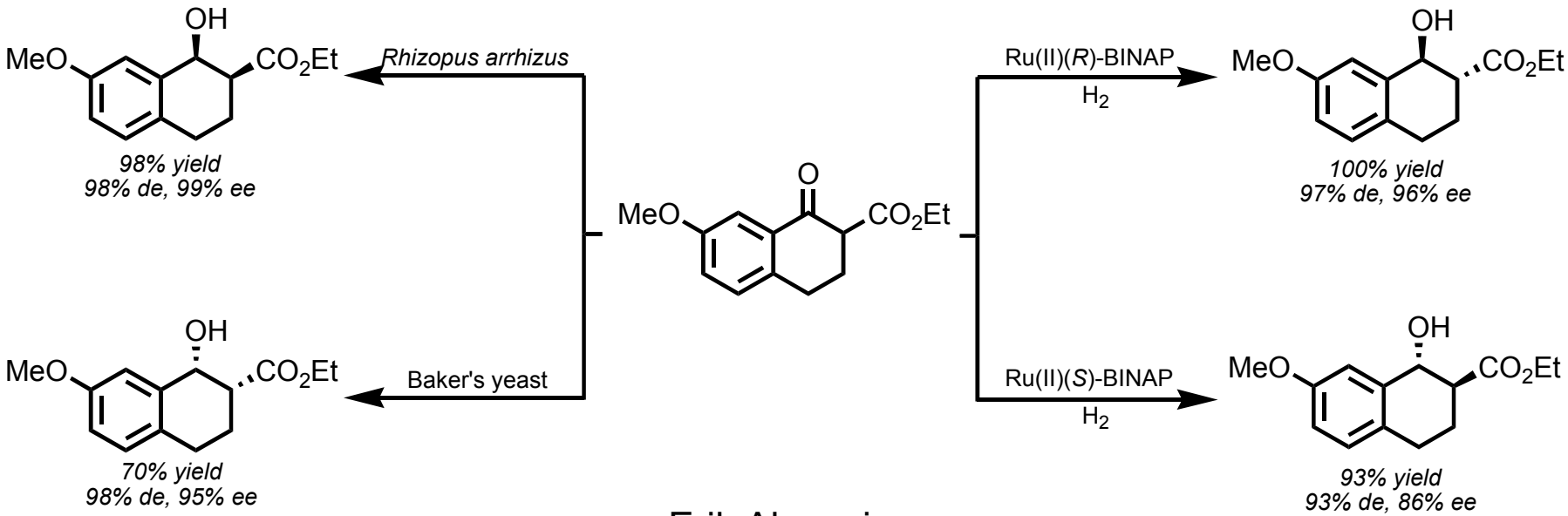
Dynamic Kinetic Resolution: A Powerful Approach to Asymmetric Synthesis



Erik Alexanian

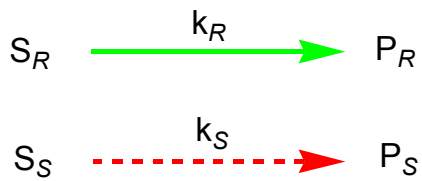
Supergroup Meeting

March 30, 2005

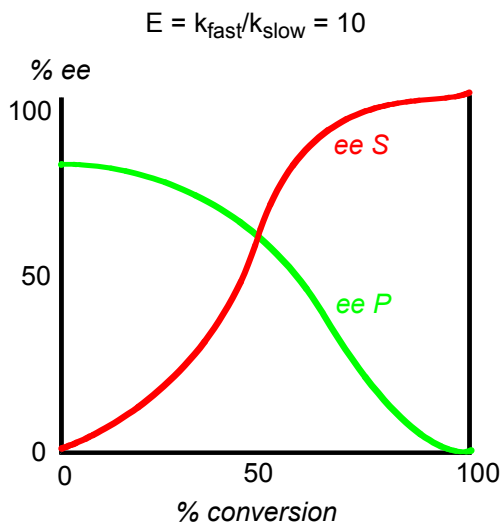
For leading references, see: Pellissier, H. *Tetrahedron* **2003**, *59*, 8291
Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247

Methods for Asymmetric Synthesis

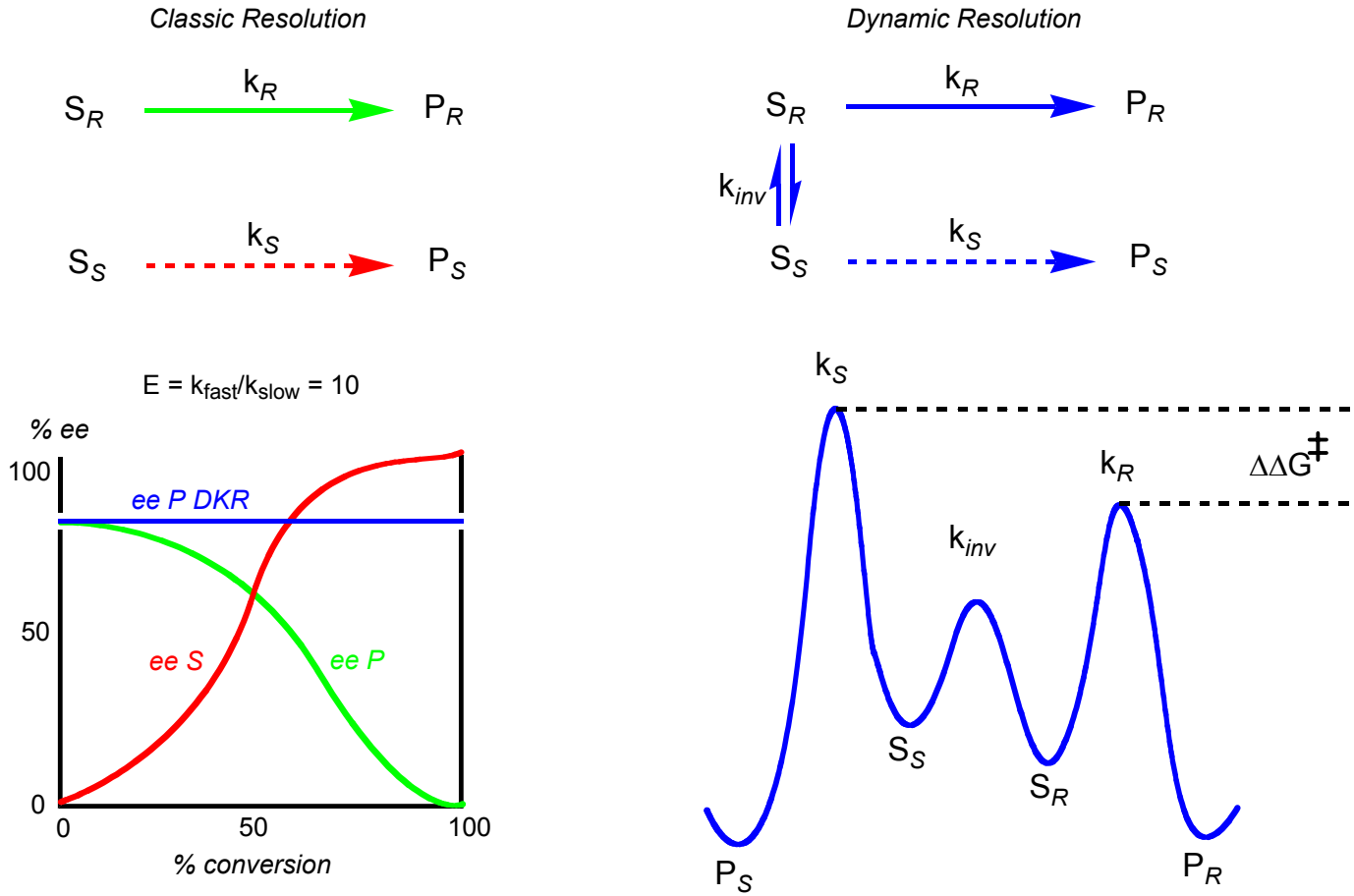
- Synthesis utilizing existing stereogenic centers (chiral substrates or auxiliaries)
- Catalytic enantioselective organic reactions
  - Chemocatalysis - metal-mediated, Lewis acid-mediated, organocatalysis
  - Biocatalysis - enzymes (hydrolases)
- Resolution
  - Conventional separation procedures
  - Kinetic resolution



- Problems associated with standard kinetic resolutions:
  - Theoretical yield = 50%
  - Separation of product from remaining substrate required
  - In the majority of processes, only one stereoisomer is desired
  - Drop in enantiomeric purity as process nears 50% conversion



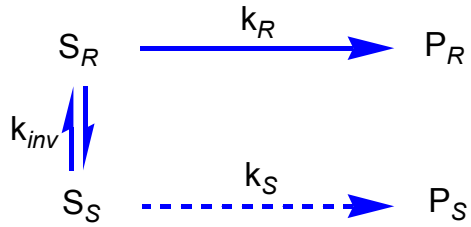
Dynamic Kinetic Resolution



- If racemization can occur concurrently with kinetic resolution, then theoretically 100% of the racemic mixture can be converted to one enantiomer. This process is known as dynamic kinetic resolution (DKR).
- DKR is an example of a Curtin-Hammett system in which the composition of products is controlled by the free energies of the transition states and not the composition of the starting materials.

Guidelines for Dynamic Kinetic Resolution

Dynamic Resolution



In order to design a successful DKR, both the inversion and resolution steps have to be carefully tuned. Here are a few established general guidelines for an efficient DKR:

(1) The kinetic resolution should be irreversible in order to ensure high enantioselectivity.

(2) The enantiomeric ratio ($E = k_R/k_S$) should be at least greater than ~20.

(3) To avoid depletion of S_R, racemization (k_{inv}) should be at least equal or greater than the reaction rate of the fast enantiomer (k_R).

(4) In case the selectivities are only moderate, k_{inv} should be greater than k_R by a factor of ~10.

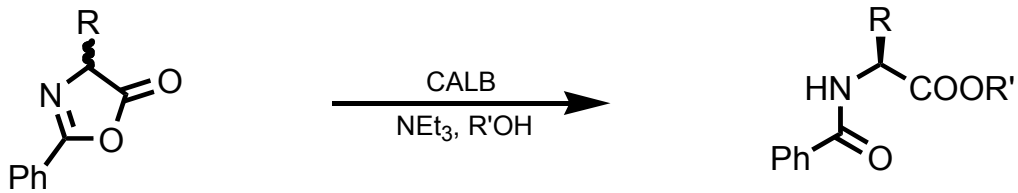
(5) Obviously, any spontaneous reaction involving the substrate enantiomers as well as racemization of the product should be absent.

Strauss, U. T.; Felfer, U.; Faber, K. *Tetrahedron: Asymmetry* **1999**, *10*, 107

Examples of Racemization

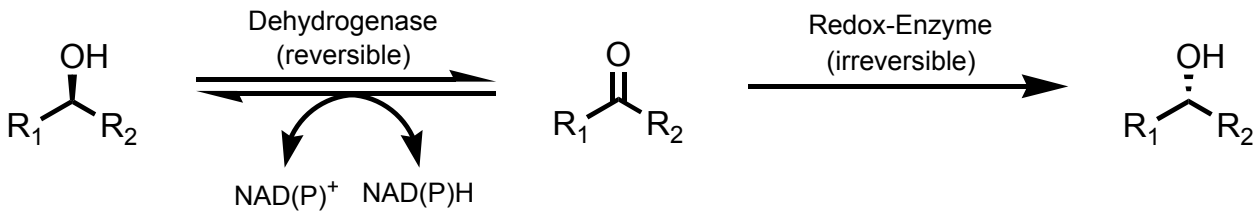
The racemization/inversion step is key to a successful DKR. Following are a number of common techniques used for this step.

1) Acid or base catalyzed racemization



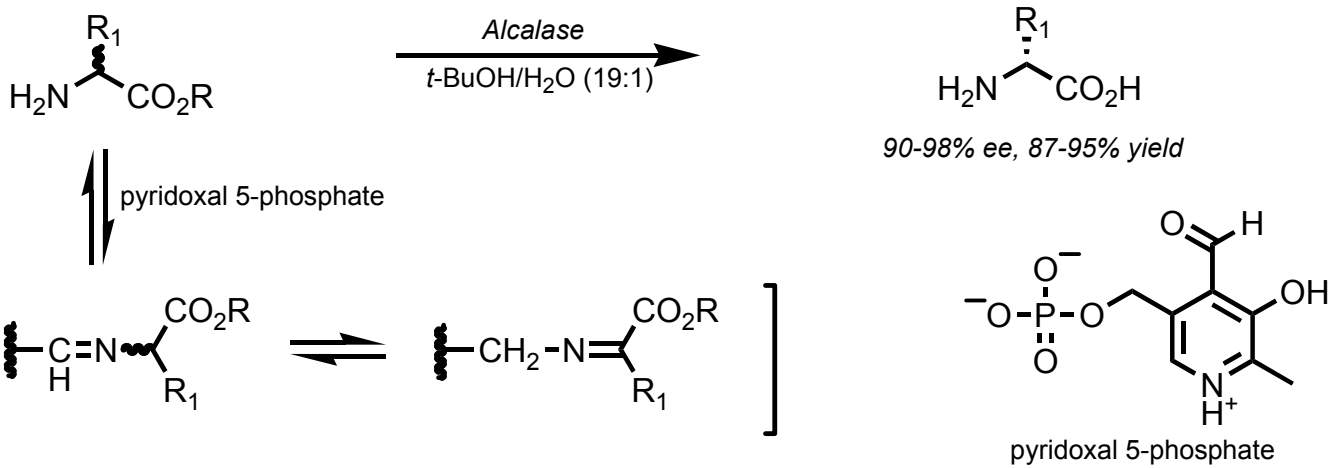
up to 96% yield
up to 98% ee

2) Enzyme catalyzed racemization

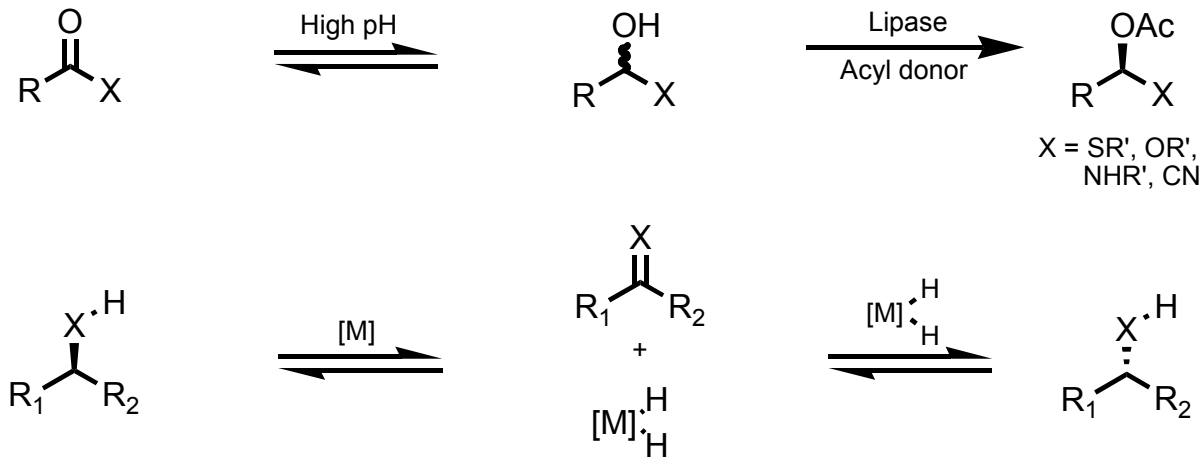


Examples of Racemization (Cont'd)

3) Schiff base-mediated racemization

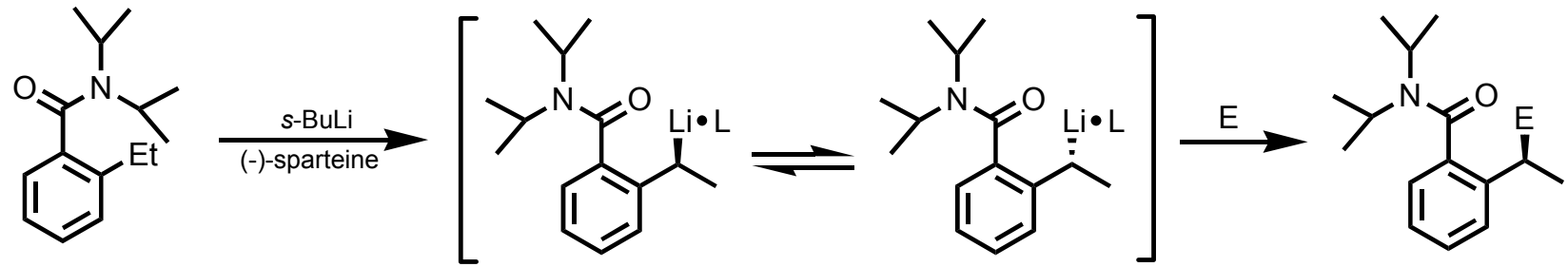


4) Racemization via sp^2 intermediates (redox, addition/elimination)

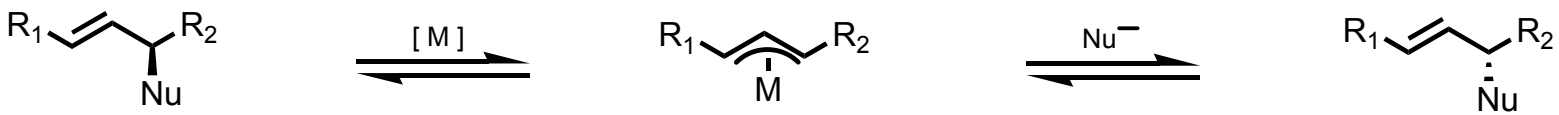


Examples of Racemization (Cont'd)

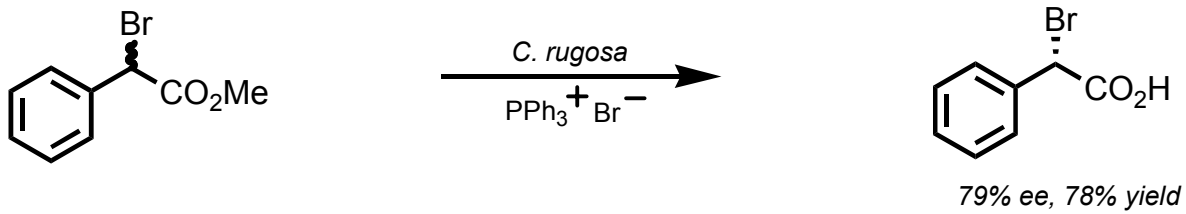
5) Anionic interconversion



6) Racemization via π-allyl intermediates

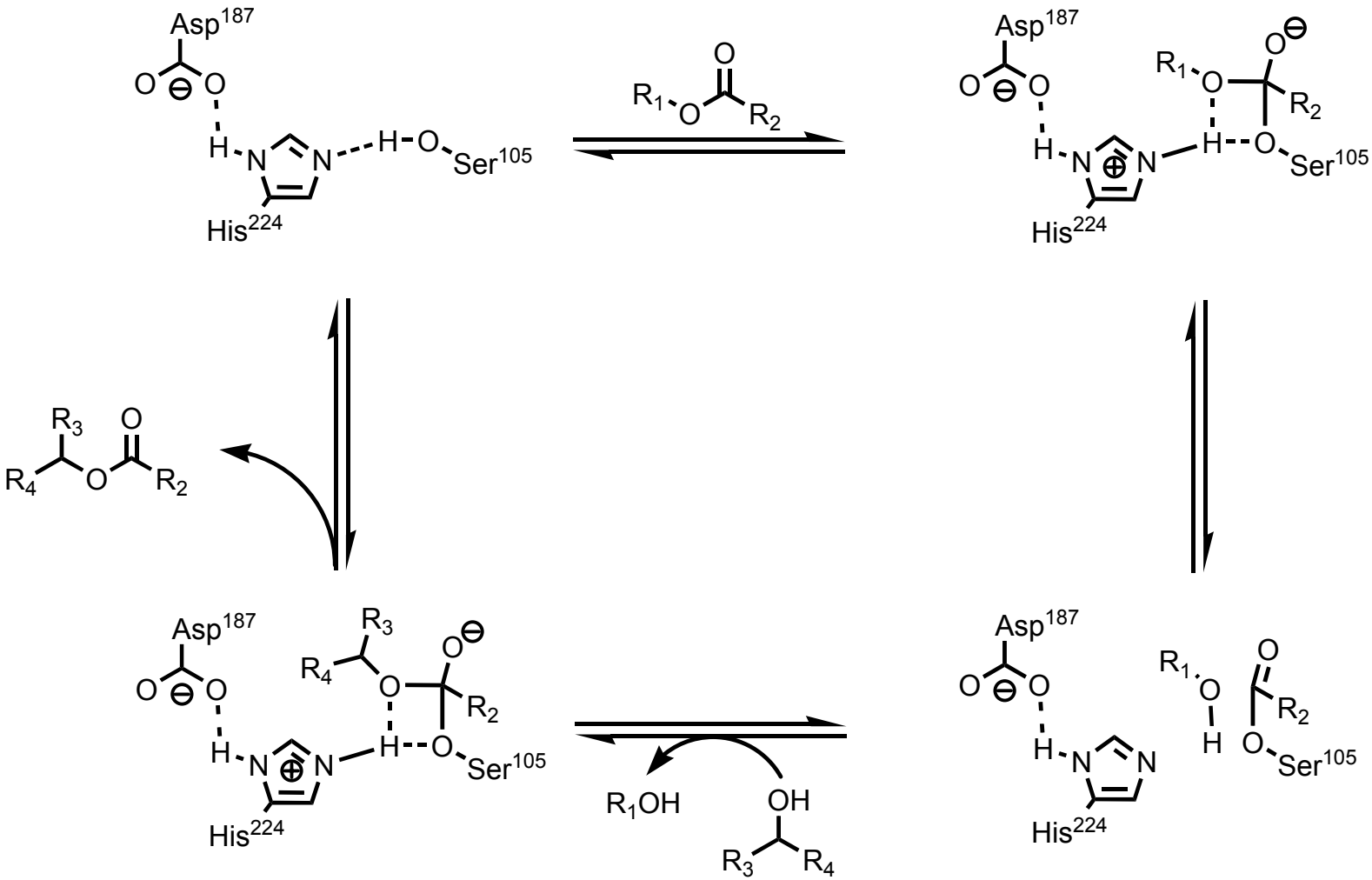


7) Racemization via S_N2 processes



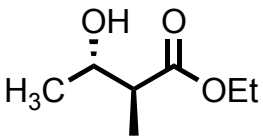
79% ee, 78% yield

The "Catalytic Triad" - Reaction Mechanism of CALB



Pamies, O; Bäckvall, J-E. *Chem. Rev.* **2003**, *103*, 3247

Enzymatic Methods - Reductions of β-Ketoesters



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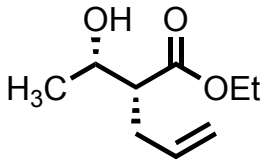

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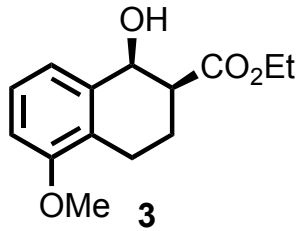

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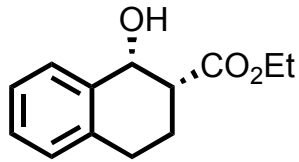

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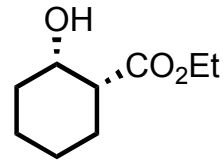

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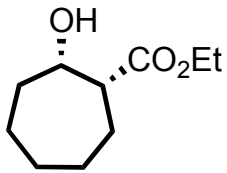

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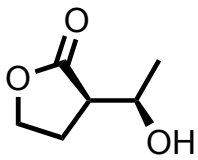

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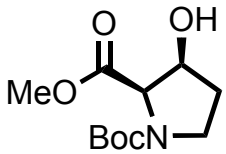

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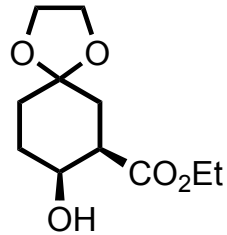

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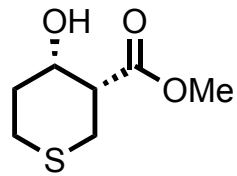


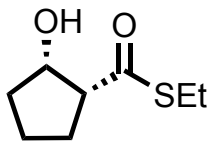
10

Product	Microorganism	Yield (%)	de (%)	ee (%)
1	*G. candidum*	80	98	98
2	*Baker's yeast*	94	92	99
3	*M. racemosus*	75	98	99
4	*Saccharomyces sp.*	95	98	98
5	*Baker's yeast*	72-85	99	99
6	*K. magna*	80	100	94
7	*Y. lipolytica*	95	-	95
8	*Dipodascus sp.*	80	-	99
9	*Baker's yeast*	74	-	98
10	*Baker's yeast*	71	98	85

Pellissier, H. *Tetrahedron* **2003**, *59*, 8291

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

Enzymatic Methods - Other Selected Reductions



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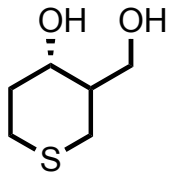

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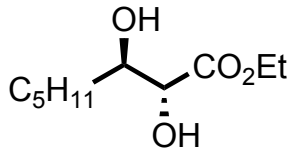

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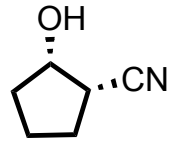

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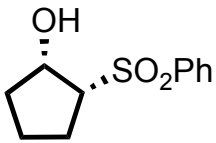

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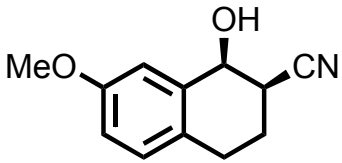

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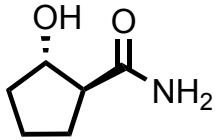

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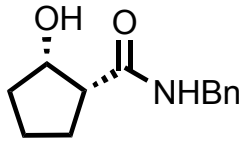


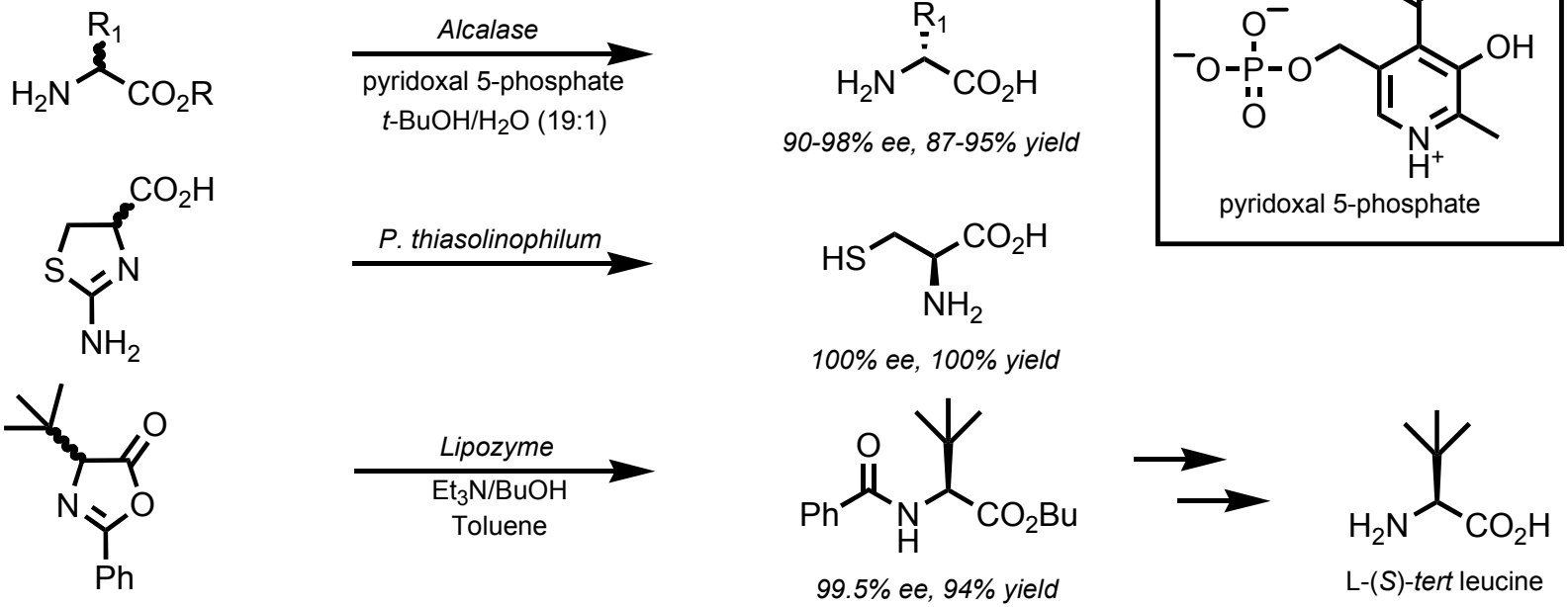
8

Product	Microorganism	Yield (%)	de (%)	ee (%)
1	*Baker's yeast*	88	100	96
2	*Baker's yeast*	82	76	99
3	*Baker's yeast*	76	-	80
4	*S. montanus*	89	-	97
5	*Baker's yeast*	95	96	98
6	*R. arrhizus*	97	98	99
7	*M. isabellina*	92	72:28 *dr*	99
8	*M. isabellina*	100	92	99

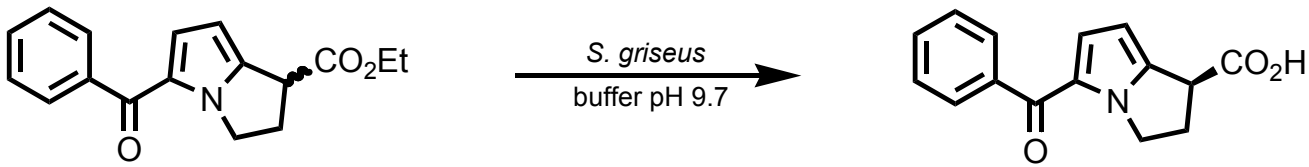
Pellissier, H. *Tetrahedron* **2003**, *59*, 8291

Enzymatic Methods - Hydrolysis

- Amino acid synthesis



- Many other useful hydrolysis systems



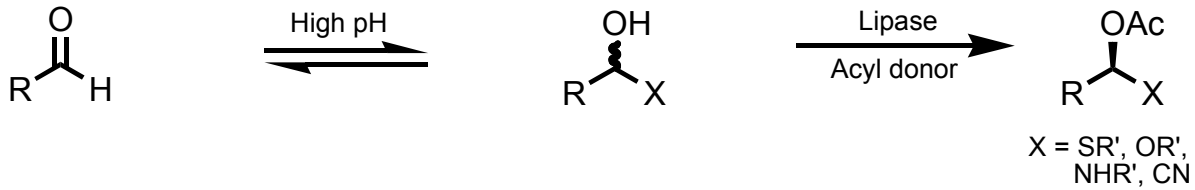
(*S*) - keterolac

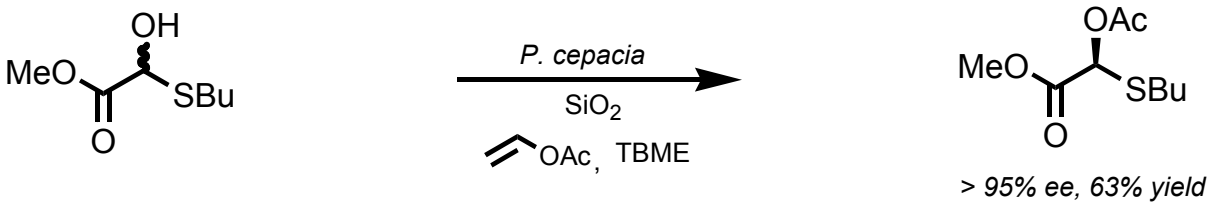
85% ee, 92% yield

Stecher, H.; Faber, K. *Synthesis* **1997**, 1

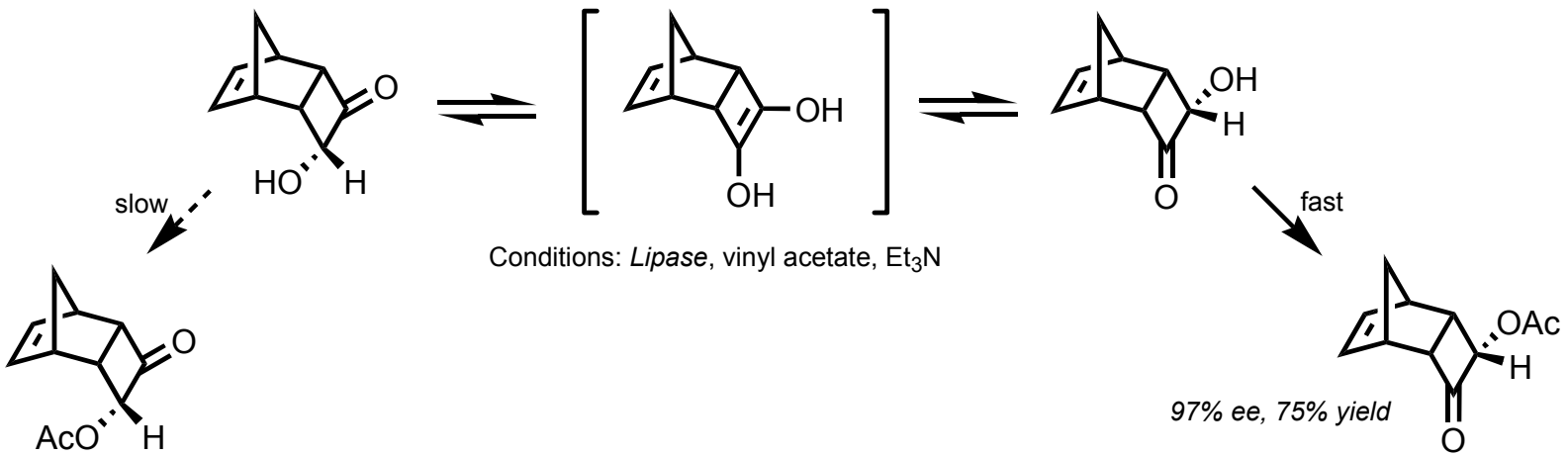
Enzymatic Methods - Esterifications

- DKR of Hemiacetals, cyanohydrins, and derivatives





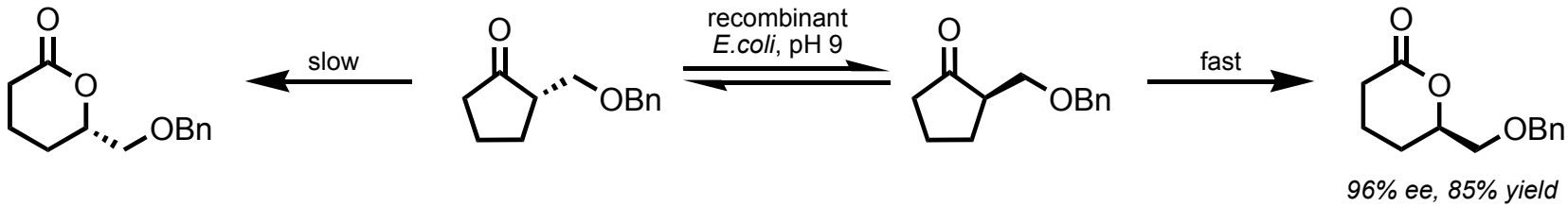
- Many other esterifications



Taniguchi, T.; Ogasawara, K. *Chem. Commun*. **1997**, 1399

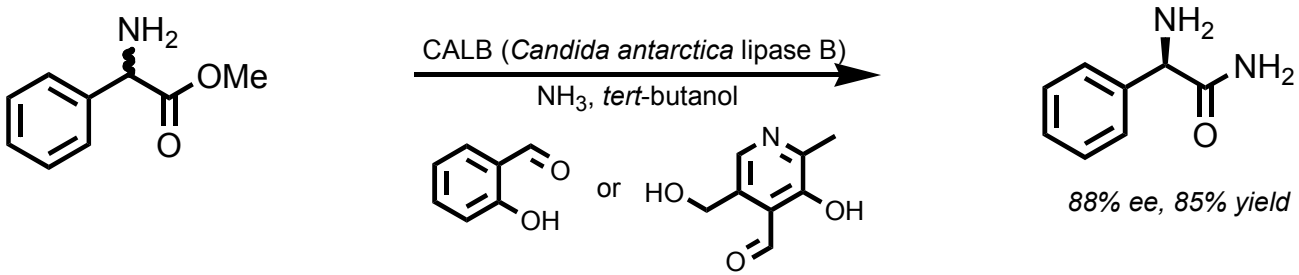
Other Enzymatic Methods via DKR

- DKR applied to microbiological Baeyer-Villiger oxidation



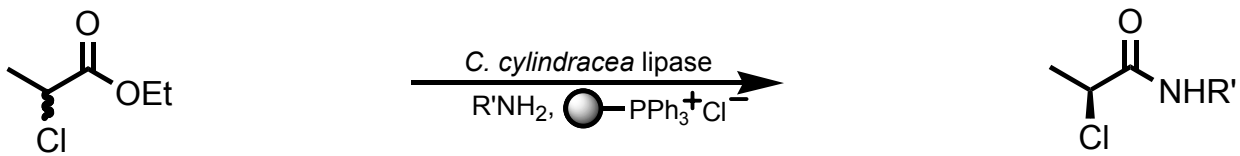
96% ee, 85% yield

- Chemoenzymatic DKR of Phenylglycine Methyl Ester



88% ee, 85% yield

- DKR combining enzyme and racemization via S_N2 displacement



up to 86% ee, up to 92% yield

Berezina, N.; Alphand, V.; Furstoss, R. *Tetrahedron: Asymmetry* **2002**, *13*, 1953

Wegman, M. A.; Hacking, A. P. J.; Rops, J.; Pereira, P.; van Rantwijk, F.; Sheldon, R. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1739

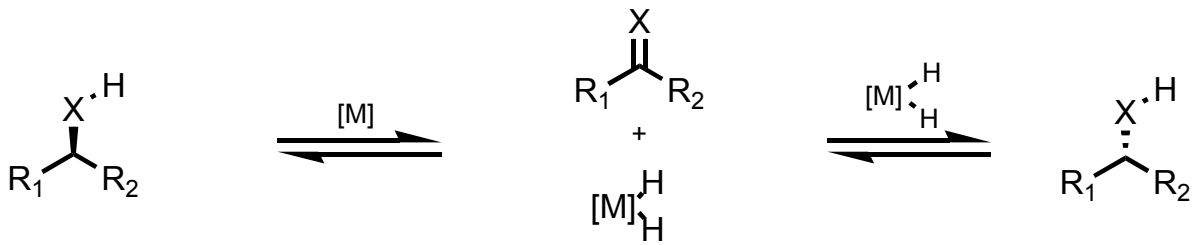
Badjic, J. D.; Kadnikova, E. N.; Kostic, N. M. *Org. Lett.* **2001**, *3*, 2025.

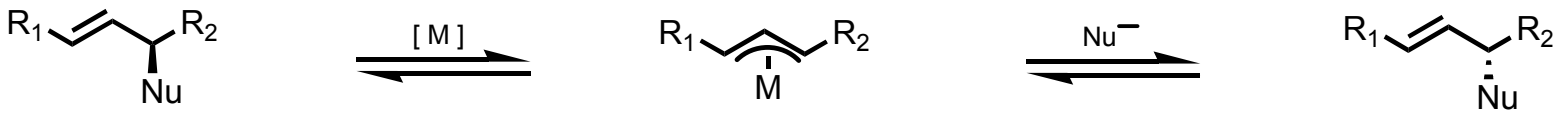
Combination of Enzymes and Transition Metals in DKR

Question: Why use anything other than simple enzymes and nonmetallic racemization methods?

Answer: These DKR approaches are mainly limited to substrates that possess a stereogenic center with an acidic proton.

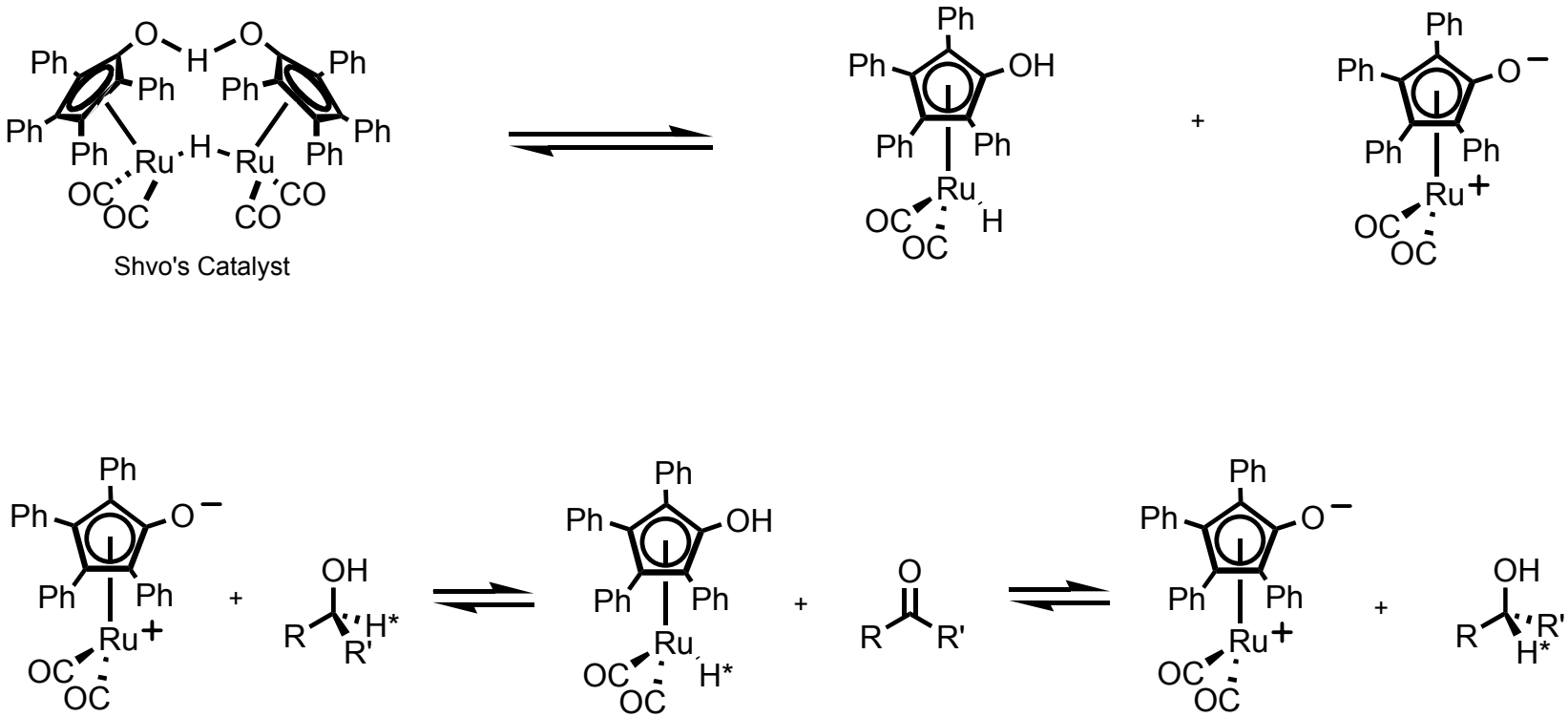
A Possible Solution: Transition Metal-Catalyzed Racemizations





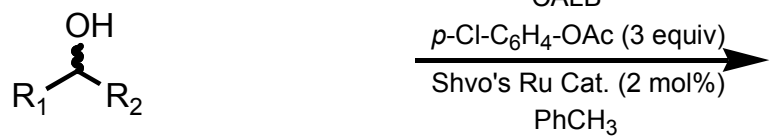
Pamies, O.; Backvall, J.-E. *Chem. Rev*. **2003**, *103*, 3247

Shvo's Catalyst - Mechanism of Action

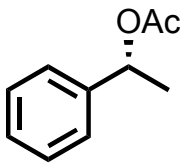


Pamies, O.; Backvall, J.-E. *Chem. Rev*. **2003**, *103*, 3247

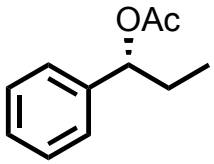
Combination Enzyme-Metal Catalysis - DKR of Alcohols/Diols



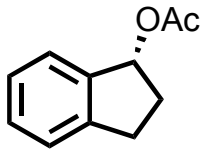
78-92% yield
91- >99% ee



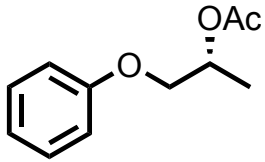
80%, >99% ee



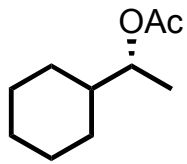
80%, 98% ee



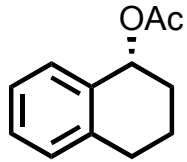
77%, >99% ee



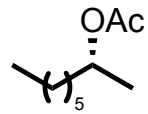
88%, >99% ee



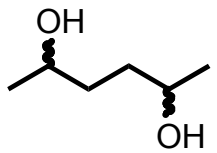
79%, >99% ee



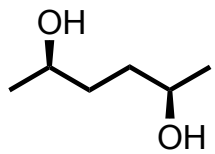
65%, >99% ee



90%, >97% ee



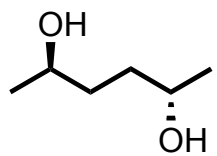
63%, >99% ee



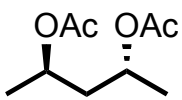
(*R,R*)-product

86 : 14

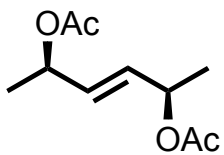
+



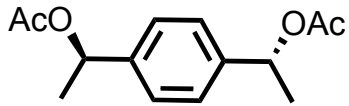
meso-product



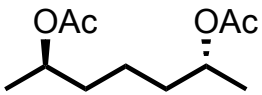
90%, >99% ee
(*R,R*:*meso*)
(*38:62*)



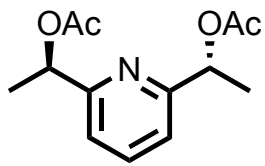
43%, >99% ee
(*74:26*)



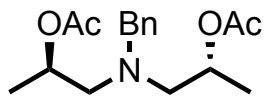
77%, >99% ee
(*98:2*)



63%, >97% ee
(*90:10*)



78%, >99% ee
(*100:0*)

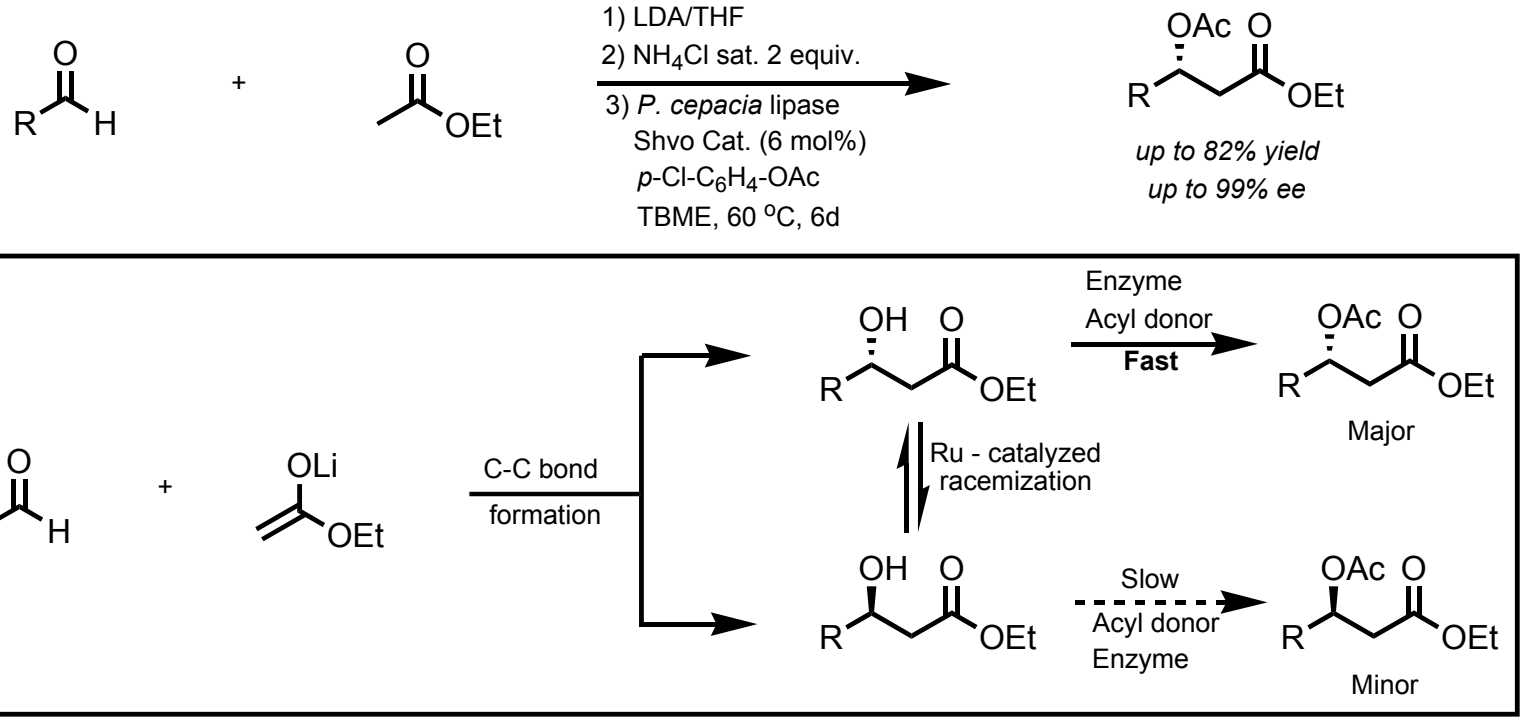


64%, >96% ee
(*89:11*)

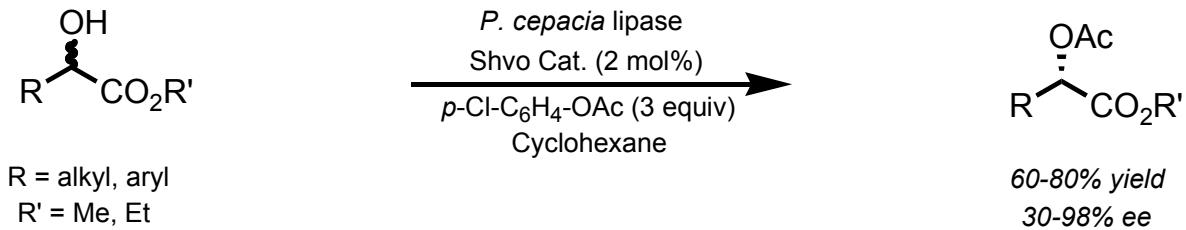
Pamies, O.; Backvall, J.-E. *Chem. Rev*. **2003**, *103*, 3247

Enzyme-Metal Catalysis - DKR of Hydroxy Acid Derivatives

- Tandem Aldol Reaction/DKR



- DKR of Racemic α-Hydroxy Esters

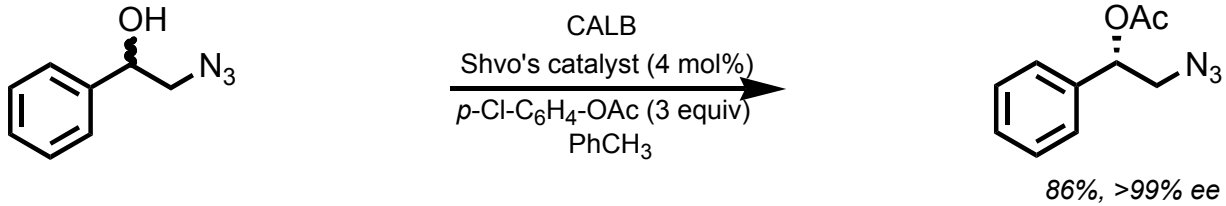


Huerta, F. F.; Bäckvall, J.-E. *Org. Lett.* **2001**, *3*, 1209

Pamies, O.; Bäckvall, J.-E. *Chem. Rev*. **2003**, *103*, 3247

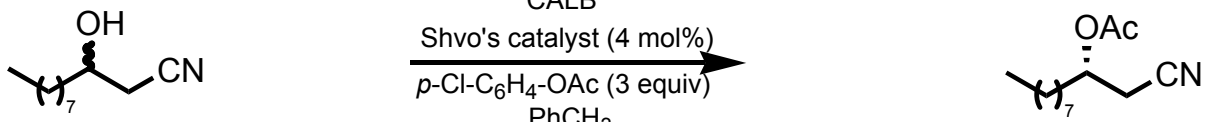
Enzyme-Metal Catalysis - Other Alcohol DKRs

- Azido Alcohols



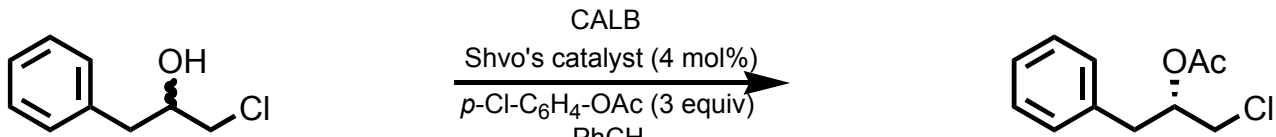
86%, >99% ee

- Hydroxy Nitriles



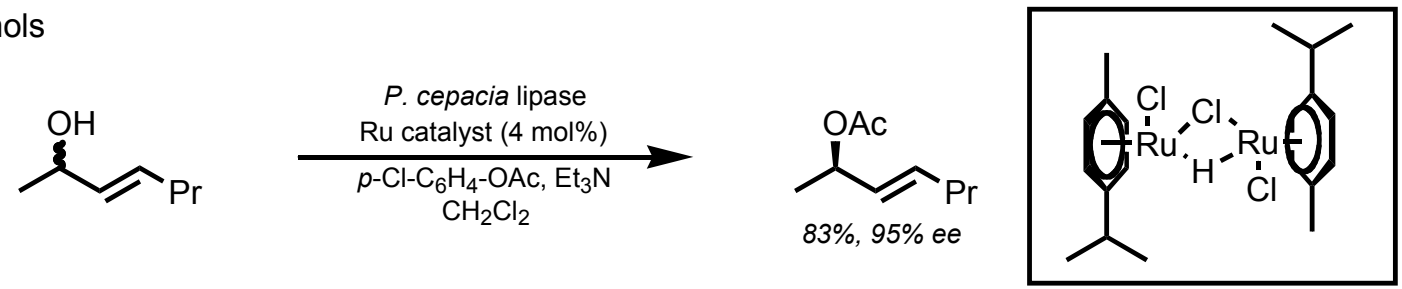
93%, 92% ee

- Halo Alcohols



74%, 91% ee

- Allylic Alcohols

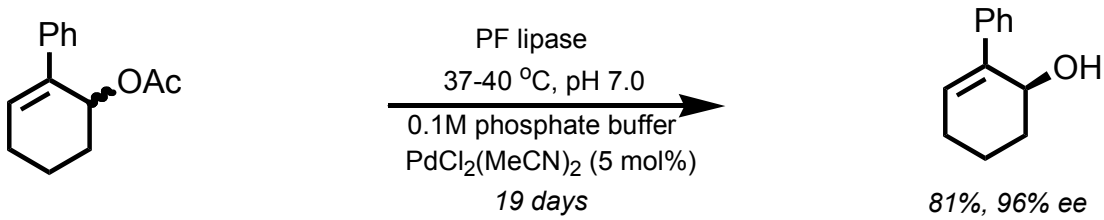


83%, 95% ee

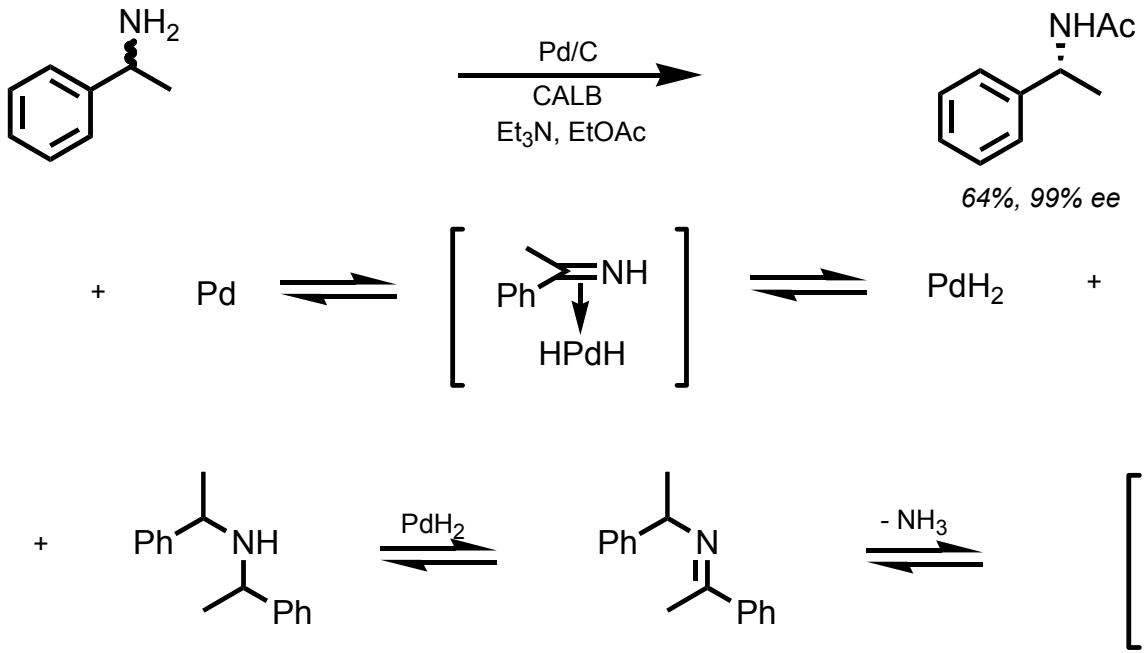
Pamies, O.; Bäckvall, J.-E. *Chem. Rev*. **2003**, *103*, 3247

Enzyme-Metal Catalysis Utilizing Palladium

- DKR of Allylic Acetates



- DKR of Amines



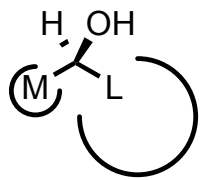
Pamies, O.; Bäckvall, J.-E. *Chem. Rev*. **2003**, *103*, 3247

Challenges w/Enzymatic DKR

Question: Why use anything other than enzymatic systems with DKR?

Answer: There are currently a number of serious drawbacks towards applications of this technology.

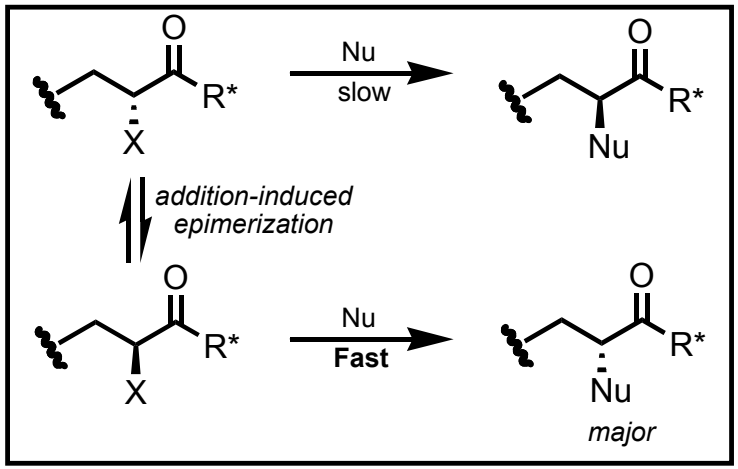
- Since enzymes and chemical catalysts usually work in different environments, their combination in a one-pot transformation in far from straightforward.
- For instance, with lipase catalyzed DKRs with transition-metal catalysts, solvents, metal, acyl donor, and temperature all need to be optimized.
- The necessary chiral recognition by enzymes can place significant constraints on substrate scope.



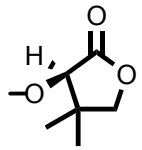
- Finally, the achilles' heel: in many cases only one enantiomer is accessible.

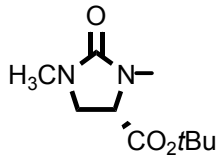
Potential Solution: Enzyme-free DKR!

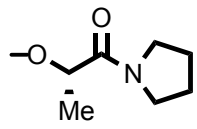
Using Chiral Auxiliaries in DKR

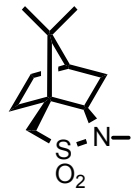


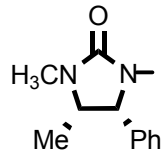
R* =

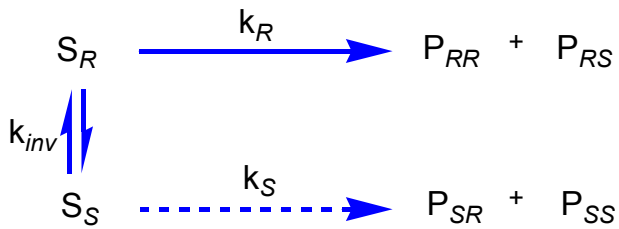

Durst

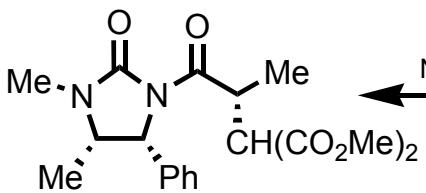

Nunami


Devine

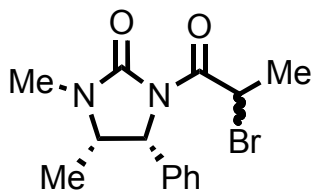

Ward


Caddick & Jenkins

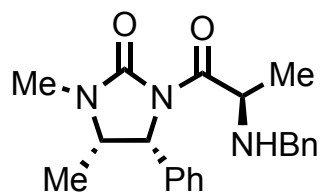



78%, 40-60% de

$NaCH(CO_2Me)_2$
TBAI
THF

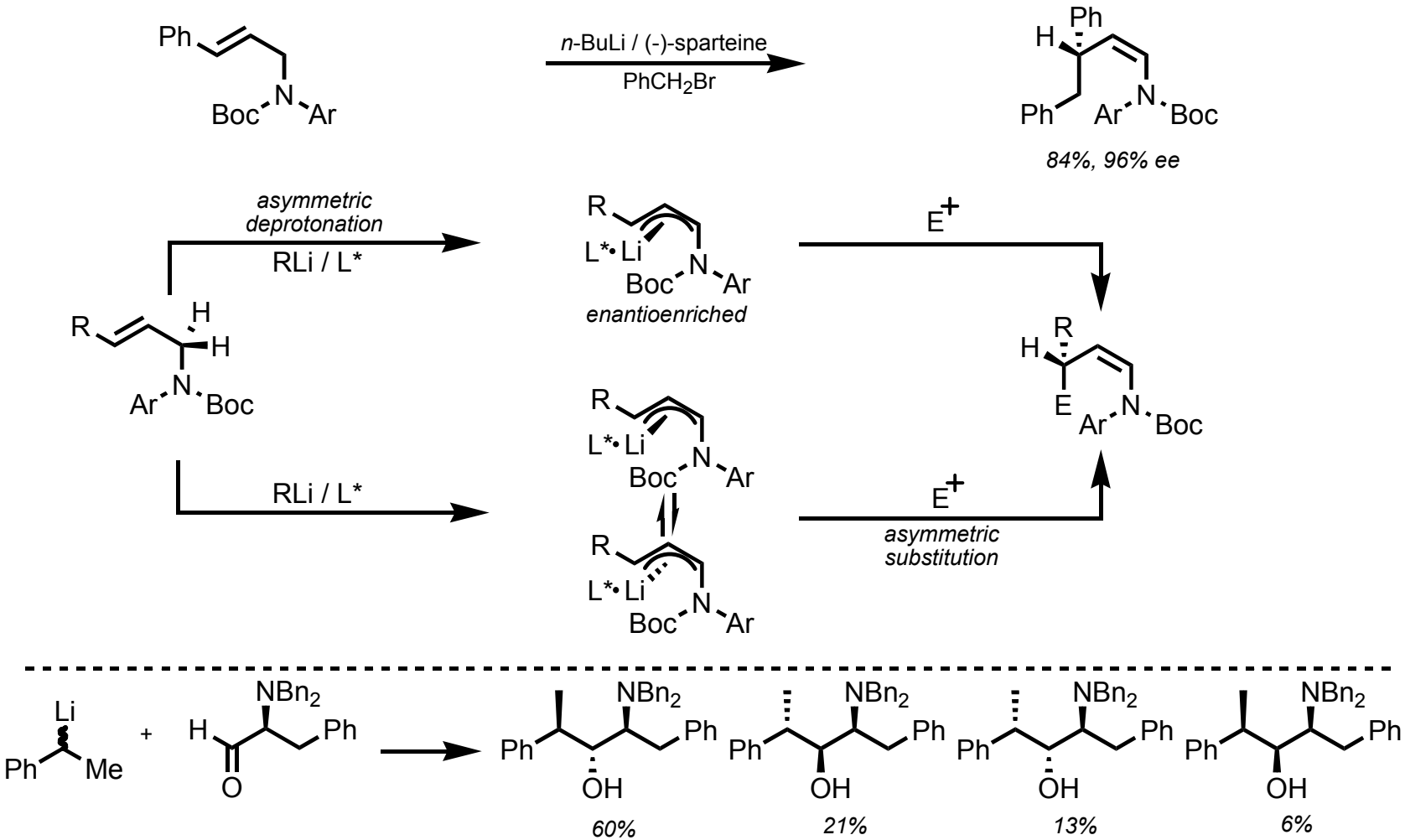


$BnNH_2$
TBAI
Et_3N / THF


100%, 74% de

Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Gil Santos, A.; Treweeke, N.; Weaving, R. *Tetrahedron* **2001**, *57*, 6589

DKR Utilizing Configurationally Labile Anions

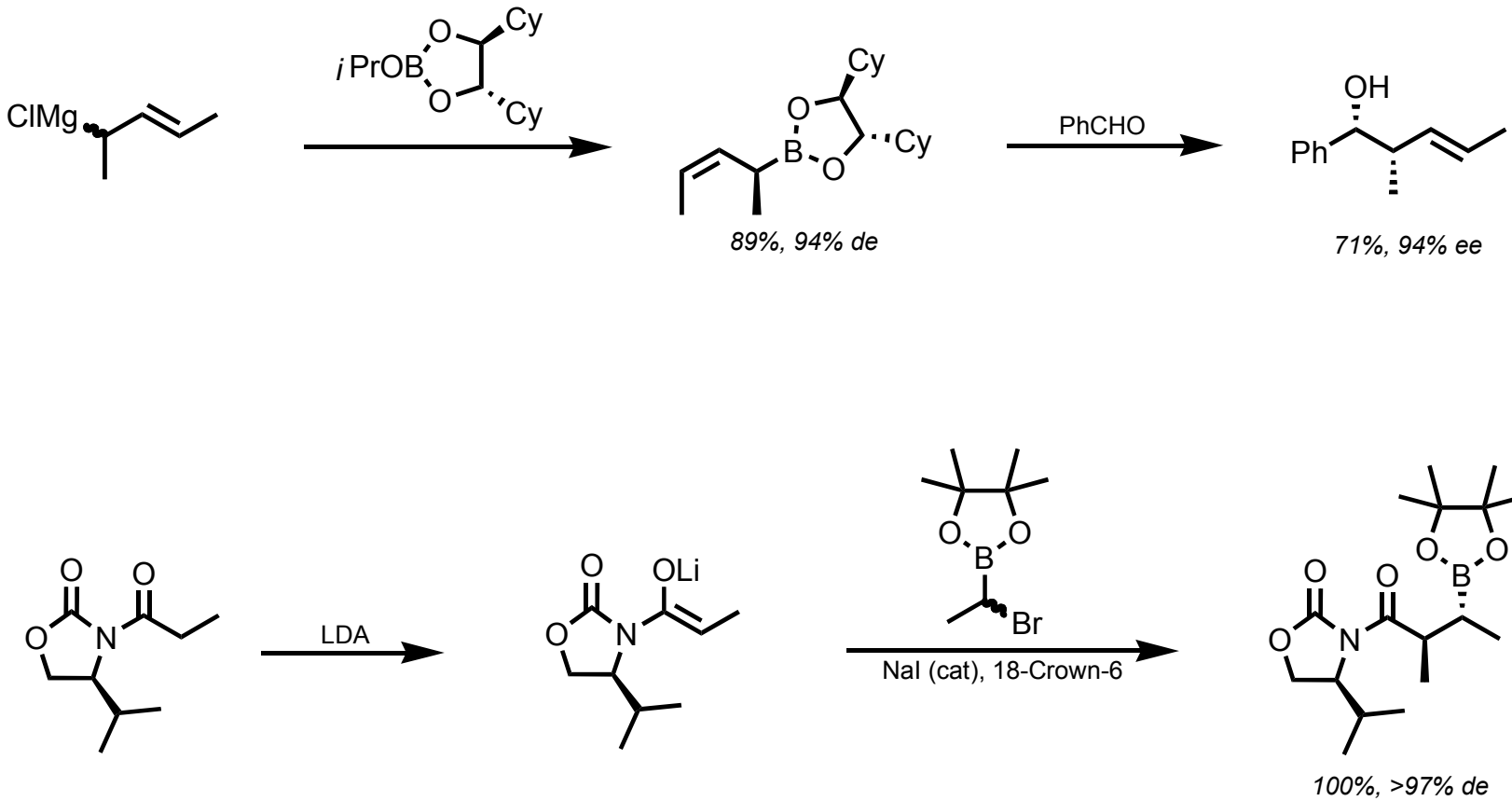


- Ratio of products identical with racemic or enatiomerically pure electrophile

Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522

Hoffmann, R. W.; Ruhl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* **1992**, 719

DKR with Boron Electrophiles

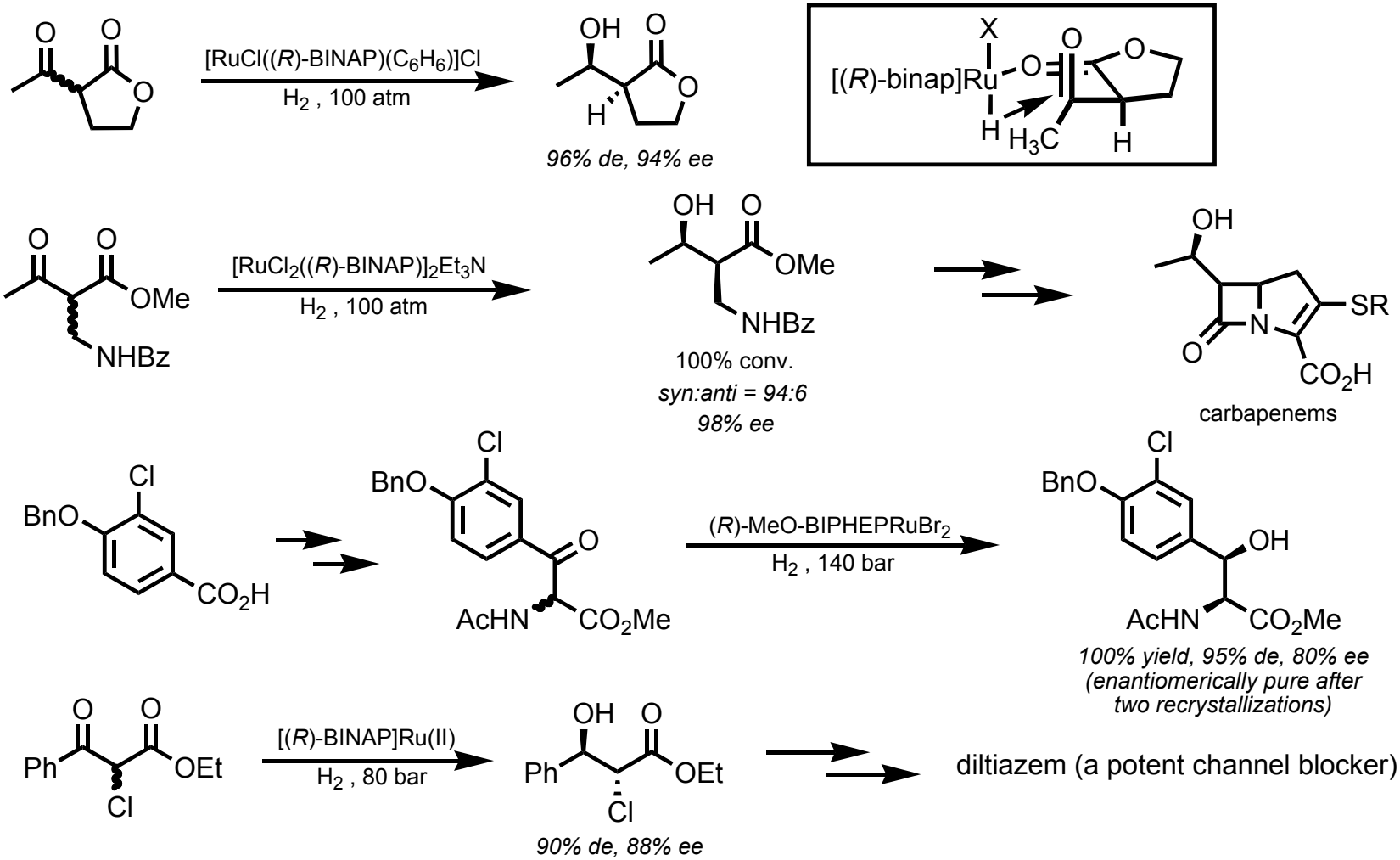


Sturmer, R. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 59

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

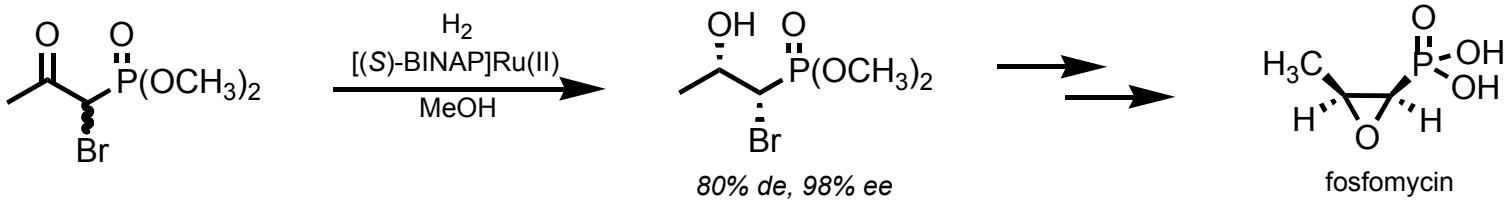
Ruthenium-Catalyzed Hydrogenation of β-Ketoesters

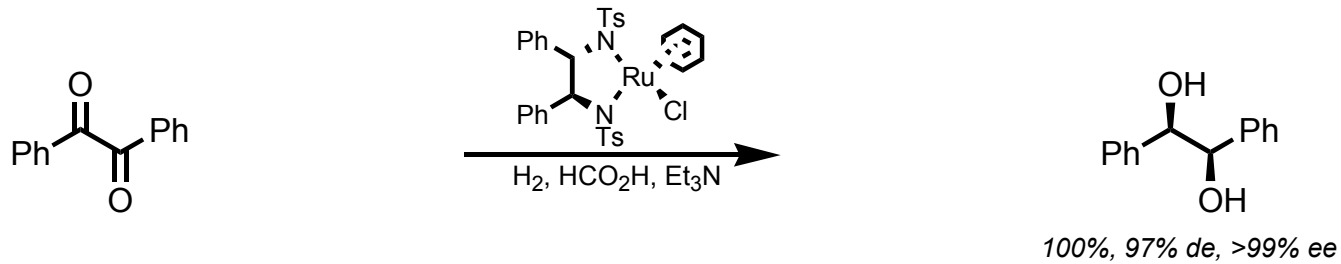
- Ru-catalyzed DKR has been developed into a powerful transformation of very broad scope

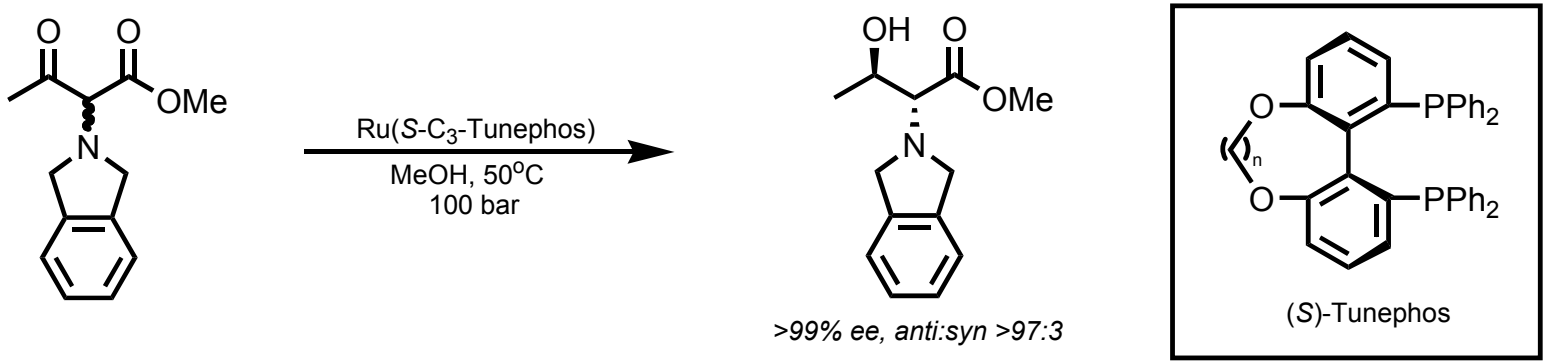


Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995** *68*, 36

Ruthenium-Catalyzed Hydrogenations (Cont'd)



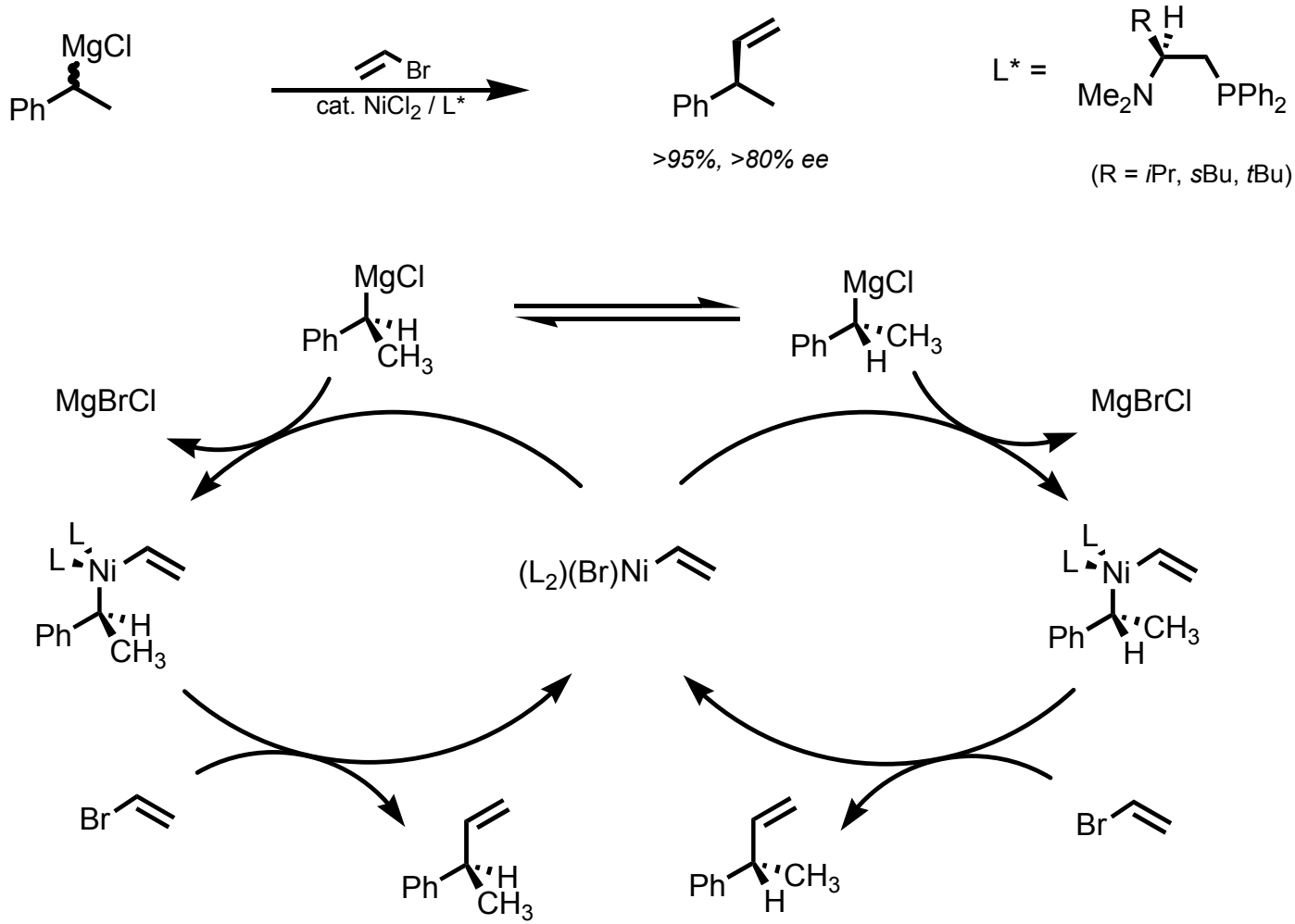




Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995** *68*, 36

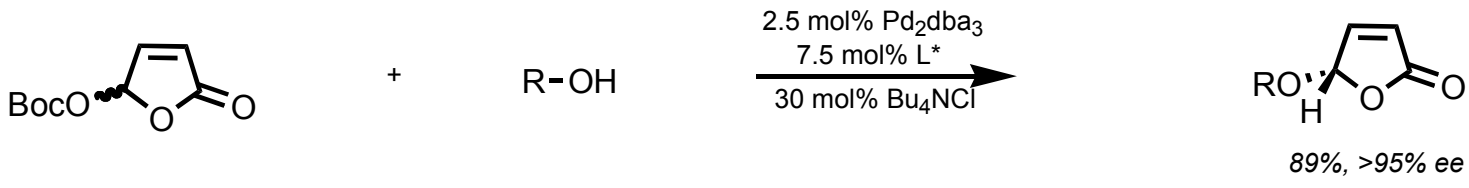
Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004** *126*, 1626

DKR via Cross-Coupling

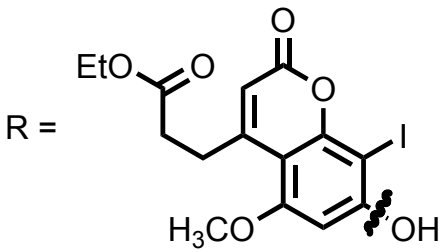


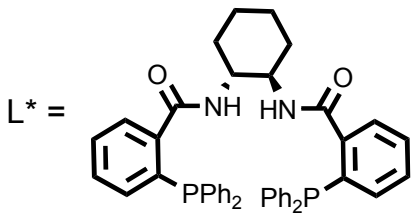
Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475

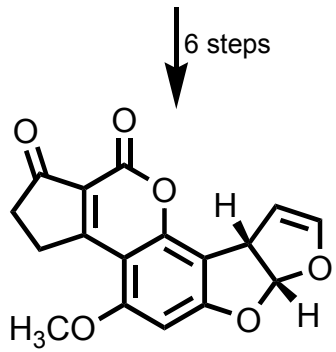
DKR *via* Pd-Catalyzed Allylic Substitution



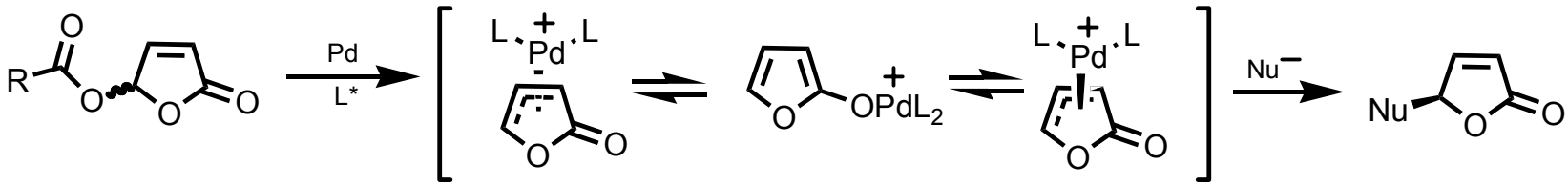
89%, >95% ee







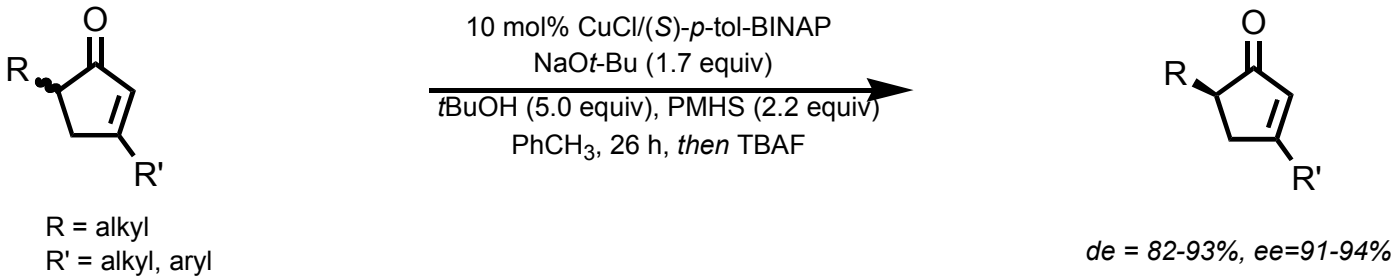
Aflatoxin B

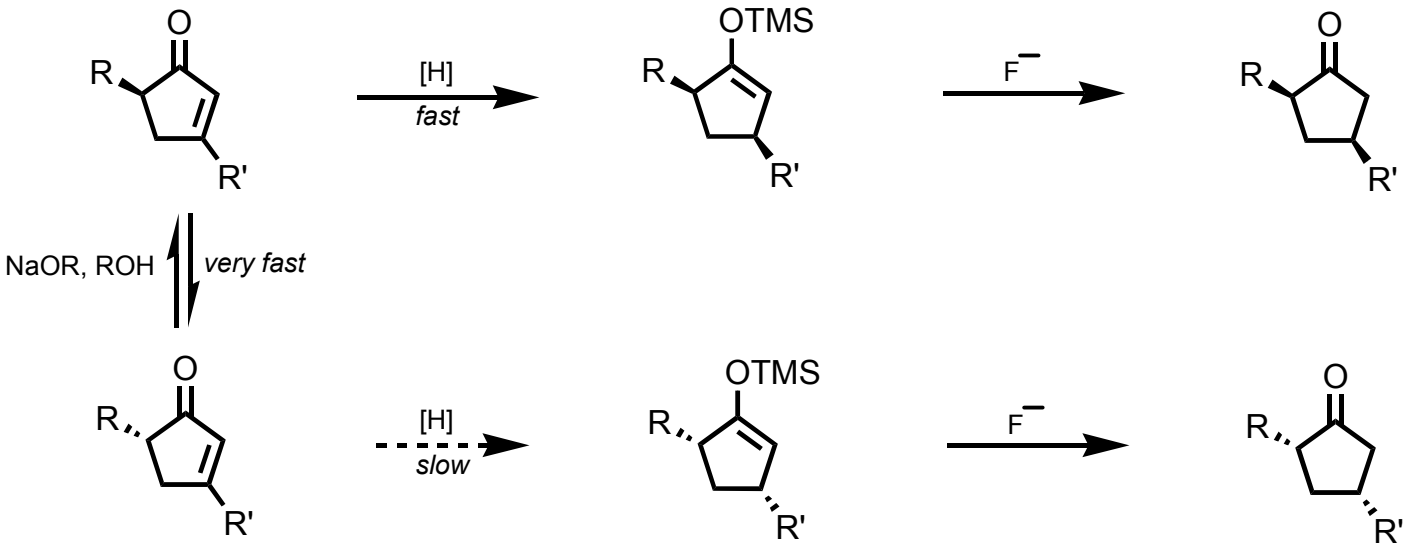


racemization via η^3-η^1 complexes

Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543

DKR *via* Asymmetric Conjugate Reduction

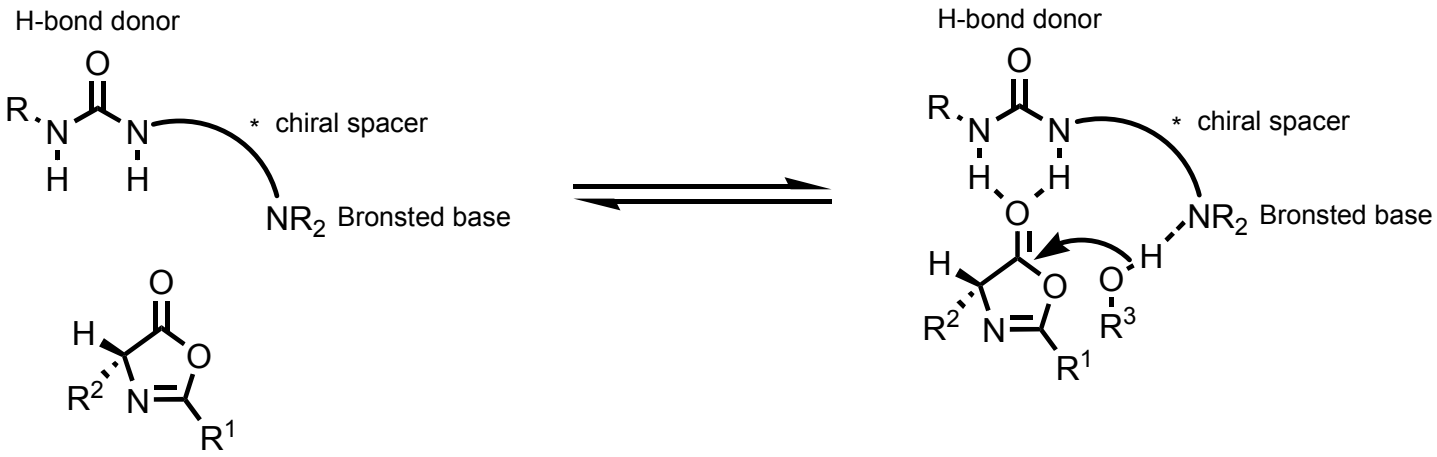


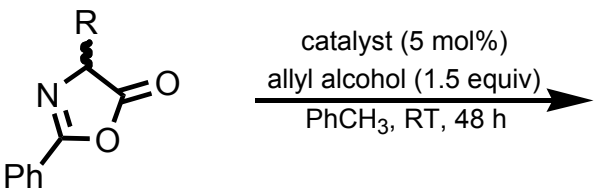


Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892

DKR Utilizing Organocatalysts

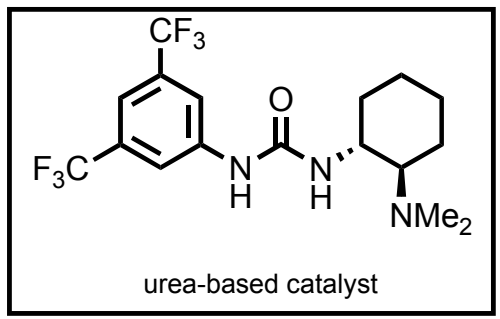
- DKR of azlactones using urea-based bifunctional organocatalysts





R = $PhCH_2$, Me, *i*Pr, *i*Bu, *t*Bu, Ph

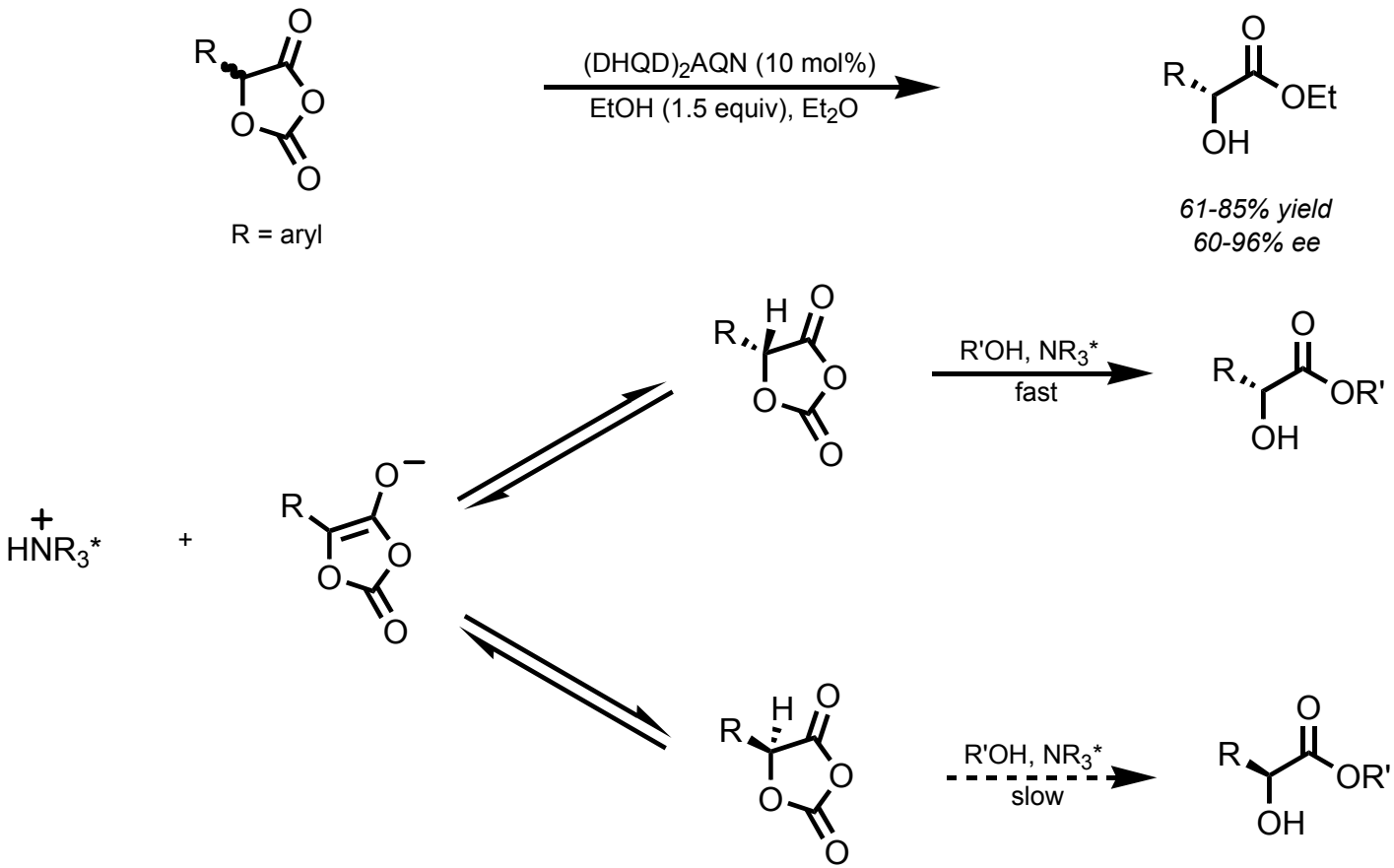
43-96% conversion, 72-87% ee



Berkessel, A.; Cleemann, F.; Mukherjee, S.; Muller, T. N.; Lex, J. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 807

DKR Utilizing Organocatalysts

- Asymmetric Synthesis of α-Hydroxy Carboxylic Acids



- Racemization rate with R=alkyl was too slow to allow for efficient DKR

Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870