (neat): ν_{max} 2921, 1705, 1607, 1347, 1089, 1015, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.31 (s, 3H, CH_3), 4.53 (s, 1H, CH), 4.80 (ABq, $\Delta\delta_{AB}$ = 0.11, J = 15.6 Hz, 2H, CH_2), 6.66 (d, J = 8 Hz, 1H, ArH), 6.88 (t, J = 7.6 Hz, 1H, ArH), 7.00-7.19 (m, 11H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 15.9, 44.0, 51.6, 109.4, 122.9, 125.2, 127.2, 127.5, 127.8, 128.5, 128.8, 128.9, 129.0, 133.6, 136.0, 138.0, 143.6, 176.1 ppm; HRMS (ESI) Calculated for $C_{22}H_{19}NOS(M+H)^+$: 346.1266 found: 346.1268.



276g

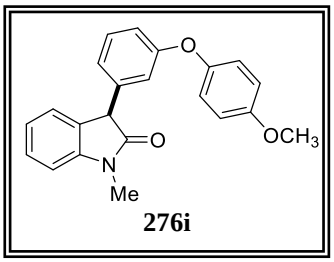
Synthesis of 1-benzyl-3-{2-[(prop-2-yn-1-yl)oxy]phenyl}-1,3-dihydro-2*H*-indol-2-one (276h): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 2-[(prop-2-yn-1-yl)oxy]benzaldehyde (**220g**, 70 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276h** (99 mg, 70%) as a white

solid according to general procedure. R_f = 0.28 (EtOAc/hexane = 1:4, v/v); mp 121-122 °C; IR (neat): ν_{max} 3287, 2922, 2121, 1706, 1607, 1488, 1353, 1018, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.45 (t, *J* = 2.2 Hz, 1H, CH), 4.51 (s, 2H, CH_2), 4.92-5.06 (m, 3H, CH_2/CH), 6.76 (d, *J* = 7.6, 1H, ArH), 6.91-7.07 (m, 4H, ArH), 7.13-7.17 (m, 2H, ArH), 7.25-7.41 (m, 6H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 48.2, 56.5, 75.5, 78.6, 108.8, 113.3, 122.1, 122.5, 124.2, 126.7, 127.6, 127.8, 128.8, 128.9, 129.7, 130.6, 136.3, 143.4, 155.8, 176.6 ppm; HRMS (ESI) Calculated for $C_{24}H_{19}NO_2(M+H)^+$: 354.1494 found: 354.2231.



276h

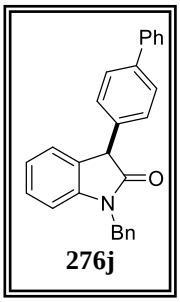
Synthesis of 3-[3-(4-methoxyphenoxy)phenyl]-1-methyl-1,3-dihydro-2*H*-indol-2-one (276i): To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 3-(4-methoxyphenoxy)benzaldehyde (**220h**, 145 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276i** (160 mg, 80%) as a white solid according to general procedure. R_f = 0.27 (EtOAc/hexane = 1:4, v/v); mp 136-137 °C; IR (neat): ν_{max} 2928, 1683, 1607, 1466, 1343, 1088, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.25 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.56 (s, 1H, CH), 6.78-7.08 (m, 9H, ArH), 7.16-7.34 (m, 3H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.5, 51.9, 55.7, 108.2, 114.9, 116.3, 118.1, 120.9, 122.4, 122.8, 125.0, 128.5, 128.6, 130.0, 138.5, 144.5, 149.9, 160.0, 158.8, 175.7 ppm; HRMS (ESI) Calculated for $C_{22}H_{19}NO_3(M+H)^+$: 346.1443 found:346.1443.



276i

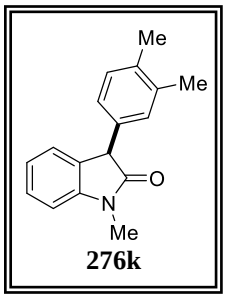
Synthesis of 1-benzyl-3-([1,1'-biphenyl]-4-yl)-1,3-dihydro-2*H*-indol-2-one (276j)[186]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40

mmol) and [1,1'-biphenyl]-4-carbaldehyde (**220i**, 80 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276j** (99 mg, 66%) as a white solid according to general procedure. R_f = 0.65 (EtOAc/hexane = 1:4, v/v); mp 118-119 °C; IR (neat): ν_{max} 2923, 1708, 1609, 1480, 1350, 1085, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.87-4.95 (m, 3H, CH_2/CH), 6.71-7.62 (m, 18H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.0, 109.0, 122.7, 124.7, 127.3, 127.5, 127.7, 128.0, 128.1, 128.8, 129.9, 130.6, 130.9, 135.1, 136.1, 140.8, 143.4, 177.0 ppm; HRMS (ESI) Calculated for $C_{27}H_{21}NO(M+H)^+$: 376.1701 found: 376.1696.



276j

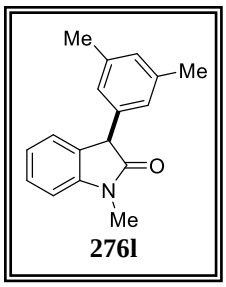
Synthesis of 3-(3,4-dimethylphenyl)-1-methyl-1,3-dihydro-2*H*-indol-2-one (276k)[172]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 3,4-dimethylbenzaldehyde (**220j**, 85 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276k** (121 mg, 83%) as a white solid according to general procedure. R_f = 0.37 (EtOAc/hexane = 1:4, v/v); mp 94-95 °C; IR (neat): ν_{max} 2926, 1707, 1608, 1480, 1350, 1085, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.19 (s, 6H, $2CH_3$), 3.21 (s, 3H, CH_3), 4.50 (s, 1H, CH), 6.84-6.94 (m, 3H, ArH), 7.00-7.06 (m, 2H, ArH), 7.12 (d, J = 7.2Hz, 1H, ArH), 7.26-7.30 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 19.5, 19.9, 26.5, 51.8, 108.2, 122.8, 125.0, 125.9, 128.4, 129.3, 129.7, 130.2, 134.1, 136.0, 137.2, 144.5, 176.4 ppm; HRMS (ESI) Calculated for $C_{17}H_{17}NO(M+H)^+$: 252.1388 found: 252.1383.



276k

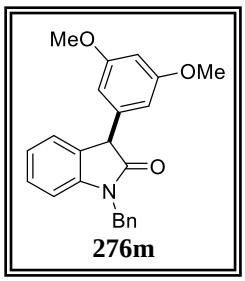
Synthesis of 3-(3,5-dimethylphenyl)-1-methyl-1,3-dihydro-2*H*-indol-2-one (276l)[172]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58

mmol) and 3,5-dimethylbenzaldehyde (**220k**, 85 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276l** (130 mg, 89%) as a white solid according to general procedure. R_f = 0.38 (EtOAc/hexane = 1:4, v/v); mp 97-98 °C; IR (neat): ν_{max} 2924, 1706, 1609, 1465, 1342, 1255, 1023, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.17 (s, 6H, CH_3), 3.14 (s, 3H, CH_3), 4.66 (s, 1H, CH), 6.76-6.81 (m, 2H, ArH), 6.89-6.95 (m, 4H, ArH), 7.17-7.21 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 19.7, 21.1, 26.4, 108.1, 122.8, 124.6, 127.1, 128.2, 129.5, 131.9, 132.5, 137.3, 144.4, 176.4 ppm; HRMS (ESI) Calculated for $C_{17}H_{17}NO$ $(M+H)^+$: 252.1388 found: 252.1382.



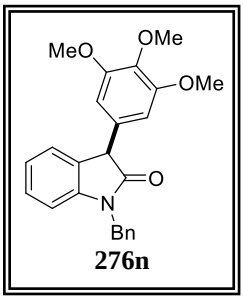
276l

Synthesis of 1-benzyl-3-(3,5-dimethoxyphenyl)-1,3-dihydro-2*H*-indol-2-one (276m): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 3,5-dimethoxybenzaldehyde (**220l**, 73 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276m** (109 mg, 85%) as a white solid according to general procedure. R_f = 0.17 (EtOAc/hexane = 1:4, v/v); mp 130-131 °C; IR (neat): ν_{max} 2936, 1708, 1606, 1460, 1247, 1024, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.79 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.63 (s, 1H, CH), 4.93 (ABq, $\Delta\delta_{AB}$ = 0.16, J = 15.6 Hz, 2H, CH_2), 6.71-6.84 (m, 4H, ArH), 7.01 (t, J = 7.6 Hz, 1H, ArH), 7.16-7.33 (m, 7H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.9, 51.6, 55.9, 56.0, 109.2, 111.5, 120.7, 122.8, 125.2, 127.5, 127.7, 128.4, 128.8, 129.1, 129.2, 136.1, 143.5, 148.6, 149.3, 176.4 ppm; HRMS (ESI) Calculated for $C_{23}H_{21}NO_3$ $(M+H)^+$: 360.1600 found: 360.1595.



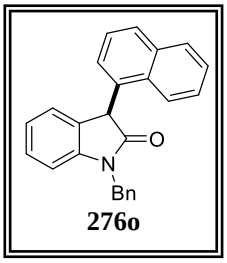
276m

Synthesis of 1-benzyl-3-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2*H*-indol-2-one (276n): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 3,4,5-trimethoxybenzaldehyde (**220m**, 86 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$.The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276n** (125 mg, 80%) as a white solid according to general procedure. R_f = 0.22 (EtOAc/hexane = 1:4, v/v); mp 151-152 °C; IR (neat): ν_{max} 2922, 1708, 1609, 1480, 1350, 1085, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.49 (s, 3H, CH_3), 3.84 (d, J = 2.8 Hz, 6H, $2CH_3$), 4.73 (s, 1H, CH), 4.98 (ABq, $\Delta\delta_{AB}$ = 0.16, J = 15.6 Hz, 2H, CH_2), 6.62-7.32 (m, 11H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.0, 48.7, 56.1, 60.5, 60.7, 107.2, 108.9, 122.4, 123.6, 124.2, 124.9, 127.6, 127.9, 128.7, 130.2, 136.2, 142.5, 143.5, 152.1, 153.7, 176.9 ppm; HRMS (ESI) Calculated for $C_{24}H_{23}NO_4$ $(M+H)^+$: 390.1705 found: 390.1700.



276n

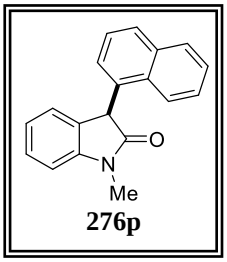
Synthesis of 1-benzyl-3-(naphthalen-1-yl)-1,3-dihydro-2*H*-indol-2-one (276o)[187b]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 1-naphthaldehyde (**220n**, 70 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276o** (99 mg, 71%) as a white semi-solid according to general procedure. R_f = 0.43 (EtOAc/hexane = 1:4, v/v); mp 65-66 °C; IR (neat): ν_{max} 2926, 1706, 1607, 1346, 1170, 1017, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.97-5.28 (m, 2H, CH_2), 5.68 (br s, 1H, CH), 6.92-7.18 (m, 4H, ArH), 7.25-7.74 (m, 9H, ArH), 7.86-7.95 (m, 2H, ArH), 8.45 (br s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.2, 52.3,



276o

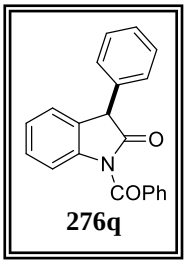
109.4, 122.9, 124.2, 125.3, 125.6, 126.0, 126.2, 126.3, 126.6, 127.5, 127.8, 128.3, 128.9, 129.6, 132.9, 133.6, 134.3, 134.4, 136.1, 143.7, 176.2 ppm; HRMS (ESI) Calculated for $C_{25}H_{19}NO$ $(M+H)^+$: 350.1545 found: 350.1540.

Synthesis of 1-methyl-3-(naphthalen-1-yl)-1,3-dihydro-2*H*-indol-2-one (276p)[172]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 1-naphthaldehyde (**220n**, 99 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276p** (101 mg, 64%) as a white semi-solid according to general procedure. R_f = 0.5.7 (EtOAc/hexane = 1:4, v/v); mp 153-154 °C; IR (neat): ν_{max} 3053, 1711, 1610, 1470, 1346, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.39 (s, 3H, CH_3), 5.57 (br, 1H, CH), 6.98-7.69 (m, 10H, ArH), 7.76 (br, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.6, 52.3, 108.4, 122.9, 124.1, 124.8, 125.6, 126.0, 126.6, 127.6, 127.7, 127.9, 128.4, 128.6, 129.0, 129.5, 134.4, 144.6, 176.2 ppm; HRMS (ESI) Calculated for $C_{19}H_{15}NO$ $(M+Na)^+$: 296.1051 found: 296.1054.



276p

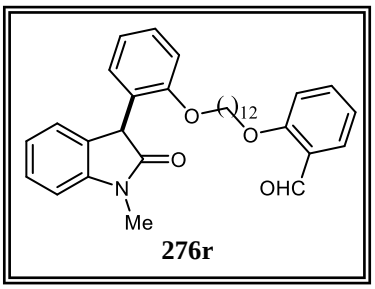
Synthesis of 1-benzoyl-3-phenyl-1,3-dihydro-2*H*-indol-2-one (276q): To a solution of 1-benzoyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63c**, 100 mg, 0.38 mmol) and benzaldehyde (**220a**, 44 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276q** (72 mg, 61%) as a white solid according to general procedure. R_f = 0.43 (EtOAc/hexane = 1:4, v/v); mp 173-174 °C; IR (neat): ν_{max} 2924, 1746, 1681, 1597, 1462, 1278, 1151, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.77 (s, 1H, CH), 7.17-7.37 (m, 10H, ArH), 7.45-7.50 (m, 1H, ArH), 7.60-7.62 (m, 2H, ArH), 7.86 (d, J = 8 Hz, 1H, ArH)



276q

ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 52.6, 115.2, 125.2, 125.3, 128.09, 128.12, 128.3, 128.5, 128.9, 129.1, 129.3, 132.9, 134.1, 136.0, 141.0, 169.6, 175.3 ppm; HRMS (ESI) Calculated for $C_{21}H_{15}NO_2$ $(M+H)^+$: 314.1181 found: 314.1178.

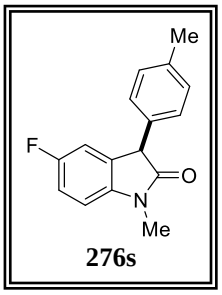
Synthesis of 2-((12-(2-(1-methyl-2-oxoindolin-3-yl)phenoxy)dodecyl)oxy) benzaldehyde (276r): To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 2,2'-(dodecane-1,12-diylbis(oxy))dibenzaldehyde (**220o**, 119 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276r** (199 mg, 65%) as a white solid according to general procedure. R_f = 0.1 (EtOAc/hexane = 1:4, v/v); mp 64-65 °C; IR (neat): ν_{max} 2927, 1690, 1600, 1462, 1243, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.15-1.49 (m, 18H, 9CH_2), 1.83-1.87 (m, 2H, CH_2), 3.28 (s, 3H, CH_3), 3.72 (s, 1H, 1/2CH_2), 3.86-3.88 (m, 1H, 1/2CH_2), 4.06-4.09 (m, 2H, CH_2), 4.72 (s, 1H, CH), 6.81-7.01 (m, 6H, ArH), 7.18-7.26 (m, 4H, ArH), 7.51-7.55 (m, 1H, ArH), 7.83 (d, *J* = 7.6 Hz, 1H, ArH), 10.52 (s, 1H, CHO) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.9, 26.1, 26.4, 29.1, 29.2, 29.36, 29.43, 29.5, 29.58, 29.6, 68.0, 68.6, 107.5, 111.8, 112.5, 120.5, 120.6, 122.3, 123.8, 125.0, 125.6, 127.7, 128.3, 128.6, 129.0, 129.9, 131.0, 135.9, 144.3, 156.9, 161.6, 176.8, 189.9 ppm; HRMS (ESI) Calculated for $C_{34}H_{41}NO_4$ $(M+H)^+$: 528.3114 found: 528.3109.



276r

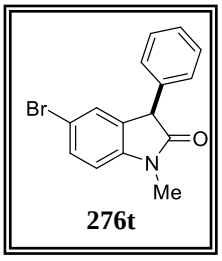
Synthesis of 5-fluoro-1-methyl-3-(4-methylphenyl)-1,3-dihydro-2*H*-indol-2-one (276s): To a solution of 3-diazo-5-fluoro-1-methyl-1,3-dihydro-*2H*-indol-2-one (**63d**, 100 mg, 0.52 mmol) and 4-methylbenzaldehyde (**220b**, 69 mg, 0.58 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C

under the open-air atmosphere to afford product **276s** (110 mg, 83%) as a white solid according to general procedure. R_f = 0.2 (EtOAc/hexane = 1:4, v/v); mp 156-157 °C; IR (neat): ν_{max} 2925, 1703, 1612, 1489, 1345, 1268, 1123, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.38 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 4.61 (s, 1H, CH), 6.84-6.87 (m, 1H, ArH), 6.95-6.97 (m, 1H, ArH), 7.04-7.21 (m, 5H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.2, 26.6, 52.0, 108.6 (d, *J* = 8 Hz), 113.1 (d, *J* = 25 Hz), 114.6 (d, *J* = 24 Hz), 128.3, 129.7, 130.7 (d, *J* = 9 Hz), 133.1, 137.5, 140.5, 159.3 (d, *J* = 239 Hz), 175.8 ppm; HRMS (ESI) Calculated for $C_{16}H_{14}FNO$ $(M+H)^+$: 256.1138 found: 256.1139.



276s

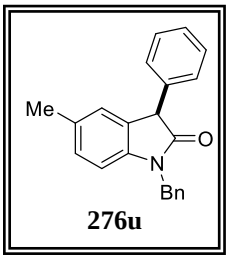
Synthesis of 5-bromo-1-methyl-3-phenyl-1,3-dihydro-2*H*-indol-2-one (276t): To a solution of 5-bromo-3-diazo-1-methyl-1,3-dihydro-*2H*-indol-2-one (**63e**, 100 mg, 0.40 mmol) and benzaldehyde (**220a**, 46 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276t** (94 mg, 78%) as a white solid according to general procedure. R_f = 0.33 (EtOAc/hexane = 1:4, v/v); mp 177-178 °C; IR (neat): ν_{max} 2923, 1695, 1599, 1485, 1337, 1095, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.28 (s, 3H, CH_3), 4.64 (s, 1H, CH), 6.82 (d, *J* = 8.4 Hz, 1H, ArH), 7.22-7.24 (m, 2H, ArH), 7.30-7.41 (m, 4H, ArH), 7.49 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.6, 52.0, 109.7, 115.4, 127.9, 128.2, 128.4, 129.1, 130.9, 131.3, 135.9, 143.5, 175.4 ppm; HRMS (ESI) Calculated for $C_{15}H_{12}{}^{79}BrNO$ $(M+H)^+$: 302.0181 found: 302.0183.



276t

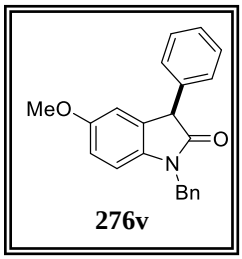
Synthesis of 1-benzyl-5-methyl-3-phenyl-1,3-dihydro-*2H*-indol-2-one (276u)[175]: To a solution of 1-benzyl-3-diazo-5-methyl-1,3-dihydro-*2H*-indol-2-one (**63f**, 100 mg,

0.38 mmol) and benzaldehyde (**220a**, 44 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276u** (109 mg, 92%) as a white solid according to general procedure. R_f = 0.49 (EtOAc/hexane = 1:4, v/v); mp 97-98 °C; IR (neat): ν_{max} 2920, 1705, 1606, 1493, 1341, 1283, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.34 (s, 3H, CH_3), 4.76 (s, 1H, CH), 5.01 (ABq, $\Delta\delta_{AB}$ = 0.1, J = 15.6 Hz, 2H, CH_2), 6.76 (d, J = 7.6 Hz, 1H, ArH), 7.06-7.09 (m, 2H, ArH), 7.32-7.44 (m, 10H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.1, 44.0, 52.3, 109.0, 126.0, 127.4, 127.66, 127.67, 128.57, 128.64, 128.9, 129.0 129.1, 132.4, 136.1, 137.1, 141.2, 176.2 ppm; HRMS (ESI) Calculated for $C_{22}H_{19}NO$ $(M+H)^+$: 314.1545 found: 314.1546.



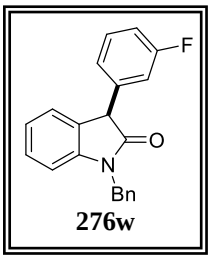
276u

Synthesis of 1-benzyl-5-methoxy-3-phenyl-1,3-dihydro-*2H*-indol-2-one (276v)[175]: To a solution of 1-benzyl-3-diazo-5-methoxy-1,3-dihydro-*2H*-indol-2-one (**63g**, 100 mg, 0.36 mmol) and benzaldehyde (**220a**, 42 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276v** (101 mg, 85%) as a white solid according to general procedure. R_f = 0.31 (EtOAc/hexane = 1:4, v/v); mp 86-87 °C; IR (neat): ν_{max} 2926, 1702, 1600, 1489, 1341, 1176, 1027, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.76 (s, 3H, CH_3), 4.75 (s, 1H, CH), 4.98 (ABq, $\Delta\delta_{AB}$ = 0.09, J = 15.6 Hz, 2H, CH_2), 6.72-6.84 (m, 3H, ArH), 7.28-7.40 (m, 10H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 52.6, 55.8, 109.6, 112.3, 112.9, 127.4, 127.7, 128.5, 128.8, 129.0, 130.3, 136.0, 136.8, 137.1, 156.2, 175.9 ppm; HRMS (ESI) Calculated for $C_{22}H_{19}NO_2$ $(M+H)^+$: 330.1494 found: 330.1484.



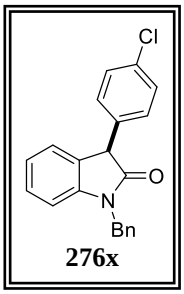
276v

Synthesis of 1-benzyl-3-(3-fluorophenyl)-1,3-dihydro-2*H*-indol-2-one (276w): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 3-fluorobenzaldehyde (**220p**, 55 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276w** (84 mg, 66%) as a white solid according to general procedure. R_f = 0.39 (EtOAc/hexane = 1:4, v/v); mp 141-142 °C; IR (neat): ν_{max} 2927, 1708, 1608, 1478, 1348, 1261, 1018, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.70 (s, 1H, CH), 4.94 (ABq, $\Delta\delta_{AB}$ = 0.07, J = 15.6 Hz, 2H, CH_2), 6.80 (d, J = 8.0 Hz, 1H, ArH), 6.92 (d, J = 9.6 Hz, 1H, ArH), 6.97-7.06 (m, 3H, ArH), 7.15-7.35 (m, 8H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 51.7, 109.4, 114.7 (d, J = 21 Hz), 115.5 (d, J = 22 Hz), 122.9, 124.3 (d, J = 3 Hz) 125.2, 127.4, 127.8, 128.2, 128.6, 128.9, 130.4 (d, J = 9 Hz), 135.8, 139.0 (d, J = 7 Hz), 143.6, 163.1 (d, J = 245 Hz), 175.5 ppm; HRMS (ESI) Calculated for $C_{21}H_{16}FNO$ $(M+H)^+$: 318.1294 found: 318.1297.



276w

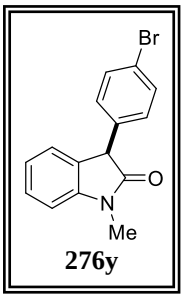
Synthesis of 1-benzyl-3-(4-chlorophenyl)-1,3-dihydro-2*H*-indol-2-one (276x)[187b]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 4-chlorobenzaldehyde (**220q**, 62 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276x** (93 mg, 70%) as a white solid according to general procedure. R_f = 0.35 (EtOAc/hexane = 1:4, v/v); mp 125-126 °C; IR (neat): ν_{max} 2923, 1709, 1608, 1489, 1352, 1018, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.62 (s, 1H, CH), 4.85 (ABq, $\Delta\delta_{AB}$ = 0.10, J = 15.6 Hz, 2H, CH_2), 6.61 (d, J = 8.4 Hz, 1H, ArH), 7.06-7.25 (m, 12H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 52.1,



276x

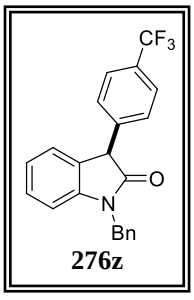
110.2, 125.6, 127.3, 127.9, 128.0, 128.2, 128.35, 128.44, 128.9, 129.2, 130.6, 135.5, 136.0, 142.1, 175.7 ppm; HRMS (ESI) Calculated for $C_{21}H_{16}{}^{35}ClNO$ $(M+H)^+$: 334.0999 found: 334.0999.

Synthesis of 3-(4-bromophenyl)-1-methyl-1,3-dihydro-2*H*-indol-2-one (276y)[194]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 4-bromobenzaldehyde (**220r**, 118 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276y** (125 mg, 72%) as a white solid according to general procedure. R_f = 0.26 (EtOAc/hexane = 1:4, v/v); mp 167-168 °C; IR (neat): ν_{max} 2921, 1688, 1606, 1484, 1345, 1081, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.22 (s, 3H, CH_3), 4.54 (s, 1H, CH), 6.89 (d, J = 7.6 Hz, 1H, ArH), 7.04-7.14 (m, 4H, ArH), 7.33 (t, J = 7.6 Hz, 1H, ArH), 7.43 (d, J = 7.6 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.6, 51.4, 108.4, 121.7, 122.9, 125.1, 128.2, 128.8, 130.2, 132.0, 135.7, 144.5, 175.4 ppm; HRMS (ESI) Calculated for $C_{15}H_{12}{}^{79}BrNO$ $(M+H)^+$: 302.0181 found: 302.0179.



276y

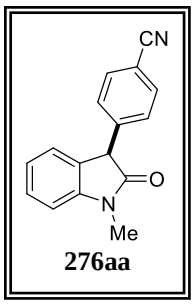
Synthesis of 1-benzyl-3-[4-(trifluoromethyl)phenyl]-1,3-dihydro-2*H*-indol-2-one (276z)[195]: To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 4-(trifluoromethyl)benzaldehyde (**220s**, 77 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276z** (110 mg, 75%) as a white solid according to general procedure. R_f = 0.43 (EtOAc/hexane = 1:4, v/v); mp 110-111 °C; IR (neat): ν_{max} 2925, 1712, 1611, 1486, 1324, 1118, 745 cm^{-1}; ^1H NMR ($CDCl_3$,



276z

400 MHz) δ = 4.77 (s, 1H, CH), 4.95 (ABq, $\Delta\delta_{AB}$ = 0.08, J = 15.6 Hz, 2H, CH_2), 6.83 (d, J = 7.6 Hz, 1H, ArH), 7.03-7.07 (m, 1H, ArH), 7.15 (d, J = 7.2 Hz, 1H, ArH), 7.23-7.37 (m, 8H, ArH), 7.61 (d, J = 8.0 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 51.8, 109.5, 123.0, 124.1 (q, J = 270 Hz, CF_3), 125.2, 125.9 (q, J = 4 Hz), 127.4, 127.8, 127.9, 128.8, 128.9, 130.0 (q, J = 32 Hz), 135.7, 140.7, 143.6, 175.3 ppm; HRMS (ESI) Calculated for $C_{22}H_{16}F_3NO$ $(M+H)^+$: 368.1262 found: 368.1268.

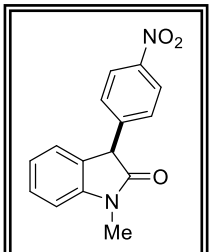
Synthesis of 4-(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)benzonitrile (276aa)[196]**:** To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 4-formylbenzonitrile (**220t**, 84 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276aa** (98 mg, 68%) as a white solid according to general procedure. R_f = 0.3 (EtOAc/hexane = 1:4, v/v); mp 161-162 °C; IR (neat): ν_{max} 2918, 2221, 1695, 1607, 1469, 1344, 1080, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.26 (s, 3H, CH_3), 4.67 (s, 1H, CH), 6.93 (d, J = 8.0 Hz, 1H, ArH), 7.09-7.16 (m, 2H, ArH), 7.34-7.40 (m, 3H, ArH), 7.63 (d, J = 8.4 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.6, 51.8, 108.6, 111.6, 118.6, 123.1, 125.1, 127.3, 129.1, 129.3, 132.6, 141.9, 144.5, 174.6 ppm; HRMS (ESI) Calculated for $C_{16}H_{12}N_2O$ $(M-H)^+$: 247.0871 found: 247.0888.



276aa

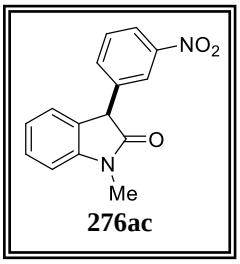
Synthesis of 1-methyl-3-(4-nitrophenyl)-1,3-dihydro-2*H*-indol-2-one (276ab)[197]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and benzaldehyde (**220u**, 96 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276ab** (110 mg, 71%) as a white solid according to general procedure.

R_f = 0.21 (EtOAc/hexane = 1.5:3.5, v/v); mp 186-187 °C; IR (neat): ν_{max} 2922, 1706, 1607, 1488, 1353, 1018, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.26 (s, 3H, CH_3), 4.61 (s, 1H, CH), 6.90 (d, J = 7.6 Hz, 1H, ArH), 7.07 (t, J = 7.6 Hz, 1H, ArH), 7.16-7.21 (m, 3H, ArH), 7.28-7.35 (m, 3H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.6, 66.1, 109.0, 122.7, 123.3, 125.5, 125.7, 129.0, 131.0, 143.3, 143.9, 147.9, 173.0 ppm; HRMS (ESI) Calculated for $C_{15}H_{12}N_2O_3$ $(M+H)^+$: 269.0926 found: 269.0921.



276ab

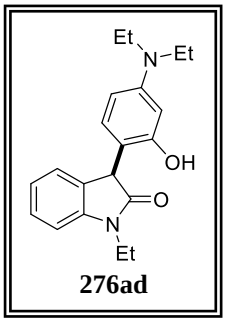
Synthesis of 1-methyl-3-(3-nitrophenyl)-1,3-dihydro-2*H*-indol-2-one (276ac)[198]: To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.58 mmol) and 3-nitrobenzaldehyde (**220v**, 96 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276ac** (98 mg, 63%) as a white solid according to general procedure. R_f = 0.21 (EtOAc/hexane = 1.5:3.5, v/v); mp 150-151 °C; IR (neat): ν_{max} 2935, 1724, 1610, 1520, 1344, 1093, 1013, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.32 (s, 3H, CH_3), 4.77 (s, 1H, CH_3), 6.99 (d, J = 7.6 Hz, 1H, ArH), 7.16-7.22 (m, 2H, ArH), 7.44 (t, J = 7.6 Hz, 1H, ArH), 7.56-7.60 (m, 1H, ArH), 7.66-7.68 (m, 1H, ArH), 8.09 (s, 1H, ArH), 8.21 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.7, 51.4, 108.7, 122.8, 123.2, 123.3, 125.1, 127.2, 129.2, 129.9, 135.0, 138.6, 144.5, 148.6, 174.8 ppm; HRMS (ESI) Calculated for $C_{15}H_{12}N_2O_3$ $(M+H)^+$: 269.0926 found: 269.0919.



276ac

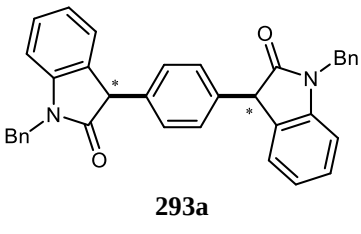
Synthesis of 3-[4-(diethylamino)-2-hydroxyphenyl]-1-ethyl-1,3-dihydro-2*H*-indol-2-one (**276ad**): To a solution 3-diazo-1-ethyl-1,3-dihydro-2*H*-indol-2-one (**63h**, 100 mg, 0.53 mmol) and 4-(diethylamino)-2-hydroxybenzaldehyde (**220w,** 113 mg, 0.59

mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **276ad** (156 mg, 91%) as a white solid according to general procedure (unstable under open-air at 60 °C). R_f = 0.54 (EtOAc/hexane = 2:3, v/v); mp 51-52 °C; IR (neat): ν_{max} 2973, 1677, 1610, 1508, 1354, 1213, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.20 (t, J = 7.0 Hz, 6H, $2CH_3$), 1.34 (t, J = 7.2 Hz, 3H, CH_3), 3.37 (q, J = 7.1 Hz, 4H, $2CH_2$), 3.83 (ABq, $\Delta\delta_{AB}$ = 0.03, J = 7.2 Hz, 2H, CH_2), 5.03 (s, 1H, CH), 6.19-6.22 (m, 1H, ArH), 6.51 (d, J = 2.8 Hz, 1H, ArH), 6.77-6.79 (m, 1H, ArH) 7.01-7.03 (m, 1H, ArH), 7.21-7.25 (m, 1H, ArH), 7.41-7.44 (m, 2H, ArH), 9.32 (br s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.7, 35.1, 44.4, 47.4, 102.3, 104.2, 109.1, 109.5, 122.9, 126.4, 127.0, 127.8, 128.4, 143.7, 149.0, 157.3, 178.9 ppm; HRMS (ESI) Calculated for $C_{20}H_{24}N_2O_2$ $(M+H)^+$: 325.1916 found: 325.1895.



276ad

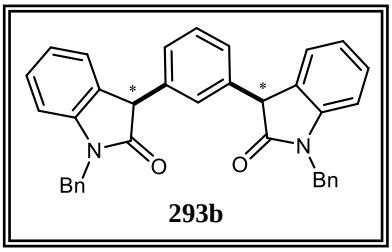
Synthesis of 3,3'-(1,4-phenylene)bis(1-benzyl-1,3-dihydro-2*H*-indol-2-one) (**293a**): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and terephthalaldehyde (**292a**, 27 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **293a** (71 mg, 68%) as a white solid according to general procedure. R_f = 0.35 (EtOAc/hexane = 2:3, v/v); mp 207-209 °C; IR (neat): ν_{max} 2924, 1707, 1609, 1480, 1350, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.62-4.63 (m, 2H, 2CH), 4.78-4.94 (m, 4H, $2CH_2$), 6.69-6.72 (m, 2H, ArH), 6.93-6.96 (m, 2H, ArH), 7.08-7.25 (m, 18H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.0, 51.7, 109.2, 122.8, 125.27, 125.32, 127.4, 127.7, 128.4, 128.7, 128.8, 129.1, 135.88, 135.91, 136.04, 136.1,



293a

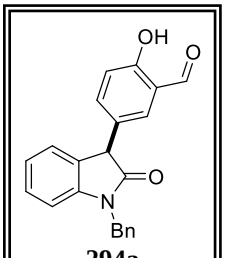
143.56, 143.59, 175.97, 176.0 ppm; HRMS (ESI) Calculated for $C_{36}H_{28}N_2O_2$ $(M+H)^+$: 521.2229 found: 521.2220.

Synthesis of 3,3'-(1,3-phenylene)bis(1-benzyl-1,3-dihydro-2*H*-indol-2-one) (**293b**): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and isophthalaldehyde (**292b**, 27 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **293b** (48 mg, 46%) as a white solid according to general procedure. R_f = 0.35 (EtOAc/hexane = 2:3, v/v); mp 187-188 °C; IR (neat): ν_{max} 2924, 1705, 1609, 1489, 1352, 1174, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.72 (s, 1H, CH), 4.79 (s, 1H, CH), 4.92-5.06 (m, 4H, $2CH_2$), 6.82-6.85 (m, 2H, ArH), 7.06-7.09 (m, 2H, ArH), 7.19-7.37 (m, 18H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.0, 51.93, 51.94, 109.24, 109.28, 122.86, 122.92, 125.30, 125.33, 127.1, 127.36, 127.38, 127.67, 127.70, 127.73, 128.4, 128.5, 128.6, 128.9, 129.5, 129.6, 130.2, 135.86, 135.89, 137.31, 137.32, 143.5, 175.9, 176.0 ppm; HRMS (ESI) Calculated for $C_{36}H_{28}N_2O_2$ $(M+Na)^+$: 543.2048 found: 543.2081.



293b

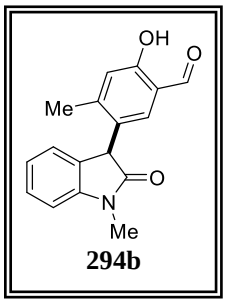
Synthesis of 5-(1-benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2-hydroxybenzaldehyde (**294a**): To a solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) and 2-hydroxybenzaldehyde (**271a**, 54 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **294a** (103 mg, 75%) as a white solid according to general procedure. R_f = 0.41 (EtOAc/hexane = 2:3, v/v); mp 157-158 °C; IR (neat): ν_{max} 3057, 1707, 1655, 1609, 1482, 1350, 1278, 1195, 737 cm^{-1}; ^1H NMR



294a

($CDCl_3$, 400 MHz) δ = 4.75 (s, 1H, CH), 4.99 (ABq, $\Delta\delta_{AB}$ = 0.05, J = 15.6 Hz, 2H, CH_2), 6.89 (d, J = 7.6 Hz, 1H, ArH), 7.03 (d, J = 8.8 Hz, 1H, ArH), 7.11 (t, J = 7.6 Hz, 1H, ArH), 7.23 (d, J = 7.2 Hz, 1H, ArH), 7.28-7.37 (m, 6H, ArH), 7.42-7.45 (m, 1H, ArH), 7.49 (d, J = 2.4 Hz, 1H, ArH), 9.88 (s, 1H, CHO), 11.05 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 50.8, 109.6, 118.5, 120.7, 123.1, 125.2, 127.5, 127.9, 128.0, 128.2, 128.8, 128.9, 133.4, 135.8, 137.0, 143.6, 161.2, 175.8, 196.5 ppm; HRMS (ESI) Calculated for $C_{22}H_{17}NO_3$ $(M+H)^+$: 344.1287 found: 344.1288.

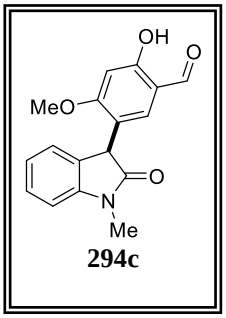
Synthesis of 2-hydroxy-4-methyl-5-(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)benzaldehyde (**294b**): To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 2-hydroxy-4-methylbenzaldehyde (**271b**, 87 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **294b** (132 mg, 81%) as a white solid according to general procedure. R_f = 0.22 (EtOAc/hexane = 2:3, v/v); mp 183-184 °C; IR (neat): ν_{max} 2924, 1704, 1651, 1613, 1464, 1345, 1264, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.46 (br s, 3H, CH_3), 3.32 (s, 3H, CH_3), 4.84 (s, 1H, CH), 6.91-7.13 (m, 5H, ArH), 7.30-7.43 (m, 1H, ArH), 9.74 (s, 1H, CHO), 10.97 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.7, 26.5, 108.4, 119.1, 119.8, 123.0, 124.5, 127.5, 128.4, 128.7, 144.4, 148.4, 160.9, 175.8, 195.7 ppm; HRMS (ESI) Calculated for $C_{17}H_{15}NO_3$ $(M+H)^+$: 282.1130 found: 282.1124.



294b

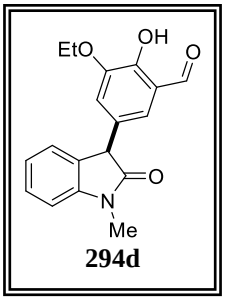
Synthesis of 2-hydroxy-4-methoxy-5-(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)benzaldehyde (**294c**): To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 2-hydroxy-4-methoxybenzaldehyde (**271c**, 97 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture

was stirred at 0 °C under the open-air atmosphere to afford product **294c** (146 mg, 85%) as a white solid according to general procedure. R_f = 0.33 (EtOAc/hexane = 2:3, v/v); mp 165-166 °C; IR (neat): ν_{max} 2920, 1694, 1640, 1463, 1349, 1204, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.34 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 4.87 (s, 1H, CH), 6.50 (s, 1H, ArH), 6.92-7.11 (m, 3H, ArH), 7.26-7.36 (m, 2H, ArH), 9.69 (s, 1H, CHO), 11.57 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.5, 47.0, 56.3, 99.7, 108.0, 114.7, 118.7, 122.7, 124.0, 128.2, 129.0, 134.9, 144.2, 164.3, 164.6, 176.2, 194.4 ppm; HRMS (ESI) Calculated for $C_{17}H_{15}NO_4$ $(M+H)^+$: 298.1079 found: 298.1055.



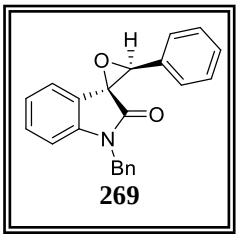
294c

Synthesis of 4-ethoxy-5-(1-ethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-2-hydroxybenzaldehyde (**294d**): To a solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) and 3-ethoxy-2-hydroxybenzaldehyde (**271d**, 106 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at 0 °C under the open-air atmosphere to afford product **294d** (132 mg, 73%) as a white solid according to general procedure. R_f = 0.30 (EtOAc/hexane = 2:3, v/v); mp 143-144 °C; IR (neat): ν_{max} 2927, 1703, 1641, 1611, 1466, 1348, 1254, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.49 (t, J = 6.8 Hz, 3H, CH_3), 3.28 (s, 3H, CH_3), 4.08-4.13 (m, 2H, CH_2), 5.22 (br s, 1H, CH), 6.45 (br s, 1H, ArH), 6.97-7.44 (m, 5H, ArH), 10.54 (br s, 1H, CHO), 12.36 (br s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.7, 26.7, 46.0, 64.8, 108.7, 118.5, 118.6, 123.0, 125.4, 127.1, 128.9, 130.0, 144.3, 147.5, 154.4, 174.9, 176.8, 195.6 ppm; HRMS (ESI) Calculated for $C_{18}H_{17}NO_4$ $(M+H)^+$: 312.1236 found: 312.1214.



294d

Synthesis of 1-benzyl-3'-phenylspiro[indole-3,2'-oxiran]-2(1*H*)-one (269): A solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (5 mL) was added dropwise to a solution containing benzaldehyde (**220a**, 47 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and rhodium(II) acetate (1 mol%) at 60 °C for the period of 2 h to afford product **269** (120 mg, 92%) as a white solid. R_f = 0.42 (EtOAc/hexane = 1:4, v/v); mp 123-124 °C; IR (neat): νmax 3054, 1726, 1614, 1461, 1354, 1176, 736 cm^{-1}; 1H NMR (CDCl3, 400 MHz) δ = 4.60 (s, 1H, CH), 4.71 (ABq, $\Delta\delta_{AB}$ = 0.15, J = 15.6 Hz, 2H, CH_2), 6.67 (d, J = 7.6 Hz, 1H, ArH), 6.94-6.98 (m, 1H, ArH), 7.10-7.32 (m, 10H, ArH), 7.52-7.54 (m, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.2, 62.0, 67.8, 109.8, 121.8, 122.8, 123.6, 127.5, 127.6, 127.8, 127.9, 128.87, 128.91, 130.2, 131.9, 135.6, 143.8, 170.1 ppm; HRMS (ESI) Calculated for $C_{22}H_{17}NO_2$ $(M+Na)^+$: 350.1157 found: 350.1158.



269

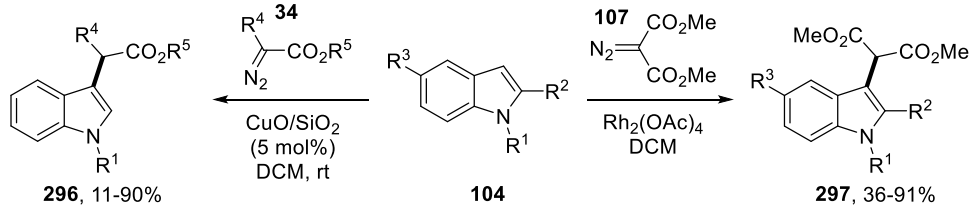
CHAPTER - IV

Indole and its variants have been identified as privileged scaffolds in bioorganic and medicinal chemistry due to their prevalence in a wide range of biologically activity and natural products.[199] Specifically, C2 and C7 substituted indoles are used to provide a wide range of medicinal applications.[200] In aspects of an atom- and step-economy, formal functionalization of a constructed indole core appears to be a highly effective strategy for diverse indoles.[201] Insertion of carbenoids produced by the metal-catalyzed decomposition of diazocarbonyl compounds represents the most precise route to a wide range of functionalized indoles. The outcome of such a transformation is determined by the original substrate's substitution pattern.[202] Because, C-3 position of the indole nucleus has a higher C–H nucleophilic nature than C-2 position electrophilic carbene insertion is commonly directed. Existing substitution at the indole C-3 position might prevent this method and force it for C-2 alkylation.

The detailed literature reports for diazocarbonyl compounds, indole derivatives and their reactions will be covered in the following sub-sections:

4.1.1. Intermolecular reaction of diazocarbonyl compounds with indoles
4.1.2. Intramolecular reaction of diazocarbonyl compounds with indoles
4.1.3. Synthesis of indole incorporated macrocycles

4.1.1. Intermolecular reaction of diazocarbonyl compounds with indoles

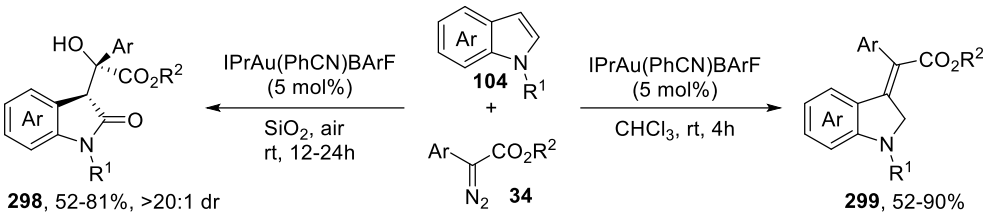


Scheme 116

Kerr, Fraile and co-workers have reported[203] that CuO/SiO_2 or $Rh_2(OAc)_4$ catalyzed the reaction of aryldiazoacetates or methyldiazomalonate **34/107** with N-alkylated indoles

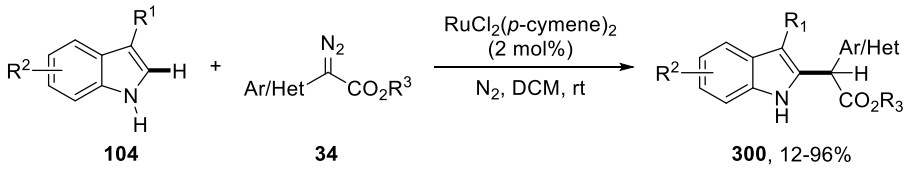
104 under mild reaction conditions gave the 3-alkylated indoles **296/297** in moderate to excellent yields (Scheme 116).

Liu and co-workers have described[204] Au-catalyzed method to obtain 3-functionalized indoles **299** with exclusive *Z*-configuration. They studied mechanism that began with the dearomatization of indoles **104** with diazoesters **34** *via* cationic catalysis by Au(I). Further, a tandem reaction of indoles with electron-donating substituent on N-atom **104** provided 3-substituted indolin-2-ones **298** (Scheme 117).

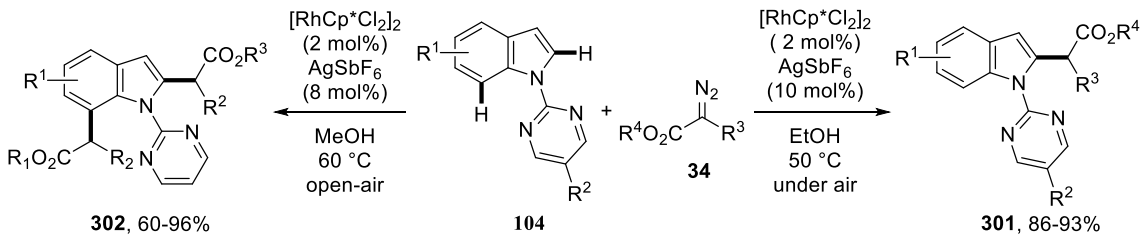


Scheme 117

The C-2 selective carbenoid functionalization of unprotected indoles **104** was performed.[205] Utilizing α-aryldiazoesters **34** as a carbenoid source and $[RuCl_2(p\text{-cymene})]_2$ as a catalyst, 2-alkylated indoles **300** were obtained in high yield (Scheme 118).



Scheme 118

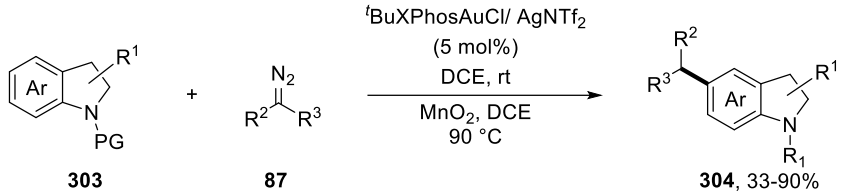


Scheme 119

Hu, Wang and co-workers have developed[206] an efficient and atom-economic protocol for the production of C2-H alkyl-substituted or C2-H, C7-H alkyl-substituted indoles

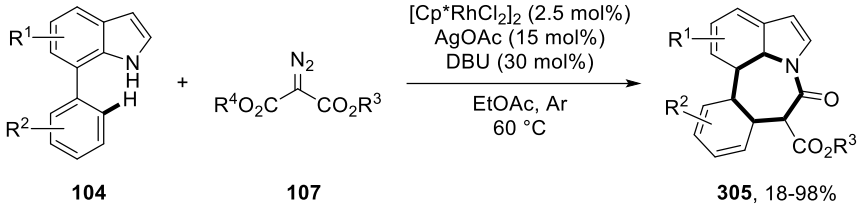
301/302 using Rh(III)-catalyzed regioselective alkylation of indoles **104** with diazo compounds **34**. Under mild conditions, the reaction might proceed and yield an array of products in good to excellent yields (Scheme 119).

A unique method for the production of C5-alkylated indoles **304** has also been developed[207] using an Au-catalyzed reaction of indolines **303** and diazo compounds **87**. The oxidative aromatization happens immediately after the addition of MnO_2 and the C5-alkylated indoles **304** were obtained in a single pot (Scheme 120).



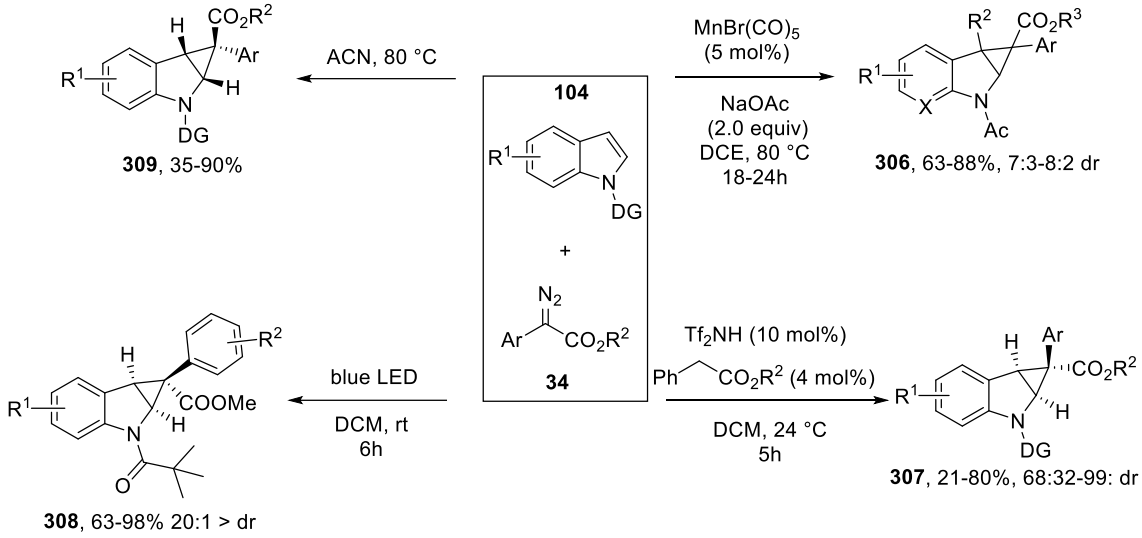
Scheme 120

An unexpected[208] Rh(III)-catalyzed regioselective C-H functionalization/base-catalyzed intramolecular amidation of 7-arylindoles **104** with diazomalonates **107** in one pot was demonstrated to provide a concise step to seven-membered azepinoindoles **305** in high yields (Scheme 121).



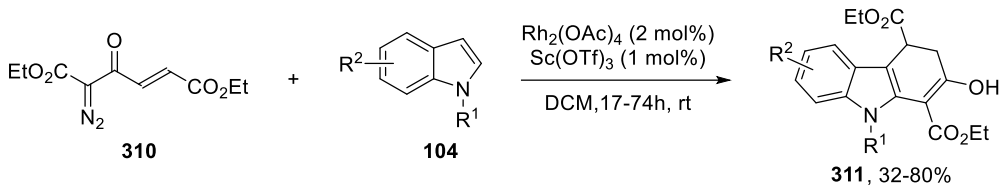
Scheme 121

Anbarasan, Song, Ravva, Matsuo and co-workers have demonstrated[209] a metal or metal-free or thermal or blue light mediated C2,C3-cyclopropanation of appropriate directing group incorporated indoles **104** with α-diazo esters **34** for the diastereoselective synthesis of cyclopropane-fused indolines **306-309**. An array of products **306-309** was obtained in excellent yields with good diastereoselectivity under mild conditions. Acetyl pyridyl, pyrimidyl, aminocarbonyl and tert-butyl groups acted as a directing group (Scheme 122).

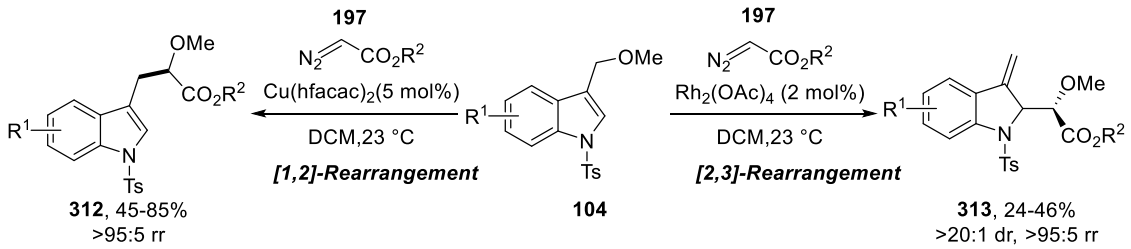


Scheme 122

Balamurugan and co-workers reported[210] the production of highly functionalized tetracarbazoles **311** *via* a one-pot Michael addition followed by a cyclization sequence catalyzed by a combination of $Rh_2(OAc)_4$/$Sc(OTf)_3$. Indoles **104** were used to annulate a seriously functionalized six-carbon building block that had been developed and used as a 1,4-diacceptor in the production of carbazoles **311** (Scheme 123).



Scheme 123

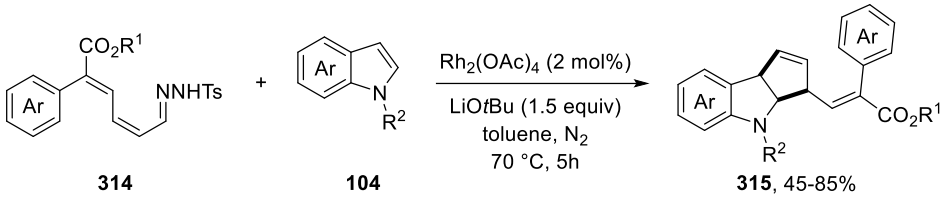


Scheme 124

Tantillo, Tambar and co-workers have delineated[211] (Scheme 124) the catalyst-controlled regiodivergent rearrangement reactions of onium-ylides from indoles **104** and diazo compounds **197**. Oxonium ylides formed *in situ* from indoles **104** to perform selective [1,2]- and [2,3]-rearrangements in the presence of Rh and Cu catalysts,

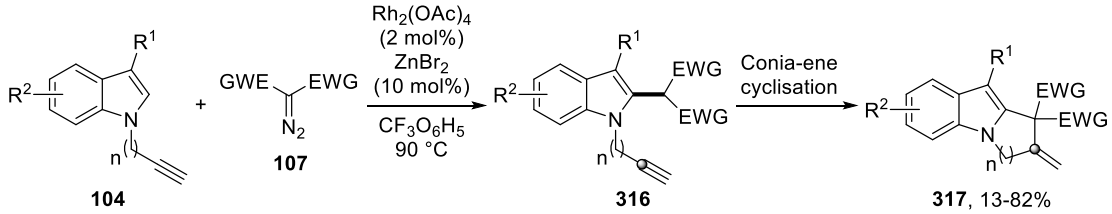
respectively.

Song and co-workers reported[212] $Rh_2(OAc)_4$/LiO^{t}Bu-catalysed synthesis of tetrahydrocyclopenta[*b*]indoles **315** from tosylhydrazones **314** and indoles **104** *via* [3+2]-annulation (Scheme 125).

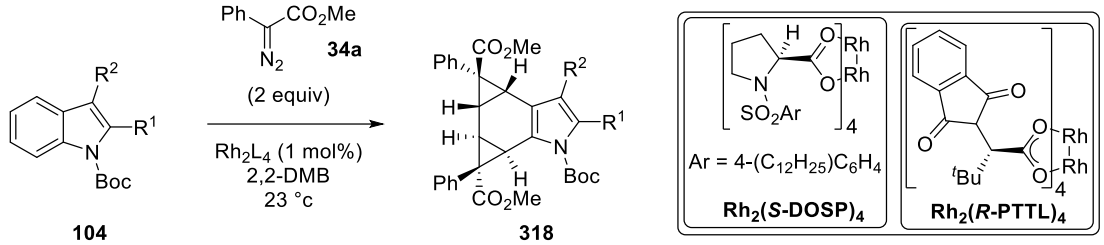


Scheme 125

Grover and co-workers established[213] a reliable dual catalyst system Rh(II)/Zn(II) for the simple formation of pyrroloindoles **317** utilizing cascade C-H functionalization followed by Coniaene annulation of *N*-propargylindoles **104** and α-diazomalonates **107** (Scheme 126).

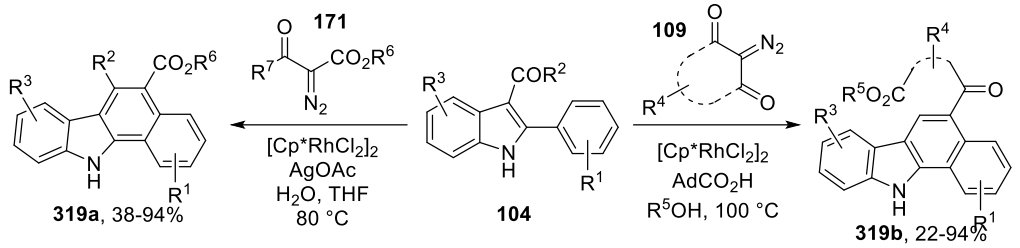


Scheme 126

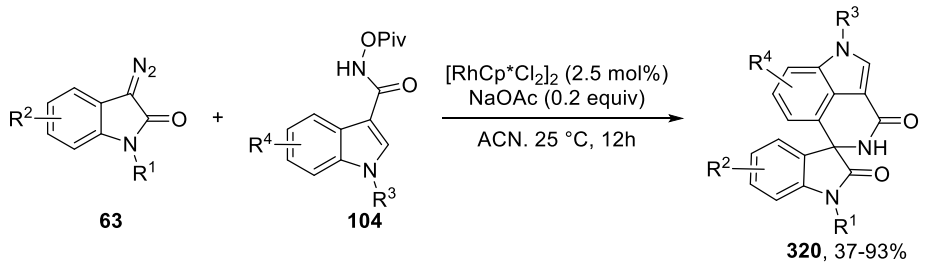


Scheme 127

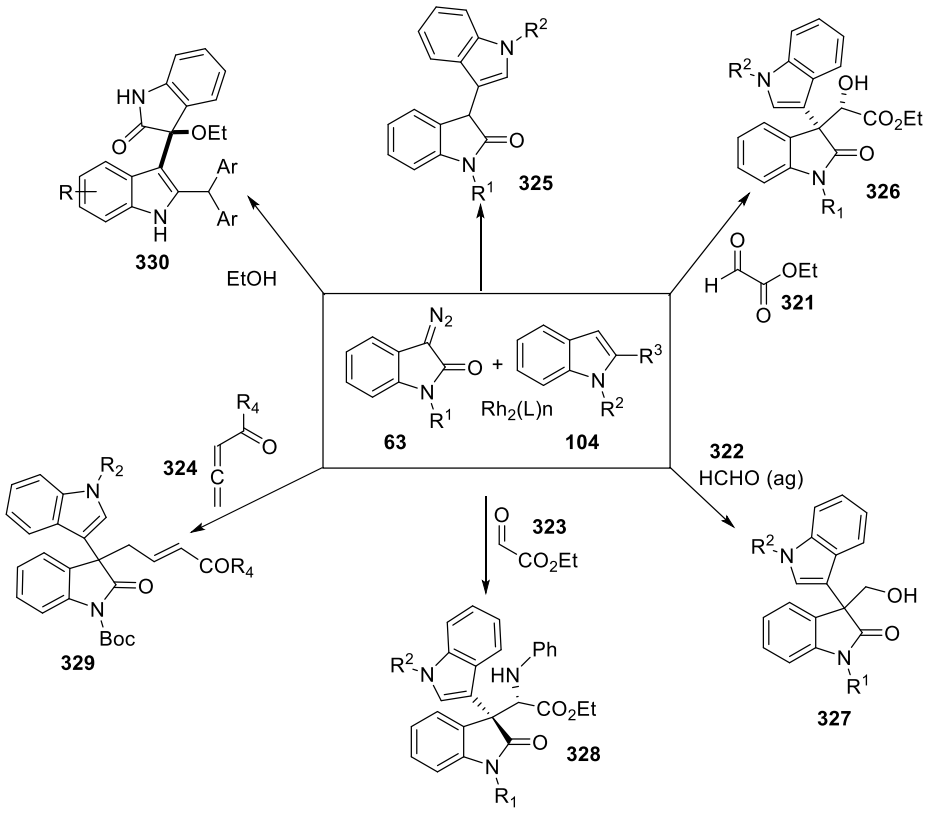
Davies and co-workers have demonstrated[214] that N-Boc protected indoles **104** having C2- or C3-substitution preventing cyclopropanation of indole **104** at C2–C3 position. These reactions underwent double cyclopropanation on benzene ring with the chiral catalysts such as Rh_2(S-DOSP)$_4$ or Rh_2(S-PTTL)$_4$ to generate tetracycles **318** as shown in Scheme 127.



Scheme 128



Scheme 129



Scheme 130. Synthesis of various 3,3'-biindoles from diazoamides and indoles derivatives

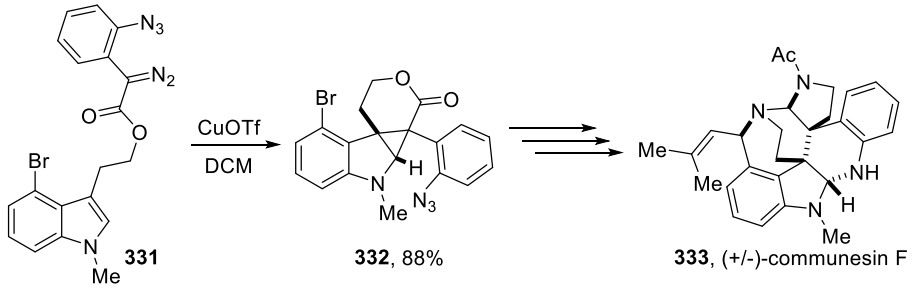
The efficient synthesis of benzo[*a*]carbazoles **319** was demonstrated[215] using a Rh(III)-catalyzed [5+1]-annulation reaction of 2-aryl-3-acyl-1*H*-indoles **104** with α-diazocarbonyl compounds **109/171**. The tandem process was achieved by a C-H bond alkylation/cyclization followed by aromatization (Scheme 128).

Biao, Xiong and co-workers have reported[216] a directing group incorporated indoles **104** with diazoamides **63** in the presence of $[RhCp^*Cl_2]_2$ to afford a novel aza-spiro[4,5]indoles **320** in moderate to excellent yields. The reaction selectively functionalized at C(4)-H activation followed by cyclization of indoles **104** with diazoamides **63** (Scheme 129).

Our research group and others documented[217] the synthesis of 3,3'-biindoles **325-330** using rhodium carbenoids with various indole derivatives **104** (Scheme 130).

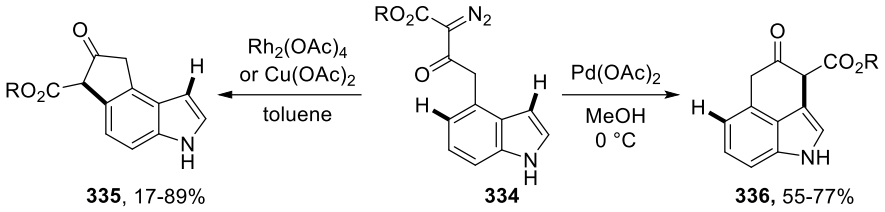
4.1.2. Intramolecular reaction of diazocarbonyl compounds with indoles

Qin and co-workers have developed[218] an unique intramolecular cyclopropanation followed by fragmentation from diazoindole **331** for the synthesis of the core of the communesin family of natural products. Cu-Catalyzed intramolecular cyclopropanation delivered cyclopropylindoline **332** in 88% yield. The consequent reduction of cyclopropylindoline **332** with concomitant ring-opening of the strained **332** enables cyclization to aminal. A few more synthetic steps gave the complex alkaloid (±)-communesin F **333** (Scheme 131).



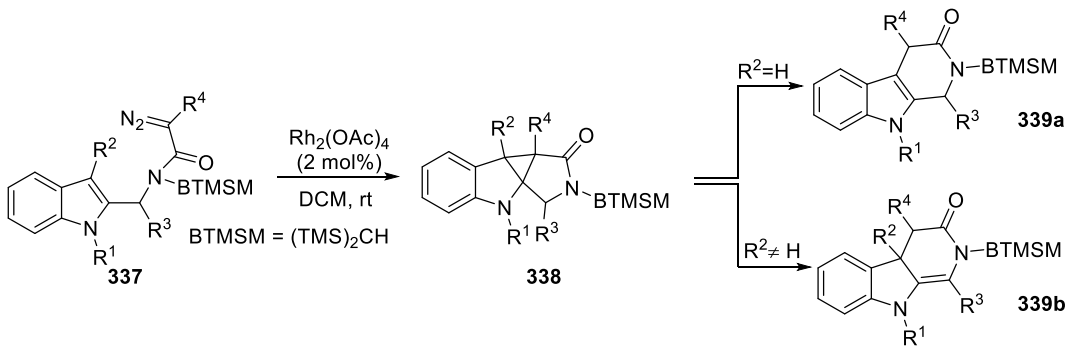
Scheme 131

Kobayashi and co-workers have identified[219] an intramolecular cyclization of diazo malonates at 4-position of indole. In the combination of a Rh(II) or Cu(II) catalyst, diazo compound **334** cyclized at C-5 of indole to yield cyclopentanone **335**. By comparison, diazo compound **334** cyclized to cyclohexanone **336** when subjected to Pd(II) catalyst (Scheme 132).



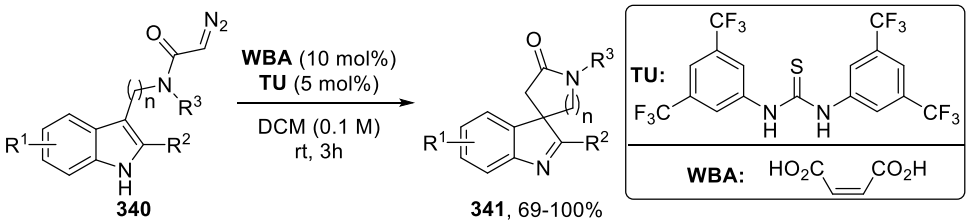
Scheme 132

Wee and co-workers have reported[220] the Rh(II) catalyzed reactions diazoamides **337** and studied the metallo-carbenoids to evaluate steric, conformational, electronic factors and the effect of chemo- and site-selectivity. Stereoselectivity models that included carbene complex intermediates were established (Scheme 133).



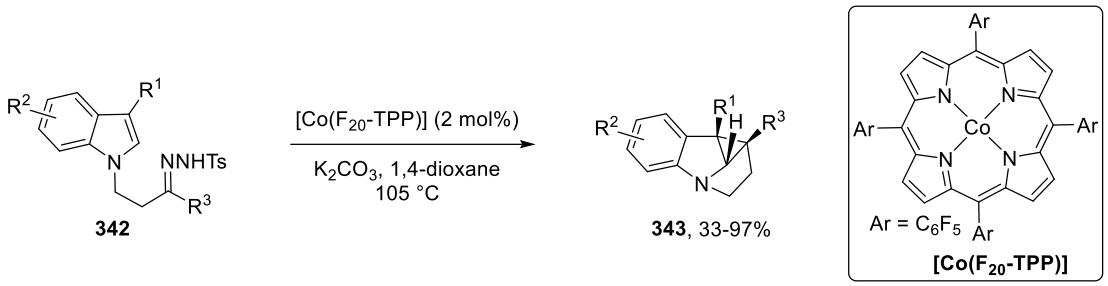
Scheme 133

Harada, Nemoto and co-workers have discovered[221] the Friedel-Crafts alkylation reaction of functionalized 3*H*-indoles **341**, maleic acid and thiourea. This low-cost strategy allowed for the chemoselective production of unique spiroindolenines **341** with bulky C2-position substituents (Scheme 134).



Scheme 134

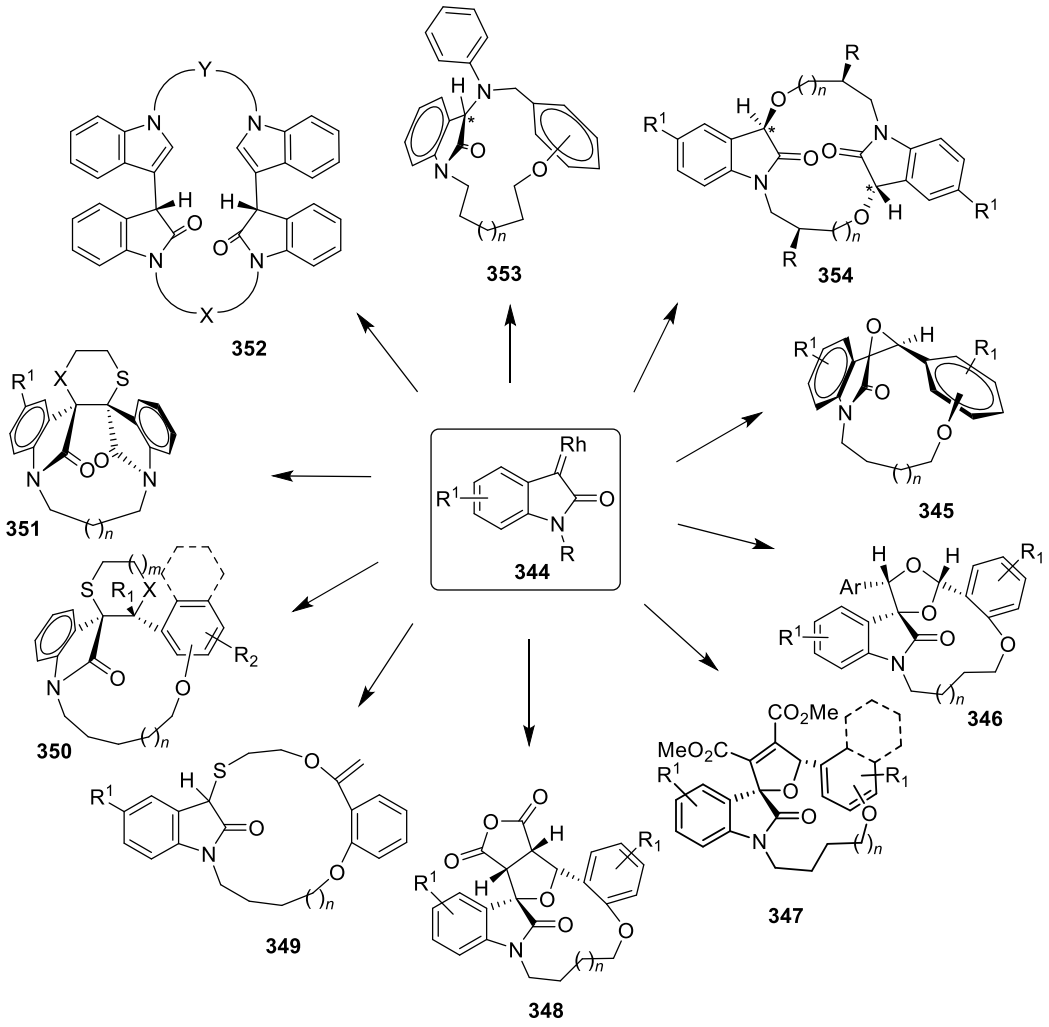
Chemoselective Cu(II)-porphyrin catalyzed intramolecular cyclopropanation of N-alkyl indoles **342** with alkylcarbenes has been reported.[222] The reaction allows for the rapid synthesis of a variety of nitrogen-having polycyclic compounds **343** from readily available materials (Scheme 135).



Scheme 135

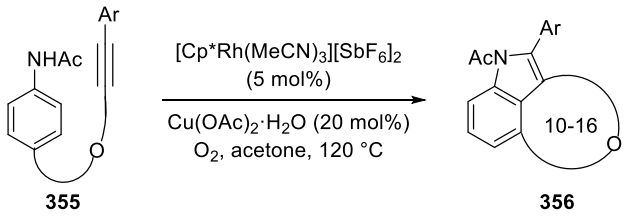
4.1.3. Synthesis of indole incorporated macrocycles

As shown in Scheme **136**, our group has developed[138b,223] several oxindoles incorporated macrocycles **345-354** using Rh(II)-carbenoids **344** *via* carbonyl-, oxonium- or sulfonium ylides or insertion reactions with diverse nucleophiles.



Scheme 136

Jia and co-workers have reported[224] the macrocyclic 3,5-fused indoles **356** from *para*-substituted acetanilides **355**. The reaction seemed to be general, producing a variety of macrocycles **356** having 10-16-membered rings and an ester / ether linker in good yields (Scheme 137).



355 **356**

Scheme 137

Scope and objectives: There was a rich body of literature that the intermolecular reactions of diazocarbonyl compounds with indole derivatives provided a competitive C-H insertion or alkylation (C2, C3, C4, C5 and C7 position of indole scaffold), cyclopropanation, annulations products and heterocycles. Significant progress has been made in recognizing the varied reactivity of metal-stabilized carbenoids generated from α-diazocarbonyl compounds. Similarly, the reactivity and selectivity of the intramolecular reactions of diazoindoles have also been investigated. Therefore, the objectives of the present work are mainly focused on the intermolecular synthesis of 2,3′-biindoles and intramolecular synthesis of indole incorporated macrocycles.

The objectives of the present work are the following:

- ❖ To study Rh(II)-catalyzed intermolecular C-2 alkylation reactions
- ❖ To study TfOH-catalyzed intramolecular C-3 alkylation reactions

RESULTS AND DISCUSSION

4.2.1. Synthesis of 2,3′-biindoles

Indole and its variants have become the most significant biological units in natural products, while they have crucial applications in medicinal chemistry including materials science.[225] As an outcome, their production and functionalization have enchanted much interest over the last few decades.[226] Besides a wide range of indole-incorporating compounds, 2,3′-biindoles have notably emerged as a potential scaffold for bioactive compounds. These molecules also have served as important intermediates in the total synthesis of a wide range of other indole alkaloids with 2,3′- and 3,3′-biindole motifs.[227] Representative compounds I-III[228-230] are natural products that contain 2,3′-biindoles, for instance, Ancorinazole (III) had been derived from marine organisms and proves therapeutic potential for neuropsychiatric disorders (Figure 25). Compound IV and V are protein p53 and IGF1-R inhibitors respectively,[231] while compound VI shows anti-bacterial activity.[232] However direct C–

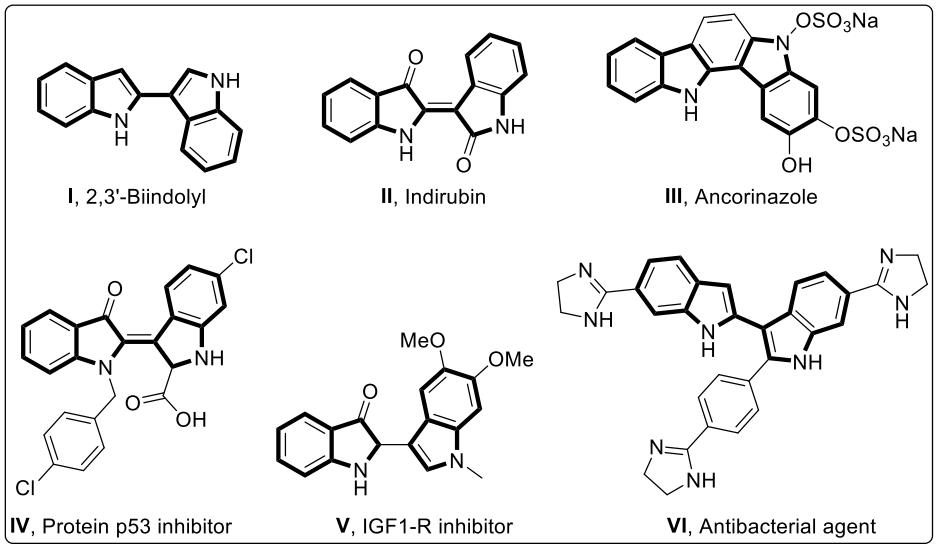


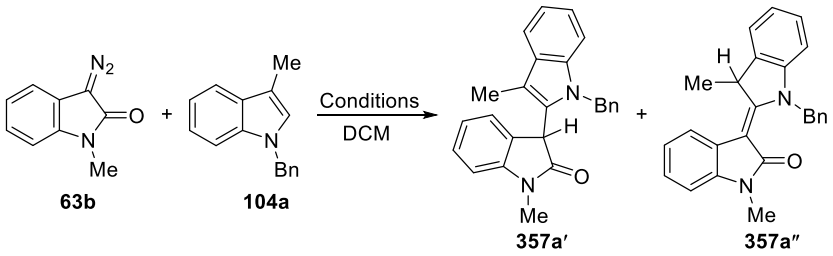
Figure 25. Representative bioactive compounds and natural alkaloids containing the biindolyl scaffold

H/C–H cross-coupling reactions to connect with organic molecules had also long been established for biaryl production, simple C–C bond renovation in the absence of directing groups becomes particularly difficult. A various synthetic method for effective construction of 2,3′-biindoles have also been documented. Under strongly acidic conditions, the traditional Fischer indole synthesis might produce 2,3'biindoles.[233a] The nucleophilic addition of imines to indoles, preceded by *p*-TSA/$FeCl_3$-caused cyclization, might result in 2,3′-biindoles.[233b] An altered Vilsmeier reaction had been described to generate 2,3′-biindoles from 5,6-dimethoxyindole-2-carboxylates and oxindoles.[233c] TsOH-catalyzed arylation reaction of tryptamines with 2-indolylmethanols is a slightly different approach.[233d] NBS or I_2 catalyzed homo-coupling reactions of two indole units produced 2,3′-biindoles.[233e,f] Pd(II)/$Cu(OAc)_2$ catalyzed reaction of two indoles undergo oxidative homo-coupling provided 2,3′-biindoles.[233g] Since the equivalent amounts of oxidants and strong acidic medium, all of the aforementioned reactions triggered environmental problems. The main focus of this chapter is a one-pot reaction that can provide a variety of substituted 2,3′-biindoles **357** as a mixture of tautomers form diazoamides **63** and 3-substituted indoles **104** in the presence of 2 mol% of $Rh_2(OAc)_4$ at room temperature under nitrogen atmosphere.

In continuation of our previous work,[217a] 3-substituted indoles utilized instead of unsubstituted indoles. A reaction of 3-methylindole **104a** with dizoamide **63b** was carried out at room temperature in the presence of 2 mol% of $Rh_2(OAc)_4$ in dichloromethane. Fortunately, 2,3′-biindoles **357a** have been obtained in 38% yield as a mixture of tautomers in the ratio of 1.2:1 and the remaining diazoamide led to the rapid decomposition (Table 10, entry 1). Product **357a** was characterized based on spectral data (IR, NMR, and HRMS). Products **357** was confirmed by NMR and mass

spectroscopic analyses and observed as a mixture of tautomers. To stop decomposition, diazoamide **63b** was gradually added with a slow rate of addition (5 mL/h) using a syringe pump in DCM to afford 2,3′-biindoles **357** in moderate yield. The reaction of diazoamide **63b** with the slow rate of addition of (2 and 0.5 mL/h) using a syringe pump was performed to provide tautomer of products **357** in 81 and 96% yields, respectively (Table 10, entries 3 and 4). A variety of catalysts, such as Cu(I)TC, $Sc(OTf)_3$ or $In(OTf_3$ were studied to optimize the reaction conditions; however, no remarkable results were achieved (Table 10, entries 5-7). The reaction was also tested for various Lewis acids ($FeCl_3$, $AlCl_3$, $InCl_3$) and Brønsted acids (*p*-TSA, TfOH and HCl) failed to deliver the expected products **357** (Table 10, entries 8 and 9). Among the optimized catalysts $Rh_2(OAc)_4$ was found to be better (entry 4). A similar quantity of

Table 10. Optimization of reaction conditions for the formation of **357**[a]



Entry	Catalyst (10 mol%)	Rate of addition **63b** (mL/h)	t (h)	Yield [%][b] **357a**
1[c]	$Rh_2(OAc)_4$	-	1	38
2[c]	$Rh_2(OAc)_4$	5	1	56
3[c]	$Rh_2(OAc)_4$	2	2	81
4[c]	**$Rh_2(OAc)_4$**	**0.5**	**8**	**96**
5	Cu(I)Tc	0.5	8	76
6	$Sc(OTf)_3$	0.5	8	56
7	$In(OTf)_3$	0.5	8	42
8[d]	Lewis acids	0.5	20	nr[e]
9[f]	Brønsted acids	0.5	25	nr[e], nd[g]
10[h]	$Rh_2(OAc)_4$	0.5	8	93

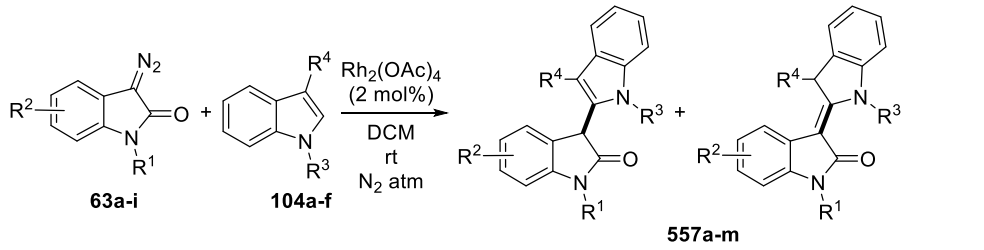
[a]Reaction conditions: diazoamide **63b** (0.53 mmol, 1 equiv) was dissolved in 4 mL of dry solvent, 3-methyl indole **104a** (0.59 mmol, 1 equiv), catalyst (10 mol%), room temperature under nitrogen atmosphere. [b]Isolated yield. [c]2 mol% of $Rh_2(OAc)_4$. [d]Various Lewis acids ($FeCl_3$, $AlCl_3$, $InCl_3$). [e]No reaction. [f]Various Brønsted acids (*p*-TSA, TfOH, con. HCl). [g]No desired product. [h]Reaction carried out at reflux utilized DCE as a solvent.

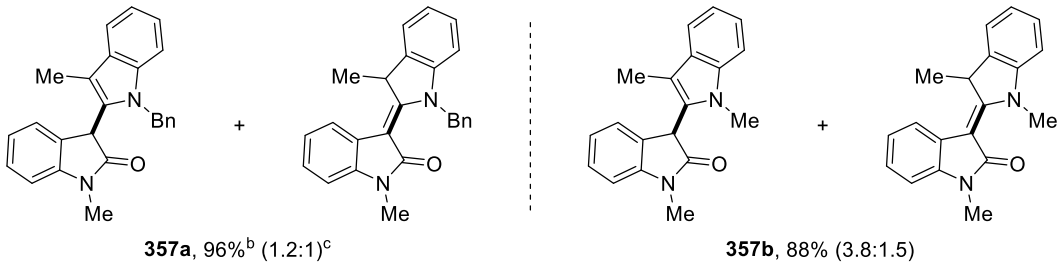
yield of products **357** was observed, when the reaction was carried out under reflux conditions in the presence of $Rh_2(OAc)_4$ as a catalyst (Table 10, entry 10). Ultimately, the resulting optimized reaction conditions were achieved: slow rate of addition of **63** (0.5 mL/h) (1 equiv), **104** (1 equiv) and $Rh_2(OAc)_4$ (2 mol%) under a nitrogen atmosphere in DCM at room temperature for 8 h (Table 10, entry 4).

The utility and applicability of this intriguing protocol for obtaining 2,3′-biindoles were examined. We then investigated the scope of $Rh_2(OAc)_4$-catalyzed alkylation reactions with a broad range of electron-donating or electron-withdrawing diazoamides under the optimizing reaction conditions. Following that a various 2,3′-biindoles **357a-m** were synthesized from diazoamides **63a-i** and indoles **104a-f** *via* cyclopropane formation followed by ring-opening, as shown in Table 11. The reaction of N-methyl substituted diaoamide **63** provided **357b** in 88% yield as a mixture of tautomers in the ratio of 3.8:1.5 based on ^{1}H-NMR. Electron-donating group of methyl and methoxy substituent on 5-position of diazoamides gave the desired products **357c,d** in excellent yields in the ratio of 3.2:1.2 and 1.2:1. 6-Methoxy substituted diazoamide provided 2,3′-biindoles **357e** in 79% yield in the ratio of 2.4:1.4. 5-Fluoro and chloro-substituted diazoamides were also discovered to be viable substrates for obtaining high yields of 2,3'-biindoles **357f,g** in the ratio of 1:1 and 4.3:1.8, respectively. When 4-bromosubstituted diazoamide was used, the desired product **357h** was detected in 71% yield with the ratio of 1.1:0.9. However, 5-nitrosubstituted diazoamide was utilized and failed to deliver the desired product **357k**. Furthermore, the N-unprotected 3-methyl indole was explored and a single isomer of alkylated products **357i',j'** obtained in 78 and 81% yields. Following that the electron-drawing nature of 3-nitrile or 3-acetyl substituted indole was used in these reactions, but in vain.

Based on our previous report,[217a] a plausible mechanism for **357** was proposed in Scheme 138. The transient Rh(II) carbenoids intermediate **A** derived from diazoamides **63**. Intermediate **A** trapped by indole **104** to form the intermediate **B**, which might undergo intramolecular cyclopropanation with C2-C3 double bond of the indole ring.

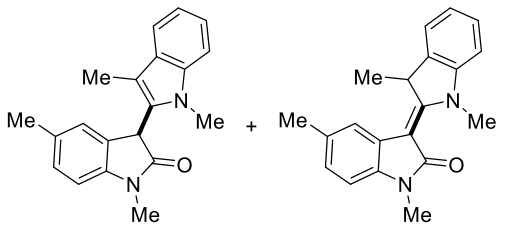
Table 11. Scope of the diazoamides and indoles[a]



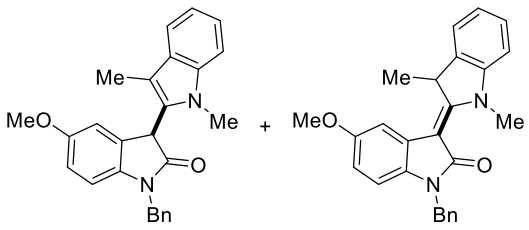


357a, 96%[b] (1.2:1)[c]

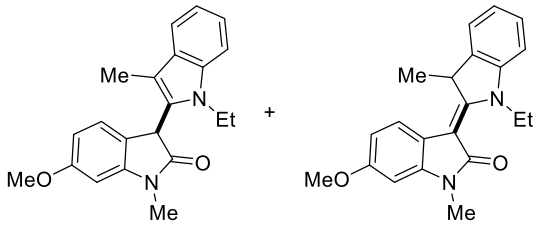
357b, 88% (3.8:1.5)



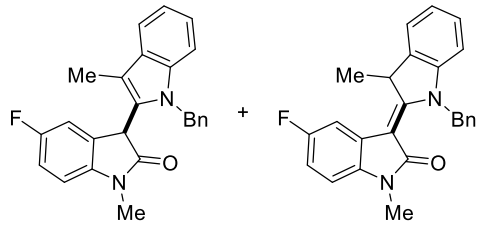
357c, 94% (3.2:1.2)



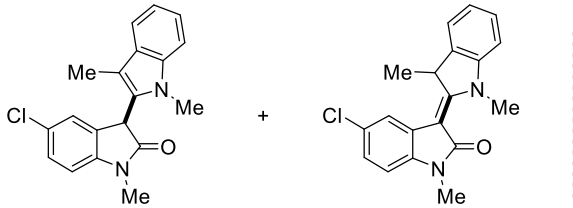
357d, 84% (1.2:1)



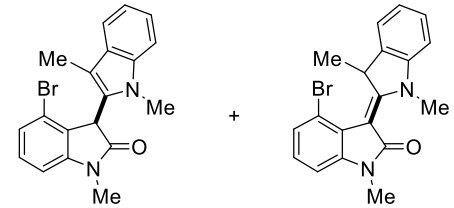
357e, 79% (2.4:1.4)



357f, 87% (1:1)



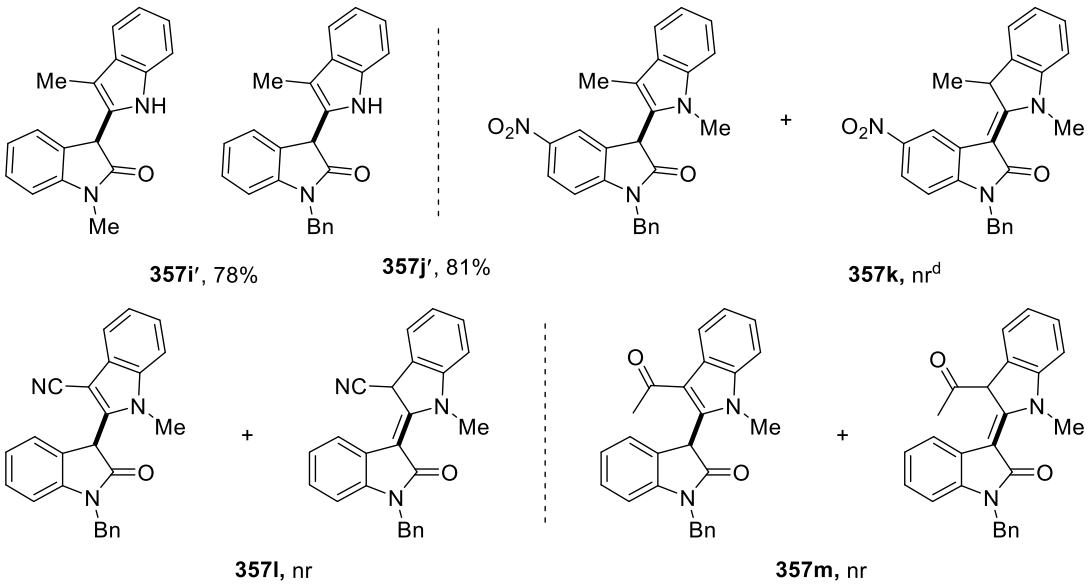
357g, 91% (4.3:1.8)



357h, 71% (1.1:0.9)

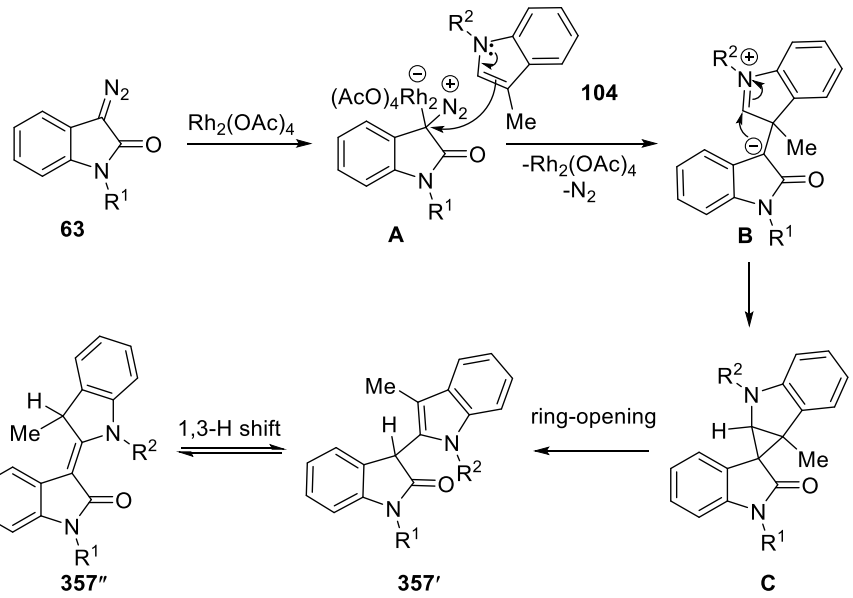
Cont….

Cont.....



[a]Reaction conditions: To the mixture containing **104** (1.1 equiv) and $Rh_2(OAc)_4$ (2 mol%) in 5 mL of dry DCM under a nitrogen atmosphere, **63** (1 equiv) in 4 mL of dry DCM was added using a syringe pump with the slow rate of 0.5 mL/h under reflux conditions.

The labile intermediate **C** underwent ring-opening to provide isomer **357'** which further undergo 1,3 proton shift gave another isomer **357''**.



Scheme 138. Plausible reaction mechanism for the formation of **357**' and **357''**

4.2.2. Synthesis of indole incorporated macrocycles

Several methods to synthesize macrocycles have been developed over the last few decades, emphasizing the importance of such compounds in biological and supramolecular studies, as well as their existence as natural products. Metallo-carbenoids seem to be transient intermediates formed when diazocarbonyl compounds react with transition metal catalysts. Acid-catalyzed reactions of α-diazocarbonyl compounds have been widely explored, and their synthetic applicability in the synthesis of various biologically active compounds and natural products has been developed.[234] Acid-catalysed reactions with α-diazocarbonyl compounds are classified into two types. The first type is Brønsted acid or Lewis acid activation of electrophiles, toward which α-diazo compounds behave as nucleophiles to produce diazonium ions as intermediates. The second type is the activation of α-diazo compounds with acids. The acid-catalyzed stimulation of α-diazocarbonyl compounds, preceded by alkylation of aromatic, alkenes and alkynes groups, has been investigated.[235] Brønsted acid-catalyzed reactions with diazocarbonyl compounds have also been developed. The synthesis of indole incorporated macrocycles has not been reported from diazo compounds.

The main focus of this chapter is on the TfOH-catalyzed reactions of indole tethered on cyclic diazoamides for C-alkylation reactions. The current study has been divided into two sub-sections.

4.2.2.1. Synthesis of indole tethered on cyclic diazoamides

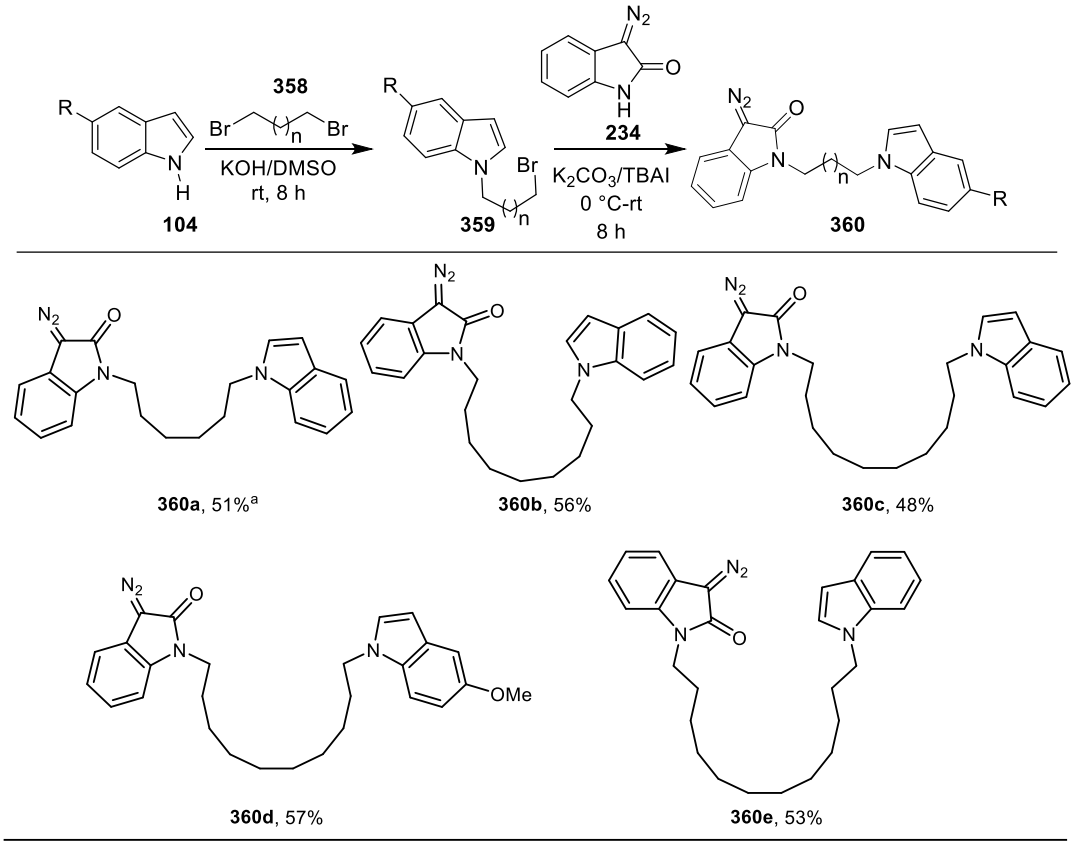
4.2.2.2. Synthesis of indole incorporated macrocycles *via* C-alkylation reactions

4.2.2.1. Synthesis of indole tethered on cyclic diazoamides

To synthesize oxindole incorporated macrocycles, the required substituted cyclic diazoamides **234** were assembled by *N*-alkylation of indole **104** using dibromoalkanes **358** in the presence of potassium hydroxide/DMSO to afford[236] the corresponding

mono-bromo alkylated indole **359** in 80-85% yields. Subsequent *N*-alkylation of diazoamides **234** using *mono*-bromo alkylatedindole **359** in the presence of potassium carbonate/DMF afforded the indole tethered on diazoamides **360** in 48-57% yields (Table 12). The strong peak that appears around 2105 cm^{-1} in the IR spectrum confirms the presence of diazo functional groups. Further, these compounds exhibited consistent NMR spectral data. Macrocycles, the distance between the diazoamide and indole functional groups was varied to synthesize indole tethered on cyclic diazoamides **360a-e** in good yields.

Table 12. Synthesis of indole tethered cyclic diazoamides **360**



[a]Isolated yield.

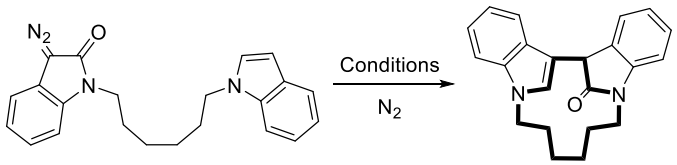
4.2.2.2. Synthesis of indole incorporated macrocycles *via* C-alkylation reactions

To synthesize indole incorporated macrocycles **361** from indole tethered on diazoamides **360** in the presence of a $Rh_2(OAc)_4$ as a catalyst, the reaction conditions were optimized using the slow rate of addition of indole tethered on diazoamides **360**.

The optimization conditions were discussed in Table 13. Based on our previous observation,[138d,191] we investigated the metal-catalyzed decomposition reactions with slow addition as well as the controlled concentration of indole tethered on diazoamides **360** to produce indole incorporated macrocycles **361** *via* intramolecular cyclopropanation followed by the ring-opening of cyclopropane. Initially, the indole tethered on diazoamide **360a** was added with a slow rate of addition (0.55 mL/h) using a syringe pump in dichloromethane (DCM) to afford the indole incorporated macrocycle **361a** in 56% yield (Table 13, entry 1).

Then Cu(I)TC, various Lewis and Brønsted acid catalysts, such as $Sc(OTf)_3$, $In(OTf)_3$, $BF_3{\cdot}OEt_2$, *p*-TSA, TfOH and con. HCl were screened (Table 13, entries 2-8); however,

Table 13. Optimization of reaction conditions for the formation of **361a**[a]



360a **361a**

Entry	Catalyst (20 mol%)	Solvent	Rate of addition **360a** (mL/h)	t (h)	Yield [%][b] **361a**
1[c]	$Rh_2(OAc)_4$	DCM	0.5	8	56
2	Cu(I)Tc	DCM	0.5	8	51
3	$Sc(OTf)_3$	DCM	0.5	8	34
4	$In(OTf)_3$	DCM	0.5	8	42
5	$BF_3{\cdot}OEt_2$	DCM	0.5	20	nr[d]
6	*p*-TSA	DCM	0.5	8	41
7	TfOH	DCM	0.5	8	61
8	Con.HCl	DCM	0.5	8	nd[e]
9	TfOH	ACN	0.5	8	75
10	TfOH	PhMe	0.5	8	46
11	TfOH	Dioxane	0.5	8	39
12	TfOH	DCE	0.5	8	61
13	TfOH	DCM	0.3/0.2	13.5/20	62/62
14[f/g]	TfOH	DCE	0.5	8	35/49
15[h]	**TfOH**	**DCM**	**0.5**	**8**	**61**
16	TfOH	DCM	0.5	8	26[i]/45[j]

[a]Reaction conditions: Indole tethered on cyclic diazoamides **360a** (0.53 mmol, 1 equiv) was dissolved in 4 mL of dry solvent, catalyst (10 mol%), and room temperature under nitrogen atmosphere. [b]isolated product. [c]2 mol% of $Rh_2(OAc)_4$. [d]No reaction. [e]No desired product. [f/g]Reaction carried out at 0 and 84 °C. [h]Reaction carried out under an open-air atmosphere. [i]10 mol% of TfOH. [j]30 mol% of TfOH.

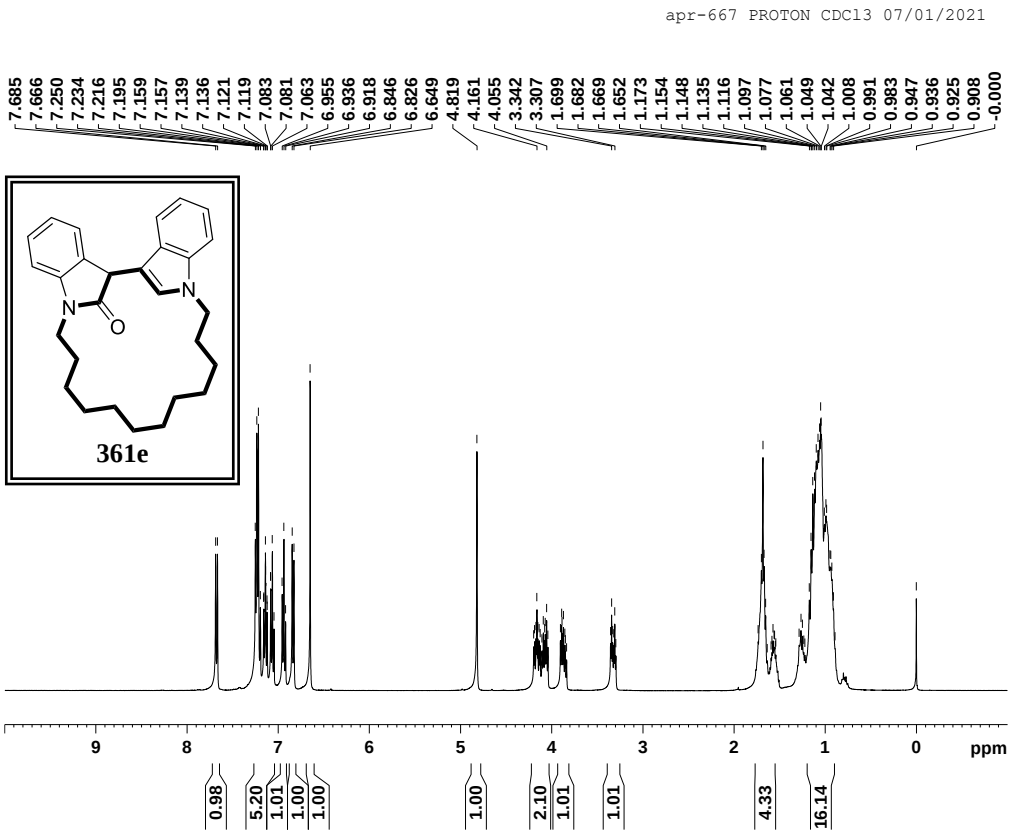


Figure 26. ^{1}H NMR (δ) spectrum of **361e**

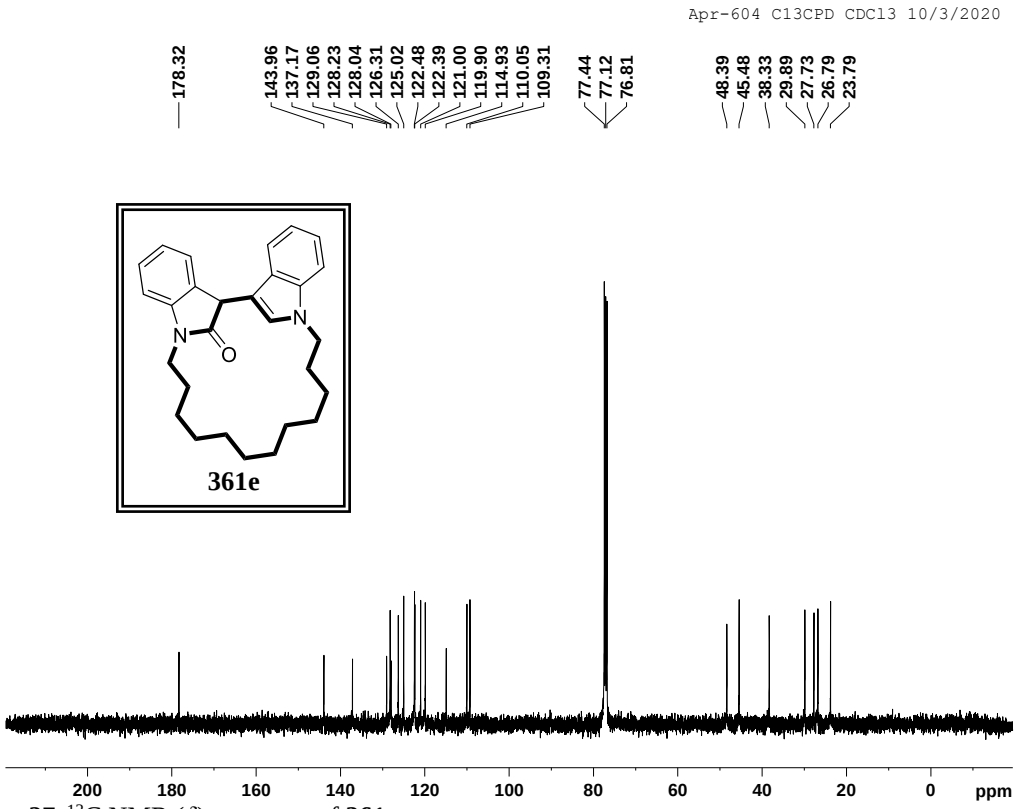


Figure 27. ^{13}C NMR (δ) spectrum of **361e**

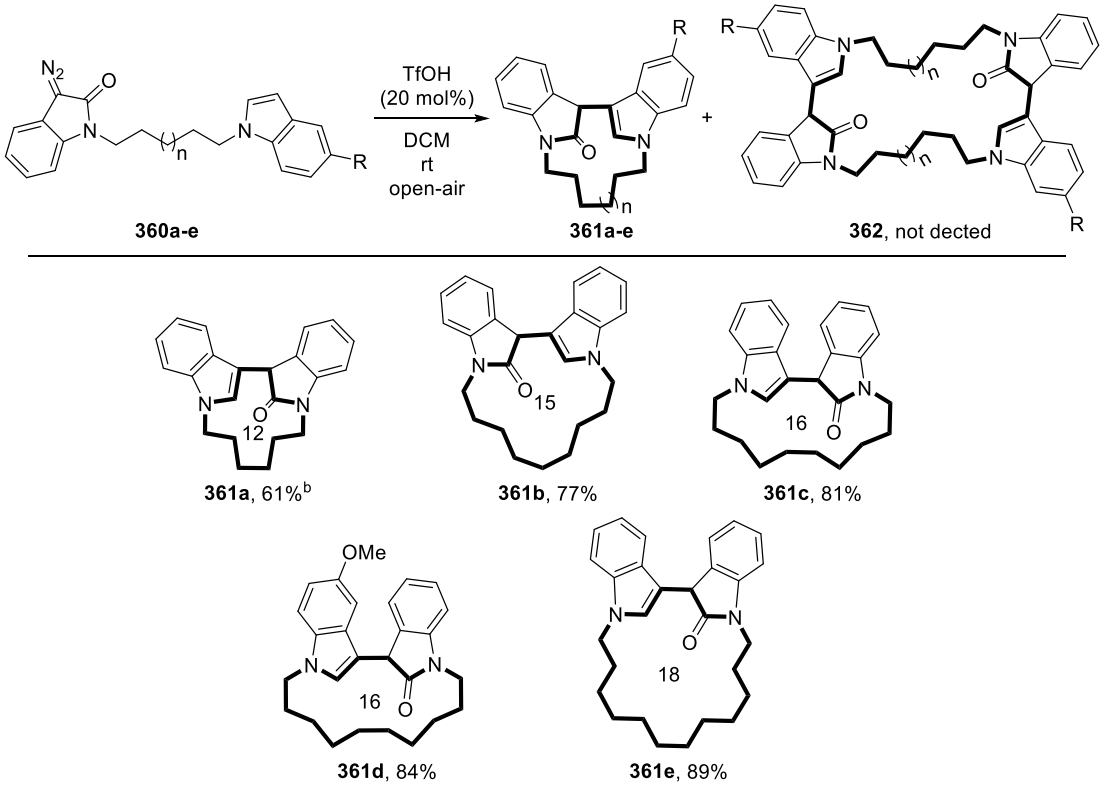
no desired product was determined in the presence of $BF_3 \cdot OEt_2$ and con. HCl. To our surprise, when the Brønsted acid TfOH was used efficiently to provide macrocycle **361a** in high yield (Table 13, entry 7). Next, various solvents, such as acetonitrile (ACN), toluene (PhMe), dioxane or dichloroethane (DCE) were screened and did not improve the yield of macrocycle **361a** (Table 13, entries 9-12). The yield of indole incorporated macrocycle **361a** was not improved when the rate of addition of indole tethered on diazoamide **360a** reduced to 0.3 mL/h or 0.2 mL/h (Table 13, entry 13). The yield of macrocycles **361a** didn't increase even under 0 °C or reflux conditions (Table 13, entry 14). Similar yield of the desired product **361a** was observed when the reaction was carried out under an open-air atmosphere (Table 13, entry 15). Reducing or increasing the quantity of catalyst had no discernible effect on product yield (Table 13, entry 16). Finally, the following optimized reaction conditions were developed: a slow rate of addition of **360** (0.5 mL/h) and TfOH (20 mol%) in DCM at room temperature for 8 h under an open-air atmosphere (Table 13, entry 15).

The characteristic spectral data confirmed the proposed structure of compound **361e** (Figure 26). The ^{1}H-NMR spectrum of product **361e** exhibited two characteristic singlets at δ 4.82 ppm representing the newly generated CH proton which indicates the formation of macrocyclic product **361e** and peak at 6.65 ppm indicates the C2-H proton of indole ring. ^{13}C-NMR spectral analyses of product **361e** showed peaks for twelve CH_2 carbons, nine aromatic CH carbons, one aliphatic CH carbon, five quaternary carbons and a carbonyl carbon at 176.5 ppm (Figure 27).

The utility and applicability of this one-pot protocol for accessing indole-incorporated macrocycles **361** were investigated. As a result, indole incorporated macrocycles **360a-e** with various spacer lengths were synthesized by generating 12-, 15-, 16-, or 18-

membered intramolecular C-alkylation products (Table 14). The head-to-tail dimerization of the C-alkylation was attempted by performing the reaction with **361b-e**, which has a shorter to longer chain length. Only 3,3'-biindole incorporated macrocycles were produced by this reaction rather than the head-to-tail dimerization product depicted in Table 14.

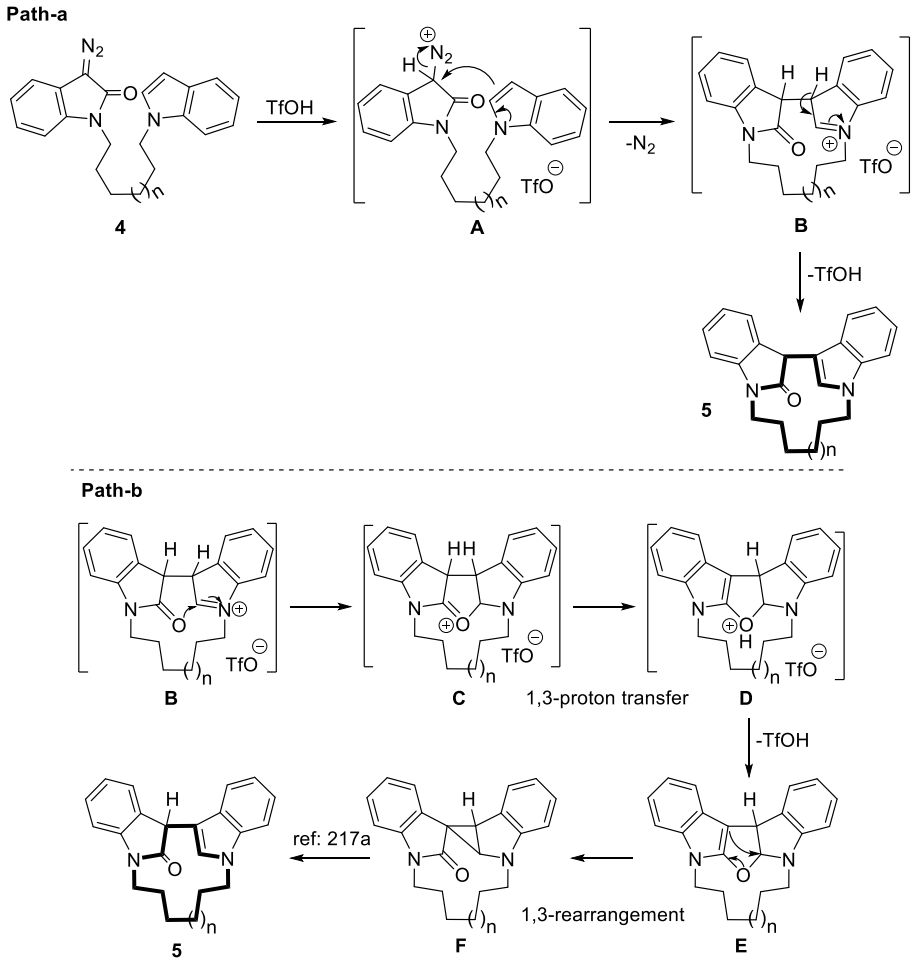
Table 14. Synthesis of indole incorporated macrocycles **361a-e**[a]



[a]Reaction conditions: To the mixture containing TfOH (20 mol%) in 2 mL of dry dichloromethane under an open-air atmosphere, **360** (1equiv) in 4 mL of dry dichloromethane was added using a syringe pump with the flow rate of 0.5 mL/h at room temperature. [b]Isolated yield.

The plausible mechanism is proposed as shown in Scheme **139** for the formation of macrocycles **361** from indole tethered on diazoamides **360**. Macrocycles may have formed the following two paths ways. The reaction of diazoamide with TfOH provides a C-protonated diazonium ion intermediate **A**. An iminium ion intermediate **B** is formed by an intramolecular nucleophilic attack on the C3-location of indole to the diazonium ion **A** and the elimination of dinitrogen. The iminium ion intermediate **B**

that is deprotonated allows for forming the macrocycle **361** (Path-a). The intramolecular trapping of an iminium ion intermediate **B** with the neighboring amide carbonyl group gives intermediate **C**. Intermediate **C** might be formed *via* an intramolecular formal [3+2]-cycloaddition of intermediate **B**. Intermediate **C** undergoes 1,3-proton transfer to form intermediate **D**, which undergoes formal-1,3-rearrangement of **D** affords macrocycle incorporated cyclopropane intermediate **F**. The labile cyclopropane intermediate **F** underwent ring-opening to provide macrocycles **361** (Path-b).



Scheme 139. Plausible reaction mechanism for the formation of indole incorporated macrocycles

General information

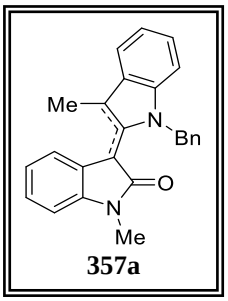
All solvents were purified by distillation following standard procedure. All reactions were carried out in oven-dried glassware under nitrogen positive pressure with magnetic stirring. $Rh_2(OAc)_4$ and TfOH were purchased from M/s Aldrich or M/s Alfa Aesar and used as provided.

Experimental Section

General experimental procedure for the synthesis of 2,3'-biindoles 357

To an oven-dried flask, a solution containing the appropriate indole (**104**, 1 equiv) and 2 mol% of $Rh_2(OAc)_4$ dissolved in 5 mL of dry DCM under a nitrogen atmosphere was added to a solution of 3-diazoindol-2-one (**63**, 1 equiv) in dry DCM (4 mL) at room temperature to afford until the reaction completed (monitored using TLC). After the completion of the reaction, the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica gel, 100-200 mesh, EtOAc/hexane 30:70) to furnish a mixture of 2,3'-biindoles **357**.

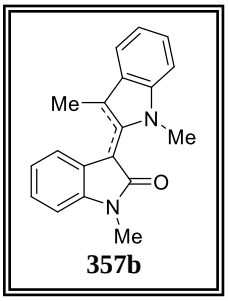
Synthesis of 2,3'-biindoles 357a: A solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 1-benzyl-3-methyl-1*H*-indole (**104a**, 128 mg, 0.58 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ (2 mol%) at room temperature to afford product **357a** (195 mg, 92%) as a light yellow solid according to general procedure. R_f = 0.39 (EtOAc/hexane = 1.5:3.5, v/v); mp 126-127 °C; IR (neat): ν_{max} 3397, 1710, 1609, 1461, 1345, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.61 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 4.58-4.63 (m, 1H,



357a

CH), 4.86-4.90 (m, 2H, CH_2), 5.17 (s, 1H, CH), 5.67 (ABq, $\Delta\delta_{AB}$ = 0.05, J = 17.6 Hz, 2H, CH_2), 6.67-7.41 (m, 24H, ArH), 7.56 (d, J = 8.0 Hz, 1H, ArH), 7.71-7.73 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.5, 9.4, 26.3, 26.5, 44.0, 44.1, 46.8, 47.1, 108.2, 108.3, 109.4, 112.9, 118.5, 119.0, 119.3, 122.0, 122.3, 122.8, 122.9, 124.6, 125.6, 126.2, 126.9, 127.4, 127.6, 128.2, 128.4, 128.7, 129.0, 129.3, 129.7, 136.9, 137.1, 137.8, 138.2, 143.8, 144.1, 173.9, 174.4 ppm; HRMS (ESI) calculated $C_{25}H_{24}N_2O$ $(M+H)^+$: 367.1810; found, 367.1823.

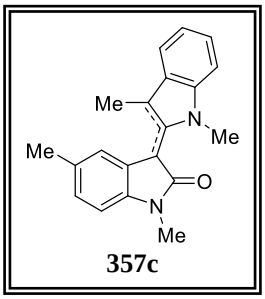
Synthesis of 2,3'-biindoles 357b: A solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 1,3-dimethyl-1*H*-indole (**104b,** 84 mg, 0.58 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ (2 mol%) at room temperature to afford product **357b** (148 mg, 88%) as a light yellow solid according to general procedure. R_f = 0.43 (EtOAc/hexane = 1:4, v/v); mp 114-115 °C; IR (neat): ν_{max} 2928, 1707, 1609, 1466, 1344, 1082, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.34 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.13-3.18 (m, 4H, CH_3/CH), 3.75 (s, 1H, CH_3), 4.76 (s, 0.39H, CH), 4.93 (s, 1H, CH), 6.75-7.19 (m, 12H, ArH), 7.19-7.20 (m, 1H, ArH), 7.30 (d, J = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.7, 9.4, 26.6, 26.8, 29.7, 30.2, 43.9, 44.2, 108.3, 108.6, 108.8, 109.3, 111.9, 118.5, 118.9, 121.6, 122.0, 123.0, 123.2, 124.6, 124.8, 127.4, 127.6, 128.1, 128.6, 128.8, 129.7, 129.9, 137.0, 137.5, 143.8, 144.2, 174.5, 175.0 ppm; HRMS (ESI) calculated $C_{19}H_{18}N_2O$ $(M-H)^+$: 289.1341; found, 289.1375.



357b

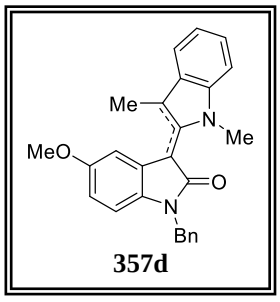
Synthesis of 2,3'-biindoles 357c: A solution of 3-diazo-1,5-dimethyl-1,3-dihydro-2*H*-indol-2-one (**63l**, 100 mg, 0.53 mmol) in dry dichloromethane (4 mL) was added

dropwise to a solution containing 1,3-dimethyl-1*H*-indole (**104b,** 78 mg, 0.53 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ (2 mol%) at room temperature to afford product **357c** (152 mg, 94%) as a light yellow solid according to general procedure. R_f = 0.36 (EtOAc/hexane = 1:4, v/v); mp 138-139 °C; IR (neat): ν_{max} 2923, 1705, 1608, 1465, 1347, 1246, 1083, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.14-2.17 (m, 4H, CH_3/CH), 2.40 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 3.18-3.22 (m, 4H, CH_3/CH), 3.81 (s, 1H, CH), 4.79 (s, 0.35H, CH), 4.95 (s, 1H, CH), 6.67-6.72 (m, 2H, ArH), 6.82 (s, 0.42H, ArH), 6.95-7.13 (m, 5H, ArH), 7.23 (d, *J* = 8.0 Hz, 0.43H, ArH), 7.35 (d, *J* = 7.6 Hz, 0.37H, ArH), 7.50 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.7, 9.3, 21.1, 26.6, 26.8, 29.7, 30.2, 43.9, 44.3, 108.1, 108.3, 108.8, 109.3, 111.8, 118.5, 118.9, 119.0, 121.6, 121.9, 125.4, 125.5, 127.4, 127.7, 128.1, 128.6, 128.8, 129.0, 129.9, 130.2, 132.6, 132.8, 137.0, 137.5, 141.4, 141.8, 174.5, 175.0 ppm; HRMS (ESI) calculated $C_{20}H_{20}N_2O$ $(M+H)^+$: 305.1654; found, 305.1653.



357c

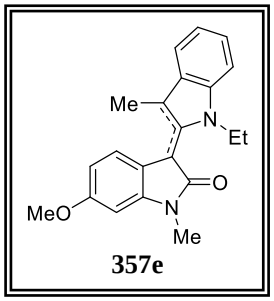
Synthesis of 2,3'-biindoles 357d: A solution of 1-benzyl-3-diazo-5-methoxy-1,3-dihydro-2*H*-indol-2-one (**63m**, 100 mg, 0.36 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 1,3-dimethyl-1*H*-indole (**104b,** 52 mg, 0.36 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ (2 mol%) at room temperature to afford product **357d** (120 mg, 84%) as a light yellow solid according to general procedure. R_f = 0.68 (EtOAc/hexane = 1.5:3.5, v/v); mp 142-143 °C; IR (neat): ν_{max} 2922, 1706, 1605, 1489, 1336, 1182, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.11-2.14 (m, 4H, CH_3/CH), 2.92 (s, 3H, CH_3), 3.82 (s, 1H,



357d

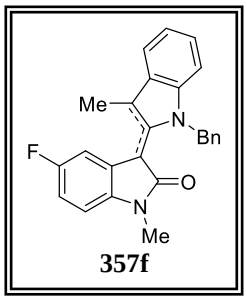
CH), 4.78-4.94 (m, 3H, CH_2/CH), 5.07 (s, 1H, CH), 6.65 (d, *J* = 8.0 Hz, 0.41H, ArH), 6.71-6.73 (m, 2H, ArH), 6.85 (s, 0.41H, ArH), 6.92-7.40 (m, 14H, ArH), 7.53 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 9.0, 9.4, 21.1, 21.2, 30.0, 30.3, 44.1, 44.3, 44.4, 44.5, 108.5, 108.9, 109.26, 109.31, 109.4, 112.0, 118.6, 119.0, 119.1, 121.8, 122.1, 125.5, 125.7, 127.6, 127.7, 127.85, 127.93, 128.1, 128.2, 128.75, 128.81, 129.0, 129.9, 130.1, 132.7, 132.9, 136.2, 137.1, 137.6, 140.6, 141.0, 174.6, 175.0 ppm; HRMS (ESI) calculated $C_{26}H_{24}N_2O$ $(M+H)^+$: 305.1654; found, 305.1653.

Synthesis of 2,3'-biindoles 357e: A solution of 3-diazo-6-methoxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63n**, 100 mg, 0.49 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 1-ethyl-3-methyl-1*H*-indole (**104c,** 78 mg, 0.49 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ (2 mol%) at room temperature to afford product **357e** (129 mg, 79%) as a colourless liquid according to general procedure. R_f = 0.49 (EtOAc/hexane = 1.5:3.5, v/v); IR (neat): ν_{max} 2931, 1711, 1618, 1460, 1364, 1079, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.83 (t, *J* = 7.2 Hz, 3H, CH_3), 1.38-1.42 (m, 2H), 2.38 (s, 3H, CH_3), 3.19-3.22 (m, 4H, CH_3/CH), 3.29-3.46 (m, 2H, CH_2), 3.73-3.74 (m, 4H, CH_3/CH), 4.19-4.38 (m, 1H, CH), 4.74 (s, 0.53H, CH), 4.95 (s, 1H, CH), 6.42-6.43 (m, 3H, ArH), 6.80-6.89 (m, 2H, ArH), 6.95-7.13 (m, 4H, ArH), 7.24 (d, *J* = 8 Hz, 0.6H, ArH), 7.35 (d, *J* = 8 Hz, 0.55H, ArH), 7.50 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.4, 9.3, 14.2, 16.1, 26.6, 26.7, 38.2, 38.6, 43.2, 43.6, 55.6, 96.4, 96.6, 106.7, 108.4, 109.07, 109.14, 111.6, 118.5, 118.8, 118.9, 190.0, 119.5, 119.7, 121.4, 121.8, 125.1, 125.2, 128.4, 128.8, 129.4, 129.5, 135.7, 136.4, 144.9, 145.4, 160.5, 160.7, 175.1, 175.6 ppm; HRMS (ESI) calculated $C_{26}H_{24}N_2O$ $(M+H)^+$: 305.1654; found, 305.1653.



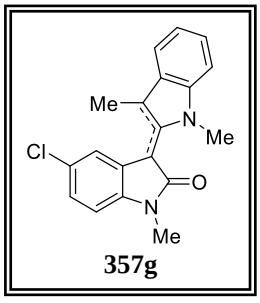
357e

Synthesis of 2,3'-biindoles 357f: A solution of 3-diazo-5-fluoro-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63f**, 100 mg, 0.52 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 1-benzyl-3-methyl-1*H*-indole (**104a,** 115 mg, 0.52 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ (2 mol%) at room temperature to afford product **357f** (174 mg, 87%) as a light yellow solid according to general procedure. R_f = 0.41 (EtOAc/hexane = 1.5:3.5, v/v); mp 144-145 °C; IR (neat): ν_{max} 2924, 1711, 1613, 1490, 1456, 1346, 1266, 1082, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.44 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 4.56-4.72 (m, 3H, CH_2/CH), 4.99 (s, 1H, CH), 5.50 (ABq, $\Delta\delta_{AB}$ = 0.1, J = 17.4 Hz, 2H, CH_2), 6.23-6.25 (m, 1H, ArH), 6.48-6.59 (m, 4H, ArH), 6.65-6.69 (m, 1H, ArH), 6.79-6.90 (m, 2H, ArH), 6.98-7.27 (m, 14H, ArH), 7.41 (d, J = 7.6 Hz, 1H, ArH), 7.55-7.57 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.5, 9.4, 26.5, 26.7, 44.2, 44.4, 46.8, 47.1, 108.55, 108.63, 108.7, 108.8, 109.4, 109.6, 112.5, 112.6, 112.8, 112.9, 113.2, 114.6, 114.8, 115.0, 118.6, 119.1, 119.4, 122.2, 122.6, 125.5, 126.2, 127.0, 127.8, 128.1, 128.2, 128.6, 128.97, 129.06, 129.10, 136.9, 137.0, 137.9, 138.2, 139.7, 140.1, 159.3 (d, J = 240.1), 159.4 (d, J = 239.8), 173.8, 174.1 ppm; HRMS (ESI) calculated $C_{25}H_{21}FN_2O$ $(M-H)^+$: 383.1560; found, 383.1570.



357f

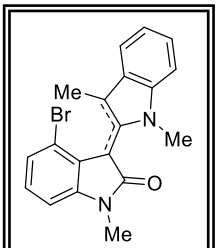
Synthesis of 2,3'-biindoles 357g: A solution of 5-chloro-3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63h**, 100 mg, 0.48 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 1,3-dimethyl-1*H*-indole (**104b,** 70 mg, 0.48 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ (2 mol%) at room temperature to afford product **357g** (142 mg, 91%) as a colourless



357g

solid according to general procedure. R_f = 0.50 (EtOAc/hexane = 1.5:3.5, v/v); mp 152-153 °C; IR (neat): ν_{max} 2928, 1711, 1608, 1472, 1338, 1095, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.56 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 3.36-3.40 (m, 4H, CH_3/CH), 3.98 (s, 1H, CH), 4.99 (s, 0.43H, CH), 5.14 (s, 1H, CH), 6.89-6.92 (m, 1H, ArH), 7.05 (s, 1H, ArH), 7.16-7.41 (m, 7H, ArH), 7.53 (d, *J* = 7.6 Hz, 0.44H, ArH), 7.67 (d, *J* = 8.0 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.7, 9.3, 26.7, 26.9, 29.8, 30.2, 43.8, 44.1, 108.6, 108.8, 109.3, 109.4, 112.2, 118.5, 119.00, 119.02, 119.1, 121.8, 122.2, 124.9, 125.1, 127.9, 128.3, 128.4, 128.5, 128.6, 128.65, 128.7, 128.96, 129.01, 129.2, 137.0, 137.5, 142.2, 142.7, 174.0, 174.5 ppm; HRMS (ESI) calculated $C_{19}H_{17}ClN_2O$ $(M+H)^+$: 325.1108; found, 325.1120.

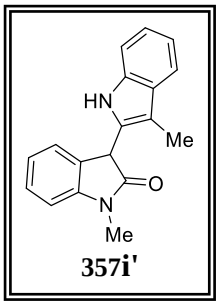
Synthesis of 2,3'-biindoles 357h: A solution of 4-bromo-3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63g**, 100 mg, 0.40 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 1,3-dimethyl-1*H*-indole (**104b,** 57 mg, 0.40 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ at room temperature to afford product **357h** (105 mg, 71%) as a light yellow solid according to general procedure. R_f = 0.45 (EtOAc/hexane = 1.5:3.5, v/v); mp 160-161 °C; IR (neat): ν_{max} 2926, 1716, 1603, 1461, 1333, 1100, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.40 (s, 3H, CH_3), 2.94 (s, 3H, CH_3), 3.15 (d, *J* = 15.2 Hz, 6H, $2CH_3$), 3.84 (s, 3H, CH_3), 4.75 (s, 1H, CH), 4.91 (s, 1H, CH), 6.70-6.73 (m, 2H, ArH), 6.93-7.11 (m, 9H, ArH), 7.21 (d, *J* = 8 Hz, 1H, ArH), 7.33 (d, *J* = 7.6 Hz, 1H, ArH), 7.48 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.0, 9.8, 26.8, 27.0, 29.5, 30.4, 45.0, 45.4, 107.3, 107.4, 108.2, 108.7, 109.3, 113.3, 118.4, 118.8, 119.0, 119.7, 119.9, 121.5, 121.8, 126.3, 126.6, 126.9, 127.1, 127.56, 127.61, 128.1, 128.4, 130.1, 130.3, 136.9, 137.4,



357h

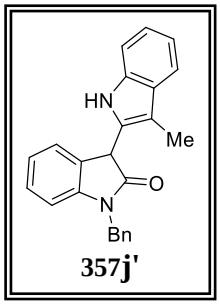
145.5, 145.9, 173.5, 173.8 ppm; HRMS (ESI) calculated $C_{19}H_{17}BrN_2O$ $(M+Na)^+$: 391.0422; found, 391.0419.

Synthesis of 2,3'-biindole 357i': A solution of 3-diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (**63b**, 100 mg, 0.58 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 3-methyl-1*H*-indole (**104f**, 76 mg, 0.58 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ at room temperature to afford product **357i'** (125 mg, 78%) as a light yellow solid according to general procedure. R_f = 0.29 (EtOAc/hexane = 1.5:3.5, v/v); mp 153-154 °C; IR (neat): ν_{max} 3296, 3054, 1691, 1616, 1460, 1377, 1343, 1234, 1170, 1081, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.35 (s, 3H, CH_3), 3.27 (S, 3H, CH_3), 4.96 (s, 1H, CH), 6.92 (d, J = 8.0 Hz, 1H, ArH), 7.05-7.19 (m, 4H, ArH), 7.25 (s, 1H, ArH), 7.34-7.38 (m, 1H, ArH), 7.53 (d, J = 7.6 Hz, 1H, ArH), 7.61 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.8, 26.6, 44.7, 108.4, 110.5, 111.0, 118.7, 119.2, 123.1, 125.1, 127.8, 128.9, 129.0, 129.3, 135.7, 144.5, 174.7 ppm; HRMS (ESI) calculated $C_{18}H_{16}N_2O$ $(M+Na)^+$: 299.1160; found, 299.1167.



357i'

Synthesis of 2,3'-biindole 357j': A solution of 1-benzyl-3-diazo-1,3-dihydro-2*H*-indol-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloromethane (4 mL) was added dropwise to a solution containing 3-methyl-1*H*-indole (**104f,** 52 mg, 0.40 mmol) dissolved in dry DCM (5 mL) and $Rh_2(OAc)_4$ at room temperature to afford product **357j'** (114 mg, 81%) as a light yellow solid according to general procedure. R_f = 0.33 (EtOAc/hexane = 1.5:3.5, v/v); mp 188-189 °C; IR (neat): ν_{max} 3290, 3051, 1696, 1610, 1491, 1465, 1370, 1348, 1237, 1170, 1085, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.41 (s,



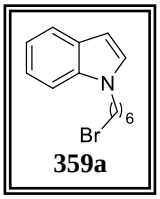
357j'

3H, CH_3), 5.01 (s, 2H, CH_2), 5.11 (s, 1H, CH), 6.91 (d, *J* = 8 Hz, 1H, ArH), 7.09-7.40 (m, 11H, ArH), 7.61 (d, *J* = 6.8 Hz, 1H, ArH), 7.70 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 8.1, 44.2, 44.8, 109.5, 110.7, 111.2, 118.7, 119.4, 122.1, 123.1, 125.1, 125.3, 127.4, 127.6, 127.8, 128.9, 129.2, 130.1, 135.7, 135.8, 143.6, 174.8 ppm; HRMS (ESI) calculated $C_{24}H_{20}N_2O$ $(M+H)^+$: 353.1654; found, 353.1661.

General procedure for synthesis of *N*-substituted indoles 359

Indole (**104**, 1 equiv) was added to a suspension of potassium hydroxide (2.5 equiv) in DMSO (10 mL) at room temperature, under a nitrogen atmosphere. The mixture was stirred for 15 minutes, then dibromo compound **358** (1.1 equiv) was added. The progress of the reaction was monitored by TLC. The mixture was extracted with ethyl acetate (3×25 mL) and the combined organic layers were washed with water (3×25 mL), brine (2×25 mL) and dried (anhydrous Na_2SO_4). The solvent was removed under reduced pressure and the resulting residue purified using silica gel column chromatography (SiO_2, hexane/ethyl acetate 80:20) to afford the *N*-alkylated indoles **359**.

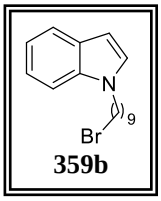
Synthesis of 1-(6-bromohexyl)-1*H*-indole (359a): A mixture of indole (**104a**, 1.0 g, 8.54 mmol) and a suspension of potassium hydroxide (1.20 g, 21.35 mmol) was taken in dry DMSO (15 mL) and stirred at room temperature for half an hour. Then 1,6-dibromohexane (**358a**, 1.4 mL, 9.39 mmol) was added slowly at room temperature over a period of 10 minutes. Then, this mixture was stirred at room temperature for 10 h to afford product **359a** (2.2 g, 92%) as a colourless liquid according to general procedure. R_f = 0.89 (EtOAc/hexane = 0.5:4.5, v/v); IR (neat): ν_{max} 2922, 1708, 1684, 1607, 1462, 1354, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.53-1.60 (m, 4H, CH_3), 1.89-1.99 (m, 4H, CH_2), 3.48 (t, *J* =



359a

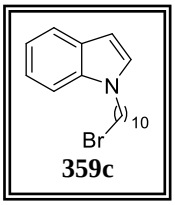
6.8 Hz, 2H, CH_2), 4.20-4.23 (m, 2H, CH_2), 6.64 (d, *J* = 2.8 Hz, 1H, ArH), 7.20-7.27 (m, 2H, ArH), 7.34-7.37 (m, 1H, ArH), 7.47 (d, *J* = 8 Hz, 1H, ArH), 7.79 (d, *J* = 8 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.3, 27.9, 30.2, 32.7, 33.9, 46.3, 101.1, 109.5, 119.4, 121.1, 121.5, 127.9, 128.7, 136.1 ppm.

Synthesis of 1-(9-bromononyl)-1*H*-indole (359b): A mixture of indole (**104a** 1.0 g, 8.54 mmol) and a suspension of potassium hydroxide (1.20 g, 21.35 mmol) was taken in dry DMSO (15 mL) and stirred at room temperature for half an hour. Then 1,9-dibromononane (**358b**, 2.4 mL, 9.39 mmol) was added slowly at room temperature over a period of 10 minutes. Then, this mixture was stirred at room temperature for 10 h to afford product **359b** (1.6 g, 90%) as a colourless liquid according to general procedure. R_f = 0.73 (EtOAc/hexane = 0.5:4.5, v/v); IR (neat): ν_{max} 2922, 1708, 1684, 1607, 1462, 1354, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.53-1.60 (m, 4H, CH_3), 1.89-1.99 (m, 4H, CH_2), 3.48 (t, *J* = 6.8 Hz, 2H, CH_2), 4.20-4.23 (m, 2H, CH_2), 6.64 (d, *J* = 2.8 Hz, 1H, ArH), 7.20-7.27 (m, 2H, ArH), 7.34-7.37 (m, 1H, ArH), 7.47 (d, *J* = 8 Hz, 1H, ArH), 7.79 (d, *J* = 8 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.3, 27.9, 30.2, 32.7, 33.9, 46.3, 101.1, 109.5, 119.4, 121.1, 121.5, 127.9, 128.7, 136.1 ppm.



359b

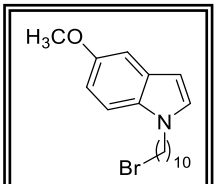
Synthesis of 1-(10-bromodecyl)-1*H*-indole (359c): A mixture of indole (**104a**, 1.0 g, 8.54 mmol) and a suspension of potassium hydroxide (1.20 g, 21.35 mmol) was taken in dry DMSO (15 mL) and stirred at room temperature for half an hour. Then 1,10-dibromodecane (**358c**, 2.1 mL, 9. mmol) was added slowly at room temperature over a period of 10 minutes. Then, this mixture was stirred at room temperature for 10 h to afford product **359c** (2.58 g, 90%) as a colourless liquid according to general procedure. R_f = 0.91 (EtOAc/hexane = 0.5:4.5,



359c

v/v); IR (neat): ν_{max} 2925, 1485, 1448, 1235, 1147, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.63-1.68 (m, 12H, CH_2) 1.87-1.93 (m, 1H, CH_2), 2.02-2.13 (m, 3H, CH_2), 3.60-3.72 (m, 2H, CH_2), 4.27-4.30 (m, 2H, CH_2), 6.78 (d, *J* = 2.8 Hz, 1H, ArH), 7.31-7.32 (m, 1H, ArH), 7.40-7.43 (m, 1H, ArH), 7.48-7.52 (m, 1H, ArH), 7.61 (d, *J* = 8 Hz, 1H, ArH), 7.95 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.6, 27.2, 28.5, 29.5, 29.8, 29.9, 30.2, 33.2, 34.3, 46.6, 101.2, 109.7, 119.5, 121.2, 121.6, 128.0, 128.9, 136.3 ppm.

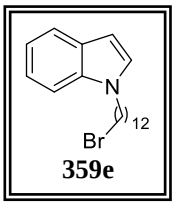
Synthesis of 1-(10-bromodecyl)-5-methoxy-1*H*-indole (359d): A mixture of 5-methoxyindole (**104b**, 1.0 g, 6.9 mmol) and a suspension of potassium hydroxide (0.95 g, 16.98 mmol) was taken in dry DMSO (15 mL) and stirred at room temperature for half an hour. Then 1,10-dibromodecane (**358c**, 1.68 mL, 7.47 mmol) was added slowly at room temperature over a period of 10 minutes. Then, this mixture was stirred at room temperature for 10 h to afford **359d** (2.2 g, 87%) as a colourless liquid according to general procedure. R_f = 0.69 (EtOAc/hexane = 0.5:4.5, v/v); IR (neat): ν_{max} 2925, 1486, 1448, 1235, 1147, 1032, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.32-1.47 (m, 12H, CH_2), 1.86-1.93 (m, 4H, CH_2), 3.45 (t, *J* = 6.8 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 4.10-4.14 (m, 2H, CH_2) 6.46 (d, *J* = 6.8 Hz, 1H, ArH), 6.91-6.94 (m, 1H, ArH), 7.11-7.30 (m, 3H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 27.0, 28.2, 28.7, 29.2, 29.35, 29.40, 30.3, 32.8, 34.1, 46.6, 55.9, 100.4, 102.5, 110.2, 111.7, 128.3, 128.9, 131.4, 153.9 ppm.



359d

Synthesis of 1-(12-bromododecyl)-1*H*-indole (359e): A mixture of indole (**104a**, 1.0 g, 8.54 mmol) and a suspension of potassium hydroxide (1.20 g, 21.35 mmol) was taken in dry DMSO (15 mL) and stirred at room temperature for half an hour. Then 1,12-dibromododecane (**358d**, 0.6 mL, 9.4 mmol) was added slowly at room

temperature over a period of 10 minutes. Then, this mixture was stirred at room temperature for 10 h to afford product **359e** (2.64 g, 85%) as a colourless liquid according to general procedure. R_f = 0.86 (EtOAc/hexane = 0.5:4.5, v/v); IR (neat): ν_{max} 2923, 1691, 1604, 1481, 1347, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.37-1.40 (m, 13H, CH_2), 1.91-1.99 (m, 5H, CH_2), 3.48-3.52 (m, 4H, CH_2), 4.19 (t, J = 7.2 Hz, 2H, CH_2), 6.59 (d, J = 3.2 Hz, 1H, ArH), 7.18-7.22 (m, 2H, ArH), 7.29-7.33 (m, 1H, ArH), 7.45 (d, J = 8 Hz, 1H, ArH), 7.74 (d, J = 7 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 27.1, 28.3, 28.88, 28.90, 29.4, 29.5, 29.56, 29.61, 29.63, 30.4, 33.0, 34.2, 46.5, 100.9, 109.5, 119.2, 121.0, 121.4, 127.9, 128.7, 136.3 ppm.



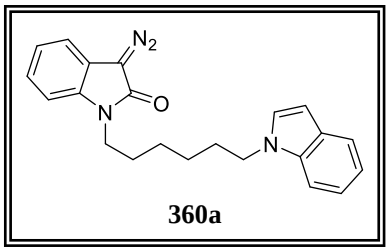
359e

General procedure for synthesis of indole tethered on diazoamides 360

To an oven-dried flask, a solution containing the appropriate diazo compound **234** (1 equiv) and potassium carbonate (2.5 equiv) in dry DMF was degassed using a nitrogen. To this reaction mixture, a solution of appropriate of *N*-substituted indole **359** (1.1 equiv) in dry DMF was slowly added over a period of 5 minutes and then a catalytic amount of tetrabutylammonium iodide. The progress of the reaction was monitored by TLC. The mixture was extracted with ethyl acetate (3×25 mL) and the combined organic layers were washed with water (3×25 mL), brine (2×25 mL) and dried (anhydrous Na_2SO_4). The solvent was removed under reduced pressure and the resulting residue purified using silica gel column chromatography (SiO_2, hexane/ethyl acetate 80:20) to afford the respective indole tethered on diazoamides **360**.

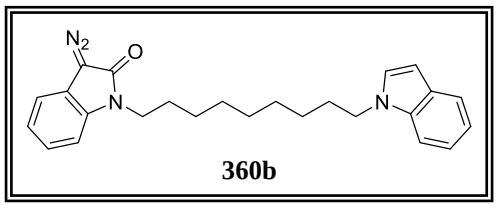
Synthesis of 1-(6-(1*H*-indol-1-yl)hexyl)-3-diazoindolin-2-one (360a): 3-Diazo-1,3-dihydro-2*H*-indol-2-one (**234**, 0.5 g, 3.14 mmol) and potassium carbonate (1.09 g, 7.85 mmol) were taken in dry DMF under a nitrogen atmosphere and stirred for 5 minutes.

1-(6-Bromohexyl)-1*H*-indole (**359a**, 0.97 g, 3.45 mmol) and a catalytic amount of tetrabutylammonium iodide were then added. The reaction mixture was allowed to stir for 8 h to yield product **360a** (0.57 g, 51%) as a red liquid based on the general procedure. R_f = 0.82 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 2924, 2088, 1682, 1606, 1463, 1349, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.22-1.24 (m, 4H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.68-1.71 (m, 2H, CH_2), 3.63-3.67 (m, 2H, CH_2), 3.94-3.97 (m, 2H, CH_2), 6.36 (d, *J* = 2.8 Hz, 1H, ArH), 6.72 (d, *J* = 7.6 Hz, 1H, ArH), 6.92-7.10 (m, 6H, ArH), 7.19 (d, *J* = 8 Hz, 1H, ArH), 7.51 (d, *J* = 8 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.5, 26.7, 28.0, 30.2, 40.6, 46.3, 101.0, 108.9, 109.4, 116.9, 118.5, 119.3, 121.0, 121.4, 122.0, 125.5, 127.9, 128.7, 133.9, 136.0, 166.8 ppm; HRMS (ESI) calculated $C_{22}H_{22}N_4O$ $(M+Na)^+$ 381.1691; found, 381.1669.



360a

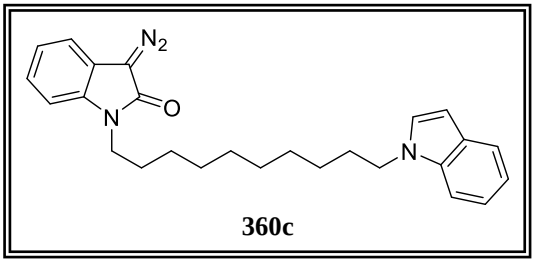
Synthesis of 1-(9-(1*H*-indol-1-yl)nonyl)-3-diazoindolin-2-one (360b): 3-Diazo-1,3-dihydro-2*H*-indol-2-one (**234**, 0.5 g, 3.14 mmol) and potassium carbonate (1.09 g, 7.85 mmol) were taken in dry DMF under a nitrogen atmosphere and stirred for 5 minutes. 1-(9-bromononyl)-1*H*-indole (**359b**, 1.25g mg, 3.45 mmol) and a catalytic amount of tetrabutylammonium iodide were then added. The reaction mixture was allowed to stir for 8 h to yield product **360b** (0.7 g, 56%) as a red liquid based on the general procedure. R_f = 0.82 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 2924, 2088, 1682, 1606, 1463, 1349, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.22-1.24 (m, 4H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.68-1.71 (m, 2H, CH_2), 3.63-3.67 (m, 2H, CH_2), 3.94-3.97 (m, 2H, CH_2), 6.36 (d, *J* = 2.8 Hz, 1H, ArH), 6.72 (d, *J* =



360b

7.6 Hz, 1H, ArH), 6.92-7.10 (m, 6H, ArH), 7.19 (d, *J* = 8 Hz, 1H, ArH), 7.51 (d, *J* = 8 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.5, 26.7, 28.0, 30.2, 40.6, 46.3, 101.0, 108.9, 109.4, 116.9, 118.5, 119.3, 121.0, 121.4, 122.0, 125.5, 127.9, 128.7, 133.9, 136.0, 166.8 ppm; HRMS (ESI) calculated $C_{25}H_{28}N_4O$ $(M+H)^+$ 401.2341; found, 401.2354.

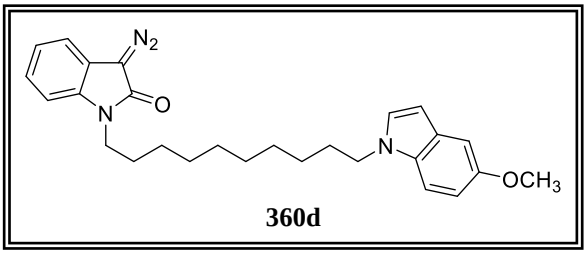
Synthesis of 1-(10-(1*H*-indol-1-yl)decyl)-3-diazoindolin-2-one (360c): 3-Diazo-1,3-dihydro-2*H*-indol-2-one (**234**, 0.5 g, 3.14 mmol) and potassium carbonate (1.09 g, 7.85 mmol) were taken in dry DMF under a nitrogen atmosphere and stirred for 5 minutes. 1-(10-bromodecyl)-1*H*-indole (**359c**, 1.16 g, 3.45 mmol) and a catalytic amount of tetrabutylammonium iodide were then added. The reaction mixture was allowed to stir for 8 h to yield product **360c** (0.62 g, 48%) as a red liquid based on the general procedure. R_f = 0.78 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 2927, 2092, 1682, 1607, 1465, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.20 (s, 12H, CH_2) 1.55-1.74 (m, 4H, CH_2), 3.69-3.72 (m, 2H, CH_2), 4.00 (t, *J* = 7.2 Hz, 2H, CH_2), 6.39 (d, *J* = 3.2 Hz, 1H, ArH), 6.81-6.83 (m, 1H, ArH), 6.95-7.14 (m, 6H, ArH), 7.25 (d, *J* = 8.4 Hz, 1H, ArH), 7.54 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.2, 26.87, 26.93, 27.0, 28.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.8, 30.3, 40.8, 46.5, 100.9, 108.9, 109.4, 116.9, 118.4, 119.2, 121.0, 121.3, 121.9, 125.4, 127.9, 128.6, 134.0, 136.0, 166.8; HRMS (ESI) calculated $C_{26}H_{30}N_4O$ $(M+H)^+$ 415.2498; found, 415.2495 ppm; HRMS (ESI) calculated $C_{26}H_{30}N_4O$ $(M+H)^+$ 415.2498; found, 415.2477.



360c

Synthesis of 3-diazo-1-(10-(5-methoxy-1*H*-indol-1-yl)decyl)indolin-2-one (360d): 3-Diazo-1,3-dihydro-2*H*-indol-2-one (**234**, 0.5 g, 3.14 mmol) and potassium carbonate

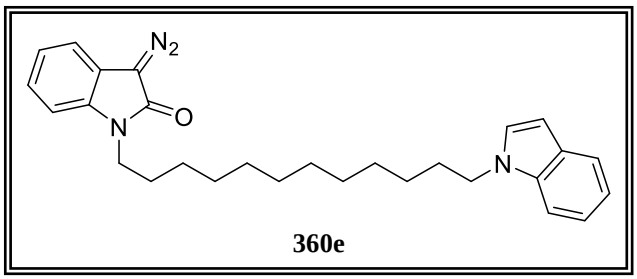
(1.09 g, 7.85 mmol) were taken in dry DMF under a nitrogen atmosphere and stirred for 5 minutes. 1-(10-Bromodecyl)-5-methoxy-1*H*-indole (**359d**, 1.26 g, 3.45 mmol) and a catalytic amount of tetrabutylammonium iodide were then added. The reaction mixture was allowed to stir for 8 h to yield product



360d

360d (0.8 g, 57%) as a red liquid based on the general procedure. R_f = 0.63 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 2926, 2090, 1681, 1609, 1474, 1235, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.14-1.18 (m, 12H, CH_2), 1.53-1.66 (m, 4H, CH_2), 3.63-3.67 (m, 2H, CH_2), 3.89 (t, *J* = 7.2 Hz, 2H, CH_2), 6.27 (d, *J* = 3.2 Hz, 1H, ArH), 6.73-6.77 (m, 2H, ArH), 6.89-7.09 (m, 6H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.9, 27.0, 27.2, 28.1, 29.26, 29.28, 29.4, 29.5, 30.4, 40.8, 46.6, 55.9, 60.7, 100.4, 102.6, 108.9, 110.2, 111.8, 112.1, 116.9, 118.4, 121.9, 125.4, 128.4, 128.7, 129.0, 131.4, 134.0, 154.0, 166.8 ppm; HRMS (ESI) calculated $C_{27}H_{32}N_4O$ $(M+H)^+$ 445.2604; found, 445.2601.

Synthesis of 1-(12-(1*H*-indol-1-yl)dodecyl)-3-diazoindolin-2-one (360e): 3-Diazo-1,3-dihydro-2*H*-indol-2-one (**234**, 0.5 g, 3.14 mmol) and potassium carbonate (1.09 g, 7.85 mmol) were taken in dry DMF under a nitrogen atmosphere and stirred for 5 minutes. 1-(12-Bromododecyl)-1*H*-indole (**359e**, 1.26 g, 3.46 mmol) and a catalytic amount of tetrabutylammonium iodide were then added. The reaction mixture was allowed to stirred for 8 h to yield product **360e** (0.6 g, 43%) as a red liquid based on the general procedure. R_f = 0.71 (EtOAc/hexane =

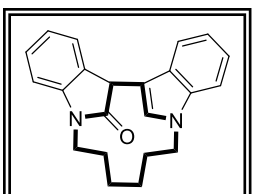


360e

1:4, v/v); IR (neat): ν_{max} 2925, 2091, 1682, 1607, 1465, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.16-1.32 (m, 18H, CH_2) 1.55-1.60 (m, 2H, CH_2), 1.69-1.76 (m, 2H, CH_2), 3.28 (t, *J* = 6.8Hz, 2H, CH_2), 3.67-3.71 (m, 2H, ArH), 6.82 (d, *J* = 8.4 Hz, 1H, ArH), 6.93-6.97 (m, 1H, ArH), 7.05-7.09 (m, 2H, ArH), 7.23-7.45 (m, 6H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.9, 28.1, 28.2, 28.8, 29.3, 29.4, 29.50, 29.52, 32.9, 34.1, 40.7, 60.6, 108.9, 116.8, 118.4, 121.8, 125.4, 133.9, 166.6 ppm: HRMS (ESI) calculated $C_{28}H_{34}N_4O$ $(M+H)^+$ 443.2811; found, 443.2827.

General experimental procedure for the synthesis of indole incorporated macrocycles 361: To an oven-dried flask, a solution containing 20 mol% TfOH dissolved in 5 mL of dry DCM under a nitrogen atmosphere was added to a solution of indole tethered on diazoamide **360** in dry DCM (4 mL) at ambient temperature to afford until the reaction completed (monitored using TLC). After the completion of the reaction, the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica gel, 100-200 mesh, EtOAc/hexane 30:70) to furnish macrocycles **361**.

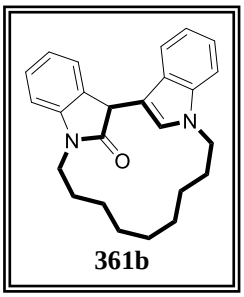
Synthesis of 1^1*H*-1,2(3,1)-diindolinacyclooctaphan-2^2-one (361a): A solution of 1-(6-(1*H*-indol-1-yl)hexyl)-3-diazoindolin-2-one (**360a**, 100 mg) in dry DCM (4 mL) was added dropwise to a solution containing TfOH (20 mol%) dissolved in dry DCM (5 mL) at room temperature to afford product **361a** (56 mg, 61%); Colourless solid; R_f = 0.46 (EtOAc/hexane = 1:4, v/v); mp 175-176 °C; IR (neat): ν_{max} 2925, 1715, 1611, 1464, 1347, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 0.80-0.82 (m, 2H, CH_2), 1.50-1.68 (m, 6H, CH_2), 3.32-3.36 (m, 1H, CH), 3.58-3.65 (m, 1H, CH), 3.82-3.90 (m, 1H, CH), 4.40 (d, *J* = 14.4 Hz, 1H, CH), 4.95 (s, 1H, CH), 6.19 (s, 1H, ArH), 6.93 (d, *J* = 7.6 Hz,



361a

1H, ArH), 7.18-7.32 (m, 4H, ArH), 7.41-7.49 (m, 2H, ArH) 8.06-8.08 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.8, 26.8, 27.7, 29.9, 38.3, 45.5, 48.4, 109.3, 110.1, 114.9, 119.9, 121.0, 122.4, 122.5, 125.0, 126.3, 128.0, 128.2, 129.1, 137.2, 144.0, 178.3 ppm; HRMS (ESI+) calculated $C_{22}H_{23}N_2O$ $(M+H)^+$: 331.1810; found, 331.1819.

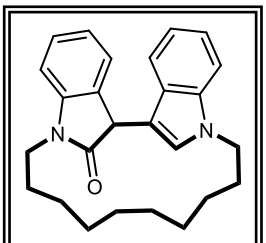
Synthesis of 1^1*H*-1,2(3,1)-diindolinacycloundecaphan-2^2-one (361b): A solution of 1-(9-(1*H*-indol-1-yl)nonyl)-3-diazoindolin-2-one (**360b**, 100 mg) in dry DCM (4 mL) was added dropwise to a solution containing TfOH (20 mol%) dissolved in dry DCM (5 mL) at room temperature to afford product **361b** (71 mg, 77%);



361b

Colourless solid; R_f = 0.75 (EtOAc/hexane = 1:4, v/v); mp 151-152 °C; IR (neat): ν_{max} 3052, 2928, 1712, 1616, 1462, 1351, 1265, 1170, 1082, 1011, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.12-1.14 (m, 12H, 6CH_2), 1.50-1.69 (m, 3H, CH_2/0.5 CH_2), 3.23-3.30 (m, 1H, 0.5 CH_2), 3.85-4.15 (m, 2H, CH_2), 4.82 (s, 1H, CH), 6.61 (s, 1H, ArH), 6.74 (d, *J* = 7.2 Hz, 1H, ArH), 6.95 (t, *J* = 7.2 Hz, 1H, ArH), 7.10-7.80 (m, 5H, ArH), 7.90 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.1, 25.7, 27.06, 27.10, 27.4, 27.6, 28.2, 39.5, 43.5, 45.1, 108.2, 109.5, 111.2, 119.4, 119.8, 122.0, 122.1, 124.1, 125.1, 127.8, 127.9, 129.6, 136.6, 144.2, 176.7. HRMS (ESI+) calculated $C_{25}H_{28}N_2O$ $(M+H)^+$ 373.2280; found, 373.2280.

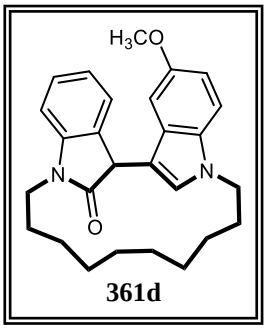
Synthesis 1^1*H*-1,2(3,1)-diindolinacyclododecaphan-2^2-one (361c): A solution of 1-(10-(1*H*-indol-1-yl)decyl)-3-diazoindolin-2-one (**360c**, 100 mg) in dry DCM (4 mL) was added dropwise to a solution containing TfOH (20 mol%) dissolved in dry DCM (5 mL) at room temperature to afford



361c

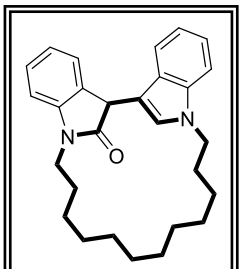
product **361c** (75 mg, 81%); Colourless solid; R_f = 0.52 (EtOAc/hexane = 1:4, v/v); mp 168-169 °C; IR (neat): ν_{max} 2929, 1714, 1611, 1466, 1356, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 0.88-1.13 (m, 12H, CH_2), 1.56-1.67 (m, 4H, CH_2), 3.31-3.37 (m, 1H, CH), 3.86-3.92 (m, 1H, CH), 4.08-4.10 (m, 1H, CH_2), 6.54 (s, 1H, ArH), 6.95-6.99 (m, 1H, ArH), 7.12-7.29 (m, 5H, ArH), 7.91 (d, *J*= 7.2 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.2, 25.9, 26.3, 27.07, 27.1, 27.4, 27.6, 28.2, 39.6, 43.5, 45.1, 108.6, 109.6, 111.4, 119.5, 119.9, 122.0, 124.9, 125.0, 127.9, 128.0, 129.7, 136.7, 144.2, 176.7 ppm; HRMS (ESI) calculated $C_{26}H_{30}N_2O$ $(M+H)^+$: 387.2436; found, 387.2442.

Synthesis of 1^5-methoxy-1^1*H*-1,2(3,1)-diindolinacyclododecaphan-2^2-one (361d): A solution of 3-diazo-1-(10-(5-methoxy-1*H*-indol-1-l)decyl)indolin-2-one (**360d**, 100 mg) in dry DCM (4 mL) was added dropwise to a solution containing TfOH (20 mol%) dissolved in dry DCM (5 mL) at room temperature to afford product **361d** (78 mg, 84%); Colourless solid; R_f = 0.41 (EtOAc/hexane = 1.5:3.5, v/v); mp 158-160 °C; IR (neat): ν_{max} 2921, 1705, 1609, 1355, 796, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 0.90-1.18 (m, 12H, CH_2), 1.58-1.64 (m, 4H, CH_2), 3.31-3.37 (m, 1H, CH), 3.80-3.85 (m, 3H, CH_3), 4.04-4.07 (m, 2H, CH_2) 6.47 (s, 1H, ArH), 6.81-6.86 (m, 2H, ArH), 6.97-7.00 (m, 1H, ArH), 7.12 (d, *J* = 9.2 Hz, 1H, ArH), 7.22-7.34 (m, 3H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.2, 26.0, 26.3, 27.0, 27.2, 27.4, 27.7, 28.3, 39.6, 43.6, 45.4, 55.88, 55.92, 101.3, 108.6, 110.5, 110.8, 112.6, 122.2, 125.1, 125.3, 128.1, 128.2, 129.6, 132.0, 144.2, 154.2, 176.8 ppm; HRMS (ESI) calculated $C_{27}H_{32}N_2O_2$ $(M+H)^+$: 417.2542; found, 417.2557.



361d

Synthesis of 1[1]*H*-1,2(3,1)-diindolinacyclotetradecaphan-2[2]-one (361e): A solution of 1-(12-(1*H*-indol-1-yl)dodecyl)-3-diazoindolin-2-one (**360e**, 100 mg) in dry DCM (4 mL) was added dropwise to a solution containing TfOH (20 mol%) dissolved in dry DCM (5 mL) at room temperature to afford product **361e** (83 mg, 89%); R_f = 0.43 (EtOAc/hexane = 2:3, v/v); mp 189-190 °C; IR (neat): ν_{max} 2924, 1710, 1609, 1461, 1350, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 0.89-1.17 (m, 16H, CH_2), 1.54-1.73 (m, 4H, CH_2), 3.30-3.35 (m, 1H, CH), 3.84-3.90 (m, 1H, CH), 4.04-4.20 (m, 2H, CH_2), 4.82 (s, 1H, CH), 6.65 (s, 1H, ArH), 6.84 (d, *J* = 8.0 Hz, 1H, ArH), 6.92-6.96 (m, 1H, ArH), 7.05-7.25 (m, 5H, ArH), 7.68 (d, *J*= 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.0, 26.2, 27.2, 27.37, 27.40, 27.6, 27.8, 28.4, 28.5, 29.3, 39.7, 43.8, 46.1, 108.6, 109.7, 110.5, 119.5, 119.7, 121.9, 122.3, 125.0, 125.3, 128.0, 129.8, 136.6, 144.0, 176.5 ppm; HRMS (ESI) calculated $C_{28}H_{34}N_2O$ $(M+H)^+$: 415.2749; found, 415.2758.



361e

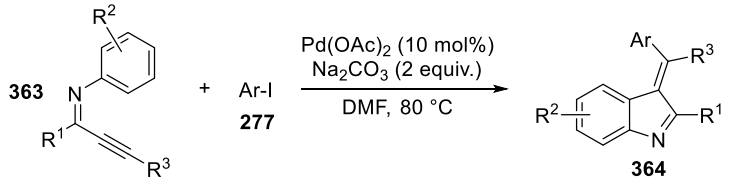
CHAPTER - V

$AlCl_3$-CATALYZED REACTIONS OF DIAZOAMIDES TOWARDS 3-ALKYLIDENE-3*H*-INDOLES

Indole derivatives are common in a variety of biologically active natural and synthetic compounds, and they serve as a privileged scaffold in medicinal chemistry.[237] Among indole family, 3*H*-indole skeletons have received a lot of attention, which could be explained by the presence of quaternary centers at C-2 and C-3 of the indolenine ring system. Moreover, 3*H*-indoles have been employed as precursors for the synthesis of various indole alkaloids, such as physovenine.[238] As a result, many researchers have investigated the development of synthetic methods for this privileged structure, most commonly through the de-aromatization of indoles.[239] Recently, several approaches for the synthesis of 3H-indole derivatives that rely on more difficult intramolecular cyclization processes have been developed.[240] Li and co-workers recently revealed an iodine-mediated synthesis of 3*H*-indoles *via* intramolecular enamine cyclization, which is particularly relevant to this work.[241] The synthesis of 3*H*-indoles will be covered in this chapter.

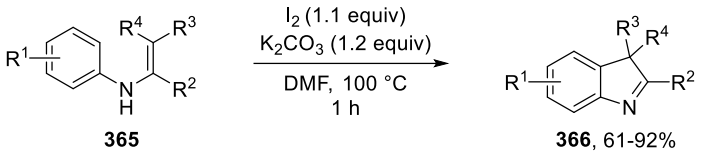
Synthesis of 3*H*-indoles

A novel Pd(II)-catalyzed[242] synthesis of substituted 3-methylene-3*H*-indoles **364** from readily available alkynylimines **363**. Through this cascade carbopalladation and C-H activation process, a broad range of 2-fluoroalkyl-3-methylene-3*H*-indoles **364** were synthesized in good to excellent yield. The primary goal of this reaction was to obtain 2-fluoroalkyl substituted 3*H*-indoles **364** (Scheme 140).



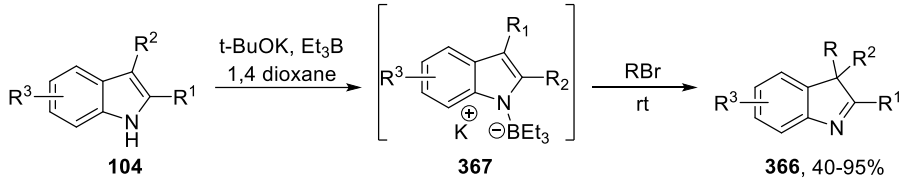
Scheme 140

Li and co-workers have demonstrated[243] that the synthesis of 3*H*-indoles **366** was accomplished through the iodine-mediated intramolecular cyclization of enamines **365**. Under transition metal-free reaction conditions, a broad range of 3*H*-indole derivatives **366** with multifunctional groups was synthesized with good to excellent yields (Scheme 141).

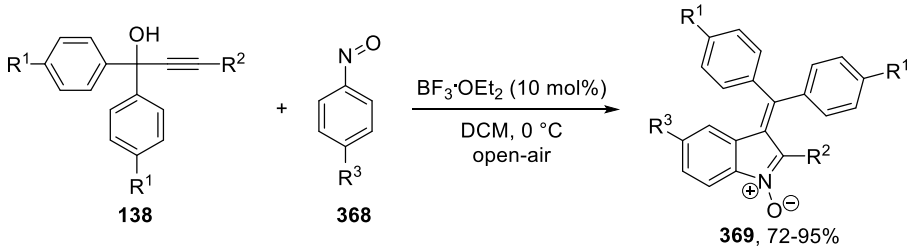


Scheme 141

Hashim and co-workers discovered[244] that N-indolyltriethylborate **367** is a valuable reagent for dearomatizing C3-alkylation of 3-substituted indoles **104** with both non-activated and activated alkyl halides to provide C3-quaternary indolenines **366** under mild reaction conditions. These reagents' utility was illustrated in the synthesis of a debromoflustramine B and pyrroloindoline-4-cholestene hybrid (Scheme 142).



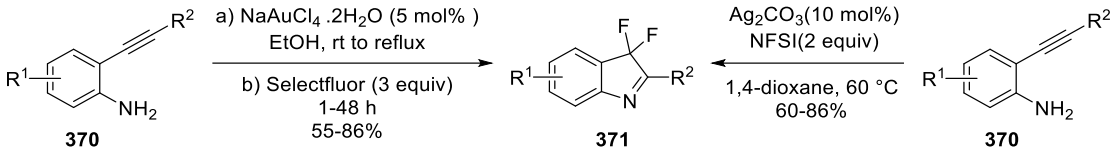
Scheme 142



Scheme 143

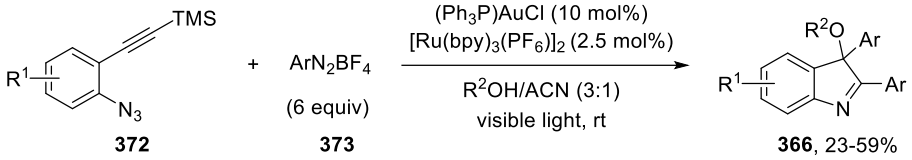
Our group has reported[245] that a tandem reaction of propargylic alcohols **138** and nitrosobenzenes **368** in the presence of ($BF_3 \cdot OEt_2$) as a catalyst afforded 3-alkylidene-3*H*-indole *N*-oxides **369** in good to excellent yield (Scheme 143).

Michelet, You and co-workers have demonstrated[246] that tandem aminocylization, fluorination, as well as a two-step, one-pot Au(III) or Ag(I)-catalyzed cyclization/electrophilic fluorination, furnished an efficient and typical method for the synthesis of 3,3-difluoro-2-substituted-3*H*-indoles **371** in moderate to good yields under mild conditions. Selectfluor or NFSI used as fluorinating reagents (Scheme 144).



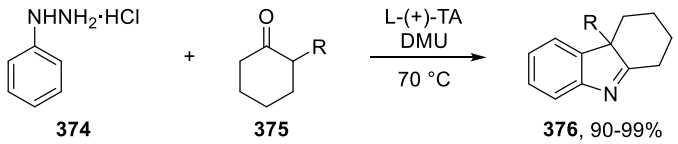
Scheme 144

According to Luna and co-workers, visible light-stimulated and Au/Ru-photoredox-catalyzed[247] reactions of heteroatom-linked alkynes **372** with arenediazonium salts **373** selectively executed to construct vicinal diaryl-substituted 3*H*-indoles **366** and other heterocycles. Furthermore, the switchable and simple preparation of other indole derivatives tested the efficacy of functionalized 3*H*-indoles **366** as precursors for more elaboration (Scheme 145).



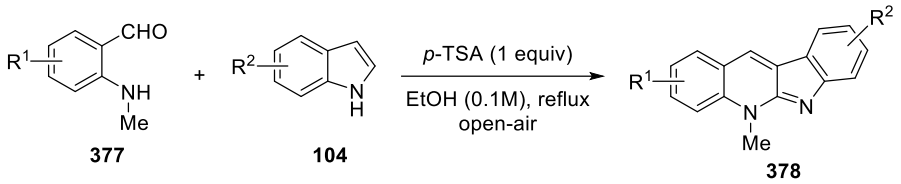
Scheme 145

Baskaran and co-workers reported[248] the synthesis of functionalized 3*H*-indoles **376** in a tartaric acid-dimethylurea melt under mild conditions utilizing cyclohexanone **375** and phenylhydrazine **374**. The tartaric acid-dimethyl urea melt acts as both a solvent and a catalyst in this reaction (Scheme 146).



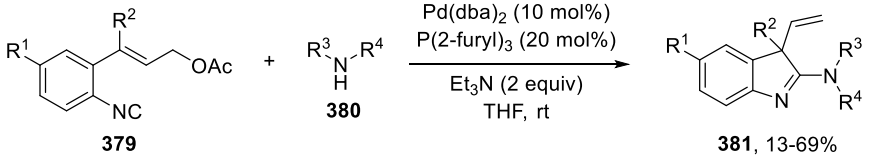
Scheme 146

A *p*-TSA-promoted[249] reaction with secondary aminobenzaldehyde **377** resulted in indole annulation preceded by spontaneous oxidation to neocryptolepine **378** and its analogs. Regrettably, when reacting with different classes of aminobenzaldehydes **377**, indole **104** exhibits a wide pattern of reactivity (Scheme 147).



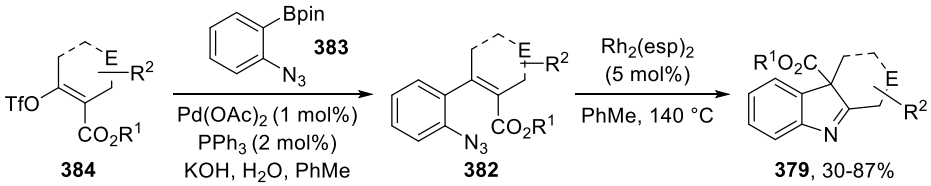
Scheme 147

Pd-catalyzed[250] allylic amidination by an isocyanide **379** was used to synthesize 3,3-disubstituted 2-aminoindolenines **381**. Isocyanides, like carbon monoxide, have been discovered to be effective building blocks in Pd-catalyzed allylic functionalizations. Under mild reaction conditions, this method allows for the direct formation of the indolenine ring **381**, formation of a quaternary carbon, and inclusion of an amino substituent all in one step (Scheme 148).



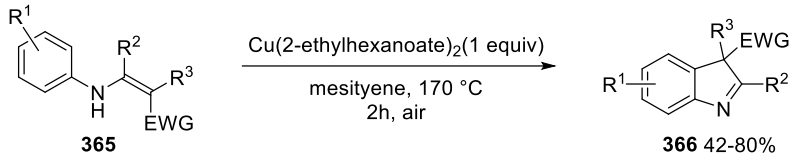
Scheme 148

Driver and co-workers documented[251] the use of $Rh_2(esp)_2$ as a catalyst to convert -carboxylate substituted styryl azides **382** to fused 3*H*-indoles **379**. By modifying the identity of the *β*-substituent, 3*H*-indoles **379** could be obtained from trisubstituted styryl azides **382**. This transformation was demonstrated to be general, tolerating a huge spectrum of substitutions on the aryl azide **382**, and allowing access to 3*H*-indoles **379** (Scheme 149).



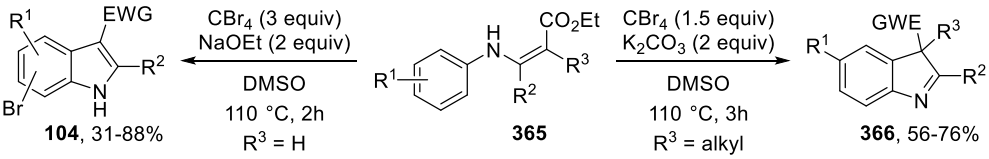
Scheme 149

Taylor and co-workers have developed[252] a simple Cu(II)-catalyzed C-H bond activation followed by a C-C bond formation procedure to synthesize 3*H*-indole derivatives **366**. Intramolecular oxidative coupling reactions of enamines **365** proceeded using a commercially accessible and air-stable copper salt, Cu(2-ethylhexanoate)$_2$, to the equivalent C-3 quaternary 3*H*-indoles **366** in good yields (Scheme 150).



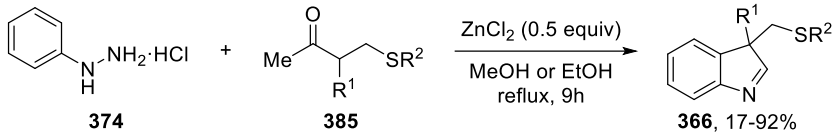
Scheme 150

A CBr_4 catalyzed efficient method for the synthesis of 1*H*- and 3*H*-indoles **104/366** has been developed.[253] The cyclization of *N*-aryl enamines **365** proceeds efficiently in the involvement of CBr_4 and a favorable base. This method also has a high level of scalability, substrate tolerability and operational simplicity (Scheme 151).



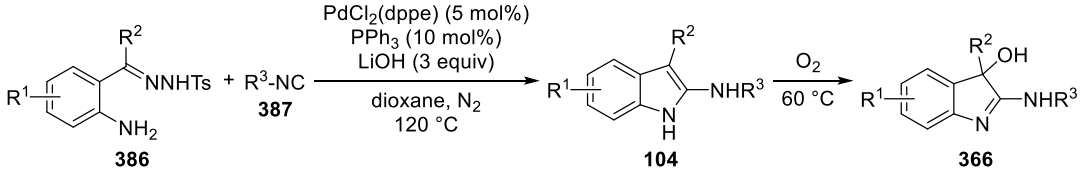
Scheme 151

Focusing on the Fischer indole synthesis with *β*-mercapto ketones **385**, a new approach to the synthesis of 3-(alkylsulfanylmethyl)-substituted 3*H*-indoles **366** has been developed.[254] Heterocyclization of 3-[(alkylsulfanyl)methyl]alkan-2-ones **385** and phenylhydrazine **374** by $ZnCl_2$ in MeOH or EtOH gave 3-alkyl-3-[(alkylsulfanyl)methyl]-2-methyl-3*H*-indoles **366** (Scheme 152).



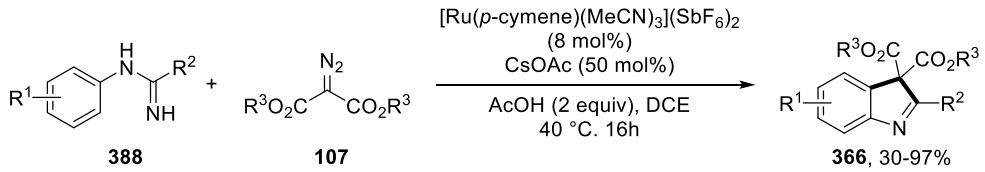
Scheme 152

Cheng and co-workers have reported[255] the formation of oxidized 2-aminoindole derivatives **104** *via* the coupling of isocyanides **387** and 2-aminophenyl-substituted tosylhydrazones **386** in a procedure in which the carbene couples with the isocyanide **387** to construct a ketenimine**,** where it cyclizes to the 2-aminoindole **104** and transforms to 2-amino-3-hydroxy-3*H*-indoles **366** after air oxidation (Scheme 153).



Scheme 153

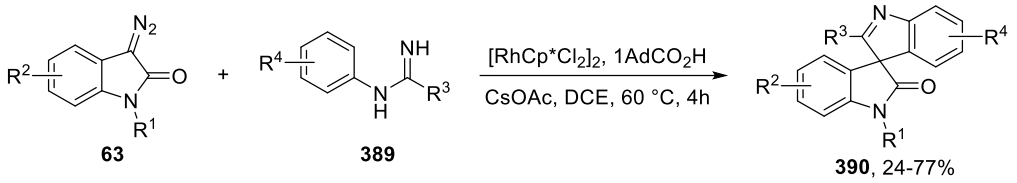
A Ru(II)-catalyzed[256] intermolecular coupling reactions between aryl imidamides **388** and diazo compounds **107** by CH activation, which allowed the synthesis of 3*H*-indole derivatives **366** *via* [4+1] annulation under mild reaction conditions. The coupling of α-diazoketoesters **107** resulted in NH indoles *via* C(N_2)-C(acyl) bond cleavage, whereas α-diazomalonates **107** resulted in 3*H*-indoles **366** *via* CN bond cleavage (Scheme 154).



Scheme 154

Zhang, Fan and co-workers have explored[257] an efficient method for synthesis of 3-spirooxindole 3*H*-indoles **390** *via* the coupling followed by spirocyclization of N-aryl amidines **389** with diazoamides **63**. The title compounds were generated *via* a tandem process that includes Rh(III)-catalyzed C(sp^2)–H bond cleavage, Rh-carbenoid

formation, insertion, intramolecular nucleophilic addition, followed by ammonia exclusion (Scheme 155).



Scheme 155

Scope and objectives: 3*H*-Indole is a key structural unit in a wide range of natural products and biologically active molecules. The importance of this class of molecules is heightened by their role as intermediates in the synthesis of different biologically active scaffolds. According to the literature methods, there are only a few reports available for synthesizing 3*H*-indoles. There are only a few methodologies available for preparing 3-alkylidene-3*H*-indole synthesis. The obtainable methods necessitate multistep precursor preparation, an expensive metal catalyst, and harsh reaction conditions. It was planned to study the Lewis acid catalyzed synthesis of 3-alkylidene-3*H*-indoles from tandem reactions of diazoamides, nitrosobenzenes, and propargylic alcohols in this chapter. Metal-free, cost-effective, shorter reaction time, eco-friendly, and high yields are some of the benefits of this sustainable approach.

- To generate a novel transition metal-free method for producing 3-alkylidene-3*H*-indoles from diazoamides, nitrosobenzenes and propargylic alcohols
- To develop $Rh_2(OAc)_4$ catalyzed direct deoxygenation of 3-alkylidene-3*H*-indole *N*-oxides towards synthesis 3-alkylidene-3*H*-indoles

RESULTS AND DISCUSSION

5.2. Synthesis of 3-alkylidene-3*H*-indoles

3*H*-Indole is a critical structural unit for gaining access to a variety of natural products and biologically active compounds (Figure 28). Among these, 3-alkylidene-3*H*-indoles have received considerable attention in the production of marine alkaloids. Fischer idolizations, condensation reactions, and indole dearomatization can all be used to create a wide range of substituted 3*H*-indoles. Unlike its tautomer, 1*H*-indole, the procedures available in the literature for the formation of 3*H*-indole derivatives are extremely scarce.[258] In this chapter, the main focus is on the sequential addition of multicomponent reactions that can afford a wide variety of highly substituted 3-alkylidene-3*H*-indoles **364** from diazoamides **63**, nitrosobenzenes **367** and propargyl alcohols **138** in the presence of 10 mol% of $AlCl_3$ at 0 °C under an open-air atmosphere.

At the outset of the literature survey,[87,245,259] we designed a multi-component reaction. Initial efforts concentrated on optimizing the reaction conditions for the model reaction between diazoamide **63a**, nitrosobenzene **367a** and propargylic alcohol **138a**. The

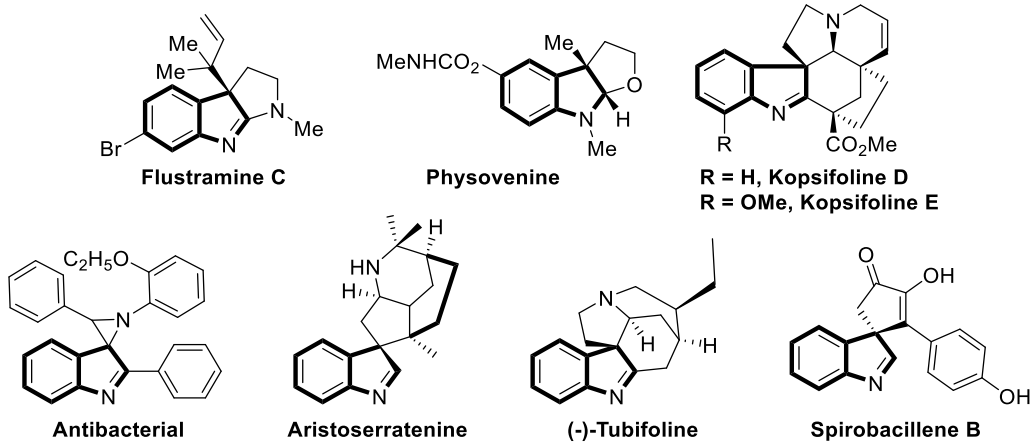
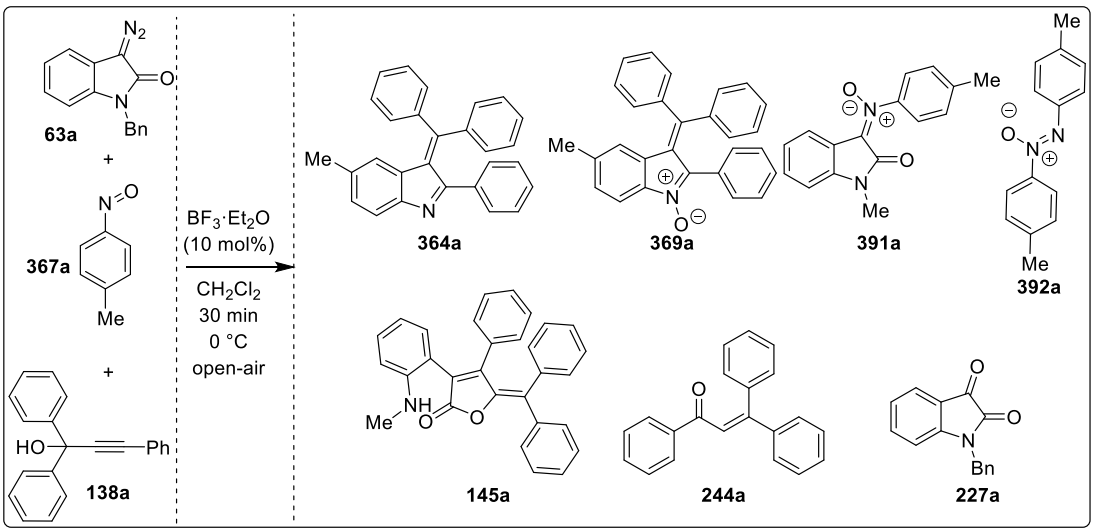


Figure 28. Examples of C-2 and C-3 quaternary indoline compounds

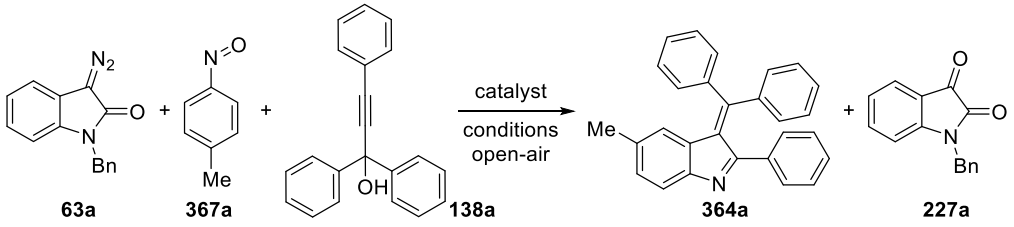
reaction was carried out 1 equiv of **63b**, 1.1 equiv of **367a** and 1 equiv **138a** in the presence of 20 mol% of $BF_3{\cdot}OEt_2$ in dichloromethane at 0 °C under an open-air atmosphere to afford a mixture of products such as 3-alkylidene-3*H*-indole **364a**, indole *N*-oxide **369a**, oxindole-nitrone **391a**, azoxybenxene **392a**, furanone **145a**, Mayer-Schuster product **244a** and isatin **227a** (Scheme 156). To avoid the mixture of products, it was planned to add reactants in a sequence manner. Before choosing the addition sequence, carefully go through the literature[259a] and identified diazoamide **63a**, nitrosobenzene **367a** and silica gel to provide oxindole-nitrone **391a**. Based on this observation, reaction of propargylic alcohol **138a** and oxindole-nitrone **391a** afforded 3-alkylidene-3*H*-indole **364a** in 70% yield along with isatin **227a** as a by-product. From the NMR and mass spectrometric analyses, 3-alkylidene-3*H*-indole **364a** was characterized. A singlet peak appeared at 2.12 ppm in the ^{1}H-NMR spectrum of product **364a** corresponds to CH_3 protons, and multiplets appeared around 6.23-7.58 ppm, indicating the presence of 18 aromatic protons (Figure 29). Peaks at 21.6 ppm in the ^{13}C-NMR spectrum of product **364a** (Figure 30) corresponds to CH_3 carbon. All of the other carbon peaks agree well with the proposed structure. HRMS data were calculated



Scheme 156. Preliminary studies of diazoamide, nitrosobenzene and propargylic alcohol

for $C_{28}H_{21}N$ $[M+H]^+$ 372.1752 and found to be 372.1739. The expected spiro-oxazoline product did not form. Next, we looked at the reaction, whether the diazoamide is involved in the reaction or not? To identify the same, the reaction was repeated without diazoamide which gave indole *N*-oxide **369a** as a product. Then, we got suspicion whether the formed indole *N*-oxide undergoes deoxygenation under prolonged time? We did the reaction but in vain. Moreover, it was identified that the reaction proceeds *via* oxindole-nitrone **391a** generated *in situ* from diazoamide **63a** and nitrosobenzene **367a** in the presence of Lewis acid. The oxindole-nitrone **391a** was prepared by the treatment of diazoamide **63a** with nitrosobenzene **267a** in the presence of silica gel. After that, the isolated oxindole-nitrone **391a** reacted with propargylic alcohol **138a** to

Table 15. Optimization of reaction conditions for **364a**[a]



63a **367a** **138a** **364a** **227a**

Entry	Lewis acids (10 mol%)	Temp (°C)	Solvents	Time (min)	Yield (%)[b] **364a**
1	$BF_3{\cdot}OEt_2$	0	DCM	10	70
2	$FeCl_3$	0	DCM	10	66
3	**$AlCl_3$**	**0**	**DCM**	**10**	**82**
4	$InCl_3$	0	DCM	10	68
5	*p*-TSA	0	DCM	10	55
6	TfOH	0	DCM	10	42
7	$CuSO_4{\cdot}5H_2O$	0	DCM	180	nd[c]
8	$AlCl_3$	0	DCE	10	65
9	$AlCl_3$	0	Toluene	10	53
10	$AlCl_3$	0	THF	10	34
11	$AlCl_3$	0	ACN	10	59
12	$AlCl_3$	30	DCE	10	73
13[d]	$AlCl_3$	0	DCM	10	52
14[e]	$AlCl_3$	0	DCM	10	60
15	$AlCl_3$	0	DCM	30	73
16[f]	--	0	DCM	60	nd

[a]Reaction conditions: **63a** (1 equiv), **367a** (1.1 equiv), 1**38a** (1 equiv). [b]Isolated yield. [c]nd = no desired product. [d]20 mol% of catalyst used. [e]5mol% of catalyst used.

give the expected 3-alkylidene-3*H*-indole **364a** as a product along with isatin **227a** as a by-product. Based on the sequential addition of multicomponent reactions, a selected 3-alkylidene-3*H*-indole **364a** as a product and other products were controlled by sequence addition of starting materials. As shown in Table 15, catalyst, temperature, solvent and time were screened to obtain 3-alkylidene-3*H*-indole **364a** in good yield. Next, the reaction was also executed with various Lewis acids such as $FeCl_3$, $AlCl_3$ or $InCl_3$, among them $AlCl_3$ to provide the desired product **364a** in 82% yield (Table 15, entries 2-4). The Brønsted acid, *p*-TSA and TfOH were also the effective catalyst of this reaction but provided the desired product in a slightly lower yield (Table 15, entries 5 and 6). The attempt was made using $CuSO_4 \cdot 5H_2O$ as a catalyst in this transformation, but in vain (Table 15, entry 7). Among the catalyst used, $AlCl_3$ was found to be better. The yield did not improve when the solvent switched to 1,2-dichloroethane (DCE), toluene, tetrahydrofuran(THF) or acetonitrile(ACN) (Table 15, entries 8-11). To improve the yield of product **364a**, the reaction was carried out at an elevated temperature in dichloroethane (Table 15, entry 12). Further, the catalyst load was increased to 20 mol% or reduced to 5 mol% not improving the yield of product **364a** (Table 15, entry 13 and 14). The reaction duration was further extended to 30 min that did not alter the yield of the product (Table 15, entry 15). No reaction occurs when the reaction was performed in the absence of a catalyst (Table 15, entry 16). Thus, the optimized reaction conditions for the formation of **364a** were found to be 10 mol% of $AlCl_3$ at 0 °C in DCM under an open-air atmosphere (Table 15, entry 3). Next, our curiosity focused on an indole *N*-oxide **369a** which acts as a dipole. Deoxygenation of heterocyclic N-oxides to their corresponding amines is a critical transformation in synthetic chemistry.[260] Heterocyclic N-oxides are widely used in synthetic organic

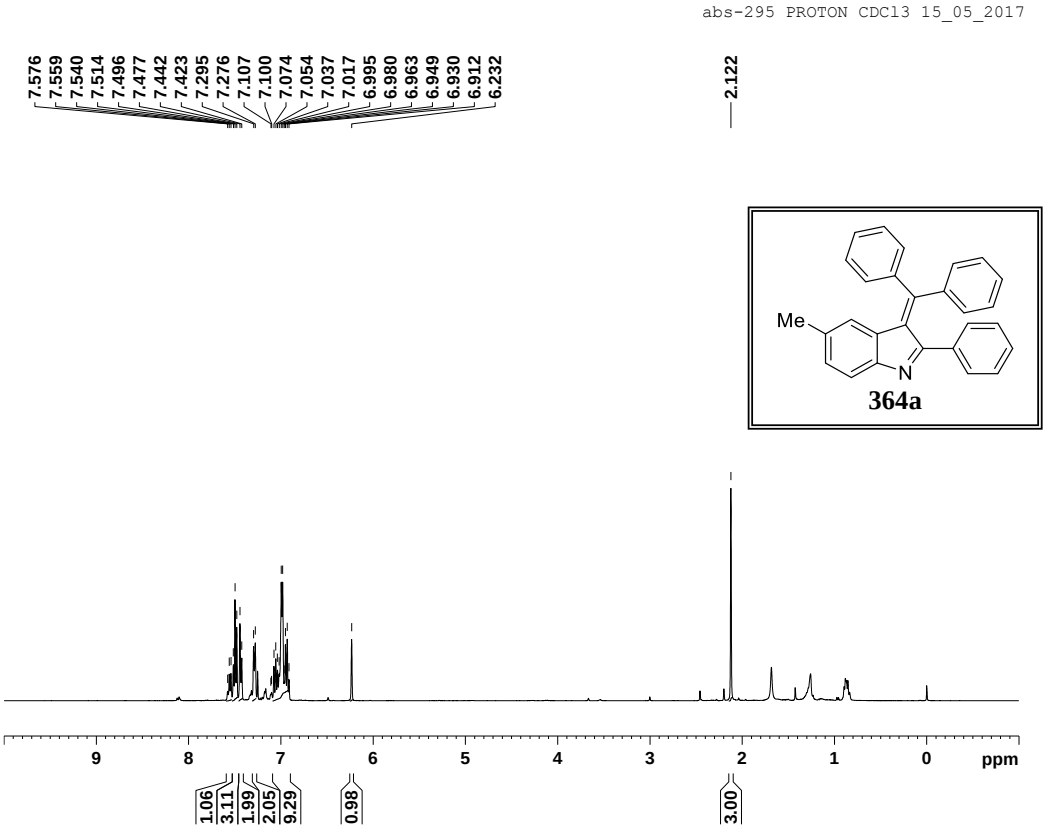


Figure 29. ^{1}H NMR (δ) spectrum of **364a**

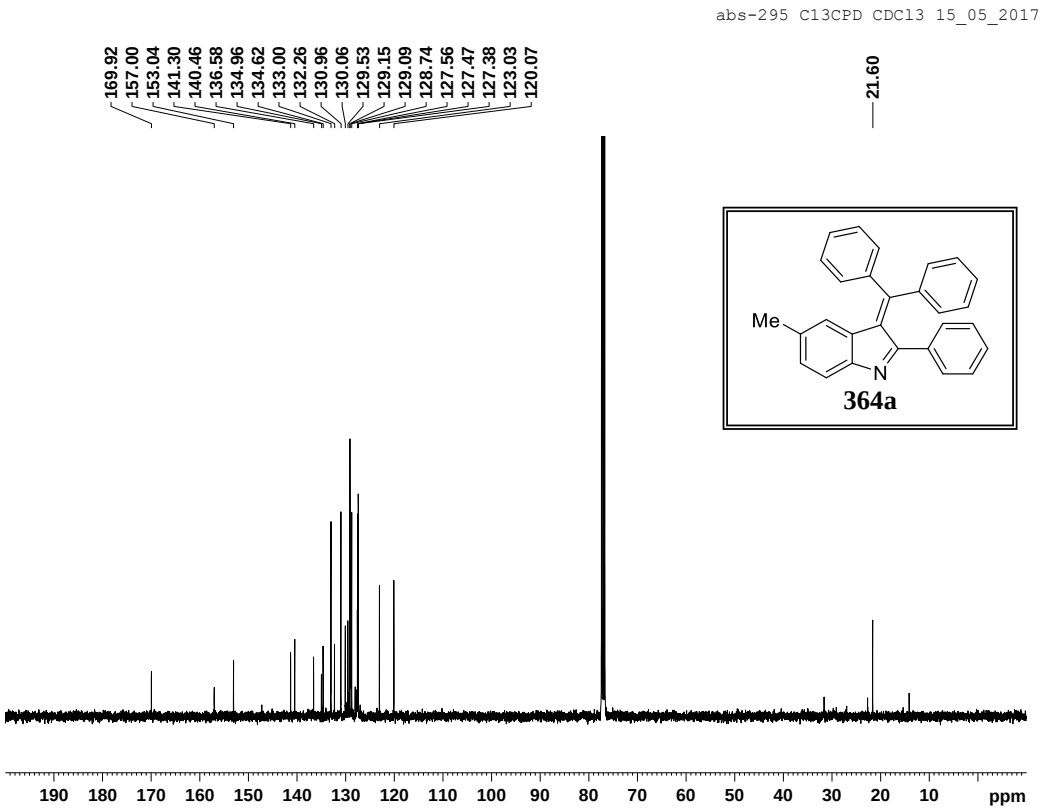
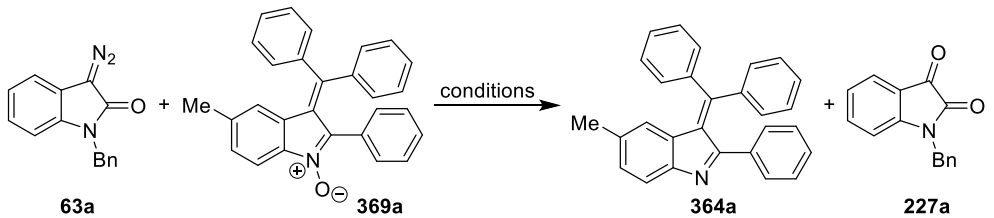


Figure 30. ^{13}C NMR (δ) spectrum of **364a**

chemistry as directing groups in many regioselective C-H insertion reactions, intermediates, oxidants, starting materials, ligands, and organocatalysts.[261] The indole *N*-oxide **369a** was prepared[245] by the treatment of nitrosobenzene **367a** with propargylic alcohol **138a** in the presence of $BF_3{\cdot}OEt_2$. The indole *N*-oxide **369a** (1 equiv) was treated with diazoamide **63a** (1 equiv) in the presence of 10 mol% of $BF_3{\cdot}OEt_2$ under an open-air atmosphere did not provide any products and the starting materials were recovered as such (Table 16, entry 1). However, the reaction screened with various Lewis/Brønsted acids did not provide any products, only diazoamide **63a** decomposed in certain conditions (Table 16, entry 2). Based on the literature, the reaction carried out with 1 mol% of $Rh_2(OAc)_4$ as a catalyst under the nitrogen atmosphere at room temperature for 2 h to afford the corresponding indole *N*-oxide reduction product **364a** in 89% yield along with the corresponding isatin **227a** (Table 16, entry 3). This current protocol indicates the deoxygenation methodology and diazoamide **227a** are not intact with the final product **364a** only oxygen atom transfers from indole *N*-oxide to diazoamide. On the other hand, we screened other metal catalysts, and solvents at different temperatures to alter the yield of the product **364a**. When the reaction was carried out with other metal catalysts such as CuOTf, $Cu(acac)_2$, $Cu(CH_3CN)_4PF_6$ or CuI, the yield of the product did not improve (Table 16, entries 4-7). $CuSO_4.5H_2O$ was also tested and found not suitable for this transformation (Table 16, entry 8). Among the catalysts, $Rh_2(OAc)_4$ is an efficient catalyst for this transformation. The investigation was continued with different solvents like DCE, $CHCl_3$, PhMe, THF or DMF, which did not improve the yield of product **364a** (Table 16, entries 9-13). Raising the temperature to reflux conditions led to a decrease in yield to 55% (Table 16, entry 14). Thus, the optimized reaction conditions for the formation

of **364a** were found to be 1 mol% of $Rh_2(OAc)_4$ at room temperature in DCM (Table 16, entry 13). With the optimized reaction conditions in hand (Table 15, entry 3 and Table 16, entry 3), the substrate scope for 3- alkylidene-3*H*-indole **364** was investigated as shown in Table 17. Encouraged by the above results a range of diazoamide **63a-c** nitrosobenzenes **367a-f** and propargylic alcohols **138a-k** or indole *N*-oxides **369a-n** and diazoamides **63** could be converted into the desired 3-alkylidene-3*H*-indole **364a-n** in the presence of $BF_3{\cdot}Et_2O$ or $Rh_2(OAc)_4$ [Method A & B] respectively. Reactions were planned to perform with various propargylic alcohols bearing electron-donating or -withdrawing groups. Reactions of propargylic alcohols bearing an electron-donating group on the phenyl ring afforded the corresponding substituted 3-alkylidene-3*H*-indoles **364a-d** in good yields (Table 17). Further, the *n*-butyl group containing propargylic alcohol yielded **364e** in 75% yield. To broaden the substrate scope,

Table 16. Optimization of reaction conditions for **364a**[a]

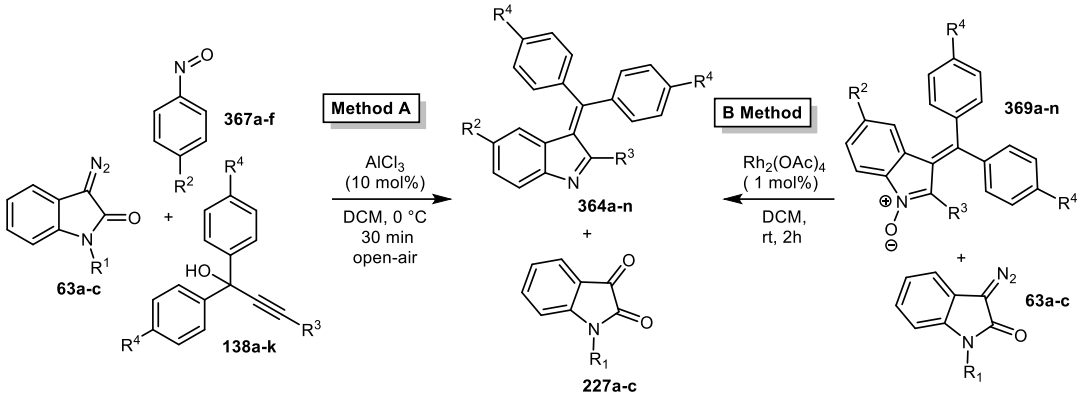


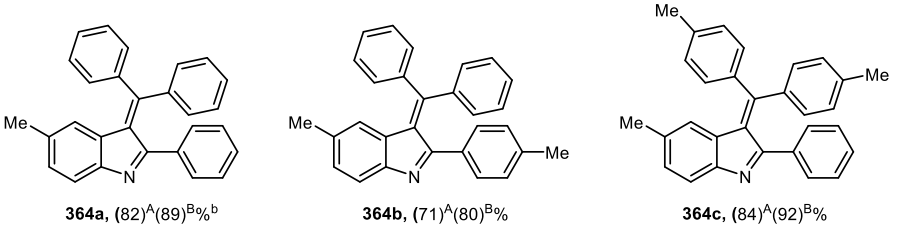
63a **369a** **364a** **227a**

Entry	Catalyst	Solvents	Temp °C)	Time (min)	Yield (%)[b] **364a**
1[c]	$BF_3{\cdot}OEt_2$	DCM	rt	120	nr[d]
2	Lewis/ Brønsted acids[e]	DCM	rt	120	nr[d]
3	**$Rh_2(OAc)_4$**	**DCM**	**rt**	**120**	**89**
4	CuOTf	DCM	rt	180	17
5	$Cu(acac)_2$	DCM	rt	120	36
6	$Cu(CH_3CN)_4PF_6$	DCM	rt	120	55
7	CuI	DCM	rt	240	14
8	$CuSO_4.5H_2O$	DCM	rt	120	nr[d]
9	$Rh_2(OAc)_4$	DCE	rt	120	75
10	$Rh_2(OAc)_4$	$CHCl_3$	rt	120	61
11	$Rh_2(OAc)_4$	PhMe	rt	120	28
12	$Rh_2(OAc)_4$	THF	rt	120	41
13	$Rh_2(OAc)_4$	DMF	rt	120	13
14	$Rh_2(OAc)_4$	DCE	reflux	120	48

[a]Reaction conditions: **63a** (1.2 mmol), **369a** (1 mmol), solvent (5 mL). [b]Isolated yield. [c]Reaction carried out at 0 °C. [d]nr = No reaction. [e]Various Lewis/ Brønsted acids: $FeCl_3$, $AlCl_3$, $InCl_3$, *p*-TSA, TfOH.

Table 17. Substrate scope for 3-alkylidene-3*H*-indoles **364a**.[a,b]

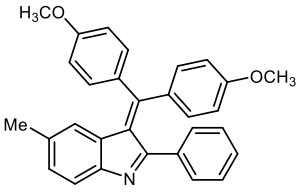




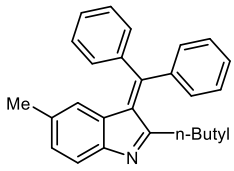
364a, (82)^{A}(89)^{B}%[b]

364b, (71)^{A}(80)^{B}%

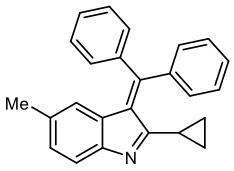
364c, (84)^{A}(92)^{B}%



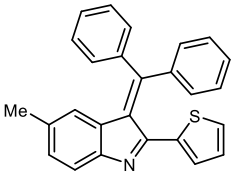
364d, (71)^{A}(77)^{B}%



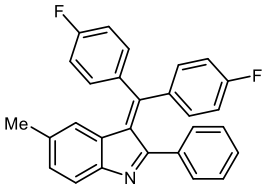
364e, (80)^{A}(87)^{B}%



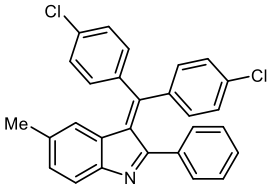
364f, (73)^{A}(76)^{B}%



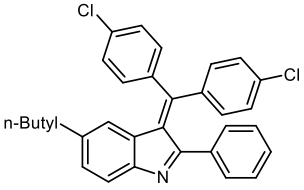
364g, (75)^{A}(72)^{B}%



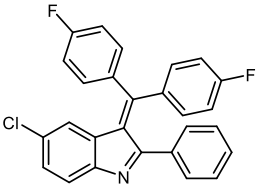
364h, (69)^{A}(74)^{B}%



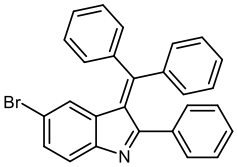
364i, (71)^{A}(78)^{B}%



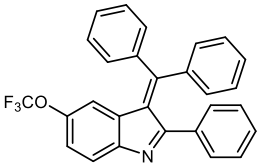
364j, (76)^{A}(81)^{B}%



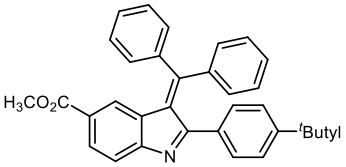
364k, (70)^{A}(75)^{B}%



364l, (76)^{A}(81)^{B}%



364m, (69)^{A}(63)^{B}%



364n, (65)^{A}(62)^{B}%

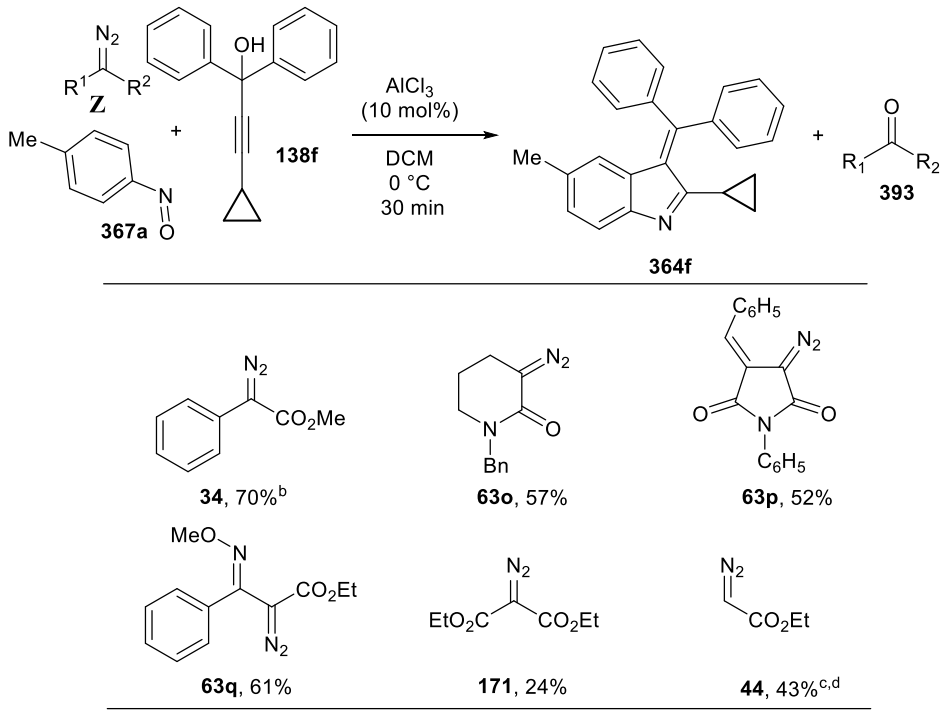
[a]Reaction conditions: equimolar amount of **63** (1 mmol), **367** (1 mmol), and **138** (1 mmol), $AlCl_3$ (10 mol%), 0 °C, DCM (5 mL), 30 min. [b]Isolated yields.

cyclopropyl tethered propargylic alcohol was also utilized for this transformation to give **364f**. The R^3 group containing thiophenyl ring also provided the expected 3-alkylidene-3*H*-indole **364g** in good yield. Reactions of propargylic alcohols bearing an electron-withdrawing group on the phenyl ring provided the corresponding 3-alkylidene-3*H*-indoles **364h-j** in good yields. Next, to move on the scope of nitrosobenzenes, halo-substituted nitrosobenzenes were also found as feasible substrates to provide 3-alkylidene-3*H*-indoles **364k,l** in good yields. Strong electron-withdrawing groups such as $-CF_3$ and $-CO_2CH_3$ substituted nitrosobenzenes also gave the desired products **364m,n** in moderate yields. The *N*-substituent on the diazo part did not alter the yield of the product. However, the propargylic alcohols bearing terminal acetylene groups failed to afford the desired products **364**. Similarly, propargylic alcohols derived from acetone and acetophenone failed to afford the corresponding products under the optimized reaction conditions indicating the phenyl groups stabilize the allene carbocations.

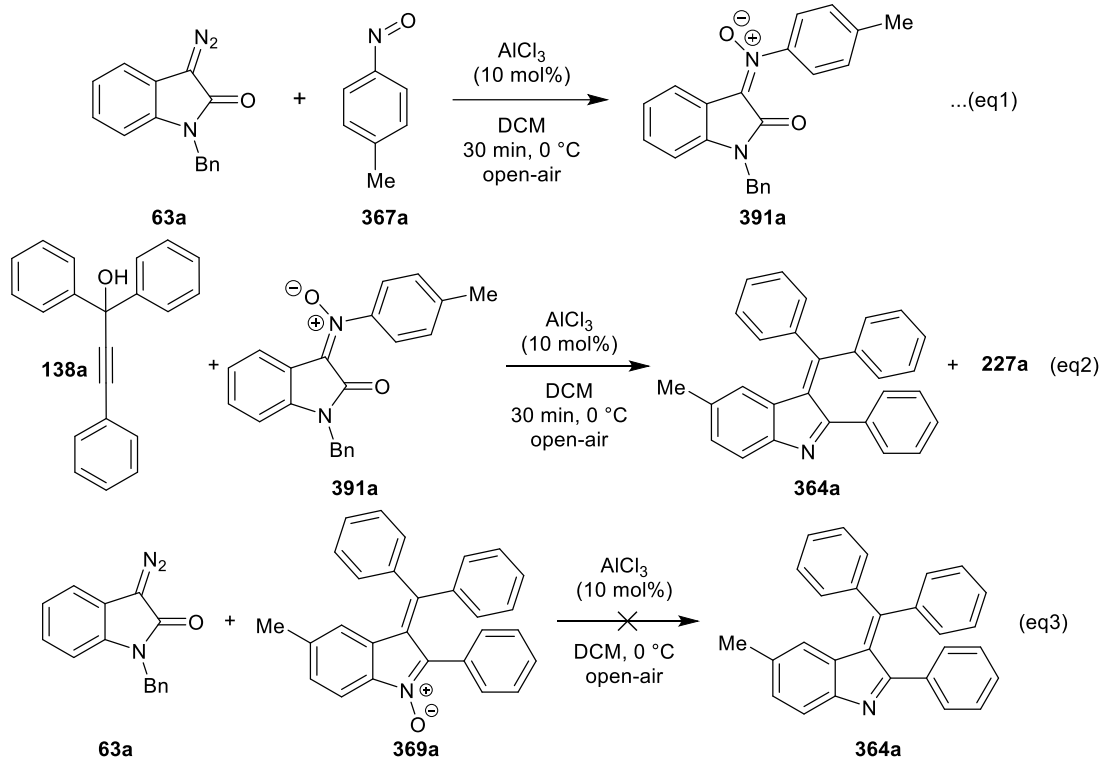
Next, the scope of this methodology was investigated with other diazocarbonyl compounds. The reactions of other diazocarbonyls (Z = 34, 63, 171, 44) afforded the corresponding 3-alkylidene-3*H*-indole **364f** in moderate to good yields (Table 18).

The following control experiment was carried out to gain insight into the reaction mechanism. Initially, the oxindole nitrone **391a** was prepared by the treatment of diazo compound **63a** with nitrosobenzene **367a** in the presence of $AlCl_3$. After that, the isolated oxindole nitrone **391a** was reacted with propargylic alcohol **138a** to give the corresponding 3-alkylidene-3*H*-indole **364a** as a product (Scheme 257, equation 1 and 2). Based on this control experiment, during the course of reaction the oxindole nitrone was formed as an intermediate based on the literature.[259a] The indole *N*-oxide **369a** and

Table 18. Substrate scope for diazocarbonyl compounds.[a]



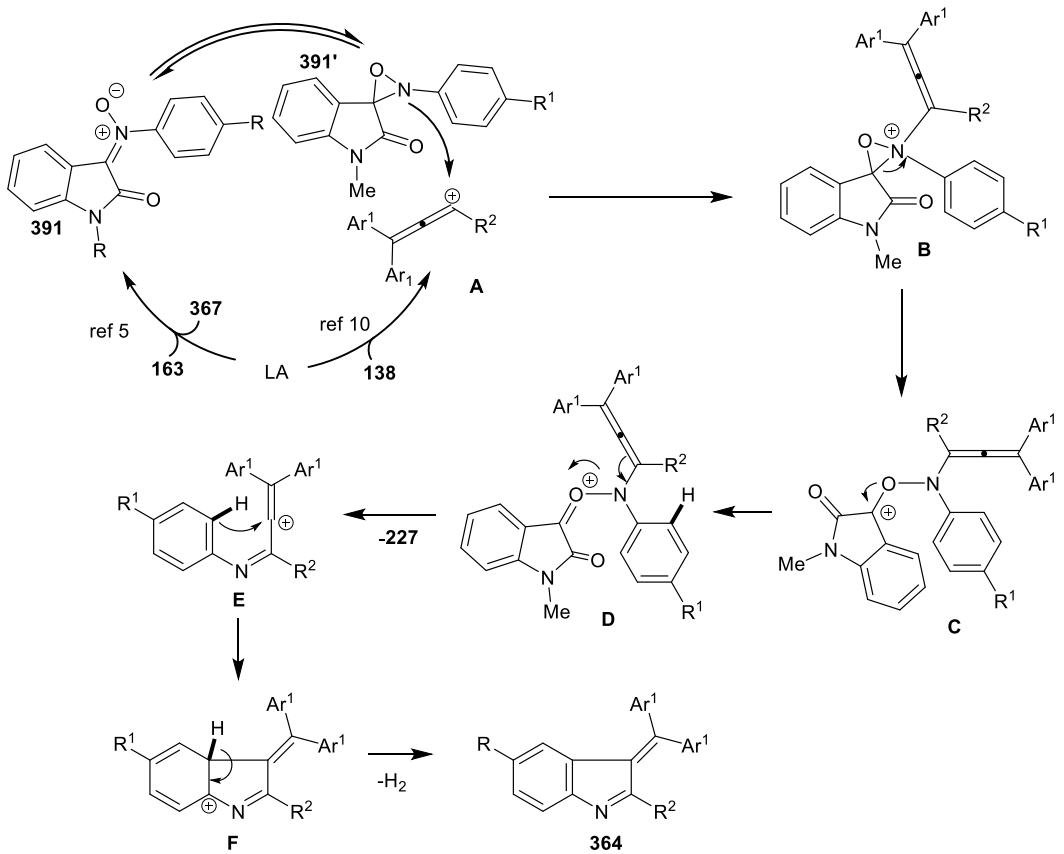
[a]Reaction conditions: equimolar amount of **Z** (34, 63, 171, 44) (1 mmol), **367a** (1 mmol), and **138f** (1 mmol), $AlCl_3$ (10 mol%), 0 °C, DCM (5 mL), (30 min). [b]Isolated yield. [c]2 equiv of EDA was used. [d]Reaction was carried out under an argon atmosphere.



Scheme 157. Control experiments

diazoamide **63a** were treated with 10 mol% of $AlCl_3$ under an open-air atmosphere and did not provide the desired product **364a**. These experiments suggested that indole *N*-oxide is not an intermediate for this reaction (Scheme 157, equation 3).

Based on the above results and related precedents,[87,259a,262-266] a plausible mechanism for the formation of 3-alkylidene-3*H*-indole **364** was proposed (Scheme 158). According to the literature[241] the generated propargylic cation underwent subsequent tautomerism to generate the allenic cation **A**. On the other hand, the diazoamide **63** and nitrosobenzene **367** are reacting under an acidic medium to generate oxindole-nitrone **391**. The oxindole-nitrone **391** was in equilibrium with spiro-oxazridine **391'**. The nucleophilic attack took place on the allene carbocation **A** by the nitrogen loan pair of spiro-oxazridine **391a'** to form intermediate **B**. Subsequently, the intermediate **C**



Scheme 158. Proposed reaction mechanism for the formation of 3-alkylidene-3*H*-indoles **364**

formed through a C-N bond cleavage led to the ring-opening of spiro-oxaziridine **B**. The oxygen atom donated a loan pair of an electron to stabilize the carbocation to form an intermediate **D**. The cleavage of the N-O bond led to vinylic carbocation **E** and losing the isatin unit **227**. Further, the vinylic carbocation underwent Friedel–Crafts cyclization led to the cationic bicyclic intermediate **F**. Deprotonation of **F** led to the formation of 3-alkylidene-3*H*-indoles **364**.

All the reactions were conducted in oven-dried glassware under a positive pressure of nitrogen with magnetic stirring. Aniline, benzophenone, oxone, phenylacetylene, $Rh_2(OAc)_4$, $AlCl_3$ and $BF_3{\cdot}OEt_2$ were purchased from M/s Aldrich, Alfa Aesar or Spectrochem and used as provided. The propargyl alcohol, nitrosobenzene and indole *N*-oxide[245] were prepared according to the literature methods.

Experimental Section

General procédure for the synthesis of 3-alkylidene-3*H*-indoles 364 (Method A)

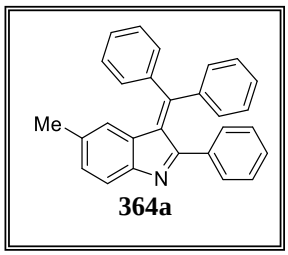
To an oven-dried flask, a solution containing diazoamides **63** (1 equiv) and nitrosobenzenes **367** (1 equiv) and 10 mol% of $BF_3{\cdot}OEt_2$ dissolved in 3 mL of DCM under an open-air atmosphere after 5 minutes was added a solution of propargylic alcohols **138** (1 equiv) in dry DCM (3 mL) at 0 °C temperature to afford until the reaction completed (monitored using TLC). After the appropriate period, the reaction mixture was diluted with DCM (20 mL) and water (20 mL). The organic phase was separated and the aqueous layer was washed with DCM (20 mL). The concentration of the combined organic layers under reduced pressure afforded the crude product, which was purified by column chromatography using silica gel to afford the corresponding 3-alkylidene-3*H*-indoles **364**.

General procédure for synthesis of 3-alkylidene-3*H*-indoles 364 (Method B)

To a solution of indole *N*-oxide **369** (1 equiv) and diazoamide **63** (1 equiv) in DCM (5 mL) was added 1 mol% of $Rh_2(OAc)_4$. The reaction mixture was stirred at room temperature under the nitrogen atmosphere and monitored by TLC until the disappearance of starting materials. After the appropriate period, the reaction mixture

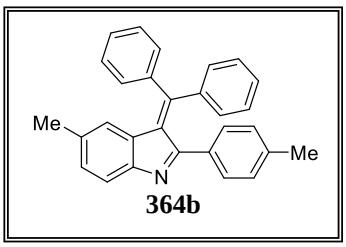
was concentrated under reduced pressure afforded the crude product, which was purified by column chromatography using silica gel to afford the corresponding 3-alkylidene-3*H*-indoles **364**.

Synthesis of 3-(diphenylmethylidene)-5-methyl-2-phenyl-3*H*-indole (364a)[245]: The title compound was prepared according to the GP A or B and purified by column chromatography to provide product **364a** as a red gum; yield 82 and 89%; R_f = 0.46 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 3057, 2923, 2856, 1579, 1483, 1447, 1339, 1276, 1073, 820, 761, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3H, ArH), 6.25 (s, 1H, ArH), 6.93-7.10 (m, 9H, ArH), 7.27-7.31 (m, 2H, ArH), 7.44-7.59 (m, 6H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 120.1, 123.0, 127.4, 127.5, 127.6, 128.7, 129.09, 129.15, 129.5, 130.1, 131.0, 132.3, 133.0, 134.6, 135.0, 136.6, 140.5, 141.3, 153.0, 157.0, 169.9 ppm. HRMS (ESI): calcd for $C_{28}H_{21}N$ $[M+H]^+$ 372.1752; found 372.1739.



364a

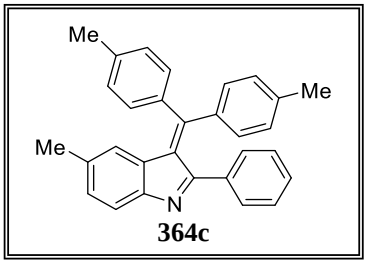
Synthesis of 3-(diphenylmethylidene)-5-methyl-2-(4-tolyl)-3*H*-indole (364b): The title compound was prepared according to the GP A or B and purified by column chromatography to provide product **364b** as a red gum; yield 71 and 80%; R_f = 0.57 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} = 3052, 2940, 2865, 1569, 1470, 1441, 1342, 1269, 1210, 1181, 1075, 824, 753, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 6.21 (s, 1H, ArH), 6.77 (d, *J* = 8.0 Hz, 2H, ArH), 6.91-6.95 (m, 2H, ArH), 6.97-7.00 (m, 2H, ArH), 7.02-7.06 (m, 2H, ArH), 7.16-7.18 (m, 2H, ArH), 7.41-7.43 (m, 2H, ArH), 7.46-7.51 (m, 3H, ArH), 7.53-7.56 (m, 1H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.6, 119.9,



364b

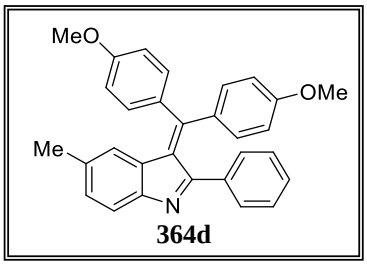
123.0, 127.4, 128.2, 128.8, 129.06, 129.12, 129.3, 130.1, 132.3, 133.1, 133.5, 134.4, 135.0, 137.4, 140.5, 141.4, 153.0, 157.0, 170.0 ppm. HRMS (ESI): calcd for $C_{29}H_{23}N$ $[M+H]^+$ 386.1903; found 386.1901.

Synthesis of 3-[bis(4-tolyl)methylidene] 5-chloro-2-phenyl-3*H*-indole (364c)[245]: The title compound was prepared according to the GP A or B and purified by column chromatography to obtain product **364c** as a red gel; yield: 84 and 92%; R_f = 0.61 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 2927, 2853, 1735, 1602, 1553, 1507, 1456, 1341, 1276, 1177, 820, 763, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.11 (s, 6H), 2.45 (s, 3H), 6.38 (s, 1H), 6.72 (d, 2H, *J* = 7.6 Hz), 6.86 (d, 2H, *J* = 8 Hz), 6.95-7.01 (m, 2H), 7.06 (d, 1H, *J* = 7.6 Hz), 7.25-7.26 (m, 3H), 7.29 (d, 2H, *J* = 8 Hz), 7.34 (d, 2H, *J* = 8 Hz), 7.49 (d, 1H, *J* = 7.6 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.3, 21.8, 21.9, 118.7, 121.7, 126.8, 127.1, 128.3, 128.5, 129.1, 129.3, 131.4, 132.5, 133.3, 134.0, 134.3, 136.7, 137.9, 138.4, 140.1, 140.6, 152.9, 157.9, 169.9 ppm. HRMS (ESI): calcd for $C_{30}H_{25}N$ $[M+H]^+$ 386.1903; found 386.1904.



364c

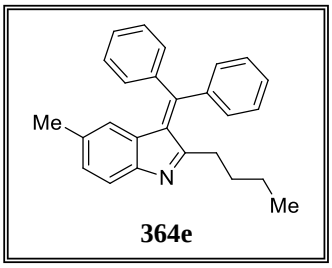
Synthesis of 3-(bis(4-methoxyphenyl)methylene)-5-methyl-2-phenyl-3*H*-indole (364d): The title compound was prepared according to the GP A or B and purified by column chromatography to furnish product **364d** as a red solid; yield: 71 and 77%; R_f = 0.36 (EtOAc/hexane = 3:2, v/v); mp 225-226 °C; IR (neat): ν_{max} 3054, 1576, 1468, 1385, 1323, 1069, 734 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.23 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 6.50-6.56 (m, 3H, ArH), 6.96-7.12 (m, 8H, ArH), 7.30-7.34 (m, 2H, ArH), 7.46-7.58 (m, 3H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.8, 55.3, 55.6, 113.0, 114.0, 119.9, 122.3, 127.2, 127.6,



364d

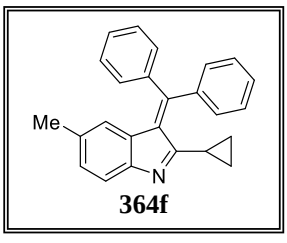
128.5, 129.2, 132.7, 132.9, 133.3, 133.8, 134.2, 135.4, 136.9, 152.7, 157.7, 161.4, 161.8, 169.7 ppm. HRMS (ESI) Calcd for $C_{30}H_{25}NO_2$ $[M+H]^+$ 432.1964; found, 432.1968.

Synthesis of 2-butyl-3-(diphenylmethylene)-5-methyl-3*H*-indole (364e): The title compound was prepared according to the GP A or B and purified by column chromatography to yield product **364e** as a red gum; yield: 80 and 87%; R_f = 0.56 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 3049, 2919, 2854, 1571, 1490, 1449, 1340, 1264, 1220, 1190, 1087, 829, 751, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.69 (t, J = 7.3 Hz, 3H, CH_3), 0.95-1.04 (m, 2H, CH_2), 1.37-1.44 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 2.28-2.32 (m, 2H, CH_2), 6.25 (s, 1H, ArH), 7.14 (d, J = 8 Hz, 1H, ArH), 7.25-7.52 (m, 10H, ArH), 7.60 (d, J = 8Hz, 1H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 21.7, 22.7, 25.2, 28.3, 113.1, 123.3, 127.6, 128.3, 128.7, 129.5, 129.7, 130.86, 130.93, 137.5, 141.2, 141.6, 142.3, 145.2, 149.6 ppm. HRMS (ESI): calcd for $C_{26}H_{25}N$ $[M+H]^+$ 352.2060; found 352.2061.



364e

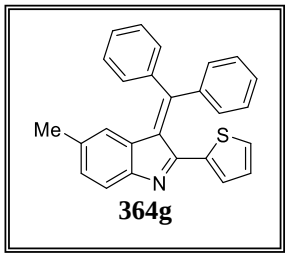
Synthesis of 2-cyclopropyl-3-(diphenylmethylidene)-5-methyl-3*H*-indole (364f): The title compound was prepared according to the GP A or B and purified by column chromatography to provide product **364f** as a red gum; yield: 73 and 76%; R_f = 0.6 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 3051, 2922, 1585, 1519, 1450, 1398, 1214, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.62-0-.66 (m, 2H, CH_2), 1.08-1.13 (m, 1H, CH), 1.15-1.19 (m, 2H, CH_2), 7.26-7.28 (m, 2H, ArH), 7.33-7.39 (m, 4H, ArH), 7.39-7.42 (m, 3H, ArH), 7.43-7.46 (m, 2H, ArH), 7.47-7.51 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 13.8, 21.4, 118.6, 123.3, 128.1, 128.7, 129.0,



364f

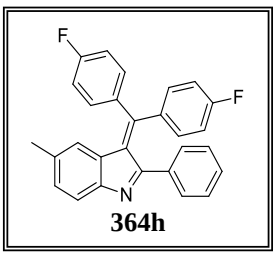
129.55, 129.59, 130.5, 131.5, 131.6, 133.3, 136.6, 141.3, 141.4, 153.2, 154.2, 173.9 ppm. HRMS (ESI): calcd for $C_{25}H_{21}N$ $[M+H]^+$ 336.1747; found 336.1749.

Synthesis of 3-(diphenylmethylidene)-5-methyl-2-(2-thiophenyl)-3*H*-indole (364g): The title compound was prepared according to the GP A or B and purified by column chromatography to provide product **364g** as a red gum; yield: 75 and 72%; R_f = 0.44 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 3054, 2930, 2864, 1565, 1491, 1448, 1334, 1269, 1209, 1180, 1067, 824, 756, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.10 (s, 3H, CH_3), 6.16 (s, 1H, ArH), 6.53 (s, 1H, ArH), 7.03-7.11 (m, 4H, ArH), 7.14-7.19 (m, 3H, ArH), 7.42-752 (m, 5H, ArH), 7.55-7.60 (m, 1H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 120.1, 122.7, 126.5, 126.8, 127.7, 128.8, 129.17, 129.2, 129.9, 130.3, 131.2, 133.1, 134.8, 135.0, 138.8, 141.0, 141.3, 152.8, 157.4, 163.0 ppm. HRMS (ESI): calcd for $C_{26}H_{19}NS$ $[M+H]^+$ 378.1311; found 378.1315.



364g

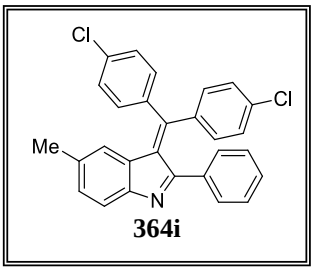
Synthesis of 3-[bis(4-fluorophenyl)methylidene]-5-methyl-2-phenyl-3*H*-indole (364h): The title compound was prepared according to the GP A or B and purified by column chromatography to afford product **364h** as a red solid; yield: 69 and 74%; m.p. 135-136 ºC; R_f = 0.49 (EtOAc/hexane = 1.5:3.5, v/v); mp 142-143 °C; IR (neat): ν_{max} 2924, 2855, 1612, 1462, 1264, 814, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3H, CH_3), 6.33 (s, 1H, ArH), 6.61-6.65 (m, 2H, ArH), 6.93-7.34 (m, 9H, ArH), 7.42-7.51 (m, 4H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 114.7 (d, J = 22 Hz), 116.1 (d, J = 21 Hz), 120.2, (d, J = 21 Hz), 122.7, 127.7, 127.8, 129.1, 129.4, 129.5, 132.0, 133.3 (d, J = 8 Hz), 134.9, 134.9 (d, J = 9 Hz), 135.1, 136.2, 136.5 (d, J =



364h

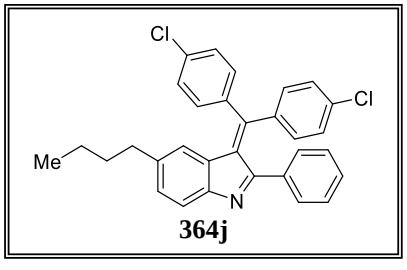
3 Hz), 136.9 (d, *J* = 3 Hz), 153.1, 154.2, 163.7 (d, *J* = 250 Hz), 164.1 (d, *J* = 250 Hz), 169.6 ppm. HRMS (ESI): calcd for $C_{28}H_{19}F_2N$ $[M+H]^+$ 408.1563; found 408.1555.

Synthesis of 3-[bis(4-chlorophenyl)methylidene]-5-methyl-2-phenyl-3*H*-indole (364i): The title compound was prepared according to the GP A or B and purified by column chromatography to provide product **364i** as a red gum; yield: 71 and 78%; R_f = 0.53 (EtOAc/hexane = 1.5:3.5, v/v); IR (neat): ν_{max} = 3057, 2922, 2855, 1575, 1489, 1451, 1337, 1274, 1217, 1183, 1077, 820, 757, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3H, CH_3), 6.38 (s, 1H, ArH), 6.86-6.91 (m, 4H, ArH), 7.01-7.04 (m, 2H, ArH), 7.09-7.11 (m, 2H, ArH), 7.22-7.26 (m, 2H, ArH), 7.38-7.40 (m, 2H, ArH), 7.48-7.51 (m, 3H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 120.4, 122.8, 127.75, 127.82, 129.0, 129.2, 129.8, 131.7, 132.6, 134.1, 135.1, 135.6, 136.1, 136.2, 136.7, 138.6, 139.0, 153.1, 153.5, 169.6 ppm. HRMS (ESI): calcd for $C_{28}H_{19}Cl_2N$ $[M+H]^+$ 440.0967; found 440.0969.



364i

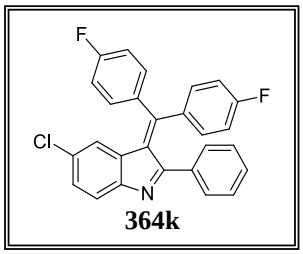
Synthesis of 3-(bis(4-chlorophenyl)methylene)-5-butyl-2-phenyl-3*H*-indole (364j): The title compound was prepared according to the GP A or B and purified by column chromatography to furnish product **364j** as a red gum; yield: 76 and 81%; R_f = 0.55 (EtOAc/hexane = 1.5:3.5, v/v); IR (neat): ν_{max} = 2925, 1581, 1480, 1338, 1089, 1011, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.76-0.88 (m, 3H, CH_3), 1.06-1.19 (m, 2H, CH_2), 1.21-1.36 (m, 2H, CH_2), 2.32-2.42 (m, 2H, CH_2), 6.24 (s, 1H, ArH), 6.78-6.83 (m, 3H, ArH), 6.88-7.13 (m, 5H, ArH), 7.14-7.17 (m, 3H, ArH), 7.29-7.31 (m, 2H, ArH), 7.39-7.42 (m, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.0, 33.4, 35.4, 110.5, 117.5, 120.3, 120.7, 122.3,



364j

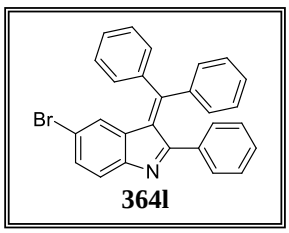
123.5, 127.8, 127.9, 129.1, 129.3, 131.5, 132.5, 133.0, 134.0, 135.7, 136.2, 136.7, 138.4, 139.1, 140.1, 145.4, 153.2, 169.6 ppm. HRMS (ESI): calcd for $C_{28}H_{19}Cl_2N$ $[M+H]^+$ 440.0967; found 440.0969.

Synthesis of 3-[bis(4-fluorophenyl)methylidene]-5-chloro-2-phenyl-3*H*-indole (364k): The title compound was prepared according to the GP A or B and purified by column chromatography to provide product **364k** as a red soild; yield: 70 and 75%; R_f = 0.44 (EtOAc/hexane = 1.5:3.5, v/v); mp 141-142 ºC; IR (neat): ν_{max} 2923, 1594, 1560, 1509, 1437, 1336, 1231, 1157, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.48 (s, 1H, ArH), 6.66 (t, *J* = 8.4 Hz, 2H, ArH), 6.94-6.98 (m, 2H, ArH), 7.02-7.06 (m, 2H, ArH), 7.08-7.12 (m, 1H, ArH), 7.22-7.26 (m, 5H, ArH), 7.42-7.46 (m, 2H, ArH), 7.53 (d, *J* = 8.4 Hz, 1H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.9 (d, *J* = 22 Hz), 116.4 (d, *J* = 22 Hz), 121.4, 122.1, 127.8, 128.1, 128.5, 129.1, 130.8, 133.3, 133.49 (d, *J* = 9 Hz), 134.1, 135.2 (d, *J* = 9 Hz), 135.7, 136.1 (d, *J* = 4 Hz), 136.2 (d, *J* = 4 Hz), 153.4, 156.5, 164.0 (d, *J* = 252 Hz), 164.4 (d, *J* = 252 Hz), 170.5 ppm. HRMS (ESI): calcd for $C_{27}H_{16}ClF_2N$ $[M+H]^+$ 428.1017; found 428.1013.



364k

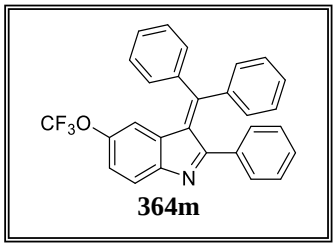
Synthesis of 5-bromo-3-(diphenylmethylidene)-2-phenyl-3*H*-indole (364l): The title compound was prepared according to the GP A or B and purified by column chromatography to yield product **364l** as a red gum; yield: 74 and 83%; R_f = 0.58 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 3061, 2923, 1562, 1476, 1439, 1336, 1206, 1072, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.53 (s, 1H, ArH), 6.93-7.04 (m, 7H, ArH), 7.06-7.09 (m, 1H, ArH), 7.26-7.30 (m, 2H, ArH), 7.35-7.38 (m, 1H, ArH), 7.42-7.48 (m, 3H, ArH), 7.53 (t, *J* = 7.6 Hz, 2H, ArH), 7.61 (t, *J* = 7.2 Hz, 1H,



364l

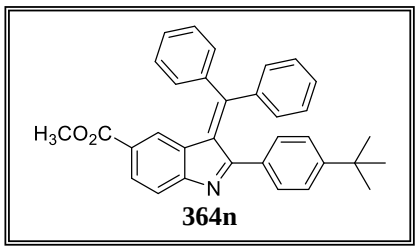
ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 118.6, 121.6, 125.3, 127.5, 127.7, 128.0, 129.0 129.1, 130.2, 130.9, 131.05, 131.11, 133.2, 133.9, 134.0, 136.0, 140.0, 140.6, 153.6, 159.7, 170.8 ppm. HRMS (ESI): calcd for $C_{27}H_{18}BrN$ $[M+H]^+$ 436.0700; found 436.0688.

Synthesis of 3-(diphenylmethylene)-2-phenyl-5-(trifluoromethoxy)-*3H*-indole (364m): The title compound was prepared according to the GP A or B and purified by column chromatography to furnish product **364m** as a red gum; yield: 69 and 63%; R_f = 0.48 (EtOAc/hexane = 1.5:3.5, v/v); IR (neat): ν_{max} 3061, 2923, 1562, 1484, 1213, 1249, 1157, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (s, 1H, ArH), 6.99-7.16 (m, 8H, ArH), 7.31-7.35 (m, 3H, ArH), 7.47-7.49 (m, 2H, ArH), 7.55-7.67 (m, 4H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.5, 119.2, 120.8, 121.2, 121.7, 127.5, 127.7, 128.0, 129.0, 129.1, 130.2, 130.8, 130.9, 133.2, 133.3, 134.1, 136.0, 139.9, 140.5, 146.6, 153.1, 159.9, 171.5 ppm. HRMS (ESI): calcd for $C_{28}H_{18}F_3NO$ $[M+H]^+$ 442.1419; found 442.1423.



364m

Synthesis of methyl 2-(4-(tert-butyl)phenyl)-3-(diphenylmethylene)-3*H*-indole-5-carboxylate (364n): The title compound was prepared according to the GP A or B and purified by column chromatography to provide product **364n** as a red gum; yield: 65 and 62%; R_f = 0.71 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 2956, 1711, 1605, 1448, 1247, 1111, 758, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 9H, $3CH_3$), 3.82 (s, 3H, CH_3), 6.96-7.09 (m, 5H, ArH), 7.15-7.36 (m, 6H, ArH), 7.57-7.69 (m, 5H, ArH), 8.0 (d, J = 8Hz, 1H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0, 34.5, 51.9, 119.9, 124.1, 124.6, 125.1,



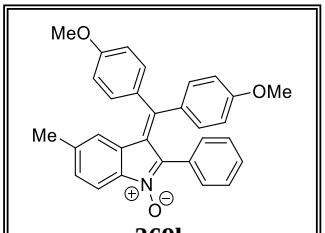
364n

127.4, 127.8, 128.0, 129.0, 129.9, 130.6, 131.1, 133.1, 140.0, 140.7, 147.0, 151.1, 158.3, 159.7, 167.2, 173.4 ppm. HRMS (ESI): calcd for $C_{33}H_{29}NO_2$ $[M+H]^+$ 472.2277; found 472.2271.

General procédure for synthesis of 3-alkylidene-3*H*-indole *N*-oxides 369

To a solution of nitrosobenzene **367** (1 equiv) and propargyl alcohol **138** (1 equiv) in DCM (5mL) was added 10 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at room temperature under an open-air atmosphere and monitored by TLC until the disappearance of the propargyl alcohol. After the appropriate period, the reaction mixture was diluted with DCM (20 mL) and water (20 mL). The organic phase was separated and the aqueous layer was washed with DCM (20 mL). The concentration of the combined organic layers under reduced pressure afforded the crude product, which was purified by column chromatography using silica gel to afford the corresponding 3-alkylidene-3*H*-indole *N*-oxides **369**.

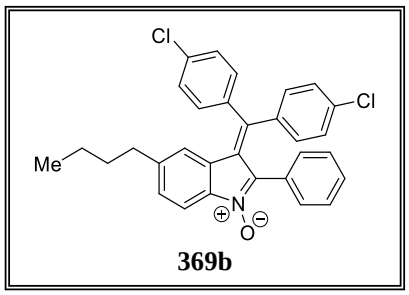
Synthesis of 3-(bis(4-methoxyphenyl)methylene)-5-methyl-2-phenyl-3*H*-indole 1-oxide (369b): To a solution of nitrosobenzene **367a** (35 mg, 0.29 mmol) and propargyl alcohol **138d** (100 mg, 0.29 mmol) in DCM (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at room temperatuer under the open-air atmosphere to afford product **369b** (114 mg, 88%) as a red solid according to general procedure. R_f = 0.27 (EtOAc/hexane = 3:2, v/v); mp 211-212 °C; IR (neat): ν_{max} 2926, 1673, 1597, 1504, 1458, 1247, 1164, 1024, 819, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.26 (s, 3H, $3H_3$), 3.69 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 6.45-6.48 (m, 3H, ArH), 6.91 (d, *J* = 8.8 Hz, 2H, ArH), 7.03-7.12 (m, 5H, ArH), 7.22 (d, *J* = 8.0 Hz, 1H, ArH), 7.41 (d, *J* = 8.8 Hz, 4H, ArH), 7.77 (d, *J* = 8.0 Hz, 1H, ArH) ppm; ^{13}C NMR



369b

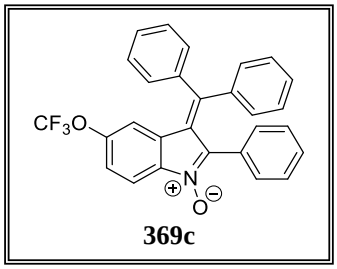
($CDCl_3$, 100 MHz) δ = 21.9, 55.3, 55.6, 113.0, 113.8, 114.1, 122.5, 125.9, 127.5, 127.6, 128.4, 128.6, 129.2, 130.4, 133.0, 133.7, 133.9, 134.4, 137.8, 141.4, 142.2, 150.9, 160.8, 161.5 ppm; HRMS (ESI) Calculated for $C_{30}H_{25}NO_3$ $(M+H)^+$: 448.1913 found: 448.1916.

Synthesis of 3-(bis(4-chlorophenyl)methylene)-5-butyl-2-phenyl-3*H*-indole 1-oxide (369b): To a solution of nitrosobenzene **367b** (46 mg, 0.28 mmol and) propargyl alcohol **138i**,(100 mg, 0.28 mmol) in DCM (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at room temperatuer under the open-air atmosphere to afford product **369b** (133 mg, 93%) as a red gum according to general procedure. R_f = 0.48 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 2951, 1581, 1462, 1386, 1343, 1082, 826, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 0.92-0.95 (m, 3H, CH_3), 1.24-1.33 (m, 2H, CH_2), 1.42-1.49 (m, 2H, CH_2), 2.52 (t, *J* = 7.6 Hz, 2H, CH_2), 6.35 (s, 1H, ArH), 6.86-6.91 (m, 4H, ArH), 7.10-7.18 (m, 3H, ArH), 7.26-7.43 (m, 5H, ArH), 7.53 (d, *J* = 8.4 Hz, 2H, ArH), 7.76 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 13.9, 22.0, 33.2, 35.5, 114.0, 122.3, 127.66, 127.69, 127.7, 128.1, 128.5, 129.0, 129.1, 129.2, 130.3, 132.8, 133.2, 135.5, 136.4, 138.2, 139.7, 140.5, 142.5, 143.6, 146.4 ppm; HRMS (ESI) Calculated for $C_{31}H_{25}Cl_2NO$ $(M+H)^+$: 498.1391 found: 498.0978.



369b

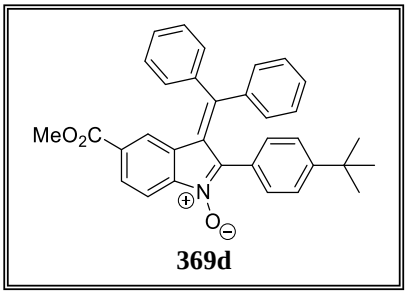
Synthesis of 3-(diphenylmethylene)-2-phenyl-5-(trifluoromethoxy)-3*H*-indole 1-oxide (369c): To a solution of nitrosobenzene **367e** (67 mg, 0.35 mmol) and propargyl alcohol **138a** (100 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at room temperatuer under



369c

the open-air atmosphere to yield product **369c** (136 mg, 85%) as a red gum according to general procedure. R_f = 0.42 (EtOAc/hexane = 1.5:3.5, v/v); IR (neat): ν_{max} 3058, 1547, 1463, 1389, 1249, 1156, 827, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 6.30 (s, 1H, ArH), 6.94-7.88 (m, 17H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 115.2, 115.5, 121.0, 121.6, 127.0, 127.5, 127.6, 128.26, 128.34, 129.0, 129.5, 129.6, 130.2, 130.6, 131.2, 132.3, 139.5, 141.0, 142.2, 142.3, 148.9, 152.6 ppm; HRMS (ESI) Calculated for $C_{28}H_{18}F_3NO_2$ $(M+H)^+$: 458.1368 found: 458.1371.

Synthesis of 2-(4-(tert-butyl)phenyl)-3-(diphenylmethylene)-5-(methoxycarbonyl)-3*H*-indole 1-oxide (369d): To a solution of nitrosobenzene **367f** (49 mg, 0.29 mmol) and propargyl alcohol **138k** (100 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) was added 20 mol% of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at room temperatuer under the open-air atmosphere to obtain product **369d** (104 mg, 74%) as a red solid according to general procedure. R_f = 0.64 (EtOAc/hexane = 1:4, v/v); mp 163-164 °C; IR (neat): ν_{max} 2958, 1720, 1545, 1460, 1384, 1286, 1113, 750, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.24 (s, 9H, $3CH_3$), 3.84 (s, 3H, CH_3), 6.96-7.03 (m, 4H, ArH), 7.04-7.05 (m, 1H, ArH), 7.09 (d, *J* = 8.8 Hz, 2H, ArH), 7.16 (d, *J* = 1.2 Hz, 1H, ArH), 7.30-7.34 (m, 2H, ArH), 7.46-7.48 (m, 2H, ArH), 7.55-7.59 (m, 2H, ArH), 7.65-7.68 (m, 1H, ArH), 7.93 (d, *J* = 8.0 Hz, 1H, ArH), 8.13 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz. 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 31.0, 34.6, 52.2, 114.0, 124.3, 124.6, 125.2, 127.4, 128.0, 128.9, 129.3, 129.7, 130.0, 130.4, 131.3, 132.3, 139.6, 141.2, 143.8, 147.0, 151.2, 152.7, 166.4 ppm; HRMS (ESI) Calculated for $C_{33}H_{29}NO_3$ $(M+H)^+$: 488.2226 found: 488.2256.



369d

CHAPTER - VI

Cu(I)TC-CATALYZED

SYNTHESIS OF SPIROINDOLOFUROBENZOPYRANS

6.1. Synthesis of spiro/non-spiro-heterocycles *via* carbonyl ylides

The use of spiro-cyclic structures in drug development has attracted much interest in recent decades, owing to major advances in synthetic chemistry.[267] Spirooxindoles are one of a huge number of well-defined three-dimensional motifs. A most interesting aspect of spirooxindoles is their affinity for natural alkaloids; this property leads to a wide range of therapeutic applications, including anticancer, antibacterial, antiviral, and antifungal drugs.[268] The explosive growth in synthetic involvement in spiro-oxindole motifs has resulted in hundreds of reports, necessitating a rationalization of the latest progress in the field. Because of the preferable biomedical assets of spiroxindole motifs, researchers have focused on either their racemic[269] and asymmetric synthesis,[270] with a focus on the organo-catalytic[271] and formal annulation methodologies.[272] The primary routes to spiro-oxindole skeletons depend on spiro-cyclization and cycloaddition methods.[273] Moreover, 1,3-dipolar cycloaddition to oxindoles with a $C=N_2$, C=O or C=C double bond in the C-3 position represent a biodiverse field for the synthesis of a wide range of spiro-oxindole compounds.[274]

Cyclic diazo compounds are a potentially very important source of spiro-cyclic scaffold due to the flexibility of diazo compounds in the construction of cyclic frameworks overall. The use of carbonyl ylides in cycloaddition reactions has been a significant and precise mechanism for the stereoselective synthesis of oxygen-containing five-membered heterocycles. The catalytic synthesis of carbonyl ylides from diazo compounds has greatly expanded their use in organic synthesis. In overall, these 1,3-dipolar species are highly reactive intermediates capable of [3+2]-cycloaddition reactions. Notably, carbonyl ylides generated by the reaction of diazo compounds with

C=O double bonds and metal catalysts were also reactive intermediates that can undergo a variety of transformations. Beside these transformations, the 1,3-dipolar cycloaddition of carbonyl ylides has been thoroughly studied and used to create complex oxa-polycyclic systems incorporating di- or tetrahydrofuran ring systems.

A three-component[275] intermolecular carbonyl ylide and subsequent [3+2]-cycloaddition reaction incorporating diazocarbonyl compounds, aryl aldehydes and dipolarophiles is a useful method for the synthesis of functionalized oxygen-containing heterocycles (Figure 31a). However, its selectivity and substrate scope have been relatively limited. In recent decades, much effort has been made to intramolecular carbonyl ylide cycloaddition, incorporating intramolecular carbonyl ylide formation followed by intermolecular [3+2]-cycloaddition (Figure 31b)[276] and intramolecular carbonyl ylide formation followed by intramolecular [3+2]-cycloaddition (Scheme 1c), [277] for the synthesis of various target molecules. Comparatively, tandem intermolecular ylide formation followed by intramolecular [3+2]-cycloaddition and analogous two component reactions have not been documented (Figure 31d).

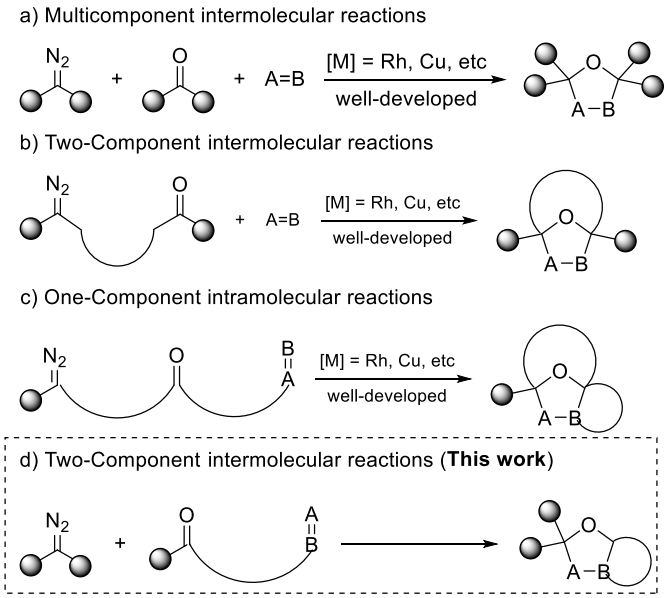
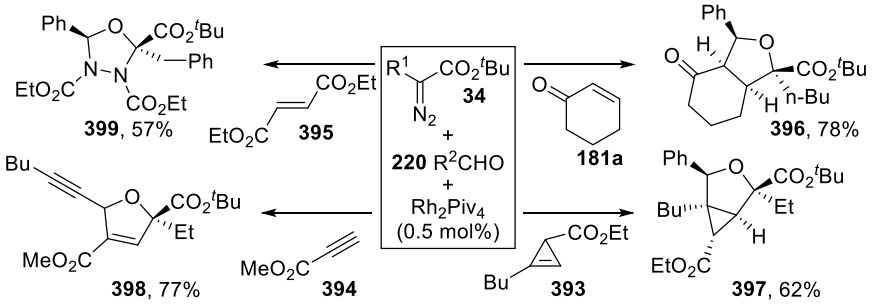


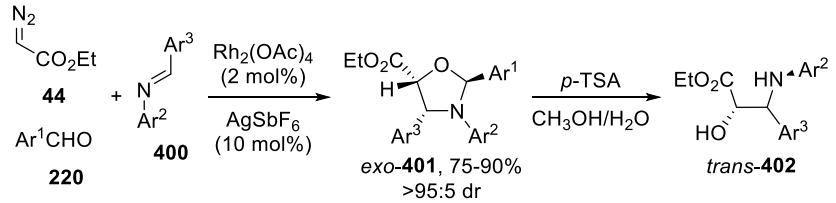
Figure 31. Previous reports of carbonyl ylides and our strategy

Fox and co-workers described[275c] for the Rh-catalysed synthesis of highly functionalized dihydro- and tetrahydrofurans **396-399** *via* three-component reactions of aldehydes **220**, α-alkyl-α-diazoesters **34** and dipolarophiles **181a/393-395**. Evidently, a wide range of dipolarophiles might trap these carbonyl ylides to produce functionalized dihydro- and tetrahydrofurans in good yield with regio- and diastereoselectivity (Scheme 159).



Scheme 159

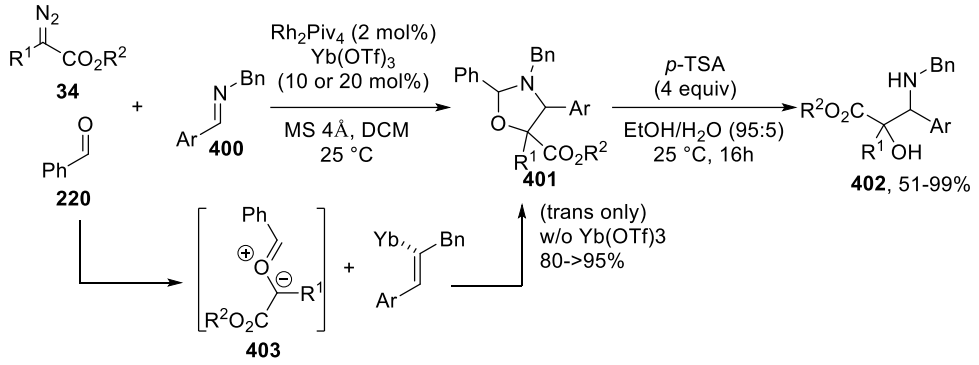
$Rh_2(OAc)_4$ and $AgSbF_6$ co-catalysed highly diastereoselective[275d] 1,3-dipolar cycloaddition of carbonyl ylides along with aldimines **400** yielded sterically disfavoured oxazolidines **401** *via* [3+2]-*exo* addition process. After the hydrolysis, high yield of trans-amino-hydroxyl ester derivatives **402** was achieved (Scheme 160).



Scheme 160

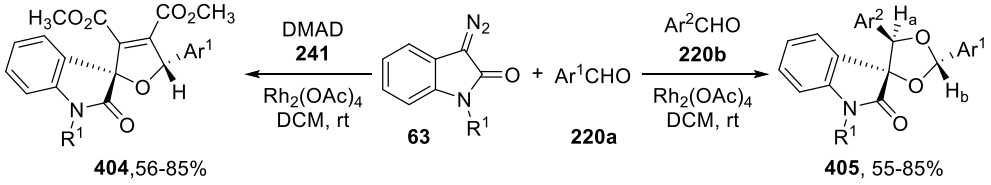
Suga and co-workers used[275f] a dual catalytic system comprised of Rh(II) and Yb(III) reactions of *α*-alkyl-*α*-diazoesters **34**, aromatic aldehydes **220**, and N-benzylidenebenzylamines **400** to yield amino alcohols **402** in excellent yield. The reactions were carried out *via* carbonyl ylide cycloaddition reactions **403** with imines

400 in the presence of Rh(II)/Yb(III) catalysis suppressing unwanted *β*-H removal and the production of epoxides and dioxolanes (Scheme 161).



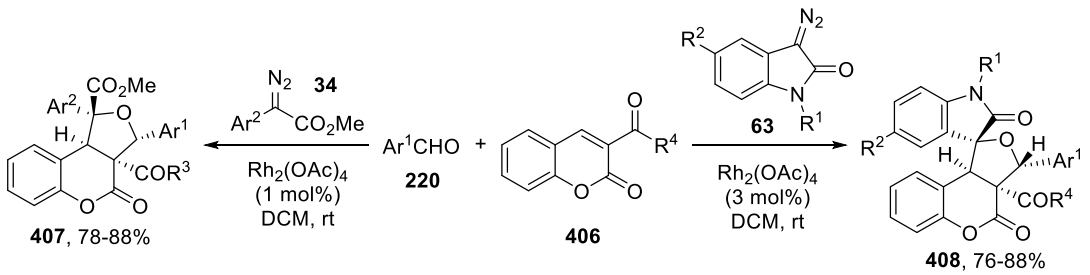
Scheme 161

A novel strategy to spirocyclic 1,3-dioxolanes **405** and spirofurans **404** has been developed by us.[278] In addition to diazoamides **63**, two different aldehydes **220** in the presence of DMAD **241** were used in the three-component reaction: an electron-rich aldehyde **220** to form a carbonyl ylide intermediate, then another aldehyde or DMAD, to undergo [3+2]-cycloaddition reaction (Scheme 162).



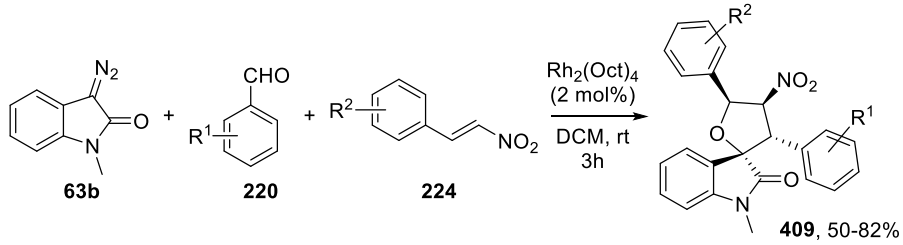
Scheme 162

A similar strategy was used[279] to synthesize spirooxindolyl furocoumarines **408** and tetrahydro-1*H*-furo[3,4-*c*]chromene-1-carboxylates **407** with diastereoselectivity. Using coumarines **406** as dipolarophiles, the required heterocycles **408** were obtained in good yields (Scheme 163).



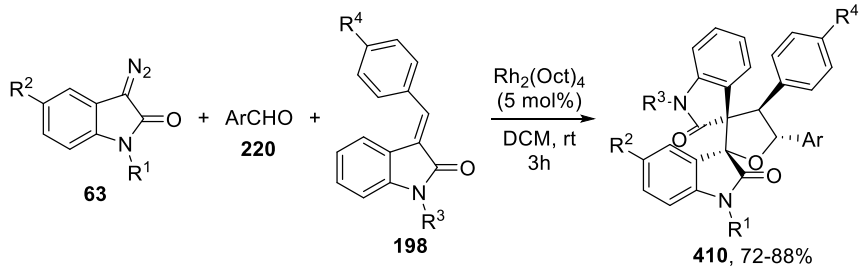
Scheme 163

The Rh(II)-catalyzed[280] three-component reaction of diazoamides **63**, aldehydes **220**, and *β*-nitrostyrenes **224** yielded biology-useful 3,3-spiro(2-tetrahydrofuranyl)oxindoles **409** in moderate to good yields with high regio- and diastereoselectivity (Scheme 164).

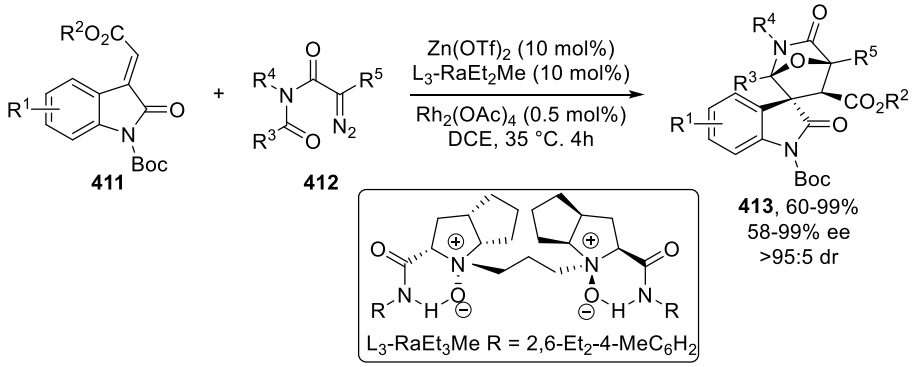


Scheme 164

Reddy and co-workers have demonstrated[281] a novel three-component method for the synthesis of 4,5-dihydrodispiro[indoline-3,2-furan-3,3-indoline]-2,2-diones **410** derived from diazoamides **63**, aldehydes **220**, and arylideneoxindoles **198**. This approach works with a wide variety of substrates and allows for the production of biologically active dispirooxindoles **410** (Scheme 165).



Scheme 165

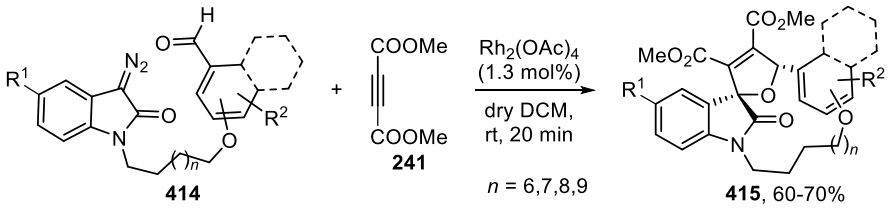


Scheme 166

Feng and co-workers have demonstrated[282] an effective 1,3-dipolar [3+2]-cycloaddition

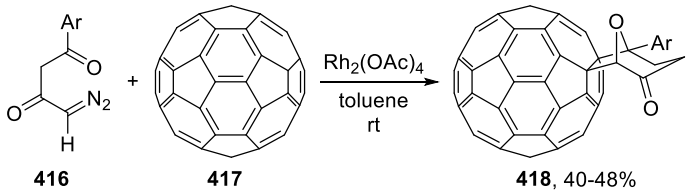
of isomunchnones to methyleneindolinones **411**. A variety of spiropiperidine oxindoles **413** were synthesized in high yields with excellent *dr* and *ee* values (Scheme 166).

Our group has also demonstrated[223c] an effective formation of intramolecular macrocyclic carbonyl ylides from aldehyde group tethered on diazoamides **414** in the presence of $Rh_2(OAc)_4$. The related macrocycles integrating spiro-indolofurans **415** were synthesised in moderate to good yield with high diastereoselectivity (Scheme 167).

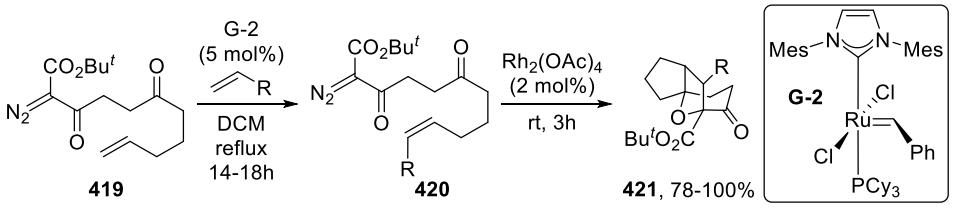


Scheme 167

Novel C60 compounds of type **418** have been produced[283] *via* 1,3-dipolar cycloaddition reactions of five-membered ring carbonyl ylides with [60]-fullerene **417**. The cycloadduct **417** was formed through the Rh(II)-catalysed transformation of the diazo ketone **416** in the presence of [60]-fullerene (Scheme 168).



Scheme 168

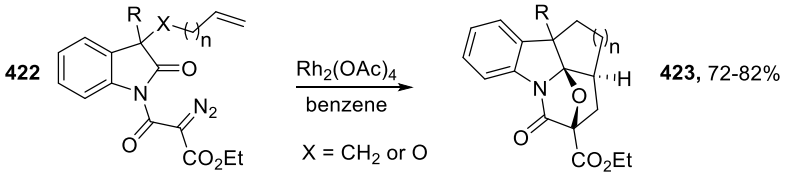


Scheme 169

Grubbs' 2nd generation Ru-carbene complex exhibited the stereoselective cross-metathesis in the existence of diazo functionality **419**. The exhausted Ru-catalyst

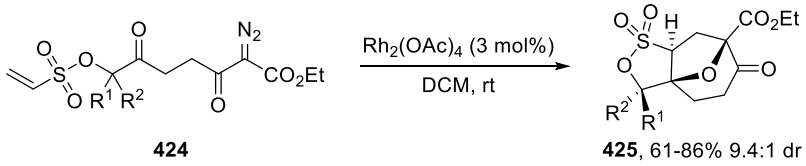
permited additional $Rh_2(OAc)_4$ to catalyze carbonyl ylide cycloaddition and demonstrated[280d] the flexibility of these two transition metal complexes catalyzing distinct carbene transfer processes sequentially (Scheme 169).

Padwa and co-workers have investigated[280f] the Rh(II)-catalyzed chemistry of many similar alkenyl ethers tethered on diazoamides **422** to generate polycylic heterocycles **423** in good yields (Scheme 170).



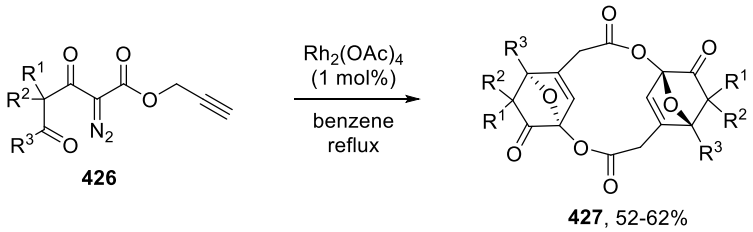
Scheme 170

Rh(II)-catalyzed intramolecular cycloaddition, vinylsulfonates were found[280g] to be excellent dipolarophiles for carbonyl ylide generated from diazoketones **424** (Scheme 49). The derived polycyclic sultones **425** were generated under mild reaction conditions in good yields with diastereoselectivity (Scheme 171).



Scheme 171

Our research group has revealed[284] the tandem reaction of α-diazo compounds with Rh(II) acetate catalyst to produce a variety of symmetric macrodiolides through the head to tail dimerization of intramolecular carbonyl ylides (Scheme 172).



Scheme 172

Scope and objectives: Carbonyl ylides formed from α-diazocarbonyl compounds must go through an array of reactions with aldehyde, olefin and nucleophiles, yielding a wide range of different structural motifs in one-pot manner, with the production of oxa-bridged poly- or heterocyclic systems being highly stereoselective. The oxa-bridged frameworks could lead to a variety of carbo- or heterocyclic systems that are prominent components in nature such as alkaloids, terpenoids and other bioactive compounds as a core skeleton. Different heterocycles or spiro-heterocycles were synthesized by utilizing carbonyl ylides. However, carbonyl ylides, generated *via* an intermolecular manner, are always considered to be synthetically unsatisfactory compared to their intramolecular counterparts because of their low selectivity and competitive reactions. No report available for intermolecular carbonyl ylides followed by intramolecular [3+2]-cycloaddition.

The objectives of the present work are the following:

- To study the competition between the electrocyclization and 1,3-dipolar cycloaddition reactions of carbonyl ylides
- To generate the intermolecular carbonyl ylides and to develop a new route for spiro-indolofuropyran systems

RESULTS AND DISCUSSION

6.2. Synthesis of spiro-indolofurobenzopyrans

Spiro-oxindoles have become a privileged motif given their broad and auspicious activities in many therapeutic areas, potential as synthetic building blocks, existence as natural products,[270b,285] and use in clinical pharmaceuticals.[286] A few bioactive spiro-oxindoles, for example, the HepG2 inhibitor[287] and an anti-cancer agent,[288] are shown in Figure 32. Moreover, furobenzopyran, the fused heterocycle, is also a key structural motif of many natural products, for example, furobinordenatin,[289] siccanin,[290] and pterocarpans[291] (Figure 32), and has been reported to exhibit a wide range of biological activities, including antibacterial,[292] antifungal,[292] antiinflammatory,[293] anti-HIV,[294] antiviral,[295] antitoxin,[295] and antisnake venom.[295] However, there are few methods[296] available for the synthesis of the furobenzopyran moiety and these involve the use of stoichiometric quantities of combined reagents, multi-step synthesis, and low

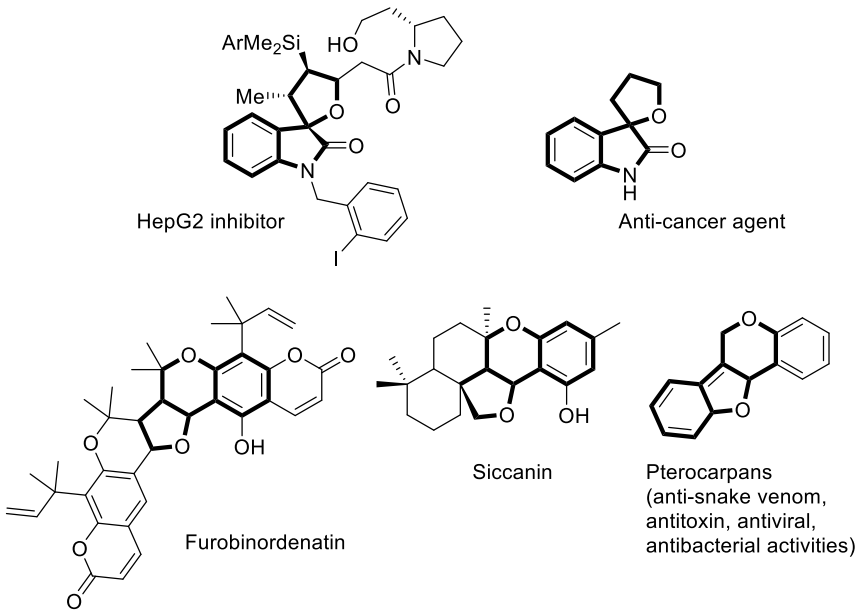


Figure 32. Selected examples of biologically important natural products bearing spiro-indolofurans and furobenzopyran moiety

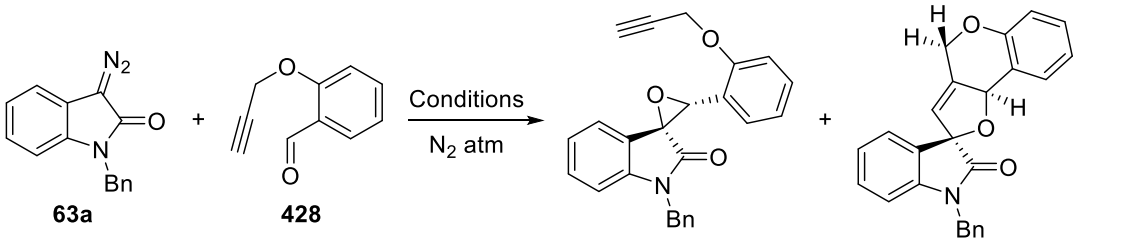
temperature. Therefore, it remains a challenging, but a very striking task to find more economical and simple methods with a wider substrate scope for the preparation of furobenzopyrans. The main focus of this chapter is an atom-economical tandem reaction that can provide a wide variety of different substituted spiro-indolofurobenzopyrans **429** from diazoamides **63** and *O*-propargyl salicylaldehydes **428** in the presence of 5 mol% of Cu(I)TC at reflux conditions under a nitrogen atmosphere.

Investigation of the reaction was planned involving the slow addition of diazoamide **63** in order to control its concentration based on our earlier studies.[297] To begin our investigation, the reactions of diazoamide **63a** and *O*-propargyl salicylaldehyde **428a** as model substrates in the presence of several catalysts were examined. To the refluxed solution containing salicylaldehyde **428a** and a catalytic amount of rhodium(II) acetate under nitrogen atmosphere, diazoamide **63a** was added with a slow rate of addition (5 mL/h) using a syringe pump in dichloroethane (DCE) to afford an isomeric mixture of spiro-indolooxiranes[169] **269a** and an interesting spiro-indolofurobenzopyran **429a** (Table 19, entry 1), based on the spectral studies. The FT-IR spectrum of compound **429a** exhibited a characteristic band at 1727 cm^{-1} indicating the presence of amide carbonyl group. In the ^{1}H-NMR spectrum (Figure 33), ABq and singlet appeared in the range of δ 4.90 and 5.00 ppm which indicated the OCH_2 and NCH_2 protons, respectively. The newly formed CH and OCH protons appeared as singlets at 5.62 and 6.30 ppm. In the ^{13}C-NMR spectrum (Figure 34), the amide carbonyl carbons showed peak at δ 175 and ppm. The newly generated CH and spiro-carbons appeared at 81.4 and 92.7 ppm. The NCH_2 and OCH_2 carbons appeared at 44.1 and 63.7 ppm. The high-resolution mass spectrum showed the required molecular ion peak at 382.1439 m/z.

The above experimental analysis confirmed the formation of compound **429a**. In order to optimize the reaction conditions, various copper catalysts such as CuI, $Cu(acac)_2$, $Cu(CH_3CN)_4PF_6$, or CuOTf were examined; however, no superior results were obtained (Table 19, entries 2-5). Treatment with $CuSO_4 \cdot 5H_2O$ was also found to be ineffective (Table 19, entry 6). To our delight, Cu(I)TC enhanced the yield of product **429a** with a trace amount of **269a** (Table 19, entry 7). Lewis acid catalysts, such as $Sc(OTf)_3$ or $Zn(OTf)_2$ were not suitable for this transformation (Table 19, entries 8 and 9). Among the copper catalysts, Cu(I)TC was found to be better and the use of common organic solvents, such as benzene, toluene, acetonitrile, or dioxane, did not improve the yield of product **429a** (Table 19, entries 10-13). The reaction was carried out at room temperature with the rate of addition of 5 mL/h to afford the spiro-indolooxirane[169] **269a** in 85% yield (Table 19, entry 14). A similar reaction without the controlled addition of diazoamide **63a** afforded the spiro-indolooxirane **269a** in 85% yield (Table 19, entry 15). A quick addition of diazoamide **63a** to the solution of salicylaldhyde **428a** under reflux conditions afforded a mixture of products **269a**/**429a** in 55 and 10% yields (Table 19, entry 16). The reaction of diazoamide **63a** with the rate of addition of 2 mL/h using a syringe pump was performed in the presence of 5 mol% of copper(I) thiophenecarboxylate to furnish a mixture of products **269a**/**429a** in 10 and 58% yields (Table 19, entry 17). The yield of spiro-indolofurobenzopyran **429a** was improved when the rate of addition of diazoamide **63a** was reduced to 0.5 mL/h (Table 19, entries 18 and 19). However, similar reaction at room temperature gave 83% yield of **269a** (Table 19, entry 20). No reaction took place in the absence of any catalyst (Table 19, entry 21). The experiments suggested that the reactions at room temperature gave a kinetically controlled product as spiro-indolooxirane **269a** (entry 15), while the

reactions under reflux conditions gave a thermodynamically controlled product as spiro-indolofurobenzopyran **429a** (**429a** has a lower energy than **269a** based on MM2 minimum energy calculations) (Figure 35). Thus, the optimized reaction conditions for the formation of thermodynamically controlled product **429a** were found to be 5 mol% of Cu(I)TC in dichloroethane under reflux conditions in a diastereoselective manner, as

Table 19. Optimization of reaction conditions for the formation of **269a** and **429a**[a]



Entry	Catalyst	Solvent	Rate of addition **63a** (mL/h)	t (h)	Yield[b] (%) **269a**/**429a**
1	$Rh_2(OAc)_4$	DCE	5	1	31/25
2	CuI	DCE	5	1	trace/13
3	$Cu(acac)_2$	DCE	5	1	trace/34
4	$Cu(CH_3CN)_4PF_6$	DCE	5	1	trace/40
5	CuOTf	DCE	5	1	trace/26
6	$CuSO_4{\cdot}5H_2O$	DCE	5	1	n.r[c]
7	Cu(I)TC	DCE	5	1	trace/53
8	$Sc(OTf)_3$	DCE	5	1	n.r[c]
9	$Zn(OTf)_2$	DCE	5	1	n.r[c]
10	Cu(I)TC	benzene	5	1	trace/23
11	Cu(I)TC	toluene	5	1	trace/47
12	Cu(I)TC	acetonitrile	5	1	trace/38
13	Cu(I)TC	dioxane	5	1	trace/55
14	Cu(I)TC	CH_2Cl_2[d]	5	1	83/0
15	Cu(I)TC	CH_2Cl_2[d]	-	1	85/0
16	Cu(I)TC	DCE	-	1	55/10
17	Cu(I)TC	DCE	2	2	10/58
18	Cu(I)TC	DCE	1	4	0/71
19	**Cu(I)TC**	**DCE**	**0.5**	**8**	**0/84**
20	Cu(I)TC	CH_2Cl_2[d]	0.5	8	83/0
21	-	DCE	0.5	20	n.r

[a]Reaction conditions: **63a** (0.53 mmol, 1 equiv) was dissolved in 4 mL of dry solvent, *O*-propargyl salicylaldehyde **428a** (0.59 mmol, 1.1 equiv), catalyst (5 mol%), and refluxed under nitrogen atmosphere. [b]isolated product. [c]no reaction. [d]reaction carried out at room temperature.

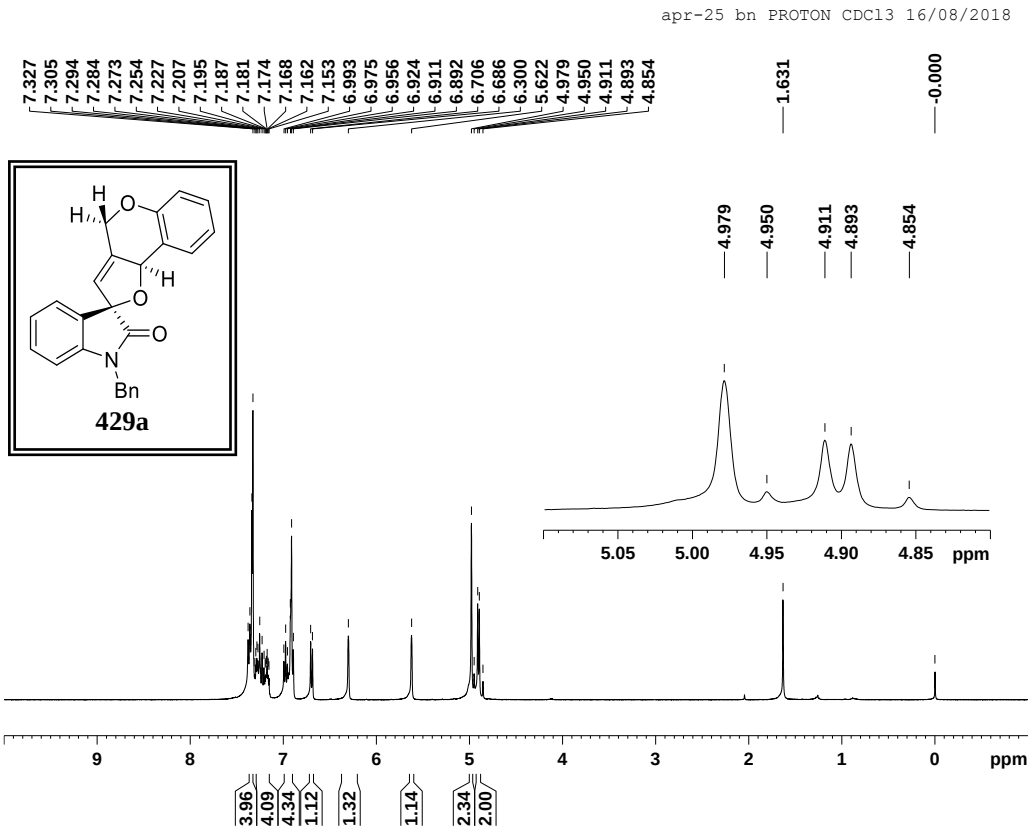


Figure 33. ^{1}H-NMR (δ) spectrum of **429a**

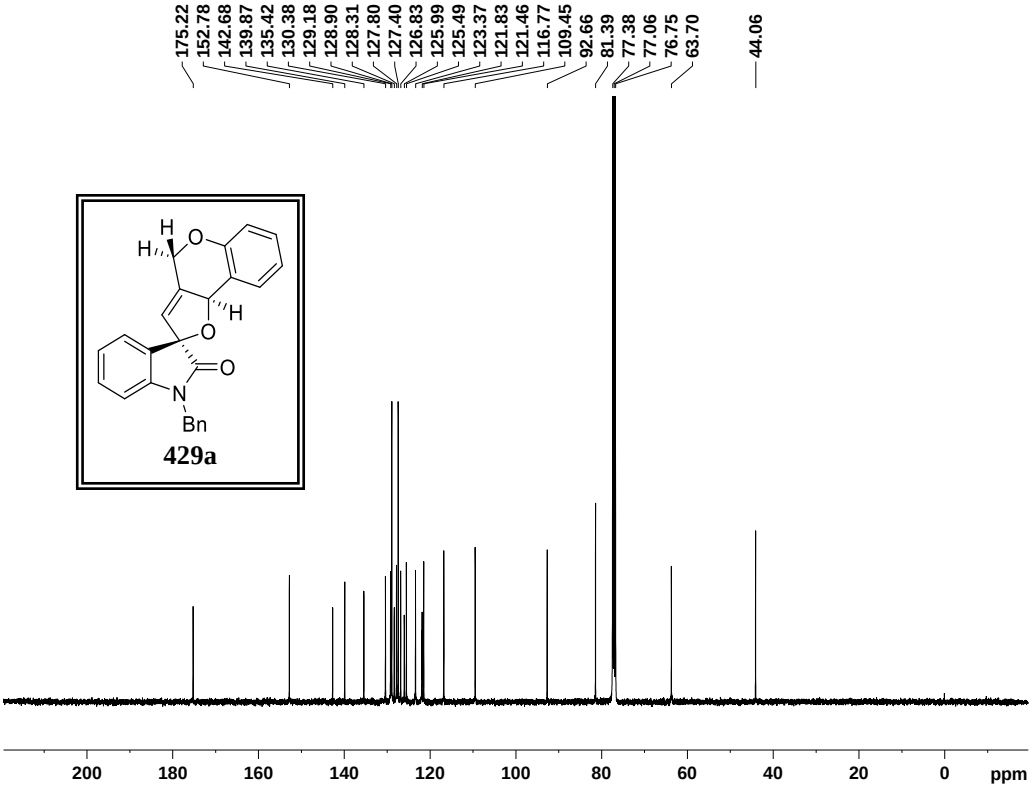


Figure 34. ^{13}C-NMR (δ) spectrum of **429a**

indicated in Table 19, entry 19. The generality and scope of this one-pot protocol for accessing spiro-indolofurobenzopyran ring system were investigated. Under the optimized reaction conditions, the feasibility of this reaction with a diversity of substrates was explored. Various substituted *O*-propargyl salicylaldehydes were subjected to the optimized reaction conditions to obtain the corresponding spiro-indolofurobenzopyrans **429** and the results are described in Table 20. Chloro-substituted salicylaldehyde provided the desired products **429b,c** in moderate yields. Bromo-substituted salicylaldehyde was also tolerated to furnish the desired product **429d** in 61% yield. A moderate yield of product **429e** was obtained with the use of salicyladehyde having an electron-withdrawing nitro-substituent. Similarly, an electrondonating methoxy group on salicylaldehyde in the presence of 5 mol% of Cu(I)TC also underwent a reaction to yield the desired products **429f** and **429g** in moderate yields. The reaction utilizing a naphthalene system also gave the corresponding spiro-indolofuronapthopyrans **429h–j** in 76-83% yields. Interestingly, the diiodo-substituted salicylaldehyde afforded the desired products **429k** and **429l** in good yields. It is noteworthy to mention that halide substituted spiro-indolofurobenzopyrans are very attractive for further synthetic transformations through cross coupling reactions. Significantly, the stereochemistry of the product **429** was

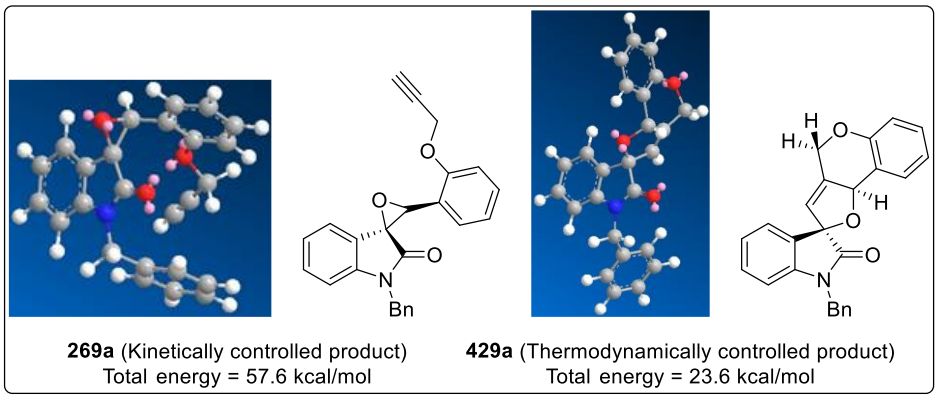
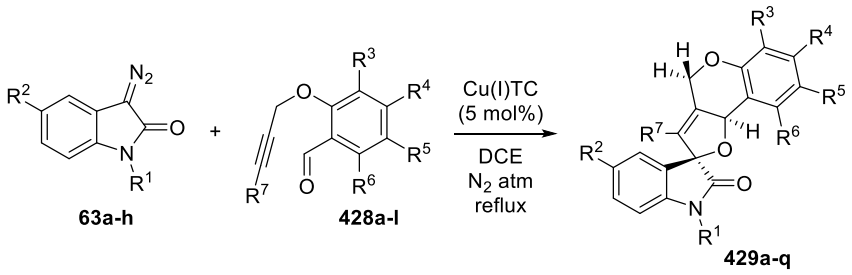
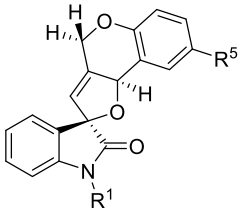


Figure 35. Energy minimization based on MM2 calculations for **269a** and **429a**

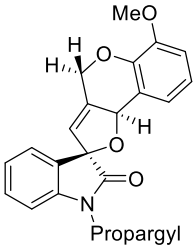
established based on the representative single-crystal X-ray analysis of spiro-indolofuronapthopyran **429i** (CCDC 1580080), where a unit cell contains two asymmetric units. Its solid-state arrangement showed the presence of three C–H–π and five intermolecular hydrogen bonding C–H···O interactions. The reaction was also

Table 20. Synthesis of thermodynamically controlled product, spiro-indolofurobenzopyrans **429**[a]

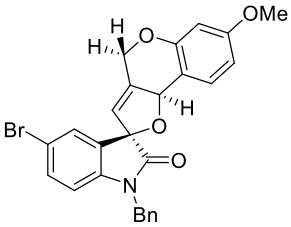




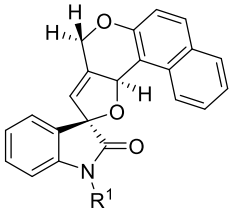
429a (R^1 = Bn, R^5 = H, 8h,84%)
429b (R^1 = Et, R^5 = Cl, 8h, 72%)
429c (R^1 = Bn, R^5 = Cl, 8.5h, 69%)
429d (R^1 = Pr, R^5 = Br, 8.5h, 61%)
429e (R^1 = Bn, R^5 = NO_2, 9h, 71%)



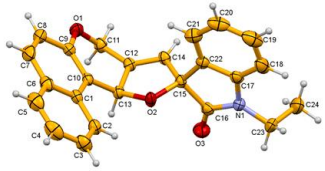
429f, 8h, 65%



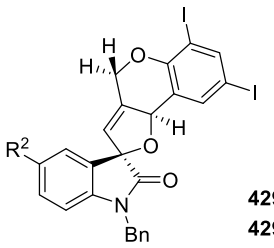
429g, 8.5h, 70%



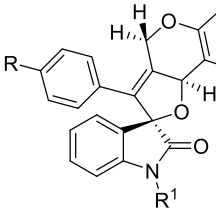
429h (R^1 = Me, 8.5h, 83%)
429i (R^1 = Et, 8.h 81%)
429j (R^1 = Bn, 8h, 76%)



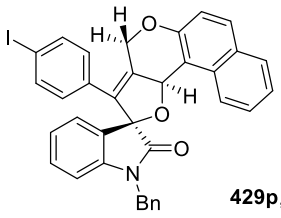
X-ray of **429i** (**CCDC.No: 1580080**),



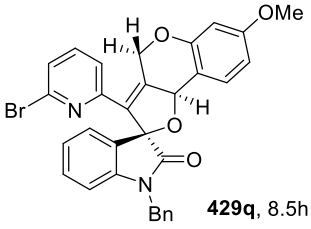
429k (R^2 = H, 8.5h, 75%)
429l (R^2 = Cl, 8.5h, 81%)



429m (R^1= Me, R = H, 9h, 84%)
429n (R^1 = Bn, R = NO_2, 8h, 81%)
429o (R^1= H, R = NO_2, 8.5h,78%)



429p, 8.5h,83%

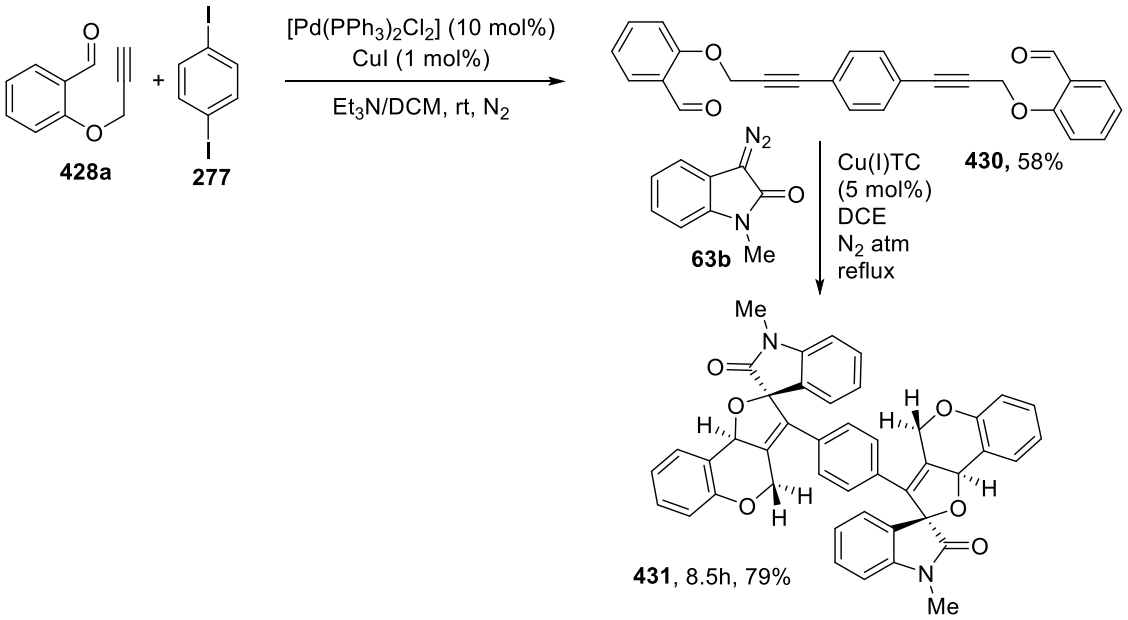


429q, 8.5h, 82%

[a]Conditions: To the mixture containing **428** (1.1 equiv) and Cu(I)TC (5 mol%) in 5 mL of dry dichloroethane under a nitrogen atmosphere was added **63** (1 equiv) in 4 mL of dry dichloroethane using syringe pump with the flow rate of 0.5 ml/h at reflux conditions.

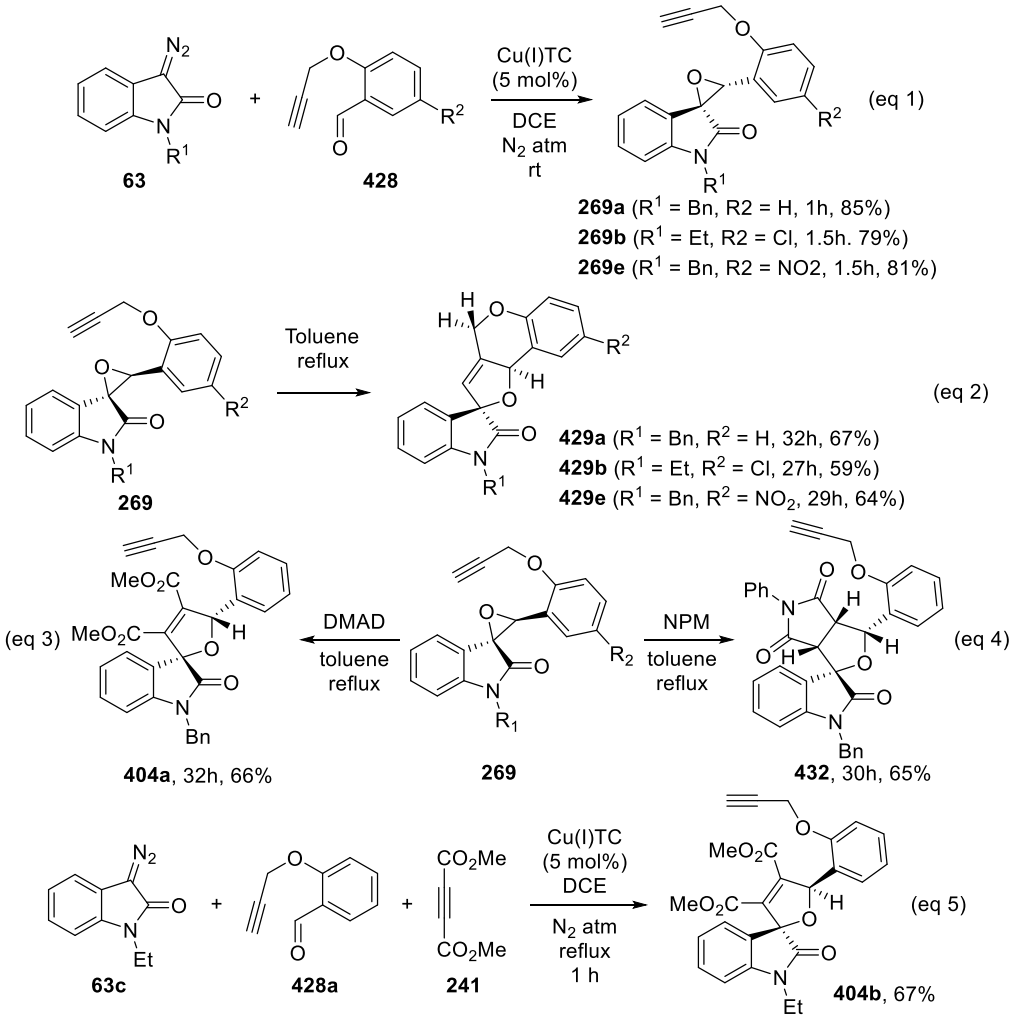
performed with salicylaldehyde having an internal alkyne group to provide the corresponding substituted spiro-indolofurobenzopyran **429m** in 84% yield. The substituent variation on the aromatic ring attached to an alkyne group was also well-tolerated to give the desired spiro-indolofurobenzopyrans **429n-q** in good yields. (Table 2). There was no effect for the substituent located on the amide nitrogen of the diazoamide. Moreover, the unsubstituted diazoamide also smoothly yielded the expected product **429o** in good yield. The scope of this process was further extended for *bis*-*O*-propargylated salicylaldehyde **430** in a similar manner. The required salicylaldehyde derivative **430** was synthesized *via* a double Sonogashira coupling reaction of diiodobenzene with *O*-propargylated salicylaldehyde. *Bis*-propargylated salicylaldehyde was reacted with diazoamide in the presence of 5 mol% of Cu(I)TC as a catalyst to furnish the respective interesting *bis*-spirocyclic complex system **431** in a diastereoselective manner (Scheme 173).

The optimized reaction conditions for the formation of spiro-indolooxirane[169] **269a** (kinetically controlled product) were found to be 5 mol% of Cu(I)TC in dichloroethane



Scheme 173. Synthesis of *bis*-spiro-indolofurobenzopyran **431**

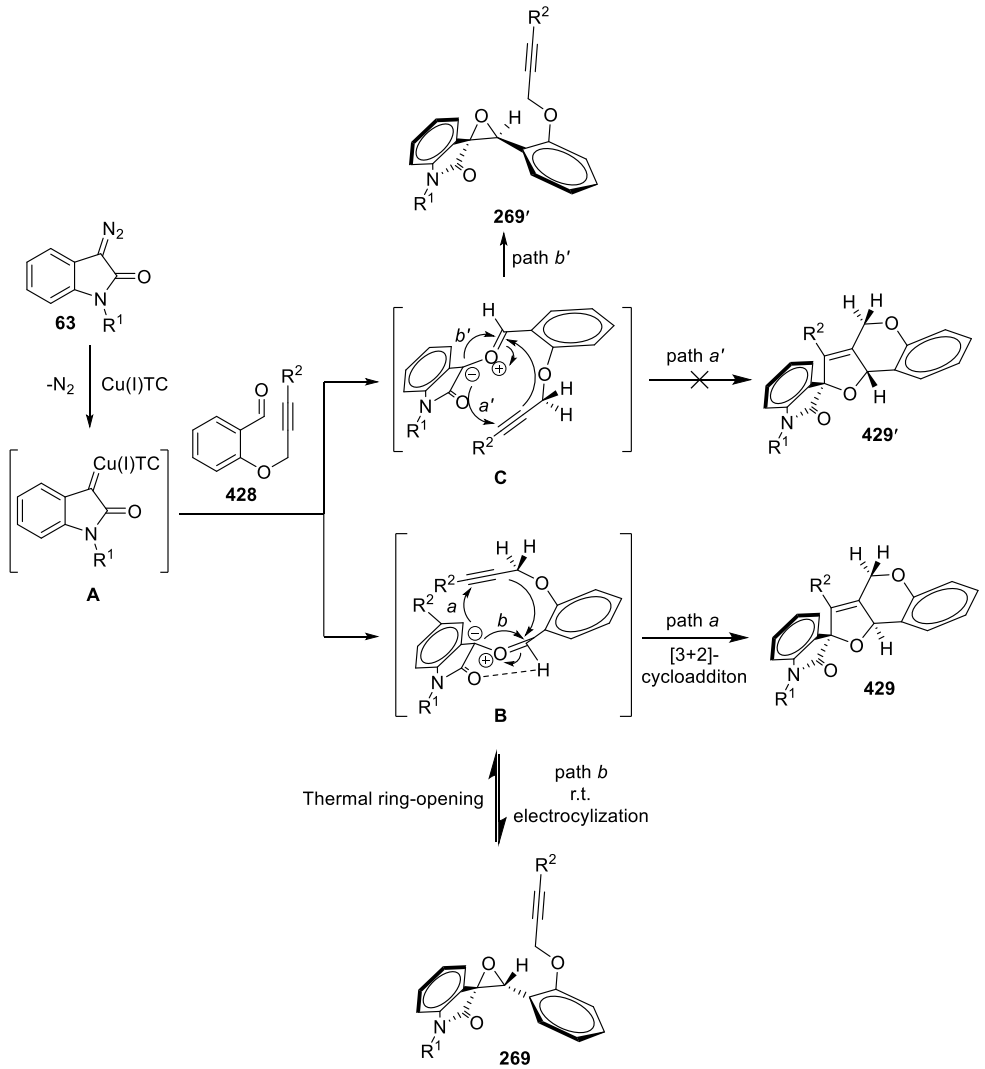
at room temperature (Table 19, entry 15). Similar reaction conditions were followed to synthesize spiro-indolooxiranes **269b** and **269e** in 79-81% yields (Scheme 174, eq 1). To gain insights into the reaction mechanism, the following control experiments were carried out. The reaction of epoxide **269a** in the presence of 5 mol% of Cu(I)TC in DCE under reflux conditions for 8h did not provide any product and the starting material was recovered. Upon prolonging the reaction time to 32h with or without Cu(I)TC, the partial disappearance of the starting material was observed with the formation of **429a** in 24% yield. This suggests that the epoxide underwent ring-opening,[298] providing carbonyl ylide intermediates to undergo [3+2]-cycloaddition with the external alkyne. Furthermore, the reaction of spiro-indolooxirane **269a** was performed in toluene under reflux conditions without a catalyst for 32h to improve the yield of **429a** (Scheme 174, eq 2). The similar reaction of the appropriate epoxide also provided **429b** and **429e**. To satisfy our curiosity, further examination in the presence of dipolarophiles was performed. Treatment of the epoxide **269a** with dimethyl acetylenedicarboxylate (DMAD) or N-phenylmaleimide (NPM) in toluene under reflux conditions afforded products **404a** and **432**, respectively (Scheme 174, eq 3 & 4). The stereochemistry of **432** was tentatively assigned based on our previous[278a] work. These results indicate that the intermolecular [3+2]-cycloaddition occurs instead of the intramolecular reaction without producing **429a**. After understanding the reaction profile, a further investigation of the diazo compound **63c** with *O*-propargyl salicylaldehyde **428a** and DMAD was carried out in the presence of Cu(I)TC in DCE under reflux conditions for 1h to obtain product **404b** (Scheme 174, eq 5). This indicated that the generated carbonyl ylides underwent intermolecular cycloaddition with electron deficient DMAD rather than the electron-rich alkyne unit.



Scheme 174. Control experiments

On the basis of the above experimental results, a plausible mechanism was put forward and is illustrated in Scheme 175. It is proposed that the electron-deficient carbenoid carbon of the copper(I) carbenoids **A** react with *O*-propargylated salicylaldehyde, affording the intermolecular carbonyl ylides **B** and **C** in two different conformations. Subsequent 1,3-dipolar cycloaddition reaction with an electron-rich external/internal alkyne group furnished the spiro-indolofurobenzopyrans **429** in a diastereoselective manner (path a). From the observed stereochemistry of the product **429**, the selective formation of rotamers of carbonyl ylides **B** is proposed rather than **C** (Scheme 175). The presence of intramolecular hydrogen bonding in **B** stabilizes the carbonyl

ylides[278b,299] and may provide the diastereoselectivity. The carbonyl ylides **B** are known[169] to proceed *via* electrocyclization to yield spiro-indolooxiranes **269** as a single isomer (path b). Interestingly, spiro-indolooxiranes **269** are also known[298] to undergo thermal ring-opening to carbonyl ylides **B** at high temperatures in an intramolecular manner. The absence of hydrogen bonding may not favour the formation of intermediate **C**; therefore, there was no observation of the isomeric products **269'** and **249'**. Thus, the most favourable transient intermediate **B** underwent 1,3-dipolar cycloaddition reaction with an electron-rich external/internal alkyne to furnish the spiro-indolofurobenzopyrans **429** in a diastereoselective manner.



Scheme 175. Proposed mechanism for spiro-indolofurobenzopyrans **269** and **429**.

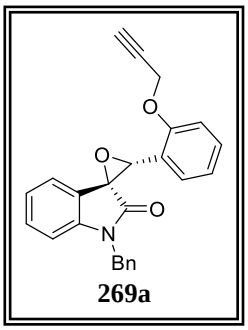
All the reactions were conducted in oven-dried glassware under a positive pressure of nitrogen with magnetic stirring. propargyl bromide (80% solution in toluene), DMAD, and NPM were purchased from M/s Aldrich, Alfa Aesar and used as provided. K_2CO_3 was dried by heating at 110 °C for 12 h and left to cool under nitrogen atmosphere. The *O*-propargyl salicylaldehydes were prepared according to the literature method.[300]

Experimental Section

General experimental procedure I for the synthesis of spiro-indolooxiranes 269

To an oven-dried flask, a solution containing the appropriate aldehyde **428** (1.1 mmol) and 5 mol% of copper(I) thiophenecarboxylate dissolved in 5 mL of dry DCE under nitrogen atmosphere was added a solution of diazoamide **63** (1 mmol) in dry DCE (4 mL) at ambient temperature to afford until the reaction completed (monitored using TLC). After the completion of reaction, the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica gel, 100-200 mesh, EtOAc/hexane 30:70) to furnish spiro-indolooxiranes **269**.

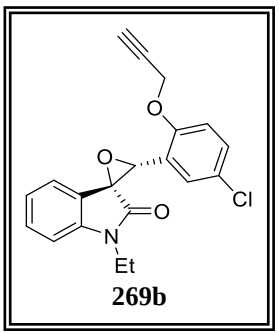
Synthesis of 1-benzyl-3'-(2-(prop-2-yn-1-yloxy)phenyl)spiro[indoline-3,2'-oxiran]-2-one (269a): A solution of 1-benzyl-3-diazoindolin-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (4 mL) was added quickly to a solution containing 2-[(prop-2-yn-1-yl)oxy]benzaldehyde (**428a**, 71 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at ambient temperature to afford product **269a** (130 mg, 85%) as a white solid according to general procedure I. R_f = 0.28 (EtOAc/hexane = 1:4, v/v); mp 104-105 °C; IR (neat): ν_{max} 3287, 2924, 2118(w), 1724, 1610, 1462, 1354, 1022, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz)



269a

δ = 2.41 (t, J = 2.4 Hz, 1H, ≡CH), 4.62 (ABqd, $\Delta\delta_{AB}$ = 0.03, J_1 = 16 Hz, J_2 = 2 Hz, 2H, OCH_2), 4.81-4.89 (m, 3H, NCH_2/OCH), 6.77 (d, J = 8 Hz, 1H, ArH), 7.00 (d, J = 8.4 Hz, 1H, ArH), 7.07-7.15 (m, 2H, ArH), 7.24-7.31 (m, 7H, ArH), 7.33-7.37 (m, 1H, ArH), 7.78 (d, J = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.0, 56.0, 61.5, 64.0, 75.7, 78.4, 109.6, 111.5, 121.1, 121.6, 121.9, 122.6, 123.7, 127.4, 127.7, 128.8, 129.0, 129.6, 130.0, 135.6, 143.8, 155.5, 170.3 ppm; HRMS (ESI) Calculated for $C_{25}H_{19}NO_3$ $(M+Na)^+$: 404.1263 found: 404.1251.

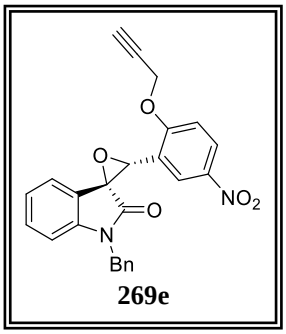
Synthesis of 3'-(5-chloro-2-(prop-2-yn-1-yloxy)phenyl)-1-ethylspiro[indoline-3,2'-oxiran]-2-one (269b): A solution of 3-diazo-1-ethylindolin-2-one (**63b**, 100 mg, 0.53 mmol) in dry dichloroethane (4 mL) was added quickly to a solution containing 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde (**428b**, 114 mg, 0.58 mmol)) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (5 mg, 5 mol%) at ambient temperature to afford product **269b** (148 mg, 79%) as a white solid according to general procedure I. R_f = 0.33 (EtOAc/hexane = 1:4, v/v); mp 157-158 °C; IR (neat): ν_{max} 3292, 2924, 2123(w), 1727, 1617, 1484, 1364, 1019, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.22 (t, J = 7.2 Hz, 3H, CH_3), 2.42 (t, J = 2.4 Hz, 1H, ≡CH), 3.66-3.76 (m, 2H, NCH_2), 4.55-4.64 (m, 2H, OCH_2), 4.74 (s, 1H, CH), 6.90-6.93 (m, 2H, ArH), 7.09-7.13 (m, 1H, ArH), 7.23-7.29 (m, 2H, ArH), 7.40 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.75 (d, J = 2.4 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.6, 35.0, 56.3, 61.4, 62.9, 76.1, 77.9, 108.8, 112.9, 122.1, 122.5, 123.4, 123.5, 126.3, 129.1, 129.3, 130.2, 143.9, 154.1, 169.5 ppm; HRMS (ESI) Calculated for $C_{20}H_{16}{}^{35}ClNO_3$ $(M+Na)^+$: 376.0716 found: 376.0715.



269b

Synthesis of 1-benzyl-3'-(5-nitro-2-(prop-2-yn-1-yloxy)phenyl)spiro[indoline-3,2'-oxiran]-2-one (269e): A solution of 1-benzyl-3-diazoindolin-2-one (**63a**, 100 mg, 0.40

mmol) in dry dichloroethane (4 mL) was added quickly to a solution containing 5-nitro-2-(prop-2-yn-1-yloxy)benzaldehyde (**428d**, 90 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at ambient temperature to afford product **269e** (138 mg, 81%) as a white solid according to general procedure I. R_f = 0.21 (EtOAc/hexane = 1.5:3.5, v/v); mp 187-189 °C; IR (neat): ν_{max} 3287, 2923, 2124(w), 1725, 1613, 1418, 1341, 1268, 1006, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.52 (t, J = 2.4 Hz, 1H, ≡CH), 4.73-4.74 (m, 2H, OCH_2), 4.79-4.89 (m, 3H, OCH/NCH_2), 6.81 (d, J = 8 Hz, 1H, ArH), 7.08-7.13 (m, 2H, ArH), 7.23-7.32 (m, 8H, ArH), 8.26 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 1H, ArH), 8.68 (d, J = 2.8 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 56.6, 61.4, 62.5, 76.8, 77.4, 109.8, 111.4, 122.1. 122.8, 122.9, 125.5, 125.7, 127.3, 127.8, 128.9, 130.5, 135.3, 141.8, 143.9, 159.8, 169.7 ppm; HRMS (ESI) Calculated for $C_{25}H_{18}N_2O_5$ $(M+H)^+$: 427.1294 found: 427.1285.



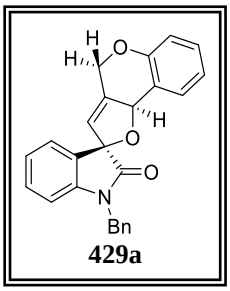
269e

General experimental procedure II to synthesize spiro-indolofurobenzopyrans 429

To an oven-dried flask, a solution containing the appropriate aldehyde **428** (1.1 mmol) and 5 mol% of copper(I) thiophenecarboxylate dissolved in 5 mL of dry dichloroethane under nitrogen atmosphere was added a solution of 3-diazoindol-2-one **63** (1 mmol) in dry DCE (4 mL) using syringe pump with the rate of addition of 0.5 mL/h at reflux conditions and continued until the reaction completed (monitored using TLC). After the completion of reaction, the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica gel, 100-200 mesh, EtOAc/hexane 15:85) to furnish spiro-indolobenzofuropyrans **429**.

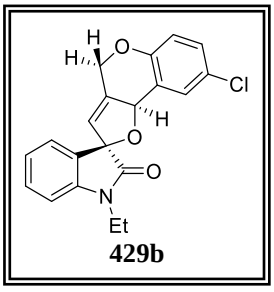
Synthesis of 1'-benzyl-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429a): A solution of 1-benzyl-3-diazoindolin-2-one (**63a**, 100 mg, 0.40 mmol) in

dry dichloroethane (4 mL) was added dropwise to a solution containing 2-[(prop-2-yn-1-yl)oxy]benzaldehyde (**428a**, 71 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to afford product **429a** (129 mg, 84%) as a white solid according to general procedure II. R_f = 0.35 (EtOAc/hexane = 1:4, v/v); mp 114-115 °C; IR (neat): ν_{max} 2924, 1723, 1613, 1490, 1360, 1215, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.90 (ABq, $\Delta\delta_{AB}$ = 0.04, J = 15.6 Hz, 2H, CH_2), 5.62 (s, 1H, CH), 6.30 (s, 1H, CH), 6.70 (d, J = 8 Hz, 1H, ArH), 6.89-6.99 (m, 4H, ArH), 7.15-7.27 (m, 4H, ArH), 7.28-7.38 (m, 4H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 63.7, 81.4, 92.7, 109.5, 116.8, 121.5, 121.8, 123.4, 125.5, 126.0, 126.8, 127.4, 127.8, 128.3, 128.9, 129.2, 130.4, 135.4, 139.9, 142.7, 152.8, 175.2 ppm; HRMS (ESI) Calculated for $C_{25}H_{19}NO_3$ $(M+H)^+$: 382.1443 found: 382.1439.



429a

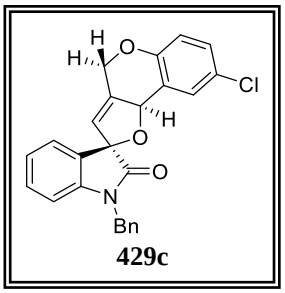
Synthesis of 7-chloro-1'-ethyl-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429b): A solution of 3-diazo-1-ethylindolin-2-one (**63b**, 100 mg, 0.53 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde (**428b**, 114 mg, 0.58 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (5 mg, 5 mol%) at reflux conditions to afford product **429b** (135 mg, 72%) as a white solid according to general procedure II. R_f = 0.23 (EtOAc/hexane = 1:4, v/v); mp 186-187 °C; IR (neat): ν_{max} 2929, 1722, 1612, 1474, 1361, 1216, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.30 (t, J = 7.2 Hz, 3H, CH_3), 3.68-3.84 (m, 2H, NCH_2), 4.96 (s, 2H, CH_2), 5.59 (s, 1H, CH), 6.19 (s, 1H, CH), 6.82-6.86 (m, 2H, ArH), 6.92-6.94 (m, 1H, ArH) 6.97-7.10 (m, 1H, ArH), 7.17 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H, ArH), 7.29-7.34 (m, 2H, ArH) ppm; ^{13}C



429b

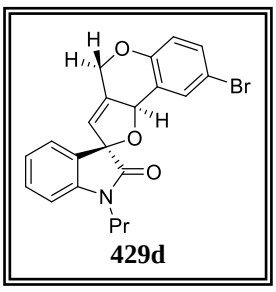
NMR ($CDCl_3$, 100 MHz) δ = 12.6, 35.0, 63.8, 80.8, 92.7, 108.6, 118.2, 122.4, 123.2, 125.6, 126.3, 126.4, 127.4, 128.2, 129.2, 130.6, 138.8, 142.7, 151.4, 174.4 ppm; HRMS (ESI) Calculated for $C_{20}H_{16}{}^{35}ClNO_3$ $(M+H)^+$: 354.0897 found: 354.0896.

Synthesis of 7-chloro-1'-benzyl-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429c): A solution of 1-benzyl-3-diazoindolin-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde (**428b**, 85 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to afford product **429c** (114 mg, 69%) as a white solid according to general procedure II. R_f = 0.29 (EtOAc/hexane = 1:4, v/v); mp 201-202 °C; IR (neat): ν_{max} 2966, 1724, 1650, 1470, 1361, 1211, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.91-5.06 (m, 4H, CH_2), 5.69 (s, 1H, CH), 6.28 (s, 1H, CH), 6.76 (d, *J* = 7.6 Hz, 1H, ArH), 6.89 (d, *J* = 8.8 Hz, 1H, ArH), 6.97-7.03 (m, 2H, ArH), 7.20-7.26 (m, 2H, ArH), 7.30-7.39 (m, 6H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 63.8, 80.9, 92.8, 109.6, 118.3, 122.4, 123.5, 125.5, 126.3, 126.5, 127.3, 127.4, 127.8, 127.9, 128.9, 129.2, 130.6, 135.3, 139.1, 142.7, 151.4, 174.9 ppm; HRMS (ESI) Calculated for $C_{25}H_{18}{}^{35}ClNO_3$ $(M+H)^+$: 416.1054 found: 416.1054.



429c

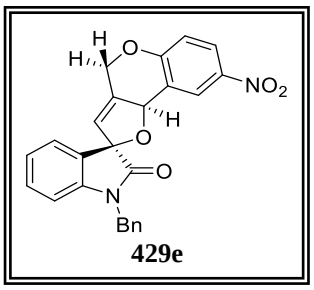
Synthesis of 7-bromo-1'-propyl-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429d): A solution of 3-diazo-1-propylindolin-2-one (**63c**, 100 mg, 0.50 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**428c**, 130 mg, 0.55 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate



429d

(5 mg, 5 mol%) at reflux conditions to afford product **429d** (126 mg, 61%) as a white solid according to general procedure II. R_f = 0.29 (EtOAc/hexane = 1:4, v/v); mp 167-168 °C; IR (neat): ν_{max} 2923, 1725, 1613, 1472, 1341, 1090, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 0.99 (t, J = 7.4 Hz, 3H, CH_3), 1.69-1.78 (m, 2H, CH_2), 3.67 (t, J = 7.2 Hz, 2H, CH_2), 4.96 (ABq distorted, 2H, CH_2), 5.60 (s, 1H, CH), 6.19 (s, 1H, CH), 6.78 (d, J = 8.8 Hz, 1H, ArH), 6.84 (d, J = 7.8 Hz, 1H, ArH), 6.92-6.94 (m, 1H, ArH), 6.97-7.01 (m, 1H, ArH), 7.29-7.33 (m, 2H, ArH), 7.46 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.4, 20.7, 41.9, 63.8, 80.7, 92.7, 108.8, 113.5, 118.7, 122.5, 123.2, 125.6, 127.8, 128.0, 129.4, 130.6, 132.1, 138.8, 143.1, 151.9, 174.7 ppm; HRMS (ESI) Calculated for $C_{21}H_{18}{}^{79}BrNO_3$ $(M+Na)^+$: 434.0368 found: 434.0364.

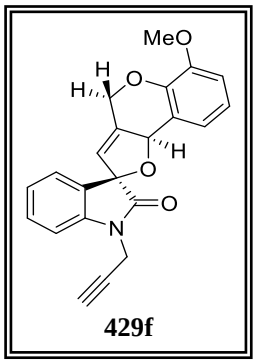
Synthesis of 7-nitro-1'-benzyl-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429e): A solution of 1-benzyl-3-diazoindolin-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 5-nitro-2-(prop-2-yn-1-yloxy)benzaldehyde (**428d**, 90 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to afford product **429e** (121 mg, 71%) as a white solid according to general procedure II. R_f = 0.19 (EtOAc/hexane = 1.5:3.5, v/v); mp 199-200 °C; IR (neat): ν_{max} 2981, 1718, 1612, 1465, 1357, 1213, 1088, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.96 (s, 2H, CH_2), 5.16 (ABq, $\Delta\delta_{AB}$ = 0.04, J = 13.2 Hz, 2H, CH_2), 5.78 (s, 1H, CH), 6.31 (s, 1H, CH), 6.77 (d, J = 8 Hz, 1H, ArH), 6.91 -6.93 (m, 1H, ArH), 6.97-7.04 (m, 2H, ArH), 7.23-7.27 (m, 1H, ArH), 7.33-7.42 (m, 5H, ArH), 8.17 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H, ArH), 8.34 (d, J = 2.8 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 64.5, 80.1, 92.9, 109.7, 117.6, 123.42, 123.46, 123.6, 125.1, 125.3,



429e

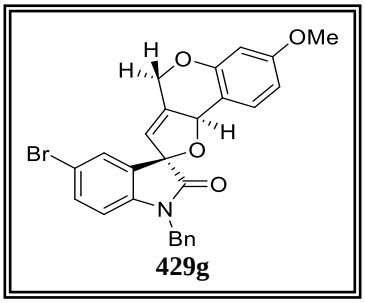
126.2, 127.3, 127.9, 129.0, 130.7, 135.2, 137.5, 142.0, 142.8, 158.0, 174.56 ppm; HRMS (ESI) Calculated for $C_{25}H_{18}N_2O_5$ $(M+H)^+$: 427.1294 found: 427.1281.

Synthesis of 6-methoxy-1'-(prop-2-yn-1-yl)-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzo pyran-2,3'-indol]-2'(1'*H*)-one (429f): A solution of 3-diazo-1-(prop-2-yn-1-yl)indolin-2-one (**63d**, 100 mg, 0.51 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 3-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde (**428e**, 106 mg, 0.56 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (5 mg, 5 mol%) at reflux conditions to afford product **429f** (119 mg, 65%) as a white solid according to general procedure II. R_f = 0.13 (EtOAc/hexane = 1:4, v/v); mp 195-196 °C; IR (neat): ν_{max} 3291, 2930, 1725, 1614, 1362, 1264, 1020, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.27 (s, 1H, CH), 3.90 (s, 3H, CH_3), 4.49 (ABqd, $\Delta\delta_{AB}$ = 0.13, J_1 = 18 Hz, J_2 = 2 Hz, 2H, CH_2), 5.04 (ABq, $\Delta\delta_{AB}$ = 0.08, J = 13.2 Hz, 2H, CH_2), 5.60 (s, 1H, CH), 6.26 (s, 1H, CH), 6.84-7.05 (m, 6H, ArH), 7.30-7.34 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.6, 56.0, 64.0, 72.8, 76.6, 81.3, 92.6, 109.5, 110.9, 118.5, 121.3, 121.7, 123.7, 125.5, 126.6, 128.1, 130.5, 139.7, 141.7, 142.1, 148.2, 174.0 ppm; HRMS (ESI) Calculated for $C_{22}H_{17}NO_4$ $(M+Na)^+$: 382.1053 found: 382.1049.



429f

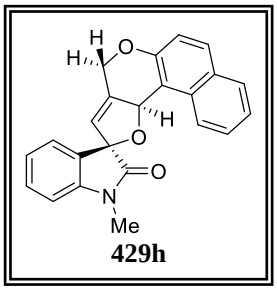
Synthesis of 5'-bromo-1'-benzyl-7-methoxy-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzo pyran-2,3'-indol]-2'(1'*H*)-one (429g): A solution of 1-benzyl-5-bromo-3-diazoindolin-2-one (**63e**, 100 mg, 0.30 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde (**428f**, 103 mg, 0.33 mmol) dissolved in dry DCE (5 mL) and



429g

copper(I) thiophenecarboxylate (3 mg, 5 mol%) at reflux conditions to afford product **429g** (102 mg, 70%) as a white solid according to general procedure II. R_f = 0.30 (EtOAc/hexane = 1:4, v/v); mp 195-196 °C; IR (neat): ν_{max} 2924, 1729, 1644, 1433, 1161, 1030, 809 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.80 (s, 3H, CH_3), 4.87 (s, 2H, CH_2), 4.94 (ABq, $\Delta\delta_{AB}$ = 0.04, J = 12.8 Hz, 2H, CH_2), 5.62 (s, 1H, CH), 6.28 (s, 1H, CH), 6.45 (s, 1H, ArH), 6.54-6.59 (m, 2H, ArH), 7.06 (s, 1H, ArH), 7.23-7.35 (m, 7H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 55.4, 63.7, 81.3, 92.1, 101.7, 108.5, 111.0, 116.1, 117.6, 121.7, 127.3, 127.89, 127.98, 128.7, 129.0, 130.2, 133.2, 134.9, 140.7, 141.7, 153.9, 160.6, 174.7 ppm; HRMS (ESI) Calculated for $C_{26}H_{20}{}^{79}BrNO_4$ $(M+H)^+$: 490.0654 found: 490.0648.

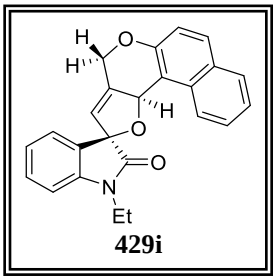
Synthesis of 1'-methyl-4*H*,11c*H*-spiro[furo[2,3-*d*]naphtho[2,1-*b*]pyran-2,3'-indol]-2'(1'*H*)-one (429h): A solution of 3-diazo-1-methylindolin-2-one (**63f**, 100 mg, 0.58 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (**428g**, 134 mg, 0.64 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (6 mg, 5 mol%) at reflux conditions to afford product **429h** (171 mg, 83%) as a white solid according to general procedure II. R_f = 0.39 (EtOAc/hexane = 1:4, v/v); mp 186-187 °C; IR (neat): ν_{max} 2254, 1720, 1617, 1466, 1088, 1015, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.23 (s, 3H, CH_3), 4.95 (ABq, $\Delta\delta_{AB}$ = 0.13, J = 12 Hz, 2H, CH_2), 5.76 (s, 1H, CH), 6.77-6.81 (m, 2H, ArH), 6.87-6.90 (m, 1H, ArH), 6.93-6.95 (m, 1H, ArH), 7.08 (d, J = 9.2 Hz, 1H, ArH), 7.23-7.27 (m, 1H, ArH), 7.31-7.35 (m, 1H, ArH), 7.40-7.44 (m, 1H, ArH), 7.71-7.75 (m, 2H, ArH), 8.21 (d, J = 8.4 Hz, 1H, ArH), ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 63.9, 80.29, 92.0, 108.3, 116.8, 118.7, 123.3, 123.8, 123.9, 125.3, 125.6,



429h

126.8, 128.0, 128.2, 129.4, 130.3, 130.4, 132.6, 140.2, 143.7, 151.8, 175.3 ppm; HRMS (ESI) Calculated for $C_{23}H_{17}NO_3$ $(M+H)^+$: 356.1287 found: 356.1280.

Synthesis of 1'-ethyl-4*H*,11*cH*-spiro[furo[2,3-*d*]naphtho[2,1-*b*]pyran-2,3'-indol]-2'(1'*H*)-one (429i): A solution of 3-diazo-1-ethylindolin-2-one (**63b**, 100 mg, 0.53 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (**428g**, 123 mg, 0.58 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (5 mg, 5 mol%) at reflux conditions to afford product **429i** (158 mg, 81%) as a white solid according to general procedure II. R_f = 0.44 (EtOAc/hexane = 1:4, v/v); mp 174-175 °C; IR (neat): ν_{max} 2976, 1722, 1464, 1360, 1216, 1033, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ =1.33 (t, J = 7.2, 3H, CH_3), 3.78 (q, J = 7.2 Hz, 2H, CH_2), 4.95 (ABq, $\Delta\delta_{AB}$ = 0.12, J = 12 Hz, 2H, CH_2), 5.76 (s, 1H, CH), 6.80-6.82 (m, 2H, ArH), 6.85-6.89 (m, 1H, ArH), 6.93-6.96 (m, 1H, ArH), 7.08 (d, J = 9.2 Hz, 1H, ArH), 7.22-7.26 (m, 1H, ArH), 7.31-7.35 (m, 1H, ArH), 7.41-7.45 (m, 1H, ArH), 7.71-7.75 (m, 2H, ArH), 8.23 (d, J = 8.4 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.7, 34.9, 63.8, 80.32, 92.0, 108.5, 116.9, 118.7, 123.0, 123.9, 125.4, 125.7, 126.8, 128.0 128.5, 129.4, 130.24, 130.28, 130.29, 132.6, 140.1, 142.8, 151.8, 174.9 ppm; HRMS (ESI) Calculated for $C_{24}H_{19}NO_3$ $(M+Na)^+$: 370.1443 found: 370.1425.

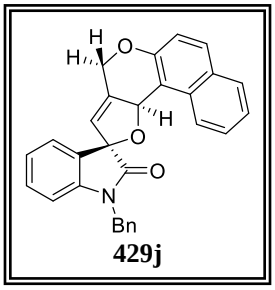


429i

Crystal data for compound **429i**: (CCDC 1580080) $C_{24}H_{19}NO_3$, white colour, diamond, M = 699.64, 0.28 × 0.19 × 0.11 mm, Triclinic, space group P-1 with a = 9.0014(13) Å, b = 9.5478(13) Å, c = 23.864(3) Å, α = 91.650(2) (2)°, β = 95.150(2) (2)°, γ = 113.925(2) (2)°, V = 1862.4(5) $Å^3$, T = 150(2) K, R_1 = 0.0465, wR_2 = 0.1282 on observed data, z = 2, D_{calcd} = 1.317 g/cm^3, $F(000)$ = 776, Absorption coefficient =

0.087 mm^{-1}, λ = 0.71073 Å, 6462 reflections were collected on a smart apex CCD single crystal diffractometer 5683 observed reflections ($I \geq 2\sigma$ (I)). The largest difference peak and hole = 0.249 and -0.226 e.$Å^{-3}$, respectively. The structure was solved by direct methods and refined by full-matrix least squares on $F2$ using SHELXL–97 software.

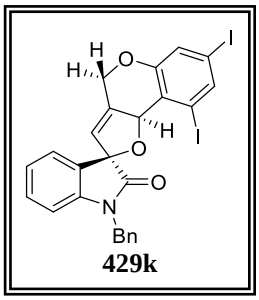
Synthesis of 1'-benzyl-4*H*,11*cH*-spiro[furo[2,3-*d*][1]naptho[2,1-b]pyran-2,3'-indol]-2'(1'*H*)-one (429j): A solution of 1-benzyl-3-diazoindolin-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (**428g**, 92 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to obtain product **429j** (131 mg, 76%) as a white solid according to general procedure II. R_f = 0.34 (EtOAc/hexane = 1:4, v/v); mp 189-190 °C; IR (neat): ν_{max} 2933, 1728, 1610, 1475, 1180, 1033, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.74-4.77 (m, 1H, CH), 4.82-4.85 (m, 1H, CH), 4.93-4.98 (m, 2H, CH_2), 5.74 (s, 1H, CH), 6.61 (d, J = 7.6 Hz, 1H, CH), 6.77-6.80 (m, 2H, ArH), 6.88 (d, J = 6.8 Hz, 1H, ArH), 7.01-7.08 (m, 2H, ArH), 7.18-7.29 (m, 6H, ArH), 7.36-7.40 (m, 1H, ArH), 7.65-7.69 (m, 2H, ArH), 8.18 (d, J = 8.4 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.1, 63.8, 80.4, 92.0, 109.3, 116.7, 118.7, 123.3, 123.9, 124.0, 125.4, 125.6, 126.7, 127.5, 127.8, 128.0, 128.3, 128.9, 129.4, 130.26, 130.3, 132.6, 135.5, 140.3, 142.8, 151.8, 175.5 ppm ; HRMS (ESI) Calculated for $C_{29}H_{21}NO_3$ $(M+H)^+$: 432.1600 found: 432.1595.



429j

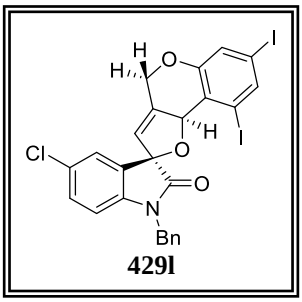
Synthesis of 1'-benzyl-6,8-diiodo-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429k): A solution of 1-benzyl-3-diazoindolin-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing

3,5-diiodo-2-(prop-2-yn-1-yloxy)benzaldehyde (**428h**, 180 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to yield product **429k** (189 mg, 75%) as a white solid according to general procedure II. R_f = 0.09 (EtOAc/hexane = 1.5:3.5, v/v); mp 215-216 °C; IR (neat): ν_{max} 2923, 1728, 1611, 1484, 1432, 1161, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.94 (s, 2H, CH_2), 5.14 (ABq, $\Delta\delta_{AB}$ = 0.05, J = 13.2 Hz, 2H, CH_2), 5.72 (s, 1H, CH), 6.27 (s, 1H, CH), 6.76 (d, J = 8 Hz, 1H, ArH), 6.99-7.05 (m, 2H, ArH), 7.24-7.41 (m, 6H, ArH), 7.67 (s, 1H, ArH), 8.04 (s, 1H, ArH) ppm ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 64.6, 80.5, 84.1, 86.2, 93.0, 109.6, 122.9, 123.5, 125.5, 127.4, 127.6, 127.9, 128.3, 129.0, 130.7, 135.3, 135.5, 138.4, 142.8, 146.2, 151.8, 174.6 ppm; HRMS (ESI) Calculated for $C_{25}H_{17}I_2NO_3$ $(M+Na)^+$: 655.9196 found: 655.9193.



429k

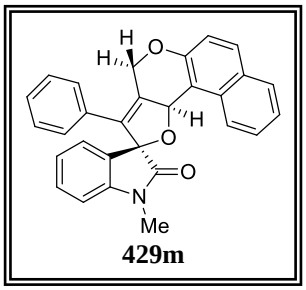
Synthesis of 5'-chloro-1'-benzyl-7,9-diiodo-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzo pyran-2,3'-indol]-2'(1'*H*)-one (429l): A solution of 1-benzyl-5-chloro-3-diazoindolin-2-one (**63g**, 100 mg, 0.35 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 3,5-diiodo-2-(prop-2-yn-1-yloxy)benzaldehyde (**428h**, 160 mg, 0.39 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to furnish product **429l** (189 mg, 81%) as a white solid according to general procedure II. R_f = 0.48 (EtOAc/hexane = 1.5:3.5, v/v); mp 229-230 °C; IR (neat): ν_{max} 2933, 1724, 1614, 1500, 1159, 1022, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.88 (ABq, $\Delta\delta_{AB}$ = 0.02, J = 16 Hz, 2H, CH_2), 5.08 (ABq, $\Delta\delta_{AB}$ = 0.06, J = 13.6 Hz, 2H, CH_2), 5.67 (s, 1H, CH), 6.23 (s, 1H, CH), 6.62 (d, J = 8.4 Hz, 1H, ArH), 6.95 (s, 1H, ArH), 7.17 (d, J = 8.4 Hz, 1H, ArH),



429l

7.27-7.34 (m, 5H, ArH), 7.61 (s, 1H, ArH), 8.00 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.2, 64.5, 80.6, 84.3, 86.3, 92.6, 110.7, 122.3, 126.0, 127.3, 127.8, 128.0, 129.00, 129.04, 129.1, 130.6, 134.8, 135.5, 139.1, 141.3, 146.4, 151.7, 174.2 ppm; HRMS (ESI) Calculated for $C_{25}H_{16}{}^{35}ClI_2NO_3$ $(M+H)^+$: 667.8986 found: 667.8979.

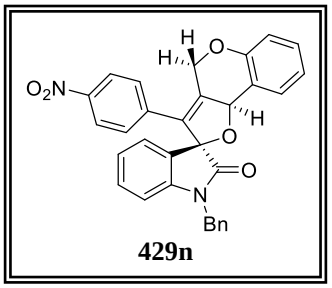
Synthesis of 3-benzyl-1'-methyl-4*H*,11c*H*-spiro[furo[2,3-*d*]naphtho[2,1-*b*]pyran-2,3'-indol]-2'(1'*H*)-one (429m): A solution of 3-diazo-1-methylindolin-2-one (**63f**, 100 mg, 0.58 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2-((3-phenylprop-2-yn-1-yl)oxy)-1-naphthaldehyde (**428i**, 183 mg, 0.64 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (6 mg, 5 mol%) at reflux conditions to provide product **429m** (210 mg, 84%) as a white solid according to general procedure II. R_f = 0.25 (EtOAc/hexane = 1.5:3.5, v/v); mp 230-231 °C; IR (neat): ν_{max} 2923, 1728, 1611, 1433, 1341, 1166, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.08 (s, 3H, CH_3), 4.93 (ABq, $\Delta\delta_{AB}$ = 0.07, J = 12.1 Hz, 2H, CH_2), 6.62 (d, J = 8 Hz, 1H, CH), 6.80-6.84 (m, 1H, ArH), 6.90-6.96 (m, 4H, ArH), 7.08 (d, J = 8.8 Hz, 1H, ArH), 7.13-7.21 (m, 4H, ArH), 7.29-7.33 (m, 1H, ArH), 7.39-7.43 (m, 1H, ArH), 7.69-7.74 (m, 2H, ArH), 8.26 (d, J = 8.4 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.4, 63.1, 80.5, 94.4, 108.4, 117.2, 118.8, 123.3, 123.9, 125.5, 125.8, 126.8, 128.0, 128.04, 128.4, 128.6, 128.7, 129.4, 130.3, 130.4, 130.9, 132.7, 135.1, 136.5, 144.1, 152.0, 175.3 ppm; HRMS (ESI) Calculated for $C_{29}H_{21}NO_3$ $(M+Na)^+$: 454.1419 found: 454.1409.



429m

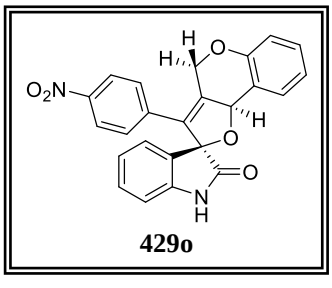
Synthesis of 5'-bromo-3-(4-nitrophenyl)-1'-benzyl-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429n): A solution of 1-benzyl-3-diazoindolin-2-

one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2-((3-(4-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**428j**, 124 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to afford product **429n** (163 mg, 81%) as a white solid according to general procedure II. R_f = 0.44 (EtOAc/hexane = 1.5:3.5, v/v); mp 248-249 °C IR (neat): ν_{max} 2923, 1705, 1601, 1457, 1335, 1166, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.57 (d, 1H, *J* = 15.6 Hz, CH), 4.86 (d, *J* = 13.6 Hz, 1H, CH), 5.01-5.09 (m, 2H, CH_2), 6.45 (s, 1H, OCH), 6.67 (d, 1H, *J* = 7.6 Hz, ArH), 6.91-7.05 (m, 8H, ArH), 7.13-7.29 (m, 4H, ArH), 7.43 (d, *J* = 7.6 Hz, 1H, ArH), 7.96 (d, *J* = 9.2 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.9, 62.8, 81.8, 94.7, 109.7, 116.8, 121.8, 123.7, 123.74, 125.6, 126.0, 126.6, 127.2, 127.4, 127.9, 128.7, 129.38, 129.44, 131.0, 132.7, 135.0, 137.3, 137.6, 142.9, 147.8, 152.7, 174.5 ppm; HRMS (ESI) Calculated for $C_{29}H_{21}NO_3$ $(M+Na)^+$: 525.1426 found: 525.1427.



429n

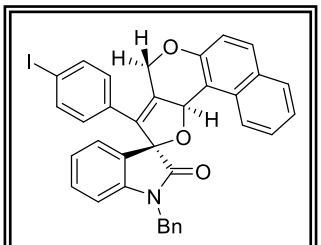
Synthesis of 3-(4-nitrophenyl)-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429o): A solution of 3-diazoindolin-2-one (**63h**, 100 mg, 0.63 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2-((3-(4-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**428j**, 195 mg, 0.69 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (6 mg, 5 mol%) at reflux conditions to afford product **429o** (203 mg, 78%) as a white solid according to general procedure II. R_f = 0.76 (EtOAc/hexane = 2:3, v/v); mp 230-231 °C; IR (neat): ν_{max} 3004, 2253, 1441, 1377, 1039, 918, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.94 (ABq, $\Delta\delta_{AB}$ = 0.18, *J* = 13.4 Hz, 2H, CH_2 6.38 (s, 1H, CH), 6.82 (d, *J* = 7.6 Hz, 1H, ArH), 6.91-7.06 (m, 5H, ArH), 7.23-7.28 (m, 3H, ArH), 7.40 (d, *J* = 7.6



429o

Hz, 1H, ArH), 8.05 (d, J = 8.8 Hz, 2H, ArH), 8.27 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 62.9, 81.8, 94.8, 110.7, 116.9, 121.8, 123.8, 123.9, 125.9, 126.0, 126.5, 127.9, 129.1, 129.5, 131.1, 132.2, 137.4, 138.1, 140.9, 147.8, 152.6, 176.6 ppm; HRMS (ESI) Calculated for $C_{24}H_{16}N_2O_5$ $(M-H)^+$: 411.0986 found: 411.0976.

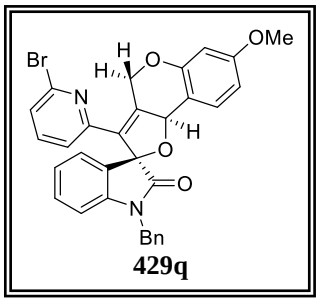
Synthesis of 1'-benzyl-3-(4-iodophenyl)-4*H*,11c*H*-spiro[furo[2,3-*d*]naphtho[2,1-*b*] pyran-2,3'-indol]-2'(1'H)-one (429p): A solution of 1-benzyl-3-diazoindolin-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2-((3-(4-iodophenyl)prop-2-yn-1-yl)oxy)-1-naphthaldehyde (**428k**, 181 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to yield product **429p** (210 mg, 83%) as a white solid according to general procedure II. R_f = 0.41 (EtOAc/hexane = 1.5:3.5, v/v); mp 245-246 °C; IR (neat): ν_{max} 2924, 1722, 1613, 1469, 1353, 1216, 952, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.43 (d, J = 16 Hz, 1H, CH_2), 4.92 (ABq, $\Delta\delta_{AB}$ = 0.02, J = 12.2 Hz, 2H, CH_2), 5.16 (d, J = 15.7, 1H, CH_2), 6.52-6.57 (m, 3H, ArH), 6.82-6.87 (m, 3H, ArH), 6.96-7.00 (m, 2H, ArH), 7.07-7.11 (m, 2H, ArH), 7.17-7.24 (m, 3H, ArH), 7.33-7.37 (m, 1H, ArH), 7.44-7.50 (m, 3H, ArH), 7.72-7.77 (m, 2H, ArH), 8.29 (d, J = 8.4 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.7, 62.9, 80.8, 94.6, 95.2, 109.6, 117.0, 118.7, 123.4, 124.0, 125.4, 125.7, 126.8, 126.9, 127.6, 127.7, 128.1, 128.8, 129.4, 130.1, 130.4, 130.6, 132.6, 135.0, 135.4, 135.9, 137.8, 143.0, 151.8, 175.2 ppm; HRMS (ESI) Calculated for $C_{35}H_{24}INO_3$ $(M+H)^+$: 634.0879 found: 634.0874.



429p

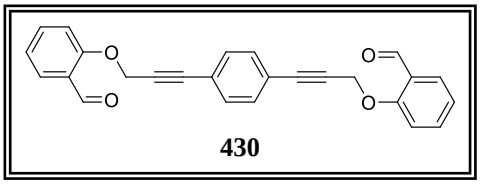
Synthesis of 1'-benzyl-3-(6-bromopyridin-2-yl)-7-methoxy-4*H*,9b*H*-spiro[furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (429q): A solution of 1-benzyl-3-

diazoindolin-2-one (**63a**, 100 mg, 0.40 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2-((3-(6-bromopyridin-2-yl)prop-2-yn-1-yl)oxy)-4-methoxybenzaldehyde (**428l**, 152 mg, 0.44 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (4 mg, 5 mol%) at reflux conditions to afford product **429q** (186 mg, 82%) as a white solid according to general procedure II. R_f = 0.40 (EtOAc/hexane = 1.5:3.5, v/v); mp 226-227 °C; IR (neat): ν_{max} 2924, 1725, 1611, 1436, 1259, 1159, 1116, 1029, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.80 (s, 3H CH_3), 4.98 (ABq, $\Delta\delta_{AB}$ = 0.10, J = 15.6 Hz, 2H, CH_2), 5.25-5.29 (m, 1H, CH_2), 5.66 (d, J = 15.2 Hz, 1H, CH_2), 6.35 (s, 1H, CH), 6.51-6.61 (m, 3H, ArH), 6.79-6.81 (m, 1H, ArH), 6.87-6.94 (m, 2H, ArH), 7.12-7. 37 (m, 9H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.3, 55.5, 65.4, 81.5, 92.7, 102.2, 108.5, 109.6, 119.7, 119.8, 123.5, 125.4, 126.2, 126.7, 127.75, 127.8, 128.4, 128.9, 129.0, 130.6, 135.7, 138.6, 141.5, 143.0, 143.5, 151.1, 154.0, 160.4, 174.9 ppm; HRMS (ESI) Calculated for $C_{31}H_{23}{}^{79}BrN_2O_4$ $(M+Na)^+$: 589.0739 found: 589.0724.



429q

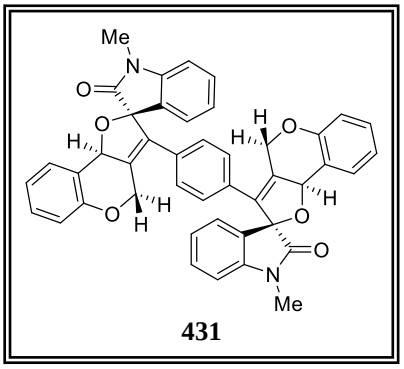
Synthesis of 2,2'-((1,4-phenylenebis(prop-2-yne-3,1-diyl))bis(oxy))dibenzaldehyde (430): To a mixture of compound (**428a**, 1 g, 6.24 mmol), 1,4-diiodobene (1.029 g, 3.12 mmol) in dry trimethylamine/dichloromethane (4:1) (5 mL) under nitrogen atmosphere were added $[Pd(PPh_3)_2Cl_2]$ (175 mg, 0.25 mmol) and CuI (24 mg, 0.12 mmol) successively. The reaction mixture was stirred at room temperature for 6 h. After that, the solvent was removed under reduced pressure, added water and extracted with dichloromethane. The crude product was purified by column chromatography using silica gel to afford *bis*-aldehyde derivative **430** (1.4 g, 58%) as a white solid. R_f = 0.19 (EtOAc/hexane = 1:4, v/v); mp 153-154 °C; IR (neat):



430

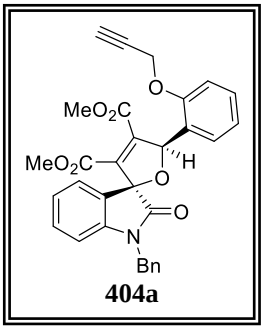
ν_{max} 2861, 1681, 1594, 1455, 1212, 1007, 834, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.05 (s, 2H, CH_2), 7.09 (t, J = 7.6 Hz, 1H, ArH), 7.17 (d, J = 8.4 Hz, 1H, ArH), 7.36 (s, 2H, ArH), 7.56-7.60 (m, 1H, ArH), 7.87 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, ArH) 10.52 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 57.25, 85.03, 87.41, 113.39, 121.69, 122.43, 125.59, 128.65, 131.74, 135.77, 159.98, 189.65 ppm; HRMS (ESI) Calculated for $C_{26}H_{18}O_4$ $(M+Na)^+$: 417.1103 found: 417.1098.

Synthesis of 1'-methyl-3-[4-(1'-methyl-2'-oxo-1',2',3'*a*,7'*a*-tetrahydro-4*H*,9b*H*-spiro[furo [3,2-*c*][1]benzopyran-2,3'-indol]-3-yl)phenyl]9a,9bdihydro 4*H*,5aHspiro [furo[3,2-*c*][1]benzopyran-2,3'-indol]-2'(1'*H*)-one (431): A solution of 1-methyl-3-diazoindolin-2-one (**63f**, 100 mg, 0.58 mmol) in dry dichloroethane (4 mL) was added dropwise to a solution containing 2,2'-((1,4-phenylenebis(prop-2-yne-3,1-diyl))bis(oxy))dibenzaldehyde (**430**, 115 mg, 0.029 mmol) dissolved in dry DCE (5 mL) and copper(I) thiophenecarboxylate (6 mg, 5 mol%) at reflux conditions to furnish product **431** (157 mg, 79%) as a white solid according to general procedure II. R_f = 0.06 (EtOAc/hexane = 1.5:3.5, v/v); mp 231-232 °C; IR (neat): ν_{max} 2923, 1716, 1608, 1471, 1215, 1109, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.09 (s, 3H, CH_3), 4.79-4.84 (m, 1H, CH_2), 4.94-5.00 (m, 1H, CH_2), 6.31 (s, 1H, CH), 6.57 (s, 1H, CH), 6.23 (s, 1H, CH), 6.74 (t, J = 8.4 Hz, 1H, ArH), 6.85-6.91 (m, 2H, ArH), 6.93-6.99 (m, 2H, ArH), 7.20-7.35 (m, 3H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.5, 63.2, 81.2, 94.3, 108.7, 116.7, 121.5, 123.5, 125.6, 126.4, 126.5, 126.6, 128.2, 128.3, 129.2, 130.7, 131.1, 133.5, 135.5, 144.0, 152.7, 174.8 ppm (due to the C_2 Symmetry we observed half-half the signal); HRMS (ESI) Calculated for $C_{44}H_{32}N_2O_6$ $(M+Na)^+$: 685.2339 found: 685.2337.



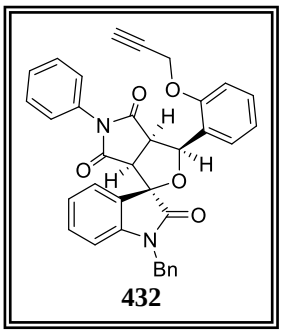
431

Synthesis of dimethyl 1'-benzyl-2'-oxo-5-(2-(prop-2-yn-1-yloxy)phenyl)-5*H*-spiro[furan-2,3'-indoline]-3,4-dicarboxylate (404a): To a mixture of spiro-indolooxirane (**269a**, 100 mg, 0.26 mmol) and dimethyl acetylenedicarboxylate (41 mg, 0.29 mmol) in dry toluene (5 mL) was stirred at reflux conditions for 32 h to afford product **404a** (90 mg, 66%) as a colorless liquid. R_f = 0.13 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 3282, 2952, 2123(w), 1723, 1611, 1259, 1022, 754. cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.52 (s, 1H, ≡CH), 3.48 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 4.63-4.74 (m, 3H, CH_2), 5.07 (d, *J* = 16 Hz, 1H, CH_2), 6.68 (d, *J* = 7.6 Hz, 1H, CH), 6.91 (s, 1H, ArH), 7.00-7.07 (m, 3H, ArH), 7.18-7.42 (m, 8H, ArH), 7.56 (d, *J* = 7.2 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.1, 52.4, 52.7, 56.1, 76.02, 78.4, 83.7, 89.5, 109.6, 112.1, 121.8, 123.2, 125.3, 126.2, 127.3, 127.4, 127.7, 128.2, 128.8, 130.1, 130.9, 135.5, 143.8, 147.3, 155.1, 161.0, 163.1, 173.8 2 ppm; HRMS (ESI) Calculated for $C_{31}H_{25}NO_7$ $(M+H)^+$: 524.1709 found: 524.1712.



404a

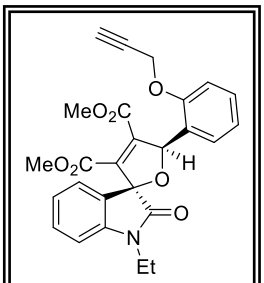
Synthesis of 1'-ethyl-5-phenyl-3-(2-(prop-2-yn-1-yloxy)phenyl)-3a,6a-dihydrospiro [furo [3,4-*c*]pyrrole-1,3'-indoline]-2',4,6(3*H*,5*H*)-trione (432): To a mixture of spiro-indolooxirane (**269a**, 100 mg, 0.26 mmol) and *N*-phenylmaleimide (50 mg, 0.30 mmol) in dry toluene (5 mL) was stirred at reflux conditions for 27 h to afford product **432** (94 mg, 65%) as a white solid. R_f = 0.13 (EtOAc/hexane = 1:4, v/v); mp 186-187 °C; IR (neat): ν_{max} 3289, 2923, 2125(w), 1714, 1614, 1339, 1267, 1006, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.55 (t, *J* = 2.4 Hz, 1H, ≡CH), 3.87 (d, *J* = 8 Hz, 1H, CH), 4.45 (t, *J* = 8.1 Hz, 1H, CH), 4.83-4.87 (m, 3H, CH_2), 4.98 (d, *J* = 15.6 Hz, 1H, CH_2), 6.54 (d, *J* = 8 Hz, 1H, ArH), 6.78 (d, *J* = 8 Hz, 1H, ArH), 6.99-7.12 (m, 5H, ArH), 7.24-7.41 (m, 11H, ArH), 7.47 (d, *J* = 7.6 Hz, 1H,



432

ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.8, 49.5, 52.0, 56.4, 75.7, 78.7, 83.9, 109.8, 111.6, 121.3, 123.1, 123.4, 125.1, 125.5, 126.1, 126.7, 127.3, 127.9, 128.6, 129.0, 129.2, 131.0, 131.6, 135.1, 143.4, 154.9, 172.9, 173.1, 175.8 ppm; HRMS (ESI) Calculated for $C_{31}H_{26}N_2O_5$ $(M+Na)^+$: 577.1739 found: 577.1734.

Synthesis of dimethyl 1'-ethyl-2'-oxo-5-(2-(prop-2-yn-1-yloxy)phenyl)-*5H*-spiro[furan-2,3'-indoline]-3,4-dicarboxylate (404b): A solution of 3-diazo-1-ethylindolin-2-one (**63b**, 100 mg, 0.53 mmol) in dry dichloroethane or toluene (4 mL) was added dropwise to a mixture of solution containing 2-[(prop-2-yn-1-yl)oxy]benzaldehyde (**428a**, 93 mg, 0.58 mmol), dimethyl acetylenedicarboxylate (83 mg, 0.58 mmol) and copper(I) thiophenecarboxylate (5 mg, 5 mol%) at reflux conditions for an hour to afford product **404b** (164 mg, 67%) as a colorless liquid.



404b

R_f = 0.09 (EtOAc/hexane = 1:4, v/v); IR (neat): ν_{max} 3281, 2923, 2123, 1720, 1610, 1257, 1018, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.33 (t, J = 7.2 Hz, 3H, CH_3), 2.57 (t, J = 2.4 Hz, 1H, ≡CH), 3.60 (s, 3H, CH_3), 3.71-3.78 (m, 1H, CH), 3.81 (s, 3H, CH_3), 3.84-3.93 (m, 1H, CH), 4.72 (ABqd, $\Delta\delta_{AB}$ = 0.06, J_1 = 15.8 Hz, J_2 = 2.3 Hz, 2H, CH_2), 6.88-6.91 (m, 2H, ArH), 7.07-7.13 (m, 3H, ArH), 7.37-7.45 (m, 3H, ArH), 7.58-7.60 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 12.3, 34.9, 52.3, 52.6, 56.1, 75.9, 78.4, 83.7, 89.5, 108.5, 112.1, 121.8, 122.9, 125.4, 126.3, 127.5, 128.2, 130.1, 130.8, 132.1, 143.7, 146.8, 155.1, 160.9, 163.1, 173.2 ppm; HRMS (ESI) Calculated for $C_{26}H_{23}NO_7$ $(M+Na)^+$: 484.1372 found: 484.1377.

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CONCLUSION

This thesis work investigates the catalytic reactions of diazoamides towards the synthesis of 3-functionalized oxindoles. The current study focuses on the synthesis of 3-substituted oxindoles, 3-alkylidene-3*H*-indoles, oxindole incorporating macrocycles and spiro-indoloheterocycles from diazocarbonyl compounds.

Chapter 1: Background

Reactions of metallo-carbenoids derived from diazocarbonyl compounds using Rh/Cu catalysts have been on the ascendancy and attracted the attention of many chemists for diverse synthetic applications. Lewis acid-catalyzed carbonyl compound reactions are capable and powerful synthetic methods for constructing a wide range of organic molecules. Due to the presence of an empty *p*-orbital, trivalent boron complex have long been utilized as Lewis acid catalysts. Many natural products having the core skeleton of oxindole ring system. Synthesis towards these heterocycles is of great interest due to wide applications in the pharmaceutical chemistry/drugs. Thus, it is a requirement to develop a method to synthesize these compounds having such skeleton.

Chapter 2: An unexpected synthesis of 3-alkylated oxindoles and spiro-indolooxiranes

Oxindole is a pharmacologically advantageous scaffold with numerous biological properties relevant to medicinal chemistry. Brief introduction about the reaction of diazocarbonyl compounds with enones was discussed. The present work on the $BF_3{\cdot}OEt_2$/CuI catalyzed synthesis of 3-alkylated oxindoles **195** and spiro-indolooxiranes **229** was discussed. The cleavage of C–C bonds has been one of the most difficult subjects in organic chemistry. The reactions of the C=C double bond have been reported involving a few metal-mediated (Cu, Fe, Ru or Pd) chemoselective

cleavage reactions. No reports are available for transition metal-free chemoselective cleavage of the C=C bond of α,β-enones.

A study of $BF_3{\cdot}OEt_2$ catalyzed reactions of diazoamides **63** and chalcones **184** was planned and performed. The reaction was optimized with various catalysts, solvents, temperature and time. Based on this study, 10 mol% $BF_3{\cdot}OEt_2$ in chloroform at 0 °C was found to be better conditioned in this transformation. The substrate scope for 3-alkylated oxindoles **195** was investigated with a range of diazoamides **63** and chalcones **184** under optimized reaction conditions. Reaction of 3-alkylated oxindoles **195** in the presence of Cu(I) and DMAP catalysts afforded the corresponding spiro-indolooxiranes **229** in a diastereoselective manner (Chart 1).

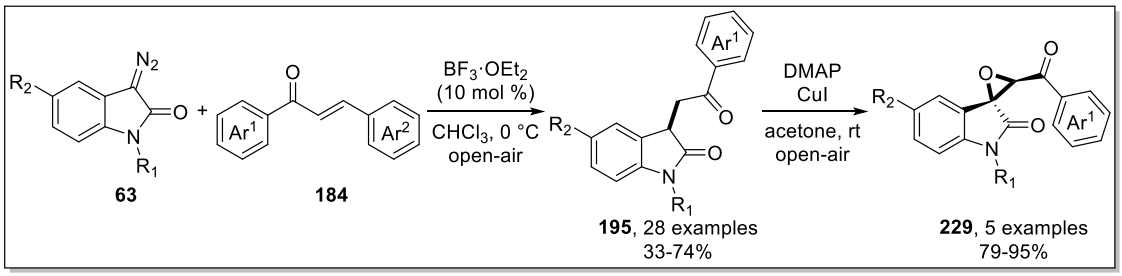

Chart 1

Chapter 3: Synthesis of substituted 3-aryloxindoles from diazoamides

3-Aryloxindoles are synthetically interesting as they found various applications in biology and pharmaceutical chemistry. Brief introduction about the reaction of diazocarbonyl compounds with aldehydes was depicted. Then, the present work on the $BF_3{\cdot}OEt_2$ catalyzed synthesis of 3-aryloxindoles **276/294** using diazoamides **63** and aryl aldehydes **220/271** was discussed in this chapter.

A study of $BF_3{\cdot}OEt_2$ catalyzed reactions of diazoamides **63** and aryl aldehydes **220/271** was carried out. The reaction was optimized with various catalysts, solvents, temperature and time. Based on this study, 20 mol% $BF_3{\cdot}OEt_2$ in DCM at 0 °C was

found to be better conditioned in this transformation. The substrate scope for 3-aryloxindoles **276/297** was investigated with a range of diazoamides **63** aryl aldehydes or unprotected salicylaldehydes **220/271** under optimized reaction conditions (Chart 2).

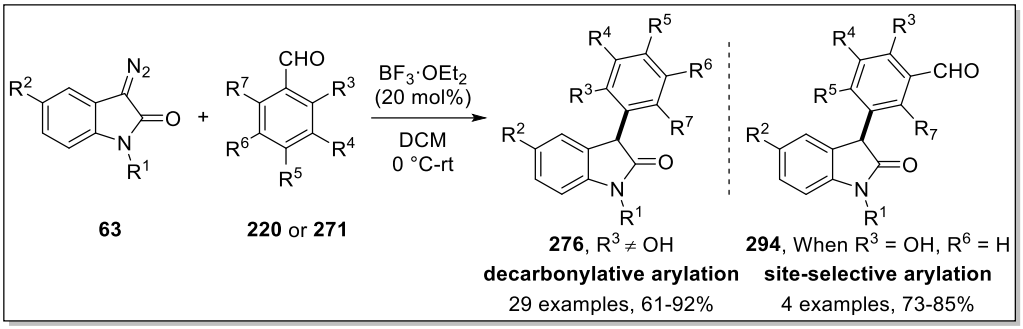

Chart 2

Chapter 4

4.1. $Rh_2(OAc)_4$-Catalyzed synthesis of 2,3′-biindoles

Indole and oxindole skeletons are present in a number of bioactive natural products and they could prove to be an appropriate starting material for further alkaloids synthesis. Brief introduction about the reaction of diazocarbonyl compounds with indoles was delineated. In continuation of our work on the reactions of diazoamides with indoles, the synthesis of 2,3′-biindoles as a mixture of tautomers using cyclic rhodium carbenoids was discussed.

Initially, a study of diazoamides **63** and 3-substituted indoles **104** was performed at room temperature in the presence of $Rh_2(OAc)_4$ as a catalyst to furnish 2,3′-biindoles **557** as a mixture of tautomers. The reaction was optimized with various catalysts, solvents, temperature and time. Based on this study, 2 mol% $Rh_2(OAc)_4$ in DCM at room temperature was found to be better conditioned in this transformation. The scope of products was explored based on the optimized reaction conditions (Chart 3).

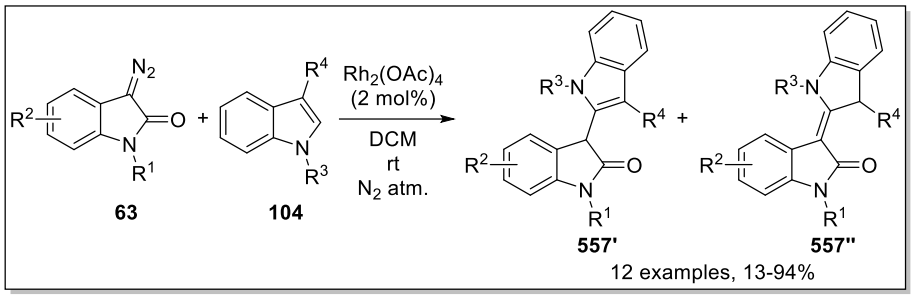

Chart 3

4.2. TfOH-Catalyzed synthesis of indole incorporated macrocycles

Macrocycles are essential organic compounds in supramolecular chemistry because they contain cavities that can be totally occupied by guest molecules and could be chemically changed to fine-tune their features. The synthesis and research of macrocycles are remarkable in organic chemistry due to their biological and ion-selective features, and also their applicability in the perfume business. The synthesis of indole incorporated macrocycles **361** was discussed in Chapter 4.2

A study of the TfOH catalyzed reactions of indole tethered on diazoamides **360** was planned and performed. The reaction was optimized with various catalysts, solvents, temperature and time. Based on the optimization study, 20 mol% TfOH in DCM at room temperature was found to be better conditioned in this transformation. The range of various ring size of macrocycles **361** was synthesized based on the optimized reaction conditions (Chart 4).

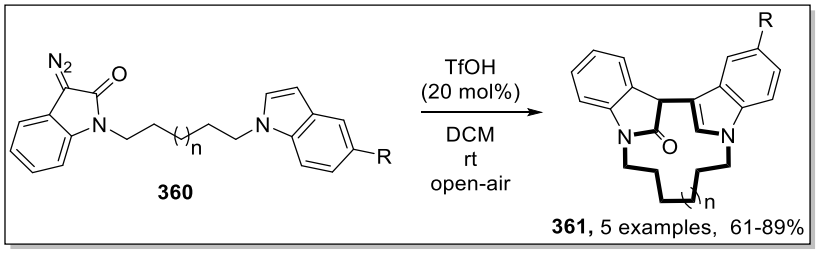

Chart 4

Chapter 5: $AlCl_3$-Catalyzed reactions of diazoamides towards 3-alkylidene-3*H*-indoles

3*H*-Indole is a critical structural unit for gaining access to a variety of natural products and biologically active compounds. The methods for synthesizing 3*H*-indole described in the literature were discussed. The current study on the $AlCl_3$ catalyzed reactions of diazoamides **63**, nitrosobenzenes **367**, and propargylic alcohols **138** towards 3-alkylidene-3*H*-indoles **364** was covered in this chapter.

$AlCl_3$ catalyzed multi-component reactions of diazoamidess **63**, nitrosobenzenes **367** and propargylic alcohols **138** were performed under various reaction conditions. The reaction conditions were optimized for the formation of 3-alkylidene-3*H*-indoles **364**. 3-Alkylidene-3*H*-indoles **364** were also achieved from direct $Rh_2(OAc)_4$-catalyzed a chemoselective deoxygenation of 3-alkylidene-3*H*-indole-*N*-oxides **369**. The synthesis of 3-alkylidene-3*H*-indoles involves the use of oxindole-nitrone intermediates (Chart 5).

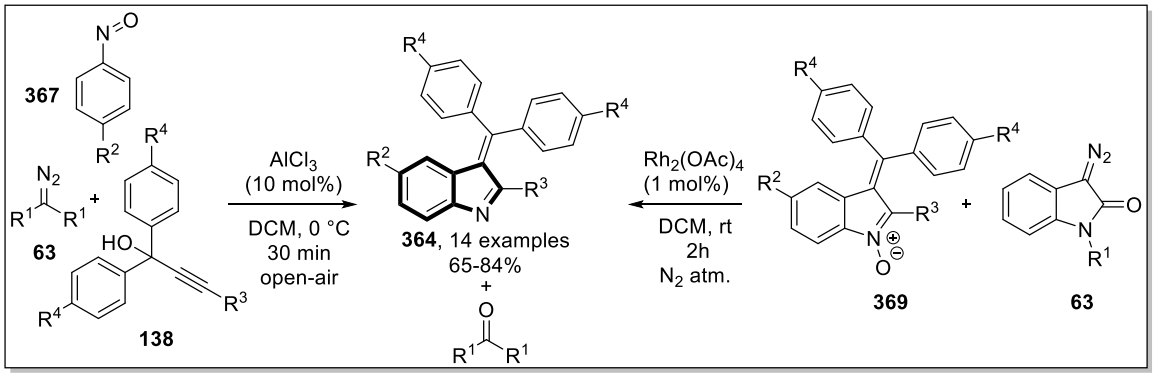

Chart 5

Chapter 6: Copper-catalyzed synthesis of spiroindolofurobenzopyrans

Spiro-oxindoles have become a privileged motif given their broad and auspicious activities in many therapeutic areas, potential as synthetic building blocks, existence as natural products and use in clinical pharmaceuticals. Brief introduction about the reaction of carbonyl ylides derived from diazocarbonyl compounds was discussed. The

diatereoselective synthesis of spiro-indolofurobenzopyrans **429** from diazoamides **63** and *O*-propargyl salicylaldehydes **428** in the presence of (Cu(I)TC) as a catalyst and involving carbonyl ylides in a tandem manner was achieved.

A study of the reactions between diazoamides **63** and *O*-propargyl salicylaldehydes **428** was planned and performed. The reaction was optimized with various catalysts, solvents, rate of addition of diazoamide **63**, temperature and time. The optimized conditions suggested that the reactions at room temperature gave a kinetically controlled product as spiro-indolooxirane **269** while the reactions under reflux conditions gave a thermodynamically controlled product as spiro-indolofurobenzopyran **429**. The reaction conditions were optimized to synthesize spiro-indolooxiranes **269** and spiro-indolofurobenzopyrans **429**. The generation of intermolecular carbonyl ylides followed by intramolecular 1,3-dipolar cycloaddition with external alkynes was involved in this chapter (Chart 6).

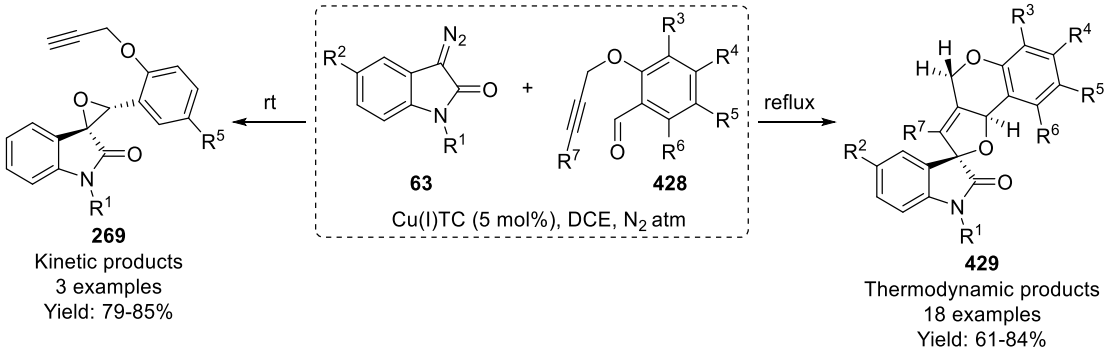

Chart 6

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APPENDIX

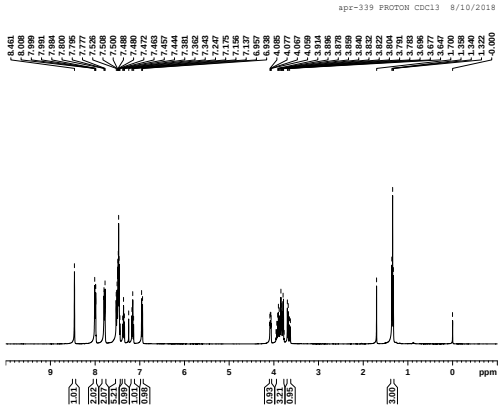

Figure 36. ^{1}H NMR spectrum of compound **195z**

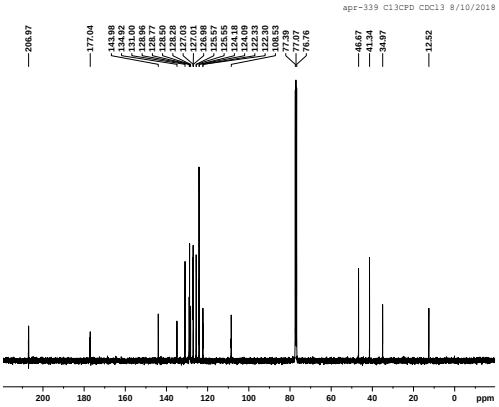

Figure 37. ^{13}C NMR spectrum of compound **195z**

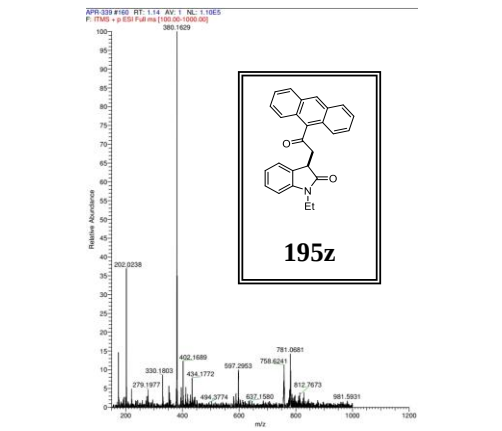

Figure 38. HRMS spectrum of compound **195z**

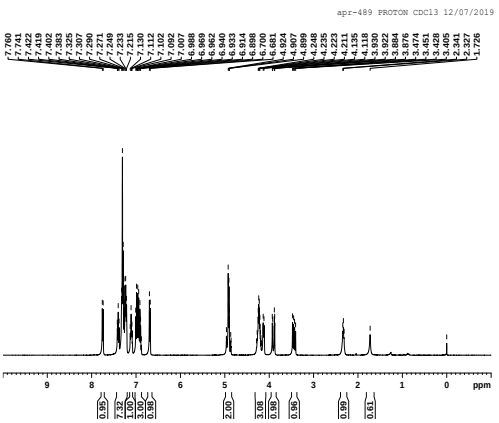

Figure 39. ^{1}H NMR spectrum of compound **240a**

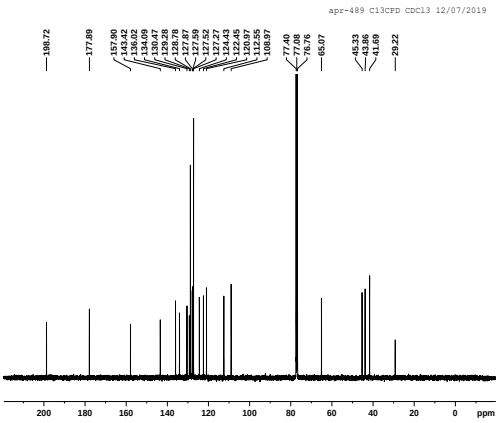

Figure 40. ^{13}C NMR spectrum of compound **240a**

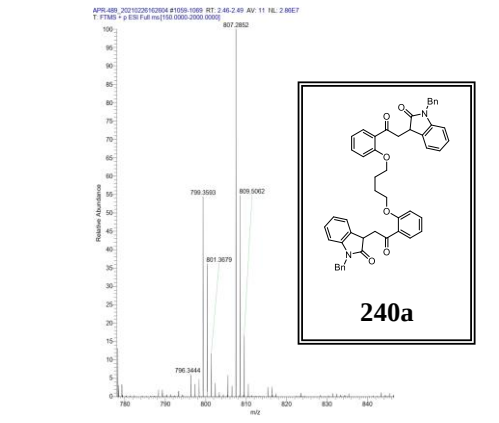

Figure 41. HRMS spectrum of compound **240a**

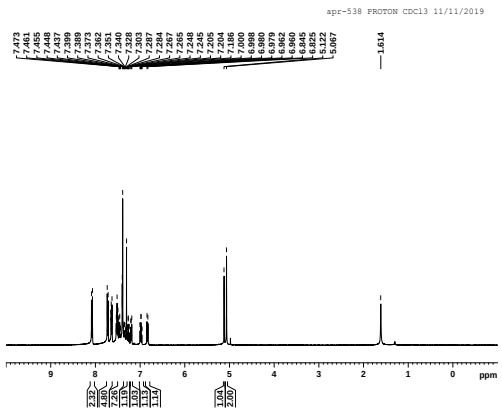

Figure 42. ^{1}H NMR spectrum of compound **229c**

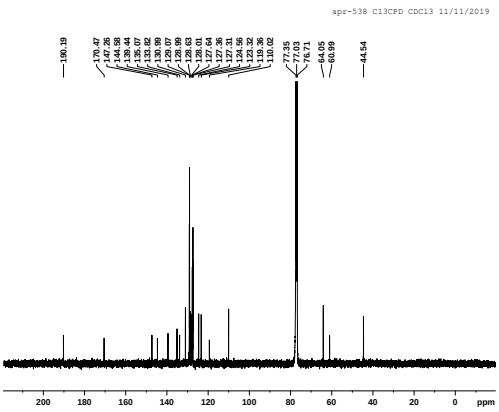

Figure 43. ^{13}C NMR spectrum of compound **229c**

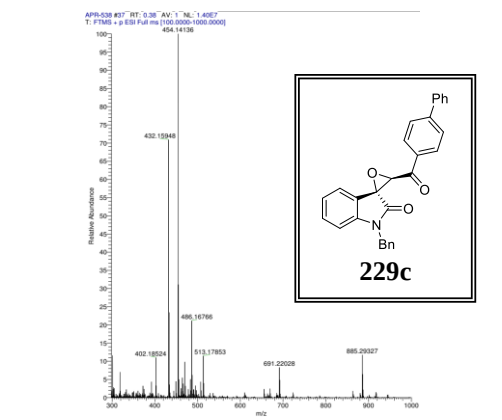

Figure 44. HRMS spectrum of compound **229c**

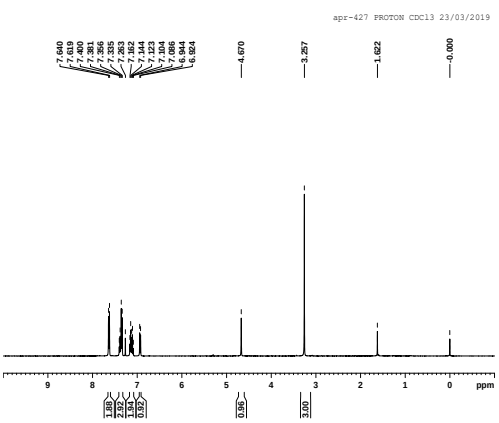

Figure 45. ^{1}H NMR spectrum of compound **276aa**

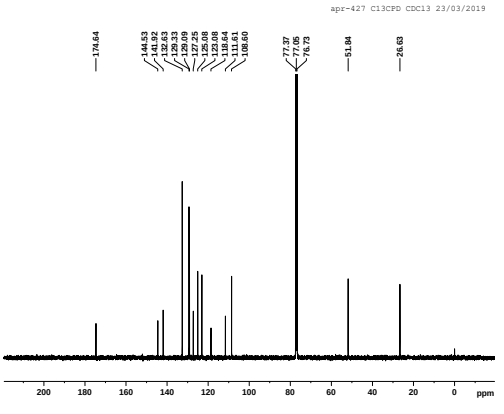

Figure 46. ^{13}C NMR spectrum of compound **276aa**

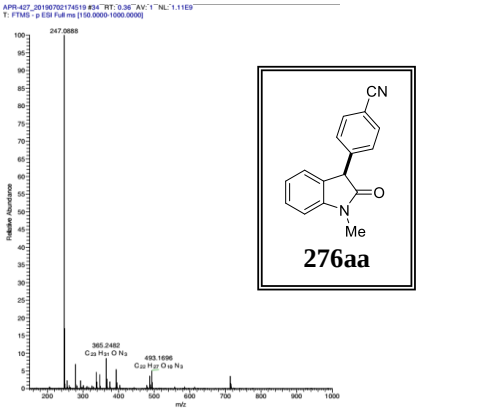

Figure 47. HRMS spectrum of compound **276aa**

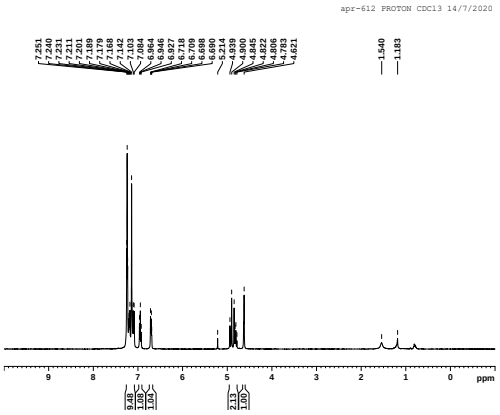

Figure 48. ^{1}H NMR spectrum of compound **293a**

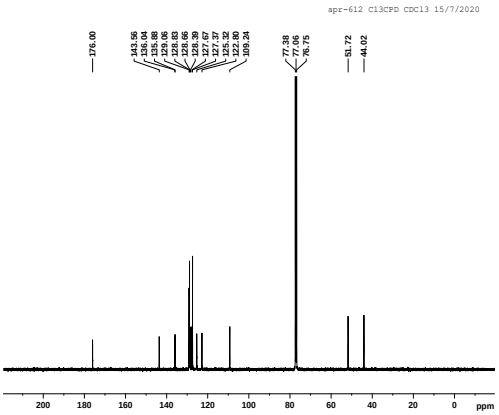

Figure 49. ^{13}C NMR spectrum of compound **293a**

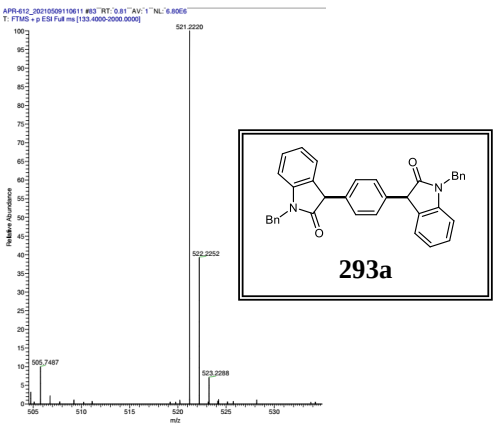

Figure 50. HRMS spectrum of compound **293a**

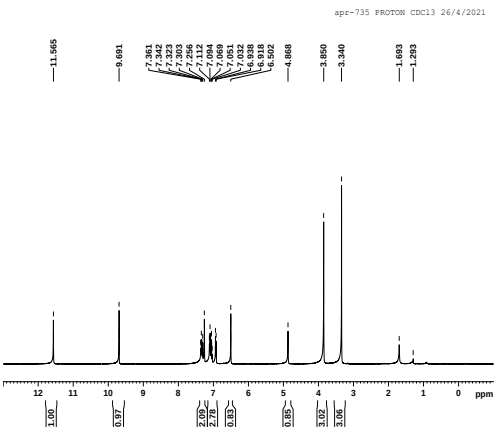

Figure 51. ^{1}H NMR spectrum of compound **294c**

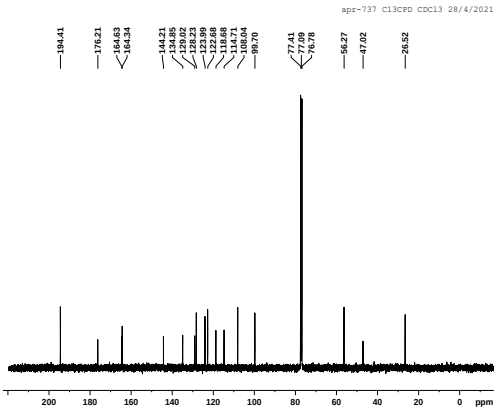

Figure 52. ^{13}C NMR spectrum of compound **294c**

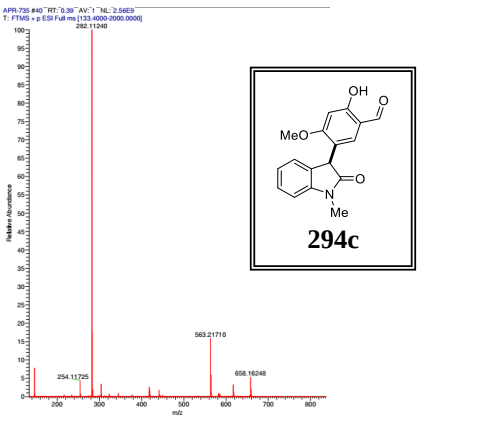

Figure 53. HRMS spectrum of compound **294c**

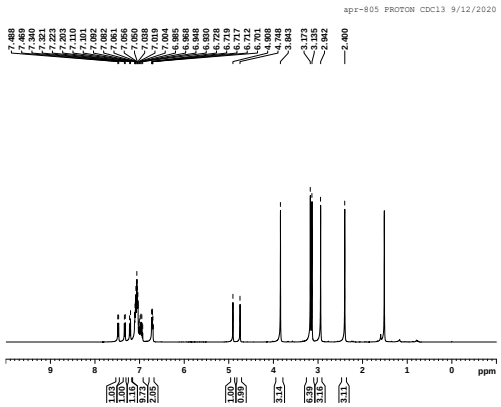

Figure 54. ^{1}H NMR spectrum of compound **357h**

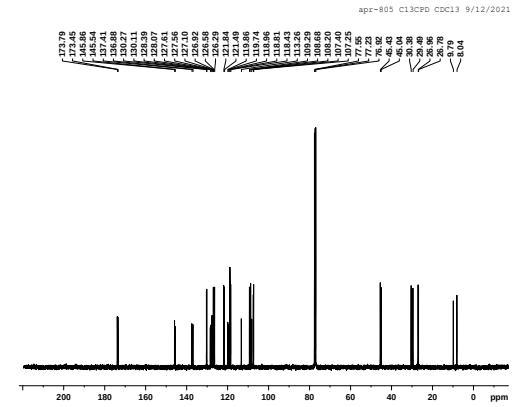

Figure 55. ^{13}C NMR spectrum of compound **357h**

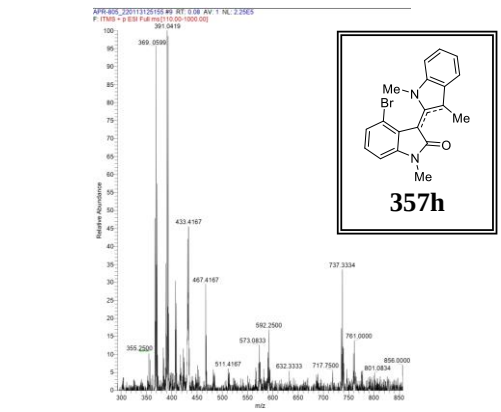

Figure 56. ^{1}H NMR spectrum of compound **357h**

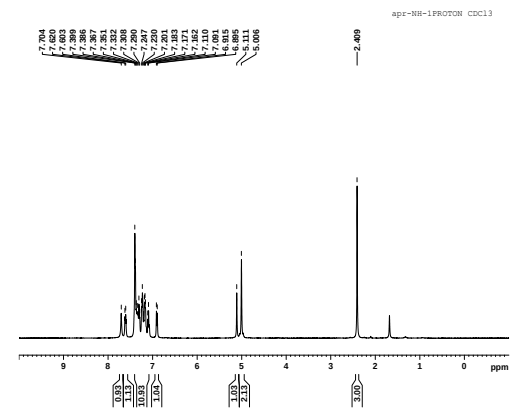

Figure 57. ^{1}H NMR spectrum of compound **357j'**

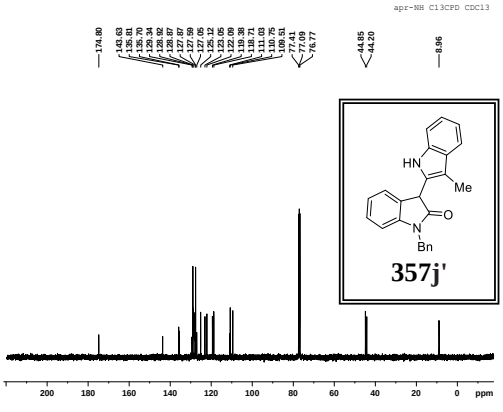

Figure 58. ^{13}C NMR spectrum of compound **357J'**

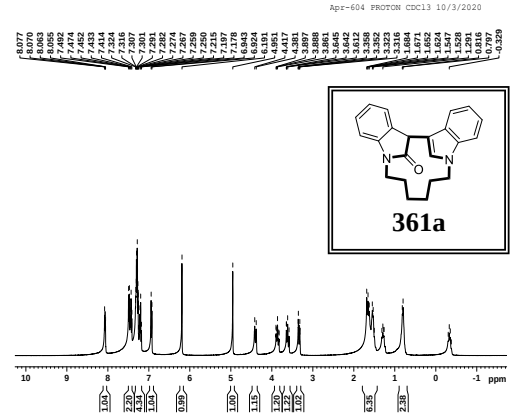

Figure 59. ^{1}H NMR spectrum of compound **361a**

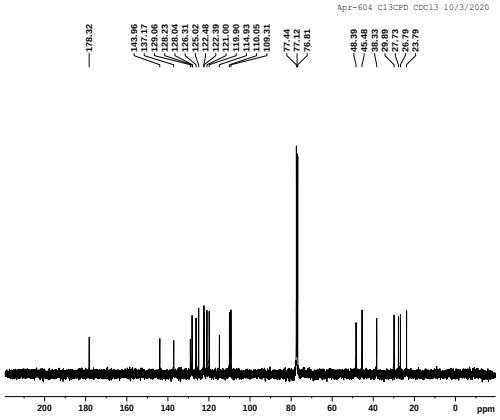

Figure 60. ^{13}C NMR spectrum of compound **361a**

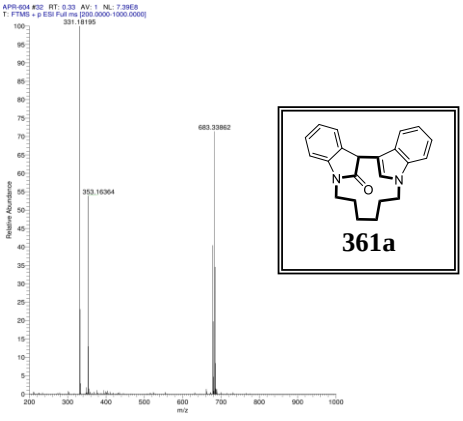

Figure 61. HRMS spectrum of compound **361a**

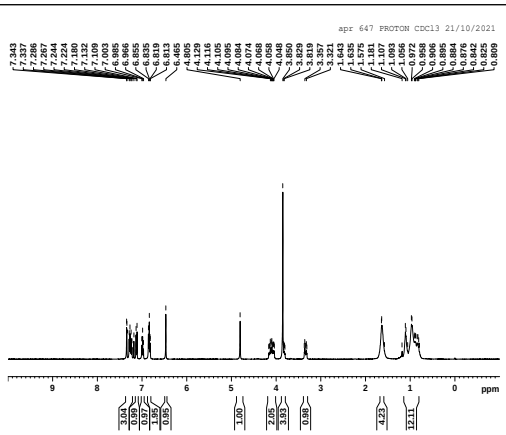

Figure 62. ^{1}H NMR spectrum of compound **361d**

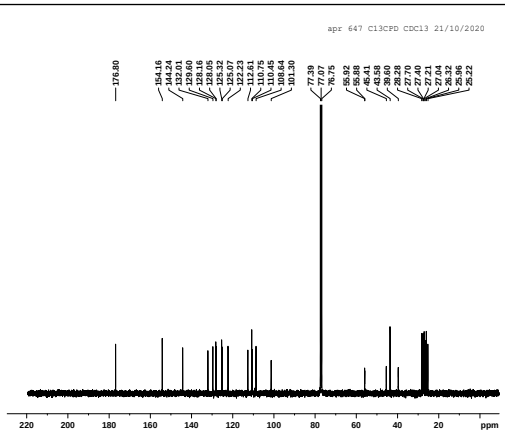

Figure 63. ^{13}C NMR spectrum of compound **361d**

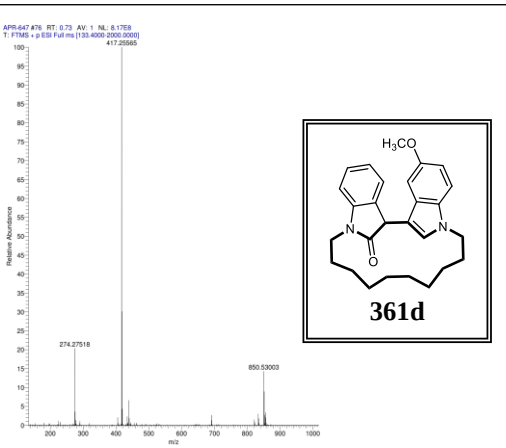

Figure 64. HRMS spectrum of compound **361d**

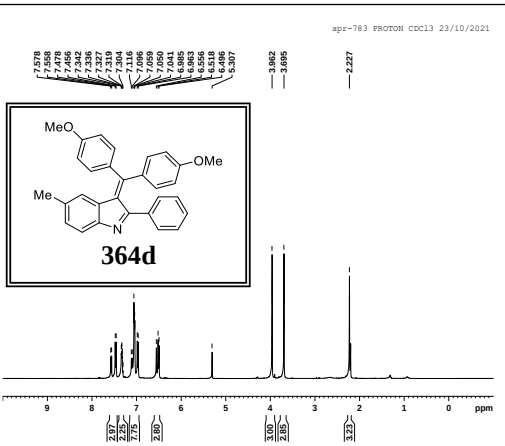

Figure 65. ^{1}H NMR spectrum of compound **364d**

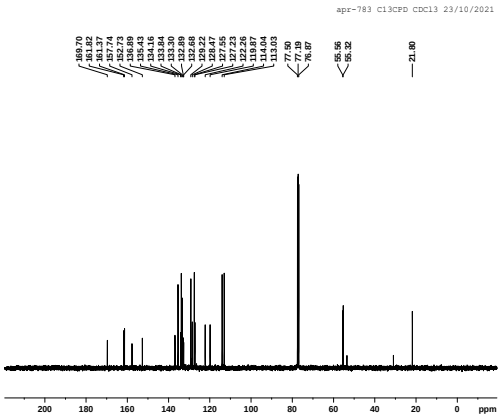

Figure 66. ^{13}C NMR spectrum of compound **364d**

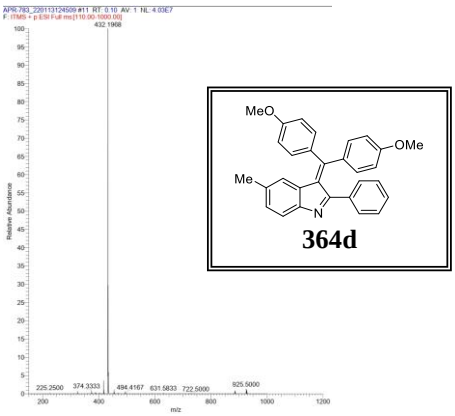

Figure 67. HRMS spectrum of compound **364d**

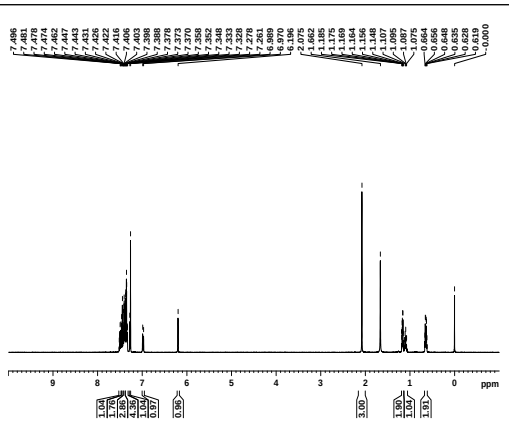

Figure 68. ^{1}H NMR spectrum of compound **364f**

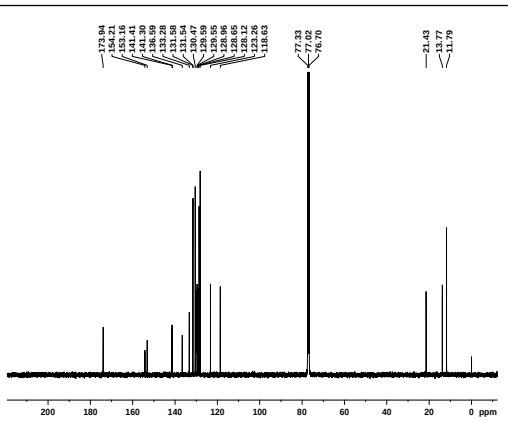

Figure 69. ^{13}C NMR spectrum of compound **364f**

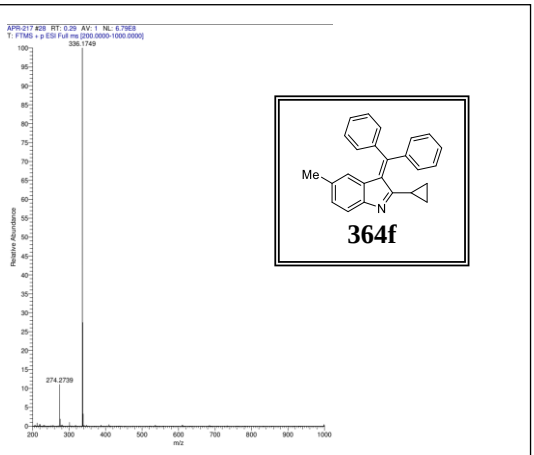

Figure 70. HRMS spectrum of compound **364f**

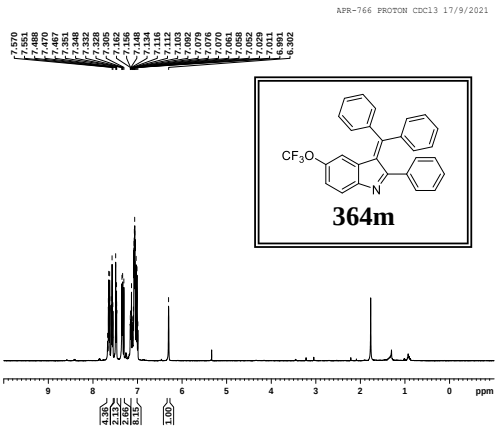

Figure 71. ^{1}H NMR spectrum of compound **364m**

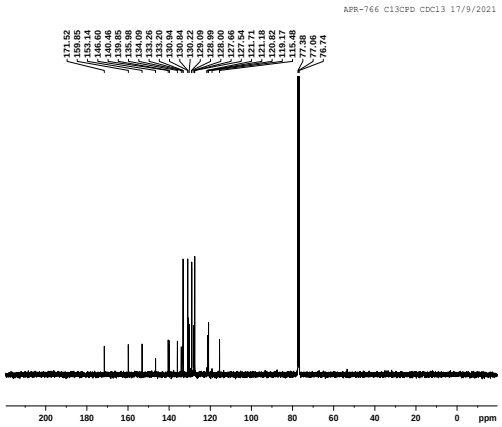

Figure 72. ^{13}C NMR spectrum of compound **364m**

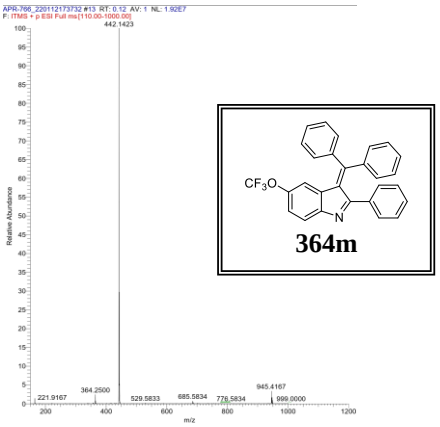

Figure 73. HRMS spectrum of compound **364m**

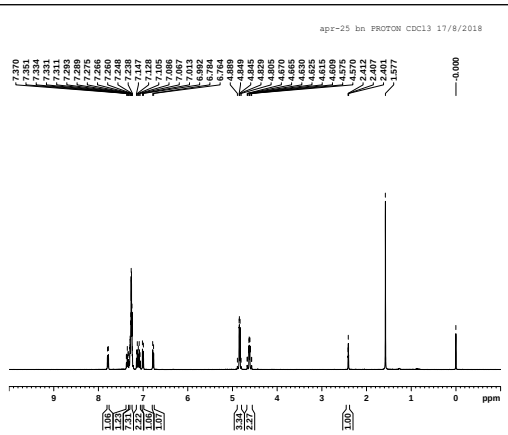

Figure 74. ^{1}H NMR spectrum of compound **269a**

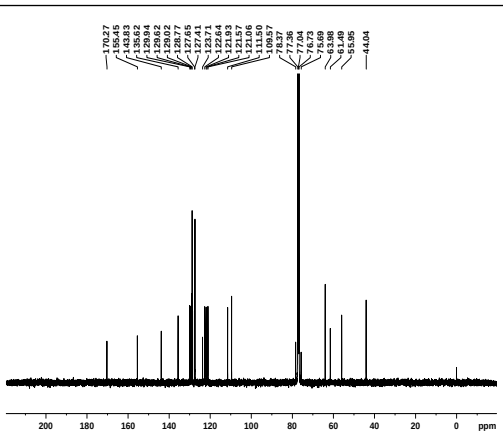

Figure 75. ^{13}C NMR spectrum of compound **269a**

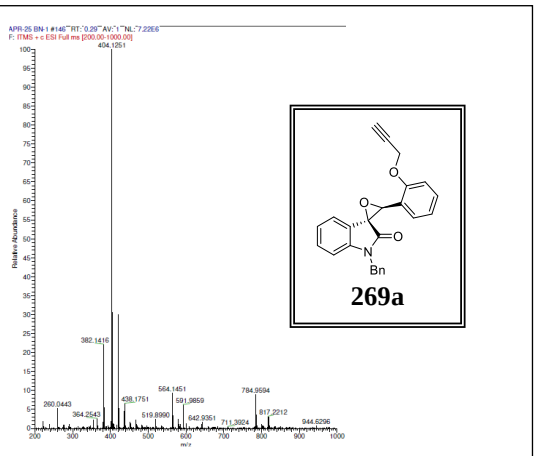

Figure 76. HRMS spectrum of compound **269a**

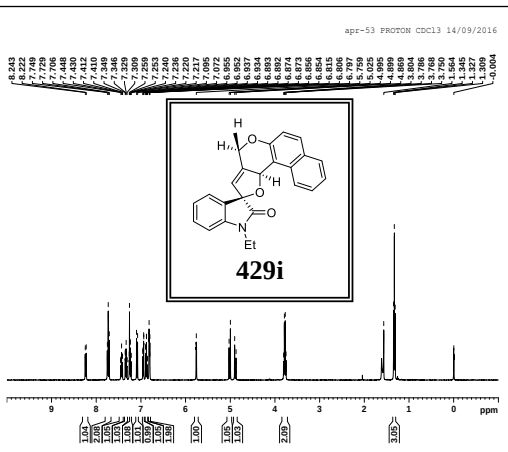

Figure 77. ^{1}H NMR spectrum of compound **429i**

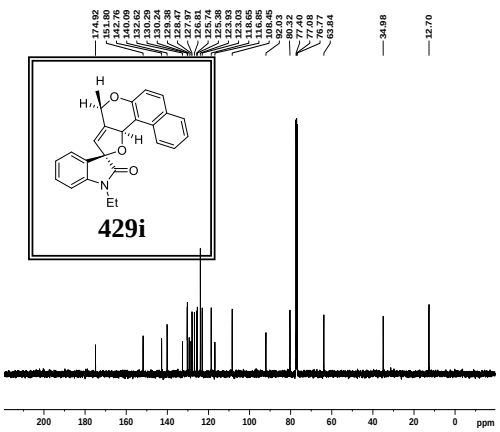

Figure 78. ^{13}C NMR spectrum of compound **429i**

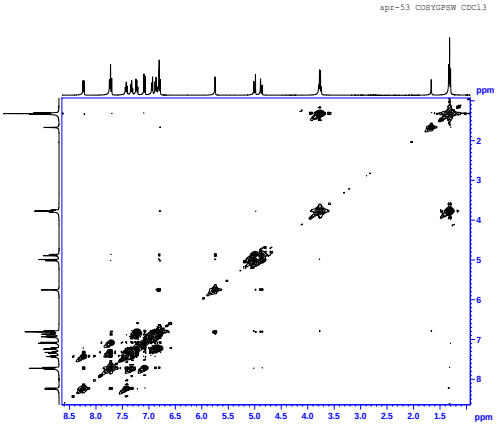

Figure 79. COSY spectrum of compound **429i**

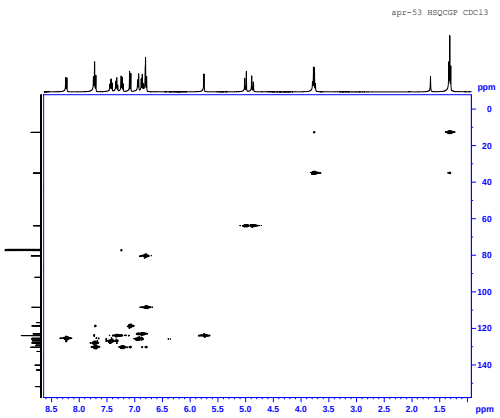

Figure 80. HSQC spectrum of compound **429i**

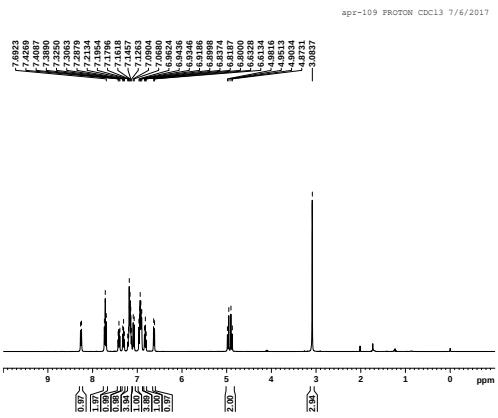

Figure 81. ^{1}H NMR spectrum of compound **429m**

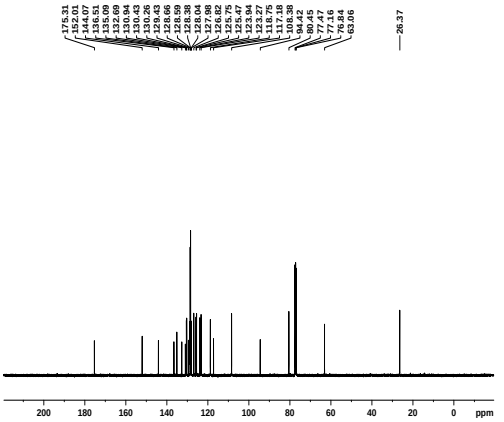

Figure 82. ^{13}C NMR spectrum of compound **429m**

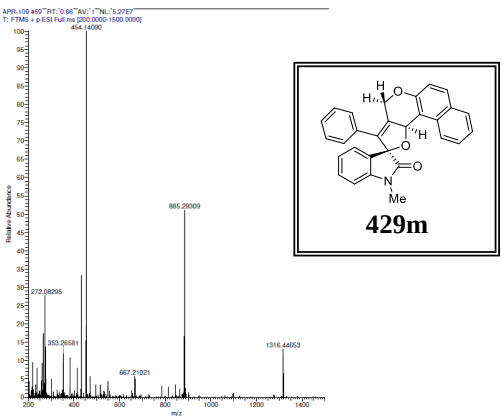

Figure 83. HRMS spectrum of compound **429m**

PUBLICATIONS & CONFERENCES

The part of the results obtained in the present thesis work has been published in the following international journals and presented in the conferences.

List of Publications

1. Muthusamy, S.; **Prabu, A.**; Suresh, E. "Copper-catalyzed synthesis of spiroindolofurobenzopyrans**:** tandem reactions of diazoamides and *O*-propargyl salicylaldehydes" *Org. Biomol. Chem.* **2019**, *17*, 8088–8093.
2. Muthusamy, S.; **Prabu, A.** "$BF_3{\cdot}OEt_2$-Catalyzed chemoselective C=C bond cleavage of α,β-enones: an unexpected synthesis of 3-alkylated oxindoles and spiro-indolooxiranes" *Org. Biomol. Chem.* **2022**, *20*, 558–564.
3. Muthusamy, S.; **Prabu, A.** "$BF_3{\cdot}OEt_2$-Catalyzed decarbonylative arylation/C–H functionalization of diazoamides with arylaldehydes: synthesis of substituted 3-aryloxindoles: synthesis of substituted 3-aryloxindoles" *Org. Biomol. Chem.,* **2022**, *20*, 2209–2216.
4. Muthusamy, S.; **Prabu, A.**; Balasubramani, A. "$AlCl_3$-Catalyzed reactions of 3-diazooxindoles, nitrosobenzenes and propargylic alcohols towards 3-alkylidene-3*H*-indoles" (manuscript under preparation).
5. Muthusamy, S.; **Prabu, A.** "$Rh_2(OAc)_4$-Catalyzed synthesis of 2,3′-biindoles" (manuscript under preparation).
6. Muthusamy, S.; **Prabu, A**. "TfOH-Catalyzed synthesis of indole incorporated macrocycles" (work under process).

Presentation in Conferences

1. 1. S. Muthusamy and **A. Prabu** "*Synthesis of spiro-indolofuropyrans: Copper-catalyzed tandem reaction of diazoamides and o-propargylated aldehydes*" Poster Presentation in 21st held at CSIR-National Symposium in Chemistry-2017, Hyderabad during July 14-16, 2017.
2. S. Muthusamy and **A. Prabu** "*Energy efficient synthesis of spiro-indolofuropyrans"* Poster Presentation in International Conference on Sustainable Energy Technologies (i-SET-2018), held at Bharathidasan University, Tiruchirappalli during June 27-28, 2018.
3. S. Muthusamy and **A. Prabu** "*$BF_3{\cdot}OEt_2$-Catalyzed synthesis of 3-alkylated oxindoles from diazoamides and chalcones"* Poster Presentation in 24th CRSI National Symposium in Chemistry (CRSI-CLRI), held at Triple Helix Auditorium, Chennai during February 8-10, 2019.

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Copper-catalyzed synthesis of spiro-indolofurobenzopyrans: tandem reactions of diazoamides and *O*-propargyl salicylaldehydes†

Sengodagounder Muthusamy, *[a] Ammasi Prabu [a] and Eringathodi Suresh [b]

An atom-economical synthesis of spiro-indolofurobenzopyrans was developed from diazoamides and *O*-propargyl salicylaldehydes in the presence of copper(I) thiophene-2-carboxylate in a diastereoselective manner. This methodology involves the preparation of carbonyl ylide intermediates followed by 1,3-dipolar cycloaddition with internal/external alkynes, offering a great potential for constructing biologically significant spiro-indolofurobenzopyrans, as thermodynamically controlled products, in a tandem manner.

Spiro-oxindoles have become a privileged motif given their broad and auspicious activities in many therapeutic areas, potential as synthetic building blocks, existence as natural products,[1] and use in clinical pharmaceuticals.[2] A few bioactive spiro-oxindoles, for example, the HepG2 inhibitor[3] and an anti-cancer agent,[4] are shown in Fig. 1. Moreover, furobenzopyran, the fused heterocycle, is also a key structural motif of many natural products, for example, furobinordenatin,[5] siccanin,[6] and pterocarpans[7] (Fig. 1), and has been reported to exhibit a wide range of biological activities, including antibacterial,[8] antifungal,[8] antiinflammatory,[9] anti-HIV,[10] antiviral,[11] antitoxin,[11] and antisnake venom.[11] However, there are few methods[12] available for the synthesis of the furobenzopyran moiety and these involve the use of stoichiometric quantities of combined reagents, multi-step synthesis, and low temperature. Therefore, it remains a challenging, but a very striking task to find more economical and simple methods with a wider substrate scope for the preparation of furobenzopyrans.

Diazocarbonyl compounds have many applications in organic chemistry.[13] Carbonyl ylides derived from diazocarbonyl compounds are important intermediates for heterocycles and natural products.[14] However, carbonyl ylides, generated *via* an intermolecular manner, are always considered to be synthetically unsatisfactory compared to their intramolecular counterparts because of their low selectivity and competitive reactions.[14] In continuation of our interest[15] on the chemistry of carbonyl ylides, we herein report the diatereoselective synthesis of spiro-indolofurobenzopyrans from diazoamides and *O*-propargyl salicylaldehydes in the presence of copper(I) thiophenecarboxylate (Cu(I)TC) as a catalyst and involving carbonyl ylides in a tandem manner.

The required diazoamides **1** and *O*-propargyl salicylaldehydes **2** were synthesized according to the literature.[16,17] Investigation of the reaction was planned involving the slow addition of diazoamide **1a** in order to control its concentration based on our earlier studies.[18] To begin our investigation, the reactions of diazoamide **1a** and *O*-propargyl salicylaldehyde **2a** as model substrates in the presence of several catalysts were examined. To the refluxed solution containing salicylaldehyde **2a** and a catalytic amount of rhodium(II) acetate under a nitro-

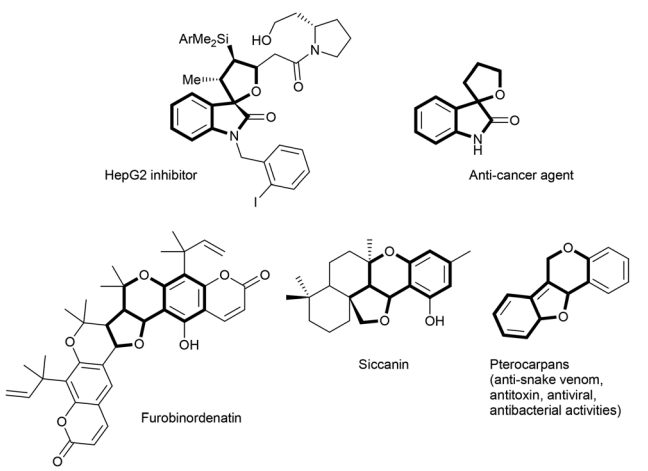

Fig. 1 Selected examples of biologically important natural products bearing spiro-indolofurans and a furobenzopyran moiety.

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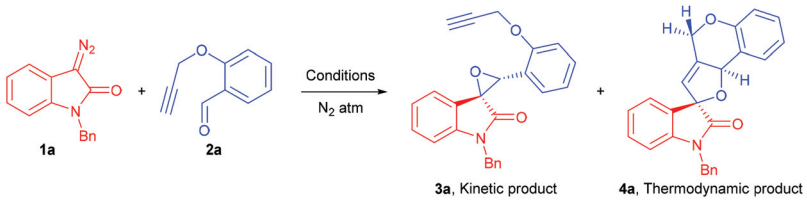
†Electronic supplementary information (ESI) available. CCDC 1580080. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob01275c

gen atmosphere, diazoamide **1a** was added with a slow rate of addition (5 mL h^{-1}) using a syringe pump in dichloroethane (DCE) to afford an isomeric mixture of spiro-indolooxirane[19] **3a** and an interesting spiro-indolofurobenzopyran **4a** (Table 1, entry 1), based on the spectral studies. In order to optimize the reaction conditions, various copper catalysts, such as CuI, $Cu(acac)_2$, $Cu(CH_3CN)_4PF_6$, or CuOTf, were examined; however, no superior results were obtained (Table 1, entries 2–5). Treatment with $CuSO_4{\cdot}5H_2O$ was also found to be ineffective (Table 1, entry 6). To our delight, Cu(I)TC enhanced the yield of product **4a** with a trace amount of **3a** (Table 1, entry 7). Lewis acid catalysts, such as $Sc(OTf)_3$ or $Zn(OTf)_2$, were not suitable for this transformation (Table 1, entries 8 and 9). Among the copper catalysts, Cu(I)TC was found to be better and the use of common organic solvents, such as benzene, toluene, acetonitrile, or dioxane, did not improve the yield of product **4a** (Table 1, entries 10–13). The reaction was carried out at room temperature with the rate of addition of 5 mL h^{-1} to afford the spiro-indolooxirane[19] **3a** in 85% yield (Table 1, entry 14). A similar reaction without the controlled addition of diazoamide **1a** afforded the spiro-indolooxirane **3a** in 85% yield (Table 1, entry 15). A quick addition of diazoamide **1a** to the solution of salicylaldhyde **2a** under reflux conditions afforded a mixture of products **3a**/**4a** in 55% and 10% yields (Table 1, entry 16). The reaction of diazoamide **1a** with the rate of addition of 2 mL h^{-1} using a syringe pump was performed in the presence of 5 mol% of copper(I) thiophenecarboxylate to afford a mixture of products **3a**/**4a** in 10% and 58% yields (Table 1, entry 17). The yield of spiro-indolofurobenzopyran **4a** was improved when the rate of addition of diazoamide **1a** was reduced to 0.5 mL h^{-1} (Table 1, entries 18 and 19). However, a similar reaction at room temperature gave an 83% yield of **3a** (Table 1, entry 20). No reaction took place in the absence of any catalyst (Table 1, entry 21). The experiments suggested that the reactions at room temperature gave a kinetically controlled product as spiro-indolooxirane **3a** (entry 15), while the reactions under reflux conditions gave a thermodynamically controlled product as spiro-indolofurobenzopyran **4a** (**4a** has a lower energy[20] than **3a** based on MM2 minimum energy calculations). Thus, the optimized reaction conditions for the formation of the thermodynamically controlled product **4a** were found to be 5 mol% of Cu(I)TC in dichloroethane under reflux conditions, as indicated in Table 1, entry 19, in a diastereoselective manner.

The generality and scope of this one-pot protocol for accessing the spiro-indolofurobenzopyran ring system were investigated. Under the optimized reaction conditions, the feasibility of this reaction with a diversity of substrates was explored. Various substituted *O*-propargyl salicylaldehydes were subjected to the optimized reaction conditions to obtain the

Table 1 Optimization of the reaction conditions for the formation of **3a** and **4a**[a]

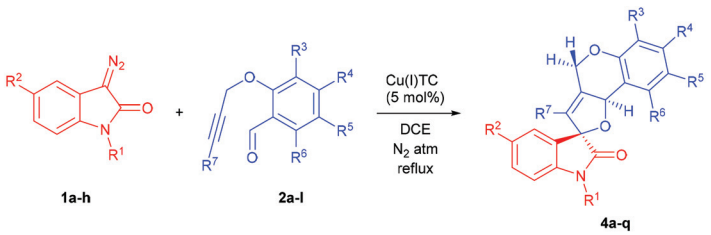


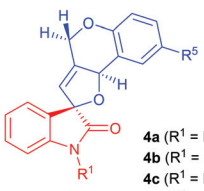
Entry	Catalyst	Solvent	Rate of addition **1a** (mL h^{-1})	*t* (h)	Yield[b] (%) **3a**/**4a**
1	$Rh_2(OAc)_4$	DCE	5	1	31/25
2	CuI	DCE	5	1	Trace/13
3	$Cu(acac)_2$	DCE	5	1	Trace/34
4	$Cu(CH_3CN)_4PF_6$	DCE	5	1	Trace/40
5	CuOTf	DCE	5	1	Trace/26
6	$CuSO_4{\cdot}5H_2O$	DCE	5	1	n.r[c]
7	Cu(I)TC	DCE	5	1	Trace/53
8	$Sc(OTf)_3$	DCE	5	1	n.r[c]
9	$Zn(OTf)_2$	DCE	5	1	n.r[c]
10	Cu(I)TC	Benzene	5	1	Trace/23
11	Cu(I)TC	Toluene	5	1	Trace/47
12	Cu(I)TC	Acetonitrile	5	1	Trace/38
13	Cu(I)TC	Dioxane	5	1	Trace/55
14	Cu(I)TC	CH_2Cl_2[d]	5	1	83/0
15	Cu(I)TC	CH_2Cl_2[d]	—	1	85/0
16	Cu(I)TC	DCE	—	1	55/10
17	Cu(I)TC	DCE	2	2	10/58
18	Cu(I)TC	DCE	1	4	0/71
19	**Cu(I)TC**	**DCE**	**0.5**	**8**	**0/84**
20	Cu(I)TC	CH_2Cl_2[d]	0.5	8	83/0
21	—	DCE	0.5	20	n.r

[a] Reaction conditions: **1a** (0.53 mmol, 1 equiv.) was dissolved in 4 mL of dry solvent, *O*-propargyl salicylaldehyde **2a** (0.59 mmol, 1.1 equiv.), catalyst (5 mol%), and refluxed under a nitrogen atmosphere. [b] Isolated product. [c] No reaction. [d] Reaction carried out at room temperature.

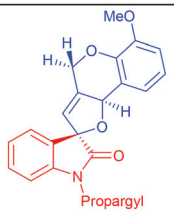
corresponding spiro-indolofurobenzopyrans **4**, and the results are described in Table 2. Chloro-substituted salicylaldehyde provided the desired products **4b,c** in moderate yields. Bromo-substituted salicylaldehyde was also tolerated to furnish the desired product **4d** in 61% yield. A moderate yield of product **4e** was obtained with the use of salicyladehyde having an electron-withdrawing nitro-substituent. Similarly, an electron-donating methoxy group on salicylaldehyde in the presence of 5 mol% of Cu(I)TC also underwent a reaction to yield the desired products **4f,g** in moderate yields. The reaction utilizing a naphthalene system also gave the corresponding spiro-indolofuronapthopyrans **4h–j** in 76–83% yields. Interestingly, the diiodo-substituted salicylaldehyde afforded the desired products **4k** and **4l** in good yields. It is noteworthy to mention that halide substituted spiro-indolofurobenzopyrans are very attractive for further synthetic transformations through cross-coupling reactions. Significantly, the stereochemistry of the product **4** was established based on the representative single-crystal X-ray[21] analysis of spiro-indolofuronapthopyran **4i** (CCDC 1580080†), where a unit cell contains two asymmetric units. Its solid-state arrangement showed[20] the presence of three C–H–π and five intermolecular hydrogen bonding C–H···O interactions. The reaction was also performed with salicylaldehyde having an internal alkyne group to provide the corresponding substituted spiro-indolofurobenzopyran **4m** in an 84% yield. The substituent variation on the aromatic ring attached to an alkyne group was also well-tolerated to give the desired spiro-indolofurobenzopyrans **4n–q** in good yields

Table 2 Synthesis of the thermodynamically controlled product, spiro-indolofurobenzopyrans **4**[a]

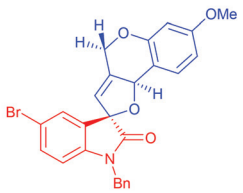




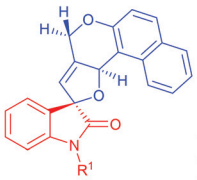
4a (R^1 = Bn, R^5 = H, 8h,84%)
4b (R^1 = Et, R^5 = Cl, 8h, 72%)
4c (R^1 = Bn, R^5 = Cl, 8.5h, 69%)
4d (R^1 = Pr, R^5 = Br, 8.5h, 61%)
4e (R^1 = Bn, R^5 = NO_2, 9h, 71%)



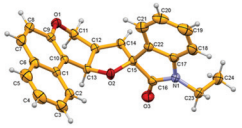
4f, 8h, 65%



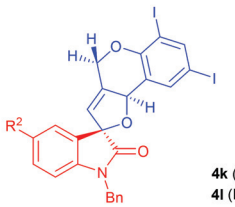
4g, 8.5h, 70%



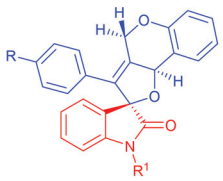
4h (R^1 = Me, 8.5h, 83%)
4i (R^1 = Et, 8.h 81%)
4j (R^1 = Bn, 8h, 76%)



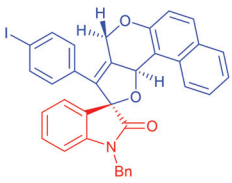
X-ray of **4i**



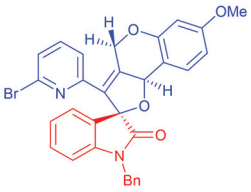
4k (R^2 = H, 8.5h, 75%)
4l (R^2 = Cl, 8.5h, 81%)



4m (R^1= Me, R = H, 9h, 84%)
4n (R^1 = Bn, R = NO_2, 8h, 81%)
4o (R^1= H, R = NO_2, 8.5h,78%)



4p, 8.5h,83%



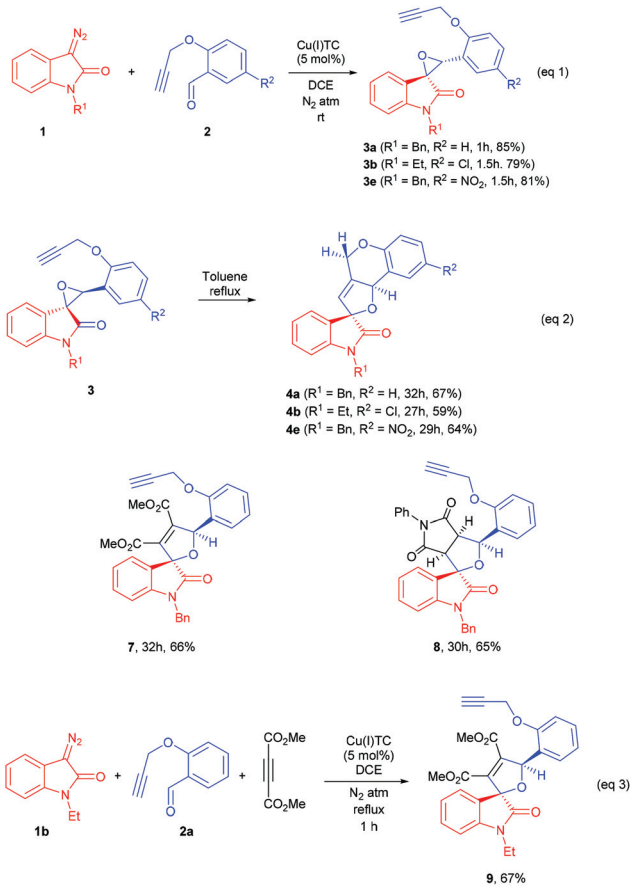
4q, 8.5h, 82%

[a] Conditions: To the mixture containing **2** (1.1 equiv.) and Cu(I)TC (5 mol%) in 5 mL of dry dichloroethane under a nitrogen atmosphere, **1** (1 equiv.) in 4 mL of dry dichloroethane was added using a syringe pump with the flow rate of 0.5 ml h^{-1} under reflux conditions.

(Table 2). There was no effect for the substituent located on the amide nitrogen of the diazoamide. Moreover, the unsubstituted diazoamide also smoothly yielded the expected product **4o** in good yield.

The scope of this process was further extended for bis-*O*-propargylated salicylaldehyde **5** in a similar manner. The required salicylaldehyde derivative **5** was synthesized *via* a double Sonogashira coupling reaction of diiodobenzene with *O*-propargylated salicylaldehyde. Bis-propargylated salicylaldehyde was reacted with diazoamide in the presence of 5 mol% of Cu(I)TC as a catalyst to furnish the respective interesting bis-spirocyclic complex system **6** in a diastereoselective manner (Scheme 1).

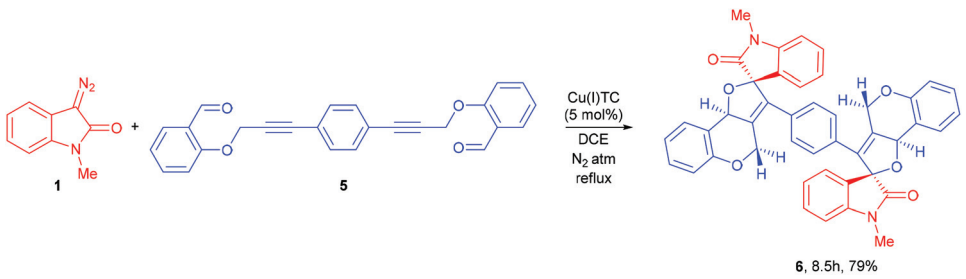
The optimized reaction conditions for the formation of spiro-indolooxirane[19] **3a** (kinetically controlled product) were found to be 5 mol% of Cu(I)TC in dichloroethane at room temperature (Table 1, entry 15). Similar reaction conditions were followed to synthesize the spiro-indolooxiranes **3b** and **3e** in 79–81% yields (Scheme 2, eqn (1)). To gain insights into the reaction mechanism, the following control experiments were carried out. The reaction of the epoxide **3a** in the presence of 5 mol% of Cu(I)TC in DCE under reflux conditions for 8 h did not provide any product and the starting material was recovered. Upon prolonging the reaction time to 32 h with or without Cu(I)TC, the partial disappearance of the starting material was observed with the formation of **4a** in 24% yield. This suggests that the epoxide underwent ring-opening,[22] providing carbonyl ylide intermediates to undergo [3 + 2]-cycloaddition with the external alkyne. Furthermore, the reaction of spiro-indolooxirane **3a** was performed in toluene under reflux conditions without a catalyst for 32 h to improve the yield of **4a** (Scheme 2, eqn (2)). The similar reaction of the appropriate epoxide also provided **4b** and **4e**. To satisfy our curiosity, further examination in the presence of dipolarophiles was performed. Treatment of the epoxide **3a** with dimethyl acetylenedicarboxylate (DMAD) or *N*-phenylmaleimide (NPM) in toluene under reflux conditions afforded the products **7** and **8**, respectively. The stereochemistry of **8** was tentatively assigned based on our previous[23] work. These results indicate that the intermolecular [3 + 2]-cycloaddition occurs instead of the intramolecular reaction without producing **4a**. After understanding the reaction profile, a further investigation of the diazo compound **1b** with *O*-propargyl salicylaldehyde **2a** and DMAD was



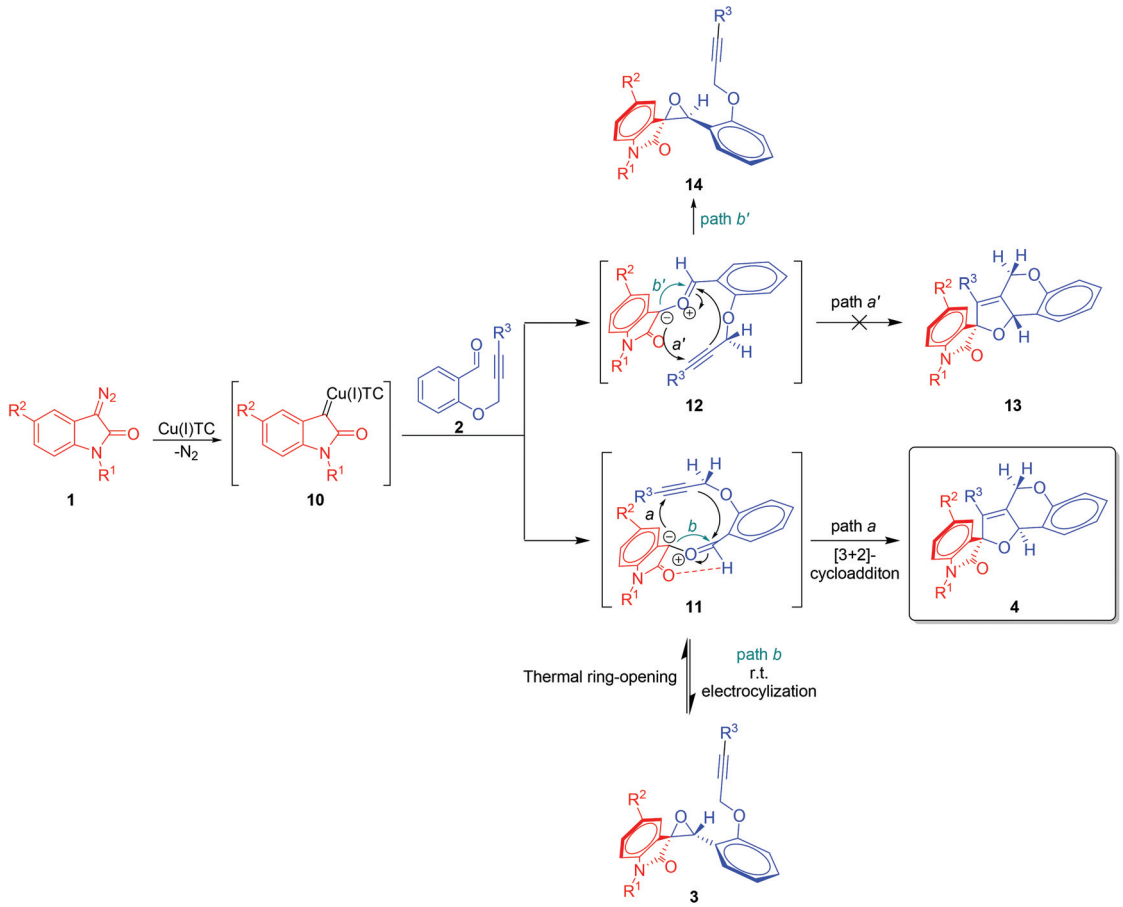
Scheme 2 Control experiments.

carried out in the presence of Cu(I)TC in DCE under reflux conditions for 1 h to obtain product **9** (Scheme 2, eqn (3)). This indicated that the generated carbonyl ylides competitively underwent intermolecular [3 + 2]-cycloaddition with electron-deficient DMAD rather than the electron-rich alkyne unit present in the substrate.

On the basis of the above experimental results, a plausible mechanism was put forward and is illustrated in Scheme 3. It is proposed that the electron-deficient carbenoid carbon of the copper(I) carbenoids **10** react with *O*-propargylated salicylaldehyde, affording the intermolecular carbonyl ylides **11** and **12** in two different conformations. Subsequent 1,3-dipolar cyclo-



Scheme 1 Synthesis of the bis-spiro-indolofurobenzopyran **6**.



Scheme 3 Proposed mechanism for the spiro-indolofurobenzopyrans **4**.

addition reaction with an electron-rich external/internal alkyne group furnished the spiro-indolofurobenzopyrans **4** in a diastereoselective manner (path *a*). From the observed stereochemistry of the product **4**, the selective formation of rotamers of carbonyl ylides **11** is proposed rather than **12** (Scheme 3). The presence of intramolecular hydrogen bonding in **11** stabilizes the carbonyl ylides[15a,f] and may provide the diastereoselectivity. The carbonyl ylides **11** are known[19] to proceed *via* electrocyclization to yield spiro-indolooxiranes **3** as a single isomer (path *b*). Interestingly, the spiro-indolooxiranes **3** are also known[22] to undergo thermal ring-opening to carbonyl ylides **11** at high temperatures in an intramolecular manner. The absence of hydrogen bonding may not favor the formation of intermediate **12**; therefore, there was no observation of the isomeric products **13** and **14**. Thus, the most favorable transient intermediate **11** underwent 1,3-dipolar cycloaddition reactions with an electron-rich external/internal alkyne to furnish the spiro-indolofurobenzopyrans **4** in a diastereoselective manner.

In conclusion, we developed an atom-economical diastereoselective synthesis of a thermodynamically controlled product, spiro-indolofurobenzopyrans, from diazoamides and *O*-propargyl salicylaldehydes in the presence of copper(I) thiophene-2-carboxylate as a catalyst in a tandem manner. This process involves the formation of two carbon–carbon bonds, a carbon–oxygen bond, and two stereogenic centers in a single synthetic step. This operationally simple protocol represents the first example of spiro-indolofurobenzopyrans involving copper(I) carbenoids from readily accessible starting materials with a number of analogues synthesized. Further application based on this chemistry is in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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$BF_3{\cdot}OEt_2$ catalyzed chemoselective C=C bond cleavage of α,β-enones: an unexpected synthesis of 3-alkylated oxindoles and spiro-indolooxiranes†

Sengodagounder Muthusamy * and Ammasi Prabu

A $BF_3{\cdot}OEt_2$ catalyzed highly chemoselective formal C=C double bond cleavage reaction of α,β-enones with diazoamides for the synthesis of 3-alkylated oxindoles is developed. Boron trifluoride etherate is found to be an effective catalyst for the chemoselective C_α–C_β cleavage of enones to obtain 3-alkylated oxindoles. The product formation indicates a selective β-carbon elimination pathway of α,β-enones using the inexpensive $BF_3{\cdot}OEt_2$ as a catalyst, transition metal-free conditions, an open-air environment, good functional tolerance and broad substrate scope. The synthetic utility of this protocol is highlighted by synthesizing spiro-indolooxiranes.

The cleavage of C–C bonds has been one of the most difficult subjects in organic chemistry.[1] For the past two decades, the functionalization of the C–C single bond,[2] double bond,[3] and triple bond[4] has been investigated. In particular, the metal-catalyzed cleavage reactions of C=C double bonds have been established as a powerful tool in organic transformations. The cleavage reactions of the C=C double bond have been reported *via* oxidative cleavage using transition metal catalysts,[5] photochemical methods[6] or oxidants[7] (ozonolysis, the Lemieux–Johnson protocol, *m*CPBA, PCC, TEMPO or aryl-γ^3-iodane-based) in combination with peroxides, peracids or other oxidizing reagents. The chemoselective cleavage of the C=C double bond is one of the most interesting and highly challenging themes in target-oriented synthesis. Few metal-mediated (Cu, Fe, Ru or Pd) chemoselective cleavage reactions of the C=C double bond of α,β-enones have also been reported.[8]

Chalcone, an easily available α,β-unsaturated ketone, is a well-known precursor in organic synthesis with a wide spectrum of medicinal applications.[9] Over the past decade, Lewis acid-catalyzed reactions of diazocarbonyl compounds with α,β-unsaturated carbonyls have been performed *via* 1,2-addition to the carbonyl group leading to the homologation reaction,[10] [3 + 2] cycloaddition to the olefin moiety leading to competitive 1,3-dipolar cycloaddition,[11] C–H/O–H insertion[12] or cyclopropanation of olefin.[13] Li and co-workers reported[14] the formation of 3-alkylated oxindoles from the gold(I)-catalysed reaction of diazoamides *via* C_α–H functionalization of enaminones (Scheme 1a). Ryu and co-workers developed[12d] a $BF_3{\cdot}OEt_2$ catalyzed C_β–H insertion of cyclic enones with diazoacetates (Scheme 1b). However, these are a few reported C=C double bond cleavage reactions that suffer from the need for expensive catalysts and require a large quantity of combined reagents, harsh reaction conditions or multi-step synthesis. A highly diastereoselective synthesis of spiro-indolocyclopropanes was reported[13e] by us from diazoamides and chalcones in the presence of $InCl_3$ as a catalyst in water (Scheme 1c). However, a similar reaction in the presence of $BF_3{\cdot}OEt_2$ in chloroform provided a new product instead of the expected cyclopropane formation with the change in the Lewis acid and solvent system. To the best of our knowledge, no reports are available for transition metal-free chemoselective cleavage of the C=C bond of α,β-enones. As a continuation of our interest in exploring the chemistry of diazoamides,[15] we herein report the unexpected 3-alkylated oxindoles obtained from diazoamides and α,β-unsaturated carbonyl compounds in the presence of $BF_3{\cdot}OEt_2$ as a catalyst under mild conditions *via* chemoselective cleavage of the $C(sp^2)$–C(CO) bond.

In order to study the cleavage of the C=C bond, the reaction of diazoamide **1a** with chalcone **2a** as an appropriate reaction partner in the presence of a Lewis acid catalyst was chosen. An initial study on the feasibility of using a solution containing diazoamide **1a** (1.0 mmol) and chalcone **2a** (1.0 mmol) in the presence of 10 mol% of $FeCl_3$ at 0 °C under an open-air atmosphere in dichloromethane (DCM) for 5 minutes afforded the unexpected and interesting 3-alkylated oxindole **3a** in 40% yield (Table 1, entry 1). From the NMR and mass spectrometric analysis, product **3a** was characterized. Benzoic acid was obtained as the by-product, based on

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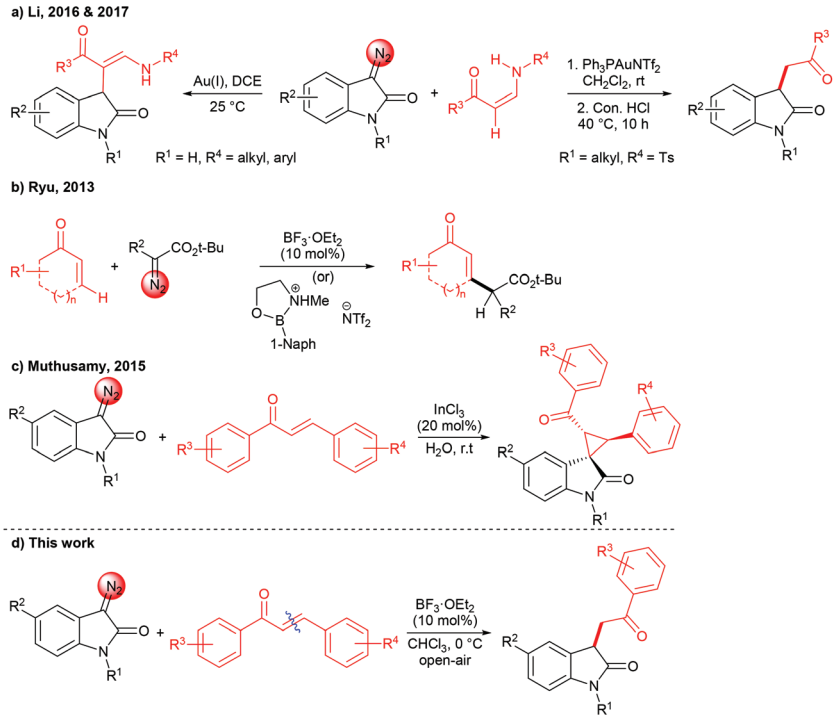
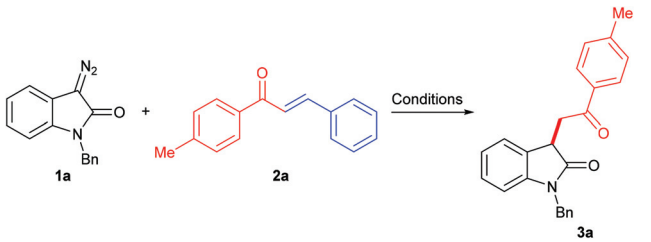


Scheme 1 Reactions of diazoamides with α,β-enones.

^{1}H-NMR studies (see the ESI†). It was confirmed that the β-portion of the chalcone has been eliminated from the reaction, indicating that the reaction may be proceeding through the chemoselective C=C bond cleavage of chalcones. Furthermore, the reaction was also performed in the presence of $AlCl_3$ or $SnCl_4$ but this did not improve the yield of the desired product **3a** (Table 1, entries 2 and 3). There was no product formation when the reaction was carried out in DCM using $InCl_3$ as a catalyst (Table 1, entry 4). Among the catalysts screened, $FeCl_3$ provided the best yield of the desired product **3a**. The reaction was also performed with various triflates, In(OTf)$_3$, Yb(OTf)$_3$, and Sc(OTf)$_3$, but this did not result in the yield of the desired product **3a** (Table 1, entries 5–7). Then various boron catalysts, such as $B(C_6F_5)_3$, $BF_3{\cdot}OEt_2$, $Tr(BF_4)$ and $Trop(BF_4)$, were screened (Table 1, entries 8–11) but no desired product was obtained in the presence of $B(C_6F_5)_3$ (Table 1, entry 8). To our delight, when the non-metal Lewis acid $BF_3{\cdot}OEt_2$ was efficiently employed in the reaction between **1a** and **2a**, **3a** was afforded in a good yield (58%; entry 9). However, the reaction with $Tr(BF_4)$ or $Trop(BF_4)$ afforded **3a** in 32 and 45% yields, respectively (Table 1, entries 10 and 11). Brønsted acids, such as TfOH and *p*-TSA, were also catalysts in this transformation, but they provided the desired product **3a** in lower yields (Table 1, entries 12 and 13). Among the catalysts, $BF_3{\cdot}OEt_2$ was found to be better. Next, the screening of several solvents, *viz.*, dichloroethane (DCE), chloroform, dioxane, toluene, and dimethylformamide (DMF), at 0 °C (Table 1, entries 14–18) revealed that commercial chloroform was the best to obtain **3a** in 73% yield. The reaction was carried out at 30 °C to afford the 3-alkylated oxindole **3a** in 45% yield (Table 1, entry 19). The yield of product **3a** did not improve when the reaction was carried out at −10 °C or when the amount of the catalyst used was changed (Table 1, entries 20 and 21). Remarkably, the desired product **3a** did not form when the reaction was performed under an argon or oxygen atmosphere in dry chloroform (Table 1, entry 22). The addition of water (10 μL) to the reaction mixture in the presence of 10 mol% of $BF_3{\cdot}OEt_2$ provided **3a** only in 13% yield (Table 1, entry 23). Entries 22 and 23 clearly indicate that the presence of moisture plays a vital role in this transformation. No reaction took place in the absence of a catalyst (Table 1, entry 24). Thus, the optimized reaction conditions for the formation of **3a** were found to be 10 mol% of $BF_3{\cdot}OEt_2$ in commercial chloroform at 0 °C under an open-air atmosphere, as shown in Table 1, entry 15. With the optimized reaction conditions in hand, the substrate scope of the reaction was examined. The scope of the Ar^1 ring of chalcones (Table 2) was explored. To this end, a series of highly substituted Ar^1 rings of chalcones were synthesized to react with diazoamides. The reactions of diazoamides with chalcones bearing electron-donating methyl and methoxy groups at the 4-position of the Ar^1 ring provided the corresponding 3-alkylated oxindoles **3a–3d** in 68–73% yields. There was some effect of the substituent located on the amide nitrogen of the diazoamide. Moreover, the unsubstituted diazoamide failed to afford the 3-alkylated oxindole **3e** and the starting materials were recovered. The bulky 4-phenyl substituted chalcone provided the desired product **3f** in a moderate yield. Importantly, the sterically demanding 2,4,6-triisopropyl substituted chalcone furnished product **3g** in 57% yield. However, the chalcone having the hydroxy substituent

Table 1 Optimization of the reaction conditions for the formation of **3a** [a]



Entry	Catalyst	Solvent	Temp. [°C]	*t* [min]	Yield[b] of **3a** [%]
1	$FeCl_3$	DCM	0	5	40
2	$AlCl_3$	DCM	0	5	21
3	$SnCl_4$	DCM	0	5	29
4	$InCl_3$	DCM	0	5	nr[c]
5	$In(OTf)_3$	DCM	0	180	nr[c]
6	$Yb(OTf)_3$	DCM	0	180	nd[d]
7	$Sc(OTf)_3$	DCM	0	180	nd[d]
8[e]	$B(C_6F_5)_3$	$CHCl_3$	0	5	nd[d]
9	$BF_3{\cdot}OEt_2$	DCM	0	5	58
10	$Tr(BF_4)$	$CHCl_3$	0	5	32
11	$Trop(BF_4)$	$CHCl_3$	0	5	45
12	TfOH	DCM	0	5	38
13	*p*-TSA	DCM	0	5	27
14	$BF_3{\cdot}OEt_2$	DCE	0	30	47
15	**$BF_3{\cdot}OEt_2$**	**$CHCl_3$**	**0**	**5**	**73**
16	$BF_3{\cdot}OEt_2$	Dioxane	0	240	nr[c]
17	$BF_3{\cdot}OEt_2$	PhMe	0	5	30
18	$BF_3{\cdot}OEt_2$	DMF	0	180	nr[c]
19	$BF_3{\cdot}OEt_2$	$CHCl_3$	30	30	45
20	$BF_3{\cdot}OEt_2$	$CHCl_3$	−10	5	49
21[f]	$BF_3{\cdot}OEt_2$	$CHCl_3$	0	5	33/70
22[g]	$BF_3{\cdot}OEt_2$	$CHCl_3$	0	5	nr[c]
23[h]	$BF_3{\cdot}OEt_2$	$CHCl_3$	0	5	13
24	—	$CHCl_3$	0	120	nr[c]

[a] Reaction conditions: the reaction was carried out by adding 10 mol% of Lewis acid to a solution of diazoamide **1a** (1.0 mmol) and chalcone **2a** (1.0 mmol) in a commercial solvent under an open air atmosphere at 0 °C. [b] Isolated yield. [c] No reaction. [d] No desired product. [e] Reaction carried out under an argon atmosphere. [f] 5 or 20 mol% of catalyst used. [g] Reactions were carried out under an argon or oxygen atmosphere in dry $CHCl_3$. [h] Addition of 10 μL of water.

did not deliver product **3h**. Electron-withdrawing substituents (F, Cl and Br) on the Ar^1 ring of chalcones were well tolerated and afforded the corresponding products **3i–l** and the halogen atom present in the resulting products could be used for further transformations. Moreover, a strong electron-withdrawing group, such as $-NO_2$, was also well tolerated to deliver the desired products **3m** and **3n** in comparable yields. Chalcones having the CN substituent did not produce the desired product **3o**. The reaction utilizing the naphthalene or anthracene system also gave the corresponding 3-alkylated oxindoles **3x–z** in moderate yields.

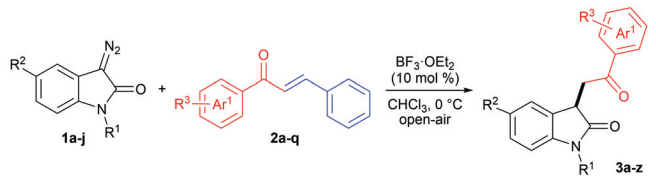
Next, the Ar^2 ring of chalcone was also examined (Table 3). A series of Ar^2 substituted chalcones were suitable for use in this reaction to give product **3c** in moderate to good yields. Electron-donating substituents at the 3-, 4- and 5-positions of Ar^2 afforded the corresponding product **3c** in moderate to good yields. The hydroxy substituent on Ar^2 of chalcone did not deliver the expected product **3c**. On the other hand, substrates with electron-withdrawing groups like F, Cl, Br, and NO_2 on the aryl ring of Ar^2 provided the desired product **3c** in a moderate yield. Next, the effect of the substituent on diazoamides **1** was examined. Electron-rich diazoamides gave the desired products **3p** and **3q** in good yields. Halo-substituted diazoamides were also found to be suitable substrates to deliver the 3-alkylated oxindoles **3r–w** in moderate yields (Table 2).

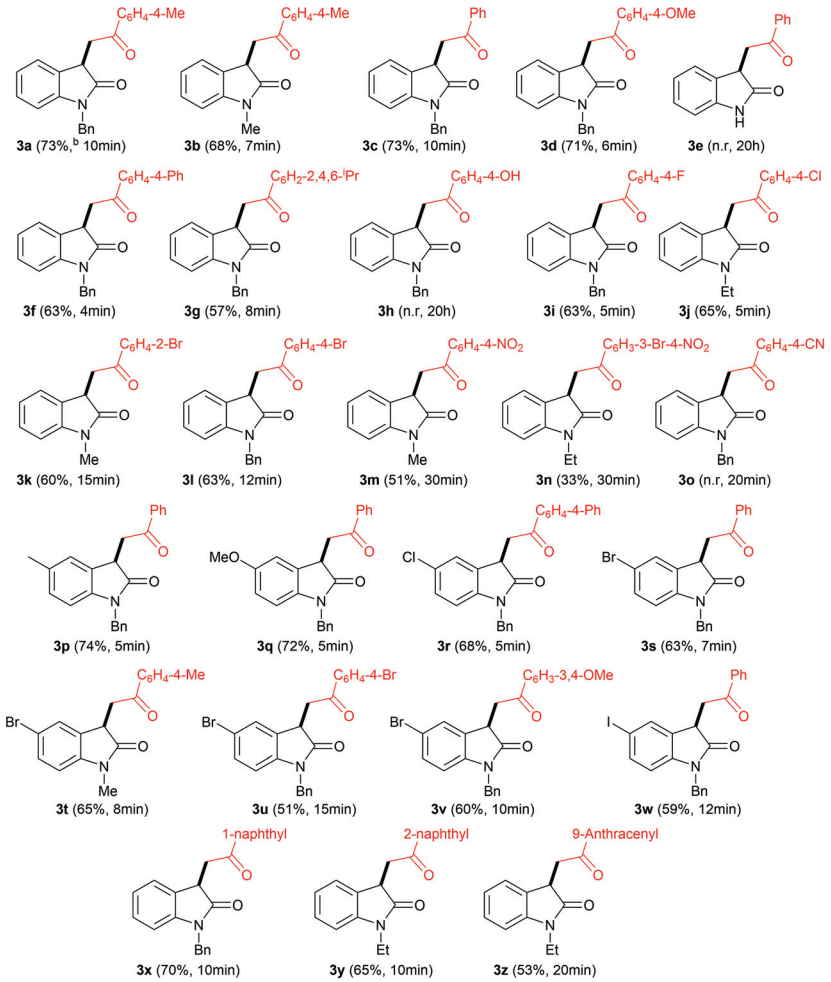
In order to further explore the scope of this methodology, reactions with other diazocarbonyl compounds were tested. The reaction of ethyl diazoacetate under the optimized conditions failed to deliver the product. The reaction with methyl phenyldiazoacetate and 2-diazo-1-tetralone afforded the corresponding cyclopropane **3aa** and a complex mixture, respectively (see the ESI†).

The efficiency of this methodology was further extended[16] to demonstrate the cleavage process of the two C=C double bonds by utilizing bis-chalcones **4**. Bis-chalcones (1 equiv.) **4a–d** were allowed to react with diazoamide (2 equiv.) **1a** under the optimized conditions and the reaction proceeded through the cleavage of two C=C double bonds, furnishing products **3a**, **3c**, **3f** and **3x** in moderate yields (Scheme 2, eqn (1)). The scope of the process was extended for other bis-chalcones **5** in a similar manner. The reaction of bis-chalcones **5a** and **5b** (1 equiv.) with two equiv. of diazoamide **1a** under the optimized conditions led to the formation of the interesting bis-3-alkylated oxindoles **6a** and **6b** (Scheme 2, eqn (2)).

To gain a crucial insight into the mechanism of this chemoselective C=C double bond cleavage of α,β-enones, a few control experiments were carried out to verify the reaction pathway. In line with the literature,[17] $BF_3{\cdot}OEt_2$ activated chalcone **2a** based on NMR titration experiments (see the ESI†). Cyclopropane may be considered[13] as an intermediate for these reactions. Hence, spirocyclopropane **7a**[13e] and its diastereomer **7b**[18] were synthesized based on the literature method. The reaction of spirocyclopropanes **7a** and **7b** in the presence of 20 mol% of $BF_3{\cdot}OEt_2$ in chloroform at 0 °C to room temperature did not provide the desired product **3c** and the starting materials were recovered (Scheme 3, eqn (1)). Next, as planned, we investigated the multicomponent reaction of diazoamide **1b** with chalcone **2a** in the presence of dimethyl acetylenedicarboxylate (DMAD) under the optimized conditions and **3b** was obtained in 68% yield and the unreacted DMAD was recovered (96%) (Scheme 3, eqn (2)). These results indicate that the reaction did not proceed *via* spirocyclopropane as an intermediate. Based on the literature,[12] C–H insertions may also be a possible intermediate for these reactions. Diazoamide **1a** was reacted with acetophenone instead of chalcone under the optimized conditions and product **3c** was not obtained, which indicates that acetophenone is not an intermediate in this transformation. The reaction was carried out in the presence of 1 equivalent of methanol to provide 3-methoxyindolin-2-one **8**[19] (86% of the isolated yield based on diazoamide **1b**) indicating that chalcone was not involved in the reaction (Scheme 3, eqn (3)). The reaction was carried out with

Table 2 Synthesis of 3-alkylated oxindoles **3**, reactivity of the Ar^1 ring[a]





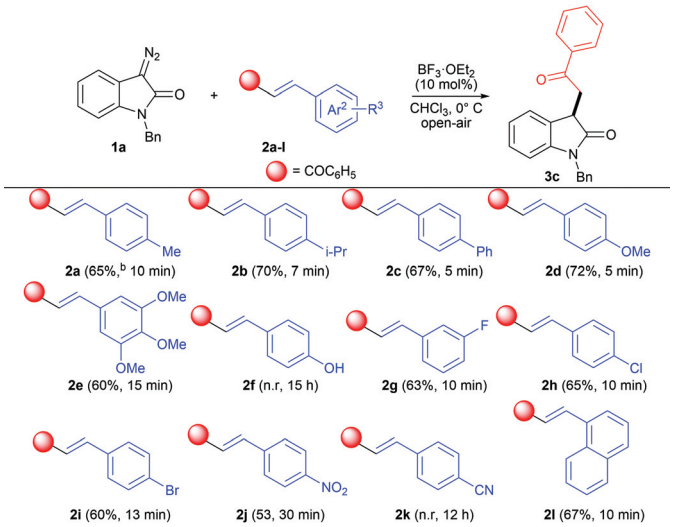
[a] Reaction conditions: equimolar amounts of **1** and **2**, $BF_3{\cdot}OEt_2$ (10 mol%), $CHCl_3$ (2 mL), 0 °C. [b] Isolated yield.

1,3-diphenylpropane-1,3-dione instead of chalcone under the optimization conditions to provide the desired product **3c** in 84% yield (Scheme 3, eqn (4)). However, when the reaction was performed with 3-hydroxy-1,3-diphenylpropan-1-one instead of chalcone under the optimization conditions, the desired product **3c** was not formed (Scheme 3, eqn (5)). The reaction with 3-phenyl substituted chalcone instead of chalcone failed to deliver the desired product **3c**, with the starting material chalcone being recovered (Scheme 3, eqn (6)), indicating the possible hydroxylation at the β-position on the chalcone.

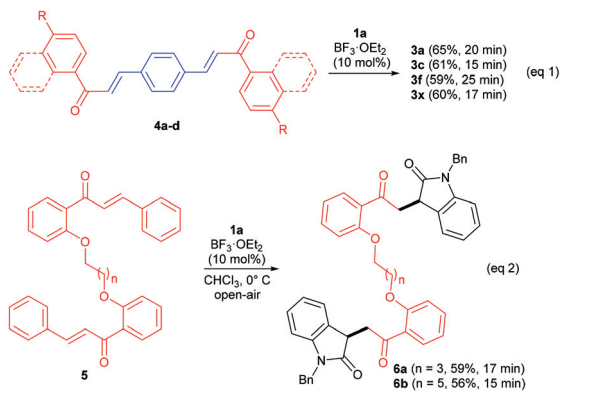
Product **3a** can be regarded to be formed from 3-alkylated oxindole *via* the formal C=C cleavage of a double bond in the presence of a Lewis acid as a catalyst. On the basis of the literature precedent and the control experiments, a plausible mechanism is shown in Scheme 4. The adduct of water and the boron reagent[17a] could potentially act as a reagent with chalcone **2** to generate boron-based enolate **A**. The nucleophilic attack of enolate **B** on the diazonium ion led to the formation of intermediate **C**. The retro-aldol reaction of **C** affords product **3** and aryl aldehyde. The aerial oxidation of aryl aldehyde in the presence of $BF_3{\cdot}OEt_2$ provided the corresponding carboxylic acid, as shown by NMR studies (see the ESI†).

Further synthetic applications of 3-alkylated oxindoles **3** using copper(I) iodide and DMAP were explored and are shown in Scheme 5 (for details, see the ESI†). Our initial investigation

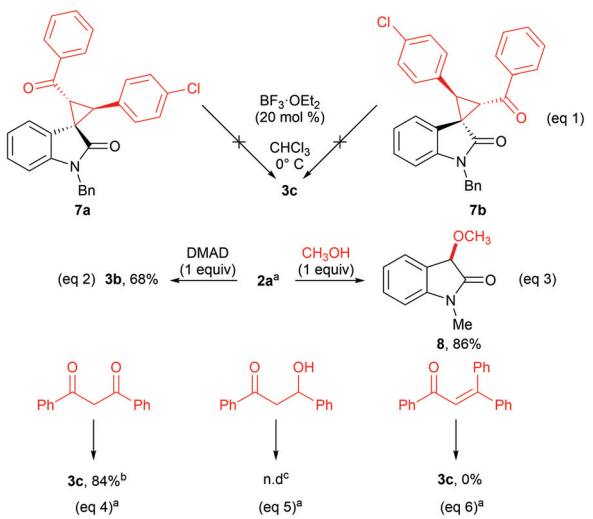
Table 3 Synthesis of 3-alkylated oxindole **3c**, reactivity of the Ar^2 ring[a]



[a] Reaction conditions: equimolar amounts of **1a** and **2**, $BF_3{\cdot}OEt_2$ (10 mol%), $CHCl_3$ (2 mL), 0 °C. [b] Isolated yield.

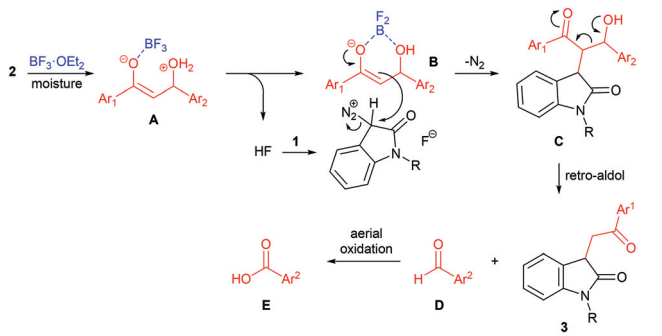


Scheme 2 Effect of reactivity of bis-chalcones.

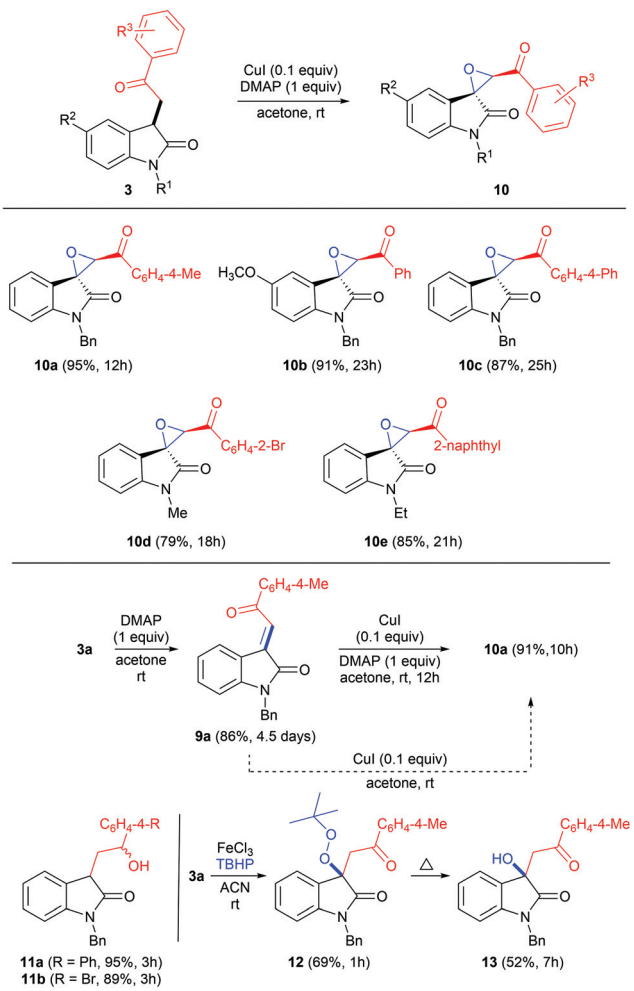


Scheme 3 Control experiments. [a] Reaction conditions: **1b**, $BF_3{\cdot}OEt_2$ (10 mol%), $CHCl_3$, 0 °C. [b] Isolated yield. [c] No desired product.

began with the reaction of 3-alkylated oxindoles **3** in the presence of CuI/DMAP at room temperature, which afforded spiroindolooxiranes **10a–e** in 79–95% yields. The stereochemistry of the product was tentatively assigned as a *trans* isomer based on the literature.[20] The functionalization of the ketone into alcohol using $NaBH_4$ was intended to produce racemic alcohols **11a** and **11b** in excellent yields. The treatment of **3a** with



Scheme 4 Plausible mechanism for the formation of **3**.



Scheme 5 Synthetic application of the current protocol.

tert-butyl hydroperoxide (TBHP) in the presence of $FeCl_3$ in acetonitrile was performed to afford **12**,[21] incorporating the peroxide functionality. Subsequent heating of **12** in acetonitrile at 80 °C produced 3-hydroxy-3-alkylated oxindole **13**. 3,3-Disubstituted oxindoles[22] are important skeletal structures commonly found in both naturally occurring alkaloids and potent bioactive compounds.

In conclusion, the reactions of diazoamides and chalcones in the presence of $BF_3{\cdot}OEt_2$ as a catalyst afforded 3-alkylated oxindoles. In this synthetic protocol, the development of a chemoselective C═C bond cleavage process involves the insertion of the *in situ* generated C_α–H followed by the cleavage of the C–C bond of α,β-enone using $BF_3{\cdot}OEt_2$ as a catalyst, without employing any metal or additive. This reaction revealed a controlled $C(sp^2)$═C(CO) bond cleavage protocol by incorporating the carbonyl part into the final products. The 3-alkylated oxindoles were further utilized for the synthesis of spiro-indolooxiranes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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$BF_3{\cdot}OEt_2$ catalyzed decarbonylative arylation/C–H functionalization of diazoamides with arylaldehydes: synthesis of substituted 3-aryloxindoles†

Sengodagounder Muthusamy * and Ammasi Prabu

A metal-free $BF_3{\cdot}OEt_2$ catalyzed direct decarbonylative arylation of diazoamides with readily accessible aryl aldehydes under an open-air atmosphere was developed to afford 3-aryloxindoles *via* 1,2-aryl migration with high selectivity. The reaction offers an efficient pathway for 3-arylation of diazoamides under relatively mild conditions, which shows a high level of functional group tolerance of both electron-donating and electron-withdrawing groups with a broad substrate scope. 3-Aryloxindoles were also obtained by a substituent-controlled chemo- and site-selective C–H bond functionalization of unprotected salicylaldehyde derivatives.

Introduction

Oxindoles are ubiquitous subunits found in a broad range of natural products and biologically active molecules and show antiviral, anti-bacterial and anti-carcinogenic properties.[1] 3-Aryl-oxindoles are synthetically interesting as they have found various applications in biology and pharmaceutical chemistry[2] (Fig. 1). These molecules have been shown to have potent bioactivity in drug discovery, for instance, as a neuroprotective agent,[3] a potent growth hormone secretagogue,[4] an anti-cancer agent[5] and a nootropic drug.[6] 3-Aryloxindoles are mostly used as precursors for the synthesis of 3,3-disubstituted oxindole or indoline derivatives, which form the core of a large number of natural products and pharmaceutical agents.[7] The reaction[8] of diazo compounds with aldehydes has been established as a valuable method for the synthesis of various ketones, homologated aldehydes and epoxides. These reactions involve[8] three different approaches: (a) C–H insertion (1,2-H shift), (b) C–C insertion (1,2-C shift), or (c) an electrocyclization reaction (Fig. 2) *via* a two-step mechanism involving carbonyl 1,2-addition of the diazo compounds, followed by a 1,2-(H or C) shift. However, the 1,2-carbon shift has been reported in other methods[9a–f] but scarcely reported involving the diazo[9g–j] functionality.

The synthesis of 3-aryloxindoles has been known *via* Grignard reagents with isatin,[10] palladium-catalyzed intramolecular cyclization of 3-aryl acetanilides,[11] palladium-catalyzed reactions of oxindoles with aryl boron reagents,[12] Ni, Fe (III) or Sc(III)-catalyzed 3-arylation of 2-oxindoles[13] and the TfOH-catalyzed[7] reaction of 3-diazooxindoles. These methodologies require the use of air-sensitive and expensive transition-metal reagents, arylating agents, additives, harsh reaction conditions, an inert atmosphere or multistep synthesis. Therefore, the development of transition metal-free, mild and efficient methods for direct/site-selective arylation is highly desirable and of prime synthetic value. In continuation of our work on the chemistry[14] of diazoamides, we herein reveal a methodology for the economical synthesis of 3-aryloxindoles from diazoamides and readily accessible aryl aldehydes or chelating aldehydes *via* $BF_3{\cdot}OEt_2$ catalysis under mild reaction conditions. The aryl aldehydes act as arylation reagents for the synthesis of 3-aryloxindoles.

Results and discussion

In order to establish the arylation methodology, diazoamide **1a** and benzaldehyde **2a** were selected as model substrates. Initial studies on the reaction of **1a** (1 equiv.) and **2a** (1.1 equiv.) in the presence of 20 mol% of $Sc(OTf)_3$ under an open-air atmosphere in dichloromethane (DCM) at room temperature for 2 h showed that 3-aryloxindole **3a** was obtained in 56% yield (Table 1, entry 1), which is quite different from our earlier[15a] work on the synthesis of spiroindolo-oxiranes *via* the reaction of diazoamides and aryl aldehydes in the presence of rhodium acetate as a catalyst (Scheme 1). From the NMR and mass spectroscopic analyses, product **3a** was confirmed and the absence of the aldehyde group was observed. The arylation product **3a** was obtained possibly *via* 1,2-aryl migration with high selectivity fol-

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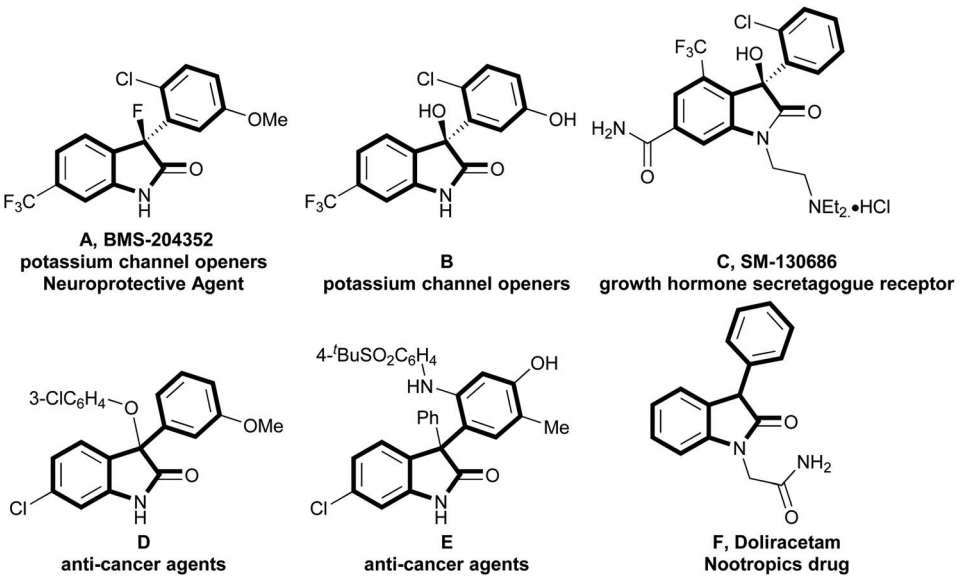


Fig. 1 3-Aryloxindole motif in bioactive molecules and natural products.

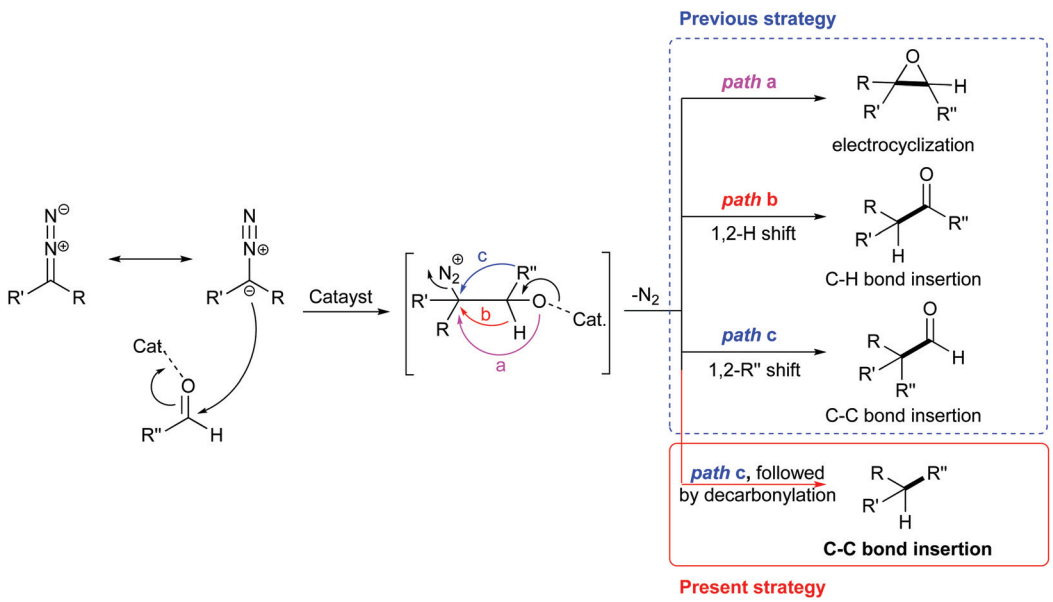
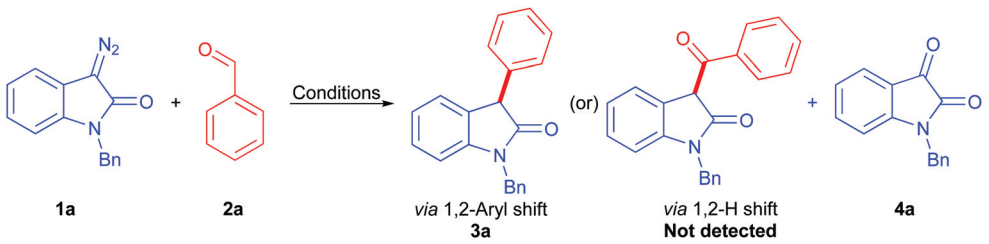


Fig. 2 Reactions of diazo compounds with aldehydes.

lowed by decarbonylation, as depicted in Fig. 2. No other competitive reactions *via* a 1,2-H shift or epoxide were observed. We screened the reaction conditions by changing the catalyst, solvent, temperature, time, *etc*. In order to optimize the reaction conditions, various Lewis acids such as $In(OTf)_3$, $AlCl_3$, $FeCl_3$ and $SnCl_4$ were investigated (Table 1, entries 2–5).

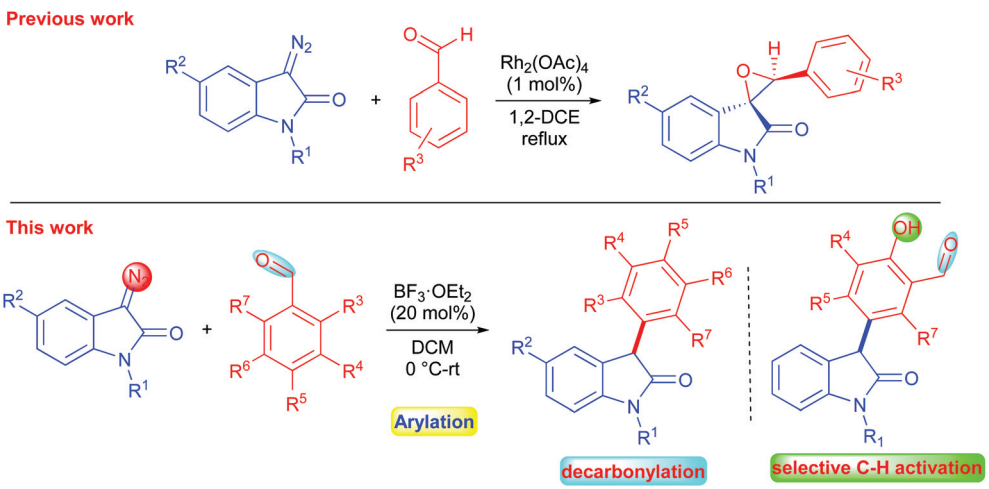
No superior results were obtained when the reaction was performed in the presence of $TiCl_4$ or silica gel (Table 1, entries 6 and 7). $TiCl_4$ provided isatin **4a** in 80% yield. Various boron catalysts, such as $BF_3{\cdot}OEt_2$, $B(C_6F_5)_3$ and $Tr(BF_4)$, were examined (Table 1, entries 8–10); among them, $BF_3{\cdot}OEt_2$ was efficiently used for the reaction between **1a** and **2a** to afford product **3a** in a remarkable yield (Table 1, entry 8). Interestingly, Brønsted acids such as *p*-TSA or TfOH were also able to promote this reaction, but only moderate yields were achieved (Table 1, entries 11 and 12). The target product **3a** was obtained in 43% yield along with 11% of isatin **4a** as a byproduct when con. HCl was used as a catalyst (Table 1, entry 13). DCM was found to be the best solvent compared to other solvents, namely, chloroform, acetonitrile, benzene or toluene (Table 1, entries 14–17). A shorter reaction duration provided a better yield of product **3a** (Table 1, entry 18). The yield of product **3a** did not improve even at reflux

Table 1 Optimization of reaction conditions for the formation of **3a**[a]



Entry	Catalyst (20 mol%)	Solvent	T (°C)	t (h)	Yield[b] [%] **3a**/**4a**
1	$Sc(OTf)_3$	DCM	rt	2	56/0
2	$In(OTf)_3$	DCM	rt	2	42/0
3	$AlCl_3$	DCM	rt	2	15/0
4	$FeCl_3$	DCM	rt	2	48/0
5	$SnCl_4$	DCM	rt	2	18/0
6	$TiCl_4$	DCM	rt	2	0/80
7	Silica gel	DCM	rt	10	nr[c]
8	$BF_3{\cdot}OEt_2$	DCM	rt	2	74/0
9	$B(C_6F_5)_3$	DCM	rt	2	nd[d]
10	$Tr(BF_4)$	DCM	rt	2	37/0
11	*p*-TSA	DCM	rt	2	41/0
12	TfOH	DCM	rt	2	59/0
13	Con. HCl	DCM	rt	2	43/11
14	$BF_3{\cdot}OEt_2$	$CHCl_3$	rt	2	59/0
15	$BF_3{\cdot}OEt_2$	ACN	rt	2	23/0
16	$BF_3{\cdot}OEt_2$	Benzene	rt	2	35/0
17	$BF_3{\cdot}OEt_2$	Toluene	rt	2	19/0
18	$BF_3{\cdot}OEt_2$	DCM	rt	0.5	75/0
19	$BF_3{\cdot}OEt_2$	DCE	Reflux	2	30/0
20	**$BF_3{\cdot}OEt_2$**	**DCM**	**0**	**0.5**	**88/0**
21[e]	$BF_3{\cdot}OEt_2$	DCM	0	0.5	87/0
22	$BF_3{\cdot}OEt_2$	DCM	−20	0.5	47/0
23	$BF_3{\cdot}OEt_2$	DCM	0	0.5	46/0[f] or 81/0[g]
24	—	DCM	0	24	nr[c]

[a] Reaction conditions: the reaction was carried out by adding 20 mol% of catalyst to a solution of diazoamide **1a** (0.40 mmol) and aldehyde **2a** (0.44 mmol) under an open-air atmosphere at 0 °C. [b] Isolated product. [c] No reaction. [d] No desired product. [e] Reactions were carried out under an oxygen or argon atmosphere in dry DCM. [f] 10 mol% of $BF_3{\cdot}OEt_2$. [g] 30 mol% of $BF_3{\cdot}OEt_2$.

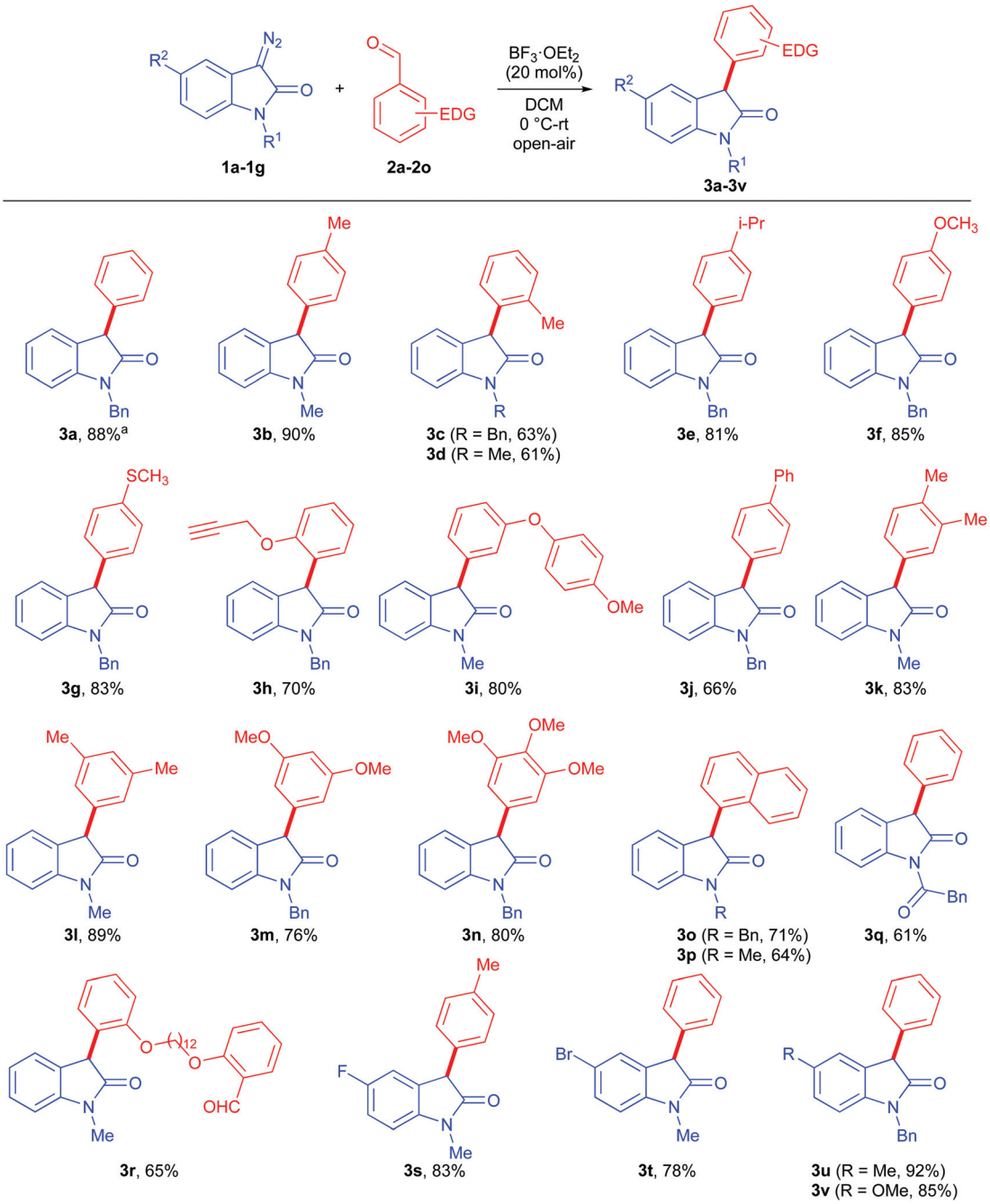


Scheme 1 Reactions of cyclic diazoamides with aldehydes.

conditions. (Table 1, entry 19); however, the yield was improved at 0 °C (Table 1, entry 20). When the reaction was performed under an oxygen or argon atmosphere in dry DCM, **3a** was afforded in 87% yield (Table 1, entry 21). Upon further reducing the temperature to −20 °C, the yield of product **3a** was reduced (Table 1, entry 22). Reducing or increasing the amount of the

catalyst did not explicitly improve the yield of the product (Table 1, entry 23). No reaction took place in the absence of a catalyst (Table 1, entry 24). Hence, the optimized reaction conditions for the formation of **3a** were found to be 20 mol% of $BF_3{\cdot}OEt_2$ in DCM at 0 °C under an open-air atmosphere (Table 1, entry 20). It is worth to note that the reaction is tolerant in an open-air atmosphere.

The generality and scope of this interesting protocol for accessing 3-aryloxindoles were investigated. With the optimized reaction conditions in hand, we next examined the scope of $BF_3{\cdot}OEt_2$-catalyzed arylation reactions with a wide range of electron-donating or electron-withdrawing aryl aldehydes. Based on the literature, the major issue identified was the presence of functional-group tolerance or strong electron-withdrawing substituents in the reported methods. The substituent effect on the diversity of aryl aldehydes was employed in this transformation. Next, the reaction afforded various 3-aryloxindoles **3b–3v** from diazoamides **1a–1g** and electron-donating aryl aldehydes **2a–2o**

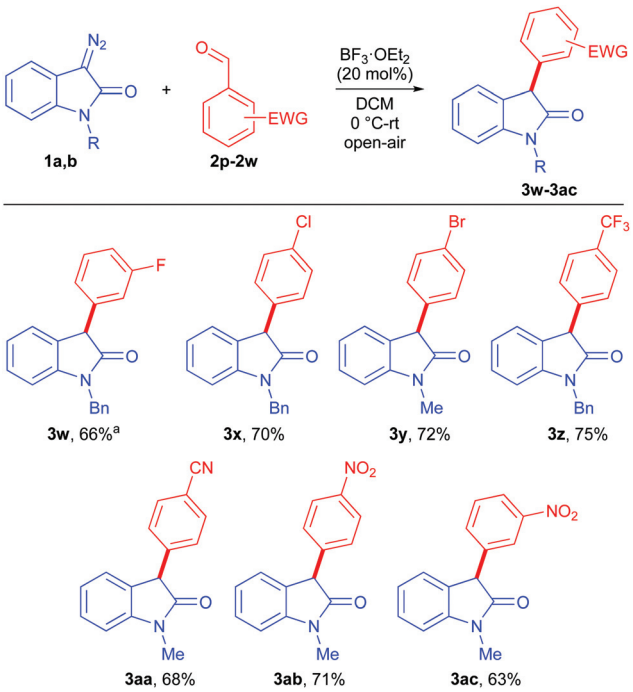


Scheme 2 Synthesis of 3-aryloxindoles **3a–3v** having Ar-EDG modification.[a] Reaction conditions: equimolar amounts of **1** and **2**, $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2 (5 mL), 0 °C. [a]Isolated yield based on **1**.

via 1,2-aryl migration followed by decarbonylation, as shown in Scheme 2. The reaction of 4-methylbenzaldehyde provided **3b** in 90% yield. The reaction with 2-methylbenzaldehyde furnished **3c** and **3d** in moderate yields and the *ortho*-CH_3 appeared[16] as a broad singlet instead of a sharp singlet, probably due to steric and electronic effects. The reaction with 4-isopropylbenzaldehyde gave the corresponding product **3e** in a good yield. A similar reaction with 4-methoxybenzaldehyde and 4-(methylthio)benzaldehyde yielded the desired products **3f** and **3g** in good yields, respectively. The presence of sterically hindered *O*-propargylated salicylaldehyde afforded the corresponding 3-aryloxindole **3h** in a moderate yield. Product **3i** was obtained in a good yield when 3-(4-methoxyphenoxy)benzaldehyde was used. The reaction with biphenyl-4-carbaldehyde provided the desired product **3j** in a moderate yield. The reaction with disubstituted benzaldehydes, 3,4-dimethylbenzaldehyde, 3,5-dimethylbenzaldehyde or 3,5-dimethoxybenzaldehyde, afforded products **3k–3m** in good yields, respectively. When trisubstituted 3,4,5-trimethoxybenzaldehyde was used, product **3n** was obtained in a good yield. The reaction employing 1-naphthaldehyde also gave the corresponding 3-aryloxindoles **3o** and **3p** in moderate yields. No reaction occurred when 9-anthracenecarboxaldehyde, 1-methyl-1*H*-indole-3-carbaldehyde or cinnamaldehyde was used. To satisfy our curiosity, reactions with aliphatic aldehydes were also investigated. Towards this end, propionaldehyde, pivaldehyde or cyclohexanecarboxaldehyde was utilized in these reactions, but the reactions failed. Subsequently, *N*-benzoyl substituted diazoamide **1c** smoothly furnished the desired product **3q** in 61% yield. Furthermore, to test the facile nature of this reaction, diazoamide **1b** (1 equiv.) was reacted with bis-arylaldehyde **2o** (0.5 equiv.) and *mono*-3-aryloxindole **3r** was obtained in 65% yield. Besides, the effect of the substituents of diazoamides **1** was examined. Halo-substituted diazoamides **1d** and **1e** were also found to be feasible substrates for obtaining 3-aryloxindoles **3s** and **3t** in good yields. Electron-donating diazoamides **1f** and **1g** gave the desired products **3u** and **3v** in excellent yields.

The electron-deficient arenes generally performed[2a,7,17] poorly than electron-rich arenes due to steric and electronic factors on the aryl ring system. Thus, electron-withdrawing group substituted arenes are rarely reported in the presence of expensive metal catalysts, stoichiometric amounts of reagents or harsh conditions. The present protocol is effective for both electron-donating and electron-withdrawing aryl aldehydes. Aryl aldehydes having trifluoro, nitrile or nitro substituents are viable substrates in this transformation (Scheme 3). 3-Fluorobenzaldehyde was also used in this reaction to afford the corresponding product **3w**.

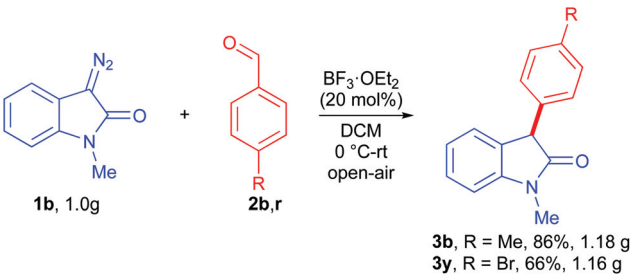
4-Chloro- or bromo-benzaldehyde was also tolerated to furnish the corresponding products **3x** and **3y** in moderate yields. 4-(Trifluoromethyl)benzaldehyde having a strong deactivating $-CF_3$ group at the *para*-position was also well tolerated to produce the expected product **3z** in 75% yield. The strong electron-withdrawing CN or NO_2 substituent on benzaldehyde was also examined and the desired products **3aa–3ac** were obtained in moderate yields.



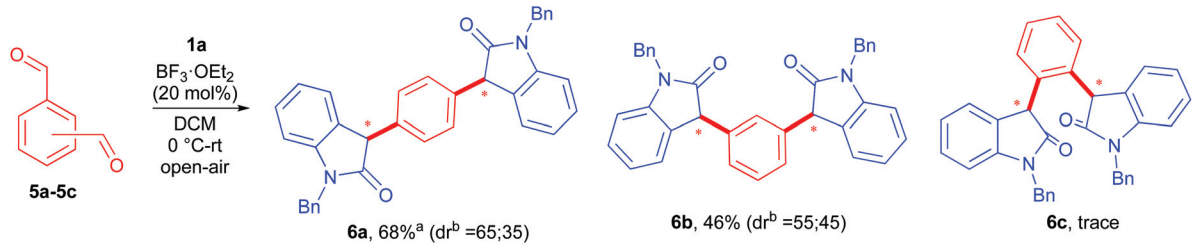
Scheme 3 Synthesis of 3-aryloxindoles **3w–3ac** having Ar-EWG modification. [a]Reaction conditions: equimolar amounts of **1** and **2**, $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2 (5 mL), 0 °C. [b]Isolated yield based on **1**.

To reveal the reliability and practicality of the present decarbonylative arylation methodology, gram-scale experiments were carried out with diazoamide **1b** and 4-methylbenzaldehyde **2b** under the optimized conditions to afford the corresponding product **3b** in only a moderate yield (Scheme 4). To improve the yield, a solution of **1b** was introduced[14f] through a syringe pump at a flow rate of 5 mL h^{-1} to afford **3b** in 86% yield. Similarly, 3-aryloxindole **3y** was also prepared. Of note, the gram-scale synthesis required the controlled addition of diazoamide to improve the yield.

The scope of this process was further extended to bis-3-arylaldehydes **5a–5c** in a similar manner. Towards this end, terephthalaldehyde **5a** was reacted with 2 equiv. of diazoamide **1a** in the presence of 20 mol% of $BF_3{\cdot}OEt_2$ as a catalyst to furnish the corresponding bis-3-aryloxindole **6a** in 68% yield as a mixture of diastereomers in a ratio of 65 : 35. Similarly, isophthalaldehyde **5b** was used as the substrate to give the corres-



Scheme 4 Gram scale preparation of 3-aryloxindoles **3b** and **3y**.

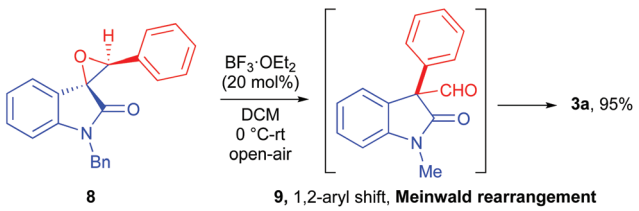


Scheme 5 Synthesis of bis-3-aryloxindoles **6a–6c**.[a,b] Reaction conditions: **1a** (0.40 mmol), **5** (0.20 mmol), $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2 (5 mL), 0 °C. [a]Isolated yield based on **5**. [b]Based on ^{1}H-NMR.

ponding bis-3-aryloxindole **6b** in 46% yield as a mixture of diastereomers in a ratio of 55 : 45. The sterically demanding *o*-phthalaldehyde **5c** provided **6c** in a trace amount (Scheme 5).

Further investigation of salicylaldehydes **2x–2aa** with diazoamides **1a** and **1b** was carried out, as shown in Scheme 6. The reactions proceeded smoothly to afford *meta* to the aldehyde **2** or *para* to the hydroxy site-selective C–H functionalization products **7a–7d** in a chemo- and regioselective manner. Notably, no other competitive reactions of annulation, the epoxide or O–H insertion reaction, were observed.[18] The hydroxy group plays a vital role in the formation of this site-selective C–H functionalization product **7**, which may be due to the presence of intramolecular hydrogen bonding in salicylaldehyde. However, *O*-propargyl salicylaldehyde provided the corresponding decarbonylative arylation product **3h** instead of the C–H functionalization product **7**.

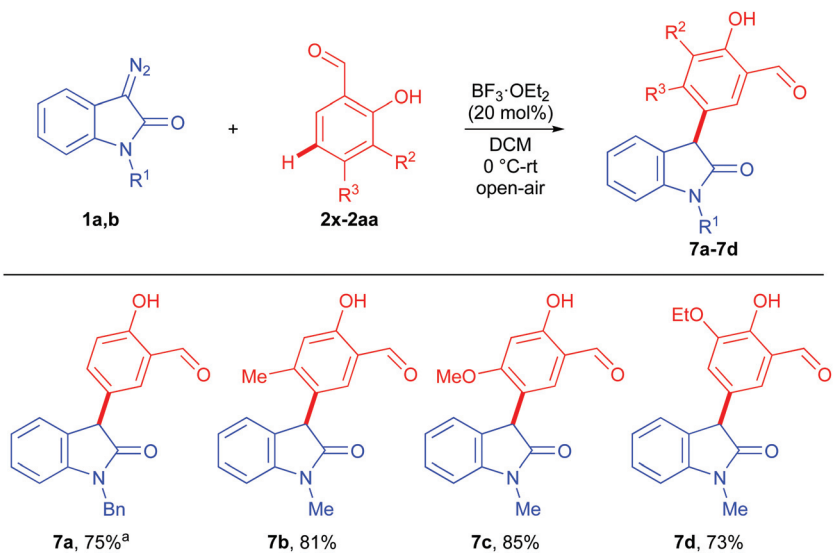
To further understand the mechanism of the arylation process, a control experiment was carried out, as shown in Scheme 7. When spiro-indolooxirane[15a] **8** was subjected to the reaction conditions, 3-aryloxindole **3a** was obtained in 95% yield *via* the 1,2-aryl shift of **9** followed by decarbonylation, whereas the corresponding product was not observed *via* the



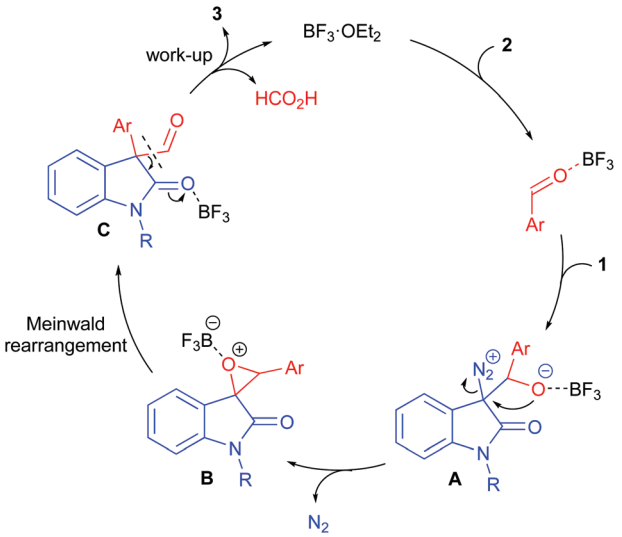
Scheme 7 The Meinwald rearrangement reaction of epoxide **8**.

1,2-H shift. This experiment indicates the possibility of the formation of an epoxide intermediate *via* the Meinwald rearrangement.

A plausible mechanism for **3** was proposed as shown in Scheme 8 based on the above results, control experiments and ^{1}H-NMR experiments (see the ESI†). In the presence of $BF_3{\cdot}OEt_2$, the nucleophilic attack on diazoamide **1** by aryl aldehyde **2** may produce intermediate **A**. Subsequently, intermediate **A** may provide spiro-indolooxiranes **B** with the elimination of nitrogen. The Meinwald rearrangement of **B** may provide **C** which on decarbonylation furnishing the desired product **3**.



Scheme 6 Synthesis of 3-aryloxindoles **7** and effect of the hydroxy substituent. Reaction conditions: equimolar amounts of **1** and **2**, $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2 (5 mL), 0 °C. [a]Isolated yield based on **1**.



Scheme 8 Plausible reaction mechanism for the formation of **3**.

In conclusion, a mild and efficient methodology has been developed for direct decarbonylative arylation to construct various 3-aryloxindoles from readily available aryl aldehydes and diazoamides *via* the $BF_3{\cdot}OEt_2$-catalyzed reaction. 3-Arylated oxindoles were obtained with high selectivity *via* 1,2-aryl migration in moderate to good yields and with good functional group compatibility of both electron-donating and electron-withdrawing aryl aldehydes. The catalytic substituent-controlled chemo- and site-selective C–H bond functionalization of unprotected salicylaldehydes with $BF_3{\cdot}OEt_2$ as a catalyst was demonstrated without affecting the aldehyde and hydroxyl functionality. This process permits the generation of a new stereogenic tertiary carbon center in the oxindole ring system.

Conflicts of interest

There are no conflicts to declare.

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