Review Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

A REVIEW ON SYNTHESIS OF BIOLOGICALLY AND PHARMACOLOGICALLY ACTIVE N - ARYLAMINES

Ashok A. Patil*[1] and Pritesh R. Jain[1]

[1*]Department of Chemistry, JET's Z.B. Patil College, Dhule - 424002, Maharashtra, India.

ABSTRACT

The N- arylamines and its derivatives are an important class of organic and heterocyclic compounds. The chemistry of these compounds revised day by day because these are one of the most useful medicinal pharmacophore which appears as an important structural part in many naturally occurring and synthetically prepared medicinal drugs and heterocyclic compounds. Literature survey reveals that in the last few decades many chemists and researchers are engaged in the synthesis of various types N- arylamines by using various methods as they are having great biological and pharmacological activities.

KEYWORDS

Synthesis of N- arylamines, Ullmann reaction and Buchwald - Hartwig amination.

Author for Correspondence:

Ashok A Patil,

Department of Chemistry,

JET's Z.B. Patil College,

Dhule, Maharashtra, India.

Email: patilashok567@gmail.com

INTRODUCTON

The N-arylation of aliphatic and aromatic amines is presently dynamic research area in organic synthesis due to its wide range of applications. Due to extensive applications of N- arylamines, several methodologies for the C-N bond formation have emerged in last decades. Still the formation of C-N bond is of significant importance and major challenge for organic chemist and researchers. These N- arylamines have found applications in the synthesis of variety of biologically active pharmacophore, agrochemicals, HIV-1-protease inhibitors, in material science[1,2] and important building block of many natural products[3]. They also have broad applications as pharmaceuticals[4],

materials for organic electronics[5] and dyes[6]. The N-arylated piperazine and morpholine derivatives are found in many important pharmaceuticals as shown in Figure No.1.

To synthesize C–N bonds traditional nucleophilic substitution[7], addition to benzyne[8], electrophilic nitration[9] and reductive amination[10] are commonly used synthetic routes. Recently, C-H bond activation has also proved efficient for N-arylation of amines[11].

Generally, three important methods have been used for C-N coupling reactions namely, Ullmann coupling reaction[12], Buchwald- Hartwig amination[13] and Chan-Lam coupling[14] as shown in Scheme No.1.

Transition metal catalyzed cross-coupling reactions have provided a wide range of N- arylamines as intermediates for pharmaceutically and biologically active compounds therefore many transition metal catalyzed reactions have been developed for the formal halide to nitrogen substitution on aryl halides.

Ullmann coupling involves the coupling of amines with aryl halides in the presence of Cu (I) source[15]. Conversely, this method suffers from certain drawbacks, such as harsh reaction conditions, high temperature, moderate yield, use of stochiometric amount of copper reagent and formation of byproducts. In order to avoid these drawbacks, use of copper (I) salts with several ligands such as 1, 10-phenanthroline[16], L-proline[17], (±)-trans-1, 2-cyclohexyldiamine[18] etc was introduced. However, none of the modification could tackle the problems of high temperature and prolong reaction time.

In view of these drawbacks, Buchwald and Hartwig developed a new protocol for the coupling of amines with aryl halides for C-N bond formation in the presence of catalytic amount of Pd (II)[19]. Although palladium compounds was used with spectacular success as catalysts for C-N bond formation, this catalysts was unable to catalyze the coupling reaction of an electron rich or o-substituted aryl halides with aromatic amines. The success of this transformation have been achieved with the use of appropriately-tuned ancillary ligands which allow more challenging substrates to be applicable in this aromatic C–N bond formation process[20]. Due to the high efficacy and good substrate spectrum Buchwald–Hartwig amination has received the most attention in this arena.

Chan and Lam in 1998, reported a new method for C-N bond formation by the arylation of amines with arylboronic acid at room temperature in the presence of Cu (II) source[21]. This protocol has several advantages over the traditional Copper-catalyzed Ullmann coupling reaction and Pd-catalyzed Buchwald-Hartwig amination. It involves mild reaction conditions and use of weak bases. The low toxicity, high thermal stability and structural diversity of arylboronic acid were found to be inborn advantages over the use of aryl halides. This method also did not require any ligands. After that, the method has been modified by the use of various additives.

LITERATURE REVIEW

In the last two decades, many transition metals have been reported to efficiently promote the C-N coupling between aryl halides and amines. Along with this many other methodologies were also developed in which bases are used to form C-N coupling in absence of transition metals.

Recently, Utpal Bora *et al* developed a Cu (II)-Salen type complex for the N-arylation of anilines and imidazole with arylboronic acids at room temperature in water and isopropyl alcohol respectively to form products in excellent yields[22] as shown in Scheme No.2.

However, this method is homogeneous in nature, where an efficient separation and subsequent recycling of the homogeneous catalyst remains a challenge and an economic concern. Therefore heterogeneous catalysis is of importance in chemistry due to easy separable and can be reused several times. The organoboron reagents have advantage of relative stability under air and moisture conditions, commercial availability, good functional group compatibility, low toxicity, and ease of synthesis.

Anuradha, Shweta Kumari and Devendra D. Pathak reported the novel heterogeneous catalyst for C-N coupling reactions of amines with arylboronic acid

under milder reaction conditions[23]. They synthesized and developed Chitosan anchored Copper (II) Schiff base complexes (C_4, C_5 and C_6) Figure No.2 as heterogeneous catalyst for N-arylation reaction. In presence of this catalyst reaction of various aliphatic or aromatic amines and derivatives of phenylboronic acid in solvent acetonitrile and base K_2CO_3 to form N- arylamines as shown in Scheme No.3. This heterogeneous catalyst can easily removed by filtration from the reaction mixture and washed with diethyl ether to use up to several times with no significant loss of catalytic activity.

A substitute to such a conversion is the use of organogermane, which eliminates the purification difficulties associated with organoboron reagents. Qiang Zhang, Lingxia Jin *et al* described first time a mild palladium- catalyzed N-arylation reaction of amines and amides via $ArGeMe_3$[24]. The catalytic system provides N-arylation products in moderate to excellent yields in the presence of monodentate phosphine ligand Ph_3P, base NaOAc and toluene as shown in Scheme No.4. The reactions have a wide scope of substrate including amides, primary and secondary or aliphatic and aromatic amines, and provide plausible opportunities in the N-arylation of nitrogen-containing compounds. In the beginning, an aryltrimethylgermane compound was synthesized via the corresponding bromobenzene through Grignard reaction.

Raymond Wai-Yin Sun, Fuk Yee Kwong and Co-workers developed Pd/CM-phos catalyst systems which promote the cross-coupling between N-nucleophiles (arylamines, primary and secondary aliphatic amines, cyclic and acyclic amines and N-heterocycles) and aryl tosylates[25] to afford various N- arylamines as shown in Scheme No.5.

Cheng-Pan Zhang *et al* developed a simple and efficient method for transition metal-free N-arylation of various amines by triarylsulfonium triflates at 80^{o}C in the presence of t-BuOK or KOH as base[26]. N-arylation of amines (aliphatic and aromatic amines including primary and secondary) with triarylsulfonium triflates as arylating agent and t-BuOK or KOH as a base readily transformed to gave corresponding N-arylated products in good to high yields under mild reaction conditions as shown in Scheme No.6. Triarylsulfonium salts have several advantages such as non-volatility, easy preparation, non-toxicity, moderate reactivity, and broad structural diversity.

Berit Olofsson and Co-workers reported an efficient, metal-free N-arylation of aliphatic amines with diaryliodonium salts under mild reaction conditions without excess reagents[27]. The method is applicable to primary amines, secondary cyclic and acyclic amines having a variety of functional groups. Electron-deficient and electron donating aryl groups, as well as heteroaryl groups can be transferred. The diaryliodonium salt and Na_2CO_3 flushed with argon then amine was added followed by anhydrous and degassed toluene and the mixture was stirred at 110^{o}C for appropriate time to afford the various N- arylamines as a product as shown in Scheme No.7.

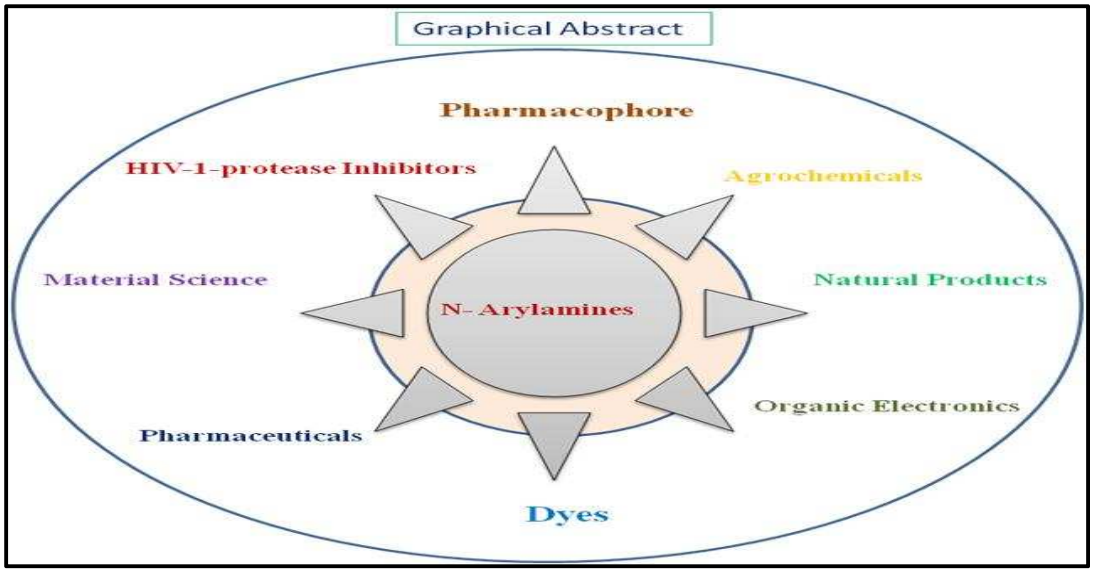
Christian Borch Jacobsen, Morten Meldal and Frederik Diness[28] developed a novel method for the N-arylation of aliphatic amines with unactivated fluorobenzene derivatives proceed readily by addition of a simple base LiHMDS as shown in Scheme No.8. The ability of the applied base to deprotonate the amine to generate the nucleophile without simultaneously degrading the electrophile fluorobenzene thus avoids the need for transition metals. The products are obtained with high regio- and chemoselectivity and the reactions are compatible with a broad range of additional substituents including alkyl, aryl, alkoxy, amine, azolyl, thioethers, fluorine and chlorine.

Ali Reza Sardarian, Hassan Eslahi and Mohsen Esmaeilpour carried out N- arylation of amines and N (H)-heterocycles by using Copper (II) complex supportesd on Fe_3O_4@SiO_2 coated by polyvinyl alcohol as reusable naoncatalyst[29]. The N- arylation of nitrogen heterocycle and alkyl amines with aryl halide in the presence of Fe_3O_4@SiO_2-TCT-PVA-Cu(II) as a catalyst, *t*-BuONa base and DMF at 100^{o}C to afford desired products in higher yields as shown in Scheme No.9.

APPLICATIONS

N- Arylamines has various applications over biologically activities.

1. Pharmacophore
2. Agrochemicals
3. HIV-1-protease inhibitors
4. Important building block of many natural products
5. They also have broad applications as pharmaceuticals
6. Materials for organic electronics
7. Dyes



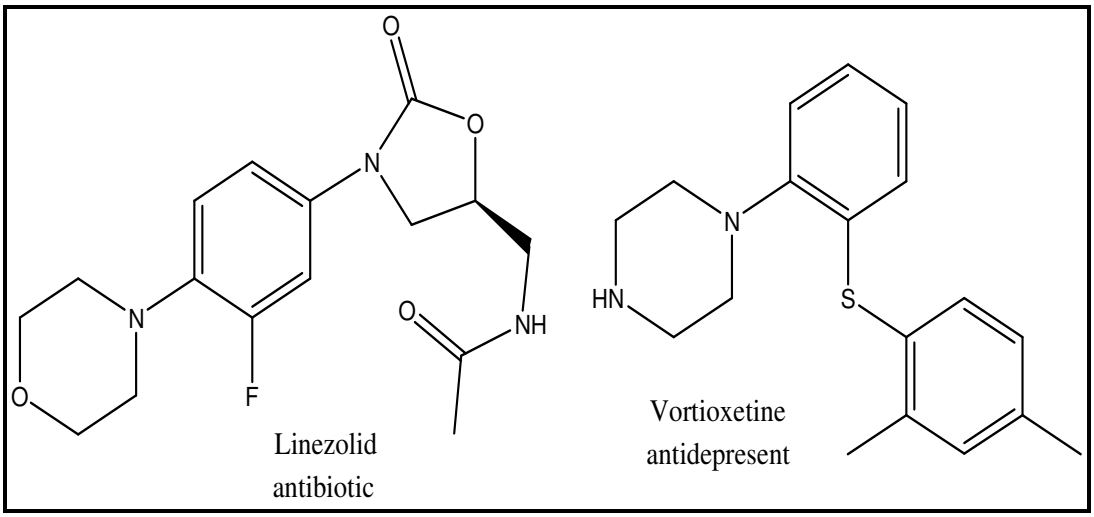


Figure No.1: Pharmaceutical drugs containing Piperazine and Morpholine

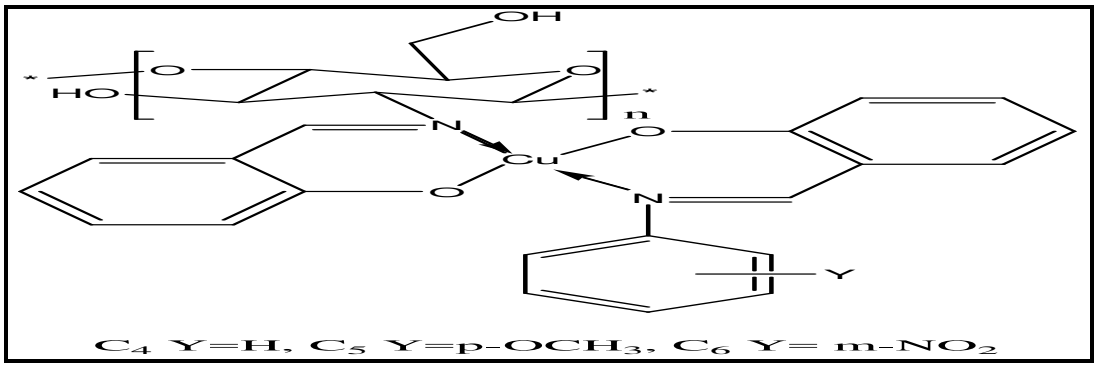
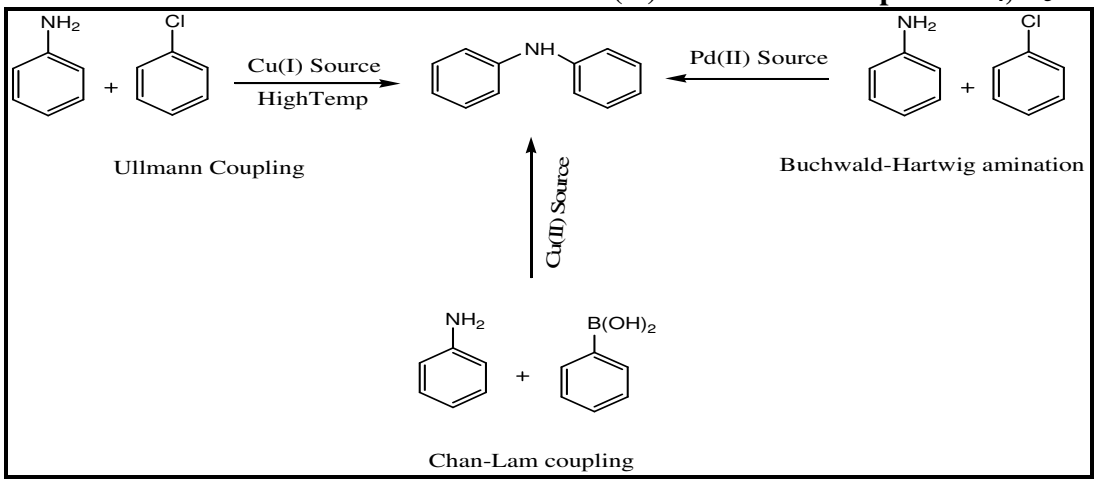
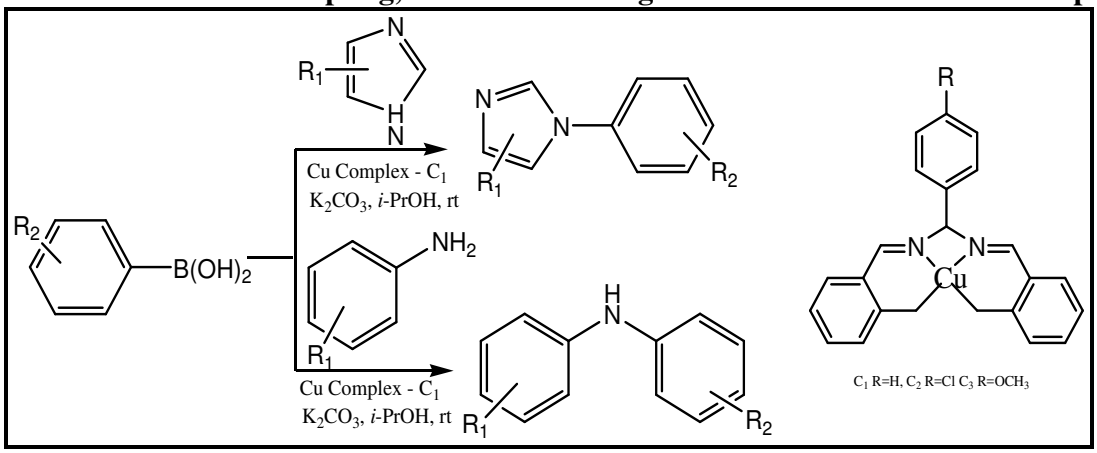


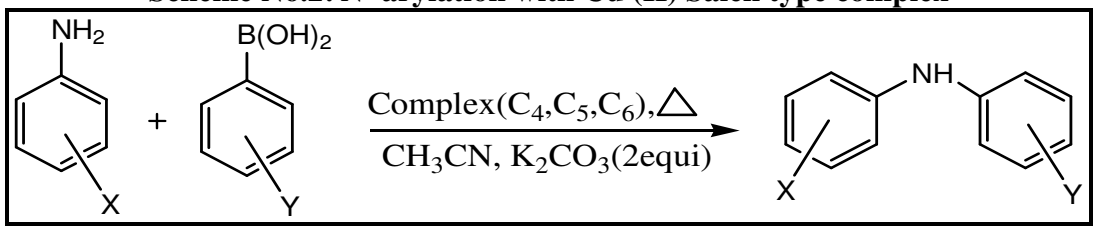
Figure No.2: Structure of Chitosan anchored Cu (II) Schiff base complexes C_4, C_5 and C_6



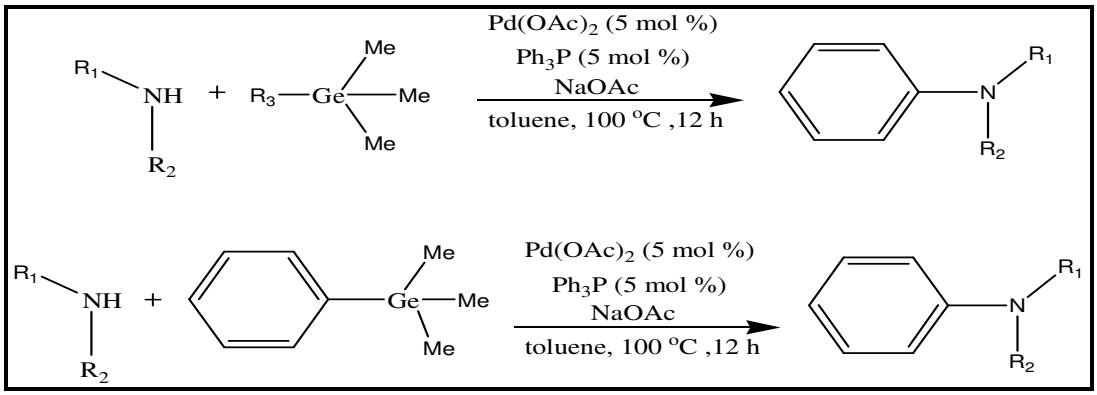
Scheme No.1: Ullmann coupling, Buchwal-Hartwig amination and Chan-Lam coupling



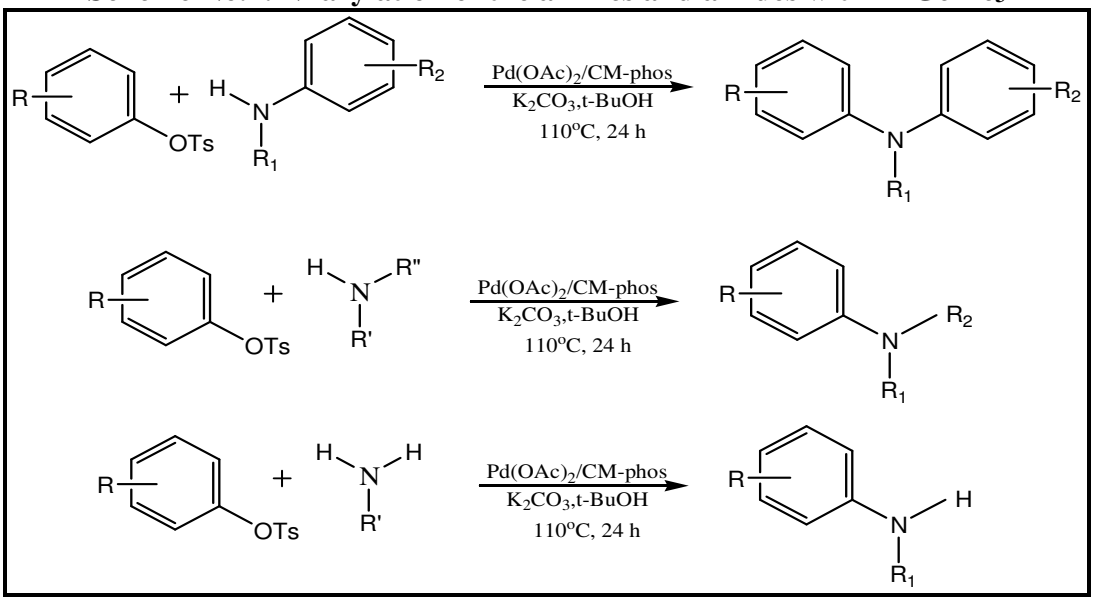
Scheme No.2: N- arylation with Cu (II) Salen type complex



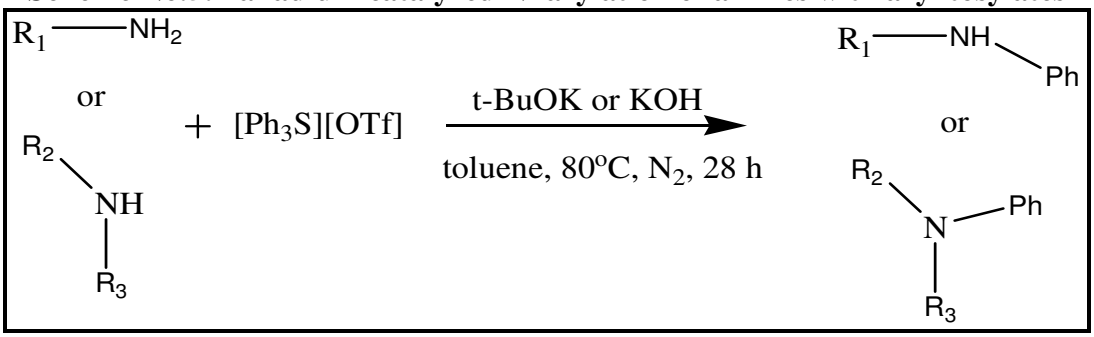
Scheme No.3: Synthesis of N- arylamines by different aryl boronic acids in the presence of base and catalyst



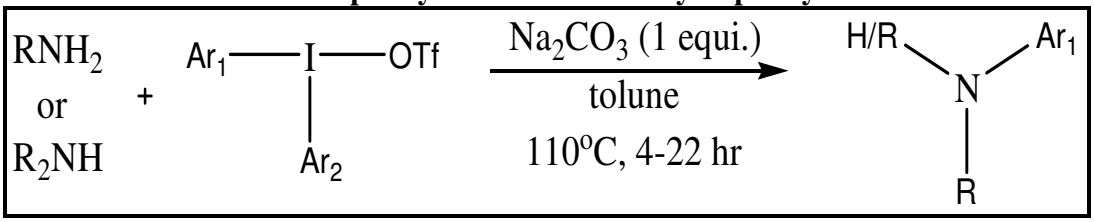
Scheme No.4: N- arylation of the amines and amides with $PhGeMe_3$



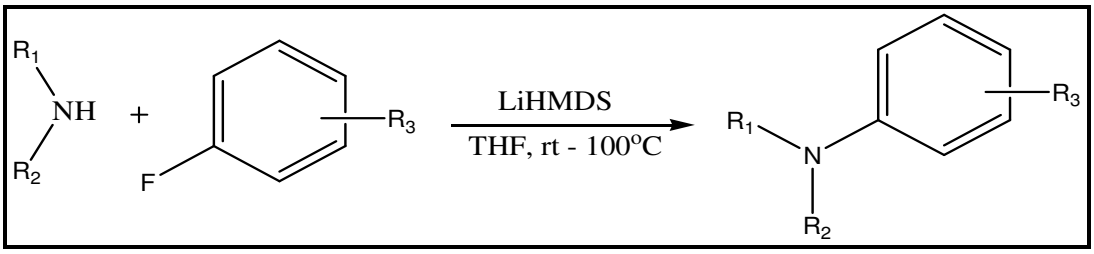
Scheme No.5: Palladium catalyzed N- arylation of amines with aryl tosylates



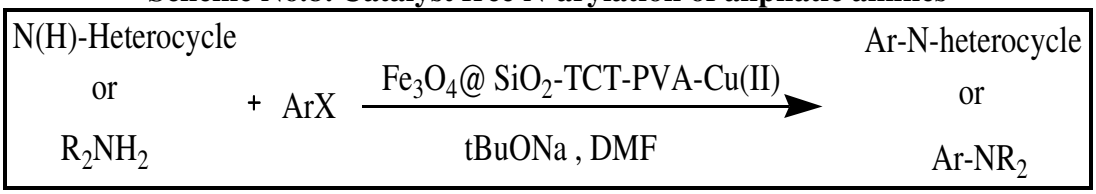
Scheme No.6: Mono N- phenylation of amines by triphenylsulfonium triflate



Scheme No.7: Metal free N- arylation of amines



Scheme No.8: Catalyst free N-arylation of aliphatic amines



Scheme No.9: Fe_3O_4@SiO_2-TCT-PVA-Cu (II) catalyzed N-arylation of N- heterocycle and alkylamines with aryl halide

CONCLUSION

In summary, we enlist the simple, efficient methods for the synthesis of various N- arylamines and its derivatives using Copper and Palladium mediated catalyst, various bases and nanoparticles as a catalyst. In last few years literature survey showed that fast growing importance towards synthesis of N-arylamines due to its ability to show important biological and pharmacological activities. The use of transition metals as catalysts associated with several disadvantages such as high costs, toxicity, need for substrate-dependent designer ligands and challenging purifications which led to an increased focus on the development of metal-free methodologies for C-N bond formation reaction. These methods offers an advantage of less reaction time, solvent free, mild reaction conditions, recyclable catalyst, economical, use of inexpensive starting material and simple workup and gives good to excellent yields of product.

ACKNOWLEDGEMENT

We great fully acknowledge Chairman, All the managing Directors and Principal JET's Z. B. Patil College, Dhule for providing lab facilities, constant encouragement and useful suggestions.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. (a) Shirota Y, *J.* Organic materials for electronic and optoelectronic devices, *Mater Chem*, 10, 2000, 1-25. (b) Goodson F E, Hartwig J F. Regiodefined Poly(N-arylaniline)s and Donor−Acceptor Copolymers via Palladium-Mediated Amination Chemistry, *Macromolecules,* 31(5), 1998, 1700-1703. (c) Goodson F E, Hauck S I, Hartwig J F. Palladium-Catalyzed Synthesis of Pure, Regiodefined Polymeric Triarylamines, *J. Am. Chem. Soc,* 121(33), 1999, 7527-7530. (d) Naya L, Larrosa M, Rodriguez R, Cruces J. *Tetrahedron Lett*, Selective copper-promoted cross-coupling reaction of anilines and alkylboranes, 53(7), 2012, 769-772.
2. (a) Ley S V, Thomas A W. Modern synthetic methods for copper-mediated C(aryl)[bond]O, C(aryl)[bond]N, and C(aryl)[bond]S bond formation, *Angew in Ed Chem*, 42(44), 2003, 5400. (b) Wiglenda T, Gust R. Structure−Activity Relationship Study To Understand the Estrogen Receptor-Dependent Gene Activation of Aryl- and Alkyl-Substituted 1H-Imidazoles, *J. Med. Chem*, 50(7), 2007, 1475.
3. (a) Magano J, Dunetz J R. Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of

Pharmaceuticals, *Chem. Rev,* 111(3), 2011, 2177. (b) Torborg C, Beller M. Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries, *Adv. Synth. Catal,* 351(18), 2009, 3027.

4. Welsch M E, Snyder S A, Stockwell B R. Privileged scaffolds for library design and drug discovery, *Curr. Opin. Chem. Biol*, 14(3), 2010, 347-361.
5. Wang C, Dong H, Hu W, Liu Y, Zhu D. Semiconducting π-conjugated systems in field-effect transistors: a material odyssey of organic electronics, *Chem. Rev,* 112(4), 2011, 2208-2267.
6. Zollinger H. In Colour Chemistry, *Wiley-VCH, Weinheim*, 3rd Edition, 2003.
7. Burnett J F, Zahler R E. Aromatic Nucleophilic Substitution Reactions, *Chem. Rev,* 49(2), 1951, 237.
8. Heaney H. The Benzyne and Related Intermediates, *Chem. Rev*, 62(2), 1962, 81.
9. Smith M B, March J. Advanced Organic Chemistry: Reaction, Mechanism and Structure, *Wiley-Inter Science,* New York, 5th Edition, 2001.
10. (a) Alinezhad H, Yavari H, Salehian F. Recent Advances in Reductive Amination Catalysis and Its Applications, *Curr. Org. Chem,* 19(11), 2015, 1021. (b) Raoufmoghaddam S. Recent advances in catalytic C–N bond formation: a comparison of cascade hydroaminomethylation and reductive amination reactions with the corresponding hydroamidomethylation and reductive amidation reactions, *Org. Biomol. Chem,* 12(37), 2014, 7179-7193. (c) Abdel-Magid A F, Carson K G, Harris B D, Maryanoff C A, Shah R D. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures (1), *J. Org. Chem,* 61(11), 1996, 3849.
11. Jiao J, Murakami K, Itami K. Catalytic Methods for Aromatic C–H Amination: An Ideal Strategy for Nitrogen-Based Functional Molecules, *ACS Catalysis,* 6(2), 2016, 610.
12. (a) Ullmann F. *Ber Dtsch. Chem. Ges,* 36, 1903, 2382-2384. (b) Ullmann F. *Chem. Ber,* 37, 1904, 853-854. (c) Goodbrand H B, Hu N X. Ligand-Accelerated Catalysis of the Ullmann Condensation: Application to Hole Conducting Triarylamines, *J. Org. Chem*, 64(2), 1999, 670-674.
13. (a) Guram A S, Buchwald S L. Palladium-Catalyzed Aromatic Aminations with in situ Generated Aminostannanes, *J. Am. Chem. Soc,* 116(17), 1994, 7901-7902. (b) Paul F, Patt J, Hartwig J F. Palladium-catalyzed formation of carbon-nitrogen bonds. Reaction intermediates and catalyst improvements in the hetero cross-coupling of aryl halides and tin amides, *J. Am. Chem. Soc,* 116(13), 1994, 5969-5970. (c) Guram A S, Rennels R A, Buchwald S L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines, *Angew. Chem. Int. Ed. Engl,* 34(12), 1995, 1348-1350. (d) Louie J, Hartwig J F. Palladium-catalyzed synthesis of arylamines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents, *Tetrahedron Lett,* 36(21), 1995, 3609-3612. (e) Hartwig J F. Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism, *Angew. Chem. Int. Ed,* 37(15), 1998, 2046-2067. (f) Hartwig J F. Carbon−Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides, *Acc. Chem. Res,* 31(12), 1998, 852- 860. (g) Wolfe J P, Wagaw S, Marcoux J F, Buchwald S L. Rational Development of Practical Catalysts for Aromatic Carbon−Nitrogen Bond Formation, *Acc. Chem. Res,* 31(12), 1998, 805-818. (h) Kiyomori A, Marcoux J F, Buchwald S L. An efficient copper-catalyzed coupling of

aryl halides with imidazoles, *Tetrahedron Lett,* 40(14), 1999, 2657-2660.

14. (a) Chan D M T, Monaco K L, Wang R P, Winters M P. New N- and O-arylations with phenylboronic acids and cupric acetate, *Tetrahedron Lett,* 39(19), 1998, 2933-2936. (b) Lam P Y S, Clark C G, Saubernt S, Adams J, Winters M P, Chan D M T, Combs A. New aryl/heteroaryl C 瑎 N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation, *Tetrahedron Lett,* 39(19), 1998, 2941-2944. (c) Lam P Y S, Vincent G, Bonne D, Clark C G, Copper-promoted/catalyzed C ·N and C ·O bond cross-coupling with vinylboronic acid and its utilities, *Tetrahedron Lett*, 44(26), 2003, 4927. (d) Evans D A, Katz J L, West T R. Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine, *Tetrahedron Lett,* 39(19), 1998, 2937-2940.
15. Ullmann F, Illgen E. Über Carbazole der Anthrachinon-Reihe, *Ber. Dtsch. Chem. Ges,* 47(1), 1914, 380-383.
16. Tang B, Guo S, Li M, Zhang J. N-Arylations of Nitrogen-Containing Heterocycles with Aryl and Heteroaryl Halides Using a Copper(I) Oxide Nanoparticle/1,10-Phenanthroline Catalytic System, *Synthesis,* 2008(11), 2008, 1707-1716.
17. Chouhan G, Wang D, Alper H. Magnetic nanoparticle-supported proline as a recyclable and recoverable ligand for the CuI catalyzed arylation of nitrogen nucleophiles, Ch*em. Commun,* 2007, 0(45), 4809-4811.
18. Antilla J C, Klapars A, Buchwald S L. A General and Efficient Copper Catalyst for the Amidation of Aryl Halides, *J. Am. Chem. Soc,* 124(25), 2002, 11684-11688.
19. (a) Hartwig J F. Discovery and Understanding of Transition-Metal-Catalyzed Aromatic Substitution Reactions, *Synlett,* 2006(9), 2009, 1283. (b) Hartwig J F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halidesn *Acc. Chem. Res,* 41(11), 2008, 1534 (c) Shen Q, Shekhar S, Stambuli J P, Hartwig J F. Highly reactive, general, and long-lived catalysts for coupling heteroaryl and aryl chlorides with primary nitrogen nucleophiles, Angew. *Chem. Int. Ed.* 44(9), 2005, 1371-1375. (d) Surry D S, Buchwald S L. Biaryl phosphane ligands in palladium-catalyzed amination, *Angew. Chem. Int. Ed,* 47(34), 2008, 6338. (e) Surry D S, Buchwald S L. Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide, *Chem. Sci,* 2(1), 2011, 27-50. (f) Tardiff B J, Mc Donald R, Ferguson M J, Stradiotto M. Rational and Predictable Chemoselective Synthesis of Oligoamines via Buchwald-Hartwig Amination of (Hetero)Aryl Chlorides Employing Mor-DalPhos, *J. Org. Chem,* 77(2), 2012, 1056-1071. (g) Meiries S, Speck K, Cordes D B, Slawin A M Z, Nolan S P. [Pd(IPr*OMe)(acac)Cl]: Tuning the N-Heterocyclic Carbene in Catalytic C–N Bond Formation, *Organometallics*, 32(1), 2013, 330-339.
20. Lemen G S, Wolfe J P. Palladium-Catalyzed sp2 C–N Bond Forming Reactions: Recent Developments and Applications, *Top Organomet. Chem*, 46, 2013, 1-54.
21. (a) Lam P Y S, Vincent G, Clark C G, Deudon S, Jadhav P K. Copper-catalyzed general C ·N and C ·O bond cross-coupling with arylboronic acid, *Tetrahedron Lett,* 42(20), 2001, 3415-3418. (b) Lam J X P Y S. Copper-Promoted Carbon-Heteroatom Bond Cross-Coupling with boronic acids and derivatives, *Synthesis,* 2011(6), 2011, 829-856. (c) Antilla J C, Buchwald S L. "Copper-Catalyzed Coupling of Arylboronic Acids and Amines, *Org. Lett,* 3(13), 2001, 2077-2079. (d) Mondal M, Sarmah G, Gogoi K, Bora U. Copper promoted Chan–Lam type O-arylation of oximes with arylboronic acids at room temperature, *Tetrahedron Lett,* 53(46), 2012, 6219-6222.

22. Gogoi A, Sarmah G, Dewan A. U. Unique copper–salen complex: an efficient catalyst for N-arylations of anilines and imidazoles at room temperature, Bora, *Tetrahedron Lett,* 55(1), 2014, 31-35.
23. Anuradha, Shweta K, Pathak D D. Synthesis and development of Chitosan anchored copper(II) Schiff base complexes as heterogeneous catalysts for N-arylation of amines, *Tetrahedron Lett,* 56(27), 2015, 4135-4142.
24. Zhang Q, Liu C, Shi J, Xu Qiong, Jin L, Zhao C, Zhang T. *Synlett Lett,* 27, 2016, A-D.
25. Choy P Y, Chung K H, Yang Q, So C M, Wai-Yin Raymond S, Kwong F Y. A General Palladium–Phosphine Complex to Explore Aryl Tosylates in the N-Arylation of Amines: Scope and Limitations, *Chem. An Asian J,* 13(17), 2018, 2465-2474.
26. Tian Z Y, Ming X X, Teng H B, Hu Y T, Zhang C P. Transition-Metal-Free N-Arylation of Amines by Triarylsulfonium Triflates, *Chem. A Eur. J*, 24(52), 2018, 13744-13748.
27. Purkait N, Kervefors G, Linde E, Olofsson B. Regiospecific N-Arylation of Aliphatic Amines under Mild and Metal-Free Reaction Conditions, *Angew. Chem. Int. Ed,* 57(35), 2018, 11427-11431.
28. Jacobsen C B, Meldal M, Diness F. Mechanism and Scope of Base-Controlled Catalyst-Free N-Arylation of Amines with Unactivated Fluorobenzenes, *Chem. A Eur. J,* 23(4), 2017, 846-851.
29. Sardarian A, Eslahi H, Esmaeilpour M. Copper(II) Complex Supported on Fe 3 O 4 @SiO 2 Coated by Polyvinyl Alcohol as Reusable Nanocatalyst in N -Arylation of Amines and N(H) - Heterocycles and Green Synthesis of 1 H –Tetrazoles, *Chemistry Select,* 3(5), 2018, 1499-1511.

Please cite this article in press as: Ashok A Patil and Pritesh R Jain. A review on synthesis of biologically and pharmacologically active n- arylamines, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 7(1), 2019, 214-223.