Dynamic Kinetic Resolutions

A MacMillan Group Meeting

Presented by Jake Wiener

On the sixth day of June, two thousand and two, at eight o'clock in the evening.

I. Overview of concept. Contrast to other types of resolutions.

II. Chemical methods.

III. Combined chemical/biocatalytic methods.

Relevant reviews:

Huerta, F.; Minidis, A. B. E.; Backvall, J-E. *Chem. Soc. Rev.*, **2001**, *30*, 321.

Ward, R. S. *Tetrahedron: Asymmetry*, **1995**, *6*, 1475.

Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.*, **1995**, *68*, 36.

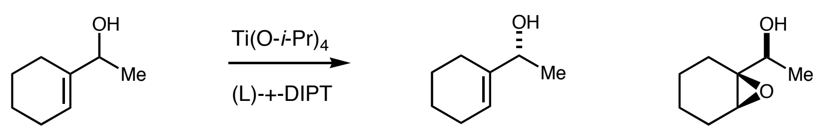
Caddick, S.; Jenkins, K. *Chem. Soc. Rev.*, **1996**, *25*, 447.

Cook, G. R. *Curr. Org. Chem.*, **2000**, *4*, 869. (Transition metal mediated kinetic resolutions only)

Stecher, H.; Faber, K. *Syntheses*, **1997**, 1. (Biocatalytic dynamic kinetic resolutions only)

Dynamic Kinetic Resolution vs. Other Types of Resolutions

■ Kinetic Resolution: One enantiomer reacts much faster than the other

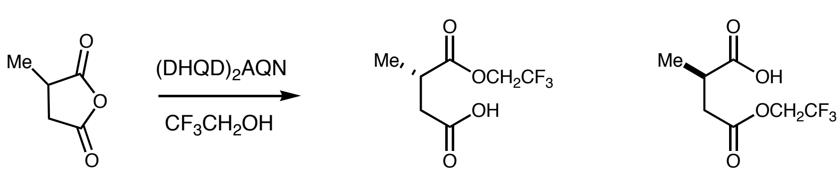


> 96% ee

55% conversion
98 : 2 dr
> 96% ee

Sharpless, *JACS*, **1981**, *103*, 6237.

■ Parallel Kinetic Resolution: Each enantiomer undergoes a different reaction



93% ee

36% yield

80% ee

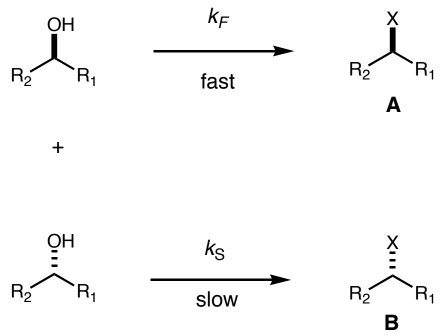
41% yield

Deng, *JACS*, **2001**, *123*, 11302.

■ In dynamic kinetic resolutions, 100% of racemic SM can be converted to enantiopure product

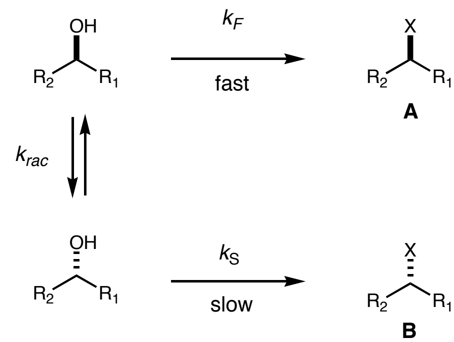
Dynamic Kinetic Resolution: Overview

■ Kinetic Resolution



50% theoretical yield of **A**

■ Dynamic Kinetic Resolution



If $k_{rac} > k_F >> k_S$ 100% theoretical yield of **A**

■ In a DKR, as with a classical KR, one enantiomer reacts slowly under the reaction conditions

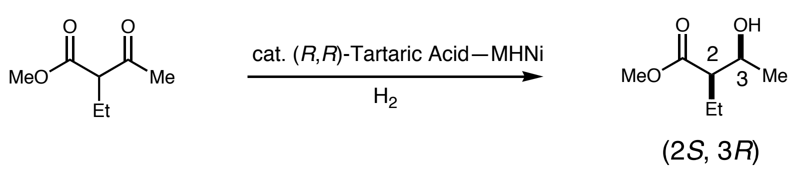
■ In a DKR, the rate of racemization of SM is fast relative the rate of the asymmetric transformation

■ Thus, using DKR, possible to convert 100% of racemic SM to enantiopure product due to equilibrating racemization of SM

■ How can we control the two processes: racemization and asymmetric transformation?

First Reported Chemical Dynamic Kinetic Resolution: β-Keto Ester Reduction

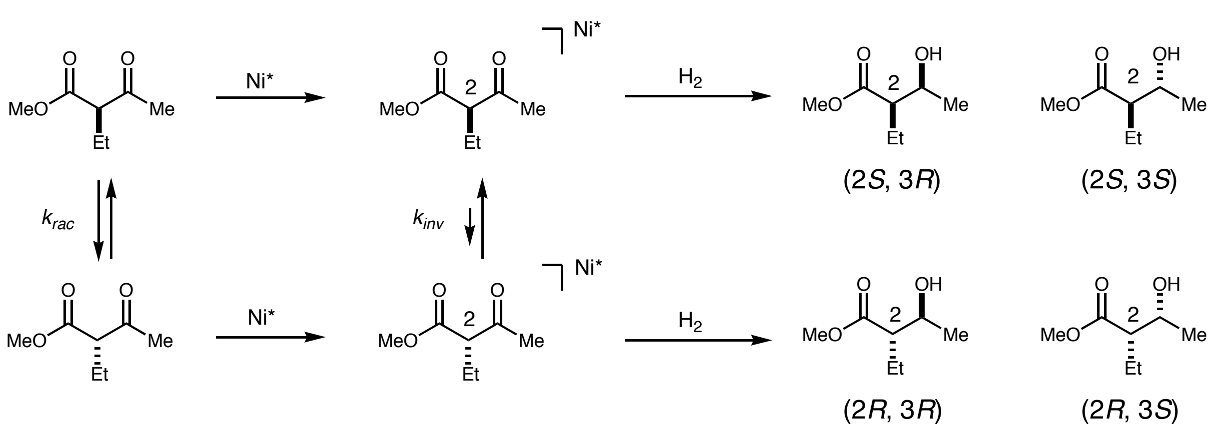
■ Tai observes DKR phenomenon in 1979



71% yield

80% ee

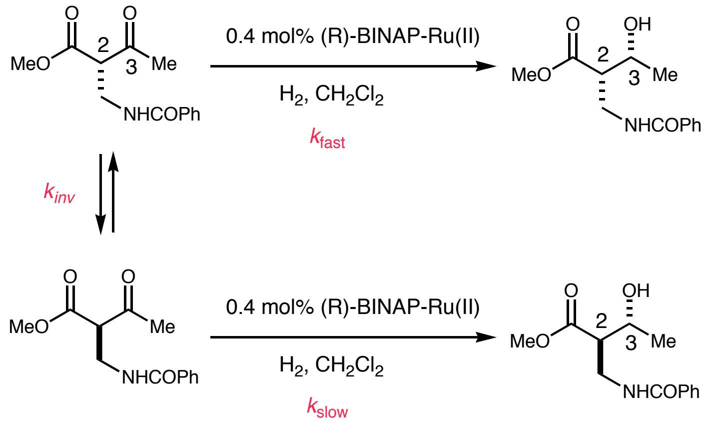
■ (2*S*) isomer attributed to influence of catalyst on epimerization of SM after complexation but prior to reduction



Tai, A. *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 1468.

Chemical Dynamic Kinetic Resolution: Noyori Reductions

■ Noyori β-keto ester reductions describe relative rates



94% de (93% ee)

k_{fast}/k_{slow} = 15

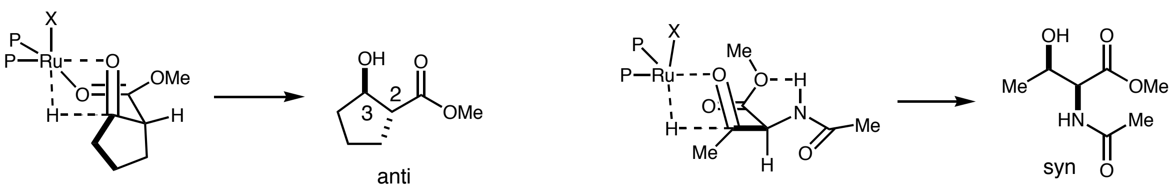
k_{inv}/k_{fast} = 6.1

k_{inv}/k_{slow} = 92

Noyori, *Bull. Chem. Soc. Jpn.*, **1995**, *68*, 36.

"The absolute configuration at C-3 is governed by the handedness of the BINAP ligand while the C-2 configuration is dependent on substrate structures."

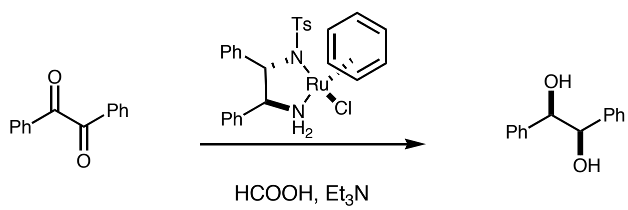
Noyori, *JACS*, **1989**, *111*, 9135.



Chemical Dynamic Kinetic Resolution: Noyori Reductions

computations predict relative rates of reactions of enantiomers

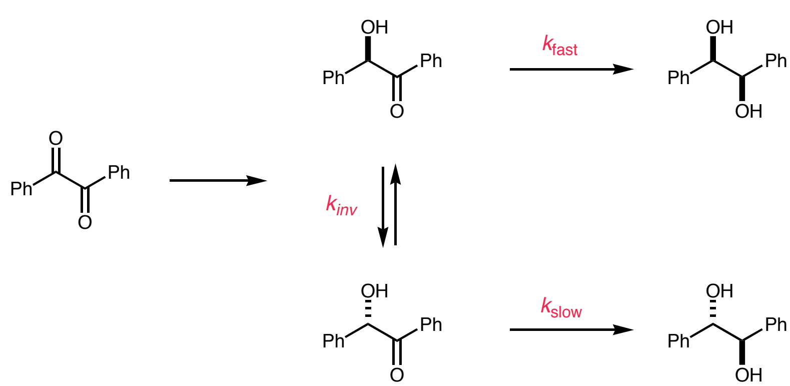
■ Chiral Ru(II) complex catalyzes benzil reduction



100% yield

>99% ee

chiral : meso = 9: 1



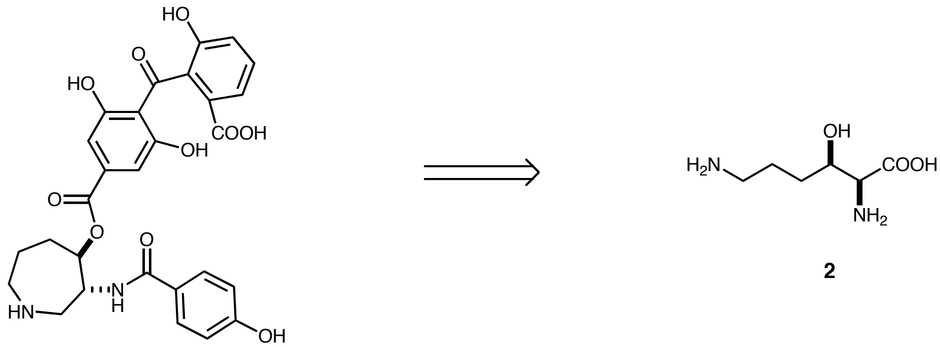
Computational modelling indicates that

k_{fast}/k_{slow} = 55

Noyori, *Org. Lett.*, **1999**, *1*, 1119.

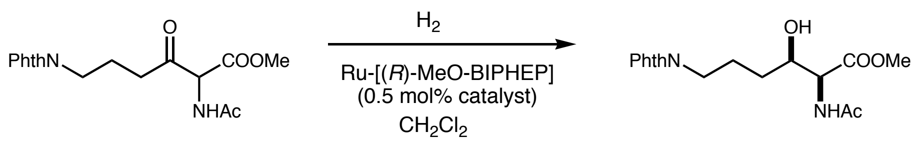
Chemical Dynamic Kinetic Resolution: Ru(II) Reductions in Synthesis

■ Formal synthesis of (—)-Balanol **1** proceeds through (2S,3R)-3-hydroxysilane **2**.



1 **2**

■ Ru(II) catalyzed DKR provides key step in synthesis of **2.**

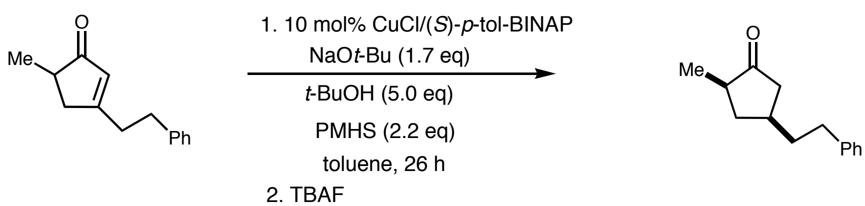


100% yield
> 99% ee
> 98% de

Genet, *Tet. Lett.*, **1998**, *39*, 6467.

Chemical Dynamic Kinetic Resolution: Conjugate Reduction

racemization of starting material induced by added base



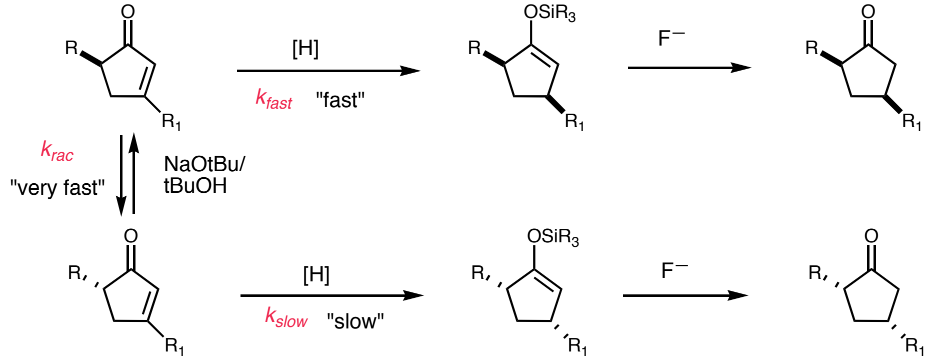
89% yield
91 : 9 syn : anti
91% ee

A variety of alkyl, aryl substituents at positions 3 and 5 are tolerated

k_{fast}/k_{slow} = 25-52

Buchwald, *JACS*, **2002**, *124*, 2892.

■ Product trapped as enol silane to prevent epimerization

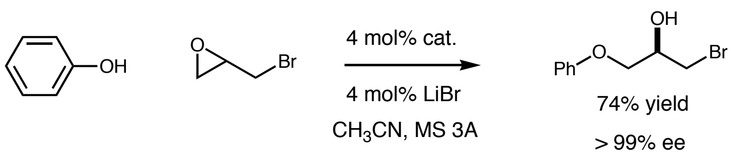


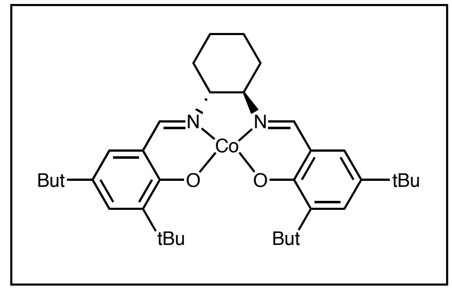
Without base, a classical KR is observed; choice of base is crucial for DKR.

Chemical Dynamic Kinetic Resolution: Epoxide Opening

Co-salen complexes catalyze DKR in phenolic epoxide opening

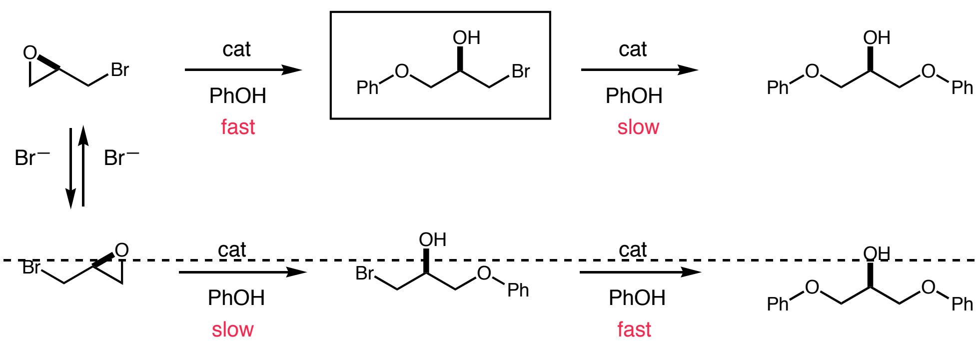
■ LiBr is required for racemization and subsequent DKR





catalyst

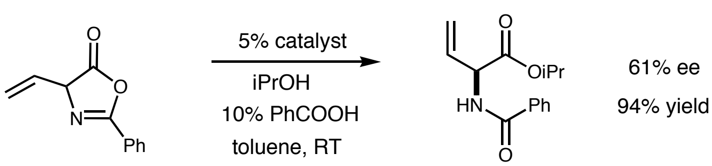
■ Exceptionally high ee attributed to further resolution of minor product

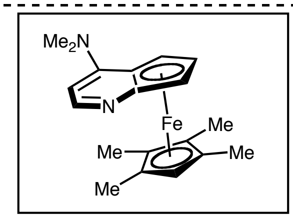


Jacobsen, *JACS*, **1999**, *121*, 6086.

Chemical Dynamic Kinetic Resolution: Azlactone and Dioxolanedione Opening

■ Azlactones (pKa ~ 9) have good propensity for racemization; DMAP known to catalyze alcoholysis



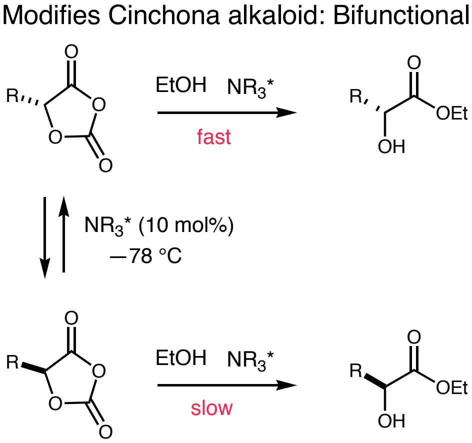


catalyst

Fu, *JOC*, **1998**, *63*, 3154.

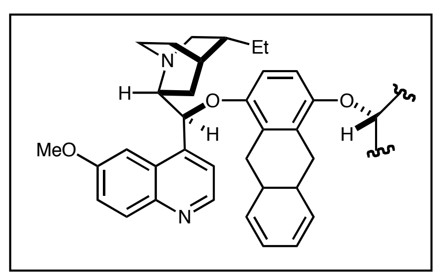
For other azlactone openings: Seebach, Tetrahedron, 1997, 53, 7539.

■ Modifies Cinchona alkaloid: Bifunctional organic catalyst



R = aryl:	91 - 95% ee 68 - 85% yield
R = alkyl:	No DKR (due to decreased acidity)

Chiral amine catalyzes both racemization and alcoholysis of dioxolanediones



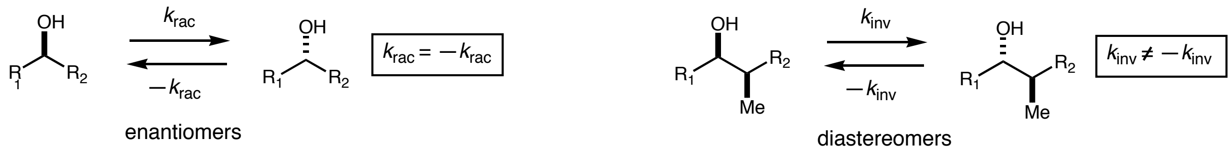
catalyst

Deng, *JACS*, **2002**, *124*, 2870.

Lactone opening: Bringmann, *Acc. Chem. Res.*, **2001**, *34*, 615.

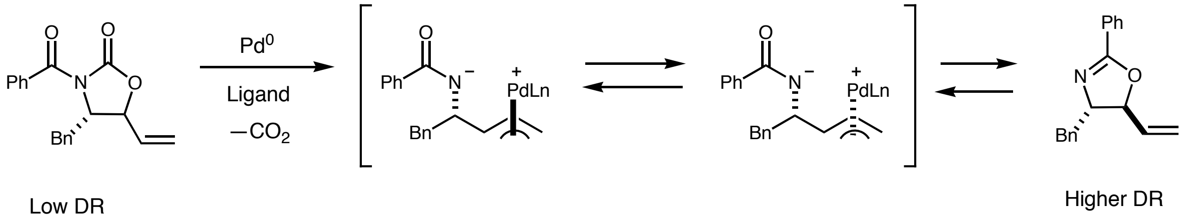
Chemical Dynamic Kinetic Resolution: π-allyl Pd Catalysis

■ Equilibration between diastereomers is not a trivial problem



The rates of epimerization of two diastereomers are not necessarily equal

■ Enhanced diastereomeric ratio after internal trapping suggests rapid equilibration of Pd complexes



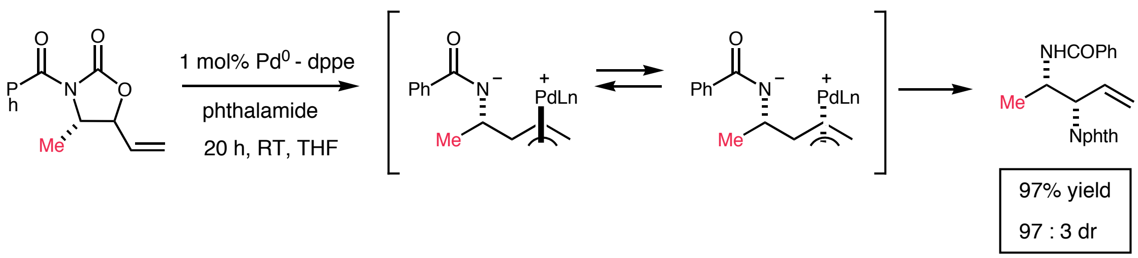
Product oxazolines are also ionized by the catalyst, giving rise to thermodynamic product mixtures

Can the epimerizing intermediates be irreversibly trapped with nitrogen nucleophiles in a DKR?

Cook, *ACIEE*, **1999**, *38*, 110.

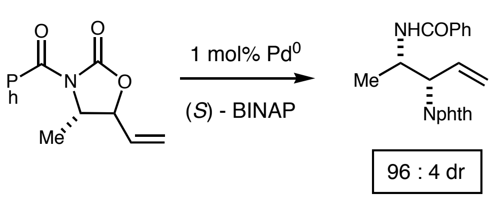
Chemical Dynamic Kinetic Resolution: π-allyl Pd Catalysis

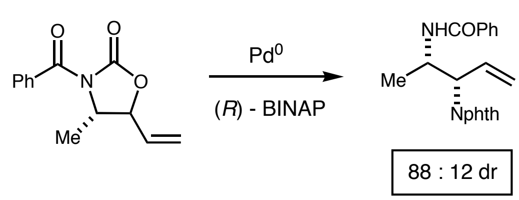
■ Phthalamide is able to trap intermediates in a dynamic kinetic resolution



As size of substituent increases, so does diastereoselectivity

■ Chiral ligands on Pd afford matched/mismatched cases

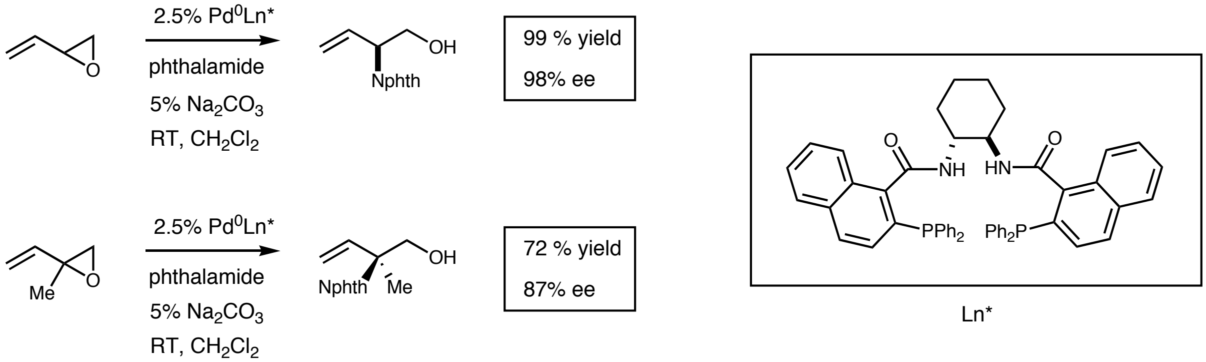




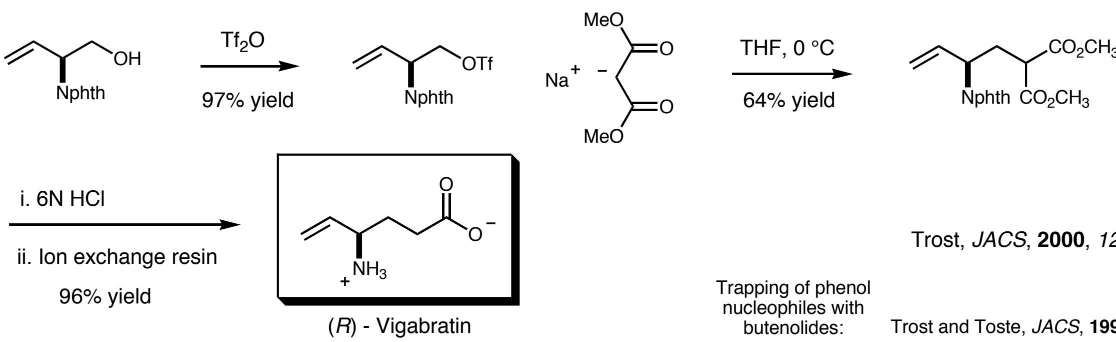
Cook, *ACIEE*, **1999**, *38*, 110.

Chemical Dynamic Kinetic Resolution: π-allyl Pd Catalysis

■ Chiral catalyst effectively opens diene monoepoxides - Trost



■ Epoxide opening facilitates synthesis of anti-epileptic drug Vigabatrin

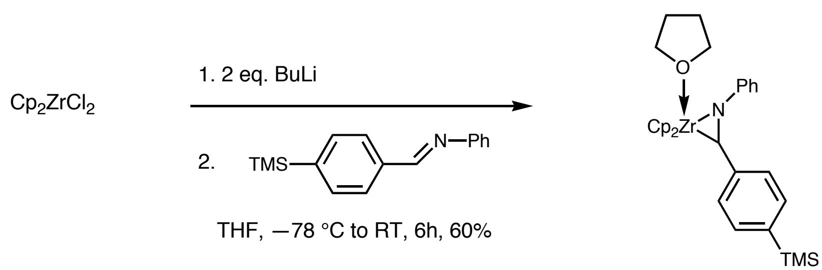


Trost, *JACS*, **2000**, *122*, 5968.

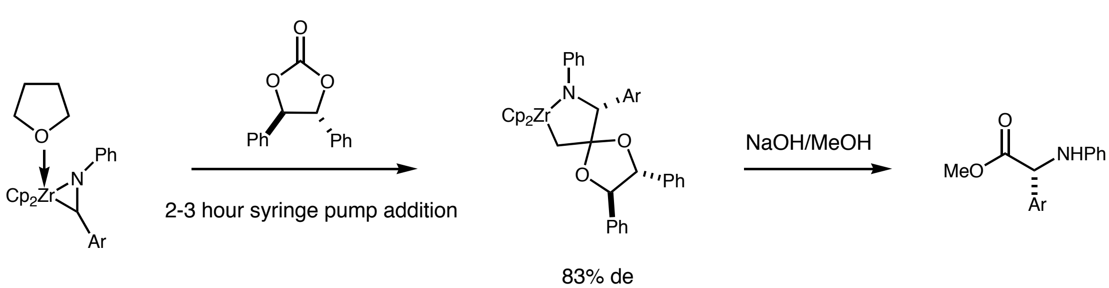
Trapping of phenol nucleophiles with butenolides: Trost and Toste, *JACS*, **1999**, *121*, 3543.

Chemical Dynamic Kinetic Resolution: Silylated α-Amino Acid Synthesis

■ Racemic zirconaaziridines are readily available



■ DKR of zirconaaziridines affords unnantural α-amino acids



Syringe pump addition required to achieve high selectivity due

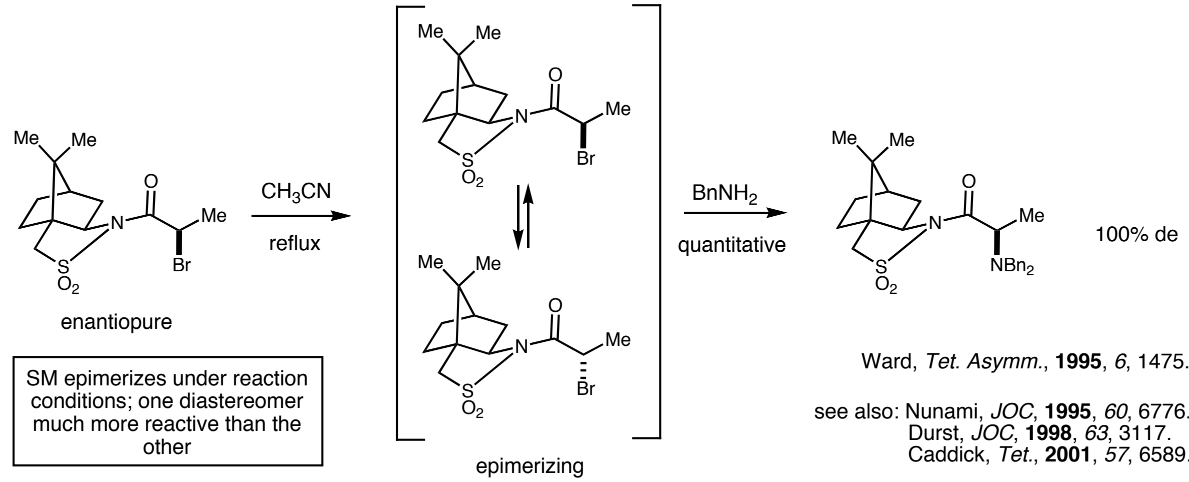
to slow racemization of SM relative to insertion

Norton, JOC, ASAP

Norton, *JACS*, **1999**, *121*, 4520.

Chemical Dynamic Kinetic Resolution: Displacements via Chiral Auxiliaries

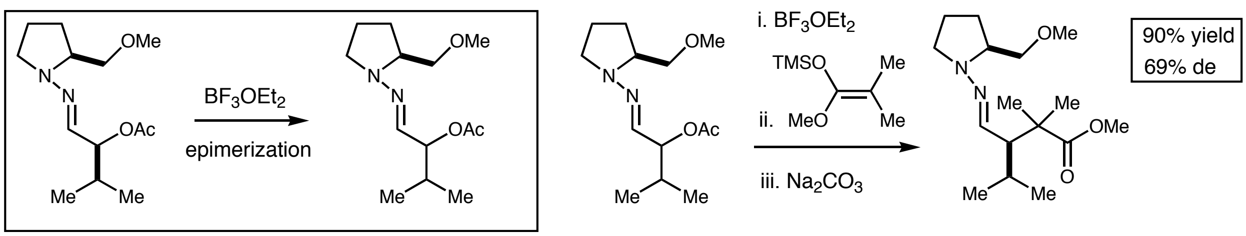
■ Chiral sultam facilitates highly selective S_N2 DKR



Ward, *Tet. Asymm.*, **1995**, *6*, 1475.

see also: Nunami, *JOC*, **1995**, *60*, 6776.
Durst, *JOC*, **1998**, *63*, 3117.
Caddick, *Tet.*, **2001**, *57*, 6589.

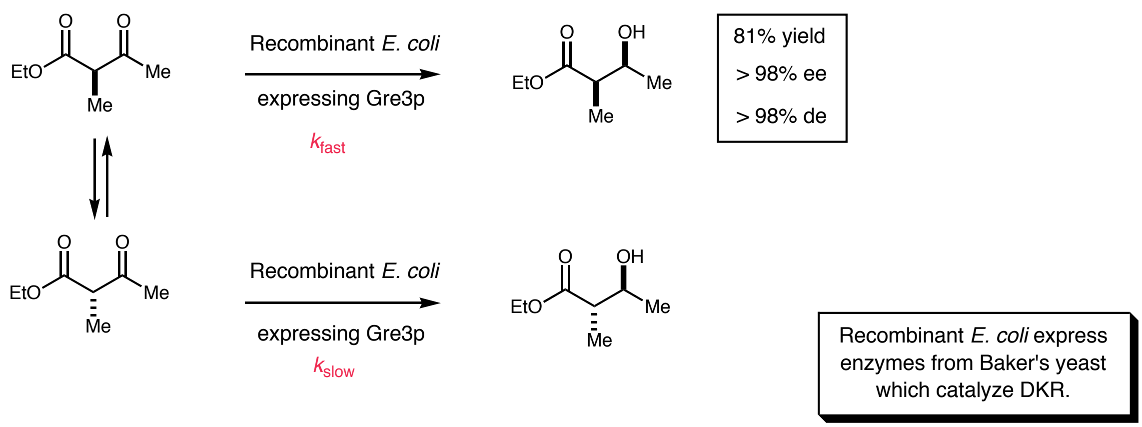
■ Hydrazones amenable to moderately selective alkylation



Enders, *Tet. Asymm.*, **1998**, *9*, 2155.

Biocatalytic Dynamic Kinetic Resolution: Enzymatic Reduction

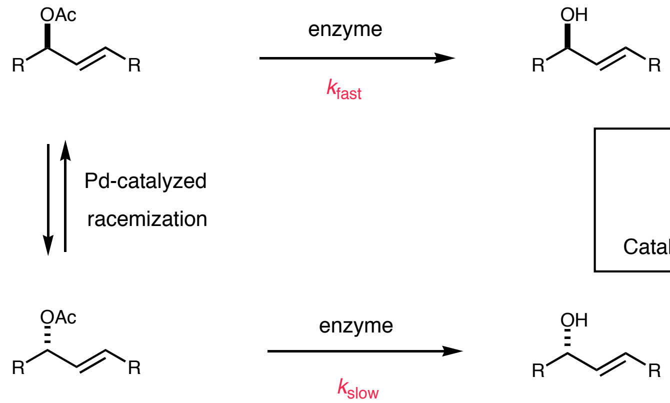
■ Relatively simple substrates are reduced in biocatalytic DKR



Stewart, *JOC*, **2000**, *65*, 2586.

Biocatalytic Dynamic Kinetic Resolution: Pd^0 in Allylic Acetate Hydrolysis

■ Can organometallic and biological reagents be used in tandem?

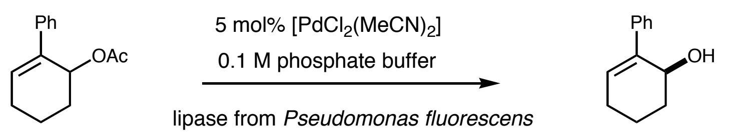


A selective enzyme is crucial

Organometallic catalyst must racemize substrate

Catalyst must not influence selectivity/reactivity of enzyme

■ π-allyl Pd complex results in facile epimerization



81% yield
96% ee
19 days

Sturmer, *ACIEE*, **1997**, *36*, 1173.

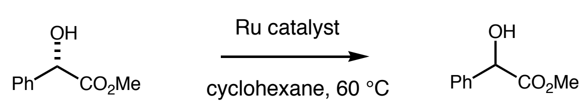
Biocatalytic Dynamic Kinetic Resolution: Esterification via Ru-Catalyzed Racemization

how else can organometallic and biological reagents be used in tandem?

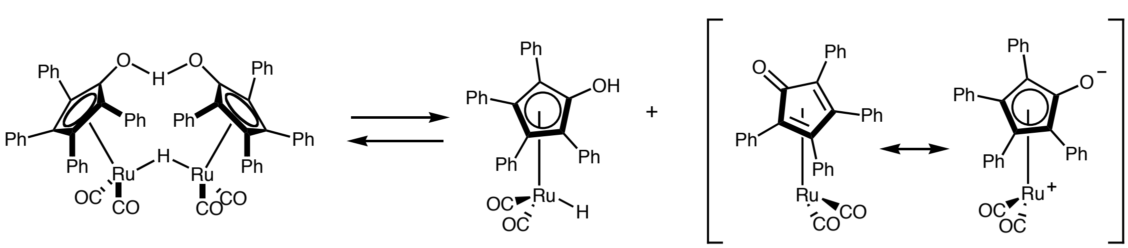
■ Backvall Ru catalyst can function without interfering with enzymes

Requirements for metal catalyzed racemization: No Base

1. No interference with enzyme in esterification
2. No direct base-catalyzed esterification



■ Ru complex functions by dissociative mechanism



acts as base for deprotonation/racemization

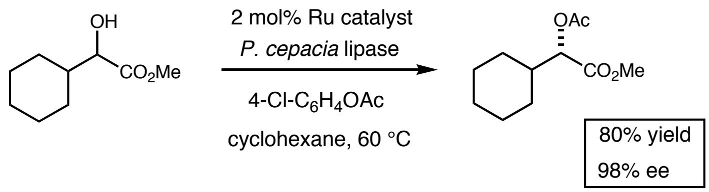
Backvall, *Org. Lett.*, **2000**, *2*, 1037.
Backvall, *Chem. Soc. Rev.*, **2001**, *30*, 321.

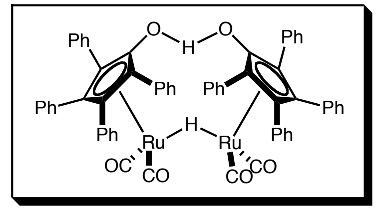
For a related process see: Park, *JOC*, **2001**, *66*, 4736.

Biocatalytic Dynamic Kinetic Resolution: Esterification via Ru-Catalyzed Racemization

organometallic catalyst functions in tandem with enzyme

■ Ru catalyzed racemization plus enzymatic esterification: DKR

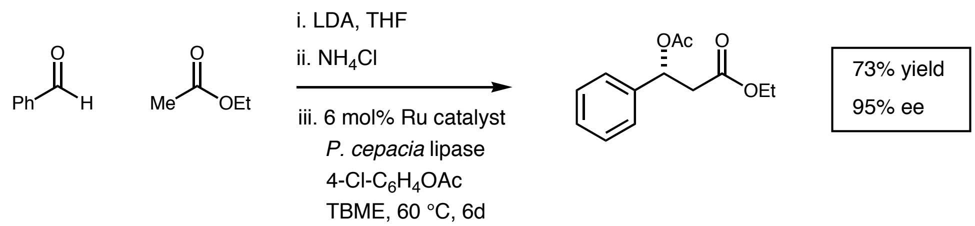




catalyst

Backvall, *Org. Lett.*, **2000**, *2*, 1037.

■ Variation: One-pot aldol reaction — DKR. First DKR of β-hydroxy esters.

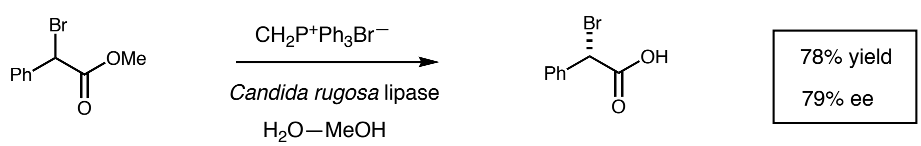


Substrate must have two differently sized groups adjacent to stereocenter
These two groups cannot exceed the size of the active site in the enzyme

Backvall, *Org. Lett.*, **2001**, *3*, 1209.

Biocatalytic Dynamic Kinetic Resolution: Ester Hydrolysis

■ α-bromo esters racemized by Br^-, resolved by enzymatic hydrolysis

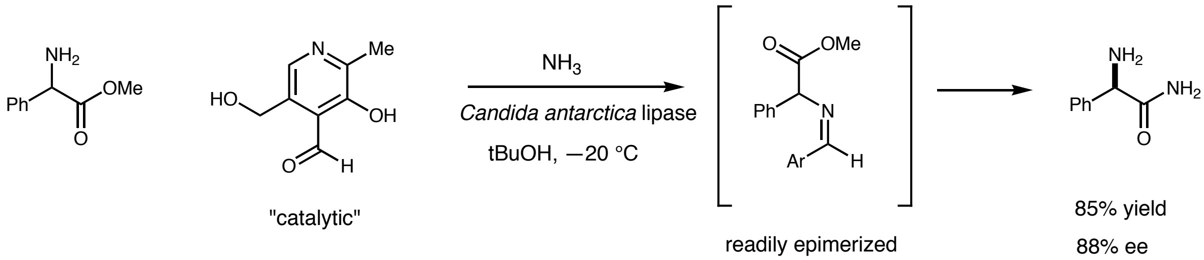


■ Enantioenriched carboxylate product cannot racemize

Williams, *Chem. Comm.*, **1998**, 2519.

Biocatalytic Dynamic Kinetic Resolution: Unique Racemization Protocols

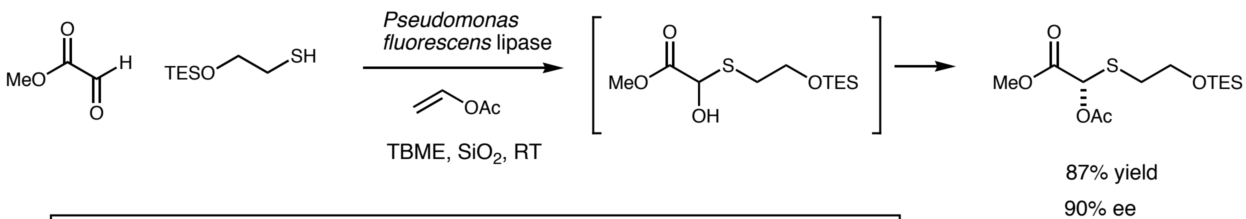
■ Racemization via Schiff base intermediate/enzymatic aminolysis



amide racemizes 30 more slowly than ester

Sheldon, *Tetrahedron: Asymmetry*, **1999**, *10*, 1739.

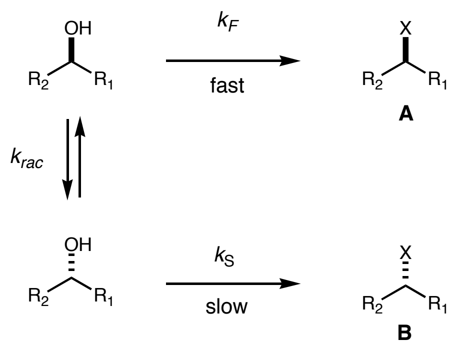
■ Racemic and readily epimerizing hemithioacetal generated and resolved by enzyme



SiO_2 promotes hemithioacetal epimerization via dissociation/recombination mechanism

Rayner, *Tet. Lett.*, **1995**, *36*, 8493.

In Conclusion



If $k_{rac} > k_F >> k_S$ 100% theoretical yield of **A**

Dynamic kinetic resolutions have attracted increased attention in the last decade as the need for inexpensive chiral materials has increased and as the understanding of asymmetric catalytic processes has blossomed.

Crucial to a succesful DKR is simultaneous epimerization and resolution: What are ways to epimerize

i. in the presence of asymetric catalysts (enzymes, metals)?

ii. without epimerizing enantio- and diastereo- enriched products?