

Aminoarenethiolate Copper(I)-Catalyzed Amination of Aryl Bromides

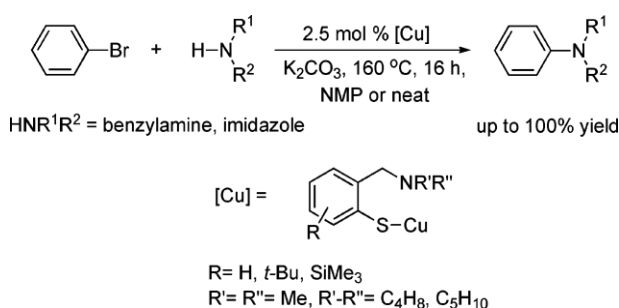
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Abstract:



Aminoarenethiolate copper(I) complexes are known to be efficient catalysts for carbon-carbon bond formation. Here, we show the first examples that these thiolate copper(I) complexes are efficient for carbon-nitrogen bond formation reactions as well. N-Arylation of benzylamine and imidazole with bromobenzene was achieved either in NMP as solvent or under solvent-free conditions in the presence of 2.5 mol % of aminoarenethiolate copper(I) complex only.

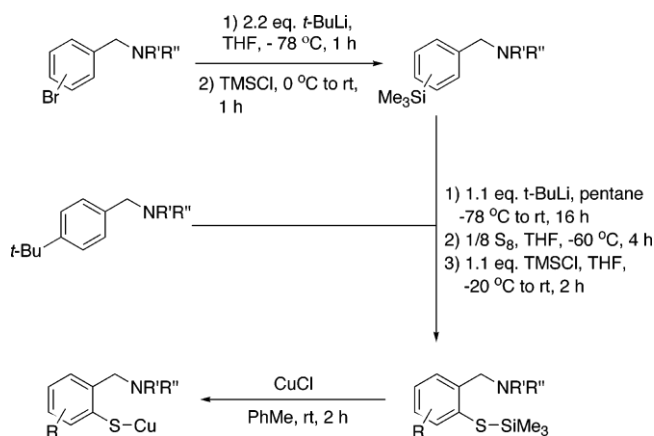
Arylamines are attractive targets in chemical synthesis because of their wide utility and occurrence in a number of interesting molecules. They have been found in biologically active compounds such as pharmaceuticals and agrochemicals.¹

At this moment, the most frequently used industrial pathway for coupling reactions is still the Ullmann-type reaction.² Copper-catalyzed carbon-nitrogen bond formation from aryl halides has often been studied over the past decade, mostly by using an in situ generated catalyst from a copper source and ligands such as amino acids,³ diamines,⁴ di-imines,⁵ and diols.⁶ Although palladium-catalyzed amination reactions are well-known,⁷ copper is a by far cheaper metal, and its environmental friendly nature led us to study the amination reaction catalyzed by aminoarenethiolate-copper-I complexes.

Aminoarenethiolate-copper(I) complexes, which have excellent solubility in common organic solvents, have been shown to be excellent catalysts for C-C bond formation by allylic substitution,⁸ cross-coupling,⁹ 1,4-addition,¹⁰ and 1,6-addition reactions.¹¹ However, to date, no investigation on the C-N bond formation has been reported with these species. Here, we present the first examples of C-N bond formation catalyzed by aminoarenethiolate-copper(I) complexes. Trimethylsilyl-protected aminoarenethiolate ligands were synthesized in a three-step procedure from benzylamine derivatives. The first step involves the heteroatom-directed ortho-lithiation of a parent arene to generate the corresponding organolithium compound. In the second step, sulfur was inserted in the carbon-lithium bond, affording the corresponding lithium arenethiolate. Subsequently, quenching by trimethylsilyl chloride

gave the trimethylsilyl-protected thio- lates. The aminoarenethiolate–copper(I) complexes were obtained by transmetalation with copper(I) chloride (Scheme 1).¹²

Scheme 1. Synthesis of Aminoarenethiolate –Copper(I) Complexes



These complexes are characterized by a nontransferable sulfur–copper bond, which makes these catalysts more robust to the harsh reaction conditions usually required for the copper-catalyzed amination reaction. It has been found that these complexes form trimeric species both in solid state and in solution.^{10,13}

A first set of complexes was synthesized with variation at the amine functionality. Dimethylamino was replaced by either a pyrrolidinyl or a piperidinyl ring. Furthermore, *tert*-butyl and trimethylsilyl groups were introduced meta to the thiocopper moiety (Figure 1).

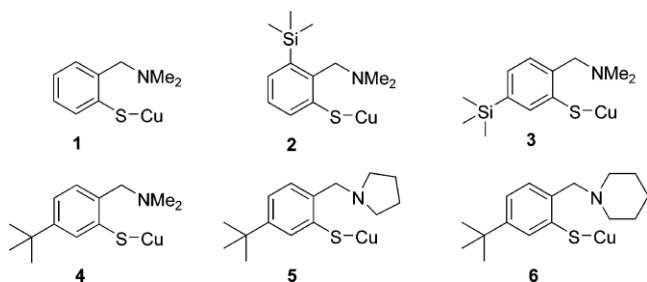


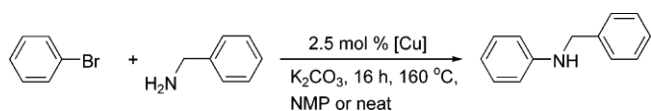
Figure 1. Aminoarenethiolate –Copper(I) Complexes.

The presence of *tert*-butyl or trimethylsilyl groups on the ligand increased the solubility of the resulting aminoarene-thiolate–copper(I) complexes in organic solvents such as toluene and pentane. This effect is furthermore reinforced by changing the dimethylamino functionality by a pyrrolidinyl or a piperidinyl ring.

These complexes were investigated in the copper-catalyzed amination of aryl halides. We chose the

coupling reaction of benzylamine with bromobenzene as a model reaction to investigate suitable reaction conditions. Initial tests in DMSO and DMF with different bases were without success. Only reactions at 160 °C in *N*-methylpyrrolidinone (NMP) as solvent using K₂CO₃ as base and 2.5 mol % of copper catalyst gave good results. The copper complexes **1–6** were subsequently tested using these reaction conditions (Scheme 2, Table 1).

Scheme 2. *N*-Arylation of Benzylamine with Bromobenzene



The aminoarenethiolate – copper(I) complexes show moderate reactivities in NMP (5 M) as *N*-benzylaniline could be

Table 1. Screening of Aminoarenethiolate – Copper(I) Complexes for *N*-Arylation of Benzylamine with Bromobenzene^a

entry	catalyst	solvent	yield ^b (%)
1	1	NMP	32
2	1	–	64
3	2	NMP	40
4	2	–	70
5	3	NMP	69
6	3	–	91
7	4	NMP	31
8	4	–	68
9	5	NMP	72
10	5	–	94 (91) ^c
11	6	NMP	56
12	6	–	84

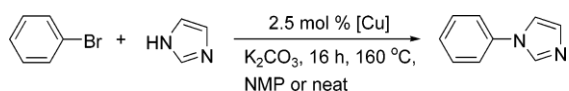
^a Reaction conditions: benzylamine (6.5 mmol), bromobenzene (5 mmol), K₂CO₃ (5.5 mmol), [Cu] (2.5 mol %), NMP (1 mL), 160 °C, 16 h, under N₂. ^b Determined by GC using dihexyl ether as internal standard. ^c Isolated yield.

obtained in yields up to 72% (entry 9, Table 1). A major breakthrough, however, was achieved when this reaction was performed under solvent-free conditions.¹⁴ Neat reaction conditions allowed us to almost double the yield up to 94% compared to the reactions using NMP as solvent for the synthesis of *N*-benzylaniline (entry 10, Table 1).

Trimethylsilyl-substituted aminoarenethiolate – copper(I) catalysts **2** and **3** show good reactivities as yields up to 91% were obtained. The position of the trimethylsilyl moiety on the aryl ring of the aminoarenethiolate ligand apparently plays an important role. With complex **2** using either NMP or neat conditions 40 and 70% yields (entries 3 and 4, Table

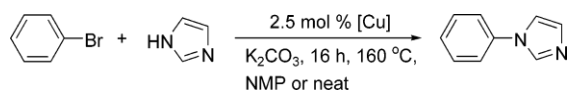
1) were obtained, respectively, while using **3** yields were raised to 69 and 91% (entries 5 and 6, Table 1), respectively. Copper complexes **4–6**, which each possess a 5-*tert*-butyl group, gave better conversions with yields up to 94% (for **5**, entry 10, Table 1). Catalyst **4** possessing the dimethylamino moiety allowed us to obtain *N*-phenylbenzylamine in 68% yield. However, changing the dimethylamino group for a piperidinyl (**6**) or pyrrolidinyl (**5**) functionality yielded, under solvent-free conditions, *N*-benzylaniline in 84 and 94% yield, respectively (entries 12 and 10, Table 1). A Possible explanation for these improved yields could be the increased solubility of the *tert*-butyl- or trimethylsilyl-substituted copper complexes. Next, we tested this reaction using other phenyl halides. However, only starting material was observed when using either chloro- or fluorobenzene instead of bromobenzene. With iodobenzene, a low conversion and the presence of only small amounts of *N,N*-diphenylbenzylamine were detected. Encouraged by the results with bromobenzene, we also investigated the *N*-arylation of a heterocyclic amine, i.e.

Scheme 3. *N*-Arylation of Imidazole with Bromobenzene



imidazole with bromobenzene under the same reaction conditions (Scheme 3 and Table 2).

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Table 2. Screening of Aminoarenethiolate – Copper(I)

Complexes for *N*-Arylation of Imidazole with Bromobenzene^a

entry	catalyst	condition	yield ^b (%)
1	1	NMP	82

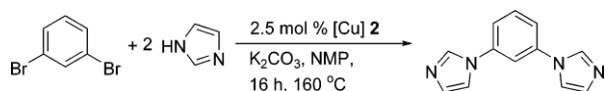
2	1	-	6
3	2	NMP	8
4	2	-	100
5	3	NMP	(98) ^c
6	3	-	66
7	4	NMP	8
8	4	-	77
9	5	NMP	6
10	5	-	2
11	6	NMP	7
12	6	-	3

^a Reaction conditions: imidazole (6.5 mmol), bromobenzene (5 mmol), K₂CO₃ (5.5 mmol), [Cu] (2.5 mol %), NMP (1 mL), 160 °C, 16 h, under N₂. ^b Determined by GC using dihexyl ether as internal standard. ^c Isolated yield.

The outcome of this reaction is opposite to the results observed with the primary amine benzylamine. Now, best reactivities were obtained using NMP (5 M) as solvent instead of the solvent-free conditions. As different substrates can exhibit different reactivities, the use of solvent improves the yield for the imidazole coupling. The nonfunctionalized aminoarenethiolate-copper(I) complex **1** showed a good reactivity with 82% yield of *N*-phenylimidazole (entry 1, Table 2). The trimethylsilyl-substituted complexes showed even better efficiencies. A total conversion to the desired product was obtained with the 3-trimethylsilyl-substituted complex **2**, whereas its 5-trimethylsilyl-substituted analogue **3** afforded the product in only 77% yield. Apparently, the buttressing effect exerted by the 3-trimethylsilyl substituent on the conformation of the coordinating nitrogen atom of the CH₂N ligand plays a role during the carbon-nitrogen bond-forming step. Also, the nature of the amino functionality plays a role as 73% yield was obtained with the dimethylamino-substituted copper complex **4** (entry 7, Table 2), whereas with the cyclic amines the yields improved to 79% (pyrrolydiny **5**) and 86% yield (piperidiny **6**) (entries 9 and 11, Table 2).

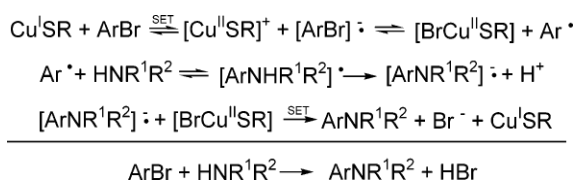
Using the optimum reaction conditions found for the *N*-arylation of imidazole with bromobenzene (entry 3, Table 2), the double amination of 1,3-dibromobenzene with imidazole was achieved (Scheme 4).

With the trimethylsilyl-substituted aminoarenethiolate-copper(I) complex **2** as catalyst, 1,3-diimidazolebenzene was



Scheme 4. *N*-Arylation of Imidazole with 1,3-Dibromobenzene

Scheme 5. Possible Single-Electron-Transfer Pathway



obtained in quantitative yield; no trace of the onoamination product was detected.

CONCLUSION,

In conclusion, the thermally very stable aminoarene- thiolate–copper(I) complexes have shown to be efficient in the copper-catalyzed *N*-arylation of benzylamine (solvent- free conditions) and imidazole (in NMP) with bromobenzene at 160 °C with only 2.5 mol % of catalysts. Using this catalytic system, the C–N coupling products, *N*-benzylaniline (94%) and *N*-phenylimidazole (quantitative), were obtained selectively in high yields. Moreover, we showed that the reaction conditions (solvent free or using NMP) play a major role to arrive at high yields for different amines.

Interestingly, the aminoarenethiolate–copper(I) (CuSR) compounds **1–6** are the first thiolate copper complexes used for C–X coupling catalysis. As a possible mechanistic pathway, a single electron transfer (SET) from the electron- rich CuSR to the aryl halide is proposed (see Scheme 5).¹⁵ Further investigations concern the study of the aggregation behavior of CuSR (e.g., pure **1** is a trimeric (CuSR)₃ aggregate in solution),¹³ their redox behavior (dimethylamino Jerphagnon, T.; van Klink, G. P. M.; van Koten, G. Manuscript in preparation. vs pyrrolidinyl vs piperidinyl), catalyst–substrate interaction (primary amines (sp³N) vs heterocyclic amines (sp²N)), and the nature of the solvent (solvent-free conditions vs NMP).

Currently, we are further investigating the scope and mechanistic aspects of this copper-catalyzed aryllic amination. In addition, further work is in progress on recycling of the aminoarenethiolate–copper(I) catalysts.^{10b}

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[12] Dry copper(I) chloride was freshly synthesized before use.

[13]