



C–N Coupling of nitrogen nucleophiles with aryl and heteroaryl bromides using aminoarenethiolato–copper(I) (pre-)catalyst

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ARTICLE INFO

Article history:

Received 21 October 2009

Received in revised form 17 February 2010

Accepted 8 March 2010

Available online 17 March 2010

ABSTRACT

The activity of a library of 2-aminoarenethiolato–copper(I) (CuSAr) (pre-)catalyst was explored in the arylation reaction of amines and N-containing heterocycles with aryl and heteroaryl bromides, respectively. These CuSAr pre-catalysts are thermally stable, are soluble in common organic solvents and show good catalytic activities in these N-arylation reactions with catalyst loadings amounting to 2.5 mol%. The targeted C–N coupling products were obtained in moderate to good yields (40–97%) for a variety of substrates.

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1. Introduction

Functionalized aromatic and heteroaromatic amines are important and widely employed building blocks for the synthesis of pharmaceutical and natural products.¹ Therefore, the development of a mild and efficient method for the preparation of N-containing aromatic compounds has received increasing interest. Recently, a large number of elegant Pd-catalyzed C–N coupling reactions have been reported,² but the scope of these methods scarcely include the arylation of, for example, N–H heterocycles.³ Besides the use of palladium and copper (vide infra), also other metals have recently been explored as catalyst for C–N bond forming reactions, e.g., catalysts based on cadmium,⁴ ruthenium,⁵ nickel,⁶ or iron.⁷

Traditionally, the C–N coupling reaction is limited to aryl halides bearing strongly electron-withdrawing substituents.⁸ Alternately, the classical copper-mediated Ullmann coupling is a commonly applied method for the coupling of a primary amine functionality with an aromatic halide.⁹ This reaction, however has the disadvantage that it requires harsh reaction conditions, such as high temperatures and the need of a stoichiometric amount of copper catalyst. These facts and the moderate yields obtained have undeniably prevented the Ullmann reaction from becoming a broadly applied method.

In spite of its limitations the Ullmann-type copper-catalyzed coupling of aryl halides with amines is still recognized as an attractive and, when compared to alternative metal protocols, economic method providing easy access to aryl amine building blocks. Recent developments have allowed this reaction to

maintain its importance in organic synthetic chemistry and it can now also be utilized for the synthesis of N-arylated heterocycles.^{9,10} New approaches involving the use of milder reaction conditions than the classical copper-mediated Ullmann coupling employ catalytic amounts of copper and stoichiometric use of transmetallating agents, such as aryllead triacetates,¹¹ arylboronic acids,¹² triarylbismuths,¹³ hypervalent aryl siloxanes,¹⁴ and arylstannanes.¹⁵ However, the application of the latter reagents also represents a major shortcoming of these methods as they are toxic and/or unstable reagents while their preparation usually requires multistep synthesis. Thus, the use of readily available aryl halides as the electrophilic coupling partner could overcome these issues.

Whilst some examples of ligand-free conditions are known,¹⁶ the addition of mono- and bidentate ligands, such as phosphines,¹⁷ diamines,¹⁸ α -diimines,¹⁹ diols and diketones,²⁰ amino alcohols,²¹ amino acids,²² salicylamide derivatives,²³ phosphoramidites,²⁴ phosphine oxides,²⁵ phosphinidenes²⁶ and phenantroline derivatives²⁷ have shown to significantly increase the yield and generality of the C–N coupling reaction. Through the use of these additives/ligands the solubility and stability of the copper species are improved, allowing the use of catalytic amounts of copper, milder reaction conditions and wider reaction scope.

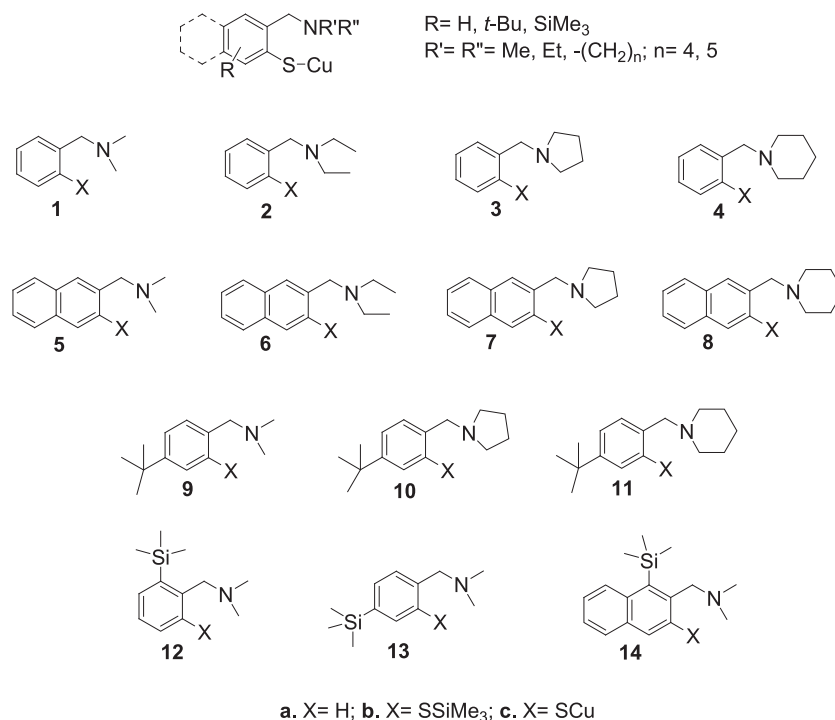
An alternative to the addition of an external ligand for the in situ formation of the complex is offered by modification of the catalyst, in order to accomplish enhanced catalyst solubility, stability and a well-defined structure. Recently, several single-component pre-catalysts have been reported to be effective in catalytic aminations. Examples of chemically well-defined, stable and soluble copper(I) complexes have been reported by Snieckus et al.²⁸ and Venkataraman and Gujadhur,²⁹ which have shown good activities in catalyzed C–N and C–O bond formation.

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Prompted by our interest in carbon–carbon³⁰ and carbon–heteroatom coupling reactions,^{16a,31} and the availability of a class of well-defined copper(I) complexes, which recently has successfully been tested, as an alternative to the commonly used insoluble copper halides, in C–C and C–O coupling reactions, we extended our studies to the C–N bond formation reaction. Herein we reported a library of 2-aminoarenethiolato–copper(I) complexes and its application in the N-arylation reaction of diverse amines and N-containing heterocycles with aryl and heteroaryl bromides, as an extension of our preliminary work.³¹

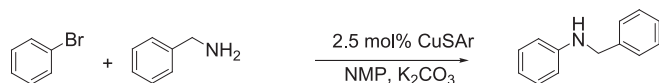
2. Results

A library of 2-aminoarenethiolato–copper(I) complexes (CuSAr, Scheme 1), which exhibit good thermal stability and solubility in common organic solvents, was achieved through a simple four-step synthesis³² with overall yields of 67–85%.^{32c} The different amines of the monoanionic, S,N-coordinating 2-aminoarenethiolato ligand were chosen to test the influence of the basicity and the steric hindrance of the amino arm of the S,N-ligand on the catalyst activity. The aryl ring could also be easily changed to the naphthyl ring, in order to check a possible effect of the backbone connecting the S and N donor atom sites. In addition, the trimethylsilyl and *tert*-butyl groups were introduced on the aromatic backbone, to possibly modify the solubility properties of the complexes in organic solvents.



Scheme 1. Library of 2-aminoarenethiolato–copper(I) complexes used in this study.

The prepared library of copper pre-catalysts was at first tested in a model reaction, involving the N-arylation of benzylamine with bromobenzene to give *N*-benzyl-aniline (Scheme 2).



Scheme 2. Coupling reaction of bromobenzene with benzylamine.

The 2-[(dimethylamino)methyl]benzenethiolato–copper(I) (**1c**, Scheme 1) pre-catalyst was used in the optimization of the reaction conditions. Blank reactions in the absence of **1c** did not give any product showing that its use was essential for obtaining the C–N coupling product.

The screened reaction conditions³¹ revealed that the optimum for product formation is at a reaction temperature of 160 °C while using *N*-methyl pyrrolidinone (NMP) as solvent. When dimethyl sulfoxide (DMSO) was used, slightly lower yields were obtained, while other solvents were tested without success. Potassium carbonate (1.1 equiv) appeared to be the preferred base for the coupling reaction whereas commonly used organic and inorganic bases (e.g., caesium carbonate, potassium *tert*-butoxide, potassium phosphate, triethylamine, 2,6-lutidine) did not give satisfactory results. The amount of catalyst was optimized to 2.5 mol% with respect to the arylating agent, which is quite low in comparison to other protocols reported in literature, where the amount of copper catalysts are in the range of 5–10 mol%.^{17–27}

Subsequently, different phenyl halides were tested under the developed reaction conditions. It clearly appeared from the results that bromobenzene was the best coupling partner since reactions with fluoro-, chloro- and iodobenzene hardly showed any conversion to the C–N coupling product (Table 1).

The importance of using the aminoarenethiolato–copper(I) complex was highlighted by the comparison of its reactivity with those of simple ligand-free copper(I) salts. As previously reported^{16a} the model reaction performed with only CuBr afforded

Table 1
Effect of the nature of the aryl halide on the arylation of benzylamine

Haloarene	Amine	Yield%
Fluorobenzene	Benzylamine	0
Chlorobenzene	Benzylamine	1
Bromobenzene	Benzylamine	61
Iodobenzene	Benzylamine	9

Reaction conditions: aryl halide (5 mmol), amine (6.5 mmol), K₂CO₃ (5.5 mmol), NMP (1 mL), complex **1** (0.125 mmol), 160 °C, 16 h.

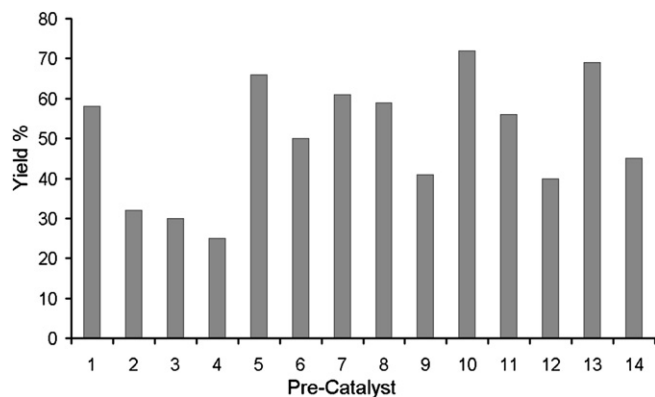


Figure 1. Screening of the CuSAr pre-catalyst library for N-arylation of benzylamine with bromobenzene. Reaction conditions: bromobenzene (5 mmol), benzylamine (6.5 mmol), K_2CO_3 (5.5 mmol), NMP (1 mL), Cu(I)-complex (0.125 mmol), 160 °C, 16 h.

N-benzylaniline in 15% yield, whereas under the same reaction conditions, the coupling with the CuSAr complex **1c** reached a yield of 61%. The positive influence of the aminoarenethiolato ligand (vide infra) on the catalytic reaction is found to be a common characteristic in the synthesised library (Fig. 1). Exception holds for catalysts **2c–4c**, **9c** and **12c**, which gave low yields of 25–41% of coupling product. The best performances were given by complexes **1c**, **5c**, **10c**, **13c**, which reached 58–72% of N-benzylaniline.

The first four pre-catalysts have the unsubstituted arene-backbone as a common structural element, while the amino-arm was different (Scheme 1). Complex **1c** gave a moderate yield of 58%, whereas increasing the basicity of the nitrogen atom led to a significant decrease of yield in product (see for **2c–4c**, yields of 32–25%). A parallel set of pre-catalyst bearing the naphthyl-backbone gave higher yields (for **5c–8c** 50–66%); with complex **5c** the best outcome of this set was obtained. It is obvious that introduction of a further substituent (in **9c–11c** a *tert*-butyl substituent was introduced in *meta* position) influenced considerably the activity of the pre-catalyst. Complex **9c** gave lower result with respect to complex **1c** (41 vs 58%), while complexes **10c** and **11c** reached yields of 72 and 56%, respectively, which is a clear improvement on the performances of complexes **3c** and **4c**. The latter set of pre-catalyst corresponds to **1c** and **5c** in which a Me_3Si -TMS substituent was introduced in different positions on the aromatic ring (Scheme 1). With the TMS group in *meta*-position the coupling product was obtained in lower amount, for CuSAr with both arene and naphthyl backbones (complex **12c**, yield 40% vs 58% with **1c**; complex **14c**, yield 45% vs 66% with **5c**). However, the 5-TMS-group induced a positive effect on the catalytic reaction, (**13c**, yield 69% vs **1c**, yield 58%).

The library of the CuSAr (pre-)catalysts was also screened for the arylation of the heterocyclic amine imidazole, in order to evaluate the effect of the nature of the catalyst on the C–N coupling reaction with a different nucleophile (Fig. 2).

As reported in an earlier communication using a smaller set of pre-catalysts,³¹ the C–N coupling between bromobenzene and imidazole gave higher yields of the C–N coupling product compared to the model reaction involving benzylamine. Throughout the whole library, good to excellent yields were obtained (72–97%). However, some differences in reactivity between the various complexes could be identified. Complex **1c** led to almost quantitative yield in N-benzylimidazole (97%), while the complexes, bearing a different amino group, again showed lower reactivity (complexes **2c–4c**, yield 72–76%). With the second set, i.e., complexes **5c–8c** having a naphthyl backbone, very good yields were obtained (78–97%) without substantial differences in reactivity among them. The *t*-Bu-substituted

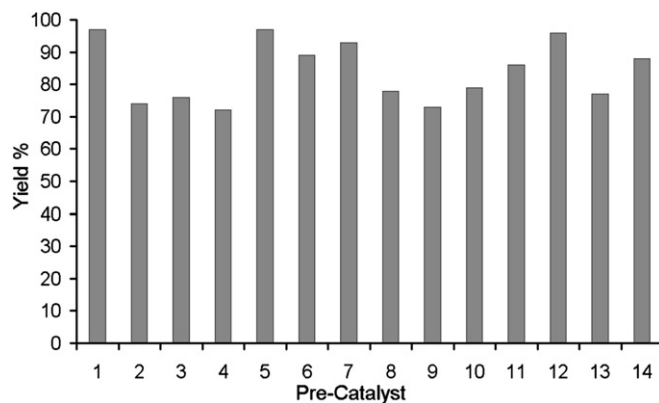


Figure 2. Screening of the CuSAr library for N-arylation of imidazole with bromobenzene. Reaction conditions: bromobenzene (5 mmol), imidazole (6.5 mmol), K_2CO_3 (5.5 mmol), NMP (1 mL), Cu(I)-complex (0.125 mmol), 160 °C, 16 h.

pre-catalysts **9** showed a different activity that its parent **1c** giving a lower yield of 73%. Replacement of the NMe_2 group in **9c** by a more basic one, **10c** and **11c**, respectively caused a slight improvement (cf. **3c** and **4c**, 79 and 86% yield, respectively). The last set, complexes **12c–14c** bearing a TMS-group on the ring, reached slightly lower results than complexes **1c** and **5c** (96, 77 and 88%).

In view of these results, diverse substrates were tested to investigate the scope of the C–N coupling reaction using **1c** as pre-catalyst because of its simple preparation and good catalytic performances (Table 2).

In the first series of reactions, bromobenzene was the arylating partner, while the nucleophile was changed among primary and secondary heterocyclic amines. Besides the model reaction with benzylamine, 1,3-diaminopropane was tested, giving only a moderate yield in diarylated product (Table 2, entry 2). The heterocyclic amine imidazole was employed in the reaction with excellent result of 97% yield (entry 3), whereas the substituted 4-methyl imidazole and 4-phenyl imidazole lowered the yield in product to 59 and 54%, respectively (entries 4 and 5), probably due to their higher steric hindrance if compared to unsubstituted imidazole. The reaction with pyrazole (entry 6) led to a 78% yield, slightly lower than reaction with imidazole. Moderate yields of the corresponding coupling products were obtained with two other nucleophiles, 2-pyrrolidinone and indole, (entries 7–8, 40–48% yield, respectively).

In another series of reactions, the arylating agent was changed to various bromopyridines and coupled with different nucleophiles. Benzylamine and 4-methylbenzylamine showed good reactivity towards the coupling with 2-bromopyridine (entries 9 and 10, yields 70 and 90%, respectively). The same holds for imidazole used as nucleophile, in the coupling with both 2- and 3-bromopyridines (entries 11 and 12), which resulted for both reactions in a yield of 89%. An example of double arylation on 2,6-dibromopyridine was performed with imidazole and the coupling product was achieved in yield of 60%, a noteworthy result if one considers that no traces of monoarylated product were found. Another interesting example is the C–N coupling between 5-bromo-2-aminopyridine and imidazole. The arylation on imidazole occurs selectively and with good yield (entry 14, yield 80%), bearing the NH_2 - functionality and leaving it intact, with no need of group protection. Subsequently, two different secondary amines, morpholine and piperidine, were coupled to 2-bromopyridine, obtaining good results of the desired products (entries 15 and 16, yields 91 and 71%). A catalytic test with 3-bromoquinoline is shown in entry 17, which reacted with imidazole affording the C–N coupling product in a moderate yield of 53%. Eventually, 2-bromothiazole was employed as heteroaryl halide and the arylated imidazole was obtained in modest yield.

Table 2
Amination of aryl and heteroaryl bromides catalyzed by aminoarenethiolato-copper(I) complex **1c**

Entry	ArX	Nucleophile	Product	Yield (%) (isolated yield)
1				61 (57)
2				43 ^a
3				97
4				59
5				54
6				78 (75)
7				40
8				48
9				70
10				90
11				89
12				89 (85)
13				60 ^b
14				80
15				91 (87)
16				71 (68)
17				53
18				51(47)

Reaction conditions: aryl halide (5 mmol), amine (6.5 mmol), K₂CO₃ (5.5 mmol), NMP (1 mL), complex **1** (0.125 mmol), 160 °C, 16 h.

^a Bromobenzene (10 mmol).

^b Imidazole (13 mmol). Yield was calculated by GC measurements, and isolated yields are reported in brackets.

3. Discussion

The CuSAr-catalytic system presented here allowed the formation of the C–N coupling product through a clean and selective reaction. In the product solutions commonly found side products^{19a,27} like biaryl compounds or hydrodehalogenated arene byproducts have not been detected, while the unreacted starting material was found unaltered at the end of the reaction. However, limitations of the protocol involve the rather high reaction temperature and long reaction time, together with some restrictions on the substrate side.

It is important to mention the fact that the CuSAr pre-catalyst is converted, in the first stages of the reaction, into neutral 2-[(dimethylamino)methyl]phenyl phenyl sulfide (PhSAr), through S-arylation of the SAr-anion with bromobenzene.³³ However, the in

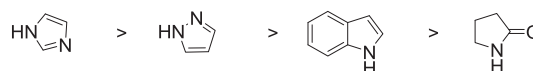
situ formation of this modified ligand PhSAr for the copper centre, positively influences its catalytic activity, i.e., the catalyst is distinctly more active than CuBr itself³³ and could act as a ligand and induce a particular mechanistic pathway.

The results show that the 2-aminoarenethiolato-copper(I) complexes of the library (Scheme 1) are all active as pre-catalysts in the N-arylation of different amines, with a low loading of the copper complex (2.5 mol%). The first characteristic of this library is the decrease of the activity of the pre-catalyst with an increase of the basicity of the amino arm of the complexes (see complexes **1c–4c** in Fig. 1). This observation could be related to the above mentioned conversion of the pre-catalyst CuSAr into PhSAr (and CuBr). In this transformation a higher basicity of the amino donor, which stabilizes the CuSAr species makes this first step, leading to the actual active catalytic species, more difficult. In line with these observations, the presence of the naphthalene backbone instead of a phenyl one has a positive effect on the catalytic activity, probably because it increases the nucleophilicity of the SAr-anion and favours in this way the initial formation of PhSAr via the S-arylation process. In both library screenings, the introduction of *tert*-butyl- or TMS-group on the aryl ring resulted in an improvement of the product yield. This effect can be attributed to an increased solubility of the copper complexes (and the corresponding CuBr/PhSAr complexes) in organic media when they bear a *tert*-butyl- or TMS-substituent on the aryl ring. However, an additional observation can be made on complexes **12c–14c**, bearing a TMS-group, when they are applied for the N-arylation of benzylamine (see Fig. 1). In the case of **12c** and **14c**, the TMS-group is in *ortho* position to the amine substituent and it can cause a lowering of the conformational flexibility of the amine substituent, i.e., buttressing effect,³⁴ which is translated in a negative effect on the activity (to compare to complex **13c**). This result is therefore an indication that the PhSAr-ligand is involved in the catalytic cycle and has an influence on the rate determining step.

Aryl halides are the arylating agents frequently employed for metal mediated C–X coupling reactions, and the commonly found order of reactivity parallels the leaving group ability of the halide ions (I[−] > Br[−] > Cl[−]).⁹ However, in the presently developed protocol we find that it is the aryl bromide that has a higher reactivity than the corresponding iodide (and chloride). This could be possibly explained by the fact the bromide ion would allow a change in oxidation state of copper, permitting a feasible catalytic cycle, while iodide ions would stabilize the copper atom in its +1 oxidation state, rendering the species stable and insoluble as CuI salt. This feature indicates that the use of CuSAr, i.e., the PhSAr/CuBr, catalyst induces a singular change in the mechanistic pathway of the C–N coupling pathway, in comparison to previously reported coupling procedures.

As presented in Table 2, moderate to good yields of coupling products were obtained when bromobenzene was coupled to primary amines, whereas also in this work (cf. Refs. 16,17) coupling of secondary cyclic amines, like morpholine or piperidine appeared to be impossible (results not shown here). Imidazole showed to be a better nucleophile, but its reactivity decreased when the ring is bearing a substituent on the fourth position (entries 4 and 5).

The relative reactivity for the azole series in the studied N-arylation with bromobenzene appeared to be the following:



This order of reactivity appears to be best related to the acidity of the nucleophiles and therefore to the ease of deprotonation of the azole by the base, since the pK_{HA} values follow the same relative trend (pK_{HA} in DMSO: imidazole=18.6; pyrazole=19.8; indole=20.95; 2-pyrrolidinone=24.2).^{35,19a} For the first three

azoles of the series, a linear relationship ($R^2=0.9835$) is found between their reactivity (expressed in yield % after 16 h) and their acidity (expressed in pK_{HA} values); after that, a further decrease of acidity does not bring an additional decrease in reactivity but this stays on the same level.

The reactivity of primary and heterocyclic amines is clearly different as can be seen from the presented results. This most probably reflects the fact that these reactions involve different mechanisms. For the C–N bond formation with primary amines we recently proposed a mechanistic pathway through electron transfer and changes between +1 and +2 oxidation states of the copper centre.^{31,33} However, in the case of heterocyclic amines it is more likely to presume a different catalytic cycle, most probably involving a σ -bond metathesis type of mechanism, through a four-centred intermediate.^{36,37,18b}

The change of arylating reagent from aryl bromides to bromopyridines brought about a considerable improvement of the yield in product (see entry 9 compared to 1), which parallels the fact that pyridines are activated substrates. Indeed bromo-pyridines couple with a variety of amines, now also including secondary amines like morpholine and piperidine (entries 15 and 16). Furthermore, 2-bromo quinoline showed to be less reactive than 2-bromo pyridine when coupled to imidazole (entries 12 and 17).

In summary, the preparation of a new library of 2-aminoarenethiolato-copper(I) complexes was described and tested in the C–N bond formation reaction between (hetero)aryl bromides and amines and N-containing heterocycles. Their versatility allow their employment in the catalysis of a variety of C–X coupling reactions in a cascade fashion, a subject, which is currently under investigation.

4. Experimental

4.1. 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. 1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian Inova 300 MHz spectrometer at 298 K unless stated otherwise. The chemical shifts (δ) are presented in ppm (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 \times 0.32 mm ID \times 0.25 μ m). GC–MS measurements were performed using an HT™-50HT (30 m \times 0.25 mm) column, and using a Perkin Elmer turbomass spectrometer with an electro ionization detector. Elemental analyses were performed by Kolbe, Mikroanalytisches Laboratorium, Mühlheim/Ruhr, Germany.

4.2. General procedure for catalyst testing

Preparation of *N*-benzyl-aniline. The catalytic tests were performed using standard Schlenk techniques. Firstly the Schlenk tube was charged with the solid base K_2CO_3 (5.5 mmol, 0.76 g). Subsequently the liquid reagents (bromobenzene: 5 mmol, 527 μ L; benzylamine: 6.5 mmol, 711 μ L) and solvent (1 mL) were added and finally the (solid) aminoarenethiolato-copper(I) (2.5 mol %, 0.0288 g) pre-catalyst. The filled Schlenk tube was flushed with nitrogen and warmed at 160 °C (in an oil bath) during 16 h. After that, the reaction mixture was diluted with dichloromethane (5 mL) while dihexyl ether (100 μ L, 0.42 mmol) was added as standard.

For preparative runs, the reaction mixture was partitioned between CH_2Cl_2 and $NaHCO_3$ aq (1 N). The organic phase was washed 4–5 times with $NaHCO_3$ aq to remove NMP, dried over $MgSO_4$ and

filtered. The solvent of the filtrate was removed under vacuum. The resulting residue was purified by chromatography on silica (hexane/ethyl acetate 15:5) to obtain the pure product as a colourless oil. Product *N*-benzyl-aniline:³¹ GC yield: 61%; isolated yield: 57%.

1H NMR (399.94 MHz, $CDCl_3$): δ 4.33 (s, 2H, CH_2), 6.74 (d, 2H, CH Ar), 6.79 (t, 1H, CH Ar), 7.19 (t, 2H, CH Ar), 7.27 (m, 1H, CH Ar), 7.33–7.38 (m, 4H, CH Ar). ^{13}C NMR (100.576 MHz, $CDCl_3$): δ 48.8 (CH_2), 113.4, 118.2, 127.5, 127.9, 128.9, 129.5, 139.4, 148.0 (Ar). M/S (EI) m/z (relative intensity): 184 (30), 183 (100), 106 (30), 91 (60).

Examples for isolation of known synthesized products (see Table 2).

1-Phenyl-pyrazole: isolated as pale yellow oil.⁶ 1H NMR (399.94 MHz, $CDCl_3$): δ 6.41 (s, 1H, CH), 7.21 (s, 1H, NCH), 7.24–7.41 (m, 2H, Ar), 7.65–7.70 (m, 3H, Ar), 7.87 (s, 1H, NCH). ^{13}C NMR (100.576 MHz, $CDCl_3$): δ 107.8, 119.4, 126.6, 126.9, 129.6, 140.4, 141.3. M/S (EI) m/z (relative intensity): 145 (35), 144 (100), 117 (40), 77 (38).

2-Pyridinyl-piperidine: isolated as pale yellow oil.³⁸ 1H NMR (399.94 MHz, $CDCl_3$): δ 1.60 (s, 6H, CH_2), 3.48 (s, 4H, NCH₂), 6.49–6.52 (m, 1H, CHpyr), 6.58–6.61 (m, 1H, CHpyr), 7.38–7.41 (m, 1H, CHpyr), 8.13–8.15 (1H, CHpyr). ^{13}C NMR (100.576 MHz, $CDCl_3$): δ 24.9, 25.7, 46.5 (Cpiperidine), 107.3, 112.6, 137.5, 148.1, 159.9 (Cpyridine). M/S (EI) m/z (relative intensity): 163 (20), 162 (100), 133 (38), 119 (55), 107 (47), 78 (70).

3-Imidazolyl-pyridine: isolated as pale yellow oil.³⁹ 1H NMR (399.94 MHz, $CDCl_3$): δ 7.26–7.40 (m, 2H, NCH₂), 7.42–7.42 (m, 1H, CHpyridine), 7.70–7.73 (m, 1H, CHpyridine), 7.89 (br s, 1H, NCHN), 8.62 (s, 1H, NCHpyridine), 8.73 (s, 1H, NCHpyridine). M/S (EI) m/z (relative intensity): 145 (100), 118 (37), 91 (32), 78 (22), 64 (15), 51 (38).

4-Piperidinyl-morpholine: isolated as yellow oil.²⁴ 1H NMR (399.94 MHz, $CDCl_3$): δ 3.43–3.46 (t, $J=4.8$ Hz, 4H, NCH₂), 3.76–3.77 (t, $J=4.4$ Hz, 4H, OCH₂), 6.57–6.62 (m, 2H, CHpyridine), 7.72–7.47 (m, 1H, CHpyridine), 8.15–8.17 (m, 1H, CHpyridine). ^{13}C NMR (100.576 MHz, $CDCl_3$): δ 45.8 (NCH₂), 66.9 (OCH₂), 107.1, 114.0, 137.7, 148.2, 159.8 (Cpyridine). M/S (EI) m/z (relative intensity): 164 (447), 163 (62), 133 (59), 119 (35), 78 (100).

2-Imidazolyl-thiazole: isolated as yellow oil.^{16d} 1H NMR (399.94 MHz, $CDCl_3$): δ 7.040–7.062 (m, 2H, CH), 7.393 (s, 1H, CH), 7.445–7.453 (m, 1H, CH), 8.073 (s, 1H, NCHN). ^{13}C NMR (100.576 MHz, $CDCl_3$): δ 115.9, 117.9, 131.0, 135.7, 140.8, 157.7. M/S (EI) m/z (relative intensity): 153 (28), 152 (50), 124 (100), 97 (25), 79 (35), 57 (65).

Diethylbenzylamine 2a. Diethylamine (13.0 mL, 0.124 mol) was added at 0 °C to a solution of benzyl bromide (8.42 g, 49.2 mmol) in dichloromethane. The mixture was allowed to reach room temperature and was stirred overnight. All volatiles were removed in vacuo and NaOH (100 mL of a 4 M aqueous solution) was added. The mixture was extracted with hexane (3 \times 80 mL). The aqueous layer was made strongly basic by adding solid sodium hydroxide and the resulting solution was extracted with diethyl ether (3 \times 80 mL). The combined organic layer was dried over magnesium sulfate, filtered and solvents were removed in vacuo affording the product as yellow oil (6.49 g, 39.8 mmol, 81%). 1H NMR (300.1 MHz, CD_2Cl_2): δ 7.36–7.32 (m, 5H, ArH), 3.59 (s, 2H, CH_2N), 2.55 (q, 4H, $^3J=7.2$ Hz, $N(CH_2CH_3)_2$), 1.07 (t, 6H, $^3J=7.2$ Hz, $N(CH_2CH_3)_2$).

4.2.1. $\{[2-(Diethylamino)methyl]thiophenyl\}trimethyl-silane$ 2b. Procedure reported in Ref. 32c.

4.2.2. $[2-(Diethylamino)methyl]thiophenolato-copper(I)$ 2c. Procedure reported in Ref. 32c.

4.2.3. (Pyrrolidinylmethyl)benzene 3a. Same procedure as 2a starting from benzyl bromide (5.05 g, 29.5 mmol) and pyrrolidine (8.00 mL, 95.9 mmol), affording the initially impure product, which was purified through column chromatography (SiO_2 , eluent hexane/ Et_2O 1:1) as a yellow oil (3.59 g, 22.6 mmol, 75%). 1H NMR

(300.1 MHz, CD₂Cl₂): δ 7.34–7.29 (m, 3H, ArH), 7.27–7.24 (m, 2H, ArH), 3.63 (s, 2H, CH₂N), 2.52 (m, 4H, N(CH₂)₂), 1.80 (m, 4H, (CH₂)₂).

4.2.4. *{[2-(Pyrrolidinyl)methyl]thiophenyl}trimethyl-silane 3b*. Procedure reported in Ref. 1, starting from **3a** (3.61 g, 22.4 mmol) in hexane, affording the product as a yellow oil (5.12 g, 21.9 mmol, 97%). ¹H NMR (300.1 MHz, C₆D₆): δ 7.62 (d, 1H, ³J=7.2 Hz, ArH), 7.47 (d, 1H, ³J=7.5 Hz, ArH), 7.07 (m, 1H, ArH), 6.9 (m, 1H, ArH), 3.93 (s, 2H, CH₂N), 2.46 (m, 4H, N(CH₂)₂), 1.56 (m, 2H, (CH₂)₂), 0.13 (s, 9H, Si(CH₃)₃). ¹³C NMR (75.5 MHz, C₆D₆): δ 139.9, 138.6, 135.8, 132.7, 126.1, 123.3 (Aryl C), 65.6 (CH₂N), 57.4 (N(CH₂)₂), 23.6 (–(CH₂)₂–).

4.2.5. *[2-(Pyrrolidinyl)methyl]thiophenolato-copper(I) 3c*. Procedure reported in Ref. 1, starting from **3b** (5.12 g, 21.9 mmol) and CuCl (1.96 g, 19.8 mmol), affording the product as a white powder (3.79 g, 14.1 mmol, 75%). ¹H NMR (300.1 MHz, C₆D₆, 358 K): δ 6.97 (m, 1H, ArH), 6.91 (m, 1H, ArH), 6.8 (m, 1H, ArH), 6.73 (m, 1H, ArH), 3.82 (br, 2H, CH₂N), 2.48 (br, 4H, N(CH₂)₂), 1.53 (br, 2H, (CH₂)₂). ¹³C NMR (75.5 MHz, C₆D₆, 358 K): δ 139.7, 136.7, 134.8, 131.5, 124.1, 122.6 (Aryl C), 64.3 (CH₂N), 57.1 (N(CH₂)₂), 23.0 (–(CH₂)₂–). Anal. Calcd for C₁₁H₁₄NSCu: C, 51.64; H, 5.52; N, 5.47. Found: C, 51.64; H, 5.22; N, 5.47.

4.2.6. *(Piperidinylmethyl)benzene 4a*. Same procedure as **2a** starting from benzyl bromide (5.23 g, 30.6 mmol) and piperidine (10 mL, excess), affording the initially impure product, which was purified through column chromatography (SiO₂, eluent hexane/Et₂O 1:1) giving a yellow oil (5.28 g, 30.1 mmol, 98%). ¹H NMR (300.1 MHz, CD₂Cl₂): δ 7.33 (m, 3H, ArH), 7.29 (m, 2H, ArH), 3.49 (s, 2H, CH₂N), 2.40 (t, 4H, ³J=5.1 Hz, N(CH₂)₂), 1.60 (m, 4H, –(CH₂)₂–), 1.46 (m, 2H, –CH₂–).

4.2.7. *{[2-(Piperidinyl)methyl]thiophenyl}trimethyl-silane 4b*. Procedure reported in Ref. 1, starting from **4a** (1.91 g, 10.9 mmol) in pentane, affording the product as a yellow oil (2.58 g, 10.5 mmol, 96%). ¹H NMR (300.1 MHz, C₆D₆): δ 7.63 (d, 1H, ³J=7.5 Hz, ArH), 7.43 (d, 1H, ³J=8.1 Hz, ArH), 7.07 (m, 1H, ArH), 6.91 (m, 1H, ArH), 3.73 (s, 2H, CH₂N), 2.36 (t, 4H, ³J=5.7 Hz, N(CH₂)₂), 1.44 (m, 4H, –(CH₂)₂–), 1.27 (m, 2H, CH₂), 0.13 (s, 9H, Si(CH₃)₃). ¹³C NMR (75.5 MHz, C₆D₆): δ 143.2, 136.7, 132.6, 131.7, 127.4, 126.9 (Aryl C), 62.2 (CH₂N), 55.1 (N(CH₂)₂), 26.6 (–(CH₂)₂–), 24.9 (–CH₂–), 1.3 Si(CH₃)₃.

4.2.8. *[2-(Piperidinyl)methyl]thiophenolato-copper(I) 4c*. Procedure reported in Ref. 1, starting from **4b** (2.58 g, 10.5 mmol) and CuCl (0.93 g, 9.4 mmol), affording the product as a light brown powder (2.01 g, 7.45 mmol, 79%). ¹H NMR (300.1 MHz, C₆D₆, 358 K): δ 7.98 (br, 1H, ArH), 7.11 (br, 1H, ArH), 6.95 (m, 1H, ArH), 6.78 (m, 1H, ArH), 3.82 (br, 1H, CH₂N), 2.28 (br, 3H, N(CH₂)₂), 1.40 (br, 4H, –(CH₂)₂–), 1.06 (br, 2H, CH₂). ¹³C NMR (75.5 MHz, C₆D₆): δ 142.3, 134.6, 132.8, 130.8, 126.5, 125.8 (Aryl C), 60.2 (CH₂N), 57.1 (N(CH₂)₂), 27.2 (–(CH₂)₂–), 25.0 (–CH₂–). Anal. Calcd for C₁₂H₁₆NSCu: C, 53.41; H, 5.98; N, 5.19. Found: C, 53.20; H, 5.91; N, 5.06.

4.2.9. *2-(Dimethylamino)methylnaphthalene 5a*. Same procedure as **2a** starting from 2-bromomethylnaphthalene (5.50 g, 24.87 mmol) and dimethylamine (50 mL, excess), affording the product as a yellow oil (3.29 g, 17.76 mmol, 92%). ¹H NMR (300.105 MHz, CD₂Cl₂, 358 K): δ 7.86–7.82 (m, 3H, ArH), 7.76 (s, 1H, ArH), 7.50–7.47 (m, 3H, ArH), 3.60 (s, 2H, CH₂N), 2.32 (s, 6H, N(CH₃)₂).

4.2.10. *{[2-(Dimethyl)methyl]thionaphthyl}trimethyl-silane 5b*. Procedure reported in Ref. 1, starting from **5a** (3.80 g, 20.50 mmol) in hexane, affording the product as an orange oil (5.22 g, 18.03 mmol, 88%). ¹H NMR (300.105 MHz, C₆D₆): δ 8.06 (s, 1H, ArH), 8.03 (s, 1H, ArH), 7.63–7.59 (m, 1H, ArH), 7.51–7.47 (m, 1H, ArH), 7.17–7.11 (m, 2H, ArH), 3.83 (s, 2H, CH₂N), 2.21 (s, 6H, N(CH₃)₂), 0.14 (s, 9H, Si(CH₃)₃). ¹³C NMR (75.469 MHz, C₆D₆):

δ 140.5, 136.2, 133.6, 133.5, 130.7, 129.0, 127.4, 136.7, 126.5 (NaphthylC), 63.33 (CH₂N), 46.04 (N(CH₃)₂), 1.4 (SSi(CH₃)₃).

4.2.11. *[2-(Dimethylamino)methyl]thionaphtholato-copper(I) 5c*. Procedure reported in Ref. 1, starting from **5b** (3.70 g, 12.78 mmol) and CuCl (1.20 g, 12.16 mmol), affording the product as a yellowish powder (2.28 g, 8.14 mmol, 67%). ¹H NMR (300.105 MHz, C₆D₆, 358 K): δ 8.05 (s, 1H, ArH), 7.73 (d, 1H, ³J=7.8 Hz, ArH), 7.62 (d, 1H, ³J=7.8 Hz, ArH), 7.48 (s, 1H, ArH), 7.40–7.27 (m, 2H, ArH), 3.87 (br s, 2H, CH₂N), 2.43 (br s, 6H, N(CH₃)₂). ¹³C NMR (75.469 MHz, C₆D₆, 358 K): δ 138.6, 134.6, 134.0, 131.8, 131.2, 130.9, 127.6, 126.5, 126.2, 124.8 (NaphthylC), 67.7 (CH₂N), 47.5 (N(CH₃)₂).

4.2.12. *2-(Diethylaminomethyl)naphthalene 6a*. Same procedure as **2a** starting from 2-(bromomethyl)naphthalene (5.50 g, 24.8 mmol) and diethylamine (7.00 mL, 67.0 mol), affording the product as orange oil (4.96 g, 23.3 mmol, 93%). ¹H NMR (300.1 MHz, CD₂Cl₂): δ 7.82–7.76 (m, 3H, ArH), 7.57 (s, 1H, ArH), 7.47–7.4 (m, 3H, ArH), 3.74 (s, 2H, CH₂N), 2.59 (q, 4H, ³J=7.02 Hz, N(CH₂CH₃)₂), 1.09 (t, 6H, ³J=7.2 Hz, N(CH₂CH₃)₂).

4.2.13. *{[2-(Diethyl)methyl]thionaphthyl}trimethyl-silane 6b*. Procedure reported in Ref. 1, starting from **6a** (4.07 g, 19.1 mmol) in hexane, affording the product as an orange oil (5.53 g, 17.4 mmol, 91%). ¹H NMR (300.1 MHz, C₆D₆): δ 8.24 (br, 1H, ArH), 8.04 (br, 1H, ArH), 7.6 (m, 1H, ArH), 7.18–7.11 (m, 3H, ArH), 4.01 (s, 2H, CH₂N), 2.53 (q, 4H, N(CH₂CH₃)₂), 1.01 (t, 6H, ³J=6.9 Hz, N(CH₂CH₃)₂), 0.15 (s, 9H, ³J=6.9 Hz, Si(CH₃)₃). ¹³C NMR (75.469 MHz, C₆D₆): δ 139.9, 137.0, 134.2, 133.7, 131.3, 128.0, 126.8, 126.5, 126.3, 125.8 (NaphthylC), 61.06 (CH₂N), 46.73 (N(CH₂CH₃)₂), 12.69 (N(CH₂CH₃)₂), 1.32 (SSi(CH₃)₃).

4.2.14. *[2-(Diethylamino)methyl]thionaphtholato-copper(I) 6c*. Procedure reported in Ref. 1, starting from **6b** (5.53 g, 17.4 mmol) and CuCl (1.38 g, 13.9 mmol), affording the product as an orange powder (3.47 g, 11.3 mmol, 81%). ¹H NMR (300.1 MHz, C₆D₆, 358 K): δ 7.71 (br, 1H, ArH), 7.52 (br, 1H, ArH), 7.37 (br, 1H, ArH), 7.21 (br, 1H, ArH), 7.05 (br, 1H, ArH), 6.98 (br, 1H, ArH), 3.82 (br, 2H, CH₂N), 2.49 (q, 4H, ³J=6.5 Hz, N(CH₂CH₃)₂), 0.93 (t, 6H, ³J=6.5 Hz, N(CH₂CH₃)₂). ¹³C NMR (75.5 MHz, C₆D₆, 358 K): δ 137.9, 136.7, 134.5, 133.2, 131.0, 129.6, 125.8, 125.5, 124.3, 1232.8 (Naphthyl C), 61.90 (CH₂N), 48.93 (N(CH₂CH₃)₂), 11.73 (N(CH₂CH₃)₂). Anal. Calcd for C₁₅H₁₈NSCu: C, 58.51; H, 5.89; N, 4.55. Found: C, 58.20; H, 5.77; N, 4.50.

4.2.15. *2-(Pyrrolidinylmethyl)naphthalene 7a*. Same procedure as **2a** starting from 2-(bromomethyl)naphthalene (6.53 g, 29.5 mmol) and pyrrolidine (13.0 mL, 0.155 mol), affording the impure product, which was purified through column chromatography (SiO₂, eluent hexane/methanol/Et₃N 100:15:2) as a yellow oil (5.34 g, 25.3 mmol, 85%). ¹H NMR (300.1 MHz, CD₂Cl₂): δ 7.84–7.77 (m, 4H, ArH), 7.53–7.44 (m, 3H, ArH), 3.79 (s, 2H, CH₂N), 2.59–2.54 (m, 4H, N(CH₂)₂), 1.84–1.79 (m, 4H, (CH₂)₂).

4.2.16. *{[2-(Pyrrolidinyl)methyl]thionaphthyl}trimethyl-silane 7b*. Procedure reported in Ref. 1, starting from **7a** (5.11 g, 24.2 mmol) in hexane, affording the product as a yellow oil (6.89 g, 21.8 mmol, 90%). ¹H NMR (300.1 MHz, C₆D₆): δ 8.12 (br, 1H, ArH), 8.04 (br, 1H, ArH), 7.6 (m, 1H, ArH), 7.18–7.15 (m, 3H, ArH), 4.09 (s, 2H, CH₂N), 2.53 (m, 4H, N(CH₂)₂), 1.59 (m, 4H, (CH₂)₂), 0.15 (s, 9H, Si(CH₃)₃). ¹³C NMR (75.469 MHz, C₆D₆): δ 140.2, 138.6, 137.5, 135.3, 133.8, 131.9, 131.1, 127.7, 126.2, 125.1 (Naphthyl C), 67.02 (CH₂N), 56.7 (N(CH₂)₂), 23.8 ((CH₂)₂), 1.31 (SSi(CH₃)₃).

4.2.17. *[2-(Pyrrolidinyl)methyl]thionaphtholato-copper(I) 7c*. Procedure reported in Ref. 1, starting from **7b** (3.44 g, 10.9 mmol) and CuCl (0.97 g, 9.80 mmol), affording the product as a yellow powder (2.39 g, 7.84 mmol, 80%). ¹H NMR (300.1 MHz, C₆D₆, 358 K): δ 8.30

(br, 1H, ArH), 7.7 (m, 2H, ArH), 7.35 (m, 1H, ArH), 7.20 (m, 2H, ArH), 3.88 (br, 2H, CH₂N), 2.3 (br, 4H, N(CH₂)₂), 1.51 (br, 4H, (CH₂)₂). ¹³C NMR (75.5 MHz, C₆D₆, 358 K): δ 139.8, 135.9, 134.5, 134.3, 133.6, 131.1, 130.1, 127.5, 126.4, 125.4 (Naphthyl C), 65.07 (CH₂N), 56.9 (N(CH₂)₂), 23.1 ((CH₂)₂). Anal. Calcd for C₁₅H₁₆NSCu: C, 58.89; H, 5.27; N, 4.58. Found: C, 58.94; H, 5.35; N, 4.50.

4.2.18. 2-(Piperidinylmethyl)naphthalene 8a. Same procedure as **2a** starting from 2-(bromomethyl)naphthalene (6.50 g, 29.4 mmol) and piperidine (15.0 mL, 0.151 mol), affording the impure product, which was purified through column chromatography (SiO₂, eluent hexane/methanol/Et₃N 100:15:2) as a yellow solid (4.91 g, 21.8 mmol, 74%). ¹H NMR (300.1 MHz, CD₂Cl₂): δ 7.82–7.78 (m, 3H, ArH), 7.74 (br, 1H, ArH), 7.52–7.43 (3H, ArH), 3.65 (s, 2H, CH₂N), 2.46 (m, 4H, N(CH₂)₂), 1.61 (m, 4H, -(CH₂)₂), 1.46 (m, 2H, CH₂).

4.2.19. [2-(Piperidinyl)methyl]thionaphthyl(trimethyl)silane 8b. Procedure reported in Ref. 1, starting from **8a** (4.91 g, 21.8 mmol) in hexane, affording the product as a yellow oil (6.80 g, 20.6 mmol, 95%). ¹H NMR (300.1 MHz, C₆D₆): δ 8.16 (br, 1H, ArH), 8.03 (br, 1H, ArH), 7.6 (m, 1H, ArH), 7.20–7.14 (m, 3H, ArH), 3.9 (s, 2H, CH₂N), 2.42 (m, 4H, N(CH₂)₂), 1.50 (m, 4H, -(CH₂)₂), 1.34 (m, 2H, CH₂), 0.15 (s, 9H, Si(CH₃)₃). ¹³C NMR (75.5 MHz, C₆D₆): δ 142.3, 137.8, 136.4, 133.7, 133.2, 132.2, 128.4, 127.5, 126.9 (Naphthyl C), 62.5 (CH₂N), 54.4 (N(CH₂)₂), 26.3 (-(CH₂)₂), 24.7 (CH₂), 1.4 (Si(CH₃)₃).

4.2.20. [2-(Piperidinyl)methyl]thionaphtholato-copper(I) 8c. Procedure reported in Ref. 1, starting from **8b** (1.70 g, 5.16 mmol) and CuCl (0.45 g, 4.54 mmol), affording the product as a yellow powder (1.13 g, 3.53 mmol, 78%). ¹H NMR (300.1 MHz, C₆D₆, 358 K): δ 8.35 (br, 1H, ArH), 7.57 (m, 3H, ArH), 7.30 (m, 3H, ArH), 3.88 (br, 2H, CH₂N), 2.28 (br, 4H, N(CH₂)₂), 1.33 (br, 4H, -(CH₂)₂), 0.85 (m, 2H, CH₂). ¹³C NMR (75.5 MHz, C₆D₆, 358 K): δ 140.5, 134.6, 134.4, 132.2, 131.0, 129.8, 128.1, 127.4, 125.4, 125.9 (Naphthyl C), 69.7 (CH₂N), 56.9 (N(CH₂)₂), 24.6 (-(CH₂)₂), 24.03 (CH₂). Anal. Calcd for C₁₆H₁₈NSCu: C, 60.07; H, 5.67; N, 4.38. Found: C, 60.18; H, 5.79; N, 4.33.

For compounds **9a–c**, **10a–c**, **11a–c**, **12a–c**, see Ref. 31.

For compounds **13a–c**, **14a–c**, see Ref. 30b.

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.

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- The four alternatives proposed in literature are: (a) oxidative addition/reductive elimination through 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).
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