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Review

Advances in Green Catalysis for the Synthesis of Medicinally Relevant *N*-Heterocycles

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Abstract: *N*-heterocycles, both saturated and unsaturated, are ubiquitous biologically active molecules that are extremely appealing scaffolds in drug discovery programs. Although classical synthetic methods have been developed to access many relevant *N*-heterocyclic scaffolds, representing well-established and reliable routes, some do not meet the needs of sustainability. In this context, several advances have been made towards the sustainable synthesis of *N*-heterocycles. This review focuses on the most recent examples from the last five years of catalytic synthesis of several heterocyclic compounds of medicinal relevance. Thus, the synthesis of isoindoloquinazolines, quinazolines and azaindoles, among others, are covered. The synthetic methods selected include the use of homogeneous and heterogeneous catalysts and the use of alternative and sustainable methods such as, for example, metal-catalyzed acceptorless coupling and one-pot reactions. The green aspects of the individual synthetic approaches are highlighted, and the scope of each methodology is described.

Keywords: green catalysis; *N*-heterocycles; synthesis; bioactive compounds; metal-catalysis

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1. Introduction

N-containing heterocycles are among the most relevant structural components of pharmaceuticals, and according to an analysis from the U.S. FDA, 59% of unique small-molecule drugs contain a nitrogen heterocycle [1].

Both saturated and unsaturated *N*-heterocycles are prevalent in biologically active molecules and constitute increasingly attractive scaffolds for the development of new medicines (Figure 1). Several indole and azaindole derivatives have been reported as potent cancer agents. Pemigatinib is a representative medicine approved by the FDA [2]. Luotonin A and tryptanthrin are bioactive quinazolines and quinazolones-based alkaloids. Quinazoline derivatives exhibit several activities such as antibacterial, antitubercular and antiviral and are potential inhibitors of epidermal growth factor (EGF) and tyrosine kinase receptors [3–9]. The pyrrole-based statin lipitor is considered as a 'blockbuster' drug being widely prescribed, improving the health of millions [10] and acting as a cholesterol-lowering drug.

Additionally, saturated *N*-heterocycles such as ritalin and veliparib are medicinally relevant molecules used for the treatment of ADHD (Attention deficit hyperactivity disorder) and as an anticancer, respectively [11]. Piperidines are the most important saturated *N*-heterocycles in therapeutic compounds, followed by piperazines and pyrrolidines [1].

Given the widespread interest in *N*-heterocycles, the synthesis of these compounds has always been among the most important research areas in synthetic chemistry. Classic named reactions have been developed to address the synthesis of *N*-heterocycles [12].

Despite the utility of the classical synthetic methods, modern developments in synthetic chemistry underline new sustainable synthetic routes focused on environmentally acceptable alternatives to the classic methods [13]. Indeed, a green and simple access to a wide variety of *N*-heterocyclic compounds is of crucial importance for drug discovery programs. Due to their widespread application and medicinal relevance to *N*-heterocycles, being present in both natural and synthetic compounds, their synthesis is an important area of research in synthetic chemistry.

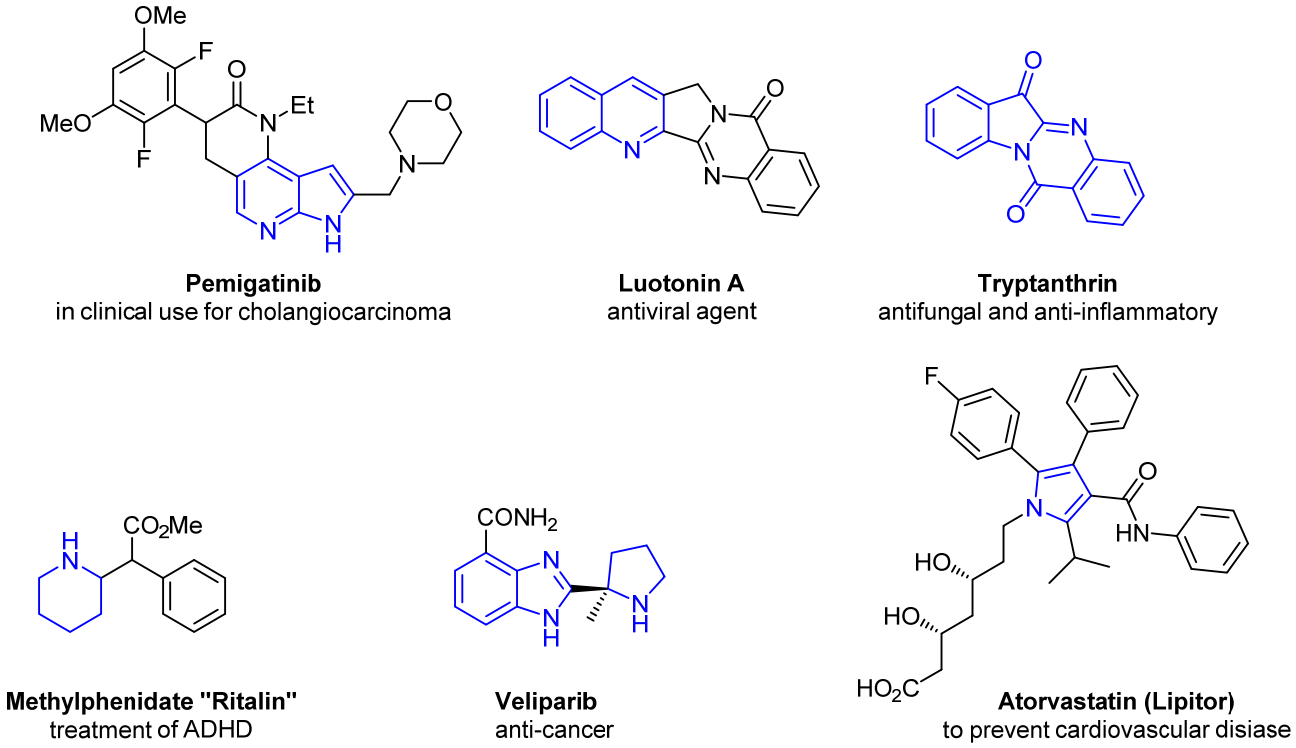


Figure 1. Representative examples of bioactive saturated and unsaturated *N*-heterocycles.

This review covers the most recent contributions to the sustainable synthesis of *N*-heterocyclic compounds, particularly the green catalytic methods reported in the last five years. Several catalytic methods are presented, involving both homogeneous and heterogeneous catalysts and recyclable catalysts combined with non-traditional activation methods such as microwave (MW) irradiation. Furthermore, examples of the use of green reagents and atom-efficient methods such as one-pot reactions and acceptorless coupling reactions, among others, as the main tools in green synthesis and catalysis are also covered. Herein, the synthesis of *N*-heterocycles of medicinal relevance using improved and green approaches are reviewed (Figure 2).

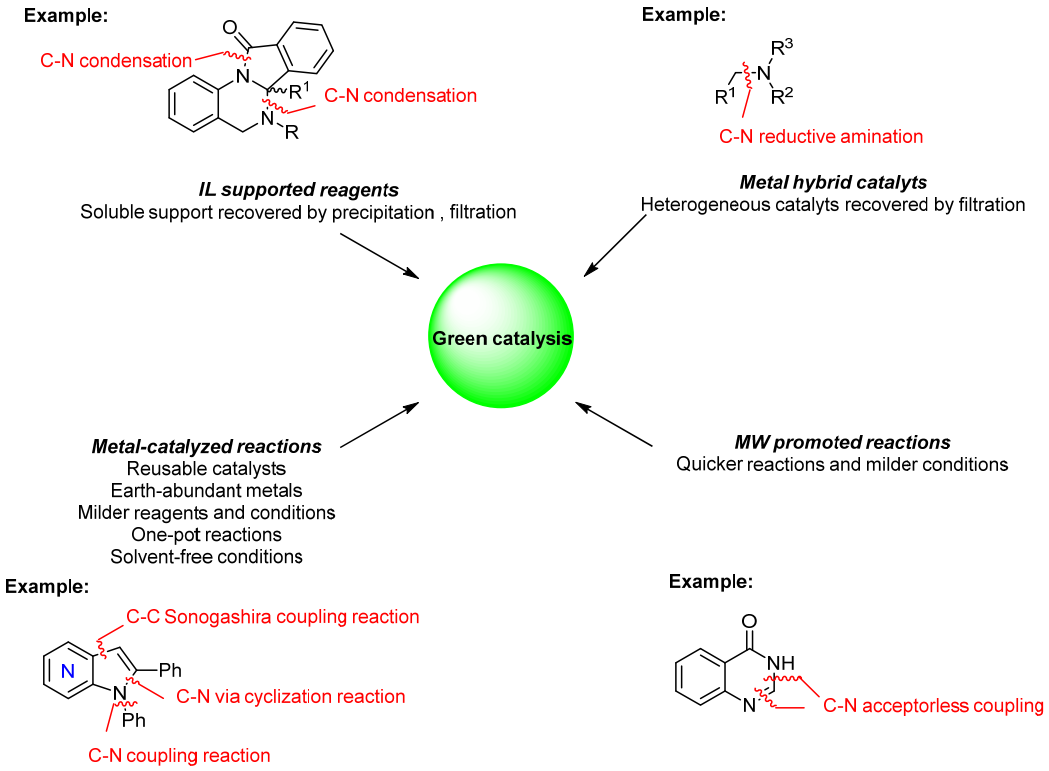


Figure 2. Examples of the green catalysis methods reviewed herein.

2. Green Catalytic Synthesis of *N*-Heterocycles

Chung-Ming and co-workers [14] reported a novel methodology based on an ionic liquid (IL) support for the synthesis of substituted isoindolo[1,2-*a*]quinazoline using MW irradiation. This reaction consisted of the acid-catalyzed heterocyclization of several substituted amino benzoates **1**, coupled to ILs, with α-ketobenzoic acids or γ-ketoaliphatic acid to generate pharmaceutically relevant *N*-heterocycles **3** (Scheme 1). First, experiments involved the synthesis of the IL-bounded diamine by the esterification of a nitrobenzoic acid derivative with an IL derivative, followed by the nucleophilic attack of an amine and finally the reduction of the nitro moiety.

To synthesize the desired isoindoloquinazoline **3**, a two-step reaction was required consisting of a cyclization and followed by the cleavage of the desired product from the IL bond. The best results were obtained using acetic acid instead of trifluoroacetic acid for the first step and sodium methoxide as the base in the cleavage for the second step.

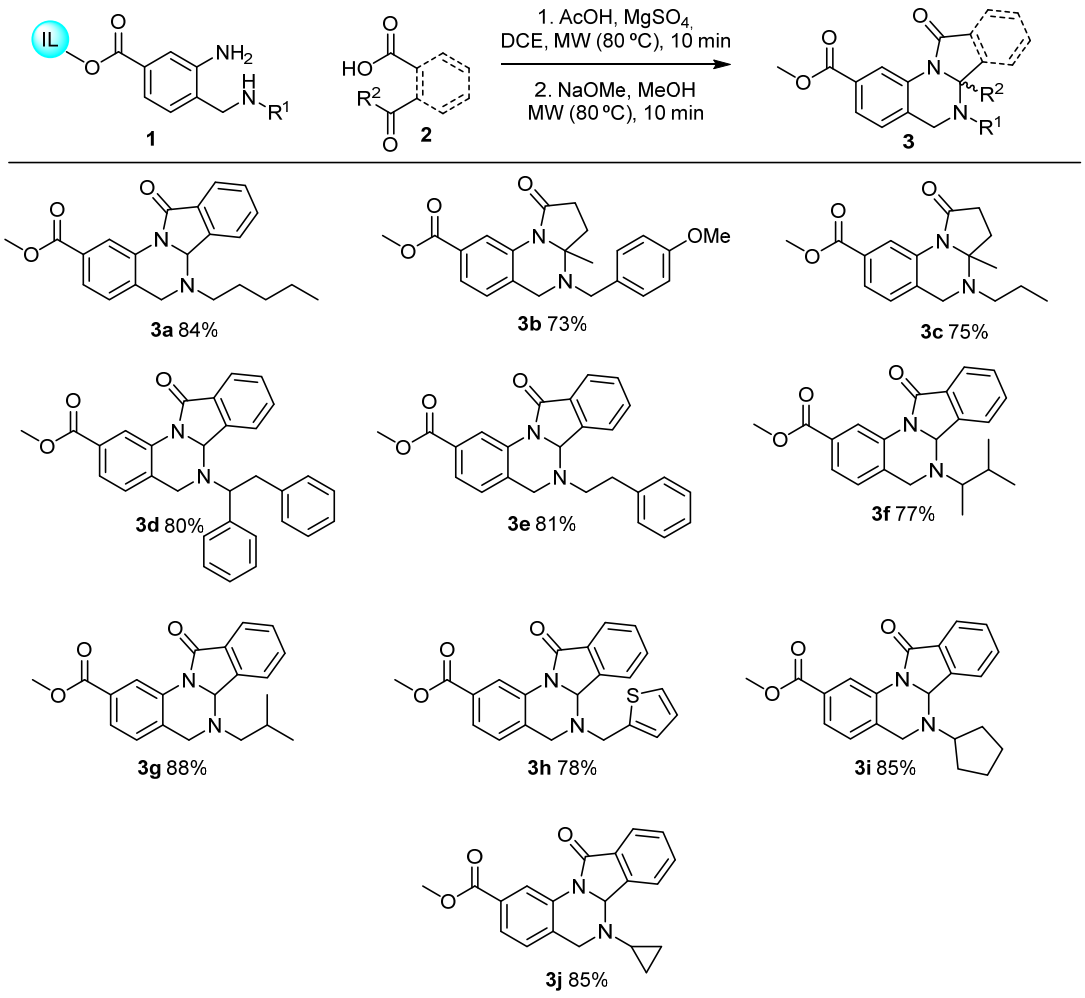
To further expand the scope of the reaction, diamines **1** was reacted with several α-ketobenzoic acids and γ-ketoaliphatic acid **2** to obtain isoindolo[1,2-*a*]quinazoline **3** with yields up to 88%. To conclude, a novel one-pot synthesis of isoindolo[1,2-*a*]quinazoline was obtained using an IL as soluble support via MW irradiation. Furthermore, the use of IL-supported substrates allowed for the purification of the products by simple precipitation, making this protocol more versatile and efficient in terms of green chemistry.

Yangs group [15] investigated a way to synthesize a variety of pyrrolizidine and indolizidine derivatives from simple aliphatic alkenyl amides. Their reaction involved an efficient palladium-catalyzed aerobic oxidative cyclization with the capability of accessing various *N*-heterocycles and the use of molecular oxygen as green oxidant.

The group had previously reported palladium catalyzed aerobic oxidative cascade cyclizations, which resulted in pyrroloindoline derivatives [16–19]. However, substrate scope in previous transformations were mostly restricted to aromatic alkenyl amides, which limited its extensive use in heterocycle synthesis. Compared to aromatic substrates containing fused phenyl ring backbones, aliphatic alkenyl amides are less appropriate for

the cyclization reaction due to the higher flexibility of their backbones and the lower acidity of aliphatic amide.

The authors selected a linear aliphatic alkenyl amide (0.3 mmol) as a model substrate, 10 mol% of various palladium catalysts, 40 mol% pyridine as the ligand and O_2 as the oxidant for their optimization experiences. It also found that the addition of 40 mol% of DABCO accelerated the reaction and increased the overall yield, since it acted as a competitive ligand and as a base to deprotonate the amido proton. The optimal temperature was determined to be 95 °C.



Scheme 1. IL supported synthesis of substituted isoindolo[1,2-a]quinazoline using MW irradiation.

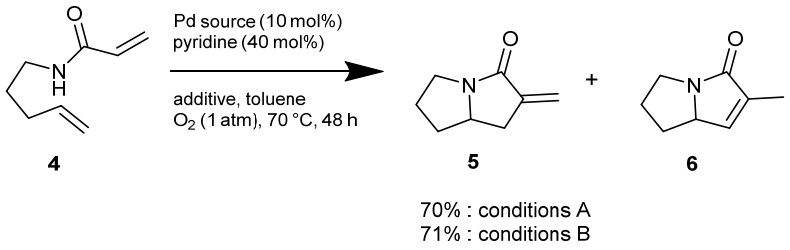
Hence, two optimal conditions were selected. Conditions A: substrate **4**, 10 mol% $Pd(TFA)_2$, 40 mol% pyridine and 40 mol% DABCO in toluene under 1 atm O_2 at 95 °C; Conditions B: substrate **4**, 10 mol% $Pd(OAc)_2$, 40 mol% pyridine and 200 mol% K_2HPO_4 in toluene under 1 atm O_2 at 95 °C (Scheme 2).

Once the conditions were optimized, the generality of this cascade cyclization reaction was explored, and it was observed that conditions A are notably faster than B.

Overall, moderate to good yields were achieved for the synthesis of various *N*-heterocycles, including pyrrolizidine and indolizidine derivatives as well as azatricyclic heterocycles. The stereochemistry of the produced *N*-heterocycles indicates that the aminopalladation step proceeds via a *syn* manner.

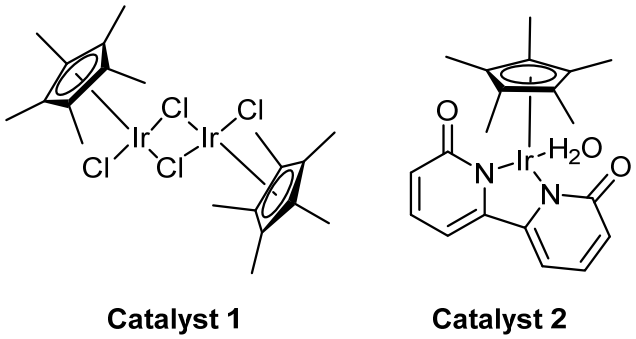
Quinazolinones are a very important class of fused *N*-heterocyclic compounds that are the key in most natural alkaloids and exhibit a broad spectrum of biological properties such as antibacterial, antiviral and anticancer activities [20]. Traditionally, they were synthesized

via the condensation between *o*-aminobenzoic acids (or their esters) and formamide with the generation of high-molecular-weight byproduct under drastic conditions, but in 2016, a group proposed a new synthesis method for quinazolinones [21].



Scheme 2. Synthesis of pyrrolizidine and indolizidine via palladium-catalyzed aerobic oxidative cyclization.

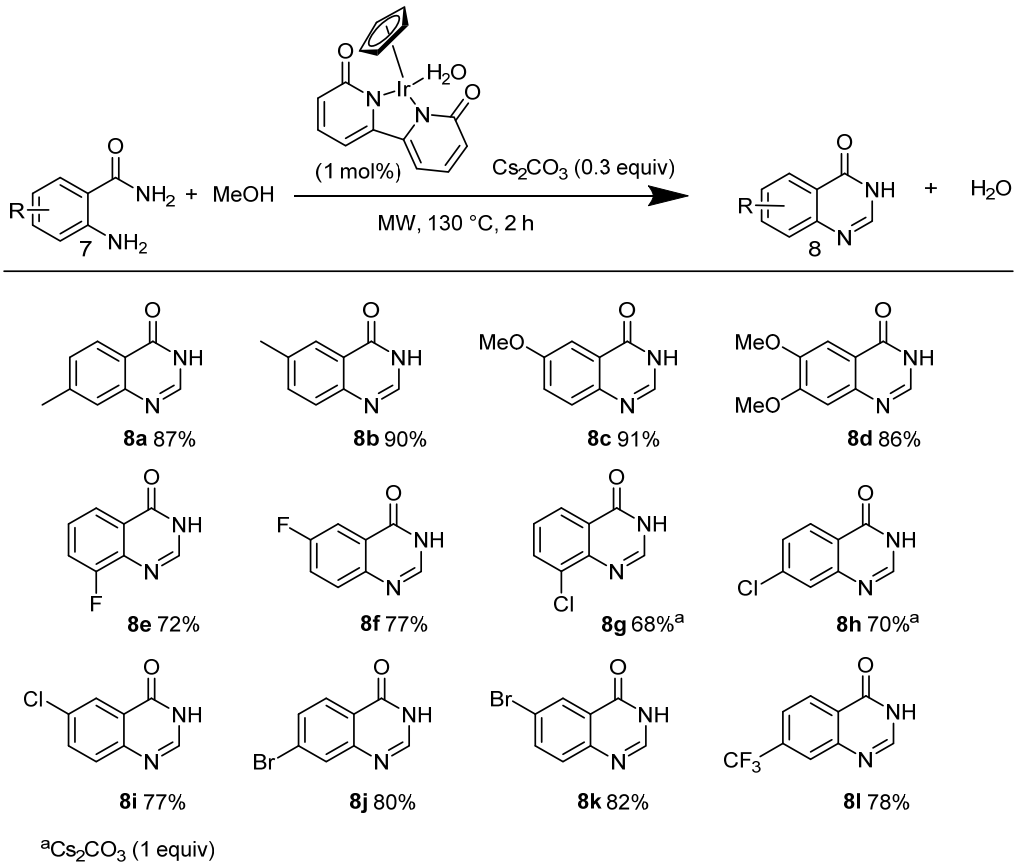
Li and his group [21] developed a strategy that involved an acceptorless coupling of *o*-aminobenzamides with methanol in the presence of the metal−ligand bifunctional **catalyst 2** [Cp*Ir(2,2′-bpyO)(H_2O)] (Scheme 3). This is a follow-up of the group's previous work on a series of iridium-catalyzed environmentally friendly reactions [22,23].



Scheme 3. Structure of some of the **catalysts 1** and **2** used in the optimization experiments.

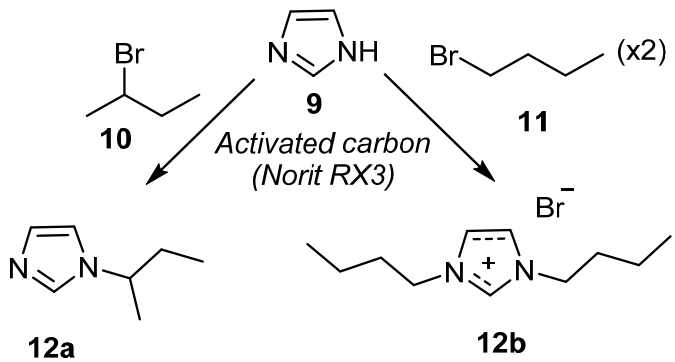
The model reaction involved the coupling of *o*-aminobenzamide with methanol as both reagent and solvent in the presence of 1 mol% of iridium catalysts and Cs_2CO_3 (0.3 eq.). The reaction was carried out at 150 °C for 12 h and the corresponding product was attained in 13% yield utilizing the $[Cp^*IrCl_2]_2$ (Cp* = pentamethylcyclopentadienyl) **catalyst 1**. During the reaction's optimization, one catalyst was found to have a superior efficacy, resulting in higher overall yields: the [Cp*Ir(2,2′-bpyO)(H_2O)] **catalyst 2** (Scheme 2). The authors also found that an increase of Cs_2CO_3 had no effect on the overall yield, so they decided to promote the reaction with MW radiation and ended up with a yield of 88% at 130 °C, under MW for only 2 h.

Once the conditions were optimized, the coupling of a range of *o*-aminobenzamides **7** with methanol was investigated, and *o*-aminobenzamides **8** bearing a fluoride or chloride atom, as well as bromated *o*-aminobenzamides, resulted in high yields of up to 82%. The transformations of *o*-aminobenzamides bearing one or two electron-donating groups gave yields of up to 91% (Scheme 4). Overall, various quinazolinones were synthesized with good to excellent yields with a minimal consumption of chemicals and energy. These catalysts exhibited the potential of the transition-metal catalyzed activation of methanol as a carbon source for the construction of *N*-heterocycles.



Scheme 4. Synthesis of quinazolinones via an acceptorless coupling of *o*-aminobenzamides.

Durán-Valle and co-workers [24] reported the use of acidic carbon materials as catalysts in the *N*-alkylation of imidazole. For that, an activated carbon (Norit RX3) was treated with different acids, including sulphuric (S), nitric (N) and sulphonitric mixture (SN), and the ability to perform as a heterogeneous catalyst was evaluated (Scheme 5). Optimization experiments consisted of the alkylation of imidazole **9** with 2-bromobutane using different acid solid catalysts at 60 °C for 180 min. The best results were obtained with the increasing acidity of the different catalysts (yields between 80–100%), with no further solvent required.



Scheme 5. *N*-alkylation of imidazoles using acidic carbon materials as catalysts (S), (N) or (SN).

To conclude, the use of acidic carbons as heterogeneous catalysts in *N*-alkylation reactions proved to be efficient. Furthermore, the acidity of the carbon is improved using different acids such as sulphuric, nitric and sulphonitric mixture, with the best results

obtained with sulphuric acid. This methodology reduced the formation of hazardous side-products and is even applicable to obtain ILs under mild conditions.

The synthesis of nitrogen-containing heterocycles, particularly naphthopyra-nopy rimidines, has gained prominence in the recent years due to the critical roles that these important scaffolds exhibit in biological and pharmacological activities such as anticonvulsant [25], analgesic [26], antitumor [27,28] and antifungal [29], among others. In addition, some molecules containing the naphthopyranopyrimidine motif act as antagonists of the neuropeptide S receptor and are being studied for the treatment of sleep and anxiety-related disorders [30] (Figure 3).

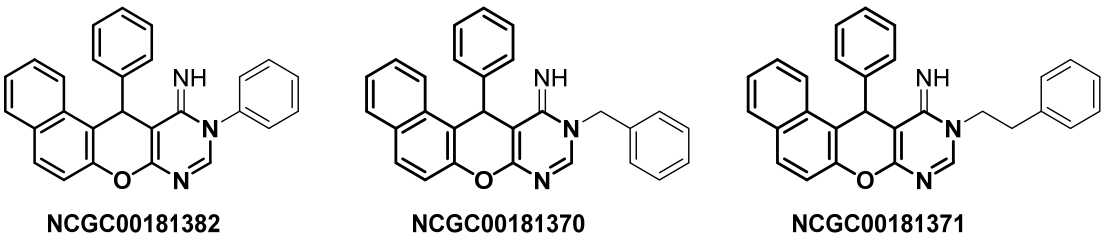


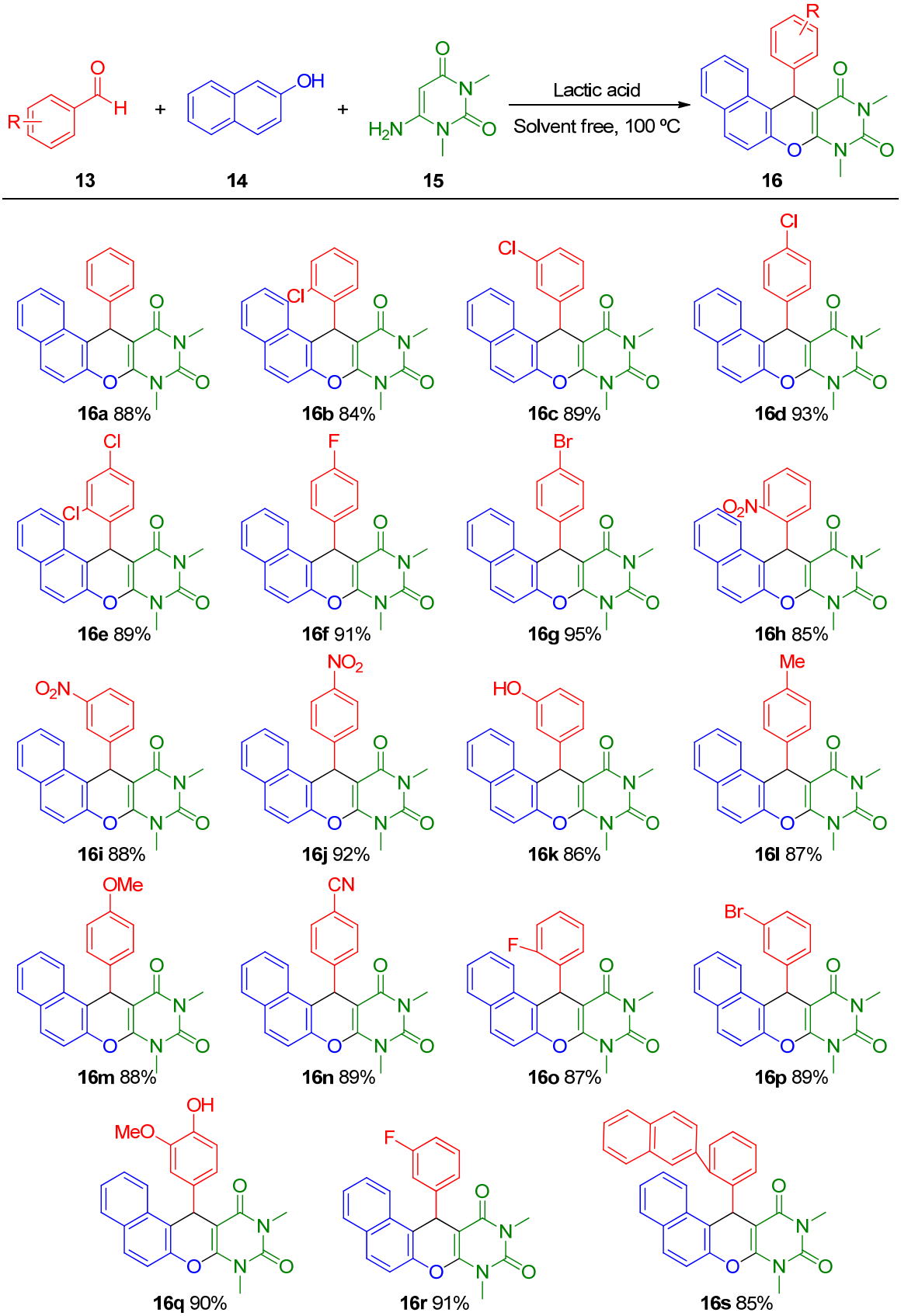
Figure 3. Naphthopyranopyrimidine-based biologically active molecules.

In this context, Fatahpour and co-workers have reported a three-component one-pot reaction between aromatic aldehydes **13**, β-naphthol **14** and 6-amino-1,3-dimethyl uracil **15** (Scheme 6) [31]. This sustainable and convenient procedure uses an inexpensive catalyst such as lactic acid, enabling the achievement of 12-aryl-8,10-dimethyl-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-9,11-dione derivatives **16** in good yields, short reaction times and under solvent-free conditions.

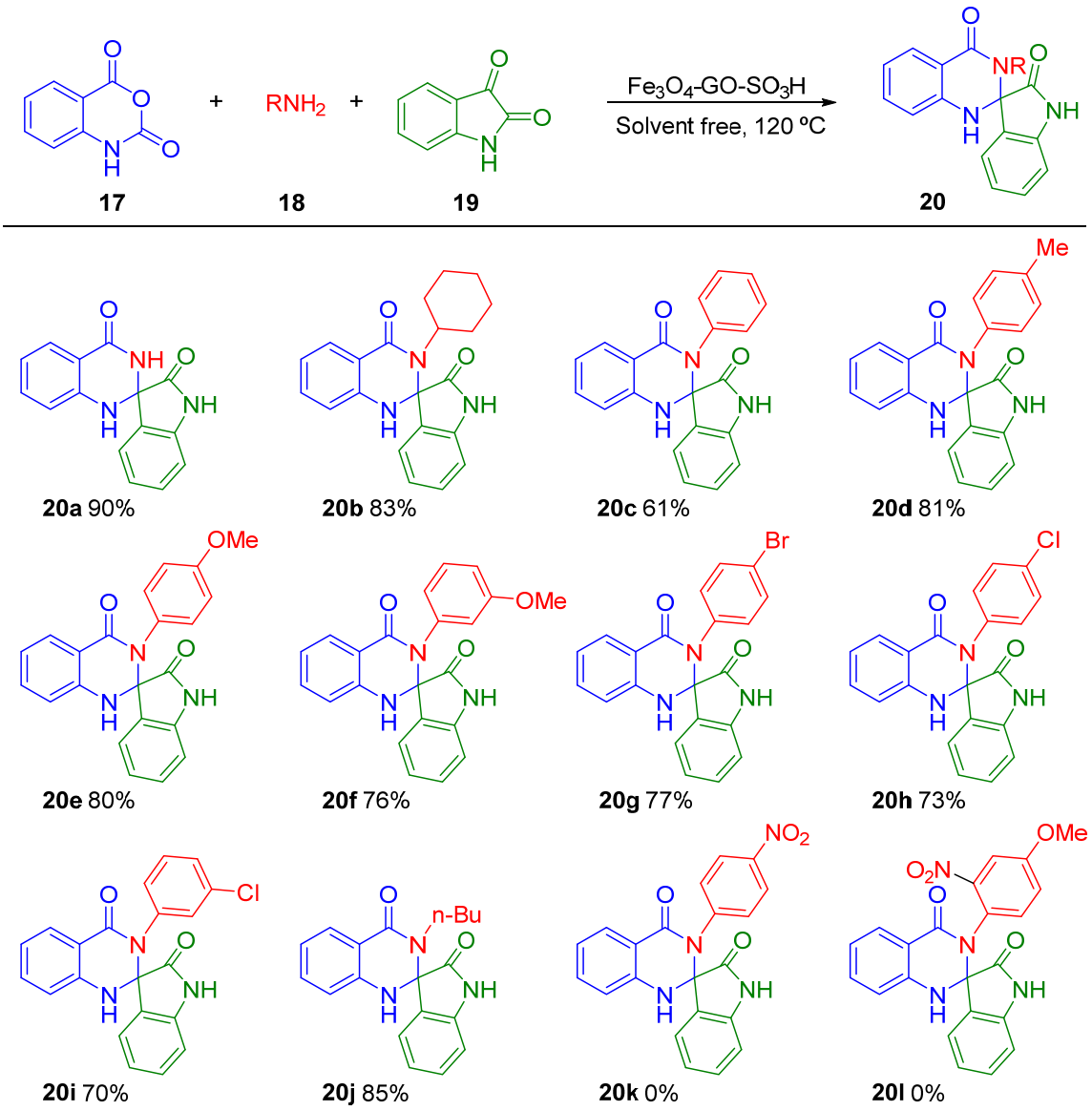
A green methodology was developed for the synthesis of 1′*H* spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione derivatives **20**, which are nothing more than a combination of oxindole **19** and 2,3-dihydroquinazolin-4(1*H*)-one structures **17**. They are historically known for their pharmacological profile [32–35] that, due to the presence of a spiro structural motif, increases the probability of being biologically active. This one-pot procedure involves three components—namely, isatoic anhydride, aliphatic or aromatic primary amines and isatin—in the presence of Fe_3O_4–GO–SO_3H (Scheme 7) [36]. This reusable and non-toxic catalyst takes advantage of the functionalization of the graphene oxide platform for the deposition of Fe_3O_4 nanoparticles, creating a magnetic and heterogeneous solid acid catalyst, which suits several transformations in diverse applications. A simple and rapid methodology was attained with high product yields and short reaction times without any solvent needed.

In 2020, Liu and coworkers [37] reported a sustainable chemoselective hydrogenation of 2-nitroacylbenzenes **21** to 2,1-benzisoxazoles **22** under ambient-mild conditions. This was achieved through the use of a cellulose-derived carbon-supported Pt (Pt/c-C) nanocatalyst capable of simultaneously catalyzing H_2-reduction and dehydration. A green and effective protocol for the synthesis of functionalized benzisoxazoles and benzisoxazoyls is of great relevance since they show a variety of activities and are found in antipsychotic drugs (such as risperidone, paliperidone, ocaperidone, and iloperidone) and in the anticonvulsant zonisamide.

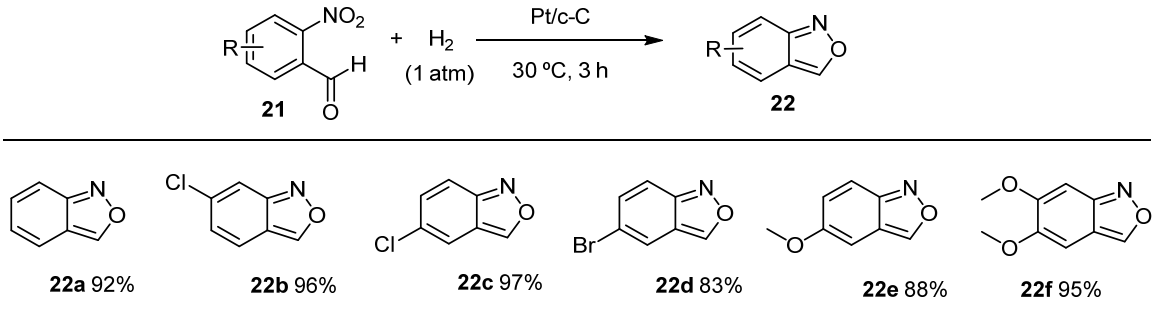
The Pt/c-C catalyst's activity and selectivity was examined for the redutive synthesis of 2,1-benzisoxazole in a high selectivity 92%, using 2-nitrobenzaldehyde and H_2 under ambient conditions (Scheme 8). Once the optimal conditions were found, the reaction was applied to the hydrogenation of various 2-nitroacylbenzenes with electron-donating or withdrawing groups, and a series of 2,1-benzisoxazoles were obtained in good to excellent yields (Scheme 8).



Scheme 6. Lactic acid catalyzed one-pot synthesis of naphthopyranopyrimidines **16**.

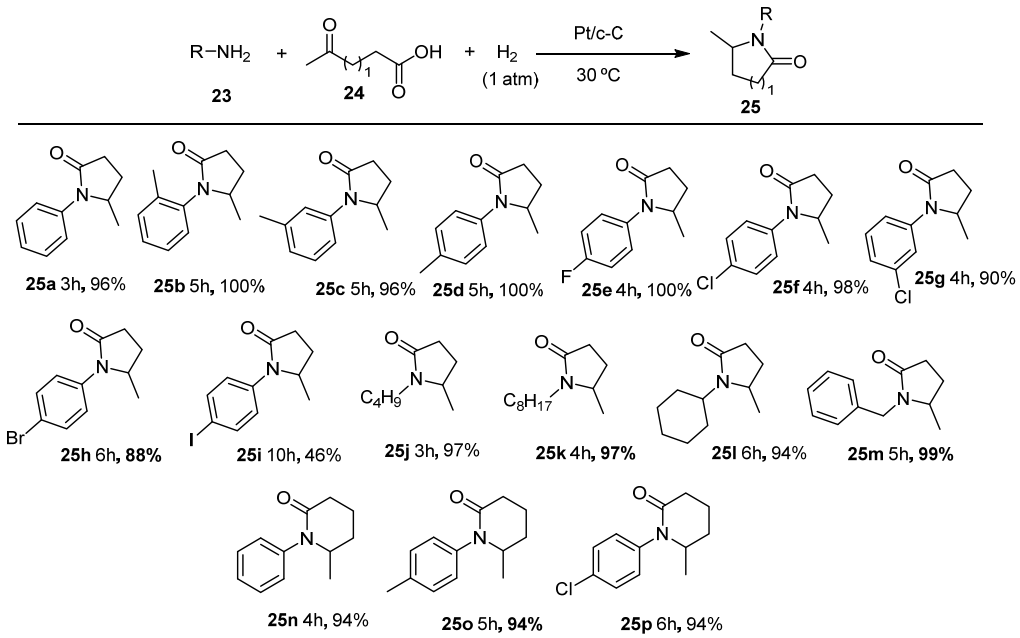


Scheme 7. Synthesis of 1′*H* spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione derivatives **20** in the presence of Fe_3O_4–GO–SO_3H nanocatalyst.



Scheme 8. Hydrogenation of 2-nitroacylbenzenes to 2,1-benzisoxazoles over Pt/c-C. Reaction conditions: substrate (1 mmol), Pt/c-C (4 mg), methanol (1 mL), 30 °C, H_2 (1 atm), 3 h.

Next, the authors also examined the reductive amination of levulinic acid **24** with H_2, where the catalyst was also found to be very effective. Various pyrrolidones were prepared in high yields (Scheme 9).



Scheme 9. Reductive amination of levulinic acid and 4-acetylbutyric acid **24** with amines **23** over Pt/c-C. Reaction conditions: amines (1 mmol), levulinic acid or 4-acetylbutyric acid (1 mmol), Pt/c-C (5 mg), methanol (1 mL), 30 °C, H_2 (1 atm).

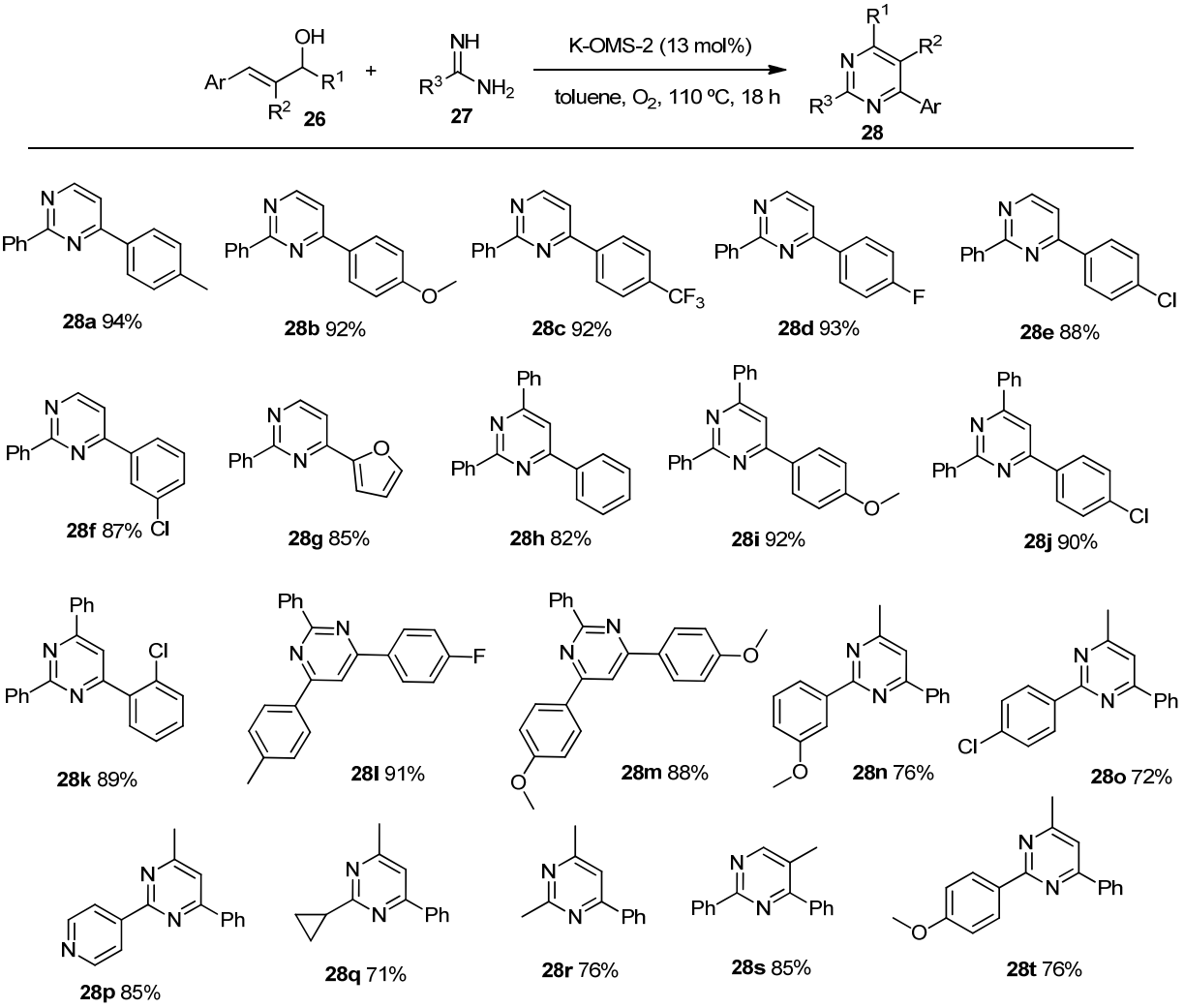
Manganese oxides are known to be active oxidants, and, in particular, octahedral molecular sieves (OMS-2) based on MnO_6 have been reported to be active and selective heterogeneous oxidation catalysts with a porous octahedral chains structure [38].

In 2020, Shen and Meng [39] observed the unexpected formation of a pyrimidine compound as the sole product in the model reaction of cinnamyl alcohol with amidine. This reaction was catalyzed by an octahedral manganese oxide molecular sieve (K-OMS-2) using O_2 as the green oxidant under base- and additive-free conditions, showing high catalytic activity, selectivity and recyclability. Moreover, optimal reaction conditions were found at 110 °C, using toluene as solvent at reflux for 18 h with a catalyst loading of 13 mol%. A wide range of cinnamyl alcohols and various amidines were investigated and good to excellent yields of the corresponding pyrimidines were observed (Scheme 10).

Zhang and coworkers [40] reported a new cobalt catalyst supported by highly dispersed manganese oxide nanorods of octahedral molecular sieve (OMS-2). Using this catalyst, the authors successfully accomplished the aerobic dehydrocyclization of neighboring diols and amidines to access various imidazolone structures. Imidazolones are a class of valuable compounds found in numerous natural and biomedical products [41,42].

To establish the optimal reaction conditions, the dehydrogenative cyclization reaction was tested on 1,2-cyclohexanediol with benzamidine hydrochloride as model substrates. The highest yield (87%) was obtained at 110 °C, using 5 mol% catalyst in the presence of air along with KOH (2 equiv) and pyridine solvent. Applying these optimal conditions, the limitations of the protocol were examined by reacting 1,2-cyclohexanediol with various amidines (Scheme 11). Likewise, the reaction of various vicinal diols with different types of amidines was also evaluated (Scheme 11). All reactions underwent subtle and efficient dehydrocyclization, yielding regioselectively multisubstituted imidazolones in moderate to high yields.

This catalytic transformation was applicable to a wide range of substrates, demonstrated good functional group compatibility and relied on the use of green molecular oxygen and reusable cobalt catalyst. This protocol consists of an important platform for the conversion of abundant and sustainable alcoholic resources into functional *N*-heterocycles.

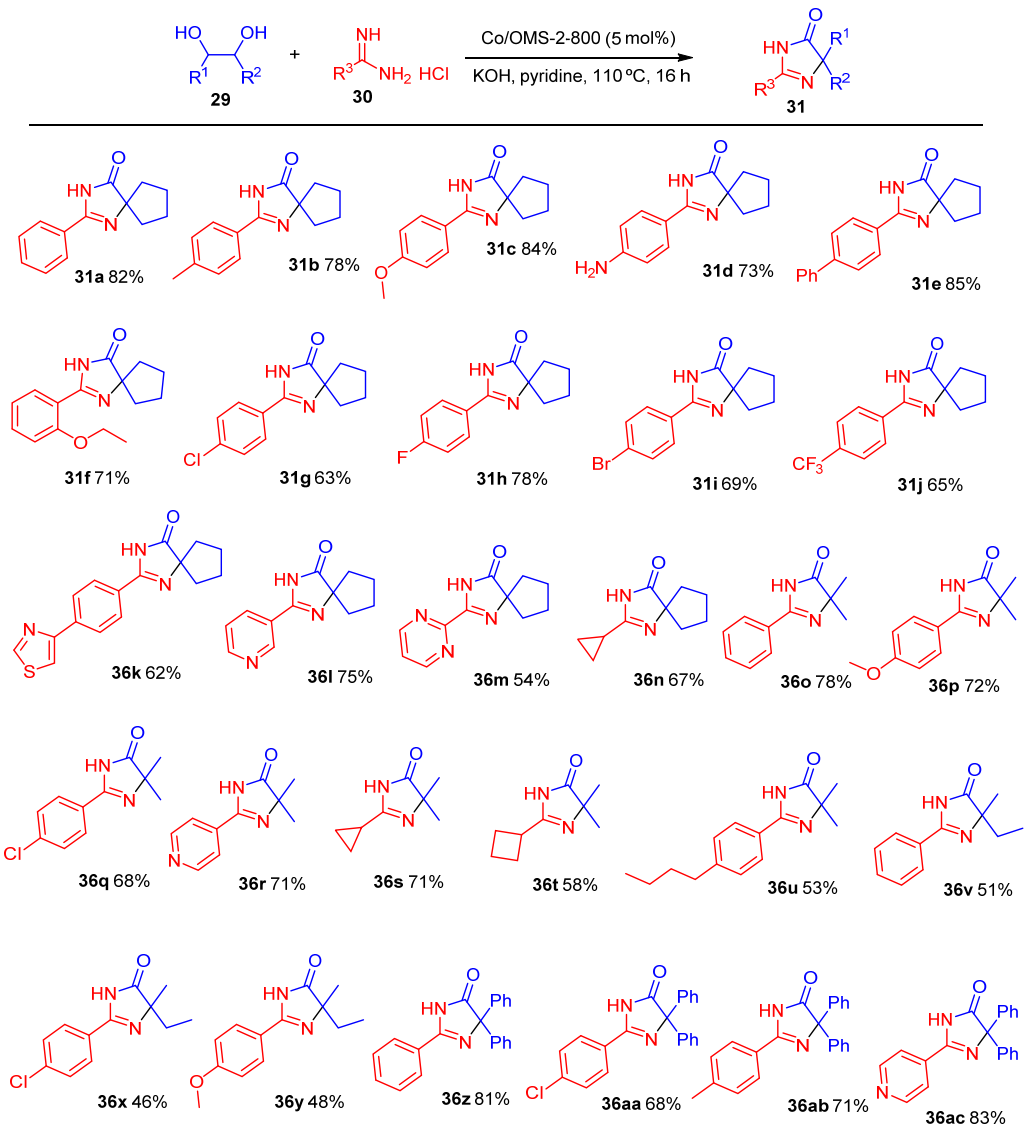


Scheme 10. Aerobic oxidative synthesis of pyrimidines catalyzed by manganese oxide octahedral molecular sieve (OMS-2). Reaction conditions: cinnamyl alcohol (0.6 mmol), amidine (0.4 mmol), K-OMS-2 (13 mol%), PhMe (2 mL), O_2, 110 °C, 18 h.

In 2021, Shibasaki and coworkers [43] reported the first copper-catalyzed chemoselective synthesis of cyclic β-amino acids from substituted isoxazolidin-5-ones. This reaction involves a copper catalyzed intramolecular amination using an alkylnitrene generated from substituted isoxazolidin-5-ones by breaking the N-O bond. In this work, the role of the copper catalyst, as well as the mechanistic insides, were carefully analyzed through a combined experimental and computational investigation.

Some of the synthesized cyclic amino acids, tetrahydroquinoline-3-carboxylic acids, are important building blocks in medicinal chemistry, such as myeloid cell leukemia-1 (Mcl-1) inhibitor (Figure 4) [44].

The optimal conditions of the copper catalyst were carefully studied, and the best results were obtained in the presence of 5 mol% of CuOTf * 0.5 C_6H_6 as the copper source, along with the use of 10 mol% of a hybrid ligand of pyridine and benzoxazole in HFIP solvent at room temperature for 12 h. From these conditions, the scope and limitations were evaluated for the selective amination of aromatic C(sp2)–H bonds, even in the presence of potentially detrimental functionalities, including double and triple bonds (Scheme 12).



Scheme 11. Aerobic dehydrocyclization of neighboring diols and amidines to access various imidazolone structures. Reaction conditions: 110 °C by using 5 mol% of catalyst, air, KOH (2 equiv) and pyridine.

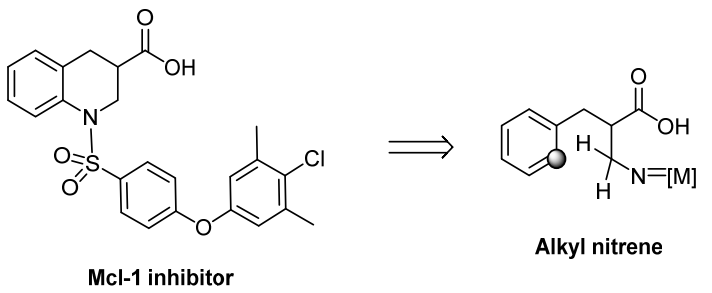
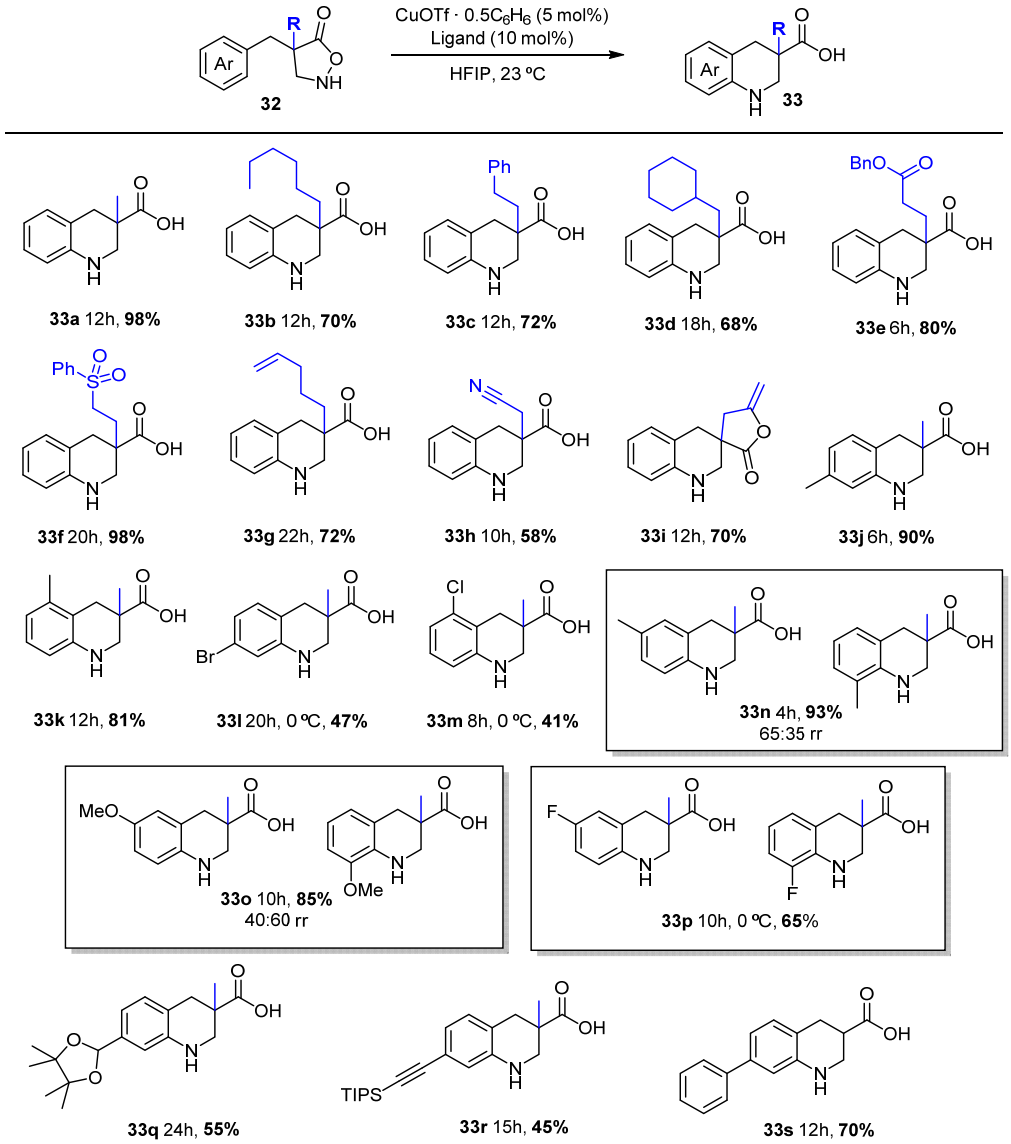


Figure 4. Retrosynthetic analysis proposed for the formation of myeloid cell leukemia-1 (Mcl-1) inhibitor.

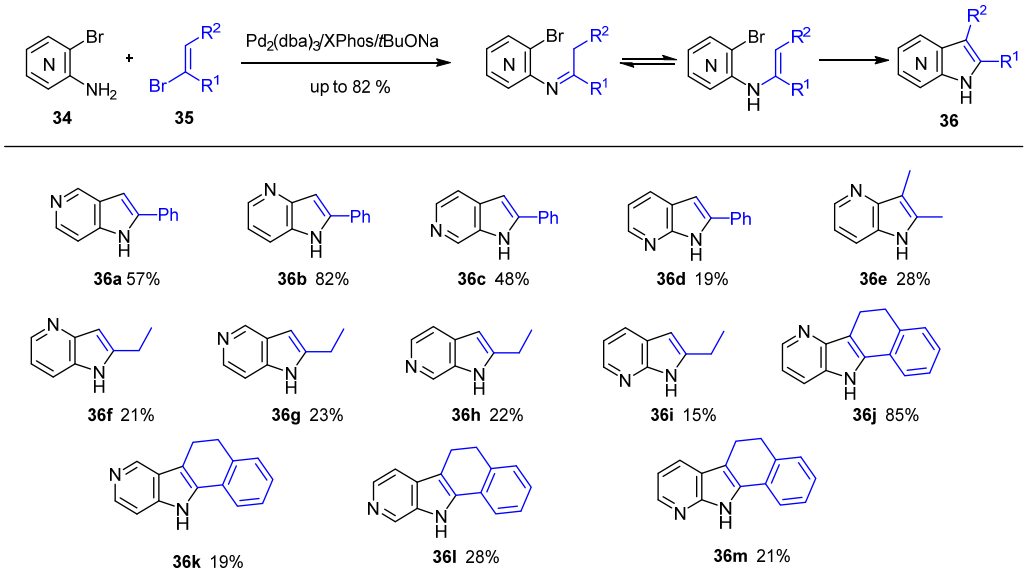


Scheme 12. Cu(I)-catalyzed cyclic β-amino acid synthesis. Reaction conditions: 5 mol% of CuOTf 0.5 C_6H_6 as the copper source, 10 mol% of a hybrid ligand of pyridine and benzoxazole in HFIP solvent at 23 °C for 12 h.

This work offers a simple method of accessing these kinds of functionalized building blocks that would otherwise be difficult to obtain.

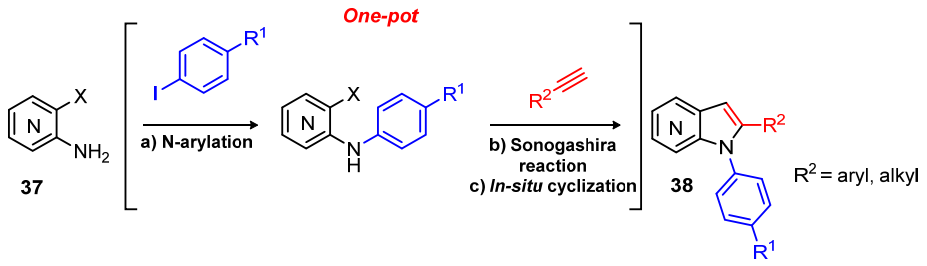
Marques and co-workers have reported a Pd-catalyzed cascade amination/Heck coupling as a practical method to synthesize azaindoles from amino-*o*-bromopyridines and alkenyl bromides (Scheme 13) [45].

The first synthetic step consisted of a C–N cross coupling of amino-*o*-bromopyridines **32** with alkenyl bromides **33** involving in situ imine/enamine formation followed by Heck reaction, affording the azaindole nucleus. The $Pd_2(dba)_3$/XPhos/*t*BuONa system has proven to be suitable for a novel straightforward synthesis of substituted 4-, 5-, 6- and 7-azaindoles. Despite the readiness of the protocol to prepare 2-substituted azaindoles, it did not work when applied to *N*-aryl amino-*o*-bromopyridines, which limits the access to 1,2-diaryl azaindoles. Alternative procedures to attain these substituted azaindoles are being investigated, avoiding the difficult *N*-arylation of 2-substituted-azaindoles [46,47].



Scheme 13. Cascade C–N/Heck cross-coupling reaction to attain azaindole derivatives [45].

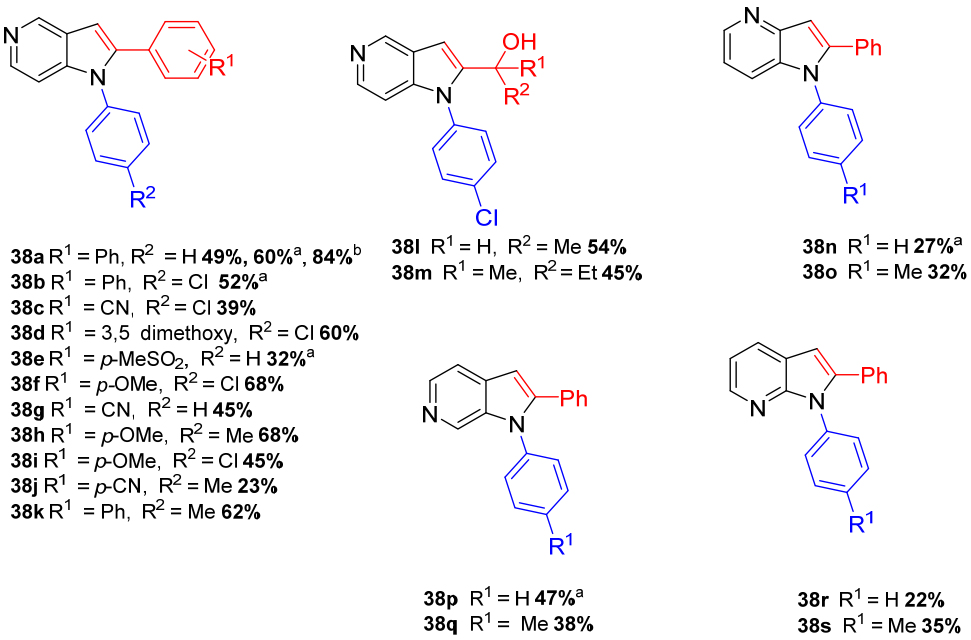
Marques' group has also been focused on the application of Sonogashira reaction as a way of developing new and improved routes to achieve important privileged structures such as azaindoles [48]. The previous methodology reported by the team involved a palladium-catalyzed cascade C–N cross-coupling/Heck reaction that allowed for a straightforward synthesis of substituted 4-, 5-, 6- and 7-azaindoles but did not work when applied to *N*-aryl amino-*o*-bromopyridines. Recently, a novel methodology for the one-pot synthesis of azaindoles has been investigated (Scheme 14) [49].



Scheme 14. General scheme for the one-pot synthesis of 1,2-disubstituted 4-, 5-, 6- and 7-azaindoles.

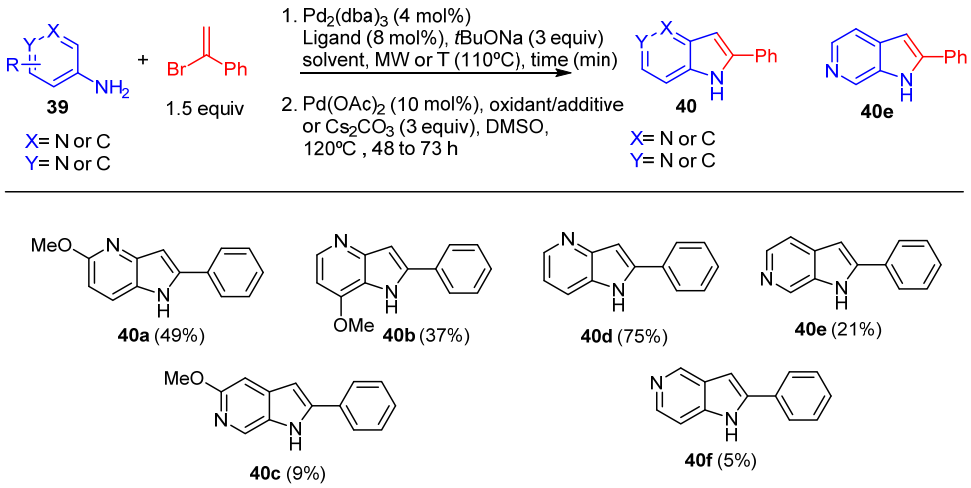
The cascade procedure involves a palladium-catalyzed *N*-arylation followed by Sonogashira reaction and subsequent cyclization in a one-pot approach. In order to study the reaction, scope several iodides were employed in the *N*-arylation reaction and several alkynes were tested in the Sonogashira reactions. The results obtained demonstrate that this methodology exhibits a wide scope and compatibility with electron-withdrawing and electron-donating groups (Scheme 15).

Marques and co-workers envisaged that halogen-free aminopyridines would provide straightforward access to azaindole derivatives via a C–H functionalization reaction [50]. Thus, the group developed a study consisting of the investigation of aminopyridine-based key synthetic intermediate (imine/enamine) generated via a Pd-mediated reaction according to a previous report [45] under C–H functionalization conditions. In this study, five different aminopyridines were tested to explore the influence of the position of the pyridine nitrogen and the methoxy group on the outcome of the reactions (Scheme 16).



[a] Reaction carried stepwise [b] Reaction carried out at 1 mmol scale.

Scheme 15. Scope of the one-pot N-arylation/Sonogashira/cyclization.

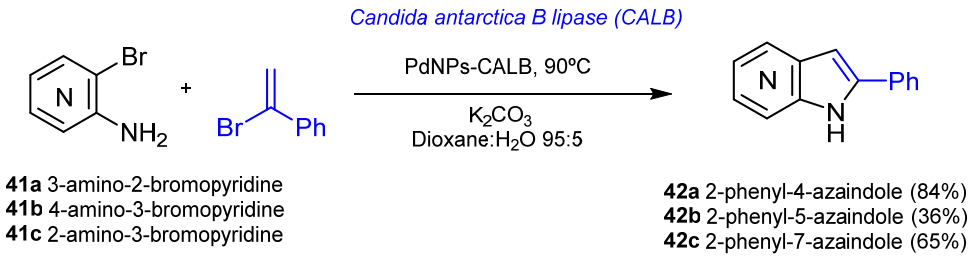


Scheme 16. Exploring simple aminopyridines as suitable scaffolds for C–N cross-coupling/C–H functionalization via imine/enamine intermediates [50].

In all experiments, the formation of the corresponding imine was observed, which was even isolated by chromatography. This strongly suggested that the mechanism involves the formation of the imine by a C–N cross-coupling reaction followed by in situ oxidative cyclization. This procedure avoids the use of amino-*o*-halopyridines [45] that are often difficult to attain, while allowing for the functionalization of the pyridine ring. Furthermore, different oxidant/additive systems were tested consisting of: (1) $Cu(OAc)_2$, Cs_2CO_3; (2) Ag_2CO_3, PivOH, which allowed for the reactivity study of several aminopyridines as well as the influence of substituents and additives in the regioselectivity of the reaction. Additionally, the employment of additives such as silver salts suggests that the

basicity of aminopyridines would be reduced by coordination, while still being affected by a hinderance effect. This one-pot approach relied on the use commercially available aminopyridines allowing for the synthesis of 4- and 6-azaindoles with yields up to 75% (Scheme 16).

Azaindoles are considered privileged structures, and their pharmacologic properties have enticed the interest of the scientific community [48,51,52]. On the follow-up of our previous work on the one-pot synthesis of azaindoles [45], novel palladium nanocatalysts were developed by J. Palomo's group [53] and in a joint collaboration were applied to the C–N cross-coupling/Heck reaction to synthesize several azaindole derivatives (Scheme 17).



41a 3-amino-2-bromopyridine
41b 4-amino-3-bromopyridine
41c 2-amino-3-bromopyridine

42a 2-phenyl-4-azaindole (84%)
42b 2-phenyl-5-azaindole (36%)
42c 2-phenyl-7-azaindole (65%)

Scheme 17. Cascade C−N Cross-Coupling/Heck Reaction using Pd-nanocatalysts.

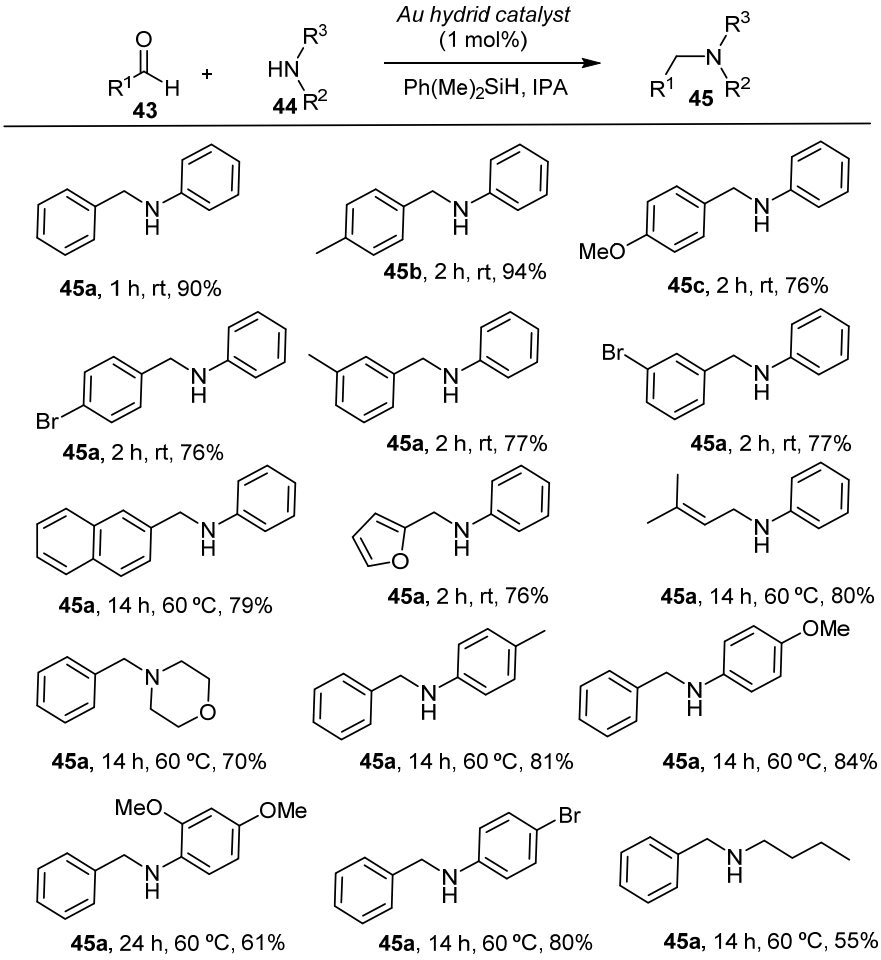
This approach emerges as a more sustainable alternative to access these challenging scaffolds, since the reaction occurs at room temperature in combination with an enzymatic support of the catalyst. Parameters such as temperature and enzyme/palladium salt ratios were investigated. Furthermore, the use of these nanohybrids allowed for the synthesis of several azaindole with moderate to good yields under milder conditions using 5% of water.

Metal-Organic Frameworks (MOFs) are defined as a class of coordination polymers with permanent porosity [54]. These structures have been subjected to particular interest as heterogeneous catalysts, since, in most cases, they allow for the use of milder reaction conditions and a straightforward isolation of the reaction product from the reaction mixture [55].

M. Pericàs and co-workers reported the study and synthesis of incorporated gold nanoparticles (AuNPS) in a mesoporous silica [56]. These were used as catalysts in the reductive amination of carbonyl compounds (Scheme 18). The first step involved the synthesis of the gold nanoparticles, which involved the incorporation of mesoporous silica in a reaction catalysed by light. Followed by the use of this catalyst in combination with dimethylphenylsilane ($Ph(Me)_2SiH$) in isopropyl alcohol (IPA).

Furthermore, this gold hybrid catalyst was used for the reductive amination of aldehydes and amines bearing aromatic and alkyl moieties that were synthesized with yields up to 94%. The authors even reported that the yield could be improved even more in some cases by using a continuous flow system consisting of a sequentially operated single catalyst cartridge containing the gold hybrid catalyst.

Classical indolization methods were applied for azaindole synthesis; however, the nature of the aminopyridines hampers the efficiency of these methods when compared with anilines [45]. Classic synthetic methods remain as an effective way to attain this type of compound; however, the preparation of these scaffolds using this type of reaction is still challenging in terms of sustainability (Table 1). For example, the Bartoli reaction uses nitrobenzenes and vinyl Grignard reagents, and when applied to azaindole synthesis, this method requires a large excess of vinyl Grignard and only affords 4- azaindole and 6-azaindole in generally low yields [57]. Furthermore, reactions such as the Hemetsberger-knittel synthesis are limited to few isomers—6-azaindole and 7-azaindole, respectively—and, additionally, can only afford azaindole structures in low to moderate yields [58,59].



Scheme 18. Reductive amination of aldehydes and amines using a gold nanohybrid catalyst [56].

The use of transition metals as catalysts has revolutionized modern organic chemistry and contributed to the development of more sustainable approaches. The metal-catalyzed synthesis of azaindole is no exception, since the application of metal-catalyzed reactions to synthesize this scaffold has continuously been improving [48]. Reactions such as Sonogashira [49] and Heck [45] and the methods reported by Lautens and Larock have been extensively applied. The metal-catalyzed methods and, in particular, the one-pot methods have strongly contributed to the access of these medicinally relevant compounds, with less challenging purification procedures and more efficient energetic sources like microwaves (Table 1) [48,52,60,61].

Table 1. Comparison of the classical methods versus metal-catalyzed reactions for the synthesis of azaindoles.

	Azaindole Synthesis	
	Classical Methods [57–59]	**Metal-Catalyzed Methods [48–50,53]**
Advantages	Effective in attaining the product Moderated yields	One-pot reactions Less waste Compatible with water Mild conditions Atom economy

Table 1. *Cont.*

	Azaindole Synthesis	
	Classical Methods [57–59]	**Metal-Catalyzed Methods [48–50,53]**
Disadvantages	Limited scope Stoichiometric reagents Strong acids High temperature Poor yields of some isomers	Catalysts may be expensive Moderate to high yields
Scope	Limited to few regioisomers	Access to all regioisomers
Energy efficiency	High energy consumption from traditional heating methods	Compatible with MW heating
Solvent	Hazardous and chlorinated	Compatible with water
N° of steps	At least 2 steps	Maximum 2 steps

3. Conclusions

This review collects some of the most recent advances in *N*-heterocycle synthesis applying more sustainable synthetic procedures. As the pharmaceutical industry is among the most environmentally problematic branches of the chemical industry, the development of green synthetic methods that facilitate the synthesis of heterocycles is mandatory. The recent examples shown include the use of starting materials attached to a soluble support, which allow for a simpler purification process as well as the use of metal hybrid catalysts like MOF that can be separated from the reaction mixture by simple filtration. Furthermore, the use of metal-catalyzed reaction has completely revolutionized the sustainable synthesis of N-heterocyclic structures. The development of novel catalysts based on Earth abundant metals and new reagents has allowed for milder reaction conditions and resulted in the reduced production of hazardous side products. All of these methods represent a step forward in the preparation of important—and often not so easy to prepare—*N*-heterocycles. Still, some challenges remain regarding the use of more efficient and versatile catalysts that can be applied to a larger scope of starting materials and be compatible with greener reaction media. Catalysis will continue to evolve and attract much attention in sustainable organic synthesis applications.

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