Metal-Promoted Heterocyclization

Subjects: Chemistry, Organic | Chemistry, Medicinal

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The recent formulation, production, and ongoing administration of vaccines represent a starting point in the battle against SARS-CoV-2, but they cannot be the only aid available. In this regard, the use of drugs capable to mitigate and fight the virus is a crucial aspect of the pharmacological strategy. Among the plethora of approved drugs, a consistent element is a heterocyclic framework inside its skeleton. Heterocycles have played a pivotal role for decades in the pharmaceutical industry due to their high bioactivity derived from anticancer, antiviral, and anti-inflammatory capabilities. In this context, the development of new performing and sustainable synthetic strategies to obtain heterocyclic molecules has become a key focus of scientists.

antiviral heterocyclization metal-promoted

1. Introduction

Heterocyclic compounds have versatile applications across many chemistry fields. N, S, and O are the most common heteroatoms, and their corresponding heterocycles can be found as the main structural units in synthetic pharmaceuticals and agrochemicals, as well as widely present in nature in plant alkaloids, nucleic acids, anthocyanins, and flavones [1]. Drugs containing a heterocyclic moiety inside their structure show antitumor, anti-inflammatory, antifungal, antidepressant, anti-HIV, antimalarial, and antiviral properties [2][3][4]. In particular, the latter three properties are central in the fight against SARS-CoV-2 [5][6][7]. Over the years, due to the importance of these small molecules, synthetic organic chemists have focused their efforts on the development of synthetic protocols which are more and more efficient, atom-economical, and environmentally friendly. Metal-catalyzed protocols, involving all metals from transition to rare-earth metals, have attracted the attention of chemists as compared to other synthetic methodologies because they directly employ easily available substrates to build multi-substituted complex molecules under mild conditions. Metal-catalyzed heterocyclization starting from acyclic precursors is considered a very performant tool in drug synthesis [8]. In this review, we focus our attention on metal-catalyzed heterocyclization methodologies for achieving pivotal scaffolds associated with molecules showing anti-COVID-19 properties.

2. Chloroquine and Hydroxychloroquine

Chloroquine (CLQ) and its hydroxyl analogue hydroxychloroquine (CLQ-OH) were developed as antimalarial drugs, and they are used in the treatment of malaria, amebiasis, rheumatoid arthritis, and lupus erythematosus syndrome [9]. Both drugs show strong antiviral effects toward SARS-CoV-2 infection with calculated IC_{50} values of 8.8 μM for CLQ and 5.47 μM for CLQ-OH [10][11]. Extensive clinical trials are ongoing to prove the efficacy of these drugs for

treating COVID-19 infection [12]. They present a similar action mechanism; chloroquine and hydroxychloroquine are able to modify the pH of host cell lysosomes. This pH increase corresponds to a modification of the cellular biological activity, leading to a cascade of processes which prevent cellular replication [13]. The fundamental effect of chloroquine and hydroxychloroquine in the treatment of different pathologies has spurred chemists to establish various routes for their synthesis. **Figure 1** reports the key intermediates used in the main strategies developed over the decades.

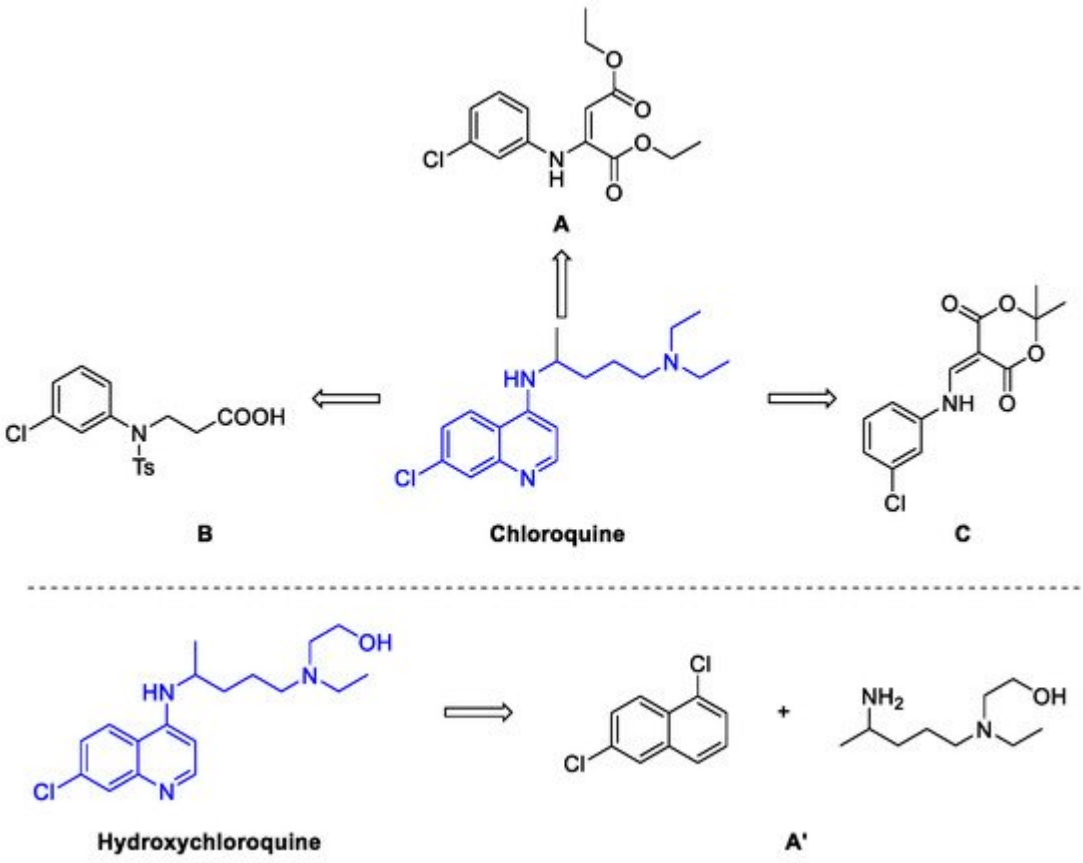
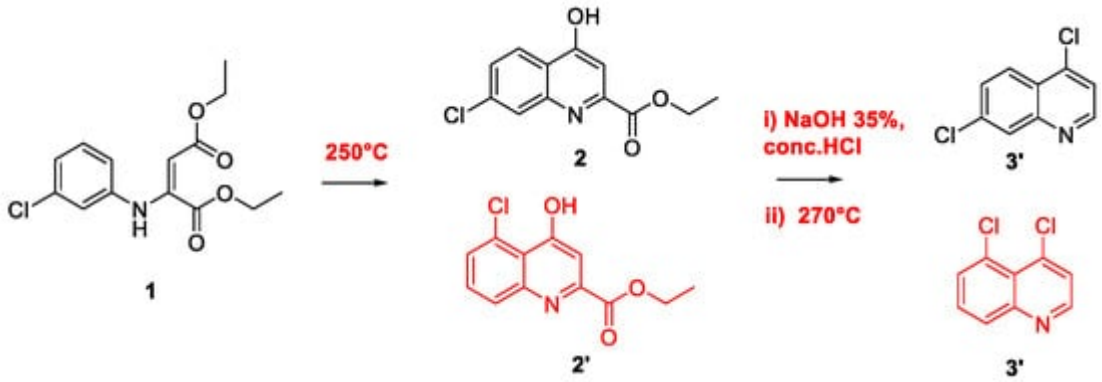


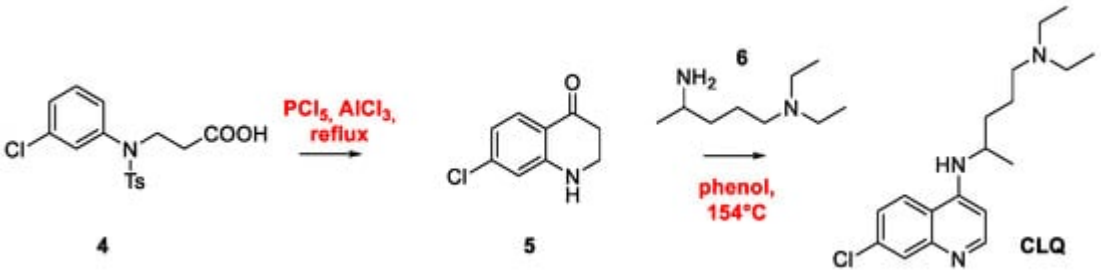
Figure 1. Key intermediates in chloroquine synthesis as reported by Hammer (**A**), Jonnson (**B**), and Margolis (**C**). The lower panel shows a common retrosynthetic approach for hydroxychloroquine synthesis as reported by Hammer, Kumar, Min, and Yu.

Synthetic routes for chloroquine are based on harsh conditions that promote byproduct formation and low overall yield of the whole process. In the first known synthesis of chloroquine, reported by Surrey and Hammer, formation of the pivotal quinoline core **2** was carried out at high temperature, which promoted the formation of undesirable isomers **2′** and **3′**. Moreover, the decarboxylation step, promoted by a strong base and a mineral acid, is not considered sustainable (Scheme 1) [14].



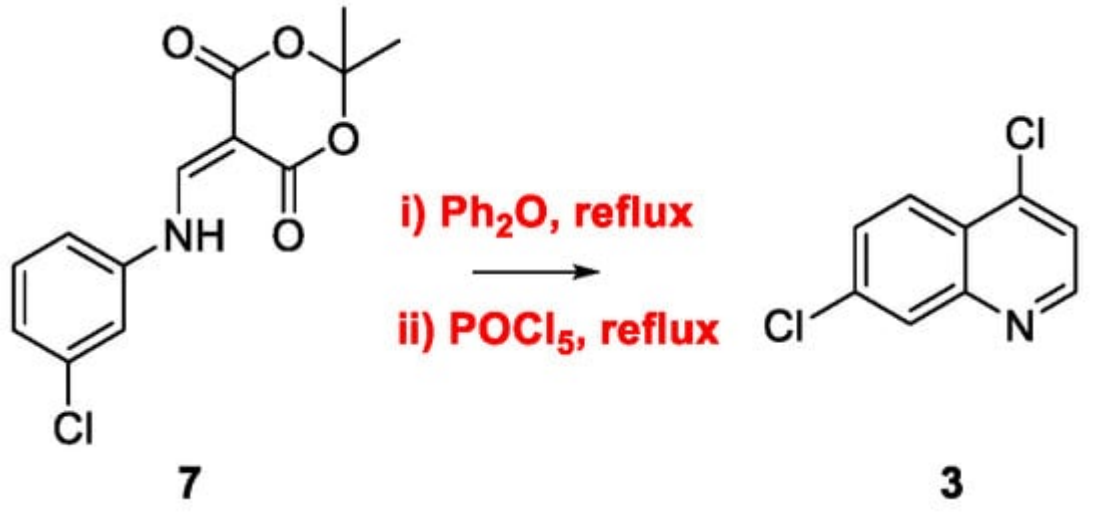
Scheme 1. Critical steps in Hammer synthesis.

Jonnson and Buell later developed a CLQ synthesis method with an improved overall yield of 25%. Unfortunately, the formation of the quinoline moiety led to the easy formation of byproducts due to the strong reaction conditions (Scheme 2) [15].



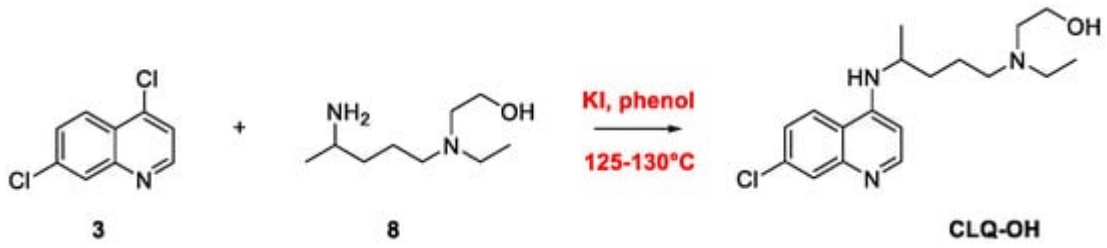
Scheme 2. Critical steps in Jonnson synthesis.

In 2007, Margolis et al. proposed a synthetic route to achieve CLQ. The relatively mild conditions of the process made it suitable for large-scale production; however, in this case, the formation of the quinoline scaffold was also promoted at high temperature, thereby favoring byproduct formation (Scheme 3) [16].



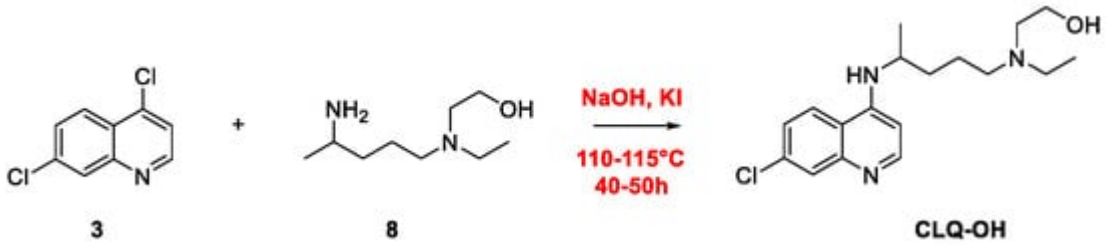
Scheme 3. Critical steps in Margolis synthesis.

Even the synthetic methodologies developed for hydroxychloroquine feature critical steps. Hammer and coworkers, in their three-step, synthesis proposed obtaining the target via an S_NAr between intermediate **8** and dichloroquinoline **3** as the final step. Low overall yield, use of phenol as the solvent, and high reaction temperature hindered the scale-up of this strategy (Scheme 4) [17].



Scheme 4. Critical steps in Hammer synthesis.

Kumar and coworkers, inspired by Hammer's work, modified the synthetic protocol and enhanced the overall yield from 18% to 40%. However, the final S_NAr step to achieve CLQ-OH was carried out in harsh conditions (high temperature and long reaction time) (Scheme 5) [18].

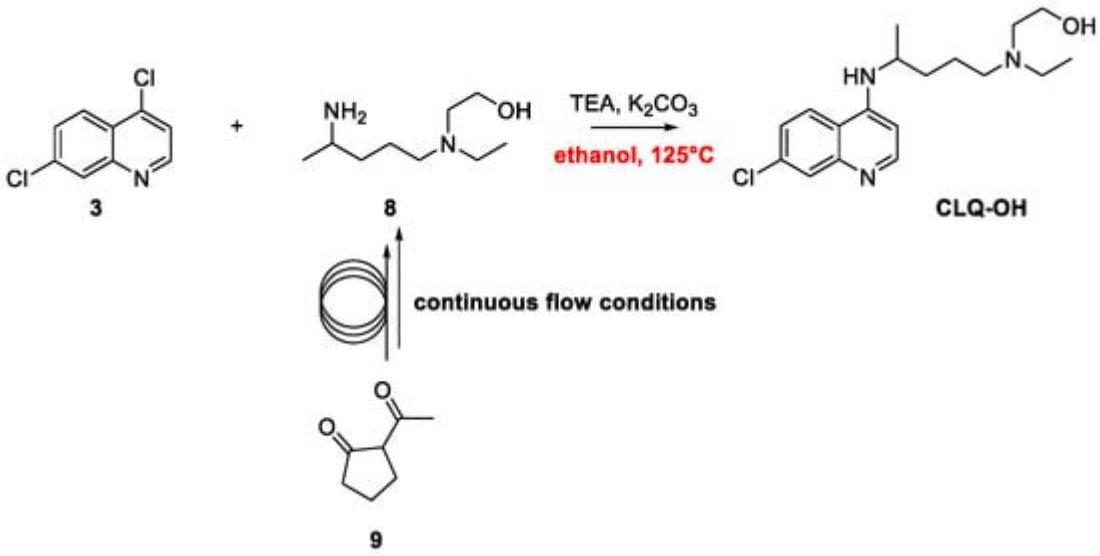


Scheme 5. Critical step in Kumar synthesis.

Recently, Min *et al*. proposed an alternative approach to functionalize quinoline **3**; however, the use of high pressure in combination with high temperature represents a safety concern (Scheme 6) [19].

Scheme 6. Critical step in Min synthesis.

Yu and Gupton exploited the continuous-flow methodology to improve the process from an industrial point of view. Starting from 2-acetylcyclopentan-1-one **9**, they were able to synthesize the key intermediate **8** while achieving a yield improvement of 52% compared to classical processes. Unfortunately, even in this case, the C–N coupling to access hydroxychloroquine was carried out in unsustainable conditions (Scheme 7) [20].



Scheme 7. Critical step in Gupton synthesis.

Quinoline Synthesis: Metal-Promoted Annulation

The biological importance of quinoline-based drugs has resulted in the synthesis of this substituted heterocycle becoming a hot topic for organic chemists worldwide [21][22][23][24]. A plethora of elegant syntheses have been developed; however, the use of harsh conditions and limitations due to the nature of some reagents have restricted the application of these protocols both in academia and in industry [25]. The recent trend of obtaining targets with high purity using sustainable conditions has resulted in the use of metal catalysts becoming central in the synthetic strategies of complex drugs.

Friedländer synthesis using 2-aminobenzaldehyde and carbonyl derivatives has been exploited for a long time to obtain substituted quinolines. Currently, modifications of this methodology have permitted the development of efficient and elegant protocols for the synthesis of this heterocyclic framework (**Figure 2**).

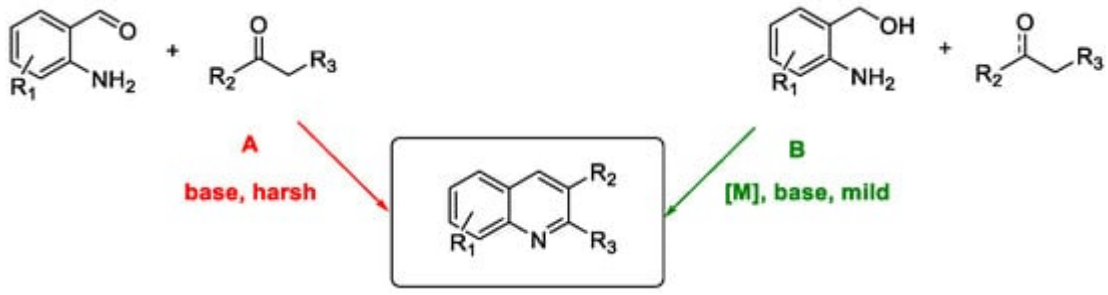
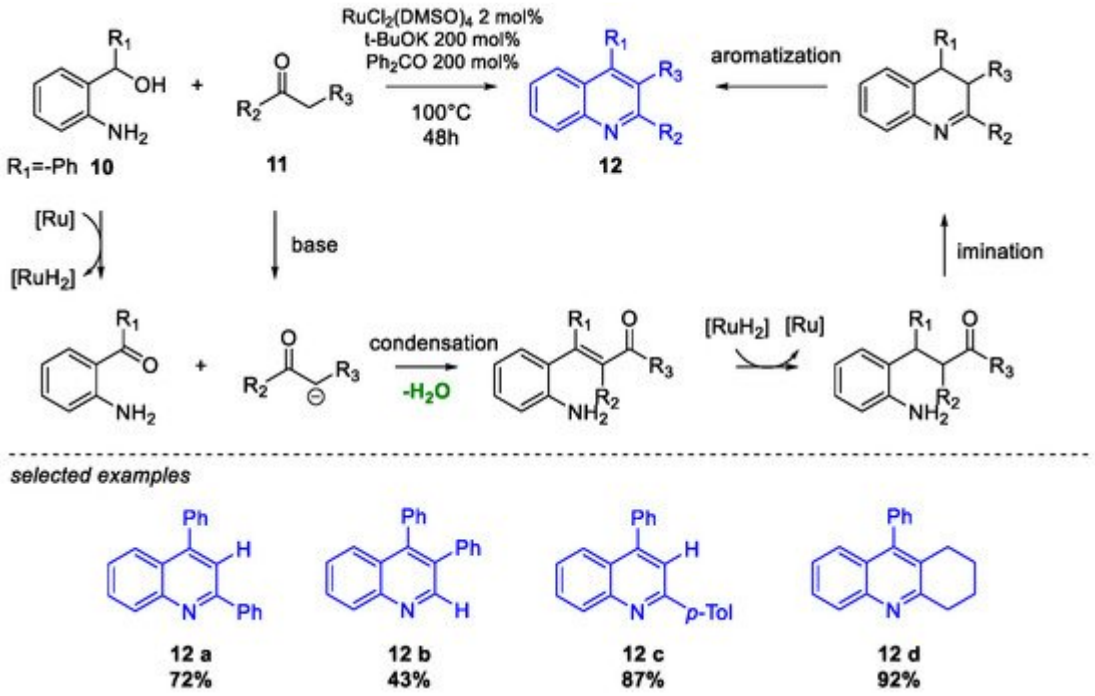


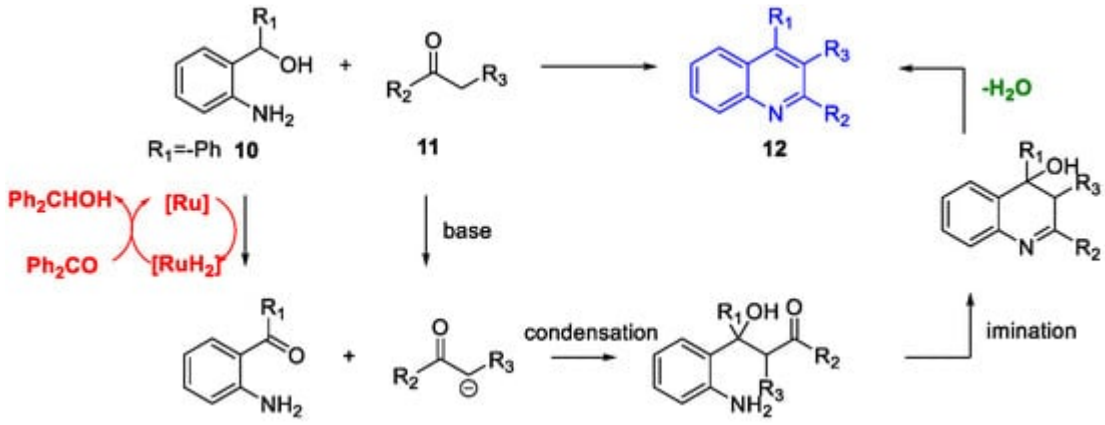
Figure 2. Friedländer classical condensation (**A**) and metal-catalyzed Friedländer condensation (**B**).

Yus *et al*. studied the condensation between (2-aminophenyl)(phenyl)methanol **10** and ketones **11** for the formation of 2,3,4-substituted quinolines **12**. The reaction is promoted by $RuCl_2(DMSO)_4$, and its ability to accept and donate H_2, thereby restoring its original oxidation, is crucial for the catalytic cycle (Scheme 8) [26].



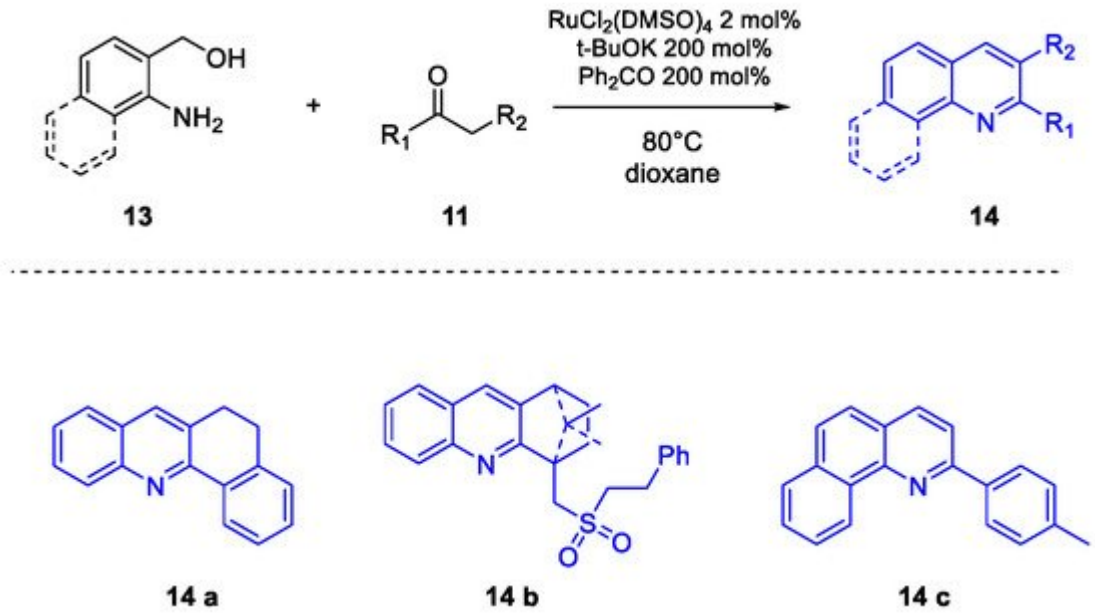
Scheme 8. Ru(II) complex triggering indirect Friedländer annulation in the study by Yus.

Optimized reaction conditions permit obtaining polysubstituted quinolines at sufficient to excellent yields in relatively mild conditions (e.g., **12 a–d**), producing water as waste. The addition of benzophenone acting as a hydrogen scavenger allows improving the final yield of the targets. This result can be explained by the partial inability of ruthenium hydride species to restore the catalytic cycle (Scheme 9) [27].



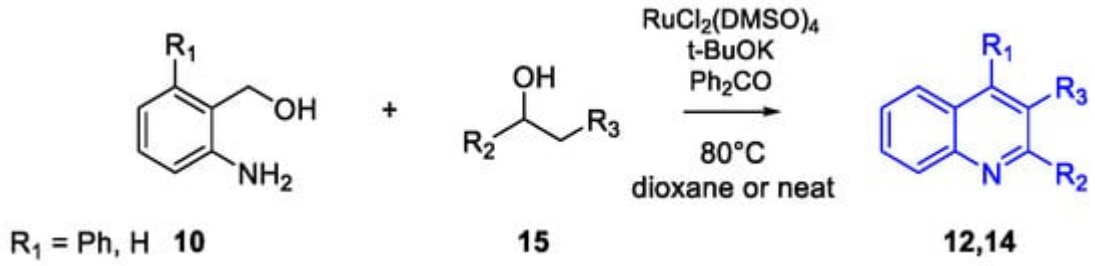
Scheme 9. Alternative pathway in Ru dehydrogenative *N*-heterocyclization.

The same synthetic protocol was applied to both sterically hindered ketones **11** and various anilines **13** for the formation of the desired quinoline derivatives **14 a–c** (Scheme 10).



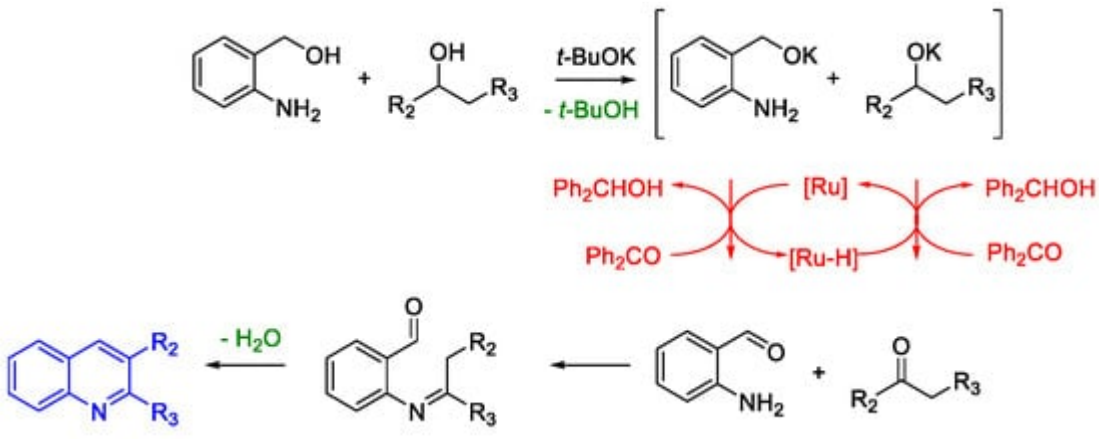
Scheme 10. Sterically hindered quinoline derivatives.

Yus proved the versatility of $RuCl_2(DMSO)_4$ as a catalyst in the hydrogen-borrowing process to obtain substituted quinolines **12, 14** by exploiting the reactivity of secondary alcohols **15** with (2-aminophenyl)methanol **10** (Scheme 11) [26][28].



Scheme 11. Secondary alcohols as an electrophilic source.

The plausible catalytic cycle involves the formation of the active corresponding potassium alkoxides. The subsequent oxidation/condensation cascade leads to the formation of the target quinoline (Scheme 12) [26].



Scheme 12. Catalytic cycle for ruthenium hydrogen-borrowing quinoline synthesis.

In addition to $RuCl_2(DMSO)_4$, an indirect Friedländer process was reportedly promoted by iridium, palladium, copper, and rhodium complexes [29][30][31][32][33][34]. **Figure 3** presents the common catalysts used in the annulation between aniline derivatives and hydroxylic scaffolds to achieve quinoline motifs.

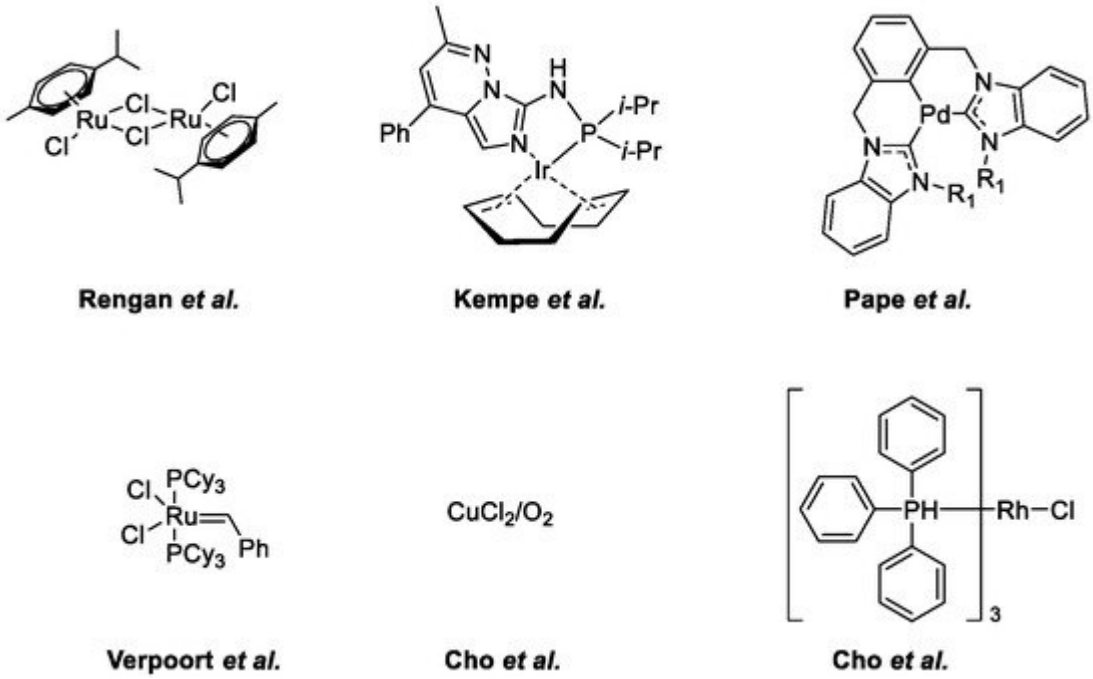
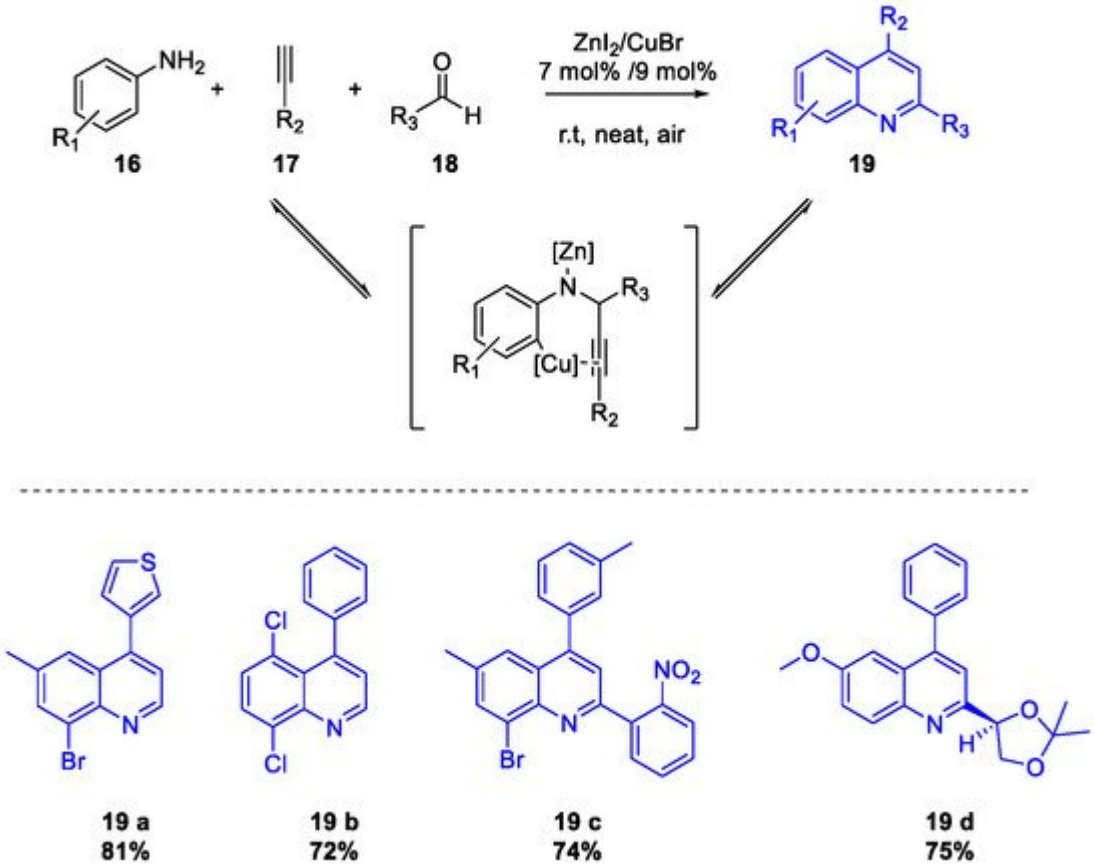


Figure 3. Metal catalysts used in indirect Friedländer annulation.

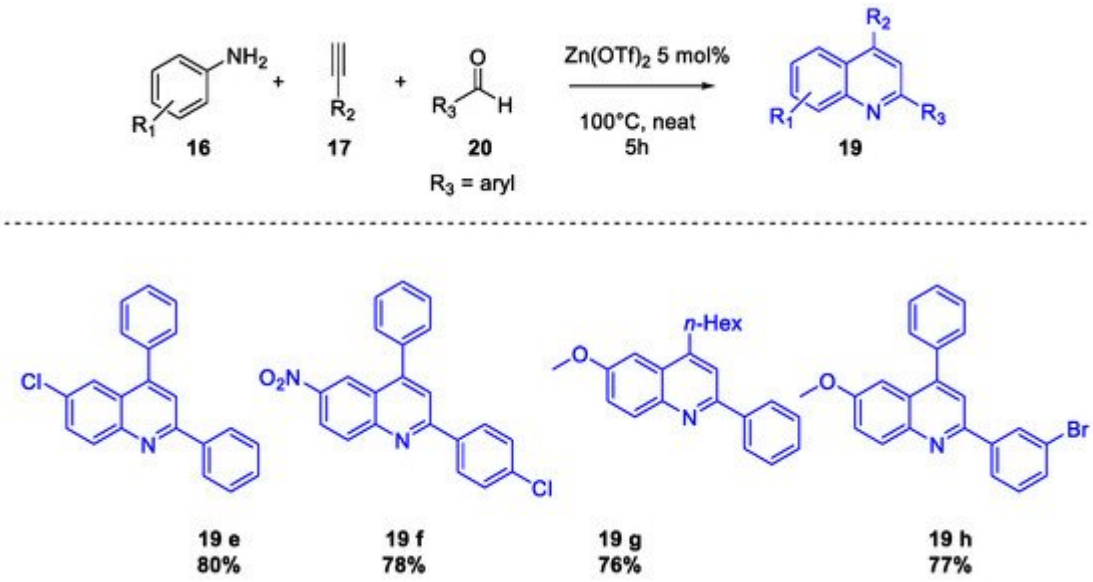
An effective alternative to the indirect Friedländer approach is represented by the one-pot alkynylation/cyclization protocol using aniline derivatives, substituted alkynes, and aldehydes. In 2016, Maiti et al. proposed an innovative solvent-free CuBr–ZnI_2 catalytic strategy to afford polysubstituted quinolines and chiral sugar-based quinolines (**19 a–d**) in sufficient to good yields (Scheme 13) [35].



Scheme 13. ZnI_2/CuBr-catalyzed complex quinoline scaffold.

In this three-component protocol, substituted aniline **16**, terminal alkynes **17**, and aldehydes **18** react fast and in mild conditions through C–C and C–N bond formation promoted by Zn(II) and an C(sp^2)–H activation promoted by Cu (I) and the transient formation of aryl Cu(III) species, followed by subsequent cyclization.

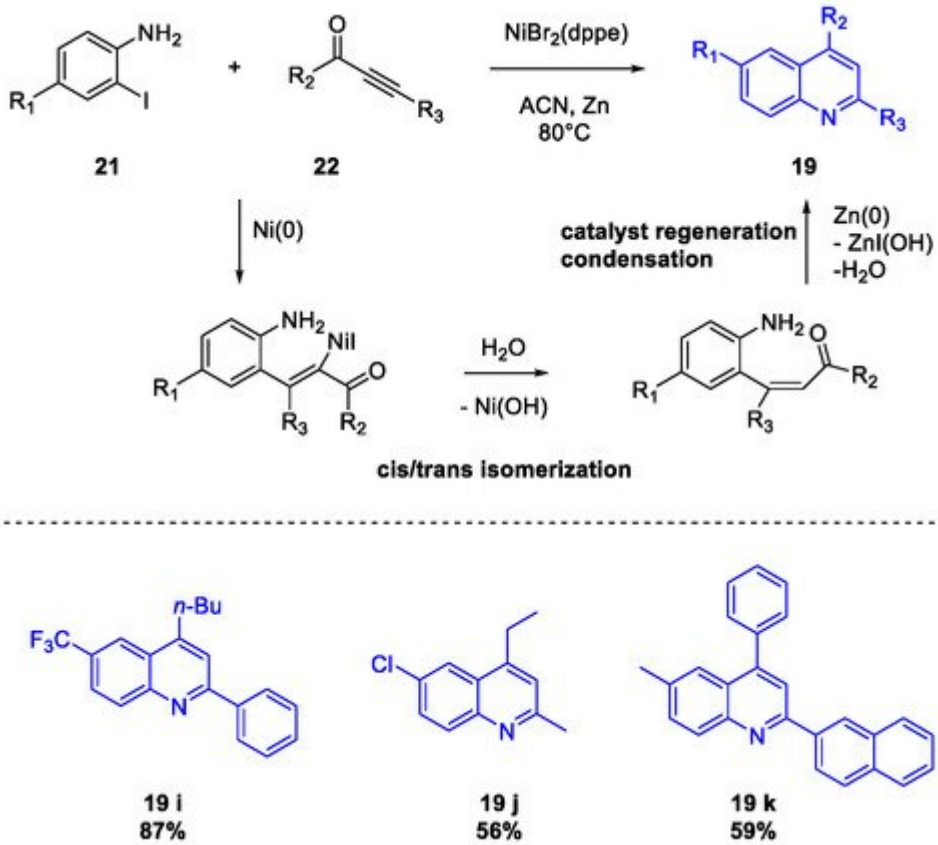
A comparable protocol was developed by Sarode and coworkers. They showed the catalytic ability of zinc(II) triflate to promote multicomponent C–C and C–N formation using anilines **16**, terminal alkynes **17**, and aryl aldehydes **20** in solvent-free conditions (Scheme 14) [36].



Scheme 14. $Zn(Otf)_2$-mediated C–H activation to achieve quinolines.

The use of inexpensive catalysts, the absence of toxic solvents and additives, and the tolerance toward different functional groups make this reaction a great candidate for scale-up processes.

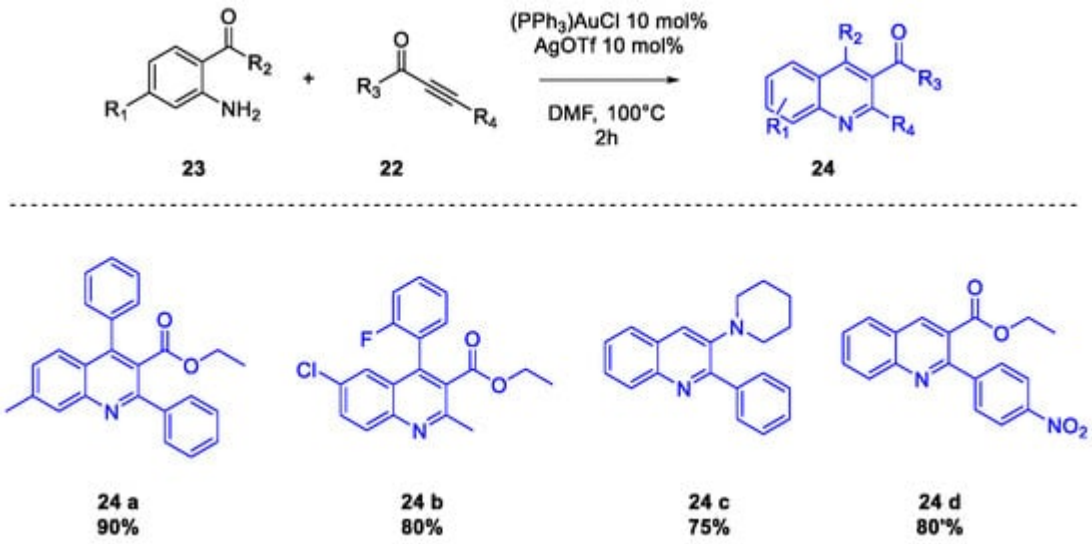
Korivi and Cheng exploited Ni catalysis to assist the annulation between iodo-anilines **21** and aroylakynes **22** (Scheme 15) [37].



Scheme 15. Ni(0)-catalyzed quinoline synthesis.

This methodology permits achieving a broad range of 2,4-disubstitued quinolines **19** in satisfactory yields. The Ni catalyst does not need an extreme inert atmosphere to work. Zn powder is necessary to regenerate the initial oxidation state of the nickel catalyst from Ni(II) to Ni(0).

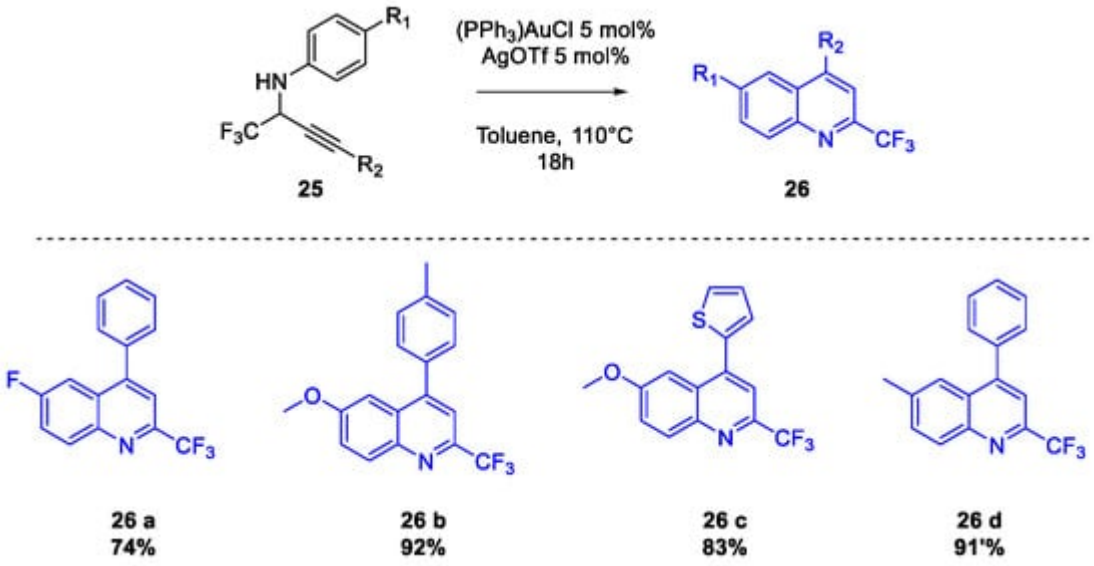
Recently, aroylakynes were exploited by Liu and coworkers to access the complex quinoline scaffold **24** (Scheme 16) [38].



Scheme 16. Au(I) complex-triggered *N*-heterocyclization in Liu work.

In this procedure, the catalytic system (Ph_3P)AuCl/AgOTf promotes the cycloaddition between 2-aminoaryl carbonyls **23** and internal alkynes **22** at good to excellent yields (e.g., **24 a–d**) in sustainable conditions, affording a plethora of polysubstituted quinolines **24** containing various functional groups. The presence of Ag(I) salt as an additive was crucial for the activation of the catalyst due to the ability of silver to dechlorinate the Au catalyst, thereby increasing the electrophilicity of the metal center. The procedure exhibits adaptability to different functional groups using both internal alkynes and aminoaryl derivatives, leading to a wide array of substrates.

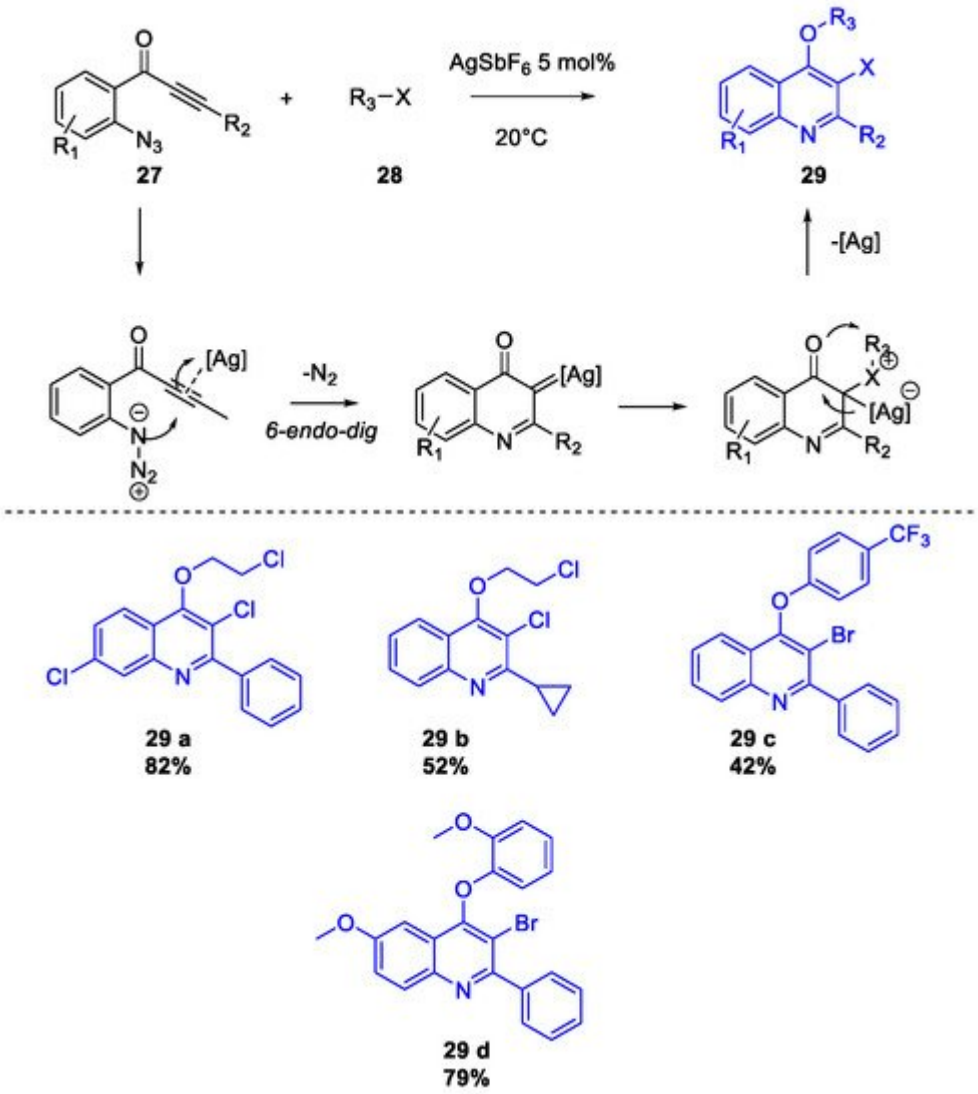
The efficiency of gold catalysis was shown in the work of Ji *et al*. The same promoting system displayed high efficiency in the cyclization of 2-trifluoromethylated propargylamines **25** (Scheme 17) [39].



Scheme 17. Obtention of 2-trifluoromethylated quinolines via gold catalysis.

A gold(I) catalyst triggers the internal cyclization of propargylamines to obtain diverse quinolines **26**. Mild conditions and a broad scope of the reaction were attained using this methodology. It is important to highlight the facile introduction of a fluorinated moiety into the target, considering the biological significance of fluorinated quinolines.

An innovative and elegant pathway to achieve polysubstituted quinolines **29** was proposed by Xu et al., whereby an Ag(I) catalyst promotes 6-endo-dig cyclization of 2-azide alkyne derivatives **27** followed by an R–X **28** insertion into the imino carbene generated in the catalytic cycle (Scheme 18) [40].



Scheme 18. Azide-alkyne 6-endo-dig cyclization promoted by $AgSbF_6$.

Readily available materials, the cheap silver catalyst, and mild reaction conditions make this procedure appealing for organic chemists. The introduction of halogens into the heterocyclic scaffold provides the possibility of target derivatization to access various quinolines.

3. Arbidol

Arbidol (umifenovir) is an oral antiviral drug with a broad spectrum of activity against many types of viruses. It has been licensed for the treatment of influenza A and B in Russia since 2003 and in China since 2006 [41]. Arbidol is a non-nucleoside membrane fusion inhibitor that prevents the interaction of the influenza virus with the host cell. Arbidol shows a binding mode with the SARS-CoV-2 spike protein similar to that with influenza virus hemagglutinin (HA) [42][43]. SAR studies on Arbidol have indicated that the indole core and the thiophenyl motifs are pivotal for the molecule bioactivity (**Figure 4**).

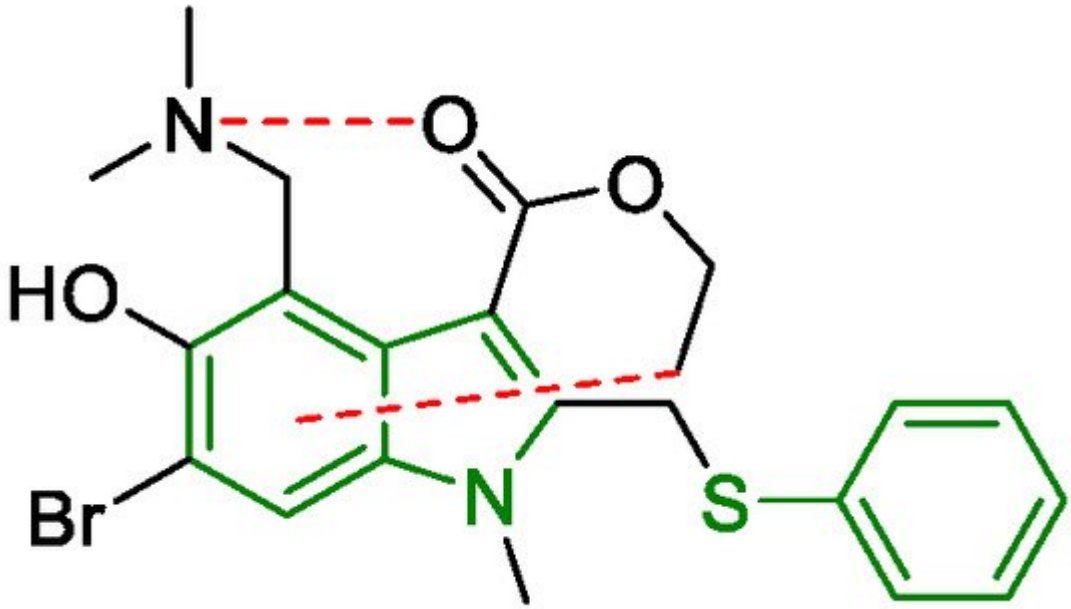
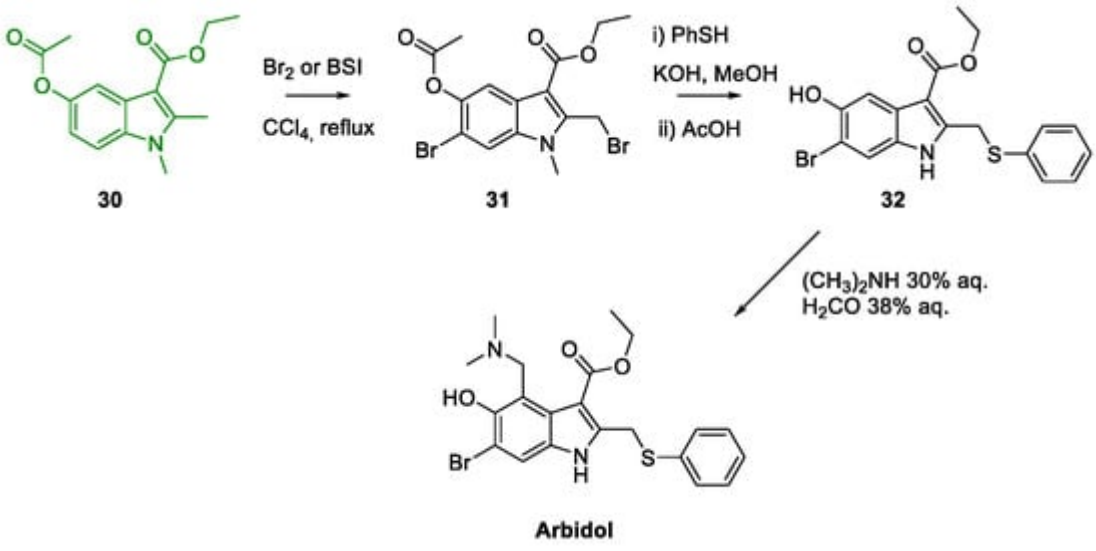


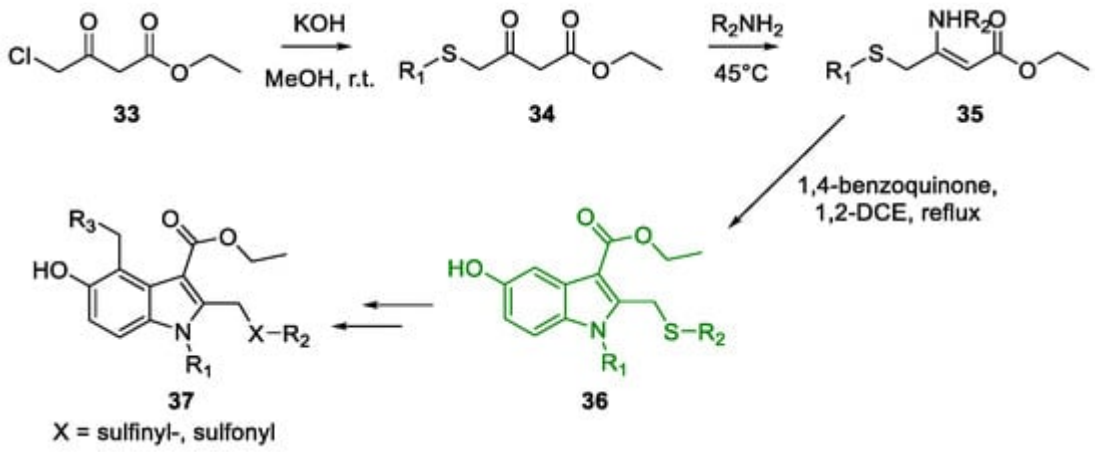
Figure 4. The indole and thiophenyl scaffold (green) interact with the hydrophobic membrane of influenza HA, whereby internal interactions (red lines) constrain the molecule to establish CH–π interactions with the amino-acid residues.

The first synthetic approach to obtain Arbidol was reported in 1993 by Trofimov, involving decoration of the aromatic ring of the indole derivatives **30** previously synthesized by the same group (Scheme 19) [44].



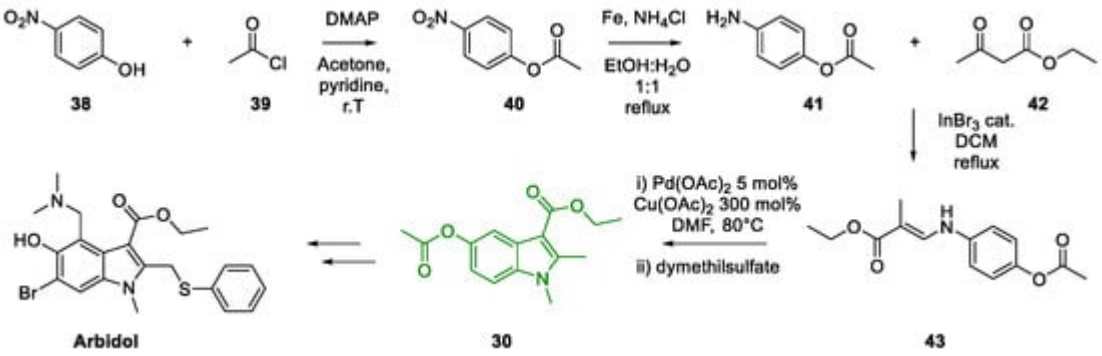
Scheme 19. First reported synthesis of Arbidol by Trofimov.

Gong and coworkers described the synthesis of various ethyl 5-hydroxy-1*H*-indole-3-carboxylates **37** with anti-hepatitis B activity. To achieve the target compounds, formation of the intermediate **36** was used as a precursor of Arbidol starting from commercially available ethyl 4-chloro-3-oxobutanoate **33** (Scheme 20) [45].



Scheme 20. Arbidol precursor synthesis reported by Gong.

In the last decade, the ongoing interest around Arbidol due to its antiviral properties has led to it becoming a target for API producers. In 2016, Gao *et al.* developed a total synthesis protocol for Arbidol starting from nitrophenol **38** (Scheme 21) [46].



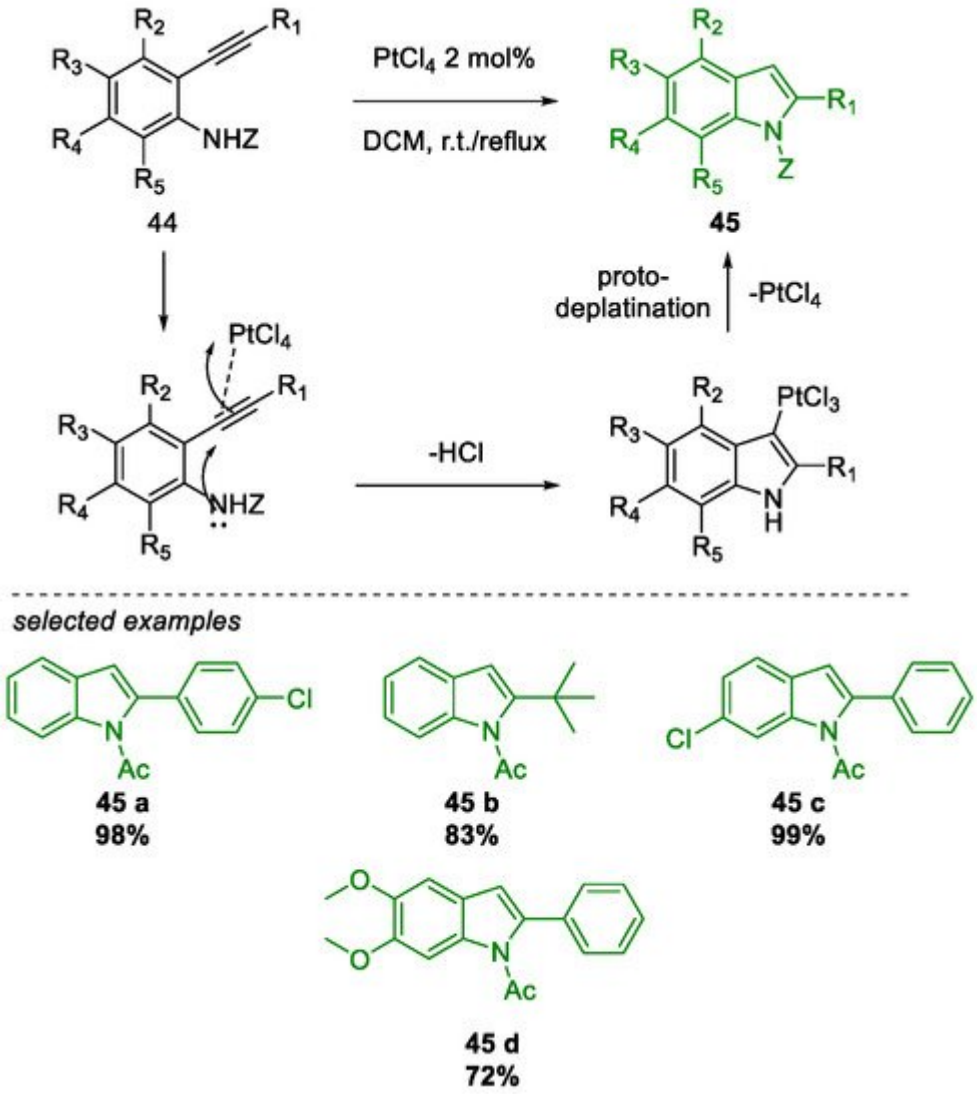
Scheme 21. Current industrial synthesis of Arbidol.

Its recent commercialization, the establishment of various synthetic protocols, and its use as a potential candidate in the therapy against SARS-Cov-2 have enhanced the interest in Arbidol. The indole scaffold has emerged as central in the existing synthesis protocols; thus, the development of alternative indole synthesis approaches involving different starting materials and metal catalysts may lead to accelerated production of this API.

Metal-Promoted Heterocyclization to Achieve Polysubstituted Indoles

Indole is one of the most common heterocyclic scaffolds, used in a large array of drugs, natural products, and agrochemicals. The importance of this aromatic *N*-heterocycle has been highlighted by the continuous work carried out on it [47]. In this section, we suggest some recent metal-catalyzed heterocyclization pathways to achieve polysubstituted indoles in an easy and accessible way with the aim of finding plausible alternative strategies for the synthesis of the indole core present in Arbidol.

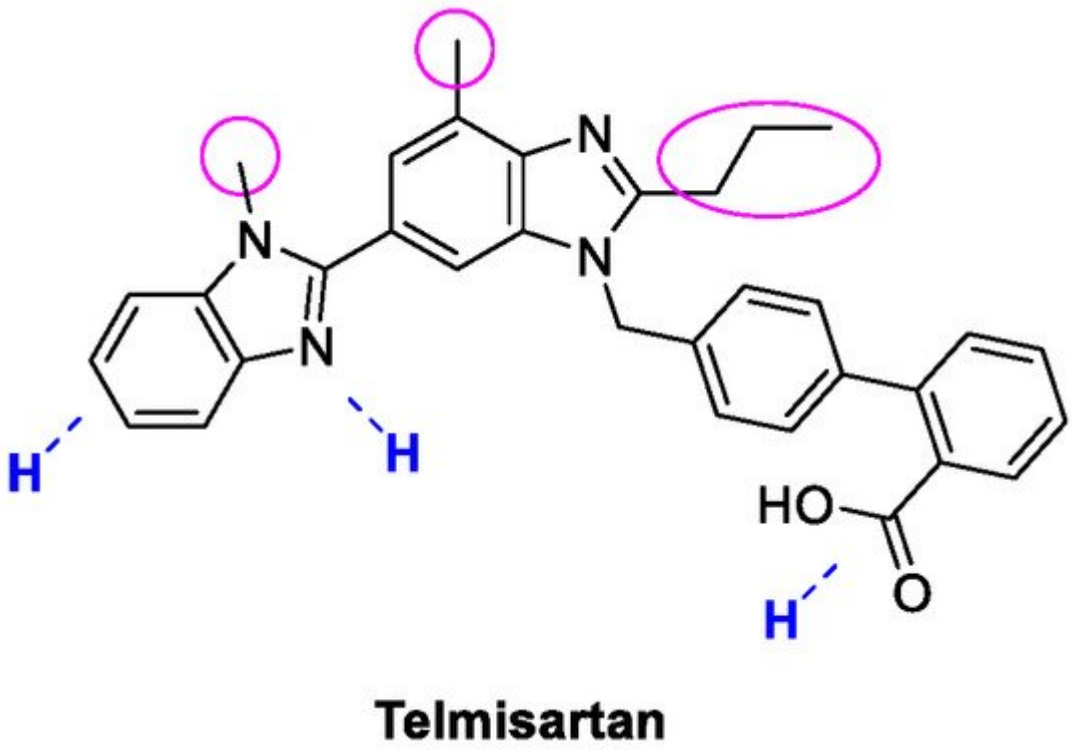
Ruchirawat *et al*. came up with an efficient and easy procedure for accessing a plethora of substituted indoles **45** (Scheme 22) [48].



Scheme 22. $PtCl_4$-catalyzed *N*-acetyl-2-alkynylaniline cyclization.

4. Telmisartan

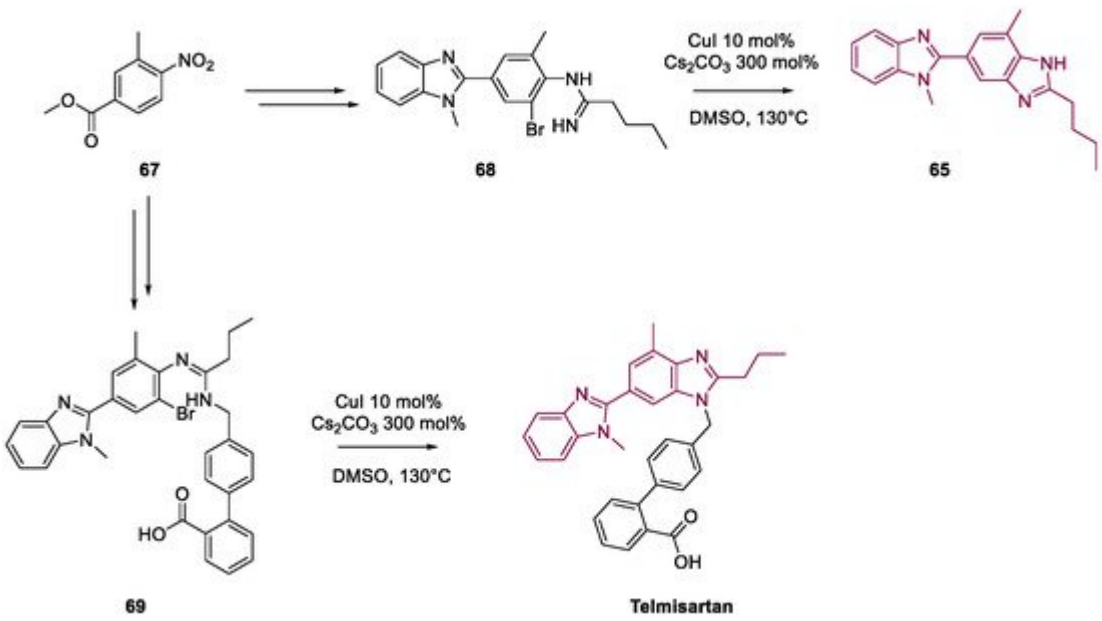
Telmisartan (commercial name Micardis®) is a potent and selective angiotensin II type 1 (AT_1) receptor antagonist. It is characterized by excellent AT_1 receptor-binding activity, a long half-life, and good tolerability (**Figure 5**) [49].



Telmisartan

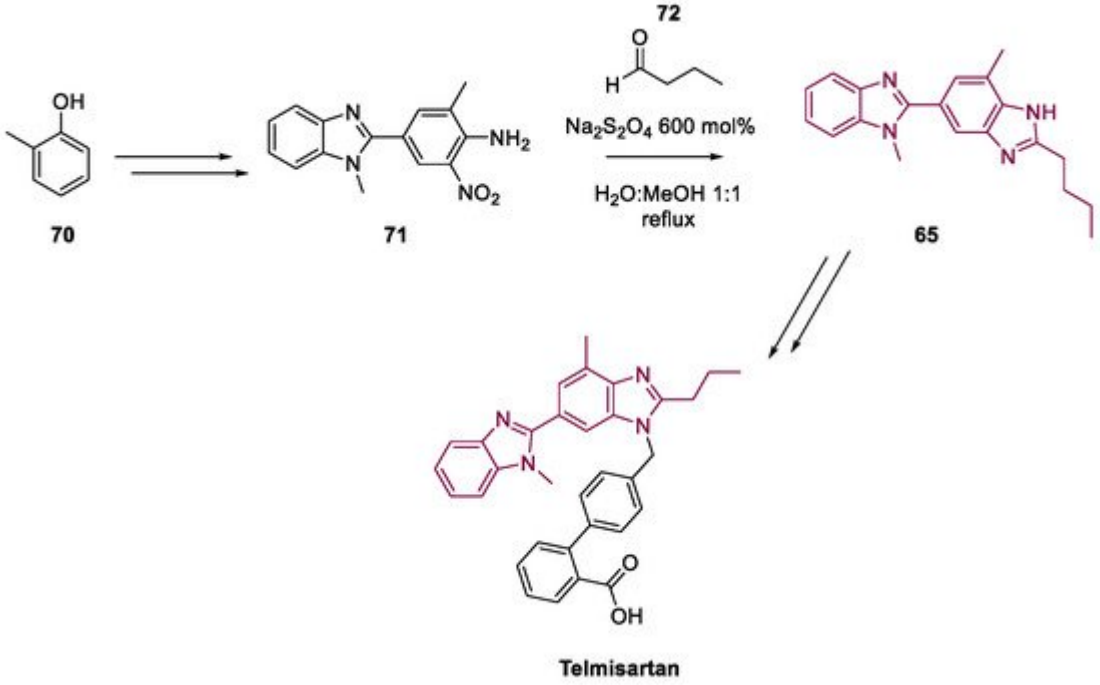
Figure 5. (Q)SAR of telmisartan. Pink circles represent lipophilic pockets; blue dashed lines represent H-bond donor sites [50].

In 2020, Shen *et al*. designed an efficient synthetic route for telmisartan. They focused their attention on the synthesis of the bis-benzimidazole intermediate **65** via Cu catalysis, avoiding PPA as a condensing agent (Scheme 23) [51].



Scheme 23. Cu(I)-catalyzed annulation in telmisartan synthesis.

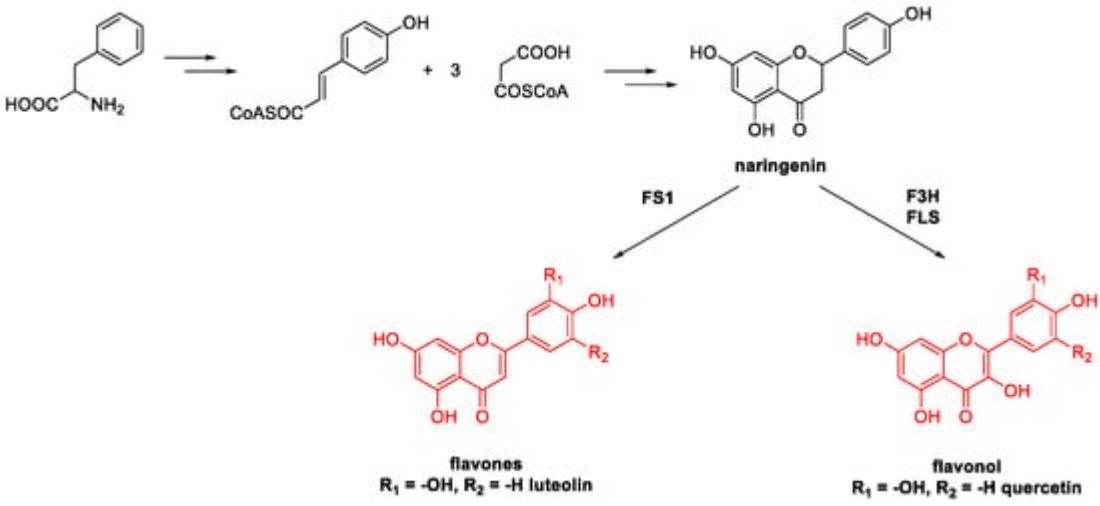
Xiang's research group described the use of a green inorganic salt to promote the synthesis of the benzimidazolic framework. They exploited $Na_2S_2O_4$ in a protic solvent to obtain the key intermediate **65** in an excellent 85% yield (Scheme 24) [52].



Scheme 24. Xiang's work.

5. Quercetin and Luteolin

Flavonoids are biosynthesized by plants starting from phenylalanine, which is rapidly converted to 4-coumaroyl-CoA. Malonyl CoA reacts in a 3:1 ratio with the coumayl-CoA derivative to give the key intermediate naringenin, catalyzed by chalchone synthase. Two different pathways lead to the formation of quercetin (via hydroxylation, promoted by flavone 3-hydroxylase F3H and dehydrogenation) and luteolin (via dehydration, promoted by flavone synthetase SI) (Scheme 25) [53].

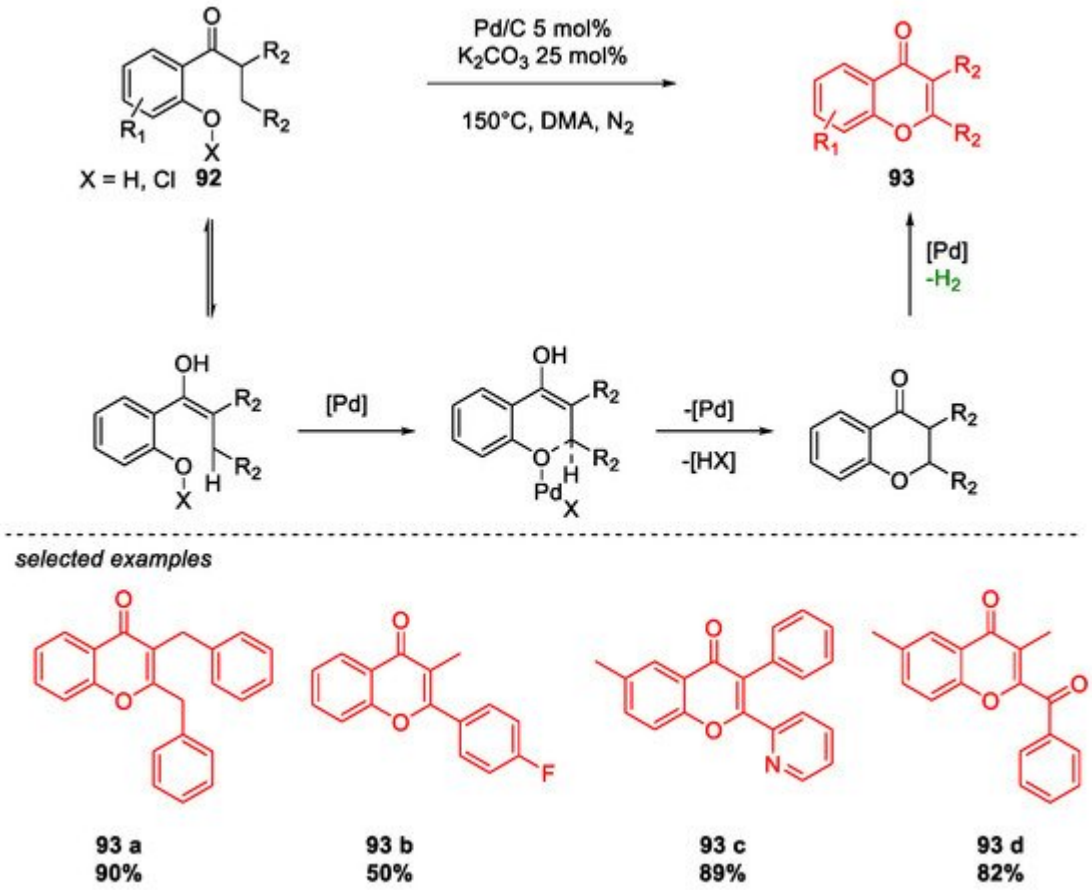


Scheme 25. Flavonoid biosynthetic pathways.

Metal-Catalyzed O-Heterocyclization to Flavonoids

The flavonoid framework is recurrent in drugs and natural products, showing unique biological properties and physiological actions. Due to their varied biomedical applications, flavones have aroused great interest in the chemistry community, leading to the development of performant and sustainable synthesis and functionalization approaches in the last decade. Metal-catalyzed heterocyclization represents an outstanding and selective strategy to obtain these scaffolds starting from readily available or easy-to-synthesize starting materials. Below, recent strategies are reported for the synthesis of substituted flavones.

Liu et al., in their work, proposed the palladium-catalyzed dehydrogenative annulation of *o*-acyl phenols **92** to flavones **93** (Scheme 26) [54].



Scheme 26. Flavonoid synthesis reported by Liu.

6. SARS-CoV-2 3CL Protease Target Drugs

The SARS-CoV-2 3C-like protease is the main protease present in the virus, and it is crucial in the translation process from polyproteins to viral RNA [55]. It was demonstrated that the catalytic domain (Cys-145 and His-41) is

particularly conserved, which makes the 3CL protease an attractive target for broad-spectrum anti-coronavirus therapies and drug discovery [56]. The SARS-CoV-2 main protease and spike protein are essential for the transmission of the virus and the severity of the infection in the host. Suppressing one or both biological targets can address the concerns linked to transmission, whereby acute COVID-19 symptoms can be drastically minimized [57]. Potential 3CL protease inhibitors reported in the literature have been screened to test their efficacy. Among the prospective bioactive molecules targeting this protein, ritonavir in combination with lopinavir and *N*-decorated isatins has shown promising results in the fight against SARS-CoV-2 [58][59][60].

Isatin and its derivatives have emerged as potential SARS-CoV-2 main protease inhibitors. Recent studies have demonstrated powerful inhibition by isatin compounds bearing a carboxamide moiety at C-5 and aromatic groups with a nitrogen atom in the isatin ring. These two functional groups tethered to the isatin framework are pivotal for the enhanced bioactivity of the molecule (**Figure 6**).

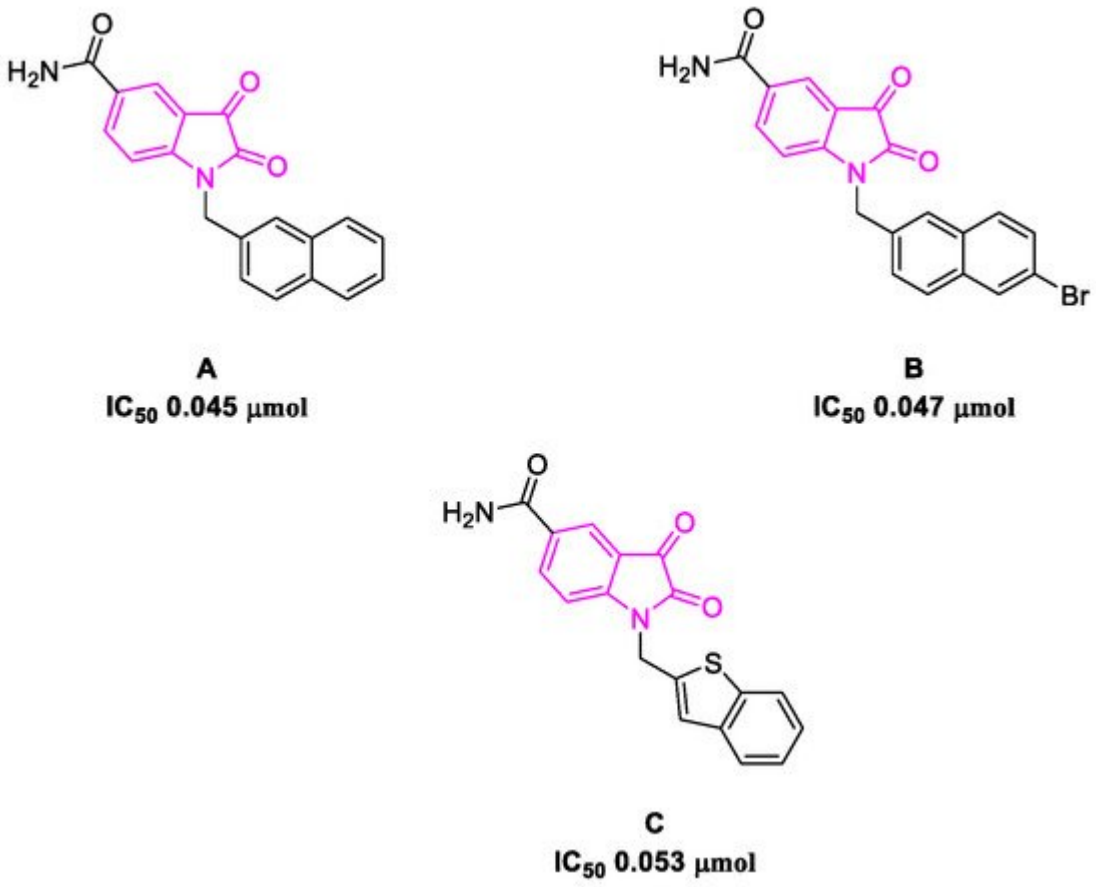
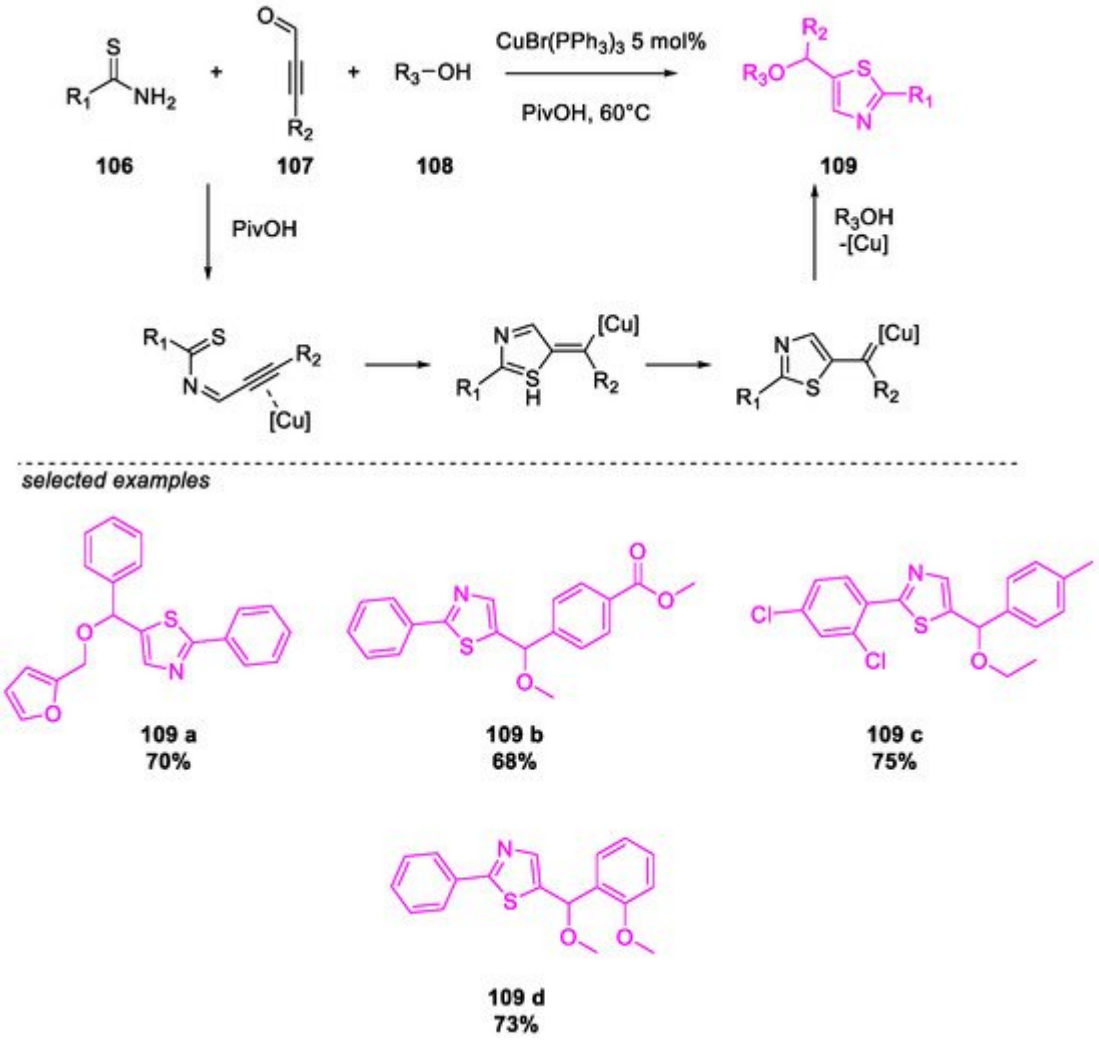


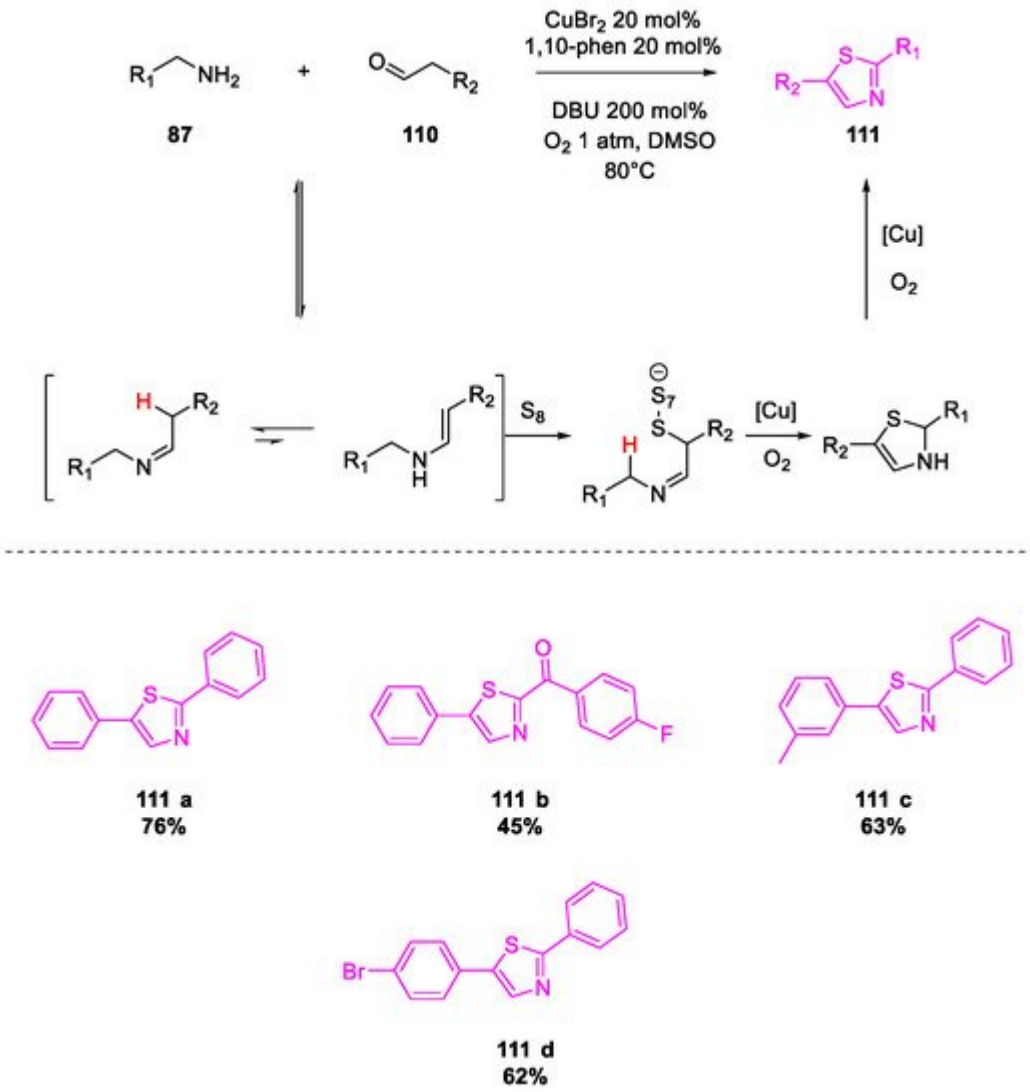
Figure 6. Lead compounds in Lai's work.

In 2020, Cao *et al.* presented a novel and straightforward strategy for the synthesis of decorated thiazoles starting from thioamides **106**, ynals **107**, and alcohols via a Cu(I)-catalyzed reaction (Scheme 27) [61].



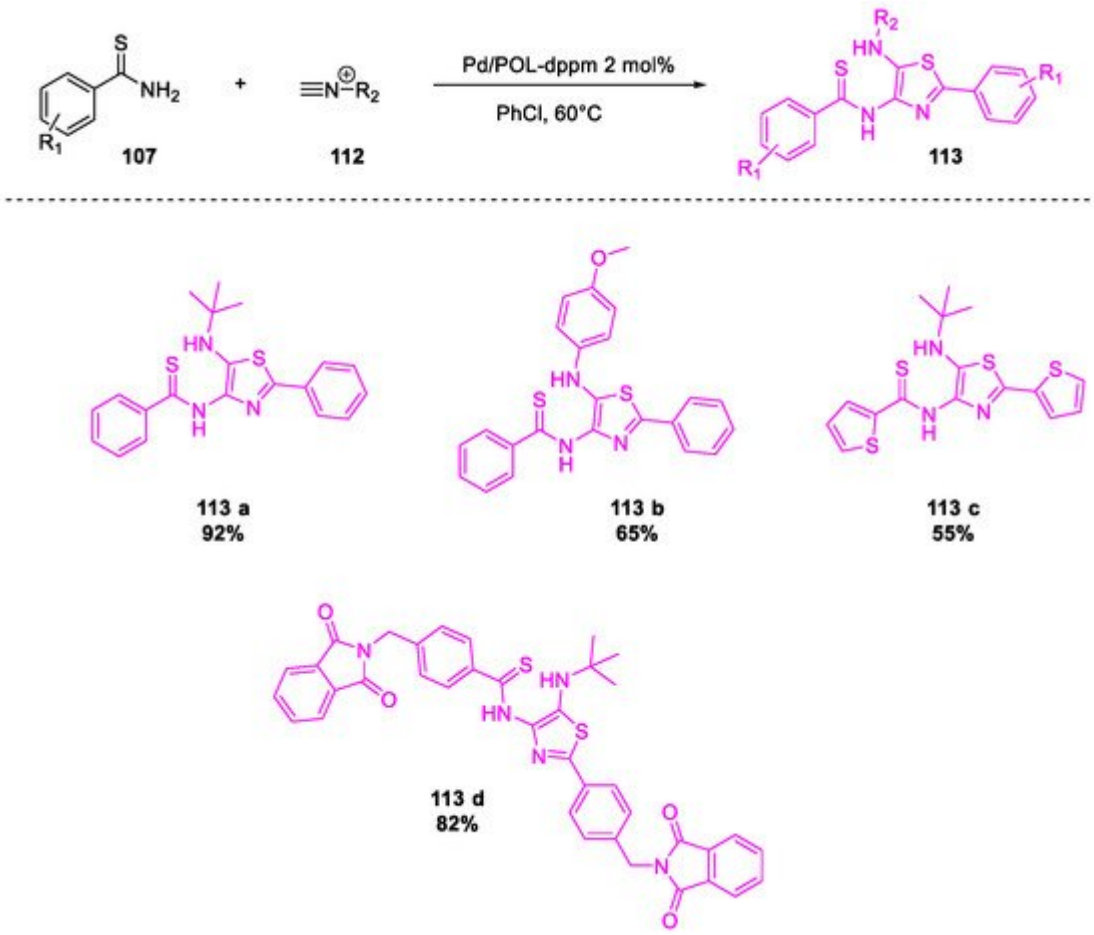
Scheme 27. Three-component synthesis of thiazoles promoted by Cu(I).

Cu catalysts have proven very effective for thiazole synthesis. Jiao and coworkers reported a practical and efficient aerobic oxidative sulfuration/annulation protocol to thiazoles via multiple C(sp^3)–H bond cleavage (Scheme 28) [62].



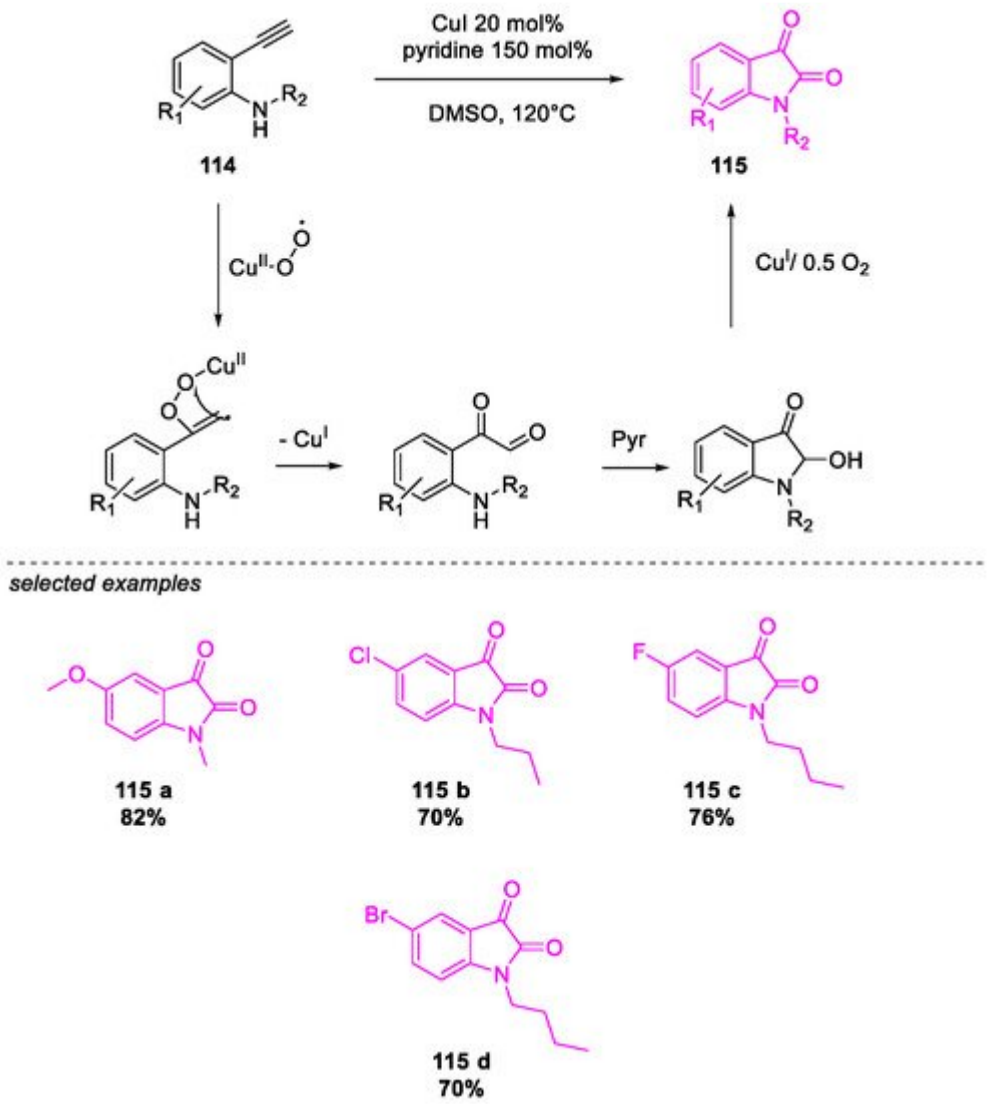
Scheme 28. Cu(I)-catalyzed sulfuration/annulation for thiazole synthesis.

Pan's research group exploited heterogeneous palladium catalysts to promote complex thiazole formation using thiobenzamides and isonitriles as precursors (Scheme 29) [63].



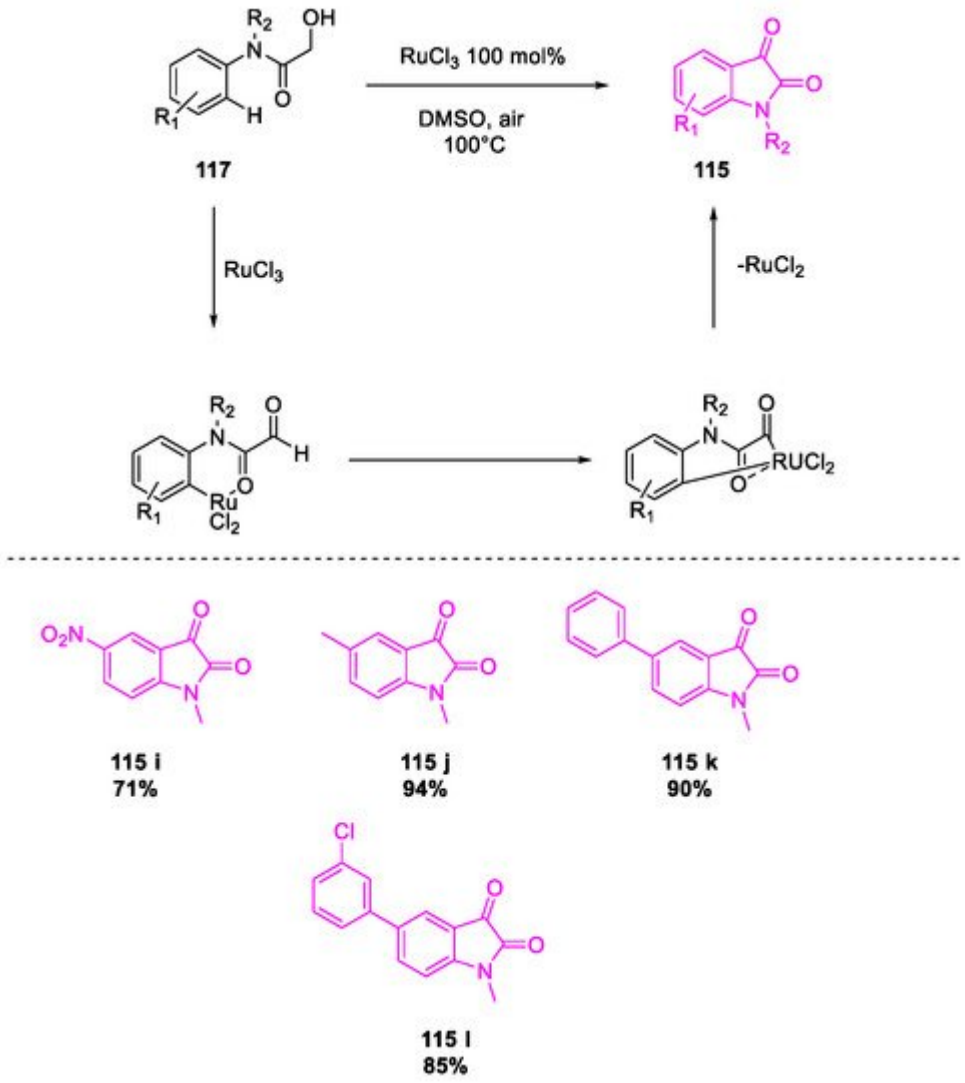
Scheme 29. Recyclable heterogeneous Pd(II) catalyst for thiazole synthesis.

In 2017, Das and coworkers developed an innovative method for the Cu(I)-catalyzed oxidative amidation of 2-aminophenylacetylenes using air oxygen as a green oxidant (Scheme 30) [64].



Scheme 30. Cu(I) oxidative annulation to isatins.

In later work, the same research group showed the capability of $RuCl_3$ to promote C(sp^2)-H activation/oxidative acylation to obtain isatin compounds starting from α-hydroxy amides **117** (Scheme 31) [65].



Scheme 31. $RuCl_3$ oxidative annulation to isatins.

$RuCl_3$ activates aromatic hydroxyl amides **107**, promoting their cyclization in mild conditions. The methodology is carried out in mild conditions and shows a high tolerability toward various functional groups tethered to the heterocyclic scaffold (e.g., **115 i–l**). Ruthenium works both as an oxidant and as an activator; thus, a stoichiometric amount of transition metal is required.

7. Conclusions

Key features of this entry are presented in **Figure 7**.

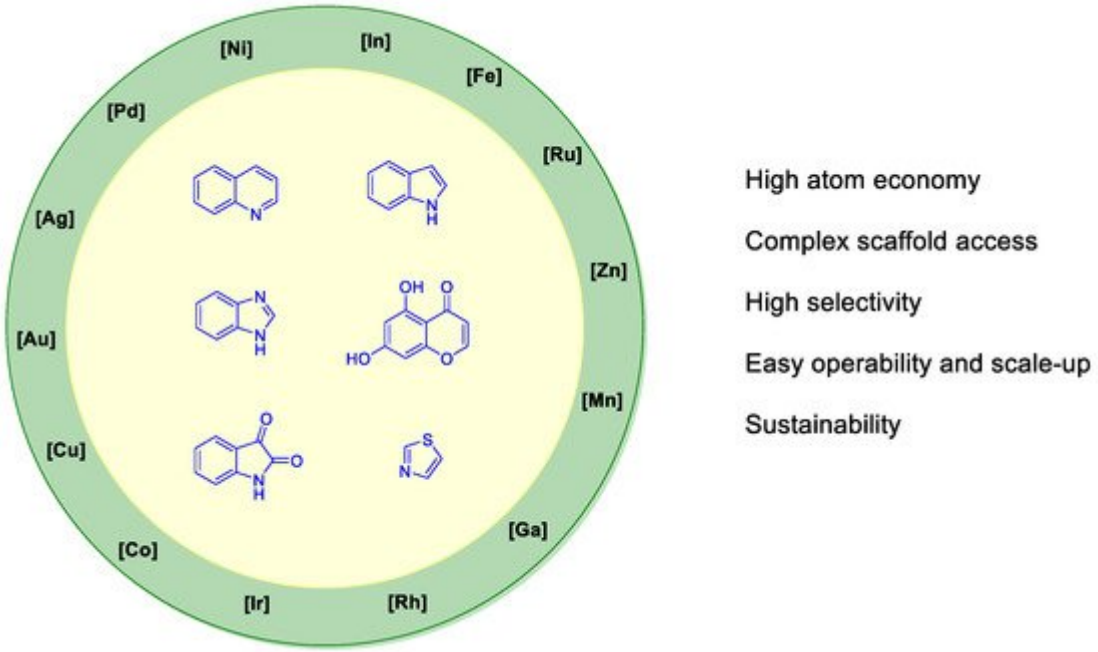


Figure 7. Key features of metal-promoted heterocyclization methodologies.

Continued research on heterocyclic scaffold synthesis is crucial to face the crisis caused by the pandemic, as well as lead to the development of innovative, practical, and easily scalable processes to produce new drugs or known APIs.

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