Today's literature presentation

=

2/5th trivia

+

2/5th hardcore chemistry

+

1/5th fun

Don't worry, Boss – it's all chemistry!

(1) Analysis of the Reactions used for the Preparation of Drug Candidate Molecules,

Carey, J. S. (GSK); Laffan, D. (Astrazeneca); Thomson, C. (Astrazeneca); Williams, M.T. (Pfizer) *Org. Biomol. Chem.* **2006**, *4*, 2337.

(2) Industrial Methods for the Production of Optically Active Intermediates,

Hauer, B. (BASF) *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 788.

(3) The Chemistry IgNobel Prizes.

Group Meeting – Literature Presentation

07.11.08

Aman Desai

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Analysis of the Reactions used for the Preparation of Drug Candidate Molecules

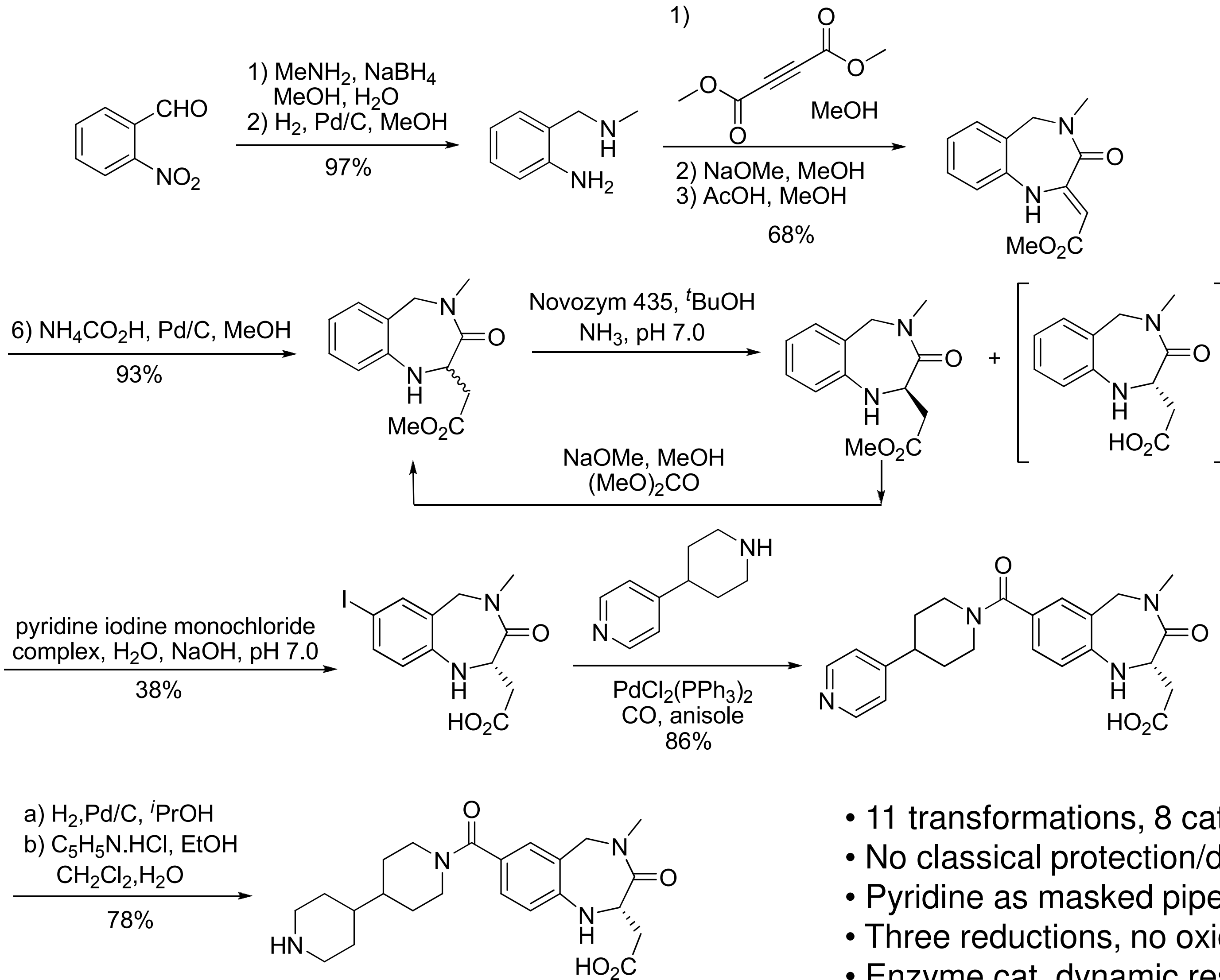
Purpose

Indicate the range of chemistries used in the manufacture of drug candidate molecules (Process Chemistry).

Methodology & Data Set

Syntheses of 128 drug candidates analyzed (equally divided between Pfizer, AstraZeneca and GlaxoSmithKline), covering all therapeutic/geographical areas.

Typical Example of a Process Chemistry R & D Synthesis



SB-214857-A

- 11 transformations, 8 catalytic.
- No classical protection/deprotection.
- Pyridine as masked piperidine.
- Three reductions, no oxidations.
- Enzyme cat. dynamic resolution.
- Overall yield of 25%

Headline data

Number of syntheses	128
Total # of chemical transformations	1039
Average # of chemical transformations per syntheses	8.1
# of chiral compounds	69
# of chiral centers	135
# of chiral centers generated	61
# of substituted aromatic s.m.	206
New aromatic heterocycles formed	54

Headline data & Reaction Categories

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Salt breaking and recrystallizations not included.

Reaction Category	
Molecular Construction Reactions	
Heteroatom alkylation & arylation	19%
Acylation	12%
C-C bond forming	11%
Aromatic heterocycle formation	5%
Modifying Reactions	
Deprotection	15%
Protection	6%
Reduction	9%
Oxidation	4%
Functional group interconversion	10%
Functionalgroup addition	3%
Resolution	3%
Miscellaneous	3%

Chirality

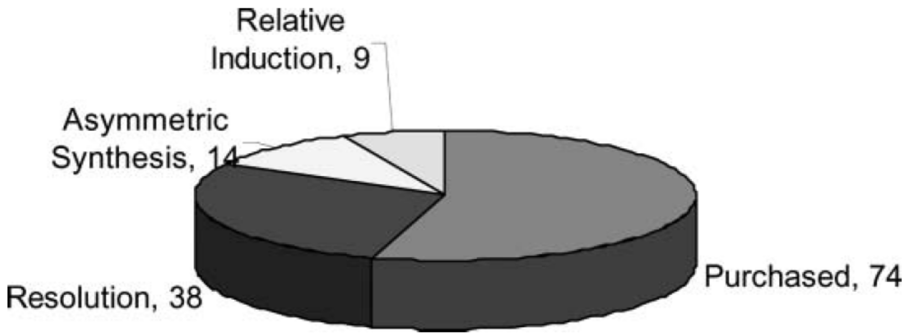


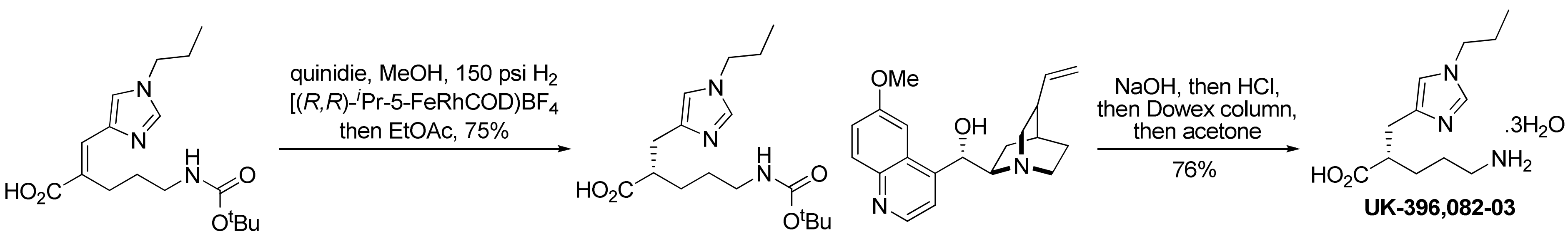
Fig. 3 Source of chiral centres

Resolution

65% – classical salt formation – preferred due to the availability of screening methods, increased understanding of crystallizations and the ease of scale-up.

Remainder – evenly distributed between dynamic kinetic, chromatographic and enzymatic.

Asymmetric synthesis often does not afford the target enantiomeric purity directly.



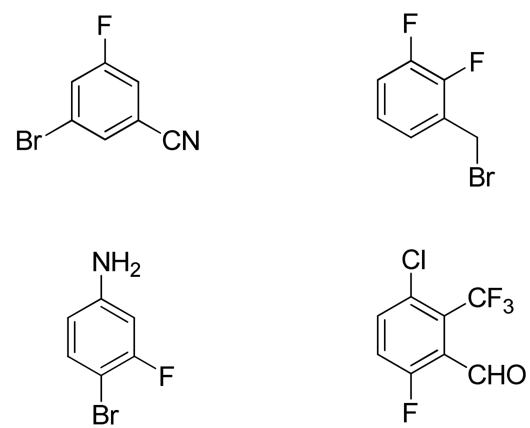
Efficient construction followed by resolution more preferred than asymmetric synthesis.

Asymmetric transformations more often carried out on small molecules by fine chemicals industry than on drug-like molecules late in synthesis.

Substituted Aromatic Starting Materials

Substitution pattern	Frequency
1,2-Ph	11%
1,3-Ph	12%
1,4-Ph	27%
1,2,3-Ph	9%
1,2,4-Ph	32%
1,3,5-Ph	4%
1,2,3,4-Ph	3%
1,2,3,5-Ph	1%
1,2,4,5-Ph	1%

Difficult to access substituted aromatic starting materials



Heterocycle Occurrence and Formation

Purchased heterocycles	# of examples	Frequency
N-containing	54	92%
O-containing	4	7%
S-containing	3	5%
Total	64	

Synthesized heterocycles	# of examples	Frequency
N-containing	53	98%
O-containing	10	19%
S-containing	5	9%
Total	68	

Most commonly occurring aromatic heterocycles

Heterocycle	# purchased	# synthesized	Total
Pyridine	23	3	26
Quinazoline	12	5	17
Pyrazole	3	5	8
Pyrimidine	4	3	7
1,2,4-Triazole	0	7	7
Thiazole	1	4	5

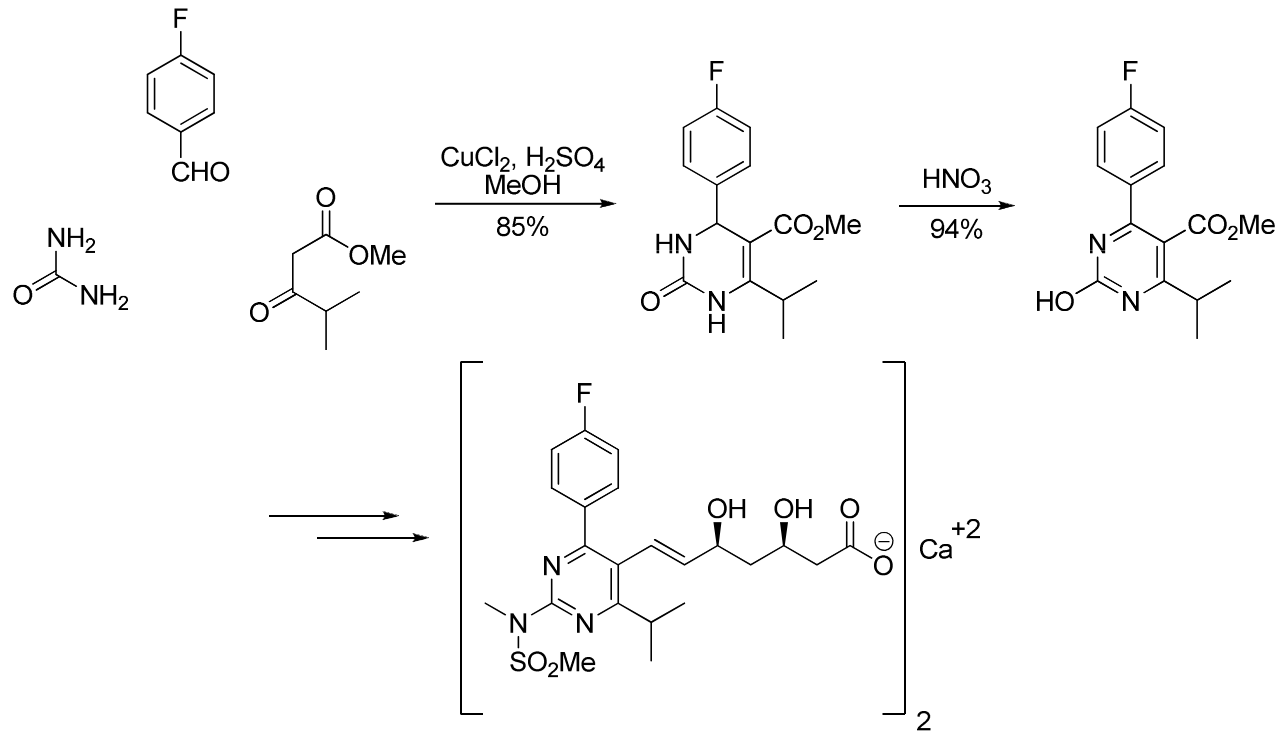
~70% of the 5-membered rings were synthesized.

~70% of the 6-membered rings were purchased.

Heterocycle Occurrence and Formation

Most of the heterocycle forming reactions were either condensations (24 examples) or cyclodehydrations (12 examples), only four examples were cycloaddition reactions.

Example of the general trend in the use of established condensation chemistry:



rosuvastatin calcium

Protections and Deprotections

Protections account for 6% of total chemical transformations.

Deprotections account for 15%.

On a positive note, 45 out of 128 syntheses were achieved without their use, and had fewer # of overall steps.

Protections

Functional group	Frequency
Amino (*N*-Boc, *N*-Cbz/Bn)	39%
Hydroxyl (*O*-Bn, *O*-SiR_3, *O*-Ac)	30%
Carboxylic acid (methyl/ethyl esters)	28%
Other	3%

Deprotections

Functional group	Frequency
Amino (*N*-Boc, *N*-Cbz/Bn)	47%
Hydroxyl (*O*-Bn, *O*-SiR_3, Ar-*OR*)	14%
Carboxylic acid (methyl/ethyl esters)	29%
Other	10%

Use of silicon protecting groups is small, since they contribute to a lack of crystallinity and can be expensive (except TMS).

Acylations

Acylations comprise of 12% of the total reactions.

Acylation	# of examples	Frequency
N-acylation to amide	84	66%
N-sulfonation to sulfonamide	12	9%
N-acylation to urea	8	6%
Carbamate/ carbonate formation	7	5%
Amidine formation	5	4%
O-acylation to ester	5	4%
Other	7	5%
Total	128	

N-acylation methods

Method	# of examples	Frequency
Acid chloride	37	44%
Coupling reagent	21	25%
Mixed anhydride	11	13%
Carbonyl diimidazole	9	11%
Other	6	7%
Total	84	

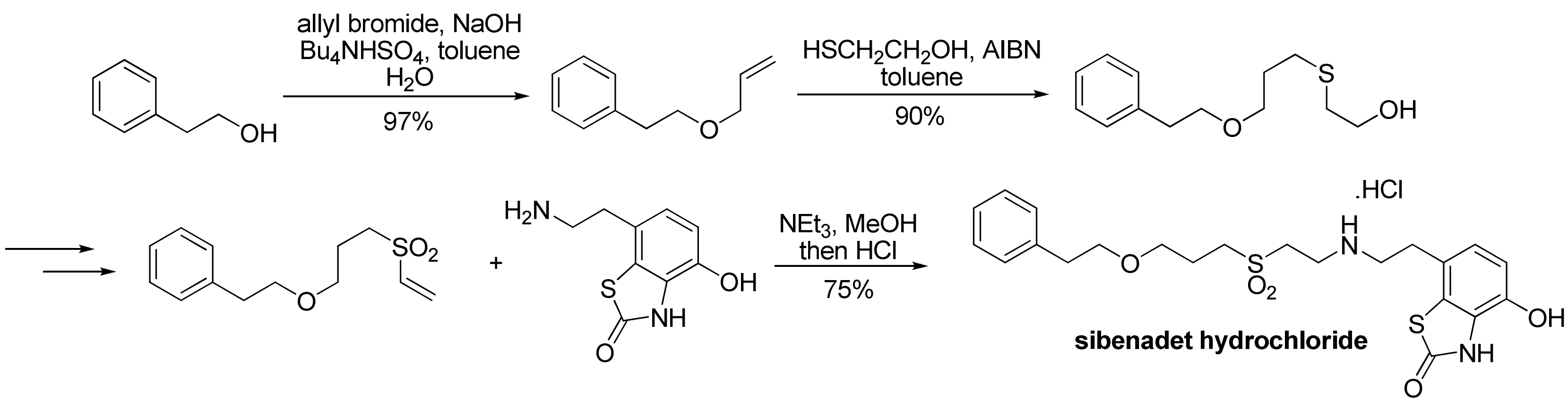
- CDI is gaining popularity, as reactions are readily scaled up, and worked up.
- Coupling reagents such as carbodiimides are frequently used for early development, not later since they are sensitisers and costly.
- Acid chlorides and mixed anhydride routes are economic, not green.

Heteroatom Alkylations and Arylations

Single largest class of reactions – 19% of total.

Typically, 90% of drugs contain N, and an higher proportion contain O.

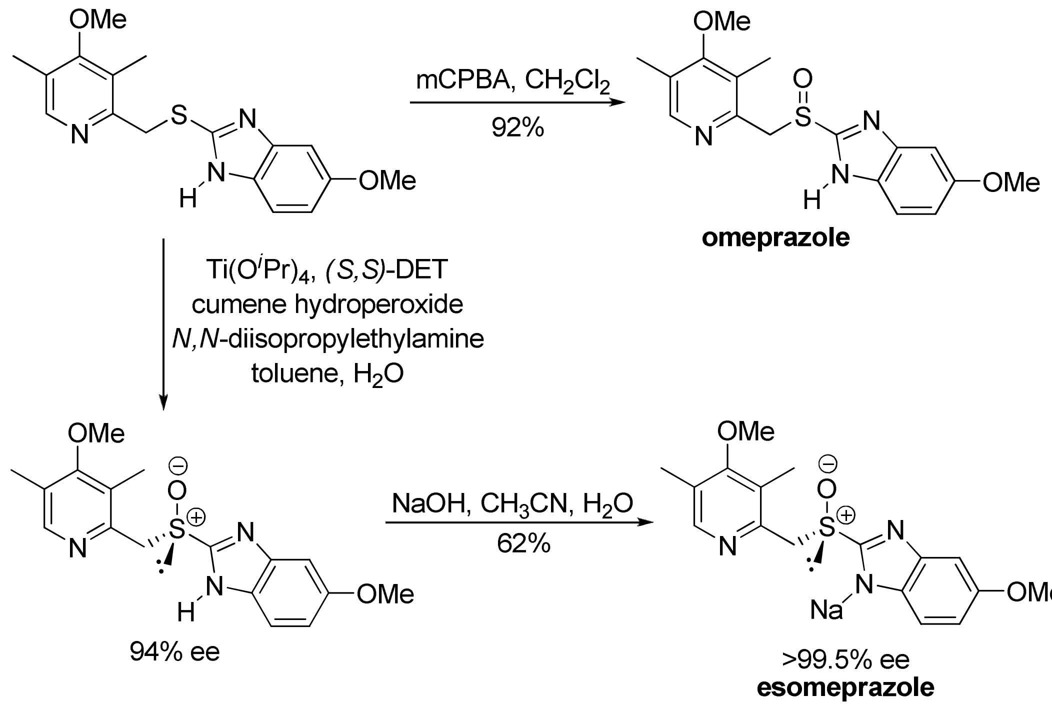
Heteroatom	Number	Frequency
N-substitution	112	57%
O-substitution	54	28%
S-substitution	16	8%
Other	14	7%
Total	196	



Oxidation Reactions

Use is low, only 4% of total.

Oxidations	Frequency
Oxidation at sulfur	25%
Alcohol oxidation	17%
Oxidation at nitrogen	15%
Alkene oxidative cleavage	15%
Benzylic/allylic oxidation	5%
Other	8%



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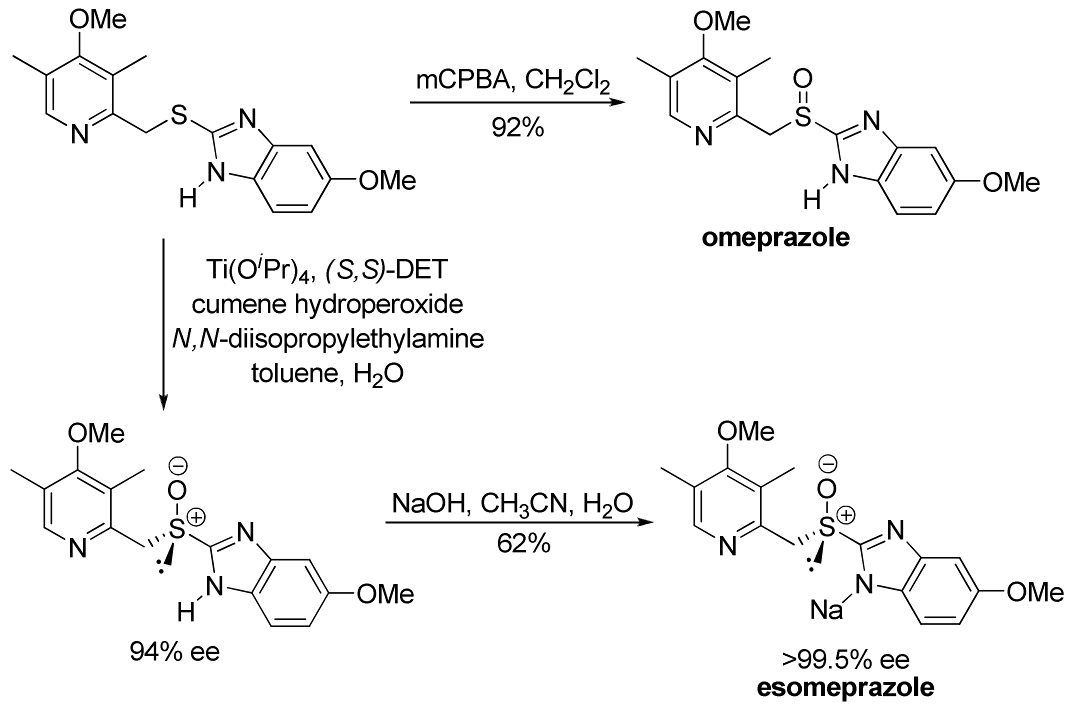


Oxidation of alcohol to carbonyl rarely used.

Heavy metals used in most of theses cause problems in removal, must be present <10 ppm levels.

Many oxidizing agents are high energy species, giving rise to thermal hazards at scale.

Reduction Reactions

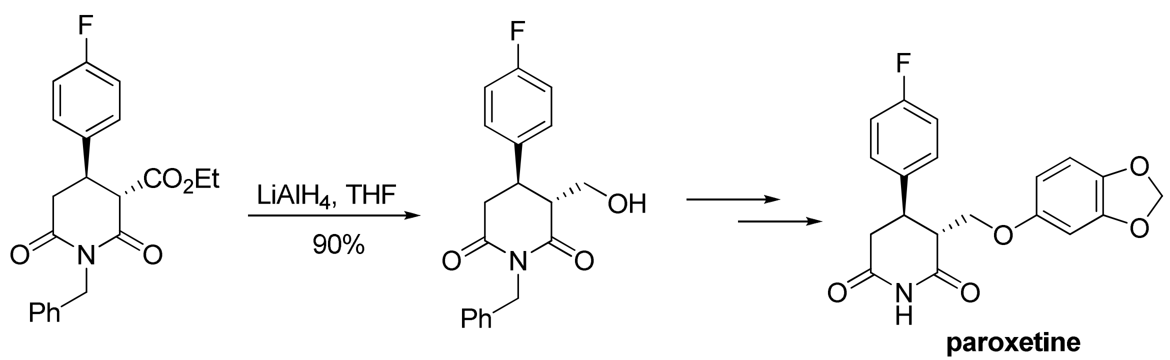
Used more than oxidations, 9% of total.

Catalytic hydrogenation over precious metal catalysts (Pd, Pt, Ni) – 47%.
Hydride ($LiAlH_4$, $NaBH_4$ and DIBALH) – 32%.
Borane – 10%.

Reductive amination done with $NaBH_3CN$ or $Na(OAc)_3BH$ at early stage, superseded with catalytic hydrogenation over appropriate catalyst at industrial scale.

Catalytic hydrogenation over H_2 gas is most atom efficient process, should be developed for all reductions.

Catalytic hydrogenation strikingly absent from reduction of carboxylic acid derivatives – huge potential.



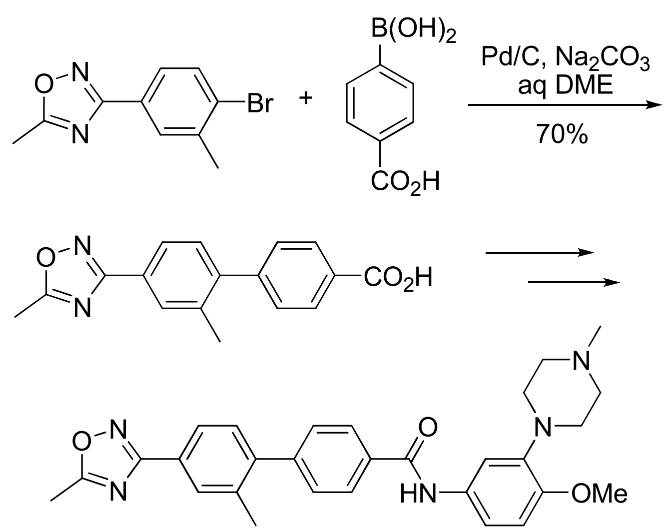
C-C Bond Forming Reactions (11%)

	Number	Frequency
Pd catalysis	26	22%
Suzuki	*13*	
Heck	*7*	
Ester condensation	16	14%
Organometallic	14	12%
Friedel-Crafts	12	10%
Other	48	41%
Total	116	

Popularity of Suzuki derived from:

- Easy accessibility of two components.
- Convenient reaction conditions.
- Broad functional group tolerance.
- Easy removal of the inorganic by-product.

Although Pd removal can be problematic.



GR127935

So much for the trivia.

Now for the stuff that a lot of us would be doing in the near future…

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Industrial Methods for the Production of Optically Active Intermediates

Amino Acids

Carboxylic Acids

Amines

Amino alcohols

Alcohols

Epoxides

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Amino Acids

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Industrial Methods for the Production of Optically Active Intermediates

Amino Acids

Carboxylic Acids

Amines

a) Classical chemical processes.

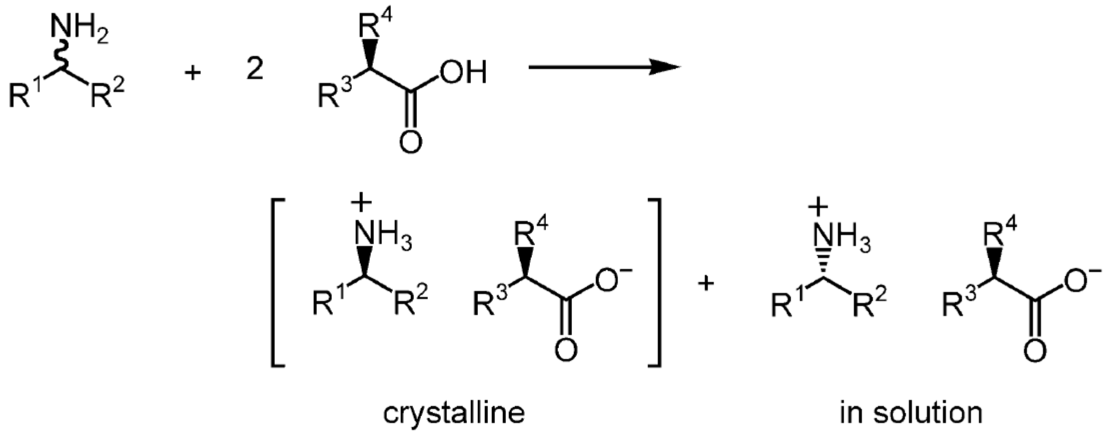
b) Biotechnological processes.

Amino alcohols

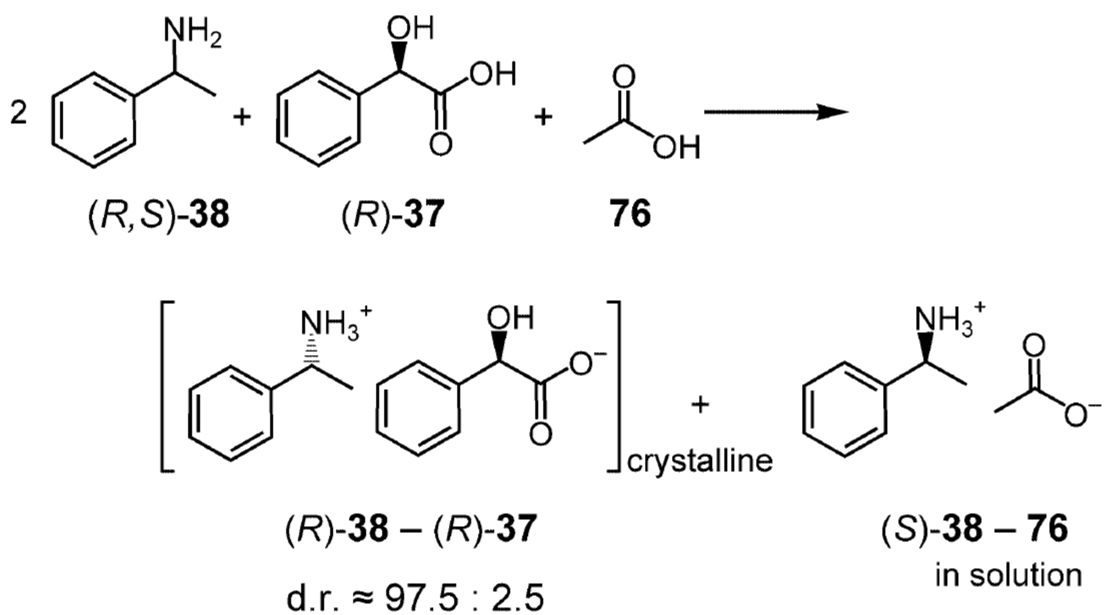
Alcohols

Epoxides

Classical Chemical Processes – Crystallization with Chiral Carboxylic Acids

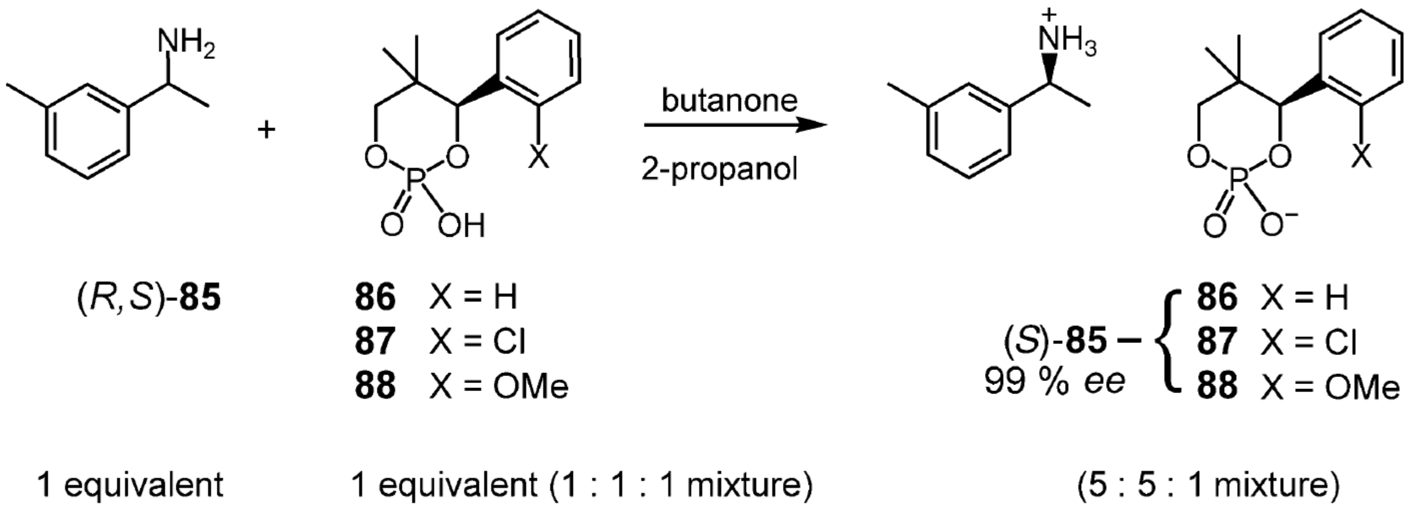


Hexcel Corp:



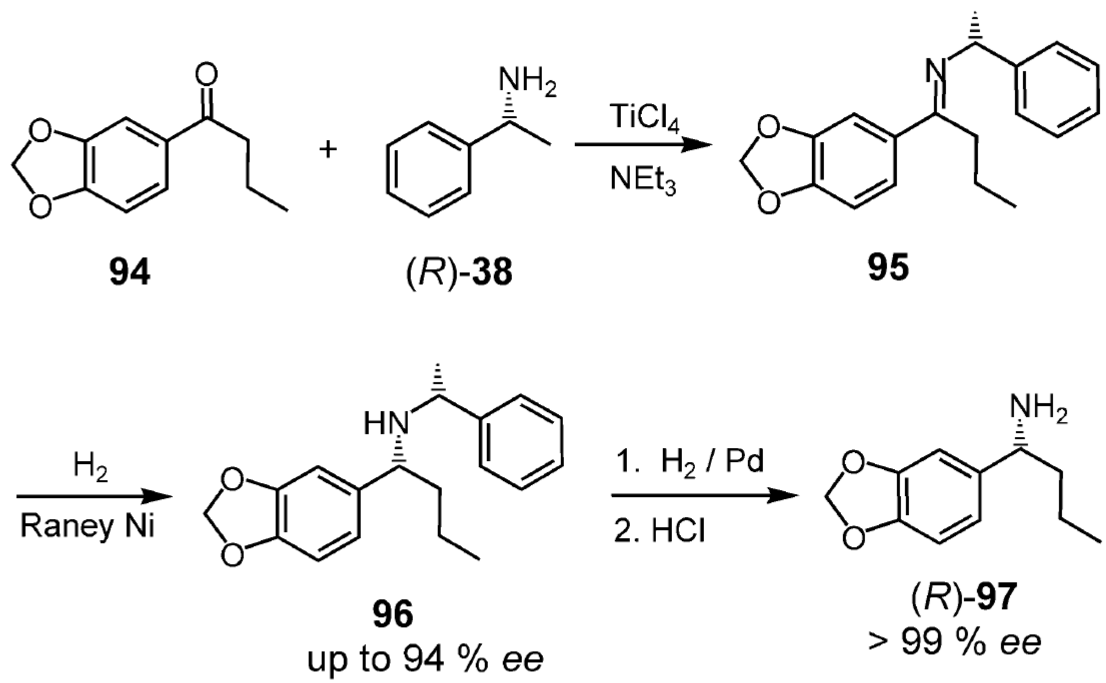
Classical Chemical Processes – Dutch Resolution (DSM & SynCom BV)

A mixture of several optically active acids is used,
whereby the salt precipitates that contains not *one*, but *several* acid anions.



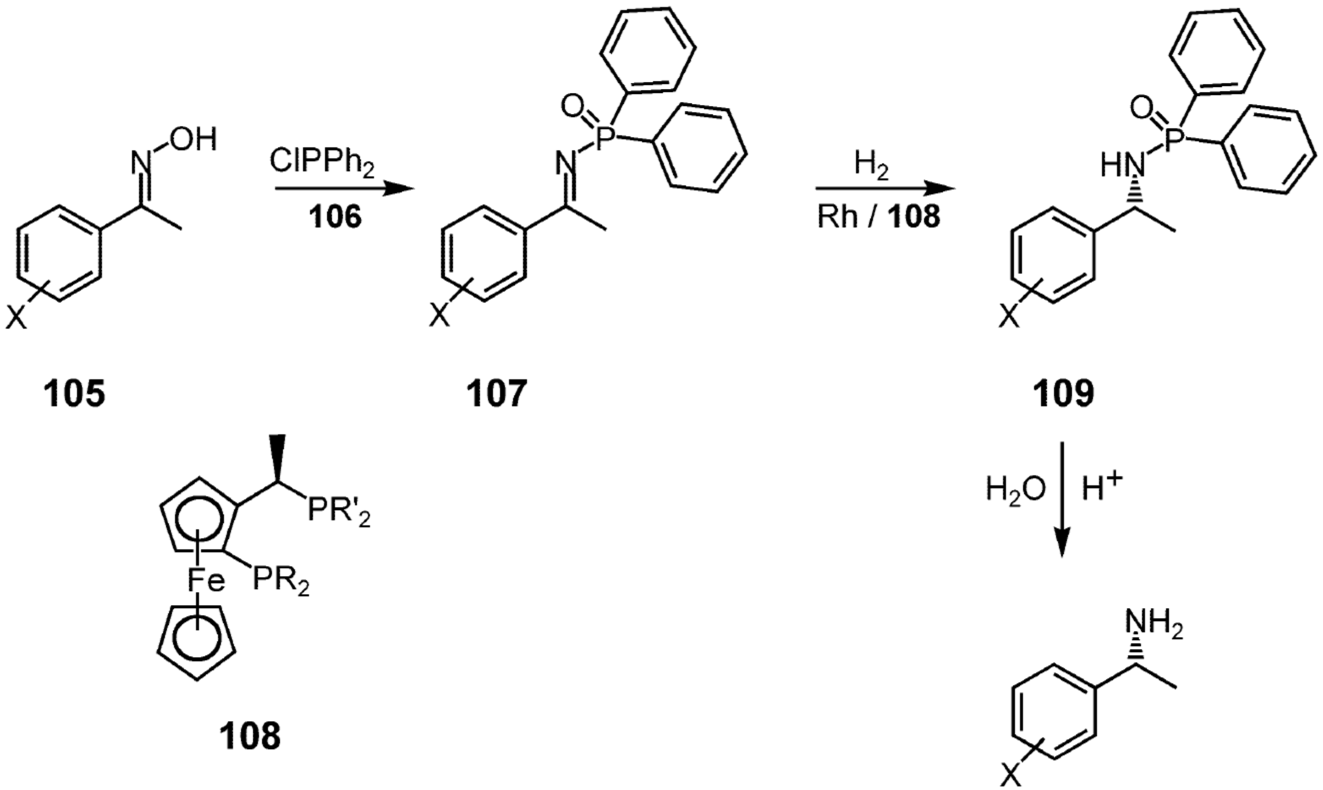
Classical Chemical Processes – Reduction of C=N Bonds

DuPont Pharmaceutical Company:



Classical Chemical Processes – Reduction of C=N Bonds

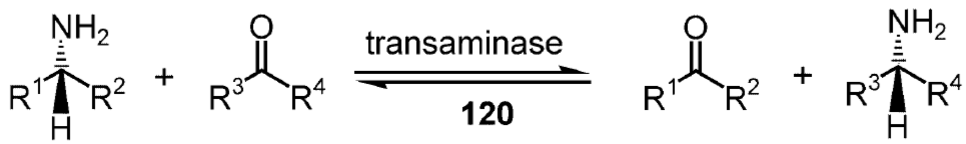
Solvias and Avecia Ltd.:



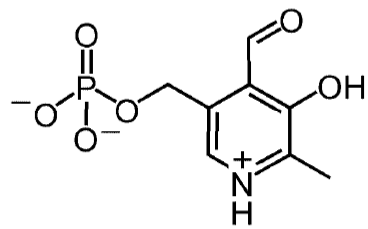
105 107 109 108 110

up to 99 % *ee*

Biotechnological Processes – Transaminations (Celgene)



116 **117** **118** **119**

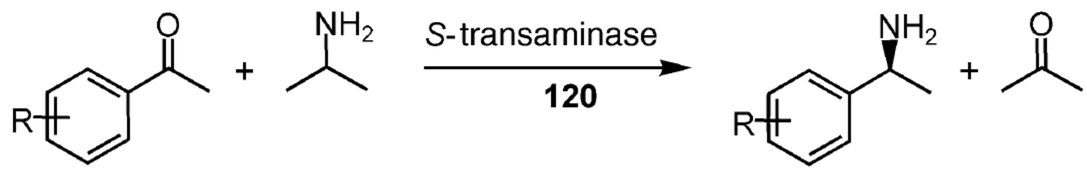


120

R- and *S*- selective transaminases afford both enantiomers of **119.**

Biotechnological Processes – Transaminations (Celgene)

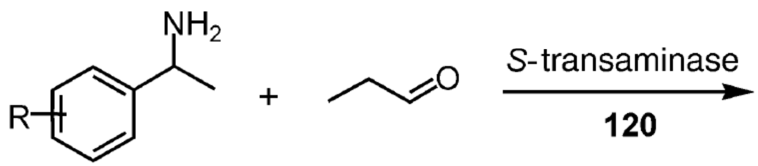
synthesis



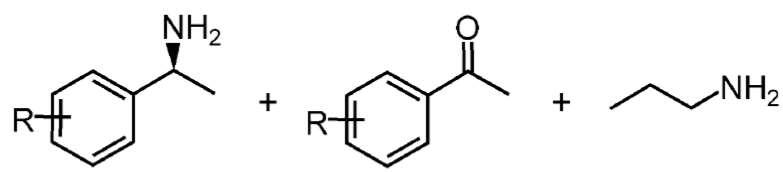
121 **122** (*S*)-**123** **124**

> 99 % *ee*

racemate resolution



(*R*,*S*)-**123** **125**



(*R*)-**123** **121** **126**

> 99 % *ee*

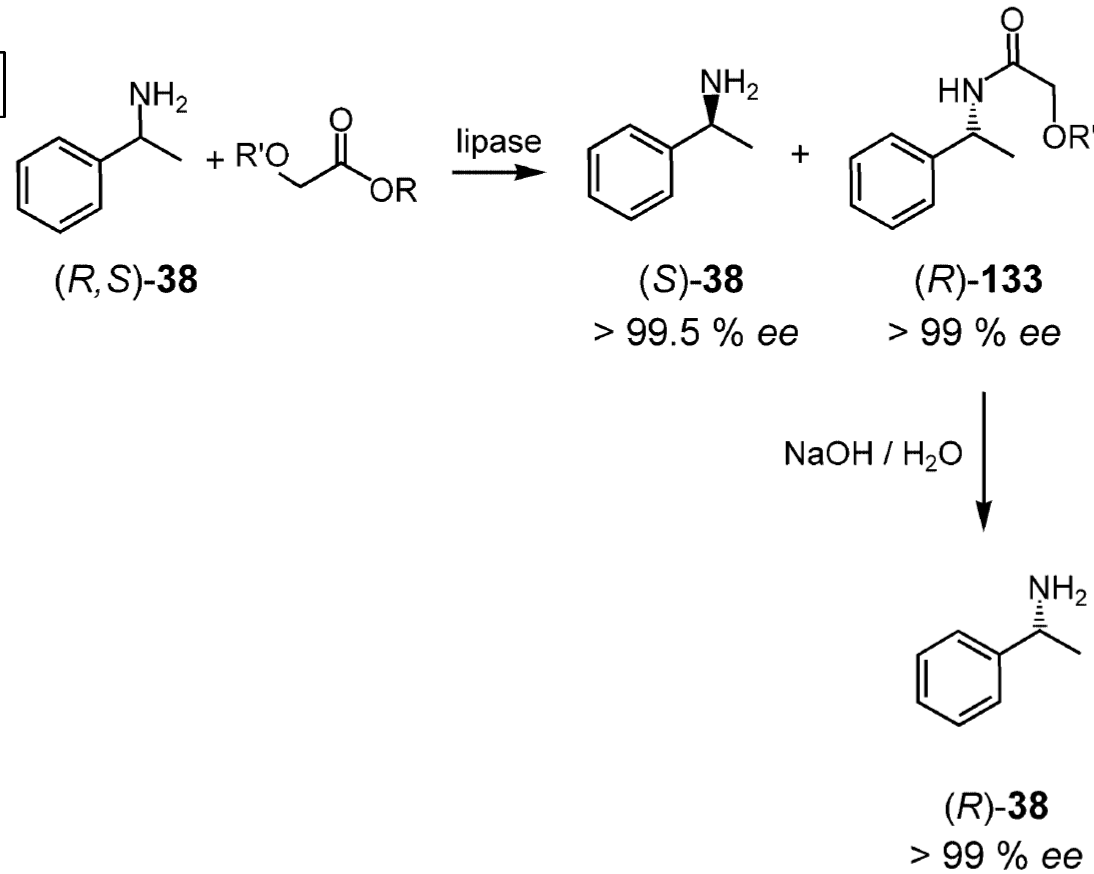
Practiced on large scales.

Variety of substrates.

Industrial Optically Active Amines

Biotechnological Processes – Kinetic Resolutions (BASF)

Broad substrate tolerance.



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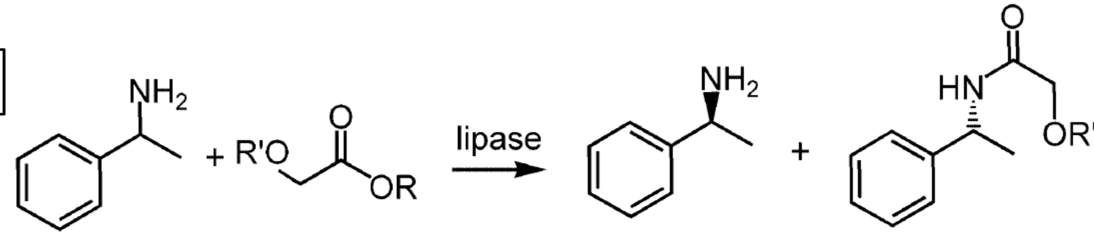
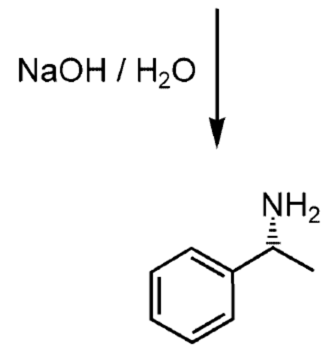


(*R*,*S*)-**38**

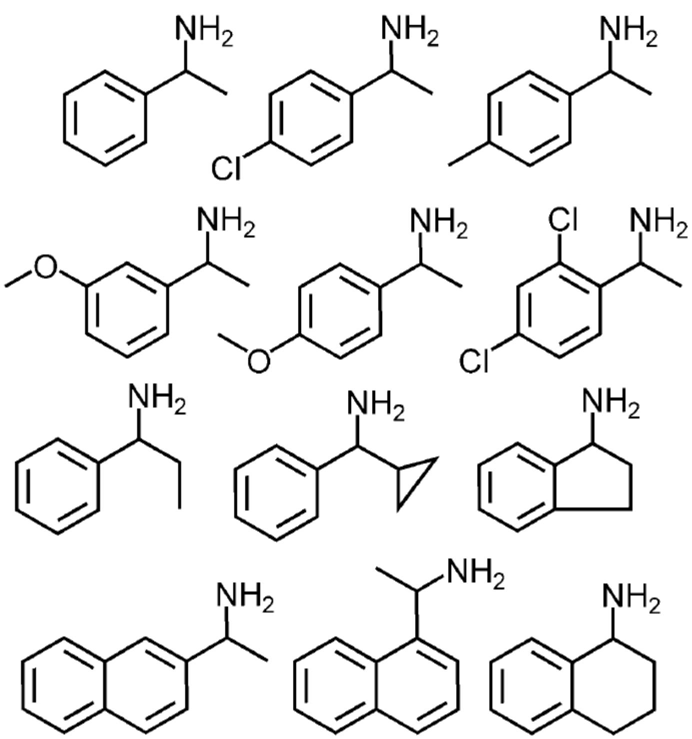
(*S*)-**38**
> 99.5 % *ee*

(*R*)-**133**
> 99 % *ee*

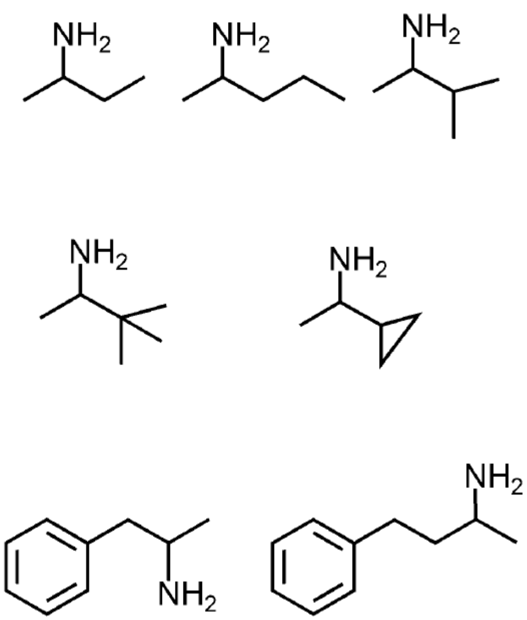


(*R*)-**38**
> 99 % *ee*

aryl alkyl amines:



alkyl amines:



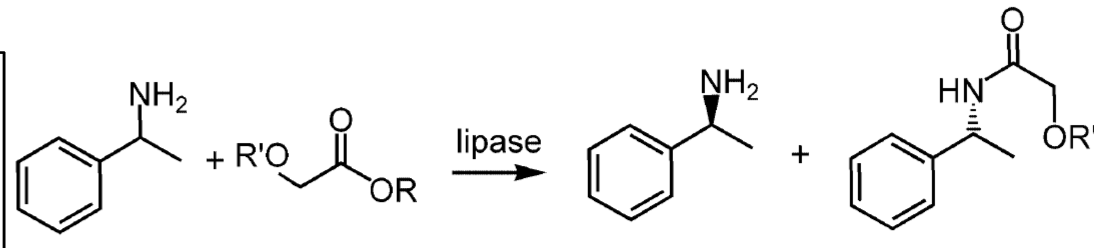
Industrial Optically Active Amines

Biotechnological Processes – Kinetic Resolutions (BASF)

Broad substrate tolerance.

Multi-ton scale practiced.

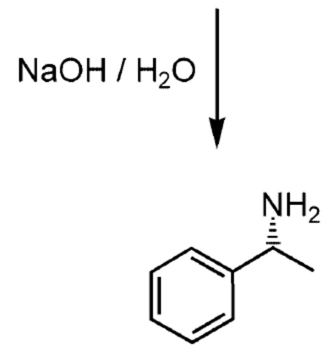
BASF c-GMP plant – 1000 ton/annum.



(*R*,*S*)-**38**

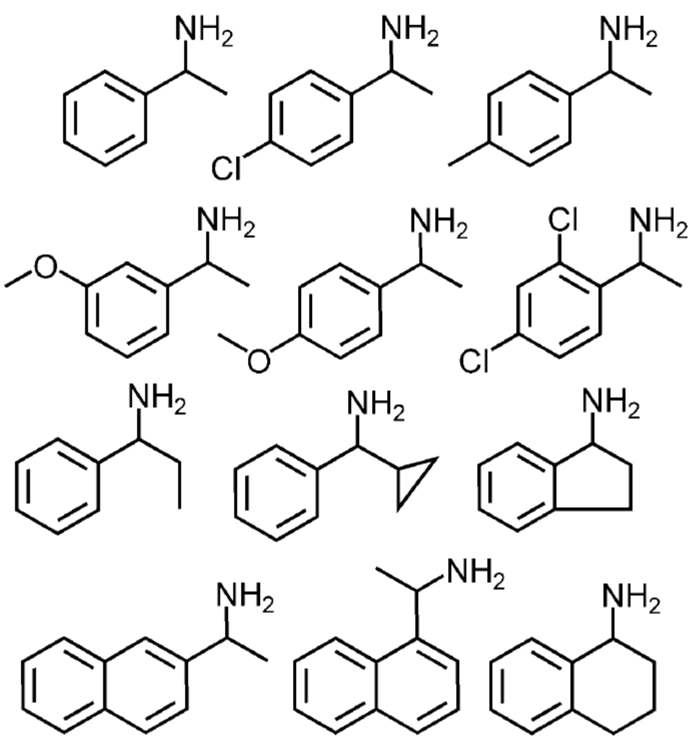
(*S*)-**38** > 99.5 % *ee*

(*R*)-**133** > 99 % *ee*

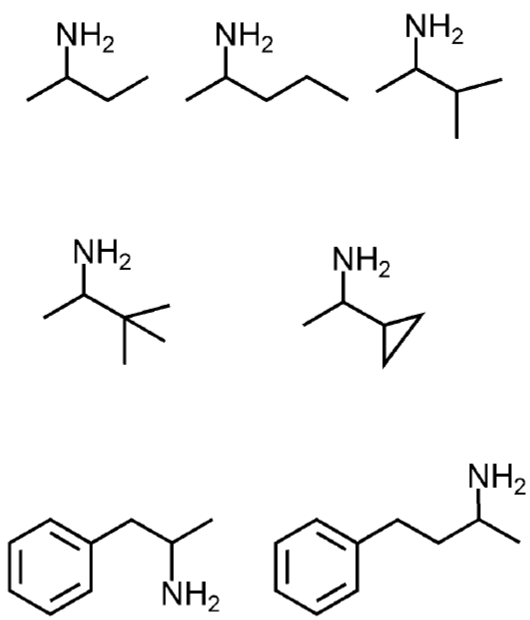


(*R*)-**38** > 99 % *ee*

aryl alkyl amines:



alkyl amines:



Industrial Methods for the Production of Optically Active Intermediates

Amino Acids

Carboxylic Acids

Amines

Amino alcohols

Alcohols

Epoxides

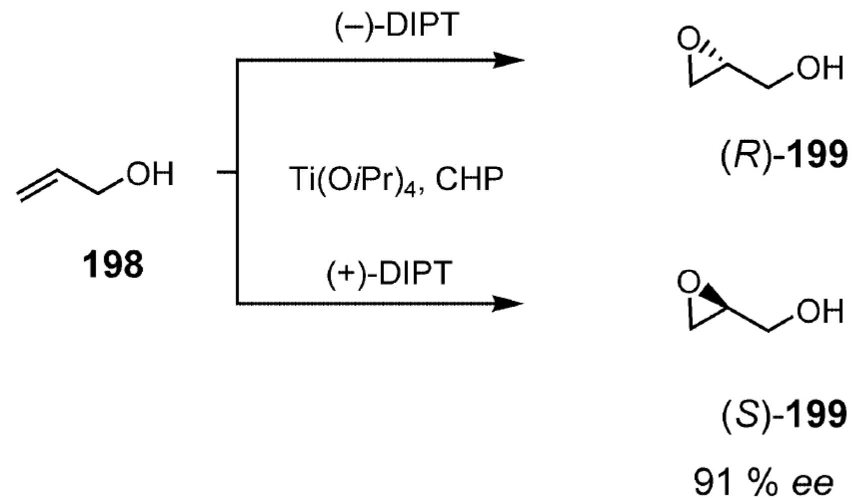
a) Chemical methods

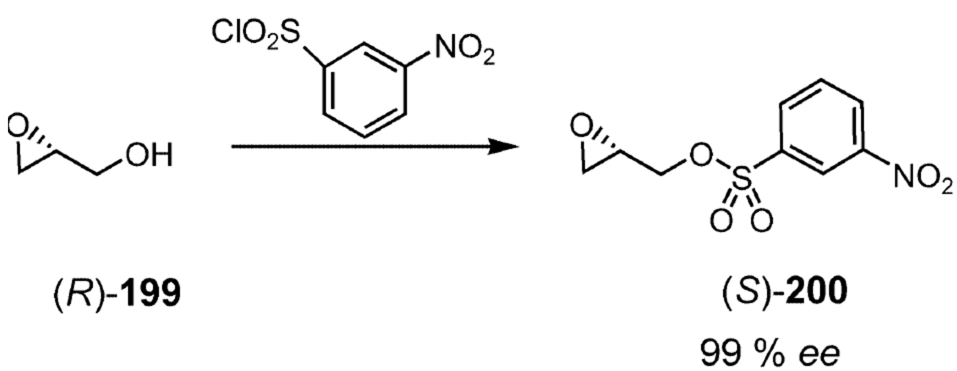
b) Biotechnological processes.

Chemical Methods – Sharpless Asymmetric Epoxidation

1986 - Breakthrough for industrial applications – Discovery that upon addition of mol. sieves, only catalytic amounts of the titanium tartrate complex were required.

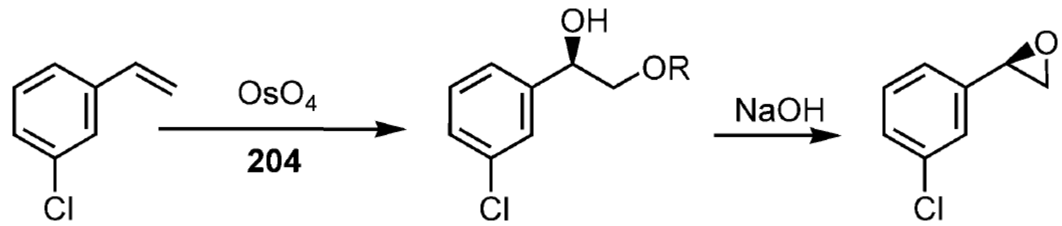
Arco Chemical / PPG-Sipsy:





Chemical Methods – Sharpless Asymmetric Dihydroxylation

Rhodia ChiRex:



203

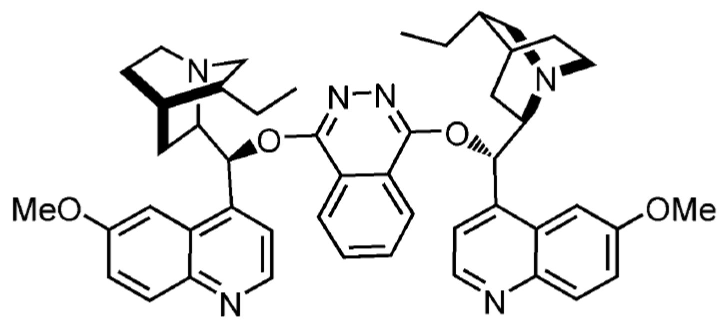
pNS–Cl

(*R*)-**205**, R = H

(*R*)-**206**, R = *p*NS

(*R*)-**207**

> 99 % *ee*

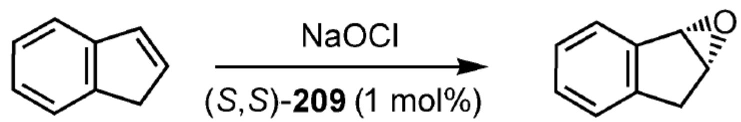


204

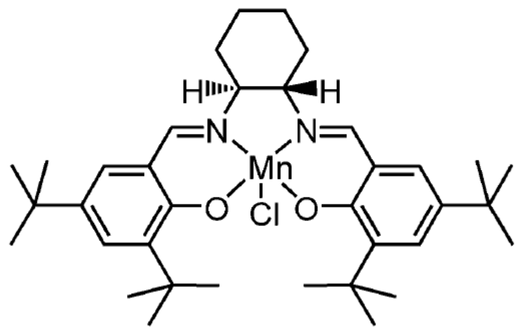
100 – 4000 L scale.

Chemical Methods – Jacobsen Asymmetric Epoxidation

ChiRex:



208 (1*S*,2*R*)-**138**

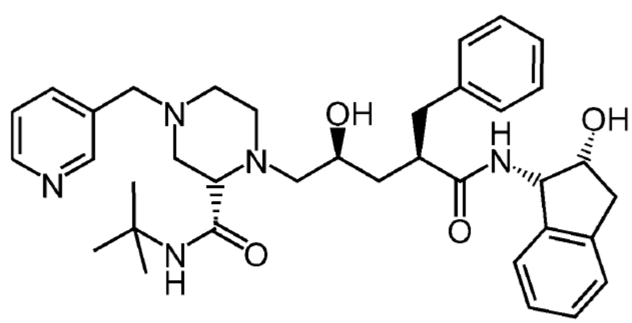


(*S*,*S*)-**209**

Limited to *cis*-alkenes.

Chirex has exclusive rights.

Multi-ton scale.

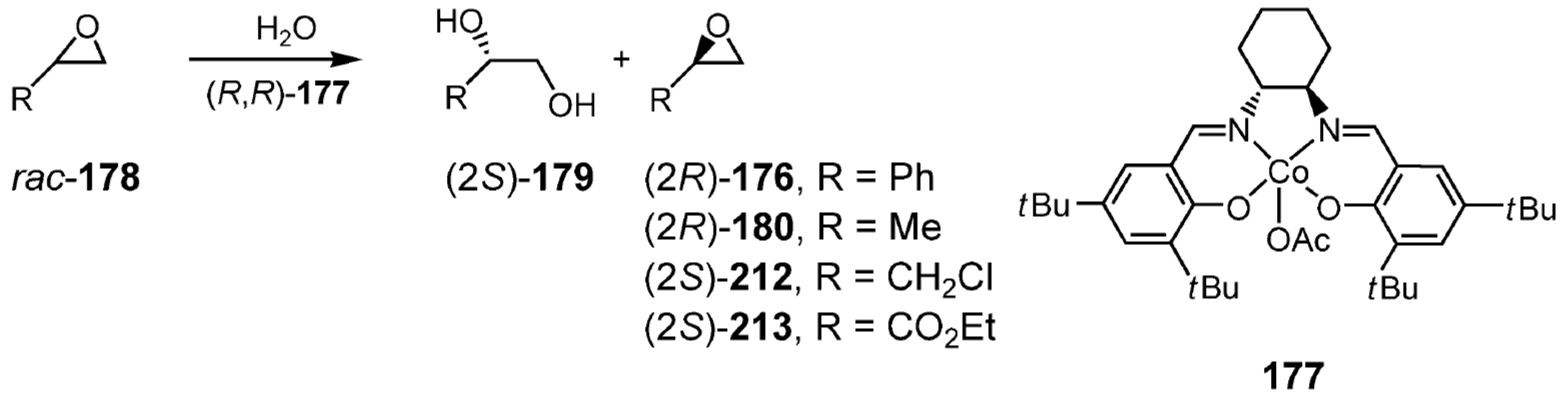


136
indinavir

Industrial Optically Active Epoxides

Chemical Methods – Jacobsen Hydrolytic Kinetic Resolution

Rhodia ChiRex:



>99% ee and 40-48% yields.

Shown examples practiced at ton scales.

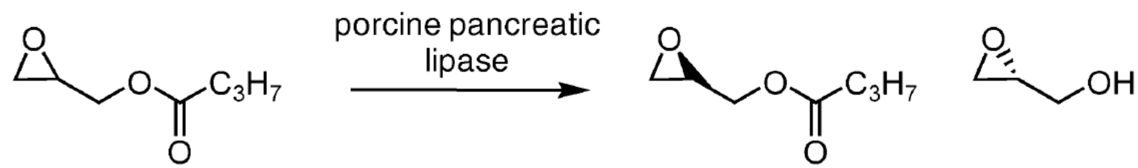
Daiso – a producer of similar intermediates by microbial resolution – recently announced a change to the Jacobsen technology – 50 ton/annum production capacity.

Licensed from ChiRex, which supplies catalyst.

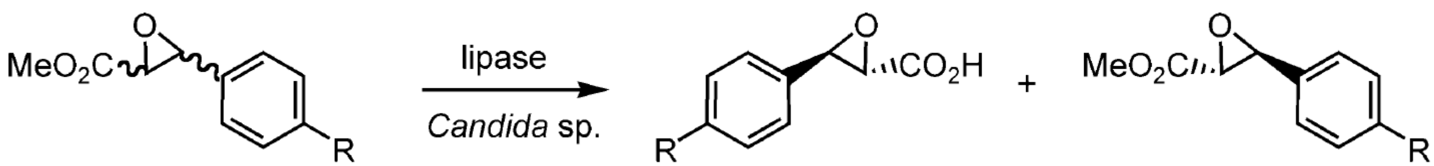
Biotechnological Processes – Racemate Resolution with Lipases

Developed by Ladner & Whitesides.

Practiced by Andeno-DSM at multi-ton scales.



rac-**218** (*R*)-**218** (*R*)-**199**

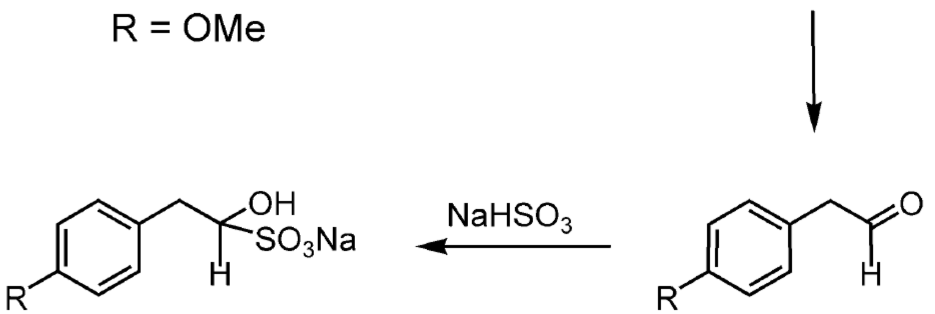


Sepracor DSM

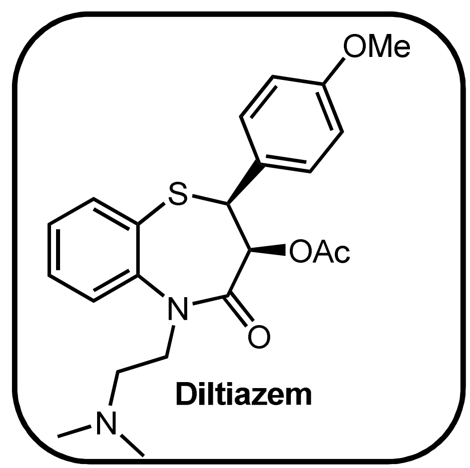
rac-**221**

R = OMe

(2*S*,3*R*)-**222** (2*R*,3*S*)-**221**

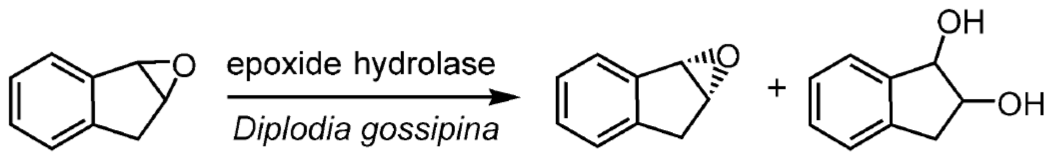


224 **223**

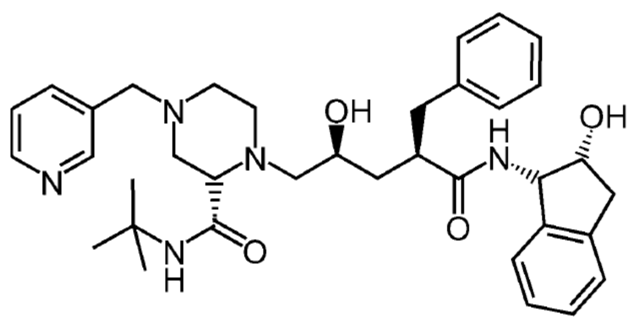


Biotechnological Processes – Racemate Resolution with Epoxide Hydrolases

Merck & Co:



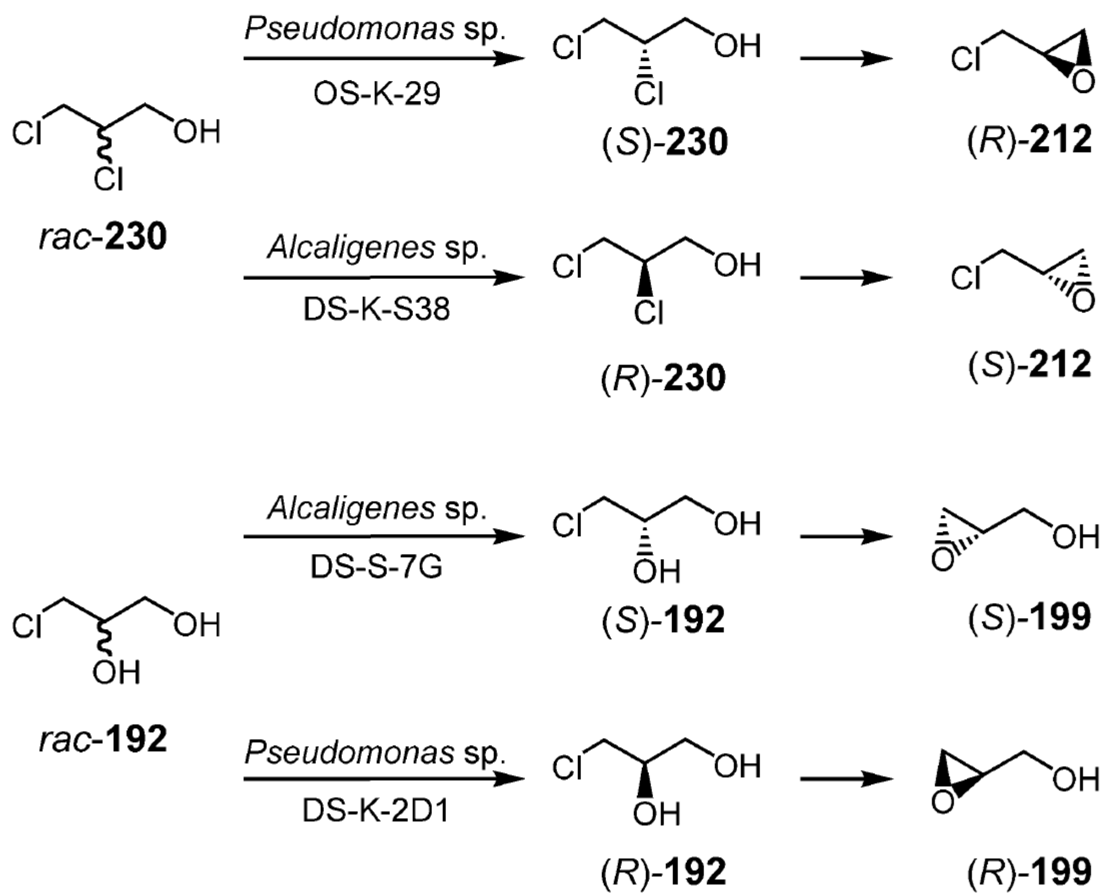
rac-**138** (1*S*,2*R*)-**138** (*R*)-**227**



136
indinavir

Biotechnological Processes – Racemate Resolution with Microbial Methods

Diaso



Enough of the serious chemistry. The fun part now!

Sorry Ding, no dirty pictures…

(1) Analysis of the Reactions used for the Preparation of Drug Candidate Molecules,

Carey, J. S. (GSK); Laffan, D. (Astrazeneca); Thomson, C. (Astrazeneca); Williams, M.T. (Pfizer) *Org. Biomol. Chem.* **2006**, *4*, 2337.

(2) Industrial Methods for the Production of Optically Active Intermediates,

Hauer, B. (BASF) *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 788.

(3) The Chemistry IgNobel Prizes.

Improbable Research

That is the name of the organization.

They publish a journal called: Annals of Improbable Research, and administer the IgNobel Prizes.

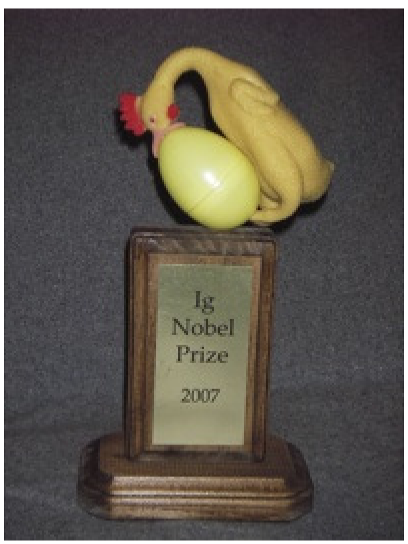
IgNobel – play on the word “ignoble” and the name “Nobel”.

“Honor achievements that first make people **laugh**, and then make them **think**.”

The ceremony takes place in Sanders Theator, Harvard University.

Winners travel at their own expense.

“The prizes are handed out by genuine, genuinely bemused Nobel Laureates, all before a standing room only audience of 1200 people.”



Lavish, fun-filled ceremony!

10 different fields.

“The IgNobel prizes are arguably the highlight of the scientific calender!” – Nature.

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The Chemistry IgNobel Prizes

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Will Humans Swim Faster or Slower in Syrup – 2005 IgNobel Chemistry

http://www.cems.umn.edu/research/cussler/pool/

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1999	Makino T., president of The Safety Detective Agency, Japan,	S-Check, an infidelity detection spray that wives can apply to their husbands' underwear.