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Direct C-C coupling of indoles with alkylamides via oxidative C-H functionalization using Fe₃O(BDC)₃ as a productive heterogeneous catalyst

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Graphical abstract



Research Highlights

- Fe₃O(BDC)₃ was used as catalyst for the direct functionalization of indoles.
- High yields of indole derivatives were obtained.
- The catalyst could be recovered and reused.

Abstract

A metal-organic framework Fe₃O(BDC)₃ was prepared, and used a recyclable heterogeneous catalyst for the direct C-C coupling of indoles with alkylamides via oxidative C-H functionalization. The catalyst expressed higher catalytic efficiency for the direct C-C coupling transformation than that of other MOFs and that of other homogeneous iron catalysts. The coupling of indoles with alkylamides could only continued to form indole derivatives in the presence of the solid framework catalyst, and the donation of leached active iron species, if any, was trivial. The Fe-MOF catalyst could be reused many times for the synthesis of indole derivatives via the direct C-C

coupling without a substantial deterioration in catalytic activity. To the best of our knowledge, this direct C-C coupling transformation was not previously accomplished using solid catalysts.

Keywords: Indoles; C-C coupling; C-H functionalization; alkylation; alkylamides.

1. Introduction

Indole derivatives have emerged as privileged scaffolds in a variety of nitrogencontaining biologically active natural products, pharmaceutical candidates, agrochemicals, and functional materials [1-8]. The conventional Friedel-Crafts alkylation using alkyl halides, alcohols, ethers, epoxides, and alkenes in the presence of a Brønsted or Lewis acid catalyst should be one of the most popular protocols to achieve Calkylation of indoles [9-13]. However, the preparation of prefunctionalized starting materials is required, being a major concern from atom-economical and environmental aspects [14-16]. The coupling transformation via direct C-H functionalization would offer shorter and more efficient synthetic schemes to achieve indole derivatives [14, 17, 18]. Li and Li previously demonstrated a CuBr-catalyzed direct C-C coupling of tetrahydroisoquinolines with indole derivatives [19]. Cai and co-workers developed a Ni(acac)₂-catalyzed direct C-C coupling of cyclic ethers with indole derivatives [20]. Hayashi and co-workers previously reported the first example of a FeCl₃-catalyzed oxidative direct C-C coupling of alkylamides with indole derivatives via the formation of

iminium ion followed by conventional Friedel-Crafts alkylation [21]. To polish the green eligibility for the direct C-C coupling transformation with regard to the simplicity of reusability, heterogeneous catalysts should be utilized [22]. Additionally, using solid catalysts would also decrease the contamination of the expected products with hazardous metals [23, 24].

Metal-organic frameworks (MOFs) have emerged as a new generation of crystalline materials with permanent porosity, constructed by joining metal ions or metal clusters with organic bridging ligands [25-29]. The properties of MOFs could be controlled by combining different metal cations of miscellaneous oxidation states and coordination geometries with appropriate organic linkers. Although significant efforts are needed for the commercialization of MOFs, promising applications of these materials in many disciplines have been extensively explored, extending from gas separation and storage to catalysis. The application of MOFs as heterogeneous catalysts has recently attracted significant interests from both academics and industry [30-33]. In principle, it would be possible to establish the catalytic active site either at each organic linker or each metal cation in the framework, thus maximizing the dispersion and the loading of useful sites [34-37]. During the last few years, a plentiful number of organic reactions using MOFs as heterogeneous catalysts have been reported in the literature [38-42]. Iron-based MOFs were previously employed as heterogeneous catalysts for a number of organic transformations, directing at oxidation reactions [43-45]. We recently synthesized quinazolinones, coumarins, and 1,5-benzodiazepines in the presence of Fe-MOFs as catalyst [46-48]. In this work, we wish to present the direct C-C coupling of indoles with

alkylamides via oxidative C-H functionalization using the iron-based metal-organic framework $Fe_3O(BDC)_3$ as a beneficial heterogeneous catalyst. To the best of our knowledge, this transformation was not previously accomplished using heterogeneous catalysts.

2. Experimental

2.1. Synthesis of the metal-organic framework Fe₃O(BDC)₃

The Fe₃O(BDC)₃ was synthesized in accordance with a literature method [49, 50]. In a representative preparation, H₂BDC (H₂BDC=1,4-benzenedicarboxylic acid; 0.199 g, 1.2 mmol), FeCl₃.6H₂O (0.325 g, 2.0 mmol) and were added to a mixture of ethanol (60 mL) and DMF (DMF = N,N'-dimethylformamide; 60 mL). The mixture was magnetically stirred for 30 min to dissolve the solids completely. The solution was equally added into eight 20-mL vials. The vials were securely covered and then heated at 85 °C for 48 h, forming the framework as light orange crystals. Subsequent to this period, the vials were cooled down to room temperature, and the crystals were collected by decantation. The as-synthesized framework was washed with DMF (3× 10 ml), and immersed in methanol (3× 10 ml). The framework crystals were then dried in a Shlenkline under vacuum at 140 °C for 6 h, producing 0.318g of Fe₃O(BDC)₃ in the form of brick red crystals (47 % yield based on H₂BDC).

2.2. Catalytic studies

In a representative experiment, a mixture of 1-methylindole (0.125 ml, 1 mmol) and diphenyl ether (0.1 ml), as an internal standard in N,N-dimethylacetamide (4 mL) was added into a 25 ml round bottom flask. The catalyst (0.014 g, 5 mol%) was then added to the flask. The catalyst concentration was calculated with regard to the iron/1methylindole molar ratio. The reaction mixture was magnetically stirred for 5 min to scatter the Fe-MOF catalyst in the liquid phase. Subsequently, di-tert-butyl peroxide (0.62 ml, 3 mmol) were added to the reaction mixture. The solution was magnetically stirred at 120 °C for 60 min. Reaction yield was monitored by withdrawing samples at different time periods, quenching with KOH solution (5% w/w, 1 ml). The organic constituents were then extracted into ethyl acetate (2 ml), dried over anhydrous Na₂SO₄, analyzed by GC concerning diphenylether internal standard. N-Methyl-N-((1-methyl-1Hindol-3-yl)methyl)acetamide was purified by column chromatography on silica gel. GC-MS, ¹H NMR, and ¹³C NMR analyses were conducted to confirm the product structure. To examine the recyclability of the catalyst, the Fe-MOF was separated from the reaction mixture by centrifugation, washed many times with dichloromethane, activated in a Shlenkline under vacuum at 140 °C for 3 h, and reused for further experiment.

3. Results and discussion

The Fe₃O(BDC)₃ was synthesized in accordance with a literature method [49, 50], and was characterized by several approaches (Fig. S1 – Fig. S7). The Fe-MOF was evaluated for its catalytic efficiency in the direct C-C coupling of 1-methylindole with N,N-dimethylacetamide via oxidative C-H functionalization to form N-methyl-N-((1-methyl-

1*H*-indol-3-yl)methyl)acetamide (**1**) as the major product (Scheme 1). Primary studies focused on the influence of temperature on the yield of (**1**). The reaction was carried out at 5 mol% catalyst for 60 min, using 43 equivalents of *N*,*N*-dimethylacetamide, in the presence of 3 equivalents of di-*tert*-butyl peroxide as the oxidant, at room temperature, 60 °C, 80 °C, 100 °C, 120 °C and 140 °C, respectively. It was noticed that no reaction occurred at room temperature, with no trace amount of (**1**) being recorded after 60 min. As expected, raising the reaction temperature led to a pronounced enhancement in the yield of the indole product. The reactor carried out at 60 °C afforded 26% GC yield of (**1**) after 60 min, while 37% yield was recorded for the reaction carried out at 80 °C. This value could be dramatically upgraded to 81% for the reaction carried out at 100 °C. Performing the transformation at 120 °C could afford 96% yield of (**1**) after 60 min. Increasing the reaction temperature to more than 120 °C was found to be unnecessary as the yield of the indole product was not enhanced any further (Fig. 1).

Comparable to other coupling reactions via the direct functionalization of C-H bonds, an oxidant should be essential for the C-C coupling reaction using the framework catalyst. It was therefore determined to investigate the influence of different oxidants on the formation of (1), having employed di*-tert*-butyl peroxide, *tert*-butyl hydroperoxide in water, cumyl hydroperoxide, *tert*-butyl hydroperoxide in decane, AgNO₃, K₂S₂O₈, and hydrogen peroxide, as the oxidant for the transformation, respectively. The reaction was carried out at 120 °C for 60 min, in the presence of 5 mol% catalyst, using 43 equivalents of *N*,*N*-dimethylacetamide, with 3 equivalents of the oxidant. AgNO₃, K₂S₂O₈, and hydrogen peroxide were found to be inappropriate for the coupling reaction, offering only 21%, 20%, and 29% yields, respectively, 60 min, while 61% yield was observed for

that using *tert*-butyl hydroperoxide in water. It was found that *tert*-butyl hydroperoxide in decane was more useful as the oxidant for the reaction than *tert*-butyl hydroperoxide in water, producing the indole product in 74% yield after 60 min. Among these oxidants, di*tert*-butyl peroxide demonstrated the best exhibition, with 96% yield of (1) being detected after 60 min. Indeed, in the first illustration of a FeCl₃-catalyzed oxidative direct C-C coupling of alkylamides with indole derivatives, Hayashi and co-workers employed di*tert*-butyl peroxide as the oxidant for the transformation [21]. Additionally, it was observed that the amount of di*tert*-butyl peroxide also influenced the coupling reaction, and best result was recorded for the transformation using 3 equivalents of the oxidant (Fig. 3).

Another point that should be studied for the C-C coupling reaction is the catalyst concentration. We then decided to explore the impact of catalyst concentration on the yield of (1). The reaction was carried out at 120 °C for 60 min, using 43 equivalents of N,N-dimethylacetamide, with 3 equivalents of di-*tert*-butyl peroxide as the oxidant, in the presence of 1 mol%, 3 mol%, 5 mol%, and 7 mol% catalyst, respectively. It should be noted that less than 5% yield of (1) was detected after 60 min in the absence of the catalyst, proving the importance of the Fe-MOF for the transformation. As expected, the presence of the catalyst led to a pronounced enhancement in the yield of (1) after 60 min, while 63% yield was observed for that using 3 mol% catalyst. As mentioned earlier, the C-C coupling reaction could produce (1) in 96% yield after 60 min in the presence of

5 mol% catalyst. Using more than 5 mol% Fe-MOF catalyst was found to be nonessential as the yield of the indole product was not upgraded any further (Fig. 4).

As the C-C coupling reaction using the framework catalyst was conducted in liquid phase, the potentiality that some of catalytically active iron sites on the solid catalyst could dissolve into the solution should be considered. In several situations, owing to the leaching phenomenon, the transformation would progress under both heterogeneous and homogeneous catalysis circumstances. In order to verify if active iron species migrated from the solid catalyst donated to the formation of (1) in the reaction, a control experiment was performed. The reaction was carried out at 120 °C for 60 min, in the presence of 5 mol% catalyst, using 43 equivalents of N,N-dimethylacetamide, with 3 equivalents of di-tert-butyl peroxide as the oxidant. After the first 10 min reaction time with 37% yield of (1) being recorded, the catalyst was isolated from the reaction mixture by centrifugation. The liquid phase was then transported to a new flask, and magnetically stirred for an additional 50 min at 120 °C with samples being analyzed by GC at varied time periods. Experimental results recommended that no additional yield of (1) was noticed after the solid catalyst was separated from the reaction mixture (Fig. 5). These observations would support that the C-C coupling reaction could only progress in the presence of the solid catalyst, and the donation of leached active iron species to the formation of (1), if any, was trivial.

To feature the superiority of using the catalyst for the C-C coupling reaction via oxidative C-H functionalization to form (1), the catalytic activity of the Fe-MOF was compared to that of common homogeneous iron catalysts such as FeCl₂, FeBr₂, FeCl₃, Fe(NO₃)₃, and Fe₂(SO₄)₃. The reaction was carried out at 120 °C for 60 min, in the presence of 5 mol% catalyst, using 43 equivalents of N,N-dimethylacetamide, with 3 equivalents of di-tert-butyl peroxide as the oxidant. In the first example of a FeCl3catalyzed oxidative direct C-C coupling of alkylamides with indole derivatives, Hayashi and co-workers employed 10 mol% FeCl₃ as catalyst for the transformation [21]. It was found that the reaction using FeCl₃ catalyst afforded 63% yield of (1) after 60 min. FeCl₂ was found to be slightly less active than FeCl₃, and 56% yield of the indole product was detected after 60 min for the reaction using this catalyst. Similarly, the FeBr₂-catalyzed direct C-C coupling reaction could proceed to 55% yield after 60 min. Fe(NO₃)₃ was also less active than FeCl₃, affording 56% yield after 60 min. Fe₂(SO₄)₃ displayed similar catalytic activity for the transformation as compared with $FeCl_3$, producing (1) in 63% yield after 60 min. Interestingly, Fe₃O(BDC)₃ catalyst presented better exhibition than these homogeneous iron catalyst, with 96% yield of (1) being achieved after 60 min (Fig. 6).

To underline the considerable aspects of using $Fe_3O(BDC)_3$ as catalyst for the C-C coupling reaction via oxidative C-H functionalization to form (1), the catalytic activity of the Fe₃O(BDC)₃ was compared with that of other MOFs such as $Co_2(BDC)_2(DABCO)$,

Ni(HBTC)(BPY), Ni₂(BDC)₂(DABCO), Cu₂(BDC)₂(DABCO), Cu(BDC), Cu₂(BPDC)₂(DABCO), Cu₂(BPDC)₂(BPY), Cu₃(BTC)₂, and Fe₃O(BPDC)₃. These MOFs were synthesized by solvothermal method, and characterized in accordance with the literature. The reaction was carried out at 120 °C for 60 min, in the presence of 5 mol% catalyst, using 43 equivalents of N,N-dimethylacetamide, with 3 equivalents of ditert-butyl peroxide as the oxidant. Co₂(BDC)₂(DABCO) offered low catalytic activity for the direct C-C coupling reaction, affording only 31% yield of (1) after 60 min. Ni(HBTC)(BPY) and $Ni_2(BDC)_2(DABCO)$ were also noticed to be unacceptable as catalyst for the transformation, with 19% and 30% yields of the product being detected after 60 min. It was observed that Cu-MOFs were more active for the reaction than Co-MOFs and Ni-MOFs. The reaction using Cu₃(BTC)₂ catalyst could progress to 42% yield of the indole product after 60 min, while 63% yield was recorded for that using Cu(BDC) catalyst. Using Cu₂(BDC)₂(DABCO) and Cu₂(BPDC)₂(DABCO) as catalyst, the reaction could produce (1) in 59% yield after 60 min. Fe-MOFs were noticed to be more active than Cu-MOFs, Co-MOFs, and Ni-MOFs. Indeed, the reaction using Fe₃O(BPDC)₃ catalyst could offer 76% yield after 60 min. Among these MOFs, Fe₃O(BDC)₃ displayed the best exhibition, with 96% yield of (1) being recorded after 60 min (Fig. 7).

To acquire perception into the mechanism of the C-C coupling reaction, further studies were performed. The reaction was carried out at 120 °C for 60 min, in the presence of 5 mol% catalyst, using 43 equivalents of *N*,*N*-dimethylacetamide, with 3 equivalents of di*tert*-butyl peroxide as the oxidant. In the first experiment series, ascorbic acid or (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (curcumin) as the antioxidant was added to the reaction mixture after the first 10 min. The mixture was

stirred for an additional 50 min at 120 °C with samples being analyzed at varied time periods. Experimental result showed that the yield of (1) was considerably influenced by the antioxidant (Fig. 8). It could be recommended that the interaction of the intermediate radicals with the antioxidant would alter the coupling transformation. In the second experiment series, control reactions were carried out using pyridine as a catalyst poison. After the first 10 min with 37% yield of (1) being detected, pyridine was added, and the resulting mixture was stirred for an additional 50 min at 120 °C. It was found that pyridine notably affected the catalytic activity of the catalyst in the coupling reaction (Fig. 9). The feature that pyridine as the catalyst poison expressed a extensive effect on the formation of (1) would recommend that the adsorption of pyridine on the Fe₃O(BDC)₃ destroyed the catalyst activity. Based on these results and the literature [21], the reaction mechanism was then suggested. Hydrogen abstraction of N,Ndimethylacetamide assisted by di-tert-butyl peroxide and the catalyst generated the radical. This radical was then converted to the corresponding iminium ion via a singleelectron transfer process. Consequently, a conventional Friedel-Crafts alkylation occurred to produce the product, sending the catalyst back to the catalytic cycle (Scheme 2).

As mentioned earlier, the $Fe_3O(BDC)_3$ provided better catalytic activity than several homogeneous and heterogeneous catalysts. To underline the superiority of this catalyst in the C-C coupling reaction via oxidative C-H functionalization to form (1), one point that should be beared in mind is the readiness of reusability of the solid catalyst. It is anticipated that the catalyst can be reused many times in this transformation. The MOFbased catalyst was therefore explored for reusability in the coupling of 1-methylindole

with *N*,*N*-dimethylacetamide over 10 consecutive runs. The reaction was carried out at 120 °C for 60 min, in the presence of 5 mol% catalyst, using 43 equivalents of *N*,*N*-dimethylacetamide, with 3 equivalents of di-*tert*-butyl peroxide as the oxidant. After the first run, the Fe-MOF catalyst was isolated from the reaction mixture by centrifugation, washed many times with dichloromethane, dried in a Shlenkline at 140 °C under vacuum for 3 h. The recovered catalyst was then reused in further experiment under duplicate conditions to those of the first run. It was noticed that the catalyst could be reused many times in the C-C coupling reaction to form (1) without a substantial deterioration in catalytic efficiency. Indeed, 85% yield of the expected product was still recorded in the 10th run (Fig. 10). Moreover, the structure of the catalyst could be preserved, as shown by XRD (Fig. 11) and FT-IR (Fig. 12) results of the recovered MOF-based catalyst.

The scope of the work was then developed to direct C-C coupling of different arenes with alkylamides. In the first reaction series, we conducted the coupling between N,N-dimethylacetamide and several arenes. The reaction was carried out at 120 °C for 60 min, in the presence of 5 mol% catalyst, using 43 equivalents of N,N-dimethylacetamide, with 3 equivalents of di-*tert*-butyl peroxide as the oxidant. The corresponding product was purified by column chromatography. Under this condition, (1) was obtained in an isolated yield of 90%. It was noticed that 1*H*-indole was less reactive than 1-methyl-1*H*-indole, producing N-((1H-indol-3-yl)methyl)-N-methylacetamide (2) in 83% yield. The coupling reaction of N,N-dimethylacetamide with 1-methoxy-4-methylbenzene proceeded to 68%

yield of N-(2-methoxy-5-methylbenzyl)-N-methylacetamide (3), while 87% yield of N-((2-methoxynaphthalen-1-yl)methyl)-N-methylacetamide (4) was recorded for the case of 2-methoxynaphthalene. As expected, anisole expressed less reactivity towards the coupling reaction than 1-methoxy-4-methylbenzene, though 62% yield of N-(2methoxybenzyl)-N-methylacetamide (5) was still obtained. 2-Methylfuran was found to be more reactive, producing N-methyl-N-((5-methylfuran-2-yl)methyl)acetamide (6) in 93% yield. In the second reaction series, we performed the coupling reaction between 1methyl-1*H*-indole with different amides, including *N*-ethylacetamide, *N*-ethyl-*N*methylacetamide, and 3-methyloxazolidin-2-one. It was found that both Nethylacetamide and N-ethyl-N-methylacetamide were less reactive than N,Ndimethylacetamide, though 77% yield of N-(1-(1-methyl-1H-indol-3-yl)ethyl)acetamide (7) and 72% yield of N-ethyl-N-((1-methyl-1H-indol-3-yl)methyl)acetamide (8) were still achieved. Moreover, the coupling reaction between 3-methyloxazolidin-2-one and 1methyl-1H-indole could progress to 87% yield of 3-methyl-4-(1-methyl-1H-indol-3yl)oxazolidin-2-one (9) (Table 1).

4. Conclusions

In summary, the iron-based metal-organic framework Fe₃O(BDC)₃ was synthesized by a solvothermal method in accordance with the literature, and was characterized by several approaches. The Fe-MOF could be used as a productive heterogeneous catalyst for the direct C-C coupling of indoles with alkylamides via oxidative C-H functionalization. The Fe₃O(BPDC)₃ expressed higher catalytic activity for the coupling transformation than

that of other **MOFs** such Co₂(BDC)₂(DABCO), Ni(HBTC)(BPY), as Ni₂(BDC)₂(DABCO), $Cu_2(BDC)_2(DABCO),$ Cu(BDC), $Cu_2(BPDC)_2(DABCO),$ Cu₂(BPDC)₂(BPY), Cu₃(BTC)₂, and Fe₃O(BPDC)₃. The Fe₃O(BDC)₃ also displayed better exhibition than other homogeneous iron catalysts such as FeCl₂, FeBr₂, FeCl₃, $Fe(NO_3)_3$, and $Fe_2(SO_4)_3$. The coupling of indoles with alkylamides via oxidative C-H functionalization could only progress in the presence of the solid catalyst, and the contribution of leached active iron species to the formation of the indole product, if any, was insignificant. The catalyst could be reused many times for the coupling reaction without a substantial deterioration in catalytic activity.

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Fig. 1. Yields of (1) at different temperatures.



Fig. 2. Yields of (1) with different oxidants.



Fig. 3. Yields of (1) at different oxidant concentrations.



Fig. 4. Yields of (1) at different catalyst concentrations.



Fig. 5. Leaching test showed that (1) was not produced in the absence of the solid catalyst.



Fig. 6. Yields of (1) with different homogeneous iron catalysts.



Fig. 7. Yields of (1) with different MOFs as catalysts.



Fig. 8. Yields of (1) with antioxidants.



Fig. 9. Yields of (1) with catalyst poison.



Fig. 10. Catalyst recycling investigation.



Fig. 11. X-ray powder diffractograms of the fresh (a) and reused (b) catalyst.



Fig. 12. FT-IR spectra of the fresh (a) and reused (b) catalyst.



Scheme 1. The direct C-C coupling of 1-methylindole with *N*,*N*-dimethylacetamide via oxidative C-H functionalization using Fe₃O(BDC)₃ catalyst.



Scheme 2. Proposed reaction mechanism.

Entry	Reactant 1	Reactant 2	Product	Isolated yields
				(%)
1	N		(1)	90
2	Z T	O N I	(2)	83
3	o-(68
4				87

Table 1. The direct C-C coupling of different reagents using Fe₃O(BDC) catalyst.

5	~o	O N I	(5)	62
6	° 	O N I	(6)	93
7	N			77
8	N		(8)	72
9	N N			87