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Recent achievements in the synthesis of benzimidazole derivatives

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Benzimidazoles are a class of heterocyclic compounds in which a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazole refers to the parent compound, while benzimidazoles are a class of heterocyclic compounds having similar ring structures, but different substituents. Benzimidazole derivatives possess a wide range of bioactivities including antimicrobial, anthelmintic, antiviral, anticancer, and antihypertensive activities. Many compounds possessing a benzimidazole skeleton have been employed as drugs in the market. The application of benzimidazoles in other fields has also been documented. The synthesis of benzimidazole derivatives has attracted much attention from chemists and numerous articles on the synthesis of this class of heterocyclic compound have been reported over the years. The condensation between 1,2-benzenediamine and aldehydes has received intensive interest, while many novel methods have been developed. In this article, we will give a comprehensive review of studies on the synthesis of benzimidazole, which date back to 2013. We have also tried to describe reaction mechanisms as much as we can. The work might be useful for chemists who work in the synthesis of heterocycles or drug chemistry.

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1. Introduction

Benzimidazole, alternatively known as 1*H*-benzimidazole or 1,3-benzodiazole, is a bicyclic heterocyclic aromatic compound in which a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Nitrogen atoms are at the 1 and 3 positions of the ring system. Benzimidazole derivatives play a crucial role in the field of medicinal chemistry because they possess a wide

range of pharmacological activities such as antimicrobial, anticancer, antifungal, antileishmanial, antitubercular, antiviral and antimalarial, and some of them have been marketed as well-known drugs.

1.1. Antimicrobial activity

Benomyl (1), carbendazim (2), fuberidazole (3), and thiabendazole (4) are benzimidazole derivatives which have been used as fungicidal agents in the market (Fig. 1). Among indole-based pyrido[1,2-*a*]benzimidazoles synthesized by Kathrotiya and Patel, compounds 5, 6, and 7 displayed considerable antibacterial activity against *S. typhi* (MIC 50, 62.5 and 12.5 $\mu\text{g mL}^{-1}$, respectively) compared to reference drugs ampicillin,

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Fig. 1 Benzimidazole compounds with antimicrobial activity.

chloramphenicol, and ciprofloxacin (MIC 100, 50 and 25 $\mu\text{g mL}^{-1}$, respectively), while compounds 6 and 8 showed promising antifungal activity against *C. albicans* (MIC 250 $\mu\text{g mL}^{-1}$) in comparison with standard griseofulvin (MIC 500 $\mu\text{g mL}^{-1}$) (Fig. 1).¹ Vasantha *et al.* demonstrated the synthesis of a series of *N*-arylidene-2-(2,4-dichlorophenyl)-1-propyl-1*H*-benzo[*d*]imidazole-5-carbohydrazide derivatives and the evaluation of these compounds for antimicrobial activity. Among them,



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compound 9 appeared to be a promising antibacterial and antifungal agent with an MIC value of 3.12 $\mu\text{g mL}^{-1}$ against most bacterial and fungal strains (Fig. 1).² A library of 2-substituted benzimidazole derivatives was synthesized and examined for antibacterial activity. Compound 10 was found to be the most potent antibacterial agent against both Gram-positive and Gram-negative bacteria compared to the reference cefadroxil, while compound 11 showed maximum activity against *A. niger* (MIC = 0.018 mM) (Fig. 1).³ Amongst a series of purine benzimidazole hybrids synthesized by Wang *et al.*, compounds 12 and 13 were the most potent antibacterial agents with MIC values ranging between 3.9 and 7.8 $\mu\text{g mL}^{-1}$ against different bacterial strains (Fig. 1).⁴

1.2. Anthelmintic activity

Many benzimidazoles have been developed as anthelmintic agents in the market such as albendazole (14), ciclo bendazole (15), fenbendazole (16), flubendazole (17), mebendazole (18), oxfendazole (19), oxibendazole (20), triclo bendazole (21), and thiabendazole (4) (Fig. 2). Faruk *et al.* synthesized a series of 5-nitrobenzimidazole derivatives (22) and tested them for anthelmintic activity against the adult Indian earth worm *P. posthuma* (Fig. 2). The results of preliminary biological tests showed that all compounds exhibited significant anthelmintic activity.⁵ Vilasrao *et al.* described the synthesis of a library of 2-substituted benzimidazoles and the evaluation of their anthelmintic activity against the adult earthworm *E. fetida*. Among them, compounds 23–25 exhibited excellent anthelmintic activities which are comparable to that of standard albendazole (Fig. 2).⁶ Sreena *et al.* synthesized benzimidazole derivatives (26) by the condensation reaction between *o*-phenylenediamine and



Fig. 2 Benzimidazole derivatives with anthelmintic activity.



acid and screened them for anthelmintic activity (Fig. 2). All the tested compounds exhibited significant anthelmintic activity compared with the standard piperazine citrate.⁷

1.3. Antiviral activity

Enviradine (27) and maribavir (28) are benzimidazole-based compounds which have been used as antiviral agents (Fig. 3). Pan *et al.* introduced the synthesis of benzimidazole derivatives and the evaluation of these compounds for anti-HIV activity. Among them, compounds 29 and 30 showed significant activity with IC_{50} values of 3.45 and 58.03 nM, respectively (Fig. 3).⁸ Masoudi *et al.* prepared a series of benzimidazole derivatives and evaluated them for anti-HIV activity. Among the tested benzimidazoles, compound 31 was found to have significant activity with EC_{50} of $1.15 \mu\text{g mL}^{-1}$ against HIV-1 and HIV-2 (Fig. 3).⁹ Ferro *et al.* synthesized two series of benzimidazol-2-one derivatives and screened them for antiviral activity against HIV-1. Compounds 32 and 33 (IC_{50} values of 1.3 and $0.79 \mu\text{M}$, respectively) were more potent than the standard drug nevirapine (IC_{50} value of $1.55 \mu\text{M}$) (Fig. 3).¹⁰ Tsay *et al.* synthesized a diverse range of benzimidazole-coumarin hybrids and evaluated them for

antiviral activity against the hepatitis C virus. Compounds 34 and 35 displayed potent activity with EC_{50} values of 3.0 and 5.5 nM, respectively (Fig. 3).¹¹ Among benzimidazoles synthesized by Shaker *et al.*, compounds 36–38 showed great potential to be used as potent antiviral agents due to their inhibitory effect against the rotavirus Wa strain (Fig. 3).¹² Benzimidazole 39, obtained by Dai *et al.*, was found to be a potent antiviral agent against Lassa virus envelope glycoprotein (LASV GP) pseudotypes with an EC_{50} value of 1.1 nM (Fig. 3).¹³

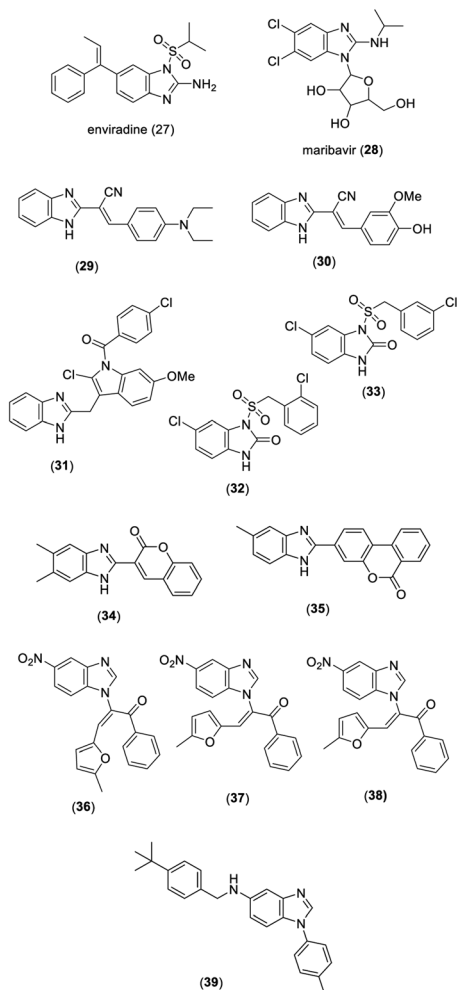


Fig. 3 Benzimidazole derivatives with antiviral activity.



Fig. 4 Benzimidazole derivatives with anticancer activity.





Fig. 5 Benzimidazole derivatives with anticancer activity.

1.4. Anticancer activity

Several benzimidazole derivatives have been marketed as anti-tumor agents such as bendamustine (40), selumetinib (41), galeterone (42), and pracinostat (43) (Fig. 4). In a study reported by Gohary *et al.*, compound 44 displayed significant anticancer activity with IC₅₀ values of 0.022, 0.014, and 0.015 μM against liver cancer (HepG2), colon cancer (HCT-116), and breast cancer (MCF-7) cells,¹⁴ respectively (Fig. 4). Wang *et al.* demonstrated the synthesis and screening for anticancer activity of the chrysin benzimidazole derivatives. Among the synthesized benzimidazoles, compound 45 exhibited excellent activity with IC₅₀ values of $25.72 \pm 3.95 \mu\text{M}$ against MCF cells (Fig. 4).¹⁵ A series of 2-((1*H*-benzo[*d*]imidazole-2-ylthio)acetamido)-*N*-(substituted-4-oxothiazolidin-3-yl)acetamides was synthesized and evaluated for anticancer activity by Yadav *et al.* Compound 46 and 47 showed remarkable activity with IC₅₀ values of 0.00005 and 0.00012 $\mu\text{M mL}^{-1}$ against the HCT116 cell line, respectively (Fig. 4).¹⁶ Among benzimidazole hydrazones prepared by Onnis *et al.*, compound 48 possessed significant anticancer activity with an IC₅₀ value of $0.98 \pm 0.02 \mu\text{M}$ against human T-lymphoblastic leukemia (CEM) cells (Fig. 4).¹⁷

Sharma *et al.* synthesized a series of benzimidazole bearing thiazolidinedione derivatives. The bioassay study indicated that compounds 49–51 possess remarkable cytotoxicity against PC-3, HeLa, A549, and HT1080 cancer cell lines with IC₅₀ values in the range of 0.096–0.63 μM (Fig. 4).¹⁸ In a study reported by Wang *et al.*, compound 52 exhibited significant activity with IC₅₀ values in the range of 0.006–1.774 μM against the K562, A431, HepG2, HeLa, and MDA-MB-435S cancer cell lines (Fig. 4).¹⁹ Among the 1,2,3,4-tetrahydro[1,2,4]triazino[4,5-*a*]

benzimidazoles synthesized by Nassan *et al.*, compound 53 displayed excellent activity with an IC₅₀ value of 0.0390 μM against the human breast adenocarcinoma cell line (Fig. 4).²⁰

1.5. Antihypertensive

Candesartan (54) and mibefradil (55) are antihypertensive drugs that contain benzimidazole rings (Fig. 5). Abou-Seri *et al.* synthesized a series of 2-alkoxy-4-aryl-6-(1*H*-benzimidazol-2-yl)-3-pyridinecarbonitrile derivatives. The bioactivity experiment revealed that all compounds showed significant vasodilation properties. In particular, compounds 56–59 showed most prominent activity with IC₅₀ values of 0.145, 0.202, 0.210, and 0.214 mM, respectively, compared to standard prazosin hydrochloride (IC₅₀ of 0.487 mM) (Fig. 5).²¹ Khan *et al.* prepared a set of 2-phenyl substituted benzimidazoles and examined the antihypertensive activity of these derivatives by using the tail cuff method. Compound 60 exhibited excellent antihypertensive properties in spontaneously hypertensive rats compared to standard losartan (Fig. 5).²² Among the 5-nitro benzimidazole derivatives synthesized by Zhu *et al.*, compound 61 was found to be the most active agent against AT1 with an IC₅₀ value of $1.03 \pm 0.26 \text{ nM}$ (Fig. 5).²³

1.6. Miscellaneous activities

Several benzimidazole derivatives have been used as antihistamines such as astemizole (63), bilastine (64), emedastine (65), mizolastine (66), and oxatomide (67) (Fig. 6). The drug bezitramide 68 has long been used as an analgesic agent (Fig. 6). Mariappan *et al.* synthesized a series of 2-substituted benzimidazole derivatives and bioactive assay revealed that compounds 69–71 showed significant analgesic and anti-inflammatory activities (Fig. 6).²⁴ In another report, compounds 72 and 73 prepared by Kumar *et al.* exhibited significant analgesic and anti-inflammatory properties.²⁵ Among *N*-benzimidazol-1-yl methyl-benzamide derivatives synthesized by Sethi *et al.*, compound 74 displayed significant analgesic and anti-inflammatory activity (Fig. 6).²⁶

Hameed *et al.* reported that compound 75 possesses significant antitubercular activity with an MIC value of 0.19 μM against fluoroquinolone-resistant strains of *M. tuberculosis* (Fig. 6).²⁷ In another study, compounds 76 and 77 were found to exhibit significant antitubercular activity at an MIC value of 1.56 $\mu\text{g mL}^{-1}$ against *M. tuberculosis* strains of H37Rv (Fig. 6).²⁸ Among the benzimidazoles developed by Arora *et al.*, compounds 78–80 showed remarkable antioxidant activity (IC₅₀ values of 19.7, 13.9 and 1.2 $\mu\text{mol L}^{-1}$, respectively) compared to standard butylated hydroxytoluene (BHT, IC₅₀ of 23.4 $\mu\text{mol L}^{-1}$) (Fig. 6).²⁹ In a report described by Mentese *et al.*, compounds 81 and 82 demonstrated significant antioxidant activity (Fig. 6).³⁰ In research accomplished by Nieto-Meneses *et al.*, a library of *N*-benzyl-1*H*-benzimidazol-2-amine derivatives was synthesized and evaluated for antileishmanial activity. Among them, compounds 83 and 84 exhibited significant antileishmanial activity against the amastigotes of *L. mexicana* and *L. braziliensis*, with IC₅₀ values of 2.62 and 3.21 μM (Fig. 6), respectively, and their activities were 5.8 and 4.8 times better than standard miltefosine (IC₅₀ of 15.34 μM).³¹ The bioactivities of





Fig. 6 Benzimidazole derivatives with other bioactivities.

benzimidazole derivatives were also demonstrated in some review articles.^{32–34}

In addition, benzimidazoles are very important intermediates in dyes and polymer synthesis.^{35–37} They have also widely been used in material science such as in chemosensing,^{38–40} crystal engineering,^{41,42} fluorescence applications,^{43–47} and corrosion science.^{48,49} Furthermore, they have been employed as important intermediates in organic reactions,^{50–52} and as ligands for asymmetric catalysis.^{53–57}

Owing to the vast importance of benzimidazoles in different areas, enormous efforts have been made to develop operationally simple synthetic methods for the construction of benzimidazole derivatives. The condensation reaction between 1,2-benzenediamines and aldehydes is one of the most efficient and straightforward methods for the synthesis of benzimidazoles and a great deal of studies based on this method have appeared in the literature. Furthermore, numerous novel approaches for the synthesis of benzimidazole-based compounds have been developed. In the literature, several benzimidazole synthesis review articles have been published. However, most of them are quite outdated^{58,59} or do not demonstrate all aspects of benzimidazole synthesis.^{60,61} In addition, in these review articles, reaction mechanisms were usually not described in detail. In this article, we give a brief description of the bioactivities of benzimidazole derivatives and a comprehensive overview of benzimidazole synthesis, which covers all aspects of thiazole synthesis studies dating back to 2012. We also try to describe reaction mechanisms as much as possible. The article might be useful for chemists who work in pharmaceuticals, organic synthesis, and the synthesis of heterocycles. We have previously produced reviews on the synthesis of furans, pyrroles, thiophenes, benzofurans, benzothiophenes, oxazoles, isoxazoles, and thiazoles,^{62–69} and this article is a continuation of our investigation into the synthesis of aromatic five-membered ring heterocycles.

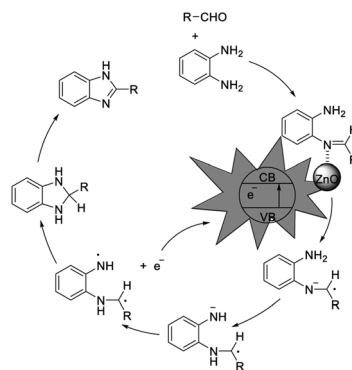
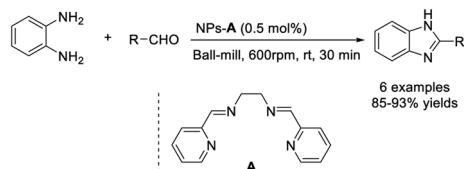
2. Benzimidazole synthesis by condensation of 1,2-benzenediamines with aldehydes

2.1. Using nanomaterial catalysts

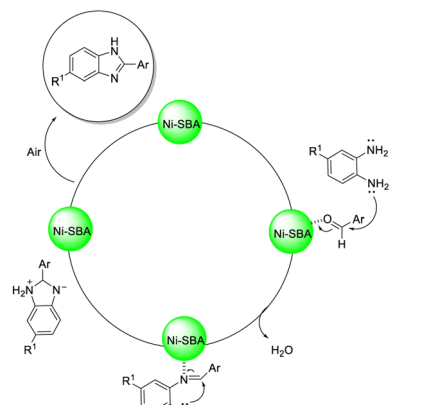
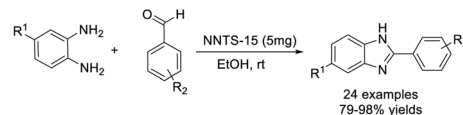
Sharma *et al.* achieved the synthesis of benzimidazole from 1,2-benzenediamine and various aldehydes using a ZnO-NP catalyst *via* a ball-milling technique. The catalyst was synthesized *via* a sol-gel method with *in situ* decoration of organic ligand **A** on the surface of the ZnO. The synthesis featured several advantages such as short reaction times, simple product purification, high efficiency, solvent-free conditions, recyclability of the ZnO-NP catalyst, and scalability.⁷⁰ A mechanistic study suggested that the role of the catalyst is to activate the imine intermediate to accept an electron (Scheme 1).

Wang *et al.* demonstrated a one-pot synthesis of a library of benzimidazoles *via* a coupling reaction between phenylenediamines and aldehydes using a cobalt nanocomposite catalyst. Broad substrate scope, high yields of products, good functional group, and scalability are the attractive features of the synthesis. Furthermore, the catalyst could be recycled by a simple procedure

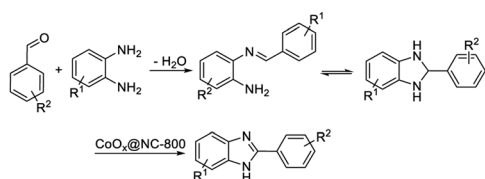
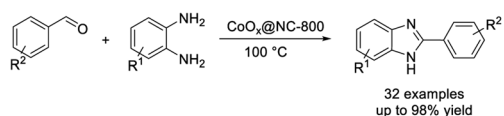




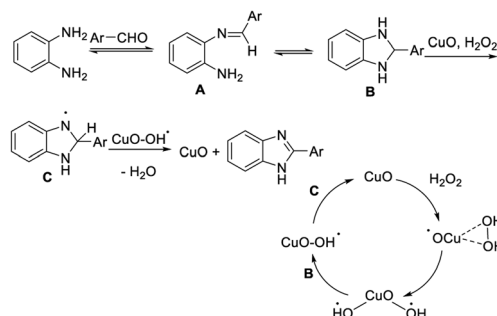
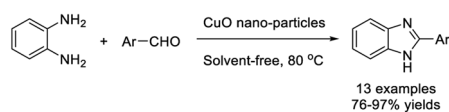
Scheme 1



Scheme 3



Scheme 2



Scheme 4

and reused for five runs without any significant decrease in reaction yields.⁷¹ The catalyst CoO_x@NC-800 catalyzes the dehydrogenation of dihydrobenzimidazole to form the desired benzimidazole with liberation of molecular hydrogen (Scheme 2).

Kalhor *et al.* prepared a nickel-decorated SBA-15 nanocomposite (Ni/TCH@SBA-15) and employed this material as a catalyst for the construction of 2-aryl-substituted benzimidazoles. The merits of the synthesis include mild reaction conditions, easy work-up procedure, good functional group tolerance, high yields of products, and reusability of the catalyst.⁷² The Ni/TCH@SBA-15 was supposed to activate the aldehyde as well as the intermediate (Scheme 3).

Fazlinia and Sheikh synthesized CuO nanoparticles and used this material for the assembly of 2-arylbenzimidazoles by the condensation reaction between 1,2-benzenediamine and aldehydes. Various 2-arylbenzimidazoles were obtained in high yields under solvent-free conditions in short times.⁷³ The catalyst could be reused for eight runs without any significant loss in its catalytic activity (Scheme 4).

Mohammadi *et al.* presented the synthesis of BiOCl/FeOCl nano rods composited with spherical nano particles of SiO₂ and the use of this nano catalyst for the preparation of 2-

arylbenzimidazoles. The procedure showed many advantages such as short reaction times, high efficiency, mild reaction conditions, simple operation and work-up, and recyclability of the catalyst.⁷⁴ The BiOCl/FeOCl/SiO₂ nano material might activate the aldehyde group *via* the formation of a coordinate bond with the Lewis acid site of BiOCl/FeOCl over the surface of SiO₂ as a mediator agent as well as the imine intermediate for ring closing reaction (Scheme 5).

Karami *et al.* described the synthesis of AlOOH-SO₃ nanoparticles (BNPs'SA) and applied this material as a recyclable catalyst for the construction of 2-aryl-1*H*-benzimidazoles. The condensation between aldehydes and *o*-phenylenediamines was performed under solvent-free conditions (Scheme 6). Other advantageous features of the synthesis include short reaction time, simple workup, and high yields of products.⁷⁵

Naeimi and Babaei reported the preparation and application of MnO₂ nanoparticles as an efficient oxidant agent for the synthesis of benzimidazoles.⁷⁶ Various benzimidazoles were

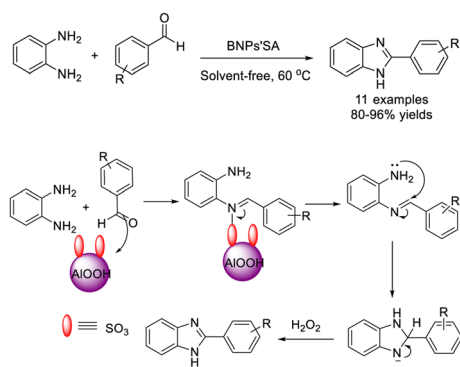




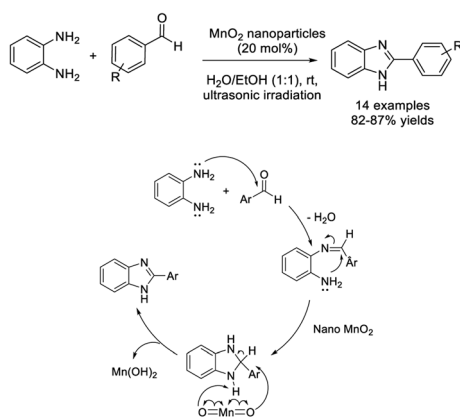
Scheme 5



Scheme 8



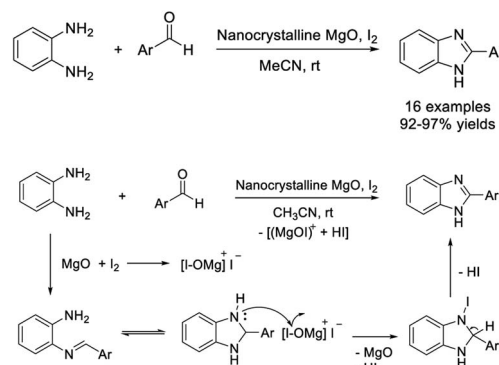
Scheme 6



Scheme 7

efficiently obtained in short times under ultrasound irradiation (Scheme 7).

In a study introduced by Bahrami *et al.*, the H₂O₂/TiO₂ P25 nanoparticle system was employed as a catalyst for the assembly of a series of 2-substituted benzimidazoles. Various products were achieved in excellent yields under solvent-free conditions from 1,2-phenylenediamines and aromatic aldehydes.⁷⁷ The proposed reaction mechanism is outlined below and the role of the catalyst is to activate the aldehyde as well as the imine intermediate (Scheme 8).



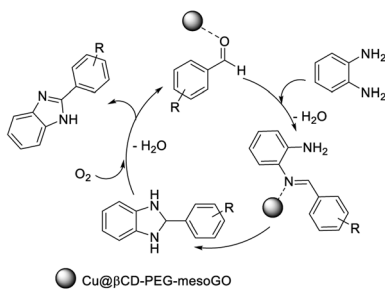
Scheme 9

Naeimi and Alishahi established an efficient protocol for the preparation of 2-substituted benzimidazole using nanocrystalline magnesium oxide as a solid base catalyst. The protocol featured some advantages such as short reaction times, mild reaction conditions, scalability, and high yields of products.⁷⁸ Moreover, the catalyst could be recovered and reused for five additional cycles without any considerable decrease in reaction yield (Scheme 9).

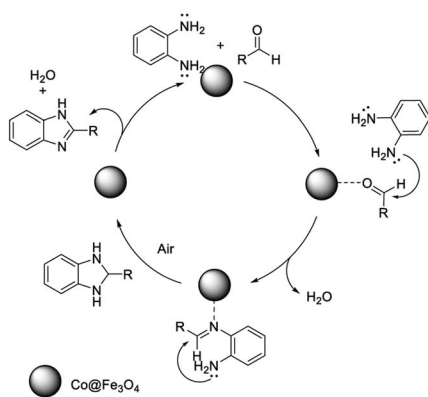
Bahadorikhalili *et al.* investigated the synthesis of benzimidazoles from *o*-phenylenediamines and benzaldehydes using a β -cyclodextrin functionalized PEGylated mesoporous silica nanoparticle-graphene oxide hybrid (Cu@ β CD-PEG-mesoGO) as a catalyst. The catalyst was prepared from a mesoporous silica nanoparticle-graphene oxide hybrid by functionalization with PEG-600 ended β -cyclodextrin followed by immobilization with Cu.⁷⁹ Attractive features of the benzimidazole synthesis include high yield of products, simple work-up procedure, mild reaction conditions, and recyclability of catalyst (Scheme 10). The tentative reaction mechanism suggested that the role of the catalyst is to activate the aldehyde and the imine intermediate.

Kumara *et al.* introduced the employment of bare Co@Fe₂O₄ and SiO₂/Co@Fe₂O₄ nanoparticles as catalysts to access 2-arylbenzimidazoles. A sequence of imine formation, cyclization,





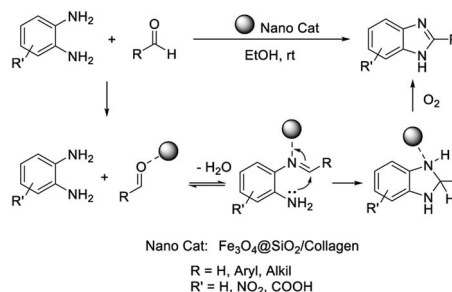
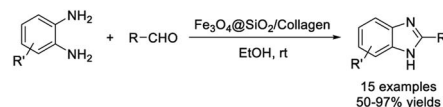
Scheme 10



Scheme 11



Scheme 12



Scheme 13

condensation, and aromatization occurs in one pot.⁸⁰ The Co@Fe₂O₄ and SiO₂/Co@Fe₂O₄ nanoparticles were easily recovered by using an external magnet, purified, and then used for the next several cycles without affecting the reaction yield (Scheme 11).

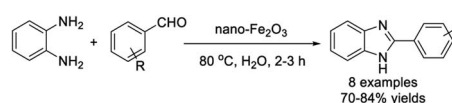
Paul *et al.* completed the synthesis of 2-benzimidazole derivatives using zinc oxide nanoparticles (ZnO NPs) under ultrasound (US) conditions. The catalyst was prepared using seed extract from the tender pods of *Parkia roxburghii*, a traditional vegetable grown abundantly in different areas of north-east India.⁸¹ Advantages of the benzimidazole synthesis include mild reaction conditions, short reaction times, recyclability of the catalyst, and excellent yields of products (Scheme 12).

Ghafuri *et al.* introduced the use of Fe₃O₄@SiO₂/collagen nanomaterial as a catalyst towards benzimidazole synthesis.⁸² Major advantages of the synthesis include good yields of products, short reaction times, mild reaction conditions, and

environmentally benign reaction conditions (Scheme 13). The role of the catalyst is to activate aldehydes as well as the imine intermediate.

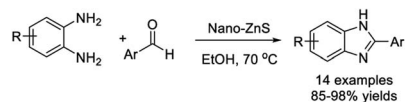
Kommula *et al.* developed an efficient protocol for the synthesis of benzimidazole from 1,2-diamino benzenes and substituted aromatic aldehydes using a nano-Fe₂O₃ catalyst (10 mol%).⁸³ Short reaction times, high efficiency, aqueous reaction medium, and recyclability of the catalyst are the main advantages of the synthesis (Scheme 14).

Hakimi *et al.* examined an efficient strategy for the construction of benzimidazole derivatives from substituted



Scheme 14





Scheme 15



Scheme 18



Scheme 16



Scheme 17

aldehydes and *o*-phenylenediamines using zinc sulfide nanoparticles as a catalyst (nano-ZnS).⁸⁴ The strategy offered several advantageous features such as high efficiency, mild reaction conditions, short reaction times, and recovery and reuse of the catalyst (Scheme 15).

Shukla *et al.* prepared Cu nanoparticle loaded, surfactant free metallovesicles (CuNPs@vesicles) and used this material for the assembly of benzimidazoles *via* a cascade reaction.⁸⁵ Products were obtained in excellent yields and the nanocatalyst could be recycled for up to five runs without affecting the reaction yields (Scheme 16).

In a study reported by Bodaghifard and Shafi, a novel ionic liquid immobilized on silica-coated cobalt-ferrite magnetic nanoparticles (CoFe₂O₄@SiO₂@PAF-IL) was synthesized, characterized, and employed as a catalyst for the synthesis of benzimidazole derivatives. The benzimidazole synthesis delivered many attractive features such as short reaction times, solvent-free and environmentally-benign conditions, high efficiency, and easy recyclability of the catalyst.⁸⁶ The role of the catalyst in the proposed reaction mechanism was also described (Scheme 17).

Kaur *et al.* demonstrated the synthesis of copper metallovesicles (CuMV) and applied this soft nanomaterial as a catalyst for the condensation reaction between *o*-phenylenediamines and aromatic aldehydes in aqueous media to access 2-aryl-benzimidazoles.⁸⁷ Excellent yields of products, mild reaction conditions, a harmless aqueous reaction medium, and recyclability of the catalyst make the synthesis a green and sustainable catalytic approach (Scheme 18).

Garazhian *et al.* established a protocol for the synthesis of benzimidazoles using amorphous {Mo₇₂Fe₃₀} nanocapsules as a safe Keplerate polyoxometalate catalyst. The condensation reaction between aromatic 1,2-diamines and aldehydes was performed under aerobic and mild conditions resulting in products in high yields.⁸⁸ In this procedure, the nanocatalyst presumably activates the aldehyde substrates and imine intermediates (Scheme 19).

In a study presented by Roy *et al.*, mesoporous TiO₂-Fe₂O₃ mixed oxide material (MTF-1E) with nanoscale porosity and a high BET surface area was utilized as a catalyst for the synthesis of benzimidazole derivatives.⁸⁹ The merits offered by this method include harmless solvent, mild reaction conditions, high regioselectivity, broad substrate scope, recyclability of the catalyst, and excellent yield of products (Scheme 20).

An efficient route for the construction of benzimidazole derivatives using a nano-Ni(II)/Y zeolite catalyst was investigated by Mobinikhaledi *et al.* The condensation reaction of *o*-phenylenediamines with aromatic aldehydes or orthoesters was

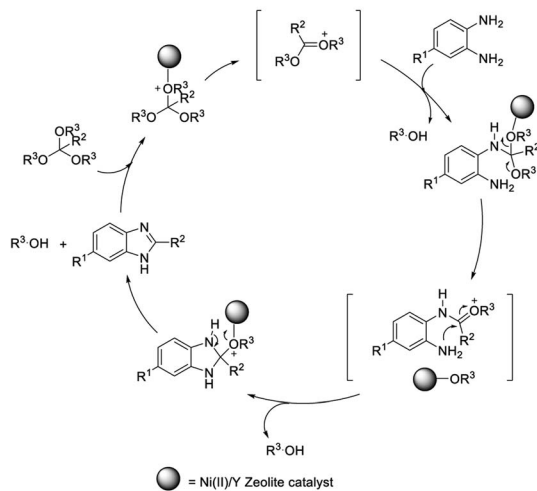


Scheme 19



Scheme 20





Scheme 21



Scheme 22

performed under solvent-free conditions providing the desired products in good to excellent yields.⁹⁰ The reaction mechanism was presented for the reaction between phenylenediamines and orthoesters (Scheme 21).

Kohli *et al.* described the synthesis of benzimidazole by the reaction between *o*-phenylenediamine and aldehydes using an Al₂O₃/CuI/PANI nanocomposite as a catalyst. A series of



Scheme 23

products were produced in excellent yields under mild conditions.⁹¹ Furthermore, the nanocatalyst was easily recovered and reused for five cycles without a significant loss of its catalytic activity (Scheme 22).

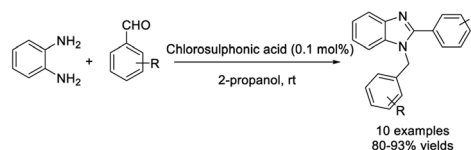
Pourmorteza *et al.* employed cobalt incorporated in the g-C₃N₄-imine/TiO₂ nano hybrid as a heterojunction photocatalyst to prepare benzimidazoles from benzaldehydes and aryl diamines.⁹² The protocol was also successfully applied to access benzimidazoles from benzylic alcohols and aryl diamines *via* a one-pot reaction sequence of aerobic photooxidation of benzylic alcohols and oxidative coupling of benzaldehydes with aryl diamines (Scheme 23).

2.2. Using acid catalysts

Shitole *et al.* accomplished the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles from phenylenediamines and aromatic aldehydes using chlorosulfonic acid as a catalyst.⁹³ Various products were afforded in good to excellent yields under mild conditions (Scheme 24).

Mathapati *et al.* demonstrated an efficient strategy to access benzimidazoles through the cyclization of 1,2-phenylenediamine with aldehydes.⁹⁴ Products were produced in high yields under mild reaction conditions (Scheme 25). In another report, H₂SO₄@HTC(II) was used as a catalyst for the synthesis of benzimidazole derivatives from *o*-phenylenediamines and aromatic aldehydes.⁹⁵ Moderate to excellent yields of products were also obtained (Scheme 26).

Singh *et al.* developed an efficient protocol for the synthesis of 1,2-disubstituted benzimidazole derivatives from *o*-phenylenediamines and aldehydes. The synthesis was catalyzed by *p*-toluenesulfonic acid and performed under grinding and solvent-free conditions.⁹⁶ Short reaction time, high efficiency, simple product isolation and purification, and mild reaction conditions are the attractive features of the protocol (Scheme 27).



Scheme 24

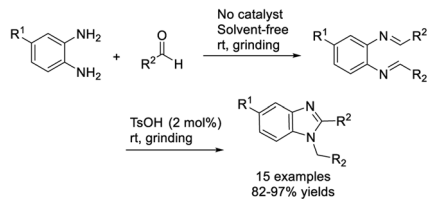


Scheme 25



Scheme 26





Scheme 27

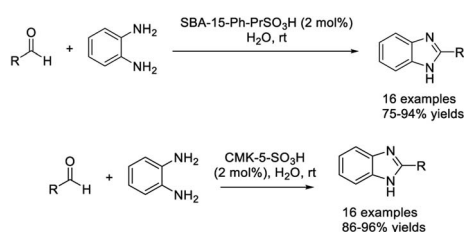


Scheme 28

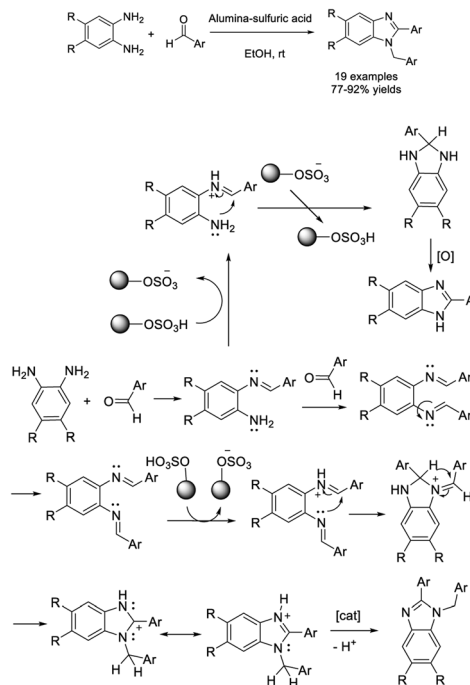
An efficient procedure for the synthesis of C-2-substituted benzimidazoles employing Brønsted acidic reduced graphene was described by Karthik and Suresh. The catalyst was prepared by a massive influx of sulphonic acid groups on the reduced graphene oxide surface.⁹⁷ A library of benzimidazoles was provided in good yields under mild reaction conditions. In addition, the catalyst could be recycled for five runs without a significant decrease in reaction yields (Scheme 28). In another study introduced by Zareyee *et al.*, organosulfonic acid-functionalized silica (SBA-15-Ph-PrSO₃H) and sulfonic acid-based nanoporous carbon (CMK-5-SO₃H) were utilized as catalysts to prepare 2-substituted benzimidazoles from aldehydes and benzene-1,2-diamine. High yields of products were observed for both catalysts under mild reaction conditions and in an aqueous medium.⁹⁸ The catalysts CMK-5-SO₃H and SBA-15-Ph-PrSO₃H were readily recovered and reused in eight and six consecutive runs, respectively, without any considerable loss of activity (Scheme 29).

Pramanik *et al.* discovered an environmentally friendly strategy for the assembly of 2-aryl-1-arylmethyl-1H-benzimidazoles using alumina-sulfuric acid as a solid acid catalyst. A wide range of products were achieved in good to excellent yields under mild reaction conditions. Furthermore, the heterogeneous solid acid catalyst could be efficiently recycled seven times.⁹⁹ A plausible reaction mechanism was also provided based on isotope labelling experiments, in which the catalytic behavior of alumina-sulfuric acid was explained (Scheme 30).

In a study reported by Thimmaraju *et al.*, a ZrO₂-Al₂O₃ solid acid synthesized by a solution combustion method was



Scheme 29



Scheme 30

employed as a catalyst for the synthesis of substituted benzimidazoles. In general, benzimidazoles were isolated in good yields under thermal conditions. The catalyst could be recycled and reused for up to five consecutive reaction cycles in the synthesis of benzimidazoles.¹⁰⁰ A proposed reaction mechanism was also described (Scheme 31).

Senapak *et al.* established an efficient protocol for the synthesis of 2-substituted benzimidazoles by the condensation reaction of *o*-phenylenediamines with aldehydes using Brønsted acidic ionic liquid [DodecIm][HSO₄] as a reusable catalyst. A library of benzimidazoles were afforded in high yield under mild reaction conditions. Noticeably, the protocol was also successfully employed for the construction of 1,2-disubstituted benzimidazoles *via* sequential one-pot reactions, when alkyl halides were added.¹⁰¹ Moreover, the catalyst could be recycled at least four times without significant loss in activity (Scheme 32).

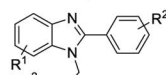
Raja *et al.* utilized glucose as a methine source for the synthesis of benzimidazoles from *o*-phenylenediamines *via* an oxidative cyclization reaction. A wide range of *N*-substituted benzimidazoles was provided in good yields using TsOH as a catalyst.¹⁰² A plausible reaction pathway was also suggested (Scheme 33).

Roudsari *et al.* designed an efficient approach for the synthesis of 2-substituted benzimidazoles using polymeric-based solid acid [PVP-SO₃H]HSO₄ as a catalyst. The synthesis could be performed in EtOH at room temperature or in solvent-free conditions at 80 °C.¹⁰³ Products were obtained in excellent yields in both cases. The solid acid catalyst could be recovered and reused for several runs without significant decrease in reaction yields (Scheme 34).

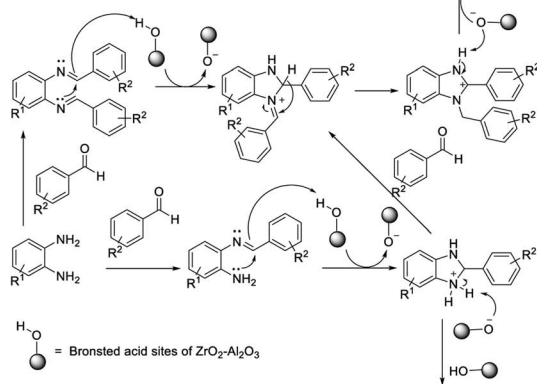
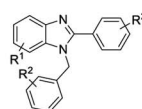




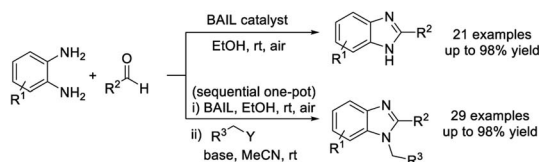
20 examples or
30-96% yields



3 examples
21-34% yields



Scheme 31

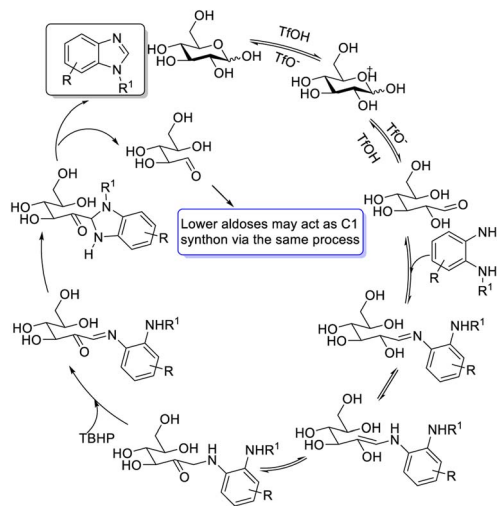
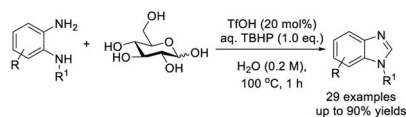


Scheme 32

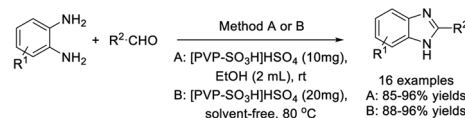
2.3. Using metal catalysts

Ghosh and Subba performed the condensation reaction of *o*-phenylenediamines with aldehydes to prepare 2-substituted benzimidazoles using $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ as a catalyst.¹⁰⁴ A series of products were obtained in high yields in short times (Scheme 35). In another report, Nagasawa *et al.* employed a small amount of MgI_2 as a catalyst to access benzimidazoles from aromatic aldehydes and diamines. The photooxidative synthesis used molecular oxygen as the terminal oxidant and showed broad substrate scope.¹⁰⁵ A diverse series of products was obtained in high yields (Scheme 36).

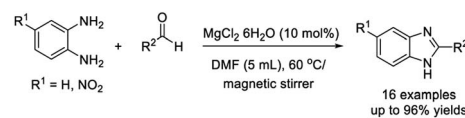
Sun *et al.* demonstrated a method for the preparation of 2-aminovinyl benzimidazoles using bis(cyclopentadienyl)-



Scheme 33



Scheme 34

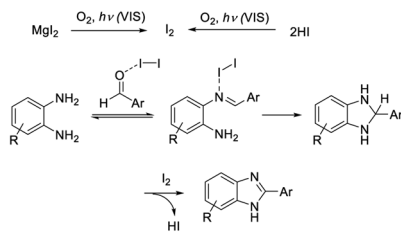
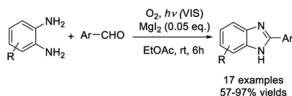


Scheme 35

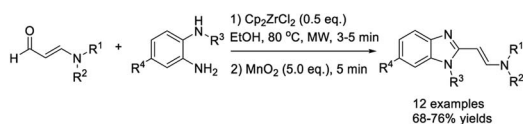
zirconium(IV) dichloride (Cp_2ZrCl_2) as a catalyst.¹⁰⁶ The condensation reaction between 1,2-phenylenediamines and *N*-arylated/*N,N*-dialkylated 3-aminoacroleins under microwave irradiation gave the desired products in short times (Scheme 37). Sajjadifar *et al.* prepared and applied a $\text{Zn}_3(\text{BTC})_2$ metal-organic framework as a catalyst for the construction of 2-aryl-1*H*-benzimidazole from aldehydes and *o*-phenylenediamines.¹⁰⁷ A wide range of products was produced in excellent yields under mild reaction conditions and the catalyst could be recycled for four additional runs without a significant loss of its catalytic activity (Scheme 38). Nale *et al.* employed *N*-substituted formamides as C1 sources for the synthesis of a series of *NH*-benzimidazoles *via* the condensation reaction with 1,2-phenylenediamines.¹⁰⁸ A diverse range of products were achieved in moderate to excellent yields under solvent-free conditions (Scheme 39).

Bardajee *et al.* demonstrated the use of periodic mesoporous silica (SBA-15) containing a Cu(II) organometallic complex as

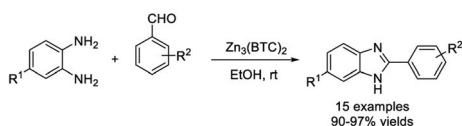




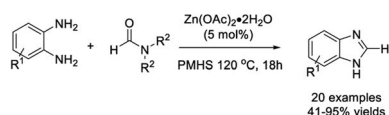
Scheme 36



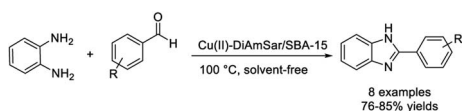
Scheme 37



Scheme 38



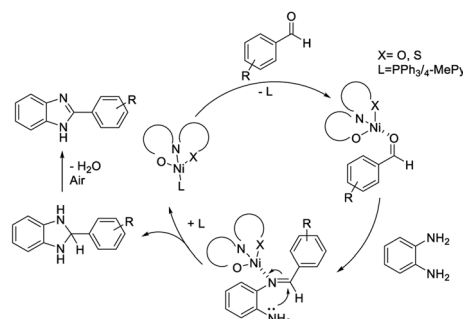
Scheme 39



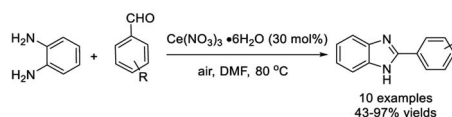
Scheme 40

a catalyst for the synthesis of benzimidazoles. The catalyst was obtained by coordination of $\text{Cu}(\text{II})$ ions with the diaminosarcophagine ligand and then grafting onto the surface of SBA-15.¹⁰⁹ Eight benzimidazoles were formed in good yields under solvent-free conditions (Scheme 40).

Agrahari *et al.* synthesized new pincer type $\text{Ni}(\text{II})$ -Schiff base complexes including $[\text{NiL}^1(\text{PPh}_3)]$, $[\text{NiL}^2(\text{PPh}_3)]$, $[\text{NiL}^3(\text{PPh}_3)]$, $[\text{NiL}^4(\text{PPh}_3)]$, and $[\text{NiL}^4(4\text{-MePy})]$ and utilized these compounds as catalysts for the condensation reaction between aldehydes and *o*-phenylenediamine. The reactions proceeded smoothly at room temperature with low catalyst loading affording products in good to excellent yields.¹¹⁰ A proposed reaction mechanism was also presented (Scheme 41).



Scheme 41

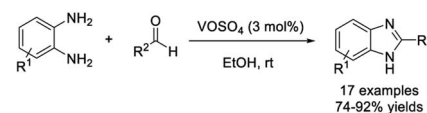


Scheme 42

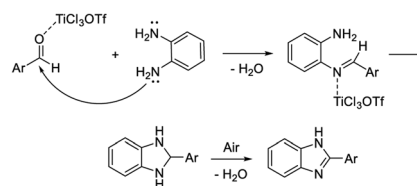
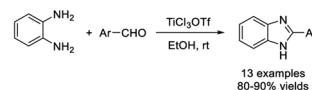
Martins *et al.* developed a strategy for the assembly of 2-substituted benzimidazoles starting from 1,2-diaminobenzene and aldehydes in good yields.¹¹¹ The synthesis used air as an efficient oxidant and $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ as a promoter (Scheme 42).

Digwal *et al.* described an efficient method for the construction of benzimidazoles using VOSO_4 as a catalyst.¹¹² The method featured many merits such as high yields of products, mild reaction conditions, broad substrate scope, scalability, and recyclability of catalyst (Scheme 43).

Azizian *et al.* established an efficient approach for the synthesis of benzimidazoles by the condensation reaction of *o*-phenylenediamine with aldehydes using TiCl_3OTf as

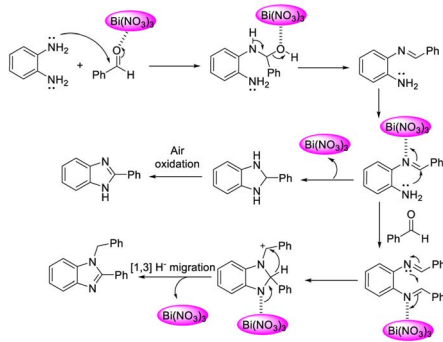


Scheme 43



Scheme 44



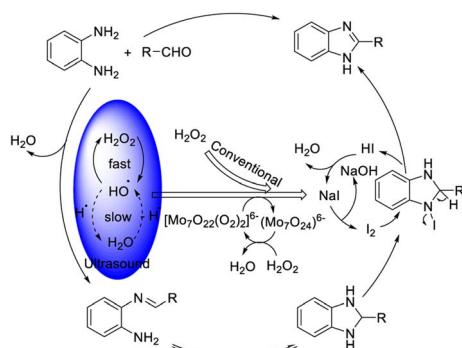


Scheme 45

a catalyst.¹¹³ Thirteen products were afforded in good to excellent yields under mild reaction conditions. The proposed reaction mechanism is also included (Scheme 44).

Mahire *et al.* accomplished the synthesis of 2-substituted benzimidazole and 1,2-disubstituted benzimidazole derivatives using bismuth nitrate as a catalyst.¹¹⁴ A wide range of products were produced in good yields at room temperature. A tentative reaction mechanism describing the role of the bismuth nitrate catalyst was also suggested (Scheme 45).

Bai *et al.* investigated an efficient strategy to access 2-substituted benzimidazoles by the reaction of aldehydes and *o*-phenylenediamine using sodium iodide and ammonium molybdate as co-catalysts and hydrogen peroxide as an oxidant.¹¹⁵ The products were obtained in high yields under



Scheme 46



Scheme 47

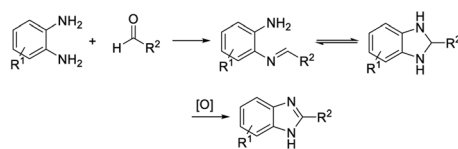
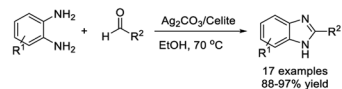
ultrasound irradiation. A plausible reaction mechanism was also outlined (Scheme 46).

A simple, convenient, and highly efficient procedure for the assembly of 2-arylbenzimidazoles using a chromium(III)-salen complex as a catalyst and air as a green oxidant was completed by Sharghi *et al.* Mild reaction conditions, short reaction times, scalability, simple isolation of products, and excellent yields are the main attractive features of the synthesis.¹¹⁶ Moreover, the catalyst could be simply recovered and used for at least eight consecutive runs without considerable loss of its catalytic activity (Scheme 47).

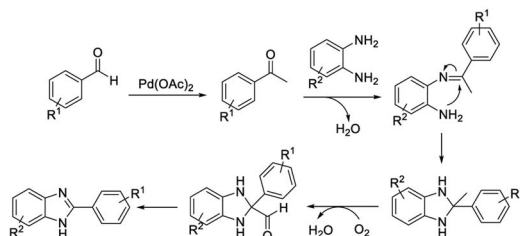
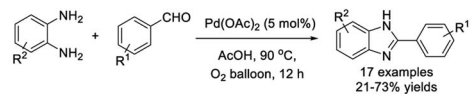
Soleimani and Khodaei designed a facile protocol for the construction of 2-substituted benzimidazoles by reactions of 1,2-phenylenediamines with aryl aldehydes using $\text{Ag}_2\text{CO}_3/\text{celite}$ as a solid catalyst.¹¹⁷ A library of products was delivered in excellent yields in short times in ethanol (Scheme 48).

A palladium catalyzed, one-pot approach for the synthesis of benzimidazoles using molecular oxygen as a sole oxidant and $\text{Pd}(\text{OAc})_2$ as a catalyst was disclosed by Shaikh *et al.* A variety of products was isolated in moderate yields.¹¹⁸ A reaction pathway was also proposed (Scheme 49).

Merroun *et al.* discovered a green methodology to prepare benzimidazoles through a condensation reaction of 1,2-

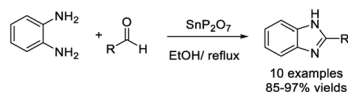


Scheme 48



Scheme 49





Scheme 50



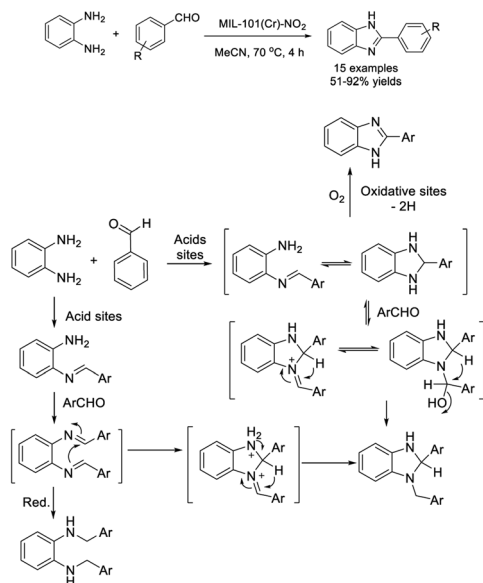
Scheme 51

diamino benzene and aromatic aldehydes using SnP_2O_7 as a catalyst.¹¹⁹ The catalyst was obtained by adding MAP to a solution of SnCl_2 . Ten products were produced with excellent yields in short reaction times, and the catalyst was reused five times without a significant decrease in the reaction yield (Scheme 50).

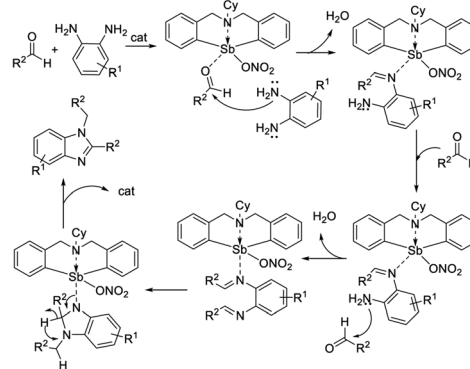
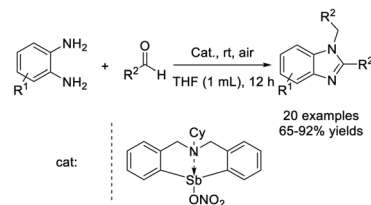
Sankar *et al.* designed a facile procedure for the synthesis of various benzimidazoles using NH_2 -MIL-125(Ti) MOF as a catalyst.¹²⁰ The products were delivered in good yields and the catalyst could be recycled for five consecutive cycles without considerable loss of activity (Scheme 51).

Vallés-García *et al.* described the preparation of a nitro functionalized chromium terephthalate [MIL-101(Cr)-NO₂] metal organic framework and the application of this material for the construction of benzimidazoles.¹²¹ Fifteen compounds were produced in high yields with good catalyst recyclability (Scheme 52).

Zhou *et al.* synthesized a novel organoantimony complex of 6-cyclohexyl-6,7-dihydrodibenzo[*c,f*][1,5]azastibocin-12(5*H*)-yl nitrate and employed this material as a catalyst for the preparation of benzimidazole derivatives starting from aldehydes and arylenediamines.¹²² A wide range of products were furnished in



Scheme 52



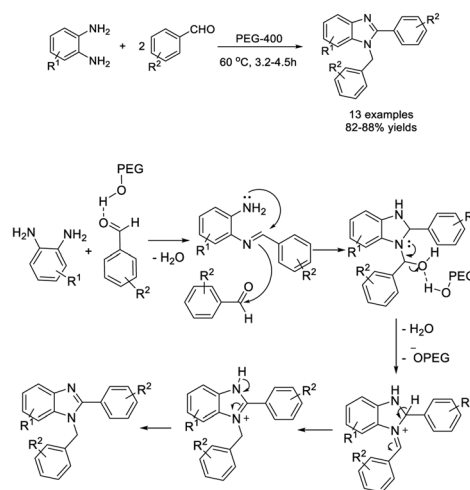
Scheme 53

good to excellent yields. Furthermore, the complex could be easily recycled five times in scale enlarged synthesis without any significant loss of catalytic activity (Scheme 53).

2.4. Without using a catalyst

Mekala *et al.* used polyethylene glycol (PEG-400) as an effective medium for the one-pot synthesis of 1,2-disubstituted benzimidazoles from 1,2-phenylenediamines and aryl aldehydes.¹²³ A set of products was synthesized in high yields and PEG-400 could be reused three times without loss of activity. A suggested reaction mechanism was also presented (Scheme 54).

Bala *et al.* obtained 2-substituted benzimidazoles from 1,2-phenylenediamines and aryl aldehydes by heating this mixture in water at 80 °C.¹²⁴ Various products were prepared in excellent yields without using a catalyst (Scheme 55). In another report,

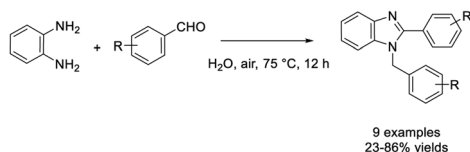


Scheme 54





Scheme 55



Scheme 56



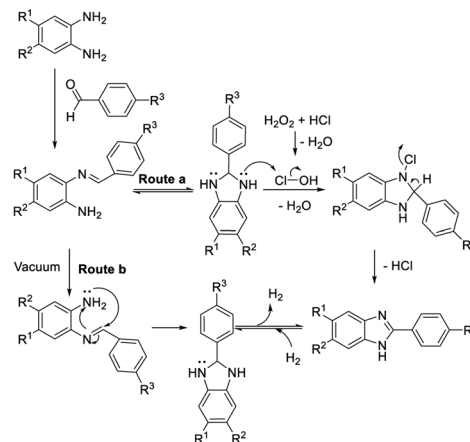
Scheme 57

Mahato *et al.* demonstrated a metal-free approach for the synthesis of 1,2-disubstituted benzimidazoles. The synthesis was performed in water in the presence of air.¹²⁵ Products were provided in high yields and the method could be applied on the gram scale (Scheme 56).

In research described by Elumalai *et al.*, MeOH was chosen as the medium for the assembly of 2-substituted benzimidazoles by the condensation of 1,2-diaminoarenes and aldehydes in the presence of air.¹²⁶ A library of products was achieved in good yields in a short time under mild, catalyst and additive-free reaction conditions. The synthesis could also be expanded to the multi-gram scale (Scheme 57). Chaturvedia *et al.* introduced the construction of 2-arylbenzimidazoles with antimycobacterial activity in a molecular sieve-MeOH system from *o*-phenylenediamines and aromatic aldehydes. In



Scheme 58



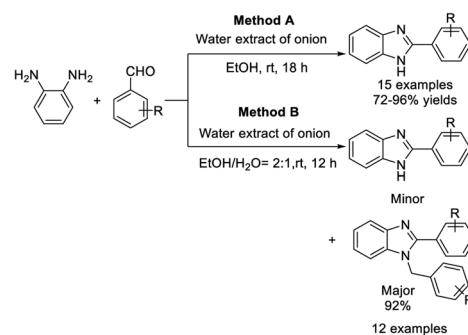
Scheme 59

general,¹²⁷ products were afforded in good yields in a relatively short time (Scheme 58). All synthesized compounds were screened for antitubercular activity against *M. tuberculosis* using the BACTEC radiometric method. Compounds **A** and **B** showed potential antitubercular activity against *M. tuberculosis* H37RV with MIC values of 16 μ M and 24 μ M, respectively (Scheme 58).

Sutapin *et al.* carried out the condensation of phenylenediamines with aromatic aldehydes to give benzimidazoles under harsh conditions without using any catalyst.¹²⁸ Two products were formed in excellent yields under reduced pressure at 66.6 Pa and at room temperature (Scheme 59).

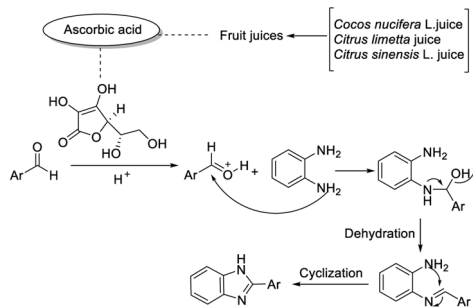
2.5. Using natural sources as catalysts

Prabakaran *et al.* developed an efficient methodology for the synthesis of 2-substituted benzimidazole derivatives using water extract of onion as a catalyst. The methodology provided 2-substituted benzimidazoles from aromatic aldehydes possessing electron-withdrawing groups, whereas aromatic aldehydes having electron donating groups selectively produced 1,2-disubstituted benzimidazoles.¹²⁹ The products were obtained in high yields under mild reaction conditions (Scheme 60).



Scheme 60





Scheme 61



Scheme 62

Gulati *et al.* introduced a facile protocol for the synthesis of benzimidazoles mediated by fruit juices including *Cocos nucifera* L. juice, *Citrus limetta* juice and *Citrus sinensis* L. juice, by the condensation of substituted aldehydes and *o*-phenylenediamine. Eight compounds were furnished under solvent-free conditions at room temperature.¹³⁰ All synthesized compounds were evaluated for herbicidal activity against *Raphanus sativus* L. (radish) seeds, antifungal activity against *R. Solani* and *C. gloeosporioides*, and antibacterial activity against *Erwinia cartovora* and *Xanthomonas citri*. The bioassay results indicated that strong electron-withdrawing groups at the phenyl ring showed a better activity profile than electron-donating groups. A reaction pathway involving ascorbic acid catalysis was also suggested (Scheme 61).



Scheme 63

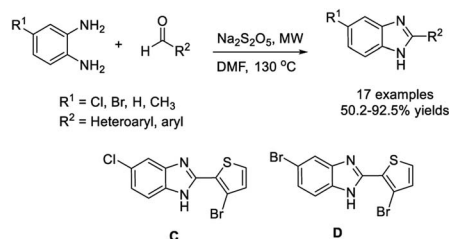
Kadu *et al.* utilized the aqueous extract of *Acacia concinna* pods as a catalyst for the synthesis of 1,2-disubstituted benzimidazole derivatives.¹³¹ A series of products were achieved in excellent yields under mild reaction conditions in short reaction times (Scheme 62).

2.6. Using other catalysts

Kovvur *et al.* demonstrated a facile method for the synthesis of functionalized benzimidazoles from *o*-phenylenediamines and aldehydes using rose bengal as a photocatalyst. A huge library of benzimidazoles were afforded under mild reaction conditions.¹³² A plausible reaction mechanism was also proposed (Scheme 63).

Shi *et al.* developed a practical method for the synthesis of 2,5-disubstituted benzimidazoles using $\text{Na}_2\text{S}_2\text{O}_5$ as a catalyst and an oxidant. A wide range of products was obtained in moderate to excellent yields under microwave irradiation.¹³³ Some synthesized compounds showed strong antibacterial and antifungal activity (Scheme 64). Bioassay study revealed that several synthesized compounds exhibited good antifungal activity and broad-spectrum antibacterial activity. The MIC of compounds **C** and **D** against the tested bacteria were both less than $4 \mu\text{g mL}^{-1}$, and the lowest one was $2 \mu\text{g mL}^{-1}$. In addition, compound **D** showed good antifungal activity against *C. albicans* with an MIC of $4 \mu\text{g mL}^{-1}$.

Tayade and Pawar illustrated the synthesis of 2-substituted benzimidazoles from aldehydes and *o*-phenylenediamine using



Scheme 64



Scheme 65



Scheme 66





Scheme 67



Scheme 70

sodium hypophosphite as a catalyst.¹³⁴ The method featured some advantages such as high yield, clean and easy work-up, readily available catalyst, and short reaction time (Scheme 65).

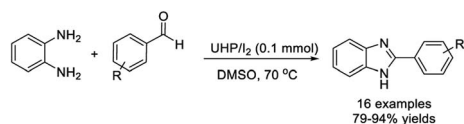
Hossein Naeimi and Zahra Babaei completed a mild and facile method for the synthesis of a series of 2-substituted benzimidazoles in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetonitrile.¹³⁵ Fourteen products were formed under mild reaction conditions in excellent yields (Scheme 66).

Benzekri *et al.* introduced a protocol for the preparation of benzimidazole derivatives using a hybrid crystal $\text{NH}_3(\text{CH}_2)_4\text{NH}_3\text{SiF}_6$ as a mild and efficient heterogeneous catalyst.¹³⁶ The protocol offered some merits such as short reaction times, absence of solvent, high efficiency, and recyclability of the catalyst (Scheme 67).

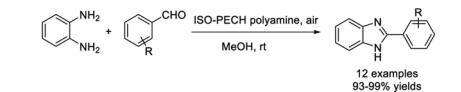
Alapati *et al.* reported an efficient strategy for the synthesis of substituted benzimidazoles from *o*-phenylenediamines and aryl aldehydes using UHP and I_2 in DMSO.¹³⁷ A wide range of products were isolated in good to excellent yields (Scheme 68).

Ramya *et al.* demonstrated a highly efficient approach for the synthesis of a variety of 2-arylbenzimidazoles using Koser's reagent $[\text{PhI}(\text{OH})\text{OTs}]$ as a catalyst. The advantageous features of the synthesis include short reaction time, simple operation, high efficiency, low catalyst loading, and scalability of the catalyst.¹³⁸ Some synthesized benzimidazoles displayed significant antiproliferative activity (Scheme 69).

Nile *et al.* established a simple method to access 2-aryl-1-arylmethyl-1*H*-benzimidazoles using Amberlite IR-120 catalyst.¹³⁹ The method exhibited several salient features such as green solvent, simple work-up procedure, short reaction time, and good to excellent yields of products (Scheme 70).



Scheme 68



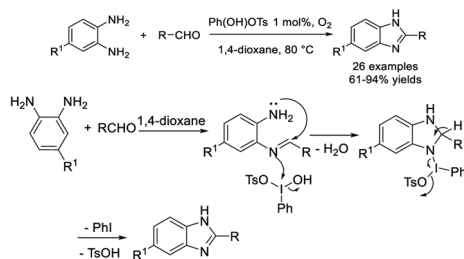
Scheme 71

Kottayil *et al.* prepared a polyamine by the ring opening polymerization of epichlorohydrin and employed it for the synthesis of 2-arylbenzimidazoles from *o*-phenylenediamine and different aldehydes.¹⁴⁰ Low catalyst loading, short reaction time, mild reaction conditions, high efficiency, simple work up and easy product purification, and recyclability of the catalyst are the salient features of the synthesis. A tentative reaction pathway was also illustrated (Scheme 71).

Akande *et al.* performed the synthesis of a diverse library of arylated benzimidazoles using sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$) as a catalyst.¹⁴¹ Products were obtained in modest to excellent yields under thermal conditions. Some synthesized compounds showed remarkable antidiabetic and antioxidant activities (Scheme 72).

Tian *et al.* achieved a methodology for the synthesis of *N*-thiomethyl benzimidazoles from *o*-phenylenediamines, thiophenols, and aldehydes. Three C–N bonds and one C–S bond were formed in one pot with high chemoselectivity.¹⁴² A vast variety of products were delivered in acceptable yields (Scheme 73).

Hu *et al.* investigated a practical method for the construction of *N*-protected benzimidazoles based on intramolecular C–H amidation using molecular iodine as an oxidant.¹⁴³ A diverse series of products were achieved in modest to excellent yields at



Scheme 69

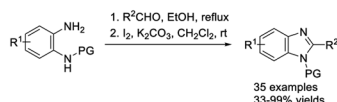


Scheme 72





Scheme 73

PG = Ts, SO₂Ph, Bz, Boc, COO^tPr, COO^tBu, Me, Ph, H

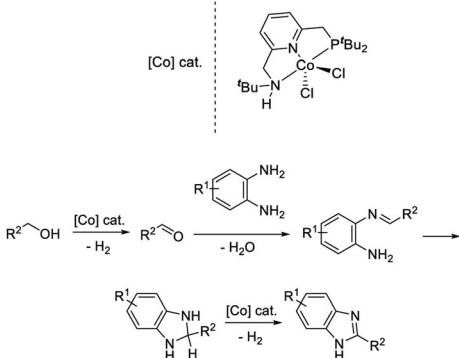
Scheme 74

room temperature with a broad substrate scope (Scheme 74). A reaction mechanism was also illustrated.

3. Benzimidazole synthesis by condensation of 1,2-benzenediamine or its analogues with other substrates

3.1. By condensation of 1,2-benzenediamines with primary alcohol

Daw *et al.* developed a base-metal-catalyzed dehydrogenative strategy for the synthesis of 2-substituted benzimidazoles from



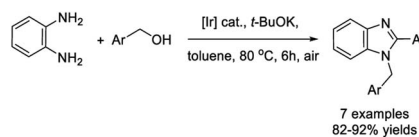
Scheme 75

primary alcohols and aromatic diamines.¹⁴⁴ A diverse series of products were provided in good yields (in most cases) under cobalt pincer complex catalysis (Scheme 75).

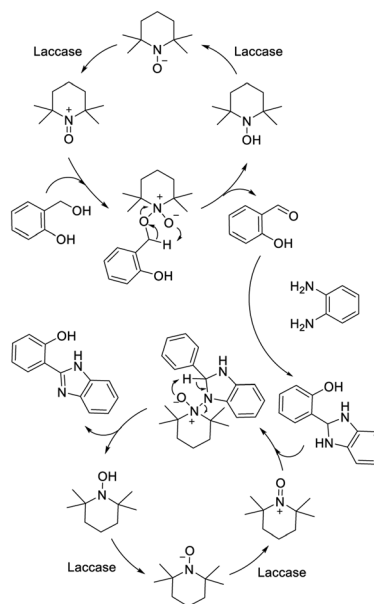
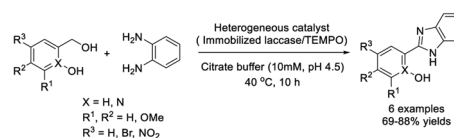
Sharma *et al.* described the synthesis of four complexes $[(\eta^5\text{-Cp}^*)\text{Ir(L)Cl}][\text{PF}_6]$ by treatment of different lignans with $[(\eta^5\text{-Cp}^*)\text{IrCl}(\mu\text{-Cl})_2]$, at 25 °C, followed by NH_4PF_6 . These complexes then were examined as catalysts for the preparation of 1,2-disubstituted benzimidazoles from benzylic alcohols and *o*-phenylenediamines.¹⁴⁵ Products were obtained in good to excellent yields under thermal and aerobic conditions (Scheme 76).

Mogharabi-Manzari *et al.* designed the synthesis of a high-performance heterogeneous catalyst by separately immobilizing laccase and TEMPO on magnetic nanoparticles. This catalyst was applied for the synthesis of benzimidazole from benzylic alcohols and *o*-phenylenediamines. Various products were afforded in good yields and the catalyst could be recycled for several runs without significant loss of catalytic activity.¹⁴⁶ A reaction pathway was also described (Scheme 77).

Wang *et al.* employed an amphiphilic catalyst TEMPO-PEG4000-NHC-Cu(II) complex for the one-pot aerobic oxidative



Scheme 76

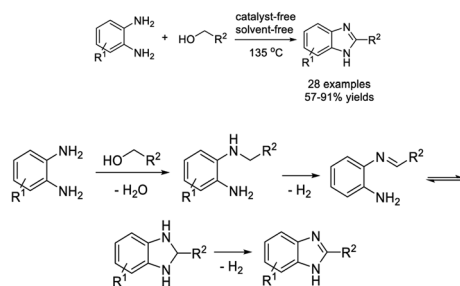


Scheme 77





Scheme 78

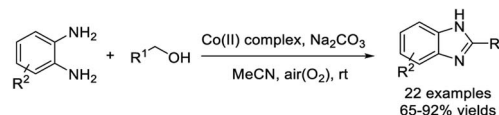


Scheme 79

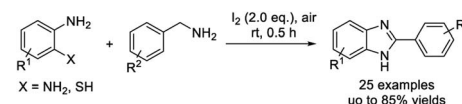
synthesis of benzimidazoles from benzyl alcohols and *o*-phenylenediamines.¹⁴⁷ Moderate to excellent yields of products were observed and the catalyst could be recycled and reused without considerable decrease in reaction yields after six runs (Scheme 78). A reaction mechanism was also suggested.

Marri *et al.* designed an efficient procedure for the one-pot synthesis of benzimidazoles by the reaction between benzyl alcohols and 1,2-diaminoarenes.¹⁴⁸ A diverse library of products was produced in moderate to excellent yield under solvent- and catalyst-free conditions (Scheme 79).

Zuo *et al.* demonstrated the synthesis of a Co(II) complex from quinalic acid and $Co(OAc)_2 \cdot 4H_2O$ and the use of this complex as a catalyst for a dehydrogenative coupling of aromatic diamines and primary alcohols to prepare 2-substituted benzimidazoles. A wide range of products were furnished in good to excellent yields under aerobic mild reaction conditions.¹⁴⁹ A plausible reaction mechanism was proposed based on functional theory study (Scheme 80). In particular, a compound with anti-Parkinson activity was obtained on the gram-scale.



Scheme 80



Scheme 81

3.2. By condensation of 1,2-benzenediamines with primary amines

A novel strategy for the synthesis of benzimidazoles from 1,2-diaminoarenes and various benzylamines was completed by Naresh *et al.*¹⁵⁰ The iodine-mediated synthesis was performed under aerobic and mild conditions to give products in moderate to good yields (Scheme 81).

Dong *et al.* disclosed an oxidative coupling of benzylamines with 1,2-diaminoarenes to prepare benzimidazole derivatives.¹⁵¹ Fourteen products were delivered in moderate to excellent yields under an atmosphere of oxygen by using a 4,6-dimethoxy-salicylic acid catalyst (Scheme 82).

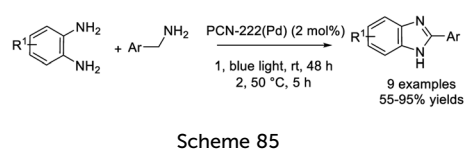
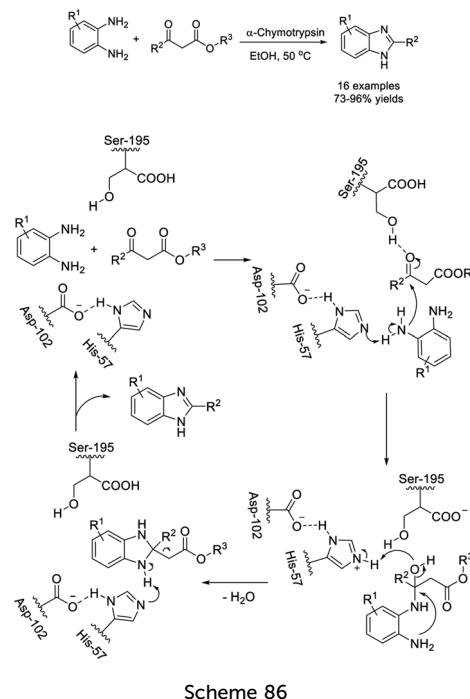
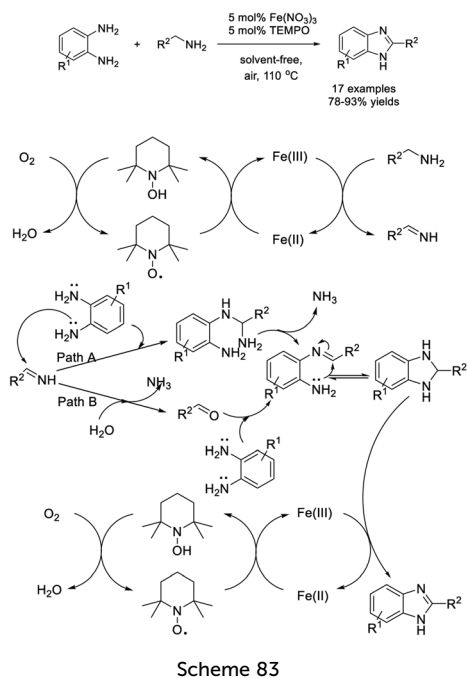
Yu *et al.* established an efficient approach to access benzimidazoles by the reaction between aromatic primary amines and *o*-phenylenediamines using $Fe(NO_3)_3$ and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as a catalytic system and air as an oxidant.¹⁵² Various products were formed in good to excellent yields under aerobic and solvent-free conditions (Scheme 83). A tentative reaction pathway was presented.

Vasu *et al.* described a straightforward approach for the assembly of benzimidazoles using an Al-MCM-41 heterogeneous catalyst. Numerous products were afforded in good yields.¹⁵³ Furthermore, the synthesis could be expanded to a gram scale reaction and the catalyst could be recycled for up to



Scheme 82



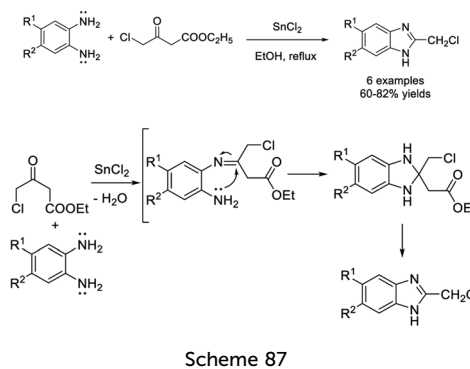


five cycles without considerable loss of its catalytic activity (Scheme 84).

Bermejo-López *et al.* discovered a new approach for the synthesis of benzimidazole, aerobic photo-oxidative cross-condensation of *o*-phenylenediamines with benzylic amines using a PCN-222 Pd complex as a catalyst. Products were obtained in moderate to excellent yields under mild conditions and blue light irradiation.¹⁵⁴ The catalyst PCN-222(Pd) could be recycled maintaining yields over 90% after five runs. The approach was efficiently applied for the synthesis of an anti-tumor agent PMX-610 (Scheme 85).

3.3. By condensation of 1,2-benzenediamines with β -keto ester

Liu *et al.* introduced the synthesis of 2-substituted benzimidazoles from *o*-phenylenediamines and diverse β -ketoesters using α -chymotrypsin as a catalyst. A wide range of benzimidazole derivatives were produced in good to excellent yields.¹⁵⁵ A reaction pathway involving the formation of a 1,5-benzodiazepinone intermediate was presented (Scheme 87).



Dayakar *et al.* developed a protocol for the construction of 1*H*-benzimidazoles through the condensation of *o*-phenylenediamines with ethyl 4-chloro-3-oxobutanoate using an SnCl_2 catalyst.¹⁵⁶ A reaction pathway was also described for the reaction (Scheme 87).

The Maiti group introduced an efficient methodology to access substituted benzimidazoles *via* the reaction between β -ketoesters or amides and *o*-phenylenediamines using silica supported ferric chloride (3 mol%) as a catalyst.¹⁵⁷ Products were isolated in high yields and the catalyst could be recycled for up to five cycles without a considerable decrease in the reaction yields (Scheme 88). A reaction mechanism involving the role of the catalyst was proposed. The group also employed 1-butyl-3-methyl imidazolium bromide as a catalyst for the assembly of benzimidazoles. The condensation reaction between 1,2-diaminobenzenes and β -ketoesters or amides occurred at elevated temperature and formed products in good to excellent yields.¹⁵⁸ A reaction pathway involving the formation of a 1,5-benzodiazepinone intermediate was presented (Scheme 89).

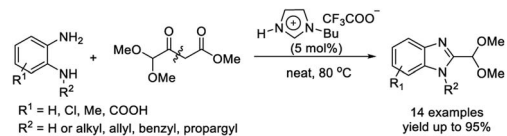




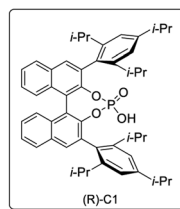
Scheme 88



Scheme 89



Scheme 90

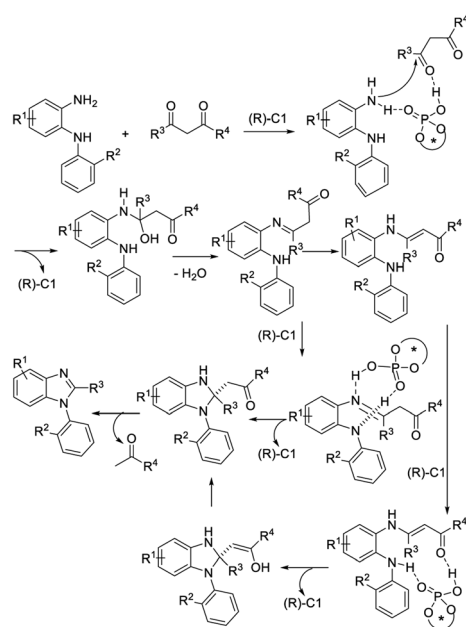


Deb *et al.* established a straightforward approach for the synthesis of dimethyl acetal protected benzimidazole-2-carboxaldehydes from 1,2-diaminobenzenes and methyl 4,4-dimethoxy-3-oxobutanoate using imidazolium ionic liquid HBIIm·TFA as a catalyst.¹⁵⁹ Advantages of the approach include short reaction times, mild reaction conditions, high efficiency, easy purification of products, recyclability of the catalyst, and scalability (Scheme 90).

Man *et al.* demonstrated a novel procedure for the preparation of *N*-aryl benzimidazoles through the condensation of *N*1-(aryl)benzene-1,2-diamines with multicarbonyl compounds. A huge library of products was achieved in high yields with excellent enantioselectivity. In addition, the synthesis could be expanded to the gram scale.¹⁶⁰ A reaction mechanism describing the catalyst's role was outlined (Scheme 91).

3.4. By condensation of 1,2-benzenediamines with carboxylic acid and its derivatives

Basuri *et al.* designed a novel route for the synthesis of benzimidazoles from 1,2-aromatic diamines and carboxylic acids. The condensation reaction occurs in electrostatically charged

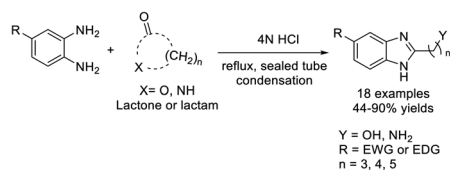


Scheme 91





Scheme 92



Scheme 93

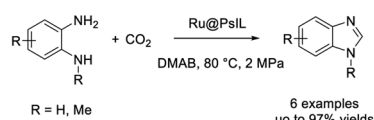
microdroplets generated using a nano-electrospray (nESI) ion source.¹⁶¹ Ten of eleven products were obtained in high yields (Scheme 92).

Castillo-Aguilera *et al.* accomplished the synthesis of a range of benzimidazol-2-yl alkylalkanols and benzimidazol-2-yl alkylamines through the reaction of *o*-phenylenediamine with lactones or lactams.¹⁶² The synthesis was suitable for a wide range of substrates (Scheme 93).

Saptal *et al.* prepared ruthenium nanoparticles (Ru NPs) supported on polymeric ionic liquids (PILs) and employed this material as a catalyst for the synthesis of benzimidazoles from 1,2 diamines and carbon dioxide.¹⁶³ Products were afforded in high yields and the catalyst could be recycled for five consecutive runs without significant decrease in reaction yield (Scheme 94). Interestingly, this protocol also could be also applied for the tandem reduction of 2-nitroamines and CO₂ to synthesize benzimidazoles, although lower yields were observed.

Khatun *et al.* synthesized copper nanoparticle embedded COF (Cu-NPs@COF) and utilized this material as a catalyst to access benzimidazoles *via* the incorporation of carbon dioxide in *o*-phenylenediamines.¹⁶⁴ Products were achieved in moderate to excellent yields. Furthermore, the catalyst could be reused for up to six cycles without considerable loss of its catalytic activity (Scheme 95).

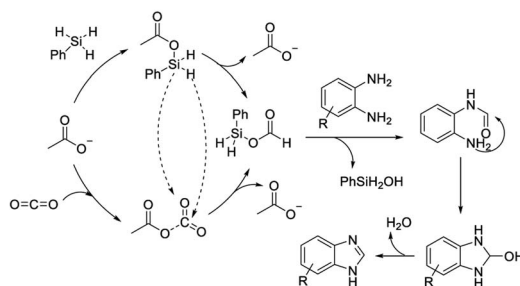
Li *et al.* utilized CO₂ as a low-cost C1 resource to obtain benzimidazole based on a base-promoted reductive functionalization with 1,2-phenylenediamines.¹⁶⁵ The synthesis used



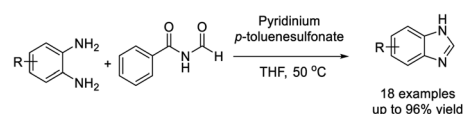
Scheme 94



Scheme 95



Scheme 96



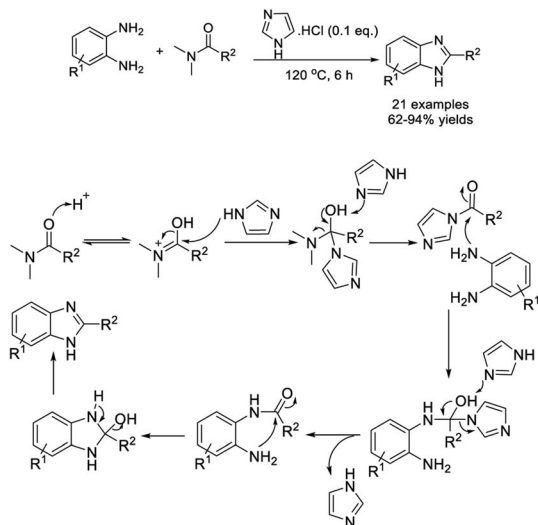
Scheme 97

inexpensive acetate salt CH₃COOK as a catalyst and delivered products in moderate to excellent yields under mild conditions (40 °C, 1 bar CO₂) (Scheme 96). A reaction pathway was also suggested.

Huang *et al.* reported the synthesis of benzimidazoles starting from *N*-formyl imide and 1,2-phenylenediamines.¹⁶⁶ Moderate to excellent reaction yields were observed for a wide variety of products (Scheme 97).

Gan *et al.* discovered a facile strategy for the construction of benzimidazoles and 2-substituted benzimidazoles by the reaction between *o*-phenylenediamines and DMF derivatives.¹⁶⁷ The imidazolium chloride-catalyzed cyclization reaction formed products in moderate to excellent yields with broad substrate scope (Scheme 98). A tentative reaction pathway was also suggested.





Scheme 98



Scheme 100

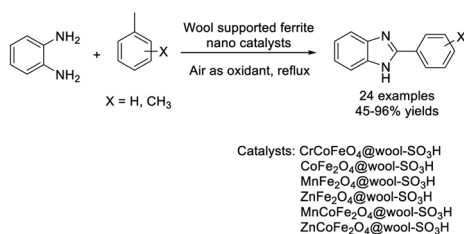
3.5. By reactions of 1,2-benzenediamines with other functional groups

Shaabani and Hezarkhani synthesized biopolymer-supported ferrite nanocatalysts and applied them as catalysts for the assembly of 2-aryl-1H-benzimidazole using air as an oxidant.¹⁶⁸ A diverse range of products were achieved in modest to excellent yields and the catalysts could be recycled several times without loss of their activity (Scheme 99).

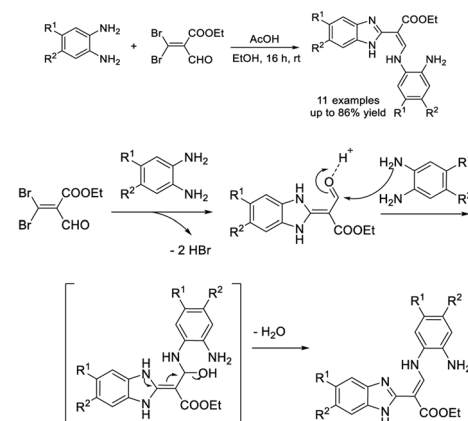
Yaragorla and Babu established an oxidative Csp³-H functionalization of 2-methylazaarenes for the construction of 2-azaarenyl benzimidazoles.¹⁶⁹ The I₂-DMSO-promoted reaction generated products in good to excellent yields (Scheme 100). A proposed reaction mechanism was illustrated for the 2-methyl quinoline substrate.

Garrido *et al.* demonstrated a straightforward approach for the preparation of functionalized benzimidazoles by the reaction between 3,3-dihaloacrolein and diaminobenzenes.¹⁷⁰ The one-pot reaction afforded products in good yields under metal-free and mild conditions (Scheme 101). A plausible reaction mechanism was also described.

Duangkamol *et al.* discovered an efficient oxidative cyclo-desulfurization method to access substituted 2-amino-benzazoles starting from isothiocyanates and *o*-phenylenediamines using periodate as a terminal oxidant.¹⁷¹ A wide range of products were furnished in moderate to excellent yields (Scheme 102).



Scheme 99



Scheme 101

Kasthuri *et al.* illustrated a facile synthesis of 2-amino-benzimidazole derivatives from *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) with various benzene-1,2-diamines.¹⁷² Products were isolated in moderate to good yields in a relatively short reaction time (Scheme 103).

Xia *et al.* disclosed an efficient methodology for the construction of benzimidazoles containing chiral side chains starting from cyclopropyl ketones with aryl 1,2-diamines under Sc(III) complex catalysis. A sequence of ring-opening/cyclization/retro-Mannich reactions was proposed to occur.¹⁷³ A huge library of products was achieved in moderate to excellent yields with excellent enantioselectivities (Scheme 104).

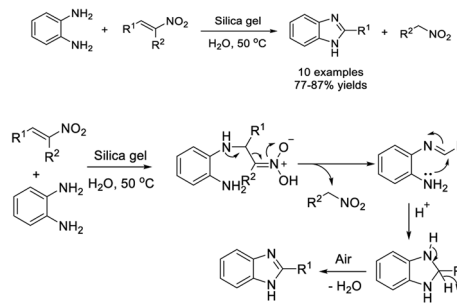
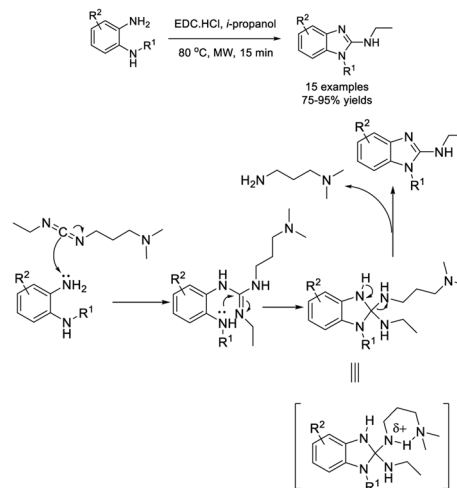
Rapolu *et al.* described an efficient one-pot procedure for the preparation of 2-ethylamino benzimidazole from *o*-phenylenediamines with EDC·HCl.¹⁷⁴ The microwave-assisted synthesis gave products in high yields in a short reaction time. A reaction mechanism was also outlined (Scheme 105).

Li *et al.* obtained benzimidazoles by treatment of nitroolefins and *o*-phenylenediamine with silica gel catalyst in water.¹⁷⁵ Products were generated in high yields with operational simplicity. A plausible reaction mechanism was described (Scheme 106).





Liu *et al.* designed a protocol to access 2-aminobenzimidazoles from 2-aminoanilines and isonitriles.¹⁷⁶ The cobalt-catalyzed synthesis delivered 2-aminobenzimidazoles in modest to excellent yields (Scheme 107).



Zhu *et al.* illustrated a practical protocol to access 2-unsubstituted benzimidazoles by treatment of 2-aminoanilines with DMSO at elevated temperature.¹⁷⁷ The NH_4OAc -promoted reaction provided products in acceptable yields with broad substrate scope (Scheme 108).

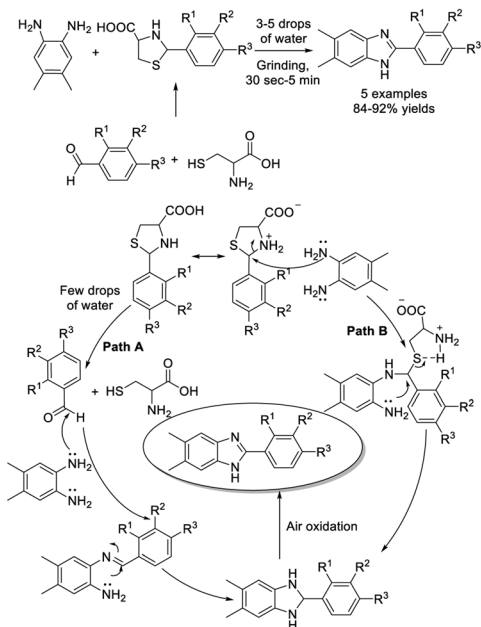
Almansour *et al.* disclosed a versatile green method for the highly selective construction of 2-aryl benzimidazoles from aromatic 1,2-diamines with a series of substituted arylthioproline.¹⁷⁸ Five products were afforded in very good yields in short reaction times under mild reaction conditions (Scheme 109).

Yu *et al.* established an efficient procedure to access benzimidazoles from imine derivatives with *o*-phenylenediamines by a $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ catalyzed aerobic oxidation reaction.¹⁷⁹ A huge





Scheme 108



Scheme 109



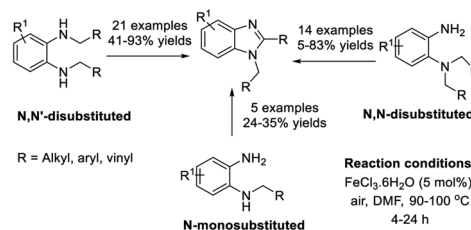
Scheme 110

library of products was furnished in moderate to excellent yields (Scheme 110).

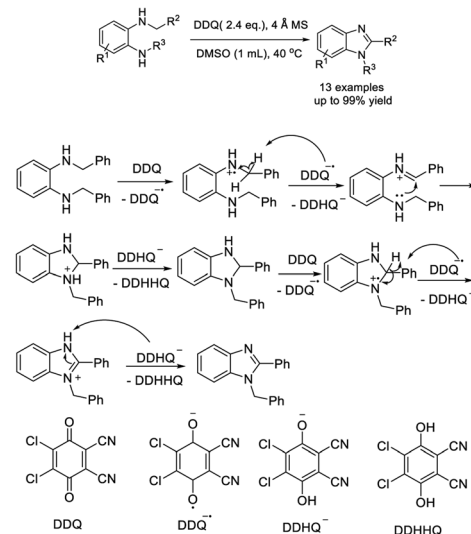
Thapa *et al.* developed an iron-catalyzed oxidative coupling approach to access 1,2-disubstituted benzimidazoles from mono- and di-substituted *ortho*-phenylenediamines.¹⁸⁰ The synthesis used O₂ as an oxidant and was suitable for a wide range of substrates (Scheme 111).

Ma *et al.* prepared 1,2-disubstituted benzimidazoles from *N,N'*-dialkyl *ortho*-phenylenediamines *via* intramolecular dehydrogenative coupling under the oxidation of DDQ.¹⁸¹ Products were furnished in high yields under mild conditions. A plausible reaction mechanism was suggested (Scheme 112).

A facile methodology for the synthesis of 2-substituted benzimidazole was introduced by Patil *et al.* *via* a tandem reaction following sp³ C–H functionalization using *tert*-butyl hydroperoxide (TBHP) as an oxidant.¹⁸² A diverse range of products were generated in moderate to excellent yields under mild conditions (Scheme 113).



Scheme 111



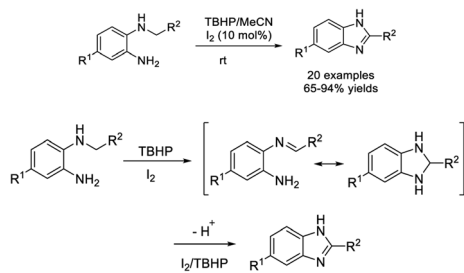
Scheme 112

3.6. By reactions of *o*-nitroaniline

Naeimi *et al.* examined an efficient protocol to access 2-substituted benzimidazoles from *o*-nitroaniline and aryl aldehydes using Na₂S₂O₄ as a catalyst.¹⁸³ A series of products was provided in excellent yields in a short time under microwave irradiation (Scheme 114).

Arya *et al.* prepared silver nanoparticles using green algae (*Botryococcus braunii*) and employed this material as a catalyst for the synthesis of benzimidazoles from *o*-nitroaniline and aldehydes.¹⁸⁴ Products were generated in moderate to good yields under mild reaction conditions (Scheme 115).





Scheme 113



Scheme 114



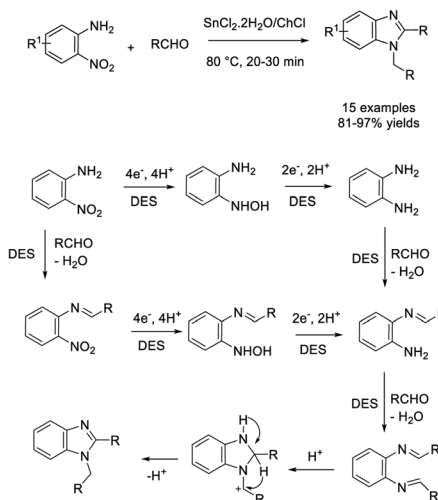
Scheme 115

Özil *et al.* designed the synthesis of a series of 2-(aryl)-6-morpholin-4-yl(or 4-methylpiperazin-1-yl)-1*H*-benzimidazole derivatives from 5-morpholin-4-yl(or 4-methylpiperazin-1-yl)-2-nitroaniline and various aldehydes. The microwave synthesis gave better yields than the conventional heating method. All the synthesized species exhibited very high radical scavenging activities using the ABTS^{•+} and DPPH[•] methods. Some compounds showed much better α -glucosidase inhibitory activity than the standard acarbose.¹⁸⁵ The α -glucosidase inhibitory study indicated that the hydroxyl group at the *para* position is essential to the exhibition of biological activity, and that the introduction of a piperazine or morpholine group would potentially increase the binding affinity and yield higher inhibitory activity. A reaction mechanism was proposed for the formation of benzimidazoles (Scheme 116).

Rodríguez-Huerta *et al.* developed an efficient method to access *N*-arylmethyl-2-substituted benzimidazoles from



Scheme 116



Scheme 117



Review

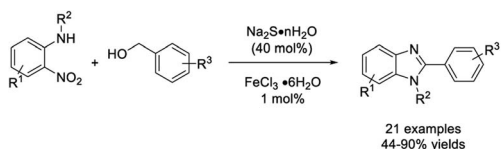
nitroarenes and aldehydes.¹⁸⁶ The synthesis was performed in a tin(II) chloride dihydrate/choline chloride eutectic mixture to provide products in good to excellent yields. A reaction pathway was also described (Scheme 117).

Kumar *et al.* introduced an efficient approach to construct 1,2-disubstituted benzimidazole-5-carboxylates from 4-(alkyl/aryl)amino-3-nitrobenzoates and aldehydes *via* a one-pot nitroreductive cyclization process using sodium dithionite.¹⁸⁷ A diverse library of products was produced in good to excellent yields in a very short reaction time (Scheme 118). A reaction mechanism was also presented.

Nguyen *et al.* completed the synthesis of benzimidazoles starting from *o*-nitroanilines and benzyl alcohols through an unbalanced redox condensation reaction using sodium sulfide (40 mol%) in combination with iron(III) chloride hexahydrate (1 mol%) as a catalyst system.¹⁸⁸ A wide range of products was furnished in modest to excellent yields (Scheme 119).



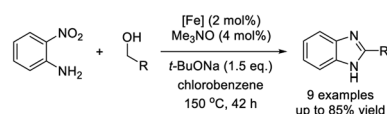
Scheme 118



Scheme 119



Scheme 120



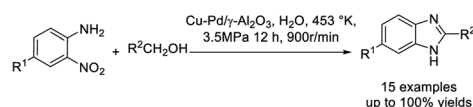
Scheme 121

Li *et al.* used [1,10-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (Pd(dppf)Cl₂) as a catalyst for the synthesis of 2-substituted benzimidazoles *via* a hydrogen-transfer strategy.¹⁸⁹ A set of 2-substituted benzimidazoles were obtained in good to excellent yields (Scheme 120).

Putta *et al.* demonstrated an iron-catalyzed hydrogen transfer protocol to access benzimidazoles *via* the redox condensation of *o*-nitroanilines with primary alcohol.¹⁹⁰ Various products were generated in good yields under thermal conditions (Scheme 121).

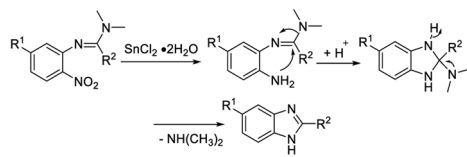
Feng *et al.* utilized a Cu-Pd/ γ -Al₂O₃ catalyst for the assembly of benzimidazole derivatives *via* a sequence of hydrogenation transfer and cyclization coupling. The use of Cu and Pd was responsible for the dehydrogenation of the primary alcohol and hydrogenation of *o*-nitroaniline.¹⁹¹ Various products were furnished in high yields and the catalyst could be recycled for several runs without a significant decrease in reaction yields (Scheme 122).

Duan *et al.* demonstrated a methodology to access 2,5-disubstituted benzimidazoles from 2-nitro-5-substituted anilines by a reductive cyclization reaction using stannous chloride dihydrate as a catalyst.¹⁹² All products were furnished in excellent yield under mild reaction conditions (Scheme 123).

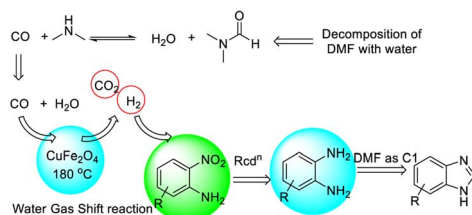


Scheme 122





Scheme 123

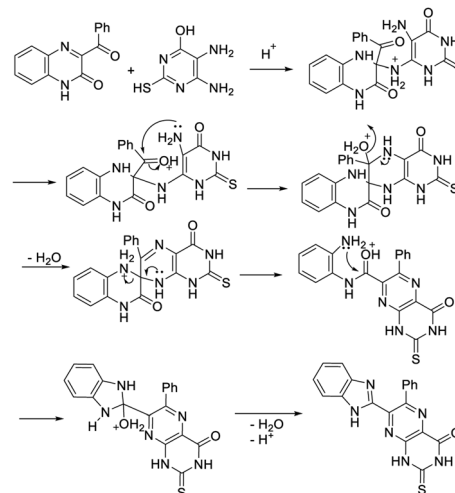


Scheme 124

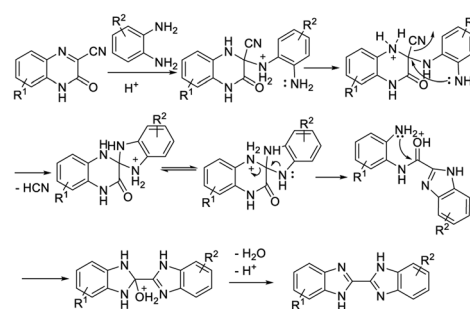
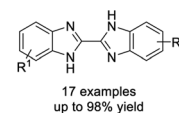
Rasal *et al.* developed a method for the one-pot synthesis of benzimidazole from *o*-nitroanilines and DMF using CuFe_2O_4 as a catalyst.¹⁹³ The catalyst was easily recovered by an external magnetic field and reused at least three times without considerable loss of its activity (Scheme 124).

4. Benzimidazole synthesis without using 1,2-benzenediamine or its analogues

The Mamedov group explored a facile approach for the assembly of 7-(benzimidazol-2-yl)lumazines (7-(benzimidazol-2-yl)pteridine-2,4(1*H*,3*H*)-diones) from quinoxalin-2-one derivatives and 2,4,5-triamino-6-oxypyrimidines. A sequence of addition of nucleophile, ring opening, and ring closure was proposed to occur in one pot.¹⁹⁴ A vast number of products was achieved in high yields (Scheme 125). The group also achieved an efficient strategy for the construction of substituted 2,2'-bibenzimidazoles starting from 3-cyanoquinoxalin-2(1*H*)-ones and 1,2-diaminobenzenes.¹⁹⁵ The reaction proceeded *via* a sequence of nucleophilic addition, electrophilic substitution, and Mamedov rearrangement. A wide range of products was obtained in high yields (Scheme 126).



Scheme 125



Scheme 126

Mahesh *et al.* established a novel methodology toward substituted benzimidazoles from anilines, aldehydes, and TMSN_3 .¹⁹⁶ The one-pot, multicomponent reaction proceeds smoothly to afford products in modest to good yields with broad substrate scope (Scheme 127). A reaction pathway was also described.

Chen *et al.* demonstrated an efficient protocol to access benzimidazole derivatives starting from *N*-alkyl-2-iodoaniline





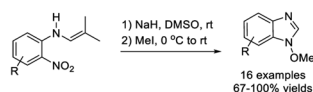
Scheme 132



Scheme 133

Various products were produced in moderate to excellent yields under mild reaction conditions. A reaction pathway was also proposed (Scheme 134).

Joardar *et al.* achieved a one-pot intramolecular nitro reduction/cyclization reaction for the synthesis of substituted benzimidazoles.²⁰⁴ A wide range of products was isolated in moderate to excellent yields under mild conditions (Scheme 135).



Scheme 134



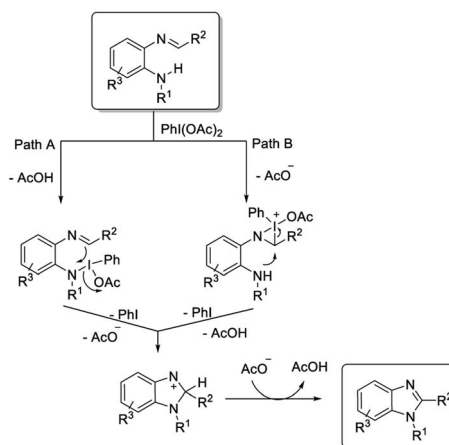
Scheme 135

Maitia and Mala introduced an efficient approach to access substituted benzimidazoles *via* phenyliodine diacetate (PIDA)-mediated $\text{C}(\text{sp}^2)\text{-H}$ amidation.²⁰⁵ A huge number of benzimidazole products were furnished in good to excellent yields under mild reaction conditions in the open air (Scheme 136).

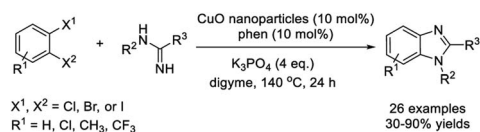
Yu *et al.* developed a procedure for the assembly of 1,2-disubstituted benzimidazoles from 1,2-dihaloarenes and *N*-arylamidines using copper oxide nanoparticles as a catalyst. In general, the products were formed in good to excellent yields.²⁰⁶ In addition, the catalyst could be recycled and reused without any considerable loss of the catalytic activity (Scheme 137).

Shaik *et al.* investigated the synthesis of 2-(*N*-arylamino) benzimidazoles involving a C-N cross-coupling reaction.²⁰⁷ A diverse range of products was achieved in moderate to excellent yields (Scheme 138).

Mirza and Zeeb established a novel method to access benzimidazole derivatives from 1-fluoro-2-nitrobenzene and various arylamines.²⁰⁸ The CuBr -catalyzed oxidation and cyclization reaction provided products in good yields (Scheme 139).

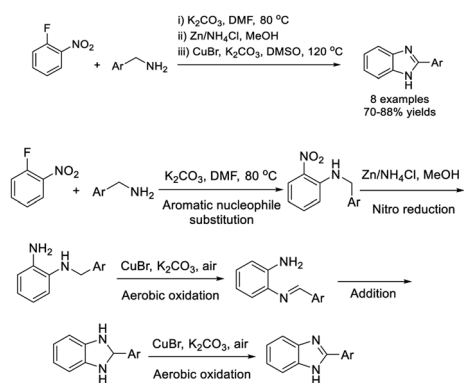
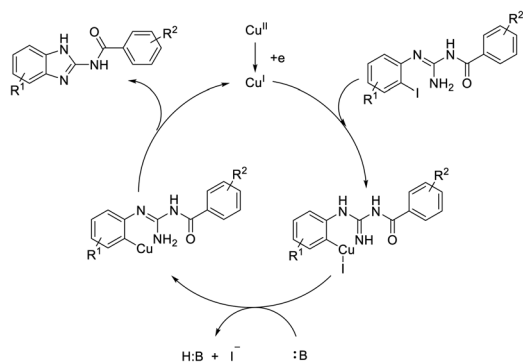


Scheme 136



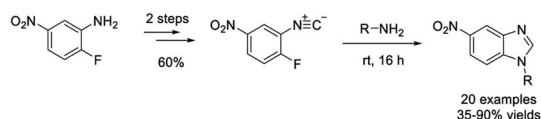
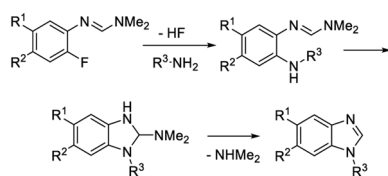
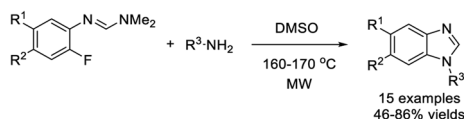
Scheme 137





Liu *et al.* demonstrated a metal-free synthesis of *N*-1-alkyl-2-unsubstituted benzimidazoles from *o*-fluoro aryl formamidines and primary amines.²⁰⁹ The one-pot displacement of -F by the primary amine and cyclization was performed in a microwave reactor (Scheme 140).

Kurhade *et al.* disclosed an efficient one-pot protocol for the construction of *N*-substituted benzimidazoles starting from 2-



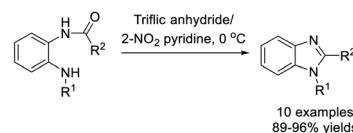
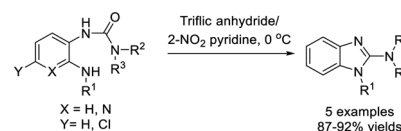
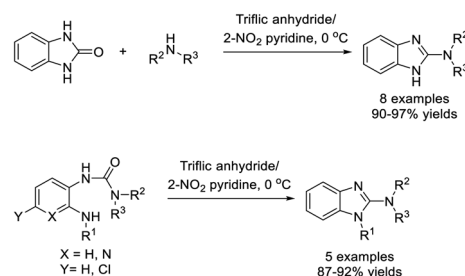
Scheme 141

fluoro-5-nitrophenylisocyanide and primary amines.²¹⁰ Various products were generated in modest to excellent yields (Scheme 141).

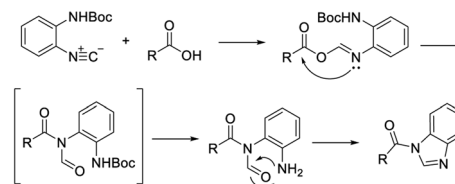
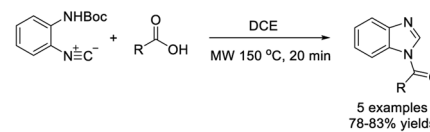
Quadri *et al.* completed the preparation of 2-substituted benzimidazoles from 2(3*H*)-benzimidazolones and amines mediated by 2-nitropyridine and triflic anhydride.²¹¹ Eight products were achieved in excellent yields (Scheme 142).

Chen *et al.* prepared benzimidazole derivatives by treatment of 2-(*N*-Boc-amino)phenylisocyanide with carboxylic acids in DCE.²¹² Five products were obtained in good yields under microwave irradiation (Scheme 143).

In a study reported by Saha *et al.*, 2-substituted benzimidazoles were synthesized from 2-aminobenzyl alcohol/2-aminobenzamide and different coupling partners (nitriles, aldehydes and 1,3-diketones). A sequence of C-N bond formation, cyclization, subsequent ring contraction and dehydrogenation was proposed to occur.²¹³ The iodine and TBHP

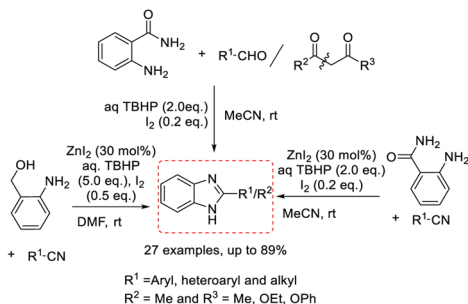


Scheme 142



Scheme 143



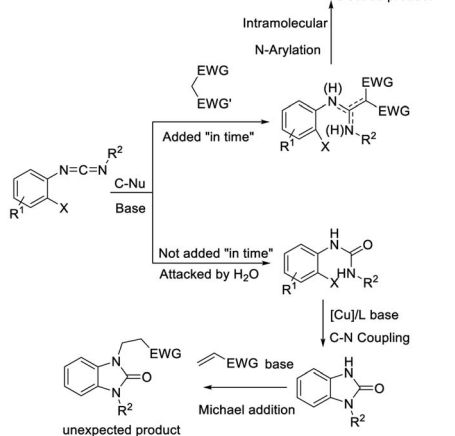
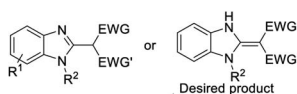
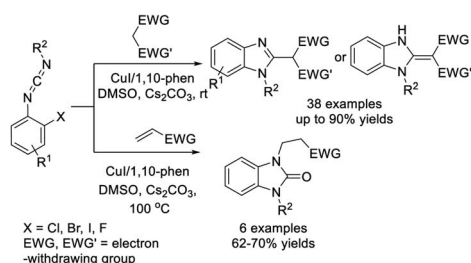


Scheme 144

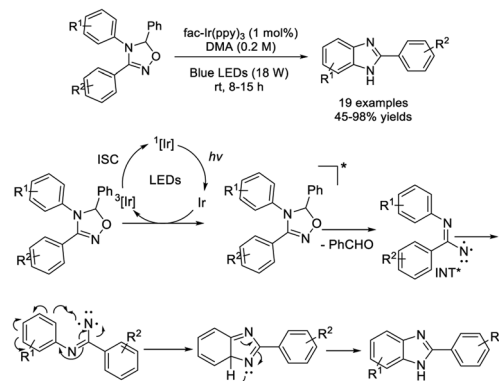
promoted syntheses furnished products in modest to good yields under mild reaction conditions (Scheme 144).

Liu *et al.* introduced a facile strategy to access 2-substituted benzimidazoles from *o*-haloarylcarbodiimides with active methylene compounds.²¹⁴ The copper-catalyzed synthesis was performed under mild reaction conditions and resulted in products in good yields (in most cases) for a wide range of substrates (Scheme 145).

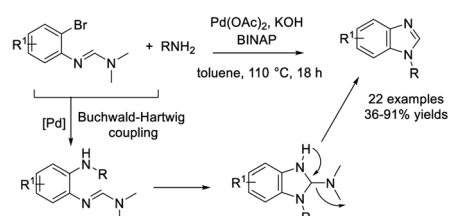
Park *et al.* developed a methodology for the assembly of benzimidazoles starting from oxadiazolines through nitrene intermediates. A sequence of homolytic N–O bond cleavage and concomitant C–N bond cleavage was proposed to generate nitrene, which then underwent intramolecular aromatic substitution to furnish functionalized benzimidazoles.²¹⁵ A wide



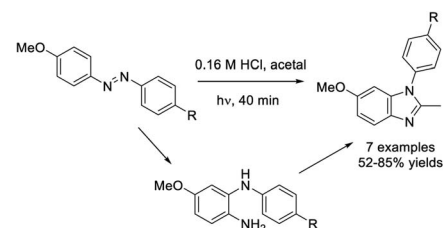
Scheme 145



Scheme 146



Scheme 147

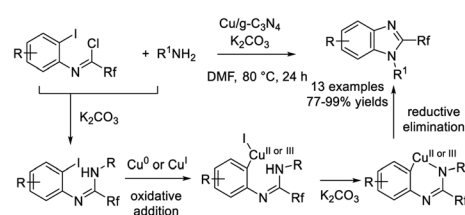


Scheme 148

range of products were afforded in acceptable to excellent yields under mild photocatalytic reaction conditions (Scheme 146).

Bie *et al.* investigated a novel approach to access *N*-substituted benzimidazoles using aromatic formamidines and primary amines as starting materials.²¹⁶ The Pd-catalyzed reaction furnished products in moderate to good yields with broad substrate scope (Scheme 147).

Chen *et al.* examined a procedure to prepare 1-aryl-1*H*-benzimidazoles from 4-methoxyazobenzenes.²¹⁷ The products were generated in good yields when the reactants were



Scheme 149



irradiated in acetal containing 0.16 M hydrochloric acid for 40 minutes (Scheme 148).

Xu *et al.* achieved an efficient protocol for the construction of 2-trifluoromethyl-benzimidazoles starting from trifluoroacetimidoyl chlorides and amines using a copper doped $g\text{-C}_3\text{N}_4$ catalyst.²¹⁸ Various products were furnished in good to excellent yields (Scheme 149).

5. Conclusion

In conclusion, this article has summarized studies on the synthesis of benzimidazole derivatives over a decade and given brief descriptions of the biological applications of benzimidazole derivatives. The condensation of 1,2-benzenediamine or its analogues with aldehydes or primary alcohols has received much attention from chemists, and numerous studies based on this method have been published recently. Furthermore, many novel methods using different substrates with high efficiency or employing environmentally benign procedures have been investigated. Undoubtedly, more facile, environmentally friendly, and efficient strategies to prepare benzimidazole-based compounds will be developed in the near future. The application of benzimidazole synthesis to natural product synthesis and drug synthesis is probably the next challenge in the field. This review article summarizes up-to-date articles, deals with a great number of studies, covers all aspects of benzimidazole synthesis, and describes the reaction pathways in most studies.

Author contributions

Vo Cong Dung: data curation; Nguyen Thi Chung: formal analysis; Dau Xuan Duc: writing original draft, review, and editing.

Conflicts of interest

There are no conflicts to declare.

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