Synthesis of triarylamines by copper-catalyzed amination of aryl halides

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Abstract

A simple and efficient methodology for the synthesis of triphenylamine (TPA) in a single step has been demonstrated using copper catalyst with a ligand. The effect of parameters such as catalyst precursors, ligands, bases and solvents on activity and selectivity to triphenylamine were studied at 115 °C. Best results were obtained using 2,6-diphenylpyridine as a ligand (94% yield of TPA).
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1. Introduction

Aryl amines are ubiquitous in numerous fields of chemistry. These are commonly encountered in natural products, pharmaceuticals, xerographic and photographic materials as well as conducting polymers. Based on the important developments by Buchwald et al. [1–4] and Hartwig [5–7], the Pd-catalyzed C–N coupling reaction of aryl halides has recently become the most important method for laboratory scale synthesis of substituted aryl amines. However, copper-mediated coupling is still the reaction of choice for large and industrial scale production of these compounds [8]. Conventionally, triarylamines are produced by Ullmann condensation of aryl iodides and diaryl amines with stoichiometric amount of copper in the form of metal, alloy, Cu(I) or Cu(II) salt. The major drawback of this method is high temperature, sensitivity to catalyst type and low to moderate yield of amines. Bis(arylation) of substituted anilines with two equivalents of aromatic halides to produce triarylamine derivatives has been reported with conventional Ullmann catalyst, however yields are substantially poor [8]. Recently, milder Ullmann-type methodology for N-arylation of aniline [9–12], imidazoles [13], amides [14] and nitrogen heterocycles [15] have been

reported. In our earlier communication we have reported efficient synthesis of triaryl amines using copper catalyst [16]. CuI in the absence of ligand was active for amination reaction with potassium tertiary butoxide (KOt-Bu) as a base at lower temperatures like 135 °C. Use of chelating ligands led to the formation of triarylamine derivatives selectively (95% yield) with high catalytic activity [16]. Looking at the potential application of copper-catalyzed amination reaction, there is a need to develop improved catalyst system. In this paper we report our results on the effect of various parameters such as catalyst precursors, bases, ligands, and solvents on activity and selectivity for amination of iodobenzene with aniline as a model reaction. We also report here for the first time, the use of monodentate N-containing ligands that give high activity and selectivity towards synthesis of triarylamines.

2. Experimental

Amination reactions were carried out in a 50 ml capacity two neck round bottomed flask. In a typical experiment, solvent (23 ml) was charged to the round bottom flask followed by iodobenzene (16.48 mmol), aniline (7.85 mmol), CuI (0.28 mmol), ligand (0.28 mmol), and base (23.5 mmol). The round bottom flask was flushed twice with nitrogen to ensure removal of air. The reaction mixture was then stirred

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by magnetic needle and heated to 115 °C in an oil bath and the reaction was continued for 3.5 h. After cooling to room temperature, the reaction solution was filtered to remove the precipitated base and washed with solvent. Initial and final samples were analyzed by GC using capillary column (Hewlett Packard GC; model HP6890; Column used HP-5: 30 m × 0.32 mm × 0.25 μm).

All solvents and aniline were freshly distilled before use (Sd. Fine chem., India, AR Grade). Iodobenzene and all ligands were purchased from Aldrich Ltd. USA, and were used without any treatment. CuI and bases were purchased from Sd. Fine chem., India and used as such.

3. Results and discussion

The stoichiometric reaction involved in the amination of iodobenzene is shown below:

Triphenylamine (TPA)
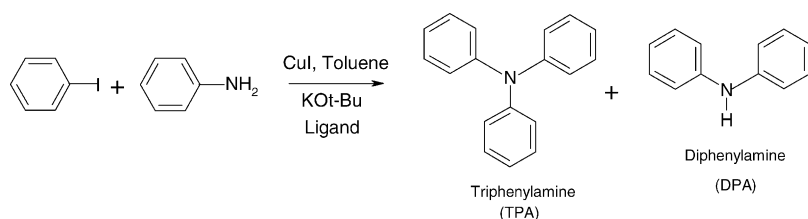
Diphenylamine (DPA)

Mono-amination of iodobenzene gives diphenylamine (DPA) as the product. DPA further reacts with iodobenzene to give triphenylamine (TPA) as the final product. The base used quenches HI formed during the reaction. In order to compare activity and selectivity pattern, effect of various reaction parameters was studied at 115 °C and 3.5 h reaction time, and the results are discussed below.

3.1. Screening of catalyst precursors

Various catalyst precursors were screened using 1,10-phenanthroline and 2,2′-bipyridine as ligands and potassium tertiary butoxide (KOt-Bu) as a base, and the results are presented in Table 1. CuI was found to be the best catalyst pre-

cursor for both the ligands (Table 1, entries 1 and 8). With 1,10-phenanthroline as a ligand, yield of TPA decreased with catalyst precursors in the order: CuI > CuBr ~ CuCl > CuOt-Bu. Activation of amine is proposed to be the first step in the conventional Ullmann condensation reaction [17], and the observed drop in activity may be due to lower activity of other catalyst precursors compared to CuI. Cu(II) salts also gave lower yield of TPA (Table 1, entries. 5, 9 and 10) compared to CuI. Cu(I) compounds are proposed to be active species in the amination reaction and Cu(II) salts used as catalyst precursors have to be reduced to give active Cu(I) intermediate leading to lower catalytic activity and lower yield of TPA. Gujadhur et al. have reported good amination activation using preformed Cu complexes Cu(PPh$_3$)$_3$Br [9] and Cu(PPh$_3$)(1,10-phenanthroline) [9] as catalyst precursors. However, yield of triarylamine was substantially lower for both the reactions under present reaction conditions (44

and 54%, respectively). Lower yield obtained with preformed complexes may be due to coordination of ligands at 3 sites. One of the coordination sites needs to be vacated to obtain high catalytic activity. Thus best results were obtained using CuI as the catalyst precursor and further work was carried out using CuI.

3.2. Screening of bases

Screening of various bases was carried out using 2,2′-bipyridine and 1,10-phenanthroline as ligands (Table 2) and potassium tertiary butoxide (KOt-Bu) was found to give high yield of TPA (Table 2, entries 1 and 5). With 2,2′-bipyridine

Table 1
Copper-catalyzed amination: screening of catalysts

Entry	Catalyst	Reaction time (h)	Conversion of aniline (%)	Triphenylamine		Diphenylamine	
				Sele. (%)	Yield (%)	Sele. (%)	Yield (%)
1	CuI	3.5	98	92	91	2	2
2	CuBr	3.5	83	79	66	22	18
3	CuCl	3.5	85	61	52	35	29
4	CuOt-Bu	5	85	58	49	11	10
5	Cu(II) CO$_3$	3.5	90	71	64	19	17
6	Cu(Phena)(PPh$_3$)Br	3.5	75	72	54	14	11
7	Cu(PPh$_3$)$_3$Br	3.5	80	55	44	26	21
8[a]	CuI	3.5	100	95	95	2	2
9[a]	Cu(II)Br	3.5	90	82	74	9	9
10[a]	Cu(OAC)$_2$	3.5	89	73	56	20	18

Reaction conditions: Iodobenzene: 16.48 mmol; aniline: 7.85 mmol; catalyst: 0.28 mmol; 1,10-phenanthroline: 0.28 mmol.

[a] For these reaction: 2,2′-bipyridine: 0.28 mmol; KOt-Bu: 23.5 mmol; toluene: 23 ml; temperature: 115 °C.
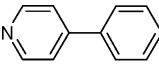
Table 2
Copper-catalyzed amination: screening of bases with ligands

Entry	Base	Ligand	Conversion of aniline (%)	Triphenylamine		Diphenylamine	
				Sele. (%)	Yield (%)	Sele. (%)	Yield (%)
1	KOt-Bu	Bipyridine	100	95	95	2	2
2	NaOt-Bu	Bipyridine	59	22	13	70	41
3	NaOMe	Bipyridine	18	43	8	44	8
4	KOH	Bipyridine	22	19	4	57	13
5	KOt-Bu	1,10-Phenanothroline	98	92	91	2	2
6	KOH	1,10-Phenanothroline	74	47	35	39	29
7	NaOH	1,10-Phenanothroline	18	73	13	6	1

Reaction conditions: Iodobenzene: 16.48 mmol; aniline: 7.85 mmol; CuI: 0.28 mmol; ligand: 0.28 mmol; base: 23.5 mmol; toluene: 23 ml; time: 3.5 h; temperature: 115 °C.

Table 3
Copper-catalyzed amination: screening of ligands
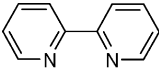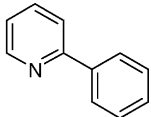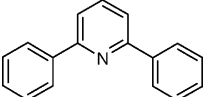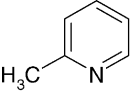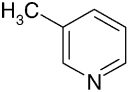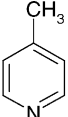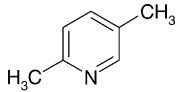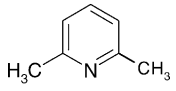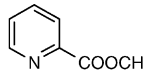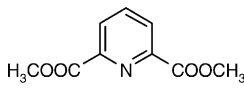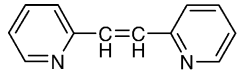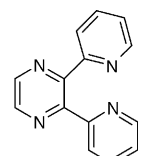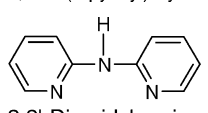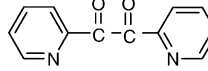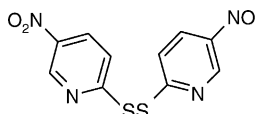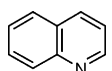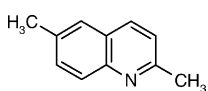
Entry	Ligand	Conversion of aniline (%)	TPA		DPA	
			Sele. (%)	Yield (%)	Sele. (%)	Yield (%)
1	Pyridine	84	69	58	18	15
2	2,2'-bipyridine	100	95	95	2	2
3	2-Phenyl pyridine	100	62	62	15	15
4	4-Phenyl pyridine	91	69	63	17	15
5	2,6-Diphenyl pyridine	100	94	94	1	1
6	2-Picoline	68	76	52	14	10
7	3-Picoline	87	79	69	15	13
8	4-Picoline	89	80	71	7	6

Table 3 (*Continued*)

Entry	Ligand	Conversion of aniline (%)	TPA		DPA	
			Sele. (%)	Yield (%)	Sele. (%)	Yield (%)
9	3,5-Lutidine	91	84	76	9	8
10	2,6-Lutidine	96	88	84	7	61
11	2-acetyl pyridine	91	68	62	7	6
12	2,6 Diacetyl pyridine	99	74	73	13	12
13	2-Chloropyridine	56	59	33	8	5
14	1,2-Bis(2-pyridyl) ethylene	97	85	83	5	5
15	2,3 Bis(2-pyridyl) Pyrazine	89	78	70	15	13
16	2,2'-Dipyridyl amine	76	71	54	19	14
17	2',2'' pyridil	68	63	43	40	27
18	2,2'-Dithiobis(5-nitropyridine)	53	38	20	25	13
19	Quinoline	87	74	62	25	22
20	2,6-Dimethyl quinoline	97	80	78	11	11

Reaction conditions: Iodobenzene: 16.48 mmol; aniline: 7.85 mmol; CuI: 0.28 mmol; ligand: 0.28 mmol; KOt-Bu: 23.5 mmol; toluene: 23 ml; time: 3.5 h; temperature: 115 °C.

as a ligand and bases like sodium tertiary butoxide (NaOt-Bu), sodium methoxide (NaOMe) and potassium hydroxide (KOH) very low yields of TPA were obtained. Lower yields obtained with NaOt-Bu are surprising (compare entries 1 and 2 of Table 2) and it is likely that the role of base is complex in nature. With KOH as a base very poor activity was obtained for 2,2′-bipyridine as a ligand compared to 1,10-phenanthroiline (compare entries 4 and 6 of Table 2). Goodbrand and Hu [8] have also obtained similar results, indicating that ligand solubility, metal binding affinity, ligand π/σ acceptor capability and bond angle, etc. and also the base used, are important factors for catalytic activity [8]. With other bases screened (sodium bicarbonate, 1,8 diazabicyclo [5.4.0] undec-7-ene, potassium diacetate, triethyl amine, cesium carbonate, N,N-dimethyl benzylamine, 1,4-biazabicyclo (2.2.2) octane and 1,5-diazabicyclo (4.3.0) non-5-ene) very poor results were obtained. Further work was carried out using KOt-Bu as a base.

3.3. Screening of ligands

Screening of various ligands was carried out using CuI as the catalyst precursor and KOt-Bu as a base (Table 3). As reported earlier [16] Pyridine gives 58% yield of TPA while bidentate ligand (2,2′-bipyridine) gives complete conversion of aniline with 95% yield of TPA (Table 3, entries 1 and 2). Various substituted pyridines were screened and it was observed that electron-donating groups (methyl, phenyl and carboxylate) led to increase in catalytic activity. Thus with 2-phenyl pyridine and 4-phenyl pyridine 62 and 63% yield of TPA was obtained respectively, while with 2,6-diphenyl pyridine complete conversion of aniline with 94% yield of TPA was obtained (Table 3, entries 3–5). Similar trend was observed with methyl and acetyl groups on the pyridine ring (Table 3, entries 6–12). With electron withdrawing group like Cl (2-chloropyridine, Table 3, entry 13), low yield (33%) of TPA was obtained. For other ligands (Table 3, entries 14–17) the yield of TPA was obtained in a range of 43–83%. Lower yields may be due to substituents between the pyridine rings and change in bond angle. For 2,2′-dithiobis(5-nitropyridine) poor yield of TPA (20%) was obtained due to electron withdrawing nitro group as well as thio bridge between the pyri-

dine rings. With 2,6-dimethyl quinoline 78% yield of TPA was obtained which is better than 61% obtained with quinoline as a ligand (Table 3, entries 19 and 20). The present work has shown that activity of the catalyst can be improved by using pyridine-based ligands with electron donating substituents and best results were obtained with 2,6-diphenyl pyridine as a ligand (94% yield of TPA). The increase in yield may be due to electron donating groups on the pyridine ring as well as steric effects. This is the first report on the use of monodentate N-containing ligands, for amination with high activity and selectivity for the synthesis of TPA.

3.4. Screening of solvents

Various solvents were screened using CuI/2,2′-bipyridine as a catalyst system (Table 4) and best results were obtained with toluene as a solvent. Reactions were carried out at 115 °C for toluene and N,N′-dimethyl formamide as solvents (Table 4, entry 1 and 5), for other solvents reactions were carried out at reflux temperatures. Low yields of TPA were obtained with polar solvents like N,N′-dimethyl formamide, tetrahydrofuran and non-polar solvents like cyclohexane. The formation of benzene (∼5%) by reduction of iodobenzene was also observed for cylcohexane and DMF solvents. For Pd-catalyzed amination also, very poor results were obtained using polar solvents like NMP and significant formation of arenes by reduction of aryl iodides was observed [18]. Solvents can be arranged in decreasing order of TPA yield as: toluene > 1,4-dioxane > acetonitrile>N,N′-dimethylformamide > 2-methyl-propane-2-ol > tetrahydrofuran > cyclohexane. Thus less polar solvents like toluene are suitable for copper-catalyzed amination reaction.

The mechanism for Cu catalyzed Ullmann condensation reaction with KOH as a base is shown below: [17]

$$Ph_2N^- + CuI_{(insol)} \xrightarrow{fast;irreversible} Ph_2NCu + I^-$$

$$Ph_2NCu + PhI \rightarrow Ph_3N + CuI$$
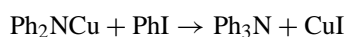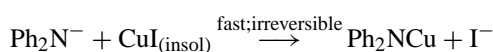
Thus the first step in the catalytic cycle is activation of amine by Cu catalyst. CuI was found to be the best catalyst precursor, indicating that activation of aniline is facile with

Table 4
Copper-catalyzed amination: screening of solvents

Entry	Solvent	Conversion of aniline (%)	TPA		DPA	
			Sele. (%)	Yield (%)	Sele. (%)	Yield (%)
1	Toluene	99	95	94	2	2
2	1,4-Dioxane	84	63	53	20	17
3	Acetonitrile	47	30	14	61	29
4	2-Methyl-propane-2-ol	34	24	8	50	17
5	N,N′-Dimethyl formamide	60	15	9	68	41
6	Tetrahydrofuran	52	6	3	50	26
7	Cyclohexane	30	6	2	24	7

Reaction conditions: Iodobenzene: 16.48 mmol; aniline: 7.85 mmol; CuI: 0.28 mmol; 2,2′-bipyridine: 0.28 mmol; KOt-Bu: 23.5 mmol; Solvent: 23 ml; time: 3.5 h; temperature: 115 °C (reflux temperature for low boiling solvents, entries 2–4, 6 and 7).

CuI. As reported previously [16] chelating bidentate ligands enhance catalytic activity significantly. In the present work we have found that electron-donating groups like methyl, phenyl attached to pyridine enhance catalytic activity considerably. With ligated Cu complex, activation of amine and elimination of iodide may be fast leading to higher activity observed. During screening of bases, very high TPA formation was observed with KOt-Bu as a base compared to NaOt-Bu. Potassium tertiary butoxide and sodium tertiary butoxide, both are strong bases and different activities are not expected. Further work is necessary to understand the exact role of KOt-Bu in improving the catalytic activity.

4. Conclusion

Amination of iodobenzene with aniline has been investigated using Cu catalyst. Catalytic activity and yield of triphenyl amine is influenced by the type of catalyst precursor, nature of ligand, type of base and solvent used. Catalyst system comprising of CuI as the catalyst precursor, 2,6-diphenylpyridine as a ligand, KOt-Bu as a base and toluene as a solvent gave good activity and selectivity (yield 94%) to triphenylamine. This is the first report on the use of monodentate N-containing ligands for Cu-catalyzed amination, with high activity and selectivity to TPA. Results obtained are mainly due to electronic as well as the steric effects of the ligand. Detailed investigations are in progress in our laboratory.

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