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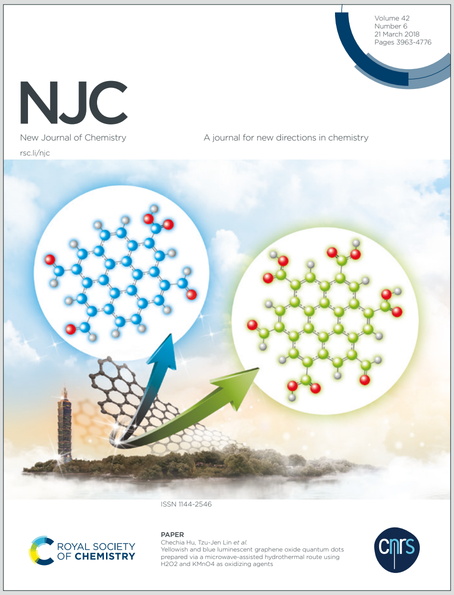

Volume 42
Number 6
21 March 2018
Pages 3963-4776

NJC
New Journal of Chemistry
rsc.li/njc

A journal for new directions in chemistry

ISSN 1144-2546

ROYAL SOCIETY OF CHEMISTRY

PAPER
Chechia Hu, Tzu-Jen Lin *et al.*
Yellowish and blue luminescent graphene oxide quantum dots prepared via a microwave-assisted hydrothermal route using H2O2 and KMnO4 as oxidizing agents

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ARTICLE

Direct synthesis of 2-substituted benzimidazoles via dehydrogenative coupling of aromatic-diamine and primary alcohol catalyzed by Co Complex

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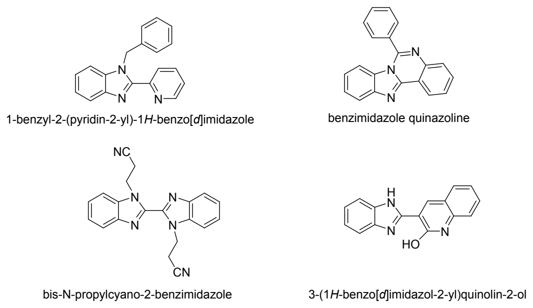
A Co (II) complex with stable structure was designed and synthesized with quinalic acid and Co $(OAc)_2{\cdot}4H_2O$. The single crystal structure of complex was characterized by X-ray diffraction. A dehydrogenative coupling of aromatic diamines and primary alcohols was developed by using the Co (II) complex as the catalyst to synthesize 2-substituted benzimidazole. A series of 2-substituted benzimidazole were obtained with good to excellent yields under mild reaction conditions. In addition, a compound with inhibit Parkinson's activity was synthesized on the gram-scale by using the method. Finally, the reaction mechanism was proposed and the energy changes in the reaction process were simulated by density functional theory (DFT).

INTRODUCTION

Benzimidazole, as an important class of biologically active heterocyclic compounds,[1] is an important structural unit of many anticancer drugs, antiviral drugs, psychotropic drugs, drugs for treating coronary heart disease, and drugs for treating Alzheimer's disease.[2,3] Benzimidazole and its derivatives have good biological activity and have important application value in anti-cancer, antibacterial and de-worming.[4,5] They are widely used in pharmaceutical and pesticide fields, and can also be used as important organic synthesis intermediates (**Scheme 1**), for example, 1-benzyl-2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole (anti-PD),[6] benzimidazole quinazoline (bacteriostatic).[7] In addition, benzimidazole compounds can emit characteristic fluorescence, which can be used as a fluorescent chemical sensor to detect metal ions. For example, bis-N-propylcyano-2-benzimidazole (fluorescent material),[8] 3-(1*H*-benzo [*d*] imidazol-2-yl) thiophene-2-ol (fluorescent sensor).[9] It is because of the significance and application of benzimidazole that the synthesis of these compounds is particularly important.

Benzimidazole and its derivatives are usually prepared by condensation of 1, 2-diaminobenzene and carbonyl derivatives.[10] However, these processes are subject to application limitations because they often require strong acidic or alkaline conditions and stoichiometric oxidants and complicated catalysts, [11-14] as well as low atomic utilization and poor functional group compatibility, and produce stoichiometric salt waste. [15] Therefore, it is an important goal to develop a synthetic method that is efficient, environmentally friendly and avoiding multi-step operations. [16]

In this case, transition metal-catalyzed dehydrogenation coupling reaction of renewable alcohols with 1,2-diaminobenzene become another synthetic method for benzimidazoles.[17-21]



Scheme 1 Representative compounds with a benzimidazole structure skeleton

In 2018, Kaliccharan Das and co-workers [22] synthesized a series of 2-substituted benzimidazole using *o*-phenylenediamine and benzyl alcohol as substrates and Mn(I) NNS- donor Complex as catalyst at 140°C (**Scheme 2a**). In the same year, Lin li and co-workers[23] synthesized benzimidazole with *o*-phenylenediamine and benzyl alcohol as substrates and Ru (II) NNN- donor Complex as catalyst at 165°C (**Scheme 2b**). In 2019, Kaushik Chakrabarti and co-workers [24] prepared 2-substituted

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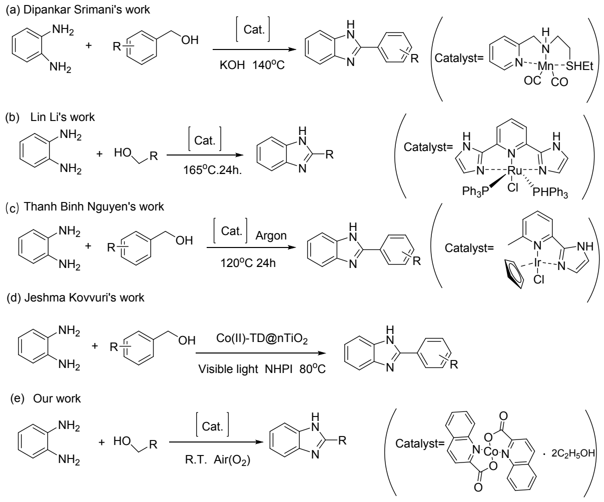
DOI: 10.1039/D0NJ02619F

benzimidazole with *o*-phenylenediamine and benzyl alcohol as substrates using Ir(II) N,N-type catalysts at 120°C (**Scheme 2c**). In addition, some research groups have also achieved synthesis of 2-substituted benzimidazole using visible light catalysis. For example, in 2018, Ameneh Eskandari and co-workers [25] synthesized a series of benzimidazole and its derivatives at 80°C with *o*-phenylenediamine and benzyl alcohol as substrates, Co(II)-TD@nTiO$_2$ as photocatalyst and NHPI as additive(**Scheme 2d**).

Although these works were effective, they were limited by noble metal catalysts and harsh reaction conditions, and most of these metal complexes require Clip-on ligands, such as tridentate NNS, PNN ligands and NNN ligands. These ligands are not only expensive and sensitive to air, but also difficult to synthesize. The photocatalytic synthesis method was used to solve the problem of harsh reaction conditions, but the synthesis steps of photocatalyst were also very complicated, and the oxidant was added in the reaction process, which increased the operation steps of the reaction.

Based on the above problems, it is necessary to design and synthesize a catalyst for the efficient synthesis of benzimidazoles. Therefore, Co (II) N, O Complex was designed and synthesized, because cobalt is abundant and has good catalytic activity and low pollution. At the same time, the synthesized Co (II) Complex was structurally stable in the air. The synthesized Co (II) Complex was used as the catalyst to prepare a series of 2-substituted benzimidazole and its derivatives with *o*-phenylenediamines and primary alcohols or benzyl alcohols as substrates at room temperature **(Scheme 2e)**. In addition, the reaction mechanism was explored by the energy changes of the whole reaction using DFT calculation.



Scheme 2 The method for synthesis of 2-substituted benzimidazoles

RESULTS AND DISCUSSION

The synthesized cobalt complex was characterized by X-ray single crystal analysis. The ORTEP of the molecular structure of the Co $(C_{10}H_{10}NO_2)_2(2C_2H_5OH)$ Complex was shown in **Figure 1** and the crystal data was listed in the support information. X-ray diffraction analysis indicated that the Co $(C_{10}H_{10}NO_2)_2(2C_2H_5OH)$ Complex crystallized in the monoclinic system and the space group $P\ 2_1/c$. The molecular structure of the complex contained a Co atom and two quinoline-2-carboxylic acid (Ligand) units, and the Co atom consisted of two quinoline nitrogen (N1, and N2) atoms and two ketone oxygens (O1, O2,) atoms. The novel Co (II) Complex as a catalyst for synthesis of a series of 2-substituted benzimidazoles and their derivatives was evaluated in this paper. (NMR, FTIR, UV-Vis, elementary analysis and mass spectrometry data are in the support information)

The structure of the complex is shown in the figure. The Co ion in the complex forms a six-coordinated octahedral configuration with the four O atoms and two N atoms of the quinalidic acid ligand; the complex is a symmetrical structure as a whole. (CShM=0.821, CShM value is calculated by Shape software) [26,27] From a horizontal perspective, Co-N1 = 2.200 Å, Co-O2 = 2.014 Å; vertical Co-O2 = 2.103 Å, it can be seen that the average value of atoms in the horizontal direction is greater than the average value in the vertical direction, the atoms at the level are far away from Co ions, which greatly increases the catalytic efficiency.

Figure 1 The molecular structure of Co $(C_{10}H_{10}NO_2)_2(2C_2H_5OH)$ Complex

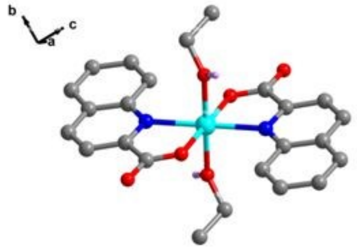
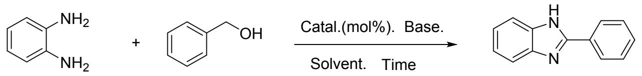


Table 1 Optimization of the reaction conditions of o-phenylenediamine and benzyl alcohol [a]



Entry	Catal.(mol%)	Solvent	Base	Time(h)	Yield (%)[b]
1	Complex(0.2mol)	CH_3CN	Na_2CO_3	2	75%
2	$CoCl_2$	CH_3CN	Na_2CO_3	2	35%
3	$Co(OAc)_2$	CH_3CN	Na_2CO_3	2	65%
4	**Complex(0.4mol)**	**CH_3CN**	**Na_2CO_3**	**2**	**92%**
5	Complex(0.6mol)	CH_3CN	Na_2CO_3	2	92%
6	Complex(0.4mol)	DCM	Na_2CO_3	2	75%
7	Complex(0.4mol)	DCE	Na_2CO_3	2	72%
8	Complex(0.4mol)	Toluene	Na_2CO_3	2	70%
9	Complex(0.4mol)	DMF	Na_2CO_3	2	45%
10	Complex(0.4mol)	DMSO	Na_2CO_3	2	46%
11	Complex(0.4mol)	CH_3CN	KOH	2	45%
12	Complex(0.4mol)	CH_3CN	Cs_2CO_3	2	50%
13	Complex(0.4mol)	CH_3CN	Na_2CO_3	1	72%
14	Complex(0.4mol)	CH_3CN	Na_2CO3	3	93%

[a] *o*-phenylenediamine (1.0 mmol), benzyl alcohol (1.0 mmol), Co(II) Complex (0.4 mol%), base (0.5 mmol), room temperature. [b] Isolated yields.

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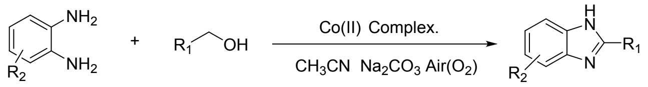
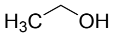
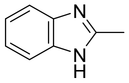
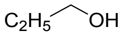
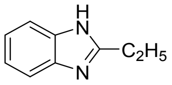
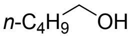
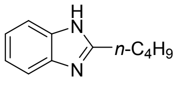
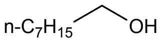
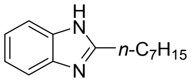
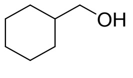
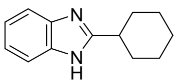
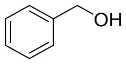
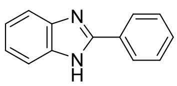
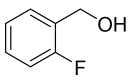
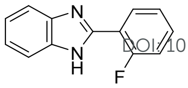
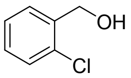
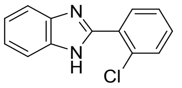
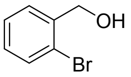
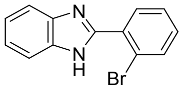
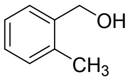
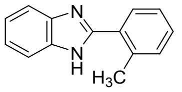
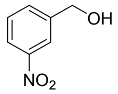
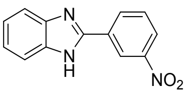
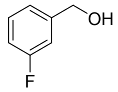
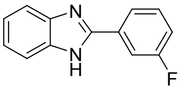
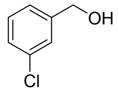
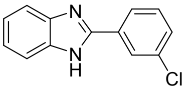
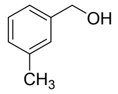
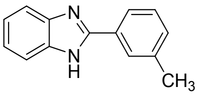
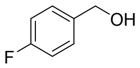
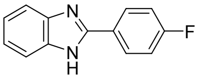
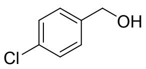
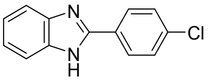
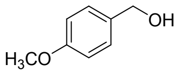
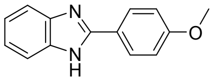
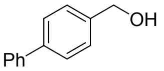
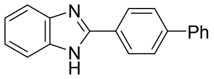
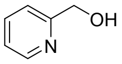
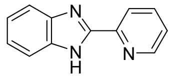
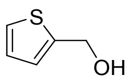
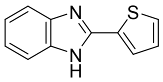
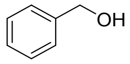
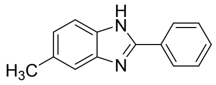
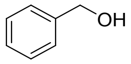
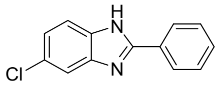
DOI: 10.1039/D0NJ03619F

Based on the initial experiments, *o*-phenylenediamine and benzyl alcohol were used as the substrates to optimize the reaction conditions, and results were summarized in **Table 1**. Primordially, the Co (II) Complex was used as a catalyst to afford corresponding product in 75% yield (**Table 1**, entry 1). Other Co (II) catalysts were also investigated; $CoCl_2$ and Co $(OAc)_2$ only gave the product in 35% and 65% yields, respectively (**Table 1**, entries 2-3). Then the amount of the complex catalyst was evaluated, when the complex was 0.4mol% equivalent of the substrate, the yield of the reaction reached 92%, but with the continuous increase of catalyst to 0.6mol%, the yield showed no significant change (**Table 1**, entries 4-5).

Subsequently, reaction solvents were investigated. Dichloromethane (DCM), 1,2-dichloroethane (DCE) and toluene as the solvents gave the product in 75%, 72%, and 70% yields, respectively (**Table 1**, entries 6-8). The use of N, N-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) only gave lower yields in 45%, 46% (**Table 1**, entries 9-10), while the use of acetonitrile (CH_3CN) gave a good yield in 92% (**Table 1**, entry 4). Then, different bases were investigated. The use of Na_2CO_3 gave a good yield in 92% (**Table 1**, entry 4), but when KOH and Cs_2CO_3 were used, the yields reduced to 45% and 50%, respectively (**Table 1**, entries 11-12). Finally, it was found that the reaction time was shortened to 1h, the yield was reduced to 72%, and the yield of the target product was not significantly improved by increasing to 3h (**Table 1**, entries 13-14).

Table 2 Substrate scope of condensation cyclization of benzyl alcohol and o-phenylenediamine [a]



Entry	Substrates	Products	Yield(%)[b]
1			75
2			72
3			68
4			65
5			79
6			92
7			82
8			85
9			88
10			80
11			89
12			86
13			88
14			83
15			90
16			91
17			83
18			88
19			76
20			73
21			90
22			91

[a] o-phenylenediamine (1.0 mmol), primary alcohol (1.0 mmol), Co(II) Complex (0.4 mol%), CH_3CN (10 ml), Na_2CO_3 (0.5 mmol.), at room temperature for 2h. [b] Isolated yields.

Base on above experimental results, it was determined that the optimal reaction system was *o*-phenylenediamine and benzyl alcohol as the reaction substrates, Co (II) Complex as

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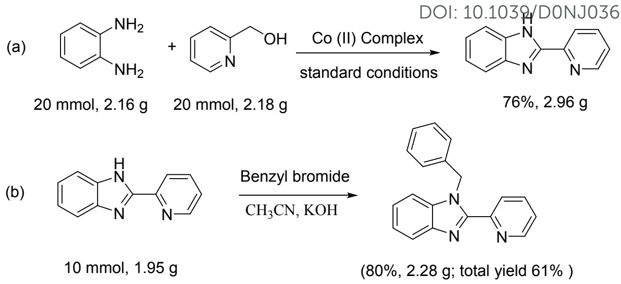
catalyst, CH_3CN as solvent, Na_2CO_3 as base, at room temperature for 2h.

With the optimized reaction conditions in hand, we turned our attention toward the scope of the substrates, and the results were summarized in **Table 2**. Firstly, aliphatic alcohols including ethanol, *n*-propanol, *n*-pentanol, *n*-octanol and cyclohexylmethanol were used as the reaction reagents to afford corresponding products with yields of 75%, 72%, 68%, 65% and 79%, respectively (**Table 2**, entries1-5). Then, aromatic alcohols were investigated. Benzyl alcohol without a substituent gave the product in a yield of 92% (**Table 2**, entry6). For *ortho*-substituents, electron-withdrawing groups (-F, -Cl and -Br) gave the corresponding product in 82%, 85% and 88% yields, respectively (**Table 2**, entries7-9), meanwhile electron-donating group (-Me) gave a yield of 80% (**Table 2**, entry 10). For *meta*- substituents, electron-withdrawing groups ($-NO_2$, -F, -Cl) gave the corresponding products in 89%, 86% and 88% yields, respectively (**Table 2**, entries11-13), electron-donating group (-Me) gave the corresponding product in 83% yield (**Table 2**, entry 14). For *para*-substituents, electron-withdrawing groups (-F, -Cl) gave the corresponding products in 90% and 91% yields, respectively (**Table 2**, entries15-16), electron-donating groups (-OMe, -Ph) gave the yields of 83% and 88%, respectively (**Table 2**, entries17-18). In addition, pyridin-2-ylmethanol and thiophen-2-ylmethanol also gave the corresponding products in 76% and 73% yields (**Table 2**, entries19-20).

According to the above experimental results, it was found that the reactivity of aliphatic alcohols was not as high as that of aromatic alcohols. This is because aromatic alcohols are more conducive to dehydrogenation than aliphatic alcohols to form aromatic aldehydes. For the substituents of aromatic alcohols, the reactivity of electron-withdrawing groups was higher than that of electron-donating groups. This is because the electron -withdrawing groups are advantageous to the dehydrogenation of aromatic alcohols to form aromatic aldehydes. In addition, the yield of *ortho*-substituents was slightly lower than that of *para*- and *meta*-substituents due to steric hindrance effect. Finally, when the substrates were benzyl alcohol, different substituents of *o*-phenylenediamine were investigated. Both electron-donating group (-Me) and electron-withdrawing group (-Cl) afforded good yields of 90% and 91% (**Table 2**, entries 21-22).

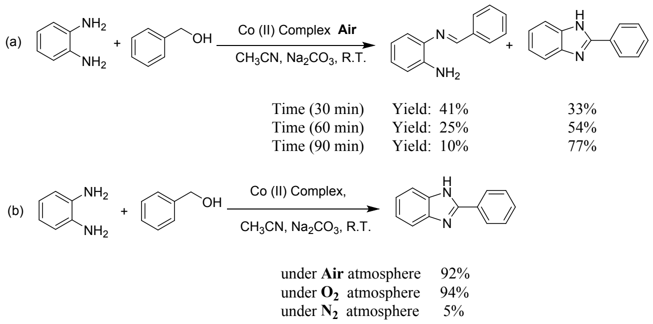
In order to further demonstrate the practicability of the catalytic system, a gram-scale reaction of *o*-phenylenediamine and pyridin-3-ylmethanol was implemented, the target product 2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole was obtained in 76% yield **(Scheme 3a)**. Then, 2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole was used as raw material to synthesize 1-benzyl-2-phenyl-1*H*-benzo[*d*]imidazole, which has an inhibitory effect on Parkinson's biological activity.[28] According to previous literatures,[29,30-36] 1-benzyl-2-phenyl-1*H*-benzo[*d*]-imidazole was obtained in a low yield and complicated conditions. Compared with the previously reported method, our protocol is more convenient and efficiently to obtain the target product with the total yield of 61% **(Scheme 3b)**.



Scheme 3 Application of synthesis of 1-benzyl-2-phenyl-1*H*-benzo[*d*]imidazole

In order to further understand the reaction mechanism, the following control experiments were carried out as shown in **Scheme 4**.The reaction time was adjusted to 30, 60 and 90 minutes, and the yields of the intermediate product 2-(benzylamine) aniline were 41%, 25% and 10%, respectively, while the yields of 2-phenyl-1*H*-benzo (*d*) imidazole were 33%, 54% and 77%, respectively **(Scheme 4a)**. The results showed that 2-(benzylideneamino) aniline is an important intermediate for synthesis of 2-phenyl-1*H*-benzo (*d*) imidazole. Then the control experiments were performed in different reaction atmospheres. It was found that the yields of the product were obtained in 92% and 94% under air atmosphere and O_2 atmosphere, while the reaction was inhibited under N_2 atmosphere to afford only a yield of 5% **(Scheme 4b)**. Therefore, O_2 in air atmosphere is necessary in this reaction system.

Scheme 4 Control Experiments



On the basis of experimental results and previous literatures reported,[14,26-27] a plausible mechanism for synthesis of 2-substituted benzimidazole catalyzed by the Co(II) Complex is described in **Scheme 5**. Initially, Co (II) Complex catalyzes benzyl alcohol (IMA) to form benzaldehyde (IMB) by a process of dehydrogenation. Subsequently, benzaldehyde reacts with o-phenylenediamine to obtain 2-(benzylideneamino) aniline (IMC) by a coupling reaction, and furtherly reacts to form a cyclic intermediate (IMD) by a cyclization. Finally, the cyclic intermediate is furtherly catalyzed by Co (II) Complex to obtain the product 2-phenyl-1*H*-benzo (*d*) imidazole (IME) by a process of dehydrogenation. During catalytic cycle, O2 in the air atmosphere can oxidize the formed Co (I) Complex to regenerate the catalyst Co (II) Complex.

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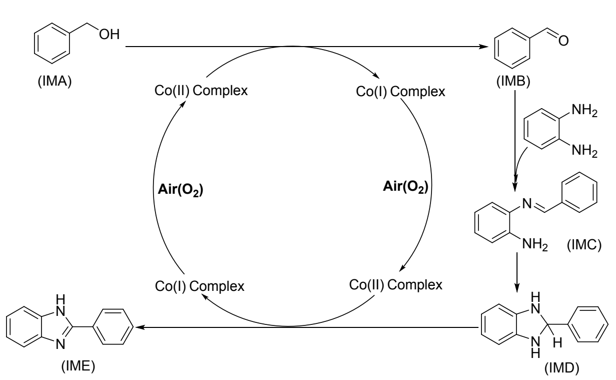

Scheme 5 Proposed Mechanisms

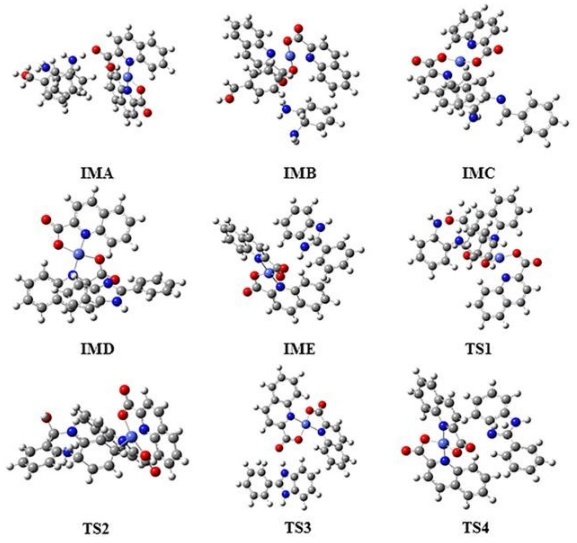

Figure 2 Optimized structures of reactants, intermediates and products

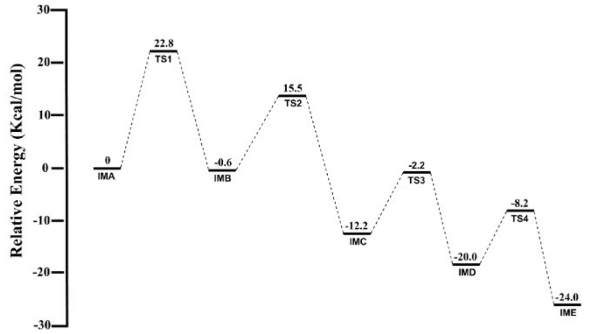

Figure 3 Energy barrier diagram

In addition, based on the above reaction mechanism, the DFT calculation method [24,37] was used to calculate the energy changes of each reaction step to verify the correctness of the reaction mechanism. IMB is formed by the release of hydrogen from IMA through TS1 with relative energy of 22.8 Kcal/mol. IMC is formed by the release of a molecule of H_2O from IMB through TS2 with relative energy of 16.1 Kcal / mol. IMC generates IMD through TS3 with relative energy of 10 Kcal / mol. Finally, IMD produces the target product IME by the dehydrogenation through TS4 with relative energy of 11.8 Kcal / mol. Therefore, the DFT calculation method more specifically confirms the rationality of the reaction mechanism **(Figure 2** and **Figure 3)**.

CONCLUSION

In summary, the stable Co (II) Complex was synthesized by using cheap raw materials of quinalic acid and Co $(OAc)_2{\cdot}4H_2O$. Its single crystal structure was characterized by X-ray diffraction. The Co (II) Complex was used as catalyst to directly synthesize a series of 2-substituted benzimidazoles with *o*-phenylenediamines and primary alcohol as the substrates under mild reaction conditions. In addition, we discussed the mechanism of the reaction and simulated the energy change during the reaction by using density functional theory (DFT). Our laboratory is designing cheaper and more efficient catalysts and studying their applicability in other reactions.

Experimental

Synthesis of complex

Quinadinoic acid (1.0 eq, 1g) and Co $(OAc)_2{\cdot}4H_2O$ (1.2 eq, 2.42g) were mixed into a 100mL round bottom flask, then 30mL of distilled water and 30mL of ethanol were added, and stirred at room temperature for 30 minutes. Then the mixture was transferred to a water bath, heated at 70^oC for 4 hours and filtered three times to obtain a clear solution. Finally, the clear solution was divided into test tubes and volatilized. After 72 hours of diffusion with ether solvent, 0.95 g of pink transparent crystals was obtained with a yield of 95%.

Catalytic reaction process

Benzyl alcohol (1.0 mmol), *o*-phenylenediamine (1.0 mmol), CH_3CN (10 mL), Na_2CO_3 (0.5 mmol) and Co (II) Complex (0.40 mol%) were added into a 25 ml flask. The mixture was stirred at room temperature for 2h. After the reaction was completed, the reaction mixture was extracted 3 times with ethyl acetate (3×15 mL). The combined organic layer was dried with anhydrous sodium sulfate. After removing the solvent by rotary evaporation, the residue was purified by column chromatography (petroleum ether / EA = 20: 1 as eluent).

Computational Method

The calculations were carried out by performing DFT by use of the B3LYP functional with the 6-31G (d) basis set as implemented in Gaussian 09 program package. All geometries for the reactants, products, intermediates, and transition states have been fully optimized. Vibrational frequency calculations have been performed for each optimized structure at the same level to identify the nature of all the stationary points (local minimum or first-order saddle point).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Fund of Natural Science Foundation of Heilongjiang Province of China (No. B2018012).

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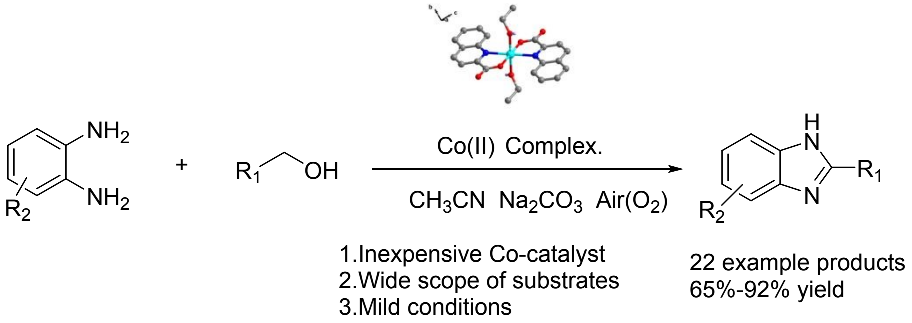

A Co (II) complex with low price was designed and synthesized with quinalic acid and Co $(OAc)_2{\cdot}4H_2O$. The catalyst was relatively easy to synthesize and did not require complex reaction conditions. The single crystal structure of was characterized by X-ray diffraction. A dehydrogenative coupling of aromatic diamines and primary alcohols was developed by using the Co (II) complex as the catalyst to synthesize 2-substituted benzimidazole. In addition, we discussed the mechanism of the reaction and simulated the energy change during the reaction by using density functional theory (DFT). Finally, a compound with inhibit Parkinson's activity was synthesized on the gram-scale by using the method.