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Formation of aryl–nitrogen bonds using a soluble copper(I) catalyst

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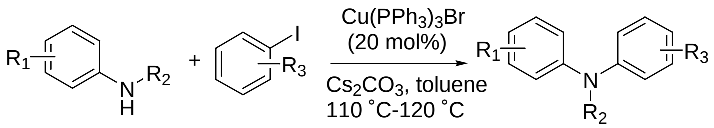
Abstract—We report a synthetic protocol for the synthesis of functionalized diaryl- and triarylamines under mild conditions, using a soluble, air-stable copper(I) complex, $Cu(PPh_3)_3Br$, as the catalyst and cesium carbonate as the base. Using this protocol, we were able to synthesize a tri-*ortho*-ester functionalized triphenylamine, which had eluded us using the palladium chemistry.

Arylamines are prevalent in compounds that are of biological, pharmaceutical and materials interest.[1–3] Their widespread importance has led to the development of many synthetic methods for the formation of aryl–nitrogen bonds.[1,4] Amongst them, the classical copper-mediated Ullmann coupling and the recently developed palladium(0)-catalyzed aryl coupling are the more commonly used methods.[5–12] The Ullmann coupling often requires high temperatures (~200°C) and the use of copper salts in greater than stoichiometric amounts. The reaction is also very sensitive to the substitution on the aryl halide. Due to these limitations, copper salts have largely been supplanted by palladium catalysts. However, it is still the reaction of choice for the synthesis of aryl amines in large and manufacturing scales.[3]

We became interested in the copper-mediated reactions because of a limitation that we encountered with palladium catalysts. In spite of using the most active ligands to date with palladium(0),[10] we were unable to synthesize a triphenylamine that was functionalized at the *ortho* positions with ester groups.[13] This inability of the palladium(0)-based catalysts coupled with well-known limitations of classical Ullmann reactions provided us the impetus to investigate the possibility of developing copper-mediated reactions, which can occur at milder temperatures and are of broad scope. In addition, there is an economic attractiveness for using copper over noble metals such as palladium.[14]

Based on our recent success in using $Cu(PPh_3)_3Br$ (**1**) as a catalyst for the formation of diaryl ethers,[15] we chose to explore the efficacy of this soluble copper(I) complex in the formation of aryl–nitrogen bonds. In this report, we extend the utility of this catalyst for the synthesis of various functionalized diaryl- and triarylamines under milder reaction conditions (Scheme 1).

Complex **1** can easily be prepared from $CuBr_2$ and triphenylphosphine.[†] It is soluble in organic solvents such as THF, dichloromethane, acetonitrile, chloro-



Scheme 1.

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[†] In an Erlenmeyer flask equipped with a Teflon stir bar, methanol (100 mL) was heated to boiling and triphenylphosphine (Acros, 6 g, 22.4 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, $CuBr_2$ (Acros, 99+%, 1.24 g, 5.27 mmol) was added as a solid, in portions. No special precautions were taken for the exclusion of air. Upon addition of the copper bromide, a white precipitate was formed. After the completion of the addition, the contents were stirred for 10 min and the flask was allowed to cool to ambient temperature. The reaction mixture was then filtered through a Buchner funnel and the white residue was washed repeatedly with ethanol and then with diethyl ether. The resultant white solid was dried under dynamic vacuum to give **1** (5.73 g, 85% yield, mp 164°C). The cell constants, contents and the space group are identical to that of the already reported structure of $Cu(PPh_3)_3Br$ (Cambridge Structural Database Refcode-FEYVAG).

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form, NMP, DMF, DMSO, toluene and benzene. However, it is not soluble in diethyl ether, hexane, ethanol or methanol. It can be stored under air for prolonged times, without any visible color change.

We first examined the propensity of **1** to act as a catalyst for the formation of triphenylamine from diphenylamine and bromobenzene or iodobenzene. We found that the reactions were complete in 24 h (by TLC) at 120°C when the aryl halide was iodobenzene and with 20 mol% of **1**, cesium carbonate as the base and toluene as the solvent. Using this protocol, we were able to synthesize a variety of functionalized triphenylamines in good yields from the readily available diphenylamine and aryl iodides (entries 1–11, Table 1).[‡] However, the reactions were incomplete in 24 h (by TLC) if NMP was used as the solvent or if the aryl halide was bromobenzene. Also, we did not observe the formation of triphenylamine if *N*,*N*-dimethylaminopyridine (DMAP), potassium carbonate or sodium methoxide was used as the base instead of Cs_2CO_3.

In general, except for entry 8, electron-deficient aryl iodides provided better yields of triarylamines than electron-rich aryl iodides. While we are unable to explain the low reactivity of methyl-4-iodobenzoate in entry 8, after various trials, we found that if diphenylamine, **1** and KO*t*Bu (instead of Cs_2CO_3) were heated in toluene for 5 min at 120°C, cooled to room temperature and then methyl-4-iodobenzoate was added and reheated to 120°C for 24 h, the corresponding triphenylamine was obtained in 62% yield (entry 9).

With Cs_2CO_3 as the base, we were able to use base-sensitive functional groups such as ketones and esters (see Table 1). Using our protocol, we were also able to selectively aminate an aryl iodide in the presence of a bromide (entry 5). Furthermore, we were able synthesize the triphenylamine, functionalized at the *ortho* positions with ester groups (entry 11)—a molecule that had eluded the palladium chemistry.

To show the effectiveness of our catalyst, in our synthetic protocol, we replaced our catalyst with 20 mol% of CuI, CuBr or 20 mol% of CuBr/60 mol% of PPh_3. In each of these reactions, we failed to observe the formation of triphenylamine. Recently, Goodbrand and Hu reported that when 1,10-phenanthroline/CuCl used as the catalyst and KOH as the base, the rate of formation of aryl–nitrogen bonds was accelerated and the reactions were complete in 6 h, at 125°C, in toluene.[3] To accommodate base-sensitive functional groups like esters, we replaced KOH with cesium carbonate in Goodbrand's protocol. However, we found that the reaction of diphenylamine and iodobenzene was incomplete even after 15 h.

We also found that **1** can be used as a catalyst for the formation of diphenylamine from substituted anilines and aryl iodides (entries 12–15, Table 1). Surprisingly, we found that these reactions were successful only if the amine, the catalyst and the base are stirred at 110°C for few minutes (~5 min for the formation of an yellow

Table 1. Reactions of arylamines with aryl iodides with 20 mol% of **1** and cesium carbonate

Entry	R_1	R_2	R_3	Time (h)	Temp. (°C)	Isolated yield (%)
1	H	Ph	H	24	120	70
2	H	Ph	*o*-CH_3	24	120	52
3	H	Ph	*o*-$COOCH_3$	24	120	69
4	H	Ph	p-CH_3	24	120	52
5	H	Ph	*p*-Br	24	120	54
6	H	Ph	*p*-$COCH_3$	24	120	68
7	H	Ph	*p*-NO_2	24	120	78
8	H	Ph	*p*-$COOCH_3$	24	120	25
9	H	Ph	*p*-$COOCH_3$	24	120	62[a]
10	*o*-$COOCH_3$	C_6H_4-*o*-$COOCH_3$	*o*-$COOCH_3$	32	120	10
11	*o*-$COOCH_3$	C_6H_4-*o*-$COOCH_3$	*o*-$COOCH_3$	32	175	40[b]
12	H	H	H	24	110	75
13	*p*-CH_3	H	H	24	110	88
14	*o*-$COOCH_3$	H	*o*-$COOCH_3$	24	110	83
15	*o*-$COOCH_3$	H	H	24	110	70

[a] With KO*t*Bu as the base.

[b] *o*-Dichlorobenzene was used as a solvent.

[‡] In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar and a rubber septum, was charged with cesium carbonate (Acros, 1.5 mmol), $Cu(PPh_3)_3Br$ (20 mol% with respect to the aryl iodide) and diphenylamine (1 mmol). The glass tube was sealed with a rubber septum and was taken out. The aryl halide (1 mmol) and toluene (15 mL) were injected into the tube through the septum. The tube was then degassed and back-filled with argon three times using a long needle. The contents were then stirred at 120°C for times indicated in Table 1. Care was taken to make sure the contents were well stirred. The reaction mixture was then cooled, mixed with 15 mL of diethyl ether, and filtered to remove any insoluble residues. The combined extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was then purified by flash column chromatography on silica gel to obtain the analytically pure product.

color) *before* the addition of the aryl iodide. If all the starting materials were added at room temperature and heated to 110°C, we observed a black precipitate and there is no formation of the diphenylamine. All of the compounds in Table 1 have been characterized by ^1H and ^{13}C NMR and elemental analyses. Entries 3, 5, 7 and 11 have also been characterized by single crystal X-ray analyses.

In conclusion, we have shown that a soluble, stable and an easy-to-prepare copper(I) complex, $Cu(PPh_3)_3Br$, can be used as a catalyst for the formation of aryl–nitrogen bonds under milder conditions. This catalyst is selective for aryl iodides and the synthetic protocol tolerates various functional groups. We are currently investigating the mechanistic aspects of this reaction and the scope of this catalyst in other palladium-catalyzed reactions.

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13. Hellwinkel and Melan had reported the synthesis of this compound in 1971 using traditional Ullmann coupling in about 20% yield (*Chem. Ber.* **1971**, *104*, 1001–1006). However, in our hands, this reaction was irreproducible. Hence, we tried the more modern Hartwig–Buchwald coupling using various ligands such as DPPF, DPPB, PPh_3 including the more recent ligands reported by Buchwald (see Ref. 10) and bases such as Cs_2CO_3, BuLi, LDA, KHDMS, NaOMe and NaO*t*Bu. From these reactions, we either recovered the starting materials (see entry 10 or 11) or an intramolecular cyclization product in moderate yields, presumably due to C–H activation of the methyl ester of 2,2′-azanediyl-bis-methylbenzoate. Van Allen, D.; Field, J. E.; Venkataraman, D., manuscript in preparation.
14. The price of palladium has risen from $100/ounce in 1995 to $800/ounce in 2001, making it one of the most expensive metals. In comparison, platinum costs $600/ounce and copper costs $0.05/ounce. For latest prices, see www.kitco.com.
15. Gujadhur, R.; Venkataraman, D. *Synth. Commun.*, in press.