

Engaging Isatins in Multicomponent
Reactions (MCRs) – Easy Access to
Structural DiversityPedro Brandão,^[a, b] Carolina S. Marques,^[b] Elisabete P. Carreiro,^[b] M. Pineiro,^[a] and
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Abstract: Multicomponent reactions (MCRs) are a valuable tool in diversity-oriented synthesis. Its application to privileged structures is gaining relevance in the fields of organic and medicinal chemistry. Isatin, due to its unique reactivity, can undergo different MCRs, affording multiple interesting scaffolds, namely oxindole-derivatives (including spirooxindoles, bis-oxindoles and 3,3-disubstituted oxindoles) and even, under certain conditions, ring-opening reactions occur that leads to other heterocyclic compounds. Over the past few years, new methodologies have been described for the application of this important and easily available starting material in MCRs. In this review, we explore these novelties, displaying them according to the structure of the final products obtained.

Keywords: isatin, multicomponent reactions, spirooxindoles, bis-oxindoles, 3,3-disubstituted oxindoles, oxindole, sustainability, catalysis, nanocatalysts, diversity oriented synthesis

1. Introduction

Multicomponent reactions (MCRs) emerged in the past decades as valuable synthetic pathways to afford small molecule libraries efficiently, working as a “highway” for molecular diversity, with a good atom, pot and step economy.^[1] By gathering into the same chemical framework three or more components, with the final product exhibiting most of the atoms which were present in the starting materials, MCRs have been widely explored in several fields in organic synthesis, including total synthesis of natural products and drug discovery programs.^[2] Due to their versatility, MCRs are often performed in a sequential manner, providing higher synthetic diversity and structural complexity.^[3]

Isatin, chemically known as indoline-2,3-dione, has been widely applied as a starting material in several MCRs. The exploration of the reactivity of this molecule is highly focused on its electron-deficient carbonyl group at position 3, which makes it an excellent electrophile, sometimes displaying reactivity similar to the one observed with aldehydes. This feature is driven by the presence of the cyclic α -keto amide moiety and is exploited in most examples of MCRs involving isatin, as will be described in this work.^[4] Substitution at position 1 or in the aromatic ring constitute valuable alternatives for synthetic approaches for new oxindole derivatives from this valuable planar bicyclic heterocycle, and while

it is frequently reported in more classic step-by-step synthetic approaches, it remains very much unexplored in MCRs. Several recent publications can be found concerning aspects of isatin chemistry, including the synthesis of the isatin core,^[5] asymmetric synthesis of derivatives,^[6] and biological activities displayed by its derivatives.^[7]

Engaging isatin in MCRs is therefore a highly desirable synthetic field, and several research groups are currently exploring different routes to expand isatin derivatives chemical space. Figure 1 shows the considerable amount of effort recently made in this field, with a considerable number of publications made in the timeframe assessed by this review. The structural diversity obtained by performing MCRs with isatin is vast, with spirooxindoles being the leading structural derivatives reported. Nevertheless, bis-oxindole, other oxindole and non-oxindole derivatives can also be synthesized through the application of different MCRs. Concerning the number of components, the number of publications decreases as the number of components increases. In the case of these reactions, 1,3-dipolar cycloadditions, Knoevenagel-initiated MCRs, isocyanide-based MCRs, among others, are some of the most popular. In this work, we will also provide some insights on the main catalytic systems used to make these compounds.

Several advantages can be gained from applying isatins in MCRs. This methodology constitutes an efficient, fast and sustainable strategy to construct new libraries of relevant chemical frameworks, when compared to step-by-step approaches. The main challenges of this methodology in this particular system that will be taken on in the coming years, include: exploring the reactivity at positions in the isatin core other than position 3 and understanding the mechanism of these complex processes, which currently are not very well understood.

In this work, we aim to review the latest trends in MCRs involving isatin. To achieve such a goal, we verified that there is no systematic review on this topic since the work of Liu *et al.*, in 2013,^[4] and therefore we decided to focus our attention on publications made in the timeframe 2013–2019 (with an exception for spirooxindole derivatives, as will be

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explained in section 2 of this work). Throughout this review, schematic representations of the approaches described are

given, and in selected examples, mechanistic representations are also provided, due to their novelty. Please note that relative



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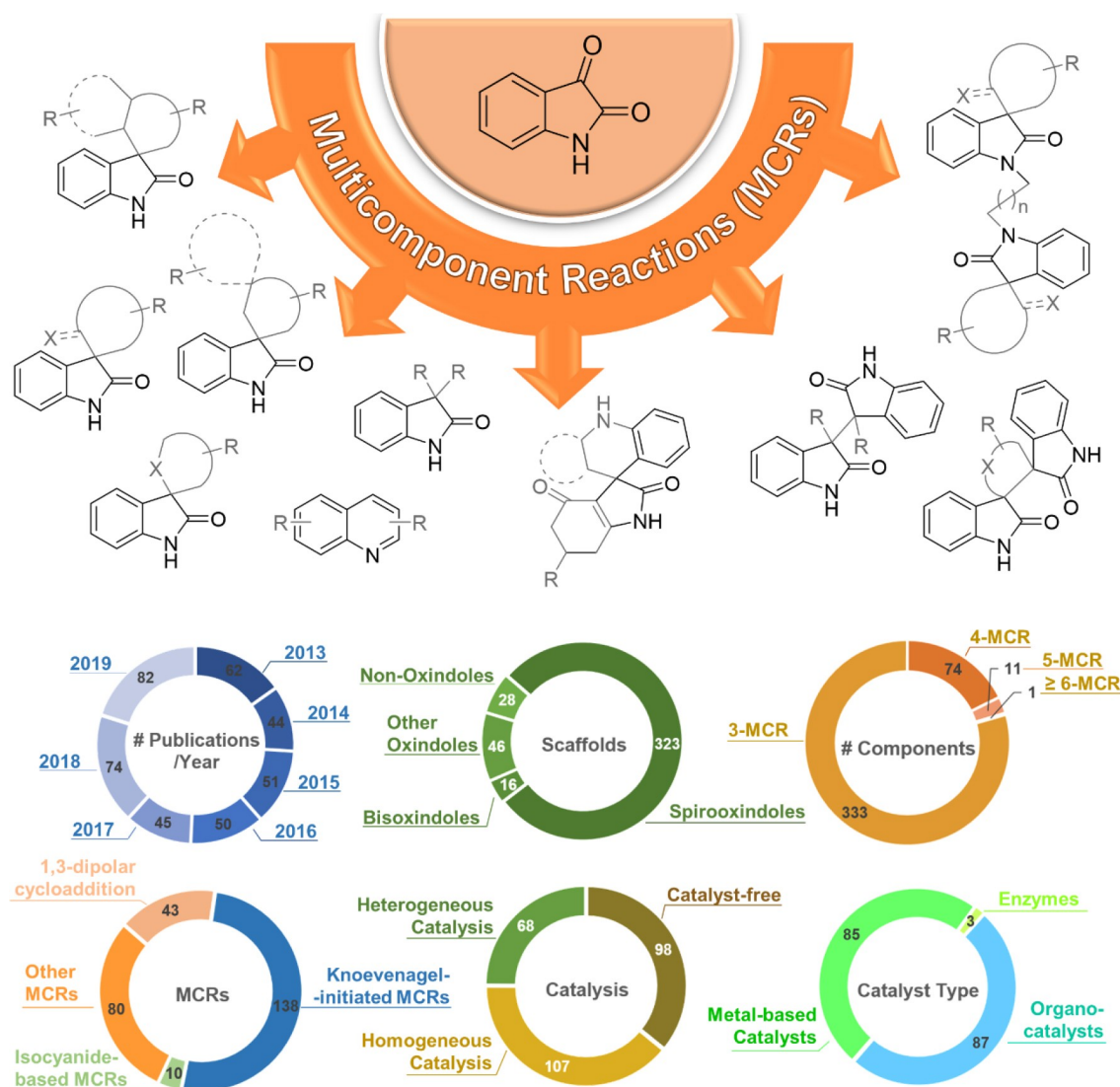


Figure 1. MCRs and isatin as key-strategy for structural diversity and main findings of this field in recent years – number of publications per year, scaffold diversity and number of components (in the timeframe 2013–2019) and reaction type, catalysis type and catalysts used in the publications addressed in this work.

and absolute stereochemistry were only assigned when described in the original reports.

2. Spirooxindole Derivatives

As shown in Figure 1, spirooxindoles play a major role in the synthesis of isatin derivatives through MCRs. This trend is highly motivated by the plethora of biological activity displayed by spiro heterocyclic compounds,^[6a,b,8] and by spirooxindole derivatives in particular, which demonstrated to exhibit anticancer, anti-inflammatory, and antimicrobial activities, among others.^[9] This made it an important topic for

several authors, as recently reviewed in the literature,^[10] and therefore for this class of compounds, we decided to focus our attention in the latest developments, covering the timeframe not reviewed in the literature so far (2016–2019).

2.1. Five-Membered Spirocyclic Systems

2.1.1. MCRs with 3 Components

2.1.1.1. 1,3-Dipolar Cycloaddition Reaction

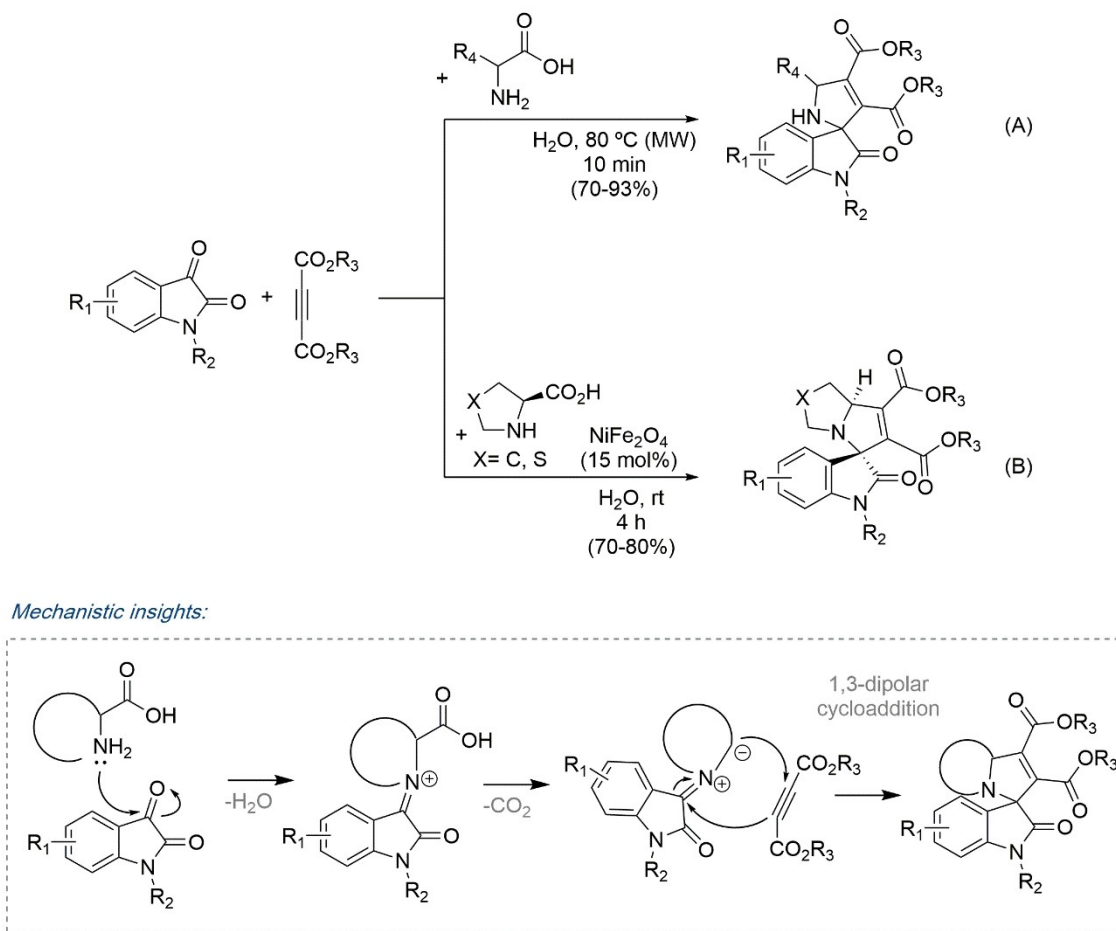
The 1,3-dipolar cycloaddition reaction is one of the most commonly used ring-forming reactions, where a 1,3-dipole derivative and a dipolarophile bind together to form a 5-

membered ring. This important transformation was exhaustively applied in the synthesis of complex molecules, like spirooxindoles, as shown in the following examples.

Mali *et al.* reported an interesting 3-MCR between isatin derivatives, but-2-ynedioates and amino acids using microwave irradiation in the synthesis of novel tetrahydrospiro[indoline-3,3'-pyrrolizine]-1,2-dicarboxylate derivatives. This catalyst-free and base-free 1,3-dipolar cycloaddition reaction exhibits several advantages like: use of water as reaction solvent, broad substrate scope (28 examples) and reduced reaction times (Scheme 1A).^[11] Soon after, Basu *et al.* reported a similar 3-MCR using *L*-proline and the corresponding *L*-4-thiazolidine-carboxylic acid along with the recyclable NiFe₂O₄ nanocatalyst, which facilitates the reaction through coordination with the carbonyl group of isatin assisting the decarboxylative step, and water as solvent. An interesting heterogeneous catalytic synthesis of spiro[indoline-3,3'-pyrrolizine] and spiro[indoline-3,5'-pyrrolo[1,2-*c*]thiazole] derivatives (20 examples) was carried out under mild reaction conditions (Scheme 1B) with

remarkable recyclability of the also synthesized NiFe₂O₄ nanopowder catalyst (up to six times without any significant loss of activity).^[12] Both groups strongly believe that the plausible mechanism for this transformation begins with the decarboxylative condensation reaction of isatin with the amino acid, furnishing the azomethine ylide intermediate by eliminating CO₂. This is followed by rapid 1,3-dipolar cycloaddition between the azomethine ylide and but-2-ynedioate to generate the desired spirooxindole derivatives (Scheme 1).

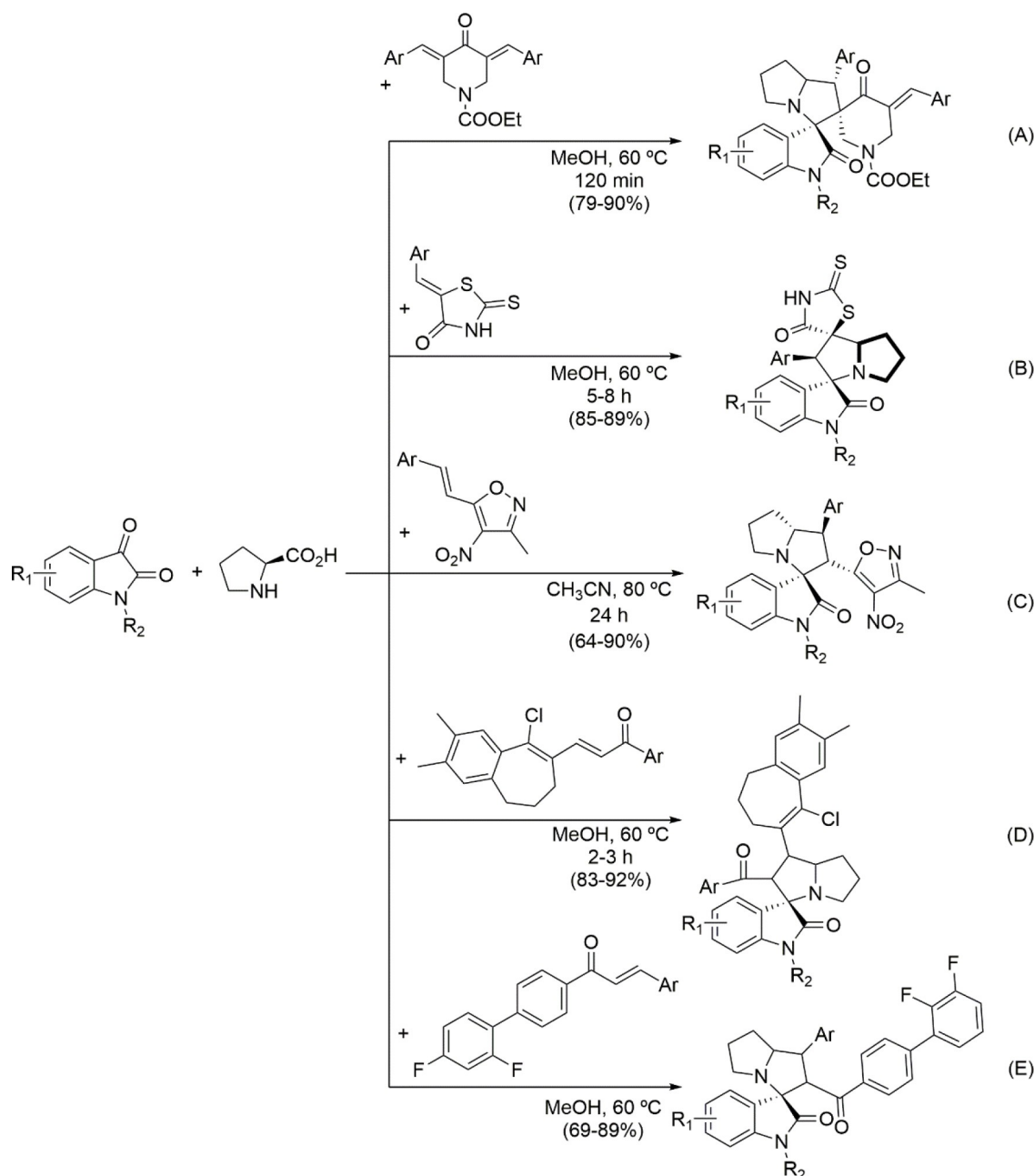
Combining several transformations in a one-pot fashion has proven its value. Proof of that is the elegant synthesis of spirooxindole core using isatin and its derivatives and amino acids as valuable substrates (generating the azomethine ylide *in situ*) and an alkene (as dipolarophile), in a 1,3-cycloaddition approach. Using a catalyst-free methodology, Hassaneen *et al.* reported an interesting 1,3-dipolar cycloaddition reaction between isatin derivatives, *L*-proline and ethyl 3,5-bis[arylmethylidene]-4-oxopiperidine-*N*-carboxylate, affording the synthesis of spirooxindole-spiropiperidinone-pyrrolizine



Scheme 1. 3-MCRs approaches using isatin derivatives, but-2-ynedioates and amino acids.

derivatives (10 examples). Short reaction times combined with simple and economically favored work-up procedure (the reaction mixture was poured onto water, and the precipitated product was collected) were reported in the synthesis of these spiro-derivatives (Scheme 2A).^[13] Barakat *et al.* reported the synthesis of new spirooxindole/pyrrolidine/thioxothiazolidin-4-one derivatives (2 examples), in good yields, using 5-arylidine-2-thioxothiazolidin-4-one as the dipolarophile

(Scheme 2B).^[14] Other similar catalyst-free approaches, using 3-methyl-4-nitro-5-alkenyl-isoxazole derivatives as dipolarophiles was reported by Liu *et al.* (Scheme 2C). The protocol showed a wide substrate scope in the synthesis of isoxazole-fused spiropyrrolidine oxindoles (also sarcosine and thioproline were efficiently used as amino acid sources) and efficacy (a gram-scale synthesis was successfully achieved under the optimized conditions, with 86% yield).^[15] Due to the bio-



Scheme 2. 3-MCRs using isatin derivatives, *L*-proline and several dipolarophiles.

logical importance of benzosuberone derivatives as antitumor agents, the group of Kasaboina *et al.* reported the synthesis of novel analogues of hexahydrospiro[indoline-pyrrolizin]-one hybrids (18 examples), in good yields, using a catalyst-free 1,3-dipolar cycloaddition approach.^[16] As dipolarophile, (*E*)-3-(9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo[7]annulen-8-yl)-1-arylprop-2-en-1-one derivatives were used, together with isatin derivatives and *L*-proline in a one-pot mode (Scheme 2D).^[16] A similar procedure using other chalcone type derivatives as dipolarophiles was reported by Fathimunnisa and co-workers. The 3-MCR between isatin, *L*-proline and (*2E*)-1-[4-(2,4-difluorophenyl)phenyl]3-arylprop-2-en-1-ones gave access to a novel family of 2'-[(2'',4''-difluorobiphenyl-4-yl)carbonyl]-1'-aryl-1',2',5',6',7',7a'-hexahydrospiro[indole-3,3'-pyrrolizin]-2(1*H*)-ones (8 examples) in good yields (Scheme 2E).^[17]

Cheap and commercially available benzylamines were used successfully in 1,3-dipolar cycloaddition of azomethine ylides, together with isatin derivatives and different dipolarophiles. Mani *et al.* reported the synthesis of spiro[indolin-3,2'-pyrrolidin]-2-one derivatives using chalcone derivatives bearing quinoline units. Six new spiro-derivatives were isolated in moderate to good yields in a facile regio- and stereoselective 3-MCR (Scheme 3).^[18] The plausible mechanism probably involves formation, *in situ*, of the azomethine ylide intermediate, with one potential nucleophilic carbon, from the condensation reaction of isatin with benzylamine derivatives, followed by a rapid 1,3-dipolar cycloaddition reaction with the alkene dipolarophile to achieve the desired spirooxindole derivatives as single regioisomers.

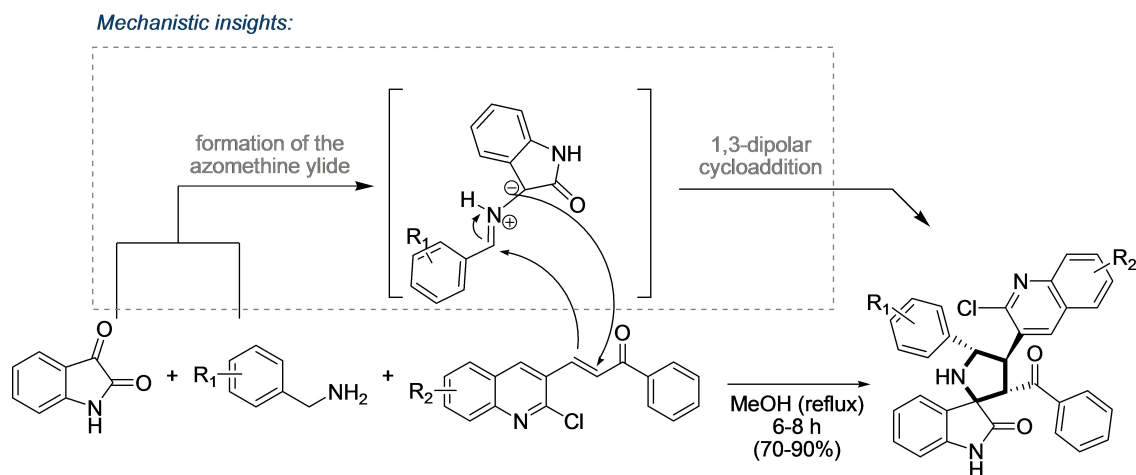
Kumar and co-workers developed a very interesting piece of work for the synthesis of highly functionalized spirooxindole-pyrrolidine heterocyclic hybrids using the one-pot 3-MCR 1,3-dipolar cyclization approach with isatin derivatives, amino acids and different dipolarophiles. Using bis-arylidene-

piperidin-4-one derivatives and also β -nitrostyrene derivatives as dipolarophiles, the reaction showed good substrate scope (Scheme 4A). The remarkable use of the ionic liquid 1-butyl-3-methylimidazolium bromide ([Bmim]Br) as solvent increases the economic and eco-friendly value of this methodology.^[19] In a recent example, another 1-butyl-3-methylimidazolium-based ionic liquid ([Bmim]BF₄) was also successfully applied in the synthesis of 1,2,4-triazol-1-yl-pyrazole-based spirooxindolopyrrolizidines (20 examples), using ultrasonication as activation technique (Scheme 4B). This methodology proved to be efficient, as short reaction times were required and good yields were obtained. Furthermore, the ionic liquid could be reused without significant loss of activity.^[20]

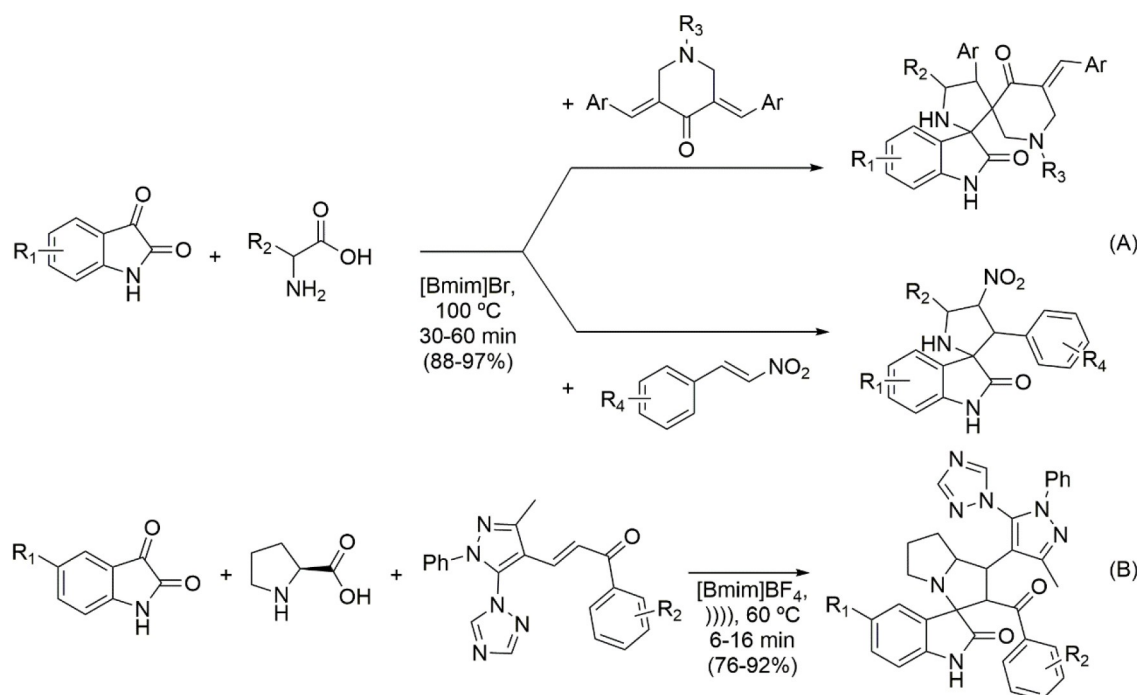
The decarboxylative condensation of isatin and amino acids leading to the generation of azomethine ylides, which could further react with a dipolarophile was explored by Sapnakumari *et al.*, this time using chalcones as dipolarophile (Scheme 5). This catalyst-free approach allowed the preparation of a small library (8 examples) in moderate yields.^[21]

Boudriga *et al.* investigated the 1,3-dipolar cycloaddition reaction using isatin derivatives and isoquinoline (forming the tetrahydroisoquinolinium-*N*-ylide *in situ*) and (*E*)-3-arylidene-1-phenyl-pyrrolidine-2,5-diones as dipolarophiles. After establishing the optimal conditions and screening many substrates, it was found that the regioselectivity (>60:40 *rr*) was quite poor (Scheme 6). However, the use of halogen substituents, like Cl or Br, in the phenyl ring of isatin were beneficial for increasing regioselectivity (>90:10 *rr*) in the synthesis of these new dispiropyrrolo[2,1-*a*]isoquinoline-fused pyrrolidine-2,5-dione derivatives bearing two adjacent spiro-carbons.^[22]

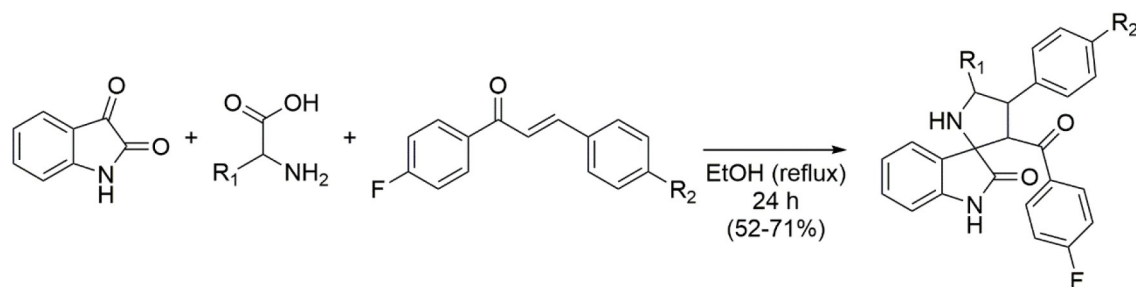
The scope of the isatin-based 1,3-dipolar cycloaddition was further explored by Nayak *et al.*, using substituted nitrochromenes as dipolarophile and proline or pipercolic acid as secondary amino acids (Scheme 7A). This regioselective



Scheme 3. Use of benzylamines in 3-MCRs for the synthesis of spiro[indolin-3,2'-pyrrolidin]-2-one derivatives.



Scheme 4. The one-pot 3-MCR in the synthesis of a family of new spirooxindole-pyrrolidine hybrids using ionic liquids as reaction media.



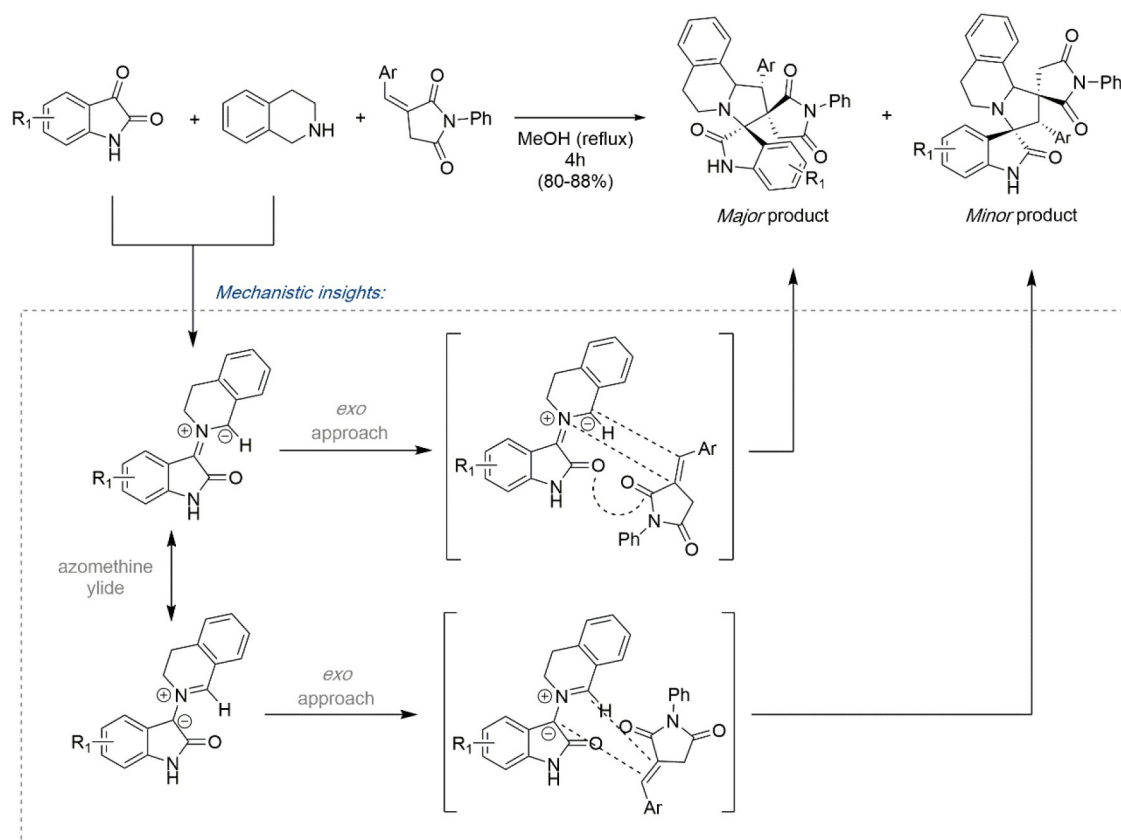
Scheme 5. The 1,3-dipolar cycloaddition using chalcones as dipolarophile.

process led to the formation of spirooxindole-pyrrolidine/piperidine fused nitrochromane derivatives (giving exclusively one isomer) in overall good yields (14 examples).^[23] Similarly, Narayanarao *et al.* reported the successful synthesis of a library of spirooxindoles (12 examples) containing the aza-indole moiety, using ethynyl azaindoles as dipolarophiles and sarcosine (Scheme 7B), proline or thioproline (Scheme 7C) as secondary amino acids.^[24]

The synthesis of new thiazolo-pyrrolidine-spirooxindole derivatives was conducted in an attempt to obtain new relevant scaffolds. Islam *et al.* reported the synthesis of a library of functionalized spirooxindole linked with 3-acetyl indole scaffold (14 examples). Chalcone derived from 3-acetyl indole was the dipolarophile used in this protocol, together with isatin and thioproline (Scheme 8A), achieving the desired thiazolo-

pyrrolidine-spirooxindole tethered to 3-acetyl indole derivatives in good yields.^[25]

Dandia *et al.* reported the use of the guanidine-based ionic liquid 1,1,3,3-tetramethylguanidine acetate ([TMG][Ac]) as a suitable and efficient solvent for the 3-MCR of isatin derivatives, thioproline and naphthoquinone followed by the spontaneous dehydrogenation for the synthesis of thiazolo-pyrrolidine-spirooxindole derivatives. This strategy allows the reaction to proceed under mild conditions, with easy work-up (no chromatographic purification) and short reaction times (Scheme 8B). Good yields of the desired cycloadducts were obtained and the [TMG][Ac] ionic liquid could be used at least four times without considerable loss of activity.^[26] The authors suspected that the azomethine ylide formed by decarboxylative condensation, undergoes 1,3-dipolar cyclo-



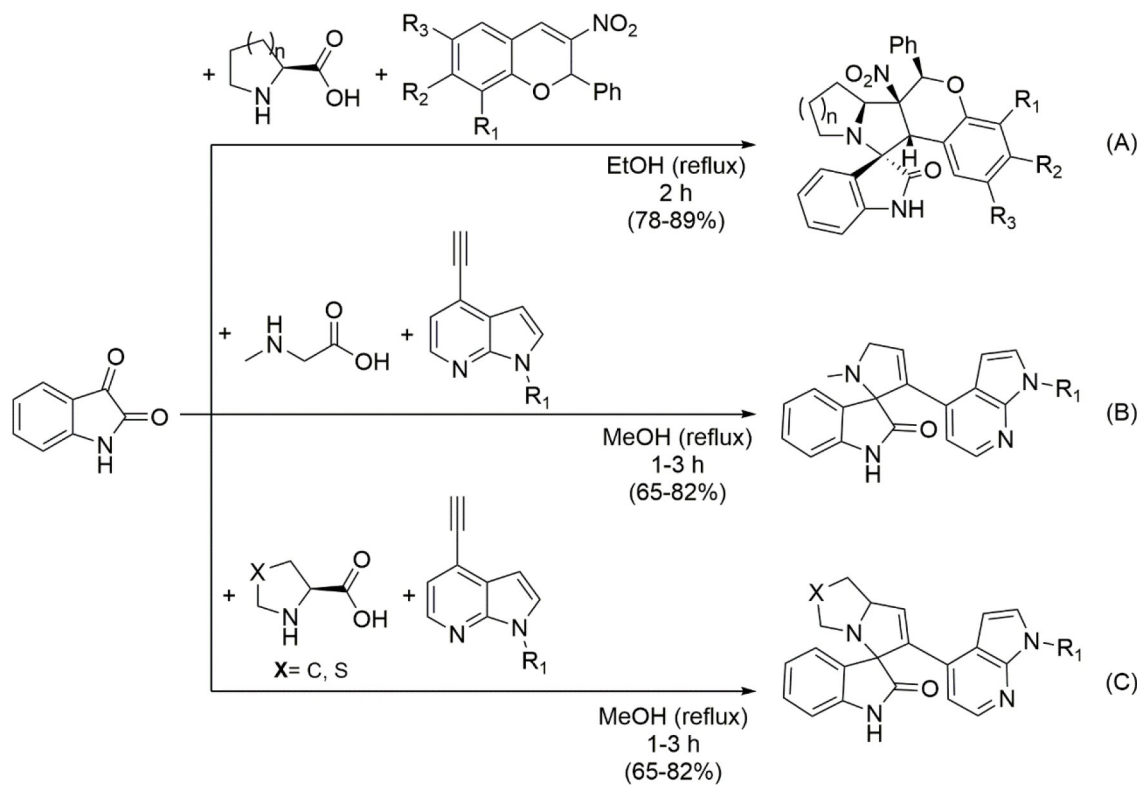
Scheme 6. Novel dispiropyrrolo[2,1-*a*]isoquinoline derivatives *via* 3-MCR.

addition reaction with the naphthoquinone affording the cycloadduct intermediate which is tautomerized to the corresponding hydronaphthoquinone derivative resulting in the desired product due to rapid oxidation under atmospheric air conditions (see Scheme 8B, mechanistic insight).

Lotfy *et al.* reported the use of 2,6-bis[(*E*)-arylmethylidene]-cyclohexanones as dipolarophiles in a similar reaction approach, giving thiazolo-pyrrolidine-spirooxindole derivatives. A library of 14 new molecules was successfully obtained in good to excellent yields, in short reaction times (Scheme 8C).^[27]

Sarcosine together with isatin forms other powerful azomethine ylide intermediate to access spiropyrrolidine oxindole derivatives in a 1,3-dipolar cycloaddition approach. Several research groups explored the use of these intermediates with different dipolarophiles to access novel hybrid architectures with promising biological activities. Liu *et al.* reported an efficient synthesis of a library of novel turmerone motif-fused spiropyrrolidine oxindole derivatives (25 examples) in moderate to good yields and good diastereoselectivity (up to >20:1 *dr*). Aryl substituted dienone derivatives were successfully applied as dipolarophiles in this 1,3-dipolar cycloaddition 3-

MCR (Scheme 9A). Higher yields were obtained with isatin derivatives bearing electron-withdrawing substituents on the aromatic ring and the same occurs with the substituents in the dienone counterpart, increasing the electron density of the aromatic ring thus accelerating the reaction. A gram-scale synthesis was also effectively accomplished (81% yield) using this methodology.^[28] Attia *et al.* reported a similar approach, using acryloyl acid or chalcone derivatives as dipolarophiles. Despite low to moderate yields and poor substrate scope (Scheme 9B), the five spiropyrrolidine derivatives obtained were used to prepare azacoumarin additives and evaluated as dye-sensitive solar cells. Also, the compounds show interesting properties as antioxidants for lubricating oils.^[29] Hussein *et al.* used (*E*)-3-aryl-1-(pyren-1-yl)prop-2-en-1-ones as dipolarophiles, with a bulky pyrene aromatic system, to access highly functionalized 1'-methyl-4'-aryl-3'-(pyrene-1-carbonyl)-spiro[indoline-3,2'-pyrrolidin]-2-ones in good yields (Scheme 9C). The authors also tested benzylamine in this 1,3-dipolar cycloaddition 3-MCR successfully. The photophysical properties of the synthesized spirooxindole derivatives were studied, particularly the absorption and emission spectral data. Furthermore, the substituents affect significantly the



Scheme 7. 3-MCR *via* 1,3-dipolar cycloaddition from isatin, secondary amino acids and nitrochromenes or ethynyl azaindoles.

fluorescence emission of the derivatives.^[30] Recently, Al-Majid *et al.* reported the synthesis of a spiroindolone analogue, using the 1,3-dipolar cycloaddition approach with isatin and sarcosine as the azomethine ylide and a particular chalcone derivative with an indole unit (Scheme 9D).^[31]

The 1,3-dipolar cycloaddition showed to be suitable even when using very complex dipolarophiles such as (*E*)-3-(2-cyclopropyl-5-(4-fluorophenyl)-quinolin-3-yl)-1-phenylprop-2-en-1-one derivatives, using as secondary amino acids sarcosine (8 examples, Scheme 10A) or *L*-proline (8 examples, Scheme 10B).^[32]

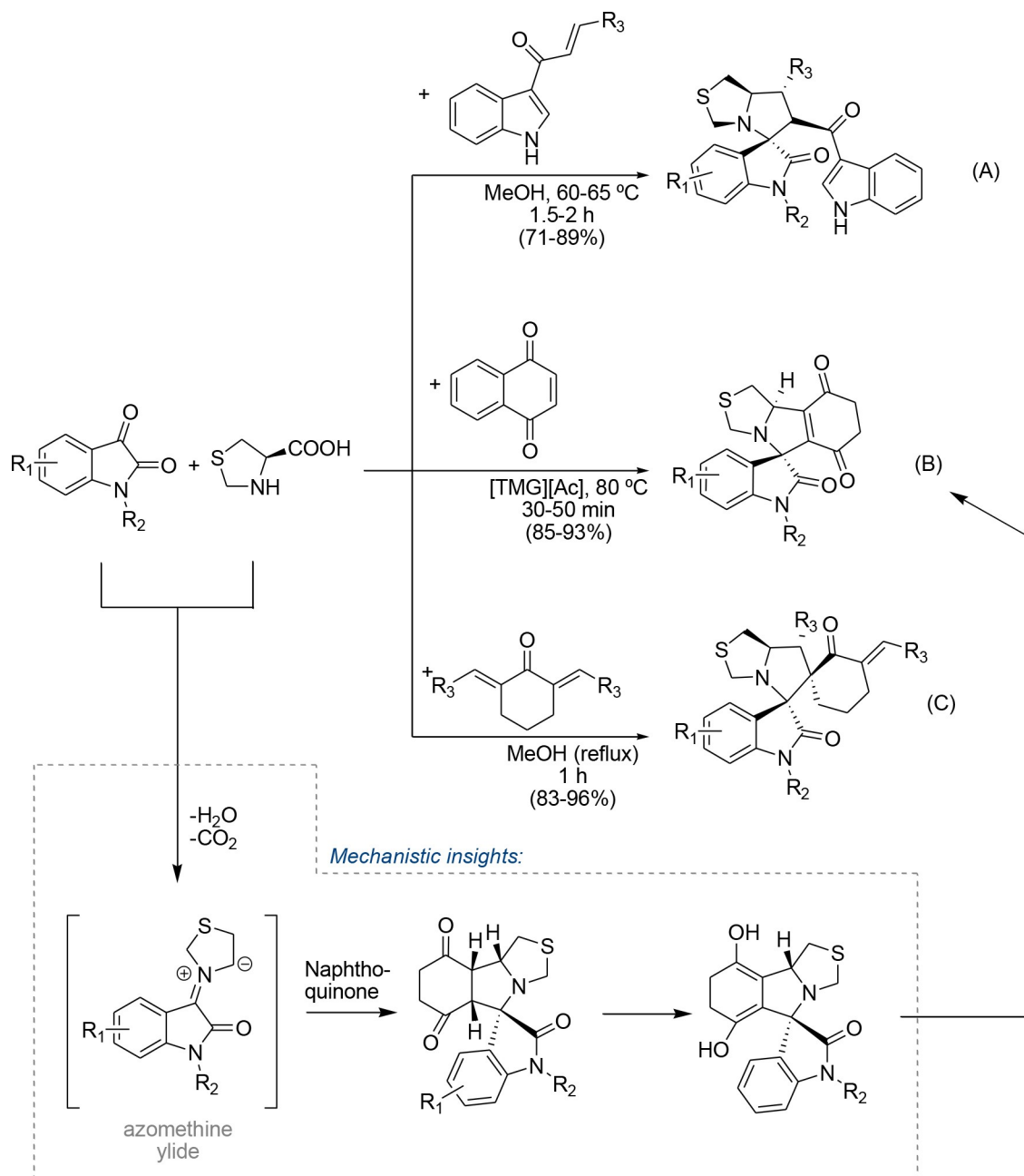
Angyal *et al.* decided to explore this 3-MCR using an azirine-based 1,3-dipolar cycloaddition, combining it with azomethine ylides generated from isatin derivatives and amines or α -amino acids. A new library of aziridine-fused spiro [imidazolidine-4,3'-oxindole] derivatives (33 examples) was successfully developed using a regio- and diastereoselective 1,3-dipolar cycloaddition of 2*H*-azirines with azomethine ylides (Scheme 11) with yields up to 81% under mild conditions. The broad scope of the protocol tolerates the use of a wide range of substrates, particularly aliphatic and aromatic amino acids and electron-rich and electron-deficient isatins.^[33]

The design of molecular systems with several degrees of complexity or, in other words, maximizing the incorporation

of useful and potentially bioactive units, while optimizing costs and processes efficiency, is a major trend in modern organic chemistry. As shown before, using complex dipolarophiles in the 1,3-dipolar cycloaddition of 3-MCRs enables easy and quick access to polynuclear spiro-heterocyclic structures. Izmet'ev *et al.* reported the use of an imidazothiazolotriazine moiety as dipolarophile. A library of new dispiro[imidazo[4,5-*e*]thiazolo[3,2-*b*]-1,2,4-triazine-6,3'-pyrrolidine-2',3''-indoles with five stereocenters was successfully accessed, *via* the 1,3-dipolar cycloaddition strategy. The azomethine ylides derived from isatin derivatives and sarcosine were used (Scheme 12A). Despite long reaction times the overall yields were moderate to good.^[34]

Another interesting class of scaffold with potential bioactivity is the benzosuberone class. Kumar *et al.* accomplished a three component 1,3-dipolar cycloaddition reaction using arylidene benzosuberone as dipolarophile. A family of benzosuberone-tethered spirooxindoles was successfully synthesized (20 examples), showing high regio- and stereoselectivity, good substrate scope and functional group tolerance (with the dipolarophile) (Scheme 12B).^[35]

Chen *et al.* decided to explore privileged heterocyclic-based chromanone derivatives as dipolarophiles with a similar reaction approach. In an attempt to construct chromanone-

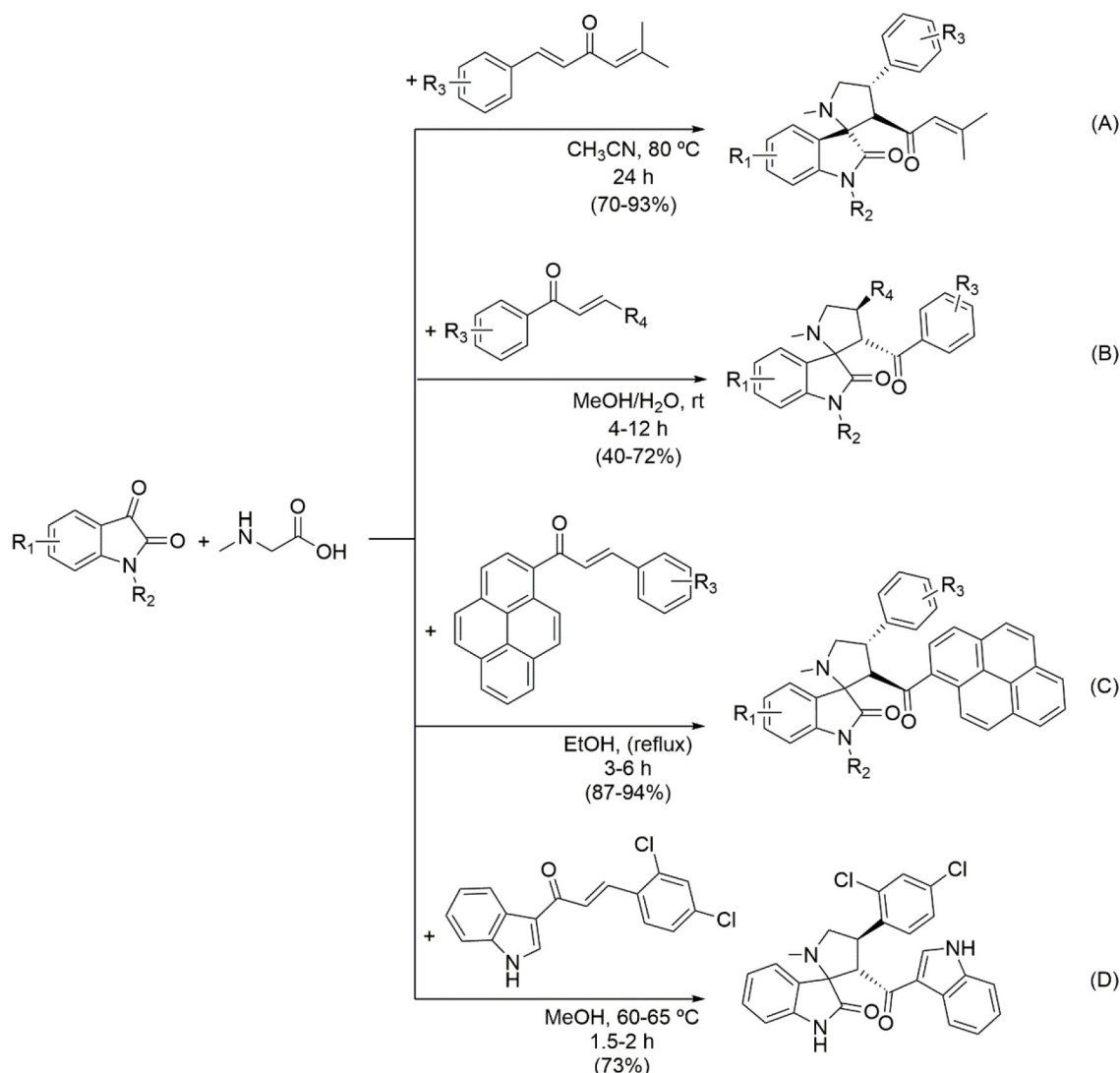


Scheme 8. Thioproline and isatin derivatives as efficient azomethine ylides in the 1,3-dipolar cycloaddition 3-MCR.

fused pyrrolidiny spirooxindole derivatives, a decarboxylative 1,3-dipolar cycloaddition reaction between azomethine ylides - thermally generated *in situ* from isatin derivatives and sarcosine - and carboxylic acid group - activated chromones was reported (Scheme 12C). The method provided libraries bearing diverse and multiple pharmacophores, with three contiguous stereocenters including a spiro quaternary stereocenter in moderate to good yields and good diastereoselectivity (up to

$> 20:1$ *dr*).^[36] A very similar approach was reported by Yue *et al.*, but with sarcosine being replaced by proline or thioproline. The library of spirooxindole derivatives (30 examples) was achieved in overall good yields (65-90%).^[37]

By using a different family of dipolarophiles, (*Z*)-2-(arylmethylidene)-1-benzothiophen-3(2*H*)-ones, Zhou *et al.* prepared a library of dispiro[1-benzothiophene-2,3'-pyrrolidine-2',3''-indoline]-2'',3-dione derivatives (6 examples) in



Scheme 9. Azomethine ylides derived from sarcosine and isatin derivatives in the 1,3-dipolar cycloaddition 3-MCR.

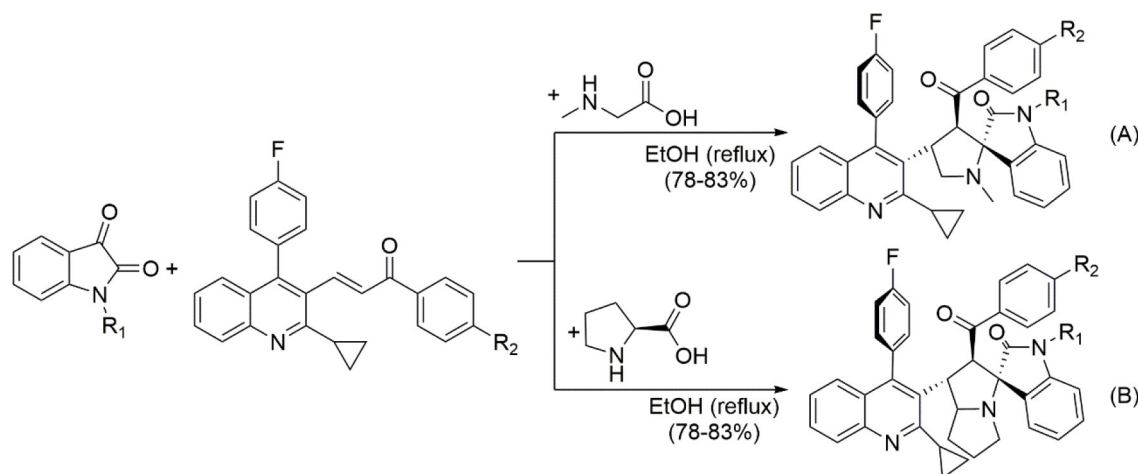
moderate yields (48-60% for the major product) (Scheme 12D).^[38]

A very similar approach was reported by Zhang *et al.*, but replacing the dipolarophile by auronones and expanding the scope to three different secondary amino acids – sarcosine (Scheme 13A), *D*-proline and thioproline (Scheme 13B). The library of dispiroheterocycles (30 examples) was achieved in moderate to good yields.^[39]

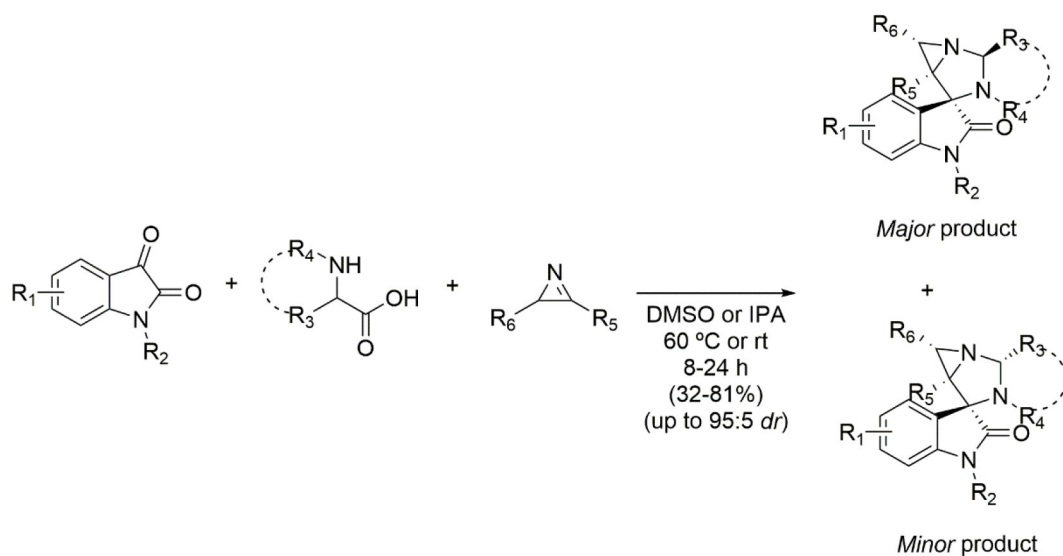
Spirooxindole-pyrrolidine derivatives (16 examples) were obtained *via* 1,3-dipolar cycloaddition by Vidya *et al.*, employing heterocyclic ylidenes and sarcosine (Scheme 14A) or α -amino acids, namely *L*-proline, thioproline (Scheme 14B) and phenyl alanine (Scheme 14C) as starting materials.^[40]

Dandia *et al.* reported a microwave assisted one-pot approach for the synthesis of spiropyrrolidine/thiapyrrolizidine

oxindole derivatives *via* a three component 1,3-dipolar cycloaddition reaction of isatin derivatives, sarcosine or thioproline and the Knoevenagel adduct 2-cyano-3-phenyl-acrylic acid ethyl ester or 2-benzylidene-malonitrile. The method is simple, using 2,2,2-trifluoroethanol as a reusable green solvent, and shows good functional group tolerance and broad scope of the substrates tested (Scheme 15).^[41] Regarding the mechanism, the authors considered that 2,2,2-trifluoroethanol also plays an important role as an acid catalyst, by forming a hydrogen bond with the 3-carbonyl group of isatin and thus increasing its electrophilicity, with rapid formation of the azomethine ylide with sarcosine. Subsequent cycloaddition reaction between the Knoevenagel adduct and the dipolarophile promotes the regioselective formation of the pyrrolidine heterocyclic ring (Scheme 15).



Scheme 10. 3-MCR 1,3-dipolar cycloaddition using (*E*)-3-(2-cyclopropyl-5-(4-fluorophenyl)-quinolin-3-yl)-1-phenylprop-2-en-1-ones as dipolarophiles.



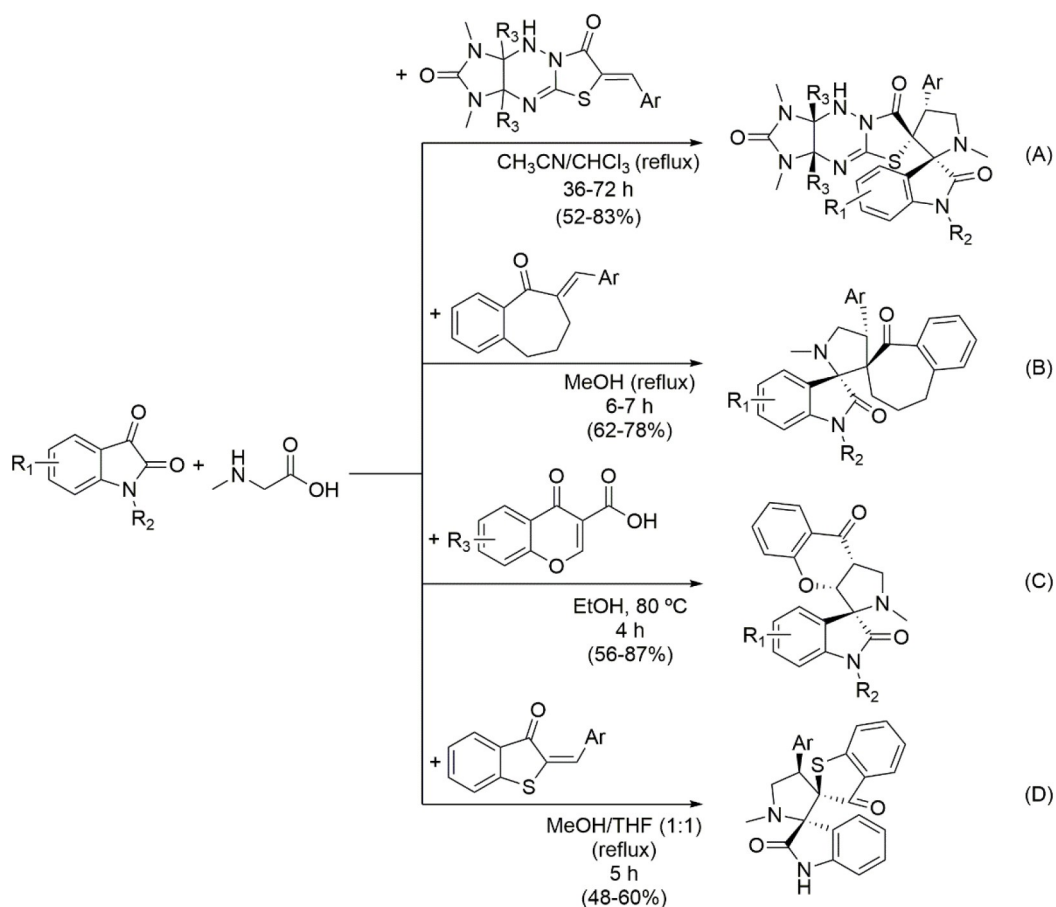
Scheme 11. Stereoselective synthesis of 1,3-diazaspiro[bicyclo[3.1.0]hexane]oxindoles by a 1,3-dipolar cycloaddition 3-MCR approach.

2.1.1.2. Knoevenagel-initiated MCRs

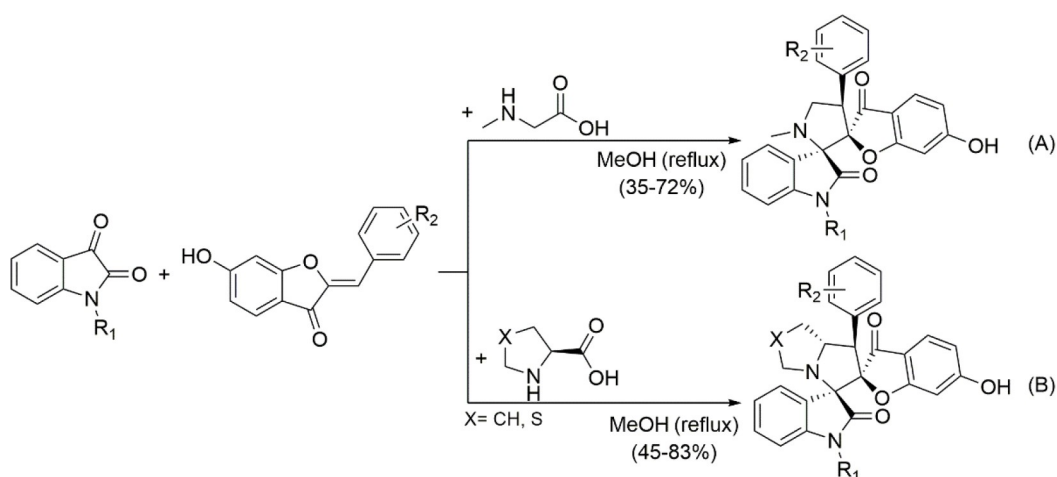
The Knoevenagel condensation is one of the most noteworthy C–C bond forming methods in organic chemistry. Combination of this transformation with other reactions in a domino manner in MCRs is also a powerful strategy for obtaining excellent structural diversity.

Very recently, Jadhav *et al.* reported the efficient synthesis of spirotriazolo[1,2-*a*]indazole-tetraone derivatives in a one-pot 3-component condensation reaction using isatin derivatives, phthalhydrazide or 4-phenylurazole and dimedone. The interest in more eco-friendly methodologies led the authors to test several acid catalysts, where the silica supported tungstic acid (STA) proved to be the best one, at 10 mol% loading.

Under solvent-free reaction conditions, 6 examples of spirotriazolo[1,2-*a*]indazole-tetraone derivatives were obtained in very good yields and short reaction times (Scheme 16). Mechanistically, the reaction occurs *via* Knoevenagel condensation between isatin and dimedone, to furnish intermediate A which act as a Michael acceptor. Following Michael addition of intermediate B with phthalhydrazide or 4-phenylurazole, intermediate B is generated, which further undergoes intramolecular cyclization with respective elimination of water, to afford the desired spirooxindole derivatives. Easy recovery of the heterogeneous solid catalyst and chromatography-free work-up contribute to the success of this methodology.^[42]



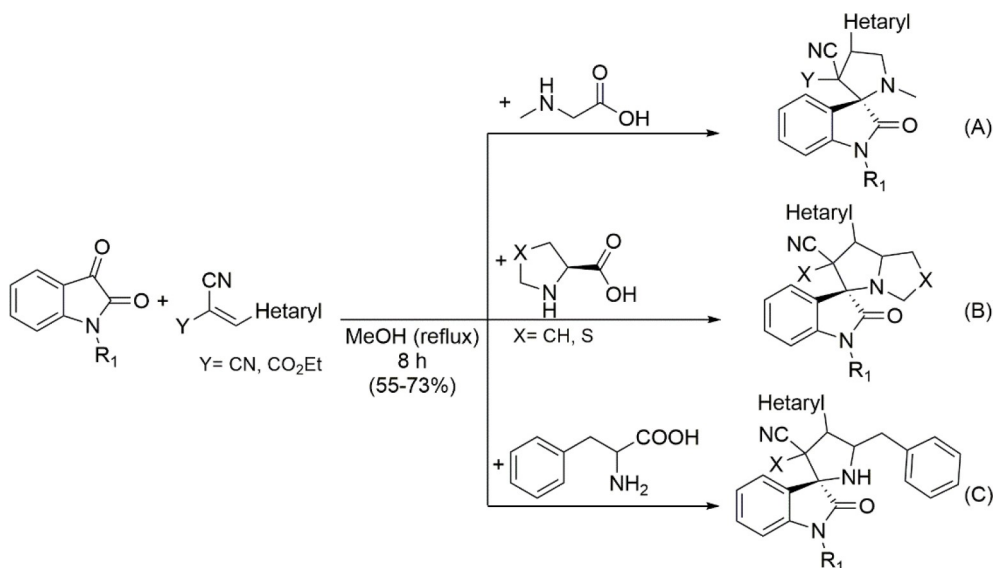
Scheme 12. 1,3-Dipolar cycloaddition 3-MCR approach to privileged pharmacophores.



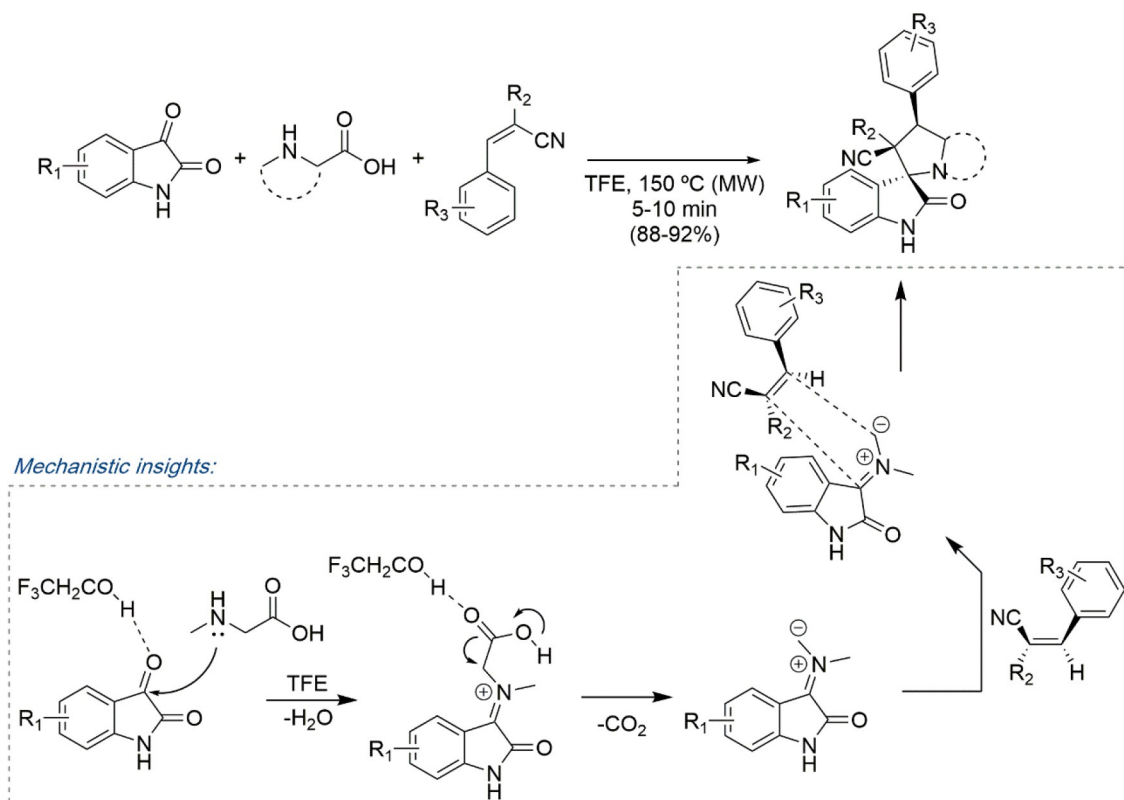
Scheme 13. Aurones as dipolarophiles in the 1,3-dipolar cycloaddition 3-MCR involving azomethines derived from isatins.

Adib *et al.* reported the synthesis of 5'-amino-2,2'-dioxo-spiro[indoline-3,3'-pyrrole]-4'-carbonitrile derivatives using an

interesting 3-MCR approach. The Knoevenagel condensation reaction between isatin derivatives and malononitrile gave the



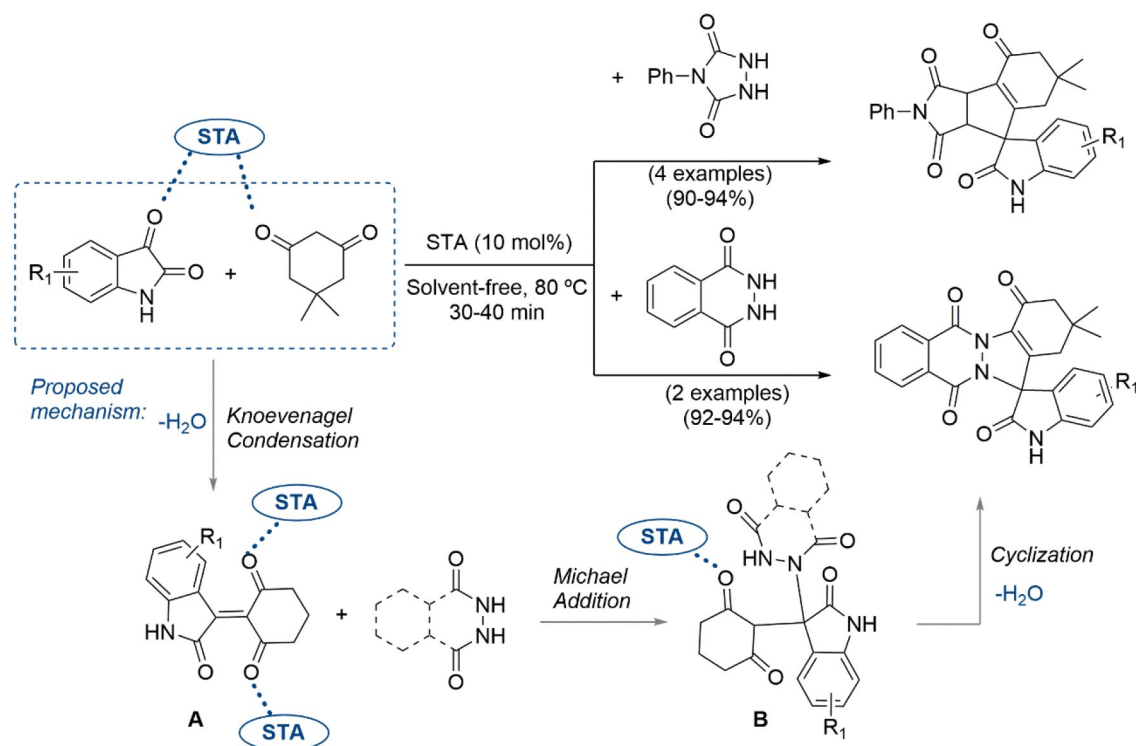
Scheme 14. Vidya *et al.* 1,3-dipolar cycloaddition approach for the synthesis of spirooxindole-pyrrolidine derivatives.



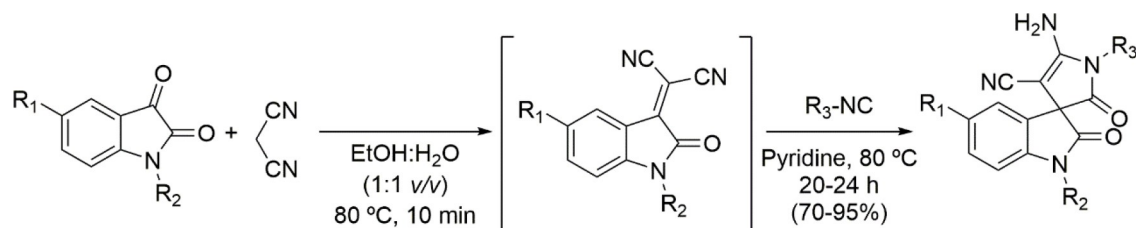
Scheme 15. Microwave-assisted one-pot route for the synthesis of spiropyrrolidine/thiapyrrolizidine oxindole derivatives.

corresponding cyclic aryl-methylenemalononitrile intermediate within 10 minutes in aqueous ethanol at 80 °C

(Scheme 17). Treatment with isocyanides and pyridine afforded the 2,2'-dioxospiro-bis- γ -lactams in good yields.^[43]



Scheme 16. Synthesis of spirotriazolo[1,2-*a*]indazole-tetraone derivatives via 3-MCR using a supported acid catalyst.



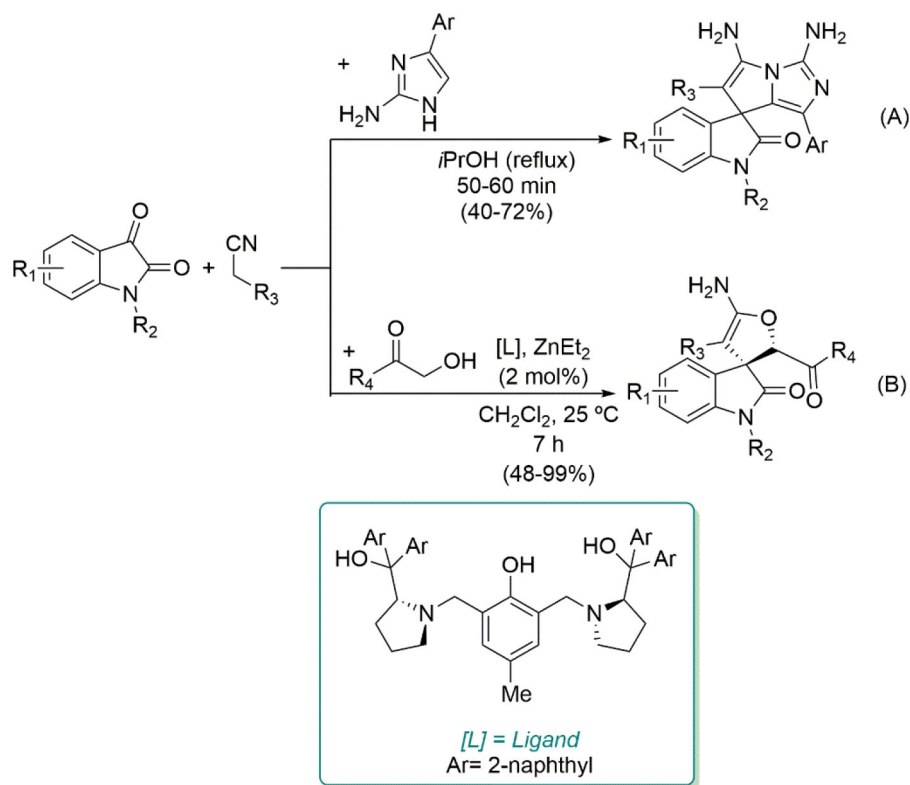
Scheme 17. 3-MCR in the synthesis of 5'-amino-2,2'-dioxospiro[indoline-3,3'-pyrrole]-4'-carbonitrile derivatives.

Lipson *et al.* reported the domino 3-MCR of 2-amino-4-arylimidazoles with isatin and methylene active compounds. The corresponding Knoevenagel-Michael adducts containing a free amino group in the imidazole fragment were obtained in moderate to good yields (Scheme 18A). The reduced reactivity of the carbonyl group of isatins and the corresponding stability of their Knoevenagel intermediates led to the formation of only one spiro compound, avoiding undesirable mixtures. However, *N*-substituted isatin derivatives must be used in this chemical transformation, to increase reactivity and in order to prevent undesired side reactions.^[44]

A dinuclear zinc cooperative catalytic asymmetric 3-MCR for the synthesis of new chiral 3,3'-dihydrofuran spirooxindoles was reported by Miao and co-workers. A domino Knoevenagel/Michael/cyclization sequence was the base of this

transformation involving isatin derivatives, malononitrile and α -hydroxyketones (Scheme 18B). Excellent yields (up to 99%), enantioselectivities (up to 99% *ee*) and diastereoselectivities (up to 99:1 *dr*) were obtained for this transformation, in the presence of low catalyst loading (2 mol%) and mild reaction conditions. The chiral dinuclear Zn catalyst (obtained *in situ* from the reaction between the ligand and ZnEt_2) (Scheme 18B) has a crucial role for achieving high enantioselectivity, determining the stereoselectivity of the key-step Michael addition reaction. Additionally, this procedure proceeds on a gram-scale without any loss in reactivity and stereoselectivity.^[45]

A taurine (2-aminoethanesulfonic acid)-catalyzed Knoevenagel reaction-Michael addition involving isatin, hydantoin and several β -diketones was applied in the synthesis of a wide



Scheme 18. 3-MC domino Knoevenagel/Michael addition sequence in the synthesis of (A) racemic 5'-amino-2,2'-dioxo-spiro[indoline-3,3'-pyrrole]-4'-carbonitriles and (B) chiral 3,3'-dihydrofuran spirooxindoles.

diversity of spirooxindole derivatives (15 examples). This synthetic methodology has proven to be eco-friendly, as it occurs in aqueous media. The products were obtained in high yields with no requirement for chromatographic purification, and taurine could be recycled and reused without significant loss of activity (Scheme 19).^[46]

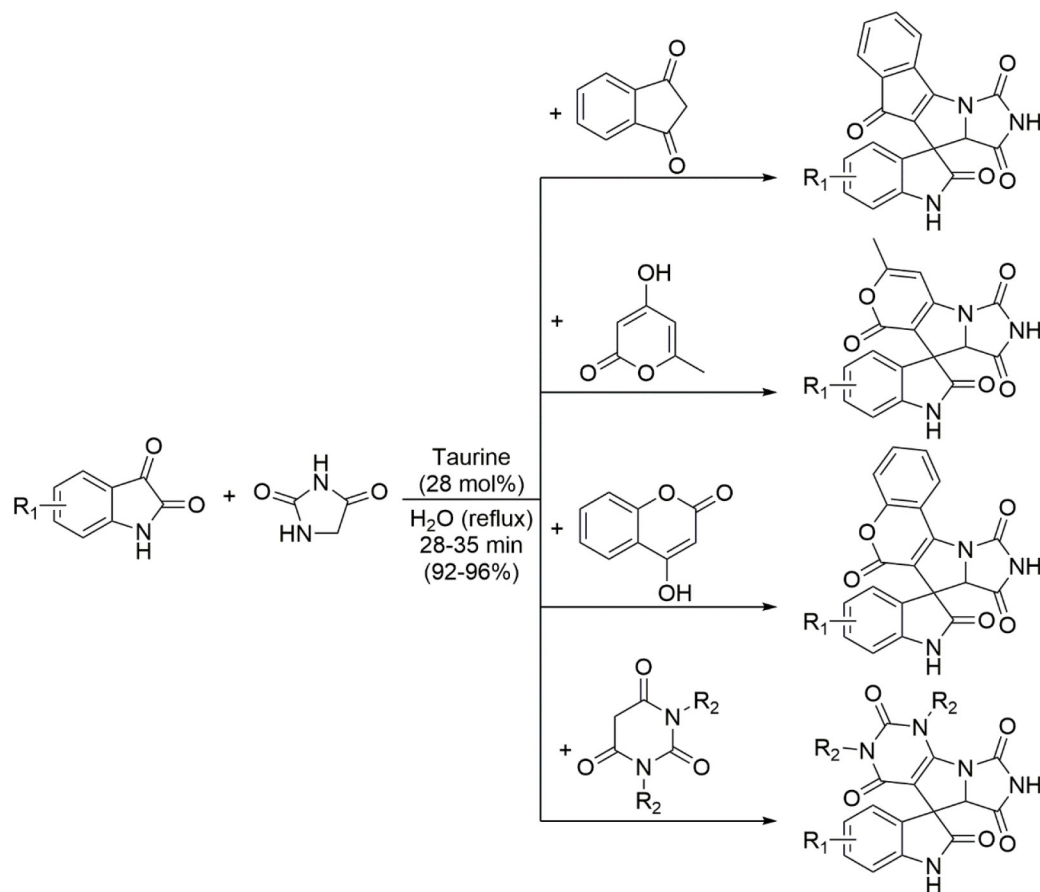
A 3-MCR between *N*-methylisatin, 4-(3,4-dichlorophenyl)-4-oxo-2-butenoic acid and thioglycolic acid allowed the preparation of spirooxindole-tetrahydrothiophene diastereoisomers, with the cycloaddition occurring in a regioselective manner (Scheme 20). The *major* product could be further transformed in a wide diversity of chemical reactions.^[47]

2.1.1.3. Miscellaneous

Recently, a silver-promoted $C_{\alpha}(sp^3)$ -H activation of benzylamines followed by a regioselective [1,3]-rearrangement involving *N*-bulky-substituted-isatins, acylenedicarboxylates, and benzylamines in equimolar conditions, was reported as a new and efficient methodology for the synthesis of spirooxindole-dihydropyrrole derivatives (13 examples) in very good yields (Scheme 21). Despite the required reaction time, this approach

allows the silver catalyst to be recycled, reducing costs and waste production.^[48]

Very recently, Abonia *et al.*, reported the use of aniline derivatives in a 3-MCR, combining it with thioglycolic acid and isatin. Several advantages of this efficient and environmentally benign approach could be underlined, namely the wide substrate scope, absence of catalyst and solvent, and the use of a sand bath instead of an oil bath. Despite the fact that a library of several *C*-2,*N*-3-disubstituted thiazolidine-4-one derivatives was obtained, only one example was reported on the application of isatin as starting material (Scheme 22A).^[49] In a very similar approach, Preetam and Nath explored the reactivity of several substituted and unsubstituted isatins, anilines or benzylamines, and thioglycolic acid under sustainable conditions, using water as solvent at room temperature, in the presence of the Brønsted acid surfactant catalyst *p*-dodecylbenzenesulfonic acid (DBSA). The spiro[indoline-3,2'-thiazolidinones] achieved were obtained in good yields, although the selectivity of the process required a pre-mixture of the isatin with the aromatic amine to form the imine intermediate (18 h), followed by the addition of thioglycolic acid and further agitation (12 h) (Scheme 22B). The catalyst, which protonates the carbonyl group of isatin and therefore



Scheme 19. Taurine-catalyzed Knoevenagel-reaction/Michael addition applied in the synthesis of spirooxindoles.

enables the formation of the imine intermediate, allows the reaction to occur under mild conditions.^[50]

A totally different approach was undertaken by Potuganti *et al.*, aiming at the synthesis of spirooxindole-oxazolidinone derivatives (15 examples). This synthetic transformation is catalyzed by copper(I), in the presence of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), and promotes the catalytic addition, hydroamination and cyclization between *N*-methylisatins, arylacetylenes and isocyanates (Scheme 23). This groundbreaking methodology allows moderate to good product yields and shows wide scope on the aromatic and aliphatic isocyanates used, leading to the formation of C–C, C–N and C–O bonds in one single step.^[51] These researchers proposed a mechanism in which initial activation of the alkyne by the copper(I) iodide catalyst by treatment with DBU allowed the formation of the copper acetylide nucleophile which provide the propargyl alcohol product. The carbamate intermediate was suggested to be formed by the nucleophilic addition of the hydroxyl group to the isocyanate carbon. Intramolecular hydroamination activated by the catalyst, followed by *exo*

cyclization provided the desired oxazolidinone product (Scheme 23).

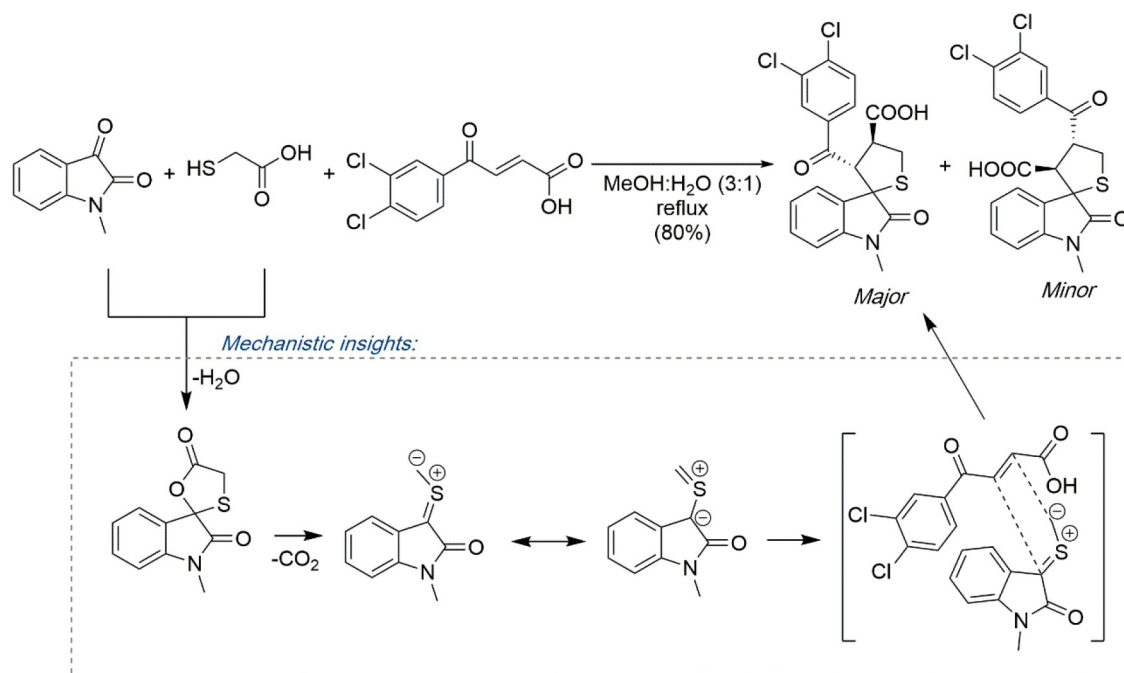
Rainoldi *et al.* explored an Asinger-type reaction between substituted isatins, ammonia and a mercapto carbonyl component. The resulting highly functionalized spirooxindole-3-thiazoline derivatives (24 examples) were obtained in moderate to very good yields (Scheme 24), requiring a pre-mixture of isatin and ammonia, in the presence of MgSO_4 as dehydrating agent, to lead to the formation of the unstable imine intermediate (8 h), followed by the addition of the mercapto carbonyl component (30 minutes). This procedure proved to be effective over a wide scope of substrates.^[52]

2.1.2. MCRs with 4 Components

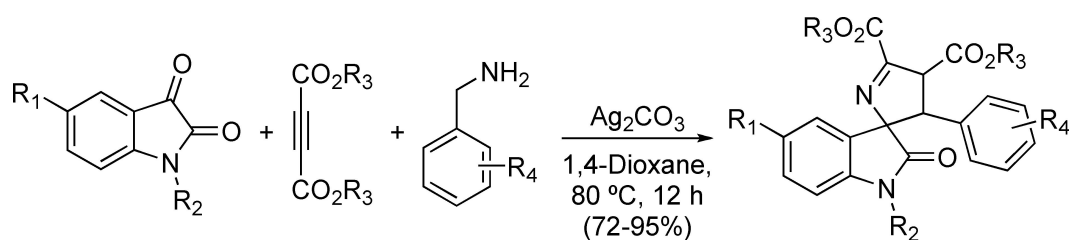
2.1.2.1. 1,3-Dipolar Cycloaddition Reaction

Some interesting work on the synthesis of 5-member-ring-spirooxindoles using 4-MCRs has been described.

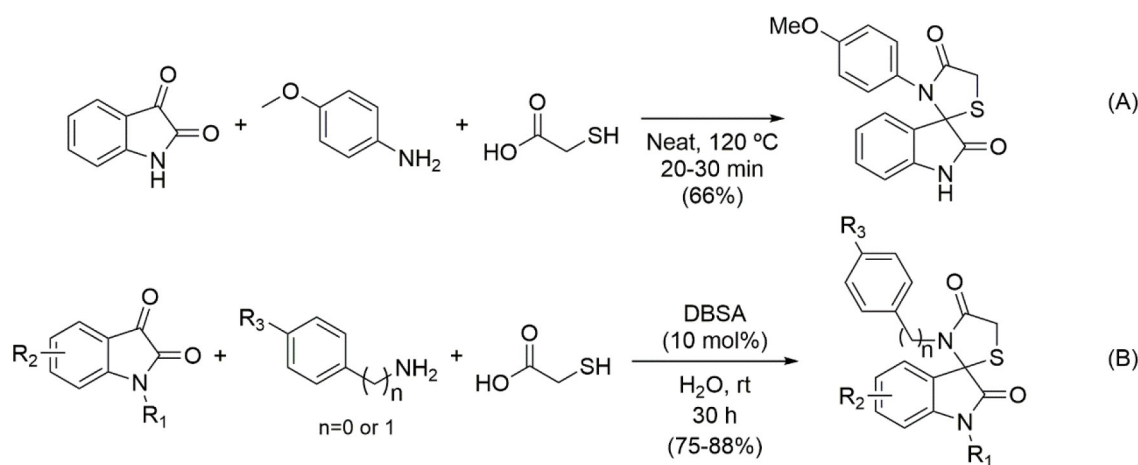
Alizadeh *et al.* reported an easy protocol to access complex polycyclic pyrrolizidine fused spirooxindole derivatives through a one-pot sequential 4-MCR combination of isatin, *L*-proline



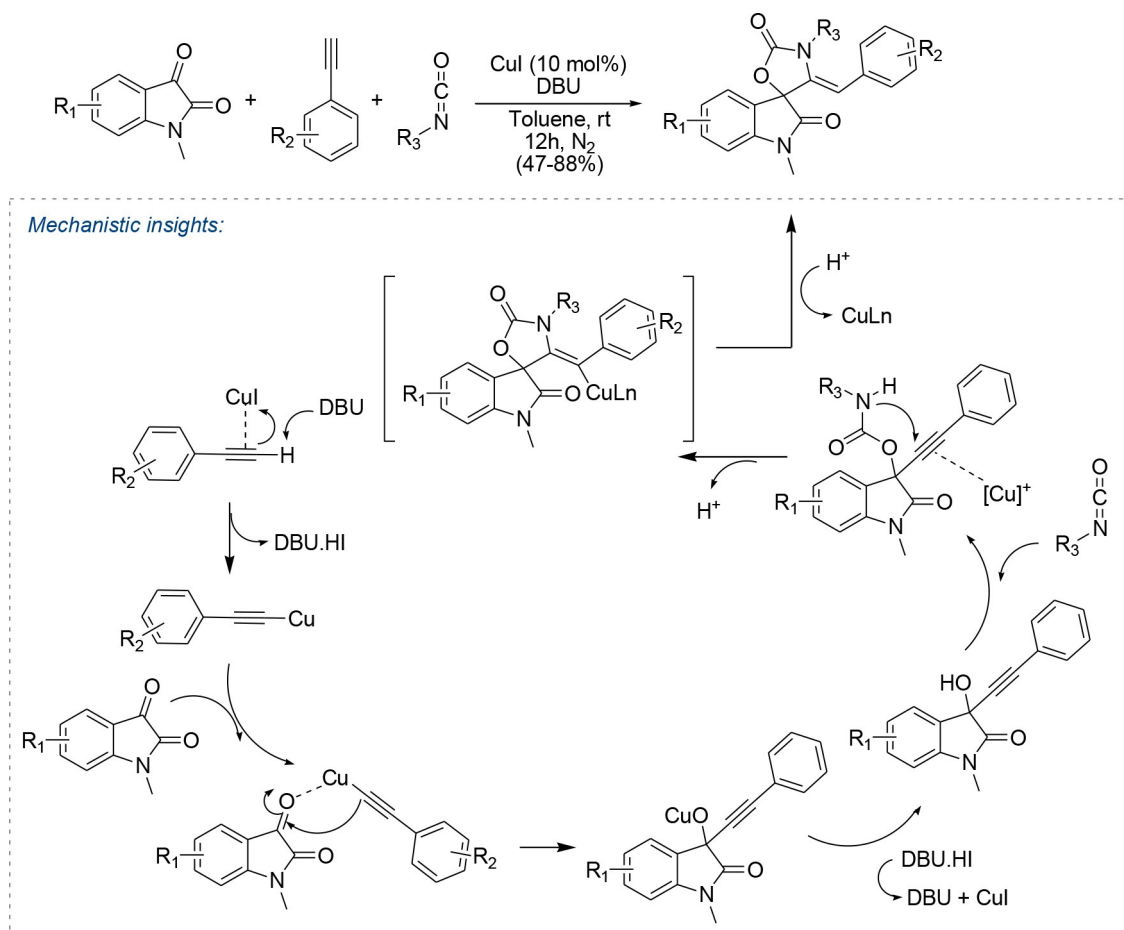
Scheme 20. Regioselective synthesis of spirooxindole-tetrahydrothiophene derivatives.



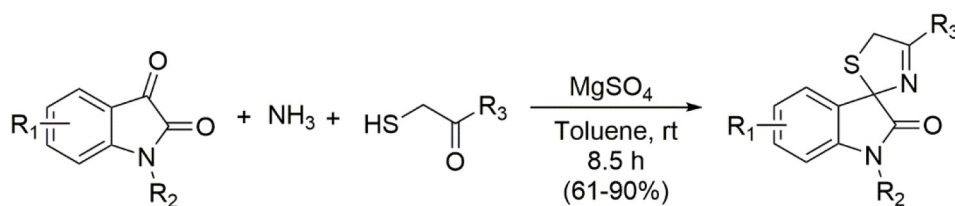
Scheme 21. Silver-promoted 3-MCR for the synthesis of spirooxindole-dihydropyrrole derivatives.



Scheme 22. 3-MCRs in the synthesis of new spirooxindole-thiazolidinone derivatives.



Scheme 23. Copper(I)-catalyzed 3-MCR for the synthesis of spirooxindole-oxazolidinone derivatives.

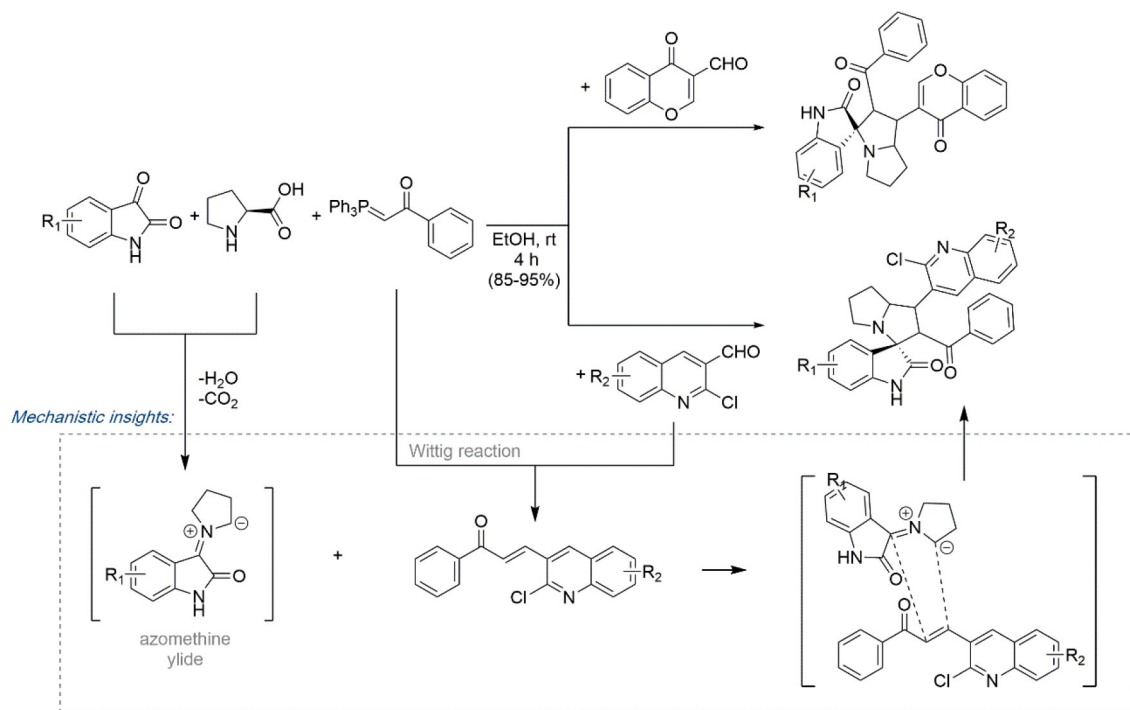


Scheme 24. Asinger-type 3-MCR applied to the synthesis of spirooxindole-3-thiazoline derivatives.

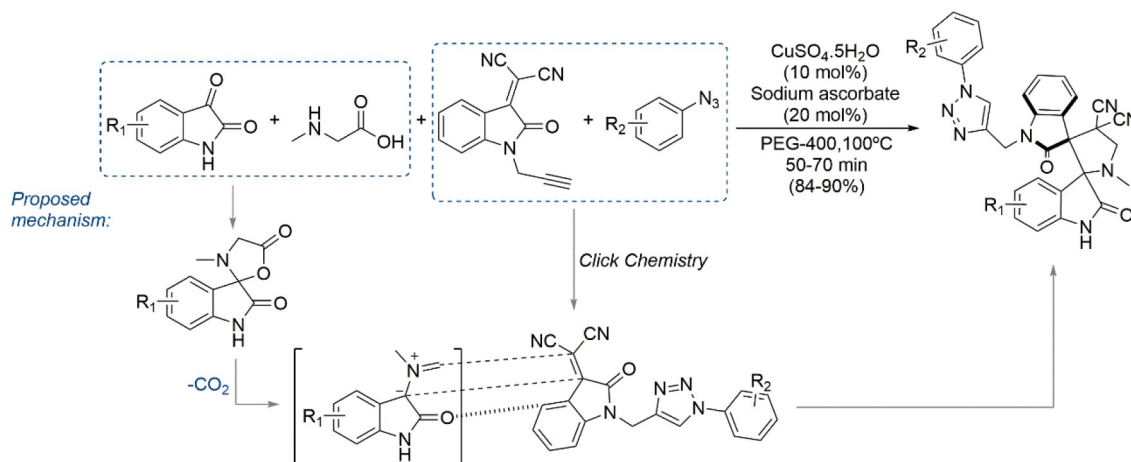
and 3-carbaldehyde-chromene or quinoline derivatives and the Wittig reagent 1-phenyl-2-(1,1,1-triphenyl- λ 5-phosphanylidene)ethan-1-one. The reaction proceeds *via* 1,3-dipolar cycloaddition of azomethine ylides (generated *in situ* from isatin derivatives and *L*-proline) with chromene/quinolinyl-based chalcones as dipolarophiles (generated *in situ* from the Wittig reagent and 4-oxo-4*H*-chromene-3-carbaldehyde or 2-choroquinoline-3-carbaldehyde derivatives) (Scheme 25). Despite poor substrate scope, the method features several advantages from an economic and sustainability point of view, including

catalyst-free reaction conditions, good to excellent yields, chromatography-free purification and easy scale-up.^[53]

A four-component condensation reaction for the synthesis of novel dispirooxindole pyrrolidine linked 1,2,3-triazole derivatives was reported by Khurana and co-workers. Isatin derivatives, sarcosine, 2-[2-oxo-1-(prop-2-ynyl)indolin-3-ylidene]malononitrile and aryl azides with Cu(I) as catalyst in polyethylene glycol (PEG-400) as reaction medium, at 100 °C (Scheme 26) gave interesting dispirooxindole pyrrolidine linked 1,2,3-triazole derivatives. This one-pot 4-MCR ap-



Scheme 25. Four component regio- and diastereoselective synthesis of pyrrolidines incorporating spirooxindole derivatives.



Scheme 26. One-pot 4-MCR condensation for the synthesis of novel dispirooxindole pyrrolidine linked 1,2,3-triazole derivatives.

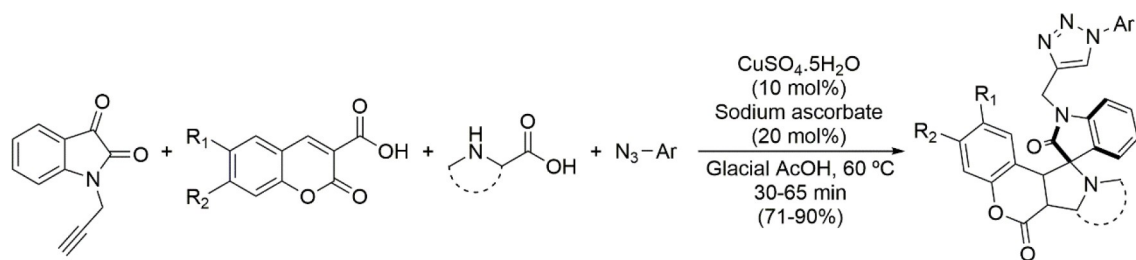
proach involves two sequential [3 + 2] cycloaddition reactions: stereoselective azide-alkyne cycloaddition, azomethine ylide and alkene cycloaddition, affording the novel structurally diverse triazole containing dispirooxindole pyrrolidine heterocycles in good yields.^[54]

Khurana and co-workers applied a similar strategy, but this time including the propargyl moiety in the isatin scaffold, and replacing the 2-[2-oxo-1-(prop-2-ynyl)indolin-3-ylidene] malononitrile by coumarin-3-carboxylic acid in a glacial acetic

acid reaction medium (Scheme 27). Besides sarcosine, *L*-proline was also used as the amino acid in this reaction, with the desired products (18 examples) being obtained with short reaction times and overall good yields.^[55]

2.1.1.2. Knoevenagel-initiated MCRs

A one-pot, two-step, 4-MCR approach was recently reported for the synthesis of spirooxindole-furo[2,3-*c*]pyrazole deriva-



Scheme 27. 4-MCR for the synthesis of spirooxindole-coumarin-triazole derivatives.

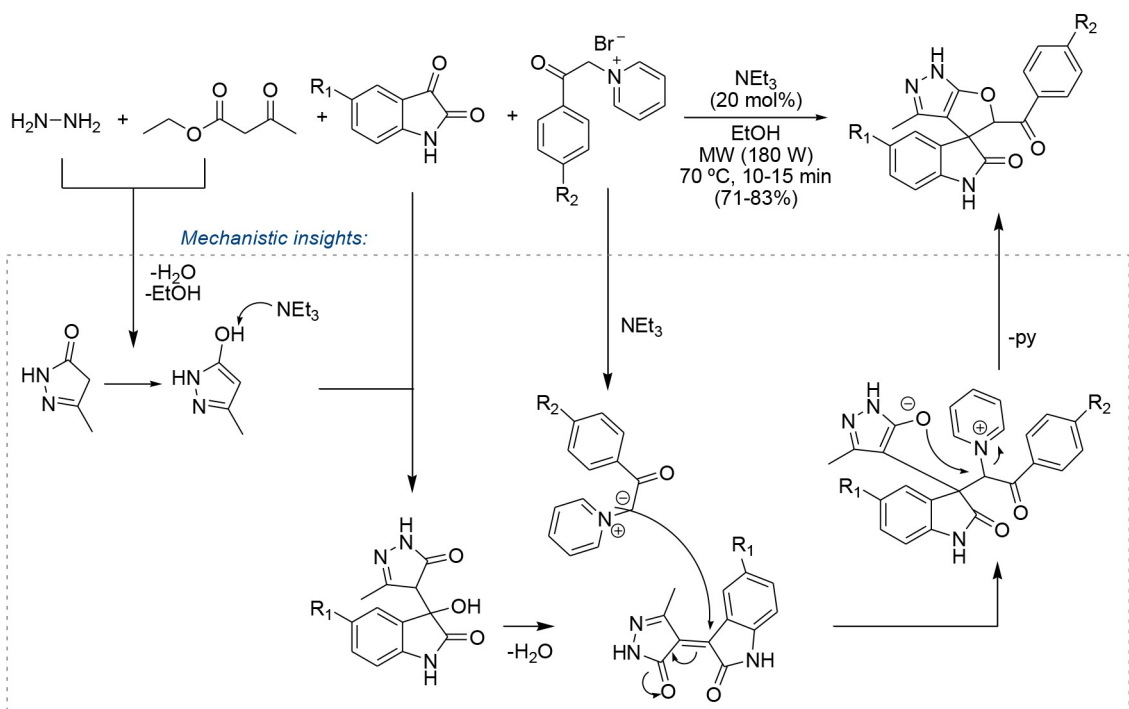
tives (10 examples). The triethylamine-catalyzed Knoevenagel reaction/Michael addition/heterocyclization process occurs with high yields in short reaction times, under microwave irradiation (Scheme 28). First, hydrazine and ethyl acetoacetate react to generate *in situ* pyrazolone, which further reacts, in the second step, with isatin and pyridinium ylide to form the desired products. Noteworthy is the formation of five new chemical bonds during this synthetic process, including two C–C, one C–O, one C–N and one C=N.^[56]

2.1.2.3. Miscellaneous

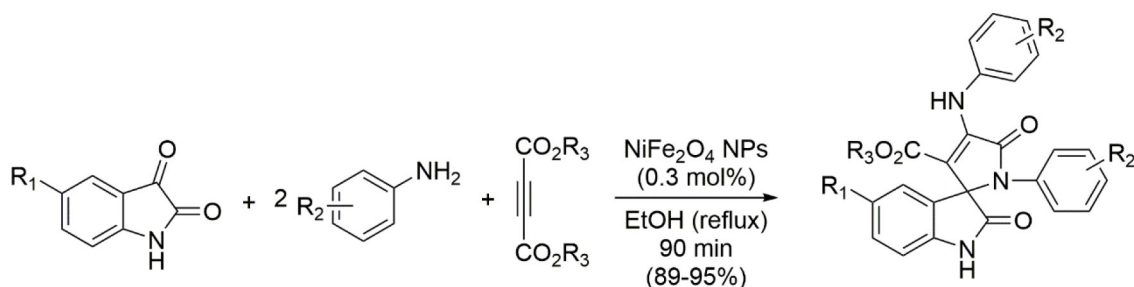
Meghyasi *et al.* reported the synthesis of spiro[indole-3,2'-pyrrole]-2,5'(1*H*,1'*H*)-diones using a straightforward and

efficient 4-MCR approach. The condensation reaction of anilines, acetylenedicarboxylates and isatin derivatives in the presence of NiFe₂O₄ nanoparticles (NPs) as catalyst (0.3 mol% loading) afforded in good yields and clean reaction profiles the desired adducts (Scheme 29). The recycling of this magnetic heterogeneous catalyst was easily made by introducing a magnet stirrer bar to the reaction mixture in order to separate the catalyst. It was found that the product yields decreased to a small extent after each reuse of the catalyst, showing good recoverability.^[57]

The silver-promoted C_α(sp³)-H activation of benzylamines already addressed in this work, reported by Mondal and Mukhopadhyay (see Scheme 21), followed by a [1,5]-rearrangement was also employed in a pseudo-4-MCR involving



Scheme 28. Triethylamine-catalyzed synthesis of spirooxindole-furo[2,3-*c*]pyrazole derivatives.



Scheme 29. NiFe₂O₄ NPs as an efficient heterogeneous catalyst in the synthesis of spiro[indole-3,2'-pyrrole]-2,5'-(1*H*,1'*H*)-diones by a 4-MCR approach.

isatin (*N*-unsubstituted and *N*-methylisatin), acetylenedicarboxylates, and benzylamines (2 equiv.) (Scheme 30). The final products were obtained in very good yields, showcasing the versatility of silver catalysis in MCRs.^[48]

2.1.3. MCRs with 5 Components

2.1.3.1 [3+2] Cycloaddition Reaction

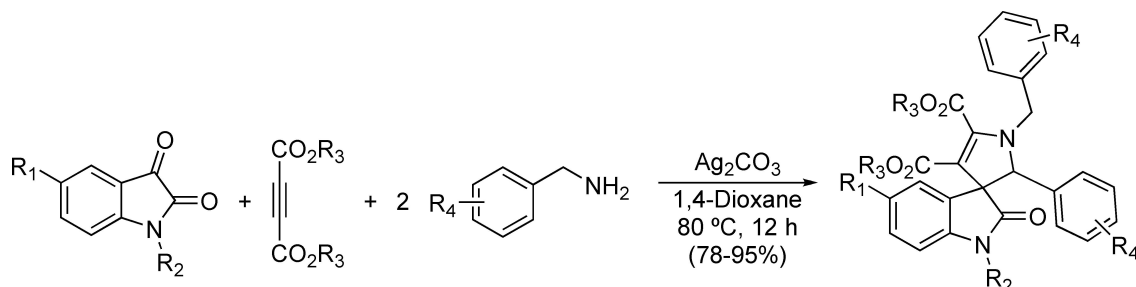
An efficient one-pot 5-MCR using acetylacetone, aryl azides, aromatic aldehydes, isatin and *L*-proline catalyzed by DBU and using PEG-400 as solvent was also successfully reported by Khurana and co-workers (Scheme 31). Both electron rich and electron deficient aryl azides and aldehydes were used effectively in this chemical transformation. The authors compared the MCR approach with a stepwise methodology, with the later requiring longer reaction times and overall poorer yields. The recyclability of the catalyst (DBU, required only for the synthesis of chalcone intermediates) was also tested, showing no significant reduction in activity.^[58] The authors suggested that the mechanism entailed a [3+2] cycloaddition reaction of the acetylacetone and the aryl-azide derivative, followed by the Aldol condensation with the aromatic aldehyde derivative to afford the chalcone intermediate that then undergoes a [3+2] cycloaddition with the azomethine ylide formed by condensation of isatin with the amino acid giving the desired spirooxindole. In the case of the second [3+2] cycloaddition reaction, the authors suggested that there was a

secondary orbital interaction between the double bond of the triazole ring and the carbonyl group of isatin, which stabilizes the transition state of the formed intermediate (Scheme 31).

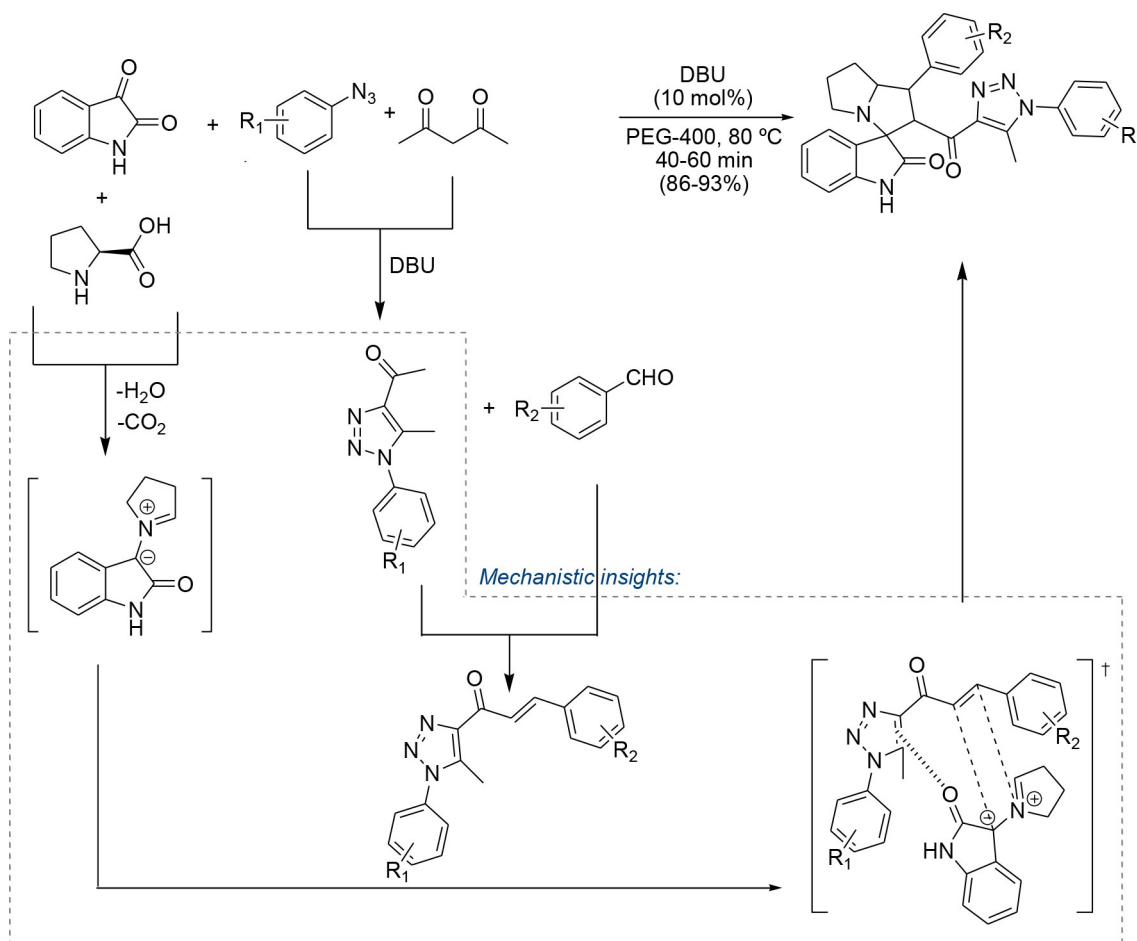
2.1.3.2. Knoevenagel-initiated MCRs

The same group further explored a 5-MCR for the efficient preparation of spirooxindolopyrrolizidines linked 1,2,3-triazole conjugates, once again employing PEG-400 as reaction medium. The Knoevenagel-initiated reaction, followed by two consecutive 1,3-dipolar cycloaddition reactions allowed the synthesis of a library (19 examples) in very good yields and short reaction times (Scheme 32).^[59]

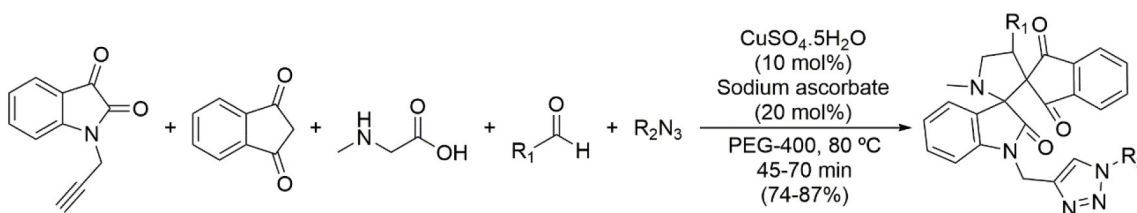
The current literature presents a great variety of methods for the synthesis of spirooxindoles. These protocols include, three-, four- and five-component MCRs, with green and eco-friendly solvents (like water or ionic liquids), short reaction times (using microwave equipment for instance) and have significant reaction scopes. The initial key step is the 1,3-dipolar cycloaddition reaction, followed by Knoevenagel condensation to form the Michael acceptor, which then reacts with an active methylene reagent *via* an intramolecular Michael reaction. Besides, other miscellaneous protocols have been reported allowing the formation of useful complex spirooxindole scaffolds, under mild reaction conditions and with cheap catalysts.



Scheme 30. Silver-promoted pseudo-4-MCR for the synthesis of spirooxindoles.



Scheme 31. Efficient 5-MCR approach for the synthesis of novel triazolyl spirocyclic oxindole derivatives.



Scheme 32. One-pot 5-MCR for the synthesis of spirooxindolopyrrolizidines linked 1,2,3-triazole conjugates.

2.2. Six-Membered Spirocyclic Systems

2.2.1. MCRs with 3 Components

2.2.1.1. Knoevenagel-initiated MCRs

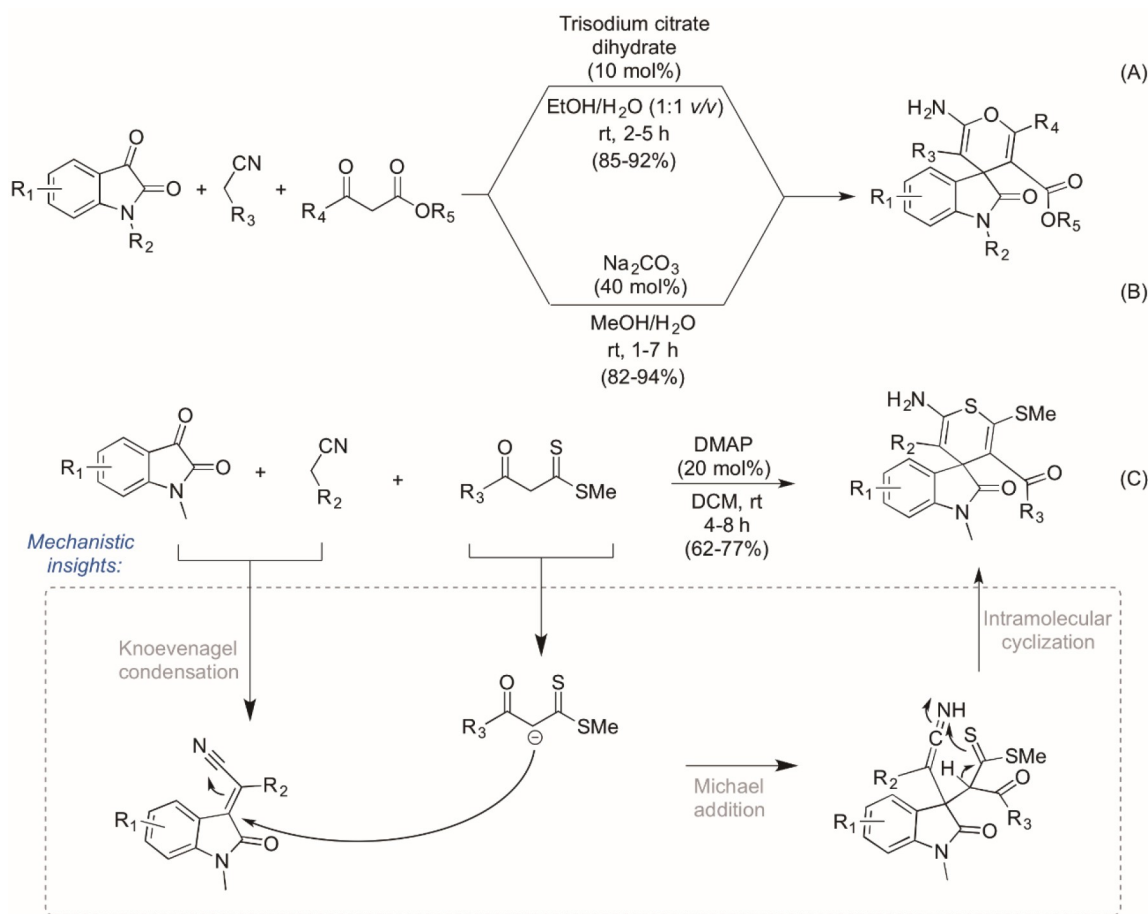
Among the vast family of heterocycle units, pyrans (or thiopyrans) are frequently found as structural subunits of a wide range of biologically active natural as well as synthetic privileged compounds. The use of MCRs as a powerful tool for rapid construction of such heterocycles is well proven by

the incredible number of reports found in literature. Brahmachari *et al.* reported an interesting tandem Knoevenagel-cyclocondensation reaction using isatin derivatives, malononitrile and several C–H activated acids in aqueous ethanol at room temperature. Upon testing several catalysts they found the catalytic superiority of trisodium citrate dihydrate, a commercially available and cheap salt, which is used as a food additive and in medicinal applications. This compound works as an organocatalyst (10 mol% catalyst loading) in the synthesis of

spiro[indoline-3,4'-pyrans] using a β -keto ester as C–H activated acid (Scheme 33A), but it also works efficiently with other C–H activated acids like hydroxycoumarins, dimedones, cyclohexadiones, etc., generating a wide range of diverse and functionalized spiro-fused *O*- and *N*-heterocycles.^[60] Basha *et al.* also reported a similar 3-MCR approach to spiro [indoline-3,4'-pyrans] using Na_2CO_3 as catalyst, but in higher catalyst loading (40 mol%). Good yields and smooth reaction conditions (Scheme 33B) without the need for chromatographic purification makes this protocol a cheap and environmentally friendly approach. 1,3-Dimethylbarbituric acid could also be used successfully in this reaction to obtain spiro [indoline-3,5'-pyrano-2,3-pyrimidine] derivatives.^[61] Kurva *et al.* reported a similar 3-MCR using previously synthesized β -oxodithioesters and 4-(dimethylamino)pyridine (DMAP) as catalyst (20 mol% loading). Despite the use of chromatographic purification methods and organic solvents as reaction medium, the privileged thiopyran fused spirooxindole derivatives were successfully obtained (24 examples) in moderate to good yields and mild reaction conditions (Scheme 33C).^[62] All

the reactions depicted in Scheme 33 occur *via* Knoevenagel reaction, Michael addition and final intramolecular cyclization sequence, that was discussed above.

Nagaraju *et al.* developed a useful homogeneous catalyst for the synthesis of a wide range of spirooxindole-chromene derivatives (68 examples), which could be easily recycled while retaining its catalytic activity (up to 5 cycles). Extensive studies were carried out in order to find the most efficient catalytic system, by screening different α -amino acids and aromatic amine combinations (as donor-acceptor pairs), with the best results achieved with *L*-proline and melamine (1,3,5-triazine-2,4,6-triamine) (3:1 ratio; 3 mol%). The catalytic efficiency is correlated with the structural features of the constituents of the catalytic system – melamine has hydrogen donor-acceptor sites, allowing it to form a stable complex with three molecules of *L*-proline *via* hydrogen bonds. Spirooxindole derivatives were obtained *via* Knoevenagel reaction, followed by Michael addition and the intramolecular cyclization sequence in excellent yields through a 3-MCR of isatins, malonitriles and a wide range of nucleophiles catalyzed by this



Scheme 33. Synthesis of spiro[indoline-3,4'-pyrans] and spiro[indoline-3,4'-thiopyrans] using 3-MCR approaches.

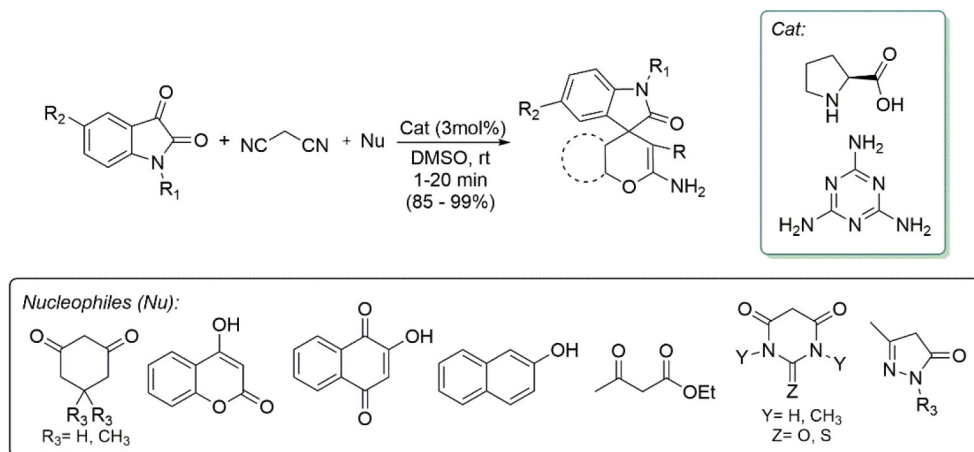
catalytic system, in DMSO at room temperature and short reaction times (Scheme 34).^[63]

Despite all the reports found in the literature on the synthesis of spiro[indoline-3,4'-pyran] derivatives, the majority are non-stereoselective or enantioselective. Konda *et al.* reported a stereoselective synthesis of similar spirooxindole derivatives catalyzed by a cinchona alkaloid thiourea organocatalyst to give valuable chiral compounds. After optimization of the reaction conditions the authors established that the use of water as additive in this 3-MC Knoevenagel/Michael/cyclization reaction increased significantly the product enantioselectivity. Isatins, malononitrile and 1,3-dicarbonyl compounds (such as acetoacetate and 1,3-diketone) together with the same commercially available cinchona organocatalyst yielded the desired spirooxindole products in good yields and moderate to high *ee* values (Scheme 35).^[64]

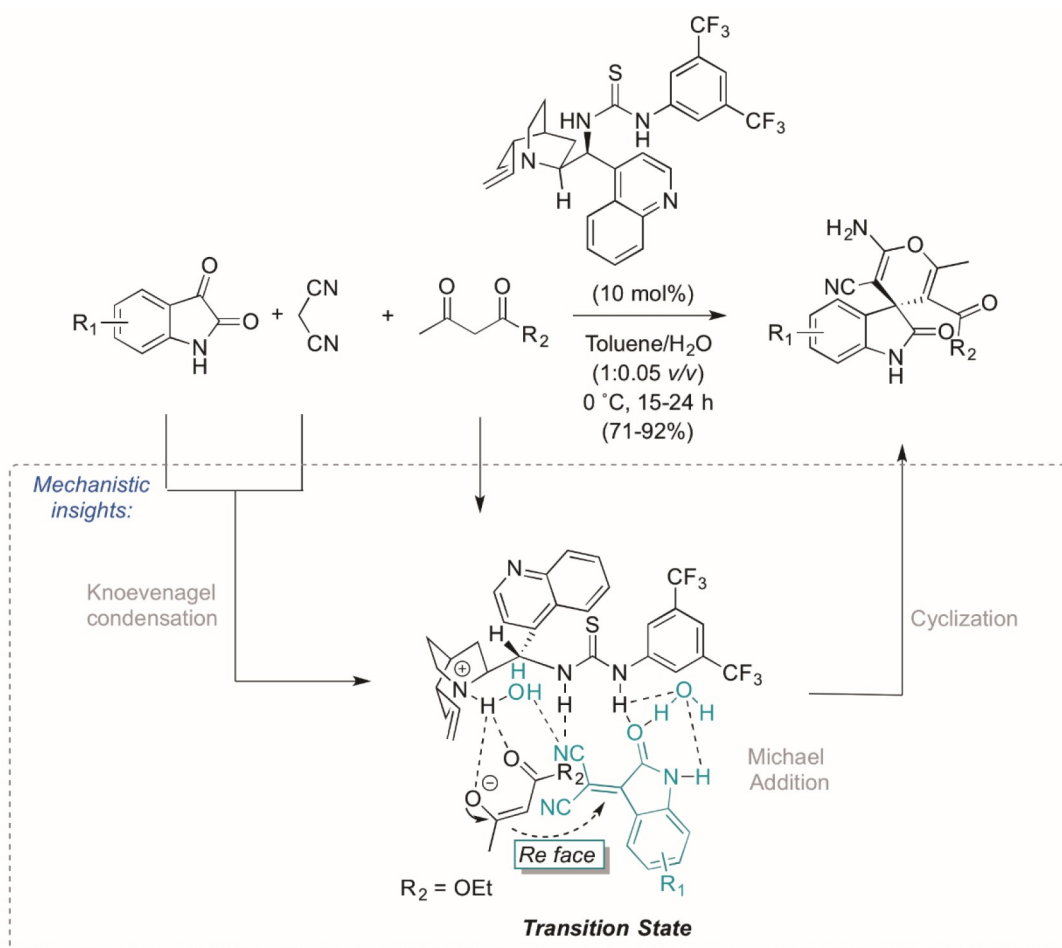
Zhu *et al.* developed the first asymmetric catalytic reaction for the synthesis of pharmacological relevant tetrahydroquinolin-5-one-based spirooxindole by a one-pot 3-component [3+3] cyclization of cyclic enaminone, isatin and malononitrile, using chiral cinchona alkaloids. After optimization of the reaction conditions through the screening of different organocatalysts (several cinchona alkaloids), solvents and additives, the best conditions are depicted in Scheme 36. The resulting library (22 examples) was prepared in moderate to excellent yields, and with enantiomeric ratios of up to 97:3. This synthetic methodology is an efficient approach for the construction of chiral tetrahydroquinolin-5-one-based spirooxindole frameworks of biological importance. The proposed mechanism for the synthesis of these enantioenriched products is believed to involve a Knoevenagel condensation, enantioselective Michael addition followed by an intramolecular nucleophilic addition.^[65]

Several groups reported the synthesis of spiro[indoline-3,4'-pyran] derivatives with different attached units (fused or not), depending on the 1,3-dicarbonyl compounds used. Various catalysts were studied in this 3-MCR using isatin derivatives, activated methylenes and 1,3-dicarbonyl compounds. Elinson *et al.* reported the synthesis of spiro[chromene-4,3'-indoline] derivatives by a simple and atypical NaOAc-catalyzed Knoevenagel/Michael cyclization 3-MCR procedure, under solvent-free conditions. Using isatin derivatives, malononitrile, and dimedone, the reaction proceeded smoothly by grinding the starting materials and the NaOAc catalyst in a mortar at room temperature. Despite the poor substrate scope that was observed, the reactions had short reaction times and afforded the target products in moderate to excellent yields (Scheme 37A).^[66] Chouha *et al.* extended the scope of this reaction by using cyanoacetic acid derivatives and also 1,3-cyclohexanedione. After several reaction optimizations they concluded that boron trifluoride diethyl etherate (BF₃·Et₂O) is a convenient and excellent catalyst choice for the synthesis of the desired spirooxindole derivatives using aqueous ethanol as the reaction medium (Scheme 37B).^[67] Molla *et al.* used Borax (sodium borate, Na₂B₄O₇), an important naturally-occurring boron mineral, as the catalyst for the synthesis of spirooxindole derivatives (29 examples) in a one-pot procedure *via* a Knoevenagel condensation followed by a Michael addition. The products were obtained with very good to excellent yields under mild reaction conditions (Scheme 37C). Under these reaction conditions, Borax produces hydroxyl anion (Brønsted base) and boric acid (Lewis acid), which catalyses the Knoevenagel condensation and Michael reactions.^[68]

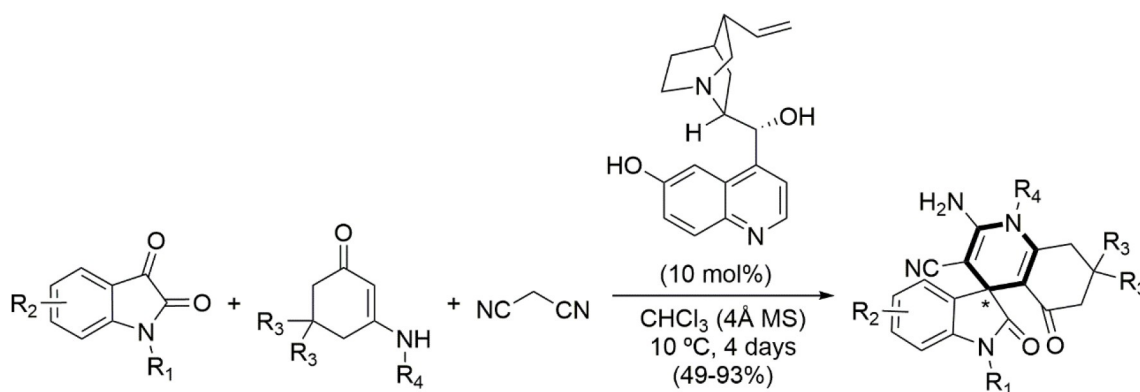
Magnetic nanoparticles have been widely used as efficient catalysts in several synthetic transformations, leading to more efficient and environmentally friendly processes. Their application in 3-MCR strategies to obtain spirooxindole derivatives



Scheme 34. Synthesis of spirochromenes in the presence of the catalytic system *L*-proline and melamine (3:1).



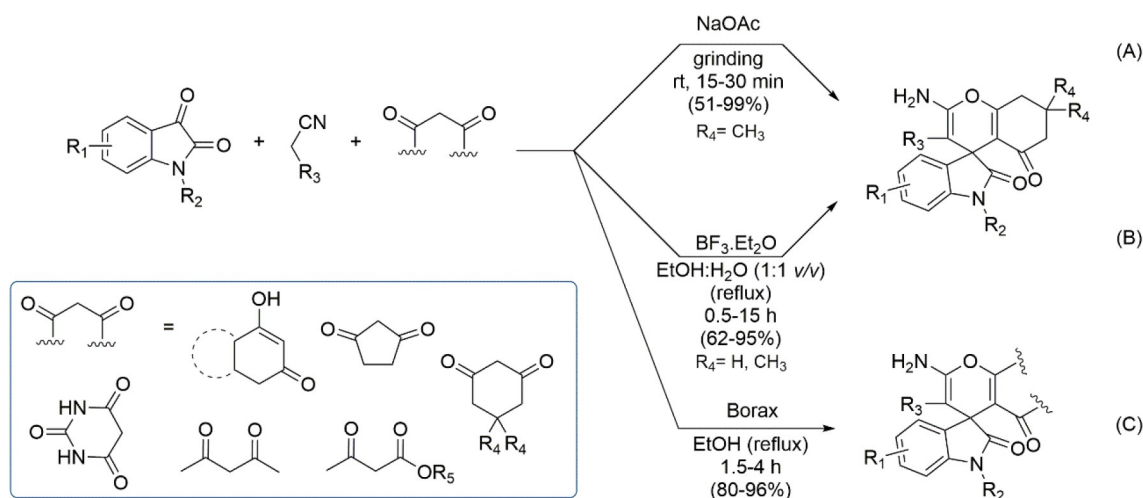
Scheme 35. Enantioselective synthesis of spiro[indoline-3,4'-pyran] derivatives catalyzed by a cinchona thiourea alkaloid organocatalyst.



Scheme 36. Asymmetric synthesis of tetrahydroquinolin-5-one-based spirooxindole derivatives.

was also explored in recent years. Mirhosseini *et al.* reported the use of previously synthesized hollow Fe₃O₄@Dopamine-

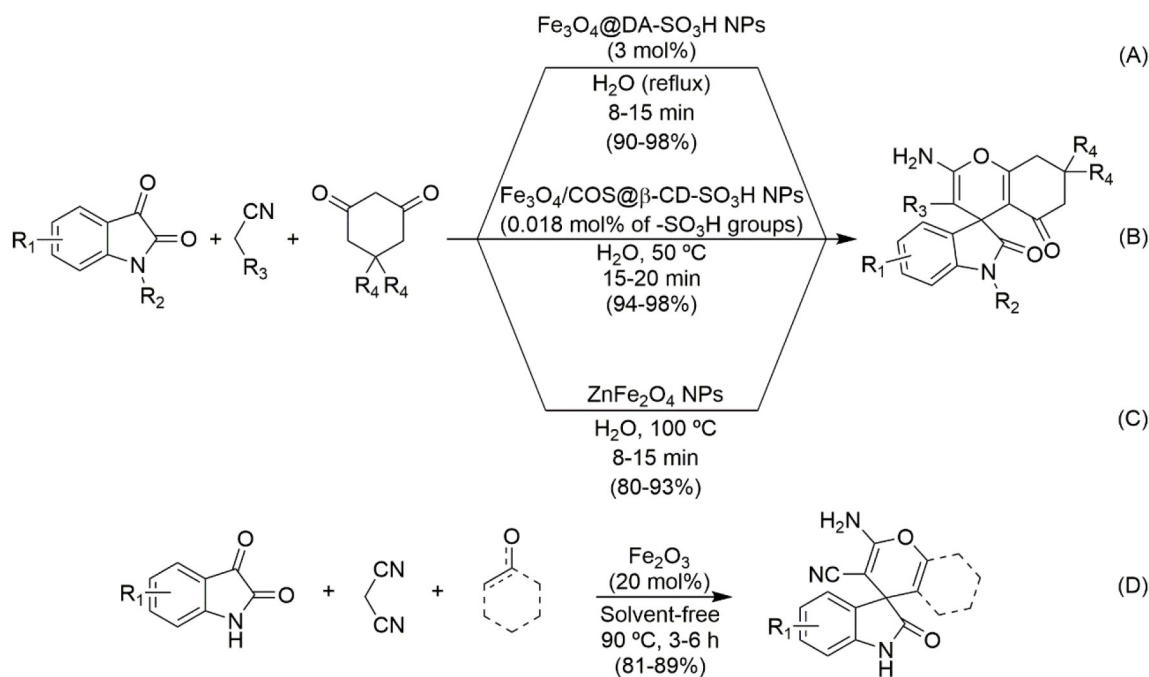
SO₃H (Fe₃O₄@DA-SO₃H) nanomagnetic catalyst in the Knoevenagel/Michael cycloaddition reaction. This method-



Scheme 37. Synthesis of spiro[chromene-4,3'-indoline] derivatives by a Knoevenagel/Michael cyclization 3-MCR procedure.

ology gave easy access to the corresponding spirooxindoles in good to excellent yields, using water as reaction medium in short reaction times (Scheme 38A). The catalyst could be recycled (using an external magnet) and reused at least six times without significant loss of activity.^[69] Similarly, Mohammadian *et al.* reported the synthesis and application of

a new magnetic nanocatalyst. The synthesized magnetic calcinated oyster shell functionalization with taurine immobilized on β -cyclodextrin ($\text{Fe}_3\text{O}_4/\text{COS}@ \beta\text{-CD-SO}_3\text{H NPs}$) has proven its efficiency in the 3-MCR of isatin derivatives, active methylene derivatives and dimedone or 1,3-cyclohexanedione (Scheme 38B). Using water as reaction medium, 16 spiroox-



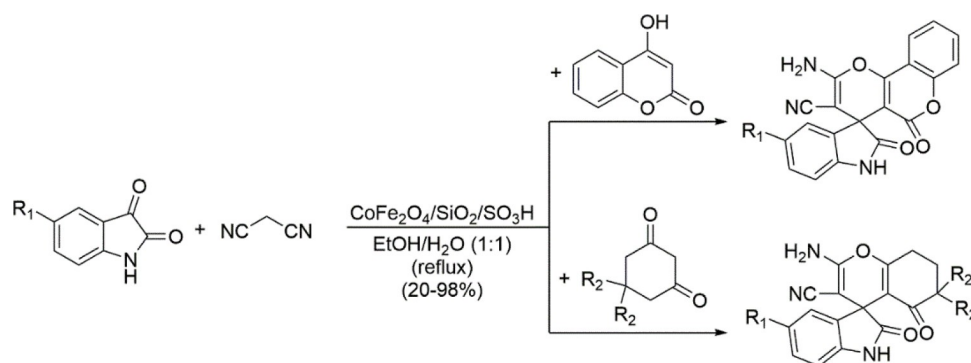
Scheme 38. Use of magnetic iron NPs and simple iron oxide as efficient catalysts in the 3-MCR to obtain spiro[indoline-3,4'-pyran] derivatives with fused chromene units.

indole derivatives with fused chromenes were obtained in good to excellent yields. The magnetic separation of the catalyst from the reaction medium and its reusability (at least eight cycles without significant changes in the observed yields) are the main advantages of this catalytic methodology.^[70] Hasani *et al.* reported the use of ZnFe_2O_4 as an efficient nanocatalyst for the same synthetic transformation. Despite poor reaction scope (only the 1,3-dicarbonyl substrate scope was evaluated), the methodology offers some advantages like easy preparation and handling of the catalyst, simple work-up, use of water as reaction medium and short reaction times (Scheme 38C). The products were obtained in good yields and the catalyst could be recycled.^[71] Ferric oxide (Fe_2O_3) can also catalyze the synthesis of spiro-4*H*-pyran derivatives, as reported by Maghsoodlou *et al.*^[72] Isatin derivatives, malononitrile and several 1,3-dicarbonyl compounds were used under solvent free conditions with this catalyst (Scheme 38D). Compared to the other iron catalysts (Scheme 38) the application of this catalyst entails longer reaction times in order to achieve good yields of the desired compounds. Solvent-free conditions, low

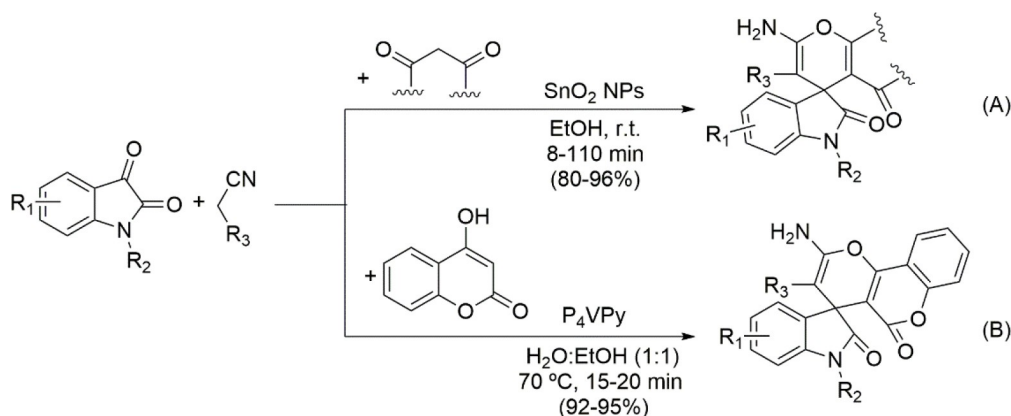
toxicity, and easy availability of the catalyst are the main advantages of the process.^[72]

The application of another heterogeneous catalytic system was recently reported as an efficient methodology for the synthesis of spirooxindoles *via* Knoevenagel reaction/Michael addition. The recyclable catalyst, consisting of sulfonic acid immobilized on the surface of a magnetic cobalt ferrite/silicate NPs ($\text{CoFe}_2\text{O}_4/\text{SiO}_2/\text{SO}_3\text{H}$), successfully promoted the reaction involving isatin, malononitrile and β -diketones, affording the final products (12 examples) in variable yields (Scheme 39). Importantly, no metal leaching was observed from the heterogeneous catalyst.^[73]

Moradi *et al.* reported an environmentally benign protocol for the synthesis of spirooxindole derivatives with potential biological activity. By using SnO_2 NPs as a catalyst, the reaction of isatin derivatives, various diketones and malononitrile or ethyl cyanoacetate in ethanol at room temperature, allowed the synthesis of a wide diversity of spirooxindole derivatives (15 examples), with very good to excellent yields (80–96%) with short reaction times (Scheme 40A). The authors compared this cheap and nontoxic catalyst with other



Scheme 39. $\text{CoFe}_2\text{O}_4/\text{SiO}_2/\text{SO}_3\text{H}$ NPs as a heterogeneous catalyst for the synthesis of spirooxindoles.



Scheme 40. Synthesis of spirooxindoles derivatives catalyzed by heterogeneous catalysts.

catalysts already described in the literature for the synthesis of similar compounds and they found that when this catalyst was used, the reactions could be run at lower temperatures, with lower reaction times, giving better yields. The catalyst could be recycled up to five times without significant loss of catalytic efficacy.^[74]

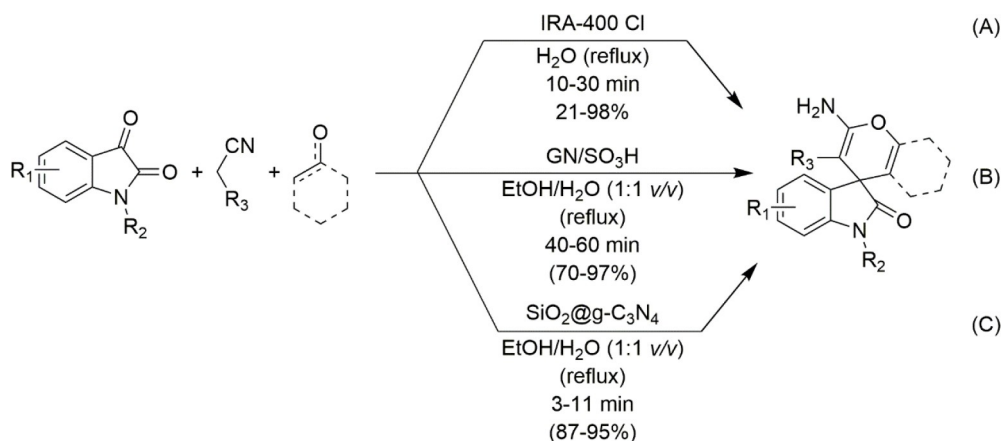
Nasirmahale *et al.* described an efficient protocol for the one-pot 3-MCR of isatin derivatives, 4-hydroxycoumarin and malononitrile catalyzed by poly(4-vinylpyridine) (P₄VPy) in a mixture of water and ethanol (1:1) at 70 °C to give the desired spirooxindole derivatives (Scheme 40B). Unfortunately, the authors only reported the synthesis of two derivatives (in excellent yields) with short reaction times. The main advantages of this basic polymeric catalyst is the cost and efficiency, as well as the preservation of its catalytic activity (for at least 5 reaction cycles).^[75]

Other catalysts were reported as good choices to perform efficiently the synthesis of spiro[indoline-3,4'-pyran] derivatives. One of them is the environmentally benign Amberlite resin IRA-400 Cl. Harichandran *et al.* reported its use as an efficient catalyst to access spirooxindole derivatives in water (Scheme 41A). Reduced reaction times, good reaction scope and reusability of the catalyst (up to four cycles) makes this protocol efficient and eco-friendly.^[76] Allahresani *et al.* explored the use of immobilized sulfuric acid as catalyst in the synthesis of spiro[indoline-3,4'-pyran] derivatives. They synthesized GN/SO₃H (Scheme 41B) by immobilization of the chlorosulfuric acid onto the surface of g-C₃N₄ (graphitic carbon nitride material) and used this nanocomposite as an efficient catalyst for the synthesis of these spiro compounds. Good to excellent yields were obtained with good reaction scope, showing the versatility of this methodology. No considerable decrease in catalytic activity was observed, even after ten cycles, which confirms its high stability.^[77] This group showed that immobilization of SiO₂ particles on the surface of

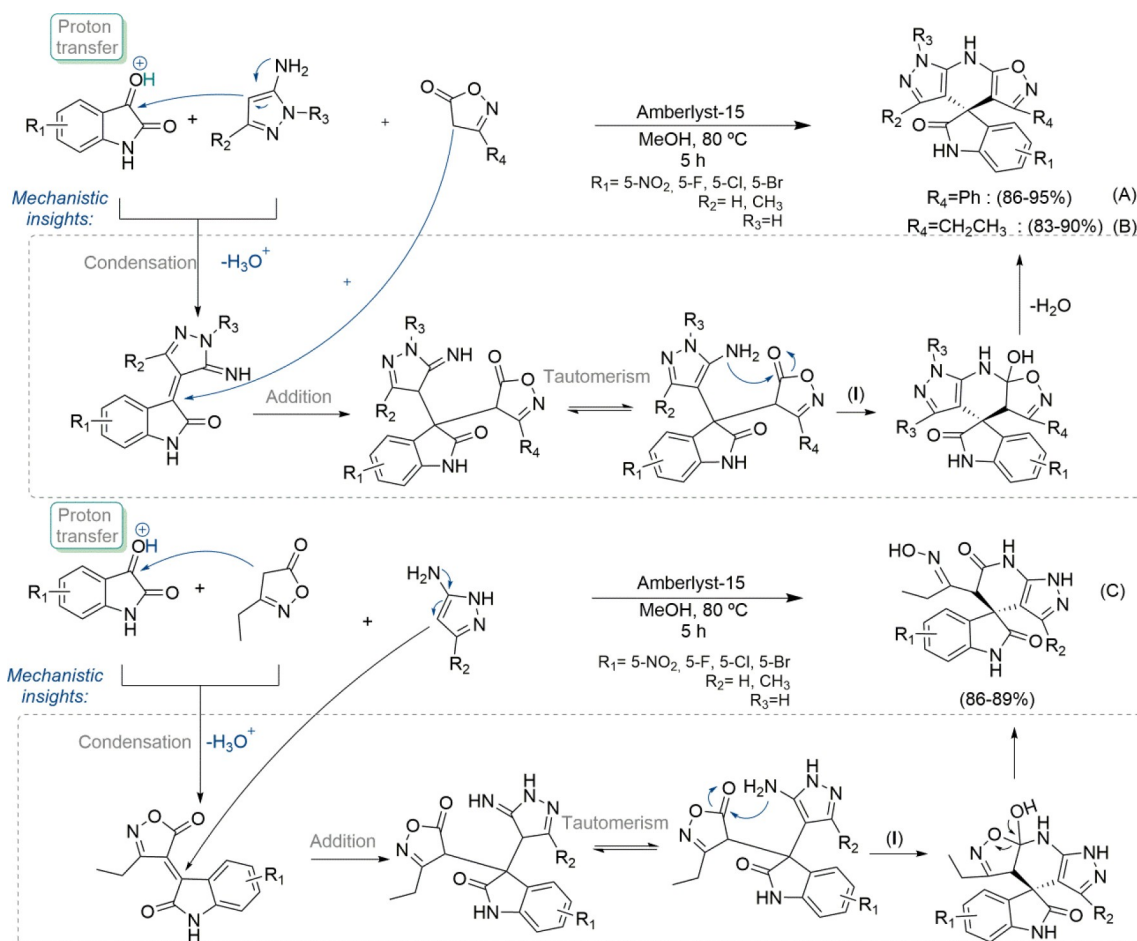
g-C₃N₄ nanosheets also represents a good catalytic system to obtain the same products. Refluxing aqueous ethanol was the best condition found for these reactions (Scheme 41C). No significant decrease in activity was verified after nine cycles.^[78]

Very recently, Niu *et al.* used the well-known ion exchange polystyrene sulfonic acid resin, Amberlyst-15, as a heterogeneous acid catalyst to perform the synthesis of a wide variety of spirooxindole derivatives. As depicted in Scheme 42, the synthesis of spiro[indoline-3,4'-isoxazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridin]-2-one (A and B – 45 examples) and spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridin]-2,6'(5'H)-dione (C-5 examples) derivatives was achieved in the presence of Amberlyst-15 catalyst. Using the same amount of catalyst and reaction conditions (such as MeOH, 80 °C and 5 h) it was possible to obtain a wide range of spirooxindole derivatives with good to excellent yields, indicating that the final products are strongly dependent on the substrate structures. Furthermore, Amberlyst-15 could be easily recovered and reused without significant loss of catalytic activity (up to seven runs).^[79] In both cases, the reaction starts with a proton-transfer step catalyzed by Amberlyst-15, followed by condensation and addition reactions. Tautomerism precedes the intramolecular cyclization (step I). In Scheme 42A and B, the loss of a water molecule leads to the formation of the desired spiro[indoline-3,4'-isoxazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridin]-2-one derivatives. In Scheme 42C, instead of dehydration, isoxazole-ring opening occurs, affording the final spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridin]-2,6'(5'H)-dione derivatives.

Another heterogeneous catalyst suitable for the synthesis of spirooxindole derivatives was described by Sadjadi *et al.*, consisting of a heteropolyacid immobilized in functionalized SBA-15 and afterwards hybridized with layered double hydroxide (HPA-F-SBA-LDH). This novel bi-functional catalyst has acid and basic properties. The one-pot three-component condensation of isatin, malononitrile and dime-



Scheme 41. Highly efficient synthesis of spirooxindole derivatives using different catalysts.

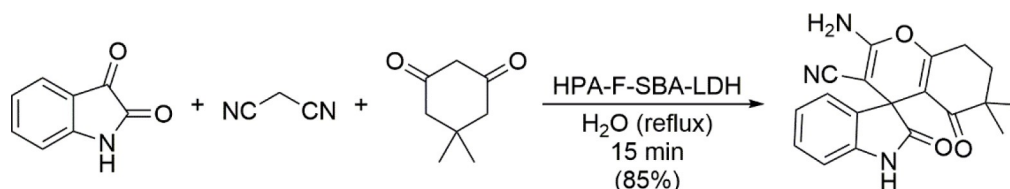


Scheme 42. Synthesis of a wide variety of spirooxindole derivatives catalyzed by Amberlyst-15.

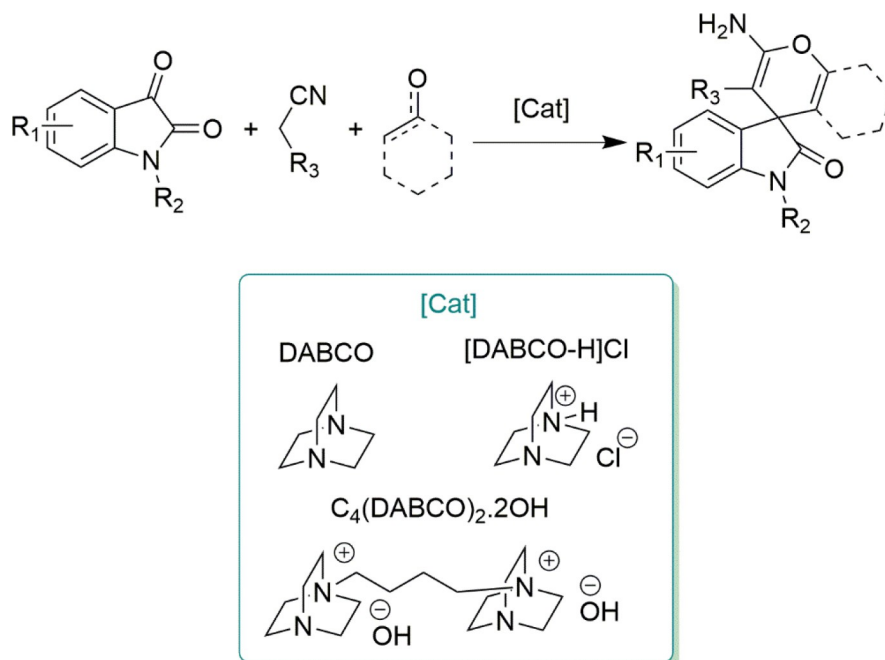
done catalyzed by HPA-F-SBA-LDH in refluxing water afforded the respective spirooxindole with 85% yield (Scheme 43). Although several aldehydes were evaluated, only one isatin derivative was prepared.^[80]

The application of 1,4-diazabicyclo[2.2.2]octane (DABCO) in organic chemistry has shown great results as a catalyst and/or as a base. It is commercially available, cheap, non-toxic and easy to handle. Several groups reported the advantages of using this efficient catalyst in the synthesis of spiro[indoline-

3,4'-pyran] derivatives (Scheme 44). Hasaninejad *et al.* reported the use of DABCO with a remarkably low catalyst loading (6 mol%) using ethanol or aqueous ethanol mixtures under reflux conditions. A wide scope of substrates was evaluated through this protocol (25 examples) using different C-H activated ketones and different malononitriles in good to excellent yields (84–98%) and short reaction times (0.2–5 hours).^[81] Dolati *et al.* reported similar synthetic transformation using DABCO as catalyst, with only 5 mol%



Scheme 43. Synthesis of a spirooxindole using HPA-F-SBA-LDH as heterogeneous catalyst.



Scheme 44. Use of DABCO or its modified versions as efficient catalysts in the synthesis of spiro-4H-pyran derivatives.

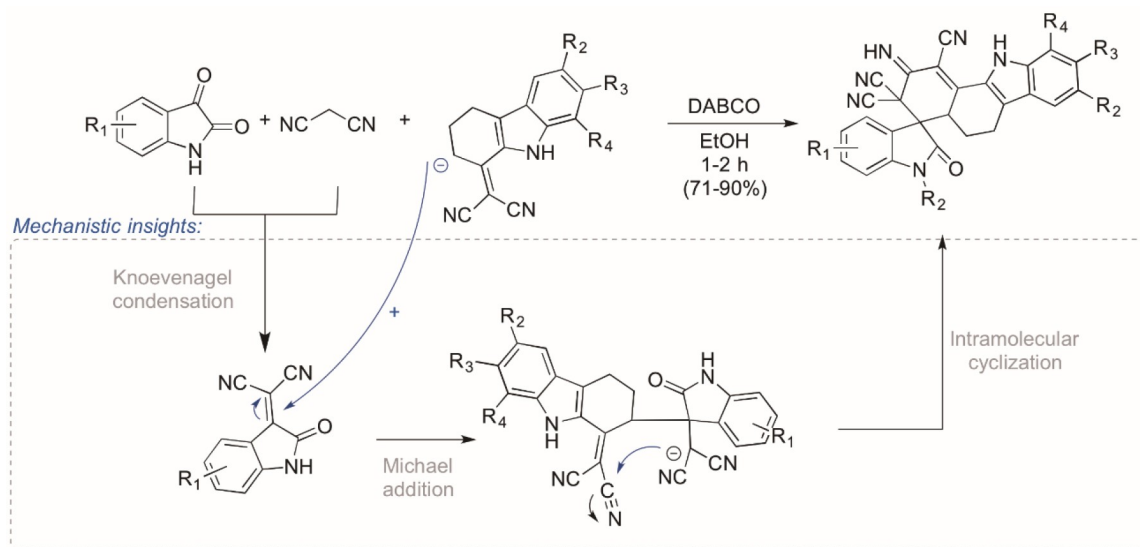
loading and using only water as solvent. Moderate reaction scope (only 13 examples) and generally good yields (73–90%) of the desired spirooxindole compounds were obtained. With a lower reaction temperature (75 °C) and shorter reaction time (4 minutes), one particular product, obtained from the reaction of isatin, malononitrile and dione was prepared in 90% yield.^[82]

Modifications of the catalyst to improve efficiency and recyclability is a common technique used by synthetic chemists. Goli-Jolodar *et al.* synthesized 1,1'-(butane-1,4-diyl) bis(1,4-diazabicyclo[2.2.2]octan-1-ium) hydroxide (C₄(DABCO)₂·2OH) with the objective of applying it as a basic ionic liquid catalyst containing dual basic functional groups for the synthesis of the same spiro-4H-pyran derivatives. It proved its efficiency in the rapid Knoevenagel/Michael/cyclization reaction (Scheme 44) (6–17 min), providing good reaction scope (19 examples) as well as excellent yields (92–97%).^[83] The group of Li *et al.* also reported the synthesis and application of a DABCO-based ionic liquid ([DABCO-H]Cl) in a similar 3-MCR (Scheme 44). Using acetonitrile as solvent, at 50 °C, the reaction showed good reaction scope and provided the products in good to excellent yields (78–98%). The catalyst could be easily recycled and reused up to five times without significant loss of activity.^[84]

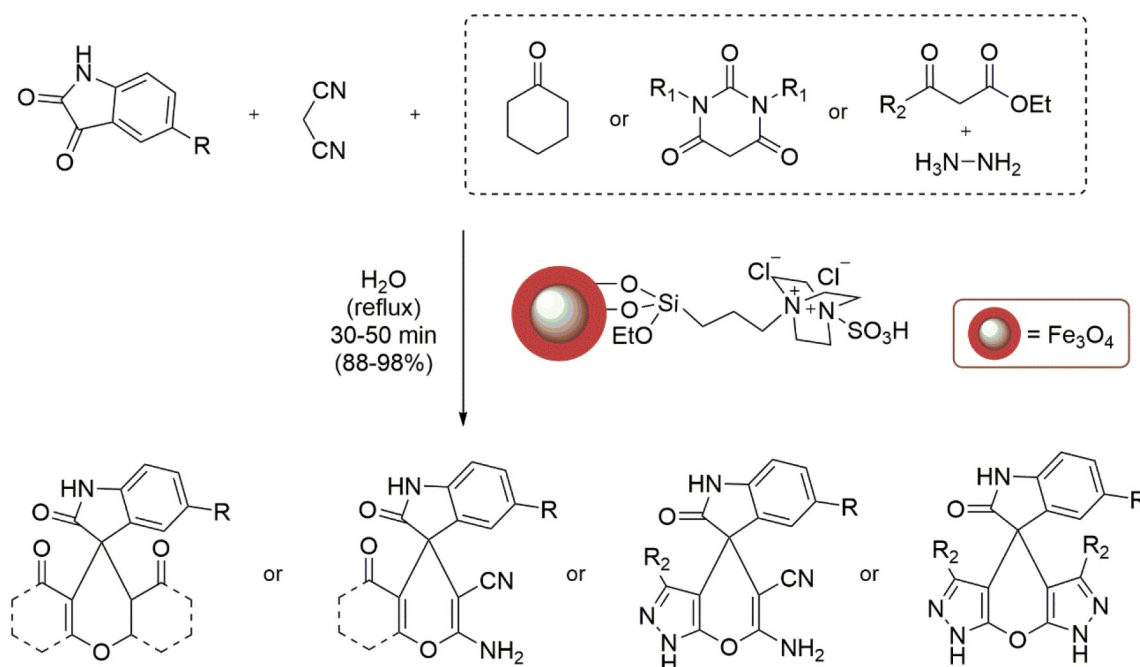
Murali *et al.* also used DABCO to promote the synthesis of new spirooxindole-benzocarbazole derivatives. They developed a green and efficient novel method for the synthesis of these derivatives *via* one-pot 3-MCR of 1-(dicyanomethylene)-

2,3,4,9-tetra-hydrocarbazole derivatives, malononitrile and substituted isatins in the presence of DABCO as catalyst (Scheme 45). 2-Imino-2'-oxo-5,6-dihydro-11H-spiro[indoline-3',4'-benzo[*a*]carbazole]-1,3,3-tricarbonitrile derivatives (12 examples) were obtained in good to very good yields under mild reaction conditions.^[85] The mechanism shown in Scheme 45 is suggested to follow the general mechanism discussed at the beginning of the section.

Zarei and co-workers reported the preparation and characterization of a new heterogeneous catalyst, sulfonic acid functionalized DABCO-based magnetic Fe₃O₄ NPs [Fe₃O₄@SiO₂@Pr-DABCO-SO₃H]Cl₂, used for the synthesis of a wide variety of spiro-pyran derivatives (23 examples) (Scheme 46). Using this nanocatalyst it was possible to achieve a broad substrate scope, as well as furnishing the desired products in very good to excellent yields, within short reaction times. Furthermore, this nanocatalyst could be recycled and reused up to 8 cycles without a notable loss in the catalytic activity. The proposed mechanism for this reaction involves a Knoevenagel condensation, Michael addition and a cyclocondensation as the final step.^[86] Similarly, the same group reported the preparation of a DABCO-based heterogeneous catalyst ([SiO₂@Pr-DABCO-SO₃H]Cl₂), for the synthesis of spiro-pyrans *via* one-pot 3-MCR of substituted isatins with barbituric acid derivatives and 1,3-dicarbonyl compounds. Fifteen spiro-pyran derivatives were prepared with excellent yields (87–95%) in short reaction times (40–90 minutes), using aqueous media under reflux conditions. The heteroge-



Scheme 45. Synthesis of novel 2-imino-2'-oxo-5,6-dihydro-11*H*-spiro[indoline-3',4-benzo[*a*]carbazole]-1,3,3-tricarbonitrile catalyzed by DABCO.

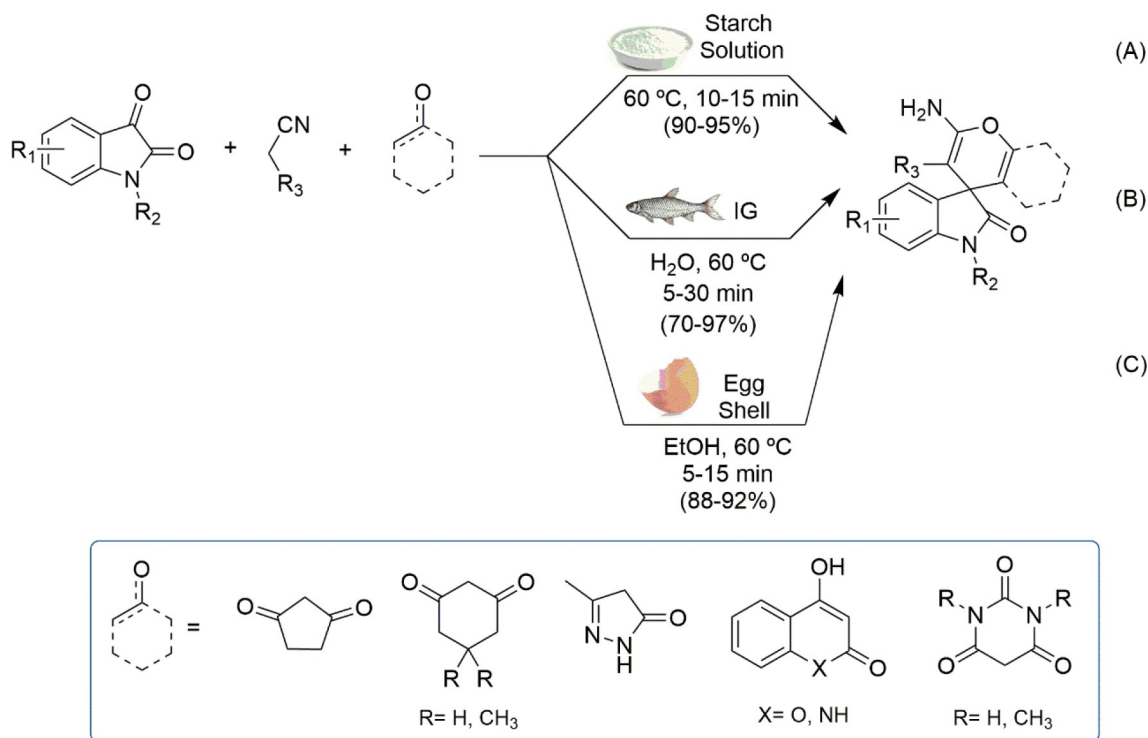


Scheme 46. Synthesis of spiro[pyran] derivatives using a heterogeneous nanocatalyst.

neous catalyst was successfully recycled over 5 runs.^[87] Moreover, the magnetic properties of the first heterogeneous nanocatalyst makes it desirable as its recovery from the reaction medium is easily performed by using an external magnet.

Other catalysts were also applied successfully for the construction of several bioactive spirooxindoles by condensation of isatin derivatives, activated methylene reagents and

activated carbonyl compounds. Chaudhary *et al.*, in their search for innovative methods to access spirooxindole derivatives found that a starch solution could be used as an efficient, eco-friendly and biodegradable catalyst. Despite the poor reaction scope (only 6 examples), the reaction showed good to excellent yields, short reaction times and easy work-up (Scheme 47A). The starch solution is easily prepared by



Scheme 47. Uncommon catalysts applied in the synthesis of spiro-4H-pyran derivatives.

stirring solid starch in water for 30 minutes at room temperature. After filtration of the suspended solids, the filtrate is used as catalyst.^[88]

Javanshir *et al.* reported the use of isinglass (IG), a form of collagen derived from swim bladders of Caspian Sea fish, as a heterogeneous biocatalyst for the synthesis of spiro-4H-pyran derivatives. Using water as solvent at 60 °C, the authors found that the method works efficiently with an extensive variety of substrates (23 examples), in good to excellent yields (Scheme 47B). The preparation of the catalyst was easy to execute and also the corresponding reusability was tested in the protocol. After conclusion of the reaction, the heterogeneous catalyst could be easily separated by filtration, reactivated and reused (some decrease of the activity was noted after four cycles).^[89]

Leila Youseftabar-Miri synthesized spiro-4H-pyran derivatives using eggshell as a natural-occurring heterogeneous basic catalyst, with good yields in short reaction time (Scheme 47C). As eggshell consists almost entirely of CaCO₃ (90%) and is porous, it is thus an excellent candidate for heterogeneous basic catalyst. Furthermore, being a waste product, it is likely to be the cheapest catalyst reported in this review, as it is obtained through simple procedures (removal of the adhering membrane, washing with warm tap-water, followed by distilled water, then drying and pulverization). The eggshell catalyst

showed higher catalytic activity than the pure CaCO₃ under similar reaction conditions. Regarding reusability, it was observed that the catalytic activity remained unaffected over five runs.^[90]

Other research groups reported the use of other catalysts that could efficiently catalyze the three component Knoevenagel/Michael cyclization reaction to access spiro-4H-pyran derivatives. Agarwal *et al.* used the caffeineium hydrogen sulfate (CHS, Figure 2) as catalyst in the same procedure, using aqueous ethanol as solvent (1:1 *v/v*) under mild reaction conditions (60 °C) and short reaction times (20–55 min). Good to excellent yields were obtained (86–96%) for the desired spirooxindole derivatives as well as broad substrate scope (32 examples). The simple work-up, without tedious chromatographic purification, underlines the importance of the protocol.^[91] An alternative method was reported by Jazinizadeh *et al.*, who used the well-known organic salt (ethylenedinitrilo)tetraacetic acid disodium salt (Na₂EDTA, Figure 2) for the facile preparation of spiro-4H-pyrans. This inexpensive reagent (Na₂EDTA) proved its efficiency in a solvent free protocol providing the desired spirooxindoles in good to excellent yield (85–95%). Despite moderate reaction scope (9 examples) the reaction is quick (10–15 min).^[92] The group of Khot *et al.* showed that *tris*-hydroxymethylaminomethane (THAM) is an effective organocatalyst in the

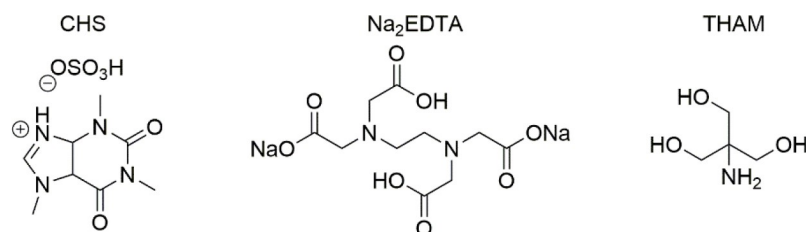


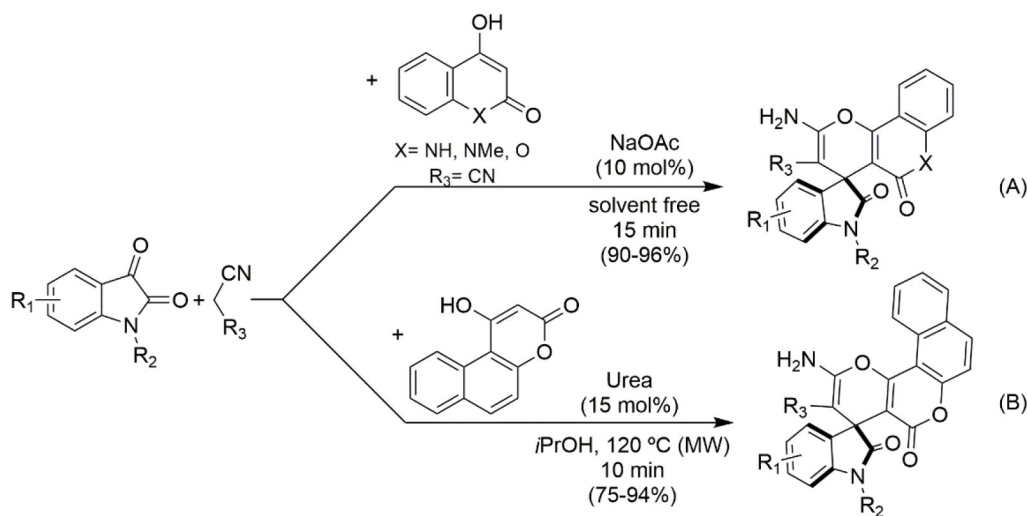
Figure 2. Chemical structures of competent catalysts for the synthesis of spiro-4*H*-pyran derivatives.

same synthetic transformation (Figure 2) – albeit the reaction is slower. Nevertheless, the reaction shows broad substrate scope (29 examples), works under mild conditions (ethanol as solvent at room temperature) and involves a simple work-up procedure furnishing the desired spirooxindole derivatives in 80–95% yields.^[93]

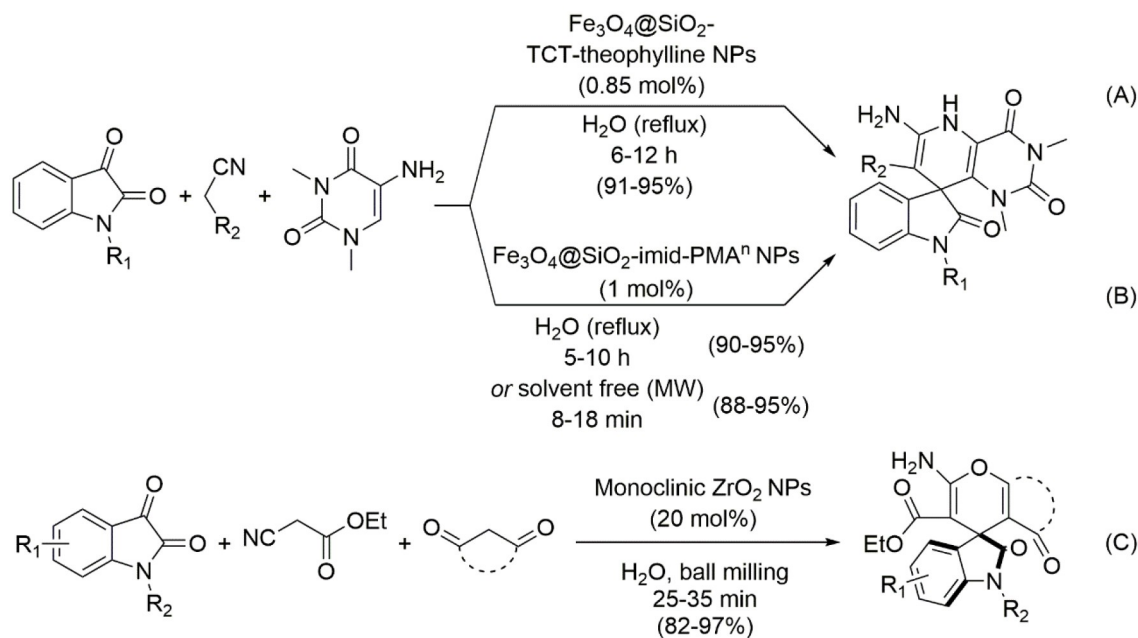
As previously described in this review, sodium acetate (NaOAc) has already proved its value as a catalyst in the 3-MCR approach involving a Knoevenagel reaction, Michael addition followed by cyclization. Elinson *et al.* reported the application of this method using bicyclic C–H acids to access spirooxindole derivatives. This interesting solvent free protocol uses isatin derivatives, malononitrile and three analogous bicyclic C–H acids: 4-hydroxy-2*H*-chromen-2-one, 4-hydroxyquinolin-2(1*H*)-one and 4-hydroxy-1-methylquinolin-2(1*H*)-one (Scheme 48A). Despite moderate substrate scope, the reaction is very fast, plus it is solvent-free.^[94] Following the same concept, the group of Bagchi *et al.* reported the same synthetic 3-MCR domino approach, using microwave conditions. With the aim to synthesize a family of spirobenzo [fused]chromene derivatives, urea was used as catalyst, under

microwave irradiation, affording the desired compounds with short reaction times (Scheme 48B). A good range of isatin substrates were investigated. Good reaction scope and chromatographic-free purification are among the main advantages of this methodology.^[95]

The use of iron NPs as successful catalysts in the synthesis of spiro[indoline-3,4'-pyran] derivatives with fused chromene units was already reported above. Esmaeilpour *et al.* reported the synthesis of theophylline supported on modified silica-coated magnetic nanoparticles (Fe₃O₄@SiO₂-TCT-theophylline) and their application in the 3-MCR synthesis of spirooxindole derivatives using isatin derivatives, malononitrile or ethyl cyanoacetate and 5-amino-1,3-dimethyluracil (Scheme 49A). The use of water as reaction medium is one of the advantages of the protocol, together with the easy separation of the catalyst from the crude reaction mixture by an external magnetic field. Reusability was also tested, showing that the nanomagnetic catalyst can be frequently applied in consecutive reactions (at least six runs) with no significant decrease in activity.^[96] The same group approached the same synthetic transformation to afford tetrahydro-2'*H*-spiro[indoline-3,8'-



Scheme 48. Synthesis of spiro-4*H*-pyran (A) and spirobenzo[fused]chromene (B) derivatives *via* three component Knoevenagel/Michael addition/cyclization route.



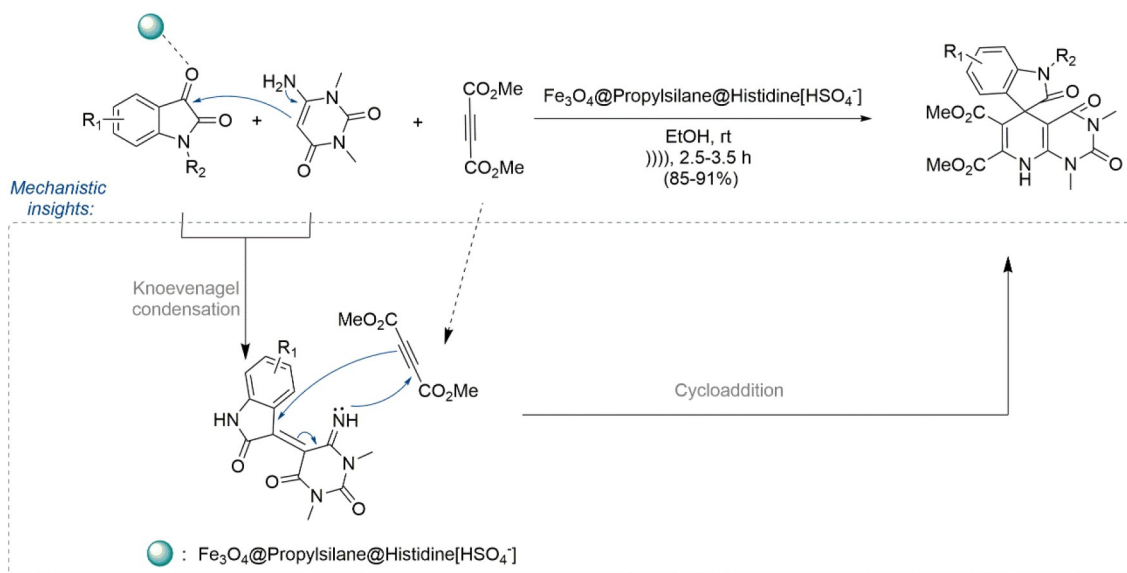
Scheme 49. Synthesis of spirooxindole derivatives using nanocatalysts.

pyrido[3,2-d]pyrimidine]-7'-carboxylate derivatives using other magnetic nanocatalysts. The particles of the nano-heteropolyacid $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ were synthesized and immobilized onto imidazole functionalized $\text{Fe}_3\text{O}_4@\text{SiO}_2$ NPs, establishing the $\text{Fe}_3\text{O}_4@\text{SiO}_2$ -imid-PMAⁿ magnetic porous nanosphere catalyst. Performing the 3-MCR using isatin derivatives, activated methylene precursors and 5-amino-1,3-dimethyluracil, in aqueous reaction medium under reflux conditions, the target products were obtained in good to excellent yields (24 examples - Scheme 49B). Furthermore, this synthetic transformation was also tested under microwave irradiation, with shorter reaction times in the absence of solvent, and the same desired compounds were obtained with similar yields. The protocol also works with other 1,3-dicarbonyl compounds.^[97]

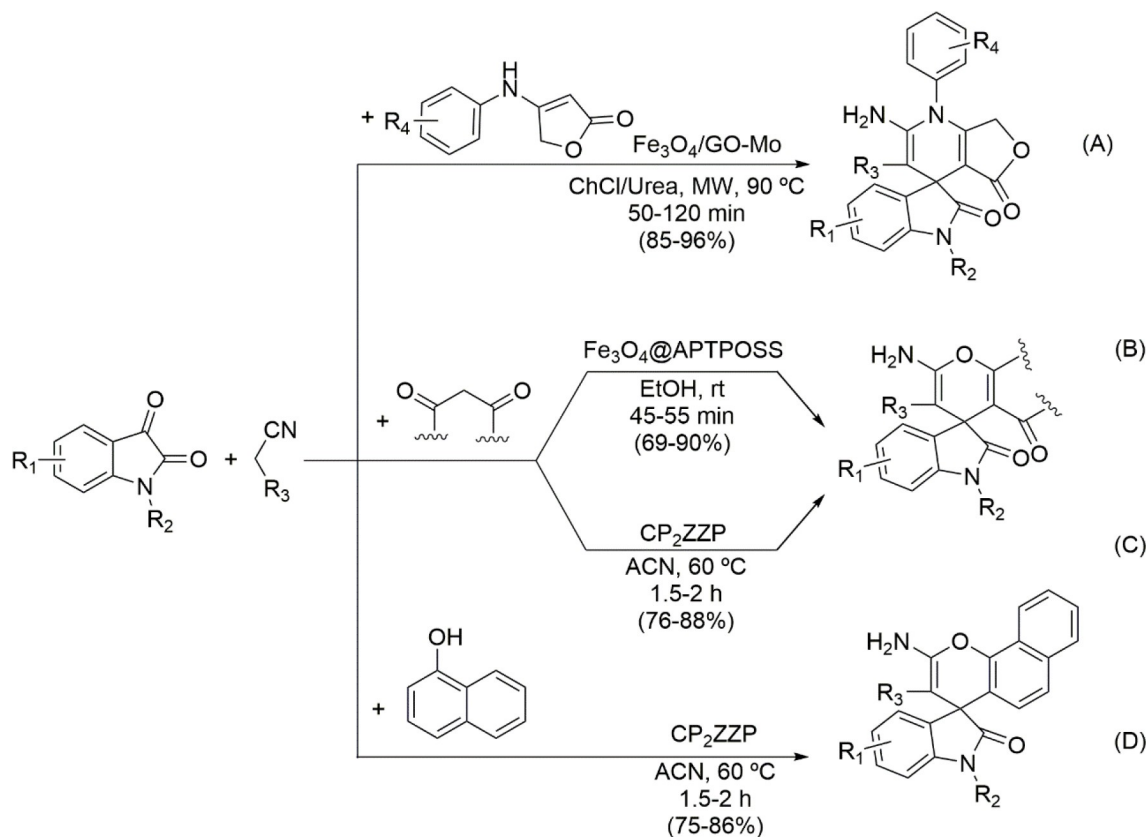
Bajpai *et al.* reported a synthetic approach to substituted spirooxindole derivatives through a monoclinic zirconia nanoparticle (ZrO_2 NPs) catalyzed one-pot 3-MCR of substituted isatin with 1,3-dicarbonyl compounds and ethyl cyanoacetate in a ball mill system (Scheme 49C). Good to excellent yields of the desired products were obtained with this protocol (18 examples), in which the authors optimized several reaction conditions, including catalyst loading, the effect of the ZrO_2 (bulk, mixed phase nano and single phase nano), the effect of the rotation frequency of the ball mill and the number of milling balls. The reusability of the catalyst was also tested, and it could be easily recovered by centrifugation, washed, dried and reused for a new run without significant loss of activity (up to ten runs).^[98]

Mousavifar *et al.* explored the synthesis of a novel small family of spiro[indoline-3,5'-pyrido[2,3-d]pyrimidine compounds (8 examples) *via* condensation of dimethyl acetylene dicarboxylate, isatin derivatives and 6-amino-1,3-dimethyluracil using $\text{Fe}_3\text{O}_4@\text{Propylsilane}@\text{Histidine}[\text{HSO}_4^-]$ as a magnetic heterogeneous catalyst under reflux and ultrasound conditions (Scheme 50). The reactions were carried out under ultrasound irradiation and furnished the products with excellent yields in shorter reaction times, even when compared to conventional heating. This green methodology allowed the easy recovery and reuse of the catalyst, as well as easy purification of the spirooxindole derivatives, without the requirement of tedious work-up procedures. As regards the mechanism, this MCR is believed to involve a Knoevenagel condensation and a cycloaddition reaction as outlined in Scheme 50.^[99]

Zhang *et al.* prepared a new magnetic nanocatalyst based on molybdenum that was immobilized onto $\text{Fe}_3\text{O}_4/\text{Graphene oxide}$ ($\text{Fe}_3\text{O}_4/\text{GO}-\text{Mo}$) and was used for the synthesis of interesting spirooxindole-dihydropyridines in a one-pot 3-MCR manner using isatin, malononitrile and anilinolactones in the deep eutectic solvent (DES) choline chloride (ChCl)/urea under microwave irradiation (Scheme 51A). The new $\text{Fe}_3\text{O}_4/\text{GO}-\text{Mo}$ catalyst was fully characterized by X-ray diffraction, scanning electron microscopy, FTIR, and vibrating sample magnetometry techniques. The reaction conditions were optimized by screening catalyst loading, temperature and solvents. In addition to the already mentioned easy recovery of



Scheme 50. Synthesis of new spiro[indoline-3,5'-pyrido[2,3-d]pyrimidine] derivatives catalyzed by magnetic NPs $\text{Fe}_3\text{O}_4@Propylsilane@Histidine[HSO_4^-]$ under ultrasonic irradiation.



Scheme 51. Synthesis of spirooxindole derivatives using various heterogeneous catalysts.

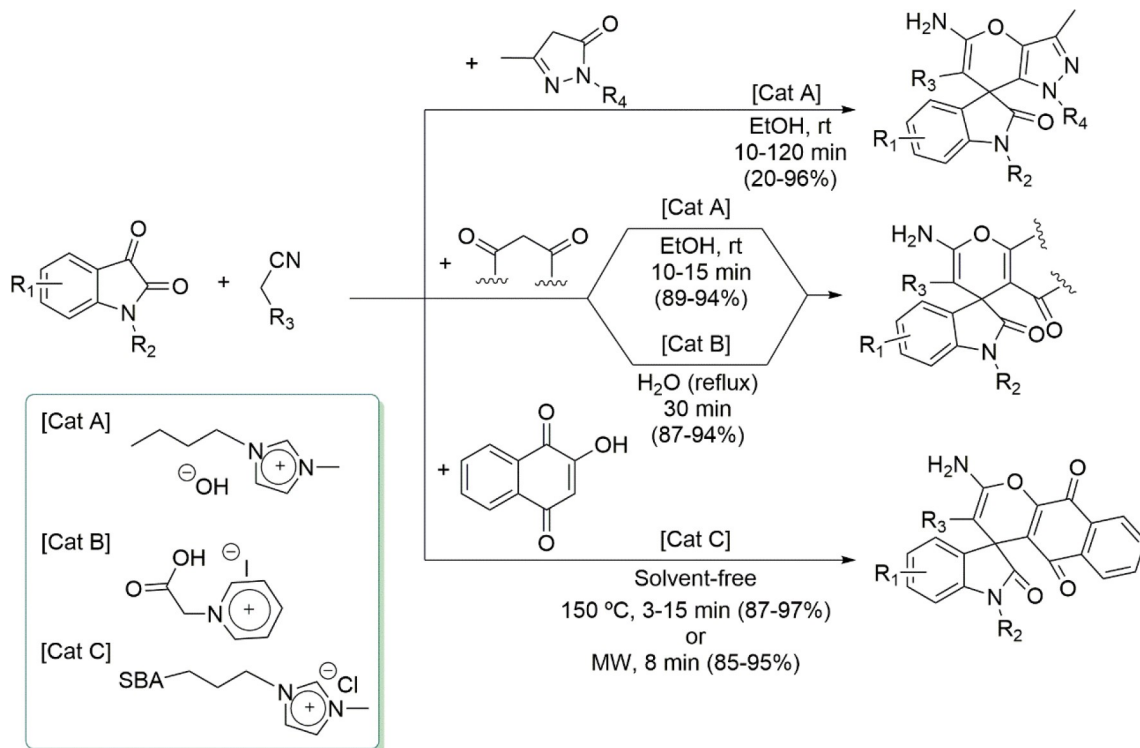
magnetic heterogeneous catalysts, the DES solvent could also be recovered and recycled, improving the sustainability of this methodology. The catalytic activity of the heterogeneous catalyst was also evaluated over 8 cycles, and gratifyingly no loss of activity was observed.^[100]

In another example of Fe_3O_4 magnetic NPs-based catalysis, Safaei-Ghomi *et al.* developed a new heterogeneous catalyst by coating these NPs with polyhedral oligomeric silsesquioxanes with eight triethoxysilane arms (APTPOSS). The full characterization of this catalyst showed that it presents several advantages, such as high surface area and internal organic content. Its catalytic activity was explored in the one-pot 3-component reaction between isatin, malononitrile and dime-done or 4-hydroxy-coumarin or barbituric acids, affording spirooxindole 2-amino-pyrano-3-carbonitrile derivatives, in very good yields (Scheme 51B). Furthermore, the aminopropyl groups display a strong catalytic activity, justifying the low catalyst loading required. This heterogeneous inorganic-organic hybrid catalyst was evaluated in relation to its recovery and recyclability in 8 consecutive runs, without loss of its catalytic activity.^[101]

Pradhan and Mishra described a new versatile $\text{Cs}_x\text{H}_{3-x}\text{PW}_{12}\text{O}_{40}$ -ZZP nanocomposite systems, based on cesium exchanged phosphotungstic acid ($\text{Cs}_x\text{H}_{3-x}\text{PW}_{12}\text{O}_{40}$) NPs dispersed in Zr-pillared-alpha-zirconium phosphate (ZZP)

material as heterogeneous catalyst for the synthesis of a wide diversity of spirooxindole derivatives. After the determination of best reaction conditions to achieve the highest catalytic performance, 11 spirooxindole derivatives were synthesized *via* 3-MCR of isatin, malononitrile, 1,3-dicarbonyl compounds/naphthol (Scheme 51C and D). Very good yields were obtained in a short reaction time and under mild conditions. The $\text{Cs}_x\text{H}_{3-x}\text{PW}_{12}\text{O}_{40}$ -ZZP catalyst was recovered and reused for three cycles without significant loss of the catalytic activity.^[102]

Padvi *et al.* developed an environmentally benign methodology based on the 3-MCR of isatin, malononitrile and carbonyl compounds containing a reactive alpha-methylene group, using the ionic liquid, 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH), as catalyst. This methodology enabled the synthesis of spirooxindole systems, with excellent yields and short reaction times (Scheme 52, [Cat A]). The [bmim]OH catalyst could easily be recycled by separation of the products, and the catalyst-solvent system could be reused up to five runs without significant loss of catalytic activity (the yield dropped from 96 to 84%). Another advantage of this methodology is the isolation of the desired products by a simple filtration and washing with ethanol, without the need for chromatography and/or recrystallization. This MCR consists of a domino Knoevenagel/Michael addition/cyclization reaction. The [bmim]OH catalyst mediates the Knoeve-



Scheme 52. Synthesis of spirooxindoles in the presence of different ionic liquid based catalysts.

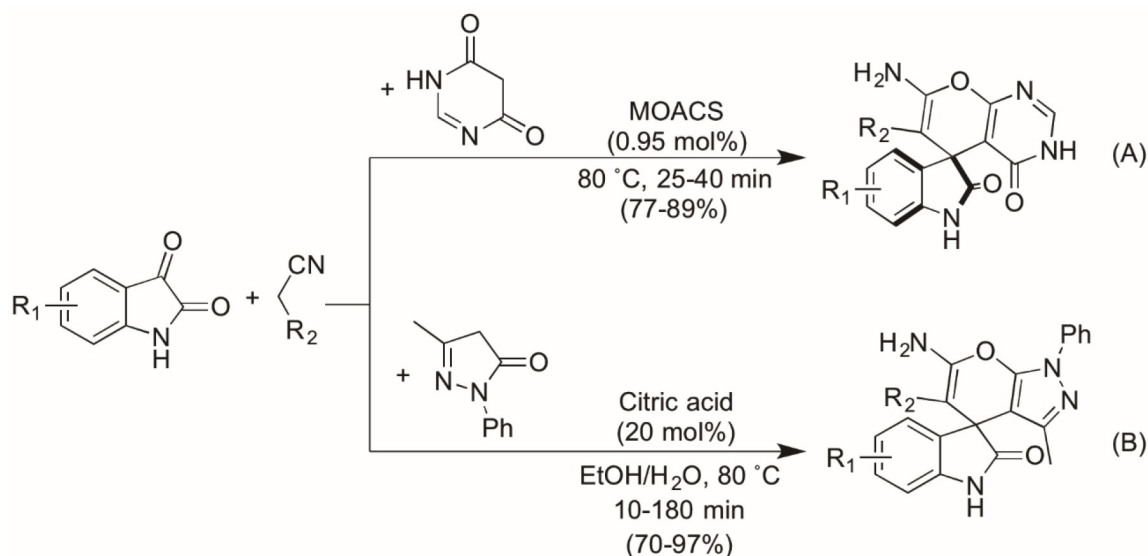
nagel and Michael-Addition reactions, with the hydroxyl group playing an important role in the reactions, as in the first reaction it will deprotonate the malononitrile, while the hydrogen from the imidazolium will activate the C-3 carbonyl from isatin forming the Knoevenagel adduct. In the case of the Michael addition the hydroxyl group will catch the proton from the active methylene group, furnishing the intermediate for the reaction.^[103]

Almost simultaneously, Moosavi-Zare *et al.* introduced another ionic liquid, based in nanostructured pyridinium salt, 1-(carboxymethyl)pyridinium iodide ([cmpy]I) as catalyst for the synthesis of a wide range of spirooxindole derivatives. The one-pot domino Knoevenagel/Michael addition/cyclization reaction of isatin derivatives, malononitrile, and 1,3-dicarbonyl compounds (Scheme 52, [Cat B]) in water under reflux conditions, afforded the desired products in short reaction times and very good yields (25 examples). This new green catalyst presented a better catalytic performance than $\text{InCl}_3/\text{SiO}_2$, β -cyclodextrin, ethylenediamine and TBAB catalysts, allowing the reaction to occur in shorter reaction times, higher yields and turn-over frequency (TOF). The catalyst system could easily be recycled over 4 runs, maintaining the same catalytic activity.^[104]

Ziarani *et al.* functionalized the SBA-15 mesoporous material with *N*-methyl-*N*-propyltrimethoxysilyl imidazolium chloride to provide SBA-IL, an heterogeneous catalyst for the synthesis of pyranonaphthoquinone-fused spirooxindoles *via* one-pot 3-MCR of isatin derivatives, activated methylene reagents, and 2-hydroxy-1,4-naphthoquinone (Scheme 52, [Cat C]). These reactions were carried out under conventional heating and microwave irradiation conditions, with both

furnishing the desired products in excellent yields. The protocol under microwave irradiation was considered more advantageous, as it allows short reaction times and milder reaction conditions. The scope of the reaction was narrower, however the authors reported a new compound with the substituents $\text{R}_1 = \text{H}$, $\text{R}_2 = 5\text{-I}$ and $\text{R}_3 = \text{CN}$, that was obtained in 90% yield under microwave irradiation and 94% under conventional heating. This catalyst could be recycled and reused up to 4 times maintaining its catalytic efficiency. The authors developed a sustainable protocol for this reaction, due to the high yields, easy work-up and solvent-free conditions.^[105]

Ahmadkhani *et al.* prepared a nearly neutral but protic, chiral room temperature ionic liquid *via* neutralization of (1*S*)-(+)-camphor-10-sulfonic acid with *N,N*-dimethyl-*n*-octylamine and used it successfully as a catalyst in the synthesis of novel pyrimidine-fused spiro[indoline-3,4'-pyran]s. The prepared *N,N*-dimethyl-*n*-octylammonium camphor-10-sulfonate (MOACS, the chiral ionic liquid) was used in a MCR approach, using 4,6(1*H*,5*H*)-pyrimidinedione as 1,3-dicarbonyl compound, in a Knoevenagel/Michael addition/cyclization reaction, obtaining the respective spirooxindole derivatives in good yields and excellent enantioselectivities (Scheme 53A). The reaction tolerates several substituents in the aromatic ring of isatin and also the use of malononitrile and ethyl cyanoacetate. The solubility of MOACS in water facilitates the separation from the reaction mixture by a simple aqueous extraction and also the reusability was guaranteed up to 5 cycles in terms of catalytic activity (but with a significant loss of asymmetric induction after the fifth catalytic cycle: the *ee* decreased by 70%).^[106] Karimi-Jaberi *et al.* showed that by



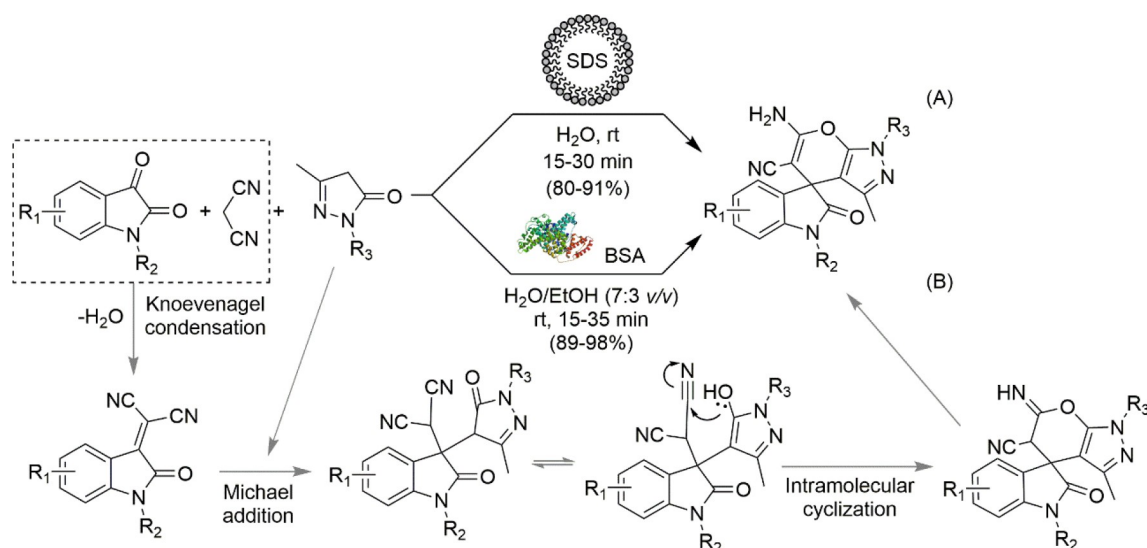
Scheme 53. Use of uncommon C–H activated acids in the 3-MCR involving the domino Knoevenagel/Michael addition/cyclization.

using 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, isatin derivatives, and malononitrile or ethyl cyanoacetate, the corresponding spirooxindole derivatives could be obtained in good to excellent yields and in short reaction times, in aqueous ethanol, using the commonly available and cheap citric acid as catalyst (Scheme 53B). Other C–H activated acids like dimedone, barbituric acid and 4-hydroxy coumarin were also tested successfully with this simple protocol.^[107]

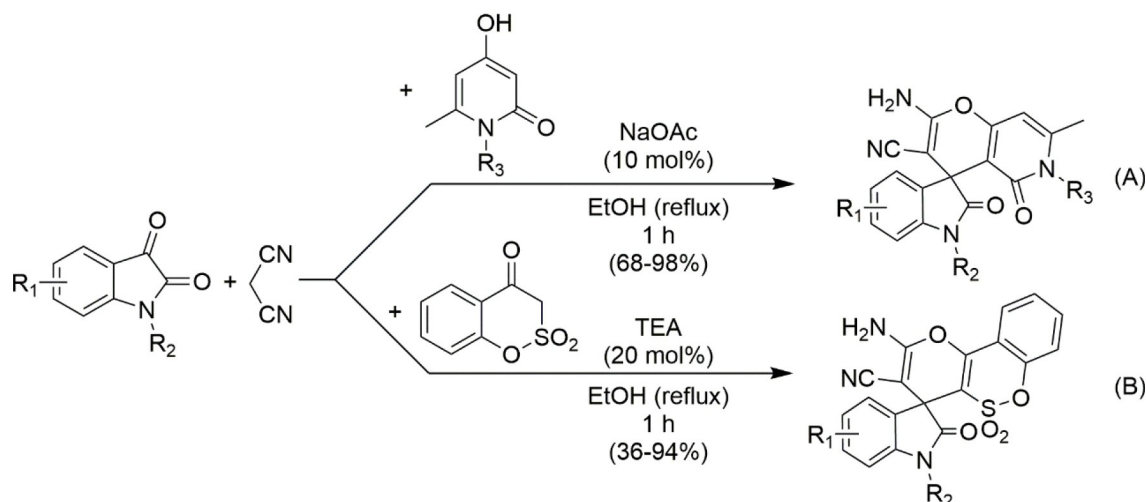
The use of 3-methyl-1*H*-pyrazol-5(4*H*)-ones as reagents in the 3-MCR involving the domino Knoevenagel/Michael addition/cyclization was also explored by two research groups, that used two different catalysts to undergo suitable and effective protocols. Devi *et al.* reported the use of sodium dodecyl sulfate (SDS) as a micellar catalyst, in water at room temperature, to get the spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazoles] in good yield (Scheme 54A). SDS is commercially available, very cheap, nontoxic and easy to handle. The reaction between isatins, malononitrile, and 3-methyl-1*H*-pyrazol-5(4*H*)-one derivatives runs very smoothly, with short reaction times. A plausible reaction mechanism was reported by the authors (as shown in Scheme 54), where the domino Knoevenagel/Michael addition/cyclization reaction occurs with the help of the surfactant catalyst, and corresponding formation of micelles in water. Due to the micelles hydrophobic core, the reagents can be easily solubilized in the interior of these structures and this proximity is the driving force for the 3-MCR. In addition, this also enhances the dehydration step during the Knoevenagel condensation and accelerates the nucleophilic addition of the 3-methyl-1*H*-pyrazol-5(4*H*)-one derivatives. A simple work-up procedure consisting of a filtration allows the isolation of the spiroox-

indole reaction products (11 examples), and SDS can be reused up to four cycles without significant differences in reaction times and product yields.^[108] The enzyme bovine serum albumin (BSA) was evaluated by Dalal *et al.* as an efficient catalyst in the synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives (10 examples). This biocatalytic approach showed a good tolerance towards several isatin derivatives and 3-methyl-1*H*-pyrazol-5(4*H*)-one derivatives, in aqueous ethanolic reaction medium, at room temperature and in short reaction times (Scheme 54B). This methodology allows an easy work-up procedure (no chromatography required) and the desired spirooxindole derivatives were obtained in good to excellent yields. The BSA remains in the water phase, which can be reused for three runs with no significant loss of activity.^[109]

The group of Elinson *et al.* reported the synthesis of spiro[indoline-3,4'-pyrano[3,2-*c*]pyridine]-2,5'(6'*H*)-diones using the 3-MCR of isatins, malononitrile, and 4-hydroxy-6-methylpyridin-2(1*H*)-ones, and the alternative C–H activated acid in this common reaction protocol. The methodology is very straightforward and uses NaOAc as catalyst and ethanol as solvent (Scheme 55A). The desired spirooxindole derivatives were obtained in moderate to excellent yields, with moderate reaction scope (only 7 examples were reported).^[110] Recently, Grygoriv *et al.* reported a similar synthetic transformation to get access to new spiro-condensed 2-amino-4*H*-pyrans (14 examples) in low to excellent yields, using isatin derivatives, malononitrile, and 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (Scheme 55B). This was in fact the first application of this reagent in multicomponent reactions. This 3-MCR of equimolar amounts of the described reagents was carried out in the



Scheme 54. Synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives using two different catalysts: a surfactant and an enzyme.



Scheme 55. Synthesis of new spirooxindole derivatives with uncommon C–H activated acids.

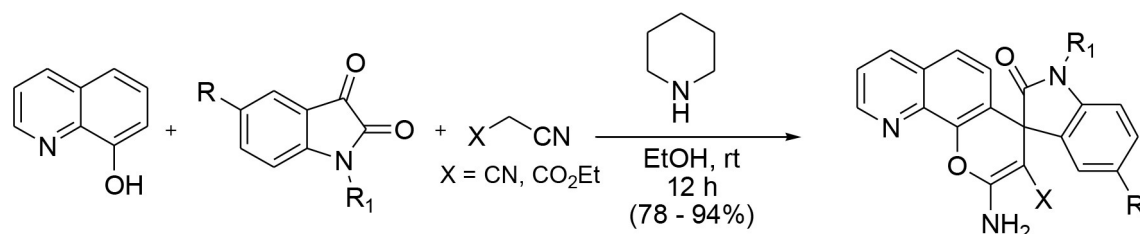
presence of triethanolamine (TEA) as the catalyst, in refluxing ethanol.^[111]

Shi *et al.* reported a new synthetic methodology for the preparation of functionalized spiro[indoline-3,4'-pyrano[3,2-*b*]quinoline] derivatives (15 examples), in very good yields. This green methodology occurs *via* one-pot 3-MCR of 8-hydroxyquinoline, isatin derivatives and malononitrile or ethyl cyanoacetoacetate, promoted by the presence of piperidine as organic base in equimolar amounts (Scheme 56). The authors compared the piperidine with other organic bases, such as triethylamine, DABCO or DBU in this multicomponent reaction, and all of them furnished the desired product in lower yields. Furthermore, the application of lower quantities of piperidine led to a decrease in reaction performance. Essentially, it is believed that this MCR goes through a condensation (to the isatin 3-oxo group), Michael addition, cyclization (amino-imine tautomerization) reactions sequence.^[112]

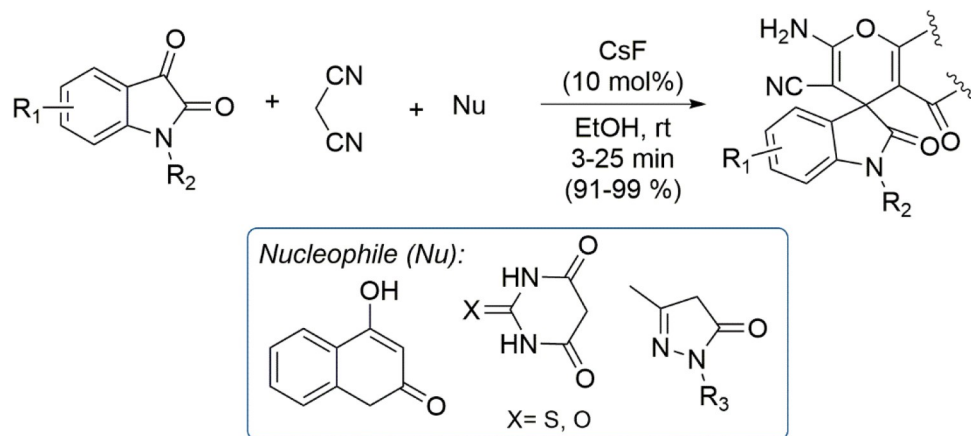
Wagh *et al.* described a new, rapid and versatile methodology for the synthesis of a wide variety of spirooxindole-pyran derivatives (27 examples). The inorganic base CsF was used as catalyst, by activating the carbonyl group. The library was

obtained through the one-pot 3-MCR of isatins, malononitrile and 4-hydroxycoumarin, 1,3-dimethylbarbituric acid, thiobarbituric acids, 1-phenyl-3-methyl-5-pyrazolone or 3-methyl-2-pyrazolin-5-one, in the presence of CsF under mild reaction conditions (Scheme 57). All compounds were prepared with excellent yields in shorter reaction times. Moreover, the final products were obtained by simple filtration, without requiring chromatographic purification.^[113]

The use of Lewis acids as efficient catalysts to promote the formation of new carbon-carbon and carbon-heteroatom bonds has been of great interest in organic synthesis. Also, in the three-component domino reaction that have been discussed extensively in this review, like the Knoevenagel/Michael addition/cyclization for the synthesis of spirooxindole derivatives with six-member rings. Their catalytic action is generally based on the Lewis acid activation of the carbonyl group. The use of mild and nontoxic molecular iodine as Lewis acid catalyst for the synthesis of spirooxindoles was reported by two different groups. Zhang *et al.* explored the synthesis of spirochromeno[4,3-*b*]indoline derivatives, exploring a wide scope of substrates, which included isatin and 4-hydroxycoumarins derivatives and different cyclic 1,3-dicarbonyl com-



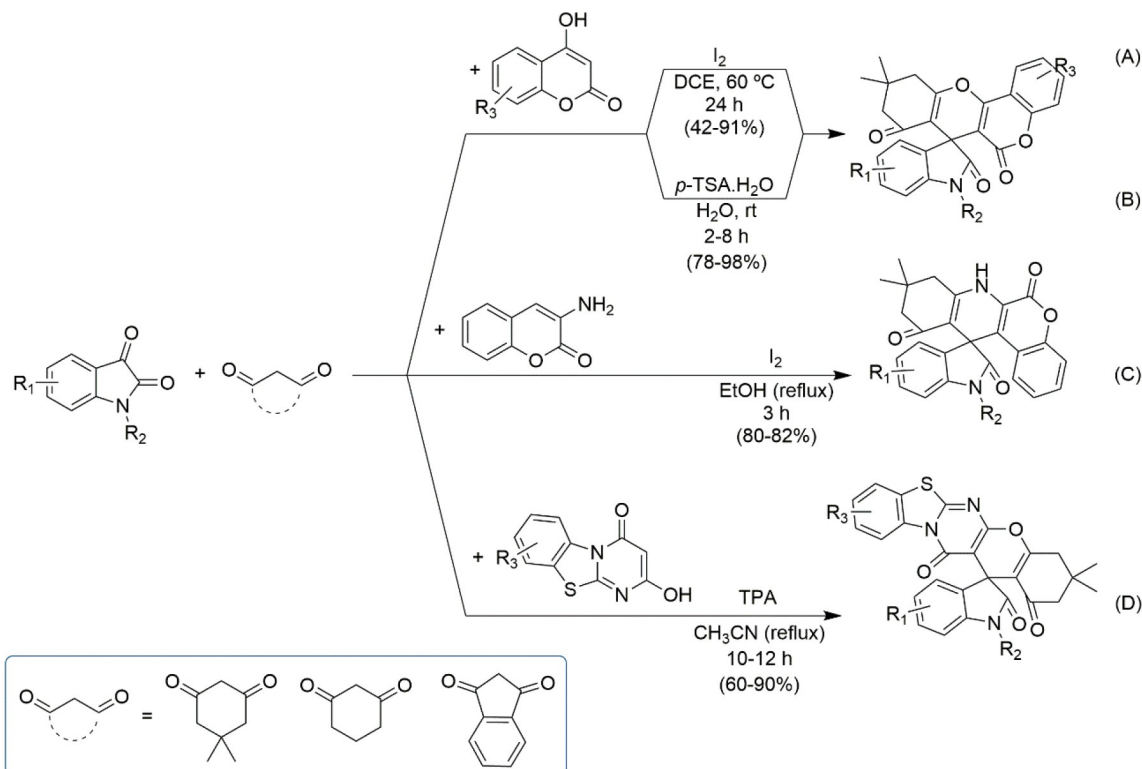
Scheme 56. Synthesis of functionalized spiro[indoline-3,4'-pyrano[3,2-*b*]quinoline] in the presence of equimolar amounts of piperidine.



Scheme 57. Synthesis of spirooxindole-pyran derivatives catalyzed by CsF.

pounds (Scheme 58A). They synthesized 25 examples *via* a 3-MCR in dichloroethane under reflux conditions, furnishing the desired products in moderate to very good yields (42–91%).^[114] In the case of the synthesis of spirochromeno[3,4-*b*]quinoline derivatives, Khan *et al.* addressed the reaction between isatin derivatives, cyclic 1,3-diketones and 3-amino-coumarins in the presence of the same catalyst, under refluxing

ethanol to afford the desired nitrogen-containing six-membered spirooxindole derivatives (Scheme 58C). Despite short reaction time and good yields, unfortunately, the authors only reported two examples of the desired compounds, demonstrating the poor scope of this route. Nonetheless, the protocol proved its efficiency by using aldehydes instead of isatins.^[115]



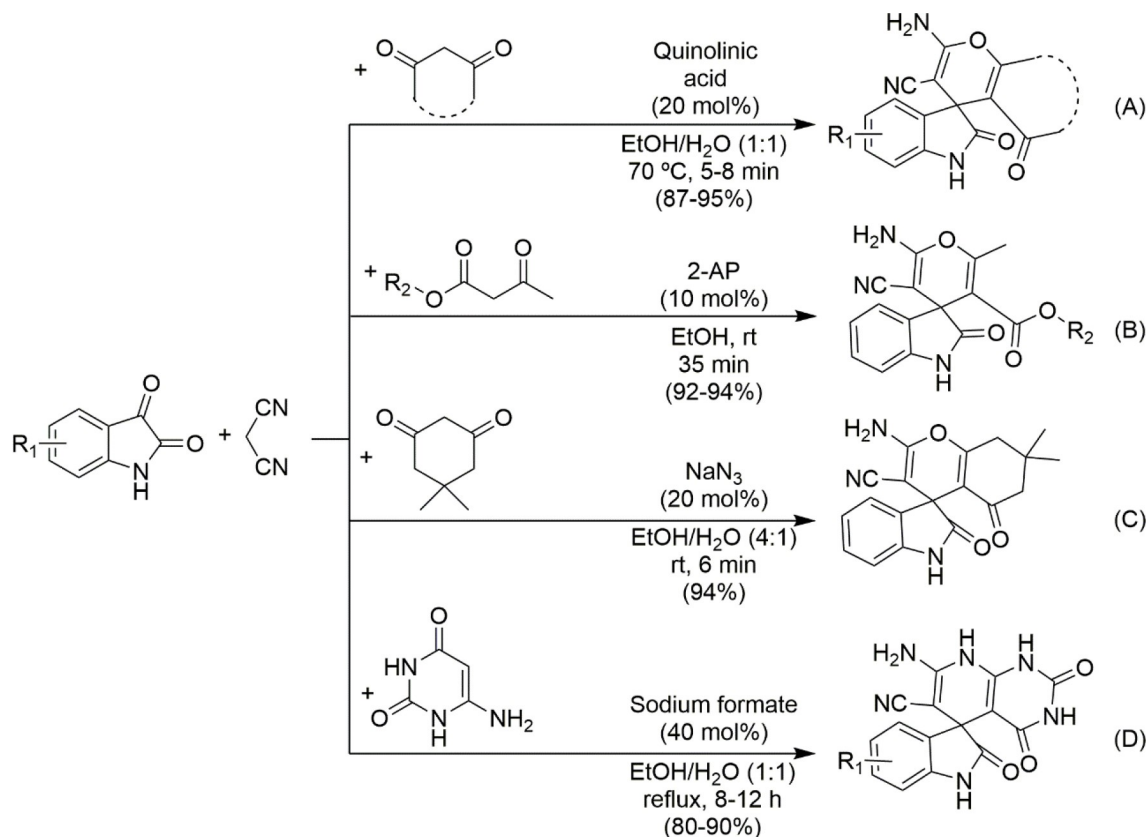
Scheme 58. Use of Lewis acid catalysts in the synthesis of *N*- and *O*-containing spirooxindole frameworks.

Shortly after, Kumar *et al.* explored the use of a different Lewis acid catalysts in the three-component synthesis of spirochromeno indoline-triones, demonstrating that *p*-toluenesulphonic acid (*p*-TSA.H₂O) gave the best reaction yields using water as solvent (Scheme 58B). A good reaction scope (14 examples) and simple work-up process (only filtration without chromatographic techniques) are the main advantages of this synthetic methodology.^[116]

The use of Lewis acid catalysts could also be useful in the synthesis of spirooxindole derivatives with a chromeno fused spiro-ring. Jannati *et al.* demonstrated that isatin derivatives, cyclic 1,3-diketones and 2-hydroxy-4*H*-benzo[4,5]thiazolo [3,2-*a*]pyrimidin-4-ones undergo a 3-MCR to produce novel spiro[benzo[4,5]thiazolo[3,2-*a*]chromeno[2,3-*d*]pyrimidine-14,3'-indoline]-1,2',13(2*H*)-trione derivatives using tungstophosphoric acid (H₃PW₁₂O₄₀, TPA) as catalyst (Scheme 58D). This strong acid catalyst was the best choice to perform this domino Knoevenagel/Michael addition/cyclization reaction sequence, affording the desired and interesting new spirooxindole derivatives with good reaction scope (10 examples) and moderate to good yield.^[117]

Using organocatalysts (Brønsted based acids/bases) to promote this type of reaction also became a popular approach among researchers. For example, Oudi *et al.* used inexpensive quinolinic acid to afford spirooxindole derivatives (7 examples) in very good to excellent yields and short reaction times (Scheme 59A).^[118] 2-Aminopyridine (2-AP) also exhibited good catalytic activity in this 3-MCR, although the reaction scope reported by Lalitha and co-workers was limited (only 2 examples reported) (Scheme 59B).^[119] The same research group prepared one spirooxindole applying sodium azide as catalyst (the scope of the reaction was directed to aldehydes, rather than isatins) (Scheme 59C).^[120] Nurjamal and Brahmachari used sodium formate to prepare a small library of spiro [indoline-3,5'-pyrido[2,3-*d*]pyrimidine] derivatives (7 examples) (Scheme 59D). Despite the high catalyst load required, this methodology presents several advantages, as this catalyst is cheap and non-toxic.^[121]

The synthesis of nitrogen-containing six-member spiro rings was reported by several other research groups using the same 3 component Knoevenagel/Michael addition/cyclization approach with isatins, C-H activated acids and amino reagents. For instance, Jadhav *et al.* used 1*H*-indazole-3-amino

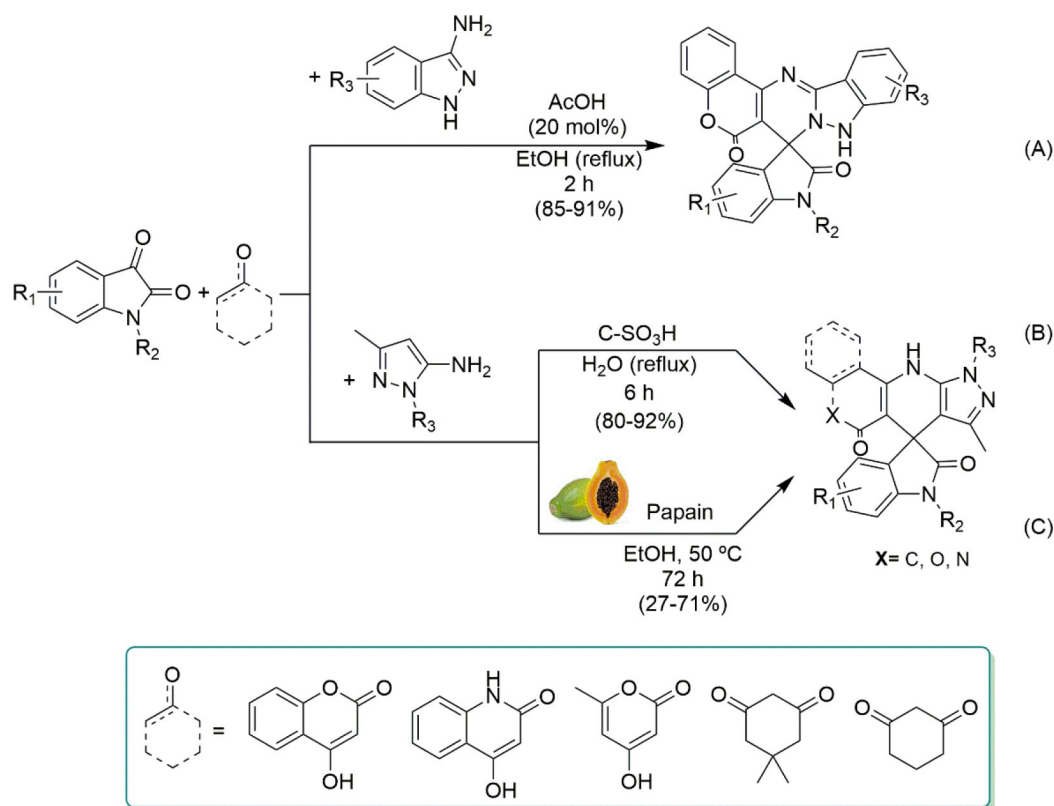


Scheme 59. Use of different organocatalysts in the preparation of *N*- and *O*-containing spirooxindole frameworks.

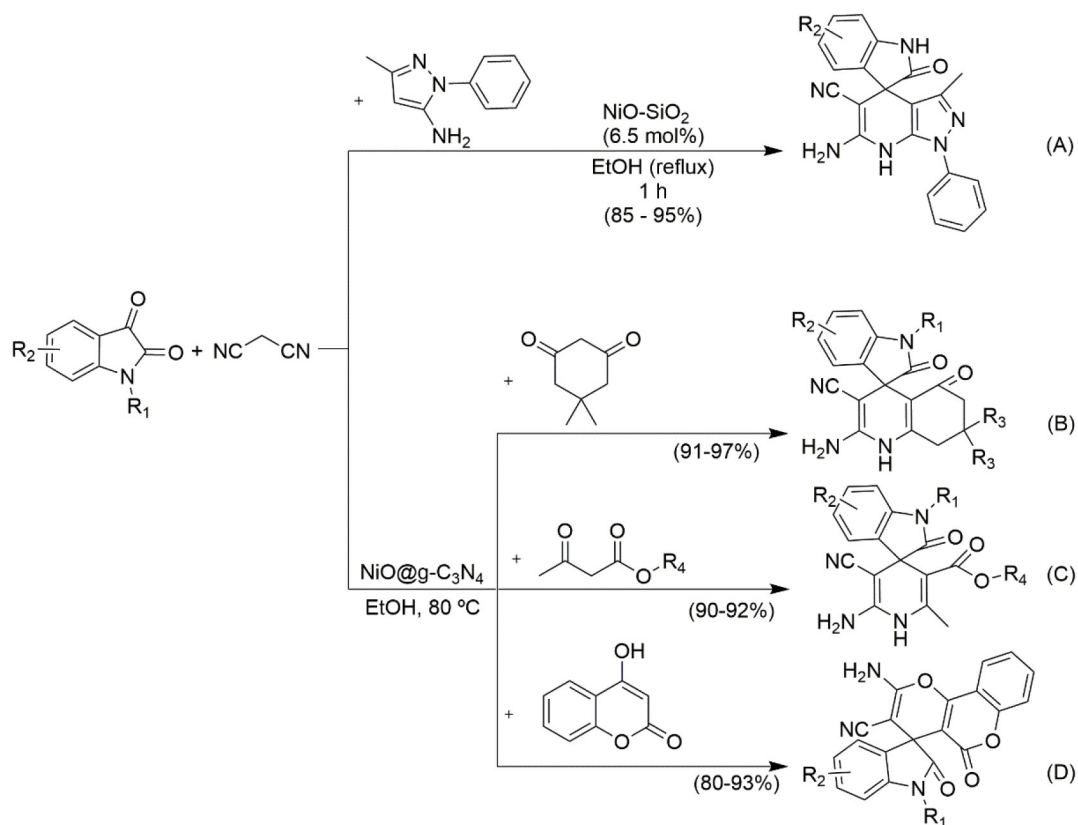
reagent, in the presence of acetic acid (AcOH) as catalyst in EtOH to get spiro[chromeno[4',3':4,5]pyrimido[1,2-*b*]indazole-7,3'-indoline]-2',6(9*H*)-dione derivatives (Scheme 60A). Short reaction times, good to excellent yields and good scope (18 examples), as well as simple work-up procedures are the main advantages of this methodology.^[122] Li and Zhang reported also a similar protocol to access spirooxindole-fused pyrazolopyridine derivatives using 3-methyl-1*H*-pyrazol-5-amine derivatives, together with isatins and several C–H activated acids with the solid acid (C-SO₃H) as catalyst (Scheme 60B). After establishing the optimal conditions (refluxing water) the scope of the reaction was expanded, proving the efficiency of the method when 4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-hydroxyquinolin-2(1*H*)-one and 4-hydroxy-2*H*-chromen-2-one were used (22 examples). The catalyst could be easily recovered from the reaction medium by filtration and reused up to at least five times without significant loss in activity.^[123] Enzymatic catalysis was tested by Liang *et al.* in the synthesis of similar spiro[pyrazolo[3,4-*b*]pyridines derivatives. To establish a simple and eco-friendly methodology, several hydrolytic enzymes (including lipases from different origins, α -amylase, among others) were investigated in the domino Knoevenagel/Michael

addition/cyclization reaction for the synthesis of spirooxindoles. After several reaction condition screenings, they found that the enzyme papain could catalyze efficiently this one-pot domino reaction, using ethanol as solvent, with several substituted isatins, 3-methyl-5-amino-pyrazoles and cyclic-1,3-diketones being tested as substrates (Scheme 60C). Despite high reaction time, a small library of 9 compounds was obtained using this protocol, in moderate yields.^[124]

Another methodology was designed by Yagnam *et al.* for the synthesis of thirteen spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridine]-5'-carbonitrile derivatives, which were prepared, in very good yields, by one-pot 3-MCR of isatin, 5-amino-3-methylpyrazole and malononitrile catalyzed by NiO-SiO₂ in refluxing ethanol (Scheme 61A). The catalyst was synthesized and characterized by several structural and morphological techniques. This methodology showed good substrate scope, short reaction times, easy recovery and reusability of the heterogeneous catalyst, but unfortunately, the catalytic activity dropped significantly after 6 cycles (from 75% in the fifth cycle to 55% in the sixth cycle). The putative pathway for this multicomponent reaction was through a well-established Knoevenagel condensation/Michael addition/cyclization-isomerization mediated by a Lewis acid.^[125]



Scheme 60. Synthesis of six-membered *N*-containing spiro-ring using different catalysts in the 3-MCR.



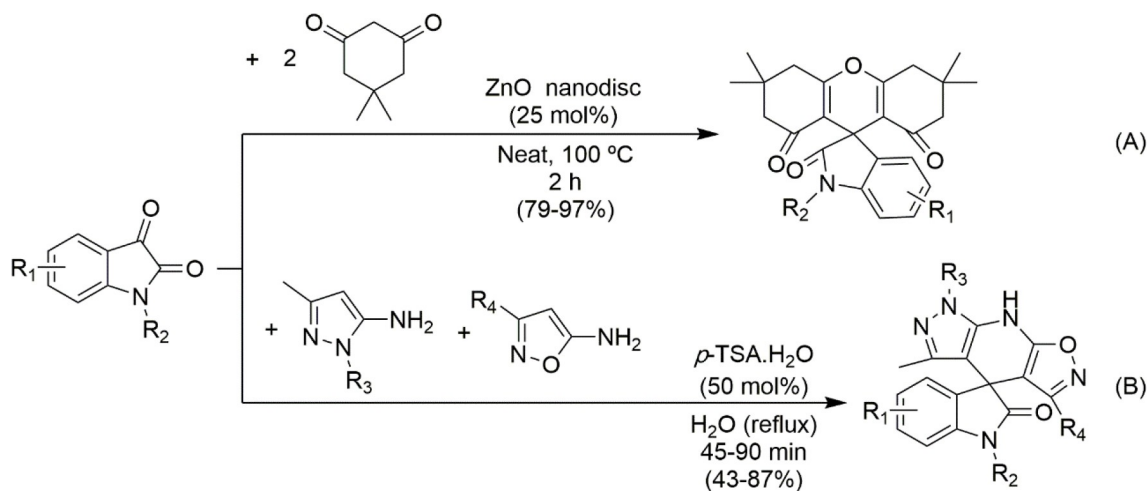
Scheme 61. Synthesis of spirooxindoles derivatives catalyzed by heterogeneous NiO, an acid Lewis.

Also, Moqadam *et al.* developed a new heterogeneous catalyst based on NiO NPs immobilized on graphite carbon nitride nanosheets (NiO@g-C₃N₄) for the one-pot synthesis of spirooxindoles derivatives. Isatin derivatives, malononitrile and dimedone (Scheme 61B), ethyl acetoacetate (Scheme 61C) or 4-hydroxycoumarin (Scheme 61D) were refluxed in ethanol, in the presence of 50 mg of NiO@g-C₃N₄ over less than seven minutes. Using this protocol, it was possible to synthesize 26 spirooxindole derivatives with excellent yields and without the need of tedious chromatographic purification. Furthermore, this catalyst could be recovered and reused up to 6 runs without loss of its catalytic efficiency. The great performance of this catalyst was probably achieved due to the homogenous distribution of the NiO NPs and their stabilization by the graphite carbon nitride nanosheets, which makes the NiO NPs more accessible on the surface of the material and therefore more available to catalyze the reaction.^[126]

Kothandapani *et al.* reported the synthesis of zinc oxide (ZnO) nanodiscs using a simple and elegant precipitation protocol. After full characterization, the Lewis acidic nature of the ZnO was tested using these ZnO nanodiscs in a pseudo 3-MCR with isatin derivatives and dimedone (2 equivalents), under solvent-free conditions at 100 °C (Scheme 62A). ZnO

has a Lewis basic nature due to the presence of oxyanions on the ZnO surface, and these oxyanions are capable of capturing the acidic protons from the active methylene group of the dimedone molecules for the MCR. Other ZnO morphologies (such as nanoflakes and nanoplatelets) were tested under similar synthetic conditions, but lower yields of the desired xanthene derivatives (7 examples) were obtained. This might be explained by the fact that ZnO nanodiscs have more catalytically active sites present on their surface.^[127] In the search for new biologically relevant heterocyclic molecules, the group of Kalita *et al.* decided to use the above mentioned *p*-TSA.H₂O as catalyst to provide the synthesis of spiro [oxindoline-3,4'-isoxazo[5,4-*b*]pyrazolo[4,3-*e*]pyridines] using water as solvent, under reflux conditions (Scheme 62B). Briefly, several isatins, 5-aminopyrazoles and 5-aminoisoxazoles react in a condensation 3-MCR in the presence of *p*-TSA.H₂O as catalyst, showing good reaction scope (15 examples) and moderate to good yields of the desired spirooxindole derivatives. The method is based upon the concept of molecular hybridization where two C–C bonds and one C–N bond are formed in a single reaction.^[128]

Pathan *et al.* reported the first one-pot 3-MCR for the synthesis of spirooxindoles through sp³ C–H activation of 2-



Scheme 62. Synthesis of novel spirooxindole derivatives with slightly different 3-MCR approaches.

methyl azaarenes, malononitrile and isatins, catalyzed by dodecatungstophosphoric acid immobilized onto silica (DTP/SiO₂). The scope of the reaction is limited, with only 8 examples reported, but with very good yields (up to 92%). The plausible mechanism proposed by the researchers (Scheme 63) involves (a) the formation of the Knoevenagel adduct A by the condensation of isatin and malononitrile; (b) the protonation of 2-methyl benzimidazole over DTP/SiO₂ catalyst (intermediate B), and (c) formation of the enamine C by C–H bond cleavage. The intermediates A and C react *via* a Michael addition, cyclization and finally an isomerization (1,3-hydrogen shift) to obtain the spirooxindole framework.^[129]

Pelit designed a very small family of spirooxindoles derivatives containing an isoxazole unit in its structure. For the synthesis of these compounds, Pelit developed a suitable, one-pot 3-MCR protocol involving isatin, β -diketones and 5-amino-3-methylisoxazole catalyzed by the (\pm)-camphor-10-sulfonic acid (CSA), as nontoxic organocatalyst, under ultrasound irradiation, furnishing the desired products (4 examples) in very good yields and short reaction times (Scheme 64).^[130]

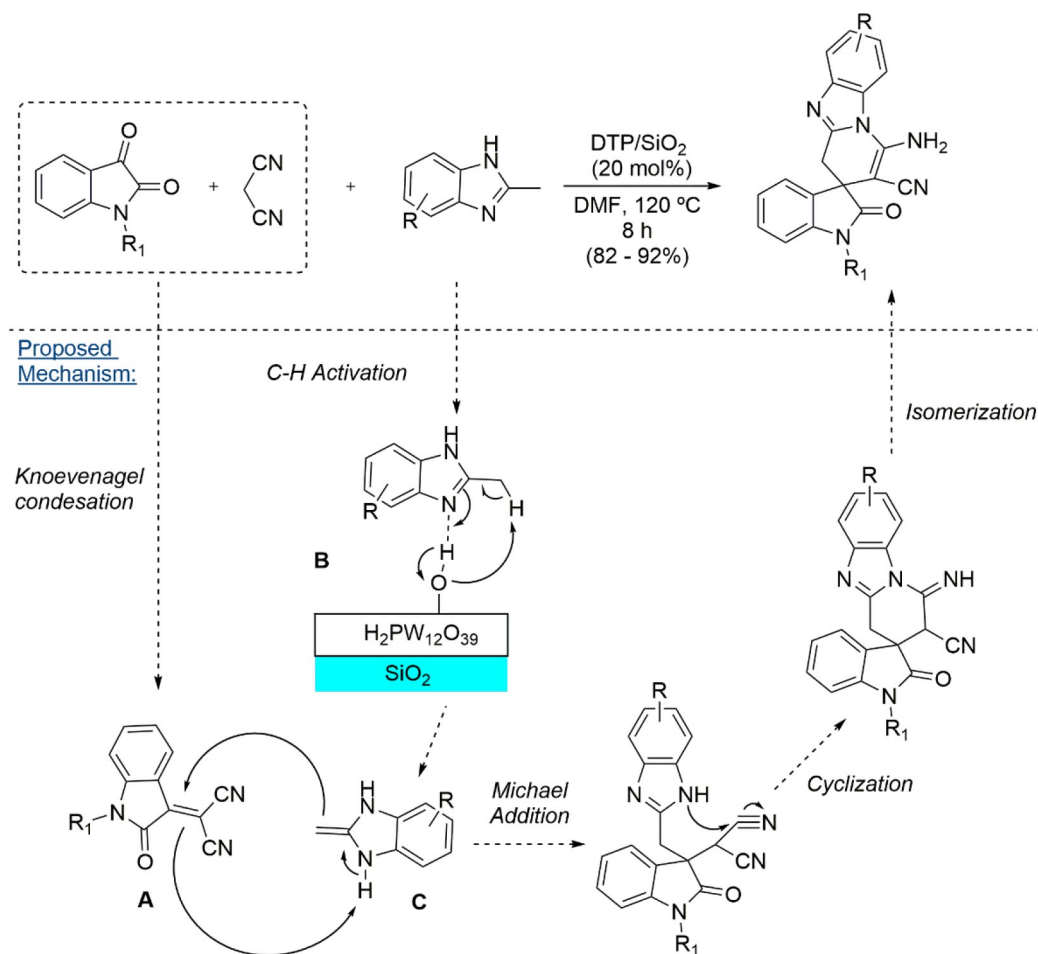
Ziarani *et al.* reported the synthesis of some novel architecturally diverse spirooxindole-dipyrimidines using a green heterogeneous catalyst, consisting of sulfonic acid supported on nanoporous silica (SBA-Pr-SO₃H). These compounds were obtained through one-pot 3-MCR between isatin derivatives, barbituric acid derivatives and uracil-based compounds, in water under reflux temperature. The scope of the reaction was not thoroughly explored, with nine examples being reported in very good to excellent yields and short reaction times (Scheme 65). This heterogeneous catalyst was shown to be very efficient for this reaction, for the following reasons: (a) the reaction proceeds inside the nano-pores; and (b) it can be easily recovered *via* filtration and washed with

acid solution and water, so it could be reused several times without loss of activity. Furthermore, the desired products were purified without chromatography. The proposed route for this reaction was a condensation/Michael addition/cyclization.^[131]

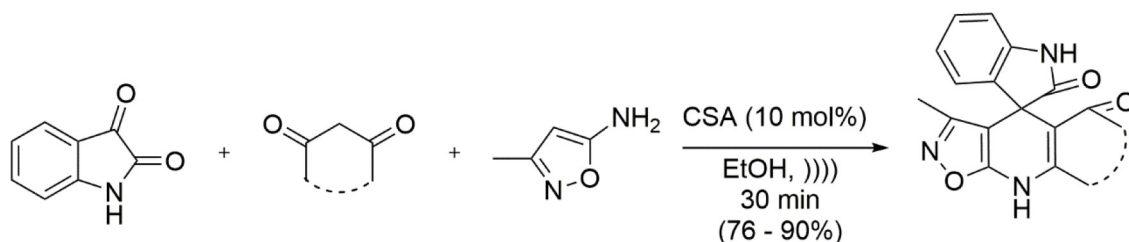
The main problem with the application of green solvents, such as water, in organic chemical transformations is the poor solubility of many starting materials in these solvents. To overcome this problem, the preparation of hydrotropic solutions helps to improve considerably the solubility of organic compounds in aqueous solutions. Patil *et al.* explored the application of 50% aqueous sodium *p*-toluene sulfonate (NaPTS) as an aqueous hydrotropic solution to promote the 3-MCR between isatin, anilines and isatoic anhydride (Scheme 66). The resulting spirooxindole-dihydroquinazolinone derivatives (14 examples) were obtained in very good yields, with the advantage that the reaction media could be recovered and reused directly in the next run, without significant loss of activity.^[132]

Ramadoss *et al.* described an environmentally benign protocol for the synthesis of spirooxindole derivatives in a one-pot, 3-component approach involving isatin, malononitrile, and cyclic 1,3-dicarbonyl reagents, catalyzed by tetrabutylammonium bromide (TBAB) in ethanol under reflux. The synthesis of six novel spirooxindole derivatives was successfully achieved in good yields and short reaction times (Scheme 67).^[133]

Kang *et al.* reported another simple catalyst-free approach for the synthesis of similar spirooxindole derivatives possessing the important trifluoromethyl unit. The one-pot, 3-MCR between isatin derivatives, cyclohexane-1,3-dione and 1-aryl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one in the presence of an excess of *p*-TSA affords the desired trifluoromethylated



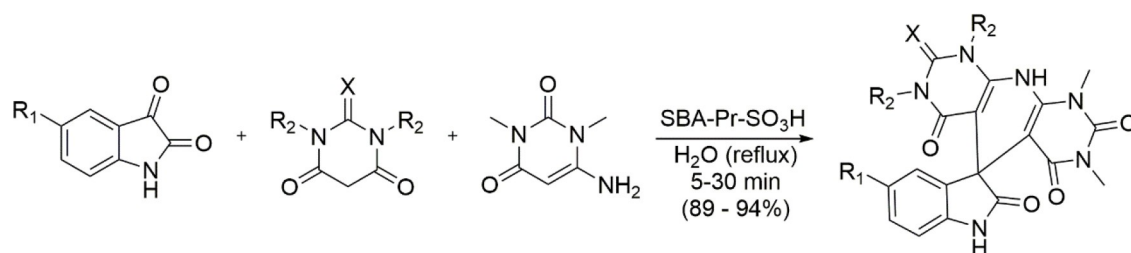
Scheme 63. Synthetic pathway with plausible mechanism for the preparation of spiro[benzo[4,5]imidazo[1,2-*a*]pyridine-3,3'-indoline] derivatives.



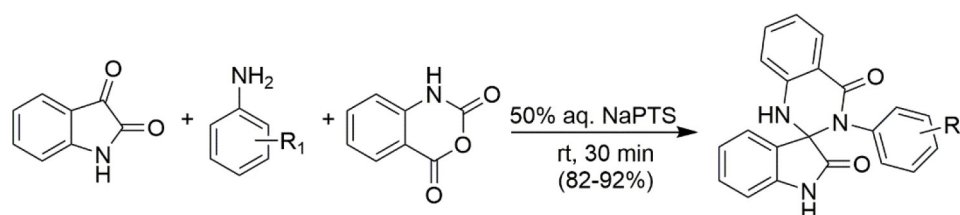
Scheme 64. Synthesis of spirooxindole derivatives catalyzed by CSA under US irradiation.

spirochromeno[2,3-*c*]-6*H*-pyrazol-2',5-dione derivatives in moderate to good yields, while exploring a good substrate scope (Scheme 68A). The Knoevenagel condensation reaction, followed by Michael addition of the 1-aryl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one derivative and subsequent intramolecular cyclization and dehydration reaction, strengthened by the presence of *p*-TSA, furnished the desired fluorine-containing heterocyclic spiro compounds.^[134] Ziarani *et al.*

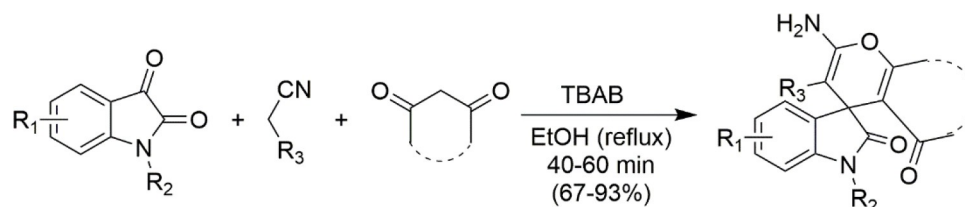
described a new and sustainable methodology for the synthesis of spiro chromeno[2,3-*c*]pyrazole-4,3'-indoline-diones derivatives (Scheme 68B) using water as solvent and SBA-Pr-SO₃H (sulfonic acid-functionalized mesoporous silica) as the catalyst. The authors synthesized eight compounds, with very good yields, by a one-pot, 3-MCR of isatin derivatives, 1,3-cyclohexadiones and pyrazolone in water under reflux conditions and using the recyclable SBA-Pr-SO₃H as a solid acid



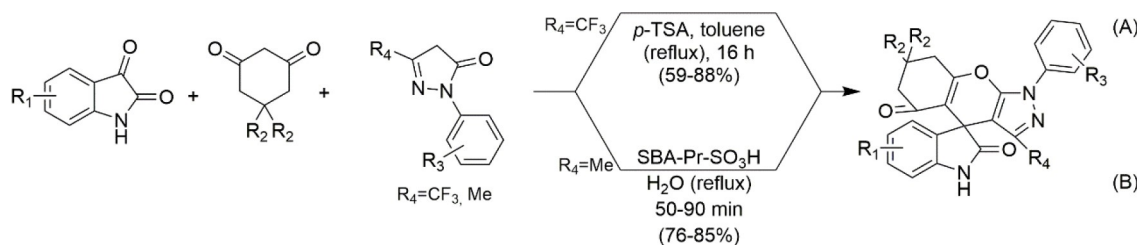
Scheme 65. Synthesis of spirooxindoles dipyrimidines derivatives catalyzed by SBA-Pr-SO₃H.



Scheme 66. Aqueous NaPTS applied in a 3-MCR with dual activity: solvent and catalyst.



Scheme 67. TBAB-catalyzed synthesis of spirooxindoles.

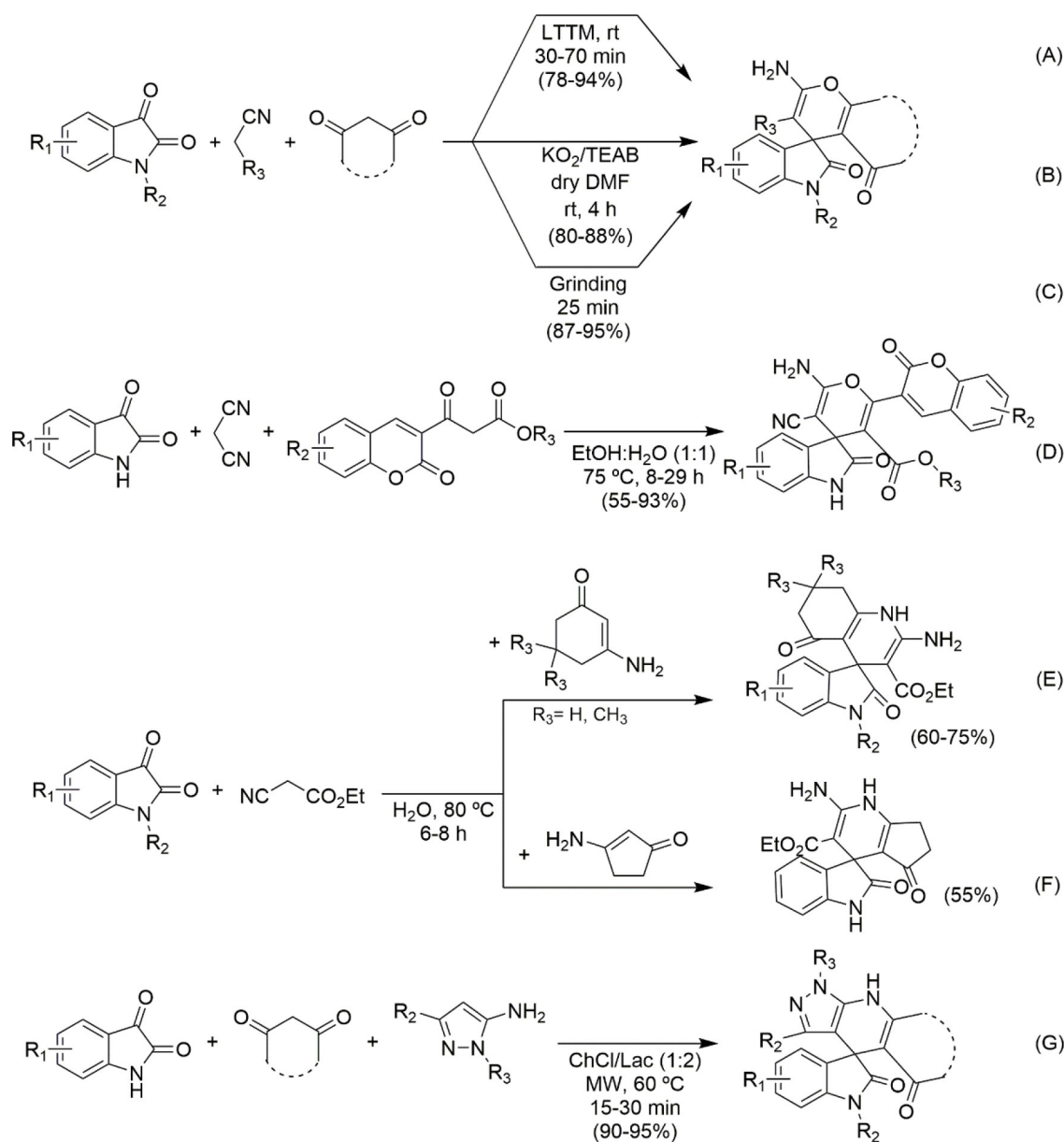


Scheme 68. Synthesis of spiro chromeno[2,3-*c*]pyrazole-4,3'-indoline-diones in the presence of *p*-TSA additive and SBA-Pr-SO₃H catalyst.

catalyst.^[135] By comparing these two methodologies, the latter presents more advantages, such as shorter reaction times, better yields, mild reaction conditions and easy work-up procedures which are efficient and eco-friendly.

The use of a catalyst is often essential to speed up the synthetic transformation or even enable the chemical transformation to occur. However, some procedures exist in the literature where catalysts are not required. Here are some catalyst-free 3-MCR approaches to these spiro[six-membering]oxindole targets. Chandam *et al.* explored alternative

solvents to successfully perform MCRs, these consisted of low transition temperature mixtures (LTTMs) or deep eutectic solvents (DES) which were found to be powerful alternative solvents for these purposes. They used an LTTM that consisted of oxalic acid dihydrate and proline (prepared with 100% atom economy from easily accessible chemicals) for a 3-MCR using isatins, malononitrile or ethyl cyanoacetate, and 1,3-dicarbonyl compounds to prepare spirooxindole derivatives at room temperature (Scheme 69A). A good reaction scope, short reaction times and good yields were obtained for the



Scheme 69. Domino Knoevenagel/Michael addition/cyclization 3-MCR using catalyst free protocols.

desired spirooxindole derivatives (25 examples) with this synthetic approach. Furthermore, the recyclability of the solvent medium was evaluated, showing that the LTTM could be reused (at least up to four cycles without a significant decrease in the yield).^[136]

Gajaganti *et al.* reported the efficient use of oxygen radical anions generated *in situ* to promote the same 3-MCR to access similar spirooxindole derivatives, under mild reaction conditions. The use of molecular oxygen in this context is not a novelty and has been an emerging area in academic and industrial processes.^[137] The authors explored the use of

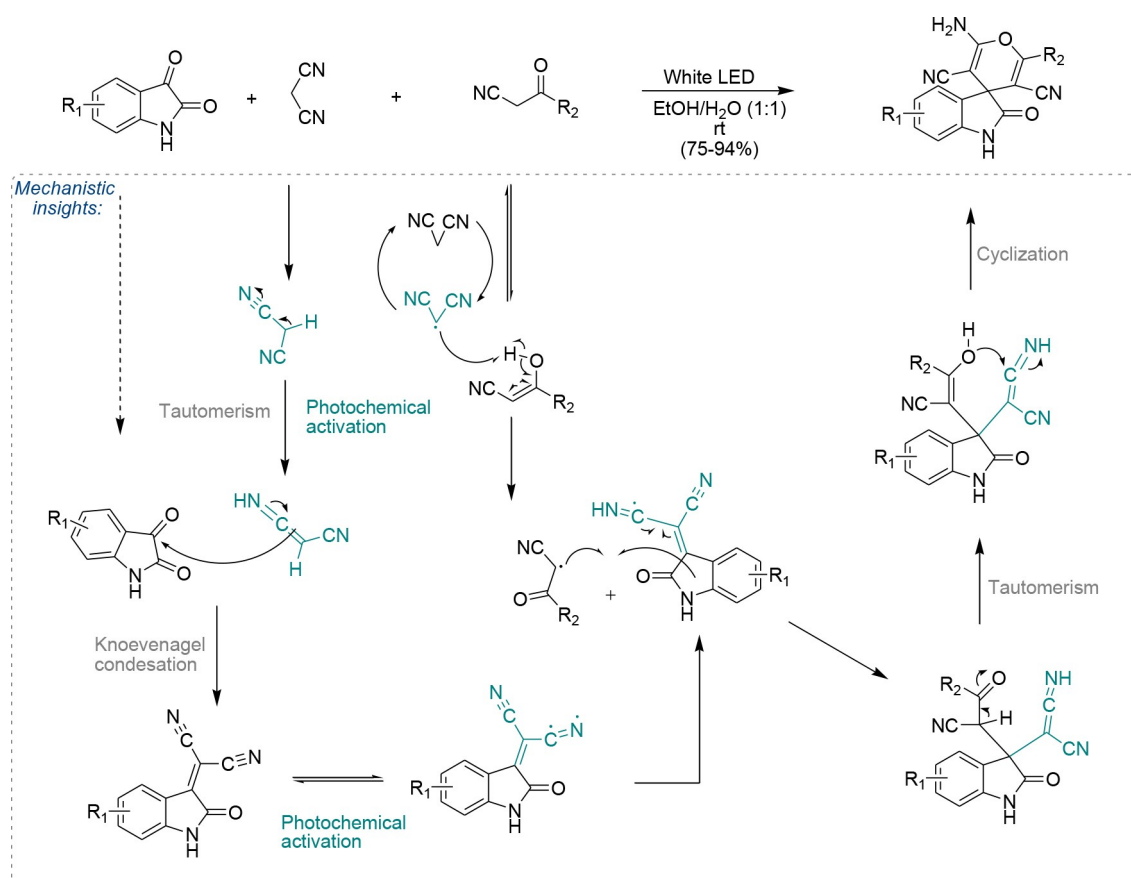
potassium superoxide (KO_2) as an efficient reagent to release the superoxide ion ($\text{O}_2^{\bullet-}$) in solution, a green oxidant and a reactive replacement of molecular oxygen. The decomposition of the stable KO_2 (2 equiv.) in the presence of tetraethylammonium bromide (TEAB, 1 equiv.), a phase transfer catalyst, act as the best combination to access the desired spirooxindoles in good yields at room temperature, through the reaction of isatins, dimedone/barbituric acid/Meldrum's acid, and malononitrile/ethyl cyanoacetate (Scheme 69B). Despite good scope, short reaction time and an innovative protocol, the use of toxic DMF as solvent and chromatographic purification

work-up turns this superoxide ion-based methodology less advantageous when compared to other procedures.^[138] In contrast, Hussen *et al.* reported the same domino multi-component bench-mark reaction using isatins, malononitrile/ethyl cyanoacetate, and enolizable 1,3-dicarbonyl compounds without any promoter or catalyst in a one-pot mechanochemical (hand-grinding) approach. A step-wise domino reaction strategy is the secret for getting high yields of the desired spirooxindole derivatives, *i.e.*, isatin and malononitrile were gently grinded first, by hand for 10 minutes, forming the Knoevenagel condensation product. With the disappearance of the starting materials from TLC, the third component (dimedone) was added (Michael addition) and grinding continued in the same manner until the reaction is finished. This green protocol based on mechanochemical activation proved to be highly efficient with good reaction scope and short reaction times (Scheme 69C), with simple work-up procedure and suitable for multigram scale (up to 92% yield of the desired compound).^[139]

Omar *et al.* prepared a series of coumarin β -keto ester derivatives to be used in a 3-MCR, affording novel coumarin-

spiro[indoline-3,4'-pyran] conjugates (19 examples), also under catalyst-free conditions (Scheme 69D).^[140] In the same way, a catalyst-free 3-MCR between isatin, ethylcyanoacetate, and cyclic enaminones was explored by Tiwarni *et al.*, in an eco-friendly manner (Scheme 69E and 69F). The library obtained (16 examples) could be prepared using only water as solvent, providing another example of a successful green approach to the synthesis of spirooxindoles.^[141] The catalyst-free preparation of a remarkable library of spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridine] derivatives (50 examples) was also successfully achieved (Scheme 69G), using choline chloride and lactic acid (ChCl/Lac) as a recyclable and reusable reaction medium, showcasing the relevance of DESs as environmentally benign contributors in the field of multicomponent reactions.^[142]

We would also like to highlight another catalyst-free approach, reported by Zhang and co-workers, that included a visible-light promoted 3-MCR involving isatin, malononitrile, and α -cyano ketones (Scheme 70). This methodology was shown to be suitable for a wide range of starting materials (29 examples), with the final products being prepared in very good



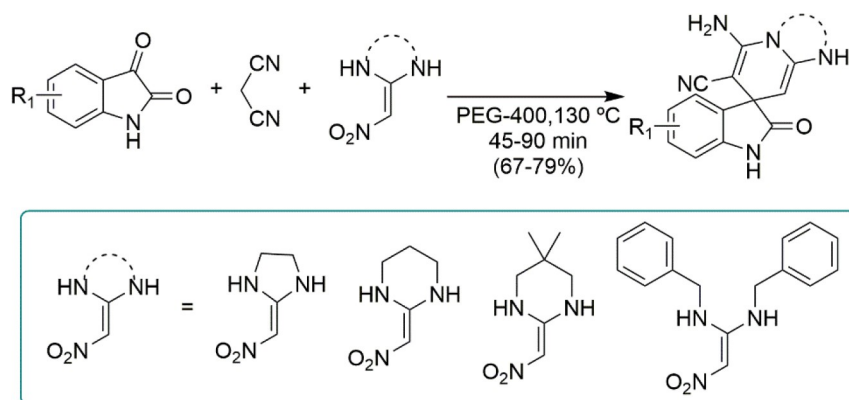
Scheme 70. Visible-light-initiated 3-MCR applied in the synthesis of spirooxindoles.

to excellent yields under mild reaction conditions.^[143] A mechanistic proposal for this reaction is depicted in Scheme 70, and it is proposed to involve the presence of a variety of radical precursors – formed by photochemical activation – and intermediates, but overall the mechanism follows the outline given at the beginning of the section.

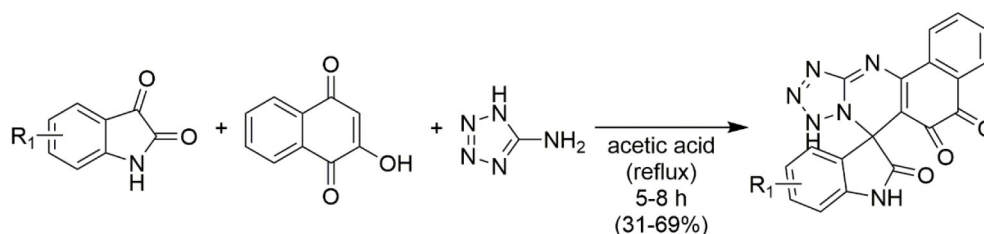
Under the umbrella of green chemistry, Maryamabadi *et al.* reported the catalyst-free synthesis of spirodihydropyridines *via* a one-pot three component condensation of isatins, malononitrile, and ketene-aminals using PEG-400 as an efficient biodegradable polymeric reaction medium (Scheme 71). A good reaction scope was evaluated in this process (16 examples) where a variety of isatin derivatives with electron-donating and electron-withdrawing groups were successfully applied. Moderate yields of the desired compounds and short reaction times showcase the versatility of this sustainable methodology.^[144]

The Knoevenagel reaction/Michael addition/intramolecular nucleophilic cyclization/dehydration process reported by Wu *et al.* allowed the preparation of spirooxindole-*O*-naphthoquinone-tetrazolo[1,5-*a*]pyrimidine hybrids (14 examples). Using acetic acid as solvent, isatins, 2-hydroxy-1,4-naphthoquinone, and 5-aminotetrazole were applied as starting materials, giving the final products in moderate yields (Scheme 72).^[145]

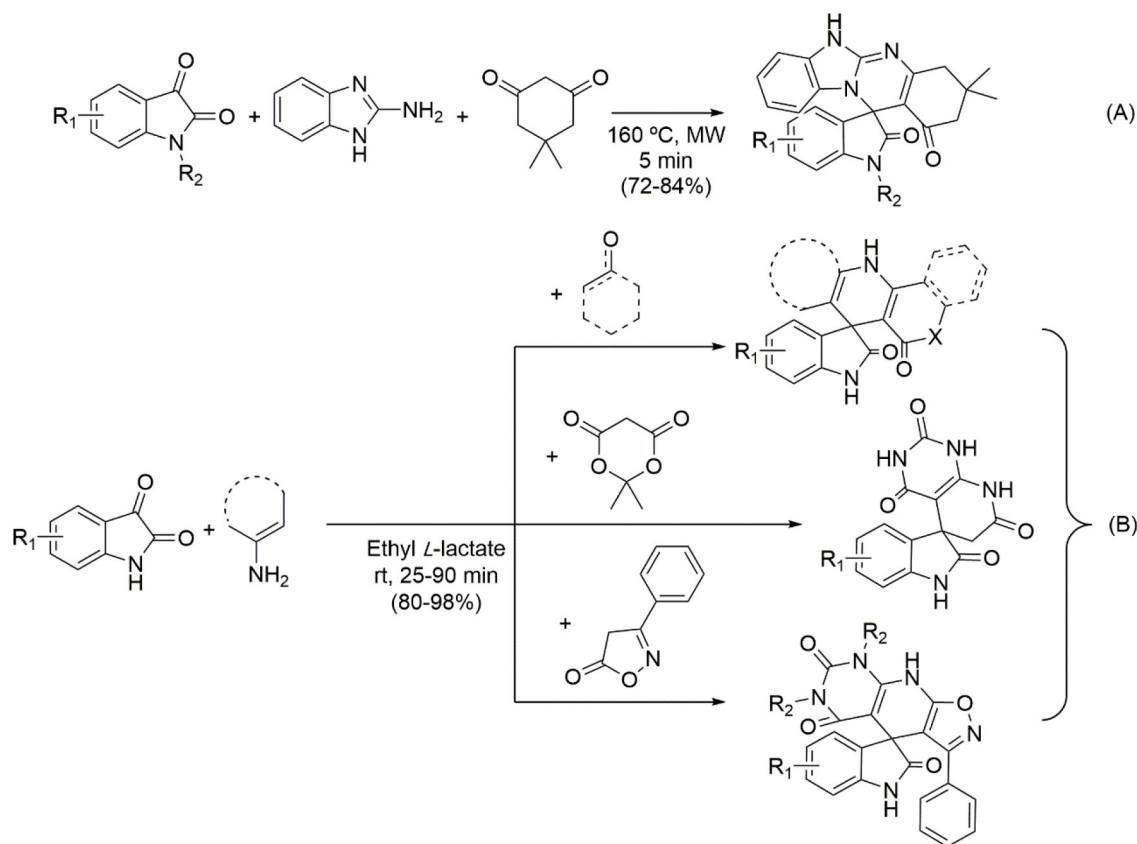
Maloo *et al.* developed a new solvent-free and catalyst-free 3-MCR for the synthesis of spirobenzimidazoquinazolines under microwave irradiation. It involves a one-pot approach *via* a Knoevenagel/Michael/imine pathway (the most favorable one) between isatin derivatives, dimedone, and 2-amino-benzimidazole (Scheme 73A). Good yields of the desired spirooxindole derivatives (14 examples) were achieved with good reaction scope and short reaction times in an environmentally benign protocol. One disadvantage of the methodology is the requirement for chromatographic purification to obtain the pure spirooxindole compounds.^[146] Kausar *et al.* expanded the scope of the reaction, using ethyl *L*-lactate as solvent at room temperature, and they found that the three component domino reaction works very well with isatin derivatives, several amino compounds (6-aminouracil; 4-aminocoumarin; 3-aminocoumarin; 2-aminopyridine; 2-aminopyrazine) and 1,3-dicarbonyl (4-hydroxycoumarin; 4-hydroxy-1-methylquinolinone; 4-hydroxy-6-methylpyranone; dimedone; Meldrum's acid) or 3-phenylisoxazolone compounds (3-phenyl isoxazolone) (Scheme 73B). A wide range of spirooxindole derivatives (35 examples) was obtained with this efficient and simple synthetic methodology, that occurs under mild reaction conditions and without tedious and expensive chromatographic purifications.^[147]



Scheme 71. Catalyst-free synthesis of spiro-dihydropyridines using PEG-400 as reaction medium.



Scheme 72. Catalyst-free synthesis of spirooxindole-*O*-naphthoquinone-tetrazolo[1,5-*a*]pyrimidine hybrids.

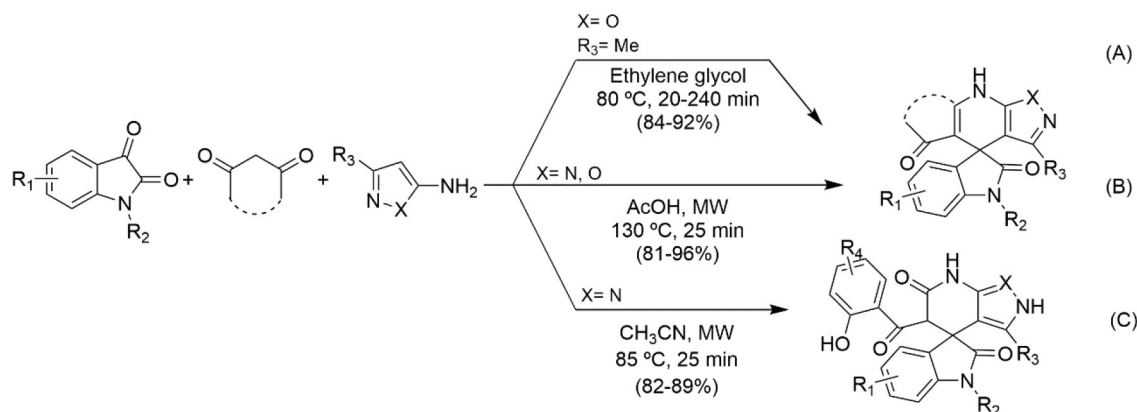


Scheme 73. Catalyst-free 3-MCR between isatins, several amino compounds and 1,3-dicarbonyl or 3-phenylisoxazolone derivatives.

Several other catalyst-free approaches for the synthesis of spirooxindole derivatives were reported, with different solvent systems. Meena *et al.* reported an efficient protocol for the synthesis of novel isoxazolo[5,4-*b*]pyridine derivatives by simple three component condensation of isatins, 3-methylisoxazol-5-amine (aminoisoxazole), and cyclic enolizable

carbonyl compounds (indane-1,3-dione, 4-hydroxycoumarin, 2-hydroxy-1,4-naphthoquinone) in ethylene glycol at 80 °C (Scheme 74A). The reaction showed good scope (16 examples) and easy work-up (no chromatography required).^[148]

An attractive methodology was developed by Mishra *et al.* where the spirooxindole scaffold obtained depends on the



Scheme 74. Catalyst-free synthesis of *N*- and *O*-containing six-membered heterocyclic spiro-rings.

reaction medium. The 3-MCRs of isatin, 4-hydroxycoumarin, and aminopyrazole/aminoisoxazole were reported under microwave irradiation for the synthesis of two different types of fused spirooxindoles: spirooxindoles fused with coumarin-dihydropyridine-pyrazole tetracycles (Scheme 74B) and spirooxindoles fused with pyrazolo-tetrahydropyridinone (Scheme 74C). For the first ones, isatin derivatives, aminopyrazole/aminoisoxazole, and 4-hydroxycoumarins react efficiently, under microwave irradiation, in acetic acid as reaction medium, with short reaction times and good yields (Scheme 74B), leading to the corresponding fused spirooxindoles having a tetracyclic coumarin-dihydropyridine-pyrazole/isoxazole moiety spiro fused with oxindoles. When the solvent was switched to acetonitrile, using microwave irradiation at lower temperature, the second library of compounds was generated *via* ring opening of the hydroxycoumarin moiety (Scheme 74C), increasing the reaction scope in good to excellent yields. The possibility to tune the reaction result using the same starting materials, by just changing the solvent system is without doubt the biggest advantage of this protocol.^[149]

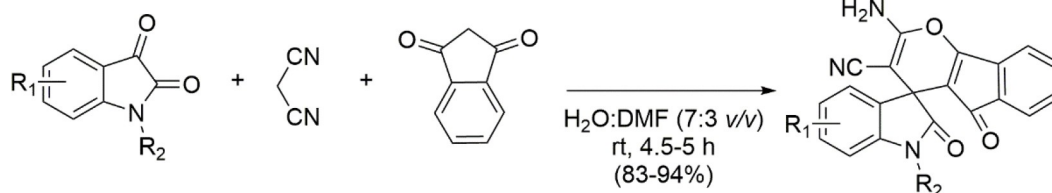
Patravale *et al.* reported an environmentally benign protocol for the synthesis of some new 2-amino-3-cyanospiro(5*H*-indeno[1,2-*b*]pyran-4,3'-indoline)-2',5'-dione in one-pot 3-component reaction of isatin, malononitrile, and 1,3-indandione in water:DMF (7:3) solvent mixture without catalyst, at room temperature. The authors noticed that it was possible to obtain the same product using two different reaction sequences, in a one-pot domino and a one-pot sequential manner. The scope of the reaction was investigated using different derivatives of isatin and 1,3-dicarbonyl compounds, with 14 examples being prepared with very good to excellent yields (Scheme 75). Furthermore, the proposed sequence proceeds *via* Knoevenagel condensation, Michael addition and cyclization following the isomerization.^[150]

As observed in this section, the Knoevenagel condensation is a very relevant first step for the synthesis of 6-membered spirooxindole derivatives. Spirooxindole derivatives bearing the pyran and chromene moieties were the most investigated by researchers in recent years, with several synthetic methods being described. Appreciable attention has been given to the sustainability and eco-friendly aspects of these processes, with recyclable homogeneous and heterogeneous catalysts (includ-

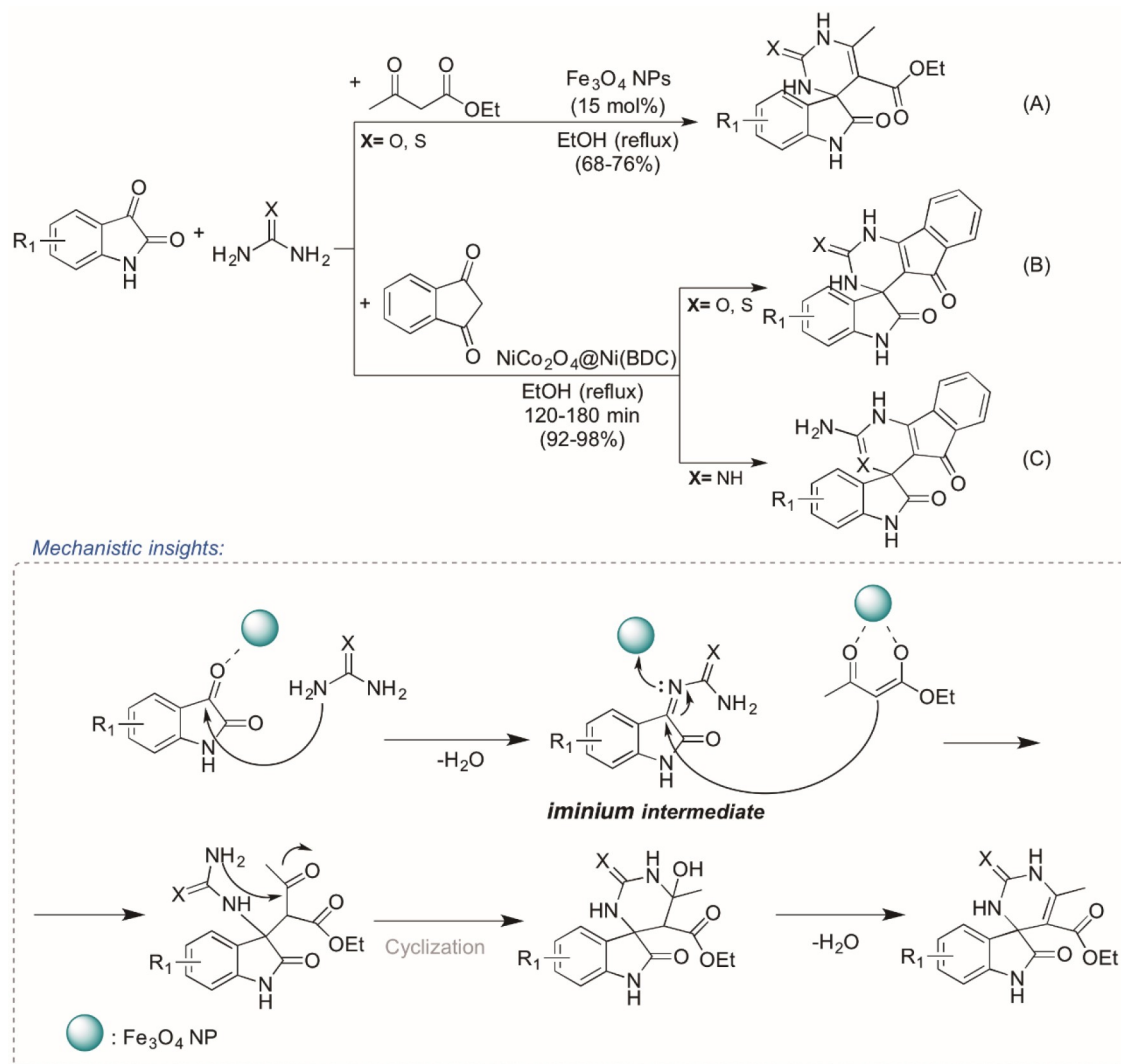
ing nanocatalysts), as well as catalyst and solvent-free methodologies have been used with great effect. In the examples given, a huge variety of C–H activated substrates were used, making it possible to increase the overall structural diversity of these compounds. It should be pointed out that the stereoselective aspects of these reactions were not discussed in any depth in the reviewed literature and this is something we hope will change in the near future considering the importance of compound stereochemistry on compound function and properties.

2.2.1.2. The Biginelli Reaction

The pyrimidine scaffold is a well-known six-membered heterocyclic moiety with a wide range of interesting properties from the medicinal chemistry point of view, and thus, a well-recognized pharmacophore. Maddela *et al.* reported the synthesis of new spiro[oxindole-pyrimidine] derivatives by an adapted Biginelli's 3-MCR using iron oxide nanoparticles (Fe₃O₄ NPs) as catalyst. For the synthesis of the targeted molecules, the authors used isatins with different substituents in the aromatic ring, urea or thiourea, and ethyl acetoacetate as activated 1,3-dicarbonyl compound, to access spirooxindole-dihydropyrimidinone compounds (10 examples) in moderate to good yields (Scheme 76A) (Unfortunately, no reaction times were given). The authors assumed that the reaction proceeds through the acid-catalyzed reaction between the carbonyl group of isatin and urea/thiourea as a first step. Then, interception of the iminium ion with ethyl acetoacetate afford an open-chain intermediate which undergoes subsequent cyclization and dehydration allowing the formation of the described products.^[151] Farhadi *et al.* reported a similar methodology for the synthesis of spiro[indene[1,2-*d*]pyrimidinones through the 3-MCR of isatin derivatives, urea/thiourea/guanidine and 1,3-indandione, in the presence of the metal-organic framework NiCo₂O₄@Ni(BDC) (terephthalic acid) nanocatalyst (Scheme 76B and C). After establishing the optimal conditions, the desired products (5 examples) were obtained in refluxing ethanol, in short reaction times and excellent yields. The catalyst was separated from the reaction mixture magnetically, washed with ethyl acetate and reused in several cycles (at least seven times, without loss of activity).^[152]



Scheme 75. Catalyst-free synthesis of 2-amino-3-cyanospiro (5*H*-indeno[1,2-*b*]pyran-4,3'-indoline)-2,5-diones.

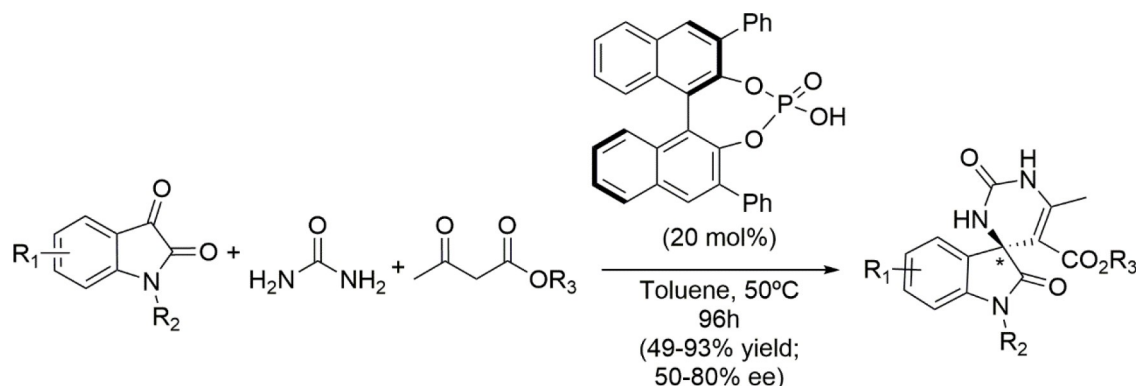


Scheme 76. 3-MCR in the synthesis of new spirooxindole-pyrimidine derivatives using isatin derivatives as precursors.

Stocchi *et al.* described the first organocatalytic asymmetric Biginelli-like reaction using isatin as the carbonyl substrate, urea and β -ketoesters for the synthesis of enantioenriched spiro (indoline-pyrimidine)-diones (10 examples). The organocatalyst selected for this reaction was a BINOL-derived phosphoric acid, and the best reaction conditions are depicted in Scheme 77. The enantioenriched products were prepared in moderate to excellent yields and moderate to very good enantiomeric excess. The (*S*)-enantiomer was the major enantiomer (the absolute configuration was determined by quantum mechanical methods and by NMR spectroscopy on diastereoisomeric derivatives). The enantioselectivity observed was further explained by computational calculations. Furthermore, the researchers showed that this reaction cannot proceed with thiourea or cyclic β -ketoesters substrates.^[153]

2.2.1.3. Miscellaneous

Spirooxindole-quinazolinone derivative scaffolds are compounds with a wide range of biological activities, including anticancer, analgesic and antimalarial. Ziarani *et al.* developed a new heterogeneous catalyst for the synthesis of these spirooxindole-quinazolinone derivatives showing several advantages when compared with other catalysts already employed in this reaction, leading to shorter reaction times, easy separation from the reaction media using an external magnet, high yields and overall good sustainability. $\text{SrFe}_{12}\text{O}_{19}$ magnetic NPs were synthesized and fully characterized using several techniques. Consecutively, the catalyst was applied in the domino 3-component reaction of isatoic anhydride, isatin and aniline derivatives, under solvent-free conditions, forming the product with very good yields (7 examples). The mechanism proposed



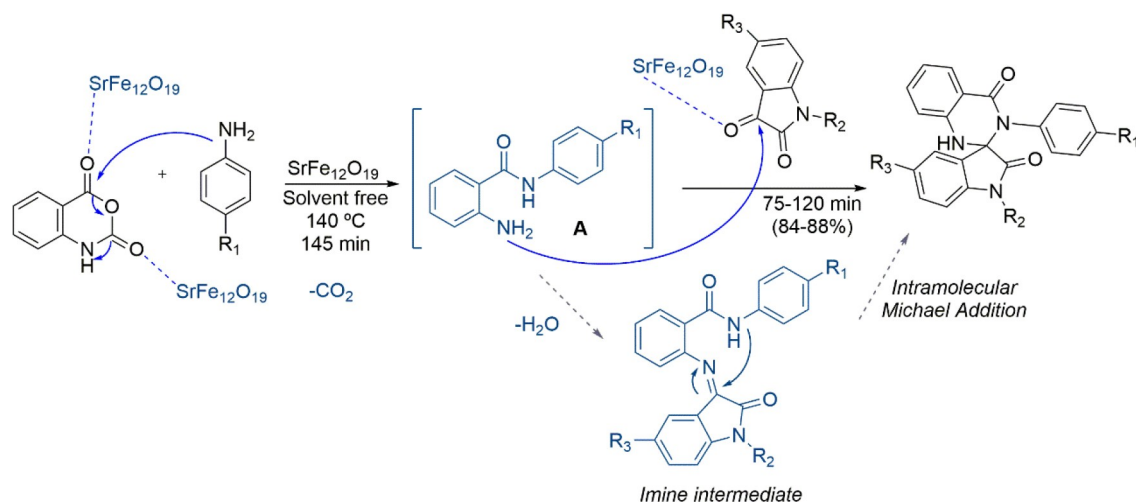
Scheme 77. Enantioselective Biginelli-like reaction using a BINOL-derived phosphoric acid organocatalyst.

is depicted in the Scheme 78, with the catalyst mediating the activation of the carbonyl group from the isatoic anhydride and isatin derivative, since strontium is an alkaline earth metal and therefore able to activate carbonyl groups by the formation of a Sr–O bond. After the activation of the carbonyl groups from the isatoic anhydride, the most reactive suffers an attack from the amine group of the aniline derivative, following by decarboxylation, forming the intermediate A. Afterwards, the NH₂ group of the latter is added to the activated carbonyl group of isatin to produce the imine intermediate. Finally, an intramolecular Michael addition occurs which affords the desired products.^[154]

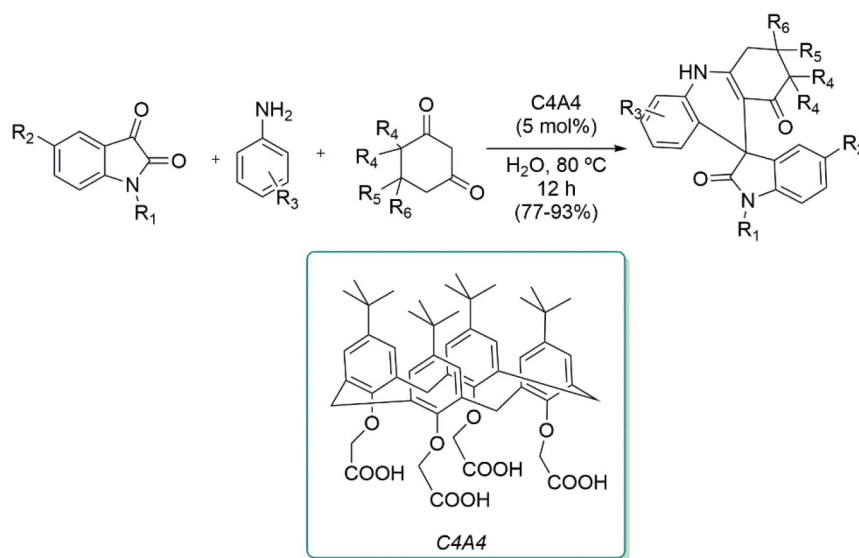
An outstanding catalytic system was developed by Sarkar *et al.* and used in an eco-friendly protocol for the synthesis of novel spirodihydropyridine-oxindoles, which proceeds *via* one-pot multicomponent Mannich reaction between isatin derivatives, substituted anilines, and cyclohexane-1,3-dione deriva-

tives. The catalyst, consisting of calix[4]arene tetracarboxylic acid (C4A4), is a nanoranged organocatalyst which can perform reactions in water. This reaction showed very good scope, with 37 examples obtained with good to very good yields (Scheme 79). The proposed mechanism for this reaction consists of the following: (a) formation of an enaminoketone intermediate (by reaction of alanine with 1,3-diketone derivatives), followed by (b) two consecutive inter- and intra-condensations: (i) the active methylene carbon of the enaminoketone reacts with the isatin 3 carbonyl group; (ii) and *ortho*-carbon of aniline group attacks the C-3 position of isatin furnishing the desired product. Additionally, this nanocatalyst can be recovered easily and reused up to six times without noticeable loss of activity.^[155]

The previously described LTTM (see Scheme 69A) was used for the synthesis of a series of spiro[indoline-3,9-xanthen]trione derivatives (8 examples) using isatin deriva-



Scheme 78. Synthesis of spirooxindole-quinazolinone derivatives using the SrFe₁₂O₁₉ magnetic NPs and respective mechanism insights.



Scheme 79. Synthesis of spiro[dihydropyridine-oxindoles] by a 3-MCR catalyzed by nano-organocatalyst C4A4.

tives with electron-donating and electron-withdrawing substituents in the phenyl ring and dimedone (2 equiv.) (Scheme 80). Shorter reaction times, good yields and convenient recyclability of the LTTM from the reaction mixture are key advantages of this methodology.^[156] It would be expected that acid-catalyzed activation, and various acid-base catalyzed steps would have an important role to play here.

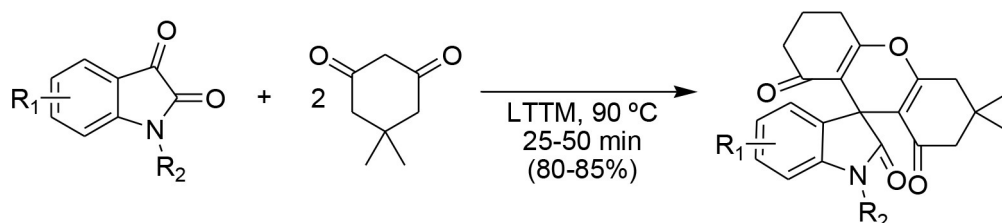
2.2.2. MCRs with 4 Components

2.2.2.1 Knoevenagel-initiated MCRs

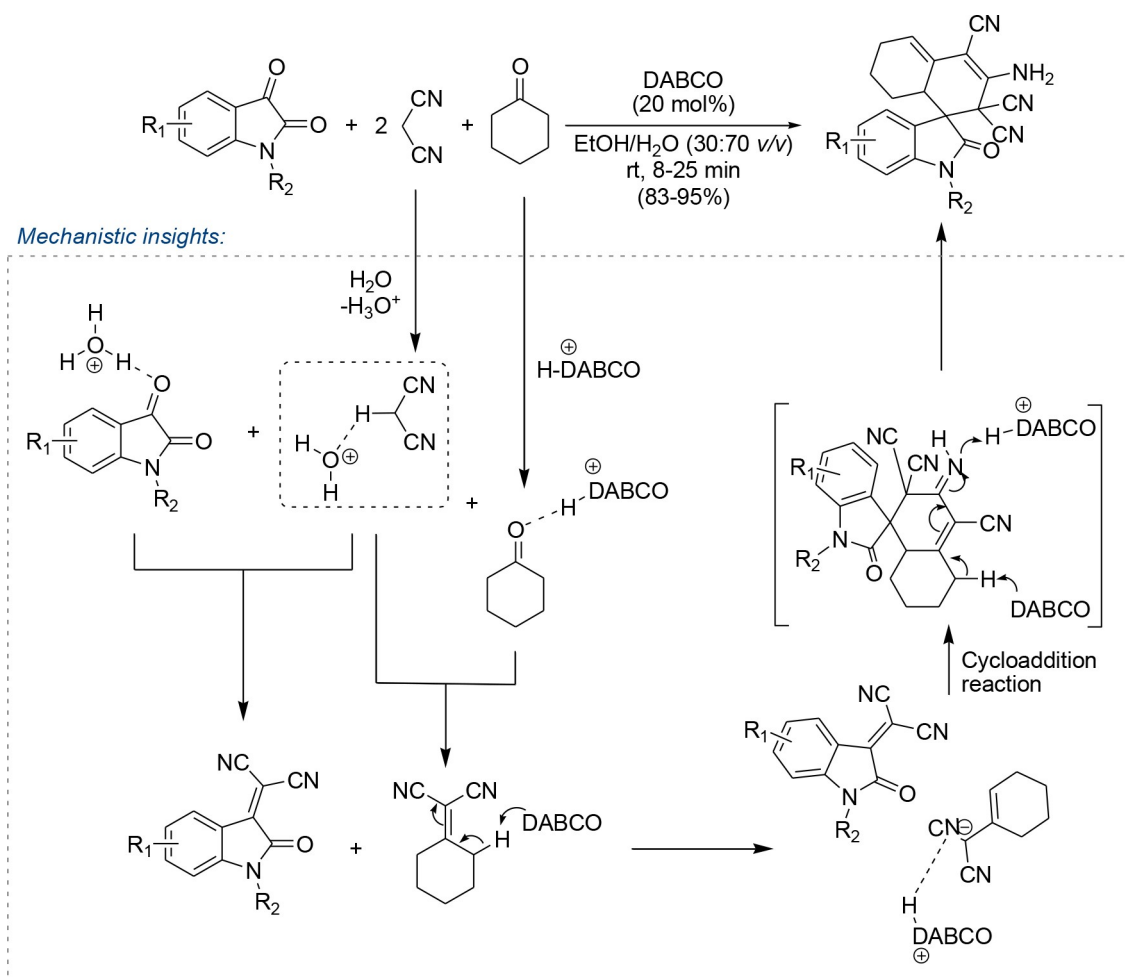
Spirooxindole derivatives with a six-member ring attached are interesting units with potential biological activity. In the literature, we have found several reports concerning their synthesis using protocols with four components (4-MCRs). Hegade *et al.* discovered that by mixing isatin, cyclohexane, and 2 equivalents of malononitrile in the presence of catalytic amounts of DABCO, a set of functionalized spirooxindoles could be prepared, under mild conditions and good yields (Scheme 81). This one-pot pseudo-four component reaction

where malononitrile participates in two reaction steps, was found to be most efficient when 30% (*v/v*) ethanol was used as solvent. Easiness in handling and work-up procedure makes this protocol an appealing route to obtain the 3'-amino-substituted-2-oxo-6',7',8',8a'-tetrahydro-2'*H*-spiro[indoline-3,1'-naphthalene]-2',2',4'-tricarbonitrile derivatives (9 examples).^[157] To get insights into mechanistic pathways, the authors carried out some studies with the reagents involved and concluded that isatyldine malononitrile was easily formed using 30% ethanol in water as solvent under catalyst free conditions. On the other hand, the formation of the vinyl-malononitrile intermediate could only be obtained using DABCO as catalyst. The water present in the reaction medium seemed to be crucial to favor the formation of the malononitrile carbanion and was also involved in the formation of the isatyldine malononitrile (Scheme 81). A putative speculative mechanism is shown in Scheme 81, where we see the importance of acid-base catalysis in the mechanism.

Balwe *et al.* reported the synthesis of a spiro[indazolo[3,2-*b*]quinazoline-7,3'-indoline] framework fused with other *N*-



Scheme 80. Synthesis of spiro[indoline-3,9-xanthen]trione derivatives by a pseudo 3-MCR using LTTM as reaction medium.



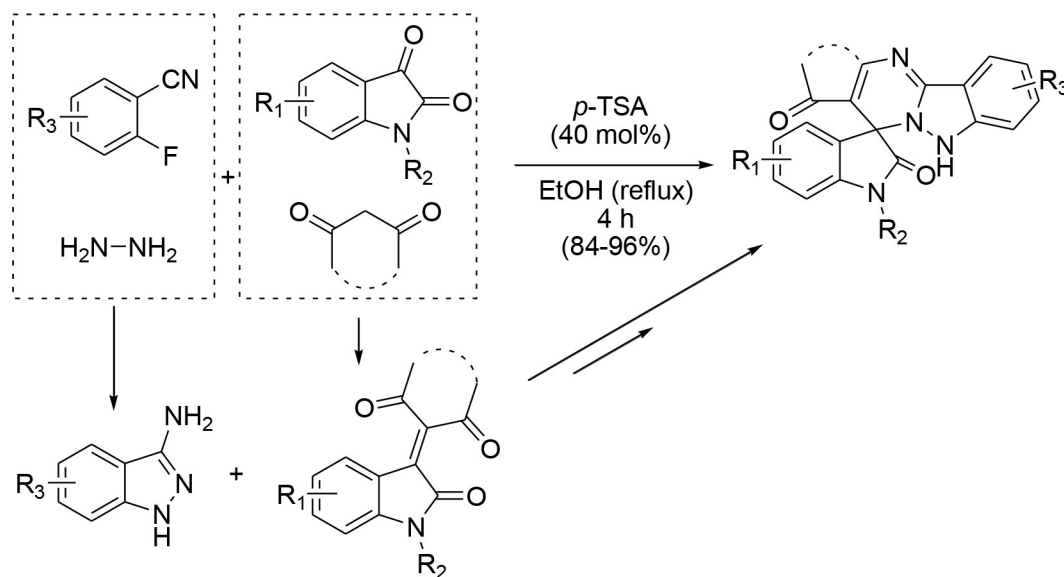
Scheme 81. DABCO as catalyst in the pseudo-4-MCR of functionalized spirooxindoles.

fused heterocycles *via* an interesting 4-MCR domino protocol. The protocol involves the *in situ* generation of the 1*H*-indazol-3-amine derivatives (employing aryl substituted 2-fluorobenzonitrile and hydrazine) followed by reaction with the cyclic 1,3-dicarbonyls and isatin derivatives to furnish the complex *N*-fused spiro-polyheterocyclic units (Scheme 82). The reaction required Brønsted acid activation to proceed (*p*-TSA). After reaction conditions optimization, *p*-TSA (40 mol% loading) in refluxing ethanol proved to be the best condition to afford the desired compounds. The reaction also proceeds with 20 mol% of *p*-TSA but with decrease in the observed yield. The protocol has good scope (18 examples) and simple work-up (no chromatography required), allowing the preparation of the bi-functionalized spiro[indazolo[3,2-*b*]quinazoline-7,3'-indoline hybrids in good to excellent yields.^[158]

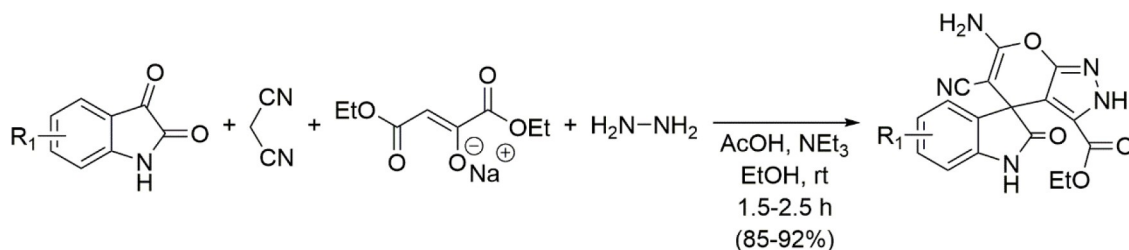
Functionalized spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazoles] are an important class of heterocyclic compounds exhibiting biological activities. Several methodologies were reported for

their synthesis using isatins, malononitrile or derivatives, hydrazine or derivatives, and β -ketoesters in a 4-MCR approach. For instance, Gein *et al.* reported a catalyst-free procedure using the uncommon diethyl oxaloacetate sodium salt as the carbonyl compound to obtain ethyl 6'-amino-5'-cyano-2-oxo-2'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-3'-carboxylate derivatives (6 examples) in good yields, mild reaction conditions, using acetic acid, triethylamine and ethanol as reaction promoters (Scheme 83). Despite poor reaction scope, an easy chromatography-free work-up is a major advantage for this procedure.^[159]

Steroid compounds are of great interest in the field of medicinal chemistry, with many drugs bearing this well-known scaffold, *e.g.* galeterone and abiraterone used for the treatment of advanced prostate cancer. Zhang *et al.* reported the synthesis of novel steroidal dihydropyridinyl-spirooxindole derivatives (15 examples), *via* one-pot 4-MCR of pregnenolone, isatin derivatives, malononitrile, and ammonium acetate, in good



Scheme 82. The 4-MCR for the synthesis of spiro[indazolo[3,2-*b*]quinazoline-7,3'-indo]-lines.



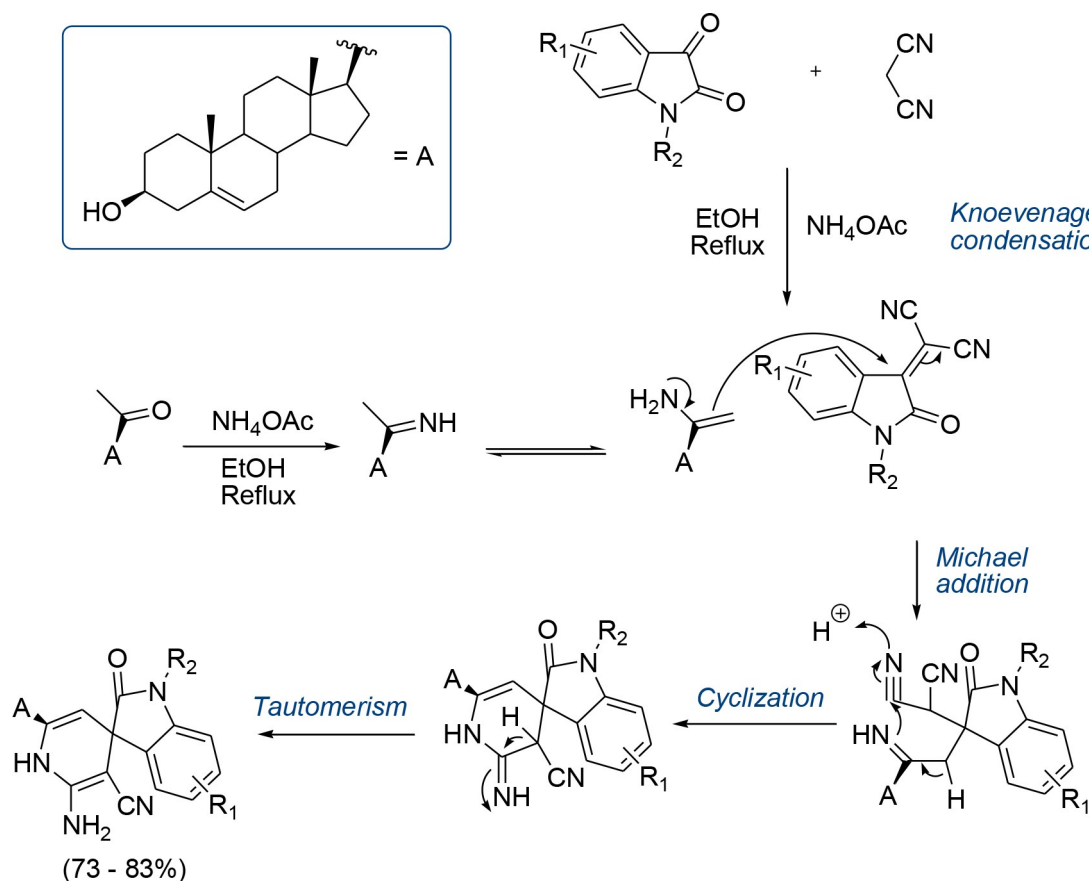
Scheme 83. A catalyst-free 4-MCR for the synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives using diethyl oxaloacetate sodium salt as a reagent.

yields (Scheme 84). In the proposed mechanistic route, the common NH_4OAc salt works as a bifunctional species, as depicted in Scheme 84, by mediating the Knoevenagel condensation forming the dicyanoalkene intermediate, and behaving as nitrogen source, furnishing the steroidal enamine intermediate. These two key intermediates react *via* a Michael addition reaction, following the isomerization-cyclization sequence and, finally, an isomerization furnishing the new steroidal dihydropyridinyl-spirooxindoles. With this one-pot protocol, it was possible to generate two C–C and two C–N bonds, as well as the carbon quaternary stereogenic center.^[160]

Nanoscale materials have demonstrated their value as powerful heterogeneous catalysts in several bench-mark reactions. The 4-MCR linking isatins, malononitrile or allyl cyanoacetate, substituted hydrazine hydrate, and allyl acetoacetate was not an exception. Alemi-Tameh *et al.* reported the synthesis and characterization of amino-functionalized magnetic nanoparticles ($\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-NH}_2$) which showed high catalytic activity in the 4-MCR described above. The spiro [indoline-3,4'-pyrano[2,3-*c*] pyrazole] derivatives were ob-

tained in mild reaction conditions, short reaction times and in good to excellent yields (Scheme 85A). The reaction also showed good scope (9 examples), where it was found that isatin derivatives possessing electron-donating (like alkyl) or electron-withdrawing (like halides or nitro) groups allow higher yields, compared to unsubstituted isatin. Reaction with malononitrile (mirroring methyl cyanoacetate) proved also to be superior in terms of yield of the corresponding spirooxindole product.^[161]

Recently, Maleki *et al.* reported a similar reaction approach using a new-cellulose-based functionalized magnetic bio-nanocomposite catalyst ($\gamma\text{-Fe}_2\text{O}_3@\text{cellulose-OSO}_3\text{H}$, Scheme 85B). The main advantage of using this type of magnetic catalysts is, as stated previously, its easy recovery from the reaction medium. This methodology has short reaction times, mild reaction conditions, good scope (11 examples) and the heterogeneous catalyst can be reused at least five times without significant loss of activity.^[162] A polyaniline iron oxide carbon nanotube nanomagnetic catalyst ($\text{PANI}/\text{Fe}_3\text{O}_4/\text{CNT}$) was prepared and fully characterized by Hojati *et al.*, for the same



Scheme 84. Synthetic pathway and putative mechanism for the preparation of steroidal-dihydropyridinyl-spirooxindoles compounds.

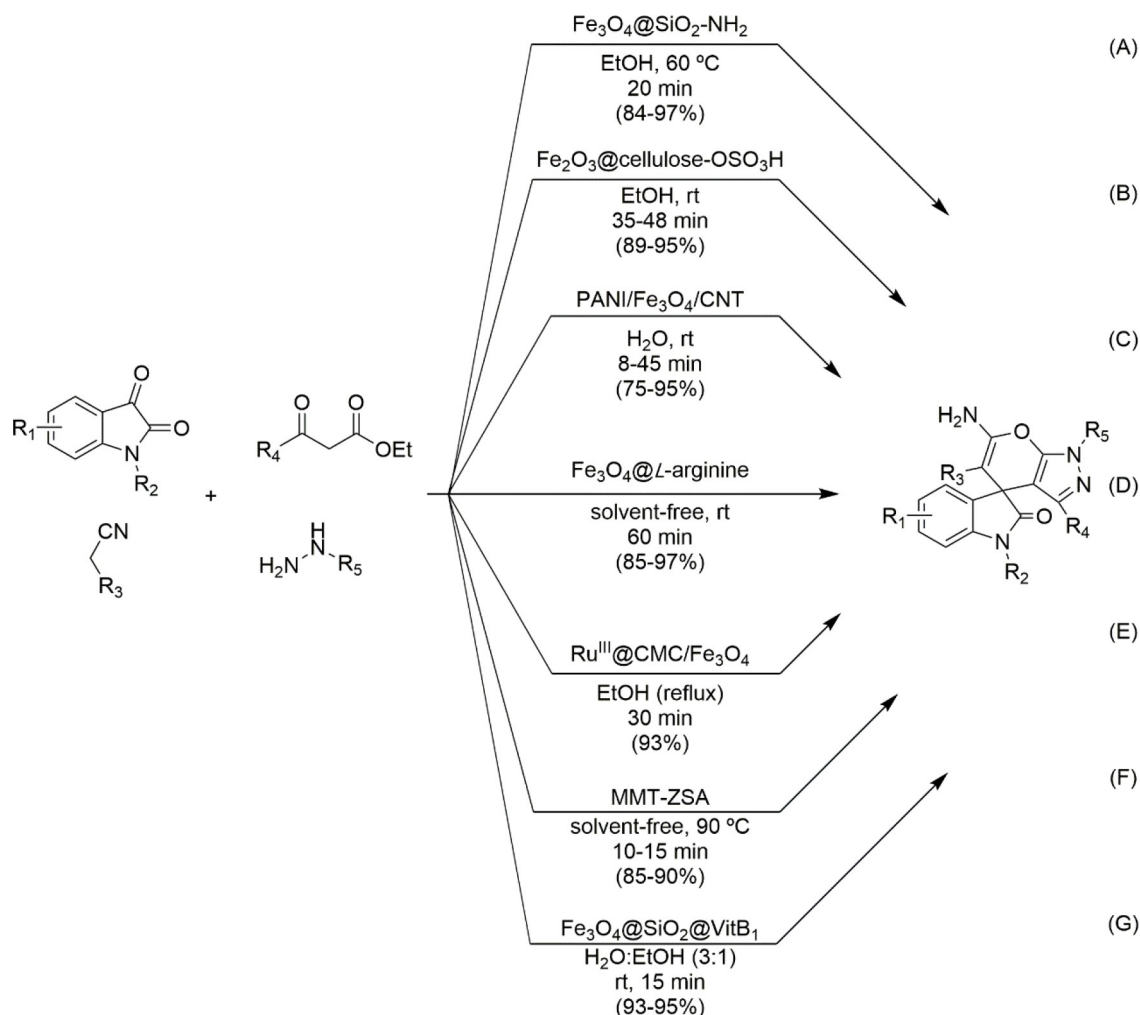
purpose, behaving as a novel, efficient and reusable catalyst in the synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives in good yields (Scheme 85C). The reported protocol allows the use of water as solvent. The reaction displayed very good scope (17 examples) and short reaction times.^[163]

Amino acid-functionalized nanomaterials have received some attention in different areas due to some crucial and unique attributes like high catalytic activity, eco-friendliness and non-toxicity in some bench-mark reactions. The group of Ghasemzadeh *et al.* reported the efficiency of Fe₃O₄@L-arginine as a robust and reusable catalyst for the synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazoles] in a solvent-free approach in good to excellent yields (Scheme 85D). Easy preparation of the catalyst, stability and low loading are the main features of this protocol.^[164] Chen *et al.* decided to incorporate ruthenium in a magnetic nanosized carboxymethylcellulose iron oxide hybrid to generate Ru^{III}@CMC/Fe₃O₄ nanocatalyst. The elemental maps confirmed that the Ru(III) species are well dispersed in a homogeneous manner in the surface of CMC/Fe₃O₄ magnetic hybrid nanoparticles. Its catalytic activity was investigated in the similar 4-MCR

presented above using several aldehydes and ketones. Unfortunately, only one example was presented using isatin (Scheme 85E). Despite insufficient reaction scope to compare protocols, it seems that the short reaction time, high reactivity and mild reaction conditions could highlight the possibility to further investigate and expand the reaction scope.^[165]

A slightly different approach was undertaken by Safari and Ahmadzadeh, using a zwitterionic sulfamic acid functionalized nanoclay as nanocatalyst (MMT-ZSA) for the same type of chemical transformation (3 examples) (Scheme 85F). This catalyst, which required short reaction times and operated under solvent-free conditions, afforded the desired spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives in very good yields. Another advantage presented by this catalyst is its recyclability and reusability (up to 5 cycles), without significant loss of activity.^[166]

A new catalyst was developed by Rahman *et al.*, consisting of magnetic NPs of vitamin B1 immobilized on silica coated ferrite (Fe₂O₃@SiO₂@VitB₁). This easily recovered and reusable catalyst could efficiently promote the reaction between *N*-unsubstituted isatins, malononitrile, ethyl acetoacetate and



Scheme 85. Heterogeneous catalysts used in the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives *via* a domino 4-MCR.

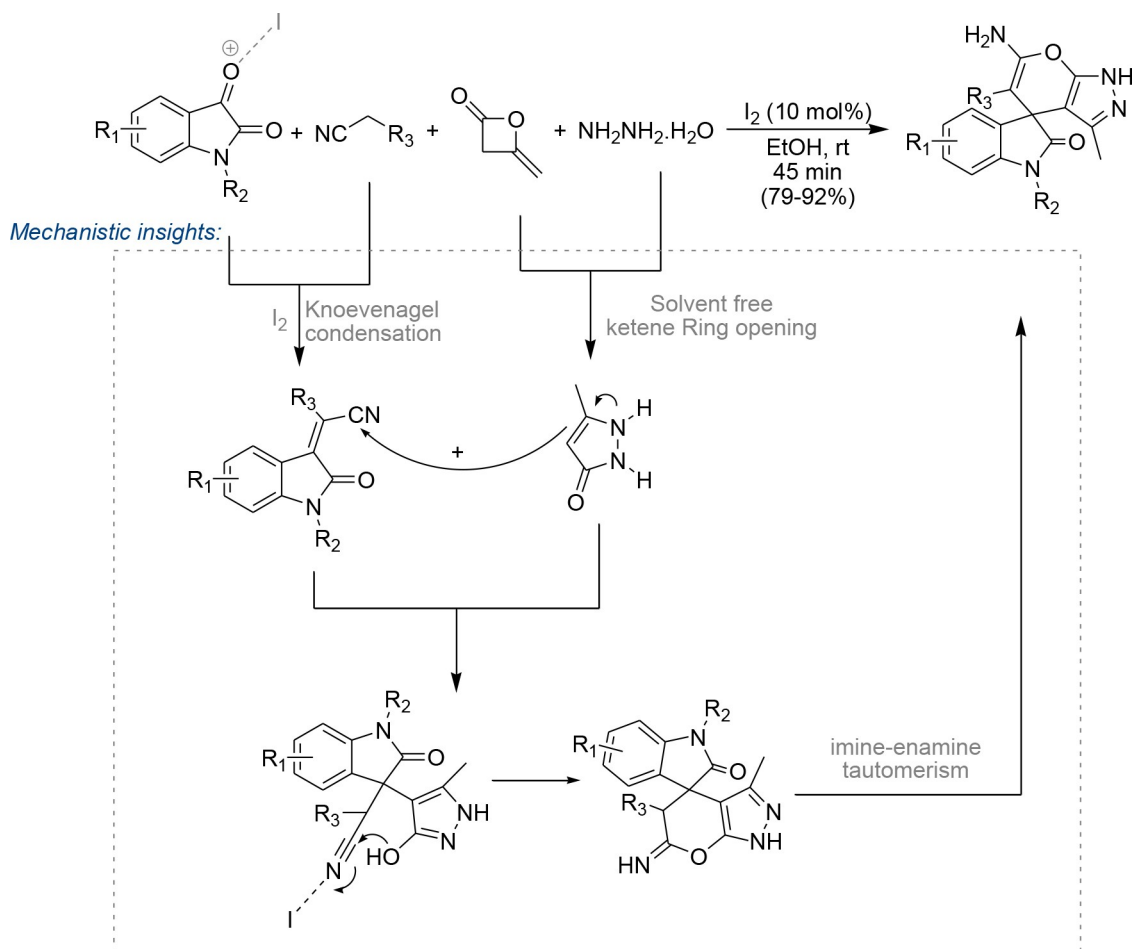
hydrazine hydrate (4 examples), without significant loss of its catalytic activity even after 6 runs. Besides the excellent yields achieved, this process proved to be highly sustainable, as it occurs with short reaction times under mild reaction conditions (Scheme 85G).^[167]

Concerning the four-component synthesis of similar spiro[pyranopyrazoles], Rezvanian *et al.* reported an iodine-catalyzed methodology, requiring mild reaction conditions. This chemical transformation, involving isatin, hydrazine hydrate, ketene, and malononitrile or ethyl cyanoacetate, afforded a library of the desired spirooxindoles (8 examples) with overall very good yields (Scheme 86).^[168] The authors postulated that after an initial condensation reaction between hydrazine hydrate and the ketene to provide the pyrazolone intermediate, there then occurs a Michael reaction with the Knoevenagel condensation intermediate, which is followed by enolization and consequent intramolecular cyclization to give

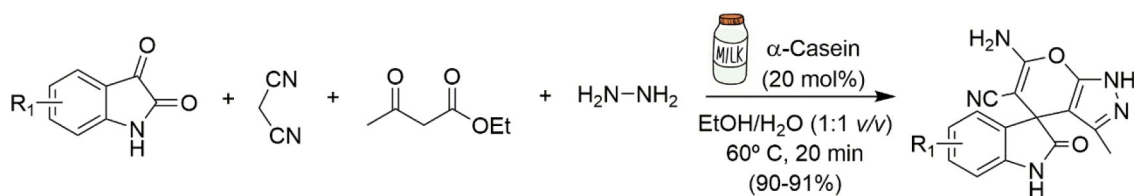
the target compounds after imine-enamine tautomerization (Scheme 86). It seems that iodine is crucial in the last step of the mechanism, in order to activate the nitrile group allowing the oxygen to attack.

Milani *et al.* reported, for the first time, the use of α -casein as an efficient and eco-friendly catalyst to perform this synthetic transformation. Mild reaction conditions, short reaction time and chromatography-free work-up are the main advantages for the use of this commercially available, cheap and recyclable catalyst (reused at least four times without significant loss of activity) (Scheme 87).^[169] Regarding the use of isatin derivatives, only two examples were reported, so further studies might be required to appreciate the value of this sustainable catalyst for this chemical transformation.

A niobium-catalyzed synthesis of spiro[pyrazole and benzo[7,8]chromene derivatives (4 and 6 examples, respectively) was reported by Manisankar and co-workers. The first library was



Scheme 86. Iodine-catalyzed synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives *via* a 4-MCR.



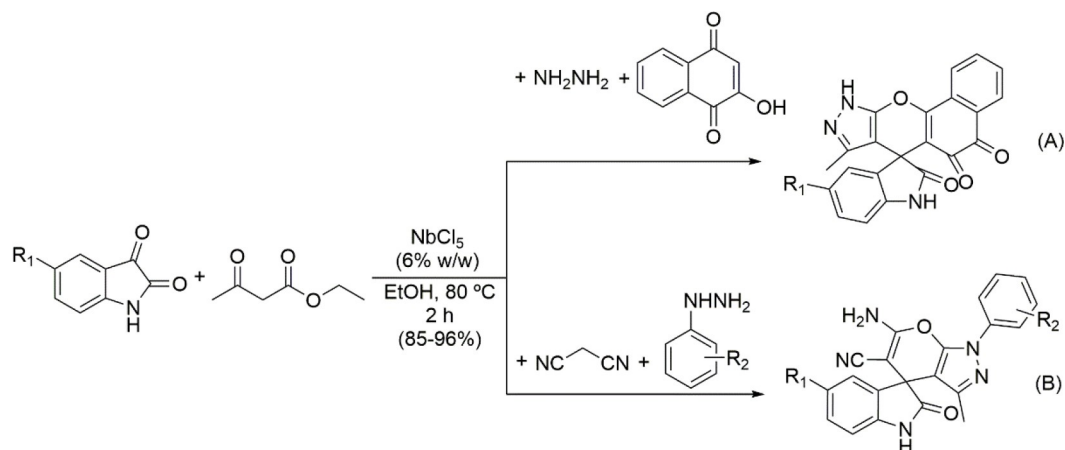
Scheme 87. 4-MCR with isatin derivatives, malononitrile, ethyl acetoacetate and ninhydrin catalyzed by α -casein.

obtained using isatin, ethyl acetoacetate, hydrazine, and 2-hydroxy-1,4-naphthoquinone as starting materials (Scheme 88A), whereas for the second library, the two last components were replaced by phenyl hydrazines and malononitrile (Scheme 88B). The high yields achieved showcase the versatility of this methodology.^[170]

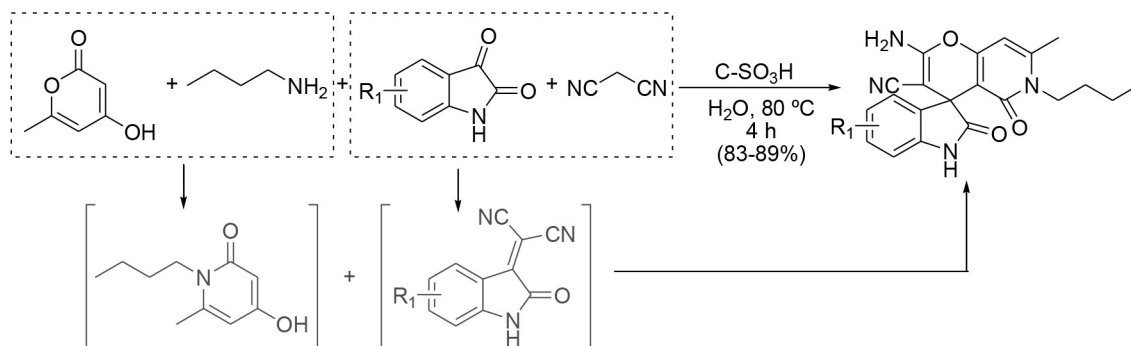
Recently, the incorporation of the pyrano[3,2-*c*]pyridine moiety in spirooxindoles was successfully achieved by Xu *et al.*, under eco-friendly conditions.^[171] The applied one-pot, two-step approach starts with the reaction between 4-hydroxy-6-

methyl-2*H*-pyran-2-one and *n*-butylamine, which further undergoes Knoevenagel reaction/Michael addition with isatin and malononitrile, affording the desired products (5 examples) in very good yields (Scheme 89). The reaction was promoted by solid sulfonic acid (C-SO₃H), which could be easily recovered from the reaction medium and reused without significant loss of activity. Further advantages of this methodology consisted in the use of water as solvent.^[171]

Ghorhani-Choghamarani *et al.* reported the synthesis of two different nanocatalysts for multicomponent domino



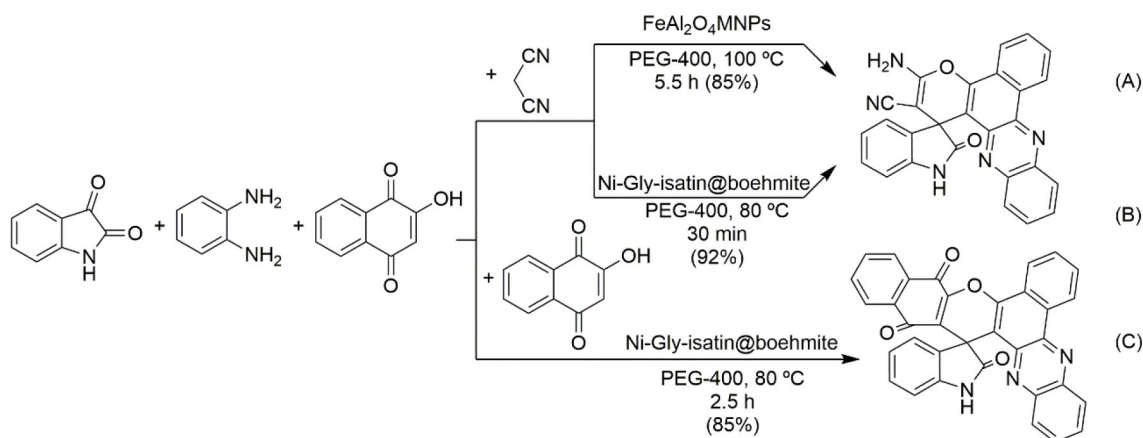
Scheme 88. Niobium-catalyzed 4-MCR.



Scheme 89. Eco-friendly synthesis of spirooxindoles bearing the pyrano[3,2-*c*]pyridine moiety.

reactions based on hercynite (FeAl_2O_4) and Nickel(II). The first one comprises spinel ferrite hercynite immobilized in

magnetic NPs (FeAl_2O_4 MNPs, Scheme 90A) which can be recycled up to 4 cycles without significant loss of activity. The

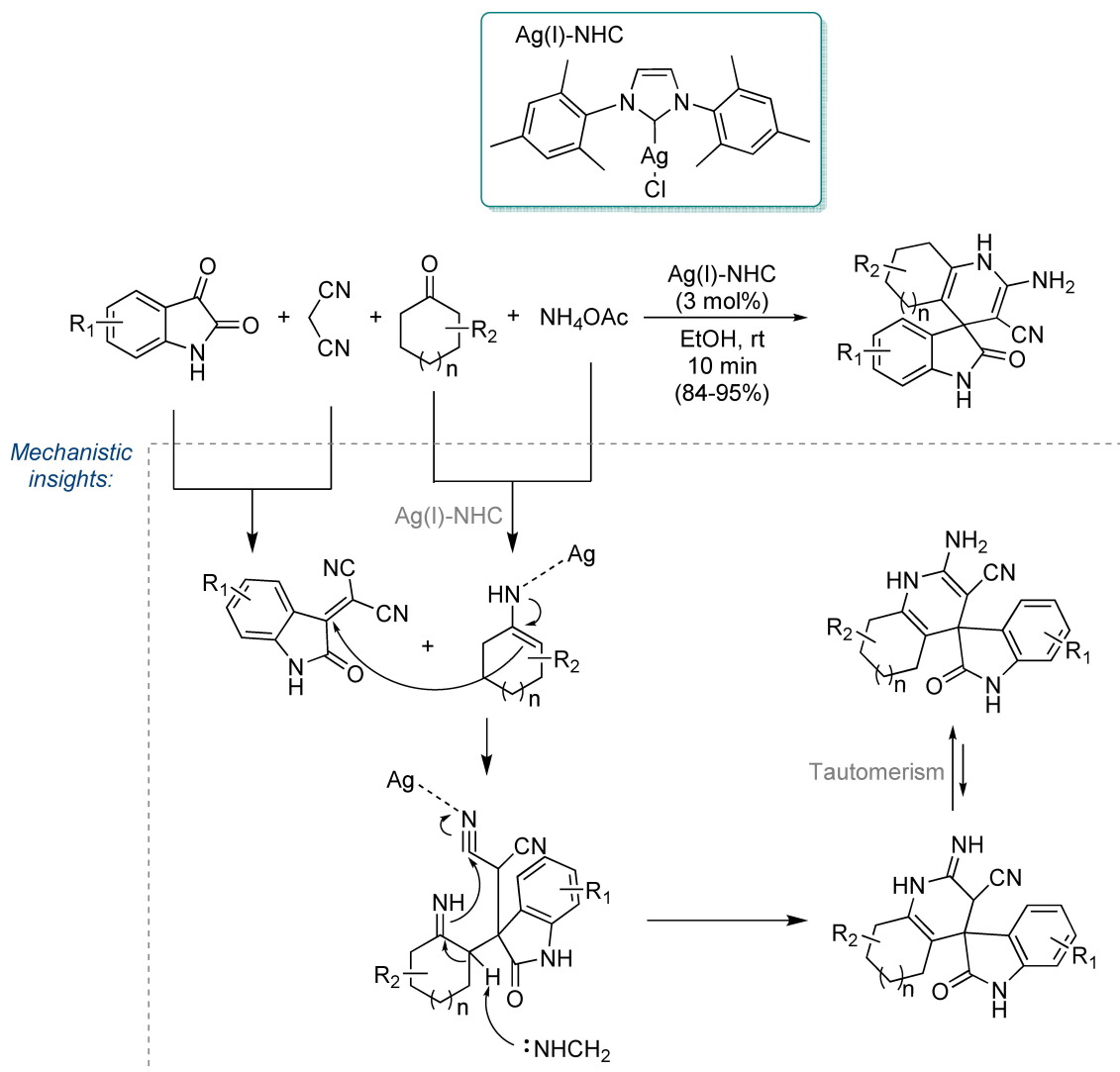


Scheme 90. The use of heterogeneous nanocatalysts in the 4-MCR using isatin, 2-hydroxy-1,4-naphthoquinone, 1,2-diamines and malononitrile (or 2-hydroxy-1,4-naphthoquinone).

second catalyst was prepared through the immobilization of Nickel(II) on modified boehmite nanostructures as supporting material (Ni-Gly-isatin@boehmite, Scheme 90B and C) and could also be reused for four consecutive runs. Both were applied successfully in the 4-MCR between aldehydes (or isatin), 2-hydroxy-1,4-naphthoquinone, 1,2-diamines, and malononitrile (or 2-hydroxy-1,4-naphthoquinone) using PEG-400 as solvent with short reaction times. Although isatin was used in both approaches, and it showed poor reaction scope, the yields of the desired spiropolyhydroquinoline derivatives were very good using both catalysts.^[172] The same compound depicted in Scheme 90C was also obtained by Pour *et al.*, but this time using superparamagnetic NPs of modified thioglycolic acid ($\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-SCH}_2\text{CO}_2\text{H}$). This recyclable and reusable heterogenous catalyst achieved the desired product

(92% yield) under mild reaction conditions (using EtOH/water 1:1 *v/v* as solvent at 70 °C, for 2 hours).^[173]

Balaboina *et al.* reported the use of Ag(I) and organo-*N*-heterocyclic carbenes (NHCs) for the one-pot 4-MCR of isatins, malononitrile, cyclic ketones, and ammonium acetate giving access to a family of substituted spirooxindole-1,4-dihydropyridines in ethanol at room temperature (Scheme 91). Studies revealed that *in situ* formed or pre-synthesized Ag(I)-NHC complexes are soft/labile in nature and work well as a source of both organo-NHC and Ag(I) ion in solution, and it is not necessary to introduce separately the Ag(I)/NHC catalyst pair for cooperative/synergistic catalysis. Ag(I)-NHCs are air-stable and exhibit an equilibrium between neutral and ionic structures in solution. This methodology allowed the researchers to develop a methodology with good reaction scopes (15



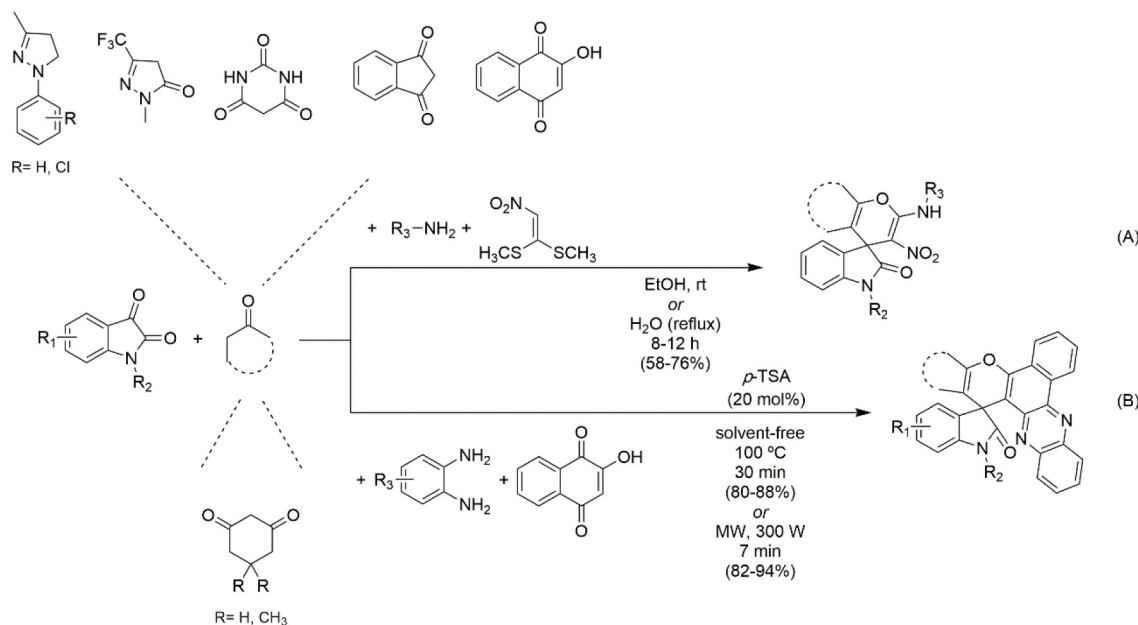
Scheme 91. 4-MCR for the synthesis of new spirooxindole-1,4-dihydropyridines catalyzed by Ag(I)-NHC complex.

examples), short reaction times under mild reaction conditions, affording the spirooxindole-1,4-dihydropyridines in good yields.^[174] In summary, the authors suggested that there is condensation of the cyclic ketone with ammonium acetate to form an enamine that undergoes Michael reaction with the isatylidene malononitrile derivatives (the Knoevenagel condensed product) to form an adduct that after heterocyclization and subsequent tautomerism affords the desired spirooxindole derivatives (Scheme 91). The Ag(I)-NHCs has a critical catalytic role to play.

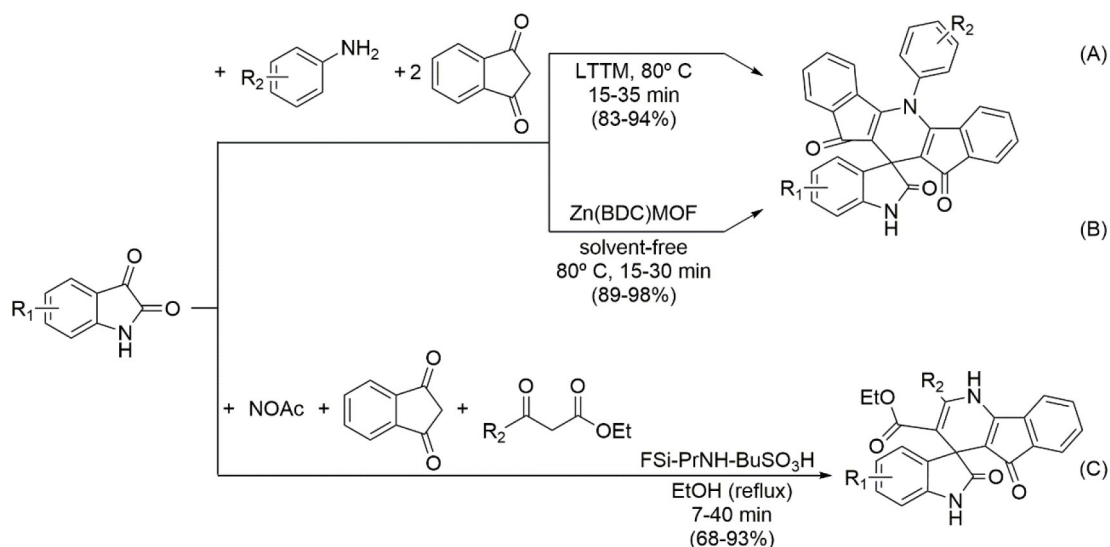
Heterocyclic spirooxindole pyrans are attractive synthetic targets for synthetic chemists due to their wide array of bioactivities. Several successful methods using isatin as one of the starting materials were described throughout this review and despite all the reports, new protocols highlighting the use of uncommon reagents, efficiency and greener approaches are constantly a challenge. Mohammadi *et al.*, for instance, developed a catalyst-free four component domino synthetic approach towards the synthesis of spirooxindole pyrans using amine derivatives (alkyl or benzyl), bis(methylthio)-2-nitroethene, isatin, and enolizable active methylene derivatives (pyrazolone, barbituric acid, 1,3-indandione and 2-hydroxy-1,4-naphthoquinone) as reagents (Scheme 92A). The authors underlined the use of ketene amins (derived from the addition of amine derivatives to nitroketene dithioacetals) for the first time in this synthetic 4-MCR. The ketene amins underwent further Michael addition with the Michael acceptor intermediate formed through Knoevenagel condensation between isatin and enolizable active methylene structures. The

final intramolecular *O*-cyclization step allows the formation of the desired multicyclic spirooxindole pyran scaffolds. Despite moderate yields, this convenient one-pot process comprises simple work-up procedures and high molecular diversity (17 examples).^[175] Mohebat *et al.* also reported a 4-MCR methodology for the synthesis of spirooxindole pyran derivatives, by promoting the reaction between 2-hydroxy-1,4-naphthoquinone, benzene-1,2-diamine, cyclic 1,3-dicarbonyl compounds and isatin using *p*-TSA as catalyst (Scheme 92B). This solvent-free protocol affords the synthesis of complex fused heterocyclic frameworks, through the formation of five new bonds (two C–C, two C=N and one C–O) and two new rings in a single operation. Despite poor reaction scope, compared to the method described above (Scheme 92A), the reaction could be performed under convectional heating or microwave irradiation.^[176]

The already described application of oxalic acid dihydrate: proline LTTM as reaction promoter was, once again, used by Chandam *et al.* in order to obtain spiro[diindenopyridine-indoline]-trione derivatives in a 4-MCR approach.^[177] The methodology uses isatin derivatives, two equivalents of 1,3-indandione, and aniline derivatives and allows, in short reaction times, access to spiro[diindenopyridine-11,3'-indoline]-trione derivatives (16 examples) in good yields and good reaction scope (Scheme 93A). Easy work-up and good recyclability of the LTTM (after four successive cycles the yield of the desired product remained unchanged) are the main advantages of this approach.^[177] Curiously, Ghasemzadeh *et al.* reported the same 4-MCR approach, using the same



Scheme 92. 4-MCR approach for the synthesis of spirooxindole-pyran derivatives.



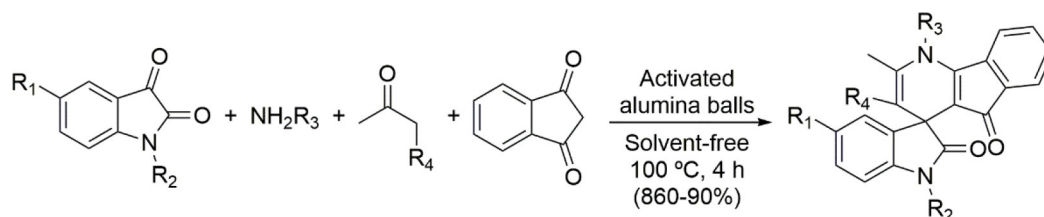
Scheme 93. Different 4-MCR approaches using isatin derivatives, amine derivatives and 1,3-dicarbonylic compounds in the synthesis of spirooxindole derivatives.

starting materials in solvent-free conditions, using zinc terephthalate metal-organic frameworks (Zn(BDC)MOF) as catalyst (Scheme 93B). Using the same reaction temperature there was no significant differences in the reaction times and yields of the various spiro[diindeno[1,2-*b*:2',1'-*e*]pyridine-11,3'-indoline]-trione products (15 examples). Zn(BDC)MOF is non-toxic, inexpensive, easy to synthesize, economical and was reused at least six times without loss of activity.^[178]

Concerning the synthesis of similar spirooxindole derivatives using a 4-MCR protocol, Bagheri *et al.* reported the use of a dual-functional silica-based catalyst (FSi-PrNH-BuSO₃H) with isatins, 1,3-indandione, ethyl acetoacetate (or ethyl benzoylacetate), and ammonium acetate (Scheme 93C). The catalyst was prepared by modifying fumed silica (FSi), a nanosized type of silica, with dual functions of acid (SO₃H) and base (NH), affording amino sulfonic acid fumed silica. In refluxing ethanol, this heterogenous catalyst proved to be efficient in the synthesis of azafluorenone derivatives. Despite short reaction times and moderate scope (8 examples), no information concerning the recyclability of the catalyst was provided by the authors.^[179]

An example of a sustainable approach for the synthesis of spiro[indololo-3,4'-indeno[1,2-*b*]pyridine] derivatives is the one reported by Mukhopadhyay and co-workers, using activated alumina balls under solvent-free conditions. The 4-MCR involving isatins, primary amines, indane-1,3-dione, and β -ketoester allowed the preparation of the desired products (12 examples) in moderate to good yields (Scheme 94). The recyclable and reusable catalyst presented a loss of approximately 10% activity after 10 cycles, and its mechanism of action was hypothesized to be related to the ability of the alumina balls to trap water molecules released during the reaction in its pores, driving the reaction in the direction of the spirooxindole derivatives.^[180]

Recently, the same research group explored a catalyst-free synthesis of dihydrospiro[indeno[1,2-*b*]pyridine-4,3'-indoline]-3-carbonitrile derivatives (26 examples), *via* a Knoevenagel condensation/Michael addition/intramolecular nucleophilic addition/cyclization. The synthetic procedure occurs with short reaction times under microwave irradiation, allowing the preparation of the desired products in very good yields



Scheme 94. Activated alumina balls promoted 4-MCR.

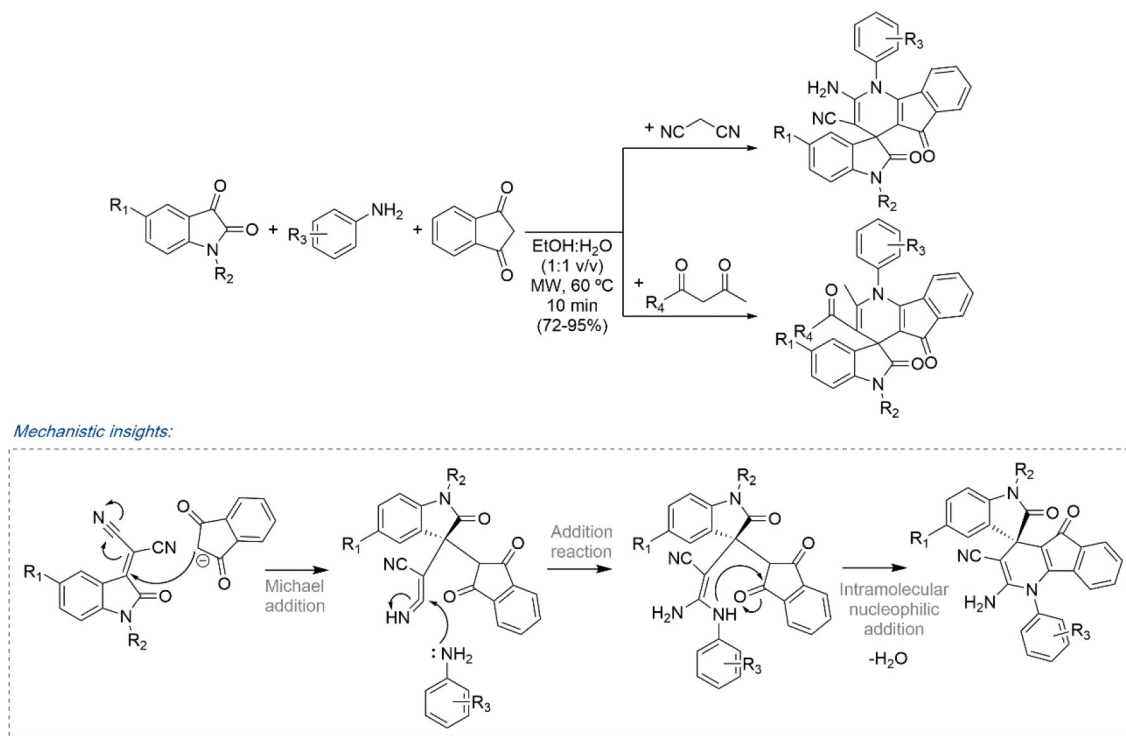
(Scheme 95).^[181] A speculative mechanism is included in Scheme 95.

Karimiyan and Rostamizadeh reported the synthesis of spirooxindole derivatives with 1,4-dihydropyridine heterocycles attached starting from isatin derivatives, 1,1-bis(methylthio)-2-nitroethylene, diamines, and malononitriles using a sulfonic functionalized magnetic graphene oxide ($\text{Fe}_3\text{O}_4\text{-GO-SO}_3\text{H}$) as catalyst (Scheme 96A and B). The 4-MCR proceeds under solvent-free conditions, with short reaction times and moderate to good yields. The recyclability of the catalyst was also studied, showing that it could be used for five runs, after being easily recovered from the reaction mixture with an external magnet. An interesting observation seen here was the fact that using malononitrile (Scheme 96A) or ethyl cyanoacetate (Scheme 96B) the formation of two distinct products was demonstrated. The authors hypothesized that the reaction was triggered by the formation of the first intermediate (product from the Knoevenagel reaction between isatin and the malononitrile derivative), then Michael addition of the ketene aminal (formed by condensation between amine derivative and the nitroethylene reagent) to the previously formed intermediate resulted in the formation of the second intermediate which undergoes intramolecular cyclization that can proceed *via* two different pathways: (a) attack of the NH group onto the cyano group (Scheme 96A) or (b) the ester

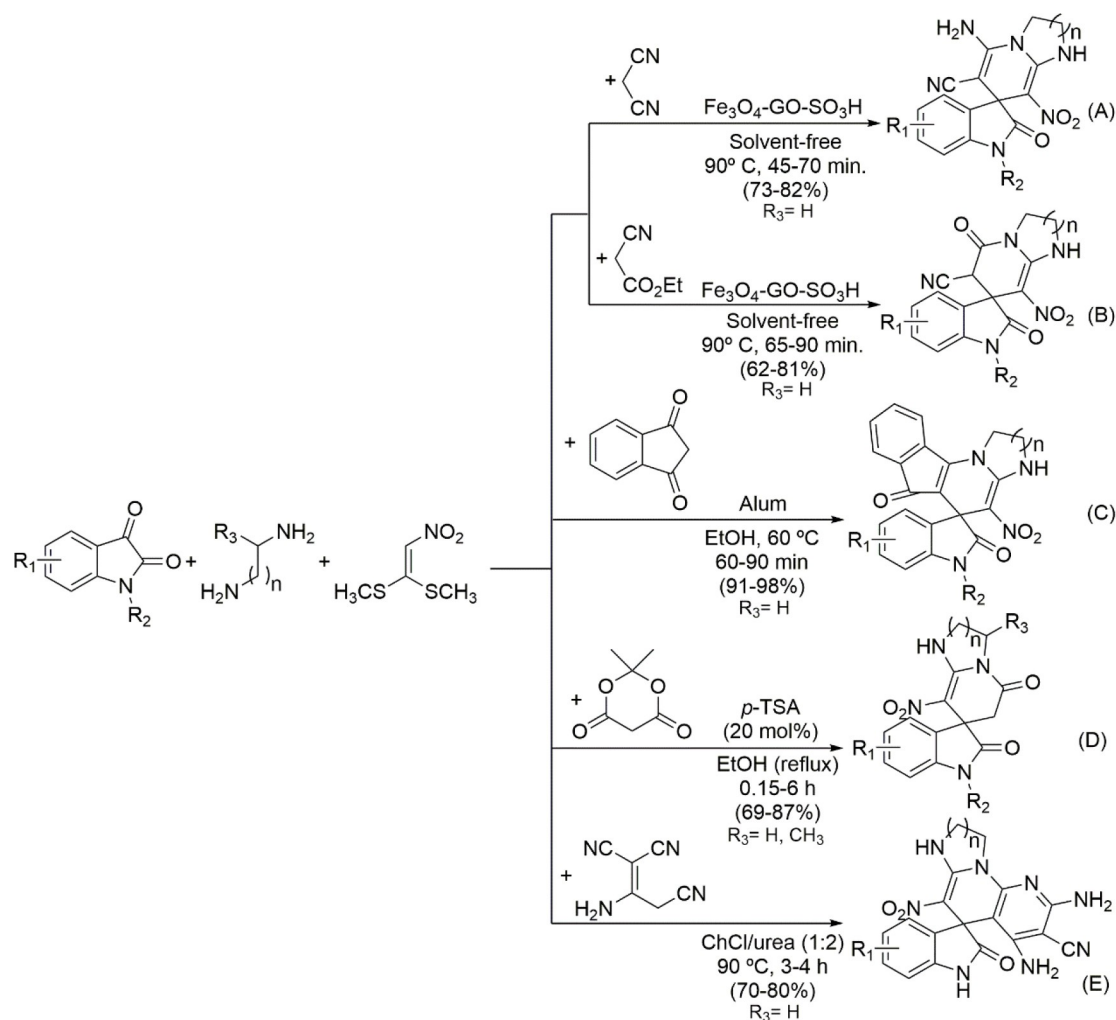
group (Scheme 96B). Unfortunately, the protocol demonstrated poor scope on the isatin components (8 examples).^[182]

The group of Mohammadi *et al.* reported a related 4-MCR using similar starting materials and a different heterogeneous catalyst (Scheme 96C). The commercially available aluminum potassium sulfate dodecahydrate ($\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ (Alum)) was found to catalyze efficiently several chemical synthetic transformations, with the advantage that it is inexpensive, nontoxic and easily available. The researchers decided to use this heterogeneous catalyst in the one-pot 4-MCR between isatin derivatives, 1,1-bis(methylthio)-2-nitroethylene, diamines and 1,3-indandione, affording the 4-nitro-2,3-dihydro-spiroimidazo[1,2-*a*]indeno[2,1-*e*]pyridine-5,3'-indoline-2',6(1*H*)-dione derivatives in good to excellent yields (10 examples). The reaction showed good scope, short reaction times, mild conditions and easy work-up.^[183]

Recently, Rahimi *et al.* used *p*-TSA as an efficient organo-catalyst for the synthesis of spirooxindole derivatives (10 examples). In this case, besides isatin, diamines, and 1,1-bis(methylthio)-2-nitroethylene, 2,2-dimethyl-1,3-dioxane-4,6-dione (or Meldrum's acid) was employed as the fourth component of the reaction (Scheme 96D).^[184] A catalyst-free methodology was described by Shaabani *et al.*, using DESs, in particular choline chloride/urea, as reaction media, to prepare a small library (3 examples) of spirooxindole-naphthyridine



Scheme 95. Catalyst-free synthesis of dihydrospiro[indeno[1,2-*b*]pyridine-4,3'-indoline]-3-carbonitrile derivatives *via* 4-MCR with a putative mechanistic pathway.



Scheme 96. Similar 4-MCR protocols to the synthesis of 4-nitro-2,3-dihydrospiro[imidazole-pyridine] compounds with different starting materials and catalysts.

derivatives. This time, the fourth component consisted of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (Scheme 96E).^[185]

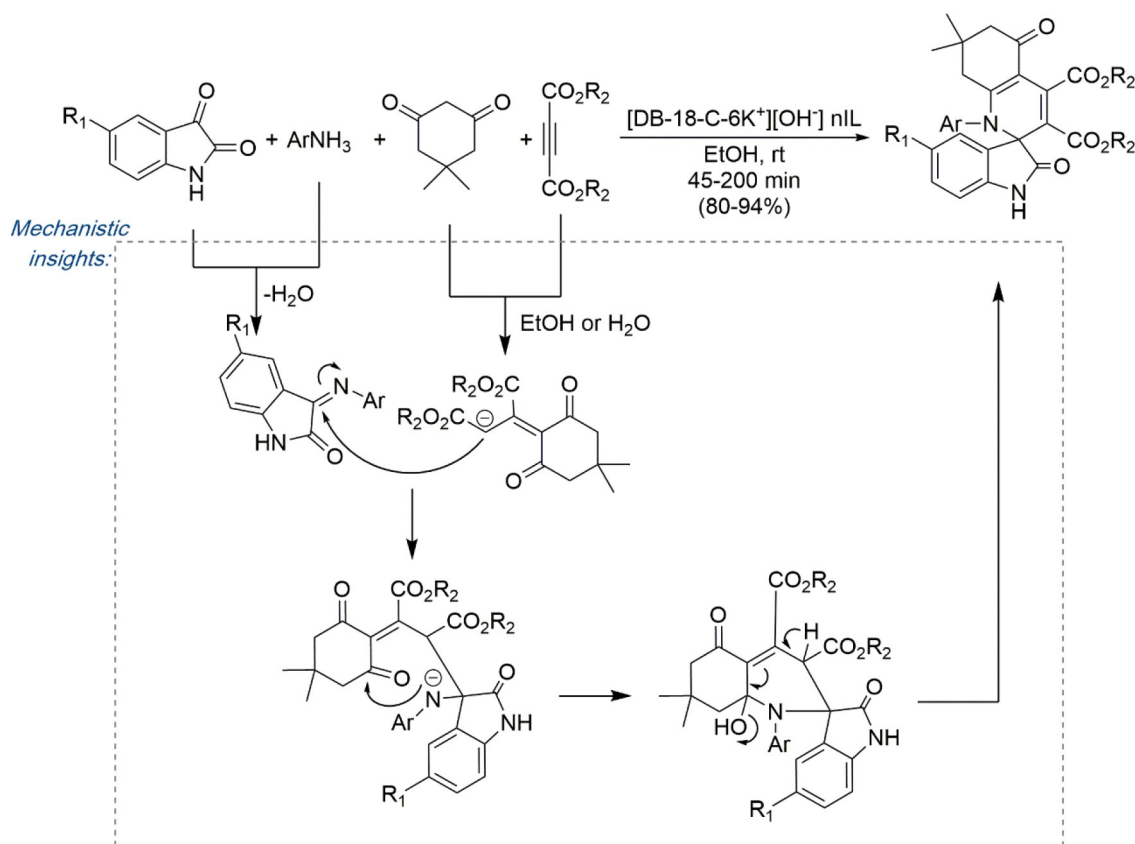
2.2.2.2. Miscellaneous

Nikoofar and Khani reported a remarkable new catalyst, consisting of a nano-sized crown ether-based ionic liquid ([DB-18-C-6 K⁺][OH⁻] nIL - based on dibenzo-18-crown-6). This catalyst allowed the 4-MCR between isatins, amines, dimedone, and dialkylacetylenedicarboxylates under mild conditions, leading to the formation of the desired spiro[indoline-3,2'-quinoline] derivatives (15 examples) in very good to excellent yields (Scheme 97).^[186] The catalyst has both acidic and basic centers which is crucial for catalyzing the reaction. The acidic unit is likely responsible for the activation of the C-3 carbonyl of isatin, facilitating the formation of the imine intermediate. Basic catalysis is presumed to be involved

in the conversion of dimedone to its enolic form, which reacts with the dialkylacetylenedicarboxylates, that is then followed by a second Michael reaction, cyclization and a key dehydration step to give the desired spiro[indoline-3,2'-quinoline] derivatives (Scheme 97).

2.2.3. MCRs with 5 Components

Sarkar and co-workers reported a very interesting synthesis of spirochromenocarbazole tethered 1,2,3-triazoles using a one-pot, 5-MCR approach between *N*-propargyl isatin derivatives, malononitrile, benzyl bromide derivatives, sodium azide, and dimedone (or 4-hydroxyl-6-methyl-2*H*-pyran-2-one or 4-hydroxycarbazole) (Scheme 98).^[187] The authors previously used cellulose-supported cuprous iodide nanoparticles (Cell-CuI NPs) as an efficient heterogenous catalyst for some synthetic transformations. In the synthesis of these spiroox-



Scheme 97. Crown ether-based ionic liquid as catalyst for a 4-MCR with the postulated mechanism.

indole derivatives with a 1,2,3-triazole moiety they successfully used the same heterogeneous catalyst, obtaining a remarkable library of several derivatives (total of 59 examples) in good yields, short reaction times and with mild reaction conditions. Upon completion of the reaction, the heterogeneous catalyst was separated by filtration from the reaction mixture and could be reused on the next run without loss of activity (at least four consecutive cycles). Studies concerning catalyst leaching were also performed, assuring no copper was released from the catalyst.^[187]

Despite the lack of examples in the literature on the synthesis of spirooxindole-pyran derivatives by a 5-MC approach, the examples that we found and reported above were interesting and of relevance, particularly from the point of view of catalysis, sustainability and eco-friendliness.

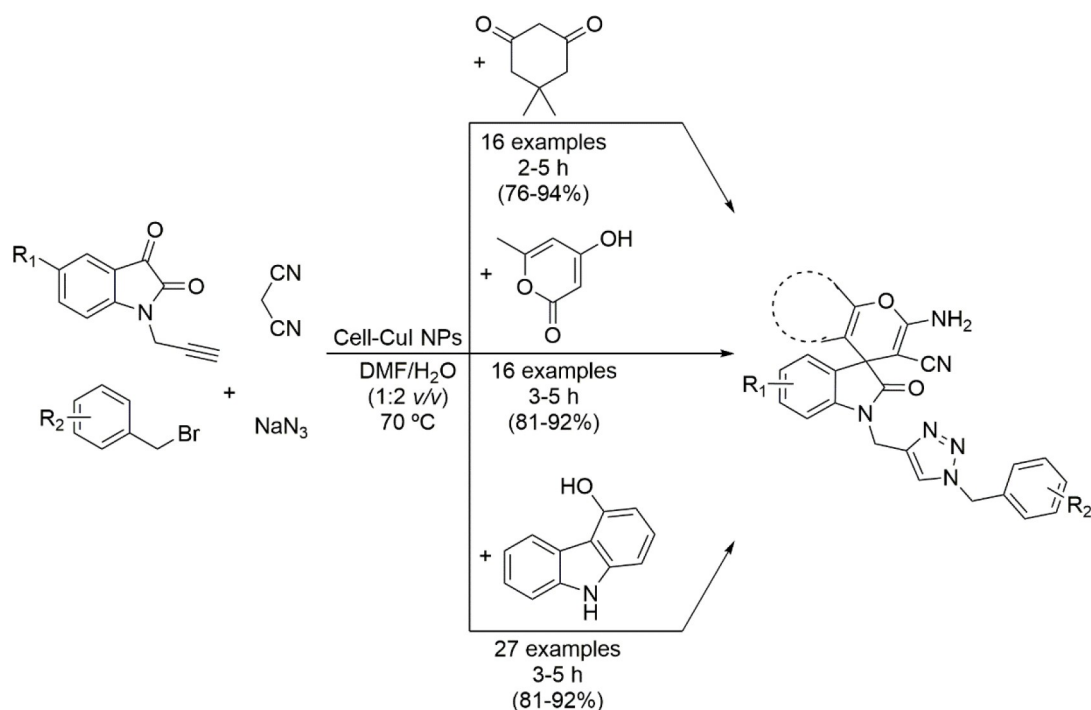
2.3. Other Ring Size-membered Spirocyclic Systems

2.3.1. MCRs with 3 Components

The dibenzo[1,4]diazepine scaffold is a seven-membered heterocycle, an important moiety present in several pharma-

ceutical and natural products with biological interest. Nagaraju *et al.* reported an efficient, one-pot, three-component and sustainable method for the synthesis of a wide variety of spirobenzodiazepine derivatives (21 examples), with excellent yields in short reaction time. The reactions were carried out using *o*-phenylenediamines, tetrone acid, and isatin derivatives, and catalyzed by the eco-friendly and cheap sulfamic acid, using water as solvent (Scheme 99). The proposed mechanism for this reaction proceeds *via* C–C and C–N bond formations (intramolecular cyclization approach).^[188]

De *et al.* reported the synthesis of spirodibenzo[1,4]diazepine derivatives (22 examples) mediated by a 3-MCR of isatins, cyclic 1,3-diketones, and 1,2-phenylenediamines (Scheme 100). After optimization of the reaction conditions, the synthesized Zeolite-Y NP nanopowder catalyst was the best choice as a heterogeneous acid catalyst, resulting in an enamine formation reaction followed by intramolecular Mannich type reaction with the starting reagents. The reaction proceeds in short reaction times, good yields and excellent scope. The catalyst could be reused at least seven times without loss of activity, which is also an advantage of this methodology.^[189] Regarding the mechanism, it is believed that the formation of



Scheme 98. One-pot 5-MCR in the synthesis of spirochromenocarbazole tethered 1,2,3-triazoles using Cell-CuI NPs as heterogeneous catalyst.

the imine intermediate is catalyzed by the acidic Zeolite-Y catalyst, followed by cyclization at the imine-carbon to give the crucial 7-membered diazepine ring (Scheme 100).

Ganata *et al.* reported a 3-MCR approach to the synthesis of spiro[indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepine]diones, similarly attractive frameworks, using also an heterogeneous nanopowder catalyst consisting of copper ferrite (CuFe₂O₄ NP). Using *N*-unsubstituted isatin derivatives, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, and 2-mercaptoacetic acid derivatives in refluxing water, the desired spiro-seven-membered ring oxindole derivatives were obtained in moderate to excellent yields (Scheme 101). The easy work-up, as well as the already described advantages of using magnetic heterogeneous catalysts, highlight the interest of this synthetic approach, despite moderate reaction scope (only 10 examples were synthesized). Recyclability of the catalyst was also evaluated over six runs, and the catalytic activity started to drop from the third run (78% and 62% yields at the third and sixth run, respectively).^[190]

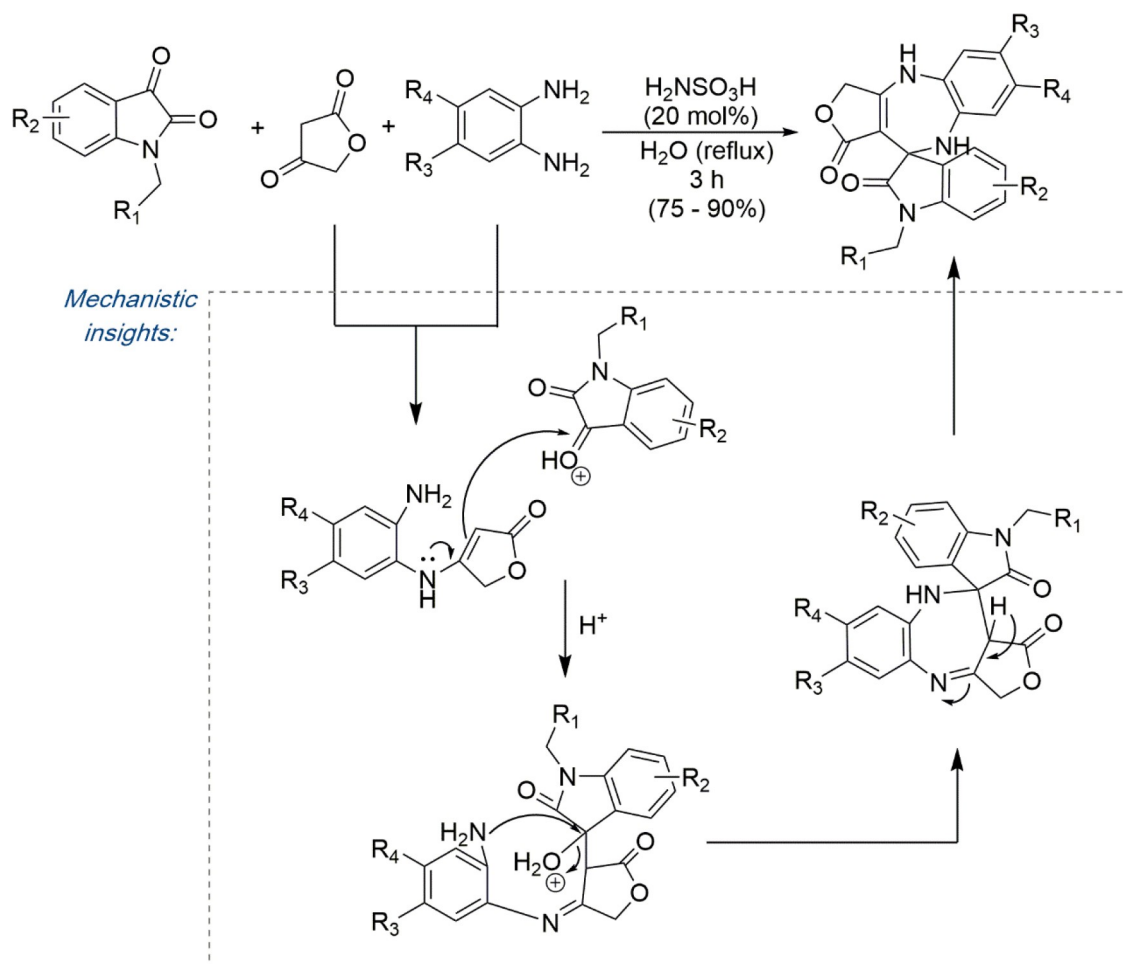
Guo *et al.* reported the copper catalyzed three component asymmetric azide-alkyne [2 + 2] cycloaddition/cascade reaction to access optically active spiroazetidinimine oxindoles (21 examples) with a high level of enantio-induction (up to >19:1 *dr* and up to 99% *ee*) as well as good to excellent isolated yields (Scheme 102). Chiral *L*-ramipril-derived guanidine was the best ligand tested to perform this synthetic

transformation among sulfonyl-azide derivatives, terminal alkynes and isatin-imines. This chiral guanidine/CuI complex traps the *in situ* generated ketenimines from azides and alkynes, affording a variety of spiroazetidinimine derivatives. The reaction had a remarkable scope and proceeded under mild reaction conditions.^[191]

2.4. Methodology Considerations

Among the different scaffolds that can be attained by using isatins in MCRs, the preparation of spirooxindole derivatives is, undoubtedly, the most commonly performed approach. Having this in consideration we decided to summarize two critical aspects of the wide variety of methodologies addressed in this work – the nature of the C–H acidic substrates (Table 1) and the catalysts used (Table 2). It is observed that while 1,3-dicarbonyl compounds, namely dione, 1,3-cyclohexadione and β-ketoesters are the most explored substrates, in recent years, the scope and structural diversity of spirooxindole derivatives was considerably widened by using less explored C–H acidic compounds, such as tetrone acid, hydantoin or isatoic anhydride, to name a few. Table 1 summarizes the structures employed in these chemical transformations.

The selection of the proper catalyst for each chemical transformation is of paramount importance. As shown in this



Scheme 99. One-pot, three-component synthesis of spirobenzodiazepine derivatives using sulfamic acid as catalyst and proposed reaction mechanism.

work, there are several types of catalysts employed in the synthesis of spirooxindole derivatives. Table 2 summarizes the main classes of catalysts, dividing them into three main classes (homogenous catalysts, heterogeneous catalysts and heterogeneous nanocatalysts, since this last one plays a very important role in recent synthetic procedures), and into different categories according to their composition and chemical properties.

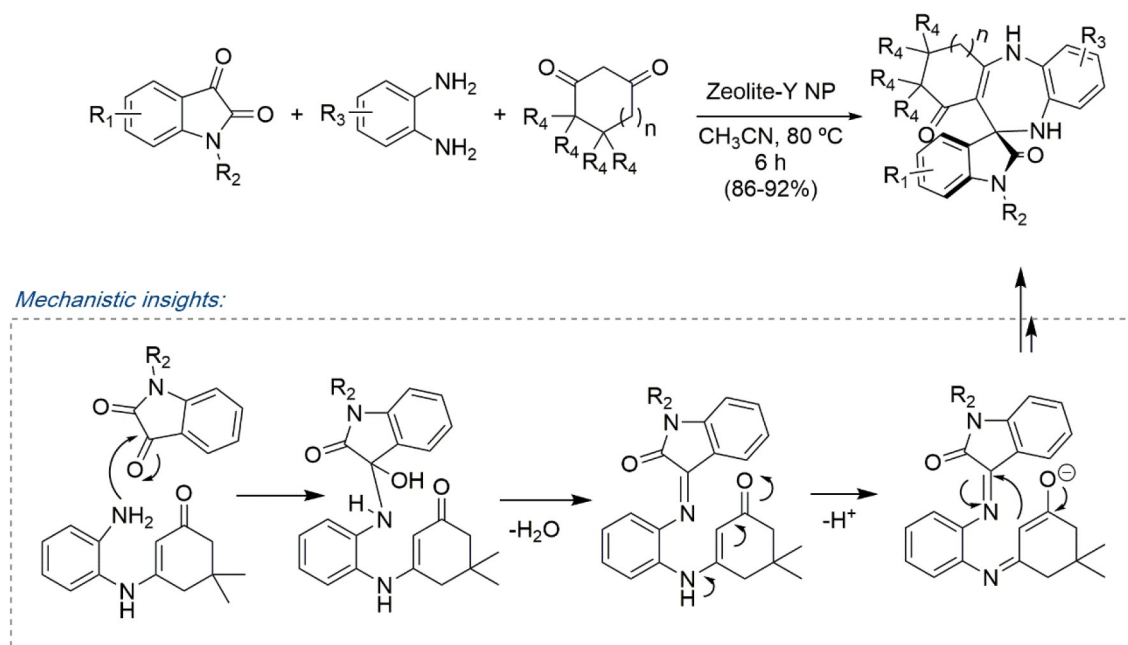
3. Bis-oxindole Derivatives

3.1. 1,3-Dipolar Cycloaddition

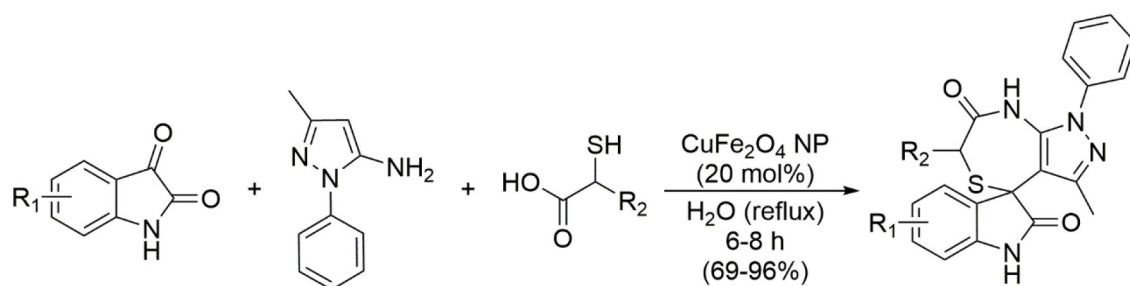
Multicomponent reactions have been widely applied in the preparation of bis-oxindole derivatives as well. In this section, we will also include spirooxindole derivatives bearing two oxindole moieties, generally obtained through the versatile and well-established 1,3-dipolar cycloaddition.^[192] The most widely

reported methodology is the three-component reaction between isatin and sarcosine (*N*-methylglycine), which generate an azomethine ylide *in situ* and a second oxindole-bearing reactant, such as 3-(1*H*-indol-3-yl)-3-oxo-2-(2-oxoindolin-3-ylidene)propanenitrile (Scheme 103A),^[193] 3-aryl-5-arylmethylenespiro[indole-3',2-[1,3]thiazolane]-2'(1*H*),4-dione (Scheme 103B)^[194] and isatylidene-chromanones (Scheme 103C).^[195] The resulting pyrrolidinyl-dispirooxindole derivatives (22 examples), tripirolyrrolidine bis-oxindole derivatives (13 examples) and chromanone-fused 3,3'-pyrrolidinyl-dispirooxindole derivatives (15 examples), respectively, were prepared in very good yields under catalyst-free conditions. A suggested mechanistic route is shown in Scheme 103.

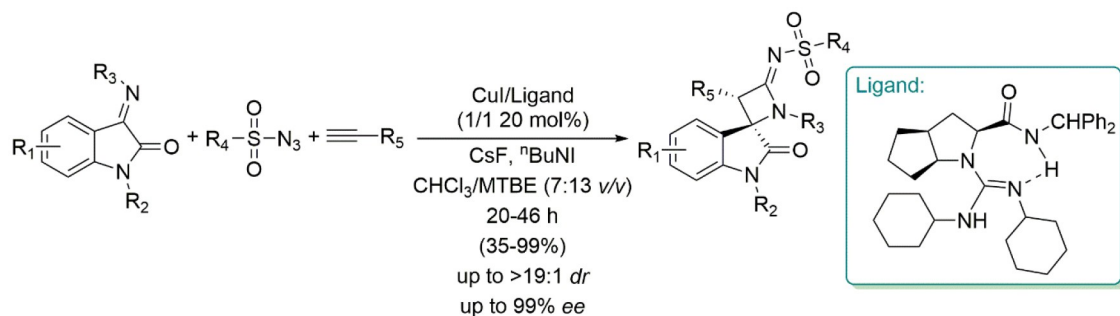
Other examples include, pyrrolidinyl-dispirooxindole derivatives obtained also through 1,3-dipolar cycloaddition, with some differences, such as the application of proline or thioproline instead of sarcosine to generate the azomethine



Scheme 100. Zeolite-Y NP catalyzed 3-MCR for easy access to spirodibenzo[1,4]diazepines with a mechanistic proposal.



Scheme 101. CuFe₂O₄ NPs as efficient heterogeneous catalyst in the synthesis of spiro[indoline-3,4-pyrazolo[3,4-e][1,4]thiazepine]diones.

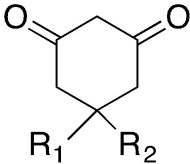
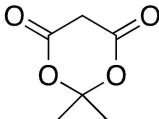
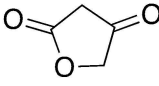
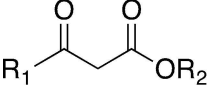
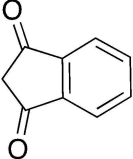

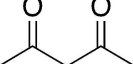
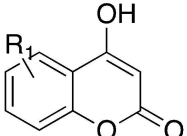
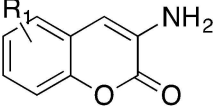
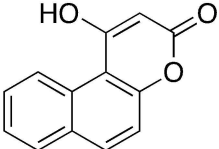
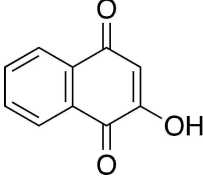


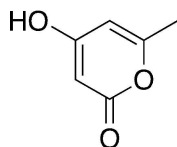
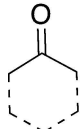
Scheme 102. Chiral guanidine/copper catalyzed asymmetric three component azide-alkyne [2+2] cycloaddition/cascade reaction.

ylide intermediate. In this example, reported by Lin *et al.* 34 different 3,3'-pyrrolidinyl-dispirooxindole derivatives were synthesized (Scheme 104A).^[196] Proline and sarcosine were also

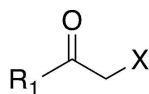
used by Taghizadeh *et al.* in a pseudo five-component reaction, using a bis-chalcone as a bis-dipolarophile, giving the final products in very good to excellent yields (18 examples)

Table 1. Scope of C–H acid substrates applied in the synthesis of spirooxindole derivatives.

1,3-Dicarbonyl substrates			
Substrate	References	Substrate	References
	[42], [60], [63], [66], [67-74], [76-78], [80], [82-84], [87-93], [98], [101-104], [114-118], [120], [124], [126-127], [130], [133-136], [138-139], [142], [146-147], [155], [156], [158], [176], [186-187], [189]		[98], [138], [147], [184]
1,3-cyclohexanediones			[188]
	[56], [60-61], [63-64], [68], [72], [76], [82-84], [86], [90], [92], [102], [119], [126], [140], [151], [153], [159], [161-167], [169-170], [179-180]		
β -ketoesters			
	[46], [59], [84], [92], [116], [130], [142], [148], [150], [152], [158], [175-181], [183]		
1,3-indandione			
Substrate	References	Substrate	References
	[68], [82], [89], [104], [114], [130]		
1,3-cyclopentadione			
	[58], [64], [68], [72]		
acetylacetone			
Other carbonyl and phenol substrates			
Substrate	References	Substrate	References
	[46], [60], [63], [68], [72-73], [75-78], [81-84], [89-94], [101], [104], [113-114], [116], [118], [122-123], [126], [139], [147-149]		[115]
4-hydroxycoumarin and derivatives			
			

1-hydroxy-3*H*-benzo[*f*]
chromen-3-one [95]4-hydroxy-6-methyl-2*H*-
pyran-2-one [46], [81], [139], [147], [171], [187]

cyclic ketones [86], [102], [157], [174]

 α -cyano ketones [143]

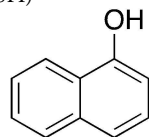
(X=CN) [45]

 α -hydroxy ketones [52]

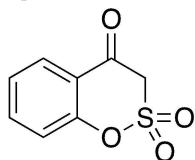
(X=OH)

 α -mercapto ketones

(X=SH)

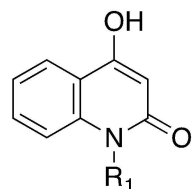
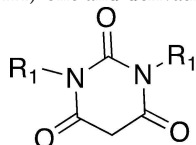
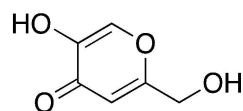
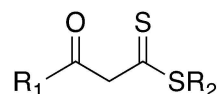
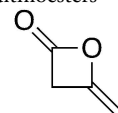


1-naphthol [83], [102]

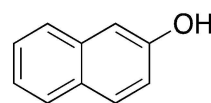
1,2-benzoxathiin-4(3*H*)-
one 2,2-dioxide [111]*O,N*-derivatives

Substrate

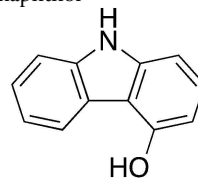
References

4-hydroxyquinolin-
2(1*H*)-one and derivatives [90], [94], [123], [147]2-hydroxy-1,4-naphthoqui-
none [63], [105], [130],
[145], [148], [172-
173], [175-176]5-hydroxy-2-(hydroxymeth-
yl)-4*H*-pyran-4-one [81], [84] β -oxodithioesters [62]

Diketene [168]



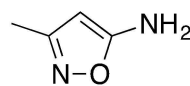
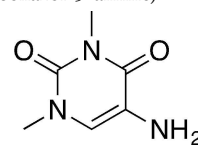
2-naphthol [63], [83-84], [102]



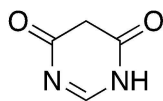
4-hydroxycarbazole [187]

Substrate

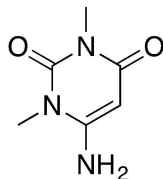
References

5-aminoisoxazoles (3-meth-
ylisoxazol-5-amine) [128], [130], [148],
[149]

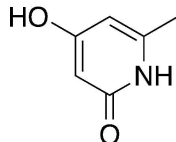
barbituric acid and derivatives [46], [60–61], [63], [68], [74], [82–84], [86–87], [89], [91–92], [96], [98], [101], [113], [118], [131], [136], [138], [142], [156], [175]



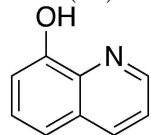
4,6-(1*H*,5*H*)-pyrimidine-dione [106]



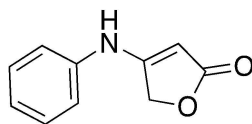
6-amino-1,3-dimethyluracil and derivatives [99], [131]



4-hydroxy-6-methylpyridin-2-(1*H*)-ones [110], [123]



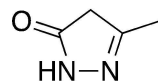
8-hydroxyquinoline [112]



Anilinolactone [100]

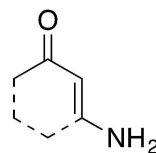
N,N-derivatives

Substrate

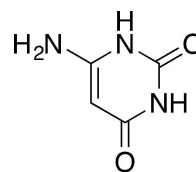


2,4-dihydro-5-methyl-pyrazol-3-one and derivatives

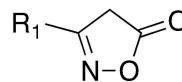
5-amino-1,3-dimethyluracil [96–97]



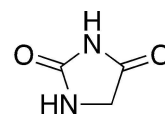
cyclic enamines [65], [141]



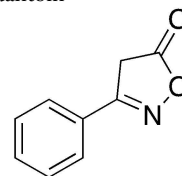
6-aminopyrimidine-2,4-(1*H*,3*H*)-dione [121]



isoxazol-5-(4*H*)-one derivatives [79]



hydantoin [46]



3-phenylisoxazolone [147]

Substrate

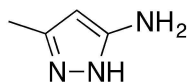
References

Substrate

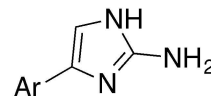
References

Substrate

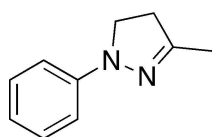
References



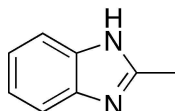
3-methyl-1*H*-pyrazol-5-amine [123–125], [128], [142], [149], [190]



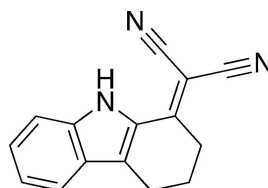
2-amino-4-arylimidazoles [44]



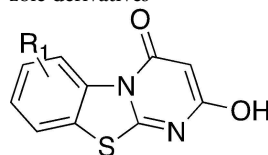
3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazole and derivatives [175]



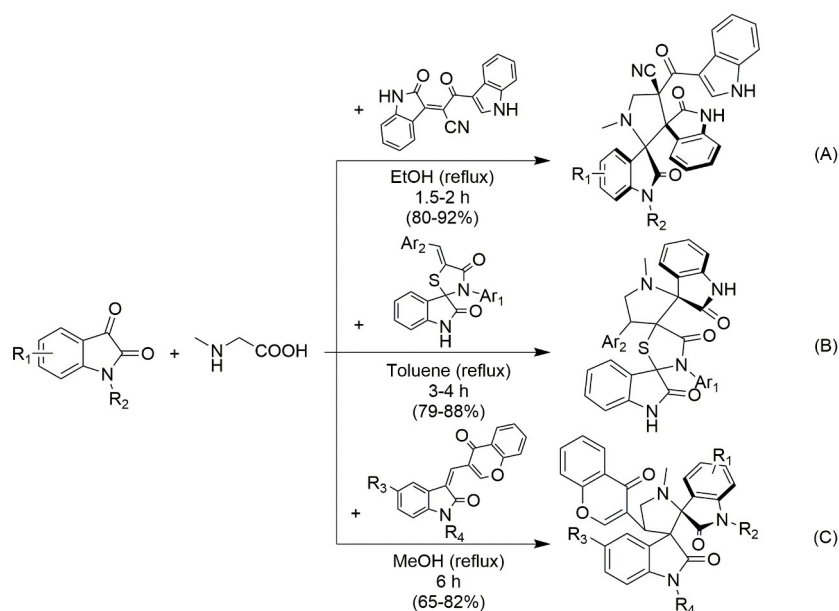
2-methylazaarenes [129]



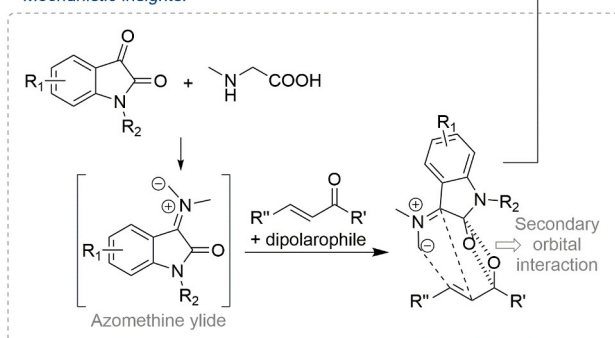
1-(dicyanomethylene)-2,3,4,9-tetrahydrocarbazole derivatives [85]



2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones [117]



Mechanistic insights:



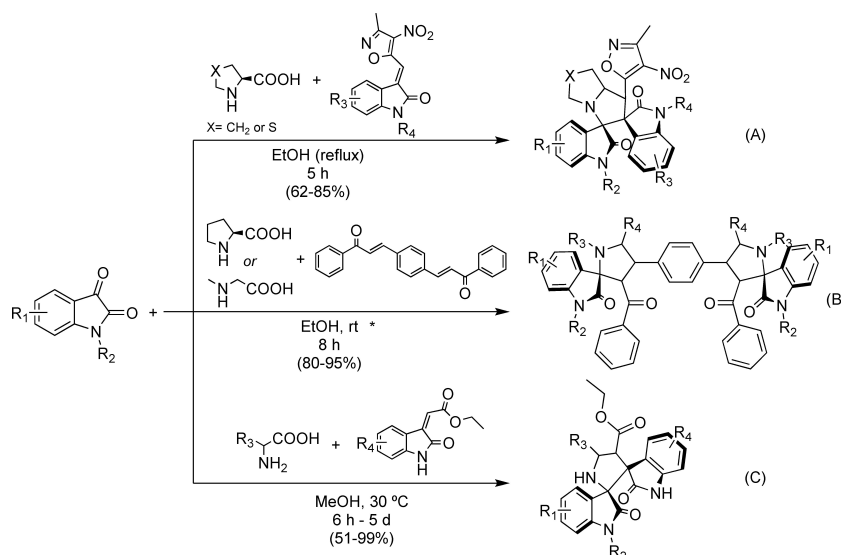
Scheme 103. Examples of 1,3-dipolar cycloadditions between isatin, sarcosine and different dipolarophiles and a putative mechanism.

Table 2. Different catalysts applied in the synthesis of spirooxindole derivatives.

Homogeneous Catalysts	Heterogeneous Catalysts	Heterogeneous Nanocatalysts
	Brønsted acids	
DBSA ^[50] caffeinium hydrogen sulphate ^[91] Na ₂ EDTA ^[92] citric acid ^[107] AcOH ^[122] sulfamic acid ^[188] taurine ^[46]	silica supported tungstic acid ^[42] GN/SO ₃ H ^[77] amberlyst-15 ^[79] SiO ₂ @Pr-DABCO-SO ₃ H]Cl ₂ ^[87] C-SO ₃ H ^[123,171] DTP/SiO ₂ ^[129] SBA-Pr-SO ₃ H ^[131,135] MMT-ZSA ^[166] FSi-PrNH-BuSO ₃ H ^[179]	Fe ₃ O ₄ @DA-SO ₃ H MNPs ^[69] Fe ₃ O ₄ /COS@β-CD-SO ₃ H NPs ^[70] CoFe ₂ O ₄ /SiO ₂ /SO ₃ H NPs ^[73] [Fe ₃ O ₄ @SiO ₂ @Pr-DABCO-SO ₃ H]Cl ₂ MNPs ^[86] Fe ₃ O ₄ @SiO ₂ -imid-PMA ^{n[97]} Fe ₂ O ₃ @cellulose-OSO ₃ H ^[162] γ-Fe ₂ O ₃ @SiO ₂ -SCH ₂ CO ₂ H ^[173] Fe ₃ O ₄ @Propylsilane@Histidine[HSO ₄ ⁻] NPs ^[99] Zeolite-Y NPs ^[189] Fe ₃ O ₄ -GO-SO ₃ H MNPs ^[182]
	Bases	
NEt ₃ ^[56] DBU ^[58] Na ₂ CO ₃ ^[61] DMAP ^[62] DABCO ^{[81], [82], [85], [157]} C ₄ (DABCO) ₂ .2OH ^[83] NaOAc ^{[94], [66], [110]} urea ^[95] TEA ^[111] CsF ^[113]	P4VPy ^[75] IRA-400 Cl ^[76]	Fe ₃ O ₄ @SiO ₂ -TCT-theophylline ^[96] Fe ₃ O ₄ @SiO ₂ -NH ₂ MNPs ^[161]
	Lewis acids	
I ₂ ^{[114], [115], [168]} p-TSA.H ₂ O ^{[116], [128], [158], [176], [184]} H ₃ PW ₁₂ O ₄ ^[117] NbCl ₅ ^[170] BF ₃ .Et ₂ O ^[67] AgCO ₃ ^[48]		NiFe ₂ O ₄ NPs ^{[12], [57]} SnO ₂ NPs ^[74] ZrO ₂ NPs ^[98] NiO-SiO ₂ ^[125] NiO@g-C ₃ N ₄ ^[126] ZnO nanodisks ^[127] SrFe ₁₂ O ₁₉ MNPs ^[154] Cell-CuI NPs ^[187]
	Organocatalysts	
L-proline and melamine ^[63] cinchona alkaloid-thiourea ^[64] cinchona alkaloids ^[65] THAM ^[93] quinolinic acid ^[118] 2-aminopyridine ^[119] NaN ₃ ^[120] sodium formate ^[121] CSA ^[130] BINOL-derivative phosphoric acid ^[153]	calix[4]arene tetracarboxylic acid (C4 A4) ^[155]	
	Biocatalysts	
BSA ^[109] papain ^[124] α-casein ^[169]		
	Ionic liquids	
[Bmim]Br ^[19] [Bmim]BF ₄ ^[20] [TMG][Ac] ^[26] DABCO-H]Cl ^[84] [Bmim]OH ^[103] [Cmpy]I ^[104] MOACS ^[106] ([DB-18-C-6K ⁺][OH ⁻]) nIL ^[186]		SBA-IL ^[105]
	Metals and MOFs	
Dinuclear Zn ^[45] CuI/DBU ^[51]	Fe ₂ O ₃ ^[72] Ni-Gly-isatin@boehmite ^[172]	ZnFe ₂ O ₄ NPs ^[71] Fe ₃ O ₄ MNPs ^[151]

Table 2. continued

Homogeneous Catalysts	Heterogeneous Catalysts	Heterogeneous Nanocatalysts
CuSO ₄ ·5H ₂ O ^{[54], [55], [59]} chiral guanidine/CuI ^[191] Ag(I)-NHC complex ^[174]	PANI/Fe ₃ O ₄ /CNT ^[163] Zn(BDC)MOF ^[178]	Fe ₂ O ₃ @SiO ₂ @VitB1 MNPs ^[167] FeAl ₂ O ₄ MNPs ^[172] Fe ₃ O ₄ @L-arginine MNPs ^[164] Ru ^{III} @CMC/Fe ₃ O ₄ MNPs ^[165] CuFe ₂ O ₄ NPs ^[190] Cell-CuI NPs ^[187]
	Miscellaneous	
trisodium citrate dehydrate ^[60] Borax ^[68] SDS ^[108] sodium <i>p</i> -toluene sulfonate ^[132] TBAB ^[133] KAl(SO ₄) ₂ ·12H ₂ O ^[183]	HPA-F-SBA-LDH ^[80] SiO ₂ @g-C ₃ N ₄ ^[78] starch ^[88] isinglass ^[89] eggshell ^[90] Fe ₃ O ₄ /GO-Mo ^[100] APTOSS ^[101] C _x H _{3-x} PW ₁₂ O ₄₀ -ZZP ^[102] NiCo ₂ O ₄ @Ni(BDC) ^[152] activated alumina balls ^[180]	
	Reaction promoters	
piperidine ^[112] <i>p</i> -TSA ^[134] NH ₄ OAc ^[160] LTTM ^[177]		



* This reaction requires 2 equiv. of isatin and 2 equiv. of sarcosine/(thio)proline

Scheme 104. Examples of 1,3-dipolar cycloaddition between isatin, (thio)proline/primary amino acids and different dipolarophiles.

(Scheme 104B).^[197] Recently, Qian *et al.* explored the use of several primary amino acids in the 1,3-dipolar cycloaddition, combining them with different isatins and methyleneindolinones as dipolarophile. The resulting pyrrolidinyl-dispirooxindole derivatives (30 examples) (Scheme 104C) were obtained using long reaction times, under mild conditions.^[198]

Also in the context of the development of the 3-MCR *via* azomethine ylide mediated 1,3-dipolar cycloaddition condensation, Kumar *et al.* reported a different synthetic approach highlighting environmentally friendly reaction conditions and the use of inexpensive catalysts. ZnO nanoparticles (NPs) were successfully applied as the heterogeneous catalyst for this

reaction, which was carried out using water as solvent at room temperature. A library of novel dispiroindolizidine bis-oxindole derivatives (10 examples) was obtained with regio- and diastereoselectivity in good yields (Scheme 105). The protocol was found to be efficient also on a gram-scale, but the efficiency of the catalyst was found to decline with the number of cycles, with significant loss of catalytic activity after three cycles, mostly due to NP aggregation. Absence of chromatographic purification steps, inexpensive heterogeneous catalyst and use of aqueous solvent medium represent the main advantages of this methodology.^[199]

PEG-400 emerged as a suitable green alternative as reaction medium in a wide variety of reactions.^[200] The versatility of this solvent was explored in the four component synthesis of bis-oxindole derivatives, through a stereoselective copper-catalyzed [3+2] azide-alkyne cycloaddition followed by the already described [3+2] azomethine ylide and alkene cycloaddition, affording a small-library of pyrrolidinyl dispirooxindole linked 1,2,3-triazole derivatives (15 examples) (Scheme 106).^[54]

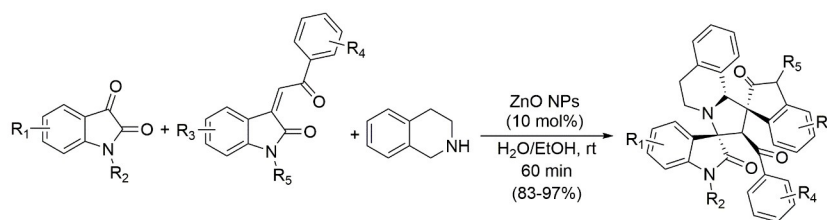
3.2. Knoevenagel-initiated MCRs

In another example of the use of PEG-400 as solvent, a Knoevenagel-initiated approach was described, where the scaffold bearing the two oxindole moieties requires a first reaction step, but since the remaining components are added to the same vessel, we decided to include it in this section. The first reaction step consists in the condensation of *N*-alkyl isatin derivatives with other isatins in the presence of K_2CO_3 . The second step consists in a pseudo five component reaction, through the addition of alkyl malonates and carbonyl

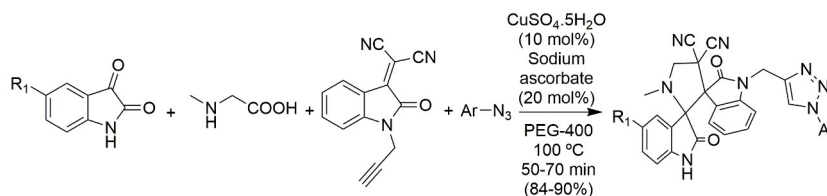
compounds, affording asymmetrical bis-spirooxindole derivatives (13 examples) in good to excellent yields and mild reaction conditions (Scheme 107).^[201] The already described methodology developed by Nagaraju *et al.* (see Scheme 34) was also employed to obtain a similar library (18 examples; 80–98% yield).^[63]

Similarly, Khanna *et al.* reported the synthesis of dispirooxindole derivatives (20 examples) in excellent yields, but this time using ethylene glycol as reaction medium for the pseudo five-component reaction between bis-isatins, cyclic carbonyls and malononitrile (Scheme 108). The reaction, which proceeded with short reaction times, allowed the preparation of these derivatives without time-consuming work-up procedures and under catalyst-free conditions.^[202] A similar library (6 examples) was also reported recently by Wagh *et al.*, using cesium fluoride (10 mol%) as catalyst. This approach allowed mild reaction conditions (using ethanol as solvent at room temperature) and short reaction times (10 minutes), affording the desired dispirooxindoles in excellent yields (92–96%).^[113] Similarly, the already described ionic-liquid promoted synthesis of spirooxindole derivatives was also used for dispirooxindole compounds (see Scheme 52) with good results (4 examples; 90–96% yield).^[103]

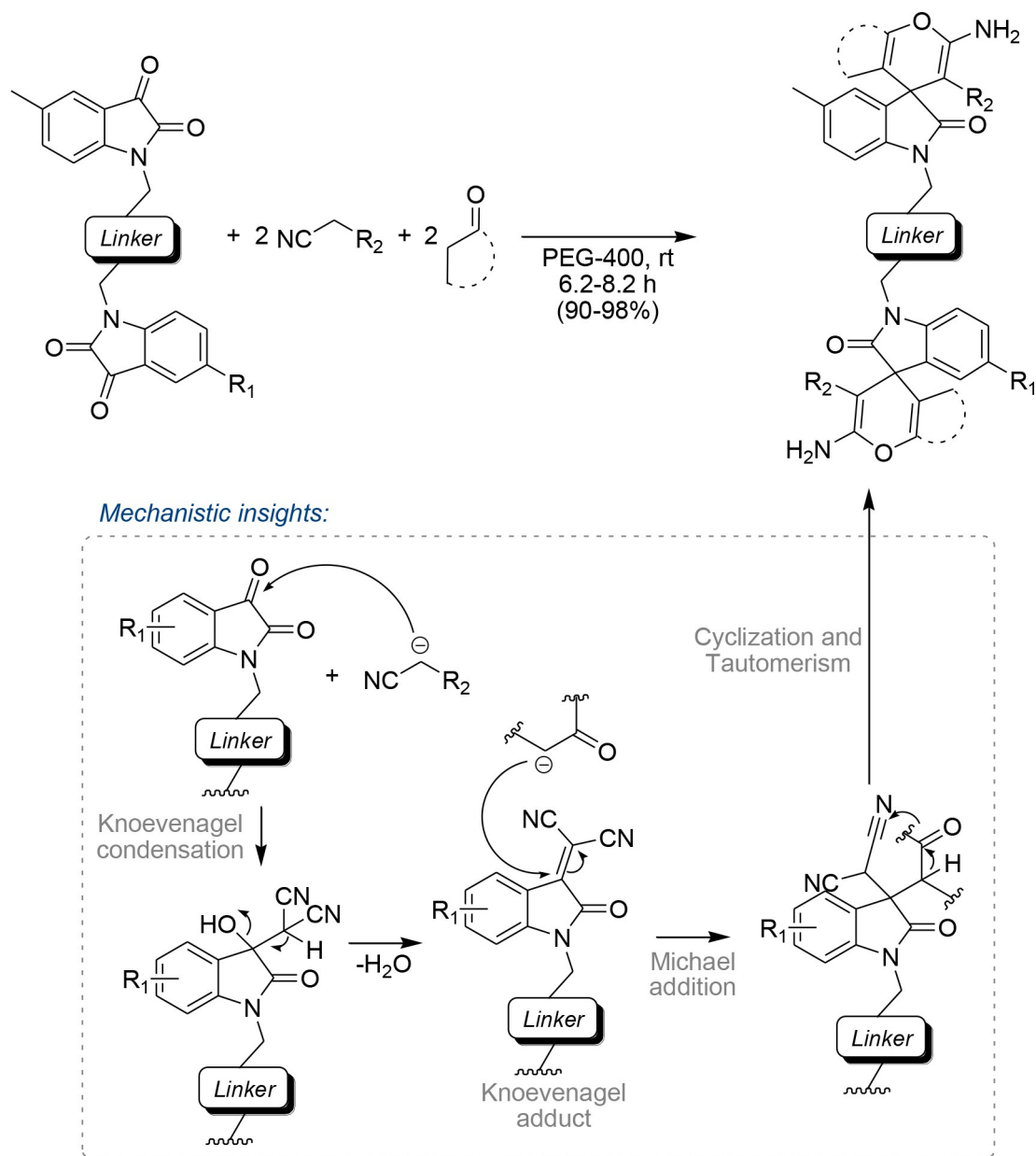
A pseudo six component reaction applied in the synthesis of spiropyrazoline derivatives was recently reported by Rezvanian *et al.* In this example, a Knoevenagel adduct was prepared *in situ* between isatin and the active methylene compound, which reacts with the *in situ* generated intermediate formed by the condensation of 1,1-dihydrazino-2-nitroethylene and an isatin molecule. This intermediate further undergoes intramolecular nucleophilic addition/cyclization of its secondary amino group to the CN group and by rapid



Scheme 105. 3-MCR *via* azomethine ylide mediated 1,3-dipolar cycloaddition using *N*-substituted indolin-2-one derivatives as dipolarophiles.



Scheme 106. 4-MCR for the synthesis of pyrrolidinyl dispirooxindole linked 1,2,3-triazole derivatives.



Scheme 107. Synthesis of bis-oxindole derivatives using PEG-400 as reaction medium and a speculative reaction mechanism.

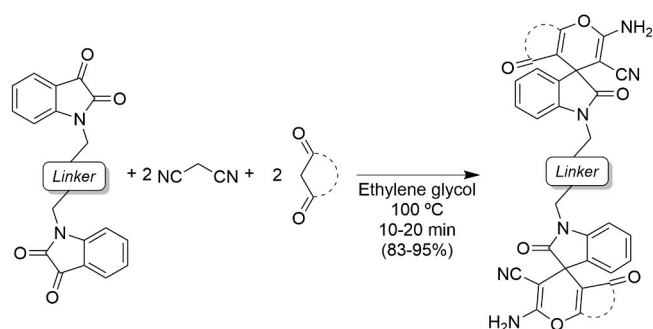
imine-enamine tautomerization affords the desired final products in good yields (5 examples) (Scheme 109).^[203]

3.3. Miscellaneous

A small library of 3-bis-oxindoles (10 examples) was reported by Lakshmi *et al.* via a rhodium(II)-catalyzed three component reaction involving isatins, 3-diazoindole and *para*-substituted benzyl alcohols (Scheme 110). Using a low catalyst loading (1 mol%), the reaction proceeded with good yields, as

well as excellent diastereoselectivity. Mechanistically, the 3-diazoindole forms a rhodium carbenoid intermediate, which further reacts with the benzyl alcohol to afford an oxonium ylide intermediate. This compound is then trapped by isatin (behaving as the electrophile), affording the final bis-oxindole derivative.^[204]

Pseudo five-component reactions allow us to achieve very complex molecular frameworks in one-step, and a wide variety of bis-oxindole products have been reported using different methodologies. Zohreh *et al.* reported a catalyst-free synthesis

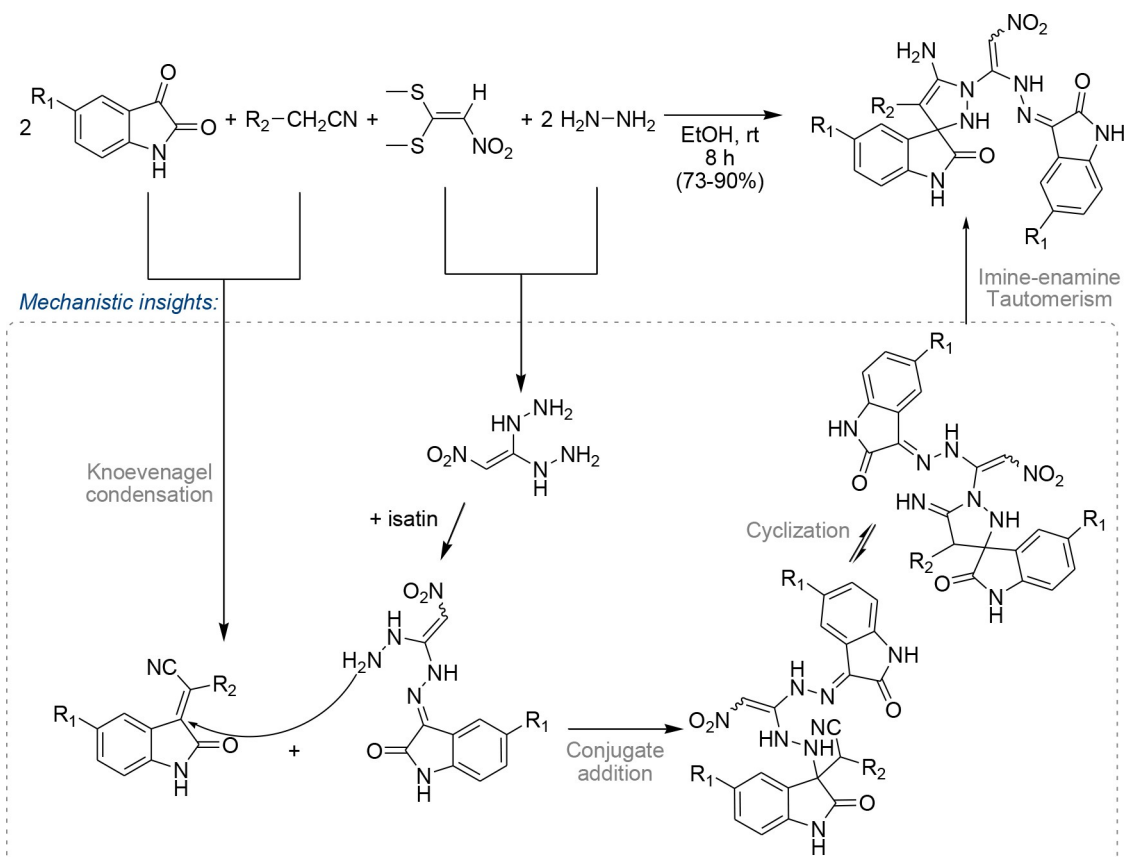


Scheme 108. Synthesis of dispirooxindole derivatives *via* a pseudo five-component reaction.

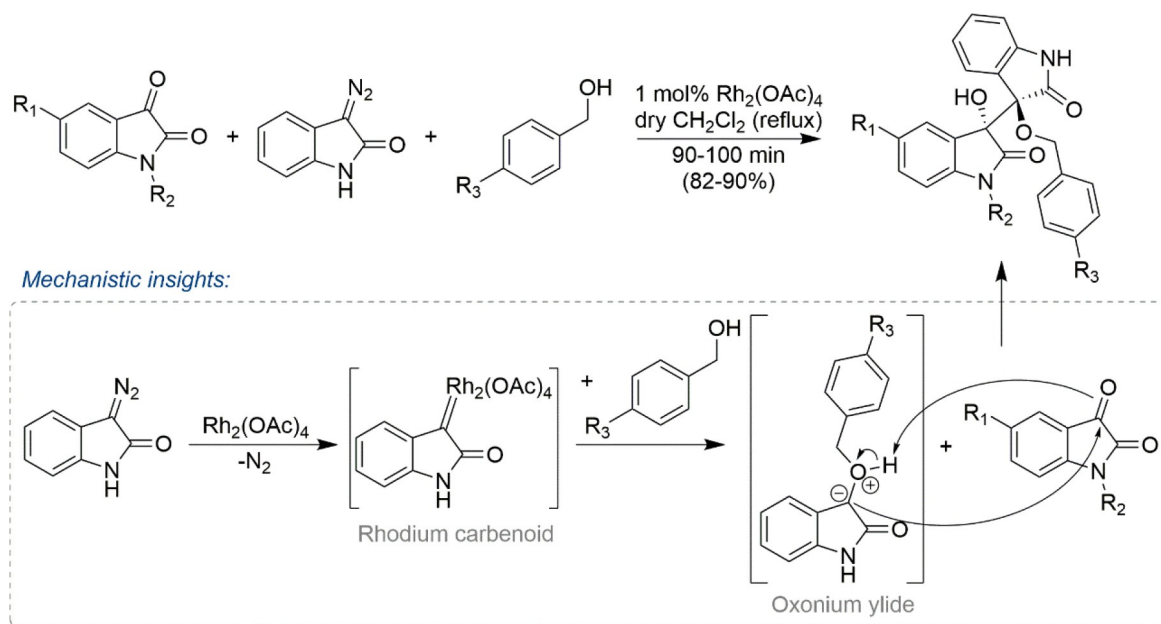
of pyrazoline-spirooxindole derivatives (8 examples) *via* a domino nucleophilic substitution/condensation/aza-ene addition cyclization reaction sequence. Briefly, hydrazine and 1,1-bis(methylthio)-2-nitroethylene generate *in situ* 1,1-dihydrazino-2-nitroethylene, which further condensates with isatin, followed by intramolecular aza-ene addition cyclization (Scheme 111A). This approach allowed the preparation of the

final derivatives in moderate yields, without the requirement for tedious work-up procedures.^[205] In a different example, Mohammadi *et al.* reported the synthesis of bis[spiro (quinazoline-oxindole)] derivatives (9 examples) from isatins, isatoic anhydride and diamines, in the presence of KAl(SO₄)₂·12H₂O (Alum) as the catalyst (Scheme 111B).^[206] This eco-friendly and versatile catalyst presents several advantages, since it presents no toxicity, it is easily available and can be reused without significant loss in activity, as recently reviewed in the literature.^[207] Recently, Sengupta *et al.* reported the wet picric acid catalyzed *syn*-diastereoselective synthesis of spiro [indole-2,2'-pyrrole] derivatives (20 examples). This complex framework was achieved through the reaction between isatins, anilines and β -keto esters, in moderate to good yields (Scheme 111C).^[208]

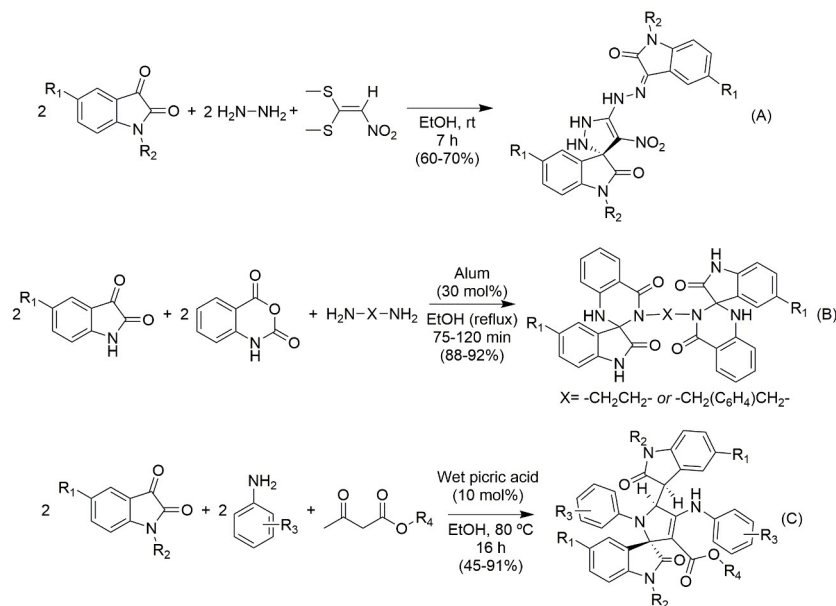
A library of bis-oxindole-tetrahydro- β -carboline derivatives (15 examples) was reported by Dai *et al.*, through an organocatalytic asymmetric three component reaction, comprising a Michael addition/Pictet-Spengler cascade. To achieve such a goal, a chiral phosphoric acid was used as catalyst, promoting the reaction between isatins, amino-ester, and isatin-derived 3-indolylmethanols (Scheme 112). The final products contain



Scheme 109. Pseudo six component reaction in the synthesis of bis-oxindole derivatives.



Scheme 110. Rhodium(II)-catalyzed bis-oxindole synthesis and a speculative mechanistic pathway.

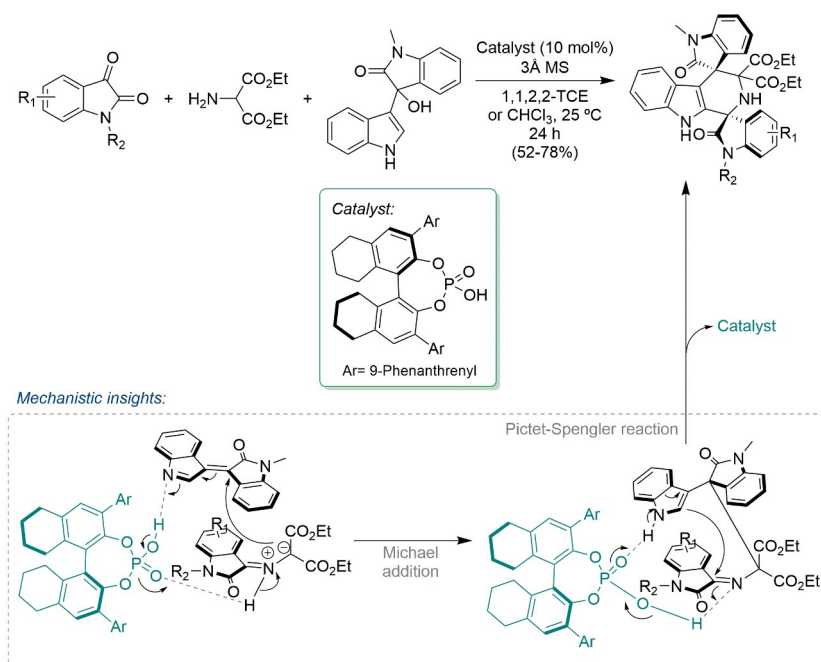


Scheme 111. Synthesis of bis-oxindole derivatives using pseudo five component reactions.

multiple quaternary stereocenters, and were achieved in moderate yields, with excellent diastereomeric ratios (all above 95:5) and enantiomeric ratios (98:2).^[209]

The application of MCRs in polymer synthesis is a field which has experienced very fast growth in the past few years.^[210] Recently, an example of oxindole-containing poly(*N*-acylsulfonamide)s synthesis was reported by Xu *et al.*, through

the polymerization of *N*-protected isatins, alkynes and sulfonyl azides, in the presence of copper iodide as catalyst and lithium hydroxide as base, under mild conditions (room temperature to 30 °C). The desired polymers were obtained in very good yields (Scheme 113). Since the monomeric unit of these products (6 examples) presents two oxindole moieties, we decided to include this example in this section.^[211] A



Scheme 112. Organocatalytic asymmetric synthesis of bis-oxindole-tetrahydro- β -carboline derivatives.

speculative mechanistic proposal is given in Scheme 113. It is proposed to involve a key copper catalyzed alkyne-azide reaction that is followed by an unusual triazole decomposition step.

Overall, the construction of bis-oxindole libraries can be obtained by a wide variety of chemical approaches. While the generation of azomethine ylides in the 1,3-dipolar cycloaddition or Knoevenagel adducts are the most popular approaches for MCR synthesis of bis-oxindoles, recent examples on the use of transition metals, such as rhodium, or chiral organocatalysts have emerged as innovative alternative approaches to these targets, as well as allowing the exploration of new reactivity with the isatin scaffold.

4. Other Oxindole Derivatives

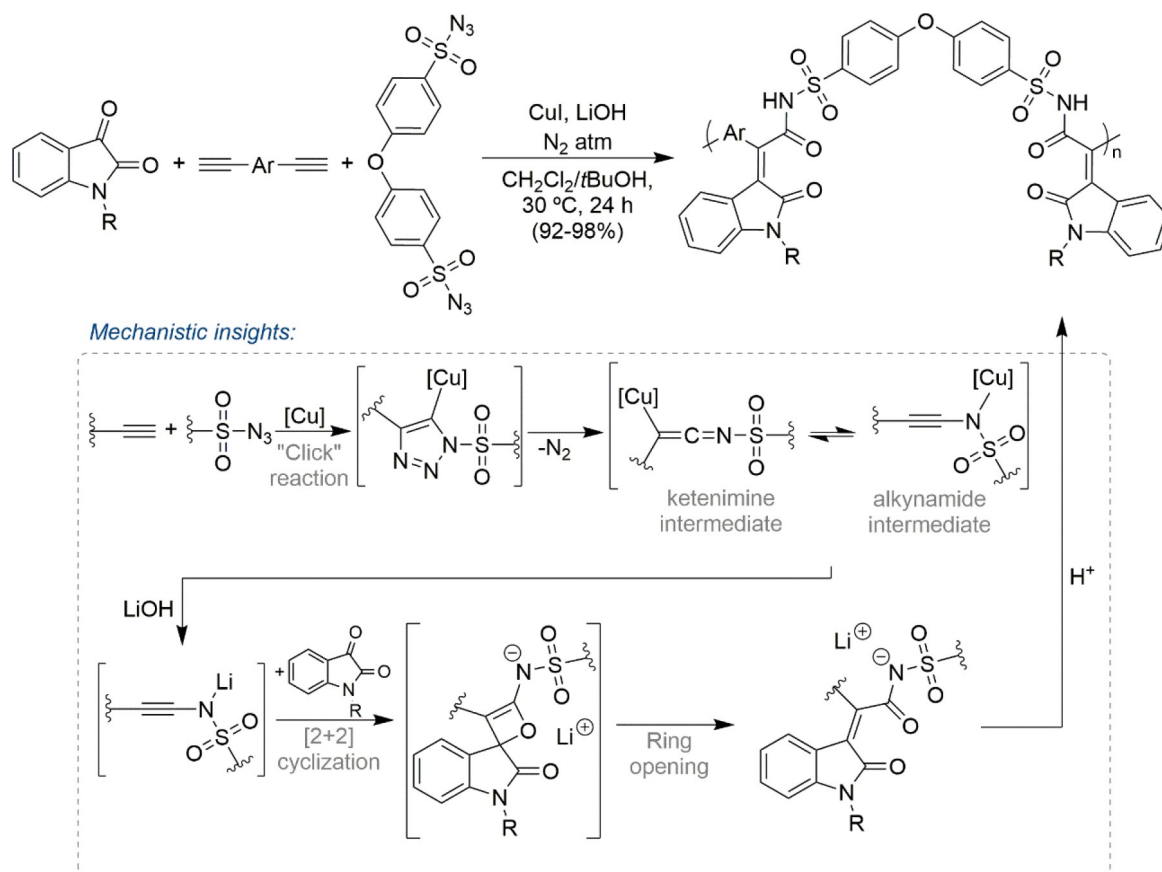
MCRs are also often applied for the preparation of 3,3-disubstituted derivatives, generating significant scaffold diversity. In this section, recent reports on the synthesis of these types of compound will be organized according to the type of reaction/scaffold obtained.

4.1. Isocyanide-based MCRs

Isocyanide-based MCRs play an outstanding role in this field. Among them, the Passerini and the Ugi reactions are extensively employed in medicinal chemistry and became very

popular topics of research over the past few years.^[212] Most commonly, the Passerini reaction occurs between an isocyanide, a carboxylic acid, and an aldehyde, generating ester and amide bonds, while the Ugi reaction involves the same three components plus a primary amine, creating two new amide bonds. However, the aldehyde can be replaced by other carbonyl compounds, and the reactivity of the carbonyl at position C3 of isatin makes this molecule a suitable candidate to be employed in these MCRs. Concerning the Passerini reaction, there are two recent examples engaging isatin in this MCR. Esmacili *et al.* reported the synthesis of isatin-Passerini adducts by reacting different isatins with cyclohexylisocyanide and excess of carboxylic acids in heated acetonitrile, in the presence of 4 Å molecular sieves (15 examples), achieving very good yields (Scheme 114A).^[213] Using a solvent-free approach, Kaicharla *et al.* explored the Passerini reaction, with variations on the isatin, carboxylic acid, and isocyanide moieties (26 examples), using the last two components in excess and achieving good to excellent yields (Scheme 114B). The authors also explored the use of an electron-deficient phenol (2-nitrophenol) as an acid surrogate (3 examples), achieving the desired product in moderate yields (Scheme 114C). This last approach allows the preparation of new products bearing an amide and an ether bond.^[214]

In what concerns the Ugi reaction, isatin is seldomly applied as the carbonyl moiety. In a recent example, Rainoldi *et al.* explored this potential, targeting the synthesis of new oxindole- β -lactam derivatives. To achieve such a goal, they



Scheme 113. Multicomponent polymerization reaction of oxindole-containing poly(*N*-acylsulfonamides) and a speculative mechanistic proposal.

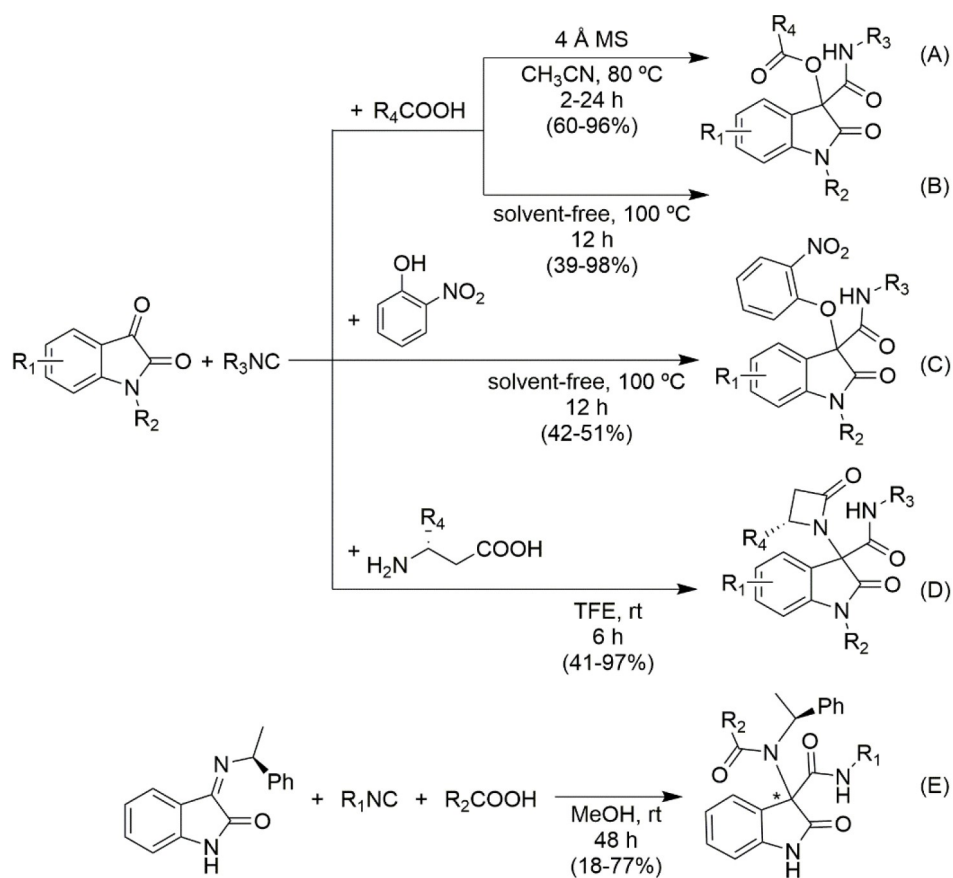
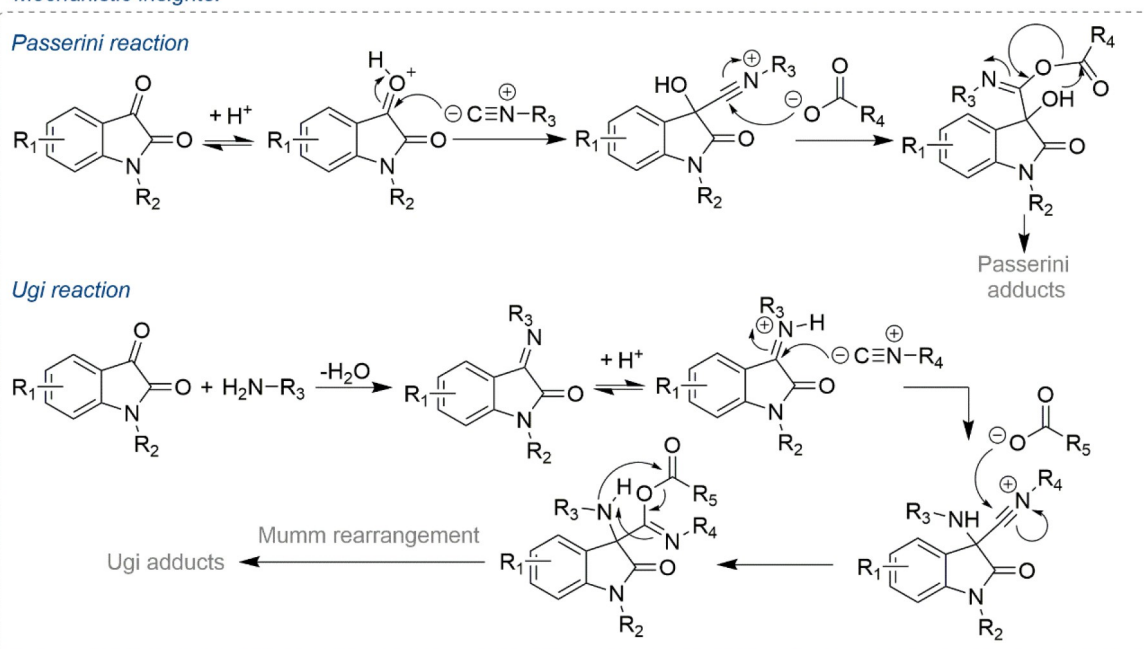
designed an Ugi 4-center three component reaction between isatins, β -amino acids, and isocyanides. The reaction proceeded under mild conditions, using the acidic 2,2,2-trifluoroethanol (TFE) as solvent at room temperature, achieving the desired hybrids (16 examples) in moderate to excellent yields (Scheme 114D).^[215] Previously, Lesma *et al.* reported a 3 component Ugi reaction for the synthesis of chiral amino-oxindole derivatives (Scheme 114E). Despite not using isatin as starting building block, this example was considered in this review, since the chiral isatin-derived ketimine employed can be easily prepared from isatin. The reaction occurred with a high level of stereocontrol due to the stereoiduction of the amine chiral residue over the new stereocenter created during the Ugi reaction (13 examples; *dr* up to 96:4).^[216]

The synthesis of a library of furochromone-oxindole hybrids was reported by Teimouri *et al.*, via a three-component reaction involving isatins, isocyanides, and 3-formylchromones (20 examples). Mechanistically, the reaction undergoes a catalyst-free [4 + 1] cycloaddition/tautomerization/Friedel-Crafts hydroxyalkylation sequence to afford the desired products in moderate to good yields under mild

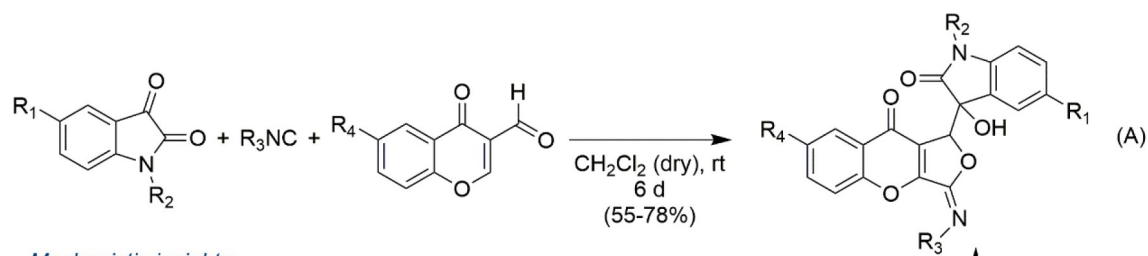
conditions (Scheme 115A).^[217] A different approach was tested by Baharfar *et al.*, using acidic derivatives of isatin as precursor for this library. The carboxylic acid moiety would react with *tert*-butyl isocyanide (2 equiv.) and dialkyl acetylenedicarboxylate to afford the final furan-isatin derivative (1 example) in very good yield (Scheme 115B). This procedure was also shown to be suitable for 5-isatinylidenerhodanine derivatives.^[218] The same research group explored this reaction further (4 examples; 82–95% yield) using the same reaction conditions, but widening the scope on the isocyanide and the dialkyl acetylenedicarboxylate.^[219] These are just two of the rarely reported literature methods where the carbonyl at position C3 is preserved in the final product, showcasing the relevance of the reactivity of this position in MCRs.

4.2. Knoevenagel-initiated MCRs

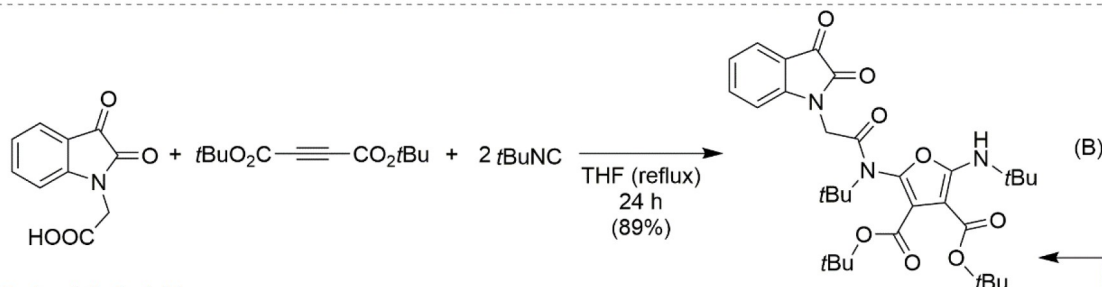
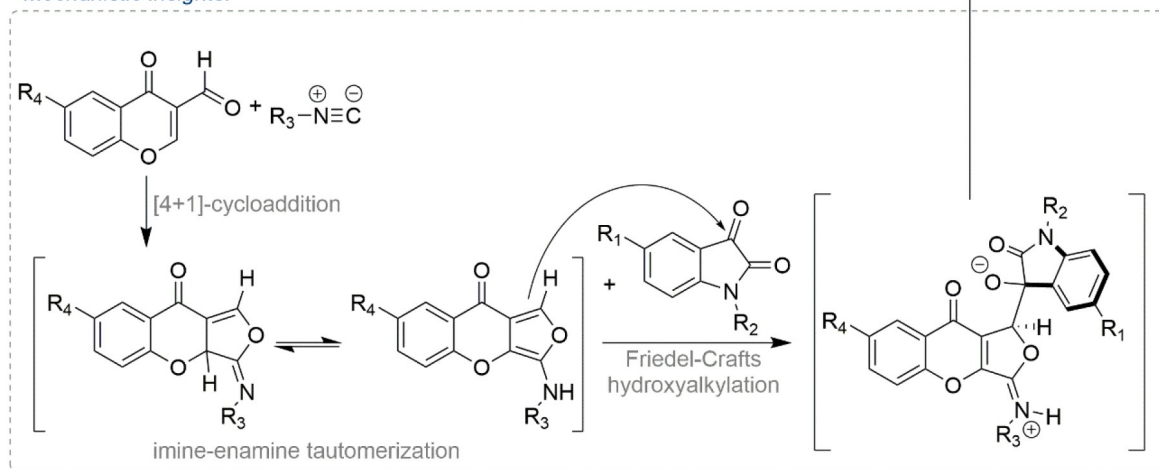
The synthesis of new disubstituted oxindole derivatives via C–H (sp^3) functionalization of methyl azaarenes has also been explored by different research groups. In one example, reported by Yaragorla *et al.*, the reaction between isatin,

*Mechanistic insights:*

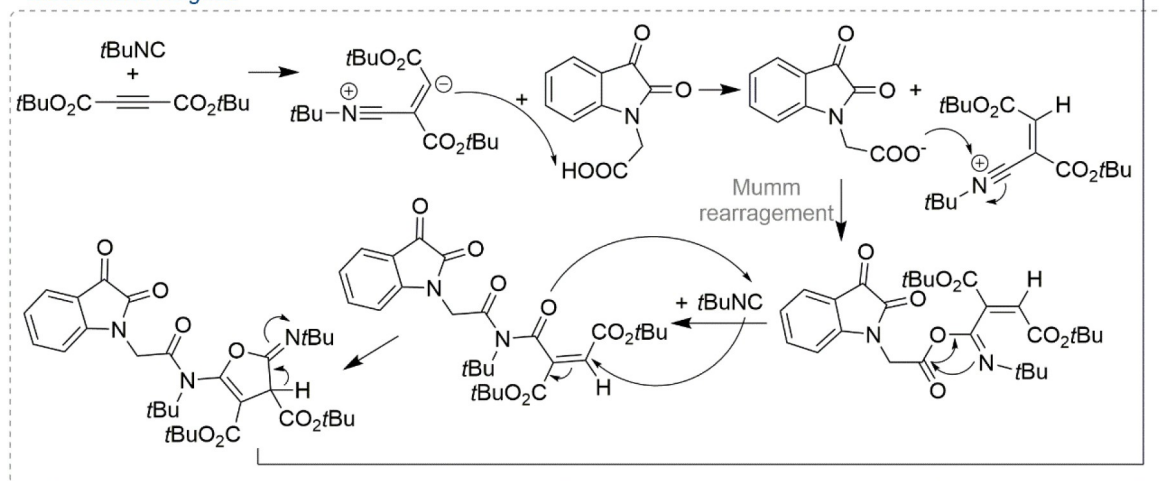
Scheme 114. Passerini (A–C) and Ugi (D–E) MCRs involving isatin (A–D) and isatin-ketimine (E) derivatives and their respective mechanisms.



Mechanistic insights:



Mechanistic insights:



Scheme 115. Other examples of isocyanide-based MCRs using isatin derivatives as starting material and putative mechanistic pathways.

malononitrile and methylazaarenes was promoted under eco-friendly conditions, using water as solvent and under catalyst-free conditions. The library (23 examples) was obtained in overall very good yields, showcasing the versatility of this methodology (Scheme 116A). The authors established two plausible synthetic pathways for this reaction, and determined that the majority of the product is attained *via* Knoevenagel condensation followed by conjugate addition.^[220] In a second example, reported by Pathan *et al.*, the MCR between isatins, malononitrile or ethyl cyanoacetate, and 2-methylazaarenes or (2-azaaryl)methanes was performed under heterogeneous catalytic conditions. Among the screened catalysts, silica-supported dodecatungstophosphoric acid (DTP/SiO₂) (previously reported in this review) proved to be the most efficient, giving the desired library (26 examples) in excellent yields (Scheme 116B).^[129] Still in the field of MCRs involving isatin and malononitrile, a couple more examples can be found in the recent literature, including a gold-catalyzed three component reaction to afford creatinine-oxindole hybrids, using a low catalyst load (1 mol%). The small library achieved (5 examples) was obtained in very good yields under green conditions and short reaction times (Scheme 116C), through a sequential condensation/Michael addition.^[221] Another interesting example is the tandem Knoevenagel/Michael addition reaction between isatins, malononitrile, and indoles, through the catalytic use of the ionic liquid, 1-(ethylacetoacetate)-1-(2-hydroxyethyl) piperidinium tetrachloroaluminate ([EAHEPiPY]⁺[AlCl₄]⁻). This methodology afforded the desired library (12 examples) in moderate to very good yields, with simple work up (no chromatography required) (Scheme 116D).^[222]

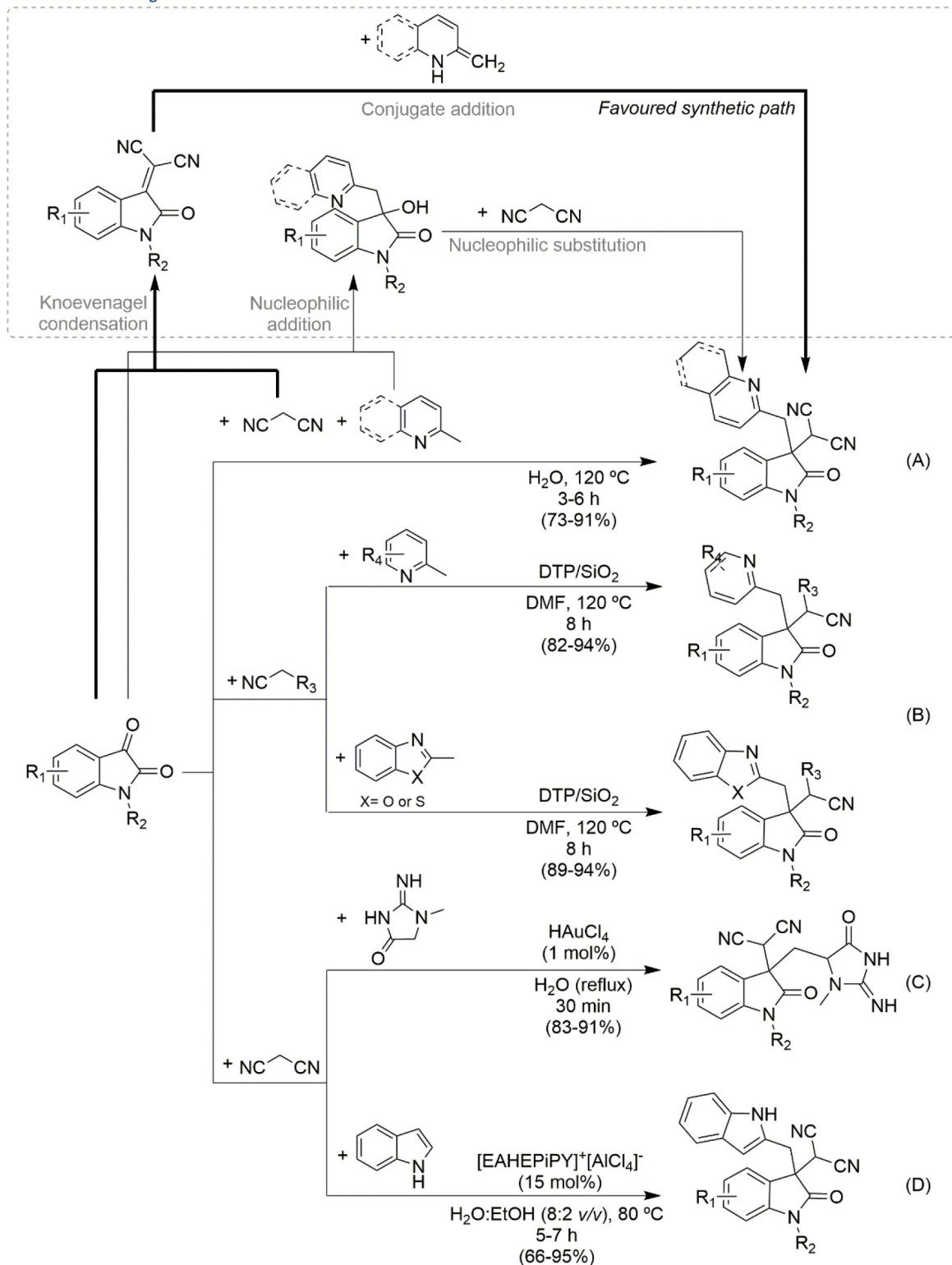
4.3. Miscellaneous

As already mentioned in this work, MCRs are especially useful for the creation of molecular hybrids comprising two relevant scaffolds, such as privileged structures. (Thio)pyrimidines are pharmacologically relevant entities and therefore are widely used in synthetic medicinal chemistry.^[223] For these reasons, it is no surprise that MCRs have been used to prepare oxindole-(thio)pyrimidine derivatives. Azimi *et al.* reported an efficient tandem process for the synthesis of oxindole substituted pyrrolo[2,3-*d*]pyrimidine derivatives under ultrasound irradiation. Fundamentally, acetophenone and isatin derivatives were sonicated in the presence of diethylamine, followed by the addition of amino-uracil derivatives in the presence of catalytic *p*-TSA. This simple procedure proved to be efficient, affording the desired hybrids (12 examples) in excellent yields, higher than the ones observed under conventional heating (Scheme 117A).^[224] Another eco-friendly and cheap catalyst, sulfamic acid,^[225] was employed in the synthesis of 1,4-naphthoquinonyl-2-oxoindolinylpyrimidine derivatives. This

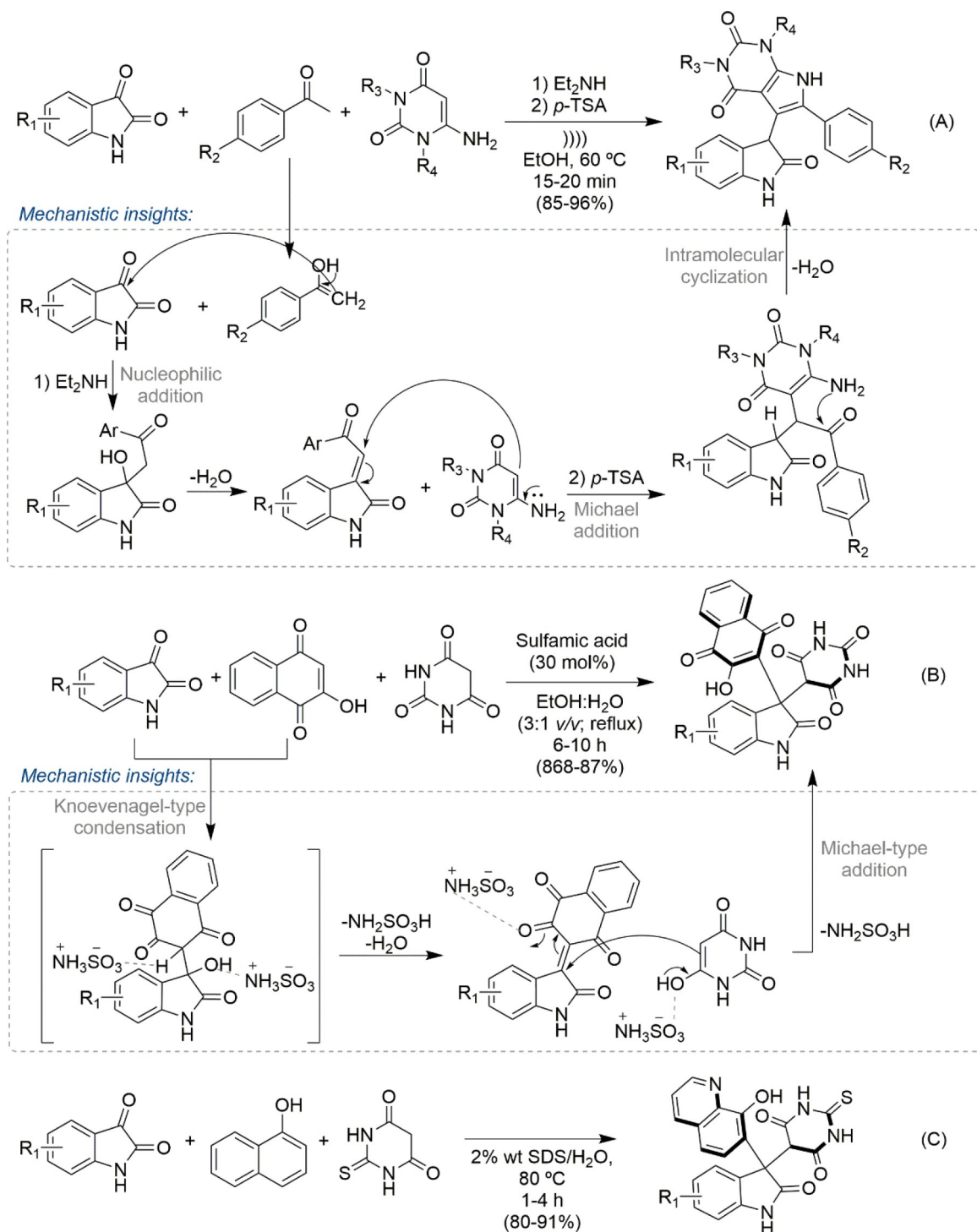
small library (8 examples) was obtained through the acid-catalyzed reaction between different isatins, 2-hydroxy-1,4-naphthoquinone and barbituric acid, achieving moderate to very good yields (Scheme 117B).^[226] In a third example, a catalyst-free three component condensation of isatins, 8-quinolinol and thiobarbituric acid in aqueous media was reported by Kong *et al.*. This environmentally sustainable process involving an easy work-up afforded a small library of oxindole-thiobarbituro-quinoline hybrids (5 examples) in very good yields (Scheme 117C). Mechanistically, water promoted tautomerism of thiobarbituric acid, allowing a Knoevenagel-type condensation with isatin, which is followed by a Michael addition with 8-quinolinol to attain the desired products.^[227]

Another very relevant scaffold, thiazole, has been widely combined with isatin to generate oxindole-thiazole hybrids, due to the great therapeutic interest of this sulfur and nitrogen containing heterocycle.^[228] Among the thiazole derivatives, the analog rhodanine (chemically 2-sulfanylidene-1,3-thiazolidin-4-one) is widely present in several bioactive molecules, displaying anticancer, antiviral and antimicrobial activity, as recently reviewed in the literature.^[229] For all these reasons, the preparation of oxindole-rhodanine hybrids is of great interest, as shown in the following examples, involving sustainable heterogeneous catalytic NP systems. The common approach consists in the reaction of isatins with rhodanine and secondary cyclic amines to afford the hybrids. To achieve such a goal, Baharfar *et al.* used MgO nanoparticles in water at room temperature, obtaining a library (16 examples) with very good yields (Scheme 118A).^[230] The same type of reaction was explored by De *et al.*, but this time using a different nanoparticle catalyst, ZnFe₂O₄. The generated library (26 examples) was achieved in excellent yields under aqueous reaction conditions (Scheme 118B).^[231] A totally different approach was described by Tiwari *et al.*, to synthesize thiazolyl hydrazono-indolin-2-one derivatives. Using glycerol micellar catalysis, the reaction between isatins, thiosemicarbazide and phenacyl bromide was promoted in the presence of catalytic amounts of cetyltrimethylammonium bromide (CTAB), as the phase transfer catalyst. Mechanistically, the reaction is triggered by the generation of a thiosemicarbazone between the C3 position of isatin and the thiosemicarbazide, which further reacts with the phenacyl bromide, followed by cyclization/aromatization to afford the thiazole ring. This green method was suitable to prepare a small library of isatin-derivatives (5 examples) in very good yields (Scheme 118C).^[232] One more example of oxindole-thiazole hybrids was reported by Saroha *et al.*, by exploring a domino multicomponent reaction for the synthesis of 2,4,4-trisubstituted thiazole derivatives. In the first step, isatin reacts with thiosemicarbazide to afford *in situ* a thiosemicarbazone (step not shown in Scheme 118D), in the presence of acetic acid. In the same reaction vessel, phenylglyoxal and 4-hydroxycoumar-

Mechanistic insights:



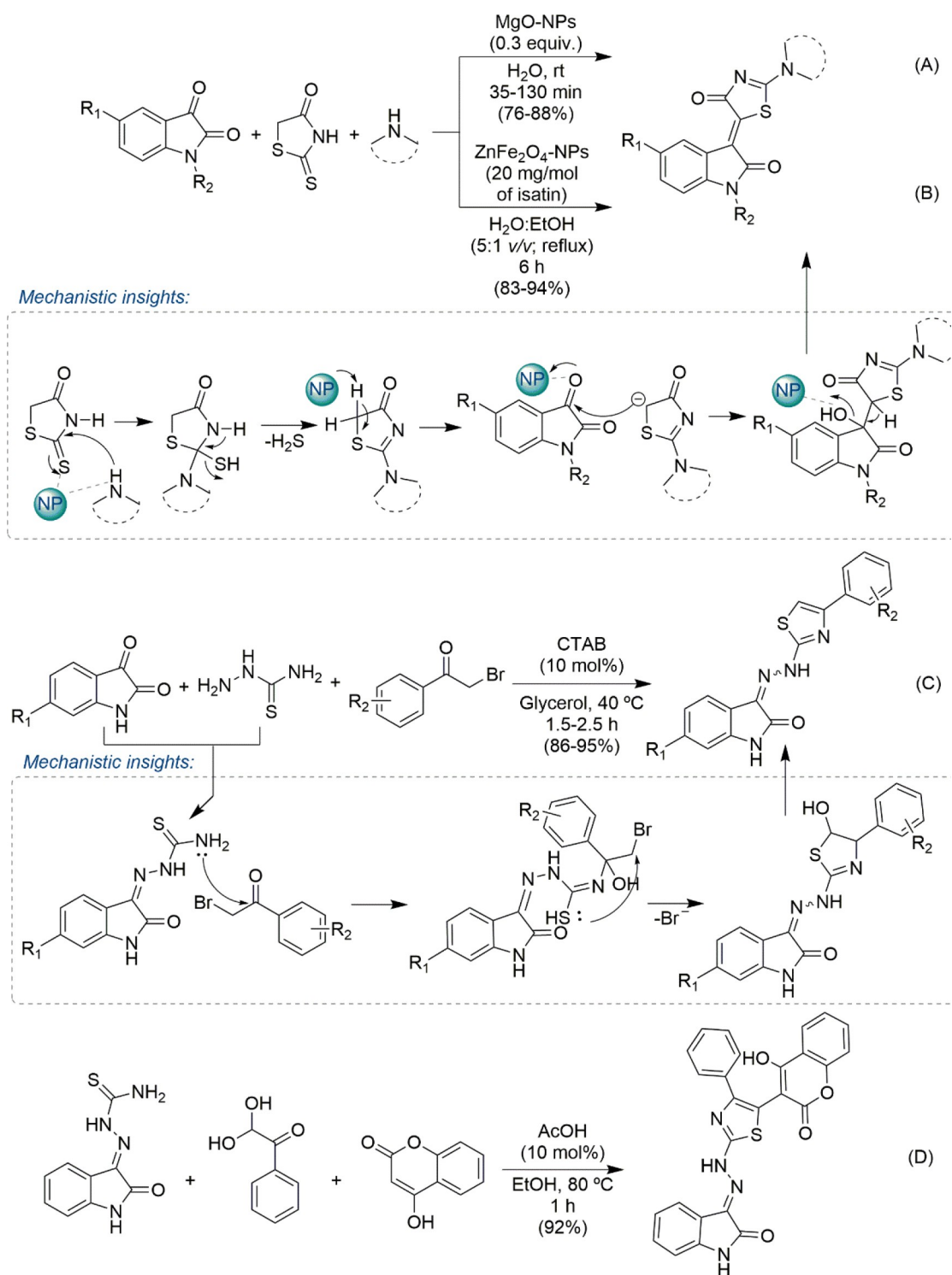
Scheme 116. Application of isatins and malononitrile in different 3 component reactions.



Scheme 117. Synthesis of oxindole-pyrimidine hybrids *via* MCRs.

in are added, and the product of the condensation of these two components undergoes a Michael addition with the *in situ* formed thiosemicarbazone, followed by tautomerization, intra-

molecular cyclization, and the final product is obtained after loss of water (Scheme 118D).^[233]



Scheme 118. Synthesis of oxindole-thiazole hybrids *via* MCRs and putative mechanistic pathways.

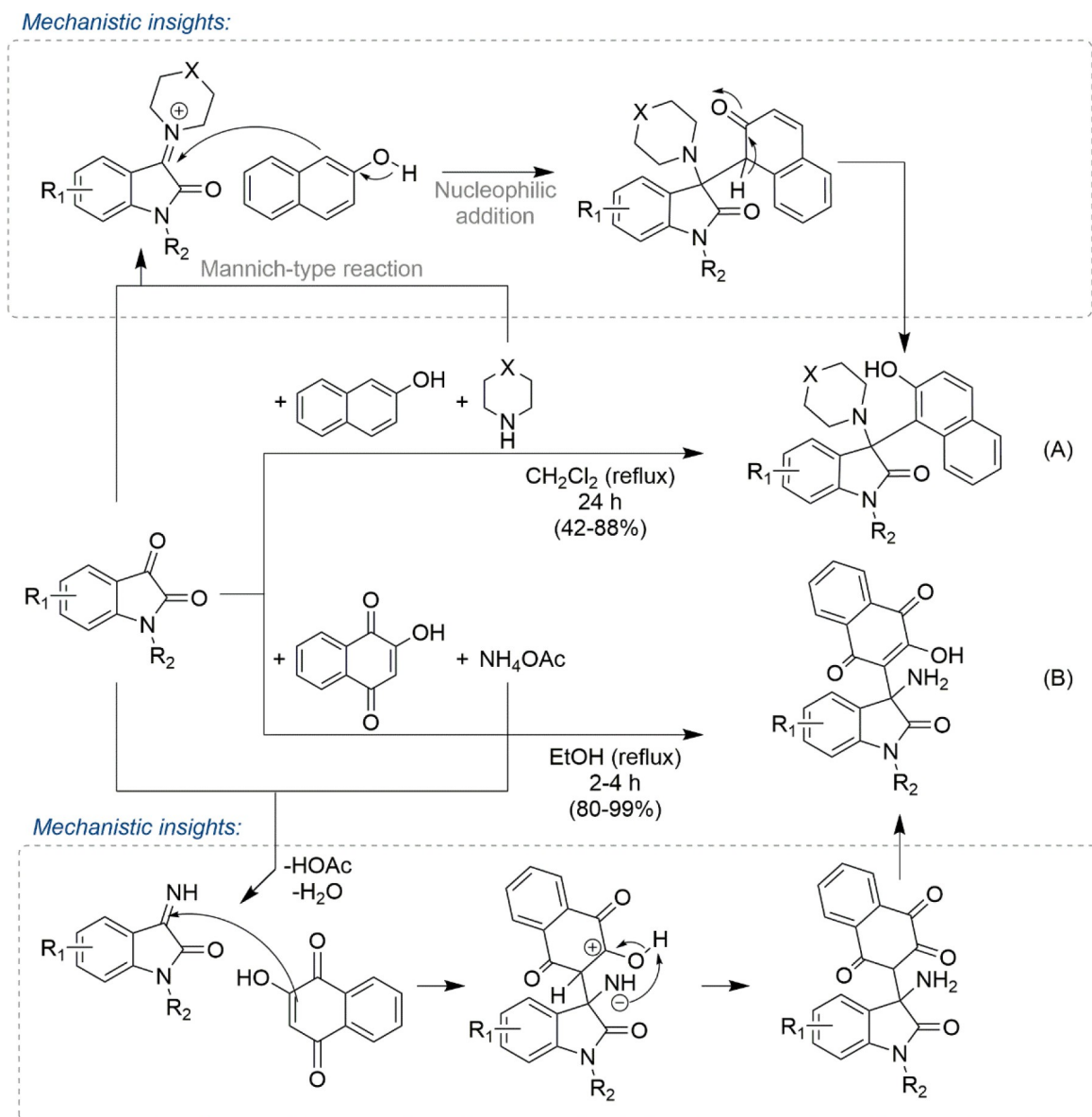
Naphtalene-derivatives have also been integrated in the same framework with oxindoles using MCRs. One example

was reported by Gao *et al.*, concerning the synthesis of new Betti bases, classically obtained *via* the reaction of an aldehyde,

2-naphthol, and ammonia.^[234] This group decided to take advantage of the unique reactivity of C3 position of isatin, and replaced the aldehyde component by this heterocycle, and performed the reaction between isatins, cyclic amines, and 2-naphthol. A library of 3,3-disubstituted oxindoles (16 examples) was achieved in moderate to good yields (Scheme 119A).^[235] In a totally different example, other isatin derivatives and ammonia reacted with 2-hydroxy-1,4-naphthoquinone to afford 2-(3-amino-2-oxindolin-3-yl)-3-hydroxynaphthalene-1,4-dione derivatives (13 examples) in very good to excellent yields (Scheme 119B).^[236] This methodology is of utmost relevance, since it introduces a primary amine at the C3

position of the oxindole scaffold, a chemical framework important in medicinal chemistry.^[64]

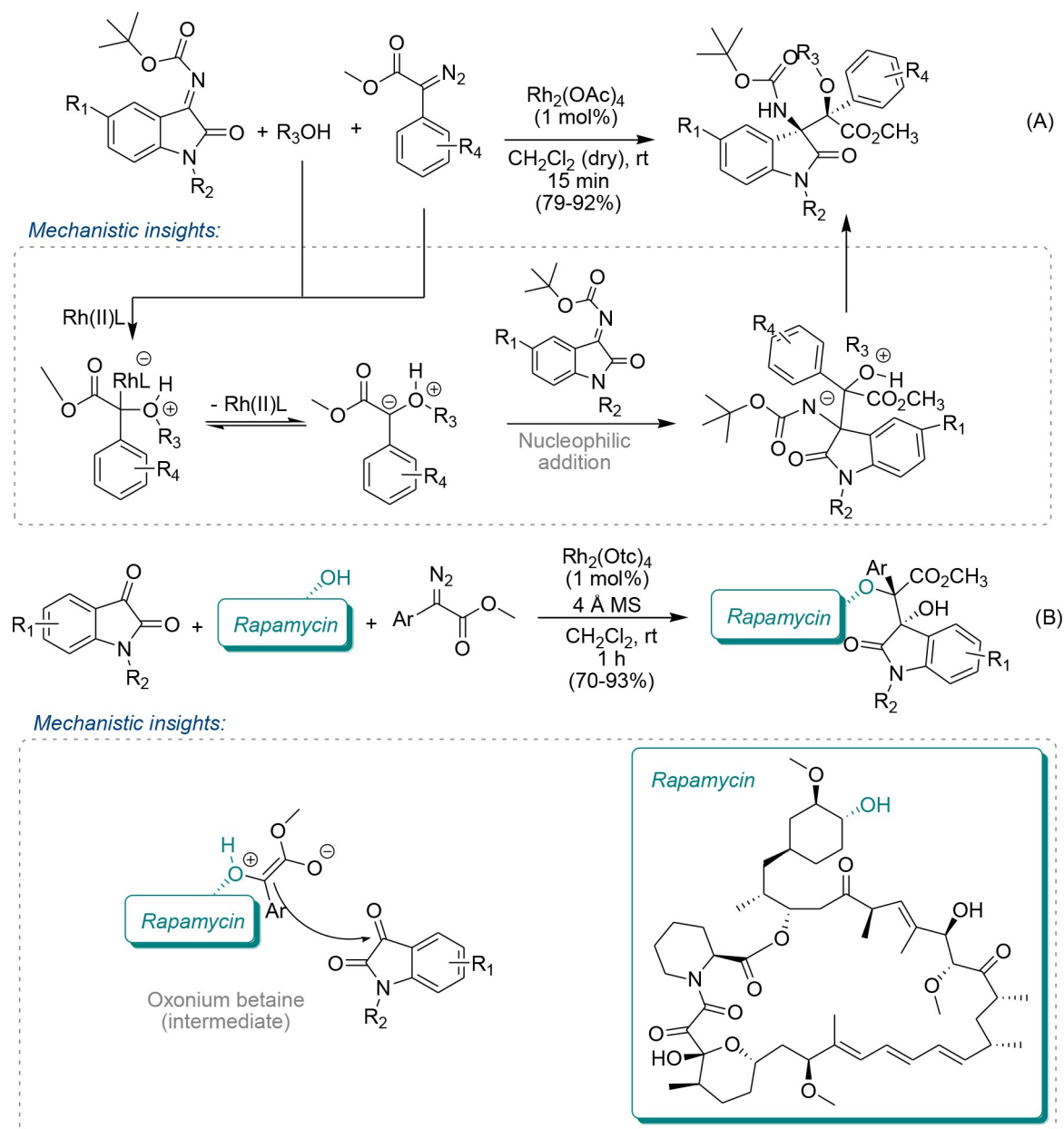
In this section we will address MCRs involving isatins (or isatin-imines) and diazo compounds. Among the recent examples, there are two metals that stand out for their potential to catalyze this type of reactions: rhodium and copper. In the case of rhodium-catalysis, Rajasekaran *et al.* explored the three-component reaction of isatin imines, α -diazoesters, and aryl alcohols. Rh₂(OAc)₄ proved to be efficient at low catalyst loading (1 mol%), under mild conditions and short reactions times, affording the desired library of compounds (23 examples) in very good yields and excellent



Scheme 119. Synthesis of 3-amino-3-substituted oxindole derivatives *via* MCRs and plausible reaction mechanisms.

diastereoselectivity (Scheme 120A). The formation of an oxonium ylide from a rhodium carbenoid and alcohol is assumed to be the driving force of this reaction. A five-membered transition state is believed to be formed by the attachment of the oxonium betaine on the *N*-Boc ketimine, leading to a Mannich-type addition product. The intramolecular H-bond between the imine nitrogen atom and the oxonium ylide hydrogen atom is believed to lead to the stabilization of this transition state. It should be noted that a possible π - π interaction established between the oxindole and

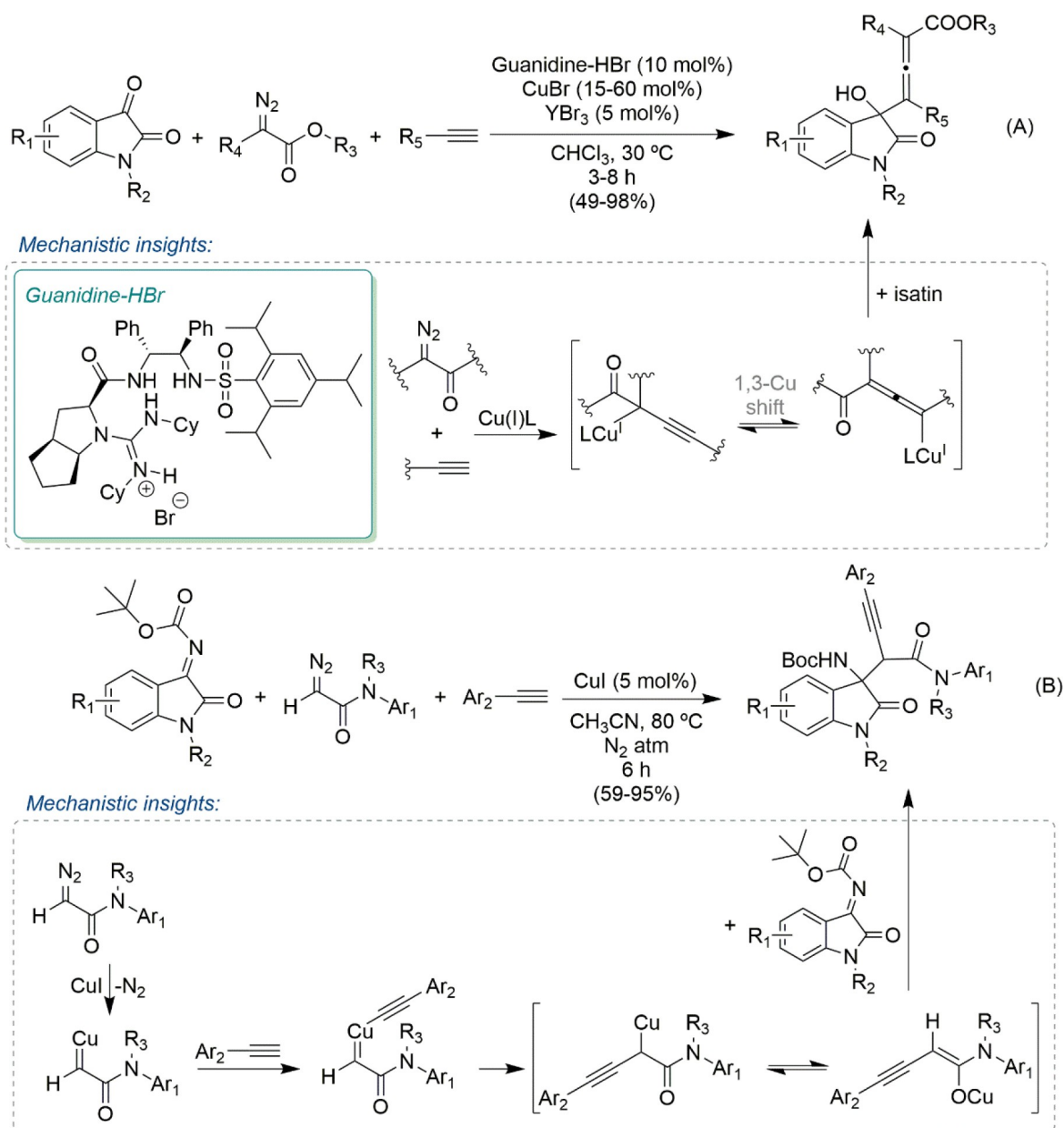
the aryl group of the diazoester in the transition state is responsible for the high degree of diastereoselectivity of this reaction (> 99%).^[237] In a more recent example, a similar approach was reported by Qiu *et al.*, but this time replacing the aryl alcohol by the immunosuppressant, rapamycin. The macrolide rapamycin, as well as its semi-synthetic analogs, *rapalogs*, possess a very interesting mechanism of action, targeting mTOR protein complexes, involved in several biological processes. These molecules, originally introduced in clinical practice as immunosuppressants, present other relevant



Scheme 120. Rh(II)-catalyzed three component reaction involving isatins, α -diazoesters and alcohols and putative mechanistic pathways.

pharmacological activities, namely in cancer, diabetes, atherosclerosis, obesity, neurological and genetic disorders.^[238] For all these reasons, the synthesis of rapamycin-oxindole hybrids emerged as an interesting approach to obtain new potentially bioactive *rapalogs*. The library (23 examples) of 3-hydroxy 3-substituted oxindoles was obtained directly from isatins, in good yields, using $\text{Rh}_2(\text{Oct})_4$ as the Rh(II) source at low catalyst loading (1 mol%) (Scheme 120B), showcasing the importance of rhodium-based catalysts in this type of transformation.^[239]

Two very recent examples of the application of copper(I) catalysis in three component reaction of isatins (or isatinimines), α -diazo compounds, and terminal alkynes, *via* electrophilic trapping of allenolate/alkynoate-copper intermediates are as follows. Tang *et al.* reported the asymmetric synthesis of a library (46 examples) of tetrasubstituted allenates, through the reaction of *N*-protected isatins, α -diazoesters, and terminal alkynes (Scheme 121A). The reaction was promoted by a combined acid system, containing a Brønsted acid (HBr) or a Lewis acid (YBr_3), and a chiral guanidine-Cu(I) complex, and



Scheme 121. Cu(I)-catalyzed three component reaction involving isatins and derivatives, α -diazo compounds and terminal alkynes. Putative mechanism outline.

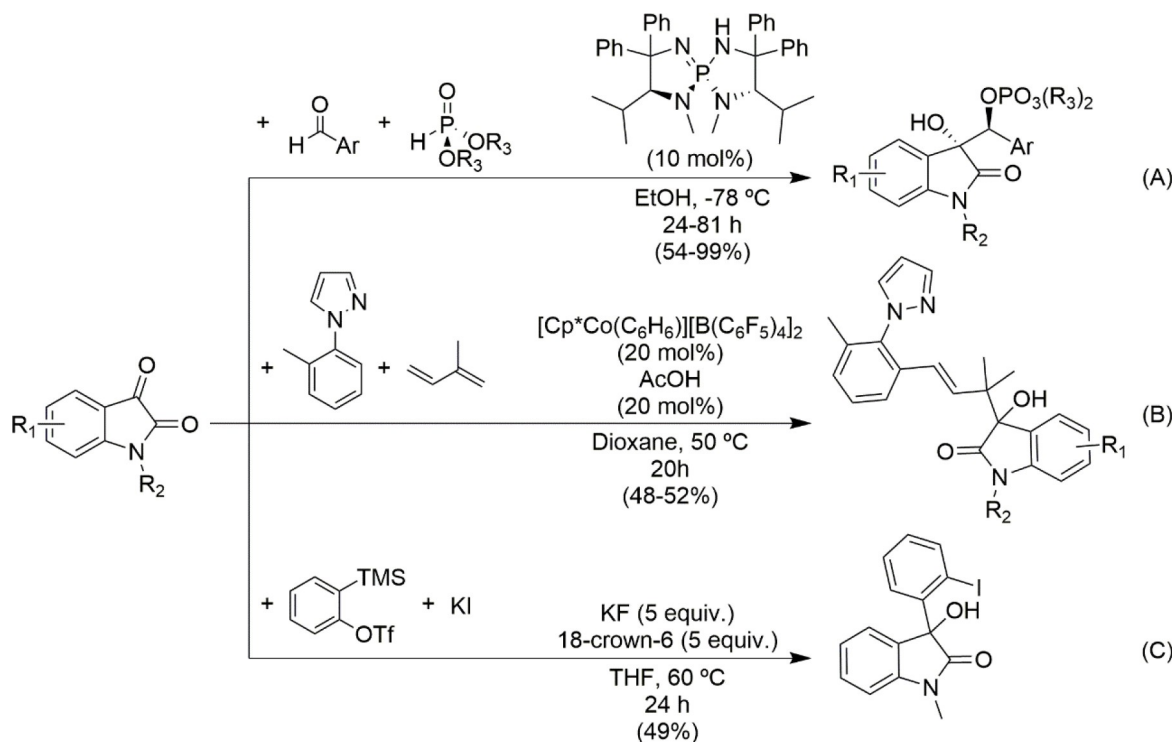
the products were obtained in moderate to excellent yields, with enantiomeric ratios of up to 98:2 and diastereomeric ratios of up to 95:5.^[240] In the other example, an isatin ketimine substrate was reacted with α -diazoamides and terminal alkynes giving a small library (16 examples) of alkynyl-containing 3,3-disubstituted oxindole derivatives (Scheme 121B), using copper iodide as the copper (I) source. Mechanistically, it was postulated that the reaction proceeds *via* a Mannich-type trapping of an alkynoate copper intermediate, formed from the terminal alkyne and the copper carbene species (see Scheme 121B).^[241]

Horwitz *et al.* reported a stereoselective reductive coupling reaction. In their approach, different isatins, aryl aldehydes, and dialkyl phosphites were used. Mechanistically, a Pudovik addition and a phosphonate/phosphate rearrangement leads to the polarity inversion on the isatin. The generated carbanions can then be trapped by the aldehyde, followed by a dialkylphosphinyl migration. To achieve enantioselectivity, a basic chiral iminophosphorane catalyst was used, allowing the preparation of a library (19 examples) in moderate to excellent yields and enantiomeric ratio of up to 99:1 (Scheme 122A).^[242] Also leading to the preparation of a library of 3-hydroxy 3-substituted oxindole derivatives, Dongbang *et al.* reported a Co(III)-catalyzed three component reaction, through C–H bond addition to internally substituted dienes

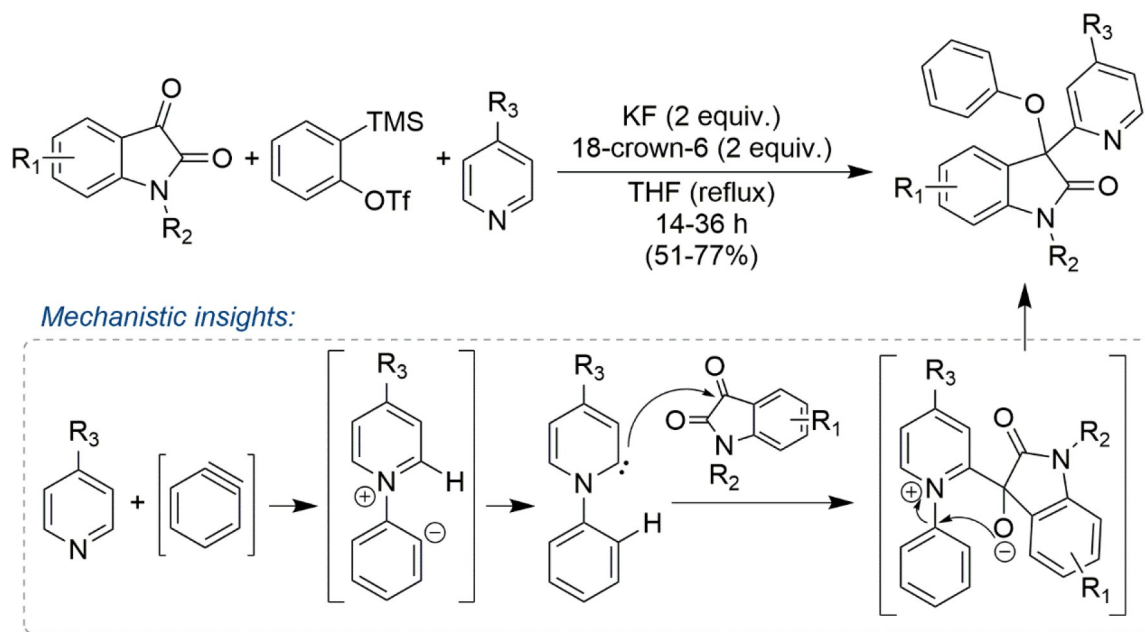
and isatins. A small library of tertiary homoallylic alcohols (4 examples) was prepared in moderate yields (Scheme 122B), although this methodology proved to be effective for a wide variety of aldehydes and activated ketones.^[243] Recently, 3-hydroxy-3-(2-iodophenyl)-1-methyloxindole was prepared *via* a aryne three-component coupling, using KI as the iodide source and nucleophilic trigger of the reaction, and *N*-methylisatin as the electrophilic component. The generation of the aryne was promoted by KF/18-crown-6 in heated THF (Scheme 122C).^[244]

The same KF/18-crown-6 system was also used to generate arynes in a different example reported by Nawaz *et al.*, leading to a small library of indolinones (10 examples) (Scheme 123). This reaction was purported to proceed through a temporary intramolecular generation of *N*-phenyl-pyrid-2-ylidenes which adds to the carbonyl group at the C3 position of isatin, generating a zwitterionic adduct, which undergoes an intramolecular aryl transfer reaction *via* a nucleophilic aromatic substitution.^[245]

A palladium-catalyzed intermolecular dehydrogenative carbamination of alkenes with *N*-substituted isatins and aromatic amines was developed by Pratap *et al.*, *via* a three-component reaction. The generated library of oxindole enamines (19 examples) was achieved in moderate to good



Scheme 122. Other examples of 3-hydroxy 3-substituted oxindoles prepared *via* 3 component reactions.



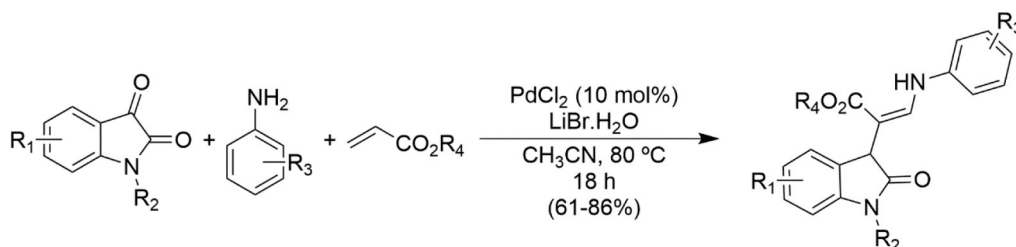
Scheme 123. MCR synthesis of 3,3-disubstituted oxindole derivatives *via* temporary intramolecular generation of pyridine carbenes.

yields, allowing the retention of the alkene double bond within the final product (Scheme 124).^[246]

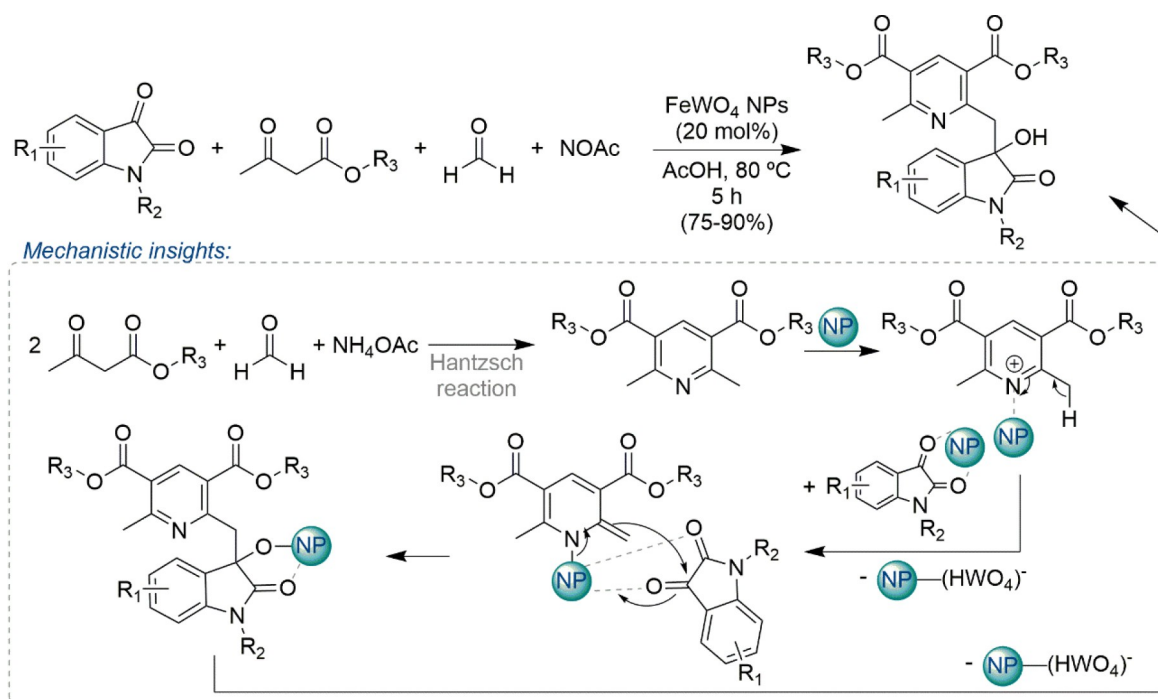
In the period covered by this review and in the context of this category of reaction, one example of a four-component reaction involving isatin was found, that afforded 3-hydroxy-2-oxindole-pyridine hybrids (Scheme 125). Paplal *et al.* showed that these products could be obtained in very good yields, using a heterogeneous catalyst, consisting of FeWO₄ NPs. Mechanistically, the reaction seems to occur through Hantzsch ester formation, followed by oxidative aromatization and sp³ C–H functionalization.^[247]

Pseudo-3-MCRs involving isatins, consisting of reactions where isatin reacts with two equivalents of a second starting material instead of three different starting materials, is another category of reactions that we will review here. A wide variety of examples can be found in literature. Wang *et al.* reported the synthesis of *E*-3-arylidene-2-oxindole derivatives (25 examples), through the reaction of isatins with α -thiocyanato

ketones, in very good yields. The reaction presented short reaction times, using microwave irradiation and sodium hydroxide as the base promoter (Scheme 126A), and mechanistically it occurs through a continuous [3 + 2] cycloaddition/ring opening and *in situ* generated 1,3-oxathiolanes/S_N2-type reaction sequence.^[248] The already described C–H (sp³) functionalization of methyl azaarenes was also explored in a pseudo-3-MCR, affording bisazaarenyl-oxindole derivatives (two examples). In the report by Yaragorla *et al.* calcium was used as the catalyst and Bu₄NPF₆ as the additive (Scheme 126B), and was suitable for a wide range of aldehydes and isatin substrates.^[249] In a recent example, a library of 3,3-di-antipyrene substituted oxindoles (14 examples) was prepared in aqueous medium, under catalyst-free conditions in moderate to very good yields (Scheme 126C).^[250] This synthetic methodology is very relevant, since antipyrene is a well-known non-opioid analgesic and non-steroid anti-inflammatory drug.^[251] A straightforward, simple and eco-friendly organocatalyzed proc-



Scheme 124. Synthesis of oxindole enamine derivatives *via* intermolecular dehydrogenative carboamination of alkenes.



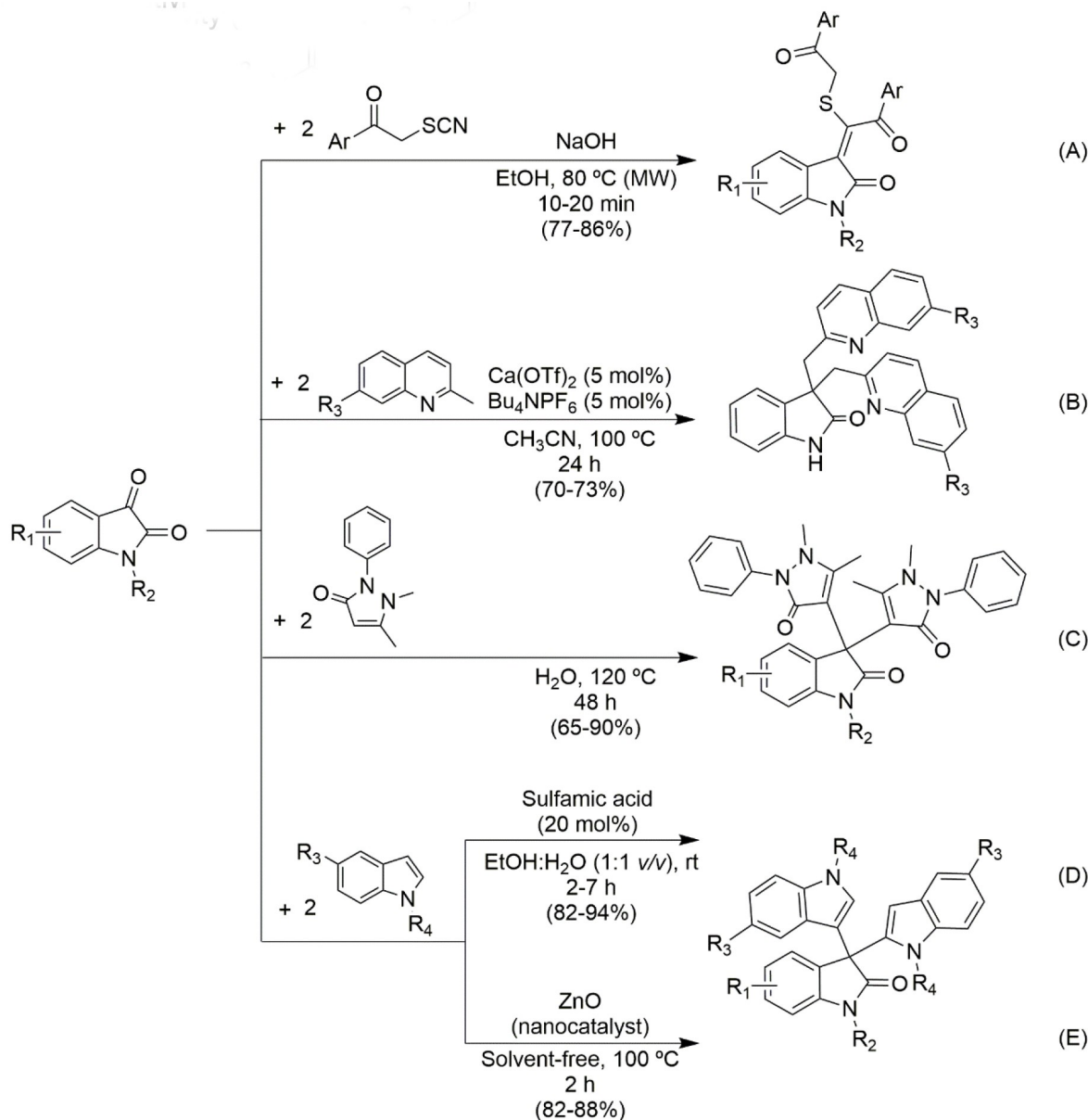
Scheme 125. Synthesis of 3-hydroxy-2-oxindole-pyridine hybrids *via* 4-MCR and the putative mechanistic pathway.

ess for the synthesis of a library of 3,3-bis(indol-3-yl)indolin-2-ones (23 examples), under mild conditions, was reported by Brahmachari *et al.* (Scheme 126D). This methodology used sulfamic acid as the catalyst and the reaction could proceed at room temperature using a water:ethanol mixture as reusable reaction medium allowing the isolation of the final products in excellent yields, with no requirement for chromatographic separation.^[252] 3,3-Bis(indol-3-yl)indolin-2-one derivatives (5 examples) have been synthesized under solvent-free conditions using ZnO. It was believed that the reaction occurs on the surface of nanostructured zinc oxide, which could be reused up to five times with no significant drop in catalytic activity (Scheme 126E).^[127]

A library of 4,4'-(2-oxindoline-3,3-diyl)bis(methylene) bis(2-aryl-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione) derivatives (22 examples) was recently reported by Mao *et al.*, *via* a pseudo-5-MCR. These scaffolds were obtained by reacting different isatins (3 equivalents) with acetoacetyl aromatic amines (2 equivalents) in the presence of *p*-toluenesulfonic acid, under mild conditions, to give the products in very good yields (Scheme 127).^[253]

The isatin-derived Michael acceptors, 3-phenacylideneoxindoles, also emerged as a valuable starting point for many MCRs to obtain oxindole derivatives. Vivekanand *et al.* reported the synthesis of a library of tetrasubstituted pyrrole-oxindole hybrids (27 examples) under environmentally benign conditions. Their approach consisted in the three-component

reaction between an isatin-derived Michael acceptor, a primary amine, and a 1,3-dicarbonyl compound, under catalyst and solvent-free conditions, achieving the desired products in good to excellent yields (Scheme 128A). The authors also investigated a series of green solvents (water, PEG-200 and glycerol), verifying that the yield results were similar to those obtained under neat conditions. Mechanistically, the reaction undergoes a sequential enamine-formation, Michael addition and intramolecular cyclization.^[254] Yan and co-workers also explored the reactivity of 3-phenacylideneoxindoles. In one example, they promoted the three-component reaction between this scaffold, dimedone, and tryptamine, to afford a library of functionalized 3-(1-[2-(1*H*-indol-3-yl)ethyl]-4,5,6,7-tetrahydro-1*H*-indol-3-yl)indolin-2-one derivatives (16 examples), using *p*-TSA as Lewis acid catalyst in refluxing acetonitrile (Scheme 128B).^[255] The same acid/solvent system was used in another set of three-component reactions, between 3-phenacylideneoxindoles, dialkyl acetylenedicarboxylate (an electron-deficient alkyne), and *o*-aminophenol, 2-aminoethanol or *o*-phenylenediamine, leading to the formation of benzo [*b*]pyrrolo[1,2-*d*][1,4]oxazine derivatives (9 examples) and pyrrolo-[2,1-*c*][1,4]oxazine derivatives (4 examples) (Scheme 128C) and quinoxalin-2(1*H*)-one-oxindole derivatives (14 examples - Scheme 128D), respectively.^[256] All these examples showcase the versatility of 3-phenacylideneoxindoles in MCRs to obtain scaffold diversity in oxindole derivatives.



Scheme 126. Synthesis of oxindole derivatives *via* pseudo-3-MCRs.

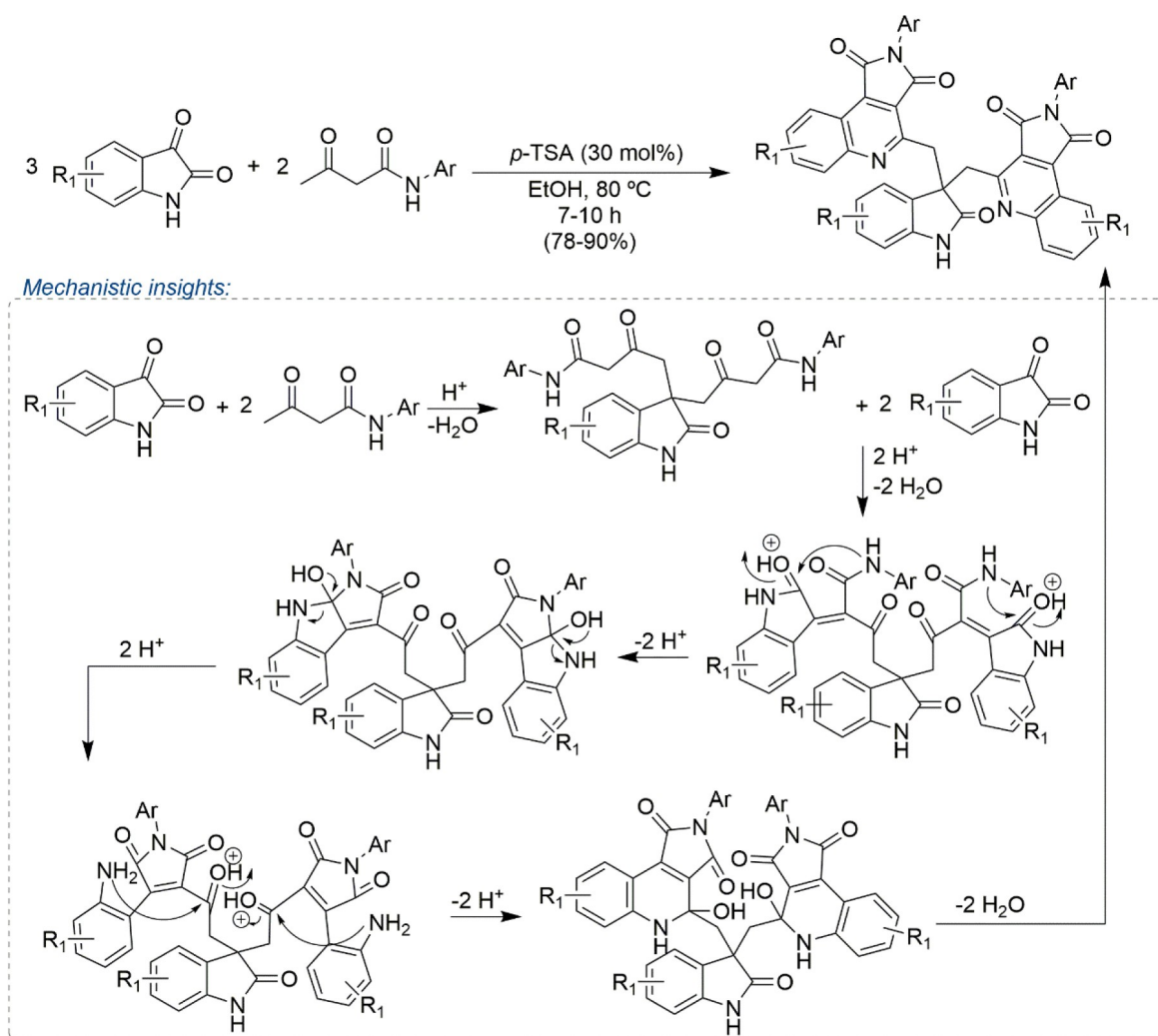
While considerably less explored than spirooxindole and bis-oxindole derivatives, the wide variety of MCRs which can be undertaken using isatin as starting materials, allow the preparation of several 3,3-disubstituted oxindole derivatives with promising synthetic utility. Among these examples, isocyanide-based MCRs constitute a valuable contribution, namely by using the Passerini and the Ugi MCRs, as well as the classic Knoevenagel and Knoevenagel-type initiated MCRs. Recent examples reporting the use of transition-metal catalysts, nanocatalysts and organocatalysts demonstrate unusual reactivities with this valuable heterocycle, and although the

mechanistic features of these new approaches might still be under scrutiny, their synthetic relevance is undeniable.

5. Non-oxindole Derivatives

5.1. Isocyanide-based MCRs

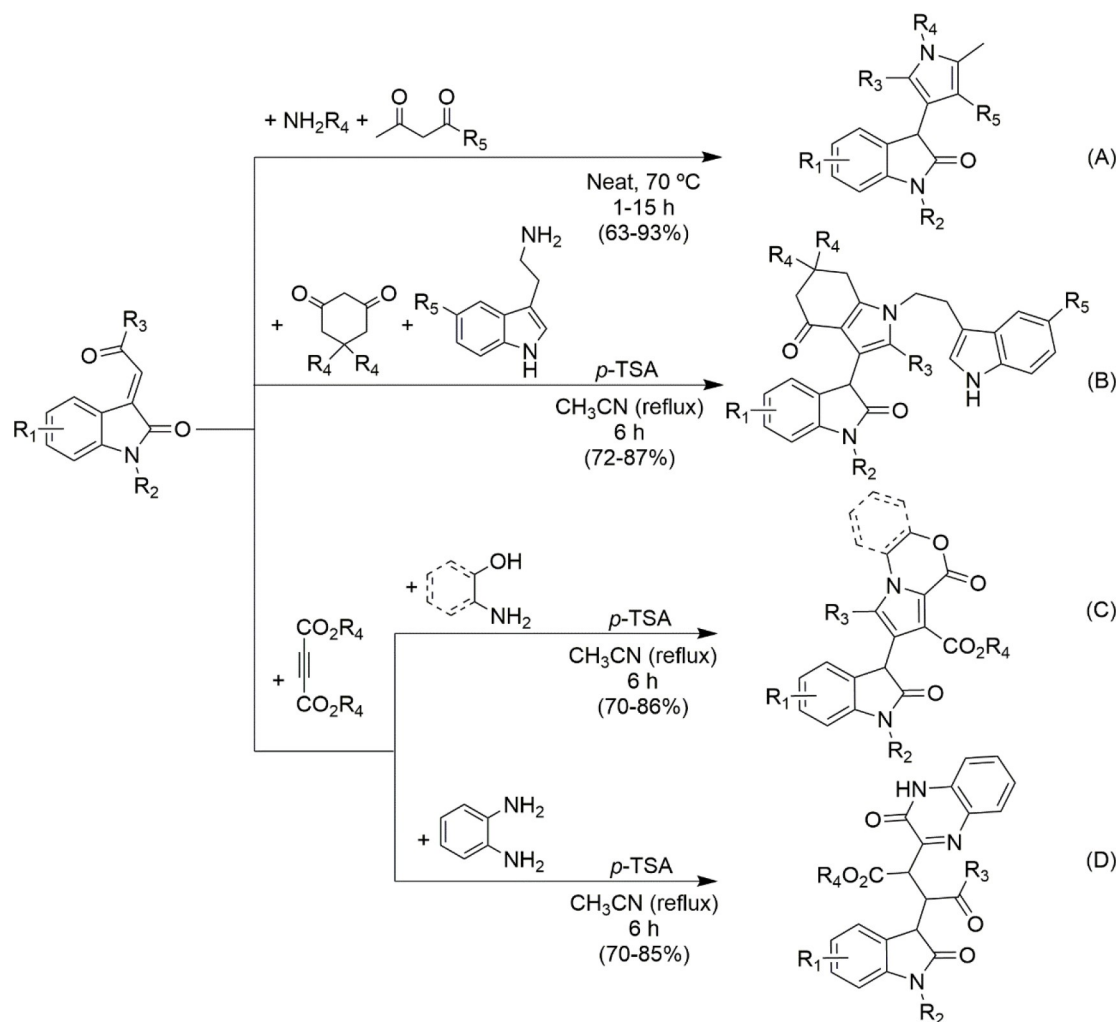
Isatin and its derivatives are often applied in MCRs aiming at the synthesis of non-oxindole derivatives, *i.e.* the final products do not bear the oxindole moiety in their framework. As previously described, isocyanide-based MCRs are very



Scheme 127. Synthesis of oxindole derivatives *via* pseudo-5-MCR and the putative mechanism.

popular and the discovery of new chemical frameworks can thrive on the application of this type of reaction. Jalli *et al.* reported a three-component [3+2] cycloaddition reaction using *N*-methyl-3-isatin-imine derivatives, *tert*-butyl isocyanide and dialkyl acetylenedicarboxylates, under catalyst-free conditions. This process allowed the preparation of novel spiro [indole-2,2'-pyrrole] derivatives (13 examples) in moderate yields (Scheme 129A), keeping the imine group of the isatin derivatives intact.^[257] Using a different approach, Kenarkoohi *et al.* developed a catalyst and solvent-free four-component reaction to obtain 2-(alkylamino)-2-oxo-1-arylethyl-6,12-dioxo-6,12-dihydroindolo[1,2-*b*]isoquinoline-11-carboxylate derivatives (7 examples) in good yields. The products were synthesized from different isatins, homophthalic anhydride, cyclohexyl isocyanide, and aromatic aldehydes (Scheme 129B) and isolated without the requirement of chromatographic

separation.^[258] Recently, an example of a Groebke-Blackburn-Bienaymé based [4+1] cycloaddition reaction was reported, using succinyl- β -cyclodextrin (Suc- β -CD) as supramolecular acidic catalyst. The reaction involving different isatins, 1*H*-indazol-3-amines, and isocyanides afforded pentacyclic indazolo[30,2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one derivatives (24 examples) in excellent yields (Scheme 129C), showcasing the importance of this supramolecular host-guest interaction-based catalytic process to obtain relevant products *via* MCR. Mechanistically, it is presumed that the free carboxylic acid of the supramolecular catalyst activates the carbonyl at C3 of isatin, which reacts with 3-amino-1*H*-indazole to give an imine intermediate. Formal [4+1] cycloaddition with isocyanide generates a spirocyclic intermediate which further undergoes [1,5]-*H* shift to allow ring expansion. A final intramolecular



Scheme 128. 3-MCR using 3-phenacylideneoxindoles as starting material.

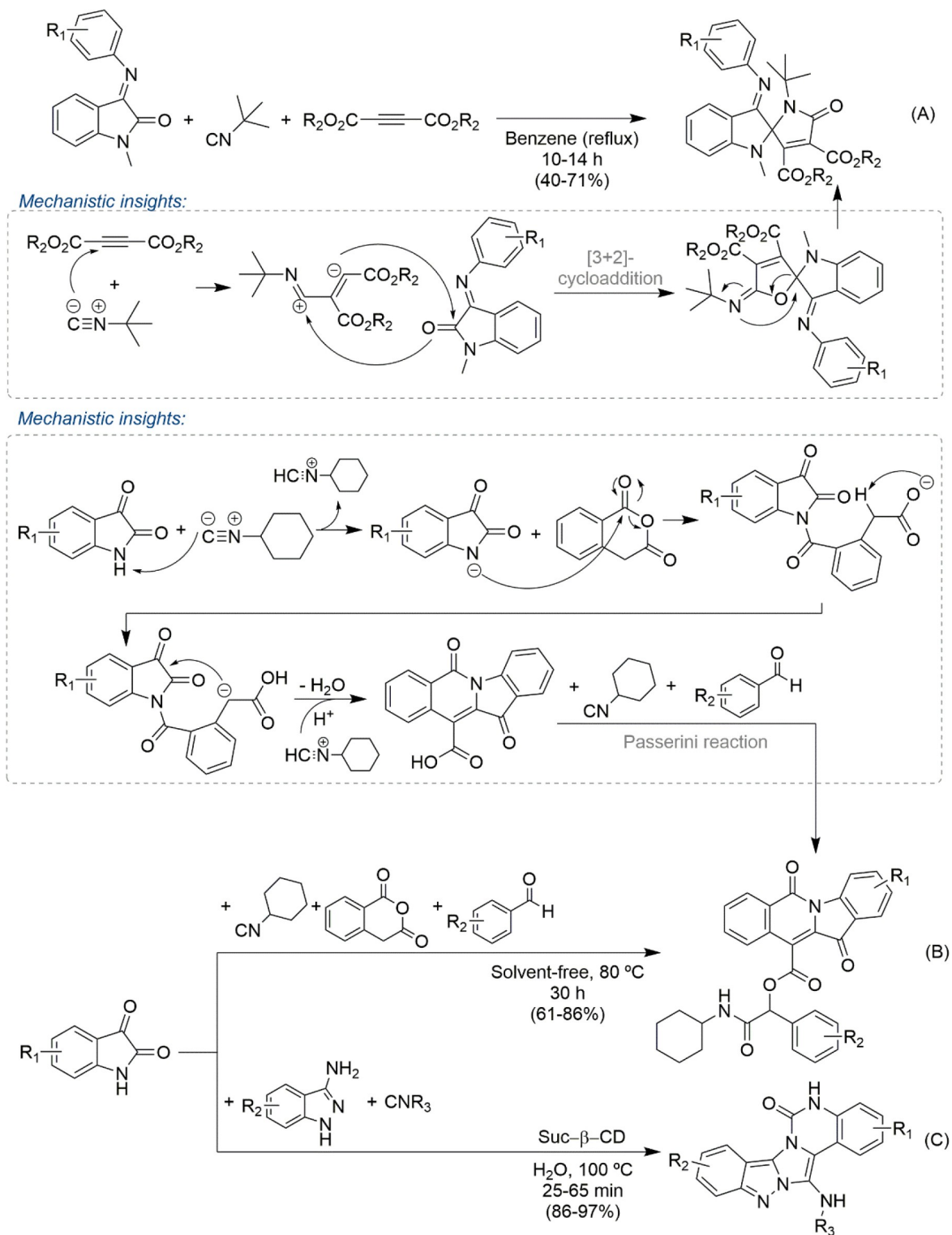
nucleophilic attack of ring nitrogen on *in situ* generated isocyanate affords the desired products.^[259]

5.2. 1,3-Dipolar Cycloaddition

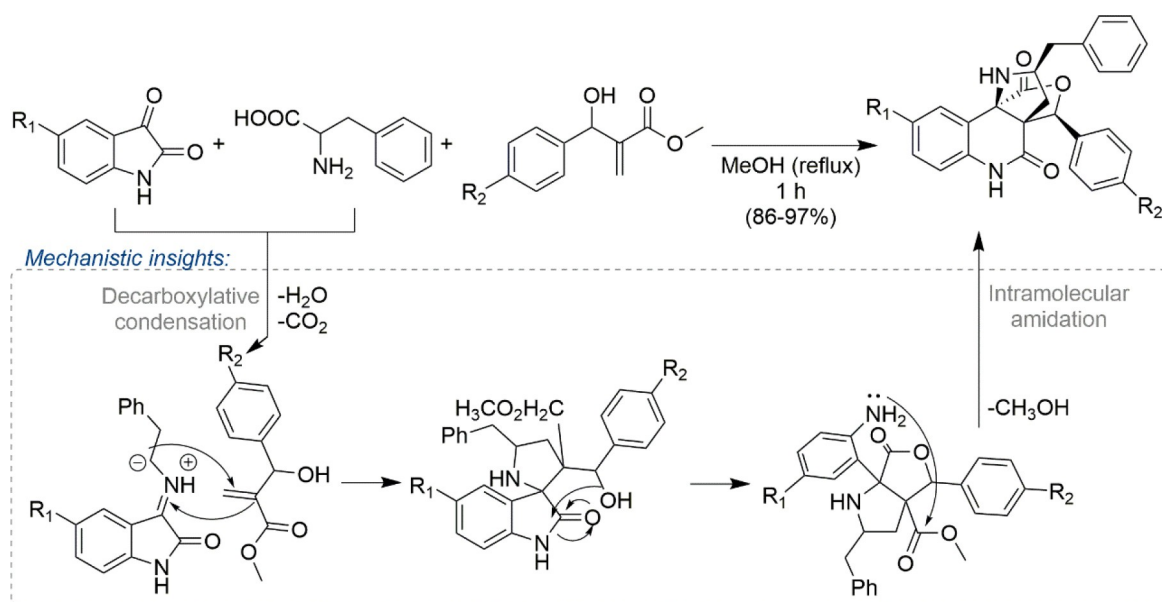
A library of bridged pyrrolo[3,2-*c*]quinolinone hybrids (12 examples) was recently reported, *via* the catalyst-free reaction between isatin, *L*-phenylalanine and Baylis-Hillman adduct dipolarophiles. These intriguing structures were obtained in excellent yields under simple reaction conditions (Scheme 130). Mechanistically, it is presumed that the reaction undergoes three reaction steps, consisting of a 1,3-dipolar cycloaddition, lactonization (induced by the hydroxyl attack on position C2 of the isatin moiety with concomitant ring opening) followed by lactamization.^[260]

5.3. Miscellaneous

The supramolecular acid catalytic activity of β -cyclodextrin (β -CD) was further explored in a different type of MCR, involving isatin, anilines and dimedone (2 equivalents), in aqueous media. This green approach proved to be a simple and efficient synthetic route to obtain spiro[acridine-9,3'-indole]-2',4,4'(1'*H*,5'*H*,10*H*)-trione derivatives (20 examples) in very good to excellent yields (Scheme 131A). Mechanistically, the most relevant step consists in the ring opening of isatin, through the cleavage of the intramolecular amide bond, followed by recyclization, as well as the “anchorage” of the carbonyl at the C3 position to a peripheral hydroxyl group of cyclodextrin.^[261] Indeed, the reaction between these three components – isatins, anilines, and dimedone – is one of the most commonly explored MCRs leading to the formation of non-oxindole products. A wide variety of catalysts have been



Scheme 129. Isocyanide-based MCRs involving isatin and its derivatives to obtain non-oxindole derivatives. Postulated mechanistic pathway.



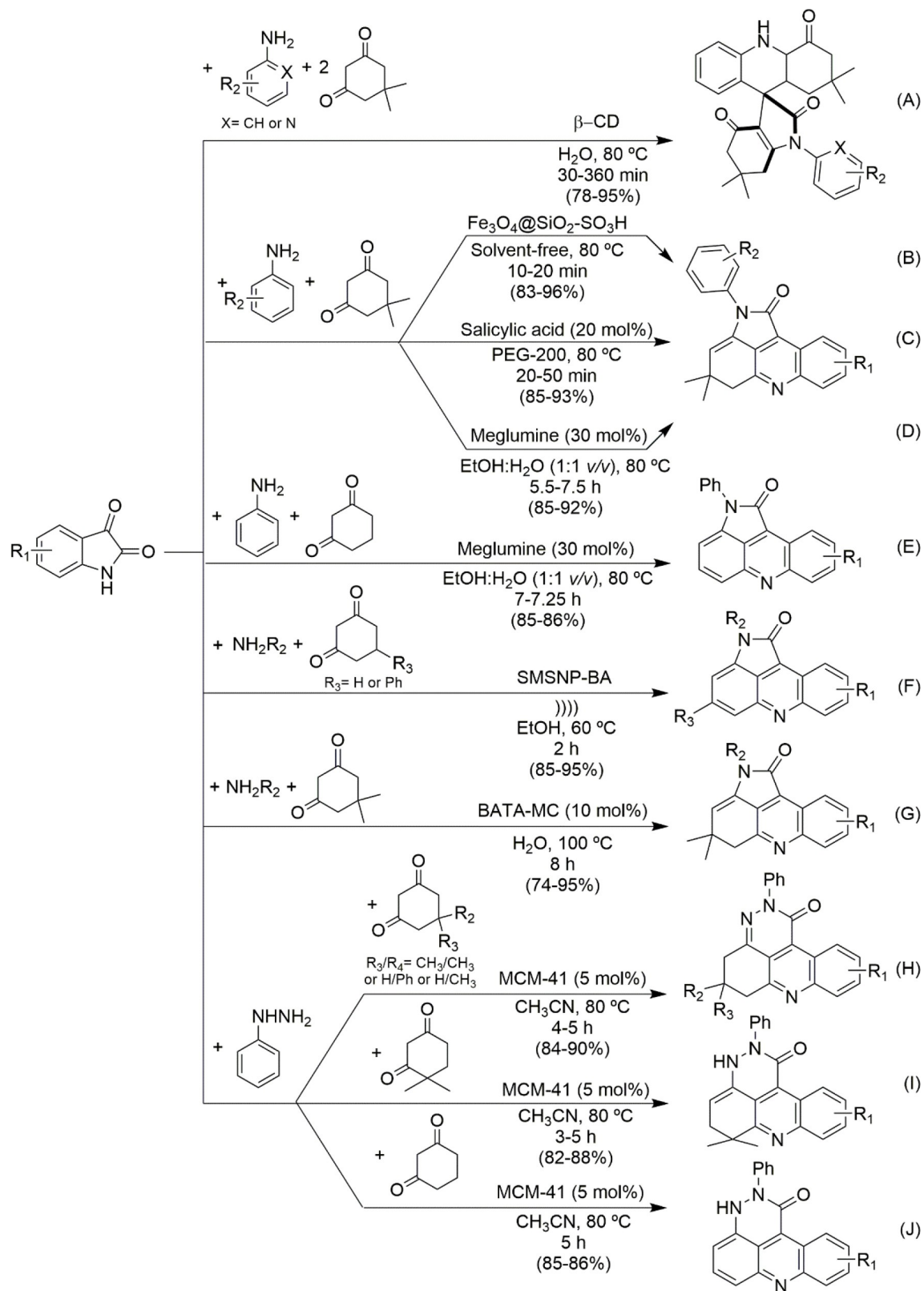
Scheme 130. Synthesis of pyrrolo[3,2-*c*]quinolinone bridged hybrids *via* MCR. Mechanistic interpretation.

explored for this MCR. Among the most recent examples, we can highlight the use of a Fe_3O_4 @silica sulfonic acid nanocomposite (Fe_3O_4 @ SiO_2 - SO_3H) by Ghasemzadeh *et al.*, under solvent-free conditions and short reaction times. The magnetic properties of this catalyst make it easy to recover, and it can be reused up to five times without significant loss in catalytic activity (96–90% yield). The reaction afforded a library of pyrroloacridin-1-(2*H*)-one derivatives (16 examples) in very good to excellent yields under the described eco-friendly conditions (Scheme 131B).^[262] The same chemical framework was obtained using sustainable organocatalytic methodologies. Niya *et al.* used salicylic acid as the catalyst and PEG-200 as the solvent, generating a small library (13 examples) in very good to excellent yields (Scheme 131C).^[263] Meglumine is an amino sugar obtained from sorbitol, a biomass-derived sugar alcohol,^[264] and was applied as organocatalyst to synthesize the same type of pyrroloacridin-1-(2*H*)-one derivatives (11 examples) in yields similar to the other methodologies (Scheme 131D). Despite the higher catalyst load, meglumine required longer reaction times, when compared to the other two catalytic systems reported, but proved to be efficient in a similar reaction, in which dimedone was replaced by cyclohexane-1,3-dione (Scheme 131E), affording tricyclic aromatic derivatives (2 examples), under the same eco-friendly conditions.^[265]

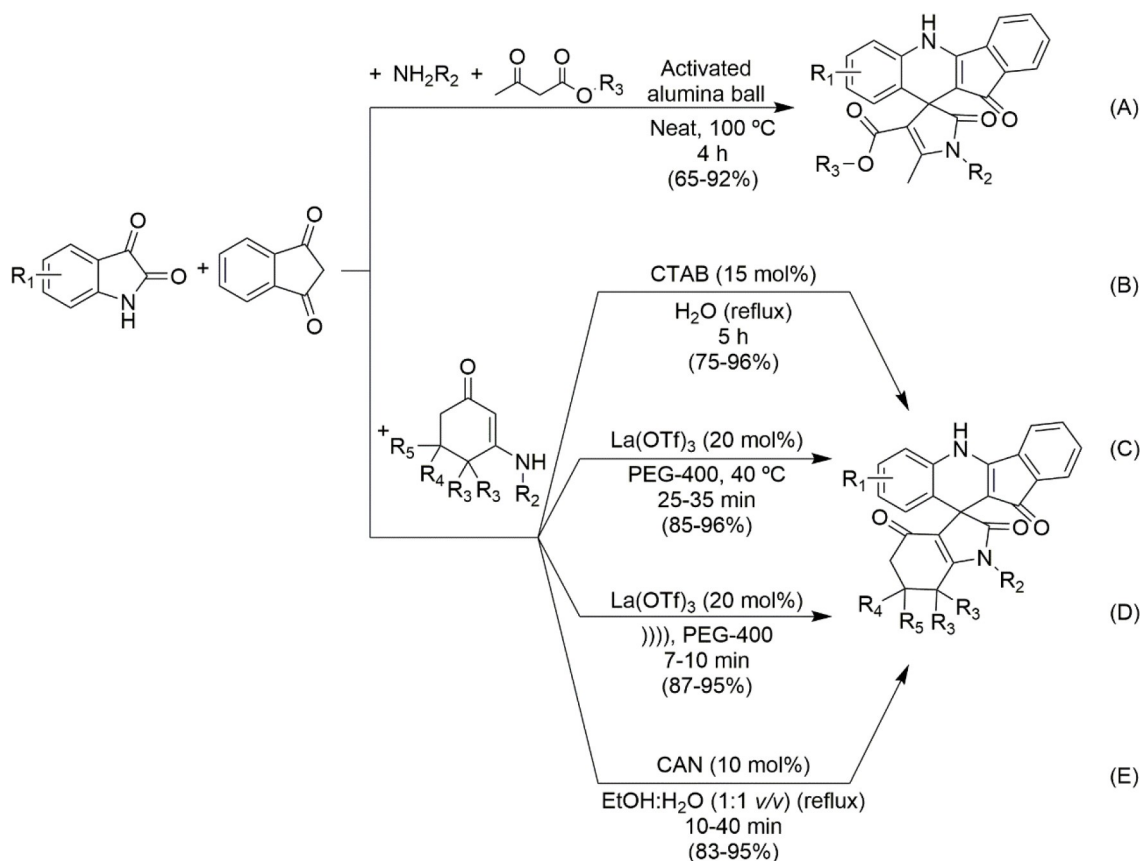
Another variation that can be found in the literature in this three-component reaction is the replacement of aniline by other primary amines, such as benzylamines and alkyl amines. Ray *et al.* reported the synthesis of a library of acridinone derivatives (14 examples) in excellent yields, by reacting *N*-

unsubstituted isatins, cyclic-1,3-diketones, and different primary amines (including anilines, benzylamines, and alkyl amines), using a sustainable heterogeneous catalyst that consisted of spherical mesoporous silica nanoparticles adsorbed with HBF_4 (SMSNP-BA) and ethanol as solvent (Scheme 131F). This eco-friendly process was developed using sonication as the activation technique.^[266] Different anilines, as well as aliphatic primary amines were used by Sharkar *et al.*, promoting the reaction in water using a macrocyclic nano-reactor. The heteroditopic catalyst consisted of a bis-amide and tris-amine functionalized macrocycle (BATA-MC), which could provide several binding sites for the reactants, hence facilitating the MCR even with a catalyst loading of 10 mol%. The final products (16 examples) were obtained in very good to excellent yields, showcasing the efficacy of this recyclable catalyst to promote this reaction in water (Scheme 131G). Under the same reaction conditions, products like the ones depicted in Scheme 131F could also be obtained (3 examples; 85–88% yield) by replacing the dimedone by the appropriate cyclic diketone.^[267]

A different approach was established by Karmakar *et al.*, by replacing aniline by phenyl hydrazine, in order to obtain 5,6-dihydro-5,5-dimethyl-2-phenyl-2*H*-pyridazino[3,4,5-*kl*]acridin-1(4*H*)-one derivatives, with some structural variations according to the cyclic-1,3-diketone used in the reaction (Scheme 131H – 6 examples; Scheme 131I – 3 examples; Scheme 131J – 2 examples). This scaffold diversity was achieved by using commercially available mesostructured silica MCM-41 (hexagonal) as heterogeneous catalyst. The final products were obtained in very good yields, demonstrating the



Scheme 131. MCRs involving isatin, primary amines (or phenyl hydrazine) and cyclic diketones.



Scheme 132. MCRs involving isatin, enaminones and indane-1,3-dione.

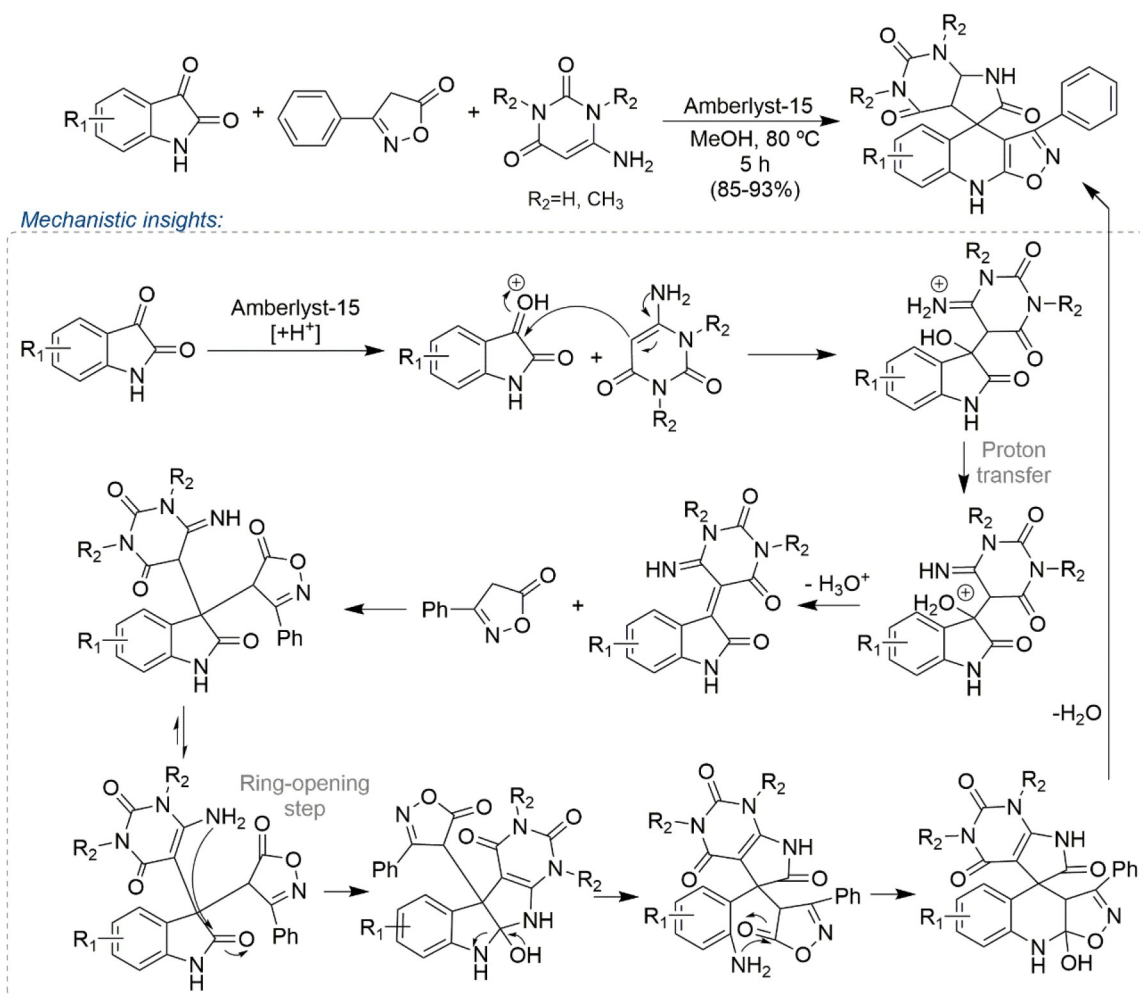
potential of this material to be employed as catalyst or as a solid-support for other catalysts.^[268]

The mechanism of all the reactions shown in Scheme 131 start with the formation of an enaminone intermediate between the cyclic diketone and the primary amine. Using this principle, several researchers started to explore the reaction between isatins, enaminones, and indane-1,3-dione. Mukhopadhyay and co-workers explored this chemistry using two different approaches. In one example, they used a 4-component reaction, generating the enaminone *in situ* from the reaction between different primary amines (anilines, benzyl amines and alkyl amines) and acyclic β -ketoesters. The resulting spiro[pyrrolo-4,10'-indeno[1,2-*b*]quinolin]-3-carboxylate derivatives (21 examples) were obtained in moderate to very good yields, under solvent-free conditions, using activated alumina balls as catalyst (Scheme 132A). The catalytic effect of the eco-friendly activated alumina balls was directly correlated with the displayed pore size, but not with pore volume or surface area.^[180] In the second example, a library of spiro [indolo-3,10'-indeno[1,2-*b*]quinolin]-2,4,11'-trione derivatives (51 examples) was obtained from isatins, indane-1,3-dione, and different enaminones using the surfactant CTAB as

catalyst (Scheme 132B) under environmentally benign conditions. The micellar catalytic effect of CTAB proved to be effective in a wide variety of starting materials and allowed the reaction to proceed in water, achieving excellent yields.^[269]

The same spiro[indolo-3,10'-indeno[1,2-*b*]quinolin]-2,4,11'-trione scaffold has been explored by other authors in recent years, with particular focus on catalyst and activation technique optimization. Kumari *et al.* explored the use of La(OTf)₃ as the Lewis acid catalyst, using PEG-400 as solvent under conventional heating (Scheme 132C) and also using ultrasonic radiation as activation technique (Scheme 132D). The desired products (22 examples) were obtained in excellent yields in both conditions, with the ultrasonic radiation allowing a considerable reaction time reduction.^[270] In another example, Meena *et al.* reported the use of ceric ammonium nitrate (CAN) as an efficient catalyst for this chemical transformation, affording the final spiro compounds (22 examples) in excellent yields under short reaction times (Scheme 132E).^[271]

Similarly, the Amberlyst-15 promoted reaction between isatins, 3-phenylisoxazol-5(4*H*)-one and 6-amino-pyrimidine-2,4(1*H*,3*H*)-dione or 6-amino-1,3-dimethylpyrimidine-



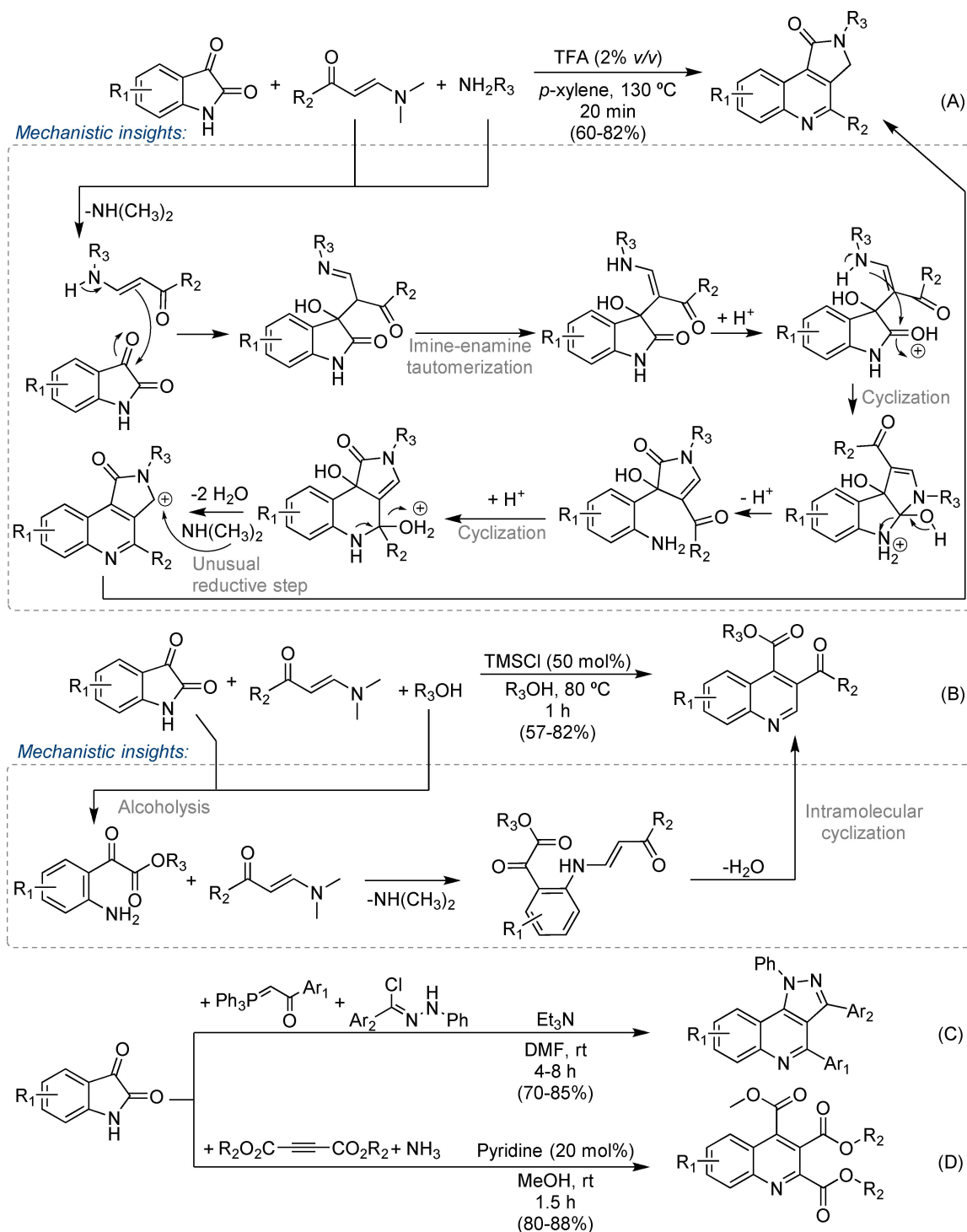
Scheme 133. Amberlyst-15-promoted 3-MCR affording non-oxindole spiro compounds. Mechanistic interpretation.

2,4(1*H*,3*H*)-dione afforded a library of spiro compounds (27 examples) in very good to excellent yields (Scheme 133). This heterogeneous catalyst proved to be effective in this chemical transformation, and could be recycled at least up to seven times without significant loss of activity.^[79]

Other types of enaminones - *N,N*-dimethylenaminones – were employed in MCRs with isatins, affording quinoline derivatives. Yu and co-workers explored the reaction of isatin, *N,N*-dimethylenaminones, and primary amines (anilines and cyclohexylamine) in the presence of catalytic amounts of trifluoroacetic acid (TFA), affording a library of pyrrolo[3,4-*c*]quinoline-1-one derivatives (35 examples) in moderate to very good yields with short reaction times (Scheme 134A).^[272] More recently, a library of quinoline-4-carboxylic esters/acids (21 examples) was synthesized by the same group, through the reaction of isatins with *N,N*-dimethylenaminones and alcohols/water, respectively, *via* a Pfitzinger reaction. In this synthetic approach, catalyzed by TMSCl, the alcohol or water

used have a dual function, working as both solvent and reagent (Scheme 134B). This procedure proved to be suitable for a wide variety of starting materials, affording the final products in moderate to very good yields.^[273]

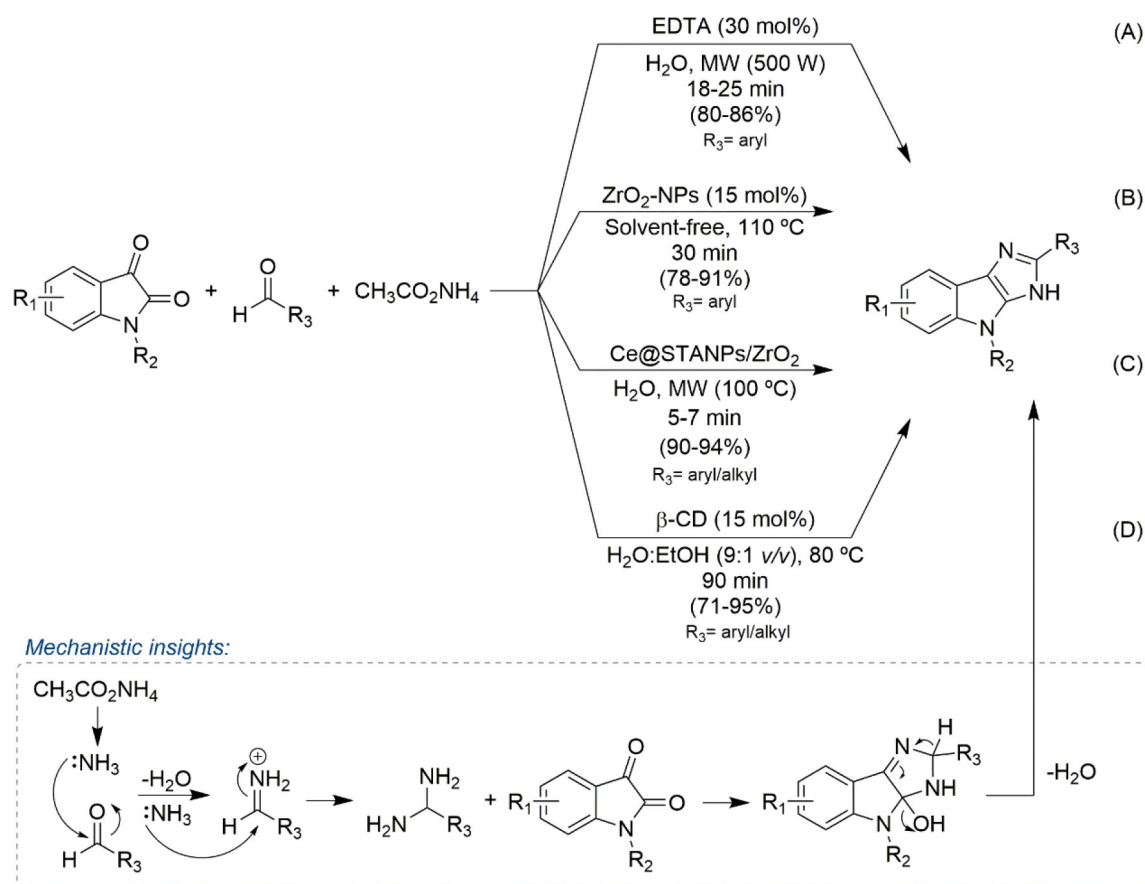
Another example of quinoline derivatives obtained *via* three-component reaction was reported by Alizadeh *et al.*, for the synthesis of a library of 1,3,4-trisubstituted pyrazolo[4,3-*c*]quinoline derivatives (7 examples). These compounds were prepared in very good yields through the reaction of isatins, 1-aryl-2-(1,1,1-triphenyl- λ^5 -phosphanylidene)-1-ethanone and hydrazonoyl chlorides, using triethylamine as catalyst (Scheme 134C). From the mechanistic point of view, the reaction starts with the condensation of isatin with 1-aryl-2-(1,1,1-triphenyl- λ^5 -phosphanylidene)-1-ethanone, leading to an intermediate which will undergo a 1,3-dipolar cycloaddition with the *in situ* formed nitrile imine, generated from the hydrazonoyl chloride in the presence of a base. Subsequent keto-enol tautomerization and hydroxyl attachment at the C2



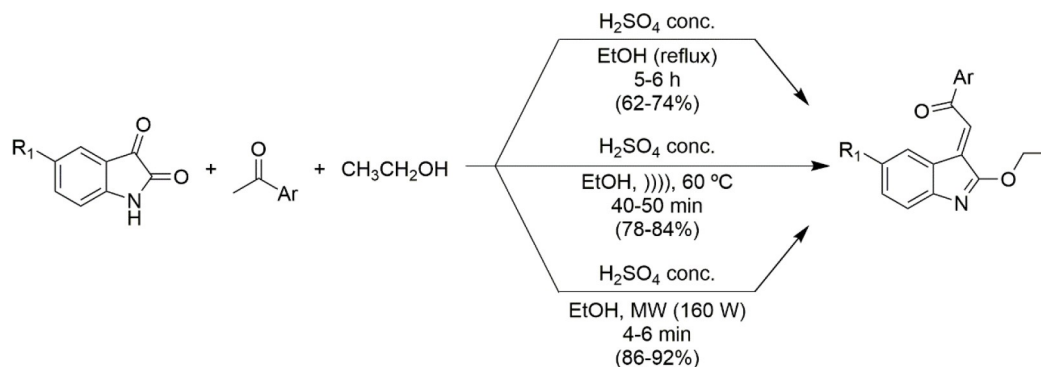
Scheme 134. Quinoline derivatives obtained *via* 3-MCR using isatin. Mechanistic interpretation.

position of isatin, leading to intramolecular amide bond cleavage and recyclization, resulting in the final product with the loss of formic acid.^[274] 2,3,4-Trisubstituted quinoline

derivatives were also prepared *via* multicomponent reaction (10 examples), by reacting *N*-unsubstituted isatin-imines (generated *in situ* through the reaction of isatin with ammonia)



Scheme 135. MCRs involving isatin for the synthesis of 3,4-dihydroimidazo[4,5-*b*]indole derivatives with a mechanistic interpretation.

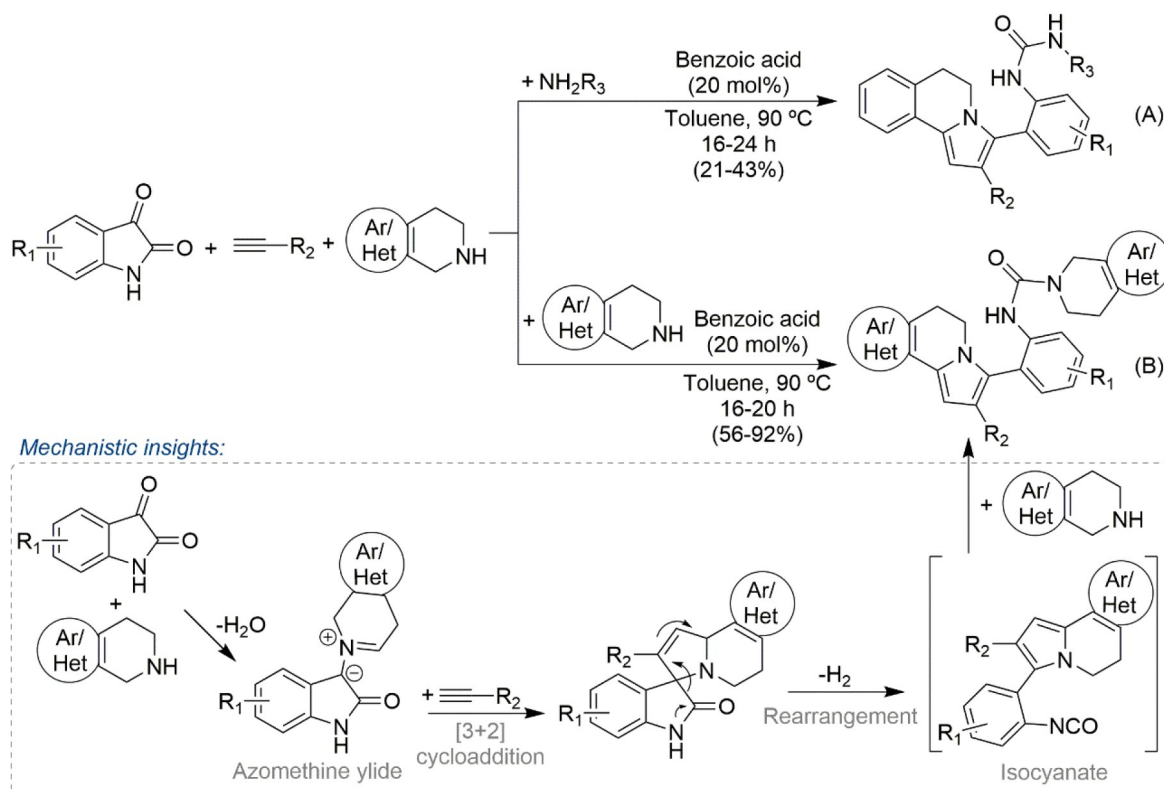


Scheme 136. Synthesis of 2-(2-ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanone derivatives *via* MCR involving isatin.

and dialkylacetylenedicarboxylates in methanol, at room temperature (Scheme 134D). Pyridine is the organocatalyst employed in this chemical transformation, which affords the desired derivatives in very good yields.^[275]

Another synthetic route involving isatins to obtain non-oxindole derivatives is the reaction between isatins, aldehydes, and ammonium acetate to afford highly substituted 3,4-

dihydroimidazo[4,5-*b*]indole derivatives. Singh and co-workers explored this reaction under microwave irradiation, using water as solvent and ethylenediaminetetraacetic acid (EDTA) as an inexpensive, easy to handle and green catalyst. The final imidazole derivatives (9 examples) were obtained in very good yields (Scheme 135A).^[276] These researchers also performed this chemical transformation under solvent-free conditions and



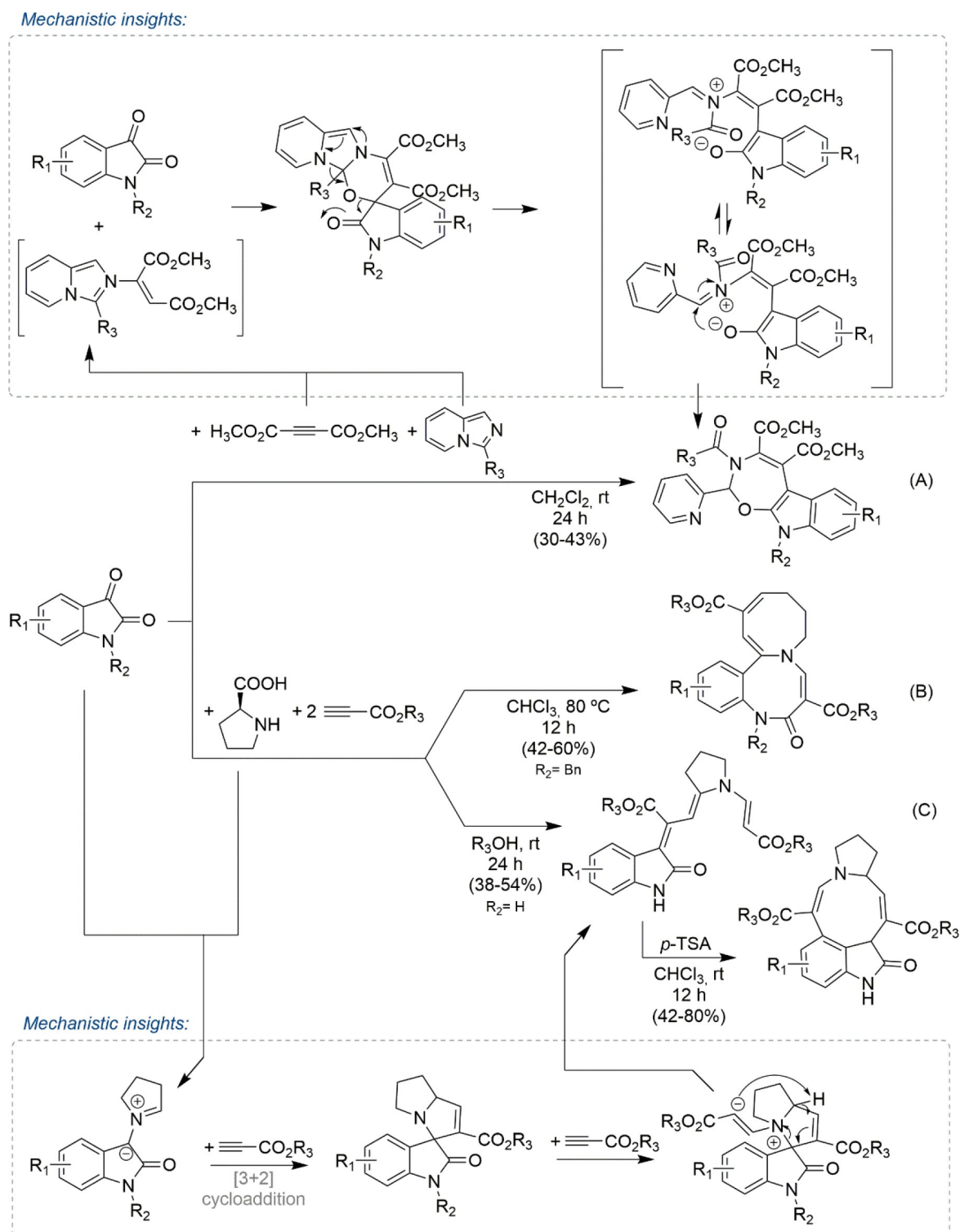
Scheme 137. Synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives *via* 4-component reaction. Mechanistic interpretation.

using an heterogeneous catalyst, zirconium dioxide nanoparticles ($\text{ZrO}_2\text{-NPs}$) (Scheme 135B). This catalyst presents several advantages, which include safety and ease of handling, as well as being non-toxic, cheap and reusable. The neat conditions tested also reinforce the sustainability of the process without considerable impact on the reaction time nor the yields, which were very good for the synthesized library of 19 compounds.^[277] Khan *et al.* synthesized and evaluated the catalytic activity of another ZrO_2 -based catalyst, consisting of cerium-immobilized silicotungstic acid nanoparticle-impregnated zirconia (Ce@STANPs/ZrO_2). This catalyst proved to be highly versatile, efficient and recyclable, while capable of catalyzing the referred chemical transformation even with non-aromatic aldehydes. Furthermore, short reaction times were observed, comparing to the previously described reactions with other catalysts. The library (12 examples) was prepared in excellent yields under environmentally friendly conditions (Scheme 135C), using water as solvent and microwave irradiation as activation technique (the synthesis of the same products under conventional heating required longer reaction times and afforded lower yields).^[278] Another sustainable and effective methodology was reported by Nipate *et al.*, by using the already described supramolecular catalyst, β -CD. The desired compounds (21 examples) were obtained in good to

excellent yields (Scheme 135D), although the use of an aliphatic aldehyde (heptanal) led to the lowest yield observed (the linear heptanal presents less structural complementarity to the core of the β -CD), showing once again the catalytic importance of this supramolecular host-guest mechanism.^[279] For all these examples, the catalysts play a pivotal role in activating the carbonyl groups of the aldehyde and isatin components.

Ashok *et al.* reported a three-component reaction for the synthesis of 2-(2-ethoxy-5-substituted-indol-3-ylidene)-1-arylethanone derivatives (19 examples) from isatin, arylmethylketones, and ethanol (which worked as both reactant and solvent), in the presence of concentrated sulfuric acid. The authors compared conventional heating with ultrasound and microwave irradiation, with the last one providing not only higher yields, but also considerably shorter reaction times (Scheme 136).^[280]

Two libraries of 5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives were prepared *via* benzoic acid catalyzed 4-component reactions. In both cases, the reactions involved isatins, a terminal alkyne, and tetrahydroisoquinoline, with the fourth component dictating the type of family obtained – if a primary amine was applied, 1-substituted-3-(2-(2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)phenyl)urea derivatives



Scheme 138. Synthesis of seven-, eight- and nine-membered rings *via* MCR involving isatin. Mechanistic interpretation.

(9 examples) were obtained in low to moderate yields (Scheme 137A); if a second tetrahydroisoquinoline equivalent

was used, the reaction resulted in *N*-(substituted-2-(2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)phenyl)-3,4-dihy-

droisoquinoline-2(1*H*)-carboxamide derivatives (22 examples) in good to excellent yields (Scheme 137B). Nevertheless, during the formation of this second family, a spirooxindole intermediate is formed, which can be exposed to primary amines and converted into the urea derivatives in excellent yields.^[281]

The synthesis of larger heterocycles (seven- eight- nine-membered rings) based on the isatin core using MCRs was also a key challenge. Sammor *et al.* explored the synthesis of novel 3,10-dihydro-2*H*-1,3-oxazepino[7,6-*b*]indole derivatives (11 examples), using a three-component reaction. Briefly, the reaction between *N*-substituted isatin, dimethyl acetylenedicarboxylate, and 3-alkyl or 3-arylimidazo[1,5-*a*]pyridines afforded the final products in moderate yields (Scheme 138A), through a 1,4-dipolar cycloaddition reaction.^[282] An intriguing tricyclic family of compounds bearing two fused eight-membered rings was synthesized using a three-component reaction between *N*-benzyl isatin, *L*-proline, and excess of alkyl propiolate. The resulting azocino[1,2-*a*]benzo[*c*][1,5]diazocine derivatives (5 examples), were obtained in moderate to good yields, in refluxing chloroform (Scheme 138B). Surprisingly, by replacing *N*-benzyl isatin with *N*-unsubstituted isatin and shifting the solvent to an alcohol (methanol or ethanol), 2-(oxindolin-3-ylidene)propylidene)pyrrolidin-1-yl)acrylate derivatives were isolated as the main products, however, a by-product bearing a nine-membered ring was also observed. Intrigued by these findings, Cao *et al.* explored further the reactivity of this new products, and through an acid-catalyzed transformation, they were successfully converted to pyrrolo[1',2':1,9]azonino [6,5,4-*cd*]indole derivatives in moderate to very good yields (9 examples) (Scheme 138C).^[283]

The versatility of isatin as a starting material goes far beyond the construction of new oxindole derivatives. In this section, we demonstrated how this heterocycle can undergo different MCRs (with isocyanide-based and 1,3-dipolar cycloaddition MCRs being the most reported) to achieve other valuable heterocycles. These reactions are mechanistically dependent on the ring-opening step, which can be promoted by a wide variety of catalysts.

6. Summary and Outlook

MCRs unlock a wide diversity of oxindole-based scaffolds. The unique reactivity of isatin, especially at the C3 position, makes it the perfect candidate to explore new multicomponent approaches. In this review, we explored the most recent developments on the application of isatin cores to the synthesis of a very diverse range of structural targets, including very desirable spirooxindole products, using a plethora of sustainable MCR approaches. We also have reviewed this approach for bis-oxindole derivatives, which are an exciting structural

family that have also gained visibility in the past few years, as well as the exploration of multicomponent approaches to prepare a wide-diversity of 3,3-disubstituted oxindoles. Reactions involving the ring-opening of the amide-bond of isatin to afford non-spirooxindole derivatives, a structural group that has gained much attention in synthetic organic chemistry over the last 10 years, mostly due to their relevance in medicinal chemistry, have also been reviewed. The increase of complexity, number of components, combined with the application of eco-friendly approaches, make MCRs applied to isatin a resourceful and productive area for synthetic organic chemistry and medicinal chemistry.

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