Asymmetric Schmidt Reaction of Hydroxyalkyl Azides with Ketones

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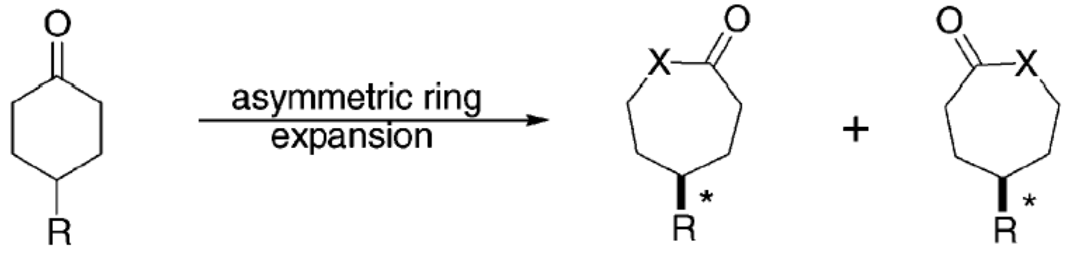
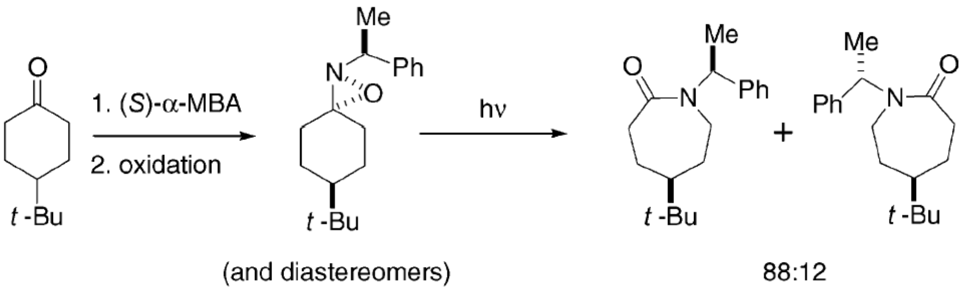
Kiran Sahasrabudhe, Vijaya Gracias, Kelly Furness, Brenton T. Smith,
Christopher E. Katz, D. Srinivasa Reddy, and Jeffrey Aubé



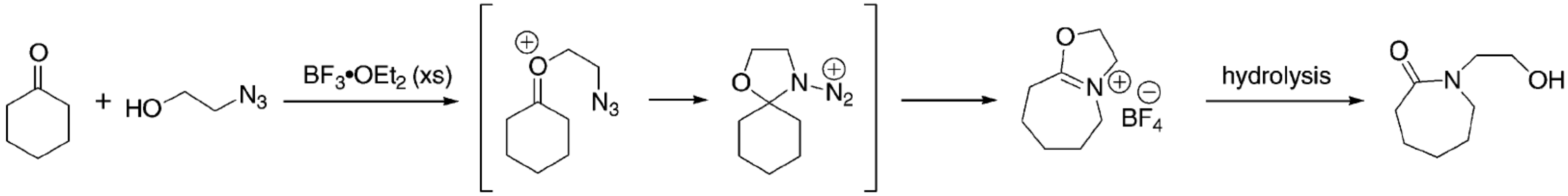
X = N

Methods for Asymmetric Conversion of Ketones to Lactams

- Photochemical rearrangement of chiral oxaziridines



- Schmidt reaction using chiral alkyl azides

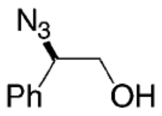


Aube, J.; Wang, Y.; Hammond, M.; Ranol, M.; Rakusagawa, F.; Vander, V, D. *J.Am. Chem. Soc*. **1990**, *112*, 4879-4891.
Furness, K.; Aube, J. *Org. Lett*. **1999**, *1*, 495-497.

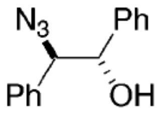
Comparation of Two Methods

Oxaziridines	Asymetric Schmidt reaction
A chiral methylbenzylamine as a stereocontrolling group	Using a chiral alkyl azide
Three discrete steps and moderate overall yield (around 70%)	One-pot, one-workup procedure and higher overall yield (85%-100%)
Relatively low stereoselectivity (88:12 as the best result)	Considerably greater stereoselectivity (49:1 as the best result)

Selection and Synthesis of Hydroxyalkyl Azides – 1,2-azido alcohol



1



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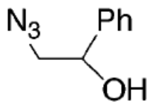
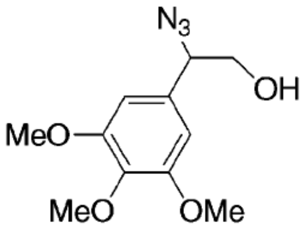
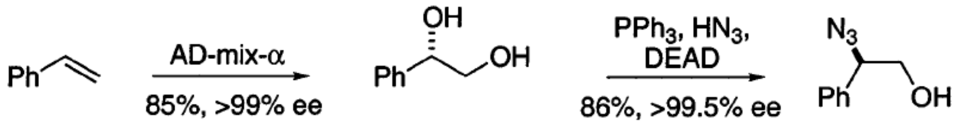


(±)-**3**



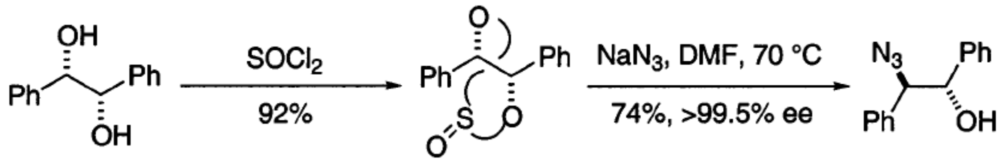
(±)-**4**

- Mitsunobu procedure:



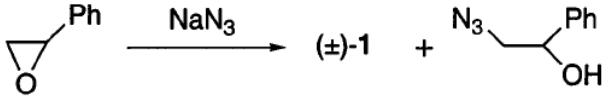
1

- Using activated diols:



2

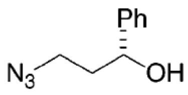
- Ring opening of epoxides:



(±)-**3**

80%, 75:25 mixture of isomers

Selection and Synthesis of Hydroxyalkyl Azides – 1,3-azido alcohol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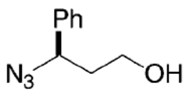
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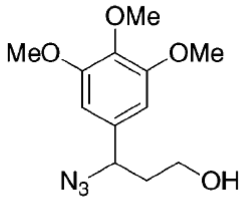
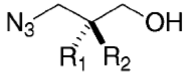
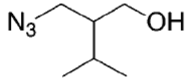
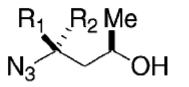
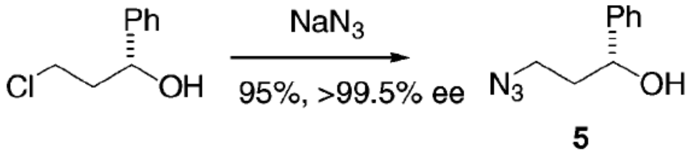

(±)-**7**


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

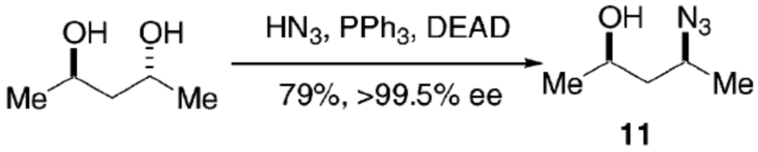

(±)-**10**


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

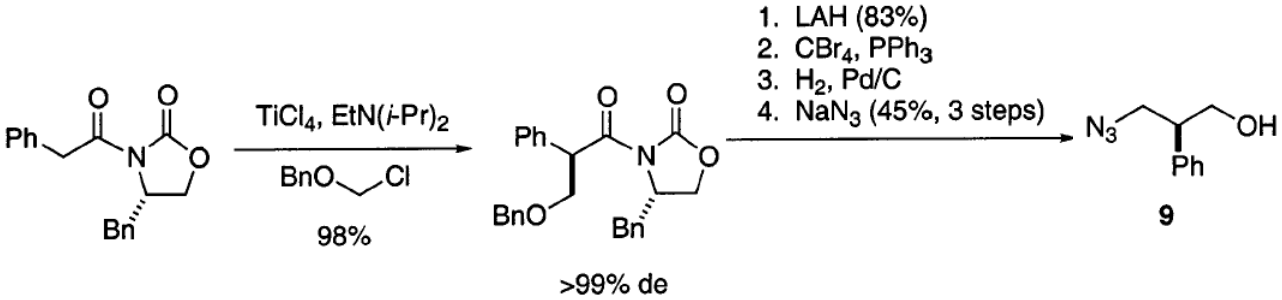
- Simple azide displacement: (compound 5 and 8)



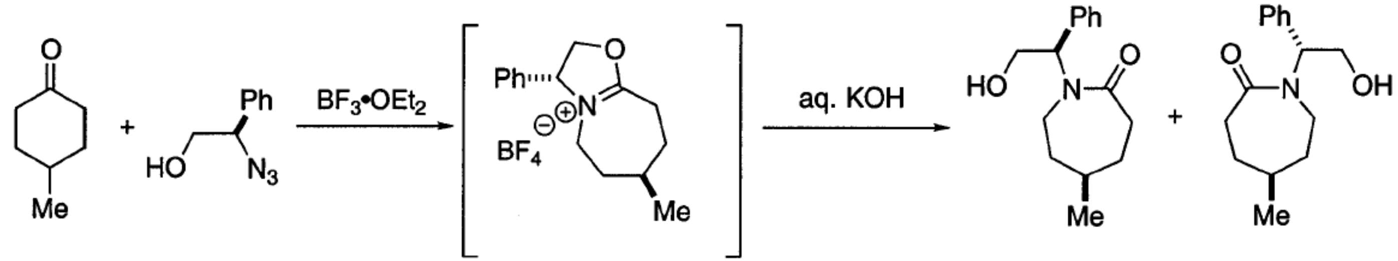
- Mitsunobu reactions: (compound 6,7,10 and 11)



- Multistep pathways: (compound 9 and 12)



Solvent Selection

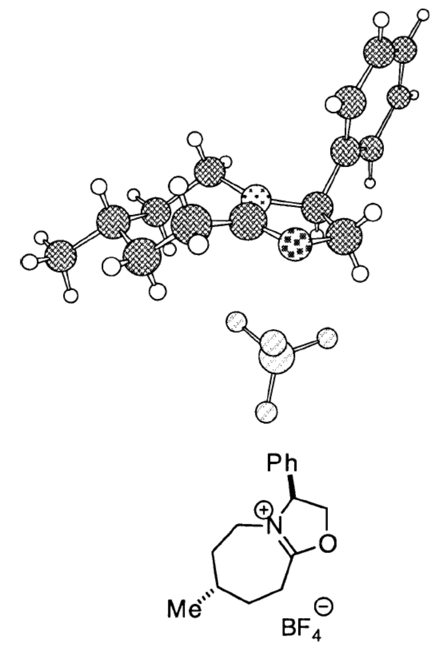


1 **13** **14a** **14b**

Table 1. Reactions of **1** with 4-Methylcyclohexanone

entry	solvent	T (°C)	time (h)	yield (%)[a]	ratio of **14a: 14b**[b]
1	THF	−78→ rt	36	0	–
2	Et_2O	0	21	3[c]	73:27
3	cyclohexane	3	18	74	73:27
4	CH_3CN	−30	18	41	69:31
5	CH_2Cl_2	−30	18	15[c]	83:17
6	CH_2Cl_2	−30	100	62	70:30
7	CH_2Cl_2	0	21	86	69:31
8	CCl_4	−20	18	97	78:22
9	*n*-pentane	−20	23	100	78:22

[a] Isolated yields except where noted. [b] Ratios determined by HPLC of crude reaction mixtures. [c] Yield for this example estimated from HPLC trace.



ent-**13**

Effects of Substituents on Ketones and 1,2-Hydroxyalkyl Azides

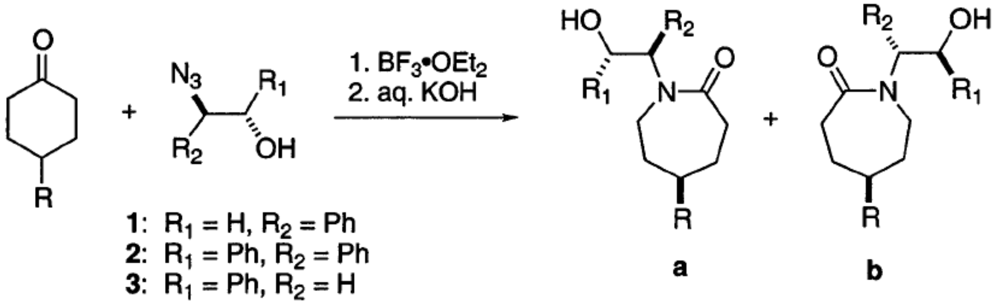


Table 2. Reactions of 1,2-Hydroxyethyl Azides with 4-substituted Ketones

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.
[c] This experiment was done using a racemic hydroxyalkyl azide. [d] Not assigned for this example.

Reactions of 1,3-Hydroxyalkyl Azides

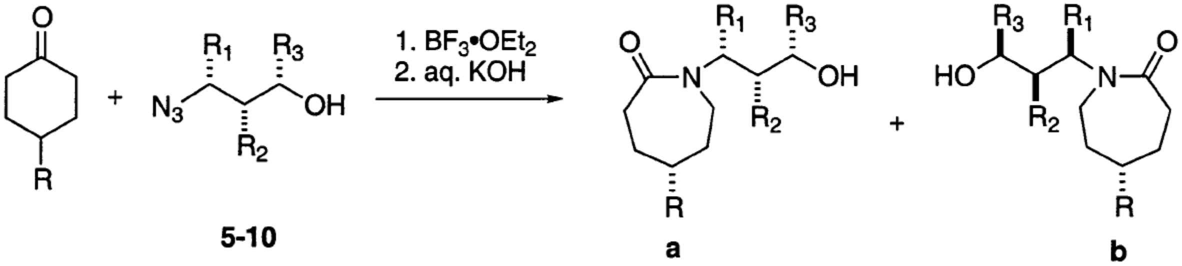


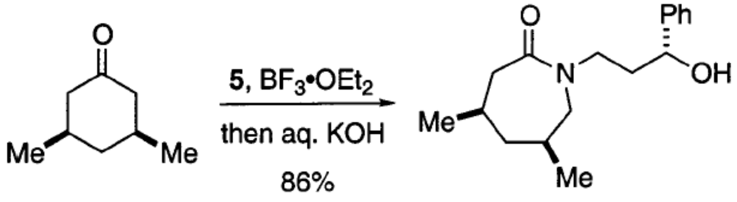
Table 3. Reactions of Monosubstituted 1,3-Hydroxyalkyl Azides with 4-Substituted Cyclohexanones

			azide					
entry	ketone R	azide	R_1	R_2	R_3	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

[a] Ratio determined by HPLC of crude reactionmixtures, except where noted. [b] Total yields of isolated purified lactams. [c] This reaction was done in the enantiomeric series to that shown in this table. [d] This experiment was done using a racemic hydroxyalkyl azide. [e] Ratio estimated by 1H NMR examination of the crude reaction mixture.

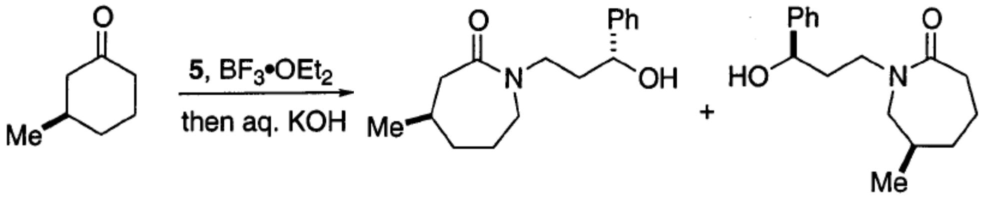
Other Effects of the Ketones

- Meso disubstituted cyclohexanone



35a (major isomer, 98:2 ratio)

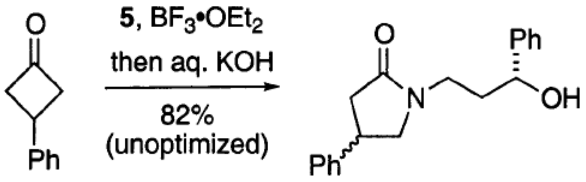
- 3-Substituted cyclohexanone



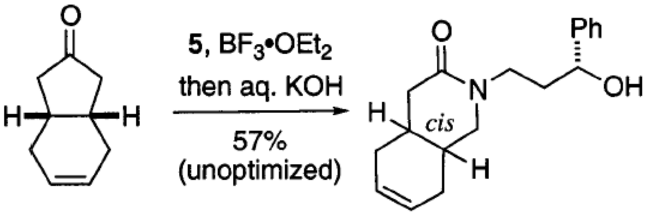
36a (major) **36b**

96% (96:4 ratio)

- Alternative ring sizes



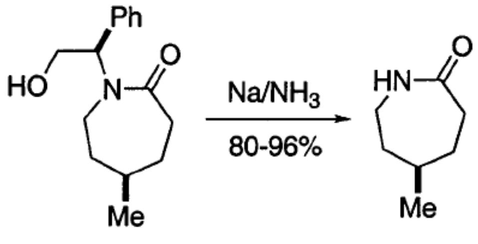
37a,b (65:35 mixture)



38a,b (60:40 mixture)

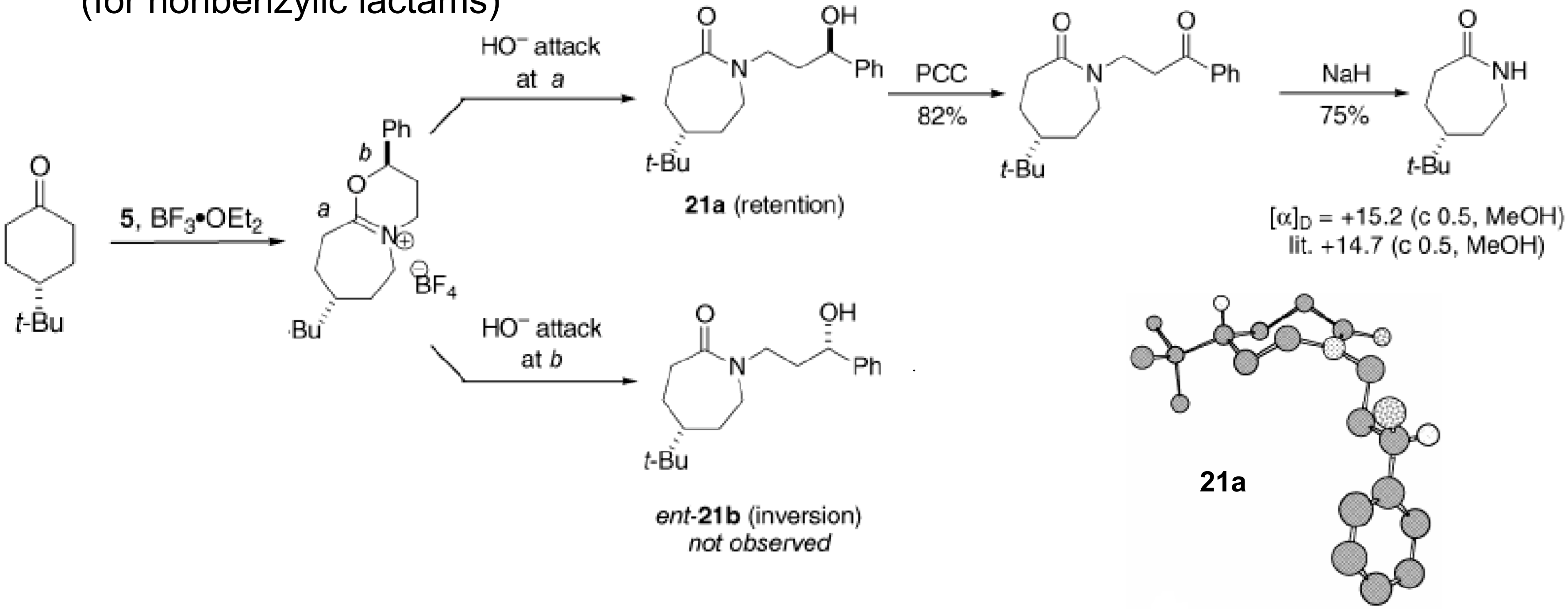
N-Dealkylation of the Lactams

- Dissolving metal reduction:
  (for benzylic lactams)



14a

- Oxidation and elimination:
  (for nonbenzylic lactams)



21a (retention)

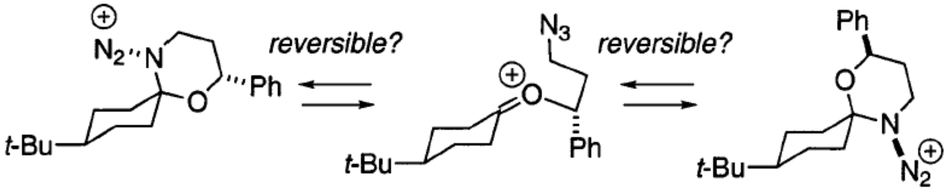
ent-**21b** (inversion)
not observed

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

21a

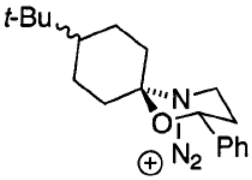
Mechanistic Hypotheses

(a) Equatorial vs. axial addition



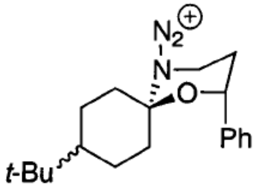
axial *equatorial*

(b) Conformation of the new ring



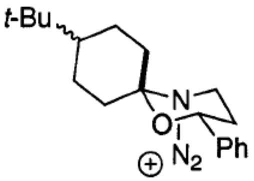
equatorial substituent

vs.

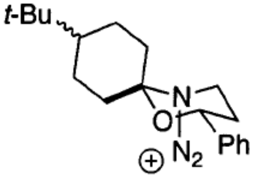


axial substituent

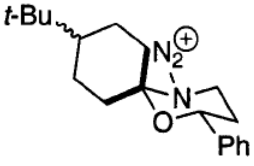
(c) Relationship between leaving group and the migrating bond (the migrating bond is darkened)



antiperiplanar/
axial N_2



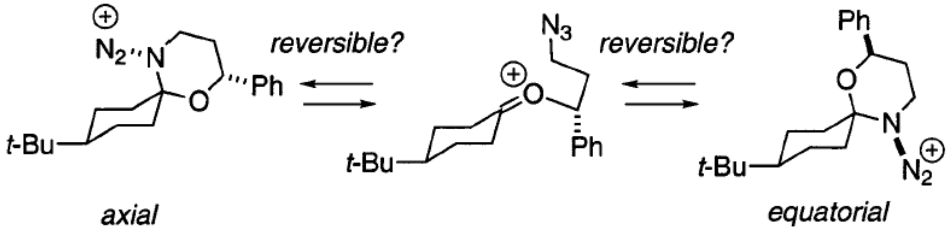
synplanar/
axial N_2



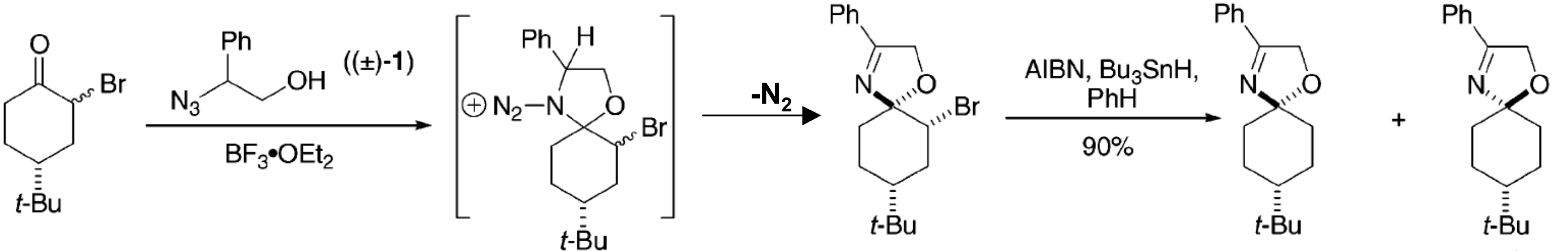
synplanar/
equatorial N_2

Either darkened bond is synplanar to the leaving group in this example.

Addition of Azides



- Example with 1,2-azido alcohol



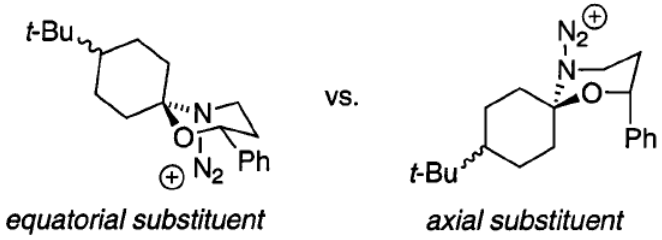
39 (major isomer shown)
47% overall yield of 4 isomers

40a

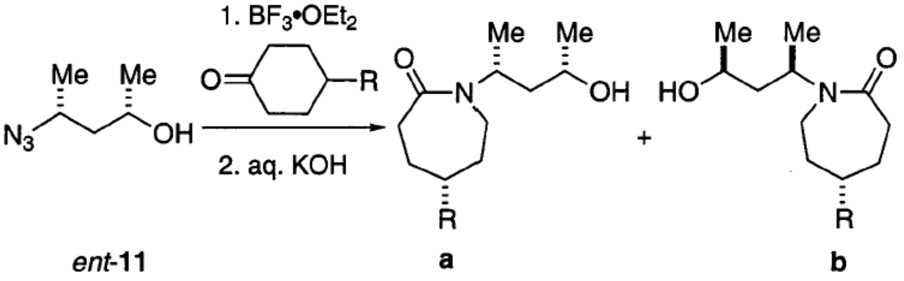
40b

a : **b** = 10 : 1

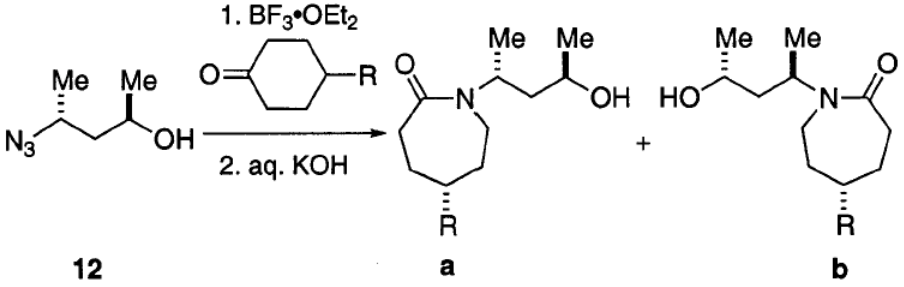
Confomation of the New Ring- A



- Example1:
  Difference in the reaction of cis- and trans- 1,3-azide



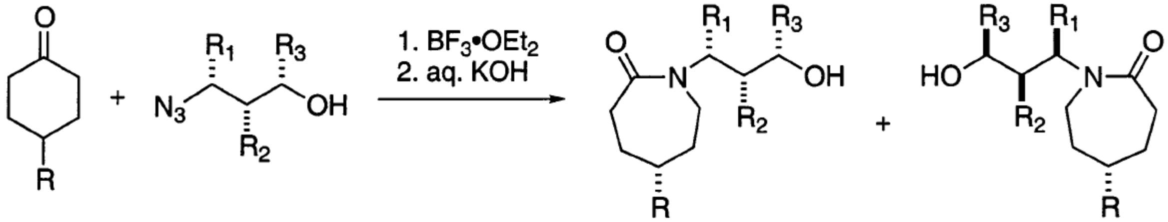
R = Me: **31a** : **31b** = 98:2 (98% yield)
R = *t*-Bu: **32a**: **32b** = 94:6 (94% yield)



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

- Example 2:
  The size of the substituent on azides affect the selectivity.
  Lower selectivity of the 2-substituted azidopropanols. (table 3)

Confomation of the New Ring- B



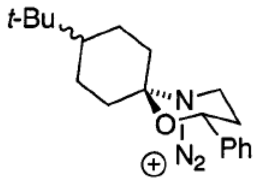
5-10

a

b

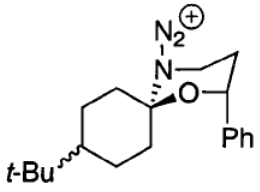
Table 3. Reactions of Monosubstituted 1,3-Hydroxyalkyl Azides with 4-Substituted Cyclohexanones

entry	ketone R	azide	azide R_1	azide R_2	azide R_3	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



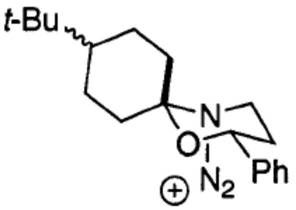
equatorial substituent

vs.

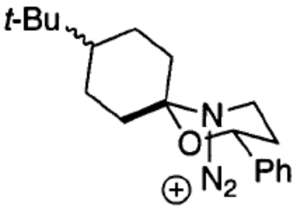


axial substituent

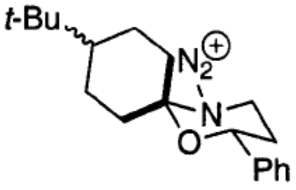
Rationale of Migration



antiperiplanar/
axial N_2



synplanar/
axial N_2

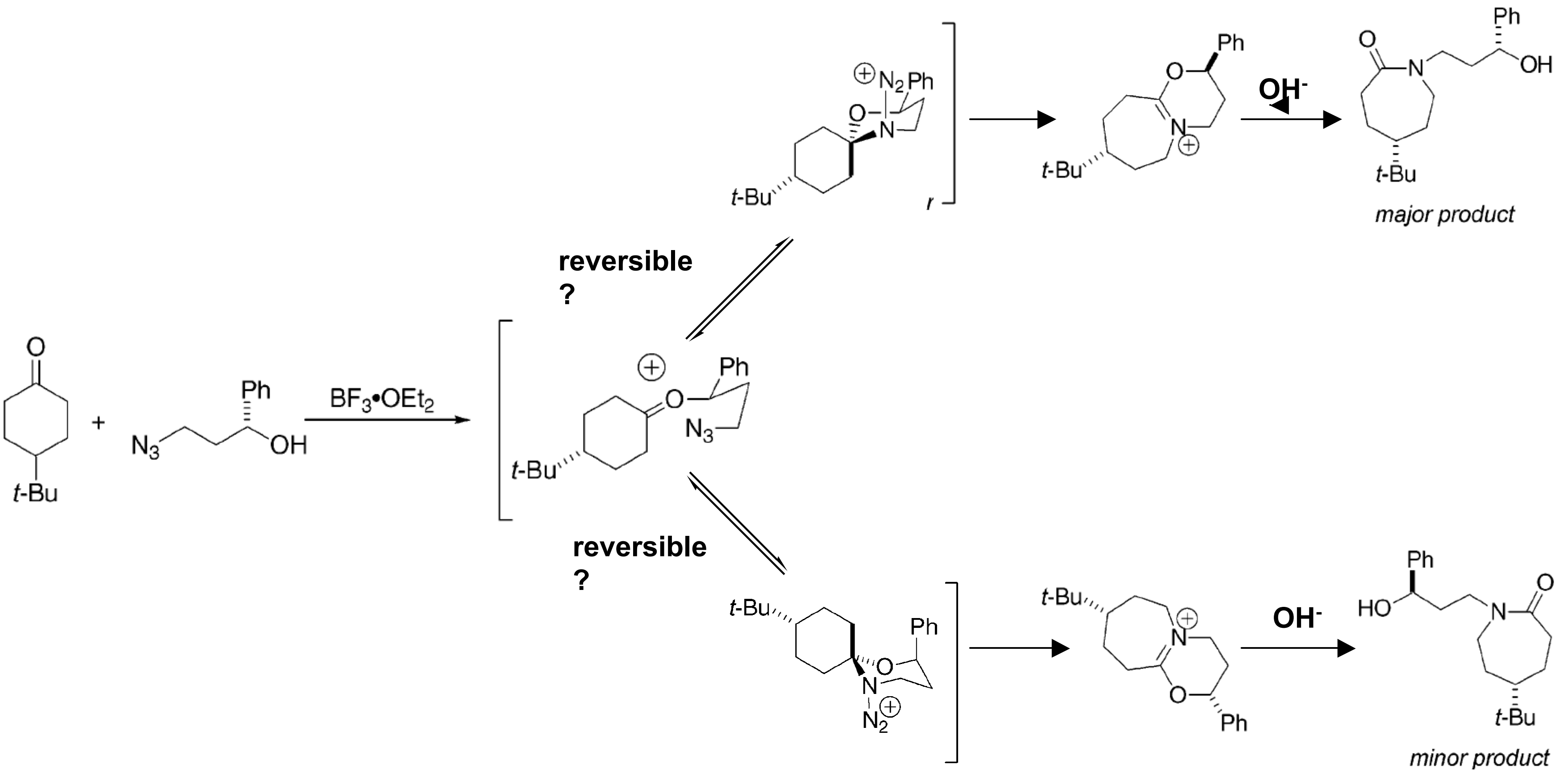


synplanar/
equatorial N_2

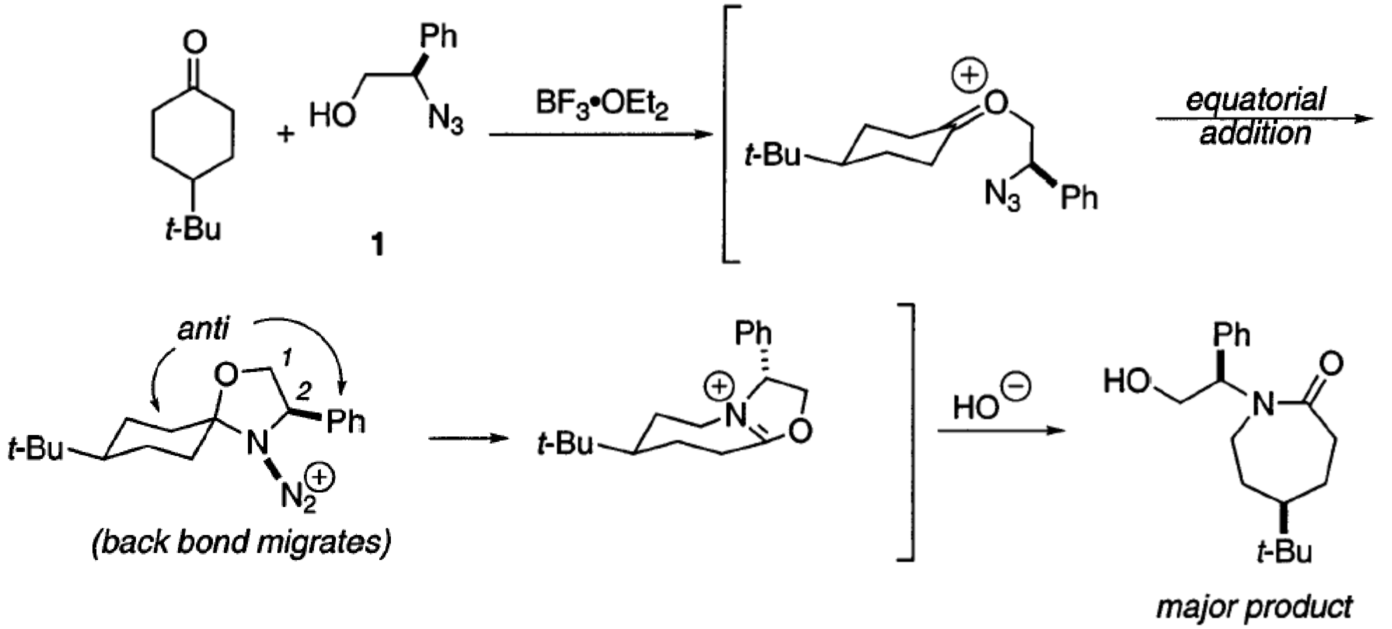
Either darkened bond is synplanar to the leaving group in this example.

- ➢ Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

Mechanistic Hypotheses for Three-Carbon Tethers



Mechanistic Hypotheses for Two-Carbon Tethers



Summary

- An asymmetric equivalent of the Schmidt reaction permits the stereocontrol in ring expansions of symmetrical cyclohexanones. Selectivities can be as high as ca. 98:2.

- 1,3-azido alcohols are generally more reactive and provide superior selectivities than 1,2-azido alcohols.

- Some initial suggestions were proposed as to how the selectivity obtained in the overall process might be achieved.