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# Highly efficient Sandmeyer reaction on immobilized $Cu^I$/$Cu^{II}$-based catalysts

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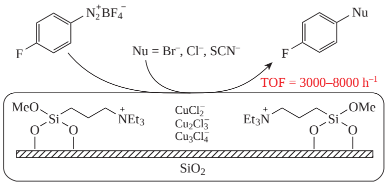
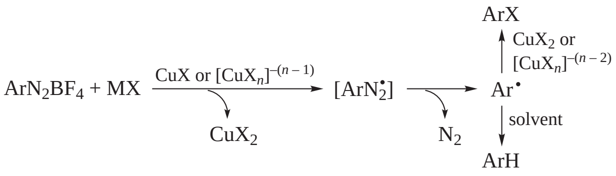
**Highly effective embodiment of Sandmeyer reaction has been revealed for Cu-based catalysts incorporating ionic liquid on Silochrom support. The most active catalyst (TOF = = 4000–8000 $h^{-1}$) contains comparable amounts of cuprous and cupric chloride anions. The reported method allows one to carry out the reaction for anilines in the one-pot mode.**



Sandmeyer reaction (S-reaction), *i.e.* conversion of anilines into aryl halides or aryl pseudohalides, is a useful method for functionalization of arenes. However, its initial embodiment required a high amount of metallic copper or its salts.[1]

According to the mechanism suggested by Kochi[2] and Zollinger,[3,4] copper salts act both as an electron-transfer agent (SET mechanism) and as a ligand-transfer oxidant (the second step in homolytic mechanism and the main step in heterolytic mechanism) (Scheme 1).



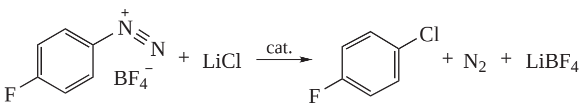
**Scheme 1**

The recent reports disclose introduction of fluoro-containing groups $CF_3$, $SCF_3$, and $SeCF_3$ into the aromatic ring using S-reaction,[6–10] which allows one to affirm that the catalytic version made this reaction popular in modern organic synthesis.[5] The initial procedure required at least 5–10 mol% of copper, sometimes one equivalent, *e.g.* in the ‘one-pot’ synthesis of fluorinated compounds catalyzed by powdered copper.[6] Recently we reported a catalytic complex consisting of CuCl and $CuCl_2$ with nitrogen-containing ligands (TMEDA, phenanthroline, and bipyridine), which provided a very fast conversion in S-reaction under mild conditions.[11,12] However, the described procedure required at least 5 mol% of the catalyst loading because its lower amount would result in reduced product yields.

Since some obtained by S-reaction compounds are interesting intermediates for pharmaceutical industry,[13,14] there is a need for an efficient heterogeneous catalyst that would contain a relatively low amount of copper and, at the same time, be recyclable.

There are no reported examples of immobilized on a solid support ionic liquids (ILs) applied in S-reaction,[15] although ILs are known as a convenient medium for it.[7] A combination of the immobilization procedure[16,17] and the methods for preparation of CuCl-containing IL[18] allowed us to synthesize several new catalysts from alkylimidazolium (or alkylammonium) and CuCl (or $CuCl_2$) on Silochrom (see Online Supplementary Materials). The copper (both $Cu^I$ and $Cu^{II}$) content in the samples was determined by synthesis conditions. According to XPS data, catalysts I (prepared from $CuCl_2$ in air atmosphere) and III (obtained from CuCl under argon) contained only $CuCl_2$ or CuCl, respectively (Table 1). Catalysts II and IV were prepared by sustained reflux of modified supports and CuCl in isooctane in air atmosphere and contained various $Cu^I$ portions (see Table 1).

The reaction of 4-fluorophenyldiazonium tetrafluoroborate with LiCl was used as a model for an initial evaluation of the catalytic properties of the samples (Scheme 2, Table 1).



**Scheme 2**

Catalysts I and III had almost no activity. Catalyst II with $Cu^I$/$Cu^{II}$ ratio of 10 : 1 demonstrated a moderate activity and good selectivity. The full conversion of 4-fluorophenyldiazonium tetrafluoroborate was achieved in 1 h using catalyst IV with $Cu^I$/$Cu^{II}$

**Table 1** Composition of the immobilized ILs and their catalytic activity.[a]

| Entry | Catalyst | Copper chloride | Grafted quaternary salt | $[Cu^I]$/$[Cu]_\Sigma$ (%)[b] | Conversion of 4-$FC_6H_4N^+{\equiv}N\,BF_4^-$ (%) |
|---|---|---|---|---|---|
| 1 | I | $CuCl_2$ | EtPrImCl | 0 | 0.6 |
| 2 | II | CuCl | EtPrImCl | 90 | 37 |
| 3 | III | CuCl (Ar) | EtPrImCl | 99 | 4 |
| 4 | IV | CuCl | $Et_3PrNCl$ | 36 | 100 |

[a] *Conditions*: Ar, [Cu] = 5 mol%, 20 °C, 1 h. [b] According to XPS data.

**Table 2** Catalysts II and IV recycling in the model reaction.[a]

| Catalyst | Number of cycles | Time of full conversion of 4-$FC_6H_4N^+{\equiv}N\,BF_4^-$/h | Yield of 4-$FC_6H_4Cl$(%) |
|---|---|---|---|
| II | 1 | 3 | 98 |
| | 2 | 3 | 97 |
| | 3 | 3 | 98 |
| IV | 1 | 1 | 98 |
| | 2 | 1 | 96 |
| | 3 | 1 | 90 |

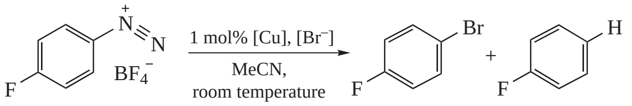
[a] See Scheme 2, the same conditions as given in Table 1.

ratio of 1:2. In S-reaction, both the $Cu^I$ oxidation (electron transfer from the $Cu^I$ anionic complex to $ArN_2^+$, see Scheme 1, the first step) and the reaction between anionic $Cu^{II}$ complex and the radical $Ar^\bullet$ that maintains the process selectivity (see Scheme 1) play the crucial role. Therefore, the process requires the simultaneous participation of two valence forms of copper.

The next step of our study was comparison between the two most active catalysts in recycling experiments (Table 2).

The complete formation of 4-chlorofluorobenzene within 3 h and in a similar yield for 3 runs was observed for catalyst II, while catalyst IV provided the full conversion in 1 h but also with a small decrease in the product yield (98, 96, and 90%). Since the copper content remained unchanged (see Online Supplementary Materials), the catalyst IV degradation occurred probably due to its lower resistance to oxidation in comparison with catalyst II, which resulted in a stepwise decrease of the copper(I) fraction.

The most active catalyst IV (1 mol% [Cu]) was selected for an optimization of the preparative reaction with bromides (Scheme 3).



**Scheme 3**

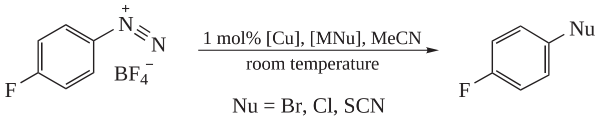
Phase-transfer catalysts, such as crown ethers or tetraalkylammonium salts,[19] can be very helpful for this reaction in case of homogeneous catalysis. However, the phase-transfer catalysis was not effective for heterogeneous reaction under above conditions, because it did not provide sufficient $Br^-$ concentration in the solution, and resulted in a side reaction of the fluorophenyl radical with the solvent, which led to the fluorobenzene formation in significant amounts (Table 3, entries 1–3).

**Table 3** Reaction of 4-fluorophenyldiazonium tetrafluoroborate with bromides.[a]

| Entry | $[Br^-]$ | Yield[b] of 4-$FC_6H_4Br$ (%) | Yield[b] of $C_6H_5F$ (%) |
|---|---|---|---|
| 1 | KBr + 10% dibenzo-18-crown-6 | 55 | 40 |
| 2 | KBr + 30% dibenzo-18-crown-6 | 70 | 27 |
| 3 | KBr + 10% $Et_3BnNCl$[c] | 50 | 47 |
| 4 | $Et_4NBr$ | 94 | 5 |
| 5 | LiBr | 96 | 2 |

[a] *Reagents and conditions*: 4-$FC_6H_4N_2[BF_4]$ (1 mmol), nucleophile (source of $[Br^-]$, 2 mmol), catalyst **IV** (1 mol% [Cu]), MeCN (dry), Ar, room temperature, stirring, 30 min. [b] According to $^{19}F$ NMR. [c] 4-$FC_6H_4Cl$ was not detected.

The best results were achieved for acetonitrile-soluble salts, such as $Et_4NBr$ and LiBr, which provided 4-$FC_6H_4Br$ in 94–96% yields (Table 3, entries 4 and 5). The same condition allowed us to obtain of 4-$FC_6H_4Cl$ and 4-$FC_6H_4SCN$ in high yields, using LiCl or $Et_3BnNCl$ and KSCN, respectively (Scheme 4).



**Scheme 4**

In all cases, catalyst IV provided the high yields within 1 h. It was surprising that the decreased catalyst loading had no effect on the yields in the reactions with LiBr, LiCl, $Et_3BnNCl$, and KSCN, which remained high even at the copper concentrations being as low as $5\times10^{-3}$ mol% (Table 4). Such concentrations in the copper catalysis look like a ‘homeopathic’ amount.[20] According to the acquired data, the turnover number (TON) could achieve up to 20000 for all substrates (see Table 4, entry 3) and TOF value reached 3000–8000 $h^{-1}$ (entries 1–3).

The reactions with LiBr, $Et_3BnNCl$, and KSCN were completed in less than 1 h at the catalyst concentration of 0.050 mol%. The reason, why heterogeneous catalysts demonstrated a higher activity in the same reaction in comparison with the homogeneous one, remains unclear. A catalyst activity examination revealed that the reaction of aryldiazonium salts with lithium bromide could also proceed in the absence of the catalyst, although at a much lower rate. In the presence of 0.005 mol% of copper, the reaction was completed within 6 h, while the full conversion without a catalyst took about 40 h (see Table 4, entry 4). Anyhow, the yield of aryl bromide remained quite high (89%). The non-catalytic reaction with thiocyanate proceeded for 30 h and resulted in 20% conversion. For chloride ions, the product was not detected even after 90 h.

Since LiCl is substantially less soluble in acetonitrile than LiBr, the reaction was carried out at noticeably higher dilution and required a longer time to be completed (Table 4, entry 3). Used as sources of the chloride ion $Et_3BnNCl$ and $Et_4NCl$ substantially increased the reaction rate.

Taking 0.025 mol% of copper allowed the reactions to proceed quite rapidly with high product yields, which revealed the substituent effect in initial diazonium salts in the reaction with KBr and KSCN (Scheme 5). In all cases, high product yields were obtained for both electron-donating and electron-withdrawing substituents.

Since diazonium salts are not optimal reactants for preparative synthesis, the *in situ* diazotization of anilines was performed using alkyl nitrites with the following halodediazotization. The one-pot reaction with LiBr or $Et_4NCl$ resulted in a series of aryl halides

**Table 4** Dependence of the substitution product yield on the catalyst IV amount.[a]

| Entry | [Cu] (mol%) | LiBr | | LiCl | | $Et_3BnNCl$ | | KSCN | |
|---|---|---|---|---|---|---|---|---|---|
| | | *t*/h | Yield[b] of 4-$FC_6H_4Br$ (%) | *t*/h | Yield[b] of 4-$FC_6H_4Cl$ (%) | *t*/h | Yield[b] of 4-$FC_6H_4Cl$ (%) | *t*/h | Yield[b] of 4-$FC_6H_4SCN$ (%) |
| 1 | 0.050 | 0.25 | 95 | 1 | 95 | 0.5 | 96 | 0.5 | 95 |
| 2 | 0.025 | 1 | 94 | 3 | 95 | 2 | 94 | 1 | 94 |
| 3 | 0.005 | 6 | 93 | 10 | 96 | 8 | 96 | 5 | 94 |
| 4 | – | 40 | 89 | 90 | – | 90 | – | 30 | 20 |

[a] See Scheme 4. [b] According to $^{19}F$ NMR.

$$\mathrm{Ar\overset{+}{N}{\equiv}NBF_4^-} \xrightarrow[\text{room temperature}]{\text{[Cu], [MNu], MeCN}} \mathrm{ArNu}$$

Nu = Br, SCN

| Ar | Isolated yield (%) | |
|---|---|---|
| | ArBr | ArSCN |
| 3-Me-4-$BrC_6H_3$ | 94 | 88 |
| 3,5-$Cl_2C_6H_3$ | 95 | 89 |
| 4-$MeOC_6H_4$ | 87 | 82 |
| 3-Me-4-$NO_2C_6H_3$ | 97 | 96 |
| 4-$IC_6H_4$ | 95 | 92 |

**Scheme 5** *Reagents and conditions*: [MNu] (6 mmol), catalyst **IV** (0.025 mol% of copper), MeCN (20 ml), Ar, stirring for 5 min (in case of ArSCN, the mixture was cooled to 0 °C); then diazonium salt (3 mmol) in MeCN (10 ml) and stirring for 1 h.

$$\mathrm{ArNH_2} \xrightarrow[\text{MeCN, 0–20 °C}]{\text{Bu}^\text{t}\text{ONO, BF}_3\text{, [Cu], LiBr or Et}_4\text{NCl}} \mathrm{ArHal}$$

| Ar | Isolated yield (%) | |
|---|---|---|
| | ArCl | ArBr |
| 4-$FC_6H_4$ | – | 82 |
| 4-$AcOC_6H_4$ | 93 | 95 |
| 4-$MeOC_6H_4$ | 77 | 80 |
| 3-Me-4-$BrC_6H_3$ | 90 | 88 |
| 3-Me-4-$NO_2C_6H_3$ | 96 | 94 |
| 2-Br-4-Me-5-$ClC_6H_2$ | 92 | 96 |

**Scheme 6** *Reagents and conditions:* $BF_3 \cdot Et_2O$ (3 mmol), aniline (3 mmol), nucleophile (6 mmol), catalyst IV (0.025 mol% of copper), MeCN, 0 °C, stirring for 10 min; then $Bu^tONO$ (4.5 mmol) in MeCN (20 ml) and stirring for 1 h.

in high yields (Scheme 6). In contrast with previous results,[11] a steric hindrance did not have a significant effect on the product yield even in the case of 2,6-substituted anilines. A methoxy group (*e.g.* at *para*-position) at the aromatic ring led to decreased product yield. The isolation of 4-fluorochlorobenzene was not performed due to difficulties caused by its volatility. The yield was 98% according to $^{19}$F NMR. This method is not applicable to the aryl thiocyanates preparation due to the reaction between the $SCN^-$ ion and $Bu^tONO$.

The aryl halide production process could easily be performed on a largescale. When the 3-methyl-4-bromophenyldiazonium tetrafluoroborate amount in the reaction with LiBr was increased from 1 to 50 mmol, 2,4-dibromotoluene was obtained in 89% yield.

Therefore, the fully recyclable heterogeneous catalyst with the excellent activity (TOF = 3000–8000 $h^{-1}$) has been developed, which allows the Sandmeyer reaction to be accomplished for several consecutive cycles. This catalyst contains comparable amounts of cuprous and cupric chlorides. The reported method provides the opportunity to carry out reactions for anilines in the one-pot mode.

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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.2018.05.010.

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