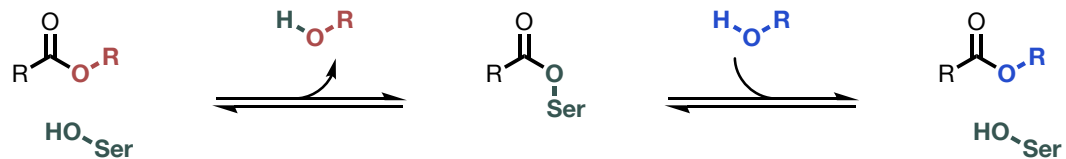
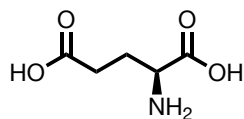


Lipase Overview

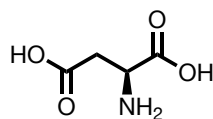


Lipases catalyze a broad range of transacylation reactions (hydrolysis, esterification, transesterification, amidation, transamidation, etc.)

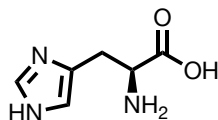


glutamic acid

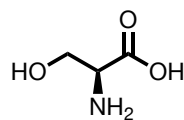
or



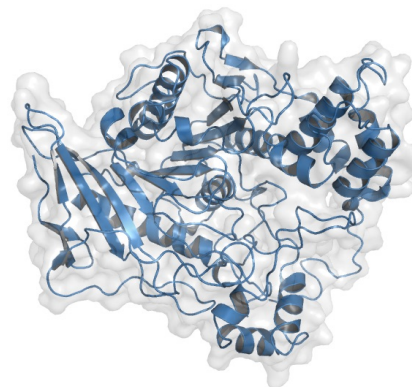
aspartic acid



histidine



serine

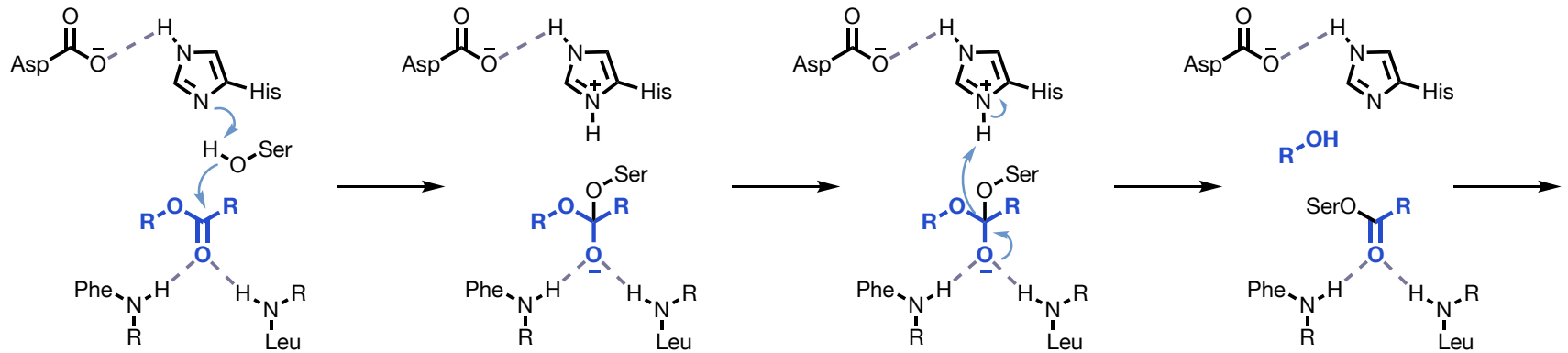


glycosylated pancreatic lipase

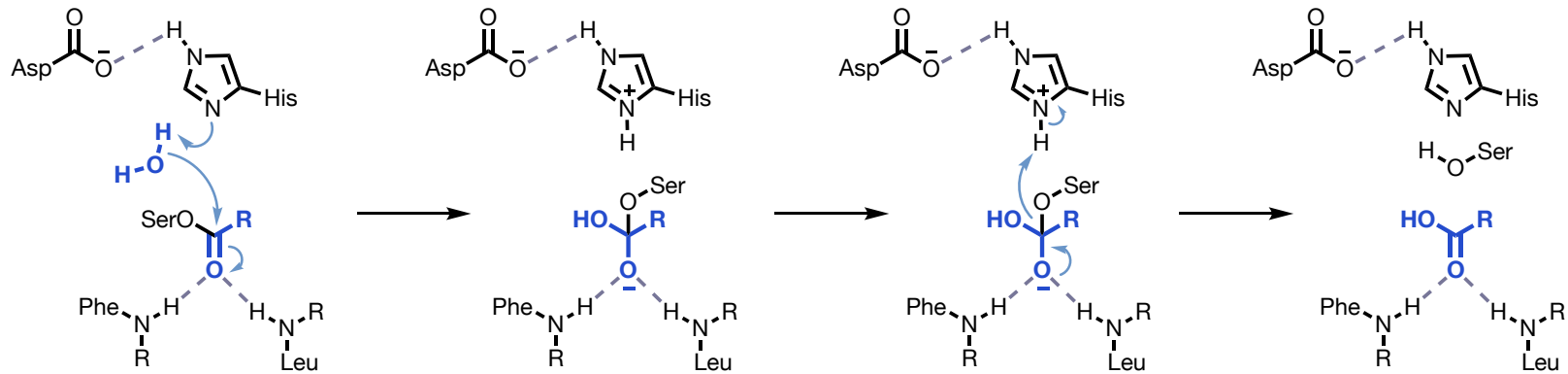
lipase reactions are mediated by a catalytic triad

Lipase Mechanism

attachment of acyl acceptor to serine residue

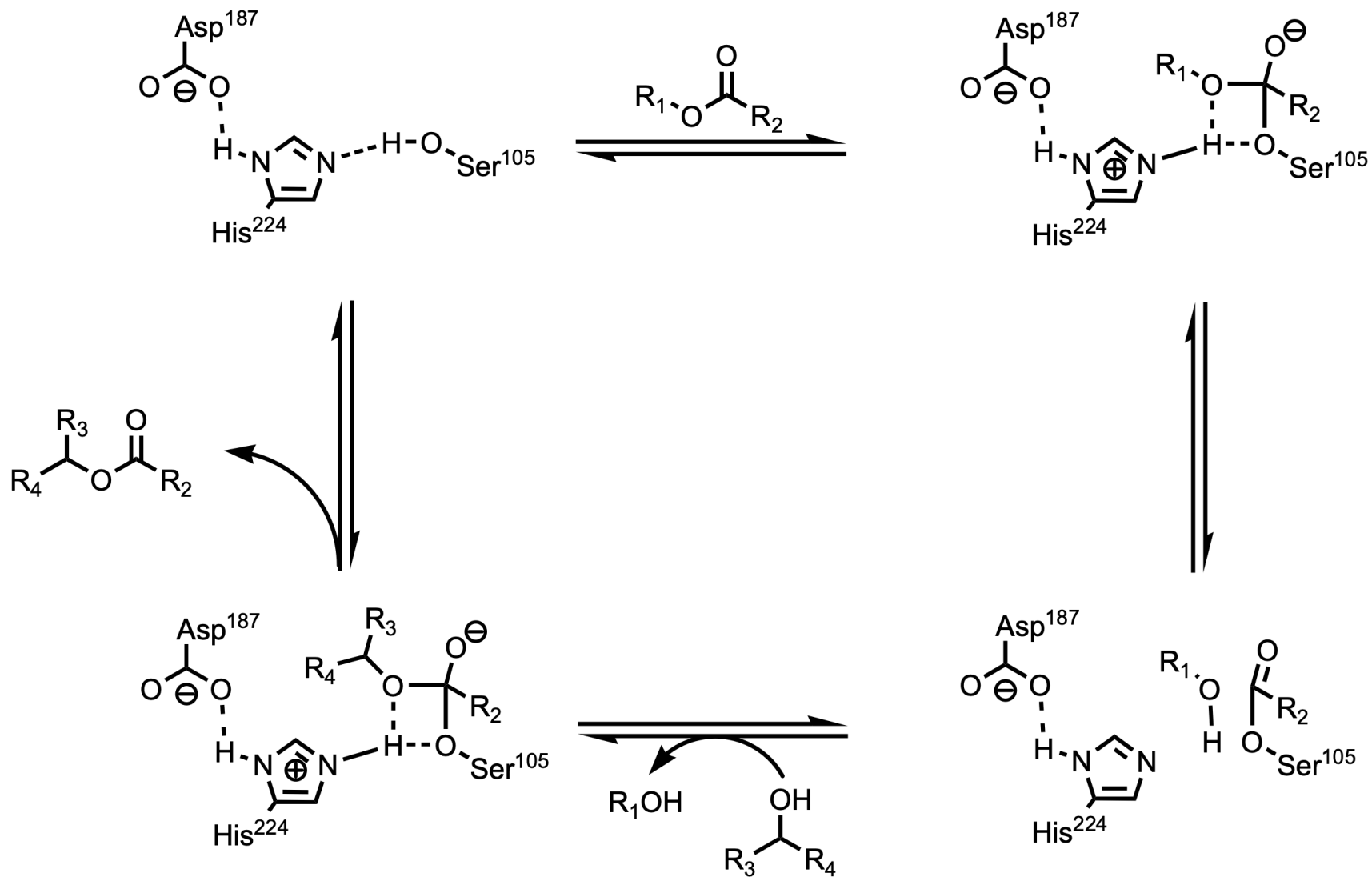


introduction of donor (nucleophile)

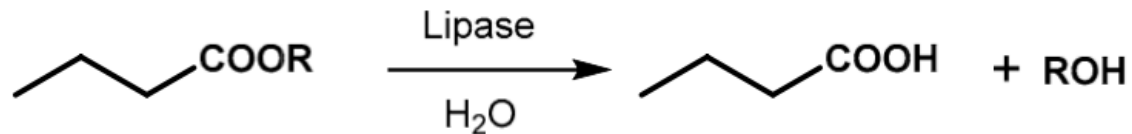


a sophisticated network of acid-base chemistry for transacylation reactions!

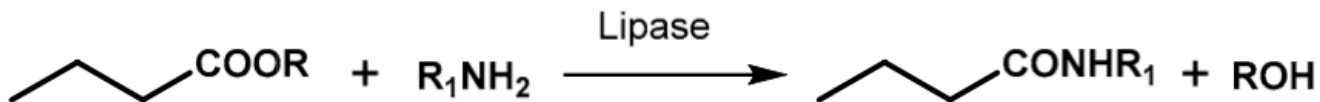
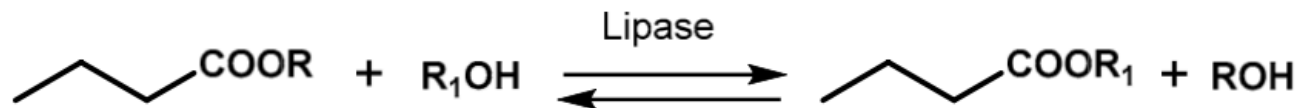
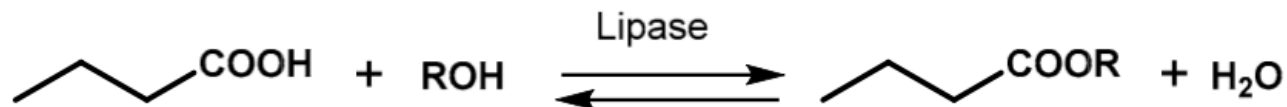
Lipase Mechanism: Abbreviated



General Representation of Lipase-Catalyzed Reactions



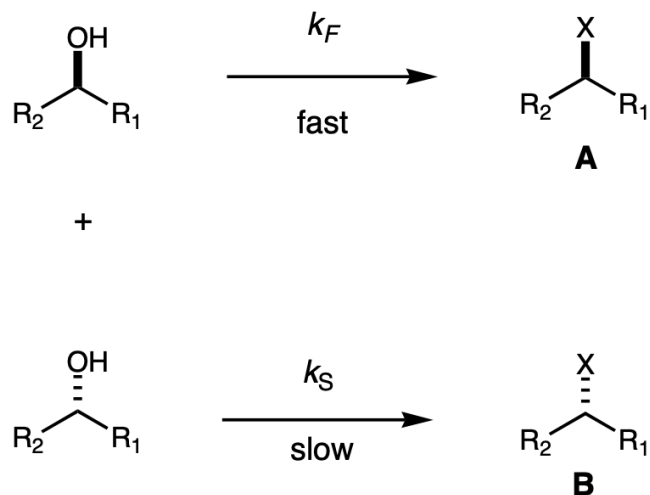
Aqueous medium



Organic solvent

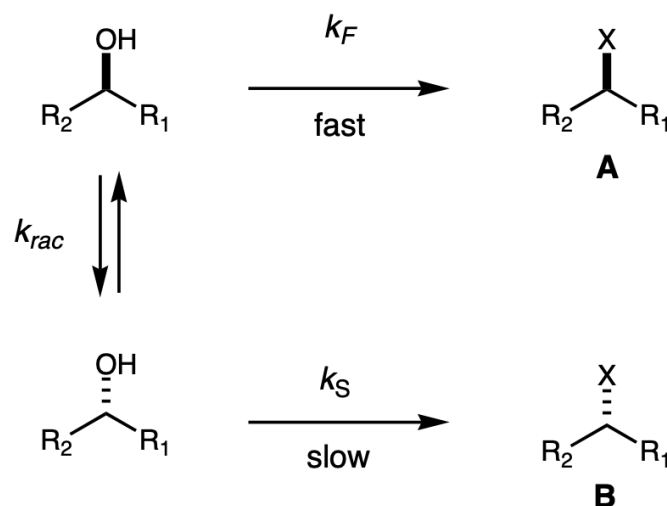
General Asymmetric Reaction Types for Biocatalysts: Lipase Edition

■ Kinetic Resolution



50% theoretical yield of **A**

■ Dynamic Kinetic Resolution

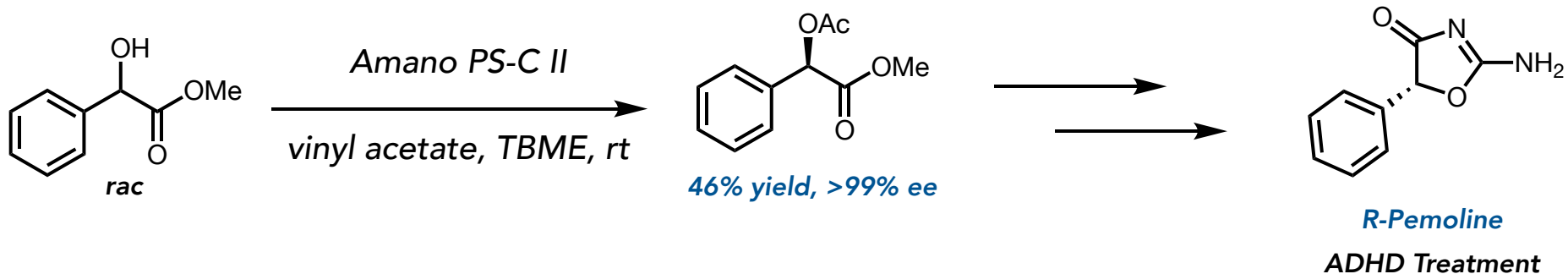


If $k_{rac} > k_F \gg k_S$ 100% theoretical yield of **A**

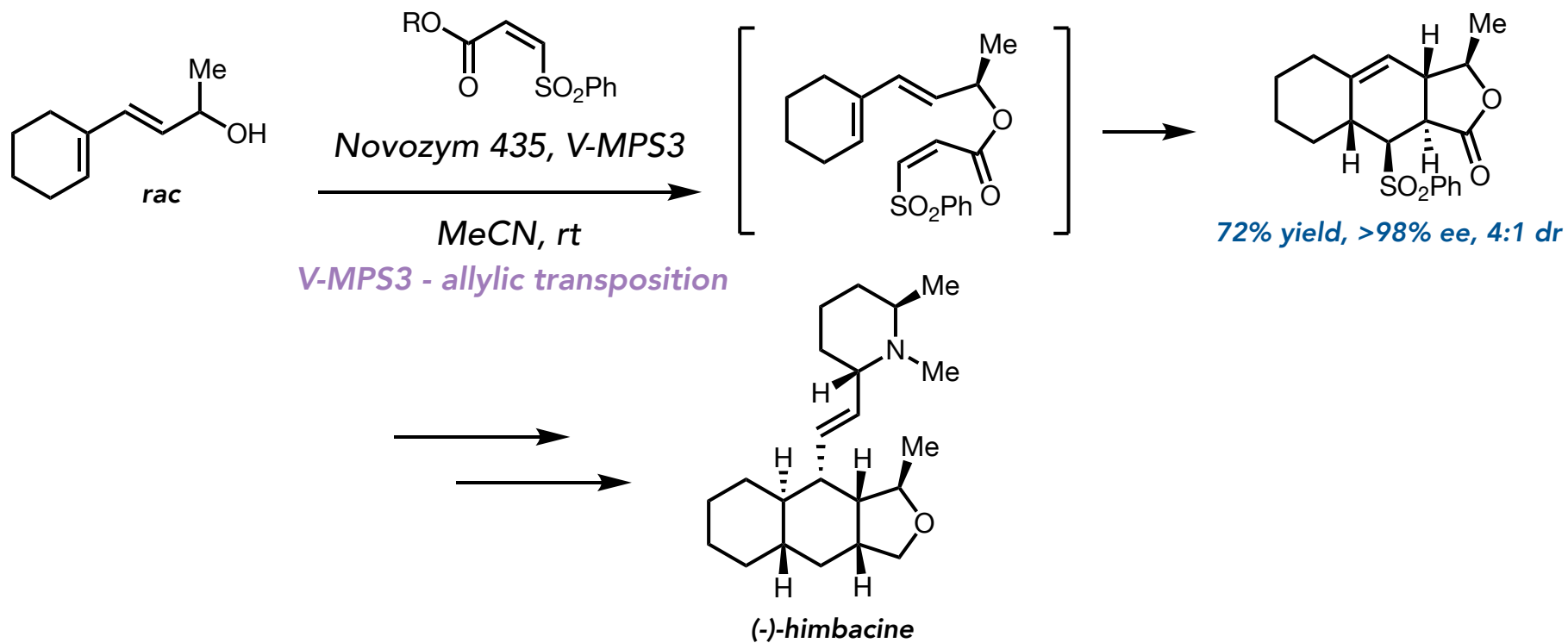
- In a DKR, as with a classical KR, one enantiomer reacts slowly under the reaction conditions
- In a DKR, the rate of racemization of SM is fast relative the rate of the asymmetric transformation
- Thus, using DKR, possible to convert 100% of racemic SM to enantiopure product due to equilibrating racemization of SM

Select Examples of Kinetic and Dynamic Kinetic Resolutions

Lipase-Mediated Kinetic Resolution



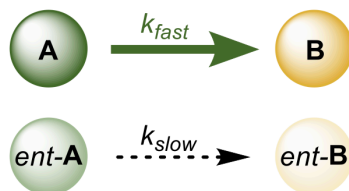
Lipase-Controlled Chemoenzymatic Dynamic Kinetic Resolution



The Selectivity Factor for Enzyme-Mediated Resolution: E-Value


The **E-Value** is a dimensionless value that provides a benchmark for resolution selectivity

- a ratio of the relative (second order) rate constants of enantiomers ($E = k_{fast}/k_{slow}$) that remains constant throughout the reaction, depending on the environment of the system (substrate, enzyme, solvent, pH, etc)



A, ent-A: substrate enantiomers

B, ent-B: product enantiomers

 : fast (preferred) reaction, (enzyme)-catalyzed

 : slow (not preferred) reaction, (enzyme)-catalyzed

The dependence of the enantioselectivity and the conversion of the reaction is

for the product:

$$E = \frac{\ln [1-c (1+e.e._p)]}{\ln [1-c (1-e.e._p)]}$$

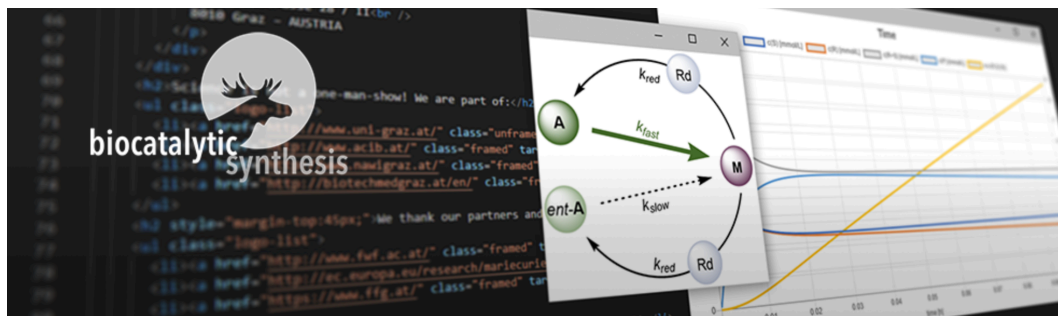
for the substrate:

$$E = \frac{\ln [(1-c) (1-e.e._s)]}{\ln [(1-c) (1+e.e._s)]}$$

c = conversion, $e.e._s$, $e.e._p$ = enantiomeric excess of substrate (S, i.e. **A** + **ent-A**) and product (P, i.e. **B** + **ent-B**); E = Enantiomeric Ratio [8].

the higher the E-Value, the more selective the resolution under the chosen set of conditions

Resource Alert: Biocatalytic Synthesis (Uni Graz): E-Factor Calculator



← Biocatalysis Tools



A, ent-A: substrate enantiomers
B, ent-B: product enantiomers

—→ : fast (preferred) reaction, (enzyme)-catalyzed
- - - - -> : slow (not preferred reaction), (enzyme)-catalyzed

This program can be used for the calculation of the selectivity of a kinetic resolution of a racemate, expressed as the “Enantiomeric Ratio” – the E-value (synonym for the selectivity “s”). The calculations are valid for irreversible reactions.

More detailed information on the theoretical background and of the merits and limits of the method is described in the [help-file](#) or in K. Faber, *Biotransformations in Organic Chemistry*, 7th edition, Springer, Heidelberg, 2018, pp. 39-43. Detailed literature can be found here: *Preparative Biotransformations*, S. M. Roberts (Ed.), Wiley, 1995, pp. 75-76; *Enzyme Microb. Technol.*, 1997, 21, pp 559-571.

Any suggestions and comments for improvements, corrections, desired additional features or hard- and software incompatibilities are highly welcome.

Further information:

- The numbers that are entered need to be between 1.0 and 99.9.
- If e.e. (Product) and Conversion are used to calculate the E-value, the Conversion must be greater than or equal to 30%. If e.e. (Substrate) and Conversion are used to calculate the E-value, the Conversion must be less than or equal to 70% to obtain meaningful E-values.
- If the calculated E-value is greater than 200 the result states “>200” due to the limits of the accuracy of the method.

input data:

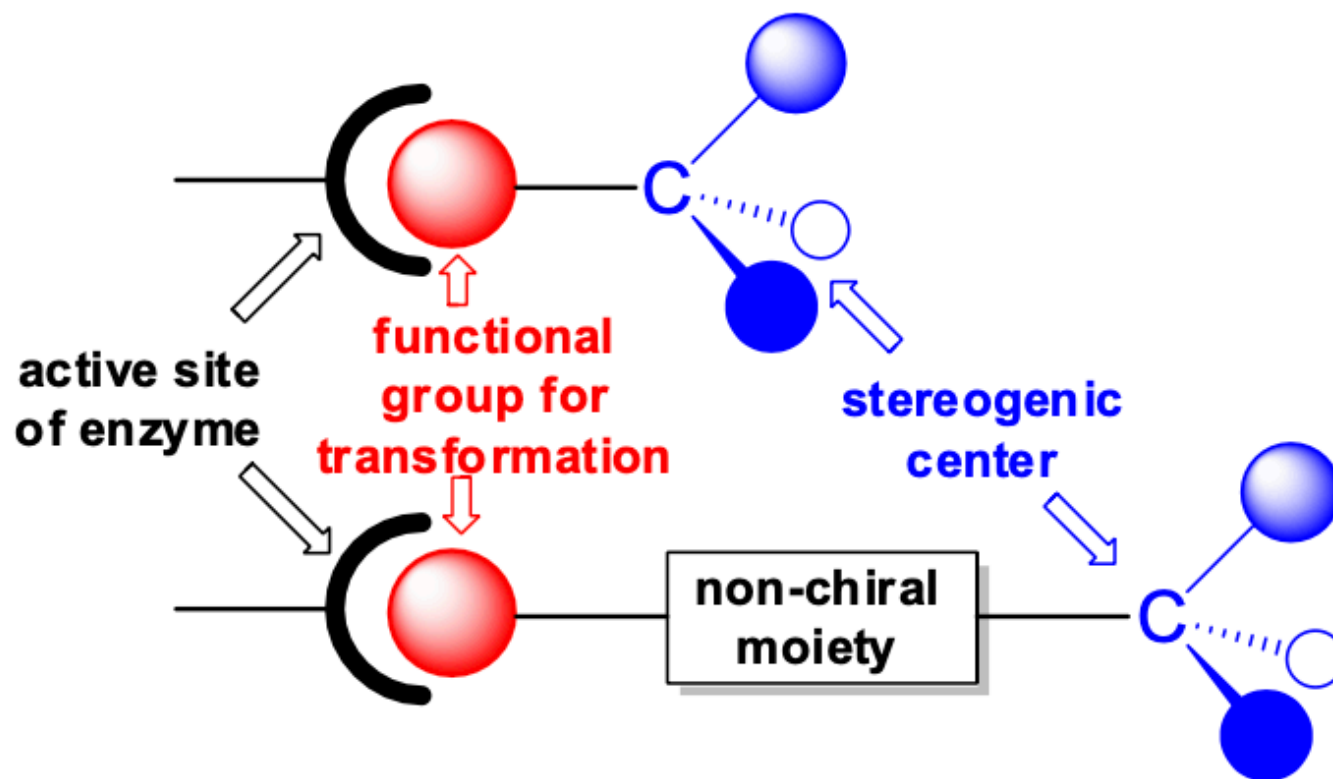
e.e. Product [%]

e.e. Substrate [%]

conversion [%]

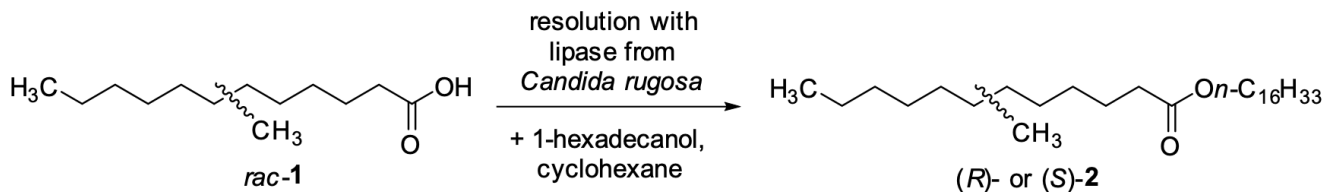
Lipase-Mediated Kinetic Resolution of Remote Stereocenters

small molecule asymmetric catalyst systems control stereoselectivity close to the reactive site

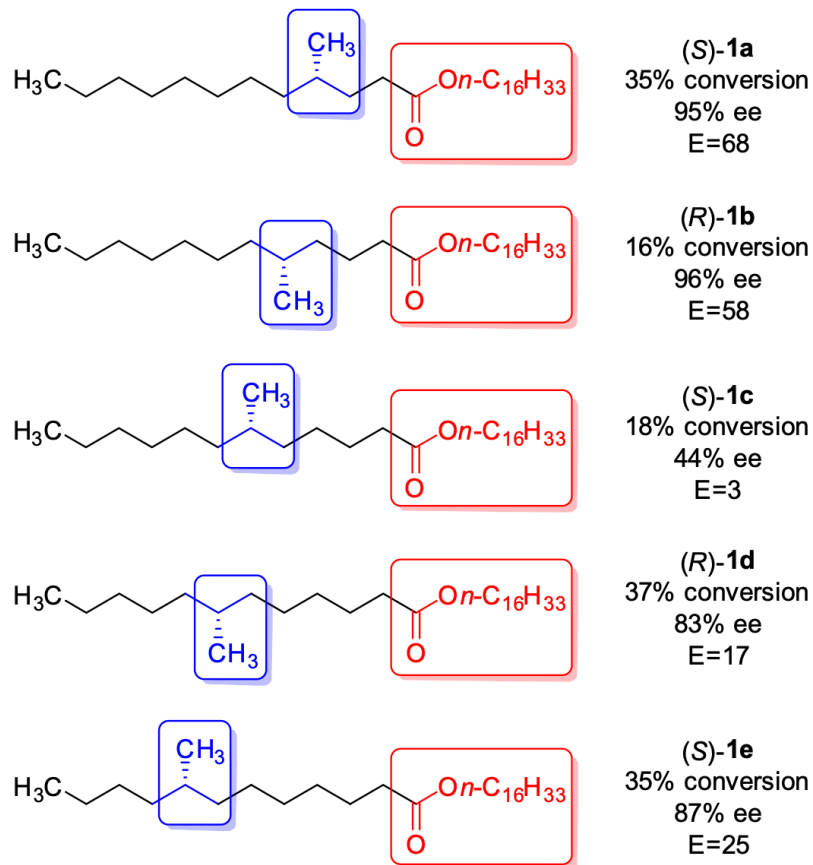


enzymes uniquely differentiate stereocenters at remote sites relative to the reactive functional group

Kinetic Resolution of Dodecanoic Acids

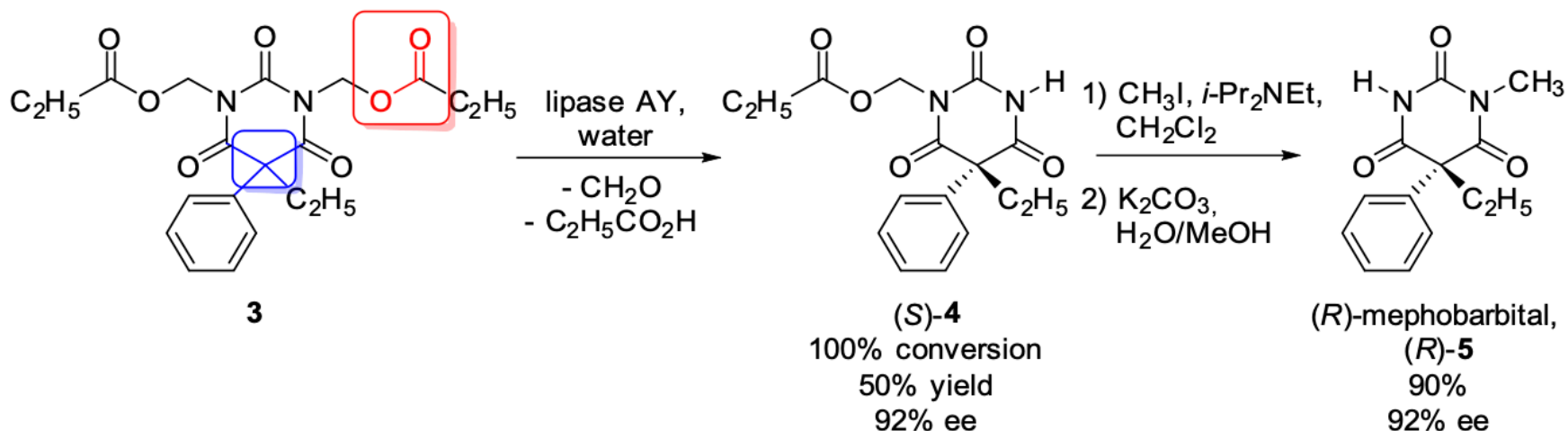


Selected examples

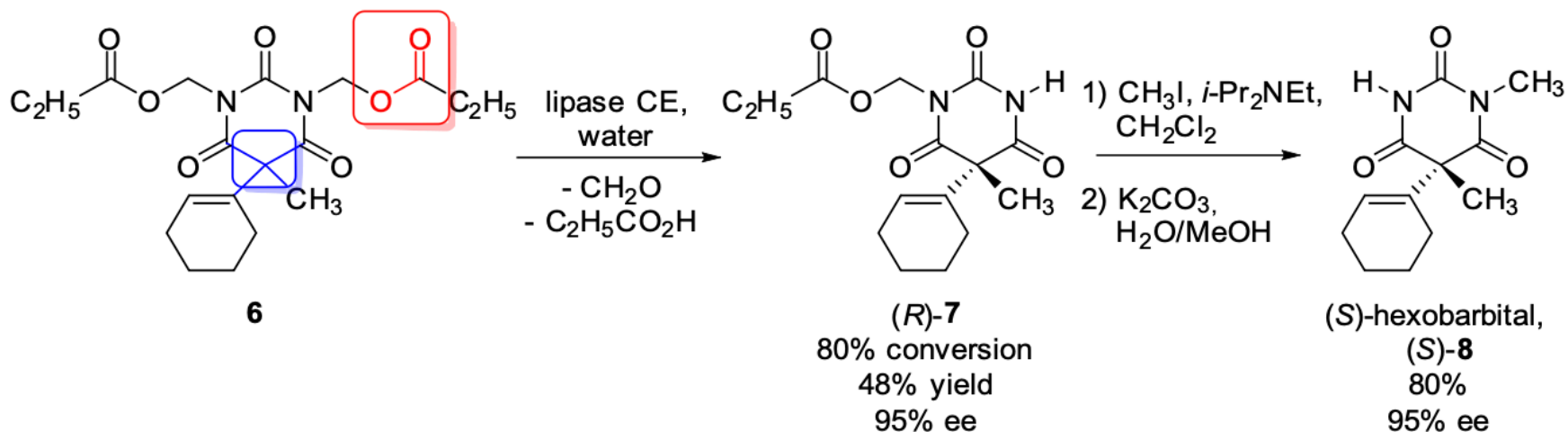


Kinetic Resolution of Barbiturates

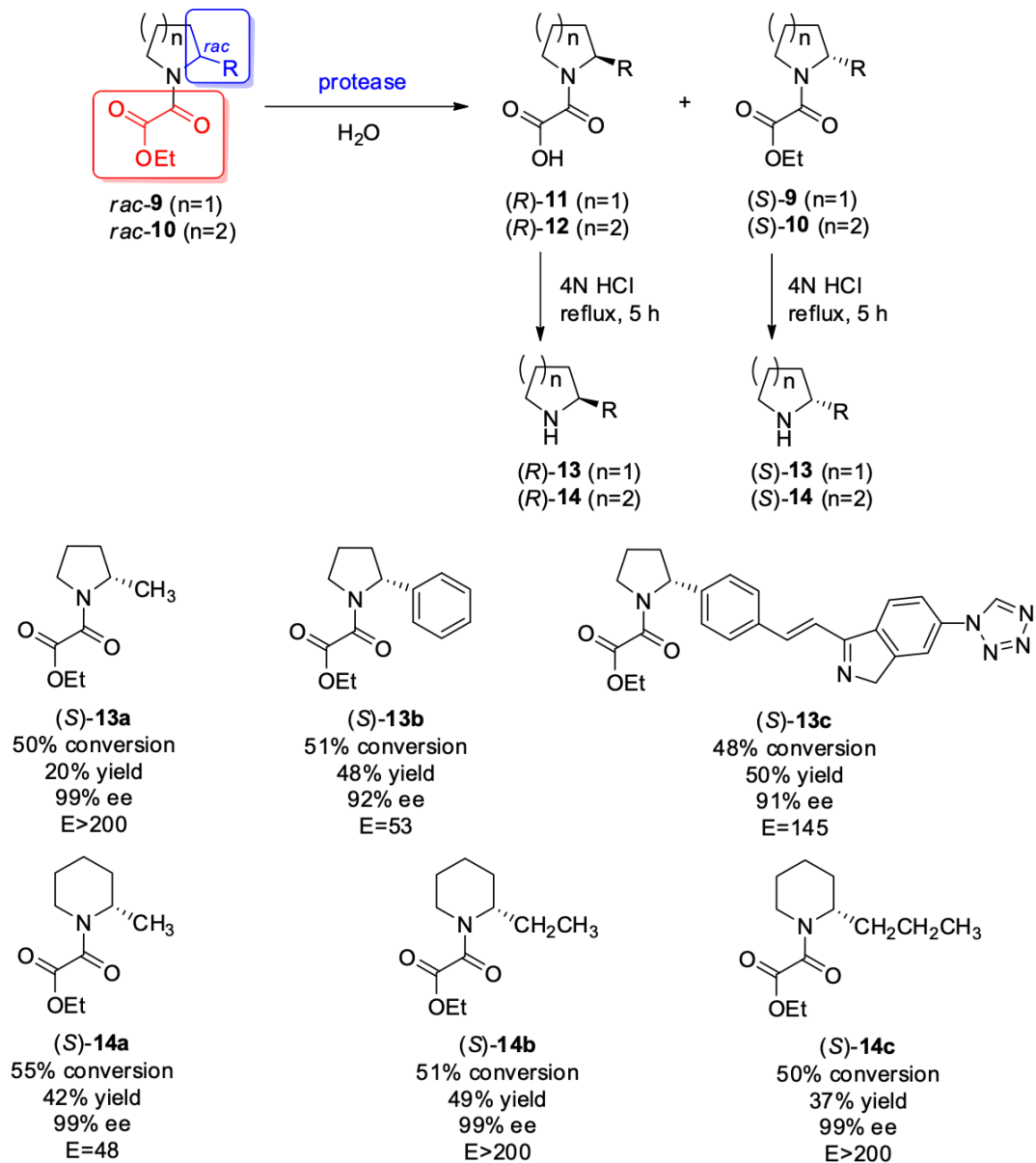
equation (1):



equation (2):

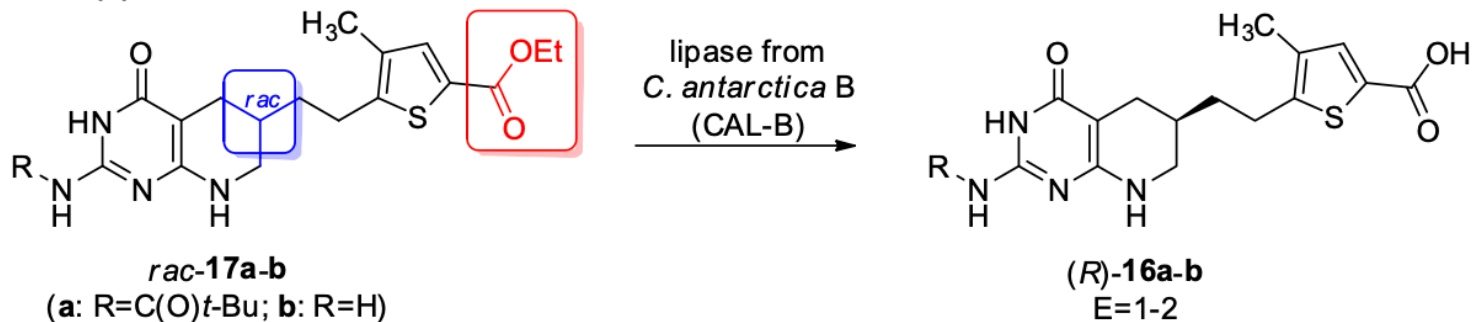


Kinetic Resolution of Oxalamic Esters

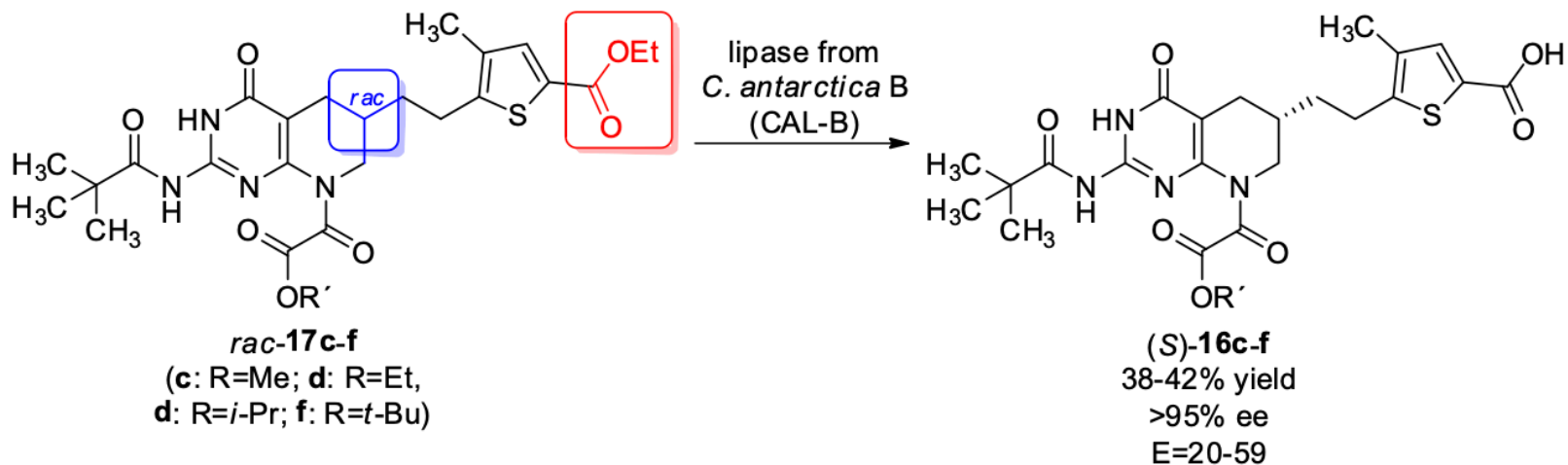


Kinetic Resolution Toward Production of Anticancer Agent Pelitrexol (Pfizer)

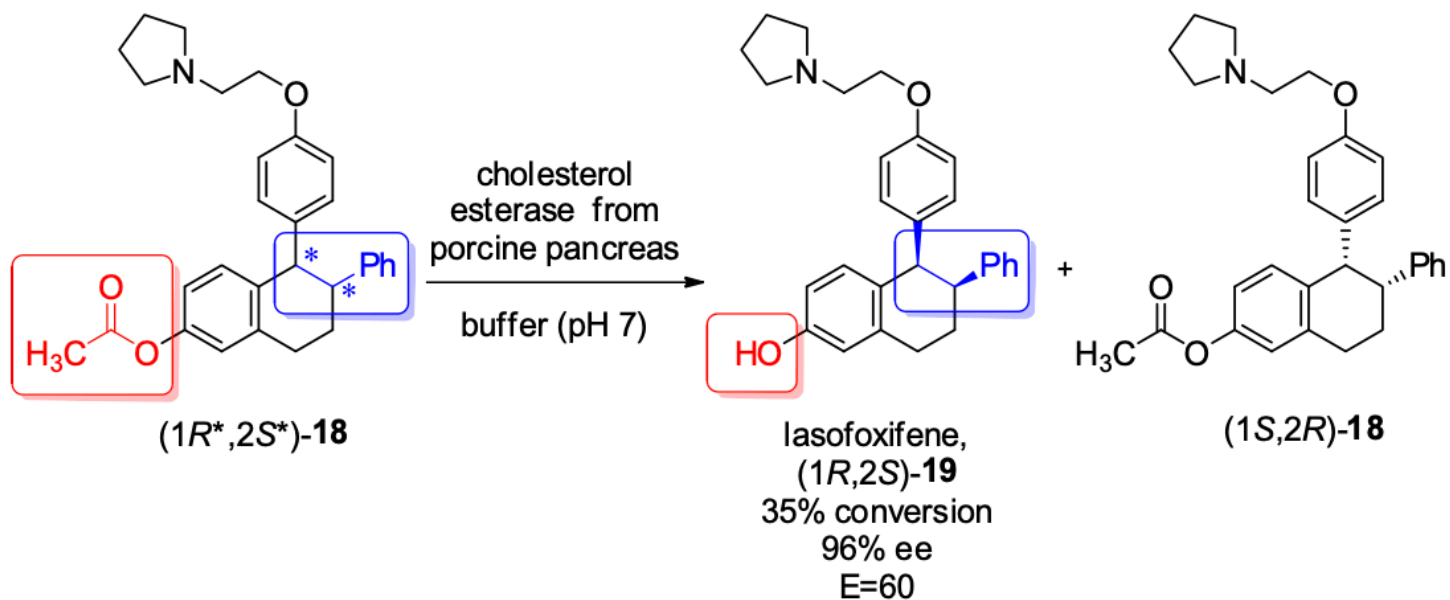
equation (1):



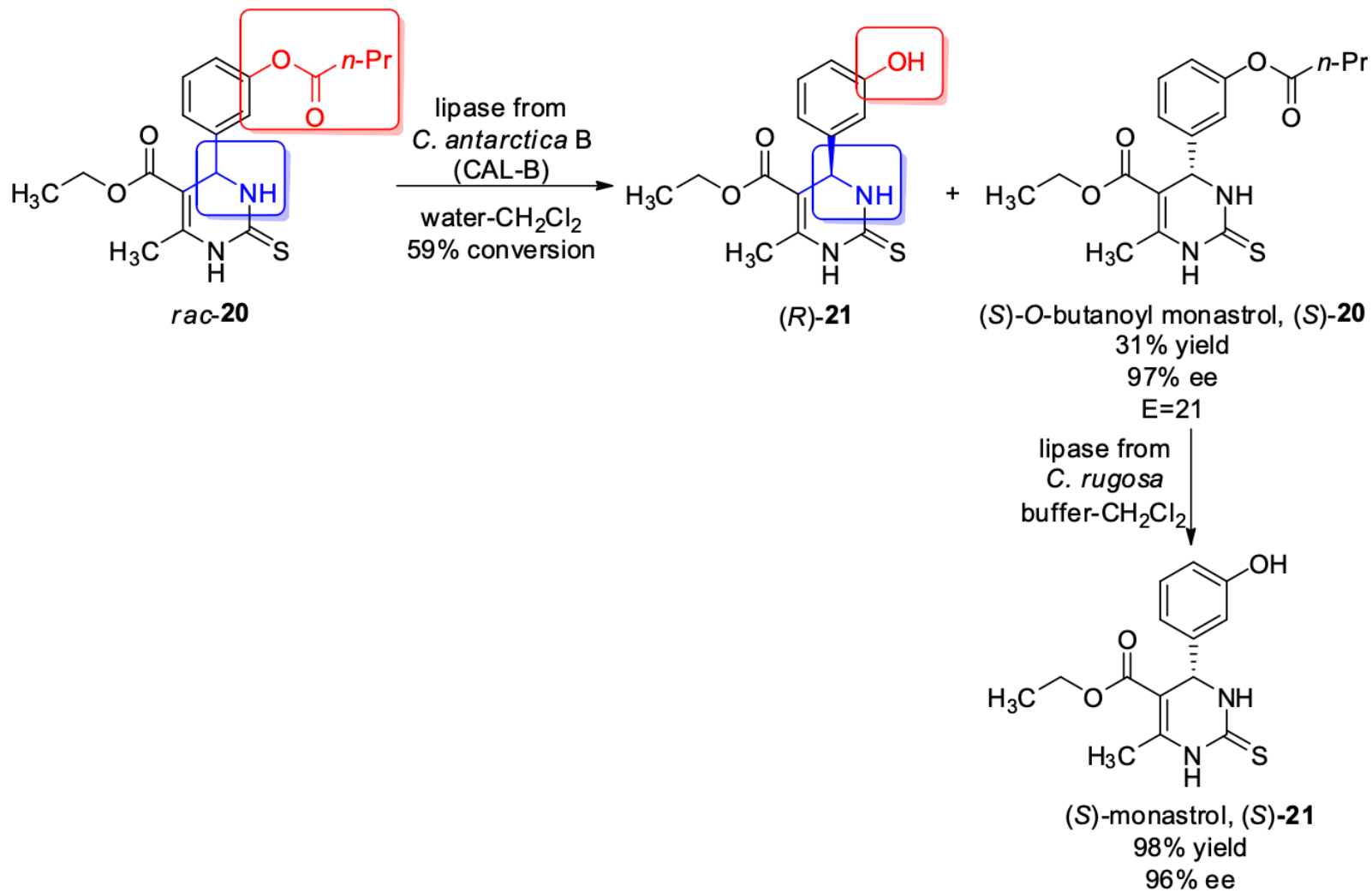
equation (2):



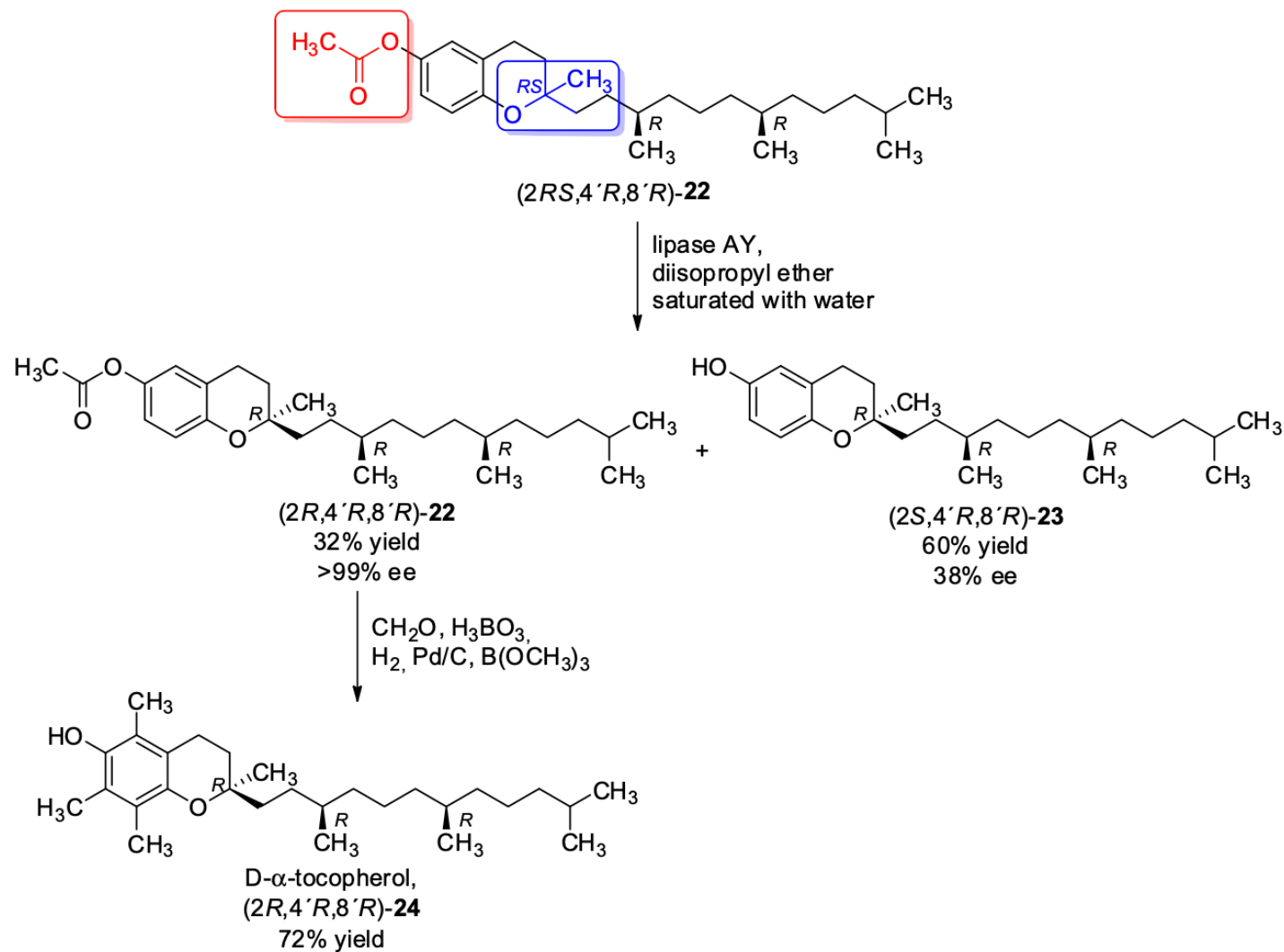
Production of Estrogen Receptor Modulator Lasofoxefine (Pfizer)



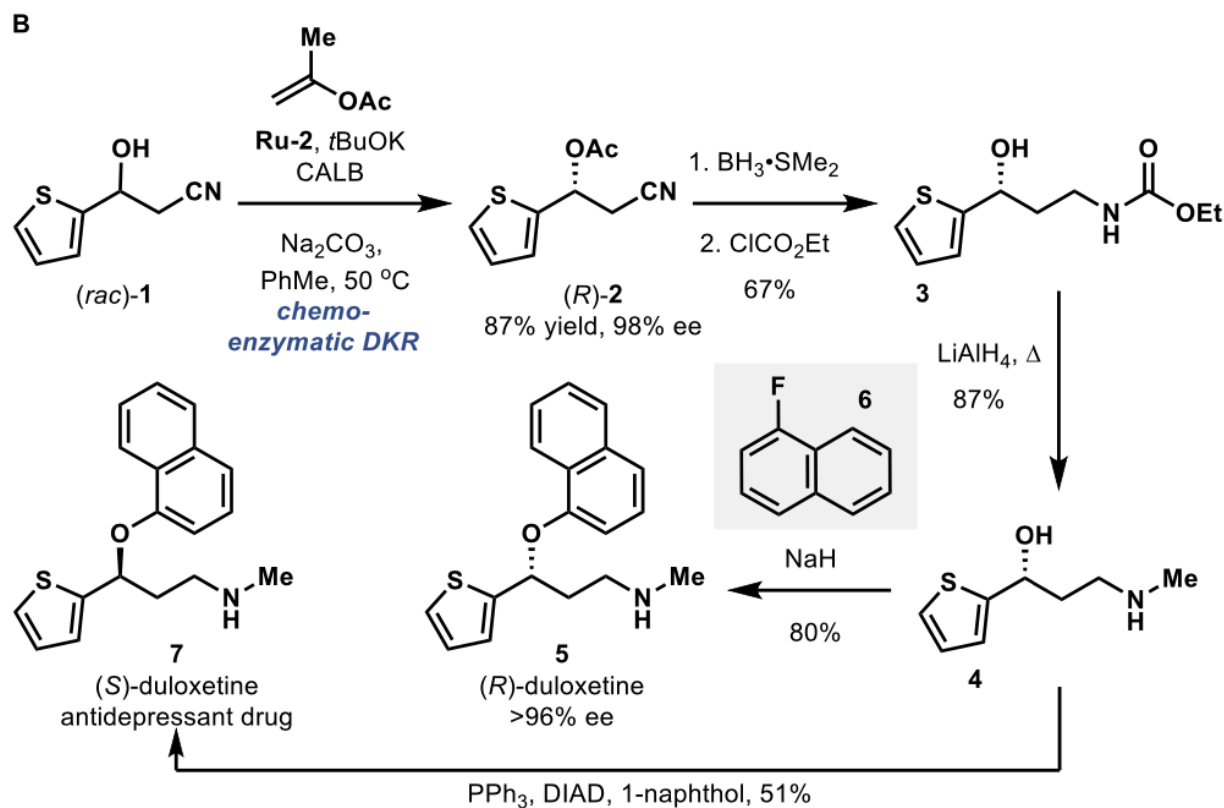
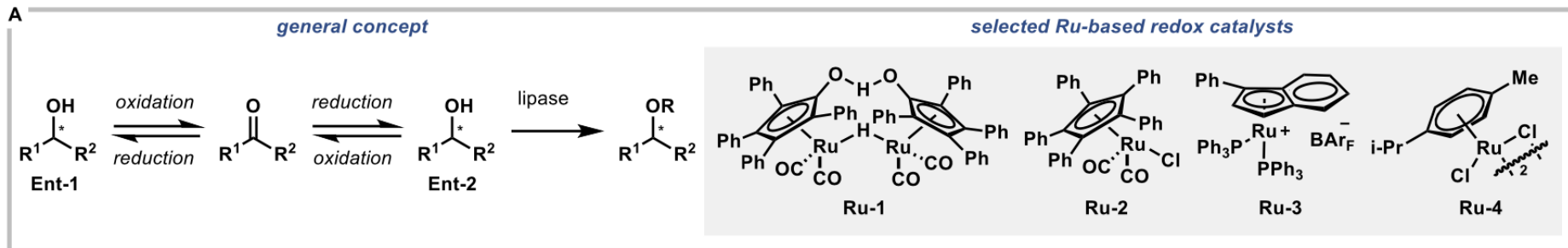
Production of Anticancer Agent Monastrol (Pfizer)



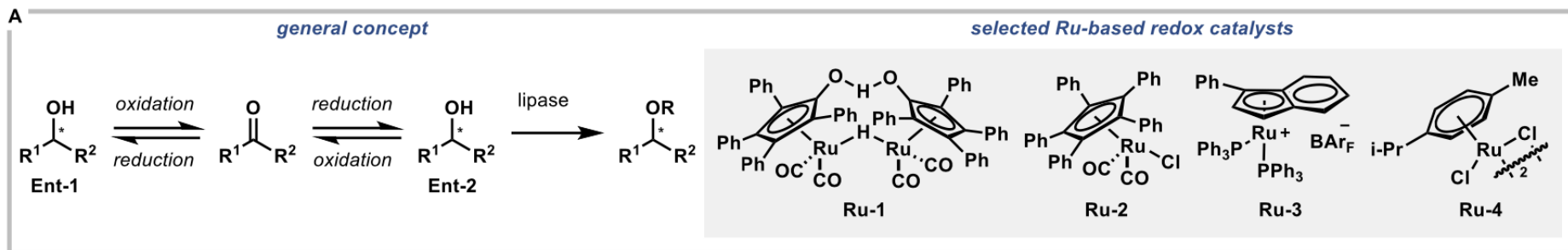
Production of Dietary Supplements (Tocopherols)



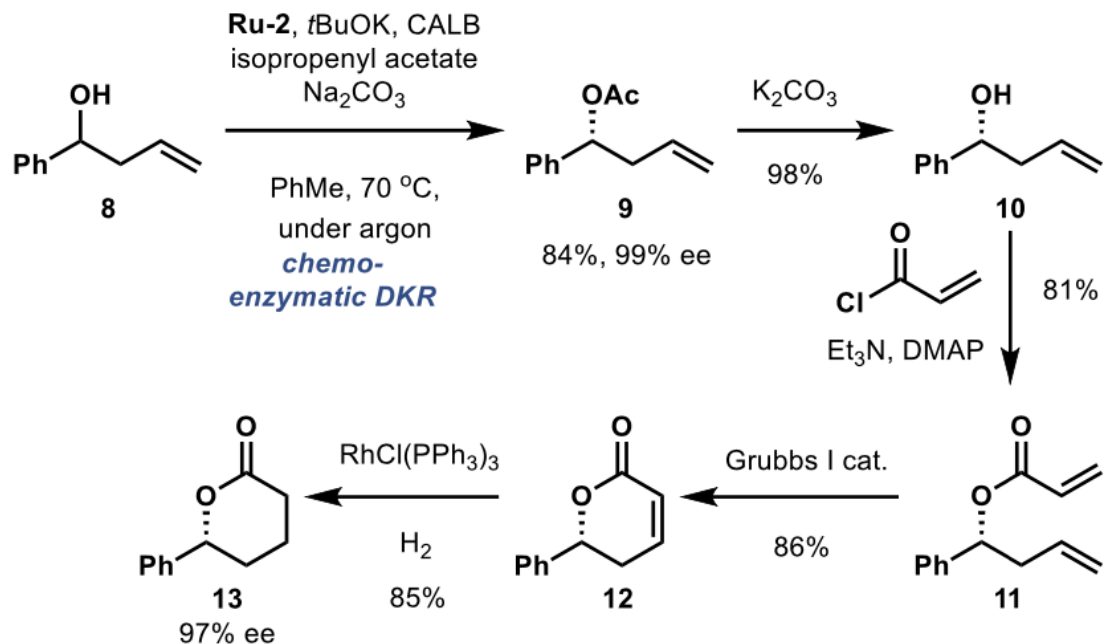
Dynamic Kinetic Resolution through Intermediacy of Oxidation-Reduction Reactions



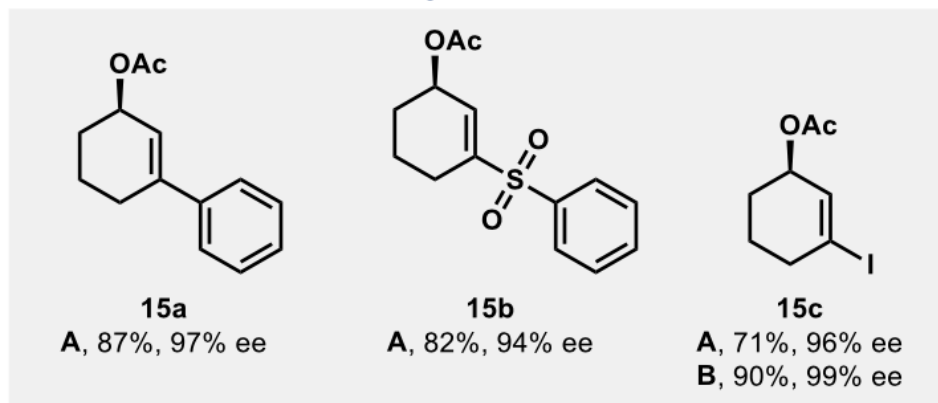
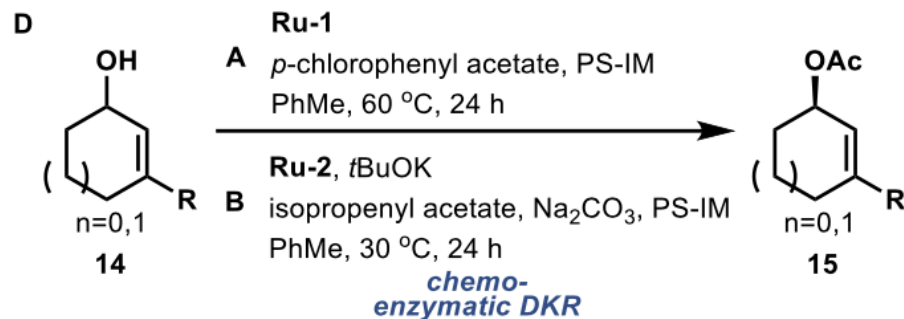
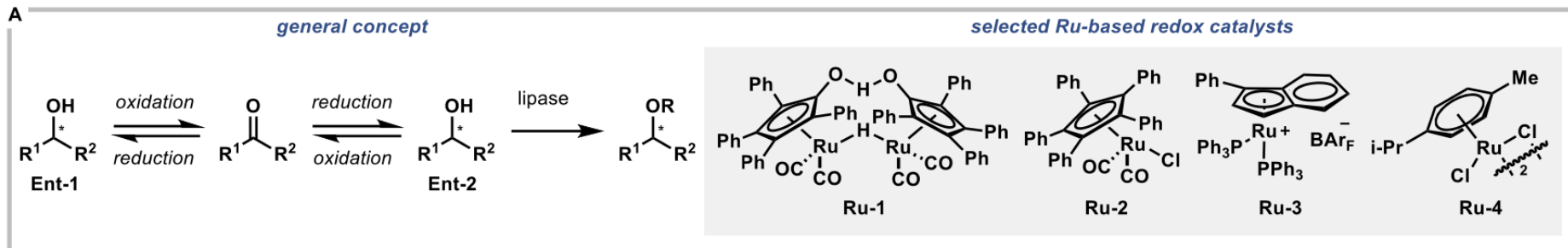
Dynamic Kinetic Resolution through Intermediacy of Oxidation-Reduction Reactions



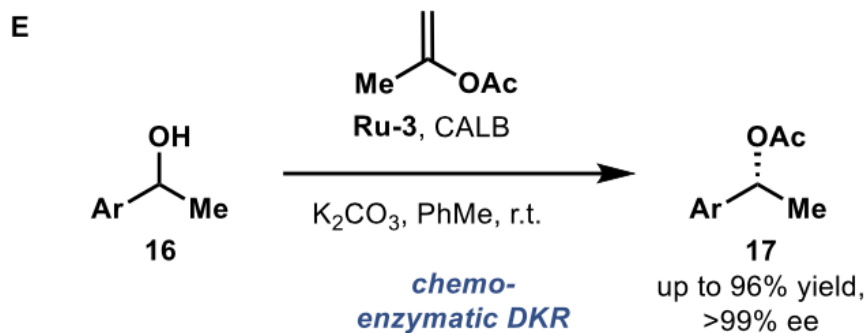
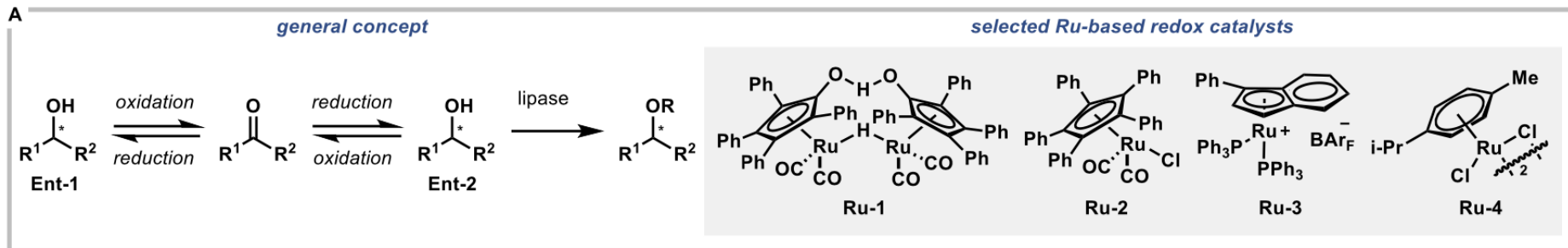
C



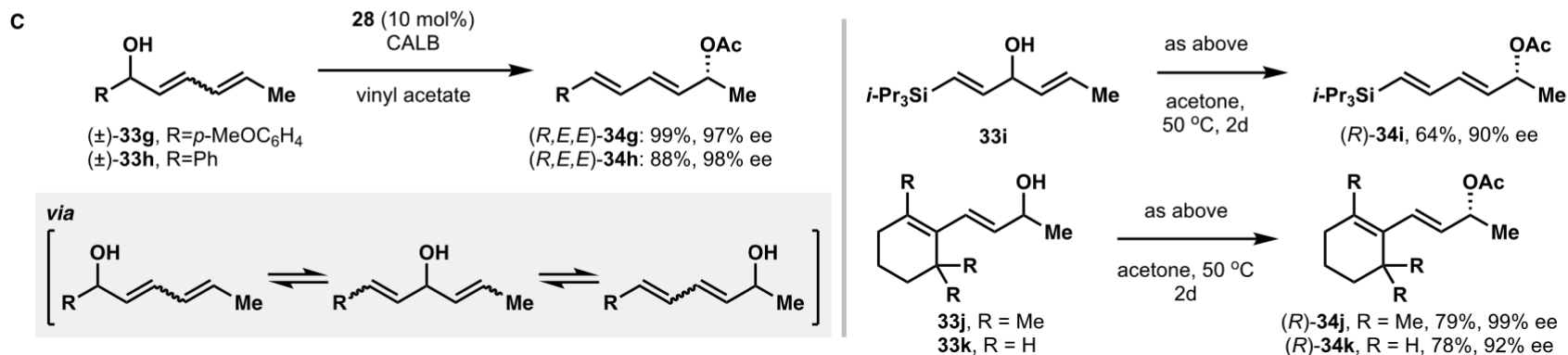
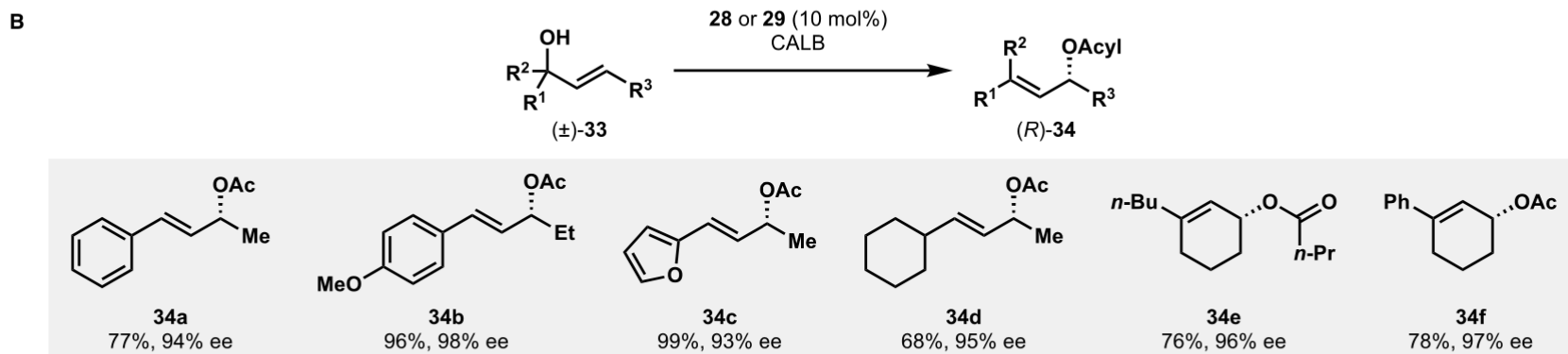
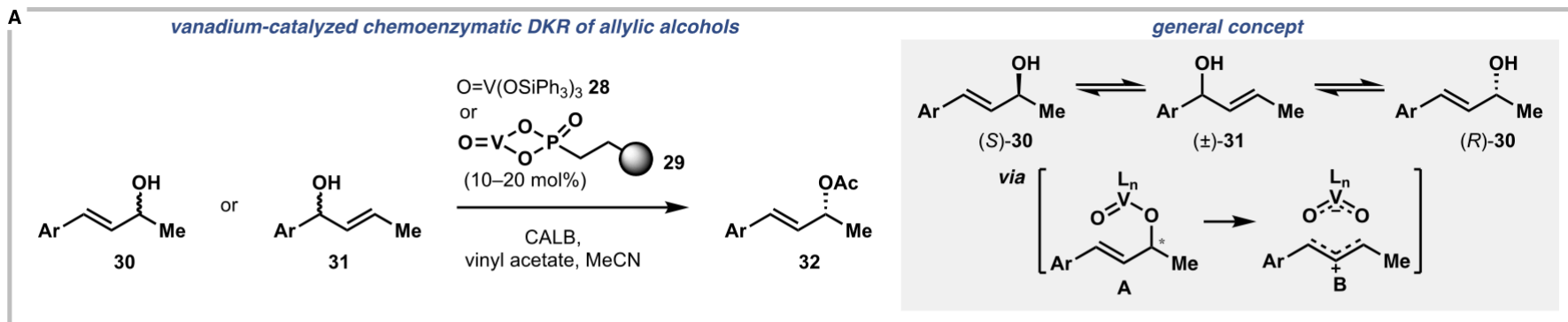
Dynamic Kinetic Resolution through Intermediacy of Oxidation-Reduction Reactions



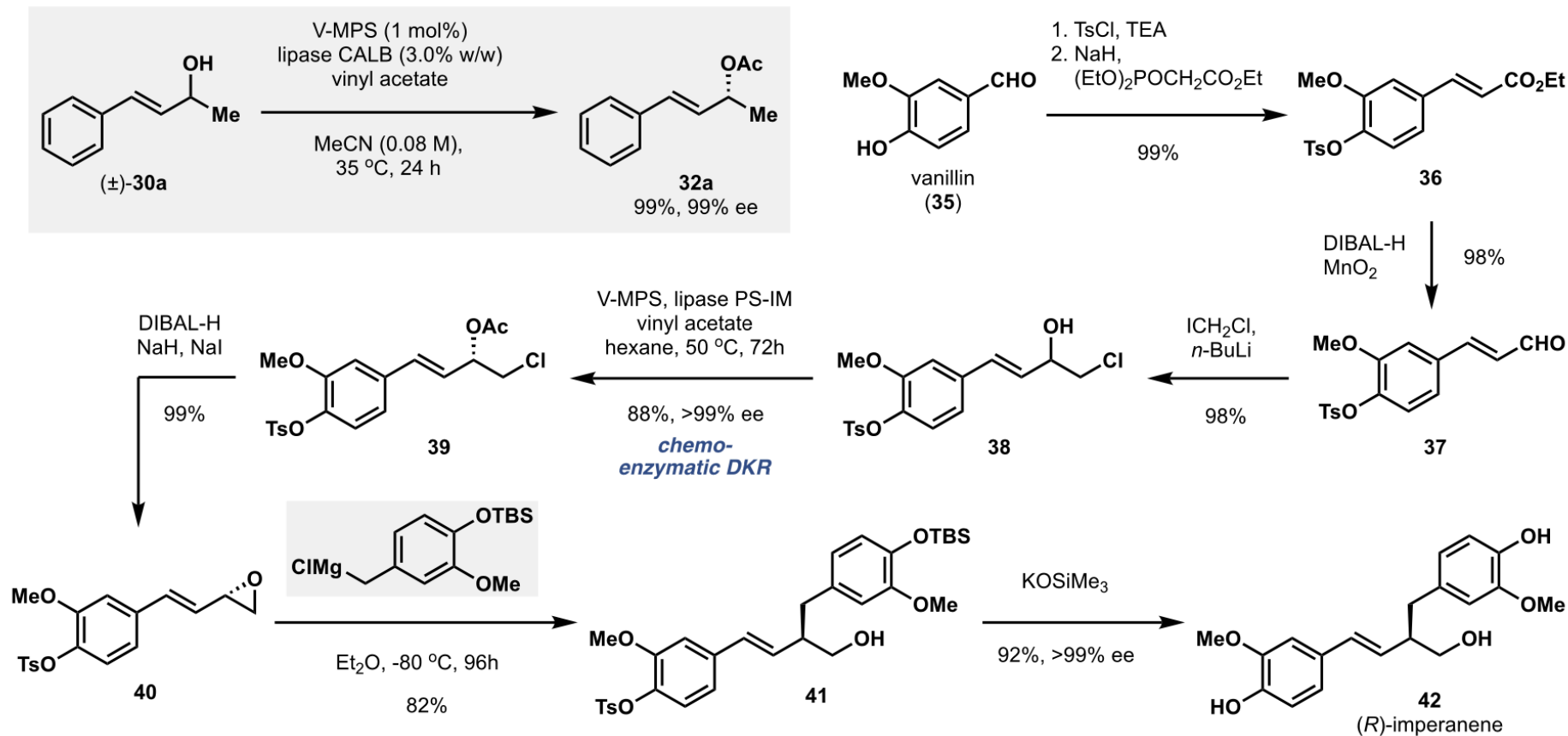
Dynamic Kinetic Resolution through Intermediacy of Oxidation-Reduction Reactions



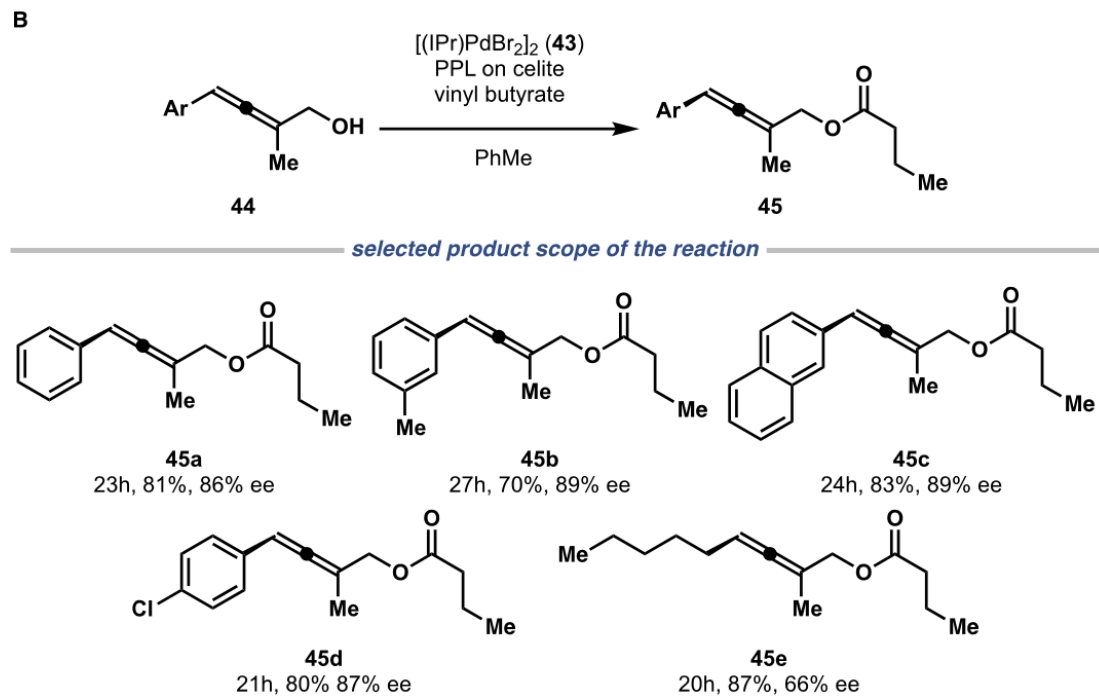
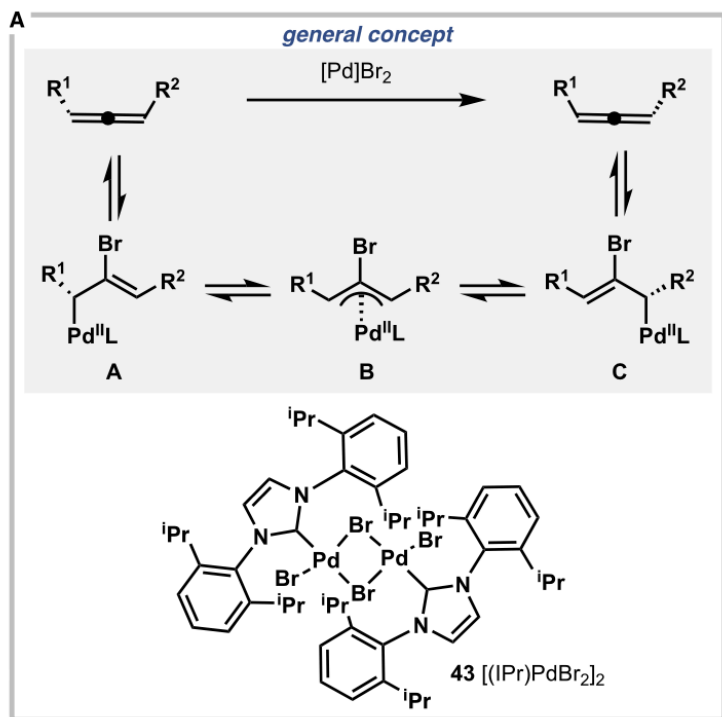
Dynamic Kinetic Resolution of Allylic Alcohols through π -Allyl Complex Formation



Dynamic Kinetic Resolution of Allylic Alcohols through π -Allyl Complex Formation

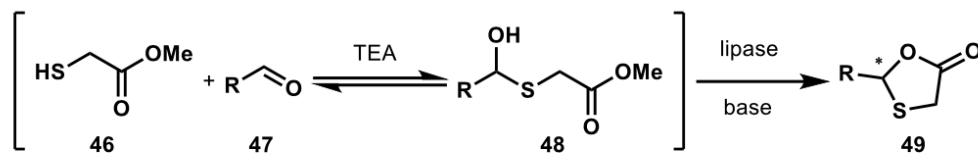


Dynamic Kinetic Resolution of Allenes

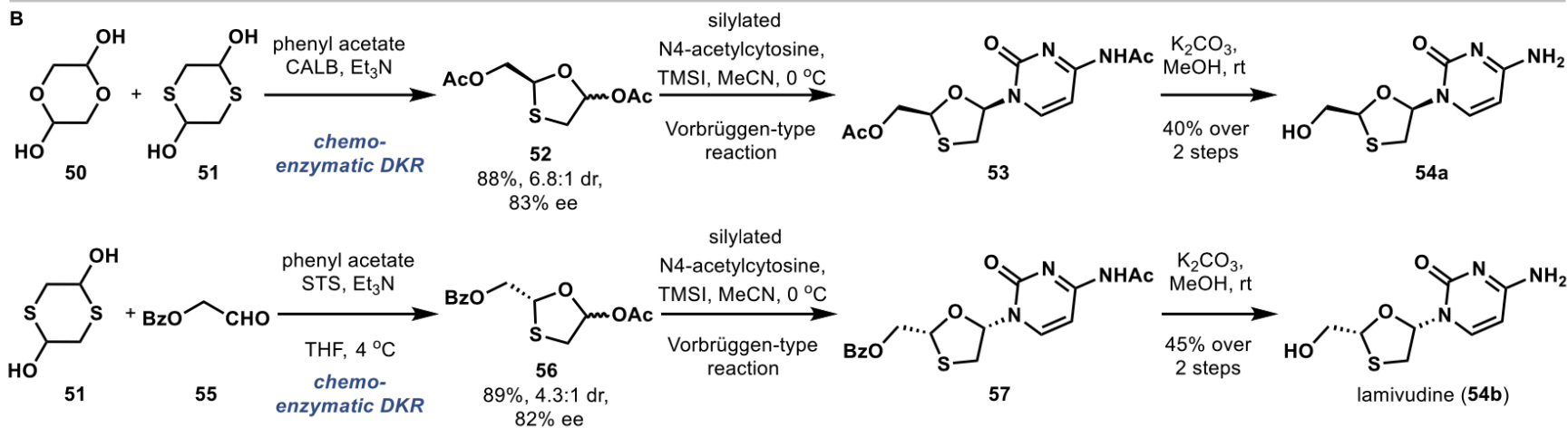


Dynamic Kinetic Resolution through Solution-Phase Equilibrium

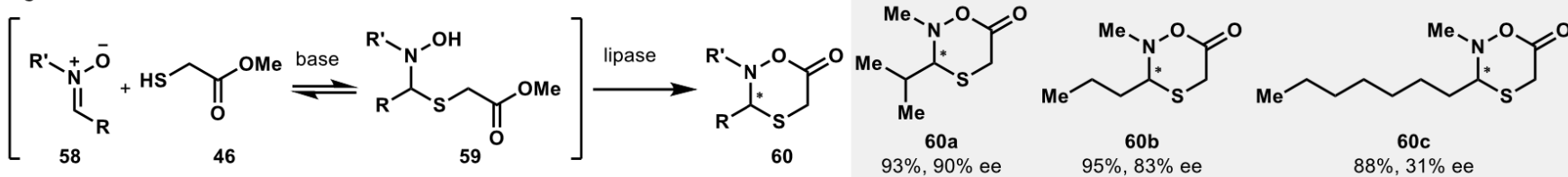
A



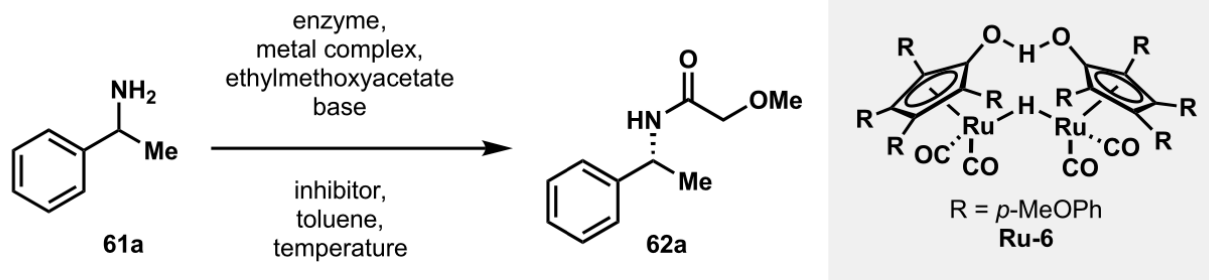
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C

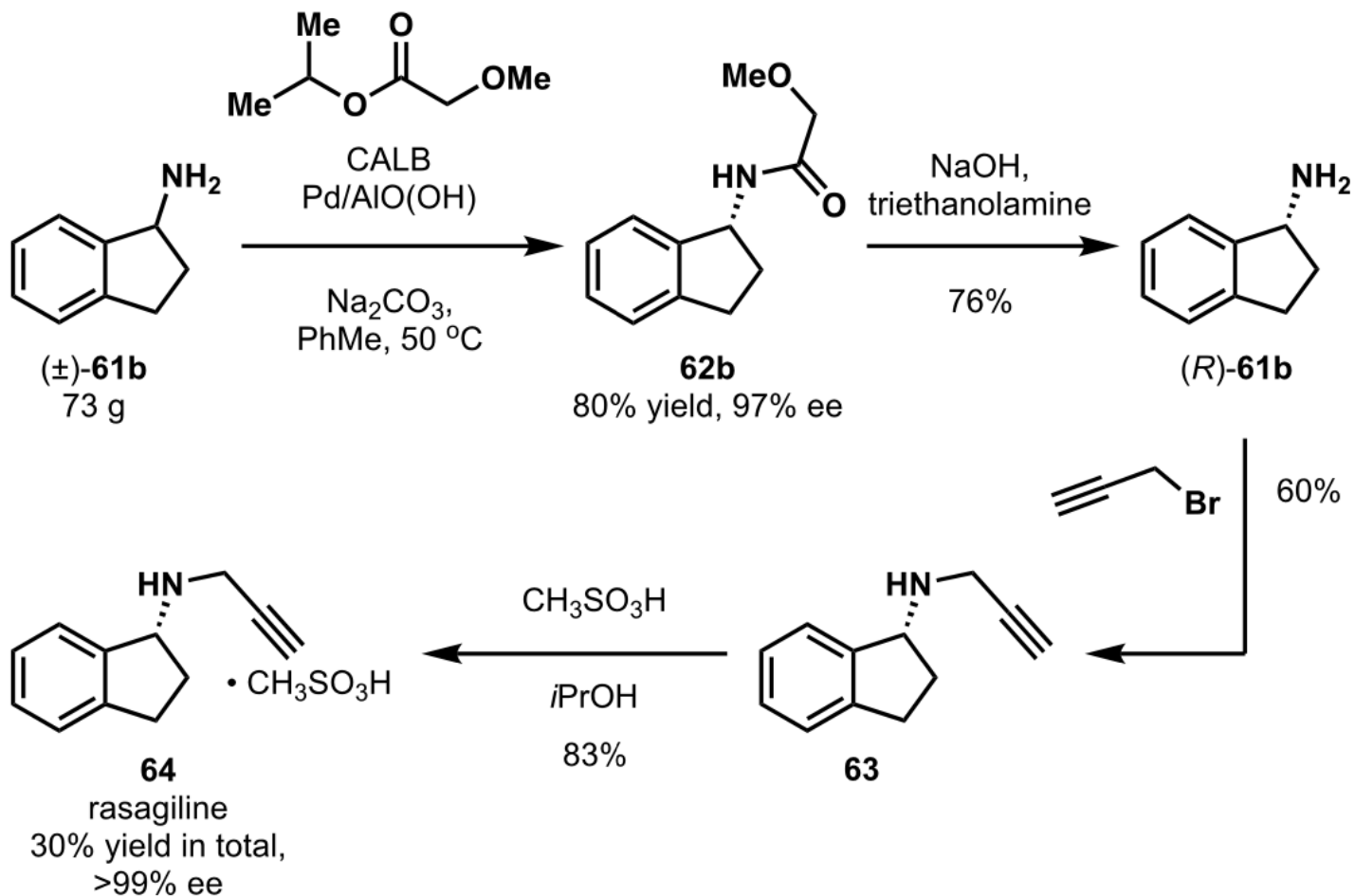


Dynamic Kinetic Resolution of Amines

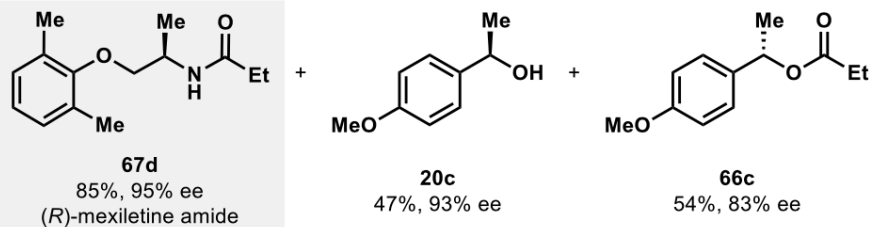
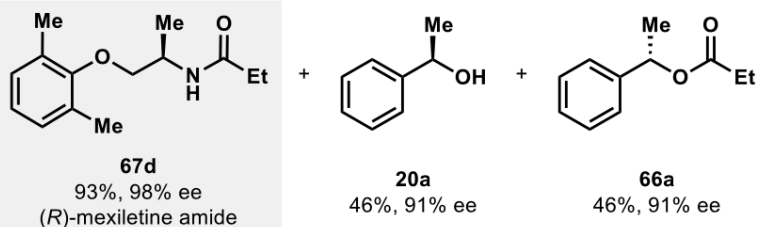
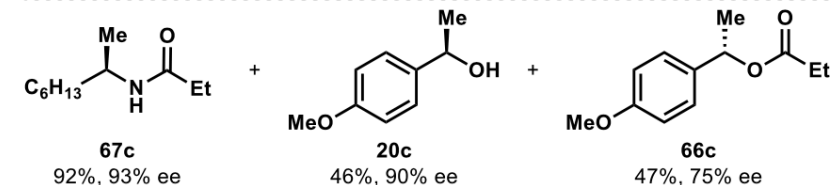
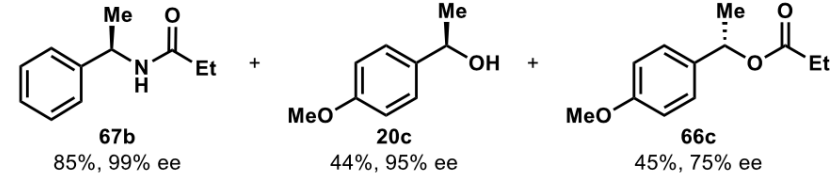
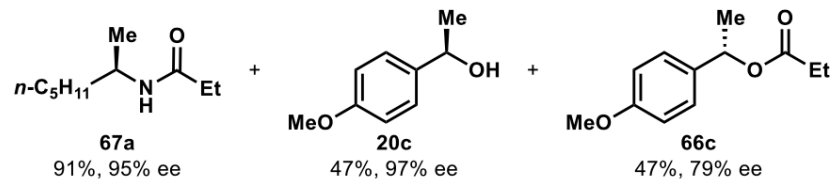
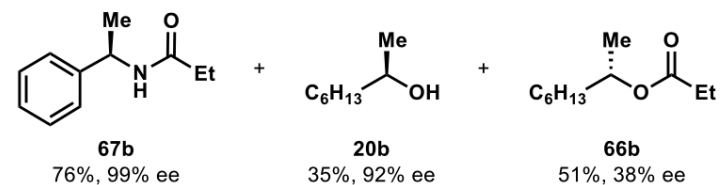
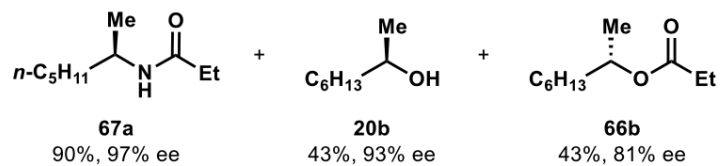
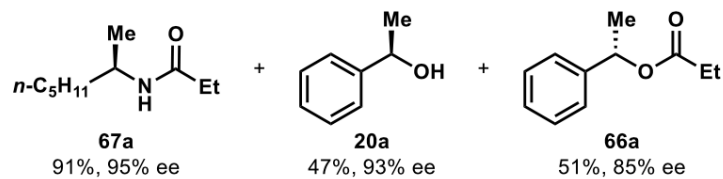
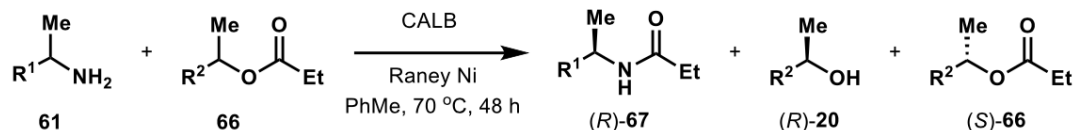


entry	enzyme	racemization reagent	base	byproduct Inhibitor	temperature (°C)	yield (%)	ee (%)	reference
1	CALB	Ru-6	Na ₂ CO ₃		100	83	98	25
2	CALB	K ₂ CO ₃ - Pd/MCF		H ₂	70	96	99	26
3	CALB	K ₂ CO ₃ - Pd/SBA-15		H ₂	70	96	99	26
4	CALB	K ₂ CO ₃ - Pd/FDU-12		H ₂	70	97	99	26
5	CALB	K ₂ CO ₃ - Pd/SiO ₂		H ₂	70	90	98	26
6	CALB	K ₂ CO ₃ -Pd/C		H ₂	70	96	99	26
7	CALB	Pd-AmP- MCF	Na ₂ CO ₃	H ₂	70	99	99	27
8	PS	Pd-AmP- MCF	Na ₂ CO ₃	H ₂	50	82	99	27
9	CALB	Pd/BaSO ₄	Na ₂ CO ₃	NH ₄ HCO ₂	70	94	99	28

Dynamic Kinetic Resolution of Amines

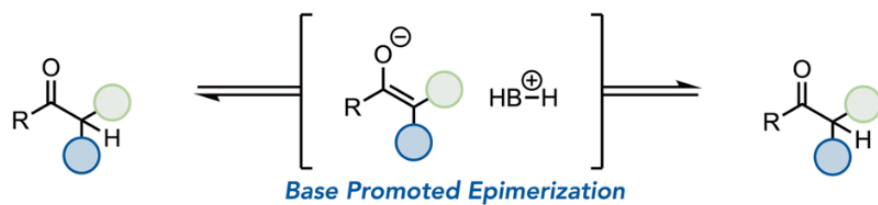
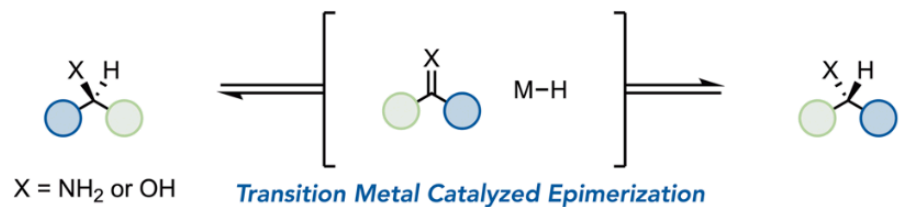


Double Dynamic Kinetic Resolution



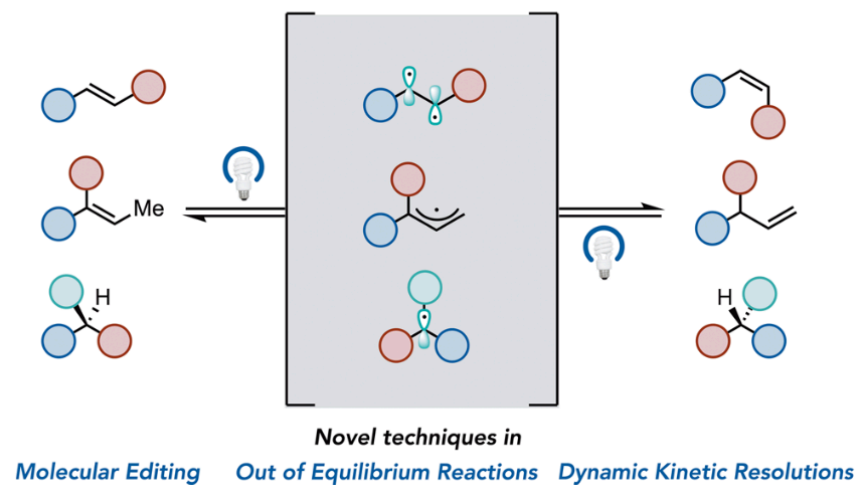
Photoinduced Dynamic Processes

A Traditional Epimerization/Racemization Mechanisms



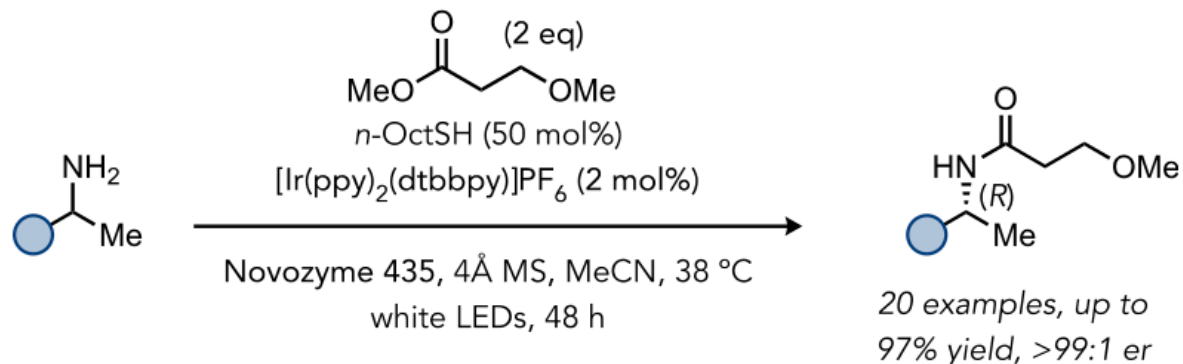
B In this Review

Photoinduced Dynamic Stereochemistry

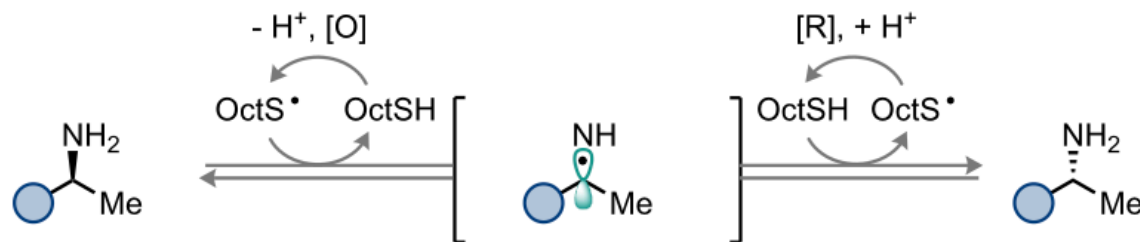


Dynamic Kinetic Resolution Using Photoredox for Amine Epimerization

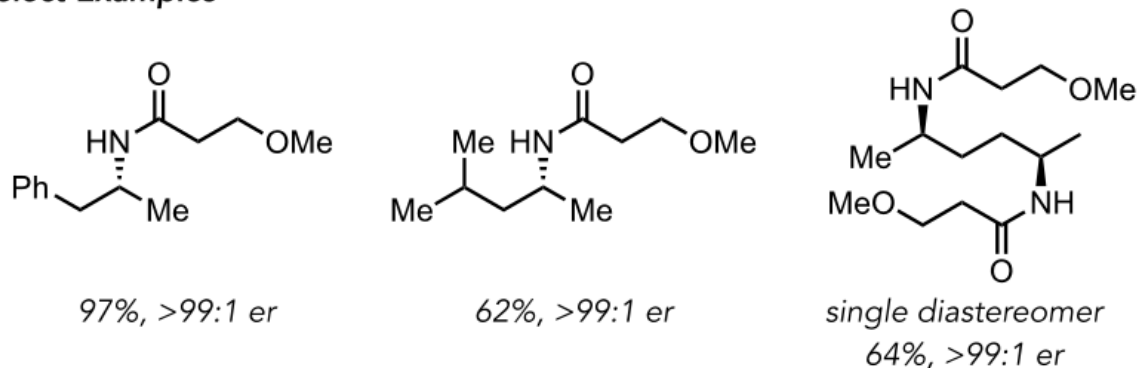
DKR Utilizing Photoredox-Based α -Amino Stereocenter Epimerization



Epimerization Mechanism



Select Examples



Breaking Symmetry with Biocatalysis: Enzymatic Desymmetrization with Lipases

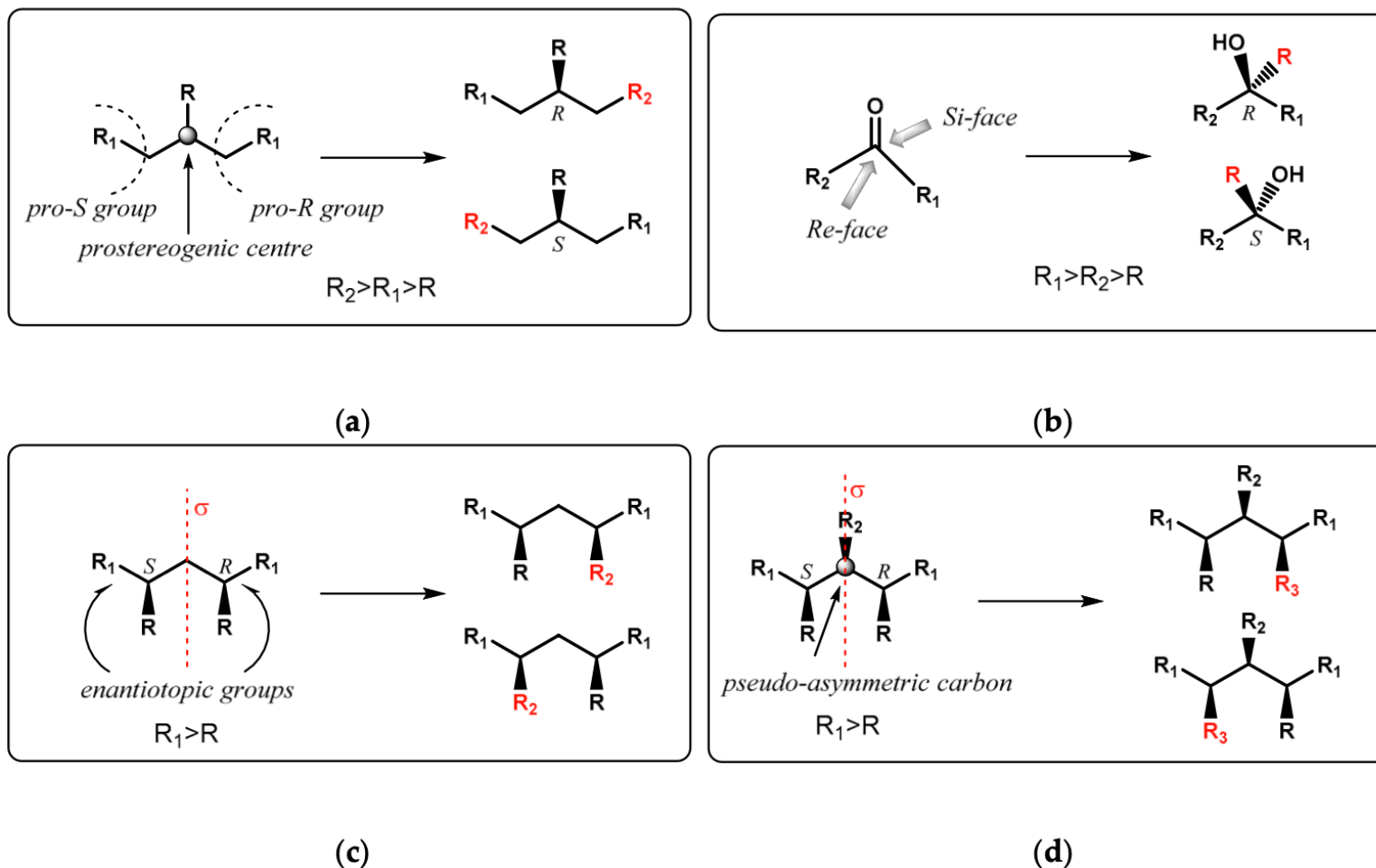
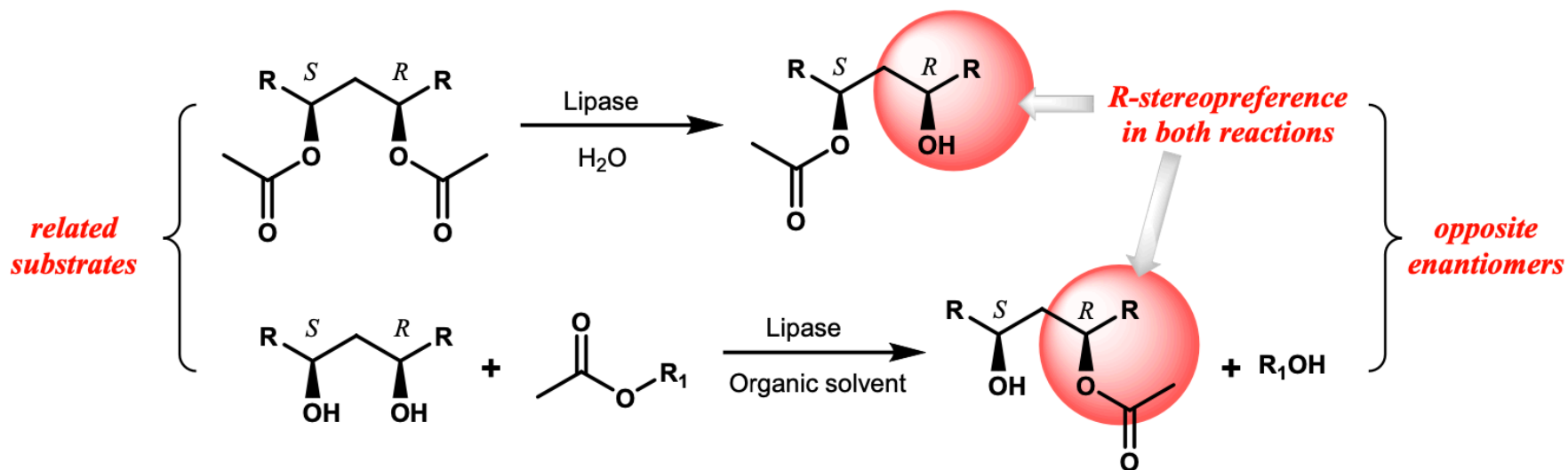


Figure 1. (a) General representation of prochiral molecules; (b) General representation of prochiral molecules with a trigonal group; (c) General representation of *meso*-molecules; (d) General representation of *meso*-molecules containing additional stereogenic centre in the symmetry plane.

Breaking Symmetry with Biocatalysis: Enzymatic Desymmetrization with Lipases



Desymmetrization of Cyclic 1,3-Diols

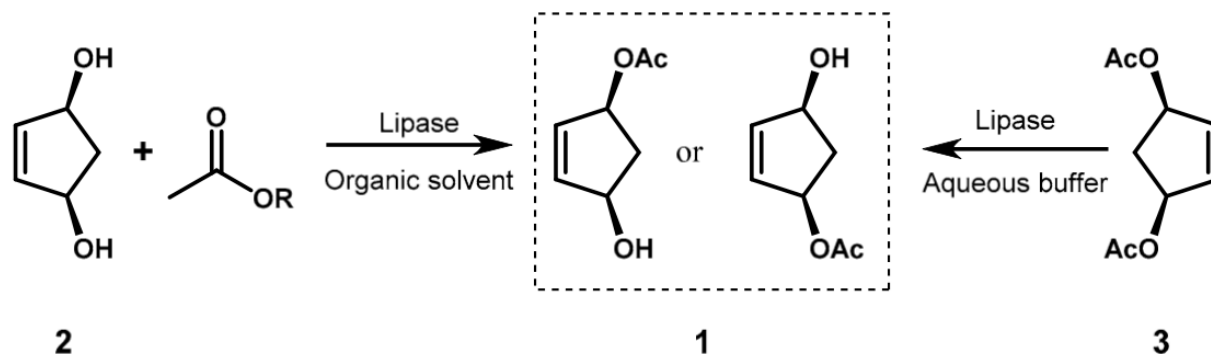
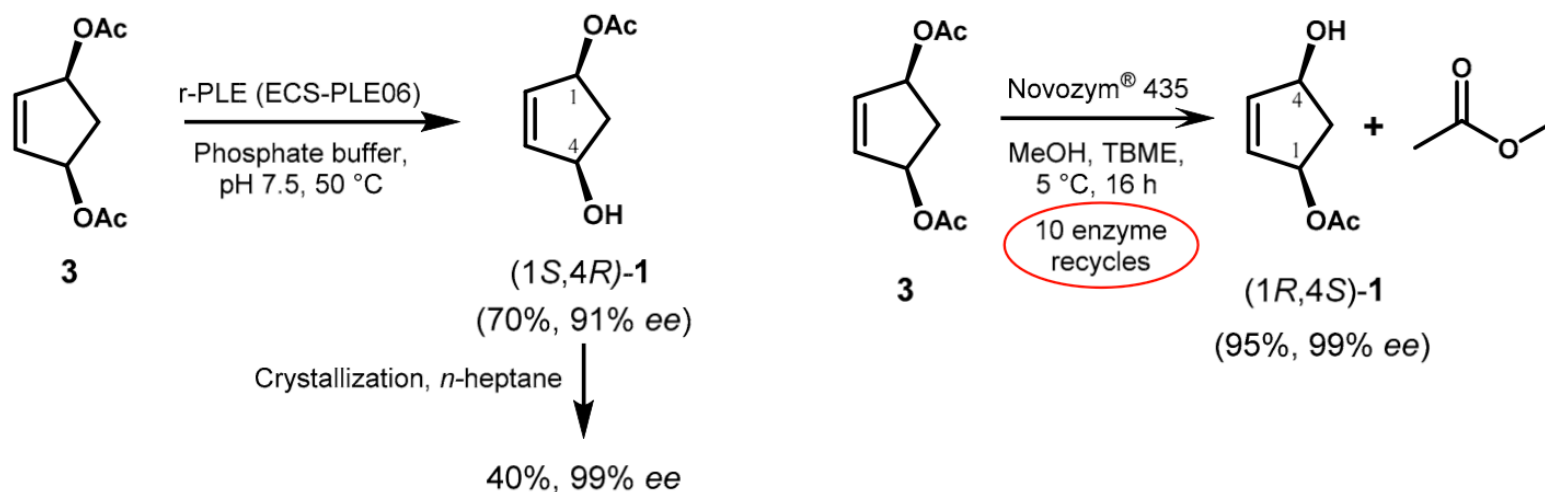


Figure 2. Synthesis of both enantiomers of monoacetate 1 by lipase-catalyzed reactions.



Desymmetrization of Hydroxymethyl Diols

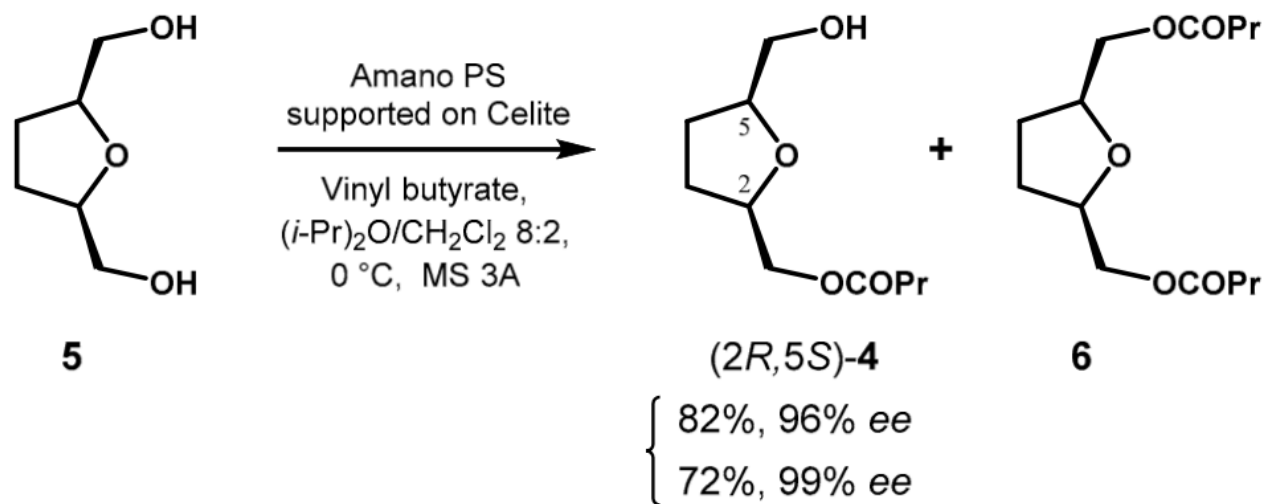


Figure 4. Desymmetrization of diol **5** by lipase-catalyzed esterification.

Desymmetrization of Hydroxymethyl Diols: Extension to Application

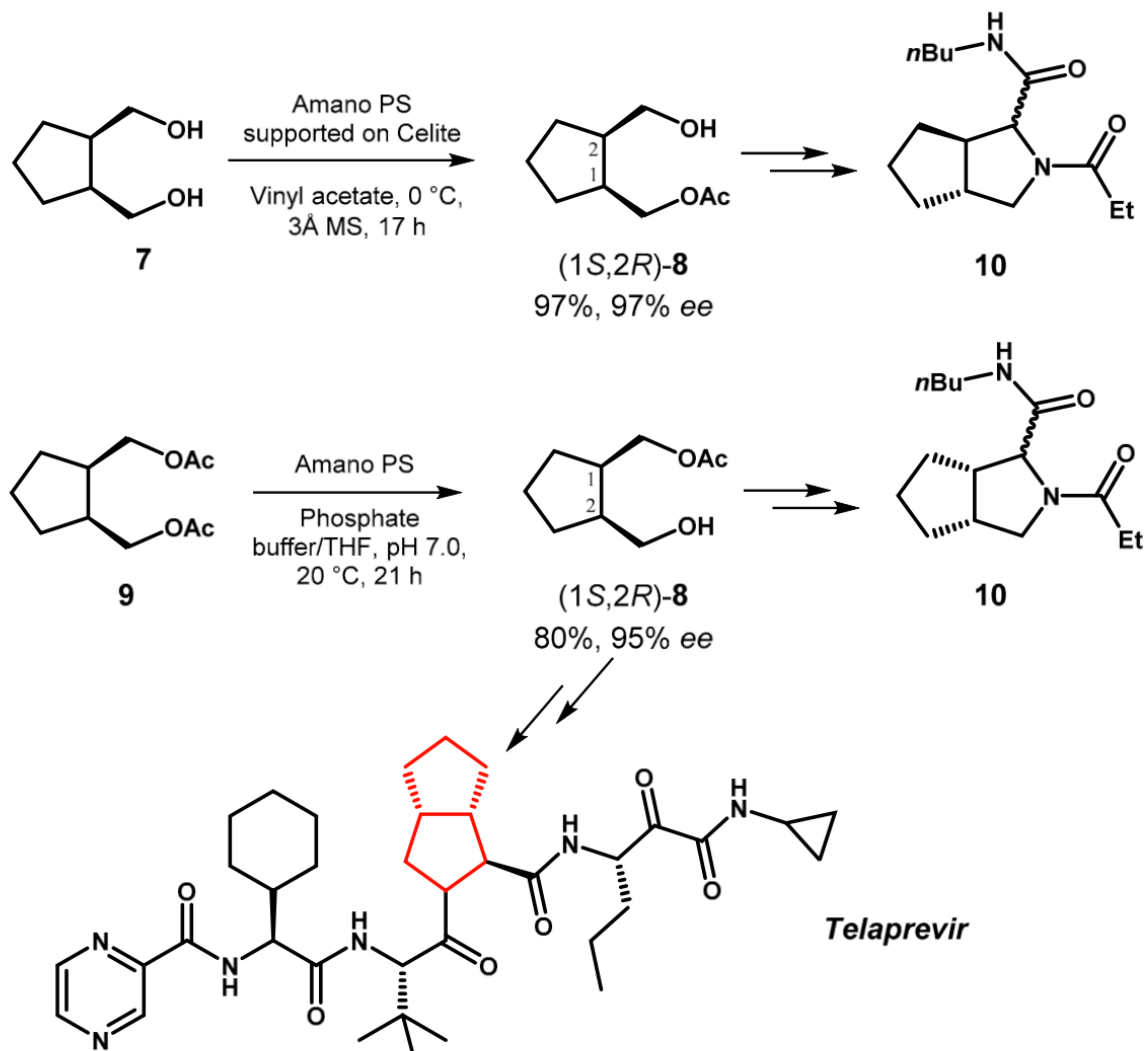


Figure 5. Complementary desymmetrization reactions for the access to both enantiomers of monoacetate **8**.

Desymmetrization of Hydroxymethyl Diols: Extension to Application

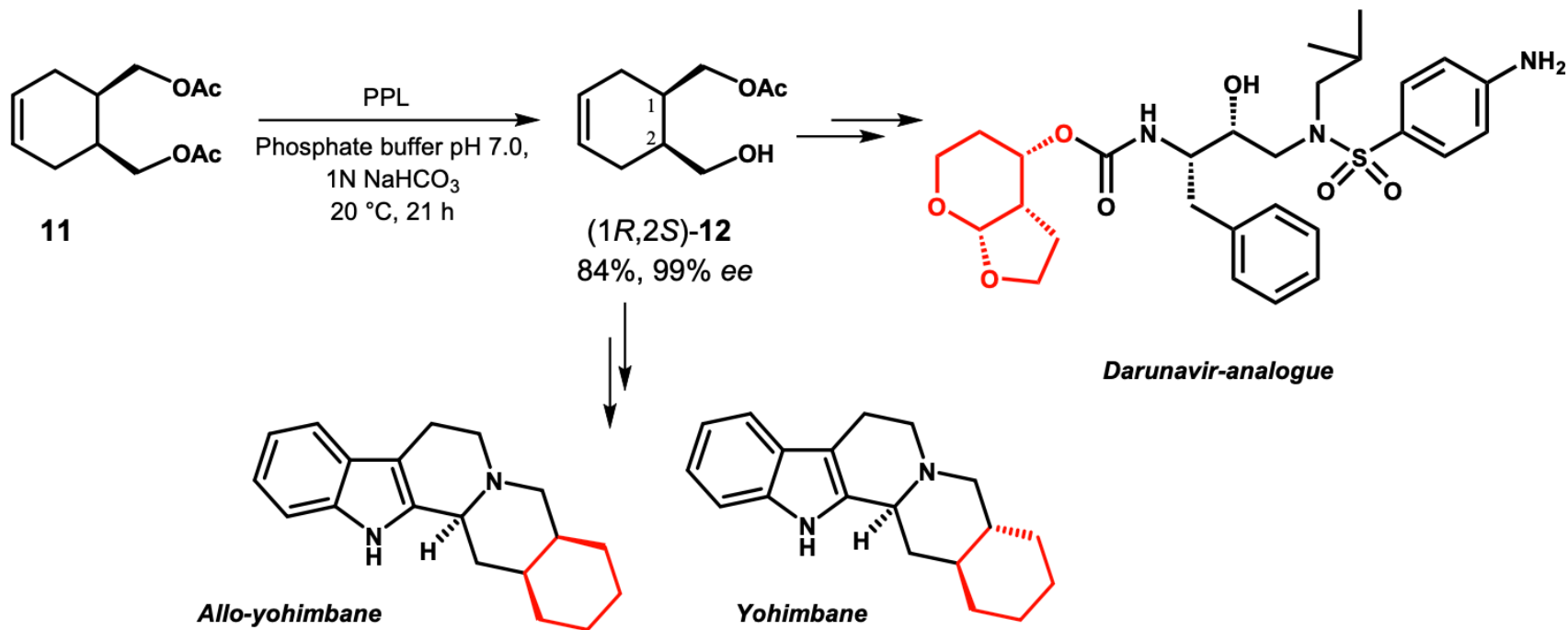


Figure 6. Synthesis of yohimbine alkaloids and darunavir analogue through hydrolytic desymmetrization of **11**.

Desymmetrization of Cyclohexyl 1,3-Diols

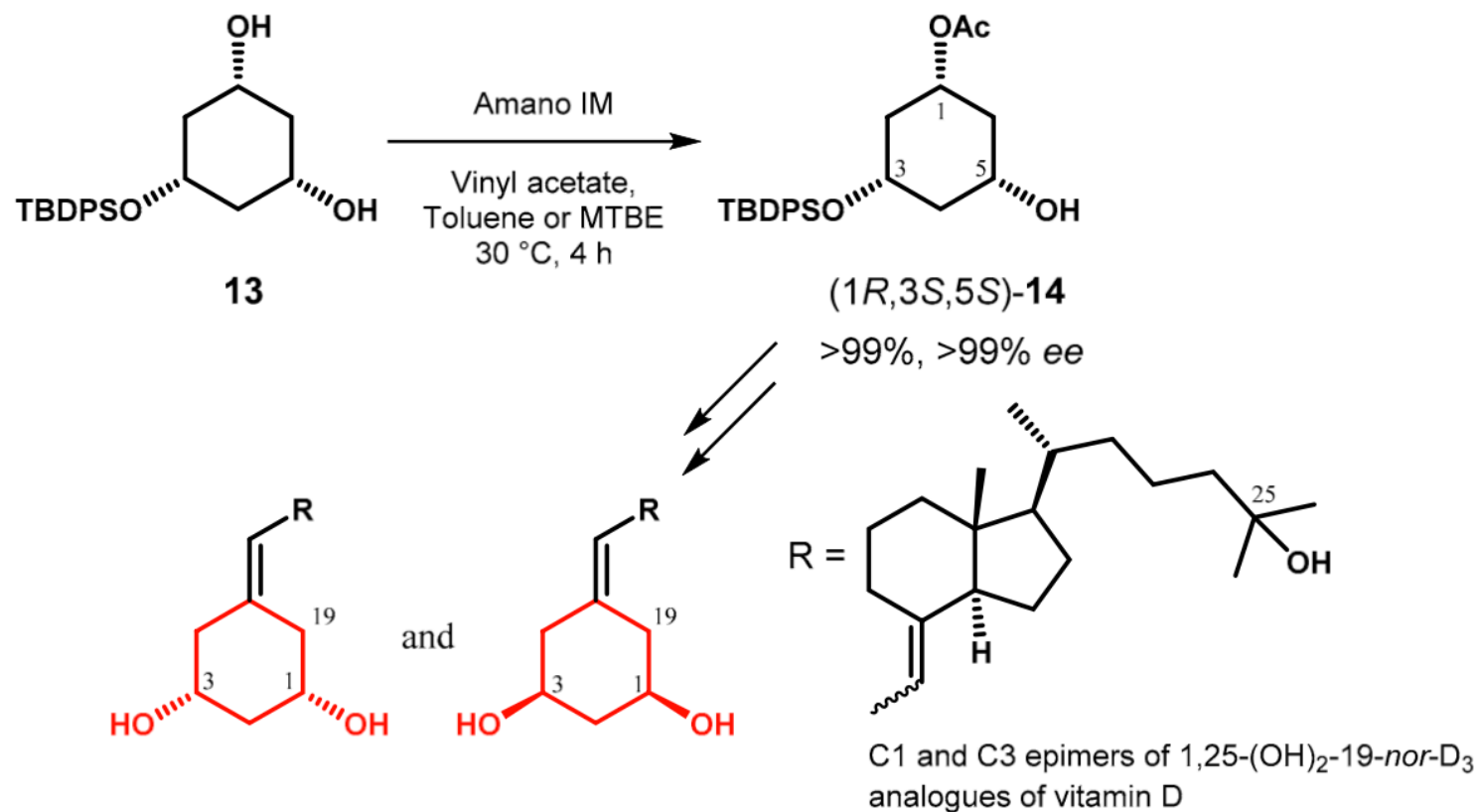


Figure 7. Synthesis analogues of vitamin D₃ through enantiotoposelective esterification of diol **13**.

Desymmetrization of Inositol



Figure 8. Desymmetrization of *myo*-inositol **15** via enantiotoposelective esterification.

Desymmetrization of 1,3-Ester Substituted Cycloalkanes

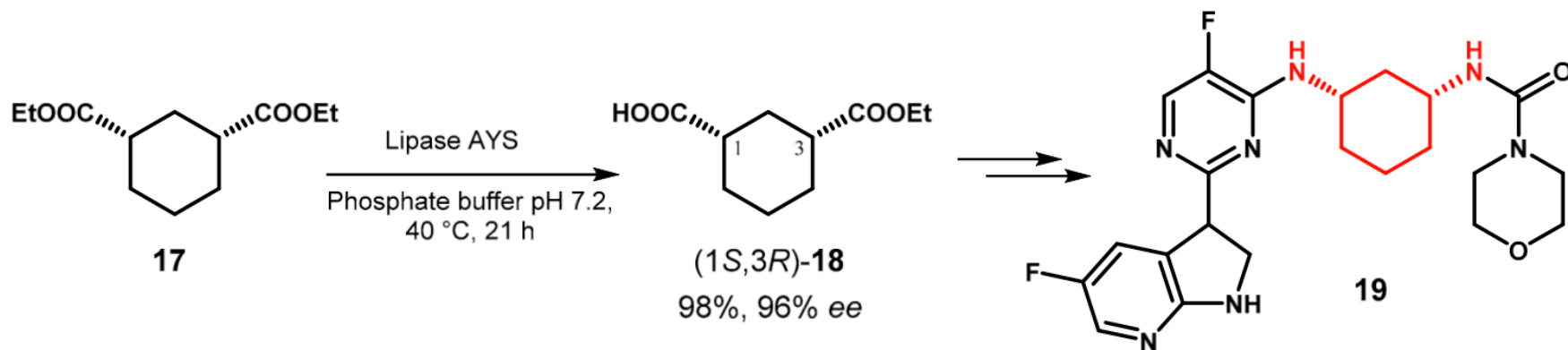


Figure 9. Desymmetrization of diester **17** via enantiotoposelective hydrolysis.

Desymmetrization of Propane 1,3-Diols

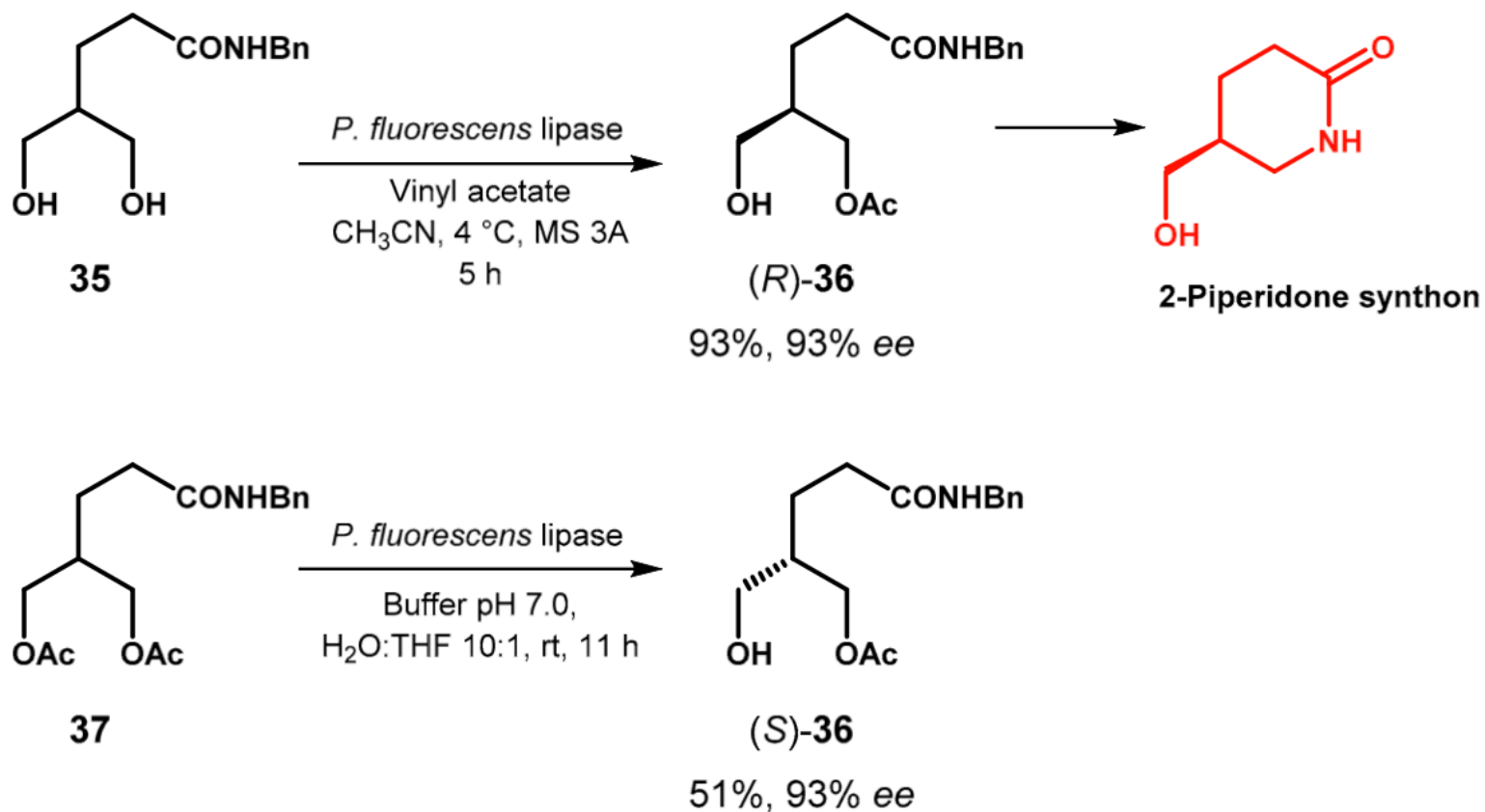


Figure 16. Lipase-catalyzed desymmetrization of propane-1,3-diol 35.

Desymmetrization of Propane 1,3-Diacetates

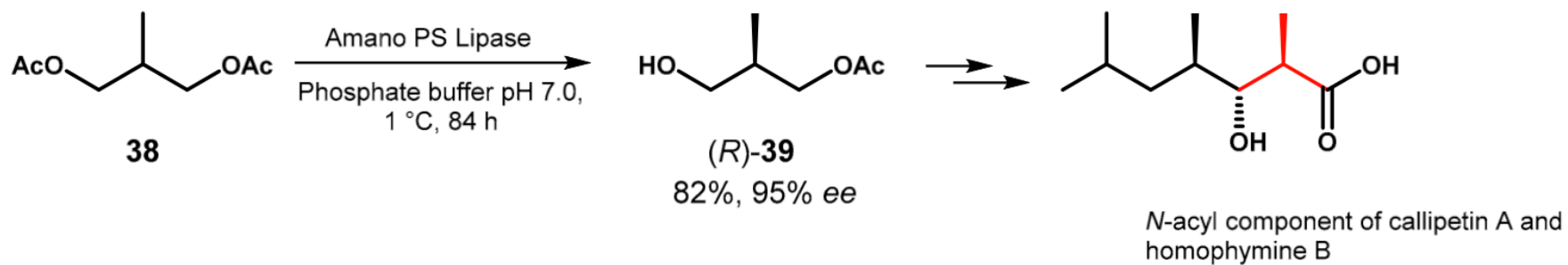


Figure 17. Lipase-catalyzed desymmetrization of propane-1,3-diacetate **38**.

Desymmetrization of Propane 1,3-Diacetates: Emerging Application

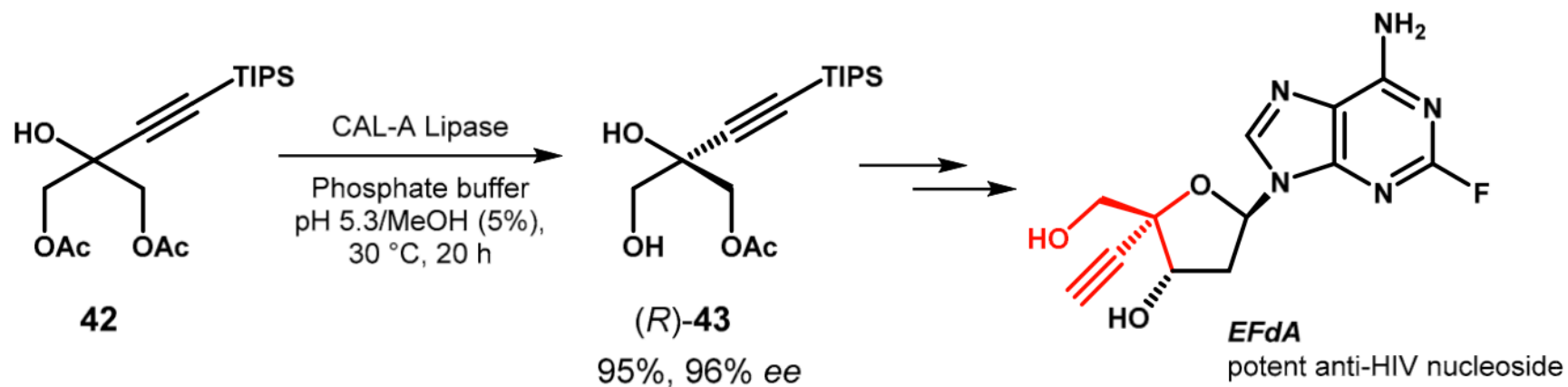


Figure 19. Synthesis of EfdA via desymmetrization of the prochiral glycerol derivative **42**.

Desymmetrization of Through Amide Hydrolysis

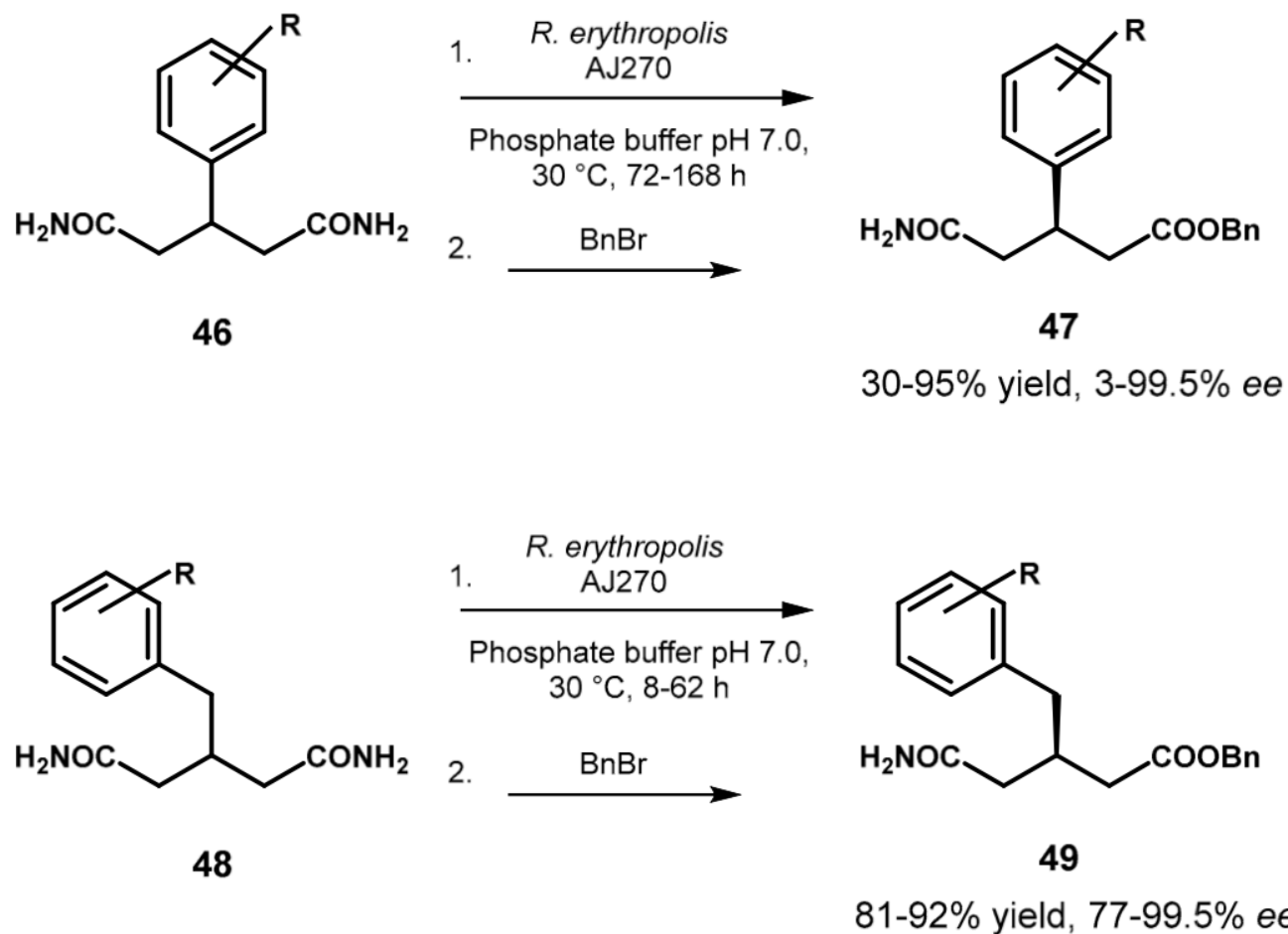
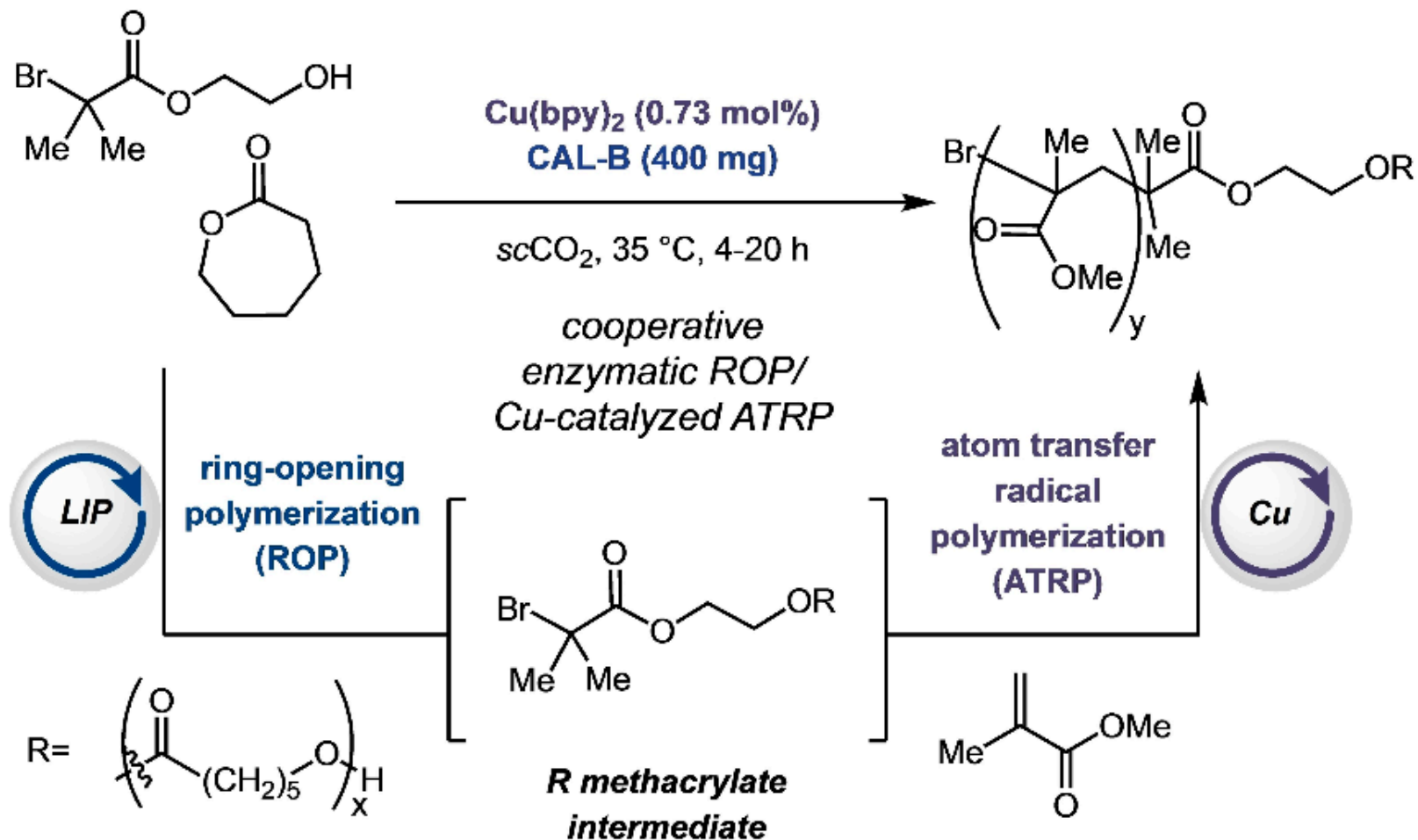
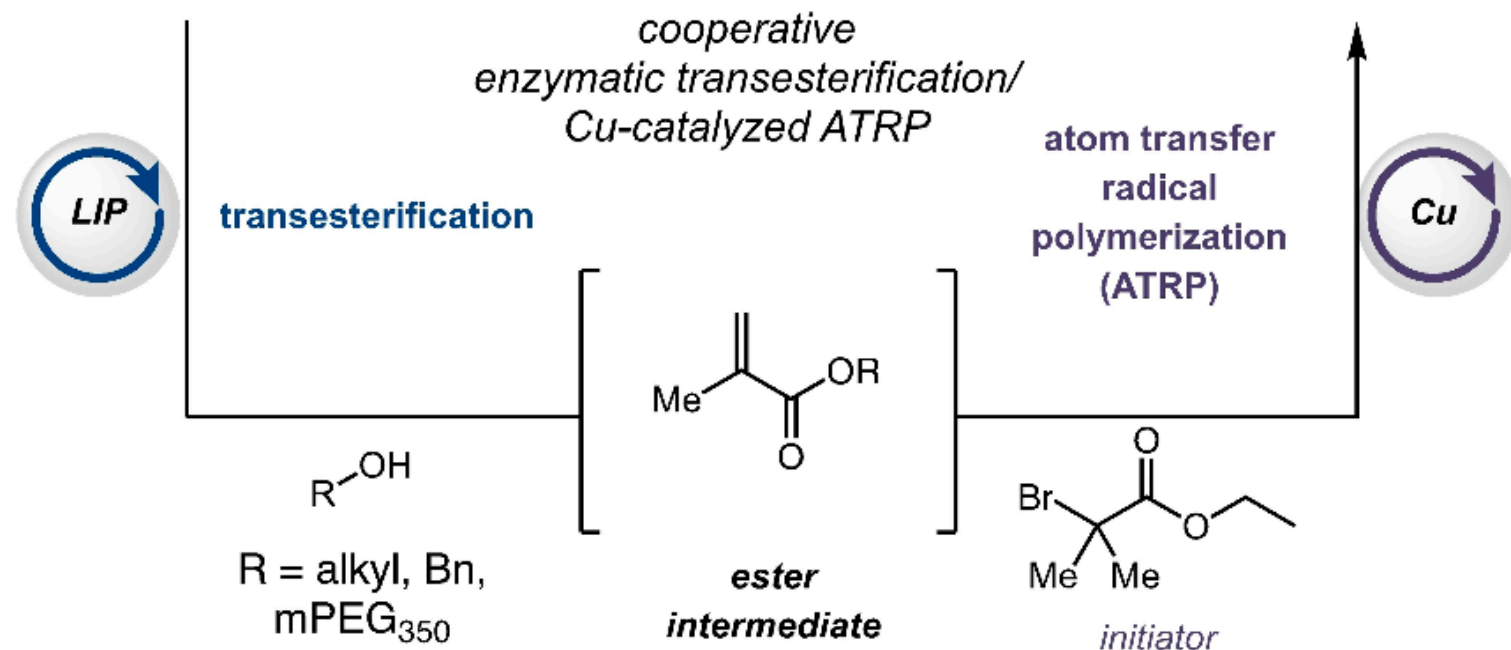
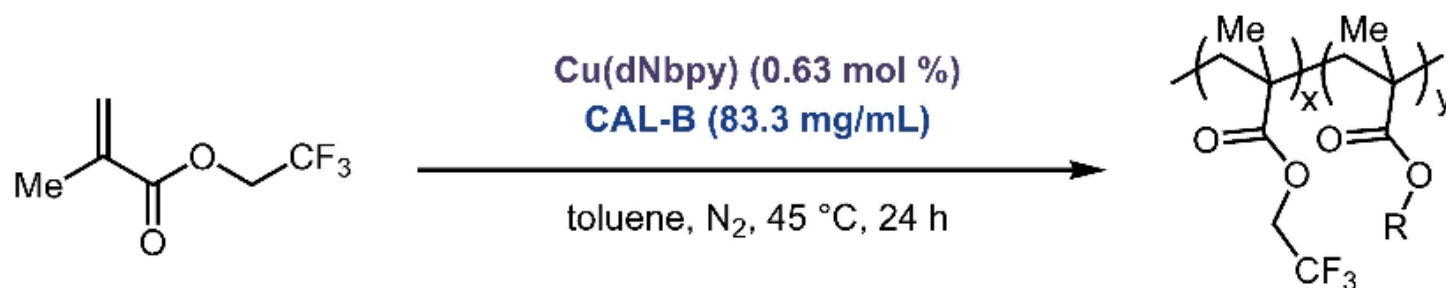


Figure 22. Amidase-catalyzed desymmetrization of 2-phenyl bisamides **46** and 2-benzyl bisamides **48**.

Lipase Application in Polymer Science: ROMP and ATRP



Lipase Application in Polymer Science: Transesterification/ATRP



Lipase Application in Polymer Science: Emergence of PETase

Common types of plastics

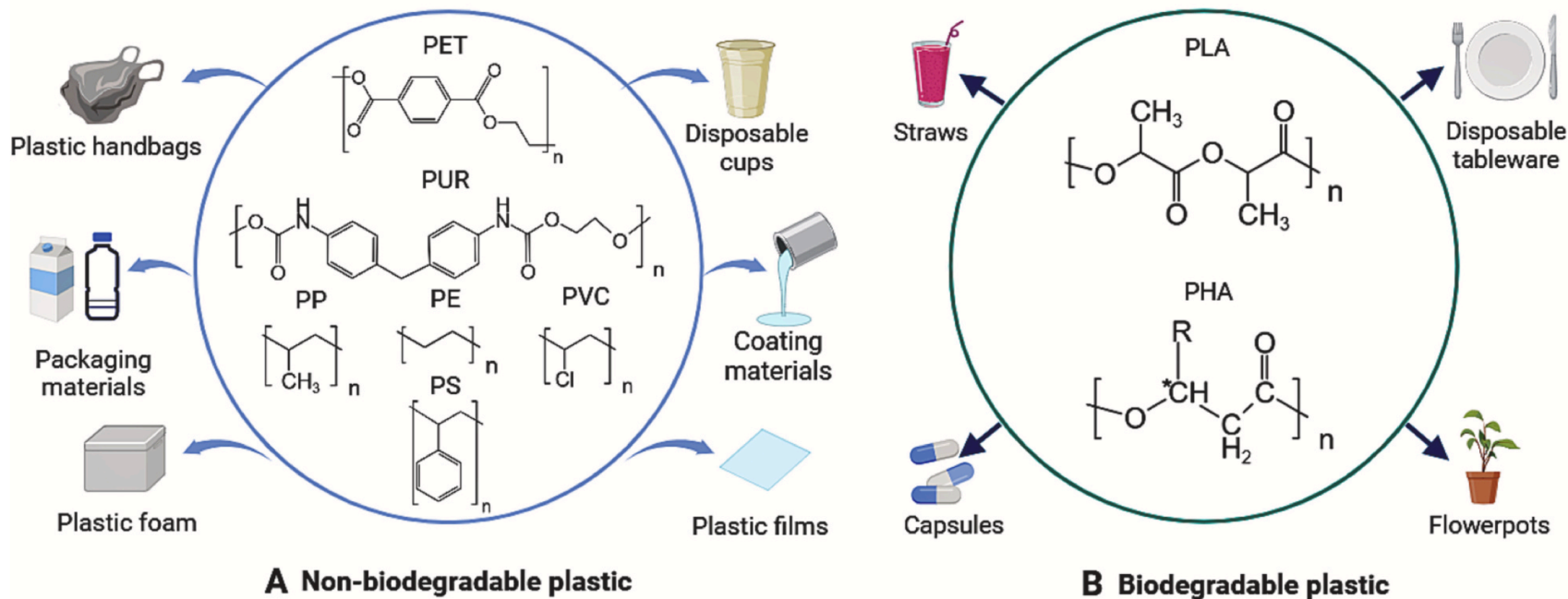
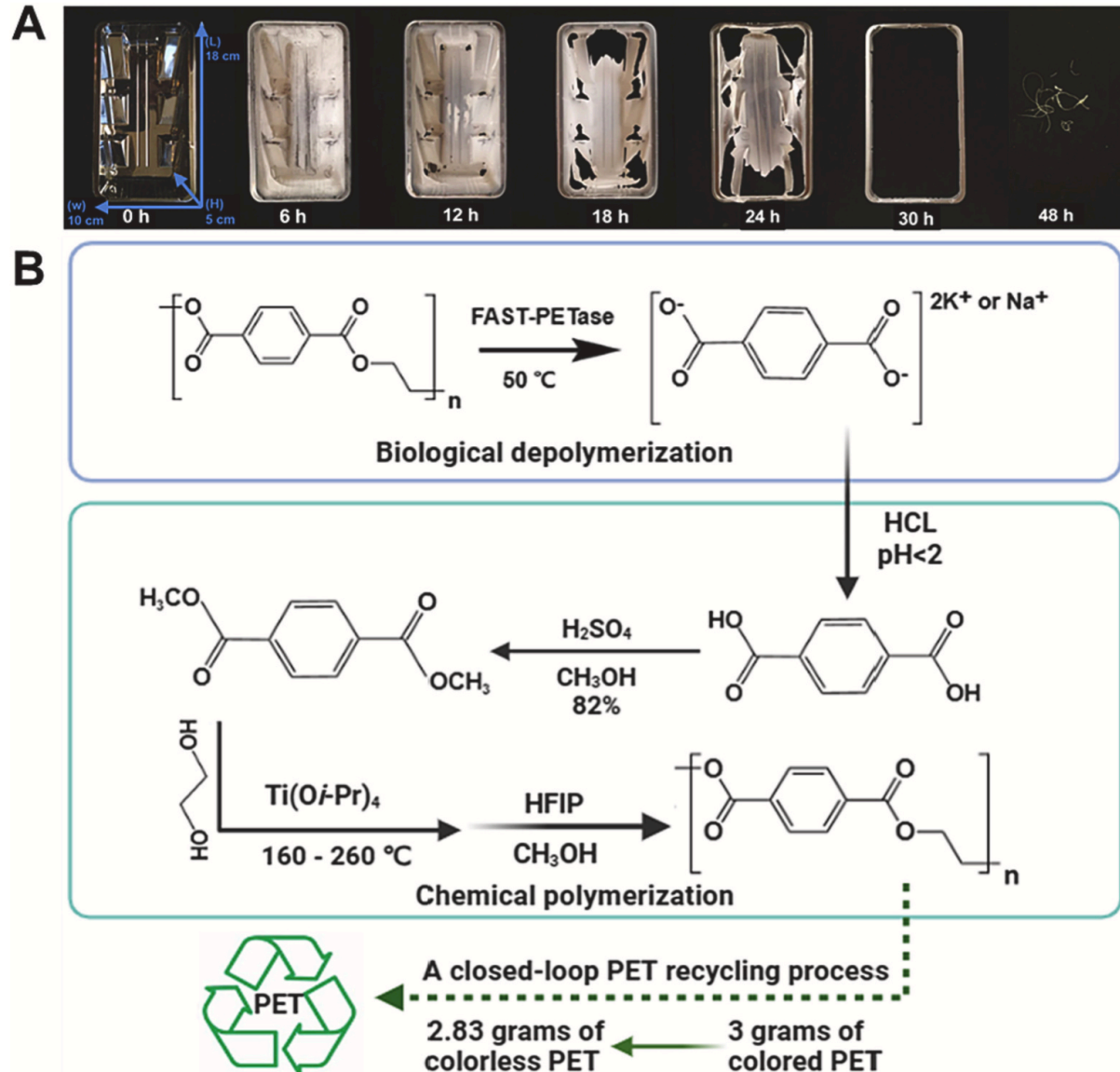


Fig. 2. Types of common plastics and their representative uses in daily life (A) non-biodegradable plastic: PET, PUR, PE, PP, PS and PVC, (B) biodegradable plastic: PLA (polylactic acid) and PHA (polyhydroxyalkanoates).

Lipase Application in Polymer Science: Emergence of PETase



R | S CHEM

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WELCOME TO R/S CHEMISTRY!

This UCLA created resource is designed to help organic chemistry students master stereochemical assignments. This project is led by [Professor Neil Garg](#) and students Francesca Ippoliti, Melinda Nguyen, Nikhil Shah, Emily Siegler, and Andrew Kelleghan.

R/S Chemistry is free for non-commercial purposes.

Credits

"Technology - Upbeat Loop", "Casual Loop #1" (ispeakwaves)

"Loop Computer Feeling Good" (LittleRobotSoundFactory)

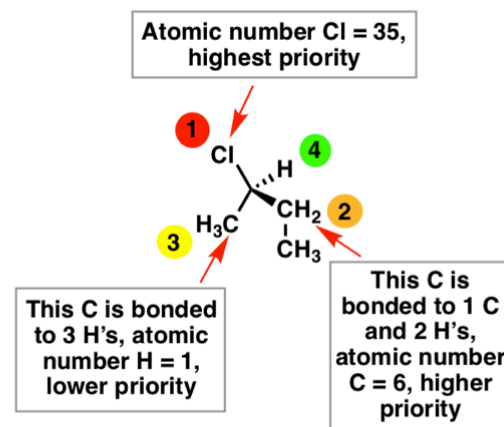
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We gratefully acknowledge the Trueblood Family, the [NIH PubChem Project](#), [Professor David Koes](#) (University of Pittsburgh), creator of [3dmol.js](#), and generous funding from [HHMI \(IDEA Grant\)](#).

How to Assign a Stereocenter

1. Assign priorities to the atoms directly bonded to the stereocenter.

- The highest atomic number is assigned the highest priority
 - If two atoms are the same, **(TIE!)**
Continue to the next atom in the chain and rank substituents, disregarding previous atoms in the chain
 - Treat a multiply bonded atom as an equivalent number of singly bonded atoms
- bonded atoms



← BACK

NEXT →

Close Tutorial

Descriptors for Helical & Axial Chirality

1. Priority rules

Groups on a stereogenic element must be ranked according to CIP rules.

Highest priority - 1 to lowest - 4.

Rule 0: Proximity - groups closer to the viewer have higher priority.

Rule 1: Atomic number - higher atomic number higher priority.

Rule 2: Move along chain - rank atoms in same position until difference found.

groups	HO	H	CH ₂ OH	CH ₂ SH
1st atom	O	H	C	C
2nd atom	O, H	H	S, H, H	H, H, H
priority	1	4	3	2

Rule 3: Multiple bonds - count as multiple single bonds to same atom.

Rule 4: Atomic mass - higher mass of an isotope takes priority.

Rule 5: Configuration - Z, R & M have higher priority than E, S & P.

2. Helical chirality

Helical chirality - some inherently chiral molecules possess helical chirality. To determine stereochemical descriptor:

(i) Identify axis - the stereogenic axis.

(ii) View along axis - rotation clockwise as move from front to back = *P* or plus while anticlockwise = *M* or minus

3. Helicity & conformers

Chiral conformers can be defined as a helix:

(i) Identify axis - the bond being rotated

(ii) Identify highest ranked groups - at front & rear of axis

(iii) Draw arrow connecting groups - start with front group & move to rear by smallest angle

(iv) Assign descriptor - clockwise arrow = *P* & anticlockwise arrow = *M*

4. Axial chirality R/S

Axially chiral compounds can be treated as an **elongated tetrahedron** and defined as *R_a* or *aR* or *S_a* or *aS*:

(i) Identify axis & view along axis - often cumulated double bonds or the bond with restricted rotation in atropisomers. Can be viewed from either end.

(ii) Rank groups - two groups closest to viewer have the highest ranks (rule 0).

(iii) Draw Newman projection - along axis from same point of view as ranking.

(iv) Assign configuration - draw arrow connecting priority 1→2→3. Clockwise = *R_a* or anticlockwise = *S_a*.

Biaryl atropisomers - are treated in exactly the same manner (see [website](#))

5. Axial chirality P/M

A stereogenic axis can be viewed as a **helix** and defined as either *P* or *M*:

(i) Identify axis & view along axis - often cumulated double bonds or the bond with restricted rotation in atropisomers.

(ii) Rank highest group - at the front of the axis and the highest at rear of axis.

(iii) Draw Newman projection - along axis (doesn't matter which end).

(iv) Assign configuration - draw arrow connecting front group to back group. Clockwise = *P* or anticlockwise = *M*.

For axial chirality only - *S_a* = *P* & *R_a* = *M*

Brief Overview of Axial Chirality

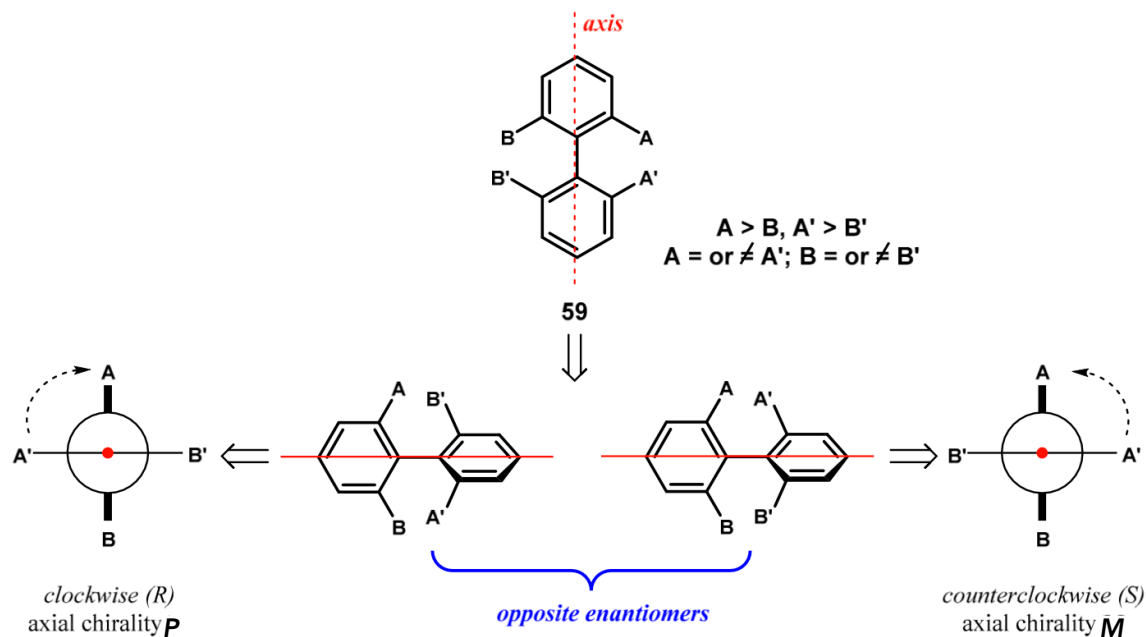


Figure 27. Enantiomeric structures for a generic conformationally stable biphenyl compound.

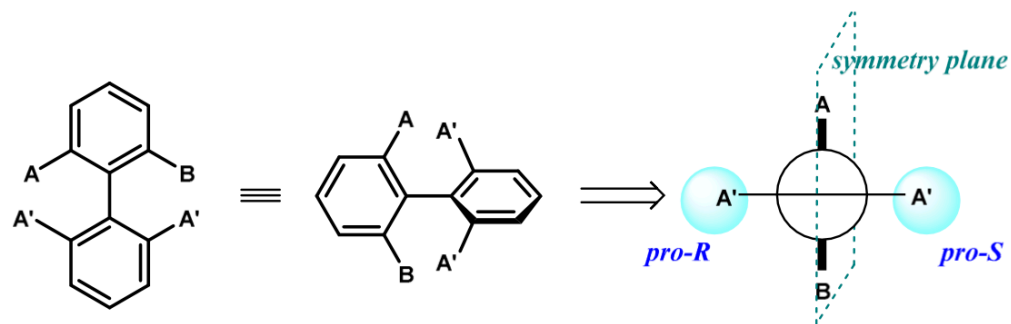


Figure 28. Prochirality in σ -symmetric biphenyls.

Lipase-Catalyzed Desymmetrization of Biphenyls

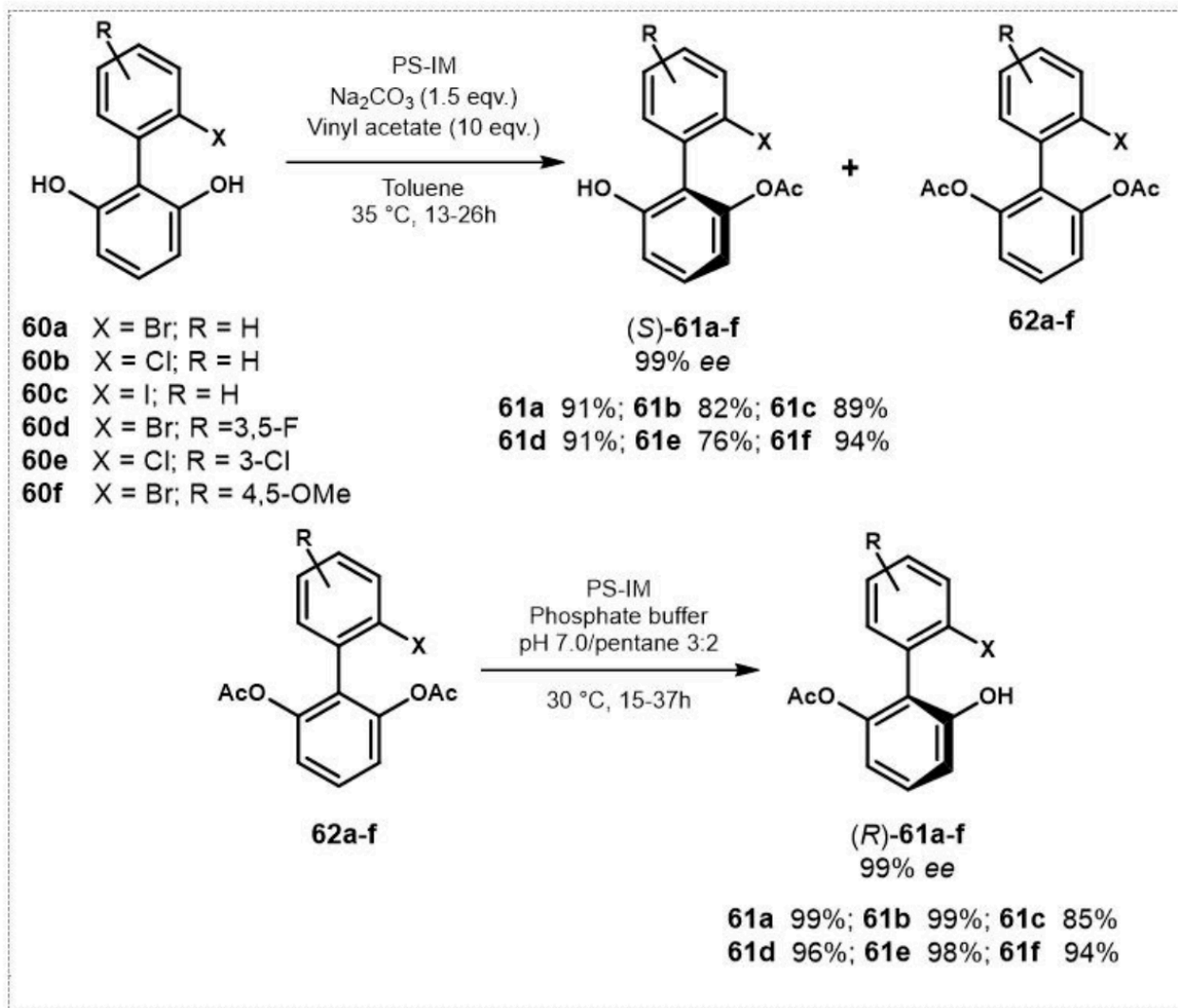


Figure 29. Enantiodivergent synthesis of optically active biphenyls 61a-f.