# GATTERMANN AND GATTERMANN-KOCH FORMYLATION

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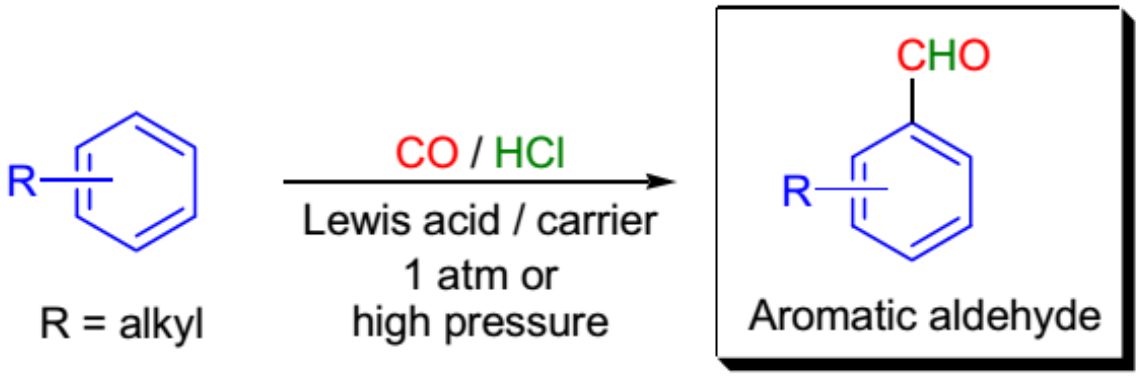
# 1. What Is Gattermann and Gattermann-Koch Formylation

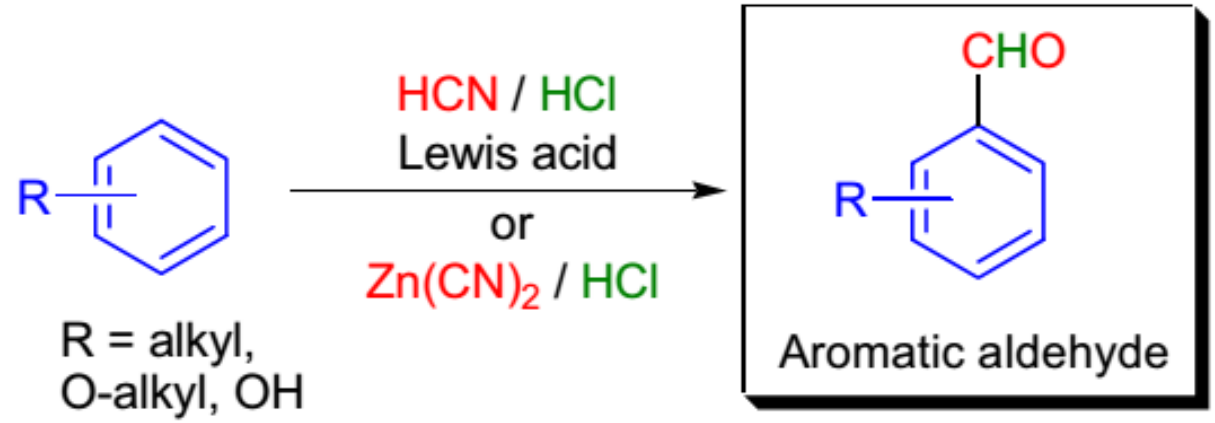
*Gattermann-Koch Formylation:*




In 1897, L. Gattermann and J.A. Koch

Lewis acid catalyst :AlX3, FeX3, where X = Cl, Br, I
carrier/activator :Cu2Cl2, TiCl4 or NiCl2

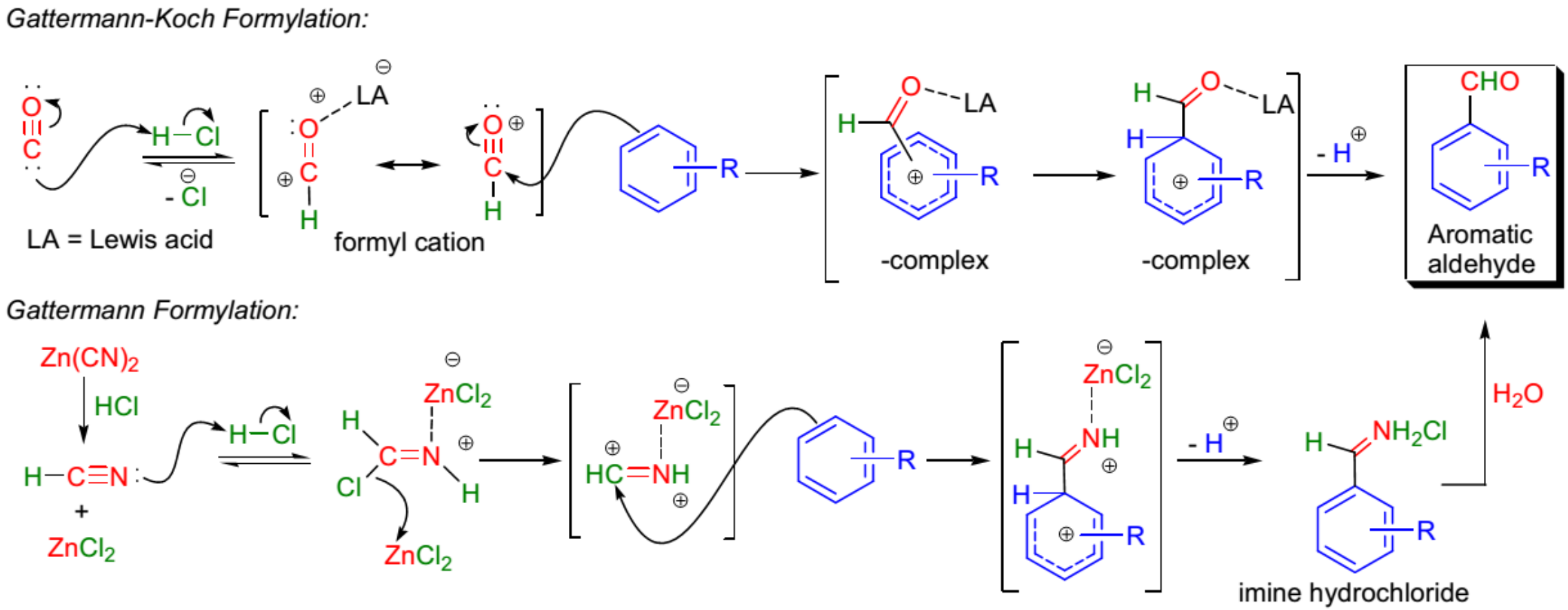
*Gattermann Formylation:*




Gattermann

Adams modification

# 2. Mechanisms of Gattermann and Gattermann-Koch Formylation




The mechanisms of the Gattermann and Gattermann-Koch formylation are not known in detail, since they have a tendency to vary from one substrate to another, and the reaction conditions may also play a role.

# 3. General Features of Gattermann and Gattermann-Koch Formylation

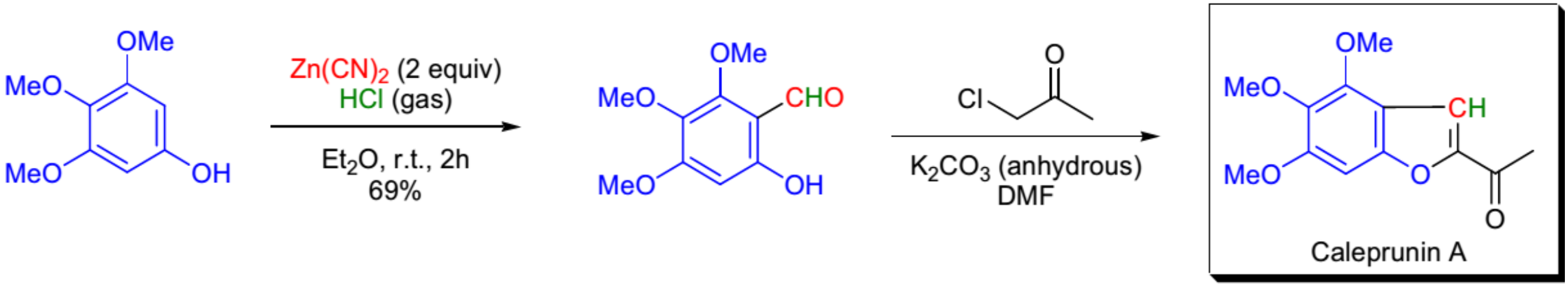
- 1) at atmospheric pressure activated aromatic compounds can be used as substrates (e.g., alkylbenzenes);
- 2) at high CO pressure (100-250 atm) the reaction rate increases significantly and even non-activated aromatics (chlorobenzene, benzene) can be formylated;
- 3) deactivated aromatic compounds (having meta-directing substituents) cannot be formylated with this method;
- 4) a carrier/activator ($Cu_2Cl_2$, $TiCl_4$ or $NiCl_2$) for the catalyst is necessary at atmospheric pressure; however,no activator is needed at high pressure;

# General Features Continuted

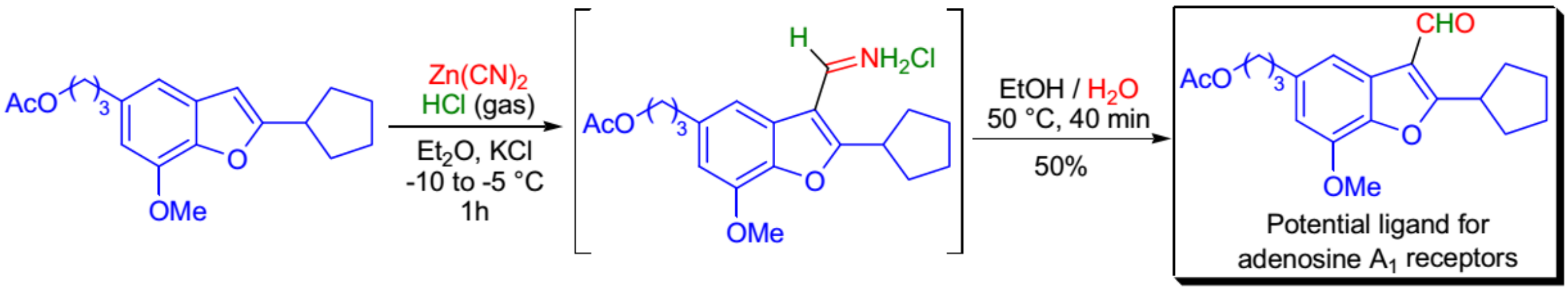
- 5) the amount and purity of the catalyst is very important and often a full equivalent of catalyst is needed;
- 6) monosubstituted substrates are formylated almost exclusively at the para position,but when there is already a para substituent present in the substrate, the formyl group is introduced at the ortho position;
- 7) just as in the Friedel-Crafts reactions, alkyl migration occurs with highly alkylated aromatic substrates;
- 8) the need for high pressures renders this method mainly useful to industrial applications.

# 4. Synthetic Applications:

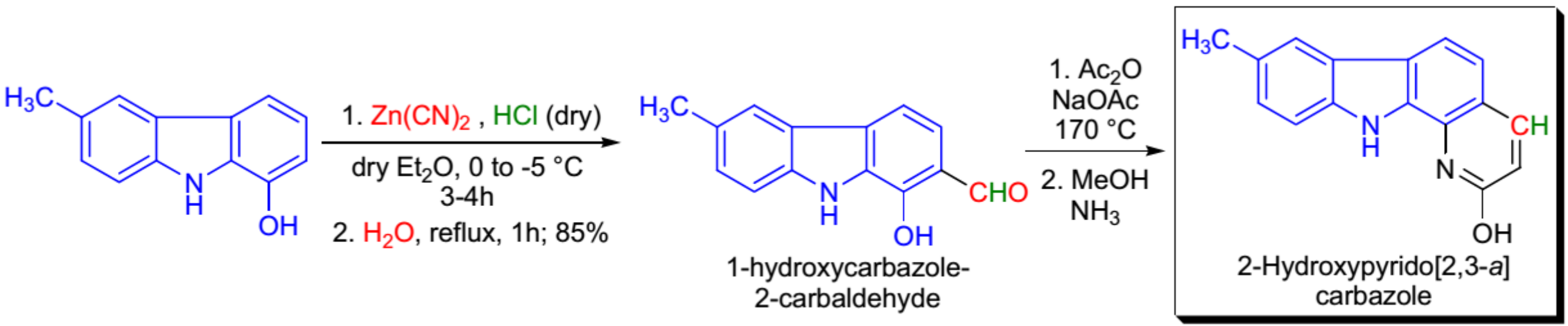
The benzofuran-derived natural product caleprunin A was synthesized by R. Stevenson et al. using the *Gattermann formylation* as the key step.[24] The starting 3,4,5-trimethoxyphenol was suspended with $Zn(CN)_2$ in ether and dry HCl gas was bubbled through the reaction mixture at room temperature for 2h. The solvent was decanted, water was added and the mixture was heated for 15 minutes. The natural product was obtained by reacting the benzaldehyde derivative with chloroacetone in DMF in the presence of anhydrous $K_2CO_3$.



The regiospecific introduction of the formyl group into the C3 postion of 2,5-dialkyl-7-methoxy-benzo[*b*]furans was achieved by H.N.C. Wong and co-workers by using the *Adam's modification of the Gattermann formylation*.[25] A potential ligand for adenosine $A_1$ receptors was prepared from 2-cyclopentyl-5-(3-hydroxypropyl)-7-methoxy-benzo[*b*]furan in 50% yield by bubbling HCl gas through its etheral solution containing $Zn(CN)_2$ at -10 °C for 1h. The resulting imine hydrochloride was hydrolyzed with a water-ethanol mixture at 50 °C.



Compounds containing the pyridocarbazole ring are known to have DNA intercalating properties and therefore they are potent antitumor agents. For example, several syntheses of pyrido[2,3-*a*]carbazole derivatives have been published, but these methods are often lengthy and low-yielding. R. Prasad and co-workers synthesized 2-hydroxypyrido[2,3-a]carbazoles starting from 1-hydroxycarbazoles.[26] The key transformation was the *Gattermann formylation* of 1-hydroxycarbazoles to obtain 1-hydroxycarbazole-2-carbaldehydes, from which the target compounds could be obtained *via* a *Perkin reaction*.



Certain aromatic analogues of natural amino acids can be used as potential fluorescent probes of peptide structure and dynamics in complex environments. The research team of M.L. McLaughlin undertook the gram scale synthesis of racemic 1- and 2-naphthol analogues of tyrosine.[27] The synthesis of the 1-naphthol tyrosine analogue started with the *Gattermann formylation* of 1-naphthol using the *Adams modification* to afford the formylated product 4-hydroxy-1-naphthaldehyde in 67% yield.