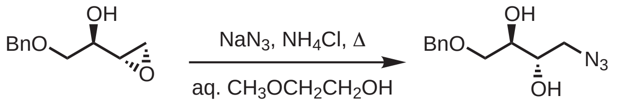
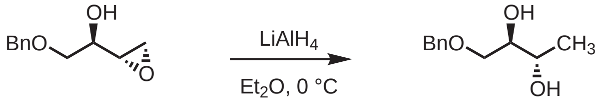
Opening of Terminal Epoxides:

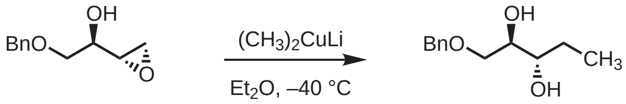
- Nucleophilic opening of terminal epoxides is often highly regioselective.



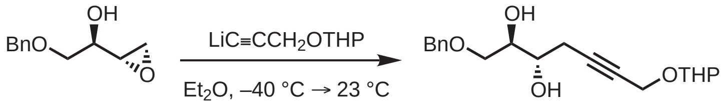
91%



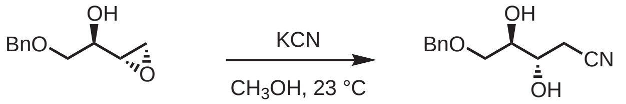
83%



74%



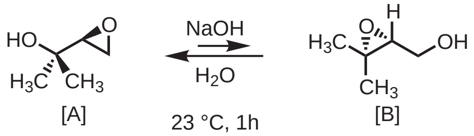
63%



50%

Behrens, C. H.; Sharpless, K. B.; *Aldrichimica Acta*, **1983**, *16*, 67-80.

Payne Rearrangement:

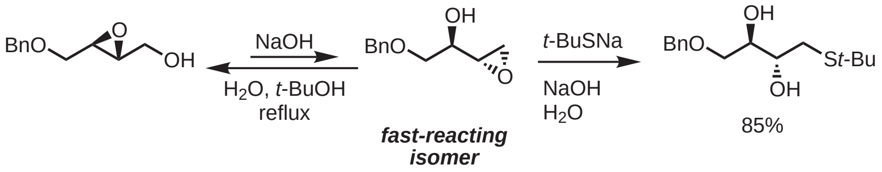


$$K_{eq} = \frac{[B]}{[A]} = \frac{92}{8}$$

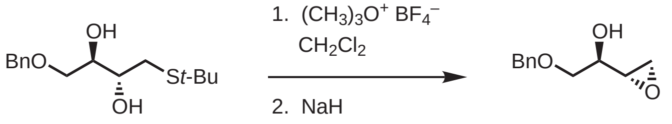
- Steric factors permitting, equilibrium generally favors the more substituted epoxide.

Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819-3822.

Payne Rearrangement-Opening Sequence:



- β-Hydroxy sulfides are readily converted into terminal epoxides.

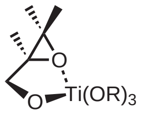


80-85%

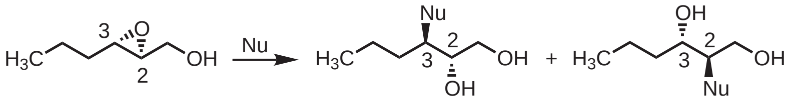
Behrens, C. H.; Sharpless, K. B.; *Aldrichimica Acta*, **1983**, *16*, 67-80.

2,3-Epoxy alcohols:

Proposed:



- Ti(O*i*-Pr)$_4$ can catalyze the addition of nucleophiles to C3 of 2,3-epoxy alcohols:



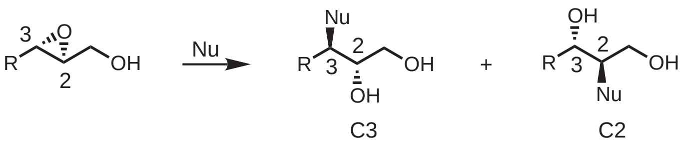
C3 C2

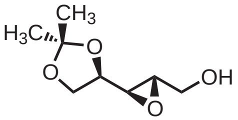
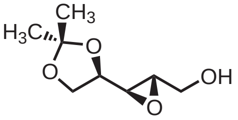
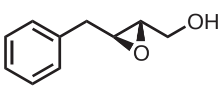
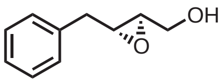
Nucleophile	Ti(O*i*Pr)$_4$	C3 : C2	yield
Et_2NH	0	3.7 : 1	4
Et_2NH	1.5	20 : 1	90
i-PrOH	0	-	0
i-PrOH	1.5	100 : 1	88
(allyl)$_2$NH	1.5	100 : 1	96
allyl alcohol	1.5	100 : 1	90
NH_4OBz	1.5	100 : 1	74
NH_4OAc	1.5	65 : 1	73
KCN	1.7	2.4 : 1	76

From: Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557-1560.

M. Movassaghi

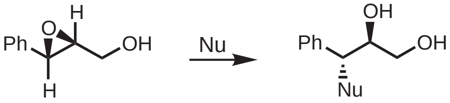
- Regioselectivity of uncatalyzed nucleophilic opening of 2,3-epoxy alcohols varies with the substrate and reaction conditions.



substrate	nucleophile	regioselectivity C3 : C2	combined yield (%)
	NaN_3	1 : 10	90
	NaSPh	1 : >10	76
	NaN_3	1.4 : 1	71
	NaSPh	1 : 1.4	72

Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696-5704.

- Phenyl substitution at C3 of 2,3-epoxy alcohols can lead to high C3-regioselectivity.

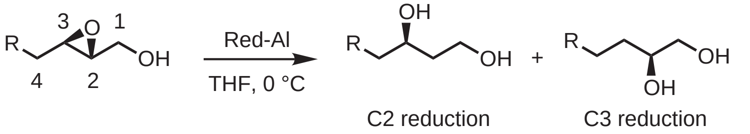


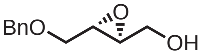
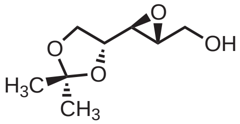
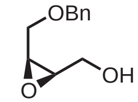
reagent	Nu	yield
allyl magnesium bromide	allyl	96
R_2CuLi or $R_2(CN)CuLi_2$	R	78-88
NaN_3/NH_4Cl	N_3	>95
R_2NH/KOH	R_2N	84
ArONa	ArO	83
PhSH/NaOH	PhS	81

From: Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437-475, and references therein.

- C2 reduction of 2,3-epoxy alcohols using Red-Al is highly selective when C4 is oxygenated.

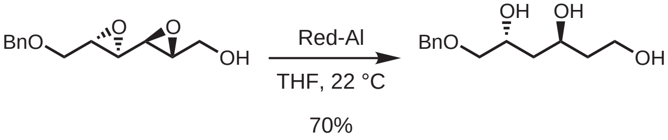
Red-Al = $[(CH_3OCH_2CH_2O)_2AlH_2]^- Na^+$



epoxy alcohol	C2 : C3	yield (%)
	1 : 1	94
	5 : 1	89
	40 : 1	98
	>100 : 1	78
	100 : 1	95

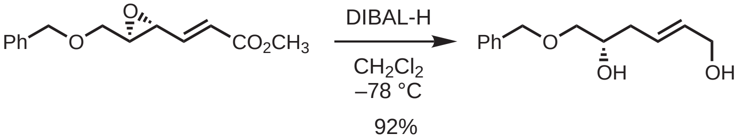
Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378-1380 and Finan, J.; Kishi Y. *Tetrahedron Lett.* **1982**, *23*, 2719-2722.

- 1,3-Bis-epoxides:



Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378-1380.

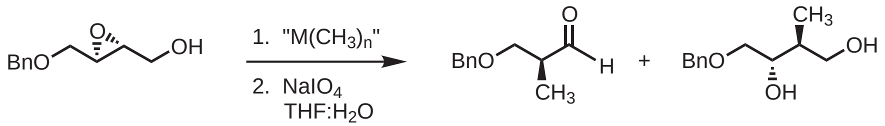
- Allylic epoxides:



Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc.*, *Chem. Commun.* **1982**, 1292-1293.

M. Movassaghi

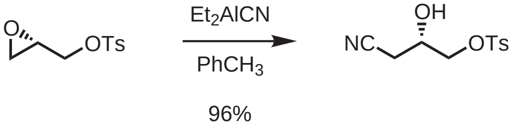
- The regioselectivity of epoxide opening can vary with the organometallic reagent.

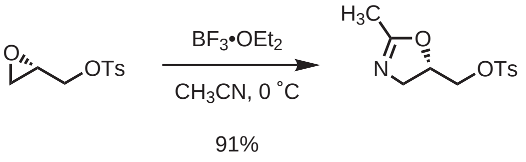


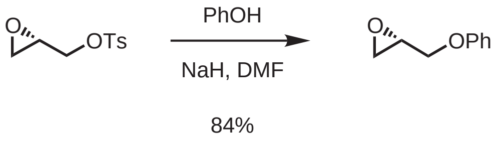
(CH$_3$)$_2$CuLi Et$_2$O, –20 °C	10-12%	74-79%
(CH$_3$)$_3$Al, CH$_2$Cl$_2$ 0 → 23 °C	69-73%	13-14%

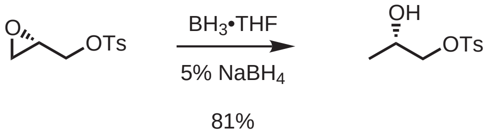
Johnson, M. R.; Nakata T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343-4346.
Roush, W. R.; Adam, M. H.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, 1377-1380.

- AE of allyl alcohol followed by in situ derivatization affords versatile chiral building blocks, such as glycidol tosylate (now commercially available).
- Reactions of glycidol tosylate:



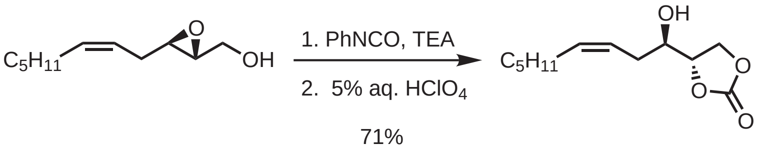




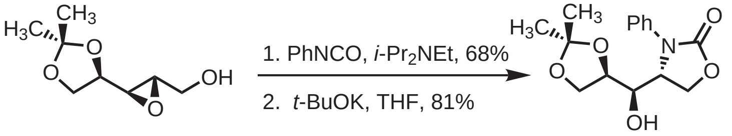


Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295-1304.
Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437-475.

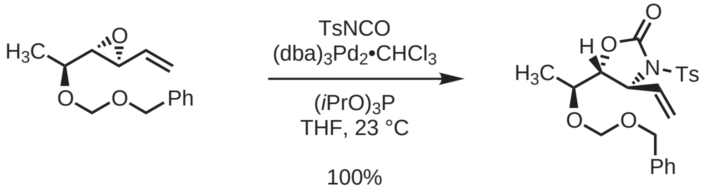
- Internal nucleophiles may be used to open 2,3-epoxy alcohols:



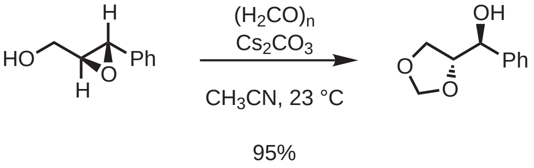
Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1980**, *102*, 7986-7987.



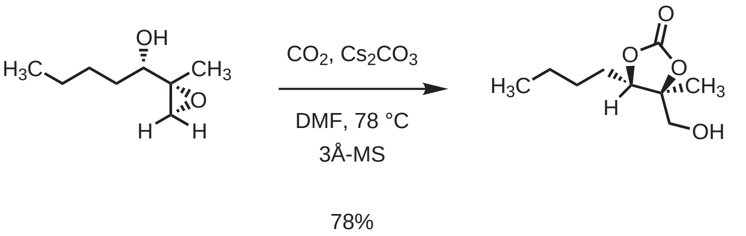
Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109-1111.



Trost B. M., Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792-3794.



McCombie, S. W.; Metz, W. A. *Tetrahedron Lett.* **1987**, *28*, 383-386.



Myers, A. G.; Widdowson, K. L. *Tetrahedron Lett.* **1988**, *29*, 6389-6392.

M. Movassaghi