Formation of Aryl–Nitrogen, Aryl–Oxygen, and Aryl–Carbon Bonds Using Well-Defined Copper(I)-Based Catalysts
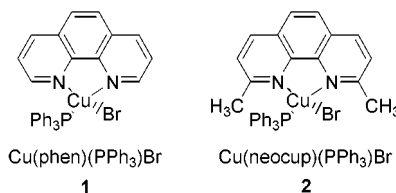
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ABSTRACT

Cu(phen)(PPh₃)Br   Cu(neocup)(PPh₃)Br
1   **2**

We report mild synthetic protocols for the formation of aryl–carbon, aryl–nitrogen, and aryl–oxygen bonds based on soluble, well-defined copper(I) catalysts. These protocols do not require the use of palladium and/or expensive ligands.

Aryl−nitrogen, aryl−oxygen, and aryl−acetylene bonds are prevalent in many compounds that are of biological, pharmaceutical, and materials interest.[1] In recognition of their widespread importance, over the years, many synthetic methods have emerged for the formation of these bonds.[1e,2] Most noteworthy among them are the aryl coupling reactions based on palladium(0) catalysts such as the Hartwig−Buchwald coupling and the Sonagashira coupling.[3] They have largely supplanted the traditional copper-mediated reactions such as the Ullmann coupling[4] and Stephens−Castro coupling.[5] Yet, copper-mediated couplings are still the reactions of choice for large- and industrial-scale formation of these bonds.[1b,6]

Traditional copper-mediated aryl coupling reactions have few drawbacks. Most copper(I) salts are insoluble in organic solvents, and hence, the reactions are often heterogeneous and require high reaction temperatures. Moreover, the reactions are sensitive to functional groups on aryl halides and the yields are often irreproducible. However, it was shown by Weingarten in 1964, Cohen in 1976, and more

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recently, by others that if the solubility of copper salts is increased then the aryl coupling reactions tend to occur at milder temperatures.[7]

In 1987, Paine concluded through mechanistic investigations that the active catalytic species in Ullmann reactions are the *soluble cuprous* ions.[8] More recently, it has been observed that certain additives can accelerate the rate of these reactions.[1b,6,9] Encouraged by these precedences, we initiated a study of *chemically well-defined, stable, and soluble* copper(I) complexes that can be *systematically modified* to act as catalysts for the formation of aryl−carbon and aryl−heteroatom bonds.[10] On the basis of these studies, we now report synthetic protocols for the formation of aryl−oxygen, aryl−nitrogen, and aryl−acetylene bonds using copper−phenanthroline complexes as catalysts. To our knowledge, this is the first copper(I)-based catalytic system that can be used for the formation of aryl−carbon *and* aryl−heteroatom bonds from aryl halides under mild reactions and tolerant to functional groups. These protocols can be considered as alternatives to palladium and do not require the use of expensive and/or air-sensitive phosphine ligands that are often required in the palladium chemistry.

Cu(phen)(PPh₃)Br
1
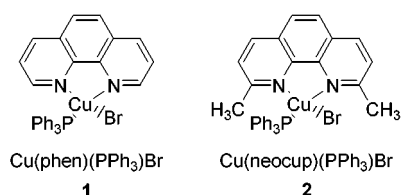
Cu(neocup)(PPh₃)Br
2

Cu(phen)(PPh$_3$)Br (**1**) and Cu(neocup)(PPh$_3$)Br (**2**) were prepared by the addition of 1,10-phenanthroline or neocuproine to a solution of tris(triphenylphosphine) copper(I) bromide in chloroform at room temperature.[11] These complexes are soluble in organic solvents such as dichloromethane, chloroform, toluene (warm), benzene, NMP, DMF, and DMSO. However, they are insoluble in diethyl ether or hexane. Unlike soluble copper(I) salts such as copper triflate, **1** and **2** are stable to air and ambient moisture.

We first chose to examine the propensity of these complexes to act as catalysts for the formation of aryl−nitrogen bonds. We found that the reaction of diphenylamine

with iodobenzene using **1** as a catalyst and KO-*t*-Bu as the base in toluene at 110 °C was complete (by GC) in 3 h. *However, the same reaction was complete in 90 min when* **2** *was used as the catalyst*. These reactions were slower when the catalyst was replaced with 10 mol % Cu(PPh$_3$)$_3$Br/10 mol % 1,10-phenanthroline.[12] We also found that the reaction rates were much faster with KO-*t*-Bu, when compared with NaO-*t*-Bu or Cs$_2$CO$_3$. Other bases such as K$_3$PO$_4$, K$_2$CO$_3$, *N*-ethylmorpholine, CsF, NaOCH$_3$, and NaH were not effective. Using this protocol, we were able to couple bromobenzene with diphenylamine to form triphenylamine in 36 h. We were also able to couple chlorobenzene with diphenylamine in moderate yields. The protocol was successfully used to couple electron-rich aryl halides with diphenylamine (Table 1). Furthermore, the reaction of

Table 1. Reactions of Aryl Halides with Diphenylamine with 10 mol% of **2**

entry	R$_1$	X	time (h)	yield (%)
1	H	I	6	78
2	H	Br	36	73
3	H	Cl	36	49[a]
4	*o*-CH$_3$	I	6	88
5	*p*-CH$_3$	I	6	70
6	*o*-CH$_3$	Br	36	50[a]

[a] GC yields.

p-toluidine with 2 equiv of bromobenzene yielded the corresponding triphenylamine in 70% yield (see the Supporting Information). We are currently exploring the scope of this reaction for the conversion of anilines to corresponding di- and triphenylamines.

We then examined the efficacy of **2** to act as a catalyst for the formation of diaryl ethers. We found that aryl bromides can be coupled with phenols to form diaryl ethers in good yields using 10 mol % of **2** as a catalyst and Cs$_2$CO$_3$ as a base in toluene at 110 °C (entries 7−10, Table 2). This protocol tolerates base-sensitive functional groups such as ketones (entry 8, Table 2). However, yields of diaryl ethers are substantially lower for aryl bromides bearing ortho substituents (entries 12 and 13, Table 2).

Both **1** and **2** can be used as catalysts for coupling of aryl iodides with aryl acetylenes using K$_2$CO$_3$ as the base, in toluene at 110 °C. However, in contrast to the formation of aryl−nitrogen bonds, **1** was a much better catalyst than **2**. Using our protocol, we were able to couple electron-rich and

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(10) For our previous work on the use of Cu(PPh$_3$)$_3$Br for the formation of aryl−oxygen and aryl−nitrogen bonds, see: (a) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791−4793. (b) Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 139−153.

(11) See the Supporting Information for the synthesis of **1** and **2**. For the synthesis of Cu(PPh$_3$)$_3$Br, see ref 10a.

(12) In contrast to Goodbrand's observation, we found that 2,2′-bipyridyl can accelerate the rate of the reaction. The yields and rates of Cu(bipy)-(PPh$_3$)Br are similar to that of Cu(phen)(PPh$_3$)Br. Detailed kinetic studies are in progress and will be reported in due course.

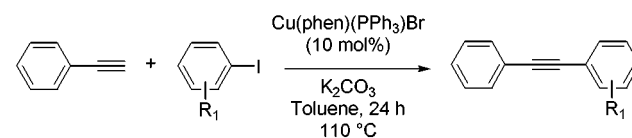**Table 2.** Reactions of Aryl Halides with Phenols with 10 mol% of **2**
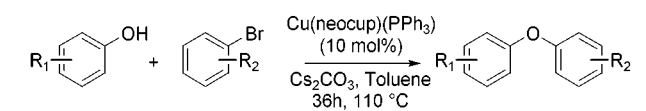
entry	R_1	R_2	yield[a] (%)
1	p-CH$_3$	p-CH$_3$	>99
2	p-CH$_3$	p-COCH$_3$	>99
3	o-CH$_3$	p-CH$_3$	83
4	H	p-NO$_2$	95
5	H	H	51
6	o-CH$_3$	o-CH$_3$	36
7	p-CH$_3$	o-CH$_3$	31

[a] GC yields.

Table 3. Reactions of Aryl Iodides with Phenylacetylene with 10 mol% of **1**

entry	R_1	yield[a] (%)
1	H	80
2	p-CH$_3$	74
3	o-CH$_3$	71
4	p-OCH$_3$	97
5	o-OCH$_3$	70
6	p-COOCH$_3$	89
7	o-COOCH$_3$	76
8	p-COCH$_3$	85

[a] Isolated yields.

electron-poor aryl iodides with phenylacetylene to give the corresponding diphenylacetylene in good yields (Table 3). Other bases such as triethylamine and KOtbu were not effective in this reaction. Noteworthy is the fact that no reaction was observed when the catalyst was replaced with 10 mol %CuBr/10 mol % phenanthroline. This observation suggests that it is better to use well-defined copper complexes rather than using additives with copper salts. We were also able to couple electron-deficient 4-cyanophenylacetylene with iodobenzene in 89% yield (see the Supporting Information). At the present time, these catalysts are not effective in the coupling of aryl bromides.

In summary, we have described here synthetic protocols for the formation of aryl−nitrogen, aryl−oxygen, and aryl−acetylene bonds using copper−phenanthroline complexes as catalysts. For formation of aryl−nitrogen and aryl−oxygen bonds, the reactions are faster with Cu(neocup)(PPh$_3$)Br (**2**). For the formation of aryl−acetylene bonds, both **1** and **2** can be used. In comparison to palladium chemistry, these protocols are simple and mild and avoid the use of air-sensitive and expensive phosphine ligands or additives.

Furthermore, there is an economic attractiveness for using copper over noble metals such as palladium. We are in the process of expanding the scope of these reactions and studying their mechanistic aspects and will be reporting on them shortly.

Supporting Information Available: Synthetic procedures and crystallographic information files (CIF) for **1** and **2**. Synthetic procedures and complete characterization data for entries in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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