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$Cu_2(BDC)_2DABCO$ as an efficient heterogeneous catalyst for the oxidative C-N coupling reaction between amides and unactivated alkanes

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ABSTRACT

A copper-organic framework $Cu_2(BDC)_2DABCO$ was synthesized, and used as a recyclable heterogeneous catalyst for C-N coupling reaction between benzamide and cyclohexane. 94% yield of N-cyclohexylbenzamide was achieved under the optimized condition. The copper-organic framework catalyst was truly heterogeneous and could be used at least 4 cycles without degradation of catalytic performance. To the best of our knowledge, the amidation of unactivated alkanes by benzamides via direct oxidative C-N coupling was previously performed under heterogeneous catalysis conditions but very rare.

Introduction

Amide is one of the basic functional groups in organic compounds, and amination reactions are crucial for the synthesis of drug candidates as well as agrochemicals.[1-2] Although amides could be prepared by amidation reaction between amines and carboxylic acid derivatives or transamidation reaction, these procedure often required harsh conditions and pre-functionalized starting materials.[3-4] Organic transformations through the direct activation of C-H bonds have emerged as an efficient tool to construct organic compounds.[5-6] In 2014, this strategy was firstly applied by Hartwig and co-workers in the C-N coupling of amides with alkanes using the catalyst system of CuI and phenanthronlines and di-tert-butyl peroxide as the oxidant.[7] Recently, Cheng and co-workers have demonstrated that changing the catalyst into copper acetylacetonate also gave excellent results for this reaction.[8] However, the number of researches employing solid catalysts in this reaction is still limited. To enhance environmentally friendly aspects of the reaction, heterogeneous catalysts for this reaction should be investigated because they are capable of being recycled and reused.

Metal–organic frameworks, or MOFs, have emerged as an extensive class of crystalline materials with ultrahigh porosity and enormous internal surface areas.[9] Due to these properties, MOFs have a plethora of potential applications in many fields.[10-14] During the last few years, a large number of organic reactions conducted using MOF as catalyst has been reported.[15-18] In this manuscript, we would like to illustrate an efficient access to N-cyclohexylbenzamide via direct oxidative C-N coupling reaction. To the best of our knowledge, this synthetic route was previously conducted under Cu-CPO-27 as a heterogeneous catalyst,[19] but the material for synthesizing this MOF is very expensive. Therefore, in this study, $Cu_2(BDC)_2DABCO$ was investigated as an alternative due to its much cheaper cost of starting materials.

Experimental

Synthesis of $Cu_2(BDC)_2DABCO$

In a typical preparation as mentioned in the previous reports,[20-21] a mixture of H_2BDC (1,4-benzenedicarboxylic; 0.506 g, 3.1 mmol), DABCO (1,4-diazabicyclo[2.2.2]octane; 0.188 g, 1.67 mmol), and $Cu(NO_3)_2.3H_2O$ (0.8 g, 3.3 mmol) was dissolved in DMF (DMF = N,N-dimethylformamide; 80 mL). The resulting solution was then distributed to 14 screw-capped 2-dram vials. After that, the vials were heated at 120 °C in an isothermal oven for 48 h, forming blue crystals. After cooling the vials to room temperature, the solid product was separated by decanting with mother liquor and washed with DMF (3 x 12 mL). The solvent exchange was carried out with methanol (3 x 12 mL) at room temperature. The collected crystals were put into a vial to be dried at 140 °C for 6 h under vacuum. Obtaining the metal-organic framework $Cu_2(BDC)_2DABCO$ as light blue crystals. The identity and the structure of the MOF were confirmed by powder XRD, FT-IR, TGA, TEM, and SEM.

Catalytic Studies

A mixture of benzamide (0.0242 g, 0.2 mmol) and cyclohexane (1.5 mL), DTBP (0.1168 g, 4 equiv) and diphenyl ether (0.2 mmol; 0.0340 g) as an internal standard was added into a 8 mL vial containing the $Cu_2(BDC)_2DABCO$ catalyst (5 %mol with respect to the copper amount in the catalyst). The reaction mixture was stirred at 120 °C for 16 h. After the completion of the reaction, the reaction mixture was diluted by adding ethyl acetate (1 mL). The reaction yield was monitored by withdrawing aliquots from the resulting mixture, quenching with H_2O. Organic compounds were extracted into ethyl acetate (3 mL), dried over anhydrous Na_2SO_4, and analyzed by GC with reference to diphenyl ether. The GC yields were calculated using a calibration curve which was established by analyzing a series of samples with different molar ratios between the product and the internal standard. To separate the product, the reaction mixture was diluted by ethyl acetate (10 mL), washed with water (3 x 2 mL), dried over Na_2SO_4, and concentrated under vacuum. The resulting residue was purified by recrystallization using cyclohexane as solvent. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.76-7.74 (m, 2H), 7.49-7.41 (m, 3H), 6.03 (s, 1H), 3.98 (tt, *J*= 10.5, 4 Hz, 1H), 2.04-2.01 (m, 2H), 1.77-1.73 (m, 2H), 1.67-1.63 (m, 1H), 1.47-1.38 (m, 2H), 1.28-1.17 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.6, 135.1, 131.2, 128.5, 126.8, 48.7, 33.2, 25.57, 24.9.

Leaching test and reusability test

For the leaching test, the reaction was firstly carried out as described procedure under the optimized conditions. After the completion of the reaction, the solid calalyst was removed by hot filtration. The filtrate was then used as the reaction media of the next run without the addition of the catalyst. The yield of the second run was observed to determine the leaching test result.

To perform reusability test, a typical reaction was performed alongside a tenfold scale-up reaction. Yield of the reusability test was reported by analyzing the small scale reaction. The catalyst in the larger scale was used to compensate for the loss of catalyst in the small scale reaction. After the two reactions were complete, the catalyst in both reactions was collected by centrifugation, washed with copious amounts of DMF, then methanol. After that, the copper MOF was dried under vacuum at 140 °C. In the next catalytic run, the small scale reaction was set up first, the larger scale one was then performed according to the remaining amount of catalyst.

Results and discussion

The copper-MOF $Cu_2(BDC)_2DABCO$ was synthesized by a solvothermal method according to the previously reported procedures.[20-21] The collected MOF was characterized by various techniques, and the results were comparable to the literature (Fig 1).[20-21] The XRD powder diffractogram patterns of the resulting $Cu_2(BDC)_2DABCO$ showed a very sharp peaks at $2\theta = 8^o$, confirming the formation of highly crystalline structure (Fig 1A). The TGA result indicated that the material was stable up to over 250 °C, which ensures its thermal stability in reaction media (Fig 1B). FT-IR spectra of the $Cu_2(BDC)_2(DABCO)$ exhibited a significant difference as compared to those of the H_2BDC and the DABCO, showing the deprotonation of –COOH groups in the H_2BDC upon the reaction with copper cations (Fig 1C). The nitrogen adsorption isotherm of the $Cu_2(BDC)_2(DABCO)$ presented a typical type-I profile with relatively high Langmuir surface area of 1172 m^2/g (Fig 1D) and a median pore width of 5.5 Å (Fig 1E). A SEM micrograph (Fig 1F) and the TEM micrograph (Fig 1G) confirmed that a highly crystalline porous material was obtained. The particle size of the catalyst was also observed in the SEM image, ranging from about 1 μm to about 50 μm.

The reaction of benzamide and cyclohexane was chosen to be the reaction model to investigate the catalytic activity of $Cu_2(BDC)_2DABCO$ in the oxidative C-N coupling reaction between amides and alkanes (Scheme 1). The optimization of the reaction conditions was summarized in Table 1.

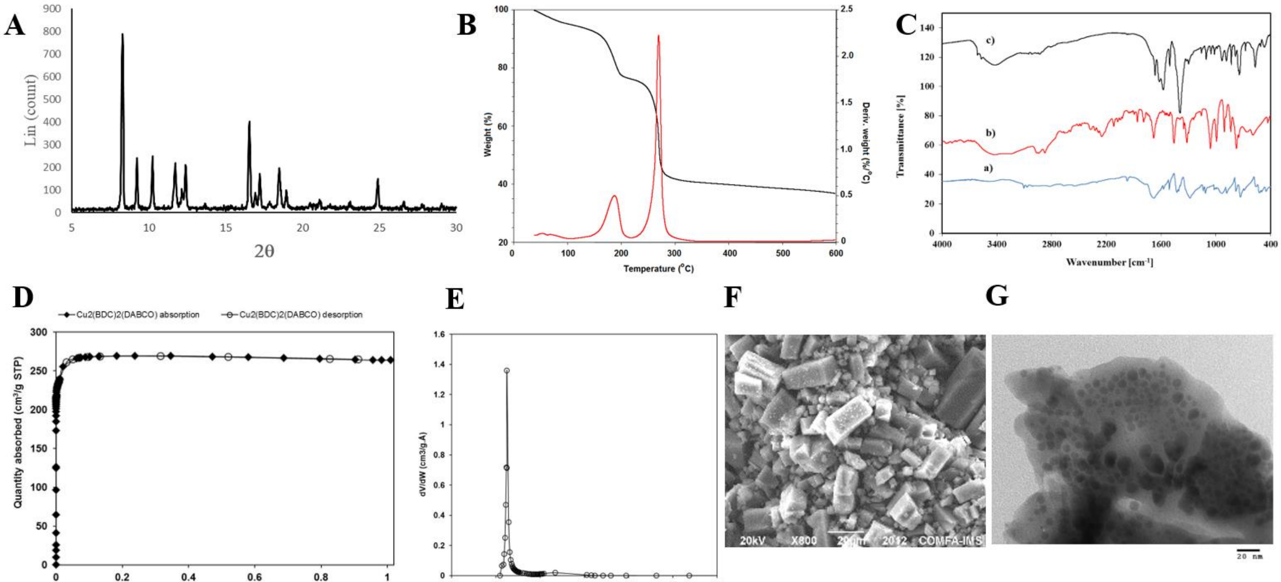
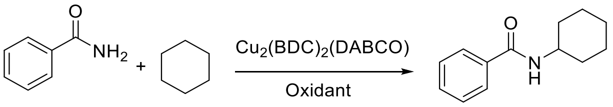


Figure 1: Characterization data of $Cu_2(BDC)_2DABCO$: A. Powder XRD pattern; B. TGA result; C. FT-IR spectra of (a) H_2BDC, (b) DABCO, and (c) Fresh $Cu_2(BDC)_2DABCO$; D. Nitrogen adsorption/desorption isotherm; E. Pore size distribution; F. SEM micrograph; G. TEM micrograph.



Scheme 1: Model reaction for screening conditions

Table 1: Screening the reaction conditions^a

Entry	Temp. (°C)	Oxidant^b (Amount)	Catalyst amount (% mol)	Yield^c (%)
1	120	DTBP (4 equiv)	10	81
2	120	TBHP^d (4 equiv)	10	0
3	120	TBHP^e (4 equiv)	10	0
4	120	DCP (4 equiv)	10	22
5	120	CHP (4 equiv)	10	0
6	120	TBPB (4 equiv)	10	0
7	120		10	0
8	120	DTBP (1 equiv)	10	20
9	120	DTBP (2 equiv)	10	36
10	120	DTBP (3 equiv)	10	53
11	120	DTBP (5 equiv)	10	97
12	120	DTBP (6 equiv)	10	81
13	80	DTBP (5 equiv)	10	0
14	100	DTBP (5 equiv)	10	3
15	140	DTBP (5 equiv)	10	92
16	120	DTBP (5 equiv)	0	7
17	120	DTBP (5 equiv)	1	14
18	120	DTBP (5 equiv)	2	77
19	**120**	**DTBP (5 equiv)**	**5**	**97 (94)**
20	120	DTBP (5 equiv)	15	89

^{a}Benzamide (0.2 mmol), cyclohexane (1.5 mL) for 16 h.
^{b}DTBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide, DCP = dicumyl peroxide, CHP = cumyl hydroperoxide, TBPB = *tert*-butyl peroxybenzoate.
^{c}GC yield, the number in parenthesis is isolated yield.
^{d}Aqueous TBHP (70%)
^{e}TBHP 5-6 M in decane

Oxidants usually play an important role in oxidative coupling reactions, so we began with exploring the effect of different oxidants on the yield of N-cyclohexylbenzamide (entries 1-7). The results show that DTBP can yield the product with 81% yield (entry 1). Other oxidants give no product under this reaction conditions, except for dicumyl peroxide with a modest yield of 22% (entry 4). The result is similar to the conclusion of Hartwig's group that copper catalysis and DTBP provide products for benzamide and cyclohexane reaction.[7] When the reaction was performed in the absence of the oxidant (entry 7), no product was observed after 16 h, which further confirms the crucial role of the oxidant in this transformation. The next factor to be investigated was the amount of the oxidant (entries 8-12). Up to 97% yield of N-cyclohexylbenzamide was achieved after 16 h in the presence of 5 equivalents of the oxidant (entry 11). As expected, decreasing the concentration of DTBP made the reaction yield decrease significantly.

Next, the reaction should be carried out at the temperatures around 100 °C with reference to the previous researches.[7-8, 19] Hence, the effect of temperature on reaction was investigated from 80 °C to 140 °C (entries 13-15). No or only trace amount of the product was detected when the reaction was carried out under 120 °C (entries 13-14). This could be explained by the fact that the decomposition temperature of DTBP is above 100 °C to give two *tert*-butoxyl radicals.[22] The temperature to more than 120 °C was not necessary since the yield was not improved noticeably (entry 15).

Another factor that would have an effect on reaction yield is the catalyst amount. The significance of the copper catalyst in this reaction was proved by the blank experiment (entry 16), affording a trace amount of product. The role of copper sites as a catalyst for the decomposition of peroxides has been proven in the literature.[23-25] Adding just a small amount of catalyst (2 mol%) boosted the yield to 77% after 16 h (entry 18). Increasing the catalyst concentration to 5 mol% led to 97% yield after 16 h (entry 19). Using more than 5 mol% catalyst was unnecessary since the yield was not improved any further. In the first report of the homogeneous copper-catalyzed amidation between benzamide and cyclohexane, Hartwig and co-workers employed 2.5 mol% CuI catalyst assisted by 4,7-dimethoxyphenanthronline ligand.[7] Cheng and co-workers implemented the same transformation deploying 10 mol% $Cu(acac)_2$ complex as catalyst.[8] While our previous method using Cu-CPO-27 used 7.5% mol of the catalyst,[19] the employment of $Cu_2(BDC)_2(DABCO)$ catalyst not only did not require additional ligands but also replaced Cu-CPO-27 by a cheaper heterogeneous catalyst.

In order to check whether active copper species dissolved from the $Cu_2(BDC)_2(DABCO)$ catalyst contributed to the reaction yield or not, a leaching test should be carried out. The reaction was carried out under the optimized condition employing 5 mol% of $Cu_2(BDC)_2(DABCO)$ catalyst. After 16 h reaction time with 97% yield being observed, the solid catalyst was separated from the reaction by hot filtration. The reaction solution was then transferred into a new vial, adding 0.2 mmol benzamide, 5 equivalents of DTBP, and stirred for an additional 16 h at 120 °C. As expected, it was found that the reaction stopped immediately after separating the catalyst (Fig 2). The results indicated that the contribution of the dissolved catalyst to product yield (if any) was trivial.

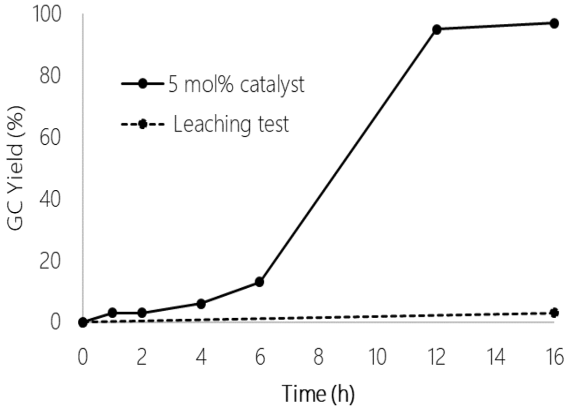


Figure 2: Leaching test result

One of the advantages of using heterogeneous catalysts in comparison to homogeneous ones is reusability. To highlight this feature, $Cu_2(BDC)_2(DABCO)$ was investigated for reusability in the direct oxidative of C-N coupling reaction over 4 successive runs under the optimized condition. After each run, the $Cu_2(BDC)_2(DABCO)$ catalyst was separated from the reaction mixture by centrifugation, washed with DMF and methanol. And then, dried at 140 °C under vacuum for 2 h, and reused in further reactions under identical conditions. The results show that the catalyst can be reused at least 4 times in the direct oxidative C-N coupling reaction between benzamide and cyclohexane, while the degradation in catalytic activity is trivial. As can be seen, 97% yield of N-cyclohexyl benzamide was still observed in the 4th run (Fig 3).

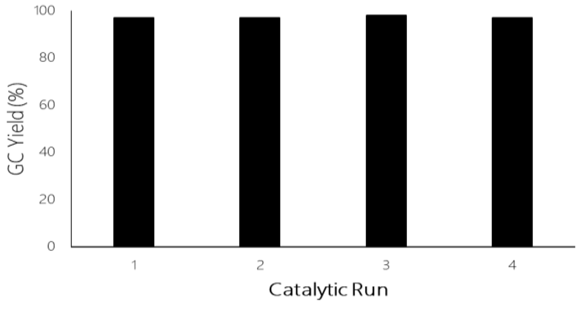


Figure 3: Catalyst reusability investigation

The crystalline structure of the catalyst was still maintained, which was confirmed by minor changes in XRD and FT-IR data of reused catalyst compared to the new one (Fig 4). However, it can be seen that the catalyst particle size was likely to decrease compared to the new catalyst. This can be explained by the fact that through many stirring times, the catalyst particles are gradually reduced in size, making it difficult to recover them by centrifuging the reaction solution.

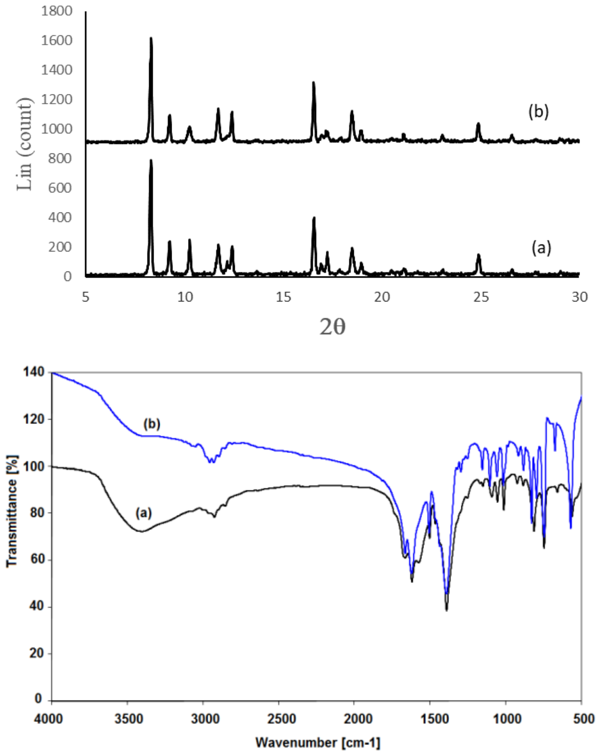


Figure 4: Powder XRD and FT-IR data of (a) Fresh and (b)Reused $Cu_2(BDC)_2(DABCO)$

To further highlight the merits of $Cu_2(BDC)_2(DABCO)$ catalyst, its catalytic performance was compared with some copper-based salts and some other copper-MOFs. These catalysts were employed in a reaction of benzamide and cyclohexane under described optimized conditions (Table 2). Although $Cu_2(BDC)_2(DABCO)$ is a heterogeneous catalyst, its catalytic activity was better than all of the tested homogeneous copper salts which are poorly soluble in cyclohexane and have much lower specific surface areas. As expected, Cu-CPO-27, which was previously reported as an effective reusable catalyst for this kind of reaction,[19] displayed an excellent catalytic feature on this survey. However, its high-cost ligand (2,5-dihydroxyterephthalic acid) is a considerable disadvantage. Some other well-known, low-cost, and commercially available MOFs such as Cu(BDC) and MOF-199 were also tested, but the reaction yields were relatively low.

Table 2: Reaction yield with different copper-based catalysts

Catalysts	GC yield
$Cu_2(BDC)_2(DABCO)$	97
Homogeneous catalysts:	
CuI	92
CuBr	88
CuCl	84
$CuBr_2$	84
$CuCl_2$	81
$Cu(OAc)_2$	67
$Cu(NO_3)_2.3H_2O$	78
Heterogeneous catalysts:	
Cu-CPO-27	95
Cu(BDC)	30
MOF-199	22

Conclusion

The copper-MOF $Cu_2(BDC)_2(DABCO)$ was synthesized by a solvothermal method and employed as a productive heterogeneous catalyst for the oxidative C-N coupling reaction between benzamide and cyclohexane. An excellent GC yield of 97% (isolated yield of 94%) was observed under optimized condition. The catalyst performed more effective than several copper salts as well as some other copper-based MOFs. The catalyst could be recovered and reused at least 4 times without significant degradation in catalytic activity. The reaction only occured in the presene of the solid $Cu_2(BDC)_2(DABCO)$, and no contribution of leached copper sites present in the liquid phase, if any, was detected. The expansion of the reaction scope is ongoing.

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