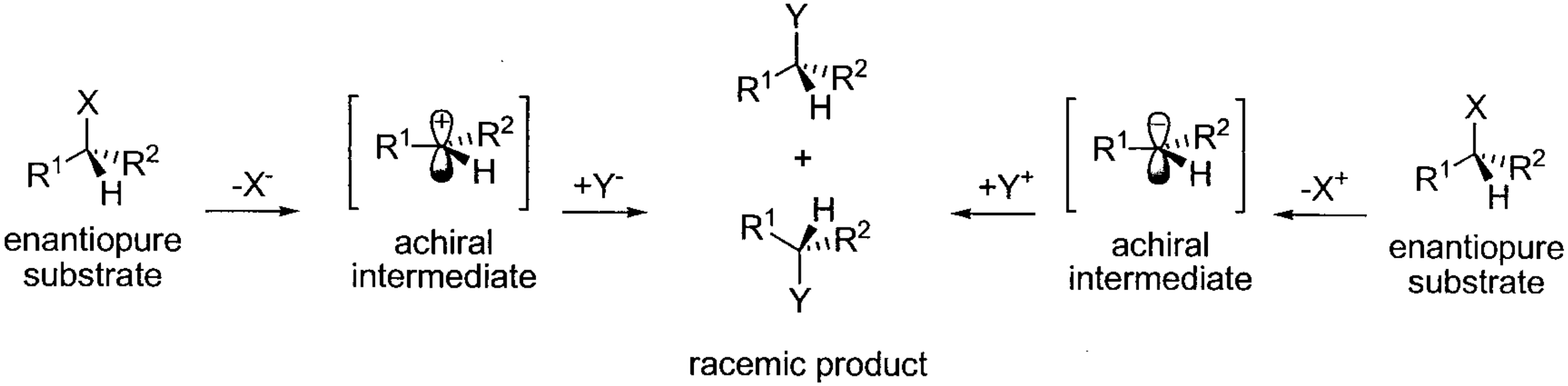
Stereochemical Memory Effects in Alkene Radical Cation/Anion Contact Ion Pairs: Effect of Substituents, and Models for Diastereoselectivity

Crich, D.; Ranganathan, K. *J. Am. Chem. Soc.* **2005**, *ASAP.*

Department of Chemistry, University of Illinois at Chicago,

Chicago, IL 60607.

Lessons From First Principles: Destruction of Chirality Through Trigonalization



Zhao, H. *et al. Synthesis* **2005**, *1*, 1.

Stereochemical Memory Effects

- *"central chirality at a carbon alpha to a carbonyl group is preserved as transient axial chirality of the intermediate enolate and is then regenerated as central chirality in the reaction product (memory of chirality)"*

  – Kawabata *et al. J. Am. Chem. Soc.* **1991**, *113,* 9694.

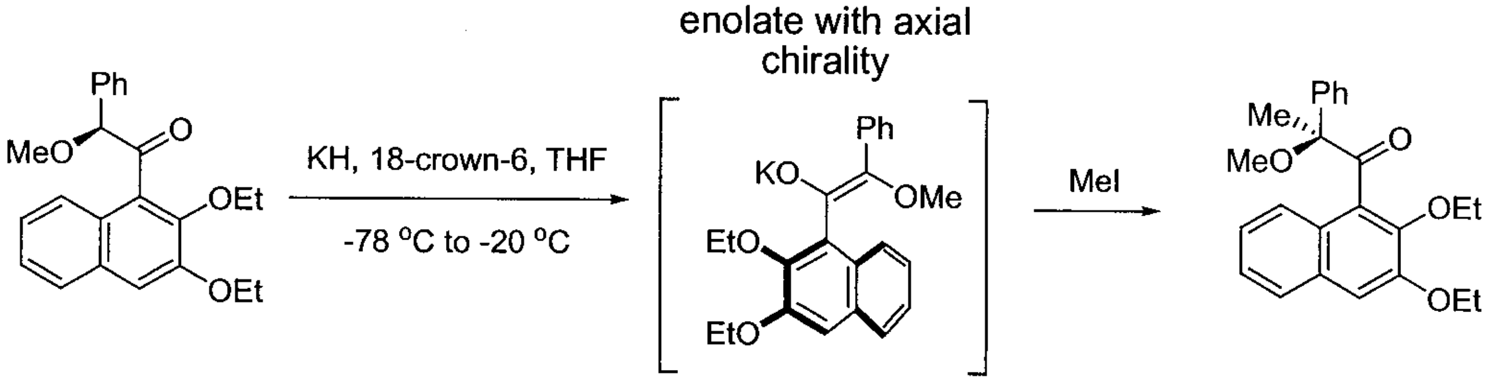
- a case in which "*the chirality of the starting material is preserved in a reactive intermediate for a limited time*"

  – Fuji, K. *et al. Chem.–Eur. J.* **1998**, *4*, 373.

- *"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"*

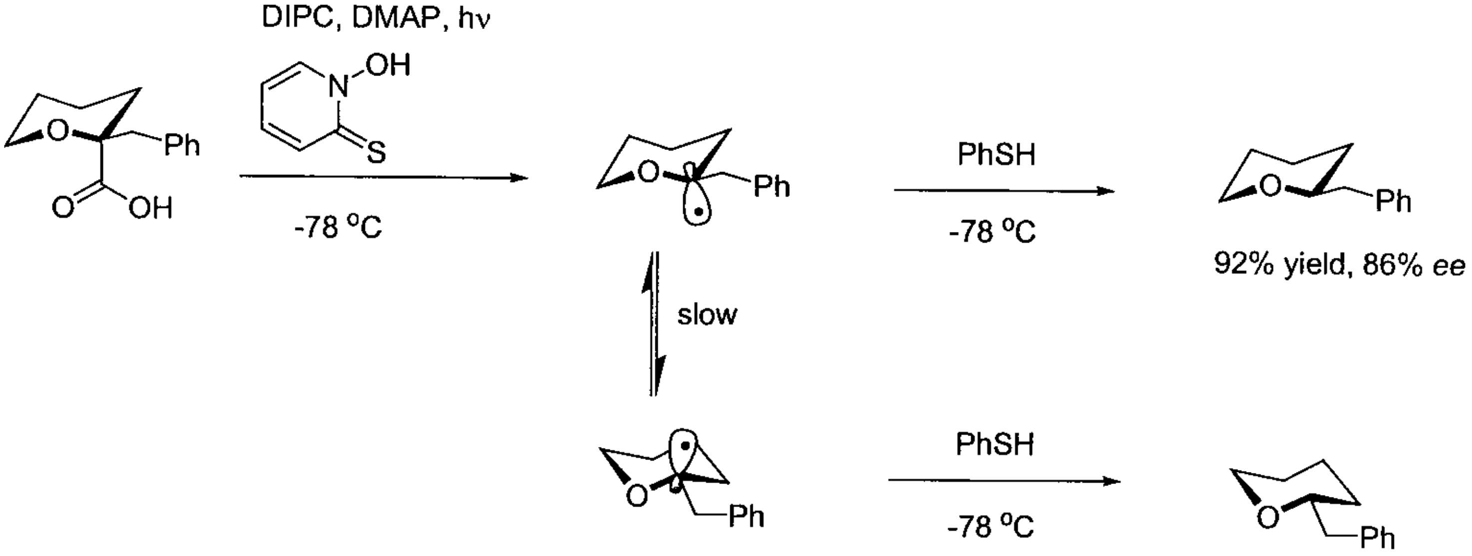
  –Zhao, H. *et al. Synthesis* **2005**, *1*, 1.

Examples of Stereochemical Memory Effects: Enolate Additions



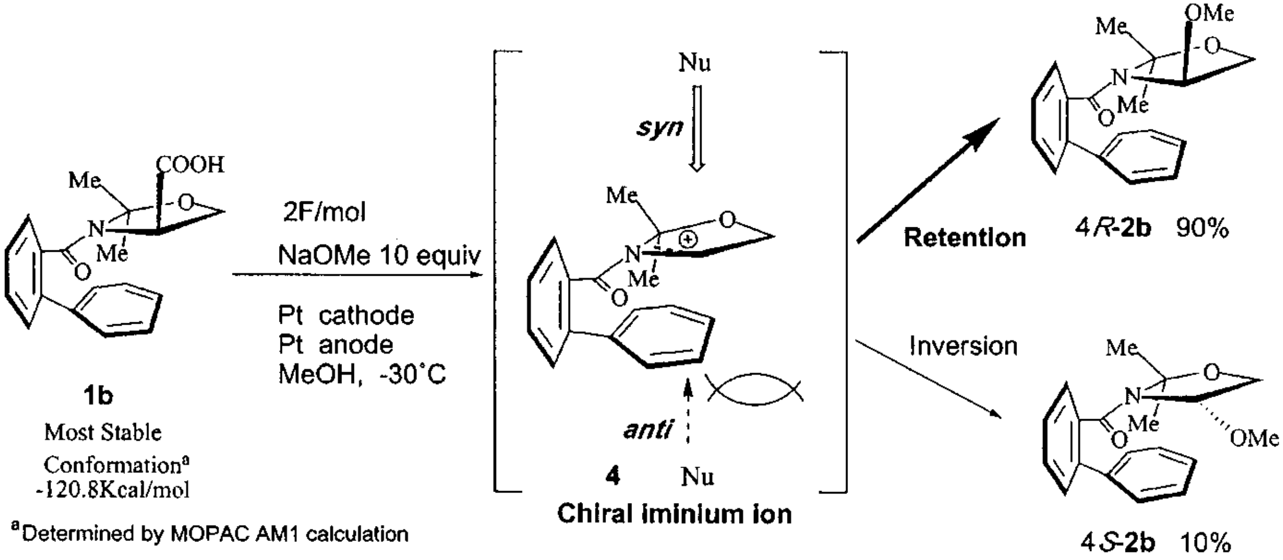
Kawabata, T. *et al.* *J. Am. Chem. Soc.* **1991**, *113*, 9694.

Examples of Stereochemical Memory Effects: Radical Trapping



Buckmelter, A. J. *et al. J. Am. Chem. Soc.* **2000**, *122*, 9386.

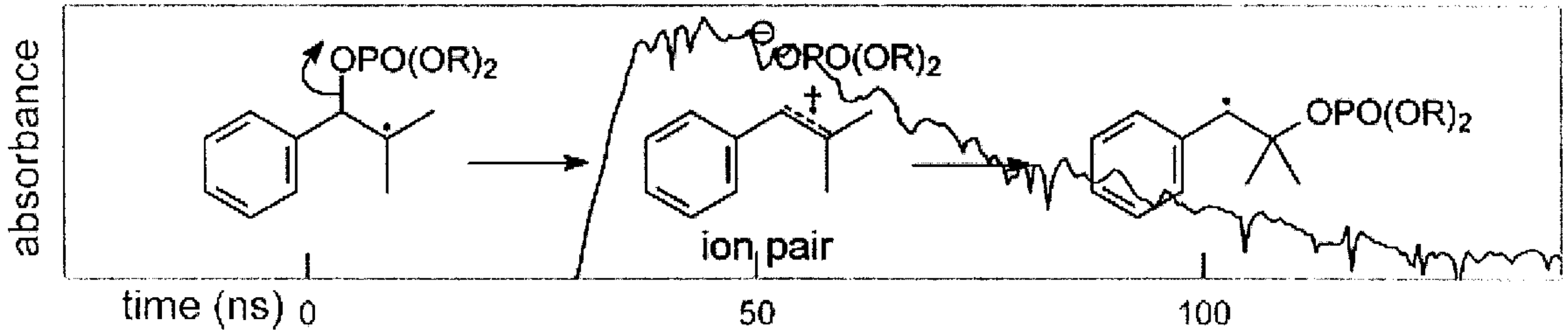
Examples of Stereochemical Memory Effects: Nucleophilic Additions to Cationic Intermediates



[a] Determined by MOPAC AM1 calculation.

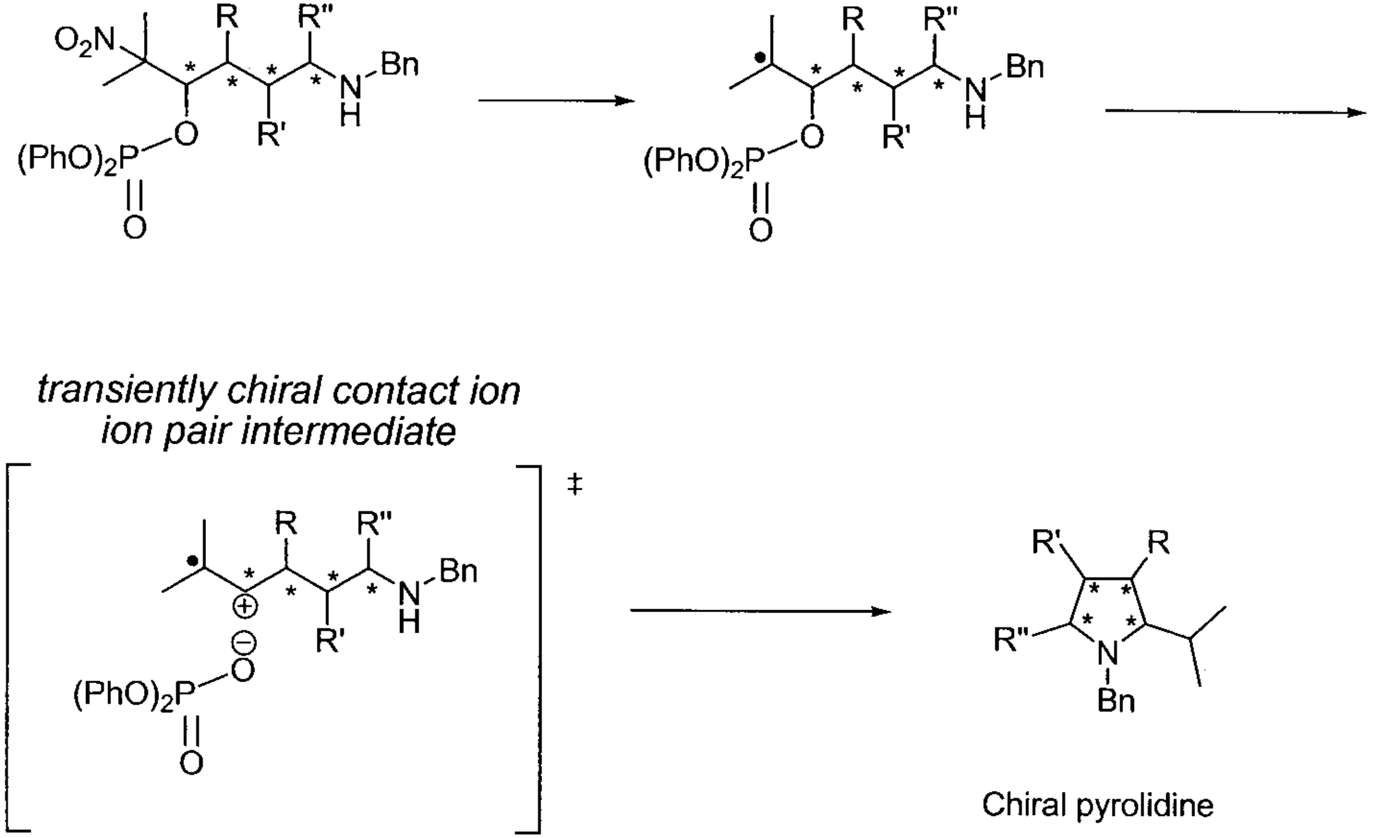
Matsumura, Y. *et al. Org. Lett.* **2002**, *4*, 1875.

Enter β-(Phosphatoxy)alkyl Radicals: Potential Applications for Stereochemical Memory Effects



Bagnol, L. *et al. Org. Lett.* **2003**, *5*, 5055.

Experimental Design



transiently chiral contact ion ion pair intermediate

Chiral pyrolidine

Crich, D. *et al. J. Am. Chem. Soc.* **2005**, *ASAP*.

Table 1. Radical–Ionic Cascade Reactions[16]

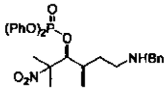
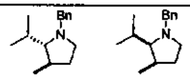
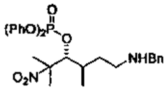
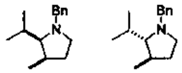
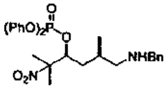
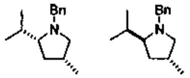
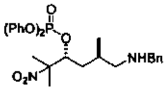
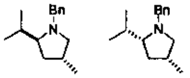
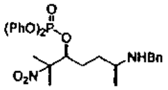
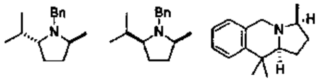
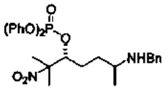
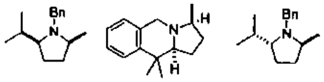
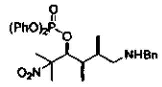
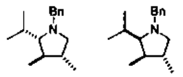
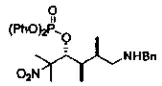
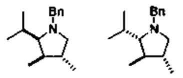
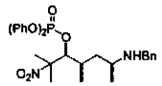
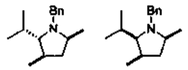
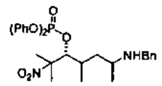
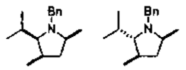
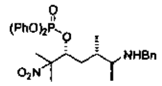
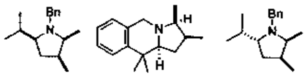
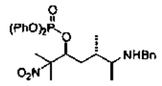
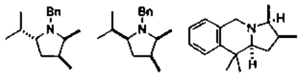
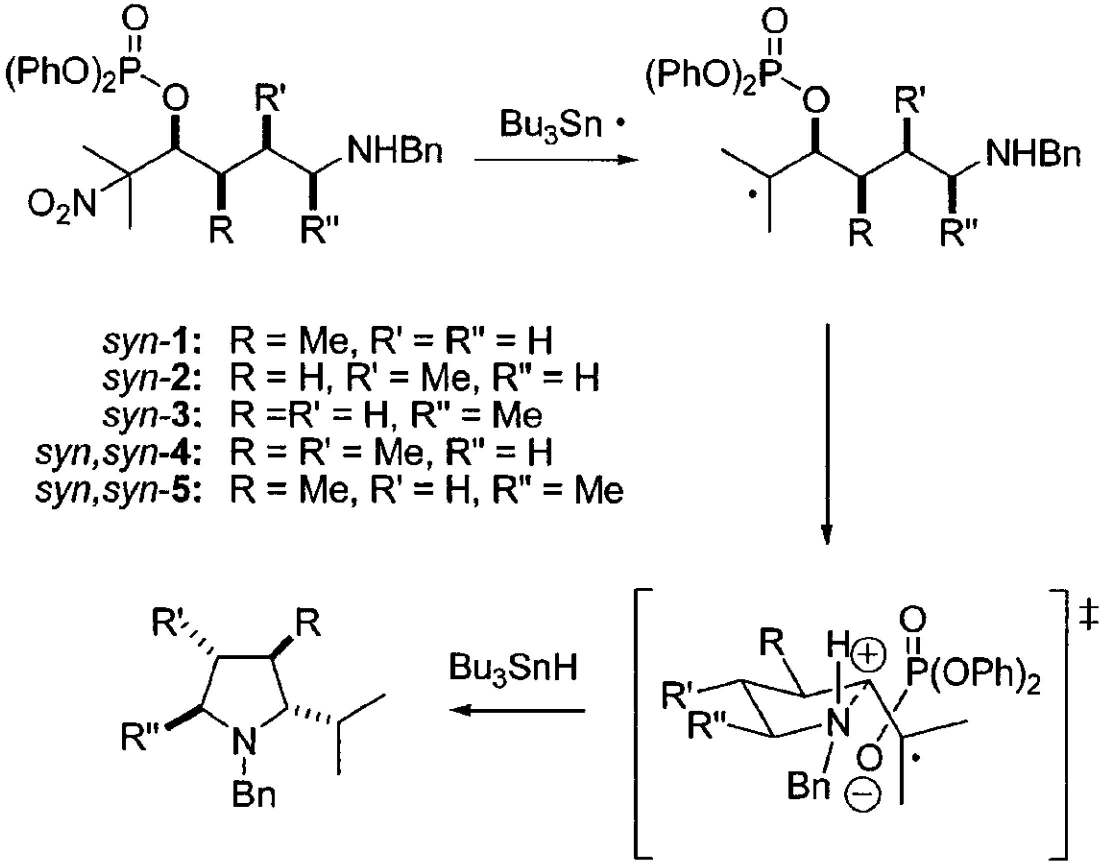
Entry	Substrate	Products, ratio	% Yield	% de	Major Mode[a]
1	 *syn*-**1**, 93% de	 *trans*-**7**, *cis*-**7** >25:1	50,	>95	inv.
2	 *anti*-**1**, 87% de	 *cis*-**7**, *trans*-**7** 1:2.4	45	40	ret.
3	 *syn*-**2**, 94% de	 *cis*-**8**, *trans*-**8** 13:1	56	86	inv
4	 *anti*-**2**, 87% de	 *trans*-**8**, *cis*-**8** 18:1	52	89	inv
5	 *syn*-**3**, 88% de	 *trans*-**9**, *cis*-**9**, **10** (*cis*-) 13:3:1	52	53	inv
6	 *anti*-**3**, 92% de	 *cis*-**9**, **10** (*cis*-), *trans*-**9** 4.2:1.7:1.0	51	71	inv

Table 1. Radical–Ionic Cascade Reactions[16]

Entry	Substrate	Products, ratio	% Yield	% de	Major Mode[a]
7	 *syn,syn*-**4**, 85% de	 *trans,trans*-**11**, *cis,trans*-**11** 16:1	38	88	inv
8	 *anti,syn*-**4**, 100% de	 *cis,trans*-**11**, *trans,trans*-**11** 1:1.7	49	26	ret
9	 *syn,syn*-**5**, 91% de	 *trans,cis*-**12**, *cis,cis*-**12** >29:1	49	>93	inv
10	 *anti,syn*-**5**, 100% de	 *cis,cis*-**12**, *trans,cis*-**12** 1:1.1	40	5	ret
11	 *syn,anti*-**6**, 100% de	 *cis,cis*-**13**, **14** (*cis,cis*), *trans,cis*-**13** 7.0:2.5:1.0	56	81	inv
12	 *anti,anti*-**6**, 100% de	 *trans,cis*-**13**, *cis,cis*-**13**, **14** (*cis,cis*) 13:2.8:1.0	55	55	inv

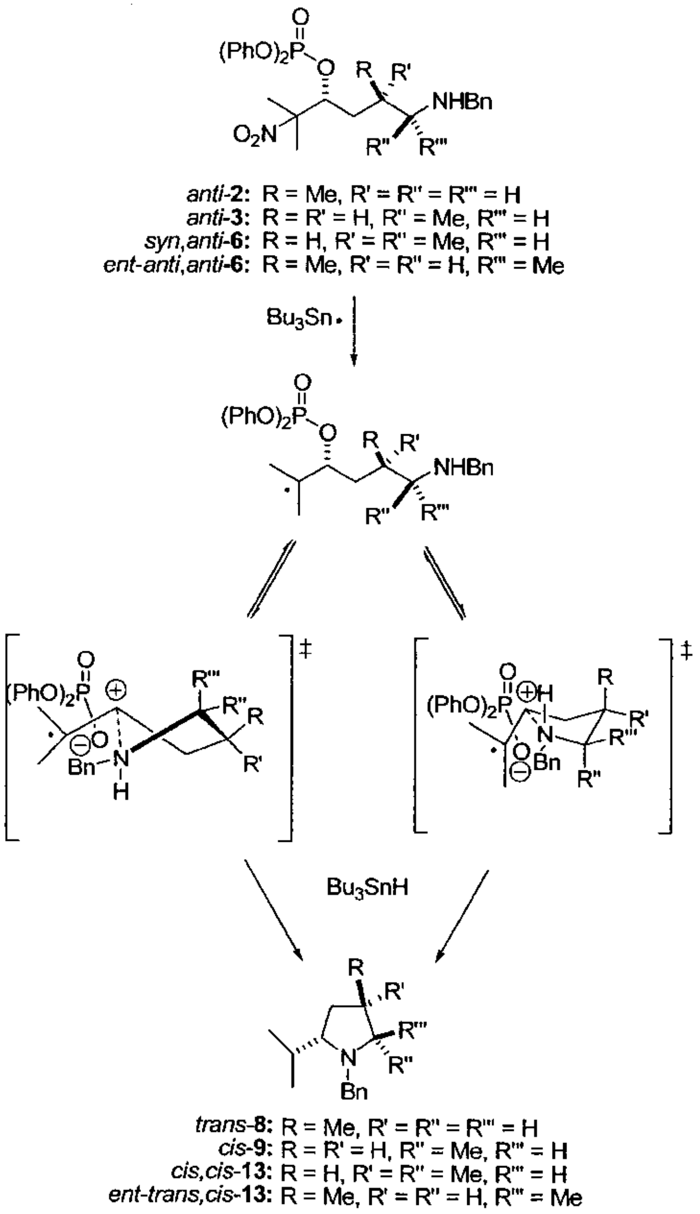
Scheme 1. Transition State Model A: All Pseudo-equatorial



syn-**1:** R = Me, R' = R" = H
syn-**2:** R = H, R' = Me, R" = H
syn-**3:** R =R' = H, R" = Me
syn,syn-**4:** R = R' = Me, R" = H
syn,syn-**5:** R = Me, R' = H, R" = Me

trans-**7:** R = Me, R' = R" = H
cis-**8:** R = H, R' = Me, R" = H
trans-**9:** R =R' = H, R" = Me
trans,trans-**11:** R = R' = Me, R" = H
trans,cis-**12:** R = Me, R' = H, R" = Me

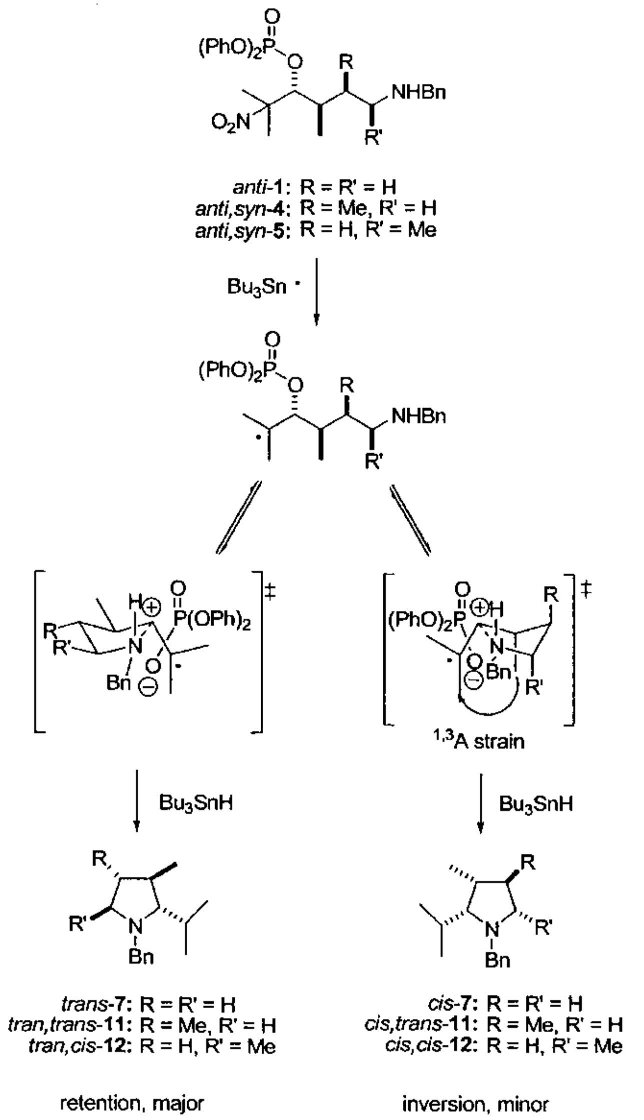
Scheme 2. Transition State Model B: Twist-Boats[18]



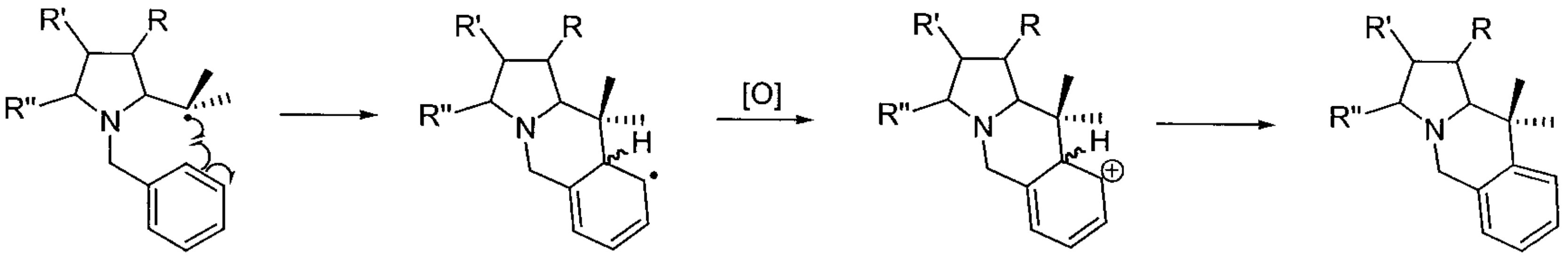
anti-**2**: R = Me, R' = R'' = R''' = H
anti-**3**: R = R' = H, R'' = Me, R''' = H
syn,anti-**6**: R = H, R' = R'' = Me, R''' = H
ent-anti,anti-**6**: R = Me, R' = R'' = H, R''' = Me

trans-**8**: R = Me, R' = R'' = R''' = H
cis-**9**: R = R' = H, R'' = Me, R''' = H
cis,cis-**13**: R = H, R' = R'' = Me, R''' = H
ent-trans,cis-**13**: R = Me, R' = R'' = H, R''' = Me

Scheme 3. Transition State Model C: Retention of Configuration



Formation of Pyrrlo[1,2-*b*]isoquinoline Side Products



Conclusions

- Alkene radical cations generated by heterolyic fragmentation of β-(phosphatoxy)alky radicals were demonstrated to undergo highly diastereoselective cyclization reations with suitably positioned nucleophiles
- The most selective cyclization reactions appear to proceed via chair-like transition states, although the possibility of twist-boat-like analogues has not been ruled out.
- 1,2-*anti* relationship between the departing phosphate and a vicinal substituent is highly detrimental to the model, owing to significant ^{1,3}A strain present within the alkene radical cation intermediate, and results in significant equilibration of the intermediate prior to quenching with he nucleophile.
- Systems possessing a substituent geminal to the amine often undergo a second oxidative radical cyclization leading to the formation of hexahydropyrrolo[1,2-*b*]isoquinolines.