Highly Efficient and Ambient-Temperature Synthesis of Benzimidazoles via Co(III)/Co(II)-Mediated Redox Catalysis

Renyuan Zhong, Wulin Xiong, Haoyuan Zhang, Tongtong Zeng, Shanshan Gong * and Qi Sun *

Abstract: An efficient method for ambient-temperature synthesis of a variety of 2-substituted and 1,2-disubstituted benzimidazoles from aldehyde and phenylenediamine substrates has been developed by utilizing Co(III)/Co(II)-mediated redox catalysis. The combination of only 1 mol% of Co(acac)2 and stoichiometric amount of hydrogen peroxide provides a fast, green, and mild access to a diversity of benzimidazoles under solvent-free conditions.

Keywords: benzimidazole; Co(acac)2; redox catalysis; oxidative dehydrogenation; multivalent transition metal catalyst

1. Introduction

Benzimidazole is the key skeleton of a great variety of pharmaceutical agents [1] and functional materials [2]. In the past few decades, many substituted benzimidazoles have been prepared and exhibited a broad spectrum of pharmacological activities [3–6]. Moreover, the antifungal activities of many benzimidazole derivatives against phytopathogenic fungi have further extended their applications in agriculture [7,8]. Therefore, a huge amount of work has been dedicated to the development of novel synthetic methods for benzimidazoles. Among the various approaches, cyclization of o-aminoaniline and aldehyde is the most commonly employed method due to its excellent starting material availability. The well-accepted reaction pathway involves sequential condensation, cycloaddition, and oxidative dehydrogenation [9–11]. Previous research on catalysis based on Lewis acids, such as Sc(OTf)3 [12], ZrOCl2 [13], Y(OTf)3 [14], ZnCl2 [15], Co(OH)2 [16], Ce(NO3)3 [17], InCl3 [18], HfCl4 [19], and montmorillonite K10 [20], and deep eutectic solvents (DESs) [21] shows that these methods typically need heating (over 80 °C) and long reaction time (at least several hours) for oxidation of benzimidazoline intermediate by atmospheric oxygen. In contrast, the catalytic approaches based on oxidants including oxone [22], 1,4-benzoquinone [23], iodobenzene diacetate [24], I2 [25], MnO2 [26], I2/UHP [27], and (NH4)2Ce(NO3)6/H2O2 [28] could proceed at faster reaction rate (several minutes to a few hours) under milder conditions (RT to 50 °C), showing that oxidative dehydrogenation is the rate-determining step. In addition, functionalized dendrimers [29], mesoporous materials [30], and nanoparticles [31–33] have also emerged as new effective catalysts for benzimidazole synthesis. However, the poor availability of these specifically prepared catalysts greatly limited their applications.

Recently, our research group rationally constructed a novel phosphomolybdic acid (PMA)-based catalytic system for benzimidazole synthesis at ambient temperature [34]. Compared to the conventional oxidative methods, insertion of the Mo(VI)/Mo(V) redox cycle between reductive benzimidazoline and oxidative tert-butyl hydroperoxide (TBHP) dramatically accelerated the oxidative dehydrogenation process. Inspired by this method, we further explored the possibility to utilize small molecular multivalent transition metal complexes to catalyze oxidative dehydrogenation. In the paper, we report the development
of a Co(acac)$_2$-based redox catalytic system for fast, green, and mild synthesis of a variety of substituted benzimidazoles.

2. Results and Discussion

In our initial attempt, MoO$_2$(acac)$_2$ was selected as a multivalent transition metal catalyst to replace PMA Keggin cluster in our previously reported redox catalytic system. The reaction of 1.05 equiv of benzaldehyde, 1 equiv of N-phenyl-o-phenylenediamine, 1 mol% of MoO$_2$(acac)$_2$, and 1.2 equiv of TBHP (5.5 M in decane) in DMSO yielded the target benzimidazole 1 in 72% yield over 2.5 h without heating. The experimental result proved the possibility to replace large polyoxometalate (POM) cluster catalyst with a small molecular multivalent transition metal complex to catalyze the oxidative dehydrogenation of benzimidazole. However, it should be noted that the yield and reaction rate of 1 were lower than those of the PMA-mediated redox catalysis due to incomplete oxidation of intermediate. The solvent effects showed that the reaction proceeded much faster in EtOH and CH$_3$CN (20–40 min), but the yields of 1 were similar to those in DMSO, THF, and DME. Interestingly, solvent-free conditions significantly promoted the consumption of benzimidazole intermediate and afforded 1 in 90% yield within 15 min (Table 1). It was observed that the originally yellow-colored reaction mixture of aldehyde and diamine turned green upon addition of MoO$_2$(acac)$_2$, indicating that Mo(VI) quickly oxidized benzimidazole and was reduced to blue-colored Mo(V) species. Upon addition of TBHP, Mo(V) was almost instantly oxidized back to Mo(VI) species to complete the redox cycle. The fact that Mo catalyst existed as yellow-colored Mo(VI) state during the reaction process implied that the rate-determining step in the redox cycle was the oxidative dehydrogenation of benzimidazole by Mo(VI).

Table 1. Solvent effects on MoO$_2$(acac)$_2$-catalyzed synthesis of 1.

| Entry | Solvent | Reaction Time (h) | Isolated Yield (%) |
|-------|---------|------------------|--------------------|
| 1     | DMSO    | 2.5              | 72$^2$             |
| 2     | THF     | 1.5              | 79$^2$             |
| 3     | DME     | 1.25             | 82$^2$             |
| 4     | CH$_3$CN| 40 min           | 80$^2$             |
| 5     | EtOH    | 20 min           | 81$^2$             |
| 6     | Solvent-free | 15 min    | 90                 |

$^1$ The reactions were performed with 1.05 mmol of benzaldehyde, 1.0 mmol of N-phenyl-o-phenyl-enediamine, 0.01 mmol of MoO$_2$(acac)$_2$, and 1.2 mmol TBHP (5.5 M in decane) in 2 mL of solvent or under solvent-free conditions. (MoO$_2$(acac)$_2$ was soluble in all the organic solvents tested). $^2$ Benzimidazole intermediate was not completely consumed when the reaction stopped.

On the basis of the solvent-free conditions, we tested the catalytic efficacy of acetylacetanotes of different multivalent transition metals. The experimental results listed in Table 2 showed that Ni(acac)$_2$ and Cu(acac)$_2$ were less effective than MoO$_2$(acac)$_2$. VO(acac)$_2$ showed similar effect to MoO$_2$(acac)$_2$, whereas Fe(acac)$_3$, Ce(acac)$_3$, Co(acac)$_2$, and Co(acac)$_3$ exhibited better reactivity than MoO$_2$(acac)$_2$. The Cu(acac)$_2$-catalyzed reaction was ultrafast and finished in only 2 min. After TBHP was added, the reaction mixture turned black immediately and resulted in lowered yield. This is possibly because the complexation of Cu(II) with N-phenyl-o-phenylenediamine promoted its oxidation. Generally, the catalytic activities of the other metal acetylacetates are in accordance with the oxidation potentials of their high-valent metal ions with the exception of Ni(acac)$_2$. The fact that the catalytic activities of the acetylacetanotes of Co(II) and Co(III) are identical implied that the oxidation of Co(II) by TBHP should be very fast. Furthermore, other
cobalt(II) salts, including CoCl$_2$ and Co(OAc)$_2$, were also tested for their catalytic activity. The experimental results indicated that Co(acac)$_2$ is the most efficient catalyst with a TOF value of no less than 1164 h$^{-1}$, while the real TOF value based on kinetic experiment was not established and could be even higher. Finally, a control experiment without multivalent transition metal catalyst confirmed their roles in promoting the formation of 1.

Table 2. The effects of multivalent transition metal catalysts on synthesis of 1.$^1$

| Entry | Catalyst       | Reaction Time (min) | Isolated Yield (%) |
|-------|----------------|---------------------|--------------------|
| 1     | Cu(acac)$_2$   | 2                   | 78                 |
| 2     | Ni(acac)$_2$   | 30                  | 87                 |
| 3     | MoO$_2$(acac)$_2$ | 15                 | 90                 |
| 4     | VO(acac)$_2$   | 15                  | 89                 |
| 5     | Fe(acac)$_3$   | 10                  | 91                 |
| 6     | Ce(acac)$_3$   | 10                  | 92                 |
| 7     | Co(acac)$_3$   | 7                   | 97                 |
| 8     | Co(acac)$_2$   | 7                   | 97                 |
| 9     | Co(OAc)$_2$    | 10                  | 92                 |
| 10    | CoCl$_2$       | 15                  | 90                 |
| 11    | No catalyst    | 360                 | 82                 |

$^1$ The reaction was performed with 1.05 mmol of benzaldehyde, 1.0 mmol of N-phenyl-o-phenylenediamine, 0.01 mmol of catalyst or no catalyst, and 1.2 mmol TBHP (5.5 M in decane) under solvent-free conditions. (Upon mixing of reactants, transparent and homogeneous mixtures were obtained).

In the following research, the effects of various peroxide oxidants were tested and listed in Table 3. The experimental results showed that more oxidative aqueous H$_2$O$_2$ resulted in a faster reaction rate. While the reactions with aqueous TBHP and urea hydrogen peroxide (UHP) proceeded slower, the reaction employing mCPBA finished in 5 min but yielded a significant amount of reddish polar byproducts on TLC plate. In addition, the experimental data also showed that 2 mol% Co(acac)$_2$ resulted in more pronounced oxidation of N-phenyl-o-phenylenediamine and lowered yield of 1, whereas 0.5 mol% Co(acac)$_2$ led to prolonged reaction time and decreased TOF. The control experiment showed that the oxidation of benzimidazoline was drastically impeded when H$_2$O$_2$ was replaced with atmospheric oxygen.

With optimized reaction conditions, we examined the substrate scope of the Co(III)/Co(II)-mediated redox catalytic system. As shown in Table 4, this new method works well with both o-phenylenediamine and N-substituted o-phenylenediamines. It maintained high catalytic activity on various substituted benzaldehydes, heteroaryl aldehydes, and cinnamaldehydes. It is noteworthy that this method exhibited an excellent catalytic effect on nitro-containing substrates, which are known as poor substrates in previous reports. The current method afforded 1,2-disubstituted benzimidazoles 1–18 in 83–97% yields over a period of 5 min–1 h at ambient temperature. The reactions with o-phenylenediamines generally took longer than those with N-substituted o-phenylenediamines. The 2-substituted benzimidazoles 19–30 were isolated in 82–95% yields after 15 min–1.5 h reaction time. As reported in the literature [9–11,35], 1,2-disubstituted benzimidazole byproducts could also form when o-phenylenediamine was used. The Co(III)/Co(II)-mediated redox method exhibited high selectivity on desired 2-substituted benzimidazoles over 1,2-disubstituted byproducts. The undesired byproduct was obtained in 4% yield in the synthesis of 19 (~96% selectivity). In other o-phenylenediamine-based reactions, the amount of 1,2-disubstituted byproduct was neglectable.
Table 3. The effects of peroxide oxidants and amounts of Co(acac)2 on synthesis of 1.

| Entry | Oxidant          | Co(acac)2 (mol%) | Reaction Time (min) | Isolated Yield (%) |
|-------|------------------|------------------|---------------------|--------------------|
| 1     | mCPBA            | 1                | 5                   | 54                 |
| 2     | UHP              | 1                | 30                  | 85                 |
| 3     | TBHP (70% aq.)   | 1                | 15                  | 94                 |
| 4     | TBHP (5.5 M in decane) | 1    | 7                  | 97                 |
| 5     | H2O2             | 1                | 5                   | 97                 |
| 6     | H2O2             | 2                | 5                   | 90                 |
| 7     | H2O2             | 0.5              | 15                  | 95                 |
| 8     | No peroxide (air only) | 1      | 24 h               | 88                 |

1 The reaction was performed with 1.05 mmol of benzaldehyde, 1.0 mmol of N-phenyl-o-phenyl-enediamine, 0.005–0.02 mmol of Co(acac)2, and 1.2 mmol oxidant under solvent-free conditions. (Upon mixing of reactants, transparent and homogeneous mixtures were obtained).

Table 4. Synthesis of benzimidazoles (1–30) via Co(III)/Co(II)-mediated redox catalysis.

As seen in Figure 1A, a Co(III)/Co(II) redox cycle-based reaction mechanism was proposed. Similar to what has been observed in our previous research on PMA/PMB-mediated redox catalysis in DMSO [34], N-phenyl-o-phenylenediamine and benzaldehyde quickly formed yellow-colored imine and benzimidazoline intermediates upon mixing. Addition of green-colored Co(acac)3 converted the reaction mixture from yellow to green instantly. However, the green color faded quickly after 5 s and the reddish-yellow color remained until the end of the reaction. This result indicated that the green Co(III) quickly oxidized the benzimidazoline intermediate and was reduced to red-colored Co(II). A more apparent green-to-red color change was visualized on TLC plate (Figure 1B). The UV-Vis absorption data showed that the peak of Co(II) appeared at ~600 nm. Upon addition to the mixture of benzaldehyde and N-phenyl-o-phenylenediamine, the green color faded quickly and the signal at ~600 nm disappeared completely (Figure S1, S2). This result is
in agreement with the color change observed both in glass vial and on TLC plate. In addition, the instant color change from red to green upon addition of aqueous H$_2$O$_2$ to a CH$_2$Cl$_2$ solution of Co(acac)$_2$ proved that H$_2$O$_2$ is capable of oxidizing Co(II) back to Co(III) efficiently (Figure 1C). The fact that cobalt catalyst existed in red-colored Co(II) state during the reaction process indicated that the rate-limiting step in the redox cycle is the oxidative conversion of Co(II) to Co(III) by H$_2$O$_2$, which is different from the reaction with MoO$_2$(acac)$_2$ and explains why Co(acac)$_2$-based redox catalysis is faster than that based on MoO$_2$(acac)$_2$.

Figure 1. Mechanistic investigation. (A) Proposed redox catalysis mechanism, (B) color change upon addition of 1 mol% of Co(acac)$_3$ to the mixture of 1.05 mmol of benzaldehyde and 1.0 mmol of $N$-phenyl-$o$-phenylenediamine under solvent-free conditions without peroxide, and (C) instant color change of Co(II) to Co(III) in CH$_2$Cl$_2$ (Co(acac)$_2$, 4 $\times$ 10$^{-3}$ M, 2 mL) upon addition of H$_2$O$_2$ (30% aq., 90 µL, 100 eq.).

3. Materials and Methods

3.1. General Methods

The solvents and chemical reagents used in the current research work were purchased from Leyan-Shanghai Haohong Scientific Co. Ltd., Shanghai, China. All of the reactions were monitored by TLC plates coated with 0.25 mm silica gel 60 F$_{254}$ and visualized by 254 nm UV. The silica gel used in column chromatography (particle size 32–63 µm) was purchased from Qingdao Haiyang Chemicals, Qingdao, China. $^1$H, $^{13}$C, and $^{19}$F NMR spectra were recorded on an AV-400 instrument (Bruker BioSpin, Fällanden, Switzerland) with chemical shifts referenced to DMSO-$d_6$ or CDCl$_3$ and reported in parts per million. Infrared spectra were obtained with a Vertex-70 instrument (Bruker Optics, Billerica, MA, USA). HRMS spectra were acquired with a micrOTOF-Q II instrument (Bruker Daltonics, Billerica, MA, USA) and reported as $m/z$. Melting points were measured on an X-4 melting point apparatus and uncorrected (Tech Instrument, Beijing, China).

3.2. General Synthetic Procedure and Characterization of Benzimidazoles

To a mixture of $N$-substituted $o$-phenylenediamine/$o$-phenylenediamine (1.0 mmol, 1.0 eq.), aldehyde (1.05 mmol, 1.05 eq.), and Co(acac)$_2$ (2.6 mg, 0.01 mmol, 0.01 eq.) in an open glass vial (10 mL) was added 30% aq. H$_2$O$_2$ (125 µL, 1.2 mmol, 1.2 eq.) dropwise. The reaction mixture was stirred at 25 °C for 5 min–1.5 h. Flash column chromatography on silicagel (PE/EA = 5:1) afforded products 1–30 in pure form. For larger-scale synthesis, dropwise slow addition of 30% aq. H$_2$O$_2$ and monitoring of reaction temperature are advised for safety precautions. The NMR spectra of new compounds are provided in the Supplementary Materials.

2-(1-Phenyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)phenol (12): a white solid, mp: 165–166 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 13.14 (s, 1H), 8.07 (s, 1H), 7.65–7.64 (m, 3H), 7.49 (d, $J$ = 8.5 Hz, 1H), 7.40 (m, 2H), 7.23 (t, $J$ = 8.0 Hz,1H), 7.15 (d, $J$ = 8.5 Hz, 1H), 7.08 (d, $J$ = 8.3 Hz, 1H), 6.84 (d, $J$ = 8.1 Hz, 1H), 6.53 (t, $J_1$ = $J_2$ = 8.0 Hz, 1H) ppm; $^{13}$C NMR
Catalysts 2022, 132.7, 131.3, 126.9, 125.8, 123.9, 122.6, 119.9, 112.5 ppm; IR (KBr): 1599, 1537, 1457, 1437, 1384, 1348, 1232, 1167, 1122, 1049, 922, 825, 770, 710 cm

2-(2-Chloro-5-nitrophenyl)-1H-benzo[d]imidazole (13): a white solid, mp: 195–196 °C. 1H NMR (400 MHz, CDCl3): δ 8.78 (d, J = 2.2 Hz, 1H), 8.49 (dd, J1 = 2.2 Hz, J2 = 8.4 Hz, 1H), 8.17 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.49–7.43 (m, 4H), 7.27–7.23 (m, 2H) ppm; 13C NMR (100 MHz, CDCl3): δ 149.1, 148.6, 148.5, 142.5, 138.1, 134.3, 134.2, 131.1, 130.4 (×2), 129.6, 127.2, 126.8 (×2), 126.2 (q, J = 32.3 Hz), 124.4 (q, J = 270.4 Hz), 121.5 (q, J = 3.4 Hz), 121.0, 118.5 (q, J = 4.1 Hz), 118.4, 111.3 ppm; 19F NMR (470 MHz, CDCl3): δ -59.1 ppm; IR (KBr): νmax 3105, 3053, 2923, 2874, 1912, 1778, 1616, 1599, 1537, 1457, 1437, 1384, 1348, 1232, 1167, 1122, 1049, 922, 825, 770, 710 cm⁻¹; HRMS (ESI+): m/z calcd for C20H12F3N3O4 [M+H]+ 355.1053; found 355.1052.

2-(2-Fluoro-4-nitrophenyl)-1-phenyl-1H-benzo[d]imidazole

7.29–7.25 (m, 2H) ppm; 1H NMR (470 MHz, CDCl3): δ 8.15, 7.94 (d, J = 8.0 Hz, 1H), 7.84–7.80 (m, 2H), 7.61–7.56 (m, 3H), 7.52–7.46 (m, 3H), 7.40–7.36 (m, 2H), 7.02–6.98 (m, 2H), 6.83–6.78 (m, 2H), 2.58 (s, 3H) ppm; IR (KBr): νmax 3348, 2955, 2924, 2870, 1912, 1676, 1592, 1549, 1545, 1498, 1478, 1451, 1381, 1347, 1267, 1191, 1120, 1079, 826, 763, 716 cm⁻¹; HRMS (ESI+): m/z calcd for C19H13FN3O2 [M+H]+ 334.0986; found 334.0986.

2-(2-Fluoro-4-nitrophenyl)-1-phenyl-1H-benzo[d]imidazole (17): a yellow solid, mp: 195–196 °C. 1H NMR (400 MHz, DMSO-d6): δ 8.17–8.10 (m, 2H), 7.99 (t, J = 8.0 Hz, 1H), 7.86–7.74 (m, 4H), 7.49 (d, J = 7.6 Hz, 2H), 7.35–7.28 (m, 2H), 7.20 (d, J = 7.6 Hz, 1H) ppm; 13C NMR (100 MHz, DMSO-d6): δ 155.4 (d, J = 263.9 Hz), 149.2, 142.8, 137.6, 137.1 (d, J = 7.4 Hz), 136.8 (d, J = 9.4 Hz), 136.2, 130.8 (×2), 129.8, 128.0 (×2), 127.5, 127.1, 124.5, 123.6, 120.1, 119.3 (d, J = 21.4 Hz), 111.1 ppm; 19F NMR (470 MHz, DMSO-d6): δ -108.8 ppm; IR (KBr): νmax 3435, 2955, 2925, 2870, 1912, 1676, 1592, 1536, 1499, 1449, 1427, 1382, 1357, 1327, 1226, 1068, 886, 809, 762, 745, 724 cm⁻¹; HRMS (ESI+): m/z calcd for C31H18F3N4O2 [M+H]+ 534.0986; found 534.0985.

2-(2-Chloro-5-nitrophenyl)-1-phenyl-1H-benzo[d]imidazole (24): a white solid, mp: 193–194 °C. 1H NMR (400 MHz, DMSO-d6): δ 13.18 (s, 1H), 8.77 (s, 1H), 8.37 (d, J = 6.0 Hz, 1H), 7.69–7.62 (m, 3H), 7.24 (s, 2H), 2.58 (s, 3H) ppm; 13C NMR (100 MHz, DMSO-d6): δ 149.8, 149.6, 134.7, 134.1 (×2), 131.1 (×2), 129.9, 123.0, 122.4 (×2), 20.0 ppm; IR (KBr): νmax 3057, 2956, 2923, 1631, 1502, 1456, 1382, 1346, 1081, 816, 745 cm⁻¹; HRMS (ESI+): m/z calcd for C14H12N3O2 [M+H]+ 254.0924; found 254.0921.
1624, 1589, 1457, 1428, 1350, 1310, 1295, 1278, 1138, 1047, 911, 883, 827, 766, 737, 711 cm⁻¹; HRMS (ESI⁺): m/z calcd for C₁₃H₉ClN₃O₂ [M+H]⁺ 274.0378; found 274.0376.

4. Conclusions
In summary, the current research proved that Co(acac)₂ could be employed as a highly efficient catalyst for the synthesis of 1,2-disubstituted and 2-substituted benzimidazoles via Co(III)/Co(II)-mediated redox catalysis, featuring low catalyst loading, mild reaction conditions, fast reaction rate, and high product yields. The easy accessibility of inexpensive Co(acac)₂ and H₂O₂ and no need for heating make this new method highly practical.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal12010059/s1, Figure S1: UV-Vis absorption change of Co(acac)₃ upon addition to benzaldehyde and N-phenyl-o-phenylenediamine; Figures S2–S19: The NMR spectra of new benzimidazoles.

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