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A General Approach to Substituted Benzimidazoles and Benzoxazoles *via* Heterogeneous Palladium-Catalyzed Hydrogen-Transfer with Primary Amines

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Abstract: The synthesis of benzimidazoles starting from *o*-phenylenediamines and amines in the presence of palladium on charcoal as catalyst is reported. Under microwave dielectric heating it is possible to use a tertiary, a secondary, and even a primary amine as the substrate for a palladium-mediated process to get 2-substituted or 1,2-disubstituted benzimidazoles, depending on the nature of the *o*-phenylenediamine employed. Primary amines are the most suitable reagents for the atom economy of the overall process that resulted to be general as several different substituted benzimidazoles were obtained in good yield. Benzoxazoles can be also prepared starting from primary amines and *o*-aminophenol. The reaction is also highly selective as no (poly)-alkylated phenylenediamines or cross-contaminated benzimidazoles are obtained starting from *N*-monoalkylphenylenediamines. This behavior was interpreted as a scarce aptitude to dehydrogenation of the methylene bonded to the aromatic NH of *N*-alkylarylamines. The experiments carried out consent to draw an almost complete picture of the reaction pathways occurring during the process. The catalyst can be recycled several times and, although far from optimal performances, catalyst TON = 90 is encouraging for further large-scale optimization protocols. In addition, the palladium on charcoal-catalyzed microwave-assisted reaction of *o*-phenylenediamine gives de-alkylation of tertiary amines and transformation into the secondary ones.

Keywords: amines; heterocycles; heterogeneous catalysis; hydrogen transfer; microwave chemistry

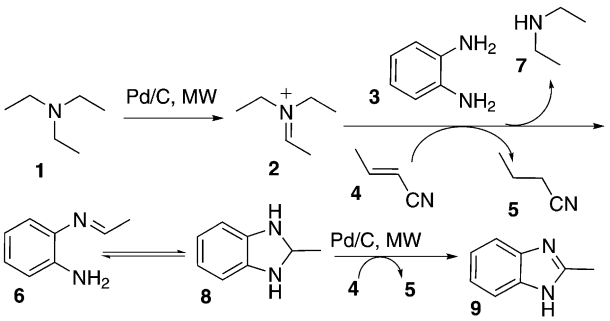
Introduction

The benzimidazole ring plays an important role in the discovery of bioactive molecules.[1] Substitution and structural modifications on this scaffold often lead to the identification of compounds with a wide range of applications throughout the field of medicinal chemistry. Several anti-infective,[2] anti-inflammatory[3] and antitumor[4] compounds or receptor agonists/antagonists[5] contain this heterocycle. Thus in recent years the synthesis of benzimidazoles has gained considerable attention.[6]

The traditional protocol for the preparation of benzimidazoles involves the reaction of 1,2-diaminobenzenes with carboxylic acids under harsh reaction conditions (such as, for example, the use of polyphosphoric, hydrochloric, boric or *p*-toluenesulfonic acids as dehydrating agents).[7] This methodology has then evolved by introducing Lewis acids[8] improving both the yield and the purity of the products obtained. An alternative way is the condensation of aldehydes and *o*-phenylenediamines to generate benzimidazoline intermediates that are subsequently oxidized in the presence of different reagents.[9] Low yields, long reaction times, drastic reaction conditions, laborious work-up procedures and the occurrence of side reactions are the main drawbacks of those classical synthetic methodologies. As a consequence, any improvement in the preparation of the benzimidazole ring overcoming the outlined limitations as well as the search for alternative, milder and more environmentally friendly methods are still challenging targets in

organic chemistry.[10,11] Looking for a convenient, uncommon and more sustainable synthetic approach to benzimidazoles, the application of a hydrogen autotransfer catalysis-based protocol has been examined. The hydrogen transfer reaction (sometimes called also borrowing hydrogen) has been applied to the oxidation of different organic substrates such as alcohols, amines or aldehydes.[12] The process is based on the (formal) removal of a hydrogen molecule from the substrate under the catalysis of a transition metal complex. The oxidized form (sometimes unstable by itself) is further treated with other reagents and the produced hydrogen molecule is charged on the acceptor compound (generally organic) in order to shift the reaction and regenerate the catalyst. Catalytic amination of alcohols,[13] synthesis of tertiary amines,[14] imines or amides[15,16] are the most explored transformations and homogeneous transition metals have been widely employed as the catalysts. Although in some cases acceptable TON values have been reached,[17] the catalysts are often expensive {e.g., $(Cp^*IrCl_2)_2$, $[Ru(p\text{-cymene})Cl_2]_2$, Shvo's catalyst $[(\eta^5\text{-}Ph_4C_4CO)]_2HRu_2(CO)_4(\mu\text{-}H)$} and require the use of ligands, introducing additional troubles for product isolation. Thus, the introduction of heterogeneous catalysis in this kind of hydrogen transfer process is highly advisable. Recent examples on the use of heterogeneous catalysts in the *N*-alkylation of amines were disclosed.[18] Recently one of us described the preparation of benzimidazoles through a Pd/C-mediated cyclization of *o*-phenylenediamine with tertiary amines.[19] The reaction was carried out by heating *o*-phenylenediamine in the presence of a stoichiometric amount of a tertiary amine, Pd/C (10 wt% loading) and crotonitrile as the hydrogen acceptor, at 170 °C under microwave (MW) dielectric heating. Different benzimidazoles were obtained in good to acceptable yields.[20] The proposed mechanism was based on the oxidation of the tertiary amine **1** to an iminium ion **2** followed by a transamination reaction of this active intermediate with *o*-phenylenediamine to generate the corresponding imine **6**.[21,22] The secondary amine **7** and butyronitrile **5** are consequently produced by a first borrowing hydrogen process required to regenerate the catalyst. Cyclization to dihydrobenzimidazole **8** followed by a second borrowing hydrogen oxidation gives the desired benzimidazole **9** with a net consumption of two molecules of H_2 (Scheme 1, taken from ref.[19]).

Heterogeneous palladium catalysis represents a convenient option to overcome the limitations due to the use of a homogeneous catalyst highlighted above. A large number of heterogeneous palladium sources are nowadays available but among these Pd on carbon can be considered as the most versatile, the less expensive and easiest to handle; it can be quickly recovered and reused many times by simple filtration.



Scheme 1. Proposed mechanism for the preparation of benzimidazoles from tertiary amines (taken from ref.[19]).

Besides, the stability in acidic or basic media and the high surface area make it the leading heterogeneous catalyst for industrial applications to date. Moreover, thanks to the rapid and efficient heat conduction from the surface of the catalyst to the reaction medium,[23] Pd/C can favorably couple with the microwaves allowing one to reach the high temperatures usually required in the hydrogen transfer reactions.

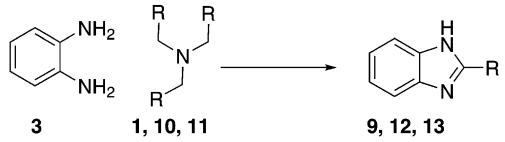
Results and Discussion

With the aim of improving the method and obtaining more information on the proposed reaction mechanism, our attention was focused on expanding the scope of the developed procedure to different substituted amines. These substrates would allow a more extensive application of the methodology leading to a high variety of possible structural modifications on the benzimidazole core. Moreover, the use of tertiary amines implies the loss of one molecule of secondary amine for each catalytic cycle. From a green chemistry point of view,[24] a waste of atoms is thus generated and the atom economy profile of the transformation proves to be poor. In this context, we tried to maximize the efficiency of the reaction by reducing nature and amount of the by-products.

In order to verify this possibility and gain more information on the reaction mechanism, the cyclization of tributylamine **10** and 1,2-phenylenediamine **3** was performed following the reported conditions[19] and monitoring the product distribution *via* GC/MS analysis (Table 1). The result was that 2-propylbenzimidazole **12** was formed in 78% yield, all *o*-phenylenediamine was consumed, and dibutylamine was detected together with a residue of unreacted tributylamine. The amount of tributylamine employed for cyclization was then reduced to 0.5 equivalents with respect to *o*-phenylenediamine.

Notwithstanding, the presence of unreacted dibutylamine and butylamine was detected in the final reaction mixture while the yield of **12** was still high (75%). It is worth noting that even using 0.35 equiva-

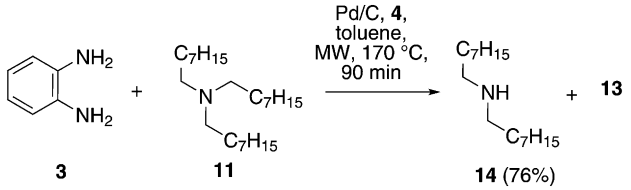
Table 1. Benzimidazole formation using a substoichiometric amount of tertiary amine with respect to *o*-diaminobenzene **3**.



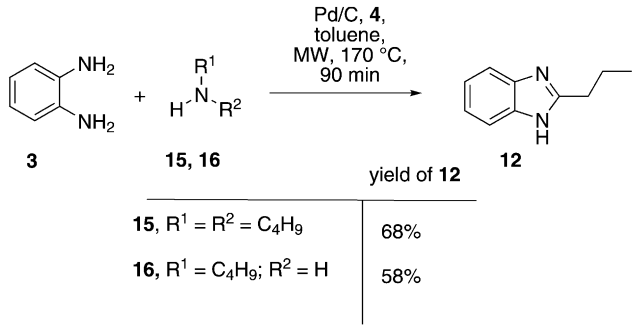
Entry	R	Amine (amount)[a]	Product, Yield[b]
1	C_3H_7	**10** (1.1 equiv.)	**12**, 78%
2	C_3H_7	**10** (0.55 equiv.)	**12**, 75%
3	C_3H_7	**10** (0.35 equiv.)	**12**, 68%
4	CH_3	**1** (0.35 equiv.)	**9**, 76%
5	C_7H_{15}	**11** (0.35 equiv.)	**13**, 70%

[a] *Reaction conditions:* *o*-phenylenediamine (1 mmol), hydrogen acceptor **4** (2.2 mmol), dry toluene (2 mL), Pd/C (10 wt%, 0.05 mmol), MW 170 °C, 90 min.
[b] Yields of isolated and fully characterized benzimidazoles.

lents of tributylamine with respect to *o*-phenylenediamine, benzimidazole **12** could be isolated in 68% yield[25] with almost complete consumption of the amine. From these data we concluded that at least two of the three groups of the tertiary amine could be transferred to benzimidazole with a neat increment in the atom economy of the process. Then, the reaction with 0.35 equivalents of amine with respect to **3** was repeated on different (symmetric) tertiary amines (**1** and **11**) and the corresponding benzimidazoles **9** and **13** were always obtained in satisfactory yields (Table 1, entries 4 and 5). Although this result could be considered as an appreciable achievement in comparison with the original discovery, from a preparative point of view, the use of tertiary amines as substrates is limited by their low availability and by the expected different selectivity in the transferred group when non-symmetrical tertiary amines are employed.[19] As exemplified in Scheme 2, a possible additional interesting aspect may be the use of *o*-phenylenediamine **3** in conjunction with Pd/C to transform a tertiary amine (such as **11**) into a secondary one (**14**), a process that is still difficult to carry out.[26] Supported by the results of Table 1, *o*-phenylenediamine **3** was subjected to cyclization using dibutylamine (**15**) and even butylamine (**16**) obtaining a satisfactory conversion into 2-propylbenzimidazole **12** (Scheme 3).



Scheme 2. Pd mediated dealkylation of a tertiary amine in the presence of *o*-phenylenediamine.



Scheme 3. Pd/C-mediated synthesis of benzimidazoles with secondary and primary amines.

As the atom economy of the process is better with a primary amine, a more deep investigation began by studying the influence of different parameters (i.e., temperature, catalysts, hydrogen acceptor, additives) on the reaction. *o*-Phenylenediamine **3** and butylamine **16** were chosen as the model substrates in order to find the best reaction conditions for high isolated yields of benzimidazole **12**. Selected results are shown in Table 2. A satisfactory conversion of **3** was observed in reactions carried out in toluene at 170 °C under MW dielectric heating and in the presence of Pd/C (10 wt%, 0.05 equiv.), although 2-propylbenzimidazole **12** was isolated only in moderate yields (Table 2, entry 1). The concentration of the reagents was then increased without any remarkable improvement. Analogously, an increment of reaction time up to 3 h had no effect. The use of solvents different from toluene (Table 2, entries 2–4) and the increase of the temperature to 190 °C (realized by adding to toluene a small quantity of ionic liquid [bmim][BF_4]; Table 2, entry 6) were detrimental for the yields. Replacement of crotonitrile **4** with 1-octene as the hydrogen acceptor seemed to have no influence on the reaction outcome (compare entries 1 and 7 in Table 2). However, a first improvement in the yield was observed upon increasing the amount of catalyst from 5 to 10% that led to isolation of compound **12** with 65% yield (Table 2, entry 8). The yields were further enhanced to 85% when a stoichiometric amount of Pd/C was employed (Table 2, entry 9). Although not synthetically profitable, this last result suggested that the use of a low molecular weight primary amine, more nucleophilic with respect to the tertiary amine described in the previous paper, could poison the catalyst by physical absorption on the surface and reduction of the active site number. Thus, the use of an acid additive was investigated. An experiment with HCl was unsuccessful, TFA and TCA gave moderate yields, while the addition of 10% AcOH afforded an almost quantitative conversion of **3** into **12** that was isolated in 87–90% yield regardless of the hydrogen acceptor molecule employed (Table 2, entries 10–14).

Table 2. Optimization for reaction between **3** and **16** to give benzimidazole **12**.

Entry	Reaction conditions[a]	Conversion [%][b]	Yield [%][c]
1	Tol., 170 °C, Pd/C (0.05 equiv.), (**4**)	72	58
2	EtOH, 170 °C,[d] Pd/C (0.05 equiv.), **4**	45	20
3	THF, 170 °C,[e] Pd/C (0.05 equiv.), **4**	40	20
4	Tol./*t*-BuOH, 1/1, 170 °C, Pd/C (0.05 equiv.), **4**	3	–
5	Tol./[bmim][BF_4], 190 °C, Pd/C (0.05 equiv.), **4**	50	36
6	[bmim][BF_4], 170 °C, Pd/C (0.05 equiv.), **4**	–	–
7	Tol., 170 °C, Pd/C (0.05 equiv.), 1-octene	76	60
8	Tol., 170 °C, Pd/C (0.1 equiv.), 1-octene	85	65
9	Tol., 170 °C, Pd/C (1 equiv.), 1-octene	98	85
10	Tol., 170 °C, Pd/C (0.1 equiv.), **4**, HCl (35% aqueous, 0.1 equiv.)	-	-
11	Tol., 170 °C, Pd/C (0.1 equiv.), **4**, TFA (0.1 equiv.)	75	53
12	Tol., 170 °C, Pd/C (0.1 equiv.), **4**, TCA (0.1 equiv.)	81	60
13	Tol., 170 °C, Pd/C (0.1 equiv.), **4**, AcOH (0.1 equiv.)	95	90
14	Tol., 170 °C, Pd/C (0.1 equiv.), 1-octene, AcOH (0.1 equiv.)	95	87
15	Tol., 170 °C, Pd/C (0.1 equiv.), **4**, AcOH (1 equiv.)	80	61
16	Tol., 170 °C, Pd/C (0.1 equiv.), **4** (20 equiv.), AcOH (1 equiv.)	98	95
17	Tol., 170 °C,[f] Pd/C (0.1 equiv.), **4**, AcOH (0.1 equiv.)	90	78
18	Tol., 170 °C, PdEnCat (0.1 equiv.), **4**, AcOH (0.1 equiv.)	–	–
19	Tol., 170 °C, Pd/TiO_2 (0.5% wt), **4**, AcOH (0.1 equiv.)	–	–
20	Tol., 170 °C, Pd CPRW (0.6% wt), **4**, AcOH (0.1 equiv.)	30	10
21	Tol., 170 °C, Ru/C (5% wt) **4**, AcOH (0.1 equiv.)	30	10
22	Tol., 170 °C, Ni/SiO_2-alumina (65% wt), **4**, AcOH (0.1 equiv.)	–	–
23	Tol., 170 °C, Pd$(OH)_2$/C (20% wt), **4**, AcOH (0.1 equiv.)	30	10

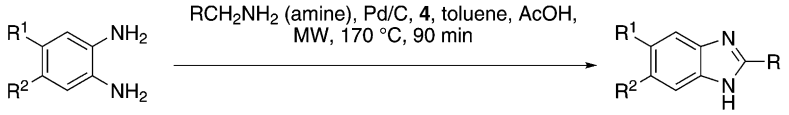
[a] Tol. = toluene. *Reaction conditions:* sealed vial, MW (maximum power and internal pressure: 200 W and 300 psi), 90 min, **3** (1 mmol), **16** (1.2 mmol), hydrogen acceptor (2.2 mmol), solvent (2 mL), N_2 atmosphere. Pd/C = 10% wt Pd on dry carbon, wet with 50% wt of H_2O.
[b] Percentage of **12** with respect to **3** in the final reaction mixture, established by GC/MS analysis.
[c] Yields of isolated compound.
[d] Uncontrolled increase of the internal pressure was observed.
[e] Heating for 4 h was required to reach 40% conversion.
[f] Reaction carried out for 12 h in a sealed tube dipped inside an oil bath pre-heated to 180 °C.

It is noteworthy that on increasing the amount of AcOH to 1 equiv., the yield went down (Table 2, entry 15). Again, increasing the reaction time (from 90 min to 3 h) had no influence in the yield. Using the improved conditions developed so far (Table 2, entry 13) the reaction was run under traditional heating (sealed vial in a pre-heated oil bath) giving, after 12 h, the expected product although in lower yield (Table 2, entry 17). The amount of the hydrogen acceptor was raised to 20 equiv. and an additional increase of the yield respect to the experiment with 2.2 equiv. was observed (compare entries 16 and 13 in Table 2). Finally different kinds of heterogeneous catalysts were screened and their activity compared to the results obtained using Pd/C.

Among the noble metals examined, none of them revealed to have a higher activity, superior efficiency, or to speed up the process with respect to Pd/C and in no cases could benzimidazole **12** be obtained in acceptable yields (Table 2, entries 18–23). The result of this large screening is that a primary amine (with the nitrogen bonded to a CH_2) can be used as the substrate in oxidative cyclization of *o*-phenylenediamine exclusively when Pd/C is used as the catalyst and under the influence of an acid additive. Best results are obtained under microwave dielectric heating (possible influence of the microwaves with the wet[27] graphite catalyst support) and also the influence of the hydrogen acceptor amount was observed, suggesting that probably the final aromatization is a key step of the overall process. When the reaction was carried out with just one equivalent of crotonitrile **4** (the double of the molar amount of the reagents as the reaction yields two molecules of H_2), only 45% of **16** was isolated together some starting material. In order to verify the reaction scope, the selected better conditions (Table 2, entry 13) were applied to different primary amines and different *o*-phenylenediamines. The results are collected in Table 3. The reaction proved to be general as most of the benzimidazoles were obtained in high yields. Especially aliphatic amines (as **23**–**26**, Table 3, entries 1–4) reacted very well giving the corresponding benzimidazoles almost pure in the crude reaction mixture. The positive influence of the hydrogen acceptor was confirmed by the exceptional results obtained with allylamine **27** that gave 2-ethyl-

benzimidazole **35** (the saturated product) in almost quantitative yield.[28] On the other hand, with benzylamines **32** and **33**, lower yields were observed due to the contemporary formation of anisole and 5-methyl-1,3-benzodioxole, respectively (25–30% estimated *via* GC/MS), the products derived from the hydrogenolysis of the amines. The introduction of a substituent on the diaminobenzene ring is also well tolerated and benzimidazoles **41**–**46** were obtained in good to acceptable yields. The yields of benzimidazoles are reduced when electron-withdrawing groups are present and the amine nucleophilicity is depressed. However,

Table 3. Preparation of different benzimidazoles from primary amines.



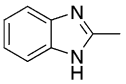
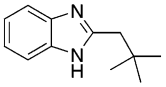
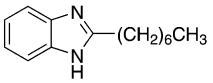
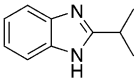
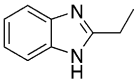
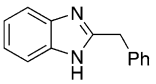
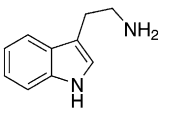
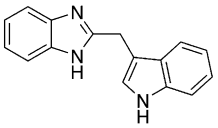
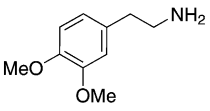
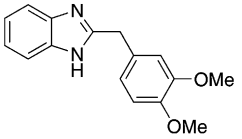
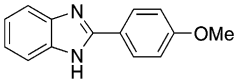
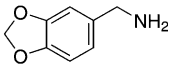
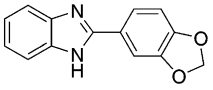
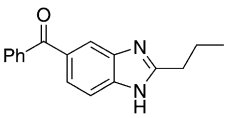
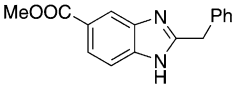
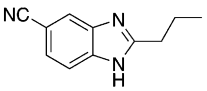
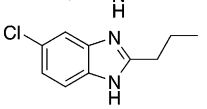
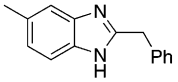
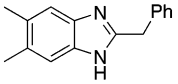
Entry	Phenylenediamine	Amine[a]		Product		Yield[b]
1	**1**	$EtNH_2$	**23**		**9**	83%
2	**1**	$Me_3CCH_2CH_2NH_2$	**24**		**33**	76%
3	**1**	$CH_3(CH_2)_6CH_2NH_2$	**25**		**13**	72%
4	**1**	$Me_2CHCH_2NH_2$	**26**		**34**	82%
5	**1**	$CH_2=CHCH_2NH_2$	**27**		**35**	95%
6	**1**	$PhCH_2CH_2NH_2$	**28**		**36**	74%[c]
7	**1**		**29**		**37**	56%[c]
8	**1**		**30**		**38**	66%[c]
9	**1**	*p*-$MeOC_6H_4CH_2NH_2$	**31**		**39**	45%[d]
10	**1**		**32**		**40**	42%[d]
11	$R^1=COPh$, $R^2=H$, **17**		**16**		**41**	77%
12	$R^1=COOMe$, $R^2=H$, **18**		**28**		**42**	70%
13	$R^1=CN$, **19**		**16**		**43**	65%
14	$R^1=Cl$, **20**		**16**		**44**	46%

Table 3. (Continued)

Entry	Phenylenediamine	Amine[a]	Product		Yield[b]
15	R^1 = Me, **21**	**28**		**45**	82%
16	$R^1 = R^2$ = Me, **22**	**28**		**46**	80%

[a] *Reaction conditions: o*-phenylendiamine (1 mmol), amine (1.2 mmol), AcOH (0.1 mmol), Pd/C (0.1 mmol), **4** (2.2 mmol), toluene (2 mL), N_2 atmosphere.
[b] Yield of isolated and fully characterized products.
[c] Small quantities of 1,2-disubstituted benzimidazoles were isolated (see below).
[d] The product of amine hydrogenolysis was also formed.

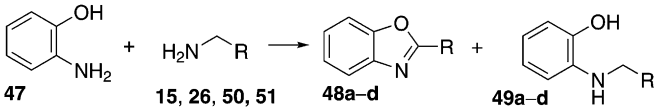
our results are better or comparable with those of previously reported procedures.[19,29]

The possibility to extend the cyclization reaction of primary amines to *o*-aminophenol **47** in order to obtain benzoxazoles was also investigated.[30] Using butylamine **15**, the standard reaction conditions proved not effective as only *N*-butylaminophenol **49a** was isolated (entry 1 in Table 4). As most of reaction conditions previously explored for benzimidazoles did not give any improvement, we tried to apply the protocol previously described for aniline alkylation (entry 2).[19]

No reaction occurred in THF and in the presence of the hydrogen acceptor, whereas a mixture of **48a** and **49a** was exclusively obtained when **4** was not added and **47** was used in excess (entry 4). In EtOH, only benzoxazole **48a** was isolated in acceptable yields (entry 6). Attempts to increase the yields under more harsh conditions gave also the formation of 2-ethylbenzoxazole derived from ethanol oxidation while the use of *t*-BuOH as the solvent did not give the formation of the oxazole (data not included in Table 4). Although yields on **48a** were not very high (46% isolated yields, 80% accounting the recovered starting material) these cyclization conditions were applied to other amines (**26**, **50**, **51**) giving benzoxazoles **48b–d** in 42–52% isolated yields.[31]

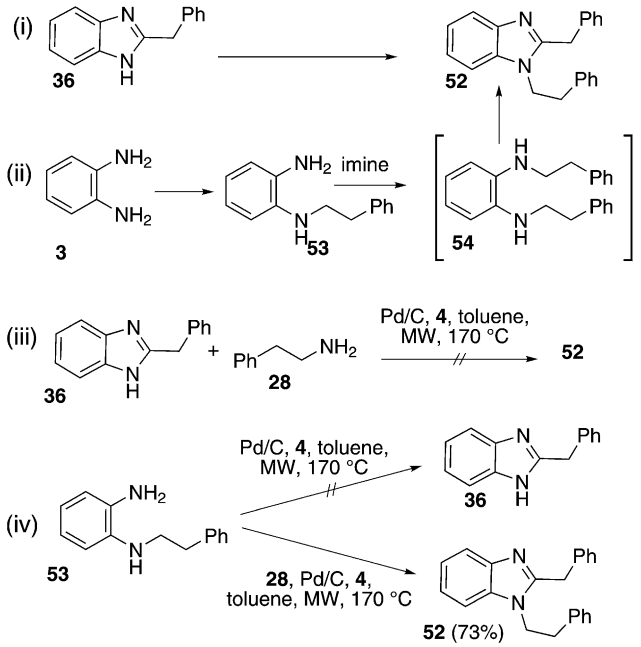
The possibility to extend the method to the preparation of disubstituted benzimidazoles was then explored based on the observation that, when 2-aryl-

Table 4. Preparation of benzoxazoles.



Entry	R	Reaction conditions[a]	**48**:**49** ratio, product, yield[b]
1	C_3H_7, **15**	Tol., 170 °C, **4** (2 equiv.), AcOH (0.1 equiv.)[c]	0:1, **49a**, 10%[f]
2	C_3H_7, **15**	THF, 170 °C, **4** (2 equiv.)[c]	0:1, **49a**, 12%[f]
3	C_3H_7, **15**	THF, 170 °C[c]	0:1, **49a**, 40%[f]
4	C_3H_7, **15**	THF, 170 °C	45:55, **48a**, 45%
5	C_3H_7, **15**	DME, 170 °C	46:54, **48a**, 45%
6	C_3H_7, **15**	EtOH, 170 °C	1:0, 48 a 46%
7	C_3H_7, **15**	EtOH, 170 °C[d]	–
8	C_3H_7, **15**	EtOH, 170 °C[e]	–
9	$CHMe_2$, **26**	EtOH, 170 °C	1:0, **48b**, 45%
10	C_2H_5, **50**	EtOH, 170 °C	1:0, **48c**, 42%
11	*cyclo*-C_6H_{11}, **51**	EtOH, 170 °C	1:0, **48d**, 52%

[a] Tol. = toluene. *Reaction conditions:* sealed vial, MW (maximum power and internal pressure: 200 W and 300 psi), 90 min, **47** (2 mmol), amine (1 mmol), Pd/C (0.1 mmol), solvent (2 mL), N_2 atmosphere.
[b] Ratio determined *via* ^{1}HNMR on the crude reaction mixture.Yield of isolated benzoxazole.
[c] 1 mmol of **47** was used.
[d] Reaction carried out in the presence of 2 mmol of **4**.
[e] Reaction carried out for 12 h in a sealed tube dipped inside an oil bath pre-heated to 180 °C.
[f] Yield of *N*-butylaminophenol.



Scheme 4. Experiments carried out in order to rationalize the formation of 1,2-disubstituted benzimidazoles.

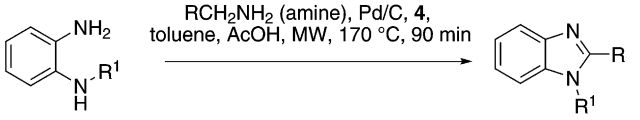
ethylamines were used (**28**–**30**), in spite of the yields of benzimidazoles **39**–**41** still being good, small amounts (never higher than 10%) of the *N*-alkylated benzimidazoles (such as **52** in Scheme 4) were obtained. This behavior was not observed with other aliphatic or benzylamines. The formation of **52** could be justified through a possible alkylation of the 2-substituted benzimidazole **36** [reaction (i) in Scheme 4] or *via* cyclization of the intermediate monoalkylated derivative **53** with the imine generated from **28** and Pd/C [reaction (ii) in Scheme 4]. At first, the postulated alkylation of the benzimidazole ring was excluded as no reaction occurred between isolated **36** and **28** with Pd/C, under standard reaction conditions [reaction (iii) in Scheme 4].

Also attempts to cyclize the mono-alkylated phenylenediamine **53** alone with Pd/C failed, while cyclization occurred when **53** was mixed with a primary amine (such as **28**), benzimidazole **52** being obtained in good yield [reaction (iv) in Scheme 4]. As mono-alkylated phenylenediamine did not seem to be intermediate in the process, it could be used as a starting material for the preparation of 1,2-disubstituted benzimidazoles, relevant scaffolds for the preparation of biologically active compounds.[6a] Thus, a series of monosubstituted *N*-alkyl-*o*-phenylenediamines (**50**–**53**)[32] was submitted to cyclization in the presence of different primary amines producing always the disubstituted benzimidazoles with high yields and purity (see Table 5).

The use of an electron-withdrawing group linked to the phenylenediamine nitrogen (e.g., tosyl) was not possible as reaction of 1-*N*-tosylphenylenediamine[33] with amine **16** in the presence of Pd/C gave a mixture of by-products and starting material. It is also worthy of note that all amines **56**–**58** failed in the cyclization to monosubstituted benzimidazoles in the absence of an additional primary amine, corroborating the hypothesis that Pd-mediated dehydrogenation at CH_2 in α-position with respect to the arylamine nitrogen does not occur.[34] In fact, when the reaction between *N*-butylaniline **65** and *o*-phenylendiamine **3** was carried out, the expected 2-propylbenzimidazole **12** was not formed (Scheme 5), while product **12** is obtained on reacting **3** with a aliphatic secondary amine (**15** in Scheme 5). The result confirms that, once the *N*-aryl-*N*-alkylamine is formed, the Pd/C-mediated oxidation at the NCH_2 is, for some reasons, prevented.

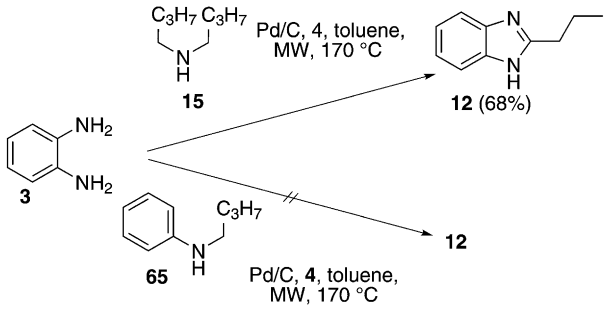
Based on the above results, a possible pathway for the overall process was proposed (Scheme 6). Palladium-mediated dehydrogenation of the primary amine generates the imine **A** that reacts with *o*-phenylendiamine (**3**) to give, after acid-catalyzed ammonia elimination, imine **B**. The imine undergoes intramolecular

Table 5. Synthesis of 1,2-disubstituted benzimidazoles.

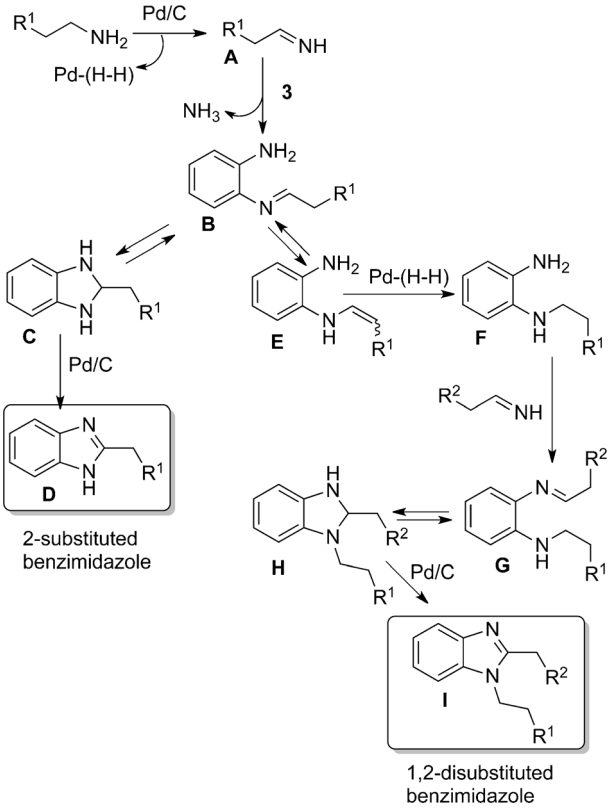


Entry	Diamine; primary amine	Product[a]	Yield[b]
1	R^1 = Ph, **55**; **16**	**59**	85%
2	R^1 = Me, **56**; **28**	**60**	65%
3	R^1 = C_3H_7, **57**; **28**	**61**	85%
4	**57**; **26**	**62**	76%
5	**57**; **27**	**63**	92%
6	R^1 = C_9H_{19}, **58**; **27**	**64**	92%
7	R^1 = CH_2CH_2Ph, **53**; **28**	**52**	73%

[a] *Reaction conditions: o*-phenylendiamine (1 mmol), amine (1.2 mmol), AcOH (0.1 mmol), Pd/C (0.1 mmol), **4** (2.2 mmol), toluene (2 mL), N_2 atmosphere.
[b] Yield of isolated and fully characterized products.



Scheme 5. Comparison of reactivity between *N*-aryl and *N*-alkyl secondary amines.



Scheme 6. Possible pathways for the hydrogen transfer synthesis of benzimidazoles from primary amines.

addition by the other arylamine group with formation of cyclic aminal **C** that is immediately oxidized to 2-substituted benzimidazole **D**. When a group promoting the imine-enamine equilibrium is located in a proper position (such as the aryl moieties present in amines **28–30** at R^1) the formation of enamine **E** occurs at the expense of cyclization intermediate **B**.

Enamine **E** is probably reduced by the Pd-(H–H) complex to amine **F**. Thus, the intramolecular cyclisation is stopped and the *ortho*-NH_2 can intermolecularly add to another imine to give the product **G**. Formation of the aminal **H** and final Pd-mediated aromatization give the 1,2 disubstituted benzimidazole **I**. This picture justifies the formation of the by-products using amine **28–30** and the clean assembly of disubstituted benzimidazoles from *N*-alkyl-*o*-phenylenediamine without formation of monosubstituted benzimidazoles or dialkylphenylenediamines. Finally, the effective possibility to reuse Pd/C was investigated with the aim of improving the overall process performance. Simple filtration, washing with CH_2Cl_2 and MeOH and further drying of the catalyst, gave a product that retains its catalytic activity (at least for four times) but with loss of efficiency (Table 6). However, washing the solid with aqueous 1 M HCl,[35] followed by water, THF to remove water and drying under vacuum, gave a product that could be employed several times (we experimented 5 times) with the same results as those of the new one.[36] The reaction performance of the catalyst showed a TON = 90 (calculated on a 10-mmol scale) that, although far from optimized activity, could be considered overall good and encouraging for a further application on a large scale.

Table 6. Reuse test for the catalyst.[a]

Reuse number	Yield [%] using Pd/C[b]	Yield [%] using acid-treated Pd/C[c]
0	90	90
1	87	89
2	87	90
3	82[d]	89
4	75[d]	88
5	–	89

[a] Applied to the synthesis of **12** using butylamine **16**.
[b] Pd/C simply recovered after filtration and washing with solvents.
[c] Pd/C treated with HCl and further washed, see text and Experimental Section for details.
[d] Some starting material was detected in the GC/MS.

Conclusions

In conclusion, the use of primary amines as suitable substrates for the heterogeneous catalyzed preparation of 2-substituted benzimidazoles or benzoxazoles and 1,2-disubstituted benzimidazoles *via* an hydrogen transfer approach was investigated. The experiments carried out allowed us also to outline a possible mechanism path for the process and for the other reactions that may occur during the transformation. The versatility of the method was demonstrated by the preparation of disubstituted benzimidazoles and suggests that the couple Pd/C–MW could be successfully utilized for other hydrogen transfer-based reactions.

Experimental Section

General Remarks

All reagents and solvents were used as purchased from commercial suppliers without further purification except toluene that was distilled from sodium. The reactions were carried out in oven-dried or flamed vessels (vials) and performed under nitrogen. Flash column chromatography was performed with Merck silica gel 60, 0.040–0.063 mm (230–400 mesh). Merck aluminum-backed plates pre-coated with silica gel 60 (UV254) were used for TLC and were visualized by staining with a solution of $KMnO_4$. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 27 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, 7.27 ppm; CD_2HOD, 3.31 ppm, CHD_2SOCD_3, 2.50 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sex = sextet, h = septet, m = multiplet and/or multiple resonances, br s = broad singlet), coupling constant (J) in Hertz and integration. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 27 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm, CD_3OD, 49.1 ppm, DMSO-d_6, 39.5 ppm). Mass spectroscopy data of the products were collected on GC/MS or LC-MS ESI mass spectrometers. GC conditions: ion trap detector equipped with a 30 m OV-101 capillary column, splitting injector at 300 °C, method: 40–60 °C 5°/min, 60–160 °C 2 °C/min, 160–200 °C 1 °C/min. LC/MS conditions: ES ionization after passage through a C-18, 35 × 5 mm, 3 μ column, elution: mixture A (99.9% water, 0.1% HCOOH); mixture B (99.9% acetonitrile, 0.1% HCOOH): 0–6.0 min, 95% mixture A; 6.0–9.0 min 95- 0% mixture A; 9.0–15 min 0–95% mixture A, flow 1.0 mL min^{-1}, T = 40 °C. Reactions carried out under MW dielectric heating were performed with a microwave oven (Discover from CEM) under monomode irradiation in a 10-mL sealed vial. The internal temperature was monitored through an internal IR sensor and the maximal internal pressure monitored and maintained under the value of 300 psi. Pd/C (10 wt%) was purchased from Sigma–Aldrich and wet with 50 wt% water.[27] Compounds **1**, **3**, **4**, **10**, **11**, **15**, **16**, **17**–**22**, **23**–**32**, **55**–**56** and **65** are commercially available. Compounds **53**, **57**, and **58** were prepared following reported procedures.[30] Products **9**,[36] **12**,[37] **13**,[38] **34**,[38] **35**,[19] **36**,[20] **37**,[39] **39**,[20] **40**,[20] **41**,[29c] **43**,[29c] **44**,[38] **48a**,[40] **48b**,[41] **48c**,[42] **48d**,[43] **59**,[37] and **60**[29c] have been previously described and showed ^{1}H NMR data in agreement with literature values (see the Supporting Information).

2-Neopentyl-1*H*-benzo[*d*]imidazole (33); General Procedure

A 10-mL vial for MW equipped with a magnetic stirrer was charged with Pd/C (10% wt wet with 50% of water, 212 mg, 0.1 mmol) under nitrogen. Dry toluene (2 mL), *o*-phenylenediamine **3** (108 mg, 1 mmol), 3,3-dimethylbutylamine **24** (121.4 mg, 1.2 mmol), crotonitrile **4** (147.4 mg, 2.2 mmol) and acetic acid (5 μL, 0.1 mmol) were subsequently added. The mixture was stirred under MW dielectric heating for 90 min at 170 °C (max internal pressure 300 psi). After cooling, the crude reaction mixture was filtered through a pad of celite inside a syringe equipped with a sintered set (frit). The filter was washed with MeOH and the collected solvent dried over dry $MgSO_4$ and further removed under vacuum. Purification by flash chromatography (petroleum ether 40–60/EtOAc 6:4) gave product **33** as a pale yellow oil; yield: 142 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 2H), 7.18 (m, 2H), 2.80 (s, 2H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (2C), 137.8, 122.1 (2C), 115.6, 43.5, 32.1, 29.8; ES/MS: m/z = 189 $[M+H]^+$; GC/MS (70 eV): m/z (%) = 189 (100%); 132 (100%); R_t = 18.54 min; HR-MS (ESI): m/z = 189.1389, calcd. for $C_{12}H_{17}N_2^+$: 189.1392.

2-(3,4-Dimethoxybenzyl)-1*H*-benzo[d]imidazole (38): Purification by flash chromatography (petroleum ether 40–60/EtOAc 6:4) gave **38** as a yellow oil; yield: 177 mg (66%) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (bs, 1H), 7.48 (m, 2H), 7.17 (m, 2H), 6.69–6.63 (m, 3H), 4.12 (s, 2H), 3.72 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 149.1, 148.1, 128.9, 122.3, 121.1, 114.8, 112.2, 111.5, 58.0 (2C), 35.4; ES/MS: m/z = 291 $[M+Na]^+$; 269 $[M+H]^+$; GC/MS (70 eV): m/z (% = 268 (100%); 253 (30%); R_t = 26.73 min; HR-MS (ESI): m/z = 269.1292, calcd. for $C_{16}H_{17}N_2O_2^+$: 269.1290.

6-Carboxymethyl-2-benzyl-1*H*-benzo[*d*]imidazole (42): Purification by flash chromatography (petroleum ether 40–60/EtOAc 6:4) gave **42** as a colourless oil; yield: 188 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.20 (m, 6H), 4.21 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 156.2, 141.7, 129.0 (2C), 128.4 (2C), 127.3 (2C), 124.4, 124.1, 117.2, 114.4, 52.1, 35.6; ES/MS: m/z = 267 $[M+H]^+$; GC/MS (70 eV): m/z (%) = 266 (100%), 235 (10%); R_t = 27.467 min; HR-MS (ESI): m/z = 267.1130, calcd. for $C_{16}H_{15}N_2O_2^+$: 267.1134.

2-Benzyl-6-methyl-1*H*-benzo[*d*]imidazole (45): Purification by flash chromatography (petroleum ether 40–60/EtOAc 6:4) gave **45** as a yellow oil; yield: 183 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.91 (bs, 1H), 7.36 (d, J = 8 Hz, 1H), 7.14 (s, 5H), 7.01 (d, J = 8 Hz, 1H), 4.13 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 139.2, 138.0, 136.6, 132.3, 128.9, 128.8 (2C), 127.0 (2C), 124.0, 119.7, 114.6, 35.2, 21.6; ES/MS: m/z = 223 $[M+H]^+$; GC/MS (70 eV): m/z (%) = 223 (100%); 222 (30%); R_t = 24.132 min; HR-MS (ESI): m/z = 223.1232, calcd. for $C_{15}H_{15}N_2^+$: 223.1235.

2-Benzyl-5,6-dimethyl-1*H*-benzo[*d*]imidazole (46): Purification by flash chromatography (petroleum ether 40–60/EtOAc 6:4) gave **46** as a yellow oil; yield: 190 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (bs, 1H), 7.24 (s, 2H), 7.16 (s, 5H), 4.13 (s, 2H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 138.0, 136.6, 136.4, 132.3, 130.6, 128.9, 128.7 (2C), 127.0 (2C), 122.5, 114,3, 35.2, 21.6, 21.1; ES/MS: m/z = 237 $[M+H]^+$; GC/MS (70 eV): m/z (%) = 237 (100%); 91 (5%); R_t = 25.387 min; HR-MS (ESI): m/z = 237.1389, calcd. for $C_{16}H_{17}N_2^+$: 237.1392.

2-Propylbenzo[*d*]oxazole (48a); General Procedure

A 10-mL vial for MW equipped with a magnetic stirrer was charged with Pd/C (10% wt wet with 50% of water, 106 mg,

0.05 mmol) under nitrogen. EtOH (2 mL), **47** (109 mg, 1 mmol), **15** (50 μL, 0.5 mmol), were subsequently added. The mixture was stirred under MW dielectric heating for 90 min at 170 °C (max internal pressure 300 psi). After cooling, the crude reaction mixture was filtered through a pad of celite inside a syringe equipped with a sintered set (frit). The filter was washed with MeOH and the collected solvent dried over dry $MgSO_4$ and further removed under vacuum. Purification by flash chromatography (petroleum ether 40–60/EtOAc 8:2) gave **48a** as a brown oil; yield: 37 mg (46%). GC/MS (70 eV): *m/z* (%) = 162 (100%); 146 (25%); 133 (100%); R_t = 13.14 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (m, 1H), 7.45 (m, 1H), 7.26 (m, 2H), 2.88 (t, J = 7.2 Hz, 2H), 1.90 (sex, J = 7.6 Hz, 2H), 1.02 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1; 150.6; 141.3; 124.0 (2C); 119.4; 110.3; 30.5; 20.3; 13.9; HR-MS (ESI): *m/z* = 184.0741, calcd. for $C_{10}H_{11}NONa^+$: 184.0738.

2-Benzyl-1-phenethyl-1*H*-benzo[*d*]imidazole (52); General Procedure for the Synthesis of Disubstituted Imidazoles

A 10-mL MW vial with magnetic stirrer was charged with Pd/C (10% wt, 50% wt water, 212 mg 0,1 mmol) under nitrogen. Dry toluene (2 mL), *N*-1-phenethylbenzene-1,2-diamine **28** (212 mg, 1 mmol), phenethylamine **3** (151 μL, 1.2 mmol), crotonitrile **4** (145 μL, 2.2 mmol) and acetic acid (5 μL, 0.1 mmol) were subsequently added. The mixture was stirred under MW dielectric heating for 90 min at 170 °C. The crude reaction mixture was filtered through a frit and washed with MeOH. The solvent was removed under vacuum and after purification by column cromatography (petroleum ether 40–60/EtOAc 6:4), **52** was obtained as a yellow oil; yield: 238 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (m, 1H), 7.26 (m, 9H), 7.16 (d, J = 6 Hz, 2H), 6.92 (d, J = 6 Hz, 2H), 4.16 (t, J = 7.6 Hz, 2H), 3.94 (s, 2H), 2.78 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 142.7, 137.8, 136.4, 136.1, 135.1, 128.9 (2C), 128.6 (2C), 128.4 (2C), 127.0 (2C), 126.4, 122.4, 122.0, 116.7, 109.4, 45.8, 35.6, 34.4; ES/MS: *m/z* = 313 [M + H] +; GC/MS (70 eV): *m/z* (%) = 312 (100%); 207 (100%); 91 (40%); 65 (20%); R_t = 28.149 min; HR-MS (ESI): *m/z* = 314.1742, calcd. for $C_{22}H_{21}N_2^+$: 314.1738.

2-Benzyl-1-propyl-1*H*-benzo[*d*]imidazole (61): Purification by flash cromatography (petroleum ether 40–60/EtOAc 6:4), gave compound **61** as a yellow oil; yield: 213 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, 1H), 7.26 (m, 7H), 4.31 (s, 2H), 3.93 (t, J = 7 Hz, 2H), 1.57 (sex, J = 7 Hz 2H), 0.83 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 136.6, 135.2, 128.8, 128.5 (2C), 128.3 (2C), 127.0, 122.3, 122.0, 119.5, 109.54, 45.6, 34.5, 22.8, 11.4; ES/MS: *m/z* = 251 $[M+H]^+$; GC/MS (70 eV): *m/z* (%) = 250 (100%), 235 (25%), 207 (25%), 91 (25%), 132 (90%); R_t = 23.687 min; HR-MS (ESI): *m/z* = 251.1546, calcd. for $C_{17}H_{19}N_2^+$: 251.1548.

2-Isopropyl-1-propyl-1*H*-benzo[*d*]imidazole (62): After flash cromatography (CH_2Cl_2/MeOH 95:5), compound **62** was obtained as a yellow oil; yield: 153 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (m, 1H), 7.33–7.24 (m, 3H), 4.10 (t, J = 6.8 Hz, 2H), 3.22 (m), 1.85 (sex, J = 6.8 Hz, 2H), 1.48 (d, J = 6.4 Hz, 6H), 0.98 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 145.1, 131.6, 122.1, 120.0, 118.3, 109.8, 43.6, 25.7, 22.8, 18.4, 9.1; ES/MS: *m/z* = 225 $[M+Na]^+$, 203 $[M+H]^+$; GC/MS (70 eV): *m/z* (%) = 202 (100%), 187 (100%), 159 (25%), 145 (30%); R_t = 18.179 min; HR-MS (ESI): *m/z* = 203.1546, calcd. for $C_{13}H_{19}N_2^+$: 203.1548.

2-Ethyl-1-propyl-1*H*-benzo[*d*]imidazole (63): After flash cromatography (CH_2Cl_2/MeOH 95:5), compound **63** was obtained as a yellow oil; yield: 173 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 7.39 (m, 2H), 7.24 (m, 2H), 4.16 (m 2H), 3.15 (m, 2H), 1.90 (m, 2H), 1.56 (m, 3H), 1.02–0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 140.7, 133.7, 122.1, 121.1, 120.1, 106.6, 47.2, 20.1, 18.5, 10.3, 9.5; ES/MS: *m/z* = 189 $[M+H]^+$; GC/MS (70 eV): *m/z* (%) = 189 (100%), 173 (30%), 159 (30%), 145 (30%); R_t = 18.277 min; HR-MS (ESI): *m/z* = 189.1393, calcd. for $C_{12}H_{17}N_2^+$: 189.1392.

1-Decyl-2-ethyl-1*H*-benzo[*d*]imidazole (64): After flash cromatography (petroleum ether 40–60/EtOAc 6:4), compound **64** was isolated as a yellow oil; yield: 264 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (m, 1H), 7.23 (m, 3H), 4.06 (t, J = 7.6 Hz, 2H), 2.88 (q, J = 7.6 Hz, 2H), 1.77 (m, 2H), 1.46 (m, 3H), 1.23 (m, 13H), 0.85 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 146.0, 136.3, 122.1, 121.9, 119.1, 109.3, 43.8, 31.9, 29.9, 29.6, 29.5, 29.3, 28.6, 27.8, 27.0, 22.7, 14.1, 12.0; ES/MS: *m/z* = 287 $[M+H]^+$; GC/MS (70 eV): *m/z* (%) = 287 (100%), 257 (50%); R_t = 24.928 min; HR-MS (ESI): *m/z* = 287.2485, calcd. for $C_{19}H_{31}N_2^+$: 287.2487..

Dealkylation of Trioctylamine

A 10-mL vial for MW equipped with a magnetic stirrer was charged with Pd/C (10% wt wet with 50% wt of water, 106 mg, 0.05 mmol) under nitrogen. Dry toluene (2 mL), *o*-phenylenediamine **3** (108 mg, 1 mmol), trioctylamine **24** (325 mg, 0.9 mmol) and crotonitrile **4** (147.4 mg, 2.2 mmol) were subsequently added. The mixture was stirred under MW dielectric heating for 90 min at 170 °C (max internal pressure 300 psi). After cooling, the crude reaction mixture was filtered through a pad of celite inside a syringe equipped with a sintered set and the solid washed on the filter with Et_2O. The solvent was carefully removed and the residue dissolved in dry MeOH (2 mL) and passed through an SCX cartridge (prepacked 6 mL tube). The column was washed several times with dry MeOH (8 mL) and dried under vacuum suction. The column was eluted with a solution of NH_3 in MeOH (10 mL of a 2 M solution, 20 mmol); the solvent was carefully evaporated to give dioctylamine **14**; yield: 168 mg (76%). The product showed a GC/MS profile and ^{1}H NMR data in agreement with those of a commercial sample.

General Procedure for Recycling the Catalyst

After reaction, the mixture was passed through a syringe equipped with a frit and Pd/C was washed with CH_2Cl_2 (3 × 10 mL), MeOH (3 × 10 mL) and diethyl ether (2 × 10 mL). Then the bottom of the syringe was closed and 1 mM aqueous HCl (3 mL) was added. After 10 min, the solvent was drained, and the residue washed with H_2O (3 × 10 mL) mL, MeOH (3 × 10 mL) and dry THF (3 × 10 mL). The Pd/C was dried under vacuum suction and removed from the syringe.

The catalyst (5% of overall weight loss) was wet with water and used a second time.

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