Kinetic Resolutions

Material outline:
For the Scientist in you:
- Definitions
- Theoretical treatment

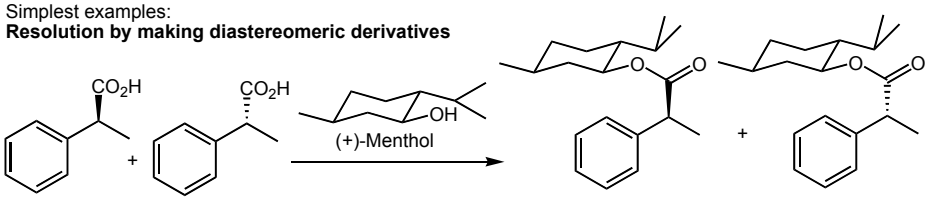
For the technician in you:
- Practical considerations
- Useful KR's
  - Oxidative KR of allylic alcohols
    - An extreme example
  - Acylation/deacylation
  - Hydrogenation
    - olefins
    - ketones
      - Dynamic kinetic resolution
  - Epoxide ring opening
    - A very extreme example
- Parallel kinetic resolution

General References:
Vedejs, ACIEE, 2005, 3974
Jacobsen, Adv. Syn. Cat. 2001, 5
Kagan, Topics in Stereochemistry, 1988, *18*, 249

Some definitions and examples

Resolution: A process leading to the separation of enantiomers, or derivatives thereof

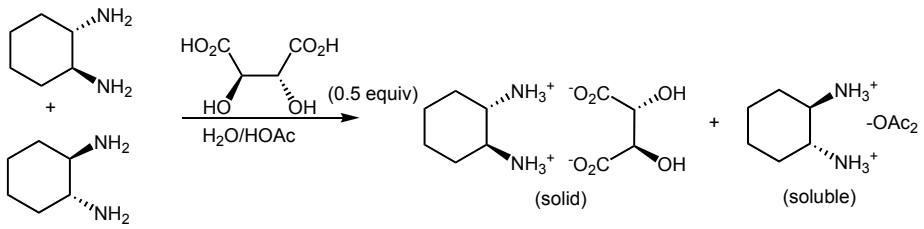
Simplest examples:
Resolution by making diastereomeric derivatives



enantiomers
(identical mp, mobilitiy on silica gel, bp, etc)

diastereomers
(different mp, mobility on silica gel, bp, etc)

Resolution via salt formation:

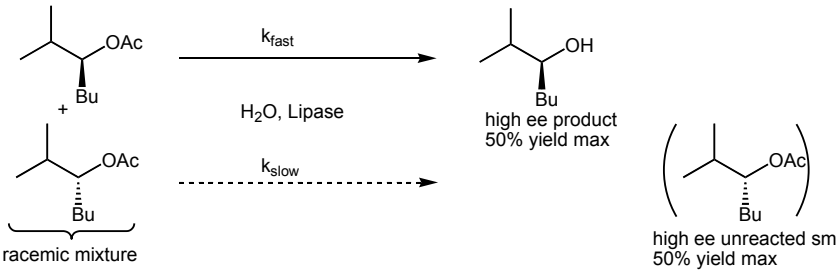


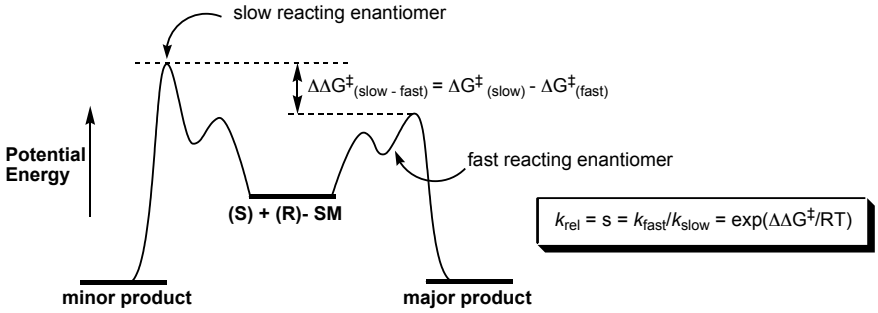
(solid) (soluble)

Larrow, Jacobsen, OS, 1998, *75*, 1

Ready; Catalysis Kinetic Resolution

Kinetic Resolution: One enantiomer reacts faster than the other:

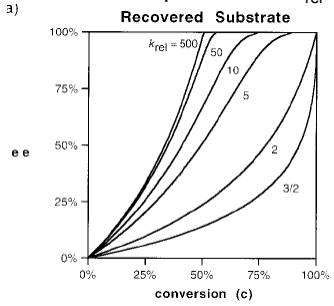




$k_{rel} = s = k_{fast}/k_{slow} = \exp(\Delta\Delta G^{\ddagger}/RT)$

Ready; Catalysis Kinetic Resolution

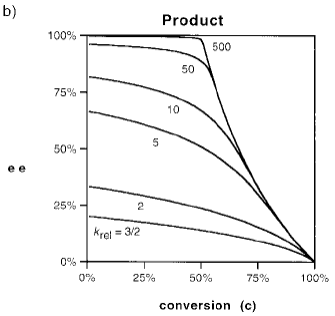
Relationships between k_{rel}, ee and conversion



$$k_{rel} = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]} \quad (1)$$

k_{rel}	$\Delta\Delta G^{\ddagger}$ (kcal/mol)	Conversion (%) required to attain: 90% ee	98% ee	>99% ee
1.5	0.24	99.9	99.99	>99.999
2	0.41	97.2	99.5	>99.7
5	0.95	74.8	84.0	>86.6
10	1.35	62.1	69.7	>72.1
50	2.31	50.4	54.0	>54.9
100	2.72	48.9	51.8	>52.4
500	3.66	47.7	50.0	>50.3

Calculated from eq 1



$$k_{rel} = \frac{\ln[1-c(1+ee)]}{\ln[1-c(1-ee)]}$$

Important Points

1. KR can give any arbitrarily high ee recovered sm with any k_{rel} >1 if you sacrifice yield

2. KR can give high ee product only if very high krel (needs to be more selective than 'normal' asymmetric reaction

(Jacobsen, 2001)

Some thoughts:

if not the only, route to optically pure allylic alcohols.[22] Another noteworthy aspect of this approach to chiral materials is that virtually any degree of enantiomeric purity can be obtained. For example, if the epoxidation of 2-methylhept-1-en-3-ol (entry 7) is carried to 60% conversion, the enantiomeric excess is calculated to be 99.999999999%,[23] and one can go much higher than this simply by proceeding to higher conversions. Such extreme en-

For the production of enantiomerically pure substances, kinetic resolution is generally regarded as a poor cousin to asymmetric synthesis. Kinetic resolution suffers from the disadvantage that at least half of the starting material is lost. However, we believe this work makes clear one striking advantage kinetic resolution holds over asymmetric synthesis. The enantiomeric excess realized in an asymmetric synthesis is simply a consequence of the energy difference ($\Delta\Delta G^{\ddagger}$) between two diastereomeric transition states; the only way to improve the % ee is to increase that energy difference. Kinetic resolution too depends on there being an energy difference between diastereomeric transition states, but the manner in which that energy difference is expressed is unique to kinetic resolutions. The energy difference, manifested as a relative rate difference, represents a constant and unrelenting differential pressure upon the two enantiomers. This winnowing should continue until the last molecule of the more reactive enantiomer is swept away, and one is left with a substance possessed of absolute enantiometric purity.[25]

-Sharpless, JACS, 1981, 6237

Note that eq 1 may not always hold:

$$k_{rel} = \frac{\text{Ln}[(1\text{-c})(1\text{-ee})]}{\text{Ln}[(1\text{-c})(1\text{+ee})]} \quad (1)$$

It assumes rxn is first order in substrate, but consider simple enzyme kinetics:

$$\text{Sub} + \text{Cat} \underset{k_1}{\overset{k_1}{\rightleftharpoons}} \text{Sub-Cat} \xrightarrow[k_2]{\text{Reagent}} \text{Product}$$

$$\text{Rate}_{(\text{R-sub})} = \frac{k_{2(R)}[\text{Reagent}][\text{Cat}]_t[\text{Sub}]}{K_M + [\text{Sub}]}$$

$K_M = (k_{-1} + k_2)/k_1$ ~ dissociation constant
Sub = substrate

For [sub]>>Km, rxn is 0 order in [sub]; equation 1 does not hold
For [sub]<<Km, rxn is 1st order, equation 1 needs modification:

$$\textit{Relative rate} = E = \frac{k_{cat(R)}K_{M(S)}}{k_{cat(S)}K_{M(R)}} = \frac{\text{Ln}[(1\text{-c})(1\text{-ee})]}{\text{Ln}[(1\text{-c})(1\text{+ee})]} \quad (2)$$

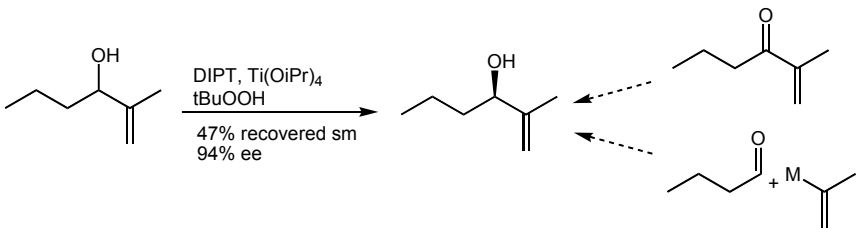
Eq. 2 is eq 1 normalized to binding affinity

Many (most?) KR's would likely show enzyme kinetics if anyone looked. Therefore they may start out zero order, then change. Also, one enantiomer could be 1st order, while the other is 0th order!

Hallmark of trouble is if k_{rel} (as calculated by eq 1) changes as a function of conversion

The real question is: what yield of what ee?

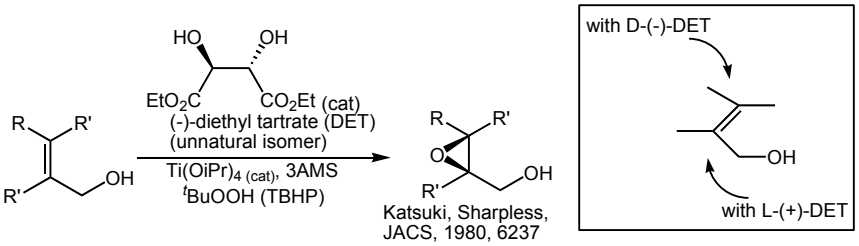
Ready; Catalysis Kinetic Resolution



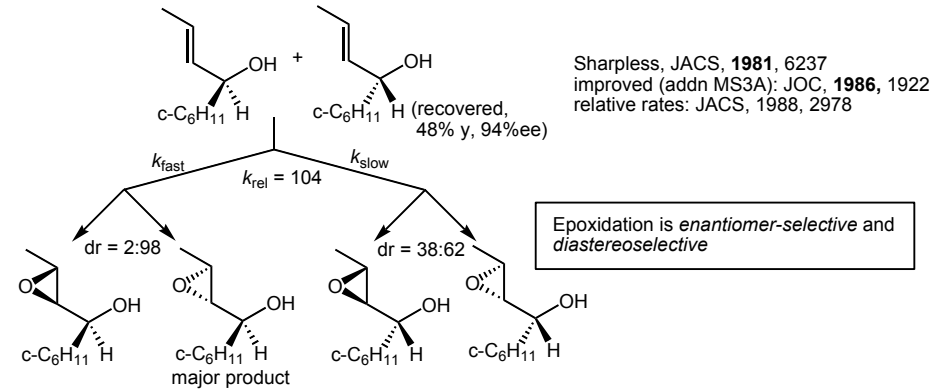
Drawbacks to KR's
Max 50% yield
Poor 'atom economy'
Viewed by some as inelegant

KR's may be useful if the following are true:
1. Very high ee needed
2. Racemate cheap; optically active hard to make
3. Resolving agent cheap
4. Products easily separable
5. Catalyst cheap and works well

Ready; Catalysis Kinetic Resolution



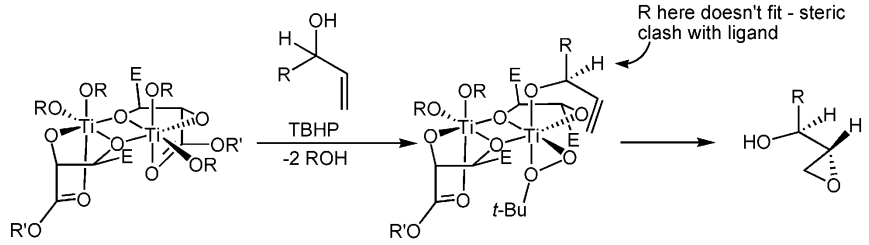
General trend: asymmetric catalytic reaction disclosed; soon after KR disclosed



Sharpless, JACS, **1981**, 6237
improved (addn MS3A): JOC, **1986,** 1922
relative rates: JACS, 1988, 2978

Epoxidation is *enantiomer-selective* and *diastereoselective*

Ready; Catalysis Kinetic Resolution



one of many interconverting ground-state structures

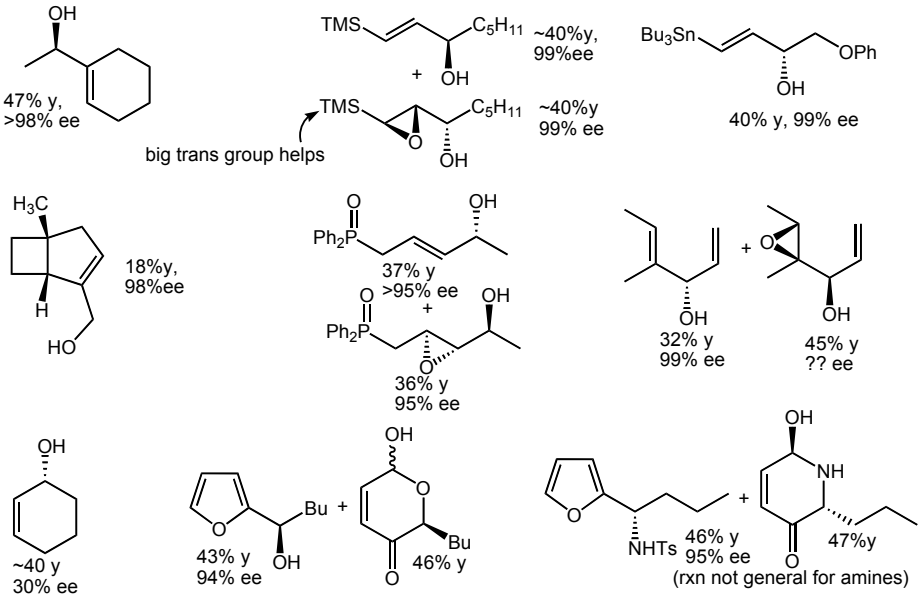
reactive conformation puts 'H' toward catalyst

$$\text{rate} = \frac{k[\text{Ti(tartrate)(OR)}_2][\text{TBHP}][\text{substrate}]}{[\text{ligand alcohol}]^2}$$

-ground state and TS dimer
-inhibited by water (that's why MS3A)
-need to loose 2 ROH ligands, coordinate [O] and substrate

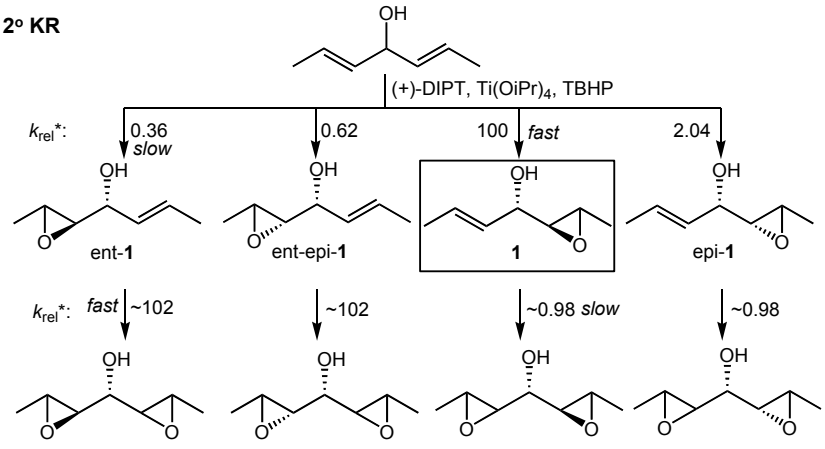
Ready; Catalysis Kinetic Resolution

Examples: isolated products shown
(for a large list, see Adv. Syn Cat, 2001, 5, supporting info)



Ready; Catalysis Kinetic Resolution

2º KR

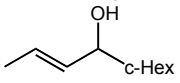


ee = %**1** - % ent-**1** de = %(**1** + ent-**1**) - %(epi-**1** + ent-epi-**1**)

predict ee and de will increase with conversion because of a **secondary kinetic resolution**

	predicted	
conversion	yield **1** (%)	ee **1** (%)
50	48	99.4
99	93 (max)	99.96
99.9	91	99.664
99.999	85	99.99999

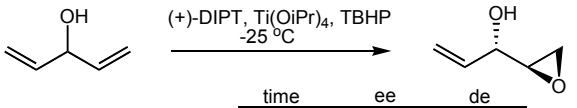
*krel calc using



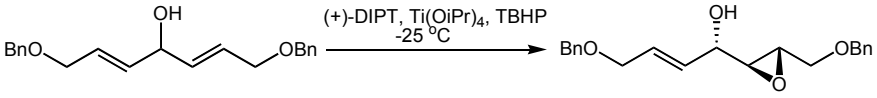
Schreiber, JACS, 1987, 1525

Ready; Catalysis Kinetic Resolution

Experimental validation



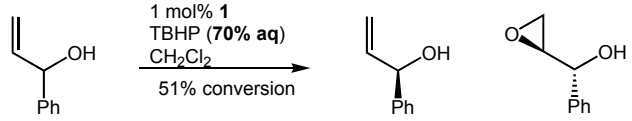
time	ee	de
3 h	84	92
24 h	93	99.7
140 h	>97	>99.7



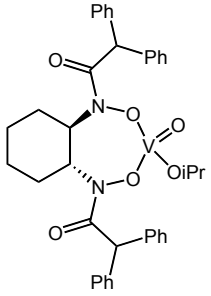
time	ee	de
1 h	93	>97
3 h	95	>97
44 h	>97	>97

Ready; Catalysis Kinetic Resolution

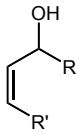
Next-generation epoxidation??



1 =



potential advantages:
aqueous conditions
substrate classes inaccessible with Sharpless:



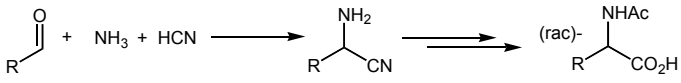
demonstrated with R = H
KR with R not H??

obvious disadvantage:
hard to beat tartrate

Yamamoto, ACIEE, 2005, 4389

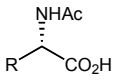
Ready; Catalysis Kinetic Resolution

Enzymatic acylation/deacylation of amines and alcohols
review: Chem Rev. 1992, 1071

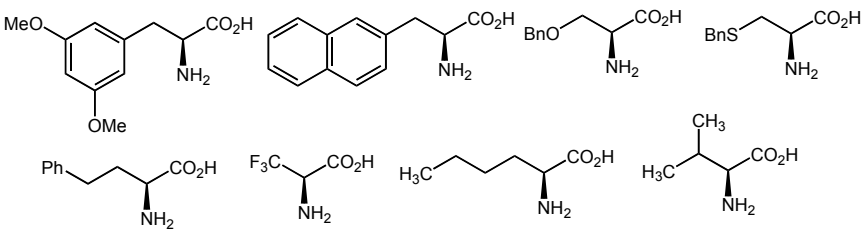


H_2O
porcine kidney acylase
(R = straight chain)

H_2O
acylase from mold
Aspergillus oryzae
(R = branched)



AA's produced by Degusa on commercial scale



Ready; Catalysis Kinetic Resolution

Enzymatic acylation/deacylation of amines and alcohols

review: Chem Rev. 1992, 1071

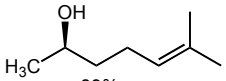
enzymes can be used to put Ac on or take Ac off. Isopropenyl acetate or vinyl acetate common acylating agents

Enzyme 'kits' are available for screening purposes from SigmaAldrich and Biocatalytics

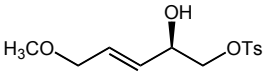
Rxns can be performed in water or organic solvents (hexane common); need exclude water from esterification reactions

General rule: an enzyme will work for almost any substrate!!:

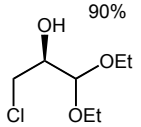
Some examples from ester hydrolysis (for details, see tables 8 - 12 in review):



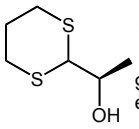
89% ee



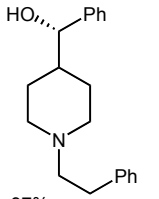
90%



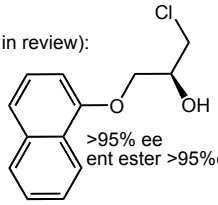
>98% ee



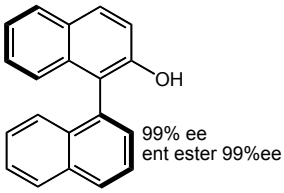
99% ee
ent ester 93% ee



>97% ee
ent ester >97% ee



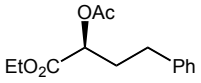
>95% ee
ent ester >95%ee



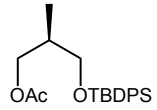
99% ee
ent ester 99%ee

Ready; Catalysis Kinetic Resolution

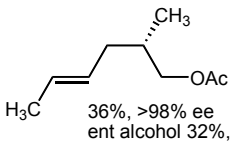
Some products from acylation:
Note cleavage of ester or acylation of alcohol gives enantiomeric product



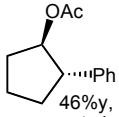
48%y, 98% ee
ent alcohol: 49% y, >98%ee



38% y, >98% ee

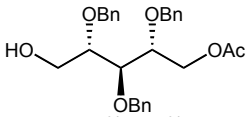


36%, >98% ee
ent alcohol 32%, 98%ee

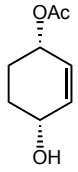


46%y, >95% ee
ent alcohol, 43%y, >95% ee

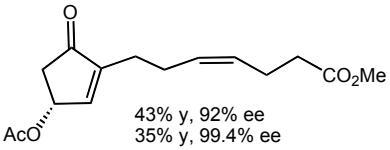
extension to desymmetrization (often with 2° KR)



70%, >95% ee



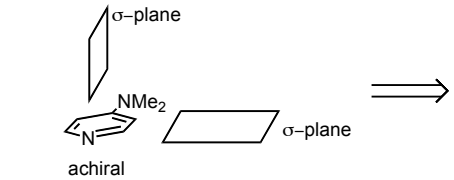
98% ee



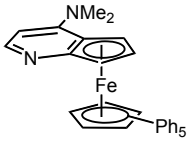
43% y, 92% ee
35% y, 99.4% ee

Ready; Catalysis Kinetic Resolution

chemical methods for KR of alcohols

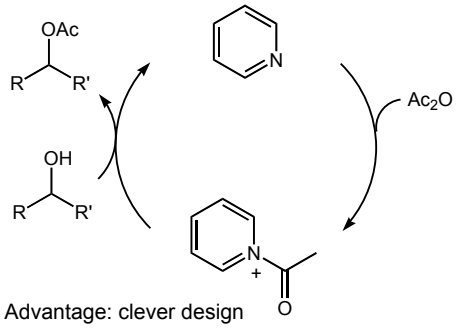


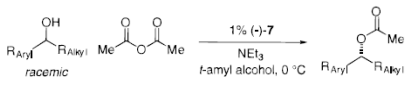
achiral



'planar chiral' version of DMAP

Fu, Accts, 2000, 412; Accts, 2004, 542



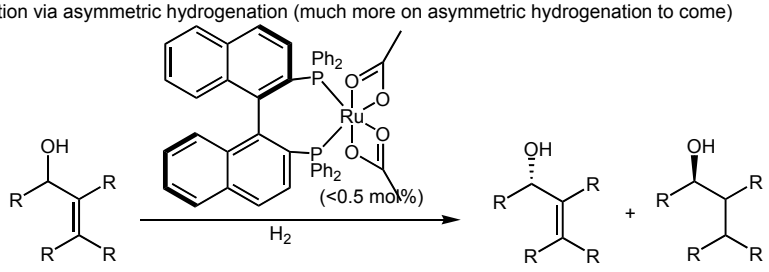


Entry	Unreacted alcohol, major enantiomer	s	% ee (% conversion)
1	R = Me	43	99 (55)
2	Et	59	99 (54)
3	*i*-Pr	87	97 (52)
4	*t*-Bu	95	96 (51)
5		32	98 (56)
6		71	99 (53)
7		65	95 (52)
8		>200	99 (51)

Advantage: clever design
Idea extended to other asymmetric reactions
One of most selective small molecule cat's
Disadvantages: $3000/mmol
Fighting lipases and Noyori hydrogenation

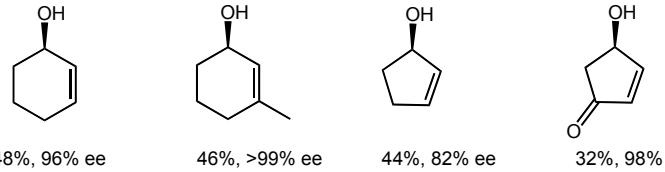
Ready; Catalysis Kinetic Resolution

Kinetic resolution via asymmetric hydrogenation (much more on asymmetric hydrogenation to come)



only useful when complementary to Sharpless
Pretty tough to separate products

Recovered allylic alcohols:

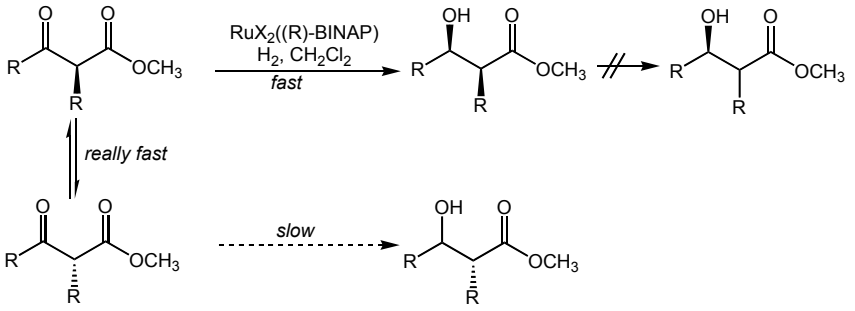


48%, 96% ee 46%, >99% ee 44%, 82% ee 32%, 98% ee

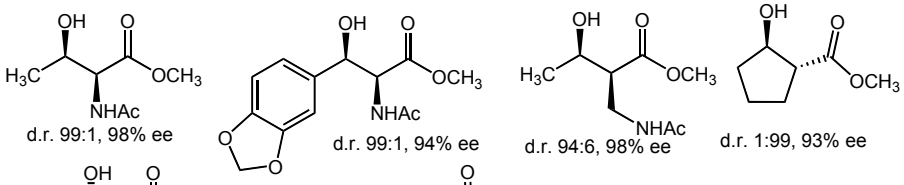
Noyori, JOC, 1988, 708

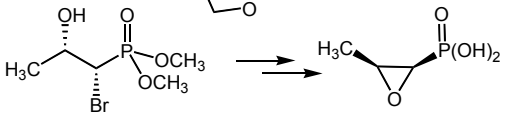
Ready; Catalysis Kinetic Resolution

1st (best?) example of dynamic kinetic resolution: racemization faster than reaction



Products:

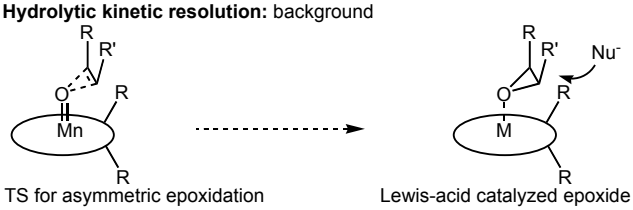




Noyori,
JACS, 1989, 9134; 1993, 144; 1995, 2931

Ready; Catalysis Kinetic Resolution

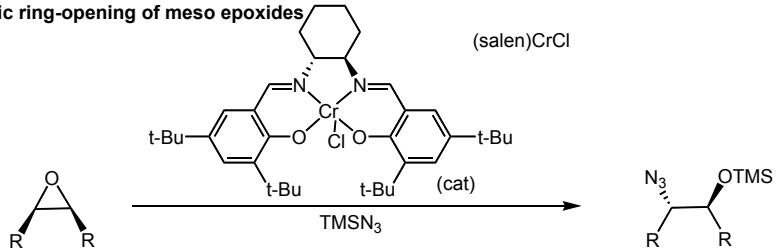
Jacobsen Hydrolytic kinetic resolution: background



proposed TS for asymmetric epoxidation

Lewis-acid catalyzed epoxide opening?

Asymmetric ring-opening of meso epoxides

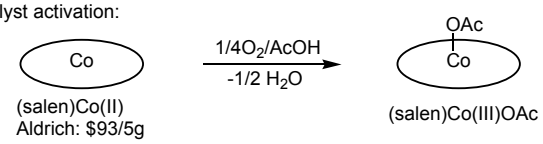


ee(%) 97 93 82 85 92

Jacobsen, Accts, 2000, 421

Ready; Catalysis — Kinetic Resolution

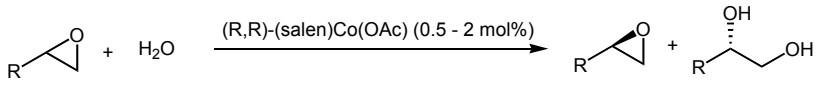
catalyst activation:



(salen)Co(II)
Aldrich: $93/5g

(salen)Co(III)OAc

hydrolytic kinetic resolution

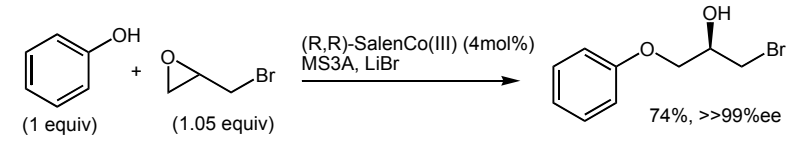


R	Unreacted epox (0.55 equiv H_2O) yield	ee	Product diol (0.45 equiv H_2O) yield	ee	k_{rel}
CH_3	46	>99	45	99	500
CH_2Ph	46	>99	40	95	96
t-Bu	41	>99	40	95	79
CH_2Cl	43	>99	40	95	190
CH_2OTBS	47	>99	42	98	250
CO_2Me	43	>99	37	97	130
Ph	44	>99	42	98	130
C≡CTBS	41	>99	41	99	420

Procedure: JACS, 2002, 1307
Mechanism and improved procedure (CoOTs): JACS, 2004, 1360

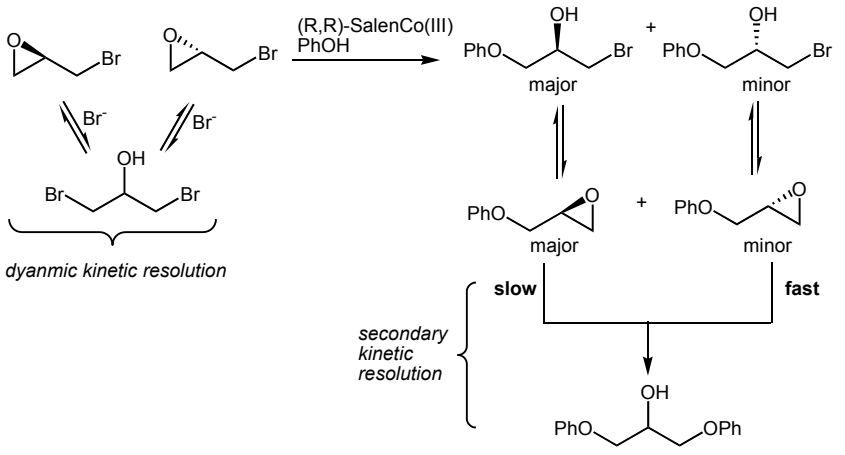
Ready; Catalysis — Kinetic Resolution

Terminal epoxides undergo simple KR with Phenols; epibromohydrin is a special case:



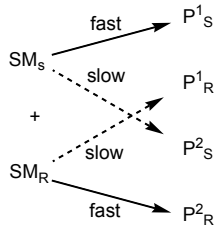
(1 equiv) (1.05 equiv)

74%, >>99%ee



JACS, 1999, 6086

Parallel kinetic resolution: Theory

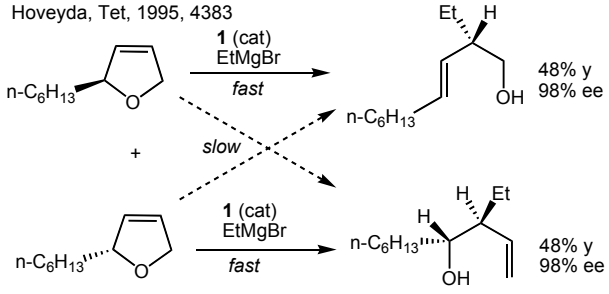


called 'parallel' because SM --> P1 is an (S)-selective KR, SM --> P2 is an (R)-selective KR

Parallel kinetic resolution: example

Often make great exam questions; rarely make useful synthetic methods

Hoveyda, Tet, 1995, 4383



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