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Efficient and Versatile Sol-Gel Immobilized Copper Catalyst for Ullmann Arylation of Phenols

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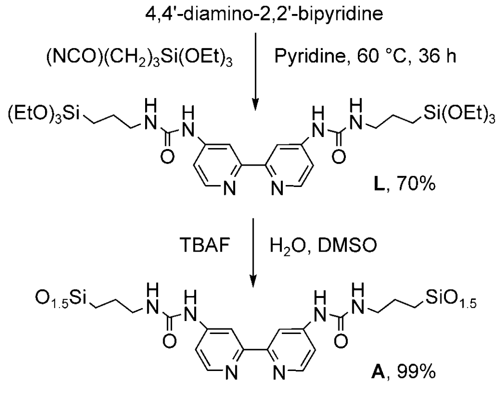
Abstract: A new hybrid silica with urea-based bipyridyl bridging units has been synthesized by a sol-gel process. The copper-complexed hybrid silica is an efficient heterogeneous catalyst for the Ullmann coupling of aryl halides with phenols. It is easily withdrawn and recovered from the reaction media by filtration. It is also a versatile catalyst for subsequent reactions with several substrates yielding products with the same efficiency even after ten reuses and with minimal leaching. This is the first example of the use of a copper-complexed bridged silsesquioxane for the preparation of a recoverable catalyst in modern Ullmann chemistry. This may represent a promising route to the reduction of waste while maintaining economic viability.

Keywords: C−O coupling; copper; heterogeneous catalysis; N ligands; sol-gel bridged silsesquioxane

Diaryl ethers constitute an important class of structural motifs for life sciences and polymer industries.[1] In the mid 1990s Hartwig's and Buchwald's groups both developed Pd-catalyzed C−O coupling reactions of aryl halides and phenols.[2] Despite the high efficiency of Pd/ligand systems in terms of TON, TOF and recyclability for cross-coupling reactions,[3] an alternative and cheaper methodology to form biaryl ethers is the classical Ullmann reaction,[4] but the harsh conditions seriously restricted this methodology (Cu in stoichiometric amount at 150–250 °C). Recently, several groups focused on the revisited Ullmann-type C−O coupling catalyzed by copper/ligand (Cu/L) systems to overcome the high cost of Pd sources.[5,6] Since 2001, our group has developed attractive Cu/L (Schiff bases) systems for the mild coupling of aryl halides with phenols.[6] Due to the attractive cost of Cu sources for Ullmann-type reactions, very few systems have been proposed to recover and reuse the catalytic species.[7] The heterogenization of the Cu/L catalyst can avoid metal residue contamination in the desired coupling product and is of high importance for purity requirements in pharmaceutical chemistry. Moreover, simple filtration reduces the time-consuming processes and the solid catalyst which is easily separated from the products can be recycled. In this context the sol-gel process provides a suitable route to active heterogeneous catalysts.[8] Indeed metal-complexed hybrid silsesquioxanes have already been reported as efficient solid catalysts for asymmetric reactions,[9a,b] metathesis[9c] and Suzuki reactions.[3b]

In the present study, we report the design of a Cu/L catalyst immobilized on silica **A** which was obtained by the sol-gel hydrolysis of a silylated bispyridinyl ligand **L** (Scheme 1) followed by complexation with

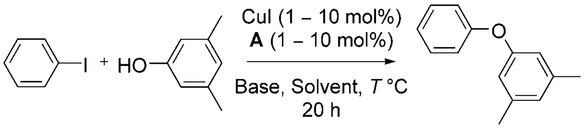


Scheme 1. Immobilization of ligand **L** leading to the hybrid silica **A** by a sol-gel process.

CuI. We also report the suitability of this technique to provide an environmentally friendly solid catalyst for the coupling of aryl halides with phenols.

Bridged silsesquioxane **A** was synthesized from 4,4′-diamino-2,2′-bipyridine[10] and 3-isocyanatopropyltriethoxysilane followed by hydrolysis (Scheme 1). During the catalytic reaction described below, we postulated that the active species of Cu is encapsulated in the hybrid silica by chelation on the two nitrogen atoms of the bipyridine moiety. Besides, this synthetic pathway allows a higher and controlled loading of the organic moiety in the hybrid, compared with the ligand grafting method on silica.[7b]

We chose the Ullmann-type coupling of iodobenzene with 3,5-dimethylphenol as the model reaction (Scheme 2) and after several screening experiments with different combinations of bases and solvents, the best conditions were determined as the following: CuI (10 mol%), **A** (10 mol%) Cs_2CO_3 (2 equiv.) in DMF at 110 °C during 20 h.[11]



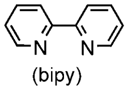
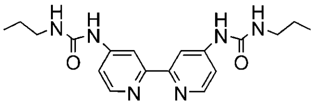
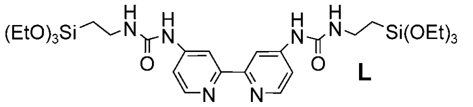
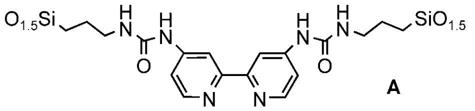
Scheme 2. Ullmann-type coupling of PhI with 3,5-dimethylphenol.

Using these optimal conditions we compared the efficiency of the Cu-complexed hybrid silica **A** to the homogeneous Cu-complexed **L**, 2,2′-bipyridine and its 4,4′-diethylurea derivative and also to the reaction performed without ligand (Table 1).

Fair yields were obtained without ligand or with bipy (entries 1 and 2), contrarily to **L** and **A** which led to almost quantitative formation of the expected product. A good yield was also obtained with the propylurea bipy derivative (entry 3). We then washed our crude media with DMF for all cases and proceeded to a second series of reactions by adding only the reactants and base without further addition of Cu or ligand sources. The high yield (99%, entry 5) observed demonstrates that our Cu-complexed catalyst **A** was highly efficient for this coupling without any loss of activity while no significant coupling reactions were observed in the other cases for the second runs (entries 1–4). Hence besides being a good candidate for this coupling reaction, the Cu-complexed hybrid **A** is also recyclable with similar activity.

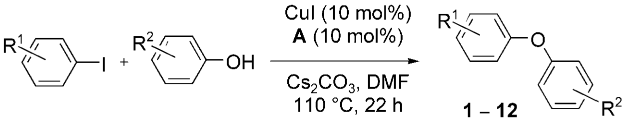
Then the substituent effect on either the aryl iodide or on the phenol was studied in the coupling reaction (Scheme 3, Table 2 and Table 3). The reactions were performed in DMF at 110 °C (22 h). 10% of catalytic system based on CuI and **A** were charged only for the first experiments (entries 1 in Table 2 and Table 3) leading to products **1** and **7**. For both cases the catalytic system was recovered. On one hand the recycling of the heterogeneous catalyst gave the corresponding ethers **2–6** by successively performing and recycling the coupling reactions of 3,5-dimethylphenol with five differently substituted aryl iodides (entries 2–6 in Table 2). On the other hand, moderate (entry 2, product **8**, Table 3) to excellent yields were obtained (en-

Table 1. Influence of the nature of the ligands on the C–O coupling.

Entry	Ligand (10%)	Yield[a] [%]
1	none	50 (<5)[b]
2	 (bipy)	60 (<5)[b]
3		85 (<5)[b]
4	 **L**	95 (<5)[b]
5	 **A**	99 (99)[b]

[a] GC yields determined with 1,3-dimethoxybenzene as internal standard.

[b] GC Yield of product after recycling the catalytic system, see Supporting Information for recycling procedure.



1 – 12
(50 – 95 %)

Scheme 3. Coupling of aryl iodides with phenol derivatives.

Table 2. Coupling of aryl iodides with 3,5-dimethylphenol.

Entry	R^1	R^2	Run	Product	Yield[a]
1	4-H	3,5-$(Me)_2$		**1**	93[b]
2	4-Me	3,5-$(Me)_2$	1	**2**	80
3	4-OMe	3,5-$(Me)_2$	2	**3**	81
4	4-NO_2	3,5-$(Me)_2$	3	**4**	91
5	4-CN	3,5-$(Me)_2$	4	**5**	87
6	4-COOMe	3,5-$(Me)_2$	5	**6**	91

[a] Isolated yield in % after flash chromatography.

[b] A copper leaching of 0.7% (185 ppm), expressed as percentage of the total copper charged, was obtained in the solution phase containing the coupling product **1**.

Table 3. Coupling of substituted phenols with iodobenzene.

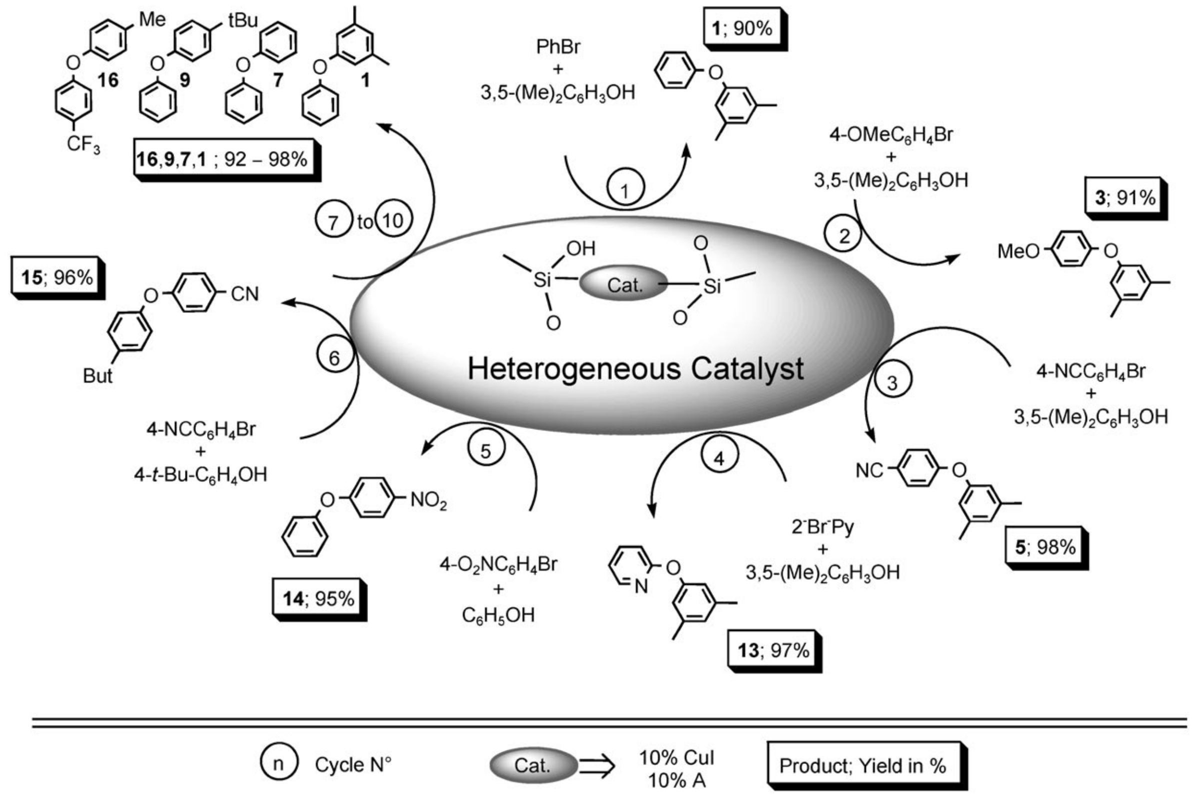
Entry	R^1	R^2	Run	Product	Yield[a]
1	H	4-H		**7**	90
2	H	4-Cl	1	**8**	50
3	H	4-*t*-Bu	2	**9**	91
4	H	4-OMe	3	**10**	95
5	H	4-Me	4	**11**	95
6	H	2-Me	5	**12**	94

[a] Isolated yield in % after flash chromatography.

tries 3–6, products **9**–**12**, Table 3) for the coupling of substituted phenols with PhI. These results clearly show the versatility of this heterogeneous catalyst which can be reused with the same efficiency whichever the substituent on the substrate.[11] Interestingly, a very low amount of copper leaching was observed with our catalytic system. For example a leaching of 0.7% of copper (expressed as percentage of the total copper charged) was measured in the solution phase containing the 3,5-dimethylphenol **1** (Table 2, entry 1).

Finally, this methodology was applied to the C–O coupling of various aryl bromides with different phenols (Scheme 4) in the presence of KI which allows "ArI" *in situ* formation by halogen exchange. The optimized reaction conditions were the following: 10% of CuI/**A** system in DMF, 0.5 equiv. KI, 2 equiv. Cs_2CO_3 at 120 °C (22 h). All the expected products (**1**, **3**, **5**, **13**–**15**) were isolated in almost quantitative yields. As above (Table 2 and Table 3), the Cu and the hybrid **A** sources were only introduced in the first experiment yielding **1**. The catalyst was recovered and reused successively for nine coupling experiments. Interestingly, even the coupling of heteroaryl bromides with 3,5-dimethylphenol gave the corresponding cross-coupling product in high yield (cycle No. 4, product **13**). Besides, similarly to the previous results on ArI, the supported catalytic system was still highly efficient for the subsequent nine runs (cycles No. 2–10). Optimizing the stirring of the media has been engaged after the cycle No. 7 by washing the heterogenized catalytic system with degassed water under nitrogen to eliminate accumulated salt residues during the seven first cycles. Coupling products in cycles No. 7 to 10 were observed in a quantitative manner by MS-GC in the presence of internal standard.

In summary, we have synthesized a new hybrid silica **A** with urea-based bipyridyl bridging units by the sol-gel process. The Cu-complexed **A** turned out as an efficient heterogeneous catalyst for the Ull-



Scheme 4. Coupling of aryl bromides with phenol derivatives with the same catalytic system supported on hybrid silica. *Conditions for cycle No. 1:* 10% CuI, 10% **A**, 2 mmol of ArBr, 3 mmol of ArOH, 0.5 equiv KI, 2 equiv Cs_2CO_3, 3 mL DMF, 120 °C, 22 h. *Conditions for cycles No. 2–10:* 2 mmol of ArBr, 3 mmol of ArOH, 0.5 equiv KI, 2 equiv Cs_2CO_3, 3 mL DMF, 120 °C, 22 h. *For cycles 7 to 10:* Product obtained in quantitative yield by GC-MS with an internal standard.

mann-type coupling of aryl halides with phenols. This hybrid is easily withdrawn and recovered from the reaction media by filtration. It proved to be a versatile catalyst for subsequent reactions with several substrates yielding products with the same efficiency even after ten re-uses. To date, this is the first example in modern Ullmann chemistry of the use of a Cu-complexed bridged silsesquioxane for the preparation of recoverable catalyst. This represents a promising route that may contribute to the reduction of the generation of waste while maintaining economic viability.

Experimental Section

General Procedure for Coupling Reaction of Phenols with Aryl Halides (Entries 1 of Table 2, Table 3 and Scheme 4)

After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Schlenk tube was charged with CuI (0.2 mmol), ligand **A** (0.2 mmol), Cs_2CO_3 (4 mmol) phenol (3 mmol) and aryl halides (2 mmol) if solids. In the case of ArBr, 0.5 equivalents of dry KI were added. The tube was then evacuated, back-filled with nitrogen and capped with a rubber septum. If liquids, phenols and aryl halides were added under a nitrogen atmosphere by syringe at room temperature. Then 3 mL of anhydrous and degassed DMF were added under a nitrogen atmosphere. The septum was removed and the Schlenk tube sealed under a positive nitrogen atmosphere and the reaction mixture stirred in an oil bath (110 °C for ArI, 120 °C for ArBr) for the required time period. After complete consumption of aryl halides, the reaction mixture was then allowed to cool to room temperature. The crude mixture was then filtered under nitrogen with a canula and washed two times with 5 mL of dry DMF. The extracted solution was then filtered on a celite plug, then concentrated under vacuum, and chromatographed on silica gel.

Supporting Information

Detailed experiments on general procedure for coupling reaction and recycling procedure are available as Supporting Information. All the products were isolated by flash chromatography on silica gel and were fully characterized by ^{1}H and ^{13}C NMR and MS-GC. Data are available in the Supporting Information.

Acknowledgements

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