Recent Advances in Sigmatropic Rearrangements and their Applications in Synthesis

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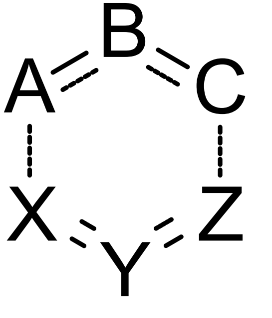
Pericyclic Reactions

Definition:
A ***pericyclic reaction*** is a type of organic reaction wherein the transition state of the molecule has a cyclic geometry, and the reaction progresses in a concerted fashion.

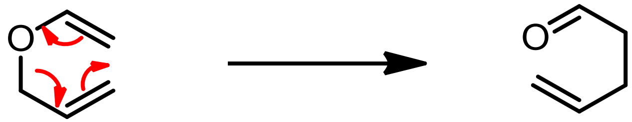
The characteristic features of pericyclic reactions are:

- No solvent effects – no change in charge during transition state
- There are no intermediates during the reaction
- They do not require nucleophiles/electrophiles
- Large negative entropy – highly ordered transition state
- Highly stereospecific – easily predicted stereochemical outcomes

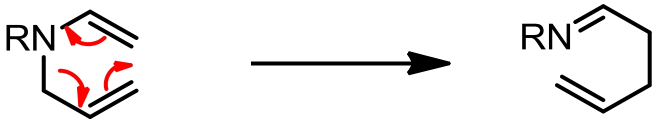


Types of Sigmatropic Rearrangements

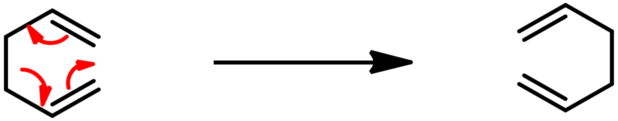
Claisen Rearrangement



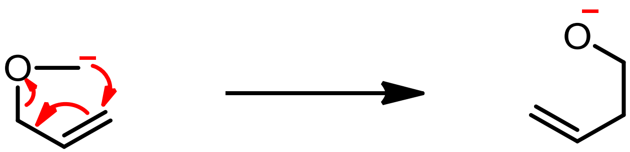
Aza-Claisen Rearrangement



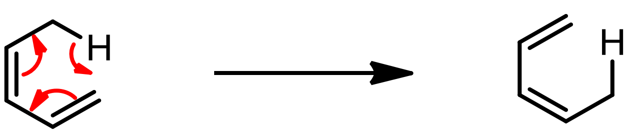
Cope Rearrangement



[2,3] Rearrangement

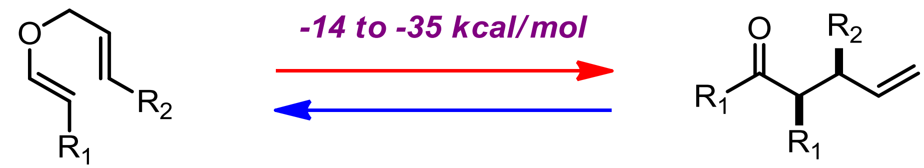


[1,n] Rearrangement



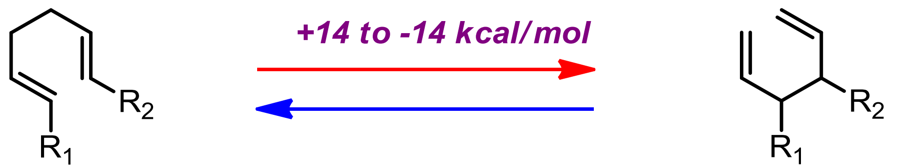
Thermodynamics of Sigmatropic Rearrangements

Claisen



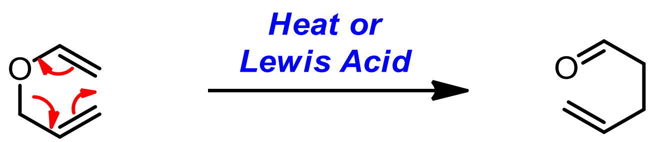
Aza-Claisen

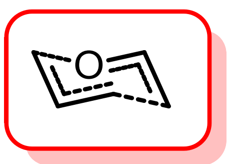
Cope

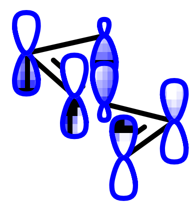


Based solely on bond energies: Claisen is favoured, aza-Claisen much less so and Cope can be energetically uphill.

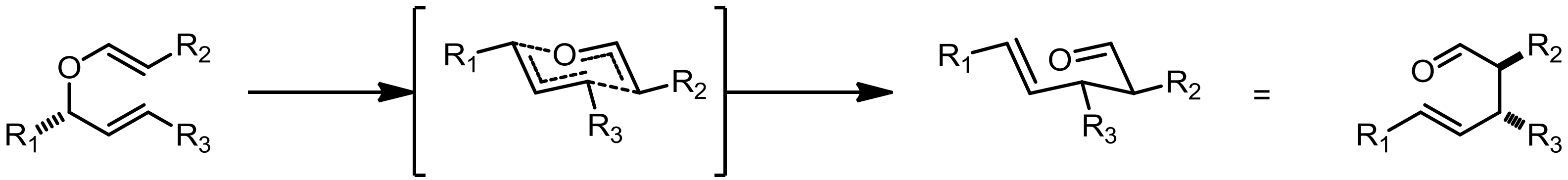
Claisen Rearrangement







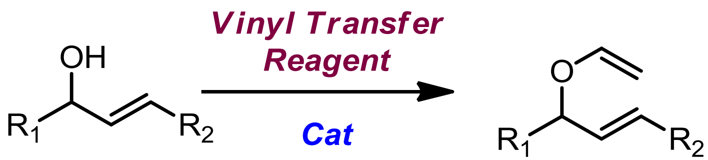
Six-membered chair-type TS
Therefore stereospecific
Aromatic: 6-electrons delocalised

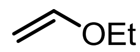
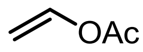
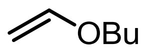
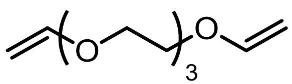


Stereochemistry is usually transferred to product
The alkene geometry determines the stereochemical outcome of reaction
Relative stereochemistry is also controlled by alkene geometry

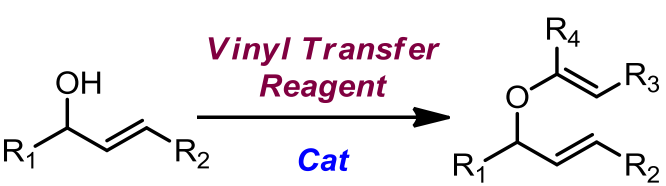
Allyl Vinyl Ethers – Direct Vinyl Etherification

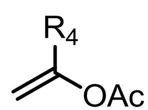
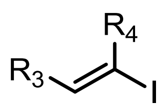
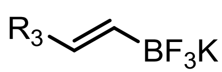
Vinyl Groups

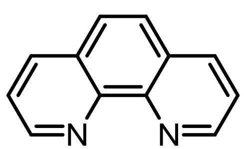


Vinyl Transfer Reagent	*Cat*	
	$Hg(OAc)_2$	**Majetich:** *Tetrahedron Lett.* **1983**, *18*, 1913
	$[Ir(COD)Cl]_2$	**Ishii:** *Org. Synth.* **2005**, *82*, 55
	$Pd(OAc)_2$Bathophen	**Schlaf:** *J. Org. Chem.* **2003**, *68*, 5225.
	$Pd(OTFA)_2$Phen	**Senenayake:** *J. Org. Chem.* **2007**, *72*, 4250.

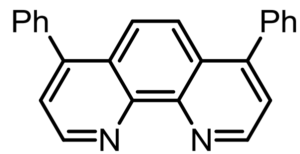
Substituted Vinyl Groups



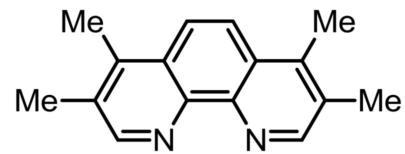
Vinyl Transfer Reagent	*Cat*	
	$[Ir(COD)Cl]_2$	**Ishii:** *Org. Synth.* **2005**, *82*, 55
	CuI/Me_4-Phen	**Buchwald:** *J. Am. Chem. Soc.* **2003**, *125*, 4978.
	$Cu(OAc)_2$, O_2	**Batey:** *Org. Lett.* **2003**, *5*, 1381.



Phen

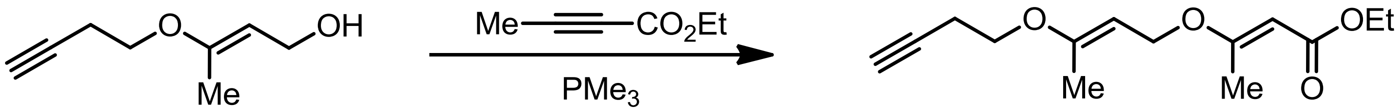


Bathophen



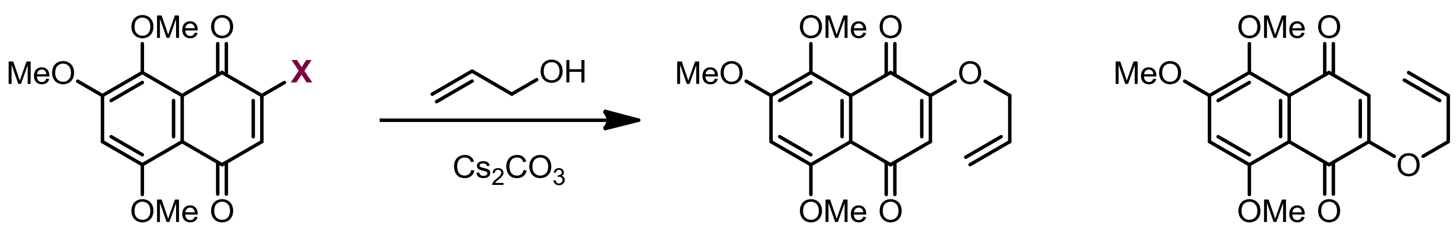
Me_4-Phen

Allyl Vinyl Ethers – Conjugate Additions



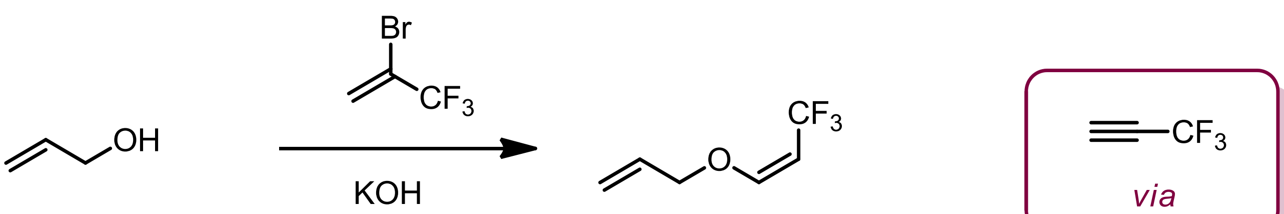
99%, 20:1 E:Z

Davies, K. A.; Wulff, J. E. *Org. Lett.* **2011**, *13,* 2497.



X = N_3	**86%**	**0%**
X = I	**0%**	**80%**

Rathwell, D. C. K.; Yang, S. –H.; Tsang, K. Y.; Brimble, M. A. *Angew. Chem. Int. Ed.* **2009**, *48,* 7996.

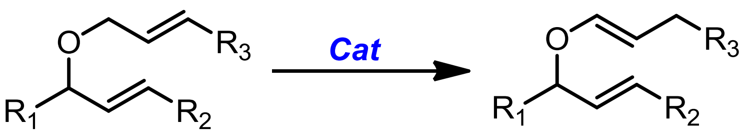


86%, >20:1 *Z:E*

Hong, F.; Hu, C. –M. *Chem. Commun.* **1996**, 57.

Allyl Vinyl Ethers – Isomersation

Transition Metal Catalysed



Cat

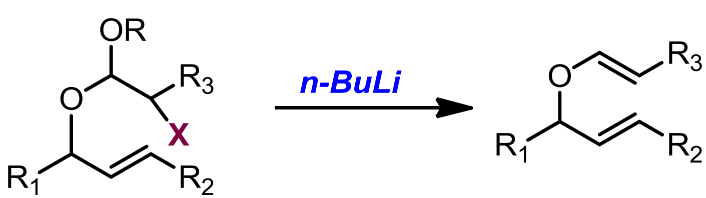
$Ru(CO)HCl(PCy_3)_2$
$[Ir(COD)Cl]_2$
$[Ir(PCy_3)_3]^+[BPh_4]^-$

Schmidt: *Synlett* **2004**, 1541.
Ishii: *Org. Lett.* **2000**, *2*, 4193.
Miyaura: *Chem. Commun.* **1998**, 1337.
Nelson: *J. Am. Chem. Soc.* **2003**, *125*, 13000.
Cook**:** *J. Org. Chem.* **2012**, *77*, 2058.

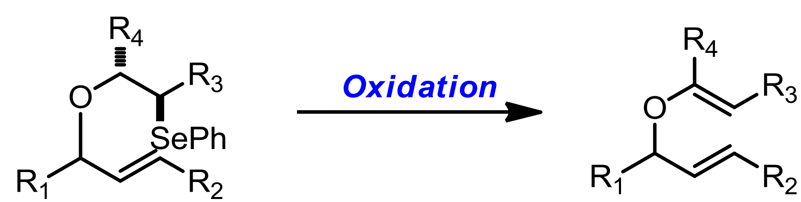
$[Ir(PCy_3)_3]^+[BPh_4]^-$ Easily synthesised *in situ.* Performs isomerisation very rapidly at room temperature.

Base mediated isomerisation generally give the *Z*-alkene geometry.

Elimination



X = $SnBu_3$ **McGarvey:** *Tetraheron Lett.* **1985**, *26*, 1419.
X = I **Utimoto:** *J. Org. Chem.* **1996**, *61*, 2262.



Sinay: *Synthesis* **1984**, 134.

For Review of vinyl ether synthesis see: Winternheimer, D.; Shade, R.; Merlic, C. *Synthesis* **2010**, 2497.

Enantioselective Sigmatropic Rearrangements

Strategies for Asymmetric Induction:

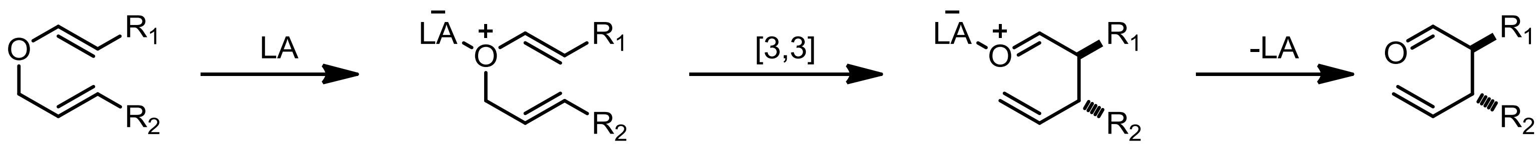
Internal Chirality Source

- **Chiral neighbouring group – diastereoselectivty**
- **Easily removed chiral auxilliary**

External Chirality Source

- **Chiral reagent or catalyst directs rearrangement**
- **Chiral catalyst forms rearrangement precursor *in situ* – covalently bound in TS followed by release.**
- **Part of a cascade reaction – forms rearrangement precursor in a high energy intermediate**

Enantioselective Claisen Rearrangement



Complexation **_Rearrangement_** **_Decomplexation_**

Enantiomeric Transition States

<u>Issues with Enantioselective Claisen</u>

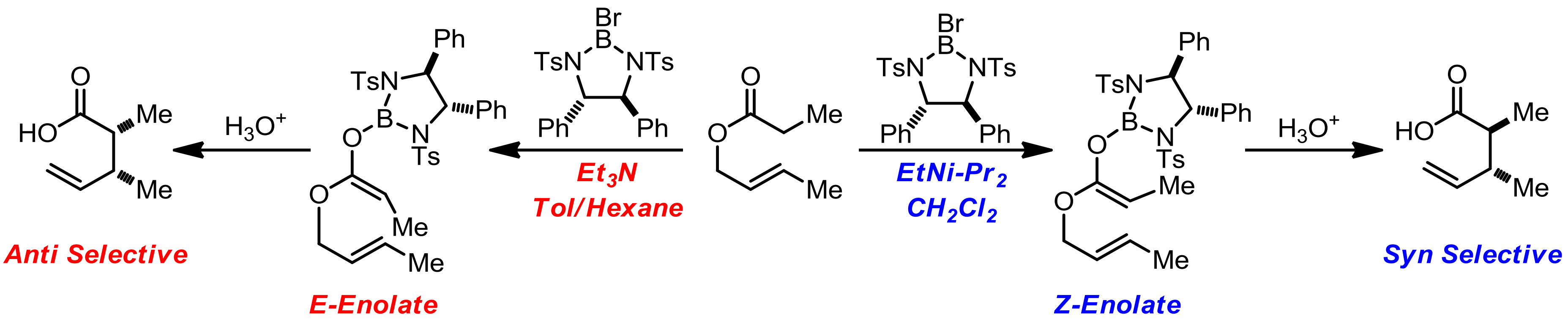
• Lewis acid discrimination between TS is difficult

• Generally carbonyl is more Lewis basic than vinyl ether

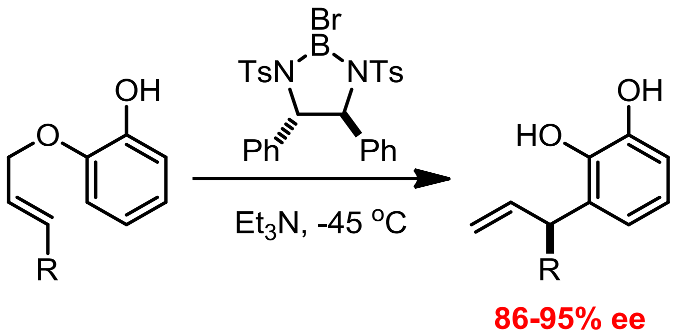
• Catalytic turnover is very slow.

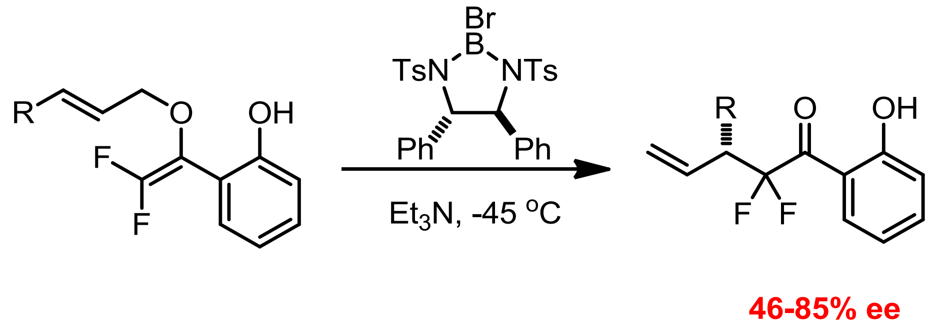
• Activated substrates usually required.

Chiral Boron Reagents



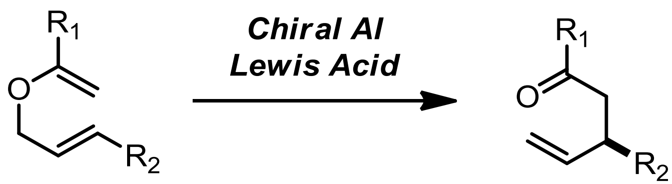
Corey, E. J.; Lee, D. H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.

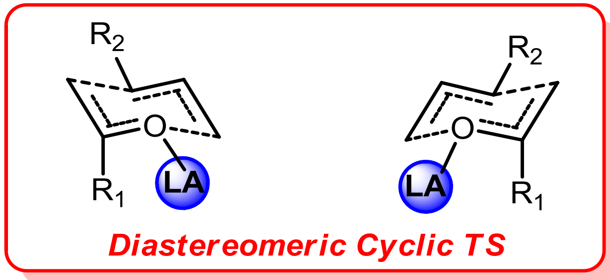


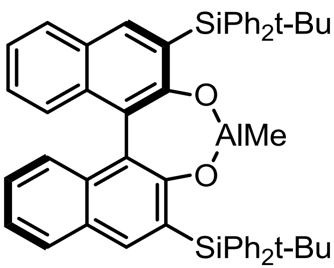


Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 4815.
Ito, H.; Sato, A.; Kobayashi, T.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1998**, 2441.

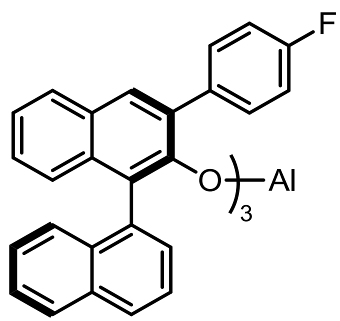
Chiral Aluminium Lewis Acids



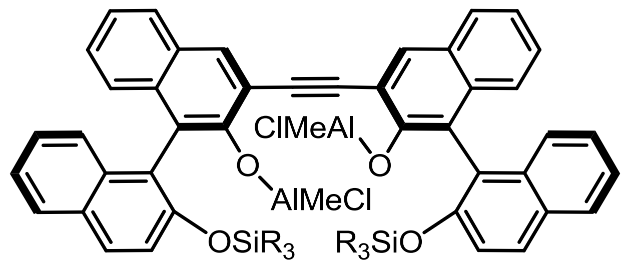




Yamamoto: **71-93% ee**
J. Am. Chem. Soc. **1990**, *112*, 7791.
Activativing group required at R_1



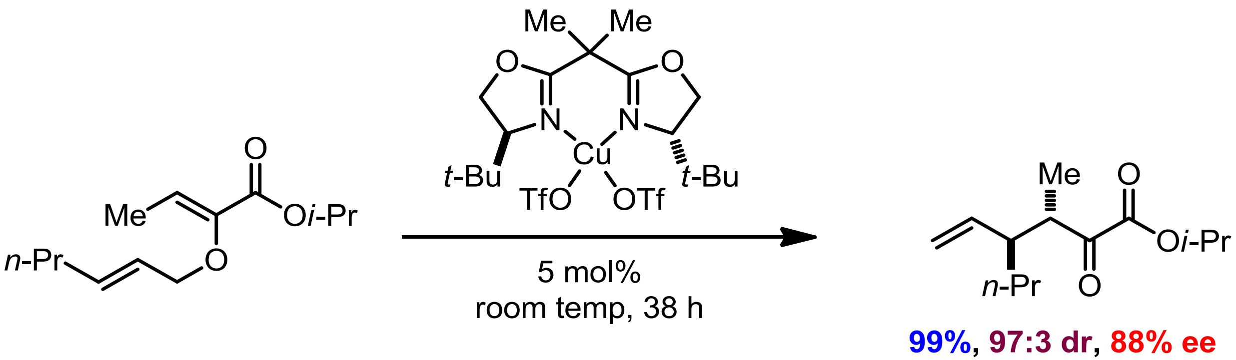
Yamamoto: **76-92% ee**
J. Am. Chem. Soc. **1995**, *117*, 1165.
No activativing group required



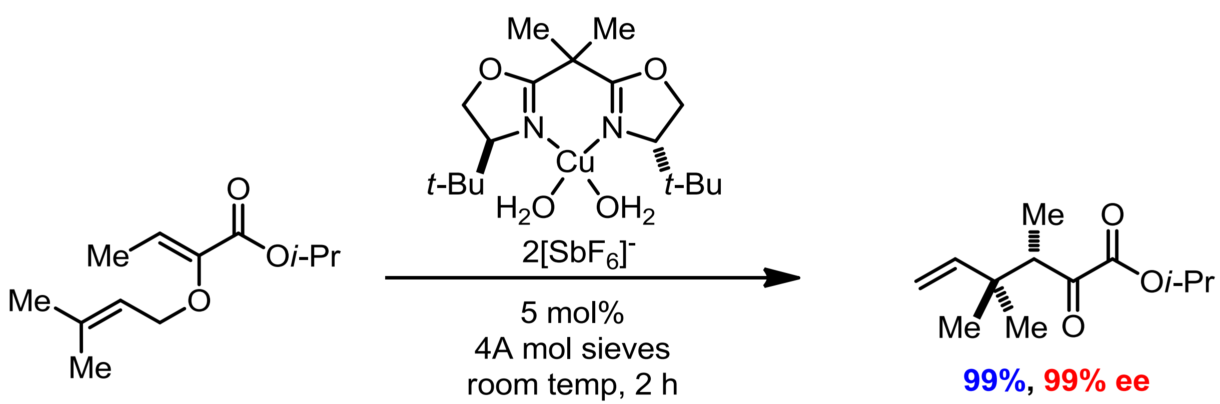
Maruoka: **57-83% ee**
Tetrahedron **2002**, *58*, 8307.
No activativing group required

- Stoichiometric amounts of Lewis acid required
- Moderate to good levels of enantiocontrol
- Chiral Scaffold is recoverable following the reaction

Enantioselective Copper Catalysed Claisen

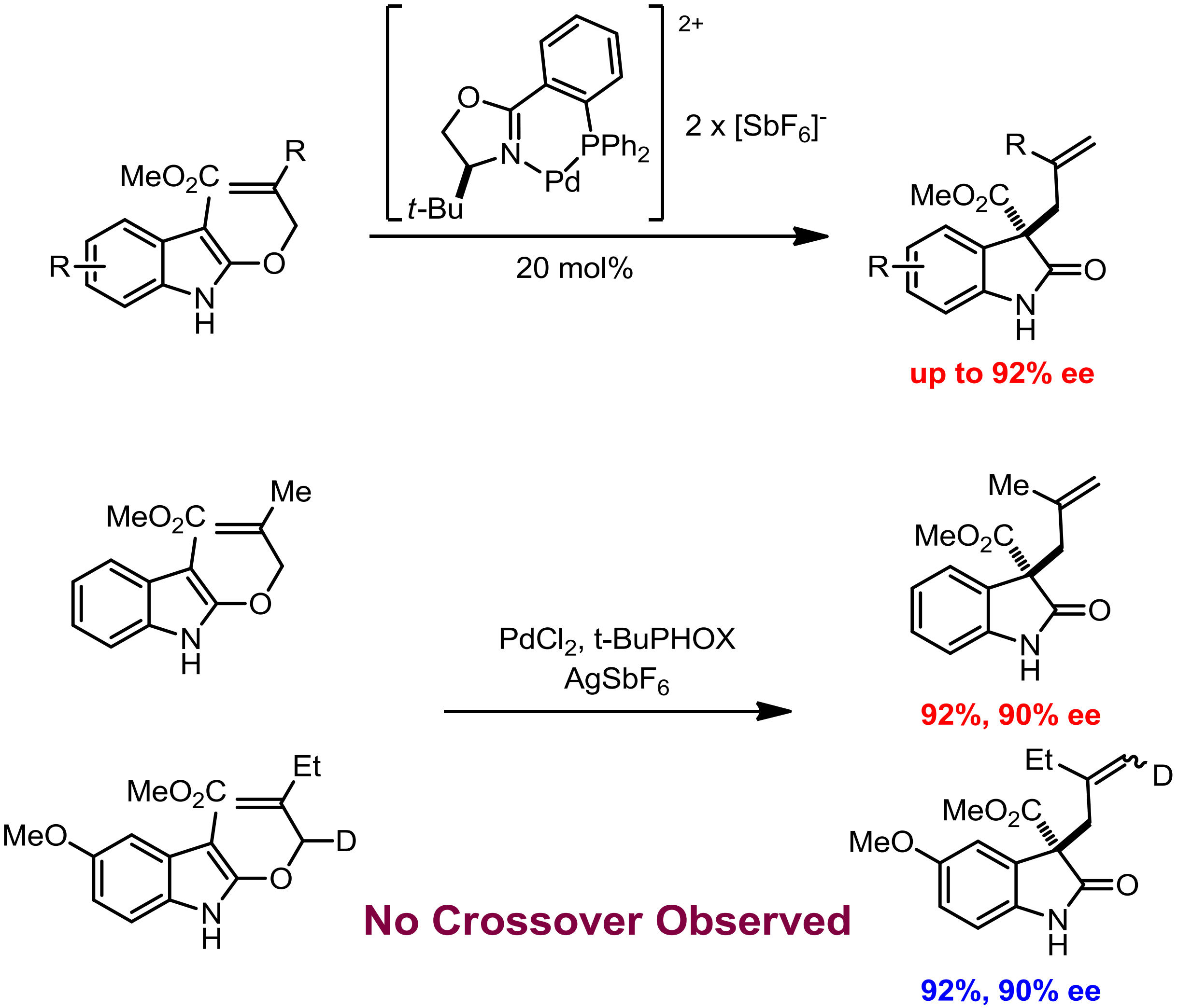


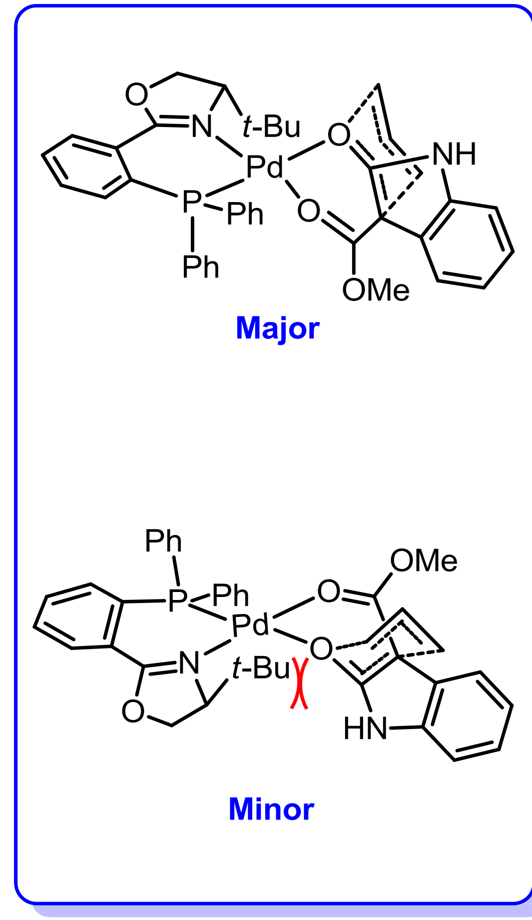
Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4700.



Abraham, L.; Körner, M.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 3647.

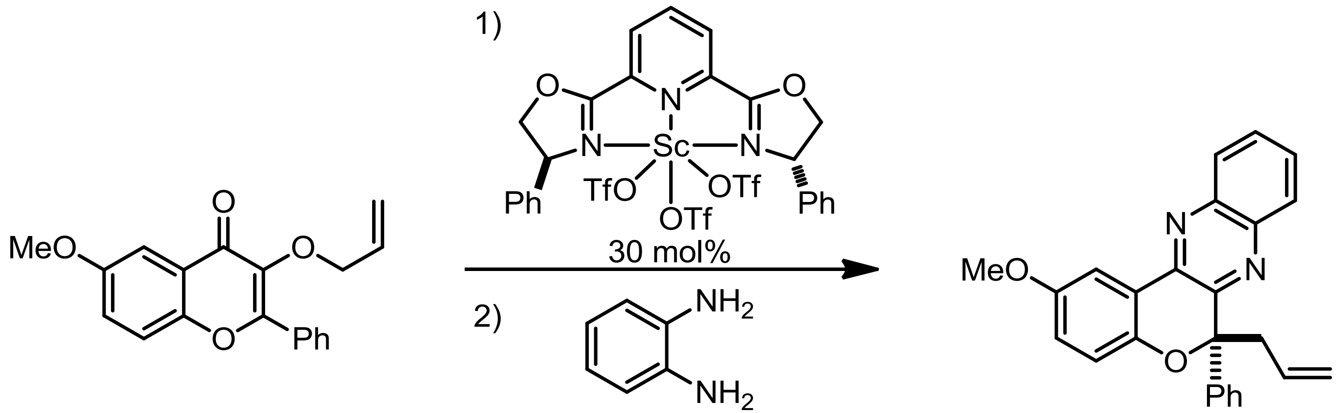
Enantioselective Palladium Catalysed Claisen





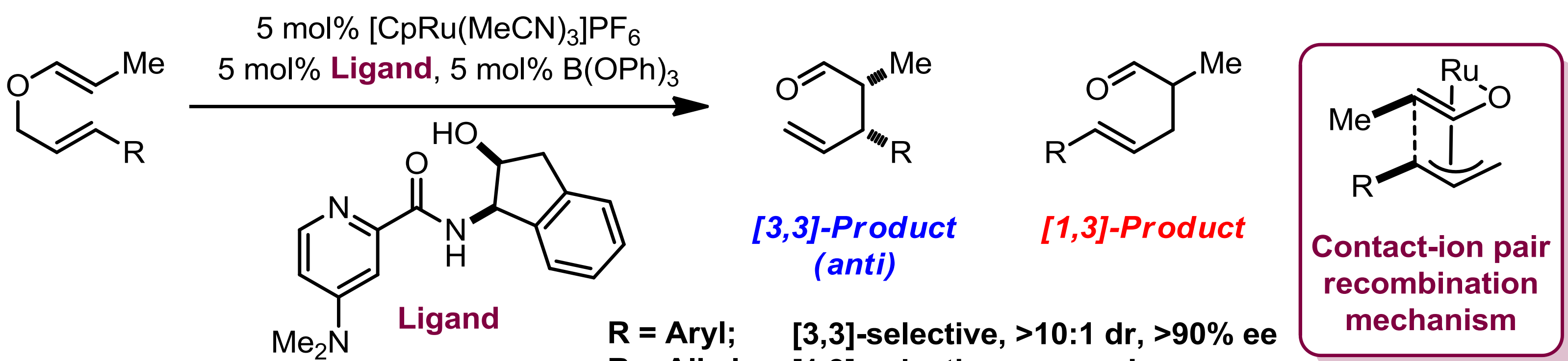
Linton, E. C.; Koslowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162.
Cao, T.; Linton, E. C.; Deitch, J.; Berrit, S.; Koslowski, M. C. *J. Org. Chem.* **2012**, *77*, 11034.

Scandium/Ruthenium Catalysts



91%, **94% ee**

Marie, J. –C.; Xiong, Y.; Min, G. K.; Yeager, A. R.; Taniguchi, T.; Berovs, N.;; Schaus, S. E.; Porco Jr., J. A.. *J. Org. Chem.* **2010**, *75*, 4584.

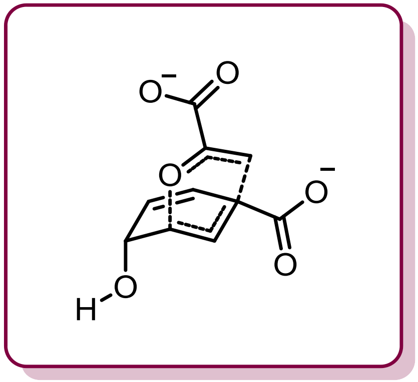


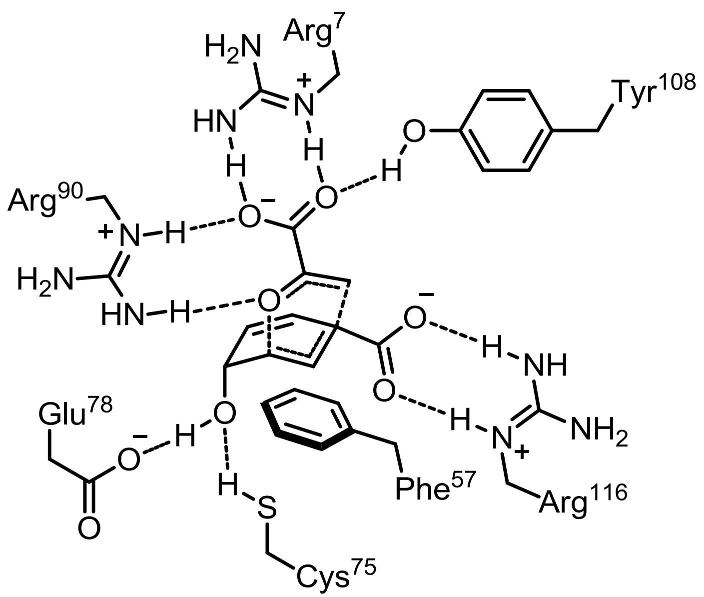
R = Aryl; [3,3]-selective, >10:1 dr, >90% ee
R = Alkyl; [1,3]-selective, poor ee's

Geherty, M. E.; Dura, R, D.; Neslon, S. G. *J. Am. Chem. Soc.* **2010**, *132*, 11875.

Organocatalytic Claisen Rearrangement

Chorisimate *Perphenate*



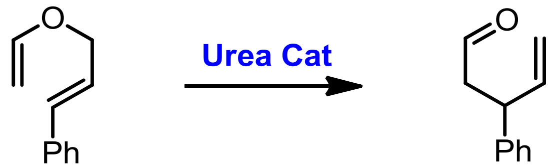


Key Interactions:

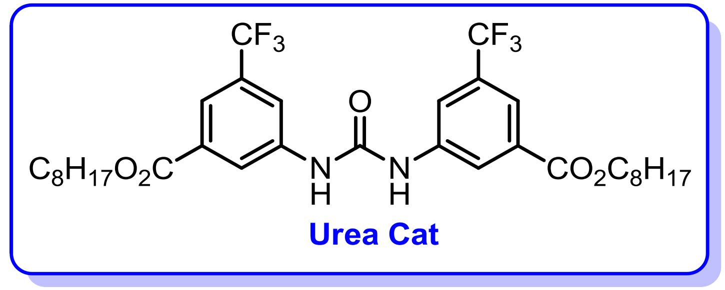
- Docked in active site by multiple H-bond interactions on CO_2^- and OH
- Phe-57 π-stacking interaction with allylic cation.
- Arg-90 Key for reactivity. When replaced >10,000 fold drop in activity
- H-bond catalysis

Chook, Y.-M.; Ke, H.; Lipscomb, W. H. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8600;. Chook, Y.-M.; Gray, J. V.; Lipscomb, W. N. *J. Mol. Biol.* **1994**, *240*, 476; Lee, A. Y.; Karplus, A.; Ganem, B.; Clardy, J. *J. Am. Chem. Soc.* **1995**, *117*, 3627.

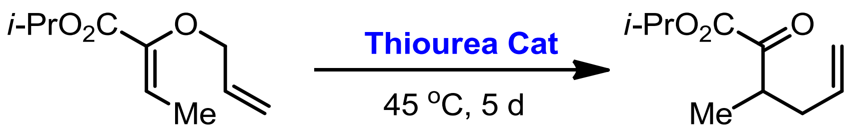
H-Bond Assisted Claisen



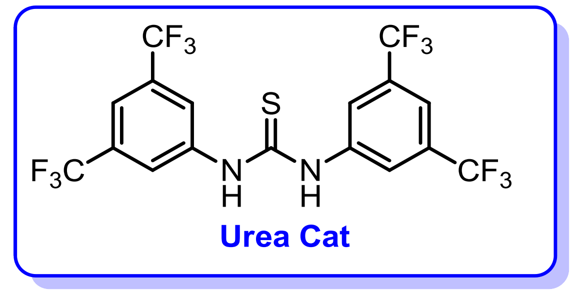
0.1 Equiv. — k_{rel} = 2.7
0.4 Equiv. — k_{rel} = 5.0
1 Equiv. — k_{rel} = 22.4



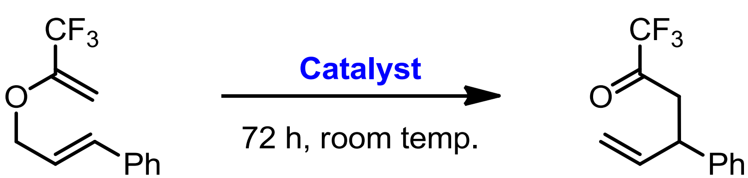
Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647.



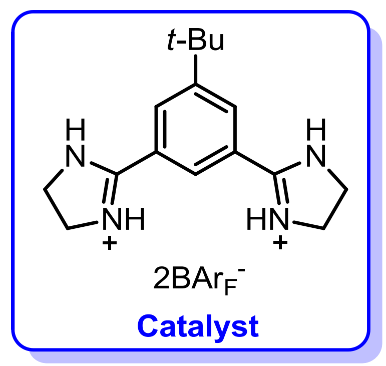
0 Equiv. — 57%
1 Equiv. — 84%

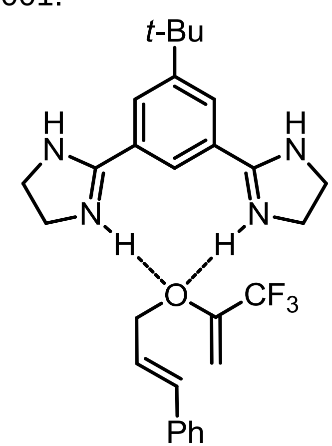


Kirsten, M.; Rehbein, J.; Hiersemann, M.; Strassner, T. J. Org. Chem. **2007**, *72*, 4001.



95% Conv

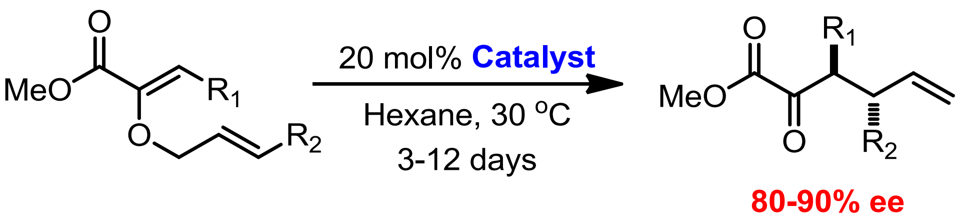


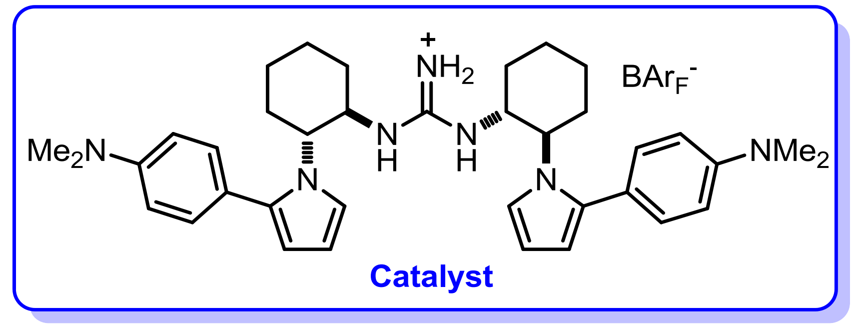


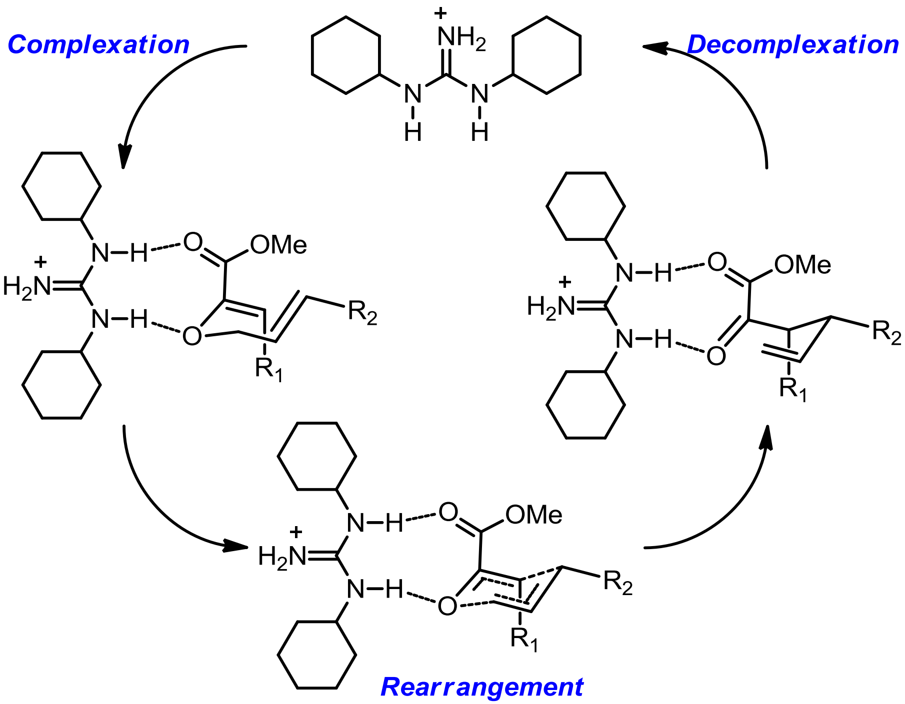
Annamali, V. R.; Linton, E. C.; Koslowski, M. C. *Org. Lett.* **2009**, *11*, 621.

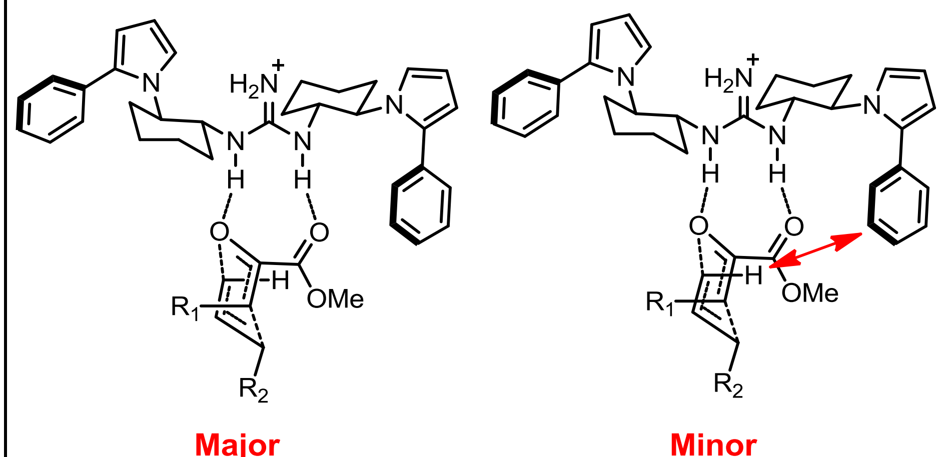
55-95-fold rate increase

Organocatalytic Rearrangement



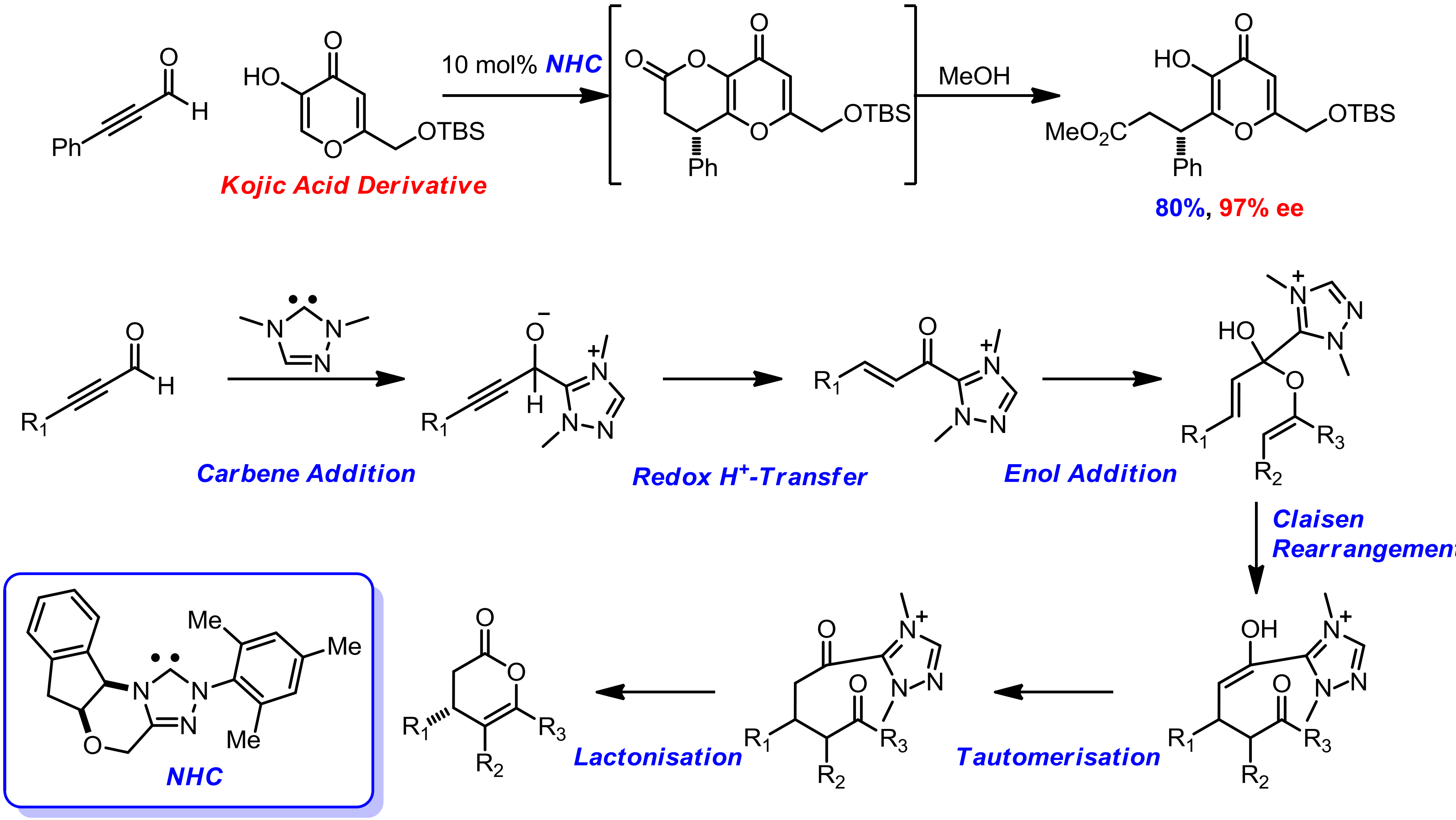






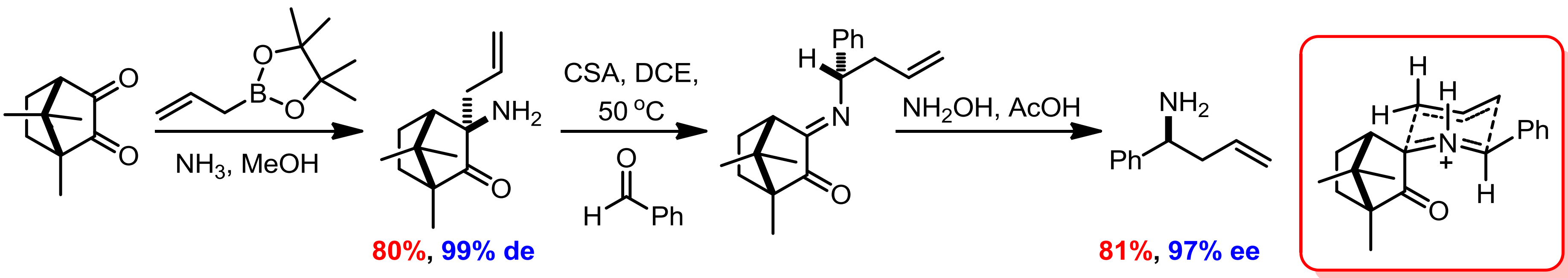
Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228.
Uyeda, C.; Rotheli, A. R.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 9753.
Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5063.

NHC Catalysed Claisen Rearrangements

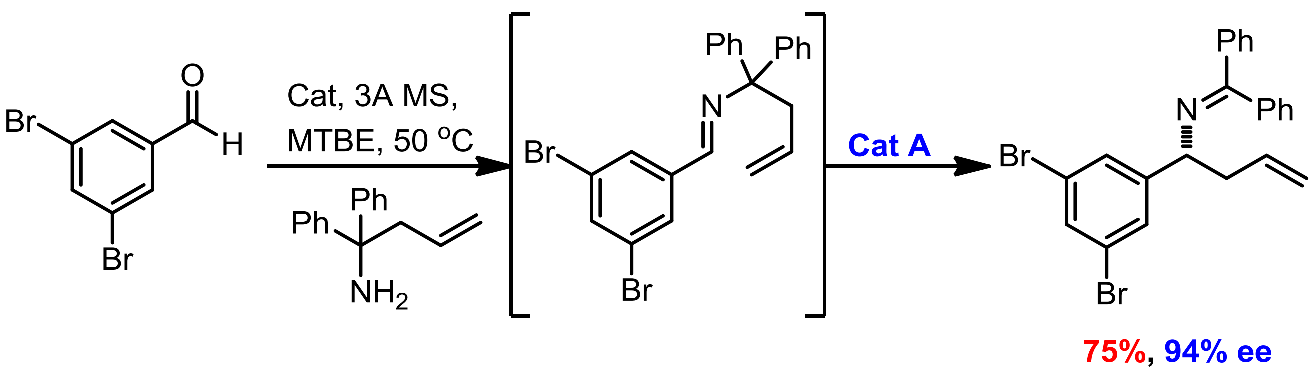


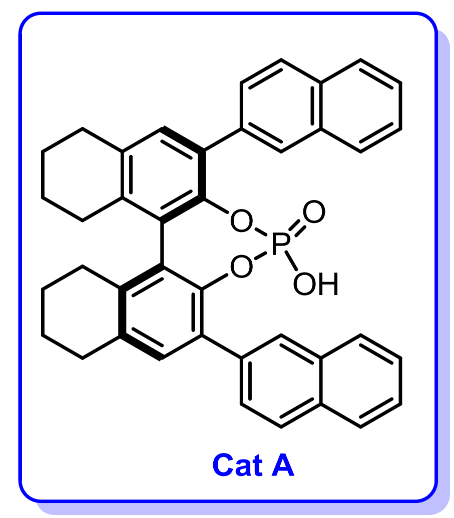
Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810.
Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.,* **2012**, *2*, 494.
For aza-Claisen see: Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378.

Enantioselective 2-aza-Claisen Rearrangement



Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038.

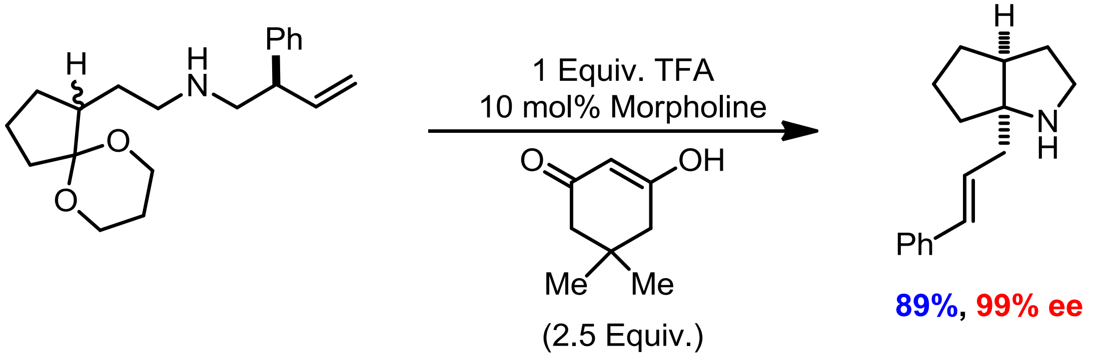


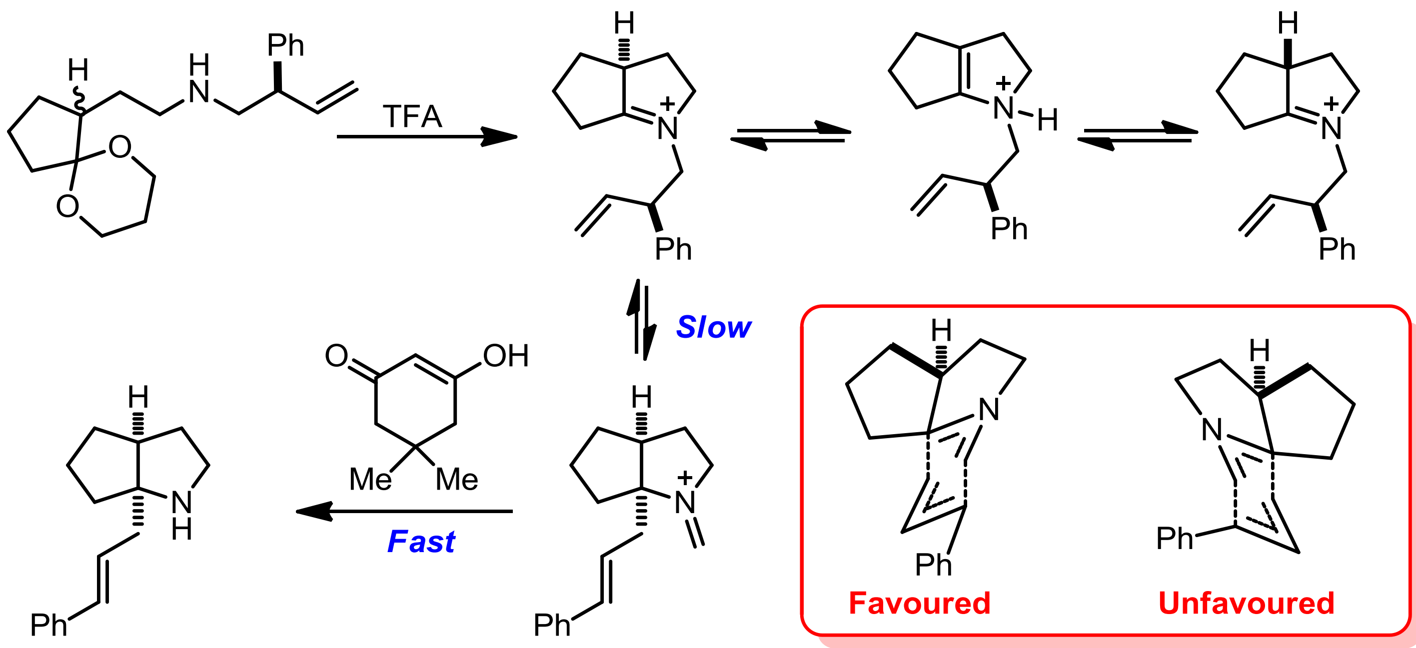


Chiral Counter-ion directed reaction

Rueping, M.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2008**, *478*, 10090.

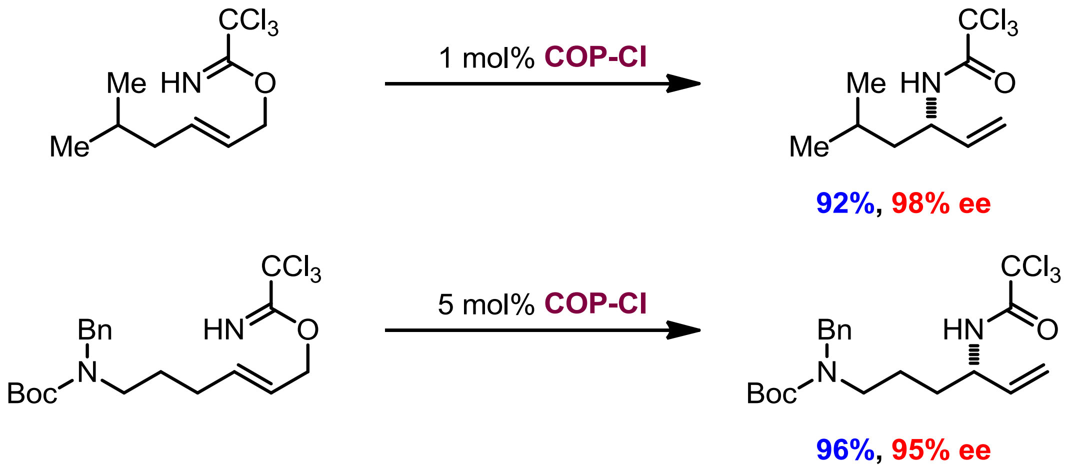
Enantioselective 2-aza-Cope Rearrangement

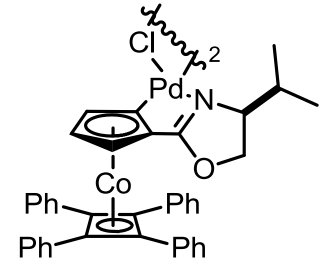




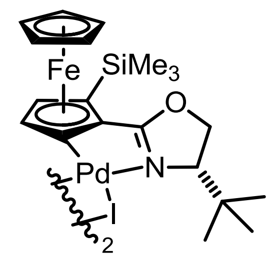
Ito, T.; Overman, L. E.; Wang, J. *J. Am. Chem. Soc.,* **2010**, *132*, 3272.

Overman Rearrangement



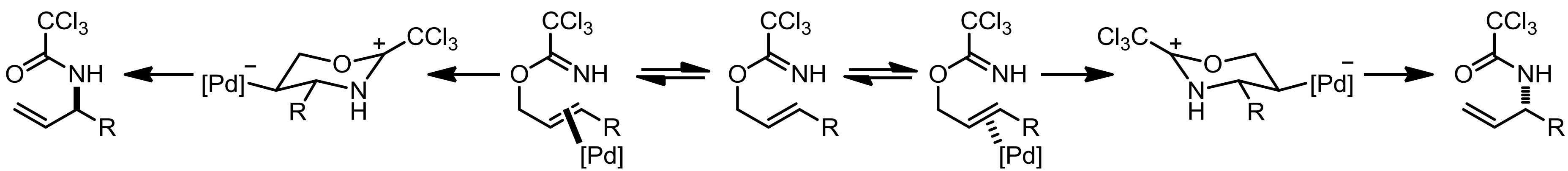


COP Catalyst



FOP Catalyst

COP catalyst see: Stevens, A. M.; Richards, C. J. Organometallics **1999**, *18*, 1346.
FOP Catalyst see: Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933.
.

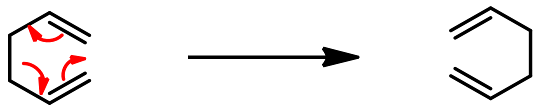


Si-Face Attack ***Re-Face Attack***

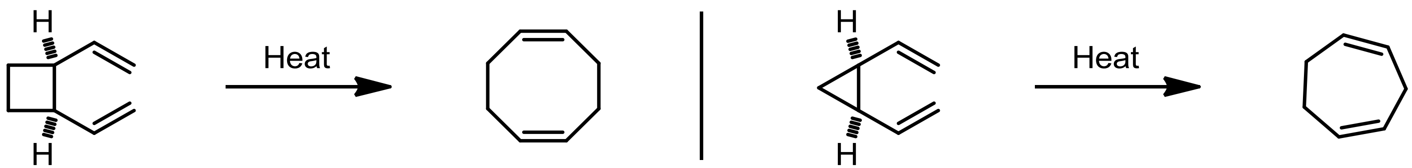
Major **Minor**

Mechanistic Investigations: Watson, M. P.‘; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031.

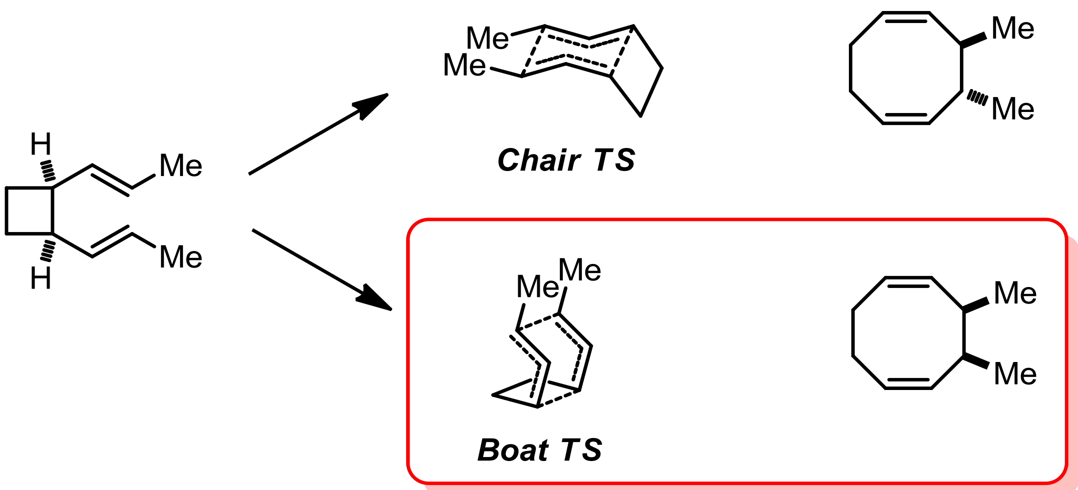
Cope Rearrangement



Rearrangement of a 1,5 diene to another 1,5-diene. Unusually difficult as there is no real energetic gain.

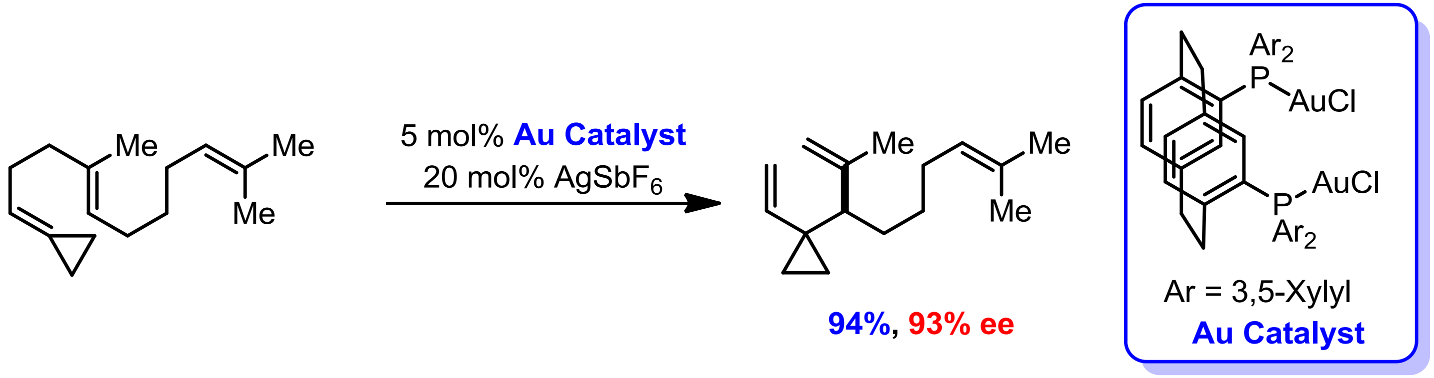


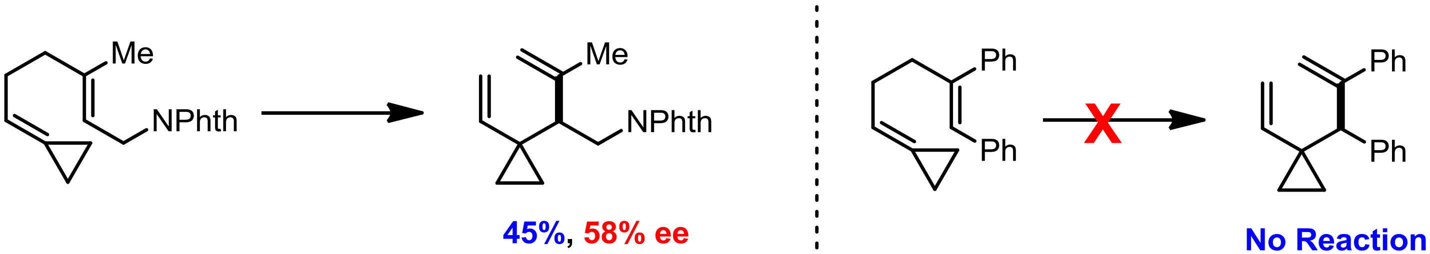
Energy barrier can be overcome through the use of small rings. These irreversibly open in the thus driving the reaction



A chair TS including a small ring is very high energy. These generally proceed via the boat instead. This can be proved by using substituted alkenes. The *syn*-product is formed which indicates the boat is in operation

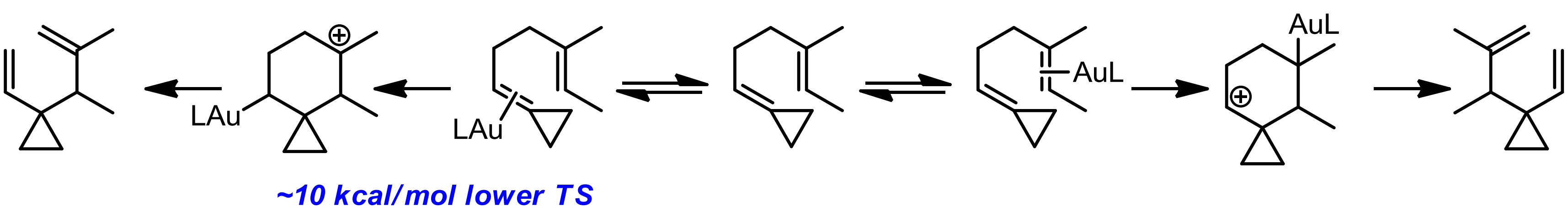
Gold Catalysed Cope-Rearrangement





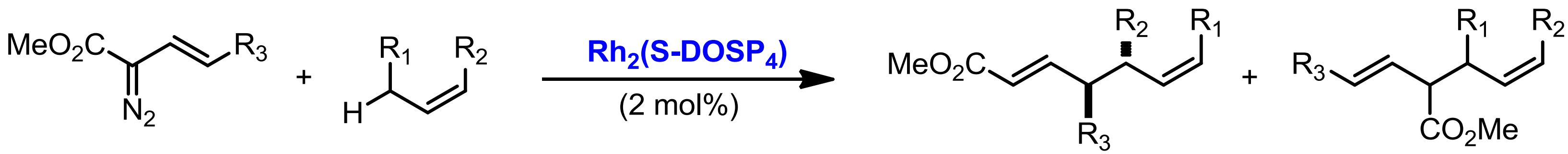
Heteroatoms reduce enantioselectivity

Highly Conjugated Systems Fail to React



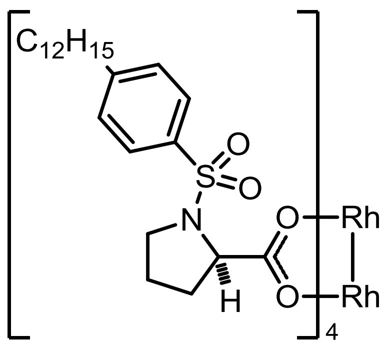
Felix, R. J.; Weber D.; Gutierrez, O.; Tantillo, D. J.; Gagne, M. R. *Nature Chem.* **2012**, *4*, 405.

C-H Activation Cope-Rearrangement

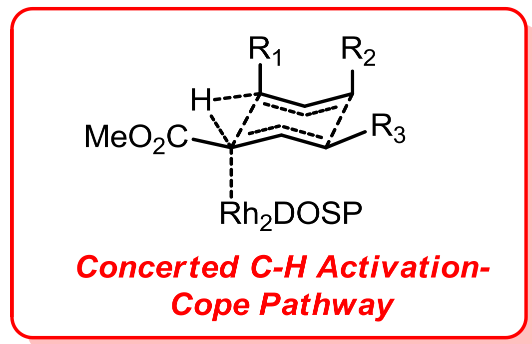


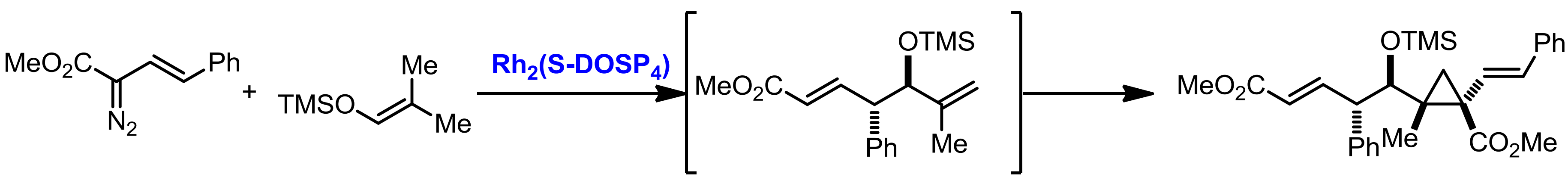
Major
C-H Activation-Cope
>98:2 dr, >95% ee

Minor
C-H Activation
Poor Selectivities



Rh_2DOSP_4

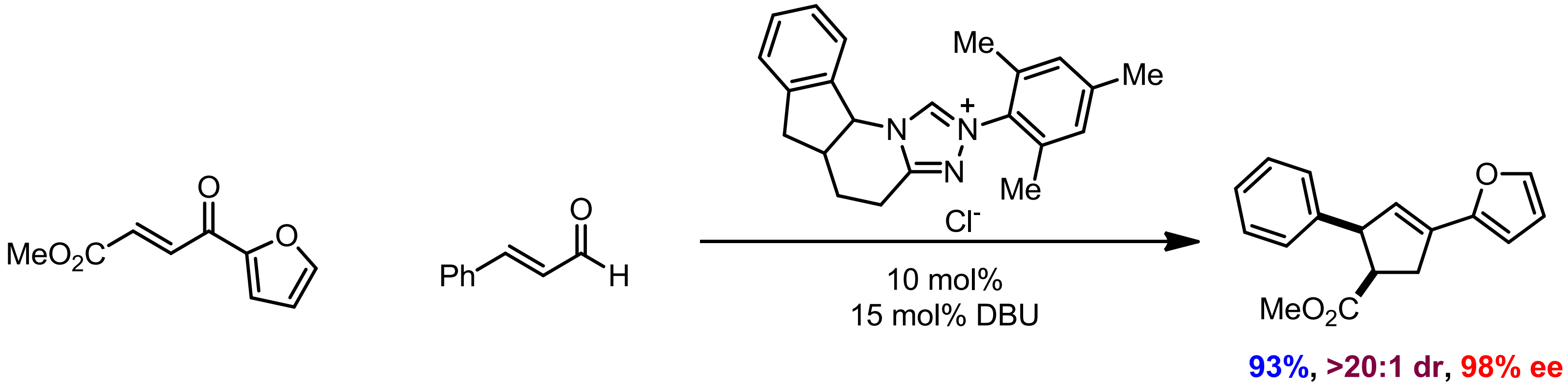


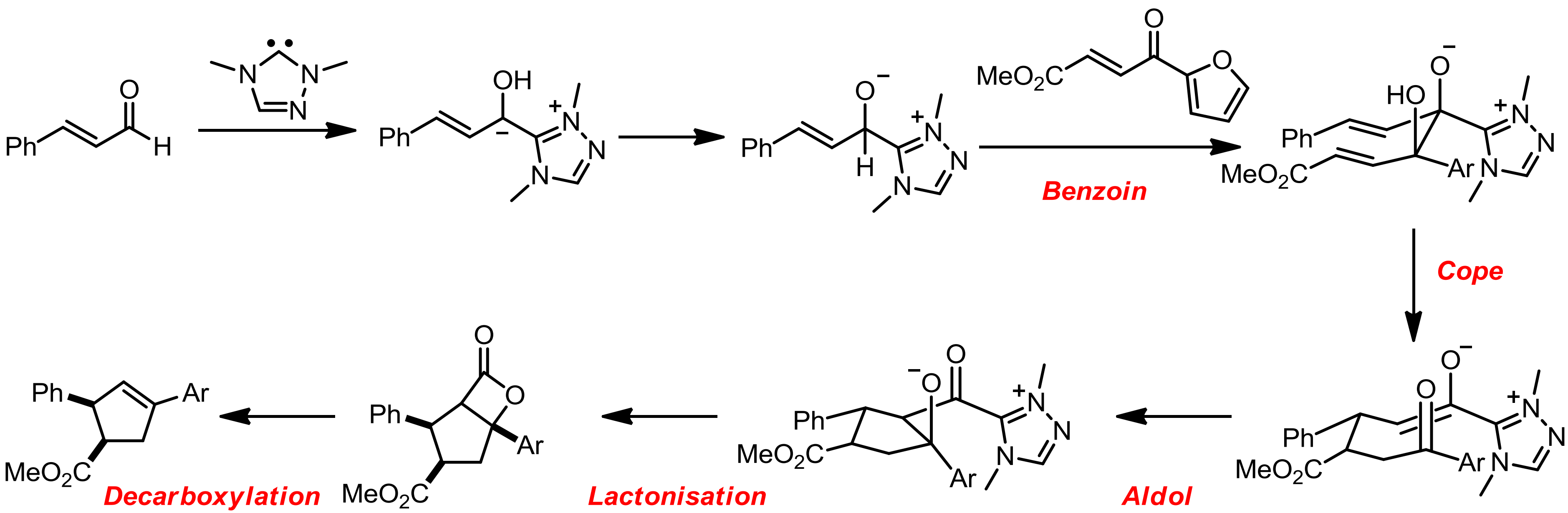


53%, >98:2 dr, 99% ee

Davies, H. M. L.; Jin, Q. *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5472.
Hansen, J. H.; Gregg, T. M.; Ovalles, S. R.; Lian, Y.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**,*133*, 5076.
Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**,*133*, 11940.

NHC Catalysed Cope-Rearrangement





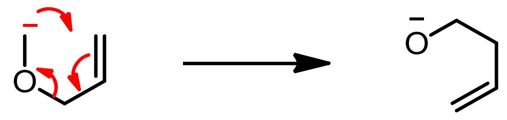
Chiang, P. –C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520.

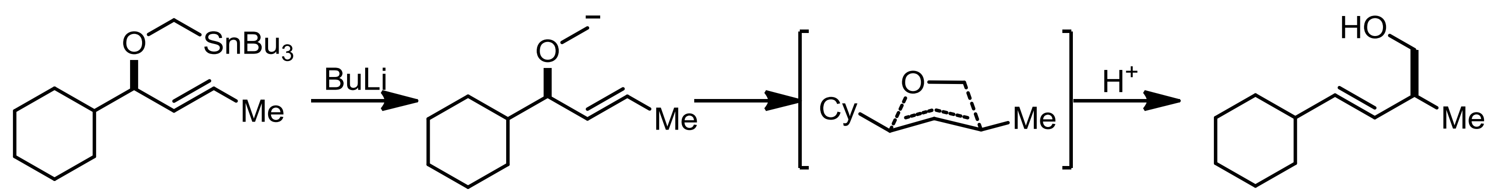
[2,3]-Rearrangement

[2,3]-Wittig Rearrangement

Rearrangement of an anionic allylic ether to afford a homoallylic alcoxide.

Very stereospecific

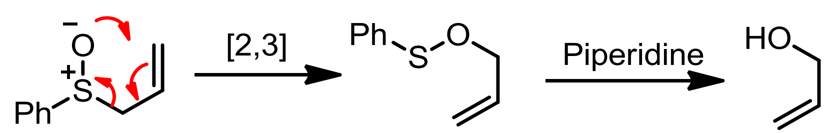


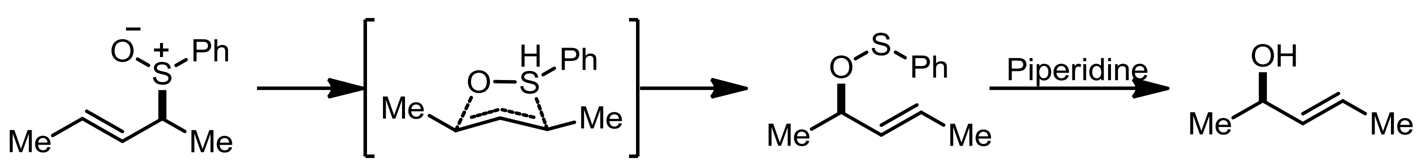


Mislow Rearrangement

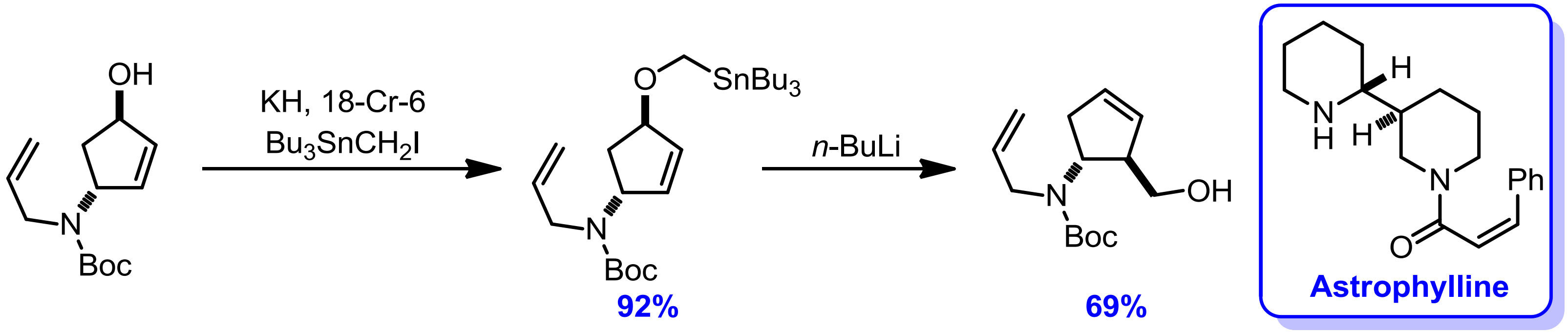
Rearrangement of an allylic sulfoxide to a sulfenate and allylic alcohol.

Again very stereospecific reaction

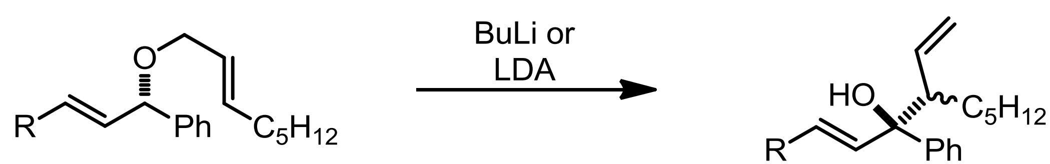




[2,3]-Wittig Preexisiting Stereocentres



Schaudt, M.; Blechert. *J. Org. Chem.* **2003**, *68*, 2913.



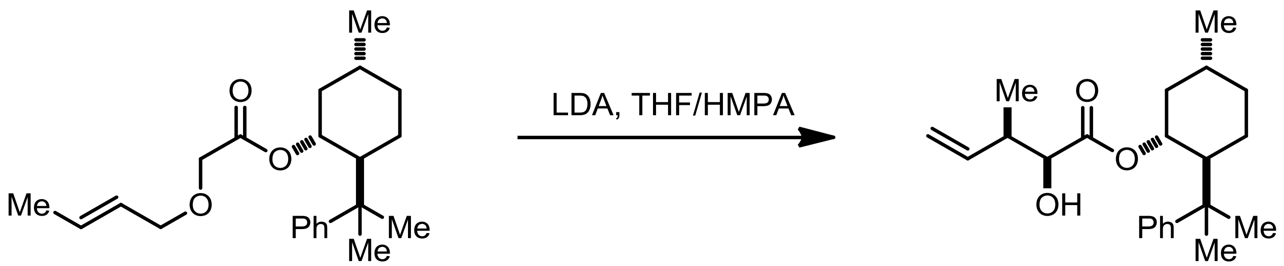
99% ee

R =	**Me;**	**32:68 dr**	**94/98% ee**
	Ph;	**45:55 dr**	**84/92% ee**
	$SiMe_3$;	**47:53 dr**	**85/86% ee**
	CN;	**50:50 dr**	**8/9% ee**
	SO_2Ph;	**63:37 dr**	**5/12% ee**
	$P(O)(OEt)_2$;	**76:24 dr**	**2/14% ee**

Good retention of enantioselectivity
Poor diastereoselectivity
EWG's erode stereo selectivity

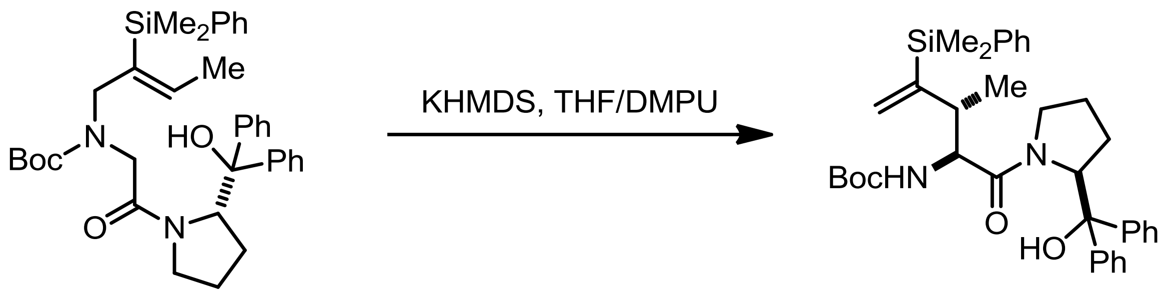
Sasaki, M.; Ikemoto, H.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Chem. Eur. J.* **2009**, *15*, 4663.

[2,3]-Wittig Chiral Auxilaries



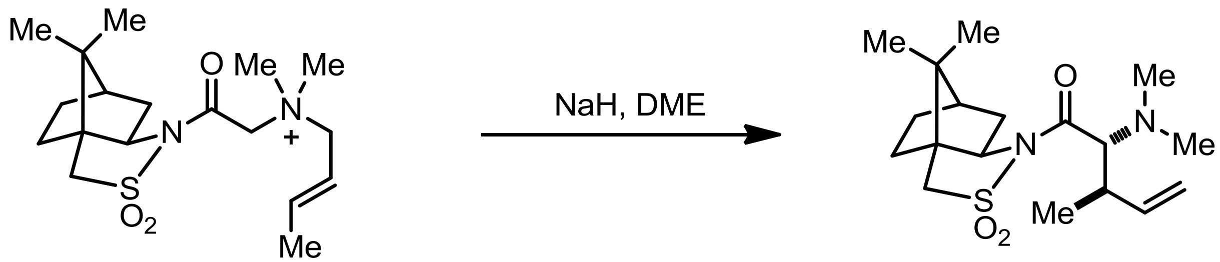
88%, 90:10 *syn:anti*, 97% de

Takahashi, O.; Mikami, K.; Nakai, T. *Chem. Lett.* **1987**, 69.



72%, >95:5 *anti:syn*, 70% de

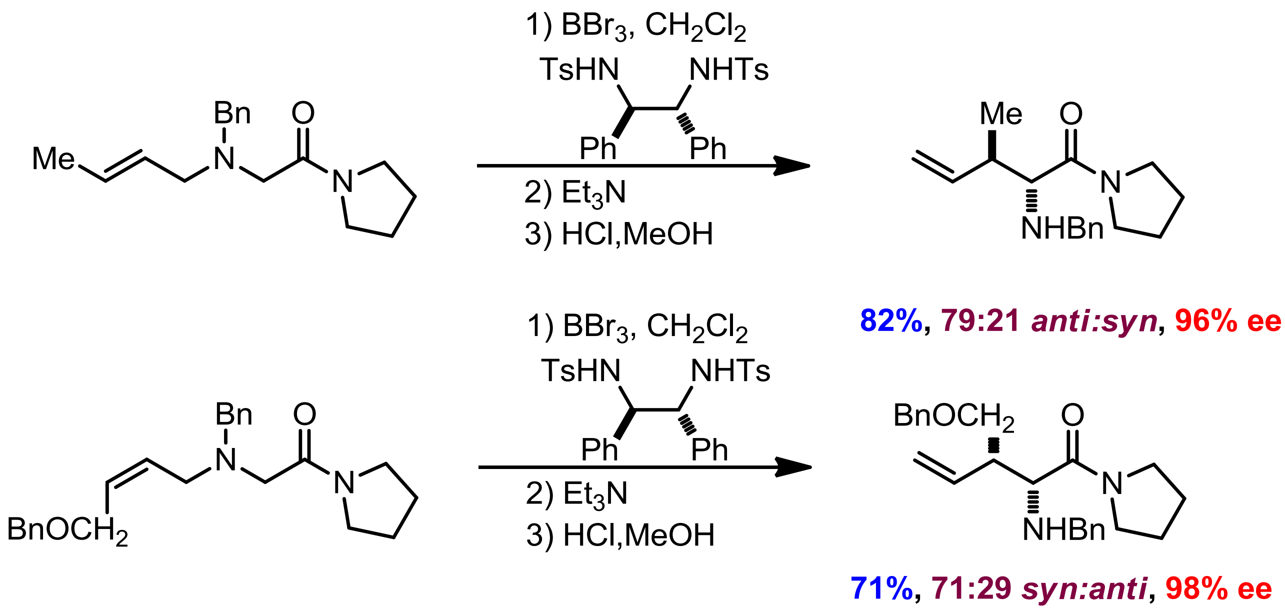
Anderson, J. C.; O’Loughlin, J. M. A.; Tornos, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2741.

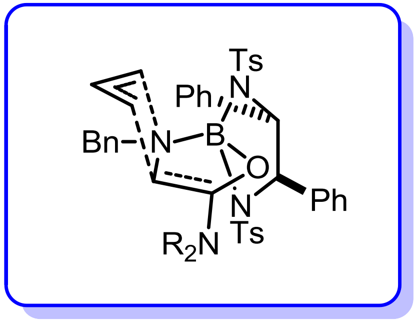


86%, >99:1 *anti:syn*, 92% de

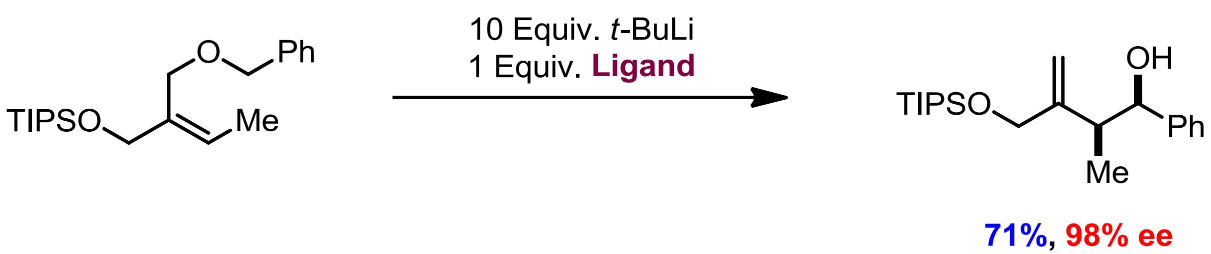
Workman, J. A.; Garrido, N. P. Sancon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B.. *J. Am. Chem. Soc.,* **2005**, *127*, 1066.

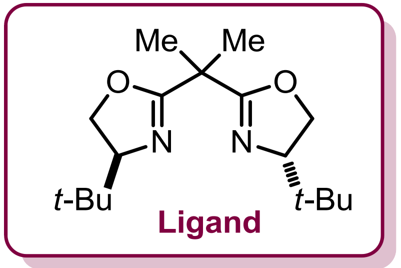
[2,3]-Chiral Reagents





Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.*, **2005**, *127*, 9352.

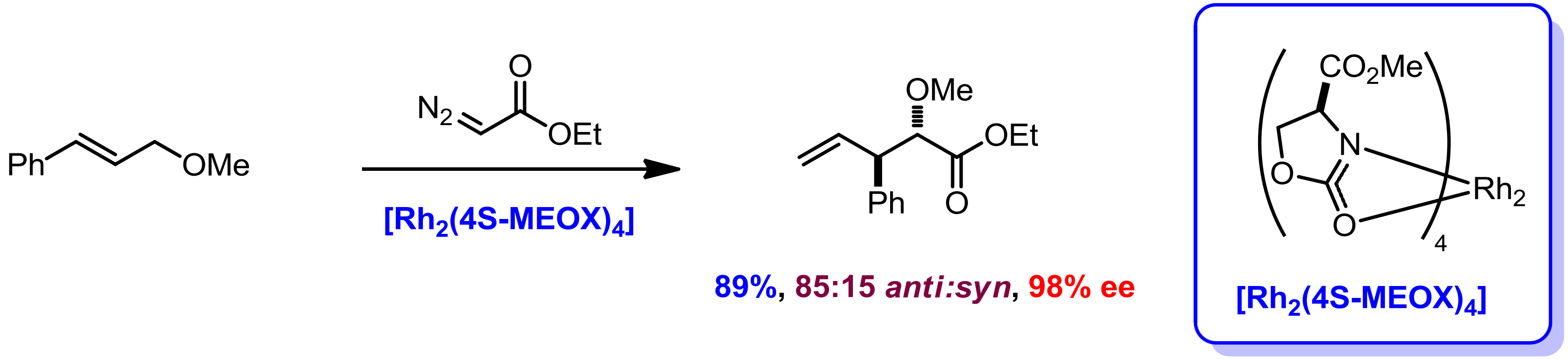




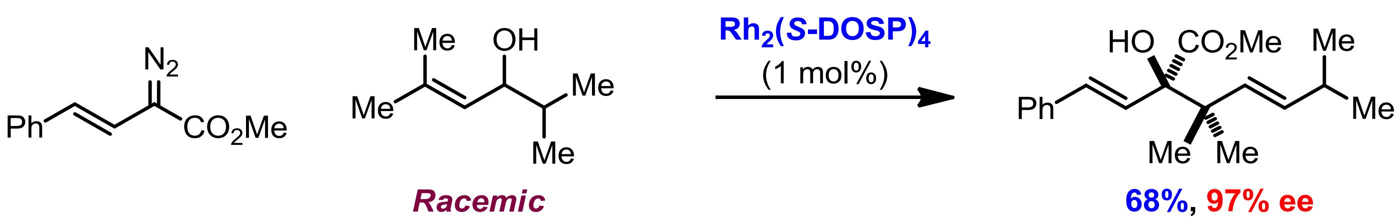
3 Equiv. *t*-BuLi, 0.1 Equiv. **Ligand** = **40%**, **96% ee**

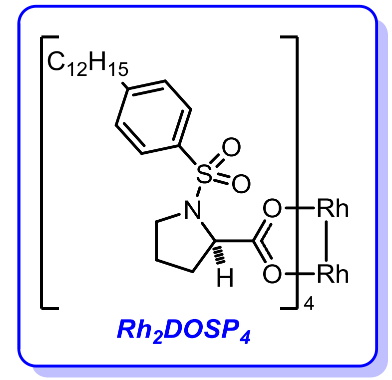
Kitamura, M.; Hirokawa, Y.; Maezaki, N. *Chem. Eur. J.* **2009**, *15*, 9911.

[2,3]-Enantioselective Catalysis

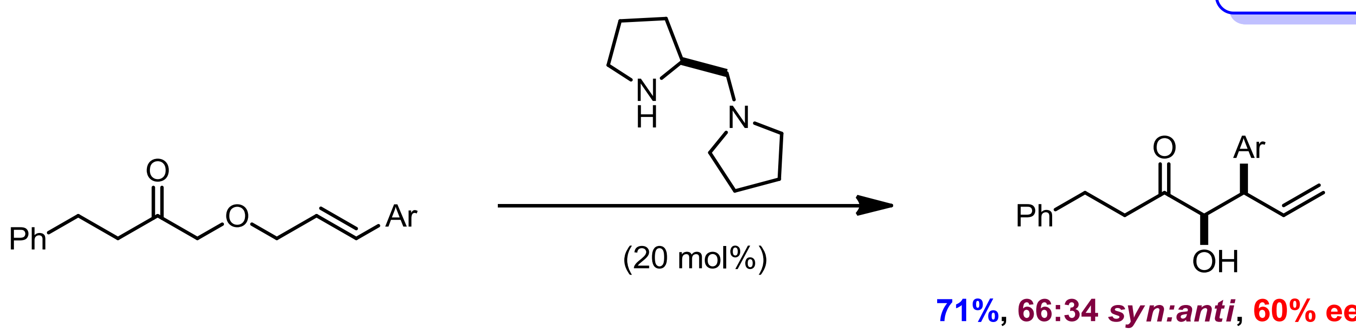


Doyle, M. P.'; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.,* **1998**, *120*, 7653.





Li, Z.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 396.



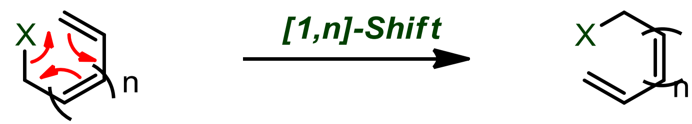
McNally, A.; Evans, B.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2116.

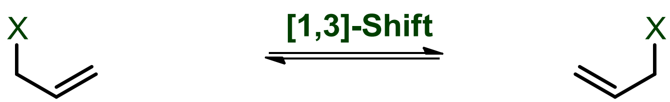
[1,n] Rearrangements

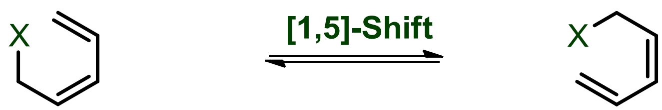
[1,n]-Rearrangement

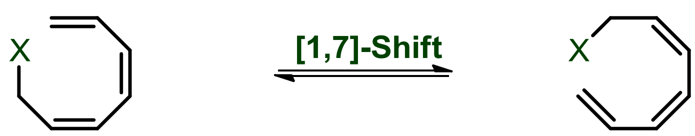
Thermally or photochemically mediated migration of a bond n-atoms.

Stereospecific with retention or inversion



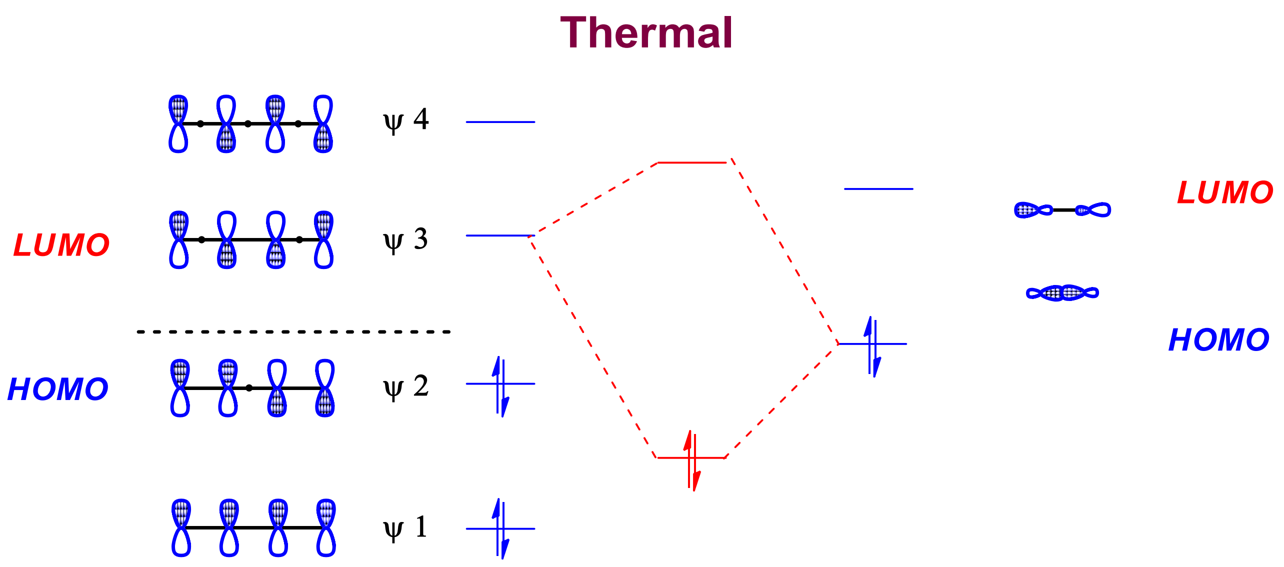


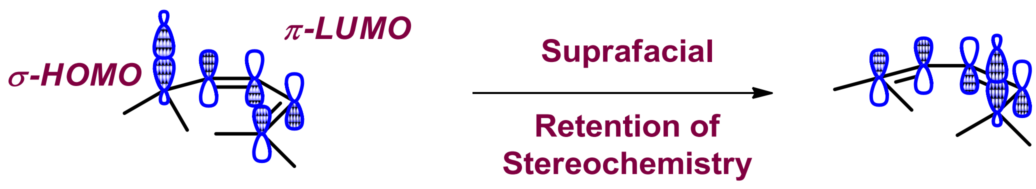




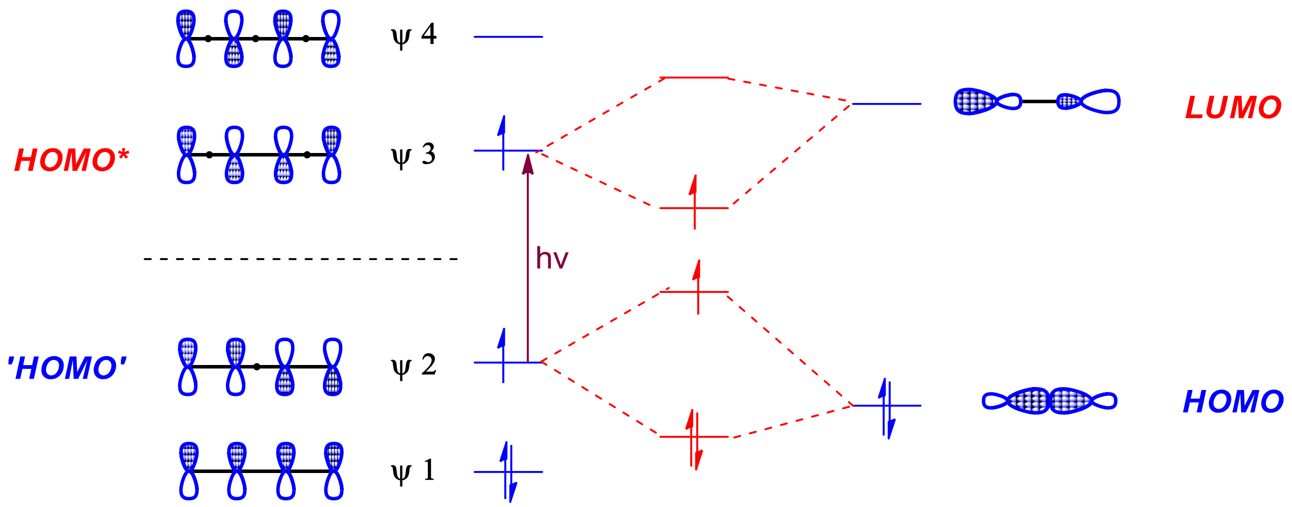
	Thermal	Photochemical
[1,3]-Shift	Antarafacial	Suprafacial
[1,5]-Shift	Suprafacial	Antarafacial
[1,7]-Shift	Antarafacial	Suprafacial

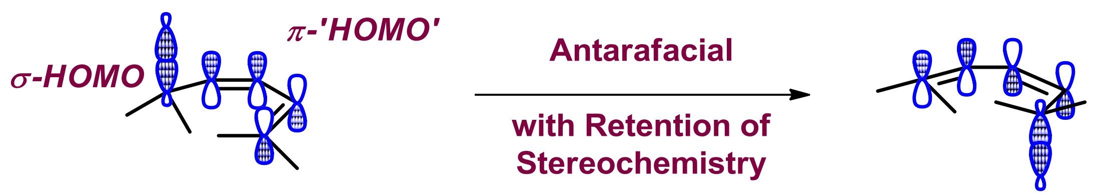
[1,5] Rearrangement

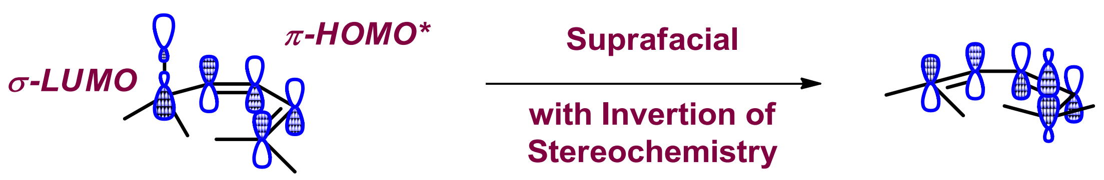




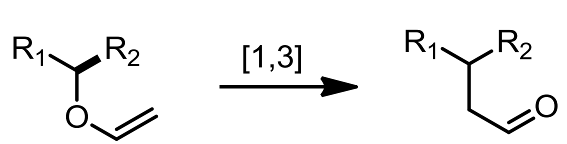
[1,5] Rearrangement

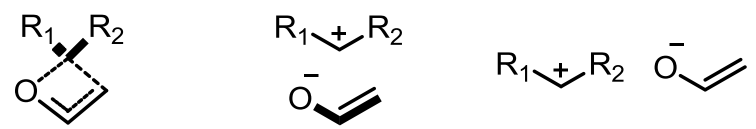






[1,3]-Rearrangements

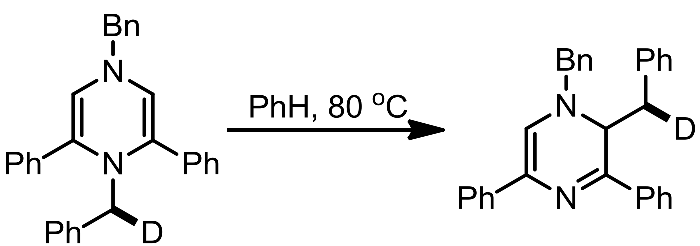




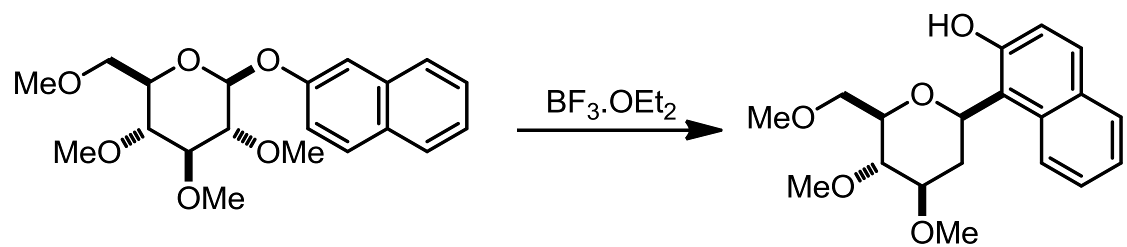
[1,3]-Suprafacial sigmatropic shift
Inversion

[1,3]-Shift Solvent Cage
Retention

[1,3]-Shift Solvent Seperated
Epimerisation

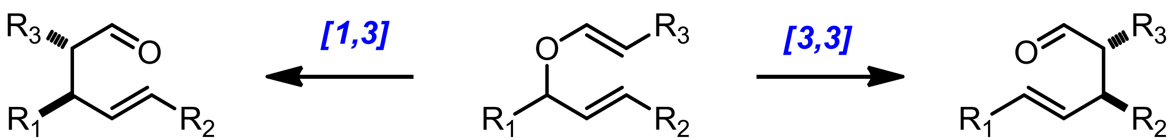


[1,3]-Sigmatropic Shift - Inversion



[1,3]-Shift - Solvent Cage - Retention

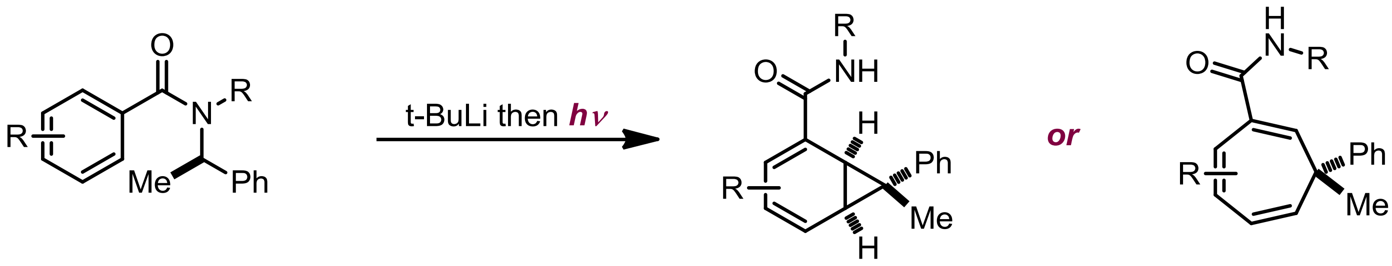
Lown, J. W.; Akhtar, M. H.; McDaniel, R. S. *J. Org. Chem.* **1974**, *39*, 1998.
Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, 1005

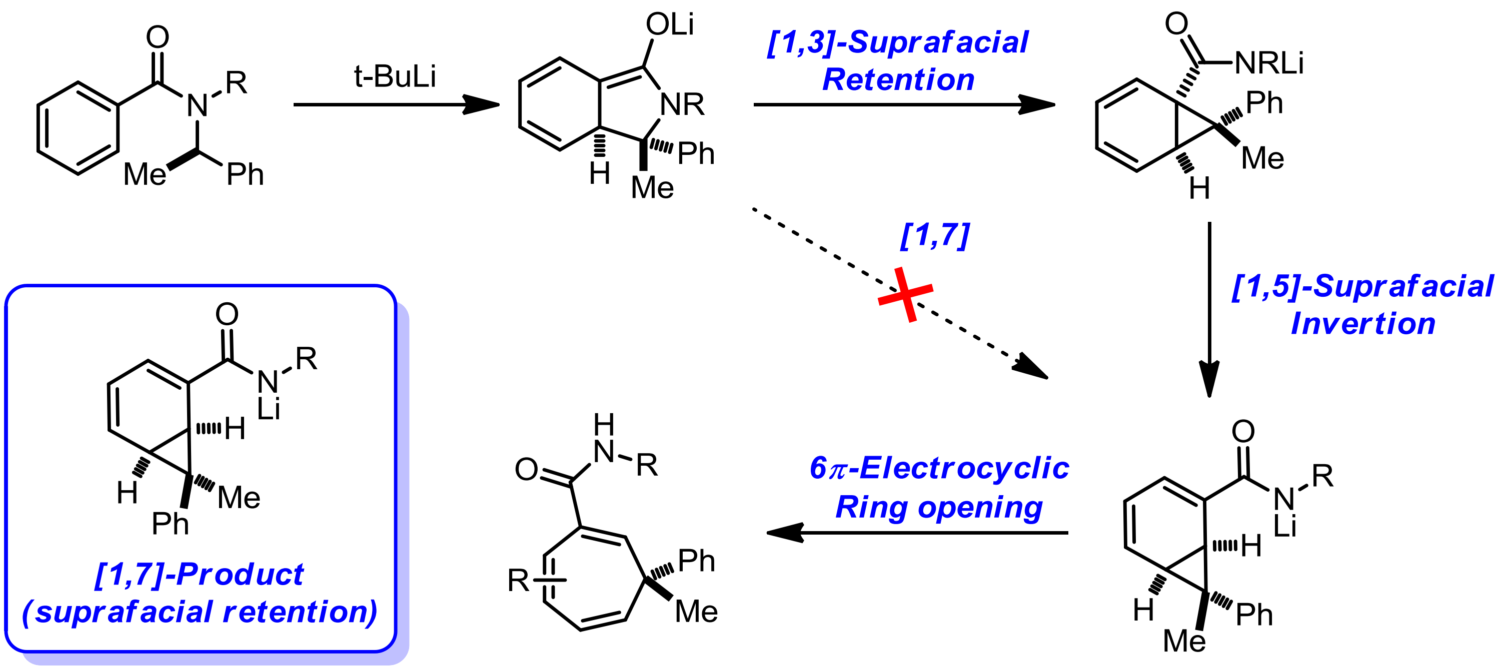


Allyl vinyl ethers can be problematic

For Review see: Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240.

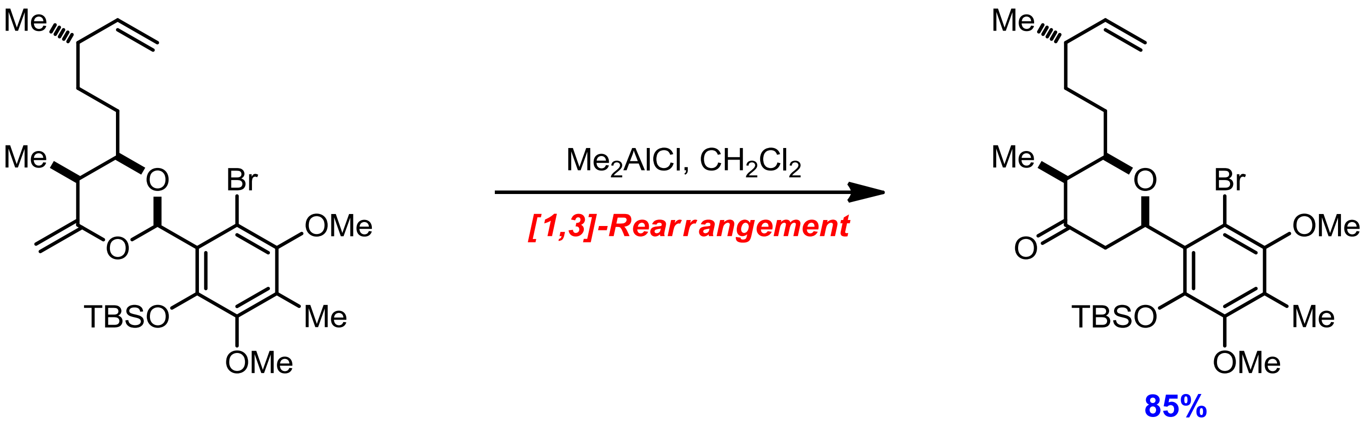
Cascade [1,n]-Rearrangements



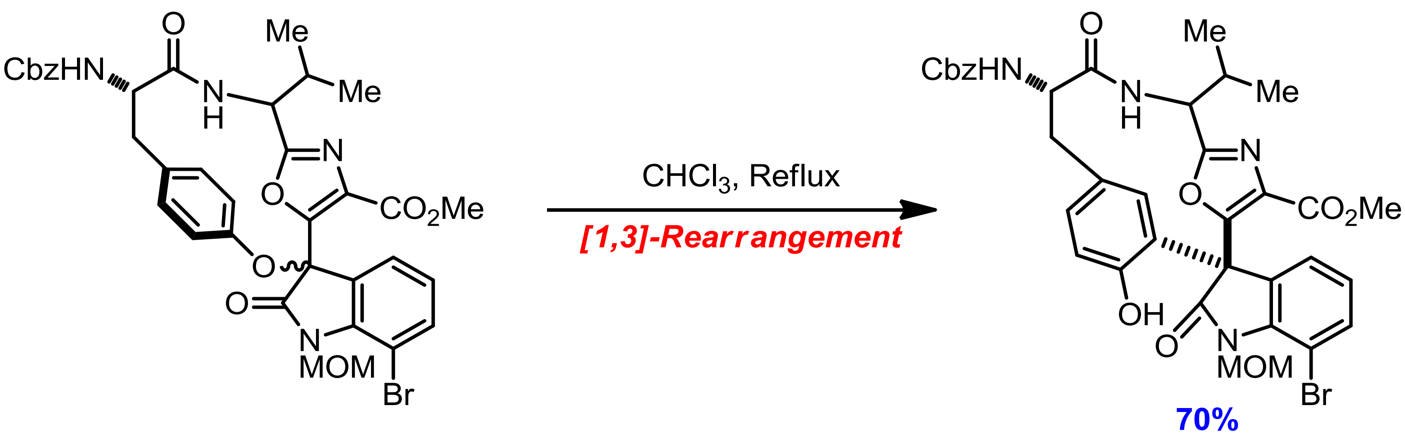


Clayden, J.; Knowles, F. E.; Menet, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9278.

[1,3]-Rearrangements in Synthesis

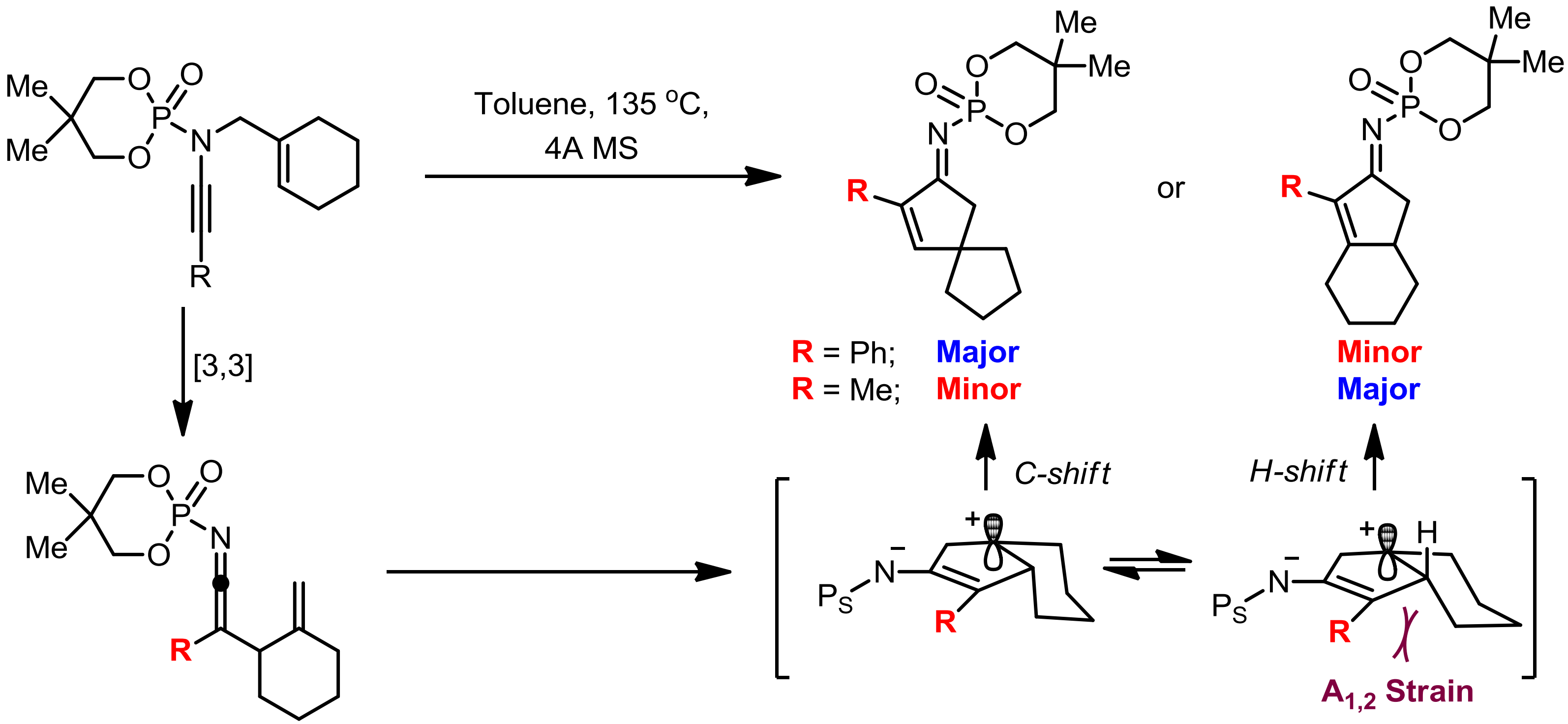


Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc*. **2006**, *128*, 5292.

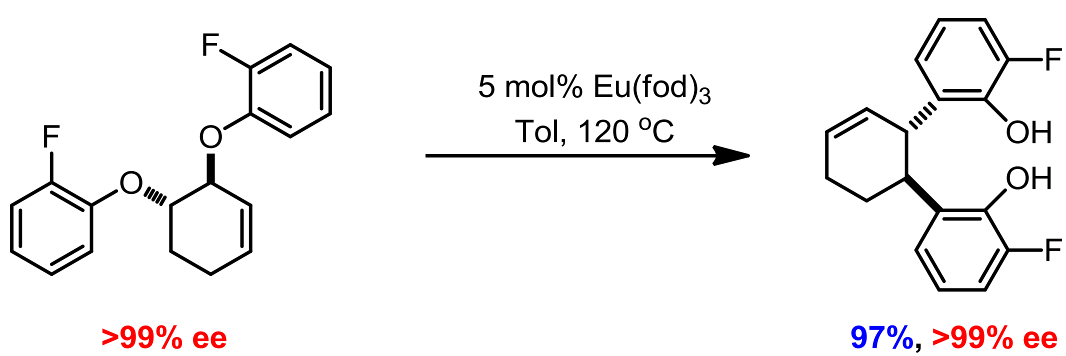


Cheung, C. –M.; Goldberg, F. W.; Magnus, P.; Russell, C. J.; Turnbull, R.; Lynch, V. *J. Am. Chem. Soc*. **2007**, *129*, 12320.

Cascade Sigmatropic Rearrangements

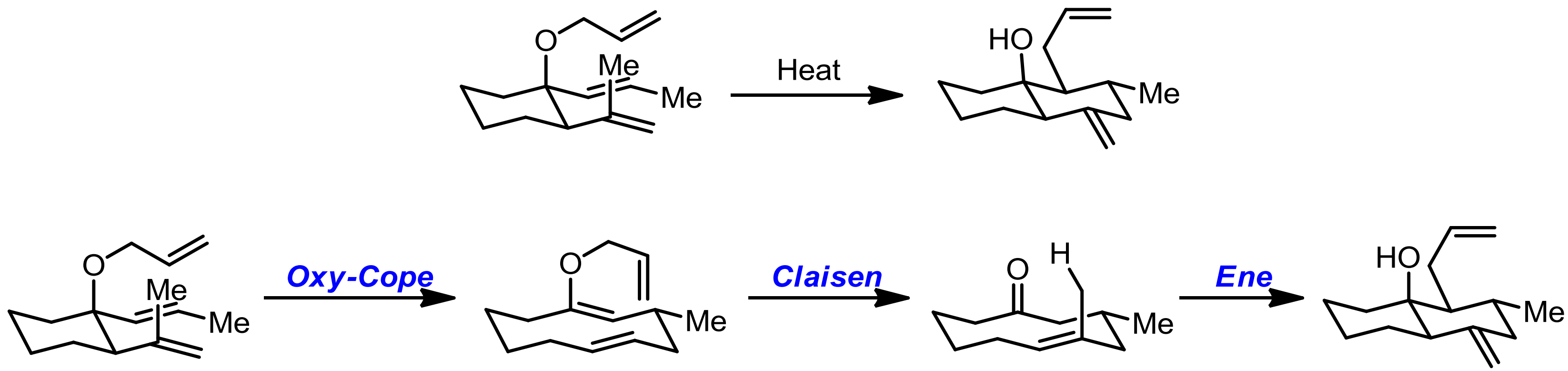


DeKorver, K. A.; Wang, X. –N.; Walton, M. C.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 1768.

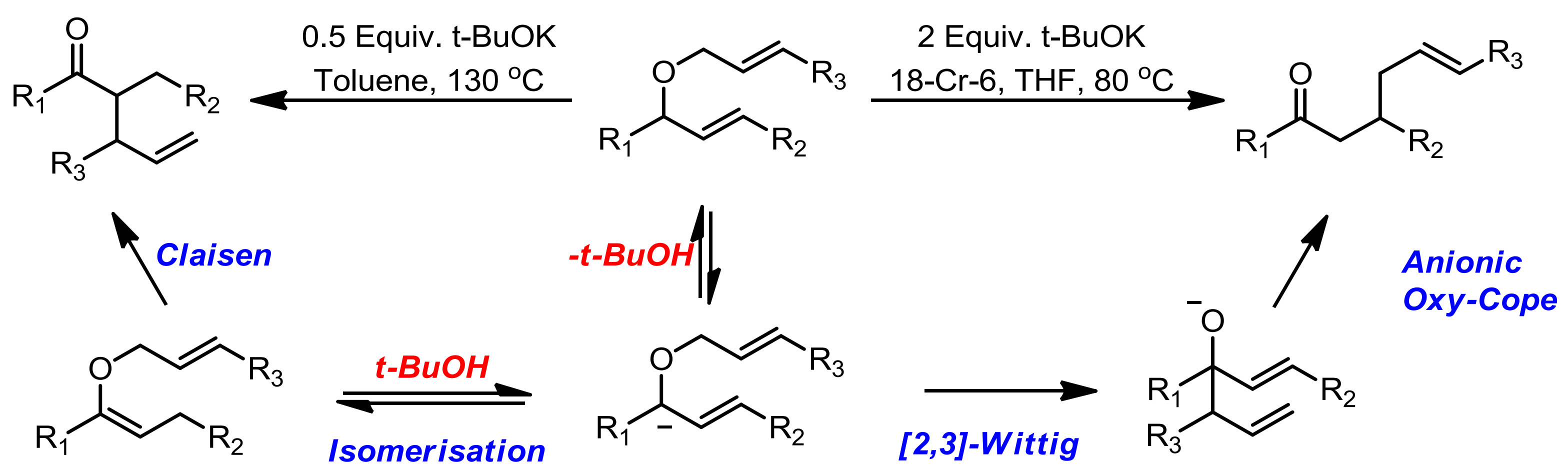


Ramadhar, T. R.; Kawakami, J. –I., Lough, A. J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 4446.

Cascade Sigmatropic Rearrangements

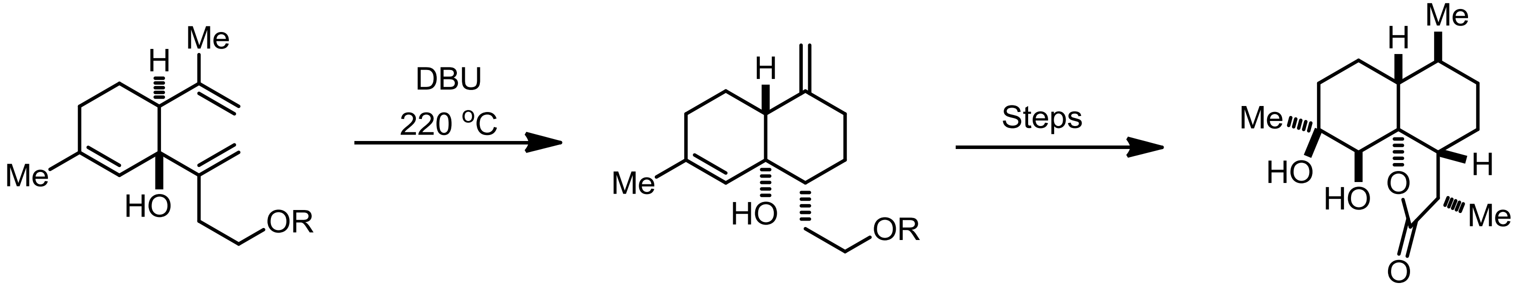


Barriault, L.; Gauvreau, D. *J. Org. Chem.* **2005**, *70*, 1382.



Reid, J. P.; Johnston, A. J. S.; McAdam, C. A.; Walter, M. W.; Cook, M. J. *Manuscript in. Preparation*

Cascade Sigmatropic Rearrangements



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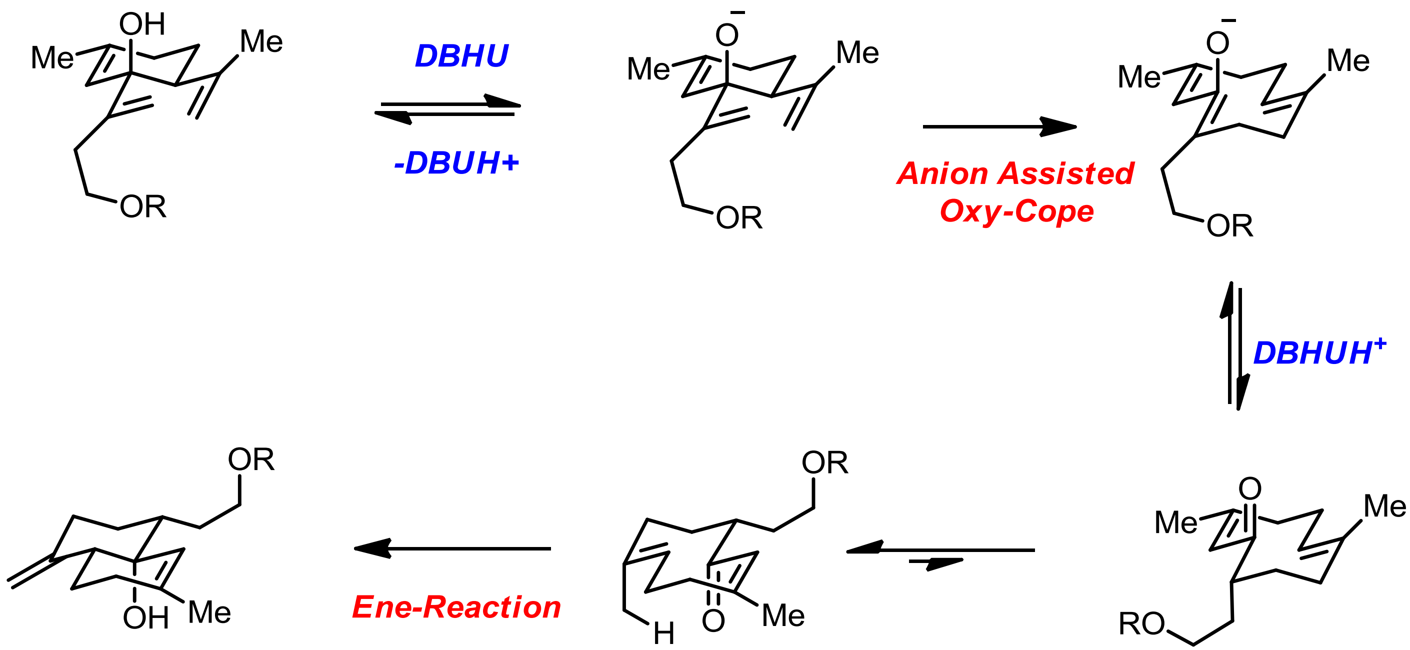
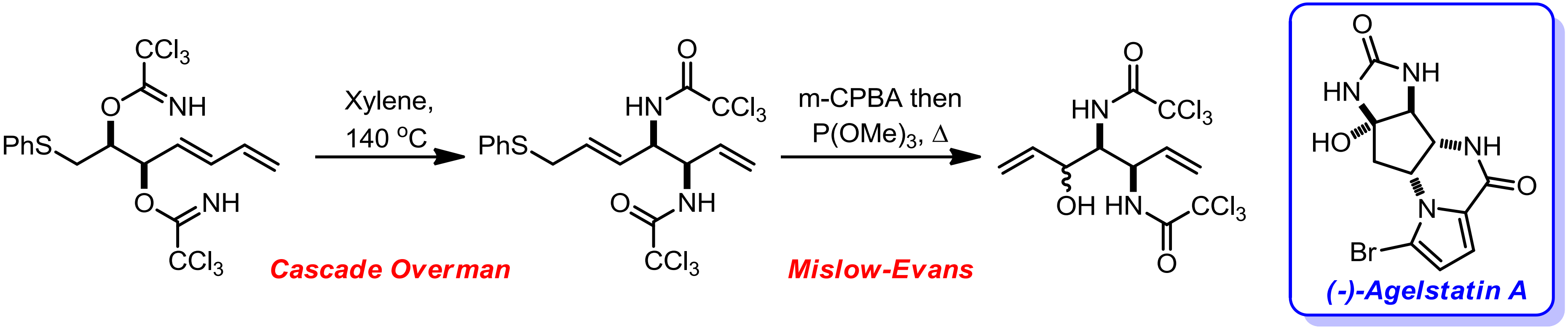
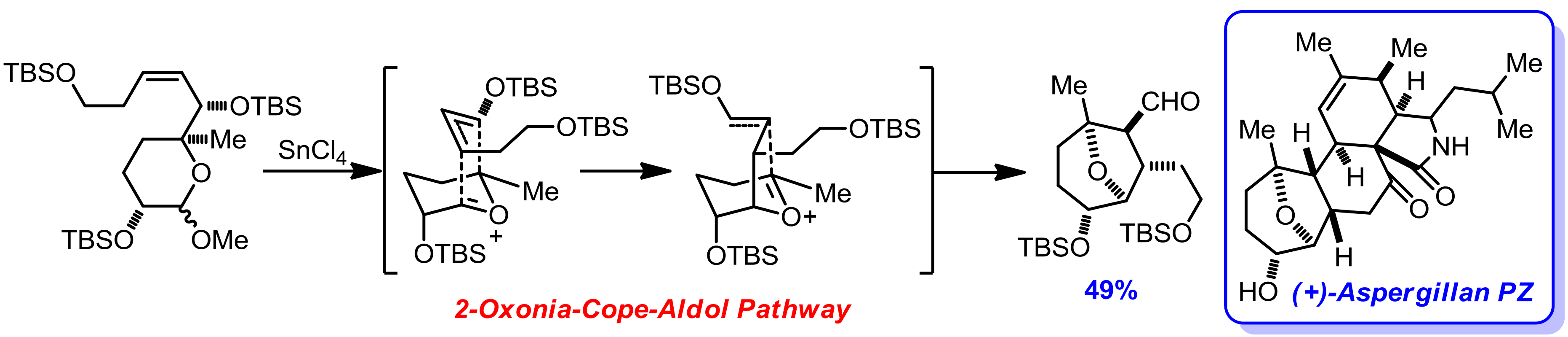


Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*, 1925.

Cascade Rearrangements in Synthesis



Hama, N.; Matsuda, T.; Sato, T.; Chida, N. *Org. Lett.* **2009**, *11*, 2689.



Canham, S. M.; Overman, L. E.; Tanis, P. S. *Tetrahedon* **2011**, *69*, 9837.

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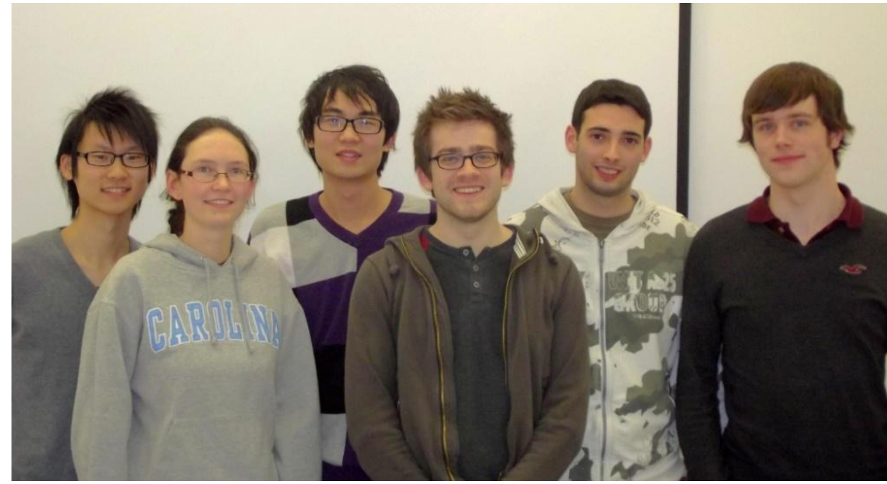

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