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Efficient and recyclable $Cu_2(BPDC)_2(DABCO)$-catalyzed direct amination of activated sp^3 C—H bonds by *N–H* heterocycles

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ABSTRACT

A metal-organic framework $Cu_2(BPDC)_2(DABCO)$ was successfully synthesized and employed as an efficient heterogeneous catalyst for the direct C—N cross-coupling reaction via sp^3 C—N bond activation between *N–H* heterocycles and amides. Kinetic investigation was thoroughly conducted. The optimal conditions involve the use of $Cu_2(BPDC)_2(DABCO)$ catalyst (3%), di-*tert*-butyl peroxide oxidant (2 equivalents) in chlorobenzene solvent at 120 °C in 2 h. The $Cu_2(BPDC)_2(DABCO)$ offered higher catalytic activity than that of other Cu-MOFs such as $Cu_2(BPDC)_2(BPY)$, $Cu_3(BTC)_2$ and $Cu_2(BDC)_2(DABCO)$, and that of several common copper salts such as CuCl, CuBr, CuI, $Cu(NO_3)_2$, and $CuSO_4$. To investigate the mechanism, catalyst poisoning experiments and reactions with added radical scavengers were conducted. Furthermore, the catalyst could be recovered and reused several times without much decline in the reaction yield.

1. Introduction

Nitrogen-containing molecules are often found to display important biological and pharmaceutical activities [1]. Therefore, significant efforts have been devoted to introduce nitrogen into molecules, commonly by constructing the C—N bonds [2–5]. Modern methodology such as Buchwald–Hartwig amination or Chan–Lam couplings often involves the use of transition metals catalysts [2,6]. However, additional steps are required to prepare the pre-functionalized coupling partners. Therefore, direct amination of C—N bonds provides a more straightforward and economic synthetic procedure. Due to the similarity of C—N bond activation energy, directing groups are frequently employed to bring the metals to the proximity of reacted C—N bonds [7]. An alternative is to use activated C—N bonds [8]. Recently, several groups have developed new methodologies for selective functionalization of C-H bonds adjacent to a nitrogen atom in simple amines and amides for CC bond formation [9]. We reported a directed protocol to activate the sp^3 C—H bond adjacent to oxygen atom in ether molecules for the C—O coupling transformation [10]. Recently, Chen and Xia demonstrated an efficient pathway for the synthesis of azole derivatives via the $FeCl_2$-catalyzed direct C—N coupling of azoles with amides through similar strategy [11]. From a viewpoint of green chemistry, the development of heterogeneous catalytic systems for these directed transformations are highly needed.

Metal-organic frameworks (MOFs) are porous and crystalline coordination polymers constructed from metal ions or metallic clusters and polyfunctional organic linkers [12,13]. Combining some special physical properties from both organic and inorganic porous materials, MOFs would be promising materials for potential applications in many fields, including gas storage media, separations, chemical sensors, thin film devices, optics, drug carriers, biomedical imaging, and catalysis [14–22]. Although the catalysis application of MOFs has just emerged as a young research area, relevant publications have increased significantly in the last few years, and it can be expected that this promising field will be extensively investigated in the near future [23–25]. Indeed, many MOFs have been explored as catalysts or catalyst supports for a variety of organic transformations, including both carbon–carbon [26–30] and carbon-heteroatom forming reactions [31–39]. Among several kinds of MOFs, it was previously reported that copper-based frameworks could be used as promising heterogeneous catalysts for many organic reactions due to their unsaturated open copper metal sites [33,40–47]. In this work, we present the direct C—N cross-coupling reaction between azoles and amides via sp^3 C—H bond activation using the metal-organic framework $Cu_2(BPDC)_2(DABCO)$ as an efficient heterogeneous catalyst. To the best of our knowledge, our work reports the first example of using heterogeneous catalytic

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systems in oxidative C—H/N—H cross couplings between activated sp^3 C—H bonds and *N–H* heterocyles.

2. Experimental

2.1. Materials and instrumentation

All reagents and starting materials were obtained commercially from Sigma–Aldrich and Merck, and were used as received without any further purification unless otherwise noted. Nitrogen physisorption measurements were conducted using a Micromeritics ASAP 2020 volumetric adsorption analyzer system. Samples were pretreated by heating under vacuum at 150 °C for 3 h. A TGA Q500 was used for thermogravimetric analysis (TGA) with a heating rate of 10 °C/min under a nitrogen atmosphere. X-ray powder diffraction (XRD) patterns were recorded using a Cu Kα radiation source on a D8 Advance Bruker powder diffractometer. Scanning electron microscopy studies were conducted on a JSM 740 Scanning Electron Microscope (SEM). Transmission electron microscopy studies were performed using a JEOL JEM 1010 Transmission Electron Microscope (TEM) at 100 kV. The $Cu_2(BPDC)_2(DABCO)$ sample was dispersed on holey carbon grids for TEM observation. Elemental analysis with atomic absorption spectrophotometry (AAS) was performed on an AA-6800 Shimadzu. Fourier transform infrared (FT-IR) spectra were obtained on a Nicolet 6700 instrument, with samples being dispersed on potassium bromide pallets. The chemisorption experiments were studied on a Micromeritics 2020 analyzer. For hydrogen temperature-programmed reduction (H_2-TPR), the sample was outgassed at 100 °C for 30 min with helium, then cooled down to room temperature, and exposed to 50 mL/min of 10% H_2/Ar as the temperature ramped at 2.5 °C/min to 600 °C. The amount of hydrogen consumption was determined from TCD signal intensities, which were calibrated using an Ag_2O reference sample.

Gas chromatographic (GC) analyses were performed using a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The temperature program for GC analysis heated samples at 120 °C and held for 1 min, then heated them from 120 °C to 180 °C at 50 °C/min; held them at 180 °C for 1 min. After that, the samples were heated up to 280 °C and were hold for 3 min at 280 °C. 4-Bromoanisole was used as an internal standard to calculate reaction conversion. GC–MS analyses were performed using a Hewlett Packard GC–MS 5972 with a RTX-5MS column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.5 μm). The temperature program for GC–MS analysis heated samples from 60 to 280 °C at 10 °C/min and held them at 280 °C for 2 min. Inlet temperature was set constant at 280 °C. MS spectra were compared with the spectra gathered in the NIST library. The ^1H and ^{13}C NMR were recorded in $CDCl_3$ using tetramethylsilane as an internal standard on a Bruker spectrophotometer at 500 MHz and 125 MHz, respectively.

2.2. Synthesis of the metal-organic framework $Cu_2(BPDC)_2(DABCO)$

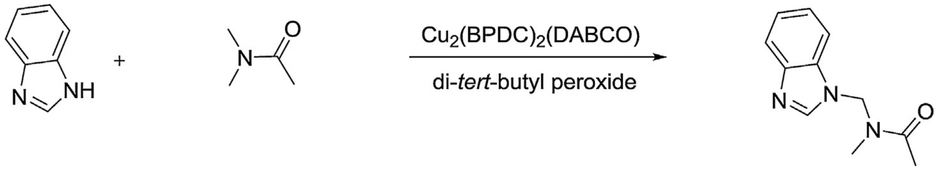
In a typical procedure [48,49], a mixture of H_2BPDC (H_2BPDC = biphenyl-4,4′-dicarboxylic acid; 120 mg, 0.50 mmol), DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane; 30 mg, 0.268 mmol), and $Cu(NO_3)_2{\cdot}3H_2O$ (120 mg, 0.50 mmol) was dissolved in a mixture of DMF (DMF = *N,N*-dimethylformamide; 35 mL), and methanol (5 mL). The solution was magnetically stirred for 2 h before centrifuging. The resulting solution was then distributed into eight 20 mL vials. The vials were heated at 120 °C in an isothermal oven for 48 h. After cooling the vials to room temperature, the solid product in each vial was recovered by decanting with mother liquor and washed with DMF (3 × 10 mL). Solvent exchange was then carried out with DCM (dichloromethane) (3 × 10 mL) at room temperature. The product was then dried at 140 °C for 6 h under vacuum, yielding 106 mg of the metal-organic framework $Cu_2(BPDC)_2(DABCO)$ as blue crystals (60% based on copper).

2.3. Catalytic studies

In a typical experiment, a mixture of benzimidazole (118 mg, 1 mmol), and 4-bromoanisole (0.1 mL, 0.8 mmol) as an internal standard in chlorobenzene (4 mL) was added into a 25 mL round bottom flask containing the $Cu_2(BPDC)_2(DABCO)$ catalyst (11 mg, 3 mol%). The catalyst concentration was calculated with respect to the copper/benzimidazole molar ratio. The reaction mixture was magnetically stirred for 3 min to disperse entirely the catalyst in the liquid phase. Dimethylacetamide (DMAc) (0.372 mL, 4 mmol) and di-*tert*-butyl hydroperoxide (0.44 mL, 2 mmol) were then added. The resulting mixture was continuously stirred at 120 °C for 120 min. Reaction conversion was monitored by withdrawing aliquots from the reaction mixture at different time intervals, quenching with aqueous KOH solution (5% (w/w), 1 mL). The organic components were then extracted into ethyl acetate (2 mL), dried over anhydrous Na_2SO_4, analyzed by GC with reference to 4-bromoanisole. The product identity was further confirmed by GC–MS, ^1H NMR, and ^{13}C NMR. The catalyst was separated from the reaction mixture by simple centrifugation, and washed with copious amounts of chlorobenzene and dichloromethane. It was then activated under vacuum at 140 °C for 3 h. For the leaching test, a catalytic reaction was stopped after 20 min, analyzed by GC, and centrifuged to remove the solid catalyst. The reaction solution was then stirred for a further 100 min. Reaction progress, if any, was monitored by GC as previously described. Reported values are average of at least 2 runs with <10% different in conversion.

3. Results and discussion

The synthesized metal-organic framework $Cu_2(BPDC)_2(DABCO)$ was characterized by several techniques, including XRD, SEM, TEM, TGA, FT-IR, ICP-MS, and H_2-TPR (Figs. S9–S14). All analytical results are in good agreement with previous studies [49]. In particular, powder X-ray diffraction pattern showed the typical reflections of a three-dimensional structure with pillar ligands of $Cu_2(BPDC)_2(DABCO)$. Thermal gravimetric analysis (TGA) of activated $Cu_2(BPDC)_2(DABCO)$ shows high thermal stability (>320 °C) and the measured mass percent of residue CuO is consistent with the EA data. ICP-MS provided 2.47 mmol/g copper content which is close to the calculated value of 2.40 mmol/g. Finally, FT-IR spectra



Scheme 1. The direct C—N cross-coupling reaction between benzimidazole and dimethylacetamide under $Cu_2(BPDC)_2(DABCO)$ catalysis.