Memory of Chirality: A Strategy for Asymmetric Synthesis

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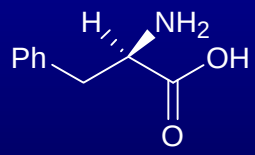
September 14, 2005

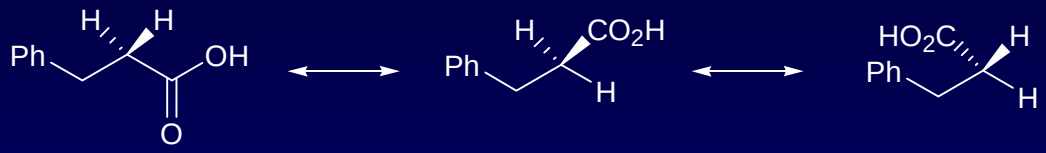
Two Forms of Chirality

Absolute (Static) Chirality

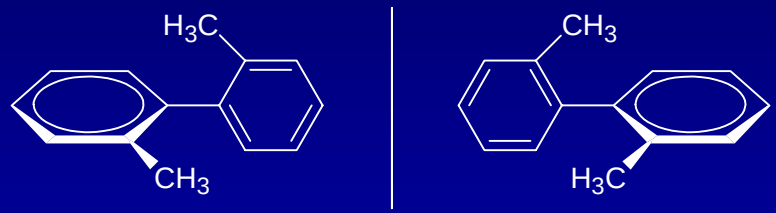


- Absolute chirality - orientation of functional groups at a stereocenter

Dynamic (Conformational) Chirality



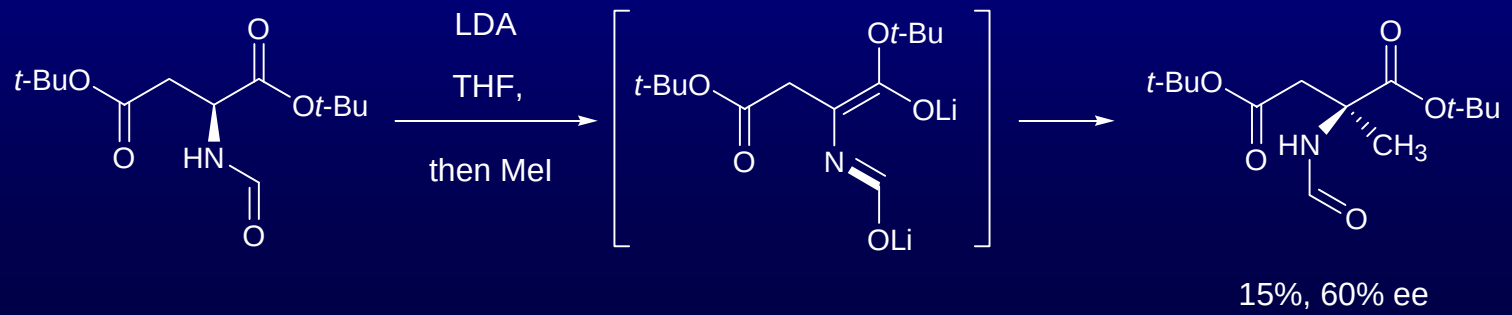
- Dynamic chirality - chirality present only when C-C single bond rotation is restricted



Barrier of rotation = 18 kcal/mol

Memory of Chirality in Enolate Chemistry

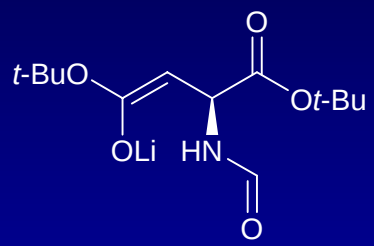
- In 1981, Seebach and Wasmuth made the following observation:



15%, 60% ee

- No mechanism was established; however, one hypothesis was that reaction occurred through an axially chiral intermediate

- Mixed aggregates involving the chiral enolate below were later implicated



Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.
Seebach, D.; Sting, A. R.; Hoffman, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.

Memory of Chirality: Definition

Problem: Can stereochemical information be retained during a process in which the sole stereogenic center of a substrate is destroyed?

> 0% ee

Memory of chirality (MOC) has been defined as a process in which:

"the chirality of the starting material is preserved in a reactive intermediate for a limited time"

Fuji, K.; Kawabata, T. *Chem.-Eur. J.* **1998**, *4*, 373-378.

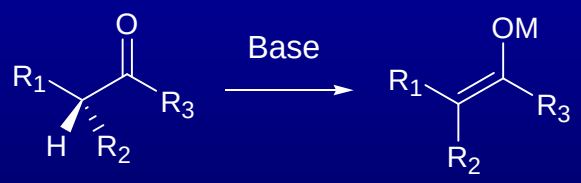
This process has also been described as follows:

"A 'memory of chirality' reaction can be defined as a formal substitution at an sp^3 stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system."

Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1-17.

Additional Review: Kawabata, T.; Fuji, K. *Top. Stereochem.* **2003**, *23*, 175-205.

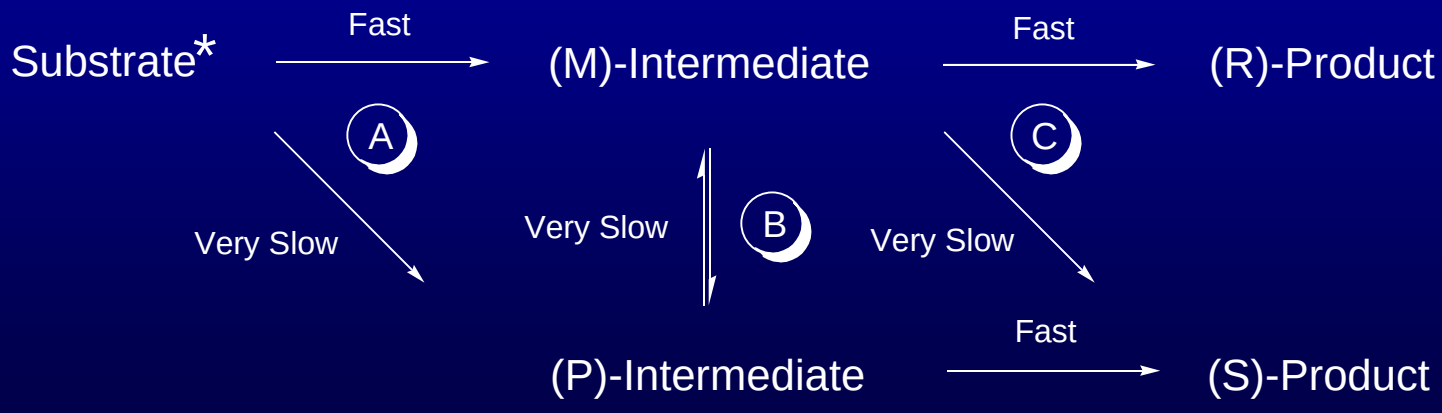
Enolate Alkylation: Design of a Memory of Chirality System



- Fuji and co-workers proposed two strategies for the establishment of conformationally chiral enolates - axially chiral enolates or planar chiral enolates

Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694.

Stereoselectivity by Memory of Chirality: General Considerations



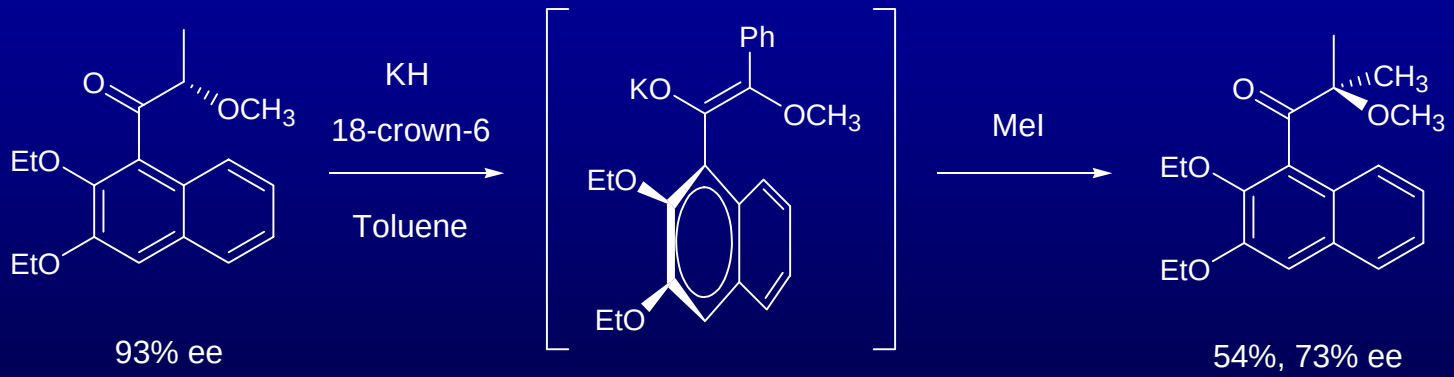
A — Reaction at stereogenic center (e.g., enolate formation) generates conformationally chiral intermediate

B — Conformationally chiral intermediate must not readily racemize

C — Reaction must occur with high stereospecificity

- Critical issue: reaction kinetics

Enolate Alkylation Utilizing Memory of Chirality (MOC)



93% ee

54%, 73% ee

65% ee

67% ee

48% ee

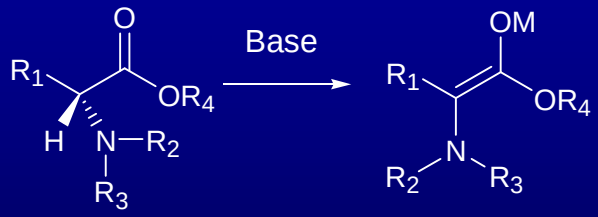
70% ee

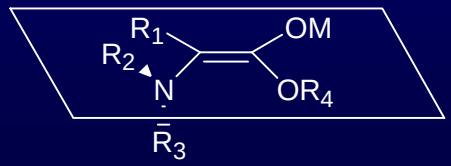
- O-methylated product also isolated in 65% ee by chiral HPLC

- Half-life of racemization determined to be 53 minutes at room temperature

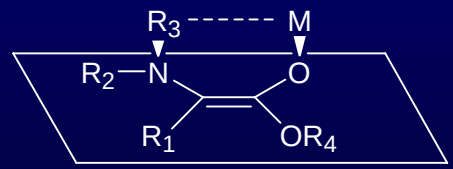
Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694.

Asymmetric Syntheses of Amino Acid Derivatives

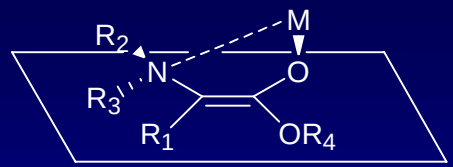




Axial Chirality



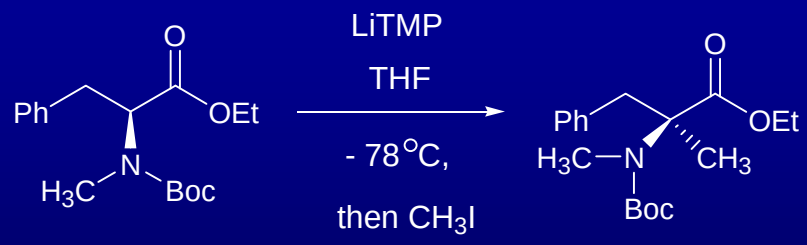
Planar Chirality



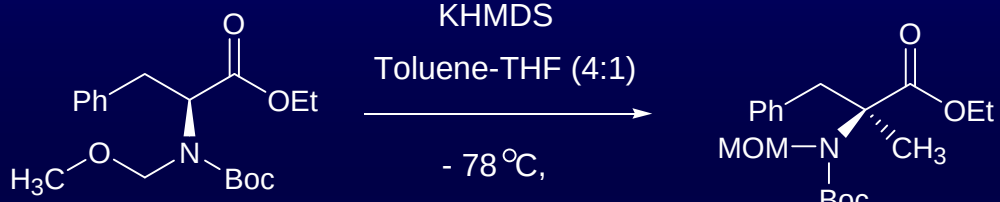
Central Chirality

Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809.

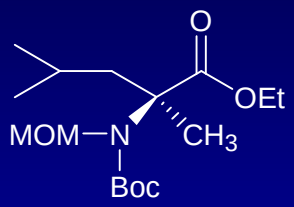
Asymmetric Alkylation of Amino Acid Esters



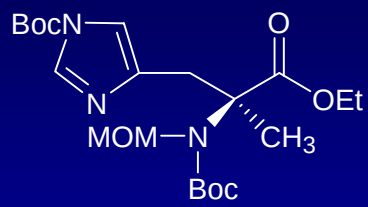
40%, 82% ee



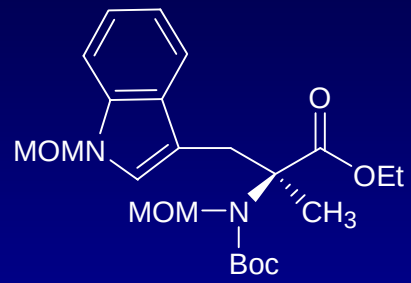
96 %, 81% ee



78%, 78% ee



83%, 93% ee

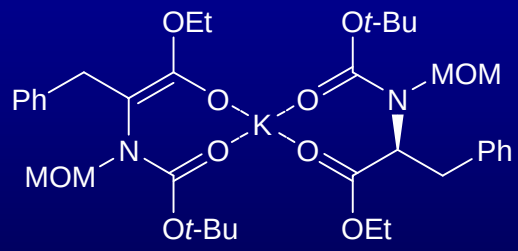


88%, 76% ee

Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809.
Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155.

Mechanism of Memory of Chirality Effect

- One possibility - mixed aggregate mechanism



- Ruled out by competition experiments

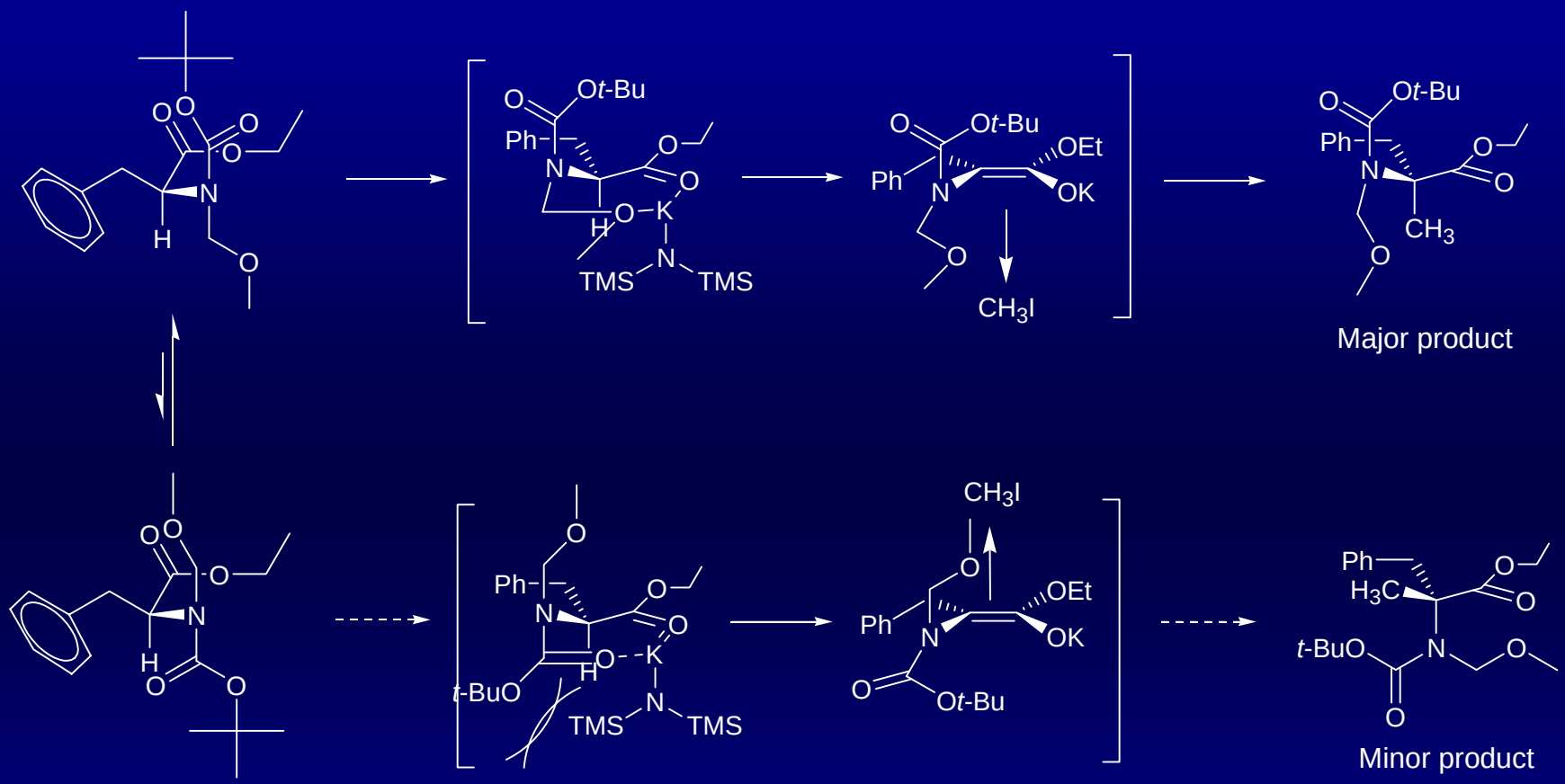
- Silyl enol ether prepared - exhibits rotational barrier of 16.8 kcal/mol by VT NMR experiments

- Half-life of approximately 7 days at -78 ℃

- Variable reaction times explored for enolate deprotonation - rotational barrier calculated as 16.0 kcal/mol

Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155.

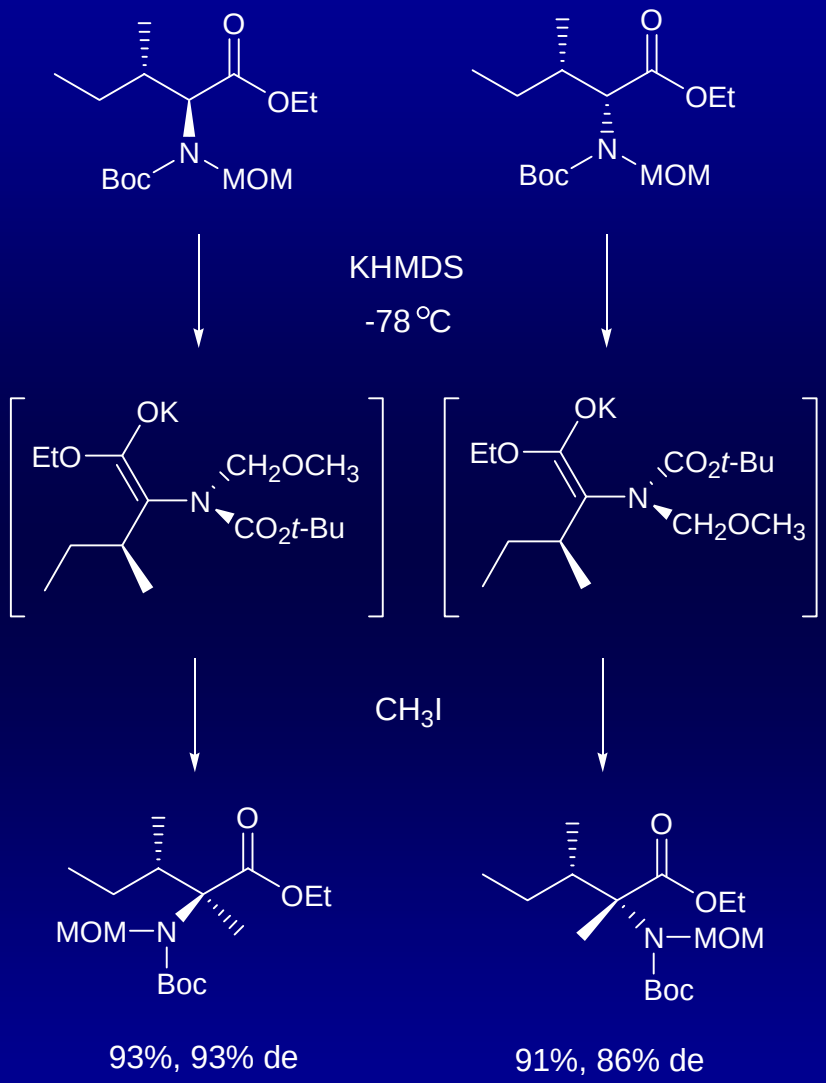
Mechanism of Memory of Chirality Effect



- Additional evidence: *di*-Boc and oxazolidinone analogs showed no enantioselectivity

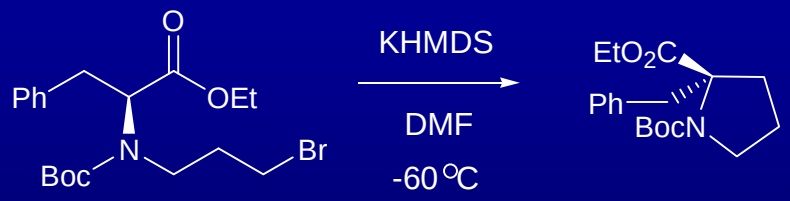
Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155.

Effect of Adjacent Stereocenters

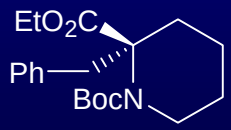


Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155.

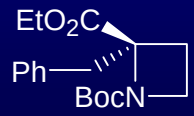
Asymmetric Alkylation - Intramolecular Cyclization



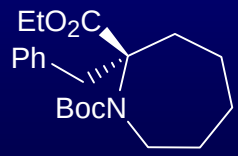
94%, 98% ee



84%, 97% ee

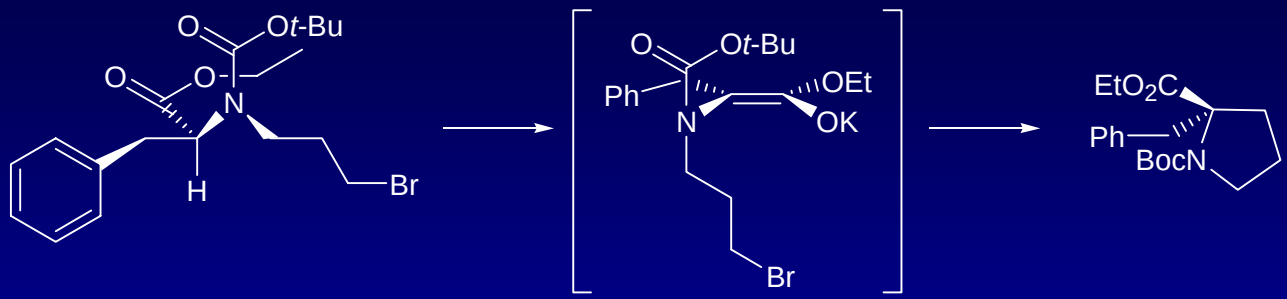


61%, 95% ee



31%, 83% ee

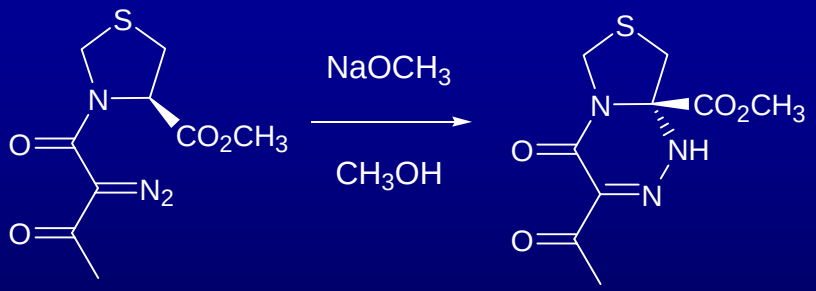
- Other six-membered rings were produced in excellent ee (94-97%)



Favored conformation

Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012.

Additional Applications of Memory of Chirality Strategy

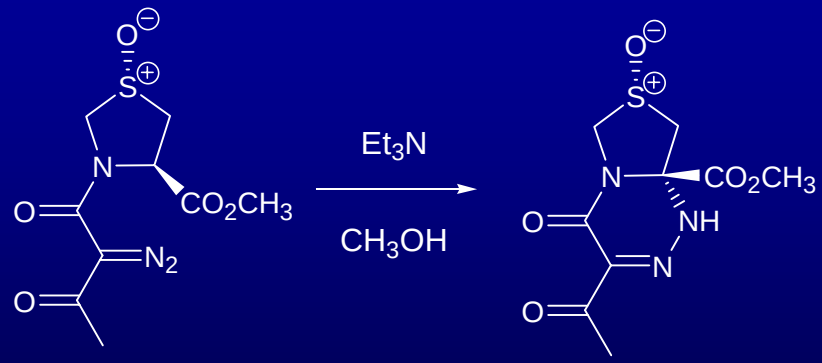


Et_3N, CH_3OH = 65%

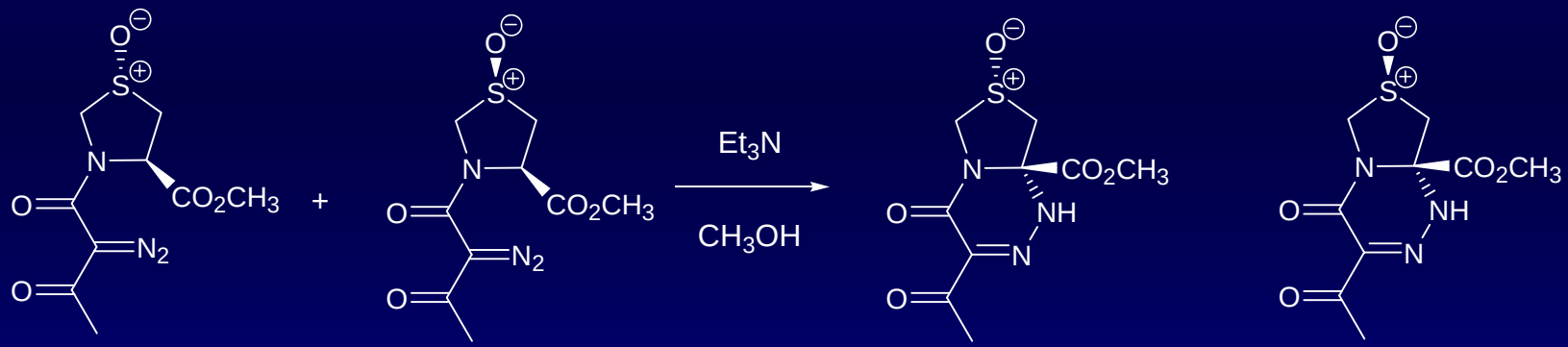
- NMR studies of SM indicate presence of three rotamers

Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Perkin Trans. I* **1993**, 1761-1770.

Extension of Methodology: Cyclization of Sulfoxides



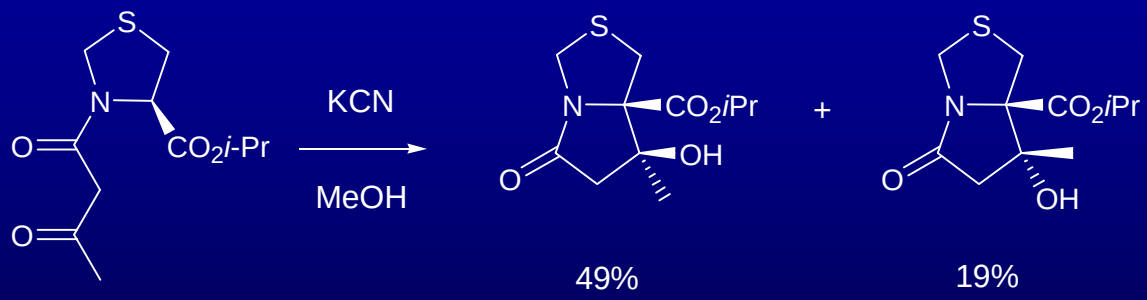
61%



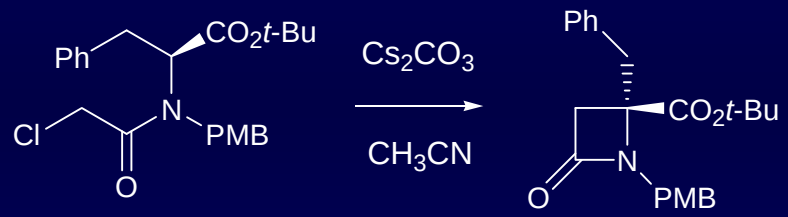
65% 35% 63% 37%

Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Perkin Trans. I*, **1999**, 1067-1072.

Additional Applications - Aldol Cyclization and Azetidinone Closure



49% 19%



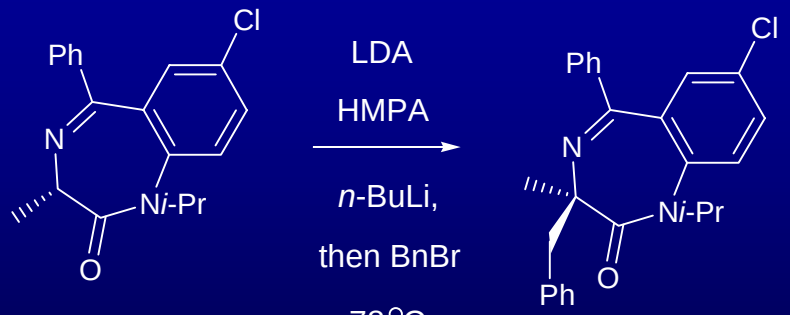
53%, 56% ee

- Enantioselectivity highly substrate dependent (0-50% ee)

- No specific models proposed - however, existence of axial chirality proposed

Brewster, A. G.; Frampton, C. S.; Jayatissa, J.; Mitchell, M. B.; Stoodley, R. *J. Chem. Commun.* **1998**, 299.
Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; Garcia-Lopez, M. T.; Gonzalez-Muniz, R. *J. Org. Chem.* **2001**, *66*, 3538.

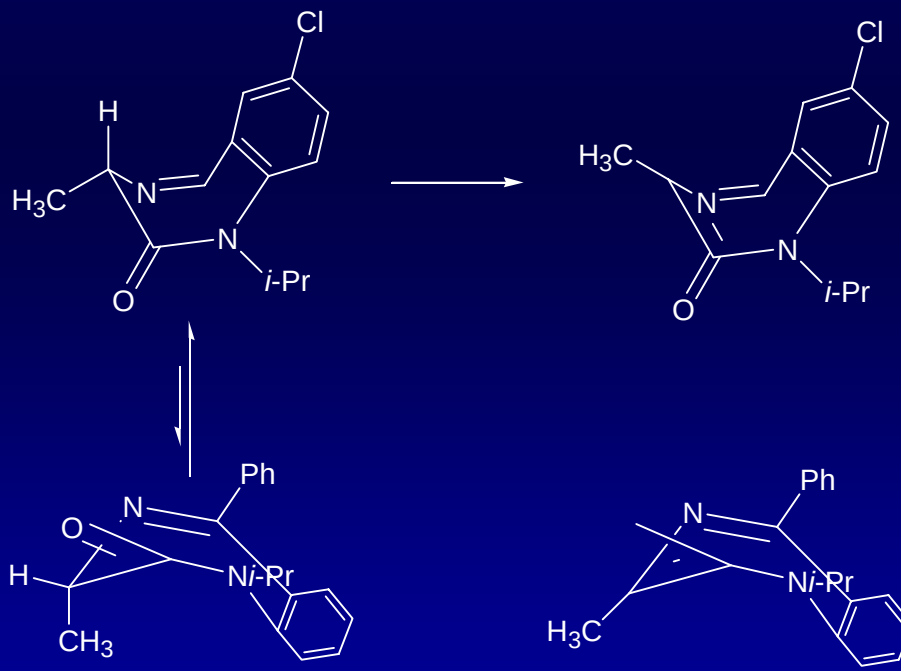
Memory of Chirality in Benzodiazepines



74%, 97% ee

- With *N*-Me amide: 0% ee

- Alkylation with other electrophiles (Me, allyl, 2-$PhC_6H_4CH_2$, 4-$MeC_6H_4CH_2$) all proceed with 94-99% ee



0.0 kcal/mol

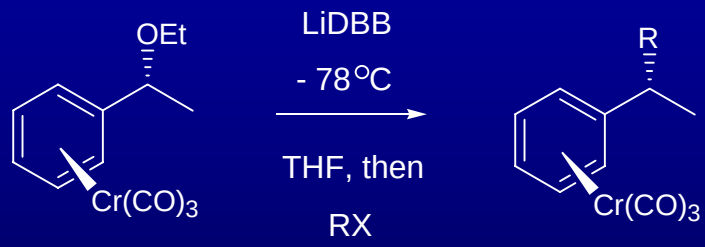
$t_{1/2}$(inversion) = 970 hours @ -78°C

+ 17.5 kcal/mol

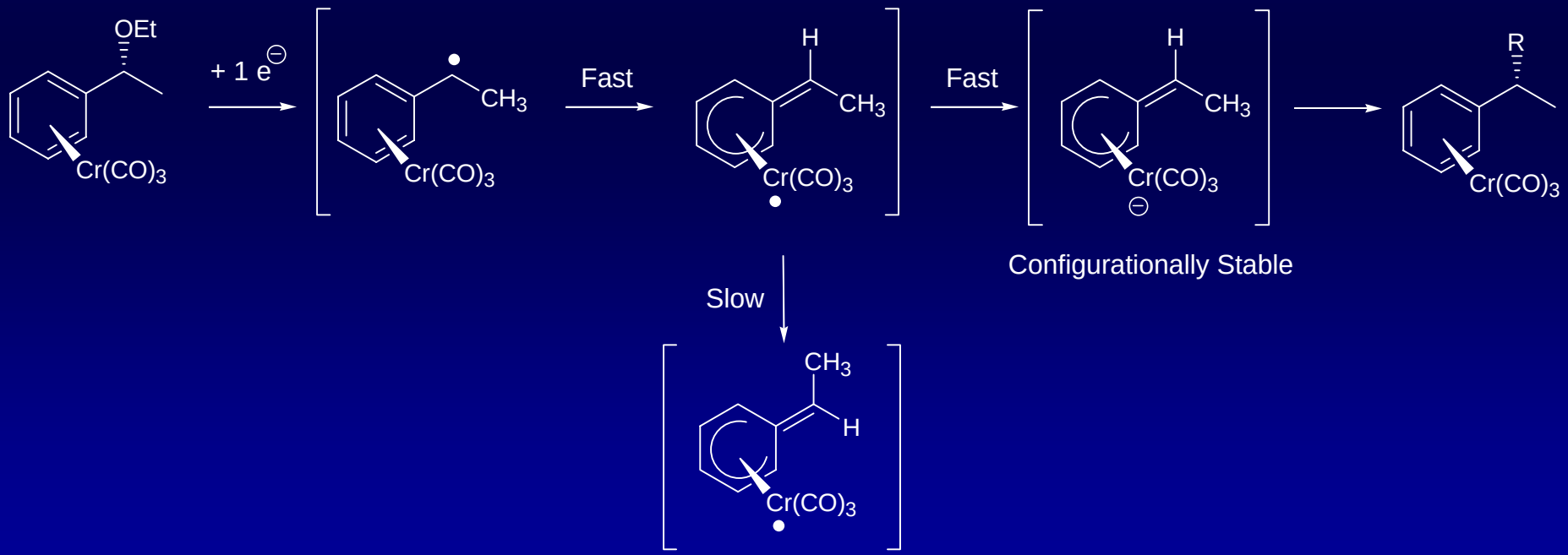
- Factors which lead to attack of electrophile on concave face yet to be determined

Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P.C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 11482.

Memory of Chirality in Radical Chemistry



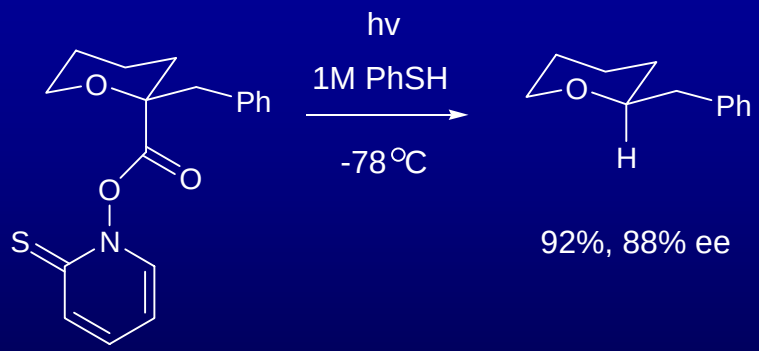
R = TMSCl; 72%, 87% ee
R = $PhCH_2Br$; 37%, 87% ee
R = $CH_3OC(O)Cl$; 67%, 86% ee
R = $(CH_3)_2NC(O)Cl$; 57%, 84% ee



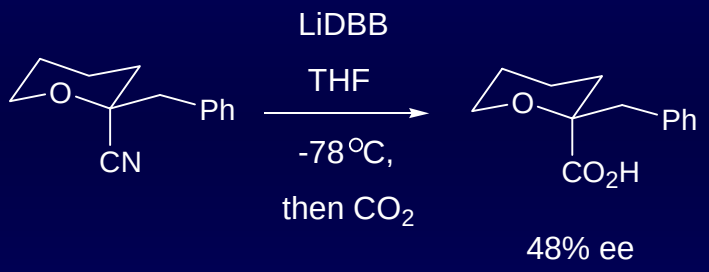
Configurationally Stable

Schmalz, H.-G.; Koning, C. B. D.; Bernicke, D.; Siegel, S.; Pfletschinger, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1620.

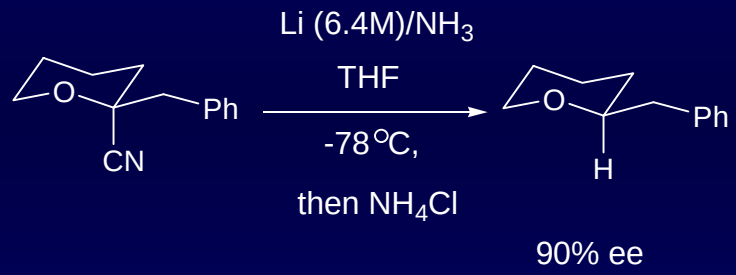
Reaction of Pyranyl Radicals



92%, 88% ee



48% ee



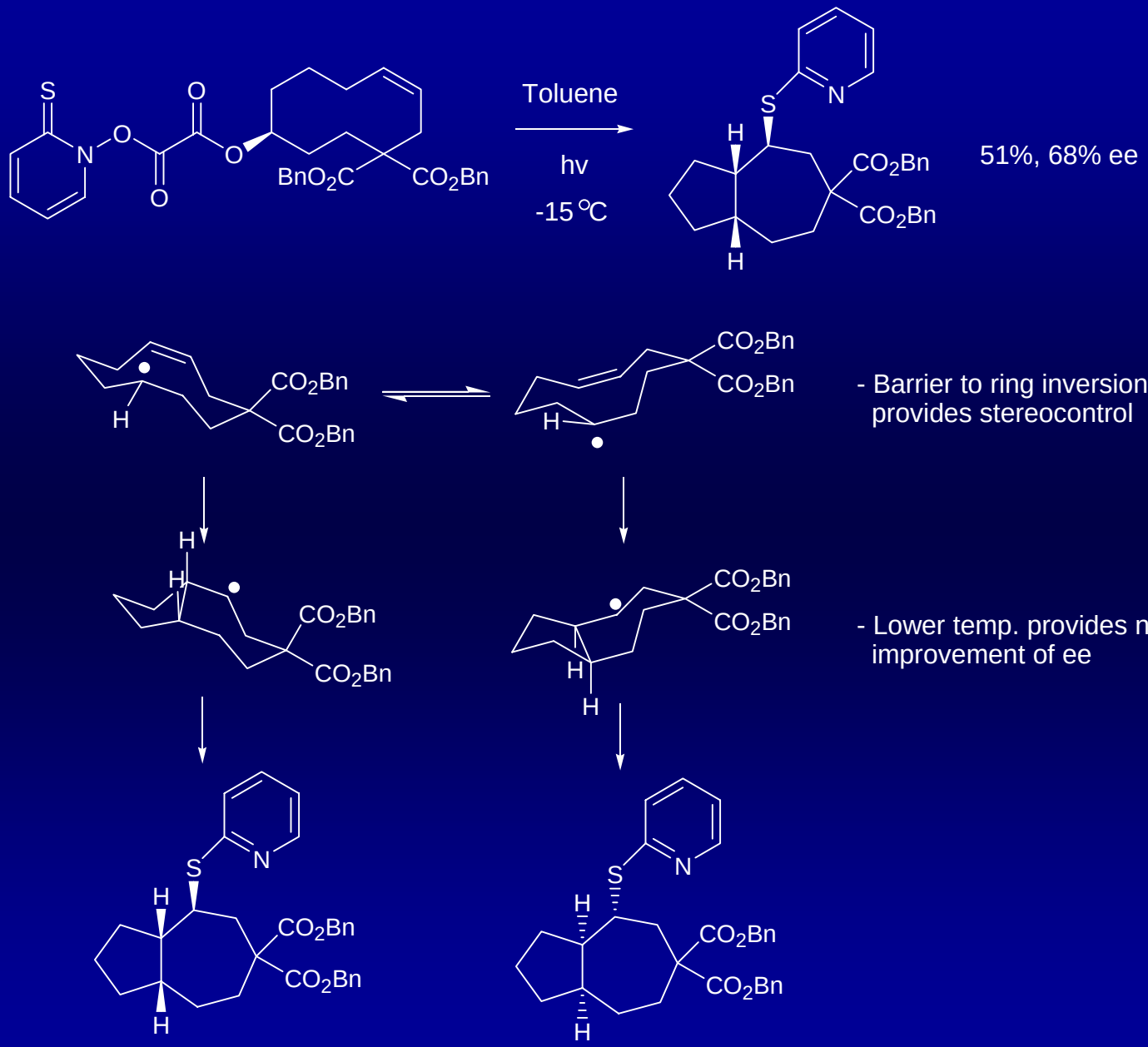
90% ee

- Memory of original chiral center retained due to ring conformational preference

- Furanyl radicals exhibit no enantioselectivity

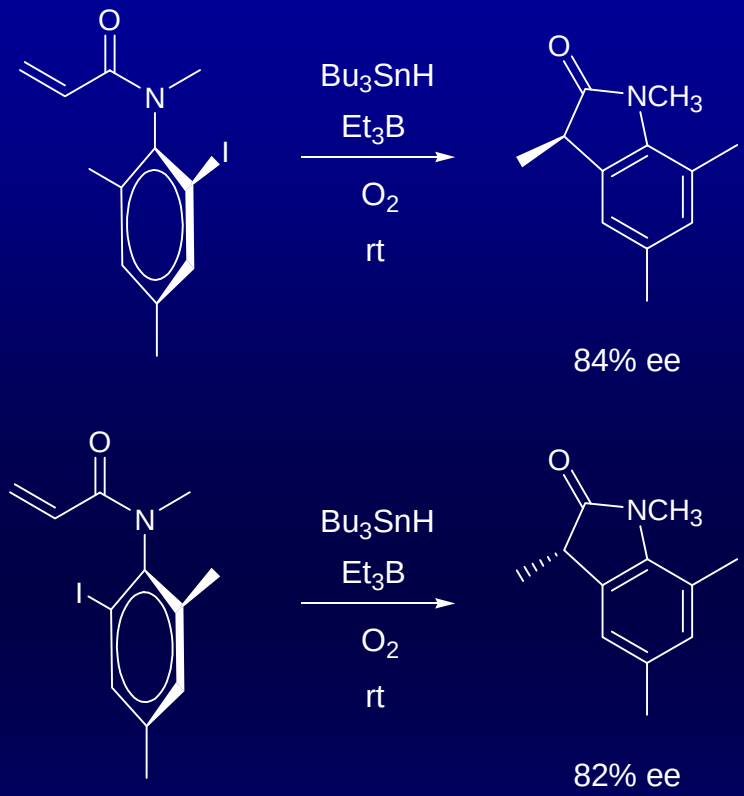
Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386.

Radical Cyclization of Cyclodecenyl Systems



Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2713-2716.

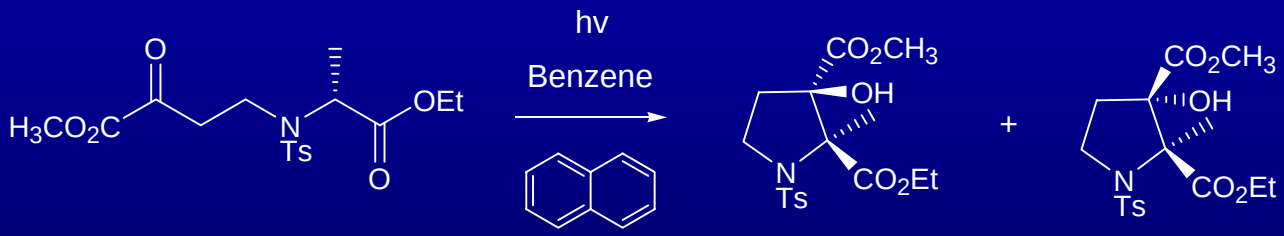
Radical Cyclization of Haloacrylanilides

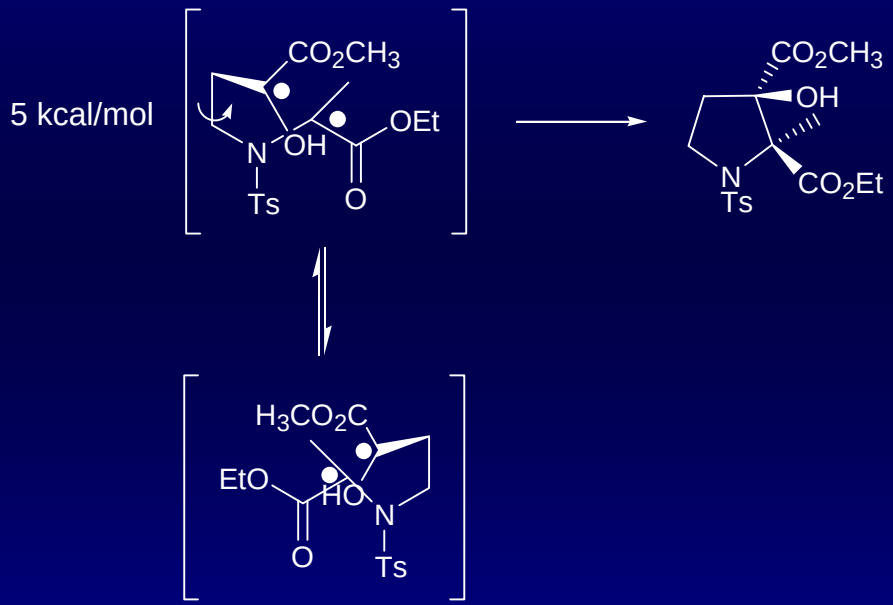


- Chirality of atropisomer is maintained in radical - cylization proceeds faster than isomerization

Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012-11013.

Radical Cyclization to Substituted Pyrrolidines



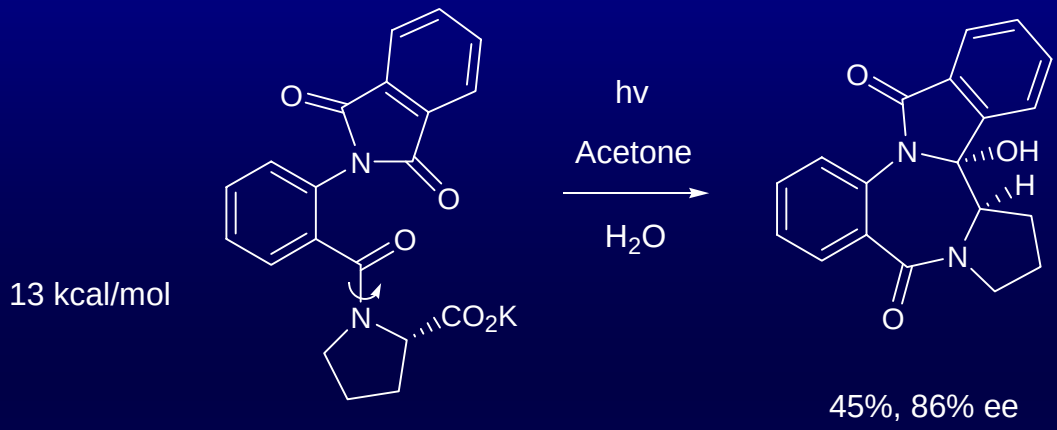


- When reaction is performed in the presence of a triplet sensitizer, no diastereoselectivity or enantionselectivity is observed

Giese, B.; Wettstein, P.; Stahelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessig, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 2586-2587.

Sinicropi, A.; Barbosa, F.; Basosi, R.; Giese, B.; Olivucci, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2390-2393.

Cyclization via Photodecarboxylation

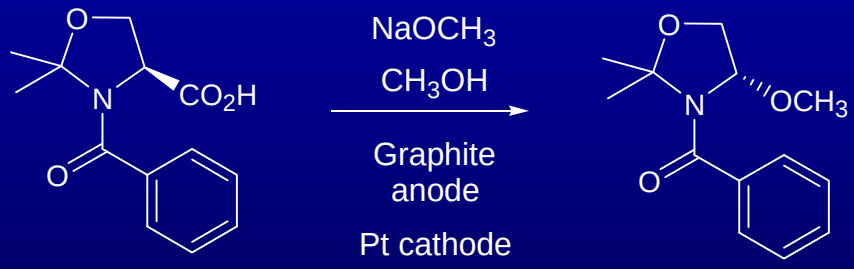


45%, 86% ee

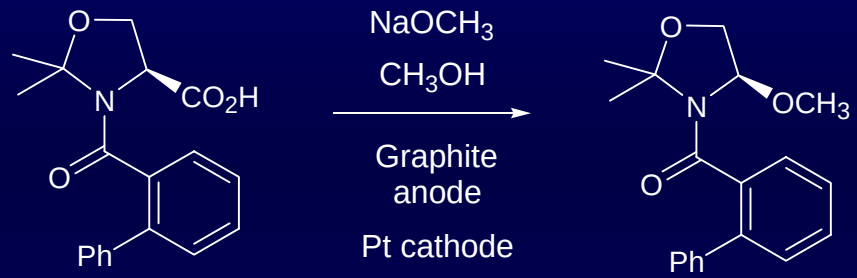
- Via triplet diradical

Griesbeck, A. G.; Kramer, W.; Lex, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 577.

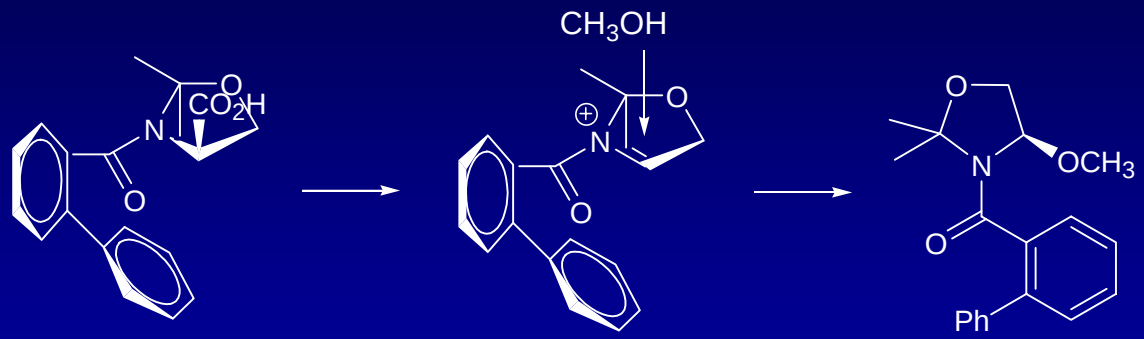
MOC via a Carbocationic Intermediate



69%, 39% ee



69%, 39% ee



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Conclusions

- Memory of chirality represents an emerging strategy in the field of stereoselective synthesis

- This method takes advantage of the dynamic, conformational chirality present in systems with restricted rotation about single bonds

- Requires no external sources of chirailty

- Highly time, temperature, and substrate dependent

- Primary application has been in the area of enolate chemistry - limited number of examples involving radical and carbocationic intermediates