



## C–H bond arylation of anilides inside copper-exchanged zeolites



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### ABSTRACT

Syntheses of fine-chemicals using heterogeneous catalysts have tremendous industrial potentials, yet C–H functionalization studies have been largely focused on homogeneous catalysis. We report here the first *meta*-selective C–H bond arylation of anilides inside copper-exchanged zeolites. Mid- or large-pore zeolite frameworks are selected as supports to access large organic molecules, and atomically distributed copper catalysts exhibit high activities (84–90% conversions) toward direct arylation of anilides with diphenyliodonium salt on 0.5 mol% copper concentration. Computational studies indicate the well-fitted copper-aryl complexes inside zeolite frameworks. Electron micrographs, elemental analyses, and reusability study show no observable leaching of catalytically active copper species during the reactions tested. These results demonstrate the practical synthetic potential of copper-exchanged zeolites as promising supported molecular catalysts to afford biaryl motifs-containing compounds with high catalytic activity, chemical stability, and recyclability.

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### 1. Introduction

One of the prime goals of synthetic chemists is to develop efficient synthetic methods to construct sophisticated organic scaffolds. Over several decades, transition metal catalysis has expedited retrosynthetic disconnections, inventing original, innovative, and concise molecular transformations [1]. Advances in selective C–H bond functionalization engender new reaction pathways for C–C bond formations [2–4]. Thanks to the pharmaceutical or fine chemical importance of biaryl structural motifs, atom economical methods for aryl–aryl bond formation have been studied extensively. Direct arylation reaction via C–H bond cleavage creates shortened synthetic operations and can also minimize by-product formation [5]. Pre-coordination allows site-selective transformation of C–H bond, and directing groups predominantly place transition metal in close proximity to arene *ortho* C–H bond [6,7].

Thereby, remote functionalization, e.g. *meta*-selective arylation, distal to directing groups is largely restricted.

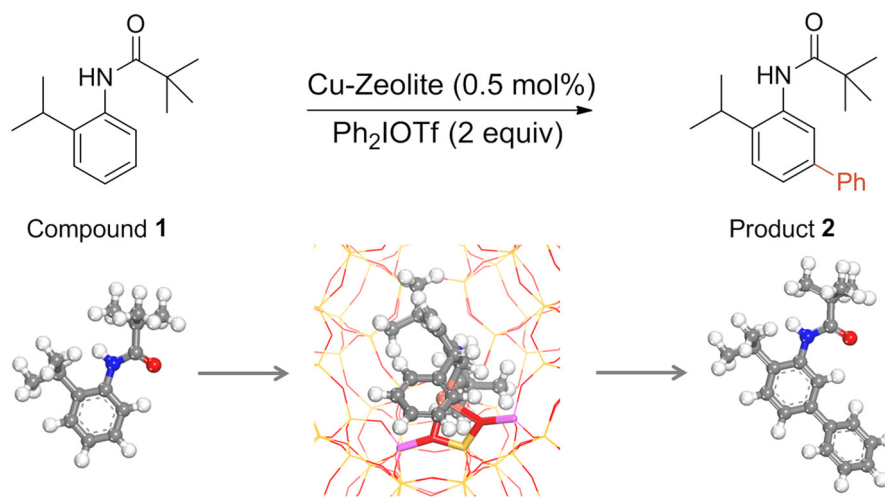
Recently, Yang et al., introduced a rationally designed U-shaped nitrile-containing template approach to the direct remote C–H transformation of indolines [8]. An electron-withdrawing sulfonamide linkage was incorporated to prevent *ortho* or *para* C–H functionalization. Furthermore, the nitrile-adjacent geminal alkyl groups were installed to tune *meta*-directing conformations through the Thorpe-Ingold effect. Luo et al. developed a *meta*-selective arylation methodology of phenols via a traceless CO<sub>2</sub> directing group relay strategy [9]. However, template-aided synthesis is accompanied by the extra burden of installation and removal of auxiliary groups. The Gaunt group developed an intriguing *meta*-selective arylation reaction of *N*-protected anilides by using diaryliodonium salts and Cu(OTf)<sub>2</sub> through innate electronic effect [10,11].

Despite the recent progresses in site-selective C–H functionalization, the reactions have been mostly restricted on homogeneous catalysis due to its molecularly defined catalytic nature and the well-established characterization protocols. In contrast, development of heterogeneous catalysis to synthesize complex organic molecules has been hampered due to uncertainties of catalytic sites and aggregation or leaching of active species during chemical reactions [12,13]. So far, a few groups reported direct arylation methods

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**(i) Reusability and High Activity**  
**(ii) C-H Bond Arylation inside Zeolites**  
**(iii) Stable Catalysts toward Leaching**

**Scheme 1.** Outline of the current direct arylation inside copper-exchanged zeolites.

based on heterogeneous catalysis using metal nanoparticles, metal oxide, or Pd/C [14–18]. Considering the industrial importance, the syntheses of fine chemicals having complex molecular structures via heterogeneous catalysis have enormous potentials. Supported molecular catalysts located at the border between homogeneous and heterogeneous catalysts have been investigated as an emerging class [19]. Atomically distributed active sites inside structurally well-defined supports can exist with near uniformity [20]. Thanks to the superior metal-ion exchange capacity and microporous crystalline structures composed of uniform window and channel sizes, zeolite frameworks are selected as catalyst supports [21–25]. Herein, we describe the first *meta*-selective C–H bond arylation of anilides using copper-exchanged zeolites with high catalytic activities (Scheme 1). Kinetic and computational studies are performed to reveal the high catalytic efficiency of the zeolite catalysts to conduct C–H bond arylation. Their chemical stabilities over the reactions are evaluated via transmission electron microscopy (TEM) and energy-dispersive X-ray spectroscopy (EDS) analyses.

## 2. Experimental

### 2.1. General procedures and materials

The starting material pivanilide **1** was prepared from 2-isopropylaniline (Alfa-Aesar) and pivaloyl chloride (Sigma-Aldrich) based on the reported protocols [10]. Diphenyliodonium triflate (Ph<sub>2</sub>IOTf) was synthesized using reported procedure [26]. Anhydrous 1,2-dichloroethane (DCE) was purchased from Sigma-Aldrich. For TLC, glasses pre-coated (0.25 mm) with Merck silica gel 60 PF<sub>254</sub> were used and visualized using a UV lamp ( $\lambda_{\text{max}}$  254 nm). Flash column chromatography was performed with Merck 9383 Kieselgel 60 silica gel (230–400 mesh). <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on an Agilent 400-MR DD2 spectrometer; chemical shifts are given on the  $\delta$ -scale in ppm, and a residual solvent peak was used as a reference.

### 2.2. Preparation and characterizations of copper-zeolites

Beta (CP 814E, Si/Al = 12.5), Y (CBV 100, Si/Al = 2.55), and mor-denite (CBV 10A, Si/Al = 6.5) zeolites were obtained from Zeolyst International Co. Cu-zeolites were synthesized by solution ion-exchange of Cu<sup>II</sup> ion on various zeolites by using 0.2 M aqueous solution of Cu(NO<sub>3</sub>)<sub>2</sub> [27]. The solution contained twice amount of Cu<sup>II</sup> ion needed for complete ion exchange. After the ion exchange step, the sample was filtered, washed, and then dried at 100 °C overnight. To ensure complete ion exchange, this entire process was repeated twice. Various transition metal ion-exchanged beta zeolites were synthesized in the same way using the aqueous solution of the corresponding transition metal nitrate precursors such as Fe(NO<sub>3</sub>)<sub>3</sub>, Cr(NO<sub>3</sub>)<sub>3</sub>, Ni(NO<sub>3</sub>)<sub>2</sub>, Co(NO<sub>3</sub>)<sub>2</sub>, Mn(NO<sub>3</sub>)<sub>2</sub>, and Zn(NO<sub>3</sub>)<sub>2</sub>. All the catalyst samples were then calcined at 500 °C for 2 h using muffle furnace under air atmosphere prior to testing and characterization. The concentration of Cu in the zeolites before and after reaction was determined by ICP-OES (Varian, 720-ES) after acid digestion using hydrofluoric acid. TEM images of Cu-zeolites before and after reaction were collected using the JEOL JEM-2100F microscope operated at 200 kV. Elemental maps for Cu, Al, and Si before and after reaction were obtained by EDS analyzer (Oxford Instrument, X-Max<sup>N</sup> 80 T). TEM samples were prepared by dusting the gently grounded zeolites samples onto a carbon coated Au-grid.

### 2.3. Protocol for the direct arylation

A mixture of pivanilide **1** (50 mg, 0.228 mmol), diphenyliodonium triflate (196 mg, 0.456 mmol), copper-zeolite catalyst (0.5 mol%) in DCE (1.25 mL) was taken in a closed glass vial and was extensively stirred (~1000 rpm) at 70 °C for 24 h. After completion of reaction (as indicated by TLC), the glass vial was centrifuged at 4500 rpm for 15 min. The heterogeneous catalyst deposited at the bottom and the clear supernatant liquid was separated and concentrated in vacuo. The residue was then subjected to flash column chromatography (*n*-hexane:ethyl acetate, 20:1) to afford the product **2** as a white solid.

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