

Resolving the Strategies for De-racemization

Brennan Rose

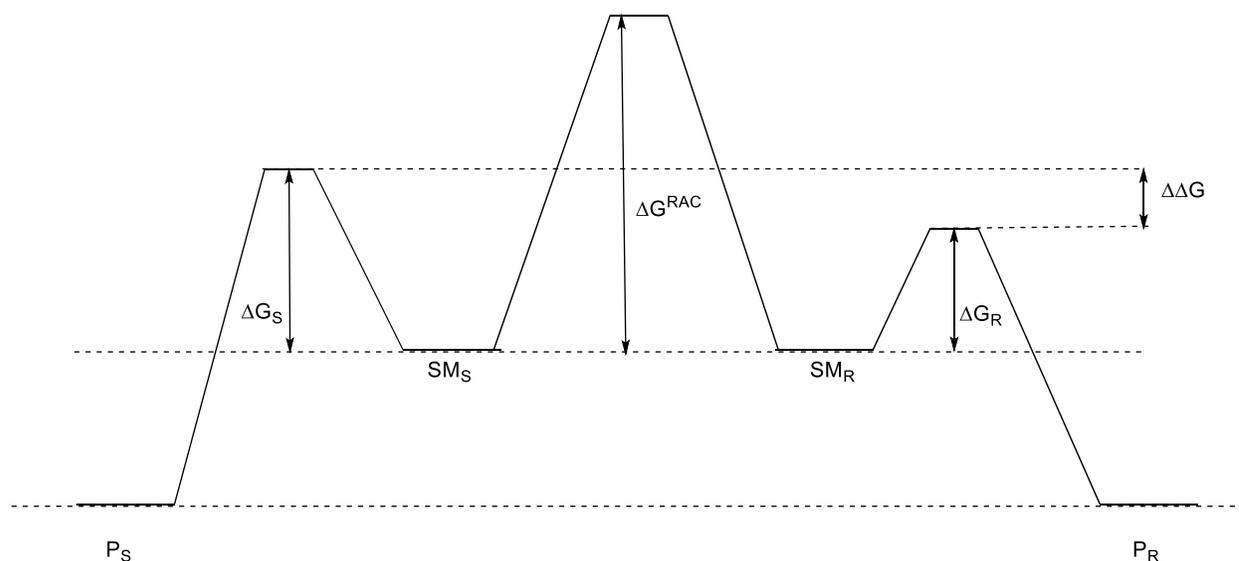
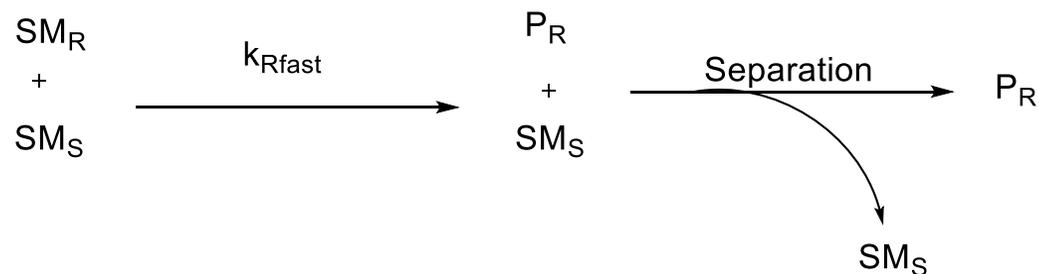
08/22/2017

Group Meeting

Overview

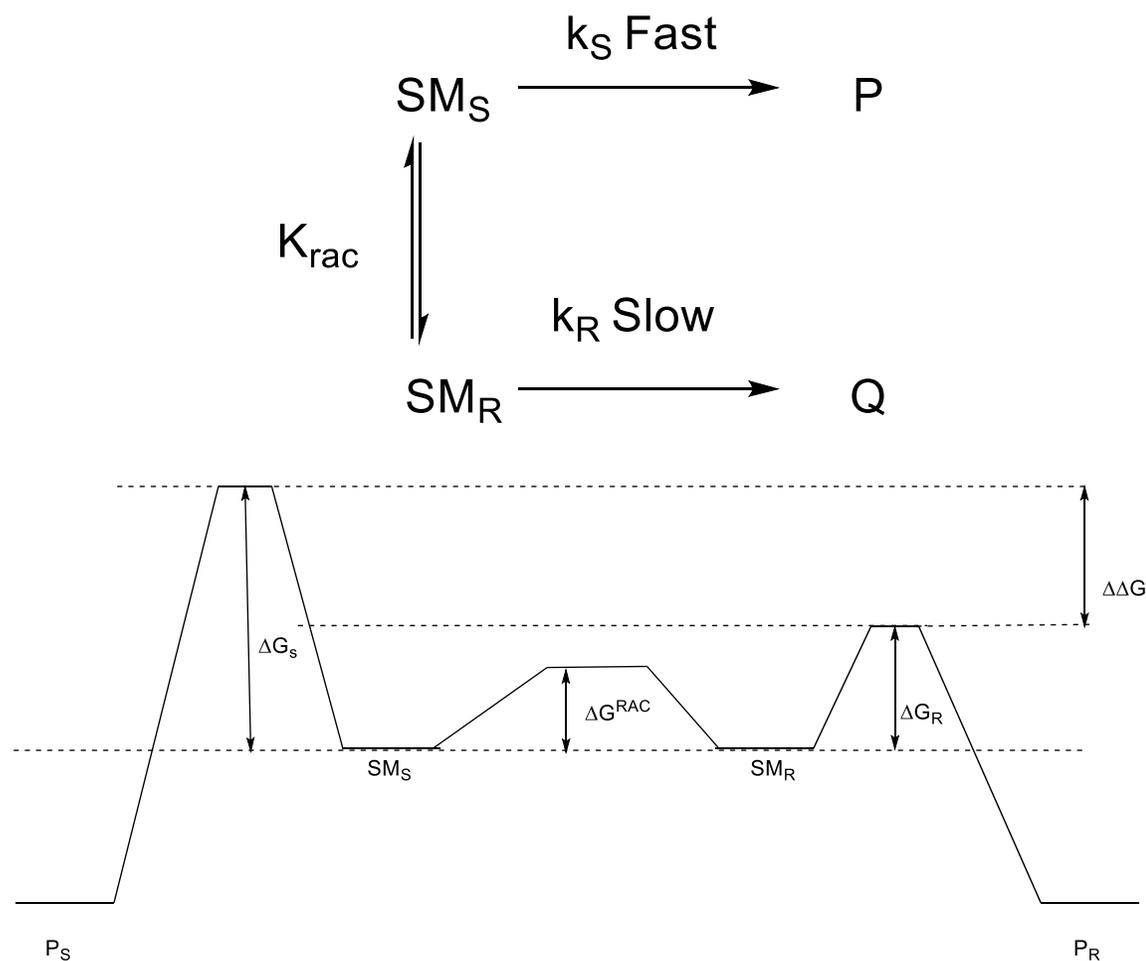
- Kinetic Resolution
- Dynamic Kinetic Resolution
- Enantio-convergent Processes
- Cyclic De-racemization
- Minor Enantiomer Recycling
- De-racemization Methods of Secondary Alcohols
- Comparisons of De-racemization Methods

Kinetic Resolution (KR)



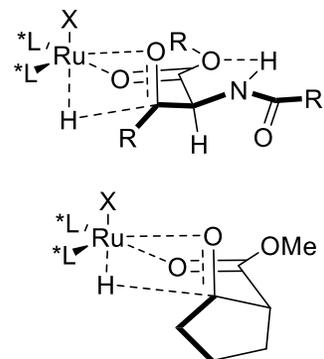
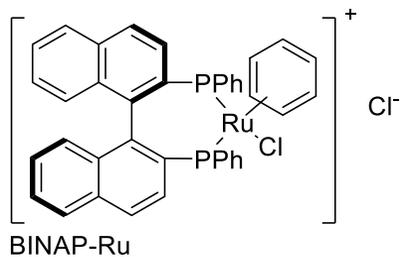
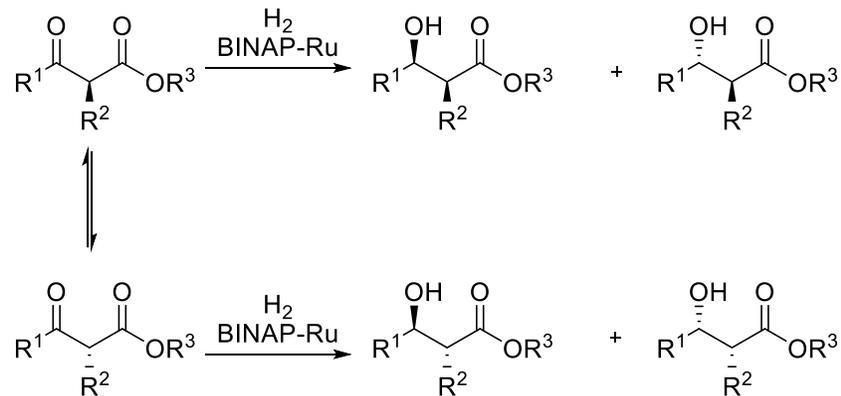
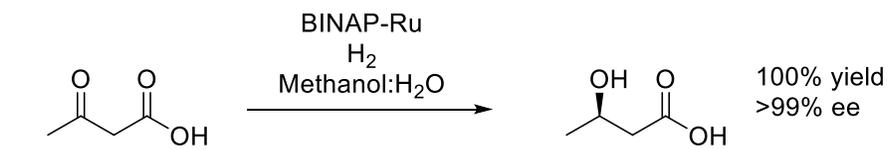
- Widely used method to obtain enantiopure compounds
- For resolution the rate of reaction for one enantiomer must be greater (I.E. $k_R \gg k_S$)
- As the reaction proceeds the enantiomeric excess varies and should only be compared at similar conversions
- The theoretical yield can never be above 50%
- A tool often used to analyze these type of reactions is selectivity (S). $S = k_R/k_S$ and is usually >10 for a synthetically useful resolution

Jacobsen's Hydrolytic Kinetic Resolution



- Requirement of facile racemization of substrate
- For an efficacious DKR: $K_{rac} \geq K_{fast}$
- Racemization is entropically driven with a $\Delta G^0 = -0.41$ kcal/mol for the mixing of two enantiomers
- Chemical methods for racemization tend to dominate due to very few racemase enzymes
- The enantioinduction is dependent on the selectivity of only the catalyst

Jacobsen's Hydrolytic Kinetic Resolution



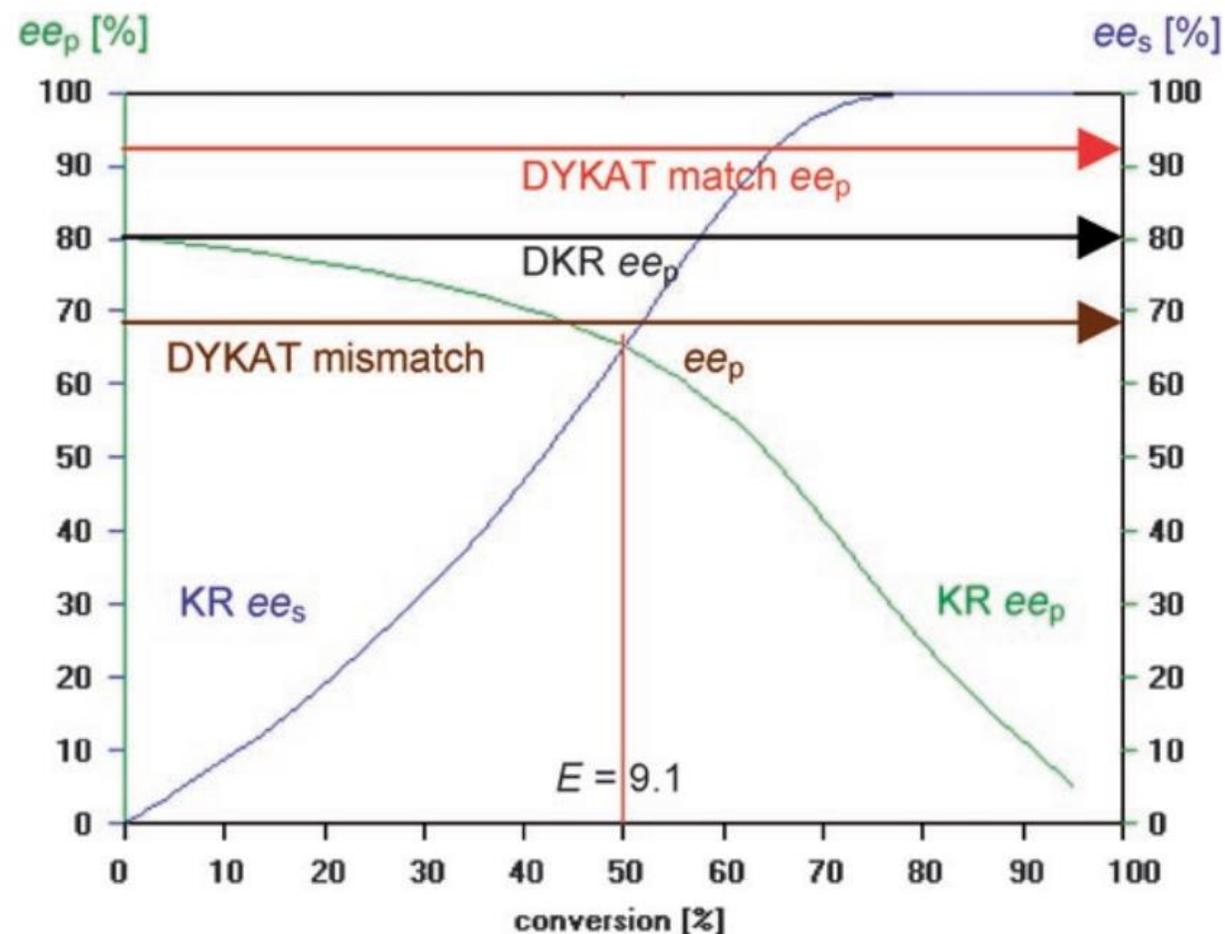
- Noyori received half of the 2001 Nobel prize for his work in asymmetric hydrogenation
- Noyori DKR relies on a rapidly enolizable proton to interconvert between two different enantiomers
- This DKR is used in the production of several pharmaceuticals

Noyori, R. *Tetrahedron: Asymmetry*, **1990**, *1*, 1–4.

Noyori, R. *et al. J. Am. Chem. Soc.*, **1989**, *111* (25), pp 9134–9135

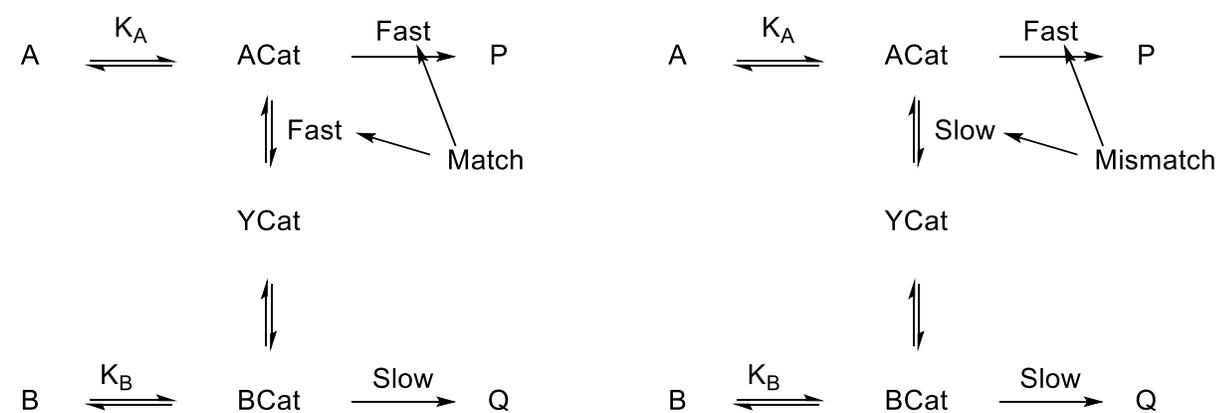
De-epimerization and Dynamic Kinetic Asymmetric Transformations (DYKATs)

- De-racemization and De-epimerization are differentiated by enthalpy
- De-Racemization $\Delta H=0$
- De-Epimerization $\Delta H \neq 0$
- De-epimerization is much easier to control than De-racemization
- This enthalpy difference is commonly exploited in preferential recrystallizations
- DYKATs: desymmetrization of a racemate or diastereomeric mixture that depends on the interconversion of diastereomeric intermediates
- 4 types of DYKATs: Type 1 and type 2 resolve enantiomeric mixtures while Type 3 and 4 resolve epimeric mixtures of diastereomers

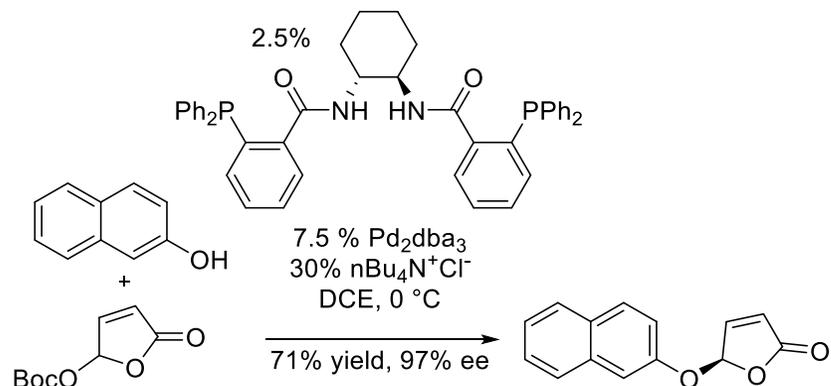
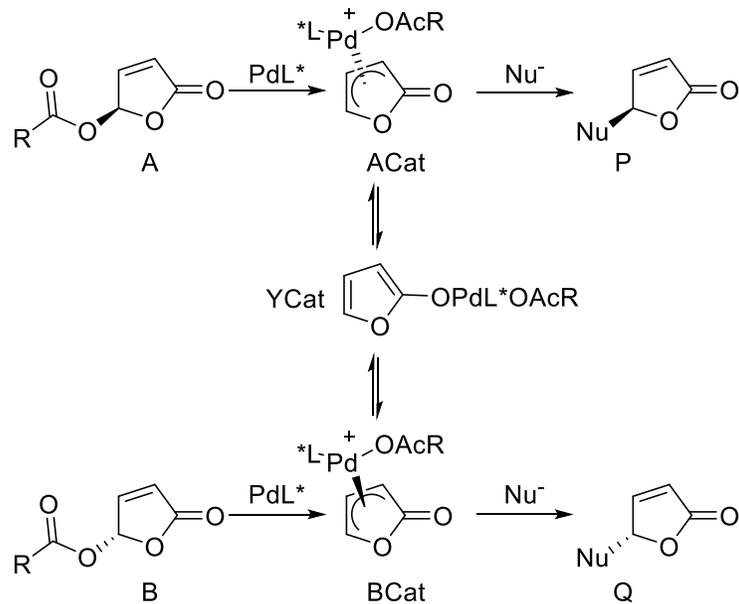


DYKAT type 1 and the matched and mismatched effect

- DYKAT type 1 is a situation where a racemate can form two diastereomeric compounds (ACat and BCat) that are in equilibrium with an achiral compound (YCAT).
- Matched: Higher enantioinduction then for DKR on the same system
- Mismatched: Lower enantioinduction then for DKR of the same system



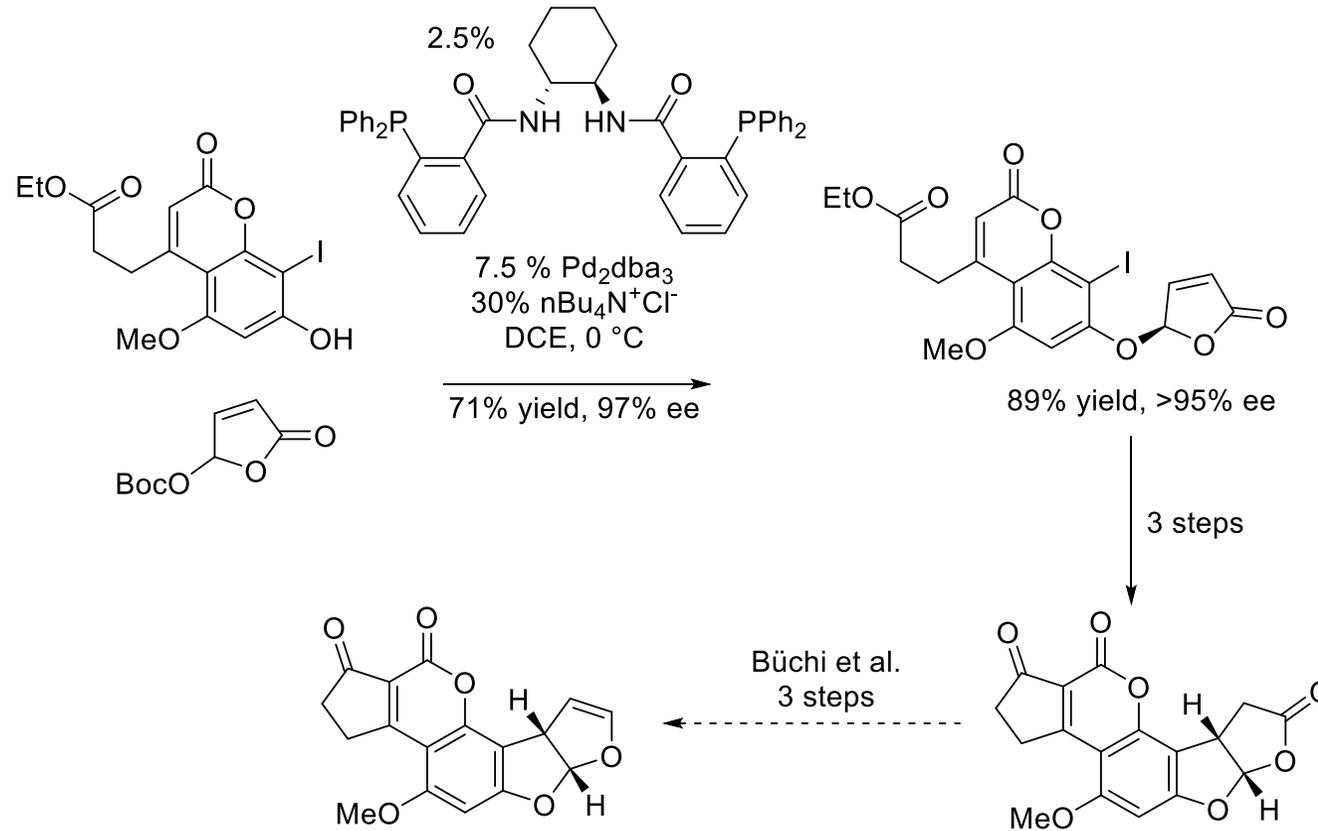
Palladium-Catalyzed DYKAT's of 5-Acyloxy-Furanones



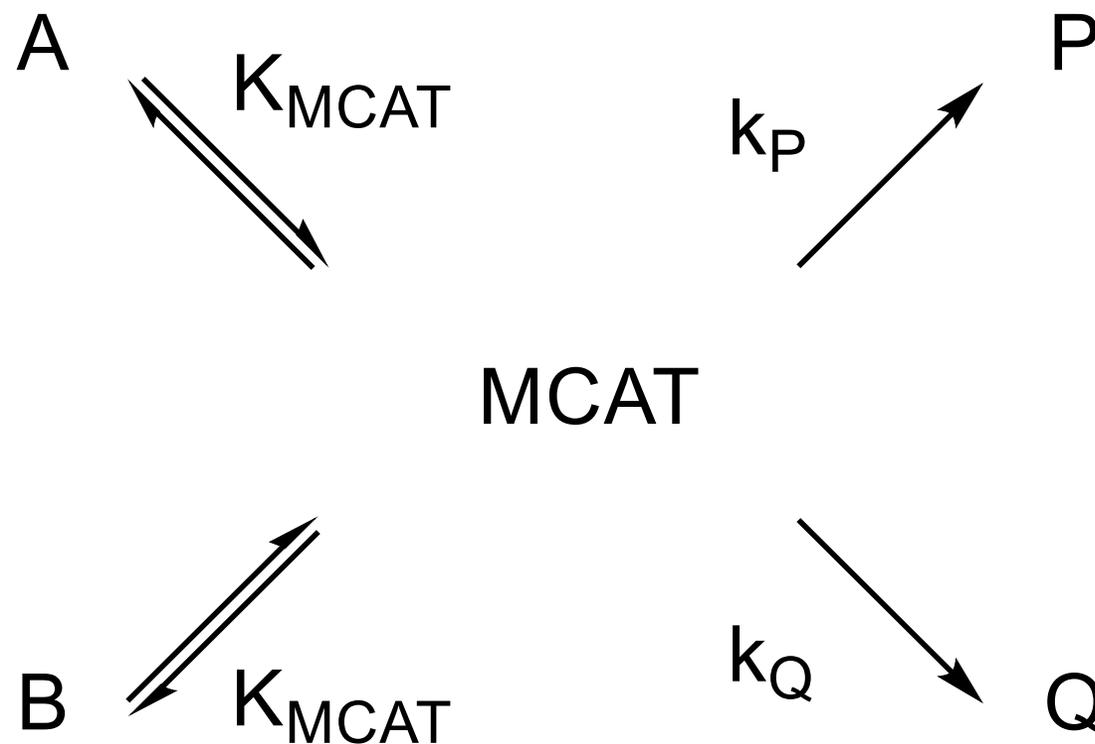
- Trost utilized the ionization of racemic A and B to form diastereomeric complexes that could interconvert readily through an achiral furan.
- Concomitant trapping with a nucleophile lead to excellent enantioselectivity of modest to good yields.

Application in Synthesis

Formal synthesis of Aflatoxin B

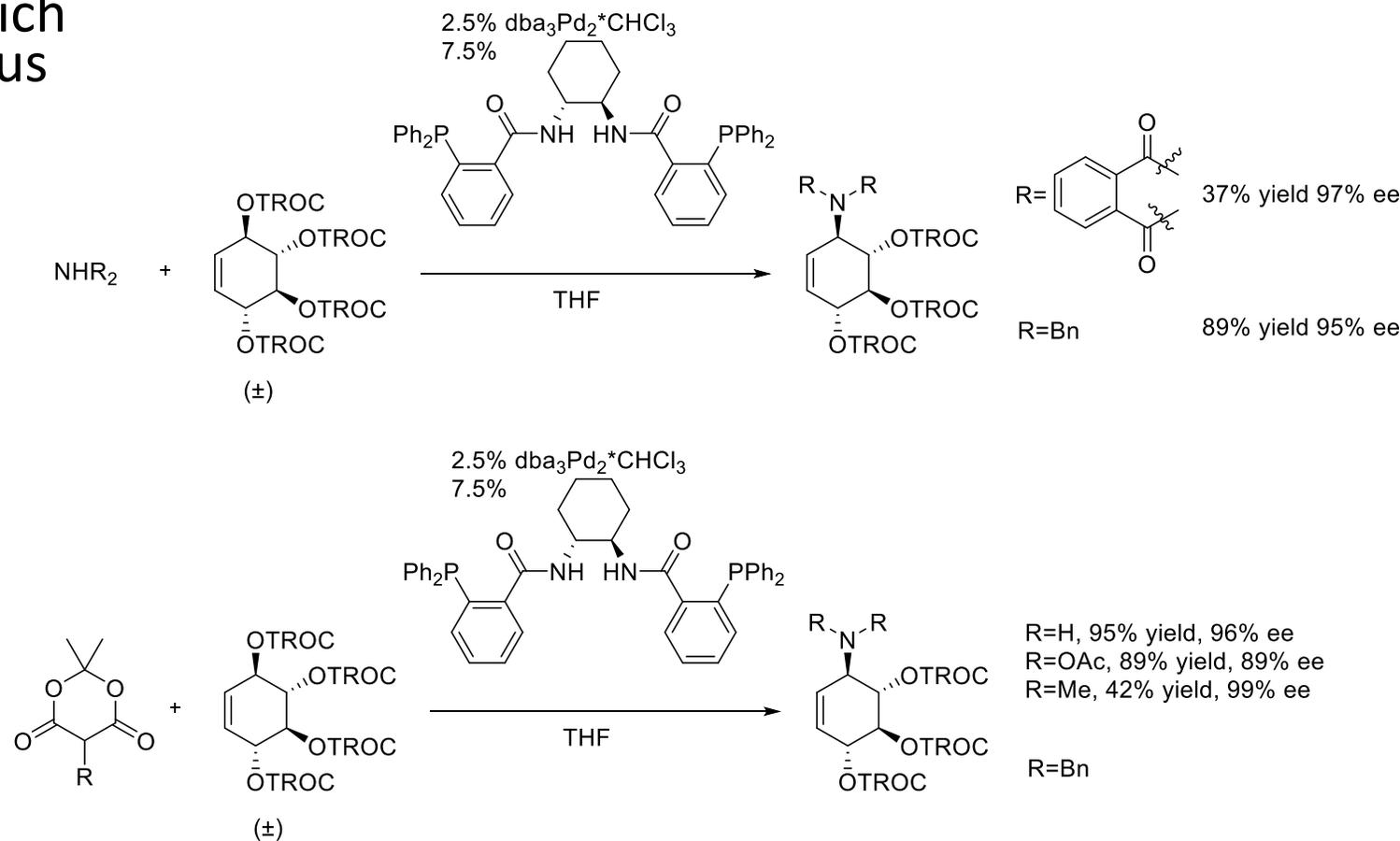
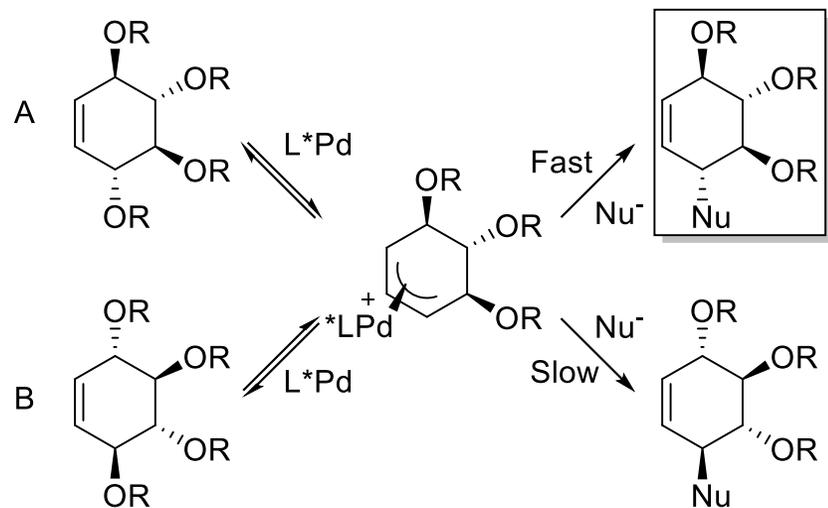


- When a racemate (A and B) loses a stereogenic center and forms a meso compound (MCAT) that can then be transformed into a new product
- The selectivity of this process is determined by the remaining chiral centers and a chiral ligand.



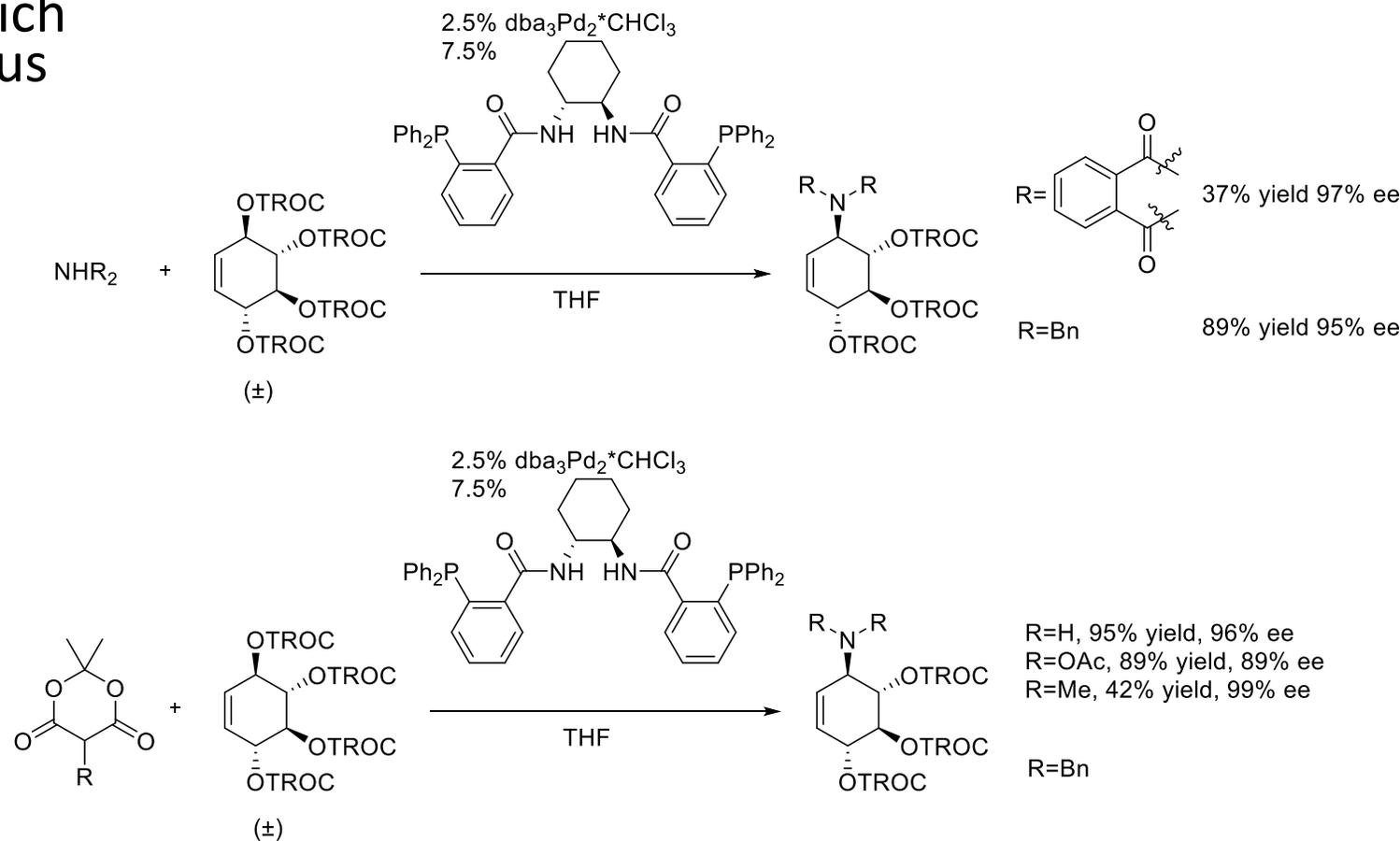
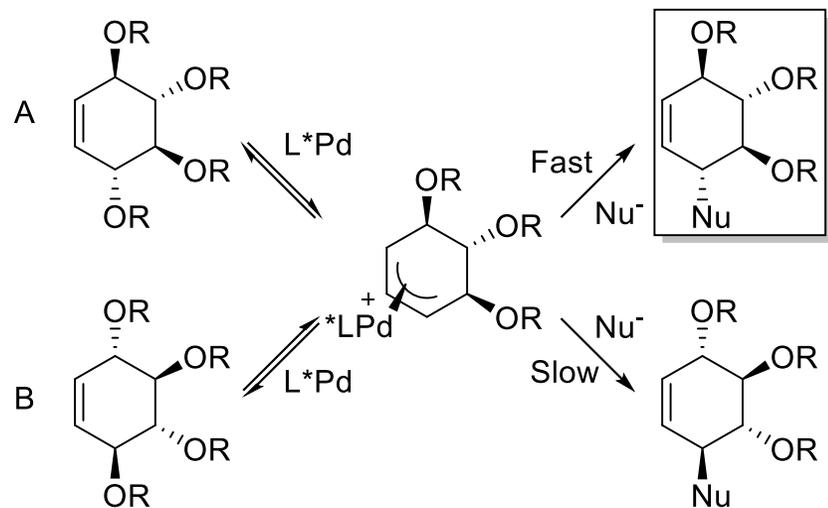
DYKAT's of Conduritol B Tetracarboxylates

- Trost showed that ionization of a racemic mixture of A and B formed the same meso intermediate which would undergo trapping of various nucleophiles.

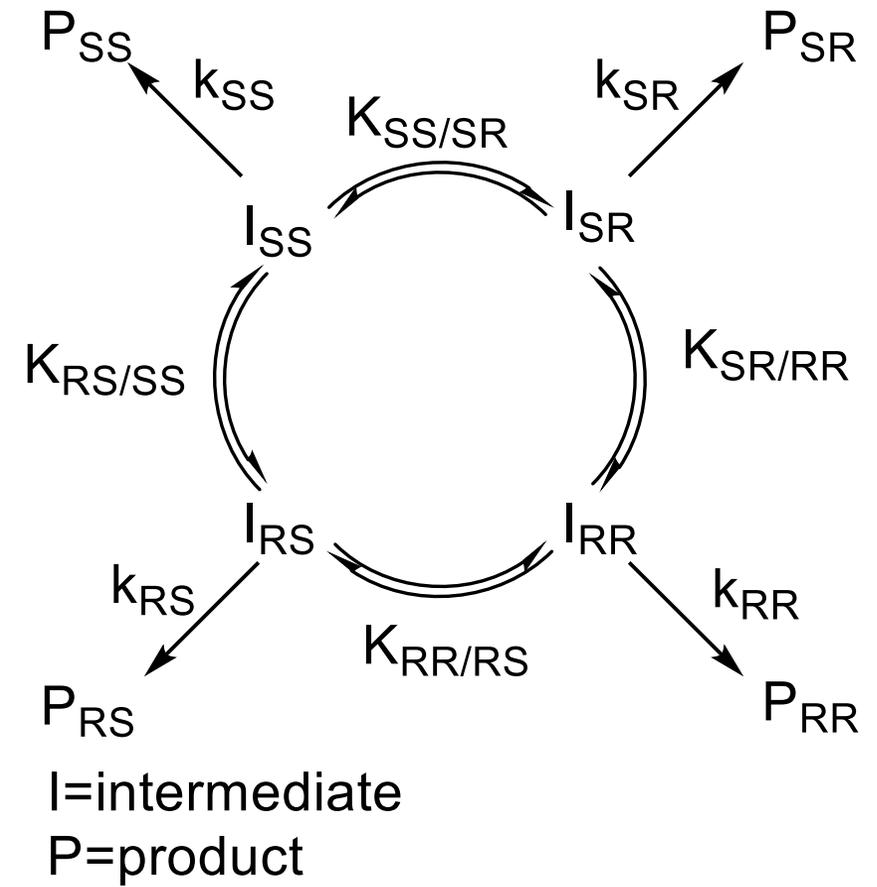


DYKAT's of Conduritol B Tetracarboxylates

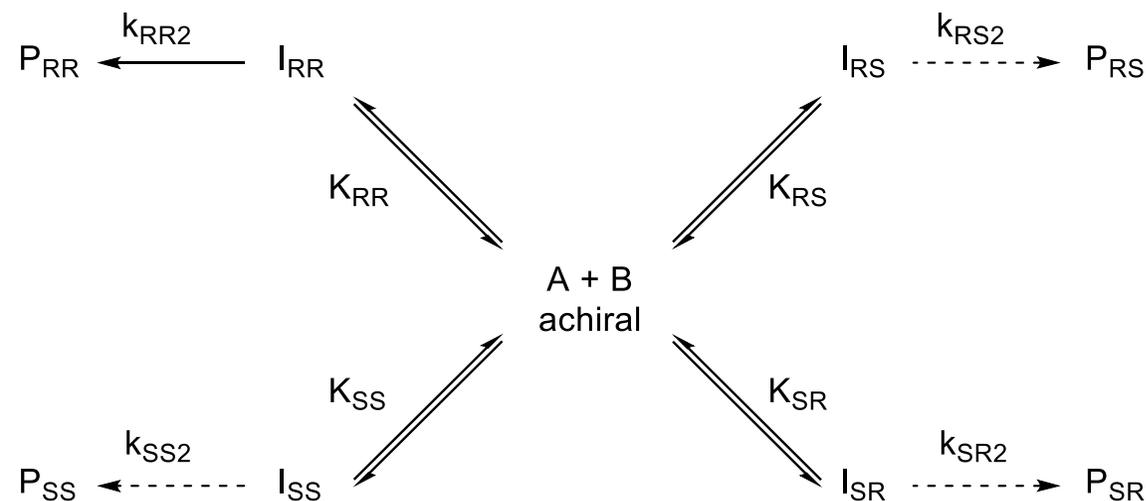
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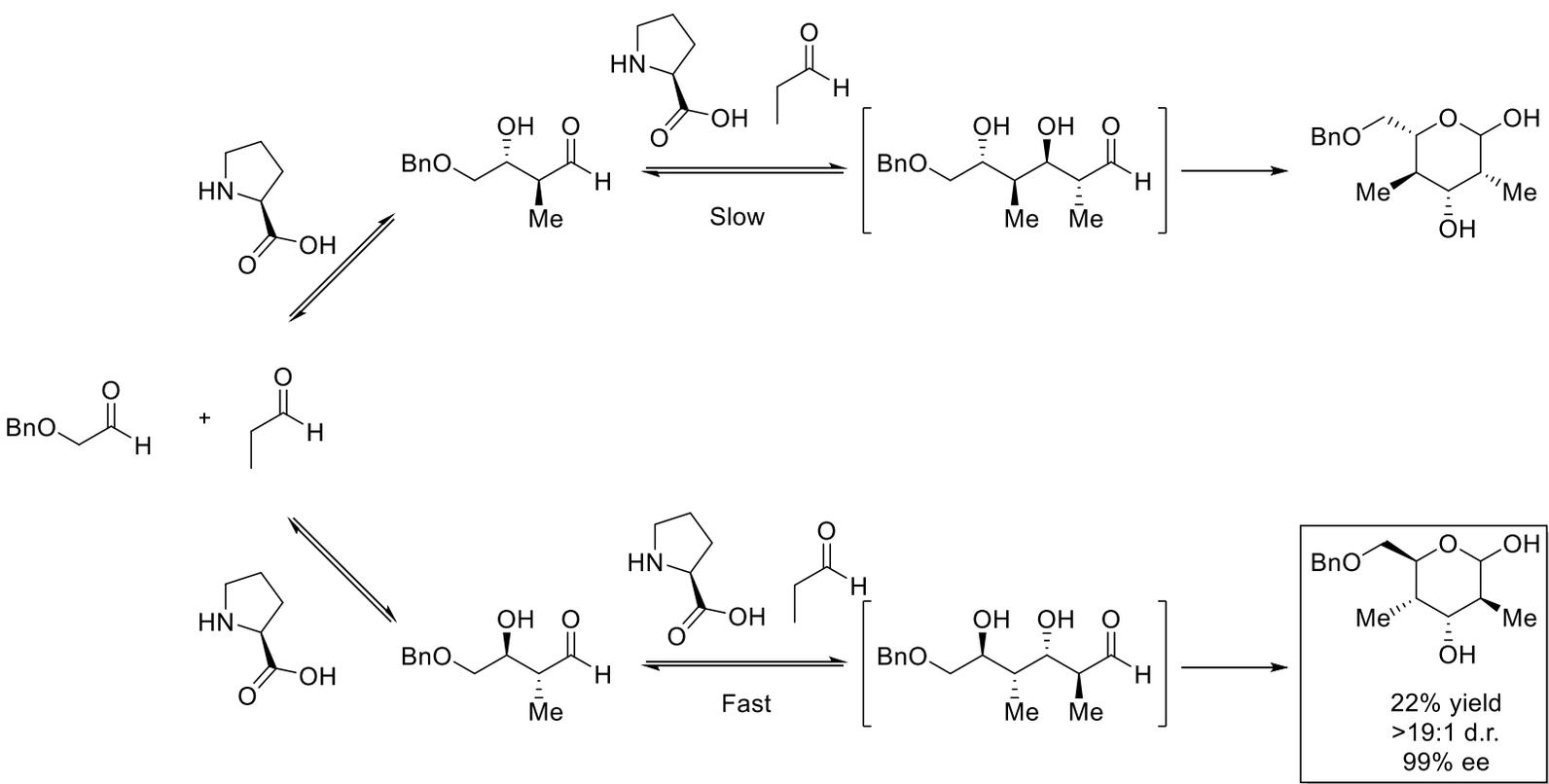
- De-epimerization of a diastereomeric mixtures
- Mixtures of all diastereomers and can allow for the highly selective formation of only one diastereomer via a series of interconversions



- The functionalization of achiral materials to form a mixture of diastereomers that will be “sunked” to one compound by an irreversible process

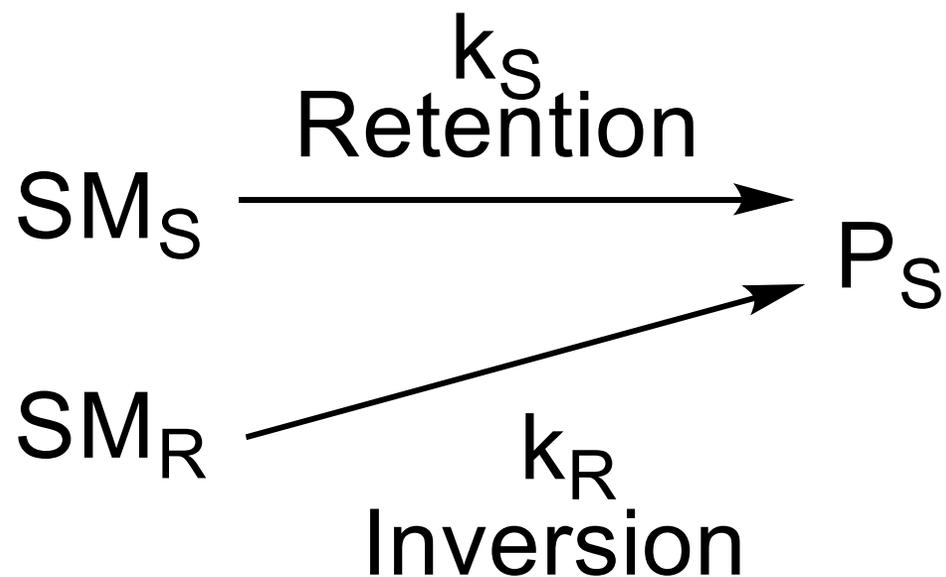


One Pot Synthesis of Enantioenriched Polyketides



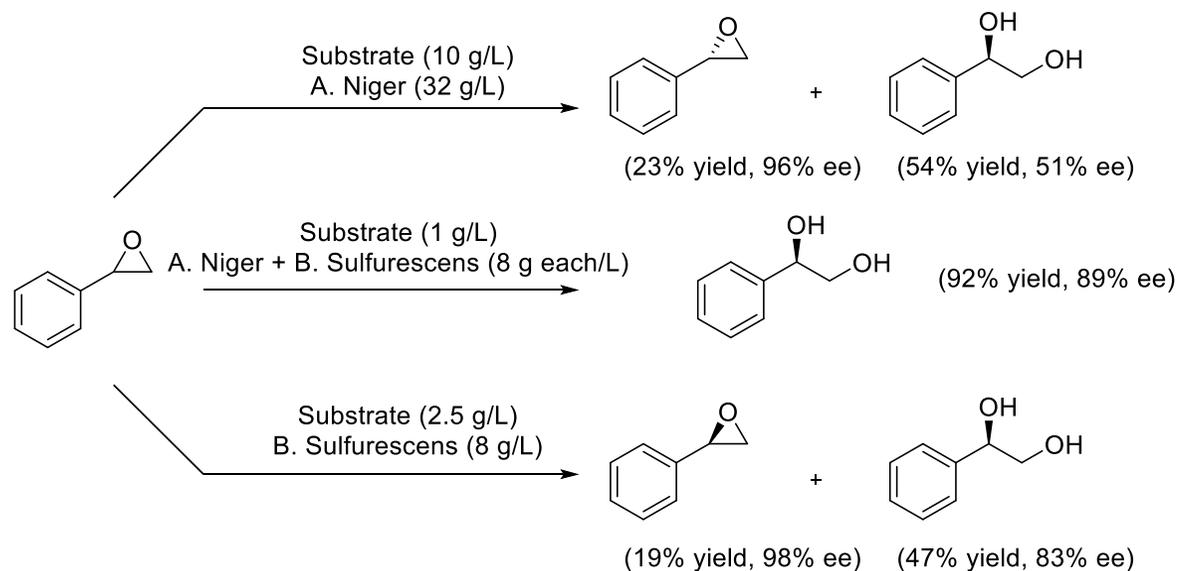
- Process is terminated by an irreversible cyclization of the linear polyketide to the sugar.
- This sequesters only a single diastereomer from the equilibrium.
- Due to the high selectivity of the proline catalyzed aldol none of the 3rd and 4th possible diastereomers are observed

Enantio-convergent Processes



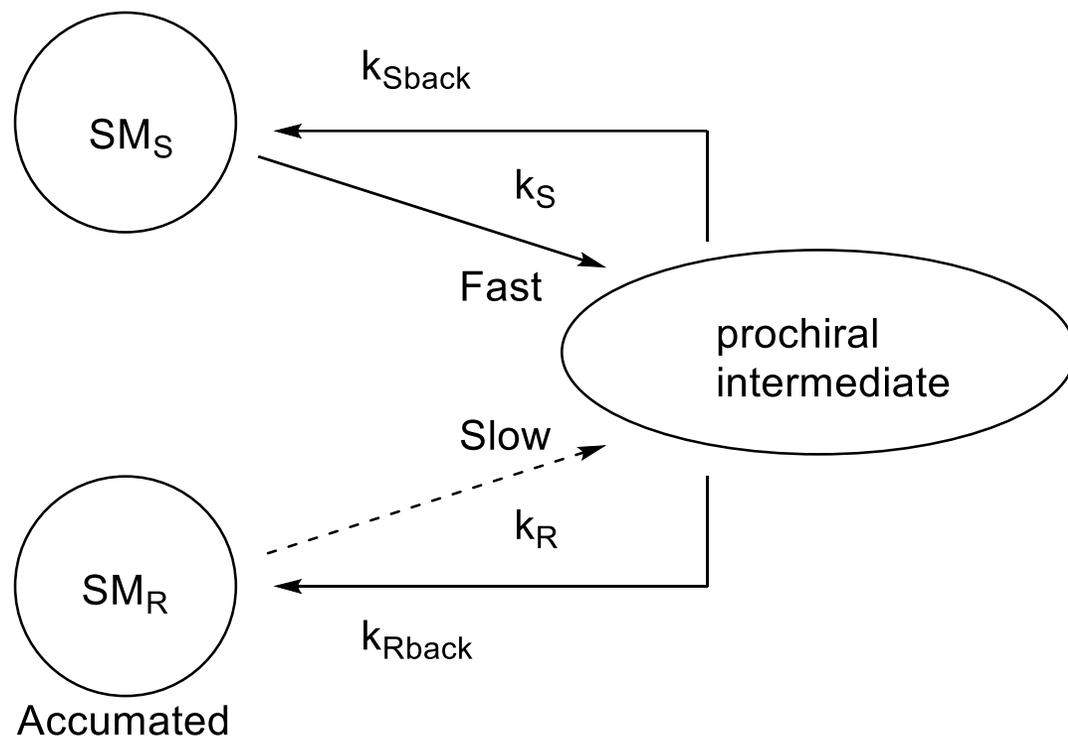
- The transformation of both enantiomers must be converted through stereochemically defined pathways
- Rare form of deracemization

Enantio-convergent Enzymatic Hydrolysis of Epoxides



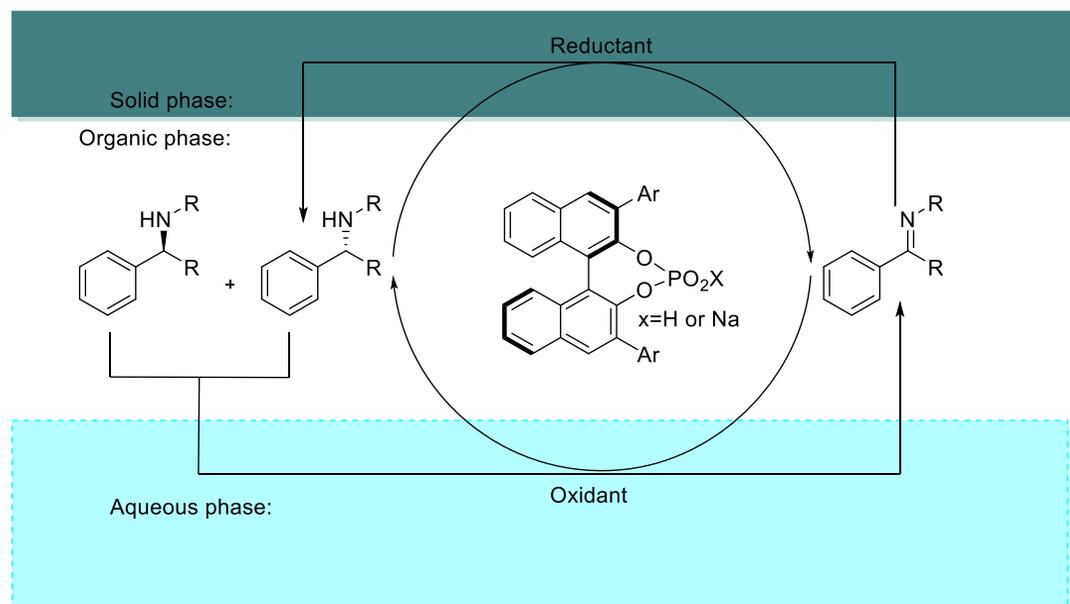
- Furstoss showed that several different microbes could perform KR's of styrene oxide and a combination of these microbes could result in an enantio-convergent synthesis of the resulting enriched diol.

Cyclic De-racemization (CycD)



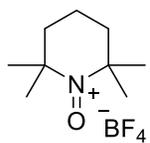
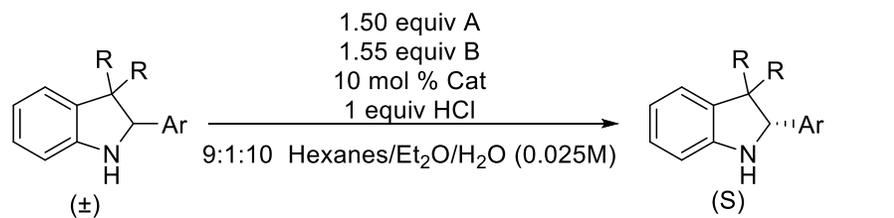
- An enantioselective process to form a prochiral intermediate followed by a selective/non selective process on this new intermediate
- The accumulated enantiomer serves as a “sink” for the process

Multiphasic Cyclic De-racemization

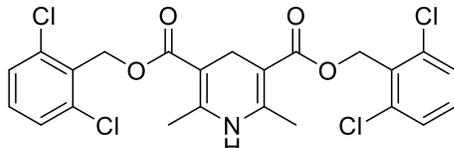


- Single pot multiphasic system used for the deracemization of cyclic amines.
- Catalyzed by a dual functional chiral phosphoric acid/anion.
- Anion promotes the oxidation
- Conjugate acid promotes the reduction

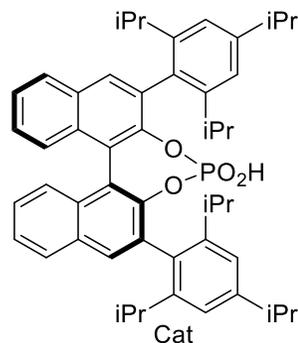
Multiphasic Cyclic De-racemization



A
oxopiperdinium oxidant



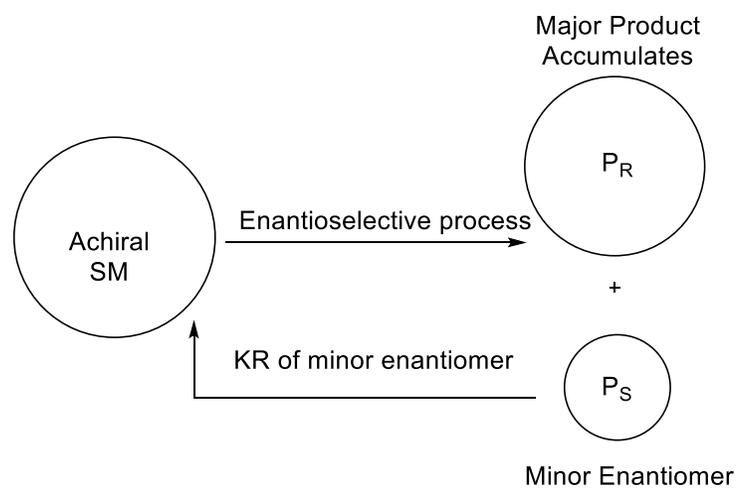
B
Hantzsch ester reductant



11 examples with yields >82% and >91% ee

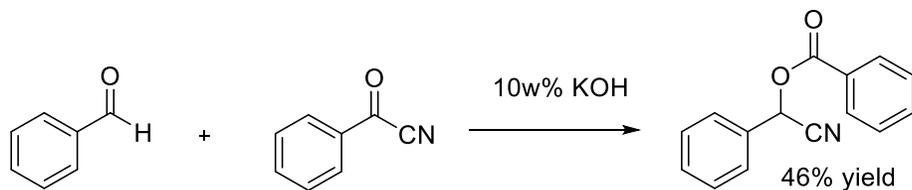
- Oxopiperdinium has poor selectivity $S=1.1$, the subsequent reduction is highly selective and contributes mostly to the enrichment.
- This unique Hantzsch ester has low solubility in aq and organic solvents
- Hantzsch esters have been previously used for similar enantioselective reductions with great selectivity
- The careful choice of reagents allowed this operation to be performed in a one pot multiphasic cycle

Recycling of the Minor Enantiomer

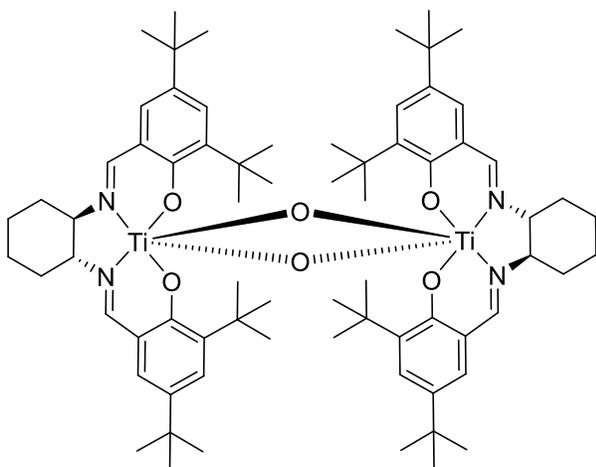
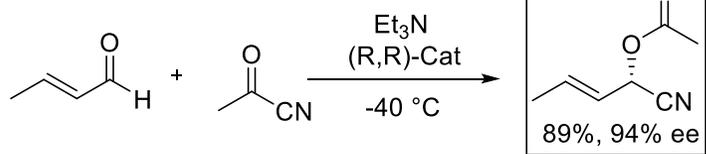


- Contains a process that converts an achiral SM to an enantioenriched product.
- Followed by an enriching step to reconvert the minor enantiomer back to achiral SM

Enantioselective formation of O-Acylated Cyanohydrins



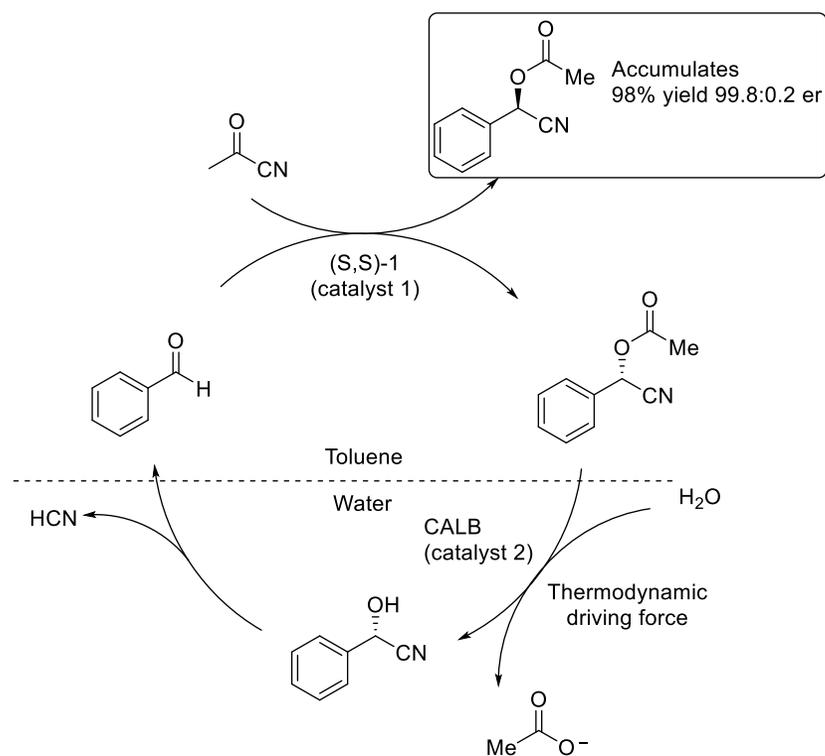
Marvel et. al. J. Am. Chem. Soc., **1949**, 71 34–35



Moberg. et. al J. Am. Chem. Soc., **2005**, 127, 11592–11593

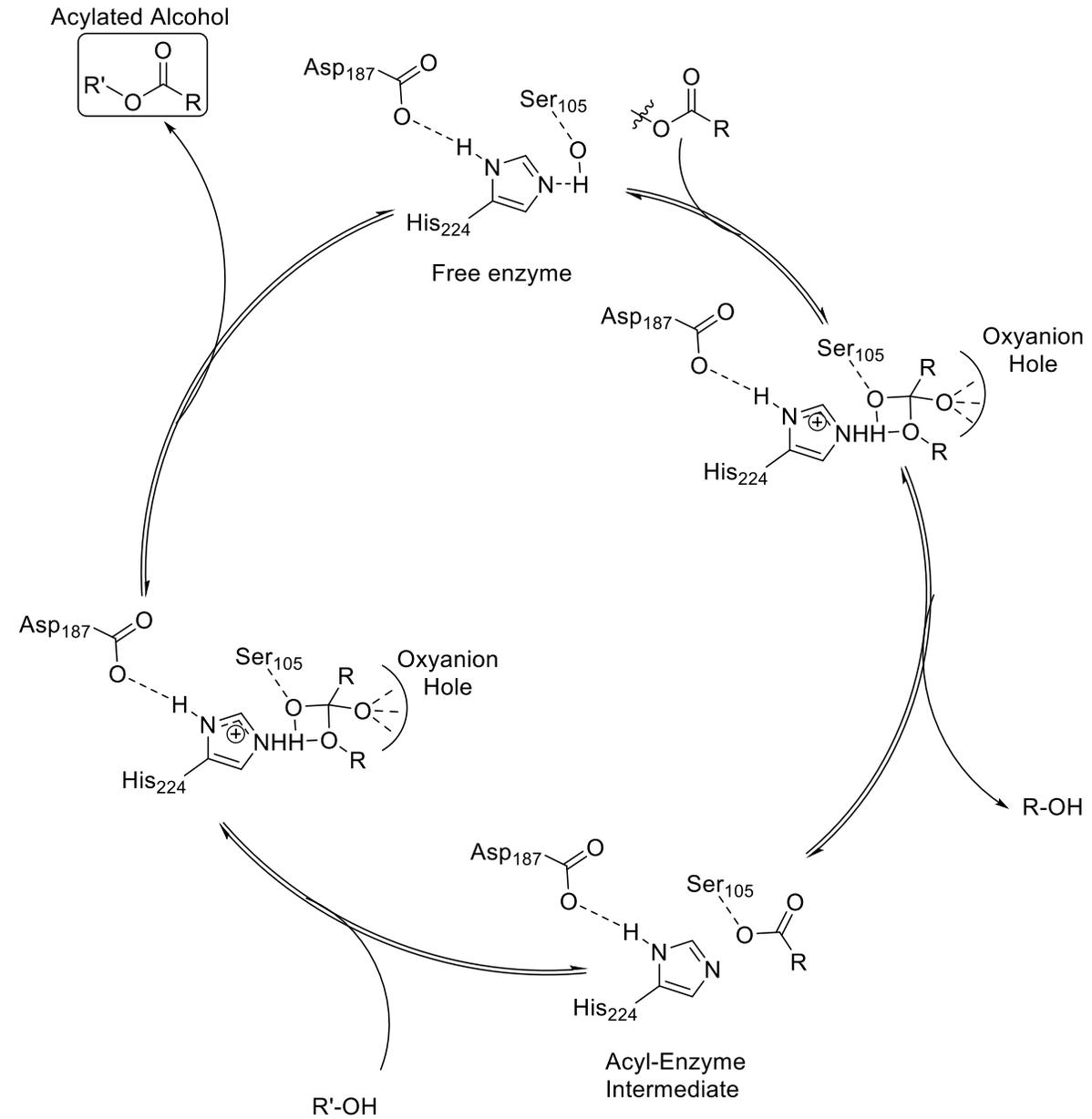
- Synthesis of racemic Cyanohydrins was carried out by Marvel et. al.
- Moberg enlisted the use of a Chiral Lewis Acid to furnish enriched Cyanohydrins in good yield and ee.
- This left a slight amount of the unwanted enantiomer

Converting the process towards MER

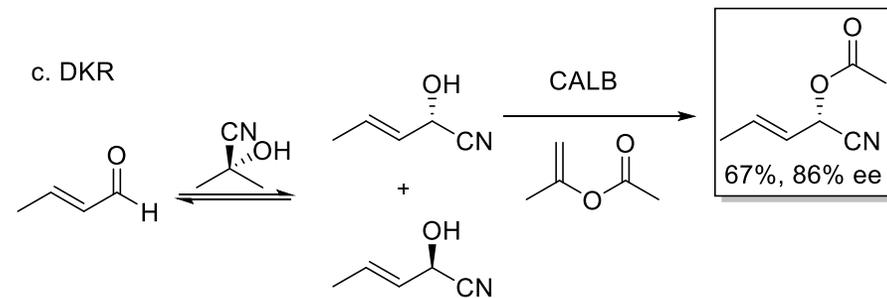
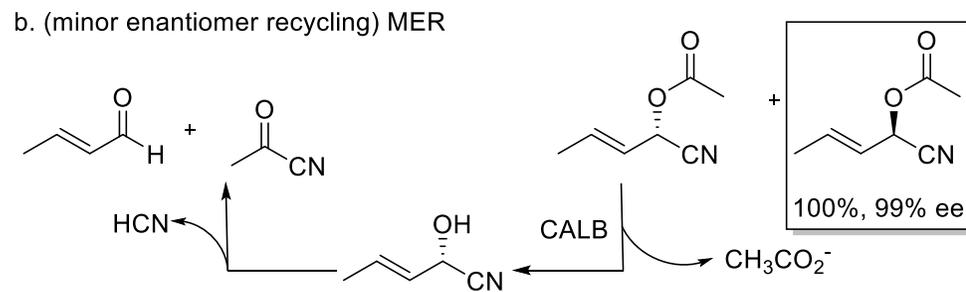
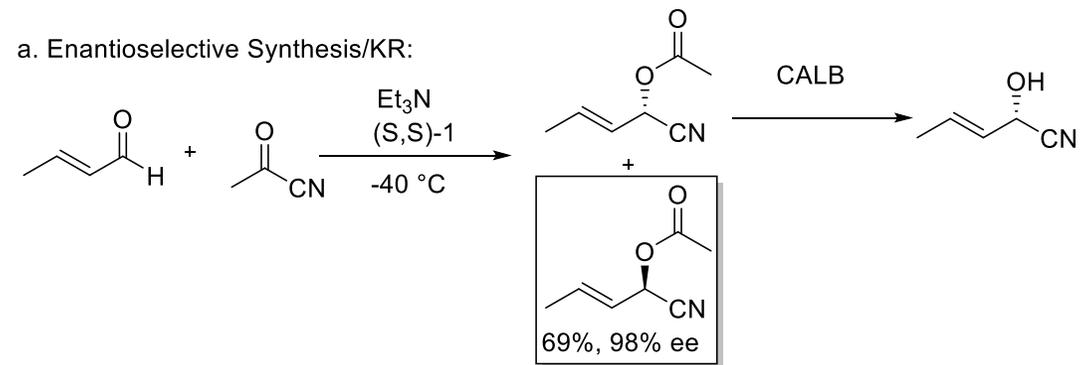


- Recycling of the minor enantiomer was achieved by the addition of an *Candida Antarctica* (CALB) yeast lipase to selectively convert the minor enantiomer back the SM.
- Slow syringe pump addition of acyl cyanide is necessary to prevent hydrolysis under these biphasic conditions.

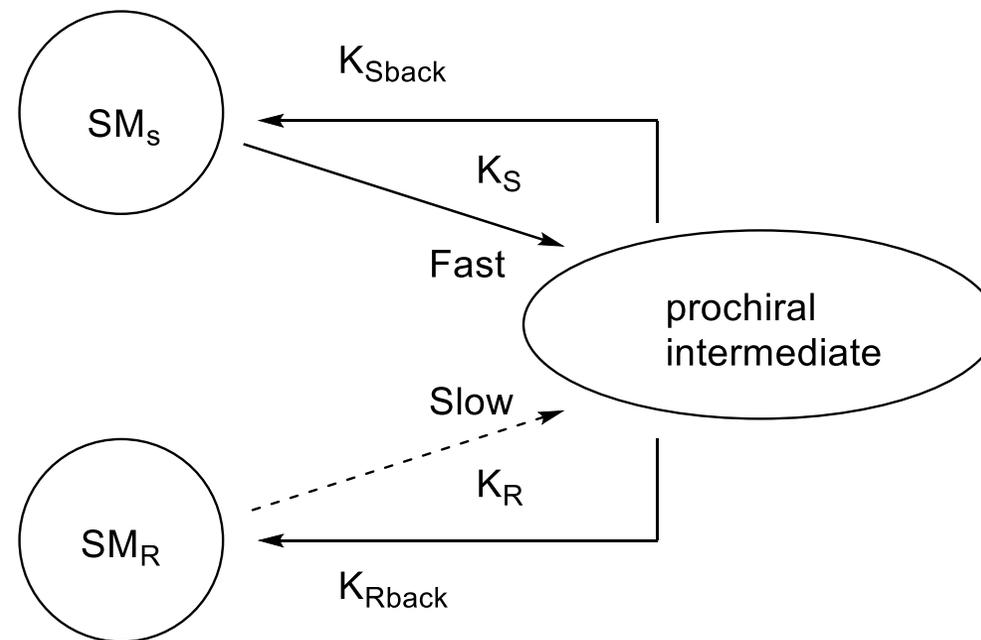
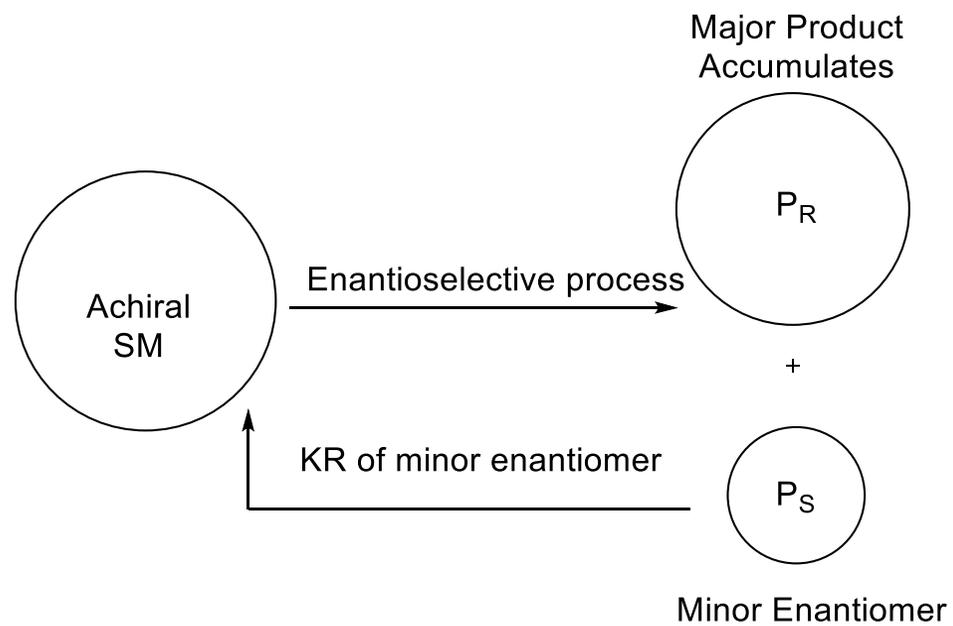
Proposed CALB Acetylation Mechanism



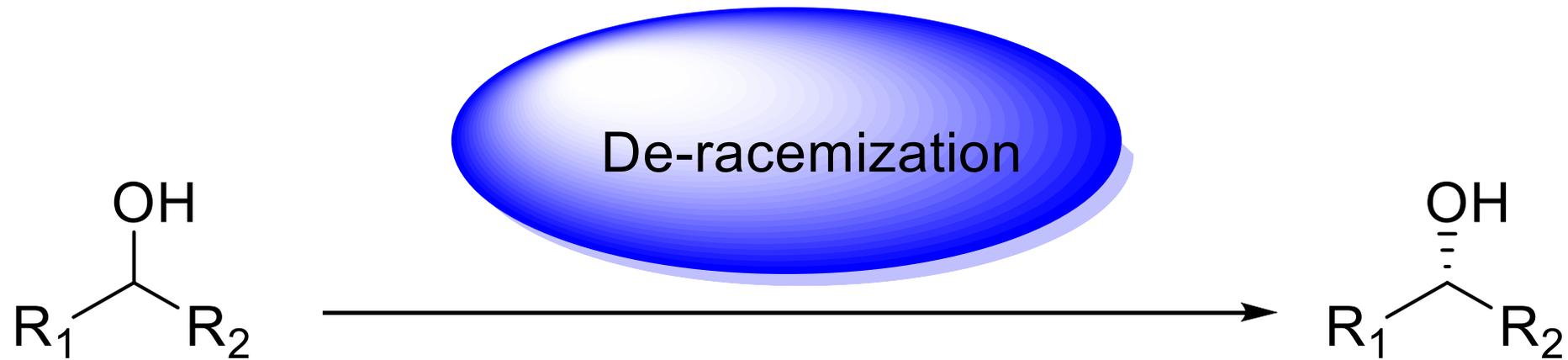
MER vs Cyclic De-racemization



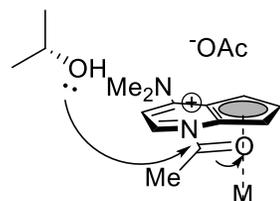
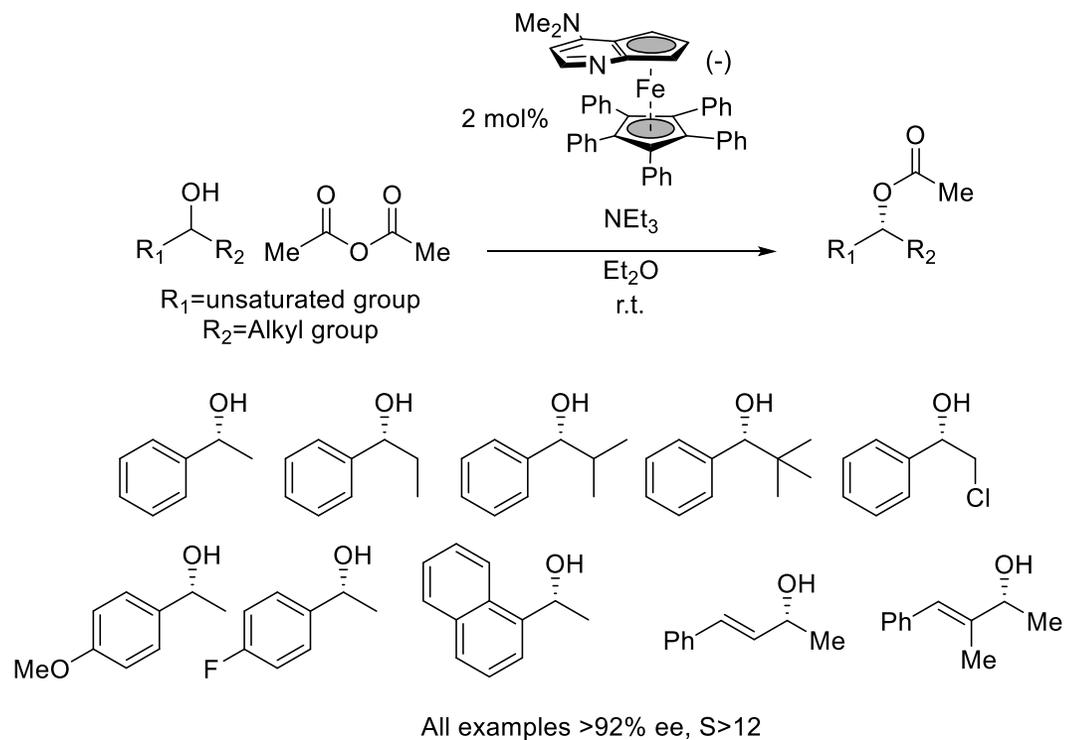
Comparison between MER and other Deracemization methods



De-racemization of Secondary Alcohols



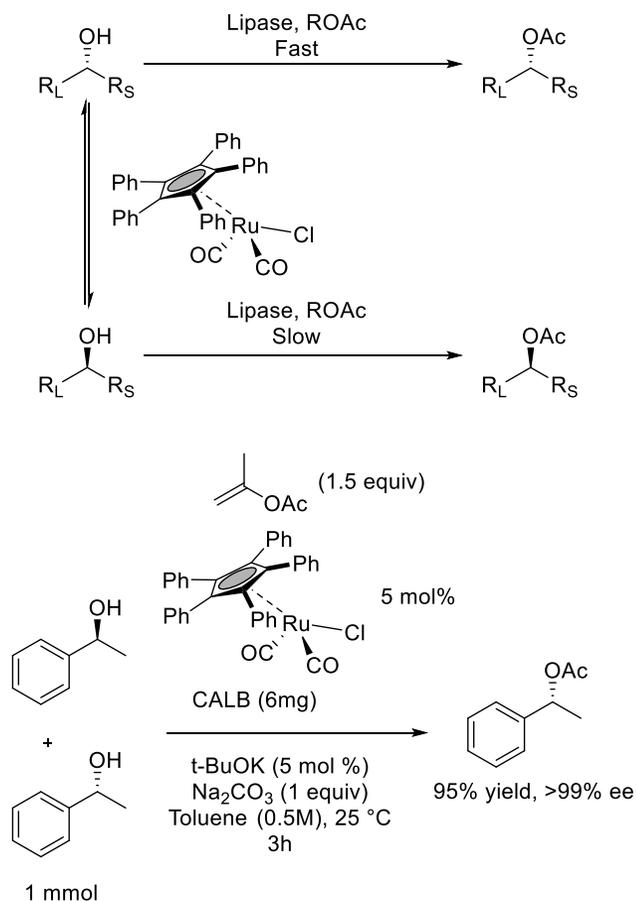
Kinetic Resolution of Secondary Alcohols



Stereochemical Model
Bulky ferrocene shields one half of the molecule allowing one enantiomer to react much more favorably.

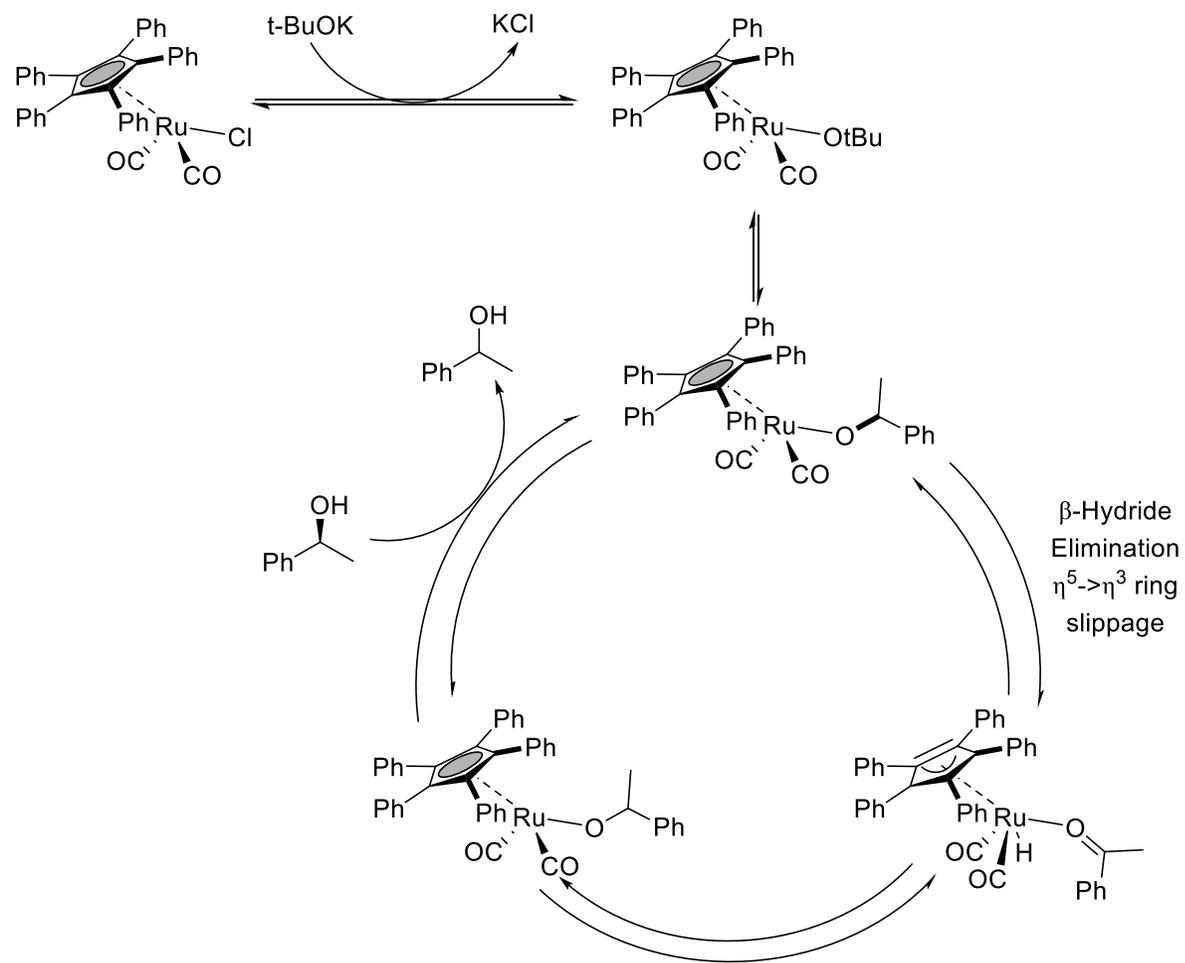
- Fu developed a chiral ferrocene derived DMAP catalyst effectively resolves racemic secondary alcohols.
- Selectivity's are greatly dependent on use of bulky η^5 -C₅Ph₅

Ruthenium(II) and Lipase Facilitated DKR of Secondary Alcohols



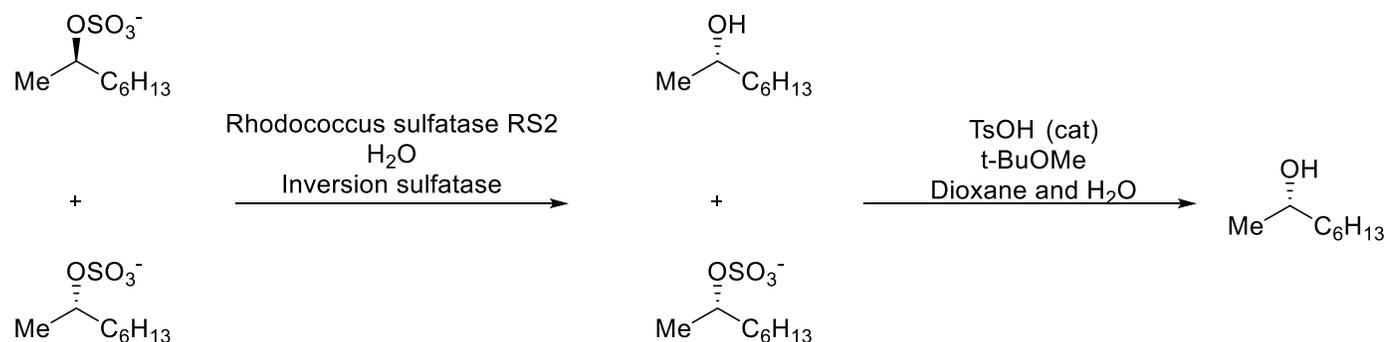
- 30 secondary alcohols shown to undergo facile de-racemization in excellent yield and selectivity
- Both aliphatic and heteroaromatic alcohols are tolerated

Proposed Racemization Mechanism

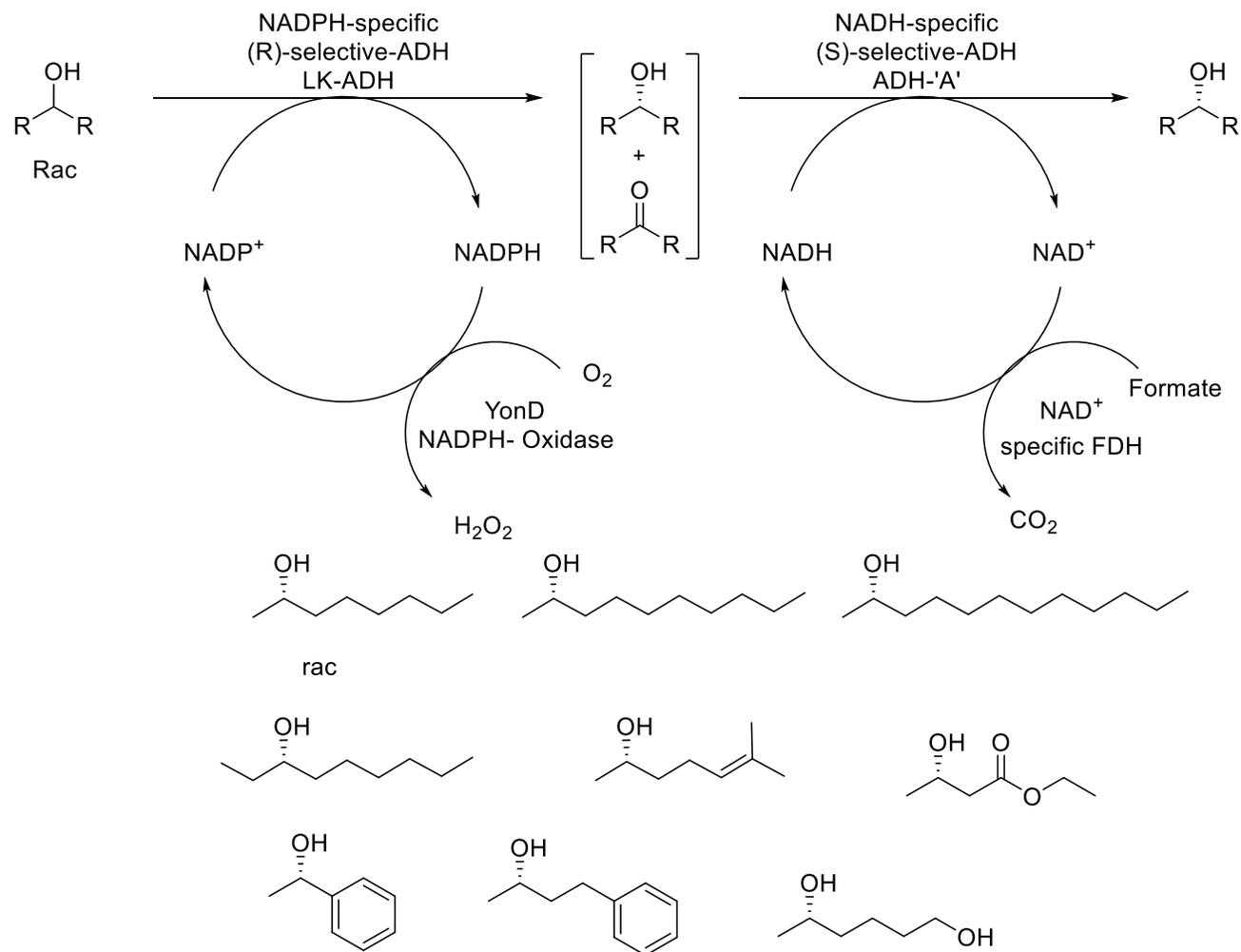


Enantio-convergent Processes of Sec-Alcohols

- Enzymatic hydrolysis of sec-sulfate esters allows for inversion of one of the enantiomers with a $S > 200$.
- Mechanism for inversion sulfatase not known
- Subsequent hydrolysis furnishes enantioenriched (*S*)-sec alcohols



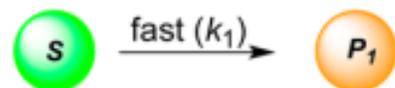
Enantio-convergent Processes of Sec-Alcohols



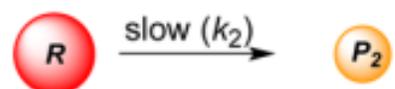
- Combination of an NADPH dependent Oxidative enzyme and NADH dependent Reductive Enzyme to de-racemize sec-alcohols
- Can switch systems to also obtain the (R) and (S) alcohols in >99% yield and >99% ee

Comparisons

A. Kinetic resolution (the desired product is either R or P_1):



+ Catalyst



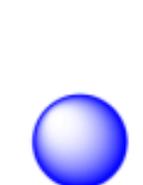
ee:

- ee of R increases over time, can always reach 100%
- ee of P_1 decreases over time (in case it is chiral)

yield:

- yields of R and $P_1 \leq 50\%$, yields dependent on $E (= k_1/k_2)$

B. Enantioselective reaction followed by kinetic resolution (the desired product is R):



(selectivity E_1)

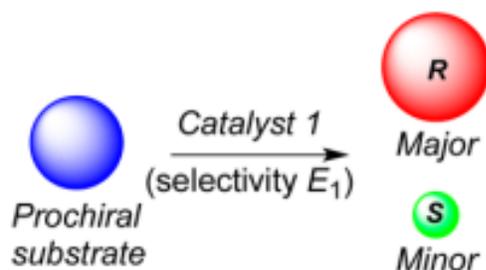


Minor (selectivity E_2)

ee: up to 100%

yield: may exceed 50%,
- dependent on E_1 and E_2

C. Minor enantiomer recycling (and cyclic deracemization; the desired product is R):



Catalyst 2 (selectivity E_2)

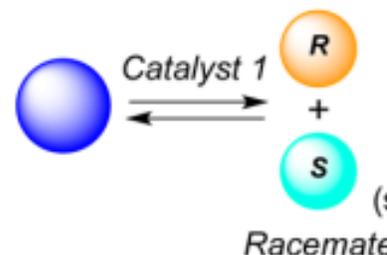
$$\text{ee: } \frac{(E_1 E_2 - 1)}{(E_1 E_2 + 1)}$$

- reinforcing effect of two chiral catalysts
- ee increases over time

yield: up to 100%

coupled exergonic process required

D. Dynamic kinetic resolution (the desired product is S_P):



(selectivity E)

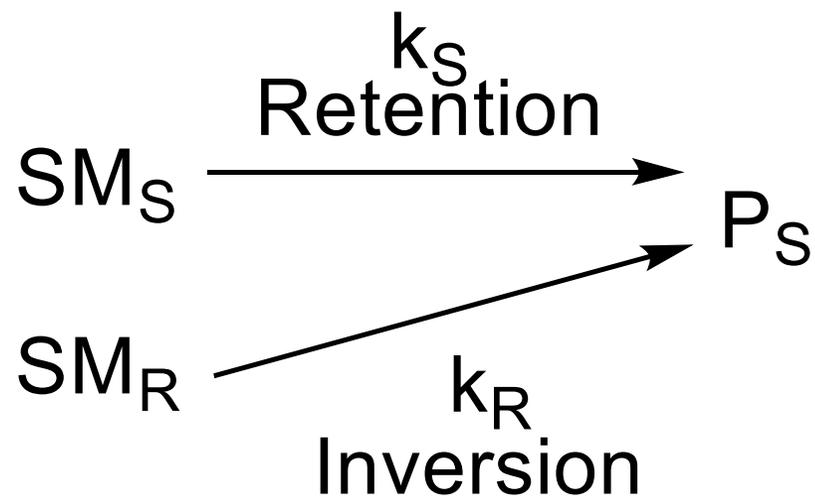
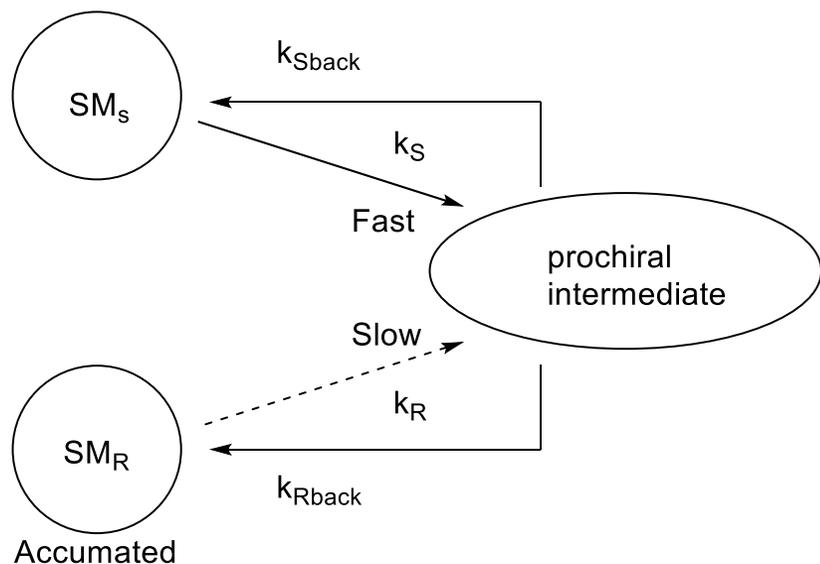


$$\text{ee: } \frac{(E-1)}{(E+1)}$$

- no reinforcing effect
- ee constant over time

yield: up to 100%

racemization needs to be rapid in relation to product formation



Cyclic De-racemization

- Wanted Enantiomer acts as “Sink” of material
- Theoretical yield and ee are 100%

- Enantio-convergent Processes
- Selectivity depends on the both retentive and invertive processes
- Theoretical yield and ee are 100%

- For general reading about KR and DKR Walsh, P. J.; Kozlowski, M. *C. Fundamentals of asymmetric catalysis*; University Science Books: Sausalito, **2009**.
- Minor Enantiomer Recycling C. Moberg *Acc. Chem. Res.* 2016, 49, 2736-2745
- DYKAT's Steinreiber, J.; Faber, K.; Griengl, H. *Chemistry - A European Journal* . **2008**, 14 (27), 8060–8072