

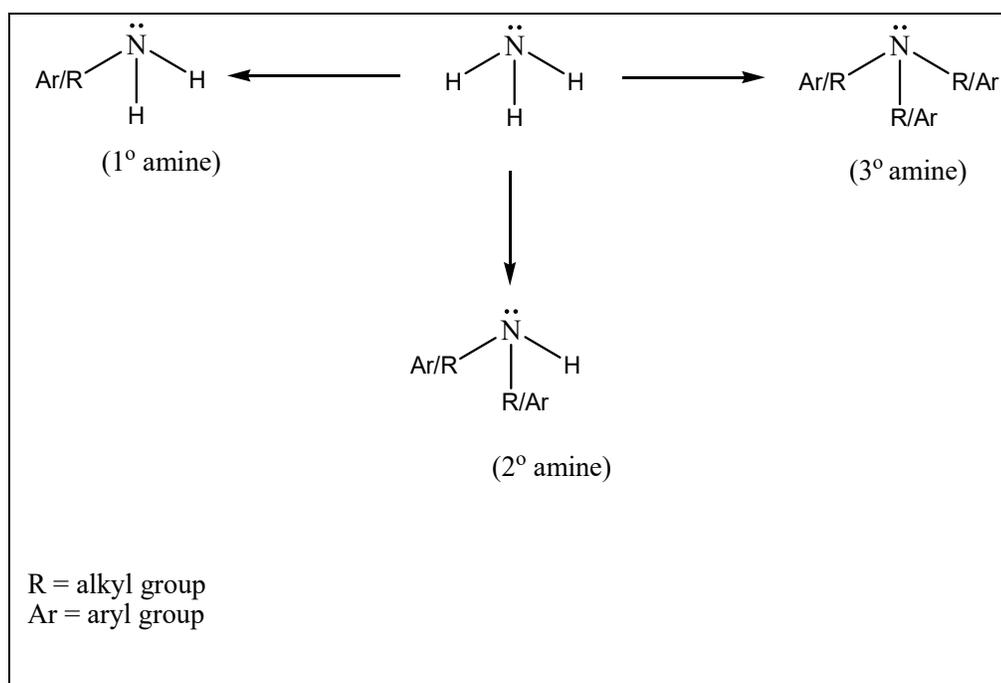
## **CHAPTER-2**

***A NOVEL APPROACH TOWARDS  
CHEMOSELECTIVE REDUCTION OF  
NITRO TO AMINE***



## II.1. Amines

By replacing one or more hydrogen atoms of ammonia molecule by alkyl/aryl group(s) we get an important class of organic compounds called amine. According to the nature of substituents on nitrogen, amines can be classified as aliphatic amines and aromatic amines. Amines, alkyl and aryl alike, are organized into three subcategories, primary ( $1^\circ$ ) amines, secondary ( $2^\circ$ ) amines, tertiary ( $3^\circ$ ) amines based on the number of carbon atoms adjacent to the nitrogen ( Figure II.1).



**Figure II.1.** Different types of amine.

## II.2. Importance of aromatic amines

Aromatic amines represent a category of chemical agents of considerable importance as witnessed by their widespread use as intermediates in the manufacture of drugs, pesticides, plastics, as antioxidants in the preparation of rubber for the manufacture of tires and cables and as curing agents in the preparation of various plastics. In addition, they are widely used as intermediates in the synthesis of several nitrogen-containing biologically active compounds, agrochemicals, dyes, polymers, etc <sup>[1]</sup>. They are the precursors for many synthetically important intermediates like amides, imines, azo compounds, isocyanates and diazonium salts which could be converted to various other functional groups <sup>[2]</sup>.



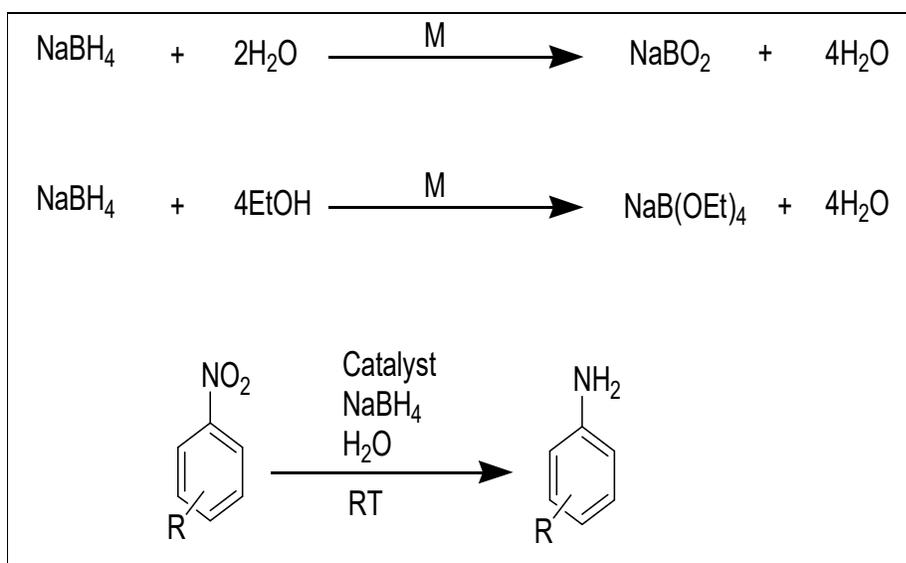
**Table II.1.** Reduction methodologies using hydrogen gas.

Entry	Catalysts	H <sub>2</sub> -pressure (atm)	Solvent, Conditions	References
1	Pd/Fe <sub>3</sub> O <sub>4</sub>	1	EtOH/THF, RT	[9]
2	Pt-Ionic liquid	10	90°C	[10]
3	Au-TiO <sub>2</sub>	9	Toluene, 100°C	[11]
4	Ni-SiO <sub>2</sub>	20-30	EtOH, 110°C	[12]
5	Ru-Reduced grapheme oxide	20	EtOH/H <sub>2</sub> O, 110°C	[13]

Catalytic hydrogenation is routinely employed in industry and in research laboratories, but it has the distinct disadvantage of the requirement of special equipment to handle high-pressure and inflammable H<sub>2</sub>. Also a large amount of hydrogen is wasted and is usually lost to the atmosphere after the reaction is over.

### II.3.B. By NaBH<sub>4</sub>

NaBH<sub>4</sub> used for reduction of nitro to amine functionality with formation of non-toxic sodium borate as a by-product (Scheme II. 2).



**Scheme II.2.** Reduction of nitroarenes using NaBH<sub>4</sub>.

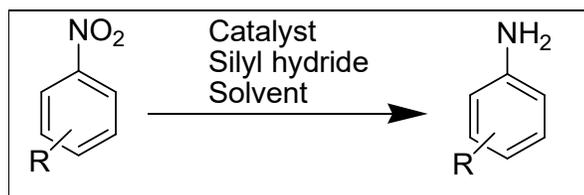
**Table II.2.** Reduction methodologies using NaBH<sub>4</sub>

Entry	Catalyst	References
1	Au-graphene hydrogel	[14]
2	Cu NPs	[15]
3	Co <sub>3</sub> S <sub>4</sub>	[16]
4	Au-Fe <sub>3</sub> O <sub>4</sub> nanocatalyst	[17]
5	Ag quantum clastures	[18]

Though NaBH<sub>4</sub> mediated reductions are safer to handle compared to catalytic hydrogenations, however they have the problem of workup to extract the product from the aqueous reaction medium. Also excess of NaBH<sub>4</sub> is required to complete the reduction process. In addition, metal reacting with NaBH<sub>4</sub> generates hydrogen, which needs to be taken care of when large-scale reductions are to be carried out. Also in most of the above cases the selectivity problem was not addressed; rather, the work centered on making NPs and demonstrating the usefulness of the NPs for catalytic processes.

### II.3.C. Silyl hydrides

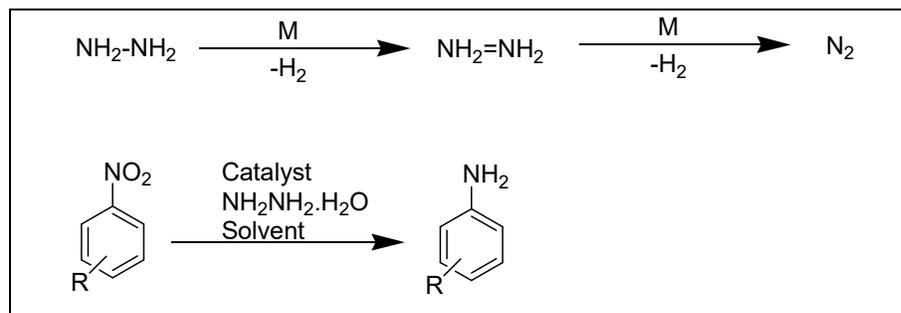
Nitro reduction with silyl hydrides proceeds through the nitroso and hydroxylamines route; the exact mechanism for this reduction process is not clear. It may take place via metalcatalyzed hydrosilylation or via hydrogenation with evolved hydrogen gas (Scheme II. 3).

**Scheme II. 3.** Reduction of nitroarenes using silyl reagents.**Table II.3.** Reduction methodologies using Silyl reagents.

Entry	Catalyst	Silanes (equivalent)	Solvent, Condition	References
1	Pd(OAc) <sub>2</sub>	PMHS(4)/KF	THF/H <sub>2</sub> O, RT	[19]
2	Fe(acac) <sub>3</sub>	TMDS(4)	THF, 60°C	[20]
3	Au-Fe <sub>3</sub> O <sub>4</sub>	TMDS (4-10)	EtOH, RT	[21]

Again like NaBH<sub>4</sub>-mediated reductions, the problem of work up, scaling up and use of excess reducing agent cannot be avoided for this system. However, the selectivity in the reduction process looks to be promising and further developments are expected.

### II.3.D. Hydrazine hydrate



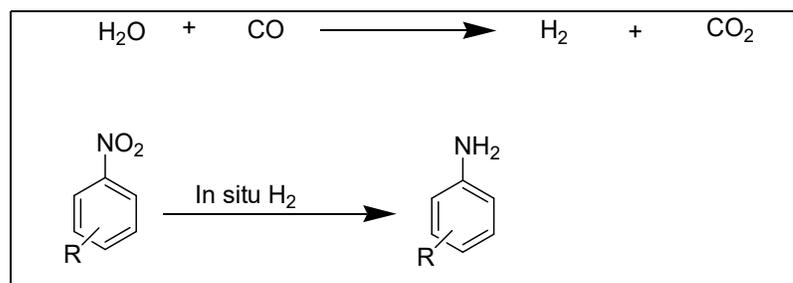
**Scheme II.4.** Reduction of nitroarenes using hydrazine.

**Table II.4.** Reduction methodologies using hydrazine.

Entry	Catalyst	Solvent, Conditions	References
1	Pd-C nanospheres	EtOH/H <sub>2</sub> O, 80°C	[22]
2	Graphene-Fe <sub>3</sub> O <sub>4</sub>	70°C	[23]
3	MoS <sub>2</sub>	Toluene, 60-80°C	[24]
4	PVP-Stabilysed Ni or Co	H <sub>2</sub> O, RT	[25]

Hydrazine hydrate-mediated reductions are much cleaner than the hydride processes as the byproducts are nitrogen and hydrogen. However, selectivity in the presence of carbon– carbon double bond, triple bond and aldehyde may be difficult to achieve, although it has been claimed in some instances.

### II.3.E. In situ hydrogen generation:



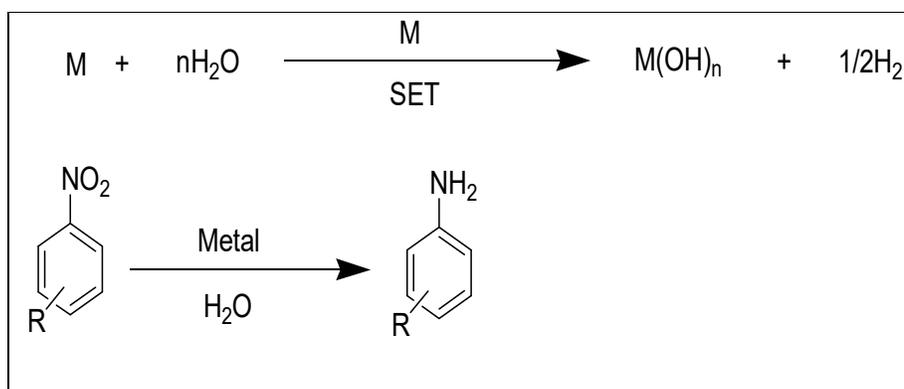
**Scheme II.5.** Reduction of nitroarenes by In situ hydrogen generation.

**Table II.5.** Reduction methodologies by In situ hydrogen generation.

Entry	Reagents(equivalents)	Solvent, Conditions	References
1	HCOOH(excess)	HTP water, 300°C	[26]
2	5% Pd/C, H <sub>3</sub> PO <sub>2</sub> (1), NaH <sub>2</sub> PO <sub>2</sub> (3)	Ultrasound	[27]
3	CeY zeolite, HCOOH or HCOONH <sub>4</sub> (1.6)	Microwave, 140°C	[28]

Milder conditions and stoichiometric use of decomposing reagents and simplified workup procedures are required to make these methods popular.

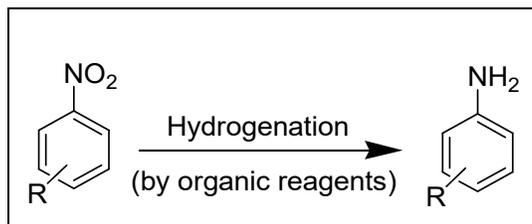
### II.3.F. Direct metal

**Scheme II.6.** Reduction of nitroarenes by using metal.**Table II.6.** Reduction methodologies using direct metal.

Entry	Metal reagent (equivalent)	Solvent	References
1	Fe NPs (3)	H <sub>2</sub> O, RT	[29]
2	Te(3)	H <sub>2</sub> O, 275°C	[30]
3	Zn,CO <sub>2</sub> (1atm)	H <sub>2</sub> O, ultrasound	[31]

Metal reductions as such are very selective in reducing the nitro functionality, but stoichiometric requirement of metals makes these processes unattractive.

### II.3.G. Organic reducing agents



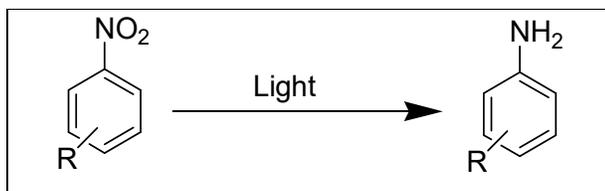
**Scheme II.7.** Reduction of nitroarenes by using organic reducing agents.

**Table II.7.** Reduction methodologies using non- classical reagents.

Entry	Reagents (equivalent)	Solvent, Conditions	References
1	D-Glucose(2), KOH(4)	H <sub>2</sub> O: DMSO, 110°C	[32]
2	Pinacol(4), MoO <sub>2</sub> Cl <sub>2</sub> (dmf) <sub>2</sub>	Toluene, MW, 150°C	[33]
3	Polymer- bound palladium, K <sub>3</sub> PO <sub>4</sub> (1.5), cyclohexanol	DMF, 110°C	[34]

Transfer hydrogenations using sustainable materials under mild conditions may go a long way in meeting the future demands of such reduction processes.

### II.3.H. Light- Induced Photocatalysis



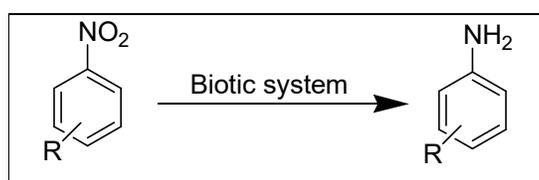
**Scheme II.8.** Reduction of nitroarenes by using light.

**Table II.8.** Reduction methodologies using light sources.

Entry	Reagents	Solvent, Conditions	References
1	Ru-dye-TiO <sub>2</sub> , TEOA, 530nm	MeCN, RT	[35]
2	PbBiO <sub>2</sub> Br, 440nm, TEOA	MeCN, RT	[36]
3	CdS nanowires, reduced graphine oxide, >420 nm, HCOONH <sub>4</sub>	H <sub>2</sub> O, RT	[37]

Direct sunlight-mediated photochemical reductions on a large scale particularly for environmental cleaning will be of great help in the future.

### II.3.I. Biotic reduction

**Scheme II.9.** Reduction of nitroarenes by using biotic system.**Table II.9.** Reduction methodologies using natural sources.

Entry	Natural sources	Conditions	References
1	Cattle tick <i>Boophilus microplus</i> , spider <i>Nephila plumipes</i>	In vivo	[38]
2	Plant cells from grapes ( <i>Vitis vinifera</i> L.)	H <sub>2</sub> O, 25°C	[39]
3	Biocatalyzed cathode	Glucose, 25°C	[40]

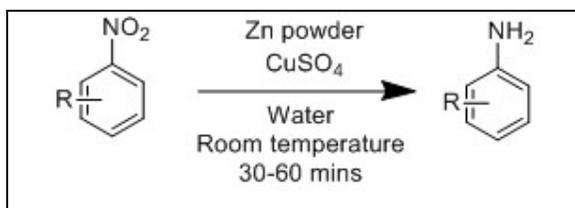
Enzymatic reductions have shown great promise, and sustained research in this field is required for future developments.

Cost-effective green alternatives of transfer hydrogenation, enzymatic and photochemical reduction methods are the ones where more progress is expected. The market potential for a new industrial application is also very high due to the demand of the final reduction product, aniline. Vastly employed method for the preparation of substituted aromatic amines is reduction of corresponding nitro substrates. But

selective reduction of a functional group in presence of other functional group which is also reducible is often a very difficult task. <sup>[41]</sup> By accepting the challenge to make difficult task to facile path, I tried and took a small step to convert aryl nitro to aryl amine.

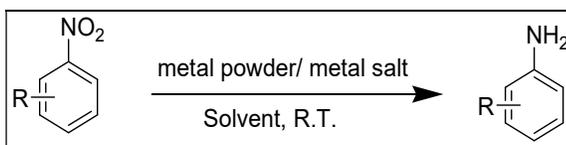
#### II.4. Present Work

Aromatic nitro compounds were reduced in good yield to the corresponding amino compounds under mild conditions in the presence of low cost and easily available metal and metal salt Zn and CuSO<sub>4</sub> respectively in water, with single product. The compound obtained were monitored by TLC and separated by column chromatography. The general scheme and reaction are shown in Scheme II.10.



**Scheme II.10.** Conversion of aryl nitro to aryl amine.

#### II.4.A. Results and discussion



**Scheme II.11.** Plan for Conversion of aryl nitro to aryl amine.

**Table II.10.** <sup>a</sup>Optimization of the reaction condition for reduction of Nitroarenes to the corresponding Anilines.

Entry	Metal/Metal salt	Solvent	Time (min.)	Temperature (°C)	<sup>b</sup> Yield (%)
1	Fe/CuSO <sub>4</sub>	Nil	180	R.T	Nil
2	Zn	H <sub>2</sub> O	180	R.T	Nil
3	Fe	H <sub>2</sub> O	180	R.T	Nil
4	CuSO <sub>4</sub>	H <sub>2</sub> O	180	R.T	Nil
5	Fe/CuSO <sub>4</sub>	H <sub>2</sub> O	180	R.T	68
6	Fe/CuSO <sub>4</sub>	H <sub>2</sub> O+EtOH	180	R.T	60

7	Fe/ CuSO <sub>4</sub>	EtOH	180	R.T	56
8	Cu/CuSO <sub>4</sub>	H <sub>2</sub> O	180	R.T	65
9	Zn/CuSO <sub>4</sub>	H <sub>2</sub> O	180	R.T	95
10	Zn/FeSO <sub>4</sub>	H <sub>2</sub> O	180	R.T	80
11	Zn/ZnSO <sub>4</sub>	H <sub>2</sub> O	180	R.T	76
12	Zn/NiSO <sub>4</sub>	H <sub>2</sub> O	180	R.T	72
13	Zn/CuSO <sub>4</sub>	H <sub>2</sub> O	120	R.T	95
<b>14</b>	<b>Zn/CuSO<sub>4</sub></b>	<b>H<sub>2</sub>O</b>	<b>60</b>	<b>R.T</b>	<b>94</b>
15	Zn/CuSO <sub>4</sub>	H <sub>2</sub> O	30	R.T	70
16	Zn/CuCl <sub>2</sub>	H <sub>2</sub> O	60	R.T	84
17	Zn/Cu(OAc) <sub>2</sub>	H <sub>2</sub> O	60	R.T	72
18	Zn/CuBr <sub>2</sub>	H <sub>2</sub> O	60	R.T	66
19	Zn/CuSO <sub>4</sub>	H <sub>2</sub> O	60	60	89
20	Zn/CuSO <sub>4</sub>	H <sub>2</sub> O	60	80	87

<sup>a</sup>Reaction of o-nitrobenzaldehyde (1mmol), Zn (3mmol), CuSO<sub>4</sub> (3mmol) in water on magnetic stirrer. <sup>b</sup>Isolated yield.

**Table II.11.** <sup>a</sup>Optimization of amount of Zn and CuSO<sub>4</sub>.

Entry	Zn (mmol)	CuSO <sub>4</sub> (mmol)	Time (min)	<sup>b</sup> Yield (%)
1	1	1	60	54
2	2	2	60	67
<b>3</b>	<b>3</b>	<b>3</b>	<b>60</b>	<b>94</b>
4	4	4	60	95

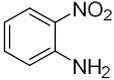
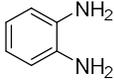
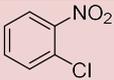
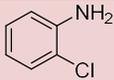
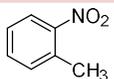
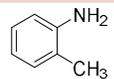
<sup>a</sup>Reaction of o-nitrobenzaldehyde (1mmol), Zn (1-4 mmol), CuSO<sub>4</sub> (1-4 mmol) in water on magnetic stirrer. <sup>b</sup>Isolated yield.

We found that both metal and additive were necessary for this reduction process (Table II.10, entries 3, 4, 5). Compared with CuSO<sub>4</sub>, other additives were inferior in terms of yield of product and reaction time. Entry 5, 8, 9 (Table II.10) implies that here Zn metal play a vital role for nitro reduction. Electro chemical series

also support our result. The reduction potential of applied metal and additive is as follows,  $E^0_{\text{Zn}^{2+}/\text{Zn}} = -0.76$ ,  $E^0_{\text{Fe}^{2+}/\text{Fe}} = -0.44$  and  $E^0_{\text{Cu}^{2+}/\text{Cu}} = +0.34$ , which clearly indicates the reduction potential difference between Zn and Cu is higher, which facilitate the transfer of electrons in the process than the other couples. This concept is in accordance with our observed results (Table II.10). But entry 11 also suggests that acidic nature of metal salts is indebted for reduction and reduction potential difference between metals amplify the potency of the process. Entries 9 to 14 implies that if we lower the time from 180 minutes to 60 minutes the yield of the product more or less same, but when we were tried to decrease the time from 60 minutes to 30 minutes then product's yield decreases remarkably. Now we were tried to optimize temperature. With the help of entries 14, 19, 20 we observed that if we increase the temperature yield of the product decreases. So with respect to time, temperature, metal/metal salt entry 14 is the optimized condition. Further we optimized the amount of Zn and  $\text{CuSO}_4$  required (Table II.11). We started our optimization with 1 mmol each. The yield was considerable but low. As the amount of reagents has been increased we reached our optimum yield at 3 mmol Zn and 3 mmol  $\text{CuSO}_4$ . No further increase in yield has been observed with increasing reagents. Considering the above mentioned points, under atmospheric pressure, 60 minutes of reaction time and room temperature is finalized as the optimum condition for this reaction (Table II.10).

This procedure is followed for all of the reactions listed in Table II. 12.

**Table II. 12.** <sup>a</sup>Zn and  $\text{CuSO}_4$  mediated reduction to amines.

Entry	Reactant	Product	Time (min)	<sup>b</sup> Yield (%)
1			50	90
2			30	85
3			30	85
4			30	95

5			30	92
6			40	80
7			30	93
8			30	93
9			30	94
10			40	93
11			50	87
12			60	89
13			50	92

<sup>a</sup>Reaction of nitro compound (1 mmol), Zn (3 mmol), CuSO<sub>4</sub> (3 mmol) in water at room temperature for different time intervals on magnetic stirrer.

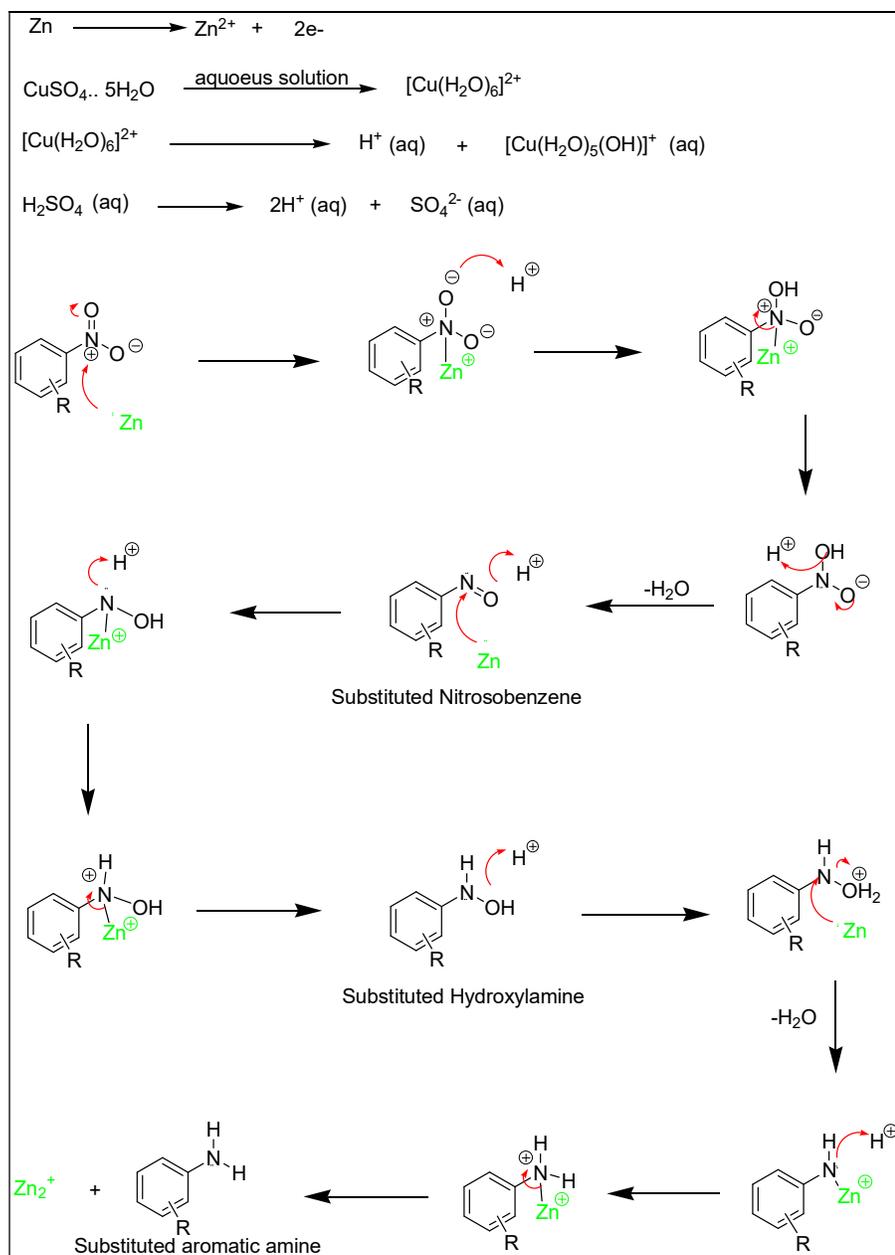
<sup>b</sup>Isolated yields

On the basis of the Table II.10, reduction of other nitroarenes was carried out by using Zn/CuSO<sub>4</sub> in water without any organic solvent at room temperature under atmospheric pressure (Table II. 11). Several substituted aromatic nitro compounds were subjected to this procedure to produce the corresponding aromatic amines. The results are presented in Table II. 11. 2-chloro, 2-iodo and 4-chloro nitro benzene (Table II. 11, entries 3, 5, 8) were cleanly reduced to the corresponding anilines

without any dehalogenation which was often encountered with several procedures such as hydrogenation. Acid, aldehyde, nitrile functionality present in aromatic ring remained unaffected during reduction of the corresponding nitro benzene by this process (Table II. 11, entries 6, 12, 13). These results demonstrate that we can employ this technique to nitroarenes containing reduction-sensitive substituents. The reaction took place smoothly and chemoselectively to produce corresponding anilines in moderate to high yields.

#### **II.4.B. Probable Mechanism**

The pentahydrated copper (II) sulphate (blue vitriol) exothermically dissolves in aqueous solution to give hexaaqua complex  $[\text{Cu}(\text{H}_2\text{O})_6]^{2+}$ , which has octahedral molecular geometry (Wikipedia). Because the central  $\text{Cu}^{2+}$  ion is positively charged, it polarizes the O–H bonds towards oxygen, which makes the hydrogens more acidic. Therefore, the ion acts as a weak Brønsted acid, with a pKa of approximately 8 (J. Phys. Chem. A, 2015, 119 (12), pp 2926–2939). Therefore with the help of  $\text{H}^+$  ion generated by the aqueous Cu (II) ion and electrons released by zinc metal (in acidic medium) aromatic nitro group smoothly converted to aromatic amine by successive steps.



**Figure II.3.** Probable mechanism of conversion of aryl nitro to aryl amine.

## II.5. Conclusion

For reduction of nitroarenes leading to aromatic amines with Zn metal, methods employing Zn/HCl<sup>[42]</sup>, Zn/aq. NaOH/EtOH<sup>[43]</sup>, Zn/NH<sub>3</sub><sup>[44]</sup>, Zn/CaCl<sub>2</sub>/EtOH<sup>[45]</sup>, Zn/near-critical water<sup>[46]</sup>, Zn/Ru-complex/H<sub>2</sub>O/KOH<sup>[47]</sup>, Zn/ether/H<sub>2</sub>O<sup>[48]</sup>, Zn/CO<sub>2</sub>/H<sub>2</sub>O<sup>[49]</sup>, Zn/SiO<sub>2</sub>-PEG<sup>[50]</sup> had been reported. However, since the conventional methods required organic solvents and/or drastic conditions using an irritant reagent such as NH<sub>3</sub>, corrosive reagents HCl, NaOH, it is difficult to contend

that these methods are environmentally harmonious. On the other hand, the reaction time is prolonged for Zn/NH<sub>3</sub> (24h), Zn/Ru-complex/H<sub>2</sub>O/KOH (16h), Zn/ether/H<sub>2</sub>O (5-11h). In addition, some special apparatus and high temperature is required for some processes. To overcome these hurdles, we have introduced our scheme using Zn metal, CuSO<sub>4</sub> and water at room temperature. The greatest advantage of our method compared with other methods is easy handling, cost effective, environmentally benign.

## II.6. Experimental

### II.6.A. General Information

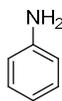
<sup>1</sup>H NMR and <sup>13</sup>C NMR were recorded using 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

### II.6.B. General Procedure for the synthesis of aryl amines from nitro compounds

A mixture of nitro compound (1 mmol), Zn powder (3 mmol), CuSO<sub>4</sub> (3 mmol) in 5 mL water at room temperature was stirred on a magnetic stirrer. The progress of the reaction was monitored by TLC. After completion of the reaction, the metallic part was filtered off. The filtrate was poured into 100 mL water and extracted with ethyl acetate, washed several times with water. Evaporation of solvent followed by column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure aryl amines. The spectroscopic data (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR) of this compound are in good agreement with those reported.

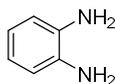
### II.6.C. Spectroscopy data of synthesized amine derivatives

#### Aniline



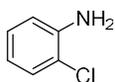
Brown liquid, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ(ppm) 3.52 (s, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 6.77 (t, *J* = 8.5 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 2H).

#### 1, 2-phenylenediamine



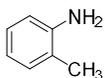
Brown solid, m.p = 101-103 °C, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ(ppm) 3.37 (s, 4H), 6.77 (s, 4H).

2-chloroaniline



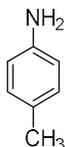
Pale yellow liquid,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta(\text{ppm})$  4.06 (s, 2H), 6.72 (t,  $J = 8.1$  Hz, 1H), 6.80 (d,  $J = 7.8\text{Hz}$ , 1H), 7.11 (t,  $J = 7.8$  Hz, 1H), 7.29 (d,  $J = 8.5$  Hz, 1H).

*o*-toluidine



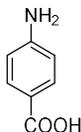
Pale yellow liquid,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta(\text{ppm})$  2.23 (s, 3H), 3.54 (s, 2H), 6.69 (d,  $J = 7.8\text{Hz}$ , 1H), 6.75 (t,  $J = 8.1$  Hz, 1H), 7.08 (t,  $J = 8.5$  Hz, 2H).

*p*-toluidine



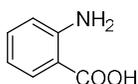
Grey solid, m.p = 42-44 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta(\text{ppm})$  2.32 (s, 3H), 3.61 (br, s, 2H), 6.76 (d,  $J = 8\text{Hz}$ , 2H), 7.12 (d,  $J = 8\text{Hz}$ , 2H).

*p*-aminobenzoic acid



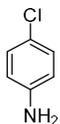
Grey solid, m.p = 183-185 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta(\text{ppm}) = 7.91$  (d,  $J = 8.56$ , 2H), 6.65 (d,  $J = 8.56$ , 2H)

*o*-aminobenzoic acid



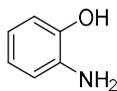
Light yellow solid, m.p = 144-146

*p*-chloroaniline



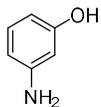
Pale yellow solid, m.p = 70-72 °C)  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta(\text{ppm})$  3.68 (br, s, 2H), 6.67 (d,  $J =$ , 2H), 7.17 (d,  $J =$ , 2H),

*o*-hydroxyaniline



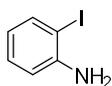
(White solid, m.p = 173-175 °C)

*m*-hydroxyaniline



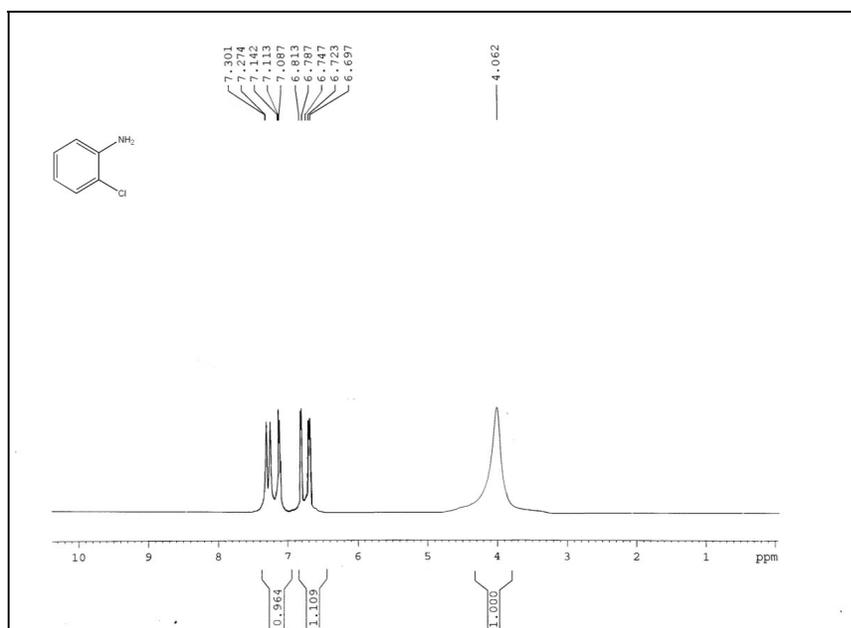
(White solid, m.p = 118-120 °C)

*o*-iodoaniline



(White solid, m.p = 57-59 °C)  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ (ppm) 4.09 (br, s, 2H), 6.58 (t,  $J =$ , 1H), 6.80 (d,  $J =$ , 1H), 7.19 (t,  $J =$ , 1H), 7.78 (d,  $J =$ , 1H).

**II.6.D. Scan copy of  $^1\text{H}$  NMR of aniline derivatives**



**Figure II. 4.**  $^1\text{H}$  NMR of 2-chloroaniline.

**II.7. References**

References are given in BIBLIOGRAPHY.