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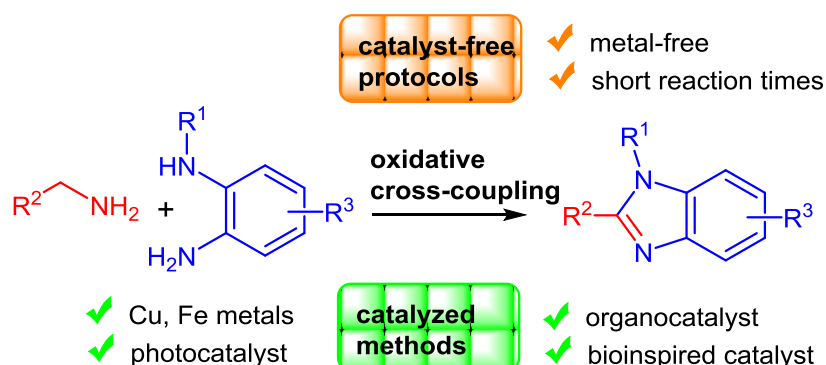
Recent Advances in the Synthesis of Benzimidazole Derivatives from the Oxidative Coupling of Primary Amines

M. Langeron^{*a}
K. M. H. Nguyen^{a,1}

^a UMR 8638 CNRS-Université Paris Descartes (Paris 5), Sorbonne Paris Cité, Faculté de Pharmacie de Paris, 4 avenue de l'Observatoire, 75270 Paris cedex 06 (France)

martine.langeron@parisdescartes.fr

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Abstract Benzimidazole belongs to the top five most commonly used five-membered aromatic nitrogen heterocycles among U.S. FDA approved pharmaceuticals. Over the last few years, a large number of improved synthetic strategies have been developed to construct the benzimidazole molecular framework under environmentally benign conditions. This review focuses on the use of primary amines as readily available substrates for the synthesis of benzimidazole derivatives through different types of oxidative cross-coupling reactions.

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Key words oxidation, homogeneous catalysis, heterogeneous catalysis, cross-coupling, amine, imine, benzimidazole

1 Introduction

Nitrogen heterocycles are among the most privileged and significant structural components of pharmaceuticals.² A recent analysis of the nitrogen heterocyclic composition of U.S. FDA (Food and Drug Administration) approved drugs has revealed the relative frequency by which the various nitrogen heterocycles have been incorporated into approved drugs architecture.³ Interestingly, benzimidazole was found to be the fifth most commonly used five-membered aromatic nitrogen heterocycles after thiazole, imidazole, indole and tetrazole. Benzimidazoles are found in thirteen U.S. FDA approved drugs exhibiting diverse pharmaceutical properties. Five of these drugs are structurally similar proton pump inhibitors including the well known omeprazole, also marketed as the single enantiomer sulfoxide variant esomeprazole (Figure 1).

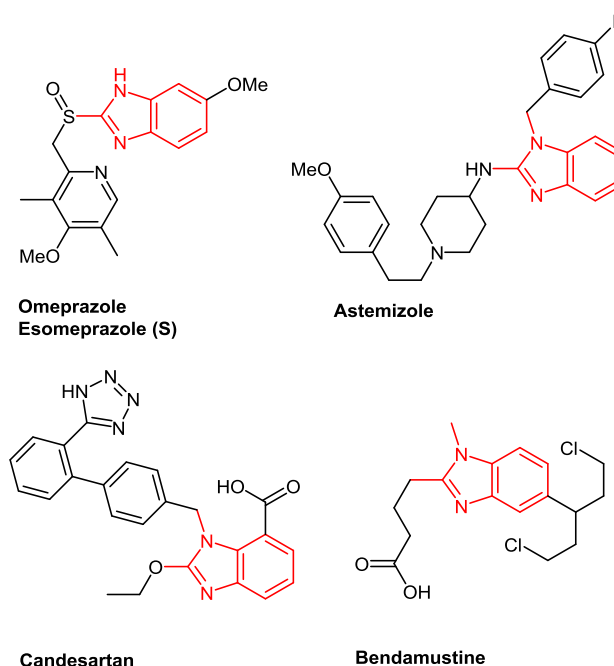


Figure 1 Representative pharmaceuticals containing a benzimidazole scaffold

Five of the benzimidazole drugs, candesartan, telmisartan, azilsartan, medoxomil and mibefradil, are used as anti-hypertensives whereas astemizole and emedastine are anti-histaminic agents. Lastly, bendamustine acts as an alkylating agent for the treatment of chronic lymphocytic leukemia and dabogatran elixilate mesylate is used to prevent the risk of stroke. Interestingly, almost all drugs are 1,2-disubstituted benzimidazole derivatives.

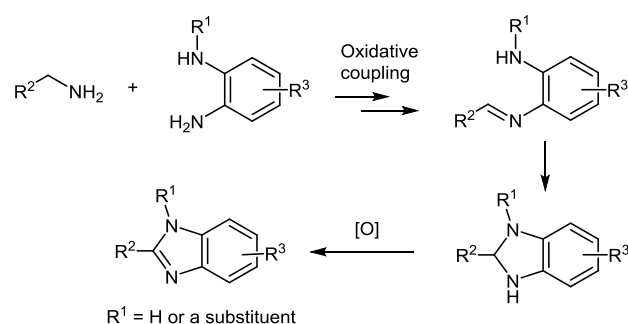
Owing to the prevalence of the benzimidazole molecular framework, tremendous efforts have been devoted to the

synthesis of functionalized benzimidazole derivatives, which are traditionally prepared from *o*-aminoanilines by condensation with carboxylic acid derivatives under harsh dehydrating conditions or by oxidative coupling with aldehydes.⁴ Although the oxidative condensation of *o*-aminoanilines with aldehydes remains the most popular way to prepare these targets, this strategy suffers some drawbacks such as air-sensitive catalysts, stoichiometric or excess amount of oxidants, low yields, high reaction temperature and the competitive formation of 2-substituted and 1,2-disubstituted benzimidazoles.⁵ Recent advances have been dominated by the development of improved procedures in terms of operational simplicity, atom economy and ecofriendly viability, which selectively lead to either 2-substituted benzimidazoles⁶ or 1,2-disubstituted benzimidazoles as the sole product.⁷

The regiodefined 1,2-disubstitution on the benzimidazole scaffold being a structural characteristic of pharmaceuticals, numerous alternative strategies have been developed for the regiocontrolled synthesis of 1,2-disubstituted benzimidazoles.⁸ In particular, catalytic amination of 2-haloacetanilides and catalyzed intramolecular C-N cross-coupling reactions starting from amidines have widely been utilized.⁹ However, these routes require special efforts to prepare the desired starting materials, thus limiting the potential applications of these methods.

Recently, oxidative cross-coupling reactions employing alcohols and *o*-aminoanilines as substrates have received great attention for selectively producing 2-substituted benzimidazoles without the concomitant formation of 1,2-disubstituted benzimidazoles.¹⁰ However, with few exceptions,^{10d,h,j} high reaction temperature (90–160 °C), oxygen pressure or expensive transition-metal catalysts are still required.

This review focuses on the utilization of primary amines as readily available substrates in the oxidative cyclocondensation reaction with *o*-aminoanilines to construct the benzimidazole framework (Scheme 1). The attractive features of this protocol include the use of commercially available amines, high atom economy and high selectivity towards the products. Furthermore, a large molecular diversity could be attained through the variation of both aliphatic amines and *o*-aminoanilines.



Scheme 1 Oxidative cyclocondensation of primary amines with *o*-aminoanilines leading to benzimidazole derivatives

Different types of oxidative cross-coupling with *o*-aminoanilines are presented, covering literature mainly

published during the last five years. Catalyzed methods are organized into three sections, for metal-catalyzed, metal-free and bioinspired reaction types.

2 Catalyst-free oxidative coupling of primary amines

Sustainable development has been accepted as a common knowledge in current society. In response to this challenge, the development of green processes, which reduce chemical waste and handling costs, is highly desirable.

Accordingly, Nguyen and co-workers have reported simple solvent-free and catalyst-free procedures for the synthesis of substituted benzimidazoles. Especially, they have performed oxidation reactions of various aliphatic amines using elemental sulfur as a readily available, nontoxic and stable oxidant, in the presence of *o*-aminoanilines, which are not sensitive to sulfur-mediated oxidation.¹¹ By heating an equimolar mixture of aliphatic amine and *o*-aminoaniline, at 150 °C, in the presence of an excess of elemental sulfur (3 equiv), under solvent-free conditions, 2-substituted benzimidazoles could be isolated in high yields. Using a slight excess of *o*-aminoaniline (1.5 equiv), the reaction temperature could be decreased to 130 °C and the isolated yield could reach 92% (Figure 2). Interestingly, aliphatic amines other than benzylic amines can be oxidized by elemental sulfur allowing introduction of alkyl substituents at the 2-position of the benzimidazole core.

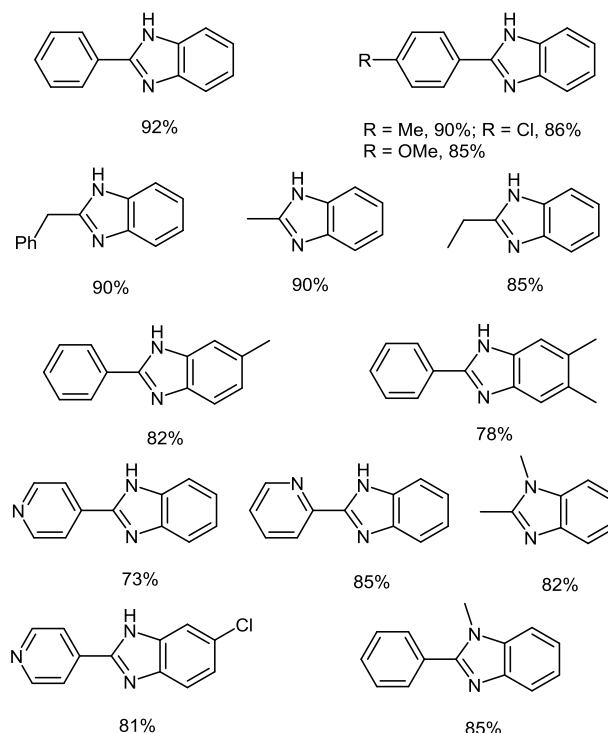
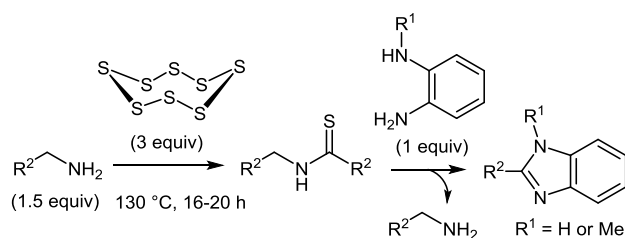


Figure 2 Yields of representative benzimidazole derivatives prepared from sulfur-mediated cross-coupling of amines¹¹

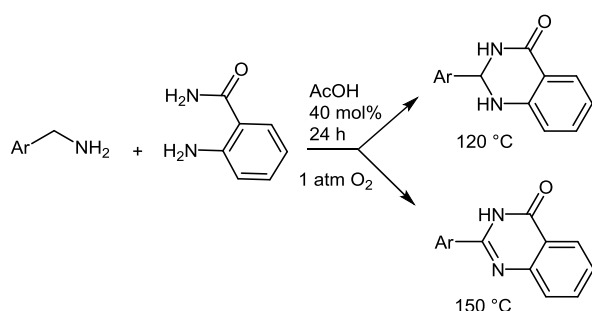
The reaction mechanism involved the intermediary formation of a homocoupled thioamide (Scheme 2), as the result of the oxidation of aliphatic amine by elemental sulfur, followed by trans-thioamidation which was energetically facilitated by

subsequent cyclization and aromatization steps (Scheme 1). So sulfur was not incorporated in the final product but was used as a traceless oxidizing reagent. Interestingly, this protocol was also effective for the preparation of benzothiazoles and benzoxazoles, the thia- and oxa-analogues of benzimidazoles.



Scheme 2 Sulfur-mediated oxidative coupling of aliphatic amines with *o*-aminoanilines affording benzimidazoles

Nguyen and co-workers have also described a solvent-free autoxidation system for the synthesis of 2-substituted benzimidazoles by simply heating a mixture of benzylic primary amines and *o*-aminoanilines, at 110 °C, under 1 atm of O₂ for 24 h, in the presence of acetic acid (20 mol%) as a cyclizing promoter.¹² Although this catalyst-free and solvent-free methodology was attractive from the viewpoint of sustainable chemistry, the substrate scope was limited to benzylic-type substrates. However, this solvent-free autoxidation system could also be applied to the synthesis of 2,3-dihydroquinazolin-4-(1*H*)-one and quinazolin-4-(3*H*)-one derivatives, in acceptable yields ranging from 60 to 72%, by changing *o*-aminoaniline to anthranilamide as the coupling partner, while increasing the amount of acetic acid to 40 mol% and the temperature to 120–150 °C (Scheme 3). Note the quinazoline framework is also part of the top 25 most commonly utilized nitrogen heterocycles found in pharmaceuticals.³



Scheme 3 Solvent-free autoxidation of benzylic amines allowing the synthesis of quinazoline derivatives

Yu and Lu have reported a similar catalyst-free and solvent-free oxidative synthesis of 2-substituted benzimidazole derivatives.¹³ Using an excess of *tert*-butyl hydroperoxide (TBHP, 4 equiv, 70% in H₂O) as the oxidant instead of 1 atm O₂,¹² a significant reduction of the reaction time (5–12 h against 24 h) was observed. Following the reaction scheme 1, various 2-substituted benzimidazoles were synthesized at 100 °C starting from 1 equiv of benzylic or allylic primary amines and 1.5 equiv of *o*-aminoanilines (Figure 3).

Recently, Kamal and co-workers have developed a metal-free one-pot protocol for the synthesis of 2-substituted

benzimidazole derivatives which proceeds through the oxidation of benzylic amines by an inexpensive mild oxidant phenyliodonium diacetate (PIDA).¹⁴

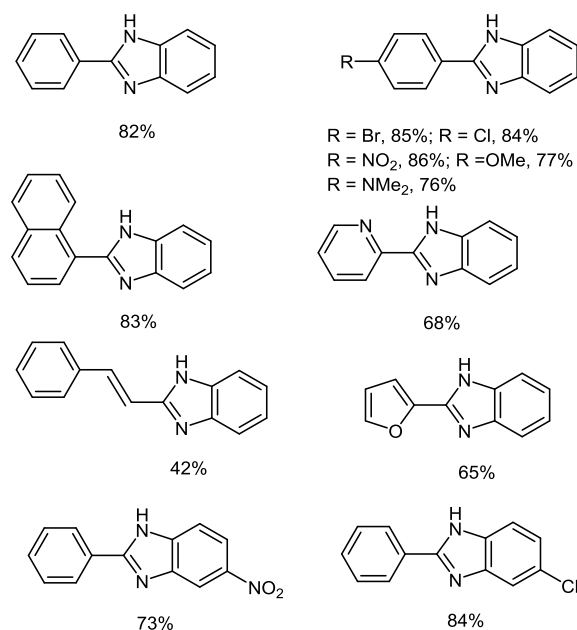
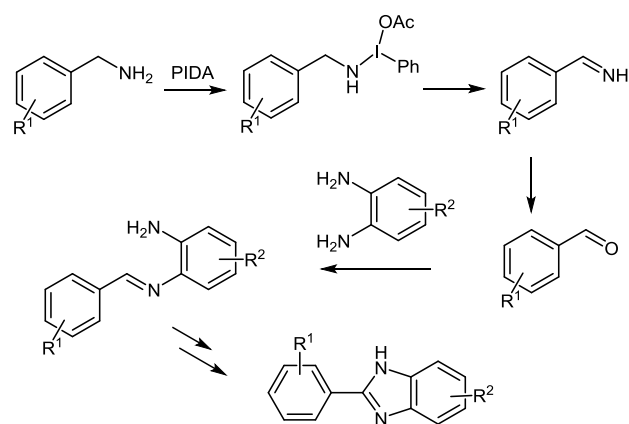


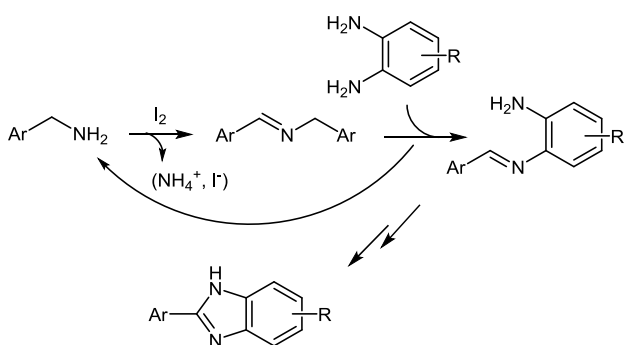
Figure 3 Yields of representative 2-substituted benzimidazoles synthesized through TBHP-mediated oxidative cross-coupling¹³

By heating 1.2 equiv of both PIDA and benzylic amine together with 1 equiv of *o*-aminoaniline, at 80 °C for 4 h, in a mixture of DMSO and H₂O (1:1 ratio) as the solvent, 2-substituted benzimidazoles could be isolated in high yields ranging from 77 to 92%. The reaction mechanism involved the oxidative addition of PIDA with benzylamine substrate, followed by the formation of a benzaldimine intermediate which rapidly hydrolyzed to give the corresponding benzaldehyde (Scheme 4). Further oxidative cyclocondensation with *o*-aminoanilines led to the corresponding 2-substituted benzimidazole product. Interestingly, the methodology could be extended to the synthesis of biologically relevant quinazolinone derivatives, when anthranilamide was used instead of *o*-aminoanilines by heating the reaction mixture at 100 °C for 6 h.



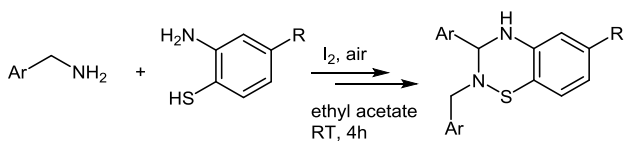
Scheme 4 Proposed reaction mechanism for the PIDA-promoted synthesis of 2-substituted benzimidazole derivatives

A last example of catalyst-free oxidative coupling of primary amines merits special note because of the exceptionally mild reaction conditions utilized. Narendra and co-workers have developed a simple method for the iodine-mediated synthesis of 2-substituted benzimidazole derivatives which allows the C-N bond formation at room temperature.¹⁵ The oxidative cross-coupling of benzylic amine (1.5 equiv) with *o*-aminoaniline (1 equiv) was promoted by 2 equiv of iodine in acetonitrile, leading to the desired benzimidazole product in only 30 min. The initial step of the reaction mechanism involves the oxidation of the benzylic amine by iodine to give, after elimination of ammonia, an homocoupled imine intermediate which could be isolated (Scheme 5). After dynamic transimination, the generated cross-coupled imine underwent intramolecular cyclization and subsequent oxidation as shown in reaction scheme 1 affording 2-substituted benzimidazoles in good yields ranging from 58 to 82%. However, aliphatic primary amines other than benzylic amines failed to provide 2-substituted benzimidazoles under the same experimental conditions.



Scheme 5 Proposed reaction mechanism for the I₂-mediated synthesis of 2-substituted benzimidazole derivatives

Replacing *o*-aminoaniline by mercaptoaniline, 2-substituted benzothiazoles could be prepared under similar reaction conditions. Furthermore, a new class of 2-benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines was discovered in ethyl acetate, which involved both metal-free C-N and S-N bond formation, illustrating the efficiency of the process (Scheme 6).



Scheme 6 I₂-mediated formation of 2-benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines

During the last five years, new and more environmentally friendly strategies for the catalyst-free oxidative coupling of primary amines to construct the benzimidazole framework have been identified.¹¹⁻¹⁵ At the same time, significant progress has resulted from the discovery of selective catalytic systems that avoid using stoichiometric or excess amounts of specific oxidants, which adversely affect the economics as well as the ecofriendly nature of the reaction.

3 Catalytic oxidative coupling of primary amines

The development of processes that satisfy environmental constraints is in current demand from the pharmaceutical and chemical industries. In this respect, the use of low loadings of catalysts, with molecular oxygen atmosphere or, much better, ambient air as the sole oxidant, is particularly attractive from the viewpoint of green chemistry.

3.1 Metal-catalyzed reactions

For years, the major weakness of metal-catalyzed reactions has been the use of expensive precious- and rare-metal catalysts, which did not meet the requirements of sustainable and green chemistry. Recently, earth abundant or biocompatible metals, especially copper and iron, have attracted much attention due to their low cost and low toxicity.¹⁶

Although the aerobic copper-catalyzed oxidation of primary amines to imines was previously described,¹⁷ Zhou and co-workers were the first to report a Cu-catalyzed aerobic oxidative cyclocondensation of benzylic amines with *o*-aminoanilines for the synthesis of 2-substituted benzimidazole derivatives.¹⁸ The reactions were carried out in toluene, at 100 °C under air for 24 h, using benzylic amines (1.2 equiv) and *o*-aminoanilines (1 equiv), in the presence of low loading of CuBr₂ (1 mol%) as the catalyst. In the presence of *o*-aminoaniline, variously substituted benzylamines afforded the corresponding 2-substituted benzimidazoles in 79-92% yields regardless of the electronic character of the substituents (Figure 4). Likewise, the reaction was not significantly affected by the substituents on the aromatic ring of *o*-aminoaniline, when benzylamine was used as the amine substrate, producing the corresponding 2-substituted benzimidazole derivatives in high yields (80-93%). Furthermore, the methodology could be extended to the synthesis of their structural isosteres, benzothiazole and benzoxazole.

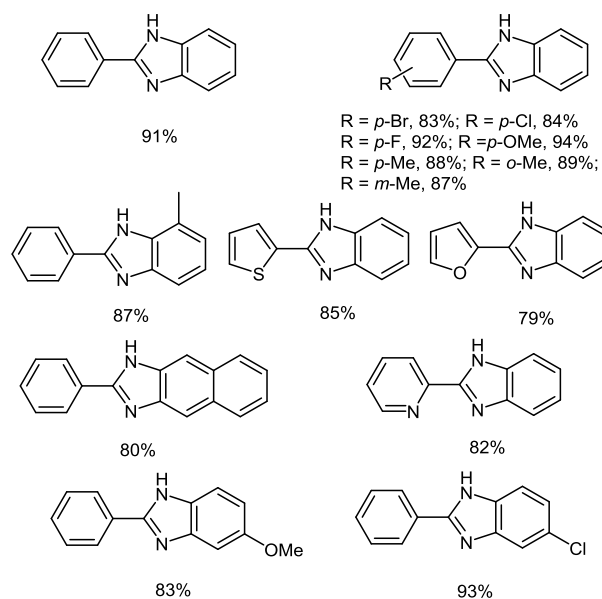
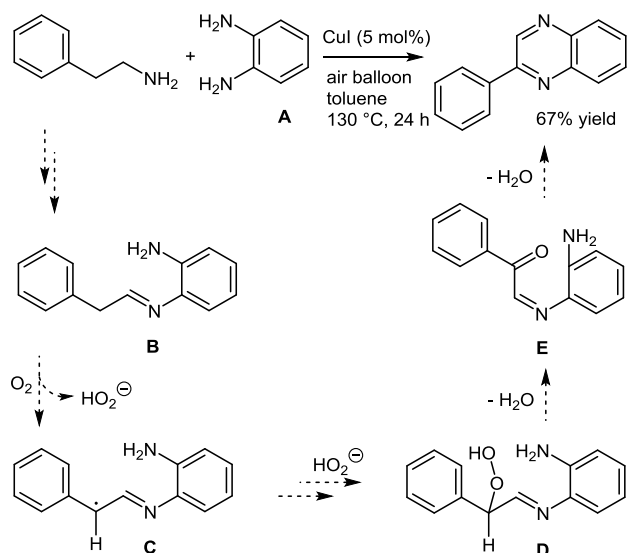


Figure 4 Yields of representative 2-substituted benzimidazoles synthesized through CuBr₂-mediated oxidative cross-coupling¹⁸

Xu and co-workers have reported a similar action of CuI (5 mol%) for the catalyzed oxidative cyclocondensation of benzylic amines (2 equiv) and *o*-aminoanilines (1 equiv) in toluene, at 100 °C under air for 48 h.¹⁹ The yields of isolated 2-substituted benzimidazole derivatives were acceptable, ranging from 41 to 83%. Noteworthy, variously substituted benzothiazoles and benzoxazoles could also be prepared through this protocol. Obviously, CuI was less effective than CuBr₂ to promote this kind of transformation.¹⁸ Nevertheless, at a slightly more elevated temperature of 130 °C for 24 h, CuI was also able to catalyze the oxidation of 2-phenylethylamine, which, in the presence of *o*-aminoaniline, was converted into a six-membered 2-phenylquinoxaline product through a reaction mechanism recently reported by Gopalaiah and co-workers for their similar CuBr-catalyzed protocol (Scheme 7, dashed arrows).²⁰ In the presence of *o*-aminoaniline **A**, copper-catalyzed aerobic oxidation of 2-phenylethylamine would produce the cross-coupled imine **B**, which after copper-catalyzed benzylic oxidation, would lead to the formation of the keto-imine **E** via benzyl radical intermediate **C** and hydroperoxide **D**.

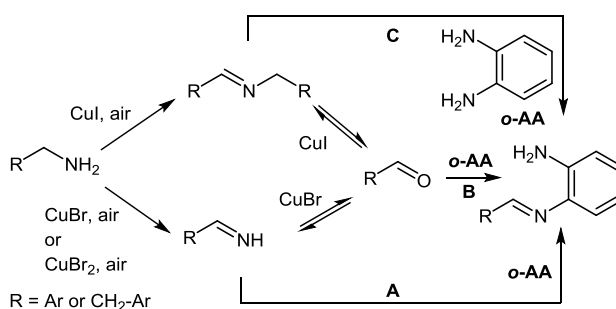


Scheme 7 CuI-catalyzed formation of 2-phenylquinoxaline

Interestingly, the CuBr-catalyzed oxidative coupling reaction of *o*-aminoanilines with 2-aryl/heteroarylethylamines described by Gopalaiah and co-workers was particularly efficient under 1 atm of molecular oxygen as the oxidant. Then, functionalized quinoxalines were isolated in high yields ranging from 78 to 97%.²⁰ The reaction proceeded rapidly within 5–16 h, in chlorobenzene, at room temperature, using 2-aryl/heteroarylethylamines (1.2 equiv) and *o*-aminoanilines (1 equiv), in the presence of CuBr (10 mol%) as the catalyst. Note that CuBr proved to be a more efficient catalyst than CuBr₂ for this transformation. In the case of 2-phenylethylamine substrate, changing CuBr to CuBr₂ led to a decreased yield in quinoxaline from 73 to 51%, under the same reaction conditions.²⁰

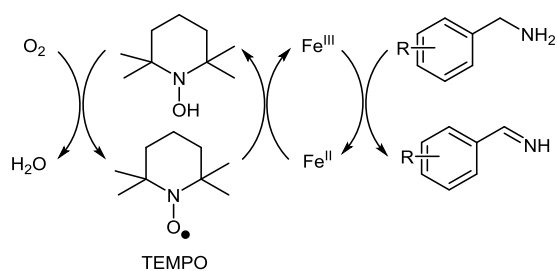
Note that different reaction pathways have been proposed for the copper-catalyzed formation of benzimidazoles (or quinoxalines) as shown in Scheme 8. Zhou and co-workers have envisioned the coordination of Cu^I to benzylic amine followed

by oxidation to generate the benzylimine intermediate, which reacts with *o*-aminoaniline giving the cross-coupled imine (path A).¹⁸ Gopalaiah and co-workers have similarly suggested direct transimination to form cross-coupled imine (path A) for their CuBr/O₂ system leading to quinoxalines, but they have also envisaged that 2-phenylethylimine may hydrolyze into phenylacetaldehyde, which, on further condensation with *o*-aminoaniline, forms the cross-coupled imine (path B).²⁰ Xu and co-workers have proposed an alternative route in which the CuI-catalyzed aerobic oxidation of amines under air produces the homocoupled imine intermediate, which then reacts with *o*-aminoaniline to give the cross-coupled imine through a transimination step (path C).¹⁹ Because of the presence of benzaldehyde as the by-product in reactions with low conversion, Xu and co-workers have also envisaged that benzylimine can hydrolyze into benzaldehyde and then affords the cross-coupled imine by condensation reaction (path B). The last steps of the process leading to the target benzimidazole heterocycle would involve intramolecular cyclization and subsequent oxidation as reported in reaction scheme 1.



Scheme 8 Possible pathways for the copper-catalyzed aerobic cross-coupling of primary amines

In addition to copper systems, iron catalysts are also ideal candidates for such transformations, because iron shows variable valences and fulfills the requirements for green chemistry. Inspired by the iron-mediated catalytic system reported by Xu and co-workers for the preparation of imines through aerobic oxidative coupling of amines under air,²¹ Lu and co-workers have demonstrated that the aerobic oxidative cyclocondensation of benzylic primary amines (1.2 equiv) and *o*-aminoaniline (1 equiv) can be achieved by the synergistic combination of Fe(NO₃)₃ (5 mol%) and electron-deficient 2,2,6,6-tetramethyl-1-piperidyl-1-oxy radical (TEMPO) (5 mol%), under solvent-free conditions, in open air.²² Various substituted benzylic amines were converted into 2-substituted benzimidazoles in high yields (78–93%), at 110 °C for 24–28 h. The first step of the proposed reaction mechanism consists of the aerobic Fe/TEMPO-catalyzed oxidation of benzylic amine to the corresponding benzylimine intermediate in a way reminiscent of that reported by Hu and Kerton for the aerobic Cu/TEMPO-catalyzed version (Scheme 9).²³ The mechanism pursues following reaction scheme 8 (path A or B).



Scheme 9 Proposed mechanism for $\text{Fe}(\text{NO}_3)_3/\text{TEMPO}$ -catalyzed aerobic oxidation of benzylic amines to benzylimines

Recently, Gopalaiah and Chandrudu have described a significantly improved Fe-catalyzed protocol for the synthesis of 2-substituted benzimidazoles, without the need of adding TEMPO.²⁴ Through optimization studies, they have compared the ability of Fe^{II} and Fe^{III} (10 mol%) to catalyze the aerobic coupling of benzylamine (1.2 equiv) and *o*-aminoniline (1 equiv), in chlorobenzene at 110°C for 18h under air. They have found that Fe^{II} , especially FeBr_2 , is the best choice for the oxidative cyclocondensation reaction leading to 2-phenylbenzimidazole in 78% yield. Using 1 atm of molecular oxygen instead of air atmosphere, the iron catalyst loading could be reduced to 5 mol%, while the yield of benzimidazole product significantly increased to 92% within only 4 h. A large molecular diversity could be attained through the variation of both benzylic amines and *o*-aminoanilines (Figure 5).

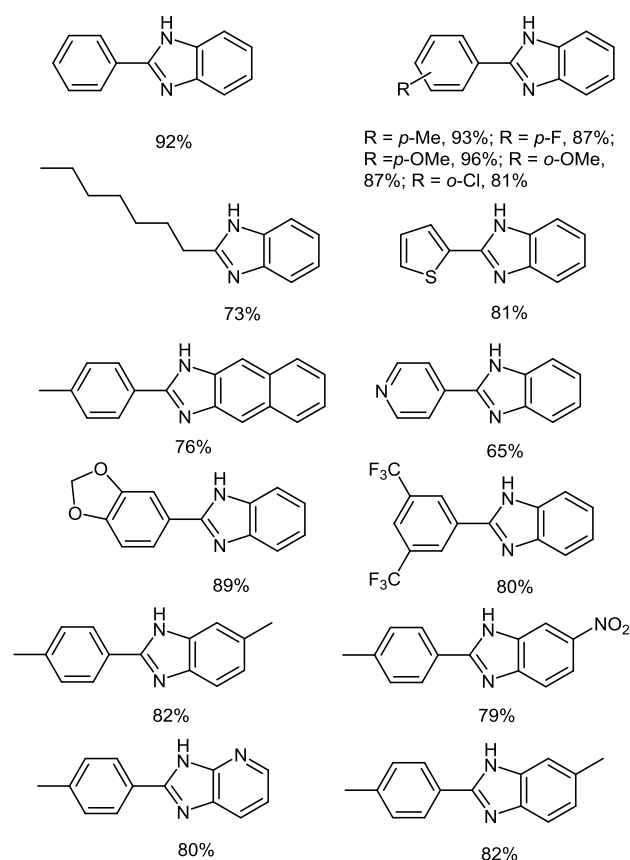


Figure 5 Yields of representative 2-substituted benzimidazoles synthesized through FeBr_2 -mediated oxidative cross-coupling²⁴

Interestingly, the non-activated primary amine *n*-octylamine was also a good substrate for this oxidative coupling reaction with *o*-aminoaniline, affording the corresponding benzimidazole in 73% yield. The proposed reaction mechanism was close to scheme 8 (path A or C) reported for the copper-mediated catalytic systems. Furthermore, the methodology could be applied to the synthesis of variously substituted benzothiazoles and benzoxazoles.

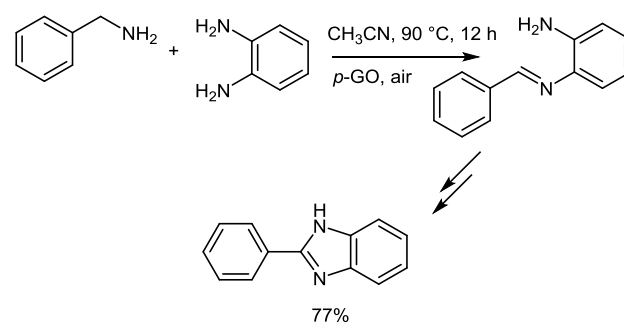
From the perspective of green chemistry and because metal residues may constitute a serious problem in the synthesis of pharmaceuticals and functional materials, chemists have shifted their attention to other eco-friendly protocols such as metal-free catalyzed reactions.

3.2 Metal-free catalyzed reactions

Alternative metal-free catalytic systems have been developed for the oxidative cross-coupling of primary amines including photocatalyzed and organocatalyzed reactions.

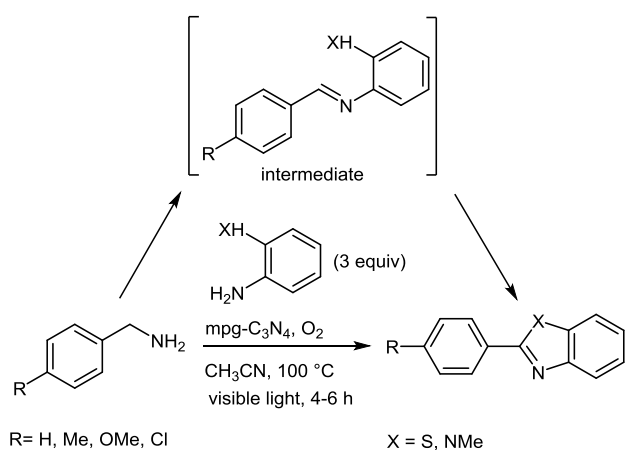
Heterogeneous metal-free catalysis

Owing to the natural abundance of carbon together with the need of minimizing the production of wastes and achieving optimal economic viability, the use of carbon catalysts has emerged in synthetic strategies.²⁵ Especially, graphene oxide (GO), a water-soluble derivative of graphene, has been utilized for the (GO)-mediated oxidative coupling of primary amines to imines.²⁶ However, most of the reactions require high weight loading of GO relative to the substrate, due to the moderate catalytic efficiency of GO when used as a substitute for metal catalysts. Loh and co-workers have reported a sequential base and acid treatment of GO that markedly improves its catalytic efficiency by generating porosity. Thanks to the utilization of porous graphene oxide (*p*-GO),²⁷ the oxidative cyclocondensation of benzylamine (1 equiv) and *o*-aminoniline (1.5 equiv) could be performed, under air in acetonitrile, at 90 °C, for 12h, affording 2-phenylbenzimidazole in 77% yield (Scheme 10). The extension of this protocol to other amine substrates has not been reported.



Scheme 10 One-pot aerobic *p*-GO catalyzed synthesis of 2-phenylbenzimidazole.²⁷

The utilization of sunlight as a non polluting energy source for chemical transformations has recently attracted much attention.²⁸ Although several aerobic photocatalytic oxidation of primary amines to imines have been developed,²⁹ a sole photocatalyzed oxidative cross-coupling reaction for the synthesis of benzimidazoles has been reported to the best of our knowledge. Blechert and co-workers have demonstrated that the utilization of mesoporous graphite carbon nitride (mpg-C₃N₄) photocatalyst, and visible light, allowed the complete conversion of benzylic amines to imines in acetonitrile at 80 °C but under high oxygen pressure (0.5 MPa).³⁰ Interestingly, the mpg-C₃N₄ photocatalyst could be easily separated and reused three times, without loss of catalytic activity. In the presence of *N*-methyl-*o*-aminoanilines (3 equiv) (or mercaptoaniline), at 100 °C, the imines resulting from the oxidative coupling reaction could be engaged in situ, in an intramolecular cycloaddition reaction and subsequent oxidation to give 1,2-disubstituted benzimidazoles (or 2-substituted benzothiazoles) with high levels of conversion (91-99%) within 4-6 h (Scheme 11).

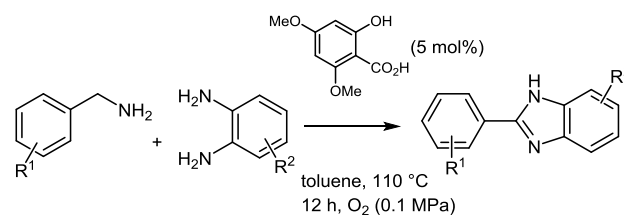


Scheme 11 One-pot aerobic photocatalytic synthesis of benzimidazoles and benzothiazoles

Homogeneous metal-free catalysis

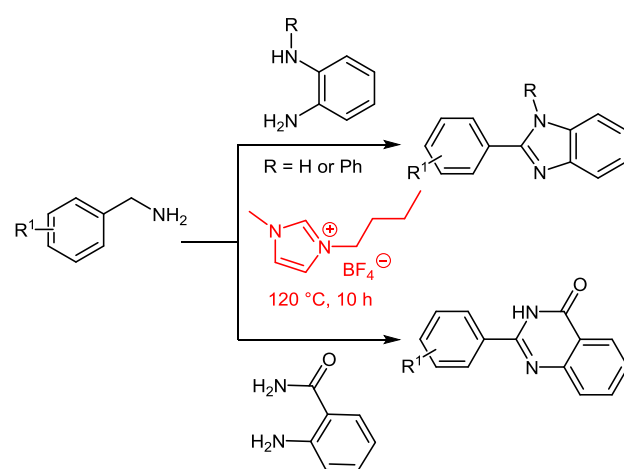
The use of small organic molecules to catalyse organic transformations, is a relatively popular field within the domain of organic synthesis.³¹ However, reports of the use of organocatalysts to mediate the aerobic oxidative cross-coupling of amines giving benzimidazole products are rather scarce.

Ogawa and co-workers have shown that the oxidative cross-coupling of primary amines could be achieved efficiently using salicylic acid derivatives as organocatalysts. Optimization studies revealed that 4,6-dimethoxysalicylic acid (5 mol %) was the most effective organocatalyst for the oxidative cyclocondensation reaction of benzylic amines (1.5 equiv) with *o*-aminoanilines (1 equiv), under an oxygen atmosphere (0.1 MPa), in toluene at 110 °C for 12h.³² Diverse substituents on the phenyl group of benzylamines or on the aromatic ring of *o*-aminoanilines were well tolerated, affording 2-substituted benzimidazole derivatives in high yields ranging from 85 to 95% (Scheme 12). Through additional experiments, the authors have demonstrated that the oxidation of benzylamine proceeds following a radical mechanism.



Scheme 12 One-pot aerobic organocatalyzed cascade reaction affording 2-substituted benzimidazole derivatives.

Except for few exceptions,^{11,30} the different oxidative cross-coupling protocols presented until now describe the synthesis of 2-substituted benzimidazole derivatives. A last example of homogeneous metal-free catalysis is attractive because it gives also access to pharmaceutically relevant 1,2-disubstituted benzimidazoles. Recently, Bharate and co-workers have developed a metal-free method for the synthesis of 1,2-disubstituted benzimidazoles from benzylamine substrates and *N*-phenyl-*o*-aminoaniline, using an imidazolium-based ionic liquid as the reaction medium, which can be recycled several times without significant loss of catalytic activity.³³ The process involves the oxidative cyclocondensation reaction of the benzylamine substrate (2 equiv) with *N*-phenyl-*o*-aminoaniline (1 equiv), in 1-butyl-3-methylimidazolium tetrafluoroborate as the ionic liquid (0.5 mL), heated at 120 °C for 10h. Various substituted benzylamines afforded the corresponding 1,2-disubstituted benzimidazoles, in high yields (88-98%), without particular electronic or steric effects of the substituents (Figure 6). Note that non-activated aliphatic amines failed to produce the corresponding benzimidazole derivatives under the same experimental conditions. This ionic-liquid-mediated process could be also applied to the synthesis of 2-phenyl-quinazolin-4-(3*H*)-one derivatives, in excellent yields ranging from 88 to 98%, by changing *o*-aminoaniline to anthranilamide as the coupling partner (Scheme 13). Interestingly, it was observed that ionic liquid mediated all of the oxidation steps, whereas air did not play a role in the oxidation since the reaction could be performed under nitrogen or argon atmosphere.



Scheme 13 Ionic-liquid mediated synthesis of benzimidazole and quinazolin-4-(3*H*)-one derivatives

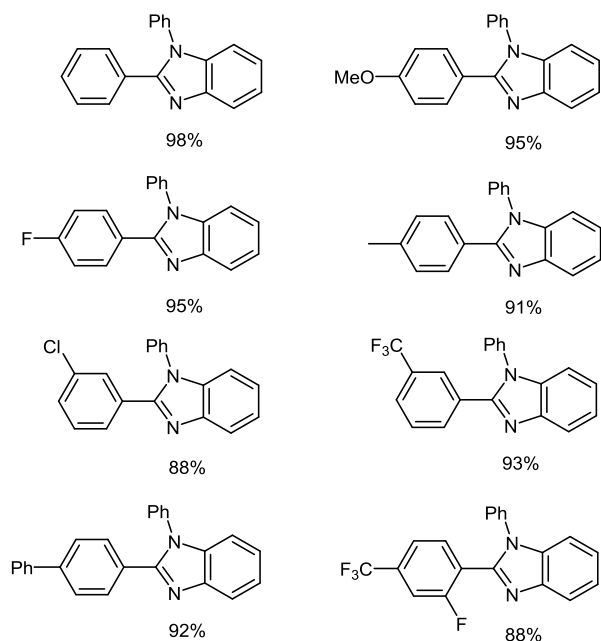


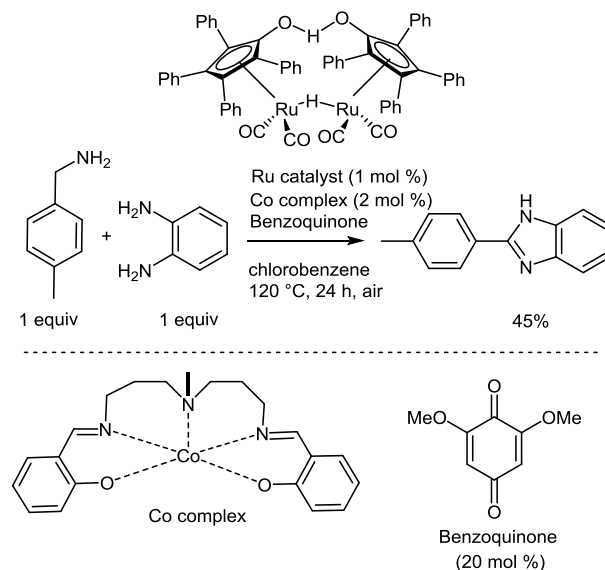
Figure 6 Yields of representative 1,2-disubstituted benzimidazoles synthesized through ionic liquid-mediated oxidative cross-coupling³³

At this stage, with only few exceptions,^{11,24} the major drawback of protocols based on the oxidative cross-coupling of amines is the difficulty of oxidizing non-activated primary amines. Accordingly, the molecular diversity is limited to derivatives bearing benzylic or allylic substituents at the 2-position of the benzimidazole framework. This compromises the overall efficiency of the reported works, because the well known coupling between an aldehyde and *o*-aminoaniline is more direct. Another weakness of these protocols is that the syntheses of 1,2-disubstituted benzimidazoles are rather scarce,^{11,30,33} while almost all pharmaceuticals are 1,2-disubstituted derivatives. The discovery of biomimetic methods that utilize air as an environmentally benign oxidant, in a way reminiscent of enzyme catalysis, has proved to be effective to surpass these limitations.

3.3 Bioinspired catalyzed reactions

In 2012, Endo and Bäckvall have been the first to develop a biomimetic electron-transfer system for the ruthenium-catalyzed oxidative coupling of primary benzylic amines and *o*-hydroxyanilines to give 2-substituted benzoxazoles in high yields.³⁴ Using 4-methylbenzylamine and *o*-aminoaniline as the amine substrates, they have been able to prepare the corresponding benzimidazole, though in 45% moderate yield (Scheme 14). The design of the system was inspired by the biological oxidation of alcohols. Instead of NAD⁺ they have used a ruthenium complex as the substrate selective catalyst which dehydrogenates the benzylic amine to the corresponding benzylimine. The hydrogen atoms abstracted are transported to the electron-rich 2,6-dimethoxy-1,4-benzoquinone which serves as an electron-transfer mediator. The resulting hydroquinone is subsequently reoxidized by air with the assistance of an oxygen-

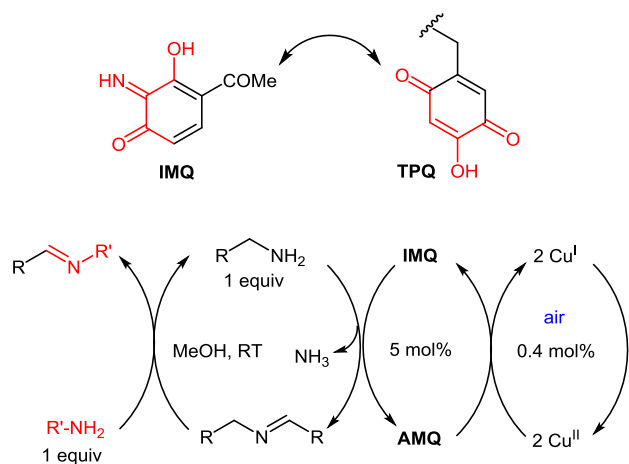
activating cobalt complex. The molecular diversity accessible through this protocol has not been explored.



Scheme 14 Ru-catalyzed oxidative coupling to give benzimidazole by using a biomimetic oxidation system

A noticeable progress has arisen from the development of biomimetic quinone-based catalytic systems inspired by natural copper amine oxidases (CuAOs), a family of metalloenzymes which catalyzes the selective oxidation of primary amines to aldehydes, through the cooperation of a quinone-based cofactor, 2,4,5-trihydroxyphenylalanine quinone (TPQ), and a copper ion.³⁵ During the last five years, organic chemists have developed various bioinspired quinone-based catalytic systems for the aerobic oxidation of amines to imines under 1 atm of dioxygen or, more preferably, ambient air as the sole oxidant, with two objectives: (a) to achieve sustainable aerobic oxidation reactions and (b) to expand the scope of possible substrates.³⁶

In this field, our group has recently described a bioinspired homogeneous catalytic system based on the cooperative action of a copper ion and a TPQ-like *o*-iminoquinone organocatalyst IMQ (Scheme 15), first discovered from electrochemical investigations.³⁷ This protocol is reminiscent of other biomimetic catalytic systems, that uses transition metals as substrate-selective catalysts coupled with electron transfer mediators.³⁸ Conversely, in our case, IMQ, which is generated in situ from the corresponding aminophenol AMQ, is the substrate-selective catalyst while the copper ion serves as an electron transfer mediator. Low catalyst loadings are sufficient to oxidize benzylic, and non-activated aliphatic amines RCH₂-NH₂, to the homocoupled imine product at room temperature under ambient air.³⁹ The oxidation process starts with atmospheric oxygen and continues in a cascade-like manner by passing the oxidation potential of oxygen through the copper salt to the organic mediator IMQ, which finally oxidizes the amine substrate. In the presence of a second primary amine R'-NH₂, the generated homocoupled imine intermediate could be converted into a cross-coupled imine with complete selectivity.⁴⁰



Scheme 15 Cu(OAc)₂/IMQ-catalyzed aerobic oxidative cross-coupling of primary amines to imines

The mild reaction conditions being highly favorable for trapping the unstable alkylimines in situ for further reactions, we have utilized our bioinspired co-catalytic system, in a one pot cascade reaction sequence, leading to 1,2-disubstituted benzimidazoles. Optimization studies realized from the aerobic oxidative cross-coupling of benzylamine (1 equiv) with *N*-phenyl-*o*-aminoaniline (1 equiv) indicated that higher yields were obtained by heating the coupling reaction mixture in methanol, at 45 °C under air, in the presence of 6 mol% of AMQ (4 mol% followed by a 2 mol% additional aliquot after 6h) and by using CuBr₂ (0.4 mol%) as the copper catalyst.⁴¹ The use of CuBr₂ as the more efficient copper catalyst had also been observed by Zhou and co-workers.¹⁸ A large molecular diversity could be attained through the variation of both coupling partners leading to 1,2-disubstituted benzimidazole derivatives in good yields. It is important to note that, with the exception of β -branched alkylamines, non-activated primary aliphatic amines were found to be good coupling partners for the CuBr₂/IMQ-mediated aerobic oxidative cyclocondensation reaction with *N*-substituted-*o*-aminoanilines provided a slightly elevated temperature of 60 °C was used (Figure 7).^{41,42}

Although MeOH proved to be the best solvent for the coupling reaction because it provides the ideal balance of IMQ solvation and reaction rate, when reactive *N*-alkyl-*o*-aminoaniline were used as in situ imine traps, a concomitant formation of *N*-alkylbenzimidazole by-product was observed, originating from the involvement of MeOH itself which acted as a carbon source. In these cases, the exclusive formation of 1,2-disubstituted benzimidazoles can be achieved in 2-propanol in the presence of water (10%), which markedly accelerates the cyclization rate to the benzimidazoline intermediate.⁴² Accordingly, Barta and co-workers had previously reported a protocol for the preparation of benzimidazoles from a range of *o*-aminoanilines by simply heating these starting materials in supercritical MeOH, which acts both as a solvent and carbon source, in the presence of copper-doped porous metal oxides.⁴³

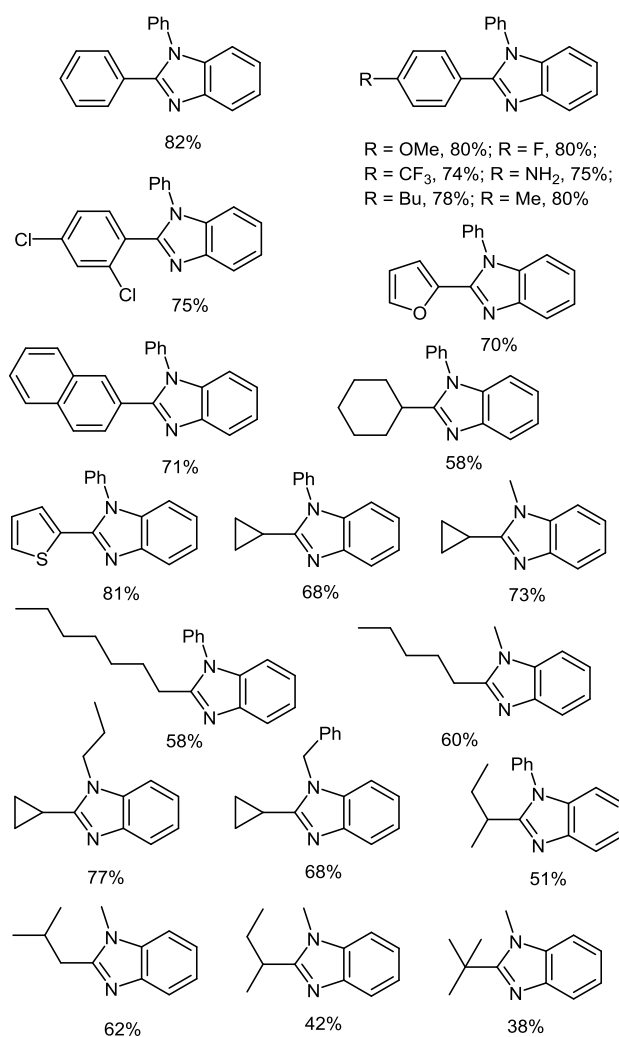
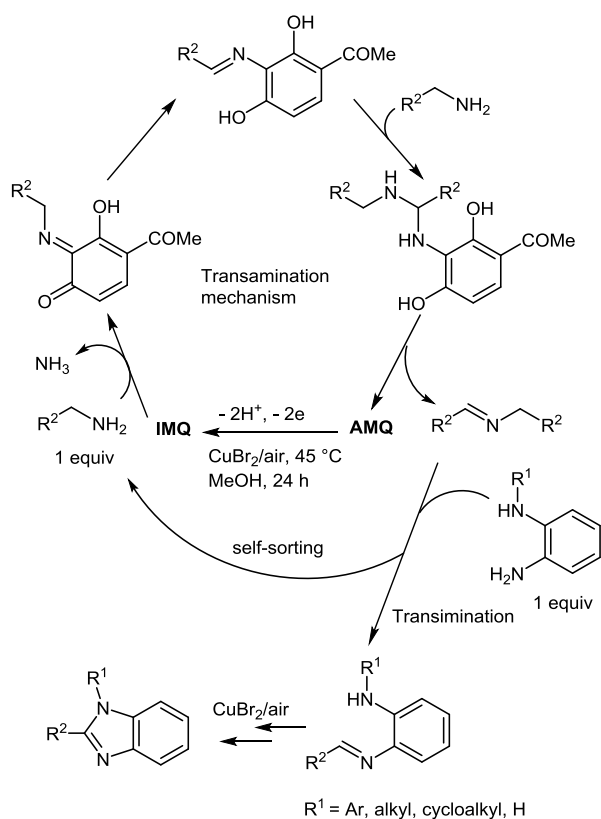


Figure 7 Yields of representative 1,2-disubstituted benzimidazoles synthesized through CuBr₂/IMQ-mediated oxidative cross-coupling

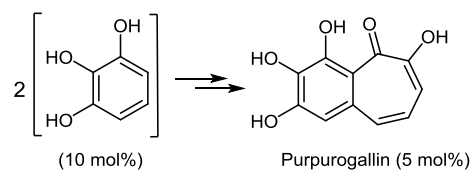
The reaction mechanism for the CuBr₂/IMQ-mediated aerobic cross-coupling reaction involves the oxidation of the primary amine R²CH₂NH₂ to the homocoupled imine intermediate through a transamination mechanism analogue to that reported for natural CuAOs (Scheme 16). In the presence of *o*-aminoaniline, the homocoupled imine intermediate is converted into cross-coupled imines through dynamic transamination. As a consequence, just one equivalent of each primary amine was sufficient to achieve exclusive formation of the cross-coupled imine product. Subsequent intramolecular cyclization to benzimidazoline and oxidation reactions as reported in reaction scheme 1 afford the 1,2-disubstituted benzimidazole derivatives with high atom economy. Note variously substituted 2-benzimidazole derivatives could also be prepared using diverse *o*-aminoanilines.⁴²



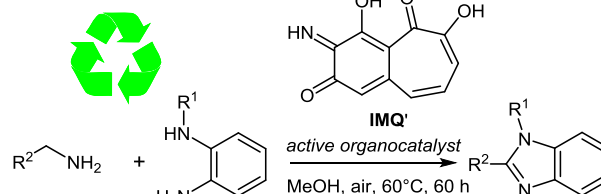
Scheme 16 Bioinspired CuBr_2/IMQ -mediated cascade reaction sequence affording 1,2-disubstituted benzimidazoles

Because the oxidation of the primary amine substrates by CuAOs is mediated by TPQ without involvement of the copper ion,⁴⁴ we have envisioned significant modifications of our initial protocol to develop procedures, avoiding contamination of the final products by metal residues. Accordingly, the use of a commercially available starting material rather than AMQ, the precursor of IMQ, whose the synthesis requires two steps from 2-nitroresorcinol,^{37e} would offer enhanced practicality while limiting the production of wastes. This is the reason why we have been drawn to the structure of natural purpurogallin (2,3,4,6-tetrahydroxy-5H-benzocyclohepten-5-one) as a potential precursor of a highly reactive *o*-quinone-based organocatalyst. However, its limited availability led us to concentrate on its biosynthesis, which involves the oxidative dimerization of pyrogallol generated from gallic acid.⁴⁵ Based on this insight, we have developed a double biomimetic reaction pathway resulting in the formation of 1,2-disubstituted benzimidazoles.⁴⁶ The reaction sequence starts from inexpensive commercially available pyrogallol and allows, under ambient air, the in situ generation of not easily accessible natural purpurogallin, which is further engaged in the transamination process analogue to that reported in reaction scheme 16, for producing, under single turnover, the active biomimetic organocatalyst IMQ' (Scheme 17). Dynamic transimination followed by intramolecular cyclization and subsequent oxidation reactions produced the 1,2-disubstituted benzimidazole derivatives.

Purpurogallin biosynthesis mimicry



CuAOs activity mimicry



Scheme 17 Bioinspired IMQ'-mediated cascade reaction sequence affording 1,2-disubstituted benzimidazoles

Because the synthesis of aliphatic imines is challenging due to their instability and isomerization into the enamine tautomer, which decomposes under ambient air, we have focused on the aerobic oxidative cyclocondensation of non-activated aliphatic amines and *N*-methyl-*o*-aminoaniline. By mixing these amines substrates in the ratio 1:1, in the presence of 10 mol% pyrogallol, thus generating 5 mol% of IMQ', good yields of 1,2-disubstituted benzimidazoles were obtained at 60 °C within 60 h (Figure 8). Note this reaction had proved to be unsuccessful in the absence of Cu^{II} cooperative catalyst when IMQ was used as the sole organocatalyst.⁴²

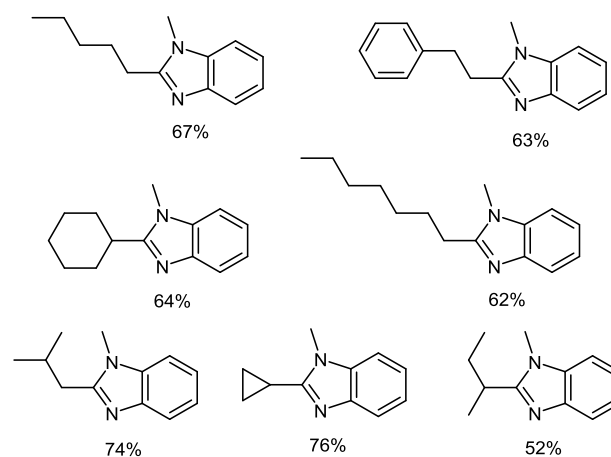


Figure 8 Yields of representative 1,2-disubstituted benzimidazoles synthesized through IMQ'-mediated oxidative cyclocondensation reaction

4 Conclusion

The oxidative cross-coupling of primary amines has received much attention over the last five years because it provides a straightforward protocol to synthesize substituted benzimidazole derivatives, through the variation of both commercially available cyclocondensation partners. Different methods have been presented including catalyst-free reactions together with catalyzed processes which encompass metal-catalyzed, organocatalyzed, photocatalyzed and bioinspired catalyzed reaction types. Each method possesses its strengths and weaknesses.

Obviously, catalyst-free systems are very simple but still suffer from the requirement of stoichiometric or excess amounts of specific oxidants and/or high reaction temperatures.

The attention on highly abundant first-row transition metals such as copper or iron was raised to develop efficient metal-catalyzed methods but the presence of metal residues may constitute a serious problem in the synthesis of drugs and functional materials.

Alternative metal-free catalytic systems have been developed to avoid metal residues contamination. However, organocatalysis still requires high catalyst loadings while photocatalyzed reactions remain scarce despite the increasing interest for visible-light photocatalysis.

Bioinspired catalytic protocols have begun to emerge in synthetic strategies because of the capacity of natural CuAOs to perform controlled aerobic oxidation of amines under mild reaction conditions. The large molecular diversity accessible is interesting but the reaction times are still long.


Due to the prevalence of the benzimidazole framework in pharmaceuticals, the next few years will certainly see the advent of new protocols that will surpass the drawbacks of each method while increasing the scope and efficiency.

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Biosketches

	<p>Martine Largeron graduated from the Pierre et Marie Curie University (Paris 6), where she also received her PhD under the supervision of Pr Maurice-Bernard Fleury. After a post-doctoral position at Rhone-Poulenc Rorer (now Sanofi), she was enlisted as a researcher at CNRS and worked at the Paris Descartes University (Paris 5). In 2004, she became Research Director at CNRS. Her current interest is focused on the discovery of bioinspired oxidation catalytic systems for synthetic applications. She has received awards from the French Society of Chemistry in 1990 and 1995 and from the National Academy of Medicine in 2004 and 2014. Since 2012 she has been a member of the National Academy of Pharmacy.</p> <p>Khac Minh Huy Nguyen graduated from the Paris Descartes University where he also received his PhD in 2016 under the supervision of Dr Martine Largeron on the subject of bioinspired catalytic systems for the synthesis of <i>N</i>-heterocycles of pharmacological interest. Since April 2016, he has been a Post-Doctoral Scholar at CEA-Saclay.</p>
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