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### Cu<sup>II</sup>/H-USY as a regenerable bifunctional catalyst for the additivefree C–H amination of azoles

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A copper-exchanged H-USY zeolite catalyst was developed for the direct C–H amination of azoles with secondary amines in HFIP. The reaction was performed under air without any external additive. The Cu/H-USY catalyst could be regenerated for further re-use without significant decrease in activity.

The formation of sp<sup>2</sup> C–N bond by transition-metal catalyzed reactions is of great interest for the preparation of (hetero)arylamines which are prevalent in biological, pharmaceutical and material sciences.<sup>1</sup> The transition metal-catalyzed amination of aryl (pseudo)halides, such as the Buchwald-Hartwig coupling,<sup>2</sup> is probably one of the most reliable ways to construct these C–N bonds. Nevertheless, the direct amination of aromatic C–H bonds is regarded as a more powerful alternative by virtue of its high atom economy, and the wide variety of available reactants with C–H bonds.<sup>3</sup>

In particular, direct C-H amination has been recently studied as a straightforward pathway to biologically relevant 2aminoazoles.<sup>4</sup> Significant progress has been realized by employing either a homogeneous<sup>5</sup> or heterogeneous<sup>6</sup> transition metal-based catalyst in combination with a simple amine under oxidative conditions. Metal-free approaches have also been described and mainly rely on the use of an iodine catalyst with stoichiometric organic oxidant, or on electrochemical synthesis.<sup>7</sup> However, despite these significant efforts, these methods require in most cases the use of high temperatures and large amounts of catalyst and/or additives. Thus, in line with our desire to develop sustainable methods in catalytic C-H activation,<sup>8</sup> we aimed at designing a simple and efficient catalyst for the direct amination of azoles. Given the success of copper catalysts in the presence of either a base or an acid additive, we reasoned that using an acid zeolite support, partially exchanged with copper ions, may provide a bifunctional catalyst that can circumvent the need for an extra

acid or base additive. Indeed, the low cost associated with the high stability, ion-exchange capacity and modularity of zeolite materials are very interesting features that can be advantageous for catalytic organic transformations.<sup>9</sup>

After testing a wide array of copper-exchanged zeolites and studying the influence of the reaction parameters, we optimized the model reaction between benzoxazole **1a** and morpholine **2a** (Tables S1 and S2, ESI<sup>+</sup>). Thus, the resulting aminoazole **3a** was obtained in 91% yield in the presence of Cu/H-USY catalyst (3 mol% Cu) after 24 h at 50 °C in HFIP. Ultrastable Y zeolite (USY), derived from zeolite Y, not only provides strong acidity, but also a sufficiently large pore size which grants the reactants access to the pores. To our delight, the reaction could be performed under air without the use of any external additive. Several other amines were tested under the optimal reaction conditions (Table 1).

Benzoxazole reacted efficiently with simple cyclic amines with 5-, 6- or 7-membered rings (89-96 % for 3b-d). Besides 2a, other heteroatom-containing cyclic amines were also shown to be suitable substrates, achieving good yields of the desired coupling products 3e-g. An exception concerns the use of thiomorpholine **2h**, a S-containing amine which led to catalyst inhibition, as only 34% yield of **3h** was obtained. Secondary aliphatic and benzylic amine derivatives were also shown react smoothly, giving the corresponding aminoazoles 3i-l with good to excellent yields. In contrast, and as observed in most of the transition-metal catalyzed azole aminations, primary aliphatic (cyclohexylamine) or aromatic (aniline) amines did not lead to any coupling product formation. The reason for such observation is not known, but we assume that they are too reactive substrates as intractable complex mixtures were obtained in both cases.

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<sup>&</sup>lt;sup>+</sup>Electronic Supplementary Information (ESI) available: DOI: 10.1039/x0xx00000x

#### COMMUNICATION





<sup>*a*</sup> *Reaction conditions*: heteroarene (0.5 mmol), **2a** (1 mmol), HFIP (2 mL), catalyst (3 mol% Cu, 200 mg), 50 °C, 24 h. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> GC conversions. <sup>*d*</sup> Reaction performed with H-USY only (200 mg). <sup>*e*</sup> Reaction performed with Cu(OAc)<sub>2</sub>.H<sub>2</sub>O only (3 mol%). <sup>*f*</sup> Reaction performed with Cu(OAc)<sub>2</sub>.H<sub>2</sub>O (3 mol%) + H-USY (200 mg).

Subsequently, we briefly examined the scope of heteroarenes in the Cu-catalyzed amination with **2a** (Table 2).

#### **Table 2** Scope of the amination of heteroarenes with **2a**<sup>a,b</sup>



mL), catalyst (3 mol% Cu, 200 mg), 50 °C, 24 h. <sup>b</sup> Isolated yields.

Unfortunately, no coupling product was obtained when using benzothiazole or 1-methylbenzimidazole. However, benzoxazoles bearing electron-donating or -withdrawing substituents at the C5 position, such as methoxy (**1b**) and chloro (**1c**) groups, reacted smoothly to give very high yields. In contrast, the reaction with 5-nitrobenzoxazole gave a low yield of the desired product. Interestingly, 5-phenyl-1,3,4-oxadiazole proved to be reactive as the coupling product was obtained with 61 % yield.

Under optimized reaction conditions, the stability and recyclability of the Cu/H-USY were evaluated in the model

reaction between **1a** and **2a**. Powder X-ray diffraction (EXRD) analysis demonstrated the structural stability<sup>1</sup>OP (MC 2001) define 2001) analysis demonstrated the structural stability<sup>1</sup>OP (MC 2001) define 2001) analysis demonstrated the structural stability<sup>1</sup>OP (MC 2001) define 2001) dependent of the structural stability<sup>1</sup>OP (MC 2001) dependent of the structural stability, and this could be performed seven times with only a slight decrease of activity (Fig. 1b).



**Fig. 1** (a) PXRD patterns of H-USY, fresh Cu/H-USY and Cu/H-USY after 4 runs; (b) catalytic activity of the regenerated Cu/H-USY after 8 runs.

In an attempt to gain insights into this Cu/zeolite-catalyzed azole amination, we first performed X-Ray absorption spectroscopy (XAS) on the freshly prepared Cu/H-USY to probe the Cu centres. Fig. 2a reports a comparison between the normalized XANES spectra collected for Cu/H-USY and  $Cu(OAc)_2$  which was used for its preparation, along with other representative Cu samples. While Cu(0) and Cu(I) references display a close but distinct pre-edge at 8982 and 8983 eV, respectively, Cu(II) reference materials (CuO and Cu(OAc)<sub>2</sub>) display a pre-edge at 8967 eV. Interestingly, the spectrum of Cu/H-USY presents a shoulder around 8967 eV which suggests that the Cu ions are mostly in the +2 oxidation state.<sup>10</sup> Also, the EXAFS spectra of Cu/H-USY and Cu(OAc)<sub>2</sub> show similar peaks at around 1.5 Å (no phase shift correction applied) which are typical of Cu-O bonds (Fig. 2b). Nevertheless, the characteristic Cu-Cu peak of Cu(OAc)<sub>2</sub> is no longer present in the Cu/H-USY sample. Instead, a new peak at around 2.6 Å appeared, which might indicate a true exchange of copper ions

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into the zeolite, rather than a simple impregnation of  $\mbox{Cu(OAc)}_2$  species.

Secondly, we performed a series of control experiments to try to understand the reaction mechanism of this C–H amination. Either running a Cu-, zeolite- or air-free reaction resulted in no reaction at all, while the in situ combination of  $Cu(OAc)_2.H_2O$  and H-USY under air gave catalytic activity (Tables 1 and S2, ESI†). This underlines the crucial role of both the copper catalyst and the zeolite, the association of which is crucial in order to reach high catalytic activity. This strongly contrasts with other metal-supported catalysts employed for similar direct azole amination where the solid support only serves as an anchor point for the metal sites.<sup>6</sup>



**Fig 2** (a) Normalized Cu-XANES spectra showing Cu(0), Cu(I) and Cu(II) model compounds with Cu/H-USY; (b) EXAFS spectra of Cu(OAc)<sub>2</sub> (blue), fresh Cu/H-USY (red) and spent Cu/H-USY (green). (c) possible mechanism for the copper-catalyzed amination of azoles

The zeolite plays three important roles here: (i) the acidic protons of Cu/H-USY activate the benzoxazole ring, which favours attack of the amine reactant on the C2-position (significantly lower activities were obtained when using either Cu/Na-USY or Cu/NH<sub>4</sub>-USY; see Table S1, ESI<sup>+</sup>); (ii) it may stabilize Cu intermediates by weak interaction, as a rather low amount of Cu can be employed compared to the literature (the large majority of homogeneous Cu-catalyzed direct aminations require at least 10 mol% Cu);<sup>5</sup> (iii) the high hydrophobicity of the strongly dealuminated Y zeolite can assist in removing water molecules that are formed in this C–H/H–N oxidative coupling; indeed, we observed lower activities with zeolites possessing lower Si/Al ratios, and which

are thus less hydrophobic (Table S1, ESI<sup>+</sup>). Anothericaspect concerns the use of HFIP as a solventPott 1819235064084586 assume that it participates in the stabilization of metal intermediates via hydrogen bonding.<sup>11</sup> Finally, we decided to investigate the potential involvement of the ring-opened amidine derivative 4 which is very commonly observed and was proven to be a true intermediate in similar azole amination processes. However, under the optimized conditions, this product was never observed by GC or <sup>1</sup>H NMR analysis of the crude mixture. In a parallel experiment, we synthesized this compound and reacted it alone with Cu/H-USY. No product formed, and full recovery of 4 was observed instead, ruling out a ring-opening step of 1a in the present reactions. All the obtained results, along with recent findings showing that Cu/O<sub>2</sub> systems likely participate in catalytic C-H functionalizations via single electron transfer processes,12 allow us to propose a plausible mechanism for this Cu/H-USY catalyzed azole amination (Fig. 2c). First, deprotonation of the amine substrate (assisted by an X ligand, which can be either a residual acetate from the preparation of Cu/H-USY or the negatively charged zeolite framework) results in the formation of a copper-amido complex. Subsequent protonation of the azole by the acid zeolite protons facilitates the addition of the amine species on the C2-position, with concomitant reduction of Cu(II) to Cu(I). Finally, oxidative rearomatization of the obtained radical intermediate occurs in order to form the product along with a water molecule, and regenerate the Cu(II) catalyst.

In conclusion, we have shown that the copper(II)exchanged zeolite, Cu/H-USY, can efficiently catalyze the direct amination of azole derivatives with secondary amines. The use of a small amount of copper, air as the oxidant and the fact that no extra additives are needed, are significant practical advantages. Furthermore, the catalyst could be recovered, regenerated and re-used three times with very little loss of activity. More work is under way in order to better understand the beneficial role of the zeolite during this process.

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#### Conflicts of interest

There are no conflicts to declare.

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# Cu<sup>II</sup>/H-USY as a regenerable bifunctional catalyst for the additive-free C<sub>10.</sub>H<sup>View Article Online</sup> amination of azoles

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The use of bifunctional Cu<sup>II</sup>/H-USY catalyst for the direct amination of azoles under air and without additive has been disclosed.