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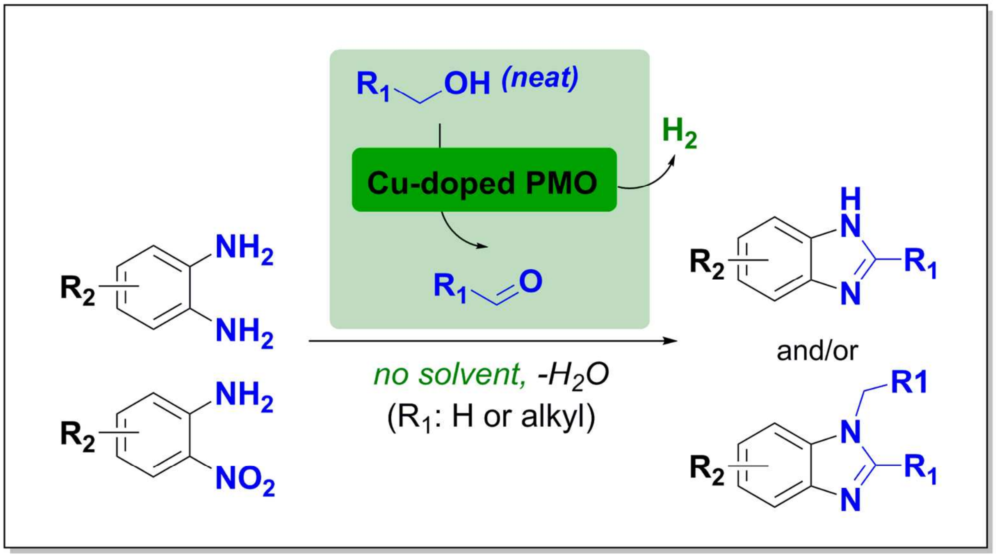

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ARTICLE

Supercritical methanol as solvent and carbon source in the catalytic conversion of 1,2-diaminobenzenes and 2-nitroanilines to benzimidazoles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Benzimidazoles and N-methylbenzimidazoles were synthesized by simply heating 1,2-diaminobenzenes in supercritical methanol over copper-doped porous metal oxides. These catalysts were derived from synthetic hydrotalcites that only contain earth-abundant starting materials. The carbon equivalents needed for the construction of the benzimidazole core originated from the solvent itself, which is known to undergo reforming to hydrogen and carbon monoxide through the formation of formaldehyde intermediate. A variety of 1,2-diaminobenzenes were converted to the corresponding mixtures of benzimidazoles and N-methylated analogues in good yields. Interestingly, the more challenging, but readily available 2-nitroanilines, which require an additional reduction step prior to cyclization, could also be successfully converted to benzimidazoles in high selectivity. Furthermore, various other alcohols were applied besides methanol, to obtain 2-alkyl- and 1,2-dialkylbenzimidazoles. Preliminary mechanistic insights into the origins of N-alkylation as well as the reactivity of the nitro derivatives are discussed.

Introduction

Benzimidazole and its derivatives are frequently targeted in medicinal chemistry research due to their prominent biological activity.[1,2] Several pharmaceutically active structures, containing the benzimidazole core, have been found to exhibit significant activity against viruses such as HIV,[3] herpes (HSV-1)[4] or influenza.[5] Furthermore, Esomeprazole (Figure 1) has been one of the top selling drugs against peptic ulcers and gastro esophageal reflux in the last decade, while Telmisartan (Micardis), containing a 1,2-disubstituted benzimidazole, is a popular antihypertensive.[6]

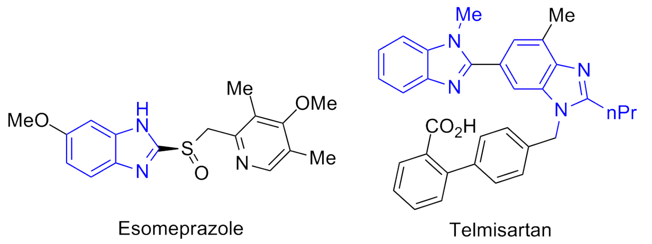

Figure 1. Commercial drugs containing a benzimidazole core unit.

Classical methods for benzimidazole synthesis involve the coupling of o-phenylenediamines with acids, acid chlorides or anhydrides (Scheme 1a), usually requiring strongly acidic conditions.[2,7] For example, a standard procedure for the synthesis of benzimidazole consists of heating 1,2-diaminobenzene in concentrated formic acid.[8] Many of the classical methods suffer from low atom economy and formation of stoichiometric amounts of waste due to substrate leaving groups or additives.[7] Recent reports focused on improving reaction conditions using aldehydes as substrates and an appropriate oxidizing agent. For example, an inorganic iodine catalyst in the presence of hydrogen peroxide afforded high benzimidazole yields from 1,2-diaminobenzenes and aldehydes at room temperature.[9] Microwave-assisted methodologies have also reduced reaction times.[10] In all the strategies detailed above, the availability of the coupling partner to o-phenylenediamine may present further limitations.

Alcohols are readily available starting materials that will become accessible by fermentation[11] or catalytic conversion of renewable lignocellulose.[12] Therefore the development of catalytic methodologies for the synthesis of benzimidazoles directly from alcohols is desired. Recent approaches involve the classical or photochemical oxidation or dehydrogenation of the alcohol to obtain the more reactive aldehyde, which subsequently reacts with the diamine to form the desired benzimidazole ring. For example, one-pot benzimidazole synthesis was carried out using bifunctional supported gold and palladium catalysts under oxygen pressure.[13] The use of an iron phthalocyanine catalyst was also reported, which afforded a variety of 2-substituted benzimidazoles from 1,2-diaminobenzenes.[14] Elegant approaches using TiO_2[15] and Pt-TiO_2[16,17] allowed for the photocatalytic (λ>300 nm) coupling of

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† Electronic Supplementary Information (ESI) available: XRD data for prepared hydrotalcite-like catalyst precursors and catalysts after calcination; Elemental composition of obtained catalysts; NMR spectroscopic data for isolated compounds. See DOI: 10.1039/x0xx00000x

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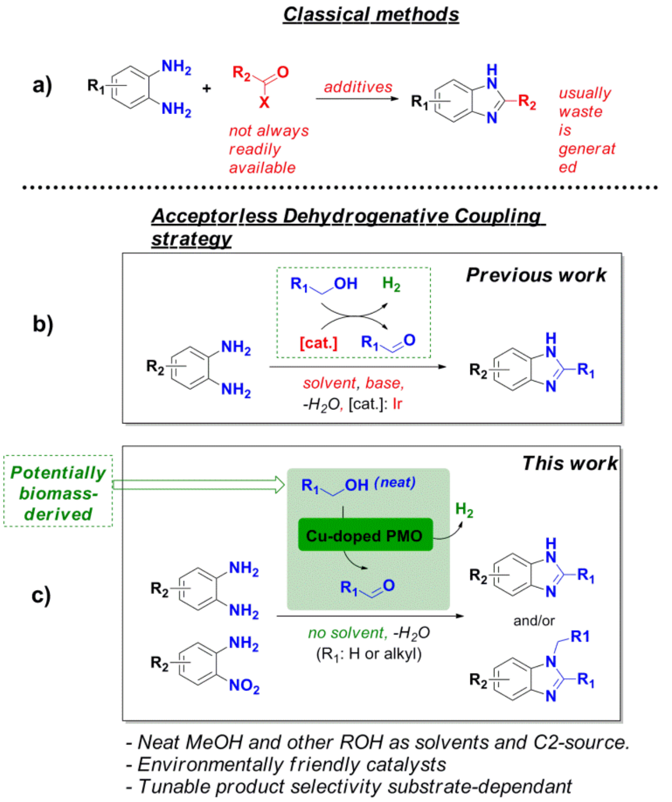

Scheme 1. Comparison of existing methods and methods developed in this paper for the synthesis of benzimidazoles from 1,2-diaminobenzenes as well as 2-nitroanilines. a) classical methods b) catalytic acceptorless dehydrogenative coupling c) the use of copper doped porous metal oxides for the transfer of useful carbon equivalents from methanol.

o-arylenediamines with a variety of alcohols. This catalytic systems could be also successfully applied to 2-nitroaniline substrates that are in-situ reduced to 1,2-diaminobenzenes.[15, 17]

Acceptorless dehydrogenative coupling (Scheme 1b and 1c)[18] has emerged as an attractive strategy for a variety of processes starting from alcohols during which only hydrogen gas and innocuous water molecules are eliminated. Through acceptorless dehydrogenative condensation, important N-heterocycles (cyclic amines, lactames, pyrroles, benzimidazoles, etc.) can be accessed in a clean and highly atom-economic manner.[19,20,21] In 2014, Kempe and coworkers reported a robust catalytic system for the synthesis of benzimidazoles and quinoxalines from aromatic 1,2-diamines using a wide range of alcohols and diols.[22] The reported iridium catalyst capable of acceptorless dehydrogenation, is highly active at very low catalyst loadings (0.04-1.4%), and requires the addition of base and diglyme solvent (scheme 1b). Homogeneous ruthenium catalysts are also known to afford a number of benzimidazoles, but only in the presence of an olefin sacrificial acceptor and catalytic amounts of acid.[23]
The use of copper doped porous metal oxides (Cu-PMO) for the depolymerization of organosolv lignin[24] and lignocellulosic biomass[25] in supercritical methanol was introduced by Ford and co-workers. In this unique catalyst system, the reductive equivalents needed for depolymerization and various hydrogenation steps were transferred from the solvent itself, which in part underwent reforming to syngas.[26]
We have devised a related concept for the synthesis of benzimidazoles using copper doped porous metal oxides in methanol, whereby in situ formed formaldehyde,[27] the primary product of methanol dehydrogenation would serve as source of useful carbon equivalents for the construction of the benzimidazole core upon reaction with 1,2-diaminobenzenes (scheme 1c). Moreover, the hydrogen produced under these reaction conditions would allow for accomplishing an additional reduction step starting from more readily available 2-nitroanilines with no other reagents needed.
Herein, we report the development of such a new, additive-free method for the preparation of benzimidazoles from various 1,2-diaminobenzenes as well as 2-nitroanilines simply by heating these starting materials in scMeOH that acts both as solvent and reactant, in presence of copper-doped porous metal oxides (Cu-PMOs). The methodology is extended to the use of different neat n-alcohols, which offer a route to 1,2-dialkylbenzimidazoles in good yields.

Experimental section

Catalyst preparation

The HTC (hydrotalcite) catalyst precursors were prepared by a coprecipitation method, according to literature.[24,29] In a typical procedure, a solution containing $AlCl_3·6H_2O$ (12.07 g, 0.05 mol), $Cu(NO_3)_2·2.5H_2O$ (6.98 g, 0.03 mol) and $MgCl_2·6H_2O$ (24.40 g, 0.12 mol) in deionized water (0.2 L) was added to a solution containing Na_2CO_3 (5.30 g, 0.05 mol) in water (0.3 L) at 60°C under vigorous stirring. The pH was kept between [illegible] and 10 by addition of small portions of a 1M solution of NaOH. The mixture was vigorously stirred at 60°C for 72 h. After cooling to room temperature, the light blue solid was filtered and resuspended in a 2M solution of Na_2CO_3 (0.3 L) and stirred overnight at 40°C. The catalyst precursor was filtered and washed with deionized water. After drying the solid for 6 h at 100°C, an hydrotalcite precursor (HTC) was obtained. The corresponding copper-porous metal oxide (Cu-PMO) was obtained after calcining this material at 460°C for 24 h in air. Other doped catalysts were prepared according to the same procedure, replacing a defined amount of Mg^{2+} and/or Al^{3+} with Zn^{2+} , Ni^{2+} and Ru^{3+}.

Catalytic reactions

In a typical experiment, the substrate (1 mmol) was placed in a Swagelok stainless steel microreactor (10 mL) and dissolved in methanol (3 mL). The appropriate amount of catalyst (50 mg) was added the reactor was sealed and placed in a pre-heated aluminum block at the desired temperature. After the indicated reaction time, the microreactor was cooled-down in an ice-water bath and the liquid sample was separated by filtration. Samples were analysed by GC-MS-FID (Hewlett Packard 5890) equipped with a Restek RTX-1701 capillary column (40 °C keep for 5 minutes, then increased to 280 °C with a rate of 10 °C/min and keep for 5 minutes). Isolated

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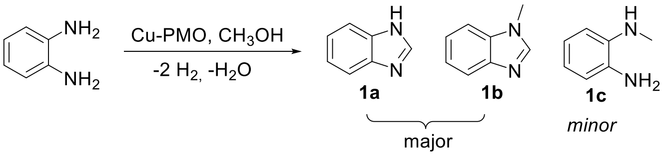
products were purified by column chromatography (silica gel, eluent dichloromethane/hexane/methanol).

Recycling tests

After a typical catalytic run (1 mmol 1,2-diaminobenzene, 100 mg Cu-PMO, 3 mL methanol, 250 °C, 6h), the catalyst was separated from the reaction solution by centrifugation and subsequent decantation, additionally washed with methanol (2×10 mL), then with acetone (1×10 mL), and dried overnight at room temperature prior to the next run.

Results and discussion

Benzimidazole formation from o-phenylendiamine



Scheme 2. Formation of benzimidazole and N-methylbenzimidazole from 1,2-diaminobenzene in scMeOH by using copper doped porous metal oxides.

Table 1. Optimization of reaction conditions for the conversion of 1,2-diaminobenzene to benzimidazole derivatives in methanol using Cu-PMO catalyst. [a]

Entry	T (°C)	Time (h)	Conversion (%)[b]	Selectivity %[b]		
				1a (%)	**1b** (%)	**1c** (%)
1	280	2	100	43	57	0
2	250	2	69	41	21	7
3	250	3	80	46	27	7
4	250	6	100	43	56	1
5	220	2	16	13	1	2
6	150	2	0	0	0	0

a. Reaction conditions: 1,2-diaminobenzene (1 mmol), Cu-PMO (50mg), methanol (3ml). b. Determined by GC analysis.

We started our investigations identifying the products formed upon heating 1,2-diaminobenzenes in supercritical methanol in the presence of a Cu-PMO. This catalyst composition, prepared by calcination of the corresponding hydrotalcite precursor at 460 °C, was previously used in our laboratory for the hydrogenation of substrates derived from renewables.[27,28] The advantages of using hydrotalcite derived copper-doped Mg-Al mixed oxides in the above-mentioned transformation are: a) the use of readily available and inexpensive metal precursors, b) modular synthesis allowing for introduction of other metal dopants, c) porous amorphous structure with optimal distribution of the active metals.

The characterization of all porous metal oxides prepared is shown in the supporting information (see composition described in table S1). The reaction using 1 mmol 1,2-diaminobenzene and 50 mg Cu-PMO catalyst at 280 °C for 2 h (table 1, entry 1) afforded full substrate conversion. The two main reaction products were identified as benzimidazole **1a** and N-methylbenzimidazole **1b**, formed in almost equimolar ratio (Scheme 2). GC-MS and GC-FID analysis using authentic standards confirmed formation of these desired products, and subsequently **1a** and **1b** were isolated by column chromatography and unambiguously characterized.

Small amounts of N-methylbenzene-1,2-diamine **1c** were also detected in the product mixture (see mechanistic considerations). Decreasing the reaction temperature to 250 °C, conversion was 69% and a 2/1 ratio between **1a** and **1b** was found. When the reaction time was prolonged to 3h and 6h higher substrate conversion of 80% and 100% respectively and lower **1a**/**1b** ratio (1.7/1 and 0.8/1) were seen. Little or no product was formed at 220 °C and 150 °C within 2 hours (table 1, entry 5 and 6).

Next, the catalyst to substrate ratio was varied by gradually increasing substrate amount from 0.6 to 2 mmol at constant catalyst loading (50 mg) and methanol volume (3 mL). These results are summarized in table S2 and figure S2. At low substrate to catalyst ratio (cca 5:1), full conversion was achieved in 3h and comparable amounts of **1a** and **1b** were observed. At higher concentration of o-phenylenediamine, the substrate was partially converted (e.g. 53% conversion when using 2 mmol substrate, 7 mol% Cu to substrate, table S2, entry 5). In all cases, **1a** was the major product and the **1a**/**1b** ratio ranged between 1.3 and 1.9. Thus it can be concluded that lower temperatures and higher substrate concentration favor benzimidazole **1a**, over its methylated analogue **1b**. N-methyl-o-phenylenediamine could also be detected in the product mixture up to 13% yield and its formation was favored at high substrate concentration (see mechanistic considerations).

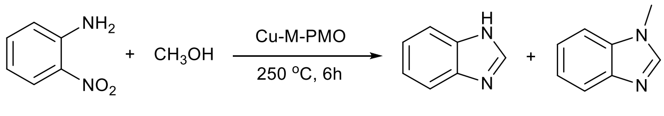
Table 2. Screening of different PMO compositions for the conversion of 1,2-diaminobenzene to benzimidazoles derivatives.[a]

Catalyst	Conversion[b] (%)	Selectivity % [b]			
		1a (%)	**1b** (%)	**1c** (%)	Not identified
Cu-PMO	80	46	27	7	0
Cu-Ni-PMO	62	45	9	5	1
Cu-Zn-PMO	92	50	35	3	4

a. Reaction conditions: 1,2-diaminobenzene (1 mmol), catalyst (50 mg) , methanol (3 ml), 250 °C, 3h. b. Determined by GC analysis.

The advantage of hydrotalcites is their modular synthesis as subtle changes in catalyst composition are expected to have an influence on catalytic activity. [29] As shown in table 2, two new catalyst compositions were prepared (see also table S1), additionally introducing 5 % of Ni^{2+} or Zn^{2+} metal dopants which did have an influence on both catalyst activity and product selectivity. With Cu-Ni-PMO 62% conversion was seen (table 2, entry 2) however **1a** selectivity improved compared to the reactions with Cu-PMO. An opposite effect was found with Cu-Zn-PMO, which was the most active among the catalysts tested, and afforded the highest selectivity to benzimidazole **1a** (50% at 92% substrate conversion, table 2, entry 3), but a lower **1a**/**1b** ratio (1.4, compared to 1.7 with Cu-PMO and 5.0 with Cu-Ni-PMO). The amount of unidentified products when the zinc-doped composition was used was 4%, which is more than in the other cases where these amounts were practically insignificant.

Formation of benzimidazoles directly from 2-nitroaniline



1a (major) **1b** (minor)

Scheme 3. One-pot synthesis of benzimidazole derivatives from 2-nitroaniline.

Table 3. Synthesis of benzimidazoles 1a and 1b using 2-nitroaniline substrate.[a]

Entry	Catalyst	Conversion (%)[b]	Selectivity %[b] **1a** (%)	**1b** (%)	Other products (%)[c]
1	Cu-PMO	38	30	4	4
2	Cu-Ni-PMO	46	41	2	3
3	Cu-Zn-PMO	100	82	11	7
4	Cu-Zn10-PMO	25	16	2	2
5	Cu-Ru-PMO	69	60	6	3
6[d]	Cu-PMO	100	79	16	5

a. Reaction conditions: catalyst (50 mg), 2-nitroaniline (1 mmol), methanol (3 ml), 250 °C, 6h. b. Determined by GC-FID. c. Other products mainly include 1-(methoxymethyl)-benzimidazole. d Reaction time was 20h.

Compared to phenylenediamines, 2-nitroanilines are more readily available substrates. Generally, 2-nitroanilines are reduced to 1,2-diaminobenzenes with zerovalent metals (Fe, Sn, Zn) and diluted mineral acids.[30] Direct catalytic methods that allow for conversion of 2-nitroanilines to benzimidazoles involve the reduction of the nitro functionality first, followed by cyclization. A number of such systems, mainly using aldehydes and acids as coupling partners are known.[31,32,33,34] However, the one-pot direct coupling of alcohols with 2-nitroanilines to benzimidazoles has only been accomplished by using photocatalysts,[15, 17, 18] and to the best of our knowledge, the present study represents the first example.

It has been previously shown that copper nanoparticles are active in reduction of nitro-aromatics.[35] Since during methanol reforming both Cu(0) nanoparticles and hydrogen gas are generated in our system,[27] we anticipated that Cu-PMO in scCH$_3$OH will be uniquely suited for the reduction of 2-nitroanilines. The Cu-PMO catalyst is expected to a) promote the formation of hydrogen gas via methanol reforming, b) reduce the nitro group by the in situ formed Cu(0) species and c) provide carbon equivalents for the construction of the benzimidazole scaffold.

Indeed, the PMO catalysts showed moderate to excellent activity (38% to full conversion in 6 hours) depending on the metal dopant (see table 3) in the direct conversion of 2-nitroanilines to benzimidazoles. More interestingly, the reaction was shown highly selective towards the formation of benzimidazole **1a** (see table 3). The Cu-PMO catalyst afforded the lowest substrate conversion (38%, table 3, entry 1) while the nickel-doped catalyst showed a moderate 46% conversion and a **1a**/**1b** ratio of 20/1. Especially when small amounts of Zn (1/3 with respect to Cu) were introduced, the substrate was fully converted after 6 hours with 82% selectivity to **1a** (table 3, entry 3). Higher Zn loadings (Cu-Zn$_{10}$-PMO , with 1/2 Zn to Cu ratio) did not improve the catalyst activity (table 3, entry 4). Surprisingly, even by introducing ruthenium noble metal in the composition the catalyst activity did not perform as good as the Cu-Zn-PMO catalyst; however, a good 69% conversion and 10/1 ratio between **1a** and **1b** was obtained (table 3, entry 5). For comparison, a reaction was also performed with Cu-PMO at longer reaction time (20h, table 3, entry 6) in order to ensure full conversion and direct comparison with Cu-Zn-PMO in terms of **1a** selectivity. Indeed, a 79% selectivity to **1a** was obtained, close to that obtained by Cu-Zn-PMO.

In summary, all PMO catalysts prepared were suitable to carry out the conversion of 2-nitroaniline to benzimidazole in methanol. Among these, significant differences were observed: the performance of Cu-PMO and Cu-Ni-PMO was comparable but considerably lower than the Ru- and Zn-doped PMO catalysts. The same trend was observed in the conversion of 1,2-diaminobenzene, but in this case, the differences were more pronounced.

In addition, figure S2 shows the product formation profile during 5 hours using Cu-Zn-PMO. The conversion increased linearly during the first 3 hours (92% conversion), with no significant changes in the composition of the product mixture. Kinetic fitting of the obtained data points, revealed a rate constant of approximately k=0.5 h^{-1} for the benzimidazole **1a** formation (see supporting information, figure S3) and a pseudo-first order regime due to supposed excess of formaldehyde generated.

Substrate scope

This new method could be successfully extended to a variety of 1,2-diaminobenzenes and 2-nitroanilines with various substituents on the aromatic ring. The reactions were carried out at 250 °C for a reaction time ensuring full substrate conversion. The main products were isolated by column chromatography. It was already discussed that 1,2-diaminobenzene affords an approximately 1:1 mixture of **1a** and **1b**. A good 78% combined isolated yield was obtained (table 4, entry 1). Using 1,2-diamino-4-methoxybenzene resulted in a similar outcome (76% combined yield, table 4, entry 2). Interestingly, a methyl group in the 4 position favored the formation of the simple benzimidazole (60%, table 4, entry 3) while the analogous t-butyl substrate favored N-methylbenzimidazole (64%, table 4, entry 4). An interesting case is offered by substrate 3,3’-diaminobenzidine, containing a diphenyl backbone and two possible reactive sites (table 4, entry 5). In this case the progress of the reaction was monitored by TLC due to the high molecular weights of the products. Three different products were detected and isolated by chromatography. The major product **5c** was isolated in good 51% yield while lower yields of two N-methylated

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benzimidazoles were obtained (15% of the bis-N-methylated **5a** and 8% of the mono-N-methylated **5b**, both present as couple of structural isomers). A diaminopyridine backbone afforded valuable imidazo-pyridine compounds, although a lower yield could be attributed to less basic NH_2 groups (table 4, entry 6). A longer reaction time (15h) did not afford higher substrate conversion. Electronic effects derived from substituents in the aromatic ring largely influenced the reactivity of 1,2-diaminobenzenes. More electron-rich substrates were more reactive. A deactivating effect was observed for a 4-chloro-1,2-diaminobenzene, which preferentially underwent methylation of the NH_2 groups affording only little benzimidazole yields (table 4, entry 7), moreover, dehalogenation also took place.

Several 2-nitroanilines were also employed to give higher yields of unsubstituted benzimidazoles, and most substrates were fully converted in only 3h in presence of the more reactive Cu-Zn-PMO catalyst. When using 2-nitroaniline, 68%

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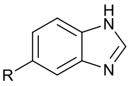
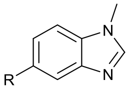
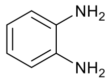
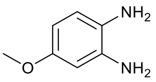
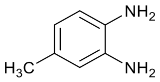
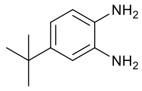
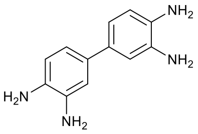
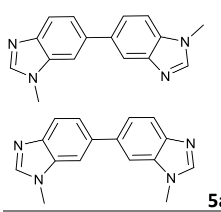
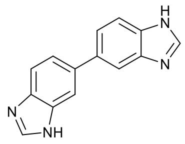
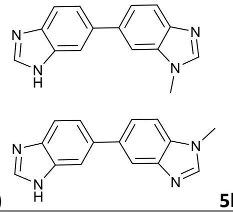
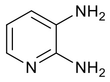
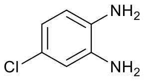
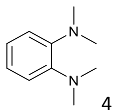
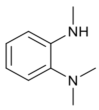
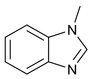
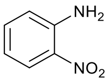
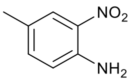
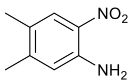
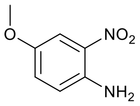
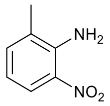
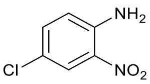
Table 4. Scope of methodology in the formation of benzimidazoles and N-methylbenzimidazoles using Cu-PMO and Cu-Zn-PMO compositions.

Entry[a]	Substrate	Time (h)	Conversion (%)[c]	Selectivity[c] (yield)[d] (%)	
				 **a**	 **b**
1		6	100	**1a,** 56[c] (42)[d]	**1b,** 44 (36)
2		6	100	**2a,** 51 (42)	**2b,** 49 (34)
3		6	100	**3a,** 70 (60)	**3b,** 28 (21)
4		6	100	**4a,** 8	**4b,** 76 (64)
5		15	100	 **5a** (15)  **5c** (51)	 **5b** (8)
6		6	40	**6a** (4)	**6b,** (22)
7		6	100	 42  16	 24
8[b]		6	100	**8a,** 82 (68)	**8b,** 11
9[b]		3	100	**9a,** 80 (73)	**9b,** 13
10[b]		3	100	**10a,** 80 (73)	**10b,** 12
11[b]		3	100	**11a,** 78 (61)	**11b,** 7
12[b]		6	100	**12a,** 90 (80)	**12b,** 3
13[b]		12	86	**13a,** (7)	**13b,** (5)

a. Reaction conditions: substrate (1 mmol), Cu-PMO (50 mg), methanol (3ml), 250 °C. b. Reaction conditions: substrate (1 mmol), Cu-Zn-PMO (50 mg), methanol (3ml), 250 °C c. Determined by GC-FID. d. Isolated yields after chromatography.

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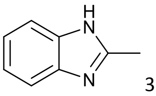
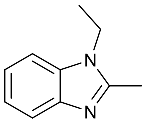
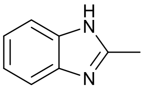
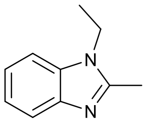
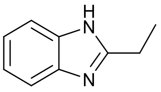
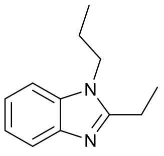
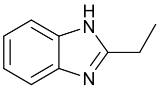
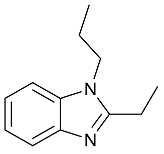
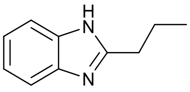
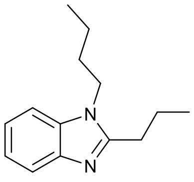
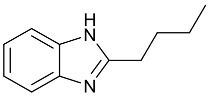
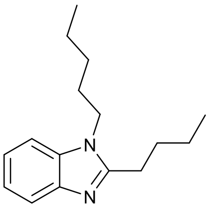
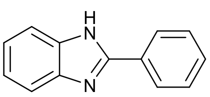
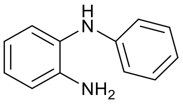
Table 5. Synthesis of 2-alkyl- and 1,2-dialkylbenzimidazoles by using different alcohols.

Entry[a]	Alcohol	Time (h)	substrate	Yield (%)[c]	
1	Ethanol	6	1,2-diaminobenzene	**14a**  37	**14b**  38
2	Ethanol	19	2-nitroaniline	**14a**  77	**14b**  16
3	1-propanol	15	1,2-diaminobenzene	**15a**  66	**15b**  23
4	1-propanol	19	2-nitroaniline	**15a**  62	**15b**  27
5	1-butanol	15	1,2-diaminobenzene	**16a**  44	**16b**  24
6	1-pentanol	15	1,2-diaminobenzene	**17a**  50	**17b**  45
7[b]	Benzyl alcohol	15	1,2-diaminobenzene	**18a**  26	**18b**  26

a) Reaction conditions: substrate (1 mmol), alcohol (3 ml), Cu-PMO (50 mg), 250 °C. Full substrate conversion. b) Reaction conditions: 1,2-diaminobenzene (1 mmol), benzyl alcohol (1 mmol), Cu-PMO (50 mg), toluene (3ml), 250 °C. 80% conversion. c) Isolated yields by column chromatography.

benzimidazole yield was achieved. In contrast to the 1,2-diaminobenzenes, alkyl substituents and electron-donating -OMe group in the aromatic ring of 2-nitroanilines did not influence to a large extent the product selectivity. Selectivity to N-methyl benzimidazoles **8b**-**12b** ranged from 3% to 13%. Very good isolated yields of benzimidazoles **8a**-**12a** were obtained (68-80%) and are shown in table 4 (entry 8-12). The presence of a halogen led to significant catalyst deactivation, and only small amounts of benzimidazole products (12% combined yield, table 4, entry 13) were obtained.

Table 4 shows that benzimidazoles unsubstituted in the 2 position can be readily prepared in methanol solvent from both 1,2-diaminobenzenes as well as 2-nitroanilines in good yields. In order to achieve variations in the 2 position, frequently related to a specific biological activity, these products may be further functionalized by C-H activation.[36] Metal-catalyzed alkylation,[37] arylation,[38] acylation[39] and annulation reactions[40] are known to proceed at this position with excellent chemoselectivity. Nonetheless, we extended the scope of our methodology established with methanol, to the use of other n-alcohols to form 2-alkylbenzimidazole products, since supported copper catalysts[41] and copper hydrotalcites are known to generally promote dehydrogenation of a variety of alcohols to the corresponding aldehydes.[42, 43] Reaction of 1,2-diaminobenzenes in ethanol gave results very similar to those observed in methanol (75% combined yield with a 1:1 product ratio, table 5, entry 1). The 2-nitroaniline in ethanol afforded higher yield of compound **14a** (77%) and smaller fraction of **14b** (16%, table 5, entry 2). When the reaction was carried out in 1-propanol, a good isolated yield of 2-

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ethylbenzimidazole was obtained from 1,2-diaminobenzene (66%, table 5, entry 3), and this amount was similar when 2-nitroaniline was used (62%, table 5, entry 4). 2-alkylbenzimidazoles were isolated as main products when 1-butanol and 1-pentanol was coupled with 1,2-diaminobenzene (table 5, entry 5 and 6). The corresponding 2,3-dialkylated products were also isolated in moderate yields (24% and 45%). A reaction between 1,2-diaminobenzene and benzyl alcohol was performed in toluene affording almost full diamine conversion, but low 2-phenylbenzimidazole yield (26%, table 5, entry 7). Interestingly, an equal amount (26%) of benzylated starting material was isolated accounting for a competition between the hydrogenation of the imine intermediate with the cyclization process.

Recycling tests and catalyst stability

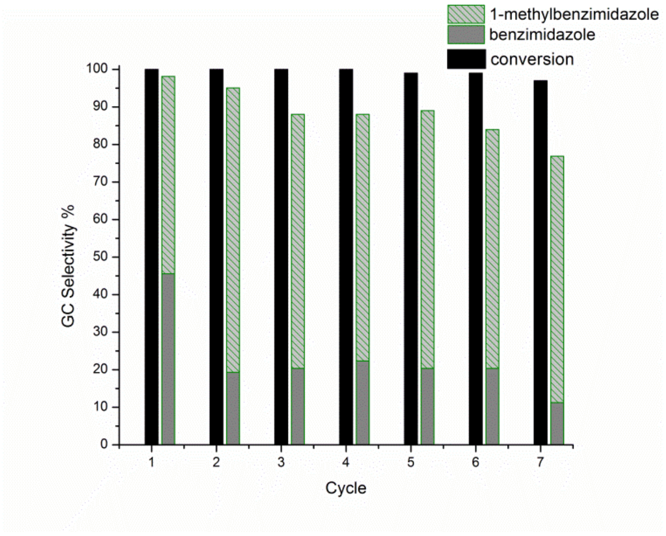


Figure 2. Catalyst recycling experiments. Conditions: 1,2-diaminobenzene (1 mmol), Cu-PMO (100 mg), methanol (3 ml), 250 °C, 6h.

Recycling experiments were conducted at 250 °C with 1,2-diaminobenzene (1 mmol and Cu-PMO (0.1 g) for 6 h (see figure 2). The catalyst was recovered at the end of each run, washed with methanol and acetone, and reused after drying. The catalyst showed excellent selectivity to benzimidazole and 1-methylbenzimidazole (>80%) for 6 cycles and after the 7th cycle still a good 75% combined selectivity was observed. The catalyst has proven considerable stability after converting more than 0.5 g 1,2-diaminobenzene in relatively harsh conditions.

Interestingly, a variation in selectivity to benzimidazole **1a** is visible between the first and the second cycle (45% vs 20% selectivity) while the relative product distribution is constant for the subsequent cycles. This trend is very likely related to the initial low concentration of active Cu^0 species, and which are formed in situ during the first cycle from CuO present in the catalyst.[27]

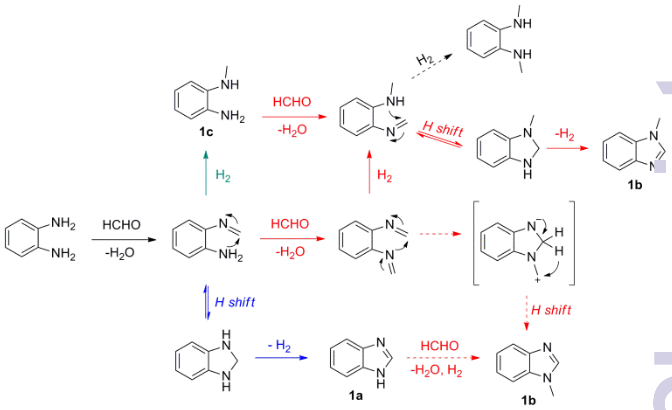
Under comparable reaction conditions (see table S3 in the supporting information), the Cu-Zn-PMO showed almost no leaching of the metals incorporated in the catalyst structure while a small Mg and Al loss was observed in the analysis of the liquid sample after reaction with the Cu-PMO catalyst.

Mechanistic considerations

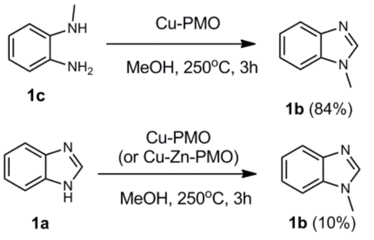
Based on previous reports[16,17,35, 36, 44] a preliminary mechanistic description can be proposed involving methanol dehydrogenation, imine formation/cyclization and dehydrogenation. The Cu-PMO catalysts have multiple roles, catalyzing methanol reforming which leads to formaldehyde[12,27] that likely represents a key intermediate.[45] Excess of formaldehyde with 1,2-diaminobenzene has been elsewhere shown to give the expected N-methylbenzimidazole.[10] In addition, we have independently verified the formation of benzimidazole with formaldehyde in presence of a Cu-PMO catalyst.

The more activated 1,2-diaminobenzene substrates may react with one or two molecules of formaldehyde (present in excess in the reaction medium) to give imine intermediates. Related imines with benzyl alcohol have been detected by Ghosh et al. at room temperature.[47] However, the imines shown on Scheme 4 will be difficult to isolate, as they should undergo rapid cyclization or hydrogenation. In fact, hydrogenation of the imine bond is plausible and would account for the formation of larger amounts of **1c** (scheme 4, green arrow).

Compound **1a** can be originated from cyclization of the mono-imine intermediate, 1,3-hydrogen shift and dehydrogenation of the corresponding benzimidazoline intermediate (scheme 4, blue arrows) analogously to previously proposed pathways.[35] The process should be further driven by the aromatization to the corresponding benzimidazole product, which would be aided by the catalyst. Related dehydrogenation of the CH-NH bond to imines and nitriles with alumina-supported Cu nanoparticles is known. [46]



Scheme 4. Proposed reaction network for the formation of **1a**, **1b** and **1c** from 1,2-diaminobenzene (solid arrows indicate the main pathways).



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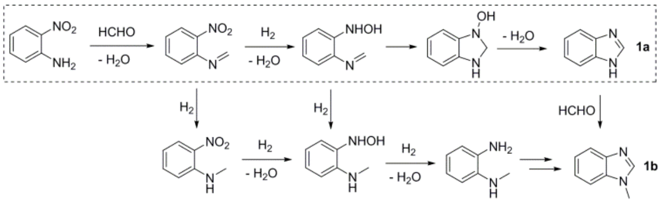
Scheme 5. Cyclization of N-methyl-o-phenylendiamine (top) and direct methylation of benzimidazole (bottom) in scMeOH and in presence of Cu-PMO.

N-methylbenzimidazole **1b** can be obtained through several possible pathways (scheme 4, solid red arrows). Compounds **1c** can be a precursor of **1b**, which can be obtained by reaction of **1c** with formaldehyde, H shift and dehydrogenation. We have verified that compound **1c** is indeed converted into **1b** in high 84% yield in 3h at 250 °C (scheme 5, top). This observation is also in agreement with the relatively low amount of **1c** in the product mixtures (1-7%, see table 1). A second, less likely possibility is the formation of a diimine intermediate followed by reduction to a monoimine and subsequent cyclization/dehydrogenation to the desired product **1b**. A third way to generate **1b** is the methylation of benzimidazole **1a**, nevertheless low conversion and product yield (~10% with both Cu-PMO and Cu-Zn-PMO, scheme 5, bottom) were obtained using benzimidazole **1a** as starting material in scMeOH, also according to the expected lower reactivity of the aromatic substrate **1a.**

Scheme 6. Proposed pathways network for the formation of **1a** and **1b** from 2-



nitroaniline.

Regarding the reactivity of 2-nitroanilines in the presence of Cu-PMO catalysts in scMeOH, we performed test reactions using 2-nitrotoluene in order to gain insight into the outcome of nitro group reduction. The reaction proceeded with full conversion to N,2-dimethylaniline (57%) and N,N,2-trimethylaniline (43%) after 6h with Cu-PMO. Under the same experimental conditions, conversion was only 38% with 2-nitroaniline as substrate (table 3, entry 1). While the reduction of aromatic nitro compounds is already known to proceed in presence of copper catalysts,[36] to the best of our knowledge no data are available on the copper-mediated cyclization of o-nitroanilines to benzimidazoles directly from alcohols. Methods employing semiconductor photocatalytic systems are known to perform the mentioned one-pot process.[15, 17, 18]

Based on thus far available experimental data and previous reports, our preliminary proposed mechanism comprises several steps, summarized in scheme 6. The high selectivity to benzimidazole 1a hints at direct cyclization of already at the hydroxylamine stage. The formed product might undergo subsequent dehydration (scheme 6). In contrast, reduction to 1,2-diaminobenzene, would instead lead to a mixture of 1a and 1b (as shown in table 1) as previously established. The competing hydrogenation of the N=CH2 bond does not take place to a large extent and the small amount of 1b in these runs seems to coincide in most cases (see table 4) with slow methylation of 1a (see scheme 5 and 6).

Another interesting point relates to the presence of dopants in the PMO compositions. In this regard, more extended studies on different compositions differing in the Zn loading should shed light on the promoting effect of this dopant towards the nitro group reduction.

Conclusions

A variety of benzimidazole derivatives have been successfully synthesized in supercritical methanol by means of inexpensive copper catalysts, that are derived from earth abundant materials, whose structure and catalytic properties are easily tunable. The solvent serves as source of in-situ formed formaldehyde, thus useful carbon for the construction of the benzimidazole core through the acceptorless dehydrogenative condensation strategy. 1,2-diaminobenzenes could be converted with moderate to excellent combined yields of benzimidazoles and N-methylbenzimidazoles. Moreover, more readily available 2-nitroanilines could also be used to yield benzimidazoles in even higher selectivity. The described methodology displays a number of advantages: a) neat methanol is both solvent and reactant and can be replaced by other n-alcohols in order to access targeted benzimidazoles or 2-alkylbenzimidazoles, b) no additives other than the solvent (oxidants, bases or acids) are needed, c) catalysts consist of readily available, inexpensive metals and d) only water and hydrogen are generated as by-products. Future efforts focus on the synthesis of valuable N- and O-heterocyclic compounds and developing more active dehydrogenation catalysts that can operate at milder reaction conditions.

Acknowledgements

We are grateful for financial support from the China Scholarship Council (grant number 201406060027) and from European Commission for an Intra-european Marie Curie fellowship (grant 622724 - Asymm.Fe.SusCat).

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