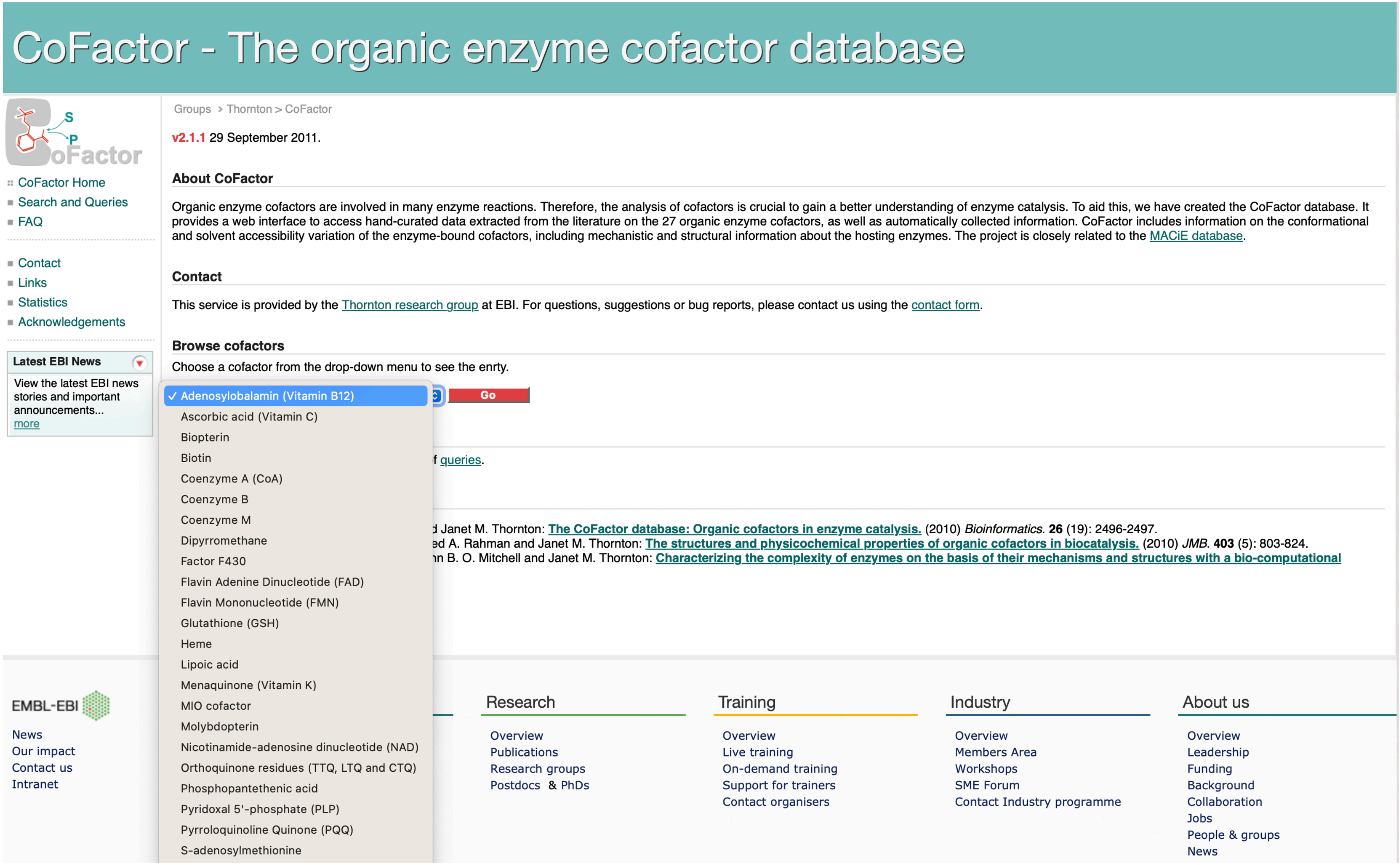
Resource Alert: Organic Enzyme Cofactor Database



CoFactor - The organic enzyme cofactor database

Groups > Thornton > CoFactor

v2.1.1 29 September 2011.

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About CoFactor

Organic enzyme cofactors are involved in many enzyme reactions. Therefore, the analysis of cofactors is crucial to gain a better understanding of enzyme catalysis. To aid this, we have created the CoFactor database. It provides a web interface to access hand-curated data extracted from the literature on the 27 organic enzyme cofactors, as well as automatically collected information. CoFactor includes information on the conformational and solvent accessibility variation of the enzyme-bound cofactors, including mechanistic and structural information about the hosting enzymes. The project is closely related to the MACiE database.

Contact

This service is provided by the Thornton research group at EBI. For questions, suggestions or bug reports, please contact us using the contact form.

Browse cofactors

Choose a cofactor from the drop-down menu to see the enrty.

✓ Adenosylobalamin (Vitamin B12)
Ascorbic acid (Vitamin C)
Biopterin
Biotin
Coenzyme A (CoA)
Coenzyme B
Coenzyme M
Dipyrromethane
Factor F430
Flavin Adenine Dinucleotide (FAD)
Flavin Mononucleotide (FMN)
Glutathione (GSH)
Heme
Lipoic acid
Menaquinone (Vitamin K)
MIO cofactor
Molybdopterin
Nicotinamide-adenosine dinucleotide (NAD)
Orthoquinone residues (TTQ, LTQ and CTQ)
Phosphopantethenic acid
Pyridoxal 5'-phosphate (PLP)
Pyrroloquinoline Quinone (PQQ)
S-adenosylmethionine

Go

f queries.

d Janet M. Thornton: The CoFactor database: Organic cofactors in enzyme catalysis. (2010) *Bioinformatics.* **26** (19): 2496-2497.
ed A. Rahman and Janet M. Thornton: The structures and physicochemical properties of organic cofactors in biocatalysis. (2010) *JMB.* **403** (5): 803-824.
n B. O. Mitchell and Janet M. Thornton: Characterizing the complexity of enzymes on the basis of their mechanisms and structures with a bio-computational

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CoFactor: Nicotinamide-adenine dinucleotide

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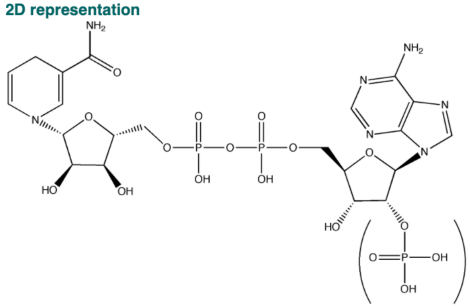
General information

2D representation



Key facts

Cofactor type	coenzyme or prosthetic group
Human metabolism	from Vitamin B_3
IUPAC name	2'-O-phosphonoadenosine 5'-{3-[1-(3-carbamoylpyridinio)-1,4-anhydro-D-ribitol-5-yl] hydrogen diphosphate}
Curator	JDF

Tags

- phosphate-containing cofactors
- nucleotide-containing cofactors

Molecular function

NAD(P) assists in hydride transfers [2]. Therefore the cofactor exists in two states: NAD(P)+ and NAD(P)H/H+.

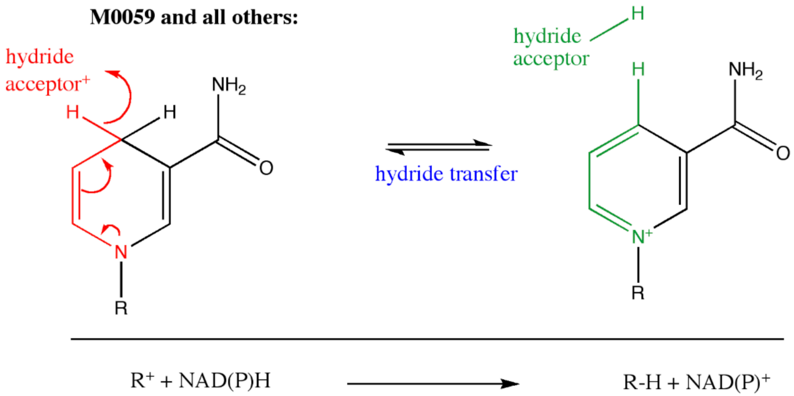
In addition to its catalytic function, NAD(P) is also involved in regulation. NAD levels in the cell influence transcriptional reprogramming and regulate physiological functions of a cell in response to perturbations in NAD(H) levels to maintain homeostatic conditions [3].

Resource Alert: Organic Enzyme Cofactor Database: Cofactor Mechanisms

Mechanisms of Nicotinamide-adenine dinucleotide

The mechanisms below have been extracted from MACiE. The substrates and products are abstracted to their essential parts, which are necessary to explain the reaction the cofactor takes part in. The atoms involved in the next step are highlighted in red, and the ones that have been changed by the last step are shown in green. Red takes precedence when both applies.

Mechanism #1 for Nicotinamide-adenine dinucleotide



Description of mechanism

The hydride transfer is initiated by the free electron pair of the N-atom. The hydride transfer is always combined with an elimination and an addition.

In liver alcohol dehydrogenase (1.1.1.1), an OH- ion (ligand of a Zinc atom) activates the C4 atom of the nicotinamide ring. Therefore NAD is indirectly linked to a catalytic metal ion [2].

The presence of a water molecule in the vicinity of nicotinamide has been found in several other protein structures [2].

Resource Alert: Organic Enzyme Cofactor Database: Enzymes and Domains

Enzymes - Nicotinamide-adenine dinucleotide

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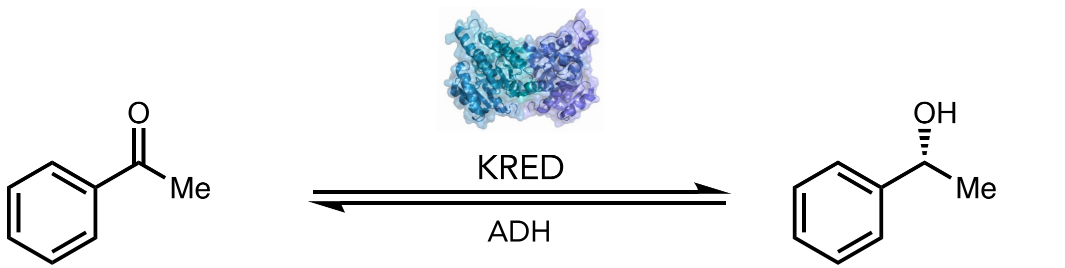
Nicotinamide-adenine dinucleotide-using

Enzymes, which use Nicotinamide-adenine dinucleotide as a cofactor

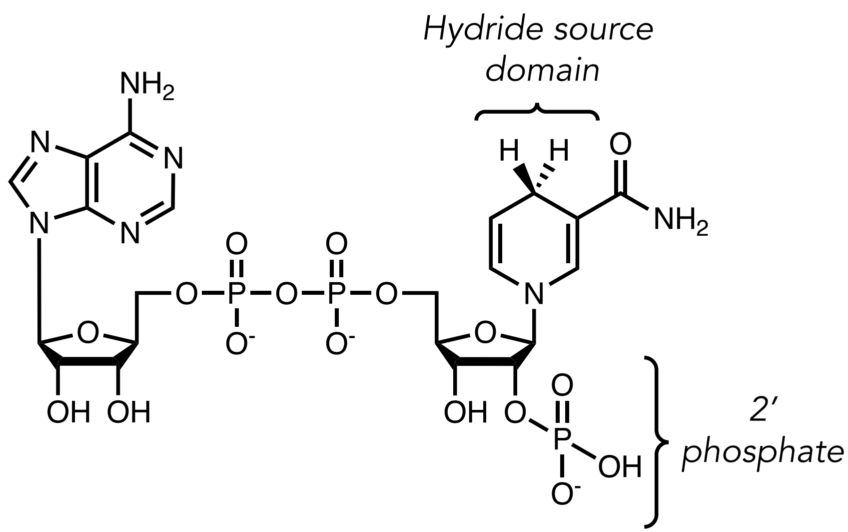
Enzyme name	E.C. number	Enzyme mechanism	CATH domain	3D structure	Species information	Reference
alcohol dehydrogenase	1.1.1.1	M0255, M0256	1.10.1040.10 1.10.287.610 see all	1a71 (PDBsum) 1agn (PDBsum) see all	species	[2]
L-xylulose reductase	1.1.1.10			1pr9 (PDBsum) 1wnt (PDBsum) see all	species	[IntEnz]
3-oxoacyl-[acyl-carrier-protein] reductase	1.1.1.100			1edo (PDBsum) 1q7b (PDBsum) see all	species	[IntEnz]
Acylglycerone-phosphate reductase	1.1.1.101				species	[IntEnz]
3-dehydrosphinganine reductase	1.1.1.102				species	[IntEnz]
L-threonine 3-dehydrogenase	1.1.1.103			2d8a (PDBsum) 2dfv (PDBsum) see all	species	[IntEnz]
4-oxoproline reductase	1.1.1.104					[IntEnz]
Retinol dehydrogenase	1.1.1.105				species	[IntEnz]
Pantoate 4-dehydrogenase	1.1.1.106					[IntEnz]
Pyridoxal 4-dehydrogenase	1.1.1.107			3nug (PDBsum)	species	[IntEnz]
Carnitine 3-dehydrogenase	1.1.1.108					[IntEnz]
D-arabinitol 4-dehydrogenase	1.1.1.11				species	[IntEnz]
Indolelactate dehydrogenase	1.1.1.110					[IntEnz]
3-(imidazol-5-yl)lactate dehydrogenase	1.1.1.111					[IntEnz]
Indanol dehydrogenase	1.1.1.112				species	[IntEnz]
L-xylose 1-dehydrogenase	1.1.1.113					[IntEnz]
Apiose 1-reductase	1.1.1.114					[IntEnz]
Ribose 1-dehydrogenase (NADP(+))	1.1.1.115					[IntEnz]
D-arabinose 1-dehydrogenase	1.1.1.116				species	[IntEnz]
D-arabinose 1-dehydrogenase (NAD(P)(+))	1.1.1.117				species	[IntEnz]
Glucose 1-dehydrogenase (NAD(+))	1.1.1.118			2zk7 (PDBsum)	species	[IntEnz]
Glucose 1-dehydrogenase (NADP(+))	1.1.1.119					[IntEnz]
L-arabinitol 4-dehydrogenase	1.1.1.12					[IntEnz]
Galactose 1-dehydrogenase (NADP(+))	1.1.1.120					[IntEnz]
Aldose 1-dehydrogenase	1.1.1.121					[IntEnz]
D-threo-aldose 1-dehydrogenase	1.1.1.122					[IntEnz]
Sorbose 5-dehydrogenase (NADP(+))	1.1.1.123					[IntEnz]

Ketoreductase (KRED) and Alcohol Dehydrogenase (ADH) Overview



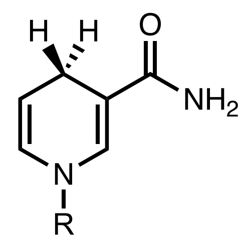
Ketoreductases (KREDs) catalyze selective reductions of aldehydes and ketones and are referred to as Alcohol Dehydrogenases (ADHs) in the reverse direction

organic cofactor



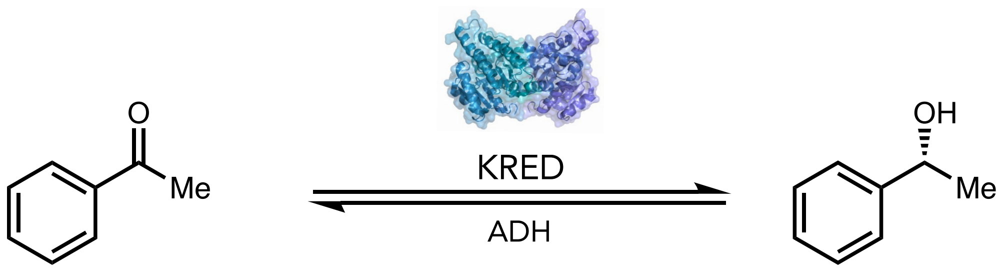
Nicotinamide Adenine Dinucleotide Phosphate (NADPH)
Reduced cofactor and hydride source

we will abbreviate as:



NAD(P)H

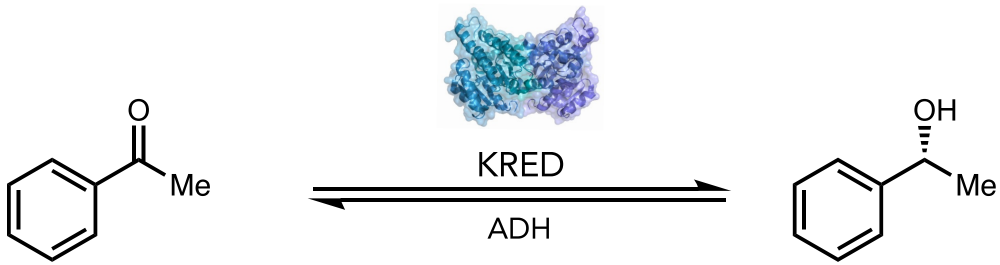
Ketoreductase (KRED) and Alcohol Dehydrogenase (ADH) Overview



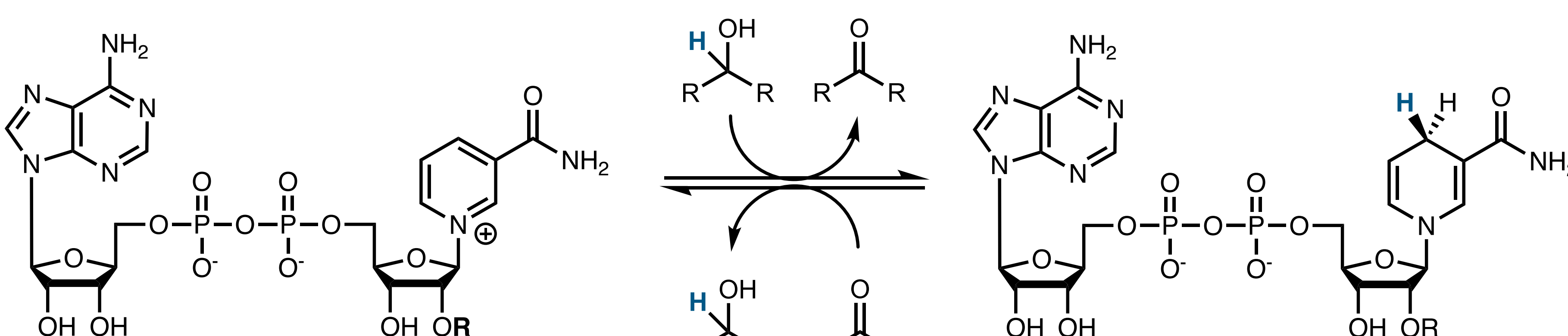
Ketoreductases (KREDs) catalyze selective reductions of aldehydes and ketones and are referred to as Alcohol Dehydrogenases (ADHs) in the reverse direction

- Also referred to as alcohol dehydrogenases (ADH)
- An oxidoreductase divided formally into five classes
  - Mechanistically, can be simplified into two groups (metal dependent or not)
  - Metal dependent KREDs often utilize divalent metal cations (e.g. Zn^{2+}, Mg^{2+})
- Dependent on NAD(P)H cofactor
  - Some KREDs use NADH, some use NADPH (difference is 2′ ribose phosphate group)
- Catalyzes both ketone reduction or alcohol oxidation, depending on conditions
  - In synthetic applications, often run in reductive direction to generate stereocenters
- Almost always coupled with some form of cofactor regeneration
  - Excess simple alcohol (*i*PrOH, EtOH)
  - Catalytic glucose dehydrogenase (GDH) and superstoichiometric glucose

Ketoreductase (KRED) and Alcohol Dehydrogenase (ADH): The Critical Equlibrium



Ketoreductases (KREDs) catalyze selective reductions of aldehydes and ketones and are referred to as Alcohol Dehydrogenases (ADHs) in the reverse direction



R = Phoshphate (NADP^{+})

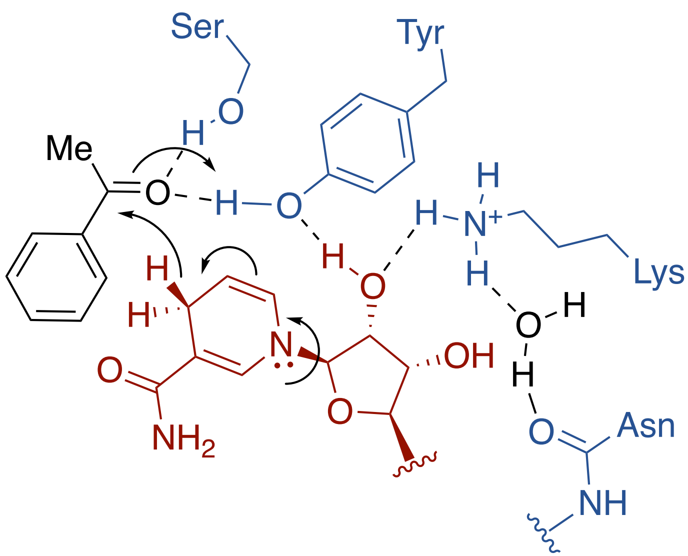
R = H (NAD^{+})

R = Phoshphate (NADP^{H})

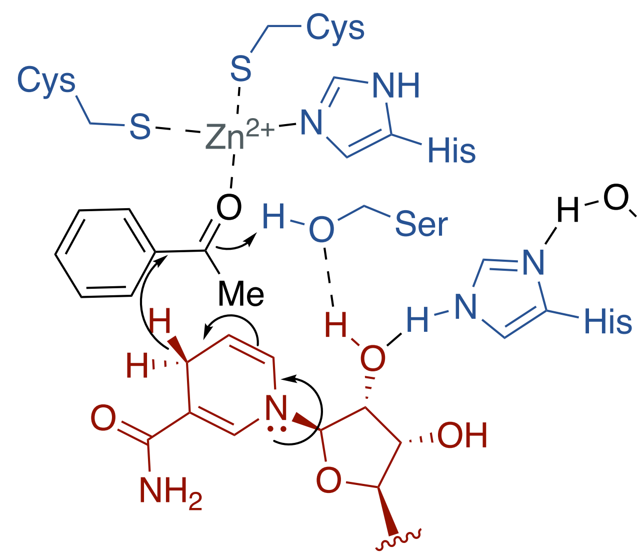
R = H (NAD^{H})

Ketoreductase (KRED) and Alcohol Hydrogenase (ADH): Mechanism

Active site for catalytic triad ketone activation



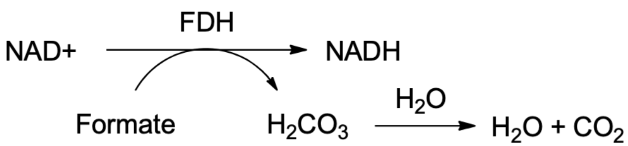
Active site for cationic divalent metal ketone activation



- Mechanism starting with reduced cofactor
  - Substrate ketone enters active site and is activated via Lewis acid (either through hydrogen bonding or a metal)
    - Triad residues can vary, though almost always contain protic moeities
  - Reduced cofactor NAD(P)H donates a hydride to the carbonyl carbon, and the carbonyl oxygen abstracts a proton from a nearby residue
    - Both cases involve a series of key residues/active site waters for proton relay
  - Product alcohol leaves active site, with cofactor now in its oxidized state NAD(P)
  - Cofactor regeneration can occur in one of two ways
    - Excess simple alcohol (*i*PrOH, EtOH) allows for the reverse reaction to occur
    - NAD(P) exits the active site, binds with GDH, and glucose reduces NAD(P) to NAD(PH), which exits and binds the KRED

Common Enzyme-Mediated Turnover Systems

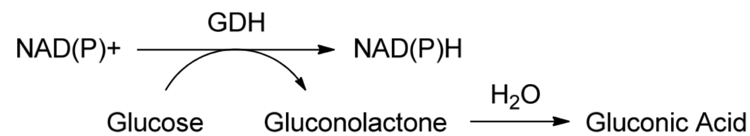
FORMATE DEHYDROGENASE



Formate Dehydrogenases (FDHs) enable the regeneration of NADH from NAD+ by catalyzing the oxidation of formate to bicarbonate. The driving force is the release of CO_2.

Our **FDH-101** is a natural enzyme with a specific activity of ≥ 1.0 U/mg.

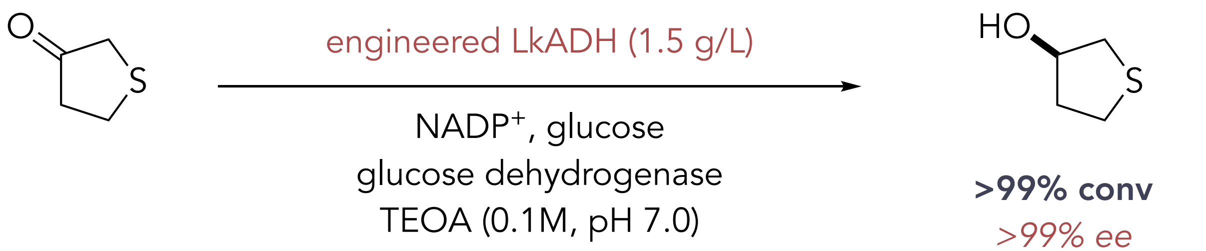
GLUCOSE DEHYDROGENASE



Glucose Dehydrogenases enable the regeneration of NAD(P)H from $NAD(P)^+$ by catalyzing the oxidation of β-D-glucose to D-glucono-1,5-lactone. Note that D-glucono-1,5-lactone is easily hydrolyzed to gluconic acid, lowering the pH of the reaction.

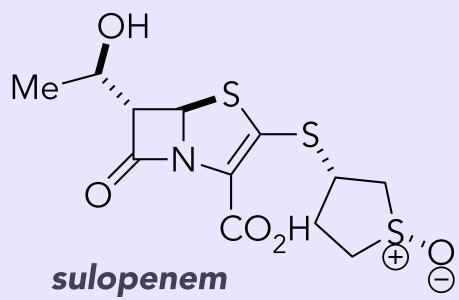
Codexis offers two different engineered GDHs: **GDH-105** and **CDX-901**. **CDX-901** has a specific activity of ≥ 50 U/mg and is more cost-effective. **GDH-105** has a specific activity of ≥ 44 U/mg and can operate at a wider pH and temperature range.

Select Biocatalysis (KRED) vs Chemical Method (CBS) Comparisons from Industry



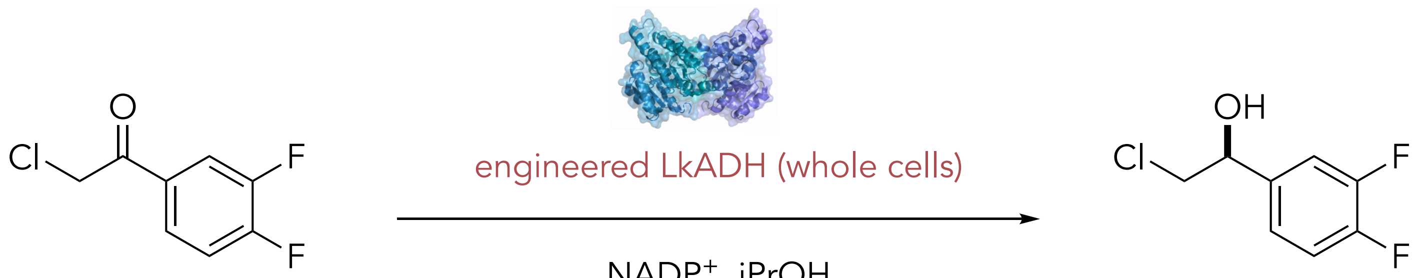
>99% conv
>99% ee

76% conv
23% ee
(with *(R)*-Me-CBS)



sulopenem
(antibacterial)

Select Biocatalysis (KRED) vs Chemical Method (CBS) Comparisons from Industry



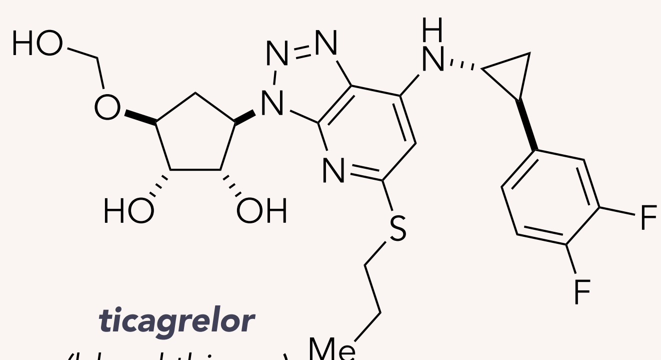
>99% conv

>99% ee

94% conv

94% ee

(with *(S)*-Me-CBS)



ticagrelor

(blood thinner)

Select Biocatalysis (KRED) vs Chemical Method (CBS) Comparisons from Industry

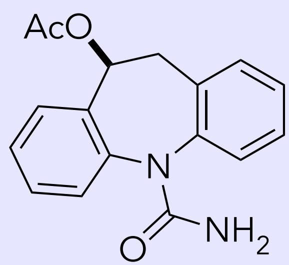
>99% conv

>99% ee

56% conv

93% ee

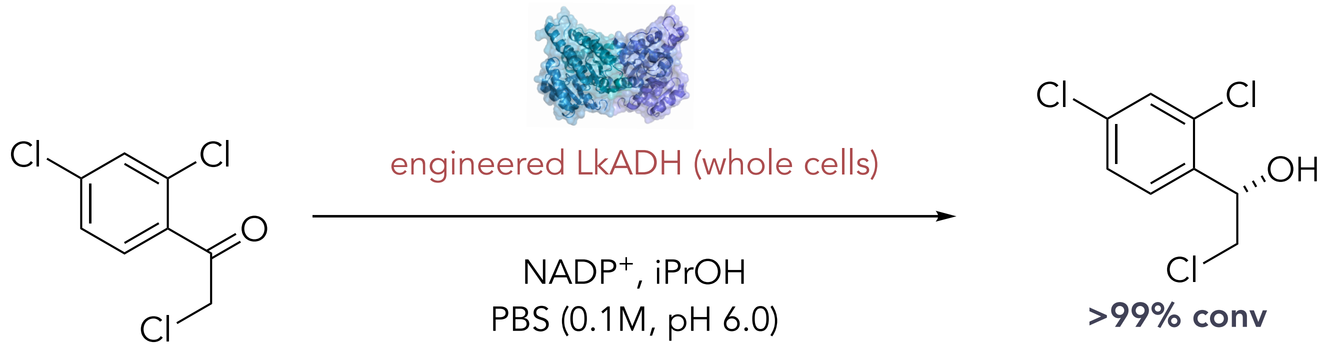
(with *(R)*-Me-CBS)



eslicarbazepine acetate

(antiepileptic)

Select Biocatalysis (KRED) vs Chemical Method (CBS) Comparisons from Industry



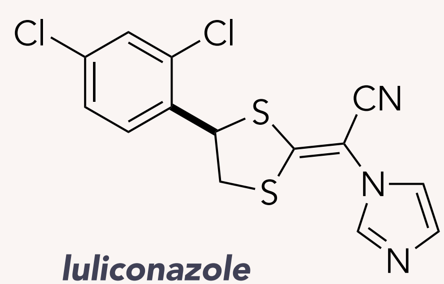
>99% conv

>99% ee

72% conv

99% ee

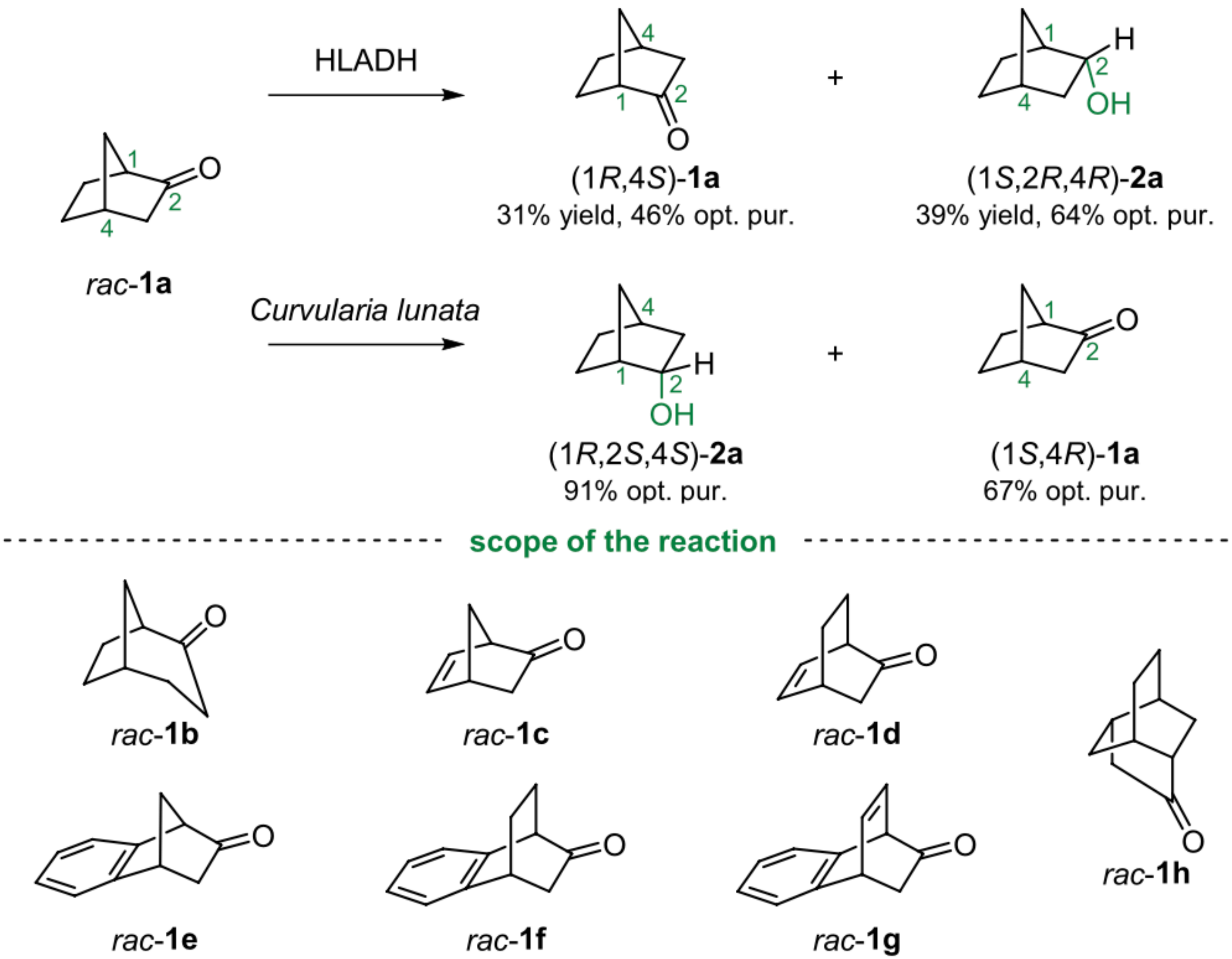
(with *(S)*-Me-CBS)



luliconazole

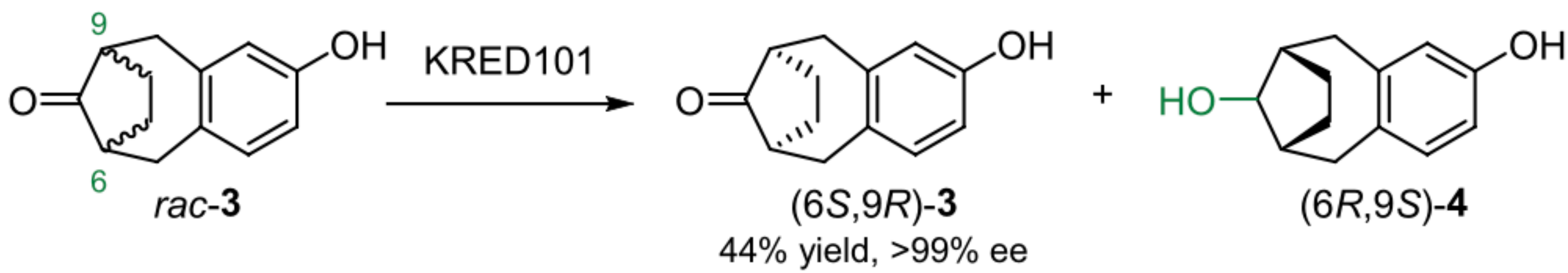
(antifungal)

Kinetic Resolution of Bridged Bicyclic Ketones



Frontiers in Bioengineering and Biotechnology ***2022***, *10*, *929784*.

Kinetic Resolution of Bridged Bicyclic Ketones



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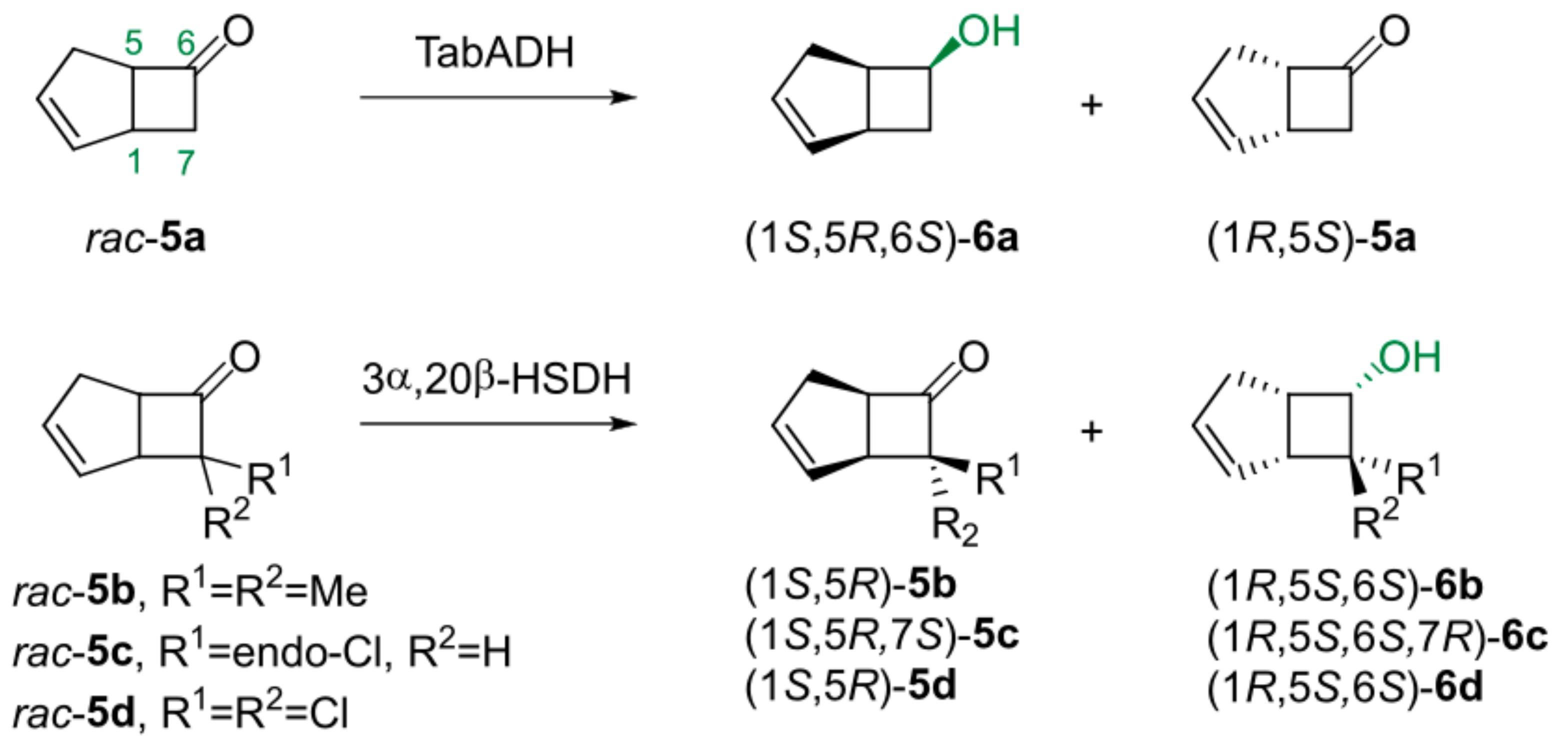
Kinetic Resolution of Bicyclic Ketones



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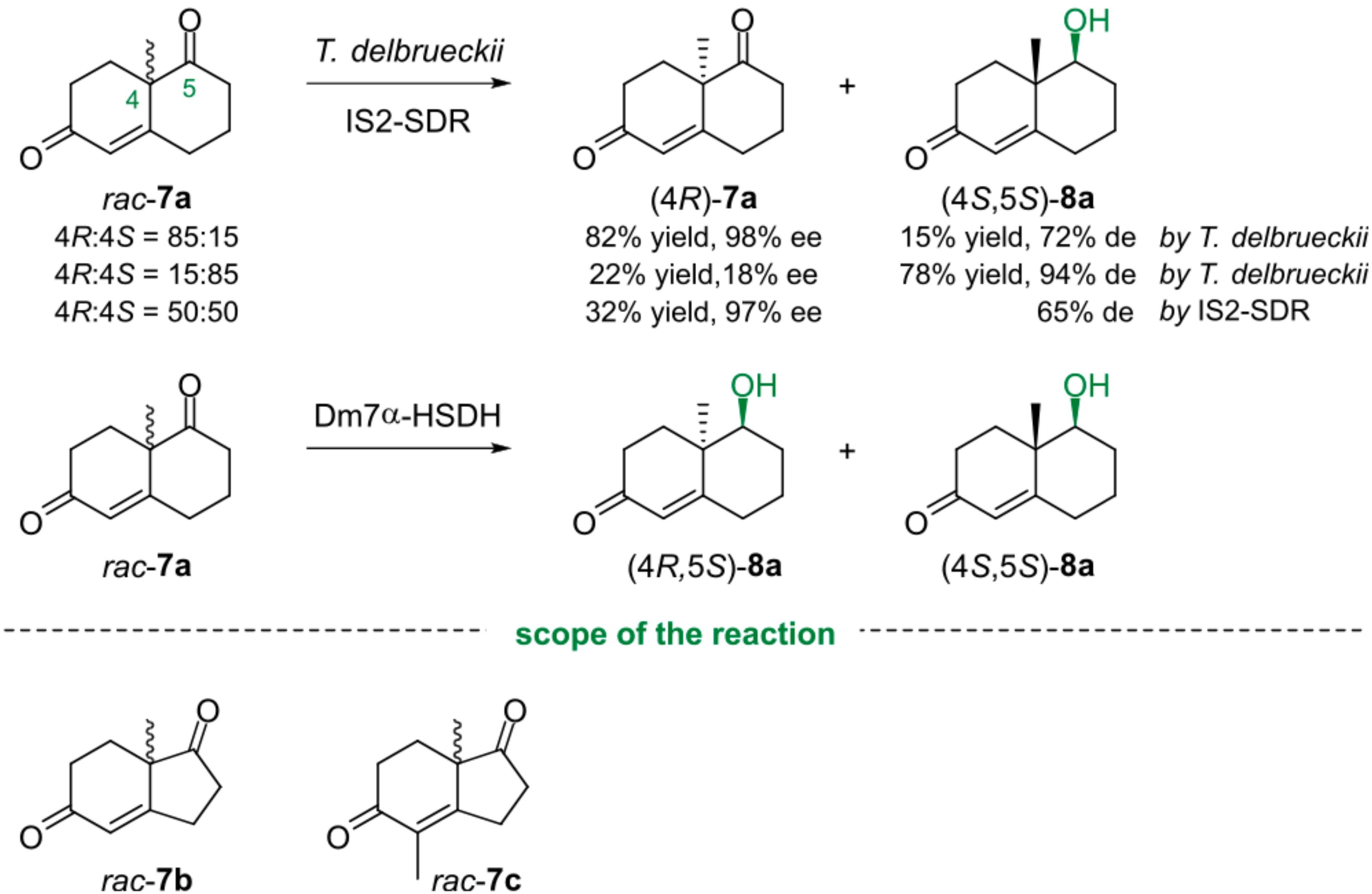
Kinetic Resolution of Wieland-Miescher and Hajos Parrish Ketones



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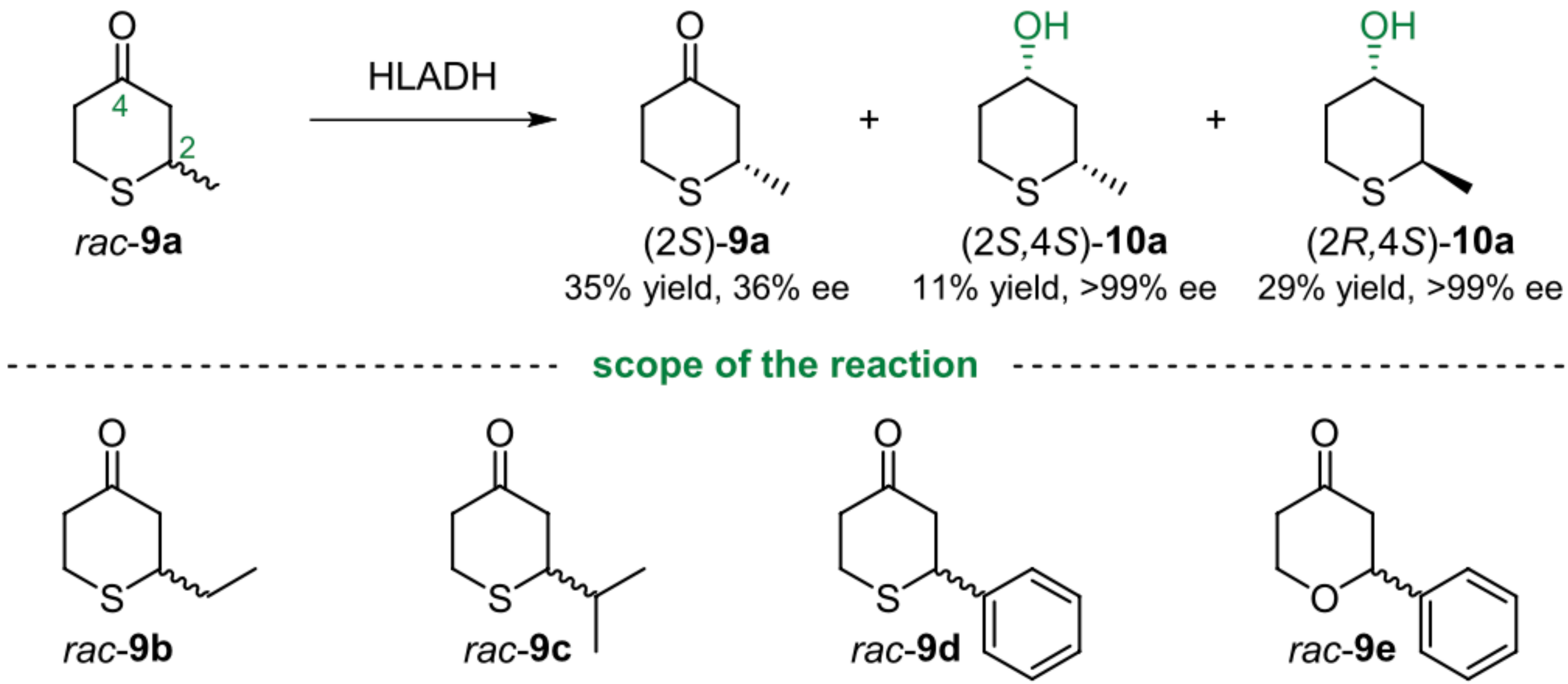
Kinetic Resolution of Ketone-Containing Heterocycles



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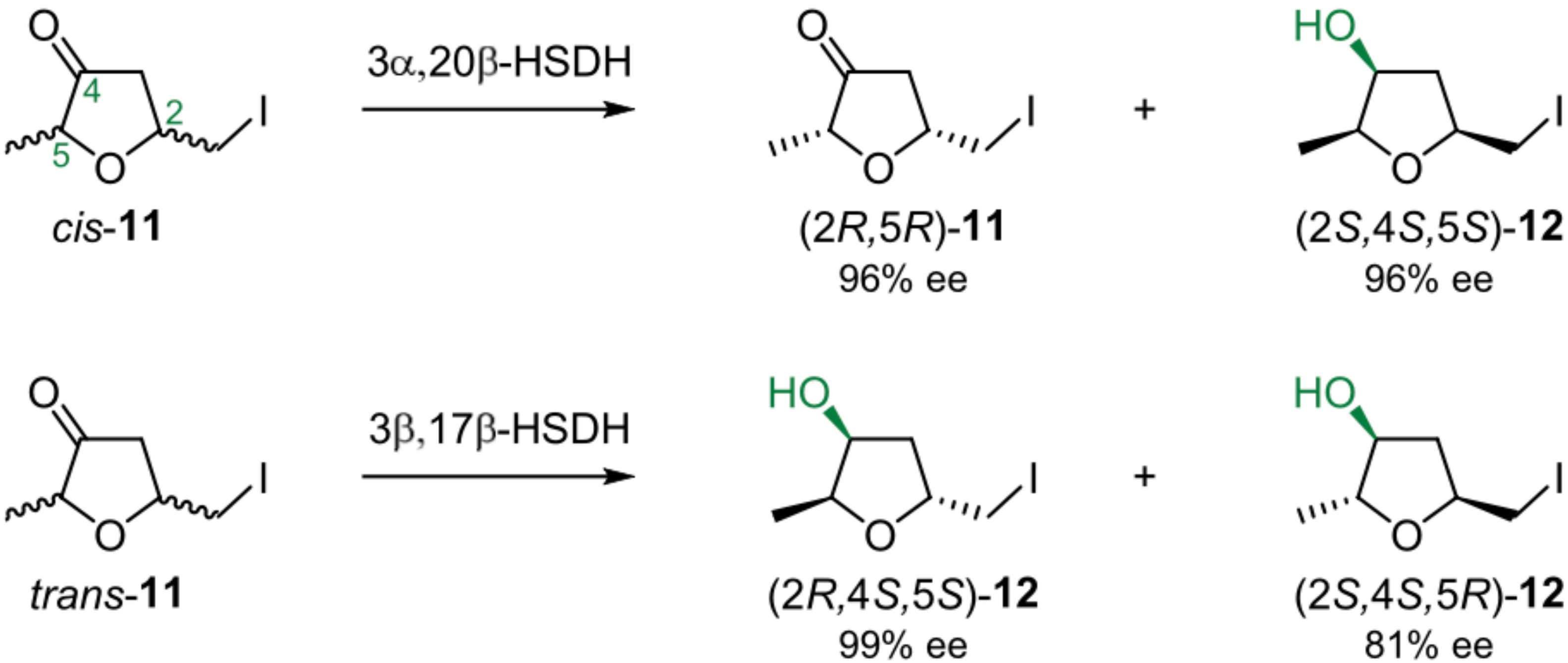
Kinetic Resolution of Ketone-Containing Heterocycles



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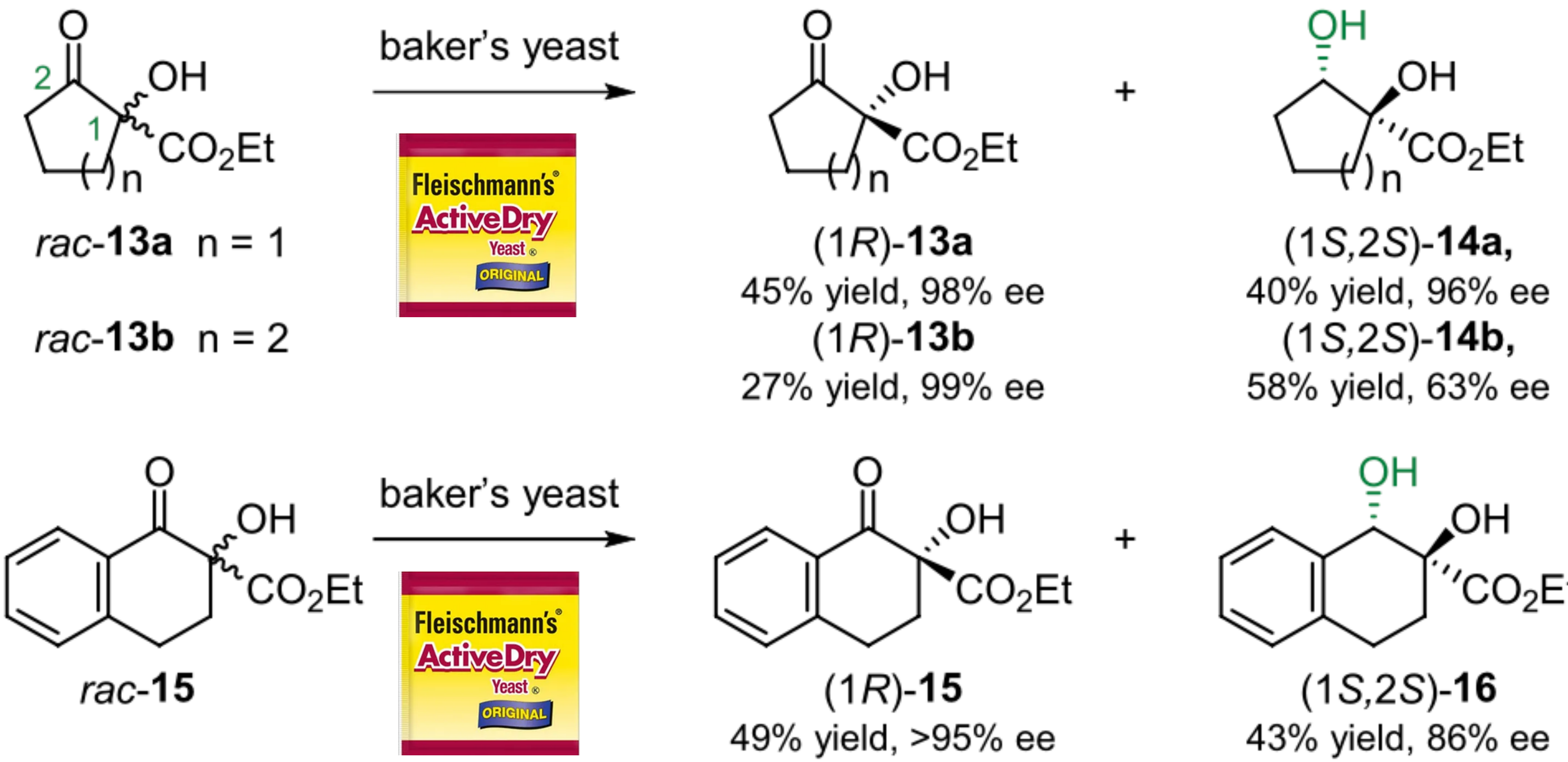
Kinetic Resolution of α-Hydroxy β-Ketoesters



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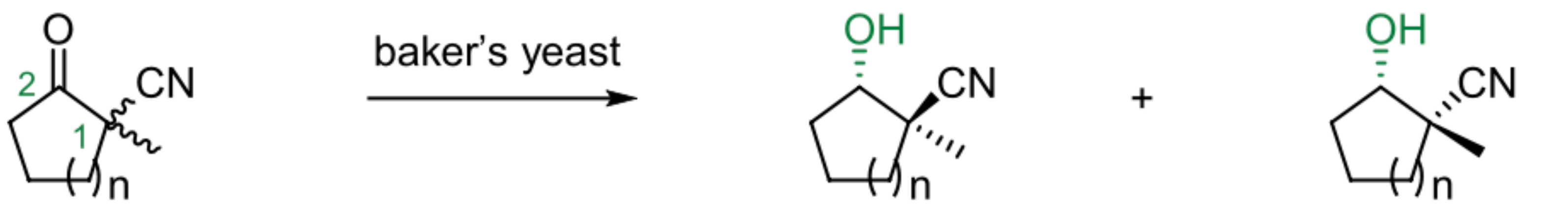
Kinetic Resolution of α-Ketonitriles



rac-**17a**, n = 1

rac-**17b**, n = 2

(1*R*,2*S*)-**18a**
38% yield, >99% ee
(1*R*,2*S*)-**18b**
34% yield, 99% ee

(1*S*,2*S*)-**18a,**
54% yield, 73% ee
(1*S*,2*S*)-**18b,**
58% yield, 61% ee

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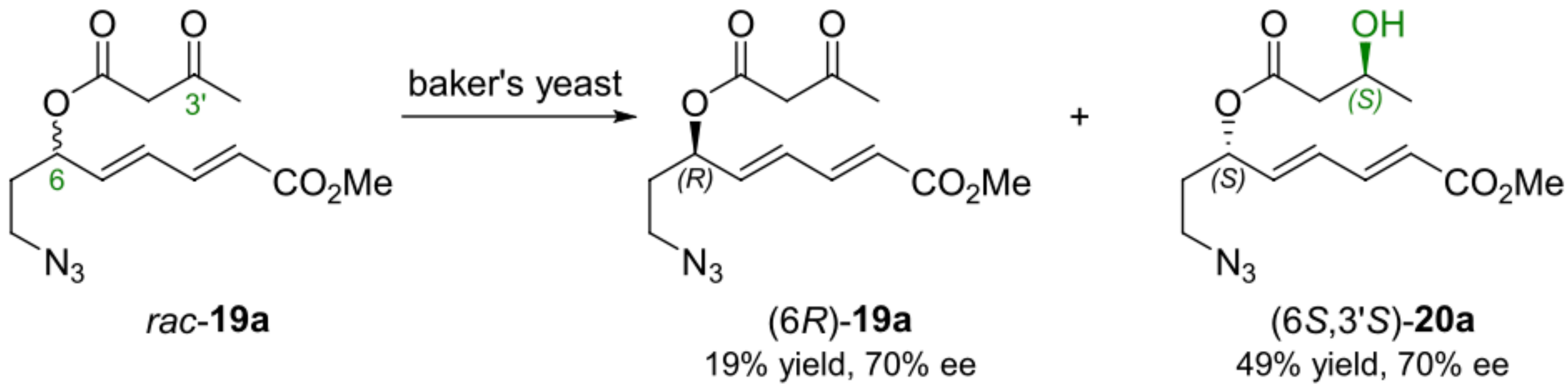
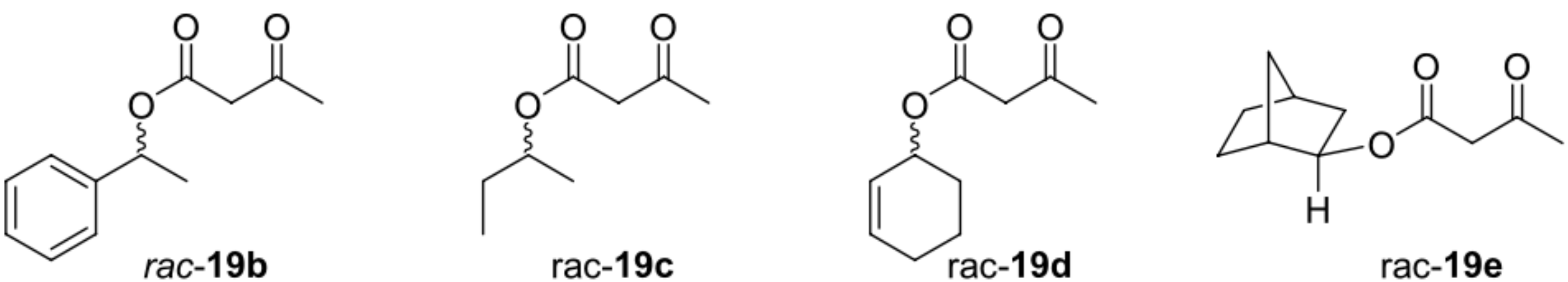
Kinetic Resolution of β-Ketoesters



scope of the reaction



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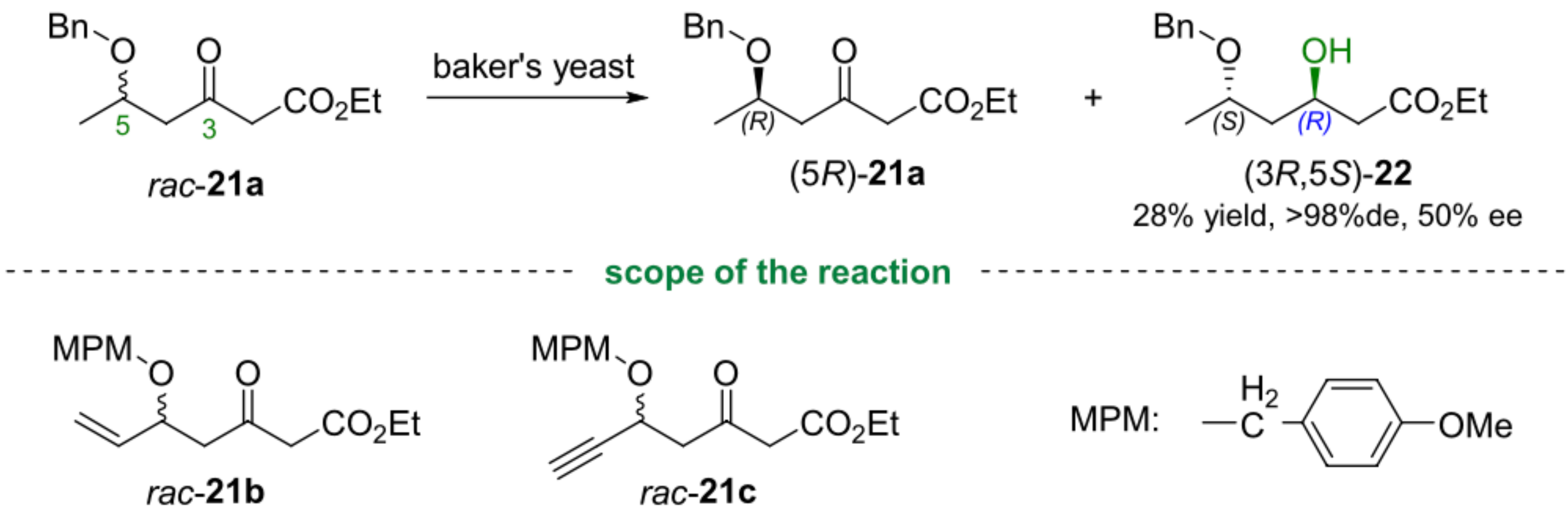
Kinetic Resolution of β-Ketoesters



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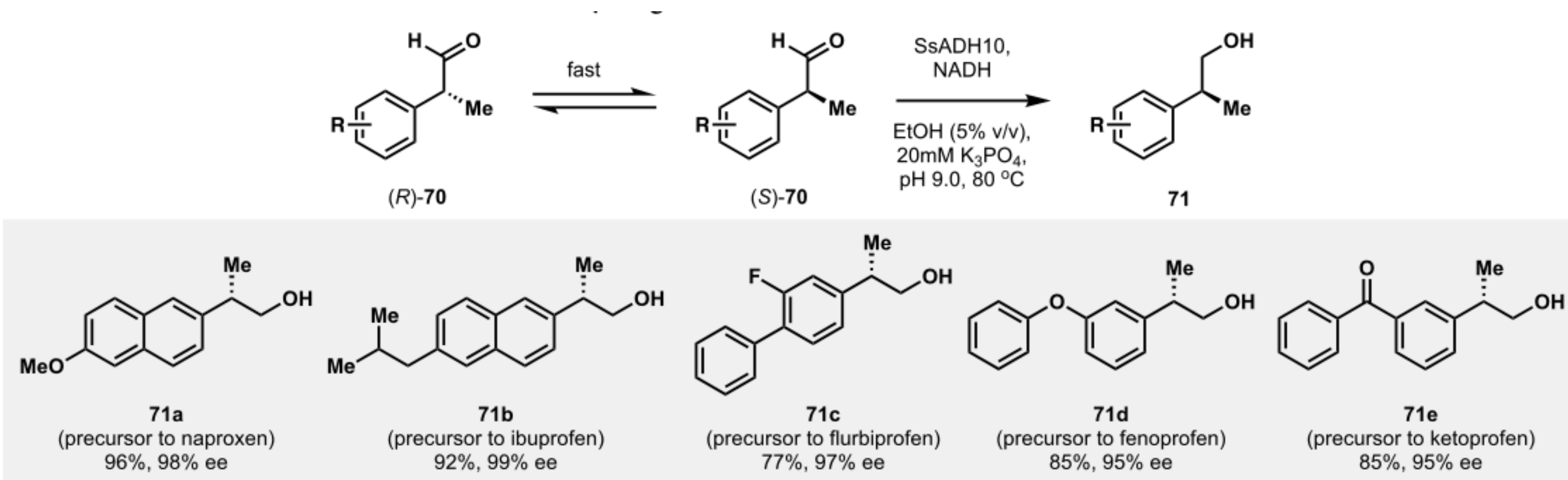
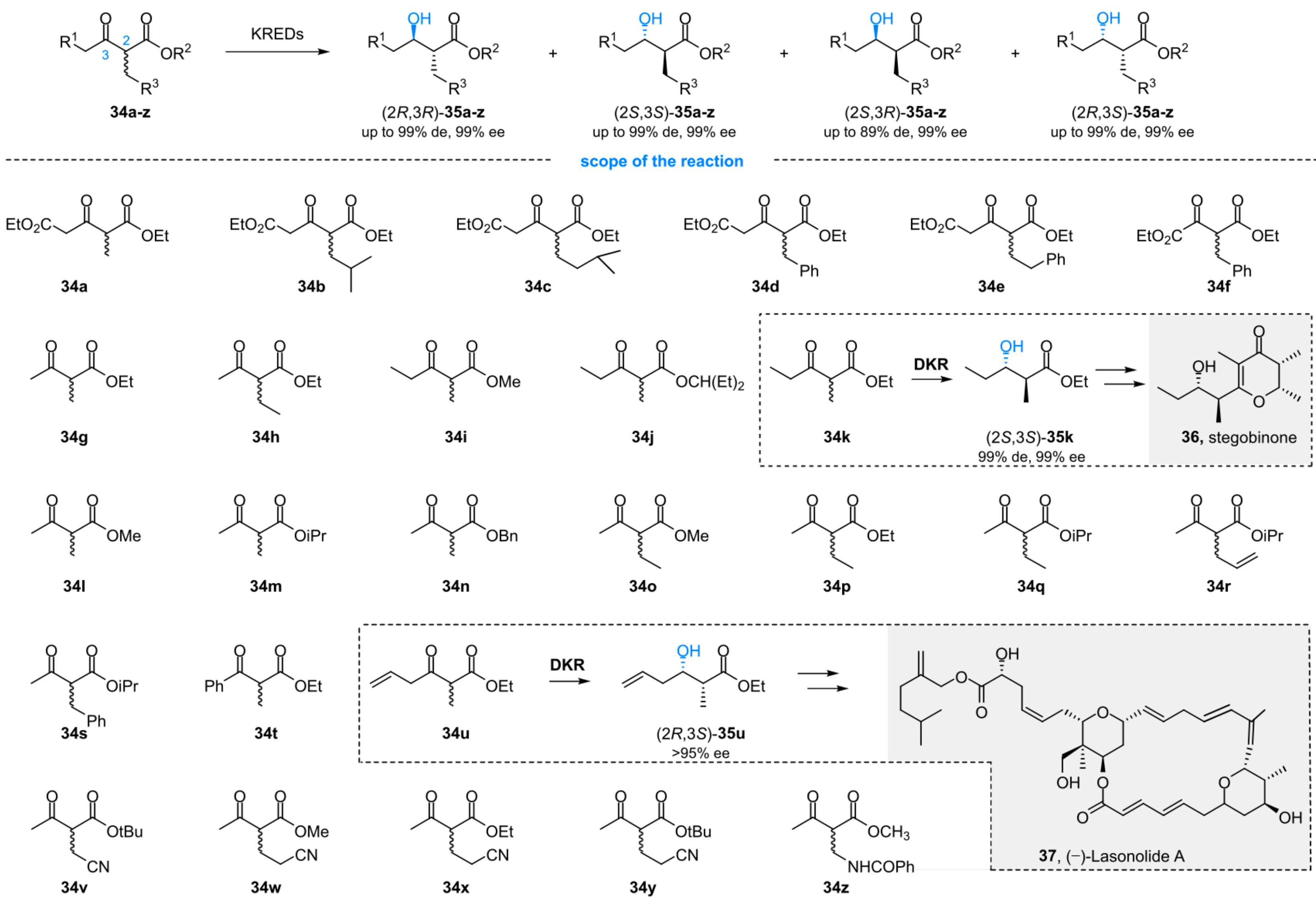
ADH-Mediated DKR of α-Disubtituted Aldehydes



Org. Process Res. Dev. ***2022***, 26, 1925-1943.

Dynamic Kinetic Resolution of α-Alkyl β-Ketoesters



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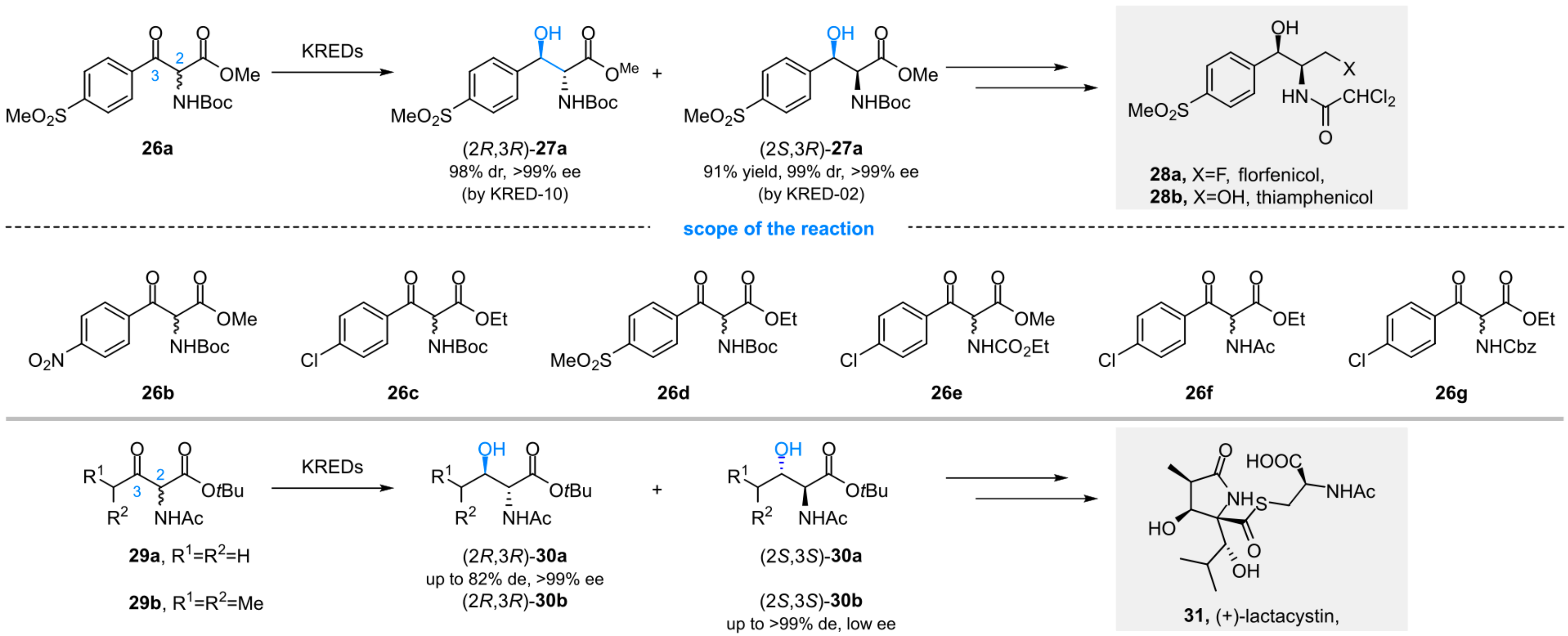
Dynamic Kinetic Resolution of α-Amido β-Ketoesters



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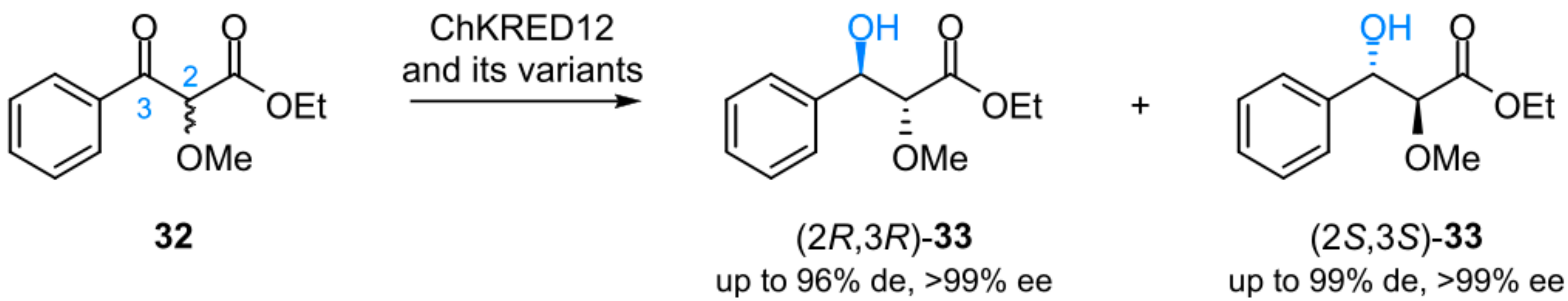
Dynamic Kinetic Resolution of α-Alkoxy β-Ketoesters



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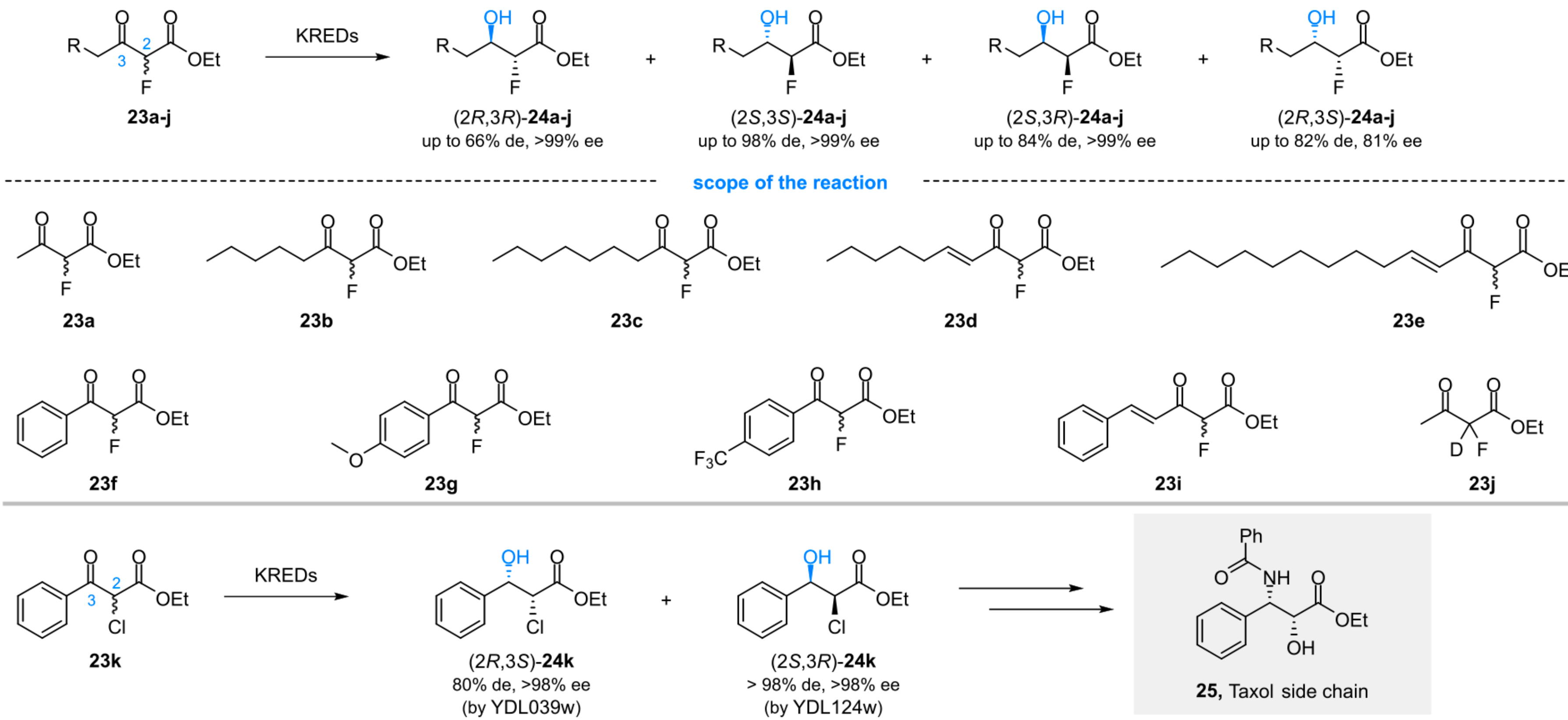
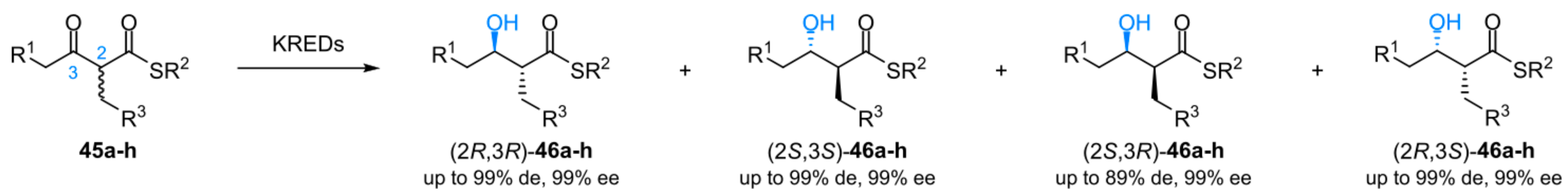
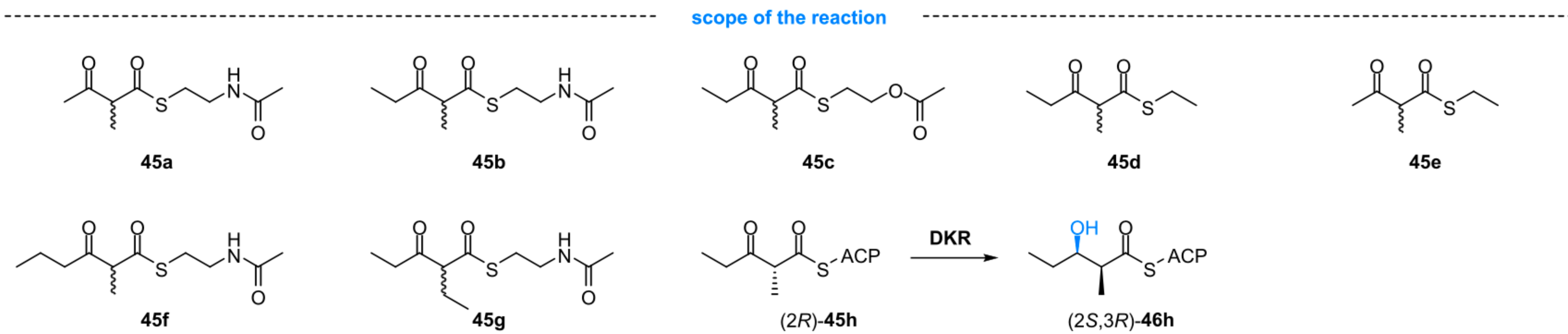
Dynamic Kinetic Resolution of α-Halo β-Ketoesters



Frontiers in Bioengineering and Biotechnology ***2022***, *10*, 929784.

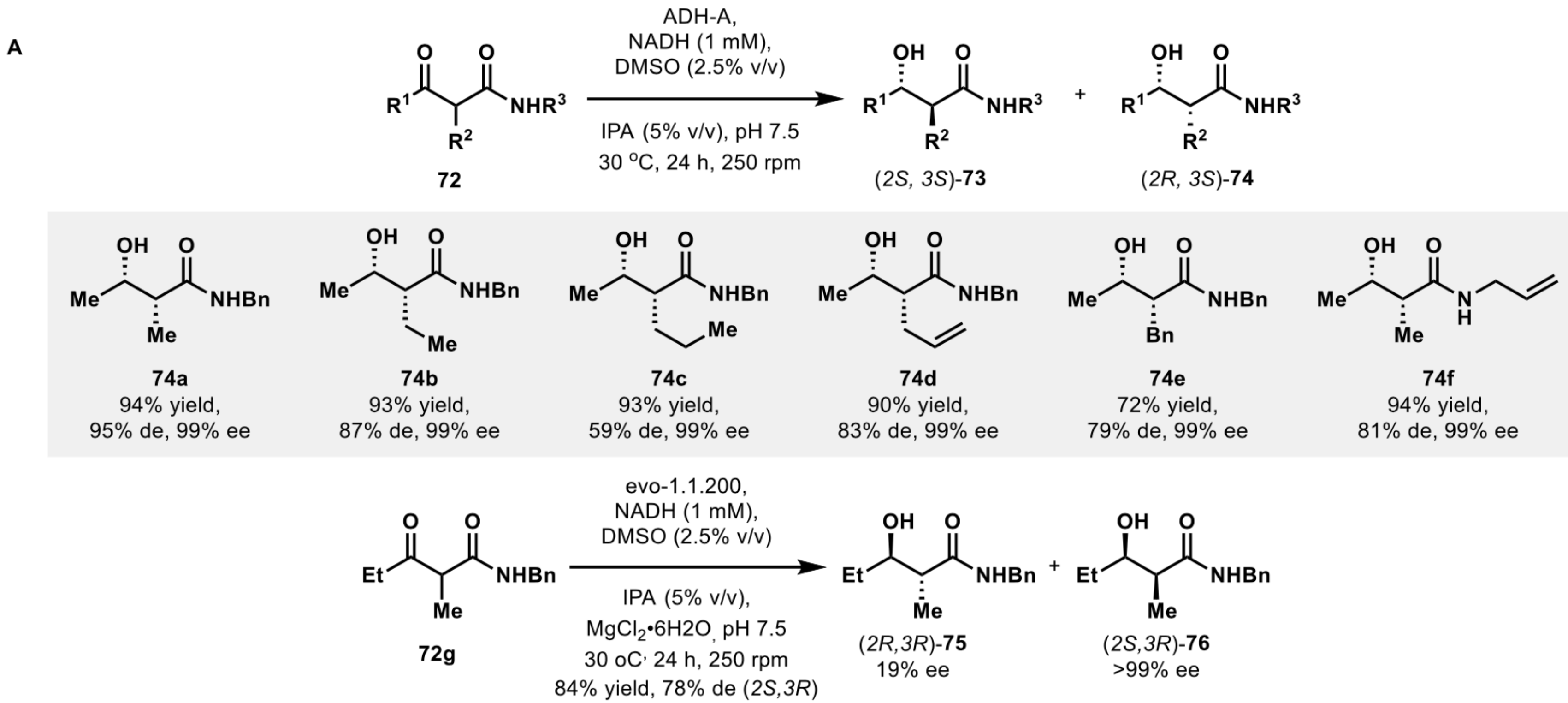
Dynamic Kinetic Resolution of α-Alkyl β-Ketothioesters





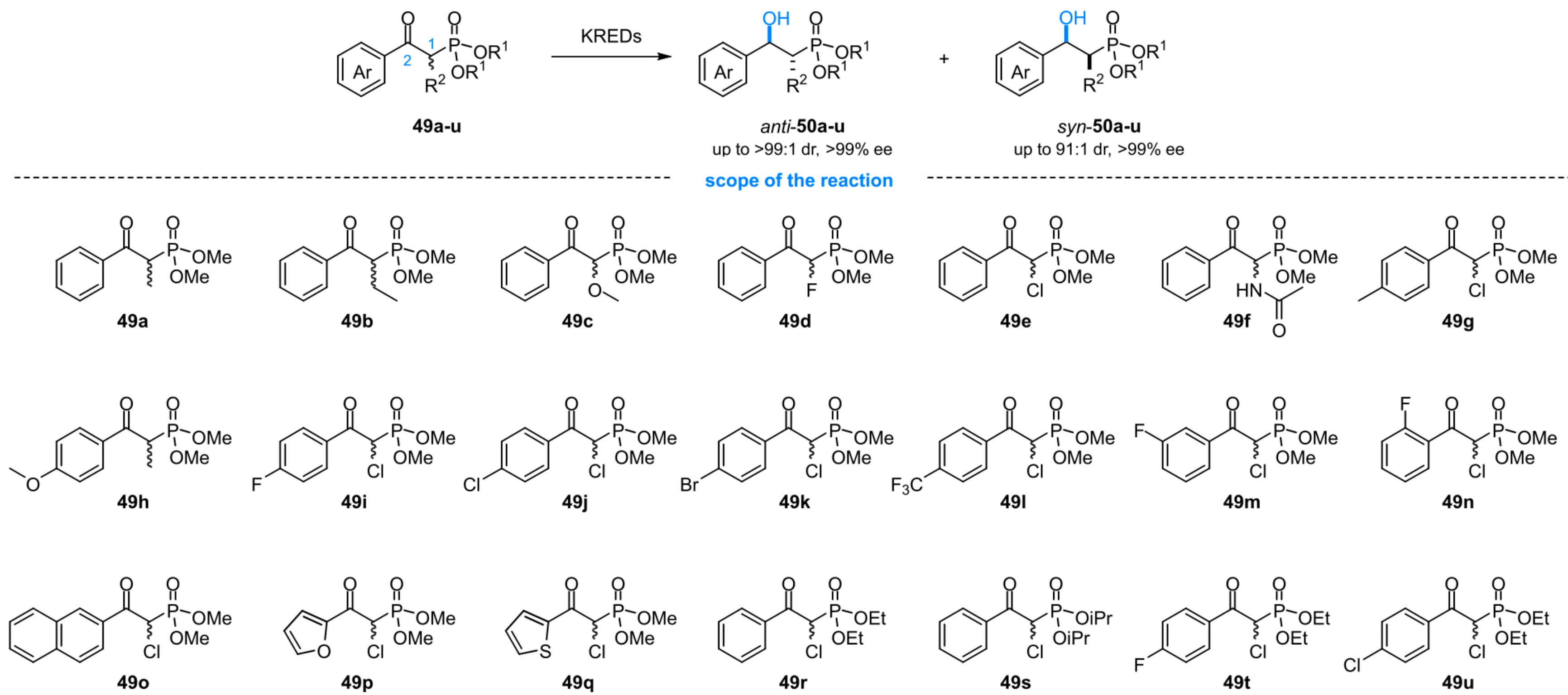
Frontiers in Bioengineering and Biotechnology ***2022***, *10*, 929784.

ADH-Mediated DKR of β-Ketoamides



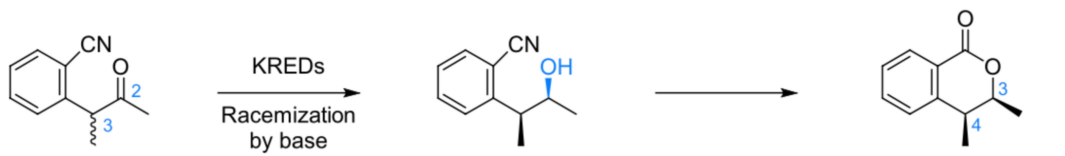
Org. Process Res. Dev. ***2022***, 26, 1925-1943.

Dynamic Kinetic Resolution of α-Substituted β-Arylphosphonates



Frontiers in Bioengineering and Biotechnology ***2022***, *10*, 929784.

Dynamic Kinetic Resolution of α-Alkylketones

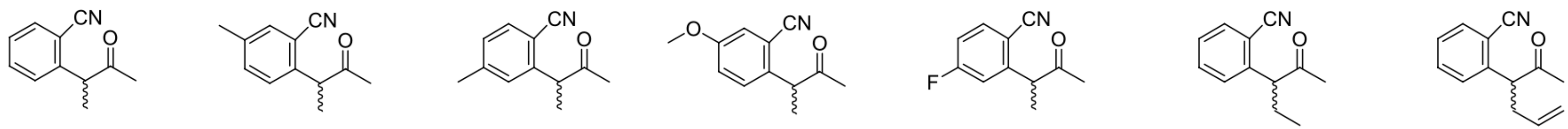


51a-g

(2*S*,3*S*)-**52a-g**
up to >99:1 dr, >99% ee

(3*S*,4*S*)-**53a-g**
up to >99:1 dr, up to 99% ee

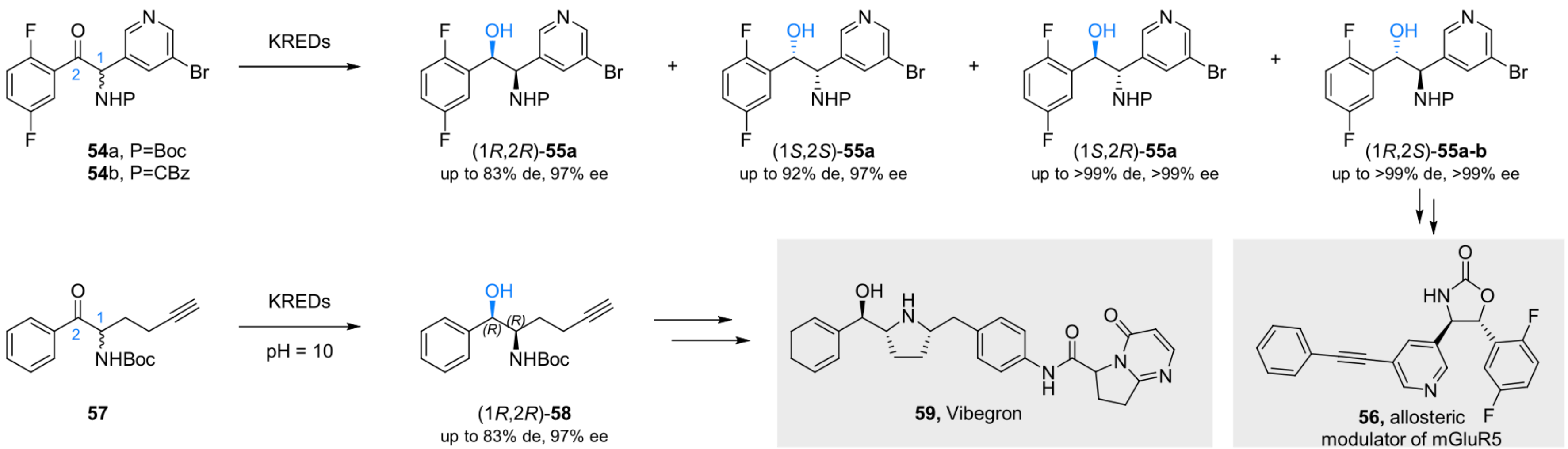
scope of the reaction



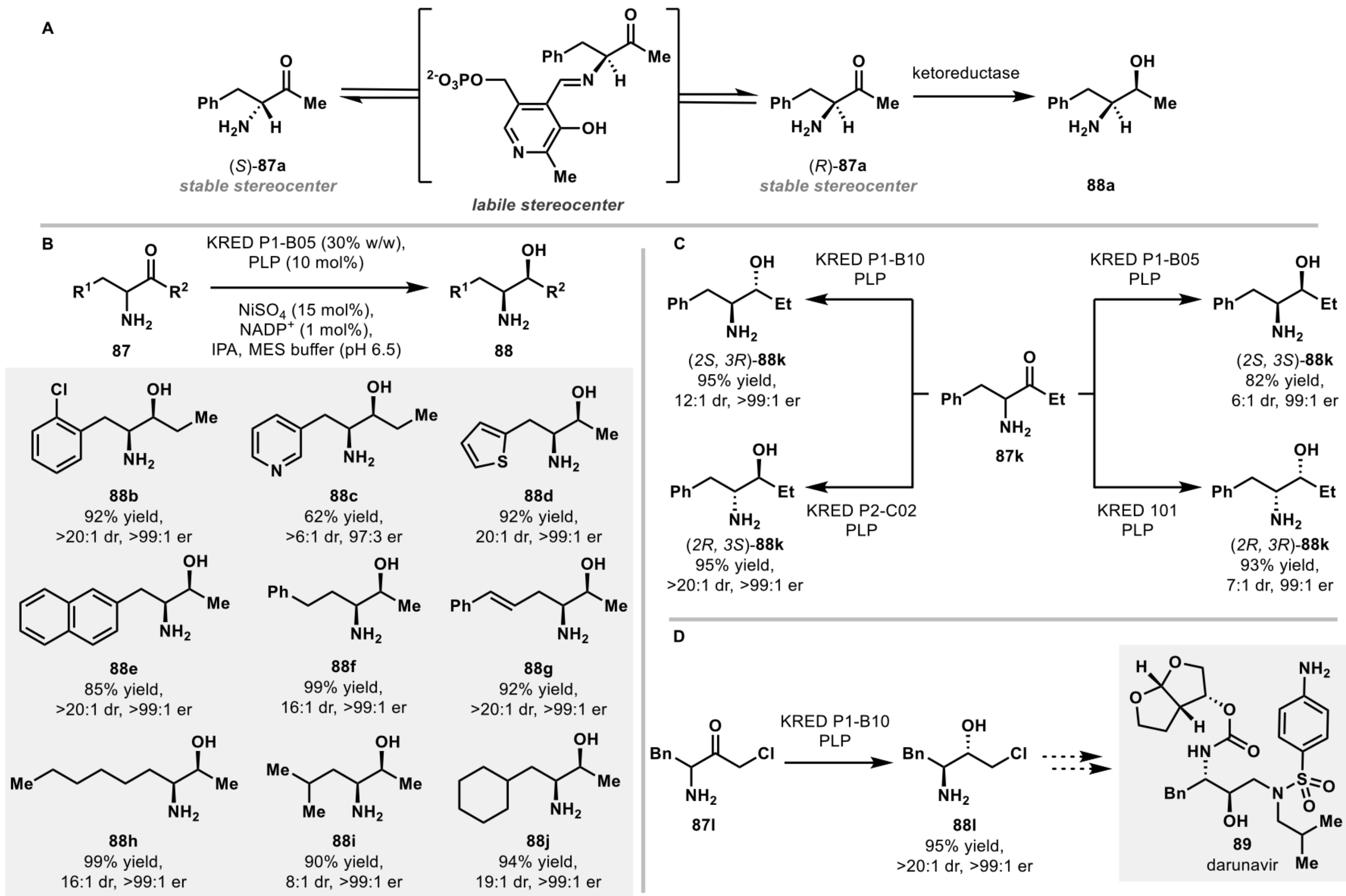
51a **51b** **51c** **51d** **51e** **51f** **51g**

Frontiers in Bioengineering and Biotechnology ***2022***, *10*, 929784.

Dynamic Kinetic Resolution of N-Protected α-Aminoketones

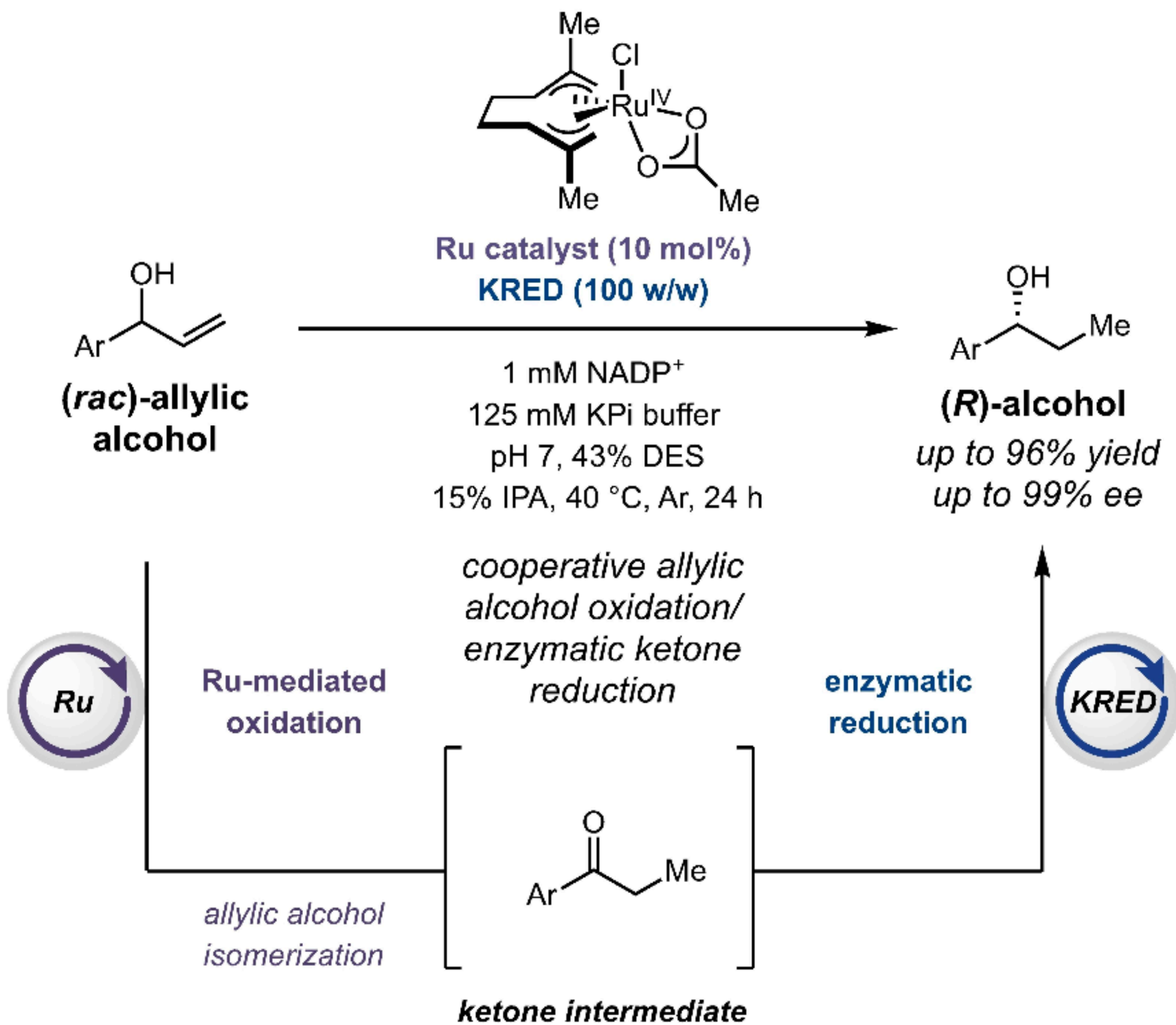


Deracemization of α-Aminoketones



Org. Process Res. Dev. ***2022***, 26, 1925-1943.

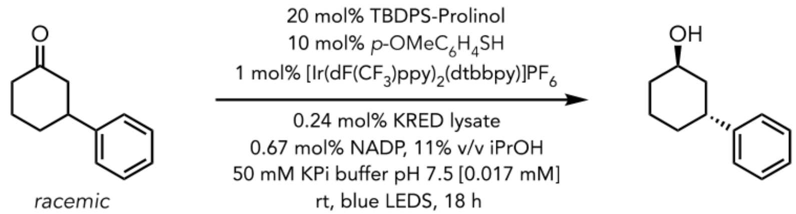
Dynamic Kinetic Resolution Through Ru-Oxidation/KRED Sequence



ChemBioChem ***2023***, *24*, e202300334.

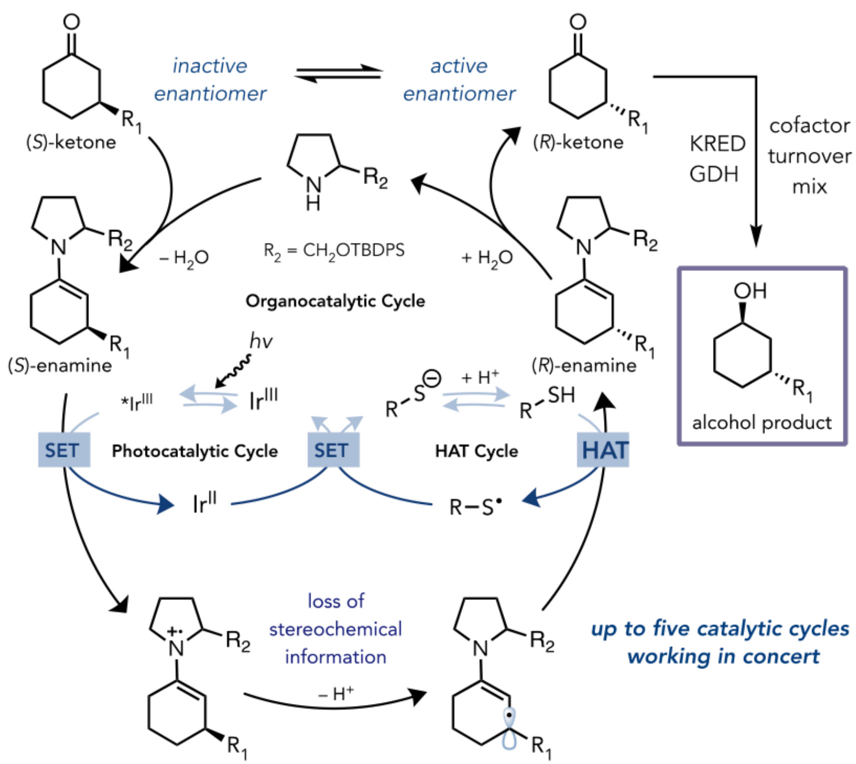
Photoenzymatic Dynamic Kinetic Resolution of β-Stereogenic Ketones

DKR of β-Stereogenic Ketones Via Synergistic Photoredox Organocatalysis

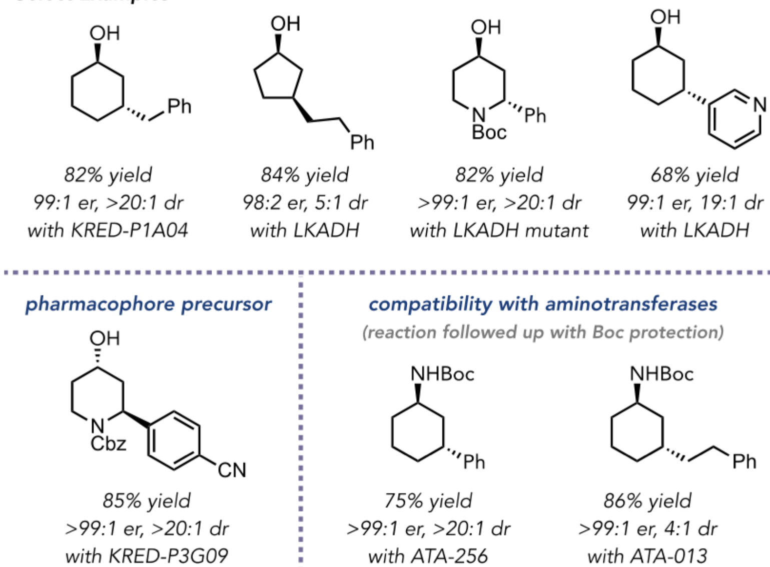


21 examples
up to 92% yield, >99:1 er, >20:1 dr

Reaction Mechanism



Select Examples



ACS Catal. ***2022***, 12, 8911-8924.

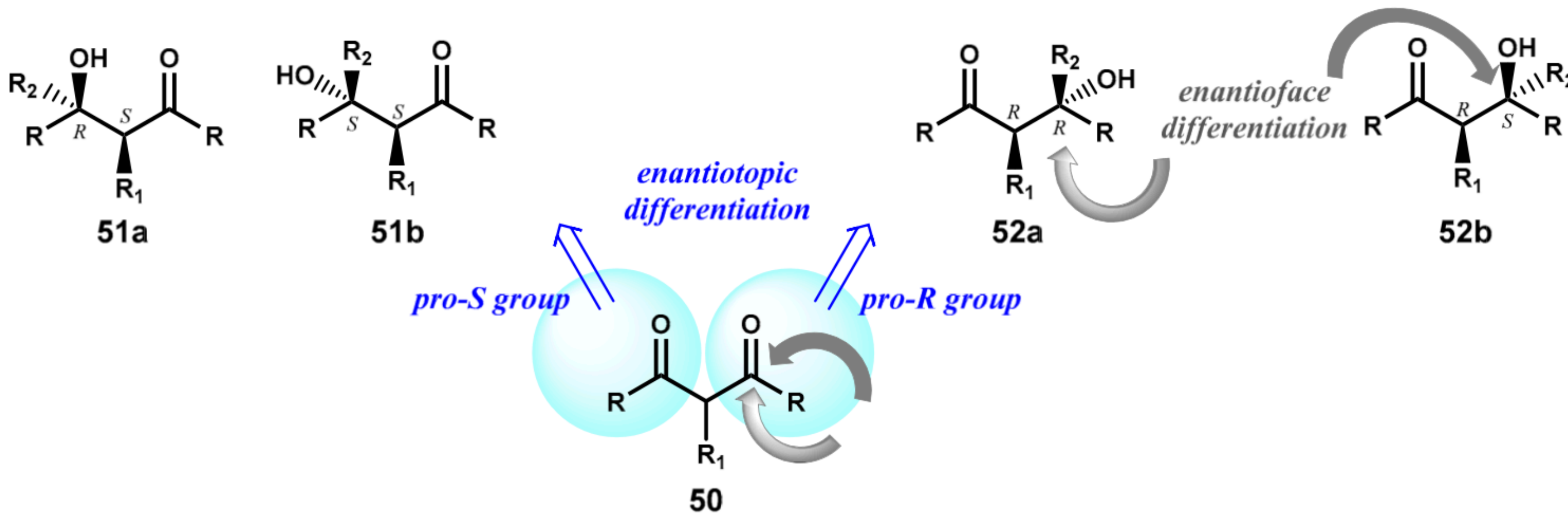
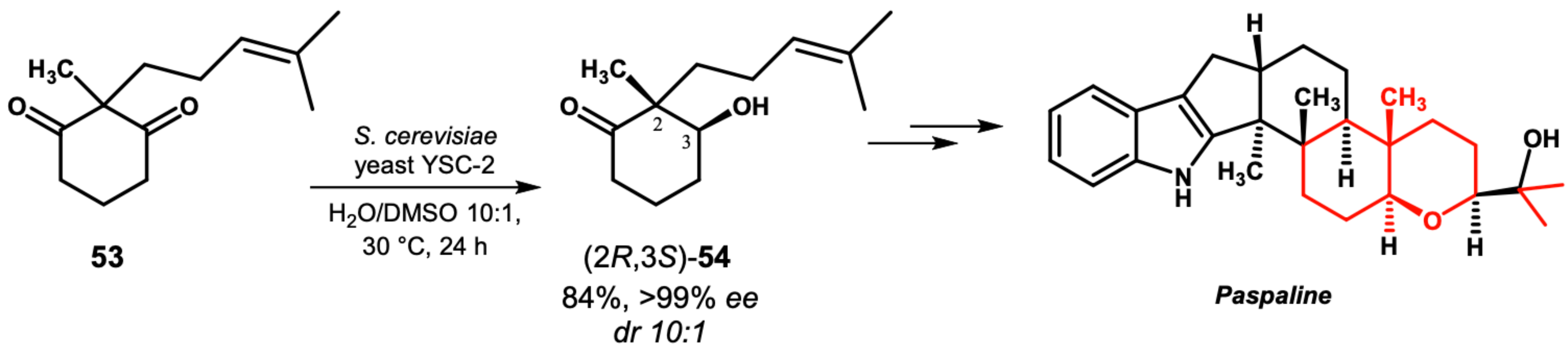


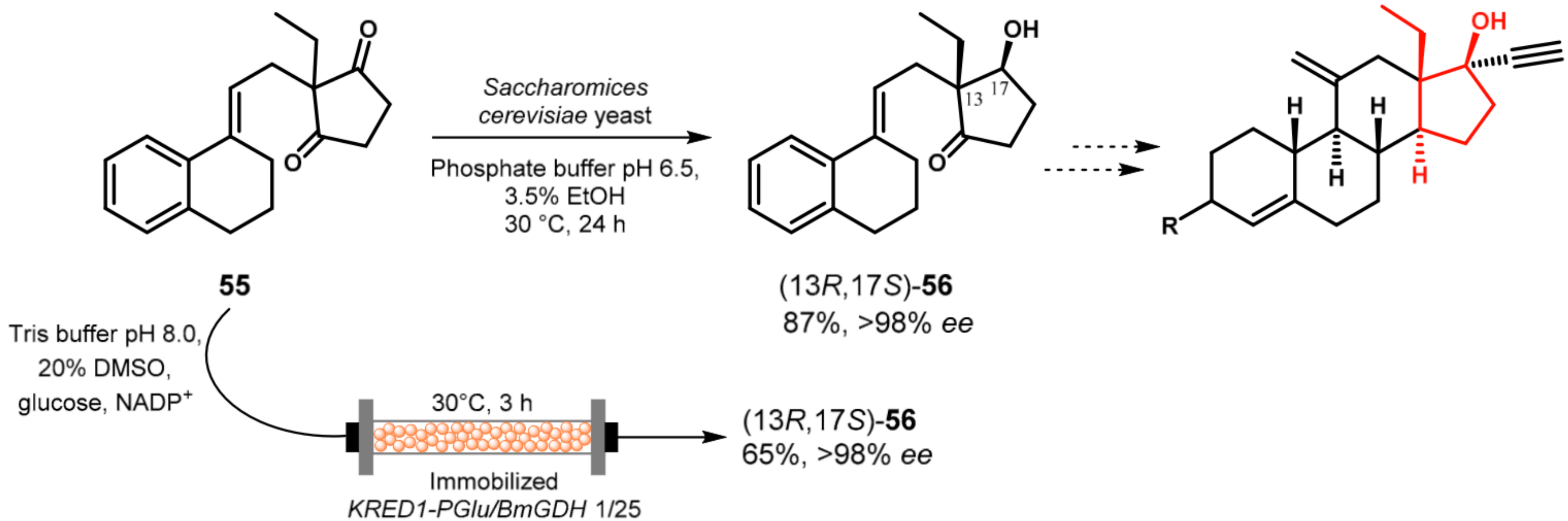
Figure 23. Possible products in the desymmetrization of a generic diketone **50**.

Desymmeterization of 1,3-Diketones



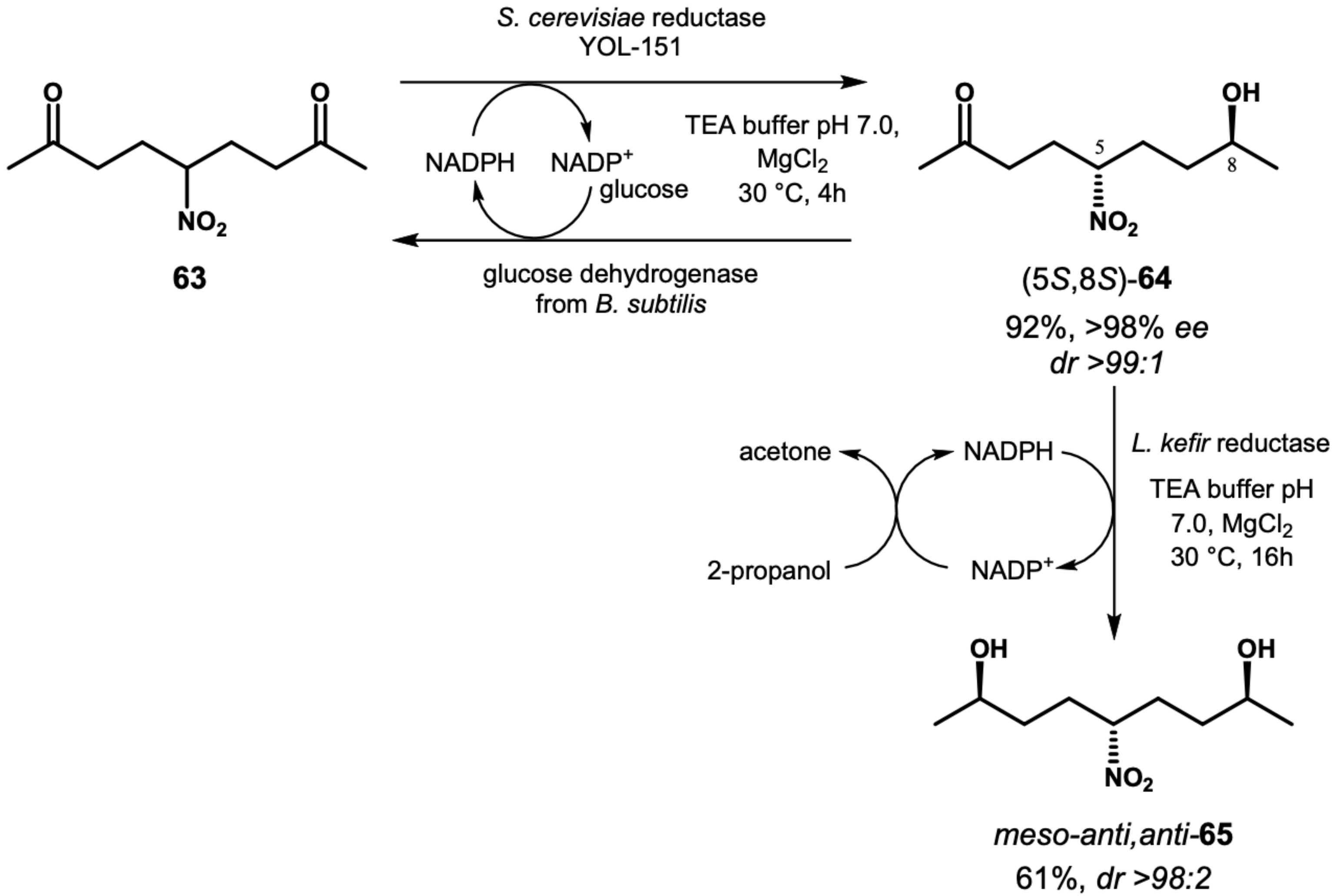
Symmetry ***2020***, 12, 1454.

Desymmeterization of 1,3-Diketones



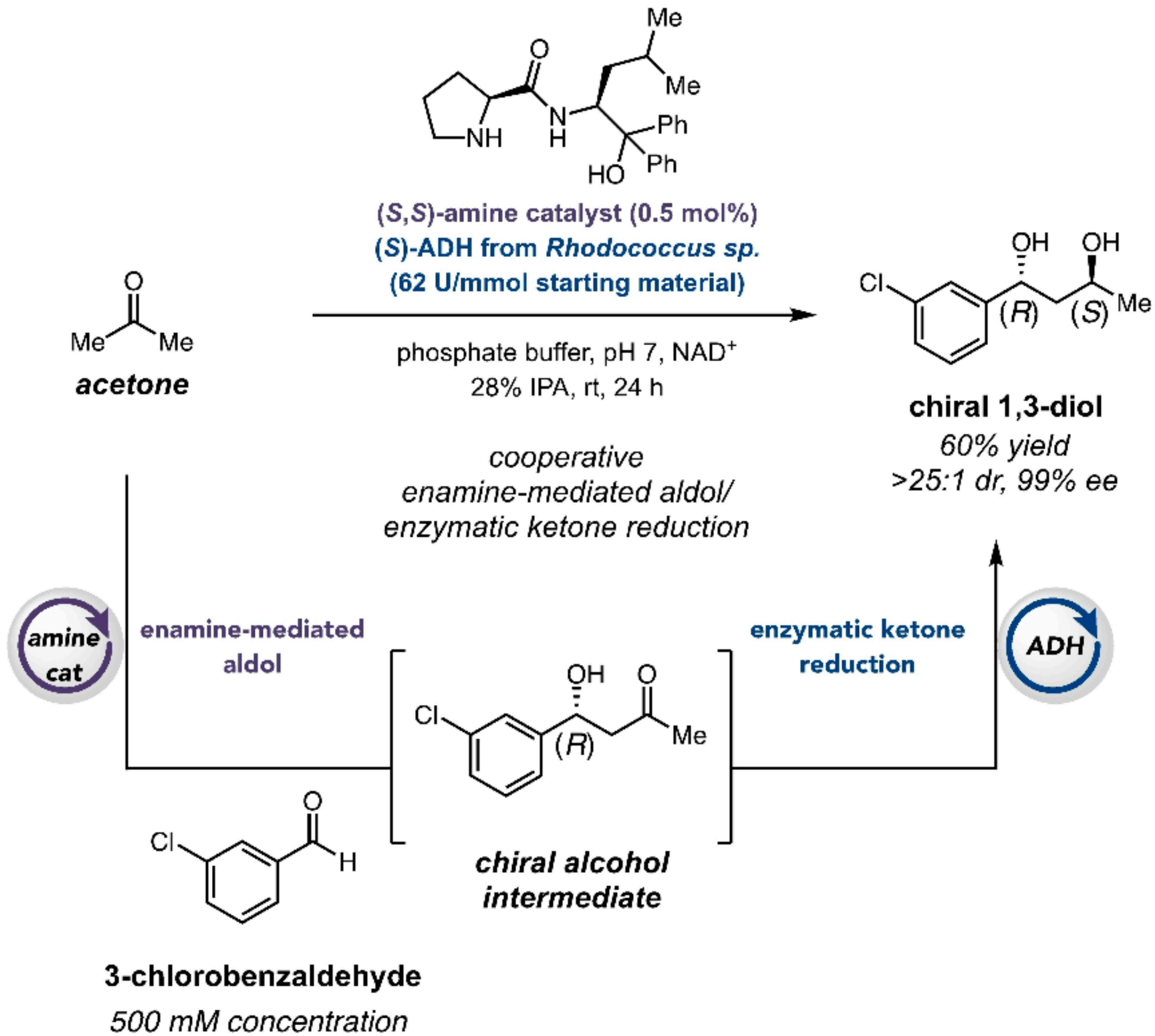
Symmetry ***2020***, 12, 1454.

Desymmeterization of a 1,7-Dione: Remote Control!



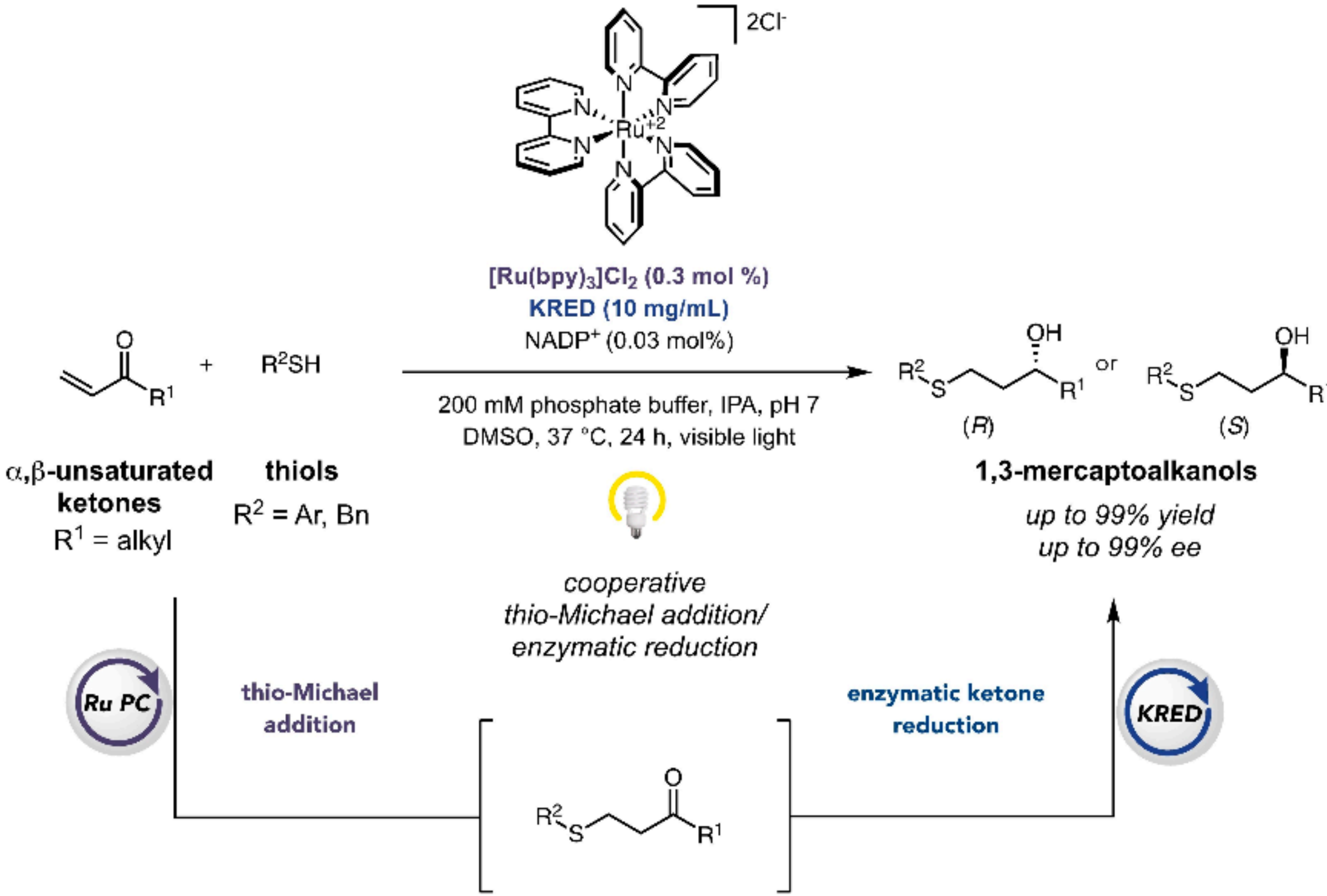
Symmetry ***2020***, 12, 1454.

Chemoenzymatic 1,3-Diol Synthesis



ChemBioChem ***2023***, *24*, e202300334.

Chemoenzymatic Thiol-Ene-Ketone Reduction



ChemBioChem ***2023***, *24*, e202300334.