Synthesis of Oxetanes

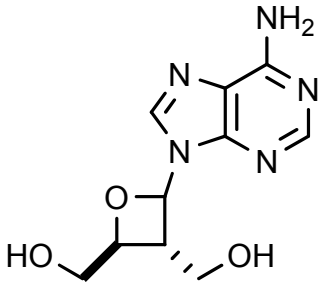
Paternò-Büchi Reaction and Cyclization Approach

Group Meeting

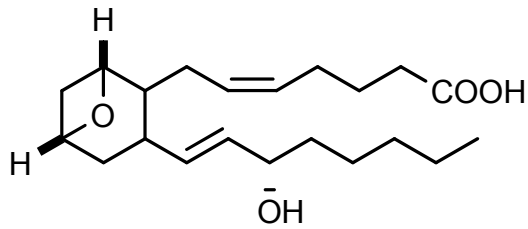
04-14-2009

Timothy Chang

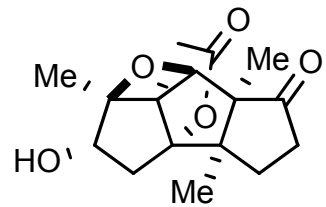
Applications of Oxetanes



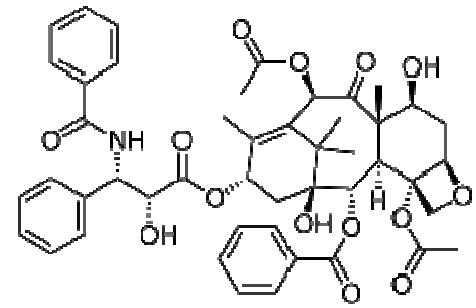
Oxetanocin



Thromboxane A_2

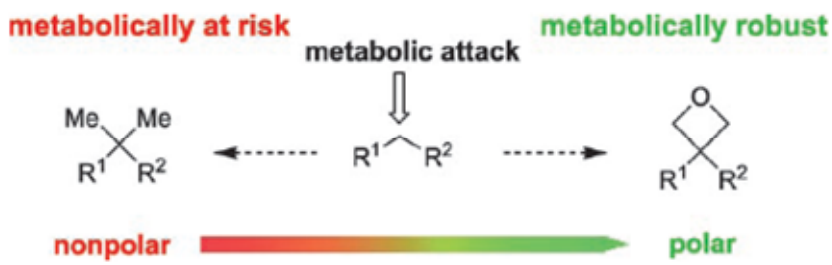


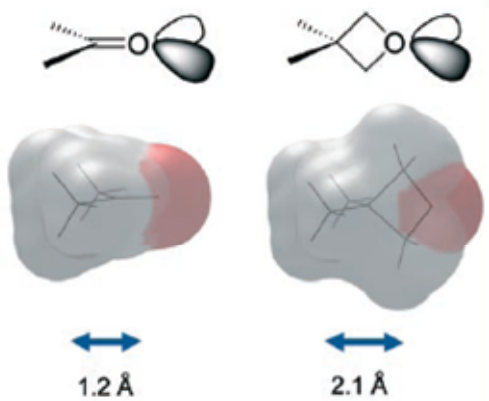
Merrilactone A



Taxol

Drug Discovery:





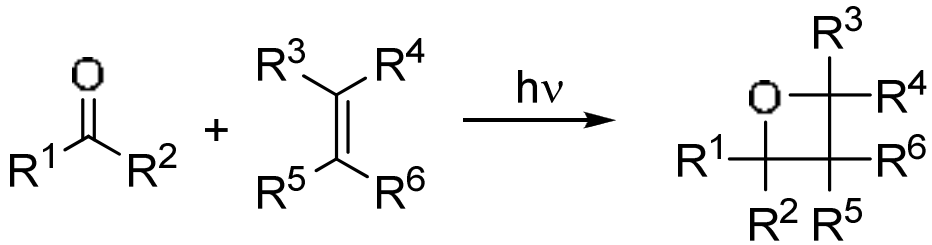
Rogers-Evans, Carreira et. al. *Angew. Chem. Int. Ed.* **2006**, *45*, 7736.
Rogers-Evans, Müller, Carreira et. al. *Angew. Chem. Int. Ed.* **2008**, *47*, 4512.

Polymer: Curing agent

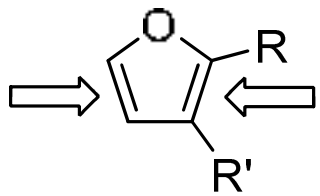
Chemical process of converting a prepolymer or a polymer into a polymer of higher molar mass and connectivity and finally into a network. Curing is typically accomplished by chemical reactions induced by heating (thermal curing), photo-irradiation (photo-curing), or electron-beam irradiation (EB curing), or by mixing with a chemical curing agent. (http://goldbook.iupac.org/CT07137.html)

General Strategies

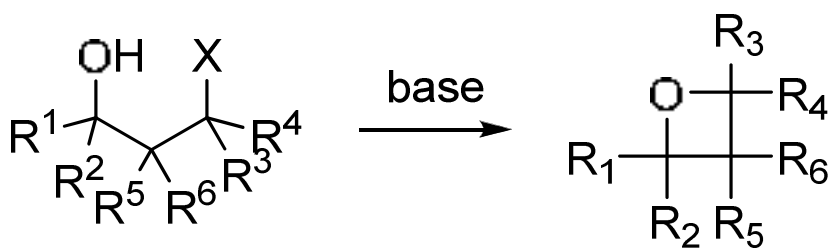
Photochemical Approach



Issues to consider:
- Regioselectivity
- Intrinsic stereoselectivity
- Site selectivity



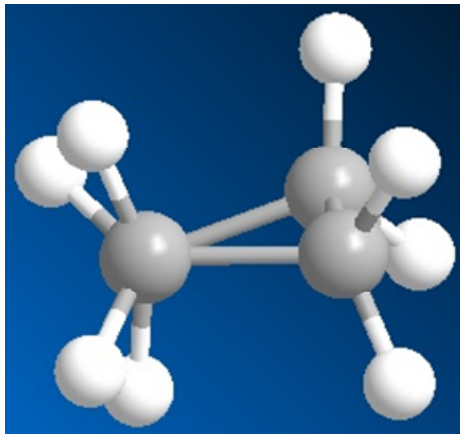
Cyclization Approach

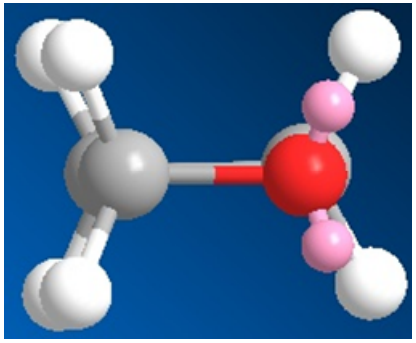


X = leaving group

Chiral alcohols can be accessed from:
- Asymmetric reduction of ketone → → 2-substitued oxetane
- SAE → → 2- or 2,2-disubstituted oxetane
- Asymmetric allylation

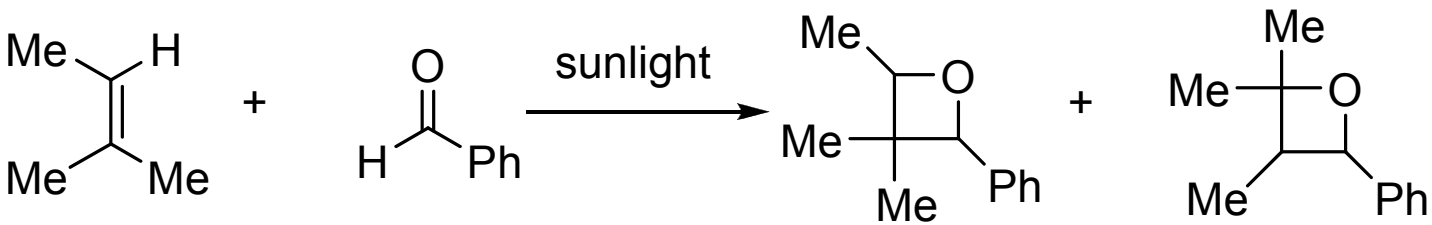
Introduction



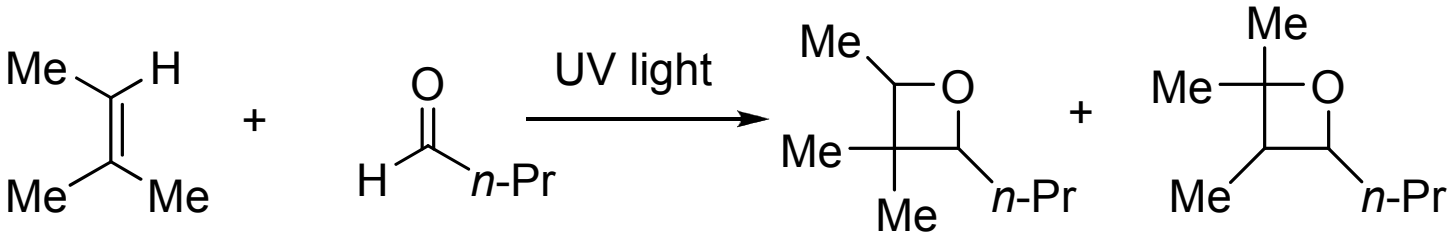


MM2 (Chem3D)

- First reported by E. Paternò and G. Chieffi in 1909.



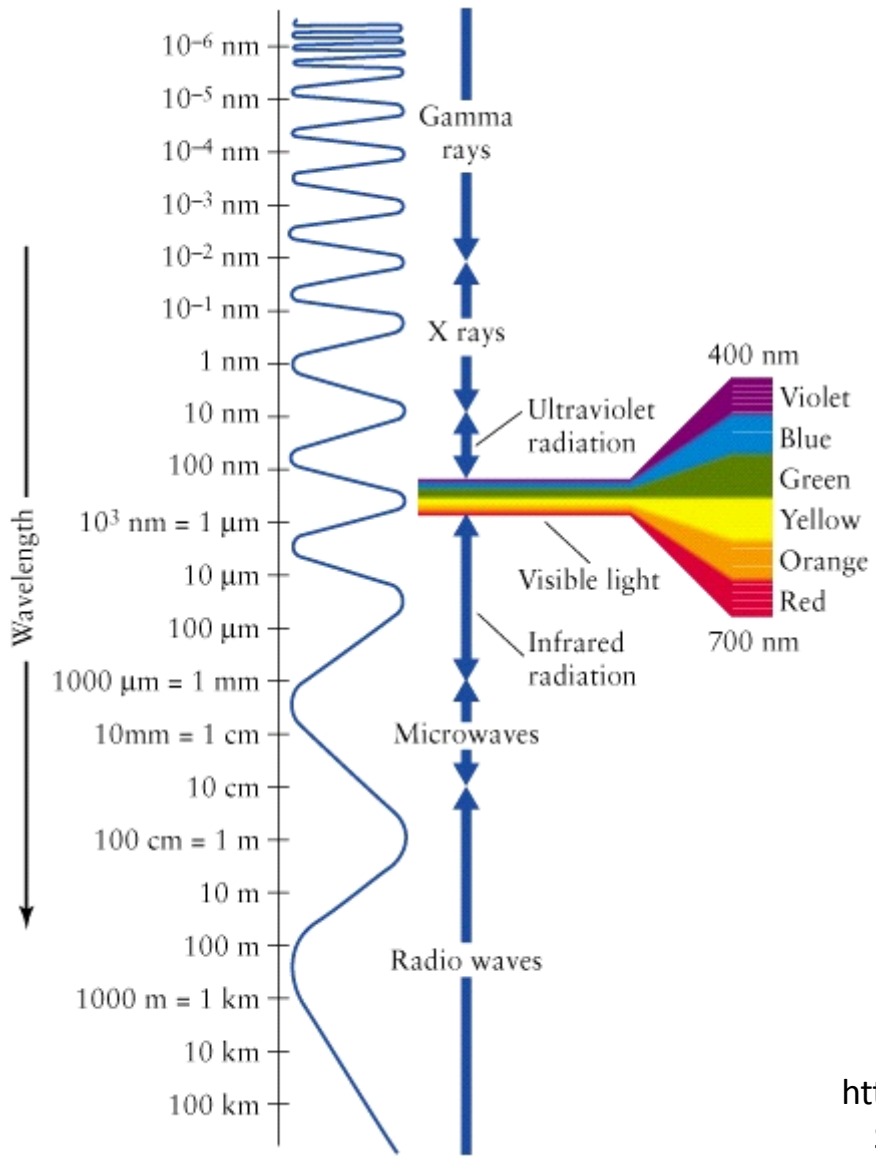
- G. Büchi determined the structure of the products in 1954.



Paterno, E. et. al. Gazz. Chim. Ital. **1909**, *39*, 341.
Büchi, G. et. al. *J. Am. Chem. Soc.* **1954**, *76*, 4327.

Light Induced Transition

$E = h\nu$, $\nu = c/\lambda$, $E = hc/\lambda$



Nuclear (0.005 - 1.4 Å)

Inner electron (0.1 - 100 Å)

Bonding electrons (10 - 780 nm)

Rotation/vibration of molecules (0.78 - 300 µm)

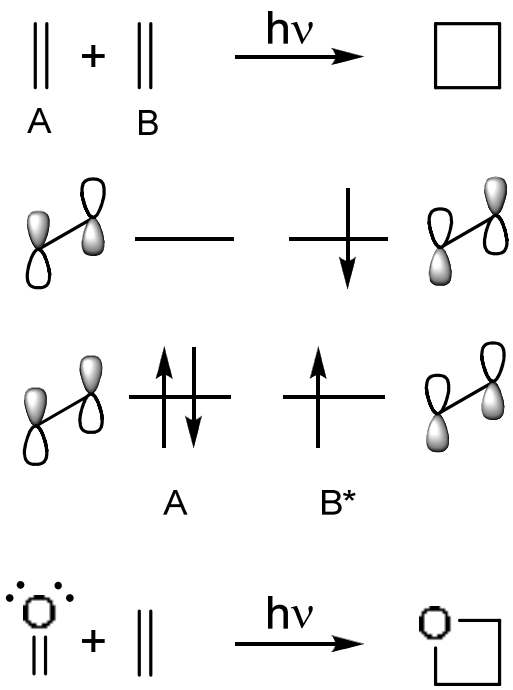
Rotation of molecules (0.73 - 3.75 mm)

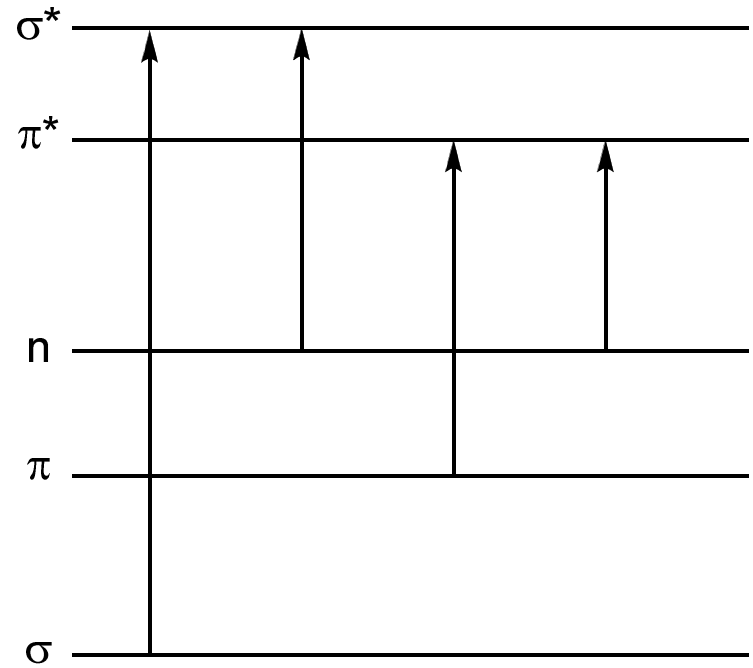
Spin of nuclei (0.6 - 10 m)

http://eosweb.larc.nasa.gov/EDDOCS/Wavelengths_for_Colors.html

Skoog, Hooller, Nieman *Principles of Instrumental Analysis*, 5th Ed.

Orbitals Involved in Electron Transitions





$\varepsilon = 8.7 \times 10^{19}$ PA

P is transition probability
A is the cross-section target area

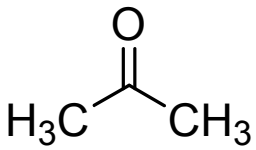
$\sigma \rightarrow \sigma^*$: λ < 185 nm e.g. CH_4, 125 nm

$n \rightarrow \sigma^*$: λ 150 - 250 nm (mostly ~200 nm)

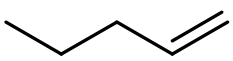
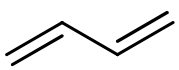
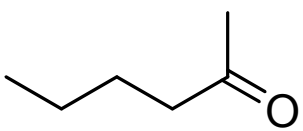
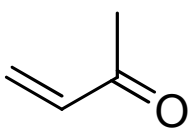
$n \rightarrow \pi^*$: λ 200 - 700 nm, ε: 10 - 100
$\pi \rightarrow \pi^*$: λ 200 - 700 nm, ε: 1000 - 10000
Both require an unsaturated functional group

Skoog, Hooller, Nieman *Principles of Instrumental Analysis*, 5th Ed.
Anslyn, Dougherty *Modern Physical Organic Chemistry*

Chromophores

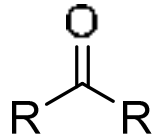
Chromophores	λ_{max} (nm)	Type of Transition	ε_{max}
$H_2C{=}CHC_6H_{13}$	177	$\pi \rightarrow \pi^*$	13000
	186 280	$\pi \rightarrow \sigma^*$ $n \rightarrow \pi^*$	1000 16

Effect of Conjugation

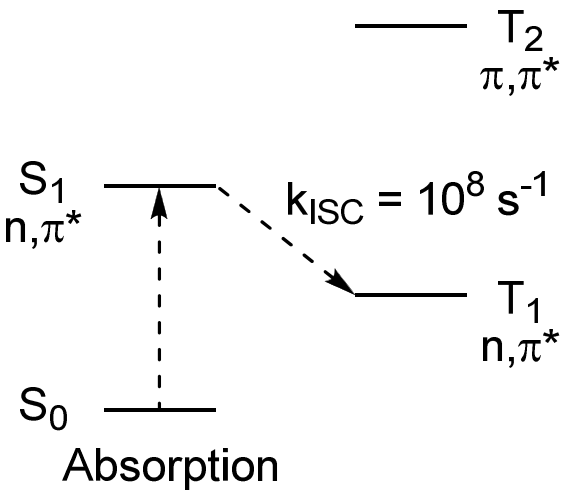
Chromophores	λ_{max} (nm)	Type of Transition	ε_{max}	
	184	$\pi \rightarrow \pi^*$	~10000	
	217	$\pi \rightarrow \pi^*$	~21000	
	282	$n \rightarrow \pi^*$	27	
	324 219	$n \rightarrow \pi^*$ $\pi \rightarrow \pi^*$	24 3600	spatially "forbidden" spatially "allowed"

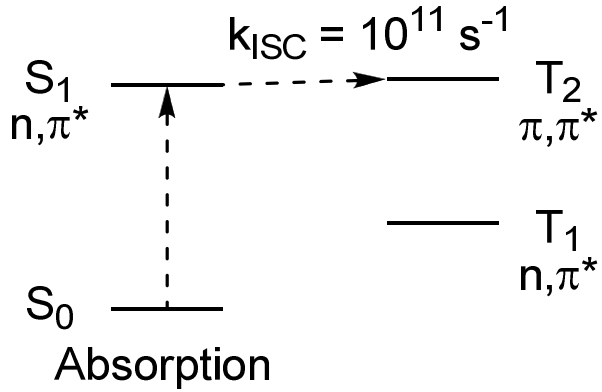
ISC and Substituent Effect on Spin State

R = Alkyl



R = Aryl

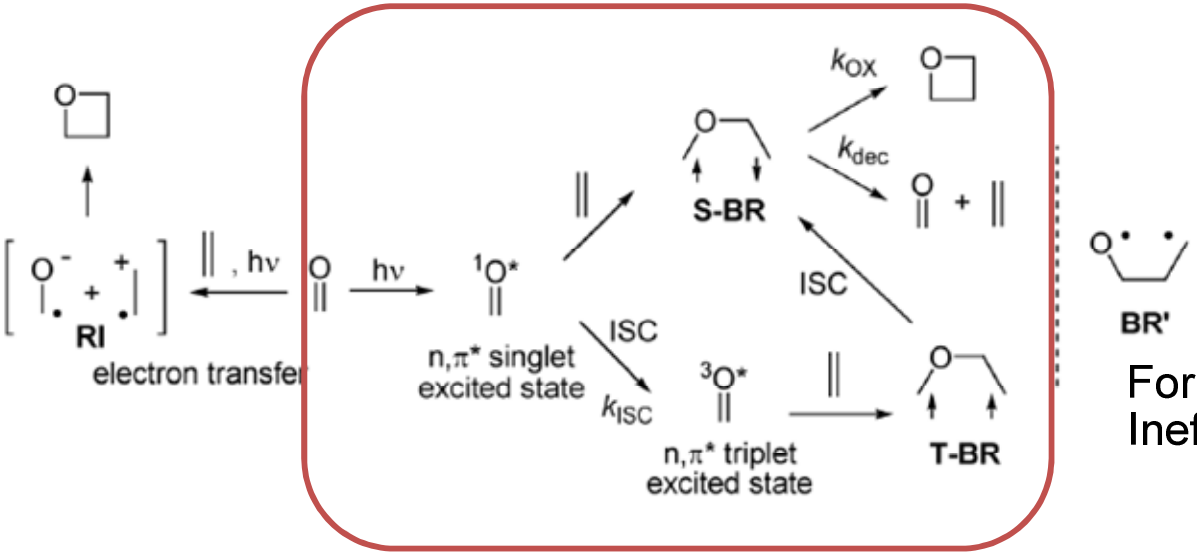




Consequence of Hund's rule: $E(T_1) < E(S_1)$
Consequence of Sayed's rule: $S_1 \rightarrow T_1$ is "forbidden", but $S_1 \rightarrow T_2$ is "allowed"

Anslyn, Dougherty *Modern Physical Organic Chemistry*

General Mechanism of PB

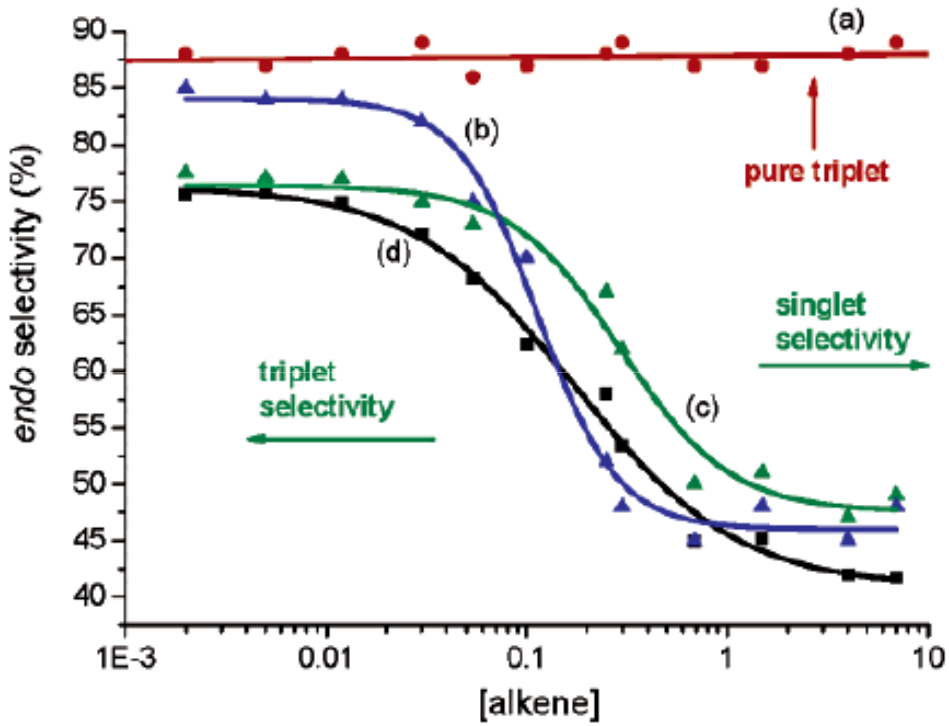


For e-poor alkene
Inefficient process

Biradicals were observed spectroscopically and trapped by biradical quenchers.

Abe, M. *JCCS* **2008**, *55*, 479.

Effect of Concentration on Endo Selectivity



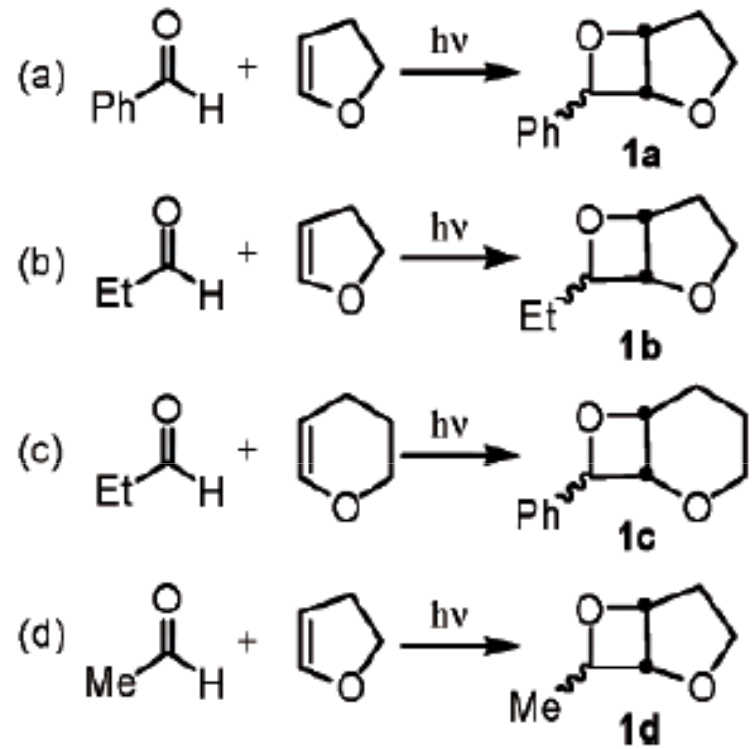
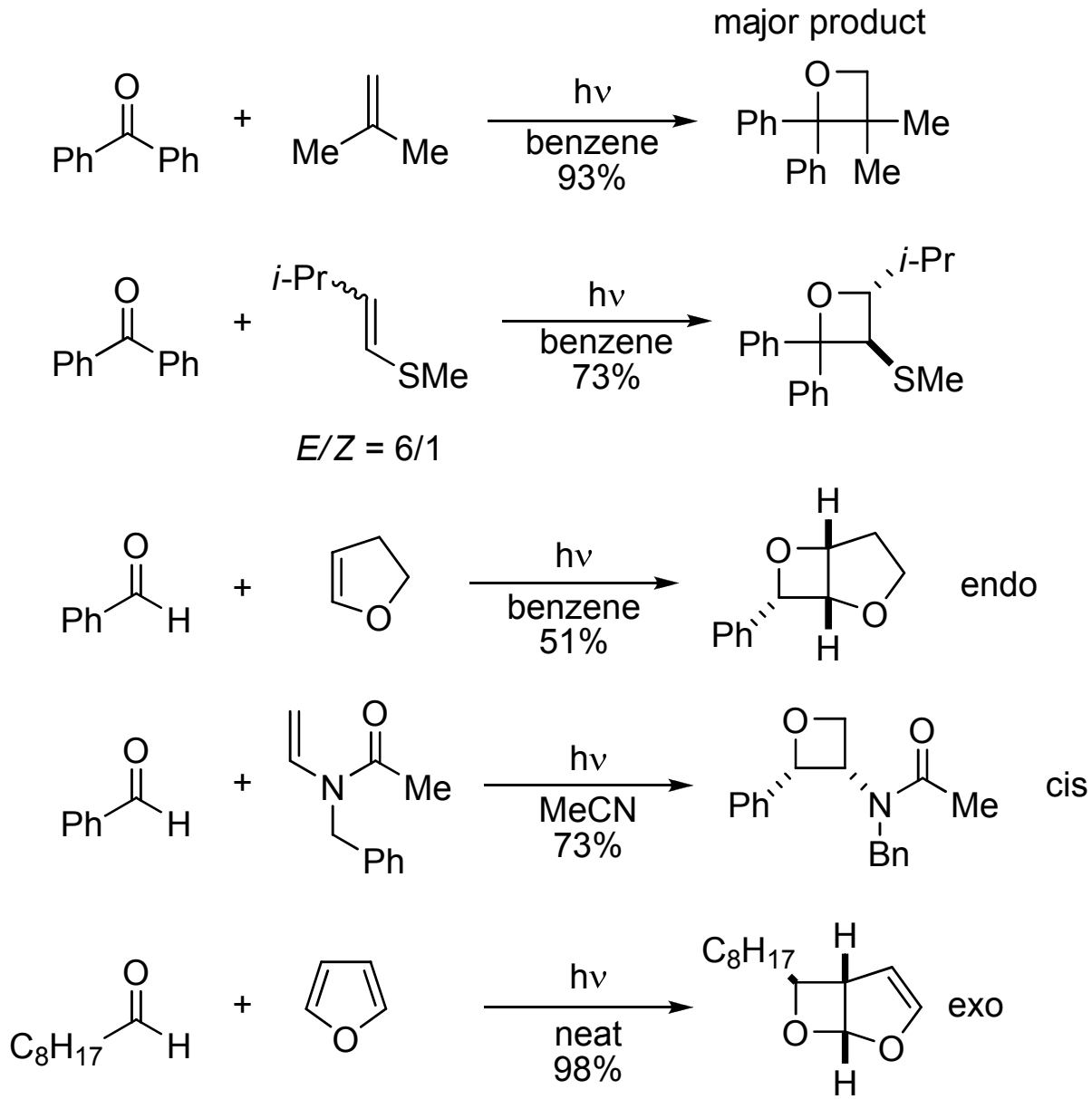


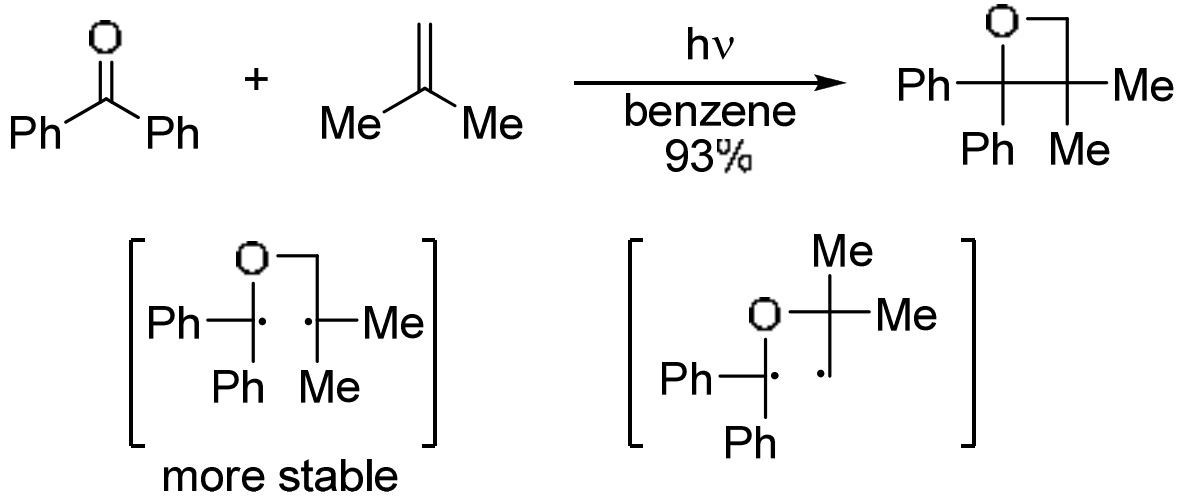
FIGURE 1. Concentration—endo selectivity profiles: (a) red circles, benzaldehyde/dihydrofuran; (b) blue triangles, propionaldehyde/dihydrofuran; (c) green triangles, propionaldehyde/dihydropyran; (d) blue squares, acetaldehyde/dihydrofuran.

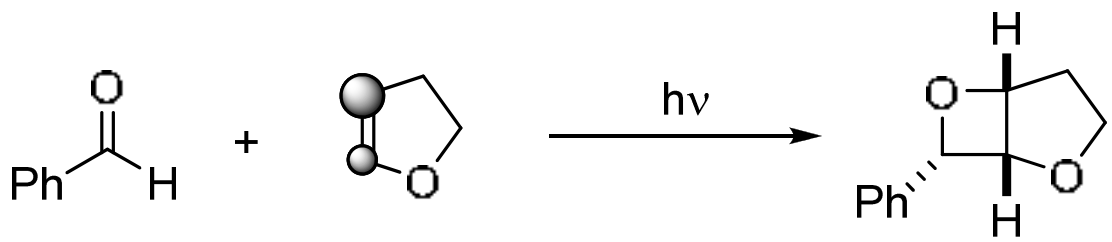
Griesbeck , A; Abe, M. et. al. *Acc. Chem. Rev.* **2004**, *37,* 919.

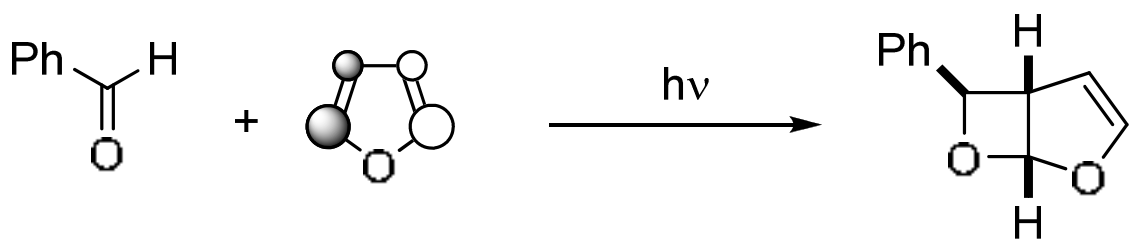
Selectivity Considerations



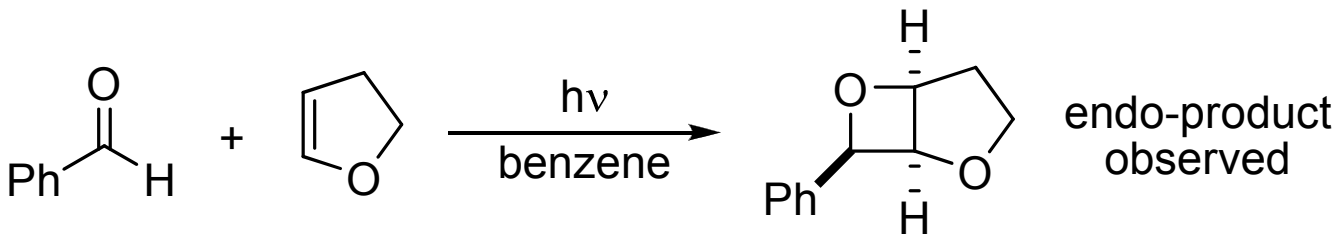
Regioselectivity





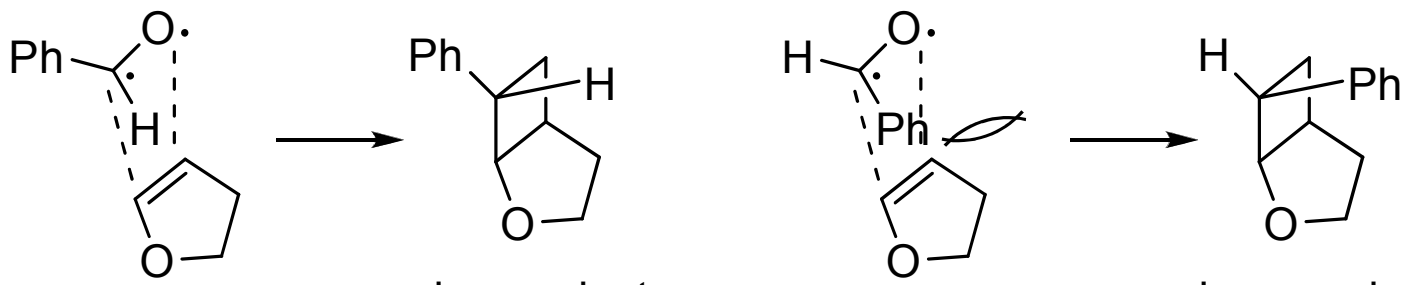


Intrinsic Diastereoselectivity



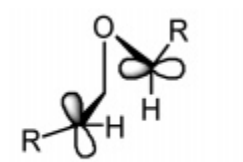
endo-product observed

If the prediction is based on the singlet state:

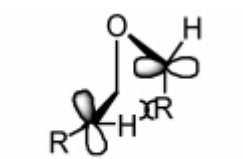


major product is exo

minor product (thermodynamically less favored)

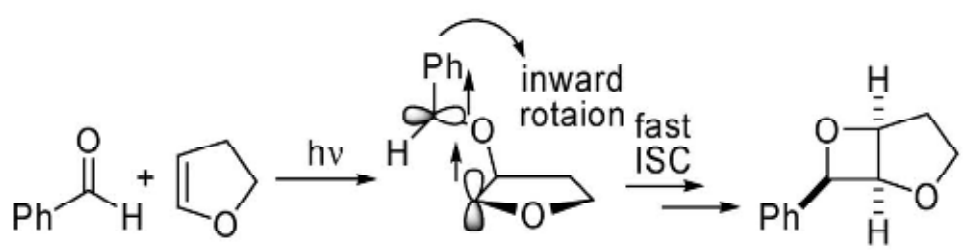


pre endo 1,4-^{3}BR

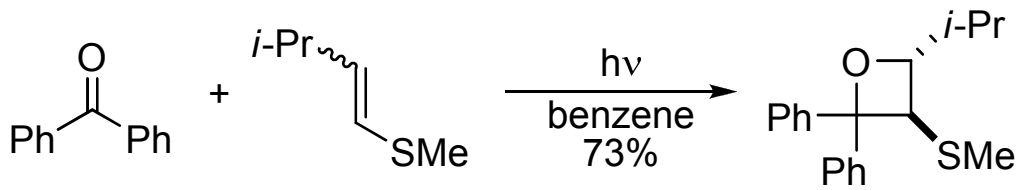


pre exo 1,4-^{3}BR

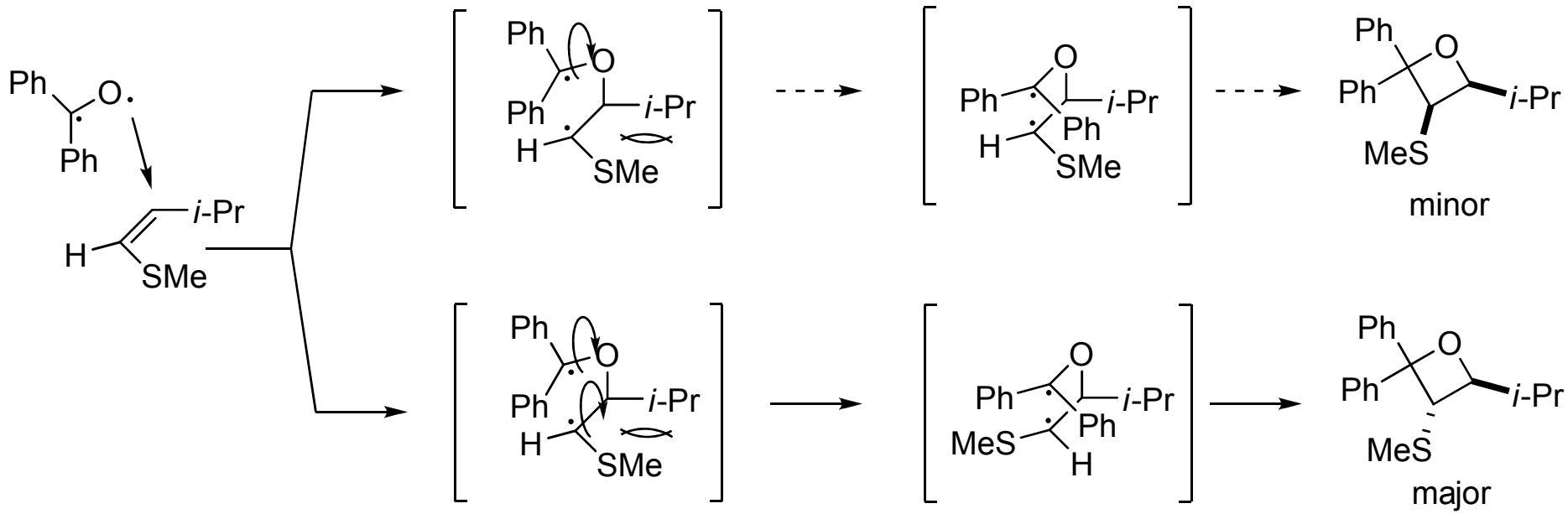
Rational: Preferred ISC Geometry



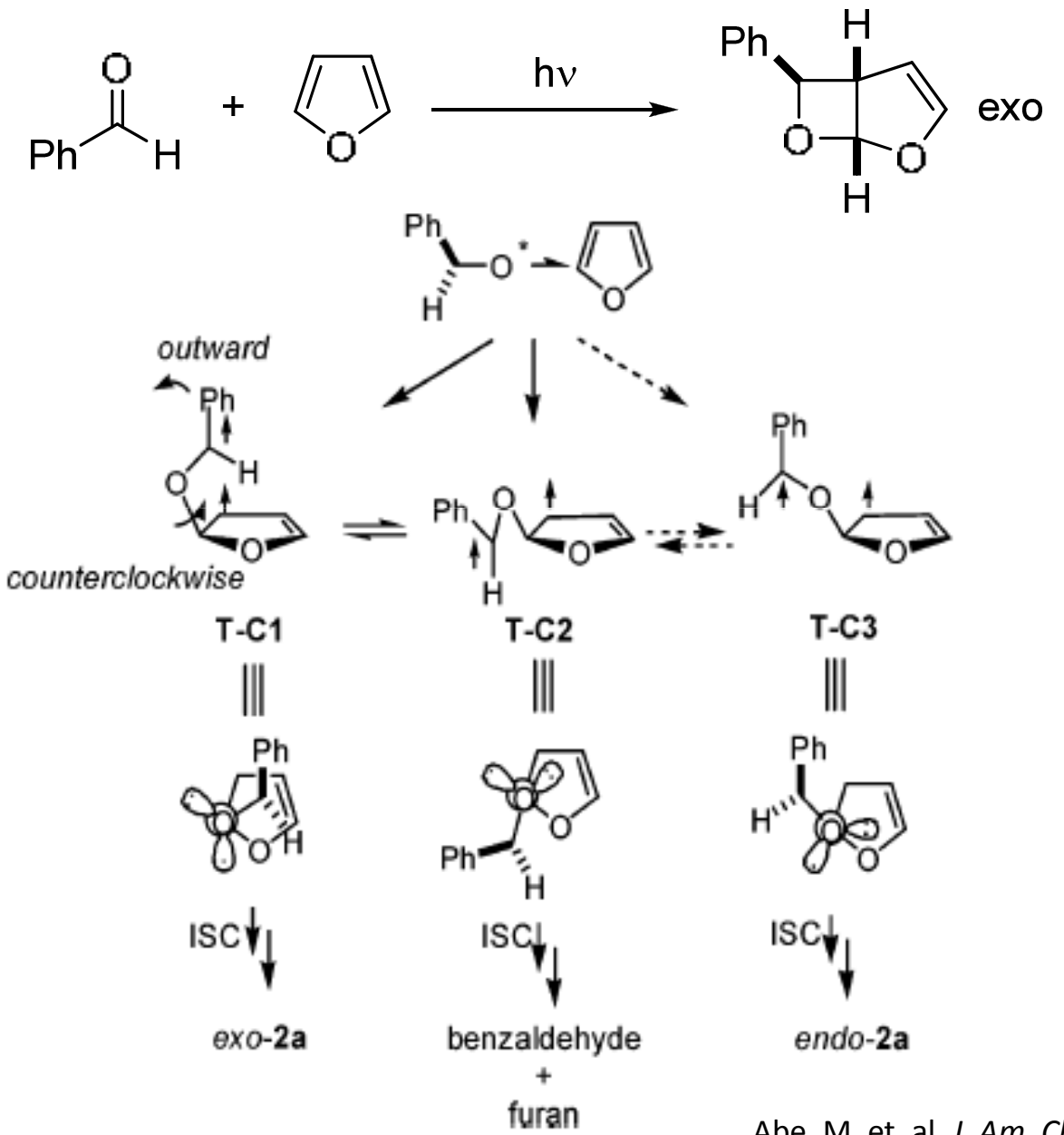
Intrinsic Diastereoselectivity



E/*Z* = 6/1

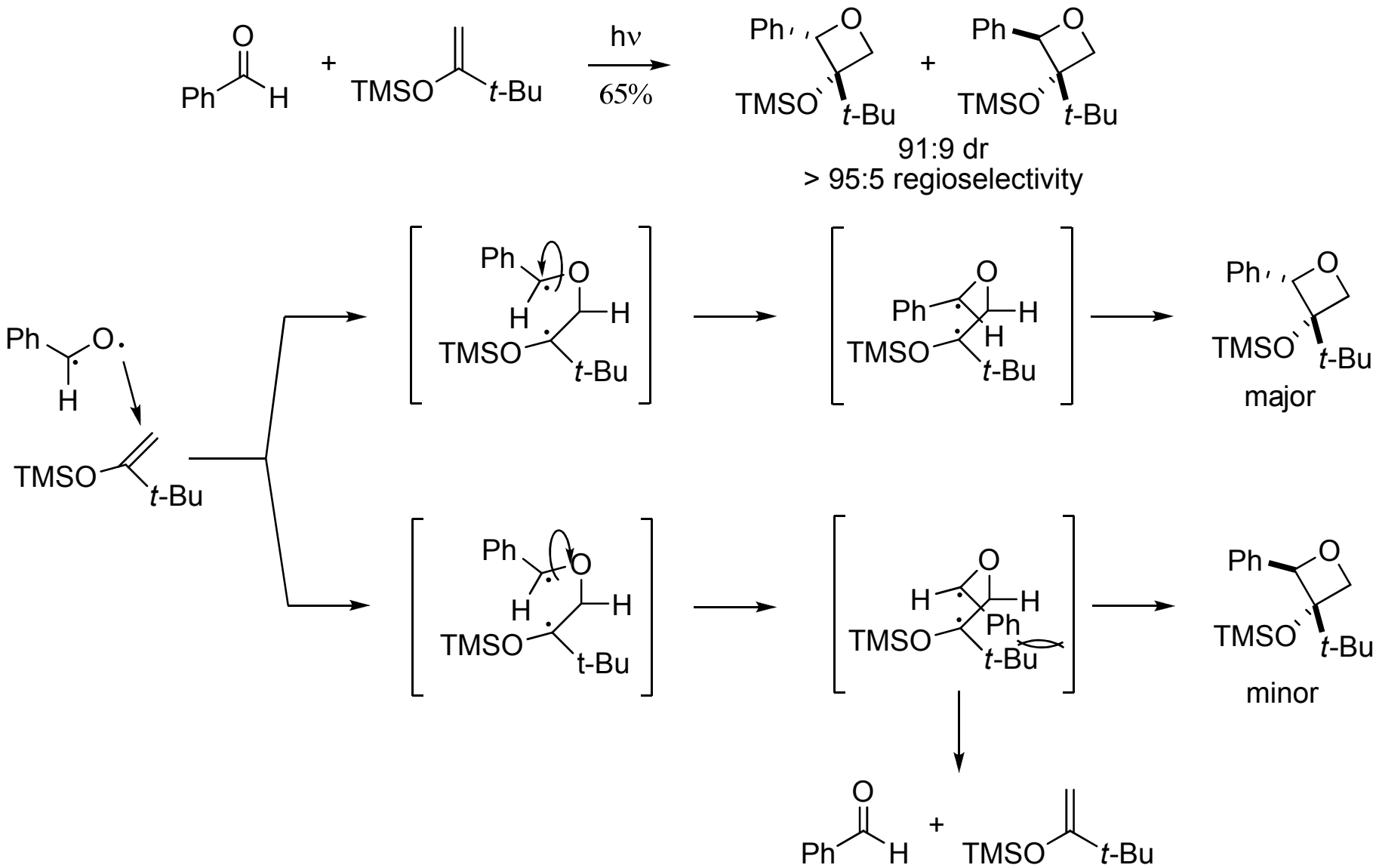


Intrinsic Diastereoselectivity



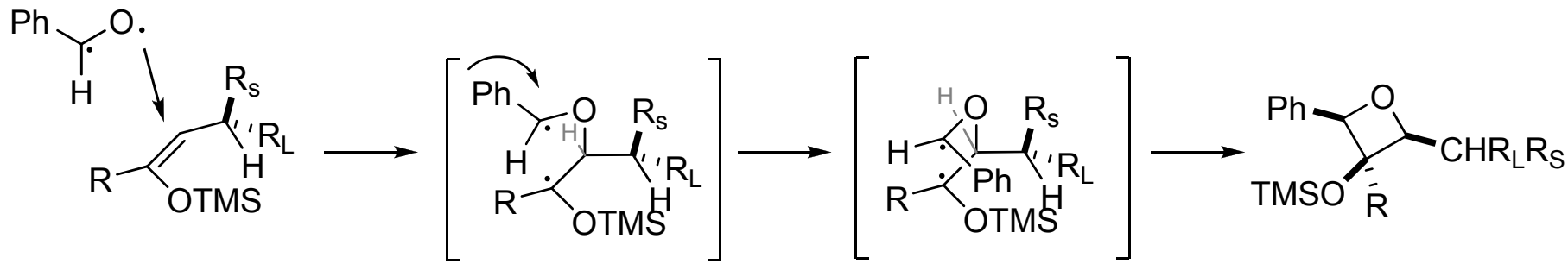
Abe, M. et. al. *J. Am. Chem Soc.* **2004**, *126,* 2838

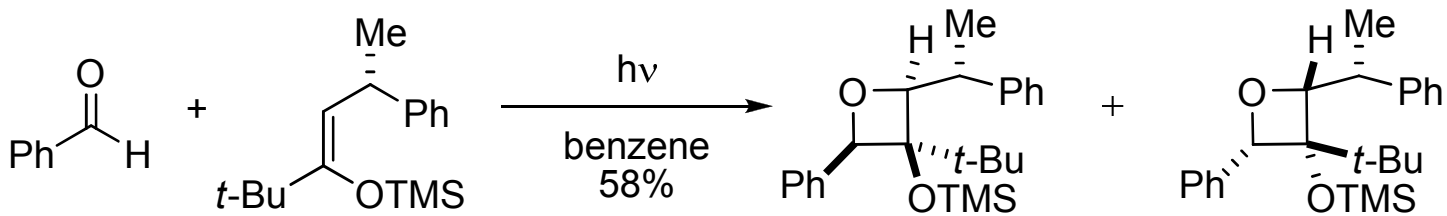
Retrocleavage Pathway



Bach, T. et. al. *Chem. Ber.* **1993**, *126,* 2457.

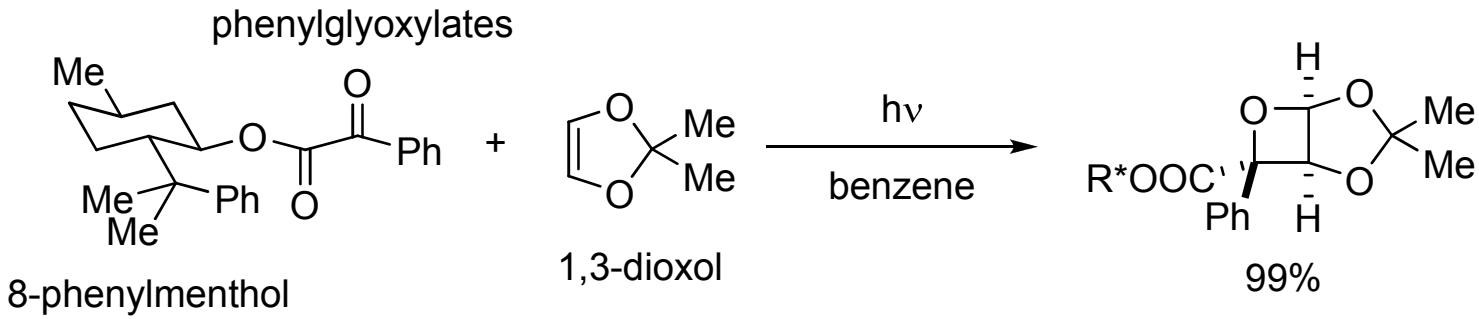
Controlling Facial Diastereoselectivity





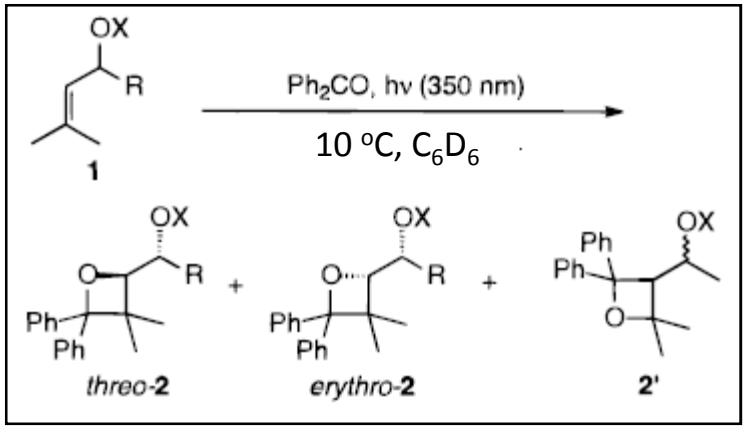
95:5 dr
75:25 regioselectivity

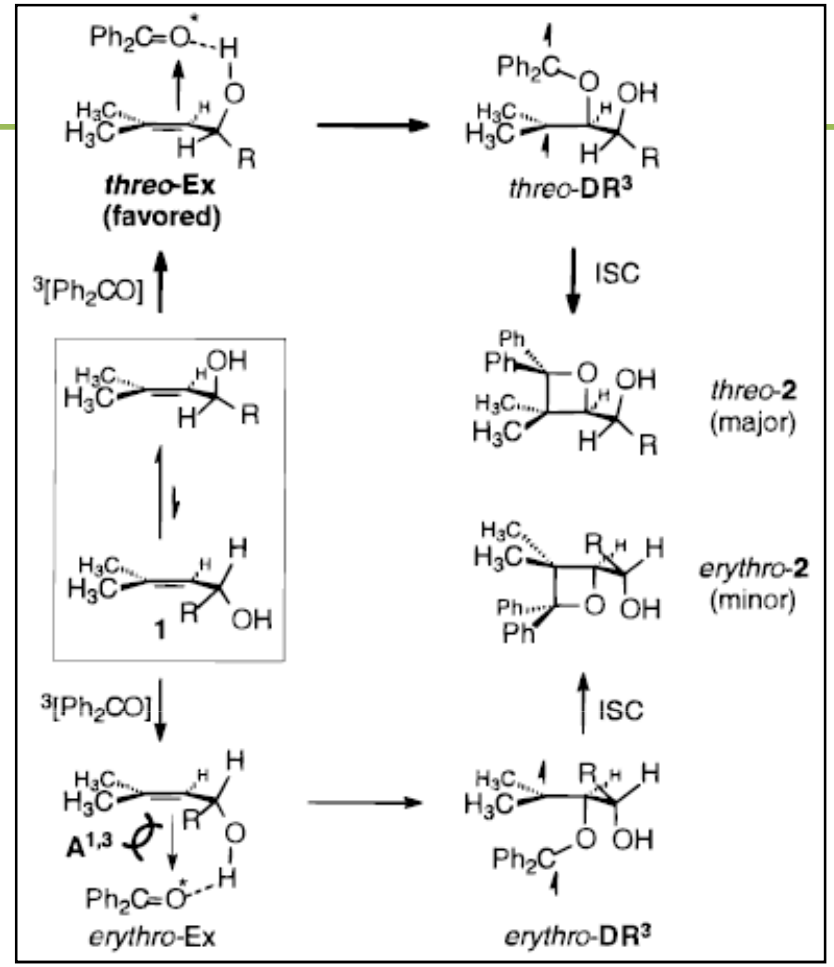
Bach, T. et. al. *J. Am. Chem. Soc.* **1997**, *119,* 2437.



Scharf, H.-D. et. al. *Angew. Chem. Int. Ed.* **1985**, *24,* 877.

Hydroxy-Directed





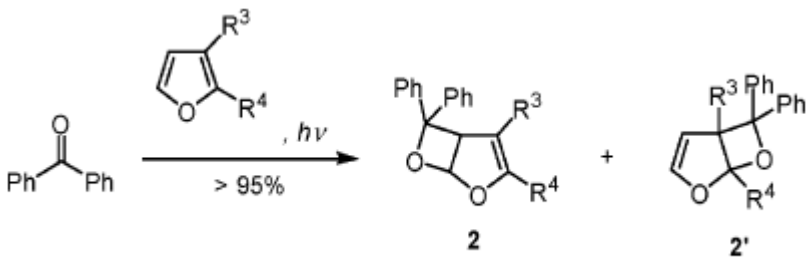
entry	substrate	X	R	solvent	time [h]	convn[a] [%]	m.b.[a,b][%]	selectivities[a] diastereo (threo:erythro)	selectivities[a] regio (2:2′)
1	**1a**	H	Me	C_6D_6	28	90	82	90:10	>95:05[c]
2	**1b**	H	Et	C_6D_6	20	90	95	93:07	>95:05[c]
3	**1c**	H	^{i}Pr	C_6D_6	20	89	91	95:05	>95:05[c]
4	**1d**	H	^{t}Bu	C_6D_6	20	92	88	>95:05	>95:05[c]
5	**1a**	H	Me	C_6D_6/D_3COD (1:1)	32	85	81	69:31	95:05[c]
6	**1e**	$SiMe_2{}^tBu$	Me	C_6D_6	32	84	85	52:48	83:17[c]

[a] Determined by ^{1}H NMR spectroscopy directly on the crude product mixture. Error limits ±5% of the given values. Internal standards: aromatic signals (entries 1, 5, 6), dimethyl isophthalate (entries 2−4). [b] Mass balance based on the allylic substrate **1**. [c] The diastereomeric ratio of the minor ~~regioisomer~~ **2′** is 78:22; the relative configurations have not been determined.

constitutional isomer

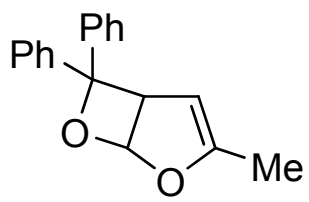
Adam, W. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 2958.

Site Selectivity

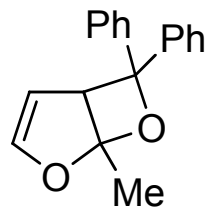


a: R^3 = H, R^4 = Me, **b**: R^3 = Me, R^4 = H

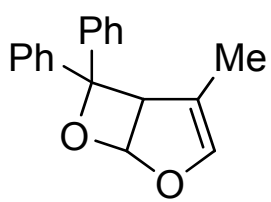
major product



2a



2a'



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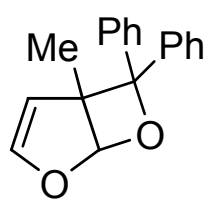
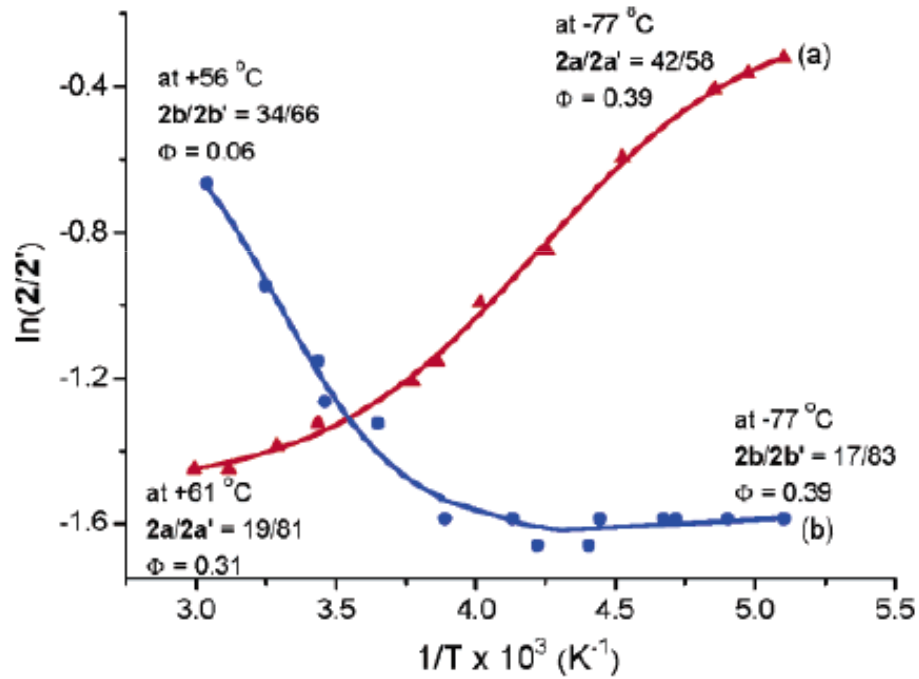


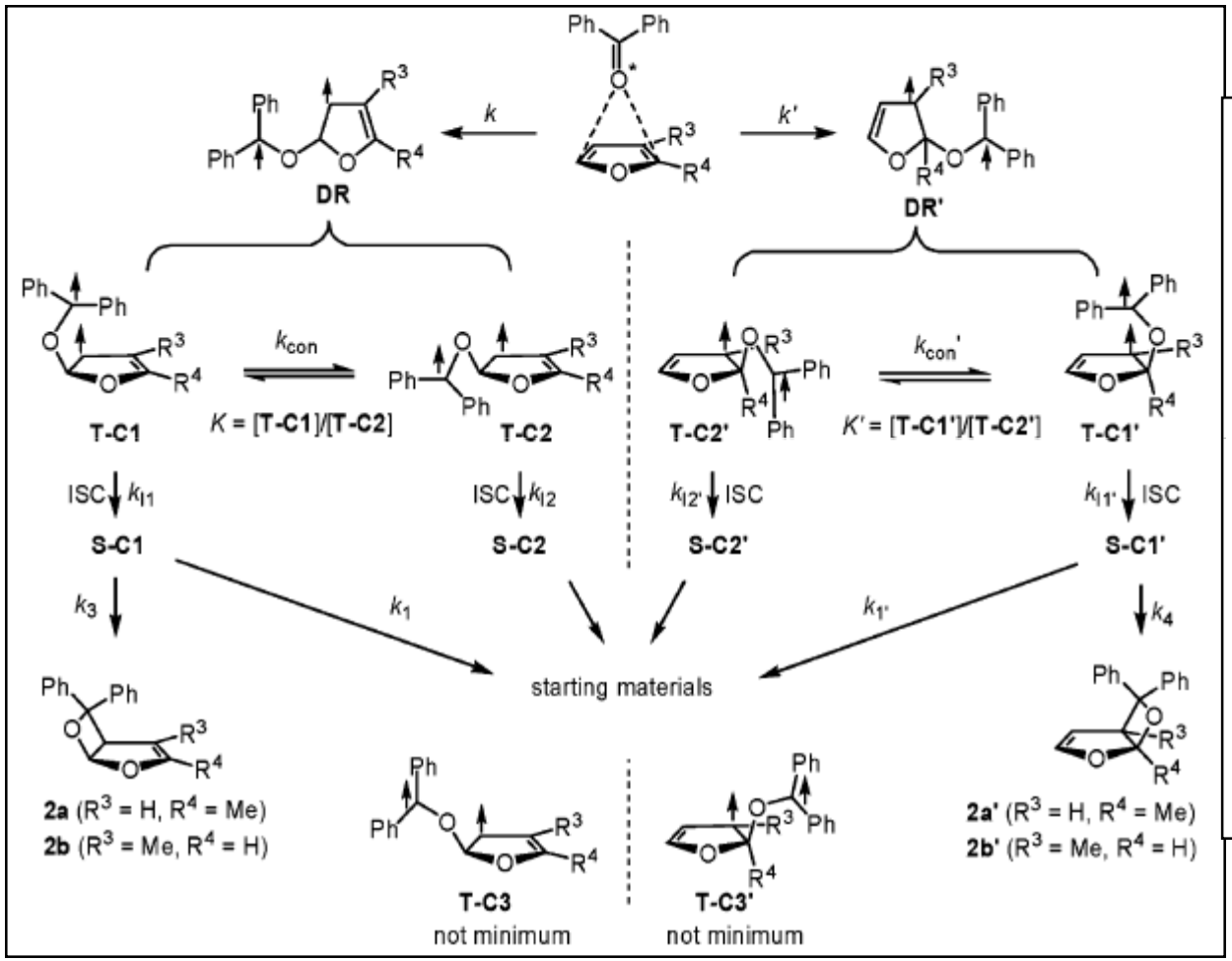
2b'

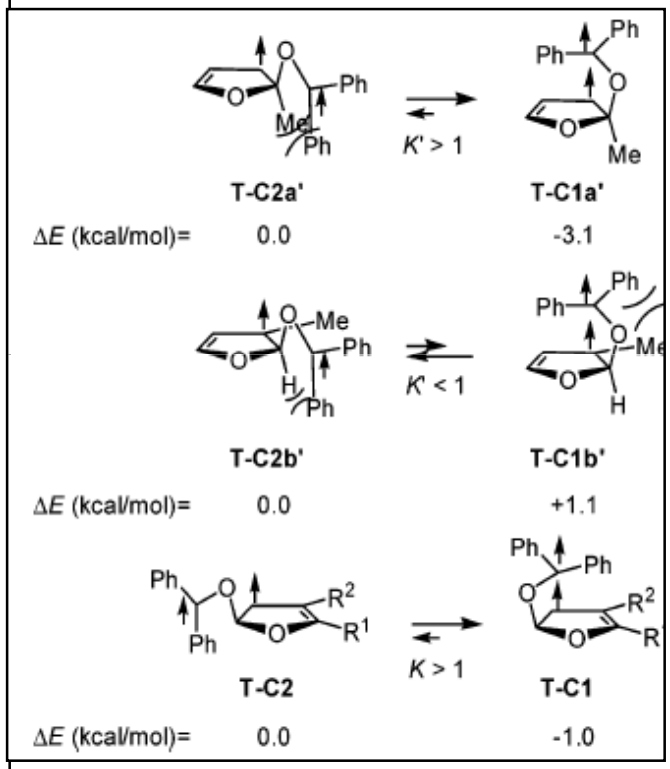
Temperature Effects on Triplet [2+2]



Griesbeck, A; Abe, M. et. al. *Acc. Chem. Rev.* **2004**, *37,* 919.
Abe, M. et. al. *J. Am. Chem. Soc.* **2004**, *126,* 2838

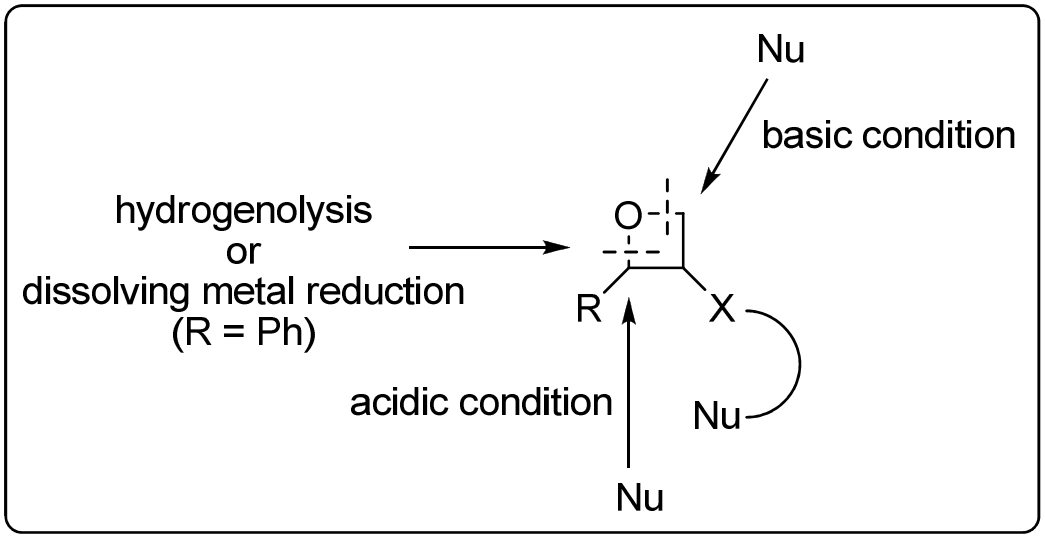
Temperature Effects on Triplet [2+2]



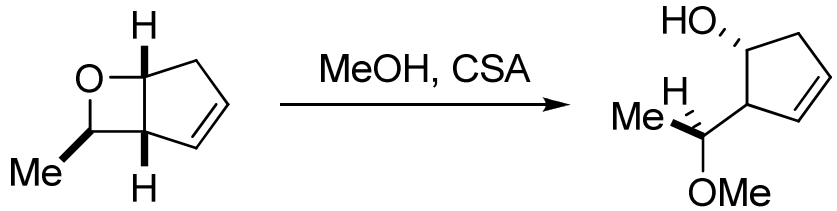


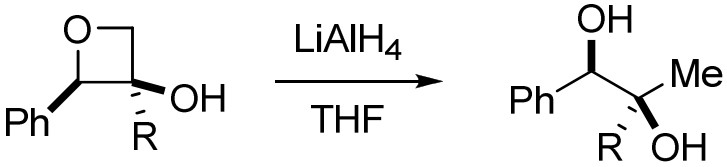
Griesbeck ,A; Abe, M. et. al. *Acc. Chem. Rev.* **2004**, *37,* 919.
Abe, M. et. al. *J. Am. Chem Soc.* **2004**, *126,* 2838

Some Transformations

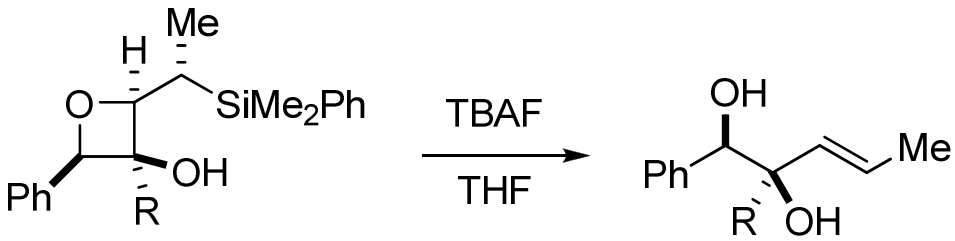


Examples:





1,2-syn diol

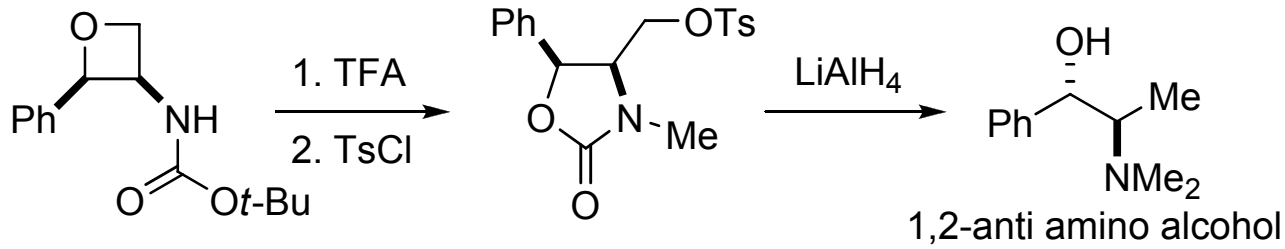


1,2-syn diol

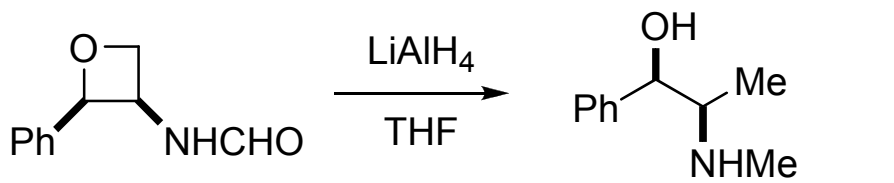
Bach, T. *Liebigs Ann./Recueil* **1997**, 1627.
Bach, T. *Synthesis* **1998**, 683.

Some Transformations

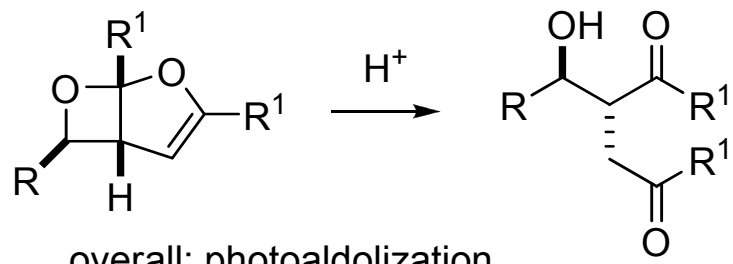
Examples:



1,2-anti amino alcohol

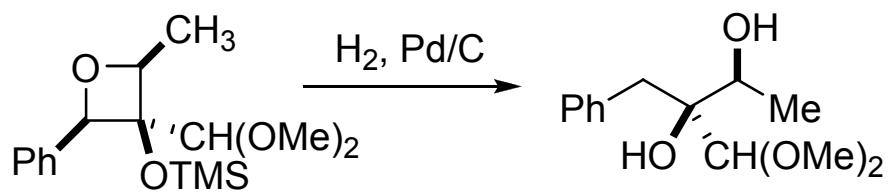


1,2-syn amino alcohol



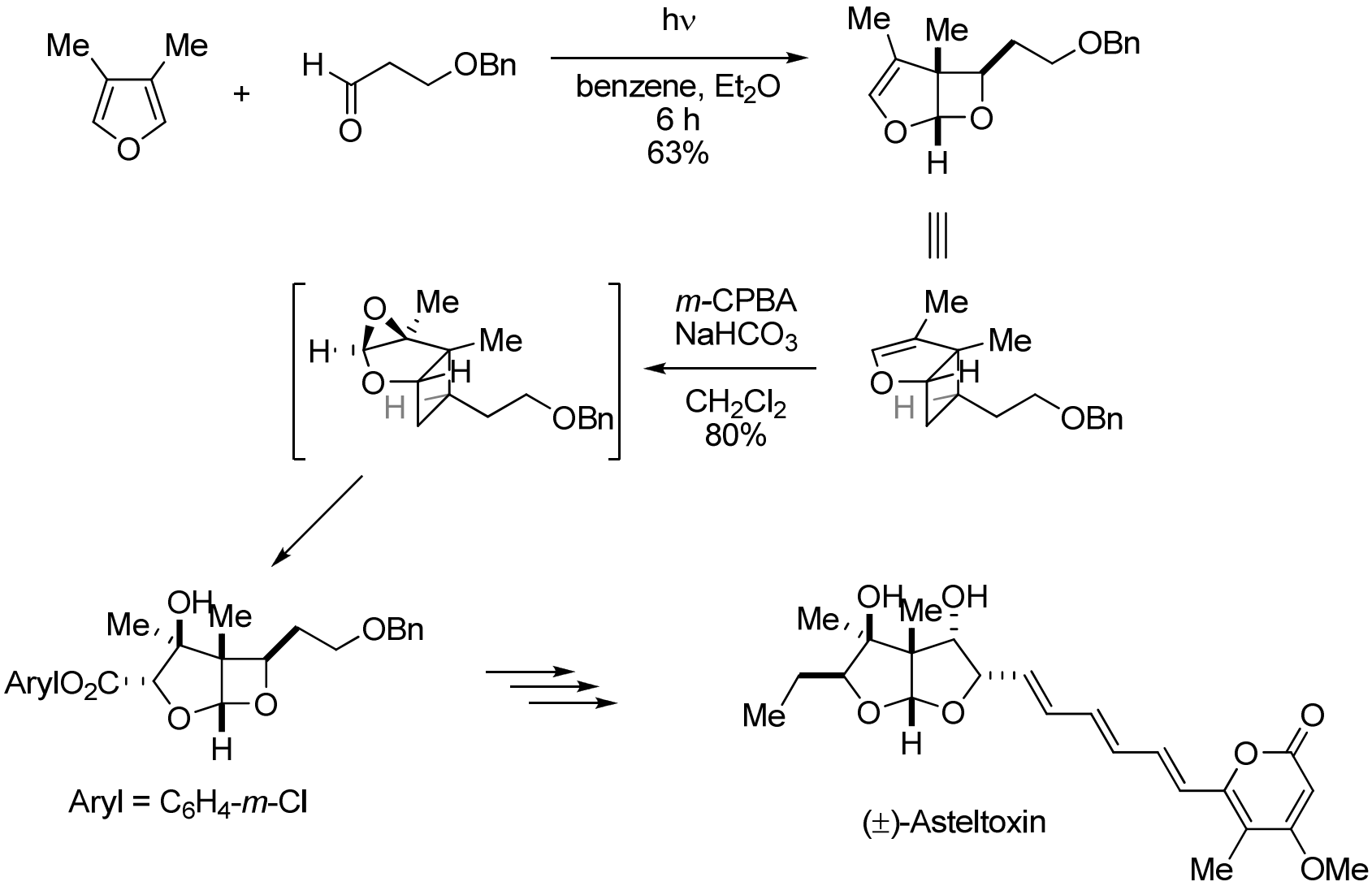
overall: photoaldolization

anti-aldol



overall: carbohydroxylation

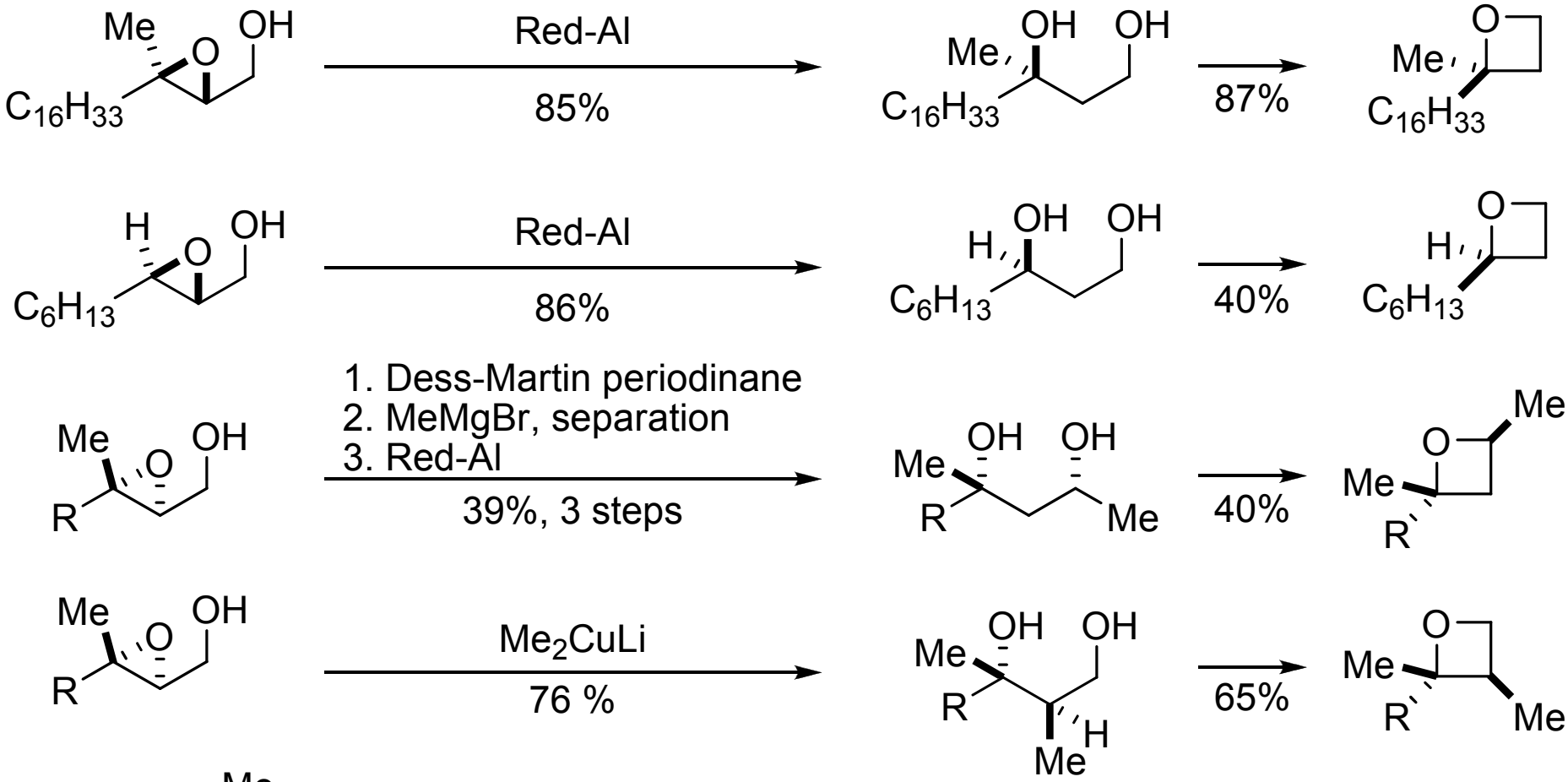
PB Reaction in the Synthesis of Asteltoxin



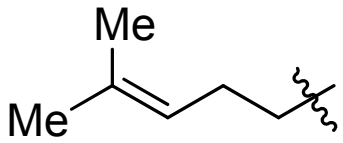
Schreiber, S. *Science* **1985**, *227,* 857.
Schreiber, S. et. al. *J. Am. Chem. Soc.* **1983**, *105,* 6723.

Ring Closing Approach from a 1,3-Diol

From SAE



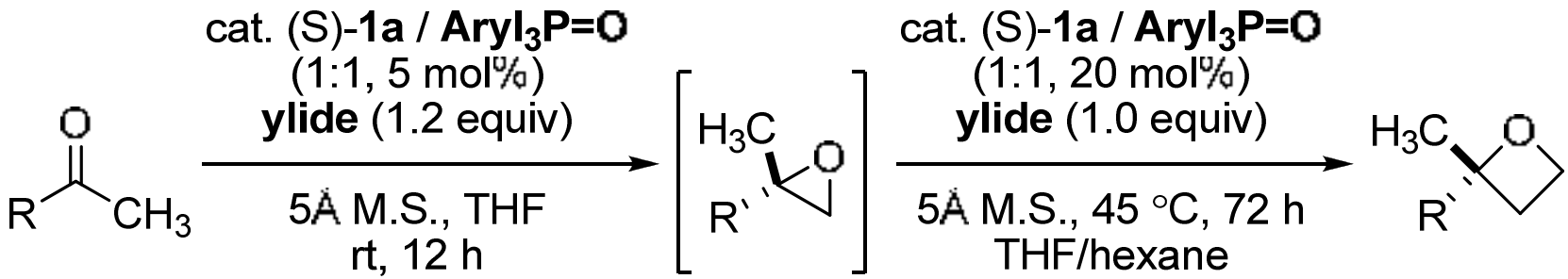
R =



Cyclization Conditions:
1. KO*t*-Bu (1 equiv), TsCl (1 equiv), THF, 0 °C
2. KO*t*-Bu (1.05 equiv)

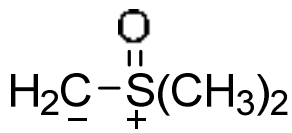
Dussault, P. et. al. *Org. Lett.* **2002**, *4,* 4591.

LLB-Catalyzed Kinetic Resolution

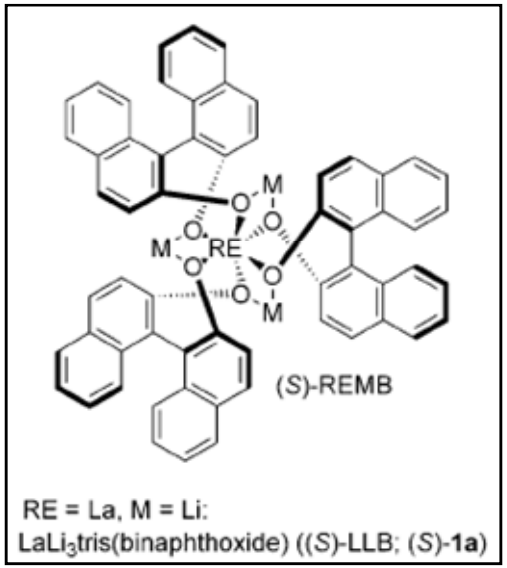


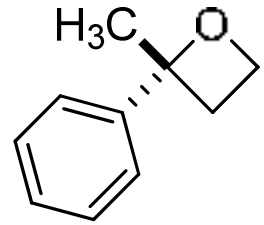
$(2,4,6\text{-}(OMe)_3\text{-}C_6H_2)_3P{=}O$

Aryl$_3$P=O

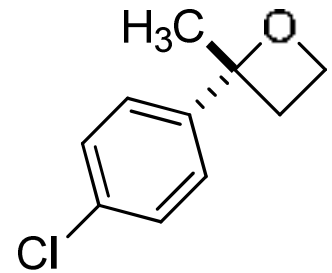


ylide





74%
[96%] 99% ee



86%
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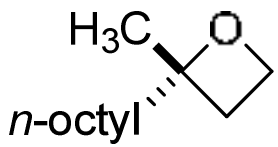
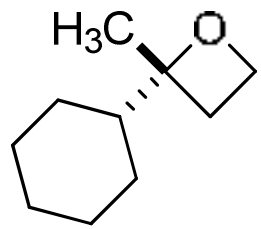


88%
[93%] 99% ee



58%
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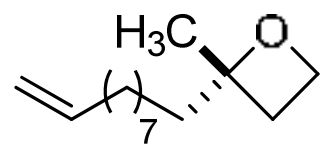

62%
[97%] > 99.5% ee

Shibasaki, M. *et. al. Angew. Chem. Int. Ed.* **2009** *48* 1677.

Conclusion

PB reaction can build up to 3 contiguous stereogenic centers at once, however
- Many selectivity issues.
- Limited approaches for the facial diastereoselective control.

To rationally design stereoselective PB reaction, one must have the proper understandings of the followings:
- Photochemistry
- Radical chemistry
- Factors controlling regio-, site- and stereoselectivity
  - Orbital interactions
  - Conformation analysis
  - Stereoelectronic effects
- Concentration, temperature and viscosity can affect the mechanisms for PB (i.e. Singlet, Triplet, PET) and degree of selectivity.
- Spin state depends on the substituents on the carbonyl component.

Factors controlling various aspects of selectivity have gradually been illuminated through continuous efforts in the experimental, theoretical and computation studies.