Letter

Direct Synthesis of Benzimidazoles by Dehydrogenative Coupling of Aromatic Diamines and Alcohols Catalyzed by Cobalt

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Direct Synthesis of Benzimidazoles by Dehydrogenative Coupling of Aromatic Diamines and Alcohols Catalyzed by Cobalt

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ABSTRACT: Herein we present the base-metal catalyzed dehydrogenative coupling of primary alcohols and aromatic diamines to selectively form functionalized 2-substituted benzimidazoles, liberating water and hydrogen gas as the sole by-products. The reaction is catalyzed by pincer complexes of earth-abundant cobalt under base-free conditions.

KEYWORDS: *Cobalt, Pincer, Benzimidazole, Alcohol, Dehydrogenative Coupling*

Benzimidazole and its derivatives are important building blocks for the pharmaceutical industry due to their prominent biological activity such as anti-arrhythmic, antihistaminic, antiulcer, anticancer, inotropic, antifungal, antihelmintic, and antiviral activities.[1] A number of drugs which exhibit significant activity against viruses such as HIV, herpes (HSV-1) or influenza contain the benzimidazole motif in the molecule. Furthermore, benzimidazoles have significant contributions to industrial chemistry applications such as in cases of chemical UVB filters, pigments, optical brighteners for coatings, and thermo stable membranes for fuel cells.[2] Typically benzimidazoles are synthesized by reaction of 1,2-diaminobenzene with carboxylic acid derivatives, under strongly acidic conditions.[3] A regular procedure for the synthesis of benzimidazole involves heating of 1,2-diaminobenzene in concentrated formic acid.[3a] This approach, although extensively used, suffers from formation of stoichiometric amounts of waste due to substrate leaving groups or additives. Recently, use of aldehydes as substrates and iodine as catalyst in the presence of hydrogen peroxide resulted in improved reaction conditions.[4]

In terms of sustainable synthesis, an environmentally benign route to the synthesis of benzimidazoles from renewable resources with high atom economy would be highly desirable. Among the methods used for the synthesis of benzimidazoles,[3b-d] dehydrogenative coupling between primary alcohols and derivatives of 1,2-phenylenediamine is an ~~one of the most efficient~~ effective synthetic pathway,[5-7] since the only by-products are stoichiometric amounts of water and two equivalent of valuable molecular hydrogen (Figure 1). Since alcohols are abundantly available, the development of efficient reactions whereby alcohols are converted into useful classes of compounds is desirable. Indeed, progress has been made in recent years on sustainable benzimidazole synthesis based on acceptorless dehydrogenation of alcohols followed by coupling with aromatic diamines using noble metal-based complexes.[5] An initial report catalysed by ruthenium phosphine complexes required a reaction temperature of over 200°C.[5a] Recently, several synthetic protocols for the synthesis of benzimidazoles were reported using homogeneous catalysts which operate at lower temperatures, but require stoichiometric amounts of hydrogen acceptors or strong bases.[5b-d,6] Kempe and co-workers recently synthesized benzimidazole derivatives via acceptorless dehydrogenative coupling of primary alcohols and 1,2-diaminobenzene catalysed by a triazine-based iridium pincer catalyst using a stoichiometric amount of base.[5b] Developments of heterogeneous catalysts for this process were also reported.[7]

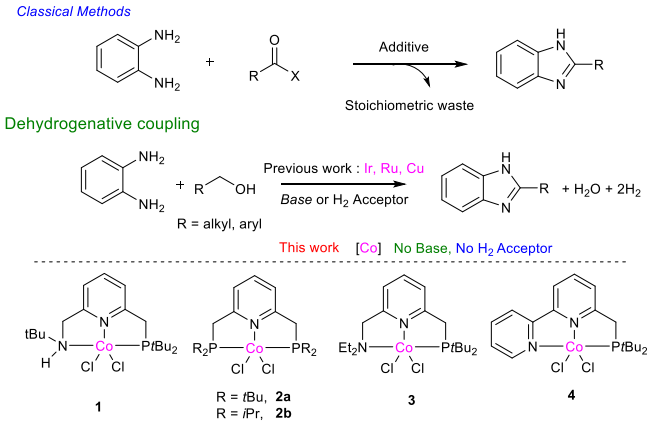
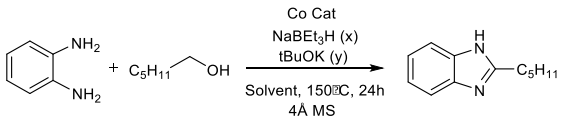


Figure 1. Synthesis of functionalised benzimidazole derivatives: Classical methods and metal catalysed dehydrogenative coupling method.

The development of synthetic reactions catalysed by base-metal complexes is a central goal in homogeneous catalysis, from the perspective of abundance, low cost, lower toxicity and sustainability of base metals. Indeed considerable progress has been made by several groups employing complexes of base metals (Fe, Co, Mn, Ni) in various (de)hydrogenation reactions.[8-10] Homogeneous cobalt catalysts have been reported in hydrogenation reactions of olefins, ketones, imines and CO_2. Ester and nitrile hydrogenation, catalyzed by a (pyridine-based PNNH pincer) Co complex, was reported by us.[11] Recently we also reported selective N-formylation of primary and secondary amines using a CO_2 and H_2 gas mixture, catalysed by a Co-^{i}PrPN^{H}P complex.[12] Homogeneous cobalt catalysts were recently exploited for dehydrogenation and dehydrogenative coupling reactions by several groups.[10a-g] We reported the dehydrogenative coupling of diols and amines to selectively form functionalized 1,2,5-substituted pyrroles, liberating water and hydrogen gas as the sole by-products employing a Co-PNNH pincer catalyst.[13]

Table 1. Optimization of the reaction conditions for the dehydrogenative coupling of 1,2-diaminobenzene and alcohols.



Entry[a]	Catalyst	$NaHBEt_3$ (x mol%)	Base (y mol%)	Yield[b] (%)
1	1	5	5	99
2	1	5	-	99
3[d]	1	5	-	48
4[e]	1	5	5	29
5[c]	1	2.5	-	87
6[c]	1	2.5	-	95
7	1	-	-	67
8	1	-	5	80
9[f]	1	5	-	92
10[g]	1	5	-	70
11[h]	1	5	-	28
12	$CoCl_2$	-	-	00
13	$CoCl_2$	5	5	00
14	-	-	-	00
15	2a	5	-	23
16	2b	5	-	34
17	3	5	-	24
18	4	5	-	53
19[c, i]	1-Cl	-	-	82

[a]Conditions: 1,2-diaminobenzene (0.5 mmol), 1-hexanol (0.5 mmol), catalyst (5 mol%), $NaHBEt_3$, base, and dry toluene (2 mL), heated in a closed Teflon Schlenk tube at 150°C (bath temperature) in the presence of 4Å molecular sieves for 24h. [b]Isolated yield. [c]catalyst (2.5 mol%) [d]At 120°C (bath temperature). [e]Reaction carried out in the absence of molecular sieves for 48h. [f]Reaction carried out in presence of 300 equivalents of Hg with respect to catalyst. [g]1,4-Dioxane used as solvent. [h]THF used as solvent. [i](PNNH)$Co^{I}Cl$ (1-Cl) used as catalyst.

Recently, formation of benzimidazoles catalysed by a Cu-triazole-phosphine complex using excess stoichiometric base was reported.[6] Redox condensation of selective o-substituted nitrobenzenes with alkylamines or alcohols, to form 2-arylbenzimidazoles catalysed by an iron complex, was reported.[14] However, to the best of our knowledge, synthesis of benzimidazoles by acceptorless dehydrogenative coupling of primary alcohols with 1,2-diaminobenzenes under base-free conditions, catalysed by a base-metal complex, was not reported. Herein, we report such a reaction, catalyzed by a cobalt complex, to selectively generate 2-substituted benzimidazoles under base-free conditions, with the extrusion of water and H_2 as the only by products.

Initially, we explored the possibility of benzimidazole formation by reaction of 1,2-diaminobenzene and alcohols using our Co-PNNH pre-catalyst **1**[11a] (Figure 1). To generate the presumed active Co(I) species, the use of one equiv. of $NaBEt_3H$ as a hydride source, and ^{t}BuOK as a base was envisioned, as observed in our earlier work on Co-PNNH catalyzed pyrrole synthesis from 2,5-hexanediol and primary amines.[13] Reaction of 1,2-diaminobenzene (0.5 mmol) with 1-hexanol (0.5 mmol) using $NaHBEt_3$ (5 mol%), ^{t}BuOK (5 mol%) and the Co-PNNH complex **1** (5 mol%) in toluene in a closed system in the presence of 4Å molecular sieves resulted in the formation of 2-pentyl benzimidazole in 99% yield at 150°C after 24 h (Table 1, entry 1). Significantly, quantitative convertion to the desired product under similar conditions took place even in absence of ^{t}BuOK (entry 2). Lowering the temperature to 120°C resulted in yield drop to 48% (entry 3). Analysis of the gas phase by GC revealed the formation of H_2.

In the absence of molecular sieves, under similar reaction conditions, a significantly lower yield of the benzimidazole derivative (29%) was obtained (entry 4) after 48h. Upon decreasing the loading of complex **1** and $NaBEt_3H$ to 2.5 mol%, the product was formed in 87% yield after 24h, and in 95% yield after 36h (entries 5 and 6) under base free conditions. Surprisingly, catalysis was observed even in the absence of $NaBEt_3H$ and ^{t}BuOK, using complex **1** (5 mol%), although benzimidazole was obtained in a lower yield of 67% (entry 7). Upon addition of 5 mol% ^{t}BuOK in the absence of $NaBEt_3H$, the product was isolated in 80% yield (entry 8). While we don't have mechanistic evidence at this stage, it seems that the Co(II) precursor can be reduced to the presumed Co(I) active species even just by the alcohol and diaminobenzene, although the process is more efficient with a hydride reagent.

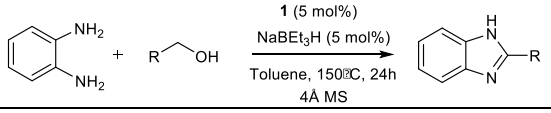
A reaction using 5 mol% pre-catalyst **1** and 5 mol% $NaBEt_3H$ under the same conditions in the presence of 300 equivalents of Hg showed no decrease in product formation or selectivity (Table 1, entry 9), indicating that Co nanoparticle formation is unlikely, and supporting the homogeneity of the reaction. Changing the solvent to 1,4-dioxane or THF using the catalyst and $NaBEt_3H$ (5 mol% each) at 150 °C resulted in a lower yield of the benzimidazole product (entries 10, 11). It should be noted that a minor amount of 1-hexyl-2-pentyl benzimidazole was observed as a side product in a few cases (Table 1, entry 4 (22%), entry 7 (7%)).

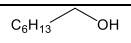
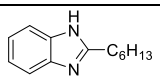
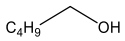
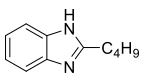
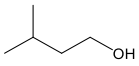
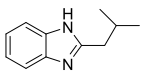
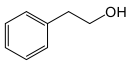
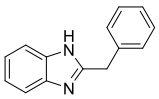
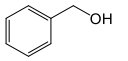
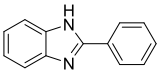
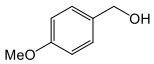
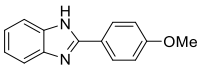
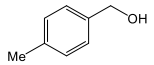
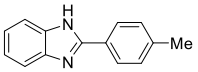
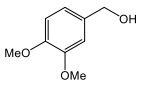
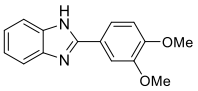
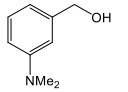
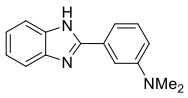
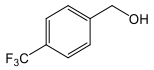
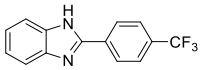
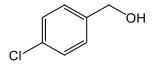
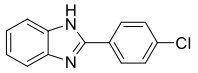
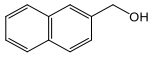
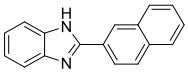
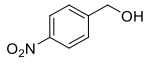
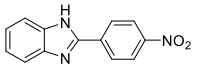
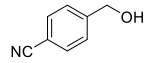
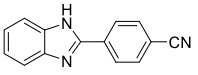
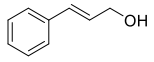
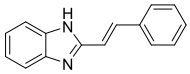
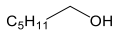
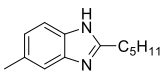
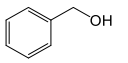
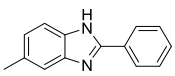
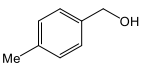
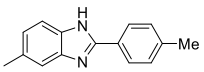
Using $CoCl_2$ as pre-catalyst, in the presence or absence of both $NaBEt_3H$ and ^{t}BuOK, under the same conditions, resulted in no product formation (entry 12, 13). No product was formed in the absence of any catalyst (entry 14).

Our previously reported dihalo Co-PNP and Co-PNN complexes **2a**, **2b**,[15] **3**[11a] and **4**[16] (Figure 1) were then screened. Employing the ^{t}Bu substituted Co-PNP complex **2a**, only 23% product yield was observed at 150°C (Table 1, entry 15), whereas the isopropyl-substituted analogue **2b** catalyzed formation of the 2-pentylbenzimidazole in 34% yield (entry 16), and complex **3** yielded 24% of the product (entry 17). A higher yield of 2-pentylbenzimidazole (53%) was obtained with the bipyridine-based Co-PNN complex **4** (entry 18). The higher catalytic activity of the PNNH complex **1** as compared with that of complexes **2**-**4** may be related to its potential ability to function by two modes of metal−ligand cooperation, amine−amide and aromatization−dearomatization, as opposed to complexes **2**-**4**.[9f,17]

Using the optimized reaction conditions *in absence of base* (toluene, 150°C, 5 mol% **1**, 5 mol% $NaHBEt_3$), the scope of this base-metal catalyzed dehydrogenative coupling reaction was probed with 1,2-diaminobenzene and various primary alcohols. As shown in Table 2, various linear primary alcohols underwent dehydrogenative coupling with 1,2-diaminobenzene to yield the corresponding 2-substituted benzimidazole derivatives in excellent isolated yields (entries 1-4). Exploring the scope further, reactions of 1,2- diaminobenzene with various substituted benzyl alcohols were studied, resulting in good isolated yields using electron rich benzyl alcohol derivatives (entries 5-9).

Table 2. Dehydrogenative coupling of 1,2-diaminobenzenes and alcohols catalyzed by complex 1[a]



Entry	Alcohols	Product	Yield (%)[b]
1			96
2			93
3			95
4			80
5			99
6			70
7			89
8[d]			92
9			87
10			74
11			55
12			50
13[e]			28
14[f]			45
15[g]			82
16[c]			99
17[c]			99
18[c]			99

[a]Conditions: 1,2-diaminobenzene (0.5 mmol), primary alcohols (0.5 mmol), catalyst **1** (5 mol%), $NaHBEt_3$ (5 mol%), and dry toluene (2 mL), heated in a closed Teflon Schlenk tube at 150°C bath temperature in the presence of 4Å molecular sieves for 24h. [b]Isolated yields. [c]3,4-Diaminotoluene was used (0.5 mmol), [d]Reaction time 36h, [e]54% GCMS conversion using mesitylene internal standard, 24% 2-(4-aminophenyl)benzimidazole as hydrogenated product. In presence of 5 mol% tBuOK, 66% GCMS conversion using mesitylene internal standard. [g] In presence of 1 mmol of crotononitrile as hydrogen acceptor.

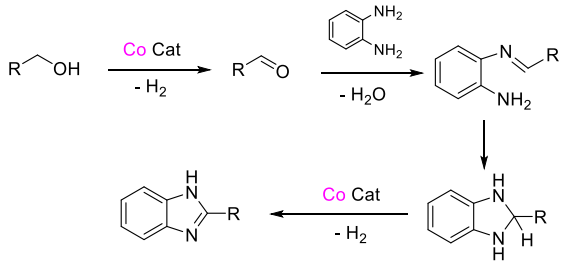
On the other hand, dehydrogenative coupling of the electron deficient trifluoromethylbenzylalcohol and 4-cholobenzylalcohol with 1,2-diaminobenzene resulted in moderate (74% and 55%) isolated yields of the corresponding benzimidazole products, respectively (entries 10, 11). 1-Naphthylmethyl alcohol dehydrogenatively coupled with 1,2-diaminobenzene to yield the corresponding product in 50% isolated yield (entry 12). Reaction of 4-nitrobenzyl alcohol and 1,2 diaminobenzene under the optimized conditions afforded 54% conversion, including 28% of the desired 2-(4-nitrophenyl) benzimidazole along with the hydrogenated product 2-(4-aminophenyl)benzimidazole as detected by GCMS (entry 13). Using the electron deficient 4-cyanobenzyl alcohol resulted in 36% conversion to a mixture of products, including 4-(1H-benzimidazol-2-yl)benzonitrile.. In the presence of 5 mol% ^{t}BuOK under the same reaction conditions, an conversion increased and 45% yield of 4-(1H-benzimidazol-2-yl)benzonitrile as major product was detected by GCMS, in addition to 1,4-bis(1H-benzoimidazol-2-yl)benzene as side product (entry 14). Reaction of 3-phenyl-2-en-1-propanol resulted in formation of 2-phenethylbenzoimidazole with hydrogenation of the conjugated double bond,, whereas in the presence of 2 equivalents of crotononitrile as hydrogen acceptor, 82% of 2-styrylbenzimidazole was formed (entry 15). The catalytic performance of **1** in the dehydrogenative coupling of primary alcohols with 3,4-diaminotoluene was also checked, producing excellent isolated yields of the corresponding substituted benzimidazole products (entries 16-18) under base-free conditions. However, 2-pyridinemethanol gave only 16% of the corresponding benzimidazole product, whereas the phenolic substrates 4-hydroxybenzyl alcohol and 2-(4-hydroxyphenyl)ethanol were completely inactive.

As we recently reported, treatment of $(PNNH)CoCl_2$ (**1**) with one equiv of $NaBEt_3H$ at room temperature gave the paramagnetic complex $(PNNH)Co^{I}Cl$, characterized by X-ray crystallography.[11a] This Co(I) complex was prepared and tested in the dehydrogenative coupling of 1,2-diaminobenzene and 1-hexanol at 150°C, in the absence of any base or hydride source, yielding 82% of 2-pentylbenzimidazole after 24 h, using 2.5 mol% catalyst loading, which is comparable to the results obtained with the Co(II) complex **1** in the presence of $NaBEt_3H$ (Table 1, entries 19). This result is in line with the Co(I) complex being the active catalyst.

To gain mechanistic insight, a toluene solution containing 1-hexanol, complex **1** (5 mol%) and $NaBEt_3H$ was heated at 150°C in a closed system for 24h, resulting in 30% yield of 1-hexanal as the sole product. Treatment of equivalent amounts of 1-hexanol and aniline under the same conditions gave a quantitative amount of N-hexylaniline as the only product. Thus, initially Co(I) catalyzed dehydrogenation of the primary alcohol to give the aldehyde and H_2 takes place. The formed aldehyde subsequently couples with the amine, forming an imine intermediate by water elimination, followed by cyclization to from 2-phenyl-2,3-dihydro-1H-benzimidazole which is rapidly dehydrogenated to form the corresponding benzimidazole derivatives (Scheme 1). A blank experiment using equivalent amounts of 1,2-diaminobenzene and benzaldehyde resulted in 28% formation of 2-phenyl benzimidazole with N-benzyl-2-phenylbenzimidazole as major product.[7e] Using 1-hexanal as the reactant also resulted in 30% yield of 2-pentylbenzimidazole, with N-hexyl-2-pentylbenzimidazole as major side-product under the same conditions. The second catalytic dehydrogenation step results in good and selective yield of the corresponding 2-substituted benzimidazole product.

In conclusion, dehydrogenative coupling of aromatic diamines and alcohols to form benzimidazoles, catalyzed for the first time under base free conditions by a homogeneous earth-abundant (Co) complex was discovered. The reaction is applicable to a wide range of primary alcohols with excellent yields. A plausible mechanism is proposed. We believe that this transformation provides an attractive benzimidazole synthesis, being environmentally benign and atom efficient, using an earth-abundant metal, and forming H_2O and H_2 as the sole by-products. Efforts aimed at the development of efficient and chemoselective catalysts based on complexes of other earth-abundant metals (Mn, Fe, Ni) for dehydrogenative coupling reactions are continuing.

Scheme 1. Plausible steps involved in benzimidazole synthesis from *o*-diaminobenzene and primary alcohols catalyzed by Co.



ASSOCIATED CONTENT

Supporting Information

Experimental procedures, GC-MS and NMR spectra of benzimidazole products are provided in the supporting information. "This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interest.

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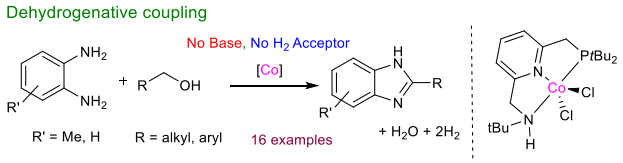
Dehydrogenative coupling
No Base, No H2 Acceptor
[Co]
NH2
NH2
R'
+
R
OH
R' = Me, H
R = alkyl, aryl
16 examples
H
N
N
R
R'
+ H2O + 2H2
PtBu2
N
Co
Cl
Cl
tBu
N
H