Sol–gel immobilized and reusable copper-catalyst for arylation of phenols from aryl bromides†

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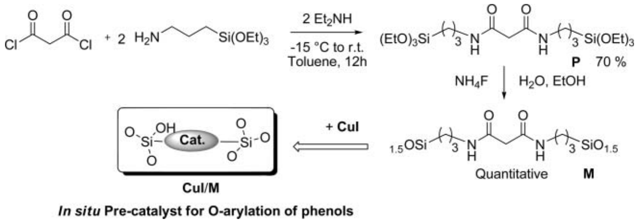
A simple β-diamide ligand was immobilized by the sol–gel process on hybrid silica for Cu-mediated *O*-arylation reactions. Combined with 5% of CuI, the latter can easily be recovered and reused to generate diarylethers under smooth conditions from cheap aryl bromides in an eco-friendly solvent (MIBK). Besides, negligible metal leaching occurred after reaction in solution from the supported catalyst.

Since a few decades numerous systems have been developed for the preparation of diarylethers, which are important backbone molecules in polymer industries[1a,b] and life science.[1c,2c] At the turn of this century, metal-mediated *O*-arylation methodologies[2] have supplanted traditional organic pathways[3] with a much better functional group tolerance under smoother conditions reactions. Hartwig *et al.* and Buchwald *et al.* have greatly contributed to novel Pd-catalyzed arylation of phenols,[4] but their systems still suffer from the expensive price of palladium and ligand sources. In the meantime,[5] a catalytic version of Cu-mediated Ullmann coupling of aryl halides and phenols was successfully developed and so offered a cheaper alternative to Pd. Thus, important efforts were invested to provide the most efficient Cu/Ligand system in terms of softening conditions reaction and widening functional tolerance.[6] Nonetheless and surprisingly, little interest was devoted to immobilize such Cu- or Pd-catalytic systems.[7] To date, only four reports described copper reusable catalytic systems for C–O coupling that allowed the recycling of active metal,[8] nevertheless only one reported leaching measurements of metal toxic residues in final products.[8d] This feature is of high importance for purity requirements in pharmaceutical industries. Therefore, mild, simple and low-cost reusable methods are highly desirable to avoid this toxic and environmentally issue.

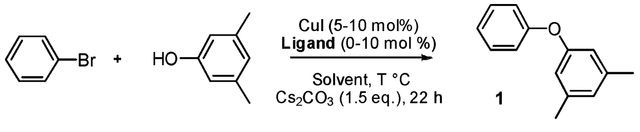
In a previous report we have successfully developed a sol–gel immobilized bipyridyl-based ligand for *O*-arylation of phenols.[8d] Though its efficiency, non-environmentally friendly DMF was used as solvent[9a] and KI was needed to facilitate coupling from aryl bromides at 120 °C. Thus a more efficient and sustainable protocol was envisaged for a smoother and greener synthesis of diaryl ethers. Since its renaissance in its catalytic version, many Cu-mediated Ullmann systems were designed with a myriad of original ligands.[2] Among them, the class of β-dicarbonyl derivatives is one the most versatile and efficient.[6j,10–13] For example they have allowed room-temperature C–N Ullmann coupling,[10a,b] *O*-arylation from aryl chlorides,[6j] C–S coupling[12] and also Sonogashira-type coupling.[13] We then decided to heterogenize a simple β-dicarbonyl derivative (in its β-diamide form) on hybrid silica by a sol–gel process,[14] and tested it in C–O coupling. It is worth noting that it is the first time that a β-diamide derivative is used as ligand in Ullmann condensations.

Starting from commercially available and cheap materials, the supported ligand **M** was obtained in two steps: condensation of malonyl dichloride with (3-aminopropyl)triethoxysilane, yielding the bis-silylated precursor **P**, followed by the sol–gel hydrolysis of the latter (Scheme 1).[15] This β-diamide-based hybrid silica **M** was further used in association with CuI to generate *in situ* heterogeneous precatalyst **CuI/M** for *O*-arylation of phenols in a green manner.



Scheme 1 Synthesis of supported ligand **M** on hybrid silica.

We chose the Ullmann-type coupling of bromobenzene with 3,5-dimethylphenol as the model reaction with Cs_2CO_3 as base (Scheme 2).



Scheme 2 Optimisation of reaction conditions for synthesis of **1**.

We have screened several experimental conditions with different combinations of ligands, solvents, and looked after the influences of amount of catalytic system, reaction concentration, and temperature (Table 1).

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Table 1 Study on the reaction conditions for synthesis of **1**

Entry	CuI (%)	Ligand (%)	T/°C	Solvent/mL	Yield (%)[a]
1	10	0	90	DMF (1)	Traces
2	10	10 (**M**)	90	DMF (1)	Traces
3	10	0	110	DMF (2)	Traces
4	10	10 (**M**)	110	DMF (2)	Traces
5	10	5 (**M**)	110	DMF (2)	46
6	10	5 (**M**)	110	DMSO (2)	47
7	10	5 (**M**)	110	DMF (1)	70
8	10	5 (**M**)	110	MIBK (2)	52
9	10	5 (**M**)	110	MIBK (1)	99
10	5	5 (**M**)	110	MIBK (1)	99
11	5	5 (**P**)	110	MIBK (1)	99 (0)[b]
12	5	5 (**M**)	110	MIBK (1)	99 (99)[b]

[a] GC-MS Yields determined with 1,3-dimethoxybenzene as internal standard. [b] In brackets, GC-MS Yield values after one recycling of the catalytic system.

First of all, we tested the coupling reaction at 90 °C in DMF with 10% of CuI with or without material **M** (10%). No coupling product **1** was observed (entries 1–2), even after heating up to 110 °C (entries 3–4). Surprisingly, we have observed that decreasing the amount of ligand **M** from 10% to 5% allowed moderate yield in 2 mL of DMF (a similar result was obtained in DMSO, entry 6) and more interestingly a better yield was obtained (70%) in more concentrated media (1 mL of DMF, entry 7). At this stage, we envisaged to replace DMF by MIBK (methylisobutylketone),[9] a solvent with low toxic potential which is highly used on an industrial scale due to its easy elimination. Interestingly under the same reaction conditions as in entry 7 but with MIBK as solvent, **1** was obtained quantitatively (entry 9) and this yield can be reproduced with an even lower amount (5%) of CuI (entry 10). To summarise, the best conditions with the ligand immobilized on hybrid silica **M**, were determined as the following: CuI (5 mol%), **M** (5 mol%) Cs_2CO_3 (1.5 equiv.) in 1 mL of MIBK at 110 °C during 22 h.

The next point was to test the recyclability of the hybrid **CuI/M** in comparison with the **CuI/P** system (entries 11–12). Indeed although the latter gave similar high yield (entry 11) for the first run, no reaction occurred for the second run with this homogeneous system. On the other hand, we observed the same reactivity for the generation of **1** after one reuse of the immobilised **CuI/M** system. Moreover it is noteworthy that we were able to elaborate an easy-handling protocol for recycling our **CuI/M** system by separating and filtering the crude solution in air without any other precaution, which constitutes a very simple pathway as a recycling procedure.

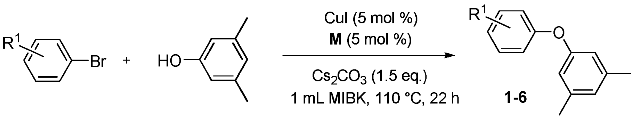
Based on these results, we have performed several series of reactions to test the versatility of our reusable system for the coupling of various aryl bromides with 3,5-dimethylphenol. In each series, 5% of CuI and **M** were charged only in the first experiment, all the other runs worked with the same reusable catalytic system. Table 2 relates the substituent effect on the aryl bromides under optimized reaction conditions found previously for the coupling from bromobenzene (Scheme 3).

After the first run affording **1** in quantitative yield, we demonstrated that re-using the same supported ligand **M** gave the corresponding products **2–6** in good to excellent yields (Entries 2–6). Besides, this reusable catalytic system is efficient even with electron-donating and electron-withdrawing groups on the aryl bromides.

Table 2 Coupling of various aryl bromides with 3,5-dimethylphenol

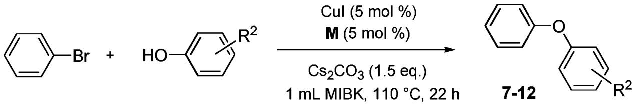
Entry	R¹	Reuse	Product	Yield (%)[a]
1	4-H		**1**	99
2	4-OMe	1	**2**	75
3	4-Me	2	**3**	77
4	4-CN	3	**4**	90
5	H[b]	4	**5**	98
6	4-NO_2	5	**6**	95

[a] Isolated yields after flash chromatography. [b] Reaction performed from 2-bromopyridine.



Scheme 3 Coupling of various aryl bromides with 3,5-dimethylphenol.

In a second time, we studied the substituent effect on the phenols for the coupling with bromobenzene (Scheme 4). Results presented in Table 3 showed moderate (Entry 2) to excellent yields, and revealed the excellent reusability of CuI/**M** system even after 6 runs.



Scheme 4 Coupling of various phenols with bromobenzene.

Table 3 Coupling of various phenols with bromobenzene

Entry	R²	Reuse	Product	Yield (%)[a]
1	4-H		**7**	87
2	4-Cl	1	**8**	65
3	4-OMe	2	**9**	92
4	4-Me	3	**10**	95
5	2-Me	4	**11**	92
6	4-*t*Bu	5	**12**	99

[a] Isolated yields in % after flash chromatography.

Finally, we have measured amounts of copper leaching in the crude solution phases containing diarylethers. For this study, we wanted first to compare copper leaching after synthesis of **1** both with homogeneous precursor ligand **P** and supported ligand **M** (similar conditions as for entry 1 of Table 2, respectively with 5% of **P** and **M**). The results clearly indicated that the immobilized system based on supported ligand **M** is a powerful and efficient chelate of Cu atom (Table 4). This latter allows a minimal leaching of copper in the crude mixture after coupling reaction (<30 ppm, entry 1), on the other hand the non-supported system **CuI/P** releases a much higher amount of copper in the crude mixture which is not acceptable for a toxic reason.[16] (1400 ppm, entry 1 of Table 4).

In a second set of results, we have measured the copper leaching at different stages of recycling protocol as followed

Table 4 Coupling of phenols with bromobenzene

Entry	Ligand	Yield of **1**	Copper leaching[a]
1	**P**	97	1400 ppm
2	**M**	98	< 30 ppm

[a] Measured by elementary analysis on the crude mixture.

in Table 2. For entries 1, 2, 4 and 6 of Table 2, we have obtained a copper leaching of only 20 ppm in all cases. These important observations could explain the high and stable reactivity of our supported system even after more than 5 cycles by the fact that copper is strongly encapsulated into the hybrid silica matrix of **M**.

In summary, we have synthesized an easy-handling supported ligand from commercially cheap materials. This ligand **M** in association with a catalytic amount of CuI allows the *O*-arylation of phenols from cheap aryl bromides under smooth conditions with a simple recyclable protocol under air atmosphere. The use of MIBK, an industrial solvent with low toxic potential, and the very low amount of copper leaching, provide a real improvement for a green and sustainable route to diarylethers *via* Cu-mediated Ullmann condensation.

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