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Transition metal-free advanced synthetic approaches for isoindolinones and their fused analogues

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Isoindolinones are the core structures of many natural products and drug molecules and are useful in materials science as fluorescent probes and synthetic dyes. The fused analogues of these blended lactams also have a wide range of applications in medicinal chemistry and chemical biology. Different synthetic approaches and the use of versatile reagents have been reported for the synthesis of these novel molecules. Different research groups have focused their efforts on improving synthetic protocols towards the synthesis of the isoindolinone frame both in the presence and absence of transition metals. However, the transition metal-based pathway requires hazardous conditions, which are toxic to the environment. In particular, the transition metal-free synthetic protocols for isoindolinones and their fused analogues are highly fascinating due to several advantages for the industrial production of these bio-active molecules. These concepts encouraged us to write this review to highlight the recent advancements in the synthetic methods involving transition-metal-free approaches from 2007 to 2021. As the main feature of this review, we summarize the synthetic pathways for the isoindolinones, highlighting the synthetic precursors, which include different *ortho*-substituted aromatic substrates *via* multistep or tandem protocols, under metal-free conditions. We also discuss the mechanistic pathway of each methodology for the formation of isoindolinones.

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Introduction

The presence of two/one carbonyl functionalities in the isoindole system is called phthalimide(1,3-dihydro-2*H*-isoindole-

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Shubhankar Samanta was born in Purba Medinipur, India in 1983. He received his MSc (Chemistry) Degree in 2006, from Vidyasagar University, India. He earned his PhD in 2011 under the supervision of Professor Jayanta Kumar Ray at the Indian Institute of Technology, Kharagpur, India. He pursued his research in organic synthesis. Presently, he is working as an Assistant Professor in Chemistry at Bidhanagar College, Kolkata, India. Dr Samanta has published 26 articles in international journals and he has completed three Governmental Research Projects to date.

Sk Asraf Ali

Dr Sk Asraf Ali was born (1984) in a village (Machinan) in Purba Medinipur, West Bengal, India. He acquired his MSc in Organic Chemistry from Ramakrishna Mission Residential College, Narendrapur (University of Calcutta) in 2010, and completed his PhD Degree (2021) in Synthetic Organic Chemistry under the supervision of Dr Shubhankar Samanta and Dr Mijanur Rahaman Molla at the University of Calcutta, Kolkata, India. Currently, he is working as a Lecturer in Physical Science at District Institute of Education and Training (DIET), North 24 Parganas, Banipur, West Bengal, India since 2016.

Fig. 1 Schematic presentation of various *c*-fused pyrroles.

1,3-dione) and isoindolinone. The isoindolinone system features a bicyclic nucleus, which is achieved through the blending of the γ-lactam ring with the benzene moiety. These types of compounds are also called phthalimidines, inner amides of the corresponding γ-amino carboxylic acid. Again, phthalimide is an analog of isoindolinone with an extra carbonyl group with respect to isoindolinone (Fig. 1). Here, we focus on isoindolinone, which has an immense impact on bioactivity when it is found in the core nucleus of natural products and pharmaceutical compounds.[1]

Bioactivity study of isoindolinones

Among the N-heterocyclic compounds, many promising drug conjugates with an isoindolinone core have been explored, which possess diverse pharmacological activities such as anthelmintic, antimicrobial, cyclooxygenase isoenzyme (COX-2), insecticidal, thrombin inhibition and specifically anticancer activity.[2] The cytotoxic phenol hericenone B isolated from the edible *Hericium erinaceus* mushroom displayed cytotoxicity to HeLa cells.[3a,b] Isoindolinone fused with chromene, which is known as stachybotrin C, belongs to the stachybotrin series obtained from the culture broth of *Stachybotrys* parvispora *F4708*, which possesses significant neuritis outgrowth in PC12 cells and has protecting properties against neuronal damage.[3c,d] Taliscanine is a phenanthrene-fused isoindolinone named aristolactams, which was extracted from *Aristolochia taliscana* and showed a wide range of biological properties as medication for neurological disorders such as Alzheimer's and Parkinson's disease.[3e] Pestalachloride A (Fig. 2) is a 2-aryl substituted isoindolinone. It was obtained from the endophytic fungus plant *Pestalotiopsis adusta*, which is active against plant pathogenic fungi. Quinocitrinine A was isolated from the biologically active substance producer fungi *Penicillium citrinum*.[3f,g] (+/−)-Chilenine and lennoxamine are multi-fused isoindolinone alkaloids obtained from *Berberis empetrifolia Lam* and *Berberis darwinii*, which are Chilean plants, respectively. These compounds exhibited various biological activities such as anxiolytic and anticonvulsant.[3h,i]

Anirban Bera

Mr Anirban Bera was born in Purba Medinipur, West Bengal, India in 1993. He studied Chemistry (Hons.) at Panskura Banamali College, Vidyasagar University in West Bengal, where he received his BSc Degree in 2014. He earned his MSc (Chemistry) Degree in 2016, from Vidyasagar University, India. After that he joined the research group of Dr Shubhankar Samanta at Bidhannagr College, India and obtained his PhD in 2018. His research is focused on the synthesis of heterocyclic compound and their photophysical studies.

Soumen Giri

Dr Soumen Giri is currently working as an Assistant Professor in C. V. Raman Global University, Bhubaneswar, Odisha. He completed his Master's Degree in Chemistry (Specialization: Organic Chemistry) from Vidyasagar University (2009) and received his PhD from the Indian Institute of Technology Kharagpur (2014). Later, he carried out his postdoctoral research at Okinawa Institute of Science and Technology, Japan (2015–17). He also previously worked as an Assistant Professor at the Regional Institute of Education (a constituent unit of NCERT, India). He has published more than 20 peer-reviewed papers and one book chapter. His current research interests include the synthesis of organic molecules and renewable energy.

Khokan Samanta

Dr Khokan Samanta was born (1981) in a village in Purba Medinipur, West Bengal, India. He obtained his MSc (2006) from Vidyasagar University, Paschim Medinipur, and PhD (2012) in Synthetic Organic Chemistry under the joint supervision of Prof. Achintya Kumar Sarkar and Prof. Gandhi Kumar Kar at Presidency University (formerly Presidency College under University of Calcutta), Kolkata, India. He carried out his postdoctoral research (2012–2013) in nanotechnology in Prof. Hyoyoung Lee's group at Sungkyunkwan University, South Korea. He has been working as an Assistant Professor (WBES) since 2015 at the Department of Chemistry, Haldia Government College, West Bengal, India. His research interest is focused on metal-catalyzed C–C coupling reactions, synthesis of bio-active heterocycles and graphene nanochemistry.

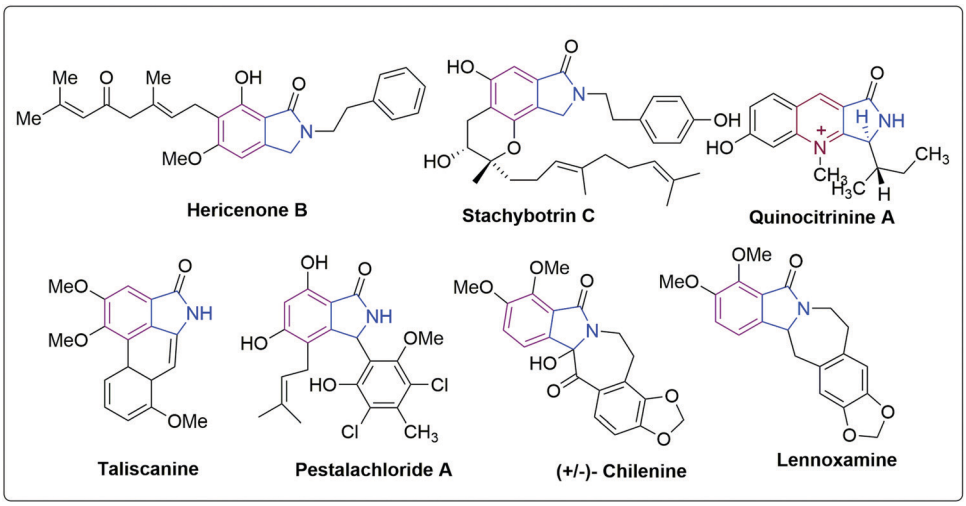


Fig. 2 Various naturally occurring compounds containing an isoindolinone core.

Different alkaloids of isoindolinones

The 3-substituted isoindolinone building block is the most common core that exists in natural alkaloids. Furthermore, many biologically active derivatives such as 3-hydroxyisoindolin-1-ones are the specific segment of natural products such as the alkaloid fumadensine, which was extracted from *Fumaria densiflora*, and another alkaloid fumaridine exhibited local anesthetic activity comparable to procaine.[4] Magallanesine is a nitrogen-containing eight-membered heterocycle fused isoindolobenzazocine (Fig. 3) obtained from *Berberis darwinii*.[4] Aporphine alkaloids contain a phenanthrene lactam core and mainly isolated from *Aristolochiaceae*, which were investigated as α-glucosidase inhibitors, antioxidants and antifungal agents.[5] Another isoindolinone-containing meroterpenoid is memnobotrin A, which was found in the *Memnoniella echinata* fungus, showing significant bioactivity.[6]

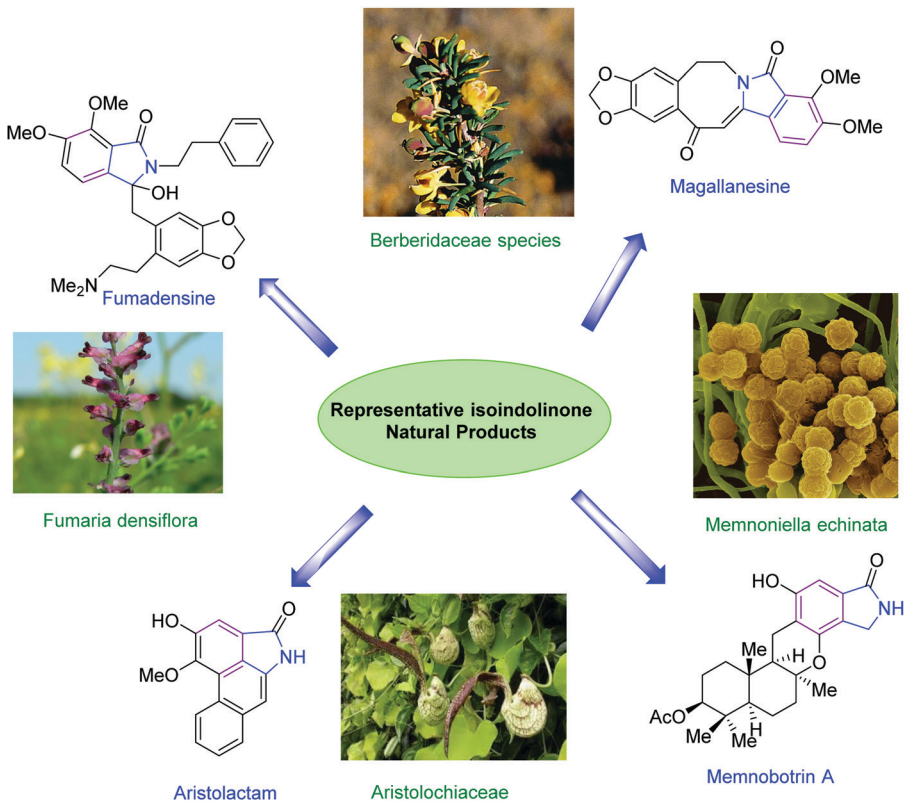


Fig. 3 Representative structures of natural products and their resources.

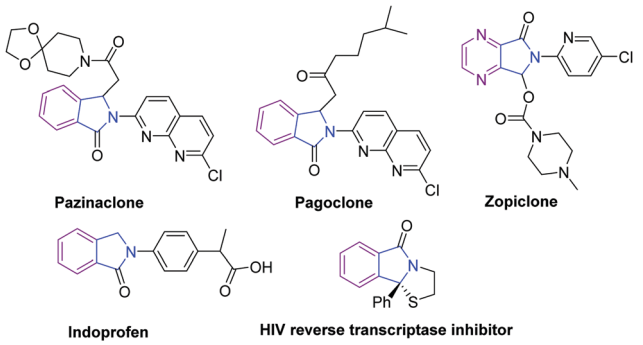


Fig. 4 Drugs containing the isoindolinone moiety.

Drugs containing isoindolinones

Inspired by the importance of natural products, we concentrate on the pharmaceutically active isoindolinone-substituted small molecules. In the case of the isoindolinone nucleus with a tertiary or quaternary stereocenter at the lactam ring, it has great importance in asymmetric synthesis for testing the biological properties of enantio-enriched compounds. The great success in the therapeutic applications and the molecular diversification of heterocycle-substituted isoindolinones such as pazinaclone, pagoclone and zopiclone (Fig. 4) has resulted in their use as sedative and muscle relaxant drug molecules. Indoprofen is used as an analgesic, antipyretic and anti-inflammatory agent. Dihydrothiazoloisoindolinone shows inhibition property towards HIV-1-contaminated MT 2 cells and HIV-1 reverse transcriptase screening assay.[7]

Application in other fields

Isoindolinone molecular systems with an extra carbonyl such as phthalimido are used for the colorimetric detection of anions, which demonstrates their environmental and biological importance to a great extent. The synthesized 4-nitro-*N*-[(1,3-dioxoisoin-dolin-2yl)benzamide] and 3,5-dinitro-*N*-[(1,3-dioxoisoindolin-2yl)benzamide] were applied as amide moiety-based fluorescent anion chemosensors (Fig. 5). These chromophores had strong fluoride ion selectivity and the fluorescence study employing tetrabutylammonium fluoride (TBAF) (5×10^{-3} M) in DMSO revealed that a colour change occurs from colorless to pink or violet depending on the respective ligands.[8]

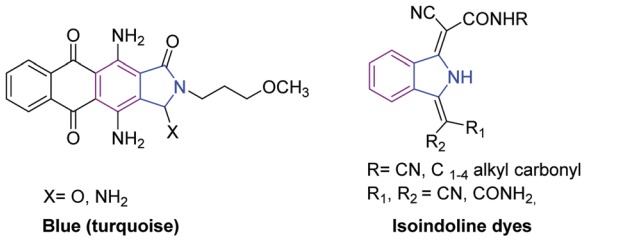


Fig. 6 Organic dyes consisting of a phthalimido ring.

Color plays a significant role in society, where in prehistoric times, the main source of color was natural resources such as plant leaf extracts, flowers, and fruits. However, presently, natural sources are insufficient to meet the high demand of color requirements. Thus, synthetic dyes have been commercialized as a source of color ingredients. There are various chromophores of different colors such as benzodifuranones, coumarins, methines, naphthalimides, quinophthalones and nitrodiphenylamines. Among these structural types, isoindolinone is one of the most important chromophores for the development of different synthetic colours (Fig. 6).[9]

Literature reports on the synthesis of isoindolinones

The broad range of physicochemical, pharmacological and domestic properties of isoindolinone derivatives has inspired researchers to find synthetic routes for the preparation of these molecules. These novel molecules have been prepared using isoindolinone precursors or non-isoindolinone scaffolds. A recent review article showed the synthetic pathways for the common naturally occurring moieties 3,3-disubstituted isoindolinones *via* nucleophilic substitution of 3-hydroxyisoindolinones or electrophilic α-functionalisation of 3-substituted isoindolinones.[10] Herein, we are interested in the synthetic pathways for isoindolinones and their fused analogues from available starting materials that do not contain any isoindolinone scaffolds in the initial step. Although there is a greater number of reports available on transition-metal catalyzed reactions[11a–g] *via* the reduction of the number of

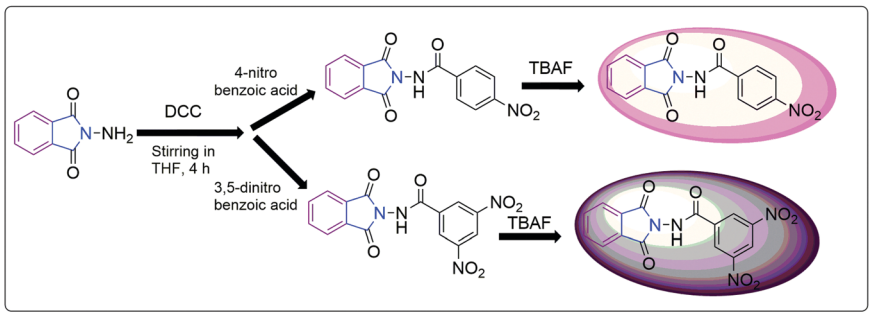


Fig. 5 Phthalimido compounds employed for the colorimetric detection of the F^- anion.

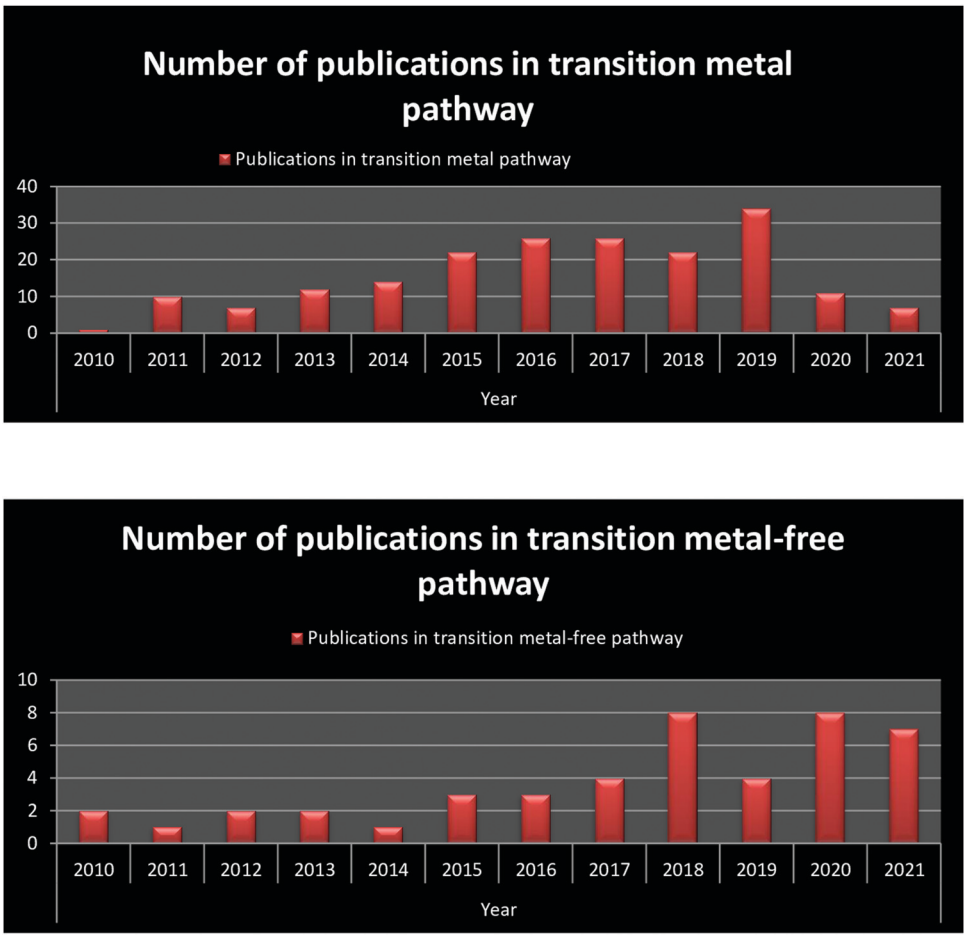


Fig. 7 Year-wise literature survey towards the synthesis of isoindolinones.

reaction steps to obtain the most available isoindolinone-based structures, transition metal-free protocols[12–53] offer various advantages over transformations involving transition metal catalysts. Transition metal-catalyzed protocols have the following drawbacks: (a) most metals are very sensitive to air and moisture, (b) toxic metals can easily mixed with drainage water during work-up, and (c) the high cost of metal catalysts is another barrier in the pharmaceutical industry. The major limitation of these catalytic reactions is the addition of co-catalysts, which are also complex, to enhance the efficiency and selectivity of chemical transformations. Hence, the use of transition metal catalyst-based protocols does not meet the requirement of sustainable synthesis. The development of environmentally benign approaches is highly economic for the preparation of heterocyclic compounds and has attracted great interest from chemists. Further, our year-wise literature survey showed that the rate of publications per year on the synthesis of isoindolinones decrease for the transition metal-catalyzed path compared to the transition metal-free path. Therefore, transition metal-free transformations under sustainable conditions are the alternative approaches to form various bonds, particularly in the synthesis of isoindolinone (Fig. 7).

In the last decade, some review articles have been published on the synthesis of isoindolinones[11a,h] but none of these reviews covered a range of metal-free isoindolinone synthetic methods including fused analogues (Fig. 8). Thus, considering the lack of availability of these metal-free reactions in the literature, herein, we present a review covering the recent literature from 2007 to 2021.

Owing to the great importance of isoindolinones, many reliable strategies have been employed for the preparation of substituted isoindolinone derivatives and their fused analogues. The most common precursors are *ortho*-substituted aryl rings with effective functionalities. These functional groups

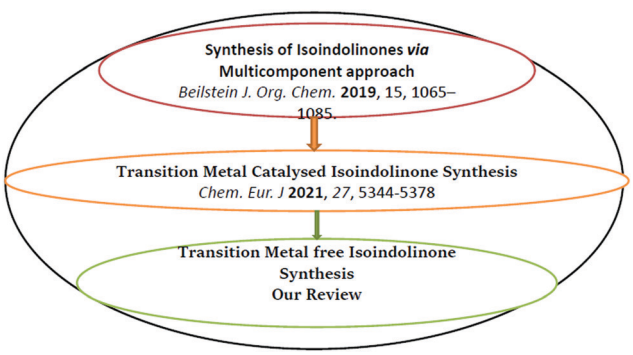


Fig. 8 Successive synthetic reviews on isoindolinones.

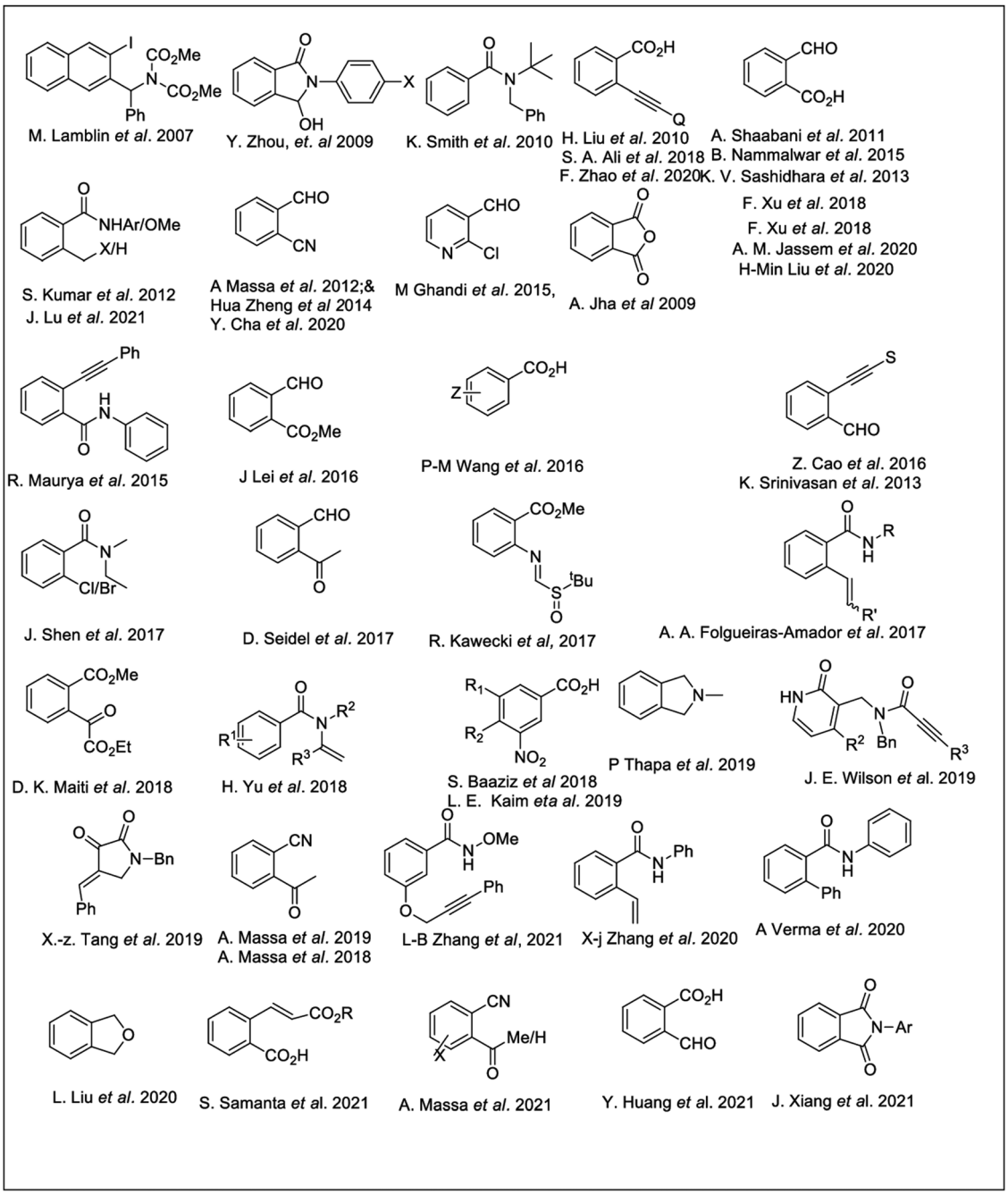
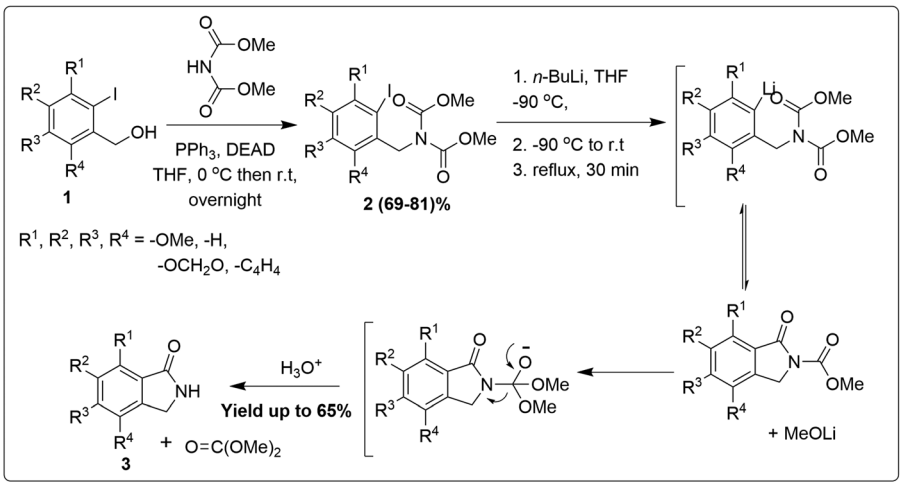


Fig. 9 Different synthetic precursors for isoindolinones and their fused analogues.

include –CHO, –CO_2H, –CONHR, –CN, –X (halogen) alkene, and alkyne. Based on our literature findings, we summarized our observations and consider *ortho*-formyl benzoic acid and *ortho*-nitrile benzaldehyde as the most reliable starting materials for the synthesis of isoindolinones *via* the transition metal-free approach. In the discussion on the protocol strategies, both intra/intermolecular paths are involved, which are carried out in multi-steps synthesis or one-pot cascade reactions. In this review, we chronologically discuss the different synthetic approaches for the preparation of isoindolinones and their fused analogues using various starting materials (Fig. 9).

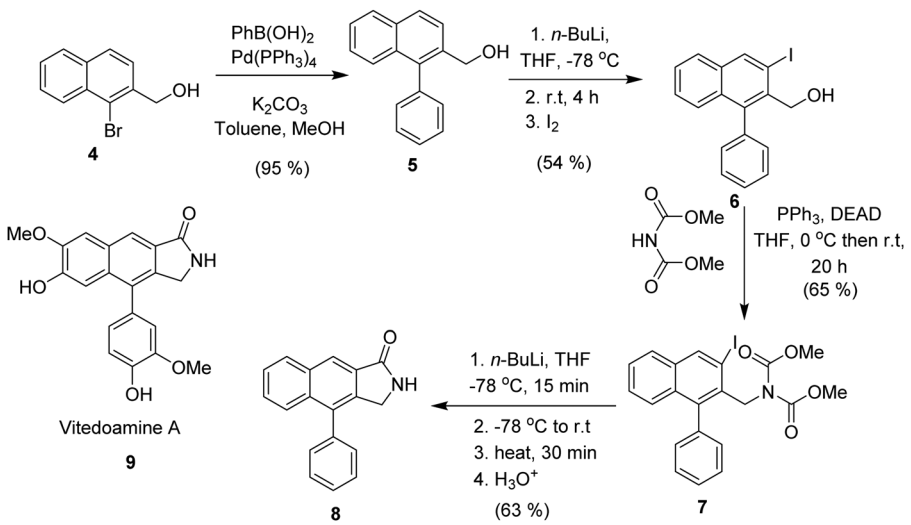
In 2007, M. Lamblin *et al.*[12] described an efficient synthetic route for 2,3-dihydro-1*H*-isoindol-1-one **3** from iodinated benzyldicarbamates **2** *via* Parham-type cyclization (Scheme 1). The starting materials for the Parham cyclization were obtained in two steps. The Mitsunobu coupling reaction of the appropriate substituted 2-iodobenzyl alcohols **1** with dimethyl iminodicarboxylate furnished intermediate **2**, which on lithium exchange reaction generated the desired precursors of the Parham cyclization. A series of 2,3-dihydro-1*H*-isoindol-1-ones **3** was afforded with satisfactory yields using different iodo-substituted aromatic benzyl alcohol **1**. In the above-mentioned



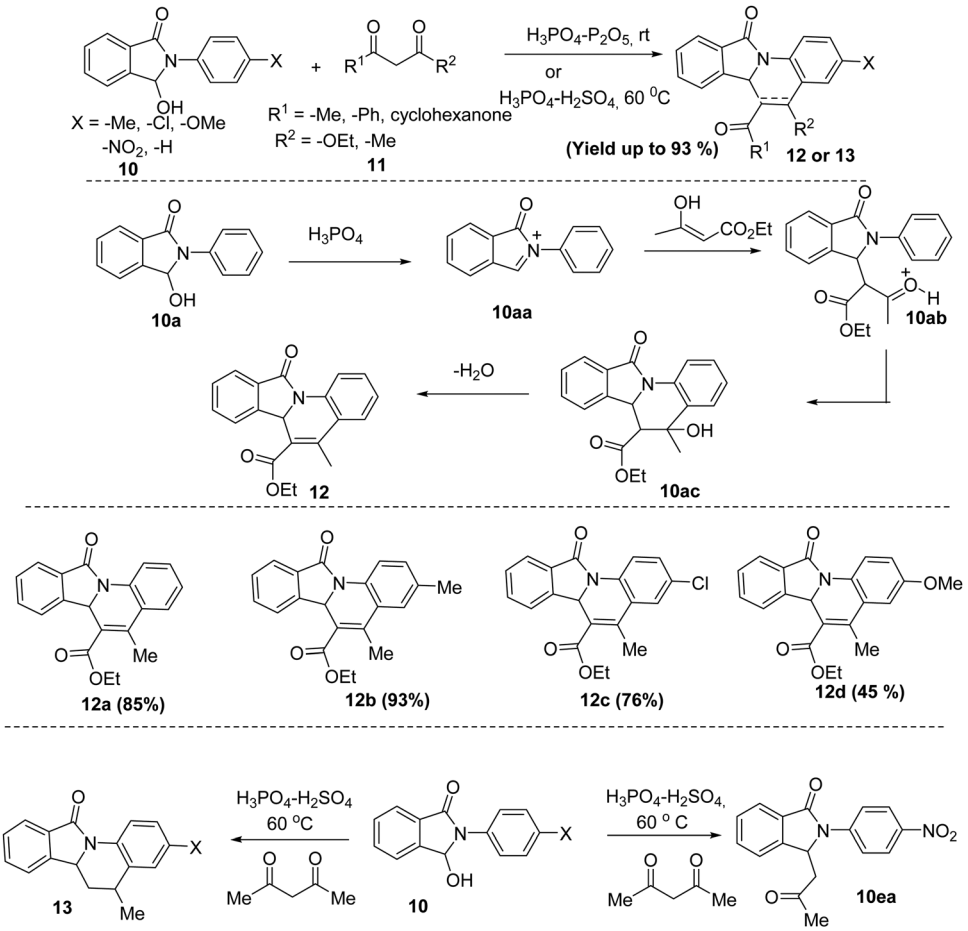
Scheme 1 Synthesis of isoindolinone *via* Parham cyclization.

reaction, only electron-donating groups were used as variants in benzyl system **1**. The main utility of this methodology was the preparation of the vitedoamine A analogue **9**, a new phenylnaphthalene-type lignan alkaloid recently isolated from the seeds of *Vitex negundo*, which are used as folk medicine for analgesia and sedation and have strong anti-oxidative activity.[12b] To achieve their goal, they first prepared exact scaffolds of the starting materials. For this purpose, Suzuki cross-coupling of phenyl boronic acid with 1-phenyl-2-naphthalenemethanol **5** followed by the same annulation strategy *via* the Parham cyclization process produced prominent alkaloids (Scheme 2).

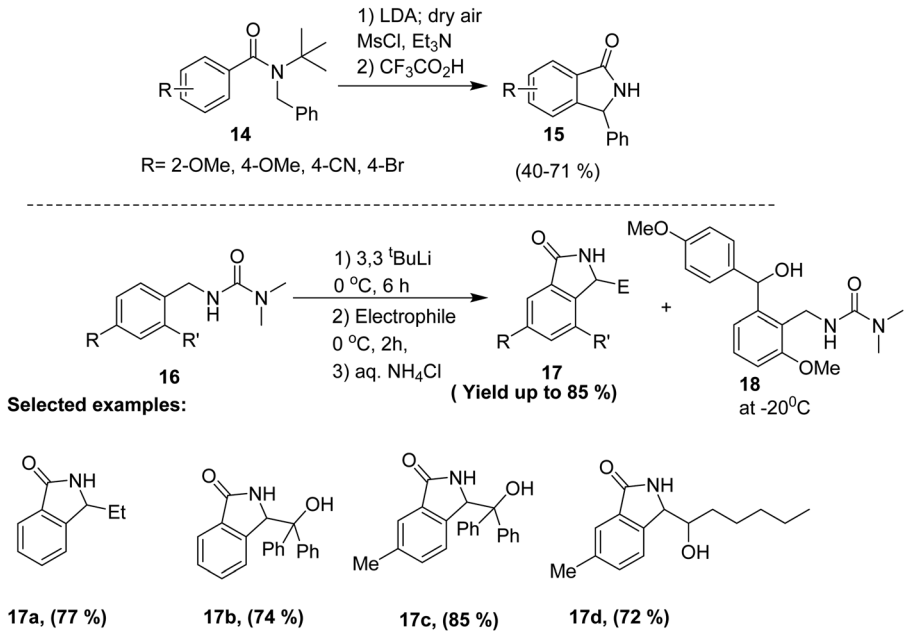
In 2009, W. Zhang *et al.* reported a synthetic route for the highly fused 6*a*,11-dihydroisoindolo[2,1-*a*]quinolin-11-ones **12** *via* the one-pot reaction of 3-hydroxy-2-aryl-isoindol-1-ones **10** and 1,3-dicarbonyls **11** (Scheme 3).[13] The reaction proceeded *via* the *N*-acyliminium ion intermediate generated from 3-hydroxy-2-aryl-isoindol-1-ones, which on nucleophilic addition followed by intramolecular Friedel–Crafts reactions catalyzed by acids led to the desired fused isoindolinone product **12**. Different Brønsted or Lewis acids ($BF_3{\cdot}OEt_2$, TFA, PTSA, and H_3PO_4) were used for the reaction of 3-hydroxy-2-arylisoindol-1-ones with 1,3-dicarbonyls. The addition of the product to isoindolinone in the presence of P_2O_5 or H_2SO_4 furnished the fused-isoindolinone with good yields. The methyl substituent in the aryl ring on the N-atom reacted at faster rate compared to the electron-withdrawing group (–Cl). Again a stronger electron-withdrawing group ($-NO_2$) in the aryl ring on N-atom was unable to produce the fused isoindolinone product, whereas it produced decarboxylated product **10ea**. The intramolecular Friedel–Crafts reactions depended on the H_3PO_4–P_2O_5 catalyst-mediated reaction at room temperature, generating the normal cyclization products **12**, but in the presence of H_3PO_4–H_2SO_4 at 60 °C, the deacetylation reduced products **13** appeared. This was the first report on the preparation of fused isoindolinones from hydroxyl isoindolinone *via* an *N*-acyliminium intermediate.



Scheme 2 Cyclization strategy for vitedoamine A.

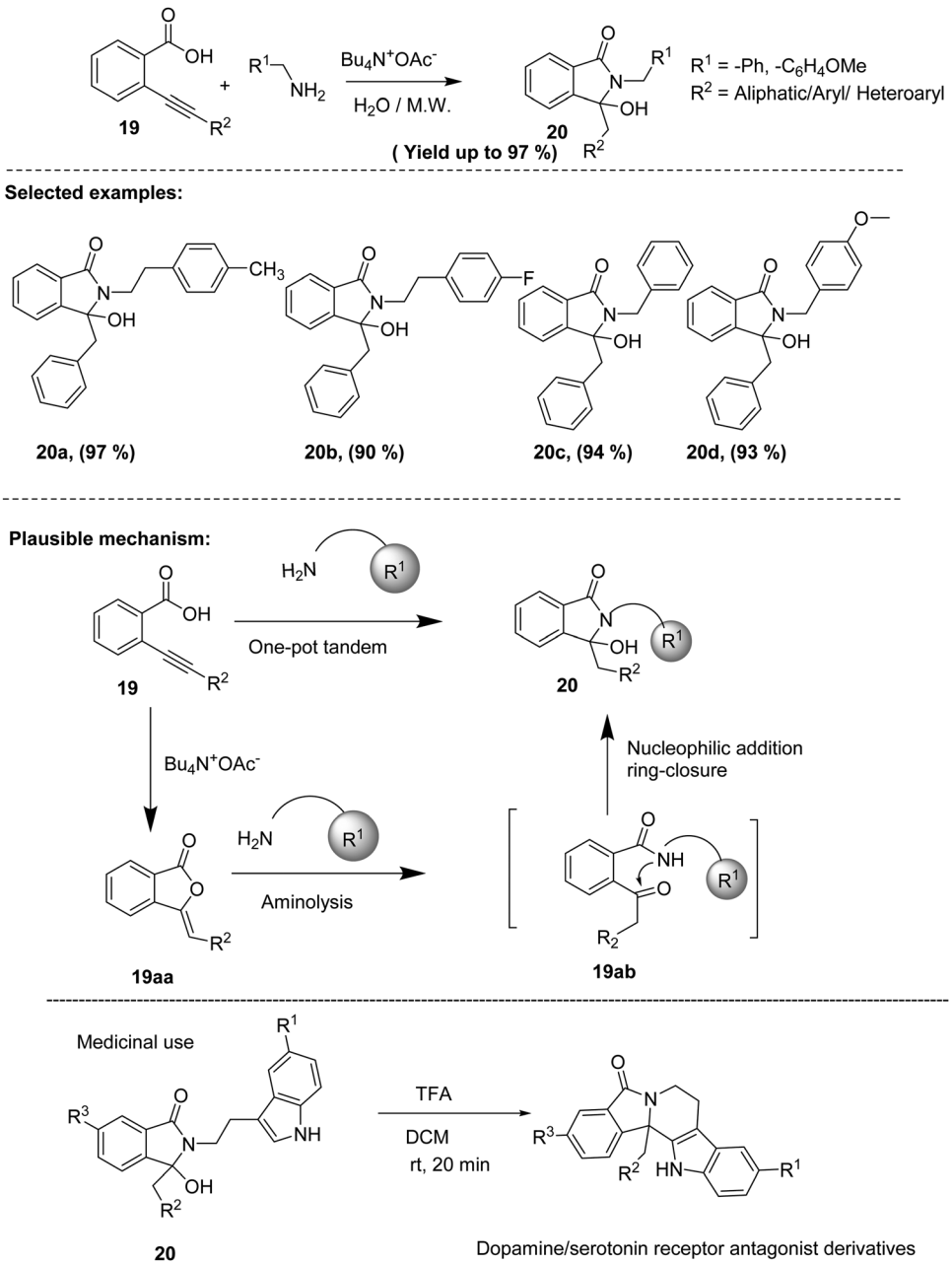


Scheme 3 Synthetic route of highly fused 6*a*,11-dihydroisoindolo[2,1-*a*]quinolin-11-ones *via* a one-pot reaction.



Scheme 4 Synthesis of isoindolinones using lithium as a chelating catalyst.

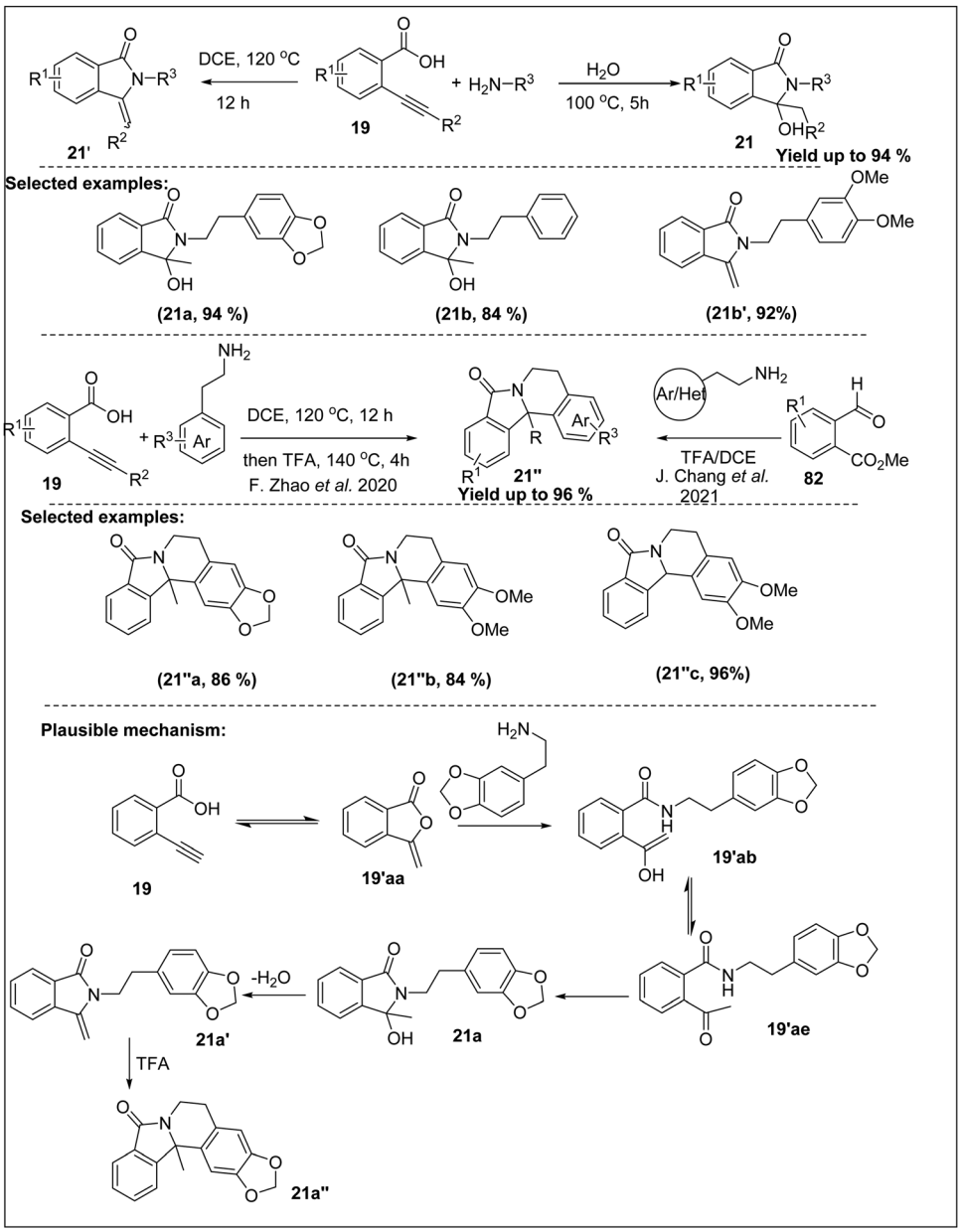
In 2010, K. Smith *et al.*[14] showed that lithium reagents are effective chelating catalysts for directed lithiation reactions, and hence this protocol was used for the synthesis of 2,3-dihydroisoindolin-1-ones. The discussed methodologies were formulated based on two reported protocols.[12a,b] The first is the introduction of any electrophile in 2,3-dihydroisoindol-l-one *via* lithiation reaction and the other method involves the generation of the isoindolin-1-one ring system **15** during the lithiation step such as cyclization of the intermediate obtained from *N*-*tert*-butyl-*N*-benzylbenzamides **14**. Based on these methodologies, K. Smith and group found that the reported reaction is temperature-dependent, and at −20 °C, molecule **16** reacted with 4-anisaldehyde, giving the simple electrophilic substitution acyclic product **18** (49% yield) and substituted isoindolinone **17** (40%). However, at 0 °C, the amide precursors furnished a good yield of isoindolinone **17** with the introduction of electrophile at 3-position (Scheme 4). The X-ray crystallography study revealed that the isoindolinone compound appeared as a single racemic diastereoisomer. Different aldehydes, ketones, and alkyl halides were used as electrophilic agents in this reaction. The scope of this reaction was also shown using other ring-substituted *N*′-benzyl-*N*,*N*-dimethylureas **16** (Scheme 4). Isolation of the final products was very easy, given that it involved simple powdering/or washing after work-up. This protocol is very simple and efficient for the synthesis of isoindolin-1-ones in a single step.



Scheme 5 Metal-free tandem transformation of 3-hydroxyisoindolin-1-ones.

Furthermore, the easy incorporation of various substituents in the benzene ring and several electrophiles to the 3-position of isoindolinone can be achieved using this reaction.

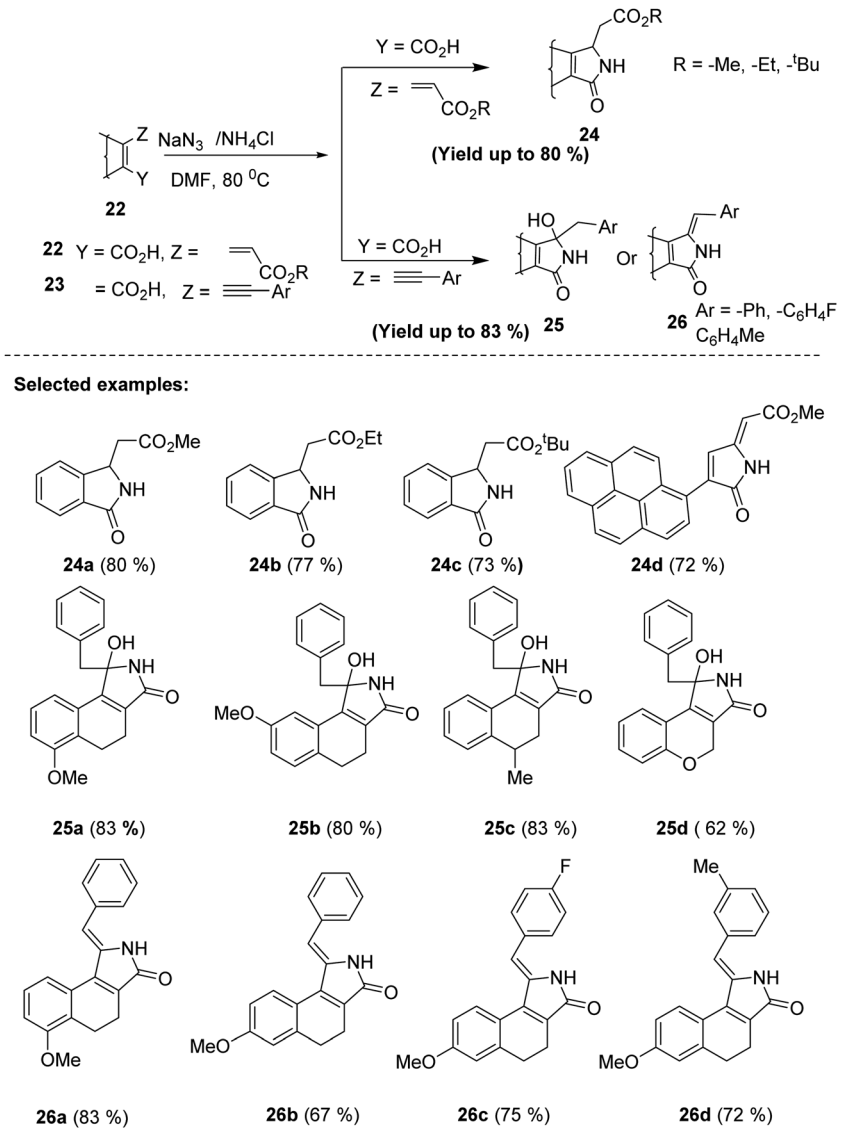
3-Hydroxyisoindolin-1-ones play a vital role in drug discovery and these derivatives are prepared *via* intramolecular cyclization of *ortho*-(substituted ethynyl)benzoic acids. Substrate **19** was cyclized in the presence of a phase-transfer catalyst and it underwent an intermolecular metal-free tandem reaction with amines to afford hydroxyisoindolinone with an excellent yield.[15a] The same strategy was applied in 2020 by S. Eisler and group for the synthesis of isoindolinones from *o*-alkynylamide *via* TBAF-promoted cyclization. The resulting isoindolinone substrates were used to synthesize thienopyrroles in good yields.[15b] The alkyne part of the *ortho*-(substituted ethynyl)benzoic acids was activated first using $Bu_4N^+OAc^-$ and formed the enol lactone-activated intermediate **19aa,** which was then attacked by the amino group to produce the aminolysis derivatives **19ab**. The resulting keto amide furnished the target product *via* an intramolecular nucleophilic addition reaction (Scheme 5). The high functional group tolerance is an advantage of this atom-economic transformation.[15] This green protocol underwent cascade cyclization with a variety of *o*-(substituted ethynyl)benzoic acids **19** and benzyl amines **20,** under the optimum conditions (Scheme 5). A range of alkylamines and aromatic-substituted benzylamines could participate in the reaction to afford hydroxyisoindolinone **21** with excellent yields (70–98%). Indole-based fused polycyclic heterocycles, which are dopamine/serotonin receptor antagonist



Scheme 6 Synthesis of three sets of isoindolinones from a single precursor.

derivatives, could be achieved by applying this green protocol, where hydroxyisoindolin-1-ones **19** could be effectively converted into more complex compounds upon being subjected to trifluoroacetic acid (TFA) in dry CH_2Cl_2 at room temperature for 20 min. Hence, this strategy is atom-economical, environmentally friendly and has broad application in the field of medicinal chemistry.

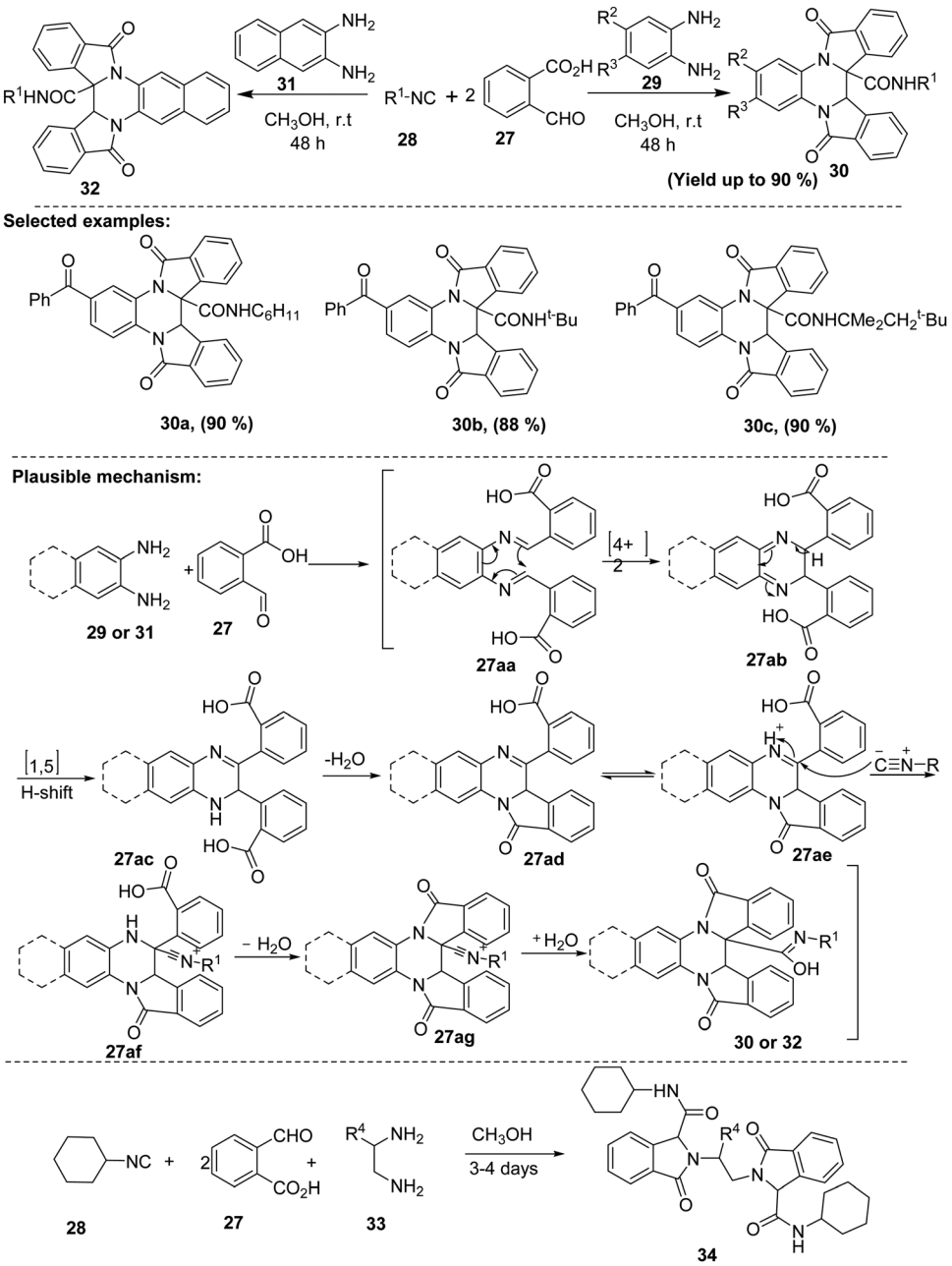
F. Zhao and group synthesized three types of isoindolinones, **21**, **21′**, and **21″**, from the precursor 2-alkynylbenzoic acids and β-amino aryl ethyl amines under three different reaction conditions in a controlled manner. They reported the synthetic pathways for 3-hydroxyisoindolinones **21** in water from readily available 2-alkynylbenzoic acids **19** and amines *via* catalyst- and additive-free conditions at 100 °C within 5 h. The same precursor **19** led to the formation of 3-methyleneisoindolinones in DCE solvent at 120 °C within 12 h but in the presence of TFA, the precursor underwent a two-component cascade transformation, leading to 5,6-dihydroisoindolo[1,2-*a*]isoquinolin-(12*bH*)-ones **21″** with good yields. This diverse oriented synthesis was broadly applied to a large number of substrates containing electron-donating/withdrawing substituents in both starting materials, giving 3-hydroxyisoindolinones in good yields. The formation of 3-methyleneisoindolinones was well-tolerated for cycloalkyl/alkyl/aryl amines and 2-alkynylbenzoic acids **19** with both electronic types. Only high electron-rich amines participated in the intramolecular cyclization and formed complex isoindolinone derivatives. They also studied the synthetic application of the final synthetic derivatives *via* methylation, hydrogenation, and $LiAlH_4$ reduction. The mechanistic observation showed that **21**, **21′**, and **21″** were formed in consecutive manner, *i.e.*, substrate **19** and amine formed **21a** *via* an enol lactone intermediate, and then the elimination of water resulted in the formation of **21a′**. Subsequently, it underwent intramolecular cyclization, giving complex derivative **21a″**.



Scheme 7 Substrate-dependent NaN_3/NH_4Cl-promoted aza-cyclization to diverse isoindolinones.

In 2021, different groups reported the synthetic route for the same fused isoindolinones scaffolds *via* the condensation reaction of 3,4-dimethoxyphenylethanamine and methyl 2-formylbenzoate **19′** (Scheme 6).[15d] Initially, they tested the reaction with different Lewis acids and found that the optimum conditions were TFA and dichloroethane at 70 °C. β-Aryl ethyl amine with an electron-donating group underwent cyclization more effectively compared to the electron-withdrawing substituent aryl part. Both the aryl/heteroaryl (indolyl/benzofuranyl/benzothiophenylethanamines) groups in the amine participated in cyclization under this methodology.

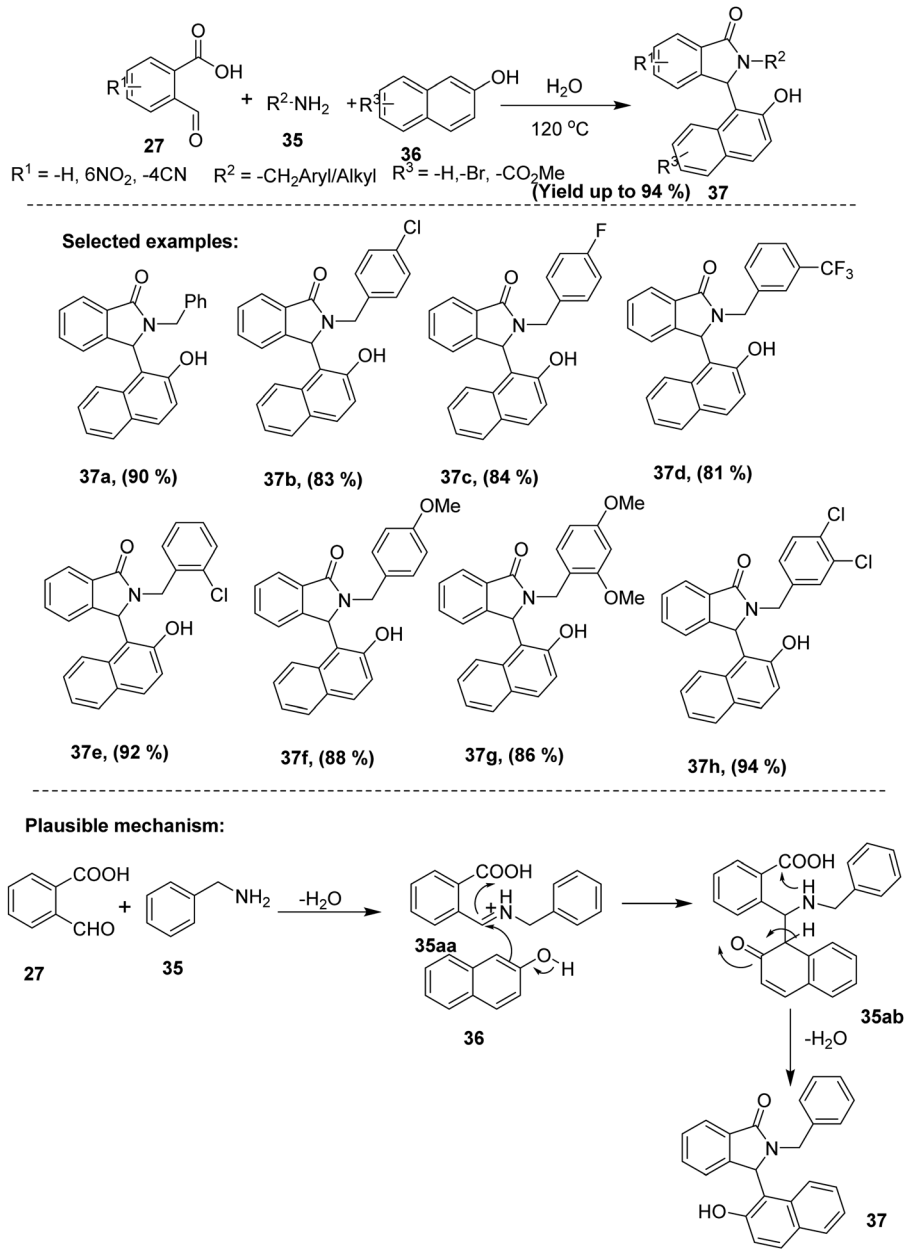
In 2018, our group established a substrate-dependent NaN_3/NH_4Cl-promoted aza-cyclization protocol for the synthesis of various bicyclic/tricyclic isoindolinone derivatives through a metal-free cascade transformation. This protocol was also employed for the synthesis of the dopamine D_4 receptor in the minimum number of steps. In continuation of our previous reported work on the preparation of heterocycles *via* intra/intermolecular aza-cyclization reactions,[16] here we developed an NaN_3/NH_4Cl-promoted substrate-dependent general route for the synthesis of bio-active isoindolinones/3-hydroxyisoindolinone/benzylidene-isoindolinones (Scheme 7).



Scheme 8 Synthesis of tetrahydrodiisoindoloquinoxaline using one-pot pseudo-four-component strategy.

The modification of the starting material was performed to convert the formyl group into a carboxyl group *via* Pinnick oxidation to achieve the three types of isoindolinones, **24**, **25** and **26**. Firstly, the azide-alkene cyclization reaction was established with acrylic ester derivatives and carboxylic acid **22** to get isoindolinone derivatives **24** *via* aza-Michael addition reaction using simple NaN_3/NH_4Cl in DMF at 80 °C. Condition-dependent azide cyclization was achieved to form tricyclic 3-hydroxyisoindolin-1-ones **25** and benzylidene-isoindolinones **26** from **23**. The use of 3 mmol NaN_3 and 3 mmol NH_4Cl furnished **25** but the addition of 6 mmol of both NaN_3/NH_4Cl produced **26**. This methodology is also well-developed to get the diastereoselective *Z*-isomer from the cycloalkenyl moiety. The pyrene-based fluorescence isoindolinone **24d** exhibited good bio-activity towards the CHO (Chinese hamster ovary) cell line and it was shown that compound **24d** was readily internalised in the targeted cell. The design of the substrate for the dopamine D_4 receptor and bio-activity study using the CHO cell line are the important outcomes of the discussed protocol.

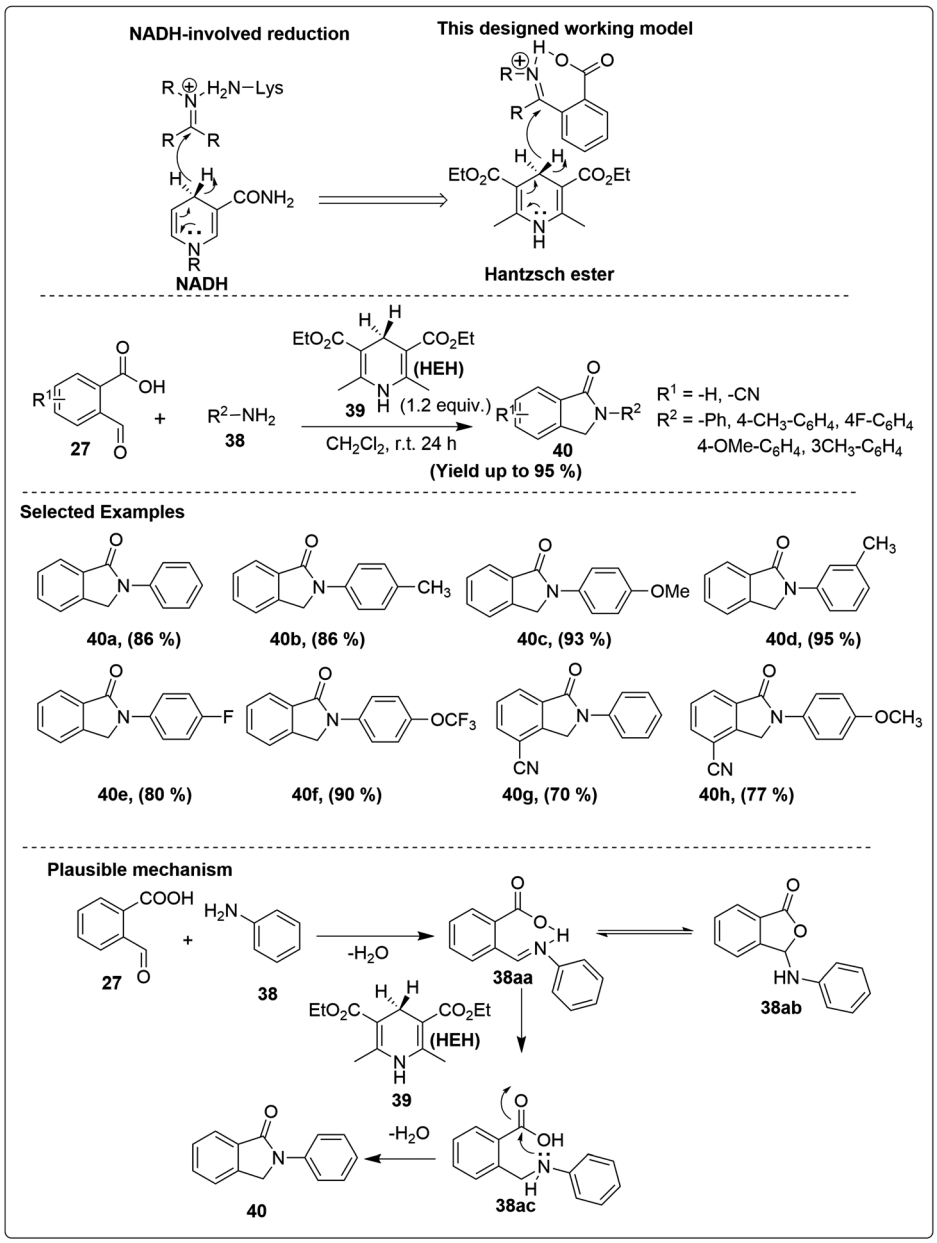
Multicomponent reactions (MCRs) are powerful tools for green synthesis given that they produce biologically relevant complex molecules with a single click. The one-pot pseudo-four-component strategy was applied for the synthesis of tetrahydrodiisoindoloquinoxaline **30** and tetrahydrobenzodiisoindoloquinoxaline **32** derivatives (Scheme 8).[17] Here, 1,2-diamines **29**, 2-formylbenzoic acid **27** (2 mol), and isocyanide



Scheme 9 Synthesis of isoindolinones *via* three-component Mannich-type cascade reaction.

28 at room temperature underwent cyclization to form multi-fused isoindolinone derivatives **30** and **32** in good yields. Naphthalene-2,3-diamine **31** in place of aromatic 1,2-diamines afforded the same diisoindoloquinoxaline derivatives **30** and **32** in good yields at room temperature. Alicyclic, aryl, alkyl, and isocyanides and different *o*-phenylenediamines with formyl benzoic acid are considered as the variants in the above-mentioned protocol. They introduce a nice mechanistic path for the synthesized complex isoindolinone derivative. Two moles of formyl benzoic acid **27** coupled with one mole of diamine derivative **29**, and then electrocyclic ring-closing produced **29aa**, followed by 1,5-H shift to generate intermediate **29ac**, which on reaction with alkyl isocyanide **28**, led to the desired compound **30**. The complex compound was confirmed by single-crystal X-ray analysis. Aliphatic diamines **33** did not give the same result, instead affording a new class of bis(oxoisoindoline) derivatives **34** in good yield. The developed synthetic procedure is important for the preparation of synthetically and pharmaceutically relevant isoindoloquinoxaline systems.

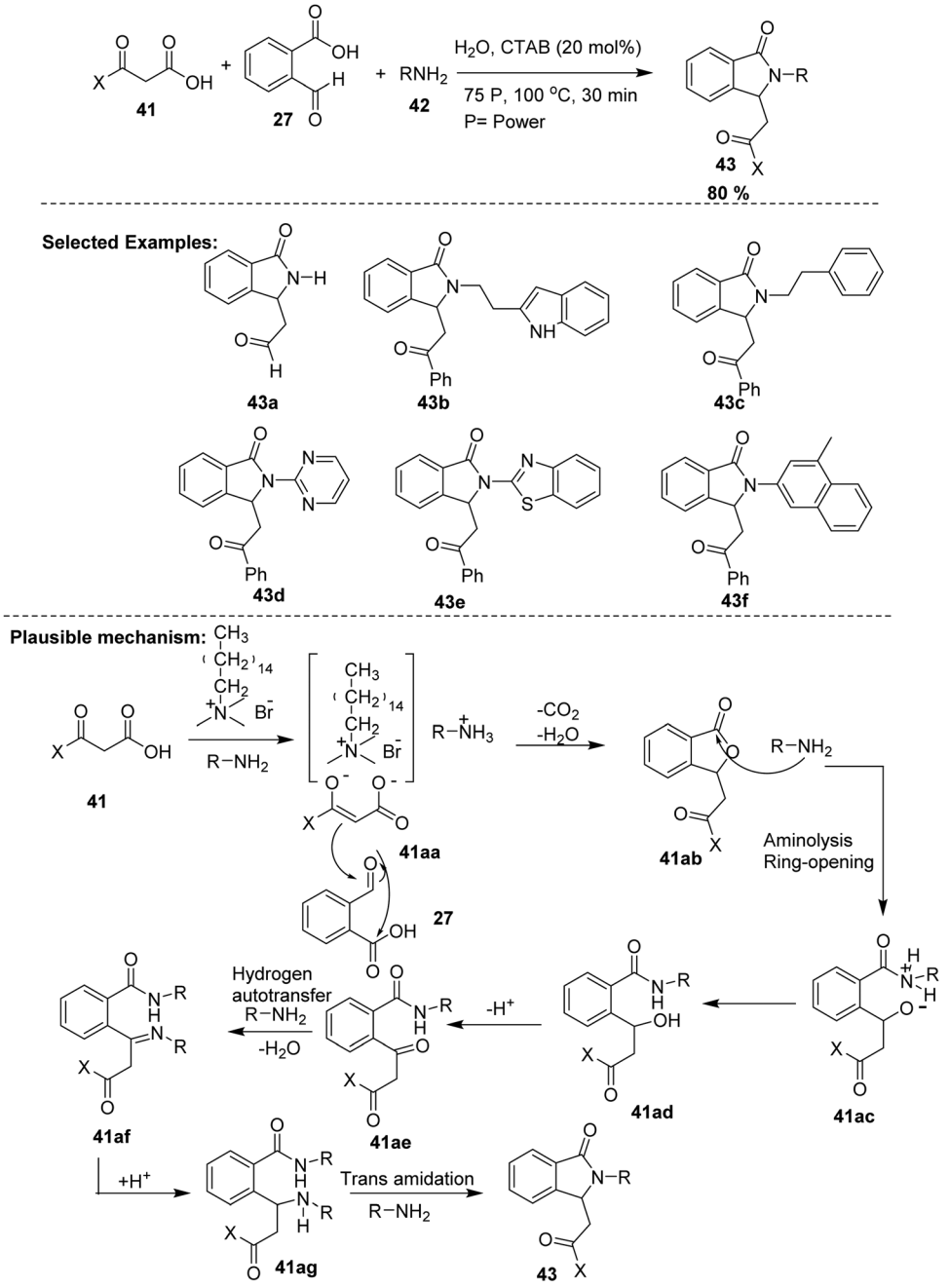
2-Naphthol-substituted isoindolinones **37** were synthesized *via* the three-component cascade reaction of primary amine **35**, 2-formylbenzoic acid **27**, and 2-naphthol **36** under catalyst-free conditions *via* a Mannich-type transformation (Scheme 9).[18] The attractive aspect of this methodology is the use of aqueous solution instead of conventional solvents. Substituted benzyl amine, furfuryl, 1-phenylethyl, 4-phenylbutyl amines and some common aliphatic amines are considered as variants in this



Scheme 10 Isoindolinone synthesis using Hantzsch ester.

sequential reaction. Isopropylamine gave the corresponding product in poor yield and *tert*-butylamine did not furnish any fruitful results due to steric hindrance. The mechanistic observation of this green protocol involves the condensation of amine **35** with phthalaldehydic acid **27**, which generates imine intermediate **35aa**. Mannich-type reaction of 2-naphthol **36** with the activated iminium intermediate **35aa** delivers intermediate **35ab**, which on intramolecular aza-cyclization, produces desired product **37**. This sustainable approach has the following advantages: (i) this protocol is atom-economical as water as the only by-product, (ii) the method is free from work-up and conventional chromatography procedure, (iii) it is free from any metal and red or yellow mark solvent in the concept of environmental terminology.

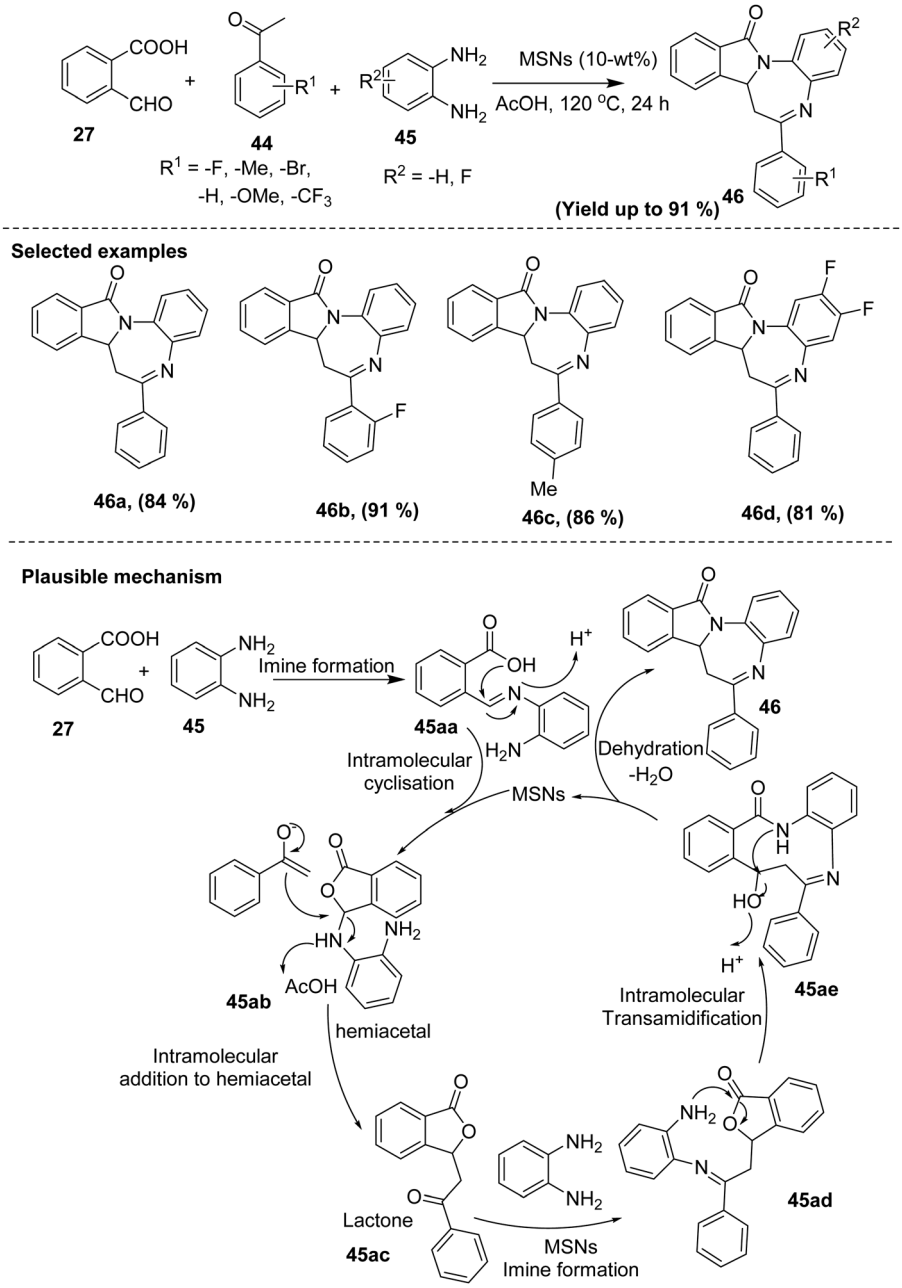
Currently, Hantzsch esters are effective reductive agents for organocatalytic base redox reactions similar to nicotinamide adenine dinucleotide (NADH), which is a coenzyme found in all living cells and serves as a hydride co-factor for a broad range of reductions. Y. Tian *et al.* designed an accessible starting materials that can undergo intramolecular reaction with Hantzsch esters to form isoindolinone-incorporated drugs under mild, facile and easy reaction conditions (Scheme 10).[19]



Scheme 11 Synthesis of 3-substituted isoindolinone derivatives using lactamisation reaction.

Phthalaldehydic acid **27** and aryl amine **38** with HEH **39** underwent amination/cyclization in DCM at room temperature, yielding isoindolinones **40**. Electron-donating/electron-withdrawing substituents at the *para* position worked equally with respect to the yield of isoindolinones **40**. 2-Naphthyl amine produced a lower yield of isoindolinone due to the steric compression. Based on their literature observation, they proposed a mechanism for the formation of isoindolinone, which is presented in Scheme 10. Initially, phthalaldehydic acid **27** reacts with aryl amine **38** to form an imine as the product, which on equilibration produces isobenzofuranone **38ab**. Thereafter, an acid-amine coupling reaction gave the ultimate target **40**. Researchers prepared the same scaffolds with the toxic CO or flammable H_2. This methodology paves a new way for transfer hydrogenation, which can furnish the desired isoindolinone **40** with effective yield. The key point of this protocol is that it employs a low-cost organo-based reducing Hantzsch ester, which avoids the conventional hydride-based (B, Al, Si, *etc.*) reducing substrates.

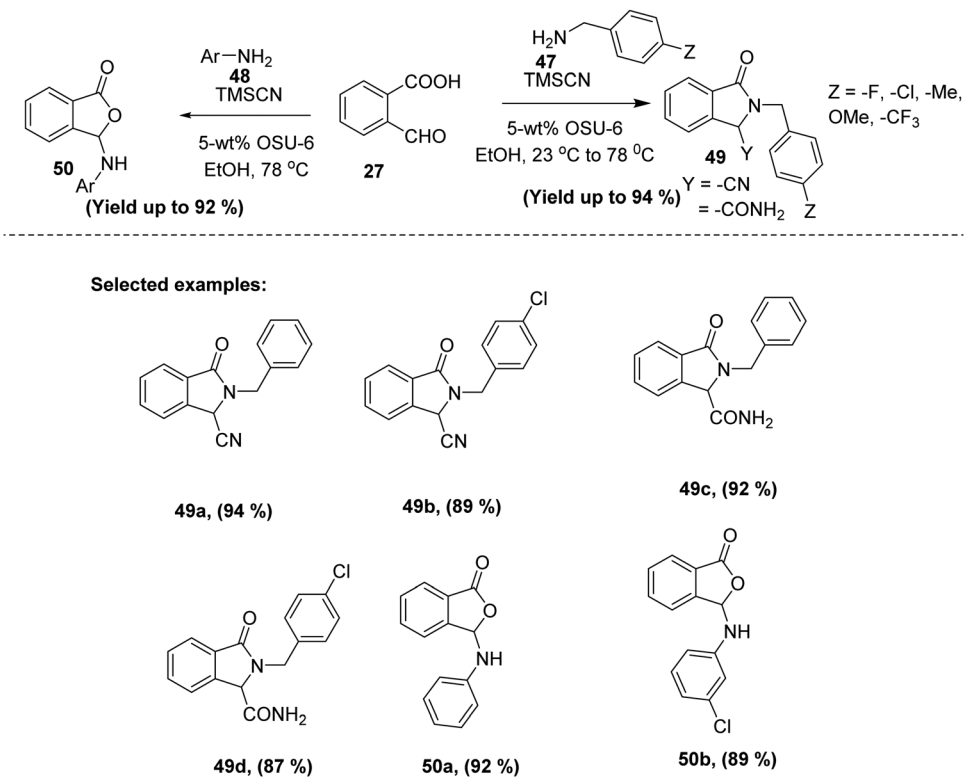
A microwave-assisted three-component green protocol was developed for the preparation of 3-substituted isoindolinone derivatives **43**. β-Ketocarboxylic acids **41**, 2-carboxybenzaldehyde **27**, various primary amines **42** and cetrimonium bromide salt were used for the multicomponent cascade



Scheme 12 Preparation of complex benzodiazepine-fused isoindolinone.

decarboxylation/lactamization reaction (Scheme 11).[20] The use of toxic solvents was avoided in this methodology, instead the most environmentally friendly green solvent, water, was used. Again, the microwave (MW) irradiation technique appears to be the most promising technology in green chemistry given that it involves direct heating of the substrate compared to the conventional heating process. Hence, it reduces the reaction time and increases the product yield. This methodology was no exception. Camphorsulphonic acid (±) CSA, L-proline, DBU and CTAB were used as the catalyst for the decarboxylative reaction. Different aliphatic amines with the aromatic substitutions were applied for the amine source. Aryl-alkyl amine with a methoxy substituent furnished a better yield compared to the unsubstituted aromatic amine. This methodology was constructed *via* dianion formation of β-ketocarboxylic acids **41** with help of amine **42** and CTAB. The dianion formed attacked the aldehyde functionality of 2-carboxybenzaldehyde **27**, and subsequently a water molecule was eliminated with the generation of lactone intermediate **41ad**. This intermediate on aminolysis by the addition of excess primary amine formed keto-amide species **41ae**, which on intramolecular water elimination, generated the desired product **42**. They investigated the antifungal and antimicrobial activity of different synthesized compounds against *Aspergillus niger*, *Fusarium Serratia*, *Staphylococcus aureus*, *Fusarium oxysporum*, *Escherichia coli*, and *Bacillus subtilis* and showed the effectiveness of the as prepared compounds on *Aspergillus niger* when the *N*-aryl-amine substituent had pyrimidyl **43d** and isothiazole moiety **43e**. The drug-like structure of the synthetic compounds was also investigated by this group.

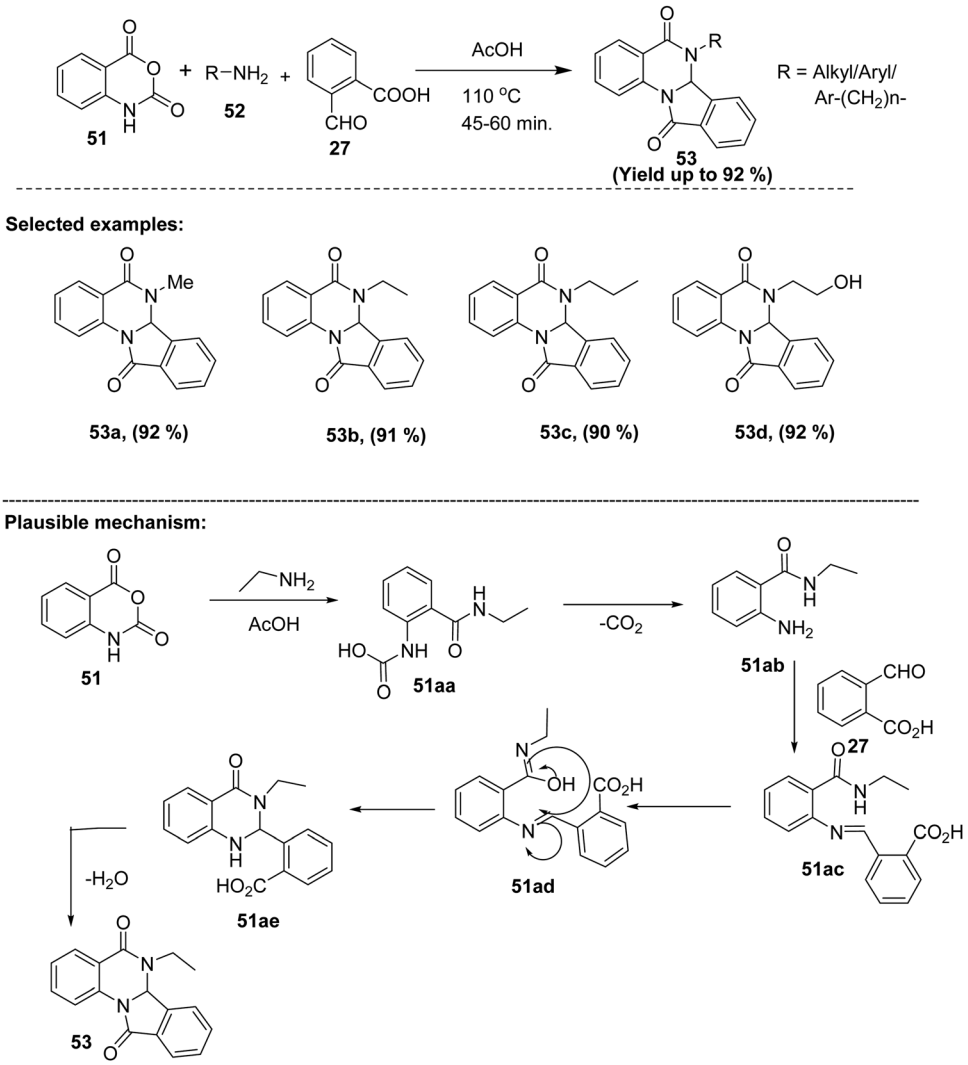
The most popular field of organic chemistry is the preparation of effective catalysts and their application in the synthesis of bio-relevant molecules. Mesoporous silica nanoparticles (MSNs) have a high surface area, low coordinating sites and act as Lewis acids during organic synthetic transformations. Furthermore, their excellent stability, ease of recovery and recyclability added new advantages to their excellent catalytic activity. The sol–gel method was used for the preparation of this type of novel catalyst, in which used base acts as the catalyst, hexadecyltrimethylammonium bromide (CTAB) as the template, and tetraethyl orthosilicate (TEOS) as the silica source. In 2020, S. Yuan *et al.*[21] used the catalytic activity of MSNs for the synthesis of pseudo natural products (NPs) containing isoindolinone as the main scaffold. They described a three-component coupling reaction for a highly fused isoindolinone derivative using 2-formylbenzoic acid **27**, acetophenone **44** and 1,2-diaminobenzene **45**. They tried different catalysts such as SiO_2, Amberlyst-15 (A-15) and Montmorillonite-K10 (Mont-K10) together with MSN catalysts but the most effective result was obtained when mesoporous silica nanoparticles were used with AcOH. The scope of the above-mentioned methodology was examined with the substituent on aryl ketone and *o*-phenylene diamine and it was found that benzodiazepine-fused isoindolinones **46** were obtained in good yield for both electronic natures of the functional group. The mechanistic part of the reaction was well-established by a



Scheme 13 Synthesis of 3-oxoisoindolines from 2-carboxybenzaldehyde.

controlled experiment and they used different proposed intermediates for the effectiveness of product formation. Hence, they proposed the catalytic pathway of the green methodology, where hemiacetal **45ab**, lactone **45ac**, and iminolactone intermediates **45ad** were used for intramolecular cyclization (Scheme 12). The developed methodology offers several advantages. It is free from any metal and benzodiazepine-fused isoindolinone, a pseudo natural product, was prepared on the gram scale. Another significance of this protocol is the construction of three C–N bonds, one C–C bond and two heterocyclic ring systems (benzodiazepine and isoindolinone) in one-pot.

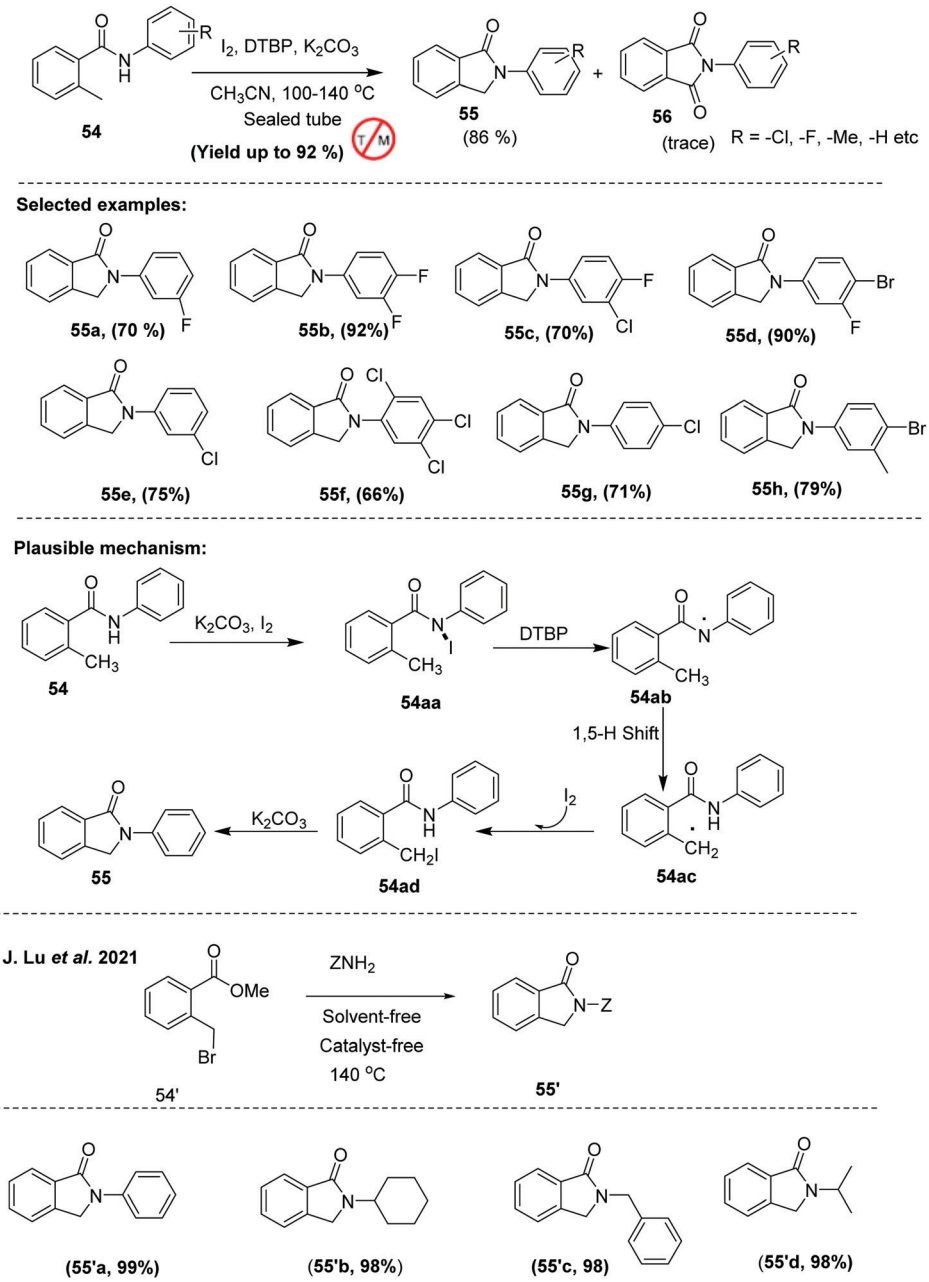
A hexagonal mesoporous silica catalyst was an efficient material for the synthesis of 3-oxoisoindolines from 2-carboxybenzaldehyde **27**, TMSCN and benzylic **48** or aliphatic amines **47**. The OSU-6 catalyst has strong Lewis acidic properties compared to the easy MCM-41-type hexagonal mesoporous silica-based catalyst. This reaction is free from traditional work-up procedures and has several advantages given that the catalyst was reused by simply separating the crude product *via* filtration. Also, its catalytic activity remained intact up to the 5th cycle and it gave the desired product up to 8% after the 5th cycle by washing with an ethanol-water mixture in a 1 : 1 ratio. Electron donating/withdrawing substituents on the aromatic ring were well-tolerated for Lewis acid-promoted intramolecular cyclization (Scheme 13).[22] This methodology is highly substrate and condition dependent. Here, TMSCN in the presence of dry OSU-6 catalyst led to the formation of 3-cyano-substituted isoindolinone at room temperature but the moisture present in the catalyst helped the cyanide to hydrolyse at 78 °C to the primary amide and form amide-substituted isoindolinone derivative **49**. Compared to the aliphatic amine, the aromatic amine gave different results for this protocol such as aniline in the presence of TMSCN and OSU-6 in refluxing anhydrous ethanol gave the isobenzofuranone **50** derivative (Scheme 13). This methodology gives us an interesting observation for the effect of moisture on the catalyst, where a trace amount of water in the catalyst promoted the hydrolysis of



Scheme 14 Synthesis of dihydroisoindoloquinazolinone using catalyst-free conditions.

nitrile to amide but the deliberate addition of water failed to produce clean amide formation.

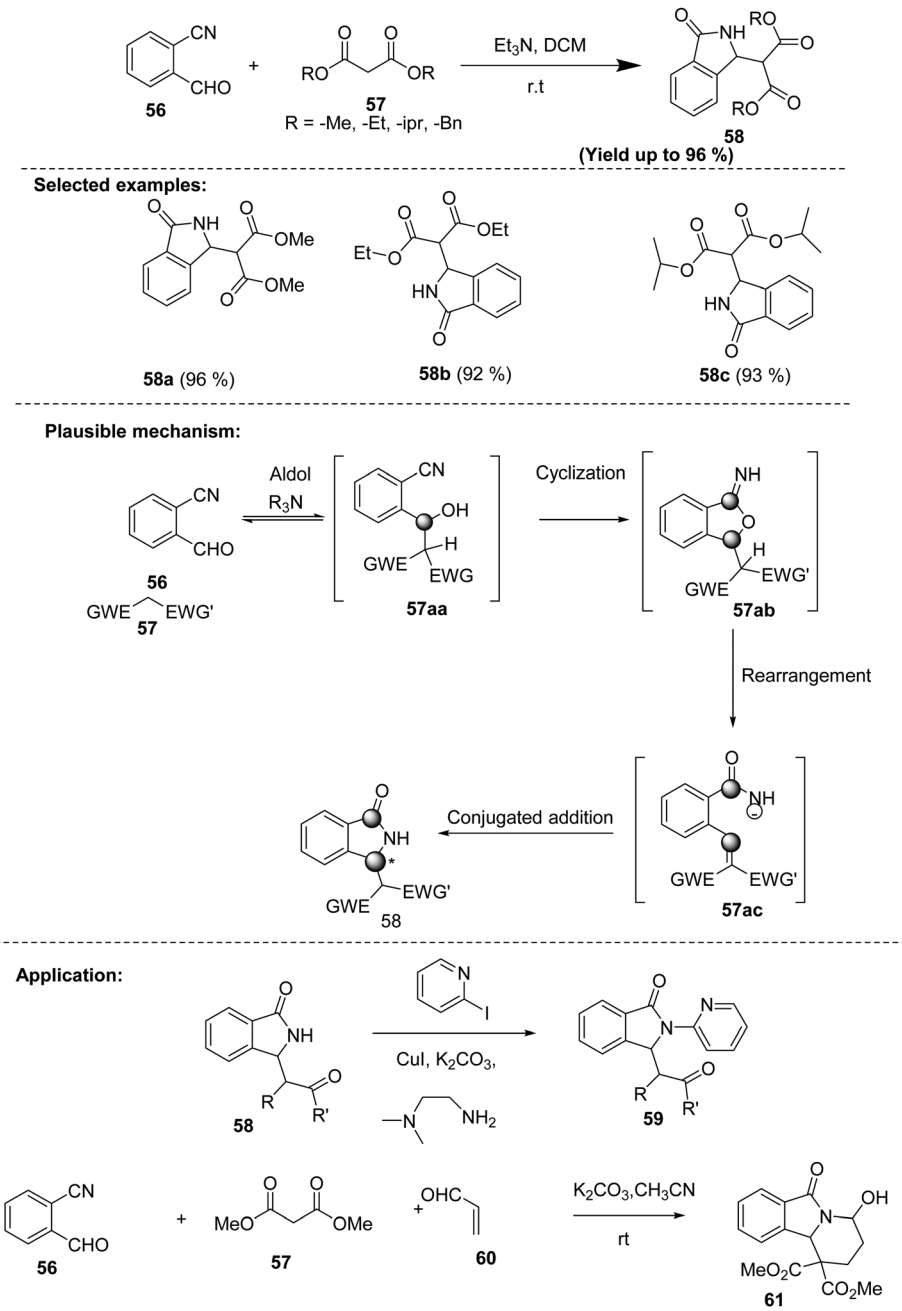
In sustainable science, multicomponent reactions (MCRs) are found to be the most powerful methods to access complex structures from simple building scaffolds and this protocol becomes more attractive when drug-like molecules are formed *via* a single synthetic operation. 6,6*a*-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives **53** in acetic acid were formed under transition metal-free conditions (Scheme 14).[23] The readily available starting material 2-formylbenzoic acid **27**, isatoic anhydride **51** and aryl/alkyl amine **52** underwent a three-component coupling reaction, affording a highly condensed isoindolinone derivative in excellent yield. This protocol was applicable for both aliphatic and aromatic amines with the substrate parameter 2-formylbenzoic acid with isatoic anhydride. The reaction was not promoted in strong acidic solvent, *i.e.*, it failed in trifluoroacetic acid medium. Hence, weak acid plays an important role in promoting acid-catalyzed three-component cyclisation. The acid-catalyzed reaction happened *via* the condensation reaction of *N*-alkyl anthranilamide **51ab** with 2-formylbenzoic acid **27**, and then intramolecular nucleophilic addition with the imine carbon generated quinazolinone intermediate **51ae**, which on subsequent water elimination, produced highly condensed dihydroisoindoloquinazolinone



Scheme 15 Synthesis of isoindolinones using transition metal-free intramolecular selective oxidative coupling.

53. The transition metal-free synthesis of highly condensed isoindolinones within a short time is the main attraction of this methodology.

Isoindolinones containing indoprofen and DWP205190 drug molecules were obtained from 2-alkylbenzamide substrates **54** *via* the transition metal-free intramolecular selective oxidative coupling of C(sp^3)–H and N–H bonds in the presence of potassium carbonate, iodine, and di-*tert*-butyl peroxide in acetonitrile at 110–140 °C (Scheme 15).[24a] Different aromatic amines were employed as the amine sources for various *N*-aryl isoindolinone derivatives **55**. Electron-donating and withdrawing substituents in the aryl rings furnished better results and they can also tolerate the steric effect in the *N*-aryl ring. The biologically important methoxy-substituted isoindolinones were synthesized, which showed the TNF-α production effect toward cancer cells, and this protocol reduced the number of steps compared to the previously reported methodology. The controlled experiment showed that the reaction was slowed down by the addition of TEMPO. This indicates that the discussed protocol follows the radical pathway. During the course of the reaction, initially 2-methyl-*N*-aryl benzamide reacts with iodine to form *N*-iodo intermediate **54aa**. Then, cleavage of the *N*-iodo bond of the intermediate furnishes the nitrogen-centered amide radical **54ab**, which on 1,5-H shift

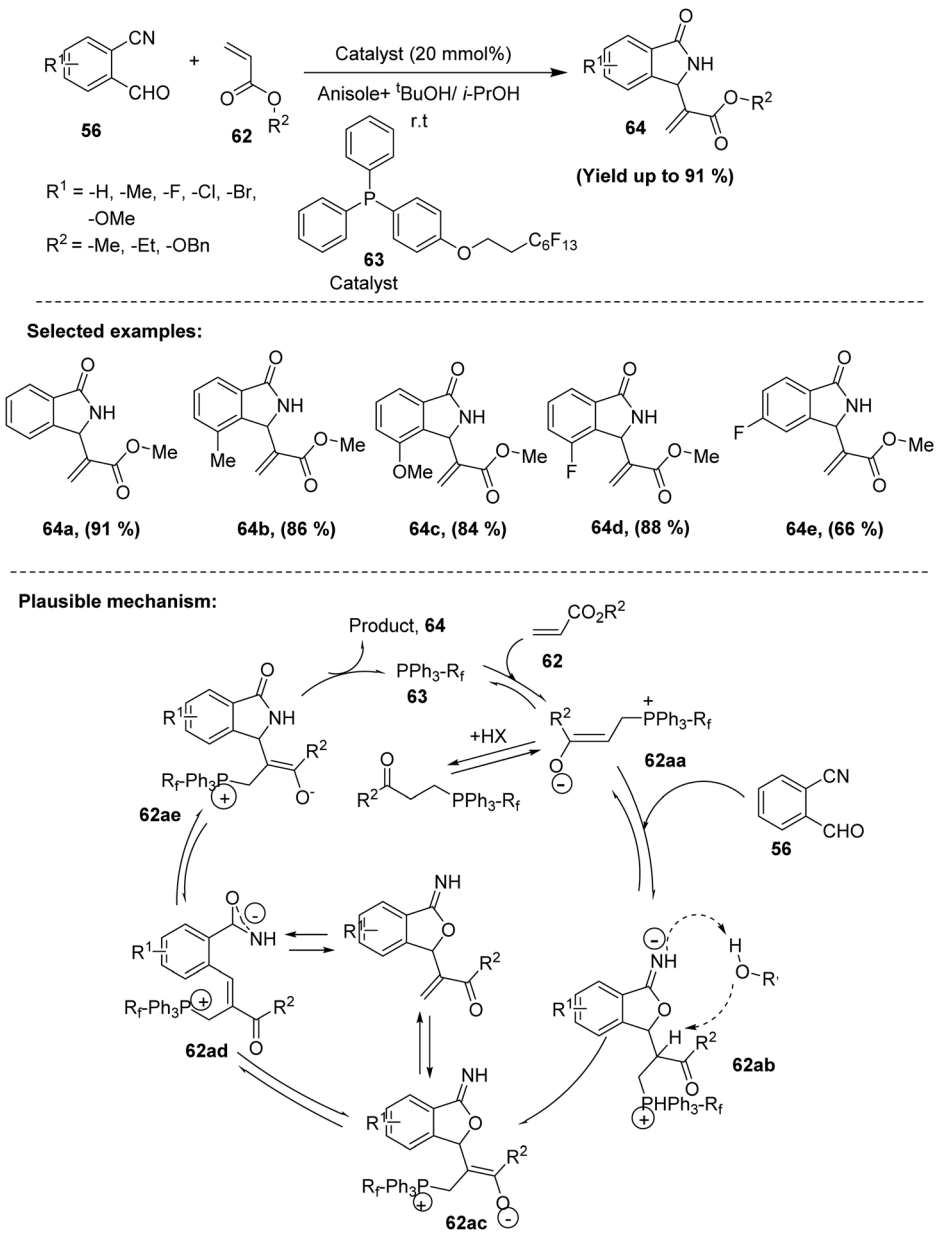


Scheme 16 Synthesis of isoindolinones *via* metal-free tandem process.

generates benzyl radical **54ac**. The capture of the iodine molecule by the benzyl radical leads to the formation of 2-(iodomethyl)-*N*-phenylbenzamide **54ad**, which on subsequent intramolecular aza-cyclization, gave isoindolinones (Scheme 15). Transition metal-free sp^3 C–H activation at the remote position is a challenging task in organic chemistry, which this methodology achieved during the synthesis of isoindolinone.

In 2021, J. Lu *et al.* synthesized isoindolinones **55′** using the same strategy under solvent-free and catalyst-free conditions (Scheme 15).[24b] They used methyl-2-(halomethyl)benzoates **54′** as the starting material during the cyclocondensation reaction. Aliphatic and aromatic amines fruitfully gave the desired isoindolinones in excellent yields. This protocol is environmentally benign and has synthetic utility for the formation of the bioactive molecule intermediate lenalidomide and DWP205190.

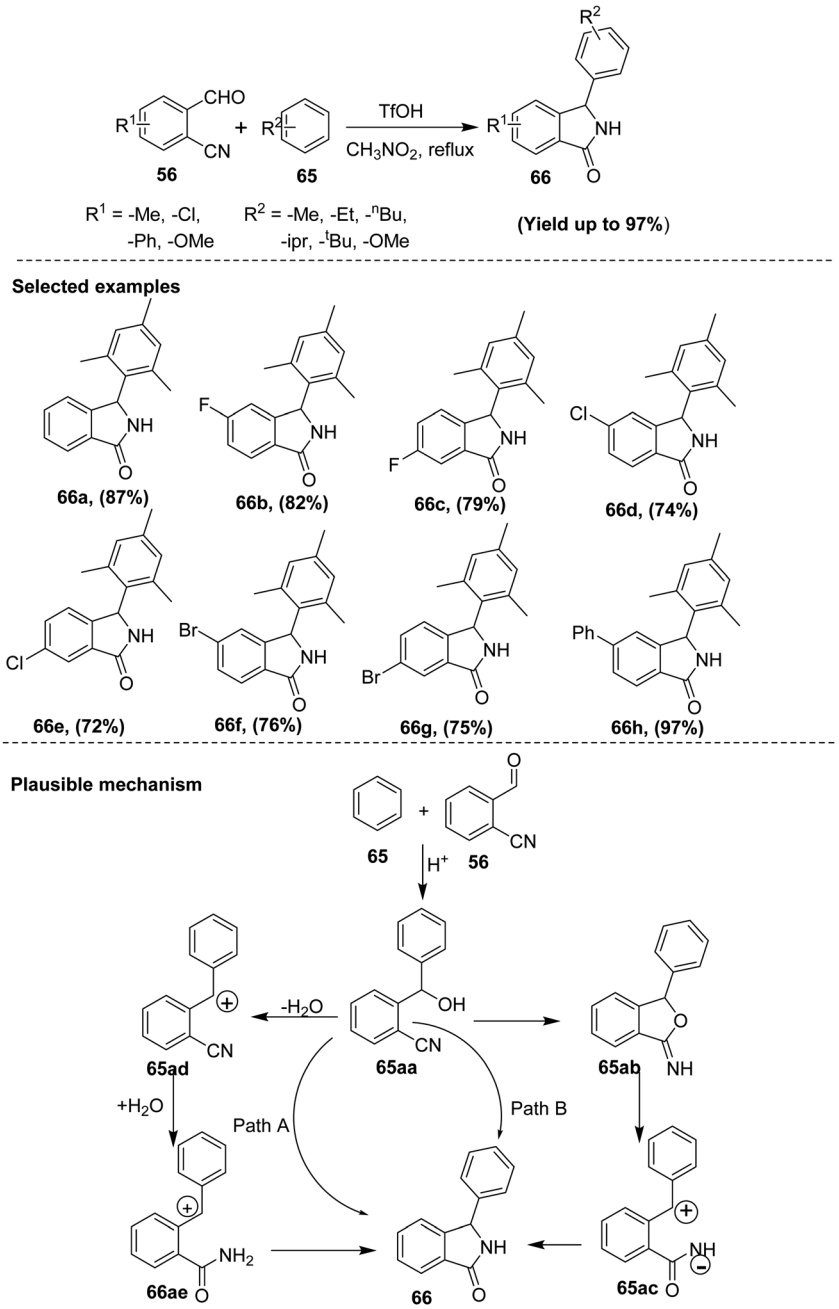
Metal-free tandem reaction is a more reliable approach compared to metal-assisted reaction given that it avoids the formation of toxic by-products during the reaction. Massa and co-workers demonstrated an easy synthetic route for isoindolinones *via* tandem aldol addition/cyclization/rearrangement, and finally aza-Michael process. This eminent synthetic process involves the formation of 3-substituted isoindolinones *via* the tandem/cyclization pathway from a compound having an active methylene group and 2-cyanobenzaldehyde **56** in the presence of triethyl amine as a base (Scheme 16).[25] Steric factors did not influence the yield of the isoindolinone derivative as the use of



Scheme 17 Synthesis of isoindolinones using green and recyclable catalyst.

the hindered di-*tert*-butyl malonate and di-(−)-menthyl malonate ester in this protocol produced the desired product **57** in good yield. *N*-Pyridyl **59** isoindolinone has several bioactivities, and hence the free NH underwent arylation *via* Buchwald's procedure in the presence CuI as a catalyst to afford **61** in moderate yield. The engaging observation of this methodology is the preparation of a highly condensed *N*-tricyclic subunit *via* one-pot Michael addition followed by cyclization at the amide group. This type of scaffold acts as a non-nucleoside HIV-1 reverse transcriptase inhibitor and can be considered an analogue of indolizidine compounds.

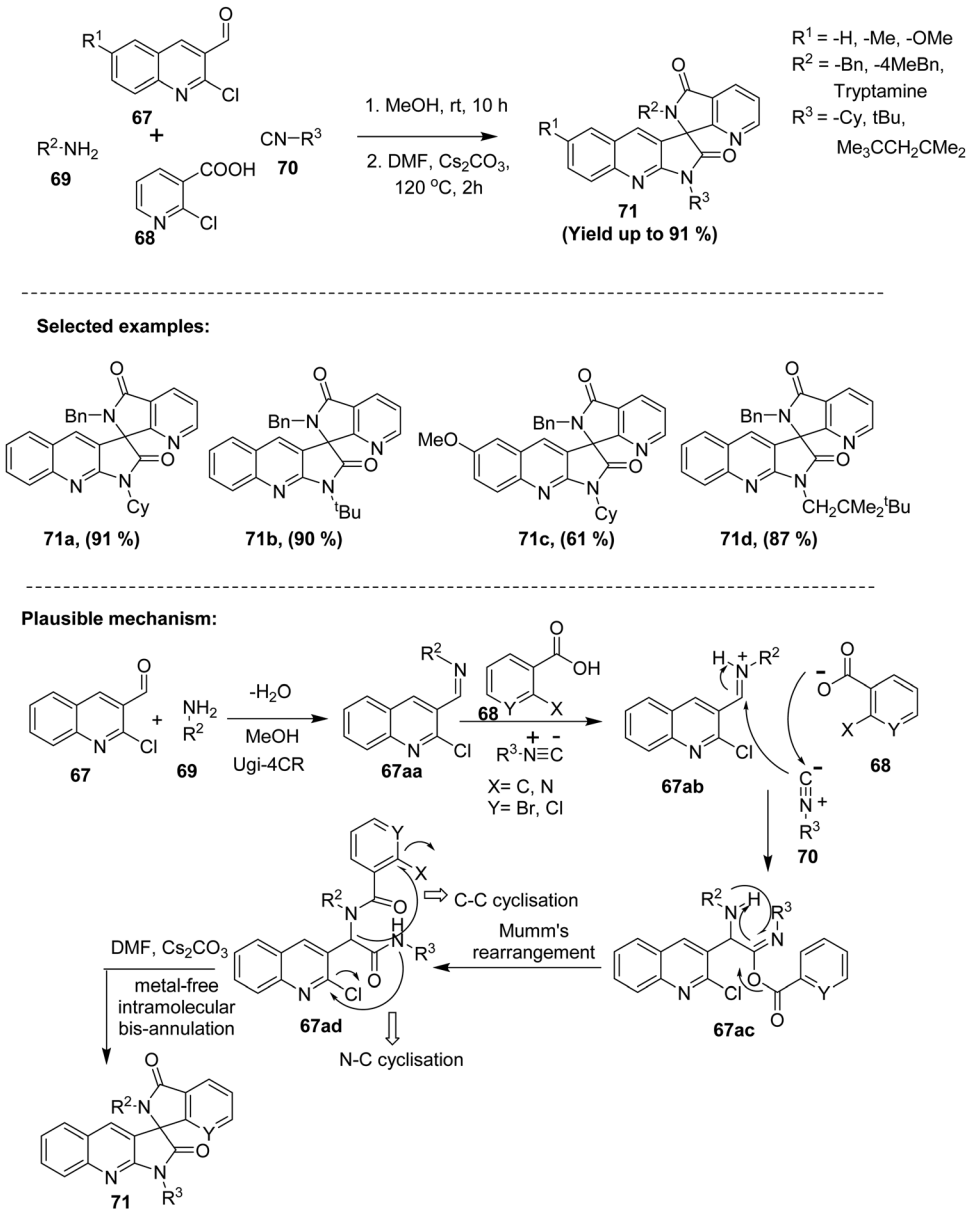
Fluorous biphasic catalysts have been used due to their recycling and good separation in organic transformations. Hence, these catalysts have broad use for the preparation of various organic compounds due to their simple and fast separation procedures. In 2020, Yonghai Chai and group demonstrated a simple and green method by applying this catalyst for the synthesis of the isoindolinone frame *via* the tandem reaction of 2-cyanobenzaldehydes **56** and α-β-unsaturated ketones/esters **62** (Scheme 17).[26] They claimed that the target compound gave a clean ^{1}H NMR spectrum *via* simple filtration and avoided all types of impurities by omitting the



Scheme 18 Synthesis of 3,3-disubstituted isoindolinones *via* asymmetric organo-catalyst.

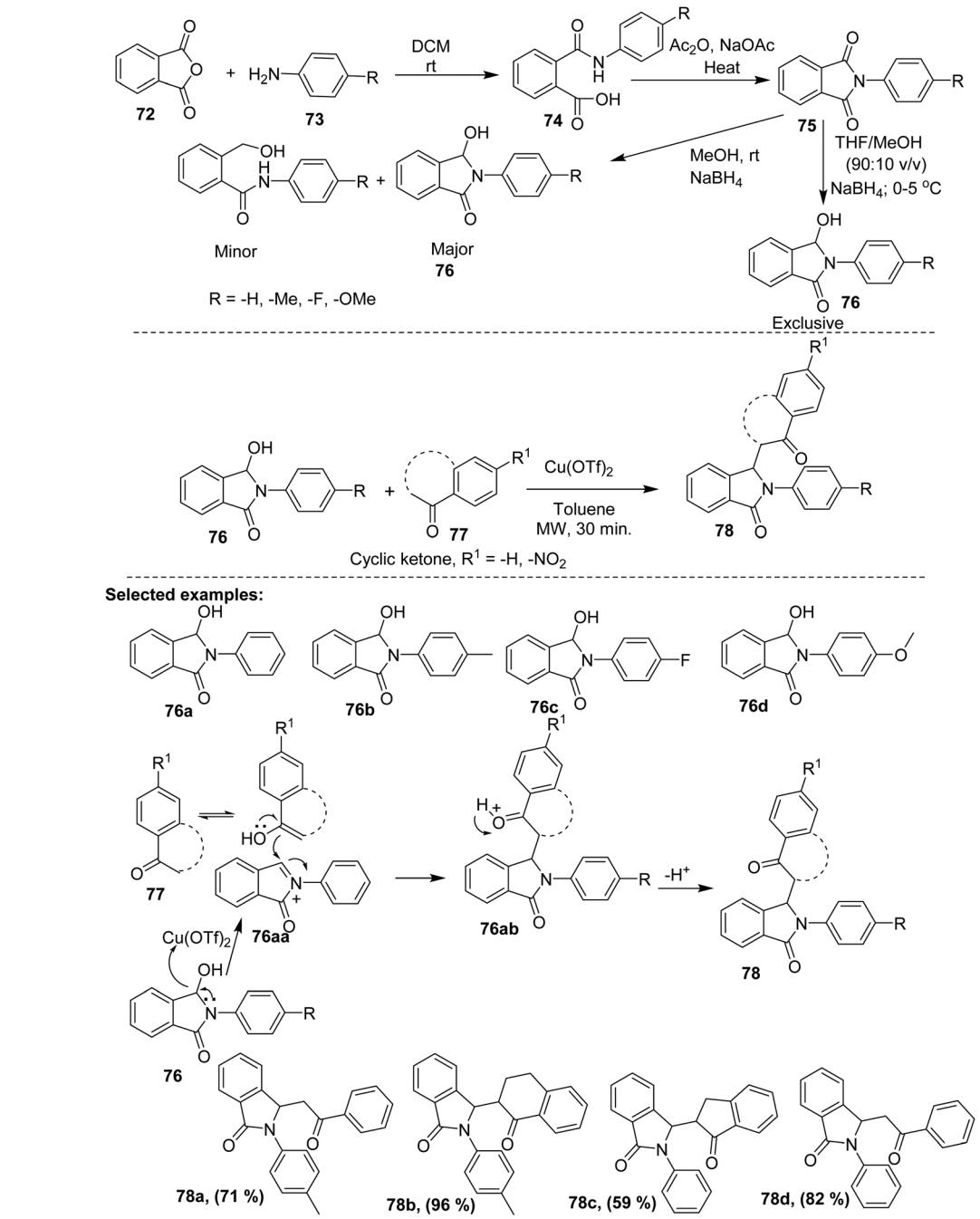
monotonous column chromatographic purification. According to the previous literature report, they proposed a mechanism where the fluorous phosphine catalyst attacks the olefin, resulting in the formation of zwitterionic enolate **62aa**, which on nucleophilic addition to the aldehyde followed by intramolecular oxa-addition to cyanide formed isobenzofuranimine intermediate **62ab** (Scheme 17). Then, hydrolysis followed by intramolecular aza-cyclization afforded isoindolinone **64** in good yield. The step economy, easy purification *via* precipitation, and the use of a recyclable catalyst present a green chemistry protocol, which has intense prospect in many fields, especially medicine.

In 2014, H. Zheng and co-workers reported a significant metal-free synthetic route for 3-arylisoindolinones from electron-rich arenes **65** and 2-formylbenzonitriles **56** using TfOH-catalyzed aromatic C–H functionalization reaction (Scheme 18).[27] This synthetic protocol was used to provide isoindolinone derivatives **65** in good to high yields by the formation of two bonds in a regioselective manner. Initially, they selected 2-formylbenzonitriles **56** and mesitylene **65** as the precursors for the synthesis of isoindolinones *via* Friedel–Crafts ring-closing reaction. Various Lewis acids and protic acids as catalysts and different solvents were used for the optimization of the reaction conditions. It was observed that the use of a protonic acid enhanced the yield of the desired product **66.** After prolonged screening, the optimized reaction conditions were established, which included TfOH (0.3 equiv.) as the catalyst and CH_3NO_2 as the solvent, providing 88% yield. 2-Formylbenzonitrile rings with electron-withdrawing substituents such as –F, –Cl, and –Br groups offered the desired



Scheme 19 One-pot synthetic strategy of spiropyrroloquinoline isoindolinone and spiropyrroloquinoline aza-isoindolinone.

isoindolinones in good yields (72–82%). The position of the electron-withdrawing groups had minimum influence on the reaction. An electron-donating group on the aromatic ring such as phenyl group provided excellent yield (97%). Then, they examined different benzene derivatives with 2-formylbenzonitriles. *p*-Xylene furnished a good yield (82%), while *m*-xylene and *o*-xylene provided the desired products with high regioselectivity in 93% and 61% yield, respectively. Different electron-donating groups containing benzene derivatives showed a similar type of effect on the reaction. Due to the steric hindrance with an increased chain length in the alkyl group, the desired products were obtained with a greater mixture of stereoisomers (*para*/*ortho* >98/2). They proposed the mechanism for the acid-catalyzed synthesis of isoindolinone. The starting material arenes **65** first reacts with the aldehyde group *via* the Friedel–Crafts pathway to form alcohol **65aa**, which then produce carbocation intermediate **65ad** *via* dehydration. Subsequently, the cyano group is converted into an amide group by hydrolysis with the strong acidic condition. Finally, the desired isoindolinone **66** products are obtained by intramolecular aza-

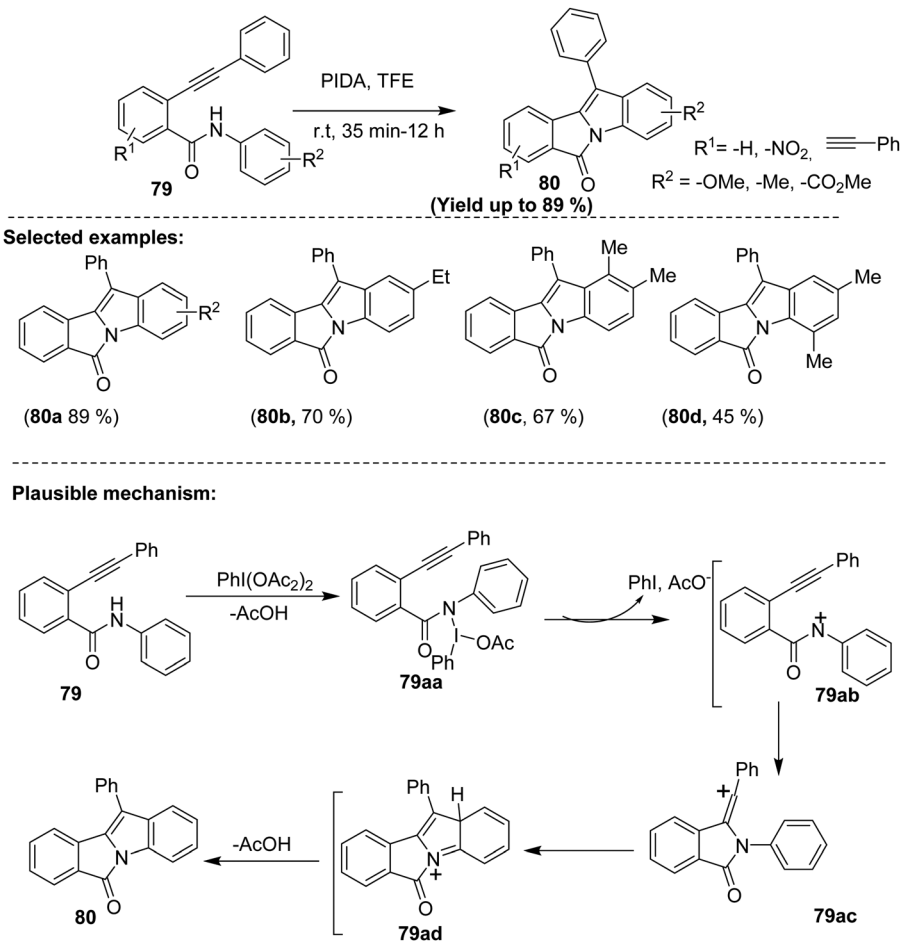


Scheme 20 Synthesis of hydroxyisoindolinones/isoindolinones *via* the reduction method.

addition reaction (Path A). Again, intermediate alcohol **65ab** can also be transformed into imine by intramolecular aza-Michael reaction, and then the imine is switched to amide **65ac** through rearrangement, and finally the desired isoindolinone **66** is obtained *via* the conjugate addition of the amide (Path B). The main utility of this methodology is the participation of highly electron-rich aromatic π-electron using a single TFA catalyst for the synthesis of isoindolinone.

In 2015, M. Ghandi and co-workers presented a one-pot synthetic strategy for spiropyrroloquinoline isoindolinone **71** (Scheme 19). The reaction pathway was the combination of metal-free four-component Ugi reaction (4CR) and intramolecular cyclization reaction. Initially, they prepared 2-chloroquinoline-3-carbaldehydes **67** using the previously reported methodology.[25] Then, spiro compound **71** was achieved in good yield (91%) by the reaction of 2-chloroquinoline-3-carbaldehydes **67**, 2-chloronicotinic acid **68**, benzylamine **14** and cyclohexyl isocyanide **70**, maintaining the optimized reaction conditions in MeOH (5 mL) at room temperature for 10 h and successive treatment with DMF (3 mL) and Cs_2CO_3 (2 equiv.) at 120 °C. The reaction mechanism was proposed *via* the Ugi reaction involving a step-by-step process of imine generation **67aa**, protonation of imine **67ab**, α-addition of iminium cation **67ac**, attacking the nucleophilic carboxylate anion in isocyanide, and finally intramolecular acyl-transfer (Mumm's rearrangement) **67ad**. Subsequently, the α-acylaminoamides underwent bis-annulated C–N bond formation under basic conditions, giving the desired spirocyclic products **71**.[28]

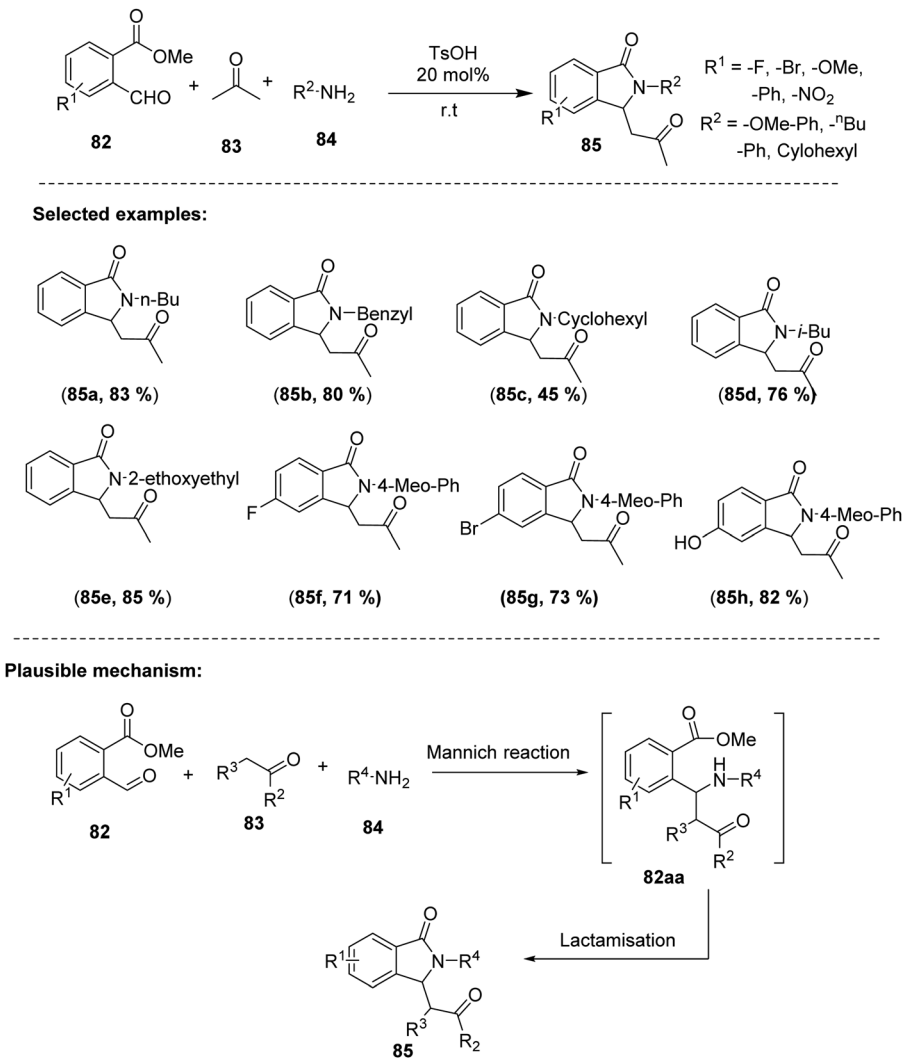
Metal-free four component cyclization to give complex isoindolinone molecules is the attraction of this methodology. A. Jha and co-workers synthesized 3-hydroxy isoindolinones **76** *via* the reduction of *N*-aryl phthalimide **75** with $NaBH_4$ in MeOH at room temperature. 2-(Arylcarbamoyl)benzoic acid **74** was synthesized from phthalic anhydride **72** and anilines **73**; subsequently *N*-aryl-1*H*-pyrrole-2,5-diones **75** were prepared through acylation with acetic anhydride and sodium acetate. They also proposed the synthetic route of **78** *via* the microwave-assisted chemical reaction of 3-hydroxy isoindolinone with alky-aryl ketone. They investigated the optimized reaction conditions by varying the Brønsted acid catalyst, solvent and neat conditions, and after prolonged evaluation, they established that optimized reaction conditions included 0.15 equiv. $Cu(OTf)_2$ (catalyst), toluene (solvent), and microwave heating at 110 °C for 0.5 h. Under these conditions, a series of 3-substituted-(2-oxo)-2-arylisoindolin-1-ones **77** was synthesized



Scheme 21 Synthesis of tetracyclic isoindolinone under metal-free conditions.

from 3-hydroxy-2-arylisoindol-1-ones **78** and diverse alkyl aryl ketones in 56–96% yield. The mechanism for this reaction was explained similar to the Mannich reaction. Firstly, *N*-acyliminium ions **76aa** are prepared by the reaction of *N*-aryl-3-hydroxyisoindolinones **77** with $Cu(OTf)_2$. Then nucleophilic attack of the enol to the *N*-acyliminium ion forms a C–C bond. Subsequently, deprotonation of intermediate **76ab** takes place, providing the 3-substituted (ketones)-2-arylisoindolin-1-ones **77** (Scheme 20).[29]

K. Dev and R. Maurya developed a synthetic route for a tetracyclic-fused isoindolinone moiety using metal-free conditions. Here, 11-aryl-6*H*-isoindolo [2,1-*a*] indol-6-ones **80** were synthesized by the iodine PIDA-mediated regioselective and chemoselective intramolecular tandem oxidative reaction of 2-(1-arylethynyl)benzamides (Scheme 21).[30] This group was the first to report the formation of a tetracyclic-fused isoindolinone moiety using hypervalent iodine(III) as the main oxidant from 2-(1-alkynyl) benzamide 79 *via* one-pot intramolecular C–N and C–C bond formation. To optimize the reaction conditions, they used a variety of hypervalent iodine reagents and solvents at room temperature and found that PIDA (1.7 equiv.) as oxidant and TFE as the solvent were the best conditions to get a good yield (89%) within 35 min. With the standardized conditions, the scope of the substrate was investigated. A variety of functional groups on the benzene ring attached to the nitrogen atom of amide group, such as hydrogen, electron-withdrawing groups, electron-donating, and halogen, was investigated for this intramolecular reaction. To establish the reaction mechanism, a series of control experiments was carried out under the optimum conditions. Initially, PIDA reacts with substrate **79** to produce *N*-iodoamido species **79aa** with the release of acetic acid. The intermediate species decomposes to form nitrenium ion **79ab**, which reacts with the alkyne to give carbonium ion intermediate **79ac**. Then, electrophilic aromatic substitution reaction takes place, leading to the formation of intermediate species **79ad**, which upon

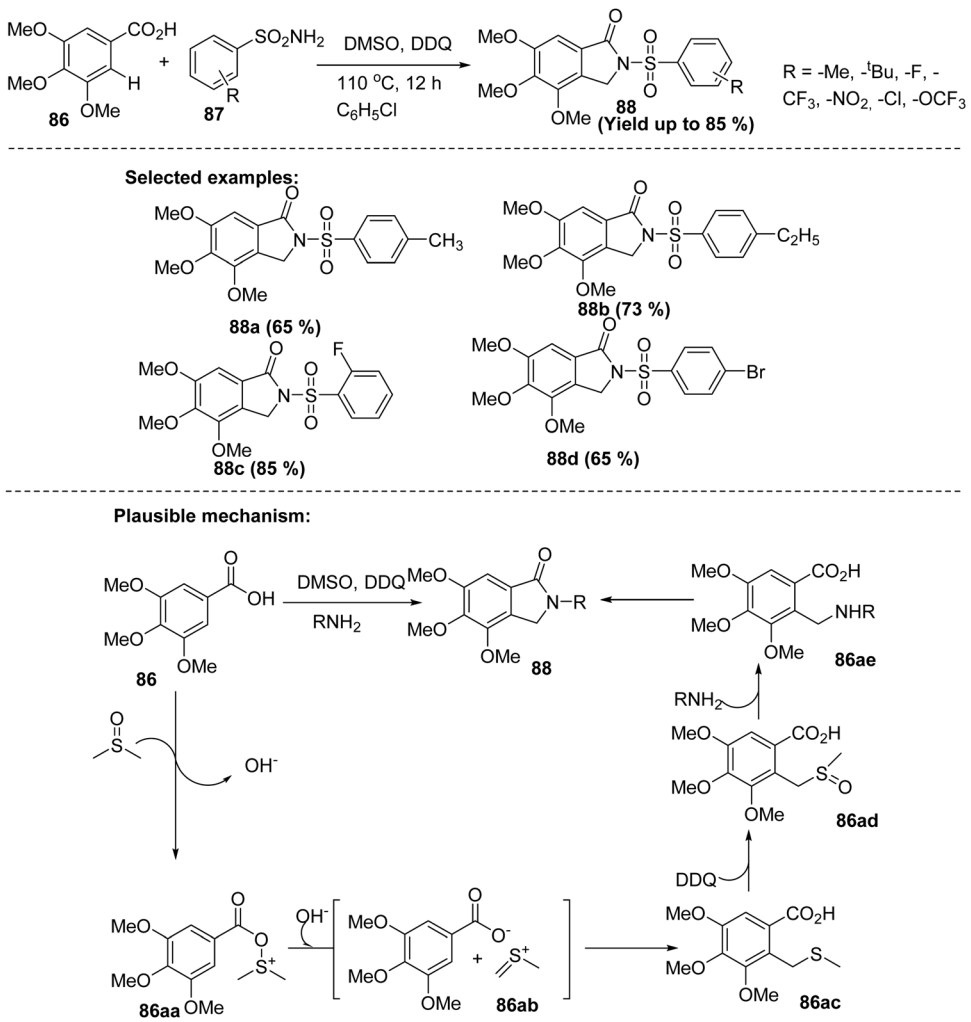


Scheme 22 Three-component approach for the synthesis of isoindolinone.

H-release by the *in situ*-generation of an acetate anion, yields the desired product **80**. The formation of two rings together with the isoindolinone is the important part of this methodology.

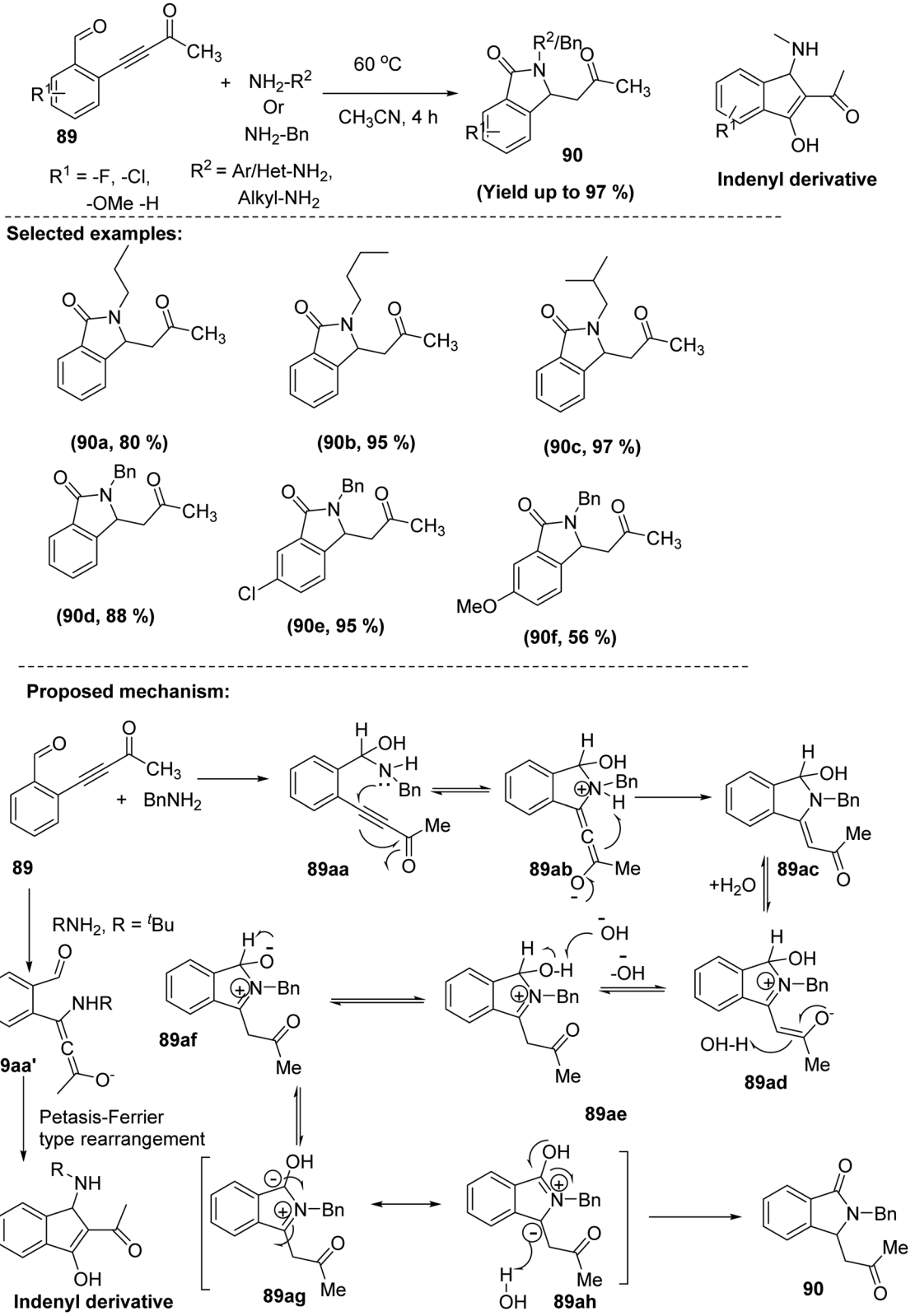
W. Duan and group demonstrated a one-pot, synthetic procedure for 3-substituted 2,3-dihydroisoindolin-1-ones **85** with acceptable yields (up to 88%) using a three-component Mannich/lactamization cascade reaction in both the presence and absence of an acid catalyst (Scheme 22). This group initially found that the reaction occurred smoothly between acetone, methyl-2-formylbenzoate **82**, and 4-methoxyaniline **84** without using *p*-toluenesulfonic acid catalyst, getting the desired 3-substituted 2,3-dihydroisoindolin-1-ones in 82% yield. In the absence of the catalyst, the reaction did not proceed in the presence of aliphatic amines such as benzylamine, *n*-butylamine, and cyclohexylamine. In the presence of *p*-toluenesulfonic acid catalyst, the unsuccessful reaction proceeded smoothly to produce the desired 3-substituted isoindolinones. The results explained that primary amines are more suitable substrates than secondary amines.[31] This methodology is a one-pot manner, three-component Mannich-lactamization procedure to achieve 3-substituted isoindolinones applying catalyst-free mild conditions in the presence of *p*-toluenesulfonic acid.

The direct cross-dehydrogenative-coupling (CDC) reaction has emerged as a useful tool for the synthesis of complex molecules from simple substrates but the majority of research groups developed this protocol using metal catalysts. In 2016, Peng-Min Wang *et al.* reported a dehydrogenative cross coupling reaction under metal-free conditions for the synthesis of isoindolinone derivatives from the most available 3,4,5-trimethoxybenzoic acid **86** and arylsufonamide derivatives **87** (Scheme 23).[32] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and DMSO at 110 °C were the optimized conditions for the tandem reaction involving sp^2 C–H and sp^3C–H CDC, C–N bond formation and intramolecular amidation. Different substituted benzenesulfonamides with 2-CH_3, 4-CH_3, 4-C_2H_5, and 4-^{t}Bu smoothly proceeded to the corresponding isoindolinones in good yields (47–70%). Pummerer-type rearrangement is the main step in acid-mediated CDC cyclization. Nucleophilic addition to DMSO by the carboxyl group generates the thionium ion ($CH_2 = S^+CH_3$) as the active species with the release of



Scheme 23 Metal-free cross-dehydrogenative coupling (CDC) reaction for the synthesis of isoindolinone.

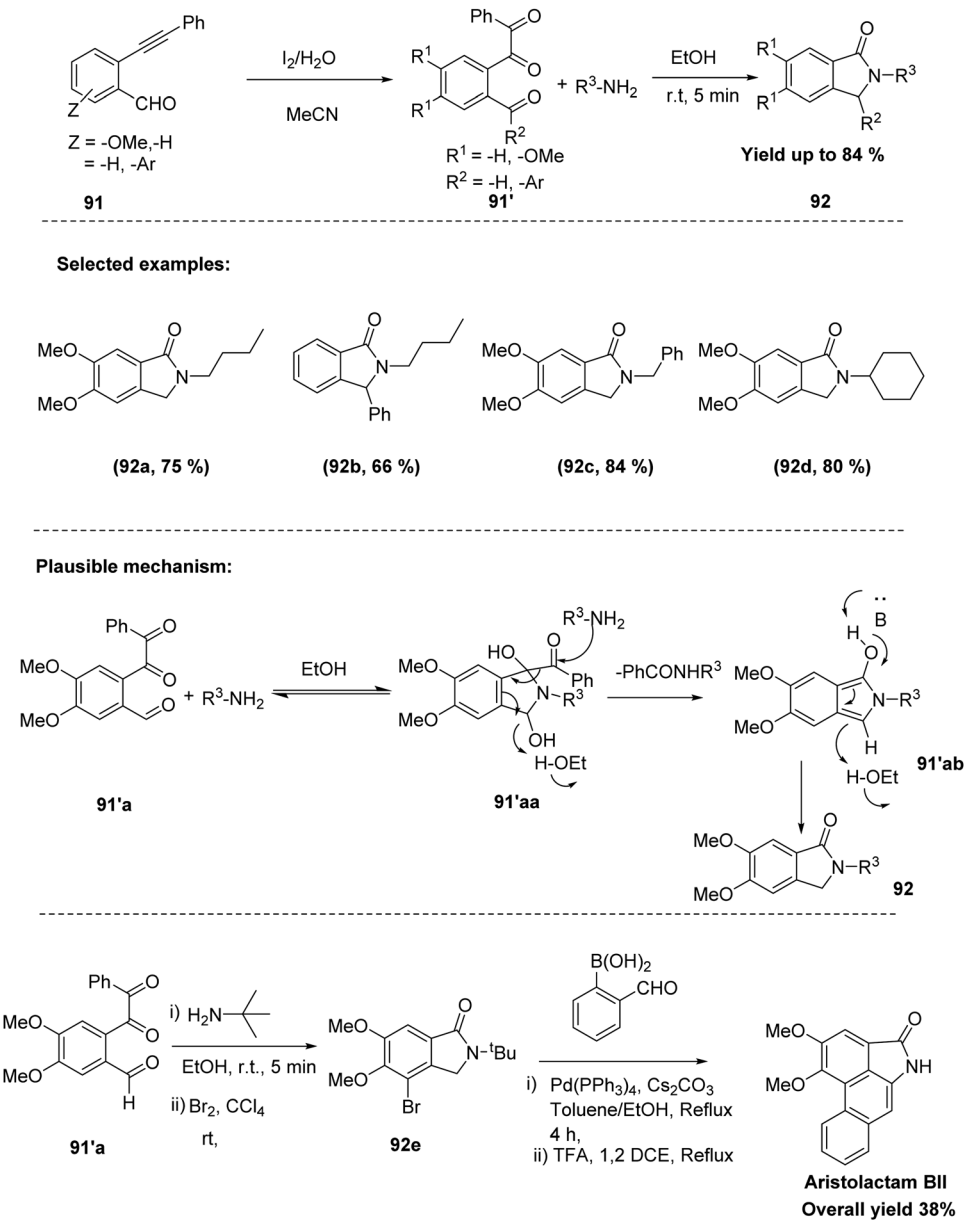
one equivalent of OH^- in the Pummerer-type rearrangement. Then reactive electrophile **86ab** attack by π-electrons of highly electron-rich aryl ring through Friedel–Crafts alkylation furnishes an intermediate, which on subsequent treatment with



Scheme 24 Metal-free synthetic route for isoindolinones from *ortho*-carbonylated alkynyl-substituted arylaldehydes.

DDQ acts as an oxidative agent and produces the corresponding sulfoxide **86ad**. The sulfoxide when reacted with aryl amine *via* the S_N2 mechanism affords the precursor amine for the isoindolinone derivative. Amine-substituted carboxylic acid with suitable functionality undergoes intramolecular acid amine coupling reaction, generating the desired cyclized isoindolinone **88**. Halogenated substrates and toxic transition metals have been used for the CDC reaction, while the development of metal-free CDC reactions for the inactivated *ortho* position to the carboxyl group is very challenging; however, this protocol activates this remote position *via* three-component tandem reactions.

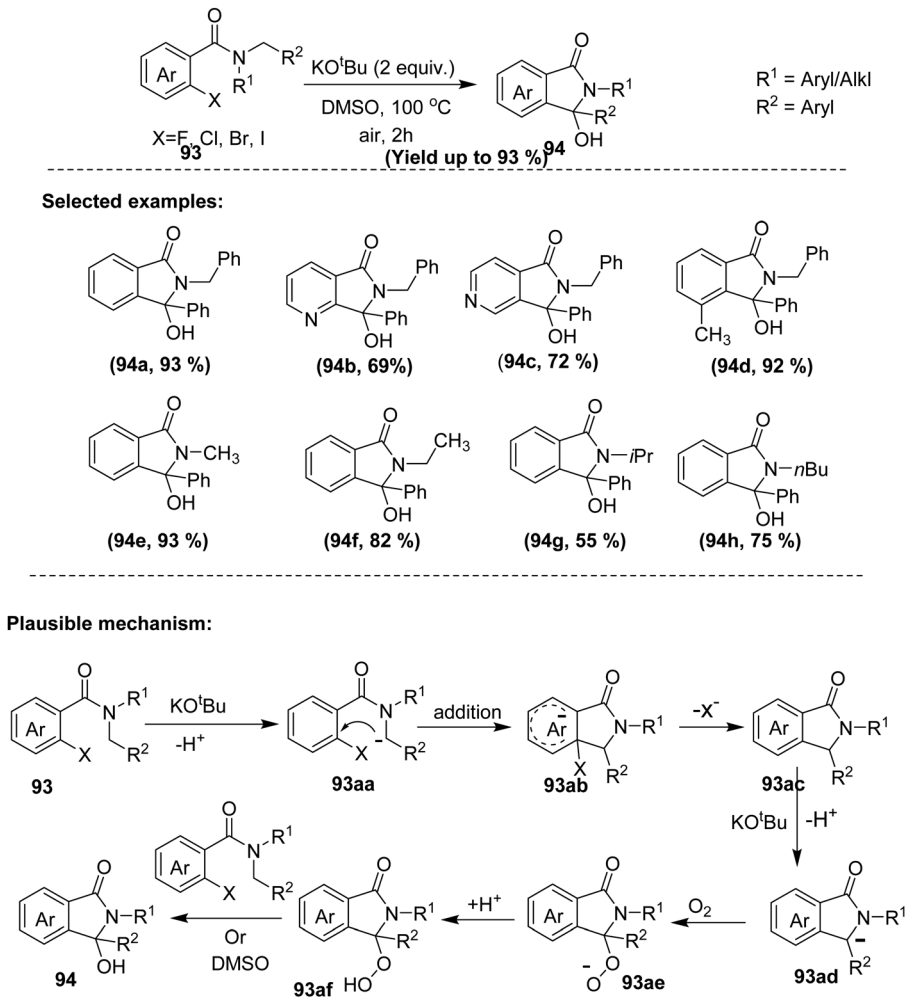
Aza-conjugate addition to *ortho*-carbonylated alkynyl-substituted arylaldehydes is another strategy for the synthesis of isoindolinone derivatives. Sonogashira coupling with propargyl alcohols and *ortho*-bromo vinyl aldehydes, and subsequent Sarett oxidation reaction provided the desired starting materials **89** for isoindolinones. Acetonitrile was a suitable solvent for the present transformation and afforded isoindolinone with moderate to excellent yields in the presence of butyl amine and substrate **89** (Scheme 24).[33a] The product yield depends on the substituent of the aryl ring, where electron-withdrawing groups at the *para* position to the triple bond in the phenyl ring gave an excellent yield of **90e** (95%), whereas an electron-donating group at the same position furnished a poor yield of **90f**. Aliphatic and aromatic substituents in the triple bond tolerated the metal-free cascade transformation. Mainly aliphatic amines with the cycloalkyl or chain formed the



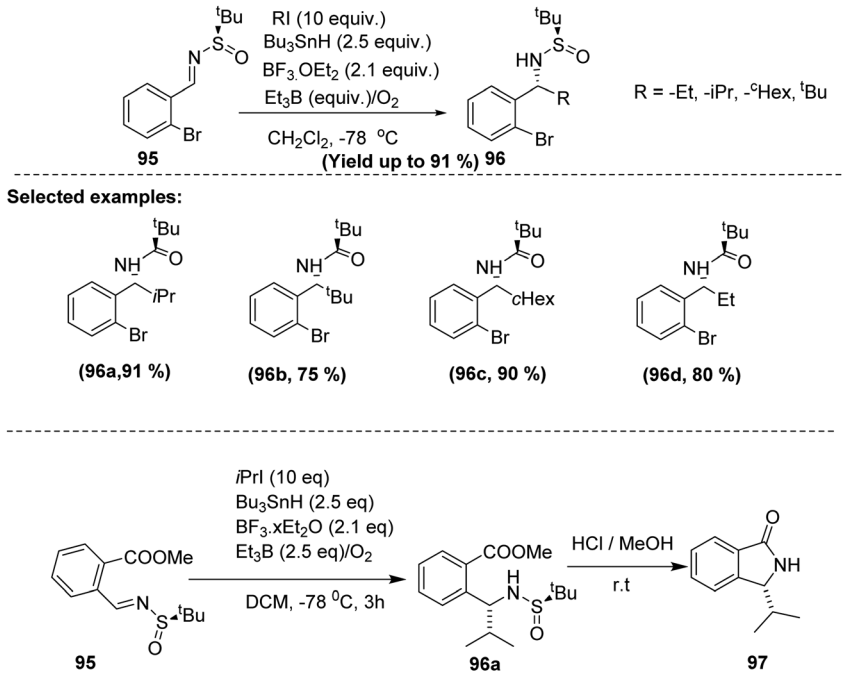
Scheme 25 Two-step synthesis of isoindolinones from *o*-substituted tricarbonyl derivatives.

isoindolinone products with 43–97% yield, but the aromatic amine (aniline) did not respond to the same reaction. They described that primary amines formed isoindolinone, whereas cyclohexylamine or the sterically demanding amines gave the 3-hydroxylindenamine products with good yields. The mechanism for the metal-free transformation involves amine-aldehyde addition followed by aza-*exo-dig* cyclization to ynone, producing enamine **89ac** *via* allenyl enolate intermediate **89ad**. Consequently, tautomerisation and isomerisation furnish the desired product **90** in good yield. The formation of 3-hydroxylindenamine can be explained by the steric effect, where the α-amino alcohol inhibits the conjugate addition to the ynone, and then the second amine (Et_3N) shows catalytic activity *via* conjugate addition to the ynone. Here, the 3-hydroxylindenamine derivative was formed by *N*-conjugate addition/aldol condensation *via* Petasis–Ferrier-type rearrangement. This protocol furnished isoindolinones and indenyl derivatives under the same conditions using different amine sources. Steric-dependent aza-cyclization is the main attraction of this methodology.

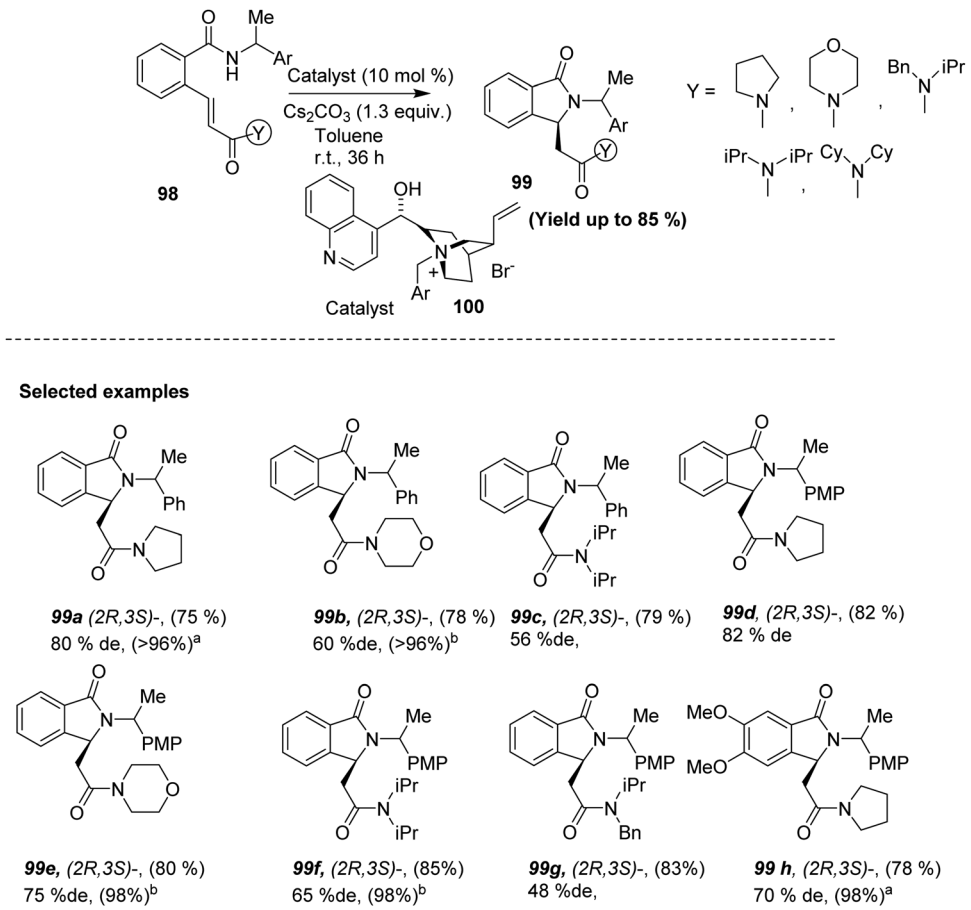
o-Alkynylarenecarbaldehydes are useful building blocks in organic synthesis given that many important scaffolds have been synthesized from these precursors *via* transition metal/transition metal-free pathways. The alkyne part-containing electron-donating group in the aryl ring was well-tolerated for oxidative tricarbonyl formation but the presence of a nitro substituent on the aryl ring in the aryl alkyne part did not give tricarbonyl derivatives **90′**. Subsequently, the tricarbonyl derivatives were subjected to reaction with a variety of amine such as *n*-butylamine, 4,4-diethoxybutylamine, cyclohexylamine, benzylamine, (*S*)-methyl-2-amino-3-phenylpropionate and (*R*)-1-phenylethylamine, and in each case isoindolinones **92** were obtained with yields in the range of 66–78% by the elimination of a formyl group (Scheme 25).[33b] The versatility of the developed methodology was also applied to prepare an antitumor agent, aristolactam BII. Aristolactam BII was prepared *via* the reaction between tricarbonyl compound **90′**a with *tert*-butylamine under the optimized conditions. Bromination and Suzuki–Miyaura coupling/aldol condensation with (2-formylphenyl)boronic acid gave the *N*-protected lactam, which



Scheme 26 Synthesis of substituted 3-hydroxyisoindolinones *via* base-promoted cascade reaction.



Scheme 27 3-Substituted asymmetric synthesis of isoindolinones using chiral auxiliary.



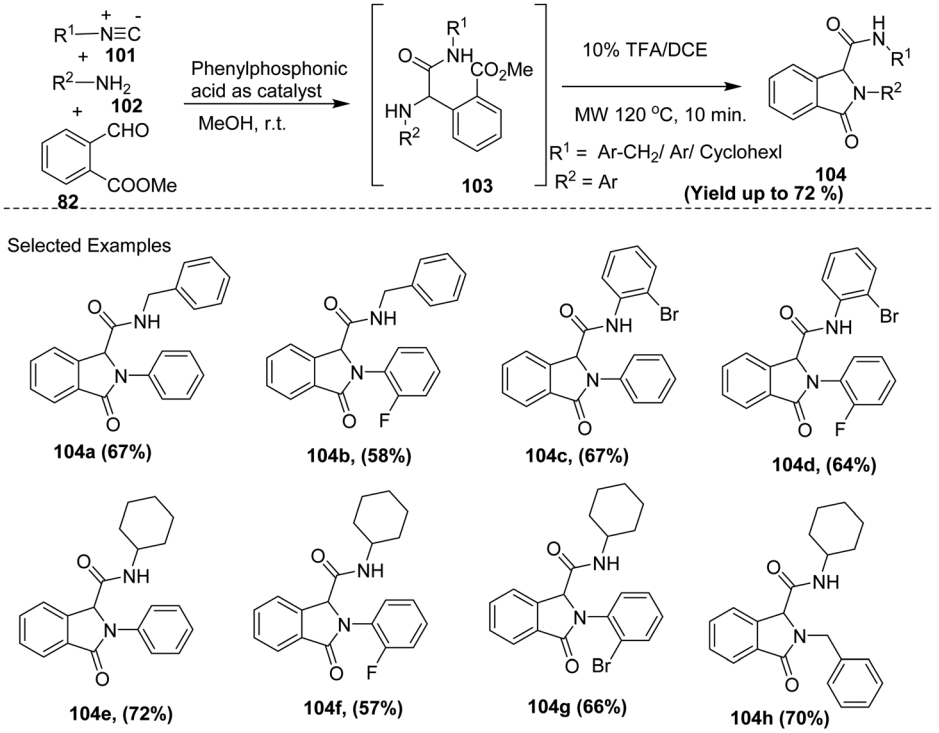
Scheme 28 Asymmetric synthetic route of isoindolinones.

on TFA-catalyzed deprotection, gave aristolactam BII with an overall yield of 38%. Transition metal-free synthesis and its application to obtain a bioactive natural product are the vital parts of this methodology.

J. Shen and co-workers reported the regiospecific synthesis of substituted 3-hydroxyisoindolinones *via* a base-promoted cascade reaction under transition metal-free conditions (Scheme 26).[34] This process involved base-promoted C–C bond coupling and N-α-sp^3C–H bond hydroxylation, which resulted in high regioselectivity and was also environmentally benign. Several substituted 3-hydroxyisoindolinones **94** were synthesized in yields up to 93%. To determine the optimized reaction conditions, this group initially chose *N*,*N*-dibenzyl-2-fluorobenzamide as a model substrate, and after prolonged variation of bases, solvents and temperature, the optimized reaction conditions were established, taking 2 equiv. of KO^{t}Bu as the additive in DMSO at 100 °C for 2 h. With the optimized conditions, the same group investigated the substrate scope with varying fluoro-, chloro-, bromo-, and iodo-substituted *N*,*N*-dibenzyl-2-halobenzamides **89** to produce the desired 3-hydroxyisoindolinones **94** in 93%, 83%, 76% and 71% yield, respectively. These results emphasize the nucleophilic substitution reaction, where the stability of the −ve charge shows a clear trend (F > Cl > Br > I). The substitution on the N-atom using methyl, ethyl, *n*-propyl, i-propyl, and *n*-butyl was also examined, giving the desired product in 55–93% yield. They proposed the tentative mechanistic path of the reaction, in which the starting material **93** is initially deprotonated by KO^{t}Bu to produce carbanion **93aa**. Then a nucleophilic aromatic substitution reaction takes place to produce isoindolinone **93ac**. Another carbanion **93ad** is generated by the deprotonation of isoindolinone. Superoxide **93ae** is produced by the reaction with O_2 and proton absorption. Finally, the desired 3-hydroxyisoindolinone is achieved by the reduction of superoxide **93af** using the starting material or DMSO. The participation of O_2 from the air in the reaction cycle is the important feature of this methodology.

A two-step sequential process for the preparation of 3-isopropyl-substituted isoindolin-1-one **97** was developed by M. C. Maestro and group from the substrate *ortho*-Br-substituted *N*-(benzylidene)-2-methylpropane-2-sulfinamides **95** (Scheme 27).[35] Initially, they performed the alkyl radical addition reaction of enantiopure (*R*)-*N*-(*tert*-butylsulfinyl)imine **95** to exclusively get (*R*,*R*)-diastereomers **96** in good yield using RI (10 equiv.), Bu_3SnH (2.5 equiv.), $BF_3{\cdot}OEt_2$ (2.1 equiv.) and Et_3B (equiv.)/O_2 in CH_2Cl_2 solvent at −78 °C. This methodology provides good diastereoselectivity with –OMe, –CN, $–CO_2Me$ and –OH in place of the –Br substituent. This protocol offers an increased yield without hampering the stereoselectivity. Finally, elimination of the sulfinyl group from the *ortho* ester of sulfinamide **96a** can be easily achieved by applying acidic conditions (HCl/MeOH) to obtain the desired isoindolinone product **97** in 89% yield. The developed synthetic methodology showed the utility of *ortho*-substituted *N*-(*tert*-butylsulfinyl)benzaldimines, which are used as excellent acceptors in the intermolecular addition reaction of alkyl radicals mediated by Et_3B/O_2.

E. Deniau and co-workers reported a synthetic route for the preparation of optically active isoindolinones **99** in excellent yields. The diastereomeric excess of the desired isoindolinone

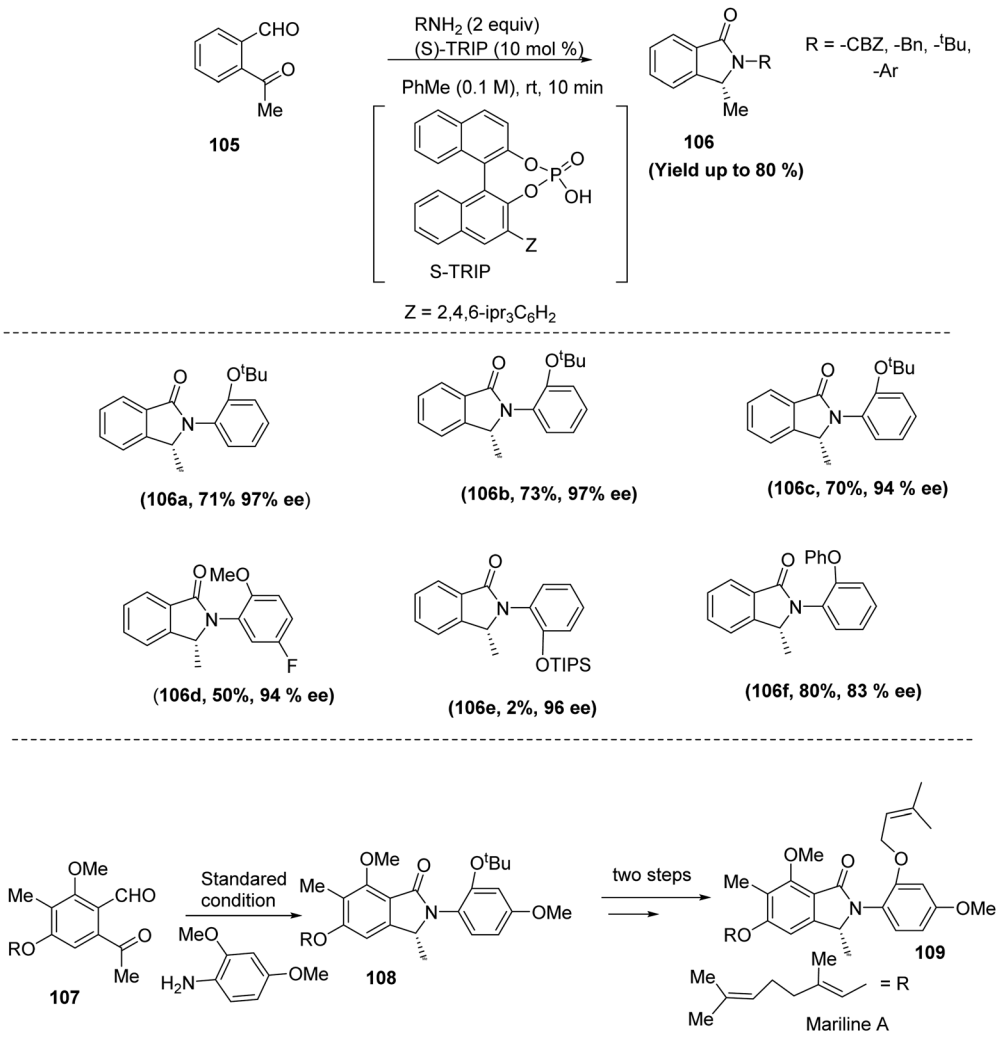


Scheme 29 Synthesis isoindolinone using Ugi-type multi-component reactions.

moiety could be ascertained *via* organocatalysed intramolecular aza-Michael reaction using cinchoninium salt as a phase-transfer catalyst (Scheme 28).[36] This methodology can also be applied to get a new pazinaclone analogue asymmetrically. This organocatalysed transformation generated a new class of pazinaclone analogues, which is of interest in the field of benzodiazepine-receptor agonists. Among the different cinchoninium salts, the *para*-substitution with a *tert*-butyl group in the aryl ring increased the diastereoselectivity with a yield of 62%. The optimum conditions for the intramolecular aza-Michael reaction of benzamide substrate **98** to achieve higher diastereoselectivity were the use of Cs_2CO_3 in toluene with cinchoninium salt **100** as the phase-transfer catalyst. Using the optimized reaction conditions and the same phase transfer catalyst, a broad range of asymmetric isoindolinones was achieved in good yields (up to 85%).

Synthetic-functionalised isoindolinones under this method are useful as agonists of GABAA (γ-aminobutyric acid type A) benzodiazepine-receptors. A four-component Ugi-type reaction was introduced for the synthesis of isoindolinone derivatives, where methyl 2-formylbenzoate **82** was used as one of the starting materials. This facile and efficient one-pot procedure was suitable for all the MCRs under acidic conditions (Scheme 29).[37] Four series of biologically active scaffolds were formed using this protocol. Methyl 2-formylbenzoate is a useful starting material in several MCRs. In this multicomponent reaction, **102** was an intermediate for acid-catalyzed amine/aldehyde/isonitrile coupling. *o*-Substituted amide **103** underwent intramolecular aza-cyclization, leading to the isoindolinone in excellent yield. Methyl 2-formylbenzoate was more suitable compared to 2-formyl benzoic acid because the methyl ester group was stabilized on decomposition in the first MCR step and it provided a better opportunity for the additional derivatization of the MCR products. The demonstrated methodology described a one-pot process, which offers new opportunities for the synthesis of isoindolin-1-one compounds using methyl 2-formylbenzoate as a starting material.

Chiral phosphoric acid was an active catalyst for the asymmetric isoindolinone transformation of **106** from the 2-fomyl acetophenone **105** (Scheme 30).[38] This chiral ligand gave 98%

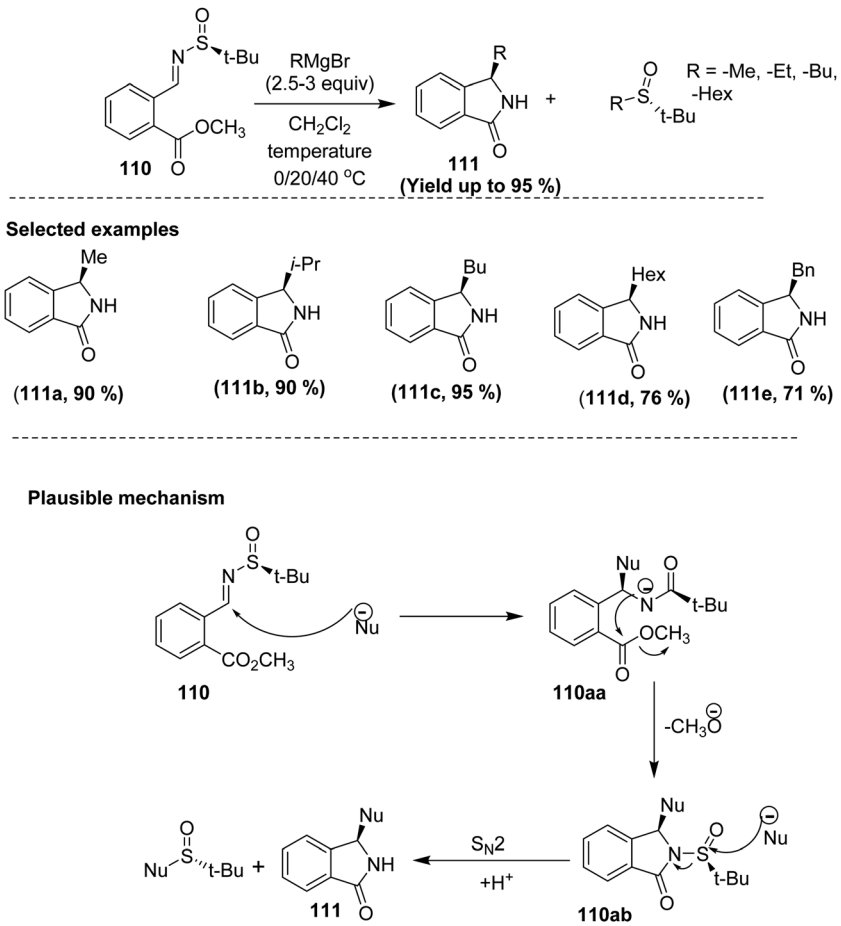


Scheme 30 Synthesis of enantioselective isoindolinones *via* the condensation of *ortho*-formyl-aryl ketones and anilines.

ee of isoindolinone derivatives. The *ortho t*-butyl-substituted aromatic amine coupled with the substrate **105** and produced cyclic amide, which showed an atropisomerism effect and enhanced the asymmetric induction of **105**. The chiral phosphoric acid with the bulky *o*-substituted aromatic amine led to a greater enantioselective reaction. This protocol offered biological application towards the synthesis of mariline A from suitable substrate **107**. The proper functionalisation and acid-catalyzed asymmetric cyclization furnished an excellent yield of the bio-active mariline A. Using this protocol, the catalytic enantioselective synthesis of 3-alkyl isoindolinones was achieved through biomimetic condensation utilizing *ortho*-formyl-aryl ketones and 2-substituted anilines as starting materials. This protocol provided the first enantioselective synthesis of mariline A.

In 2017, Robert Kawęcki and co-workers reported a reaction for the formation of enantioenriched isoindolinones **111** and *tert*-butyl sulfoxides using optically pure *N*-sulfinyl imine **110** and Grignard reagents (Scheme 31).[39] *N*-Sulfinyl imine isoindolinone **110ab** was formed by Grignard addition to the *N*-sulfinyl imine followed by intramolecular azide addition. S_N2 displacement of *N-tert*-butylsulfinyl isoindolinone furnished N–H-substituted isoindolinone with enantiomeric excess. The enantioselectivity of isoindolinones strongly depends on the reaction conditions. The effects of different solvents, temperature, and the additives were used to optimize the condition to achieve the best results. The best results were obtained when dichloromethane was used as the solvent. The highest stereoselectivity was observed at 40 °C. Both high yields and high ee of sulfoxides were achieved when the reaction was carried out at room temperature or 0 °C. At 40 °C, the yields were 90%, 95% and 71% when the R group was i-Pr, Bu, and Bn, respectively. However, at 20 °C, the yield was 90% when the R group was Me. The main advantage of this protocol is that it is free from the chromatography technique.

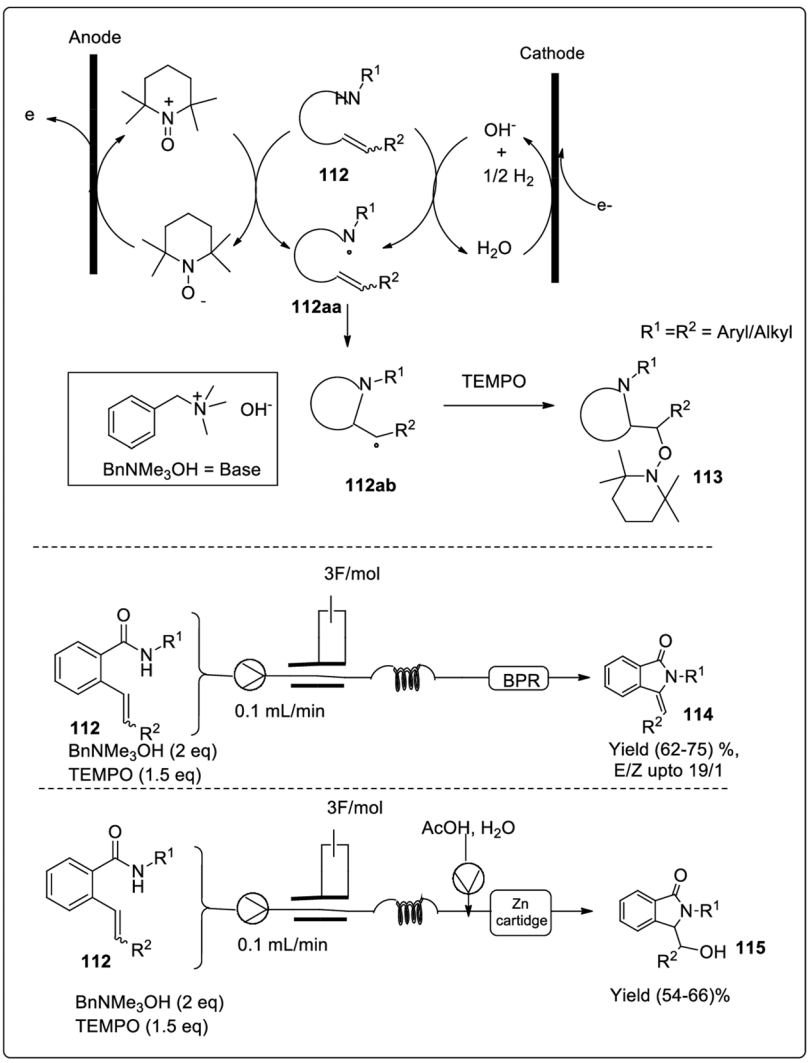
In 2017, T. Wirth *et al.* developed the synthetic transformation of isoindolinone by applying an organic electrochemical flow reactor (Scheme 32).[40] They prepared a second-generation electrochemical flow microreactor, which consisted of platinum as the cathode and boron-doped diamond (BDD) as the anode, separated by FEP (fluorinated ethylene propylene). The reaction was optimized with different bases and solvents, and they found that an acetonitrile/water mixture is the optimum solvent for electrochemical transformation. It was observed that on application of 3 F mol^{-1} electric supply, triethyl amine, 2,6-lutidine and sodium carbonate as the base in the reactor did not produce a good yield of the cyclized product. In the case of sodium carbonate, the reaction also proceeded but the



Scheme 31 Formation of enantio-enriched isoindolinones and *tert*-butyl sulfoxides using an optically pure *N*-sulfinyl imine.

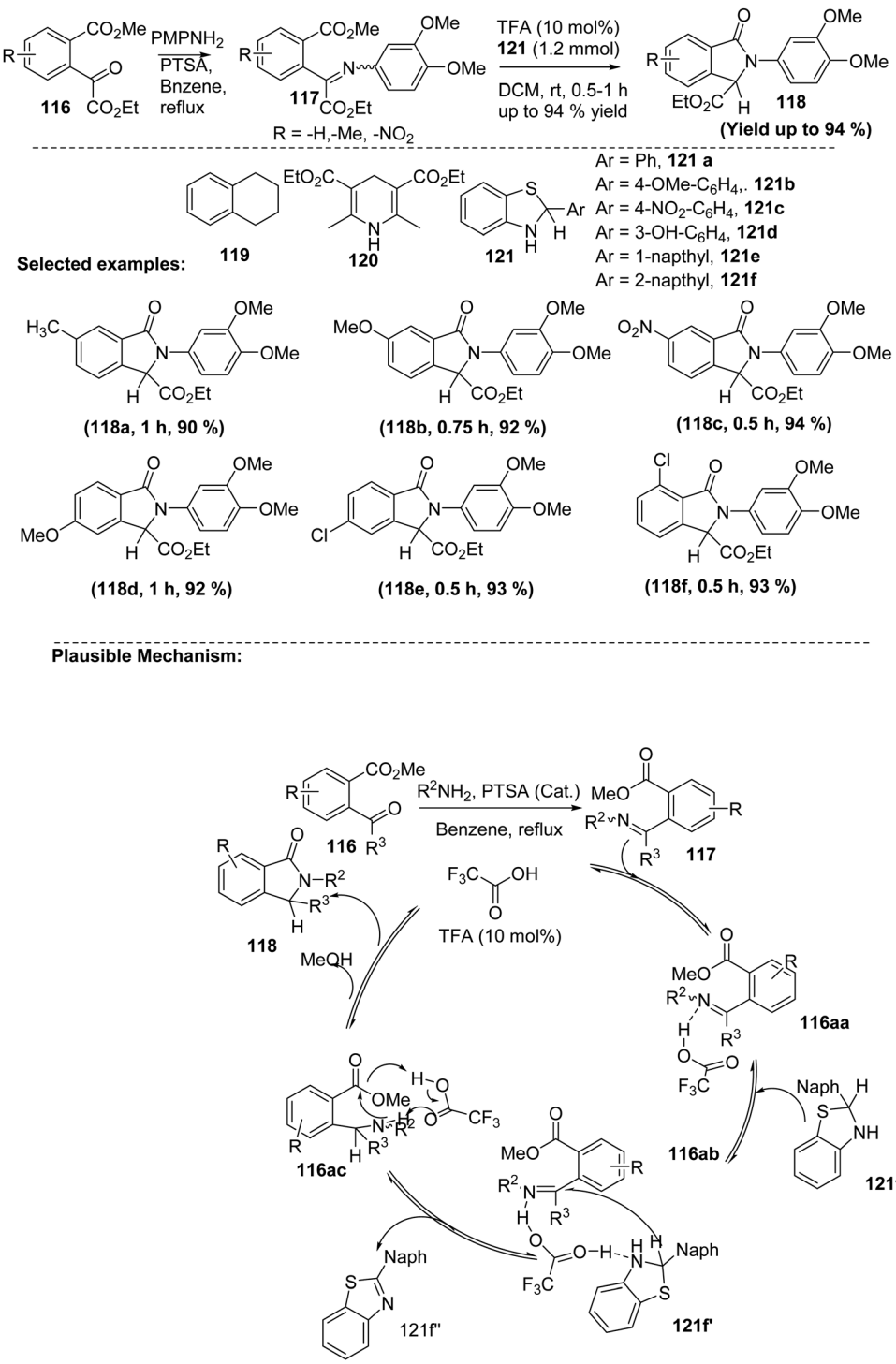
amount of water had to be increased, which led to lower solubility of the product and precipitation and blocking of the flow system after 10 min. Hence, they used benzyltrimethylammonium hydroxide (0.5 equivalents) as the base and TEMPO to achieve the full conversion of the desired product **113** together with 3 F mol^{-1} electric supply and 0.1 mL min^{-1} flow of reactant **112**. With the optimum conditions in hand, they prepared *N*-aryl/alkyl isoindolinones with different diastereoselectivity and good selectivity was observed on amide substitution of isopropyl and alkene substitution on phenyl. An electron-donating substituent on the amide nitrogen of **112** destabilised the radical, and hence a poor yield was observed. An electron-withdrawing substituent on the alkene moieties furnished the completely reduced product together with a TEMPO-embedded product. Vinyl phenyl substituents on amide gave moderate diastereoselective product, which on reduction with Zn in acetic acid, isolated separate diastereomer with moderate yield. In the presence of 2 equivalent benzyltrimethylammonium hydroxide as the base at 85 °C, 2.8 bar with 25 min, alkylidene-substituted isoindolinones **114** were formed with *E*-selectivity. The N–O bond reduction in flow was performed with a hot Zn cartridge and acetic acid at 40 °C to achieve full conversion to the corresponding alcohols **115** and the overall yields of the reduced compounds were 54–80%. The design of the electrochemical flow reactor and its vast application in the synthesis of bioactive organic compounds are the main attractions of this study.

Recently, D. K. Maiti *et al.* established an efficient synthetic protocol for isoindolinones **118** using a suitable organocatalyst and organoreductant. This organocatalyst-based transformation has broad utility given that it maintains green synthetic conditions compared to that with metal catalysts. Here, Hantzsch ester **120**, thiazoline-based reducing agents **121**, and 1,2,3,4-tetrahydronaphthalene **119** were used in the organoreduction process (Scheme 33).[41] However, the less reactive ketoimine intermediate **117** was more susceptible to capture of a hydride ion from 2-(naphthalen-2-yl)-2,3-dihydrobenzo[*d*] thiazole in the presence of TFA. Different aromatic amines



Scheme 32 Synthesis of isoindolinones using organic electrochemical flow reactor.

and methyl benzoate derivatives underwent this hydrogen transfer reaction. Both electronic-type aromatic compounds were found to generate *N*-aryl isoindolinone with good yields (90–96)%. Here, TFA was the main activating source for the organocatalyzed hydride transformation from 2-naphthyl-benzothiazoline to ketoimines, which was further supported by the ESI-MS kinetic data from an aliquot of the ongoing reaction, showing the characteristic mass peaks for intermediates **117**, **121f′** and **116ac** together with the isoindolinone. To prove the wide utility of the developed methodology, they also studied the photophysical properties of the newly synthesized molecules. They measured the absorption maxima of the newly synthesized molecules, which a showed bathochromic shift with a change from nonpolar to polar solvents. The highest

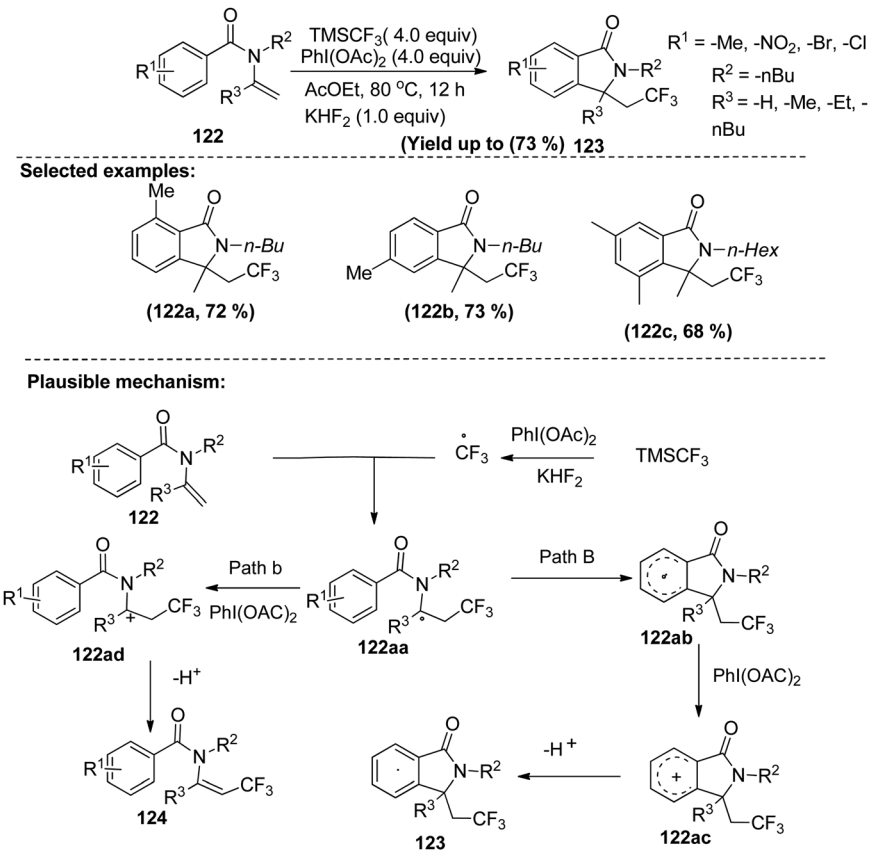


Scheme 33 Synthesis of isoindolinones using an organoreductant.

quantum yield was observed in DMSO solvent. This methodology has certain characteristic features. (i) It is the report on the TFA-catalyzed 5-annulation of ketoimine to isoindolinones, (ii) the organoreductive pathway furnished excellent yields with a variety of substrates and (iii) the process is environmentally benign and furnished fluorescent molecules, which may be used in the medical field in the future.

A trifluoromethyl radical-initiated tandem transformation was developed for the synthesis of isoindolinones. $TMSCF_3$ (radical source), $PhI(OAc)_2$ (oxidant) and KHF_2 (additive) were used for this conversion to obtain the isoindolinone in excellent yield at 80 °C in CH_3CN, taking *n*-butyl-*N*-(2-propenyl) benzamide **122** as the starting substrate (Scheme 34).[42] They tried with different additives including NaF, KHF_2, and $NaHF_2$ to obtain the desired product with fruitful yields. Different *N*-substitutions, *n*-Bu, *n*-propyl, and cyclopropyl gave the target product with good to moderate yields. This protocol also generated spirocyclicisoindolinone with moderate yield. However this method failed to generate the isoindolinone **123** derivative with a stronger electron-withdrawing aryl ring ($-NO_2$). This can be explained by the destabilization of carbocation **122ad**, which inhibits further cyclization. They investigated the mechanism *via* a control experiment, which showed that the yield of the desired product decreased significantly with the addition of TEMPO. This observation indicated that the reaction may proceed *via* the radical pathway. Hence, KHF_2 and $TMSCF_3$ reacted with $PhI(OAc)_2$ to generate the CF_3 radical, which immediately attacked the alkene, and subsequent oxidation generated the carbocation intermediate. Intramolecular cyclization of the resulting intermediate by aromatic π-electron formed the desired isoindolinone product **123**. *N*-2-Propenyl substituted furanamide could not be cyclized to the isoindolinone product, rather it underwent further elimination, leading to isomeric alkene **124**. The main utility of this protocol is its broad substrate scope to prepare highly substituted isoindolinonetrifluoromethyl-containing azaheterocycles which have attracted much attention due to their potential application.

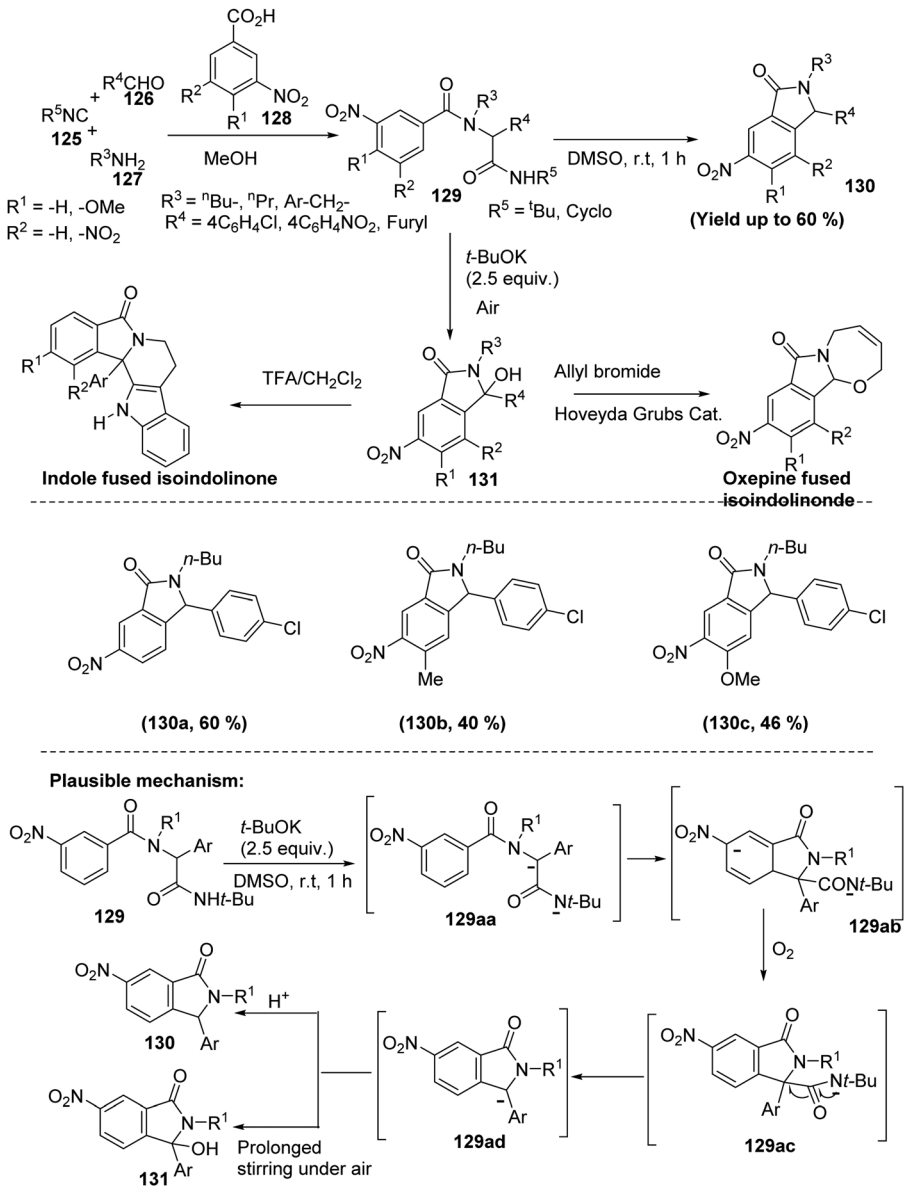
Multicomponent Ugi reaction is an environmentally benign tool for the preparation of a broad range of heterocyclic molecules, and the synthesis of isoindolinones is no exception. In 2018, Laurent El Kaïm and group synthesized these molecules *via* a Ugi/oxidative vicarious nucleophilic substitution sequence starting from 3-nitrobenzoic acid **128**, aromatic aldehydes **126**, alkyl isonitrile **125** and alkylamine **127** by eliminating different leaving groups (Scheme 35).[43a] The two-step reaction, involving Ugi reaction and base-mediated intramolecular nucleophilic addition followed by amide fragmentation provided *N*-alkyl-substituted isoindolinones **130** in good yields. The yield of isoindolinone formation completely depends on the stabilization of the anionic intermediate **129ab** generated in the basic medium on the tertiary (methinic)



Scheme 34 Trifluoromethyl radical-initiated synthesis of isoindolinones.

carbanions. Hence, the aldehyde component in the Ugi reaction with an electron-donating group (–OMe) gave poor yields and the isoindolinones obtained readily underwent aerial oxidation, leading to hydroxyl isoindolinone with 3-pyridyl substitution in the aldehyde components. The main barrier of this protocol is the presence of a nitro substituent *meta* to the carboxyl group and the other position of $-NO_2$ was not susceptible to nucleophilic substation. The reactions were well-tolerated with *n*-butyl/*n*-propyl/aryl substitution in the amine and cyclohexyl/*tert*-arylbutyl isonitrile furnished moderate yield of isoindolinone. Prolonged stirring in air in the presence of potassium *tert*-butoxide gave hydroxyisoindolinone **131** *via* aerial oxidation. Intramolecular vicarious nucleophilic substitution (IVNS) (special type of aromatic substitution, which replaces a hydrogen instead of halogen in the aromatic nucleophilic substitution) was involved in the Ugi product during the synthesis of isoindolinone, demonstrating interesting chemistry in the synthetic study. This transition metal-free transformation involves four components, which results in the formation of a huge number of variants in the synthesis of isoindolinone.

In 2019, the same group reported the synthetic route of fused isoindolinones *via* Ugi reaction from hydroxyisoindolinone precursor **131** (Scheme 35).[43b] Pictet–Spengler-type cyclization or metathesis sequence gave polycyclic isoindolinone in moderate yield. Indole-substituted **131** underwent intramolecular cyclization, forming interesting biologically active compounds, which showed an effect against malaria. RCM of *N*-allyl-*O*-allyl and cyclization of the isoindolinone derivative using Grubbs II catalyst furnished isoindolyl-oxazepines. The

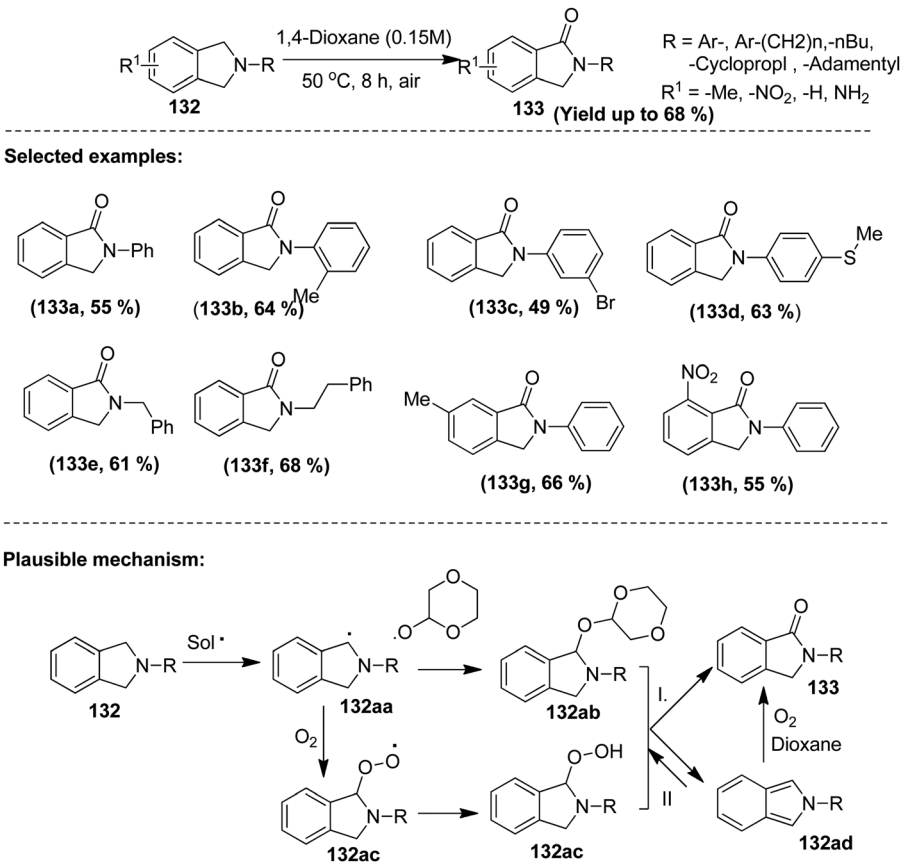


Scheme 35 Four-component Ugi reaction for the synthesis of isoindolinones.

development of this methodology and further synthetic application enriched the importance of the Ugi reaction.

In 2019, Frank W. Foss and co-workers reported a special type of chemo-selective oxidation of isoindolinone **132** using dioxane solvent. This reaction involves a selective H atom transfer, which eliminates several oxidation side products of isoindolinones. In this protocol, a catalyst-free and solvent-promoted oxidative method was described (Scheme 36).[44] Several types of isoindolines were prepared and oxidized in the air/dioxane system, giving good yields. This reaction is independent of additional solvent interaction. During the course of the reaction, isoindolinone radical intermediate **132aa** was formed *via* dioxane autoxidation and it has greater capability for autooxidation due to the β-effect of the additional oxygen in the dioxane solvent. Consequently, the radical changed to form 1-hydroperoxy-isoindoline **132ad**. The reaction could proceed to the product by a second –H atom transfer and elimination of the hydroxy radical following the type-I pathway or by the nonradical intermolecular dehydration reaction between two molecules of 1-hydroperoxy-isoindoline. Isoindole formation was observed under autoxidation conditions *via* the type II pathway (Scheme 36). The isoindole formation pathway was a productive pathway. Different aliphatic and aromatic amines furnished good yield of isoindolinones *via* the solvent-enhancing auto-oxidation method. The described protocol is a simple oxidative strategy for the preparation of isoindolinones from isoindolines. Here, O_2 was used as the terminal oxidant without a catalyst.

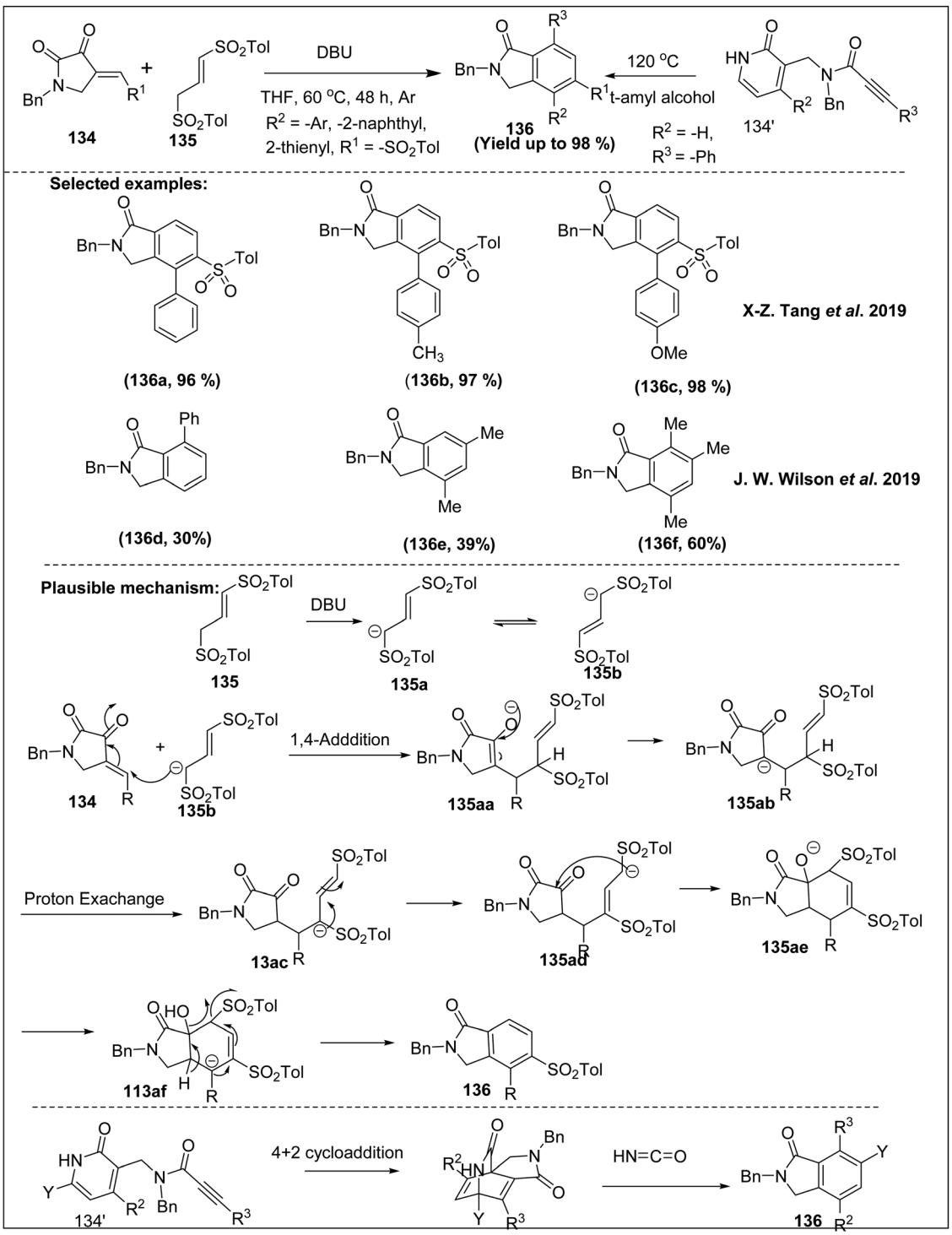
In 2018, Ming Yan and co-workers reported a synthetic route for isoindolinones **136** *via* [3+3] benzannulation of 4-arylmethylene-2,3-dioxopyrrolidines and 1,3-bissulfonylpropenes (or 4-sulfonylcrotonates) (Scheme 37).[45a] It was observed that the reaction gave a series of functionalized isoindolinones in excellent yields (>90%). The reactions were carried out with **134** (0.21 mmol), **135** (0.20 mmol) and DBU (0.24 mmol) in THF (4 mL) at 60 °C for 48 h. The reaction was carried out under metal-free conditions, producing **136** in excellent yield. The sulfonyl group at **135** acted as an activating group in the first stage, which left at the end of the reaction. When the R^2 group was phenyl, the reaction gave 96% yield. The substitution of the benzene ring with an electron-donating group (such as –Me and –OMe) or electron-withdrawing group (such as halogen, $-CF_3$) was tolerated very well. A methyl group on the phenyl ring at the 4-position provided 97% yield. A methoxy group attach to the 4-position of the phenyl ring provided 98% yield. A phenyl ring containing a highly electron-withdrawing group such as –F, –Cl, and –Br provided 98%, 95%, and 95% yield, respectively. Michael addition followed by aldol condensation is the main step for the synthesis of isoindolinones. Initially, **134** undergoes 1,4-addition with substrate **135a**, and then intramolecular proton exchange furnishes intermediate **135ad**. Intramolecular aldol condensation with sulfone and water elimination form



Scheme 36 Solvent-promoted autooxidation to isoindolinone.

the desired product in good yield. Most of the transition metal-free strategies involve the use of a benzoid precursor in the initial step but here the same scaffolds were prepared from a non-benzoid precursor *via* [3+3] benzoannulation reaction.

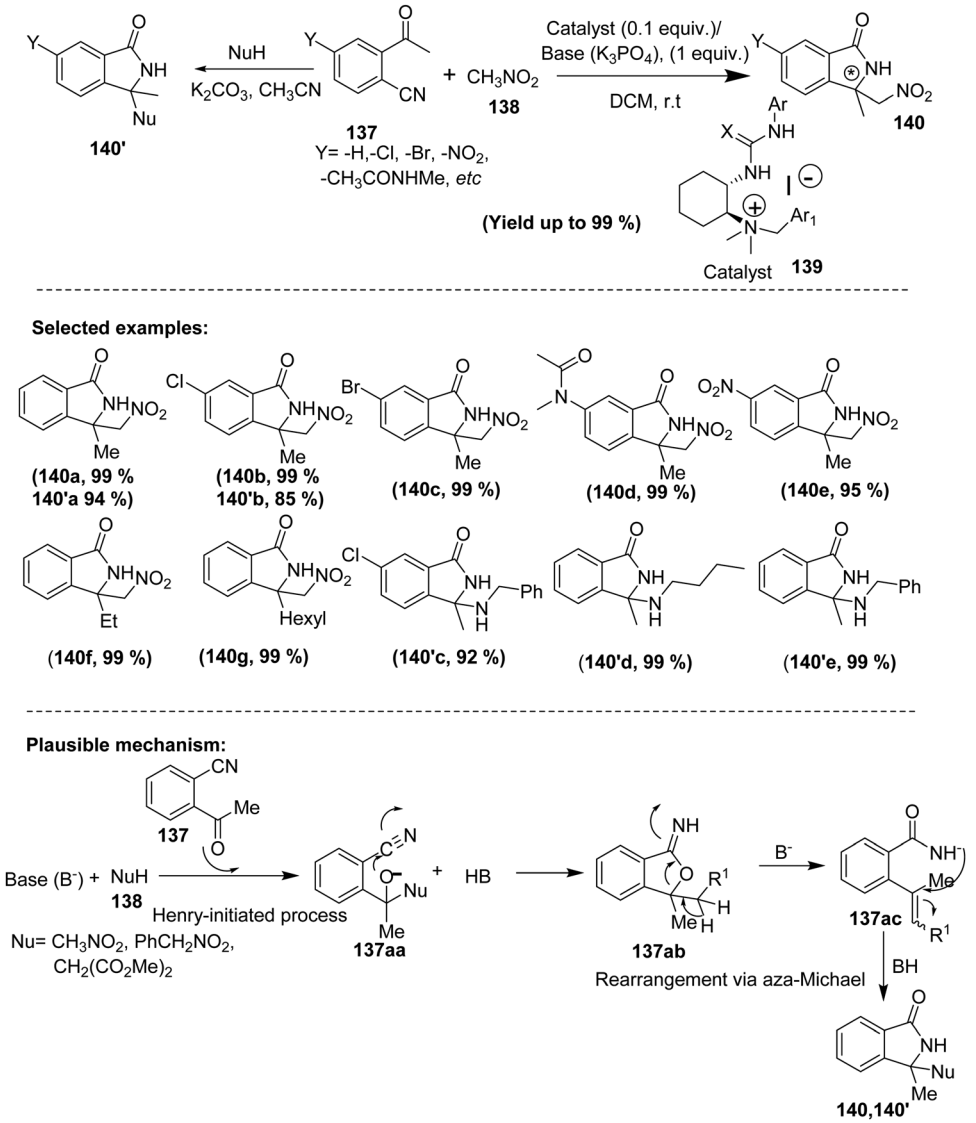
[4+2] cycloaddition reactions are well known pericyclic reactions in organic synthesis given that they produce a large number of complex carbocyclic and heterocycles from suitably designed substrates. Here, the reaction proceeded *via* intramolecular [4+2] cycloaddition of a pyridone with a tethered propiolamide **134′** moiety followed by the extrusion of isocyanic acid, forming isoindolinones **136** (Scheme 37).[45b] Different solvents were used for the optimization of the reaction conditions and it was found that *t*-amyl alcohol and dioxane solvents gave very clean LCMS for product **136**. The dilution of the



Scheme 37 Synthesis of isoindolinones *via* [3+3]/[4+2] benzannulation.

substrate in the solvent is the essential condition for intermolecular cyclization, which was effective in 0.1 M concentration. A wide range of substrates was studied under this protocol to form isoindolinones with moderate to good yields (22–80%).

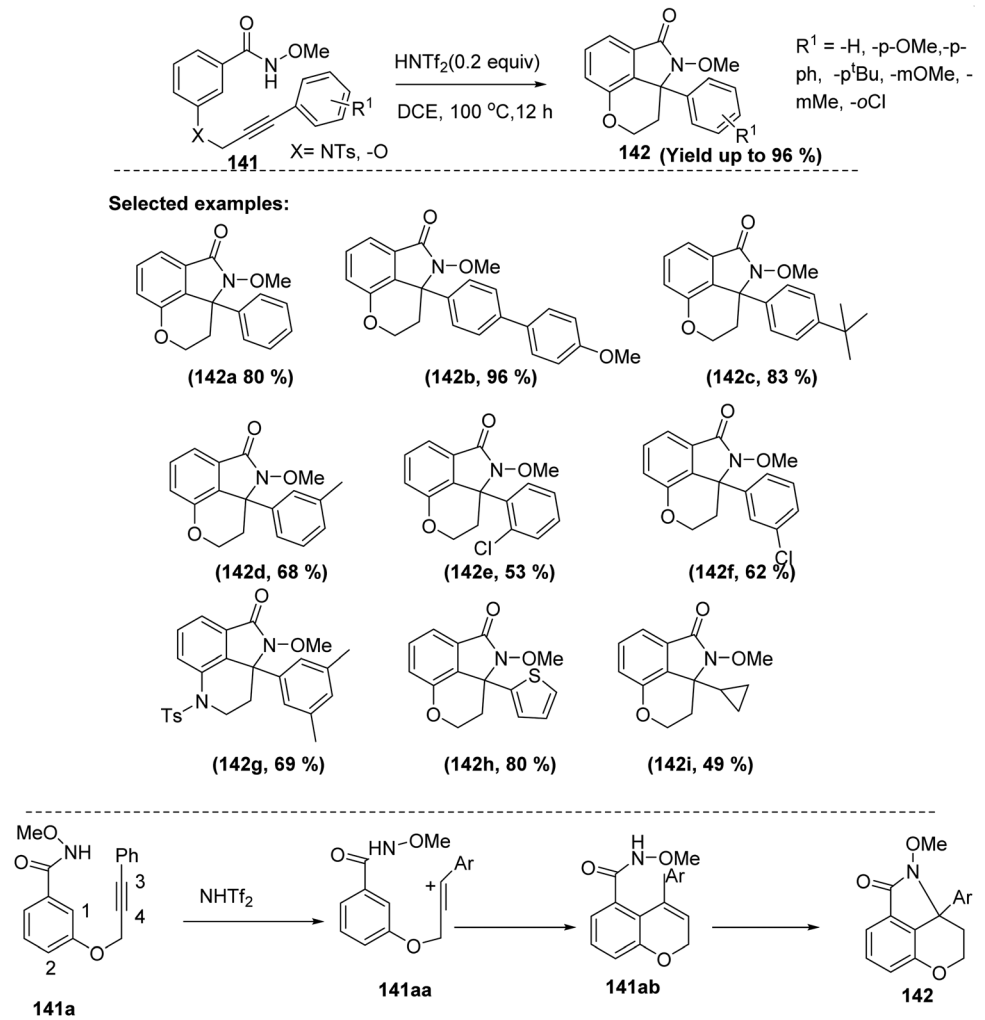
In 2019, A. Massa and co-workers reported a synthetic route for 3,3-disubstituted isoindolinone *via* an organocatalytic tandem approach. This cascade transformation involves a two-component condensation reaction between 2-acylbenzonitrile **137** and nitromethane (Scheme 38).[46] Chiral bi-functional ammonium salt **139** acts as the asymmetric catalyst for the chiral induction at the 3-center of isoindolinone derivatives **137**. In this reaction, moderate enantioselectivity was observed. The reactions performed better at room temperature and were accelerated more in diluted solutions. The enantioselectivity was not improved by the modification of the substituents on catalyst. The best results were obtained when C1, a strong electron-withdrawing group, remain on both aromatic rings. By examining the catalytic activity under different reaction conditions, it was concluded that enantioselectivity was observed using K_3PO_4 as the base in a solid/liquid heterogeneous system. The reaction gave the best result in the presence of DCM solvent. This reaction provided a very good yield (99%) and ee of nearly 40% of **140a**. The mechanistic observation showed that simple aldol-type addition followed by rearrangement *via* aza-Michael reaction furnished isoindolinone **140** in excellent yield. Chiral induction at the 3-position of isoindolinones is an area in high demand area in organic synthesis given that it produces bio-activities. This methodology allows this using chiral bifunctional ammonium salt **139**. In 2018, the same group reported the preparation of isoindolinone derivatives from the same scaffolds using 2-acylbenzonitriles, which were obtained from 2-ethyl benzonitrile and NBS reaction followed by hydrolysis. They obtained the desired 3-substituted isoindolinones under very mild conditions *via*



Scheme 38 Synthesis of 3,3-disubstituted isoindolinones *via* cascade reactions of 2-acylbenzonitriles.

nucleophilic addition and Dimroth rearrangement. The asymmetric induction of isoindolinones *via* a tandem protocol is the main advantage of this methodology.

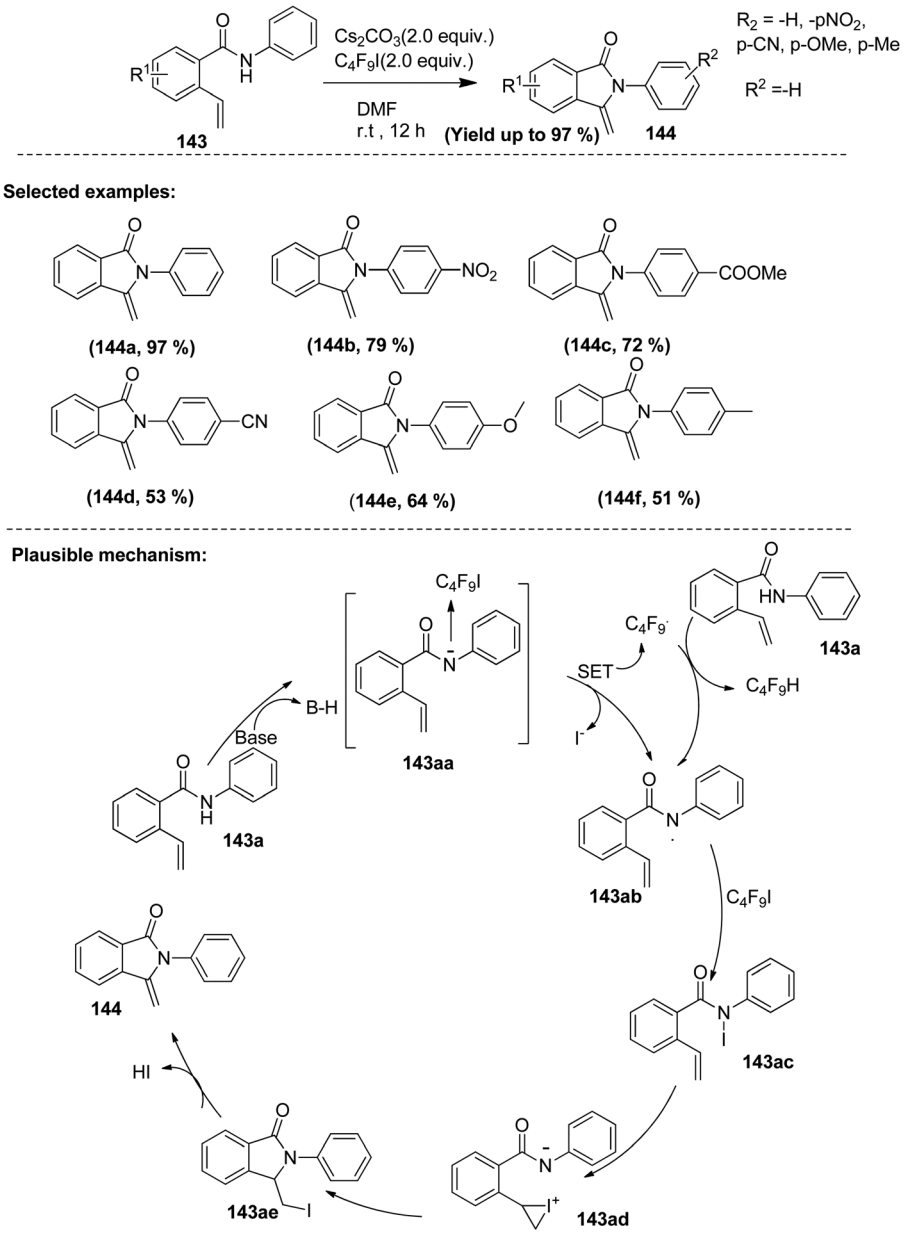
Triflimide ($HNTf_2$) can catalyze the synthesis of fused isoindolinones given that it has high acidity and good solubility in most organic solvents, and this catalyst has also been used for C–C and C–X bond formation, which is beneficial for cascade reactions *via* the single click activation of functional groups. This one-pot single catalyst *via* a series of reactions furnished chromane-fused isoindolinones from the substrate *N*-methoxy-3-((3-arenylprop-2-yn-1-yl)oxy)benzamide **141** (Scheme 39).[47] Different Lewis acid catalysts such as zinc, copper, scandium, indium and ytterbium salt were used for the cascade transformation, but 20 mol% of triflimide ($HNTf_2$) in DCE solvent at 100 °C was the optimum condition for the formation of product **142**. *N*-Methoxybenzamide with electron-withdrawing groups –F, –Cl, –Br and CF_3 was found to produce lower yields compared with an electron-donating substituent in the aryl ring at the alkyne substituent. Tetrahydroquinoline fused isoindolinones were also synthesized using the same optimum conditions by employing an aniline-type-*N*-methoxybenzamide, which gave moderate yields with an electron-donating substituent. To observe the practical application, they carried out the gram-scale preparation of fused isoindolinone with 61% yield. C–O and N–O bond cleavage occurred using NaH and SmI_2, respectively, and the obtained products showed anti-HIV13 and anti-inflammatory activity. They had performed a controlled experiment to understand the mechanism pathway. In this case, they observed that the addition of a radical inhibitor did not stop the progress of the reaction, and hence the reaction may not follow the radical pathway. Initially, the Brønsted acid triflimide ($HNTf_2$) protonates the alkyne bond, furnishing the carbocation intermediate. This carbocation has two types of probable cyclizations. DFT calculation showed that C-1 and C-3 electrophilic cyclisation by aromatic π-electron **141aa** is more affordable given that it requires a lower activation compared with *p*-cyclization. Intramolecular aza-cyclization by the amide N-atom generates the desired product **142**. This protocol is very interesting in the mechanistic pathway and provided a large array of different chromane/tetrahydroquinoline fused isoindolinones **142** and explains all the electronic aspects with theoretical data.



Scheme 39 Triflimide-catalyzed synthesis of highly fused isoindolinones.

In 2020, X. Zhang and co-workers reported a synthetic approach for isoindolinones **144** through intramolecular amidation of *ortho*-vinyl benzamides **143** (Scheme 40).[48] This reaction gave a variety of *N*-aryl isoindolinone derivatives in moderate to excellent yields with the help of perfluorobutyl iodide. It was observed that the reaction proceeded faster at room temperature. It took almost 12 h for the reaction to be completed. Anionic intermediate **143aa** was formed in the presence of base. Then, an EDA complex was formed by the reaction between *N*-anionic intermediate **143aa** and C_4F_9I. Single-electron transfer from **143aa** and an iodide ion generated *ortho*-vinyl benzamide N-radical **143ab**, which on oxidation by C_4F_9I, gave intermediate **143ac**. The C=C bond of styrene may be activated by the iodonium ion to form iodonium intermediate **143ad**. Intramolecular nucleophilic addition with a nitrogen anion generated iodo-isoindolinone intermediate **143ae**, which led to the desired product **144** by releasing one molecule of HI. This protocol explained a concise synthetic route for isoindolinones *via* the intramolecular amidation of *o*-vinyl benzamides. They first used perfluorobutyl iodide as a unique oxidant to get a variety of *N*-aryl isoindolinone derivatives in good yields.

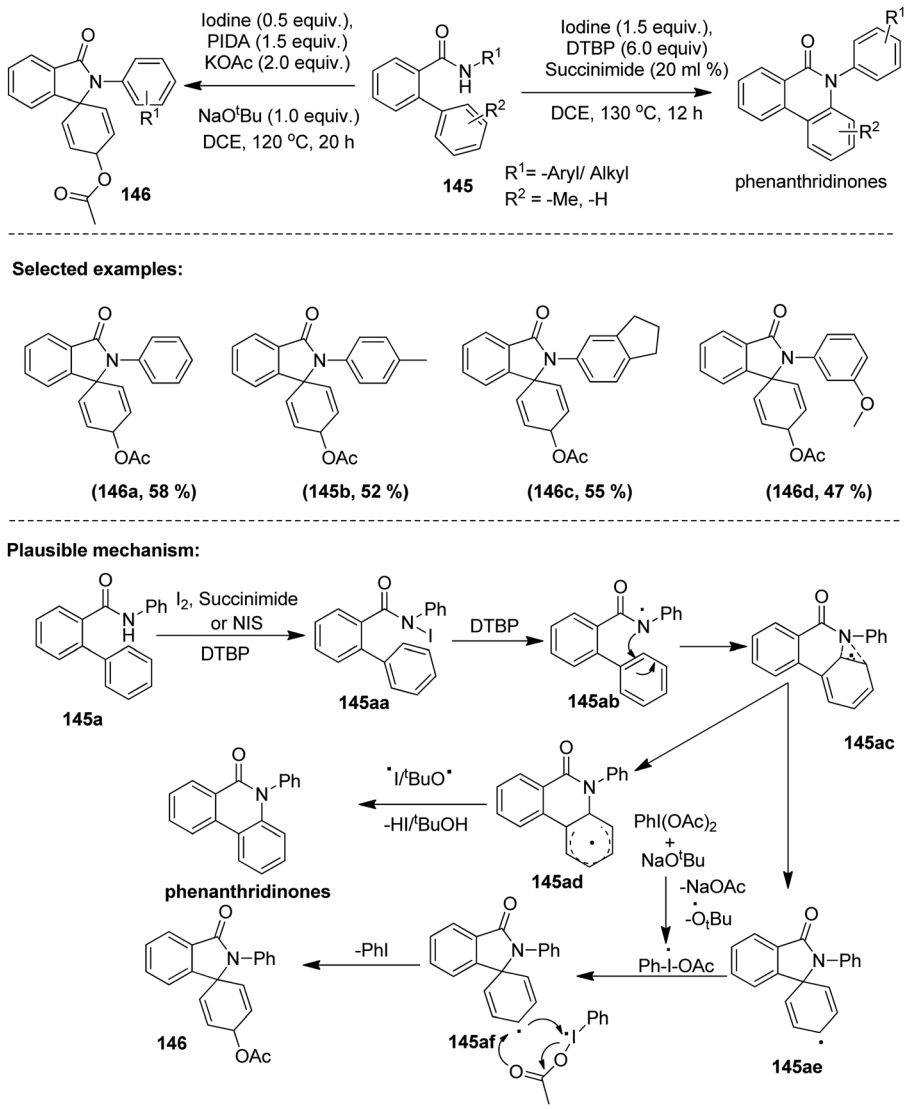
In 2020, S. Kumar and group reported a transition metal-free synthetic route for isoindolinone *via* an iodine-assisted radical pathway from the substrate 2-phenyl-*N*-phenyl benzamide **145**. Here, I_2-mediated intramolecular coupling occurred between the N–H and sp^2 C–H bonds. Condition-dependent intramolecular cyclization was achieved to form two types of



Scheme 40 Synthesis of isoindolinones through intramolecular amidation of *ortho*-vinyl benzamides.

phenanthridinones and spiro-isoindolinones **146** (Scheme 41).[49a] I_2/succinamide in the presence of DTBP or PIFA with base furnished phenanthridinone. Changing the conditions, I_2 with PIDA afforded isoindolinone in good yield. After the addition of potassium acetate and sodium *tert*-butoxide to the reaction mixture, the yield (58%) of the product increased. This methodology provided a library of spiro-isoindolinones containing methyl, methoxy, phenyl substitution on the *N*-phenyl ring in 40–58% yield by C–N and intermolecular C–O coupling reactions, where concomitant de-aromatization of the phenyl ring occurred. The mechanistic observation showed that the reaction stopped in the presence of TEMPO. Thus, this reaction follows the radical pathway. An amide N-centered radical was formed by the cleavage of the N–I bond, which was formed from substrate **145aa**. Succinimide and iodine *in situ* generated NIS in the presence of DTBP, which gave **145a**. Radical **145ab** intramolecularly added to the phenyl *via* the cyclopropyl intermediate, resulting in the formation of **145ac**. Further, the N-radical added to the *exo*/*endo* face of the arene-π-bond, and then proton transfer to $^{t}BuO^{\bullet}$ or $I^{\bullet}$ radical formed phenanthridinone. In the presence of PIDA and *tert*-butoxide base, the formation of $PhI^{\bullet}OAc$ and $^{t}BuO^{\bullet}$ takes place. An electron transfers from the radical to $PhI^{\bullet}OAc$ *via* a five-membered TS with the transfer of acetate to cyclohexadienyl group, leading to dearomatized novel spirocyclic isoindolinone **146**. This protocol showed the regent-dependent cyclization of *N*-alkylated phenanthridinones and isoindolinones using iodine/DTBP and iodine/PIDA, respectively.

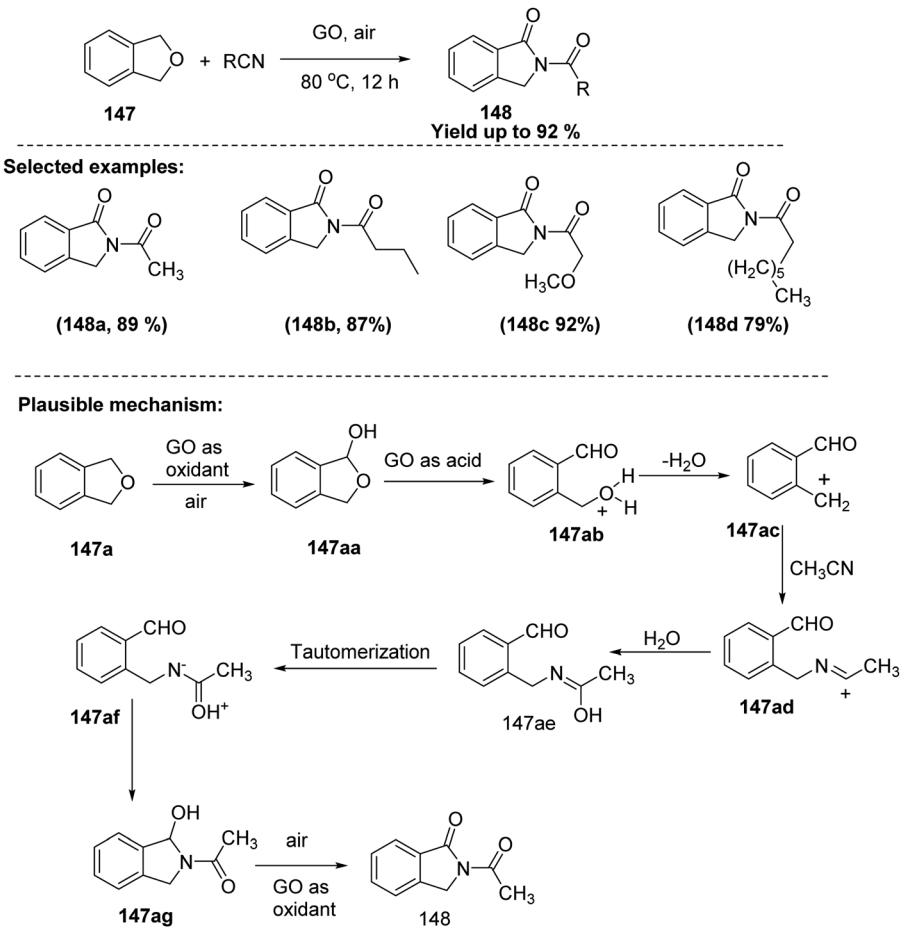
Graphene oxide (GO) can be used as a carbocatalytic material for a variety of chemical transformations, such as C–O, thiol and C–H oxidation and alkyne hydration, polymerization, and C–C and carbon–X bond-forming reactions. The novel structural aspects of graphene oxide (high surface area and various functional groups: hydroxyl, carboxyl, and epoxide groups) help it to exhibit a broad range of catalytic properties. It has been used as a substituted reagent for transition metal-catalyzed reactions. Here, graphene oxide was used as an oxidant for the



Scheme 41 Synthesis of *N*-substituted phenanthridinones and spiro-isoindolinones using iodine *via* the radical pathway.

synthesis of isoindolinone derivatives. Initially, a model study was carried out with isobenzofuran **147** and 2-phenyl acetonitrile in the presence of GO as a catalyst (150 wt%) at 80 °C and it was found that the reaction successfully produced *N*-acylisoindolin-1-ones in excellent yield under neat conditions instead of using common solvents such as ethyl acetate, 1,4-dioxane, EtOH, DMF, toluene, $ClCH_2CH_2Cl$, and CH_2Cl_2 (Scheme 42).[49b] Aliphatic- or aromatic-substituted acetonitrile smoothly responded to this reaction, producing **148** in up to 92% yield but benzonitrile and its substituent failed to yield isoindolinone derivatives under these conditions. The mechanism of the methodology was well-established by a series of controlled experiments. They investigated the mechanism using the radical trapping agent TEMPO, which showed that the reaction did not happen *via* a radical pathway. Again, in another path, they observed *via* an isotopic labeling experiment and established that the isoindolinone oxygen came from the air and *N*-acyl oxygen came from water molecules. They proposed the mechanism based on these experiments and proposed that the isobenzofuran was first oxidized by GO in the presence of air, yielding hydroxyisoindolone **147aa**, which on cleavage by the acid catalyst GO gave intermediate **147ac**. This intermediate on nucleophilic addition by alkynitrile and isomerization, and then aza-cyclization followed by oxidation provided the desired product **148**. Oxidation at the remote position of **147** without a metal catalyst in the presence of air with GO is the attractive part of this developed protocol.

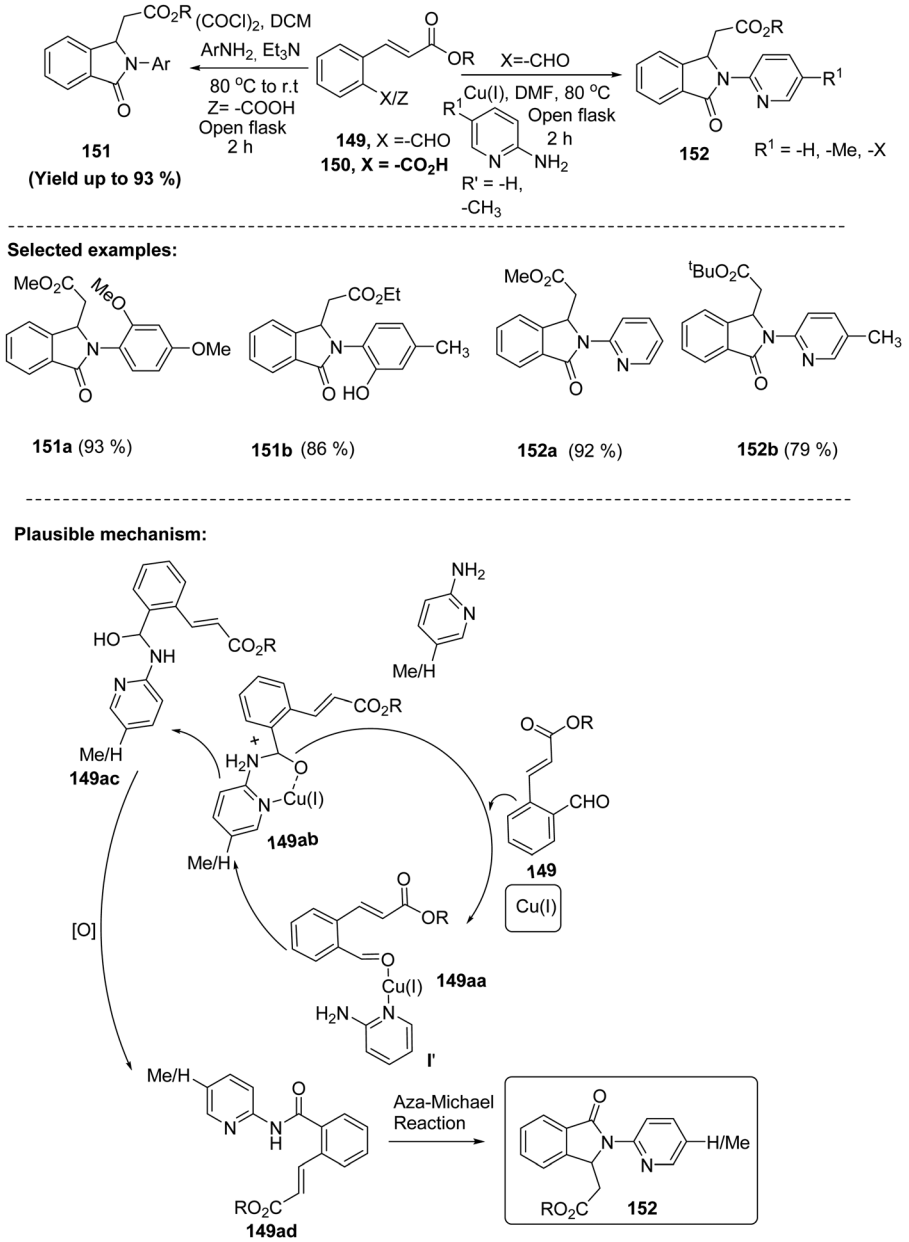
Recently, our group published a synthetic route for 3-substituted *N*-aryl isoindolinones by intramolecular aza-Michael reaction from the substrate alkyl (*E*)-3-(2-formylphenyl)acrylate. *N*-Aryl-substituted isoindolinones **151** were synthesized from (*E*)-2-(3-alkoxy-3-oxoprop-1-en-1-yl)benzoic acid **150** *via* aza-Michael reactions (Scheme 43).[50] The desired *N*-aryl isoindolinones were obtained by converting the starting material from formyl vinyl acrylic ester to its acid derivative *via* Pinnick oxidation. This acid derivative thereafter converts into its acid chloride by using oxalyl chloride at 80 °C and added to a solution of aryl amine in triethyl amine at 0 °C to furnish the desired *N*-aryl-substituted isoindolinones in excellent yield (93%). During the course of our reaction, we also developed *N*-pyridinyl isoindolinone **152** *via* oxidative amidation from the same substrate. Firstly, we took methyl (*E*)-3-(2-formylphenyl)acrylate **149** and 2-amino pyridine for the tandem oxidative amidation and aza-Michael reaction. For that reaction, the optimized reaction conditions were found to be CuI as the catalyst in DMF at 80 °C. Using these conditions, a series of *N*-pyridinyl isoindolinones were synthesized with good yield (92%). However, these conditions did not provide *N*-aryl



Scheme 42 GO-catalyzed synthesis of isoindolinones.

isoindolinones. The plausible mechanism can be explained for the synthesis of isoindolinones by electron-rich amino pyridines, such as methyl derivative by the (i) formation of hemiaminal intermediate **148ac** *via* six-membered cyclic intermediate **148ab**, which is stabilized by Cu(I) complexation and (ii) then air oxidation of **148ac** followed by intramolecular aza-Michael reaction to convert into *N*-pyridyl isoindolinones through oxidative amidation. Amidation and aza-Michael reactions using suitable aryl amines are the important aspects of this methodology.

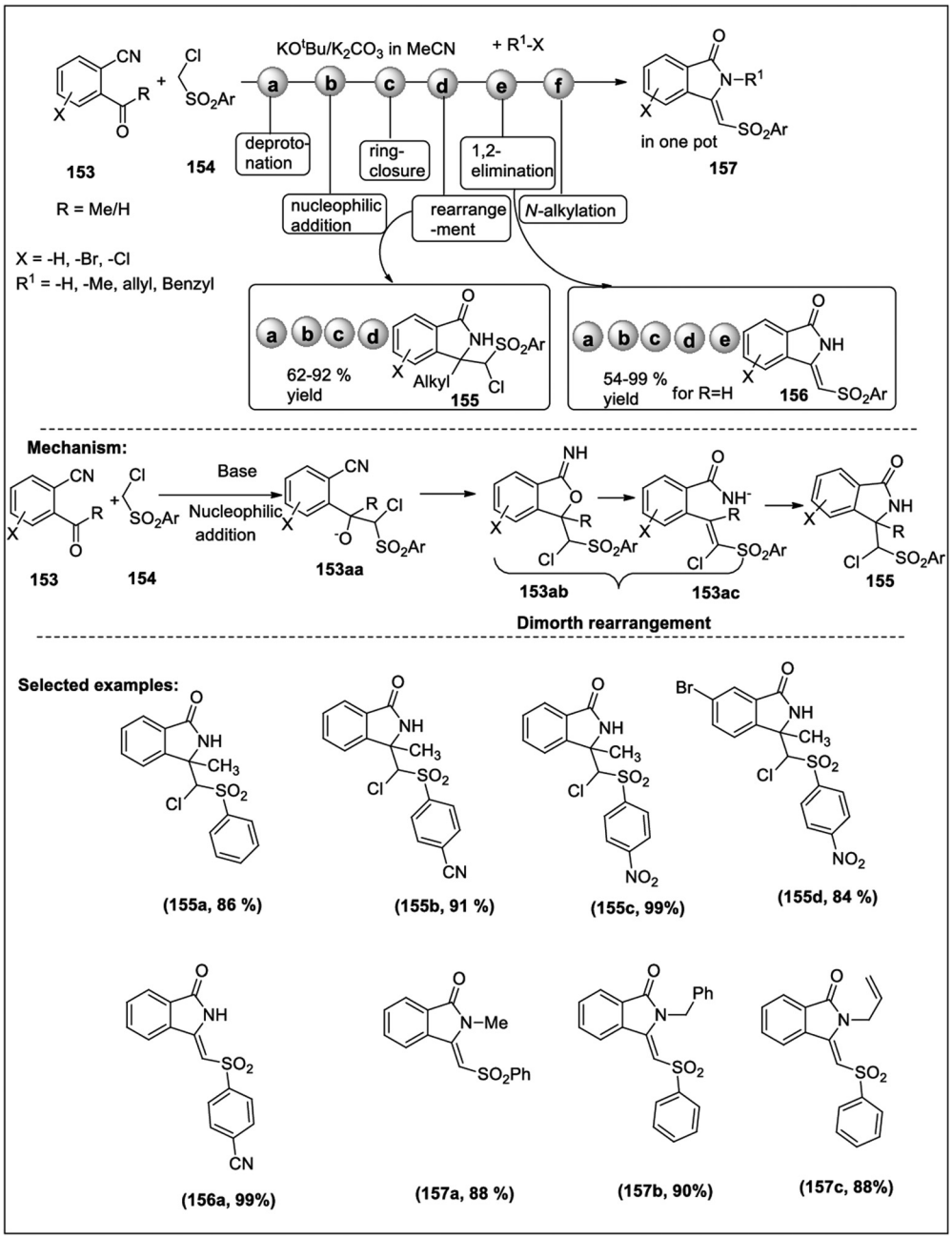
Massa and group designed a strategy in which *ortho*-carbonyl-substituted benzonitriles **153** and ((chloromethyl)sulfonyl)benzenes **154** undergo cascade reactions to furnish multi-substituted isoindolinones **157** decorated at the C-3 position with tetra-substituents (Scheme 44).[51] This type of environmentally benign protocol is highly cost-effective given that six elementary steps are performed in a single reaction vessel, and furthermore KO^{t}Bu/K_2CO_3 in acetonitrile is used as a base for promoting the reactions. The precursor 2-acyl benzonitriles were unable to cyclize with Et_3N but in the presence of K_2CO_3, furnished the desired isoindolinone derivatives in poor yield. Firstly, the ((chloromethyl)sulfonyl)benzenes **154** were added to the carbonyl group of the benzonitrile derivatives **153** *via* nucleophilic addition reaction in the presence of a base. They proved that in the competitive reaction, the addition product did not proceed further *via* the epoxide intermediate, rather it underwent cyclization with the cyano group to form iminophthalan intermediate **153ab**, which on subsequent



Scheme 43 One-pot synthetic strategy of isoindolinone *via* intramolecular aza-Michael reaction.

rearrangement reaction led to the formation of isoindolinone derivatives **155** in good yields. In each case, diastereomeric excess up to 95% was achieved through (a) activation of the pronucleophile by deprotonation, (b) nucleophilic addition to the carbonyl group, (c) ring closure, and (d) Dimroth rearrangement of the heterocycle. 2-Formyl benzonitrile follow the same path as 2-acyl benzonitrile in up to sequential four steps, but due to the presence of a β-H atom, the –Cl group is capable of forming alkene by the elimination of HCl. In all cases, they provided *Z*-selectivity instead of *E*-selectivity for lowering the steric interaction. One extra step is also performed in the presence alkyl halide together with ((chloromethyl)sulfonyl)-benzenes **153** and 2-formyl benzonitrile **154** in which consecutive coupling reactions gave the desired *N*-alkyl isoindolinones **157** with *Z*-selectivity. In this case, the intramolecular H-bonding stabilized the *Z*-selectivity of the isoindolinone derivatives. They studied the mechanistic details *via* DFT experiments and found the exact pathway of cyclization. Six steps in one-pot is the main green aspect of this methodology for the synthesis of substituted isoindolinone derivatives and chronological explanation of each step *via* isolation of the intermediates is also another valuable part of this protocol.

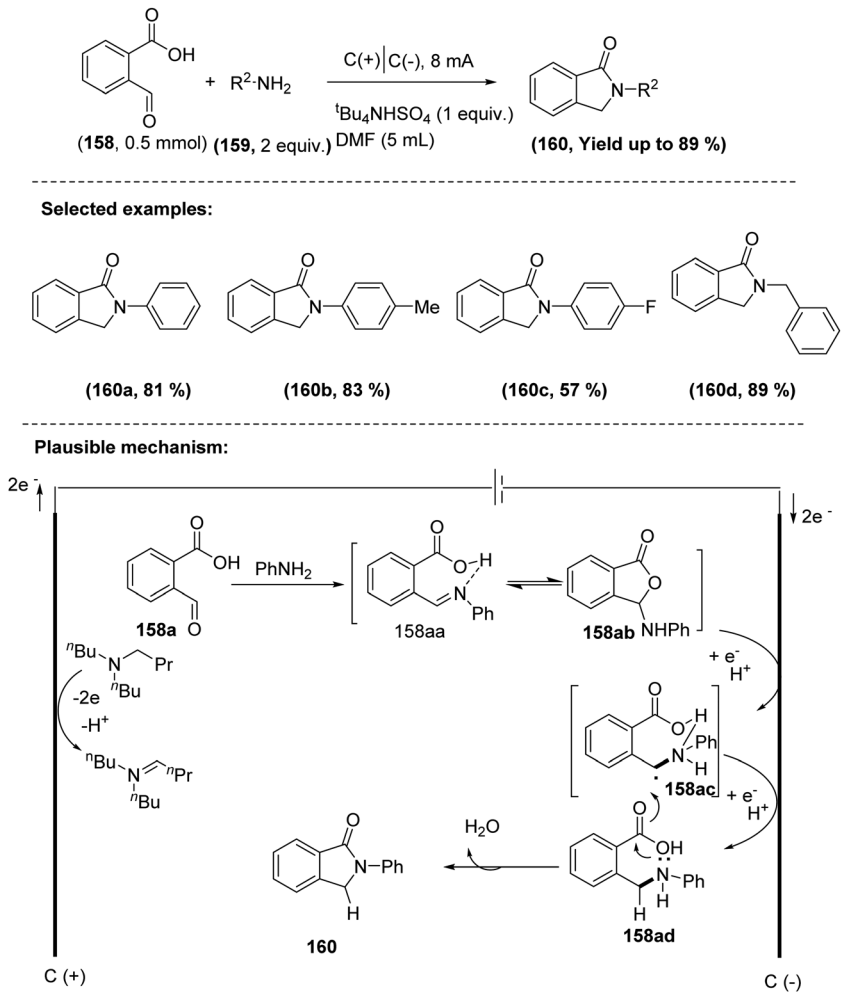
The electrochemical synthesis technique is a useful tool for the production of different organic molecules without any external oxidant/reductant in the reaction vessel. Owing to the importance of C–N bond formation in the synthesis of



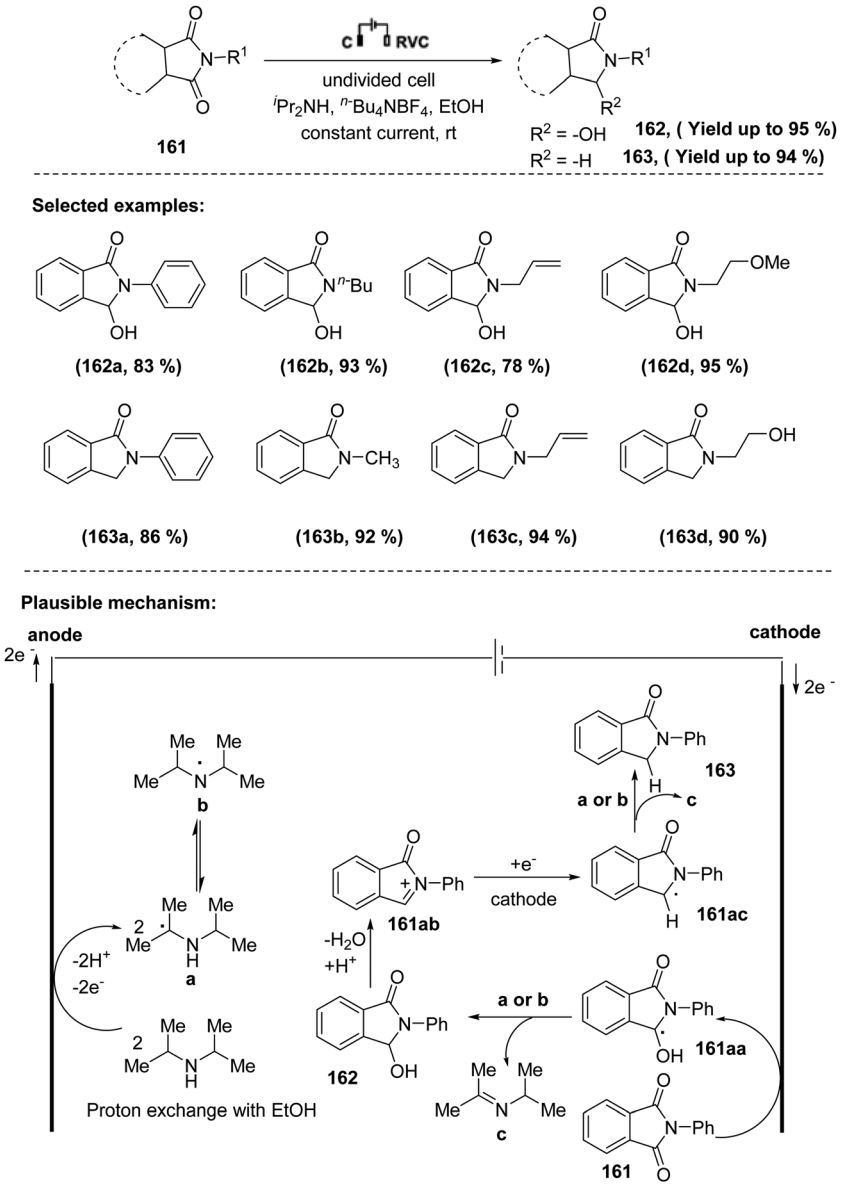
Scheme 44 Step economy pathway for the synthesis of isoindolinones.

heterocycles, isoindolinones were synthesized *via* the electrochemical method from 2-carboxybenzaldehydes **158** and arylamines **159** (Scheme 45).[52] This electrochemical technique was initially checked with an undivided cell equipped with graphite rods as the anode and cathode, using $^{n}Bu_4NHSO_4$ as the electrolyte and DMF as the solvent under a constant current of 8 mA in the presence of 2-carboxybenzaldehydes and aniline. The yields of the desired products diminished in ethanol or DMSO solvents and with Pt as the anode instead of a carbon anode. Aryl/cycloalkyl/heteroaryl amine underwent a coupling reaction with 2-carboxybenzaldehydes, leading to the formation of the desired product in good yields. Substituents in the ring at the *meta*/*para*-position were well-tolerated compared to *o*-substituents due to the steric influence, which controlled the formation of isoindolinone. To establish the exact mechanistic pathway, a series of controlled experiments were performed. When they used methyl 2-formylbenzoate instead of 2-carboxybenzaldehyde, the desired product was furnished in a trace amount, indicating that the carboxyl group in the substrate plays a vital role in the electrochemical reaction. Further, 2-carboxybenzaldehyde with aniline in DCM produced isobenzofuranone **158ab** during the electrochemical reaction, yielding the desired product, and hence the transformation occurs *via* intermediate **158ab**. Again, in the radical trapping experiment, they found that the reaction stopped with the use of TEMPO, and thus the reaction occurs *via* a radical pathway. Based on the experiment, they proposed the reaction proceed through the formation of the isobenzofuranone **158ab** intermediate, which remains in equilibration with imine intermediate **158aa**, stabilized by intramolecular hydrogen bonding. This intermediate on electrochemical reduction followed by aza-cyclization gave the isoindolinone products **160**. This electrochemical transformation is a new method for reductive aza-cyclization, which can furnish different N-heterocycles using the developed methodology.

Electrochemical chemoselective transformation is a growing field in the modern era, and hence J. Xiang and group synthesized hydroxyisoindolinone/isoindolinone *via* partial or complete reduction of *N*-phenylphthalimide derivatives **161** *via* the highly selective and controlled reduction of imides using a simple undivided cell with inexpensive carbon electrodes (Scheme 46).[53] The optimum conditions for this



Scheme 45 Electrochemical synthetic pathway of isoindolinones.



Scheme 46 Chemoselective transformation to isoindolinones using the electrochemical technique.

electrochemical reduction were graphite as the anode and reticulated vitreous carbon (RVC) as the cathode in a cell containing *N*-phenylphthalimide as the reactant and i-Pr_2NH as the proton donor and *n*-Bu_4NBF_4 as the electrolyte with a constant flow of current 20 mA to 25 mA. The formation of hydroxyl isoindolinone **162** and isoindolinone derivatives **163** completely depends on the time the electric current passes to the reaction medium and the substituent parameter of the *N*-aryl group. The electron-donating group furnished two isomers, **162** and **163**, but the electron-withdrawing group gave only one isomer, **163**. They performed a controlled experiment to study the mechanism, which showed that the reaction did not proceed in a polar aprotic solvent such as CH_2Cl_2. Deuterium exchange occurred during the reduction with EtOD, indicating that the presence of a protic solvent is the essential factor to promote the reaction. Again, the rate of the reaction was retarded with TEMPO, and hence the reaction follows the radical pathway during the electrochemical reduction. Here, the phthalide reduction occurred in two steps, as follows: (i) reduction in cathode and proton exchange with the solvent and (ii) elimination of water and further reduction in the cathode to produce the isoindolinone derivative. Chemoselective controlled reduction by the passage of an electric current is the main advantage of this methodology.

Conclusion

In this review, different synthetic aspects of isoindolinones such as promising drug conjugates, anthelmintic, antimicrobial,

cyclooxygenase isoenzyme (COX-2), insecticidal, thrombin inhibition and specifically anticancer activity were discussed. This broad range of physicochemical, pharmacological and inherent properties of isoindolinone compounds has inspired the synthesis of these novel molecules *via* both transition metal-catalyzed and transition metal-free approaches. However, transition metal-free approaches are more reliable according to the environmental and sustainable concept. We focused on the above-mentioned green chemical transformation to isoindolinone moieties, which will help researchers gain new ideas on the synthesis of new isoindolinone derivatives in a greener way. On account of their great importance, many reliable strategies have been employed for the preparation of substituted isoindolinone derivatives and their fused analogues. In the discussion on the protocol strategies, both intra/intermolecular fashions were involved given that they were carried out in multi-step synthesis or one-pot cascade reactions. It can be concluded that isoindolinones and their derivatives have been employed to form many important drugs and synthetic colours, which have immense biological and social impacts. Hence, we strongly believe that this review will pave the new way for the further development of this compound in the near future.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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