

I. The Kharasch-Sosnovsky Reaction

II. The Asymmetric Baeyer-Villiger Reaction

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Evans Group Seminar
Tuesday, December 13, 1999

Overview

- I. The Kharasch-Sosnovsky Reaction
 - a) mechanism
 - b) applications
 - c) asymmetric variants
- II. The Asymmetric Baeyer-Villiger Reaction

Lead References:

Kharasch-Sosnovsky:

General: Rawlinson, Sosnovsky, *Synthesis* **1972**, 1

Mechanism: Kochi, Mains, *J. Org. Chem.* **1965**, *30*, 1862

Beckwith, Zavitsas, *J. Am. Chem. Soc.* **1986**, *108*, 8230

Asymmetric: Brunel, Buono, *C.R. Acad. Sci. Paris, T. 2, Serie II c* **1999**, 19

Asymmetric Baeyer-Villiger

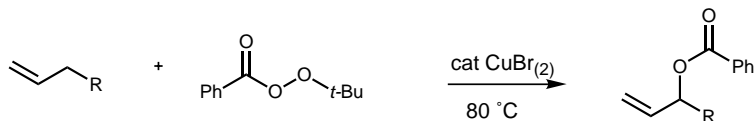
General: Bolm, *Adv. Cat. Proc.* **1997**, *2*, 43

Metal catalyzed: Bolm, *Tran. Met. Org. Synth.* **1998**, *2*, 213

Strukul, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1198

Enzymatic: Roberts, *J. Mol. Cat. B: Enz.* **1998**, *4*, 111

Kharasch-Sosnovsky Reaction



Either Cu(I) and Cu(II) may be used

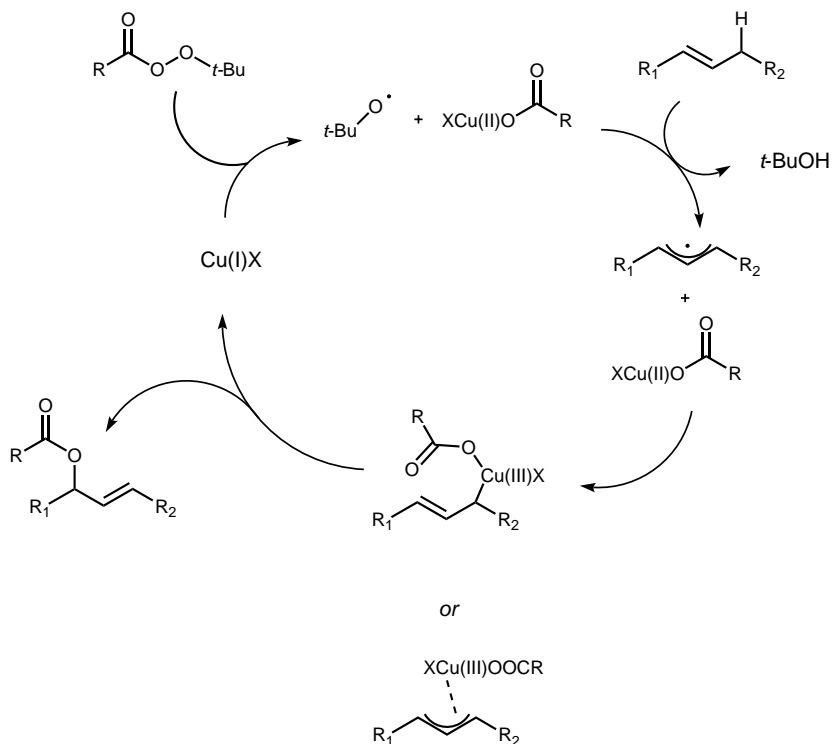
Terminal olefin products predominate from terminal or internal olefin reactants

Peroxides may also be used as the oxidant

Reaction without copper salt leads to mixtures of substitution products

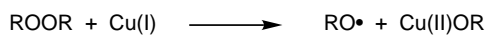
Reaction carried out with excess of olefin

Mechanistic Proposal



Beckwith, Zavitsas, *J. Am. Chem. Soc.* **1986**, 108, 8230

What are the Reactive Species?

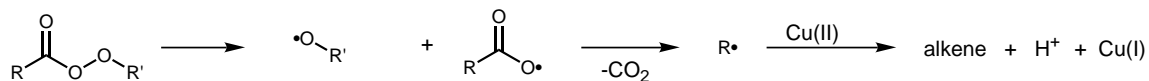


Cu(I) the initiating species

In peroxide and diacyl peroxide decomposition studies, the use of Cu(II) shows a long induction period. Cu(I) generated *in situ* shows no induction period, and the rate of decomposition is proportional to the concentration of Cu(I).

Kochi, Bemis, *Tet.* **1968**, 24, 5099

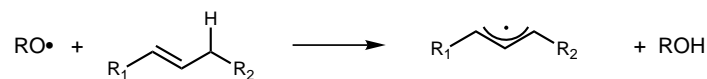
How is the reaction initiated if only Cu(II) is used?



Cu(II) and R• combination is diffusion controlled.

Kochi, *J. Org. Chem.* **1965**, 30, 1862

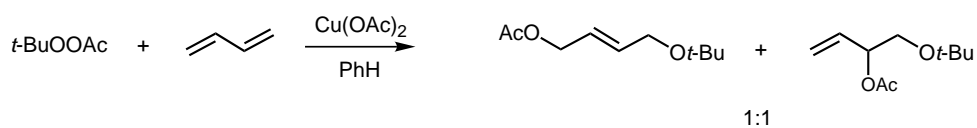
What are the Reactive Species?



H• abstraction via alkoxy radicals

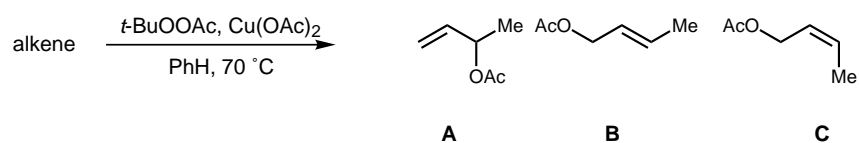
If free $t\text{-BuO}\cdot$ is involved in the reaction, relative reactivities of different substrates should be identical with those observed towards $t\text{-BuO}\cdot$ radicals produced in other reactions. Free radical chlorinations of alkenes employing $t\text{-BuOCl}$ show identical rates of alkene disappearance as the corresponding reaction with Cu salts and peresters.

Walling, Zavitsas, *J. Am. Chem. Soc.* **1963**, *85*, 2084

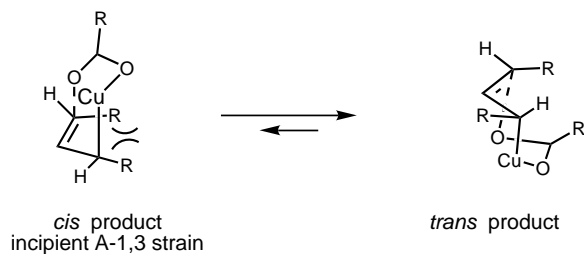


Kochi, *J. Am. Chem. Soc.* **1962**, *84*, 3271

Allylic Intermediates

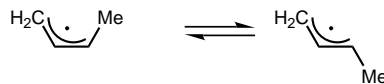


alkene	A:B:C
<i>trans</i> -2-butene	93:7:0
<i>cis</i> -2-butene	97:2.9:0.1
1-butene	95:5:0



Beckwith, Zavitsas, *J. Am. Chem. Soc.* **1986**, *108*, 8230

Allylic Radical Intermediates



21 kcal/mol interconversion barrier at 126 °C in gas phase

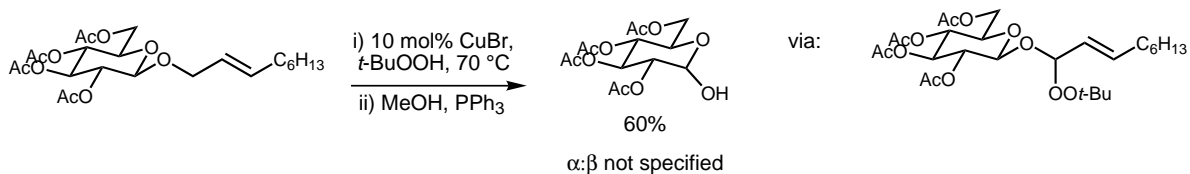
allylic radical reacts with Cu(II) 100 times more rapidly than interconversion



Beckwith, Zavitsas, *J. Am. Chem. Soc.* **1986**, 108, 8230

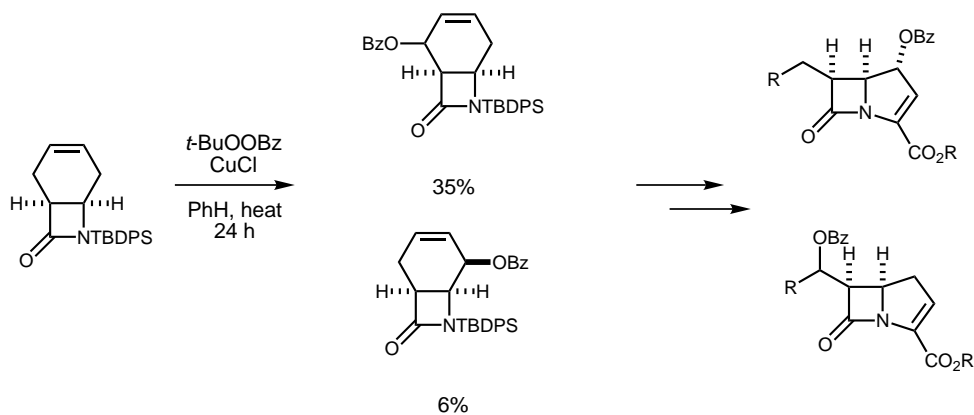
Applications of the Kharasch Reaction

Oxidative deprotection of allyl glycosides:



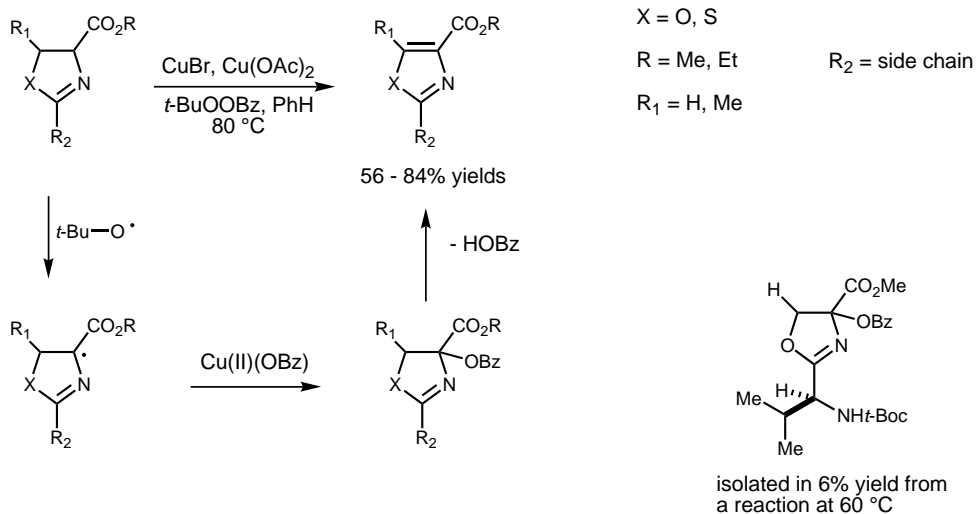
Welzel, *Tet.* **1998**, 54, 10753

Intermediates of Olivanic acid analogues:



Bateson, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2399

Oxidation of Oxazolines and Thiazolines

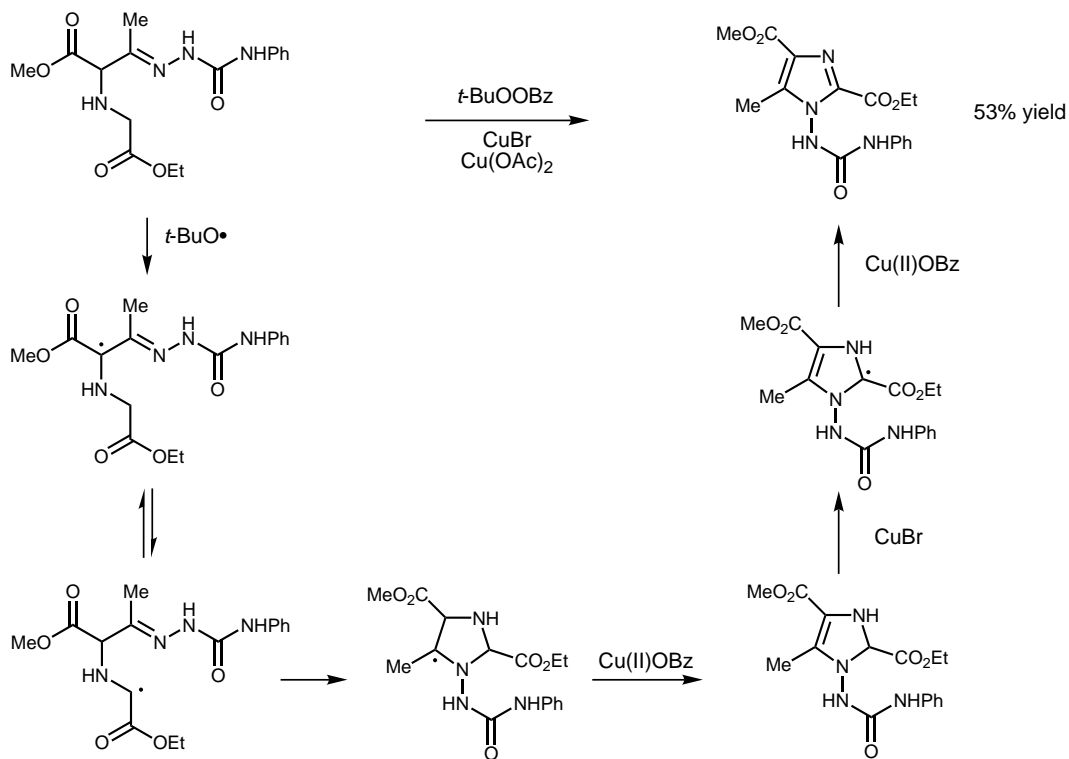


reaction rate enhanced by Cu(II) salts

ester group crucial for reactivity

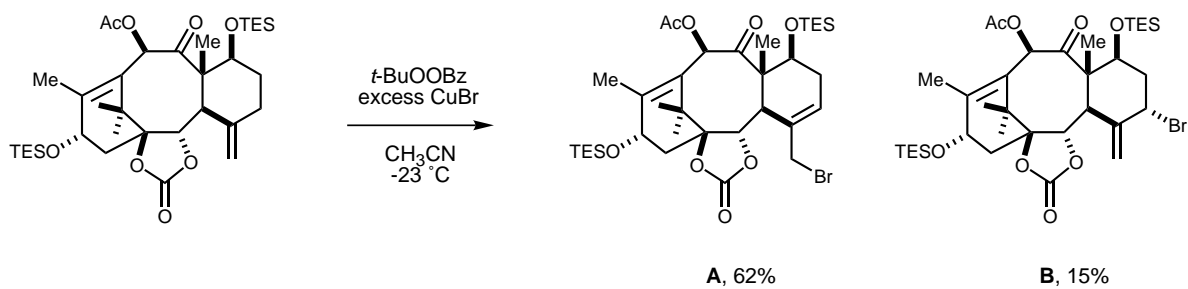
Meyers, *J. Org. Chem.* **1996**, *61*, 8207

An Annulation Reaction



Arcadi, *Tet. Lett.* **1997**, *38*, 2329

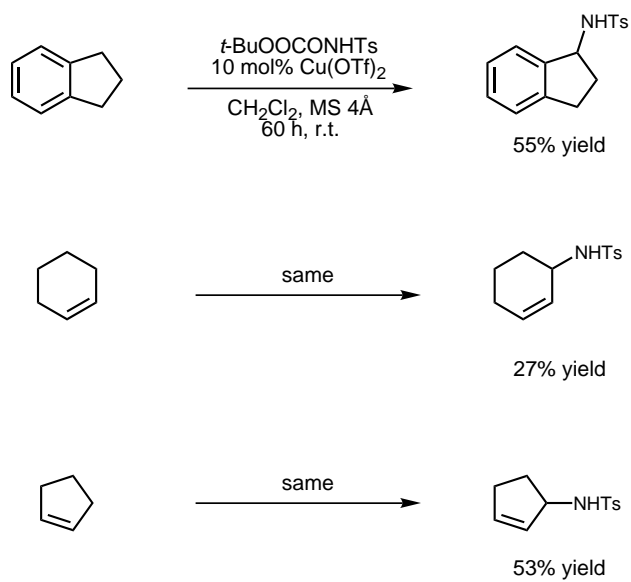
Modified Kharasch-Sosnovsky Reaction Towards Taxol



A may be converted to a 2.5:1 mixture of **B:A** by heating in CH_3CN
 SeO_2 , PCC unsuccessful in promoting desired oxidation

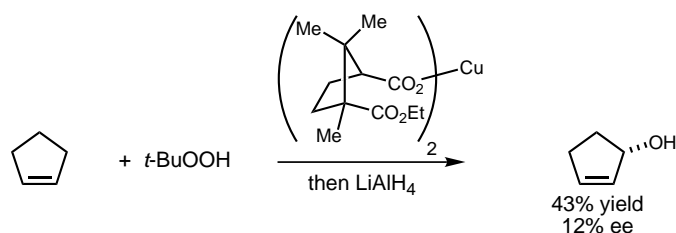
Mukaiyama, *Chem. Eur. J.* **1999**, 5, 121

Benzylic and Allylic Amination



Katsuki, *Synlett* **1997**, 1456

Optical Activity: The Early Years



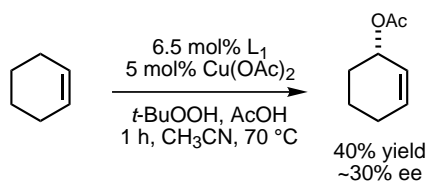
"The choice of these substances may or may not be good and it is clear that others may be far superior." (footnote)

Denney, *J. Org. Chem.* **1965**, *30*, 3151

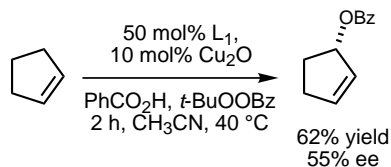
From the patent literature: "Optically active esters were prepared by the oxidation of an olefin with *t*-BuOOBz in the presence of an optically active Cu complex with a Schiff base or an amino acid [and acetic acid]. Thus, cyclohexene was oxidized... to give 2-cyclohexenyl acetate ($\alpha_D = -23.69^\circ$) (16% ee)."

Araki, Nagase, *Chem. Abstr.* **1977**, *86*, 120886r

Catalytic Copper/Amino Acid Complexes

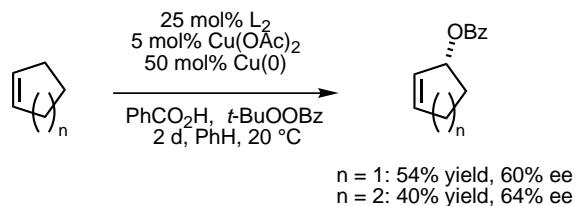


Muzart *J. Mol. Cat.* **1991**, *64*, 381

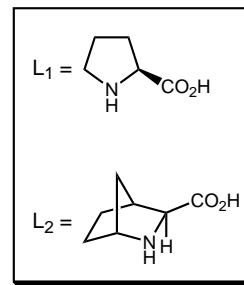


Muzart *Synth. Comm.* **1995**, *25*, 1789

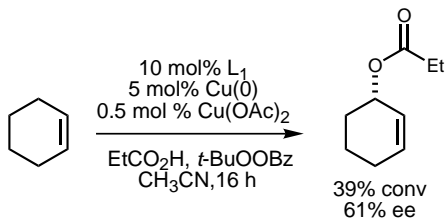
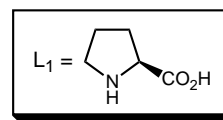
Further studies in reaction conditions: Muzart, *Tet. Asym.* **1995**, *6*, 147



Andersson, *Tet. Lett.* **1996**, *37*, 7577

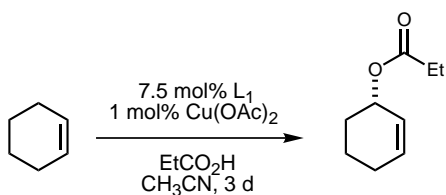


Catalytic Copper/Amino Acid Complexes



decreasing ligand loading and increasing Cu(II)/Cu(0) loading increases conversion but slightly decreases selectivity

Feringa *Tet. Asym.* **1995**, 6, 661

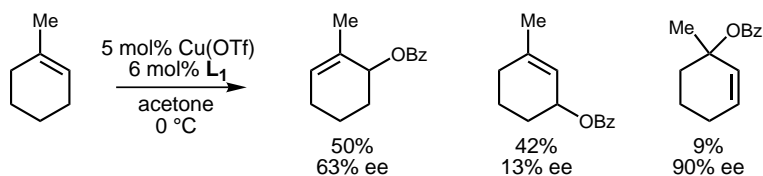
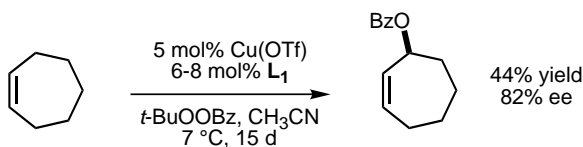
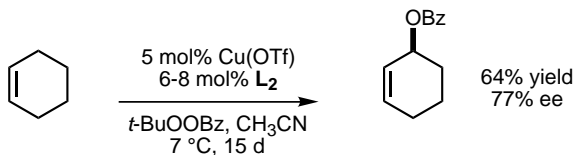
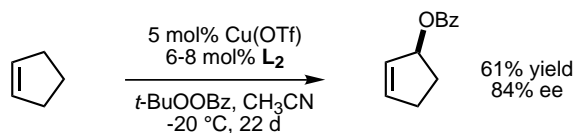
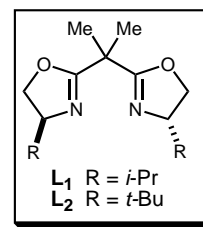


anthraquinone (eq to Cu)	oxidant	% yield	% ee
0	<i>t</i> -BuOOH	89	45
4	<i>t</i> -BuOOH	80	60
200	<i>t</i> -BuOOH	60	56
4	<i>t</i> -BuOOBz	81	46

The system shows a positive non-linear effect with anthraquinone and a negative effect without.

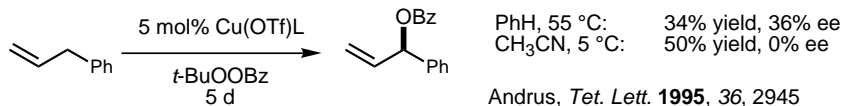
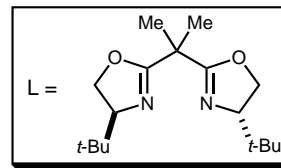
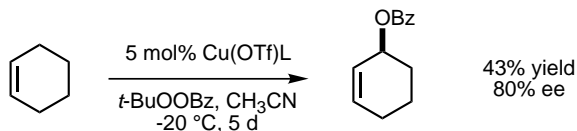
Feringa *Tet. Asym.* **1996**, 7, 1895

Copper/Bisoxazoline Complexes



Pfaltz, *Tet. Lett.* **1995**, 36, 1831

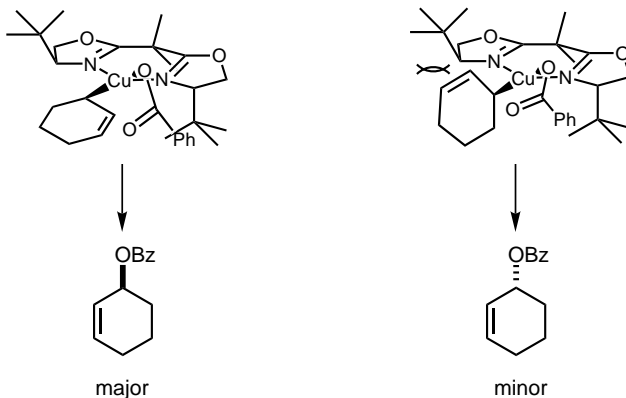
Andrus System



Andrus, *Tet. Lett.* **1995**, 36, 2945

use of CuPF_6 and/or more electron deficient perbenzoates give higher yields

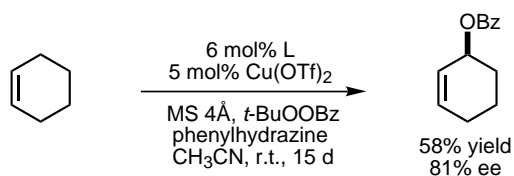
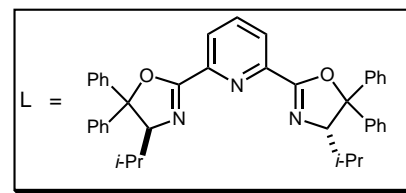
Andrus, *Tet.* **1997**, 53, 16229



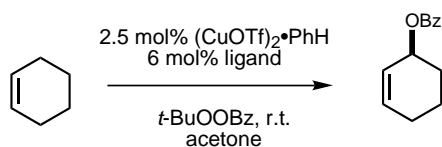
major

minor

Use of Pybox Ligands



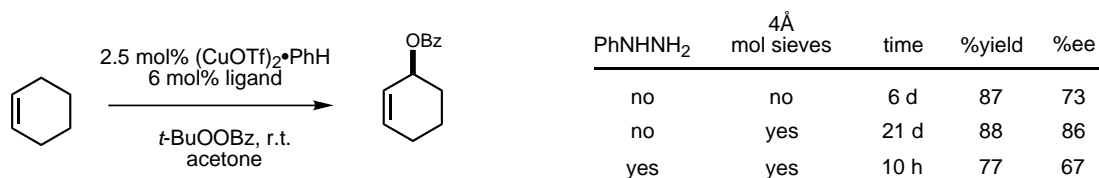
Singh, *Tet. Lett.* **1996**, 37, 2633



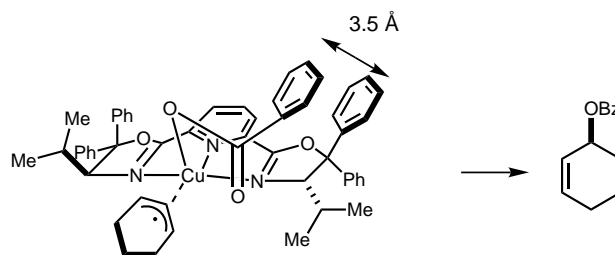
PhNHNH ₂	time	%yield	%ee
no	6 d	87	73
yes	5 h	78	70

Singh, *J. Org. Chem.* **1998**, 63, 2661

Molecular Sieves Affect Reactivity

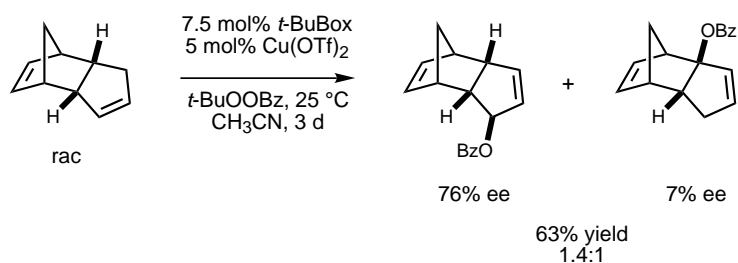


Singh's Model For Asymmetric Induction

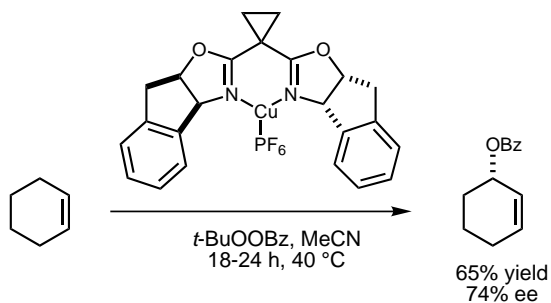


Singh, *J. Org. Chem.* **1998**, 63, 2661

The Bisoxazoline Saga Continues

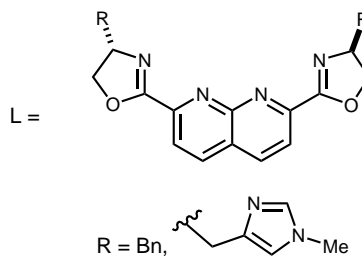
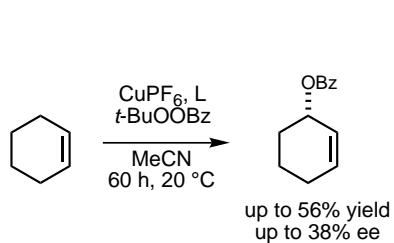


Katsuki, *Synlett* **1999**, 1231

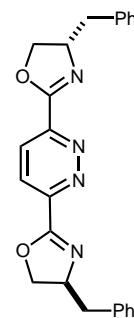
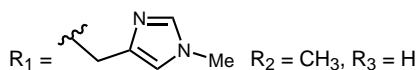
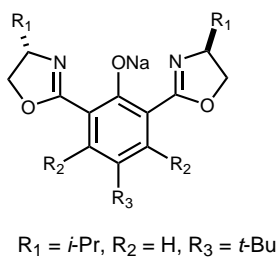
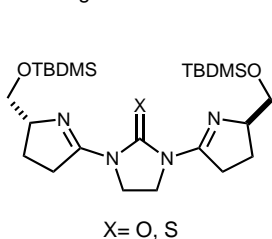


Clark, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1168

Chiral Dinuclear Copper Complexes



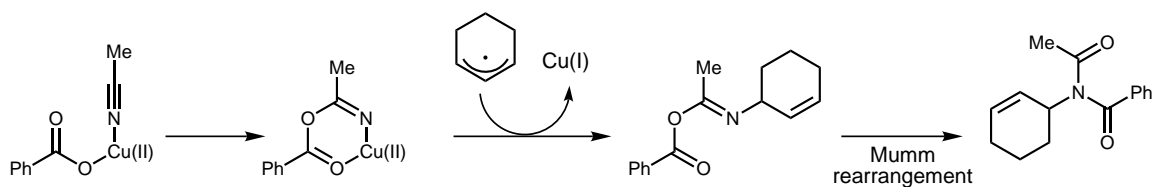
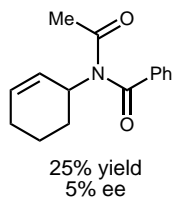
Other ligands



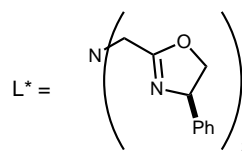
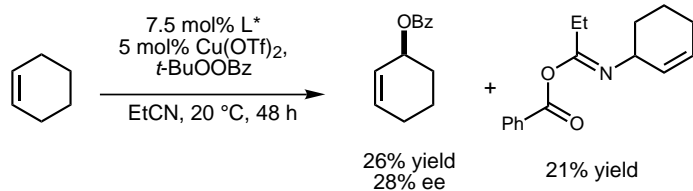
Fahrni, *Tet.* **1998**, 54, 5465

A Mysterious Side Product

The following product was observed:

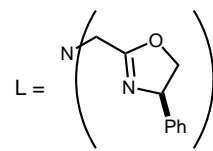
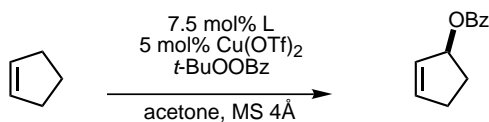


Fahrni, *Tet.* **1998**, 54, 5465



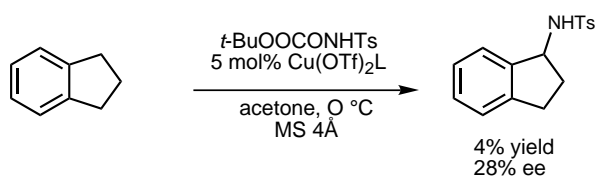
Katsuki, *Synlett* **1995**, 1245

Tris(oxazoline) Ligands



temp (0 °C)	time (h)	%yield	%ee
r.t	16	83	76
0	150	81	83
-20	200	30	93

Katsuki, *Tet.* **1997**, 53, 6337

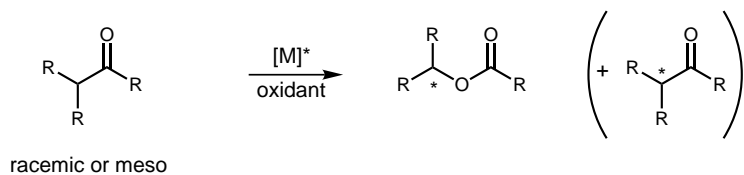


Katsuki, *Synlett* **1997**, 1456

Kharasch Reaction: Conclusion

- The mechanism of the Kharasch reaction has yet to be fully elucidated. The nature of the copper/allyl species is key to understanding the reaction.
- Synthetic applications of the Kharasch reaction are somewhat limited.
- Asymmetric Kharasch transformations are an emerging field. The reactions are still "black box."
 What role does anthraquinone play?
 What role does phenylhydrazine play?
 Why do some reactions work best with Cu(I), and others Cu(II)?

Asymmetric Baeyer-Villiger



Reviews

"Catalyzed Baeyer-Villiger Reactions," Bolm, *Adv. Cat. Proc.* **1997**, 2, 43

"Metal Catalyzed Baeyer-Villiger Reactions," Bolm, *Tran. Met. Org. Synth.* **1998**, 2, 213

"Transition Metal Catalysis in the Baeyer-Villiger Oxidation of Ketones," Strukul, *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 1198

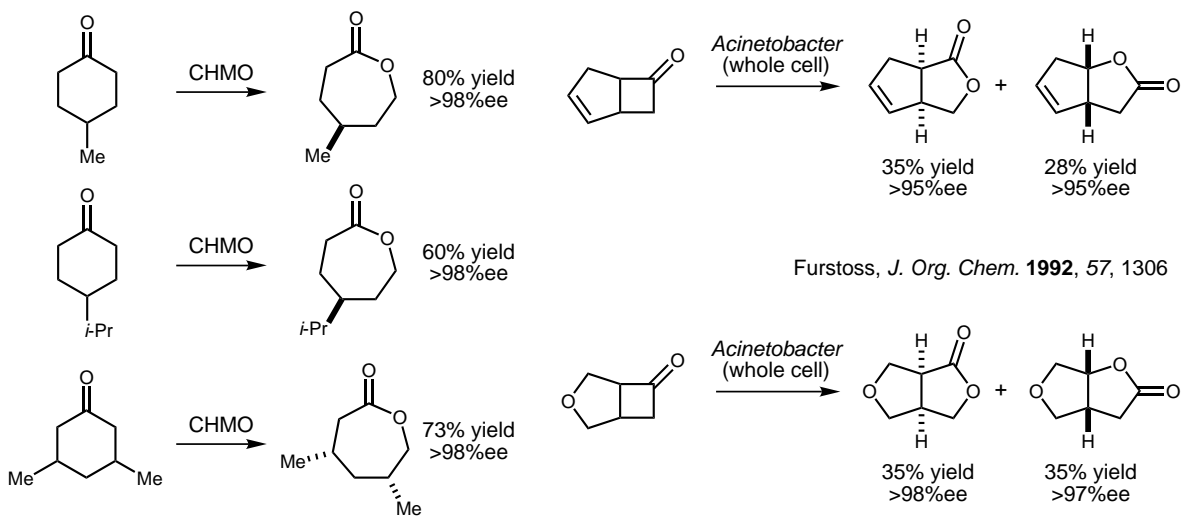
Enzymatic

Current method of choice for asymmetric Baeyer-Villiger

"The most popular whole cell biocatalyst is *Acinetobacter calcoaceticus* ... a Class 2 organism and hence should be used in a properly sealed and ventilated laboratory [which] restricts its use from the non-specialist."

"Enzyme-Catalysed Baeyer-Villiger Oxidations," Roberts, *J. Mol. Cat. B: Enz.* **1998**, 4, 111

Examples From Enzymes



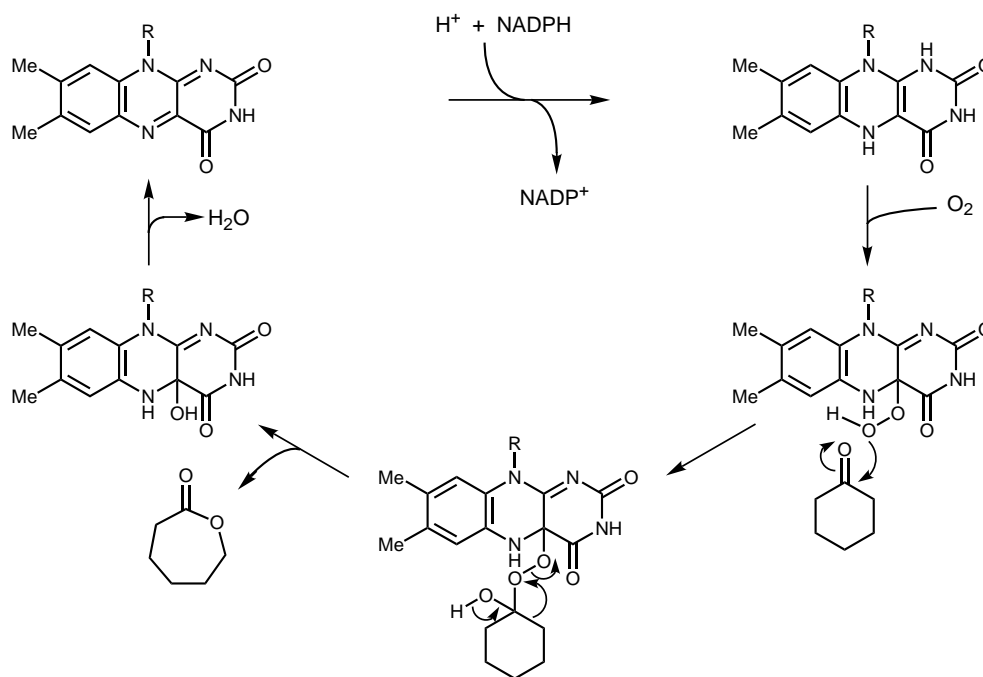
Furstoss, *J. Org. Chem.* **1992**, 57, 1306

Furstoss, *Tet. Asym.* **1993**, 4, 1341

CHMO = cyclohexanemonooxygenase

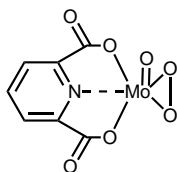
Enzymatic Mechanism

Baeyer-Villiger enzymes are flavin dependent monooxygenases



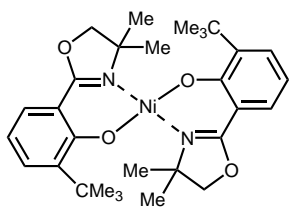
Roberts, *J. Mol. Cat. B: Enz.* **1998**, 4, 111

Transition Metal Catalysts for Baeyer-Villiger Oxidation



Jacobsen, *J. Chem. Soc. Chem. Comm.* **1978**, 888

Campestrini, *J. Mol. Cat.* **1993**, 79, 13



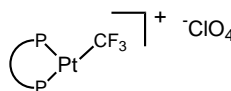
Cu(OAc)₂

Bolm, *Tet. Lett.* **1993**, 34, 3408

MeReO₃
Hermann, *J. Mol. Cat.* **1994**, 94, 213

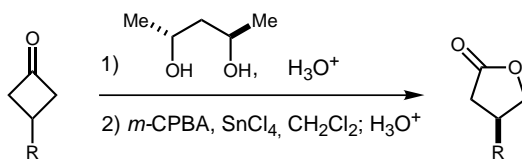
Fe₂O₃
Murahashi, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2443

Ni(dpm)₂, Ni(dmp)₂
Mukaiyama, *Chem. Lett.* **1991**, 641
Mukaiyama, *Chem. Lett.* **1994**, 535



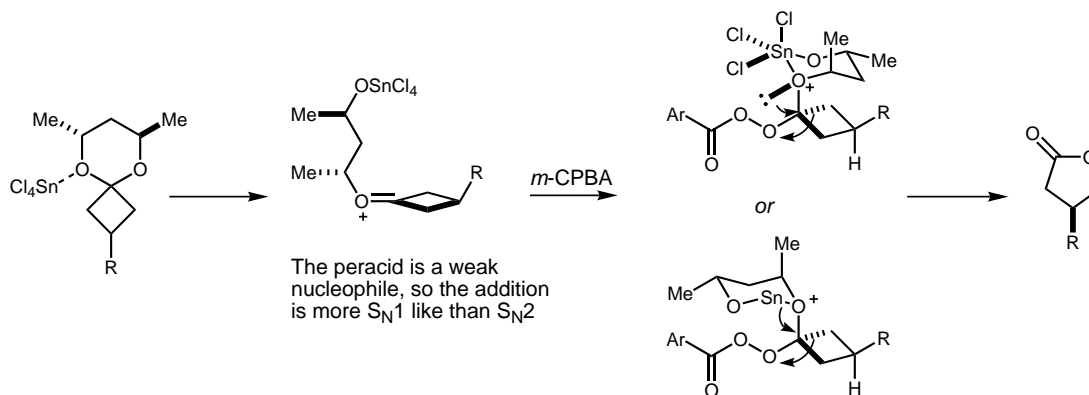
Strukul, *Organometallics*, **1993**, 12, 148

Lewis Acid Diastereodifferentiating Oxidation



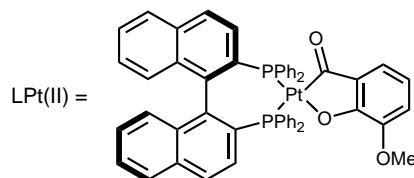
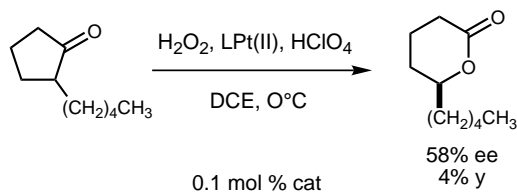
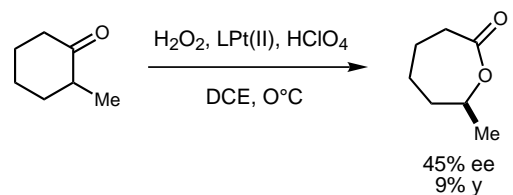
R = aryl (21 - 89% ee)
R = alkyl (52 - 59% ee)

89%ee: R = Ph, 2 eq *m*-CPBA, 5 eq SnCl₄, -100 °C

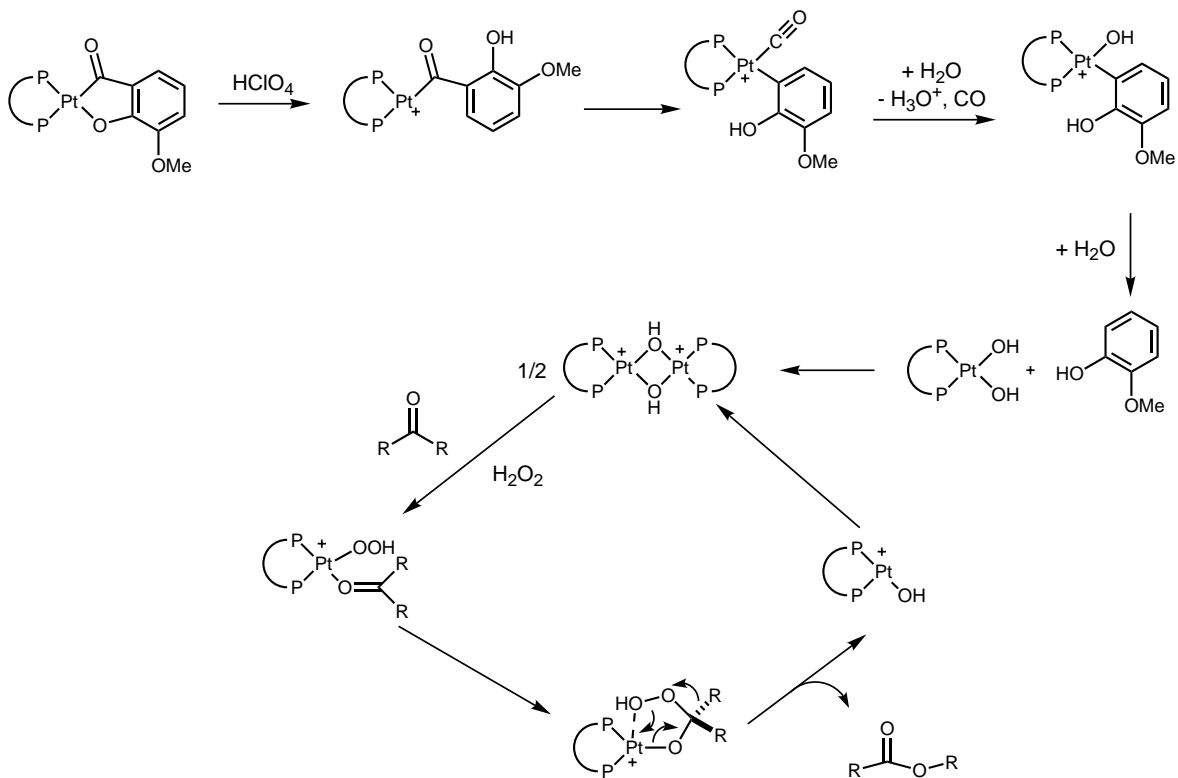


Sugimura, *Tet. Lett.* **1997**, 34, 6019

Platinum Catalysis

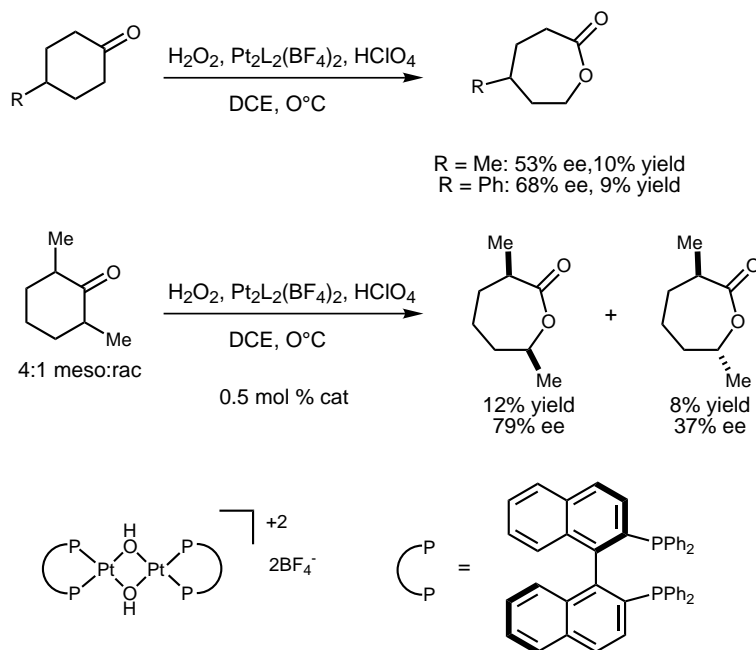


Platinum Catalysis- Mechanism



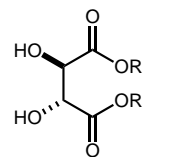
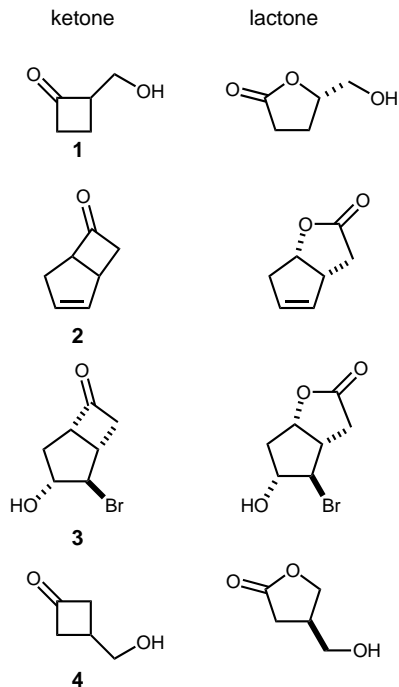
Strukul, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1198

Recent Platinum Catalysis Results



Strukul, *Organometallics*, **1999**, *18*, 5057

Sharpless Conditions



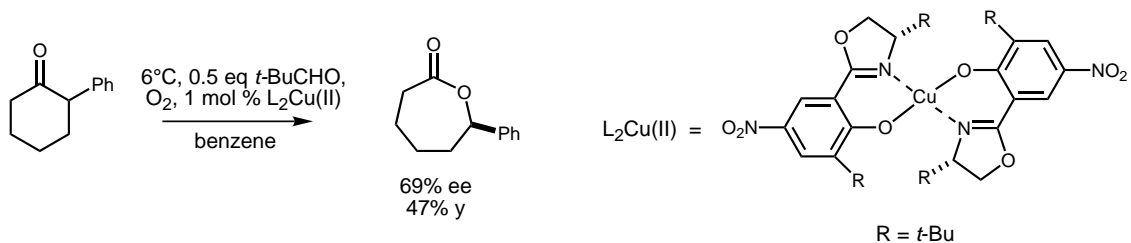
oxidant: *t*-BuOOH
metal: Ti(O-*i*-Pr)₄
stoichiometric

ketone	R = Me		R = Et		R = <i>i</i> -Pr	
	%conv	%ee	%conv	%ee	%conv	%ee
1	—	—	35	37	35	34
2	—	—	7	53	8	34
3	49	34	40	75	28	67
4	9	27	14	40	22	33

Ti-TADDOL affords lower selectivities

Lopp, *Tet. Lett.* **1996**, 37, 7583
Lopp, *Tet. Asym.* **1998**, 9, 4475

The Bolm Examples



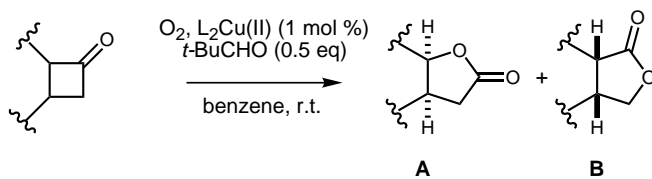
The corresponding Ni complex gave racemic product

Unreacted ketone isolated in 10 - 30% ee

Use of MS 4Å or NaHCO₃ as additives gave racemic product

Corresponding cyclopentanones react more slowly, cycloheptanones do not react

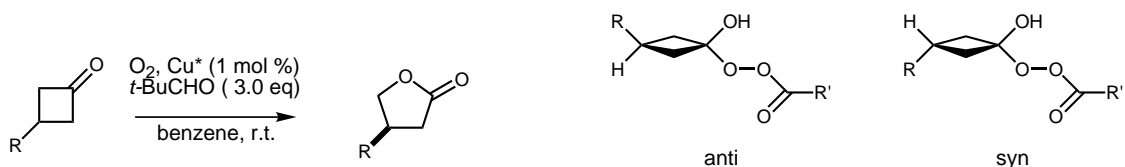
Cyclobutanone Oxidation



	%ee (A)	%ee (B)	yield (%) (A:B)
	67	92	61 (3:1)
	61	94	74 (2:1)
	76	95	32 (3:2)
	59	93	59 (1:1.3)

Bolm, *J. Chem. Soc., Chem. Comm.* **1995**, 1247

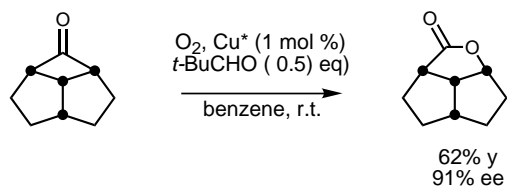
More Cyclobutanones



R	%ee	yield (%)
octyl	31	77
<i>t</i> -Bu	47	85
Ph	44	88
Bn	29	90
CO ₂ <i>t</i> -Bu	36	92
CO ₂ Bn	26	82
CH ₂ OBn	23	80

Poor selectivity in formation of two diastereomeric Criegee intermediates can lead to poor enantioselectivity.

Use substrate with one diastereoface inaccessible:



Asymmetric Baeyer-Villiger: Conclusion

- Operationally, the asymmetric Baeyer-Villiger reactions are intriguing due to the use of O_2 or H_2O_2 as oxidants.
 - A drawback is the need for reactive substrates.
 - Strukul's Pt work points towards potentially useful transformations.
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