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Aminoarenethiolato-copper(I) as (pre-)-catalyst for the synthesis of diaryl ethers from aryl bromides and sequential C–O/C–S and C–N/C–S cross coupling reactions

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ABSTRACT

A small library of 2-aminoarenethiolato-copper(I) (CuSAr) complexes was tested as (pre-)catalysts in the arylation reaction of phenols with aryl bromides. These copper(I) (pre-)catalysts are thermally stable, soluble in common organic solvents, and allow reactions of 6 h at 160 °C with low catalyst loadings of 2.5 mol %. Among the (pre-)catalysts screened, 2-[(dimethylamino)methyl]benzenethiolato-copper(I) (1c) led to the best results and provided good to excellent yields of various substituted diaryl ethers. Mechanistic studies showed that at early stages of the C–O coupling reaction the CuSAr complex is converted into CuBr(PPh3) via selective coupling of the monoanionic arenethiolato ligand with phenyl bromide with formation of CuBr. In addition, the first results are shown involving a multi-component reaction (MCR) protocol for the in situ synthesis of propargylamines and their subsequent conversion involving a C–O cross coupling reaction. Furthermore, two examples of sequential C–O/C–S and C–N/C–S cross coupling reactions have been carried out on the same dihalo-pyridine substrate in a one-pot process with the same (CuSAr) (pre-)catalyst (overall yields 40–80%).

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1. Introduction

The diaryl ether unit is a common structural unit widely encountered in biologically active molecules and natural products as well as in monomers for the synthesis of functional polymers. This structural moiety is part of various important pharmaceuticals with antibiotic activity, such as vancomycin, teicoplanin, the antiviral peptide K-13, the antitumoral bouvardin and many others. Common routes for the preparation of these ethers, i.e., through C–O bond formation, involve the classical Ullmann diaryl synthesis, which however has several drawbacks related to harsh reaction conditions and stoichiometric use of the copper mediator. Recently, new approaches have been developed to overcome these disadvantages, for example, through the use of organobismuth, organostannane, organotrifluoroborate reagents or aryloboronic acids. However, the applicability of these aryl donors is still restricted because of their limited accessibility (multi-step synthetic procedures) and other disadvantages (i.e., production of heavy metal waste).

In recent years elegant and efficient palladium-catalyzed arylations of phenols have been reported, employing commercially available aryl halides as arylating agents and in situ generated metal ligand complexes as catalysts, using either bulky alkyphosphines or pyrrol and indole based monophosphine ligands. Nevertheless, there remains a quest for low-cost alternatives involving cheaper and more abundant metals and cheaper ligands (or ideally no ligands or other additives at all) for large-scale and industrial applications. These are offered by copper-based protocols in which the copper salt is present in a catalytic amount.

A drawback of the use of copper salts and copper–ligand complexes is their generally poor solubility and stability in the commonly used organic media. These problems have been addressed by the use of suitable ligands, like for instance amino acids, ketones, phenantroline derivatives and nitrogen- and oxygen-containing ligands for the in situ generation of soluble, catalytically active copper complexes. An alternate option is the use of pre-prepared, soluble and air-stable copper salt–ligand complexes, for example, ionic Cu[MeCN]4PF6 or neutral CuBr(neocup)(PPh3) and many of these have already shown to be good (pre-)catalysts in diaryl ether synthesis.

In recent years we explored a class of well-defined neutral copper(I) complexes, i.e., the 2-aminocarbethiolato-copper(I) complexes (CuSAr, Fig. 1) as (pre-)catalysts for various types of C–X bond forming reactions and have tested these as (pre-)catalyst in allylic substitution, addition reactions and aromatic N-arylation reactions.
The complexes have excellent solubility in a range of useful solvents. In addition, electronic and physical properties can easily be fine-tuned by introducing substituents at the arene ring or the amino-functionality.

In the present study the reactivity of a small library of differently substituted 2-aminoarenethiolato-copper(I) complexes as (pre-)catalysts in the O-arylation of phenols with aryl bromides is reported. The copper complexes studied show good catalytic activity in C–O coupling reactions affording diaryl ethers, at a catalyst loading of only 2.5 mol % within relatively short reaction times. The fate of the CuSAr pre-catalyst during initial stages of the reaction has also been studied. Moreover, we report the first experiments making use of the versatility of the CuSAr pre-catalyst to combine diverse sequential reactions on the same substrate molecule catalyzed by a single catalyst in a one-pot procedure. These experiments provided promising results for the synthesis of target molecules with interesting combinations of (hetero)aryl building blocks, starting from 2-bromo-5-iodopyridine.

2. Results

A series of 2-aminoarenethiolato-copper(I) complexes, see Fig. 2, was prepared through a synthesis involving a one-pot procedure of the four steps (Scheme 1), i.e., a heteroatom directed ortho-lithiation, insertion of sulfur in the formed carbon-lithium bond, a quench with trimethylsilyl chloride resulting in the formation of the trimethylsilyl thioester, which subsequently was used in a reaction with CuCl in toluene to afford the desired 2-aminoarenethiolato-copper(I) complexes as pure materials in 67–85% yield.

This straightforward synthetic protocol allowed easy preparation of a series of differently substituted complexes. The various amines were chosen to test the influence of the basicity of the N-amine centre as well as of the steric constraints of the amino ortho-substituent in the ligand on the outcome of the C–O coupling reaction and the catalytic activity. The aryl ring was varied to the naphthyl ring, in order to check possible steric effects of the backbone. Moreover, various substituent patterns, meta- to the C–S bond, were tested to possibly modify the solubility properties of the resulting copper (pre-)catalyst.

The coupling of bromobenzene with phenol was chosen as a model reaction mediated by 2.5 mol % of 1c as (pre-)catalyst (Scheme 2). The solvent of choice appeared to be N-methylpyrrolidinone (NMP) at a reaction temperature of 160 °C. Indeed, other solvents as dioxane, toluene, acetonitrile, which were tested at 90–110 °C, and in all cases afforded the ethers in yields lower than 30% (calculated on bromobenzene) within 16 h. Only DMSO and DMF gave results comparable to those obtained for reactions in NMP, probably due to the need to achieve a reaction temperature of 160 °C.

The search for an appropriate base led to a choice of cesium carbonate after a series of organic and inorganic bases had been screened (Table 1). Soluble organic bases, for example, NEt₃, Hunig’s base, pyridine and 2,6-lutidine gave poor product yields. Likewise, moderate results were obtained with either potassium...
carbonate or phosphate (Table 1; entries 1 and 4), whereas quite good yields of diphenyl ether were achieved in the presence of potassium tert-butoxide (Table 1; entry 3) as a base. Notably, with Cs₂CO₃ the C–O coupling product was obtained in almost quantitative yield (98%, Table 1; entry 2). The latter excellent results possibly relate to the good solubility characteristics of cesium phenolate formed as intermediate in polar aprotic solvents, cf. the so-called ‘cesium-effect’.31

Different aryl halides were tested under the chosen reaction conditions, but fluoro and chlorobenzene did not react (notably no formation of the arene reduction product was detected), whereas in the reaction with iodobenzene the maximum yield of diphenyl ether amounted to only 36%. Consequently further investigations were concentrated on the use of bromoarene derivatives. The library of 2-aminoareniethiolato-copper(I) complexes was tested under the optimized conditions established for the C–O coupling reaction between bromobenzene and phenol. The yield of diphenyl ether for each CuSAr (pre-)catalyst was monitored after 16 h (Table 2). Parent complex 1c gave excellent results (Table 2; entry 1), while an increase of the basicity of the nitrogen atom in the catalyst resulted in a slight decrease of the yield (87–90%, entries 2–4). Good to excellent yields were achieved with 2-[(dimethylamino)methyl] naphthalene-3-thiolato-copper(I) 5c (74% entry 5), while the replacement of the dimethylamino group in 5c by diethylamine (6c) or pyrrolidinyl (7c) caused an increase in the yield of diphenyl ether to 93%. Introduction of substituents, on either the phenyl or the naphthyl ring did increase the solubility of the complexes but did not affect the catalytic activity in a substantial way (entries 9–14).

Further studies were carried out with 1c as the (pre-)catalyst of choice. The scope of the reaction was studied by reacting a variety of combinations of functionalized bromoarenes and phenols as coupling partners. Comparisons of the reactivity of the various substrates were obtained by comparison of the yield of the respective C–O coupling products by interrupting each reaction after 6 h (Table 3). In all reactions total selectivity was accomplished and formation of biaryl products or isomeric diaryl ethers was never observed, while dehalogenated arenes (reduction product) appeared to be present in the reaction mixtures in amounts below 2%.

### Table 1
Effect of the nature of the base on the C–O coupling of phenol with aryl bromide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yielda %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>KO-t-Bu</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>K₂PO₄</td>
<td>52</td>
</tr>
</tbody>
</table>

Reaction conditions: phenol (6.5 mmol), aryl bromide (5 mmol), base (5.5 mmol), CuSAr catalyst 1c (2.5 mol %), solvent (1 mL), 16 h, 160 °C, under N₂.

a Determined by GC using dihexyl ether as internal standard, based on phenyl bromide.

### Table 2
Screening of the reactivity of 2-aminoareniethiolato-copper(I) complexesa in reaction of Scheme 2

<table>
<thead>
<tr>
<th>Complex</th>
<th>Aryl</th>
<th>R</th>
<th>R', R''</th>
<th>Yieldb %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenyl</td>
<td>H</td>
<td>Me, Me</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Phenyl</td>
<td>H</td>
<td>Et, Et</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>Phenyl</td>
<td>H</td>
<td>–(CH₂)₄–</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Phenyl</td>
<td>H</td>
<td>–(CH₂)₃–</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>Naphthyl</td>
<td>H</td>
<td>Me, Me</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>Naphthyl</td>
<td>H</td>
<td>Et, Et</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>Naphthyl</td>
<td>H</td>
<td>–(CH₂)₄–</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>Naphthyl</td>
<td>H</td>
<td>–(CH₂)₃–</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>Phenyl</td>
<td>5-t-Bu</td>
<td>Me, Me</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>Phenyl</td>
<td>5-t-Bu</td>
<td>–(CH₂)₄–</td>
<td>83</td>
</tr>
<tr>
<td>11</td>
<td>Phenyl</td>
<td>5-t-Bu</td>
<td>–(CH₂)₃–</td>
<td>71</td>
</tr>
<tr>
<td>12</td>
<td>Phenyl</td>
<td>3-TMS</td>
<td>Me, Me</td>
<td>81</td>
</tr>
<tr>
<td>13</td>
<td>Phenyl</td>
<td>5-TMS</td>
<td>Me, Me</td>
<td>87</td>
</tr>
<tr>
<td>14</td>
<td>Naphthyl</td>
<td>3-TMS</td>
<td>Me, Me</td>
<td>84</td>
</tr>
</tbody>
</table>

a For R, R', R'' see Figs. 1 and 2. Reaction conditions: phenol (6.5 mmol), bromobenzene (5 mmol), Cs₂CO₃ (5.5 mmol), [Cu] (2.5 mol %), solvent (1 mL), 16 h, under N₂, 160 °C.

b Determined by GC using dihexyl ether as internal standard, based on phenyl bromide.

### Table 3
Etherification of aryl bromides catalyzed by CuSAr 1c after 6 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArBr</th>
<th>Phenol</th>
<th>Yieldb %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>HO</td>
<td>90b</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>HO</td>
<td>85b</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>HO</td>
<td>85b</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>HO</td>
<td>81b</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>HO</td>
<td>13c</td>
</tr>
<tr>
<td>6</td>
<td>Ac</td>
<td>Br</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>MeO</td>
<td>Br</td>
<td>77b</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>HO</td>
<td>87b</td>
</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>HO</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>HO</td>
<td>50d</td>
</tr>
<tr>
<td>11</td>
<td>Br</td>
<td>HO</td>
<td>79b</td>
</tr>
<tr>
<td>12</td>
<td>Br</td>
<td>HO</td>
<td>79b</td>
</tr>
<tr>
<td>13</td>
<td>MeO</td>
<td>Br</td>
<td>82b</td>
</tr>
<tr>
<td>14</td>
<td>Br</td>
<td>HO</td>
<td>64</td>
</tr>
</tbody>
</table>

(continued on next page)
of the diaryl ethers in good yields (64\% and 4-bromoacetophenone, with phenol gave rise to the formation of some of these starting materials but produced moderate results. The reactivity of the present 2-amino-arenethiolato-copper(I) (pre-)catalyst was investigated employing arenethiolato-copper(I) (pre-)catalyst was investigated employing

**Table 3 (continued)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \text{ArBr} )</th>
<th>( \text{PhOH} )</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>( \begin{align*} &amp;\text{Br} \end{align*} )</td>
<td>( \begin{align*} &amp;\text{HO} \end{align*} )</td>
<td>65</td>
</tr>
<tr>
<td>16</td>
<td>( \begin{align*} &amp;\text{Br} \end{align*} )</td>
<td>2.5 mol%</td>
<td>2</td>
</tr>
</tbody>
</table>

Reaction conditions: phenol (6.5 mmol), bromoarene (5 mmol), \( \text{Cs}_2\text{CO}_3 \) (5.5 mmol), \( \text{Cu} \) (2.5 mol %), NMP (1 mL), 160 °C, 6 h, under \( \text{N}_2 \).

**Scheme 3.** Sequential C–O/C–S couplings on 2-bromo-5-iodopyridine in one pot.

**Scheme 4.** Sequential C–N/C–S coupling reactions on 2-bromo-5-iodopyridine.

In preliminary experiments \( \text{CuSAr} \) (2.5 mol \%) was added only at the beginning of the reaction sequences (see Schemes 3 and 4), which were carried out in one-pot without isolation or purification of the intermediates. However in these set-ups, yields of the desired products, 15 and 16, respectively, never exceeded 30\%, while the yield of side products, i.e., dietheri-cation side-product was present in the reaction mixture in low amounts <5\%. A second product was identified as N-benzyl-benzylidenediamine, oxidation product of benzylamine and the reason for its formation was already recognized.\textsuperscript{34} It is worthwhile to note that in both examples of Schemes 3 and 4, the presence of copper catalyst is required to obtained formation of products.

**2.2. Study of the (pre-)catalyst**

Analysis of the reaction mixtures had revealed the presence of a compound which could be identified as 2-[(dimethylamino)methyl]phenyl phenyl sulfide (\( \text{PhSAr} \) in Scheme 5). The formation of \( \text{PhSAr} \) results from the reaction of \( \text{CuSAr} \) with bromobenzene. This reaction was proven by an independent experiment, performed under the same conditions as the catalytic reaction, involving the reaction in NMP of bromobenzene with \( \text{CuSAr} \) in 1:1 M ratio (see experimental). Exclusively \( \text{PhSAr} \) (and \( \text{CuBr} \)) was formed which was isolated in 80\% yield. Consequently, it can be concluded that \( \text{PhSAr} \) is formed in the reaction mixture through S-arylation of the SAR-anion with bromobenzene, which is present in the reaction mixture in large excess. Experiments conducted at different temperatures (80–160 °C) showed that \( \text{PhSAr} \) is only formed at reaction temperatures \( \geq 100 \) °C.

**Scheme 5.** Formation of 2-[(dimethylamino)methyl]phenyl phenyl sulfide (\( \text{PhSAr} \)).
This result shows that in fact the 2.5 mol % of the 2-aminoarenethiolato-copper(I) complex is converted into an equimolar mixture of PhSAr and CuBr. Obviously, this in situ formation of the C=S coupling product PhSAr (and consequently CuBr) leads to a copper salt–ligand combination, which affects positively the catalytic C-O coupling process. The C-O coupling reaction was also performed with pure CuBr (2.5 mol %) and additional, preformed, PhSAr (2.5 mol %) instead of the pre-catalyst CuSAr. Under the same conditions, the reaction gave a lower yield of diaryl ether of 87% (vs 98% with CuSAr). This underlines the positive influence of PhSAr as a ligand, and the presence of a more complicated catalytic system as well. Indeed it shows that the in situ formation of the [CuBr–PhSAr] complex from the pre-catalyst CuSAr and the substrate PhBr is more efficient than the combination reached via pure CuBr and PhSAr separately.

The different results of the CuSAr- and CuBr-catalyzed reactions strongly suggest that the S-coupling product PhSAr apparently acts as suitable N,S-ligand for the CuBr formed in early stages of the reaction. To verify this hypothesis and study in more detail the effect of PhSAr, we sought independent proof for the formation of possible complexes between PhSAr and copper.

A mixture of only CuSAr (2.5 mol % relative to bromobenzene) with bromobenzene (reaction of 30 min, 120 °C, Scheme 5) was studied by mass spectrometry (FIA-ESI-MS, Flow Injection Analysis-Electrospray Ionization-Mass Spectrometry). The main peaks displayed by the positive ESI-MS spectrum matched with those in the spectrum of pure PhSAr confirming the presence and formation of the S-coupling product. In addition the presence of two adducts was observed, one with a 1:1 [CuPhSAr]+ and another one with a 2:1 [Cu(PhSAr)2]⁺ ligand-to-copper molar ratio, each displaying the characteristic isotopic distributions for their molecular cations (Scheme 6).

Attempts to prepare independently and isolate these 1:1 (17) and 2:1 (18) ligand-to-copper complexes appeared to be difficult and in the case of the 1:1 complex did not result in the isolation of a distinct, pure complex. Therefore the nature of the 1:1 complex (17) was studied on in situ formed material. Pure PhSAr and the reaction mixture of the reaction of PhSAr with CuBr in 1:1 M ratio (reaction of 180 min, 120 °C) in DMSO-d6 were both analyzed by 1H NMR spectroscopy (see Experimental). The 1H NMR spectrum for PhSAr showed a clear pattern, with a singlet resonance at 2.13 ppm for the methyl protons, another singlet resonance at 3.48 ppm for the benzylic protons and a multiplet pattern for the aromatic protons (7.15–7.43 ppm). The 1H NMR spectrum of the reaction mixture of PhSAr with CuBr showed a similar pattern to the previous spectrum, but revealed down-field shifts, commonly observed upon ligand coordination to a metal, for the methyl protons (Δδ=−0.17 ppm), for the benzylic protons (Δδ=−0.05 ppm) and a different pattern for the aromatic protons. These NMR data pointed to the presence of a [CuBr–PhSAr] species in solution (Scheme 6).

Independent preparation of the 2:1 complex (18) was achieved through addition of a solution of ligand PhSAr to a suspension of [Cu(MeCN)4]BF3 in benzene, in 2:1 M ratio. The isolated off-white powder analyzed as [Cu(PhSAr)2]BF4 showed poor solubility in common organic solvents. However, 1H NMR spectrum of a solution of [Cu(PhSAr)2]BF4 in methanol-d4 showed, when compared to the spectrum of free PhSAr, a down-field shift for both benzylic (Δδ=−0.20 ppm) and methyl protons (Δδ=−0.24 ppm), which indicates a coordination of the ligand to the metal centre. The methyl and benzylic proton resonances of [Cu(PhSAr)2]BF4 appeared as broad singlets under the conditions employed (methanol-d4, 298 K). The temperature dependency of the 1H NMR spectra of [Cu(PhSAr)2]BF4 could not be studied for temperatures below 298 K, because of its poor solubility in methanol-d4, whereas at higher temperature (328 K) no change was observed. Analysis of the MALDI-TOF MS (Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry) spectrum of authentic [Cu(PhSAr)2]BF4 showed the presence of the ions [Cu(PhSAr)2]⁺ (m/z 549.3817) with the characteristic isotopic patterns, confirming the nature and coordination of PhSAr to Cu(I) in the species 17 and 18 found in the reaction mixture.

These data do not provide information about the coordination geometry around the metal centre of the complex in solution. However, it is known that copper(I) adopt preferentially a tetrahedral or a square planar configuration, which can be achieved via the complexation of tetradeinate ligands or two bidentate ligands.

These tetradeinate complexes are generally represented by the formula [CuL2]+ and in particular, when CuBr salt is present, the anion Y can also be [CuBr2]−. Structures reported in literature, which involved N2S2-ligands and extensive studies related to metal-containing proteins, i.e., blue copper proteins, showed the frequent tetrahedral geometry of coordination around Cu(I). In view of the close similarity of the donor atoms of these complexes with the ones used in this report, we expect for complex [Cu(PhSAr)2]BF4 a similar tetrahedral structure for the cation, with two neutral NS-bidentate coordinating ligands PhSAr and BF4 as counter anion. Correspondingly, complex 18 is expected to present an analogous structure [Cu (PhSAr)2][CuBr2], with [CuBr2]− as counter anion. In the case of a 1:1 coordination of the NS-ligand PhSAr, as expected for complex 17, an additional mode of coordination can be involved, which includes the formation of Cu–X bridges, where X is Br− in our case. Similar structures have been reported, including N,N−, S,S−, and N,S-ligands. Therefore, complex 1 is most likely present as a species, in which the N,S-ligated copper maintains a tetrahedral/square planar configuration via two bridging bromide anions, with a general formula of [CuL2]X2.

3. Discussion

The present study shows that, with 2-aminoarenethiolato-copper(I) complexes as (pre-)catalyst and starting from aryl bromides, the desired dialyl ethers are formed in yields of 50–98%. The scope of the reaction is quite broad, and tolerates arene substituents ranging from electron-withdrawing to electron-donating groupings in ortho-, meta- and para-positions, on both the phenol and the aryl bromide derivatives. The protocol developed involves a low loading of the cheap metal copper (only 2.5 mol %) and leads to a clean and selective formation of the dialyl ether product, as no side products were detected beside starting materials, which could be recovered at the end of the reaction. Limitations of the present protocol regard the rather high reaction temperature (160 °C) and lack of coupling when the phenol bears an electron-withdrawing group on the ring.

Competitive reduction of the aryl halide to the corresponding dehalogenated arene, the formation of isomeric biaryl compounds via substitution through an elimination–addition mechanism and the reductive homocoupling of the aryl halide (Scheme 7) are commonly encountered features in the Ullmann biaryl ether synthesis. However, it is worth mentioning that in our studies (Tables 2 and 3) using the optimized protocol, high selectivities
were accomplished. Formation of biphenyls and isomeric diaryl ethers were not observed, while dehalogenated arenes were detected only in trace amounts (<2%).

Up to now the reported copper-catalyzed biaryl ether syntheses use a copper source in amount of 5–10 mol % and a suitable ligand in 10–20 mol % with reaction temperatures ranging from 80 to 150 °C and reaction times from 16 to 24 h. An obvious difference is the fact that whereas our catalytic protocol tolerates a lower loading of 2.5 mol % of the copper-catalyst, a reaction temperature as high as 160 °C is still needed. Moreover, while commonly aryl iodides show higher reactivity than bromides and chlorides, in our case aryl bromides are the most reactive partners for the coupling. This can be an indication that the use of 2-aminophenol and aryl alcohols are the most active partners for the coupling. This can be an indication that the use of 2-aminophenol and aryl alcohols is an interesting catalytic pathway in which the oxidation state of the copper changes throughout the catalytic cycle, rather than a mechanistic proposal in which the copper centre maintains its +1 oxidation state.

3.1. Proposed mechanism

In Scheme 8 a reaction sequence for the present reactions between arene alcohols and aryl bromides is proposed following the proposal put forward by Buchwald et al. The catalytic cycle starts with the formation of the PhSAr ligand and CuBr. The aryl alcohol is then converted into a metal phenolate/cuprate-like intermediate [Cu(OR)L]. Activation of the aryl bromide occurs via its coordination to the copper centre allowing inner electron transfer from the copper(I) centre to the aryl moiety. Concomitant C–O coupling via a concerted process inside the aggregate would then lead to the formation of the coupling product Ar–OR. The role of the S- and N-donor atoms of the PhSAr ligand during the coupling process is not clear yet but it is obvious that the PhSAr is a versatile ligand that can act as mono- or bidentate ligand supporting the switches of the oxidation state of the copper centre during this coupling process.

4. Conclusions

In the present report the preparation of a new library of aryl arene thiolato-copper(I) complexes was described, including a variety of thiolato-ligands derived from diverse amine derivatives and aryl and naphthyl backbones. It was found that prior to the C–O coupling reaction the CuSAr catalyst is converted into a CuBr(PhSAr) complex via selective coupling of the monooxoniolic arenethiolato ligand with phenyl bromide. A mechanistic sequence in which this complex subsequently catalyzes the C–O coupling reaction has been proposed. The present results also show that CuSAr 1c is an interesting pre-catalyst for one-pot sequential reactions. Indeed, its high solubility, good catalytic activity and chemoselectivity towards Br- or I-functionalities in C–O/C–N and C–S couplings, respectively, are important features. In these sequential multistep reactions there was no need for work-up after the first step, allowing a simple synthesis of the products.

5. Experimental

5.1. General remarks

All reactions were performed using Schlenk techniques under an inert atmosphere unless stated otherwise. Chemicals were purchased from Acros or Aldrich. Solvents used in the catalyst synthesis were carefully dried and distilled prior to use. Solvent used for catalytic tests were used as received. Chloro-trimethylsilane was distilled and passed through basic alumina prior to use. 1H and 13C{1H} NMR spectra were recorded on a Varian Inova 300 MHz spectrometer at 298 K unless stated otherwise. The chemical shifts (δ) are presented in parts per million referenced to residual solvent resonances. Gas chromatography analyses were performed on a Perkin-Elmer Clarus 500 GC equipped with an Alltech EC-5 column (30 m × 0.32 mm ID × 0.25 μm). Elemental analyses were performed by Kolbe, Mikroanalytisches Laboratorium, Mühlheim/Ruhr, Germany. MS measurements were carried out on an Applied Biosystems Voyager DE-STR MALDI-TOF MS and on SCIEX API 150 EX FIA-ESI mass spectrometer with positive ion electrospray.

5.2. General procedure for the etherification-catalytic tests

The catalytic tests were performed using standard Schlenk techniques. In a general procedure, the Schlenk tube was charged with the base (5.50 mmol) and solid substrate. Liquid reagents (aryl halide: 5.00 mmol; phenol: 6.50 mmol) and solvent (1 mL) were then added and finally the copper(I) catalyst was added (0.125 mmol). The reactor was kept under inert atmosphere and placed, under stirring, in a pre-heated oil bath at 160 °C for 6–16 h. Subsequently, the reaction mixture was allowed to cool to room temperature and diluted with acetonitrile (5 mL) and dihexyl ether (100 μL, 0.425 mmol) was added.
5.2.1. 2-Phenoxy-5-phenylsulfanylpyridine (15). A reaction vessel was first charged with Cs2CO3 (0.36 g, 1.1 mmol), 2-bromo-5iodopyridine (0.284 g, 1.4 mmol), phenol (94 mg, 1.00 mmol) and DMSO (0.5 mL) and DMSO (0.5 mL) was then added. The aminoarenethiolato-copper(I) complex 1 (6.0 mg, 0.025 mmol, 2.5 mol %) was then added and the reaction mixture heated at 160 °C for 16 h with good stirring. Afterwards, the heating was stopped, the reaction vessel cooled down and K2CO3 (0.152 g, 1.1 mmol), thiophenol (0.11 g, 1.1 mmol) and 1 (0.006 g, 0.025 mmol, 2.5 mol %) were added to the reaction mixture. The heating (160 °C) and stirring were again started for 16 h, after which the reaction was stopped. Isolation of the crude product (yield 87%) was performed by washing with NaHCO3 (1 N)/pentane (4-50 mL), drying over MgSO4, and, after filtration, removing the solvent in vacuo. The product was purified by column chromatography on silica gel (eluent: ethyl acetate/hexane 1:5), to give the product as colorless oil (yield 7%).

1H NMR (399.9 MHz, CDCl3): δ 8.25 (br s, 1H, PyrC), 7.79-7.68 (m, 1H, PyrC), 7.45-7.39 (m, 3H, Ar), 7.29-7.22 (m, 5H, Ar), 7.19-7.14 (m, 2H, Ar), 6.85 (br s, 1H, PyrC); 13C NMR (100.6 MHz, CDCl3): δ 153.7, 143.9, 136.2, 135.0, 130.8, 129.8, 129.5, 129.3, 129.2, 127.44, 128.82, 121.28; (M+H) (relative intensity): 195 (72), 194 (68), 117 (34), 89 (100), 65 (70). MS (EI) m/z (relative intensity): 279.02 (15%), 250.03 (20%), 176.05 (46%), 115.09 (37%), 104.05 (50%), 77.09 (30%), 65.08 (18%); HR-ESI-MS: MH+ found 280.0796.

5.2.2. N-(5-Phenylsulfanylpyridin-2-yl)benzylamine (16). A reaction vessel was first charged with K2CO3 (0.45 g, 3.57 mmol), 2-bromo-5-iodopyridine (0.85 g, 2.98 mmol), benzylamine (0.38 g, 3.57 mmol) and DMSO (1 mL) and DMSO (1 mL) was then added. At last, the aminoarenethiolato-copper(I) complex 1 (17.0 mg, 0.0739 mmol, 2.5 mol %) was added and the reaction mixture heated at 160 °C for 16 h, under good stirring. Afterwards, the heating was stopped, the reaction vessel cooled down and K2CO3 (0.45 g, 3.57 mmol), thiophenol (393 mg, 3.57 mmol) and a fresh portion of CuSAr 1 (17.0 mg, 0.0739 mmol, 2.5 mol %) were added to the reaction mixture. The heating and stirring were started again for 16 h, after which the reaction was stopped. Isolation of the crude product (yield 60%) was performed by washing the mixture with NaHCO3 (1 N)/pentane (4-50 mL), drying over MgSO4 and, after filtration, removing the solvent in vacuo. The product was purified by column chromatography on silica gel (eluent: ethyl acetate/hexane 1:5), to give the product as colorless oil (yield 54%).

1H NMR (399.9 MHz, CDCl3): δ 8.21 (br s, 1H, PyrC), 7.76-7.35 (m, 3H, Ar), 7.33-7.28 (m, 2H, Ar), 7.26-7.21 (m, 2H, Ar), 7.15-7.11 (m, 3H, Ar), 6.42 (d, 1H, J=8.8 Hz, PyrC), 5.52 (br s, 1H, NH), 4.53 (d, 2H, J=5.6 Hz, CH2); 13C NMR (100.6 MHz, CDCl3): δ 158.2, 152.8, 144.6, 138.6, 138.5, 129.2, 129.0, 127.89, 127.6, 120.6, 124.7, 116.9, 108.1, 46.5; (M+H) (liquid film) 3437, 3054, 2986, 1657, 1595, 1265, 738 cm⁻¹; MS (EI) m/z (relative intensity): 292.05 (15%), 215.07 (25%), 187.08 (25%), 147.02 (15%), 106.11 (50%), 91.09 (100%), 65.08 (35%); HR-ESI-MS: MH+ found 293.1087. C18H16N2S requires 293.1112.

5.2.3. 2-[(Dimethylamino)methyl]phenyl phenyl sulphide, PhSAr (Scheme 5). A solution of t-BuLi (170 mL, 1.5 M in pentane, 25.5 mmol, 1.1 equiv) was added to a solution of N,N-dimethylaniline (3.00 g, 22.18 mmol, 1 equiv) in dry pentane (60 mL) at room temperature, under nitrogen atmosphere. After stirring the orange solution overnight, the solvent was removed in vacuo and cold THF (0 °C, 40 mL) was added in an ice bath was used to maintain the low temperature. The resulting brown solution was stirred for 1.5 h, then 1,2-diphenyl disulfane (5.567 g, 25.5 mmol, 1.1 equiv) was added and the mixture heated at 160 °C. The mixture was stirred for 30 min, then 15 mL of demineralized water were added and the stirring maintained for 30 min. The mixture was washed first with brine, extracted with diethyl ether, dried over MgSO4 and, concentrated in vacuum to obtain orange oil. Crude yield: 5.6 g, 90%. The crude product was purified via silica gel column chromatography (elucent: hexane/ethylacetate 5:1) to obtain the pure product as yellow oil. Isolated yield: 85%.

1H NMR (399.94 MHz, CDCl3): δ 2.29 (s, 6H, N(CH3)2), 3.61 (s, 2H, CH2), 7.15-7.19 (m, 1H, Ar), 7.23-7.35 (m, 7H, Ar), 7.45-7.47 (d, 1H, Ar); 13C NMR (100.576 MHz, CDCl3): δ 139.9, 136.6, 136.1, 132.3, 131.2, 130.4, 129.4, 128.1, 127.2, 127.1, 62.27, 45.63. MS (EI) m/z (relative intensity): 195 (72), 194 (68), 117 (34), 89 (100), 65 (70). Anal. Calcld for C18H22N2S: C 74.03, H 7.04, N 5.76. Found: C 73.94, H 7.10, N 5.69.

(b) Following the general procedure for a catalytic test, a reaction mixture was prepared, which contained NMP (1 mL), bromobenzene: (5 mmol, 527 µL), internal standard dihexyl ether (100 µL, 0.42 mmol) and CuSAr complex (5 mmol, 1.149 g). Product: 2-[(dimethylamino)methyl]phenyl phenyl sulphide (PhSAr). GC yield: 80%.

5.2.4. Catalytic test with CuBr and PhSAr. Following the general procedure for a catalytic test, the reaction mixture was prepared using freshly prepared CuBr (17.9 mg, 0.125 mmol) and PhSAr (28.7 mg, 0.125 mmol) instead of CuSAr as pre-catalyst. All the other conditions were kept (160 °C, 16 h, base Cs2CO3, PhBr and PhOH) as previously described. The reaction mixture was analyzed by GC (diethyl ether as internal standard) and showed a yield of diaryl ether of 87% (vs 98% with CuSAr pre-catalyst).

5.2.5. Preparation of samples for mass-spectrometry analysis. A mixture of CuSAr (200 mg, 0.874 mmol) and bromobenzene (3.59 g, 35 mmol) in NMP (7 mL) was prepared in a round-bottomed flask under a positive pressure of nitrogen. The mixture was heated at 120 °C for 30 min, afterwards a sample was taken and analysed by FIA-ESI-MS (positive ionization).

Identified ions signals: PhSAr [M+H]+ m/z found: 244.30; calcld: 244.38; complex 1, m/z found: 306.10 (100%), 307.00 (20%), 308.02 (51%), 309.00 (8%), 310.10 (1%); complex 2, m/z found: 549.30 (100%), 550.00 (35%), 551.30 (65%), 552.00 (20%), 553.20 (4%), calcd: 549.15. A mixture of PhSAr (0.86 mmol) and
Cu(MeCN)₄BF₄ (0.43 mmol) in methanol (10 mL) was prepared in a round-bottomed flask under a positive pressure of nitrogen. The mixture was heated at 120 °C for 30 min, afterwards a sample was taken, and analysed by MALDI-TOF-MS (DHB Matrix).

Identified ions signals: PhSAr [M+H]+ m/z found: 244.3694; calcd: 244.3730; complex 1, m/z found: 306.3092 (100%), 307.3129 (20%), 308.3099 (50%), calcd: 306.04; complex 2, m/z found: 549.38 (100%), 550.3785 (40%), 551.3837 (57%), calcd: 549.15.

Applied Biosystems Voyager System 6347

Mode of operation: Reflectron
Extraction mode: Delayed
Polarity: Positive
Acquisition control: Manual
Accelerating voltage: 20000 V
Grid voltage: 76.3%
Mirror voltage ratio: 1.12
Guide wire: 0.0785
Extraction delay time: 96 nsec
Acquisition mass range: 100–200 Da
Number of laser shots: 1000
Laser intensity: 2110
Laser Rep Rate: 20 Hz
Calibration type: Default
Calibration matrix: 2,5-dihydroxybenzoic acid
Low mass gate: 100 Da
Tuned ion selector: Off
Digitizer start time: 14.345 µs
Bin size: 0.5 nsec
Number of data points: 61154
Vertical scale: 0
Vertical offset: 0.3
Input bandwidth: 500 MHz

Sample well: 69
Plate ID: PLATE 1
Serial number: 6347
Instrument name: Voyager-DE PRO
Plate type file name: C:\Voyager1100.well
Lab name: PE Biosystems

Absolute x-position: 42330.5
Absolute y-position: 15328.9
Relative x-position: 3.93079
Relative y-position: 241.93
Shots in spectrum: 150
Source pressure: 2.336e-007
Mirror pressure: 0.918e-006
TCZ pressure: 0.914e-005
TCI gate width: 1
TCI flight length: 687.7
A reaction mixture was prepared (as described in Kinetic experiments in HEL auto-MATE working station section), a sample was taken and analysed by FIA-ESI-MS (positive ionization).

Identified ions signals: PhSAr [M+H]+ m/z found: 244.40; calcld: 244.38; complex 1, m/z found: 306.30 (100%), 307.00 (20%), 308.20 (45%), calcld: 306.04; complex 2, m/z found: 549.30 (100%), 550.00 (40%), 551.20 (60%), 552.30 (23%), 553.00 (7%), 554.30 (4%), calcld: 549.15; complex C29H30CuN2S [Cu(PhSAr)BBA]+ m/z found: 501.30 (100%), 502.00 (40%), 503.20 (60%), calcld: 501.15. Non-identified ions signals: m/z 269.30, 395.20, 419.30, 539.0.
5.2.6. Coordination evidences for complex 17, \([\text{CuPhSAr}]^+\). A mixture of PhSAr (0.125 mmol) and freshly synthesised CuBr (0.125 mmol) in DMSO-\(d_6\) (1 mL) was prepared in a schlenk tube under nitrogen atmosphere. The mixture was heated at 120 °C for 180 min, afterwards a sample was taken and analysed by \(^1\)H NMR.

\[^1\text{H NMR (399.94 MHz, DMSO-d}_6\text{):} \delta 2.29 (s, 6H, N(CH}_3)_2\text{), 3.53 (s, 2H, NCH}_2\text{), 7.18–7.20 (m, 1H, Ar), 7.30–7.44 (m, 8H, Ar).\]

(For comparison to) PhSAr: \[^1\text{H NMR (399.94 MHz, DMSO-d}_6\text{):} \delta 2.12 (s, 6H, N(CH}_3)_2\text{), 3.48 (s, 2H, NCH}_2\text{), 7.14–7.34 (m, 8H, Ar), 7.43 (d, 1H, Ar).\]
H NMR spectra in DMSO-d$_6$, at room temperature. (a) Spectrum of Ph$_3$SAr; (b) spectrum of Ph$_2$SAr and CuBr in 1:1 M ratio, after 3 h at 120 °C in DMSO-d$_6$.

5.2.7. Preparation of complex $[Cu(Ph$_3$SAr)$_2$BF$_4$]. A solution of 2(N,N-dimethyl benzylamino)-phenyl sulfide (0.211 g, 0.86 mmol, 2 equiv) in distilled and deoxygenated benzene (10 mL) was transferred under nitrogen via cannula to a suspension of Cu(MeCN)$_4$BF$_4$ (136 mg, 0.43 mmol, 1 equiv) in distilled and deoxygenated benzene (15 mL). The mixture was stirred under nitrogen at room temperature overnight, while a yellow solid precipitated. The pale yellow precipitate was then filtered and washed with dry Et$_2$O (2×5 mL). The solvent was then removed and the off-white powder dried under reduced pressure (yield 76%, 0.21 g, 0.326 mmol).

H NMR (399.94 MHz, CD$_2$OD): $\delta$ 2.49 (s, 6H, CH$_3$), 3.81 (br s, 2H, CH$_2$), 7.20 (3H, Ar), 7.33–7.46 (m, 6H, Ar).

FT-IR (ATR, cm$^{-1}$): 3062.90, 2986.15, 2846.50, 1588.11, 1473.95, 1463.94, 1440.34, 1045.59, 1032.90, 975.85, 873.94, 837.10, 752.48, 707.71, 693.83, 681.42.

Anal. Calcd for Cu$_3$H$_6$BCuF$_4$N$_2$S$_2$: C 56.56, H 5.38, N 4.40. Found: C 55.53; H 5.03; N 4.10.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.09.019.

References and notes


44. The four alternatives proposed in literature are: (a) oxidative addition/reductive elimination of ArX on copper; (b) Aryl radical intermediates. (c) $\pi$-Bond metathesis through a four-centred intermediate. (d) $\pi$-Complexation of copper (I) on ArX (see also Chapter 1 of this thesis).


47. Recently a paper appeared in literature that support the formation of the O-arylation reaction via atom transfer or single electron transfer mechanism, depending on the nature of the ligand used, see: Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. J. Am. Chem. Soc. 2010, 132, 6205–6213.