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A comparison of homogeneous and heterogeneous copper catalyzed arylation of amines

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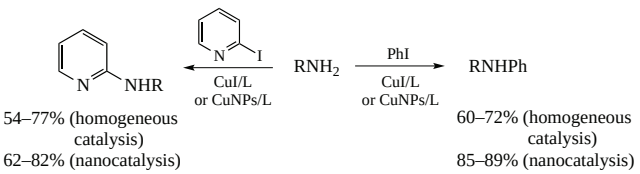
Comparison of the homogeneous and heterogeneous copper-catalyzed arylation of model primary amines with (hetero)-aryl iodides in DMSO revealed a comparable efficiency of CuI and commercially available unsupported copper nanoparticles (25 nm size) in the presence of 2-isobutyryl-cyclohexanone or L-proline.



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The aim of the present research was to find out enough cheap and efficient catalyst for the arylation of aliphatic amines. At present, copper nanoparticles (CuNPs) of 25, 40 and 60 nm size became commercially available. Taking into account that in some reactions nanocatalysts were found to be fully competitive with the homogeneous catalysis, it is important to explore the possibility of using such CuNPs in the amination of aryl halides. Although the palladium-catalyzed cross-coupling allowing the formation of various C(sp^2)–heteroatom bonds (S, Se, P, N, O) seriously changed the strategy of organic synthesis, a dramatic increase in the price of palladium makes it economically less efficient; moreover, it poorly fits the principles of the green chemistry due to the use of expensive and toxic phosphine ligands.[1] New possibilities arise from the copper-catalyzed reactions, due to the fact that the old 'Ullmann chemistry' has experienced tremendous improvements in the course of the introduction of appropriate ligands.[2–4] This phenomenon was baptized the 'Renaissance of Ullmann chemistry' and opened the way to cross-coupling reactions, especially of C(sp^2)–N bonds formation, in the presence of cheap copper complexes, available ligands and under rather mild conditions.[5] The heterogeneous catalysis using CuNPs of small sizes immobilized on supports was also studied and found generally less efficient than the homogeneous Cu^I-catalyzed amination.[6–9]

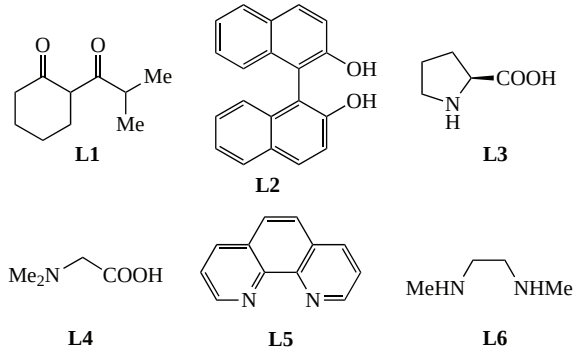
Earlier we studied the homogeneous metal-catalyzed (hetero)-arylation of the amines containing an adamantane fragment[10,11] which is widespread in various pharmaceuticals due to its renown lipophilicity.[12–14] It was shown that though Pd^0-catalyzed reactions provided target products generally in good to high yields, Cu^I-catalyzed (hetero)arylation helped to avoid the formation of *N*,*N*-di(hetero)arylated products especially in the case of active halopyridines[15,16] thus being quite competitive with the palladium-mediated processes.

In the trend of investigation of the scope of copper-catalyzed reactions,[17,18] the present work was aimed at the comparison of the efficiency of the homogeneous and heterogeneous copper-catalyzed arylation and heteroarylation of the primary amines using model *n*-octylamine **1a** and a series of adamantane-containing amines **1b**–**h** which are interesting for their biological activity and which differ by the sterical hindrances at the amino group. The envisaged products of the arylation of **1a**, *N*-octylaniline **2a** and 2-(octylamino)pyridine **3a**, are well-studied extragents for various metals,[19–21] including noble metals[22–25] and uranium.[26]

The efficiency of the reactions catalyzed by several copper(I) complexes under the homogeneous conditions were compared with the results of the coupling run under heterogeneous conditions using commercially available unsupported copper nanoparticles (CuNPs) of 25, 40 and 60 nm size produced by electrophysical methods.[27] Though the application of supported CuNPs in the amination of aryl halides has been reported in literature,[28–31] the use of unsupported CuNPs in such coupling has not yet been studied. Application of heterogeneous nanocatalysts is interesting, first of all, for their possibility of recycling and reuse, easy separation of the products from the catalyst in a two-phase system, what makes them promising for industry.

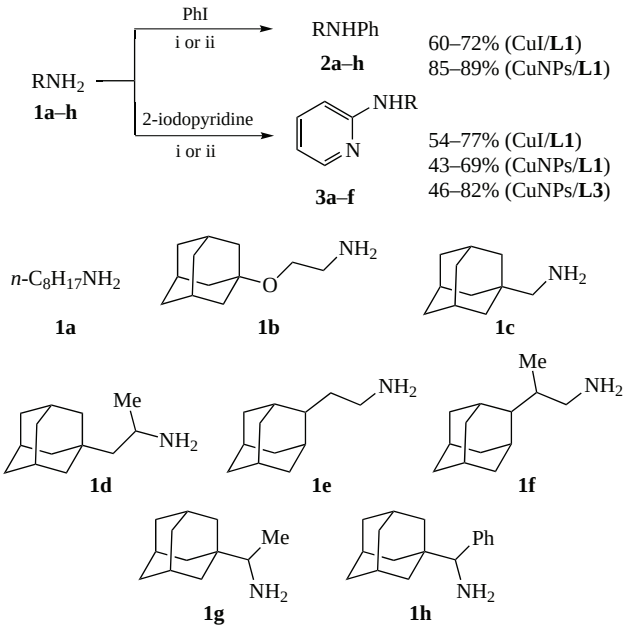
The homogeneous catalytic reactions were run in anhydrous DMSO at 110 °C for 24 h using 1 : 1.25 mole ratio of amine to PhI or 2-iodopyridine and Cs_2CO_3 as a base; Cu^I/**L** 10/20 mol% catalytic loadings were employed. The following ligands, which are widely used in the Cu^I-catalyzed amination reactions, were tested in this process: 2-isobutyrylcyclohexanone **L1** and *rac*-BINOL **L2** (O,O-ligands), L-proline **L3** and *N*,*N*-dimethylglycine **L4** (N,O-ligands), 1,10-phenanthroline **L5** and *N*,*N*′-dimethylethylenediamine **L6** (N,N-ligands).

The best result in the arylation with iodobenzene of the amine **1a** in the presence of CuI was achieved with 2-isobutyryl-cyclohexanone **L1** which provided 69% yield of the target compound **2a** (Scheme 1 and Table 1, entry 1). Arylation of the amines **1b**–**f** gave similar yields (60–72%) of the corresponding products **2b**–**f** (see Scheme 1, for the full data see Online



L1 **L2** **L3** **L4** **L5** **L6**

Supplementary Materials, Table S1). With the use of 20/40 mol% of the CuI/**L1** system, the yield of **2b** was somewhat higher (76%, see Table 1, entry 6). It was helpful to apply 20 mol% catalyst for the arylation of more sterically demanding amine **1g** to provide 62% yield of **2g**, however, in the case of the amine **1h** the yield of **2h** was only 31%. The application of other ligands substantially decreased the yields of the product **2b** (33% with **L2**, 21% with **L3**, and 2–5% with other ligands **L4**–**L6**). Other



Scheme 1 *Reagents and conditions*: i, CuI (10–20 mol%), ligand **L1**–**L6** (20–40 mol%), Cs_2CO_3, DMSO, 110 °C, 24 h; ii, CuNPs (5–20 mol%), ligand **L1** or **L3** (5–40 mol%), Cs_2CO_3, DMSO, 110 °C, 24 h. For details, see Online Supplementary Materials.

Table 1 Representative examples of homogeneous and heterogeneous copper-catalyzed *N*-arylation of amines.[a]

Entry	Reactants	[Cu]	Product	Yield (%)
1	**1a** + PhI	CuI	**2a**	69 (21[b])
2	**1a** + PhI	CuNPs	**2a**	89 (86[b])
3	**1a** + PhI	CuNPs[c]	**2a**	78, 72, 74, 75, 75, 72, 77, 74, 72, 69[c]
4	**1a** + PyI	CuI	**3a**	66
5	**1a** + PyI	CuNPs	**3a**	64 (82[b], 75[d])
6	**1b** + PhI	CuI	**2b**	69 (76[e])
7	**1b** + PhI	CuNPs	**2b**	88 (77[b], 75[d])
8	**1b** + PyI	CuI	**3b**	73 (77[e])
9	**1b** + PyI	CuNPs	**3b**	69

[a] Conditions: [Cu] (10 mol%), **L1** (20 mol%), Cs_2CO_3 (1 equiv.), DMSO, 110 °C, 24 h. [b] With ligand **L3**. [c] Ten runs of recycling experiments with CuNPs/**L1** (20/20 mol%) system, run time was 6 h. [d] With ligand **L4**. [e] With 20 mol% CuI and 40 mol% **L1**.

Cu^I compounds like CuOAc, CuOTf and Cu_2O were also tested in the reaction with **1b**, however, they provided somewhat lower yields of **2b** (55–66%), what makes CuI/**L1** catalytic system the best performing. Analysis of the reaction mixtures revealed that only products and unreacted starting compounds were present after completion of reaction, no side products were formed in all cases. The products were isolated by working up the reaction mixtures with CH_2Cl_2/H_2O. It is to be noted that the use of DMSO (110 °C) as a solvent is preferable to previously used DMF (140 °C) as it helped to improve the yields, to lower the reaction temperature and to diminish the amine to aryl iodide ratio.

The reaction of the amine **1a** with 2-iodopyridine catalyzed by CuI/**L1** (10/20 mol%) gave 66% yield of the target product **3a**, whereas the reactions with some adamantane-containing amines were found to be less efficient. While the heteroarylation of **1b**,**e**,**f** resulted in the corresponding compounds **3b**,**e**,**f** in 73, 70, and 54% yields, respectively, the reactions with more sterically hindered amines **1c**,**d** demanded the application of 20 mol% catalyst to ensure normal yields (62 and 71%) of the products **3c**,**d** (see Table S1). Ligand **L1** again performed better than other ligands **L2**–**L6** which provided 38–57% yields with amine **1b**.

Heterogeneous amination with the model amines **1a**,**b** in the presence of the copper nanoparticles runs *via* quite different mechanism involving Cu^0 species. The reactions were conducted using 5–10 mol% CuNPs in DMSO at 110 °C for 24 h in the presence of Cs_2CO_3. It was found that the arylation with PhI almost did not proceed without additional ligands notwithstanding the size of CuNPs (25, 40, or 60 nm), and the conversion of amines did not exceed 1–2% (see Table S2 for details). The addition of **L1** ligand dramatically improved the result, and the arylation proceeded smoothly with CuNPs of 25 nm size. It was possible to increase the yields of compounds **2a**,**b** to 89 and 86%, respectively, using 5/5 mol% CuNPs/**L1** system (see also Table 1, entries 2 and 7), what is much better than in the case of the homogeneous catalysis. Application of CuNPs 25 nm (10 mol%) with L-proline (**L3**) was also efficient as it provided 86 and 77% yields of compounds **3a**,**b**, however, the use of 5 mol% catalyst with **L3** led to a dramatic decrease in the yield. System CuNPs/**L1** (5/5 mol%) was tested in the reactions with amines **1c**–**f** and provided 85–86% yields of products **2c**–**f**, which are substantially higher than those in the homogeneous process. The nanoparticles of greater size, *i.e.* 40 and 60 nm, in the reaction of amine **1a** with iodobenzene in the presence of **L1** ligand were also active but provided notably poorer yields under similar conditions (52 and 45%, respectively).

In the reaction of *n*-octylamine **1a** with 2-iodopyridine catalyzed with CuNPs (10 mol%), **L3** and **L4** ligands proved to be more efficient than **L1** ligand as they provided 75–82% yields of compound **3a** (*cf.* 64–68% with **L1**). In the cases of 2-iodopyridine, the formation of 2,2′-bipyridne, the homo-coupling product, was noted, though. The choice of the best performing ligand is ambiguous in the reactions of adamantane-containing amines **1b**–**f** with 2-iodopyridine. Thus, **L1** was preferable for the reactions with **1b**,**f**, in which the compounds **3b**,**f** were obtained in 69 and 62% yields, **L3** was better for the reactions of **1c**–**e** providing 64, 73 and 76% yields of the corresponding products **3c**–**e**.

The experiments on the repeated use of unsupported CuNPs were exemplified on the reaction of *n*-octylamine **1a** with PhI in the presence of CuNPs/**L1** (20/20 mol%) catalytic system (see Table 1, entry 3). The reactions were carried out for 6 h and after the first run 78% yield of compound **2a** was observed. The catalyst was filtered off and washed with DMSO after each run. The yields in the 2–9 runs ranged from 72 to 77%, while in the

10th run the yield was 69%. Further investigations are to be done to explore possible leaching and the dependence of the recyclability on the nature of amine and ligand used.

To sum up, the results of this investigation clearly demonstrate the possibility to use unsupported copper(0) nanoparticles as catalysts for C(sp^2)–N bond formation in the presence of certain ligands. The yields in the heterogeneous reaction versions are higher than in homogeneous analogs. The possibility of reusing the CuNPs in nine cycles was shown.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.01.029.

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