Asymmetric Schmidt Reaction of Hydroxyalkyl Azides with Ketones

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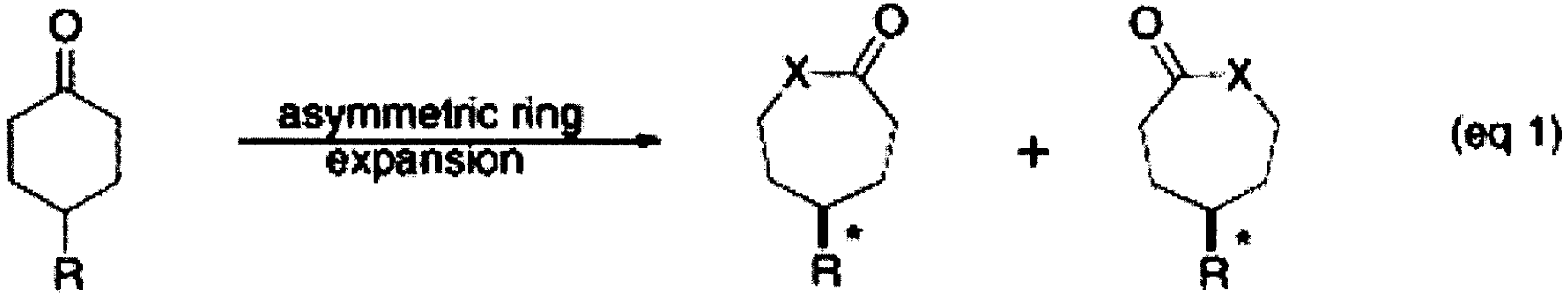
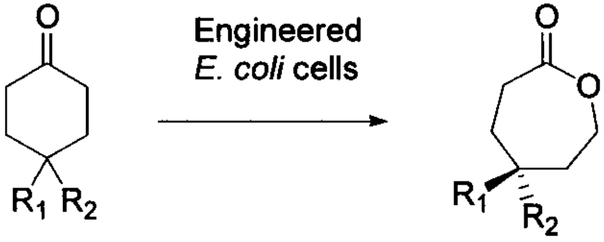
***J. Am. Chem. Soc.*, 125 (26), 7914 -7922, 2003.**



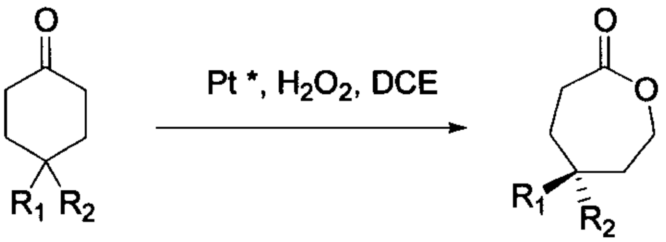
X = N. as high as 98:2

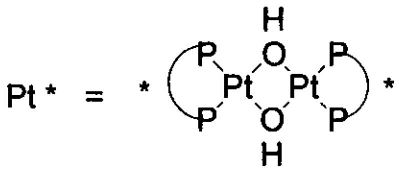
Baeyer-Villiger Rxn



R1	R2	Yield	ee%
Me	H	61	98
Et	H	91	97
Et	Me	91	75
OH	H	61	9.1
Et	OH	54	94
OMe	H	84	78
Br	H	63	97
I	H	60	97

Mihovilovic, M. D. et al. *J. Org. Chem.* **2001,** *66,* 733-738





in some cases ee's above 50%

Paneghetti, C. et al. *Organometallics* **1999,** *18,* 5057-5065

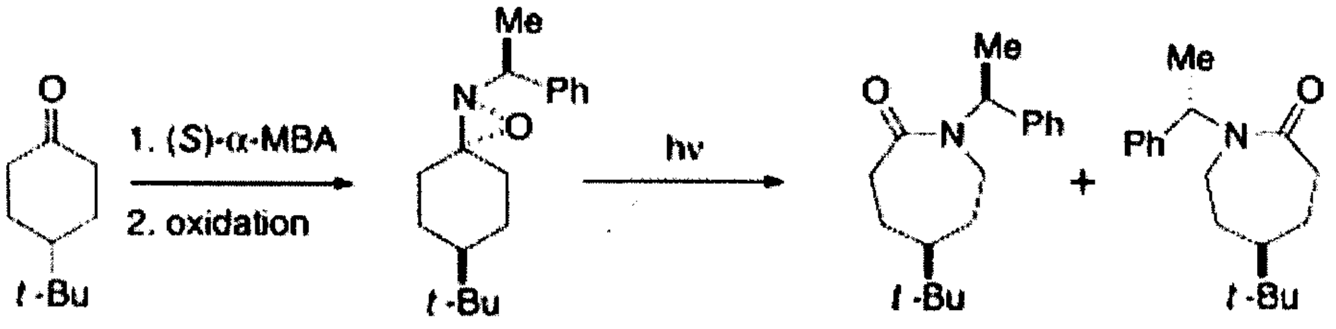
79 %ee

80 % ee

Toda, F. et al. *J. Org. Chem.* **1990**,55, 4973-4974

asymmetric nitrogen ring expansion.

chiral oxaziridine

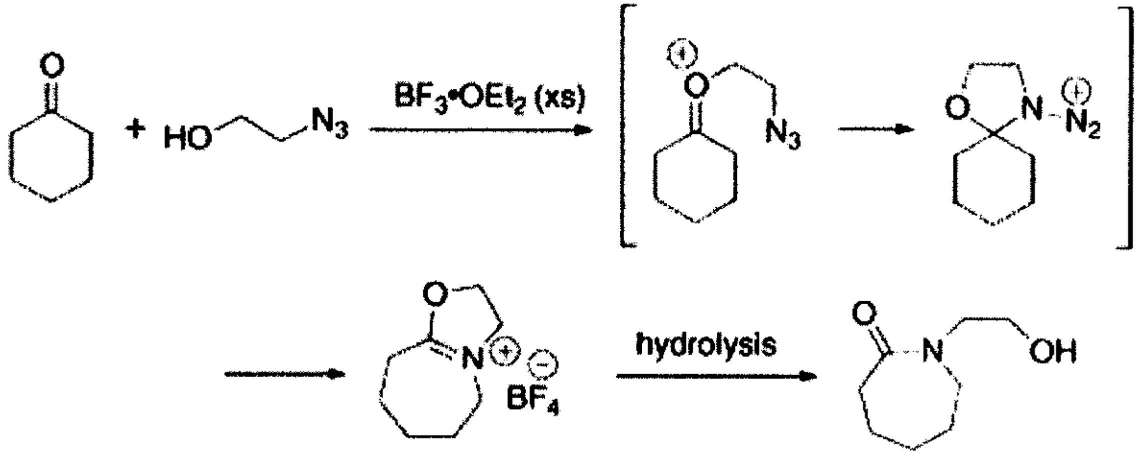


(and diastereomers)

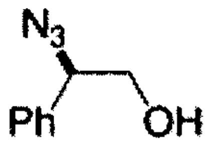
88:12

oxaziridines can be prepared easily in diastereo- and enantiomerically enriched form
3 steps

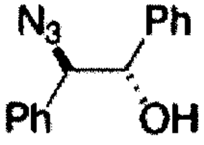
‘in situ-tethering’



1,2- and 1,3-hydroxyalkyl azides



1



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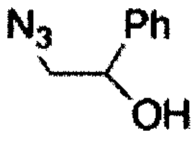
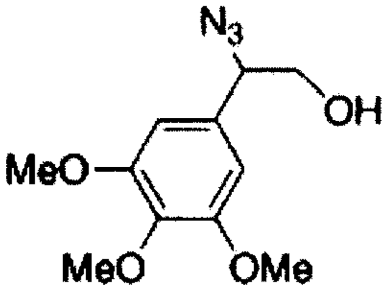
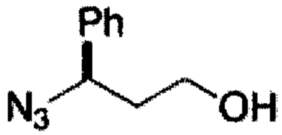


(±)-3

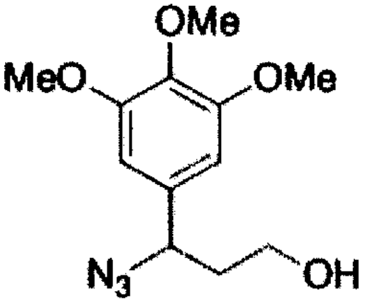


(±)-4

5



6



(±)-7

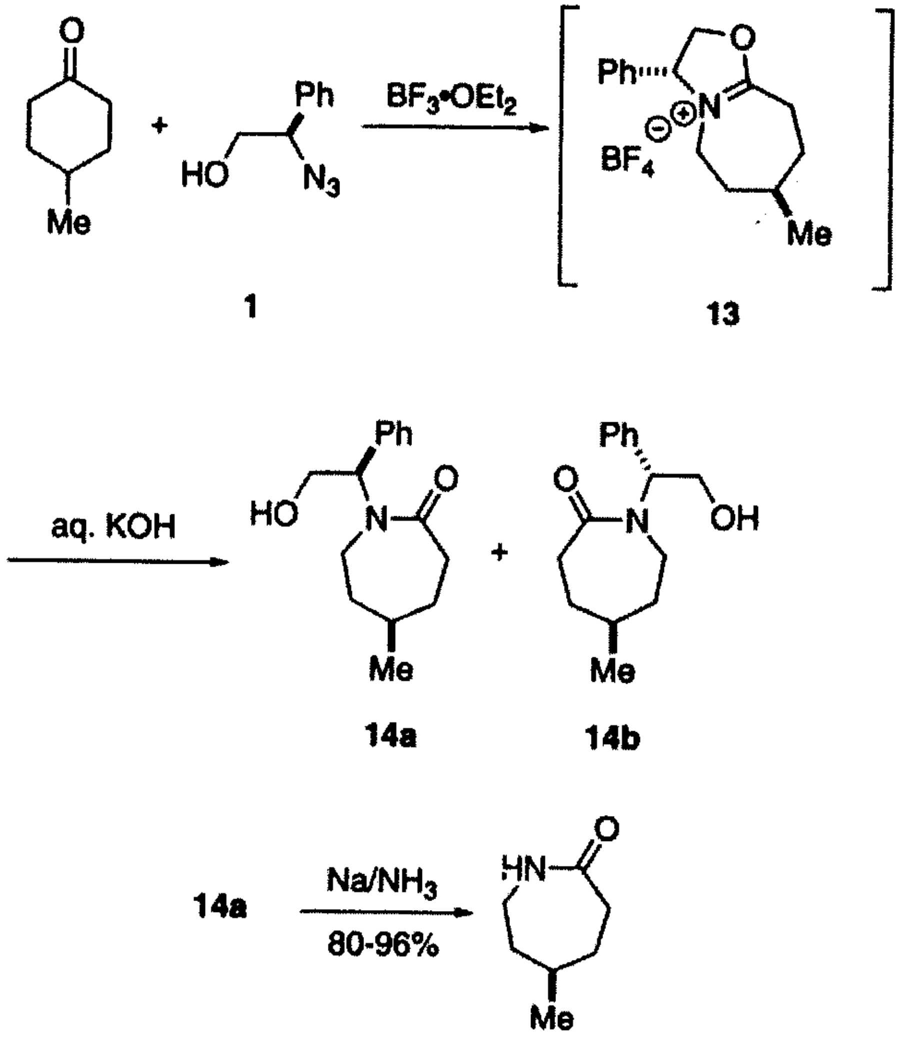
8, R_1 = Me, R_2 = H
9, R_1 = H, R_2 = Ph

(±)-10

11, R_1 = Me, R_2 = H
12, R_1 = H, R_2 = Me

the ready availability of chiral hydroxyalkyl azides

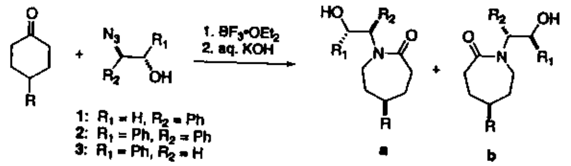
Optimal solvent and temperature conditions



- $BF_3 \cdot Et_2O$ as a superior Lewis acid.
- 1.5 equiv of **1** and 3.0 equiv of $BF_3 \cdot Et_2O$.
- the X-ray crystallographic analysis of iminium ether **13.**
- Et_2O and THF were inappropriate media.
- CH_2Cl_2 and hydrocarbon solvents were considerably better.
- *n*-pentane and CCl_4 afford the highest yields in the shortest time.
- -30 °C and -20 °C.
- ratios ranging from 74:26 to 84:16 comparable to the oxaziridine route

Reactions of 1,2-Hydroxyalkyl Azides and 1,3-Hydroxyalkyl Azides

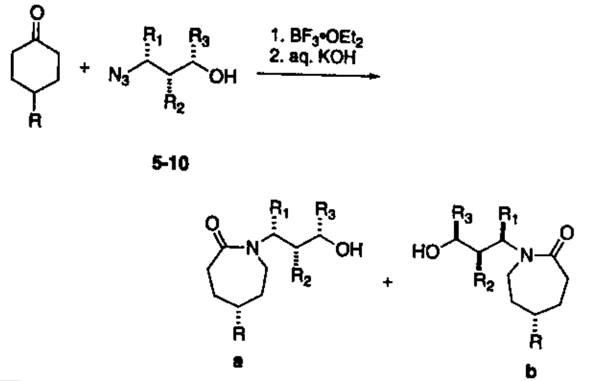
Table 2. Reactions of 1,2-Hydroxyethyl Azides with 4-Substituted Ketones



entry	azide	ketone R	major product	yield (%)[a]	ratio a:b[b]
1	**1**	Me	**14a**	97	78:22
2	**1**	*t*-Bu	**15a**	83	85:15
3	**2**	Me	**16a**	51	87:13
4	**2**	*t*-Bu	**17a**	64	88:12
5	**3**[c]	*t*-Bu	**18a** or **18b**[d]	73	56:44

[a] Isolated yield. [b] Ratio determined by HPLC trace of the crude reaction mixture; see text and Supporting Information for stereostructure determinations. [c] This experiment was done using a racemic hydroxyalkyl azide. [d] Not assigned for this example.

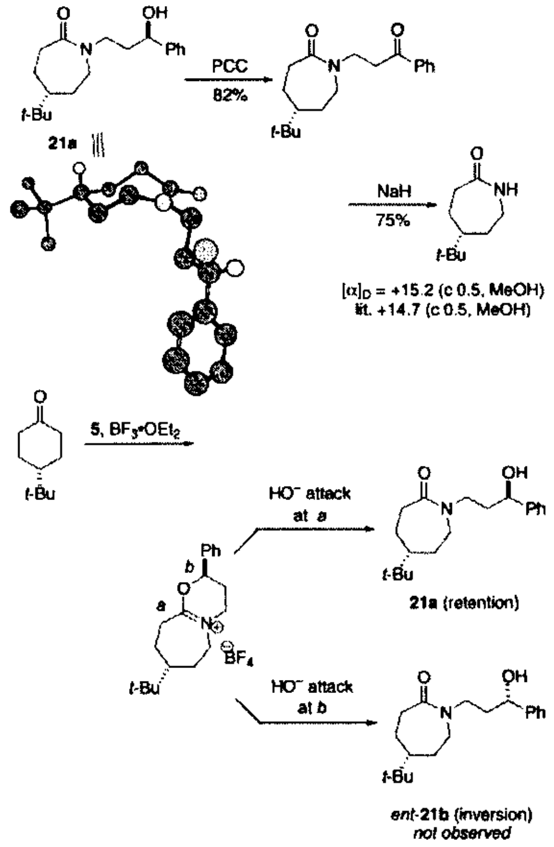
Table 3. Reactions of Monosubstituted 1,3-Hydroxyalkyl Azides with 4-Substituted Cyclohexanones



entry	ketone R	azide	azide R1	azide R2	azide R3	products	ratio a:b[a]	yield (%)[b]
1	Me	**5**	H	H	Ph	**19**	93:7	98
2	Ph	**5**	H	H	Ph	**20**	96:4	99
3	*t*-Bu	**5**	H	H	Ph	**21**	95:5	100
4	Me	**6**[c]	Ph	H	H	**22**[c]	89:11	96
5	*t*-Bu	**6**[c]	Ph	H	H	**23**[c]	90:10	94
6	*t*-Bu	**7**[d]	$-C_6H(OMe)_3$	H	H	**24**[d]	90:10[d,e]	90
7	Me	**8**	H	Me	H	**25**	78:22	93
8	*t*-Bu	**8**	H	Me	H	**26**	74:26	98
9	Me	**9**[c]	H	Ph	H	**27**[c]	60:40	93
10	*t*-Bu	**9**[c]	H	Ph	H	**28**[c]	60:40	98
11	Me	**10**[d]	H	*i*-Pr	H	**29**[d]	88:12[d]	88
12	*t*-Bu	**10**[d]	H	*i*-Pr	H	**30**[d]	88:12[d]	85

more selective

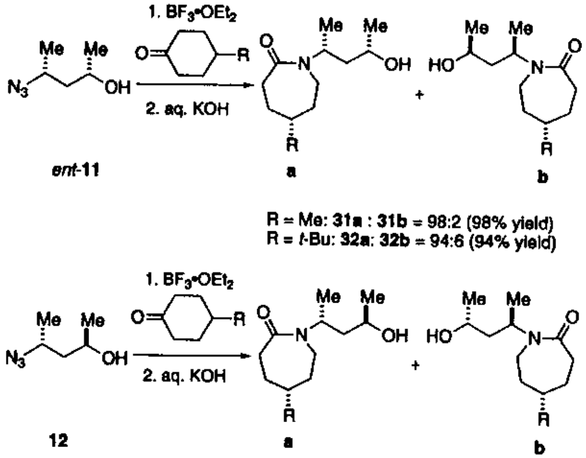
Scheme 7



$[\alpha]_D$ = +15.2 (c 0.5, MeOH)
lit. +14.7 (c 0.5, MeOH)

ent-21b (inversion)
not observed

Scheme 8

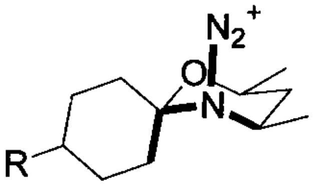


R = Me: **31a** : **31b** = 98:2 (98% yield)
R = *t*-Bu: **32a**: **32b** = 94:6 (94% yield)

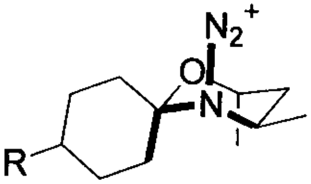
R = Me: **33a,b*** = 59:41 (98% yield)
R = *t*-Bu: **34a,b*** = 60:40 (98% yield)

*Stereostructures not assigned

NOTE: The enantiomers of compounds **11**, **31a,b**, and **32a,b** are used in this scheme to allow easy comparison with examples given in Table 3. See Supporting Information for correct structures.



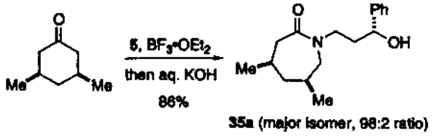
11



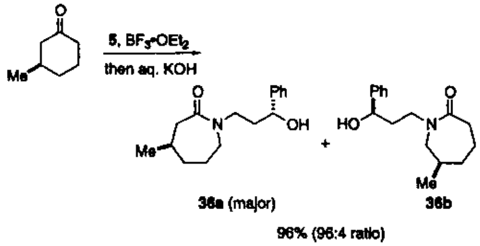
12

Scheme 9

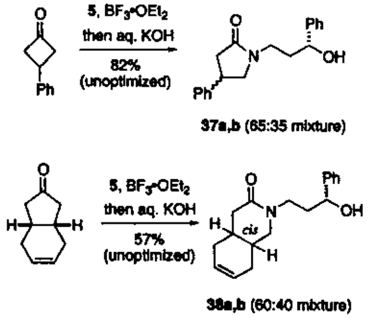
(a) Meso disubstituted cyclohexanone



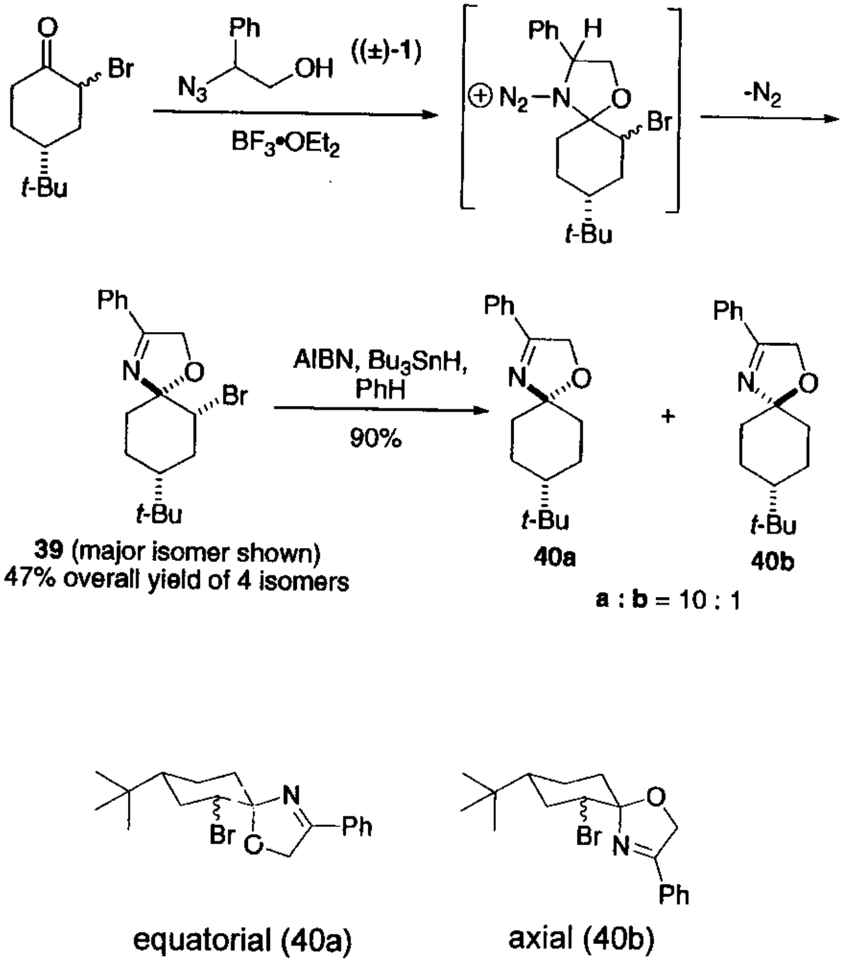
(b) 3-Substituted cyclohexanone: selective formation of a particular constitutional isomer



(c) Alternative ring sizes

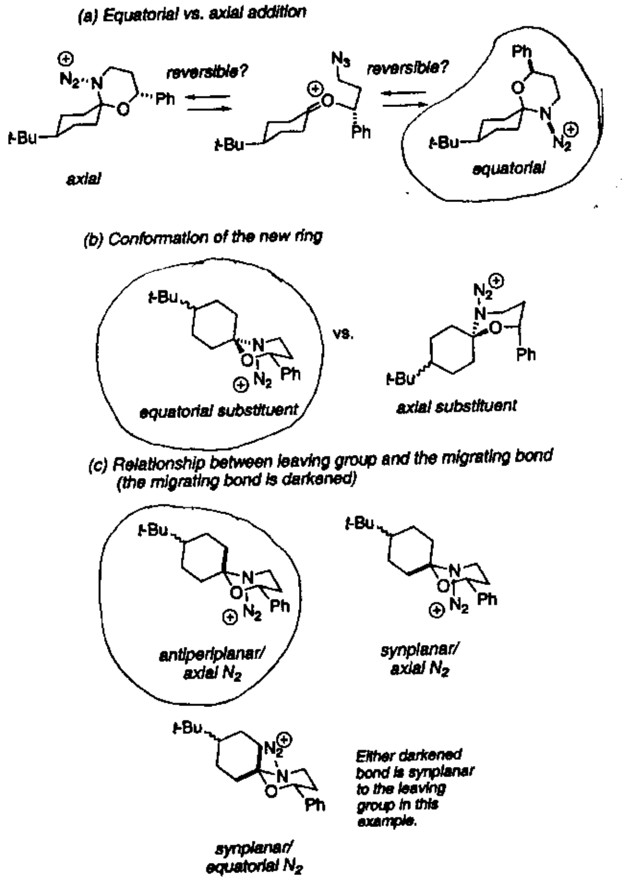


Scheme 10

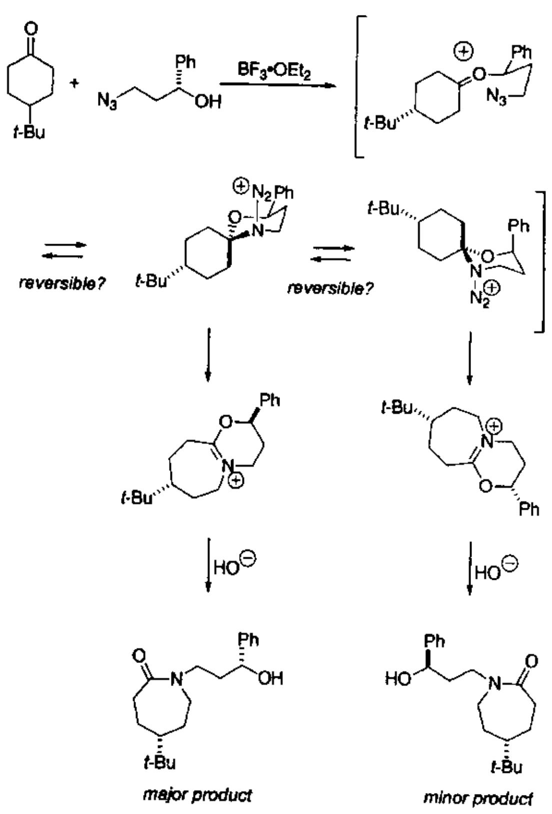


Mechanistic Hypotheses: Three-Carbon Tethers

Scheme 11



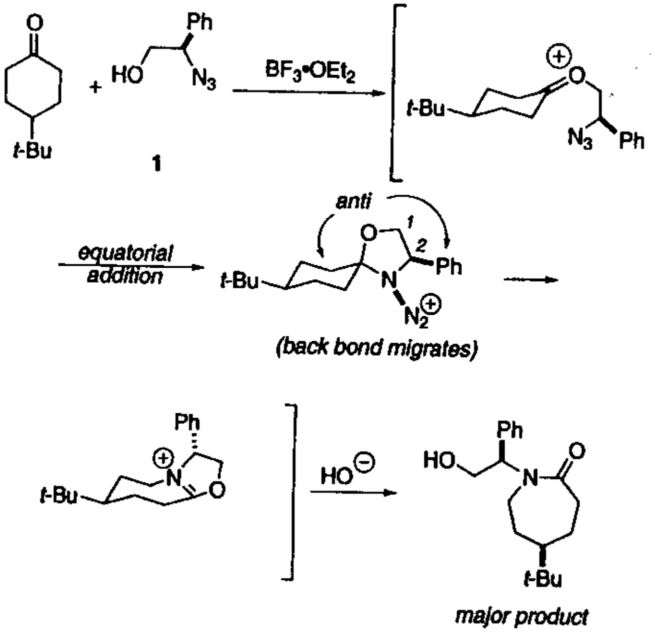
Scheme 12



on a **favored equatorial addition** by (1) assuming **antiperiplanar migration**, (2) assuming formation of the **more stable chairlike tetrahydrooxazine ring**, and (3) correlating the absolute configurations with the starting materials and products

Mechanistic Hypotheses: Two-Carbon Tethers

Scheme 13



- One pot.
- Better selectivity than previous methods.
- High yield.