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COMMUNICATION

D-Glucosamine as a green ligand for copper catalyzed synthesis of primary aryl amines from aryl halides and ammonia[†]

Krishna Gopal Thakur, Dhandapani Ganapathy and Govindasamy Sekar*

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Replacing conventional reagents with environment friendly reagents is one of the primary goals of modern synthetic methodology and in this very primitive study about utilizing green, naturally available carbohydrate molecules as ligands in transition metal catalyzed reactions, we report Cu/D-glucosamine as an efficient catalyst for aniline synthesis.

Carbohydrates are one of the most naturally abundant organic molecules. They are available in nature mainly as disaccharides and polysaccharides. Many natural products as well as molecules of high biological, medicinal and material importance are synthesized from monosaccharide precursors.¹ Organic chemistry is enriched with an enormous number of successful utilization of carbohydrates in many technically important fields such as asymmetric induction in a reaction using carbohydrate derivatives as chiral auxiliaries.² Many phosphorus, nitrogen, oxygen and sulfur based ligands with carbohydrate backbone have been successfully utilized in a variety of asymmetric reactions.² In spite of the high potential, the direct use of monosaccharide molecules as ligands is highly limited. The very cheap, especially high environmental friendly nature of monosaccharide molecules has driven us to explore their capabilities as ligands in transition metal catalyzed reactions.

We started our study with D-glucose as a ligand for coppercatalyzed primary aryl amine formation reaction from aryl halides and ammonia through coupling reaction. Since ammonia is the most abundant amine source, it has been selected as the nitrogen source for this reaction. In the last decade, a lot of work has been done on primary aryl amine synthesis from aromatic halides through coupling reaction methodologies, mostly using palladium³ and copper^{4,5} as catalyzing metals. For palladium catalyzed reactions, in 2006, Hartwig and co-workers for the first time reported aniline formation from aryl halides and ammonia using ferrocene based phosphine ligands.^{3a} Although having high substrate scopes, these methods often suffer from appreciable amounts of secondary and tertiary amine formation as by-product even if there is a little

Fax: +91 44 2257 4202; Tel: +91 44 2257 4229



Scheme 1 Copper catalyzed aniline synthesis.

deviation from the exact reaction condition.^{3a,b,d} Later on, even though additional methodologies have been reported using palladium,^{3b-d} di-arylation persisted as the major problem in many cases; may be because of the hyper catalytic activity of palladium which reduces the selectivity. The problem has been substantially solved^{3c} using less reactive substrates (by means of electronic, steric or leaving group ability factors) wherein the selectivity is more. In recent years, copper has started enjoying much attention not only because of its very low cost as compared to palladium but also due to its compatibility with much cheaper, stable oxygen and nitrogen based donor ligands as compared to unstable, high cost phosphine ligands (Scheme 1). While starting with copper, numerous reports came during the last decade, especially in the last two years on amine synthesis from aryl halides using either direct⁴ or indirect amine sources.⁵ The major problem with indirect methods is the requirement of multistep process and thus suffers from low atom economy. In 2001, Lang reported copper catalyzed amination of some heterocyclic aromatic halides using ammonia at 100 °C wherein, ethylene glycol served the purpose of solvent as well as ligand. Later on many improvements have been encountered in this reaction, especially during last two years. However, only a few of these provided successful generalized method for aniline synthesis using aqueous ammonia.⁴ But these methods often suffer from the requirement of higher temperature, environmentally hazardous aliphatic acid solvent system and ligands. During the course of our reaction, Zhao and Wan separately reported efficient methods for primary aryl amine formation from aryl halides. They covered various classes of substrates that undergo the reaction. The high reaction temperature, usage of very high equivalence of ammonia (40 equivalents) and synthetic ligand make the former protocol less attractive whereas high loading of synthetic ligand and usage of huge amounts of quaternary ammonium salt (50 mol%) make the latter one less attractive especially for large scale reactions. So, there is still a requirement to develop a methodology using low catalyst loading, cheaper, environment friendly catalyst and solvent system.

Department of Chemistry, Indian Institute of Technology Madras, Chennai, 600 036, India. E-mail: gsekar@iitm.ac.in; Fax: + 01 44 2257 4200; Tal: + 01 44 2257 4200

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Fig. 1 Optimization and comparison of reactivity between monosaccharide ligands and conventional ligands.

As part of our ongoing research towards the development of eco-friendly organic transformations, we recently reported aerobic oxidation methodologies for various alcohols.⁶ In a parallel research, we developed various copper catalyzed carbon-carbon and carbon-heteroatom bond forming reactions.7 In this communication, we report our initial finding about D-glucosamine/CuI complex catalyzed aryl amine formation using aq. NH₃ as the amine source. This procedure is very simple, economic and environmentally friendly. D-Glucosamine is one of the most naturally abundant molecules. It is present in the exoskeleton of several arthropods, in the cell wall and bones of higher organisms.

We started our preliminary study with CuI as copper source and D-glucose L1 (Fig. 1) as ligand in acetone/ H_2O (1:1) mixture as solvent system for the coupling of 4-iodoanisole and ammonia. In the very first reaction, we obtained 65% isolated yield of the product. This encouraged us to continue the screening using other monosaccharide molecules as ligands. Some of the very well known conventional ligands were also used for coupling reactions for a better comparison and understanding. The results have been shown in Fig. 1. We found that D-glucosamine L5 as ligand performs the best by providing a maximum of 90% yield for the product 4-methoxyaniline. Upon considering reactions with carbohydrate based ligands, many of them outperformed some well known conventional ligands in coupling chemistry. Then the reaction was carried out without ligand L5 using 10 mol% of CuI and the coupling reaction provided only 9% of product 4-methoxy aniline after 24 h at 90 °C. This result clearly shows that ligand L5 is necessary for the best performance of the coupling reaction. Then we carried out copper salt screening for better performance of the reaction and CuI has been found as the best copper salt with L5 for this coupling reaction (Fig. 2).

We also screened several organic solvent/H₂O (1:1) mixtures, bases and various temperatures for this reaction.⁸ It has been found that acetone/H₂O performed most efficiently as solvent system among the various solvent mixtures screened, whereas K_2CO_3 is the best base among the several bases screened. All the bases, either milder like NaOAc or stronger like NaOMe, compared to K₂CO₃ provided lesser yield of the product aniline. While checking the minimum requirement of catalyst



Fig. 2 Optimization of copper salts.

Table 1 CuI-L5 catalyzed reaction between various aryl halides and aq. ammonia

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3

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8

9



Table 1 (continued)

Entry	Aryl halide	Time (h)	Product	Yield (%) ^a
15	Ph I	30	$\overset{NO_2}{\underset{H_2N}{\overset{NO_2}}{\overset{NO_2}}{\overset{NO_2}{\overset{NO_2}}{\overset{NO_2}}{\overset{NO_2}}{\overset{NO_2}}{\overset{NO_2}}{\overset{NO_2}}}{\overset{NO_2}{\overset{NO_2}}{\overset{NO_2}}{\overset{NO_2}}{\overset{NO_2}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}$	50
16	H ₃ C	26	H ₃ C-	68
17		30	\rightarrow H_2N	70
18	o Br	30	NH ₂	62
19	Br NO ₂	24	NH ₂ NO ₂	83
20	Br	28	H ₂ N MeO	78
21		30		60

^{*a*} Isolated yield. Reaction was performed in 0.5 mmol scale of aryl halide.

loading for the best performance of the reaction, it has been found that 10 mol% of CuI/L5 is the optimal catalyst requirement. On either decreasing or increasing the catalyst loading, the yield of the product got affected. Surprisingly, when the catalyst loading is as high as 20 mol%, the product yield was drastically reduced to 49%. When the reaction was performed at 60 °C and 80 °C, the reaction was found to be inefficient. At 60 °C, even after 48 h the product yield was only 41% whereas at 80 °C 62% of product amine was formed. While trying the reaction using only water as solvent, only 9% product was obtained. However, aniline formation was increased to 20% when 0.5 equivalent of ⁿ-Bu₄NBr bromide was used as phase transfer catalyst. The further optimization of the reaction in water medium using phase transfer catalyst has not been carried out because acetone is more compatible with environment than ammonium salts. Moreover use of a huge amount of additives is not encouraged especially for bulk scale synthesis.

After optimizing all parameters such as ligand, Cu-salt, solvent, base, catalyst loading and reaction temperature, we initiated our investigation into the scope of the D-glucosamine L5-CuI catalyzed amination of several aryl halides and the results are summarized in Table 1. Various aryl iodides and aryl bromides provided good to excellent yield of the products. Activated aryl iodides (entries 2, 9, 10, 12 and 13), as well as deactivated aryl iodides (entries 3, 5, 6 and 16) with electron-donating groups provided good to excellent yields of the products. Activated aryl bromides (entries 1, 8, 18–19) and deactivated aryl bromides both (entries 4,7 and 20) provided high yields of the corresponding primary amines. Both the iodo and bromo substrates with sterically bulky *ortho* substitution (entries 5, 14, 15, 17, 19 and 20) also performed

very well towards the reaction. Many base sensitive carbonyl groups were well survived within the course of reaction. Herein, for the first time we have reported the amination of some aryl iodides (entries 12–15, and 17) which contain ketone group as substitution, among these, all *ortho*-amino ketones (entries 14–15 and 17) have high potential to be used as precursor for various inhibitor synthesis.⁹ It is very important to mention that the water soluble ligand **L5** along with copper can be easily removed from product aniline by simple water workup process. However, along with ligand **L5**, inorganic components such as K_2CO_3 , KI and copper are also water soluble and making the recovery of ligand **L5** in pure form difficult.

In conclusion, we have developed an efficient and environmentally friendly catalytic system which can convert various aryl halides to corresponding primary aryl amines in the presence of aqueous ammonia. The solvent $acetone/H_2O$ mixture is also green in nature. The catalyst is the cheapest among the various reports available in literature and contains naturally available chiral ligand. This can open a new scope for enantioselective synthesis of various important optically active amines as well as kinetic resolution of various optically active aryl halides in one of the most economic ways.

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