

Dutch Resolution

- Resolution by diastereomeric salt formation using a family of resolving agents
- High resolution efficiency (high e.e. of resolved product)
- All resolving agents of the family are incorporated in the crystals
- Over 200 examples of successful resolutions (success rate > 90%)
- Technology used in close cooperation with Syncom (Groningen, NL)
- Efficient resolution technology at lab scale; gives fast clue for identifying single resolving agent for scale-up

References Dutch Resolution

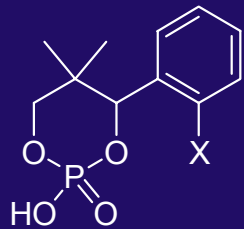
Eur. Pat. Appl. EP 838,448 (1998), to DSM

T. Vries et al, *Angew. Chem. Int. Ed.* (1998) 37, 2349.

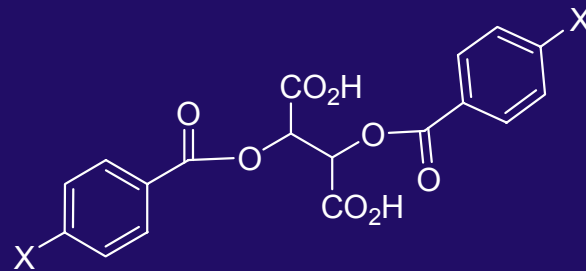
Role of nucleation inhibition:

J.W. Nieuwenhuijzen et al, *Angew. Chem. Int. Ed.* (2002) 41, 4281.

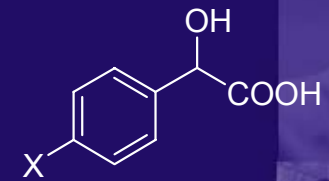
Families of resolving agents



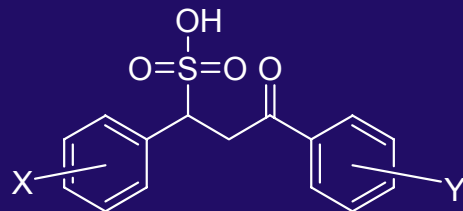
X = H, Cl, OMe



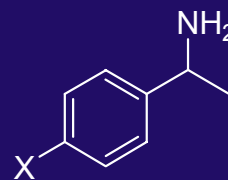
X = H, Me, OMe



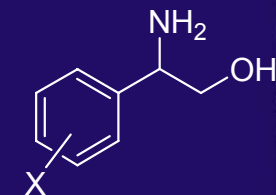
X = H, Me, Br



X, Y = H, Cl, OMe

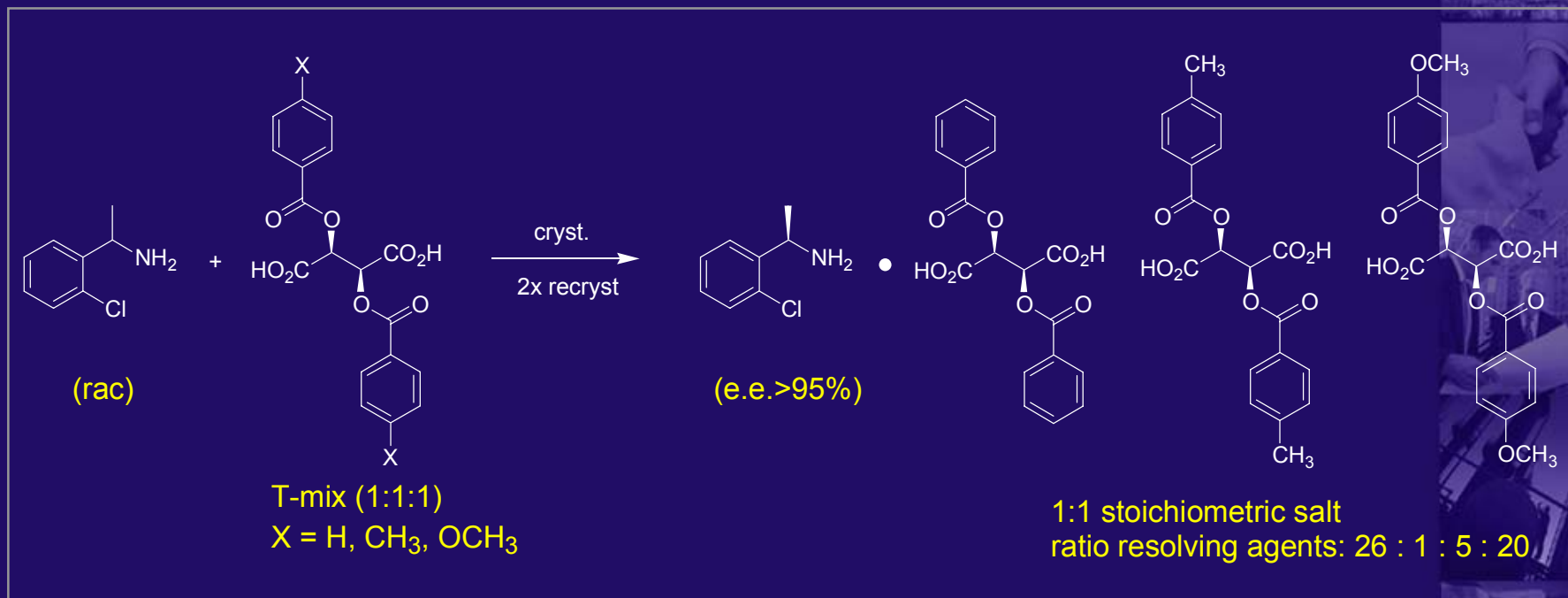


X = Cl, Br, Me
X = H, 2-NO₂, 4-NO₂



X = H, Me, Br

Dutch Resolution: Example 1

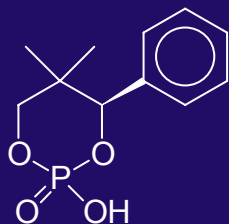


Standard procedure: to a racemate solution (3 mmol) is added one equivalent of a DR family, *i.e.* 3 mmol of a 1:1:1 mix of resolving agents

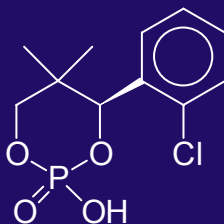
Dutch Resolution: Example 2

Unlimited. **DSM**

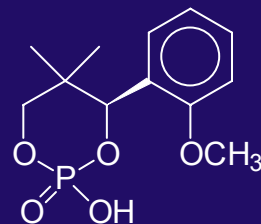
P-mix:



phencyphos

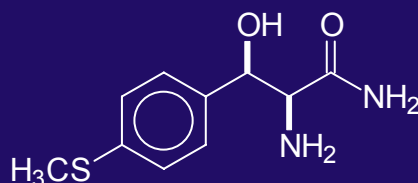


chlocyphos



anicyphos

Racemate; DL-threo-amide:



Resolving agent	yield (%)	e.e. (%)	mix -ratio
(-)-Phencyphos	47	52 (2R,3S)	--
(-)-Chlocyphos	55	17 (2R,3S)	--
(-)-Anicyphos	41	67 (2S,3R)	--
(-)-P-mix (1:1:1)	25	98.8 (2S,3R)	12 : 35 : 53 (P:C:A)