

The Asymmetric Baeyer-Villiger Oxidation

Traditional Synthetic Methods Versus Enzymes

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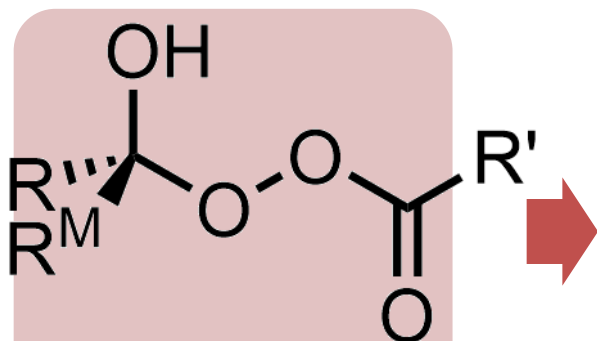
Group Meeting Presentation

16 July 2013

Online Version

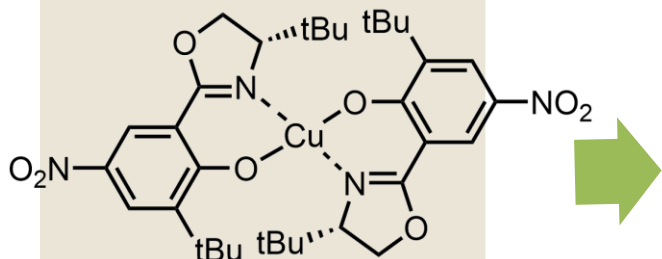


Outline



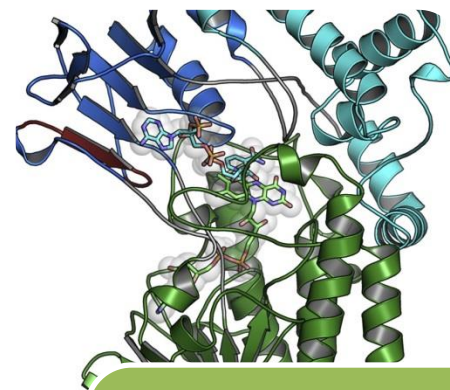
Background

- History
- Mechanism
- Chem, Regio, Stereoselectivity



Traditional Chemical Methods

- Metal Catalyzed
- Chiral Acid

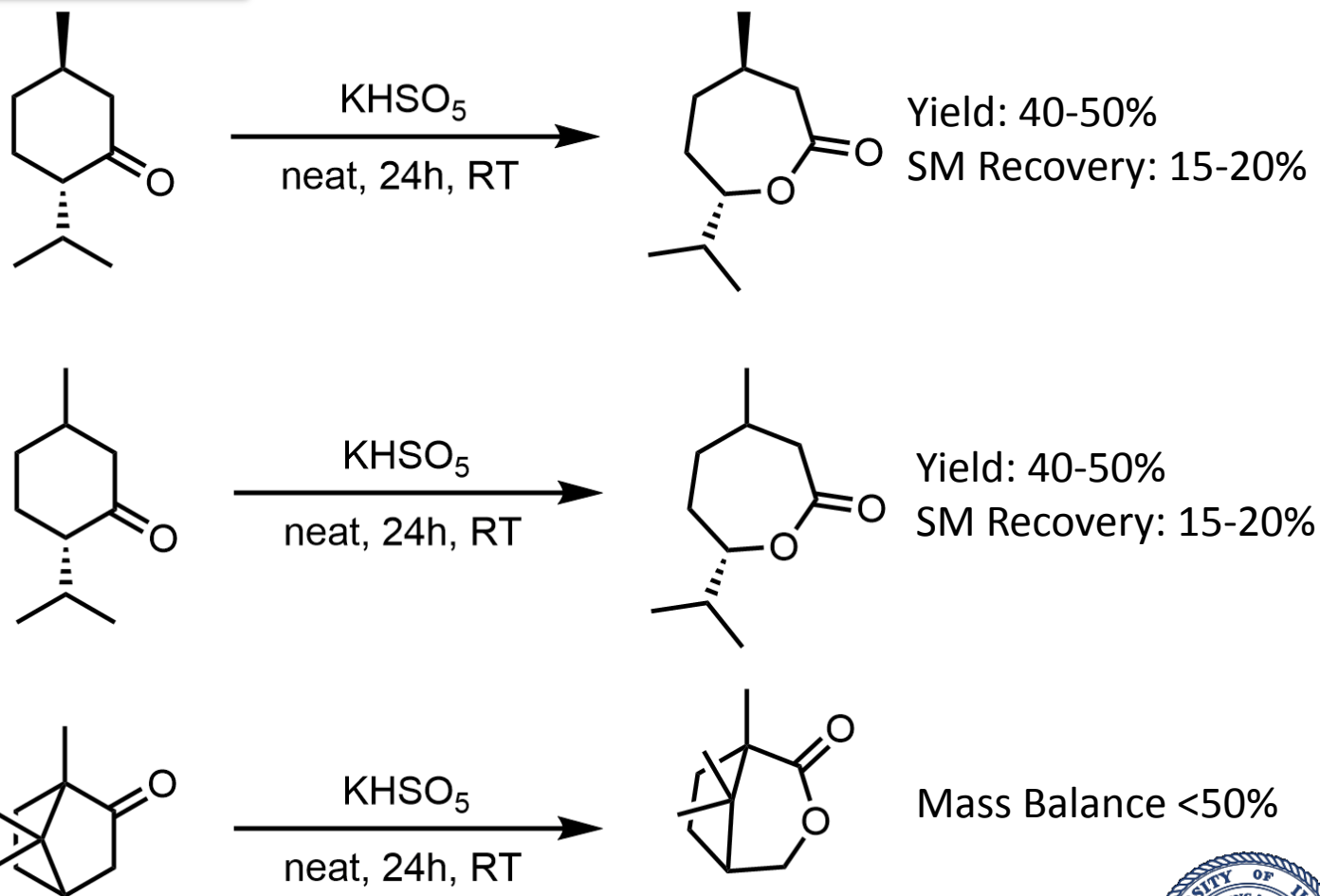


Enzyme Methods

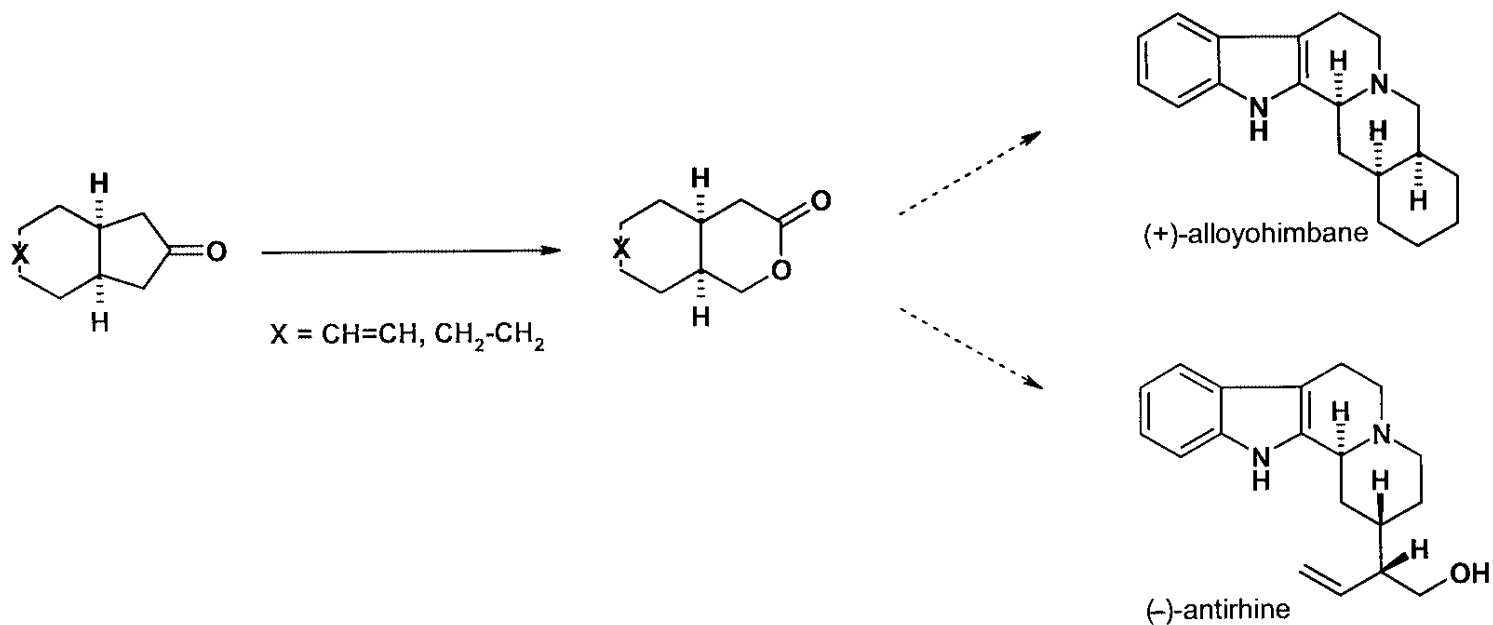
- Background
- Structural Mechanism
- How to use

The Baeyer-Villiger Reaction

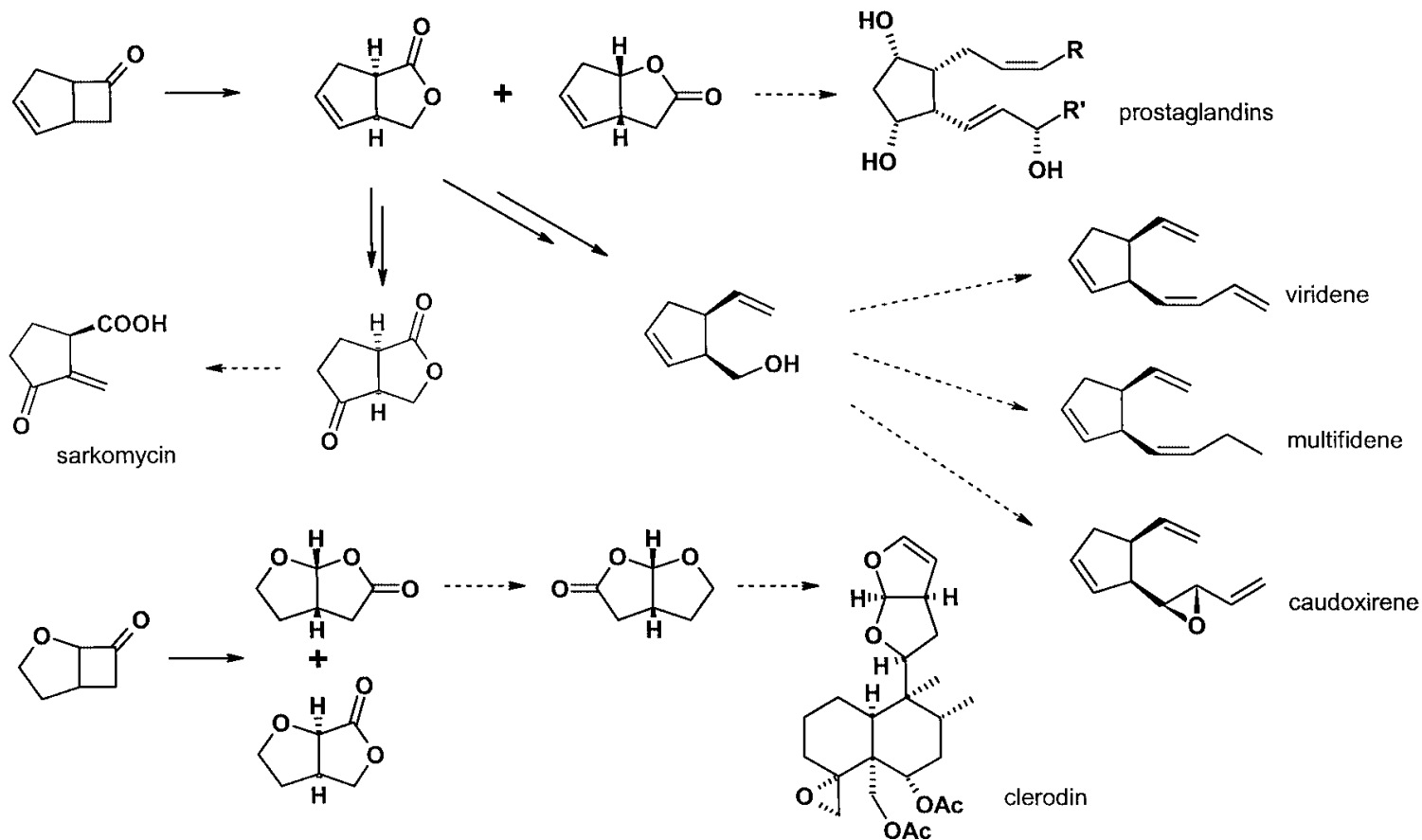
Baeyer and Villiger, 1899



The Baeyer-Villiger Reaction: Applications

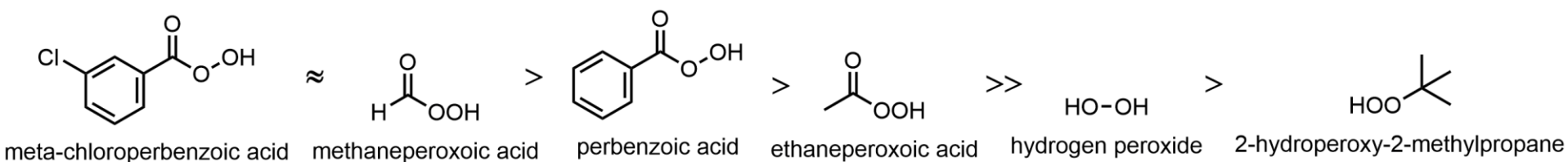
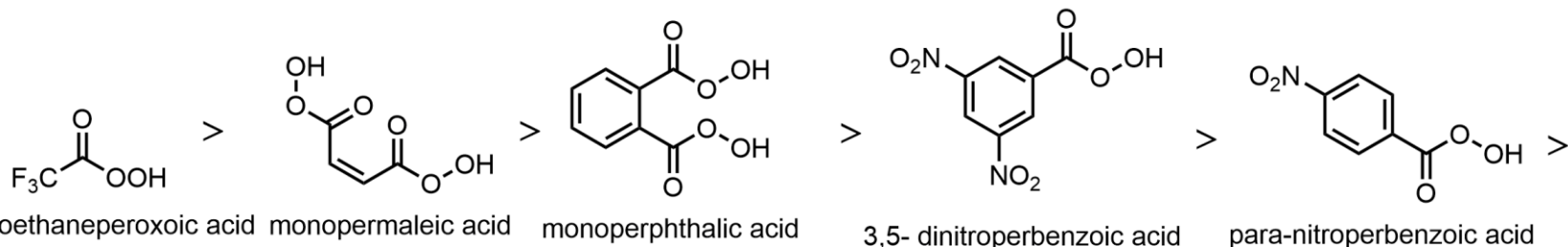
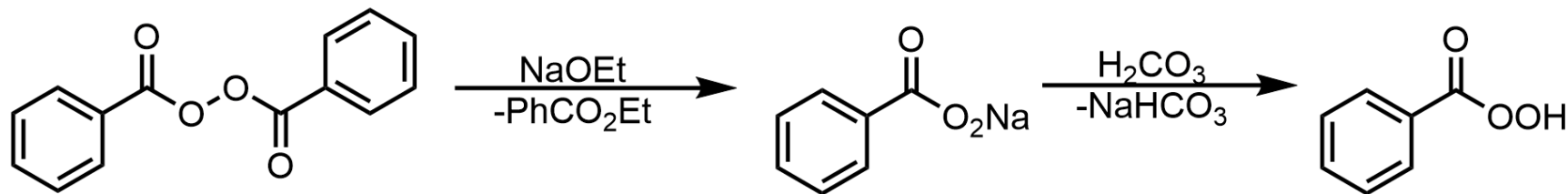


The Baeyer-Villiger Reaction: Applications



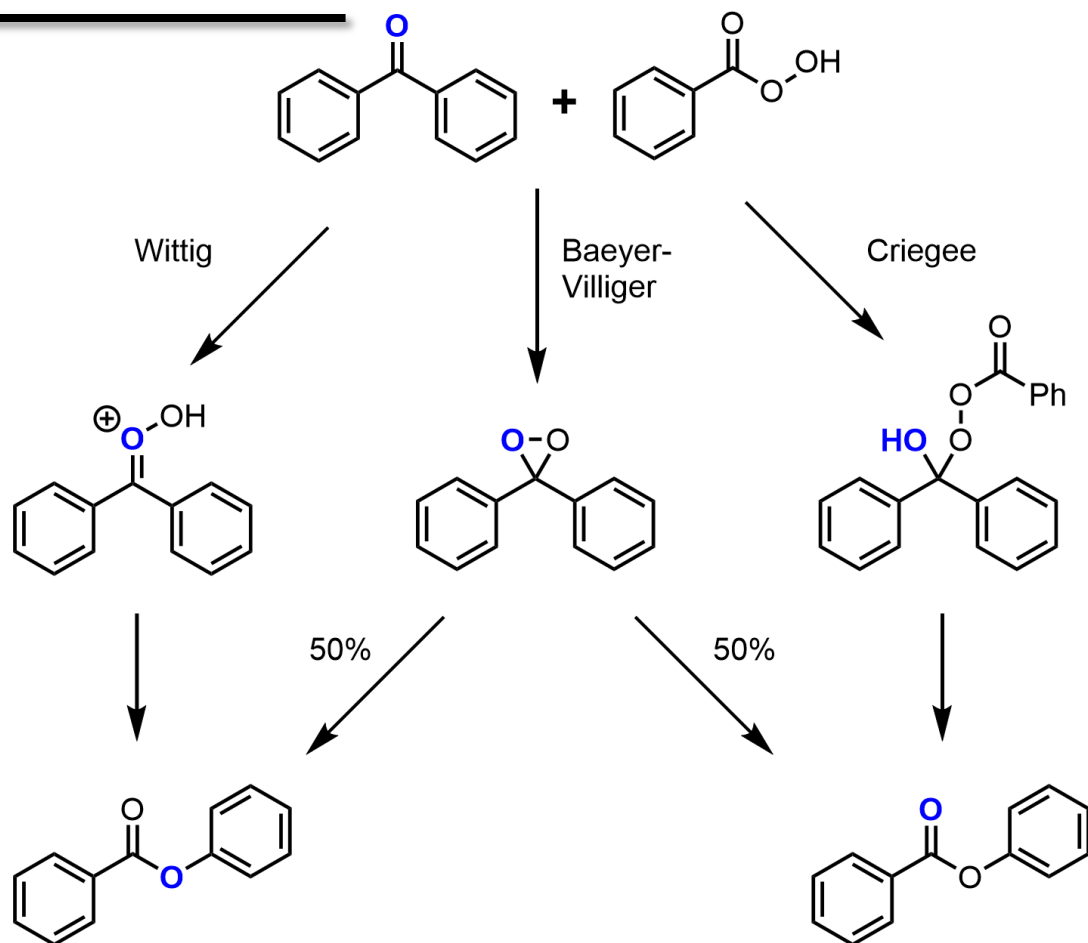
The Baeyer-Villiger Reaction

Baeyer and Villiger, 1900

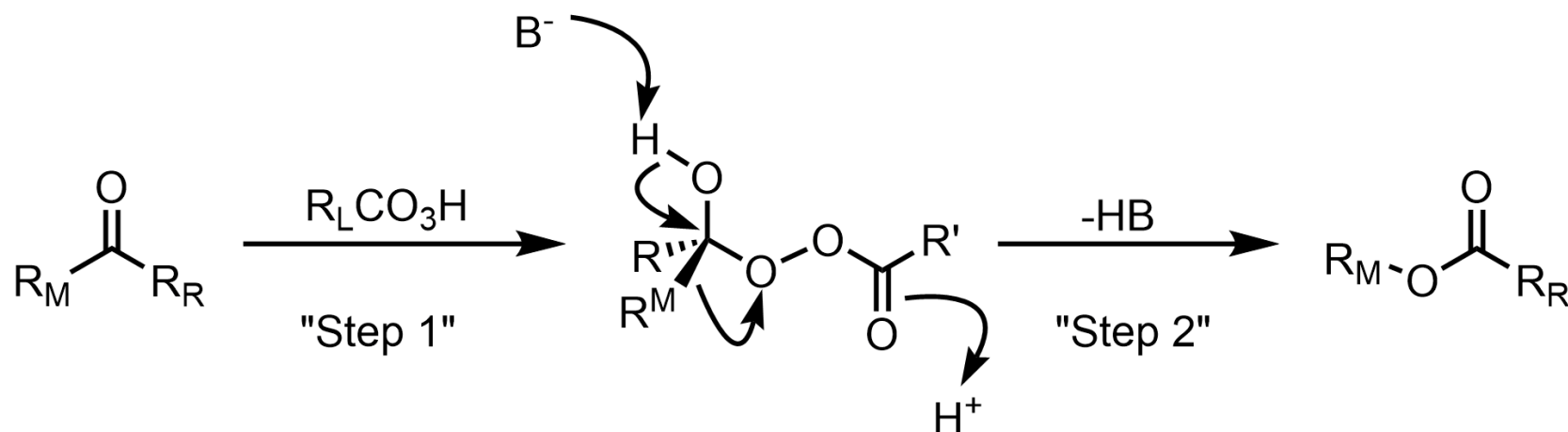


The BV Reaction: Mechanism

Doering and Dorfman, 1953



The BV Reaction: Mechanism

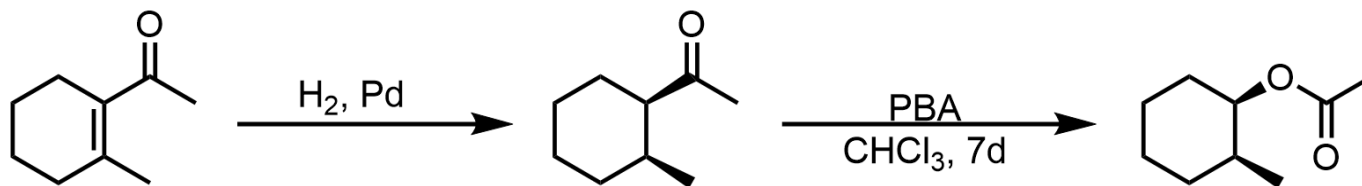


- Step one can be catalyzed by acid or base. Base is typically not used as it can lead to racemization.
- Step two is typically the rate determining step. Step one can become the rate determining step if the ketone is significantly electron deficient or if there is steric bulk around the carbonyl.

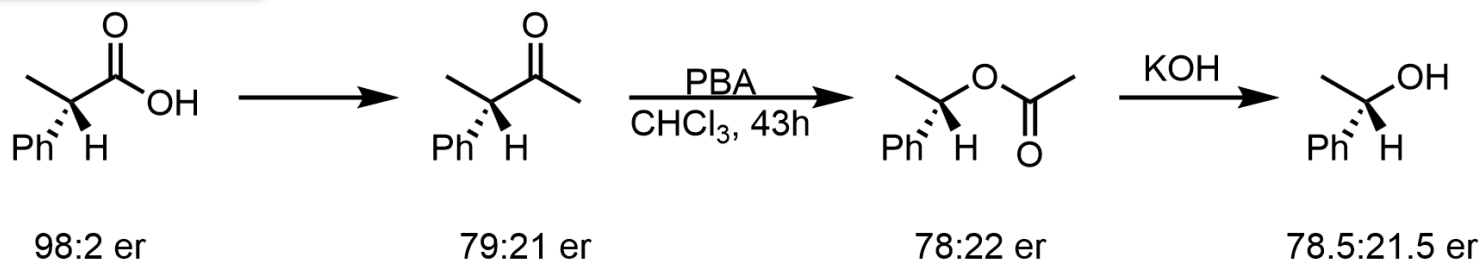


The BV Reaction: Retention Of Stereochemistry

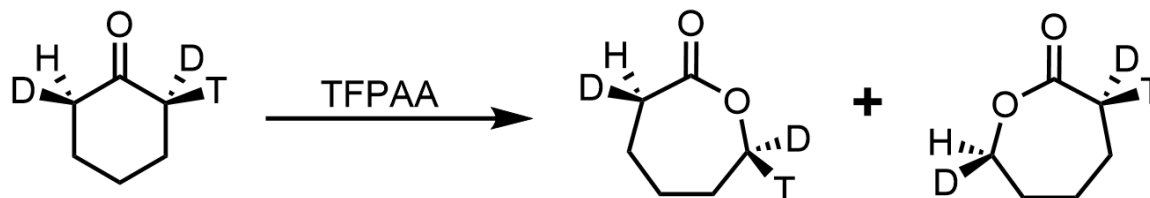
Turner, 1950



Mislow and Brenner, 1953



Benner, 1983



The BV Reaction: Migratory Aptitude

- General scale:

tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > cyclopentyl ~ cyclopropyl > methyl

- Groups that are better able to stabilize positive charge are more apt to migrate.

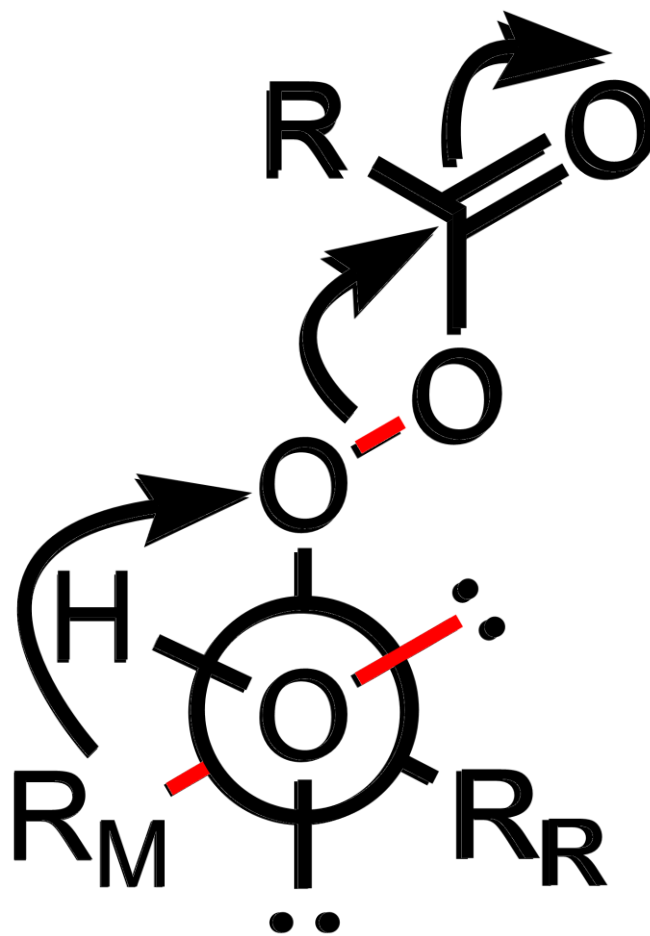
- α -ethers and α -acetate groups directs migration.

- Restriction of a substrate's conformation can prevent the proper antiperiplanar orientation for required migration.

- The Organic Reactions chapter on the Baeyer-Villiger Oxidation provides 1000's of examples. (Volume 43 in our library)

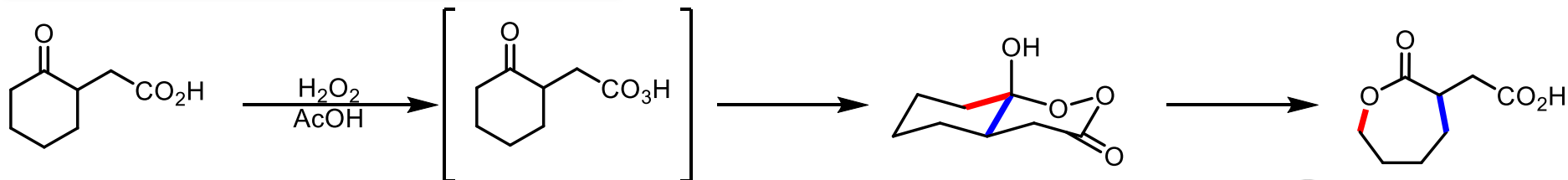


The BV Reaction: Stereoelectronic Requirements

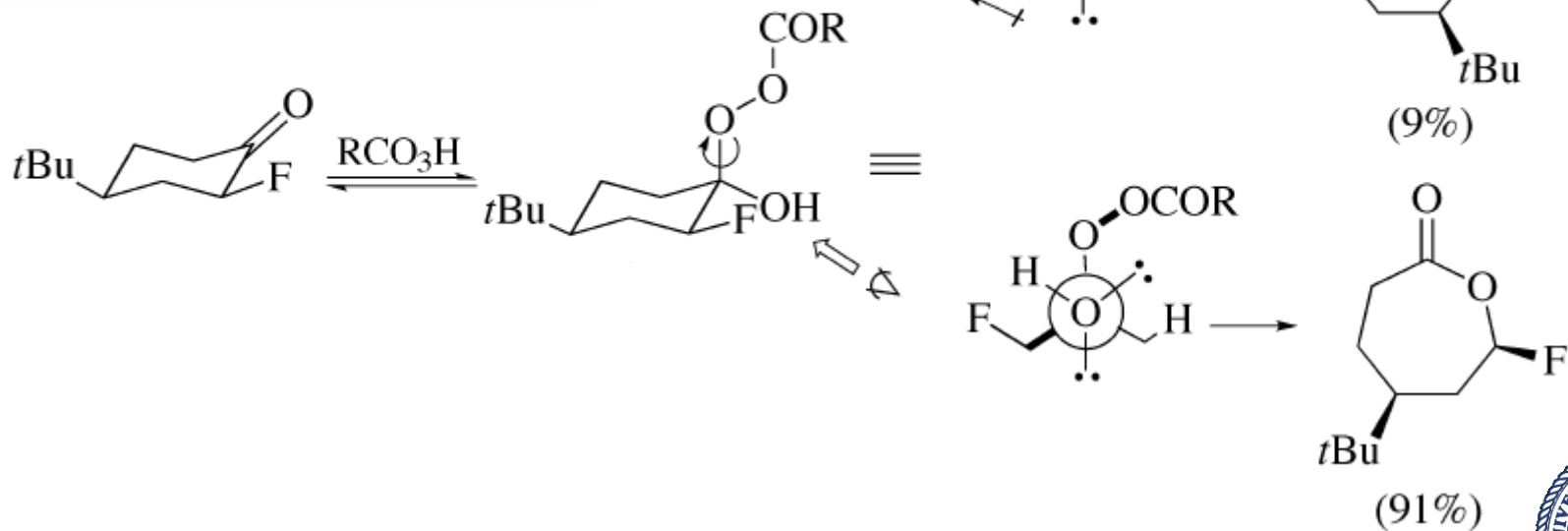


Primary Stereoelectronic Requirements

Chandrasekhar and Roy, 1994

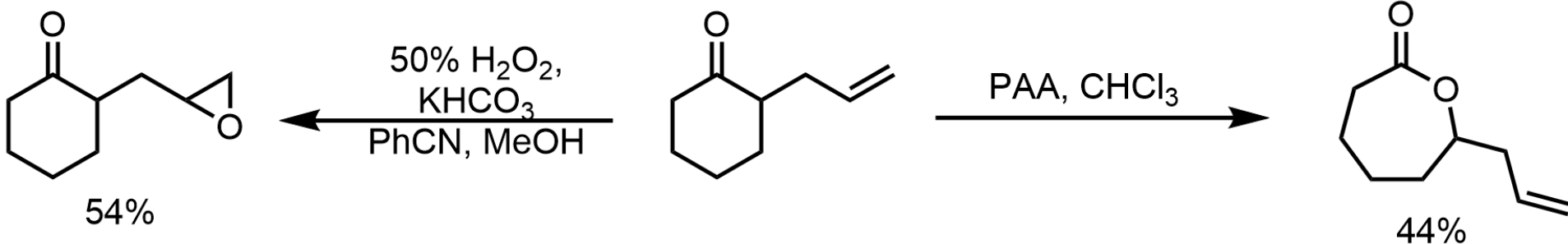


Crudden, 2000



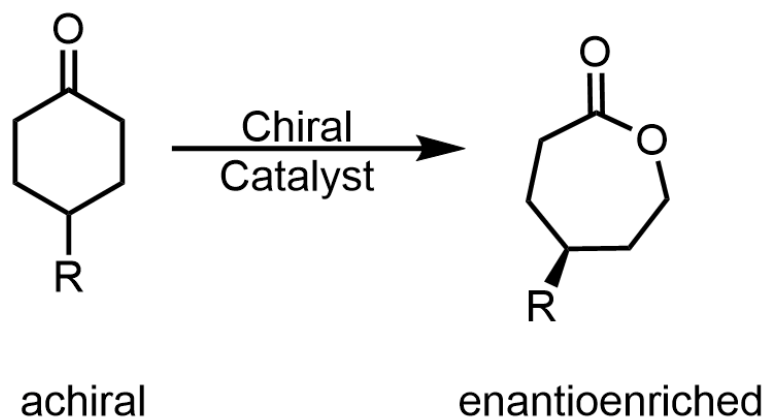
The BV Reaction: Chemoselectivity

- Baeyer-Villiger type oxidations can occur in the presence of amino acids, amines, pyridines, or anilines.
- Chemoselectivity in the presence of olefins depends upon structure and oxidizing agent.
 - Olefin oxidation of non-conjugated acyclic enones with peracids is generally faster than the Baeyer-Villiger Reaction
 - Electron poor olefins typically under go BV Oxidation.

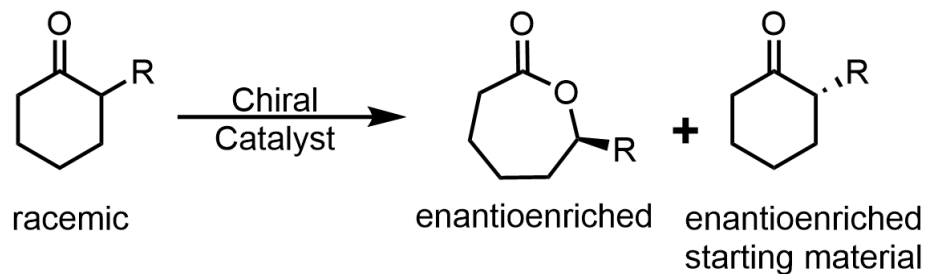


Asymmetric Synthesis v. Kinetic Resolution

Asymmetric Synthesis

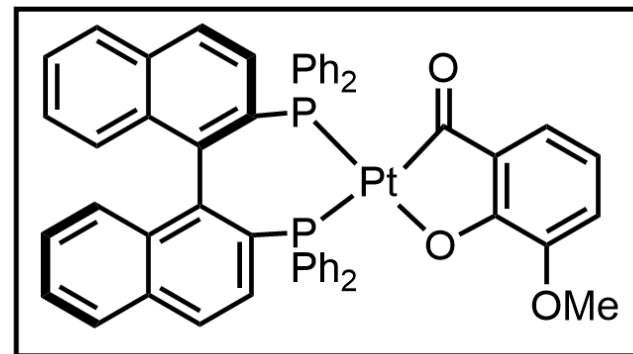
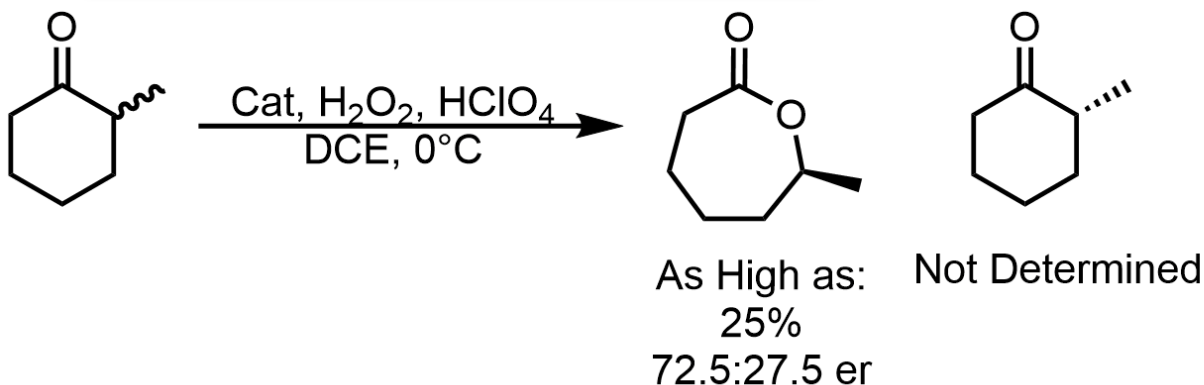


Kinetic Resolution

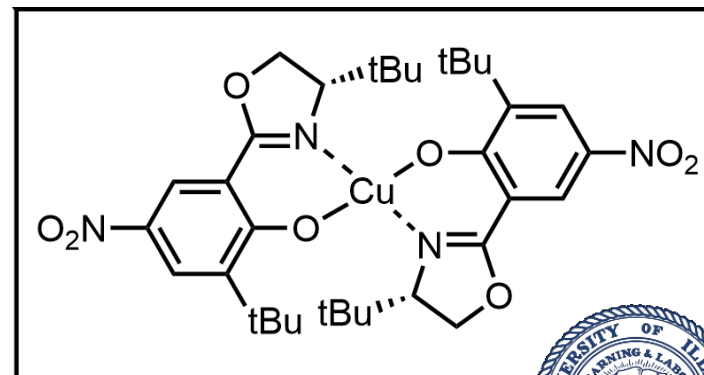
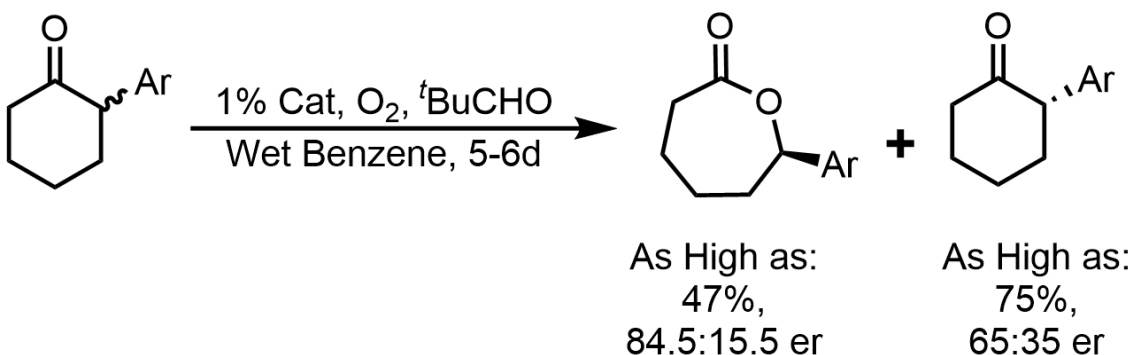


First Catalytic Enantioselective BV Reaction via Kinetic Resolution

Strukul, December 1993

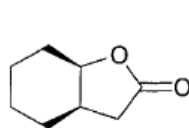


Bolm, April 1994

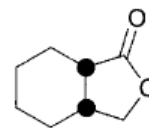


Cyclobutanones with Bolm's Methodology

Bolm, 1997



'normal'
lactone **a**



'abnormal'
lactone **b**

Ketone	e.e. of a (%)	e.e. of b (%)	Yield (%) (a : b) ^a
4	67	92	61 (3:1)
5	61	94	74 (2:1)
6	76	95	32 (3:2)
7	59	93	59 (1:1.3)

^a Ratio after work-up and product isolation.



First Catalytic Enantioselective BV Reaction Using Achiral Substrates

Bolm, 1997

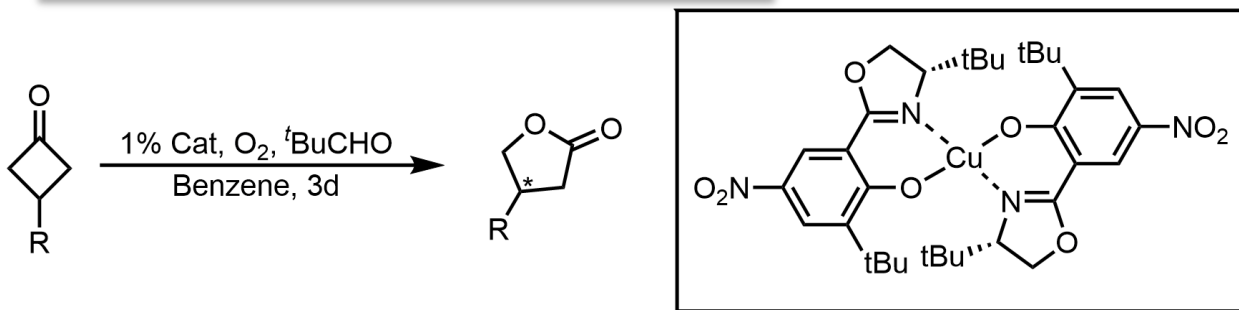


Table. Asymmetric Baeyer-Villiger-type oxidation of cyclobutanones with dioxygen and pivaldehyde catalyzed by 1 mol% of

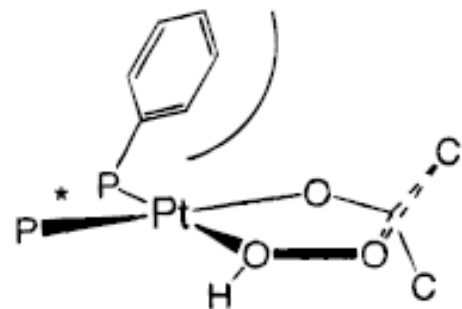
Entry	R'	Yield	<i>Ee</i>
1	octyl	77	31 65.5: 34.5
2	<i>t</i> Bu	85	47 73.5: 26.5
3	Ph	88	44 72: 28
4	Bn	90	29 64.5: 35.5
5	CO ₂ <i>t</i> Bu	92	36 68: 32
6	CO ₂ Bn	82	26 63: 37
7	CH ₂ OBn	80	23 61.5: 38.5

- 4-substituted cyclohexanones did not work using Bolm's methodology. 3-substituted were chosen as they are more reactive in Bayer-Villiger reactions.
- There was one example of 95.5: 4.5 er with a bulky tricyclic ketone.

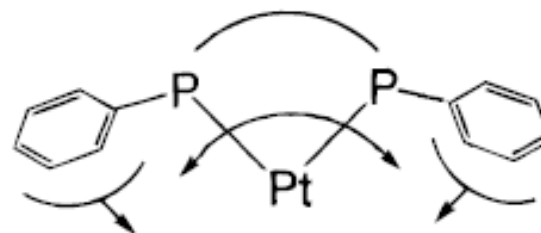
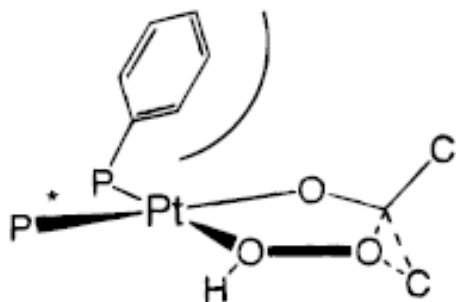


Strukul's Enantioselective BV Reaction Using Achiral Substrates

Strukul, 1999



(a)

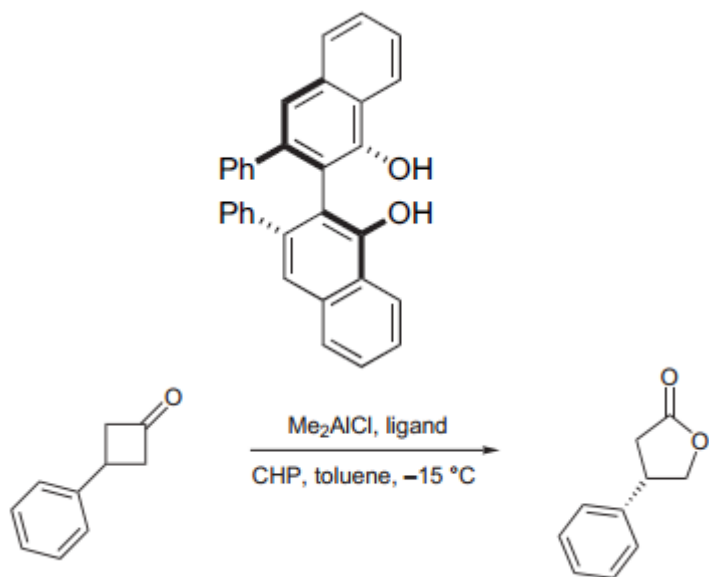


P-Pt-P bond angle increases depending on the ring size

(b)

Bolm's Aluminum Enantioselective BV Reaction

Bolm, 2001-2006



Catalyst (mol%)	Conversion (%) ^b	ee (%) ^c
50	100 ^d	84
20	100 ^e	83
10	83	43
5	43	14

Entry	R	Substrate	Yield (%) of 7 ^a	ee (%) of 7 ^{b,c}
1		6a	92	84
2		6b	84	41
3		6c	96	34
4		6d	93	37
5	<i>n</i> -octyl	6e	86	69

^a As determined by NMR spectroscopy.

Bolm's Aluminum Enantioselective BV Reaction

Bolm, 2001-2006

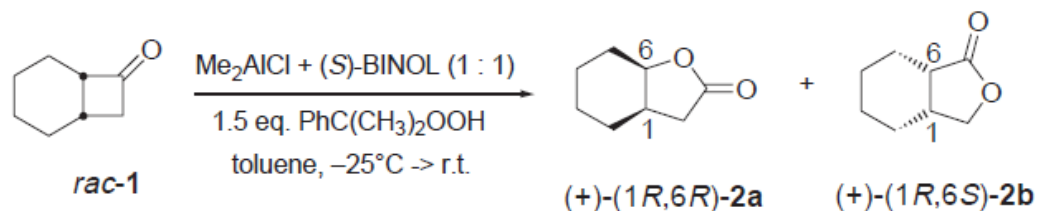
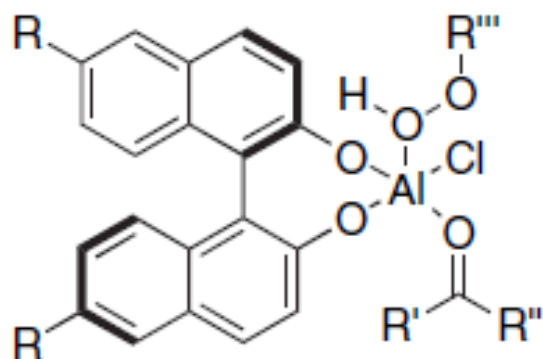


Table 1. Asymmetric Baeyer-Villiger reaction of various cyclobutanone derivatives mediated by the (*S*)-BINOL-Al system (50 mol%).

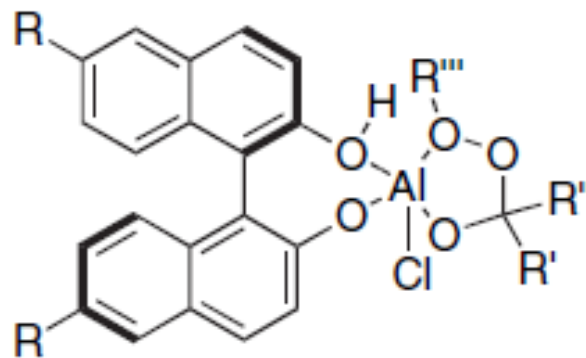
Entry	Ketone	Product(s)	ee (%) of product(s)	Ratio of lactones a:b ^a
1	<i>rac-1</i>	(+)-(1 <i>R</i> ,6 <i>R</i>)-2a (+)-(1 <i>R</i> ,6 <i>S</i>)-2b	34 (2a) 96 (2b)	2.7
2	<i>rac-3</i>	(+)-(1 <i>R</i> ,5 <i>S</i>)-4a (+)-(1 <i>S</i> ,5 <i>R</i>)-4b	79 (4a) ^b 74 (4b)	0.8
3	<i>rac-5</i>	6a 6b	78 (6a) 68 (6b)	0.9

Bolm's Aluminum Enantioselective BV Reaction

Bolm, 2001-2006



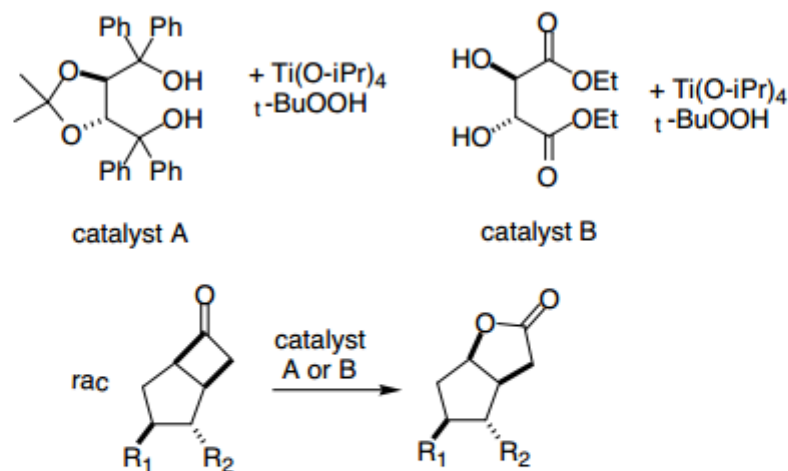
A



B

Lopp's Use of Sharpless' Epoxidation Conditions

Lopp, 1996, 1998: Use of TADDOL

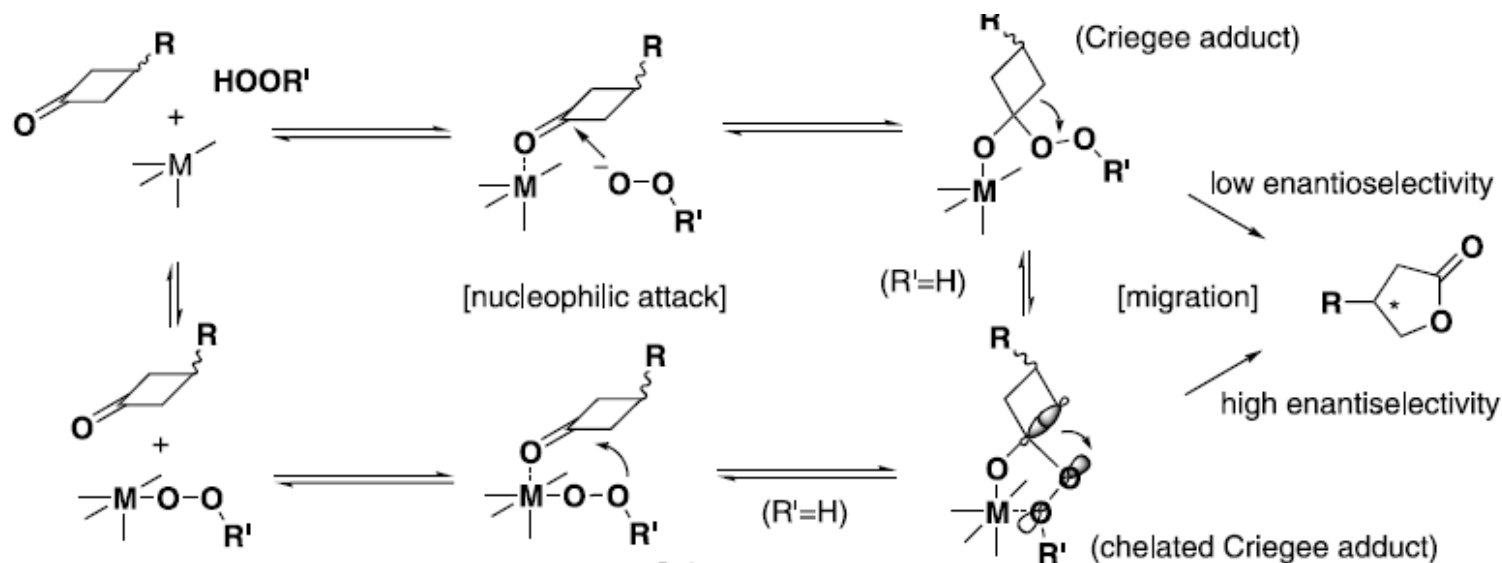


R ₁	R ₂	cat. A ee	yield	cat B. ee	yield
OH	Br	41	33	75	40
OH	Ph	39	20	59	31
Ph	OH	31	35	-	-



Salen Ligand by Katsuki

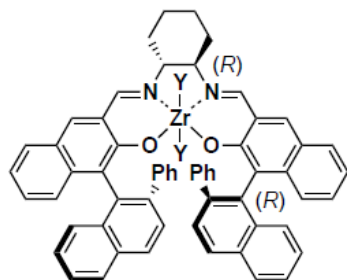
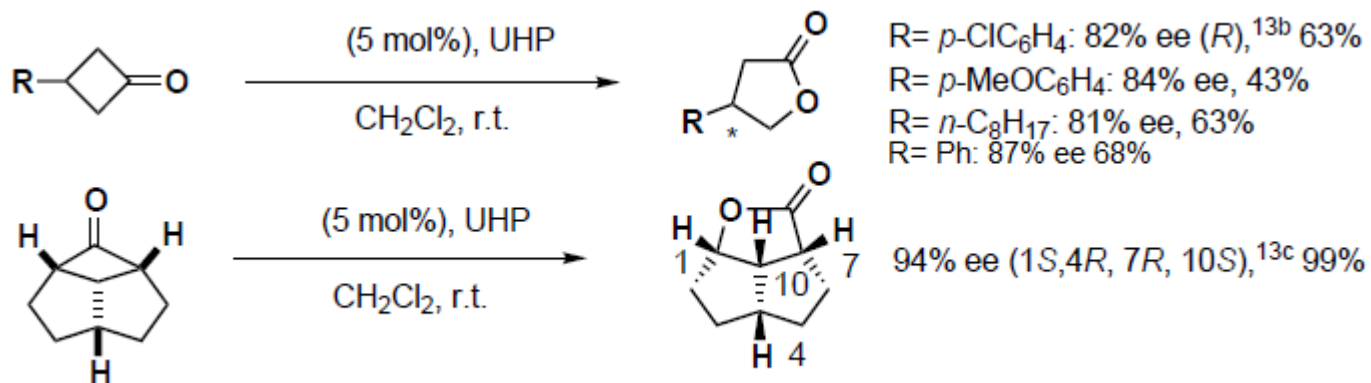
Katsuki, 2001: Co



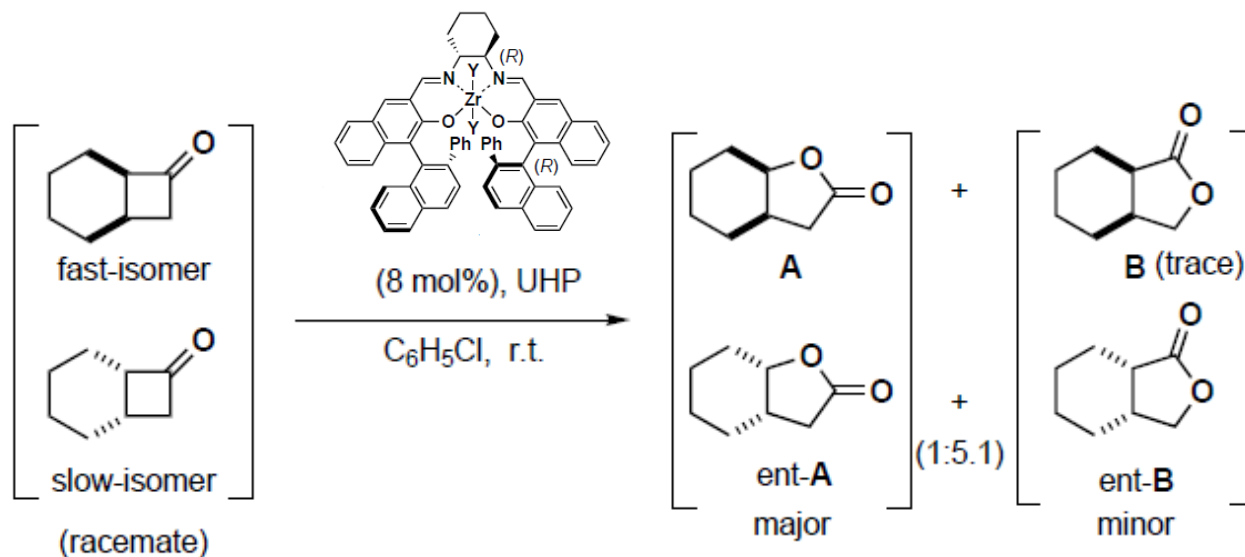
Salen Ligand by Katsuki

Katsuki, 2001: Co

Katsuki, 2002: Zr



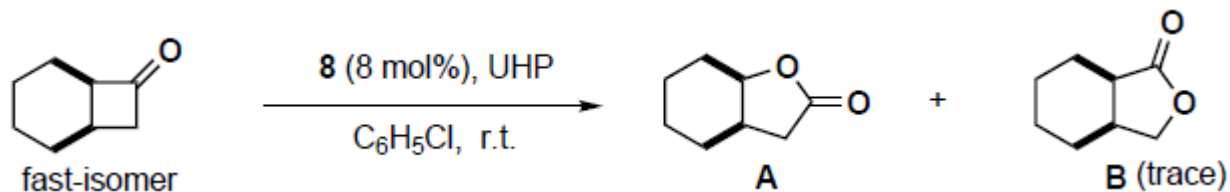
Salen Ligand by Katsuki



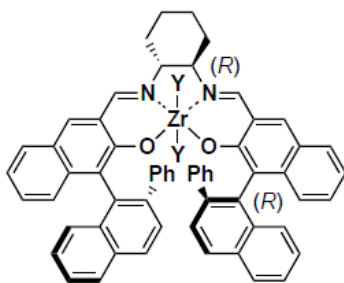
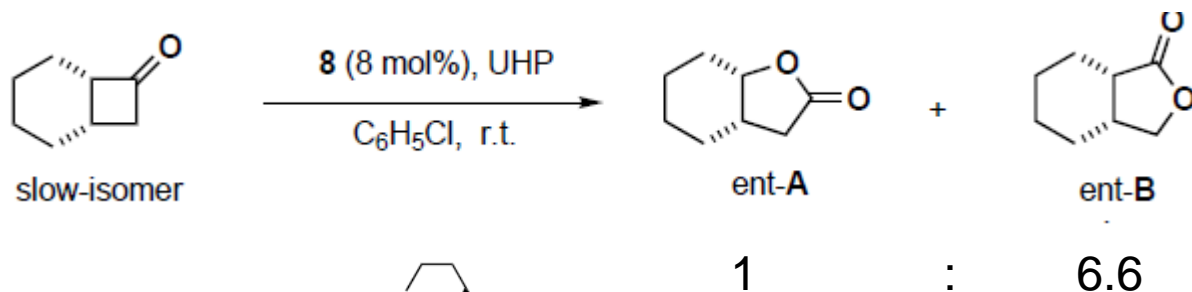
Run	Ketone			A		B	
	Conv. (%) ^a	% ee ^b	k_{rel}	Yield (%) ^a	% ee ^b	Yield (%) ^a	% ee ^b
1	76	86	4.2	54	82	22	> 99
2	83	92	3.8	51	82	24	> 99
3	76	82	3.5	53	85	21	> 99
4	71	77	4.1	48	85	20	> 99
5	83	94	4.1	55	80	25	> 99



Salen Ligand by Katsuki

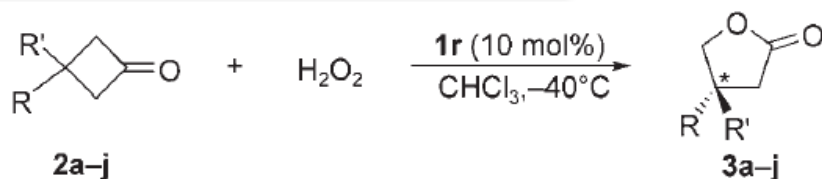


The reaction of the fast isomer gave normal product **A** almost exclusively

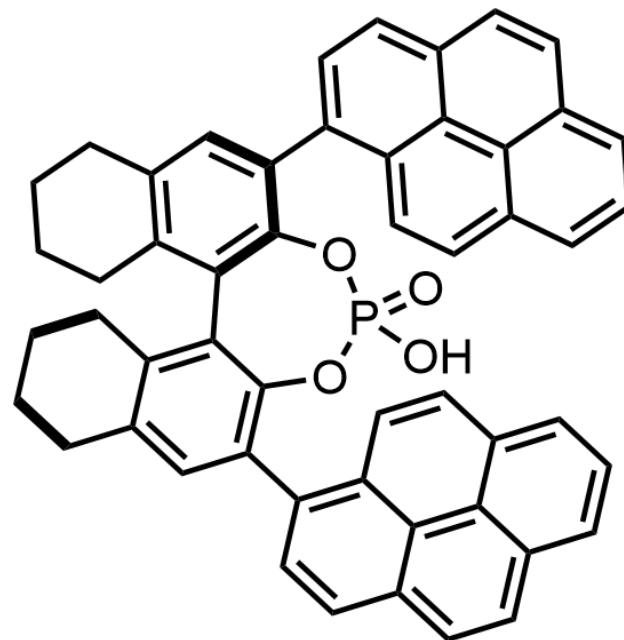


Chiral Brønsted Acid Catalyzed Asymmetric BV

Ding, 2008

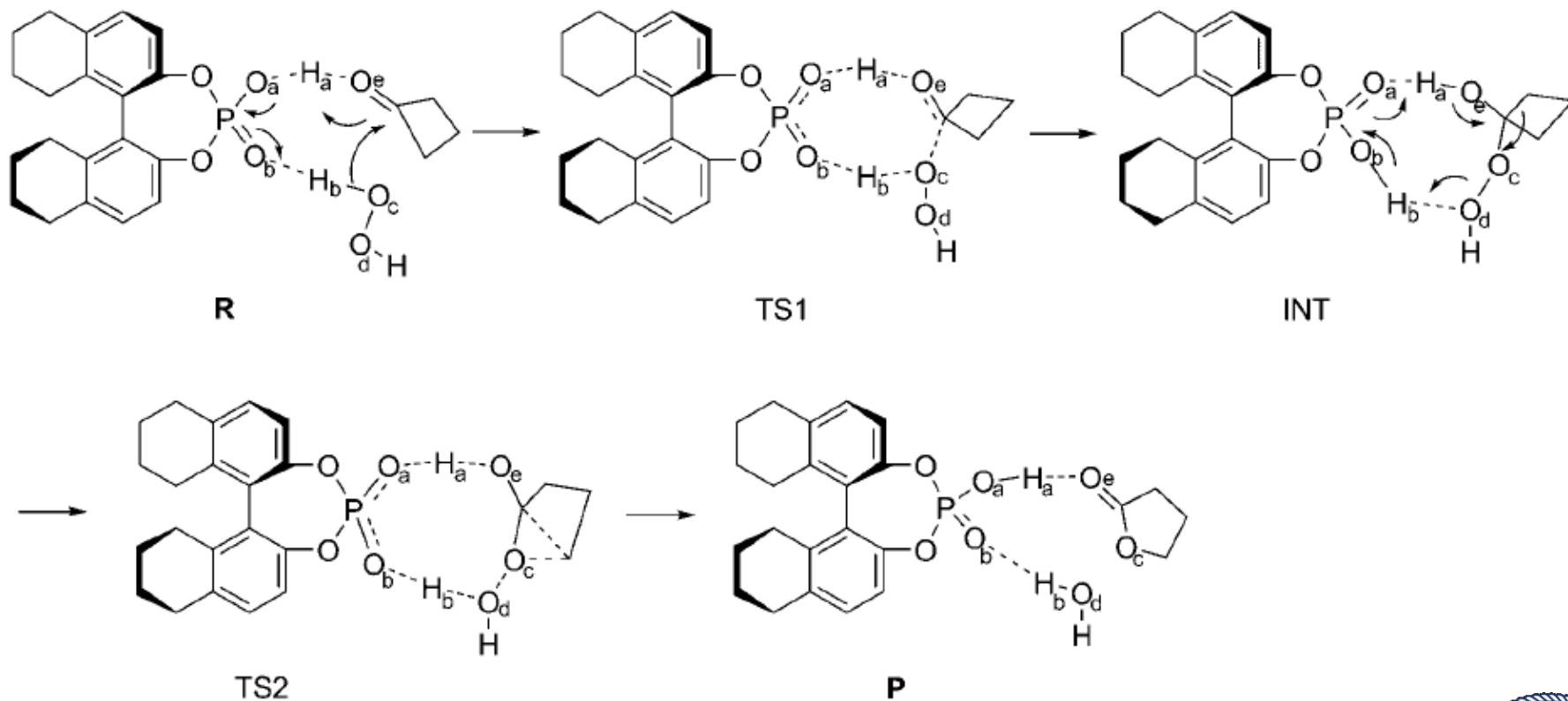


Entry	R	R'	t [h]	Yield [%] ^[b]	ee [%] ^[c] (Conf.) ^[d]
1	C_6H_5 (a)	H	18	99	88(<i>R</i>)
2	4-Me C_6H_4 (b)	H	18	99	93(<i>R</i>)
3	4-MeOC $_6\text{H}_4$ (c)	H	18	99	85(<i>R</i>)
4	4-Br C_6H_4 (d)	H	18	99	83(<i>R</i>)
5	4-Cl C_6H_4 (e)	H	18	99	82(<i>R</i>)
6	4-FC $_6\text{H}_4$ (f)	H	18	99	84(<i>R</i>)
7	2-naphthyl (g)	H	18	91	86(<i>R</i>)
8 ^[e]	4-Me C_6H_4 (b)	H	80	95	93(<i>R</i>)
9	$\text{C}_6\text{H}_5\text{CH}_2$ (h)	H	18	99	58(<i>S</i>)
10	4-MeOC $_6\text{H}_4\text{CH}_2$ (i)	H	18	99	57(<i>S</i>)
11	3,4-(MeO) $_2\text{C}_6\text{H}_3\text{CH}_2$ (j)	H	36	99	55(<i>S</i>)
12	C_6H_5 (k)	CH_3	24	99	(+)-61 (n.d.) ^[f]



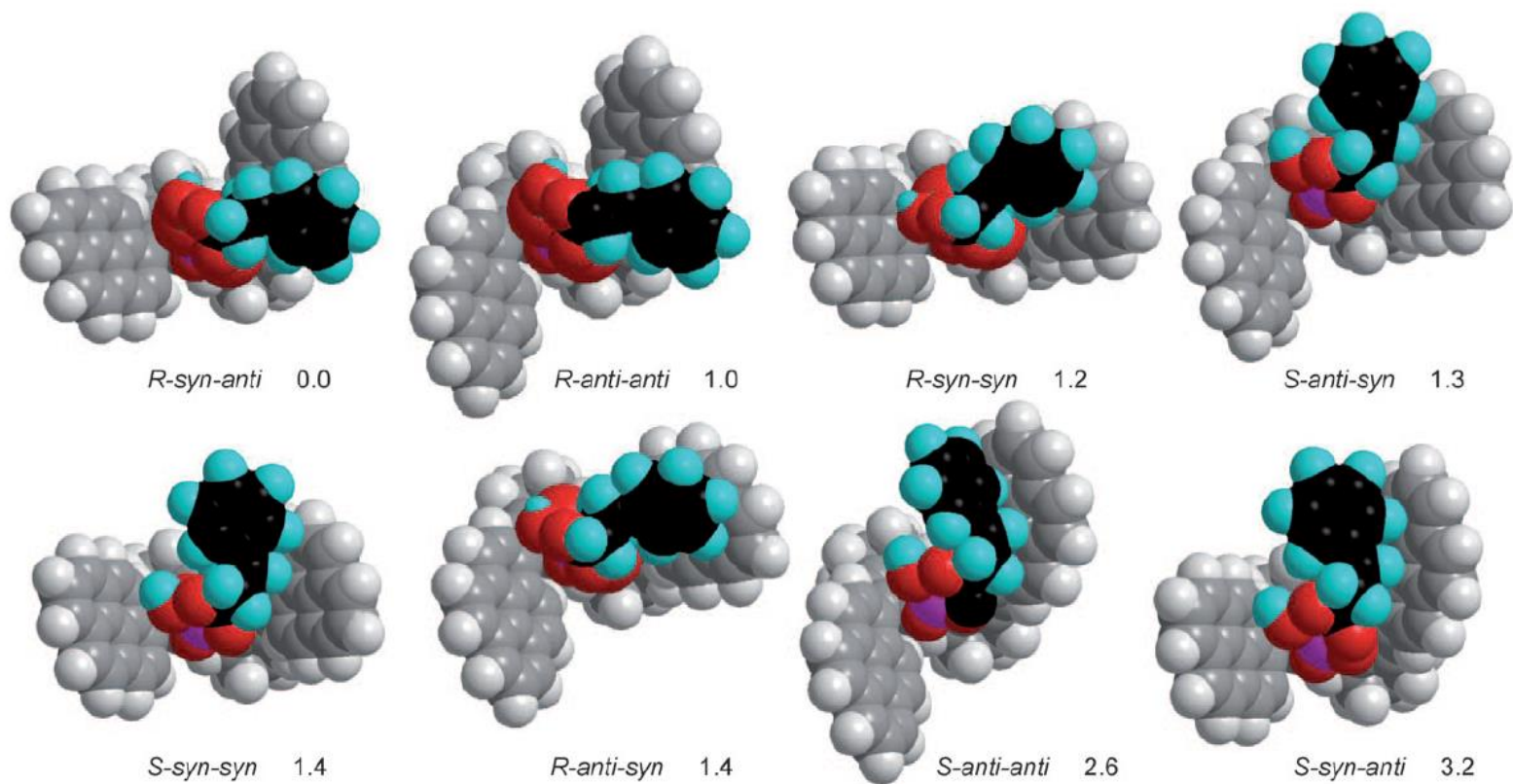
Brønsted Acid Catalyzed Asymmetric BV Proposed Mechanism

Ding, 2010



Brønsted Acid Catalyzed Asymmetric BV Proposed Mechanism

Ding, 2010

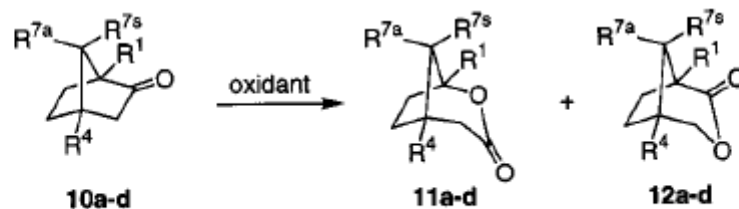


Summary of Asymmetric Reactions

System	By	Prochiral yields	Prochiral er		Racemate yields*	Racemate er*	Cat Loading
Copper	Bolm	92%	73.5:26.5		76%	88: 12	1 mol %
Platinum	Strukul	10%	84:16		25%	79: 21	1%
Aluminum	Bolm	Quant.	92: 8		Quant.	89: 11	20%
Titanium	Lopp	Not examined	Not examined		40%	87.5: 12.5	150 %
Zirconium	Katsuki	68%	93.5: 6.5		53%	92.5: 7.5	5-8 %
Chiral Acid	Ding	Quant.	96.5: 3.5		Quant.	69:31	10%



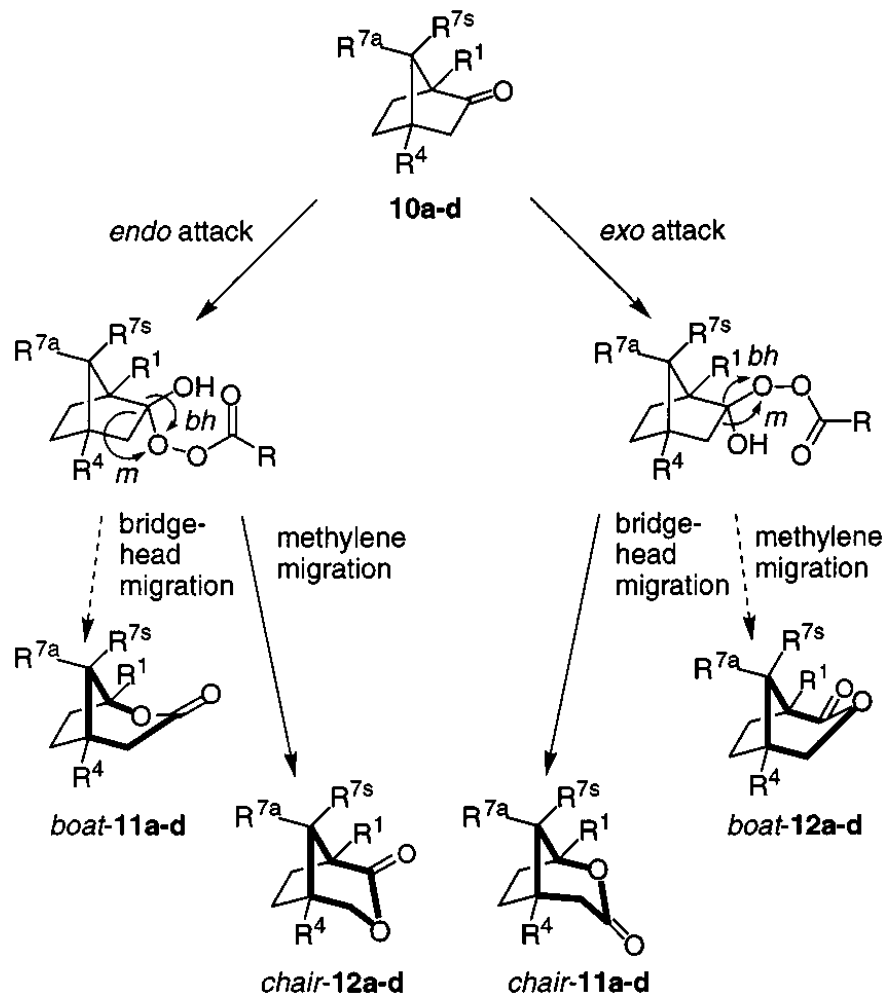
Group Problem



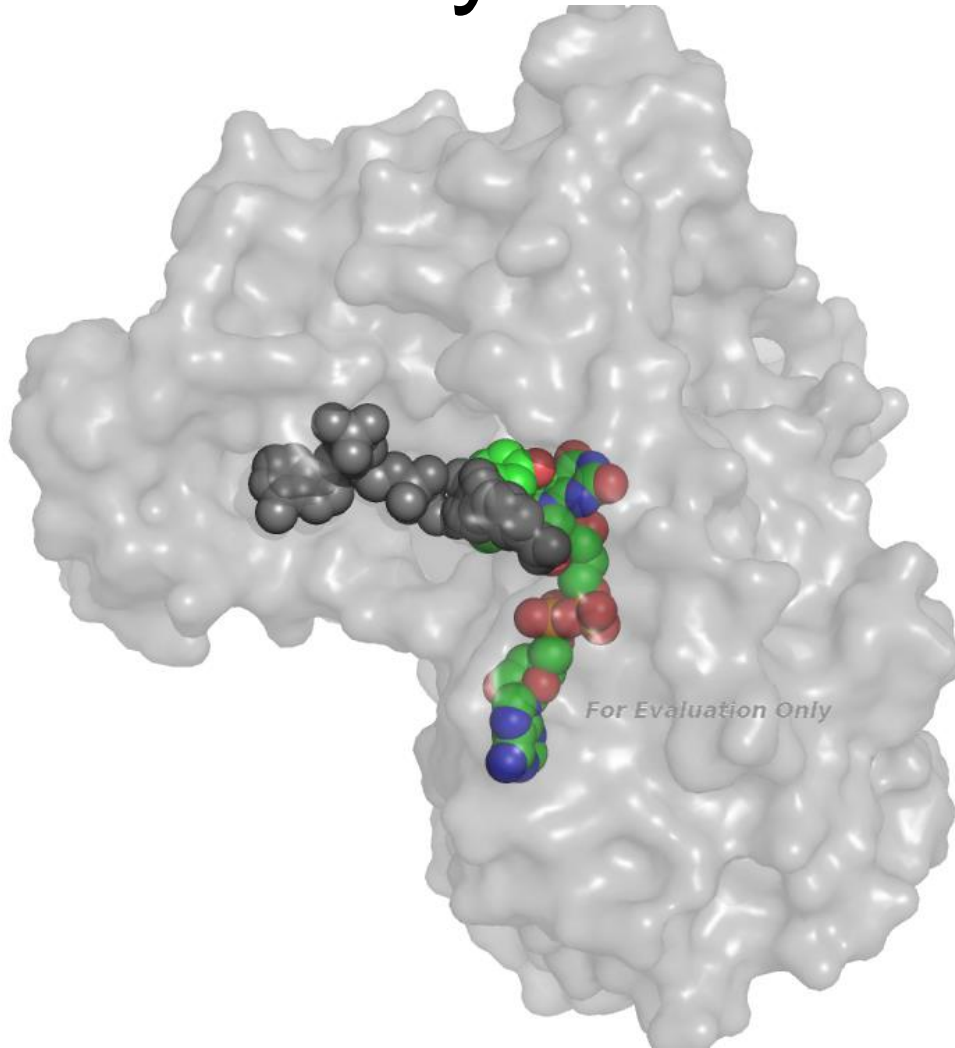
	R ¹	Substrate R ⁴	R ^{7a}	R ^{7s}	Oxidation	Yield [%]	Product distribution 11/12
10a	H	H	H	H	CF ₃ CO ₃ H, Na ₂ HPO ₄ ⁻	100	100:0
10b	Me	H	H	H	40% PAA, buffer	42	100:0
10c	Me	H	Me	Me	40% PAA in 40:60 H ₂ SO ₄ /HOAc	30	0:100
10d	Me	Me	Me	Me	40% PAA, NaOAc	94	0:100



Group Problem



Enzyme Catalyzed BV Reaction



Whole Cell Vs. Isolated Protein

Whole Cell

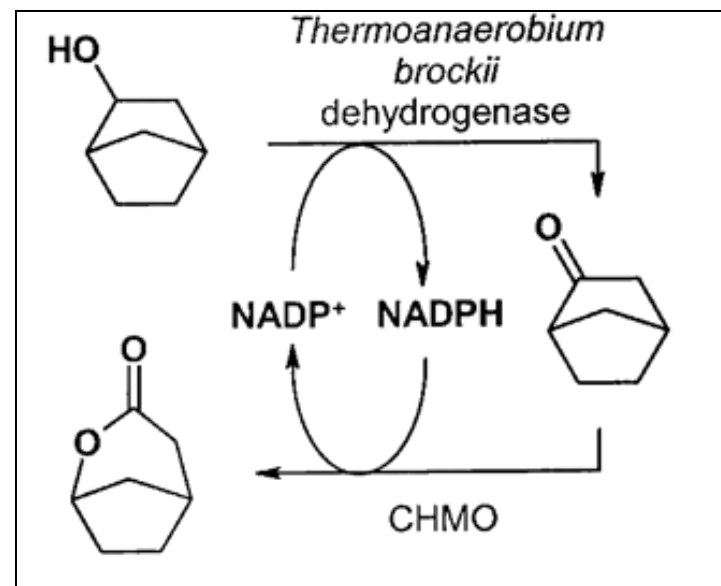
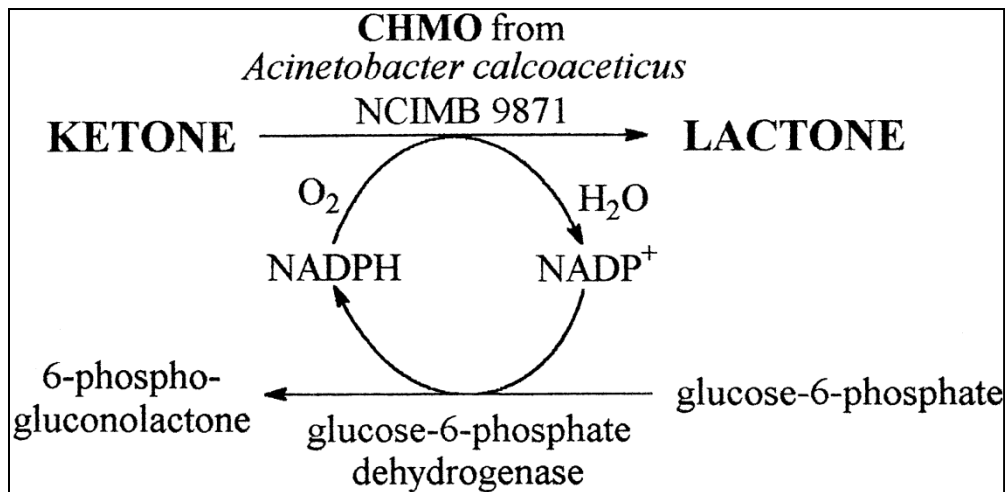
- Has a built in method to recycle NADP+.
- No Purification.
- Regrowable source.
- Other enzymes can perform undesired reactions.
 - Mitigated with over-expression
- More “resilient” to reaction conditions.

Isolated Protein

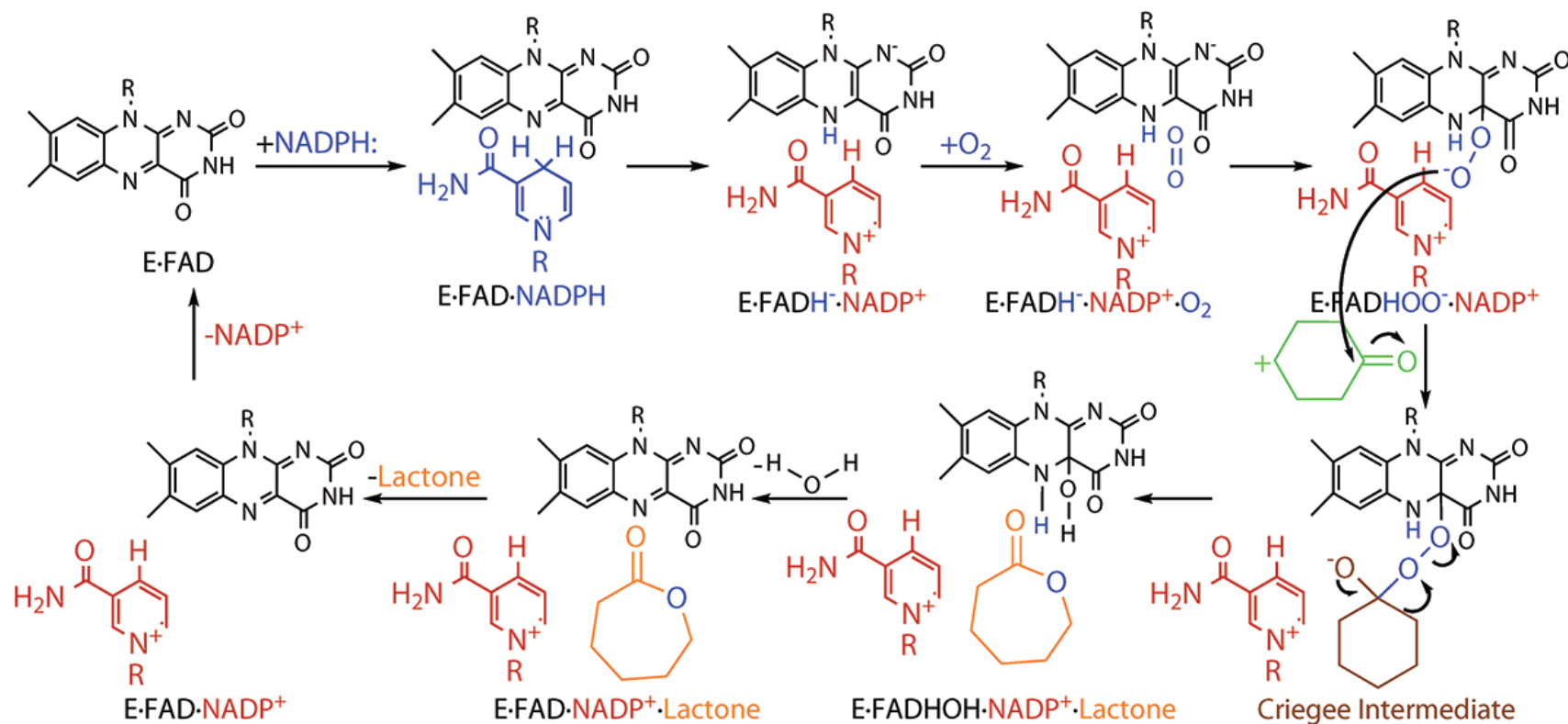
- Regeneration cycled must be established.
- Required Purification.
- Can only be used a few times (<4).
- Eliminates side reactions
- May loose activity based on reaction conditions.

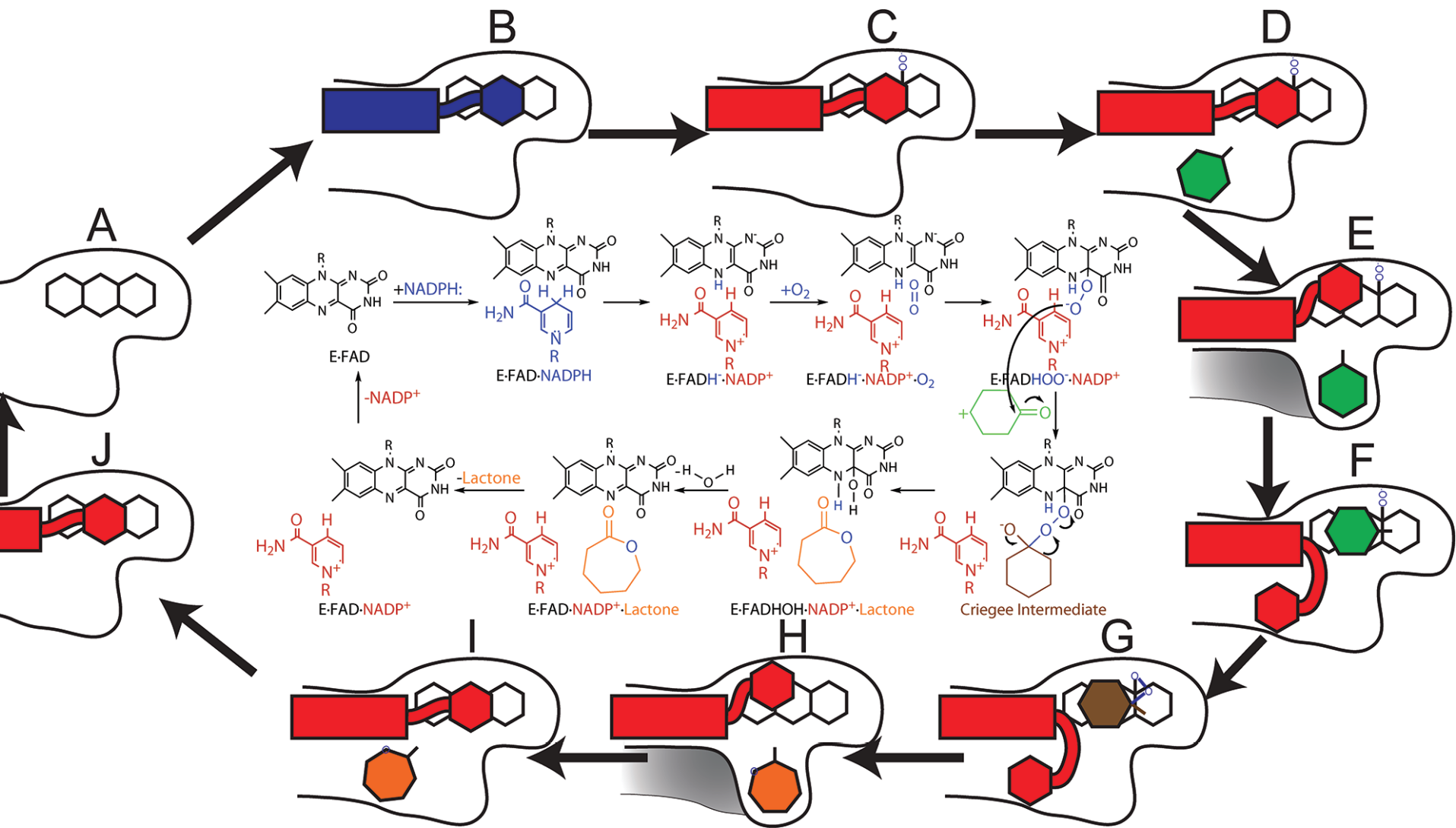


Cofactor Recycling

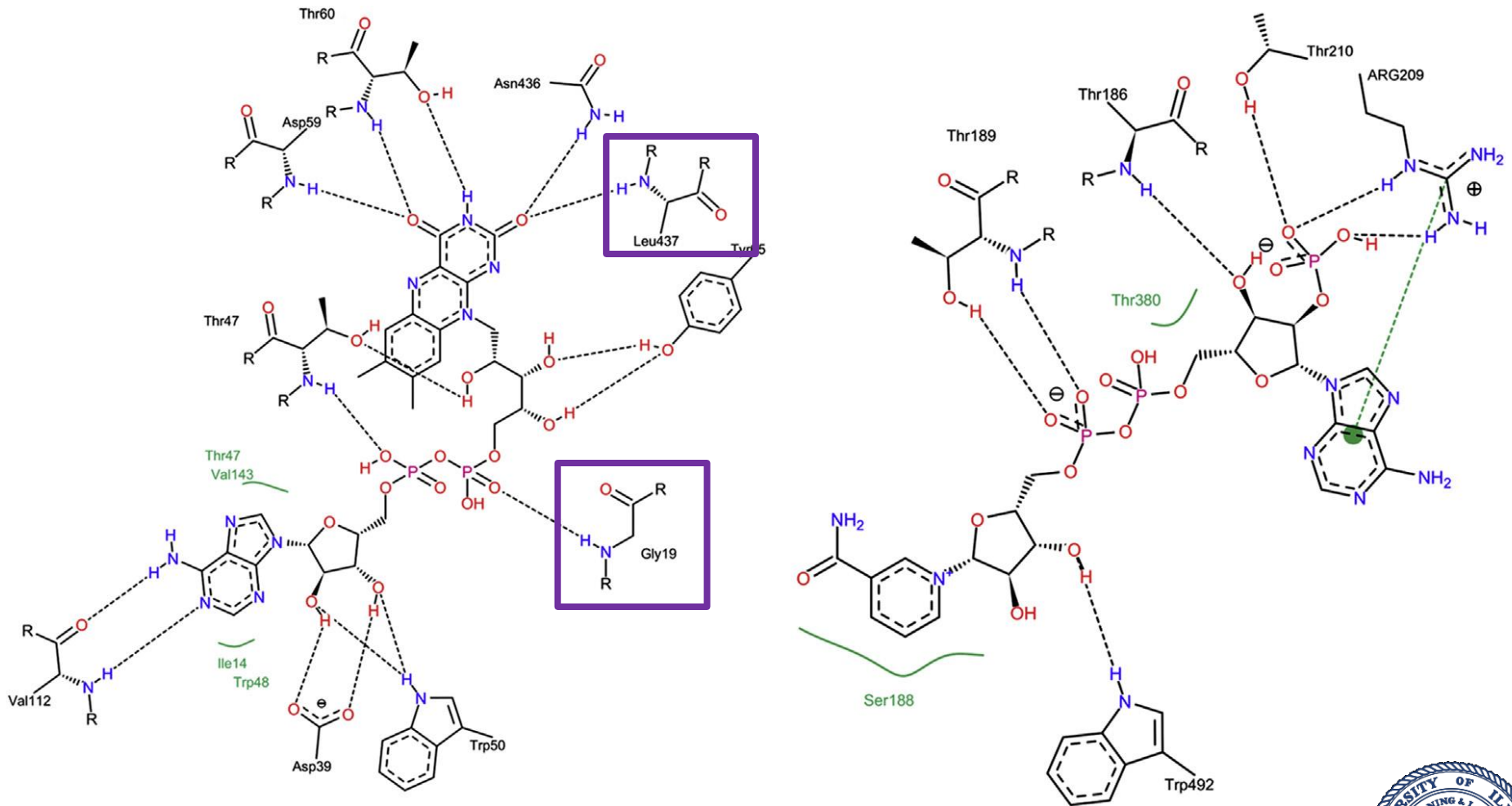


Enzymatic Baeyer-Villiger: Mechanism

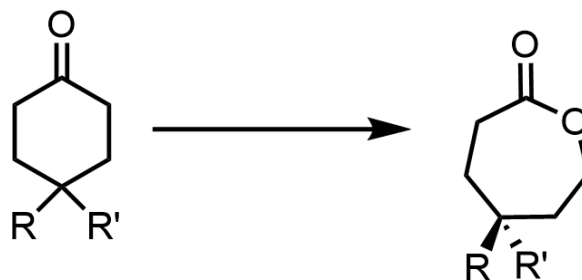




Conserved Residues



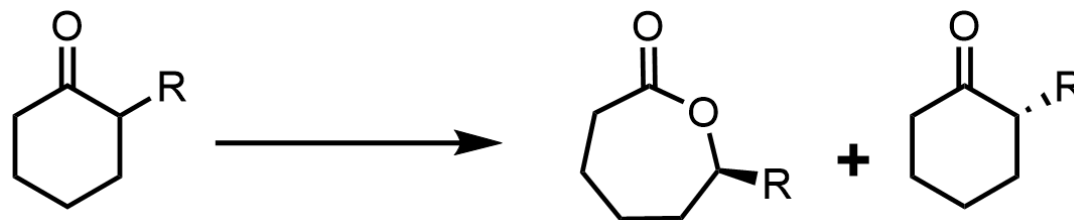
Achiral Oxidation via Enzyme



R	R'	R''	Yield	ee
H	Me	H	61%	≥ 98%
Me	Me	Me	61%	n.a.
Et	Et	H	91%	97%
	Et	Me	91%	75%
Pr	Et	Et	60%	n.a.
Bu	<i>cyclo</i> -CH ₂ CH ₂		74%	n.a.
<i>i</i> Pr	<i>cyclo</i> -OCH ₂ CH ₂ O		40%	n.a.
<i>t</i> Bu				
allyl				62%/95% ee (yeast)
Ph	14%/95% ee (EtOH)			
	80%/60% ee (glycol)			
OMe	76%/75% ee		84%/78% ee (<i>E. coli</i>)	
Br			63%/97% ee (<i>E. coli</i>)	
I			60%/97% ee (<i>E. coli</i>)	



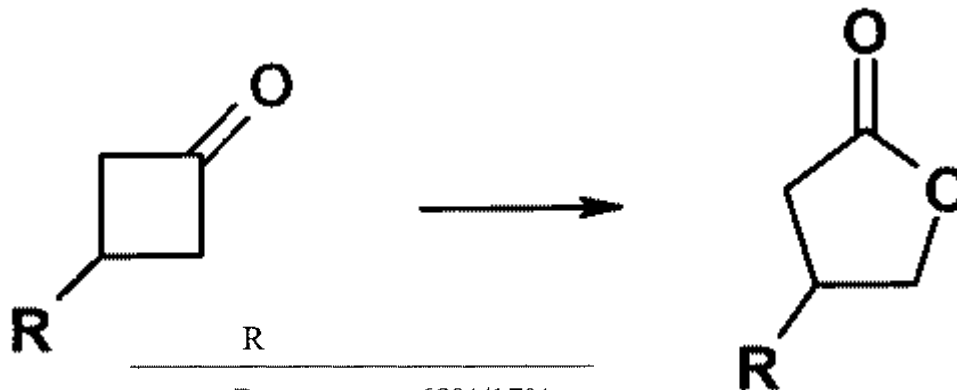
Racemic Oxidation via Enzyme

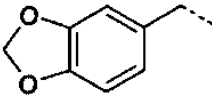


R	Isol. enzyme	Native cells	Recombinant cells
Me	n.r./n.r. n.r./ca. 30% <i>ee</i>	35%/61% <i>ee</i> 52%/35% <i>ee</i>	50%/49% <i>ee</i> (yeast)
Et		60%/38% <i>ee</i> 10%/> 98% <i>ee</i>	79%/95% <i>ee</i> (yeast) 69%/> 98% <i>ee</i>
Pr			54%/97% <i>ee</i> (yeast) 66%/92% <i>ee</i>
<i>i</i> Pr			41%/> 98% <i>ee</i> (yeast) 46%/96% <i>ee</i>
allyl			59%/> 98% <i>ee</i> (yeast) 58%/> 98% <i>ee</i>
Bu		6%/> 98% <i>ee</i> 37%/10% <i>ee</i>	59%/> 98% <i>ee</i> (yeast) 64%/98% <i>ee</i>
C ₆ H ₁₃		23%/98% <i>ee</i> 25%/35% <i>ee</i>	
C ₉ H ₁₉		26%/85% <i>ee</i> 32%/42% <i>ee</i>	
Ph		40%/> 98% <i>ee</i> 48%/86% <i>ee</i>	
Bn		22%/> 96% <i>ee</i> 28%/78% <i>ee</i>	
CH ₂ COOEt	39%/> 99% <i>ee</i> 60%/64% <i>ee</i>		
CH ₂ CH ₂ OAc	34%/> 99% <i>ee</i> 66%/76% <i>ee</i>		



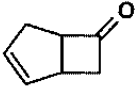
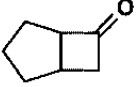
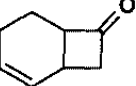
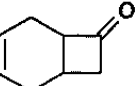
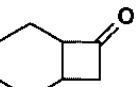
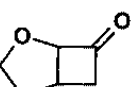
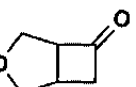
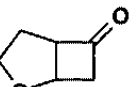
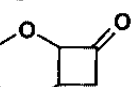
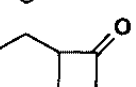
Racemic Oxidation via Enzyme



R	
Bu	68%/17% <i>ee</i>
<i>i</i> Bu	56%/84% <i>ee</i>
Ph	65%/98% <i>ee</i>
4-FC ₆ H ₄	80%/> 98% <i>ee</i>
4-ClC ₆ H ₄	30%/> 98% <i>ee</i>
4-MeC ₆ H ₄	73%/91% <i>ee</i>
Bn	57%/82% <i>ee</i>
3-MeOC ₆ H ₄ CH ₂	83%/96% <i>ee</i>
	83%/95% <i>ee</i>
PhCH ₂ OCH ₂	74%/98% <i>ee</i>
<i>t</i> BuOCH ₂	25%/> 98% <i>ee</i>

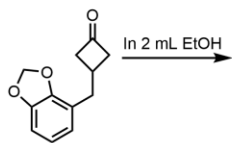


Fused Cyclobutanone Oxidation via Enzyme

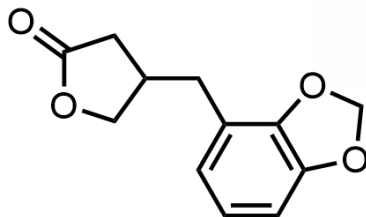
Substrate ketone	"Normal" lactone	"Abnormal" lactone
	44%/> 95% <i>ee</i>	42%/> 95% <i>ee</i>
	36%/> 95% <i>ee</i>	31%/> 95% <i>ee</i>
	43%/> 95% <i>ee</i>	37%/> 95% <i>ee</i>
	41%/86% <i>ee</i>	36%/> 95% <i>ee</i>
	52%/60% <i>ee</i>	28%/> 95% <i>ee</i>
	35%/90% <i>ee</i>	32%/> 98% <i>ee</i>
	35%/97% <i>ee</i>	35%/> 98% <i>ee</i>
	33%/> 98% <i>ee</i>	41%/> 98% <i>ee</i>
	33%/70% <i>ee</i>	33%/> 98% <i>ee</i>
	60%/33% <i>ee</i>	18%/> 98% <i>ee</i>



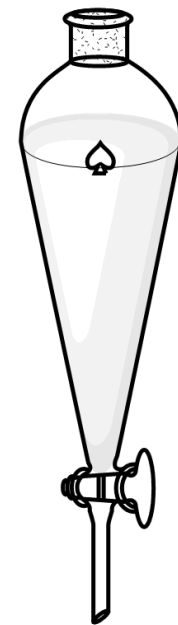
Step-By-Step Instructions



Cells suspended in a standard phosphate buffer
pH=7 (200 mL)



83%
97.2:2.5 er



Extracted 3 times with 30 mL
EtOAc

Conclusions

- The enzymatic BV oxidation is superior to current chemical methods.
- The enzymatic BV is becoming more available to the organic chemist and is increasing in versatility.
- There is still room for development using traditional chemical synthesis.



Selected Readings

- **Reviews:**

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