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Catalytic Oxidative Coupling of Primary Amines under Air: A Flexible Route to Benzimidazole Derivatives

Khac Minh Huy Nguyen, and Martine Largeton*^[a]

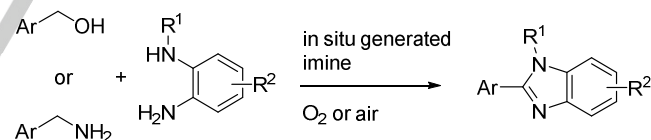
Abstract: Benzimidazoles are of fundamental importance in chemistry and biology, and the development of efficient environmentally benign methods for their preparation remains a key challenge for organic chemists. In a biomimetic approach inspired by copper amine oxidases, we disclose herein the scope and factors influencing the success of the cooperative action of CuBr₂ electron transfer mediator and topaquinone-like substrate-selective catalyst in the oxidative cyclocondensation of primary amines with *o*-aminoanilines. This one-pot atom-economical multistep process, that works under green conditions with ambient air as the terminal oxidant, low loadings of catalysts together with equimolar amounts of commercially available amine substrates, is particularly suitable for the preparation of 1,2-disubstituted benzimidazoles. Furthermore, it allows the functionalization of non-activated primary aliphatic amines that are known to be challenging substrates for non-enzymatic catalytic aerobic systems.

Introduction

Benzimidazoles are recognized as essential chemical motifs present in a variety of natural products, agrochemicals and bioactive molecules.^[1] The most prominent benzimidazole derivative in nature is *N*-ribosyl-dimethylbenzimidazole which serves as an axial ligand for cobalt in vitamin B₁₂.^[2] More importantly, benzimidazoles are privileged targets in drug discovery, as shown by the profusion in the market of pharmaceutical products such as telmisartan and candesartan as antihypertensives, omeprazole as proton pump inhibitor or astemizole, clemizole, and bilastine as antihistaminic agents.^[3] Over the years, massive efforts have been dedicated to the synthesis of functionalized benzimidazole derivatives which are commonly prepared from *o*-aminoanilines by condensation with carboxylic acid derivatives under harsh dehydrating conditions or oxidative couplings with aldehydes.^[4] Although the oxidative condensation of *o*-aminoanilines with aldehydes has received unabated attention from chemists, a major limitation of this strategy is the competitive formation of 2-substituted and 1,2-disubstituted benzimidazoles.^[5] Subsequent advances have been dominated by the development of improved procedures that selectively synthesize either 2-substituted benzimidazoles^[6]

or 1,2-disubstituted benzimidazoles^[7] as the sole product. Regiocontrolled syntheses of 1,2-disubstituted benzimidazoles have also been achieved by catalytic amination of 2-haloacetanilides or catalyzed intramolecular C-N cross-coupling reactions starting from amidines.^[8] However, these routes require special efforts to prepare the desired starting materials.

Recently, catalytic oxidative reactions, using molecular oxygen or air as the terminal oxidant, have received much attention because of their green chemistry and atom economy aspects.^[9] Meanwhile, considerable progress has been made in developing catalytic aerobic oxidation of alcohols and amines to imines.^[10] Taken together, the use of primary alcohols or amines as easily available substrates for the synthesis of benzimidazoles has emerged in synthetic strategies (Scheme 1). Interestingly, these routes are attractive to produce selectively 2-substituted benzimidazoles (R¹ = H), without the concomitant formation of 1,2-disubstituted benzimidazoles. However, except for a few exceptions,^[11] catalytic aerobic reactions suffer drawbacks such as elevated temperature (90-160°C) and/or oxygen pressure. In addition, non-activated primary alcohols or amines are generally ineffective starting materials for this cascade reaction sequence.^[12] Catalyst-free aerobic oxidative condensation reactions of *o*-amino anilines with primary alcohols or amines have also been described, but the scope is limited to benzylic-type substrates thus limiting the potential applications of these methods.^[13]



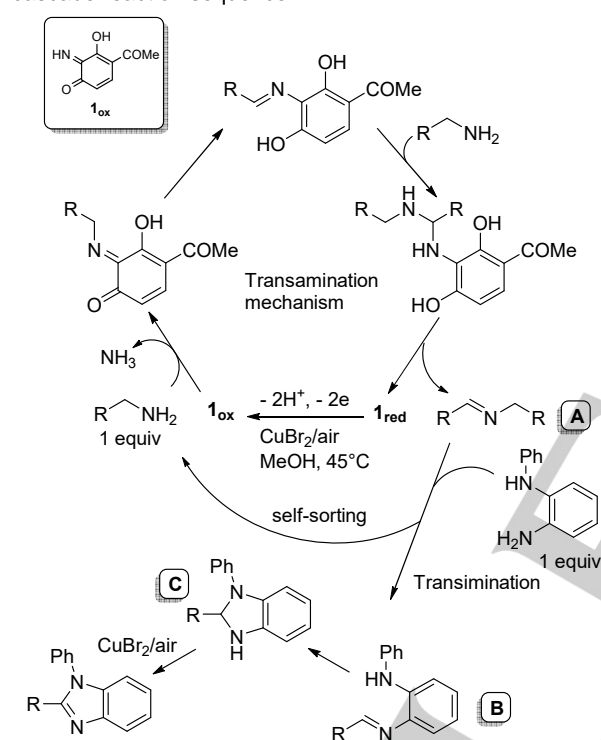
Scheme 1. Catalytic aerobic oxidative condensation of *o*-aminoanilines with primary alcohols or amines.

In this vein, we recently described a bioinspired catalytic oxidative coupling of a diverse range of primary amines with *o*-aminoanilines, under ambient air, that leads to *N*-phenyl-2-substituted benzimidazoles through multistep oxidation and nucleophilic addition reactions.^[14] The catalytic process, inspired by the copper amine oxidases activity, associates two redox couples in a way reminiscent of other biomimetic catalytic systems.^[9b,15] low loadings of biocompatible CuBr₂ electron transfer mediator and topaquinone-like substrate-selective catalyst **1_{ox}** (Scheme 2), are sufficient to activate the α -C-H bond of aliphatic primary amines which are converted, in the presence of *o*-aminoanilines, to cross-coupled imines **B** through a transamination process that leads to the homocoupled imine intermediate **A**, followed by dynamic transamination.^[16] Further intramolecular cyclization to benzimidazoline **C** and subsequent oxidation afford the *N*-phenyl-2-substituted-benzimidazole derivatives under environmentally benign conditions. Of

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particular note, this one-pot atom-economical multi-step process allows the oxidative C-H functionalization of non-activated primary amines, which are known to be challenging substrates leading to 1,2-disubstituted benzimidazoles in moderate to good yields.

At this stage, mainly *N*-phenyl-*o*-aminoaniline had been engaged in the oxidative condensation with a range of primary amine substrates to produce *N*-phenyl-2-substituted benzimidazoles.^[14] For a more comprehensive investigation of the potential of the bioinspired cooperative catalytic system, the variation of the *o*-aminoaniline substrate proved to be essential. In this prospect, there were several challenges inherent to this cascade reaction sequence which needed to be addressed. In this full paper, we present the results of new experiments aimed at exploring further the synthetic potential of this atom-economical cascade reaction sequence.



Scheme 2. Bioinspired $\text{CuBr}_2/1_{\text{ox}}$ -mediated cascade reaction sequence leading to *N*-phenyl-2-substituted benzimidazole derivatives.

Results and Discussion

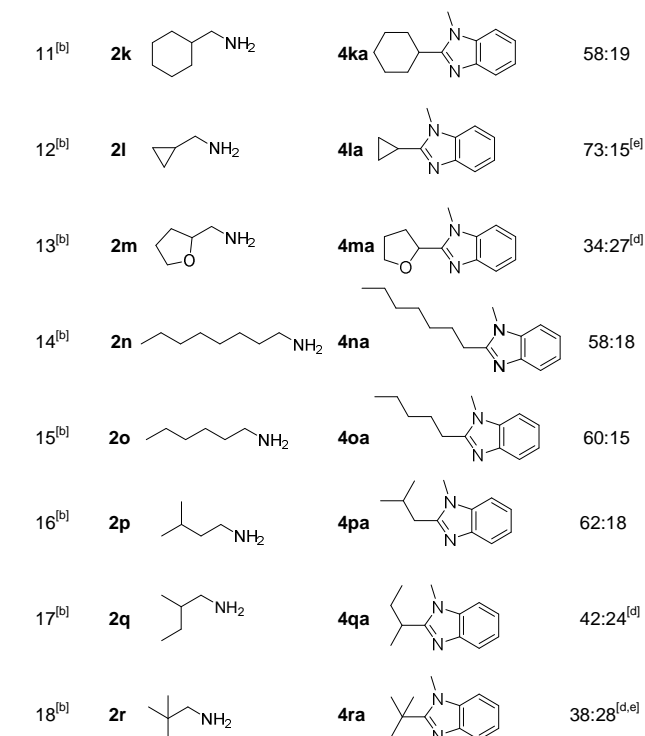
$\text{CuBr}_2/1_{\text{ox}}$ -catalyzed aerobic condensation of a range of primary aliphatic amines with *N*-methyl-*o*-aminoaniline

First, we examined the aerobic oxidative cross-coupling of a range of primary amines **2** with *N*-methyl-*o*-aminoaniline **3a** as in situ imine trap (Table 1). This promised to be a trivial exercise due to the related chemistry we had recently reported from its *N*-phenyl congener.^[14] However, applying the conditions that had proven most effective (6 mol% 1_{ox} , 0.4 mol% CuBr_2 , MeOH, 45°C, under air), the oxidative condensation of *N*-methyl-*o*-aminoaniline **3a** with a range of primary amines **2** was not selective affording, in addition to the desired 1,2-disubstituted

benzimidazole product **4**, *N*-methylbenzimidazole **5a** as the minor product. Its formation, with up to 28% isolated yield, was favored when the rate of the main reaction was affected either by steric effects in the case of benzylic amines (Table 1, entry 7), or by the decreased reactivity for β -branched alkylamines (Table 1, entries 17 and 18). Because **5a** was detected regardless of the nature of the condensed primary amine, the carbon source for the construction of the benzimidazole core seemed to have arisen from the solvent itself through the formation of a formaldehyde intermediate.^[17] To verify this hypothesis, *o*-aminoaniline **3a** was reacted in MeOH under the same experimental conditions, in the absence of the primary amine substrate **2**. Then, **5a** was isolated in 15% yield after 24h. Note **5a** could not be detected in the absence of CuBr_2 , which proved to be essential for MeOH dehydrogenation to formaldehyde. Moreover, as the yield of **5a** was lower than several data reported in Table 1, it could not be excluded that the primary

Table 1. $\text{CuBr}_2/1_{\text{ox}}$ -catalyzed aerobic oxidative coupling of a range of primary amines **2** with *N*-methyl-*o*-aminoaniline **3a** in MeOH.^[a]

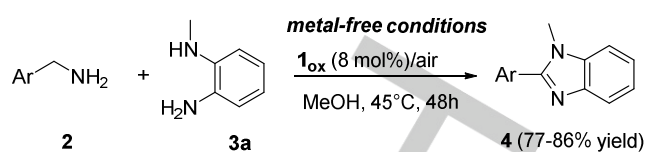
Entry	Amine Substrate 2	Benzimidazole Product 4	Yield 4:5a [%] ^[c]
1	2a	4aa	81:10
2	2b	4ba	77:09
3	2c	4ca	78:10
4	2d	4da	80:10
5	2e	4ea	74:13
6	2f	4fa	68:18
7	2g	4ga	61:28
8	2h	4ha	71:18
9	2i	4ia	67:15
10	2j	4ja	67:16



[a] The reactions were carried out using equimolar amounts of primary amines **2** and *N*-methyl-*o*-aminoaniline **3a** on a 1.25 mmol scale, in the presence of 4 mol% of **1_{red}** and 0.4 mol% of CuBr₂, in 25 mL of MeOH, under ambient air for 24h. After 6h, an additional aliquot of **1_{red}** (2 mol%) was added; [b] the reaction was conducted at 60°C to facilitate the cyclocondensation reaction, thus avoiding the competitive isomerisation of the generated alkylimine intermediate to the enamine tautomer;^[14,18,19] [c] yield of isolated products; [d] yield after 48h; an additional aliquot of **1_{red}** (2 mol%) was added after 24h; [e] as volatile alkylamines **2l** and **2r** were lost at 60°C, an additional 0.5 equiv of alkylamine was added after 6h (entries 12 and 18).

amine substrate **2** could participate in MeOH dehydrogenation to formaldehyde through a base catalysis.

At this stage, the formation of **5a** was an unexpected complication and efforts were pursued to obtain selectively the desired 1,2-disubstituted benzimidazoles **4**. Since CuBr₂ was required for the formation of the side product **5a**, we targeted a close catalytic oxidative process in the absence of CuBr₂ catalyst. After 24h, the aerobic oxidative condensation of benzylamine **2a** with *o*-aminoaniline **3a** produced 1,2-benzimidazole **4aa** in 66% yield (70% conversion), owing to the spontaneous aerobic oxidation of **1_{red}** to organocatalyst **1_{ox}**. This result indicated that *N*-methyl-*o*-aminoaniline **3a** was much more reactive than its *N*-phenyl congener, as only 30% (45% conversion) of the related 1,2-benzimidazole was isolated under the same experimental conditions.^[14] Full conversion of **3a** could be achieved after 48h leading to benzimidazole **4aa** in 86% yield (Scheme 3). We attempted to reduce the reaction time by increasing the temperature to 60°C but, after 24h, the yield of benzimidazole **4aa** decreased to 37% yield (45% conversion) due to the slow decomposition of the *o*-iminoquinone organocatalyst **1_{ox}** to melanin-like polymers.

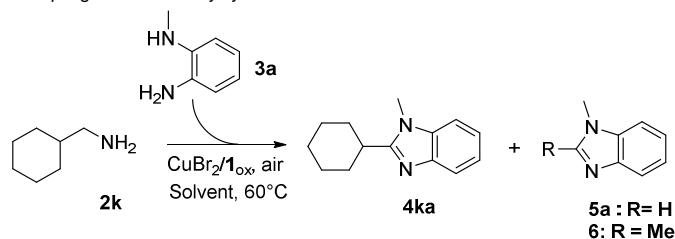


Scheme 3. Metal-free **1_{ox}**-mediated aerobic oxidative condensation of *N*-methyl-*o*-aminoaniline **3a** with a range of benzylic amines **2**.

These encouraging results led us to envisage a metal-free **1_{ox}**-mediated strategy to produce selectively *N*-methyl-2-substituted-benzimidazoles **4**. With the optimized reaction conditions in hand (8 mol% **1_{ox}**, MeOH, 45°C, under air), we examined the reaction of a series of primary amine substrates (See Table in the Supporting Information). After 48h, variously substituted benzylamines were converted to the corresponding 1,2-benzimidazoles in high yields (77-86%), regardless of the electronic character of the substituents. However, heterocyclic compounds such as 2-thiophenemethylamine **2i** and furfurylamine **2j** were found to be inferior substrates, leading to roughly 65% yield of benzimidazoles **4ia** and **4ja**, with a 72h prolonged reaction time, while non-activated primary amines such as aminomethylcyclohexane **2k** proved to be poor substrates for the organocatalyzed reaction, affording the desired benzimidazole **4ka** in only 10% yield (44% conversion after 48h).

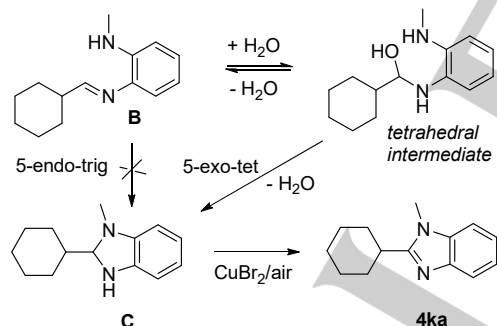
These data confirmed that organocatalyst **1_{ox}** and CuBr₂ must work cooperatively to facilitate the aerobic oxidation of non-activated primary amines to imines under air.^[14] Therefore, the unique possibility to avoid the formation of byproduct **5a** which originated with MeOH was to change the nature of the solvent. So, we performed optimization studies of the CuBr₂/**1_{ox}**-mediated aerobic oxidative condensation of *o*-aminoaniline **3a** with non-activated aminomethylcyclohexane **2k** as the amine substrate (Table 2). Taking into account our previous investigations,^[14] alcohols were retained as the best efficient solvents because strong solvation of the *o*-iminoquinone **1_{ox}** by MeOH had been shown to enhance the electrophilicity of its quinonoid moiety, thereby favoring the nucleophilic attack of the amine substrate.^[16b,20]

As expected, in EtOH attempts to isolate 1,2-benzimidazole **4ka** as the single product were thwarted by the occurrence of the solvent as reactant, providing 1,2-dimethylbenzimidazole **6** as the side product in 37% isolated yield (Table 2, entry 2). In contrast, exclusive formation of **4ka** could be achieved in 2-propanol that was unable to produce an aldehyde species, but the yield of **4ka** was limited to 40% under the standard experimental conditions as the cascade reaction sequence proceeded too slowly (70% conversion after 24h). When the oxidative condensation reaction was conducted at higher temperature, the yield of **4ka** remained almost unchanged (Table 2, entry 3).^[14] Previous studies on metal-free aerobic oxidative condensation of *o*-aminoanilines with aldehydes had demonstrated that water significantly accelerated the conversion to benzimidazoles by changing the disfavored 5-endo-trig cyclization of imines to the favored 5-exo-tet cyclization through a tetrahedral intermediate (Scheme 4).^[6h]

Table 2. Optimization of the CuBr₂/1_{ox}-catalyzed aerobic oxidative cross-coupling of aminomethylcyclohexane **2k** with *o*-aminoaniline **3a**.^[a]

Entry	Solvent	CuBr ₂ [mol%]	Conversion [%]	Yield of 4ka [%] ^[b]
1	MeOH	0.4	100	58:19 (4ka : 5a)
2	EtOH	0.4	100	47:37 (4ka : 6)
3	<i>i</i> PrOH	0.4	70 (60°C) 70 (80°C)	40 43
4	<i>i</i> PrOH:H ₂ O (9:1)	0.4	70	58
5	<i>i</i> PrOH:H ₂ O (5:5)	0.4	100	46
6	<i>i</i> PrOH:H ₂ O (9:1)	0.8	100	66

[a] The reactions were carried out using equimolar amounts of aminomethylcyclohexane **2k** and *o*-aminoaniline **3a** on a 1.25 mmol scale, in the presence of 4 mol% of 1_{red}, in 25 mL of solvent, at 60°C, under ambient air for 24h. After 6h, an additional aliquot of 1_{red} (2 mol%) was added; [b] yield of isolated product.

**Scheme 4.** Postulated route for the oxidative cyclization of the cross-coupled imine intermediate **B** to 1,2-benzimidazole **4ka**, in a 9:1 mixture of 2-propanol:H₂O according to reference 6h.

Accordingly, addition of 10% water was found to facilitate the formation of benzimidazole **4ka** (Table 2, entry 4) which was isolated in 58% yield (70% conversion after 24h). Increasing the amount of water to 50% led to complete conversion after 24h, but the yield of **4ka** decreased to 46% (Table 2, entry 5), presumably due to the partial hydrolysis of the cross-coupled imine intermediate **B** to give the aldehyde, a side reaction that would interfere with the cyclization to benzimidazoline **C**.^[18] As we had previously shown that CuBr₂ also mediated the ultimate oxidation step yielding the benzimidazole product,^[14] we chose to increase the amount of CuBr₂ to 0.8 mol% (Table 2, entry 6). Then, full conversion was observed after 24h and the yield of

4ka attained 66%. These optimized reaction conditions were further applied to the oxidative condensation of a diverse range of activated and non-activated primary amines with *N*-methyl-*o*-aminoaniline **3a** (Table 3). Not surprisingly, high yields of 1,2-benzimidazoles were obtained from variously substituted benzylamines **2a–f** (Table 3, entries 1–4), except for sterically constrained benzylamine **2g**, which gave benzimidazole **4ga** in 66% yield despite a prolonged reaction time (Table 3, entry 5).

Table 3. CuBr₂/1_{ox}-catalyzed aerobic oxidative cross-coupling of primary amines **2** with *o*-aminoaniline **3a** in *i*PrOH:H₂O 9:1 v/v.^[a]

Entry	R	Amine Substrate 2	Benzimidazole Product 4	Yield [%] ^[c]
1	C ₆ H ₅	2a	4aa	85
2	<i>p</i> -tBu-C ₆ H ₄	2c	4ca	85
3	<i>p</i> -MeO-C ₆ H ₄	2d	4da	86
4	<i>p</i> -CF ₃ -C ₆ H ₄	2f	4fa	77
5	<i>o</i> , <i>p</i> -Cl ₂ -C ₆ H ₃	2g	4ga	66 ^[d]
6	naphthyl	2h	4ha	78
7	2-thienyl	2i	4ia	75 ^[d]
8	2-furyl	2j	4ja	74 ^[d]
9 ^[b]	<i>c</i> Hex	2k	4ka	66
10 ^[b]	<i>c</i> Pr	2l	4la	75 ^[e]
11 ^[b]	2-tetrahydrofuryl	2m	4ma	32 ^[d]
12 ^[b]	<i>n</i> Octyl	2n	4na	60
13 ^[b]	<i>n</i> Hex	2o	4oa	65
14 ^[b]	<i>i</i> Pr	2p	4pa	72
15 ^[b]	CH(Me)Et	2q	4qa	44
16 ^[b]	<i>t</i> Bu	2r	4ra	17 ^[d,e]

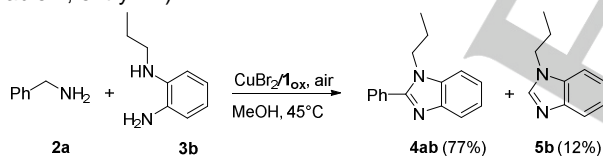
[a] The reactions were carried out using equimolar amounts of primary amines **2** and *o*-aminoaniline **3a** on a 1.25 mmol scale, in the presence of 4 mol% of 1_{red} and 0.8 mol% of CuBr₂, in 25 mL *i*PrOH:H₂O 9:1 v/v, under ambient air for 24h. After 6h, an additional aliquot of 1_{red} (2 mol%) was added; [b] the reaction was conducted at 60°C; [c] yield of isolated products; [d] yield after 48h; an additional aliquot of 1_{red} (2 mol%) was added after 24h; [e] As volatile alkylamine **2l** and **2r** were lost at 60°C, additional 0.5 equiv of alkylamine was added after 6h (entries 10 and 16).

Likewise, 1-naphthylmethylamine **2h** could also be used as the amine substrate affording benzimidazole **4ha** in 78% yield (Table 3, entry 6), while heterocyclic amines **2i** and **2j**, containing sulfur or oxygen atoms, gave 1,2-benzimidazoles **4ia** and **4ja** in roughly 75% yields after 48h (Table 3, entries 7 and

8). More challenging, the reaction scope could be expanded to the non-activated primary aliphatic amines (Table 3, entries 9-16). This type of experiments has generally been reported as unsuccessful.^[11-13] Except for tetrahydrofurfurylamine (Table 3, entry 11) and β -branched alkylamines (Table 3, entries 15 and 16), non-activated primary amines were converted to the desired 1,2-benzimidazoles in acceptable yields ranging from 60 to 75%. Therefore, changing MeOH to a 9:1 mixture of 2-propanol and water proved to be efficient to prepare selectively the 1,2-disubstituted benzimidazole derivatives. Note that undesired byproduct arising from the reaction of MeOH had not been observed when *N*-phenyl-*o*-aminoaniline was used instead of *N*-methyl-*o*-aminoaniline.^[14]

CuBr₂/1_{ox}-catalyzed aerobic condensation of benzylamine or aminomethylcyclopropane with a range of diverse *o*-aminoanilines.

To further investigate the substrate scope of this bioinspired cascade reaction sequence, variation in the structure of the condensed *o*-aminoaniline was also explored using benzylamine as the primary amine substrate (Table 4). The process was effective with *N*-substituted *o*-aminoanilines **3a-e**, leading to the corresponding 1,2-benzimidazoles **4aa-ae** in high yields ranging from 70 to 84% (Table 4, entries 1-5). In MeOH, oxidative condensation of benzylamine with *N*-propyl-*o*-aminoaniline **3b** led to the desired 1,2-benzimidazole **4ab** in 77% yield (Table 4, entry 2), along with *N*-propylbenzimidazole byproduct **5b** in 12% yield (Scheme 5), a result close to that reported from its *N*-methyl analog **3a** (Table 4, entry 1). Similarly, the formation of **5b** could be prevented by working in a 9:1 mixture of 2-propanol:H₂O giving exclusive formation of **4ab** in 81% yield (Table 4, entry 2^[d]).



Scheme 5. CuBr₂/1_{ox}-mediated aerobic oxidative condensation of benzylamine **2a** with *N*-propyl-*o*-aminoaniline **3b** in MeOH.

It is noteworthy that appreciable amounts of byproduct **5** were only detected with the more reactive *N*-alkyl-*o*-aminoanilines, whereas exclusive formation of 1,2-disubstituted benzimidazoles was observed using *N*-benzyl or *N*-aryl-*o*-aminoaniline substrates (Table 4, entries 3-5). Consequently, MeOH was selected for further experiments because it provided the ideal balance of 1_{ox} solvation and reaction rate.

In a second series of experiments, we focused on the preparation of 2-substituted benzimidazoles using a range of *o*-aminoanilines **3f-l**. Oxidative coupling of benzylamine **2a** with electron-rich *o*-aminoanilines **3f-h** afforded the 2-substituted benzimidazoles **4af-ah** in suitable yields ranging from 60 to 70% (Table 4, entries 6-8). These yields were slightly lower than those obtained from more reactive *N*-substituted *o*-aminoanilines **3a-e**, but the decreased yield could not be assigned to the formation of the benzimidazole byproduct originated from MeOH itself since no change was observed by working in a 9:1 mixture

Table 4. CuBr₂/1_{ox}-catalyzed aerobic oxidative cross-coupling of benzylamine **2a** with a range of diverse *o*-aminoanilines **3** in MeOH.^[a]

Entry	<i>o</i> -aminoaniline 3	Benzimidazole Product 4	Yield [%] ^[b]
1	3a	4aa	81 ^[c] 86 ^[d]
2	3b	4ab	77 ^[c] 81 ^[d]
3	3c	4ac	68 70 ^[d]
4	3d	4ad	82
5	3e	4ae	84
6	3f	4af	60 62 ^[d]
7	3g	4ag	61
8	3h	4ah	70 70 ^[d]
9	3i	4ai	70 ^[e]
10	3j	4aj	63 ^[e]
11	3k	4ak	56 ^[e]
12	3l	4al	25 ^[e]

[a] The reactions were carried out using equimolar amounts of benzylamine **2a** and *o*-aminoaniline **3** on a 1.25 mmol scale, in the presence of 4 mol% of **1_{red}** and 0.4 mol% of CuBr₂, in 25 mL of MeOH, under ambient air for 24h. After 6h, an additional aliquot of **1_{red}** (2 mol%) was added; [b] yield of isolated products; [c] byproducts **5a** (10%, entry 1) and **5b** (12%, entry 2) arising from MeOH as carbon source were also isolated; [d] the reaction was conducted in *i*PrOH:H₂O 9:1 v/v; [e] yield after 72h; an additional aliquot of **1_{red}** (2 mol%) was added after 24h.

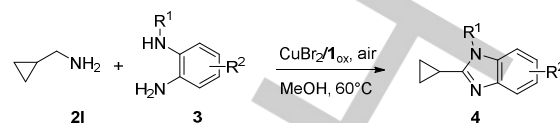
of 2-propanol:H₂O (Table 4, entries 6^[d] and 8^[d]). Haloaminoanilines **3i-k** work very slowly affording the desired 2-substituted benzimidazoles **4ai-ak** in decent yields only after a 72h prolonged reaction time (Table 4, entries 9-11). Regarding the use of *o*-aminoaniline **3l** which is a strongly electron-deficient substrate, a poor yield (25%) of benzimidazole product **4al** was obtained because the rate of the reaction was adversely affected by the electronic withdrawing effect of the nitro group (Table 4, entry 12).

Oxidative coupling of non-activated aminomethyl cyclopropane **2l** was similarly tested with a range of *N*-substituted *o*-aminoaniline **3a-e** together with its parent *o*-aminoaniline **3f** (Table 5). The process works efficiently with *N*-substituted *o*-aminoanilines **3a-e** affording the corresponding 1,2-disubstituted benzimidazole products **4la-le** in suitable yields ranging from 68 to 75%, at the exclusion of *N*-benzyl *o*-aminoaniline **3c** that proved somewhat unstable during the oxidative process giving 1,2-benzimidazole **4lc** in lower isolated yield (Table 5, entry 3). Much less reactive parent *o*-aminoaniline **3f** afforded 2-benzimidazole **4lf** in only 30% isolated yield, because of the rapid isomerisation of the generated alkylimine intermediate into its enamine tautomer (Table 5, entry 6).^[16b,18,19]

Conclusions

New insights into the scope and factors influencing the success of a bioinspired CuBr₂/topaquinone-like catalytic oxidative coupling of primary aliphatic amines with *o*-aminoanilines, that leads to benzimidazole frameworks, are disclosed through the variation of both solvent and coupling partners. MeOH proves to be the best solvent for this transformation because it provides the ideal balance of **1_{ox}** solvation and reaction rate, except when reactive *N*-alkyl *o*-aminoanilines are used as in situ imine traps, due to the concomitant formation of a benzimidazole byproduct originated from MeOH itself. In these cases, 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. Our one-pot atom-economical multistep process, that works under green conditions with ambient air, low loadings of biocompatible CuBr₂ and topaquinone-like organocatalyst, together with equimolar amounts of commercially available coupling partners, is well-suited to the functionalization of unactivated primary aliphatic amines that are known to be challenging substrates for non-enzymatic catalytic aerobic systems. Further synthetic applications involving unstable alkylimine intermediates generated through this biomimetic environmentally benign protocol are envisioned.

Table 5. CuBr₂/**1_{ox}**-catalyzed aerobic oxidative cross-coupling of aminomethylcyclopropane **2l** with a range of *o*-aminoanilines **3**, in MeOH.^[a]



Entry	<i>o</i> -aminoaniline 3	Benzimidazole Product 4	Yield [%] ^[b]
1	3a 	4la 	73 ^[c] 75 ^[d]
2	3b 	4lb 	73
3	3c 	4lc 	55
4	3d 	4ld 	68
5	3e 	4le 	72 ^[e]
6	3f 	4lf 	30

[a] The reactions were carried out using equimolar amounts of aminomethylcyclopropane **2l** and *o*-aminoanilines **3** on a 1.25 mmol scale, in the presence of 4 mol% of **1_{red}** and 0.4 mol% of CuBr₂, in 25 mL of MeOH, under ambient air for 24h. After 6h, an additional aliquot of **1_{red}** (2 mol%) was added together with an additional 0.5 equivalent of **2l** because of its volatility at 60°C; [b] yield of isolated products; [c] the corresponding by-product **5a** (15%) arising from MeOH as carbon source was also isolated; [d] the reaction was conducted in *i*PrOH:H₂O 9:1 v/v; [e] yield after 48h; an additional aliquot of **1_{red}** (2 mol%) was added after 24h.

Experimental Section

General considerations: ¹H NMR and 1D proton decoupled ¹³C NMR spectra were recorded in CDCl₃ on a Bruker AC-300 spectrometer operating at 300 MHz and 75 MHz respectively. Chemical shifts δ , are given in ppm relative to TMS and coupling constants *J*, in hertz. The measurements were carried out using the standard pulse-sequences. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer operating in the positive ion mode. Chemicals were commercial products of the highest available purity and were used as supplied. Reduced catalyst **1_{red}** was synthesized in two steps from commercially available 2-nitroresorcinol.^[21]

General experimental procedure for the CuBr₂/1_{ox}-catalyzed aerobic oxidative coupling reaction that gives substituted benzimidazoles.

Equimolar amounts of benzylamine **2** (1.25 mmol) and *o*-amino-aniline **3** (1.25 mmol) with reduced organocatalyst **1_{red}**^[21] (0.05 mmol, 4 mol%), and copper (II) bromide (0.005 mmol, 0.4 mol%), were mixed in methanol (25 mL), in an air atmosphere. The reaction mixture was stirred at 45°C for 6h. Then, an additional aliquot of 0.025 mmol of **1_{red}** (2 mol%) was introduced into the reaction mixture and the reaction was continued for 18h. The solvent was then removed by evaporation under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether 50/50 v/v) to afford the desired benzimidazole **4**, at the exception of 2-benzimidazoles **4af**–**4ai** and **4if** which were directly recrystallized from the crude material (See the Supporting Information).

The above procedure is generally representative for all the products shown in Tables 1 and 4. Any deviations from this protocol are specified in the footnotes of the tables.

Representative experimental procedure for the CuBr₂/1_{ox}-catalyzed aerobic condensation of primary amines with *N*-alkyl-*o*-aminoanilines.

Equimolar amounts of *n*-octylamine **2n** (1.25 mmol) and *N*-methyl-*o*-aminoaniline **3a** (1.25 mmol) with reduced organocatalyst **1_{red}**^[21] (0.05 mmol, 4 mol%) and copper (II) bromide (0.01 mmol, 0.8 mol%), were mixed in a 9:1 mixture of 2-propanol:water (25 mL) in an air atmosphere. The reaction mixture was stirred at 60°C for 6h. Then, an additional aliquot of 0.025 mmol of **1_{red}** (2 mol%) was introduced in the reaction mixture and the reaction was continued for 18h. The solvent was then removed by evaporation under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether 50/50 v/v) to give 1,2-benzimidazole **4na** (60% yield) as a new compound.

1,2-Benzimidazole 4na: White solid (recrystallized from petroleum ether) m.p. 40–44°C; ¹H NMR (300 MHz, CDCl₃, 25°C, TMS): δ = 0.86–0.89 (t, *J* = 6.7 Hz, 3H, CH₃), 1.28–1.42 (m, 8H, CH₂), 1.81–1.83 (m, 2H, CH₂), 2.77–2.81 (t, *J* = 7.7 Hz, 2H, CH₂), 3.60 (s, 3H, N-CH₃), 7.19–7.2 (m, 3H, Ar), 7.69–7.71 (m, 1H, Ar); ¹³C NMR (75 MHz, CDCl₃, 25°C, TMS): δ = 14.1 (CH₃), 22.7 (CH₂), 27.5 (CH₂), 27.7 (CH₂), 29.1 (CH₂), 29.5 (CH₂), 29.6 (CH₃), 31.7 (CH₂), 108.8 (CH, Ar), 119.1 (CH, Ar), 121.6 (CH, Ar), 121.8 (CH, Ar), 135.7 (Cq), 142.5 (Cq), 155.4 (Cq); HRMS (ESI+) *m/z* calcd for C₁₅H₂₃N₂ [M+H]⁺ 231.1861. Found 231.1872.

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Keywords: aerobic oxidation • amines • benzimidazoles • cross-coupling • homogeneous catalysis

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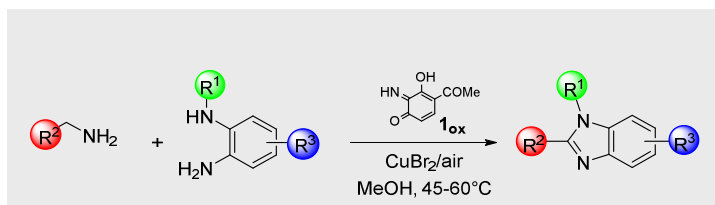
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Atom Economical: Factors influencing the success of the biomimetic cooperative action of CuBr₂ electron transfer mediator and topaquinone-like substrate-selective catalyst in the oxidative cyclocondensation of primary aliphatic amines with o-aminoanilines are disclosed in order to provide a flexible route to benzimidazole derivatives under green conditions.