

Synopsis of the thesis entitled  
**“Re-investigating Tollens’ Reaction”**



To be submitted to  
The Maharaja Sayajirao University of Baroda  
For the Degree of

**DOCTOR OF PHILOSOPHY**

In

**CHEMISTRY**

By

**Khushboo D. Bhanderi**

Under the guidance of

**Prof. Prasanna S. Ghalsasi**

Department of Chemistry

Faculty of Science

The Maharaja Sayajirao University of Baroda

Vadodara, 390 002

INDIA

**December, 2020**

# Synopsis of The Thesis

To be Submitted to The Maharaja Sayajirao University of Baroda for the award of the Degree of Doctor of Philosophy in Chemistry.

Name of the Student: **Khushboo Dhirajlal Bhanderi**

Title of the thesis: “ **Re-investigating Tollens’ Reaction**”

Name of Supervisor: Prof. Prasanna S. Ghalsasi  
The Maharaja Sayajirao University of Baroda

Faculty: Faculty of Science, The Maharaja Sayajirao University of Baroda.

Department: Department of Chemistry

Registration No.: FOS/1968

Registration date: 09-03-2016

Khushboo Dhirajlal Bhanderi  
Research Student

Prof. Prasanna Ghalsasi  
Research Guide

Department of Chemistry,  
Faculty of Science,  
The Maharaja Sayajirao University of Baroda  
Vadodara.-390002. GUJARAT-INDIA.

# Content

## **Chapter 1: Tollens' reaction**

- Introduction of Tollens' Reaction
- Rational of the work / research objective

## **Chapter 2: C-C Oxidative Homo-Coupling of Phenol and naphthol derivatives**

- C-C coupling reaction of phenol and 2-naphthol derivatives and characterization
- Catalytic reuse of the reagent

## **Chapter 3: C-C Oxidative Cross-Coupling of Phenol and 2-naphthol derivatives**

- Cross-coupling Reaction of 2-Naphthol and Phenol derivatives and characterization
- Use of Macroscopic surface for selective Cross-coupling Reactions
- Optimization of reaction and study of mechanism

## **Chapter 4: Approach to Asymmetric Synthesis of BINOL**

- Study of chiral additive's effect on coupling product
- Investigation of active role of Macroscopic surface Quartz on silver ammine complex mediated asymmetric C-C coupling reaction
- Novel method to preparation silver surfaces which is explored for asymmetric C-C coupling reaction

## **Chapter 5: Extension Activity of Tollens' reaction**

- Study of selective oxidation reactions
- Explore methodologies to carry out reaction
- Synthesis of Silver Nanoparticles

## **Chapter 6: Summary and general conclusions**

## Chapter-1 Introduction

The Tollens' reagent is named after its inventor, "Bernard Christian Gottfried Tollens" (1841-1918). Tollens' reagent is a silver(I) ammine complex, which is prepared by mixing silver nitrate ( $\text{AgNO}_3$ ), sodium hydroxide ( $\text{NaOH}$ ) and Ammonia ( $\text{NH}_3$ ). The Tollens' reagent,  $[\text{Ag}(\text{NH}_3)_2]^+$  selectively oxidizes aldehyde functional group into corresponding acid and thus helpful in confirming absence of ketonic functional group. During oxidation of aldehyde functional group  $[\text{Ag}(\text{NH}_3)_2]^+$  gets reduced to metallic silver which subsequently deposited on the inner walls of test tube. This latter part of the test leads to a beautiful observation and hence name -Silver Mirror test, as shown in figure 1.1. Thus, overall simplicity and wide applicability of this reagent made this redox-reaction as a common test in undergraduate Organic Chemistry practical's around world. [1] [2] Interestingly this test remained Apart from that it is not explored for other organic transformation.

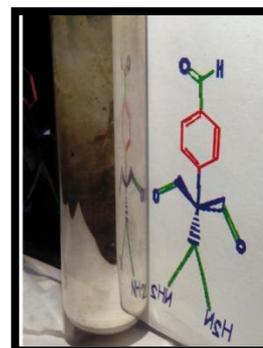


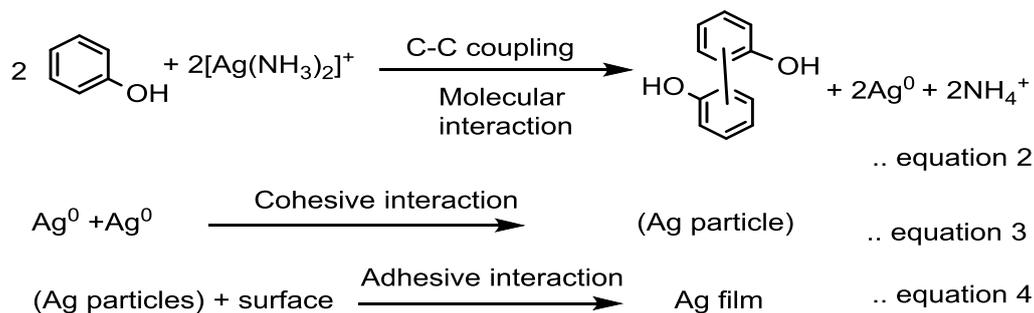
Figure 1.1 Silver Mirror in test tube



Tollens' reagent and its modification received application in thin silver mirror film formation for telescopes, conducting materials and more importantly in last 2-3 decades for generating silver nanoparticles. Literature cites only few reducing agents for reducing  $\text{AgNO}_3$  into metallic silver, but explored range of surfactants and polymer assemblies for controlling shape, size and overall growth of nanoparticles. [3]–[5]

On this background, when we re-looked at Tollens' test, it is a clean and clear redox reaction with distinct separation of oxidizing and reducing component. So, initial attempts were made to explore the mild oxidizing power of  $[\text{Ag}(\text{NH}_3)_2]^+$  for more challenging C-C oxidative coupling reaction, to the best of our knowledge not reported in literature.[3] Derivative of easily oxidizing phenols and naphthol derivatives were explored, and are represented by equation 2. But the work took interesting turn after a curious experiment- Tollens' test in polyethylene (Eppendorf) tube rather than borosilicate glass test tube. Former experiment yielded floating silver particles rather than silver mirror on the walls of test tube. That means, silver film formation depends upon the surface, necessary of an adhesive interaction between Ag particles and glass surface. This observation prompted us to extend equation 2, common equation for Tollens' test, with equations 3 and 4. Although, redox reaction ends after the

formation of oxidized product and reduced product, it is the role of continuous growth of  $\text{Ag}^0$  into silver film driven by cohesive and adhesive interaction elude us.



## 1.1 Objectives of my Research

Thus, present work revolves around in-depth understanding of Tollens' reaction. The thesis will be arranged in five chapters, in which 1<sup>st</sup> chapter is introduction and 6<sup>th</sup> chapter summarizes with conclusion. The specific aims for each chapter are heightened below:

- To investigate use of silver ammine complex for C-C oxidative coupling reaction of phenols and naphthol derivatives.
- Optimization of reaction conditions to obtain desired products, and recycling of generated Silver.
- To obtain selectivity for oxidative C-C homo-coupling, and/or C-C cross-coupling of phenol derivatives using surface as a non-conventional method.
- To elucidate role of silver particle/film formation.
- To correlate silver formation to organic product formation.
- To explore role of  $\text{Ag}^0$  growth for generating and/or separating enantiomerically rich BINOL or explore growth of  $\text{Ag}^0$  for asymmetric synthesis.
- To develop novel methodologies for carrying Tollens' reaction which can be find use in material science such as silver nanoparticles, silver coating on different substrates.
- Designing experiments for understanding Tollens' reaction not limited to educational activity, such as sublimation, but for oxidation of heterocyclic compounds.

## Chapter 2: C-C Oxidative Homo-Coupling of Phenol and naphthol derivatives using Tollens' Reagent or silver ammine complex

### 2.1 Introduction

The Carbon-Carbon coupling reaction (C-C coupling reactions), remained as a fundamental and most challenging reaction in organic chemistry. The C-C coupling of phenol and Naphthol derivatives results in to Biphenols and Binaphthols, respectively. Biphenol and its derivatives with  $C_1$  and  $C_2$  symmetry were reorganized as structural building block of many natural products. Derivatives of Biphenol and 1,1'-Binaphthol [7] are used to prepare ligands, chiral auxiliaries and transition metal complexes which are further used in material preparation[8]–[12], in asymmetric transformations and asymmetric catalysis.[9], [13] Recently its use is highlighted as a basic unit of nano-motor[14]. Oxidative C-C coupling reaction of phenols are mainly reported using transition metal salts and their complexes such as Iron, Copper, Manganese, Vanadium, Aluminum, Ruthenium and Titanium.[15] These procedures requires harsh conditions and hazardous solvent system and generates stoichiometric toxic waste. Research is still going on to develop new catalytic system and reagents to overcome critical challenges such as recovery, regeneration and re-activation, recyclability of catalyst. Literature shows the oxidation potential of silver ammine complex (+0.34 eV) quite matching with oxidation potential of phenols. Therefore, Tollens' test was performed initially on 2-naphthol. To our surprise, Tollens' test of 2-naphthol resulted in silver mirror formation on the walls of test tube.

### 2.2 Research objectives

- To explore use of silver ammine complex for oxidative C-C coupling reaction of phenol and naphthol derivatives with in-depth characterization.
- If possible propose mechanism for the product formation

Optimize reaction condition to obtain desired products and recycle generated Silver

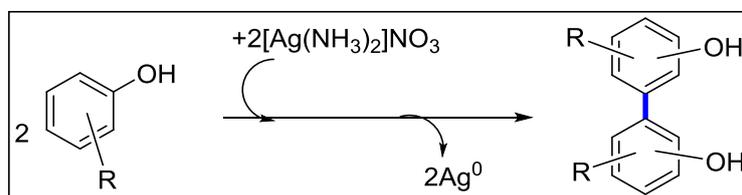
### 2.3 Experimental

Modified Tollens' Reaction of phenols and naphthol derivatives were carried out using scheme 1. Recycling of silver was carried out using scheme 2.

#### **Scheme 2.3.1 C-C coupling Reaction of Phenol derivatives using Tollens' reagent.**

Silver nitrate (0.0340 g, 0.2 mmol) was dissolved into liq. ammonia (~0.2 ml) using magnetic stirrer bar in a test tube to prepare Silver-ammine complex solution. 1.0 ml solution of phenol (0.2 mmol) in ethanol was added into the silver-ammonia complex solution. The reaction was

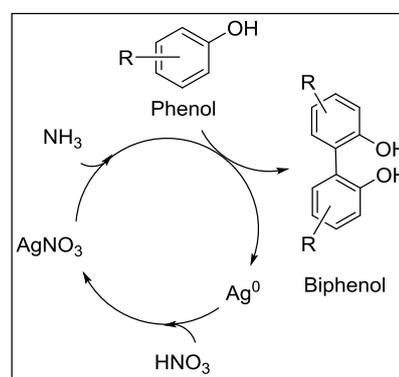
optimized by varying time and temperature in oil bath, as shown in table 2.1. The reaction mixture was separated from crude metallic silver by simple filtration, and then extracted using ethyl acetate and dichloromethane. The volatiles were removed under reduce pressure



Scheme 2.3.1: shows general scheme for reaction of phenol derivative using Tollens' reagent and the crude was purified using column chromatography on silica gel.

### Scheme 2.3.2 Recycling and reuse of reagent

Obtained silver mirror film was subjected for washings using ethyl acetate followed by water. Minimum amount of nitric acid (10 N) was added into it and heated for 2-5 minutes. This results in regeneration of silver nitrate. It is then treated with ammonia until basic and used directly for next cycle as shown in Scheme 2.3.2. Recycling was carried out till 5 cycles, with last cycle resulting in over 90% yield. The recovered silver solution was also quantified by conductometric titration with standard potassium chloride solution.



Scheme 2.3.2: shows general scheme for Recycling experiments of silver ammine complex reagent for C-C oxidative coupling and reuse

## 2.4 Result and discussion

The reaction of 2-naphthol is carried out by varying reaction conditions such as reagent preparation method, reactant amount, reagent stoichiometry, solvent, dilution, temperature and purging gas to optimize reaction conditions. From this reaction, column purified BINOL was obtained with 93% of isolated yield. Gram scale reaction of 2-naphthol resulted in 63.4% isolated column purified BINOL. The product was isolated and characterized, completely. [3] After optimization of reaction condition, commercially available total 8 derivatives of phenol and naphthol were chosen and reacted with  $[\text{Ag}(\text{NH}_3)_2]^+$  for C-C oxidative coupling as shown in scheme 2.3.1. Products were isolated and purified using column chromatographically as shown in table 2.1. All the products were characterized using  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR, FT-IR spectroscopy and ESI-MS/GC-MS spectrometric analysis, which are matching with literature.[16] Mainly *ortho-ortho* homo-coupling were observed

during biphenyl formation. When the *ortho*- positions are substituted by *tert*-butyl/methoxy/methyl groups, then *para-para* homo-coupling took place as shown in table 2.1. Study observed that addition of quantitative amount of NaOH in the *para-para* coupling reaction led to substantial quinone formation.

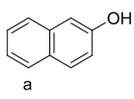
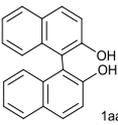
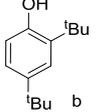
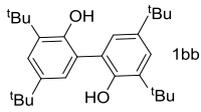
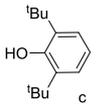
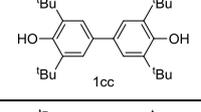
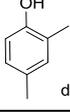
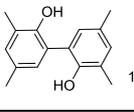
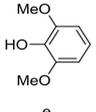
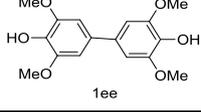
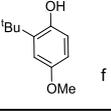
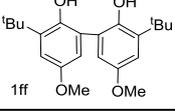
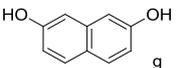
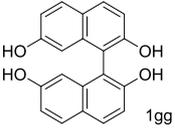
Substrate	Product	Reagent	Solvent	T	Time	yield
 a	 1aa	AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	30°C	48 hr	93%
		AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	70°C	15 min	75%
		AgNO <sub>3</sub> +NaOH+NH <sub>3</sub>	Ab. ethanol	30°C	48 hr	84%
		0.5AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	70°C	20 min	39%
		2 AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	70°C	20 min	39%
 b	 1bb	AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	30°C	1 hr	95%
		AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	70°C	5 min	82%
		AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	50°C	5 min	79%
 c	 1cc	AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	30°C	5 min	70%
		AgNO <sub>3</sub> +NaOH+NH <sub>3</sub>	Ab. ethanol	50°C	5 min	78%
 d	 1dd	AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	30°C	30 min	85 %
		AgNO <sub>3</sub> +NaOH+NH <sub>3</sub>	Ab. ethanol	50°C	5 min	83%
		AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	30°C	5 min	79%
 e	 1ee	AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	30°C	5 min	70%
		AgNO <sub>3</sub> +NaOH+NH <sub>3</sub>	Ab. ethanol	70°C	5 min	25%
 f	 1ff	AgNO <sub>3</sub> +NH <sub>3</sub>	H <sub>2</sub> O	30°C	5 min	74%
 g	 1gg	AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	30°C	72 hr	62 <sup>a</sup> %
		AgNO <sub>3</sub> +NH <sub>3</sub>	Ab. ethanol	70°C	3 hr	51%

Table 2.1: Oxidative C-C homo-coupling of substituted phenols. Isolated yield of column purified product is reported. (Typical reaction parameters are- AgNO<sub>3</sub> (0.2 mmol), liquor ammonia (0.2ml), substrate (0.2 mmol), absolute ethanol (0.5 ml)).

The C-C oxidative coupling reaction proceeds homogeneously with silver ammine complex thus ensuing complete conversion of reactants. Interestingly, product formation happens with heterogeneous metallic silver formation for easy recovery of the products. Thus recycling and recovery of reagent was carried out using scheme 2.3.2. Here around 99.5 % recovery of silver was achieved even after 5<sup>th</sup> reuse, which was quantified using *conductometric* titration as shown in figure 2.1.

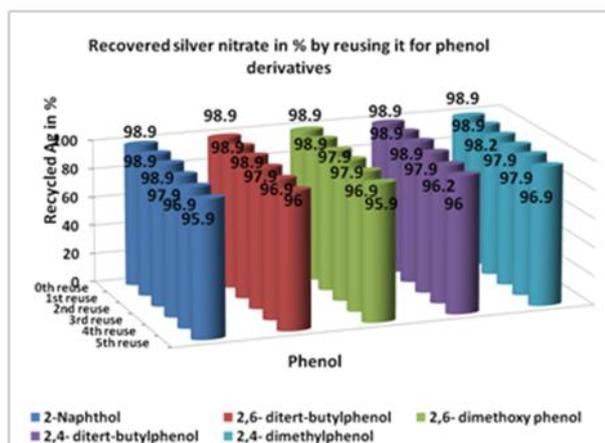


Figure 2.1 graph of recovered silver nitrate (%) after each C-C oxidative coupling reaction between phenol or naphthol derivatives.

## 2.5 Conclusions

In conclusion silver ammine complex is an efficient reagent for C-C oxidative coupling of phenol and naphthol derivatives. This reagent requires mild conditions to carry out reaction. Apart from this  $[\text{Ag}(\text{NH}_3)_2]^+$  catalyzes the reaction with Homogeneously and transform into Heterogeneous with product formation. This latter aspect helps in complete and recyclable recovery of silver. All oxidized biphenyl products were obtained quantitatively (around 70-90% yield ) and characterized using <sup>1</sup>H- NMR and <sup>13</sup>C-NMR, FT-IR spectroscopy and ESI-MS/GC-MS analysis.

## Chapter 3: C-C Oxidative Cross-Coupling of Phenol and naphthol derivatives

### 3.1 Introduction

The cross-coupling processes were investigated from beginning of 19<sup>th</sup> century but still huge research is going on this topic. Recently Richard Heck, Eiichi Negishi, and Akira Suzuki were awarded Nobel Prize 2010 for development of palladium catalyzed cross-coupling reactions.[17] Transition metal catalyzed cross-coupling reactions are used to prepare biaryl bonds (Ar-Ar) with high selectivity and yield, but multiple step synthesis reaction are required to functionalized starting material thus large quantitative toxic waste and lavish process makes these substitution reactions economically poor. In alternatively, oxidative

coupling reactions offer a single-step approach for preparing biaryl bonds by merging two arenes but the challenging part herein to overcome kinetically favored homo-coupling by-product formation.[17] In literature different strategies are used to improve selectivity using mechanistic approach. Pappo, Jeganmohan, Kozlowskis, Kocovsky, Waldvogel, Hovorka and Zavada groups studied the selective oxidative cross-coupling reaction of phenols either using metal salen and porpholelene complexes of Fe, V, Cu, Cr and Mn or using electrochemical process. They observed selectivity when phenols having oxidation potential difference more than 0.25 eV are used for reaction and yields were improved by taking the least oxidizable phenol in large excess. Interestingly this strategy works better in fluorinated solvents only and when methoxy substituted phenol is used as a one of the coupling partner. Key for its success lies in controlled molecular interactions so as to predominantly favor radical-anion interaction over radical-radical and radical-cation interaction.[18], [19] However, the basic principles guiding cross-coupling selectivity in these oxidation systems remained unclear and it is interest of study for many researchers. Inspired from these we have planned to carryout cross-coupling reaction using silver ammine complex.

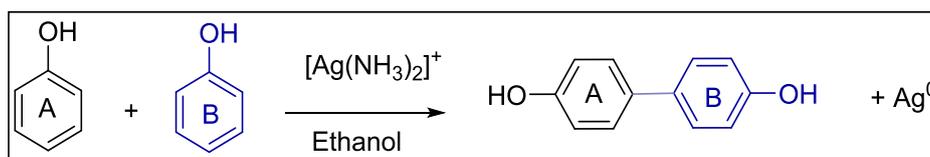
### 3.2 Research objectives

- To investigate use of silver ammine complex for C-C oxidative cross-coupling of phenols and naphthol derivatives and characterization.
- To obtain selectivity for oxidative C-C homo-coupling, and/or C-C cross-coupling of phenol derivatives using surface as a non-conventional method.
- To elucidate role of silver particle/film formation.
- To correlate growth of silver film formation to organic product formation.

### 3.3 Scheme

In this chapter the Cross-coupling reaction study was divided in 2 schemes in which cross-coupling of phenol derivatives were carried out as shown in scheme 3.3.1 and further selectivity for oxidative C-C homo-coupling, and/or C-C cross-coupling of phenol derivatives were studied using surface as a non-conventional method using scheme 3.3.2.

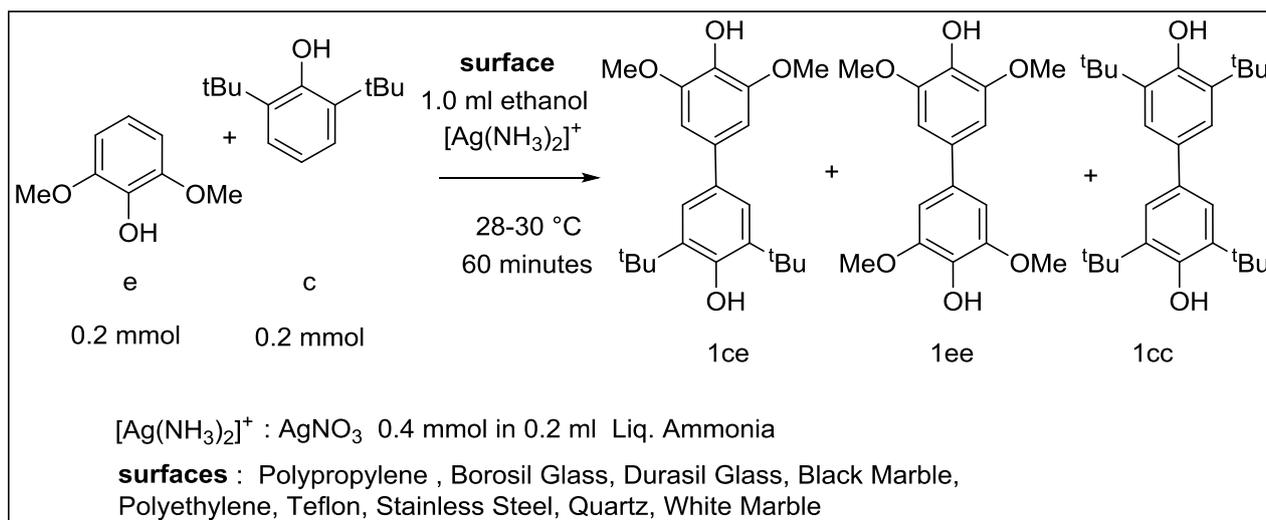
#### Scheme 3.3.1: Cross-coupling reaction of phenol derivatives



Scheme 3.3.1: shows general scheme of cross-coupling of phenol derivatives using silver ammine complex

Silver ammine complex was prepared by dissolving silver nitrate (0.034 g, 0.2 mmol) into liquor ammonia solution (0.2 ml). Phenol A (0.1 mmol) and phenol B (0.1 mmol) were dissolved in absolute ethanol (0.5 ml) and added to vessel (borosilicate). The silver-ammonia complex solution was added into the solution of phenol at 30 °C and kept for 1 hr to 48 hr.

**Scheme 3.3.2: Cross-coupling Reaction of Phenol derivatives (e and c) in different surfaces:**



Scheme 3.3.2: shows C-C cross-coupling of phenols e and c in presence of different surfaces

Ammonical silver nitrate complex was prepared by dissolving silver nitrate (0.034 g, 0.2 mmol) into liquor ammonia solution (0.2 ml). 2,6-dimethoxy phenol (0.016 g, 0.1 mmol) and 2,6-di-tert-butylphenol (0.021 g, 0.1 mmol) was dissolved in absolute ethanol (0.5 ml) and added to vessel (borosilicate). The silver-ammonia complex solution was added into the solution of phenol at 30 °C and kept for 1 hr after mixing by shaking the vessel for few seconds. The product was extracted from reaction mixture using DCM and ethyl acetate solvent (2-5 ml of each in 0.5 ml fraction). The extract was dried and residue was purified using column chromatography on silica gel using ethyl acetate in petroleum ether

### 3.4 Result and discussion

In this chapter silver ammine complex reagent has been explored for C-C oxidative cross-coupling reactions as shown in scheme 3.3.1 and 3.3.2 using Phenol and naphthol derivatives (a-h). Reaction of phenols were carried out at 30°C temperature, but reaction involving naphthol derivatives were carried out at 70°C due to difference in reactivity as shown in table 3.1. Overall total 6 different C-C Cross-Coupled products were obtained quantitatively and characterized using mass spectrometry,  $^1H$ -NMR and  $^{13}C$ -NMR spectroscopy analysis. The

results show consistency with literature. Initially, on the basis of oxidation potential difference and nucleophilicity, observed in the literature, 2,6-dimethyl phenol, 2,6-dimethoxyphenol and 2,6-di-*tert*-butylphenol were chosen for mechanistic study. To obtain selectively in cross-coupled products, reactions were carried out by varying reaction conditions such as temperature, dilution, solvent and stoichiometry of reagent. Enhanced yields were not achieved more by varying mole ratio of phenols from 1:1, cross coupling reactions will be discussed. We observed some increase in cross-coupling product with dilution of the reaction mixture.

Phenol 1	Phenol 2	Tem <sup>a</sup>	Time <sup>b</sup>	Observations and Cross-coupled Product <sup>c</sup>	yield <sup>d</sup>
a	c	70°C	3 hr	1-(4'-Hydroxy-3',5'-di- <i>tert</i> -butyl phenyl)-2-naphthol ( <b>1ac</b> )	10%
	e	70°C	3 hr	1-(4'-Hydroxy-3',5'-dimethoxyphenyl)-2-naphthol ( <b>1ae</b> )	8%
	g	30°C	3 day	1,1'-binaphthyl-2,7,2'-triol ( <b>1ag</b> )	12 %
		70°C	3hr		16%
c	d	30°C	1 hr	3,5-di- <i>tert</i> -butyl-3',5'-di-methyl-(1,1'-biphenyl)-4,2'-diol ( <b>1cd</b> )	9%
	e	30°C	1 hr	3,5-di- <i>tert</i> -butyl-3',5'-di-methoxy-(1,1'-biphenyl)-4,4'-diol ( <b>1ce</b> )	58%
e	h	30°C	30 min	3,5-di-methoxy-3',5'-di-methyl-(1,1'-biphenyl)-4,4'-diol ( <b>1eh</b> )	16%

Table 3.1: Oxidative C-C cross-coupling of substituted phenols, a, b reaction conditions, d isolated yield of column purified product using scheme 3.3.1

Reaction optimization experiments and study are illustrated in detail which follow proposed radical-radical coupling mechanism. drive reaction through anion-radical coupling mechanism, suitable for chemo-selectivity on the basis of literature[18], [20], reactions were carried out in Hexa-Floro-IsoPropanol (HFIP) as a solvent. Mainly homo-coupled products were obtained. To confirm our experimental observation, C-C homo-coupling of 2,6-dimethoxy phenol was performed in presence of HFIP. But this experiment

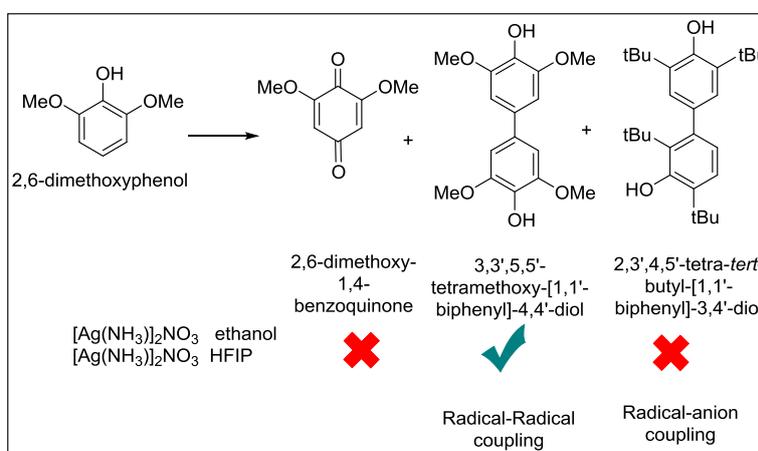


Figure 3.1: shows results of C-C coupling reaction of 2,6-dimethoxy phenol using silver ammine complex in HFIP and ethanol solvent

resulted in only *para-para* coupling product instead of expected *meta-para* coupled product, as shown in figure 3.1.

These results show that radical-radical coupling mechanism is favored, and radical-anionic coupling mechanism is not possible with fluorinated solvent. These observations resulted in a question, “Is it possible to obtain chemo-selectivity using any other mechanism?”. In our earlier attempt, we observed that if coupling reactions carried out in plastic or polypropylene surfaces result in silver particle formation rather than silver mirror. This observation prompted us to study the effect of macroscopic surface and thus adhesive and cohesive interactions to obtain chemo-selectivity in cross-coupling reactions.

### Cross-coupling Reaction of Phenol derivatives on different surfaces: Optimization of reaction and study of mechanism

We proposed a hypothesis for cross-coupling reaction, the surface may affect (Ag-particle)-surface adhesive interaction and hence Ag-Ag cohesive interaction, which might influence oxidative product formation. To our surprise, selective cross-coupling over homo-coupling was observed by simply changing the surface of the reaction vessel from glass to plastic, or silicones, without ‘addition’ of any extra reagent as shown in Scheme 3.3.2 and figure 3.2. These reactions were repeated several times to check reproducibility on all eight (8) different surfaces. The cross-coupling reaction of 2,6-dimethoxyphenol and 2,6-di-*tert*-butylphenol resulted in cross-coupling product formation along with homo-coupled byproduct, these reactions were studied broadly for surface-induced chemo-selectivity. On changing the surface of the reaction vessel from glass to polyethylene or Teflon material, without adding extra reagent, cross-coupled product was obtained from 15% to 70%. The surface selectivity has been found

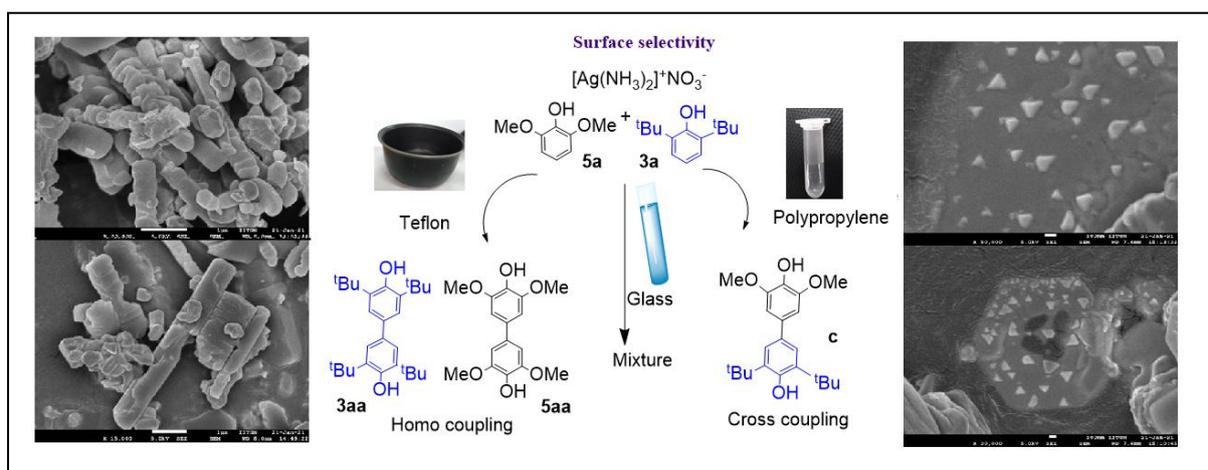


Figure 3.2: shows C-C cross-coupling of phenols results into predominantly cross-coupling product formation and homo-coupling product formation in plastic and teflon surface respectively and mixture of both in glass surface and FESEM images of silver obtained from reactions

to be substrate selective.

To understand surface directed chemo selectivity, coupling reaction of 2,6-di-methoxy phenol were carried out using ethanol and HFIP solvent, but no effect was observed confirming surface has no direct role in the selectivity of product formation. Apart from that other cross-coupling reactions were also carried out and will be discussed. Results of these reactions show that, the chemo-selectivity observed herein is substrate selective.

Although these results show reaction following radical-radical coupling mechanism it is a effect of macroscopic surface or aggregation of silver ( $\text{Ag}^0$ ) remained key aspect on selectivity of product formation. One can say that the adhesive (or repulsive) force of surface results in restricted growth of silver cluster, which ultimately drive oxidative coupling reaction. The silver clusters resulted from these reactions was analyzed using optical microscopy and field emission scanning electron microscopy (FESEM) and SEM, which confirms different macroscopic and microscopic level morphology of silver as shown in fig. 3.2. Further scope to understand this reaction from *in-situ* macroscopic growth/particle generation or intermediate formation will be undertaken in due course. But to reaffirm claim on proposed hypothesis, a new synthetic scheme is designed and is discussed in chapter 4.

### **3.5 Summary**

In summary our experimental results manifest that silver ammine complex has been investigated as an efficient reagent for cross-coupling reactions, not only due to ease of preparation of reagent from readily available chemicals but also due to simple isolation. Total six (6) C-C cross-Coupled products were obtained quantitatively and characterized using mass spectrometry,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  and FT-IR spectroscopy analysis. All data is consistent with the literature. The experimental results have shown the reaction follows radical-radical coupling mechanism. This is the first example where macroscopic interaction are employed for manipulating molecular level interactions and hence product formation.

## **Chapter 4: Approach to Asymmetric Synthesis of BINOL**

### **4.1 Introduction**

tropoisomers contains chiral axis which are available in many natural products/resources, with display of completely different biological profiles. Recently it was recognized that controlling the chirality of unsymmetrical biaryl structures may contribute enormous implications in the future development of pharmaceuticals.[9] BINOL and its derivatives are one of the most privileged molecular entities in material science largely and more specific to organic and physical chemistry because of  $\text{C}_2$  axis of symmetry. Optically pure BINOL

routinely synthesized in either racemic form and then resolved or synthesized in pure enantiomeric form. The resolution of BINOL is reported with enzymatic, kinetic resolution using chiral derivatizing agent and/or spontaneous resolution. Asymmetric BINOL is also synthesized using asymmetric induction or chiral catalysis. [21] [13]

## 4.2 Research objectives

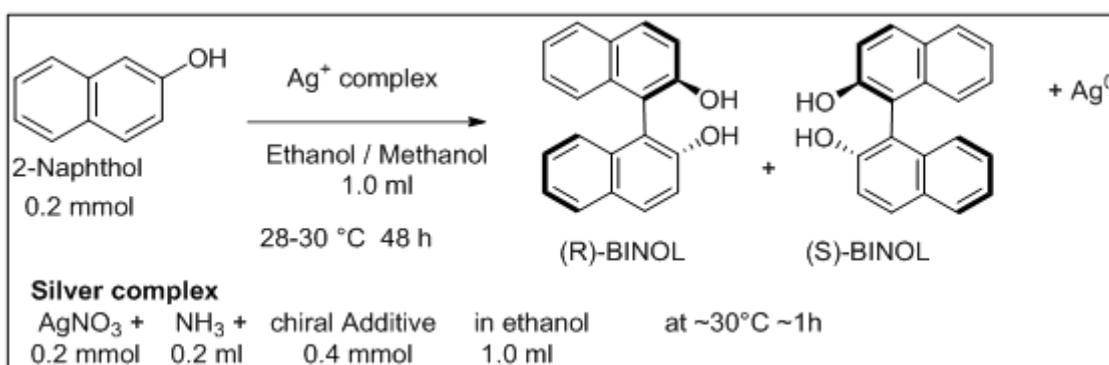
- To explore possibility of Tollens' reagent for synthesis of enantiomerically pure BINOL
- To design avenues for growth of silver aggregation/particle formation and hence driving organic product formation
- To explore and correlate role of  $\text{Ag}^0$  growth for generating and/or separating enantiomerically rich BINOL or make an attempt to drive asymmetric synthesis using growth of  $\text{Ag}^0$ .

## 4.3 Experimental Strategy (Schemes)

In this chapter the reaction of 2-naphthol was carried out to obtain enantiomerically enriched BINOL by using 3 schemes shown below.

### Scheme 4.3.1 Coupling reaction of 2-naphthol in presence of chiral additive

Silver nitrate (0.043 g, 0.25 mmol) was dissolved in 1.0 ml liquor ammonia. Chiral additive (0.5 mmol) was added into it. After 30 minutes 2-naphthol (0.036 g, 0.25 mmol) in 0.5 ml absolute ethanol was added and mixed by shaking the solution. This solution was kept in dark at 28-30 °C for 48 hour. This experiment is depicted as Scheme 4.3.1. Attempts were also made to vary concentrations of chiral reagents and/or other experimental conditions.

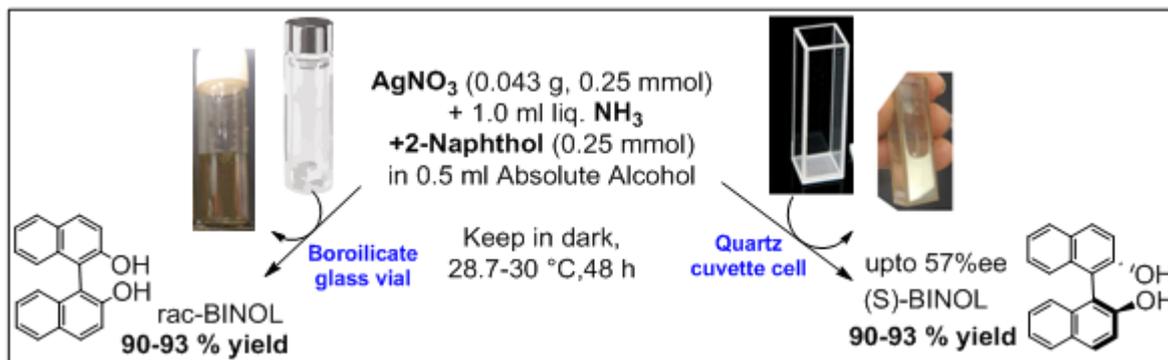


Scheme 4.3.1: C-C coupling of 2-naphthol using silver complex in presence of chiral additive

### 4.3.2: Coupling reaction of 2-naphthol in quartz surface

Silver nitrate (0.043 g, 0.25 mmol) was dissolved in 1.0 ml liquor ammonia in to the quartz tube. After 5 minutes 2-naphthol (0.036 g, 0.25 mmol) and 0.5 ml Absolute ethanol was added into it and mixed by shaking the solution and kept in dark for 48 hr at 28-30 °C. This

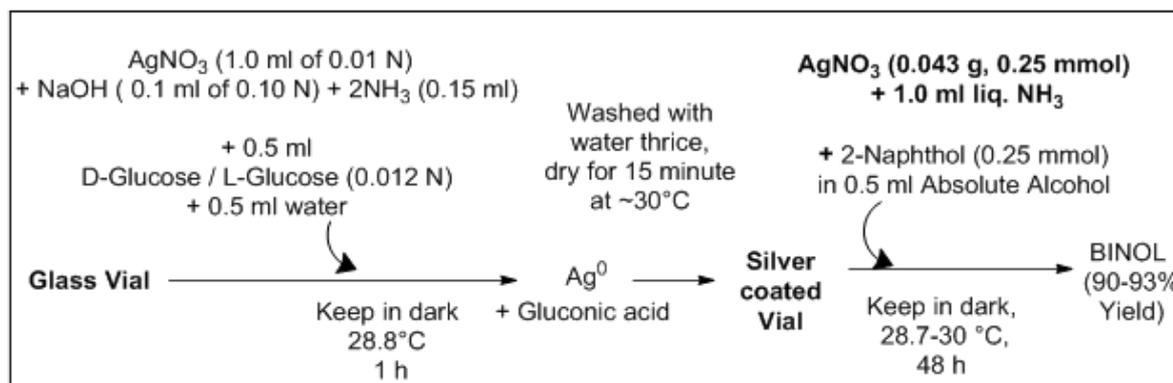
experiment is depicted as Scheme 4.3.2. Attempts were also made to vary other experimental conditions.



Scheme 4.3.2: C-C coupling of 2-naphthol using silver ammine complex in quartz surface

### Scheme 4.3.3: Coupling reaction of 2-naphthol in silver coated surface

1.0 ml of 0.01 N Silver nitrate solution was added to the oven dried glass vial. 0.1 ml of 0.10 N sodium hydroxide solution and 0.15 ml ammonia solution (0.0025 % w/v) were added into it. 0.5 ml 0.012 N glucose solution and 0.5 ml water into it. This reaction mixture was kept in the dark at 28-30 °C for 1 hr. Solution in the vial was discarded and washed with water thrice and kept 1-2 hour for drying at room temperature. This silver coated surface was used instead of quartz for further C-C coupling reaction of 2-naphthol using same procedure given in 4.3.2. This experiment is depicted as Scheme 4.3.3.



Scheme 4.3.3: C-C coupling of 2-naphthol using silver ammine complex in silver coated surface

## 4.4 Result and discussion

The reaction of silver ammine complex and 2-Naphthol results in the rac-BINOL formation in standard procedures carried out borosilicate glass tube. In literature Asymmetric synthesis and chiral resolution method has been widely studied to obtain optically pure BINOL. Inspired from reported methods, optically pure chiral amine and amino acids were chosen as additives/ligand to discover novel simple technique for synthesis of optically pure BINOL as

shown in scheme 4.3.1. Different chiral amines employed during this strategy were: L-tyrosine, (2S,4R)-4-hydroxypyrrolidine-2-carboxylic acid, L-proline, (1S,2S)-cyclohexane-1,2-diamine, (R)-1-(4-bromophenyl)ethan-1-amine, (S)-1-phenylethan-1-amine, L-arginine, (R)-1-phenylethan-1-amine, (1R,2R)-1,2-diphenylethane-1,2-diamine, (S)-1-phenylpropan-1-amine, and (R)-1-phenylpropan-1-amine. The reagent was prepared by replacing ammonia with chiral amine and amino acid and its reaction with 2-Naphthol was carried out. Many times un-reacted starting material was obtained. To overcome these issue the coupling reactions were carried out in presence of these additives (listed above) as shown in scheme 4.3.1, by expecting complete conversion along with diastereomer formation. But the racemic BINOL crystals were only obtained in some cases. Details will be discussed.

After failure of this strategy we designed novel way to induce chirality based on literature and our earlier hypothesis. Surface phenomenon was used for enhancement of enantioselectivity in autocatalysis reaction, in which naturally available minerals optically active d-/l- quartz and d-/l- NaClO<sub>3</sub> were used to enhance chirality, [22]. To our best knowledge, C-C coupling or asymmetric synthesis of axially chiral compounds are not at all reported using surface phenomena.

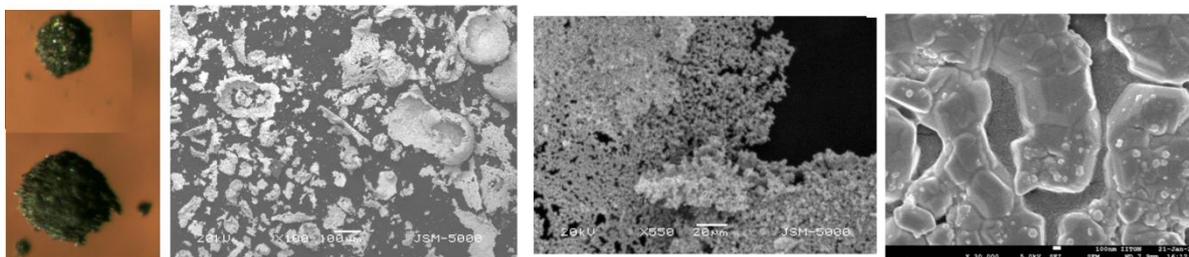


Figure 4.1: shows images of silver obtained from quartz surface : optical image, SEM and FESEM images

We have already observed effect of macroscopic forces into the product formation, inspired from these we planned to carry out coupling reaction in presence of available quartz material. Interestingly oxidation of 2-naphthol in quartz tube yielded enantioselective BINOL formation using scheme 4.3.2 with up to 57% ee BINOL and more than 90% yield. Experiments were repeated several times to confirm observation. Polarimeter was used for optical measurement, and are aware of its limitation. But the repeated experiments confirm reagent's efficiency and symmetry breaking capability of quartz surface in cooperative action with silver ammine reagent.[23] Details will be discussed.

The optically active quartz is mainly available naturally and not easy to prepare. On the other hand literature shows generation of chiral silver clusters using redox reaction in presence of

optically pure amine. [24] With this background, and our hypothesis we carried out Tollens' reaction with d/l-glucose in borosilicate glass tube and 'imagined' that the obtained silver coating is of optically active silver, as shown in scheme 4.3.3. This borosilicate glass tube is then employed for BINOL formation. In this strategy also we could get up to 38% of ee (S-BINOL) with over 90% yield. Polarimeter was used for optical measurement, and are aware of its limitation. Details will be discussed. However, the enantiomeric excess (ee) obtained by these method was not consistent. Therefore resultant silver was analyzed using optical microscopy and field emission scanning electron microscopy (FESEM) and SEM. Figure 4.1 shows uncommon ball like structures of silver aggregation/assembly, which is not common in literature. [25] Details will be discussed.

## **4.5 Conclusion**

Aggregate formation of Silver during Tollens' test is correlated as a driving force for enantiomerically rich BINOL synthesis. To the best of our knowledge, this attempt is one of its kind and has not reported in literature, and will be discussed in thesis. Although the attempt is in primary stage and involve many factors, it's in depth analysis will be provided in due course. We would like to mention that enantiomeric rich product confirmation was carried out by polarimetrically , X-ray diffraction and microscopic measurements.

## **Chapter 5: Extension activities of Tollens' reaction**

### **5.1 Introduction**

This chapter contributes different efforts designed for understanding Tollens' reagent. Although the oxidation reactions of aldehydes are well established in the literature selectivity of Tollens' reagent in presence of other functional group is not studied in detail. This chapter makes an effort on this aspect. Apart from this separate and distinct formation of reduced Ag particles and oxidized organic component prompted us to think out-of-box methods to carry out this reaction, which may or may not find application, such as (a) reaction directly on TLC plate, (b) reaction in sublimation assembly and (c) reaction in melting point capillary tubes. These methods initially developed for educational activity. Silver nanoparticle is still challenging and intriguing field, and therefore efforts are made to synthesize silver nanoparticles using modified Tollens' reagent and variety of reducing agents. All these experiments were repeated many times and wherever possible yields obtained are quantitatively standardized.

## 5.2 Research objectives

- Understanding reactivity of Tollens' reagent for oxidation of two functional groups and/or heterocyclic compounds.
- Designing experiments for understanding Tollens' reaction not limited to educational activity, such as sublimation, capillary action.
- To develop novel methodologies for carrying Tollens' reaction which can be find use in material science such as silver nanoparticles, silver coating on different substrates.

## 5.3 Study oxidation reaction and selectivity study for Aromatic and Heterocyclic derivatives of aldehyde, alcohol and phenol

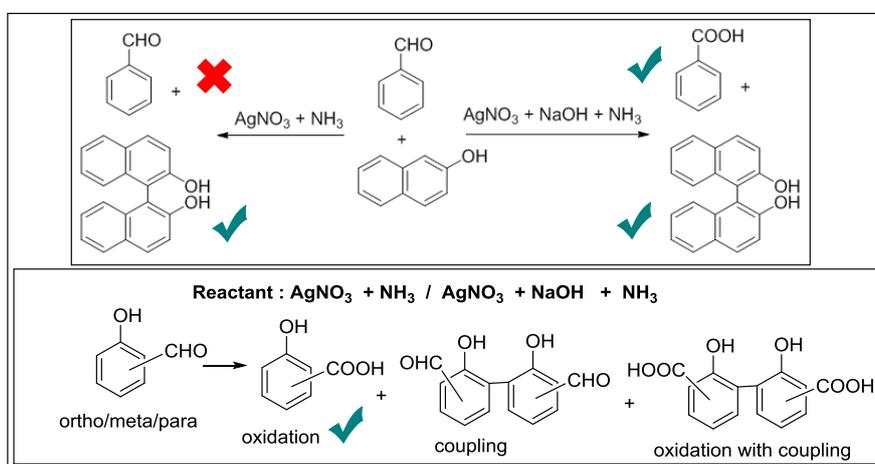


Figure 5.1: shows selectivity study for oxidation and coupling reaction of phenol and aldehyde derivatives

We posed a simple question, what will happen first if the reaction mixture has two molecules one with aldehyde functional group and other with phenols for C-C oxidative coupling reaction? Then we posed 2<sup>nd</sup> question if an aromatic molecule has both phenolic and aldehydic function group, whose oxidation reaction will go to completion? The competition reaction of aldehyde and phenol oxidation using Tollens' reagent were carried out to study selectivity of the reagent as shown in figure 5.1. Using standard Tollens' reagent both reaction products formation was observed and effect of reactivity was also noted on complete conversion. The selective C-C coupling of phenol was obtained over oxidation of aldehydes when reagent was prepared by dissolving silver nitrate in ammonia. Tollens' tests of phenol containing aldehyde functional group were carried out and brief study will be discussed in this section.

The oxidation of 5-(hydroxymethyl)-2-Furfural (HMF) is industrially important reaction, which is carried out using Tollens' reagent. Interestingly 5-formylfuran-2-carboxylic acid is

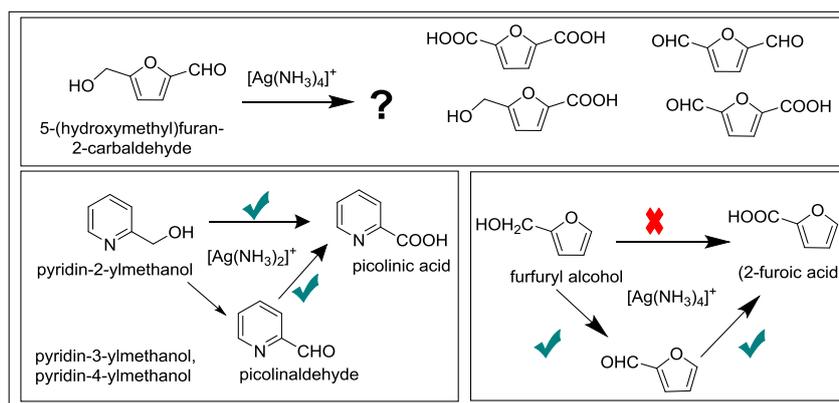


Figure 5.2: shows possible oxidation products formation of heterocyclic aldehyde and alcohol

obtained as a major product instead of 5-(hydroxymethyl) -2-furyl-carboxylic acid. This product formation is possible due to double oxidation or multi oxidation thus to understand this conversion oxidation reaction of heterocyclic (pyridine and furan) alcohol and aldehyde derivatives were carried out, as shown in figure 5.2. This study will be discussed in detail.

#### 5.4 Explore different methodology to carry out reaction

Educational robustness of the reaction can be perceived by carrying out reaction on (i) collecting sublimed 2-naphthol on wet  $[Ag(NH_3)_2]^+$  filter paper, (ii) inserting melting point capillaries in Tollens test with d-glucose, (iii) Making reactants, Tollens' reagent and glucose solution, meet on filter paper directly using capillary action (iv) Use of TLC plate co-spotting

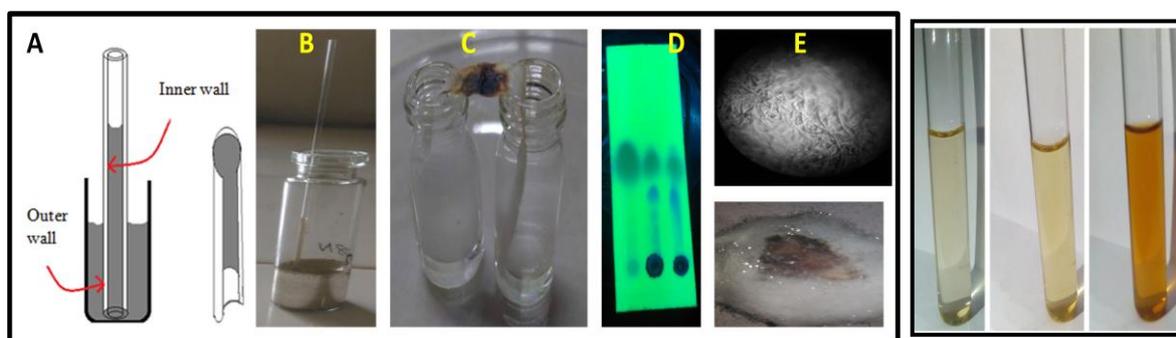


Figure 5.32: shows images of methods used to carry out reaction: A cartoon and B show image of silver deposition in capillary action C. selective mirror deposition on strip due to capillary action D coupling reaction on TLC plate , E microscopic images of silver deposition cotton purge using sublimation method And last one silver nanoparticle solutions

method, support for carrying out oxidative C-C coupling reaction, shown in figure 5.3. Sublimation driven coupling reaction were successfully carried out for two different substrates, (a) 2,4-di-*tert*-butylphenol and (b) 2-naphthol. Homo-coupled products in both cases were isolated and quantified. Herein the metallic silver was remained stained over filter paper and/or cotton plug which showed significant conductive in nature. Microscopic images

of silver stain over filter paper and cotton purge are captured. The results show simple method to synthesize conductive flexible fabric preparation.

C-C oxidative coupling reactions of phenol with silver ammine complex were successfully carried out on TLC plate, which resulted in silver stain along with product formation.

The selective deposition of silver on an inner side of wall of capillary is confirmed experimentally. Attempts were made to understand geometric aspect on selective silver deposition over different surface using capillary action.

### **5.5 Study of Silver nanoparticle synthesis by modifying Tollens' reagent**

The Tollens' reagent is modified to get silver nanoparticle. Interestingly, the growth of thin film formation in the Tollens' test can be arrested and transformed into (or restricted to) nanoparticles. Different sizes of nanoparticles can be observed by changing reaction conditions, aldehyde used and its concentrations as shown in figure 5.3. Properties of different sized nanoparticles and their stabilization before coagulation into thin film will be discussed.

## **Chapter 6: Summary and general conclusions**

In summary, oxidation reactions using Silver ammine complex (Tollens' reagent) have been investigated as shown in figure 6.1. The silver ammine complex was found to be mild and novel reagent for C-C oxidative coupling reactions of phenol and 2-naphthol derivatives. All C-C homo-coupled products were easily separable and obtained with good yields (for most of the cases around 90%). The reagent has shown over 95% recovery and , recycling ability with complete efficiency. The recycled reagents was quantitatively measured using conductometric titration.

The cross-coupling reaction of phenols were also carried out and proposed radical-radical coupling mechanism. Curious experiments were designed in the form of different surfaces for these reactions was undertaken. During oxidative cross-coupling reaction concurrent adhesion of silver particle on different surfaces resulted in chemo-selectivity Reaction carried out in polyethylene (Eppendorf vial) tube resulted in major homo-coupled product while teflon surface resulted in major cross-coupled product. Repeated average yields of coupled products during these reactions were around 90%.

Attempts were made to obtain enantiomerically pure BINOL. After failure attempts of direct chiral induction, quartz surface showed promising route. Quartz surface yielded 90-93% BINOL with and upto 57% ee *s*-BINOL. These results are based on optical rotation data for bulk BINOL product collected using polarimeter, other methods will be incorporated during final submission of thesis. The complete study on mechanism needs more multidisciplinary perspective which will be discussed. In short, novel surface directed reaction mechanism is proposed. Presently, we think the reaction gets driven by the growth of Ag particles, due to  $\text{Ag}^0$ - $\text{Ag}^0$  cohesive interactions and adhesive interaction between Ag-particle and surface. The selectivity of the reagent towards oxidation was further extended to some heteroaromatic

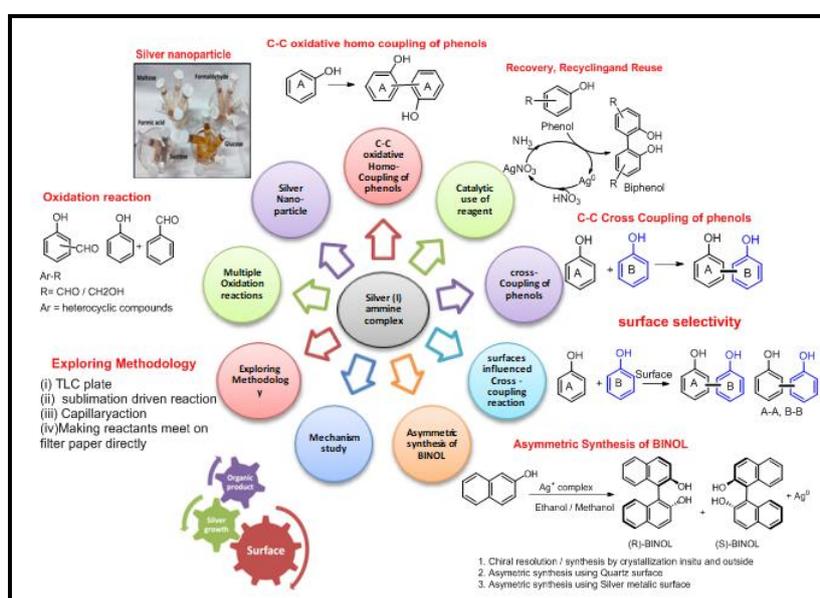


Figure 6.1 shows Summary of Thesis

and aromatic aldehyde, phenols and alcohols. Tollens' reactions were also carried out using non-conventional methodologies to understand and explore different aspects of chemistry, such as sublimation, reaction directly on TLC plate, and conducting silver coating on paper/fabric. Apart from this different sizes of silver nanoparticles were also synthesized using this modified reagent and number of reducing agents..

**Reference:**

- [1] A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford, and P. W. G. Smith, *Vogel's textbook of practical organic chemistry*, 5th ed. New York, 1989.
- [2] M. I. Elzagheid, "Laboratory Activities to Introduce Carbohydrates Qualitative Analysis to College Students," *World J. Chem. Educ.*, vol. 6, no. 2, pp. 82–86, 2018.
- [3] G. Fang, X. Cong, G. Zanoni, Q. Liu, and X. Bi, "Silver-Based Radical Reactions : Development and Insights," *Adv. Synth. Catal.*, vol. 359, no. 9, pp. 1422–1502, 2017.
- [4] L. Han, P. Xing, and B. Jiang, "Selective Aerobic Oxidation of Alcohols to Aldehydes, Carboxylic Acids, and Imines Catalyzed by a Ag-NHC Complex," *Org. Lett.*, vol. 16, no. 13, p. 3428–3431, 2014.
- [5] M. Liu, H. Wang, H. Zeng, and C. J. Li, "Silver(I) as a widely applicable, homogeneous catalyst for aerobic oxidation of aldehydes toward carboxylic acids in water-"silver mirror": From stoichiometric to catalytic," *Sci. Adv.*, vol. 1, no. 2, p. e1500020, 2015.
- [6] C. Marseille, "Enantioselective Silver-Catalyzed Transformations," *Chem. Rev.*, vol. 116, no. 23, pp. 14868–14917, 2016.
- [7] A. Hossain, A. Bhattacharyya, and O. Reiser, "Copper's rapid ascent in visible-light photoredox catalysis," *Science*, vol. 364, no. 6439, 2019.
- [8] G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, and M. Breuning, "Atroposelective synthesis of axially chiral biaryl compounds," *Angew. Chemie - Int. Ed.*, vol. 44, no. 34, pp. 5384–5427, 2005.
- [9] J. M. Brunel, "BINOL : A Versatile Chiral Reagent," *Chem. Rev.*, vol. 105, no. 3, pp. 857–897, 2005.
- [10] M. Grzybowski, B. Sadowski, H. Butenschön, and D. T. Gryko, "Synthetic Applications of Oxidative Aromatic Coupling—From Biphenols to Nanographenes," *Angew. Chemie - Int. Ed.*, vol. 59, no. 8, pp. 2998–3027, 2020.
- [11] L. Bayeh, P. Q. Le, and U. K. Tambar, "Catalytic allylic oxidation of internal alkenes to a multifunctional chiral building block," *Nature*, vol. 547, no. 7662, pp. 196–200, 2017.
- [12] I. Kanwal *et al.*, "Palladium and Copper Catalyzed Sonogashira cross Coupling an Excellent Methodology for C-C Bond Formation over 17 Years: A Review," *Catalysts*, vol. 10, no. 4, p. 443, 2020.
- [13] L. Y. Wu, M. Usman, and W. B. Liu, "Enantioselective Iron/Bisquinolyldiamine Ligand-Catalyzed Oxidative Coupling Reaction of 2-Naphthol," *Molecules*, vol. 25, no. 4, p. 852, 2020.
- [14] T. Orlova, F. Lancia, C. Loussert, S. Iamsaard, N. Katsonis, and E. Brasselet, "Revolving supramolecular chiral structures powered by light in nanomotor-doped liquid crystals," *Nat. Nanotechnol.*, vol. 13, no. 4, pp. 304–308, 2018.
- [15] H. Reiss, H. Shalit, V. Vershinin, N. Y. More, H. Forckosh, and D. Pappo, "Cobalt(II)[salen]-

- Catalyzed Selective Aerobic Oxidative Cross-Coupling between Electron-Rich Phenols and 2-Naphthols," *J. Org. Chem.*, vol. 84, no. 12, pp. 7950–7960, 2019.
- [16] P. S. Ghalsasi and K. D. Bhanderi, "C-C oxidative coupling of phenols and its derivatives catalyzed by silver ammonia complex," 333913, 2020.
- [17] C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, and V. Snieckus, "Palladium-catalyzed cross-coupling: A historical contextual perspective to the 2010 nobel prize," *Angew. Chemie - Int. Ed.*, vol. 51, no. 21, pp. 5062–5085, 2012.
- [18] H. Shalit, A. Dyadyuk, and D. Pappo, "Selective Oxidative Phenol Coupling by Iron Catalysis," *J. Org. Chem.*, vol. 84, no. 4, pp. 1677–1686, 2019.
- [19] J. L. Röckl, D. Pollok, R. Franke, and S. R. Waldvogel, "A Decade of Electrochemical Dehydrogenative C,C-Coupling of Aryls," *Acc. Chem. Res.*, vol. 53, no. 1, pp. 45–61, 2020.
- [20] K. Niederer, P. H. Gilmarin, and M. Kozlowski, "Oxidative Photocatalytic Homo- and Cross-Coupling of Phenols: Non-Enzymatic, Catalytic Method for Coupling Tyrosine," 2020.
- [21] J. M. Brunel, "Update 1 of: BINOL : A Versatile Chiral Reagent," *Chem. Rev.*, vol. 107, no. 9, pp. 1–45, 2007.
- [22] K. Soai, "Asymmetric autocatalysis . Chiral symmetry breaking and the origins of homochirality of organic molecules," *Proc. Jpn. Acad., Ser. B*, vol. 95, no. 3, pp. 89–109, 2019.
- [23] P. S. Ghalsasi and K. D. Bhanderi, "Microscopic cavity to Macroscopic Surface for Asymmetric Synthesis," 201721039245, 2017.
- [24] L. Ma, Y. Cao, Y. Duan, L. Han, and S. Che, "Silver Films with Hierarchical Chirality," *Angew. Chemie - Int. Ed.*, vol. 56, no. 30, pp. 8657–8662, 2017.
- [25] K. Bhanderi, P. S. Ghalsasi, and K. Inoue, "Nonconventional driving force for selective oxidative C–C coupling reaction due to concurrent and curious formation of Ag<sub>0</sub>," *Sci. Rep.*, vol. 11, no. 1, pp. 1–11, 2021.

**Ms. Khushboo D. Bhanderi**  
Research Scholar

**Prof. (Dr.) Prasanna Ghalsasi**  
Research Supervisor

**Department of Chemistry,**  
**Faculty of Science,**  
The Maharaja Sayajirao University of Baroda  
Vadodara.-390002. GUJARAT-INDIA.

**Department of Chemistry**

**HEAD**  
**Department of Chemistry**  
**Faculty of Science,**  
The Maharaja Sayajirao University of Baroda  
Vadodara- 390002. Gujarat - INDIA