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Cu^{I}–USY as a Ligand-Free and Recyclable Catalytic System for the Ullmann-Type Diaryl Ether Synthesis

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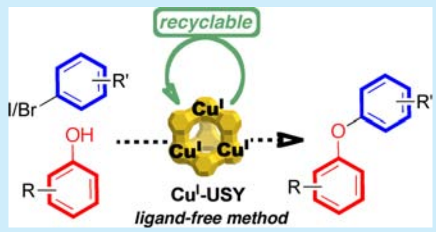
Supporting Information

ABSTRACT: The catalytic potential of copper(I)-exchanged zeolites was evaluated in the Ullmann-type synthesis of diaryl ethers. Among four investigated zeolites (i.e., USY, MOR, *β*, and ZSM5), Cu^{I}–USY was the best catalyst and proved efficient under ligand-free conditions in toluene at 120 °C. Cu^{I}–USY was also easy to recover and was recyclable up to five times without significant loss of activity.



The diaryl ether motif is encountered in numerous bioactive natural products,[1] such as the antitumor riccardin C,[2] the antibiotic piperazinomycin,[3] and the hormone thyroxin,[4] as well as in non-natural useful agrochemicals, such as insecticidal cyper- and deltamethrin[5] (Figure 1).

This motif is also found in many natural and synthetic polymers,[6] lignin[7] being archetypal and the most common of them.

Because of their relevance in life and materials sciences, diaryl ethers have thus received much attention from synthetic organic chemists.[8] This special attention has given rise to various synthetic methods, among which the most utilized and practical ones remain metal-mediated cross-coupling reactions of aryl halides with phenols.[1a,8] Pioneered by Ullmann in the early 1900s using harsh reaction conditions and stoichiometric amounts of copper powder/salts as metal source,[9] such coupling reactions have undergone a major breakthrough a hundred years later with the discovery of adequate and versatile Pd^{0}-[10] and Cu^{I}-based[11] catalytic systems. Since then, many ligand/metal salt combinations have been reported as catalysts for diaryl ether synthesis under homogeneous and much milder conditions. In contrast, only a few heterogeneous versions have been mentioned, despite the practical benefits of this catalysis mode (i.e., easier isolation of products/catalyst, recyclability of the catalyst, etc.). Often, catalysts for the Ullmann coupling have been grafted on of organic polymers[12] as well as on carbon[13] or silica[14] materials. Simple nanoparticles, in which copper is at either the +I or +II oxidation state,[15] and metal–organic frameworks made up of copper ions[16] were also reported as effective catalytic systems. Whatever the performance of these heterogeneous materials, there is still a demand for alternative catalysts enabling this transformation of high industrial relevance.

As we have recently shown, zeolite materials are powerful supports for copper species, especially Cu^{I} species.[17] The Cu^{I} immobilization on such cheap supports gave fully inorganic and insoluble Cu^{I}-based materials and resulted in efficient ligand-free catalysts for organic transformations as various as Huisgen[18] and Dorn[19] cycloadditions, multicomponent reac-

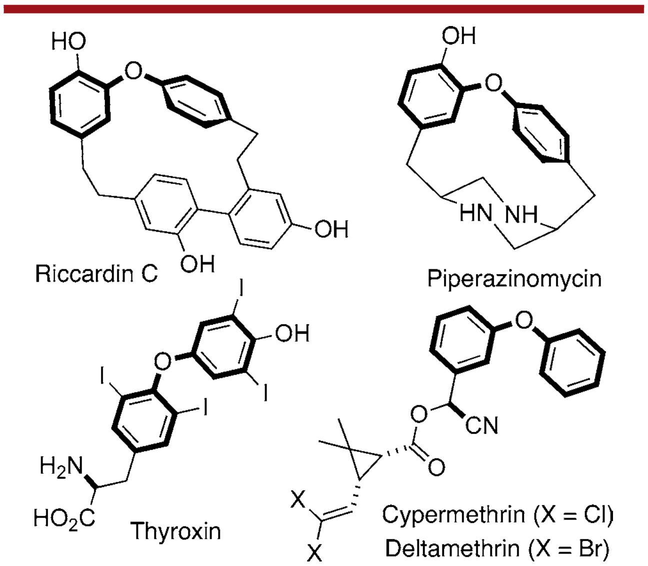


Figure 1. Representative examples of bioactive compounds exhibiting the diaryl ether motif.

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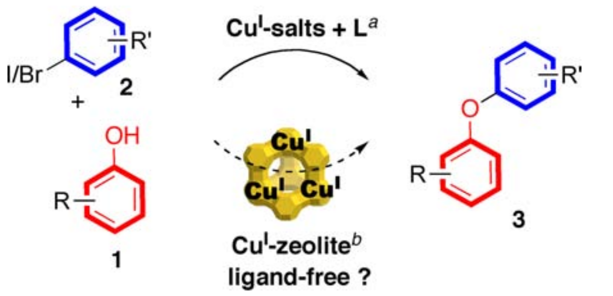
tions,[20] and Glaser homocoupling.[21] In order to further expand our Cu^I–zeolite chemistry toolbox, herein we report their catalytic efficiency in the arylation of phenols with either aryl iodides or bromides (Scheme 1).

Scheme 1. From (a) Standard Homogeneous Catalytic Systems (L = ligand) to (b) the Here-Investigated Heterogeneous Ligand-Free Version



In a first set of experiments, we evaluated the arylation potential of a series of Cu^I–zeolites, easily prepared by thermally driven ion-exchange from four representative and cheap zeolites (i.e., H-USY, H-MOR, H-*β*, and H-ZSM5) (Table 1).[22] This preliminary survey was performed under standard Ullmann-type reaction conditions (i.e., Cs_2CO_3 as base and DMF as solvent) using 3,5-dimethylphenol **1a** and iodobenzene **2a** as model coupling partners. Analyses of the reaction mixtures after 20 h of stirring at 120 °C revealed highly distinct catalytic behaviors regarding the nature of the zeolitic support. Cu^I–USY appeared as the best system in the absence of any additional ligand. While only poor conversions and low yields were obtained with Cu^I–MOR, Cu^I–*β*, and Cu^I–ZSM5 as catalysts (Table 1, entries 2–4), Cu^I–USY indeed gave full conversion with a promising 75% yield in diaryl ether **3a** (Table 1, entry 1). This catalytic trend in favor of Cu^I–USY compared to other Cu^I-modified zeolites is reminiscent of our previous observations for other Cu^I–zeolite-catalyzed reactions.[17–21] The catalyst loading was also scrutinized (Table 1, entries 5 and 6). Lowering the Cu^I loading to 5 mol % resulted in a sharp decrease in conversion and thus in yield (Table 1, entry 5). Its increase to 20 mol % led to complete conversion but with only 55% yield of diaryl ether **3a** (Table 1, entry 6). Likewise, reduced conversions and yields were obtained when the **1a**/**2a** ratio was lowered from 1.5:1 to either 1:1 or 1:1.5 (Table 1, entries 7 and 8 vs 1). Regarding reagent concentration, we observed that the more concentrated in **2a** the more efficient the Cu^I–USY catalyst was (Table 1, entries 9 and 10). A 1 M concentration of **2a** in DMF was found to be optimal, furnishing **3a** in an excellent yield of 89% (Table 1, entry 10).

Table 1. Evaluation of Cu^I–Zeolites for the Phenylation of 3,5-Dimethylphenol 1a with Iodobenzene 2a[a]

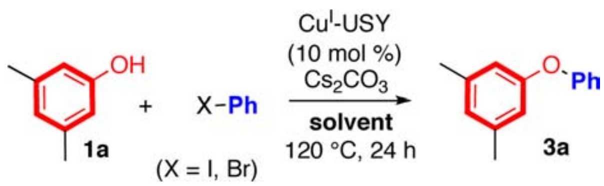
entry	catalyst	loading (mol %)	yield[b] (%)
1	Cu^I–USY	10	75
2	Cu^I–MOR	10	39[c]
3	Cu^I–*β*	10	13[c]
4	Cu^I–ZSM5	10	11[c]
5	Cu^I–USY	5	18[c]
6	Cu^I–USY	20	55
7	Cu^I–USY	10	48[d]
8	Cu^I–USY	10	58[e]
9	Cu^I–USY	10	19[c,f]
10	Cu^I–USY	10	89[g]
11	none		[h]
12	H-USY	10	[h]
13	CuCl	10	33[c]

[a]Reactions run with **1a** (1.5 equiv), **2a** (1.0 equiv with a 0.5 M concentration), and Cs_2CO_3 (2.0 equiv), unless otherwise stated. [b]Yields of isolated pure product **3a**. [c]Incomplete conversion. [d]Reaction run with a **1a**/**2a** ratio of 1:1. [e]Reaction run with a **1a**/**2a** ratio of 1:1.5. [f]Reaction run with a 0.1 M concentration of **2a**. [g]Reaction run with a 1 M concentration of **2a**. [h]No conversion.

Control experiments (Table 1, entries 11–13) confirmed that the reaction was not promoted without catalyst (entry 11) or with the native H-USY (entry 12). With CuCl alone as catalyst (i.e., under homogeneous and ligand-free conditions), the reaction was promoted but with a substantially lower efficiency in terms of conversion and yield (Table 1, entry 13 vs 1). Unsurprisingly, the coupling process was ineffective in the presence of the native H-USY (Table 1, entry 13). These data revealed the key and synergic effect of the Cu^I ions and the USY framework supporting these ions for catalyzing the coupling reaction under ligand-free conditions.

With Cu^I–USY as the most efficient catalyst, we then screened various solvents to fine-tune the reaction conditions (Table 2). Among the solvents screened, DMF, acetonitrile, and toluene gave the best results (Table 2, entries 1–3). DMSO, though a common solvent for Ullmann-type reactions, and dioxane led to lower conversions and yields (Table 2, entries 4 and 5). In protic sovents such as ethanol or water, the coupling process proved even less effective, furnishing, respectively, the expected **3a** in low yield or trace amounts (Table 2, entries 6 and 7). In ethanol, ethoxybenzene was also

Table 2. Screening of Solvents for the Cu^I–USY-Catalyzed Phenylation of 1a[a]



entry	solvent	yield[b] (%)
1	DMF	89 (58)[c,d]
2	$PhCH_3$	85 (83)[c]
3	CH_3CN	79 (69)[c,d]
4	DMSO	44[d]
5	1,4-dioxane	52[d]
6	EtOH	15[d,e]
7	H_2O	traces[d]
8	none	60

[a]Reactions run with **1a** (1.5 equiv), PhI (1.0 equiv with a 1 M concentration), and Cs_2CO_3 (2.0 equiv), unless otherwise stated. [b]Yields of isolated pure product **3a**. [c]Reactions run with PhBr (i.e., X = Br) in place of PhI (i.e., X = I). [d]Incomplete conversion. [e]Traces of ethoxybenzene were detected.

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formed as a byproduct, probably through the competitive coupling of iodobenzene with ethanol. Cu^I–USY was also able to provide **3a** under solvent-free conditions but with a moderate efficiency (Table 2, entry 8). Cu^I–USY could also catalyze the phenylation process with bromobenzene in place of iodobenzene. The latter reaction was faster in toluene than in DMF or acetonitrile (Table 2, entries 1 and 3 vs 2), the yield in toluene being very similar regardless the nature of the halogen. Here, it is also worth noticing that toluene often appeared as the best solvent for organic reactions catalyzed by Cu^I–zeolites, although it was quite unusual for Ullmann-type coupling reactions.

The effect of base on the coupling process was further examined in toluene as solvent (Table 3). No reaction was observed in the absence of base as well as in the presence of sodium carbonate or hydroxide (Table 3, entries 1–3). Only traces of diaryl ether **3a** were detected when the reaction was conducted with triethylamine as organic base (Table 3, entry 4). Shifting from sodium to potassium salts enabled the coupling reaction but with low efficiency in the case of the carbonate and the hydroxide (Table 3, entries 5 and 6). The phosphate was much more effective and gave high yield of the coupling product, despite incomplete conversion (Table 3, entry 7). Potassium phosphate and cesium carbonate are standard bases for such coupling, but with Cu^I–USY as catalyst, cesium carbonate proved to be the best, being more effective as potassium phosphate in terms of conversion and yield (Table 3, entry 8). Interestingly enough, these conditions combined to provide a workup procedure that gave the expected crude product **3a** in a > 95% purity as revealed by ^1H NMR spectroscopy (see the Supporting Information).

Table 3. Screening of Bases for the Cu^I–USY-Catalyzed Phenylation of 1a with 2a[a]

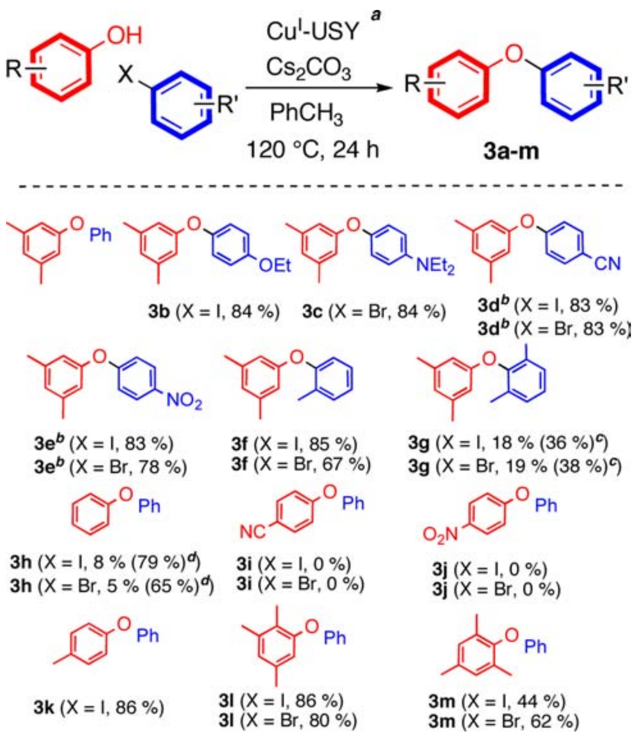
entry	base	yield[b] (%)
1	none	[c]
2	Na_2CO_3	[c]
3	NaOH	[c]
4	Et_3N	traces[d]
5	K_2CO_3	18[d]
6	KOH	23[d]
7	K_3PO_4	82[d]
8	Cs_2CO_3	85

[a]Reactions run with **1a** (1.5 equiv), **2a** (1.0 equiv with a 1 M concentration), and base (2.0 equiv), unless otherwise stated. [b]Yields of isolated pure product **3a**. [c]No conversion. [d]Incomplete conversion.

Under the so-optimized conditions, the recyclability and stability of Cu^I–USY were evaluated in the model coupling reaction with 3,5-dimethylphenol **1a** and iodobenzene **2a**. Filtration of the crude mixture followed by washing of the resulting solid allowed the easy recovery of the catalyst. The latter could be recycled up to five times without loss in activity. ICP-AES analyses were conducted on fresh and reused catalysts and revealed almost the same copper content. The crude mixtures were also analyzed, and no significant amount of copper species was detected.

With these reaction conditions in hands, we then explored the scope of this ligand-free Cu^I–USY-catalyzed diaryl ether synthesis (Scheme 2). In order to investigate electronic and steric effects, 3,5-dimethylphenol was submitted to coupling with diversely substituted aryl halides.

Scheme 2. Scope of the Cu^I–USY-Catalyzed Diaryl Ether Synthesis



[a]Reactions run with Cu^I–USY (10 mol %), phenol (1.5 equiv), aryl halide (1.0 equiv) and Cs_2CO_3 (2.0 equiv), unless otherwise stated. [b]Only modest conversion (< 30%) obtained in the absence of Cu^I–USY. [c]Reactions run at 140 °C. [d]Reactions run in DMF in place of $PhCH_3$.

Aryl iodides or bromides, *para*-substituted by either electron-donating or -withdrawing groups, led to the formation of expected diaryl ethers **3b–e** in very similar yields, thus revealing no significant electronic effects regarding the aryl halides. With aryl halides bearing cyano or nitro groups, control experiments were conducted in the absence of Cu^I–USY. In both cases, the coupling reactions were much slower than in the presence of catalyst (Scheme 2). These results confirmed that the reactions leading to diaryl ethers **3d** and **3e** were not under pure SNAr control and that Cu^I–USY clearly promoted the coupling under our conditions.[23]

Steric effects were briefly investigated by submitting 2-halotoluenes and 2,6-dimethylphenyl halides to this coupling. Although 2-iodotoluene smoothly reacted to furnish diaryl ether **3f** in high yield, its brominated counterpart proved more difficult to couple. As expected, the more hindered 2,6-dimethylphenyl iodide or bromide proved more difficult to react, even by increasing the temperature to 140 °C. However, they both behaved in the same way, giving the corresponding diaryl ether **3g** in low to modest yields.

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Surprisingly, the coupling of phenol proved difficult in toluene, giving diphenyl ether **3h** in very low yields. However, performing the reaction in DMF restored the reactivity and allowed to isolate **3h** in good to high yields. Less surprisingly, diaryl ethers **3i** and **3j** could not be formed from respectively the electron-poor 4-cyano- and 4-nitrophenols, even in DMF as solvent or at higher temperatures. These results were in line with previous works reporting the ineffectiveness of electron-poor substrates in Ullmann-type coupling.[24]

In contrast, more electron-rich phenols fortunately proved to be better coupling partners, and diaryl ethers **3k** and **3l** were efficiently obtained from *p*-cresol and 2,3,5-trimethylphenol, respectively. The more hindered 2,4,6-trimethylphenol gave the corresponding diaryl ether **3m** in a satisfactory yield, especially with bromobenzene as coupling partner.

In conclusion, we have shown that the copper(I)-exchanged zeolite Cu^I–USY can efficiently catalyze the Ullmann-type synthesis of diaryl ethers under ligand-free conditions. In addition, the catalyst can be easily recovered and recycled up to five times without dramatic loss of activity. Further work is now underway in our groups in order to extend the use of Cu^I–USY as a catalyst in other relevant C–C, C–N, and C–S coupling reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02167.

Full experimental details and characterization data for all products as well as their ^{1}H, DEPT, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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