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C1-alkynylation of tetrahydroisoquinoline by A^3 reaction using metal-organic framework $Cu_2(BPDC)_2(BPY)$ as an efficient heterogeneous catalyst

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ABSTRACT

A metal-organic framework $Cu_2(BPDC)_2(BPY)$ was synthesized and used as a heterogeneous catalyst for the copper-catalyzed A^3 reaction of tetrahydroisoquinoline, aldehydes, and alkynes to form C1-alkynylated tetrahydroisoquinolines. High regioselectivity to the *endo*-yne-product was achieved, with more than 99% of 2-benzyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline and less than 1% of 2-(1,3-diphenylprop-2-ynyl)-1,2,3,4-tetrahydroisoquinoline, being observed in the product mixture. The $Cu_2(BPDC)_2(BPY)$ also exhibited higher catalytic activity for the transformation than that of other Cu-MOFs such as Cu(BDC), $Cu_2(BDC)_2(BPY)$, $Cu_2(EDB)_2(BPY)$, $Cu_3(BTC)_2$ and $Cu_2(BDC)_2(DABCO)$. No product was detected for the reaction using other MOFs including Mn(BDC), Co-MOF-74, Zn-IRMOF-61, and $Ni_2(BDC)_2(DABCO)$. The $Cu_2(BPDC)_2(BPY)$ catalyst could be recovered and reused several times without a significant degradation in catalytic activity.

1. Introduction

Tetrahydroisoquinolines have emerged as an important class of natural product with diverse biological properties [1,2]. C1-substituted tetrahydroisoquinolines were previously achieved by using the direct cross-dehydrogenative coupling protocol with CuBr as catalyst and *tert*-butyl hydrogen peroxide as an oxidant [3]. However, tetrahydroisoquinolines with *N*-aromatic or *N*-acyl substitutions must be employed, thus, limiting the scope of the approach. Luz et al. previously employed Cu-MOFs such as $[Cu(2\text{-pymo})_2]$ and Cu(BDC) as catalyst for the three-component couplings of amines, aldehydes, and alkynes to form the corresponding propargylamines [4]. Yang et al. also demonstrated a postsynthetic modification of IRMOF-3 to prepare a heterogeneous catalyst for similar reactions [5]. Lili et al. performed the same transformation using the gold functionalized CUP-1 as catalyst [6]. However, secondary amines such as piperidines, pyrrolidines, morpholines, and dialkylamines were used as starting materials, giving no opportunity to investigate the regioselectivity of the protocol. Recently, Zheng et al. developed a first CuI-catalyzed A^3 reaction of tetrahydroisoquinolines, aldehydes, and alkynes to form C1-alkynylated tetrahydroisoquinolines with high regioselectivity to the *endo*-yne-product (95%) [7]. Although interesting results have been obtained for the transformation, the development of more environmentally benign approaches is still the target of further research in the near future. To achieve greener processes, solid catalysts should be explored for the transformation with advantages in terms of the ease of handling, simple workup, recyclability and reusability [8].

Metal-organic frameworks (MOFs) have emerged as a relatively new class of porous, crystalline materials constructed from metal ions or metallic clusters and multidirectional organic linkers [9,10]. As MOFs contain both inorganic and organic components in the network structure leading to special physical properties, they are considered as promising materials for potential applications in several fields, including gas storage media, separations, chemical sensors, thin film devices, optics, drug carriers, biomedical imaging, and catalysis [11–19]. Although the application of MOFs in catalysis is still in its infancy, relevant publications have recently increased significantly, and this promising field would be extensively investigated in the near future [20–22]. Indeed, many MOFs have been investigated as catalysts or catalyst supports for a variety of liquid-phase organic transformations, including both carbon–carbon [23–28] and carbon–heteroatom forming reactions [29–39]. Among several kinds of MOFs as heterogeneous catalysts, copper-based MOFs exhibited promising activity for many organic reactions due to their unsaturated open copper metal

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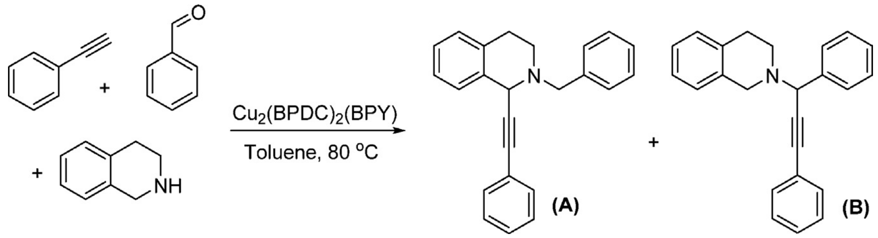

Scheme 1. The A3 reaction of tetrahydroisoquinoline, benzaldehyde, and phenylacetylene using Cu2(BPDC)2(BPY) catalyst.

sites [31,40–47]. In this work, we wish to present the heterogeneous copper-catalyzed A^3 reaction of tetrahydroisoquinoline, aldehydes, and alkynes to form C1-alkynylated tetrahydroisoquinolines with high regioselectivity to the *endo*-yne-product using the metal-organic framework $Cu_2(BPDC)_2(BPY)$ as a recyclable catalyst. The $Cu_2(BPDC)_2(BPY)$ also exhibited higher catalytic activity for the transformation than that of other Cu-MOFs such as Cu(BDC), $Cu_2(BDC)_2(BPY)$, $Cu_2(EDB)_2(BPY)$, $Cu_3(BTC)_2$ and $Cu_2(BDC)_2(DABCO)$.

2. Experimental

2.1. Synthesis of the metal-organic framework $Cu_2(BPDC)_2(BPY)$

In a typical preparation [48], a solid mixture of H_2BPDC (H_2BPDC = 4,4′-biphenyldicarboxylic acid; 0.630 g, 2.4 mmol), bpy (bpy = 4,4′-bipyridine; 0.198 g, 1.2 mmol), and $Cu(NO_3)_2 \cdot 3H_2O$ (0.630 g, 2.4 mmol) was dissolved in a mixture of DMF (DMF = *N*,*N*′-dimethylformamide; 180 mL), pyridine (1.8 mL), and methanol (18 mL). The resulting solution was stirred at 70 °C for 5 min, and then distributed to 20 mL vials. The vials were then heated at 120 °C in an isothermal oven for 24 h. After cooling the vials to room temperature, the solid product was removed by decanting with mother liquor and washed in DMF (3 × 20 mL) for 3 days. Solvent exchange was carried out with methanol (3 × 20 mL) at room temperature for 3 days. The material was then evacuated under vacuum at 140 °C for 6 h, yielding 0.605 g of $Cu_2(BPDC)_2(BPY)$ in the form of blue crystals, correspond to 66% based on copper.

2.2. Catalytic studies

In a typical experiment, a mixture of phenylacetylene (0.11 mL, 1.0 mmol) and diphenyl ether (0.07 mL) as an internal standard in toluene (4 mL) was added into a 25 mL flask containing the pre-determining amount of $Cu_2(BPDC)_2(BPY)$ catalyst. The catalyst concentration was calculated with respect to the copper/phenylacetylene molar ratio. The reaction mixture was flushed with argon and then stirred at 80 °C for 180 min. Reaction conversion was monitored by withdrawing aliquots from the reaction mixture at different time intervals, quenching with water (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 diphenyl ether. The product identity was further confirmed by GC–MS and NMR. To investigate the recyclability of the $Cu_2(BPDC)_2(BPY)$, the catalyst was separated from the reaction mixture by simple centrifugation, washed with copious amounts of methanol, dried 140 °C under vacuum in 2 h, and reused if necessary. For the leaching test, a catalytic reaction was stopped after 15 min, analyzed by GC, and centrifuged to remove the solid catalyst. The reaction solution was stirred for a further 165 min at 80 °C. Reaction progress, if any, was monitored by GC as previously described.

3. Results and discussion

The metal-organic framework $Cu_2(BPDC)_2(BPY)$ was synthesized according to a modified literature procedure [48], and was characterized by several techniques, including XRD, SEM, TEM, TGA, FT-IR, AAS, H_2-TPR, and nitrogen physisorption measurements (Figs. S1–S8). The $Cu_2(BPDC)_2(BPY)$ was then used as catalyst for the A^3 reaction of 1,2,3,4-tetrahydroisoquinoline, benzaldehyde, and phenylacetylene to form 2-benzyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (product A, Scheme 1) as the principal product, and 2-(1,3-diphenylprop-2-ynyl)-1,2,3,4-tetrahydroisoquinoline (product B, Scheme 1) as the by-product. Initial studies addressed the effect of phenylacetylene:benzaldehyde:tetrahydroisoquinoline molar ratio on the reaction conversion. The C1-alkynylation reaction of tetrahydroisoquinoline was carried out in toluene at 80 °C for 180 min, in the presence of 5 mol% $Cu_2(BPDC)_2(BPY)$ catalyst, using reagent molar ratio of 1:1:1, 1:1.1:1.1, 1:1.2:1.2, and 1:1.5:1.5, respectively. Aliquots were withdrawn from the reaction mixture at different time intervals and analyzed by GC, giving kinetic data during the course of the reaction (Fig. 1). It was found that the reaction using one equivalent of benzaldehyde and one equivalent of tetrahydroisoquinoline afforded 88% conversion after 180 min. Increasing the amount of benzaldehyde and tetrahydroisoquinoline to 1.1 equivalents led to 94% conversion after 180 min. The reaction using more than 1.1 equivalents of benzaldehyde and tetrahydroisoquinoline afforded similar conversion even though it proceeded more readily. It was found that the $Cu_2(BPDC)_2(BPY)$-catalyzed C1-alkynylation reaction of tetrahydroisoquinoline offered high regioselectivity to the *endo*-yne-product. Indeed, more than 99% of (A) was achieved, leaving less than 1% of (B) in the product mixture.

In the first example of the same A^3 reaction using CuI catalyst, the reaction was carried out at 50 °C, though the reaction

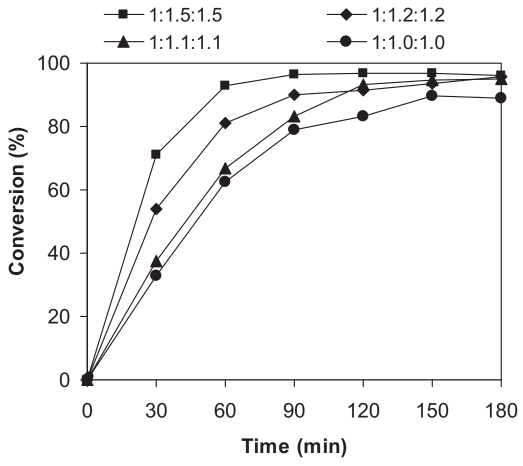

Fig. 1. Effect of phenylacetylene:benzaldehyde:tetrahydroisoquinoline molar ratios on the reaction conversion.