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COMPREHENSIVE REVIEW

First-row transition metal for isocyanide-involving multicomponent reactions (IMCR)

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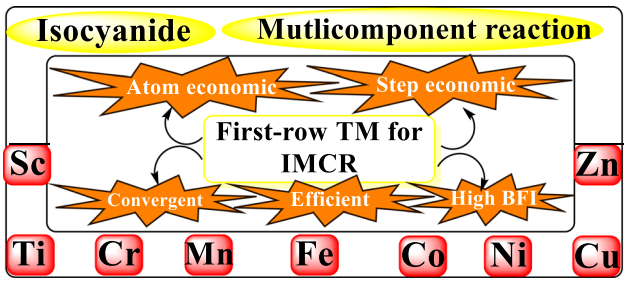
Abstract

First-row transition metal catalyzed transformations that are able to construct complex molecules from simple, readily obtainable feedstocks have become a keystone of modern synthetic organic chemistry. Particularly, the multicomponent reaction (MCR) involving carbon–carbon (C–C) as well as carbon–heteroatom (C–X) bond formation plays an essential role in many chemical conversions, and insurgencies in these reactions powerfully improve the overall synthetic efficiency. Recently, MCRs emerges rapidly because of its greener sides like eco-friendly nature, swift and straightforward execution, high atom/step economy, and construction of aimed product with lowest or no by-product, usually in quantitative yield. Curiously, the exceptional divalent carbon atoms of isocyanides make them predominantly useful components in multicomponent reactions. As a result of widespread research over the past few decades, numerous well-designed and effective procedures for the first-row TM-catalyzed MCR to afford the various entities have been reported. These aspects are summarized in this review article. A particular focus on comparative discussion of various first-row transition-metal catalyzed isocyanide-based multicomponent reactions through mechanistic details included in the review article.

Graphical abstract



Keywords First-row transition-metal catalyst · Isocyanide · Multicomponent reaction (MCR)

Introduction

Isocyanide, a linear molecule isoelectronic with carbon monoxide, display high inclination among scientific community because of the profound influences in the field of synthetic, agrochemical, medicinal, material and combinatorial chemistry [1–3]. They are isomer of the corresponding cyanides (–C≡N), so they are represented by prefix iso. Isocyanide are versatile building blocks having unique synthetic potentials like reacting with radicals, electrophiles, and nucleophiles. Moreover, isocyanides are used in oligo- and polymerizations as well as two-electron-donating ligands in organometallic chemistry [4–7]. Historically, an isocyanide (allyl isocyanide) was produced by alkylation of silver cyanide by Lieke in 1859 [8]. In view of molecular structure, the terminal carbon atom of isocyanides bearing a lone pair of

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electrons and has a partial negative charge, exhibiting strong electron-donating nature, while the nitrogen atom has a partial positive charge, representing electrophilic properties. Consequently, the exclusive molecular characteristic of isocyanides leads to diverse types of chemical reactions. In this context, the expansion of innovative synthetic approaches for the straightforward generation of various heterocyclic scaffolds via employment of isocyanide has been prospered owing to their ubiquity in numerous natural products and pharmaceuticals that exhibits extensive range of biological properties.

Multicomponent reactions (MCRs) are one-pot reactions which involve at least three simply accessible components to form a single product integrating basically the atoms of the reacting components and which come off as the main subdivision of tandem reactions [9–17]. MCRs are thus truthful environmentally benevolent and ideal systems where the diversity of anticipated product formation could be accomplished only in single synthetic operation by altering the substrate partner. The three crucial methods were summarized by S. L. Schreiber and M. D. Burke to populate the chemical space: (i) Target Oriented Synthesis (TOS), (ii) Diversity Oriented Synthesis (DOS) and (iii) Combinatorial Chemistry (CC) [18]. Particularly, Isocyanides are considered as one of the simply accessible, most viable, and bench-stable chemicals. However, these compounds persisted laboratory inquisitiveness for long periods, as their strong disgusting smell barred most chemists from working with them. In context of isocyanide, MCRs are divided into two main classes, irrespective of the number of components involved: (i) Non-isocyanide-based multicomponent reactions (NI-MCRs) and (ii) Iso-cyanide-based multicomponent reactions (I-MCRs) [19]. One of the pioneer works that accomplished the one-pot three-component reaction between carboxylic acids, aldehyde/ketone compounds, and isocyanides to synthesize α-acyloxy carboxamides was demonstrated by Passerini in 1921 [20]. In the same vein, Ugi and his co-workers in 1959, further expanded this Passerini multicomponent reaction to afford a diamide product by adding amines as a fourth component [21]. In 1998, Groebkee-Blackburne-Bienayme (GBB) reaction was divulged independently by three research groups; Hugues Bienayme (France), Christopher Blackburn (Cambridge, USA) and Katrin Groebke (Switzerland). The GBB reaction is a three-component, four-center reaction, which essentially involves a reaction between isonitrile, 2-aminoazine and aldehyde in the presence of a suitable catalyst, which is generally a Bronsted acid or Lewis acid. Meanwhile, the Ugi and Passerini reactions were well documented, isocyanides involving multicomponent reactions have been well established with the benefits of functional group tolerance, diversity in skeletons of products, impressive regio-, stereo-, and chemo- selectivities, and atom as well as step economy [22–26].

The emergence of transition-metal-catalysts in selective construction and functionalization of the biologically pertinent heterocycles via multicomponent reaction would make this approach more striking for practical applications [27]. Particularly, first-row TM salts retain many advantages compared to other transition-metal catalysts, such as ready availability, low cost, high efficiency, insensitivity to air, low toxicity, and can be easily handled have turned out to be the most competent catalysts for MCR. The overwhelming redox chemistry of first-row TM catalysts under aerobic environments has been subjugated in several synthetic applications, both in industry and academia. In the view of sustainable and cost-effective characteristics of earth-rich first row (3d) transition metals, the advancement of cheaper, less toxic 3d metal catalysts for multicomponent reaction has gained substantial topical impetus for more economically attractive and environmentally caring alternative [28, 29]. In the past few decades, many elegant reviews have been documented on I-MCRs [30–39]. However, the 3d transition-metal catalyzed I-MCRs is not exclusively explored. Hence a review article concentrating on this topic is highly desirable and important. In this context, we have summarized the current developments made in the comining arena of I-MCRs and 3d transition-metal catalysis. All significant discoveries related to this 3d transition-metal catalyzed I-MCRs have been encompassed and discussed in this review. With the intention to restrict the extensiveness of this review, the detailed emphasis is typically on the use of catalysts based on Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn. Insightful mechanistic aspects and substrate scopes have been conferred in details. Thus, we predict this scheming discussion will offer a reference devise to the synthetic chemists concerned in I-MCRs with the 3d transition metal catalysts.

First-row transition-metal catalyzed IMCR

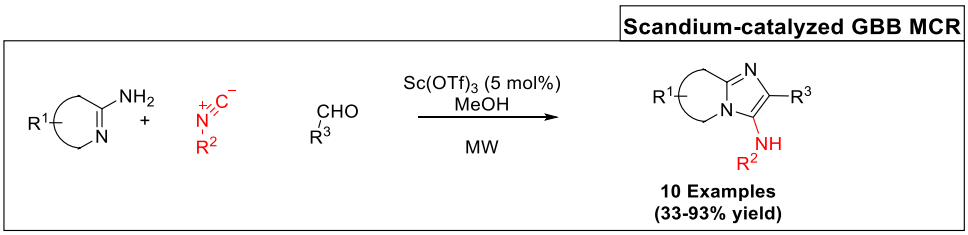
Scandium-catalyzed isocyanide-involving multicomponent reaction

The microwave assisted synthetic approaches in parallel and combinatorial synthesis have concerned much curiosity due to their high efficiency. The catalytic activity of scandium triflate has been reported for the preparation of a various fused 3-aminoimidazoles in microwave assisted GBB three-component coupling approach in methanol as solvent (Scheme 1) [40]. The reaction used heterocyclic amidine, isocyanide and aldehyde compounds as the building blocks for the construction of two C–N and one C–C bonds in the product. It is remarkable that only a 25% conversion was achieved in the nonattendance of scandium triflate after 2 h in the microwave at 160 °C. Interestingly, use of ethyl isocyanoacetate as the isocyanide offered somewhat lowered

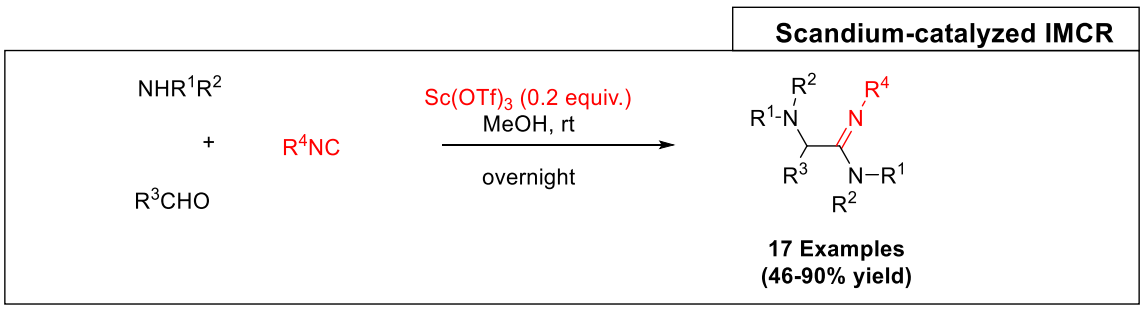
yields than those of benzylisocyanide and it was essential to utilize ethanol as solvent to circumvent complications with partial transesterification.

The advancement of new method that permits the general formation of a-amino amidine at RT and more normally under mild conditions is a topic of substantial interest. The example of Sc-mediated three-component Ugi condensation protocol was achieved at room temperature between amines, isonitrile and aldehydes, which require 0.25 equiv. of Sc(OTf)3 in methanol (Scheme 2) [41]. Other Lewis acids such as indium triflate, copper triflate, ytterbium triflate, silver triflate, yttrium triflate, and lanthanum triflate were also tested. None delivered superior outcomes in comparison to that obtained with scandium triflate, which led to the formation of product in 99% yield with 79% purity. The substrate scope for the conversion was recognized with diverse amines including amino esters, anilines and benzylamine resulted in the formation of exclusive product. The synthetic utility of this transformation is explained by reacting p-nitrochloroformate with amino amidines to the consistent hydantoin imide in unoptimized yield of 57%.

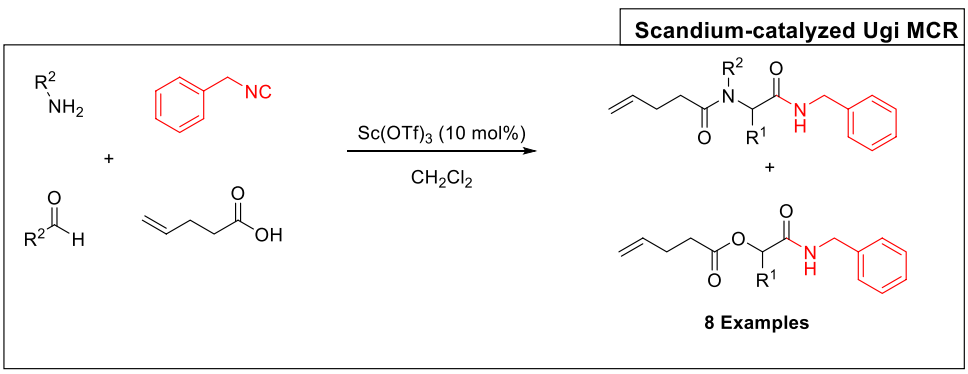
Rare earth metal triflates like $Yb(OTf)_3$ and $Sc(OTf)_3$ are identified to catalyze transformations of imines, such as imino-aldol reactions, cyanations, allylations, aza Diels–Alder reactions, and asymmetric three-component reactions. Sello and co-workers devised a coherent synthetic way to two- to sevenfold enhancement of the yield of Ugi four component coupling reactions of benzyl isocyanide, aromatic aldehydes, 4-pentenoic acid, and amines in presence of substoichiometric amounts of ytterbium and scandium triflate (Scheme 3) [42]. Substrate scope survey divulged that $Sc(OTf)_3$ shown to be a well promoter than $Yb(OTf)_3$. The decline in yield of Ugi 4CC reactions with aliphatic aldehydes by the metal triflates is attributed to repressive coordination of the secondary amine of the nitrilium species with the metals.



Scheme 1 Synthesis of fused 3-aminoimidazoles via Sc-catalyzed GBB MCR



Scheme 2 Synthesis of α-amino amidine via Sc-catalyzed IMCR



Scheme 3 Synthesis of R-acylamino carboxamides via Sc-catalyzed Ugi MCR

In 2013, scandium(III) triflate-catalyzed GBB reaction was reported via three-component protocol utilizing diversely substituted isonitriles, aldehydes, and benzimidazole-linked amino pyridines (Scheme 4) [43]. This reaction furnishes a series of potential drug candidates and biologically appropriate benzimidazole-imidazo[1,2-a] pyridine derivatives under solvent-free environments. A model reaction of benzimidazole-linked aminopyridine, 4-nitrobenzaldehyde and cyclopentyl isonitrile using $Sc(OTf)_3$ as the catalyst at 135 °C temperature in 10 min afforded the desired adduct. Compared with reported methods, the described method has the superiorities such as excellent yields, high purity and structural diversity to enlarge chemical space. Mechanistic pathway consists of initial imine intermediate formation followed by nucleophilic addition. In the next step, 5-exodig cyclization with isonitrile furnished the imidazo-[1,2-a]pyridine species, which provided the final product upon rearomatization.

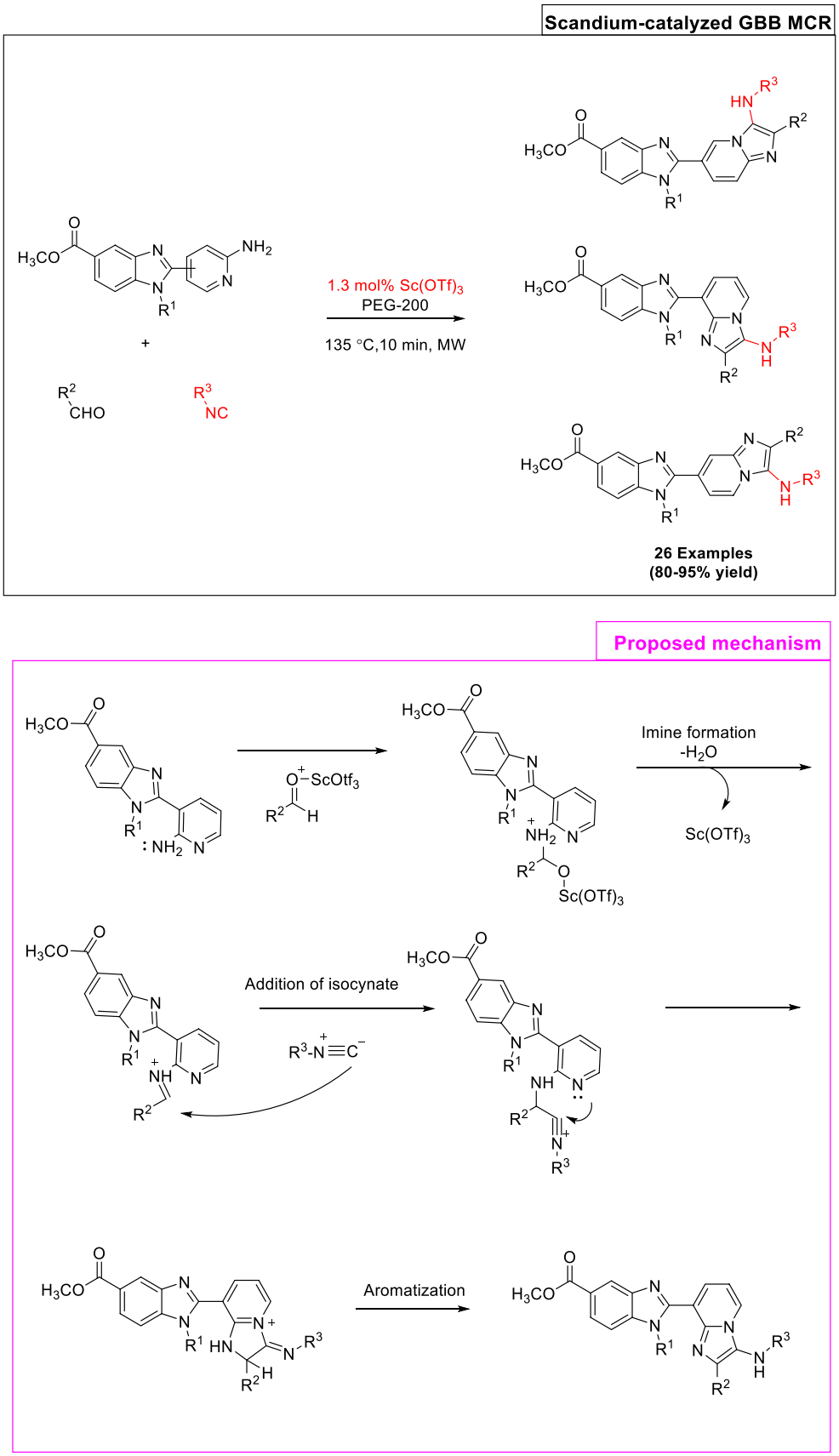
Imidazopyrimidines are found to keep important pharmacological properties including antimicrobial, anti-bacterials, anticancer, anti-inflammatory agents, and are also utilized for their antituberculosis activity. The synthesis of imidazo-fused heterocycles have been reported various research group employing different strategy, however the use of hazardous and toxic approach in chemical processes is considered an issue with regard to health and safety as well as environmental pollution [44–47]. The GBB three-component condensation between isocyanide, aldehyde, and aminopyrazolo[3,4-d]pyrimidine has been considered from the viewpoint of expedient formation of combinative arrays of imidazo[1,2-c]pyrazolo[3,4-d]pyridimidine derivatives that deliver virtuous scenarios for fluorescence-based biomedical and clinical applications (Scheme 5) [48]. Gratifyingly, the reaction is fruitfully compatible with two isocyanides, namely tert-butyl isocyanide and cyclohexyl isocyanide. It was detected that 4-OMe substituent containing benzaldehyde afforded the corresponding product with the highest fluorescence intensity. More importantly, the advantages of the present reaction system are as follows: Non-aqueous work-up, simplicity, and higher yield of the products.

An efficient protocol was reported for the construction of a big library of different compounds including pyridotriazines, dihydroindazoles, and triazolopyridines via switchable and sophisticated three-component reactions. The one-step addition reaction between an aldehyde derivatives, hydrazines and isocyanides has been executed from the consideration of expedient preparation of pyridotriazines (Scheme 6) [49]. The proposed mechanism comprises a nonconcerted [5 + 1]-cycloaddition between the corresponding Schiff base and isocyanides to generate bicyclic product. Five-membered triazolopyridine scaffolds are endowed by replacement of the nucleophilic isocyanide component with diverse electrophiles such as acyl chlorides, cyclic anhydrides, isothiocyanates, and isocyanates with minor alteration of reaction conditions. The robust nature, decent functional tolerance, wide substrate scope, and associated chemistry make this protocol interesting for medicinal chemists working in either specific target-related drug discovery operations or file improvement.

In 2015, González-Zamora et al. disclosed an effective Sc-catalyzed multicomponent preparation of polysubstituted equivalents of cyclic HMBPA (hexamethylenebis(3-pyridine)amide) from simple and easily accessible starting materials based on combination of a Ugi – 3CR and aza-Diels – Alder transformation as a post-functionalization in a single-pot method (Scheme 7) [50]. The basis of the reaction and the reason for the scandium catalyst choice lies in earlier report on synthesis of tetracyclic lactam system. The reaction was performed by heating a benzene solution of suitably functionalized isocyanoacetamide, aldehyde, and diamine to afford a crucial intermediate 5-aminooxazol, which was then employed as a branching point to yield the cyclic analogue of HMBPA by use of maleic anhydride through aza-Diels – Alder intermolecular cycloaddition and lactamization.

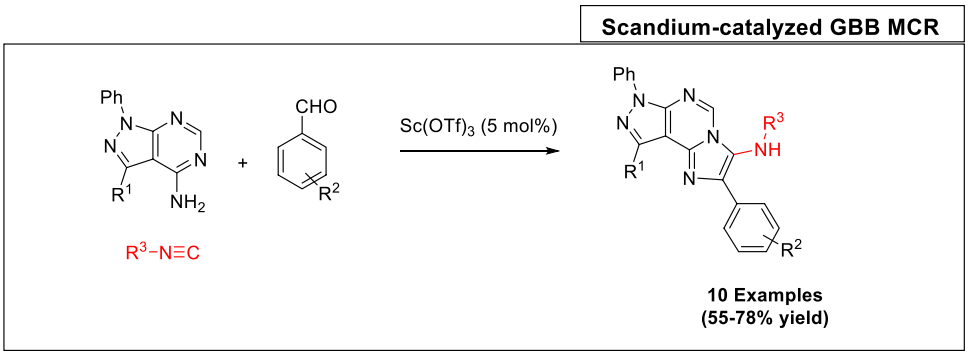
The GBB-type multicomponent construction of imidazo[2,1-c][1,2,4]triazoles involving the coupling of aromatic aldehyde, isocyanide and 5-amino-1,2,4-triazole derivatives through the formation of an iminium intermediate trailed by a [4 + 1] cycloaddition with the isocyanides was documented by Aouali and associates in 2015 (Scheme 8) [51]. In the presence of scandium triflate $Sc(OTf)_3$, all three components react together under reflux conditions for 30 h to furnish pharmaceutically relevant products in good yields. Additionally, all synthesized substances were examined in vitro for the antioxidant property using DPPH assay. It has been observed that most of them have exhibited very good DPPH radical-scavenging properties than those of the standard BHA and α-tocopherol.

An innovative procedure for the preparation of fused, substituted, tricyclic 6,7-dihydro-1H,5H-pyrido[1,2,3-de]quinoxalin-3-amines in moderate to excellent yield by scandium-catalyzed three-component sequence from isocyanides, aldehydes, and 1,2,3,4-tetrahydroquinolin-8-amine was demonstrated by Narula et al. (Scheme 9) [52]. The reaction was carried out in the existence of 10 mol% additives (DMAP and TMSOTf) and 10 mol% catalyst $Sc(OTf)_3$ in 1,2-dimethoxyethane solvent. After augmenting the reaction mediums, the substrate scope of isocyanides was discovered. Also it was observed that aliphatic aldehydes afford the anticipated product in better yields with low reaction times as compared to aromatic aldehydes. The generation of base-stabilized imine synthon by attack of DMAP on nitrilium ion is assumed to be accountable for the reaction.

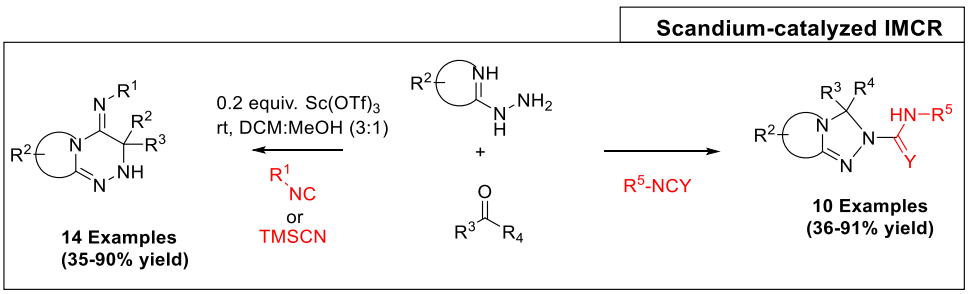


Scheme 4 Synthesis of benzimidazolylimidazo[1,2-a]-pyridine via Sc-catalyzed GBB MCR

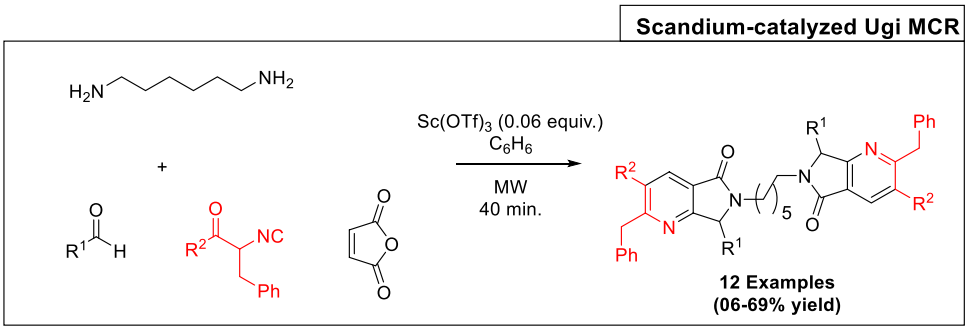
Scheme 5 Synthesis of imidazo[1,2-c]pyrazolo[3,4-d] pyridimidine via Sc-catalyzed GBB MCR



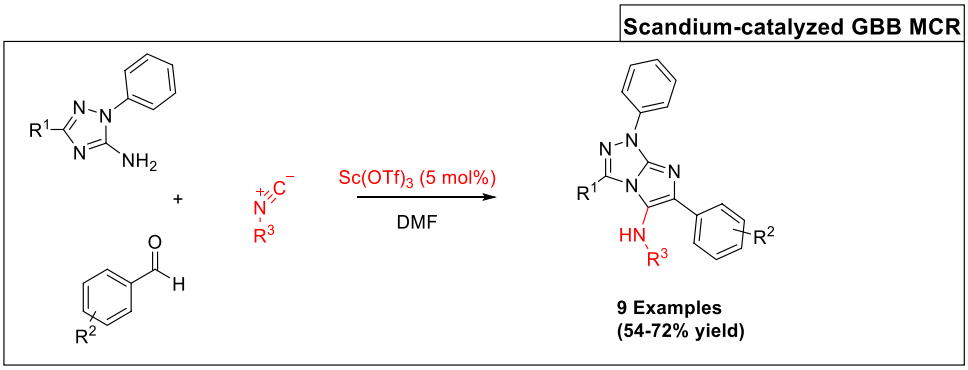
Scheme 6 Synthesis of nitrogen-enriched heterocycles via Sc-catalyzed IMCR



Scheme 7 Synthesis of HMBPA via Sc-catalyzed Ugi MCR



Scheme 8 Synthesis of 5-amino-1-phenyl[1,2,4] triazoles via Sc-catalyzed GBB MCR



Titanium-catalyzed isocyanide-involving multicomponent reaction

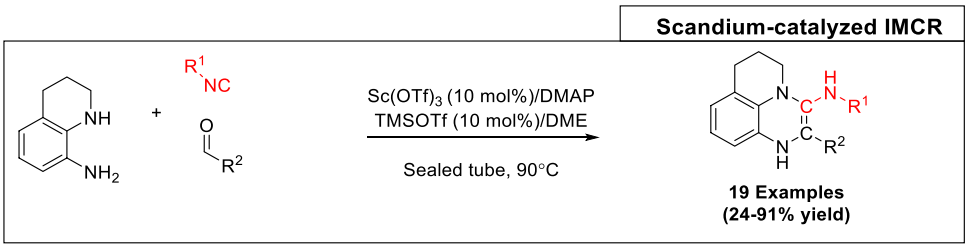
The enantioselective isocyanide based Passerini reaction (P-3CR) is very difficult. However, in 2003, Domling and co-workers overcame this problem by screening hundreds of Lewis acid/ligand blends for stereochemical induction with enantiomeric excesses between 32 and 42% in the Passerini multicomponent strategy. The optimized ideal reaction involved coupling of isobutyric aldehyde, benzoic acid, and

benzyl isocyanide carried out in the existence of catalytic system consisting of titan tetraisopropylate and (4S,5S)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (Scheme 10) [53]. The catalyst-to-educt ratio was either 0.5/1 or 1/1 found suitable. The substantial loss of enantiomeric excess was observed when reaction executed with sub-stoichiometric amounts of Ti and ligand.

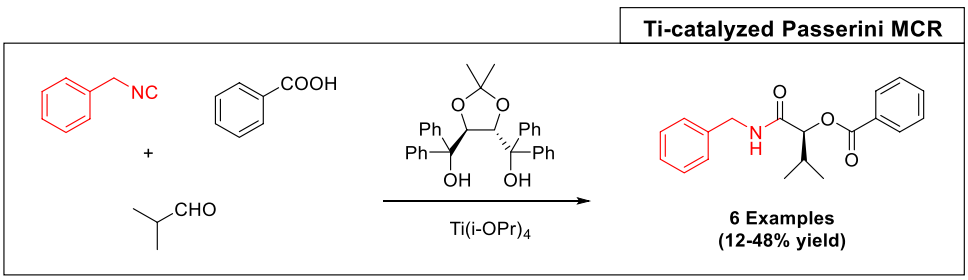
In IMCRs, the employment of an isocyanide as an amine surrogates was first reported by Dai and coworkers. The report pronounces an oxophilic titanium-catalyzed phenol-Passerini three-component transformation of carboxylic or phenolic acids, isocyanides, and aromatic aldehydes without added amines to yield both U-4CR and phenol-U-4CR (Scheme 11) [54]. They performed the initial phenol-U-4CR reaction using benzaldehyde, cyclohexyl isocyanide and methyl 4-hydroxy-3-nitrobenzoate as the model substrates and the optimized reaction conditions were as follows: Ti(O-i-Pr)$_4$ (5 mol%) as the catalyst in methanol as the solvent at 60 °C for 18 h. A variety of aldehydes were found companionable in this transformation. Interestingly, furan-containing aldehyde is also revealed to be a feasible substrate, producing a consistent product in 64% yield.

Pyrimidine core is of general significance in medicinal and chemical research because of its existence in several pharmaceutically active molecules and natural products, such as first approved drug, zidovudine, dealing with AIDS and HIV infection. In 1893, Pietro Biginelli reported the acid-catalyzed one-pot three-component synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) eploying easily available starting materials, namely, (thio)urea, ethyl acetoacetate and benzaldehyde, in protic solvents. This reaction has come to be widely known as Biginelli reaction, and has prompted much attention owing to diverse applications of DHPMs [55–57]. The diversity oriented and proficient synthetic protocol has been demonstrated to synthesize pyrimidine derivatives by means of isocyanide based multicomponent reaction in the existence of the titanium catalyst (Scheme 12) [58]. Remarkably, both aliphatic as well as aromatic amine are efficiently involved in conversion to give the corresponding pyrimidines. The regioselectivity in terms of alkyne component was controlled by altering the catalyst between [Ti(NMe)$_2$dpma] and [Ti(NMe)$_2$dpm].

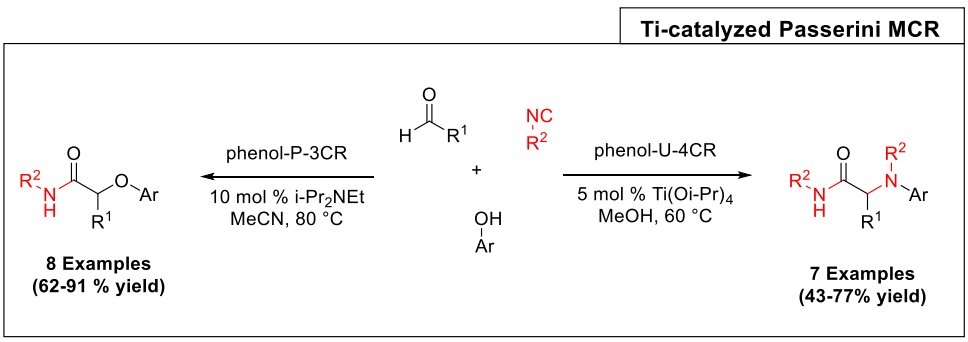
Thereafter in 2013, Rueping et al. realized innovative method for the synthesis of α-amino amides through



Scheme 9 Synthesis of 6,7-dihydro-1H,5H-pyrido[1,2,3-de]quinoxalin-3-amine via Sc-catalyzed IMCR

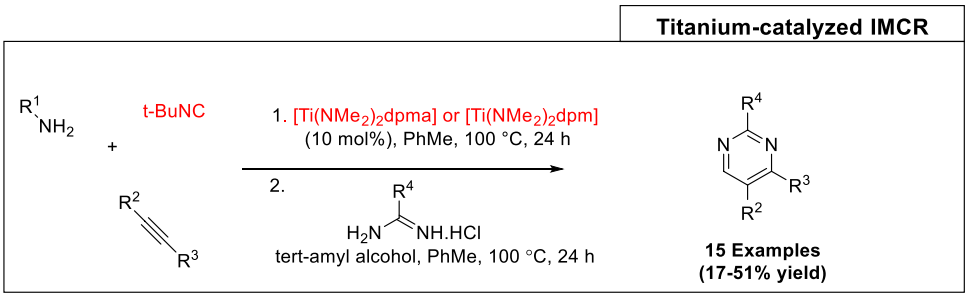


Scheme 10 Synthesis of enantioselective amide via Ti-catalyzed Passerini MCR



Scheme 11 Synthesis of Ugi adduct via Ti-catalyzed Passerini MCR

Scheme 12 Synthesis of pyrimidines via Ti-catalyzed IMCR



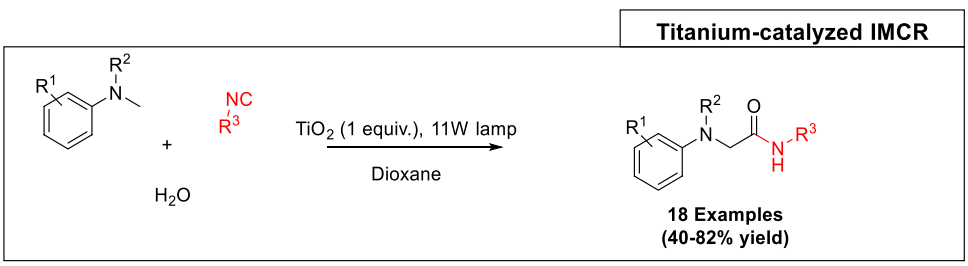
heterogeneous C–H functionalization of tertiary amines under visible-light irradiation (Scheme 13) [59]. The optimum reaction conditions involves the stirring of the starting materials using titanium dioxide (1 equiv.) as the catalyst under irradiation with an 11 W fluorescent lamp in 1 ml of dioxane for 24–96 h at 30 °C. A noteworthy decline in the yield of the product was found when ZnO was used as a photocatalyst. Also, the TiO_2 was recycled and worked without loss of activity even after five consecutive catalytic runs, highlighting the ability of TiO_2 as a photocatalyst for the Ugi multi-component type transformations.

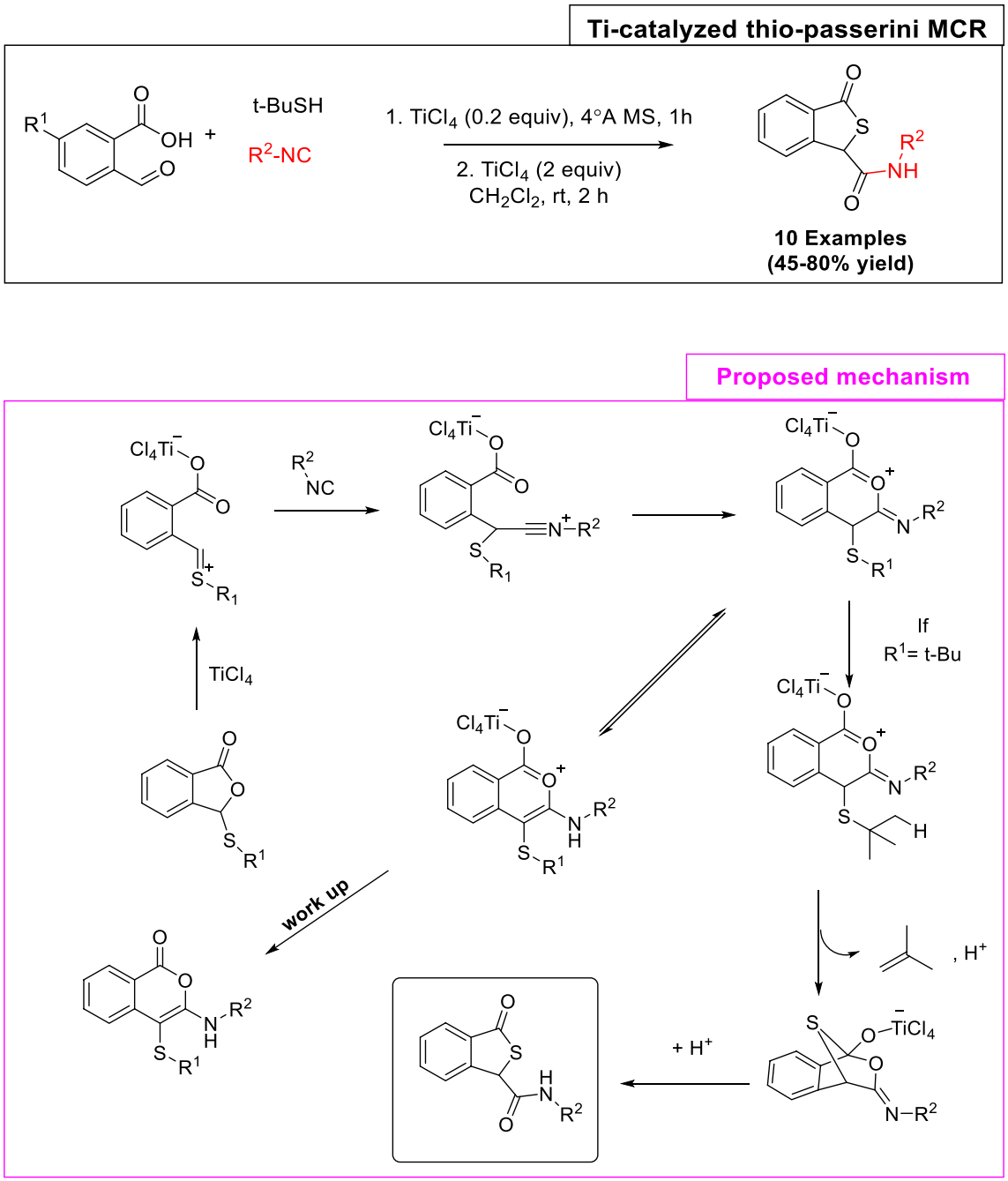
The thiophthalide unit is present in many pharmaceutically active compounds with analgesic, antithrombotic, and anticonvulsant properties. Consequently, the development of novel approaches to offer access to substituted thiophthalides is an active area of research. An efficient example of formal thio-Passerini reactions based on the coupling between isocyanide, carboxylic acid and thiocarbonyl surrogate in presence of multifaceted active titanium tetrachloride was developed first time by Vitale and colleagues (Scheme 14) [60]. When tert-butyl thiol is employed, a thiophthalide ensuing from a 1,5-Mumm rearrangement is isolated because of the deprotection of the tert-butyl group. Here, two-step procedure for three-component synthesis of thiophthalides involves the in situ formation of a sulfanyl-phthalide species by submitting 2-formyl benzoic acids to tBuSH and subsequent $TiCl_4$-mediated isocyanide insertion reaction (Scheme 14).

The double addition of Grignard reagents to isocyanides was studied for the construction of acyclic diamino alcohols, prenylated amino alcohols, and functionalized 2-aminomorpholines from various unsaturated electrophiles, aromatic Grignard reagents, and 2-lithiated 2-oxazolines mediated by $[Ti(OiPr)_4]$ (Scheme 15) [61]. The functionalized isonitrile partners are prepared in situ through lithiation of achiral and chiral 2-oxazolines in the presence of tert-butyllithium (1.0 equiv). The substrate scope was sufficiently examined and yields for the one-pot, multi-step process range from modest to good. The proposed mechanism shows the formation of titanaaziridine species as key intermediates via the double insertion of an isonitrile moiety into Ti−C bonds. The protolytic discharge of the secondary amine in the last step was established by workup with D_2O, causing quantitative deuteration of the isonitrile-derived carbon site.

The nanocomposite materials are important green catalysts for innovative industrial processes. Particularly, p-TSA modified TiO_2 nanoparticles with unique catalytic activity are used as strong acid catalyst to facilitate the organic transformations. Kumar et al. magnificently achieved the preparation of spirooxindoles spiroannulated with imidazo [4,5-c] [2,7]naphthyridines, imidazo[4, 5-b]thieno[2,3-d]pyridines, and imidazo[4, 5-c]isoquinolines via surface modified TiO_2 nanoparticles with p-TSA-catalyzed procedure involving merging of GBB transformation and its post-modification with Pictet–Spengler transformation in an aqueous medium (Scheme 16) [62]. Notably, existence of both Bronsted and Lewis acid sites are exist on the surface of TiO_2 nanoparticles and the acid strength is unusually augmented by the inductive effect on the S=O bonds are the best features of the present synthetic protocol. In the proposed mechanism, the initial step was the of catalyst facilitated formation of imine intermediate, which further experience attack of isocyanide followed by intramolecular annulation to generate cyclic adduct. The cyclic adduct then suffers aromatization

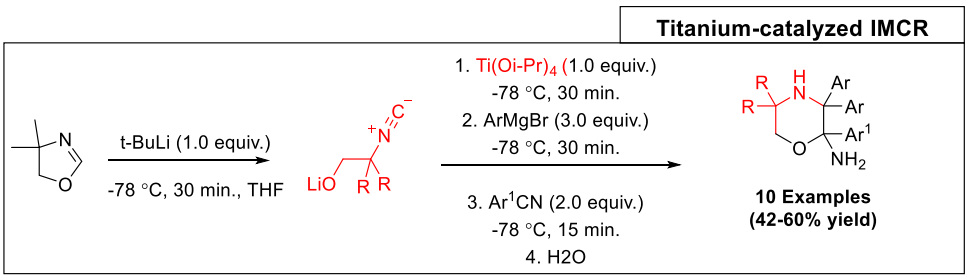
Scheme 13 Synthesis of α-amino amidesvia Ti-catalyzed Ugi-type MCR

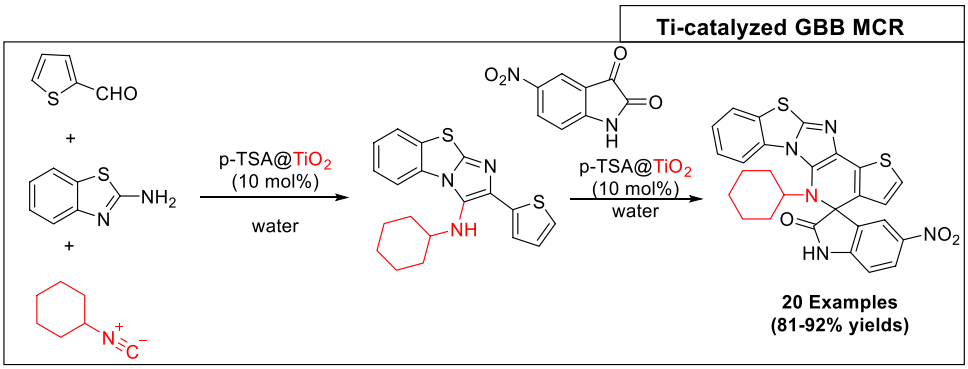




Scheme 14 Synthesis of thiophthalides via Ti-catalyzed formal thio-passerini reaction

Scheme 15 Synthesis of 2-aminomorpholines via Ti-catalyzed IMCR





Scheme 16 Synthesis of spirooxindoles via Ti-catalyzed GBB MCR

via 1,3-H shift to deliver the GBB product. Then post-modification including Pictet-Spengler reaction afford the desired product.

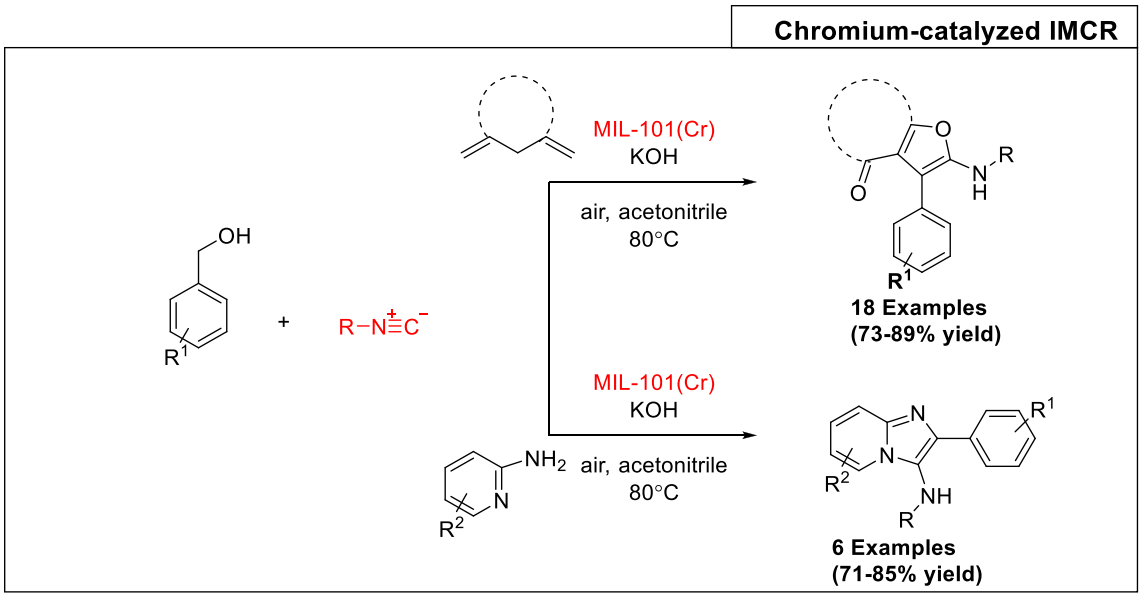
Chromium-catalyzed isocyanide-involving multicomponent reaction

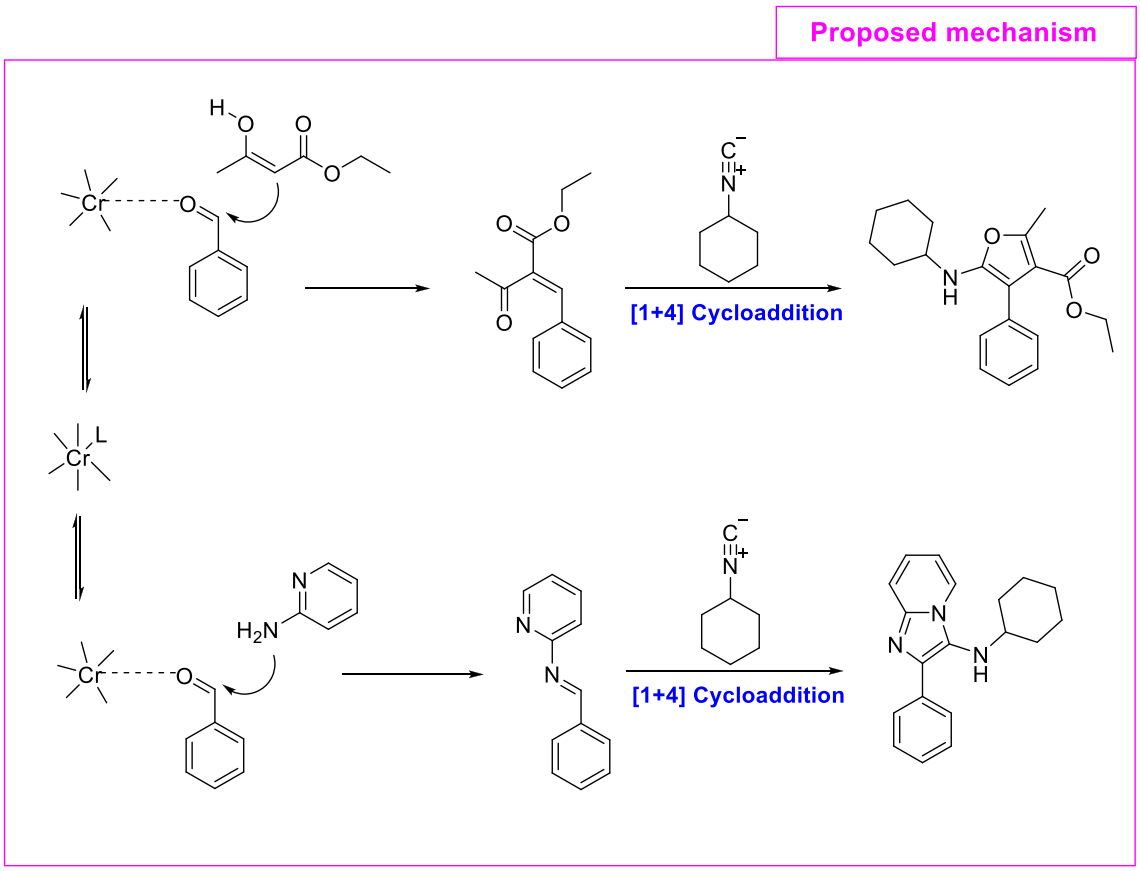
Metal–organic frameworks (MOFs) have been recognized as much fascinating, multifunctional materials with attractive characteristics including tunable pores, high surface area, and accessible and large accessible cages. In 2018, Shaabani and colleagues documented MIL-101(Cr)-catalyzed tandem oxidative three-component isocyanide-based cycloaddition methodology for the formation of two types of the heterocycles such as imidazopyridines and furans (Scheme 17) [63]. They used MIL-101(Cr) as the catalyst along with KOH in acetonitrile at 80 °C under air atmosphere for model reaction between benzyl alcohol, cyclohexyl isocyanide and N,N-dimethyl barbituric acid. Different solvents viz. dimethylsulfoxide, water, toluene, acetonitrile, n-hexane, 1,2-dichlorobenzene, and N,N-dimethylformamide were inspected and detected that acetonitrile was the superlative solvent for this conversion. Additionally, cyclohexyl isocyanide and 2-aminopyridine was reacted with benzyl alcohol to synthesize fully substituted furan derivatives under oxidation conditions. Mechanism investigation divulged that the conversion proceeds in the existence of the MIL-101(Cr) via in situ aerobic oxidation of benzyl alcohols to conforming benzaldehydes.

Mn-catalyzed isocyanide-involving multicomponent reaction

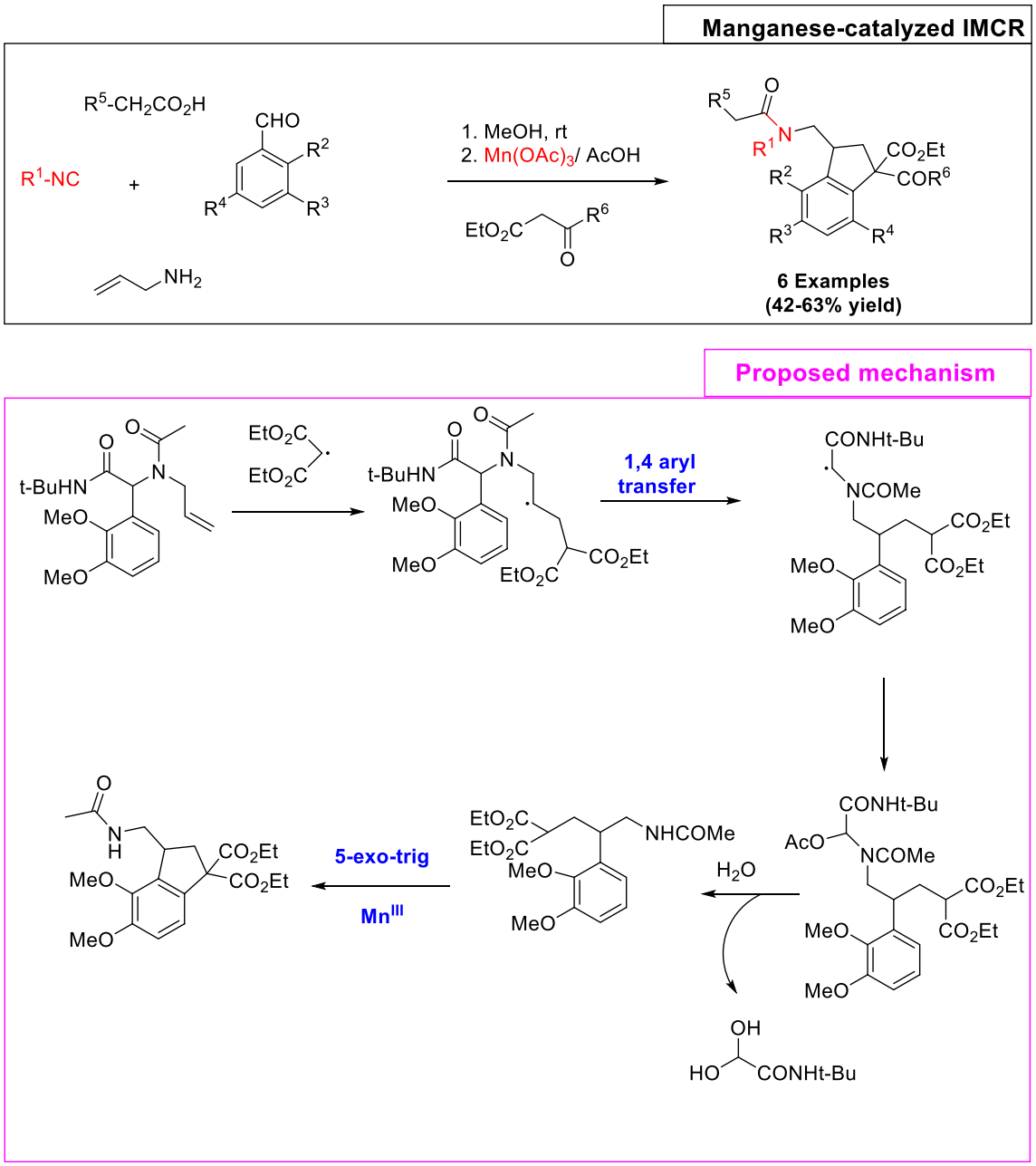
Indane derivatives are serving as active parts in various families of drugs such as antihypertensive, anti-HIV, and thrombin inhibitors. In 2007, Vieu and co-workers demonstrated an efficient manganese(III)-induced radical cascades for the synthesis of δ-amidomalonate and Indane scaffolds (Scheme 18) [64]. Initially, Ugi adduct are prepared by the reaction of tert-butylisocyanide, 2,3-dimethoxybenzaldehyde, allylamine, and acetic acid in methanol at room temperature, which further reacted with manganese acetate (6 equiv.) and diethylmalonate in refluxing acetic acid to access corresponding substituted indane skeleton. In place of malonyl group, this synthetic protocol was viable to other activated methylene derivatives such as ethylacetoacetate to deliver new indanes as a blend of diastereomer with low diastereoselectivity. Interestingly, employment of 4.5 equiv. of manganese acetate led to formation of the uncyclized malonate in decent yield. A reasonable mechanism of this transformation which operated via a sequential intramolecular aryl transfer/oxidative cleavage/cyclization pathway has been presented in Scheme 18.

In 2016, Shaabani and co-workers inspected oxidative domino three-component Ugi-type transformation of aromatic hydrocarbons of petroleum naphtha for the preparation of α-amino amides, 4H-benzo [b][1,4]thiazin-2-amine, 3,4-dihydroquinoxalin-2-amine, and cyanophenylaminoacetamide derivatives via employment of two biopolymers supported MnO_2 nanostructured catalysts which is very convenient from a practical viewpoint (Scheme 19) [65]. Interestingly, the double nature of the prepared MnO_2 nanocatalysts (acidic property and oxidation capability) is responsible for viability of this protocol. Primarily, in the step-1, toluene underwent oxidation in the existence of the MnO_2@wool–SO_3H or MnO_2@cellulose–SO_3H catalyst at reflux temperature. After cooling the reaction medium in the step-2, cyclohexyl isocyanide and 2-amino-5-methylphenol were allowed to interact in organic solvents to explore optimum conditions at room temperature. The reaction was also pertinent to o-phenylenediamine, 2-aminobenzamide, 2-aminothiophenol, and 2,3-diaminomaleonitrile. Fascinating products such as 4H-benzo [b][1,4]thiazin2-amines and 3,4-dihydroquinoxalin-2-amines were attained because of intramolecular nucleophilic attack of SH and NH moiety to the activated nitrile functionality. Particularly, the annulation product was not found in the case of 2-aminobenzamide and 2-amino-5-methylphenol.



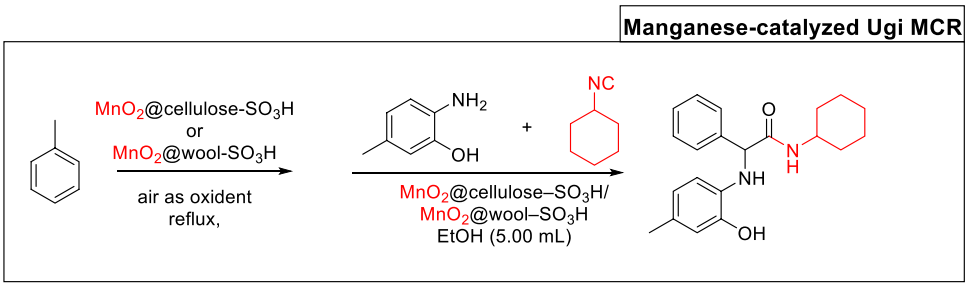


Scheme 17 Synthesis of imidazopyridines and furans via Cr-catalyzed IMCR

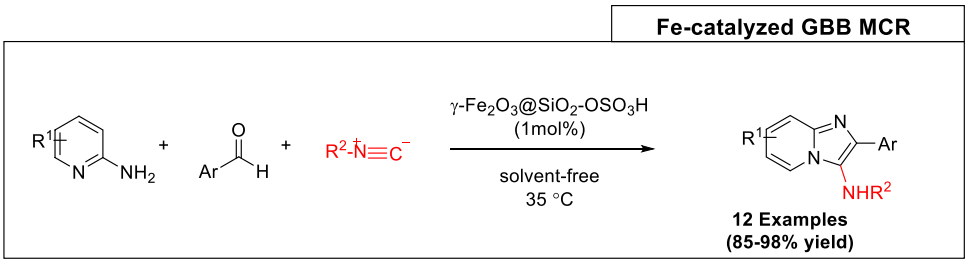


Scheme 18 Synthesis of δ-amidomalonate and indane via Mn-catalyzed IMCR

Scheme 19 Synthesis of α-amino amides via Mn-catalyzed Ugi MCR



Scheme 20 Synthesis of aminoimidazopyridines via Fe-catalyzed GBB MCR



Fe for isocyanide-involving multicomponent reaction

Much attention has been directed toward the assembly of magnetic nanoparticles since they have both fundamental and practical values due to their potential applications in chemical and materials science. The strategy of magnetic separation, taking benefit of magnetic nanoparticles, is naturally more operative than filtration or centrifugation as it avoids loss of the catalyst.

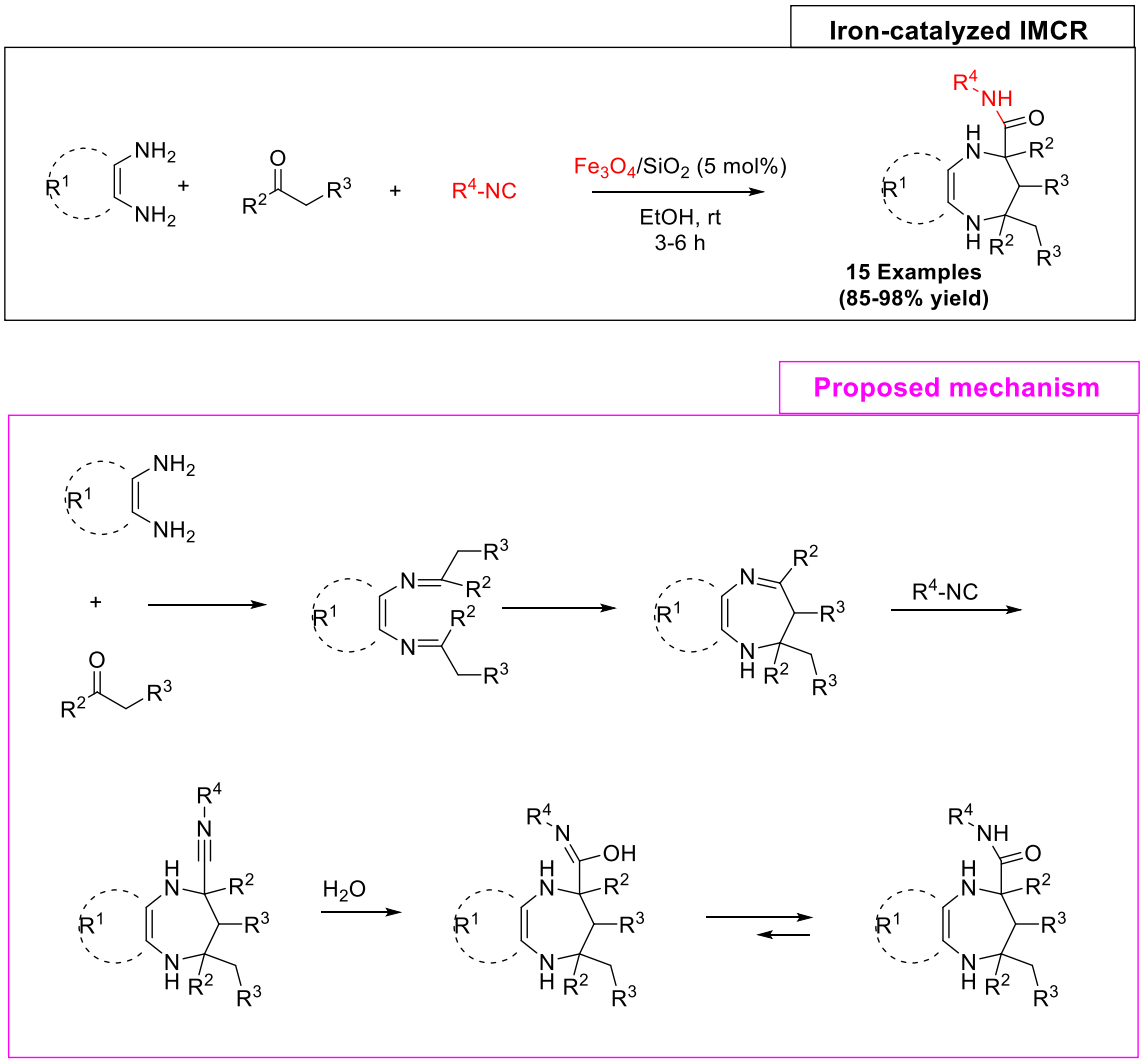
In 2012, another elegant and environmentally benign one-pot γ-Fe_2O_3@SiO_2-OSO_3H (nanomagnetically modified sulfuric acid)-catalyzed three-component GBB transformation has been proposed in which of 2-amino-heterocycles react with aldehyde and isocyanide to get aminoimidazopyridine scaffolds without any additives (Scheme 20) [66]. In this protocol, reaction was catalyzed by acid functionality and Fe_2O_3 perform as magnetic segment for easy seperation and recyclablity. The optimized conditions for this transformation is: γ-Fe_2O_3@SiO_2-OSO_3H (1 mol%) as the catalyst under solvent-free medium at 35 °C for 1 h. They accomplished the preliminary reaction using 2-aminopyridine, benzaldehyde and cyclohexyl isocyanide as typical substrates. Remarkably, low yield was detected when the reaction was executed in the presence of other solvents such as CH_2Cl_2, MeOH, EtOH, and H_2O. Moreover, benzaldehyde containing electron-poor functionalities such as nitro and chloro were found compatible with this method.

The first accomplishment to synthesize structurally useful diazepine derivatives via silica-supported iron oxide nanoparticles (Fe_3O_4/SiO_2)-catalyzed one-pot multicomponent reaction of isocyanide, 1,2-diamine, and linear or cyclic ketone was divulged from the laboratory of Maleki (Scheme 21) [67]. The optimized reaction conditions for benchmark reactions involving acetone (2 mmol), o-phenylenediamine (1 mmol), and benzylisocyanide (1 mmol) were found as: Fe_3O_4/SiO_2 nanoparticles (0.05 mmol) as the catalyst in ethanol as the solvent at room temperature for 5 h. They reported a wide series of substrate scopes of isocyanide, e.g., benzyl-, cyclohexyl-, 1,1,3,3-tetramethylbutyl-, 2,6-dimethylpheny-l, and tert-butyl-isocyanide as a coupling partner. It was also observed that this reaction was highly regioselective in the instance of asymmetric aromatic diamines as the 1,2-diamine partners. Mechanistically, the initial formation of a diimine in the existence of S-MMNPs followed by its intramolecular imine-enamine cyclization was proposed.

In 2013, a unique one-pot tactic to access the diazepine derivatives via silica-supported superparamagnetic iron oxide nanoparticles-catalyzed multicomponent reaction of isocyanide, terminal alkynes, and 1,2-diamines in ethanol as a green reaction media was introduced by Maleki (Scheme 22) [68]. Operational simplicity, easy work-up procedure, a broad substrate scope, excellent yields, reusability of the catalyst and high atom economy are the advantages of present procedure. Firstly, in step-1, 2,3-diaminomaleonitrile is treated with phenyl acetylene in the existence of Fe_3O_4/SiO_2 nanocatalyst in ethanol at room temperature to form intermediate. In the step-2, the intermediate is reacted with cyclohexyl isocyanide under same condition to provide target product. Remarkably, nanocatalyst was washed with EtOH, air-dried, and used directly in subsequent cycles without additional purification.

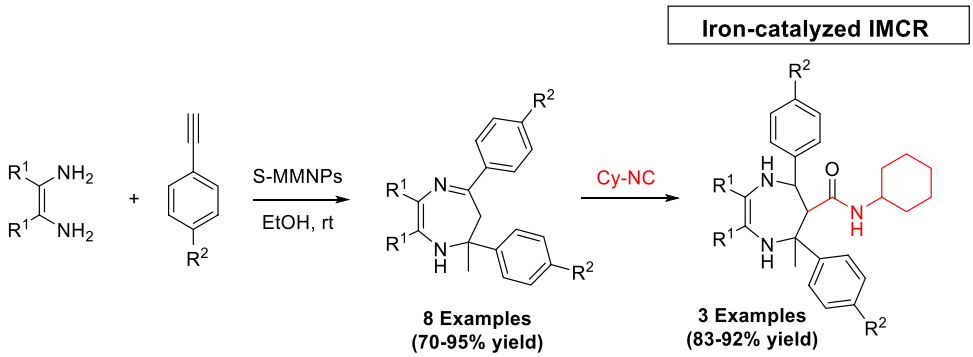
In 2015, Dianat et al. documented a γ-Fe_2O_3-HAp-$(CH_2)_3$-$NHSO_3H$ (sulfamic acid functionalized hydroxyapatite encapsulated γ-Fe_2O_3 nanoparticles) catalyzed synthesis of innovative conjugated imidazo[2,1-b]thiazol-quinoline and imidazo[1,2-a]pyridine derivatives under solvent-free condition (Scheme 23) [69]. They employed tert-butyl isocyanide (1.2 mmol), pyridin-2-amine (1 mmol) and 2-chloro-3-formyl quinolone (1 mmol) as a model substrate with γ-Fe_2O_3-HAp-$(CH_2)_3$-$NHSO_3H$ (10 mg) as the catalyst at 40 °C for 2 h. The catalyst was simply detached by an external magnet after completion of reaction. They mentioned a wide range of substrate scopes of pyridin-2-amines. Various substitutes such as methyl, bromide, chloride were endured nicely in this method.

In 2013, Shaabani's group developed an outstanding methodology for the synthesis of 3-aminoimidazo[1,2-a] pyridine derivatives through a condensation reaction of aryl or alkyl isocyanide aldehyde, and 2-aminopyridine in the existence of a catalytic quantity of cellulose@Fe_2O_3 as a magnetically recoverable heterogeneous catalyst (Scheme 24) [70]. Among the various tested solvents such as toluene, DCM, acetonitrile, and methanol, the best result was obtained by utilizing methanol at reflux



Scheme 21 Synthesis of diazepines via Fe-catalyzed IMCR

Scheme 22 Synthesis of diazepines via Fe-catalyzed IMCR



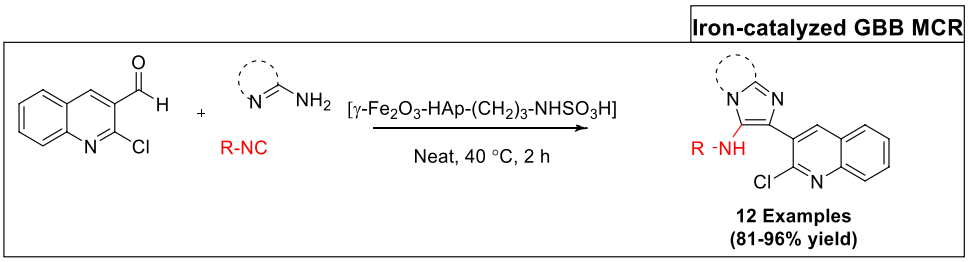
temperature and no product was formed in the water. The unique advantages of the present approach are simple procedure, easy work-up, use of reusable catalyst, and cleaner reaction.

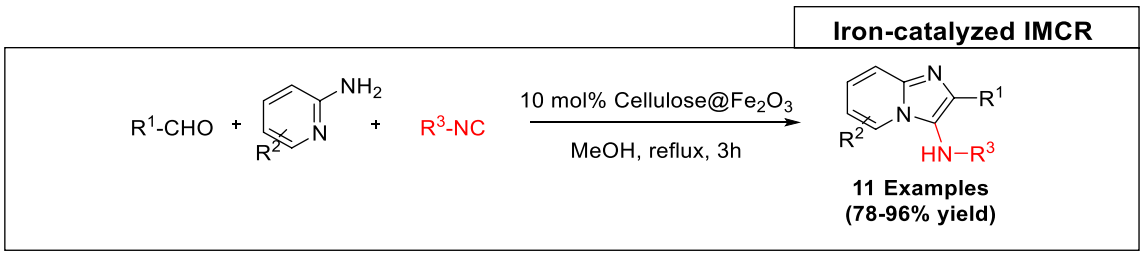
In conceivable mechanism, the initial event is cellulose@Fe_2O_3 catalyzed condensation between aldehyde and 2-aminopyridine to produce imine. Then, [4 + 1] cycloaddition between isocyanide and imine led to formation of the

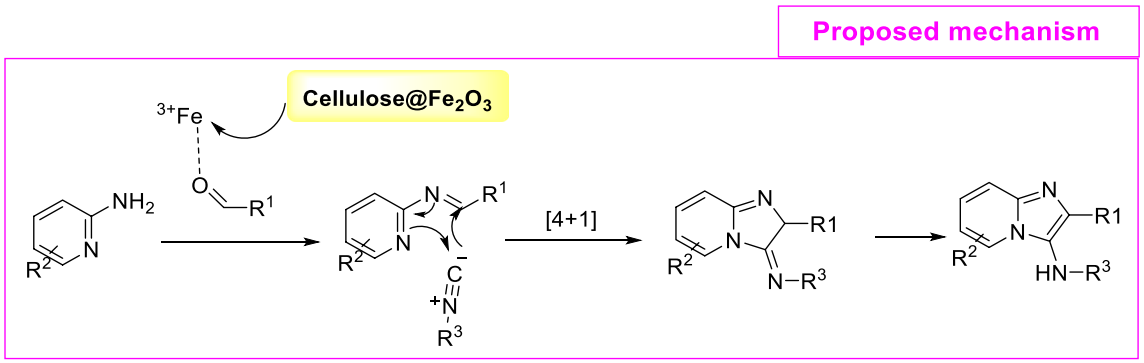
bicyclic adduct, which underwent rearomatization via 1,3-H shift to deliver target product.

In 2015, Batra et al. reported an efficient example of one-step Ugi-type three-component reaction technique using (arylmethyl)amines as the imine precursor to access a library of α-acylamino amides under air as an environmentally benign oxidant (Scheme 25) [71]. Optimization study for the model reaction between benzoic acid (1.0 equiv.), benzylamine (2.0 equiv.), and tert-butylisonitrile (1.0 equiv.) revealed that $Fe(NO_3)_3{\cdot}9H_2O$ (10 mol%) as the catalyst, and TEMPO (10 mol%) in acetonitrile at 70 °C under air atmosphere for 24 h delivered the best outcomes affording the anticipated product in 82% isolated yield. Compared to iron catalysts like $FeCl_3{\cdot}6H_2O$, $Fe(acac)_3$, $Fe_2(SO_4)_3$ and $FeBr_3$; $Fe(NO_3)_3{\cdot}9H_2O$ was exemplary and delivered the superlative yield for the aforesaid reaction. In this technique, both electron-deficient and electron-rich

Scheme 23 Synthesis of N-fused imidazole-quinoline via Fe-catalyzed GBB MCR

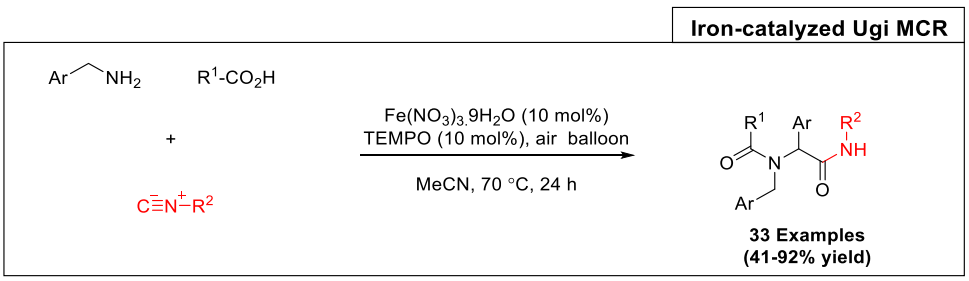


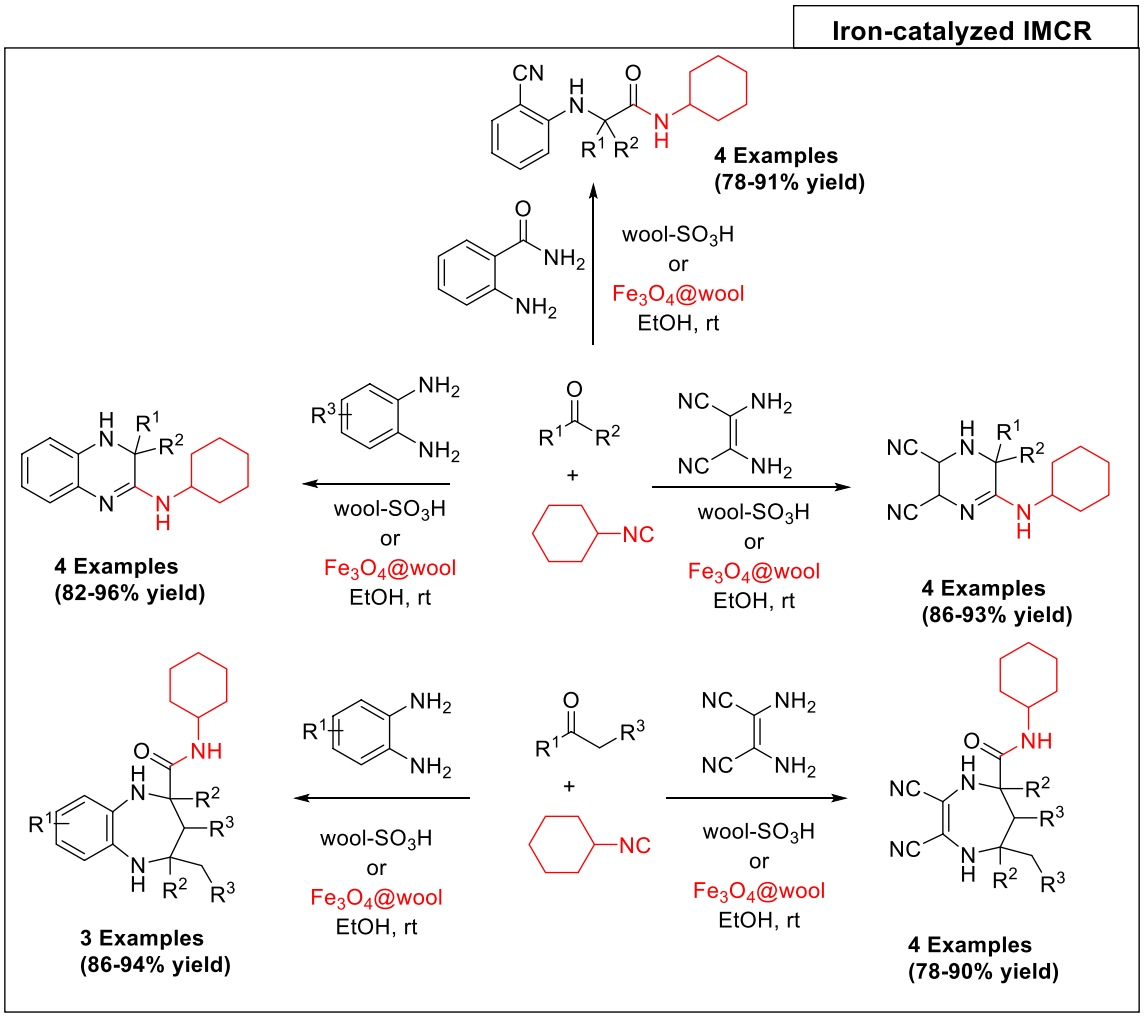




Scheme 24 Synthesis of 3-aminoimidazo[1,2-a]pyridines via Fe-catalyzed IMCR

Scheme 25 Synthesis of α-acylamino amides via Fe-catalyzed Ugi MCR





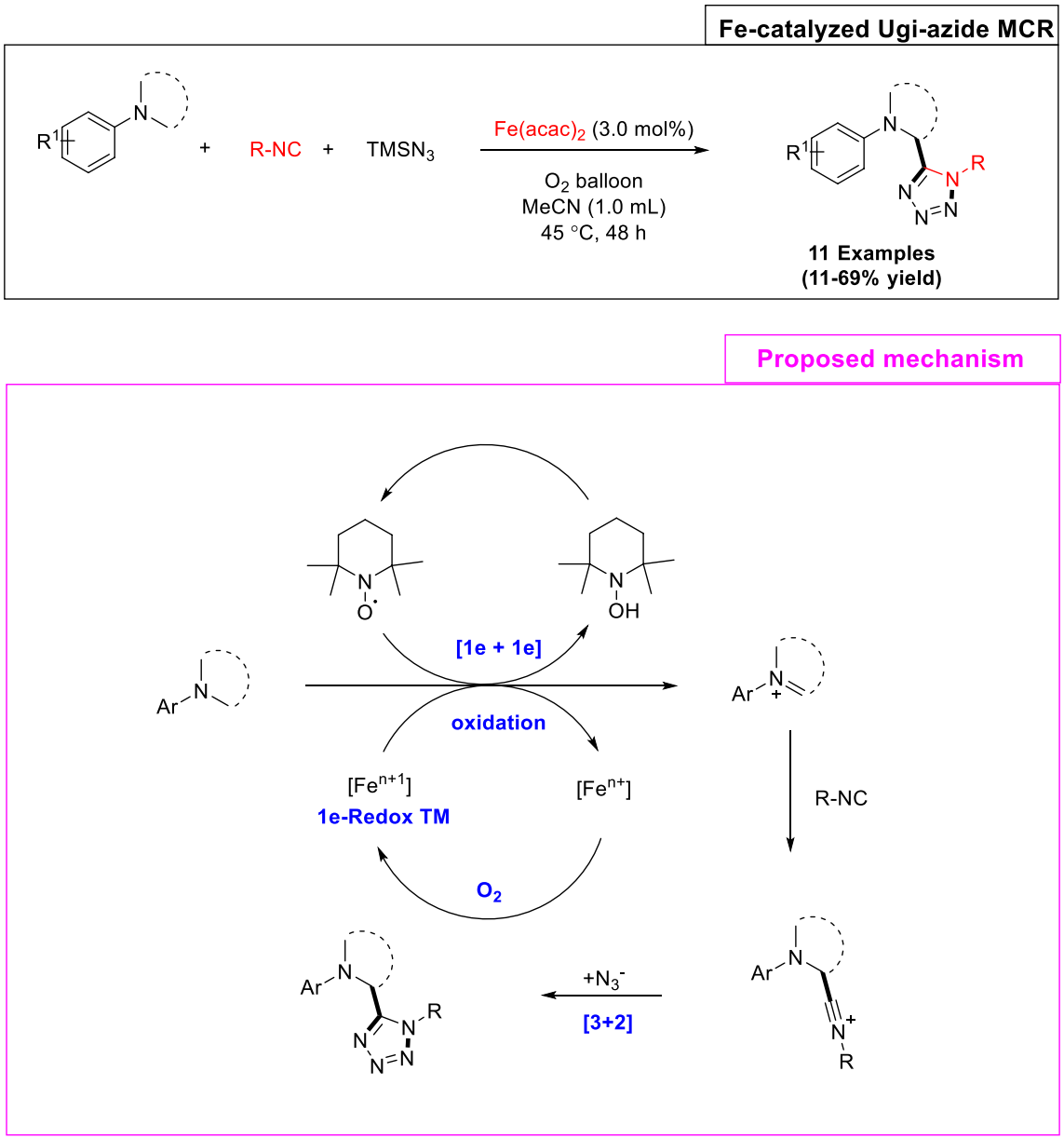
Scheme 26 Synthesis of N-heterocycles via Fe-catalyzed IMCR

groups existing on the benzylamine worked better and afforded the anticipated products in decent yields.

In 2019, Shaabani and coworkers demonstrated wool-supported Fe3O4 nanoparticles (nano-Fe_3O_4@wool)- or natural wool sulfonic acid (wool-SO_3H)- catalyzed multicomponent annulation of isocyanide with amine and carbonyl compound for the preparation of (cyanophenylamino)acetamide, tetrahydro-1H-1,5-benzodiazepin-2-carboxamide, 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazin-2,3-dicarbonitrile, and 4,5,6,7-tetrahydro-1H-1,4-diazepin-5-carboxamide derivatives (Scheme 26) [72]. The biodegradable catalytic system with exceedingly loaded Fe_3O_4 nanoparticles was straightforwardly prepared and characterized by flame atomic, thermogravimetric analysis, X-ray diffraction, and scanning electron microscopy absorption spectroscopy. Substrate scope exploration divulged the effective reaction of both electron-poor and electron-rich substituted carbonyl compounds, affords the corresponding products in decent yields.

In 2020, Lei and colleagues divulged base metals (copper- or iron)-catalyzed Ugi-azide multicomponent reaction of tertiary amines with isocyanide and azido trimethylsilane under mild conditions for the construction of α-aminotetrazole derivatives (Scheme 27) [73]. Generally, this iron-catalyzed procedure involves the combination of 3 mol% $Fe(acac)_2$ as the catalyst, 10 mol% TEMPO as the additive in acetonitrile as the solvent at 45 °C under oxygen atmosphere for 48 h to promote the formal C(sp^3)-H activation of the tertiary amines obviating the pre-functionalization. Fascinatingly, alkyl isocyanides showed impressive diversity. Adamantyl and cyclohexyl isocyanides successfully underwent the MCR to the N-substituted tetrazoles (25–69%) with good yields in this tactic.

Regarding the reaction mechanism, TEMPO mediated oxidation of tertiary amine would be the initial step, which is followed by the addition of isocyanide to afford a nitrilium ion (II) intermediate. In the further intermolecular [3 + 2] annulation process, α-tetrazolo motif is generated.

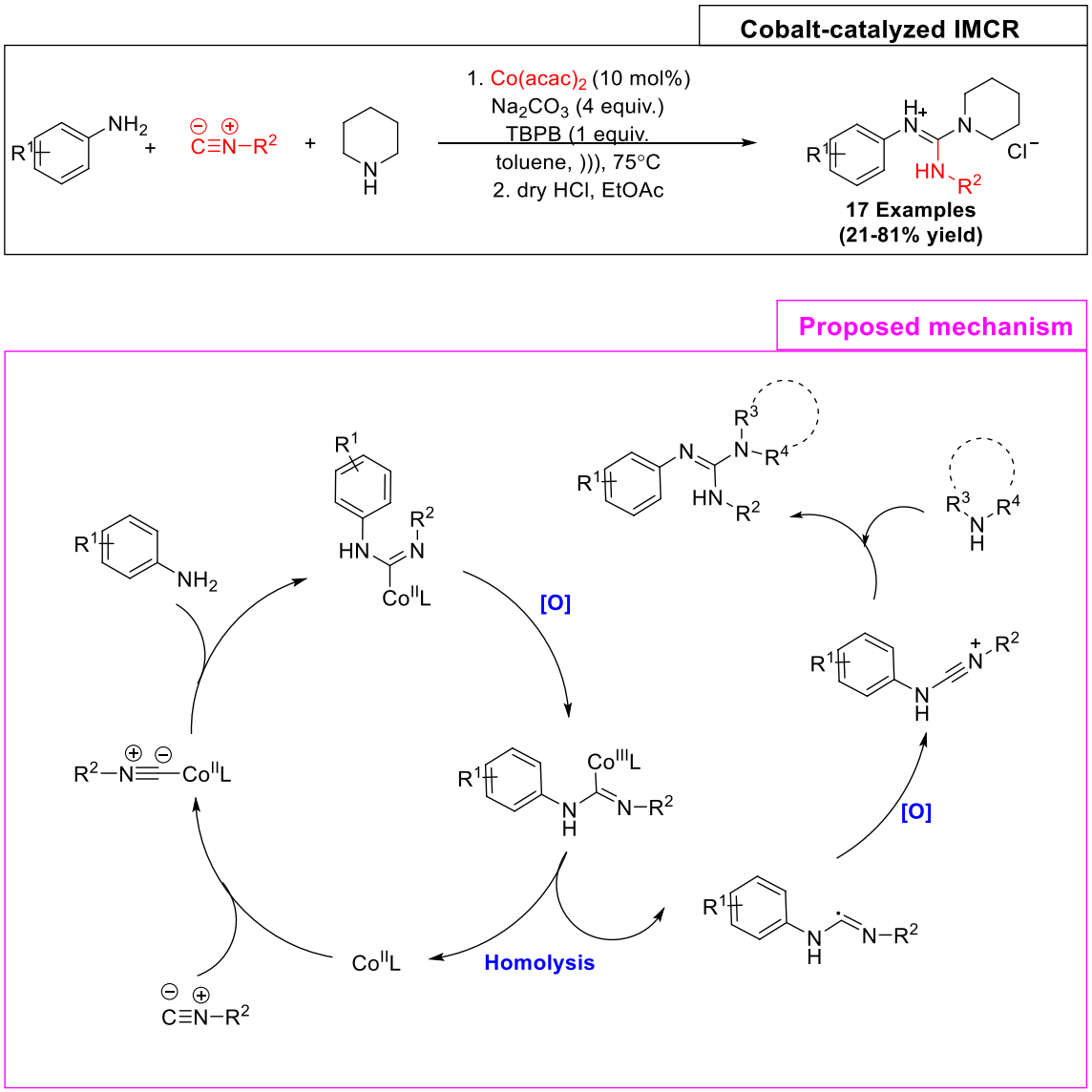


Scheme 27 Synthesis of α-aminotetrazoles via Fe-catalyzed Ugi-azide MCR

Co-catalyzed isocyanide-involving multicomponent reaction

An efficient and innovative method for oxidative isocyanide insertion with amines in existence of $Co(acac)_2$ catalyst via two C-N bond construction reactions was advanced by Ji and co-workers (Scheme 28) [74]. In this approach, catalytic system was irradiated by ultrasound at 75 °C for a suitable time. The scope of the transformation was also considered with substituted aniline in which the presence of electron-rich functionalities at the para-position of the phenyl moiety could provide consistent products in decent yields. Though, the yields fall to 21% and 39% with anilines containing electron-deficient groups like NO_2 and CN. A reasonable reaction cycle was projected which is started by formation of more stable Co(II) carbene complex from Co(II) complex, which suffers oxidation to generate the cobalt(III) complex. This intermediate then undergoes homolysis to provide the active imidoyl radical followed by the oxidation to nitrilium intermediate. Lastly, nitrilium ion is stacked by amine and isomerization, furnishing the target product.

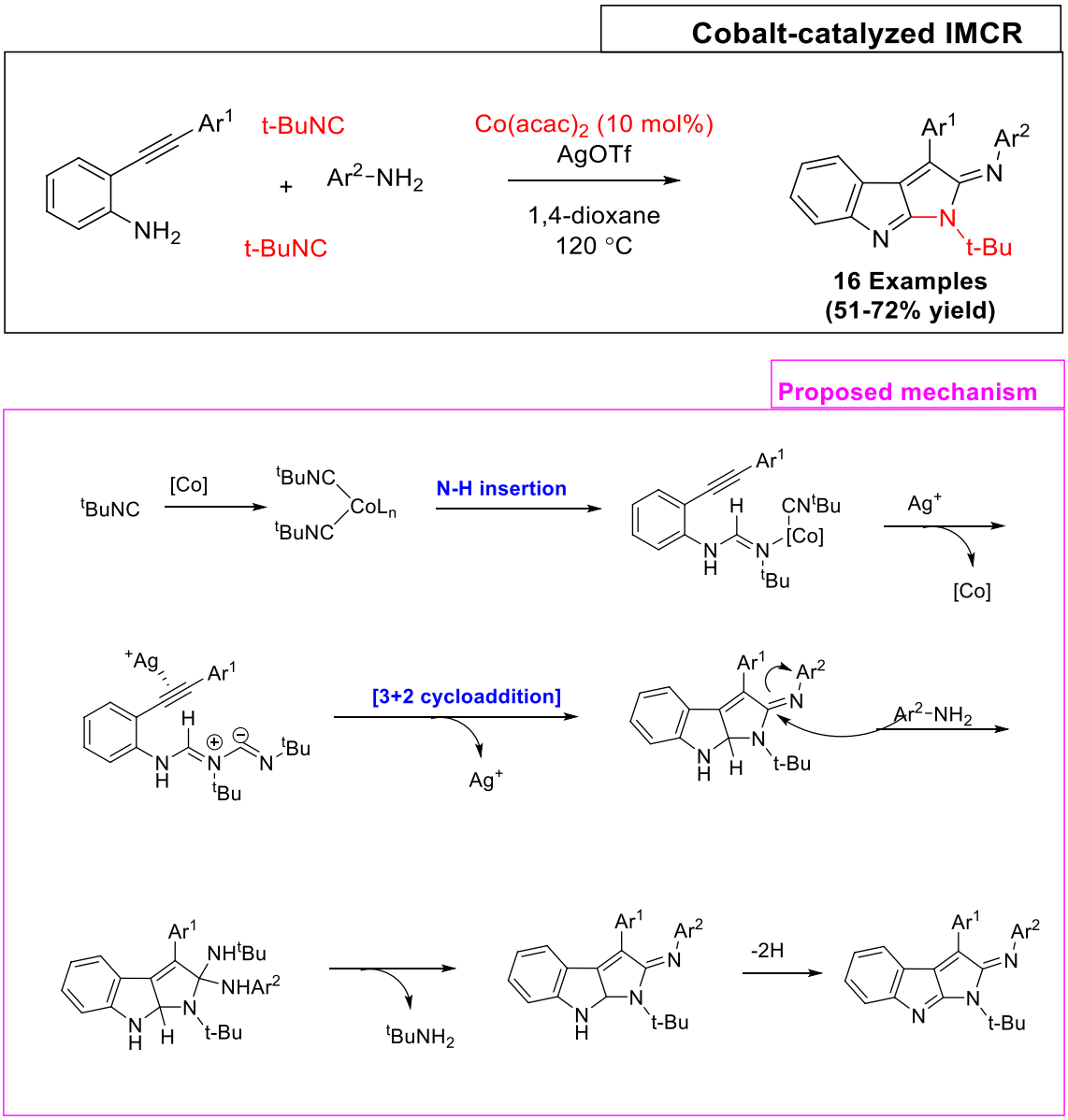
A chemoselective synthetic way to aryliminatedpyrrolo[2,3-b]indole derivatives was developed by a single-pot reaction of arylamines, 2-ethynylanilines, and tert-butyl isocyanide, which proceeds through dual cobalt(II)/silver catalysis (Scheme 29) [75]. One molecule



Scheme 28 Synthesis of guanidines via Co-catalyzed IMCR

of arylethynylaniline, two molecules of isocyanides and one molecule of aryl amine are combined into the targeted products in this protocol. The scope of the aryl amines component was discovered. It was observed that the conversions of anilines bearing electron-rich, -neutral, and electron-deficient substituents at the para-positions of the phenyl moiety proceed smoothly to furnish the series of highly substituted pyrrolo [2,3-b]indoles in 53–67% yields. The mechanistic pathway revealed that the ligated isocyanide undergoes insertion into N–H bond of arylethynylanilines to form enyne-imine, which is transformed into 1,3-dipoles. Subsequently, intramolecular 1,3-dipolar cycloadditions yielded pyrrolo[2,3-b]indole species, trailed by imination substitution with arylamines to furnish aimed product through dihydrogen.

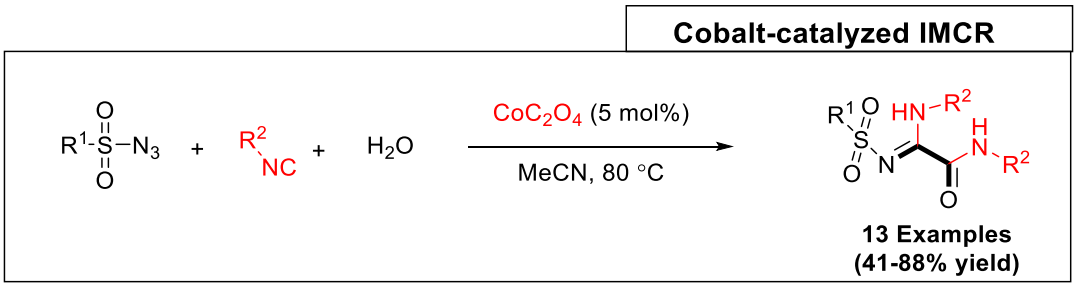
Wang and Ji achieved the preparation of 3-imine indole and sulfonylamidyl amide with high chemoselectivity through a CoC_2O_4-catalyzed psuedo four component coupling of isocyanides, water and sulfonyl azides (Scheme 30) [76]. It was observed that the optimal reaction conditions include CoC_2O_4 (5 mol%) as the catalyst in acetonitrile solvent under air atmosphere at 80 °C and product could be formed in 92% LC-yield. Electronic effects have noteworthy impact on the productivity of the reaction. Although the halogen-substituted benzenesulfonyl azides could deliver good yields, those with electron-rich groups offered inferior yields. To ascertain whether the oxygen atom of carbonyl comes from H_2O, $H_2{}^{18}O$ was added instead of H_2O under standard conditions.

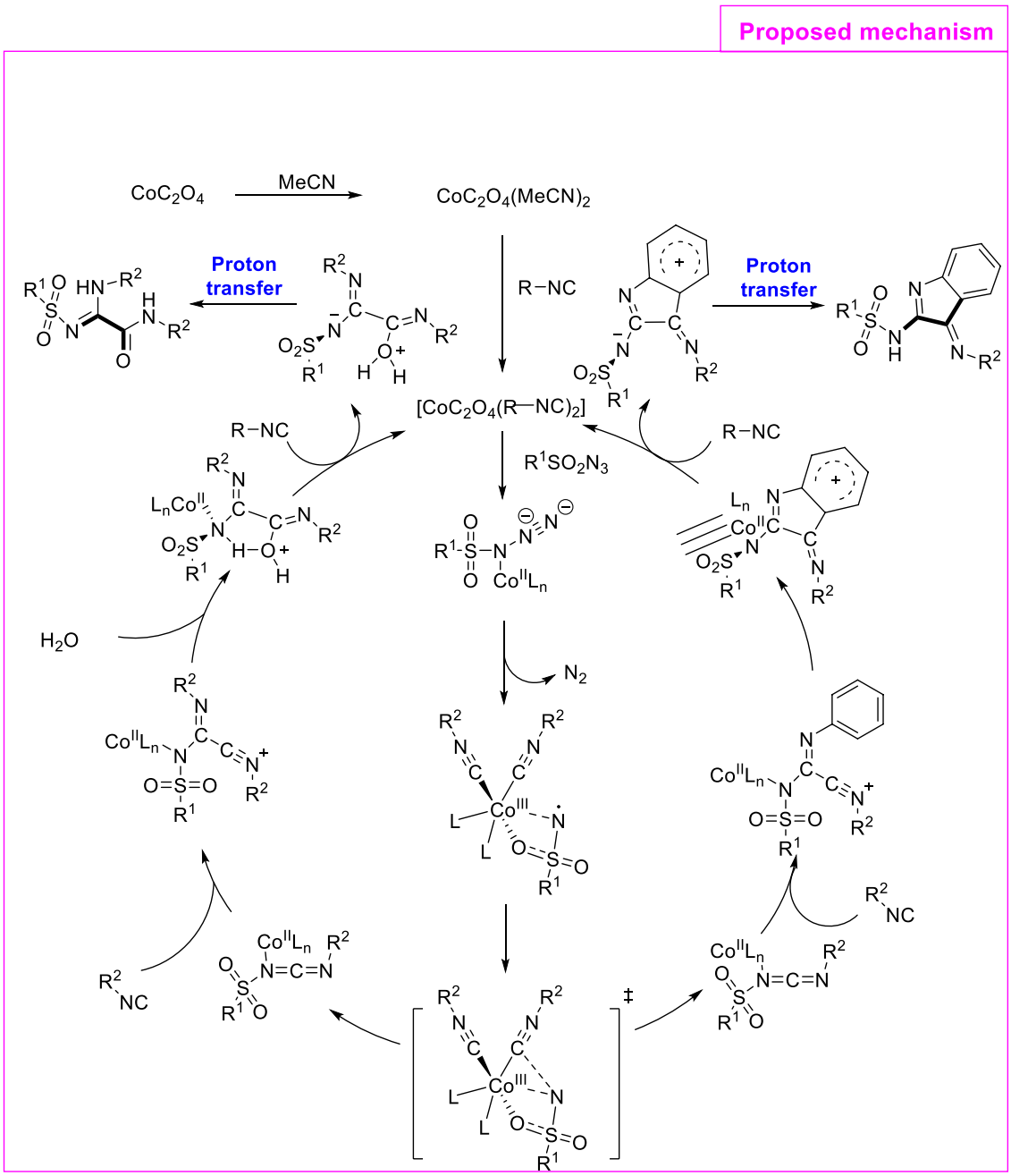


Scheme 29 Synthesis of aryliminatedpyrrolo[2,3-b]indoles via Co-catalyzed IMCR

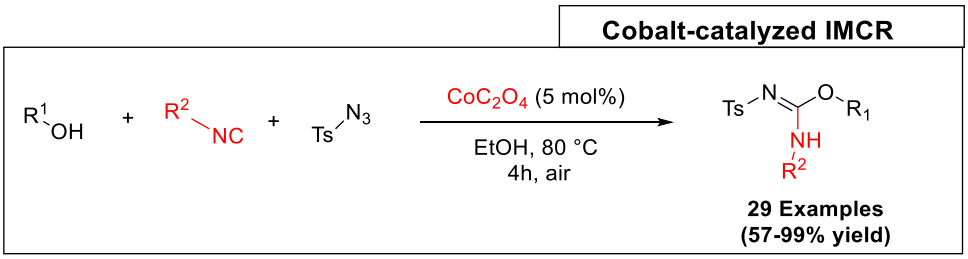
Since isourea moieties have gained significant concern of scientific society, Ji et al. unveiled a single-pot multi-component strategy for synthesis of sulfonyl isoureas via nitrene intermediate by interacting isocyanides, sulfonyl azides and alcohols under mild conditions with 5 mol% of CoC_2O_4 catalysis (Scheme 31) [77]. About 90% yield was attained when the transformation was performed under air atmosphere at 80 °C in existence of ethanol as solvent. Other metal catalysts, such as $Cu(OAc)_2$, $Pd(OAc)_2$, $PdCl_2$, were proven to be unproductive for this conversion. The reactions of adamantanyl isocyanide and cyclohexyl isocyanide with tosylazide ensued smoothly furnishes the desired products in admirable yields. Regrettably, when n-butylisocyanide was exposed to the conversion, only traces of the anticipated products were noticed owing to the decomposition of isocyanide under optimized conditions.

An innovative procedure for the preparation of sulfonyl guanidines was revealed (Scheme 32) [78]. The cascade reaction of sulfonyl azides with anilines and o-diisocyano arenes using 5 mol% of $Co(acac)_2$ in MeCN with 100 µl water at 80 °C for 6 h dispensed the anticipated product in average to decent yields. The heterocyclic sulfonyl azides such as thiophene-2-sulfonyl azide and pyridine-3-sulfonyl azide exhibited a comparable reactivity and the product gained in 66% and 79% yields, respectively. It is notable that the anticipated product could not be gained





Scheme 30 Synthesis of sulfonylamidyl amides via Co-catalyzed IMCR



Scheme 31 Synthesis of sulfonyl Isoureas via Co-catalyzed IMCR

with pyrimidin-2-amine, while this strategy is applicable to naphthalen-2-amine, provides the conforming product in 33% yield.

The straightforward multi-component reaction between amines, isocyanides, and diazo compounds as carbene sources using $CoBr_2$ as catalyst has been reported (Scheme 33) [79]. This atom- and step-economic approach offered synthetically appreciated, substituted derivatives of amidines in excellent yields. Dinitrogen (N_2) is formed as the only side-product. To demonstrate the practical efficacy of this approach, the reaction was also executed on a gram scale, and the final product was obtained in 81% yield (1.45 g). When the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was incorporated into the reaction blend under standard conditions, only trace amount of anticipated product was found, suggesting that radical process may intricated under this cobalt-catalysis.

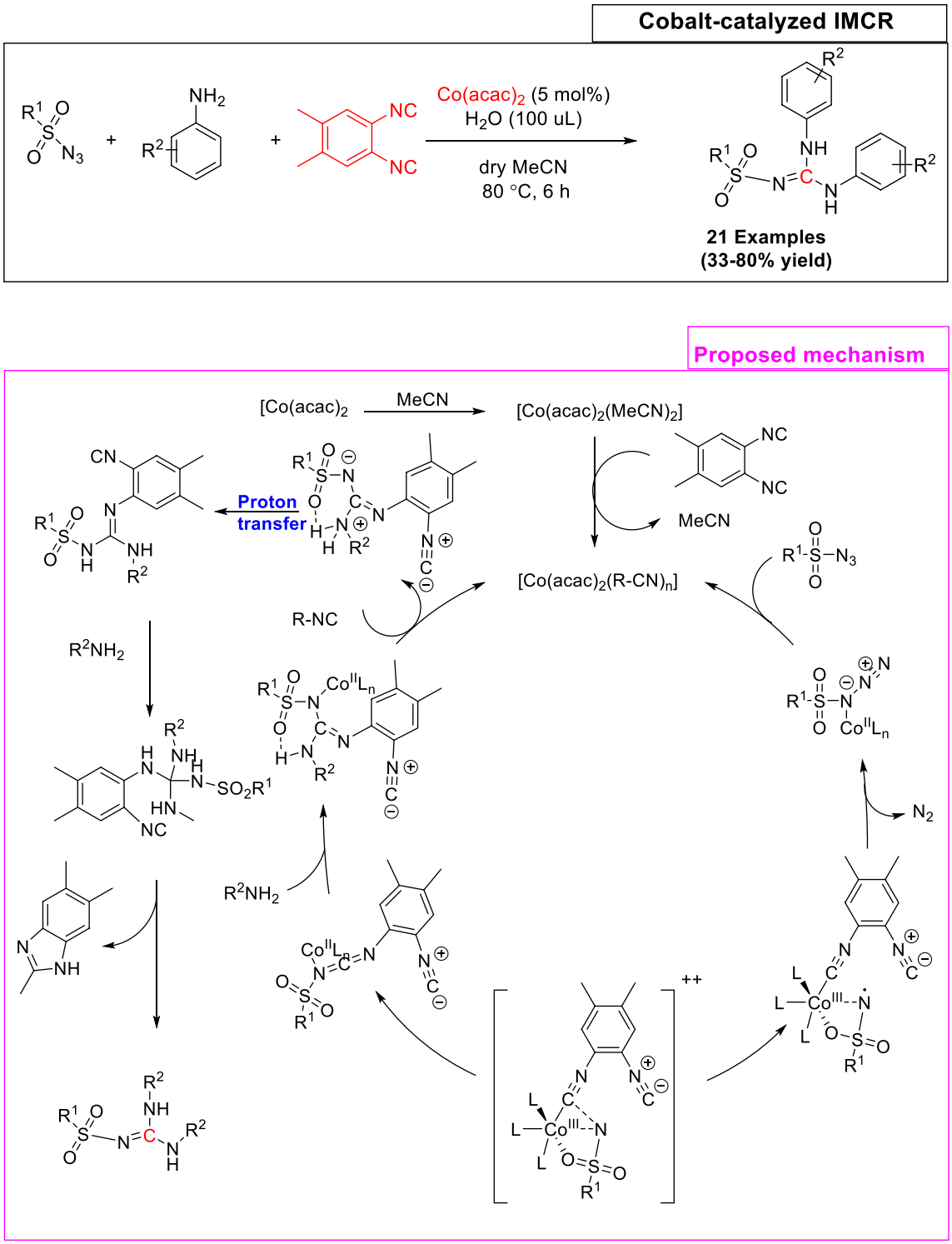
Ni-catalyzed isocyanide-involving multicomponent reaction

The alkyl amide moiety is present in numerous medicines, polymers, agrochemicals, and terrestrial products and many of which keep powerful biological activity. Previously reported aminocarbonylation of unactivated alkyl halide via palladium-catalysis necessitates the use of high energy irradiation, high-pressure CO gas, multiple CO insertion, and poisonous organotin initiators. The ability of nickel catalyst to promote recognized aminocarbonylation of secondary and primary unactivated aliphatic iodides with isocyanides has been demonstrated for the first time which led to the synthesis of alkyl amide derivatives (Scheme 34) [80]. Furthermore, the convenient construction of alkyl carboxylic acid was achieved through single-pot hydrolysis of reaction blends under acidic environments. The tentative mechanism of this protocol follows the discerning mono migratory insertion of isocyanides with alkyl iodides, succeeding β-hydride elimination, and hydrolysis step.

Despite the prevalence of phenylacetamide as functional moiety in organic chemistry and its nifty role as building blocks in natural products, drugs, and bulk chemicals, the method for the synthesis of α-position substituted phenylacetamides with restricted steric hindrance are limited. In this regard, secondary benzyl chlorides derivatives on treatment with tert-butyl isocyanide as the carbonyl and amine surrogate in presence of catalytic system made up of 1.5 equiv. NaOtBu and 10 mol% $Ni(cod)_2$ in toluene experienced aminocarbonylation reaction at 100 °C affording a range of phenylacetamides in good yields (Scheme 35) [81]. The existence of functional groups, such as fluorine, chlorine and bromine on various aromatic as well as heteroaromatic rings (pyridine and pyrazine) were nicelyendured under optimized environments. The existence of these groups in the products offers prospects for subsequent synthetic manipulation.

In 2020, Zhou and his group members developed the single-pot preparation of various amide derivatives in average to admirable yields (Scheme 36) [82]. Initially, the reaction of tert-butyl isocyanide, 2-bromonaphthalene, and H_2O was accomplished in toluene at 120 °C to generate the desired product. Combination of bench-stable 10 mol% $NiCl_2$(dppp), 20 mol% NHC ligand and 2 equiv. tBuONa can initiate this conversion, therefore permitting easy process and adding practical worth. Different kinds of nitrogen nor phosphine ligands were investigated but could not promote the reaction at all. Substrate scope studies disclosed an extensive functional group acceptance and generalization of aryl triflates, and organic halides (including aryl, alkenyl, and allyl halides) in this protocol.

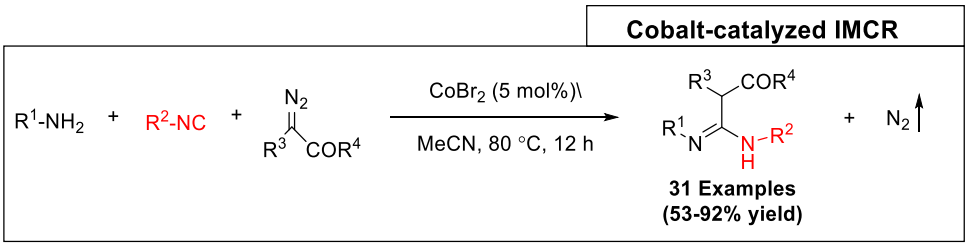
In 2020, Liu, Zhou, and colleagues have proposed that an innovative multi-component coupling reaction between isocyanides, alkyl halides, and H_2O in acetonitrile under nickel-catalysis could produce the alkyl amides derivatives in good yields (Scheme 37) [83]. The preliminary reaction of tert-butyl isocyanide, (3-bromopropyl)benzene, and H_2O in presence of 10 mol% $NiCl_2$(dppp), and 2 equiv. tBuONa at 40 °C for 22 h afforded the amide product in 92% yield. The employment of 4,4′-di-tert-butyl-2,2′-bipyridine, 1,10-phenanthroline, and NHC salt did not make any positive effect on the reaction. Meanwhile, various functional groups such as bromo, chloro, fluoro, formyl and acetyl were well tolerable, and the steric and electronic nature of the substituents did not display noticeable effect on the yield. Some control experiments were executed to realize the mechanistic pathway of this reaction. The sharp decrease in yield was observed when reaction was carried out in presence of well-known radical

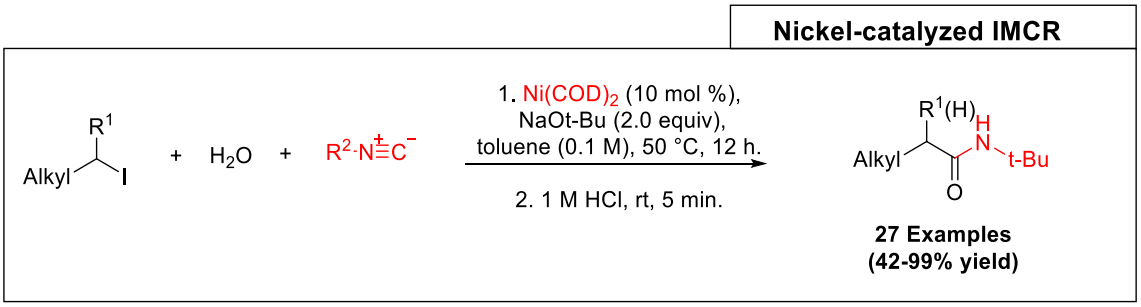


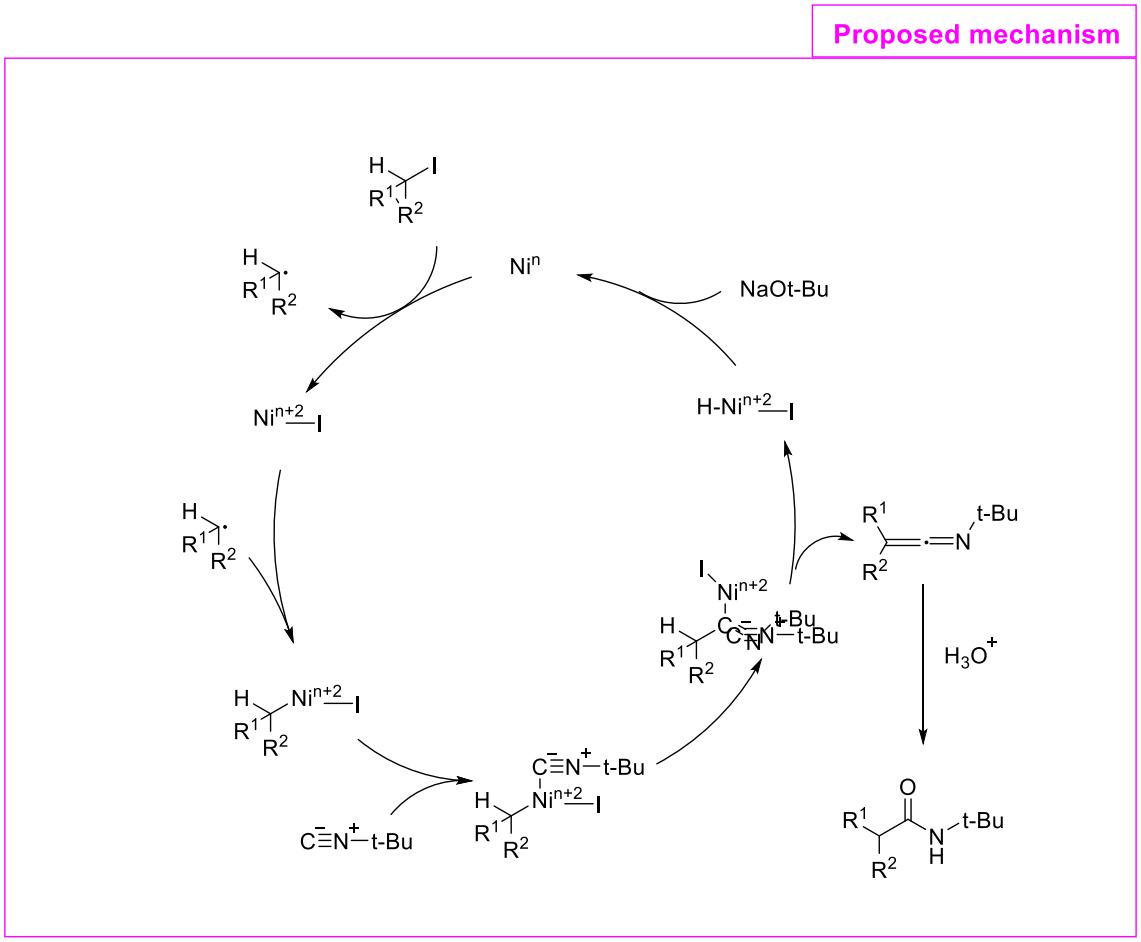
Scheme 32 Synthesis of N-sulfonyl guanidines via Co-catalyzed IMCR

inhibitors, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), indicating that the reaction might follow a SET (single-electron transfer) route. Furthermore, a result of radical clock experiment suggested that an alkyl radical intricated in this process. A detailed mechanistic route is delineated in Scheme 35.

Scheme 33 Synthesis of amidines via Co-catalyzed IMCR

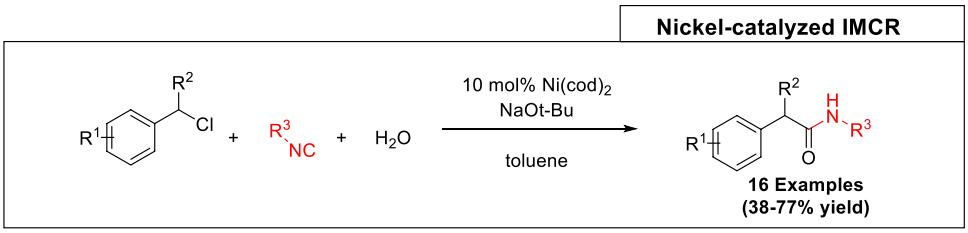




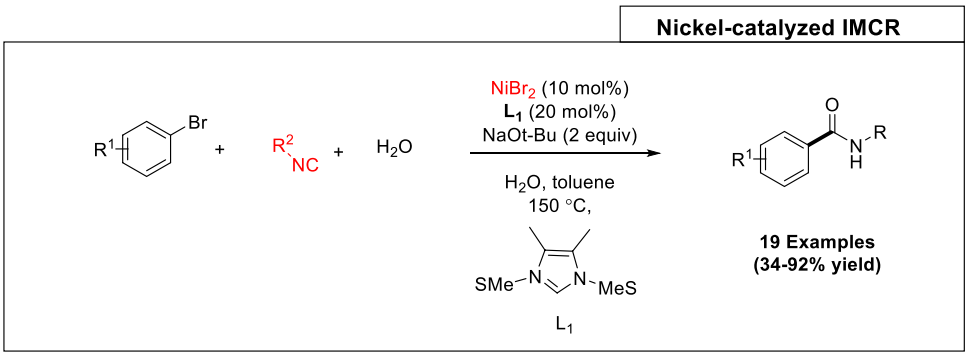


Scheme 34 Synthesis of alkyl amides via Ni-catalyzed IMCR

Scheme 35 Synthesis of α-substituted phenylacetamide via Ni-catalyzed IMCR



Scheme 36 Synthesis of amides via Ni-catalyzed IMCR



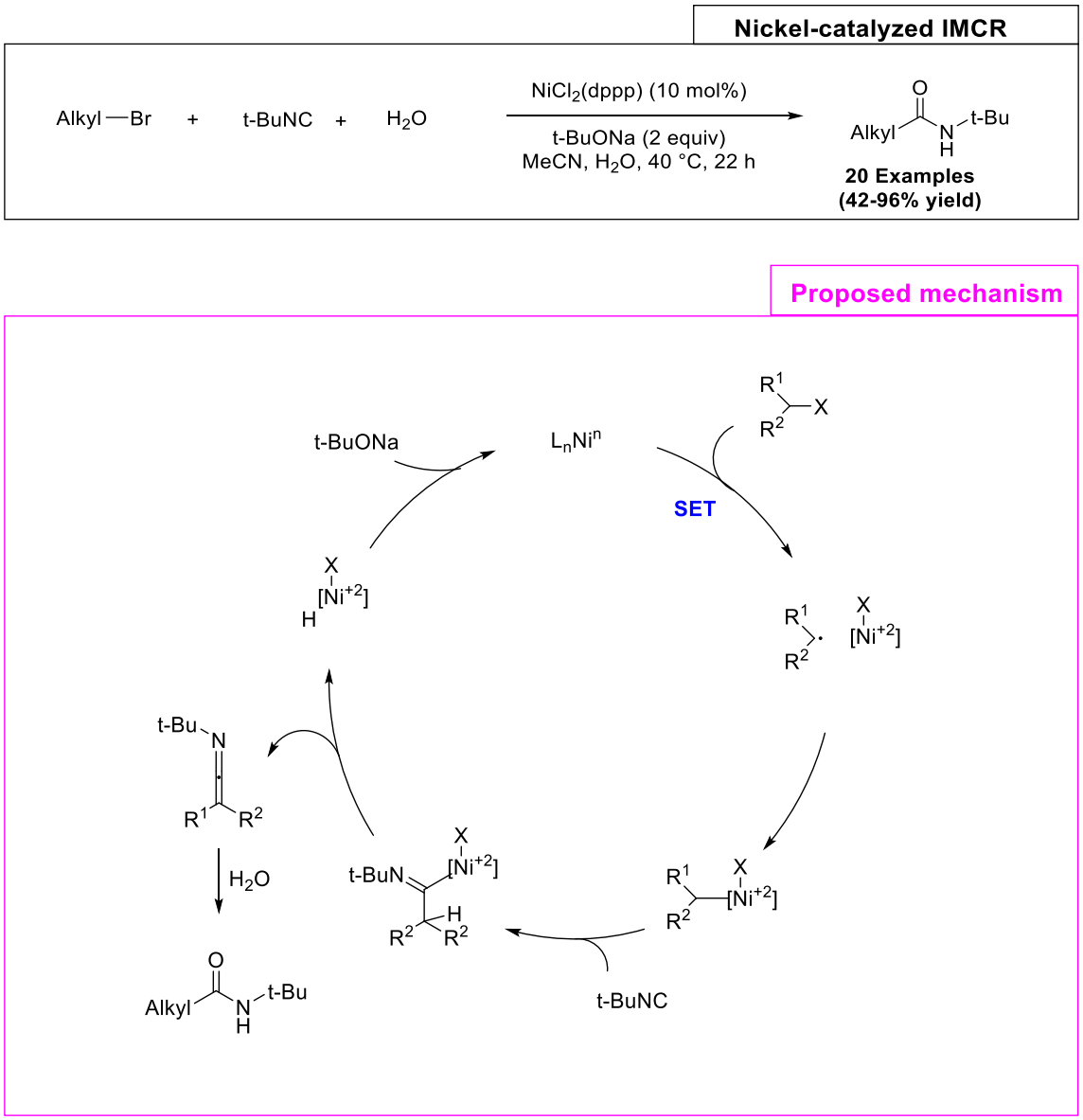
Cu-catalyzed isocyanide-involving multicomponent reaction

Many variants of Ugi reactions that utilize primary amines and carbonyl components have been investigated to synthesize α-amino amides. The Liu group was too able to develop a new and upfront tactic for the preparation of α-amino amides by the isocyanide-compatible oxidative copper–peroxide conditions in the existence of water (Scheme 38) [84]. Halogen substituents such as chloro, bromo even iodo on the substrate persisted intact which is valuable for further cross-coupling reactions to study molecular complexity. The mechanistic pathway occurs via copper and peroxide-promoted formation of electrophilic iminiums ion. Afterward, the tandem nucleophilic attack of water and isocyanides formed the iminal intermediates, which isomerize into the desired product.

A copper(II)-catalyzed procedure for the preparation of 5-acetamidoimidazoles via three-component reaction of TosMIC or α-isocyanoacetates, carbodiimides and acyl chlorides has been achieved by Zhu and associates (Scheme 39) [85]. In their representative study on the three-component reaction of ethyl α-isocyanoacetate with acetyl chloride and N,N′-dicyclohexylcarbodiimide, various copper catalysts such as CuO, CuBr, CuCl, $Cu(OAc)_2$, $CuSO_4$, CuI and different solvents like DMSO, THF, DCM, MeCN were tried. Finally, it was observed that the use of 0.2 equiv. of CuI, and 2.5 equiv. of Et_3N in MeCN, provided the superlative possible yield. A probable mechanism of this transformation is assumed and presented in Scheme 37. The reaction is seemingly started with the reaction of acyl chloride with carbodiimide to produce the N-acyl chloroformamidine, which is transformed to N-acylimminium salt by addition of CuI. Enolate is generated through deprotonation of the copper(I)-coordinated ethyl α-isocyanoacetate, followed by its nucleophilic addition. Finally, imidazole is created by successive deprotonation of the α-protons, intramolecular attack of secondary amine to the isonitrile and followed by protonation.

In 2014, the Xu group reported an elegant copper-mediated multi-component reaction for construction of unsymmetrical tetrasubstituted urea derivatives (Scheme 40) [86]. It is noteworthy that $Cu(OAc)_2.H_2O$ work as both reagent and catalyst. In view that urea derivatives are essential structural motifs in diverse supramolecular chemistry and drug discovery. The advancement of highly efficient, new, and functional group lenient protocols for synthesis of this valuable structural unit is an imperative endeavor. In this admiration, the process reported by Xu and co-workers functions with broad substrate generalization that is intrinsic to copper catalysis and would be tough to realize with base-metals. The authors suggested that the reaction involves the following steps: (i) Isocyanide insertions into less reactive N–H bonds of secondary arylamines, (ii) Reductive elimination of CuH, and (iii) [1,3]Acyl transfer processes.

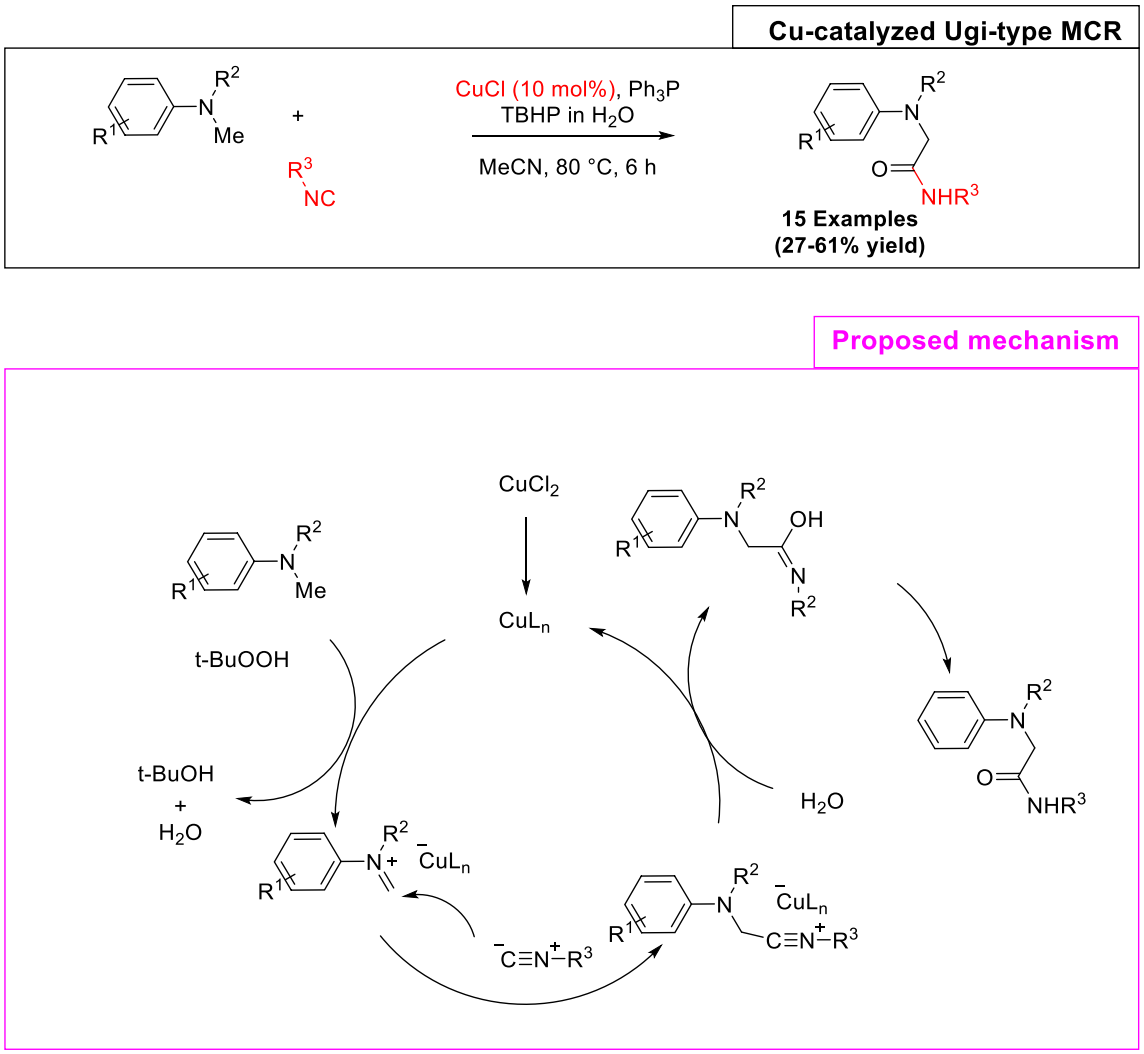
The four-component ligand-promoted copper(I)-catalyzed technique for the preparation of decidedly



Scheme 37 Synthesis of alkyl amides via Ni-catalyzed IMCR

functionalized carbamimidoselenoates has been advanced by the treatment of selenium, amines, aryl iodides and isocyanides in modest to good yields (Scheme 41) [87]. The reaction conditions optimized by alteration of the solvent, ligand, Cu source, temperature and time. The optimized reaction conditions involved 1-isocyano-3-nitrobenzene (1.0 equiv.), iodobenzene (2.0 equiv), elemental selenium (1.5 equiv), diethylamine (1.5 equiv), 10 mol % CuI, 15 mol % 1,10-phen, and Cs_2CO_3 (2 equiv.) in THF at 70 °C for 12 h. Remarkably, reaction stopped completely and no desired product was obtained when replacing the ligand 1,10-phen to bpy, PPh_3, and dppe. The merits of this protocol is commercially accessible, easily handled and stable elemental selenium powder as a perfect selenium source. The methodology found extensive use in organic synthesis for the synthesis of organoselenium scaffolds encompassing an acyclic isoselenourea moiety with possible medicinal and biological activities.

In 2016, Mahdavi and coworkers reported a four-component copper-catalyzed preparation of imidazo[1,2-a]pyridines via GBB reaction from sodium azide, 2-bromopyridine, isocyanides and aldehydes (Scheme 42) [88]. They observed CuI the most suitable catalyst instead of other copper-catalysts such as CuBr, Cu_2O, CuCl, and $CuCl_2$. Synthesis of pharmacologically important imidazo[1,2-a]pyridines from 2-aminopyridine was known, but they revealed the employment of 2-bromopyridine in the presence of L-proline (10 mol%) as the ligand and CuI (5 mol%)



Scheme 38 Synthesis of α-amino amides via Cu-catalyzed Ugi-type MCR

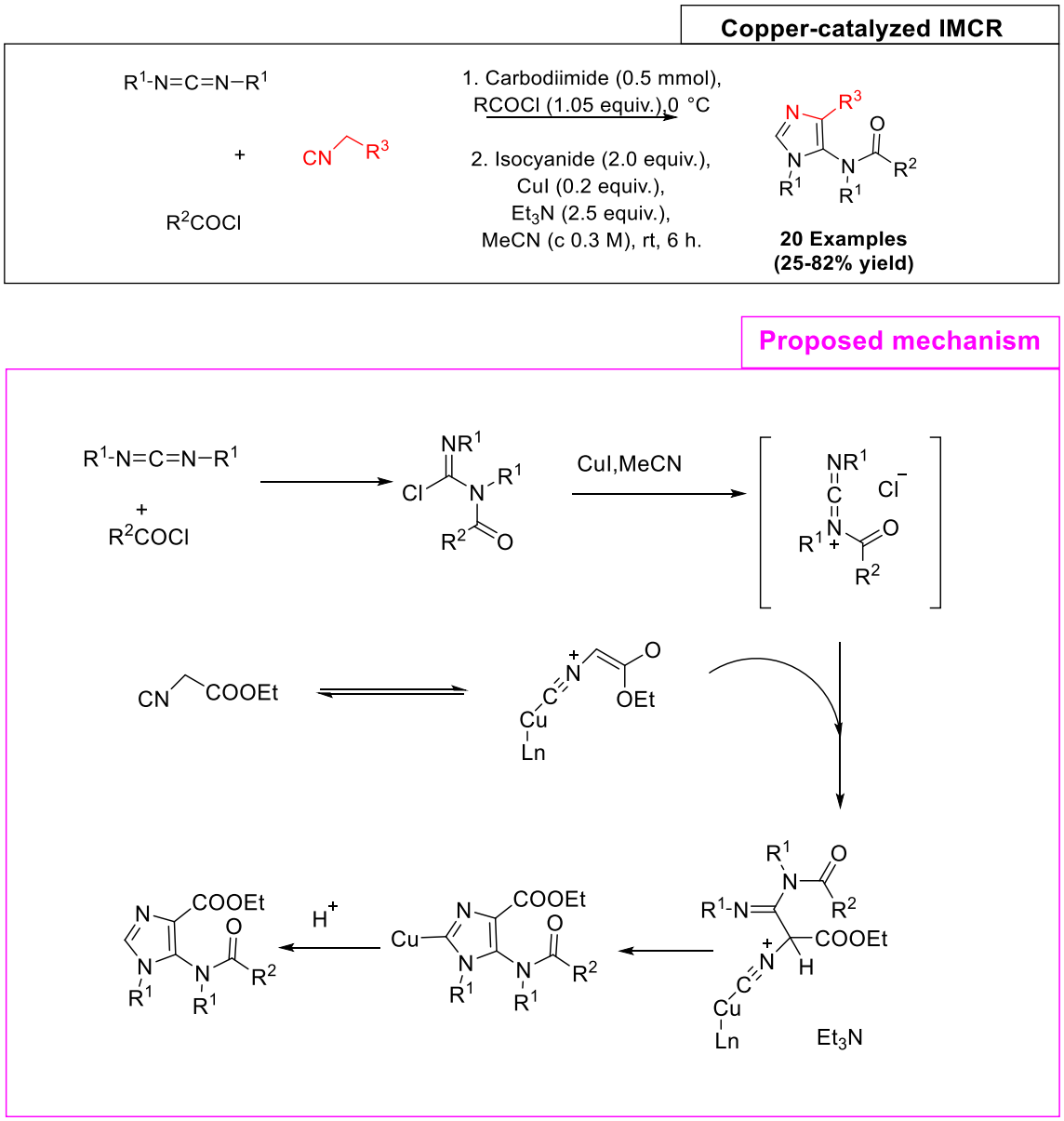
as the catalyst in DMSO as the solvent at 100 °C. Good to outstanding yields of the anticipated products were produced within 3 h. This reaction procedure exhibited diversity in the scope of substrate with respect aryl aldehyde having either electron-poor or electron-donating groups, irrespective of their location on the phenyl nucleus.

The plausible reaction mechanism involves copper-catalyzed formation of 2-aminopyridine from 2-bromopyridine and sodium azide, which underwent condensation with the aldehyde to provide imine intermediate. Next, intramolecular cyclization followed by tautomerization led to the titled product.

In 2017, Tabatabai and his research team established one-pot and three-component assembly of a new class of substituted quinazolines via reaction of adducts of tri- or di-chloroacetonitrile and anilines with isocyanides, followed by intramolecular C–H activation at room temperature (Scheme 43) [89]. A catalyst screen disclosed that CuI was the superlative choice for the conversion. They conducted model reaction for the formation of N-phenyl-2-(trichloromethyl)quinazolin-4-amine in presence of Cs_2CO_3 (2.0 mmol) as the base, CuI (5 mol%) as the catalyst and L-proline (20 mol%) as the ligand. The approach was operative for diverse anilines bearing functionalities like –Cl, $–NO_2$, –Br, Me, –OMe. The corresponding quinazolines were not isolated when reaction performed with 2-chloroacetonitrile, benzonitrile and acetonitrile.

The reaction was initiated by the generation of five-membered chelate A from L-proline and CuI which reacted with the amidine to afford intermediate B. Upon reductive elimination, the catalyst chelate A is regenerated and intermediate B converted into intermediate C. Finally, Tautomerization of C then affords the quinazoline.

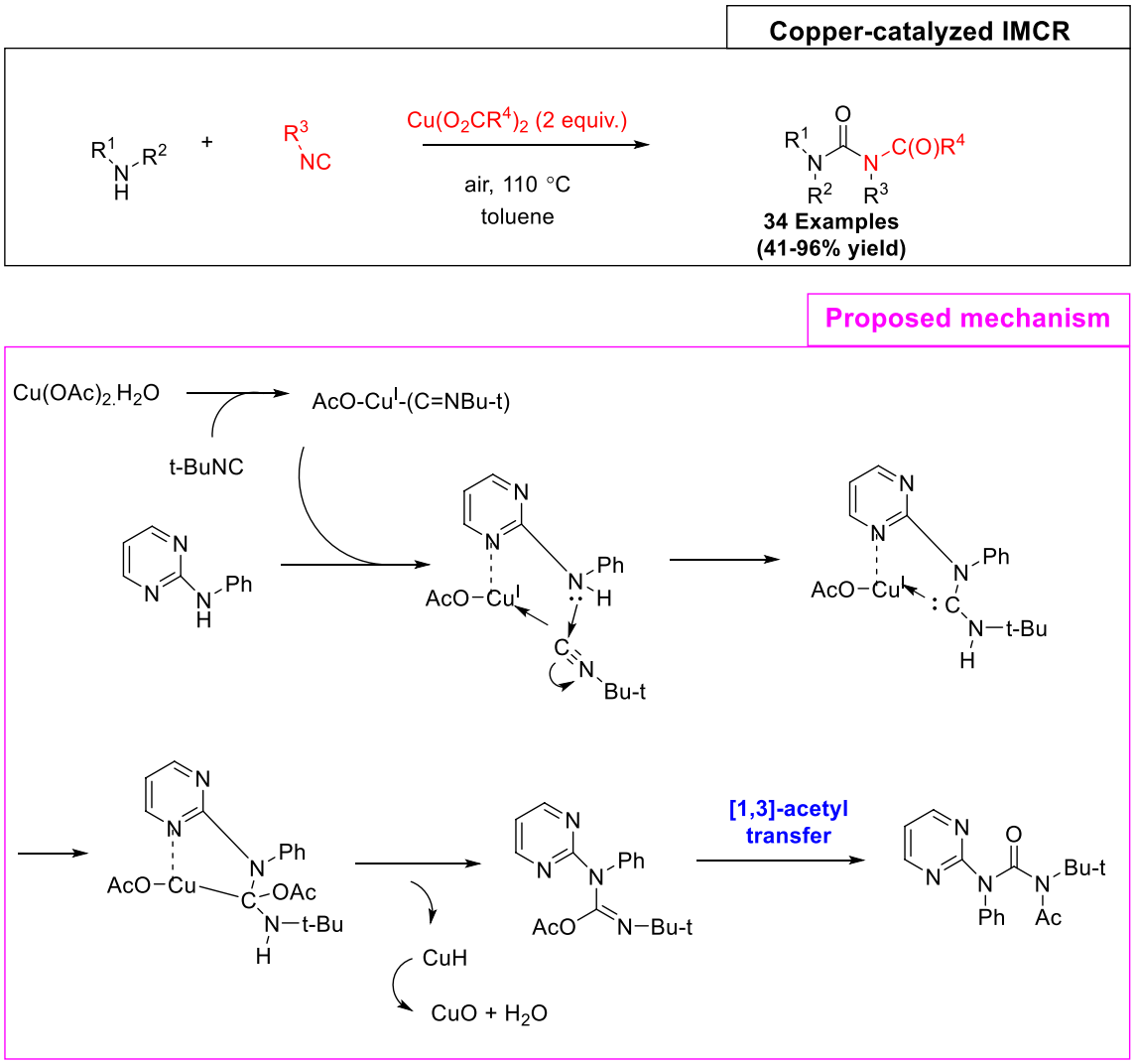
Liu et al. pronounced a copper-catalyzed radical cyanotrifluoromethylation for the preparation of various trifluoroacetimidoyl nitrile derivatives in good to



Scheme 39 Synthesis of 5-acetamidoimidazoles via Cu-catalyzed IMCR

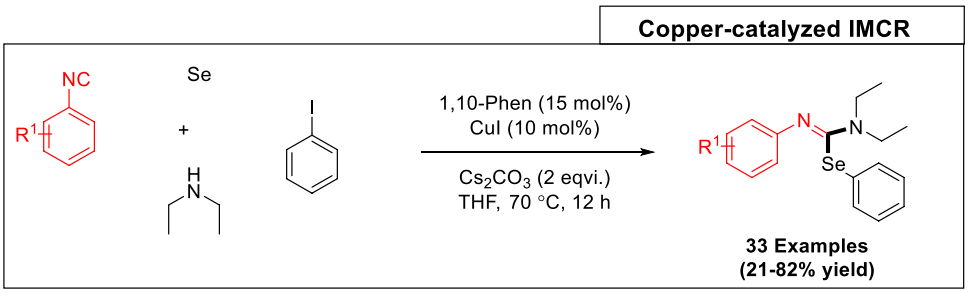
moderate yields (Scheme 44) [90]. The optimal conditions were affirmed as Tpy (20 mol %), $Cu(CH_3CN)_4PF_6$ (10 mol %), Togni's reagent (1.5 equiv.), and TMSCN (2.0 equiv.) in MeCN at 60 °C for 6 h under an argon atmosphere. In this unique reaction, merging of two valued functionalities cyano (CN) and trifluoromethyl (CF_3) occur on the similar C atom of the isocyanide group. Meanwhile, various functional groups on biphenyl isocyanide including MeO, Me, F, Cl, Br, and phenyl were well accepted. The steric and electronic properties of the substituents did not demonstrate evident impact on the isolated yield. The scale-up experimentation displays the practical usefulness of the present methodology. Radical scavenger such as TEMPO was employed under standard conditions, and no desired products were pragmatic. These results direct that a free radical process is implicated in the cyanotrifluoromethylation.

An ultrasound-assisted reaction has been proved as an efficient tool in various types of organic synthesis owing to its several advantages in which generation of exclusive products in more yields, improved rates of reaction, and milder reaction environments compared with conventional methods. Bearing in mind the inordinate success of the ultrasound approach in C-H activation reaction, in 2019, the Tabatabai group developed copper(I) iodide catalyzed simplistic sonochemical path for the construction of benzo[1,3]thiazine

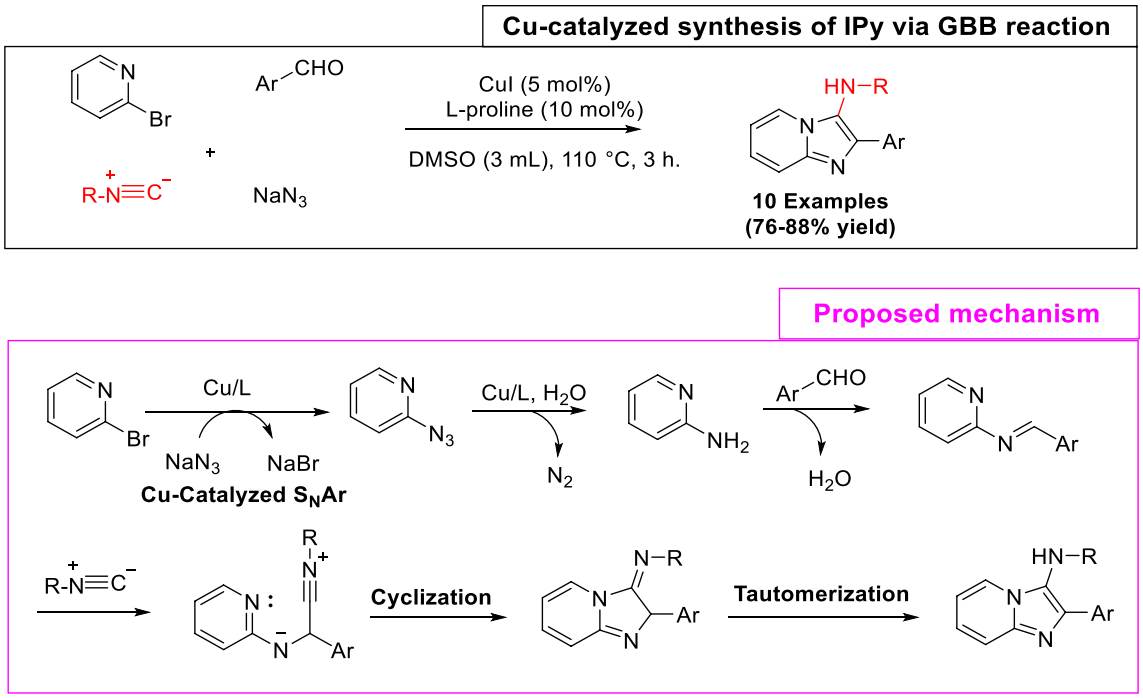


Scheme 40 Synthesis of tetrasubstituted ureas via Cu-catalyzed IMCR

Scheme 41 Synthesis of carbamimidoselenoates via Cu-catalyzed IMCR



derivatives via a three-component conversion of isocyanide, benzoyl isothiocyanate and aniline derivatives (Scheme 45) [91]. The optimized reaction was conducted under ultrasonic irradiation at 60 W power employing 10 mol% of CuI as the catalyst, 20 mol% of L-proline as the ligand, and 1.5 mmol of Cs_2CO_3 as the base. It must be noted that the reaction productivity is negligible when the transformation was executed under silent conditions in the same environment. The mainspring for the augmented efficacy of ultrasound protocol is explained on the basis of raise in the temperature that related to a rise in the surface impact of the reactant via the cavitation event.

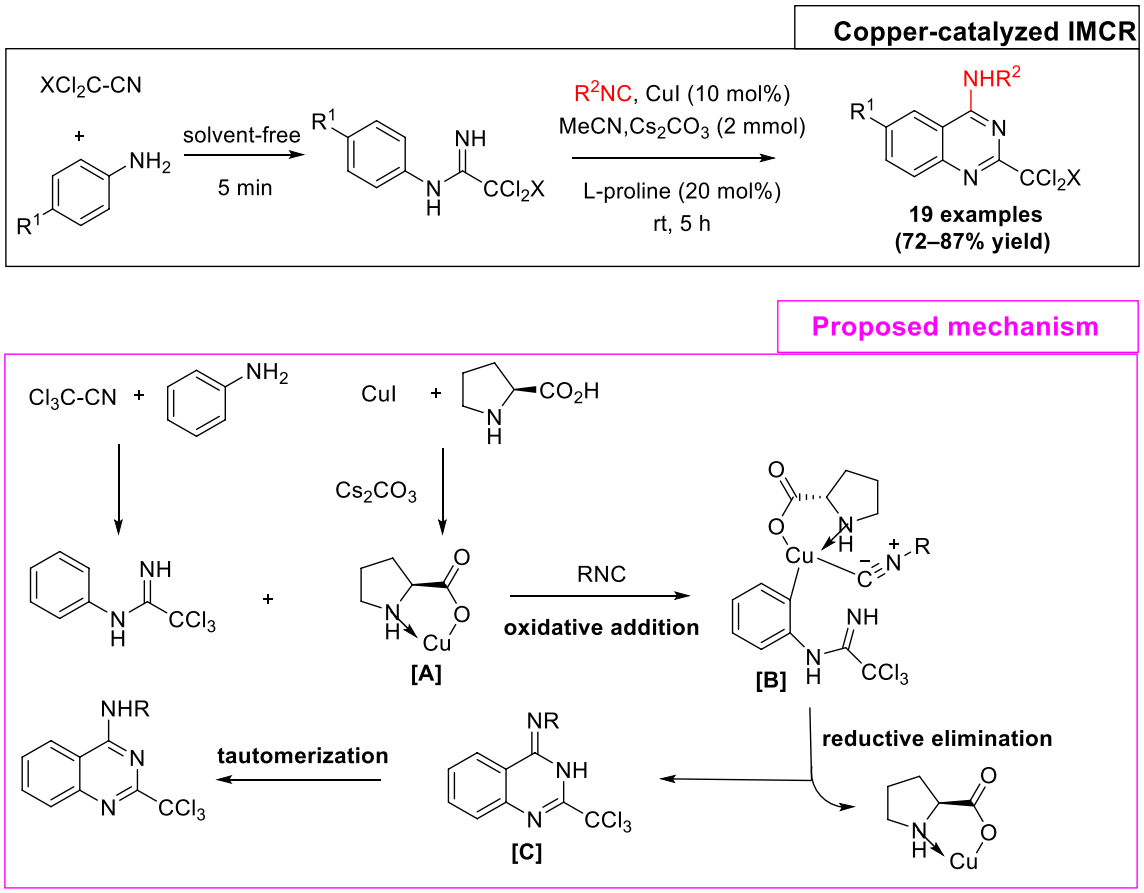


Scheme 42 Cu-catalyzed synthesis of imidazo[1,2-a]pyridines via GBB reaction

Advancements in green chemistry include the work of Hossaini et al., where a four-component preparation of 1,3-cyclopentadiene was achieved by the use of isocyanides, sulfonyl azides, terminal alkynes, and activated acetylenic compounds (Scheme 46) [92]. Captivatingly, antioxidant activity of some newly prepared compounds was examined utilizing the DPPH radical trapping and reduction potential analysis of ferric ion and relating results with synthetic antioxidants like BHT and TBHQ. The practicality and significance of this method are highlighted by its eco-friendly and benign nature, reusability of ZnO, easy workup, non-toxic starting materials, and cleaner reaction profile.

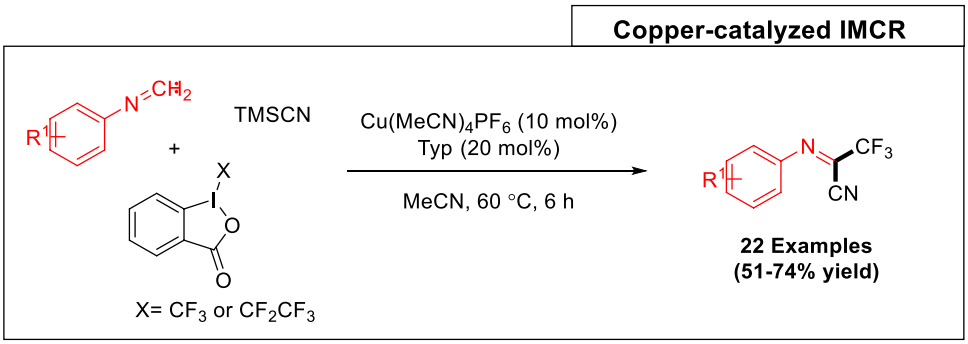
In 2015, Ji and co-workers utilized the readily available aryl isocyanides with arylsulfonothioates, and active methylene compounds for the construction of sulfur-bearing trisubstituted imidazoles via [3 + 2] cyclo-addition reaction. Interestingly, formation of C–C, C–S and C–N bond takes place in one step in this tactic (Scheme 47) [93]. The optimum conditions found consisted of mixing methyl 2-isocyanoacetate, 1-isocyano-4-nitrobenzene, S-phenyl benzenesulfonothioate and Cu_2O (15 mol%) in 1.0 ml MeCN, and Et_3N (2.5 equiv.) at 80 °C temperature under argon environment. Remarkably, active methylene isocyanides such as 2-isocyano-1-morpholinoethan-1-one and 1-((isocyanomethyl) sulfonyl)-4-methylbenzene reacted well, albeit in very low yields. The reaction mechanism for the isocyanide-isocyanide [3 + 2] cycloaddition was explored, which suggested that the reaction of methyl 2-isocyanoacetate with Cu2O caused intermediate A or its tautomer A', which undergo the nucleophilic addition to 1-isocyano-4-nitrobenzene to produce intermediate B. Then, intramolecular addition in copper intermediate C followed by reaction with S-phenyl benzenesulfonothioate furnishes the wanted product.

To establish the broad applicability of multifunctional copper catalyst supported on β-cyclodextrin functionalized magnetic graphene oxide, in 2020, Mahdavi ad coworkers have reported the first protocol for the simplistic preparation of N-alkyl-2-phenylimidazo[1,2-a]pyridin-3-amine via C-O oxidation followed by multicomponent cyclization (Scheme 48) [94]. In this strategy, combination of Cu-catalyst and aerobic O_2 mainly oxidizes benzylic alcohols to aldehydes, which takes part in situ in a three-component transformation with isocyanides and pyridin-2-amine to generate corresponding anticipated product. The robust catalyst attained cumulative turnover number (TON) of about 1500 over 10 consecutive runs. The eminent advantage of this work comprises high proficiency, straightforwardness and generality which cause high yields, a cleaner reaction outline and easy recyclability of much stable heterogeneous catalyst by a simple magnet separation.



Scheme 43 Synthesis of functionalized quinazolines via Cu-catalyzed IMCR

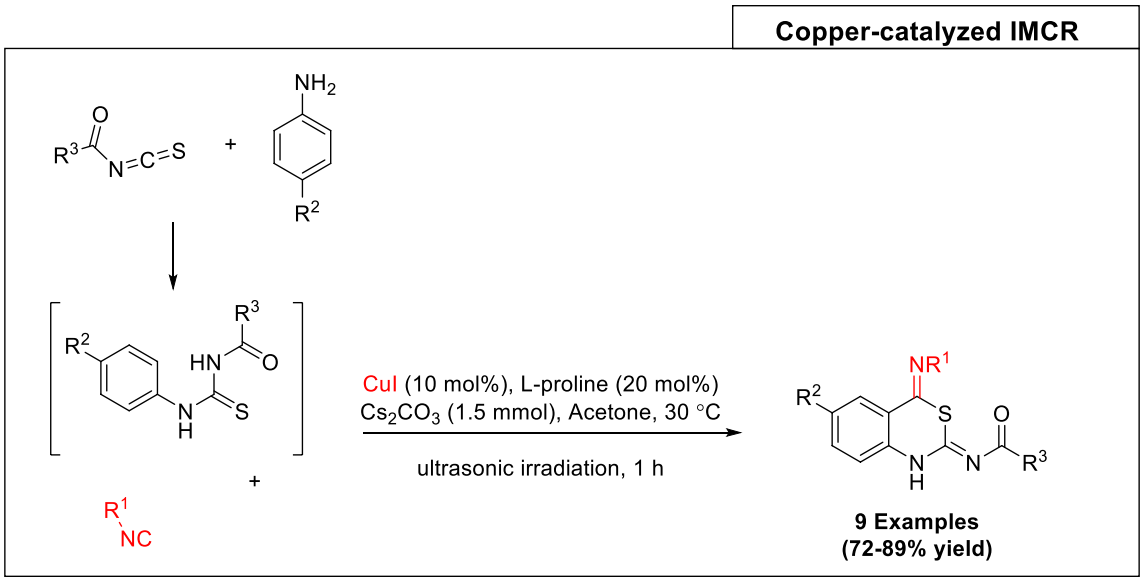
Scheme 44 Synthesis of trifluoroacetimidoyl nitriles via Cu-catalyzed IMCR



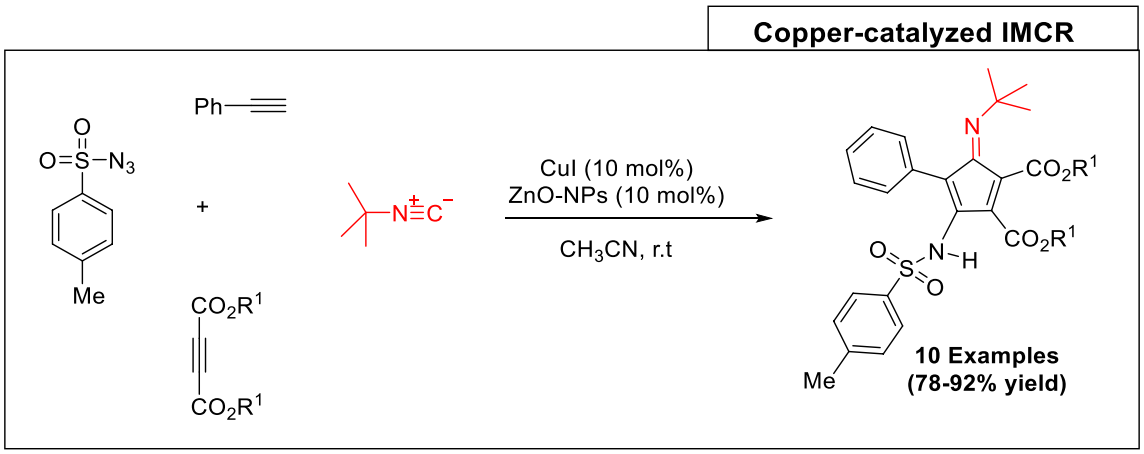
Zn-catalyzed isocyanide-involving multicomponent reaction

In 2007, Rousseau et al. put forth an exciting idea of zinc catalyzed three-component GBB reaction for the preparation of imidazo[1,2-a]pyridines from an array of substrates using either microwave irradiation or conventional heating (Scheme 49) [95]. Expectedly, the catalytic system inclined by diverse reaction parameters, such as solvent system, temperature, time and amount of the used catalyst. At ambient temperature, $Sc(OTf)_3$ dispensed the desired product in good yield, but long reaction times were required. It was experiential that 1,4-dioxane evidenced to be the good preference for this reaction over mixed organic solvent systems such as MeOH/DCM. In this protocol, $ZnCl_2$ (5 mol %) was found to be active with most aldehydes, but montmorillonite clay K10 was used as the alternative catalyst in case of the reactions with nicotinaldehyde.

An outstanding work by Shaabani and co-workers pronounced the three-component Ugi transformation of



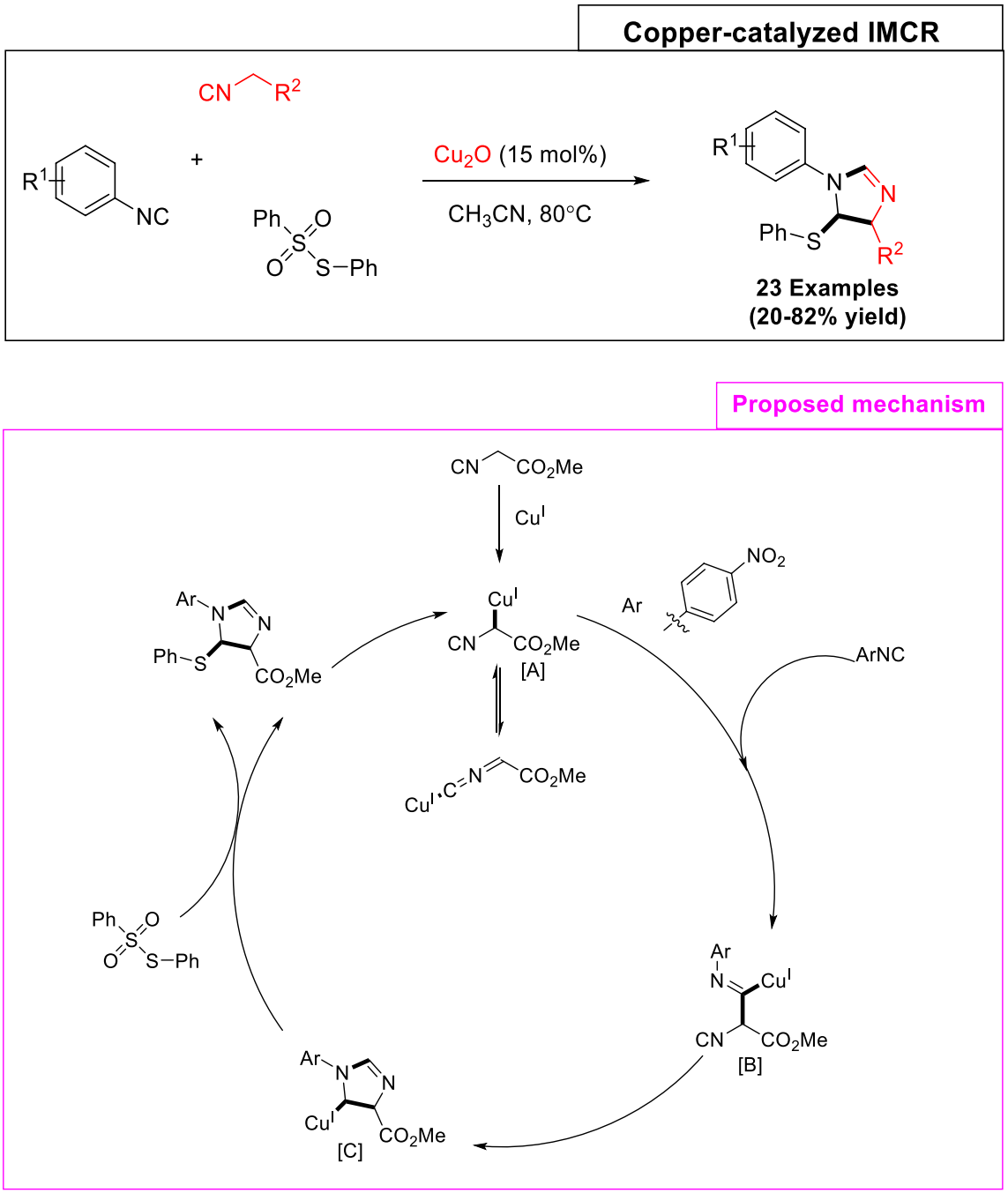
Scheme 45 Synthesis of benzo[1,3]thiazine via Cu-catalyzed IMCR



Scheme 46 Synthesis of 1,3-cyclopentadienes via Cu-catalyzed IMCR

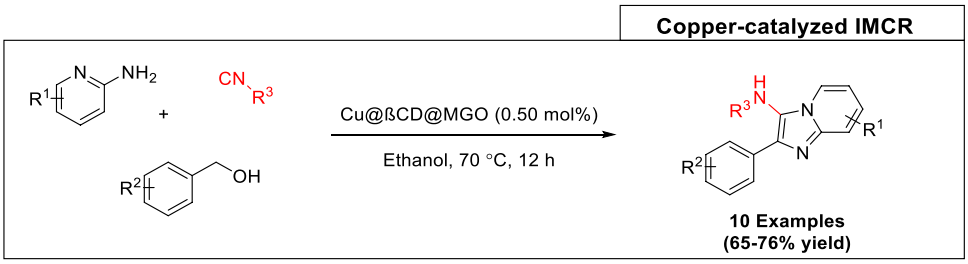
cyclohexyl isocyanide, aromatic or aliphatic aldehydes, and 2-aminophenols in methanol at room temperature produced functionalized N-cyclohexyl-2-(2-hydroxyphenylamino) amide excellent yields (Scheme 50) [96]. The scope and limitations of this procedure was examined using numerous aldehydes bearing electron-poor and electron-rich groups. Unfortunately, when aniline, o-phenylenediamine and 2-aminobenzenethiol are subjected to the optimized conditions in place of 2-aminophenols, no desired product is obtained. A plausible mechanism for this strategy involves initial formation of imine which is readily converted into Zn(II) coordinated iminium species. Then, the nitrilium ion generated by addition of iminium ion to the isocyanide. It is expected that H_2O which is released during imine formation interacts further to cause the final products.

Safaei-Ghomi et al. efficaciously carried out the construction of N-cyclohexyl-3-aryl-quinoxaline-2-amines via a multi-component reaction of cyclohexyl isocyanide, o-phenylenediamine and aldehyde utilizing ZnO nanoparticles as a heterogeneous recyclable catalyst in single pot (Scheme 51) [97]. Under optimized conditions (4 mol% of ZnO nanoparticles in ethanol under reflux), the substrate scope studies were performed with different aldehydes and observed that both electron-releasing and electron-deficient groups attached to the aromatic ring are suitable with the conversion and provided good to excellent yields. Mechanistically, the initial event is the reaction of the aromatic aldehyde with o-phenylenediamine trailed by an attack of cyclohexyl isocyanide. Finally, cyclization and dehydrogenation sequence in intermediate engender the products.

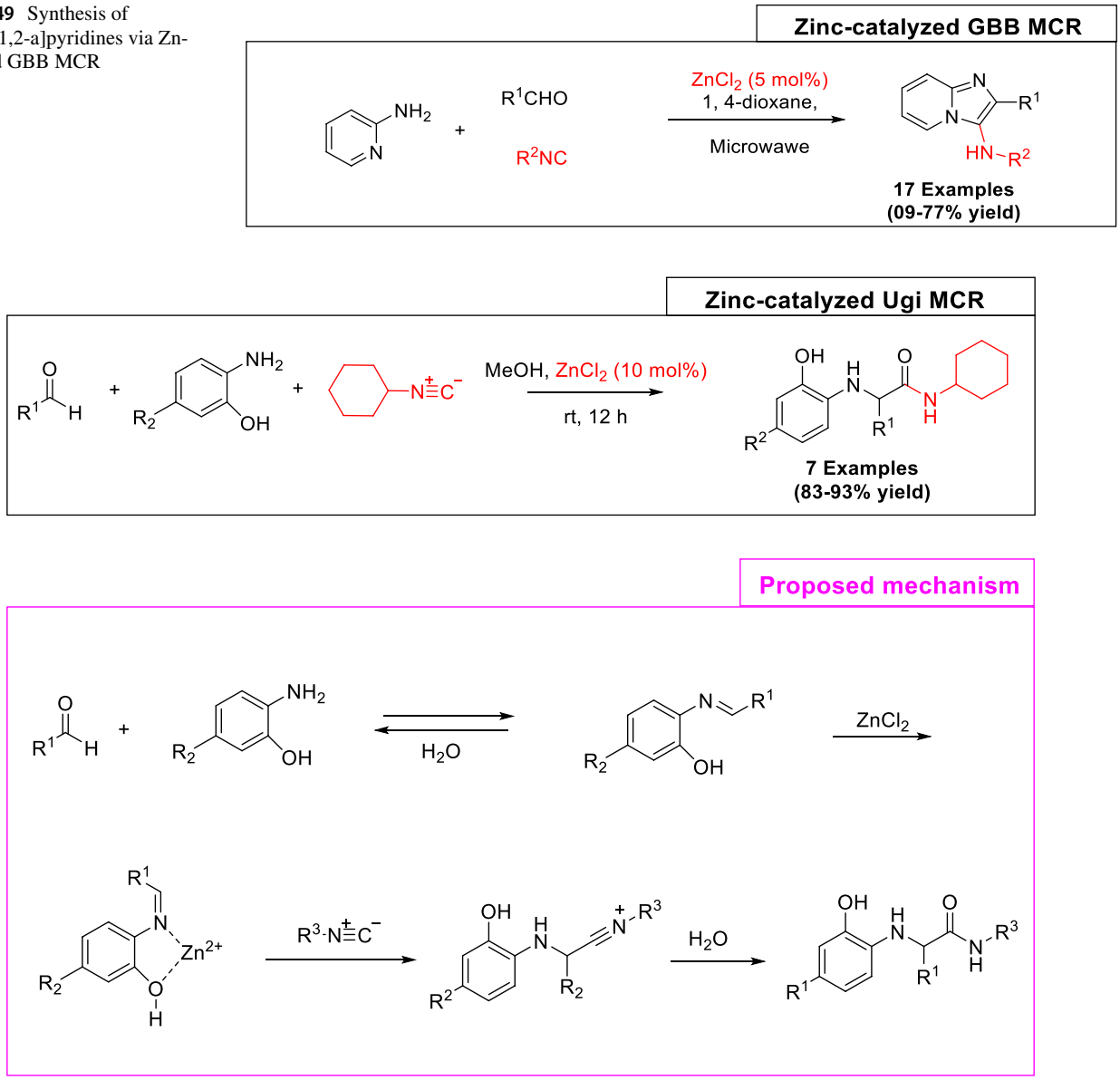


Scheme 47 Synthesis of imidazoles via Cu-catalyzed IMCR

Scheme 48 Synthesis of phenylimidazo[1,2-a]pyridines via Cu-catalyzed IMCR



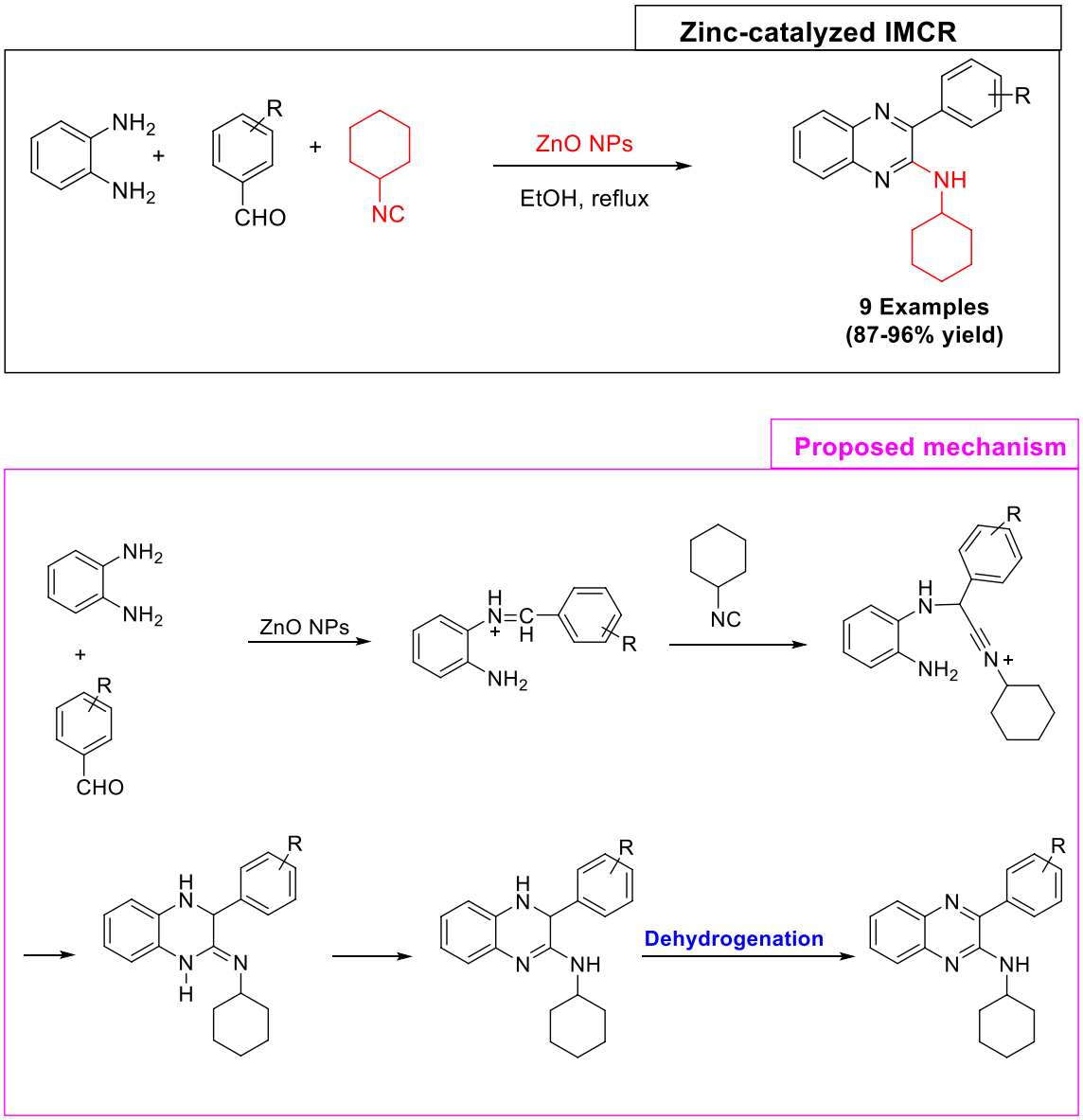
Scheme 49 Synthesis of imidazo[1,2-a]pyridines via Zn-catalyzed GBB MCR



Scheme 50 Synthesis of N-cyclohexyl amides via Zn-catalyzed Ugi MCR

The ability of $Zn(OTf)_2$ as a Lewis acid to promote the three-component condensation of isocyanides with N-formylmethyl-substituted tertiary amides and aliphatic amines in acetonitrile at room temperature is documented by Wang et al. (Scheme 52) [98]. It should be pointed out that improved chemical yields could be achieved when imines were pre-prepared by the interaction of amines and aldehydes. An ^{18}O-labeling study divulges a captivating mechanism concerning presumably the bridged heterocyclic intermediate. Mechanistically, the initial event is consecutive formation of imine, Zn-activated imines and nitrilium intermediates. Then, two plausible pathways A and B were proposed for transformation of nitrilium intermediates into bridged intermediates. Lastly, ring opening conversion through the cleavage of the C–O bond gives the production of imidazolinium triflates.

Chromenes as one of the privileged structures, present in huge amounts in the diet of humans because of their origin in plants. Their therapeutic applications include antitubulin, antiviral, antifungal, tyrosine and protein kinase C inhibitors, and antihypertensive agents. In 2015, Shaabani et al. explored the one-pot method for the preparation of highly functionalized imidazo-chromen-4-ones in fairly good yields via three-component GBB reaction involving 4-oxo-4H-chromene-3-carbaldehydes, 2-aminoazines and isocyanides(Scheme 53) [99]. The reaction proceeds smoothly in presence of catalytic system consisting of p-TSOH/$ZnCl_2$ under reflux conditions in methanol as a

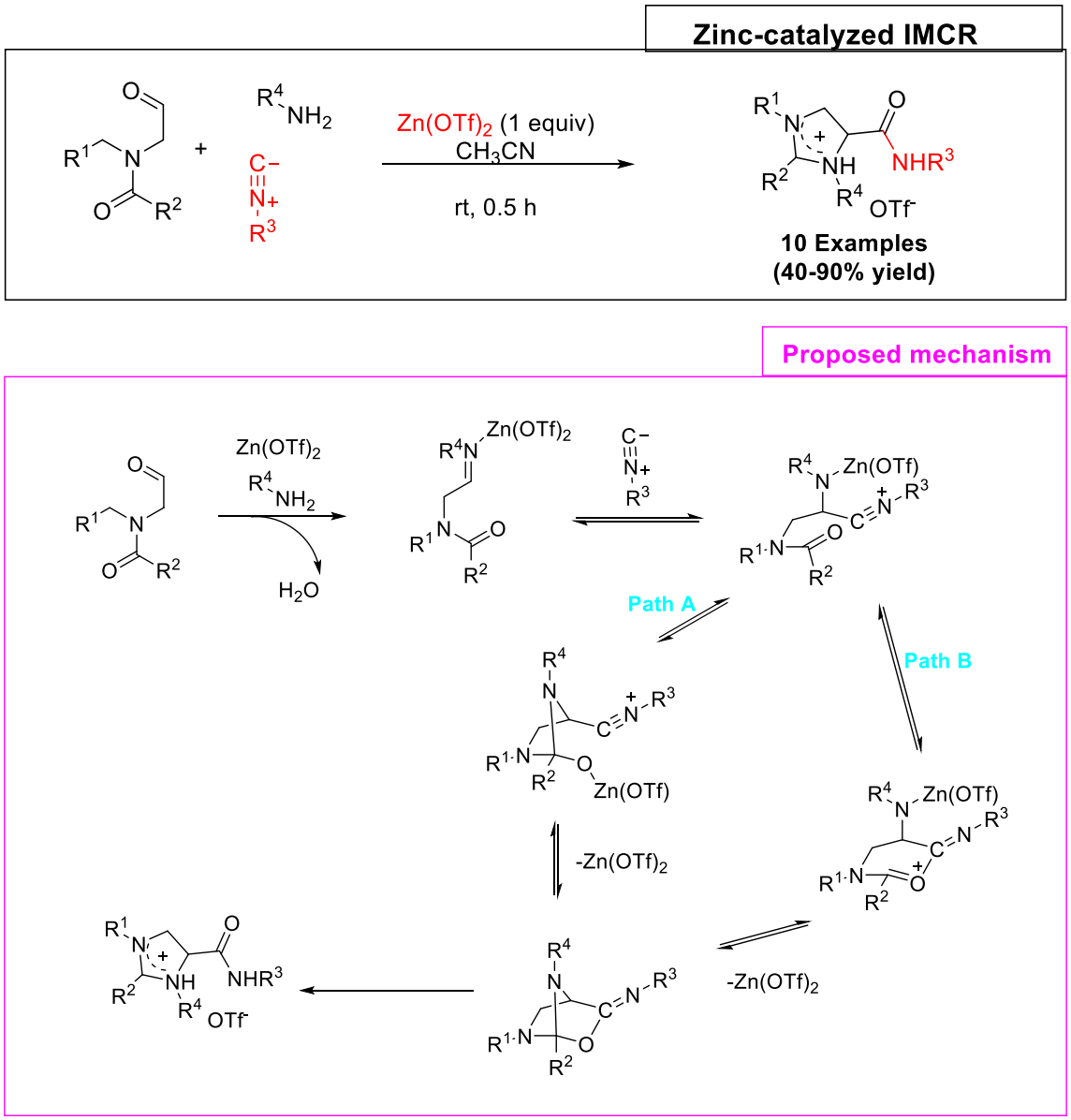


Scheme 51 Synthesis quinoxaline-2-amines of via Zn-catalyzed IMCR

solvent. The control experiment suggested that the reaction was not operative in the presence of either $ZnCl_2$ or p-TSOH, but both of them are essential for obtaining anticipated yield.

The combination of $ZnBr_2$ and PEG-400 enables multicomponent reaction of oxiranes, isocyanides, and dialkyl malonates under mild environments, permit low-cost and easy synthesis to functionalized 5,6-dihydropyran-2-ones (Scheme 54) [100]. Various catalysts and solvents were inspected to find optimum conditions. Screening of catalyst indicated that $BF_3{\cdot}Et_2O$ proved to be unsuccessful, while late-transition-metal salts gave disappointing results in this conversion. Substrate scope study revealed that electron-neutral and electron-rich substituents in the aryl oxiranes part were found to be favoring good yields while electron-withdrawing group was found to be lowering the yields. The reaction of cyclooctene and cyclopentene oxides furnished low yields of the predicted products. It should be noted that the reactions of sterically bulky aryl isocyanide lead to the subsequent product in an adequate yield, demonstrating that steric bulkiness in the isocyanide was not a problematic.

The coumarin scaffolds is mainly recognized as an imperative scaffold in pharmaceutical industry. In particular, the heteroannulated coumarin skeleton possesses a extensive range of potential medicinal activities such as antibacterial, anti-inflammatory, antimicrobial, antioxidant, and anticancer. A general technique for the synthesis of new furo[3,2-c]coumarins from hydroxycoumarin, isocyanide

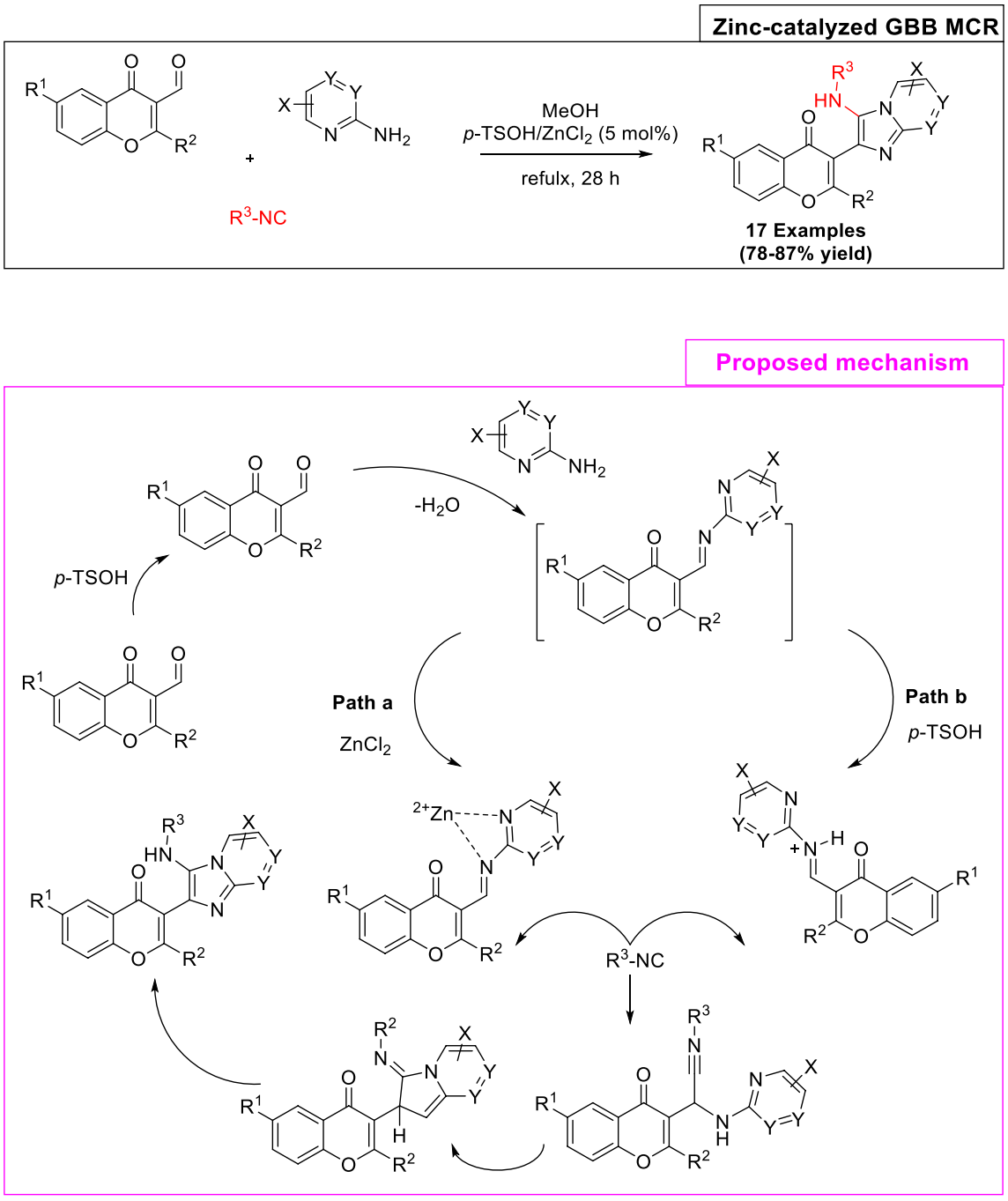


Scheme 52 Synthesis of imidazoliniums via Zn-catalyzed IMCR

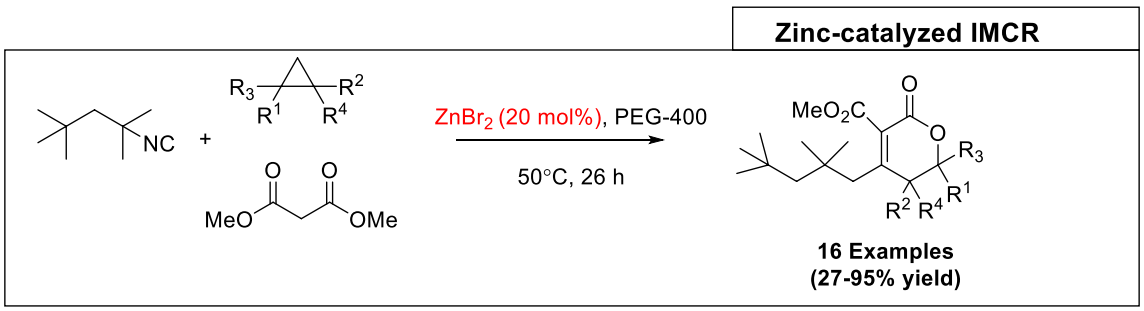
and selected aldehyde derivatives employing zinc oxide loaded on fluorapatite (ZnO/FAp) as catalyst has been described (Scheme 55) [101]. Mild reaction conditions, admirable reusability, high atom economy and no use of column chromatography make this procedure appropriate for the combinatorial synthesis of chemical libraries. The reaction pathway consists of the following steps; the early step is the formation of chroman-2,4-dione (I), which is converted to the intermediate (II) by the [4 + 1] cycloaddition with isocyanide. Ring closer via intramolecular cyclization facilitates intermediate dihydrofuran (III), followed by 1,3-proton shift gives the wanted product.

Conclusions and outlook

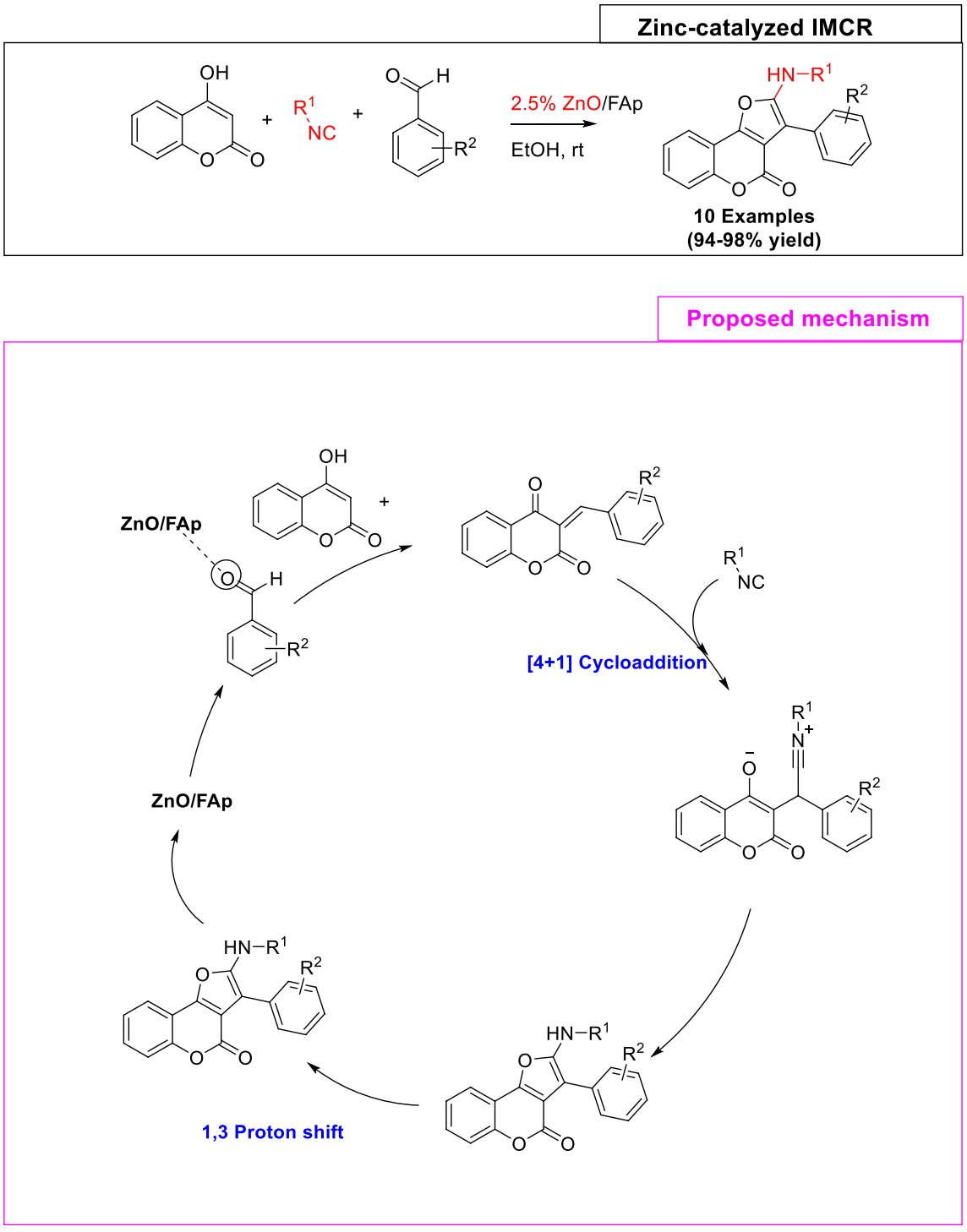
In conclusion, we have made our best efforts to present series of synthetic documents on 3d transition-metal catalyzed multicomponent reactions employing isocyanide as constant coupling component to construct an extensive array of heterocyclic scaffolds. The discussion is classified on the basis of the first-row TM catalyzed involved and explained with demonstrative examples and mechanism. While foremost advances had been executed with expensive 4d and 5d transition metals, a momentous recent stimulus has been expanded by the use of cost-effective, earth-abundant, and



Scheme 53 Synthesis of functionalized imidazo-chromen-4-ones via Zn-catalyzed GBB MCR



Scheme 54 Synthesis of 5,6-dihydropyran-2-ones via Zn-catalyzed IMCR



Scheme 55 Synthesis of furo[3,2-c]coumarins via Zn-catalyzed IMCR

less poisonous first row transition metal catalysts. Given the sustainable characteristic of multicomponent reactions with earth-abundant first-row TM, further stimulating advances are predictable in this rapidly evolving research field. However a plethora of resourceful conversions has been accomplished, there is still scope for advance in first-row TM catalyzed IMCR transformations that sanction synthetic chemists with effective device are anticipated. Agreeingly, no comprehensive review on first-row TM catalyzed IMCR with suitable mechanistic perceptions has been found so far and the present review article will reimburse for this problem. Furthermore, it will confer a stage to disclose

innovative surfaces for both the medicinal and synthetic chemists.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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