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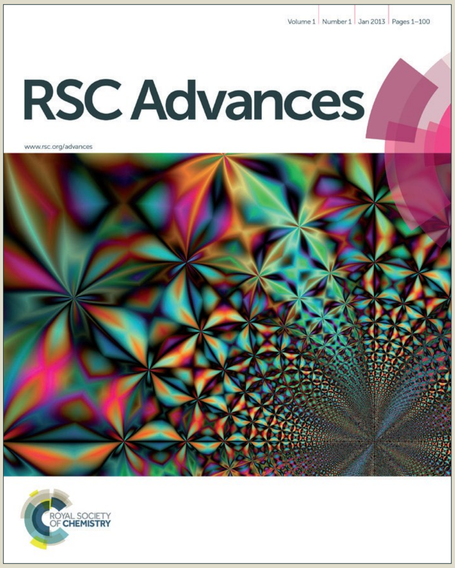

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PAPER

Cu-Pd/γ-Al_2O_3 Catalyzed the Coupling of Multi-step Reaction: Direct Synthesis of Benzimidazole Derivatives

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The coupling of multi-step reaction catalyzed by heterogeneous catalyst is an important path to accomplish some unconventional chemical transformations. Since the starting materials generated from previous steps were adsorbed on the catalyst, the activation energy of following step was largely decreased, and thus the reaction conditions were more mild and environmental friendly. Catalyzed by multifunctional Cu-Pd/γ-Al_2O_3 catalyst, the hydrogenation transfer and successive cyclization coupling reaction from *o*-nitroaniline and alcohol to afford benzimidazole derivatives in high yield was realized. The catalyst could be reused for several times without loss of activities. The synergies of reforming hydrogenation of Cu-Pd bimetal and support acidity of γ-Al_2O_3 were responsible for this catalytic transformation.

Introduction

The synthesis of complex organic compounds often required multi-step reaction, in which harsh reaction conditions and complex catalysts were frequently used in several steps. In recent decades, use of easily recyclable solid acid replacing liquid acid in the acid-catalyzed reaction was largely developed and considered as a major goal of green chemistry.[1] The reactants generated from previous step were *in situ* adsorbed on the catalyst surface, which reduced the activation energy for the subsequent steps of the catalyst acidic requirements (Fig. 1).

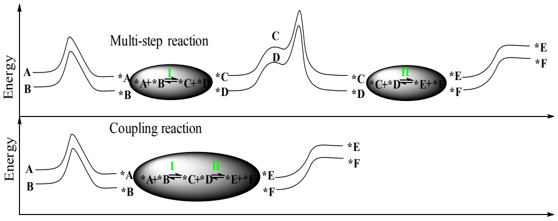

Fig. 1 Possible mechanism of coupling reaction

The gas-liquid-solid three-phase catalytic hydrogenation for the reduction of nitro compounds to amines is an important and conventional technology.[2] The solvent, hydrogen, noble metal catalyst is essential in this catalytic transformation. Although this method is effective, the main drawback is high pressure and temperature, equipment requirements, and at the same time transfer and transport of hydrogen is tedious and dangerous. Recently Dumesic[3-8] reported a new hydrogen production method based on transition or noble metal-catalyzed aqueous-reforming technology. Thus, this liquid-solid two phase catalytic transfer hydrogenation provides an efficient route to replace the three-phase catalytic hydrogenation for certain reactions. Use of *in situ* produced and adsorbed hydrogen on catalyst, nitro compounds are successfully reduced to amines[9,10] by this method. And by tuning the acid-base and surface characteristics of support, the multi-step successive coupling reactions of adsorbed intermediates on catalyst may be realized. According to these requirements, modified multifunctional heterogeneous catalyst is an important means to realize this kind of coupling reactions. Based on these, recently the direct reductive *N*-alkylation of nitrobenzene catalyzed by Raney Ni[11] and synthesis of quinoline derivatives from nitrobenzene and alcohol catalyzed by Cu-Pd/γ-Al_2O_3 was successfully established[12] by our group.

Heterocycles are ubiquitous intermediates for the synthesis of pharmaceuticals,[13-15] dyes,[16,17] organic functional materials[18,19]. Among these, the five-membered nitrogen heterocycles, especially benzimidazole derivatives, are widely applied in fungicidal[20] and pharmaceutical[13-15]. Normally, the condensation of *o*-phenylenediamine with acid derivatives or *o*-phenylenediamine with aldehydes in the presence of an

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appropriate oxidant is a typical way for the synthesis of benzimidazole[21-24]. However, the traditional methods mostly suffer from use of strong inorganic acid, formation of large amount of waste, difficult recycling of catalyst, and low atom economy.

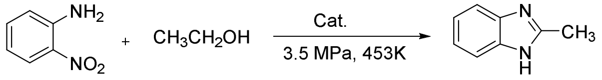
Comply with the green chemistry trend, heterogeneous catalytic systems[25-37] and microwave technology[26,31,38,39] were applied for the synthesis of benzimidazoles recently, such as using P-Mo or P-W heteropoly acid,[26,35] modified zeolite,[27,28] mesoporous Si-Al material,[29] transition metal oxides,[30,31] alumina supported potassium fluoride[36] and supported noble metal[37,39] as catalysts, and using air or oxygen as oxidant[40,41]. For instance, Gadekar[27] reported that modified zeolite catalyst gave 83~96% yield of benzimidazoles from *o*-phenylenediamine and aldehydes. Rathod[31] reported that benzimidazoles were obtained in 92~94% yield from *o*-phenylenediamine and aromatic aldehyde using MoO_3/CeO_2-ZrO_2 as catalyst under solvent free condition. Compared with *o*-phenylenediamines, *o*-nitroanilines are more readily available substrates. The reductive cyclization of *o*-nitroaniline with carbonyl derivatives or alcohols is another pathway for the synthesis of benzimidazole.[42-50] The direct continuous catalysis in one pot including dehydrogenation of alcohols, successive reduction of *o*-nitroaniline and cyclization simplified the synthesis process obviously. Based on this concept, Sun[50] reported the synthesis of benzimidazole derivatives using methanol both as solvent and carbon source under supercritical condition over copper-doped porous metal oxide catalysts. However, the yield of benzimidazole and *N*-methylbenzimidazole were 82% and 11% respectively, and the purify procedure was tedious. Selvam[44] reported the one-pot photocatalytic synthesis of disubstituted benzimidazoles from *N*-substituted 2-nitroanilines or 1,2-diamines with good yield (40~96%) over Pt-TiO_2 catalyst using solar and UV-A light. The efficiency and yield of target product were found to be higher in UV light than in solar light.

Herein we wish to disclose a convenient way to synthesize benzimidazole derivatives in moderate to excellent yields from *o*-nitroaniline and alcohol catalyzed by Cu-Pd/γ-Al_2O_3. The catalysts are rationally designed by the cooperative catalysis concept, where the metal center acts as dehydrogenation and hydrogenation site while the weak acid site acts for the condensation process.

Results and discussion

Firstly, monometallic or bimetal nanoparticles supported on γ-Al_2O_3 were synthesized. Subsequently, ethanol and *o*-nitroaniline was chosen as a model compound to evaluate the catalytic activity of catalyst, and the results were listed in Table 1. Monometallic Pd (5% weight amount) loaded on γ-Al_2O_3 as a catalyst gave very low conversion and yield (entry 1). However, upon alloying palladium with copper, activity of catalysts improved greatly, and different Pd/Cu ratio does not result in significant difference in activity or yield. 2-methylbenzimidazole was selectively obtained in 98.2% yield catalyzed by Cu_5-Pd_5/γ-Al_2O_3 (entry 4). Since monometallic Cu/γ-Al_2O_3 was totally inactive for this reaction (entry 6), the improved performance of Cu-Pd/γ-Al_2O_3 catalyst can be ascribed to the modification of palladium properties by alloying with copper. Changing the bimetal component to Cu-Ni, Cu-Pt, Fe-Pd, Fe-Pt, Zn-Ni, the conversion and yield are disappointing (entries 7-11). Use of 5% weight amount of Zn and Pd loaded on γ-Al_2O_3, only moderate conversion and yield were obtained (entry 12). From these, it can be concluded that Ni or Pt show lower dehydrogenation and hydrogenation performance, compared with that of Pd.

Table 1 Evaluation of the catalytic activity of metal component



Entry	Catalyst	Con. (%)	Yield[a] (%)	Selectivity (%)
1	Pd/γ- Al_2O_3	6.5	6.5	100
2	Cu_5-Pd_1[b]/γ-Al_2O_3	23.0	21.9	95.2
3	Cu_5-Pd_3/γ-Al_2O	69.4	68.2	98.3
4	Cu_5-Pd_5/γ-Al_2O_3	100	98.2	98.2
5	Cu_5-Pd_{10}/γ-Al_2O_3	100	95.4	95.4
6	Cu/γ-Al_2O_3	-	-	-
7	Cu-Ni/γ-Al_2O_3	23.5	22.5	95.7
8	Cu-Pt/γ-Al_2O_3	18.7	14.6	78.1
9	Fe-Pd/γ-Al_2O_3	63.0	12.2	19.4
10	Fe-Pt/γ-Al_2O_3	21.3	8.7	40.8
11	Zn-Ni/γ-Al_2O_3	12.0	10.2	85.0
12	Zn-Pd/γ-Al_2O_3	73.5	52.0	70.7

Reaction conditions: 1 g of catalyst and 5% loading for each metal, 6 g of *o*-nitroaniline, 100 mL of ethanol, 50 mL of H_2O, 453 K, 3.5 MPa, 12 hrs, 900r/min. [a] checked by HPLC. [b] 1% loading for Pd.

Then different supports were estimated (Table 2). The 5% weight amount of Cu and Pd loaded on α-Al_2O_3 or γ-Al_2O_3 as the catalysts were used to check the effect of different alumina carriers on this reaction. The more acidic γ-Al_2O_3 support gave better result and yield of 2-methylbenzimidazole could be reached 98.2% (entry 2). The selectivity and yield of 2-methylbenzimidazole are very low when MgO were used as a support, maybe because alkaline MgO support is disadvantage for the condensation of aldehyde and *o*-

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phenylenediamine. Use of activated carbon as a support gave slightly high yield (entry 4). TiO_2 or CeO_2 as the supports gave only moderate selectivity, compared with that of γ-Al_2O_3 (entries 5-6).

Table 2 Effect of support on this reaction

Entry	Catalyst	Conversion (%)	Yield (%)[a]	Selectivity (%)
1	Cu-Pd/α-Al_2O_3	73.0	42.2	57.8
2	Cu-Pd/γ-Al_2O_3	100	98.2	98.2
3	Cu-Pd/MgO	59.5	8.5	11.7
4	Cu-Pd/C	72.9	38.7	53.1
5	Cu-Pd/TiO_2	62.8	40.3	64.2
6	Cu-Pd/CeO_2	95.6	70.1	73.3

Reaction conditions: 1 g of catalyst and 5% loading for each metal, 6 g of *o*-nitroaniline, 100 mL of ethanol, 50 mL of H_2O, 453 K, 3.5 MPa, 12 hrs, 900 r/min. [a] checked by HPLC

In addition, the recovery and reuse of the developed Cu-Pd/γ-Al_2O_3 catalyst could be achieved by a simple phase separation. The catalyst can be reused for at least 6 times without loss of activity when ethanol and *o*-nitroaniline were used, as shown in Fig. 2. The conversion of each time is 100% and the yield is 97.3%, 96.2%, 97.5%, 95.3%, 96.2% and 95.8%, respectively. This demonstrated that the component, structure and surface characteristic of catalyst are stable after several times of uses.

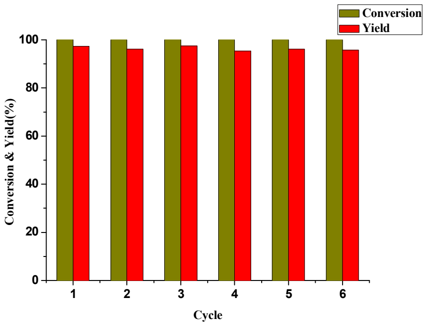

Fig. 2 Recycling of Cu-Pd/γ-Al_2O_3 for the synthesis of 2-methylbenzimidazole. Reaction conditions: 0.8 g of catalyst, 8 g of *o*-nitroaniline, 120 mL of ethanol, 80 mL of H_2O, 453 K, 3.5 MPa, 12 hrs, 900 r/min.

Catalyst characterization

The prepared catalyst was characterized by different techniques to give its structure information. The physical structure parameters of γ-Al_2O_3, fresh Cu-Pd/γ-Al_2O_3 and spent Cu-Pd/γ-Al_2O_3 (reused for 6 times) were measured and results are listed in Table 3. The EDS showed that the Pd and Cu content of fresh Pd-Cu/γ-Al_2O_3 was around 5%, which was in accordance with the theoretical loading. And the metal contents of spent catalyst were very close to fresh catalyst, indicating no obvious metal components loss during the reaction. The BET analysis disclosed that the specific surface area of prepared catalyst is slightly increased. The total pore volume and average pore size were reduced, compared with that of γ-Al_2O_3. And the spent catalyst underwent a very slight loss of surface area and pore volume. TEM and SEM (Fig. 3) results showed that the metal particles were loaded on γ-Al_2O_3 surface with high dispersion, and the average size of metal particles was about 6.9 nm (based on TEM results). Fig. 4 showed X-ray diffraction patterns of Cu-Pd/γ-Al_2O_3. The XRD spectrum showed that at 2θ=41.6°, 48.3° and 71.3°, which were attributed to obvious and weak characteristic diffraction peaks of Cu-Pd bimetal, respectively. The peak of elemental Pd was found at 2θ=39.8°, while the peak of elemental copper could not be found from the XRD spectrum. From these, it is concluded that there has a little elemental palladium existing on the surface of γ-Al_2O_3 support, whereas the existence of copper should be as an alloy of Cu-Pd. Compared with the fresh catalyst, no obvious change was observed for the spent catalyst XRD spectrum, which indicated that Cu-Pd/γ-Al_2O_3 kept constant crystalline phase after reused for 6 times. According to these characterization and recycling test results, it could be confirmed that Cu-Pd/γ-Al_2O_3 remained stable properties and performances in this one-pot synthesis process. In addition, NH_3-TPD analysis revealed that the acidity of prepared catalyst was decreased (Fig. 5).

Table 3 Physical structure parameters of catalysts

Sample	Pd loading[a] (wt%)	Cu loading[a] (wt%)	Surface area (m^2 g^{-1})	Pore volume (cm^3g^{-1})	Average pore diameter (nm)
γ-Al_2O_3	-	-	124.9	0.92	26.54
Cu-Pd/γ-Al_2O_3 (Fresh)	5.58	4.93	139.2	0.69	19.27
Cu-Pd/γ-Al_2O_3 (Spent)	5.53	4.75	129.6	0.61	18.83

[a] Based on EDS results.

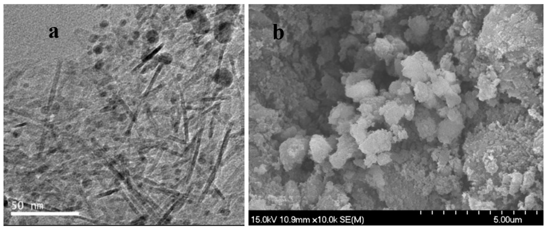

Fig. 3 TEM (a) and SEM (b) images of Cu-Pd/γ-Al_2O_3

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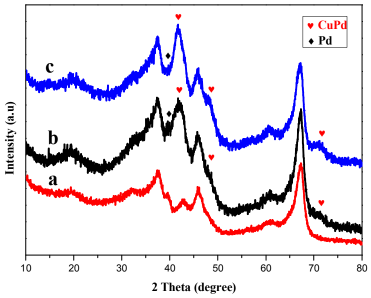


Fig. 4 XRD patterns of (a) γ-Al_2O_3, (b) Cu-Pd/γ-Al_2O_3 (Fresh), and (c) Cu-Pd/γ-Al_2O_3 (Spent)

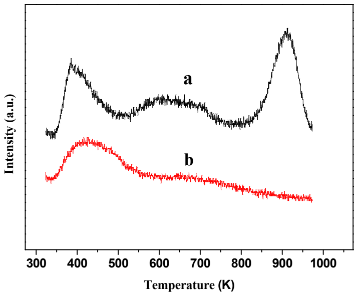
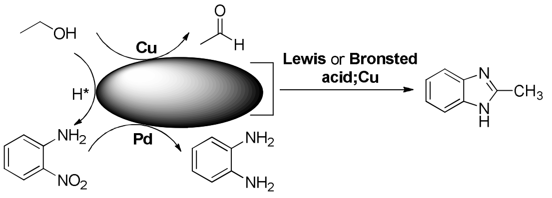


Fig. 5 NH_3-TPD profiles of (a) γ-Al_2O_3 and (b) Cu-Pd/γ-Al_2O_3

Possible reaction mechanism

Based on previous reports[44,46,50-53] and experimental results, the possible mechanism is shown as below (Scheme 1). Dehydrogenation of ethanol is well known to be effectively catalyzed by Cu[50,54-58] which lead to acetaldehyde and active hydrogen that likely be the key intermediates for successive reaction. Subsequently the transfer hydrogenation reduction of *o*-nitroaniline with the adsorbed active hydrogen by Pd gave *o*-phenylenediamine,[10,12] which then condensed with acetaldehyde on Lewis or Bronsted acid center to give Schiff base.[21] The desired product was obtained after molecular nucleophilic cyclization and dehydrogenation on the surface of Pd-Cu/γ-Al_2O_3. Recently, the solid acid such as modified zeolite and transition-metal oxides[27,28,30,31] was reported to be used as the acid catalyst for this condensation process. However, in this work relative weak acidic γ-Al_2O_3 could also successfully act as the acid center for the condensation of *o*-phenylendiamine and acetaldehyde. It may be ascribed to that the *in situ* formed *o*-phenylendiamine and acetaldehyde which adsorbed on the catalyst surface lower the requirements of activation energy and the catalyst acidity. Finally, the corresponding benzimidazole product was obtained by dehydrogenation of dihydrobenzimidazole intermediate which would be usually aided by the alumina supported Cu catalyst.[59] According to the analysis above, it can be concluded that this coupling reaction system was catalyzed by the synergy effect of Cu-Pd/γ-Al_2O_3 catalyst's multiple roles including dehydrogenation (**Cu**), transfer hydrogenation (**Pd**) centers, and Lewis or Bronsted acid sites of γ-Al_2O_3.

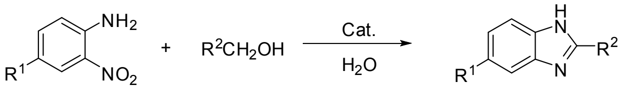


Scheme 1 Possible mechanism for the direct synthesis of 2-methylbenzimidazole from ethanol and *o*-nitroaniline

Synthesis of derivatives

With the optimized conditions in hand, several types of *o*-nitroaniline and alcohol derivatives were tried (Table 4). The methyl or methoxyl substituted *o*-nitroanilines can act as good partners. However yields of the corresponding benzimidazole derivatives were very low, when the chloro or fluoro substituted *o*-nitroaniline was used as the starting material. The reason may be the nucleophilic of amino group was decreased due to electron-withdrawing ability of chloro or fluoro atom. Methanol, ethanol, *n*-propanol, *n*-butanol, benzyl alcohol were all appropriate candidates.

Table 4 Scope of substrate



Entry	R^1	R^2	Cat. (g)	Conversion (%)	Yield (%)[a]
1	H	H	0.8	100	96.5
2	H	Me	0.8	100	97.4
3	H	Et	0.8	100	96.2
4	H	n-Pr	1.2	100	98.7
5	H	Ph	0.8	100	100
6	Me	H	0.8	100	98.7
7	Me	Me	0.8	100	97.5
8	Me	Et	0.8	100	97.5
9	MeO	H	0.8	100	97.6
10	MeO	Me	0.8	100	98.5
11	MeO	Et	0.8	100	96.8
12	Cl	H	0.8	15.8	9.3[b]
13	Cl	Me	0.8	10.5	5.8[b]
14	F	H	0.8	22.9	17.5[b]
15	F	Me	0.8	23.8	13.9[b]

Reaction conditions: 8 g of *o*-nitroaniline, 120 mL of alcohol, 80 mL of H_2O, 453 K, 3.5 MPa, 12 hrs, 900 r/min; [a] checked by HPLC

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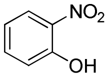
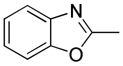
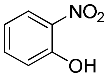
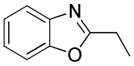
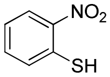
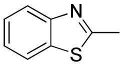
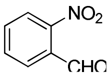
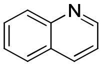
To further establish the general utility of these transformations, *o*-nitroaniline was replaced with different nitro-compounds for the synthesis of other heterocyclic compounds (Table 5), affording the corresponding benzoxazole, benzothiazole and quinoline compound. But yields of the corresponding heterocyclic compounds were relatively low.

Table 5 The synthesis of other heterocyclic compounds

Entry	Substrate	Alcohols	Product	Conversion (%)	Yield (%)[a]
1		ethanol		100	30.7
2		propanol		100	36.7
3		ethanol		95.2	5.3
4		ethanol		100	78.4

Reaction conditions: 0.8 g of catalyst, 8 g of substrate, 120 mL of alcohol, 80 mL of H_2O, 453 K, 3.5 MPa, 16 hrs, 900 r/min; [a] checked by HPLC.

Conclusions

In conclusion, the direct synthesis of benzimidazole from the *o*-nitroaniline and alcohol was successfully established by tuning the types of metal and support. The combination of Cu and Pd was responsible for the dehydrogenation of alcohol and hydrogenation of *o*-nitroaniline. The γ-Al_2O_3 carrier supplied the Lewis or Bronsted acid center to promote the condensation of *in situ* formed *o*-phenylenediamine and aldehyde, which gave the desired benzimidazole derivatives after oxidation dehydrogenation. The method described here has the advantage of easily available starting materials, high efficiency, and simple procedure.

Experimental

Catalyst preparation

The Cu-Pd/γ-Al_2O_3 catalyst was prepared by impregnation with precursors of aqueous solution of $Cu(NO_3)_2$ (0.05 g_{metal}/mL) and H_2PdCl_4 (0.05 g_{metal}/mL). After γ-Al_2O_3 support was stirred in distilled water for 10 minutes at 80℃, H_2PdCl_4 solution was added dropwise followed by aqueous solution of $Cu(NO_3)_2$, and kept the solution at 80℃ for 5 hours. Then pH value was adjusted to 8-9 by adding aqueous $NaHCO_3$. After maintained at this condition for 5 minutes, the solid was filtered and washed to neutral by distilled water, then washed by ethanol, distilled water, successively. The resulting solid was dried in vacuo at 383 K and then calcined at 533 K for 3 hours, finally reduced by H_2 at 533 K for 2 hours to give the catalyst.

Characterization of catalysts

The bulk composition of the samples was determined via Energy-dispersive X-ray spectroscopy (EDS) on Noran VANTAGE-ESI spectrometer. The surface area and porosity analysis of catalysts were measured with N_2 physisorption at 77 K on a Micromeritics ASAP 2020. Transmission electron microscope (TEM) analysis was performed with a Tencnai G2 F30 S-Twin instrument operating at 300 kV. Average particle size was calculated by 300 particles which were randomly measured. Scanning electron microscopy (SEM) was analysed on a Hitachi S-4700 instrument at 15 kV. X-ray powder diffraction (XRD) was obtained on a Thermo ARL SCINTAG X' TRA diffractometer using Cu Ka radiation (λ= 0.15406 nm) at 45 kV and 40 mA. The scanning range is from 2θ=10°-80°with a scanning rate of 28 min^{-1}. The diffraction peaks obtained were referred to the JCPDS cards. Prior to each experiment, catalyst (0.075 g) was heated in a flow of He (30 ml/min) at 533 K for 40 min, followed by cooling to 323 K under He flow. Then, the catalyst was exposed to a flow of 100% NH_3 for 30 min. After being purged in He for 60 min, the catalyst was heated linearly at 10 $K{\cdot}min^{-1}$ to 973 K in a flow of He, and NH_3 (m/e=17) in the outlet gas were analyzed by the mass spectrometer (BELMASS).

Synthesis of benzimidazoles

The reaction was performed in a 500 mL stainless steel autoclave, which was charged with 8 g of the nitroaromatic compound,120 ml alcohol, 80 ml deionized water and 0.8 g of the catalyst. The batch reactor was initially purged five times with pure N_2 to replace the air in the system. The reactor was then heated to the desired temperature at the desired N_2 pressure and at a stirring rate of 900 rpm. After the complete conversion of the reactant, the catalyst was filtered from the mixture for subsequent use, and the corresponding product was separated from the aqueous phase using a separatory funnel. The products were identified by gas chromatography-mass spectrometry (GC-MS, Agilent 5973N) and were analyzed by HPLC using a Baseline C_{18} column (150mm× 2.1nm) with a mobile phase of ethanol-ethyl acetate-water (7:1:2 by

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volume) at a 1.2 mL min^{-1} constant flow. Quantitative analysis was conducted using the area-normalization method.

Recycling tests

After a typical catalytic run (8 g o-nitroaniline, 120 mL ethanol, 80 mL H_2O, 0.8 g Cu-Pd/γ-Al_2O_3 catalyst, 453 K, 3.5 MPa, 900 r/min, 12 h), the catalyst was filtered, additionally washed with alcohol and deionized water, and reused after dried in vacuo at 383 K.

Acknowledgements

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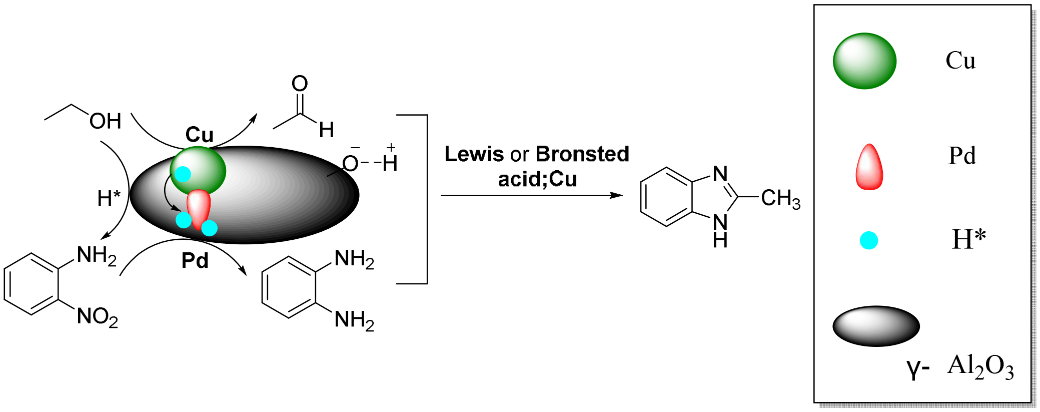

The coupling of multi-step reaction catalyzed by heterogeneous catalyst is an important path to accomplish some unconventional chemical transformations. Since the starting materials generated from previous steps were adsorbed on the catalyst, the activation energy requirements of following steps were largely decreased. Thus the reaction conditions were more mild and environmental friendly. Catalyzed by multifunctional Cu-Pd/γ-Al_2O_3 solid acid catalyst, the transfer hydrogenation and successive cyclization coupling reaction from *o*-nitroaniline and alcohol to afford benzimidazole derivatives in high yield was realized. The catalyst could be reused for several times without loss of activities. The synergies of reforming hydrogenation of Cu-Pd bimetal and support acidity of γ-Al_2O_3 were responsible for this catalytic transformation.