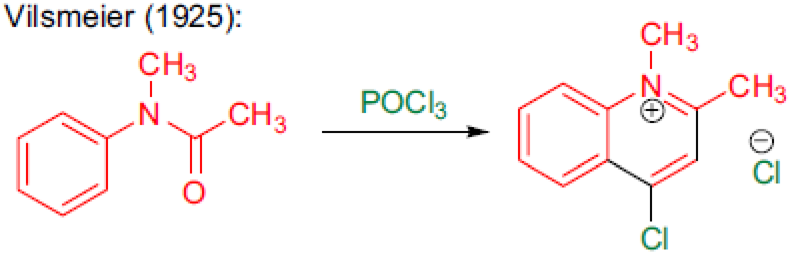
VILSMEIER-HAACK FORMYLATION

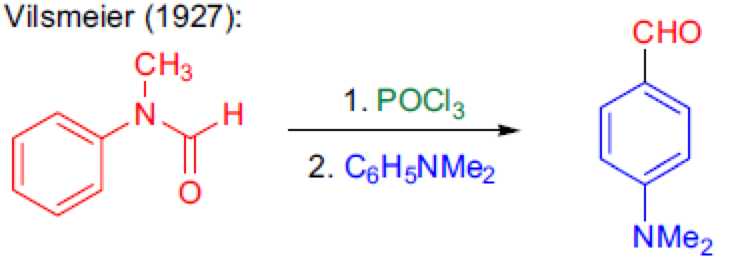
Vilsmeier (1925):



N-methyl-*N*-phenyl-acetamide

4-chloro-1,2-dimethyl-quinolinium chloride

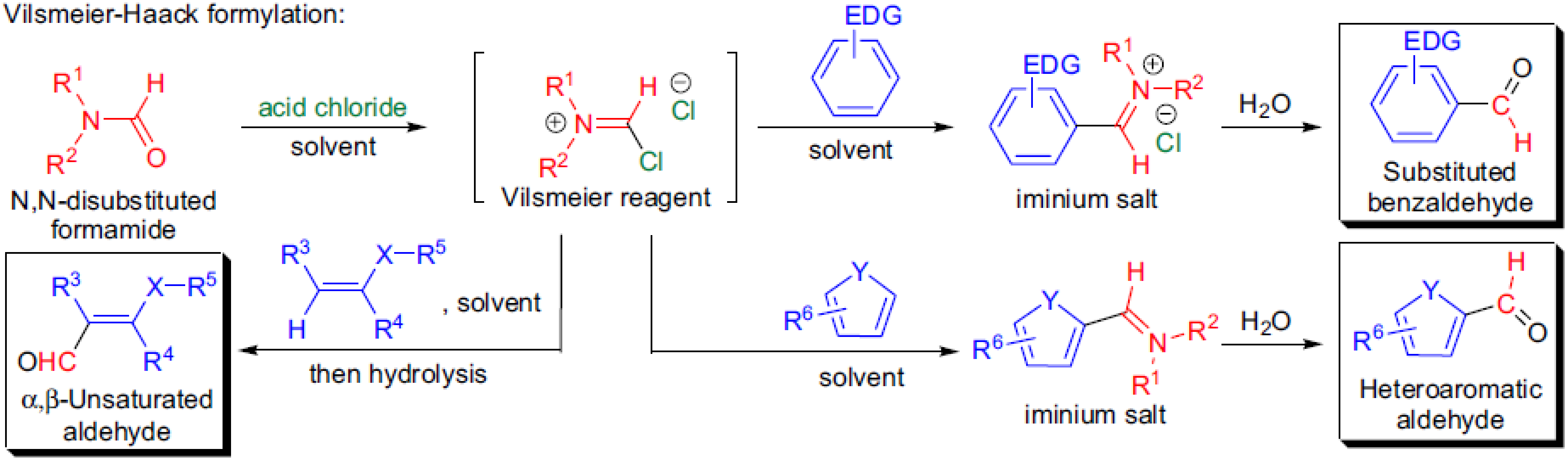
Vilsmeier (1927):



N-methyl-*N*-phenyl-formamide

4-dimethylamino benzaldehyde

Vilsmeier-Haack formylation:

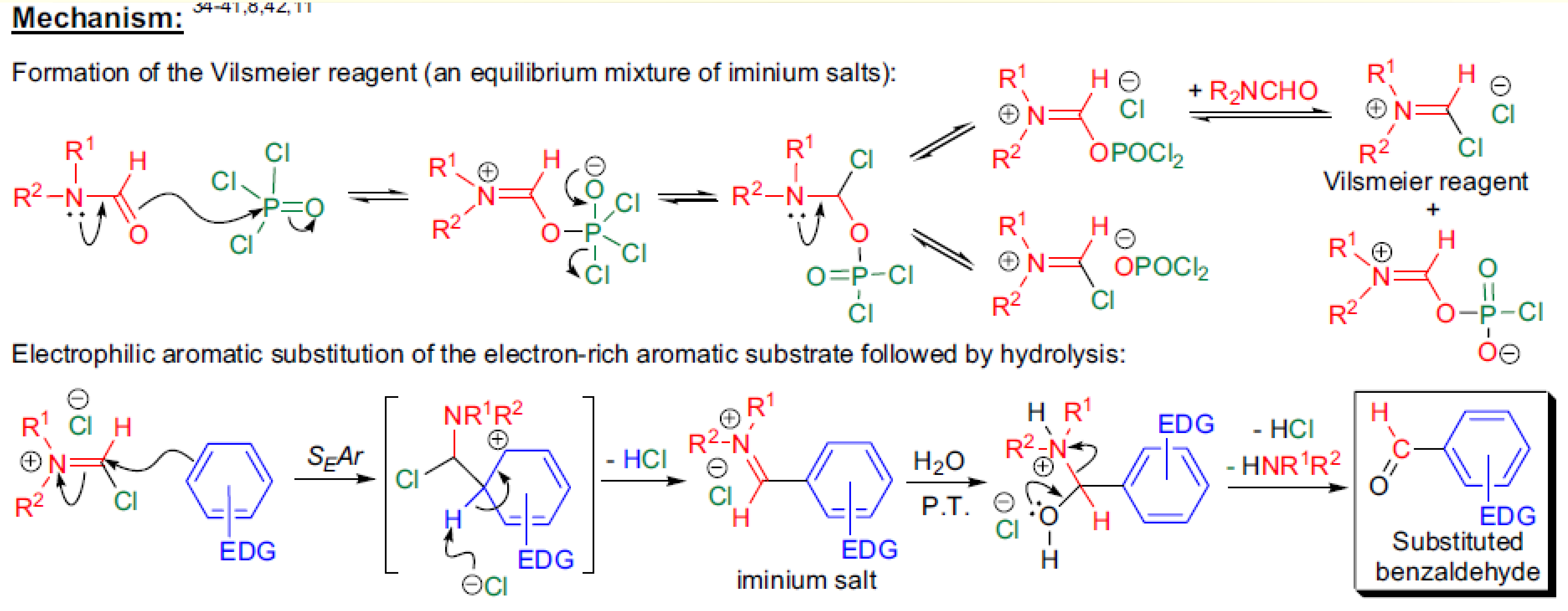


R^{1-2} = alkyl, aryl; acid chloride: POCl$_3$, SOCl$_2$,COCl$_2$, (COCl)$_2$, Ph$_3$PBr$_2$, 2,4,6-trichloro-1,3,5-triazine; solvent: DCM, DMF, POCl$_3$; EDG = OH, *O*-alkyl, *O*-aryl, NR$_2$; R^{3-4} = H, alkyl, aryl; R^5 = alkyl, aryl; X = O, NR, CH$_2$, CR$_2$; Y = O, S, NR, NH; R^6 = H, alkyl, aryl

features

1) the Vilsmeier reagent is prepared from any *N,N*-disubstituted formamide by reacting it with an acid chloride (e.g., $POCl_3$, $SOCl_2$, oxalyl chloride);
2) most often the combination of DMF and $POCl_3$ is used and the resulting Vilsmeier reagent is usually isolated before use;
3) mostly electron-rich aromatic or heteroaromatic compounds as well as electron-rich alkenes and 1,3-dienes are substrates for the transformation, since the Vilsmeier reagent is a weak electrophile;
4) the relative reactivity of five-membered heterocycles is pyrrole > furan >thiophene;
5) the solvent is usually a halogenated hydrocarbon, DMF or POCl3 and the nature of the solvent has a profound effect on the electrophilicity of the reagent, so it should be carefully chosen;
6) the required reaction temperature varies widely depending on the reactivity of the substrate and it ranges from below 0^oC up to 80^oC;
7)the initial product is an iminium salt, which can be hydrolyzed with water to the corresponding aldehyde, treated with H_2S to afford thioaldehydes, reacted with hydroxylamine to afford nitriles, or reduced to give amines;
8) the transformation is regioselective favoring the less sterically hindered position (this means the *para* position on a substituted benzene ring); but electronic effects can also influence the product distribution
9) Vinylogous chloromethyliminium salts undergo similar reaction to afford the corresponding α,β-unsaturated carbonyl compounds upon hydrolysis.

mechanism

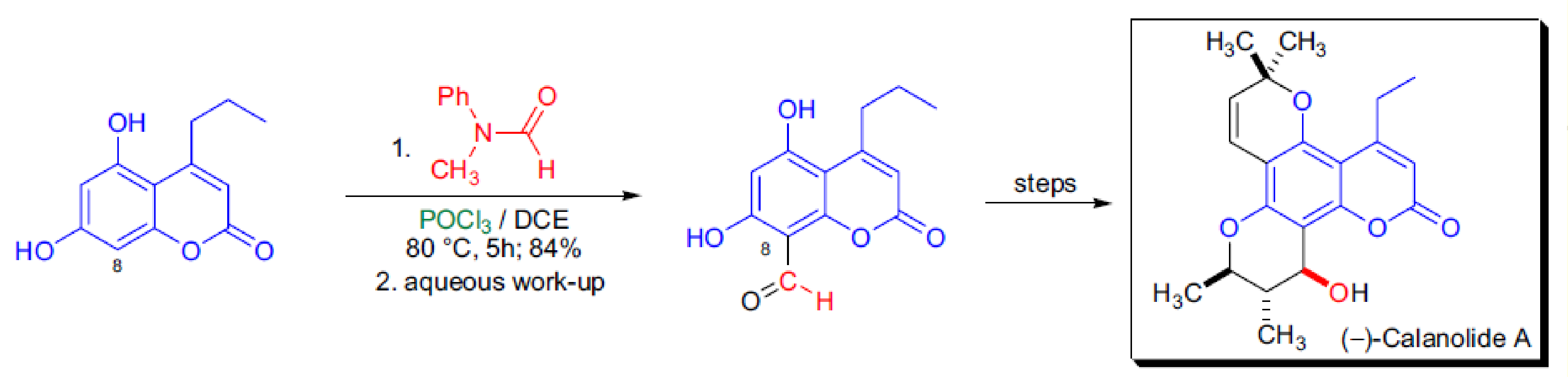


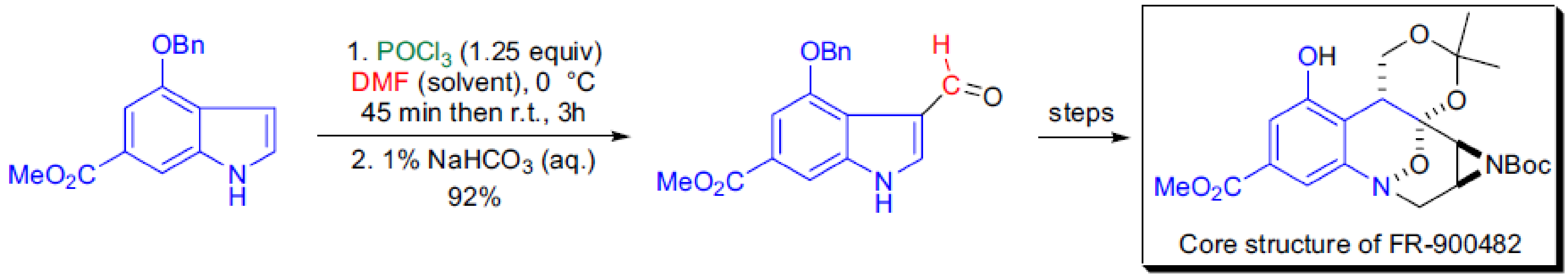
Mechanism:[34-41,8,42,11]

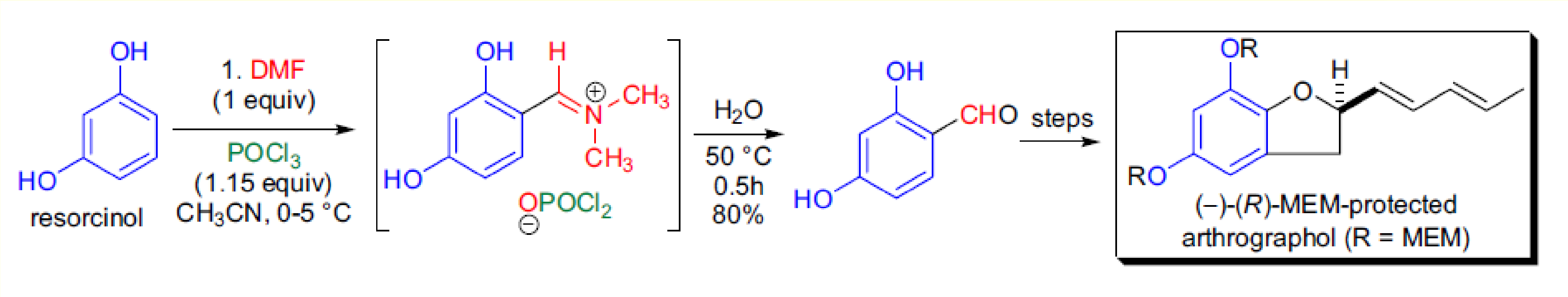
Formation of the Vilsmeier reagent (an equilibrium mixture of iminium salts):

Electrophilic aromatic substitution of the electron-rich aromatic substrate followed by hydrolysis:

application



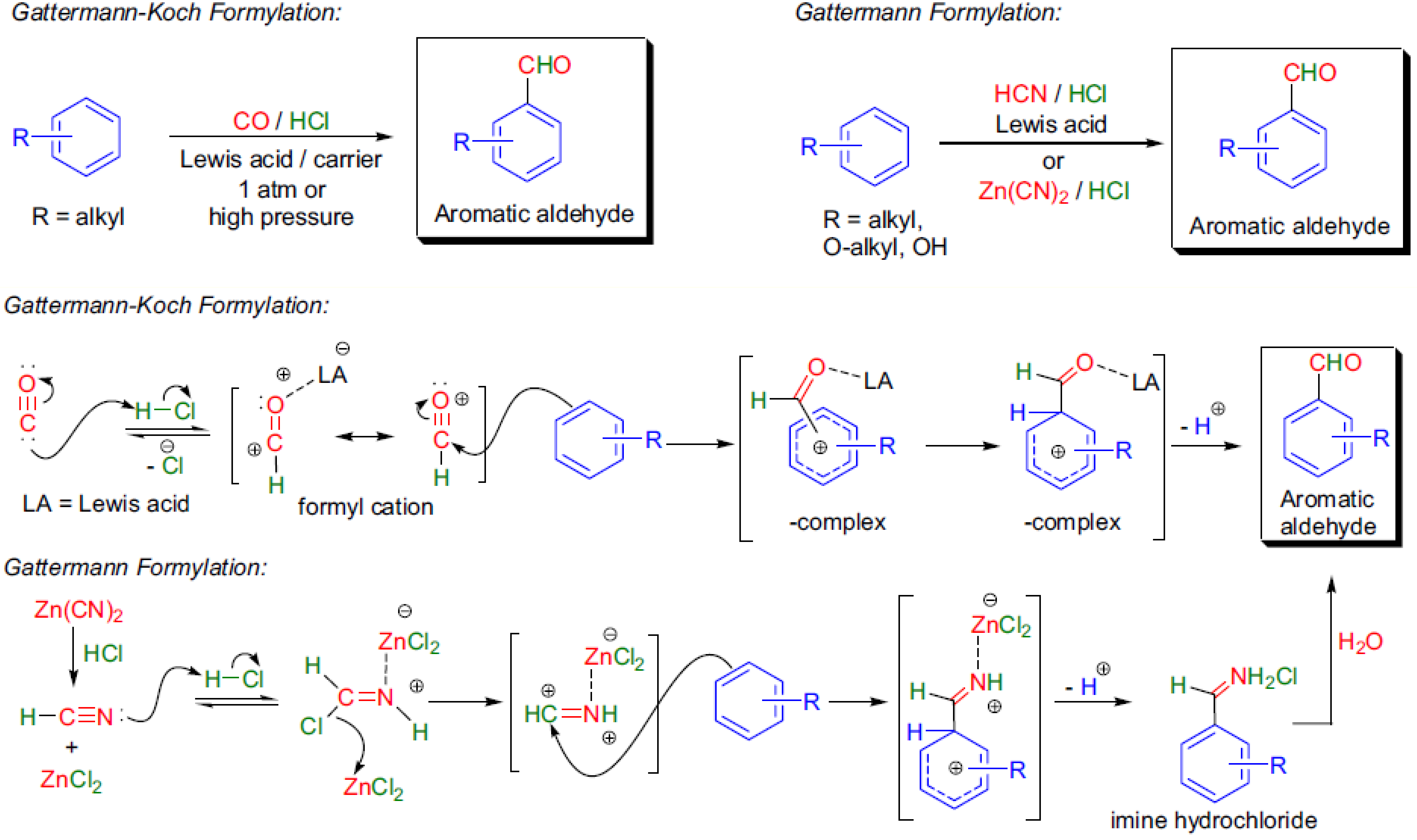




Other Formylation reactions

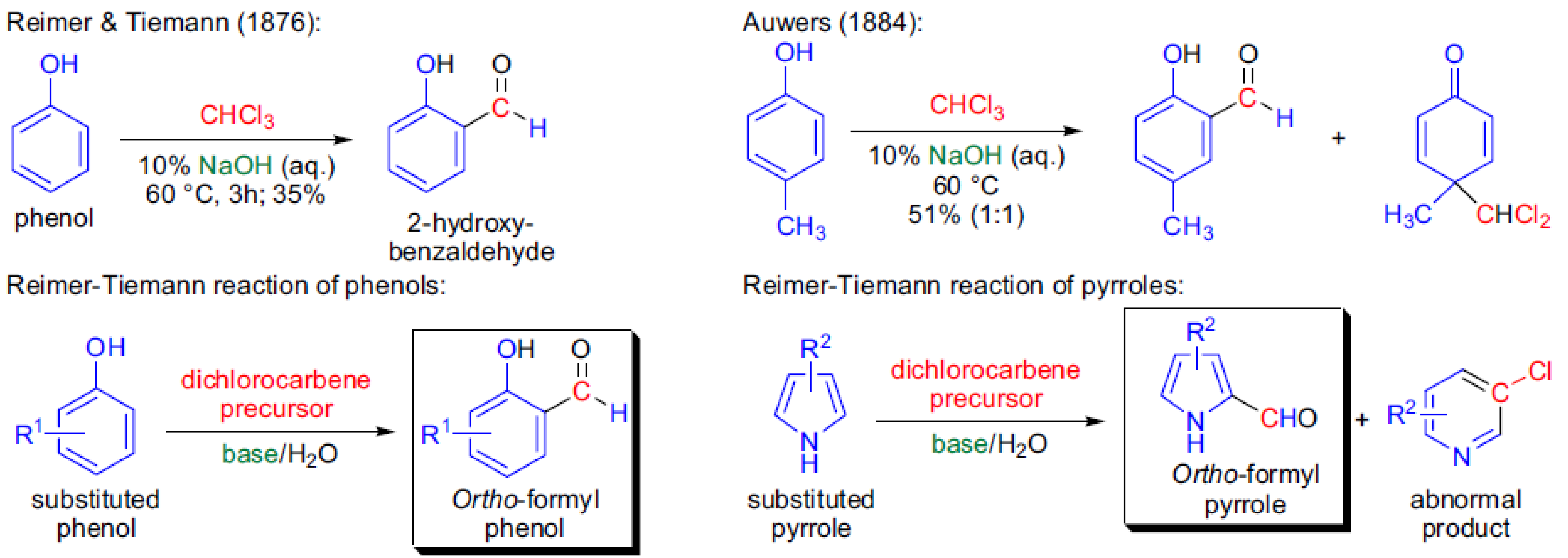
GATTERMANN AND GATTERMANN-KOCH FORMYLATION

1897



Other Formylation reactions

REIMER-TIEMANN REACTION



R^1 = H, alkyl, OH, *O*-alkyl, CO_2H, NO_2, Cl, Br, I; R^2 = H, alkyl; dichlorocarbene precursor: $CHCl_3$, Cl_3CCO_2H, Cl_3CCHO, Cl_3CNO_2;
base: NaOH, KOH, CsOH;

1)the regioselectivity is not high, but *ortho*-formyl products tend to predominate;
2) when the *ortho*-position is already substituted, *para*-formyl phenols are obtained;
3) in the case of pyrroles, when the *ortho* substituent is a CO2H or CO2R group, decarboxylation is observed and the *o*-formyl product is formed (similar findings were reported for an *o*-alkoxy phenol where the alkoxy group was eliminated to give an *o*-formyl phenol);
4) when the reaction is conducted in the presence of cyclodextrins, the *p*-formyl product is formed predominantly.

Other Formylation reactions

REIMER-TIEMANN REACTION