PINNICK OXIDATION

Lindgren (1973):
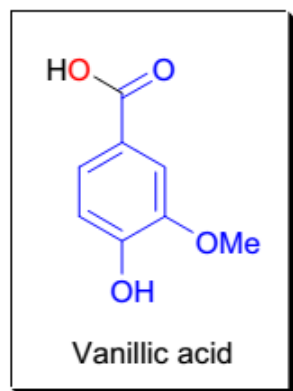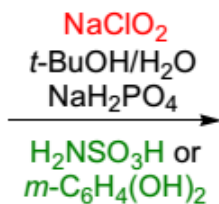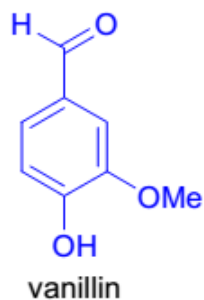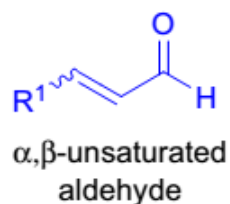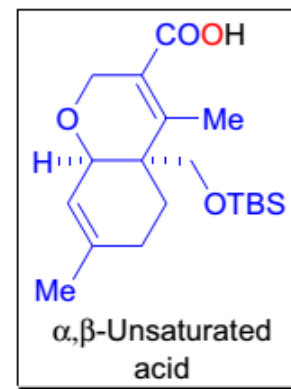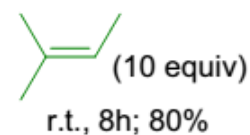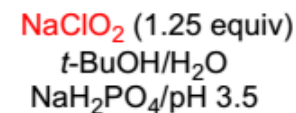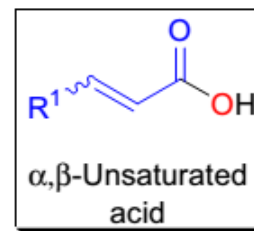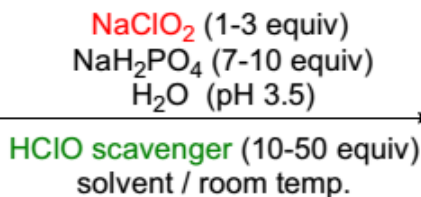
vanillin → Vanillic acid

NaClO$_2$
t-BuOH/H$_2$O
NaH$_2$PO$_4$

H$_2$NSO$_3$H or
m-C$_6$H$_4$(OH)$_2$

Kraus (1980):

α,β-unsaturated aldehyde → α,β-Unsaturated acid

NaClO$_2$ (1.25 equiv)
t-BuOH/H$_2$O
NaH$_2$PO$_4$/pH 3.5

(10 equiv)
r.t., 8h; 80%

α,β-unsaturated aldehyde   or   aliphatic or aromatic aldehyde

NaClO$_2$ (1-3 equiv)
NaH$_2$PO$_4$ (7-10 equiv)
H$_2$O (pH 3.5)

HClO scavenger (10-50 equiv)
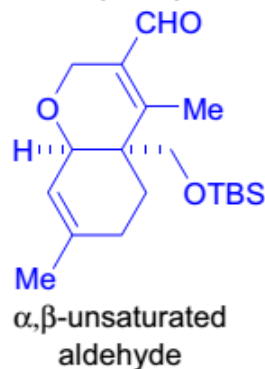solvent / room temp.

α,β-Unsaturated acid   or   Aliphatic or aromatic acid

R^1 = H, alkyl, aryl, alkenyl, allyl; R^2 = alkyl, aryl, allyl, homoallyl; scavenger = 2-methyl-2-butene, H$_2$O$_2$, H$_2$NSO$_3$H,
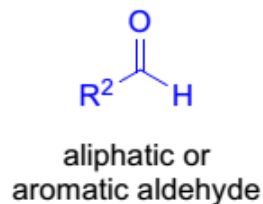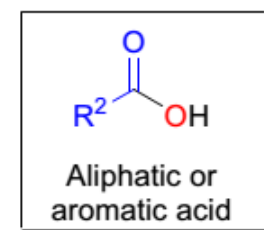m-C$_6$H$_4$(OH)$_2$, DMSO; solvent = t-BuOH, t-BuOH/THF

Features
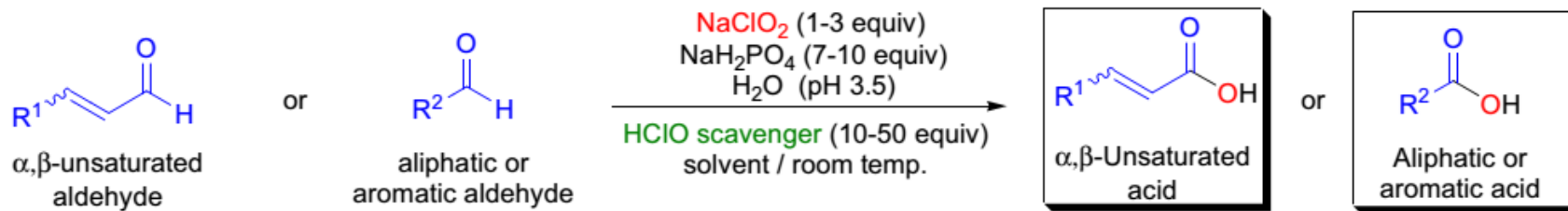

R^1 = H, alkyl, aryl, alkenyl, allyl; R^2 = alkyl, aryl, allyl, homoallyl; scavenger = 2-methyl-2-butene, H$_2$O$_2$, H$_2$NSO$_3$H, m-C$_6$H$_4$(OH)$_2$, DMSO; solvent = t-BuOH, t-BuOH/THF

✓ In a typical procedure, the aldehyde is dissolved in tert-butanol (often in combination with another solvent such as THF) along with the large excess of the scavenger followed by the dropwise addition of the aqueous solution of sodium dihydrogen phosphate buffer (NaH$_2$PO$_4$) and NaClO$_2$ at room temperature.

✓ To ensure a constant pH value, the use of several equivalents of NaH$_2$PO$_4$ is recommended.

✓ With certain substrates the purity of the reagents is crucial, and the oxidation sometimes stops after a few percent of conversion.

✓ Due to the sensitivity/instability of the NaClO$_2$ in acidic medium in the presence of transition metal complexes the use of a steel needle for the addition of the oxidant should be avoided (use a Pasteur pipette instead).

✓ Stereocenters at the α-position of aldehydes are unaffected.

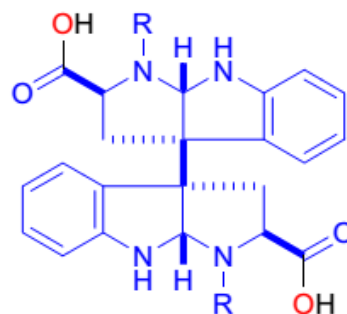✓ Functional group tolerance is excellent, and hydroxyl groups do not need to be protected.

Mechanism

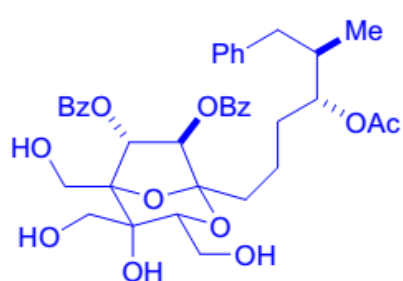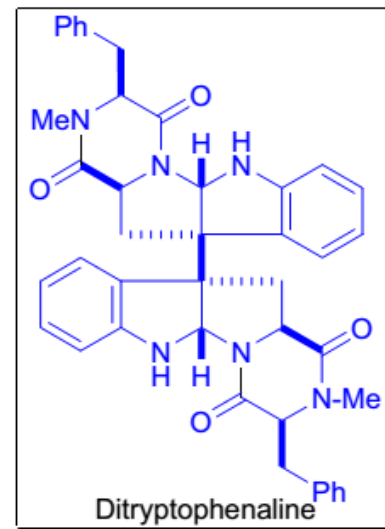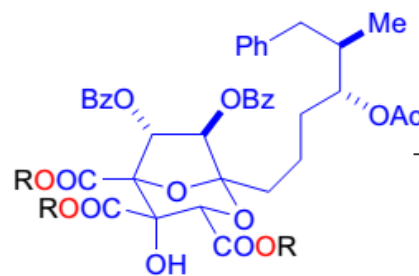# Synthetic Applications

R = FMOC-(S)-MePhe
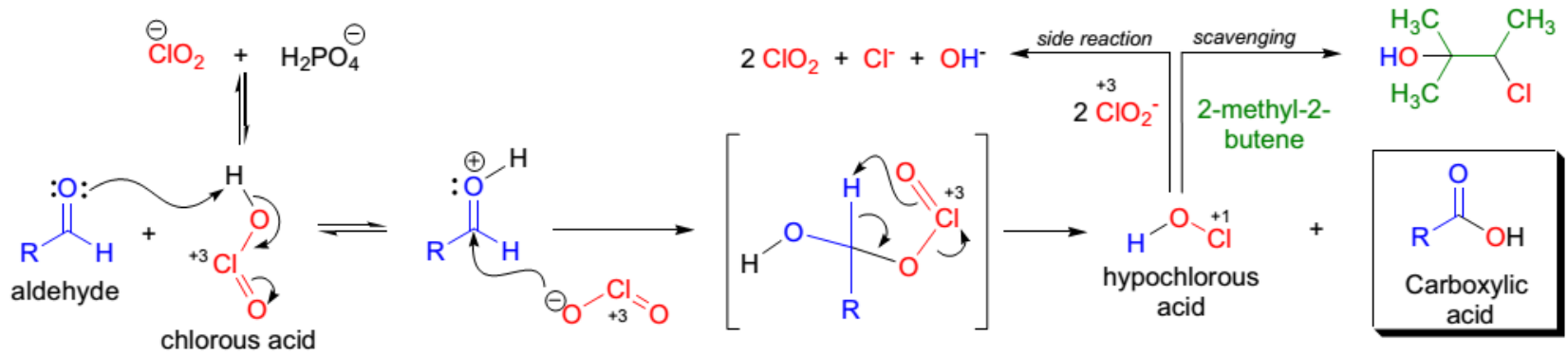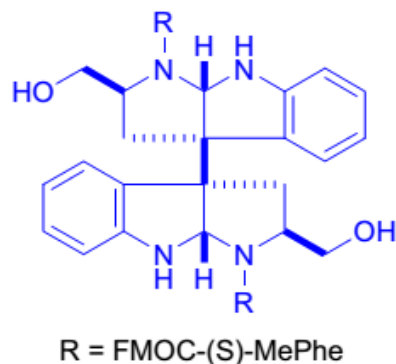
1. DMP (3 equiv)
   DCM, r.t., 48h
2. NaClO$_2$ (4 equiv)
   NaH$_2$PO$_4$ (8 equiv)
   THF:H$_2$O:t-BuOH
   (4:4:1)
   2-Me-2-butene (xs)
   r.t., 15h; 73%
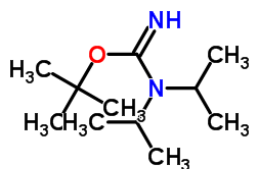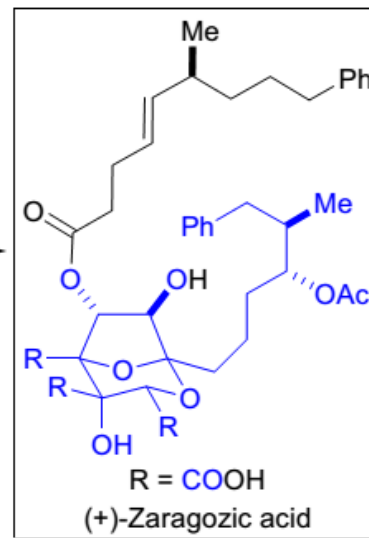
steps

Ditryptophenaline

1. (COCl)$_2$: DMSO
   (3.5:7 equiv)
   DCM, -78 °C
   NEt$_3$ (10.5 equiv)
2. NaClO$_2$ (15.2 equiv)
   NaH$_2$PO$_4$ (15.2 equiv)
   t-BuOH:2-Me-2-butene
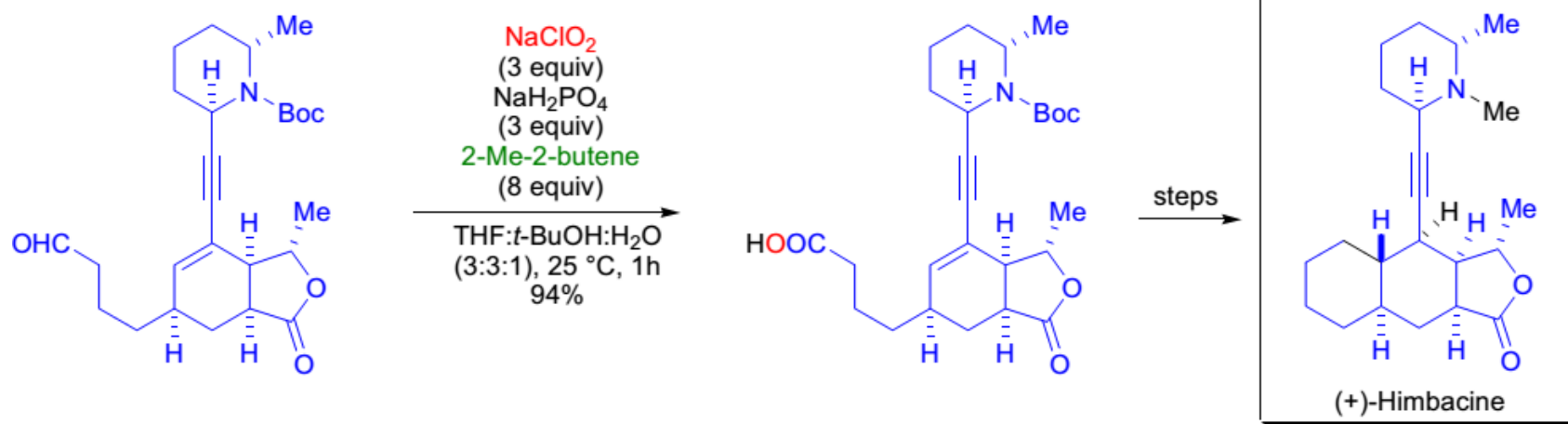   (5:1.2); 0 °C, 3h
3. N,N-diisopropyl-O-
   t-butylisourea, DCM

R = t-Bu
33% for 3 steps

steps

R = COOH
(+)-Zaragozic acid

O-tert-butyl N,N-diisopropylisourea

Synthetic Applications

(+)-Himbacine

Thanks