$A^{1,3}$ Strain and the Anomeric Effect

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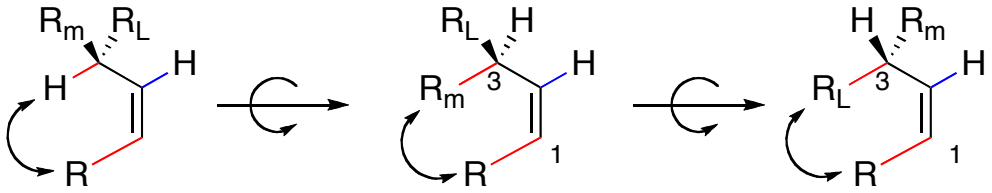
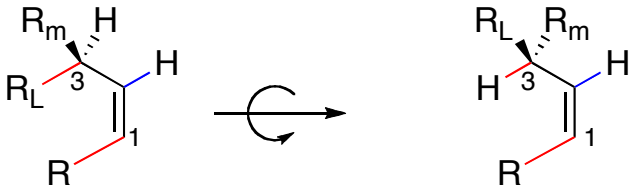
Chem. Topics

Feb. 6, 2012

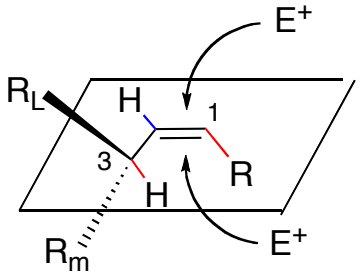
Introduction: Definition of $A^{1,3}$ Strain



Rotation about σ-bond between α-stereocenter and olefin is associated with an energetic cost (steric/van der Waals interaction).



Rotation about allylic stereocenter to a lower energy confirmation = $A^{1,3}$ strain minimization.



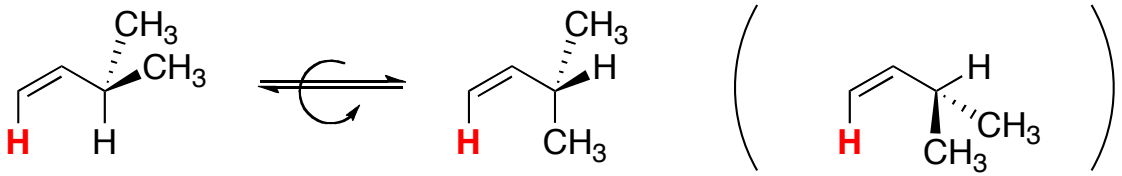
Confirmational preferences based upon minimization of $A^{1,3}$ strain can differentiate diastereofacial faces of pro-chiral nucleophiles and electrophiles (i.e. π-bonds).

- Can lead to diastereoselective reactions if significant differences in steric bulk are realized between R, R_m, and R_L.

Energy Differences Upon Sigma-Bond Rotation

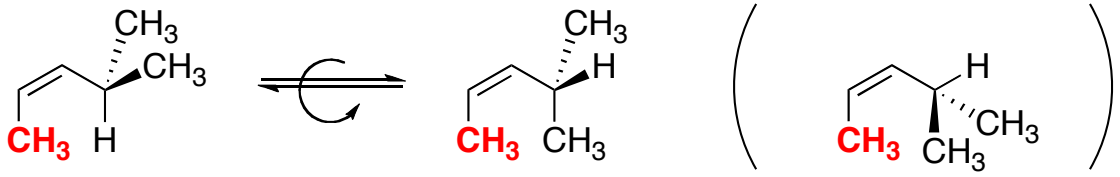
ab initio calculations: MP2-6-31G (Houk)

Mono-substituted olefins:



0 kcal/mol + 0.73 kcal/mol > + 2.0 kcal/mol

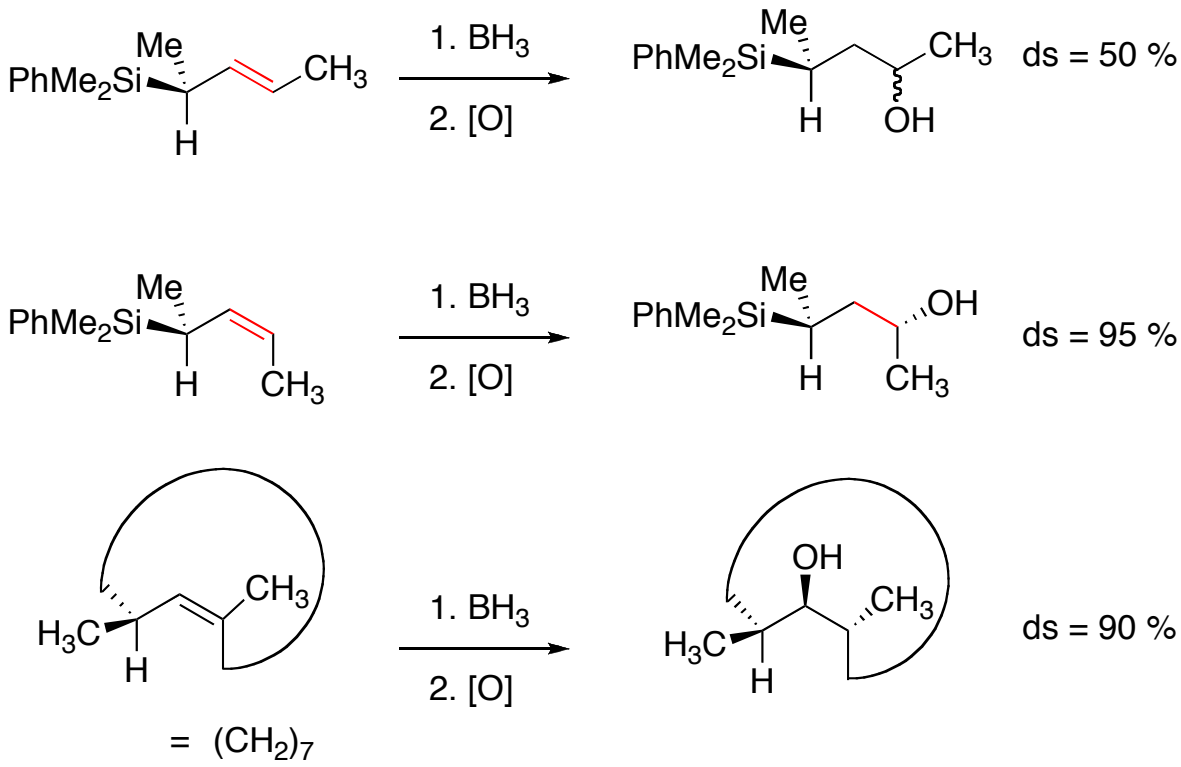
Z-substituted olefins:



0 kcal/mol + > 4.0 kcal/mol > + 3.44 kcal/mol

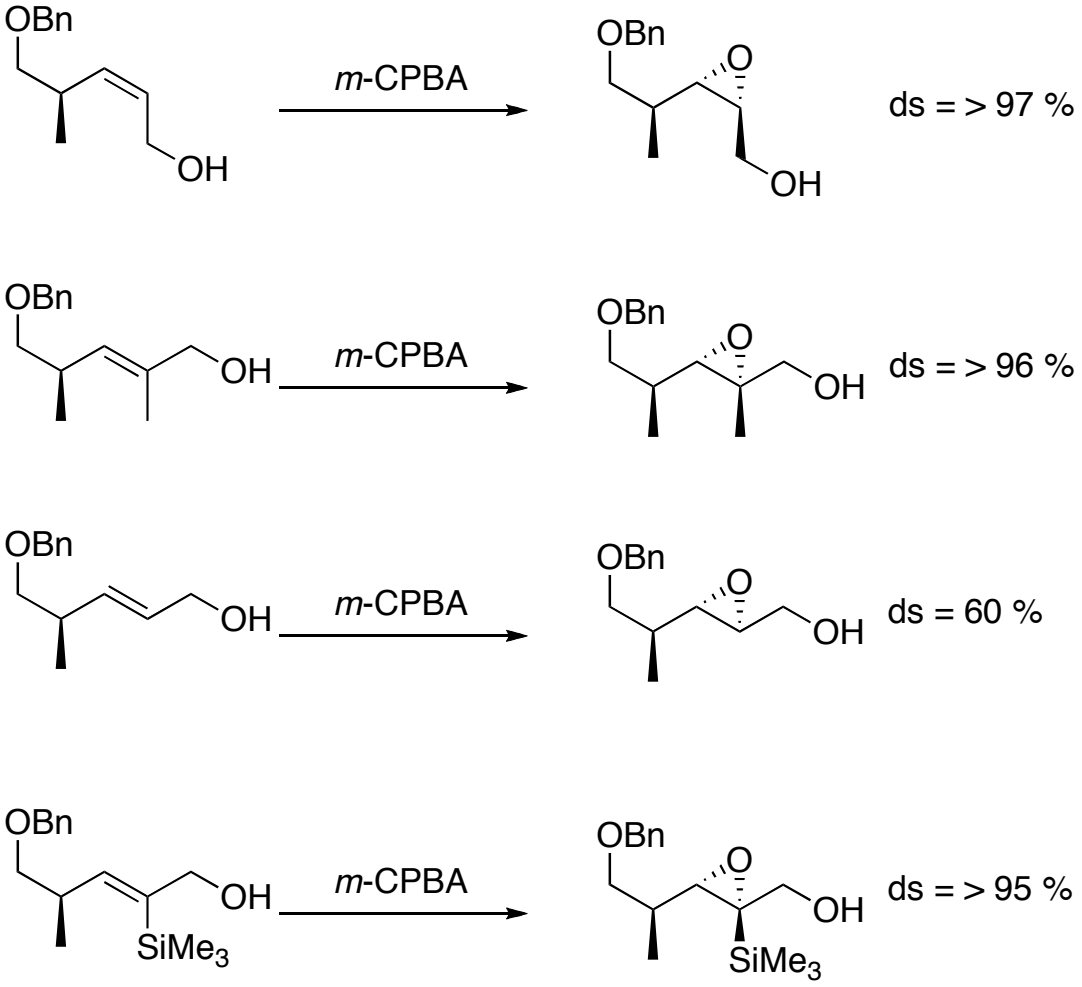
Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1880.

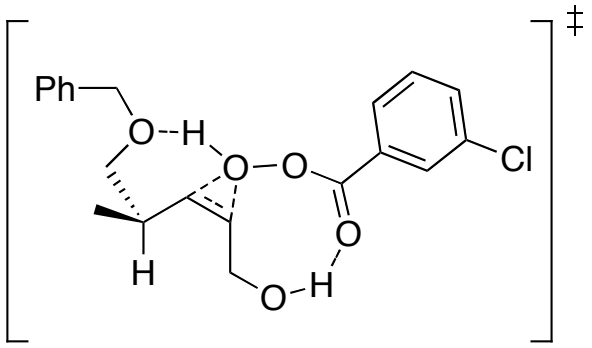
A Warm-Up: Hydroboration



Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1880.

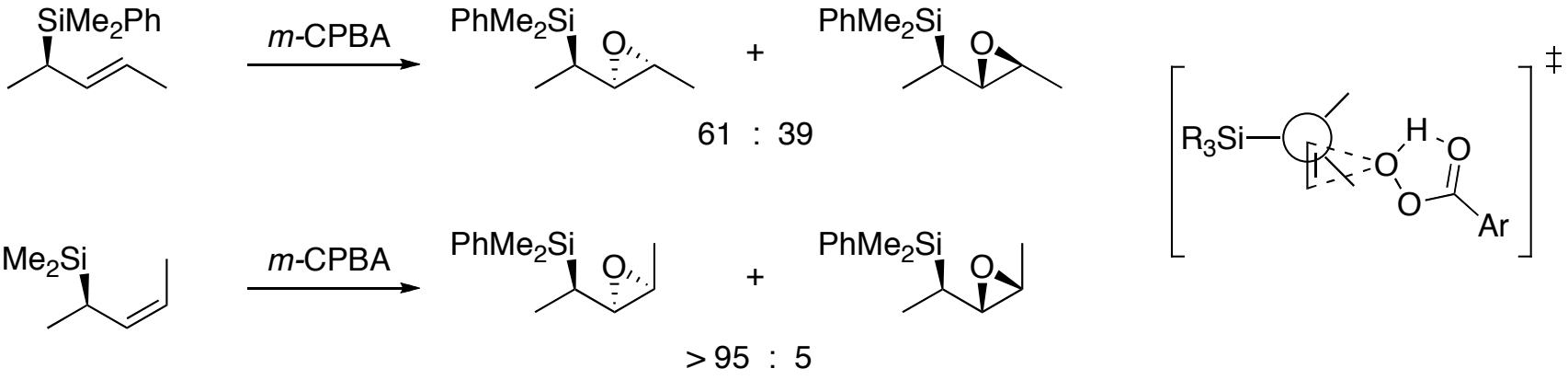
Diastereoselective Epoxidation of Olefins: A Classical Case

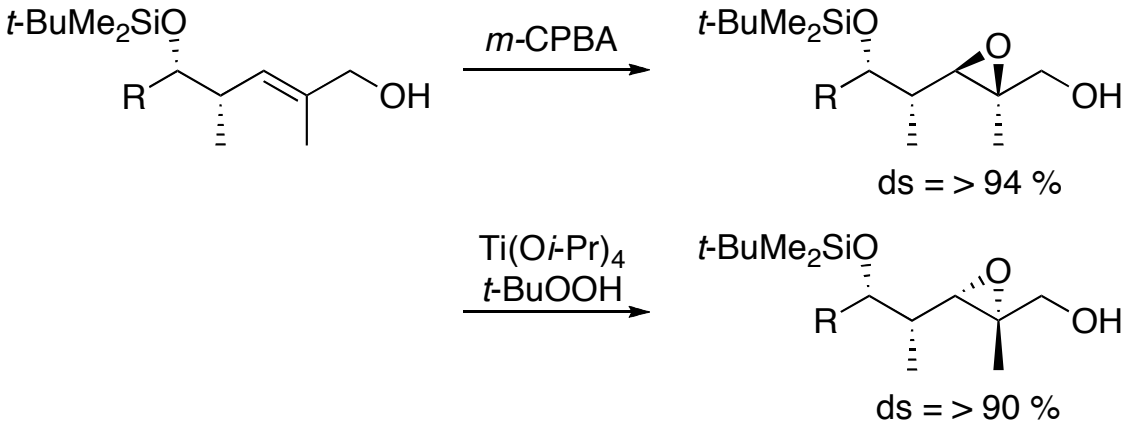


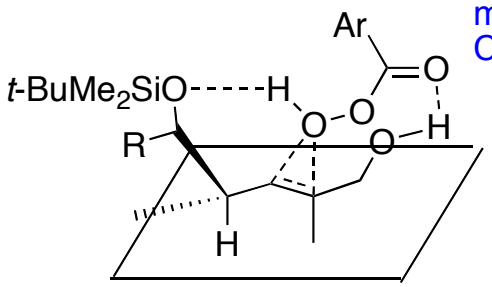


Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1880.

Diastereoselective Epoxidation of Olefins: Allylic Silanes and Siloxyethers







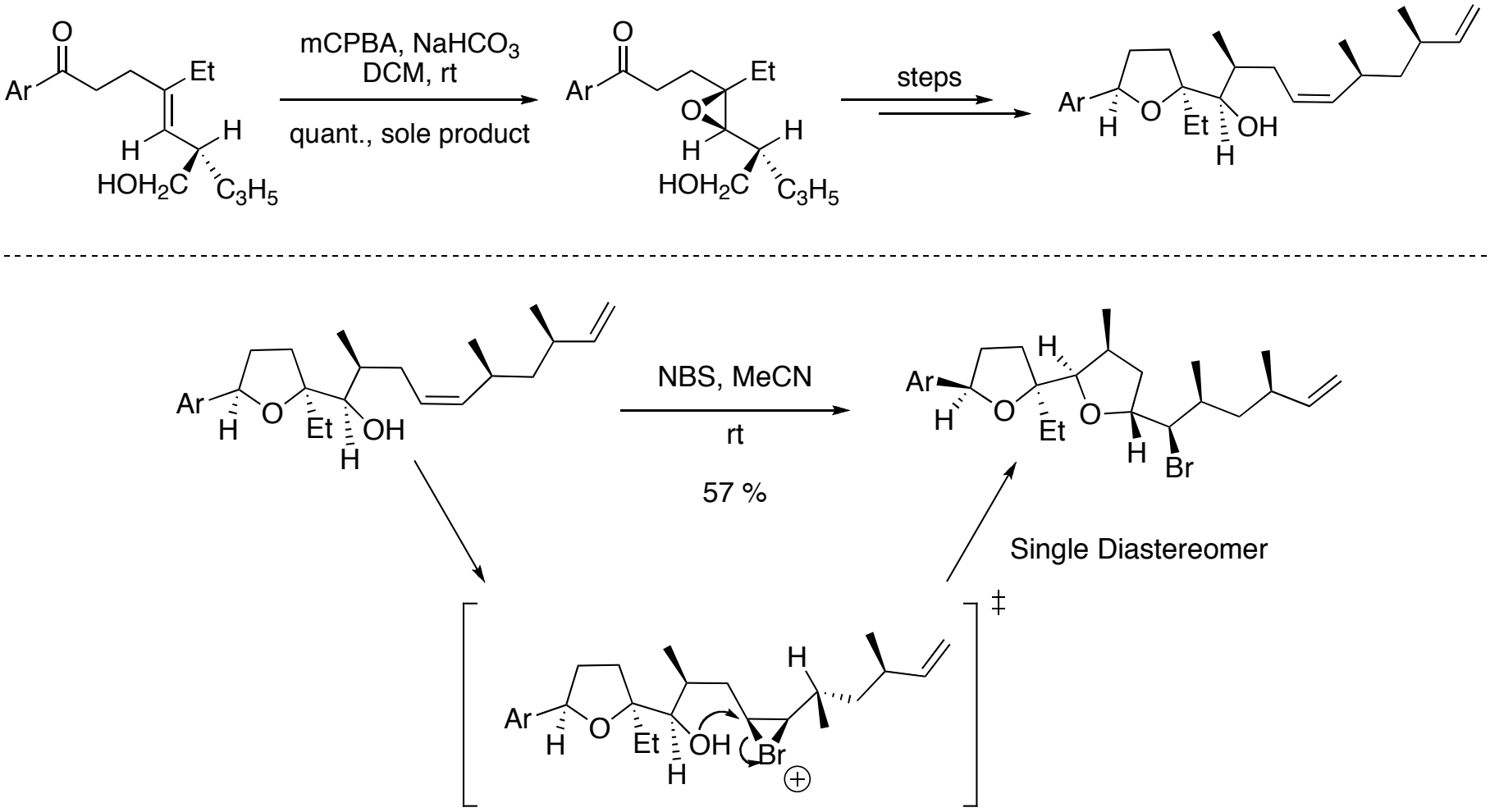
mCPBA Coordination

Minimized $A^{1,3}$ Strain

No Coordination: Attack from less hindered face

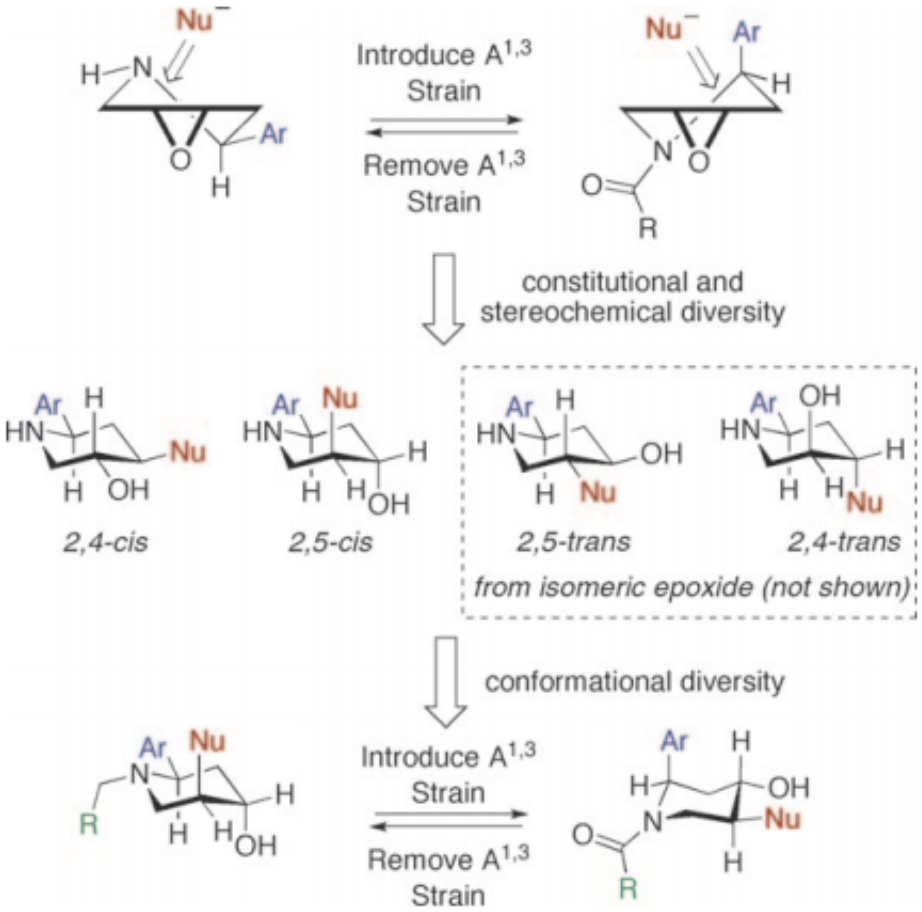
Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1880.

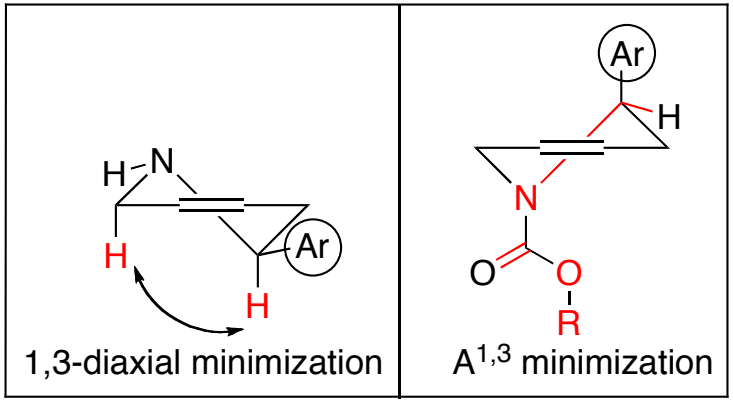
Classical Synthetic Example: Kishi's Total Synthesis of Monensin



Schmid, G.; Fukuyama, T.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260–262.

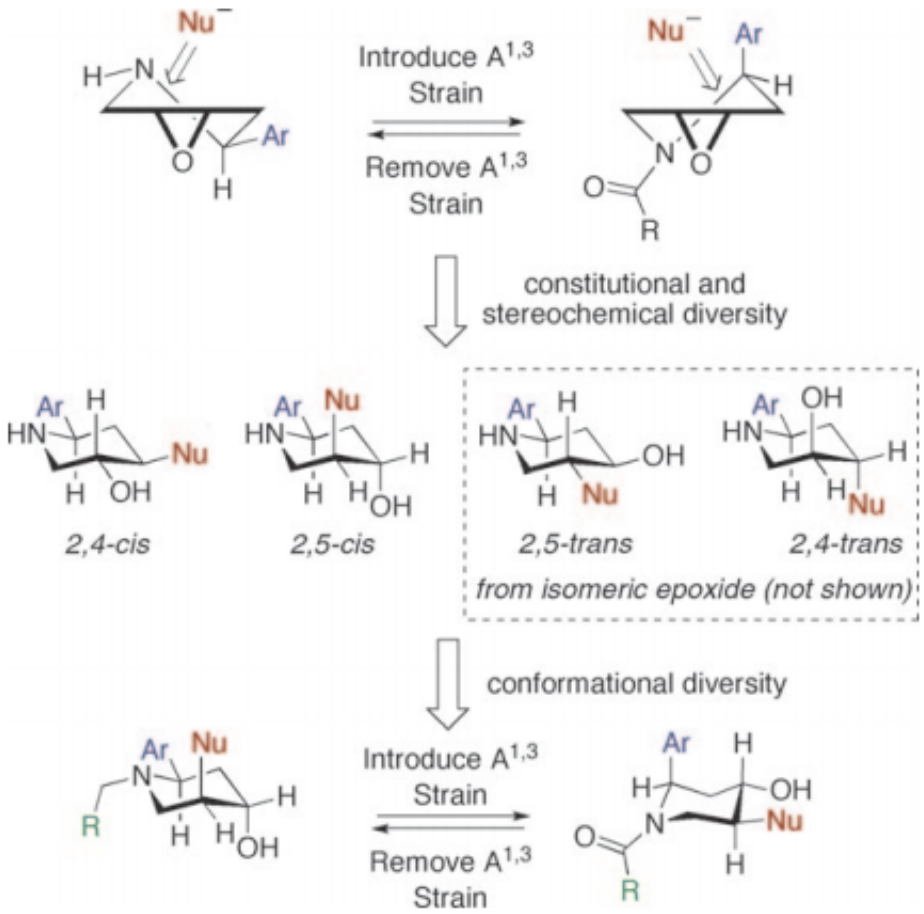
Diastereoselective Epoxidation of Olefins: A Recent Application to Library Synthesis

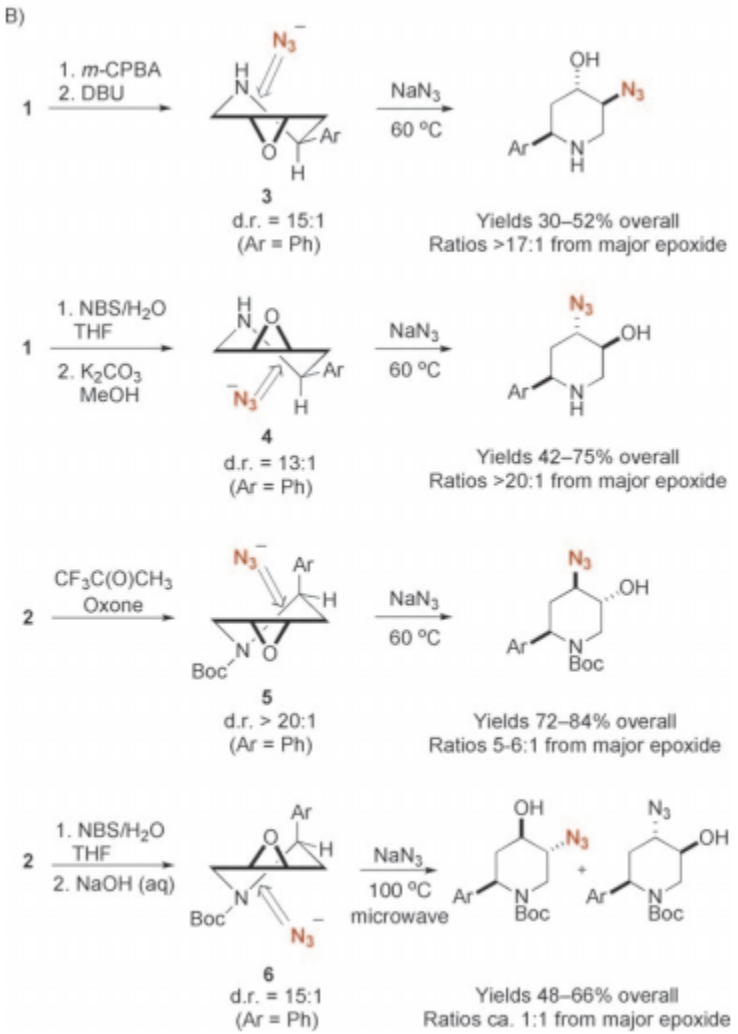




Coombs, T.C.; Lushington, G. H.; Douglas, J.; Aube, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 2734–2737.

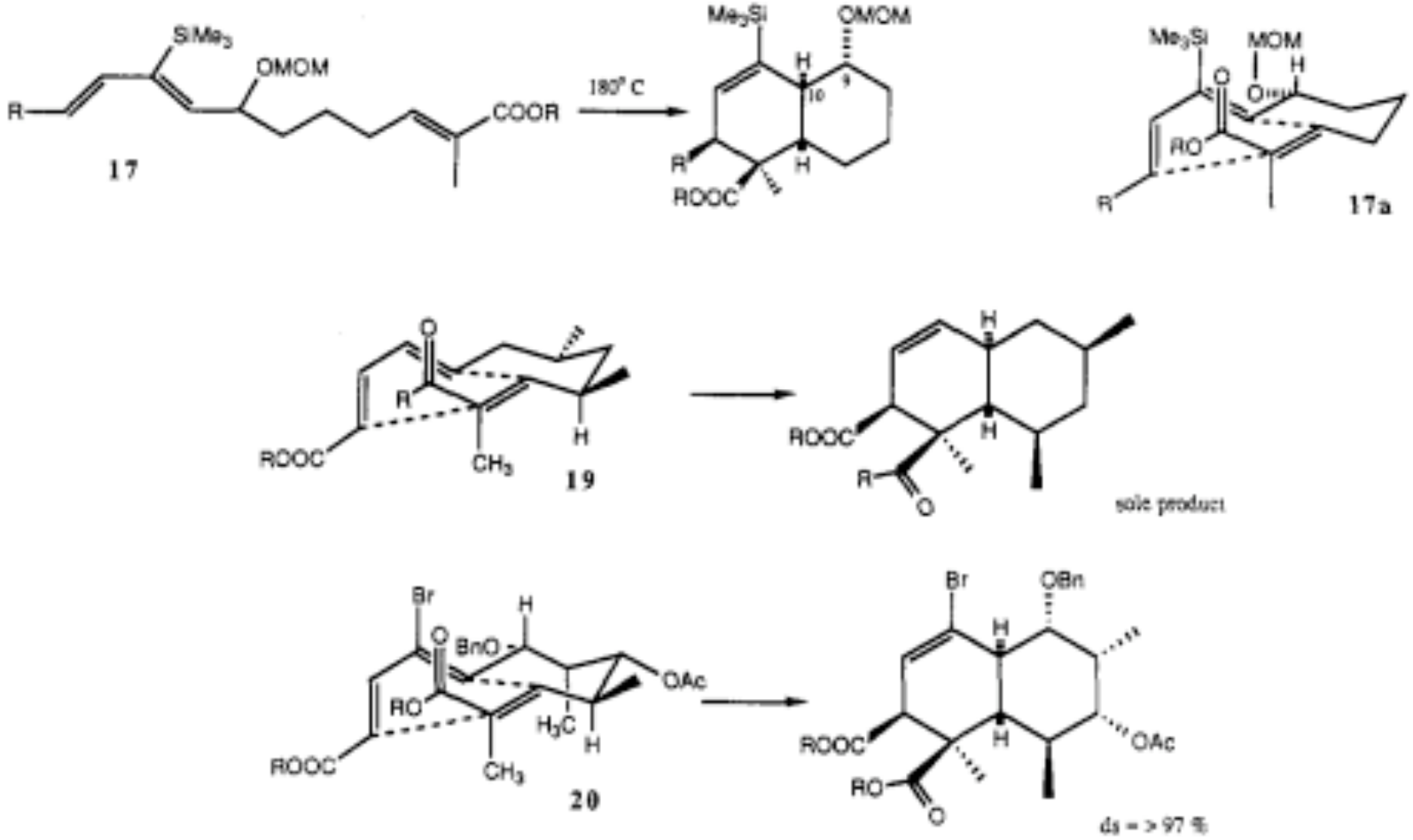
Diastereoselective Epoxidation of Olefins: A Recent Application to Library Synthesis





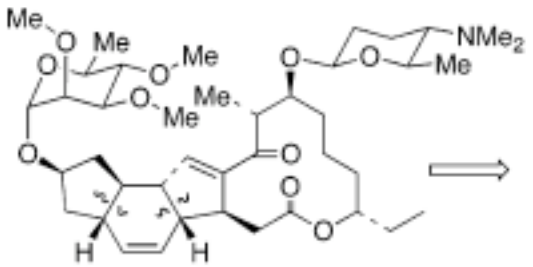
Coombs, T.C.; Lushington, G. H.; Douglas, J.; Aube, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 2734–2737.

$A^{1,3}$ Control in Cycloadditions: A Classical Example

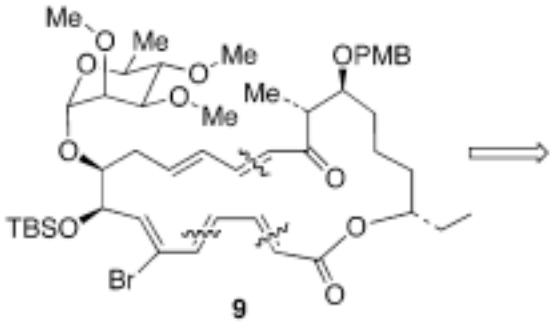


Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1880.

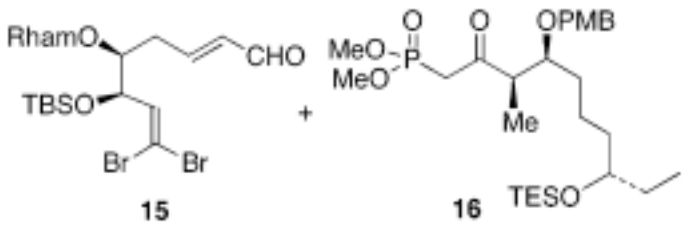
Roush: Total Synthesis of Spinosyn A



(–)-spinosyn A, **1**



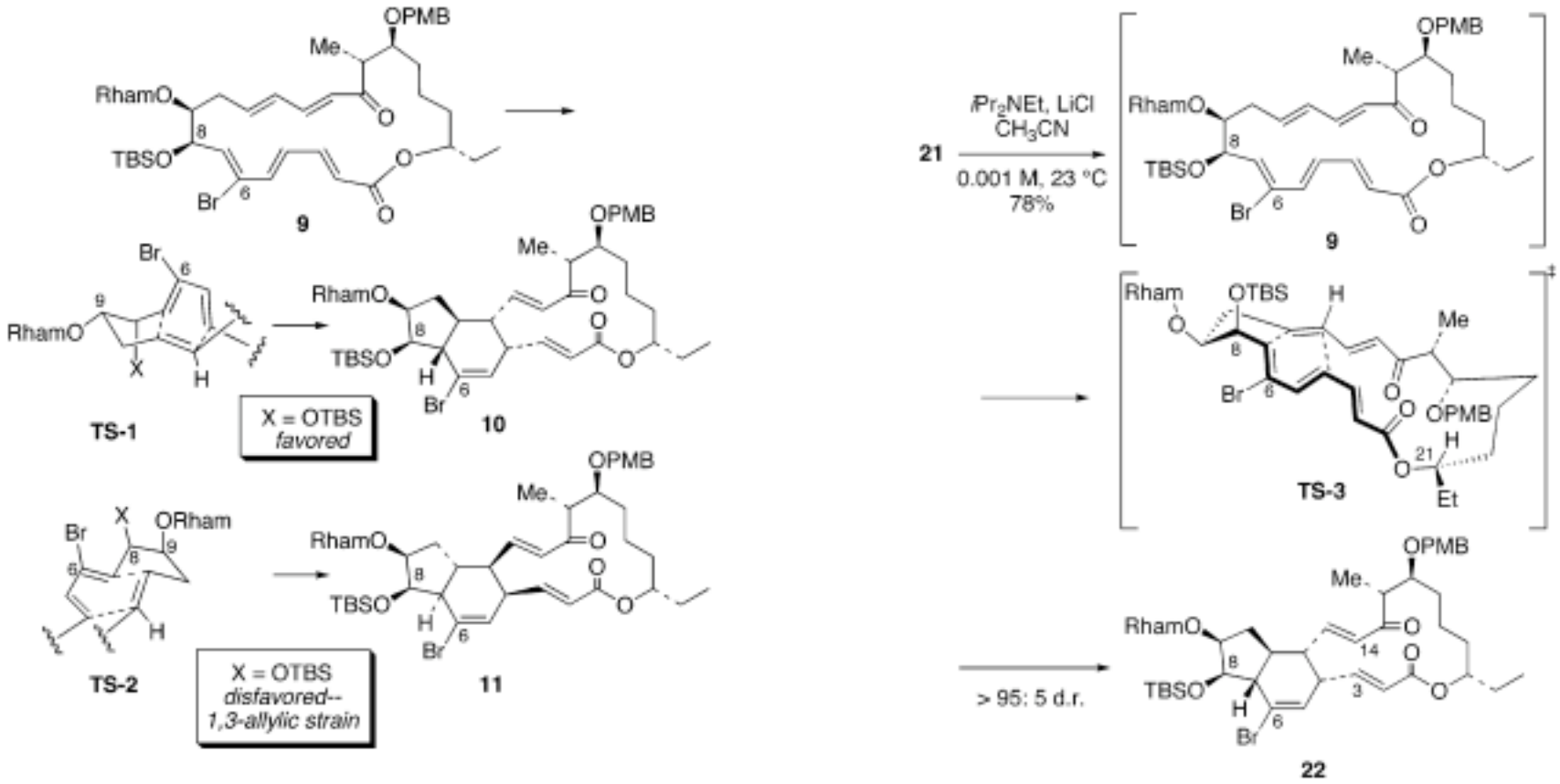
9



15 + **16**

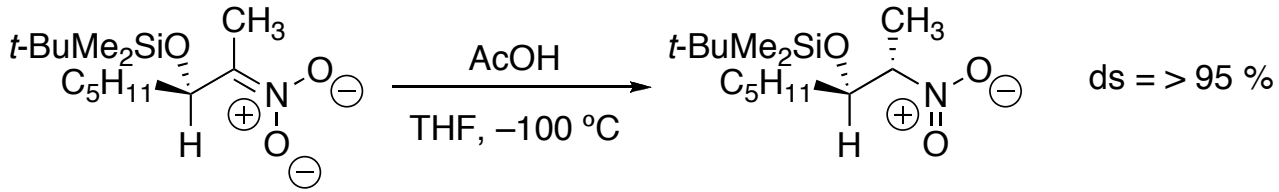
Winbush, S. M.; Mergott, D.J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818–1829.

$A^{1,3}$ Control in Cycloadditions: Roush Synthesis of Spinosyn A

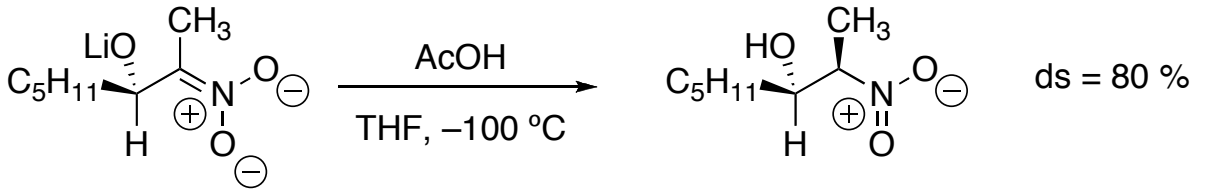


Winbush, S. M.; Mergott, D.J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818–1829.

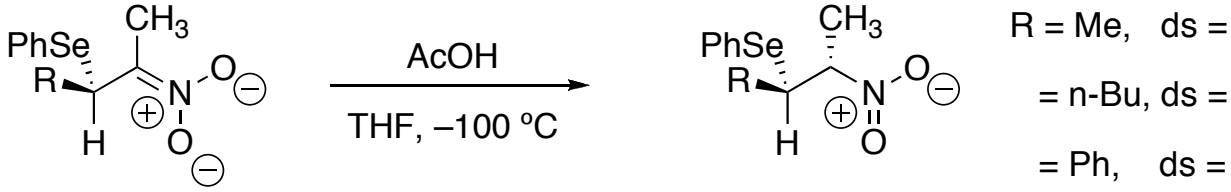
$A^{1,3}$ and Control in Addition to Nitrones



ds = > 95 %



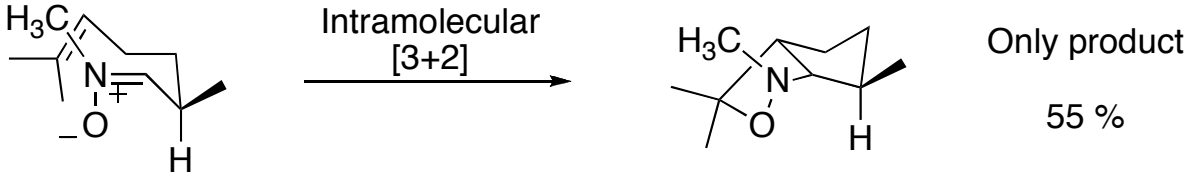
ds = 80 %



R = Me, ds = 91 %

= n-Bu, ds = 95 %

= Ph, ds = 80 %

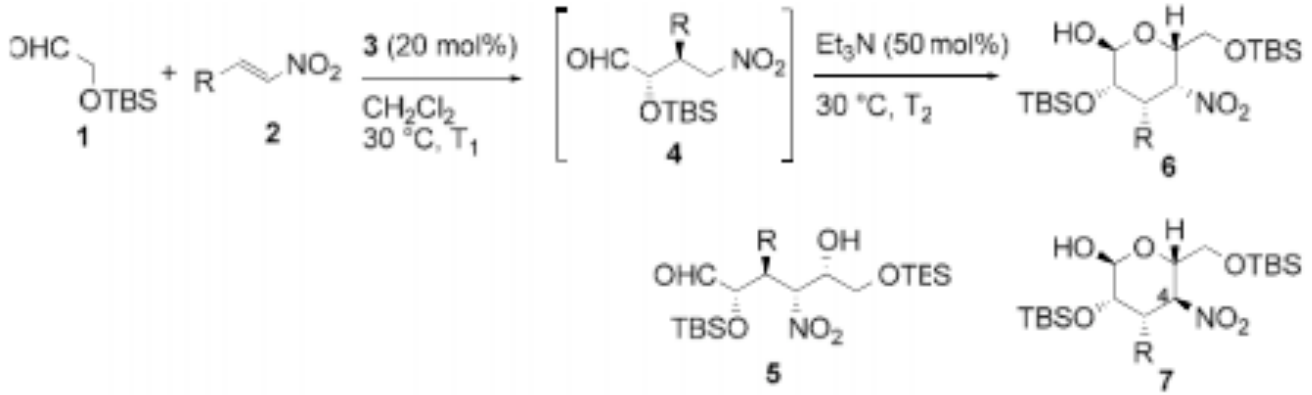


Only product

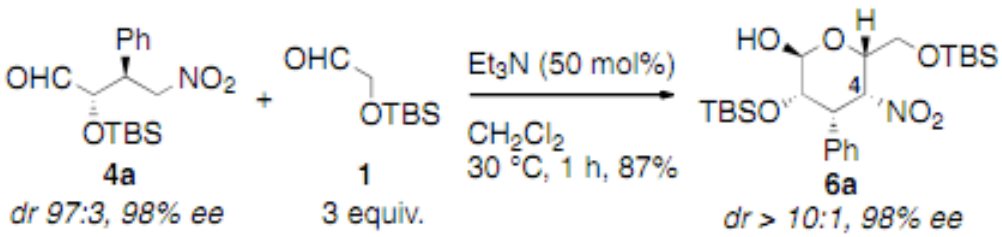
55 %

Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1880.

Barbas Carbohydrate Synthesis: Asymmetric Organocatalytic Michael-Henry Reactions

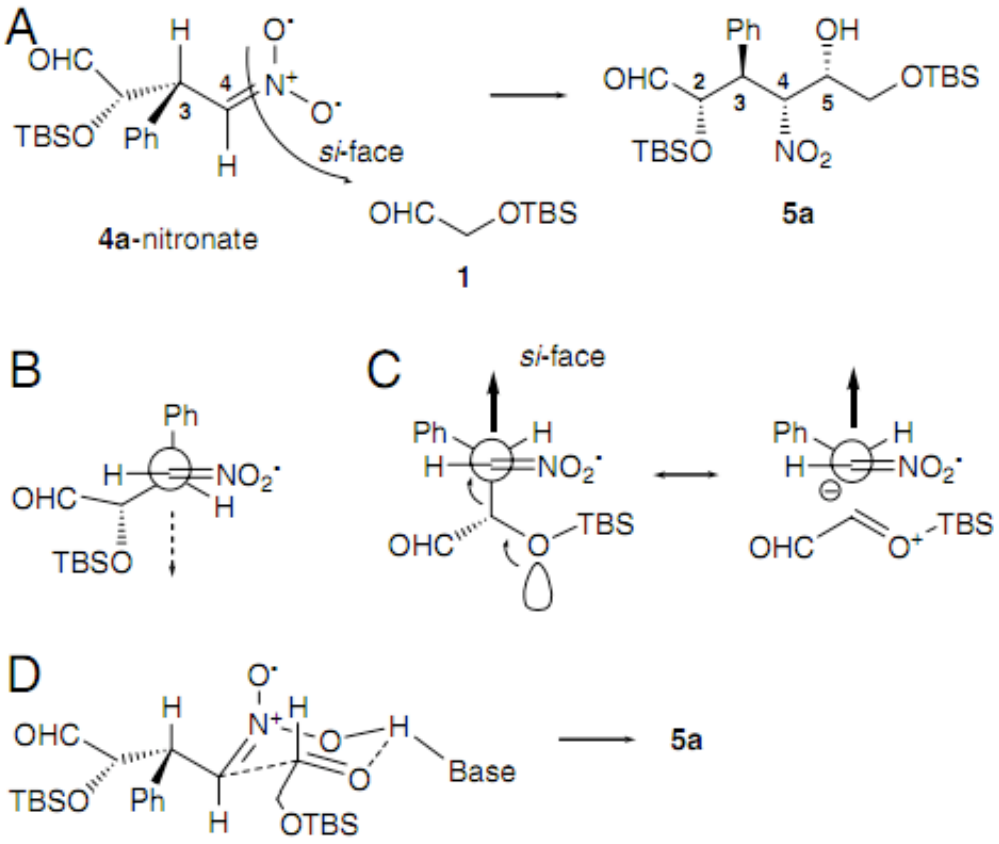


d.r. (6 + 5:7) = usually > 10:1; 36 % to 76 % yield (2 steps)



Uehara, H.; Imashiro, R.; Hernandez-Torres, G.; Barbas III, C. F. *PNAS,* **2010**, *107*, 20672– 20677.

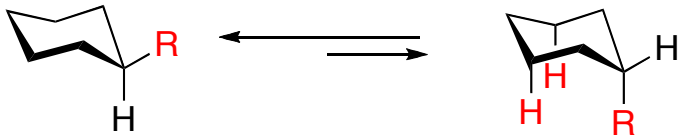
Barbas Carbohydrate Synthesis: Model for Diastereoselectivity



Uehara, H.; Imashiro, R.; Hernandez-Torres, G.; Barbas III, C. F. *PNAS,* **2010**, *107*, 20672–20677.

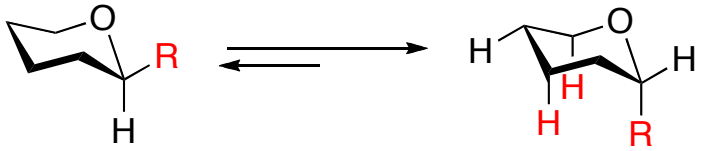
Introduction: The Anomeric Effect

Steric Preference:

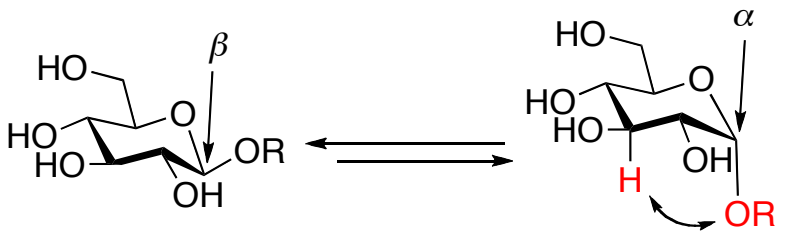


R = alkyl

Contra-Steric Preference: Anomeric Effect = Electrostatic Effect



R = polar group - i.e. OMe, Halogen, OAc, etc.

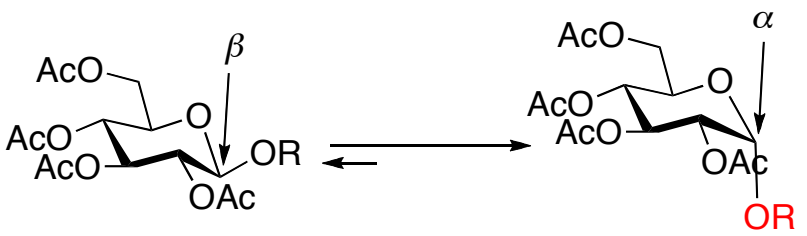


β-glucopyranose α-glucopyranose

R = H	64	:	36
R = Me	33	:	67

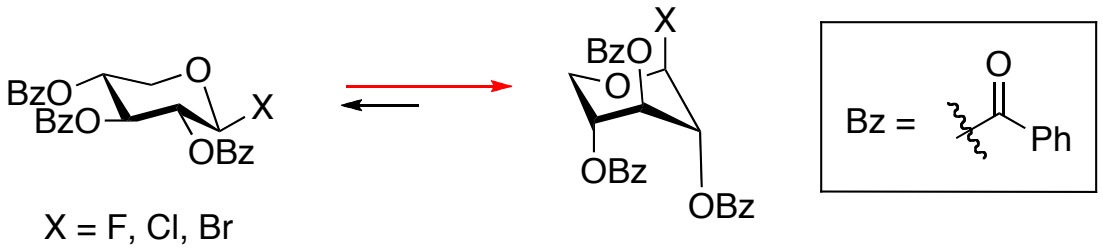
Kirby, A. J. *Oxford Chemistry Primers: Stereoelectronic Effects* **1996**, Oxford University Press.

Introduction: The Anomeric Effect



β-glucopyranose α-glucopyranose

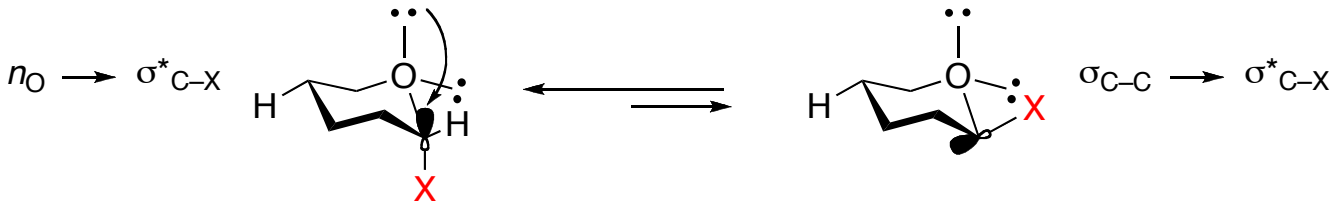
R = OAc	14	:	86
R = Cl	6	:	94



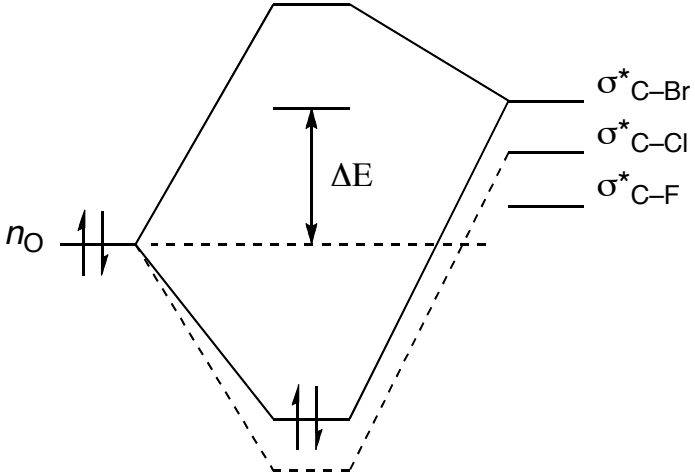
X = F, Cl, Br

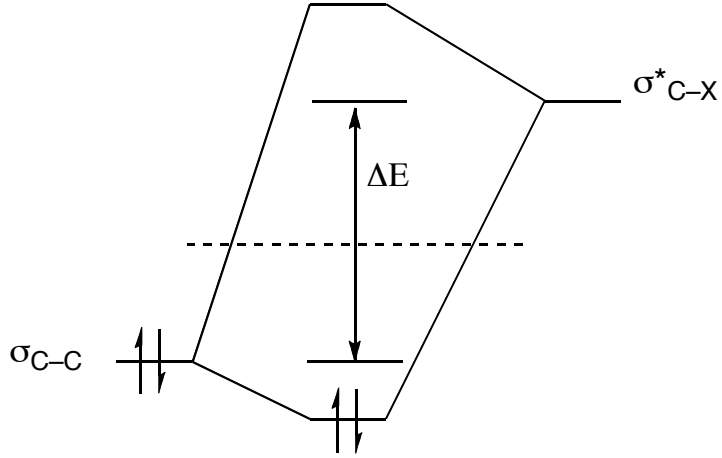
Kirby, A. J. *Oxford Chemistry Primers: Stereoelectronic Effects* **1996**, Oxford University Press.

Explaining the Anomeric Effect: Electrostatics

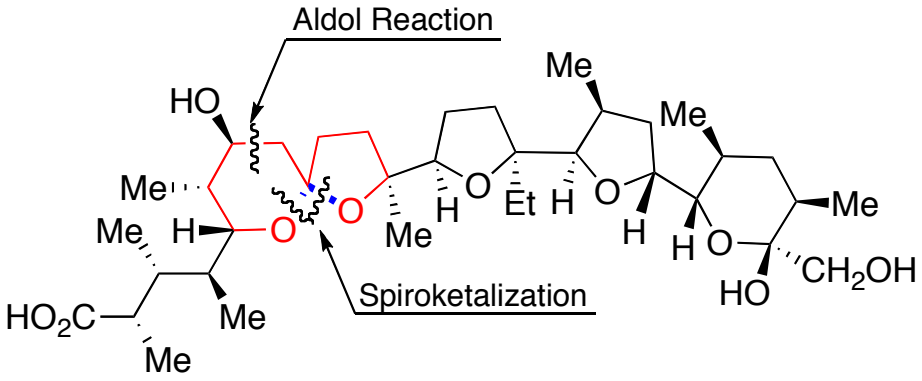


Just considering electrostatics:

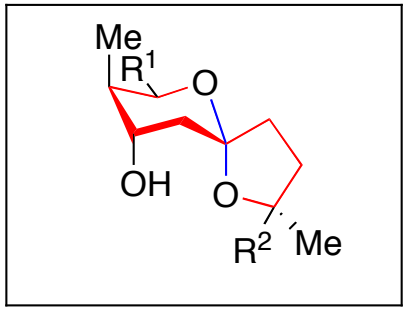




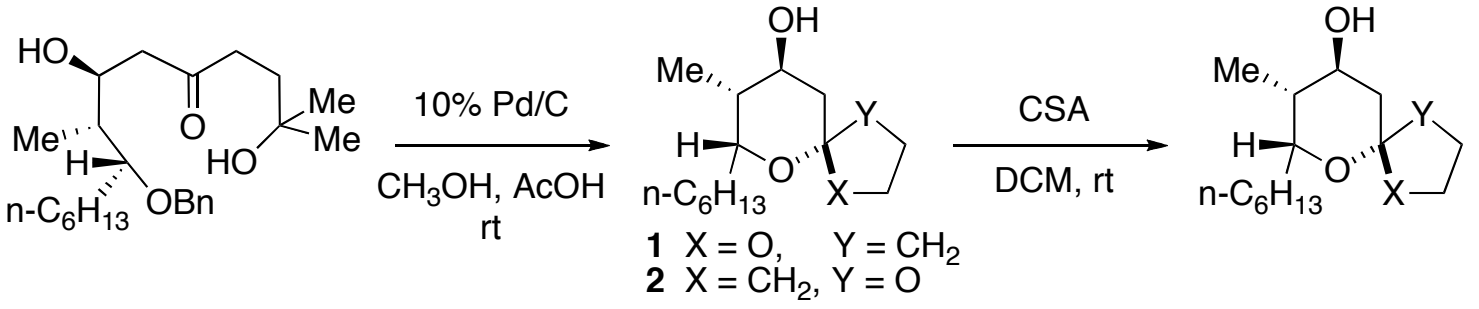
The Anomeric Effect is General and Predictable: Kishi's Monesin Total Synthesis



Monensin

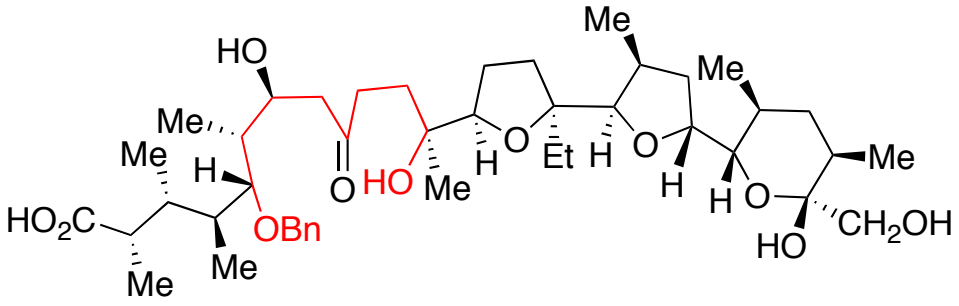


From Degradation Studies followed by X-ray



1:1 ratio of anomers **1**:**2**

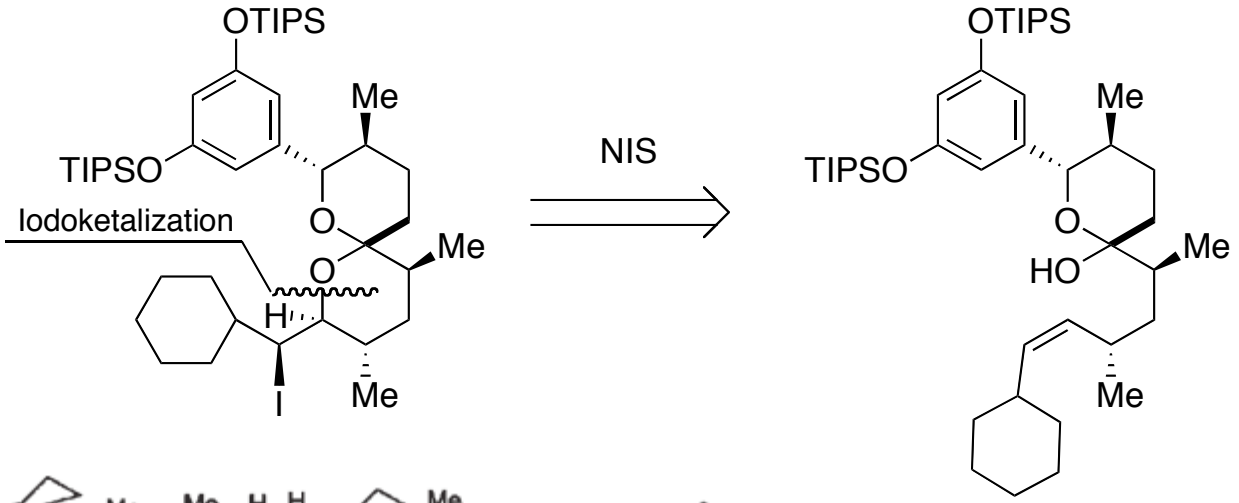
Only **1** (anomeric)

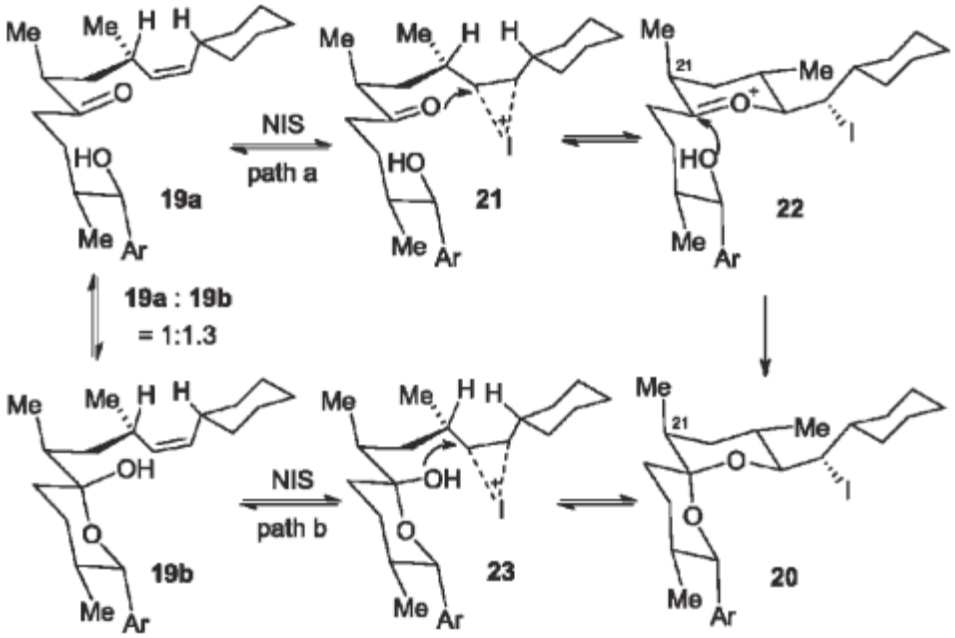


Monensin

Kishi, Y. et. al. *J. Am. Chem. Soc.* **1979**, *101*, 262–263.

Roush: Toward the Total Synthesis of Integramycin

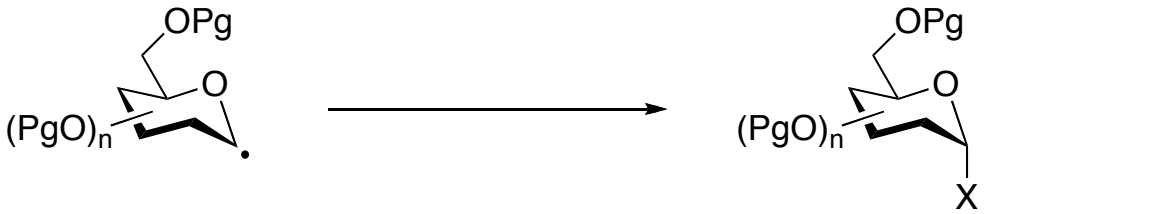




- $A^{1,3}$ minimization controls π-bond facial selectivity in the iodonium formation.
- Also formation of the doubly anomeric conformation should drive the equilibrium

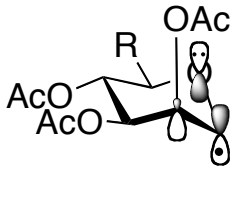
Sun, H.; Abbott, J. R.; Roush, W. R. *Org. Lett.* **2011**, *13*, 2734–2737.

Stereoselectivity in Glycosidic Bond Formation: Radical Reactions



α-selectivity dominates

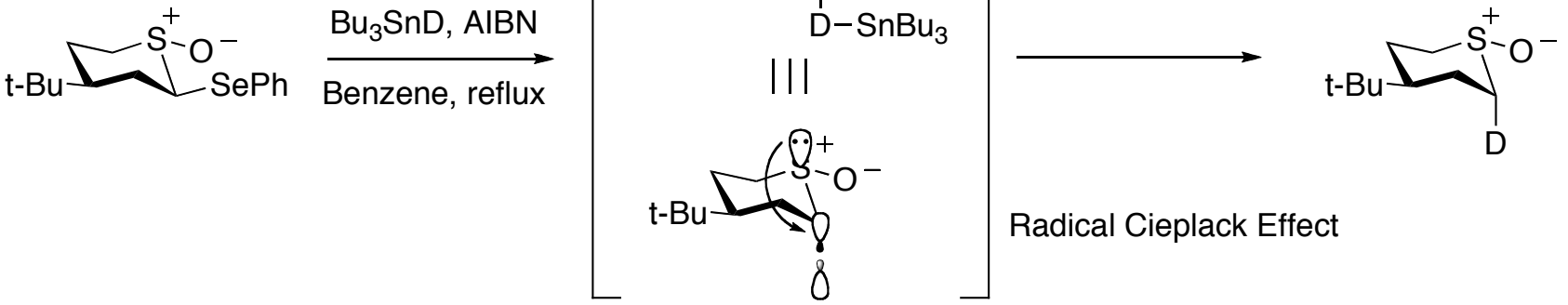
X = D, CH_2CH_2CN, n-$BuSnC_3H_6$



n_O → SOMO (anomeric stabilization)

SOMO → σ^*_{C2}

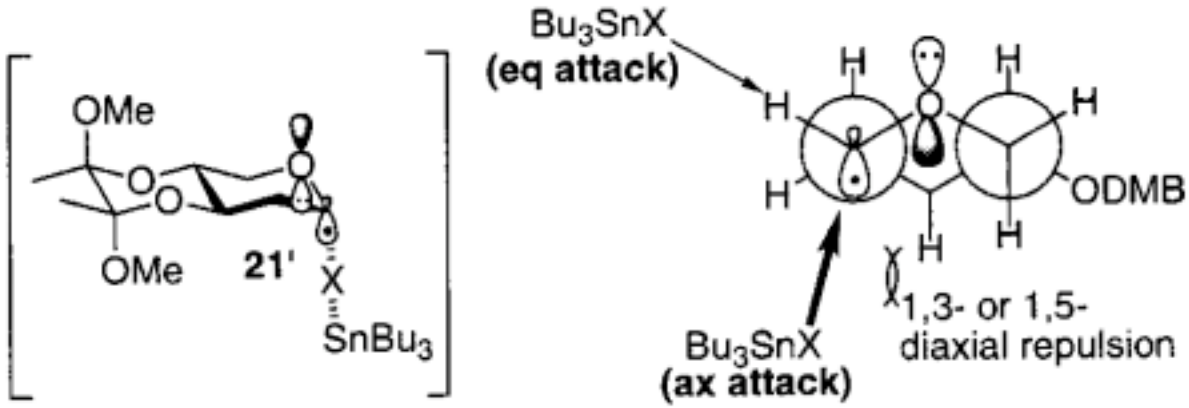
Studies by Giese

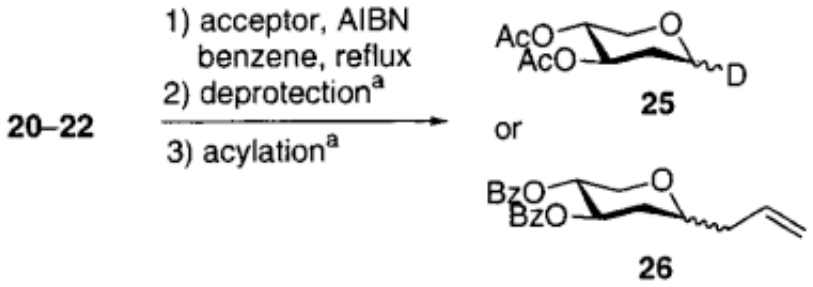


Radical Cieplack Effect

Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 11870–11882.

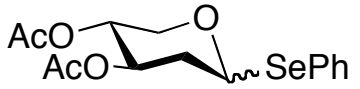
Conformationally Locking in α-Glycosylation: α-Selective Substrates



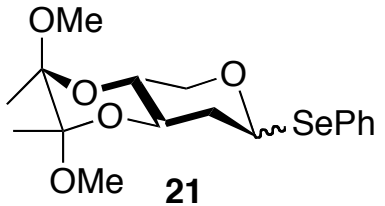


entry	substrate	conformation	acceptor[b]	product	α/β (yield %)
1	**20**	unrestricted	A	**25**[c]	84:16[d] (97)
2	**21**	$^4C_1$	A	**25**[c]	99:1[d] (61)
3	**21**	$^4C_1$	B	**26**	98:2[e] (74)

Acceptor: A = *n*-Bu_3SnD, B = *n*-$Bu_3SnC_3H_5$



20



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(α/β) = 1:1

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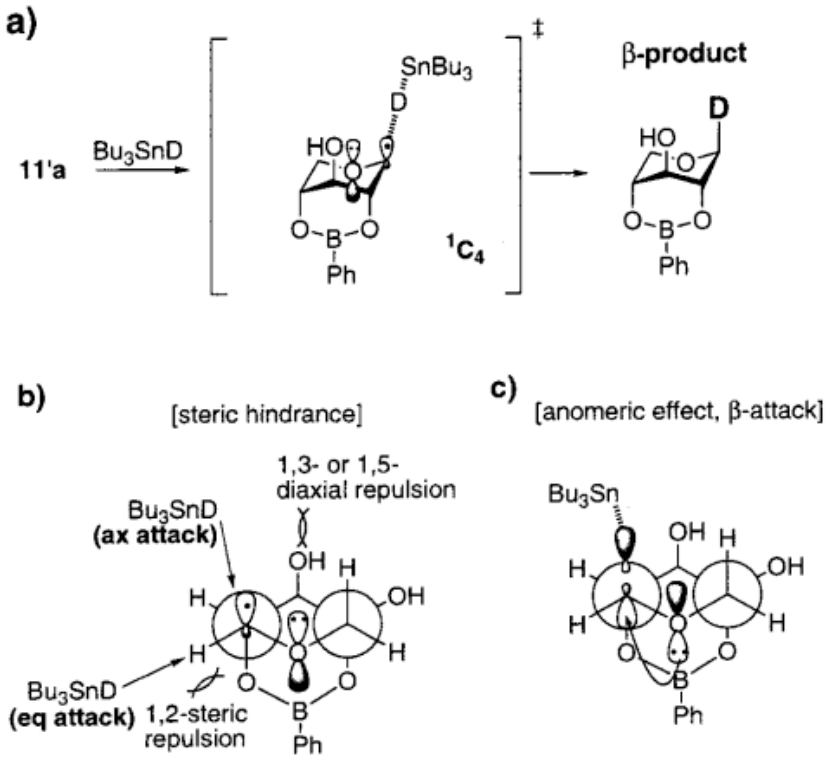
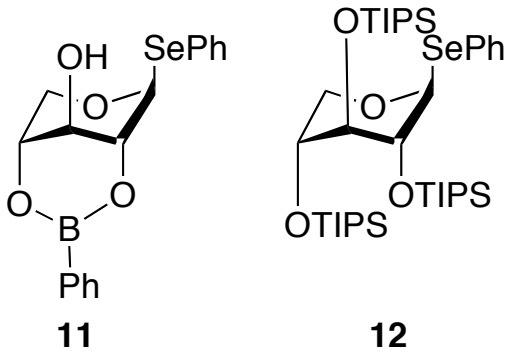
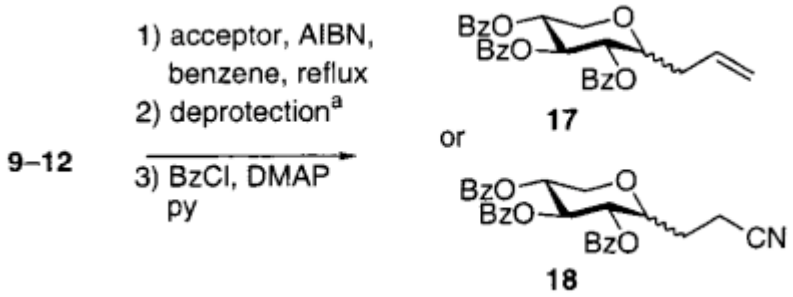
Conformationally Locking in β-Glycosylation: β-Selective Substrates







entry	substrate	conformation	acceptor[b]	product	α/β[c] (yield, %)
1	**9**	$^4C_1$	A	**17**	85:15 (73)
2	**10**	$^4C_1$	A	**17**	91:9 (69)
3	**11**	$^1C_4$	A	**17**	1:99 (61)
4	**12**	$^1C_4$	A	**17**	1:99 (26)[d]
5	**12**	$^1C_4$	B	**18**	0:100 (66)

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