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Review on Oxidative and Reductive Mannich Reaction

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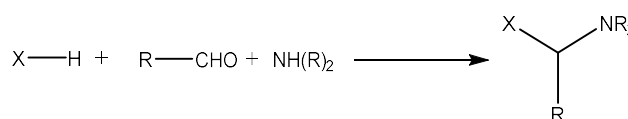
The development of diastereoselective, catalytic methodologies for synthesis of Mannich products presents specific promise for synthetic applications. Only highly reactive aldehydes such as formaldehyde and acetaldehyde, secondary amine, have been ruled out of the classical Mannich reaction. Highly stereoselective Mannich reactions have been extensively studied and reported. The most powerful enantioselective and diastereoselective C-C bond forming reactions include the asymmetric Mannich reaction such as oxidative and reductive Mannich-reaction. In oxidative type, an oxidizing agent such as oxygen, air, *etc.* is used. Whereas in reductive Mannich reaction, a reducing agent produces enolate for the generation of a reactive iminium ion. Cross-dehydrogenative coupling reactions (CDC) are a method for generating more complex amines from simpler materials by oxidatively functionalizing amine -CH bonds. Besides, the redox-Mannich reaction uses the same raw materials but includes an isomerization step that makes it simple to create ring-substituted -amino ketones. In this review article, we have tried to study the research that has been done in recent years for oxidative and reductive Mannich reactions.

Keywords: Oxidative, Reductive, Mannich reaction, CDC reactions

INTRODUCTION

The development in chemical methodologies that include environment compatibility, atomic economy, and practicability is one of the greatest challenges among modern organic synthesis. Great attention is attracted to the multicomponent reactions (MCRs) because of their high versatility, reproducibility, reducing the number of synthetic steps, low energy utilization, and waste production [1]. Among them, the three-component condensation Mannich reaction is a powerful method for carbon-carbon bond forming which leads to a class of compounds generally known as Mannich bases that occurred between structurally diverse substrates (X-H) containing at least one activated hydrogen atom, an aldehyde (generally R-CHO) and an amine [2]. A general classification of the most usual types of Mannich bases with respect of the substrates from which they derive is given in Scheme 1.

The Mannich reaction's products are mainly β -amino carbonyl



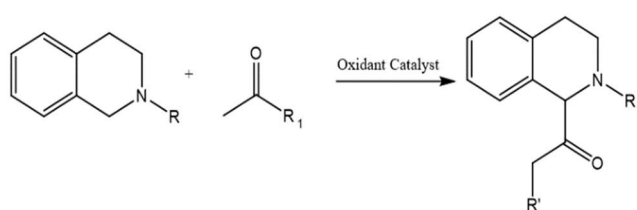
Scheme 1. General type of Mannich reaction

compounds and its derivatives, which used for the synthesis of amino alcohols, peptides, lactams and precursors to optically active amino acids [3]. Practical applications have been introduced for Mannich in the treatment of natural macromolecular materials such as leather, paper, and textiles, the production of synthetic polymers, as additives used by the petroleum industry, as products used in water treatment, analytical reagents, cosmetics, dyes, *etc.* [4]. Also, there are compounds that bearing 1,3 arrangements of amino and oxygenated groups, which found in various biologically active natural products [5]. Another important class of such compounds is the 1-(α -aminoalkyl)-2-naphthols, the 'so-called' Betti bases [6]. These compounds could be changed into derivatives which have antibacterial, hypotensive, and bradycardiac activities [7]. Two

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groups of phenolic hydroxyl and amino could be used in developing several synthetic building blocks [8,9].

Classic Mannich reaction has been reviewed extensively in different timeframes [1,10-15]. Among the most extensively studied variants are oxidative two-component approaches with tertiary amines that provide access to ring substituted β -amino ketones, products which not available by the classic Mannich approach (Scheme 2).



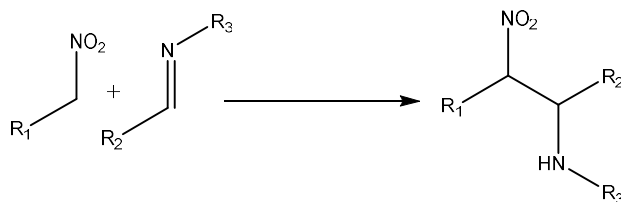
Scheme 2. Oxidative Mannich reaction

The development of diastereoselective, catalytic methodologies for synthesis of Mannich products presents specific promise for synthetic applications. Despite this potential, it is only recently that aromatic frameworks have been employed successfully as nucleophiles in asymmetric, catalytic reactions, and many important challenges in this area remain unmet. Diastereoselective reactions controlled by chiral auxiliaries organize the methods for the majority of stereocontrolled transformations of this type [16].

The oxidative functionalization of amine α -C-H bonds via cross-dehydrogenative coupling reactions (CDC) is a way for the generation of more complex amines from simpler materials. CDC is the class of reaction for the formation of C-C or C-N bond directly from two unmodified C-H bonds (for C-C bond formation) or C-H and N-H bonds (for C-N bond formation) [17]. Different oxidants and strategies including photoredox approaches have been utilized [18]. *Via* Mannich reaction, a varied range of products are used as pharmaceuticals, as exemplified by acetylenic amino alcohols pargyline, an antidepressant and antihypertensive drug, tremorine, a cholinomimetic drug, or ethynylcyclohexyl allophanate, a soporific agent [1].

On the other hand, the reductive Mannich reaction is a classic example of a redox-neutral amine α -C-H bond functionalization

process which the majority of methods typically utilize tertiary amines as starting materials [19]. The nitro-Mannich reaction is the nucleophilic addition of nitroalkanes to imines, which gives β -nitroamines and the nitro group can be converted to the amino group and provides the vicinal diamines [20].

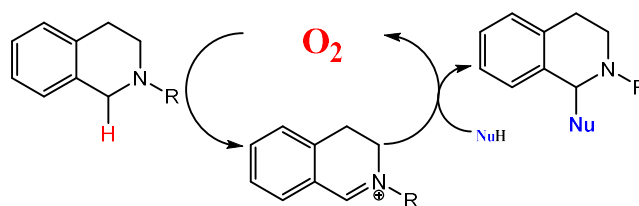


Scheme 3. Reductive Mannich reaction

One of the interests of our research team has always been the Mannich reactions that we have been investigating over the years [21-31]. In this review, we tried to investigate the period of the last years in the progress of oxidative Mannich reaction.

Oxidative Mannich Reaction

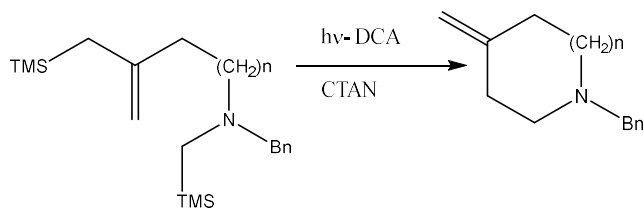
The Mannich reaction is a fundamentally important carbon-carbon bond-forming reaction in organic synthesis. Due to the importance of synthetic products from the Mannich method, many attempts have been made to synthesize a wide range of these group compounds. The oxidative Mannich reaction is a special branch of classic Mannich reaction that finds its own adherent among the chemists in recent years. The general mechanism of the reaction is shown in Scheme 4.



Scheme 4. Mechanism of oxidative Mannich reaction

For the first time, in 1998, Wu *et al.*, have published an Oxidative Mannich Cyclization Methodology for the

Stereocontrolled Synthesis of Highly Functionalized Piperidines. They demonstrated that the oxidation procedure is ideally suited for intermediate *N*-acyliminium cation generation in stereo-controlled reactions of *R*-silylamido allylsilanes (Scheme 5) [32].



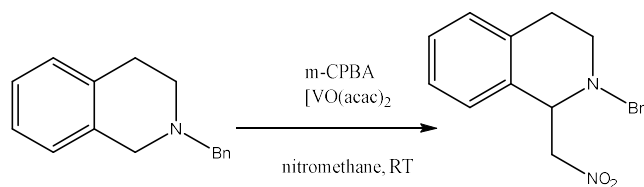
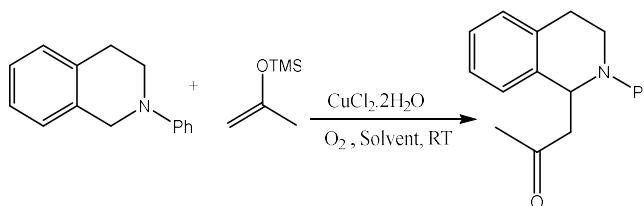
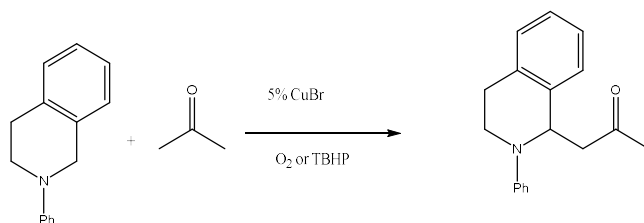
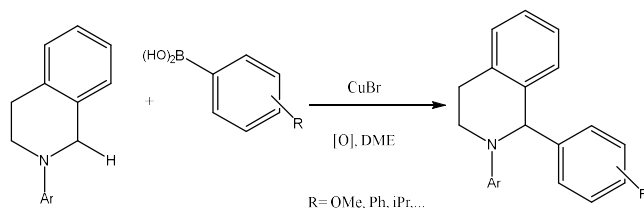
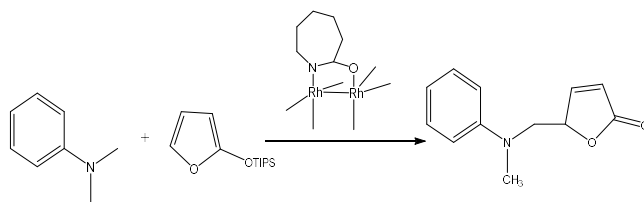
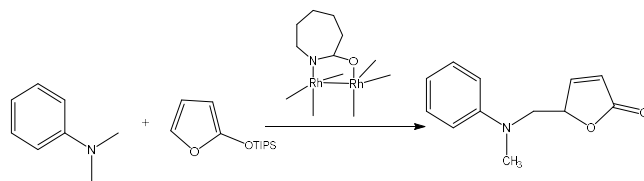
Scheme 5. First oxidative Mannich reaction

Catalytic Oxidative Mannich Reaction

Metal-based Catalysts

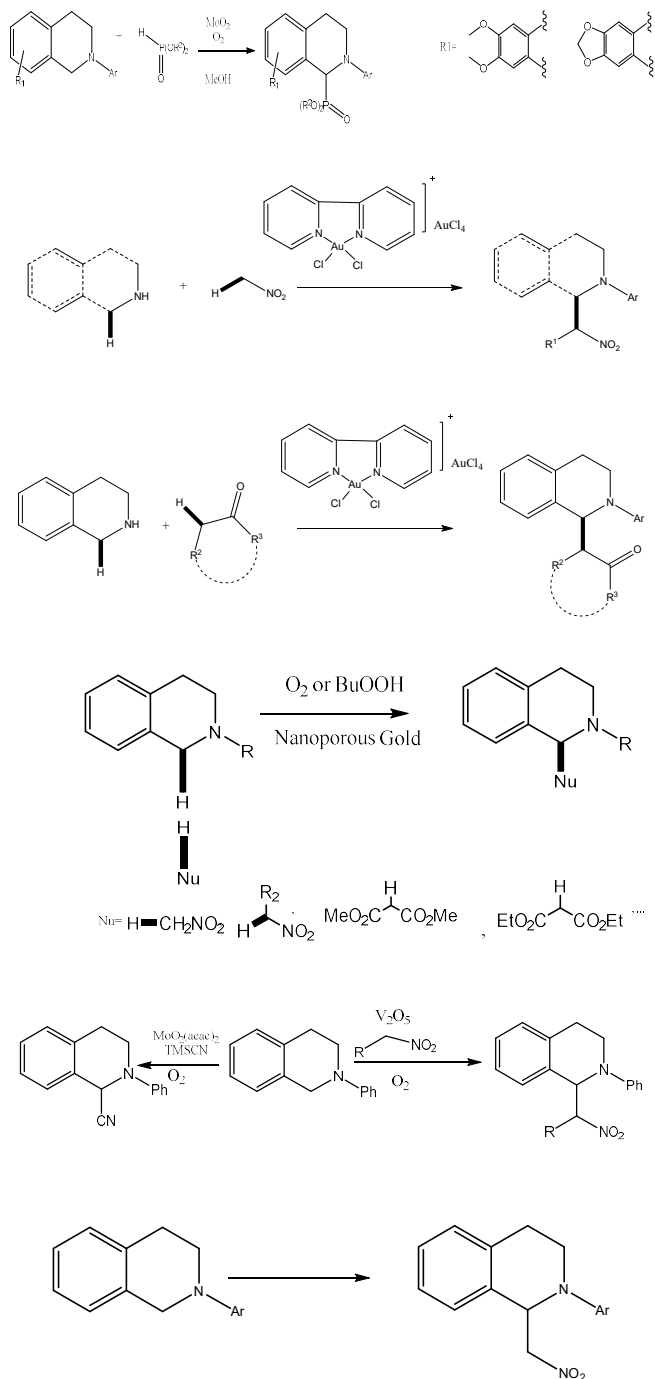
The oxidative Mannich reaction is an attractive alternative, which involves the direct catalytic C-H oxidation of a tertiary amine followed by nucleophilic attack [33]. In 2006, Catino *et al.*, described a mild, selective, and efficient oxidative Mannich reaction catalyzed by dirhodium caprolactamate [Rh₂(cap)₄] for the rapid construction of γ -aminoalkyl butenolides [34]. An oxidative method was developed by Baslé and Li in 2008 for arylation of sp³ C-H bonds using copper bromide as catalyst [35]. Shen *et al.*, in 2009 reported copper-catalyzed oxidative Mannich reaction between tertiary amines and methyl ketones [36]. Also, Boess *et al.*, reported Cu as a catalyst in aerobic oxidative coupling reaction with *N*-Phenyl Tetrahydroisoquinoline [37]. Jones *et al.*, synthesized *N*-Alkyl Tetrahydroisoquinoline derivatives through Vanadium catalyzed oxidative coupling in 2012 [38] (Scheme 6).

In the same year, Xie *et al.*, used Gold as a catalyst and air as an oxidant for C-C coupling reaction for the synthesis of two different derivatives of Mannich product [39]. Ho *et al.*, also used a nanoporous gold skeleton catalyst for highly efficient heterogeneous aerobic cross-dehydrogenative coupling *via* C-H functionalization of tertiary amines [40]. Alagiri *et al.*, used molybdenum trioxide (MoO₃) as a catalyst for oxidative cross-dehydrogenative-coupling (CDC) method for C-H functionalization of *N*-aryl tetrahydroisoquinolines have been explored [41]. Alagiri also tried



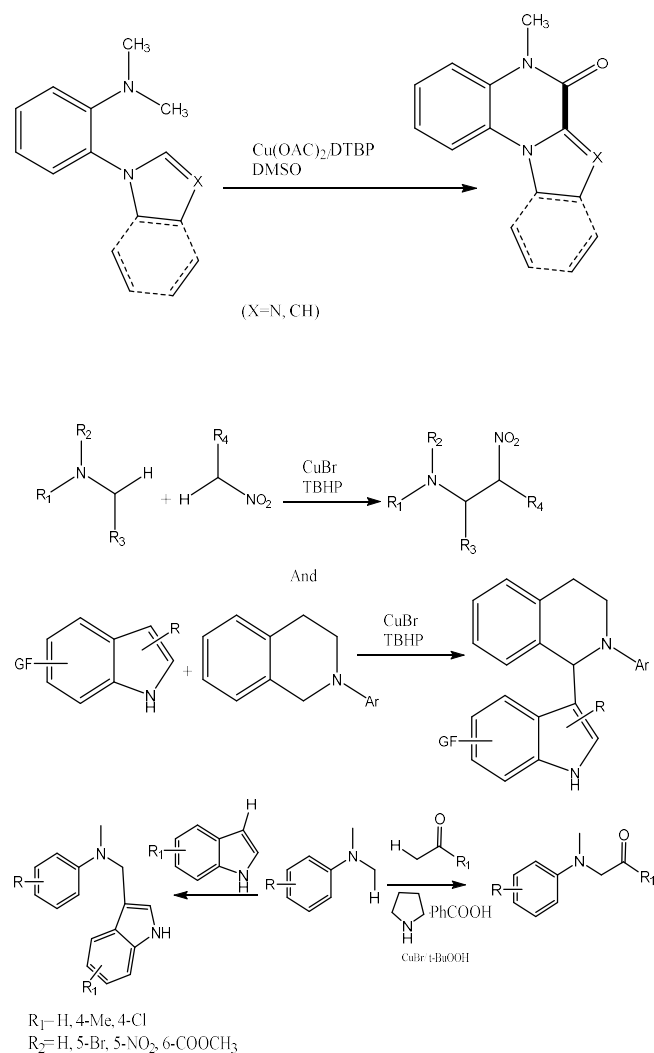
Scheme 6

In the same year, Xie *et al.*, molybdenum(VI) acetylacetonate and vanadium pentoxide for the synthesis of α -aminonitriles and β -nitroamines under aerobic condition [42]. In 2018, Li *et al.*, used WO_3 nanospheres with improved catalytic activity for induction of CDC reaction [43] (Scheme 7).



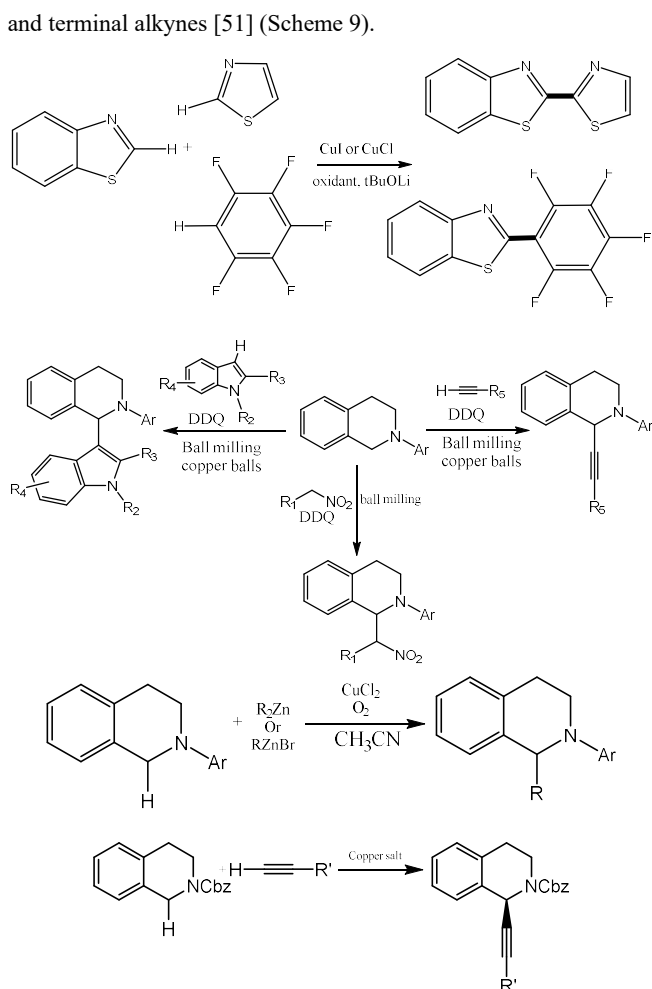
Scheme 7

In the search for heterogeneous and reusable catalysts, Gogoi *et al.* showed that the Copper(II) catalyzed the oxidative Mannich reaction for the synthesis of Indoloquinoxalin-6-ones [44]. A novel method for C–C bond formation was developed by Li, in 2005, for CDC reaction catalyzed by using copper bromide in the presence of an oxidizing reagent, *t*-BuOOH [45,46]. In another study by Yang *et al.*, the reaction of *N,N*-dimethylanilines with methyl ketones by cooperative copper and aminocatalysis has been developed, which leads to the formation of β -arylamino ketones. Moreover, the copper-catalyzed alkylation of free (NH) indoles with *N,N*-dimethylanilines via CDC reaction is also presented, affording alkylated indoles [47] (Scheme 8).



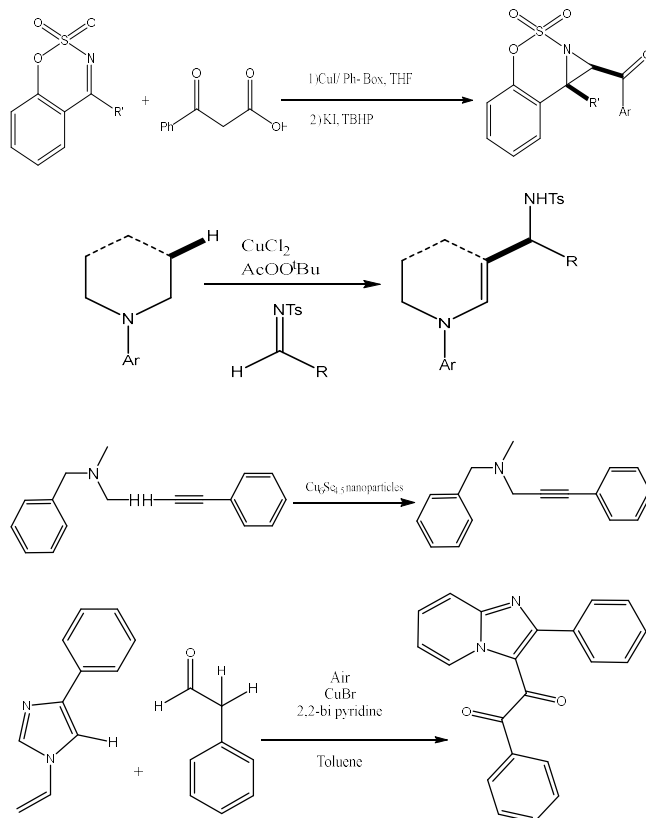
Scheme 8

A copper-catalyzed dehydrogenative cross-coupling of benzothiazoles with thiazoles and polyfluoroarene with a straightforward and operationally simple method for the synthesis of the 2,2'-linkage of thiazoles and 2-polyfluoroarylthiazoles is described by Fan *et al.*, in 2012 [48]. Su *et al.*, used a high-speed ball milling technique to CDC reactions between tetrahydroisoquinolines and three types of pronucleophiles such as nitroalkanes, alkynes, and indoles and the reactions catalyzed efficiently by recoverable copper balls without any additional metal catalyst [49]. Continued use of popular copper metal as a catalyst, Wang *et al.*, utilized CuCl_2 as an efficient catalyst in aerobic oxidative cross-coupling of THIQs with organozinc Reagents [50]. In 2015, Sun *et al.*, employed CuCl as a highly enantioselective catalyst for coupling between *N*-carbamoyl tetrahydroisoquinolines and terminal alkynes [51] (Scheme 9).



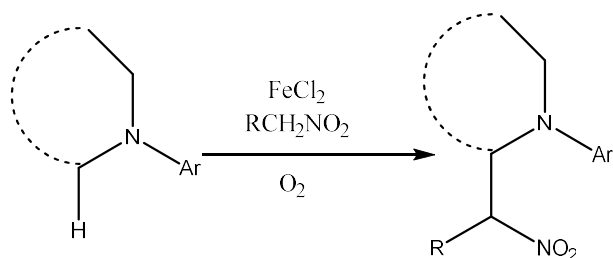
Scheme 9

In 2016, Lai *et al.*, described a novel one-pot sequential transformation via decarboxylative Mannich reaction (DMR) and oxidative C–H amination of cyclic imines with β -ketoacids. With this methodology, they have access to fused aziridines with excellent diastereoselectivity [52]. A copper-catalyzed Mannich-type oxidative β -functionalization reaction of tertiary amines in the presence of an oxidant has been developed by Zhou *et al.* [53]. The use of $\text{Cu}_6\text{Se}_{4.5}$ nanoparticles for an efficient and regioselective reaction of tertiary amines with terminal alkynes in the presence of *tert*-butyl hydroperoxide as the oxidant is demonstrated for the first time by Gupta *et al.*, [54]. An article, which published in 2016 by Abdul Shakoor *et al.*, claimed that copper catalyzed direct aerobic double-oxidative cross-dehydrogenative coupling of imidazo heterocycles with aryl acetaldehydes [55] (Scheme 10).



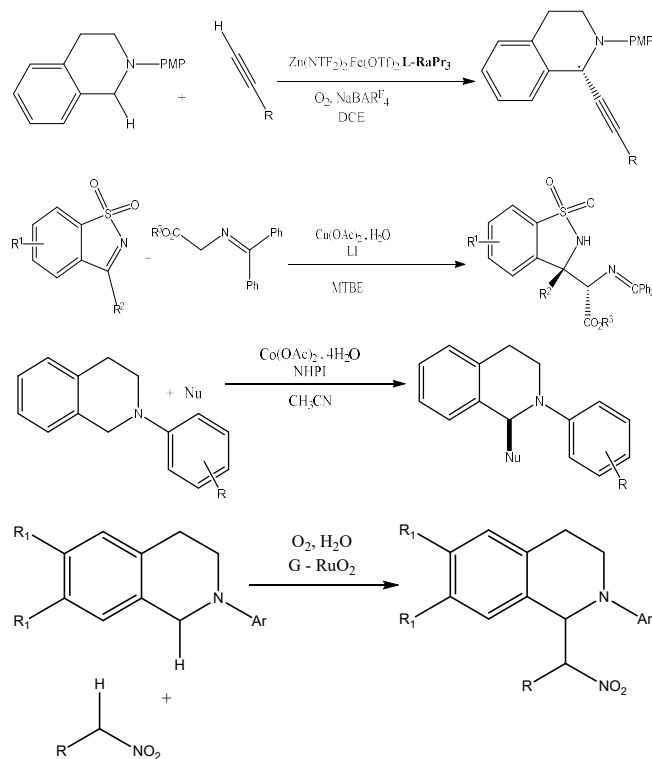
Scheme 10

One of the most widely used metals, as a catalyst is iron. In 2015, Brzozowski *et al.*, used FeCl_2 in direct α - $\text{C}(\text{sp}^3)$ -H functionalization of *N*-aryl tetrahydroisoquinolines for aerobic nitro-Mannich reaction [56] (Scheme 11).



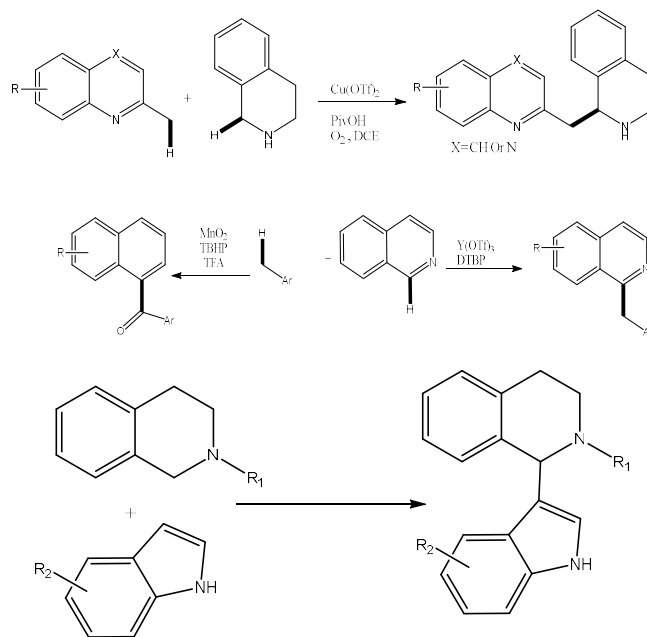
Scheme 11

Huang *et al.* used a chiral N,N' -dioxide/zinc(II)/iron(II) bimetallic cooperative catalytic system for the formation of various α -alkynyl substituted tetrahydroisoquinolines in good to excellent yields and enantioselectivities (Scheme 7) [57]. In 2018, Shao *et al.*, Copper/RuPHOX-Catalyzed Mannich reaction with cyclic ketimines (Scheme 8) [58]. In the same year, Cobalt (II)/ N -Hydroxyphthalimide has used as a catalyst for reaction under aerobic condition [59]. In order to react between the tertiary amines and the nitroalkanes *via* a CDC, Meng *et al.*, utilized graphene-supported RuO_2 nanoparticles as a catalyst for efficient aerobic cross-dehydrogenative coupling reaction in water [60] (Scheme 12).



Scheme 12

In 2014, Wang *et al.*, developed a copper/Brønsted acid dual-catalyst for promotion of oxidative CDC of alkylazaarenes and tertiary amines forming $C(sp^3)-C(sp^3)$, which used dioxygen as the terminal oxidant [61]. Wan *et al.*, claimed that the direct use of methyl arenes as coupling partners avoids unproductive steps for preactivating the functional group installation. They afforded exclusive benzylated products in the presence of DTBP and a catalytic amount of $Y(OTf)_3$, and yielding benzoylated ones with TBHP and a catalytic amount of MnO_2 [62]. Dutta *et al.*, disclosed a novel, heterogeneous catalytic approach for selective coupling of C1 of N -aryltetrahydroisoquinolines with C3 of indoles in the presence of mesoporous manganese oxides [63] (Scheme 13).

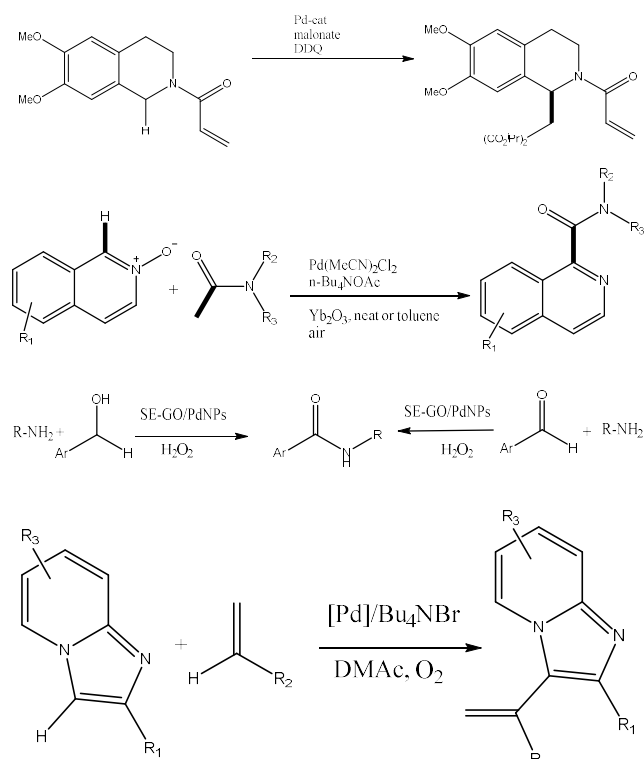


Scheme 13

Dubs *et al.*, found that an N, O -acetal which generated in situ by the reaction of dihydroisoquinolines (DHIQs) with $(Boc)_2O$, and cooperative action of the Pd(II) complex as an acid-base catalyst allowed the formation of a chiral Pd enolate and a reactive iminium ion *via* R-fragmentation. The iminium ion was also attainable via oxidation with DDQ as an oxidant, and a catalytic asymmetric oxidative Mannich-type reaction was achieved with tetrahydroisoquinolines (THIQs) as starting materials [64]. Yao *et al.*, established a palladium-catalyzed oxidative carbamoylation reaction of isoquinoline N -oxides with formylamides for the

synthesis of isoquinoline-1-carboxamides. They claimed that this method represents the first example of the carbamoylation of isoquinoline *N*-oxides with formylamides to furnish arylamides using the dual C–H oxidation strategy [65]. In 2015, Rostamia *et al.*, used Pd nanoparticles deposited onto graphene oxide nanosheets for one-pot conversion of alcohols to amides in the presence of various amines [66].

Ghosh *et al.*, in 2014, reported the vinylation of imidazopyridines through a cross-dehydrogenative coupling reaction *via* Palladium as a catalyst. The reaction proceeds with the aid of molecular oxygen as the sole oxidant [67] (Scheme 14).

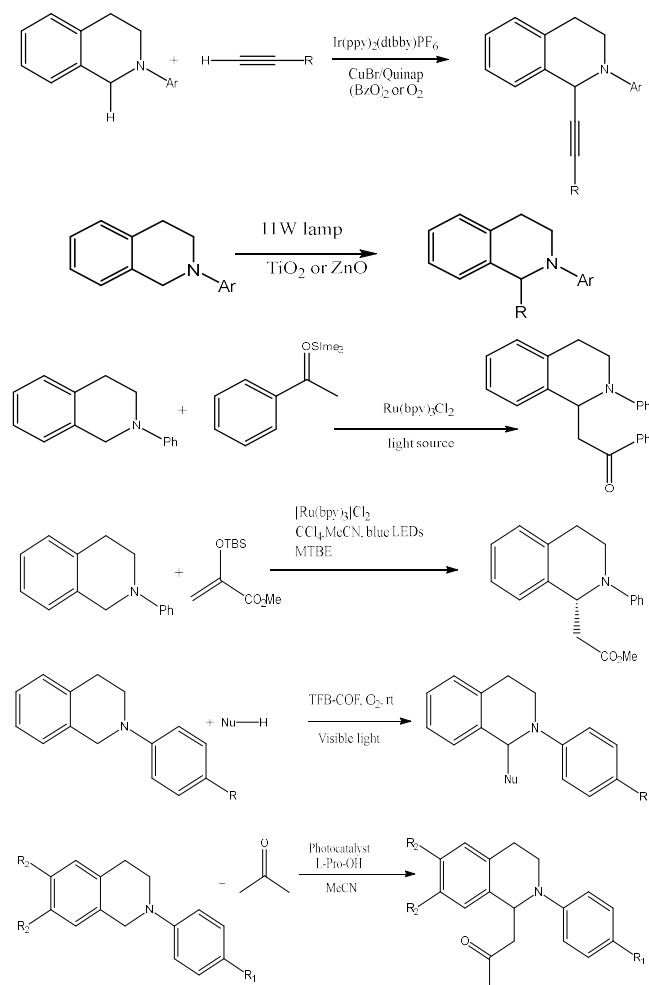


Scheme 14

Photocatalyst

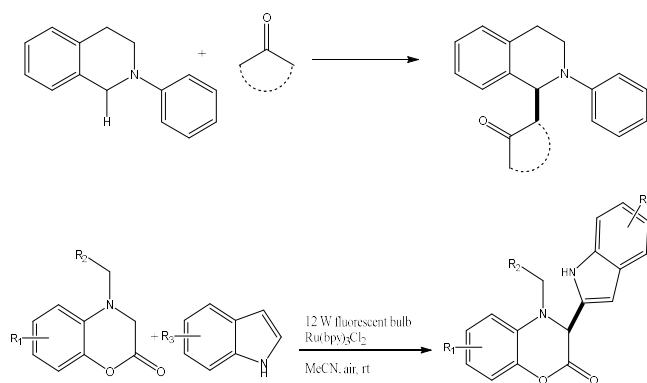
Photoredox catalysis has emerged as a powerful tool for organic synthesis [68]. Zhao *et al.*, in 2012, researched on oxidative coupling of tertiary amines using metal-based dyes (*e.g.* Ru(bpy)₃Cl₂)₁₅ as photoredox catalyst. They encountered that the generated reactive iminium ions could be intercepted by nucleophilic enol silanes, which eliminated the Me₃Si⁺ to yield the

desired Mannich-type product [69]. Rueping *et al.*, utilized a heterogeneous photocatalytic system based on recyclable TiO₂ or ZnO for reactions of tertiary amines [70]. In 2014, Bergonzini *et al.*, proposed dual catalytic reaction design in enantioselective oxidative Mannich reactions to access tetrahydroisoquinoline derived β-amino esters [71]. Perepichka *et al.*, developed an asymmetric alkylation of prochiral CH₂ groups in tetrahydroisoquinoline by using of copper as a catalyst via cross-dehydrogenative-coupling of sp³ and sp C–H bonds with the assistance of a photocatalyst and visible light [72]. In 2017, Liu *et al.* used a hydrazone-based covalent organic framework as an efficient and reusable photocatalyst for the CDC reaction of *N*-aryltetrahydroisoquinolines [73]. Luo *et al.*, have used efficient visible-light photocatalyst in aerobic oxidation reactions [74] (Scheme 15).



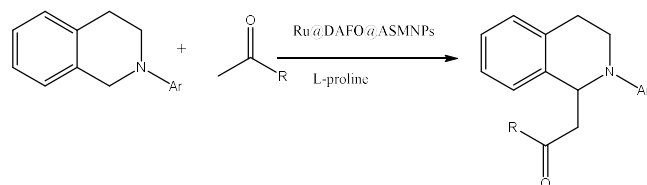
Scheme 15

Zhang *et al.*, introduced a bifunctional organic sponge photocatalyst for efficient CDC of tertiary amines to ketones [75]. The generation of an α -amino radical intermediate *via* Ru(bpy)₃Cl₂ as a photoredox catalyst under visible-light irradiation at room temperature were reported by Zhang *et al.*, in 2018. This intermediate was oxidized by O₂ as terminal oxidant [76] (Scheme 16).



Scheme 16

Rana *et al.*, reported the fabrication of a highly versatile ruthenium-based magnetically recoverable photoredox nanocatalyst. They referred to the visible light as the nanocatalyst harvesting which was effectively used for CDC *via* C–H activation between tertiary amines and various carbon nucleophiles with high regioselectivity to afford the C–C coupled products in good to excellent yield using air as an oxidant under ambient conditions [77] (Scheme 17).



Scheme 17

Organocatalyst

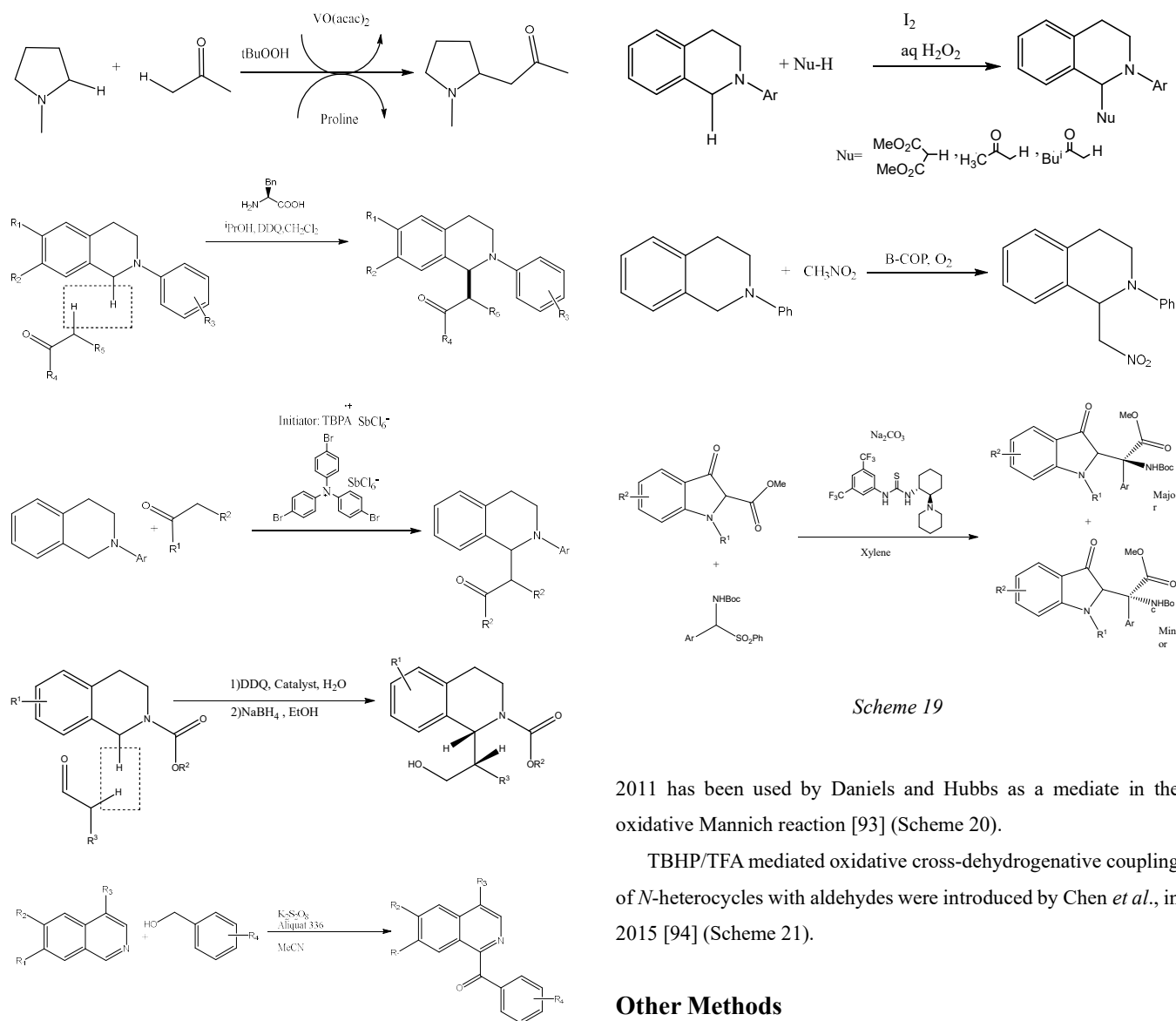
The term “organocatalysis” was introduced by MacMillan *et al.* in 2000 [78] and can be defined as “the acceleration of chemical

reactions by employing a sub-stoichiometric quantity of a chiral organic compound that does not contain a metal atom” [79]. Organocatalysts have several advantages such as nontoxicity, stability, availability and easy to synthesize [80]. The combination of vanadium- and organocatalysis allows for the direct oxidative coupling of cyclic tertiary amines with non-activated ketones without the need for preformed leaving groups. Sud *et al.*, in 2009 utilized this combination for the synthesis of 1-(1-methylpyrrolidin-2-yl)propan-2-one [81]. In 2013, Zhang *et al.*, have revealed the first example on metal-free catalytic asymmetric oxidative coupling reaction of tertiary amines with simple ketones *via* a chiral ion-pair catalysis strategy for the construction of a C–C bond under mild conditions using a natural α -amino acid as the catalyst [82]. Huo *et al.*, used catalytic amounts of triarylammonium salt (TBPA) induced C–C bond formation protocol between tertiary amines and unmodified ketones with air as a sustainable and efficient oxidant in oxidative Mannich reaction [83]. In 2016, Xie *et al.*, have introduced enantioselective Cross-Dehydrogenative Coupling of *N*-Carbamoyl Cyclic Amines with Aldehydes by using an organocatalyst [84]. An acylation of quinolines and isoquinolines by use of arylmethanols as the acylating agents through a C–C bond formation *via* an oxidative CDC strategy is described by Adib *et al.*, [85] (Scheme 18).

In 2013, Nobuta *et al.*, reported that the molecular Iodine catalyzed coupling reaction between two sp³ C–H Bonds using hydrogen peroxide as an oxidant [86]. In 2019, there have been many cases of oxidative Mannich reactions, including the article by Liu *et al.*, in which difluoroborate-based conjugated organic polymer (B-COP) has been used as a high-performance heterogeneous photocatalyst for oxidative coupling reactions [87]. In another research, Kumar *et al.*, used thiourea as an organocatalyst in enantioselective Mannich reaction for the synthesis of chiral β -amino esters [88] (Scheme 19).

Natural Medium in Oxidative Mannich Reaction

Usage of abundant natural products as synthetic launching points for diversity-oriented synthesis (DOS) has attracted significant attention, as highly complex compounds can be rapidly prepared for biological evaluation [89]. Grenning *et al.*, report a two-step diversity-oriented synthesis strategy using cascade



Scheme 18

cyclization and oxidative Mannich reactions, reminiscent of natural product biosynthesis, yielding alkaloid-like structures with high levels of complexity [90].

Jo *et al.* introduced Sequential DDQ-Mediated oxidative Mannich reactions of *N*-aryl pyrrolidines for the synthesis of 8-Azabicyclo[3.2.1]octanes [91]. Likewise, Yu *et al.* used DDQ-mediate for mild and chemo-selective coupling of *N*-Boc tetrahydroquinolines and ketones [92]. Selectfluor is a commercially available electrophilic fluorinating reagent that in

Scheme 19

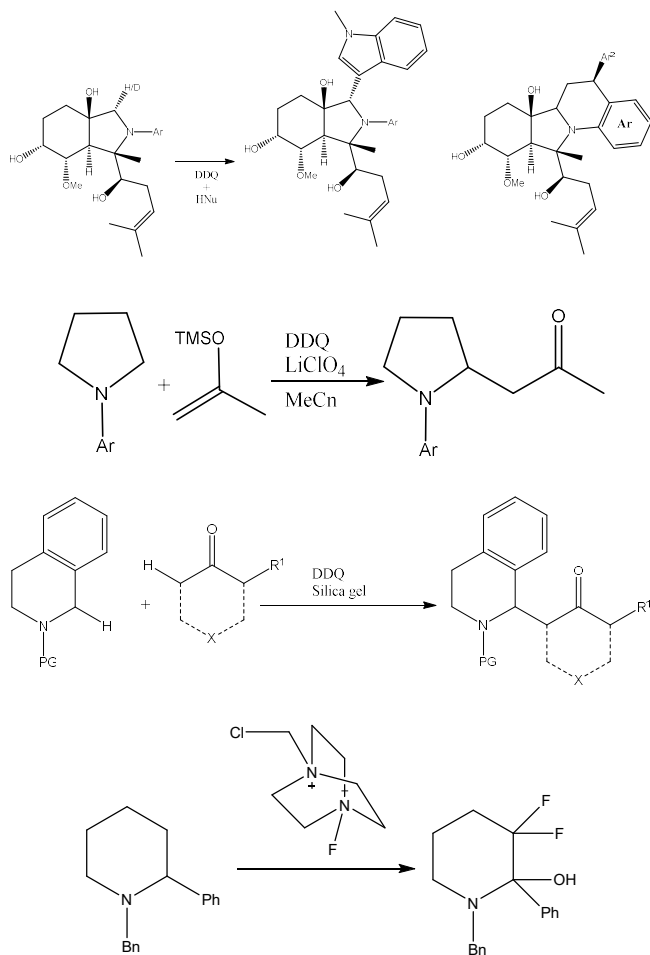
2011 has been used by Daniels and Hubbs as a mediate in the oxidative Mannich reaction [93] (Scheme 20).

TBHP/TFA mediated oxidative cross-dehydrogenative coupling of *N*-heterocycles with aldehydes were introduced by Chen *et al.*, in 2015 [94] (Scheme 21).

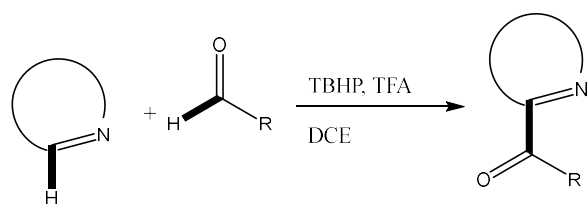
Other Methods

Matsou *et al.*, has reported oxidative Mannich Reaction of *N*-Carbobenzyloxy Amines with 1,3-Dicarbonyl Compounds (Scheme 22) [95]. They considered that the mild generation of imines would be possible by utilizing the oxidation of amines with *N*-*tert*-butylbenzenesulfinimidoyl chloride which oxidizes various amines to the corresponding imines under mild conditions.

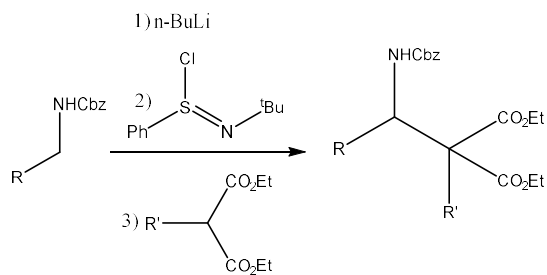
Transition metal-free acylation of isoquinoline, quinoline, and quinoxaline derivatives has been developed by Siddaraju *et al.*, via a cross dehydrogenative coupling reaction with aldehydes using substoichiometric amount of TBAB (tetrabutylammonium bromide) and $K_2S_2O_8$ as an oxidant [96]. In 2013, Matcha and Antonchick, synthesized a range of heterocyclic compounds by a novel, metal-



Scheme 20

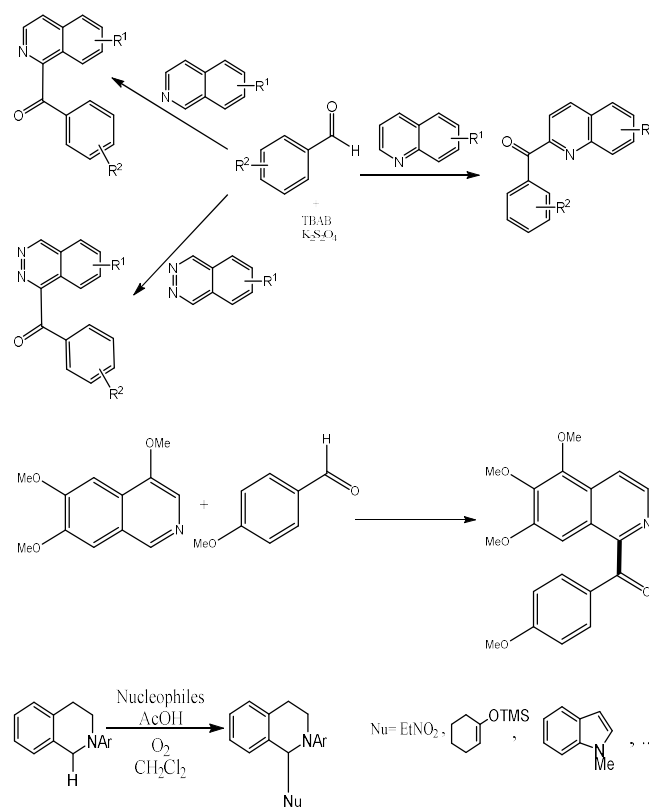


Scheme 21



Scheme 22

free coupling between heterocycles and aldehydes under mild reaction conditions that are not sensitive to moisture [97]. Ueda *et al.*, proceeded C–C bond forming reactions with a range of nucleophiles (nitroalkane, enol silyl ether, indole, allylstannane, and tetrabutylammonium cyanide) under metal-free conditions and an oxygen atmosphere. They were demonstrated that acetic acid caused a significant acceleration effect [98] (Scheme 23).

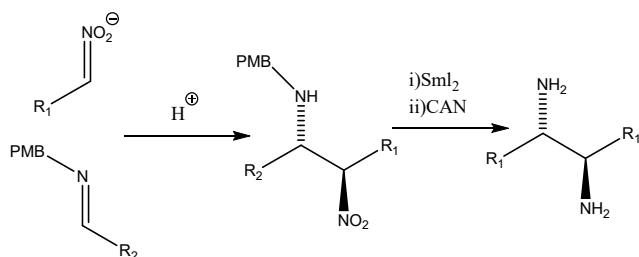


Scheme 23

Reductive Mannich Reaction

A complement to the classic three-component Mannich reaction, the redox-Mannich reaction, utilizes the same starting materials but incorporates an isomerization step that enables the facile preparation of ring-substituted β -amino ketones. Reactions occur under relatively mild conditions and are facilitated by benzoic acid [18]. Compared to oxidative reactions, reduced reactions are less frequent. Whilst the Mannich reactions have been extensively studied, the nitro-Mannich reactions, which react *via* a nitronate species, have been much less well researched [99]. Due to the high potential of

the nitro-Mannich reaction products, the reaction had not received much attention until 1998 when the Anderson *et al.*, for the first time published diastereoselective procedure [100] (Scheme 24).



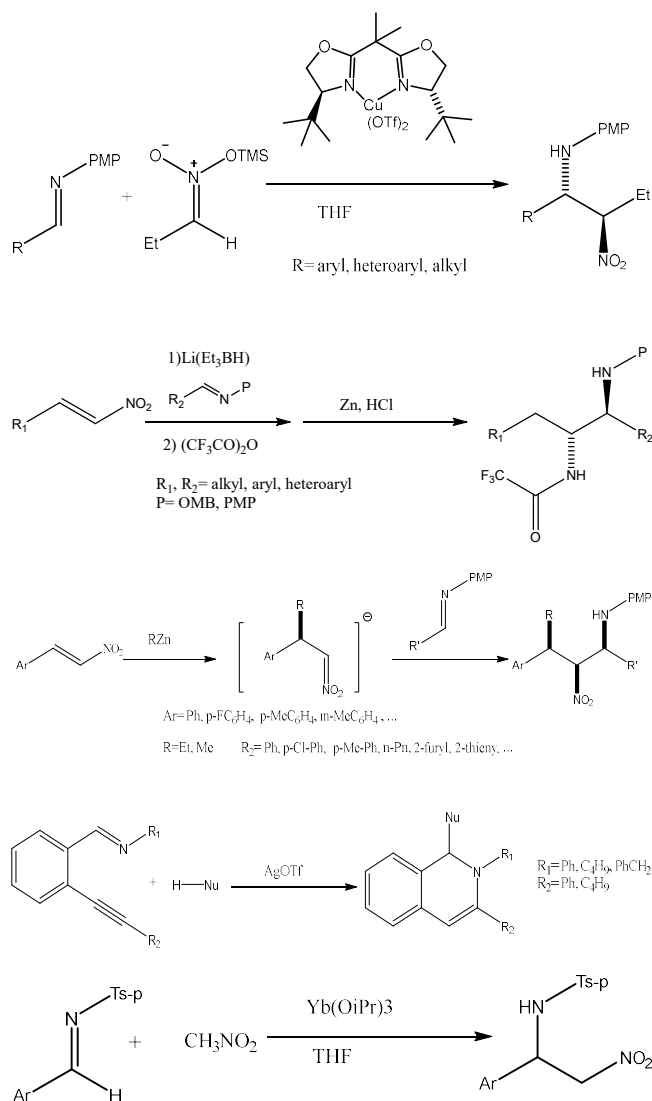
Scheme 24. First reductive Mannich reaction

Catalytic Reductive Mannich Reaction

Metal-based Catalysts

In 2005, a protocol is described by Anderson *et al.*, for the enantioselective nitro-Mannich coupling between alkyl, aryl, and heterocyclic *p*-methoxybenzylamines and trimethylsilylnitropropanate catalyzed by a chiral tBu-BOX Cu(II) catalyst is described [101]. In another research by this group, a range of nitroalkenes and imines derived from alkyl, aryl, and heteroaryl aldehydes underwent a tandem 1,4-hydride addition nitro-Mannich reaction to afford anti-rich β -nitroamines [102]. A variety of 1,2-dihydroisoquinoline derivatives have been synthesized by Assoc *et al.*, which AgOTf-catalyzed the reaction of ortho-alkynylaryl aldimines with various pronucleophiles [103]. They also reported an enantioselective conjugate addition nitro-Mannich reaction protocol which combines dialkylzinc, aromatic nitro alkene, and imine to form two C–C bonds and three contiguous stereocenters in one reaction [104]. Qian *et al.*, was found that a catalytic amount of Yb(OiPr)₃ could be an excellent and practical catalyst for the nitro-Mannich reaction of nitromethane with sulfonylimines under extremely mild reaction conditions [105] (Scheme 25).

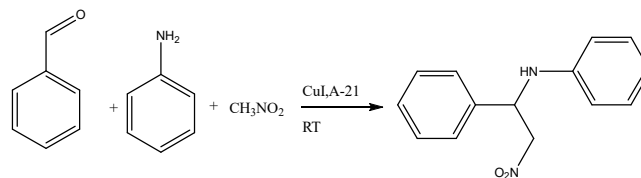
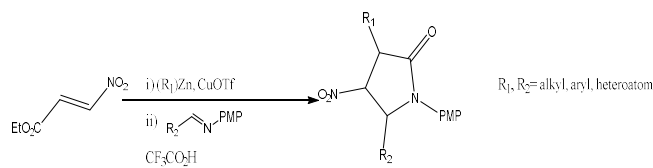
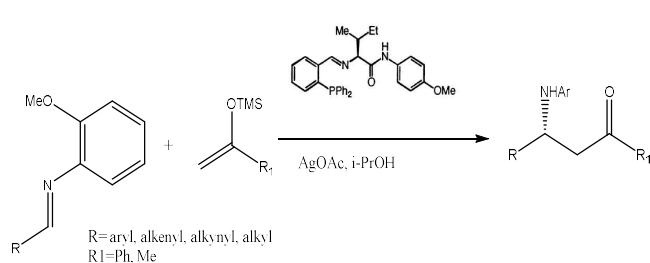
A large variety of β -amino ketones synthesized by the reaction between trimethylsilyl enol ethers derived from acetone and acetophenone and aryl, alkenyl, alkynyl, and alkyl imines which is described by Josephson *et al.*, in the presence of 1-5 mol % AgOAc as the catalyst and amino acid-derived phosphine [106]. Handa *et al.*, have reported a syn-Selective catalytic asymmetric nitro-Mannich reactions using a heterobimetallic Cu/Sm/Schiff base



Scheme 25

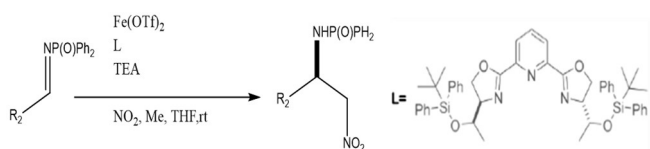
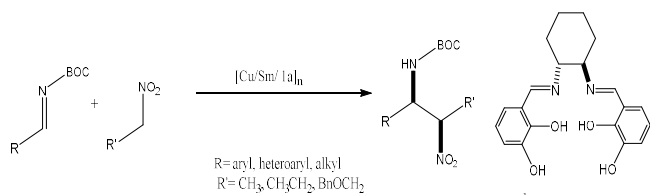
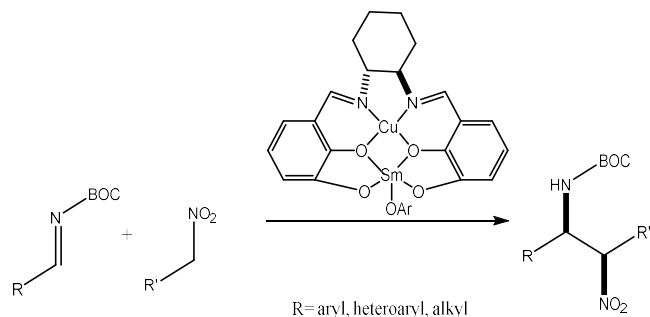
complex. They claimed that both Cu and Sm metals were essential to realizing high syn-selectivity [107]. In another research published by this group in 2010, they used the first-generation system prepared from Cu(OAc)₂/Sm(O-iPr)₃/Schiff base 1a = 1:1:1 with an achiral phenol additive for catalytic asymmetric nitro-Mannich reaction [108]. The enantioselective addition of nitroalkanes to imines (nitro-Mannich reaction), mediated by an iron(II) catalyst assembled by a hindered hydroxyethyl-pybox ligand, is described by Dudek and Mlynarski [109] (Scheme 26).

Stereoselective synthesis of densely functionalized pyrrolidin-2-ones by a conjugate addition/nitro-Mannich catalyzed by Copper

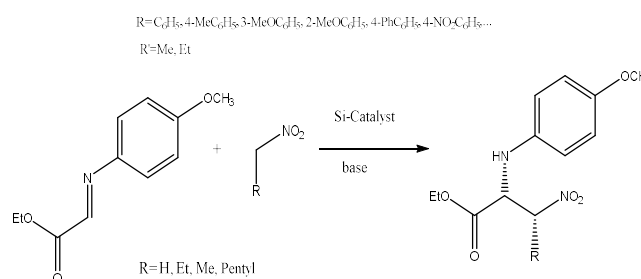
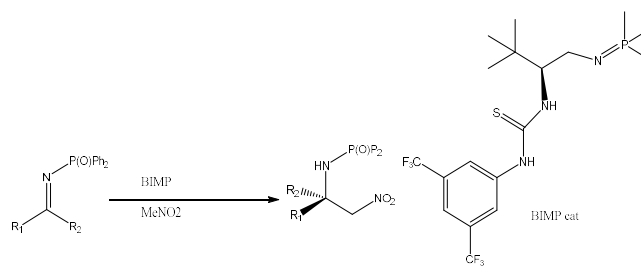


Scheme 27

immobilized on mesoporous silica (SBA-15) and examined in an asymmetric heterogeneous nitro-Mannich reaction by Lee *et al.*, in 2004 [113] (Scheme 28).



Scheme 26



Scheme 28

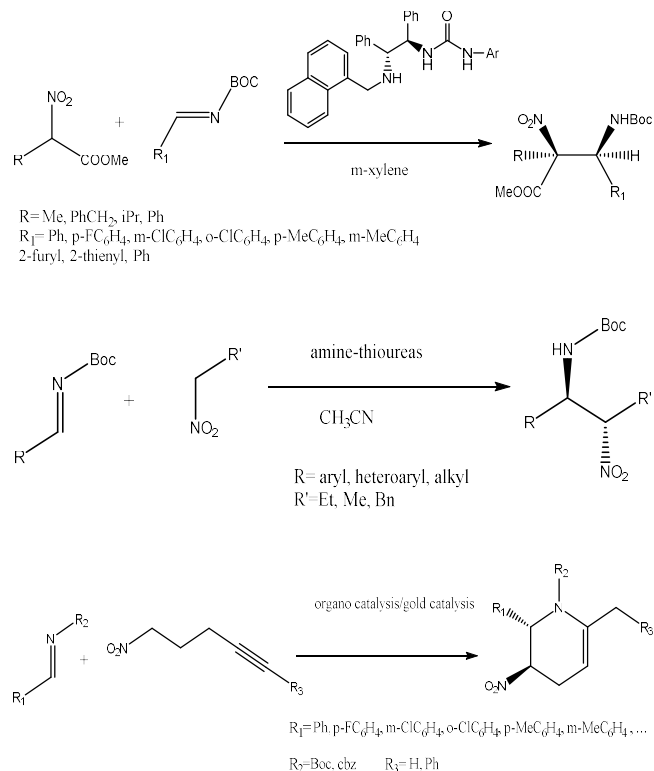
has been reported by Anderson *et al.*, in 2012 [110]. Bosica and Zammit found that the amberlyst A-21 supported CuI could be an efficient catalyst for the three-component nitro-Mannich reaction between aldehydes, amines, and nitroalkanes. The developed protocol is performed in a solvent-free medium to produce a variety of β -nitroamines in good to excellent yields [111] (Scheme 27).

Organocatalysts

Núñez *et al.*, introduced the new generation of the organocatalyst which incorporates a triaryliminophosphorane as the Brønsted basic moiety and has been utilized in general enantioselective organocatalytic nitro-Mannich reaction of nitromethane to unactivated ketone-derived imines for the synthesis of β -nitroamines [112]. A chiral bis(oxazoline) ligand was

A stereoselective nitro-Mannich reaction of α -substituted nitroacetates and *N*-Boc aldimines was investigated catalyzed by novel chiral bifunctional thiourea/secondary-amine systems by Han *et al.*, [114]. In the same year, Wang *et al.*, used the chiral bifunctional multiple hydrogen-bonding-donor amine-thioureas as the catalyst for the nitro-Mannich reaction [115]. The enantioselective preparation of synthetically useful tetrahydropyridine derivatives employing a one-pot nitro-Mannich/hydroamination cascade is reported by Barber *et al.*, which utilized an asymmetric organocatalytic nitro-Mannich reaction

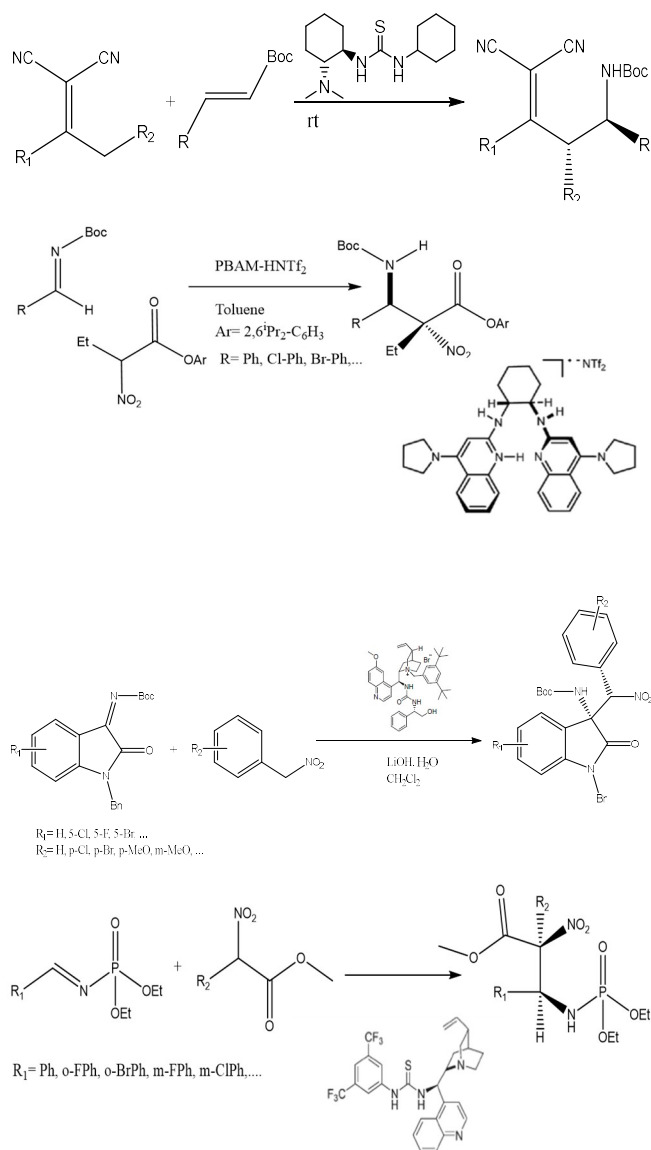
followed by a gold-catalyzed alkyne hydroamination/isomerization sequence [116] (Scheme 29).



Scheme 29

Liu *et al.*, used an organocatalyst in direct asymmetric vinylogous Mannich (AVM) reaction [117]. The utilization of the BAM (bis(AMidine)) catalyst has been reported by Sprague *et al.*, in reductive Mannich reaction [118]. A reductive Mannich reaction of isatin-derived ketimines with α -aryl nitromethane catalyzed by Cinchona alkaloid-derived phase-transfer catalysts bearing multiple hydrogen-bonding donors was developed by Liu *et al.*, in 2018 [119]. Fan *et al.*, performed a reaction of *N*-phosphoryl imines with α -substituted nitroacetates by using cinchona alkaloid thioureas as organocatalysts in toluene [120] (Scheme 30).

Zhang *et al.*, synthesized the chiral bis(betaïne)s, containing two catalytically active centers have by an organocatalyst [121]. Bandar and Lambert showed that cyclopropenimine catalyze Mannich reactions between glycine imines and *N*-Boc-aldimines with high levels of enantio- and diastereocontrol [122]. In 2021, ascorbic acid

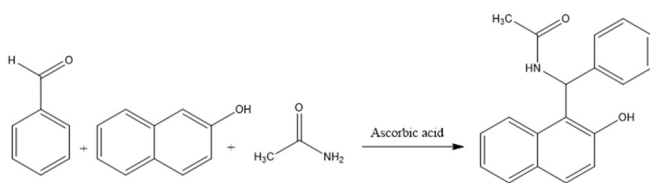
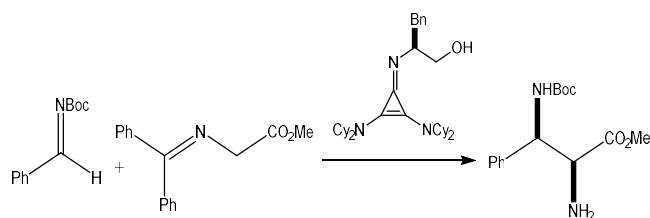
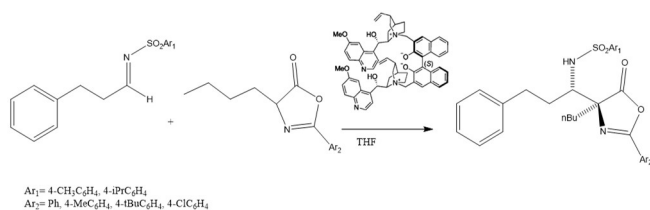


Scheme 30

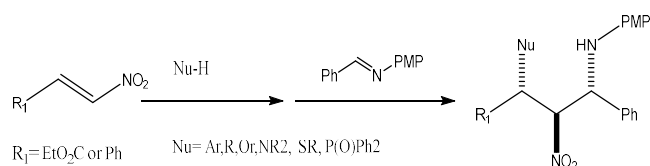
used as a natural and water-soluble catalyst for synthesis of amido alkyl β -naphthol and amidoalky naphthoquinones [123] (Scheme 31).

Other Methods

The nitro-Mannich reactions of ethyl- β -nitroacrylate and β -nitrostyrene with electron-rich aromatic nucleophiles, stabilized carbanions, alcohols, amines, thiols, and diphenyl phosphine oxide was investigated by Anderson *et al.*, in 2014 [124] (Scheme 32).



Scheme 31



Scheme 32

CONCLUSION

It has been proven that multicomponent Mannich reaction is an excellent synthetic method for the synthesis of biological active compounds *via* several methods involving different reaction conditions, such as aqueous medium, usage of different kinds of catalysts, solvent and catalyst-free reactions, usage of ultrasound and microwave irradiation, among others, emphasizing recent advances in sustainable protocols according to the Green Chemistry. In this review, we have tried to study the recent researches on the oxidative and reductive Mannich reaction. By means of this group of reactions, products have been synthesized by using a wide variety of methods, such as the use of metallic, organic catalysts or without a catalyst. In the oxidative Mannich reaction we need the presence

of an oxidizing agent such as oxygen, air, etc. Finally, we hope that the nature of this article will incite future researches in the development of more organic and catalytic reactions.

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