

## One-Pot Catalyzed Synthesis of Arylamines

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Primary arylamines are important compounds and intermediates in the synthesis of pharmaceutical entities and other molecules used as pigments, dyes, agrochemicals and cosmetics. Arylamines are classically synthesized by amination reaction from the corresponding aryl halides through the aryne route. Ammonia is the nucleophile often used in the reaction. Ammonia is a low cost reagent that is still one of the most important nitrogen sources in Organic Chemistry. The major drawbacks of this type of reaction are the drastic conditions –high temperature and high pressure–that are usually needed, as well as the instability of the aryne intermediates. In addition, it was found that several functional groups are not tolerated in the starting material due to the drastic amination conditions (specially the elevated temperature and the concentrated ammonia). Due to these difficulties, the classic reaction has suffered numerous changes, mainly related to the recent developments of the transition metal catalysis. In recent years, palladium- or copper-catalyzed coupling of aryl halides with ammonia or ammonia surrogates were the utmost described reactions to afford the respective amines. Palladium catalysis is described to be an expensive and a non-clean process, since some products may be contaminated by it. Although improvements in the reaction conditions have been ascribed to these methodologies, an ideal method is still needed. To surpass the mentioned problems, ammonia surrogates like benzophenone imine, allylamines and lithium bis(trimethylsilyl) amine have been used. The protection of the nitrogen group was found to be a very important step for the optimization of the reaction. Therefore, in recent studies, ammonia was substituted for the crystalline 2,2,2-trifluoroacetamide. The ammonia surrogate has proven to be satisfactorily active in the C-N catalyzed cross-coupling reaction. The trifluoroacetic acid formed during the reaction is eliminated under soft conditions with a mixture methanol/water. The presence of  $K_2CO_3$  in the medium allows promoting the trifluoroacetic hydrolysis when the water is added. After removing the protective group, the arylamine is then obtained. Primary aromatic amines have successfully obtained by economically efficient C-N cross-coupling reactions using this new ammonia surrogate and Cu-catalyzed approach.

Comparing with other methodologies, the synthetic route herein described is efficient, clean, one-pot and less expensive. From previous studies, it was concluded that N,N'-dimethylethylenediamine (DMEDA) was the best ligand. Under these conditions, a temperature of 75 °C and CuI/DMEDA catalytic system were found to be proficient to promote the reaction. The one-pot methodology is found to be versatile, efficient and can proceed without the isolation of the unstable intermediate entities. Several compounds can be prepared from the corresponding aryl halides by one-pot Cu-catalyzed cross-coupling reaction with  $K_2CO_3$ , 2,2,2-trifluoroacetamide and DMEDA, using dioxane as solvent, at 75 °C.

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