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Zirconocene catalyzed synthesis of 2-substituted benzimidazole derivatives

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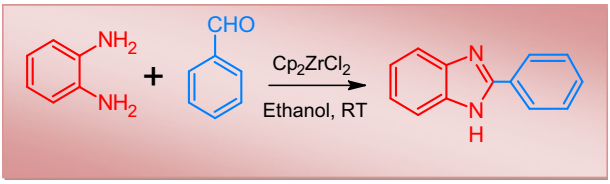
Abstract Zirconocene dichloride (Cp_2ZrCl_2) in the presence of ethanol is found to be a highly efficient catalyst for the one-pot synthesis of structurally diverse 2-substituted benzimidazole derivatives by reaction of *o*-phenylenediamine and aromatic aldehydes at ambient temperature.

Graphical Abstract



Keywords Zirconocene dichloride · *o*-Phenylenediamine · Aromatic aldehydes · 2-Substituted benzimidazole derivatives · Ambient temperature

Introduction

Organozirconocenes represent an important class of metallocenes that have garnered intensive research interest on account of their fascinating sandwich structure and unusual properties. Zirconocene dichloride is an air and moisture stable, non-hazardous, 16 electron, d^0 organozirconocene that has been the

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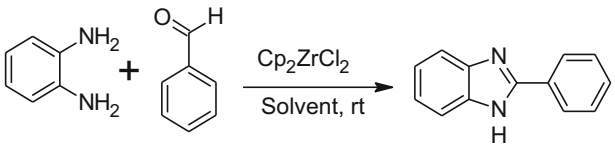
subject of an intense research competition in the industrial sector. It is one of the most widely used metallocene-based catalysts for ethylene polymerization [1]. The catalytic activity of Cp_2ZrCl_2 and other structurally related metallocenes are attributed to their Lewis acidic character [2, 3]. Despite the interesting catalytic potential of Cp_2ZrCl_2, its applications in organic synthesis are scarcely reported [4–6]. The catalytic phenomena occurring with Cp_2ZrCl_2 include the formation of unsaturated di-and polycyclic aluminacarbocycles [7], quinozolin-4(3H)-ones [8], 1-amidoalkyl-2-naphthols [9], 1,5-benzodiazepines [10], cyclobutenylphosphaonates [11], 5-hydroxy-1-alkenyboronates [12], intramolecular cyclization [13], pinacol coupling of aromatic aldehydes and ketones [14], and direct amide bond formation between carboxylic esters and amines [15]. The impressive catalytic potential of Cp_2ZrCl_2 prompted us to exploit its usefulness in the synthesis of medicinally privileged heterocyclic scaffolds.

Benzimidazole and their derivatives have attracted considerable interest as they represent promising building blocks with potential applications in diverse fields. They are a privileged core in natural products, which exhibit illustrious biological [16–18] and pharmacological properties [19–21] such as ulcerative, anti-cancer, anti-diabetic, anti-bacterial, anti-microbial, anti-hypertensive, anti-viral, anti-inflammatory, anti-convulsant, and anti-parasitic as well as FXa inhibitory activity [22, 23]. In addition, they display significant activity against many viruses including influenza [24], HIV [25], human cytomegalovirus (HCMV) [26], etc. Moreover, they act as topoisomerase-I inhibitors [27], angiotensin-II inhibitors [28], and selective neuropeptide YY1 receptor antagonists [29] as well as selective 5-HT_3 antagonists in the isolated guinea pig ileum [30]. The multifarious biological applications of substituted benzimidazoles have stimulated the development of numerous methodologies for their synthesis. The most popular approach for synthesis of 2-substituted benzimidazoles involves condensation of *o*-phenylenediamine with aromatic aldehydes. A variety of catalysts such as TiO_2 NPs [31], UHP/I_2 [32], $CeCl_3{\cdot}7H_2O$ [33], saccharose [34], imidazolium trifluoroacetate protic ionic liquid [35], carbon disulfide [36], CAN/methanol [37], solid acid scolecite [38], $CoCl_2{\cdot}6H_2O$ [39], heteropoly acid [40], zeolite [41], etc. have been reported to catalyze this reaction. Nevertheless, most of these methodologies are associated with drawbacks such as low yields, harsh reaction conditions, use of excess catalyst, formation of undesirable products, high temperature conditions, prolonged reaction time, and tedious workup procedure. Thus, there is a scope for improvement towards developing a simple and an efficient protocol for the synthesis of 2-substituted benzimidazoles especially using metallocene-based catalyst at ambient temperature.

In continuation of our research in the development of highly convenient methodologies for the synthesis of bioactive heterocyclic moieties [10, 42], we report herein the zirconocene dichloride catalyzed synthesis of 2-substituted benzimidazole derivatives by condensation of *o*-phenylenediamine with various aromatic aldehydes at ambient temperature (Scheme 1).



Scheme 1 Cp_2ZrCl_2 catalyzed synthesis of 2-phenyl-1*H*-benzimidazole

Experimental

All the chemicals were obtained from Sigma Aldrich and Spectrochem and used without further purification. Melting points were determined in an open capillary and are uncorrected. All the reactions were carried out under open atmosphere in dried glassware. IR spectra were recorded on a Perkin-Elmer Spectrum one FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avanche (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and Tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm) values with TMS as the internal reference, and coupling constants are expressed in hertz (Hz). Mass spectra were recorded on a Shimadzu QP2010 GCMS.

General procedure for the synthesis of 2-substituted benzimidazole derivatives

A mixture of *o*-phenylenediamine (1 mmol), aryl aldehyde (1 mmol), and zirconocene dichloride (5 mol%) in ethanol (5 mL) was stirred at room temperature till the completion of the reaction as monitored by thin layer chromatography (TLC). After the completion of the reaction, cold water was added to quench the reaction mixture. The resultant solution was extracted with ethyl acetate and combined organic layers were dried over anhydrous Na_2SO_4. After the evaporation of solvent, crude solid obtained was purified by silica gel column chromatography (Merck, 60–120 mesh, ethyl acetate: petroleum ether as an eluent) to afford the pure product, which was characterized by spectroscopic techniques.

Spectral data of representative compounds

2-Phenyl-1H-benzimidazole (Table 3, entry 1)

Mp: 290–292 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.88–7.91 (m, 1H, benzimidazole-H_4), 7.69–7.73 (m, 2H, Ph-H_2, H_2'), 7.47–7.49 (t, 2H, $J = 3.65$ Hz, benzimidazole-H_5, H_6), 7.42–7.63 (m, 3H, Ph-H_3, H_3', H_4), 7.12–7.15 (t, 1H, $J = 3.9$ Hz, benzimidazole-H_7), 5.49 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.5 (benzimidazole-C_5), 120.0 (benzimidazole-C_6), 123.0 (benzimidazole-C_4), 125.9 (benzimidazole-C_7), 127.7 (Ph-C_4), 128.7 (Ph-C_2'), 129.0 (Ph-C_2), 129.2 (Ph-C_3), 129.9 (Ph-C_3'), 130.1 (Ph-C_1), 136.4 (benzimidazole-C_{3a}), 143.1 (benzimidazole-C_{7a}), 154.1 (benzimidazole-C_2); IR (KBr) (cm^{-1}): 3374, 3053, 2922, 1518, 1393, 1343, 1276, 970, 820, 741, 670; MS(EI): *m/z* 194 $[M]^+$.

2-(4-Nitrophenyl)-1H-benzimidazole (Table 3, entry 2)

Mp: >300 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.33–8.36 (d, 2H, $J = 9$ Hz, Ph-H_3, H_3'), 8.05–8.11 (m, 2H, Ph-H_2, H_2'), 7.13–7.17 (m, 2H, benzimidazole-H_4, H_7), 6.79–6.84 (m, 2H, benzimidazole-H_5, H_6), 4.35 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.8 (benzimidazole-C_7), 116.8 (benzimidazole-C_4), 118.4 (benzimidazole-C_5), 120.6 (benzimidazole-C_6), 124.1 (Ph-C_3), 127.6 (Ph-C_3'), 129.1 (Ph-C_2), 135.6 (Ph-C_2'), 141.9 (benzimidazole-C_{3a}), 143.7 (benzimidazole-C_{7a}), 149.0 (Ph-C_1), 153.7 (benzimidazole-C_2), 158.9 (Ph-C_4); IR (KBr) (cm^{-1}): 3461, 3073, 2918, 1594, 1339, 1262, 958, 892, 844, 709, 686; MS(EI): *m/z* 239 $[M]^+$.

2-(4-Chlorophenyl)-1H-benzimidazole (Table 3, entry 3)

Mp: 300–302 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.35 (t, 2H, $J = 6.9$ Hz, Ph-H_3, H_3'), 7.83–7.92 (m, 4H, benzimidazole-H_4, H_5, H_6, H_7), 7.65–7.75 (m, 2H, Ph-H_2, H_2'), 5.86 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.8 (benzimidazole-C_4, C_7), 114.3 (benzimidazole-C_5, C_6), 118.4 (Ph-C_1), 124.6 (Ph-C_3, C_3'), 129.5 (Ph-C_2, C_2'), 144.7 (benzimidazole-C_{3a}, C_{7a}), 150.6 (Ph-C_4), 156.9 (benzimidazole-C_2); IR (KBr) (cm^{-1}): 3443, 3017, 1625, 1572, 976, 848, 749; MS(EI): *m/z* 228 $[M]^+$.

2-(4-Bromophenyl)-1H-benzimidazole (Table 3, entry 4)

Mp: 281–283 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.15 (dd, 2H, $J = 6.8$, 1.6 Hz, Ph-H_3, H_3'), 7.73–7.96 (m, 4H, benzimidazole-H_4, H_5, H_6, H_7), 7.63–7.77 (m, 2H, Ph-H_2, H_2'), 5.98 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.2 (benzimidazole-C_4, C_7), 115.3 (benzimidazole-C_5, C_6), 119.4 (Ph-C_4), 125.6 (Ph-C_2, C_2'), 130.5 (Ph-C_3, C_3'), 145.7 (Ph-C_1), 153.6 (benzimidazole-C_{3a}), 157.9 (benzimidazole-C_{7a}), 158.2 (benzimidazole-C_2); IR (KBr) (cm^{-1}): 3431, 3057, 1675, 1577, 1499, 978, 898, 840, 748, 699; MS(EI): *m/z* 273 $[M]^+$.

2-(4-Hydroxyphenyl)-1H-benzimidazole (Table 3, entry 5)

Mp: 252–255 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.63 (bs, 1H, OH), 7.80–7.82 (dd, 2H, $J = 9$ Hz, Ph-H_2, H_2'), 7.52–7.76 (m, 4H, benzimidazole-H_4, H_5, H_6, H_7), 7.43–7.46 (m, 2H, Ph-H_3, H_3'), 5.94 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.3 (benzimidazole-C_4, C_7), 115.9 (Ph-C_3, C_3'), 121.6 (benzimidazole-C_5, C_6), 126.4 (Ph-C_2, C_2'), 128.6 (Ph-C_1), 142.8 (benzimidazole-C_{3a}), 145.1 (benzimidazole-C_{7a}), 152.4 (benzimidazole-C_2), 158.9 (Ph-C_4); IR (KBr) (cm^{-1}): 3567, 3396, 3034, 1618, 912, 834, 789, 642; MS(EI): *m/z* 210 $[M]^+$.

2-(4-Methoxyphenyl)-1H-benzimidazole (Table 3, entry 6)

Mp: 223–225 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) δ 7.62 (t, 2H, $J = 5.4$ Hz, benzimidazole-H_4, H_7), 7.48 (d, 2H, $J = 3.0$ Hz, Ph-H_2, H_2'), 7.19 (d, 2H,

$J = 2.4$ Hz, Ph-H_3, H_3'), 7.11–7.18 (m, 2H, benzimidazole-H_5, H_6), 5.73 (s, 1H, NH), 3.82 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.3 (OCH_3), 111.3 (Ph-C_3, C_3'), 114.5 (benzimidazole-C_4), 118.8 (benzimidazole-C_7), 122.8 (Ph-C_1), 124.7 (benzimidazole-C_5), 125.1 (benzimidazole-C_6), 128.4 (Ph-C_2), 128.9 (Ph-C_2'), 148.9 (benzimidazole- C_{3a}, C_{7a}), 151.4 (benzimidazole-C_2), 160.1 (Ph-C_4); IR (KBr) (cm^{-1}): 3596, 3381, 2965, 1641, 1528, 817, 754, 601; MS(EI): *m/z* 224 $[M]^+$.

2-(3-Methoxyphenyl)-1H-benzimidazole (Table 3, entry 7)

Mp: 212–214 °C, ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.89 (t, 2H, $J = 5.5$ Hz, benzimidazole-H_4, H_7), 7.48 (d, 2H, $J = 3.4$ Hz, benzimidazole-H_5, H_6), 7.11–7.18 (m, 4H, Ph-H_2, H_2', H_3', H_4), 5.83 (s, 1H, NH) 3.74 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.3 (OCH_3), 110.3 (benzimidazole-C_4, C_7), 111.5 (Ph-C_2), 113.5 (Ph-C_4), 119.8 (Ph-C_2'), 123.8 (benzimidazole-C_5, C_6), 126.1 (Ph-C_3'), 129.4 (Ph-C_1), 142.9 (benzimidazole-C_{3a}), 148.9 (benzimidazole-C_{7a}), 152.4 (benzimidazole-C_2), 159.1 (Ph-C_3); IR (KBr) (cm^{-1}): 3546, 3343, 2962, 1638, 1531, 845, 741; MS(EI): *m/z* 224 $[M]^+$.

2-(4-Methylphenyl)-1H- benzimidazole (Table 3, entry 8)

Mp: 268–270 °C, ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.16–8.18 (d, 2H, $J = 6.9$ Hz, benzimidazole-H_4, H_7), 7.54–7.44 (m, 2H, benzimidazole-H_5, H_6), 7.34–7.40 (m, 4H, Ph-H_2, H_2', H_3, H_3'), 5.80 (bs, 1H, NH), 2.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 (CH_3), 111.8 (benzimidazole-C_4, C_7), 115.7 (benzimidazole-C_5, C_6), 122.6 (Ph-C_2), 124.3 (Ph-C_2'), 127.4 (Ph-C_1), 129.4 (Ph-C_3, C_3'), 138.7 (Ph-C_4), 143.2 (benzimidazole-C_{3a}), 152.4 (benzimidazole-C_{7a}), 156.3 (benzimidazole-C_2); IR (KBr) (cm^{-1}): 3446, 3022, 1632, 858, 761, 681; MS(EI): *m/z* 208 $[M]^+$.

2-(2-Hydroxyphenyl)-1H-benzimidazole (Table 3, entry 9)

Mp: 238–240 °C, ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 12.61 (bs, 1H, OH), 7.73–7.82 (d, 2H, $J = 9$ Hz, benzimidazole-H_4, H_7), 7.52–7.69 (m, 4H, Ph-H_3, H_3', H_4, H_2'), 7.38–7.49 (m, 2H, benzimidazole-H_5, H_6), 5.84 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.3 (benzimidazole-C_4, C_7), 113.9 (benzimidazole-C_5, C_6), 114.6 (Ph-C_3), 118.2 (Ph-C_1), 122.5 (Ph-C_3'), 126.7 (Ph-C_2'), 127.6 (Ph-C_4), 143.7 (benzimidazole-C_{3a}), 145.8 (benzimidazole-C_{7a}), 153.4 (benzimidazole-C_2), 155.4 (Ph-C_2); IR (KBr) (cm^{-1}): 3533, 3436, 3054, 1658, 854, 769, 632; MS(EI): *m/z* 210 $[M]^+$.

2-(3, 4, 5-Trimethoxyphenyl)-1H-benzimidazole (Table 3, entry 10)

Mp: 212–214 °C, ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 12.85 (bs, 1H, NH), 7.63–7.66 (m, 2H, benzimidazole-H_4, H_7), 7.51–7.54 (dd, 2H, $J = 6$, 1.8 Hz, benzimidazole-H_5, H_6), 7.43 (s, 2H, Ph-H_2, H_2'), 3.92 (s, 9H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.1 (OCH_3), 61.2 (OCH_3), 105.8 (benzimidazole-C_4),

111.4 (benzimidazole-C_7), 119.7 (benzimidazole-C_5), 122.7 (benzimidazole-C_6), 124.4 (Ph-C_1), 125.8 (Ph-C_2, C_2'), 138.9 (benzimidazole-C_{3a}, C_{7a}), 147.9 (Ph-C_4), 151.3 (benzimidazole-C_2), 156.2 (Ph-C_3, C_3'); IR (KBr) (cm^{-1}): 3447, 3078, 1620, 1540, 823, 768, 691; MS(EI): *m/z* 284 $[M]^+$.

2-(Furan-2-yl)-1H-benzimidazole (Table 3, entry 11)

Mp: 283–284 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.87–7.90 (dd, 2H, $J = 6.0$, 1.8 Hz, benzimidazole-H_4, H_7), 7.71–7.84 (d, $J = 9$ Hz, 2H, benzimidazole-H_5, H_6), 7.52–7.66 (m, 3H, furan-H_3, H_4, H_5), 5.91 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.8 (furan-C_4), 114.3 (furan-C_5), 119.7 (benzimidazole-C_4, C_7), 124.5 (benzimidazole-C_5, C_6), 138.3 (benzimidazole-C_{3a}, C_{7a}), 147.7 (benzimidazole-C_2), 149.2 (furan-C_3), 156.1 (furan-C_1); IR (KBr) (cm^{-1}): 3411, 3023, 1634, 1312, 812, 721, 617; MS(EI): *m/z* 184 $[M]^+$.

2-(Thiophen-2-yl)-1H-benzimidazole (Table 3, entry 12)

Mp: >300 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.81–7.84 (dd, 2H, $J = 6$, 3 Hz, benzimidazole-H_4, H_7), 7.76–7.78 (d, 2H, $J = 7.8$ Hz, benzimidazole-H_5, H_6), 7.56–7.68 (m, 3H, thiophene-H_3, H_4, H_5), 5.98 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.1 (benzimidazole-C_4), 116.5 (benzimidazole-C_7), 123.9 (benzimidazole-C_5), 124.6 (benzimidazole-C_6), 127.8 (thiophene-C_3), 128.3 (thiophene-C_4), 129.8 (thiophene-C_5), 136.9 (benzimidazole-C_{3a}, C_{7a}), 145.0 (benzimidazole-C_2), 148.6 (thiophene-C_1); IR (KBr) (cm^{-1}): 3418, 3033, 1614, 815, 727, 686; MS(EI): *m/z* 200 $[M]^+$.

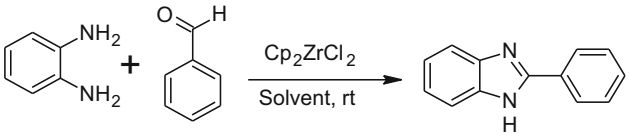
2-(Ferrocenyl)-1H-benzimidazole (Table 3, entry 13)

Mp: 208–210 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 12.29 (s, 1H, NH), 7.47 (s, 2H, benzimidazole-H_4, H_7), 7.09–7.12 (m, 2H, benzimidazole-H_5, H_6), 5.03 (s, 2H, C_5H_4), 4.42 (s, 2H, C_5H_4), 4.07 (s, 5H, C_5H_5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 60.09 (C_5H_4), 67.6 (C_5H_4), 69.7 (C_5H_5), 70.0 (C_5H_5), 74.5 (C_5H_5), 78.7 (C_5H_4, C_{ipso}), 114.3 (benzimidazole-C_4, C_7), 121.6 (benzimidazole-C_5, C_6), 139.2 (benzimidazole-C_{3a}, C_{7a}), 153.4 (benzimidazole-C_2); IR (KBr) (cm^{-1}): 3413, 3047, 1635, 1579, 926, 818, 729; MS(EI): *m/z* 302 $[M]^+$.

Result and discussion

Our initial efforts were focused on optimization of reaction conditions. The reaction between *o*-phenylenediamine and benzaldehyde was considered as a model reaction for investigating the effectiveness of different polar and non polar solvents using a catalytic amount of the Cp_2ZrCl_2 (5 mol%). Solvent optimization clearly suggested that ethanol is the best solvent for the desired transformation due to a fast reaction rate and a high yield (Table 1, entry 9). The other polar protic solvents such as water and methanol gave the desired product in lower yields (Table 1, entries 7–8) while

Table 1 Optimization of the reaction conditions using different solvents



Entry	Solvent	Reaction time (h)	Yield (%)[a]
1	1, 4-Dioxane	2.0	35
2	Toluene	2.5	38
3	Chloroform	3.5	45
4	Ethylene dichloride	3.5	50
5	THF	4.5	70
6	Acetonitrile	4.0	75
7	Water	5.0	55
8	Methanol	2.0	56
9	Ethanol	1.5	94

Reaction conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), and Cp_2ZrCl_2 (5 mol%) in solvent (5 mL) were stirred at room temperature

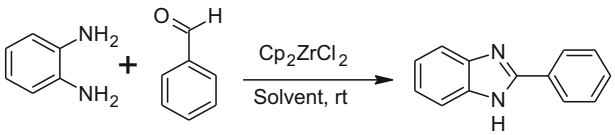
[a] Isolated yields after column chromatography

polar aprotic solvents like EDC, THF, and acetonitrile displayed slow reaction rates leading to moderate yields of the product (Table 1, entries 4–6). On the other hand, nonpolar solvents such as 1–4 dioxane, toluene, and chloroform afforded the desired condensation products in lower yields (Table 1, entries 1–3). The higher reaction rate in ethanol can be attributed to the coordination between ethanol and Cp_2ZrCl_2 that causes enhancement in Lewis acidity of the zirconium centre thereby improving its catalytic efficiency [43].

We have carried out the model reaction using different stoichiometric amounts of catalyst. The catalyst screening results are summarized in Table 2. It was observed that the excellent yield was achieved by using 5 mol% of Cp_2ZrCl_2 (Table 2, entry 3). Further increase in catalyst quantity beyond 5 mol% did not increase the yield of the product significantly (Table 2, entry 4–5).

After investigating the influence of different reaction parameters on the model reaction, we turned our attention towards the synthesis of benzimidazole derivatives using *o*-phenylenediamine and a variety of substituted aromatic aldehydes, and the results are summarized in Table 3. In all the cases, 2-substituted benzimidazoles were the sole products and no anomalies, such as 1, 2-disubstitued benzimidazole, were noted. With the both electron-poor and electron-rich benzaldehydes (Table 3, entries 2–4 and 5–8), the corresponding 2-substituted benzimidazole derivatives were obtained in good to excellent yields. The sterically hindered aldehydes such as salicylaldehyde as well as 3, 4, 5-trimethoxy benzaldehyde (Table 3, entries 9 and 10) were also tolerated with equal chemical efficiency although yields were comparatively moderate. Remarkably, heterocyclic aldehydes such as furfural and

Table 2 Optimization study for the amount of Cp_2ZrCl_2



Entry	Amount of catalyst (mol%)	Reaction time (h)	Yield (%)[a]
1	01	1.5	40
2	02	1.5	72
3	05	1.5	94
4	10	1.5	94
5	20	1.5	94

Reaction conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), and Cp_2ZrCl_2 in ethanol (5 mL) were stirred at room temperature

[a] Isolated yields of purified products

thiophene-2-aldehyde (Table 3, entries 11 and 12) reacted smoothly with *o*-phenylenediamine furnishing the anticipated products in excellent yields. Furthermore, organometallic aldehyde such as ferrocenecarboxyldehyde also reacted efficiently with *o*-phenylenediamine affording the desired product in excellent yields (Table 3, entry 13).

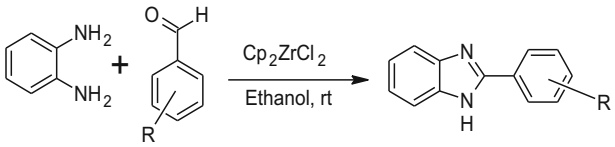
The plausible mechanism of Cp_2ZrCl_2 catalyzed synthesis of 2-substituted benzimidazoles from *o*-phenylenediamine and benzaldehyde with the probable sequence of events is shown in Scheme 2. In the beginning, Cp_2ZrCl_2 coordinates with the carbonyl group of benzaldehyde causing its electrophilic activation, which facilitates nucleophilic attack of the amino group from *o*-phenylenediamine leading to formation of the intermediate (II) which loses a water molecule and undergoes subsequent air oxidation to form the desired product.

In order to show the advantages of Cp_2ZrCl_2 in comparison with other catalysts used for similar reaction, we have summarized several results for the preparation of 2-phenyl-1*H*-benzimidazole from *o*-phenylenediamine and benzaldehyde in Table 4. It is clear that Cp_2ZrCl_2 is highly effective catalyst for the synthesis of 2-substituted benzimidazole derivatives at ambient temperature.

Conclusion

We have described a one-pot, simple, and efficient method for the synthesis of benzimidazole derivatives using *o*-phenylenediamine and a variety of aryl aldehydes at ambient temperature by using a catalytic amount of Cp_2ZrCl_2. The present protocol offers several advantages such as high yield, operational simplicity, shorter reaction times, mild reaction conditions, and a simple experimental and workup procedure.

Table 3 Cp_2ZrCl_2 catalyzed reaction of *o*-phenylenediamine and aryl aldehydes



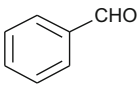
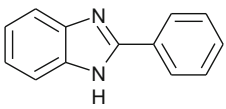
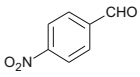
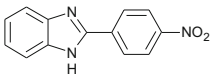
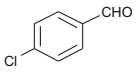
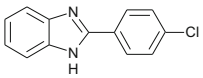
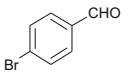
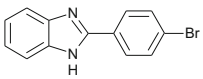
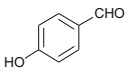
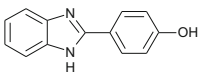
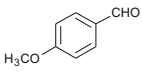
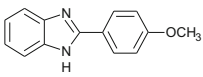
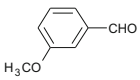
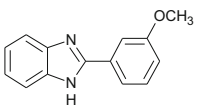
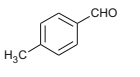
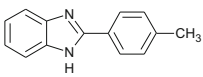
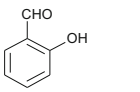
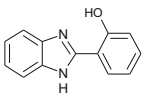
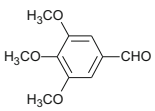
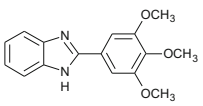
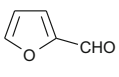
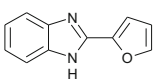
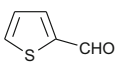
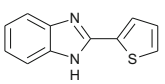
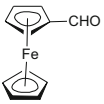
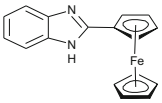
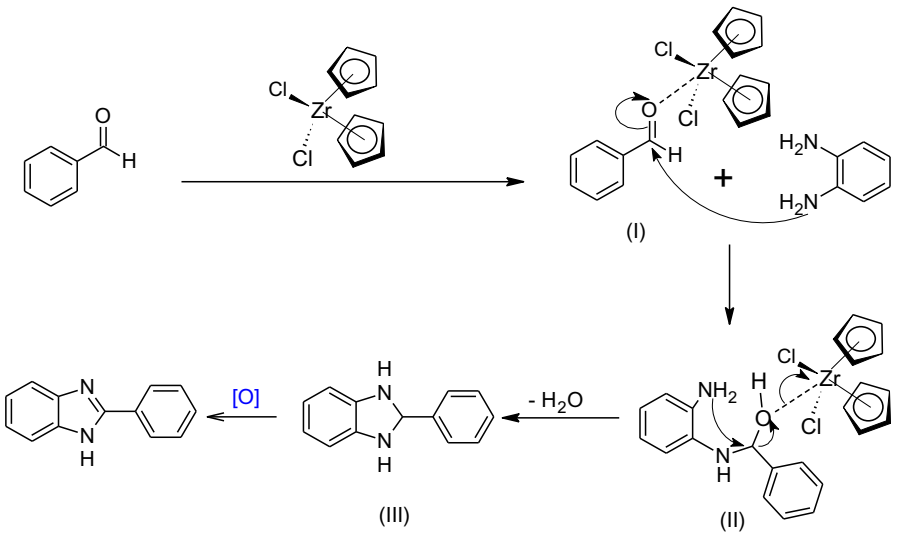
Entries	Aryl aldehyde	Product	Time (min)	Yield %[a]	Mp (°C) [References]
1			90	94	290–292 (290–293) [44]
2			80	92	>300 (322–323) [44]
3			75	94	300–302 (301) [45]
4			80	85	281–283 (283–284) [46]
5			110	88	252–255 (254–256) [47]
6			90	90	223–225 (223–226) [49]
7			95	87	212–214 (214–215) [50]
8			95	87	268–270 (270) [50]
9			100	82	238–240 (242) [48]
10			110	75	260
11			85	82	283–284 (284–286) [51]
12			90	86	>300 (330) [49]

Table 3 continued

Entries	Aryl aldehyde	Product	Time (min)	Yield %[a]	Mp (°C) [References]
13			90	85	208–210

Reaction conditions: *o*-phenylenediamine (1 mmol), aryl aldehyde (1 mmol), and Cp_2ZrCl_2 (5 mol%) in ethanol (5 mL) were stirred at room temperature

[a] Isolated yields of purified products



Scheme 2 Plausible mechanistic pathway for the formation of 2-phenyl-1*H*-benzimidazole

Table 4 Comparison of a variety of catalysts for the reaction of *o*-phenylenediamine and aryl aldehyde

Sr. no.	Catalyst used	Amount of catalyst	Temp (°C)	Time	Yield (%)	References
1	UHP/I_2	20 mol%	70	30 min	87	[32]
2	$CeCl_3{\cdot}7H_2O$	0.3 eqvt.	RT	2.5 h	87	[33]
3	Saccharose	20 mol%	45	1 h	80	[34]
4	$CoCl_2{\cdot}6H_2O$	10 mol%	RT	4 h	81	[39]
5	Zeolite	800 mg	130	10 h	54	[41]
6	NH_4OAc	100 mol%	75	4.5 h	95	[48]
7	$MgCl_2{\cdot}6H_2O$	10 mol%	60	100 min	93	[52]
8	Cp_2ZrCl_2	5 mol%	RT	1.5 h	94	This work

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