# 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

Sperotto, Elena; Klink, Gerard P.M. van; de Vries, Johannes G.; Koten, Gerard van

*Published in:*
Tetrahedron

*DOI:*
10.1016/j.tet.2010.09.019



*Publication date:*
2010

Tetrahedron 66 (2010) 9009–9020

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# 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

Elena Sperotto [a], Gerard P.M. van Klink [a], Johannes G. de Vries [b], Gerard van Koten [a,*]

[a] Chemical Biology & Organic Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands
[b] DSM Research, Life Science, Advanced Synthesis and Catalysis, PO Box 18, 6160 MD Geleen, The Netherlands

ARTICLE INFO

*Article history:*
Received 24 March 2010
Received in revised form 14 August 2010
Accepted 6 September 2010
Available online 21 September 2010

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(PhSAr) 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%).



## 1. Introduction

The diaryl ether unit is a common structural unit widely encountered in biologically active molecules and natural products[1] as well as in monomers for the synthesis of functional polymers.[2] This structural moiety is part of various important pharmaceuticals with antibiotic activity, such as vancomycin,[3] teicoplanin,[4] the antiviral peptide K-13,[5] the antitumoral bouvardin[6] and many others.[7] Common routes for the preparation of these ethers, i.e., through C–O bond formation, involve the classical Ullmann diaryl synthesis,[8] which however has several drawbacks related to harsh reaction conditions and stoichiometric use of the copper mediator.[9] Recently, new approaches have been developed to overcome these disadvantages, for example, through the use of organobismuth,[10] organostannane,[11] organotrifluoroborate[10b,12] reagents or arylboronic acids.[13] 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 alkylphosphines,[14] or pyrrol and indole[15] based monophosphine ligands. Nevertheless, there remains a quest for low-cost alternatives involving cheaper and more abundant metals[16] and cheaper ligands (or ideally no ligands or other additives at all)[17] 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.[18] These problems have been addressed by the use of suitable ligands,[9,19] like for instance aminoacids,[20] ketones,[21] phenantroline derivatives[22] and nitrogen- and oxygen-containing ligands[23] 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 $[Cu(MeCN)_4]PF_6$[24] or neutral $[CuBr(neocup)(PPh_3)]$,[25] and many of these have already shown to be good (pre-)catalysts in diaryl ether synthesis.[9]

In recent years we explored a class of well-defined neutral copper (I) complexes, i.e., the 2-aminoarenethiolato-copper(I) complexes (CuSAr, Fig. 1)[26] as (pre-)catalysts for various types of C–X bond forming reactions and have tested these as (pre-)catalyst in allylic substitution,[27] 1,4-,[28] and 1,6-[29] addition reactions and aromatic N-arylation[30] reactions.

* Corresponding author. Fax: +31 30 252 3615; e-mail address: g.vankoten@uu.nl (G. van Koten).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.09.019

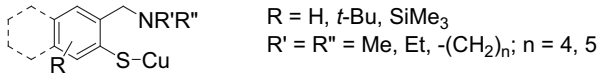



**Fig. 1.** 2-Aminoarenethiolato-copper(I) complexes.

The complexes have excellent solubility in a range of useful solvents.[26] In addition, electronic and physical properties can easily be fine-tuned by introducing substituents at the arene ring or the amino-functionality.

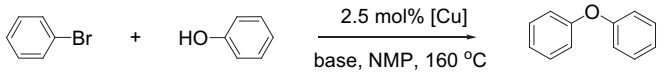
In the present study the reactivity of a small library of differently substituted 2-aminoarenethiolato–copper(I) complexes as (pre-) catalysts in the O-arylation of phenols with aryl bromides is reported. The copper complexes studied show good catalytic activity in C–O coupling reactions affording diaryl 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.[26]

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.




**Scheme 2.** Coupling reaction of bromobenzene with phenol.

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, $NEt_3$, Hunig's base, pyridine and 2,6-luitidine gave poor product yields. Likewise, moderate results were obtained with either potassium

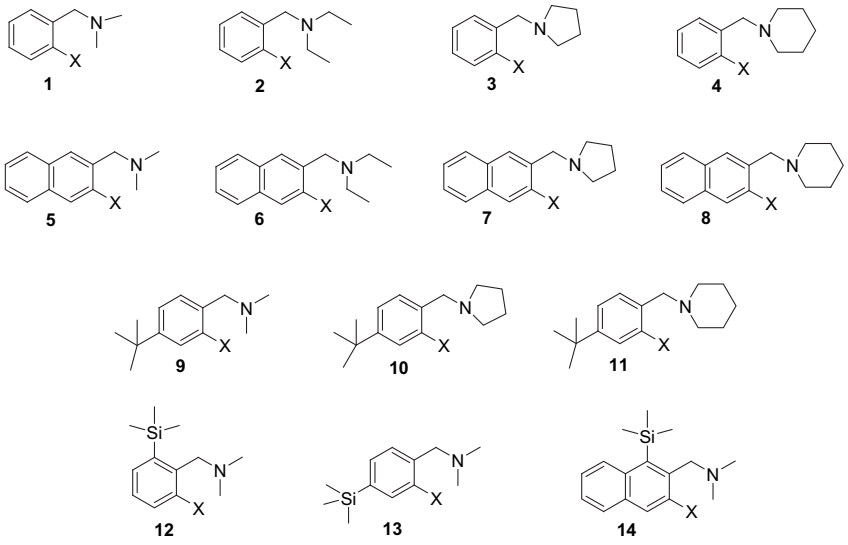
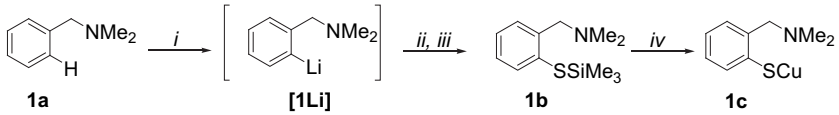



**Fig. 2.** Library of 2-aminoarenethiolato-copper(I) complexes used in this study.




*i*. *t*-BuLi, pentane, -78 °C; ii. 1/8 $S_8$, THF, -78 °C to -20 °C; *iii*. $SiMe_3Cl$, -20 °C to rt; *iv*. CuCl, toluene, rt

**Scheme 1.** General procedure for the synthesis of aminoarenethiolato-copper(I) complexes exemplified by the synthesis of **1c**.

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

| Entry | Base | Yield[a] % |
|---|---|---|
| 1 | $K_2CO_3$ | 43 |
| 2 | $Cs_2CO_3$ | 98 |
| 3 | KO-*t*-Bu | 89 |
| 4 | $K_3PO_4$ | 52 |

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 $N_2$.
[a] Determined by GC using dihexyl ether as internal standard, based on phenyl bromide.

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 $Cs_2CO_3$ 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-aminoarenethiolato-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).

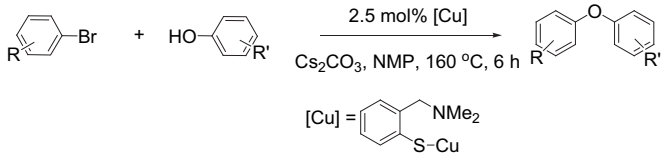
**Table 2**
Screening of the reactivity of 2-aminoarenethiolato-copper(I) complexes[a] in reaction of Scheme 2

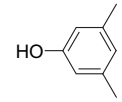
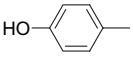
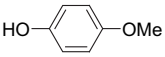
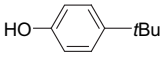
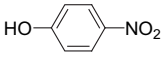
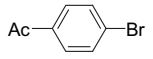
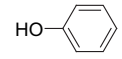
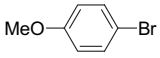
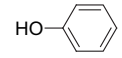
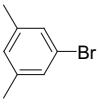
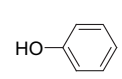
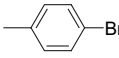
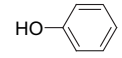
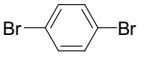
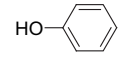
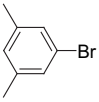
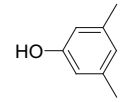
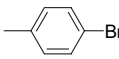
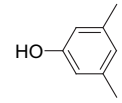
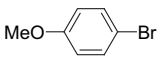
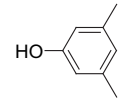
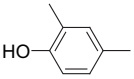
| Complex | Aryl | R | R′, R″ | Yield[b] % |
|---|---|---|---|---|
| 1 | Phenyl | H | Me, Me | 98 |
| 2 | Phenyl | H | Et, Et | 87 |
| 3 | Phenyl | H | $-(CH_2)_4-$ | 90 |
| 4 | Phenyl | H | $-(CH_2)_5-$ | 89 |
| 5 | Naphthyl | H | Me, Me | 74 |
| 6 | Naphthyl | H | Et, Et | 96 |
| 7 | Naphthyl | H | $-(CH_2)_4-$ | 96 |
| 8 | Naphthyl | H | $-(CH_2)_5-$ | 87 |
| 9 | Phenyl | 5-*t*-Bu | Me, Me | 89 |
| 10 | Phenyl | 5-*t*-Bu | $-(CH_2)_4-$ | 83 |
| 11 | Phenyl | 5-*t*-Bu | $-(CH_2)_5-$ | 71 |
| 12 | Phenyl | 3-TMS | Me, Me | 81 |
| 13 | Phenyl | 5-TMS | Me, Me | 87 |
| 14 | Naphthyl | 3-TMS | Me, Me | 84 |

[a] For R, R′, R″ see Figs. 1 and 2. Reaction conditions: phenol (6.5 mmol), bromobenzene (5 mmol), $Cs_2CO_3$ (5.5 mmol), [Cu] (2.5 mol %), solvent (1 mL), 16 h, under $N_2$, 160 °C.
[b] Determined by GC using dihexyl ether as internal standard, based on phenyl bromide.

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%.

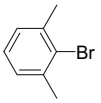
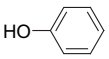
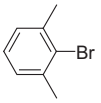
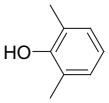
**Table 3**
Etherification of aryl bromides catalyzed by CuSAr **1c** after 6 h




| Entry | ArBr | Phenol | Yield[a] % |
|---|---|---|---|
| 1 |  |  | 90[b] |
| 2 |  |  | 85[b] |
| 3 |  |  | 85[b] |
| 4 |  |  | 81[b] |
| 5 |  |  | 13[c] |
| 6 |  |  | 64 |
| 7 |  |  | 77[b] |
| 8 |  |  | 87[b] |
| 9 |  |  | 85 |
| 10 |  |  | 50[d] 63[e] |
| 11 |  |  | 79[b] |
| 12 |  |  | 79[b] |
| 13 |  |  | 82[b] |
| 14 |  |  | 64 |

(*continued on next page*)

**Table 3** (*continued*)

| Entry | ArBr | Phenol | Yield[a] % |
|---|---|---|---|
| 15 |  |  | 65 |
| 16 |  |  | 2 |

Reaction conditions: phenol (6.5 mmol), bromoarene (5 mmol), $Cs_2CO_3$ (5.5 mmol), [Cu] (2.5 mol %), NMP (1 mL), 160 °C, 6 h, under $N_2$.

[a] Determined by GC and GC–MS using dihexyl ether as internal standard, based on aryl bromide.

[b] Isolated yield; see supporting information for analytical data.

[c] Reaction time (16 h).

[d] Using 1.3 equiv of phenol, yield of monosubstituted product.

[e] Using 2.6 equiv of phenol, yield of disubstituted product.

Reaction of bromobenzene with electron-rich phenols resulted in the formation of the corresponding asymmetric diaryl ethers in good yields (81–90%, entries 1–4), both for *para*- and *meta*-substituted phenols.

Following a general trend in the field of C–O coupling reactions,[21] 4-nitrophenol, which bears a strong electron-withdrawing $NO_2$-group proved to be a less efficient substrate for the desired O-arylation reaction, even after 16 h when the product was present in a yield of 13% (entry 5), and conversion was 15% based on the starting bromobenzene.

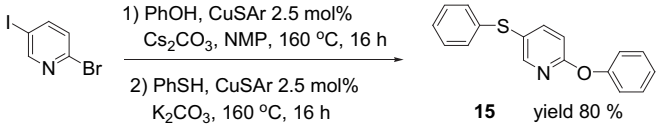
When the arylating reagent was changed from bromobenzene to *meta*- or *para*-substituted aryl bromides, just a slight decrease in reactivity and yield in product was noticed. The etherification of electron-rich bromoarene derivatives with 3,5-dimethylphenol afforded the respective diaryl ethers in good yields (79–82%, entries 11–13). The coupling of aryl bromides with either electron-donating or -withdrawing substituents, i.e., 4-bromoanisole, 4-bromotoluene and 4-bromoacetophenone, with phenol gave rise to the formation of the diaryl ethers in good yields (64–87%, entries 6–9).

More sterically hindered aryl bromides and phenols are challenging substrates which are not often tested but highly important with respect to the scope of the diaryl ether reaction.[28] Coupling partners such as *ortho*-disubstituted arenes or phenols commonly give quite poor results. The reactivity of the present 2-aminoarenethiolato-copper(I) (pre-)catalyst was investigated employing some of these starting materials but produced moderate results (64–65%, entries 14 and 15), in concert with results obtained with other copper(I) catalysts.[32,33] Only traces of product were detected in the mixture of the reaction of 2,6-dimethylbromobenzene with 2,6-dimethylphenol in the presence of **1c** (2%, entry 16).

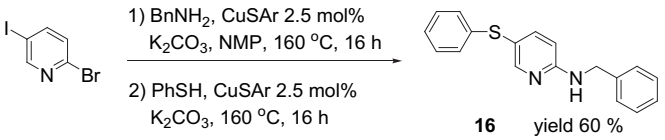
### 2.1. Sequential C–X cross coupling reactions on 2-bromo-5-iodopyridine

In this section the starting material of choice was 2-bromo-5-iodopyridine, because of its commercial availability and good reactivity. One example is shown in Scheme 3, in which initially 2-bromo-5-iodopyridine reacts selectively with phenol on its bromide-functionality to form a new C–O bond and then, after addition of the second set of reagents, reacts on the iodide-functionality with thiophenol to form the new C–S bond. The optimized reaction conditions for the two separate couplings, C–O and C–S, respectively, appeared to be suitable for the C–O/C–S combination as well. Although the reagents were added in sequence to favor the chemoselectivity of the two coupling processes, the overall reaction was conducted in one-pot without isolation/purification of intermediates and the desired product **15** was isolated in 80% yield. Two additional side products, identified by GC/MS analysis, are the dietherification (<5%) and the dithioetherification (<10%) products, respectively.

A second example is shown in Scheme 4, following the same strategy for the synthesis of **15**. At first, the C–N bond is formed between pyridine and benzylamine with high chemoselectivity at the C–Br bond. The following step is then initiated by the addition of thiophenol and a fresh portion of catalyst **1**, to give the desired C–N/C–S coupled product **16** in 60% overall yield. As detected by GC/MS, the dithioetherification side-product was present in the reaction mixture in low amounts <5%. A second product was identified as *N*-benzyl-benzylideneamine, oxidation product of benzylamine and the reason for its formation was already recognized.[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.




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

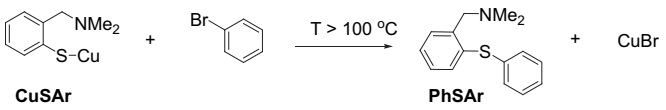



**Scheme 4.** Sequential C–N/C–S coupling reactions on 2-bromo-5-iodopyridine.

In preliminary experiments 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., dietherification and dithioetherification products, increased to 15–20%.

### 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 (PhSAr in Scheme 5). The formation of PhSAr results from the reaction of 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 CuSAr in 1: 1 M ratio (see experimental). Exclusively PhSAr (and CuBr) was formed which was isolated in 80% yield. Consequently, it can be concluded that 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 PhSAr is only formed at reaction temperatures ≥100 °C.

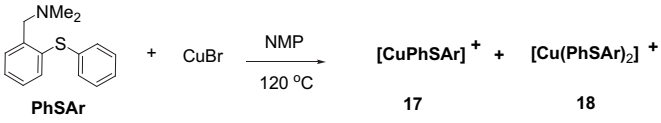



**Scheme 5.** Formation of 2-[(dimethylamino)methyl]phenyl phenyl sulfide (PhSAr).

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 % respect 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).




**Scheme 6.** Complexes **17** and **18**.

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-$d_6$[35] were both analyzed by $^1$H NMR spectroscopy (see Experimental). The $^1$H 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 $^1$H 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 ($\Delta\delta$=0.17 ppm), for the benzylic protons ($\Delta\delta$=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).

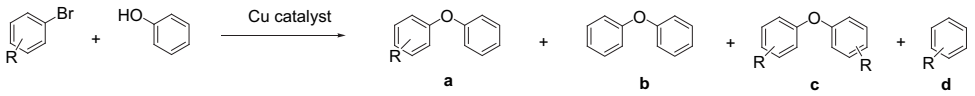
Independent preparation of the 2:1 complex (**18**) was achieved through addition of a solution of ligand PhSAr to a suspension of $[Cu(MeCN)_4]BF_4$ in benzene, in 2:1 M ratio.[36] The isolated off-white powder analyzed as $[Cu(PhSAr)_2]BF_4$ showed poor solubility in common organic solvents. However, $^1$H NMR spectrum of a solution of $[Cu(PhSAr)_2]BF_4$ in methanol-$d_4$ showed, when compared to the spectrum of free PhSAr, a down-field shift for both benzylic ($\Delta\delta$=0.20 ppm) and methyl protons ($\Delta\delta$=0.24 ppm), which indicates a coordination of the ligand to the metal centre. The methyl and benzylic proton resonances of $[Cu(PhSAr)_2]BF_4$ appeared as broad singlets under the conditions employed (methanol-$d_4$, 298 K). The temperature dependency of the $^1$H NMR spectra of $[Cu(PhSAr)_2]BF_4$ could not be studied for temperatures below 298 K, because of its poor solubility in methanol-$d_4$, 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 $[Cu(PhSAr)_2]BF_4$ showed the presence of the ions $[CuPhSAr]^+$ ($m/z$ 306.3092) and $[Cu(PhSAr)_2]^+$ ($m/z$ 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 tetradentate ligands or two bidentate ligands.[37] These cationic complexes are generally represented by the formula $[Cu^IL_2]$ [Y] and in particular, when $Cu^IBr$ salt is present, the anion Y can also be $[CuBr_2]^-$. Structures reported in literature, which involved $N_2S_2$-ligands,[38] and extensive studies related to metal-containing proteins, i.e., blue copper proteins,[39] 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 $[Cu(PhSAr)_2]BF_4$ a similar tetrahedral structure for the cation, with two neutral *N*,*S*-bidentate coordinating ligands PhSAr and $BF_4$ as counter anion. Correspondingly, complex **18** is expected to present an analogous structure $[Cu(PhSAr)_2][CuBr_2]$, with $[CuBr_2]^-$ as counter anion. In the case of a 1:1 coordination of the N,S-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-,[40a–c] S,S-,[40d] and N,S-ligands.[40e] 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 $[Cu_2L_2]X_2$.

## 3. Discussion

The present study shows that, with 2-aminoarenethiolato-copper(I) complexes as (pre-)catalyst and starting from aryl bromides, the desired diaryl 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 diaryl 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)[13a,21a,41] 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




**Scheme 7.** Possible competitive reactions besides the cross-coupling product formation (a: desired product, b: biphenyl, c: isomeric biaryl ether, d: dehalogenated arene).

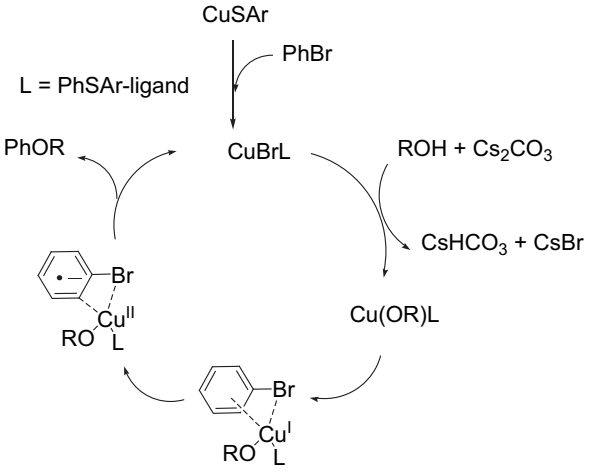
were accomplished. Formation of biphenyls and isomeric diaryl ethers were not observed, while dehalogenated arenes were detected only in trace amounts (<2%).

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[22,23,32] 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-aminoarenethiolato-copper(I) complexes as (pre-)catalyst causes a substantial shift in the mechanistic pathway of the C–O coupling process.[32a,42]

As the coupling reaction shows a preference for bromide anions, the nature of the halide anion present in the reaction mixture also plays a fundamental role. It is noteworthy that in contrast to bromide (and chloride), iodide ions stabilize the copper atom in its +1 oxidation state.[18,43] These observations seem to support a mechanistic 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.[44]

### 3.1. Proposed mechanism

In Scheme 8 a reaction sequence for the present reactions between arene alcohols and arene bromides is proposed following the proposal put forward by Buchwald et al.[45] The catalytic cycle starts with the formation of the PhSAr ligand and CuBr. The arene 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.[13a,46] 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.




**Scheme 8.** Proposed mechanism for the copper-catalyzed etherification reaction.[47]

## 4. Conclusions

In the present report the preparation of a new library of aminoarenethiolato-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 monoanionic 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

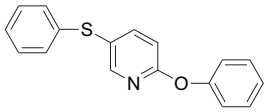
All reactions were performed using Schlenk techniques under an inert atmosphere unless stated otherwise. Chemicals were purchased from Across or Aldrich. Solvents used in the catalyst syntheses were carefully dried and distilled prior to use. Solvents used for catalytic tests were used as received. Chlorotrimethylsilane was distilled and passed through basic alumina prior to use. $^{1}H$ and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Varian Inova 300 MHz spectrometer at 298 K unless stated otherwise. The chemicals shifts ($\delta$) 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 preheated 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

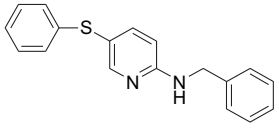
as external standard. All samples were analyzed by gas chromatography to obtain the data presented. The reaction mixture was filtered through a plug of Celite, the solvent removed in vacuo to yield the crude product, which was purified by silica gel chromatography.

For the library of (pre-)catalysts, see: Sperotto, E.; van Klink, G.P.M.; de Vries, J.G.; van Koten, G. *Tetrahedron*. **2010**, *66*, 3478–3484.



*5.2.1. 2-Phenoxy-5-phenylsulfanylpyridine (**15**).* A reaction vessel was first charged with $Cs_2CO_3$ (0.36 g 1.1 mmol), 2-bromo-5-iodopyridine (0.284 g, 1.00 mmol), phenol (94 mg, 1.00 mmol) 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 $K_2CO_3$ (0.152 g, 1.1 mmol), thiophenol (0.11 g, 1 mmol) and a fresh portion of **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 80%) was performed by washing the mixture with $NaHCO_3$ (1 N)/pentane (4×50 mL), drying over $MgSO_4$ and, after filtration, removing the solvent in vacuo. The product was purified by column chromatography on silica gel (eluent: ethyl acetate/hexane 1:4), to give the product as colorless oil (yield 75%).

$^1$H NMR (399.9 MHz, $CDCl_3$): $\delta$ 8.25 (br s, 1H, PyrC*H*), 7.79–7.68 (m, 1H, PyrC*H*), 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*H*); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 153.7, 143.9, 136.2, 135.0, 130.8, 129.8, 129.7, 129.5, 129.3, 129.2, 127.44, 126.82, 121.28; $\nu_{max}$ (liquid film) 3059, 2925, 1577, 1457, 1268, 691 cm$^{-1}$; MS (EI) *m*/*z* (relative intensity): 279.02 ([M]$^+$, 100%), 250.03 (20%), 176.05 (46%), 115.09 (37%), 104.05 (50%), 77.09 (30%), 65.08 (18%); HR-ESI-MS: MH$^+$, found 280.0810. $C_{17}H_{13}NOS$ requires 280.0796.



*5.2.2. N-(5-Phenylsulfanylpyridin-2-yl)benzylamine (**16**).* A reaction vessel was first charged with $K_2CO_3$ (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) 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 $K_2CO_3$ (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 $NaHCO_3$ (1 N)/pentane (4×50 mL), drying over $MgSO_4$ 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%).

$^1$H NMR (399.9 MHz, $CDCl_3$): $\delta$ 8.21 (br s, 1H, PyrC*H*), 7.54 (d, 1H, *J*=8.8 Hz, PyrC*H*), 7.36–7.35 (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*H*), 5.52 (br s, 1H, N*H*), 4.53 (d, 2H, *J*=5.6 Hz, $CH_2$); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 158.2, 152.8, 144.6, 138.6, 138.5, 129.2, 129.0, 127.89, 127.6, 126.0, 124.7, 116.9, 108.1, 46.5; $\nu_{max}$ (liquid film) 3437, 3054, 2986, 1657, 1595, 1265, 738 cm$^{-1}$; MS (EI) *m*/*z* (relative intensity): 292.05 ([M]$^+$, 80%), 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. $C_{18}H_{16}N_2S$ requires 293.1112.

*5.2.3. 2-[(Dimethylamino)methyl]phenyl phenyl sulphide, PhSAr (Scheme 5).* (a)A solution of *t*-BuLi (17.0 mL, 1.5 M in pentane, 25.5 mmol, 1.1 equiv) was added to a solution of *N*,*N*-dimethylbenzylamine (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 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 reaction mixture turned to a grey turbid colour. The stirring was kept for 1.5 h, when the ice bath was removed. The reaction mixture was stirred for additional 30 min, after that 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 $MgSO_4$ and concentrated in vacuum to obtain orange oil. Crude yield: 5.6 g, 90%. The crude product was purified via silica gel column chromatography (eluent: hexane/ethylacetate 5:1) to obtain the pure product as yellow oil. Isolated yield: 85%.

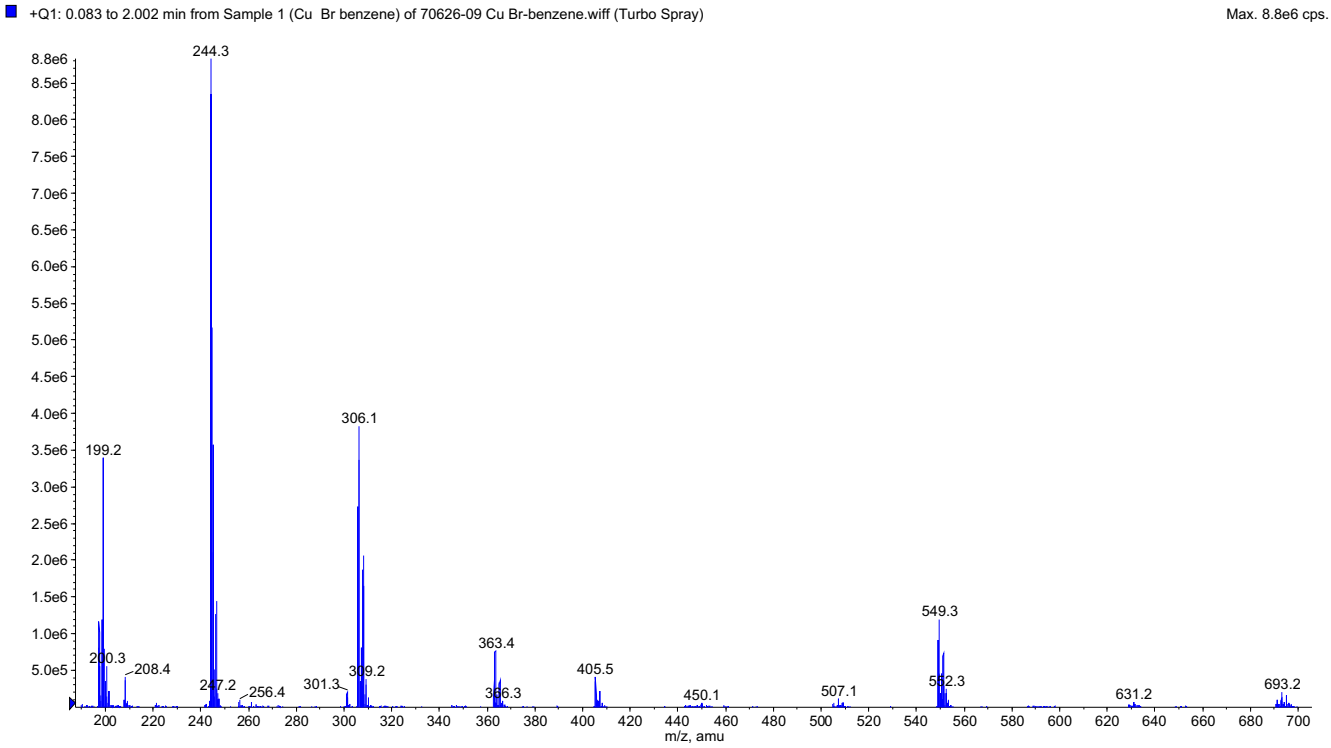
$^1$H NMR (399.94 MHz, $CDCl_3$): $\delta$ 2.29 (s, 6H, N($CH_3$)$_2$), 3.61 (s, 2H, $CH_2$), 7.15–7.19 (m, 1H, Ar), 7.23–7.35 (m, 7H, Ar), 7.45–7.47 (d, 1H, Ar); $^{13}$C NMR (100.576 MHz, $CDCl_3$): $\delta$ 139.9, 136.6, 136.1, 132.3, 131.2, 130.4, 129.4, 128.1, 127.2, 127.1, 62.27, 45.63. MS (EI) *m*/*z* (relative intensity): 195 (72), 194 (68), 117 (34), 89 (100), 65 (70). Anal. Calcd for $C_{15}H_{17}NS$: 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 $Cs_2CO_3$, PhBr and PhOH) as previously described. The reaction mixture was analyzed by GC (dihexyl ether as internal standard) and showed a yield of diaryl ether of 87% (vs 98% with CuSAr pre-catalyst).

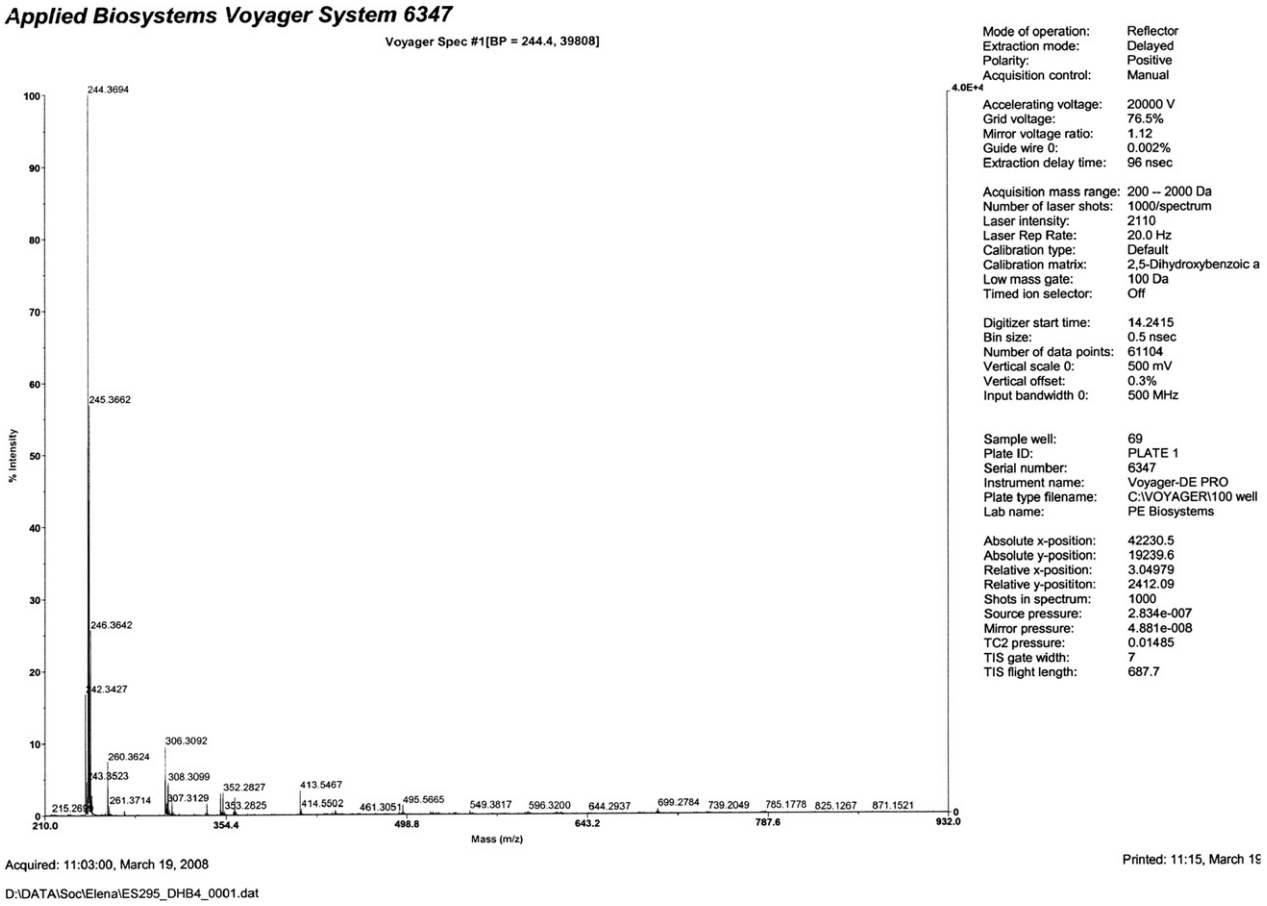
*5.2.5. Preparation of samples for mass-spectrometry analysis.* A mixture of CuSAr (200 mg, 0.874 mmol) and bromobenzene (5.49 g, 35 mmol) in NMP (7 mL) was prepared in a round-bottomed flask under a positive pressure of nitrogen. The mixture was heated at 120 °C for 30 min, afterwards a sample was taken and analysed by FIA-ESI-MS (positive ionization).

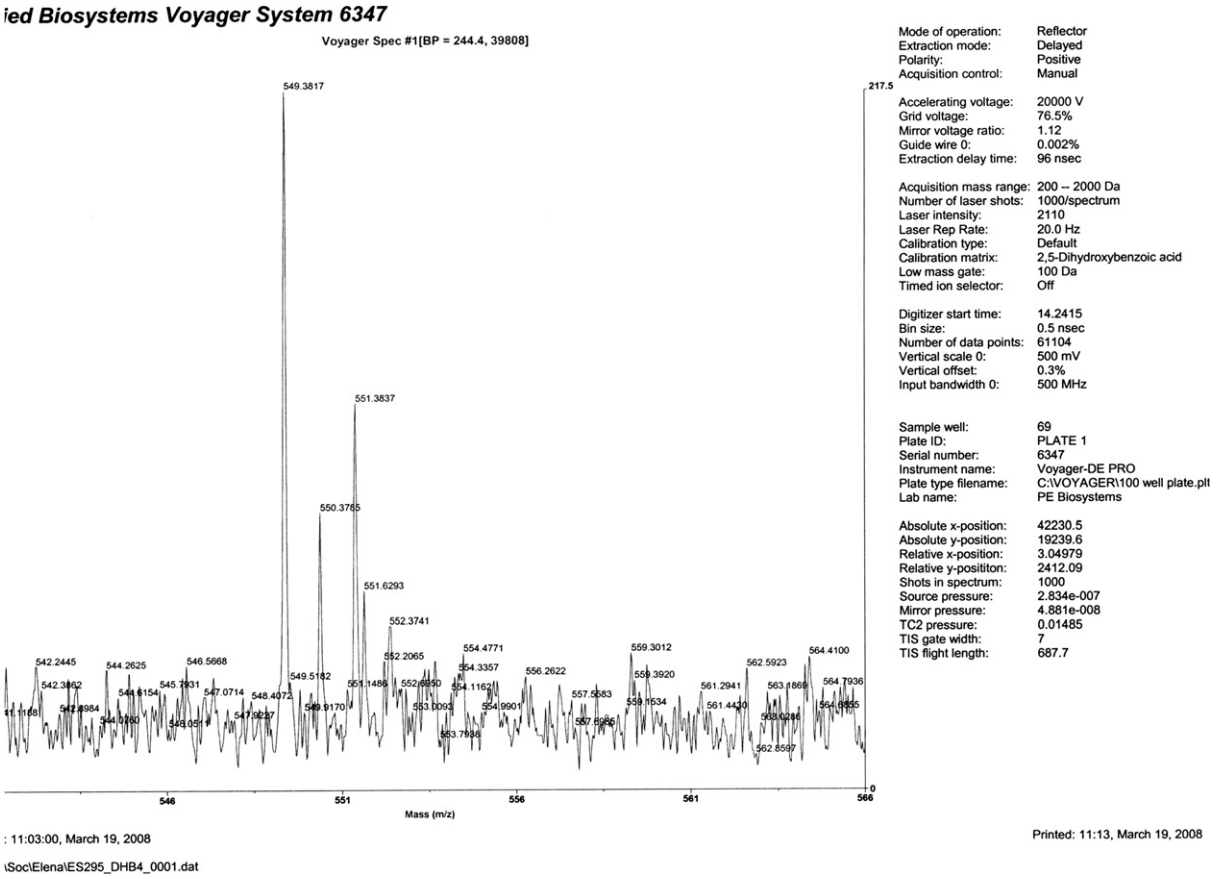
Identified ions signals: PhSAr, [M+H]$^+$ *m*/*z* found: 244.30; calcd: 244.38; complex **1**, *m*/*z* found: 306.10 (100%), 307.00 (20%), 308.02 (51%), 309.00 (8%), 310.10 (1%), calcd: 306.04; complex **2**, *m*/*z* found: 549.30 (100%), 550.00 (35%), 551.30 (65%), 552.00 (20%), 553.20 (4%), calcd: 549.15. A mixture of PhSAr (0.86 mmol) and




$Cu(MeCN)_4BF_4$ (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).

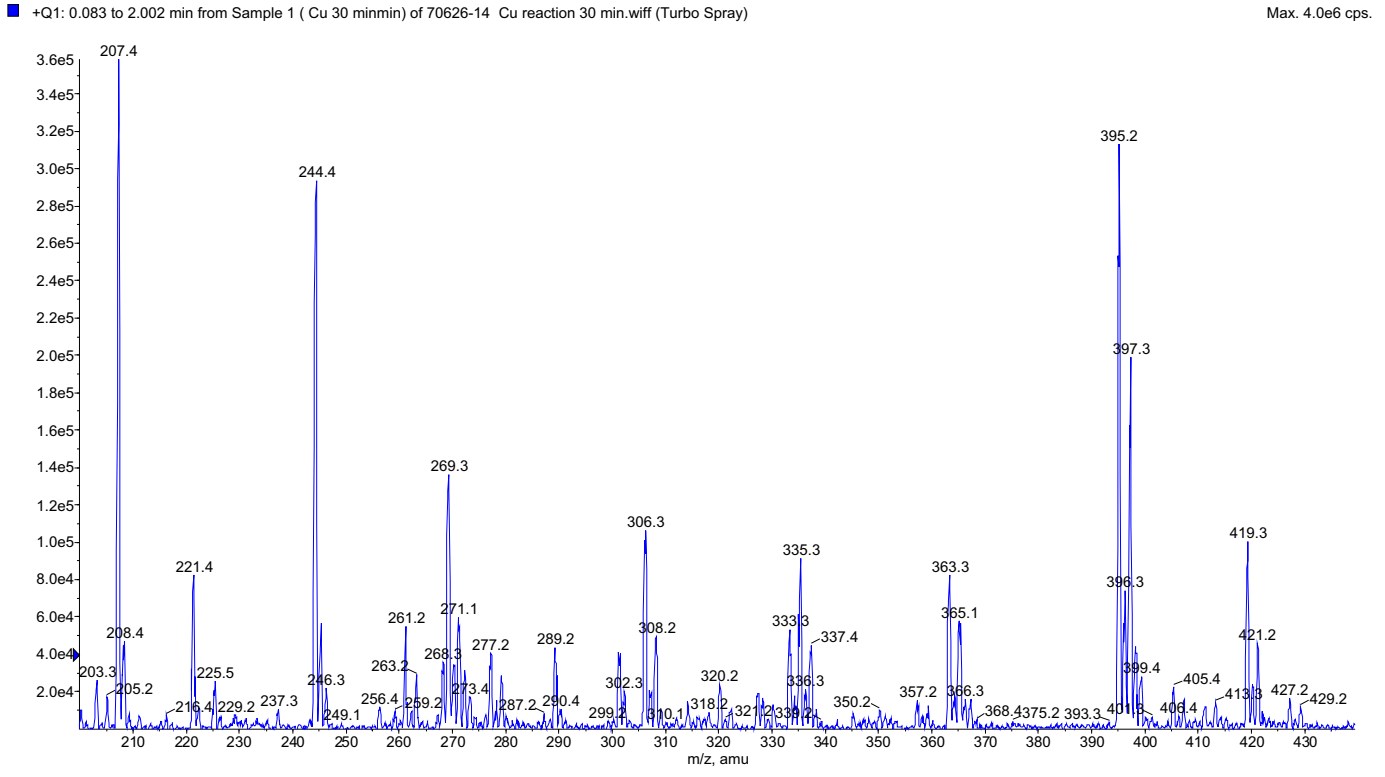
Identified ions signals: PhSAr $[M+H]^+$ *m*/*z* found: 244.3694; calcd: 244.3730; complex **1**, *m*/*z* found: 306.3092 (100%), 307.3129 (20%), 308.3099 (50%), calcd: 306.04; complex **2**, *m*/*z* found: 549.38 (100%), 550.3785 (40%), 551.3837 (57%), calcd: 549.15.

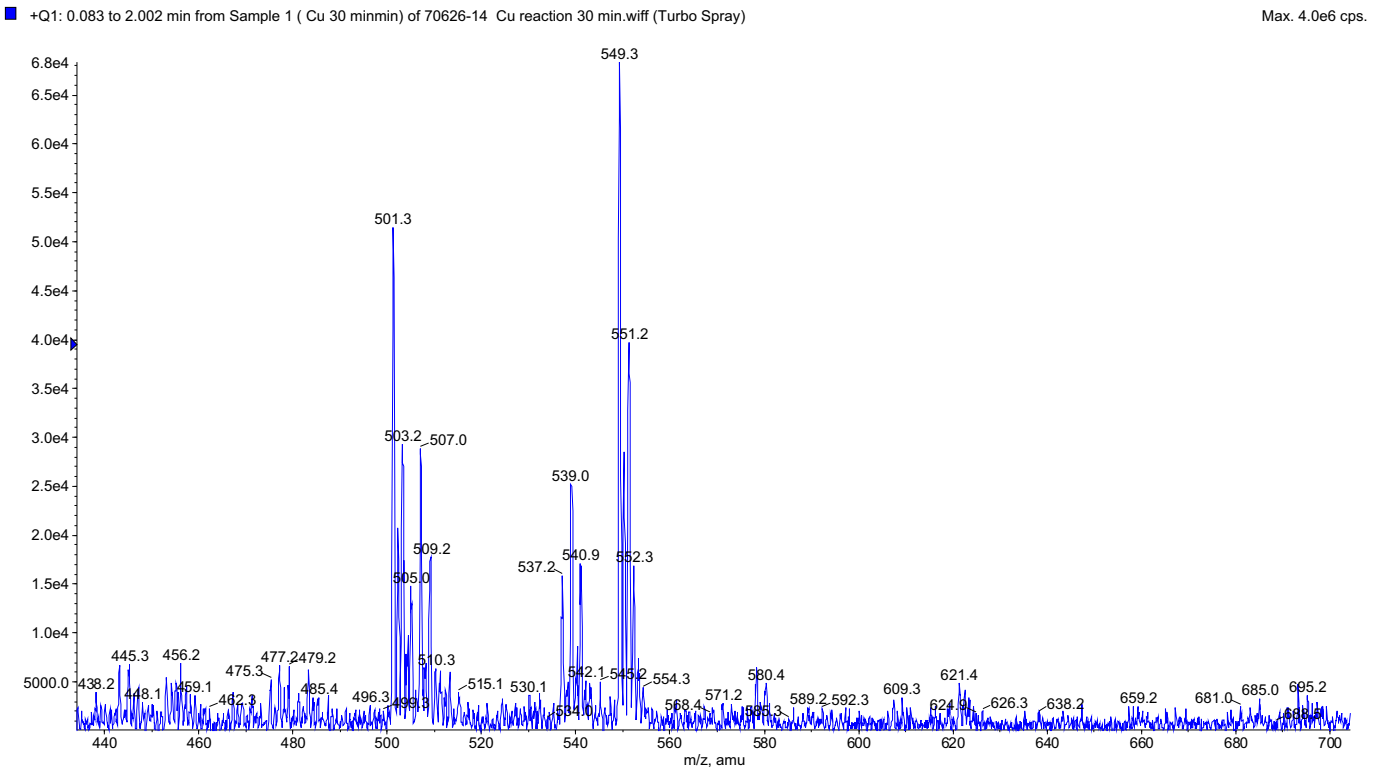





A reaction mixture was prepared (as described in Kinetic experiments in HEL auto-MATE working station section), a sample was taken and analysed by FIA-ESI-MS (positive ionization).

Identified ions signals: PhSAr $[M+H]^+$ *m*/*z* found: 244.40; calcd: 244.38; complex **1**, *m*/*z* found: 306.30 (100%), 307.00 (20%), 308.20 (45%), calcd: 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%), calcd: 549.15; complex $C_{29}H_{30}CuN_2S$ $[Cu(PhSAr)BBA]^+$ *m*/*z* found: 501.30 (100%), 502.00 (40%), 503.20 (60%), calcd: 501.15. Non-identified ions signals: *m*/*z* 269.30, 395.20, 419.30, 539.0.

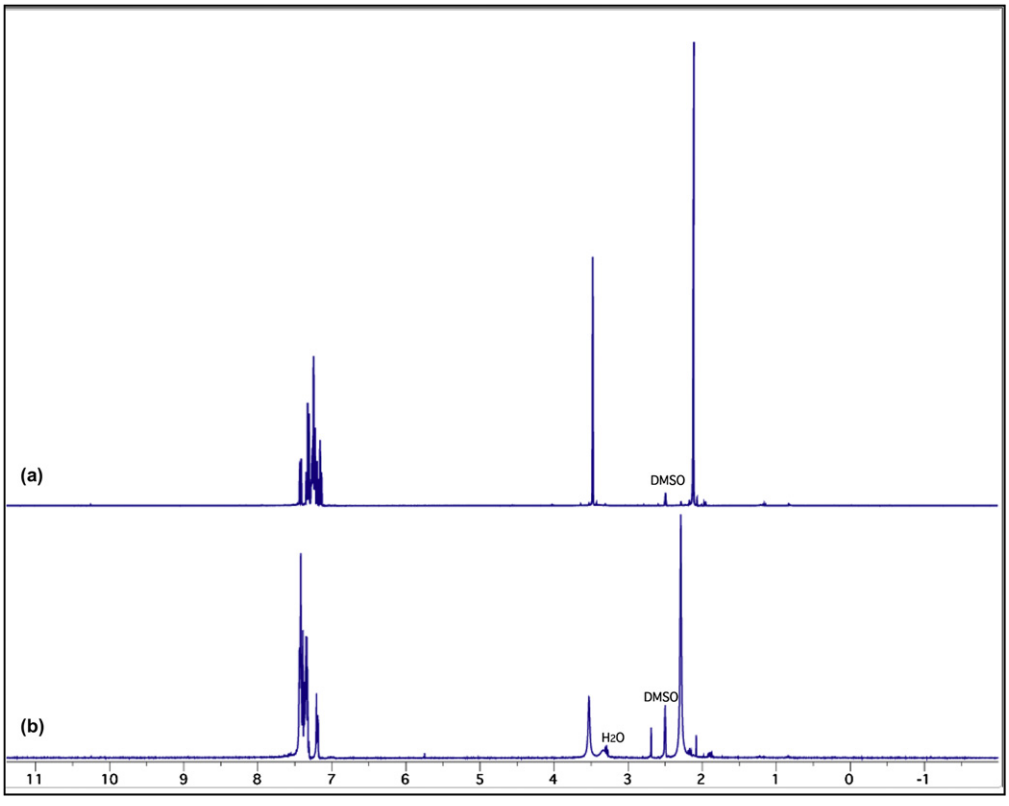





*5.2.6. Coordination evidences for complex* ***17****, [CuPhSAr]*$^{+}$. A mixture of PhSAr (0.125 mmol) and freshly synthesised CuBr (0.125 mmol) in DMSO-$d_6$ (1 mL) was prepared in a schlenk tube under nitrogen atmosphere. The mixture was heated at 120 °C for 180 min, afterwards a sample was taken and analysed by $^{1}$H NMR.

$^{1}$H NMR (399.94 MHz, DMSO-$d_6$): $\delta$ 2.29 (s, 6H, N($CH_3$)$_2$), 3.53 (s, 2H, $NCH_2$), 7.18–7.20 (m, 1H, Ar), 7.30–7.44 (m, 8H, Ar).

(For comparison to) PhSAr: $^{1}$H NMR (399.94 MHz, DMSO-$d_6$): $\delta$ 2.12 (s, 6H, N($CH_3$)$_2$), 3.48 (s, 2H, $NCH_2$), 7.14–7.34 (m, 8H, Ar), 7.43 (d, 1H, Ar).



$^1$H NMR spectra in DMSO-$d_6$, at room temperature. (a) Spectrum of PhSAr; (b) spectrum of PhSAr and CuBr in 1:1 M ratio, after 3 h at 120 °C in DMSO-$d_6$.

*5.2.7. Preparation of complex [Cu(PhSAr)$_2$]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).

$^1$H NMR (399.94 MHz, CD$_3$OD): $\delta$ 2.49 (s, 6H, CH$_3$), 3.81 (br s, 2H, CH$_2$), 7.20 (s, 3H, Ar), 7.33–7.46 (m, 6H, Ar).

FT-IR (ATR, cm$^{-1}$): 3062.90, 2886.15, 2846.50, 1588.11, 1473.95, 1463.94, 1440.34, 1045.59, 1032.90, 976.85, 873.94, 837.10, 752.48, 707.71, 693.83, 681.42.

Anal. Calcd for $C_{30}H_{34}BCuF_4N_2S_2$: C 56.56, H 5.38, N 4.40. Found: C 55.55; H 5.03, N 4.10.

## Acknowledgements

We thank the Dutch Ministry of Economic Affairs, NWO/CW, NRSC-C and Chemspeed Technologies for the financial support given to the CW/CombiChem programme and Dr. T. Jerphagnon for help and discussions.

## 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

1. (a) Nicolau, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152; (b) Zhu, J. *Synlett* **1997**, 133–144.
2. Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345–2347 and references therein.
3. (a) Nicolaou, K. C.; Boddy, C. N. C. *J. Am. Chem. Soc.* **2002**, *124*, 10451–10455; (b) Evans, D. A.; Wood, M. R.; Trostter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700–2704; (c) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trostter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2704–2708; (d) Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2717–2719; (e) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226–3227.
4. (a) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hintermann, T. *J. Am. Chem. Soc.* **2001**, *123*, 12411–12413; (b) Boger, D. L.; Kim, S. H.; Miyazaki, S.; Strittmatter, H.; Wang, J.-H.; Mori, Y.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 7416–7417; (c) Boger, D. L.; Kim, S. H.; Mori, Y.; Wang, J.-H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862–1871.
5. (a) Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 6488–6495; (b) Rao, A. V. R.; Chakraborty, T. K.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1992**, *33*, 4799–4802; (c) Bigot, A.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 4573–4577.
6. (a) Hitotsuyanagi, Y.; Ishikawa, H.; Naito, S.; Takeya, K. *Tetrahedron Lett.* **2003**, *44*, 5901–5903; (b) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544–8556.
7. Scott Sawyer, J. *Tetrahedron* **2000**, *56*, 5045–5065.
8. Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853–857.
9. For reviews see: (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456; (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449; (c) Frlan, R.; Kikelj, D. *Synthesis* **2006**, *14*, 2271–2285; (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439; (e) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131; (f) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971.
10. First example: (a) David, S.; Thieffry, A. *Tetrahedron Lett.* **1981**, *22*, 5063–5066 Review: (b) Finet, J.-P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597–626.
11. Vakalopoulos, A.; Kavazoudi, X.; Schoof, J. *Tetrahedron Lett.* **2006**, *47*, 8607–8610.
12. (a) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381–1384; (b) Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 18057–18059.
13. (a) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937–2940; (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.
14. For selected examples: (a) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321–4326; (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378; (c) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225; (d) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719; (e) Fleckenstain, C. A.; Plenio, H. *Chem. Soc. Rev.* **2010**, *39*, 694–711; (f) Hu, T.; Schulz, T.; Torborg, C.; Chen, X.; Wang, J.; Beller, M.; Huang, J. *Chem. Commun.* **2009**, 7330–7332.
15. Harkal, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237–3240.
16. For iron-catalyzed C–O coupling examples: (a) Bistri, O.; Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 586–588; (b) Bonnamour, J.; Bolm, C. *Org. Lett.* **2008**, *10*, 2665–2667; (c) Xia, N.; Taillefer, M. *Chem.—Eur. J.* **2008**, *14*, 6037–6039.
17. (a) Sperotto, E.; de Vries, J. G.; van Klink, G. P. M.; van Koten, G. *Tetrahedron Lett.* **2007**, *48*, 7366–7370; (b) Chang, J. W. W.; Chee, S.; Mak, S.; Buranaprasertsuk, P.; Chavasiri, W.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2018–2022; (c) He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, 3445–3446; (d) Chauhan, S. M. S.; Jain, N.; Kumar, A.; Srinivas, K. A. *Synth. Commun.* **2003**, *33*, 3607–3614; (e) Zhang, J.; Zhang, Z.; Wang, Y.; Zheng, X.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 5112–5116.
18. Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*; John Wiley: New York, NY, 1999, pp 854–876.
19. Saphier, M.; Burg, A.; Sheps, S.; Cohen, H.; Meyerstein, D. *J. Chem. Soc., Dalton Trans.* **1999**, 1845–1850.
20. (a) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276–1279; (b) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799–3802; (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460.
21. (a) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623–1626; (b) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863–3867.
22. (a) Shapir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491; (b) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286; (c) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973–976 and references therein; (d) Lipshutz, B. H.; Unger, J. B.; Taft, B. R. *Org. Lett.* **2007**, *9*, 1089–1092; (e) Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8729–8732.
23. (a) Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913–916 and references therein; (b) Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906–1916; (c) Schareina, Y.; Zapf, A.; Cotté, A.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 1851–1854; (d) Niu, J.; Zhou, H.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2008**, *73*, 7814–7817; (e) Naidu, A. B.; Jaseer, E. A.; Sekar, G. *J. Org. Chem.* **2009**, *74*, 3675–3679; (f) Benyahya, S.; Monnier, F.; Taillefer, M.; Wong Chi Man, M.; Bied, C.; Ouazzani, F. *Adv. Synth. Catal.* **2008**, *350*, 2205–2208; (g) Niu, J.; Guo, P.; Kang, J.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2009**, *74*, 5075–5078; (h) Maiti, D.; Buchwald, S. L. *J. Org. Chem.* **2010**, *75*, 1791–1794.
24. Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986–2987.
25. (a) Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 2865–2879; (b) Gujadhur, R.; Bates, G. C.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317.
26. (a) Knotter, D. M.; van Maanen, H. L.; Grove, D. M.; Spek, A. L.; van Koten, G. *Inorg. Chem.* **1991**, *30*, 3309–3317; (b) Janssen, M. D.; Grove, D. M.; van Koten, G. *Prog. Inorg. Chem.* **1997**, *46*, 97–149; (c) For detailed synthetic procedure: Sperotto, E.; van Klink, G. P. M.; van Koten, G. *Org. Synth.* **2008**, *85*, 209–218.
27. (a) Persson, E. S. M.; van Klaveren, M.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Chem.—Eur. J.* **1995**, *1*, 351–359; (b) Meuzelaar, G. J.; Karlström, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, A.; van Koten, G.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2895–2903 and references therein.
28. (a) Arink, A. M.; Braam, T. W.; Keeris, R.; Jastrzebski, J. T. B. H.; Benhaim, C.; Rosset, S.; Alexakis, A.; van Koten, G. *Org. Lett.* **2004**, *6*, 1959–1962 and references therein; (b) Knotter, D. M.; Grove, D. M.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1992**, *114*, 3400–3410.
29. Haubrich, A.; van Klaveren, M.; van Koten, G.; Handke, G.; Krause, N. *J. Org. Chem.* **1993**, *58*, 5849–5852.
30. Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241–5244.
31. Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230–4234.
32. See for example: (a) Ouali, A.; Spindler, J.-F.; Cristau, H.-J.; Taillefer, M. *Adv. Synth. Catal.* **2006**, *348*, 499–505 with yield of 55% for reaction with 2-methylbromobenzene; (b) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540 with yield of 20-30% for reaction with 2,6-dimethylphenol.
33. Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198–3209.
34. Note: formation of *N*-benzyl-benzylideneamine was detected when *N*-benzylamine was used as coupling partner in copper-catalyzed C–N bond formation.
35. DMSO-$d_6$ is used in order to mimic the catalytic reaction conditions, i.e., NMP and DMSO are the first two best solvents
36. Note: [Cu(MeCN)$_4$]BF$_4$ was chosen because of the easier synthetic route compared to CuBr, which did not give any good results because of solubility problems.
37. (a) Wilkinson, G. *Comprehensive Coordination Chemistry*; Pergamon: New York, NY, 1987; (b) Hataway, B. J. *Coord. Chem. Rev.* **1981**, *35*, 211–252.

38. (a) Sarkar, S.; Patra, A.; Drew, M. G. B.; Zangrando, E.; Chattopadhyay, P. *Polyhedron* **2009**, *28*, 1–6; (b) Brubaker, G. R.; Brown, J. N.; Yoo, M. K.; Kisey, R. A.; Kutchan, T. M.; Mottel, E. A. *Inorg. Chem.* **1979**, *18*, 299–302; (c) Pal, S.; Mukherjee, G.; Poddar, S. N. *Trans. Met. Chem.* **1994**, *19*, 99–102; (d) van Stein, G. C.; van Koten, G.; Vrieze, K.; Spek, A. L.; Klop, E. A.; Brevard, C. *Inorg. Chem.* **1985**, *24*, 1367–1375.
39. (a) Solomon, E. I.; Szilagyi, R. K.; DeBeer George, S.; Basumallick, L. *Chem. Rev.* **2004**, *104*, 419–458; (b) Holm, R. H.; Kennepohl, P.; Solomon, E. I. *Chem. Rev.* **1996**, *96*, 2239–2314.
40. (a) Pintauer, T.; Matyjaszewski, K. *Coord. Chem. Rev.* **2005**, *249*, 1155–1184 and references therein; (b) Haldon, E.; Alvarez, E.; Nicasio, M. C.; Perez, P. J. *Organometallics* **2009**, *28*, 3815–3821; (c) Peng, R.; Li, D.; Wu, T.; Zhou, X.-P.; Ng, S. W. *Inorg. Chem.* **2006**, *45*, 4035–4046; (d) Iobana, T. S.; Sultana, R.; Hundal, G.; Castineiras, A. *Polyhedron* **2009**, *28*, 1573–1577; (e) Dance, I. *Polyhedron* **1986**, *5*, 1037–1104.
41. Cohen, T.; Wood, J.; Dietz, A. G., Jr. *Tetrahedron Lett.* **1974**, 3555–3558.
42. Examples of mechanistic study: (a) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78–88; (b) Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546–4554; (c) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4121; (d) Mansour, M.; Giacovazzi, R.; Ouali, A.; Taillefer, M.; Jutand, A. *Chem. Commun.* **2008**, 6051–6053; (e) Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 9971–9983; (f) Sperotto, E.; de Vries, J.G.; van Klink, G.P.M.; van Koten, G., Dalton Transactions, in press.
43. Chambers, C.; Holliday, A. K. *Modern Inorganic Chemistry*; Rhadon; Butterworths: London, 1975, pp 408–416.
44. The four alternatives proposed in literature are: (a) oxidative addition/reductive elimination of ArX on copper; (b) Aryl radical intermediates. (c) σ-Bond metathesis through a four-centred intermediate. (d) π-Complexation of copper (I) on ArX (see also Chapter 1 of this thesis).
45. Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613–9620.
46. Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565–5578.
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.