



# Copper-catalyzed amination of aryl halides: single-step synthesis of triarylamines

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**Abstract**—A simple and efficient methodology for the synthesis of triarylamines in a single step has been demonstrated using a ligand-free CuI catalyst and potassium tertiary butoxide as the base. Use of chelating ligands leads to the formation of triarylamine derivatives selectively (95% yield) with high catalytic activity. © 2002 Published by Elsevier Science Ltd.

Arylamines are attractive targets for chemical synthesis because of their wide utility in fine chemicals, dyes and polymers.<sup>1,2</sup> Based on the important developments by Buchwald<sup>3,4</sup> and Hartwig,<sup>5,6</sup> the Pd-catalyzed C–N coupling reaction of aryl halides has recently become the most important method for laboratory scale synthesis of substituted arylamines.<sup>3–6</sup> However, copper-mediated coupling is still the reaction of choice for large- and industrial-scale production of these compounds.<sup>7,8</sup> High purity triarylamines find applications in xerographic photoreceptors, as constituents of non-linear optical chromophores useful in the design of integrated electrooptic switches and modulators, and as hole-transport materials for organic electroluminescent (EL) display devices.<sup>7</sup> Conventionally, triarylamines are pro-

duced by Ullmann condensation of aryl iodides and diarylamines with copper (stoichiometric or catalytic quantities) in the form of a metal, alloy or Cu(I)/Cu(II) salt.<sup>9–11</sup> Major drawbacks of this method are the requirement of high temperature (200°C),<sup>12</sup> sensitivity to catalyst type and low to moderate yield of amines.<sup>7</sup> Bis-arylation of substituted anilines with 2 equiv. of an aromatic halide to produce triarylamine derivatives has been reported with the conventional Ullmann catalyst, however yields are substantially poor.<sup>7</sup> Recently, milder Ullmann-type methodologies for the *N*-arylation of anilines,<sup>12–14</sup> imidazoles,<sup>15</sup> amides<sup>16</sup> and nitrogen heterocycles<sup>17</sup> have been reported. Gujadhur et al.<sup>12</sup> have found that the copper complex Cu(PPh<sub>3</sub>)<sub>3</sub>Br, is active for amination of mono- and diarylamines to di- and triarylamines, respectively, using Cs<sub>2</sub>CO<sub>3</sub> as a base at 120°C. However, CuI and CuBr with or without PPh<sub>3</sub> as a ligand were not active for this reaction. Similarly, Goodbrand and Hu<sup>7</sup> have reported ligand-accelerated single-step catalytic synthesis of triarylamines with high selectivity using CuCl/1,10-phenanthroline catalyst system and KOH as a base at 125°C. However, in this case also, CuCl alone (in the absence of 1,10-phenanthroline as a ligand) produced very low yields of triarylamines. Thus, copper salts in the absence of ligands such as PPh<sub>3</sub> or 1,10-phenanthroline exhibit poor catalytic activity and selectivity for the synthesis of triarylamines at lower temperatures such as 110–125°C.

Our efforts have been directed towards the development of a facile and single-step catalytic synthesis of triarylamines. It is desirable to develop a cheaper catalyst system with high activity and selectivity for the synthesis of triarylamines.<sup>18</sup> We wish to report here the

**Table 1.** Copper-catalyzed amination: screening of bases\*

Entry	Base	Conv. (%)	Yield (%)	
			1	2
1	KOt-Bu	88	72	8
2 <sup>#</sup>	KOt-Bu	51	7	12
3	NaOt-Bu	50	6	19
4	DBU <sup>§</sup>	21	4	4
5	NaOMe	25	–	–
6	KOH	19	–	–

*Reaction conditions:* aniline: 4.0 mmol; iodo benzene: 12.0 mmol; CuI: 0.08 mmol; base: 12.0 mmol; solvent: toluene 20 ml; temperature: 135°C; agitation: 900 rpm; reaction time: 14 h.

<sup>§</sup> 1,8-Diazabicyclo[5.4.0]undec-7-ene.

<sup>#</sup> Reaction without CuI catalyst.

\* Analysis by GC.

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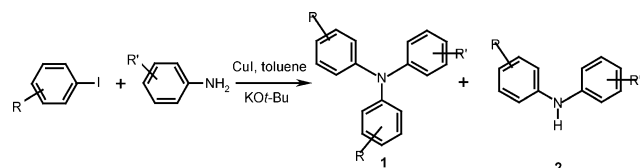
role of  $\text{KO}t\text{-Bu}$  as a base to develop ligand-free catalysts for selective and efficient synthesis of triarylamines at lower temperature ( $135^\circ\text{C}$ ). The role of chelating bidentate ligands in improving activity and selectivity to triarylamines is also presented.

A number of bases were screened with  $\text{CuI}$  as a catalyst. With  $\text{KO}t\text{-Bu}$  as a base, 72% yield of triphenylamine was obtained (Table 1, entry 1). This is the first report on the catalytic synthesis of triarylamines with a  $\text{Cu}$  catalyst in the absence of promoting ligands under relatively mild temperature conditions ( $135^\circ\text{C}$ ). Catalytic turnover numbers in a range of 35–40 were obtained. In order to check the catalytic effect of  $\text{CuI}$ , a non-catalytic reaction was carried out using iodobenzene and aniline as reactants (Table 1, entry 2). In this reaction, 51% conversion of aniline with a poor yield of triphenylamine (7%) was obtained with many by-products. Comparison of the results (Table 1, entries 1 and 2) clearly show that  $\text{CuI}$  enhances the conversion as well as selectivity to triphenylamine. With other bases like  $\text{NaO}t\text{-Bu}$ , and  $\text{DBU}$  (Table 1, entries 3 and 4), 50 and 21% conversion of aniline was obtained with very poor yields of triphenylamine. However, in these cases the yield of diphenylamine was higher or comparable to triphenylamine, even though iodobenzene was used in large excess. With all other bases studied ( $\text{NaOMe}$ ,  $\text{Cs}_2\text{CO}_3$ ,  $\text{KOH}$ ,  $\text{NaHCO}_3$ ) trace amounts of triphenylamine formation were observed.  $\text{KO}t\text{-Bu}$  as a base gave the best results for triarylamine synthesis and further work has been carried out with  $\text{KO}t\text{-Bu}$  as the base. A few aryl halides were screened as substrates and it was observed that aryl iodides gave higher yields

(70–82%) of triphenylamine (Table 2). Activity varies with aryl halides in the order  $\text{I} > \text{Br} > \text{Cl}$ . The highest yield of triarylamine was obtained with *p*-iodoanisole as the reactant (81%; Table 2, entry 4). A few substituted amines were also tested and the catalyst was found to be tolerant of substituents present on the ring except for a nitro group. Higher yields of triarylamine were obtained with the electron donating *p*-methoxy group as a substituent for both aryl halide and aniline as the reactants (Table 2, entries 4, 5 and 7), but the reaction did not proceed with *o*- and *p*-nitroaniline as reactants.

A variety of *N*- or *P*-containing ligands were examined using iodobenzene and aniline as model substrates and  $\text{CuI}$  as a catalyst: with chelating bidentate ligands, higher activity was observed (Table 3). With  $\text{PPh}_3$  as a ligand (1 equiv. to  $\text{Cu}$ , Table 3, entry 1) the reaction did not proceed as observed by Gujadhari et al.<sup>12</sup> Gujadhari et al. observed that the copper complexes  $\text{Cu}(\text{PPh}_3)_3\text{Br}^{12}$  and  $\text{Cu}(\text{PPh}_3)(1,10\text{-phenanthroline})\text{Br}^{13}$  were good amination catalysts. It is possible that  $\text{PPh}_3$  (1 equiv. to  $\text{Cu}$ ) is able to bind at only one site and not able to form an active catalyst. Reaction carried out with a  $\text{PPh}_3:\text{Cu}$  ratio of 3 did result in the formation of **1** 59% in 7 h. This indicates that a ligand: $\text{Cu}$  ratio of 2 or more is required for catalytic activity with  $\text{PPh}_3$  as a ligand. With pyridine or quinoline as a ligand (1 equiv. to  $\text{Cu}$ ) 62 and 38% yields of **1** were obtained, respectively (Table 3, entries 3 and 4). However, with chelating ligands such as 1,3-bis(diphenylphosphino)propane) (DPPP), 2,2'-bipyridine and 8-hydroxyquinoline (1 equiv. to  $\text{Cu}$ ), higher yields of **1** were obtained (Table 3, compare entries 1, 2 with 10, entry 3 with 5 and entry 4 with 7). In a previous report<sup>7</sup> using  $\text{CuCl}$  as a catalyst and  $\text{KOH}$  as a base, rate enhancement was not obtained with 2,2'-bipyridine or 8-hydroxyquinoline as ligands. From the results obtained, it is clear that chelating ligands give improved amination activity with a higher yield of triphenylamine. A series of chelating diphosphines were tested and the best results (89% yield) were obtained with DPPP as a ligand. Activity as well as yield of **1** increased with increase in carbon chain length initially (C1–C3) and decreased with further increase in carbon chain length between the phosphines. It is likely that the ligands (DPPT and DPPH) behave as monodentate ligands leading to lower activity. A similar trend was observed for alkyldiamine ligands (Table 3, entries 13–15). Substituted phenanthroline derivatives were tested as ligands which revealed that best results (yield of 91% in 2 h) were obtained using 1,10-phenanthroline as a ligand. To compare these results with those of the well defined  $\text{Cu}$  complexes, reactions were carried out using  $\text{Cu}(\text{PPh}_3)_3\text{Br}^{12}$  and  $\text{Cu}(\text{PPh}_3)(1,10\text{-phenanthroline})\text{Br}^{13}$  as catalysts. The yield of **1** was substantially lower (44 and 54%, respectively) in these cases. The results obtained clearly show a significant improvement in the yield of **1** with the use of chelating ligands (1 equiv. to  $\text{Cu}$ ) and  $\text{KO}t\text{-Bu}$  as base. Best results were obtained using 1,10-phenanthroline (91% **1** in 2 h) and 2,2'-bipyridine (96% in 3.5 h) as ligands. The higher activity obtained using chelating ligands (1 equiv. to  $\text{Cu}$ ) may

**Table 2.** Copper-catalyzed amination: screening of aryl halides and aryl amines



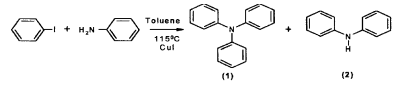
Entry	R	R'	Conv. (%)	Yield (%) <sup>*</sup>	
				1	2
1	H	H	89	70	7
2 <sup>#</sup>	H	H	81	45	12
3 <sup>§</sup>	H	H	57	28	12
4	<i>p</i> -OCH <sub>3</sub>	H	99	81	8
5	H	<i>p</i> -OCH <sub>3</sub>	99	82	12
6	H	<i>o</i> -CH <sub>3</sub>	96	73	15
7	<i>p</i> -OCH <sub>3</sub>	<i>p</i> -OCH <sub>3</sub>	96	79	9
8	<i>p</i> -OCH <sub>3</sub>	<i>o</i> -CH <sub>3</sub>	95	71	14








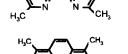
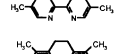

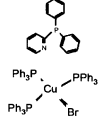

**Reaction conditions:** aryl amine: 4.0 mmol; aryl halide: 12.0 mmol;  $\text{CuI}$ : 0.08 mmol;  $\text{KO}t\text{-Bu}$ : 12.0 mmol; solvent: toluene; temperature:  $135^\circ\text{C}$ ; agitation: 900 rpm; reaction time: 14 h.

<sup>#</sup> Reaction with bromobenzene.

<sup>§</sup> Reaction with chlorobenzene.

\* Isolated yields.

**Table 3.** Copper-catalyzed amination: screening of ligands<sup>§</sup>


Entry	Ligand	Conv. Of Aniline (%)	Yield (%)	
			1	2
1	PPh <sub>3</sub>	-	-	-
2	PPh <sub>3</sub>	17	15	17
		85 <sup>#</sup>	59 <sup>#</sup>	17 <sup>#</sup>
3		84	62	15
4		87	38	22
5		100	95	2
6		100	90	5
7		91	73	13
8	Ph <sub>2</sub> P-CH <sub>2</sub> -PPh <sub>2</sub> (DPPM)	83	30	22
	(DPPM)			
9	Ph <sub>2</sub> P-CH=CH-PPh <sub>2</sub> (DPPE)	86	63	19
10	Ph <sub>2</sub> P-(CH <sub>2</sub> ) <sub>3</sub> -PPh <sub>2</sub> (DPPP)	90	80	6
11	Ph <sub>2</sub> P-(CH <sub>2</sub> ) <sub>5</sub> -PPh <sub>2</sub> (DPPT)	72	36	24
12	Ph <sub>2</sub> P-(CH <sub>2</sub> ) <sub>6</sub> -PPh <sub>2</sub> (DPPH)	40	10	24
13	(CH <sub>3</sub> ) <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -N(CH <sub>3</sub> ) <sub>2</sub>	92	74	8
14	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	88	72	10
15	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-(CH <sub>2</sub> ) <sub>3</sub> -N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	91	58	17
16		98	91	4
17		98	90	3
18		99	90	5
19		89	77	9
20		92	83	6
21		80	44	21
		97 <sup>*</sup>	90 <sup>*</sup>	3 <sup>*</sup>
22		75	54	11

Reaction conditions: iodobenzene: 16.48 mmol; aniline: 7.85 mmol; CuI: 0.28 mmol; ligand: 0.28 mmol; KO<sup>t</sup>-Bu: 23.5 mmol; toluene: 23 ml; time: 3.5 h; temperature: 115°C.

<sup>#</sup> Reaction time: 7 h.

<sup>\*</sup> Reaction time: 5 h.

<sup>§</sup> Analysis by GC.

be due to blocking of adjacent *cis* sites of the Cu catalyst. Thus, coordination of the amine and aryl group from the aryl halide in *cis* mode, may be favorable for the amination reaction.

Lower yields obtained with preformed Cu complexes may be due to non-availability of a vacant site as a result of three sites of coordination. Further work is however, necessary to understand the role of chelating bidentate ligands. A few aryl halides and substituted anilines were screened using CuI-2,2'-bipyridine as a catalyst system (Table 4). In all these reactions an isolated yield of 95% triarylamine was achieved in 3.5 h. This is the first report of the synthesis of triarylamines in a single step with very high yield in a reaction time of 3.5 h at 115°C.

In summary, we have demonstrated for the first time higher yields in ligand-free Cu-catalyzed amination of primary amines to triarylamines. The role of KO<sup>t</sup>-Bu is important in the development of a ligand-free Cu catalyst system. Use of chelating ligands (1 equiv. to Cu) gave triarylamines with high activity and selectivity. Exploration of the future scope and mechanism of this reaction is in progress in our laboratory.

### Experimental procedure

(a) Amination reactions were carried out in a 50 ml capacity high-pressure autoclave (Parr Instruments, USA), toluene used as a solvent (20 ml) was charged to the reactor followed by arylamine (4 mmol), aryl halide (12 mmol), CuI (0.08 mmol) and a base (12 mmol). The reactor was flushed twice with nitrogen to ensure removal of air. The autoclave was then stirred and heated to 135°C and the reaction was continued for 14 h. After cooling to room temperature, the reaction solution was filtered to remove the precipitated base and washed with toluene. The solution was concentrated to obtain the crude product, which was chromatographed to obtain the pure product. The products separated, were characterized by IR and NMR analysis and compared with authentic samples by GC analysis whenever possible.

**Table 4.** CuI-2,2'-bipyridine-catalyzed amination: screening of aryl halides and aryl amines<sup>\*</sup>

Entry	R	R'	Conv. (%)	Yield (%)
1	<i>p</i> -OCH <sub>3</sub>	<i>p</i> -OCH <sub>3</sub>	100	95
2	<i>p</i> -OCH <sub>3</sub>	H	100	95
3	H	<i>p</i> -OCH <sub>3</sub>	100	94
4	H	<i>p</i> -CH <sub>3</sub>	100	95

Reaction conditions: aryl halides: 16.48 mmol; aryl amine: 7.85 mmol; CuI: 0.28 mmol; 2,2'-bipyridine: 0.28 mmol; KO<sup>t</sup>-Bu: 23.5 mmol; toluene: 23 ml; time: 3.5 h; temperature: 115°C.

<sup>\*</sup> Isolated yields.

(b) Experimental procedures were the same for experiments reported in Tables 3 and 4, except that the reactions were carried out at 115°C. These reactions were carried out in a 50 ml round-bottom flask under a nitrogen blanket. Reaction conditions used are given in Tables 3 and 4.

### Acknowledgements

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### References

1. Negwer, M. *Organic-Chemical Drugs and Their Synonyms: An International Survey*, 7th ed.; Academic: Berlin, 1994.
2. MacDiarmid, A. G.; Epstein, A. J. In *Science and Applications of Conducting Polymers*; Salaneck, W. R.; Clark, D. T.; Samuelsen, E. J., Eds.; Hilger: New York, 1991.
3. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146.
4. Wolfe, J. P.; Wagsaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.
5. (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046–2067; (b) Barnano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287–305.
6. Hartwig, J. F. *Synlett* **1996**, *4*, 329–340.
7. Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670–674.
8. Fagan, R. D.; Hauptman, E.; Shaprio, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051.
9. Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.
10. Gauthier, S.; Frechet, J. M. H. *Synthesis* **1987**, 383–385.
11. Hagan, F. D. *Org. Synth. Vol. 1* **1948**, 544.
12. Gujadhur, R.; Venkataraman, D.; Kintig, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791–4793.
13. Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317.
14. Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 139–153.
15. Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2637–2640.
16. Klapars, A.; Antilla, J.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
17. Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803–3805.
18. For palladium prices see <http://www.kitco.com> and for copper see <http://www.metalprices.com>.