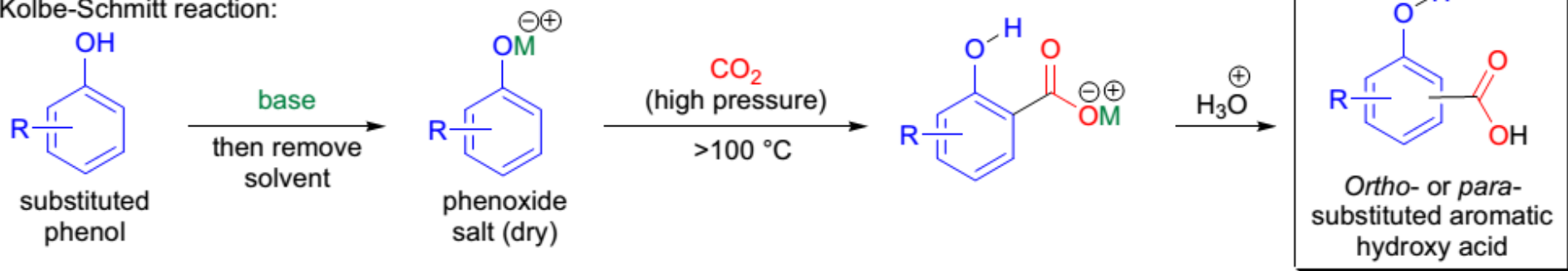


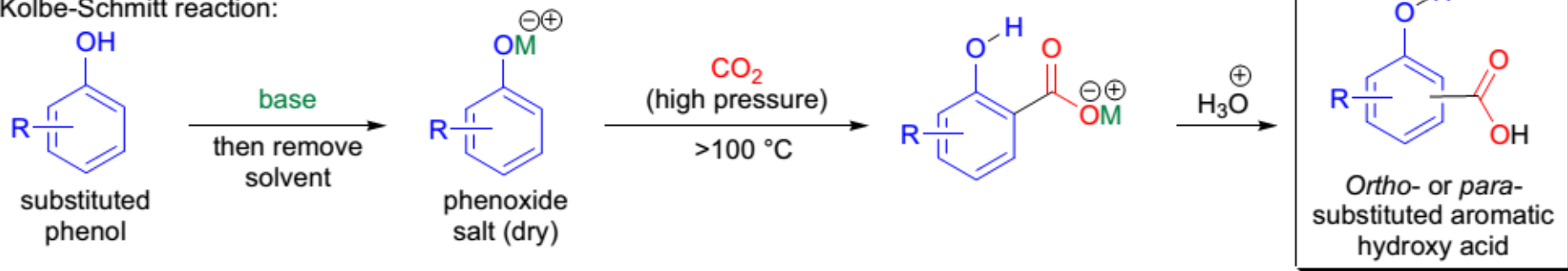
KOLBE-SCHMITT REACTION

Kolbe-Schmitt reaction:



R = H, alkyl, aryl, OH, O-alkyl, NR_2 ; base: alkali metal hydroxides (e.g., NaOH, KOH, CsOH), K_2CO_3 , KHCO_3

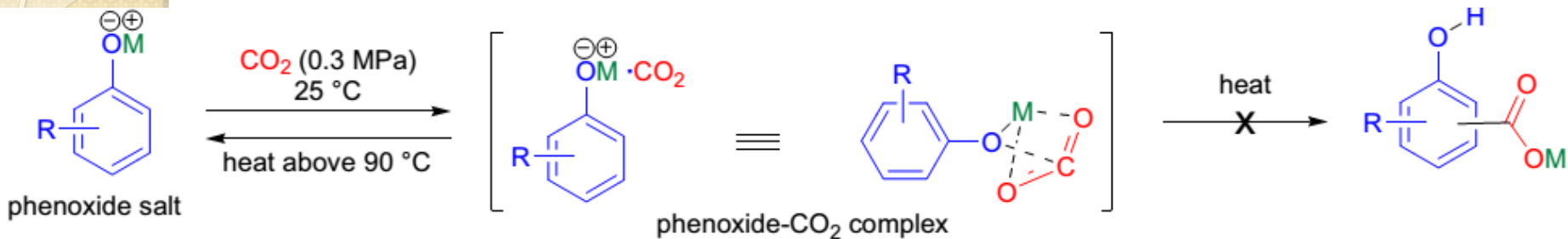
Kolbe-Schmitt reaction:



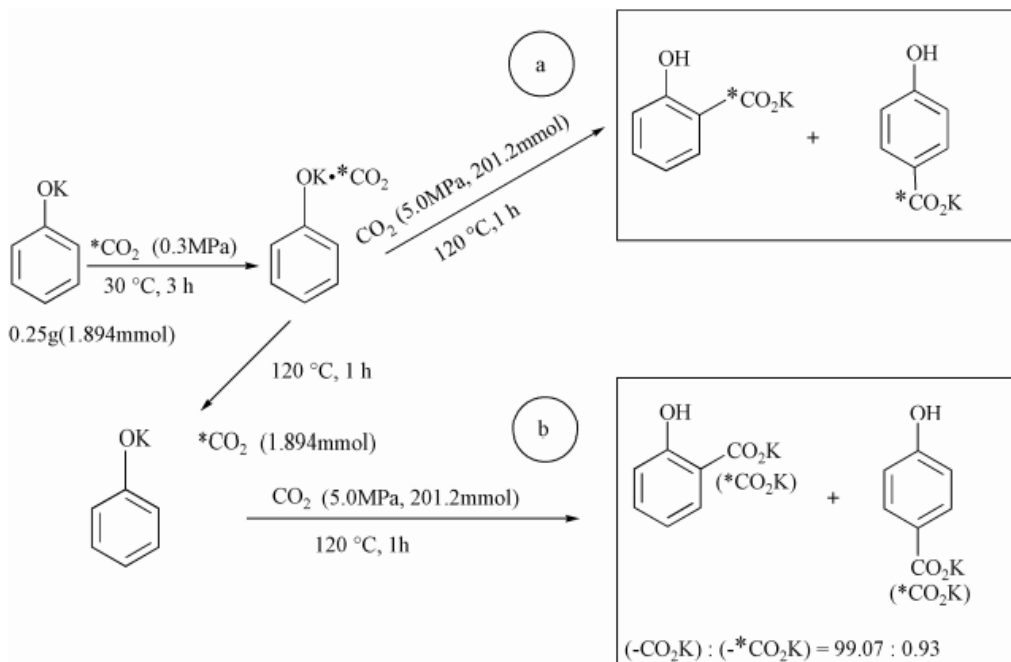
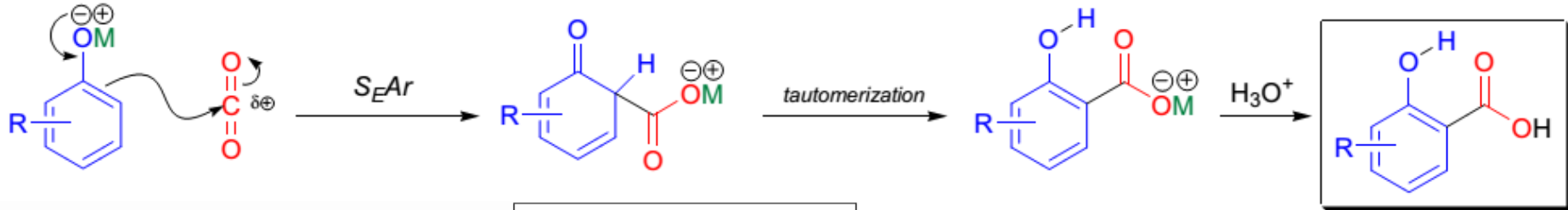
R = H, alkyl, aryl, OH, O-alkyl, NR_2 ; base: alkali metal hydroxides (e.g., NaOH, KOH, CsOH), K_2CO_3 , KHCO_3

- Phenols, substituted phenols, naphthols, and electron-rich heteroaromatic are good substrates;
- Monohydric phenols are first converted to the corresponding alkali or alkali earth phenoxides, dried and then heated in the presence of pressurized CO_2 (5-100 atm);
- Di- or polyhydric phenols (with more than two hydroxyl groups) can be carboxylated with carbon dioxide at atmospheric pressure;
- The size of the alkali metals greatly influences the position of attack, the use of large alkali metal ions such as Rb^+ or Cs^+ gives rise to p-hydroxybenzoic acid derivatives, whereas smaller alkali metal ions (Na^+ or K^+) afford salicylic acid derivatives;
- The presence of even trace amounts of water significantly decreases the yield of the product.

Mechanism



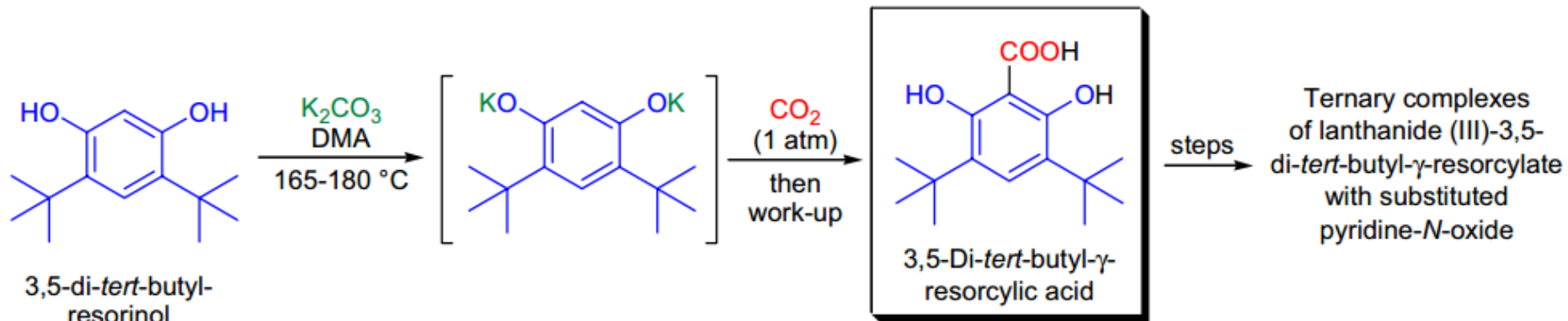
Direct attack of CO₂ on the aromatic ring:



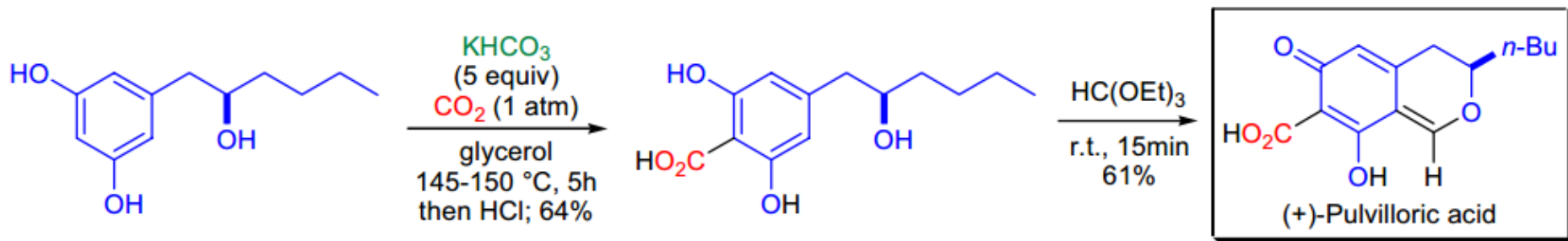
Kosugi, Y. etc. *Org. Biomol. Chem.* **2003**, 1, 817-821.

Synthetic Applications

Phenols that have more than one hydroxyl group may be carboxylated with CO₂ at atmospheric pressure under basic conditions. The research team of Y.-C. Gao synthesized 3,5-di-*tert*-butyl- γ -resorcylic acid from 4,6-di-*tert*-butyl resorcinol using the *Kolbe-Schmitt reaction* under these conditions.²⁶ The resorcylic acid derivative was needed in order to prepare ternary complexes of lanthanide(III)-3,5-di-*tert*-butyl- γ -resorcylate with substituted pyridine-*N*-oxide.



The first enantioselective total synthesis of the fungal metabolite (+)-pulvilloric acid was accomplished by H. Gerlach et al.²⁸ At the final stages of the synthetic effort the carboxylic acid moiety was installed *via* the *Kolbe-Schmitt reaction* using CO₂ at atmospheric pressure. The final formylation and ring-closure were achieved with triethyl orthoformate.



Synthetic Applications

B.S. Green and co-workers developed an improved preparation of the clathrate host compound **tri-*o*-thymotide (TOT)** and other trisalicylide derivatives.²⁷ The synthesis began with the preparation of *ortho*-thymotic acid from thymol using the *Kolbe-Schmitt reaction*. The authors found that the yield of the product was dramatically increased when the reactants, solvents, and reagents were dried before use. Thus, thymol was dissolved in dry xylene, sodium metal was added and the temperature was kept at 130 °C for 20h in a dry carbon dioxide atmosphere. The desired carboxylated product was isolated in good yield. Finally, cyclodehydration with POCl₃ afforded TOT in almost quantitative yield.

