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# New route for the synthesis of benzimidazoles by a one-pot multistep process with mono and bifunctional solid catalysts

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ABSTRACT

One-pot multistep reactions involving a new environmentally friendly catalytic procedure have been developed for the synthesis of benzimidazoles. Benzimidazole derivatives with biological and pharmaceutical interest have been prepared by a one-pot four step process with a solid catalyst containing basic and oxidation sites. The four steps refer to: (a) oxidation of the alcohol; (b) cyclocondensation of the aldehyde formed with *ortho*-phenylenediamines, (c) oxidation of the carbon–nitrogen bond, (d) *N*-alkylation reaction. The process is illustrated by the synthesis of 1,2-disubstituted benzimidazole derivative with antiviral activity.



## 1. Introduction

Benzimidazoles are important organic molecules, which find applications as antiulcers, antihypertensives, antivirals, antifungals, anticancer, and antihistaminics among others.[1–3] Owing to their interesting properties, great attention has been paid to the synthesis of benzimidazole derived compounds and two main synthesis methods have been developed. One of them involves the coupling of phenylenediamines and carboxylic acids or their derivatives, a process that requires strong acidic conditions and sometimes combines very high temperatures or the use of microwave.[4–6] The other synthesis route involves a two-step procedure that includes the *cyclo*-dehydrogenation of aniline Schiff's bases, which are often generated in situ from the condensation of phenylenediamines and aldehydes, followed by oxidation with stoichiometric oxidants, as for instance, nitrobenzene, 1,4-benzoquinone, $MnO_2$, Oxone, $NaHSO_3$, or $I_2/KI/K_2CO_3/H_2O$, and more recently with air.[7,8]

We present here, a one-pot multistep catalytic process for the synthesis of benzimidazoles starting form alcohols or aldehydes. If one can start with the aldehyde, then this can be coupled with a diamine, and in a second reaction process, the carbon–nitrogen bond is oxidized to afford the imidazole cycle. When the stability or the handling of the aldehyde is an issue, the catalyst presented here allows to start the reaction from the corresponding alcohols that will be oxidized to generate 'in situ' the aldehyde. Working on these bases it will be presented here that it is possible to afford the synthesis of a disubstituted benzimidazole derivative, 1(2,6-difluorobenzyl)-2-phenylbenzimidazole, which is a molecule with inhibitory activity against human immunodeficiency virus type-1 (HIV-1), through a one-pot four step process, by using a bifunctional base oxidation catalyst.

## 2. Results and discussion

### 2.1. The one-pot process and catalysts involved

In order to see if the synthesis route presented above could be used to produce benzimidazoles with good conversions and selectivities we reacted benzyl alcohol and *o*-phenylenediamine using gold and palladium-based catalysts that have shown to be active and selective aerobic oxidative catalysts.[9–18] In this case the global process will require: (i) a metal catalyzed aerobic oxidation to afford benzaldehyde, (ii) the cyclocondensation reaction with *o*-phenylenediamine and (iii) the catalytic aerobic oxidation of the C–N bond to give the final substituted benzimidazole according to Scheme 1.

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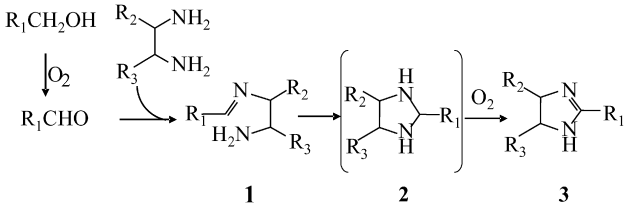
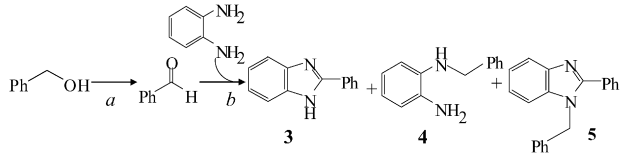


**Scheme 1.** Schematic representation of the synthesis of benzimidazole heterocycle **3** in a single pot with gold and/or palladium catalyst and oxygen as terminal oxidant.

Since preliminary experiments showed that the oxidation of benzyl alcohol did not occur in the presence of the diamine, probably due to a strong competitive adsorption of the latter on the metal, the one-pot three-step synthesis was devised in such a way that the diamine was incorporated when almost all benzyl alcohol was oxidized. Thus, with few exceptions, the oxidation of benzyl alcohol to benzaldehyde proceeds rapidly at 90 °C under oxygen in the presence of palladium and gold supported catalysts (see entries 1–10, Table 1),[19] and good yields of the desired 2-phenyl-1-H-benzimidazole **3** were obtained with Pd on carbon or MgO, as well as with gold on nanoparticulated $CeO_2$ (see entries 1–3 in Table 1).[19]

**Table 1**
Synthesis of 2-phenyl-1*H*-benzimidazole **3** using heterogeneous gold and palladium-based catalysts[a]



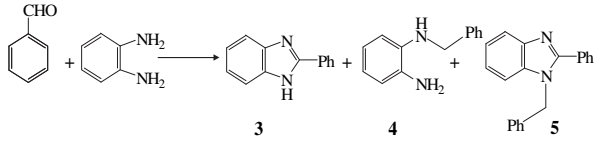
| Entry | Catalyst | Conv[b](%) step a | Conv[c](%) step b | Y[d](%) | | |
|---|---|---|---|---|---|---|
| | | | | **3** | **4** | **5** |
| 1 | Pd–MgO | 93 | 100 | 85 | — | — |
| 2 | Pd–C | 97 | 100 | 90 | — | 2 |
| 3 | Au–$CeO_2$ | 89 | 100 | 85 | — | — |
| 4 | Au–$CeO_2$[e] | 89 | 99 | 62 | 2 | 12 |
| 5 | Pd–MgO[e] | 93 | 97 | 37 | 51 | traces |
| 6 | Pd–C[e] | 96 | 96 | 36 | 5 | 20 |
| 7 | Pd-HAP[e,f] | 67 | 99 | 27 | traces | 40 |
| 8 | Au/Pd–$TiO_2$[e] | 70 | 99 | 33 | — | 6 |
| 9 | Au–$TiO_2$ | 30 | 100 | 29 | — | — |
| 10 | Au–$Fe_2O_3$ | 11 | 75 | 8 | — | — |

[a] Reaction conditions: 1 mmol benzyl alcohol, 1 mmol diamine, catalyst (0.05 mmol metal), 1 ml trifluorotoluene, $T$=90 °C, $P_{O2}$=5 bar.
[b] Calculated by GC on the basis of the amount of benzyl alcohol transformed.
[c] Calculated by GC on the basis of the amount of benzaldehyde transformed.
[d] Isolated yield.
[e] Cyclocondensation step carried out under $N_2$.
[f] Pd-HAP refers to palladium supported on hydroxyapatite.

With respect to gold based catalysts, we have found significant differences in reactivity and yield of benzimidazole derivatives depending on the support. The highest activity and selectivity have been achieved when gold was deposited onto $CeO_2$ (entry 3, Table 1) under oxygen, whereas benzyl alcohol hardly reacts when Au was supported on $TiO_2$ or $Fe_2O_3$ (see entries 9–10 in Table 1). Similarly, the yield of the hydrogenated product **4** was lower with Au–$CeO_2$ than with Pd–MgO (see entries 4–5, Table 1) working under inert atmosphere. The reason for this relies in the lower tendency of gold to form hydrides together with their lower stability and reactivity as compared to palladium hydrides.[20]

It has to be emphasized that the desired compound **3** (see Scheme 1) precipitates in the reaction medium, while being produced, making very easy its isolation. The reaction sequence in Scheme 1 was verified by disrupting or decreasing the reaction temperature immediately after adding the diamine. In this case, it was possible to stop the synthetic sequence and to detect the formation of the intermediate compound **1** (see Scheme 1). In striking contrast, the intermediate **2** reacts very fast and was not detected under our experimental conditions (see Scheme 1).

It is important to remark that both reaction steps (oxidation and cyclization) have to be carried out under oxygen pressure ($P_{O2}$=5 bar), since in the absence of oxygen (or even under air) the yield of benzimidazolic compound **3** decreases and product **4** can be isolated by column chromatography (in some cases as the major product) together with compound **5** (see entries 4–8 in Table 1 and Scheme 2).



**Scheme 2.** Product distribution obtained after the cyclization step under inert atmosphere.

## 2.2. The formation of byproducts 4 and 5

The formation of compound **4** is associated to a catalytic transfer hydrogenation reaction. In general, the transfer hydrogenation methodology involves the use of an alcohol (or any other donor molecule) that should be dehydrogenated with the aid of a metal catalyst to give an oxidized compound and a metal hydride (metal monohydride and/or dihydride intermediate), which would selectively hydrogenate a multiple bond, in this case the imine.[21] Taking into account that the aromatic alcohol has been almost completely transformed into benzaldehyde before adding the diamine, benzyl alcohol cannot be the hydrogen donor and therefore there is only one compound that may behave as potential donor molecule for this reaction. That is, the intermediate benzimidazoline **2**, a heterocyclic precursor formed by a benzene ring fused with an imidazoline, which may undergo oxidative removal of hydrogen to afford our target product benzimidazole together with a metal hydride.[22] This metal hydride can hydrogenate the imine **1** to afford **4** as byproduct as depicted in the Figure 1.

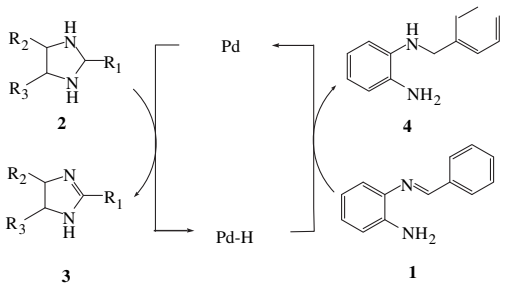


**Figure 1.** Schematic representation of the Pd–MgO catalyzed hydrogenation transfer reaction for the formation of compound **4** with benzimidazoline as hydrogen donor.

The formation of **5** takes also place in the absence of catalyst and, in accordance to this, the 1,2-disubstituted benzimidazole **5** is again formed with moderate yields when using an inert support like Pd–C under inert atmosphere (entry 6, Table 1). Formation of compound **5** through an intermediate diimine has been proposed in the literature.[23] Nevertheless, and as was said above, it is possible to obtain high yields of the desired compound **3** with gold and palladium supported catalysts and working under oxygen pressure (see entries 1–3 in Table 1).

In close connection to this, it is interesting to note that recently a synthesis of benzazoles by hydrogen transfer catalysis from alcohols has been reported. Nonetheless, the use of hydrogen transfer

effectively requires the presence of a convenient acceptor for the generation of the aldehyde in the presence of Ru and Ir complexes.[22b]

### 2.3. Scope of the reaction

To test the general scope and versatility of this synthetic procedure a number of differently substituted aryl alcohols and phenylenediamines were examined. For doing this, stoichiometric amounts of *ortho*-phenylenediamines were incorporated to the reaction vessel after completing the alcohol transformation to aldehyde at 90 °C in the presence of Au–$CeO_2$ under oxygen. Conversions and yields of isolated benzimidazole derivatives are indicated in Table 2.

As described previously, all benzimidazole derivatives were insoluble in the reaction media, thus being isolated by filtration. It was found that introduction of a donor methoxy group at the *para* position of the aromatic alcohol speeds up the oxidation reaction to obtain the aromatic aldehyde, being the yields of the benzimidazole heterocycles from moderate to high (see entries 2–3, Table 2). With a methyl group at the *para* position the yields were moderate (entry 4, Table 2).

Starting from piperonyl alcohol and *ortho*-phenylenediamine, moderate yields of the corresponding benzimidazole derivative could be obtained (entry 7, Table 2).

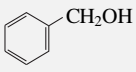
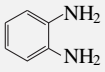
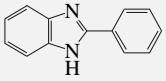
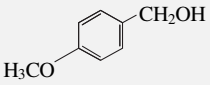
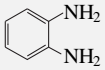
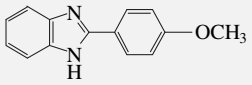
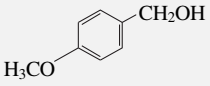
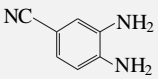
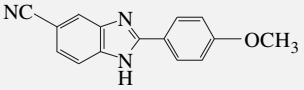
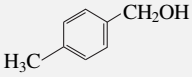
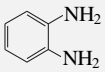
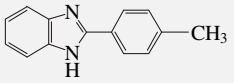
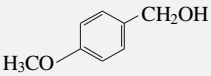
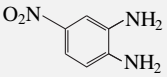
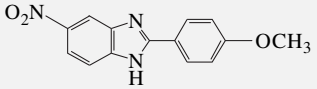
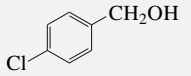
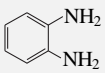
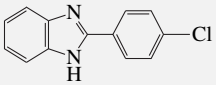
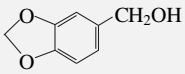
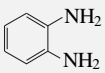
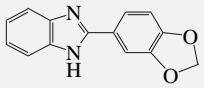
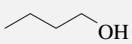
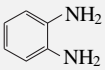
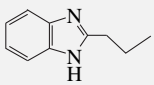
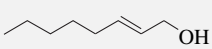
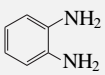
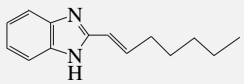
With electron-acceptor substituents on the aromatic diamine the cyclization/oxidation reaction proceeds more slowly and, accordingly, lower yields of the desired benzimidazole were obtained after prolonged heating (entry 5, Table 2). The same effect was observed when the electronwithdrawing substituent was at the aromatic alcohol (entry 6, Table 2).

On the other hand, 1-butanol afforded very poor yields of the corresponding heterocycle provided this aliphatic alcohol hardly converted to the corresponding aldehyde (entry 8, Table 2). In striking contrast the conjugated alcohol 2-octen-1-ol converted up to 80% to the corresponding aldehyde, albeit the latter hardly reacted with the diamine to afford the desired heterocycle (entry 9, Table 2).

### 2.4. Synthesis of a target molecule in a one-pot four step synthesis

Since in general, the experimental procedure described is chemoselective and operates under mild reaction conditions, we

**Table 2**
Au–$CeO_2$ catalyzed synthesis of benzimidazole derivatives from aromatic alcohols and phenylenediamines under oxygen[a]

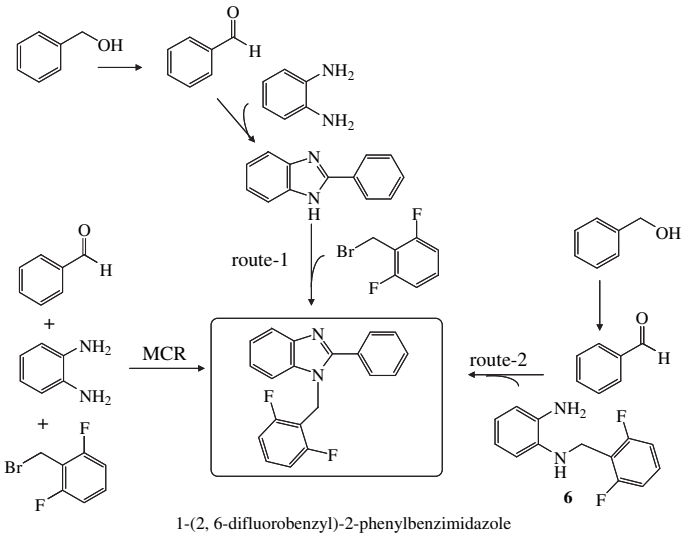
| Entry | Alcohol | Diamine | Product | C[b] (%) | Y[c](%) |
|---|---|---|---|---|---|
| 1[d] |  |  |  | 89 (>99%) | 85 |
| 2[e] |  |  |  | > (>99%) | 91 |
| 3[f] |  |  |  | 94 (>99%) | 70 |
| 4[e] |  |  |  | 84 | 60 |
| 5[g] |  |  |  | >99 (>99%) | 55 |
| 6[h] |  |  |  | >99 | 40 |
| 7[i] |  |  |  | 87 | 53 |
| 8 |  |  |  | 40 | 13[j] |
| 9 |  |  |  | 80 | 22 |

[a] Reactions were performed at 90 °C by using 1 mmol of alcohol, 1 mmol diamine, Au–$CeO_2$ (0.5% mmol), 1 ml of trifluorotoluene, and oxygen ($P_{O2}$=5 bar).
[b] Calculated on the amount of transformed alcohol ; selectivity is given in parenthesis.
[c] Isolated yields.
[d] Ref 24a.
[e] Ref 24b.
[f] Ref 24c.
[g] Ref 24d.
[h] Ref 24e.
[i] Ref 24f.
[j] Calculated by GC.

thought that the same protocol could be applied to the synthesis of benzimidazoles with pharmaceutical and biological interest as can be the synthesis of non-nucleoside antivirals. Effectively, a key target in the search for effective drugs useful for AIDS therapy is the search of viral enzymes that play key roles in the life cycle of the human immunodeficiency virus type-1 (HIV-1). One such essential enzyme is reverse transcriptase (RT), an enzyme that contains both a DNA polymerase activity (which can use either RNA or DNA as a template), and a ribonuclease H activity.[25,26] Inhibition of RT provides an effective means of blocking HIV-1 replication.[27,28] In close connection to this, a number of inhibitors have been developed for antiviral chemotherapy and among them it can be pointed out the non-nucleoside RT inhibitor with *N*-benzylbenzimidazole structure 1-(2,6-difluorobenzyl)-2-phenyl benzimidazole, that it is synthesized in 40% yield through a multistep process.[3]

A priori, the challenge of adapting the one-pot methodology described above to the synthesis of this antiviral becomes apparent when considering the retrosynthetic analysis of this molecule. Indeed, we thought that the molecule could be synthesized via a *N*-alkylation reaction of the corresponding 2-arylbenzimidazole structure, which in turn should be obtained by coupling the diamine and benzaldehyde through the previously described one-pot sequence.

In a first approach we selected palladium deposited on a basic support as catalyst. The use of this basic solid could allow the introduction of a *N*-alkylation reaction to the original one-pot sequence described before, resulting in a oxidation/cyclization/*N*-alkylation global sequence (Scheme 3).




**Scheme 3.** Diverse synthetic strategies for the synthesis of 2-arylbenzimidazole antiviral 1-(2, 6-difluorobenzyl)-2-phenylbenzimidazole [Ref. 29].

For achieving this, Pd–MgO was used to afford the 2-phenylbenzimidazole heterocycle above mentioned (see details of their preparation in the Experimental section) and once the formation of 2-phenylbenzimidazole was completed, the *N*-alkylation reaction with 2,6-difluorobenzylbromide afforded the desired target product, i.e., 1-(2, 6-difluorobenzyl)-2-phenylbenzimidazole, with moderate yields (entry 1, Table 3 and Scheme 3).

A closely related one-pot procedure was alternatively developed using the same bifunctional catalysts Pd–MgO, as well as Au–$CeO_2$ via route 2 in Scheme 3. For achieving this, the monoalkylated diamine *N*-(2,6-difluorobenzyl)benzene-1,2-diamine (**6**) was obtained in parallel (see details of its preparation in the Experimental section), being incorporated after the aromatic alcohol transformation to benzaldehyde (see Scheme 3). This convergent synthetic approach afforded the highest yields (88 and 85%) of the target compound 1-(2, 6-difluorobenzyl)-2-phenylbenzimidazole (see entries 2, 3 in Table 3).

**Table 3**
Synthesis of 1-(2,6-difluorobenzyl)-2-phenylbenzimidazole through different synthetic strategies[a]

| Entry | Route | Catalyst | Oxidation[b] (%) | Cyclization[c] (%) | Yield[d] (%) |
|---|---|---|---|---|---|
| 1 | route-1 | Pd–MgO | 95 | 91 | 40 |
| 2 | route-2 | Pd–MgO | 93 | 95 | 88 |
| 3 | route-2 | Au–$CeO_2$ | 89 | 95 | 85 |
| 4 | MCR | Pd–MgO | — | — | 44 |
| 5 | route-2 | Pd–$MgO_2$[e] | 90 | 90 | 86 |
| 6 | route-2 | Au–$CeO_2$[e] | 88 | 96 | 82 |

[a] Reaction conditions: 1 mmol of alcohol, 1 mmol diamine, 1 mmol 2,6-difluorobenzylbromide, 0.5% mmol metal (Au–$CeO_2$ or Pd–MgO), 1 ml of trifluorotoluene, oxygen ($PO_2$=5 bar), $T$=90 °C and 0.2 ml of DMF as co-solvent to carry out the *N*-alkylation step.
[b] Conversion calculated by GC on the bases of benzyl alcohol transformed.
[c] Conversion calculated by GC on the bases of benzaldehyde transformed.
[d] Isolated yield.
[e] Recovered and reused catalysts.

Finally, in the search for a synthetic strategy to build up the best cascade reaction, the final product was assembled through a reaction in which the three starting materials benzaldehyde, *ortho*-phenylenediamine and the alkyl bromide were simultaneously reacted (Scheme 3). The reaction was performed in the presence of Pd–MgO, and moderated yields of the target product were obtained (see entry 4 in Table 3), that were in the same order that in previously reported synthesis procedure through a multistep process.[28]

It has to be pointed out the excellent reusability of both catalysts for which no metal leaching or deactivation was observed, maintaining its initial activity and selectivity after two uses (see entries 5, 6 in Table 3).

## 3. Conclusions

An effective strategy has been developed for the rapid and efficient one-pot synthesis of benzimidazoles from easily available alcohols and diamines. This strategy allows access to a structurally diverse array of products. The one-pot process in which a first alcohol oxidation is combined with further formation of imidazoline ring, takes place in several steps wherein each product becomes the substrate for the next reaction. The one-pot reactions are controlled by means of the sequential addition of diamines after ensuring the almost complete consumption of the starting alcohol. After amine addition, the formation of a Schiff base intermediate takes place, which will cyclize to the benzimidazoline (not detected) and is oxidized to afford the benzimidazole derivative, hence minimizing the number of operations to be performed.

The main side reactions were: catalytic hydrogenation reaction of the imine **1** to afford **4**, and the formation of 1,2-dialkylated benzimidazole **5**. Both reactions were completely inhibited under oxygen pressure affording high yields of the desired product **3**.

The deposition of the metal on a solid basic support allows planning diverse multistep routes for the synthesis of a 2-aryl substituted benzimidazole, a molecule with inhibitory activity against human immunodeficiency virus type-1 (HIV-1).

## 4. Experimental section

### 4.1. Materials

Commercial Pd–C was purchased from Aldrich; Au–$TiO_2$ and Au–$Fe_2O_3$ catalysts were obtained from Gold World Council Co. and used without further purifications.

Au–$CeO_2$[17b], AuPd–$TiO_2$[16a] and Pd-HAP[29] were prepared according to previous reported procedures.

Solvent trifluorotoluene and all commercially available alcohols and phenylenediamines were employed without further purification.

### 4.2. Typical procedure for synthesis of benzimidazole derivatives (Tables 1 and 2)

1 mmol of aromatic alcohol and palladium or gold catalyst (0.5% mol) were added to a autoclave containing 1 ml of trifluorotoluene. The reaction mixture was heated at 90 °C under continuous stirring under oxygen ($P_{O2}$=5 bar). In most cases the aromatic aldehyde was produced with high yield. Nonetheless, since benzyl benzoate ester was detected at high alcohol conversion, the *o*-phenylenediamine was incorporated before the ester formation, in order to scavenge benzaldehyde and avoid the overoxidation to benzoic acid and the subsequent esterification reaction. Then, after almost complete consumption of the starting alcohol, stoichiometric amounts of 1, 2-phenylenediamine (1 mmol) were added and heating was prolonged to total diamine consumption. The progress of the one-pot reaction was monitored by GC. All benzimidazole derivatives were insoluble in the reaction medium and precipitated being isolated by filtration.

### 4.3. Experimental procedure for the one-pot 1 synthesis of 1-(2,6-difluorobenzyl)-2-phenyl 1-*H*-benzimidazole (route 1)

1 mmol of benzyl alcohol and 0.043 g Pd–MgO were incorporated into a reactor containing 1 ml of trifluorotoluene. The reaction mixture was heated at 90 °C under continuous stirring and oxygen ($P_{O2}$=5 bar). After almost complete oxidation of the starting alcohol to aldehyde (before detecting the formation of the benzoic acid ester derivative), stoichiometric amounts of 1,2-*ortho*-phenylenediamine (1 mmol, 0.108 g) were added and heating was prolonged to total diamine consumption. After this, stoichiometric amounts of 2,6-difluorobenzylbromide (1 mmol, 0.207 g) and 0.2 ml of DMF were added and heating was prolonged under inert atmosphere. The reaction was monitored by TLC. After completing the reaction, the solvent was evaporated under vacuum and the final product was purified by column chromatography by using $Cl_2CH_2$:MeOH (99:1) as eluent to get 0.13 g (40% yield) of 1-(2,6-difluorobenzyl)-2-phenyl-1*H*-benzimidazole.

### 4.4. Experimental procedure for the one-pot 2 synthesis of 1-(2,6-difluorobenzyl)-2-phenyl 1-*H*-benzimidazole (route 2)

0.054 mg of benzyl alcohol (0.5 mmol) and 0.022 g Pd–MgO (0.4% mol) (or 0.018 g Au–$CeO_2$) were incorporated into a reactor containing 1 ml of trifluorotoluene. The reaction mixture was heated at 90 °C under continuous stirring and oxygen ($P_{O2}$=5 bar). After almost complete oxidation of the starting alcohol to aldehyde (before detecting the formation of aromatic acid), stoichiometric amounts of **6** (0.117 g, 0.5 mmol) were added and heating was prolonged to total diamine consumption.

The reaction was monitored by TLC. After completing the reaction, the solvent was evaporated under vacuum and the final product was purified by column chromatography by using $Cl_2CH_2$:MeOH (99:1) as eluent to get 0.282 g of 1-(2,6-difluorobenzyl)-2-phenyl-1*H*-benzimidazole (88% yield using Pd–MgO as catalyst) and 0.272 g of the same compound (85% yield using Au–$CeO_2$ as catalyst).

### 4.5. Experimental procedure for the MCR synthesis of 1-(2,6-difluorobenzyl)-2-phenyl-1-*H*-benzimidazole

Stoichiometric amounts of benzaldehyde (0.2 mmol), *o*-phenylenediamine (0.2 mmol), and 2,6-difluorobenzylbromide (0.2 mmol), were incorporated into a reactor containing 0.5 ml of trifluorotoluene and Pd–MgO (0.002 g, 0.4%) under oxygen ($P_{O2}$=5 bar). The mixture was stirred at 90 °C for 24 h. The reaction was monitored by GC.

### 4.6. Synthesis of *N*-(2,6-difluorobenzyl)benzene-1,2-diamine (6)

A 100 mL round bottom flask was charged with 0.108 g (1 mmol) of 1,2-*ortho*-phenylenediamine, 0.207 g (1 mmol) of 2,6-difluorobenzylbromide, 0.101 g (1 mmol) $NEt_3$ and 5 ml of THF. The mixture was stirred at reflux temperature for 24 h. The solvent was evaporated under vacuum and the solid was purified by column chromatography using an eluent mixture of $Cl_2CH_2$:MeOH. (99:1) to get 0.140 g (60% yield) of the compound *N*-(2,6-difluorobenzyl)benzene-1,2-diamine and showing the following elemental composition: C, 66.93%; H, 5.35%; N, 11.45%; $C_{13}H_{12}N_2F_2$ requires C, 66.66%; H, 5.16%; N, 11.96%. $^1$H NMR (300 MHz, DMSO-$d_6$); $\delta$=7.41 (*m*, 1H), 7.11 (*t*, *J*=8.1 Hz, 2H), 6.50 (*m*, 4H), 4.56 (*t*, *J*=5.5 Hz, 1H), 4.69 (br *s*, 2H), 4.26 (*d*, *J*=5.8 Hz, 2H) ppm $^{13}$C NMR (300 MHz, DMSO-$d_6$); 75 MHz, DMSO-$d_6$: d=163.0, 159.7, 135.4, 135.1, 129.7, 117.6, 117.3, 115.2, 114.8, 111.7, 111.5, 110.0, 35.4 ppm.

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## References and notes

1. (a) Erhadt, P. W. *J. Med. Chem.* **1987**, *30*, 231–237; (b) Tomczuk, B. E.; Taylor, C. R., Jr.; Moses, L. M.; Sutherland, D. B.; Lo, Y. S.; Johnson, D. N.; Kinnier, W. B.; Kilpatrick, B. F. *J. Med. Chem.* **1991**, *34*, 2993–3006; (c) Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharm. Chem. J.* **1999**, *33*, 232–243; (d) Soderlind, K. J.; Gorodetsky, B.; Singh, A. K.; Bachur, N.; Miller, G. G.; Lown, J. W. *Anticancer Drug Des.* **1999**, *14*, 19–36.
2. (a) Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **1996**, *39*, 992–998; (b) Woynarowski, J. M.; McHugh, M. M.; Sigmud, R. D.; Beerman, T. A. *Mol. Pharmacol.* **1989**, *35*, 177–182.
3. Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W., Jr.; Michejda, C. J. *J. Med. Chem.* **1997**, *40*, 4199–4207.
4. Preston, P. N. In *The Chemistry of Heterocyclic Compounds, Part I*; Weissberger, A., Taylor, E. C., Eds.; Wiley-VCH: New York, NY, 1981; Vol. 40, pp 6–60.
5. Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 457–487.
6. Benincori, T.; Sannicoló, F. *J. Heterocycl. Chem.* **1988**, *25*, 1029–1033.
7. Gogoi, P.; Konwar, D. *Tetrahedron Lett.* **2006**, *47*, 79–82.
8. Lin, S.; Yang, L. *Tetrahedron Lett.* **2005**, *46*, 4315–4319.
9. (a) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563; (b) Nishima, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314–3317; (c) Fukuda, Y.; Utimoto, K.; Nozaki, H. *Heterocycles* **1987**, *25*, 297–300; (d) Müller, T. E. *Tetrahedron Lett* **1998**, *39*, 5961–5962; (e) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859; (f) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655; (g) Faza, O. N.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437; (h) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925–3927; (i) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443; (j) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661–662.
10. (a) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51–65; (b) Höffmann-Roder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387–391; (c) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Curr. Org. Chem.* **2004**, *8*, 795–812; (d) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200–203; (e) Corma, A.; Concepción, P.; Domínguez, I.; Fornés, V.; Sabater, M. J. *J. Catal.* **2007**, *251*, 39–47; (f) Santos, L. L.; Ruiz, V. R.; Sabater, M. J.; Corma, A. *Tetrahedron* **2008**, *64*, 7902–7909; (g) Corma, A.; Domínguez, I.; Ródenas, T.; Sabater, M. J. *J. Catal.* **2008**, *259*, 26–35.
11. Haruta, M.; Yamada, N.; Kobayashi, T.; Ilima, S. *J. Catal.* **1989**, *115*, 301–309.
12. (a) Hashmi, A. S. K. *Chem.Rev.* **2007**, *107*, 3180–3211; (b) Bond, G. C.; Thompson, D. T. *Catal. Rev. Sci. Eng.* **1999**, *41*, 319–388.

13. (a) Bond, G. C. *J. Mol. Catal. A: Chem.* **2000**, *156*, 1–20; (b) Landon, P.; Collier, P. J.; Papworth, A. J.; Kiely, C. J.; Hutchings, G. J. *Chem. Commun.* **2002**, 2058–2059.
14. Su, F–Z.; Liu, Y.-M.; Wang, L.-C.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2008**, *47*, 334–337.
15. (a) Boronat, M.; Concepción, P.; Corma, A.; González, S.; Illas, F.; Serna, P. *J. Am. Chem. Soc.* **2007**, *129*, 16230–16237; (b) Carrettin, S.; Guzman, J.; Corma, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2242–2245.
16. (a) Edwars, J. K.; Solsona, B.; Landon, P.; Carley, A. F.; Herzing, A.; Kiely, C. J.; Hutchings, G. J. *J. Catal.* **2005**, *236*, 69–79; (b) Enache, D. I.; Edwards, J. K.; Landon, P.; Solsona, B.; Carley, A. F.; Herzing, A. A.; Watanabe, M.; Kiely, C. J.; Knight, D. W.; Hutchings, G. J. *Science* **2006**, *311*, 362–365.
17. (a) Abad, A.; Concepcion, P.; Corma, A.; Garcia, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4066–4069; (b) Carretin, S.; Concepcion, P.; Corma, A.; Lopez Nieto, J. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2538–2540; (c) Carretin, S.; Concepcion, P.; Corma, A.; Lopez-Nieto, J.M. PCT ES04/107109, 2004; (d) Corma, A.; Domine, M. E. *Chem. Commun.* **2005**, 4042–4044; (e) Corma, A.; Domínguez, I.; Doménech, A.; Fornés, V.; Gómez-García, C. J.; Ródenas, T.; Sabater, M. J.; Corma, A.; Domínguez, I.; Doménech, A.; Fornés, V.; Gómez-García, C. J.; Ródenas, T.; Sabater, M. J. *J. Catal.* **2009**, *265*, 238–244.
18. (a) Kakiuchi, N.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 6620–6625; (b) Gomez-Bengoa, E.; Noheda, P.; Echavarren, A. M. *Tetrahedron Lett.* **1994**, *35*, 7097–7098; (c) Kaneda, K.; Fujii, M.; Morioka, K. *J. Org. Chem.* **1996**, *61*, 4502–4503; (d) Kaneda, K.; Fujie, Y.; Ebitani, K. *Tetrahedron Lett.* **1997**, *38*, 9023–9026; (e) Noronha, G.; Henry, P. M. *J. Mol. Catal. A* **1997**, *120*, 75–87; (f) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185–3189; (g) Ebitani, K.; Fujie, Y.; Kaneda, K. *Langmuir* **1999**, *15*, 3557–3562; (h) Nagata, H.; Ogasawara, K. *Tetrahedron Lett.* **1999**, *40*, 6617–6620; (i) ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636–1639; (j) Besson, M.; Callezot, P. *Catal. Today* **2000**, *57*, 127–141; (k) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726; (l) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476; (m) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755; (n) Peterson, K. P.; Larock, R. C. *J. Am. Chem. Soc.* **1998**, *63*, 3185–3189.
19. The catalyzed oxidation of alcohols to aldehydes has been also involved in a multicomponent reaction to obtain α-acyloxy carboxamides: Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3495–3497.
20. (a) Deng, J.-P.; Shih, W.-C.; Mou, C.-Y. *Chem. Phys. Chem.* **2005**, *6*, 2021–2025; (b) Hashmi, A. S. K.; Salathe, R.; Frost, T. M.; Schwarz, L.; Choi, J.-H. *Appl. Catal., A* **2005**, *291*, 238–246; (c) Gimeno, M. C.; Laguna, A. In *Comprehensive Coordination Chemistry II*; Cleverty, J. A., Meyer, T. J., Eds.; Elsevier Pergamon: 2004; Vol. 6; (d) Puddephatt, R. J. In *Comprehensive Organometallic Chemistry II: Nickel, Palladium and Platinum*, 5th ed.; Pudepphatt, R. J., Ed.; Elsevier Science Ltd: Oxford, 1995; Vol. 9; (e) Khairallah, G. N.; O'Hair, R. A. J.; Bruced, M. I. *Dalton Trans.* **2006**, 3699–3707.
21. (a) Augustine, R. L. *Adv. Catal.* **1976**, *25*, 56–80; (b) Rylander, P. *Catalytic Hydrogenation in Organic Synthesis*; Academic: New York, NY, 1979; (c) Hudlicky, M. *Reductions in Organic Chemistry*; Wiley-VCH: New York, NY, 1984; (d) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, Chapter 3.1; (e) Takaya, H.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, Chapter 3.2; (f) Keinan, E.; Greenspoon, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, Chapter 3.5; (g) Hudlicky, M. *Reductions in Organic Chemistry*, 2nd ed.; American Chemical Society: Washington, D.C, 1996, Chapter 13; (h) Gladiali, S.; Alberico, E. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2; (i) Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *712*, 8023–8027.
22. (a) Schwarz, D. E.; Cameron, T. M.; Jeffrey Hay, P.; Scott, B. L.; Tumas, W.; Thorn, D. L. *Chem. Commun.* **2005**, 5919–5921; (b) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039–2042.
23. (a) Jacob, R. G.; Dutra, L. G.; Radatz, C. S.; Mendes, S. R.; Perin, G.; Lenardao, E. J. *Tetrahedron Lett.* **2009**, *50*, 1495–1497; (b) Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 4823–4826.
24. (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934; (b) Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1993**, *58*, 7016–7021; (c) Sun, Q.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **1995**, *38*, 3638–3644; (d) Estrada-Soto, S.; Villalobos-Molina, R.; Aguirre-Crespo, F.; Vergara-Galicia, J.; Moreno-Díaz, H.; Torres-Piedra, M.; Navarrete-Vázquez, G. *Life Sci.* **2006**, *79*, 430–435; (e) Sharghi, H.; Aberi, M.; Doroodmand, M. M. *Adv. Synth. Catal.* **2008**, *350*, 2380–2390; (f) Kadri, H.; Matthews, C. S.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 641–647.
25. Katz, R. A.; Skalka, A. M. *Annu. Rev. Biochem.* **1984**, *63*, 133–173.
26. Vaishnav, Y. N.; Wong-Stall, F. *Annu. Rev. Biochem.* **1991**, *60*, 57–630.
27. De Clerck, E. *Med. Res. Rev.* **1993**, *13*, 229–300.
28. De Clerck, E. *J. Med. Chem.* **1995**, *38*, 2491–2517.
29. Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572–11573.