Chemical Process Development

Development NCE

Applications of co-crystals in API synthesis

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Chemical Process Development

Boehringer Ingelheim

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Content

- General considerations on co-crystals
- 1st case study: Development of a new API form
- 2nd case study: Purification of an API
- 3rd case study: Optical resolution of an intermediate
- 4th case study: Optical resolution of an API

Boehringer Ingelheim Pharma GmbH

- German family owned pharmaceutical company
- TOP 15 of pharmaceutical companies

- Chemical Process Development
  - From Research to Production
  - ~200 FTE
  - Two locations
    - Biberach: early stage development (~80 FTE) up to Phase IIa (up to 100Kg API)
    - Ingelheim: late stage development (~120 FTE)

- Technology (TEC) Lab in early development (~3 FTE)
  - Optimization of reactions
  - Optimization of crystallizations (isolation of API and intermediates, optical resolutions)
  - PAT
  - Technology scouting

General considerations

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Definition

LETTER www.rsc.org/crystengcomm | CrystEngComm

What is a co-crystal?

Andrew D. Bond

Received 29th May 2007, Accepted 13th June 2007
First published as an Advance Article on the web 11th July 2007
DOI: 10.1039/b708112j

The term "co-crystal" is failing as a clear and consistent scientific descriptor. If it is to be retained, it should be used only as a synonym for "multi-component molecular crystal".

- Crystal structure of two or more molecules, which are solids under ambient conditions, with no covalent bonds

- EMA: a co-crystal is a not a new drug substance and requirements are essentially the same as for a salt
- FDA:
  - In the past: a co-crystal is a drug product
  - Now (Feb. 2018): a co-crystal is like a polymorph, as the solvates are, of the initial drug substance

Definition

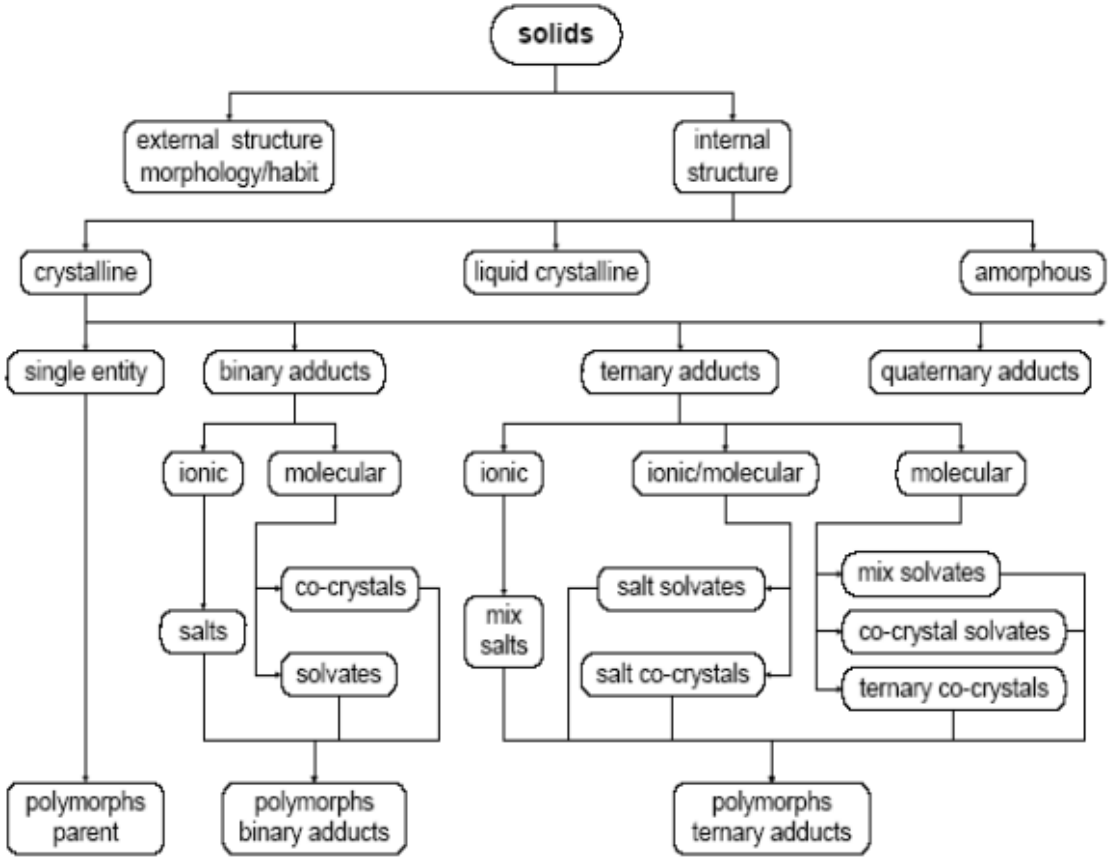

Figure 1: Subdivision of solid state materials.

From the reflection paper on the use of cocrystals of active substances in medicinal products of the EMA:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500189927.pdf

1st case study
Development of a new API form

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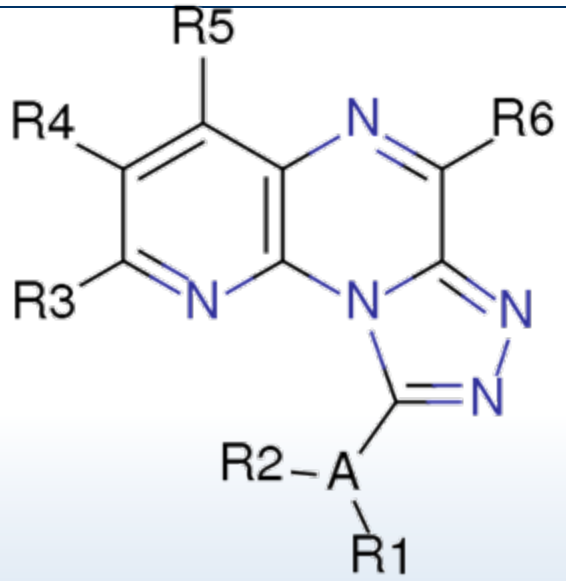
Development of a new API form



- Neutral molecule
- More than 16 solvates identified but no hydrate
- Solvates were in a large majority unstable in presence of water
- Issues:
  - Polymorph control during crystallization
  - Residual solvent content

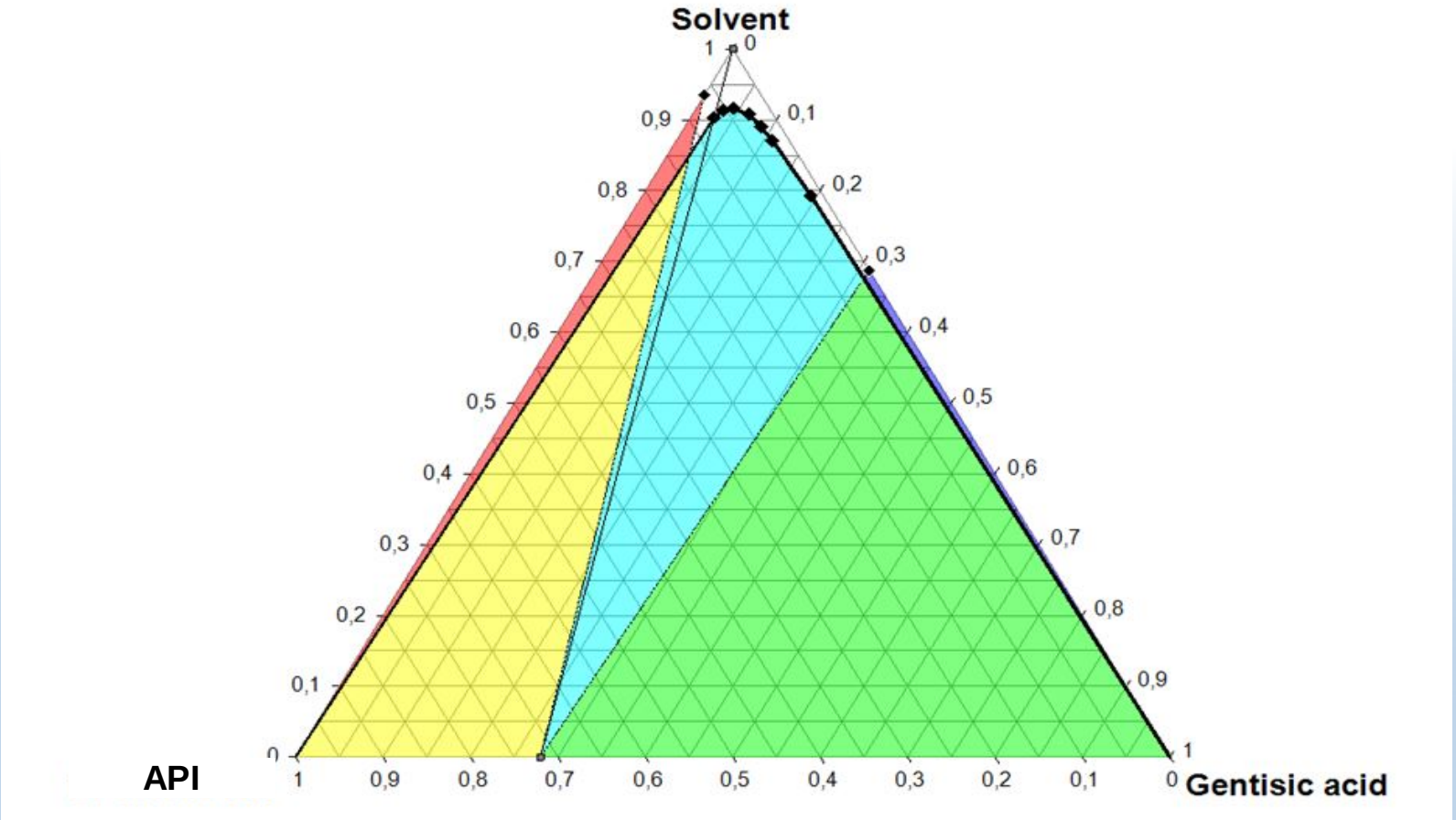
Development of a new API form

- 4 co-crystals identified in screening with:
  - Benzoic acid (1:0,5)
  - Salicylic acid (1:0,5)
  - Gentisic acid (1:1)
  - Saccharin (1:0,5)

- Up-scaling
  - Saccharin: no stable stoichiometry from 0,2 to 0,5eq.
  - Benzoic acid and salicylic acid: long thin needles, suspensions not good stirrable
  - Gentisic acid: rod-like crystals, good stirrable

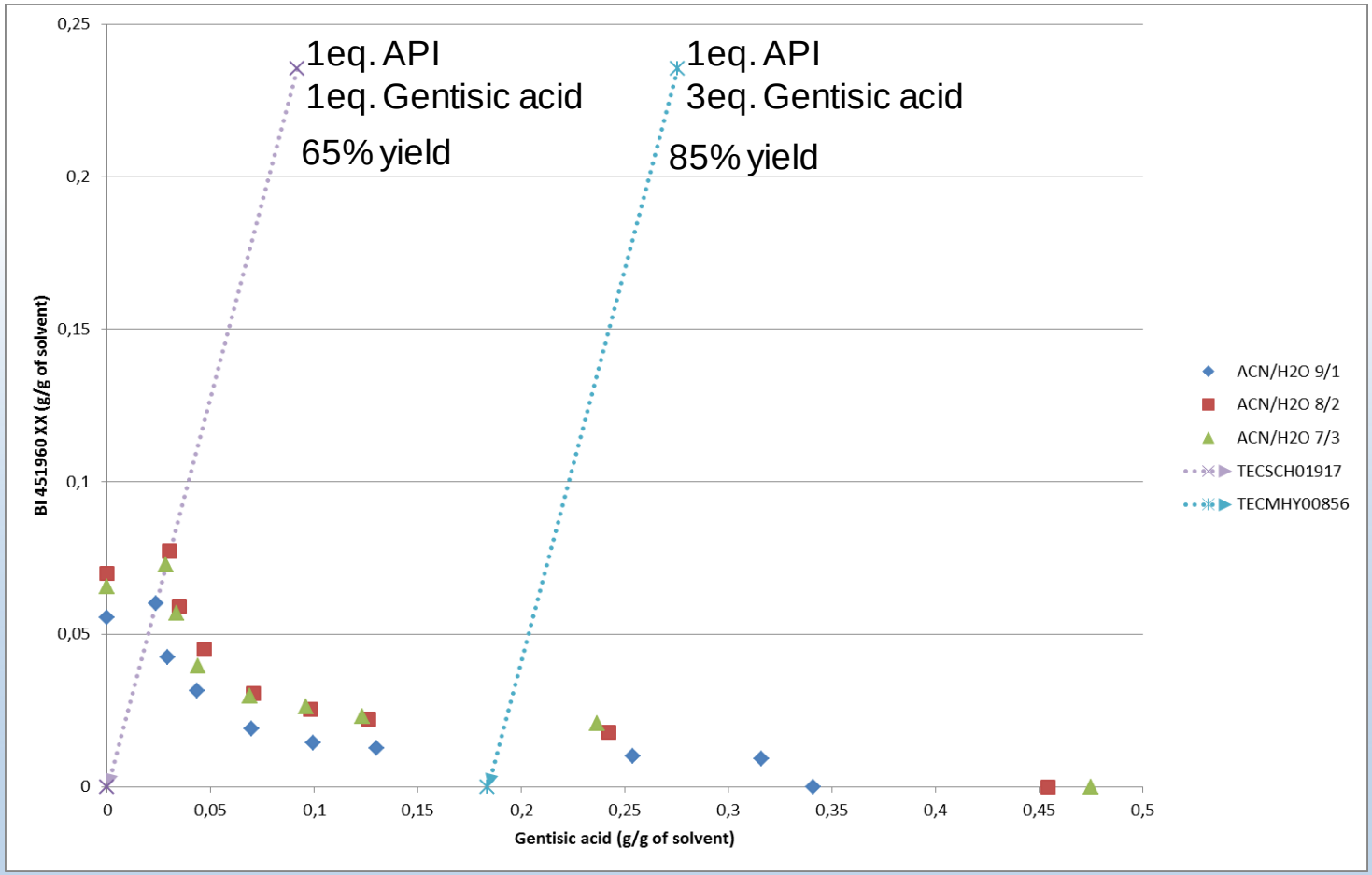
Development of a new API form

- Phase diagram gentisic co-crystal (in weight composition) in ACN/water



Development of a new API form

- Pushing the yield and stability by using excess of co-crystal former



Development of a new API form

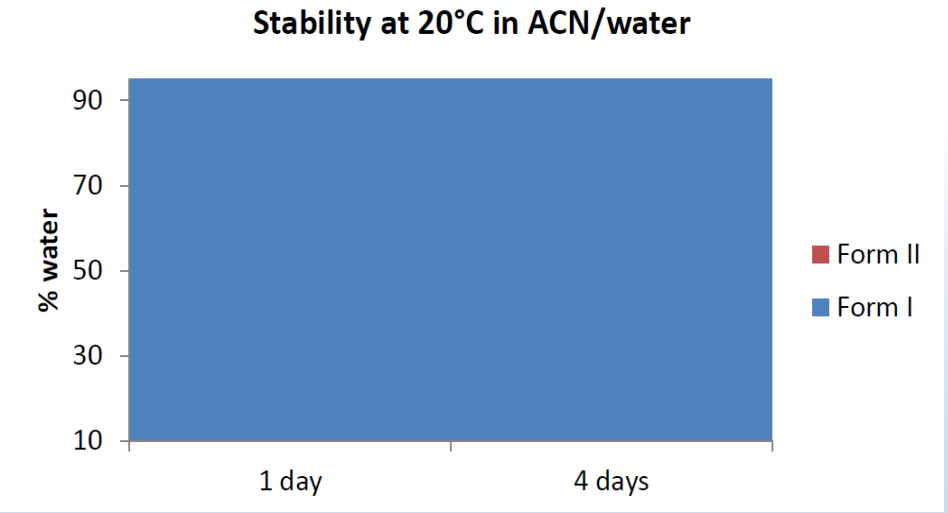
- Co-crystals are not as stable as salts, especially when competing with solvates

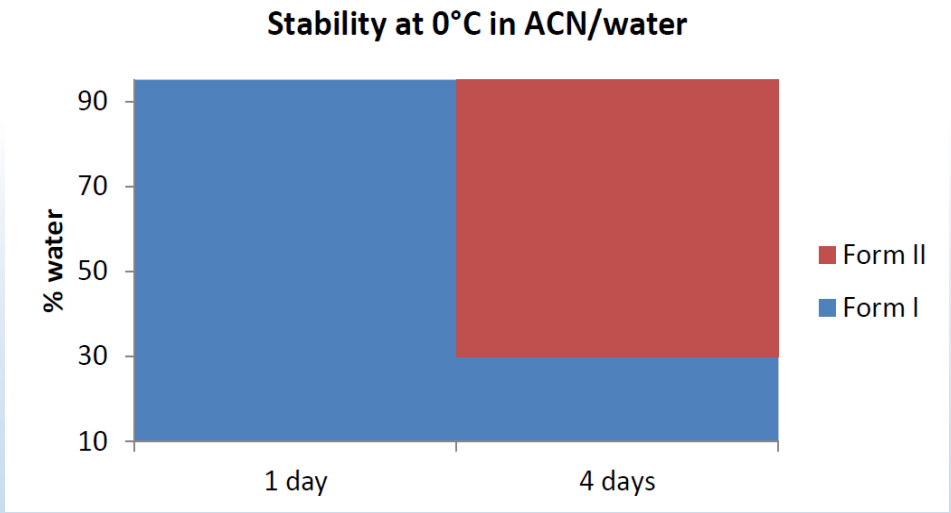
TECSCH01938					
BI 451960 GE			TECSCH1933PA1		
PA1 EtOH Form I + XX	PA5 iPrOH/H2O 9/1 Form I	PA9 ACN Form I	PA13 Eisessig Form I	PA17 nBuOAc Form I + XX	
PA2 EtOH/H2O 9/1 Form I + XX	PA6 Aceton Form I + XX	PA10 ACN/H2O 9/1 Lösung	PA14 THF XX	PA18 MiBK Form I + XX	
PA3 EtOH/H2O 1/1 Form I	PA7 Aceton/H2O 9/1 XX	PA11 ACN/H2O 1/1 Form I	PA15 EtOAc Form I	PA19 MEK Form I + XX	
PA4 iPrOH Form I + XX	PA8 Aceton/H2O 1/1 Form I + XX	PA12 H2O Form I	PA16 iPrOAc Form I	PA20 nHeptan Form I	

Form I
BI 451960 XX (solvent-free)
BI 451960 XX (solvate)
Lösung

Development of a new API form

- Co-crystals, like any other compound, can have polymorphs, hydrates, solvates…





- Form II is an hydrate
- Form I and II are enantiotropic related
- Interconversion temperature is around 20°C, determined by Raman spectroscopy in Crystalline

2nd case study
Purification of an API

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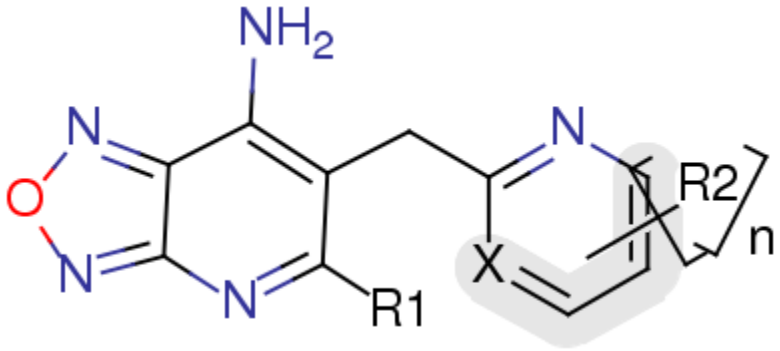
Purification of an API



- Last chemical step: organometallic chemistry
  - Metallation: Lithium
  - Transmetallation: Zinc
  - Coupling: Copper
- CuCl builds a strong complex with the API
  - Cu residual content: 7 750ppm
- Product in the reaction mixture has a 67% purity
- Isolated product has 85%-90% purity

Purification of an API

- pKa=3,5
- Salt formation only with strong acids (i.e. sulfonic acids), but no real improvement of the purity and heavy-metal content

- No strong synthons, but single crystal structure of the free molecule demonstrates π-π interactions

- Co-crystal screening mainly with aromatic compounds ➔ 4 hits:
  - Benzoic acid
  - Salicylic acid
  - Gentisic acid
  - 3-hydroxy-2-naphtoic acid

Purification of an API

- Co-crystal with benzoic acid was the most stable and reproducible
- Purity improved from 85%-90% to 99%
- Residual copper reduced to 30ppm
- Single crystal structure of the benzoic acid co-crystal demonstrates π-π interactions with the API and H-bond between the carboxylic acid and the different nitrogens breaking the CuCl complex
- Cleavage to the free molecule with ammonia in water

3rd case study
Optical resolution of an intermediate

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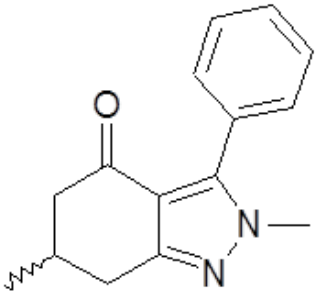
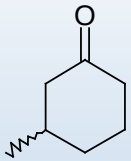
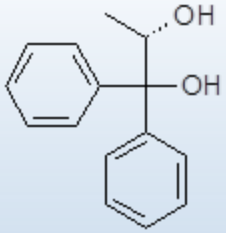
Optical resolution of an intermediate

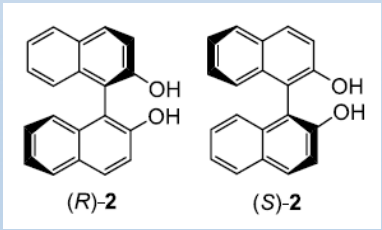


- Weber et al. (JCS, Chemical Communications, 1992) proposed for the resolution of 3-methylcyclohexanone to use 2,2-di-benzoyl-2,3-propanediol





- No classical co-crystal synthon
- Screening of chiral acids and aromatic compounds with a racemic mixture
- One new XRPD pattern with (S)-BINOL



⇒ We have a diastereomeric co-crystal, can we do an optical resolution?

Optical resolution of an intermediate

- Solvent screening (50mg) with 0,5eq. (S)-BINOL (i.e. in Crystal16)

Methanol	Methanol/H2O 9/1	Ethanol	Ethanol/H2O 9/1	2-Propanol	Acetone
Y: 47% e.e.: 34%	Y: 46% e.e.: 34%	Y: 46% e.e.: 24%	Y: 40% e.e.: 7%	Y: 58% e.e.: 6%	Y: 24% e.e.: 67%
Acetone/H2O 9/1	methylisobutyl ketone	Ethylacetate	Tetrahydro furane	Toluene	Acetonitrile
Clear solution	Y: 39,5% e.e.: 1%	Y: 18% e.e.: 61%	Clear solution	Y: 40% e.e.: 1%	Y: 48% e.e.: 39%

- Scale-up (300mg) (i.e. in Crystalline)

Methanol 0,5eq. BINOL	Acetone 0,5eq. BINOL	Ethylacetate 0,5eq. BINOL	Acetonitrile 0,5eq. BINOL
Y: 41% e.e.: 53%	Y: 28% e.e.: 52%	Y: 27% e.e.: 30%	Y: 48% e.e.: 56%
Methanol 0,7eq. BINOL	Acetone 1,0eq. BINOL	Ethylacetate 1,0eq. BINOL	Acetonitrile 0,7eq. BINOL
Y: 53% e.e.: -3%	Y: 40% e.e.: 62%	Y: 56% e.e.: 8%	Y: 52% e.e.:49%

Optical resolution of an intermediate

- Solvent screening for reslurry with enriched material (e.e. 52%)

Acetone	Methylethyl ketone	Methylisobutyl ketone	2-Butanol	n-Butylacetate	t-Butylmethyl ether
Y: 29% e.e.: 97%	Clear solution	Y: 34% e.e.: 53%	Y: 69% e.e.: 50%	Y: 67% e.e.: 87%	Y: 50% e.e.: 52%

⇒ Acetone and n-butylacetate selected for further optimizations

⇒ Design of Experiment (DoE)

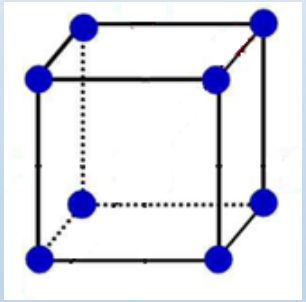
- Solubility measurement to set DoE boundaries

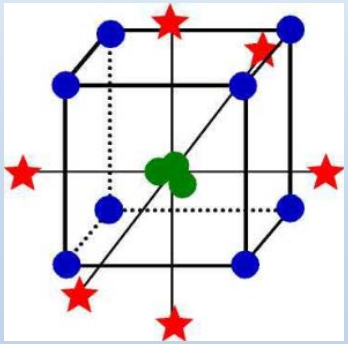
	intermediate			**(S)-BINOL**	
	0°C	**20°C**	**40°C**	**0°C**	**20°C**
Acetone		>200g/L		>100g/L	>220g/L
n-Butylacetate	81g/L	136g/L	>200g/L	>100g/L	>140g/L

Optical resolution of an intermediate

- DoE in n-butylacetate was not efficient enough (max. e.e.: 48%)
- DoE in acetone
  - Full Factorial Design with 3 parameters ➔ 8 experiments
  - Completed with a Central Composite Design ➔ 11 experiments (incl. 5 center points)

Parameter	-1	+1	-1,66	0	+1,66
A – Concentration	200 mg/mL	300mg/mL	166 mg/mL	250 mg/mL	333 mg/mL
B – Equivalents of BINOL	1	1,5	0,83	1,25	1,67
C – Isolation temperature	0°C	20°C	-7°C	10°C	27°C





  - No effect of the isolation temperature on the efficiency (compensation yield/e.e.)
  - Good reproducibility of the center points: Efficiency=72,1% ±2,1%

Optical resolution of an intermediate

- Confirmatory runs (10g) using center point conditions but varying the isolation temperature confirmed the results of the DoE

isol. temp.	yield	e.e.	S
0°C	61,2%	62,8%	76,9%
10°C	54,8%	61,8%	67,7%
20°C	49,6%	74,2%	73,6%

- No total resolution could be obtained from the co-crystal formation

$\Rightarrow$ The optically enriched co-crystal needs to be recrystallized

$\Rightarrow$ Solubility measurement

Optical resolution of an intermediate

- First solubility of both diastereomeric co-crystals was measured

Cocrystal	Solvent	Solubility (g/L) at 20°C
(R)-enantiomer/(S)-BINOL	Acetone	71
	n-Butylacetate	38
	Acetonitrile	14
(S)-enantiomer/(S)-BINOL	Acetone	271
	n-Butylacetate	84
	Acetonitrile	97

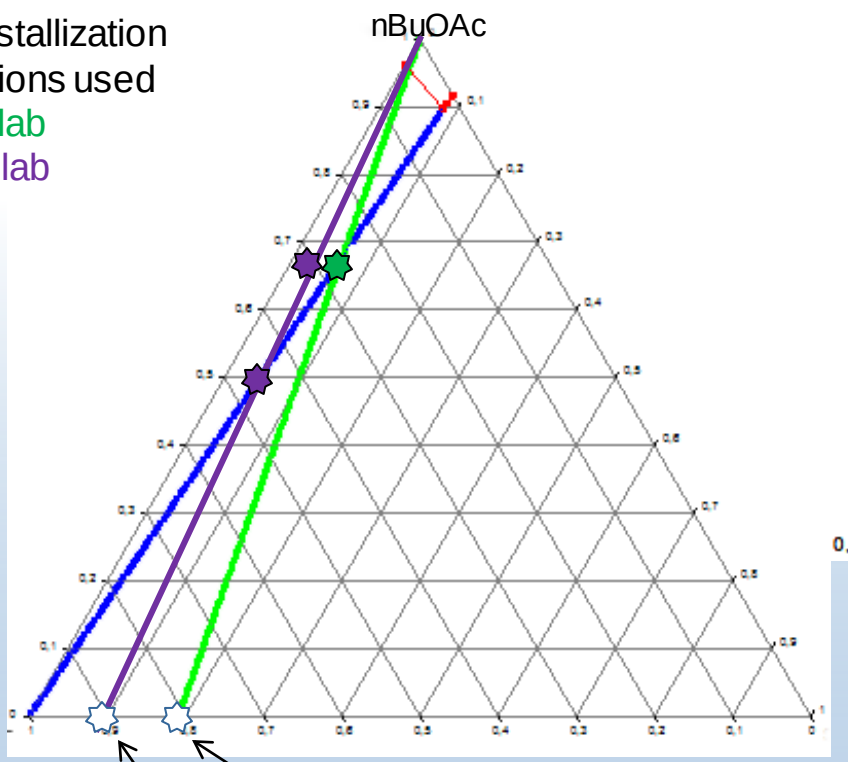
- In acetone it needs to be too concentrated to reach acceptable yield
- n-butylacetate and acetonitrile are well suited for recrystallization
- n-butylacetate allows a complete dissolution with less solvent (higher solubility, higher boiling point)

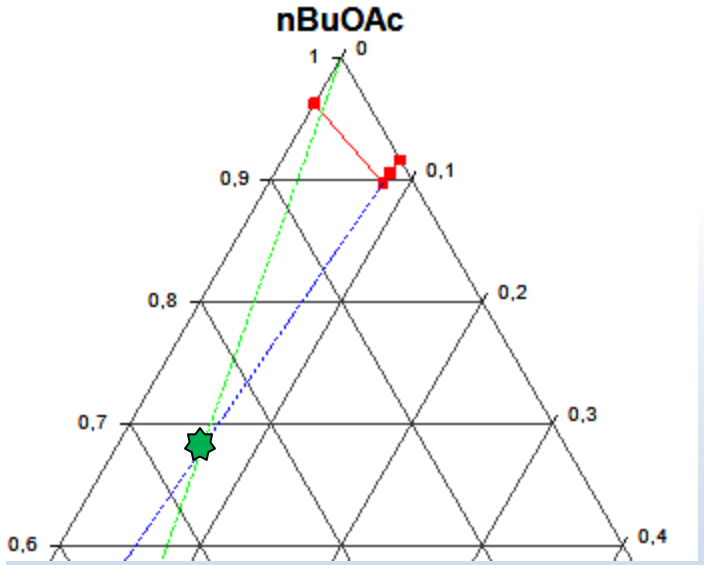
$\Rightarrow$ Building of Ternary Phase Diagram in n-butylacetate

Optical resolution of an intermediate

- Determination of the eutectic composition and solubility
  - Solubility measurement of mixtures of both diastereomeric co-crystals, with excess of both
  - Measure of the solubility and composition of the solution

Recrystallization conditions used
In Teclab
In Kilolab





R-enantiomer/
S-binol

S-enantiomer/
S-binol

Material enrichment after cocrystal formation in Teclab

Material enrichment after cocrystal formation in Kilolab

After recrystallization an e.e. of 92(Teclab)-95(Kilolab)% was obtained, the thermodynamic equilibrium was probably not yet reached

Optical resolution of an intermediate

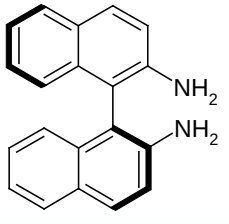
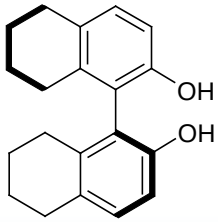
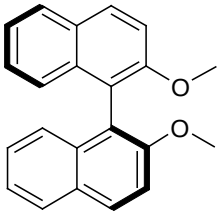
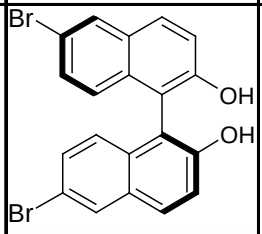
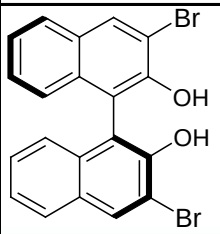
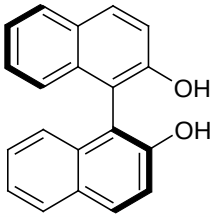
- Cleavage of the co-crystal
  - The intermediate is neutral and has a low solubility in water
  - BINOL presents a moderate acidity and its sodium salt has a pretty good solubility in water
  - Cleavage was done with 1N NaOH
  - The e.e. improved up to 96-98%

- Summary of the results

	TECLAB	Multikilo
Amount of racemate	10 g	19 kg
e.e. after co-crystalization	63,0%	78,0%
e.e. after recrystallization	91,8%	96,0%
e.e. after cleavage	96,4%	97,7%
Overall yield	40,5%	37,8%
Efficiency	78,1%	74,0%

Optical resolution of an intermediate

- Does it work with BINOL derivates or analogs

		API : CCF 1:1	API : CCF 1:1	API : CCF 1:1	API : CCF 1:1	API : CCF 1:1	API : CCF 1:1
							
		#1	#2	#3	#4	#5	#6
Methanol	A					Form I	Form I
Dichloromethane	B					Form II	Form I
Acetone	C						mixture of forms
Acetonitrile	D						Form I
Toluene	E					low crystallinity	Form II
Ethyl acetate	F						mixture of forms
Isopropyl alcohol	G						Form II
Ethanol	H					Form I	mixture of forms
MTBE	J					low crystallinity	Form II

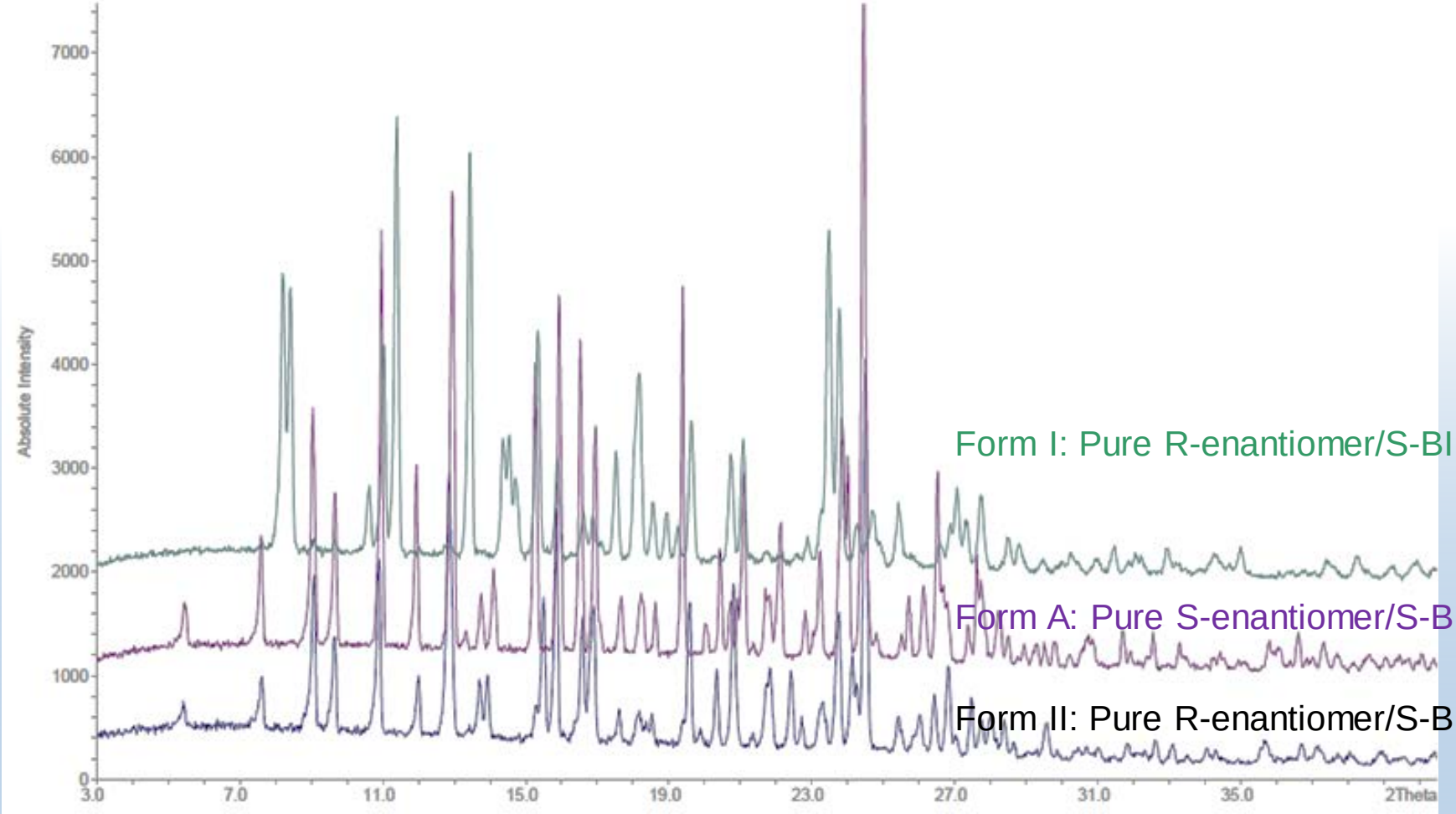
	new crystalline form
	physical mixture
	oiled out - no crystals observed

2 factors in the formation of the co-crystal:

- Binaphtyl
- Phenol

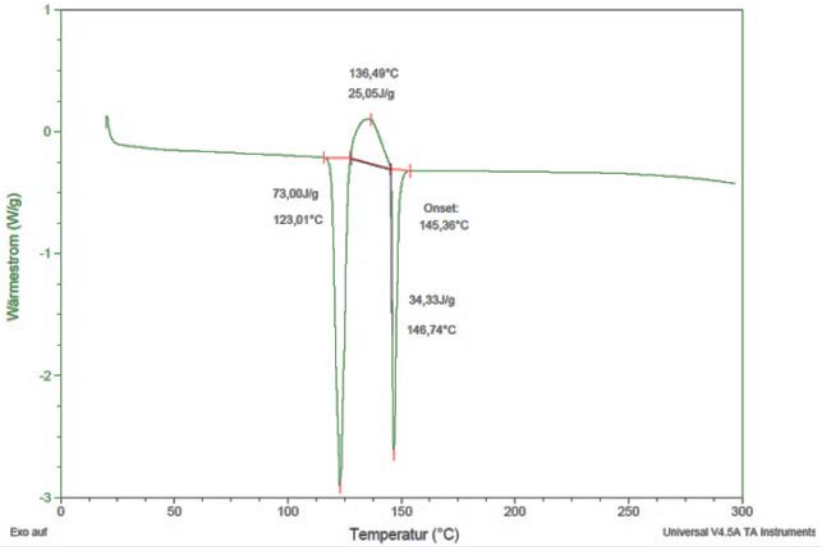
Optical resolution of an intermediate

- Comparison of Form I and Form II

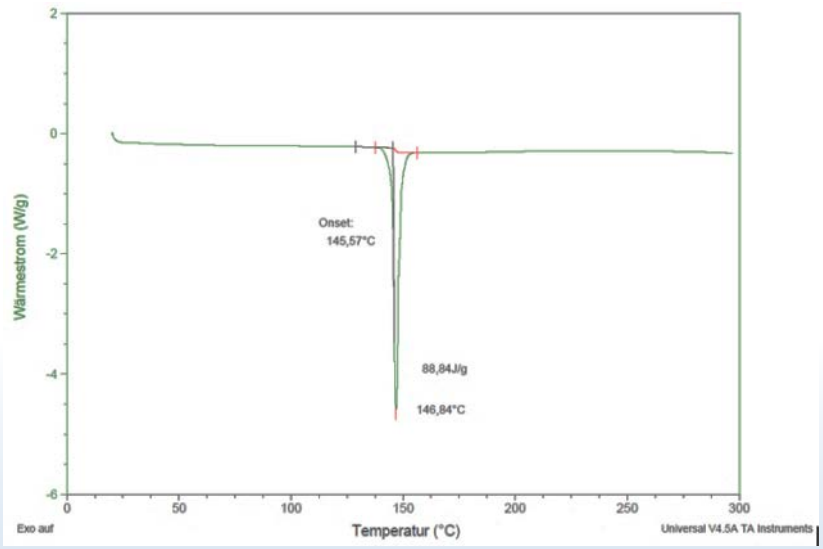


Optical resolution of an intermediate

Form I



Form II



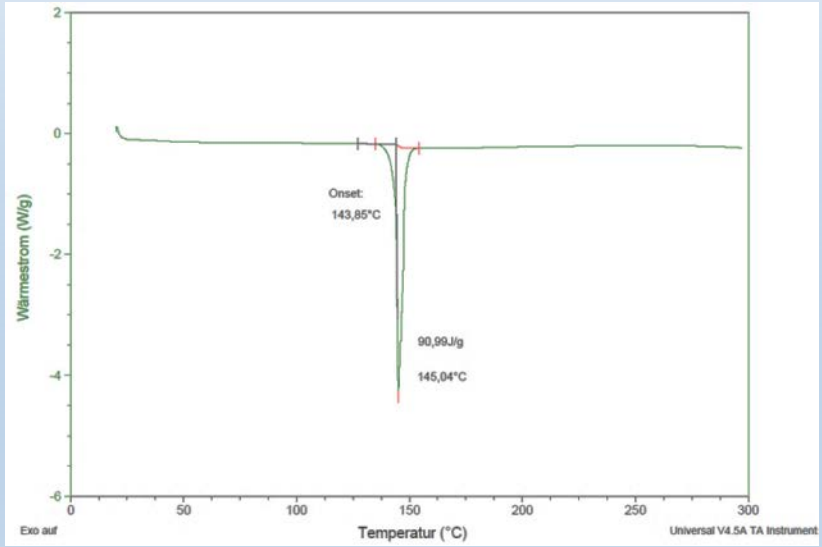
Form II and Form A are very close one to another:

- XRPD isomorphic
- Melting point difference 1-2°C

Form I has a lower melting point and a lower enthalpy of fusion:
According to Burger‘s rules : Form I is metastable

Theoretically should Form I not be isolated
Form II and Form A are so close that probably no optical resolution is possible

Form A



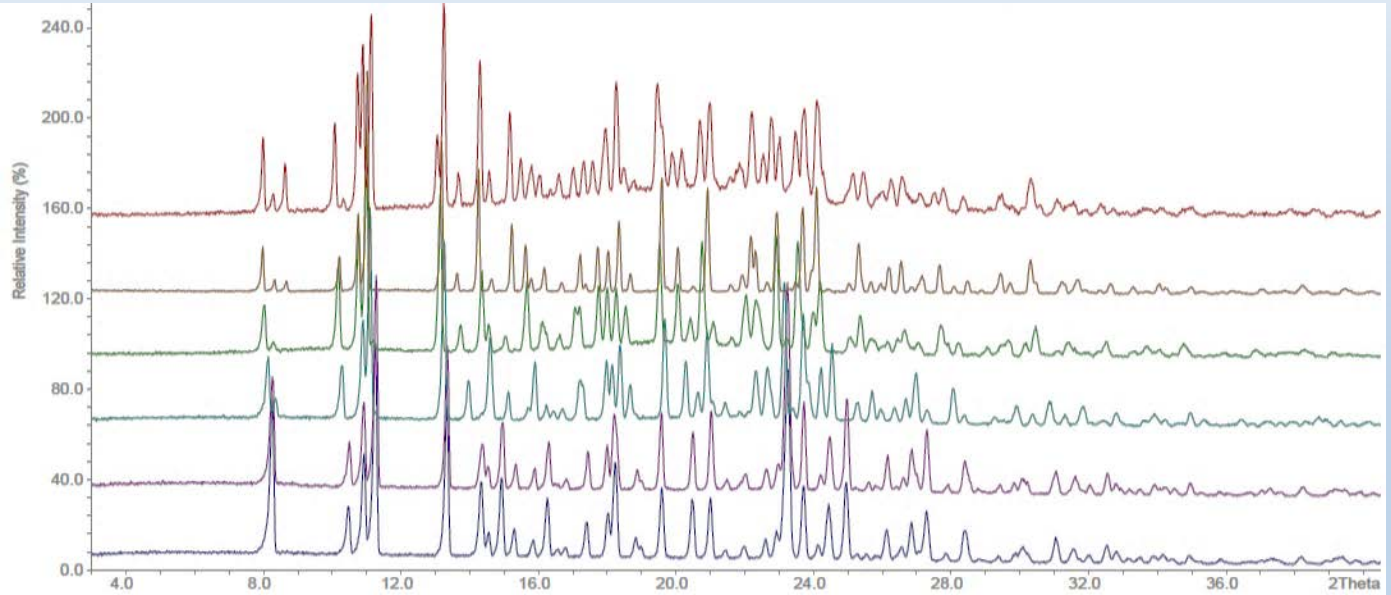
Optical resolution of an intermediate

- Solubility of Form II and Form A

starting Form/solvent	Toluene		Acetonitrile	
	Solubility (g/L) @ RT	isolated Form	Solubility (g/L) @ RT	isolated Form
Form II	50	Form II	14	Form I
Form A	50	Form A	97	Form A

- DSC tells us that Form II is the most stable form
- Solubility tells us Form I is the most stable form
- Slurry of Form II in different solvents

?



nBuOAc Solvate

EtOAc Solvate

iPrOH Solvate

EtOH Solvate

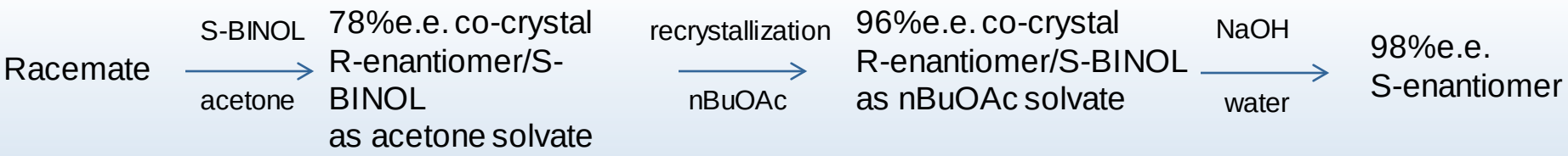
ACN Solvate

MeOH Solvate

Optical resolution of an intermediate

- Optical resolution of a neutral compound by co-crystallization is possible and mainly not different as a normal acid-base chiral resolution

- In the end, unusual intermediate forms:



- General remarks:
  - Cleavage method if needed can be tricky
  - Co-crystallization is a viable alternative to chiral chromatography
  - Do not limit to 1 solvent
  - And always characterize your solid, it may hide a surprise!!!

4th case study
Optical resolution of an API

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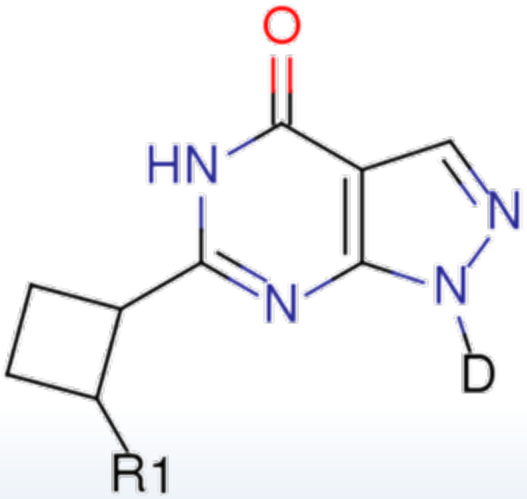
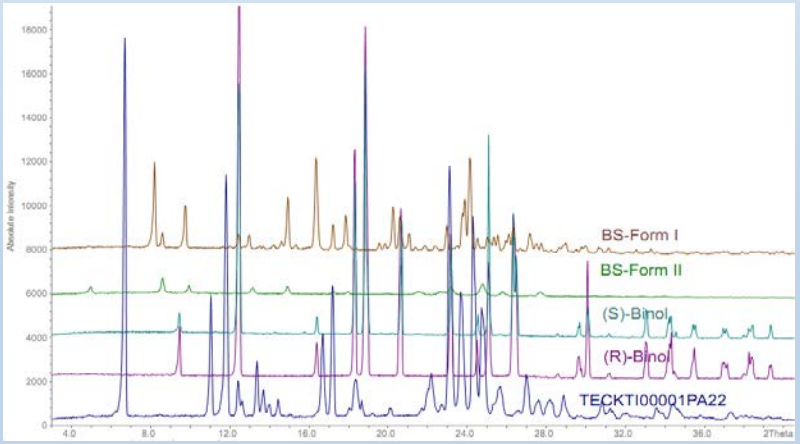
Optical resolution of an API



- Late introduction of the chiral centers
- Reactive intermediates
  – Impossible to use carboxylic acids

- Co-crystal screening done on enantiopure compound (distomer of the API)
- Screening of both enantiomers of classical chiral acids, amino-acids and BINOL with the enantiopure distomer of the API
- New XRPD pattern only with R-BINOL



Optical resolution of an API

- Solvent screening ➔ 3 different stoichiometries API:BINOL (2:1, 1:1, 1:2)
- Best resolution in Methanol with 1:2 cocrystal
- Optimization through DoE
- Scale-up to 20g:
  - Primary co-crystal formation
    - 77% enantiomeric excess
    - 47% yield
  - Reslurry in ethylacetate:
    - 98% enantiomeric excess
    - 84% yield ➔ 40% yield over the two steps
- Cleavage:
  - Unable to cleave with NaOH (as in case study #3)
  - Formation of a chloride salt of the API, which dissolves in water
  - Extraction of BINOL in an organic phase ➔ possible recycling of BINOL
  - 99,9% eantiomeric excess
  - 84% yield ➔ 33% overall yield

Acknowledgement

- TEC Lab
  - Dr. Marco Santogostino
  - Philipp Kollmus
  - Simone Krüger
  - Sonja Steigmiller
  - Till Köllges (internship)
- IPT Lab
- Drug Discovery Science Department
- Technobis

Thank you for your attention.

Questions?

Boehringer Ingelheim

Back-up

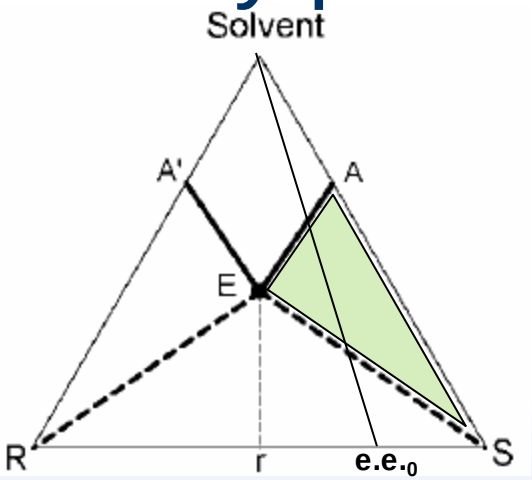
Boehringer Ingelheim

Screening methodology

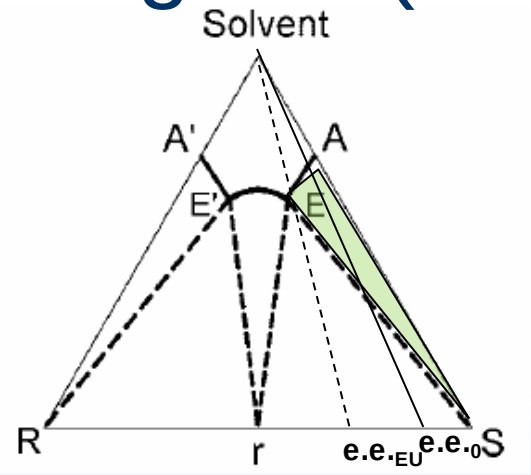
- Close related to mechanochemistry (milling, compression)
- Centrifuge vials are filled with 50/100mg compound and 1.0/2.0 equivalent cocrystal former (CCF). A few µL of solvent are added.
- The vials are finally placed on a floating foam platform and sonicated for 10 to 30 minutes.
- Each vials is analyzed per XRPD to identify new patterns.

Morisson et al., OPRD, 2013, 17, 533-539

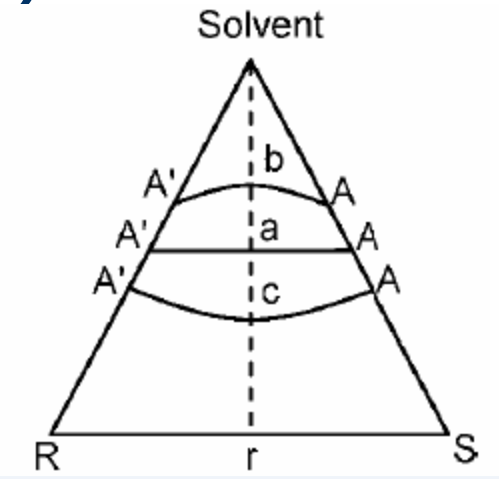
Which type of racemate ?
Ternary phase diagram (TPD)



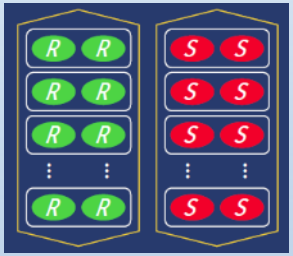
conglomerate (5-10%)
mechanical mixture of crystals of the two pure enantiomers



racemic compound
the two enantiomers are present in equal quantities in a well-defined arrangement in the crystal lattice.

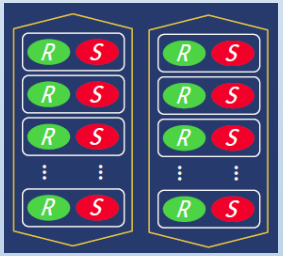


solid solution (<1%)
two enantiomers coexisting in an unordered manner in the crystal



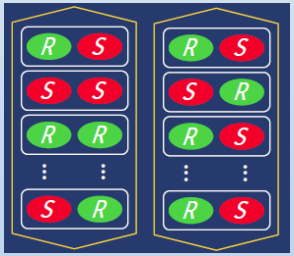
XRPD same as that of (R) or (S)

enriched in solid if e.e. > e.e.$_{EU}$ = 0%



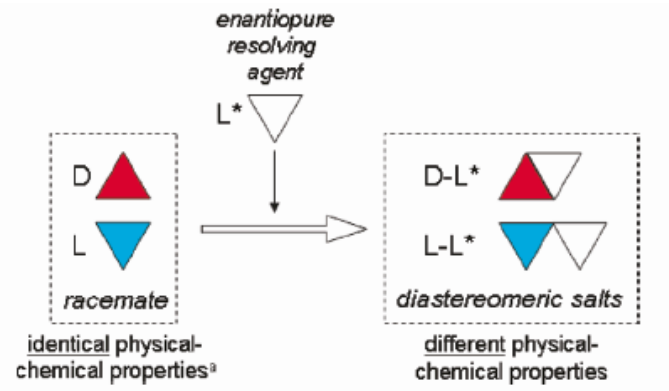
XRPD of (r) different from (R) or (S)
confirmation with slurry exp.s

enriched in solid if e.e.$_0$ >

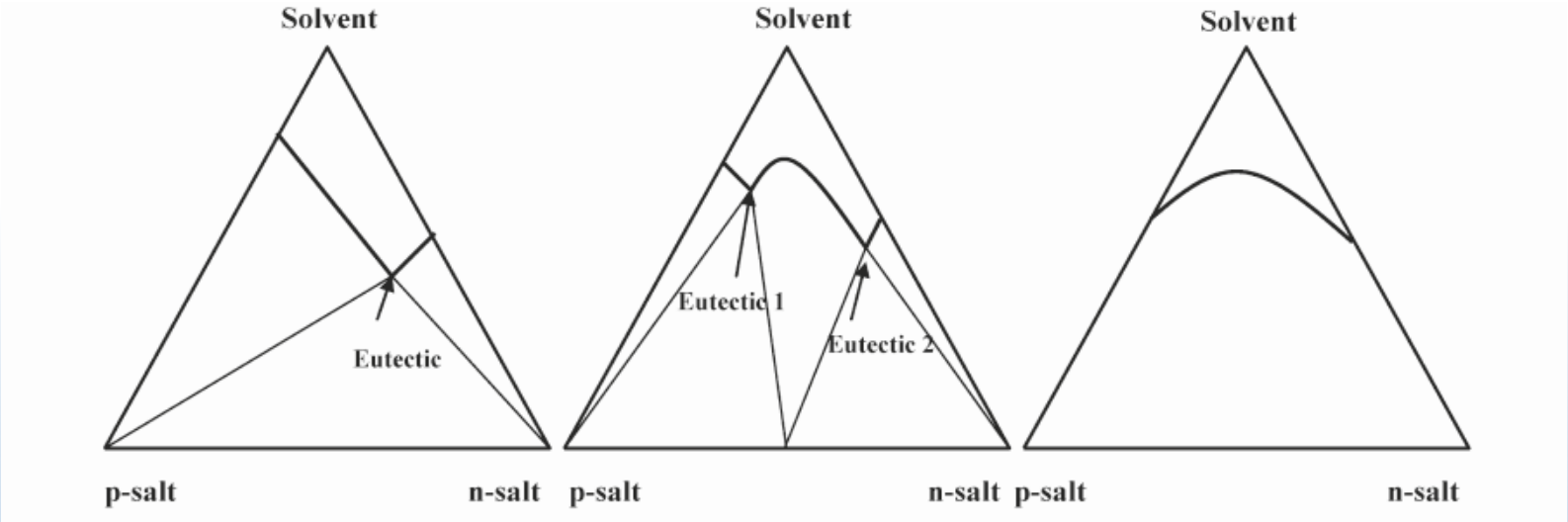


enrichment in not feasible

TPD for diastereomeric sa



Different physicochemical properties
(e.g. solubility, XRPD, FTIR)



simple eutectic (20%)

XRPD of a 50:50 p-/n-mixture does not show new reflexes

resolution possible from a racemic mixture ([p] = [n])

double salts
formation of intermediate compounds

XRPD of a 50:50 p-/n-mixture different than that of pure salts

preliminary enrichment necessary

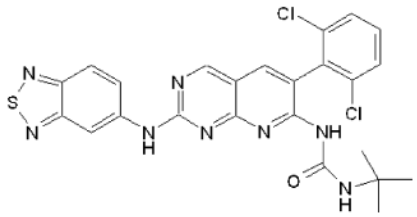
mixed crystals
miscibility in the solid state

Some bibliography

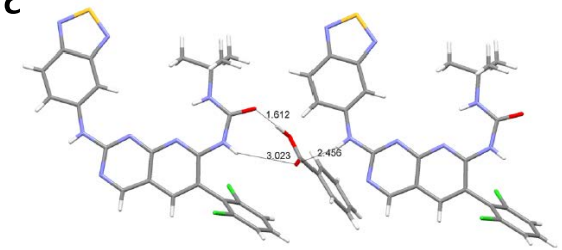
Boehringer Ingelheim

Literature review: Purification

- Billot et al. (Org. Process Res. Dev., 2013) presented the purification of an API (SAR1) through cocrystallization and its scale-up at kilogram-scale.



- Crude SAR1 has to be recovered after three telescoped reactions from a dark solution containing only 60% of the target molecule.
- Chromatography, adsorption and repeated crystallization didn‘t allow a purity higher than 90%.
- High solvatomorphism, but difficulties to isolate them from reaction mixture.
- 5 cocrystals: oxalic, malonic, fumaric, succinic and benzoic acid

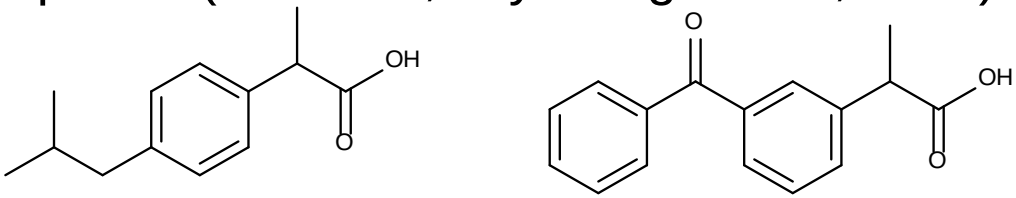


Literature review: Purification

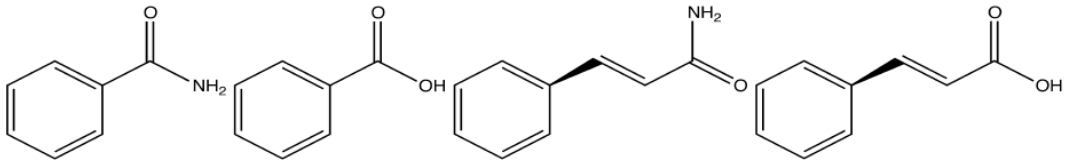
- Optimization of the benzoic acid cocrystal by ternary phase diagram determination in different solvents with pure API.
- Adaptation of the conditions to the crude API.
- Purity increased to 99,5%.
- Cleavage by reslurry in the area of the ternary phase diagram, where only the API crystallizes due to incongruent solubilities of the API and benzoic acid

Literature review: Purification

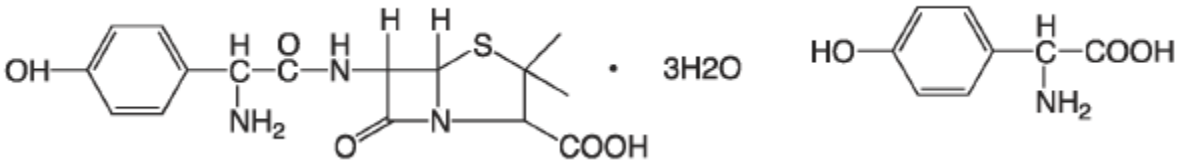
- Myerson‘s group uses the affinity of impurities to build cocrystals to complex and hold them in solution. They looked at different target/impurity systems:
- Ibuprofen/ketoprofen (Hsi et al., CrystEngComm, 2012)



- Benzamide/benzoic acid and cinnamide/cinnamic acid (Hsi et al., Cryst. Growth Des., 2013; Weber et al., Cryst Growth Des., 2014)

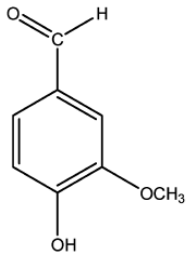


- Amoxicillin/4-hydroxyphenylglycine (Hsi et al., CrystEngComm, 2013)

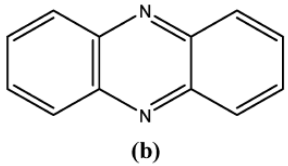


Literature review: Isolation/Purification

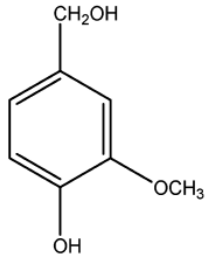
- Lee et al. (Cryst. Growth Des., 2012) use cocrystallization of vanillin with phenazine to extract vanillin produced by microorganisms and rejection of vanillyl alcohol.



(a)

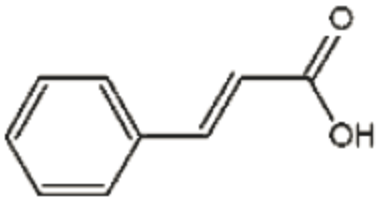


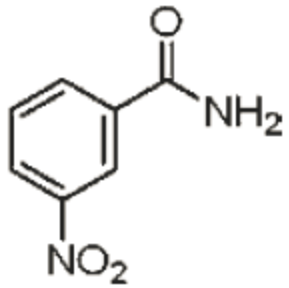
(b)



(c)

- Urbanus et al. (Cryst. Growth Des., 2010) mimic the recovery of cinnamic acid from a fermentation process by cocrystallization with 3-nitrobenzamide



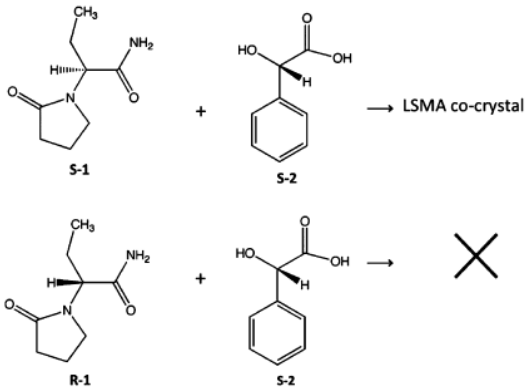


Literature review: Racemic resolution

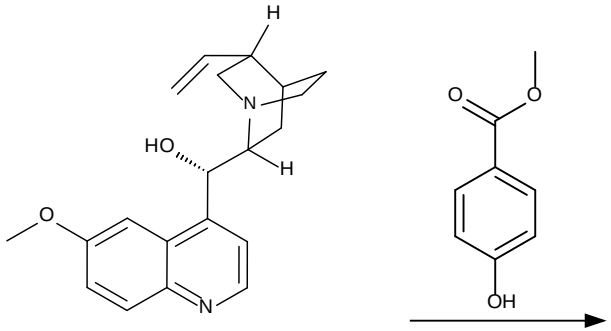
- Springuel et al. (Cryst. Growth Des, 2014, 3996-4004) studied the propensity of chiral APIs to build cocrystal with chiral agents.
- Compared to diastereomeric salt formation, which is formed with both enantiomers, cocrystals are in a large majority enantiospecific, means that only one enantiomer is forming a cocrystal.
- ⇨ Secondary interactions (π-stacking, hydrophobicity, electrostatic potential) important parameters

- Eddleston et al. (Chem.Commun., 2012, 48, 11340-11342) reported on one hand how racemic malic acid could build distinct diastereomeric cocrystals with L-tartaric acid but on the other hand how L-malic acid no cocrystal with racemic tartaric acid build.
- ⇨Stability of the racemate sometimes higher than the one of cocrystal

Literature review - Racemic resolution

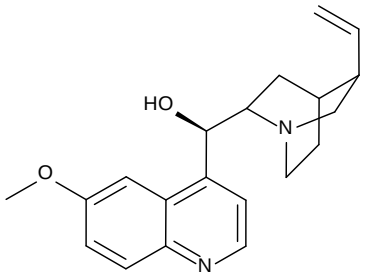


2-(2-oxopyrrolidin-1-yl)butanamide
Springuel et al. (Cryst. Growth Des., 2012)

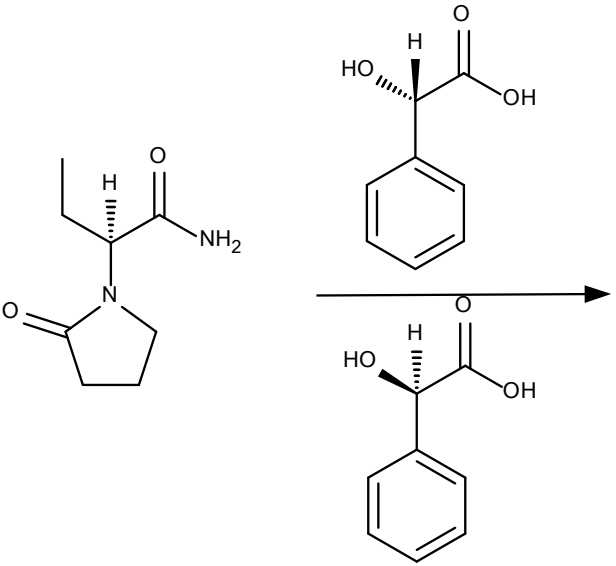


1:1 cocrystal

Quinidine/Quinine
Khan et al.
(JACS, 2010)



no cocrystal

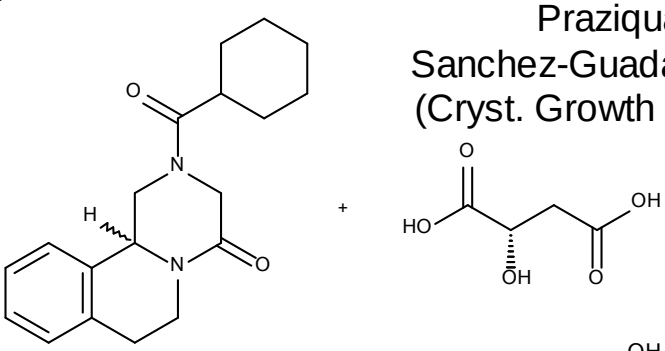


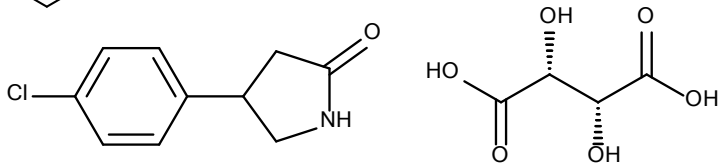
1:1 cocrystal

no cocrystal

Levetiracetam
Habgood (Cryst. Growth Des., 2013)

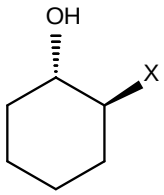
Praziquantel
Sanchez-Guadarrama et al.
(Cryst. Growth Des., 2016)

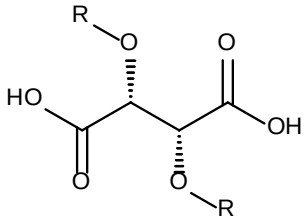




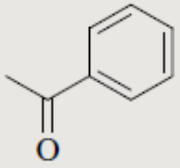
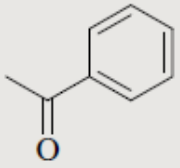
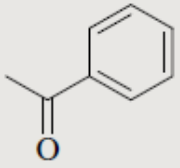
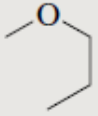
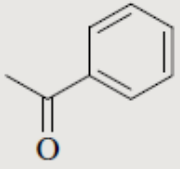
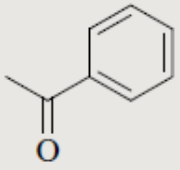
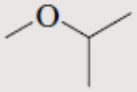
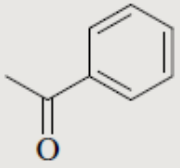
4-amino-p-chlorobutyric acid lactam
Caira et al. (J. Chem Crystallogr., 1996)

Literature review - Racemic resolution

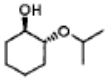
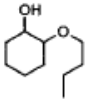
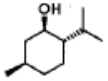
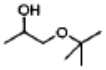
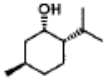
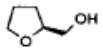


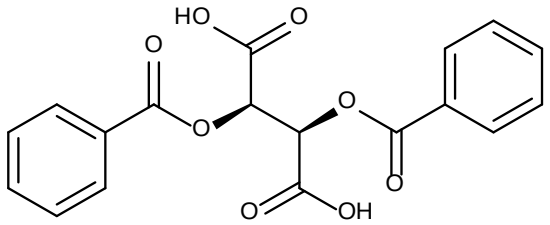


Trans-2-substituted-cyclohexane-1-ol
Molnár et al. (Tetrahedron:Asymmetry., 2008)

X	R
Cl	
Br	
I	
	
	
	
OH	H

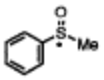
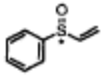
Literature review - Racemic resolution

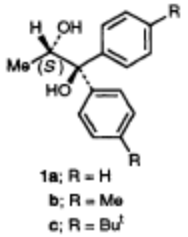
No.	Compound#	From crystalline phase e.e.	Yield	S	No.	Compound#	From crystalline phase e.e.	Yield	S
1		0	0.48	0	12		0.61	0.71	0.433
2		0	0.59	0	13		No solid phase		
3		0.20	0.63	0.126	14		0.50	0.74	0.370
4		0.28	0.91	0.255	15		0.15	0.60	0.090
5		0.05	0.19	0.009	16		0.44	0.66	0.290
6		0	0.11	0	17		0	0.46	0
7		0.07	0.66	0.046	18		0.83	0.45	0.374
8		0	0.93	0	19		No complex formation		
9		0.10	0.34	0.034	20		No complex formation		
10		0.35	0.74	0.259	21		No solid phase		
11		0.56	0.63	0.353	22		0.21	0.55	0.115



Racemic alcohols
Kassai et al. (Tetrahedron., 2000)

Literature review - Racemic resolution

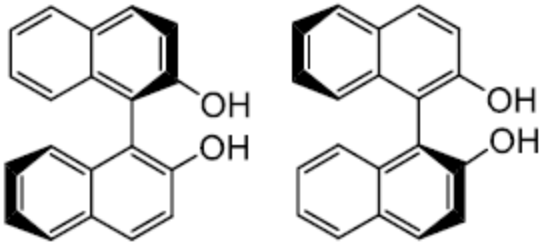
Racemic compound	Clathrate former	Stoichiometry (clathrate)[a]	Yield (%)[b]	Enantiomeric excess (% e.e.)[b,c] *via* crystallization[d]	Enantiomeric excess (% e.e.)[b,c] *via* sorption
	**1a**	2:1	90	14.5 (*R*)	3.0 (*R*)
	**1a**	2:1	86	>99 (*R*) [28.0][g]	71.0 (*R*)
	**1a**	2:1	67	12.0 (*R*) [3.1][g]	15.0 (*R*)
	**1a**	2:1	90	9.3 (*R*) [5.0][g]	25.0 (*R*)
 *cis*	**1a** **1c**	1:1 1:2	50 80	53.0 (*S*) 2.1 (*R*)	— —
 *trans*	**1a** **1c**	1:1 1:2	64 85	35.3 (*S*) 18.3 (*R*)	— —
	**1a**	1:1	75	8.0 (*R*)	2.7 (*R*)
	**1a** **1c**	2:1 2:1	[e] [e]	[e] [e]	8.5 (*S*) 16.2 (*R*)
	**1a**	1:1	72	32.8 (*S*) [4.4][g]	—
	**1a**	1:1	77	30.0 (*R*)	—



1a; R = H
b; R = Me
c; R = Bu^t

3-Methylcyclohexanone
Weber et al. (J.Chem.Soc., 1992)

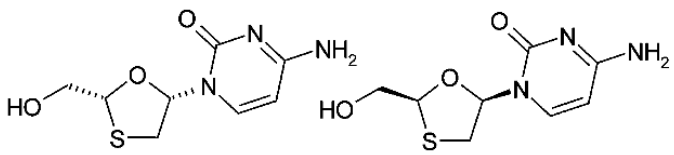
Literature review – Racemic resolution BINOL a potent CCF



(*R*)-**2** (*S*)-**2**

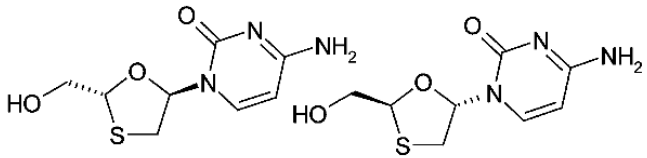
- 1,1‘-Bi-2-naphtol (BINOL)
- is a general ligand/additive for enantioselective synthesis
- presents axial chirality
- Can build cocrystal through π-stacking and hydrogen bonding

Literature review – Racemic resolution BINOL a potent CCF



A *cis* (-) (2R, 5S)

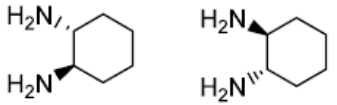
B *cis* (+) (2S, 5R)



C *trans* (-) (2R, 5R)

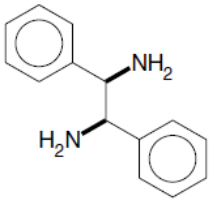
D *trans* (+) (2S, 5S)

Lamivudine
Roy et al.
(Org. Process Res. Dev., 2009)



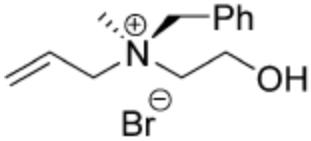
(*R,R*)-**1** (*S,S*)-**1**

Trans-cyclohexane-1,2-diamine
Schanz et al.
(Tetrahedron:Asymmetry, 2003)

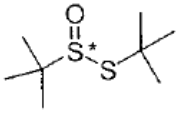


(*R,R*)-**3**

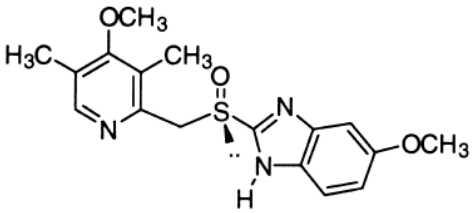
(R,R)-1,2-diamino-1,2-diphenylethane
Ratajczak-Sitarz et al.
(Tetrahedron:Asymmetry, 2007)



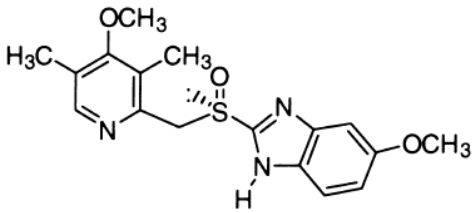
β-hydroxy-tetraalkylammonium salt
Tayama et Tanaka
(Tetrahedron Lett., 2007)



(R)-tert-butanethiosulfinate
Liao et al.
(Chem.Eur.J., 2003)



(S)-(-)-Omeprazole **1**



(R)-(+)-Omeprazole **1**

Omeprazole
Deng et al.
(Tetrahedron:Asymmetry, 2000)

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