

# Chapter - 5

## Different Routes for Cinnamaldehyde Synthesis

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**Abstract**—Cinnamaldehyde is considered to be one of the classical compounds that have high biological and pharmacological significance. It has also found many applications as flavoring agent, antimicrobial, antifungal compounds. However, the synthesis of cinnamaldehyde is rather typical, and its biosynthesis process involves many multiple steps using coenzymes. Commonly known procedures for the synthesis of cinnamaldehyde are discussed in this chapter.

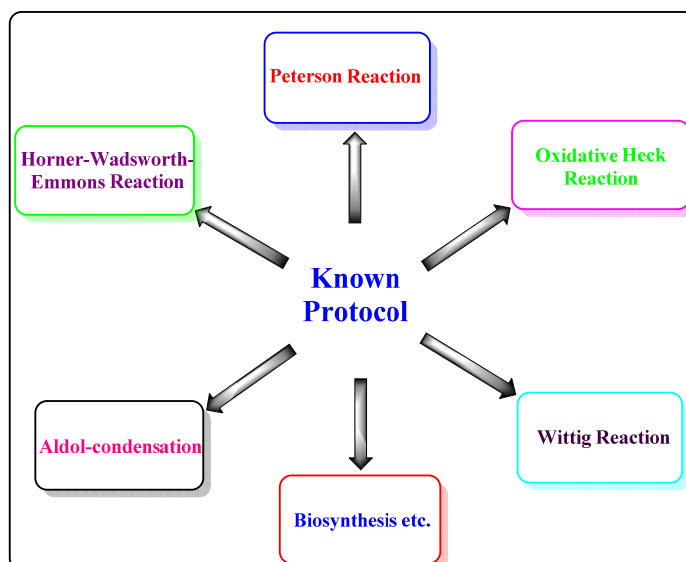
### Introduction

Cinnamaldehyde is considered as one of the classical organic compounds with chemical formula  $C_6H_5CH=CHCHO$  that have high biological and pharmacological significance.<sup>1,2</sup> Cinnamaldehyde occurs naturally in the E (trans) stereoisomer, the parent class of cinnamaldehyde. Cassia trees are the natural source of cinnamon, and the essential oil of cinnamon bark is about 90% cinnamaldehyde. Cinnamaldehyde has also found many applications as antimicrobial, antifungal compounds, etc.<sup>1-3</sup> The properties like low toxicity make cinnamaldehyde ideal to be beneficial in agriculture

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and are also effective insecticide repellent. It is also known as a corrosion inhibitor for steel and other ferrous alloys in corrosive fluids.<sup>4</sup> However, cinnamaldehyde in high concentration can cause skin irritant, but till now, no such agencies have suspected or reported any health hazard or any carcinogen activities.<sup>5</sup>

On the other hand, the synthesis of cinnamaldehyde is rather typical, and its biosynthesis process involves several multiple steps using coenzymes.<sup>6</sup> Several laboratory preparation methods of cinnamaldehyde are known, but cinnamaldehyde is mostly produced by cross-aldol condensation of benzaldehyde with acetaldehyde ( $\text{CH}_3\text{CHO}$ ) in the presence of a dilute basic condition, such as KOH, NaOH, etc.<sup>3</sup> Other processes of synthesis of cinnamaldehyde include Peterson reaction,<sup>7</sup> Horner-Wadsworth-Emmons (HWE) reaction,<sup>8</sup> and Wittig reaction.<sup>1</sup> Nordqvist *et al.* synthesized several derivatives of cinnamaldehyde by an oxidative Heck reaction between acrolein and phenylboronic acids (Scheme 1).<sup>2</sup> However, the synthesis of cinnamaldehyde by *in situ* formations of  $\text{CH}_3\text{CHO}$  through partial oxidation of ethanol has not been reported so far in literature. As the cost of  $\text{C}_2\text{H}_5\text{OH}$  is lower than  $\text{CH}_3\text{CHO}$ , therefore the preparation of cinnamaldehyde through  $\text{C}_2\text{H}_5\text{OH}$  oxidation would be a highly economically beneficial process and this area can be further extended for the replacement of acetaldehyde.



**Scheme 1.** Schematic representation showing some known protocols for the synthesis of cinnamaldehyde.

The transition metal ions have outermost d orbital that is incompletely filled with electrons, and that is why they can easily give and take electrons. This makes transition metals and transition metal complexes prime candidates for catalysis. The production of many industrially important chemicals, biochemically significant processes, organic synthesis processes are also catalyzed by transition metals. Because of the tunable chemical and physical properties of the transition metals, in recent years, it has attracted more industrial applications.<sup>9-18</sup> Palladium-based catalysts facilitate a large number of carbon-carbon bonding reactions in organic chemistry and few examples include Heck reaction, Suzuki coupling, Wacker process, Negishi reaction, Stille coupling, Sonogashira coupling, etc. Due to such excellent catalytic characteristics, palladium-based

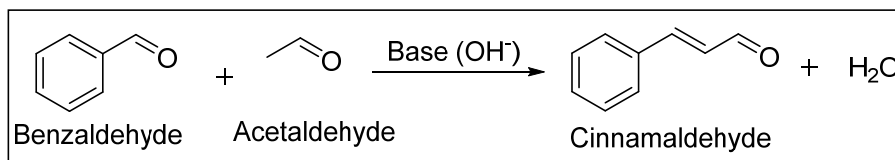
materials have been studied exclusively in recent years.<sup>9-11</sup> On the other hand, gold (Au) nanoparticle with its unique catalytic activities also attracted much attention in many organic syntheses at laboratory and industrial applications.<sup>17-19</sup> For alcohol oxidation, Au-based catalysts are found to be very effective.<sup>13,14,16,20</sup>

In comparison with the monometallic nanoparticles, the catalytic activities of bimetallic nanoclusters or metal oxides show better activity due to the symbiosis existing between two different metals.<sup>9,13,14,15</sup> It also shows significantly different properties from those of pure individual monometallic because of the surface electronic properties and thereby control the overall leaching process. Besides this, alloying of palladium with other metal is also a particularly important technique in the field of catalysis as it reduces the leaching process.<sup>14,15</sup> In the bimetallic nanocluster, electronic heterogeneity exists due to the electronegativity difference between the two metals center and this system greatly enhances the interaction between the residing NPs and the incoming substrate. Additionally, the synergistic effect enhances the reactivity and stability of the catalyst.

### **Cinnamaldehyde synthesis**

Cinnamaldehyde is usually produced by cross-aldol condensation of benzaldehyde (which have no  $\alpha$ -hydrogen) with acetaldehyde (having  $\alpha$ -hydrogen), in the presence of a base like sodium hydroxide (NaOH) or potassium hydroxide (KOH).<sup>3</sup> This base catalyze condensation reaction is carried out at moderately elevated temperature in the range of 60-80 °C,

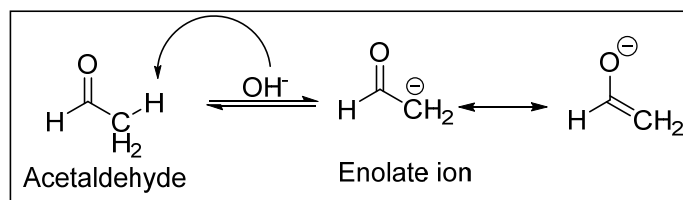
and the yield of the cinnamaldehyde is dependent upon the molecular proportion of both benzaldehyde and acetaldehyde.<sup>3</sup> The reaction mixture should be maintained in an alkaline pH by the addition of base from time to time in the range of 8 to 12. A schematic diagram for the synthesis of cinnamaldehyde is given in Scheme 2.



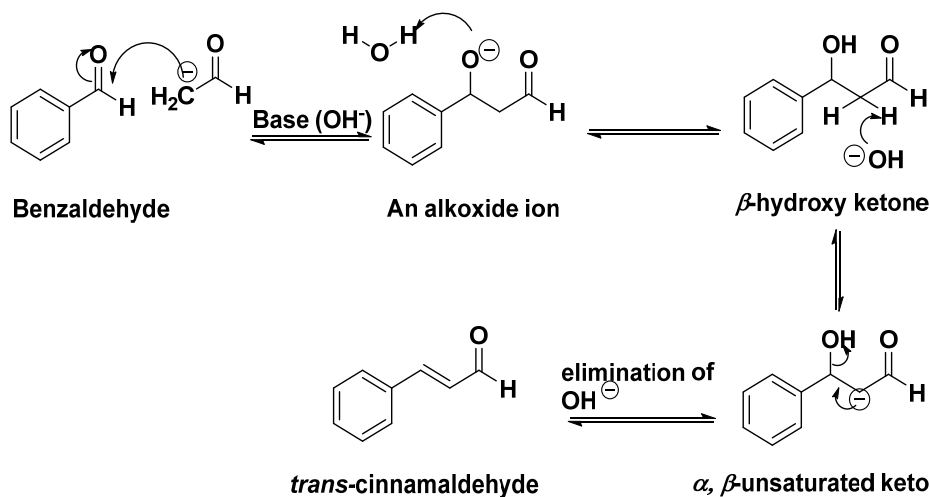
**Scheme 2.** Preparation of cinnamaldehyde by the base catalyze condensation of acetaldehyde and benzaldehyde.

### Mechanism of cinnamaldehyde synthesis

We know that aldol condensation of a mixture of two different aldehydes or ketones each containing a  $\alpha$ -hydrogen gives a mixture of four products. The produced enolate anion adds to the compound leading to an aldol condensation product. However, in the case of cross-aldol condensation, the other two products arise when different carbonyl compounds are used. The cross aldol condensation has no synthetic value except when one of the carbonyl compounds has no  $\alpha$ -hydrogen. In the reaction between benzaldehyde, which have no  $\alpha$ -hydrogen and acetaldehyde, having  $\alpha$ -hydrogen, the cross aldol product easily losses water molecule to give cinnamaldehyde. The first step of this reaction is the formation of acetaldehyde enolate anion, which is given in Scheme 3 as follows.



**Scheme 3.** A plausible approach for the enolate ion formation.

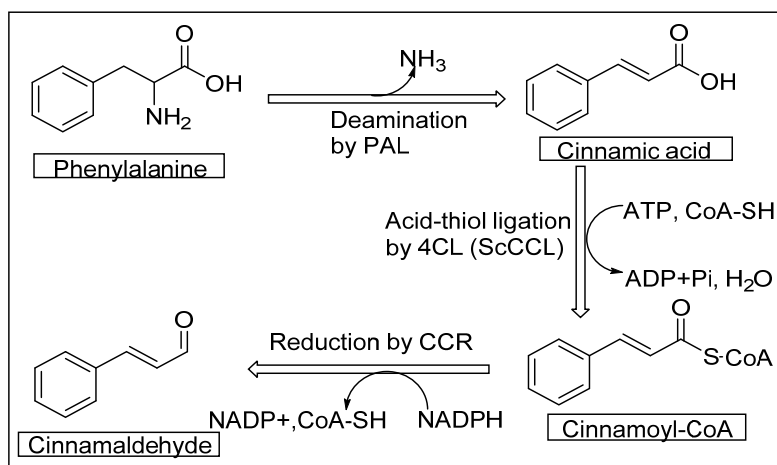


**Scheme 4.** The base-catalyzed reaction mechanism for the formation of cinnamaldehyde from benzaldehyde and acetaldehyde.

We know enolate is nucleophilic, and its attack to the electrophilic carbonyl carbon center of benzaldehyde forming an alkoxide ion followed by  $\alpha$ -hydroxy ketone (Scheme 4). The electron pair on the carbon is used to eliminate the hydroxide ion, forming an  $\alpha, \beta$ -unsaturated ketone, the desired product, *trans*-cinnamaldehyde (Scheme 4). Nordqvist *et al.* synthesized several derivatives of cinnamaldehyde by an oxidative Heck reaction between acrolein and phenylboronic acids.<sup>2</sup>

### Biosynthesis of cinnamaldehyde

Bang *et al.* utilized *Escherichia coli* as an eco-friendly biological platform for the production of cinnamaldehyde and synthesized from intracellular L-phenylalanine. The first step of the biosynthesis of cinnamaldehyde begins with deamination of L-phenylalanine into *trans*-cinnamic acid by the action of phenylalanine ammonia-lyase (PAL) enzyme.<sup>21</sup> In the second step, 4-coumarate–CoA ligase converts cinnamic acid to cinnamoyl-CoA by an acid–thiolligation. 4-coumarate–CoA ligase (4CL) uses ATP hydrolysis to catalyze the formation of cinnamoyl-CoA. The third step comprises the reduction of cinnamoyl-CoA to cinnamaldehyde and the Cinnamoyl-CoA is reduced by NADPH and catalyzed by cinnamoyl-CoA reductase (CCR) enzyme.<sup>21</sup> The synthetic pathway is given below in Scheme 5.

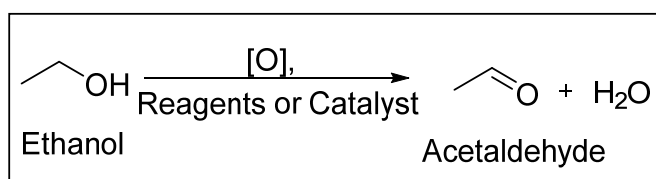


**Scheme 5.** Biosynthetic route of production of cinnamaldehyde.

### Ethanol oxidation

We know that oxidation of alcohol is an important organic reaction. Primary alcohols can be oxidized either to aldehydes or carboxylic acids,

while the oxidation of secondary alcohols normally terminates at the ketones. Tertiary alcohols are resistant to oxidation and partial oxidation of alcohols yields aldehydes and its further oxidation generates the over-oxidized product, i.e., carboxylic acid. Various types of reagents and catalysts are employed for this purpose.<sup>22</sup> Recently, various types of catalysts like Au-CuOx, Cu/ZrO<sub>2</sub>, and Au/MgCuCr<sub>2</sub>O<sub>4</sub> are reported to be active for complete or partial oxidation of ethanol, Scheme 6.<sup>23</sup> Pd-Au catalysts are also known to be active for the oxidation of C<sub>2</sub>H<sub>5</sub>OH.<sup>24, 25</sup>



**Scheme 6.** Ethanol oxidation process using catalyst or reagents.

Nowadays, several supported catalysts are found to be more significant in different organic reactions. In this regard, several organic and inorganic supports such as zeolite, silica, MOF, etc were used to anchor Pd(II) or Pd(0) complexes.<sup>26,27</sup> At the very beginning of organic reaction, the catalysts mainly used were homogenous catalysts with bulky ligand systems such as Pd (PPh<sub>3</sub>)<sub>4</sub>, Pd (OAc)<sub>2</sub>, etc.<sup>26</sup> The choice of ligands was an important issue as the size and nature of ligands plays an important role in the reaction and stability of the catalyst. Several developments were made in ligands systems such as phosphanes, N-heterocyclic carbenes with time (details of ligands are provided in chapter 2).<sup>27</sup> The interest was then shifted to heterogeneous catalysts for their manifold advantages over homogenous catalyst.<sup>12,28-31</sup> In general, heterogeneous catalysts are easier



to isolate from the reaction mixture and are also easily recycled. Furthermore, heterogeneous catalysts provide greater surface area for reaction to take place.

### Conclusion

In concluding remark, this chapter briefly describes the different synthetic procedures for cinnamaldehyde synthesis along with their applications. The use of in situ oxidized ethanol to acetaldehyde can further be explored in the synthesis of cinnamaldehyde.

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