

# Development and Applications of the Intramolecular Schmidt Reaction

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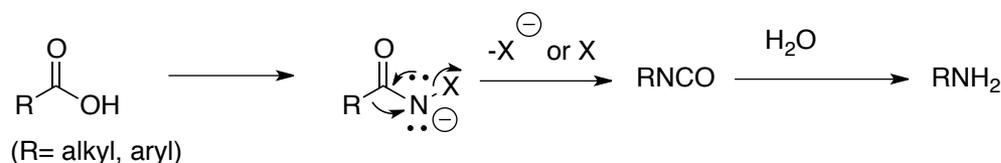
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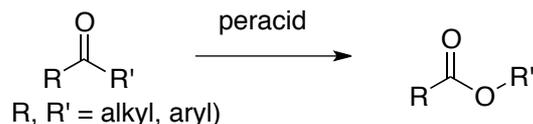
# Overview: Selected Rearrangements

- Carboxylic Acid Derivatives

- X = Br (Hoffmann), N<sub>2</sub> (Curtius)

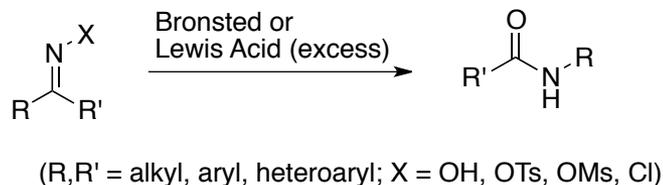


- Baeyer-Villiger Oxidation



- Beckmann Rearrangement:

- Can never form primary amides
- Harsh reaction conditions
- Isomerization of oxime can occur.

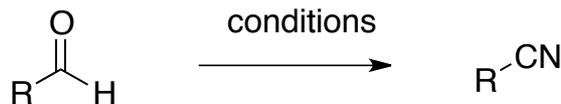
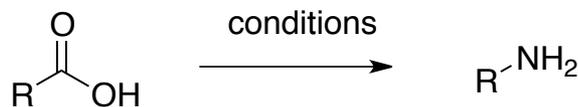
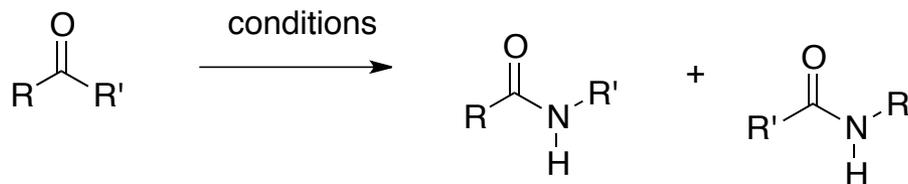


E. Beckmann, Chem. Ber., 89, 998 (1886).

Kürti, Czakó. Strategic Applications of Named Reactions in Organic Synthesis. Burlington: Elsevier, 2005. 4

# Discovery of the Schmidt Reaction

- Classic Schmidt Conditions: Strongly Acidic



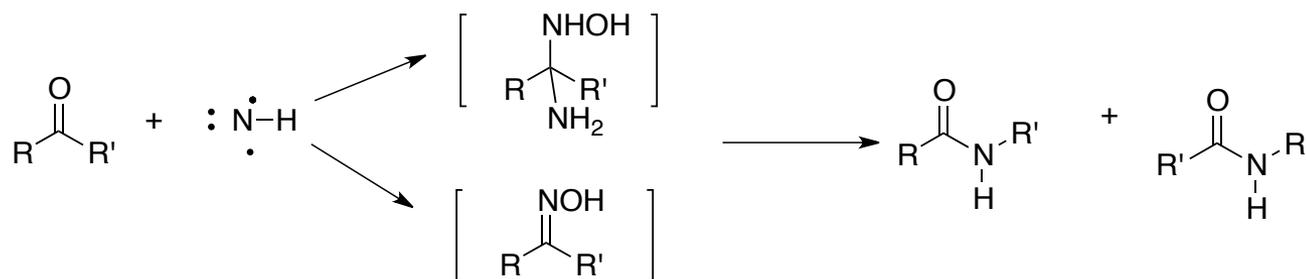
(conditions =  $\text{HN}_3$  (1.0 eq.), conc.  $\text{H}_2\text{SO}_4$  (cat.), benzene)

K.F. Schmidt. Z. Angew. Chem., 1923, 36, 511.

K.F. Schmidt, Ber., 1924, 57, 704.

# Early Mechanistic Proposal

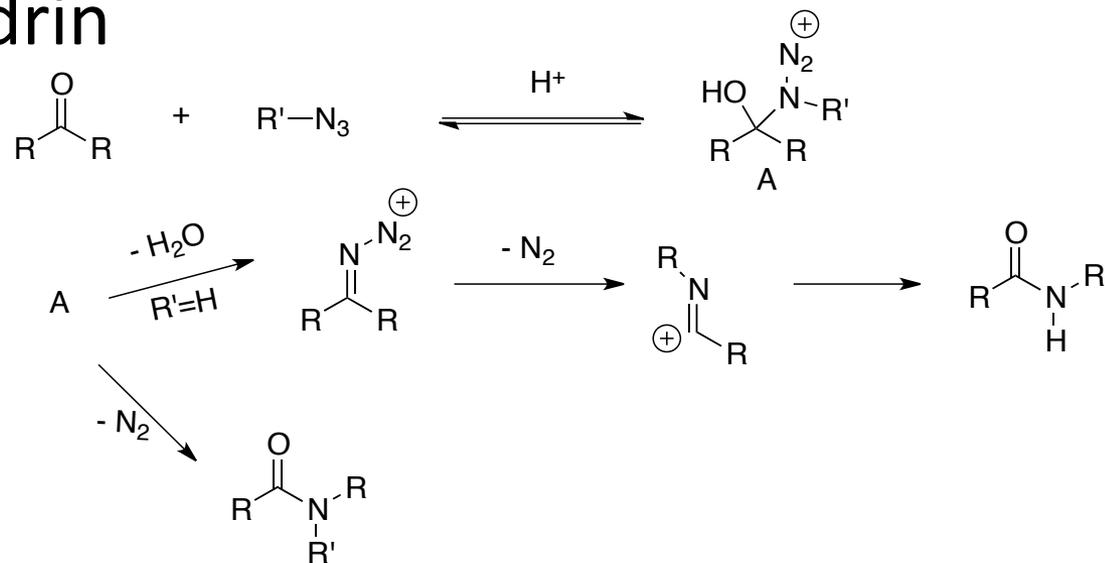
- Schmidt: Hydrazoic acid cleaved into [NH] radical and dinitrogen
  - This nitrene mechanism was ruled out in favor of the accepted pathway, which involves an azidohydrin.



Koldobskii, et. al. Russian Chemical Reviews, 40 (10), 835.

# Modern Understanding of Mechanism

- Two possible decomposition pathways of azidohydrin



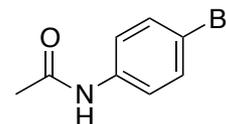
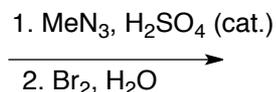
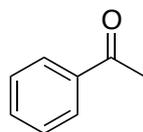
- Direct loss of dinitrogen from A likely occurs when R' ≠ H

Aubé, et. al. J. Am. Chem. Soc. 1995, 117, 10449.

# Attempts to use Alkyl Azides

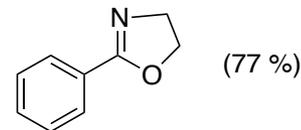
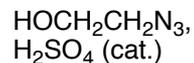
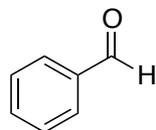
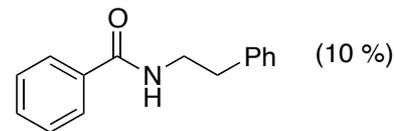
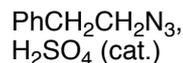
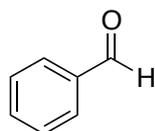
- Almost all alkyl azides unreactive under classical Schmidt conditions

Briggs, Smith (1940s)



(0.9-2.6 %, No N-methyl amides detected)

Boyer (1950s)



(3) (a) Briggs, L. H.; De Ath, G. C.; Ellis, S. R. *J. Chem. Soc.* **1942**, 61–63. (b) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320–323.

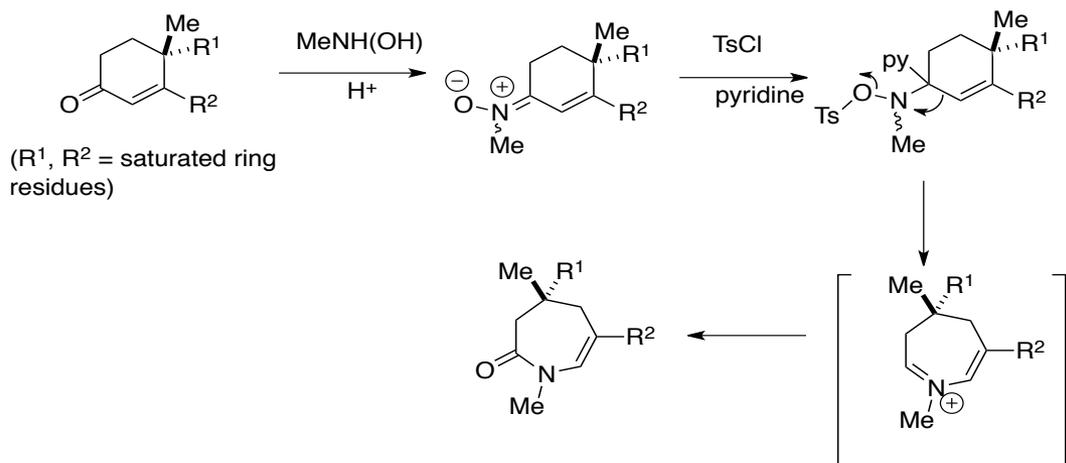
(4) (a) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951–954. (b) Boyer, J. H.; Canter, F. C.; Hamer, J.; Putney, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 325–327. (c) Boyer, J. H.; Morgan, L. R., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 2020–2021. (d) Boyer, J. H.; Morgan, L. R., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 3369–3372. (e) Boyer, J. H.; Morgan, L. R., Jr. *J. Org. Chem.* **1959**, *24*, 561–562.

# Evolution of the Reaction up to the 1990s

- Barton (1971)
- Jeffs (1973)
- Wasserman (1971, 1973)
- Hoffmann (1989)

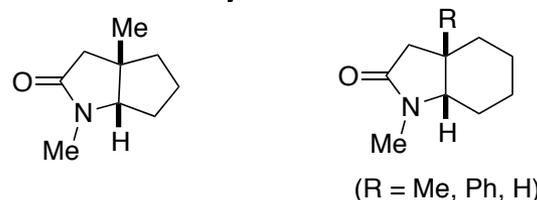
# Barton and Jeffs

- Barton:  $\alpha,\beta$ -unsaturated cyclic hydroxylamines to generate N-methylamides.



- Jeffs extended this method to generate N-methyloctahydroindoles and 2-azabicyclo[3.3.0]octan-3-ones from cyclobutanones.

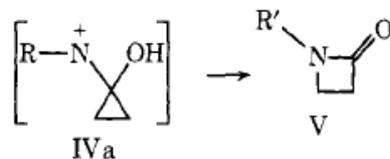
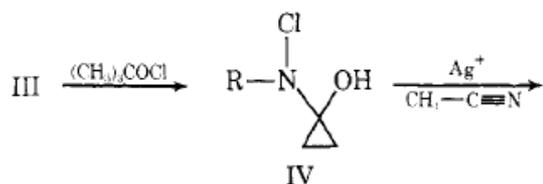
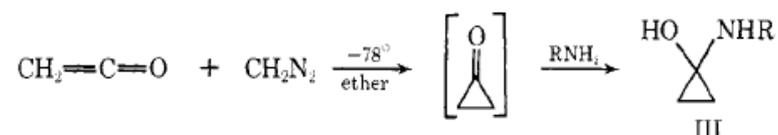
– Same reagents as above



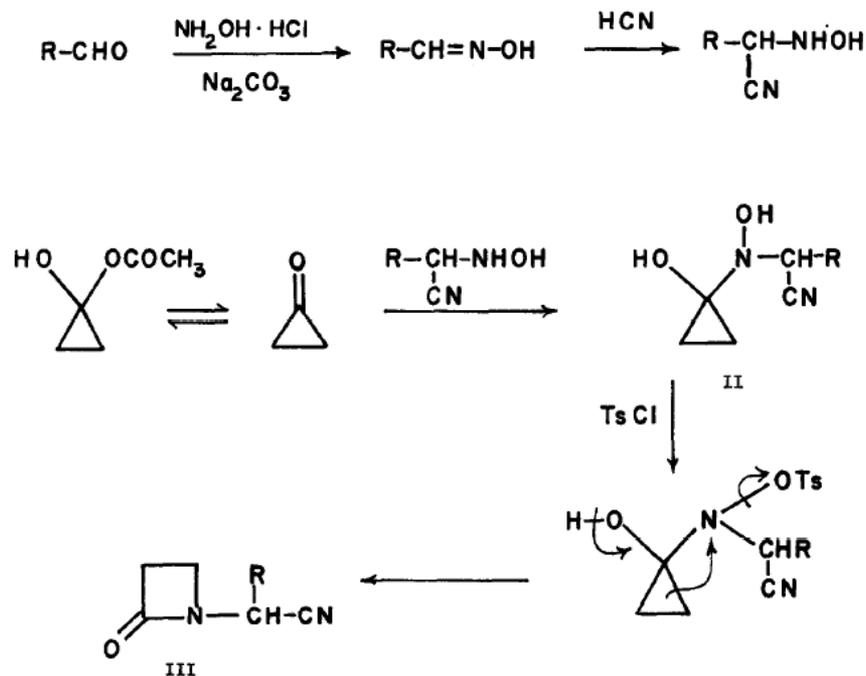
a. Barton, D.H.R.; Day, M. J.; Hesse, R. H.; Pechet, M. M., Chem. Commun., 1971, 945. b. *ibid.*, J. Chem. Soc., Perkins Trans. 1, 1975, 1764. c. Jeffs, P. W.; Molina, G., Chem. Commun., 1973, 3.

# Wasserman

- Wasserman, et. al. generated  $\beta$ -lactams from cyclopropanones



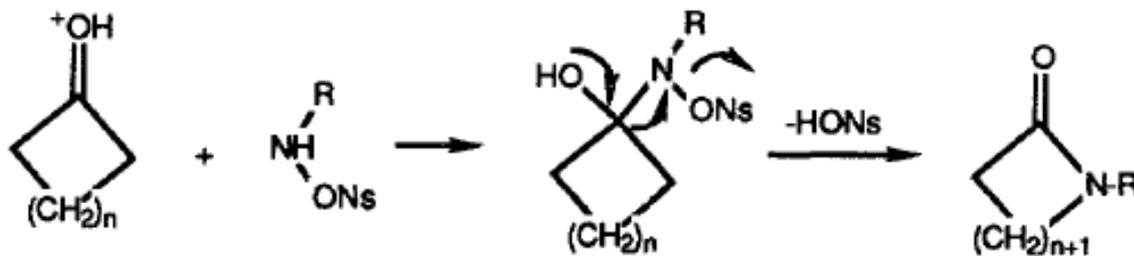
R' = n-hexyl, n-butyl, sec-butyl,  
 $\alpha$ -(ethyl propionate)



R = n-propyl, iso-propyl, n-butyl, isobutyl, Ph

# Hoffmann

- Hoffmann used N-nosylmethylamines to generate N-methyl lactones with ring sizes from 5 to 8 in high yields ( $n=1$  to  $n=4$ ).



- R is only variable when  $n=1$  (R = allyl, propargyl, butyl, benzyl)

R.V. Hoffmann, et. al. Tet. Lett. 1989, 30, 4207.

# Schultz

- Azidoenone chemistry

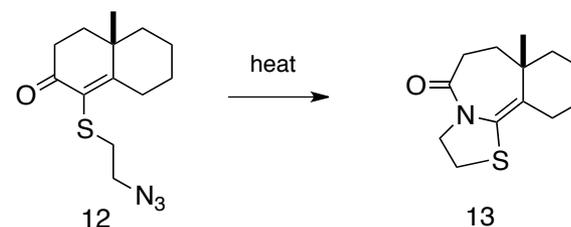
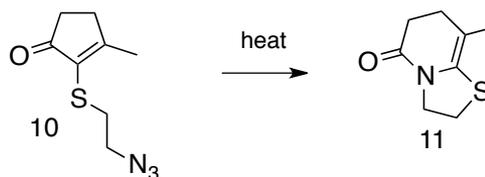
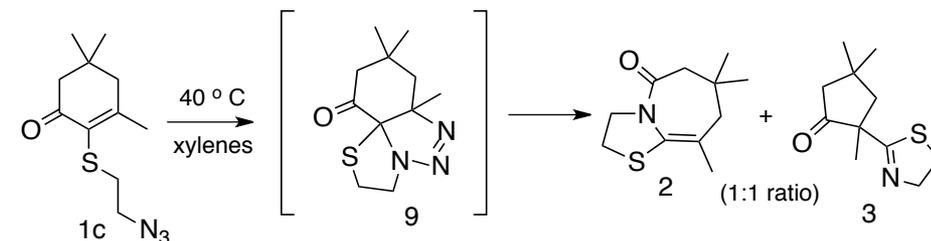
- Both ring expansion and contraction possible

- Outcome is substrate-dependent
- Ring contraction via acyl migration

- Authors propose a [3+2] cycloaddition pathway

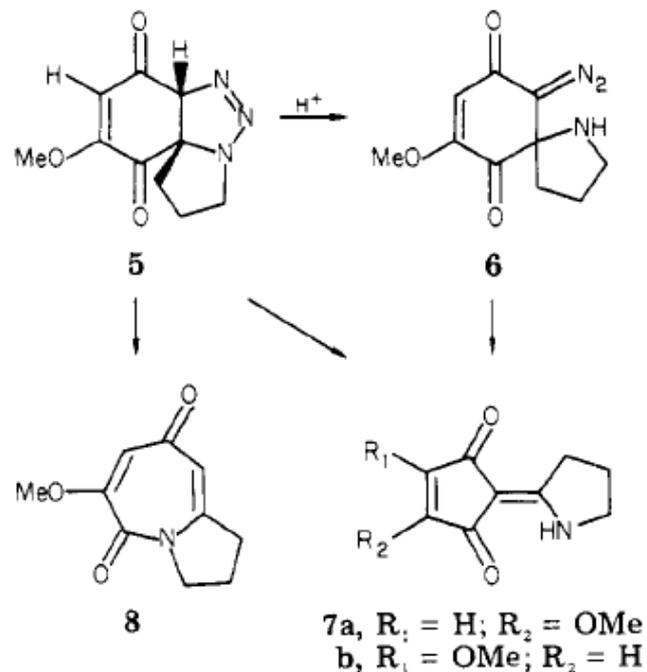
- Control experiments rule out possibility of direct intramolecular Schmidt reaction

- 1c simply decomposed to the corresponding aldehyde in concentrated  $\text{H}_2\text{SO}_4$  ( $\text{RSCH}_2\text{CHO}$ )



# Schultz (cont.)

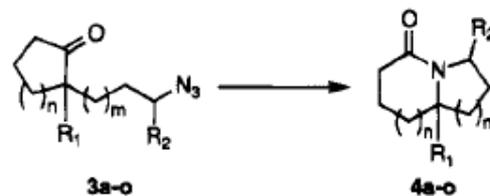
- (Azidoalkyl)-1,4-benzoquinones
  - Authors propose that dinitrogen loss occurs in the same step as ring expansion or contraction.
  - 6 is not an intermediate in the transformation of 5 to 8 or 5 to 7a/7b



(6) (a) Schultz, A. G.; Ravichandran, R. *J. Org. Chem.* **1980**, *45*, 5008–5009. (b) Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676–1678.

# Intramolecular Schmidt Reaction with Cyclic Ketones

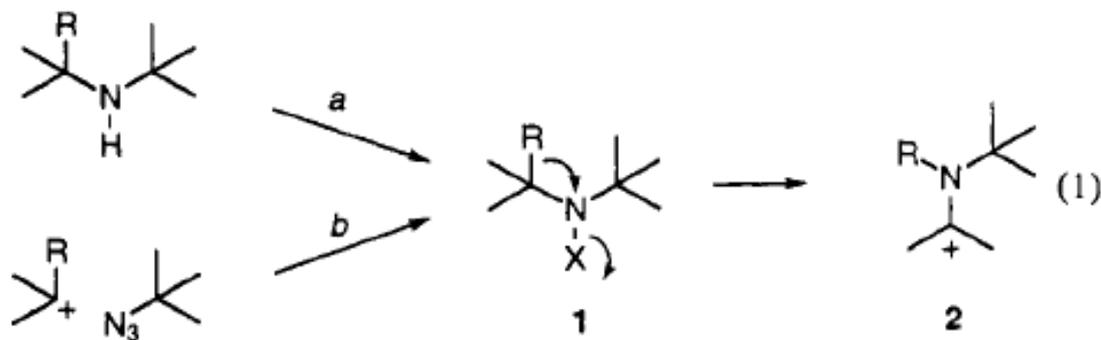
- Tethered azide will necessarily have smaller entropy change upon azidohydrin formation.
- Aubé establishes reaction conditions and importance of tether length ( $m=1$ ).
- Variety of ring sizes lead to high yields ( $n=0$  to  $n=8$ ) for cyclic ketones.



entry	compd <sup>a</sup>	$n$	$m$	$R_1$	$R_2$	conditions <sup>b</sup>	yield (%) <sup>c</sup>
1	<b>a</b>	0	1	Me	H	TFA, 0.25 h	66
2	<b>b</b>	1	1	H	H	TFA, 0.75 h	83
3	<b>b</b>					TiCl <sub>4</sub> , 16 h	64
4	<b>c</b>	1	1	CO <sub>2</sub> Me	H	TFA, 16 h	66
5	<b>c</b>					TiCl <sub>4</sub> , 0.5 h	70
6	<b>d</b>	1	1	H	Me	TiCl <sub>4</sub> , 16 h	68
7	<b>e</b>	1	2	H	H	TiCl <sub>4</sub> , 16 h	56
8	<b>f</b>	2	0	H	H	TFA, 24 h	0 <sup>d</sup>
9	<b>g</b>	2	1	H	H	TFA, 3.5 h	85
10	<b>h</b>	2	1	CO <sub>2</sub> Et	H	TFA, 1 h	93
11	<b>i</b>	2	1	H	Me	TFA, 0.25 h	74
12	<b>j</b>	2	2	H	H	TFA, 16 h	0 <sup>d</sup>
13	<b>j</b>					BF <sub>3</sub> ·OEt <sub>2</sub> , 16 h	29
14	<b>j</b>					TiCl <sub>4</sub> , 16 h	91
15	<b>k</b>	2	3	H	H	TiCl <sub>4</sub> , 16 h	0 <sup>d</sup>
16	<b>l</b>	3	1	H	H	TFA, 3 h	80
17	<b>m</b>	3	2	H	H	TiCl <sub>4</sub> , 16 h	0 <sup>d</sup>
18	<b>n</b>	4	1	H	H	TFA, 16 h	96
19	<b>o</b>	8	1	H	H	TFA, 2 h	89

# Intramolecular Schmidt Reaction with Azido alkenes and azido alcohols

- Pearson built upon Aubé's work to generate bridged and fused bicyclic amines
  - Lewis acid (TfOH or TfOH/Tf<sub>2</sub>O) typically present in superstoichiometric amounts

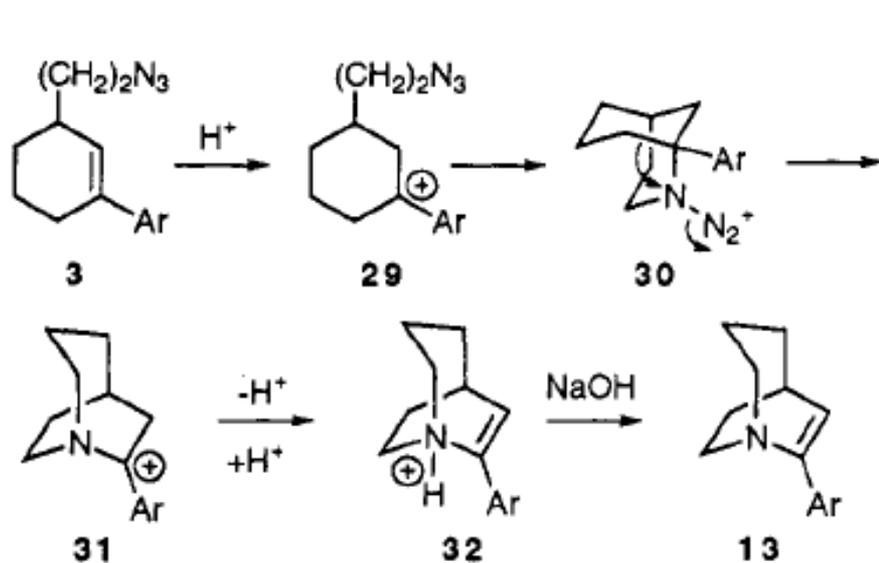


Stieglitz: X = Cl, OSO<sub>2</sub>Ar, etc.

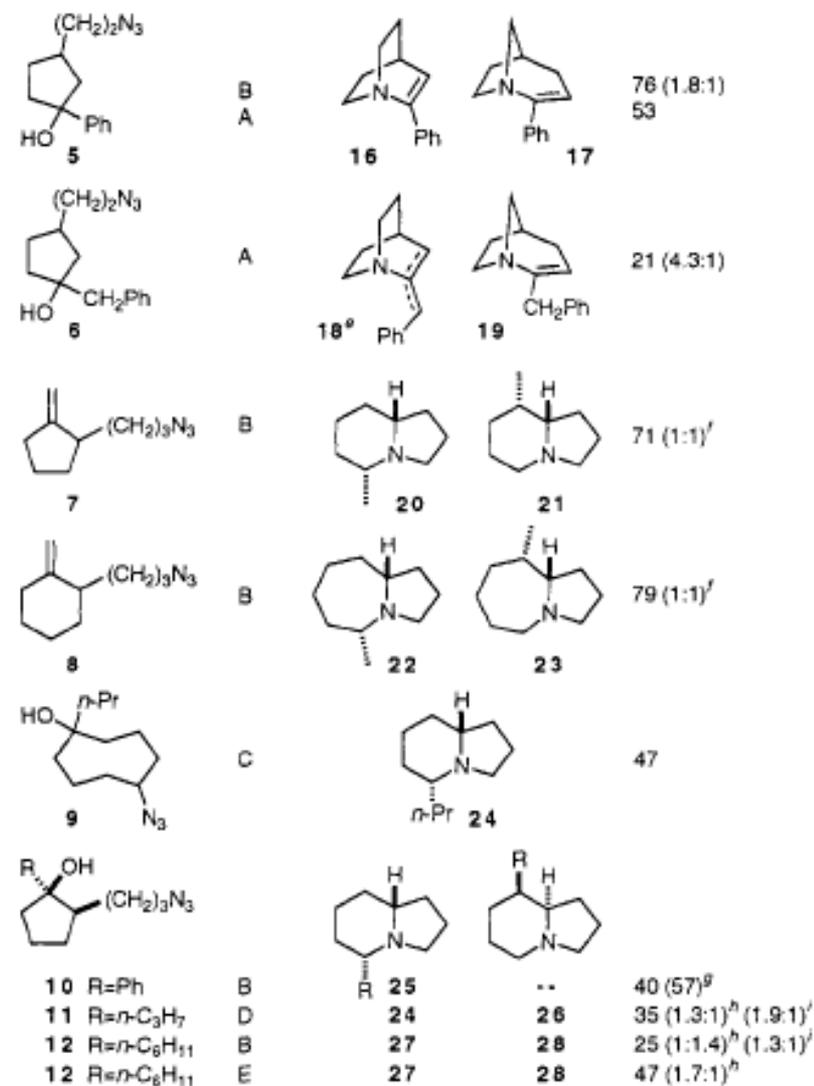
Schmidt: X = N<sub>2</sub><sup>+</sup>

(12) (a) Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.* **1992**, *33*, 5291–5294. (b) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183–10194. (c) Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682–2684.

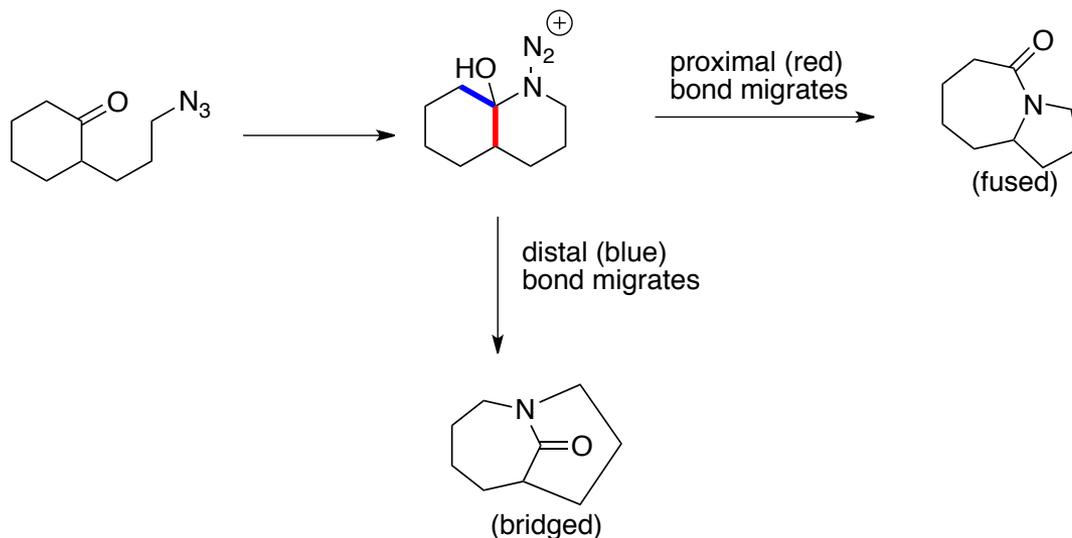
# Pearson (cont.)



- d.r. and regioselectivity generally low



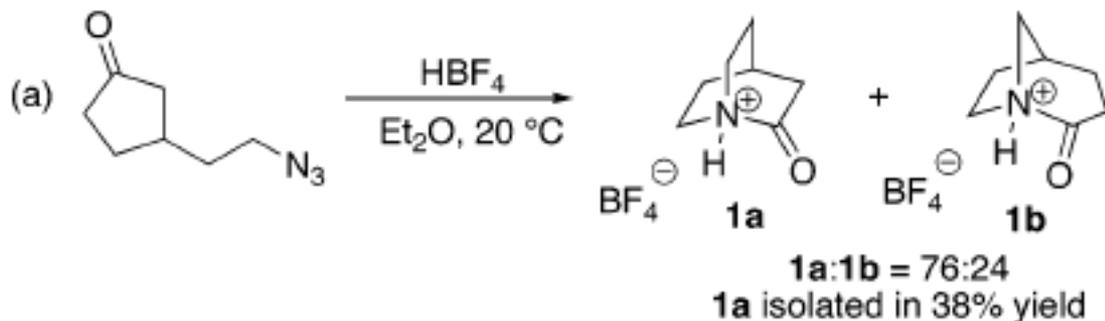
# Cyclic Ketone: Migrational Possibilities



- Azidoalkyl group in the position  $\alpha$  to the carbonyl leads to two possible migrations

# $\beta$ -(azidoalkyl)ketones

- Only bridged lactams possible
  - Intermediate is automatically bridged
    - Selectivity: *which* bridged lactam is formed
  - Familiar quinuclidone prepared by Stoltz

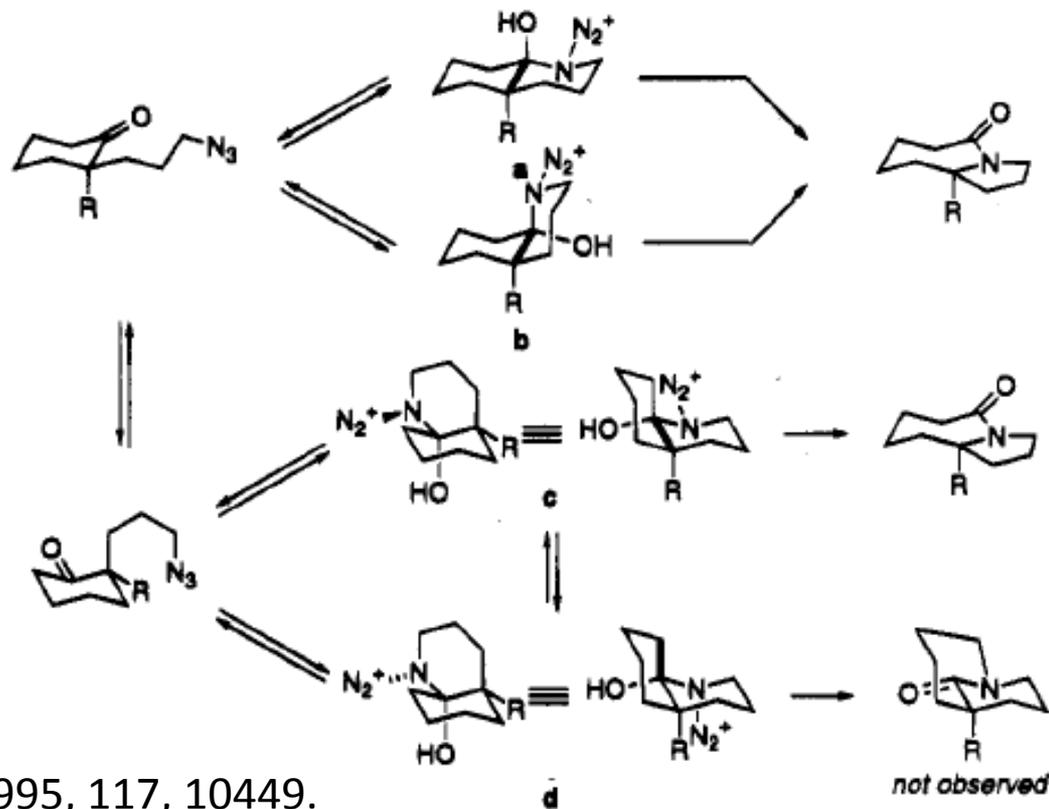


Aubé, et. al. J. Org. Chem. 2010, 75, 1235.

Tani, K.; Stoltz, B.M. Nature 2006, 441, 731.

# Migrational result on Constitution

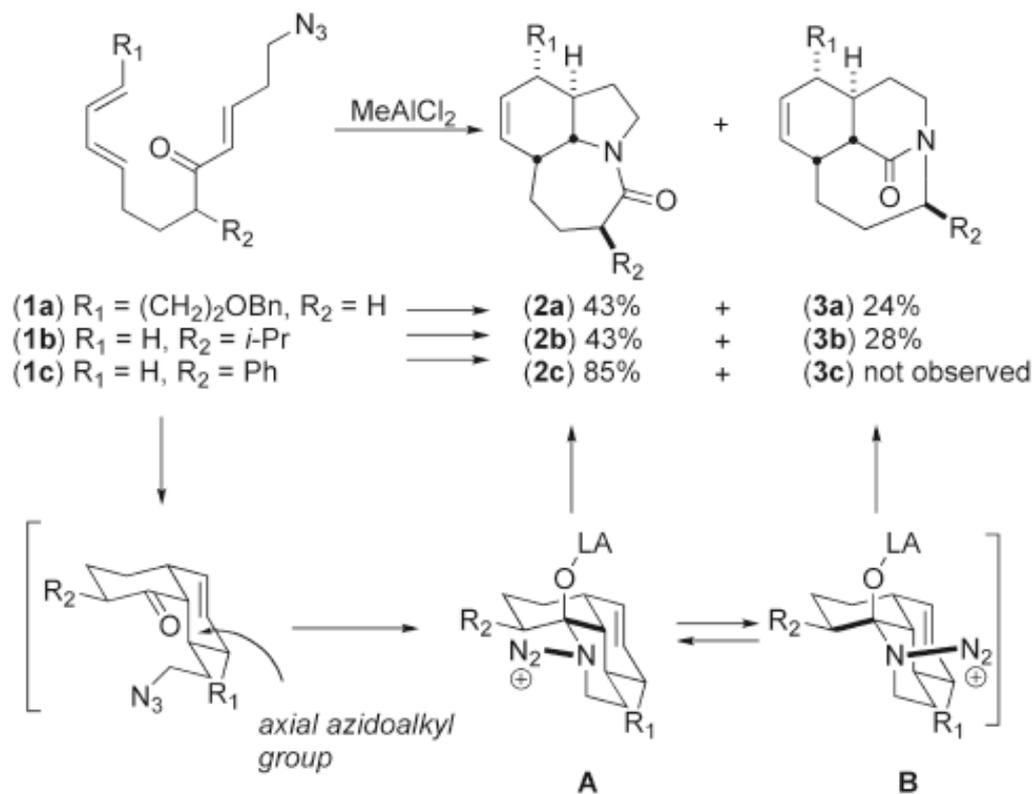
- Fused product can form from either axial or equatorial azidoalkyl group
- Bridged can only form from axial orientation.



Aubé, et. al. J. Am. Chem. Soc. 1995, 117, 10449.

# Unexpected Bridged Products

- Unexpected bridged lactam (stenine synthesis).
- Key insight: consequence of axial/equatorial leaving group

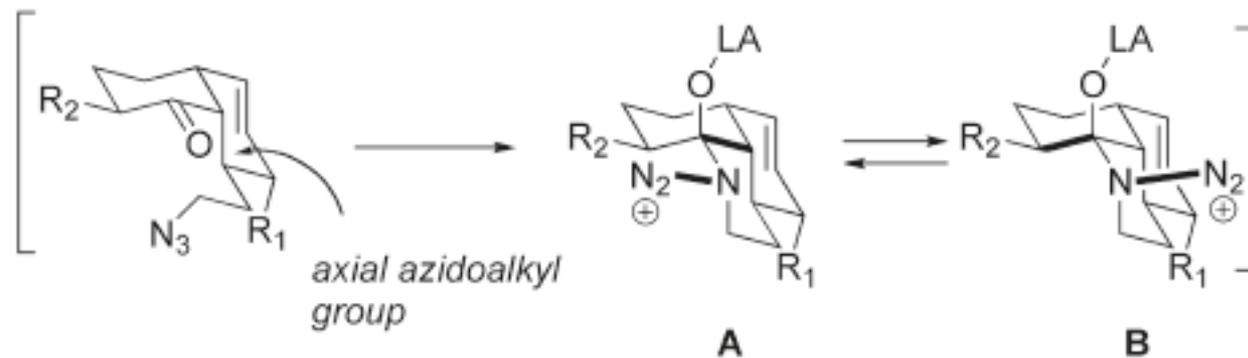


Aubé, et. al. *Angew. Chem. Int. Ed.* 2002, 41, 4316.

Aubé, et. al. *J. Org. Chem.* 2010, 75, 1235.

# Extensions

- Aubé puts *i*-Pr at R<sup>2</sup> to disfavor conformer A
  - Selectivity unchanged
- Ph tested at R<sup>2</sup> on the basis of *A* values
  - Dramatic increase in fused:bridged ratio
  - Cation- $\pi$  interaction invoked



# Development of a Model System

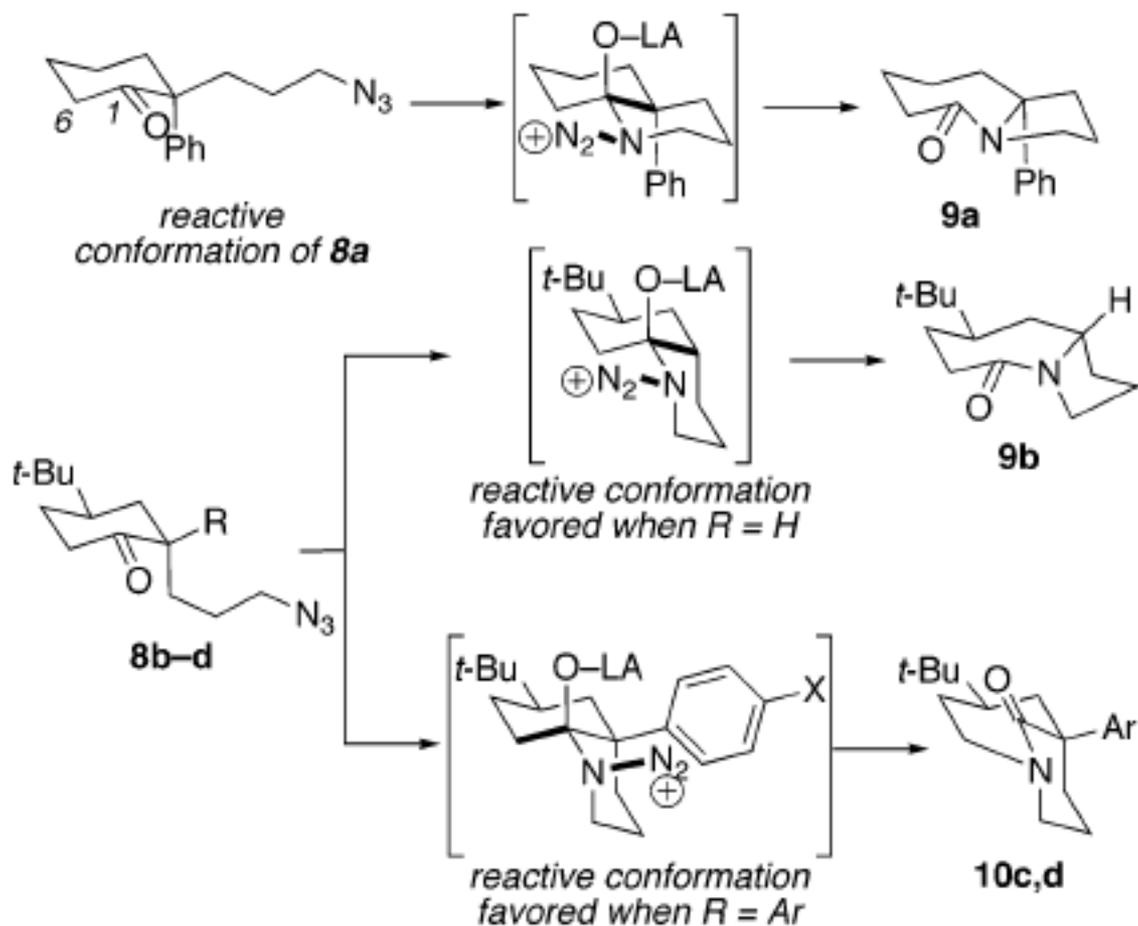
- Goal: Dissect what factors govern bridged selectivity
- Cyclohexanones as model substrates
  - Aryl group alone is insufficient (entry 1)
  - 4-tert-butylcyclohexanones used to favor axial azidoalkyl conformation
- Conclusion:
  - Both the axial azidoalkyl tether and a 1,3 diaxial interaction between the leaving group and an aryl group are required.
  - Azido alkyl must also be in the 2-position

**Table 1.** Synthesis of Fused and Bridged Lactams



entry	8-10	R <sub>1</sub>	R <sub>2</sub>	yield (%)	
				9	10
1	a	H	Ph	96	0
2	b	<i>t</i> -Bu	H	57	17
3	c	<i>t</i> -Bu	Ph	20	51
4	d	<i>t</i> -Bu	<i>p</i> -(MeO)C <sub>6</sub> H <sub>4</sub>	10	65

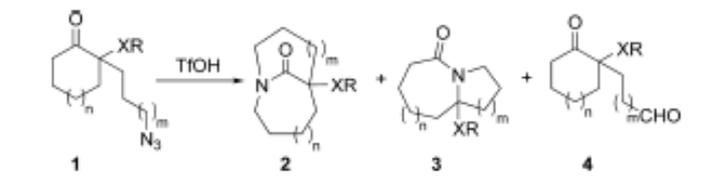
# Conformational Rationale of cation- $\pi$ Interaction



# Other Cation-stabilizing groups

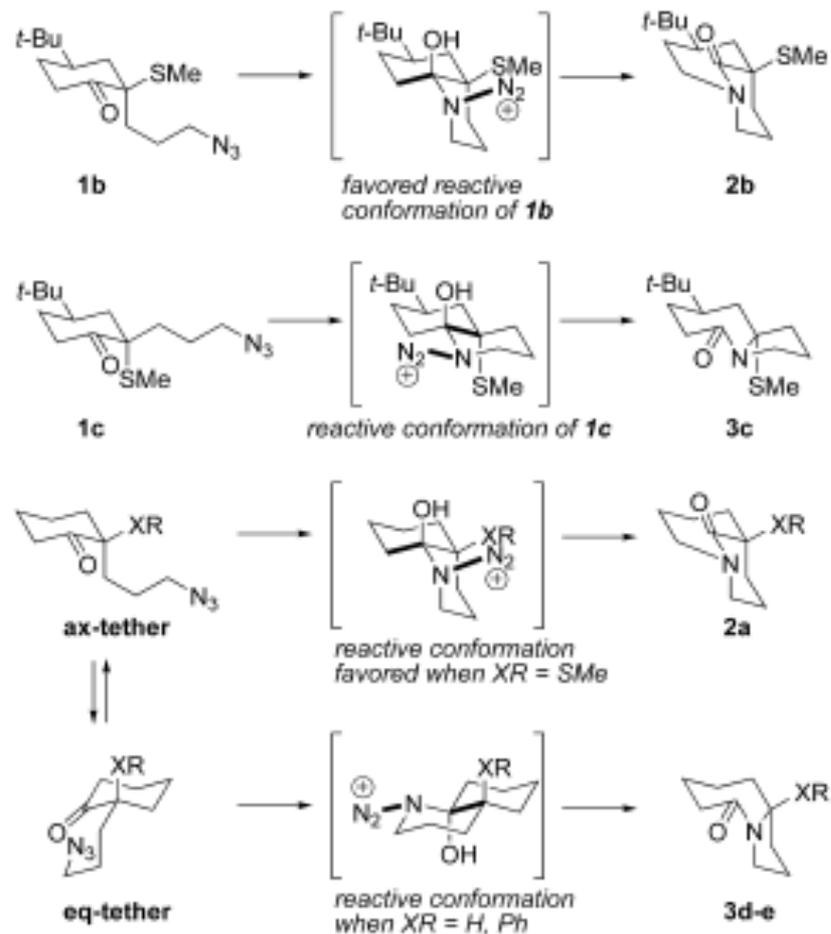
- Thioalkyl (SR) group stabilizes cations in a through-space interaction with cationic leaving group
- Sulfone apparently allows for cation-pi interaction
- Tether length important

**Table 2.** Effect of Substituents and Ring Sizes on Synthesis of Bridged and Fused Lactams



entry	azide	XR	n	m	yield (%)		
					2	3	4
1	<b>1a</b>	SMe	1	1	65	15	-
2	<b>1g</b>	SPh	1	1	35	32	-
3	<b>1h</b>	OMe	1	1	23	52 <sup>a</sup>	-
4	<b>1i</b>	SO <sub>2</sub> Me	1	1	48	13 <sup>a</sup>	-
5	<b>1j</b>	SMe	0	1	-	43	-
6	<b>1k</b>	SMe	2	1	62	11 <sup>a</sup>	20
7	<b>1l</b>	SMe	3	1	-	-	30
8	<b>1m</b>	SMe	1	2	-	-	53

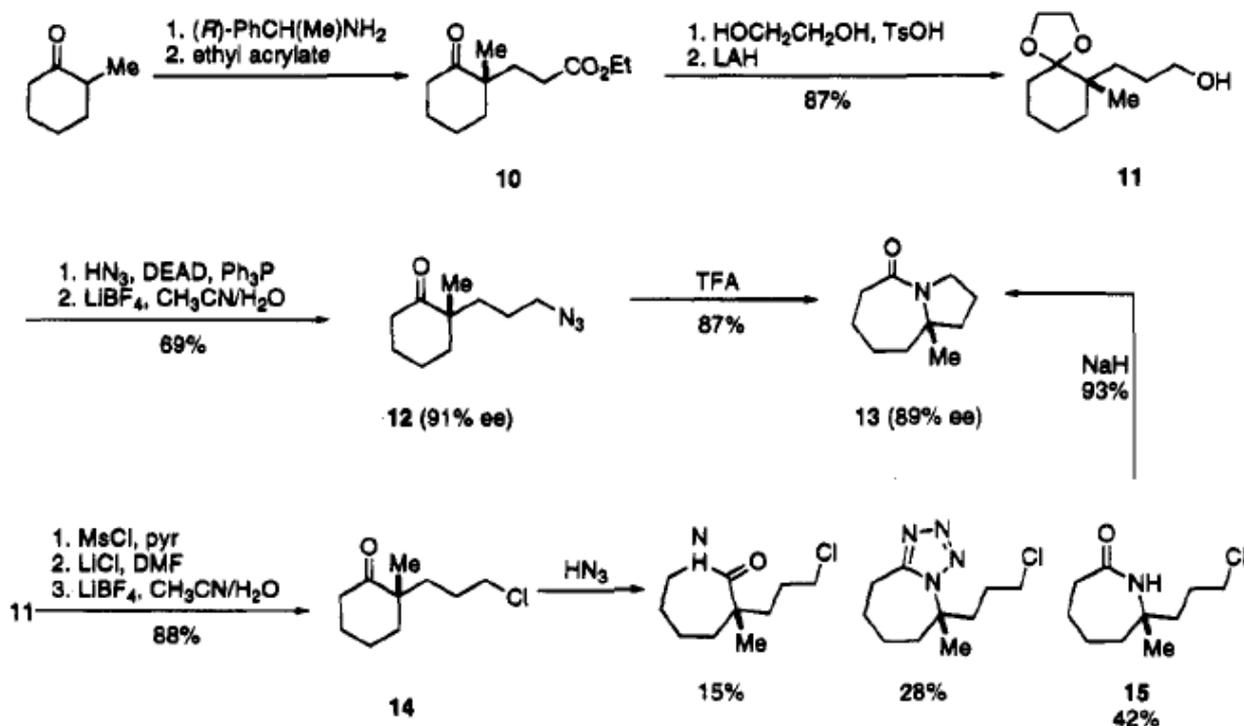
<sup>a</sup> Combined yield of elimination products;<sup>11</sup> see Supporting Information for full details.



Aubé, et. al. Org. Lett, 2009, 11, 4386.

# Stereochemistry of the Migrating Carbon

- Model substrate shows retention of stereochemistry



Aubé, et. al. J. Am. Chem. Soc. 1995, 117, 10449.

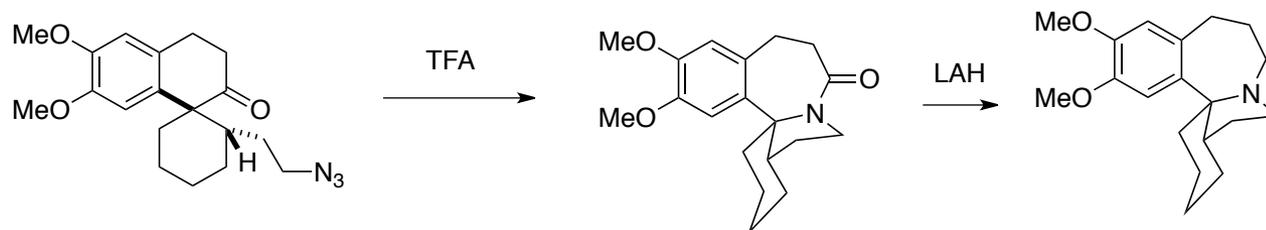
# Stereochemistry

- No epimerization takes place under reaction conditions.



- Few asymmetric variants developed
  - One diastereoselective variant discovered in the total synthesis of ( $\pm$ )-demethoxy-1,2-dihydrocomosidine

# (±)-demethoxy-1,2-dihydrocomosidine



- Jean d'Angelo, et. al. were looking for new routes to Homoerythrina Alkaloids
  - All stereocenters are set prior to the intramolecular Schmidt reaction via tandem alkylation/Michael addition of 2-tetralone to 7-iodo-tert-butylhept-2-eneoate

# Optimization of the Reaction

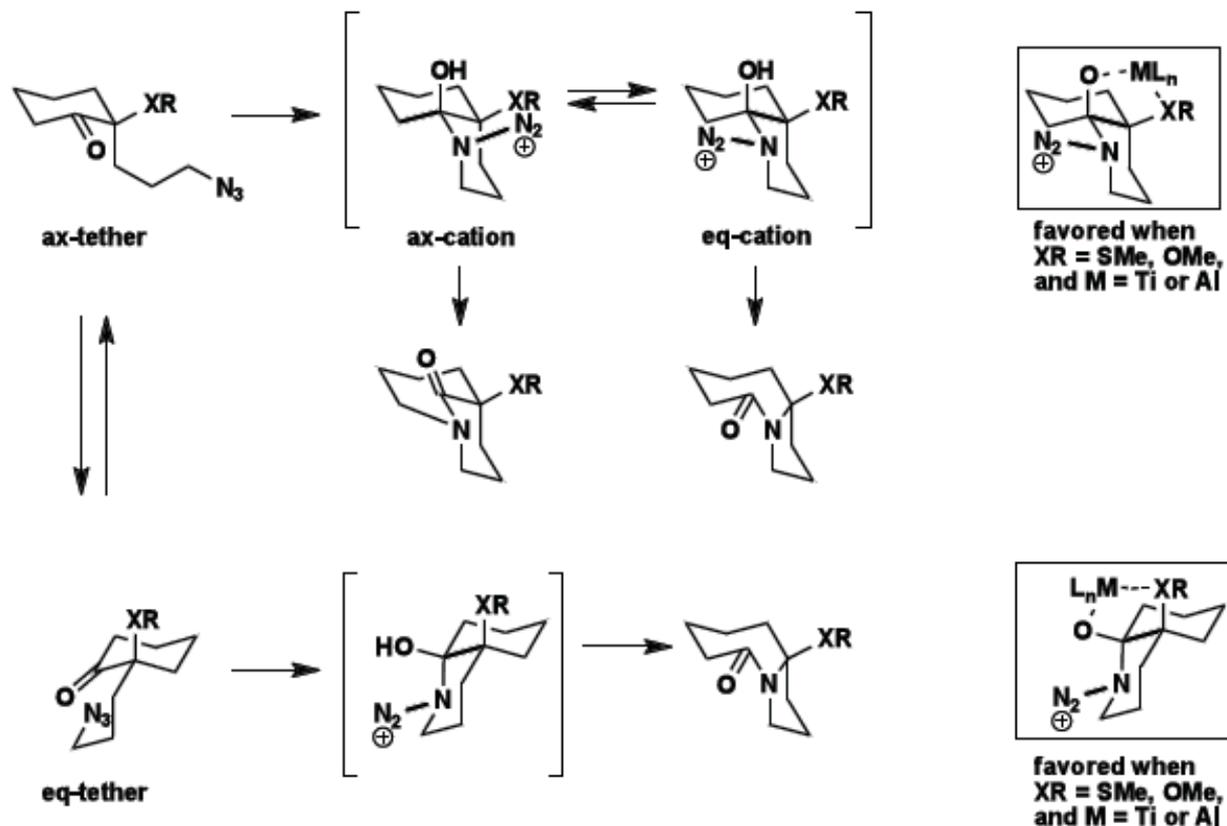
- Choice of Lewis Acid is substrate-specific
  - Few general trends
  - Typically 1.0-4.0 eq.
    - $\text{TiCl}_4$ , TFA, TfOH (cyclic ketones, linear RCHO)
    - $\text{MeAlCl}_2$  (tandem Diels-Alder/Schmidt)
    - $\text{BF}_3$  (orthoamides): bridged selectivity
- Use of orthoamides
  - Moderate to high yields of exclusively bridged lactams

Aubé, et. al. J. Am. Chem. Soc. 1995, 117, 10449.

Aubé, et. al. J. Org. Chem. 2010, 75, 1235.

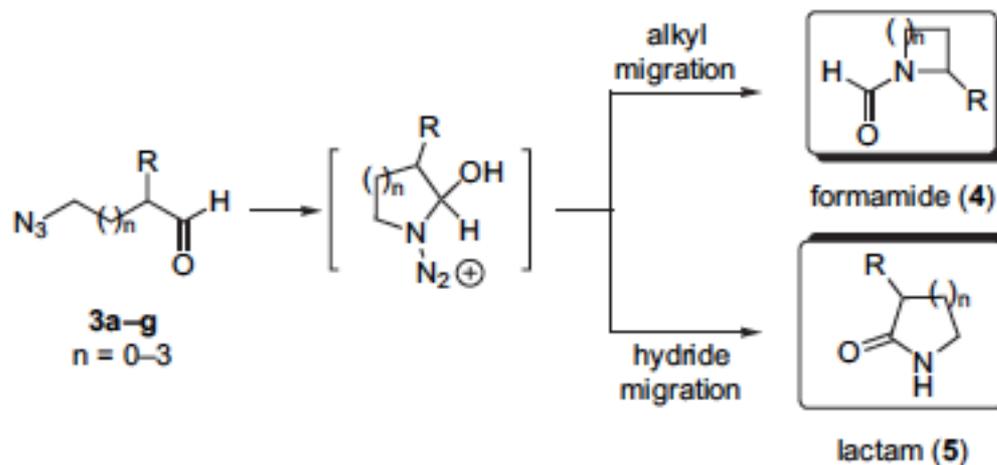
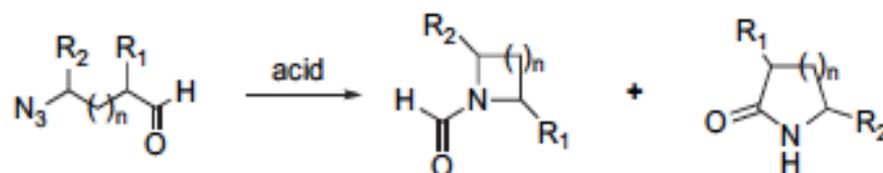
Aubé, et. al. J. Am. Chem. Soc. 2010, 132, 2530.

# Role of Lewis Acid: Thiomethyl, methoxy



# Reaction Scope

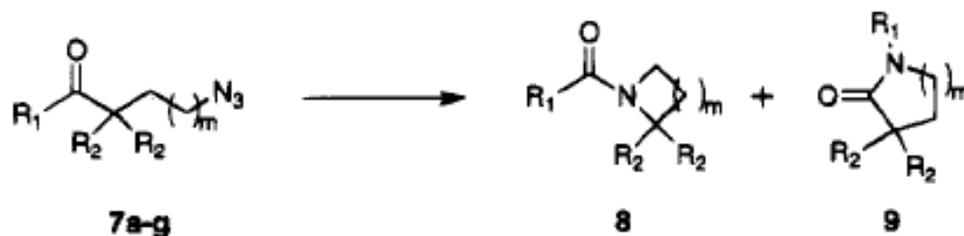
- Aldehydes
  - Variable tether lengths ( $n=0$  to  $n=3$ )
  - $R^1$ : allyl, benzyl
  - $R^2$ : H
  - No enantioselectivity



# Scope (cont.)

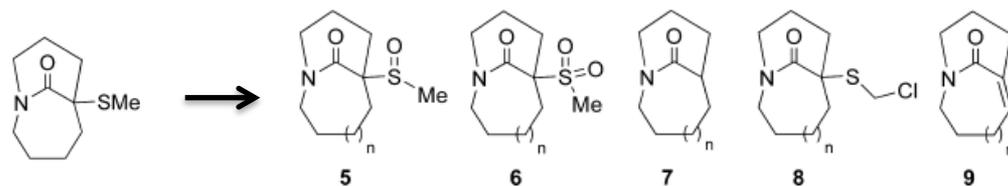
## • Acyclic Ketones

- N-acylazetidines generated from acyclic keto azides (yields 0-81 %),  $m=2$
- Yields of lactams generally low (0-29 %)



## • Cyclic Ketones

- Facile access to indolizidine and pyrrolizidine scaffolds
- Limitation of tether length (4-carbon separation)
- Incompatibilities
  - 2-(azidoalkyl)-1,3-diones
  - 2-(azidoalkyl)-cyclohex-2-en-1-ones
- Thiomethyl is versatile synthetic handle.



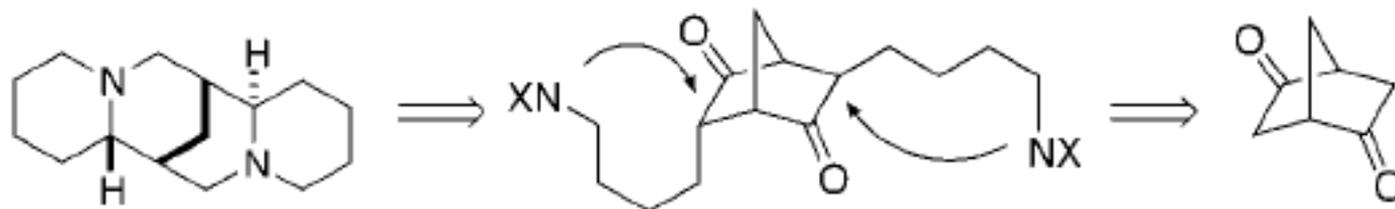
<sup>a</sup> Conditions: 5 ( $n = 2$ ), *m*CPBA (1.0 equiv), 72%. 6 ( $n = 1$ ), *m*CPBA (2.0 equiv), 67%. 7 ( $n = 2$ ), Raney Ni, 86%. 8 ( $n = 2$ ), NCS, 58%. 9 ( $n = 2$ ), i. *m*CPBA (1.0 equiv), ii. 110 °C, 72 h, 36%.

Aubé, et. al. *Org. Lett.*, 2009, 11, 4386.

Aubé, et. al. *J. Am. Chem. Soc.* 1995, 117, 10449.

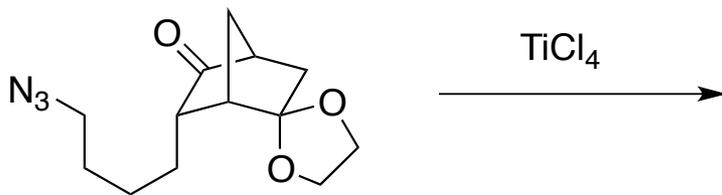
# Applications to Natural Products

- (+)-Sparteine
  - First asymmetric total synthesis

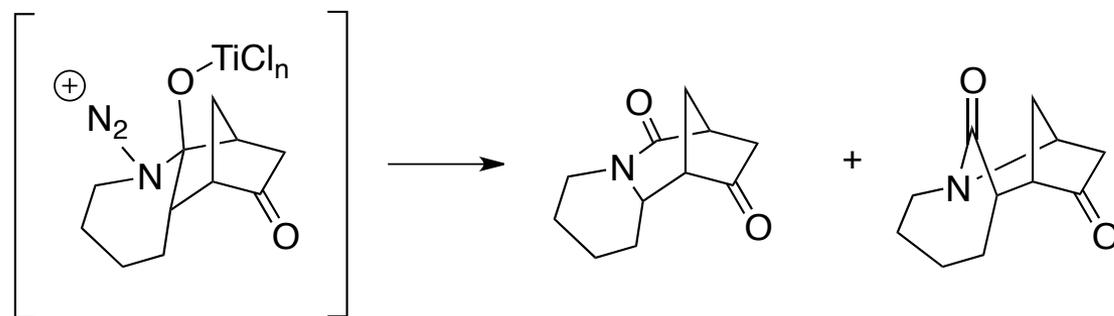


- Group Problem:

Draw the bridged and fused lactam products of the following Schmidt reaction, including the key tetrahedral intermediate.

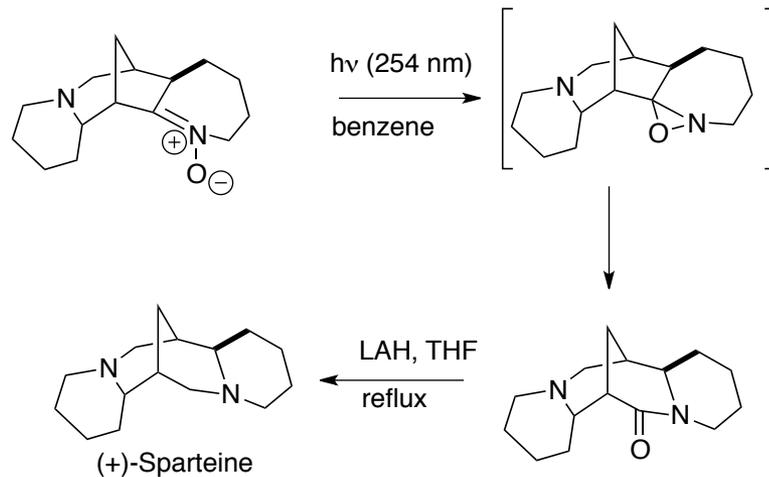


# Solution

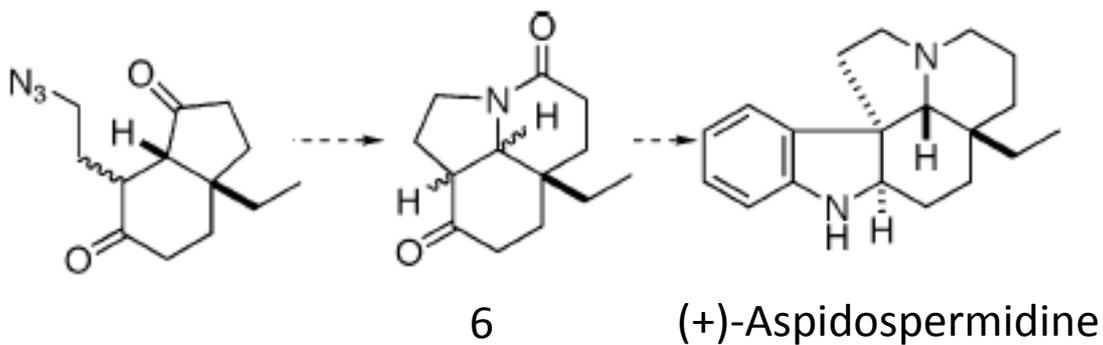


# Noteworthy Steps

- A photo-Beckmann rearrangement is required to install the second piperidine moiety.

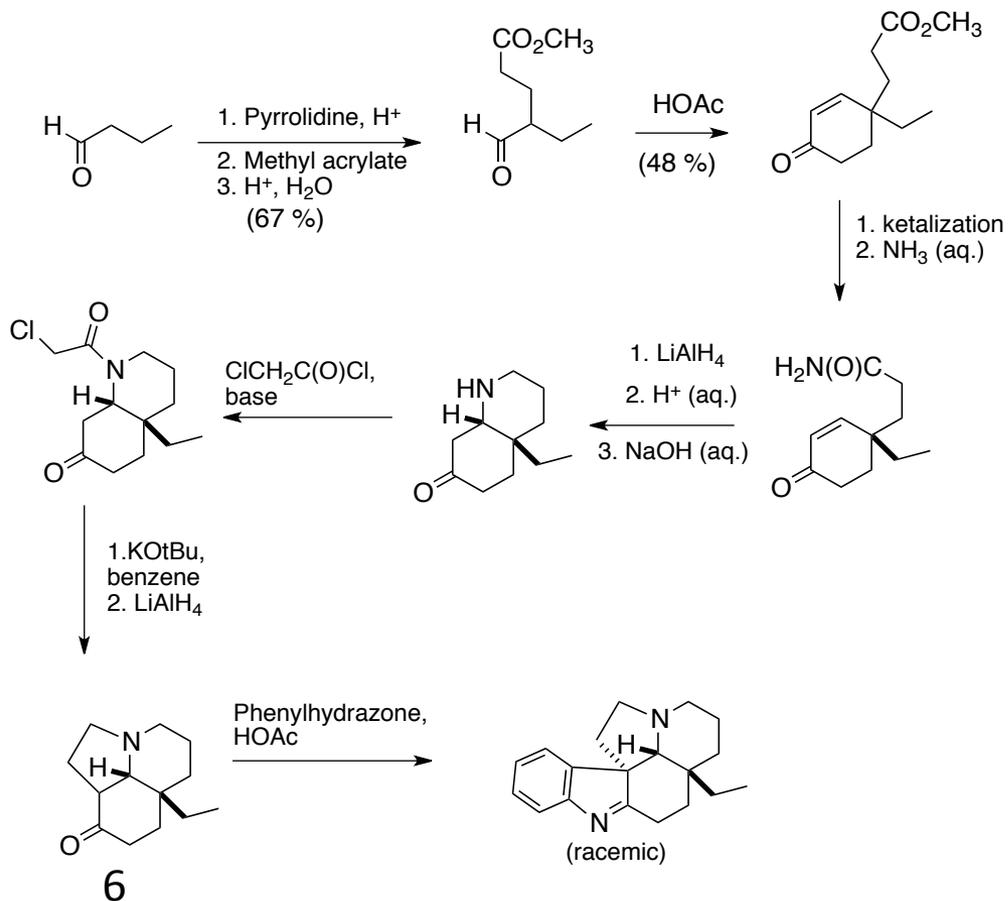


# (+)-Aspidospermidine

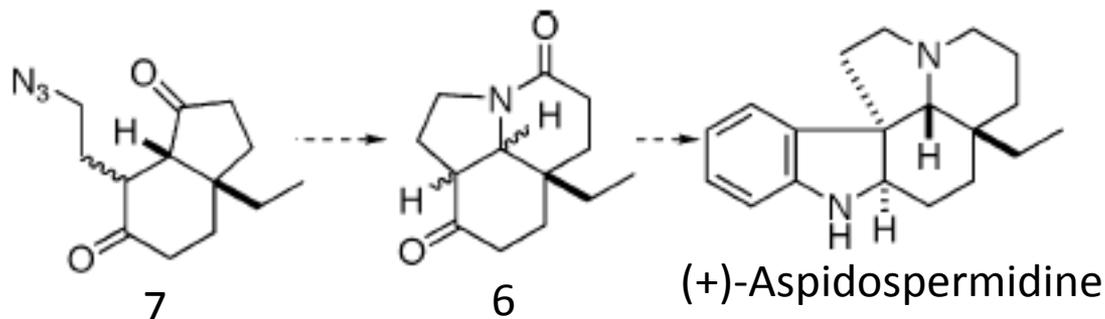


# Synthetic Route (Stork)

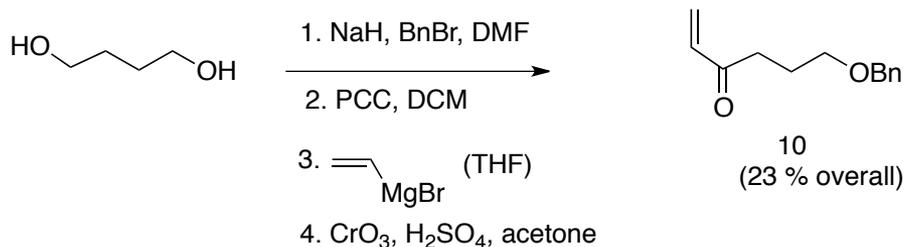
- 10 steps to reach the key intermediate, 7
- Yields not reported for most steps



# Synthetic Route: Aubé



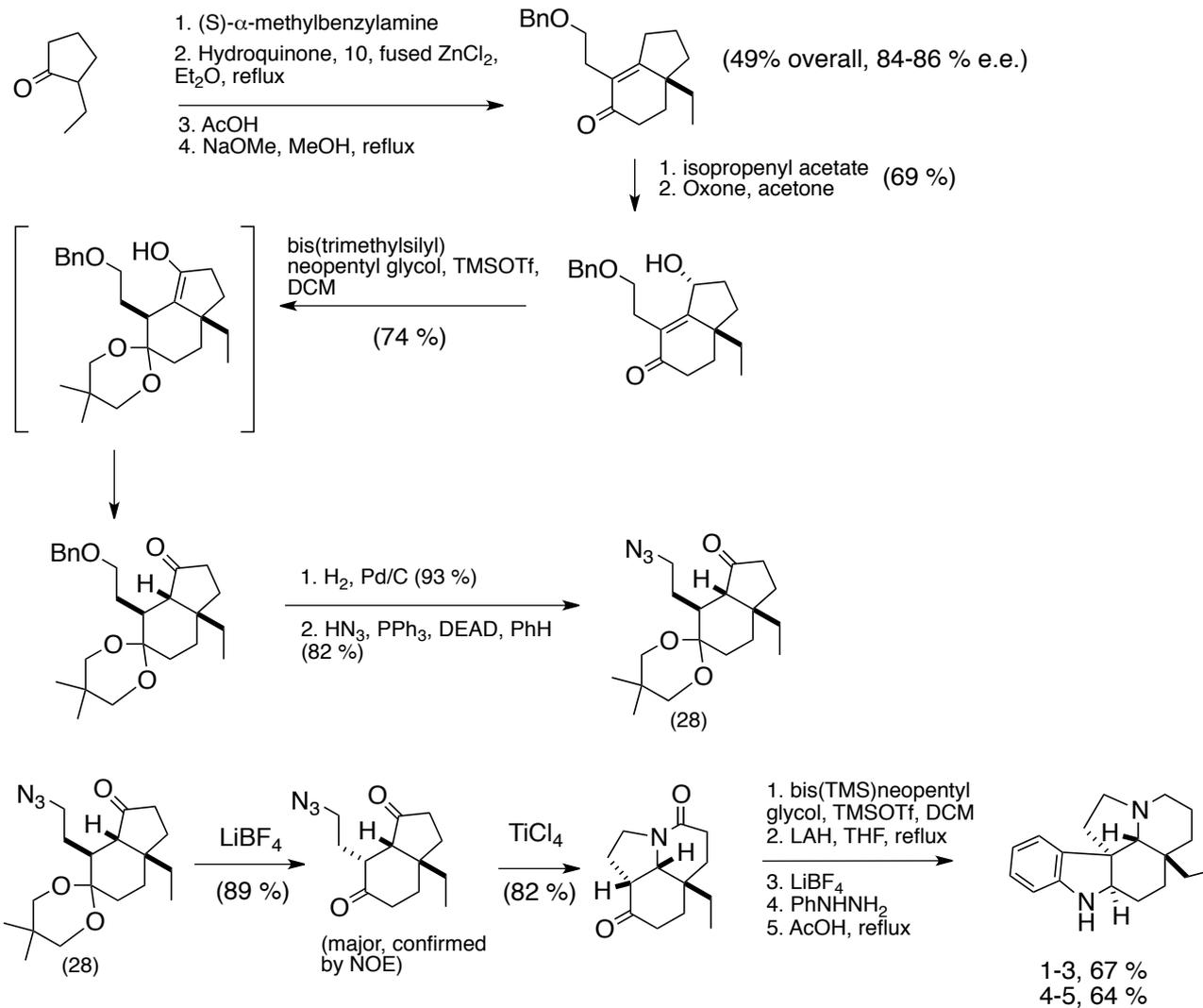
- Similar to Stork's pathway
  - Common ketoamide 6 as Fischer indolization substrate
- Route



Aubé, et. al. *Org. Lett.* 2000, 2, 1625.

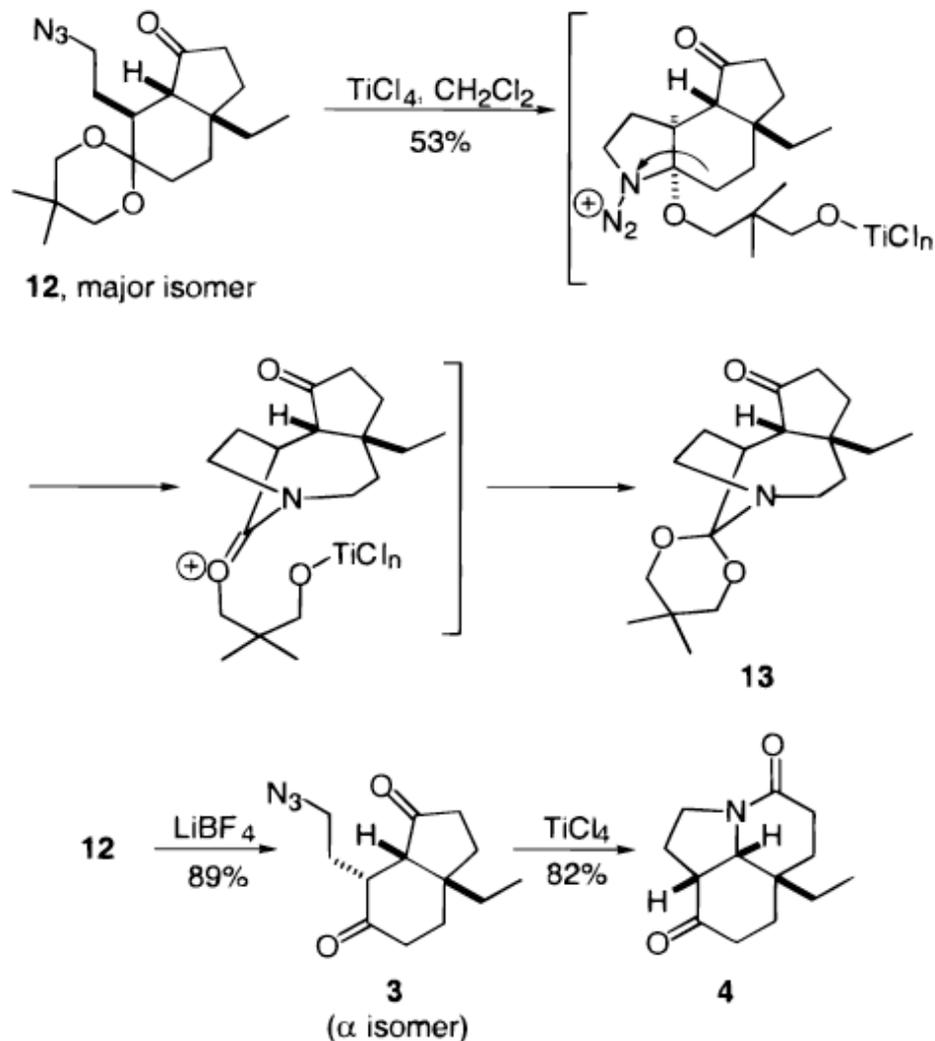
Aubé, et. al. *J. Org. Chem.* 2005, 70, 10645.

# Synthetic Route (cont.)



# Schmidt Methodology

- Deprotection before Schmidt reaction prevents bridged product formation

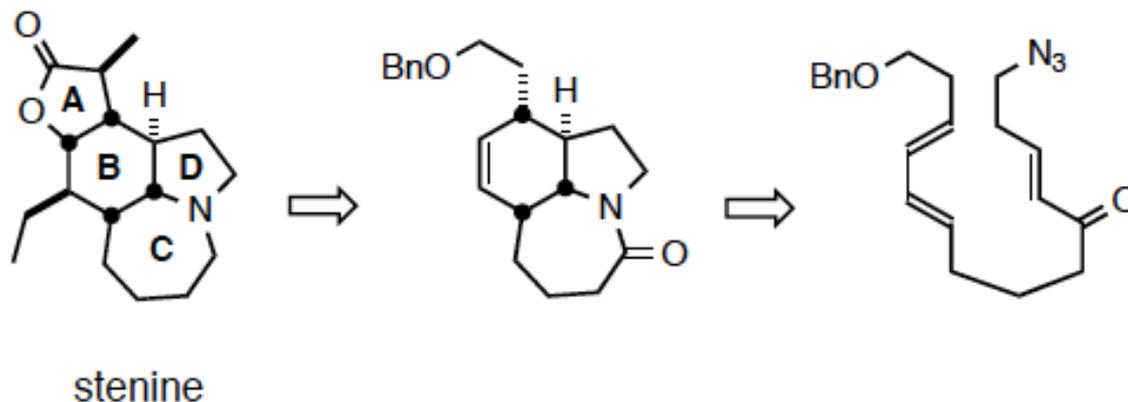


# Summary of Aubé's Synthesis

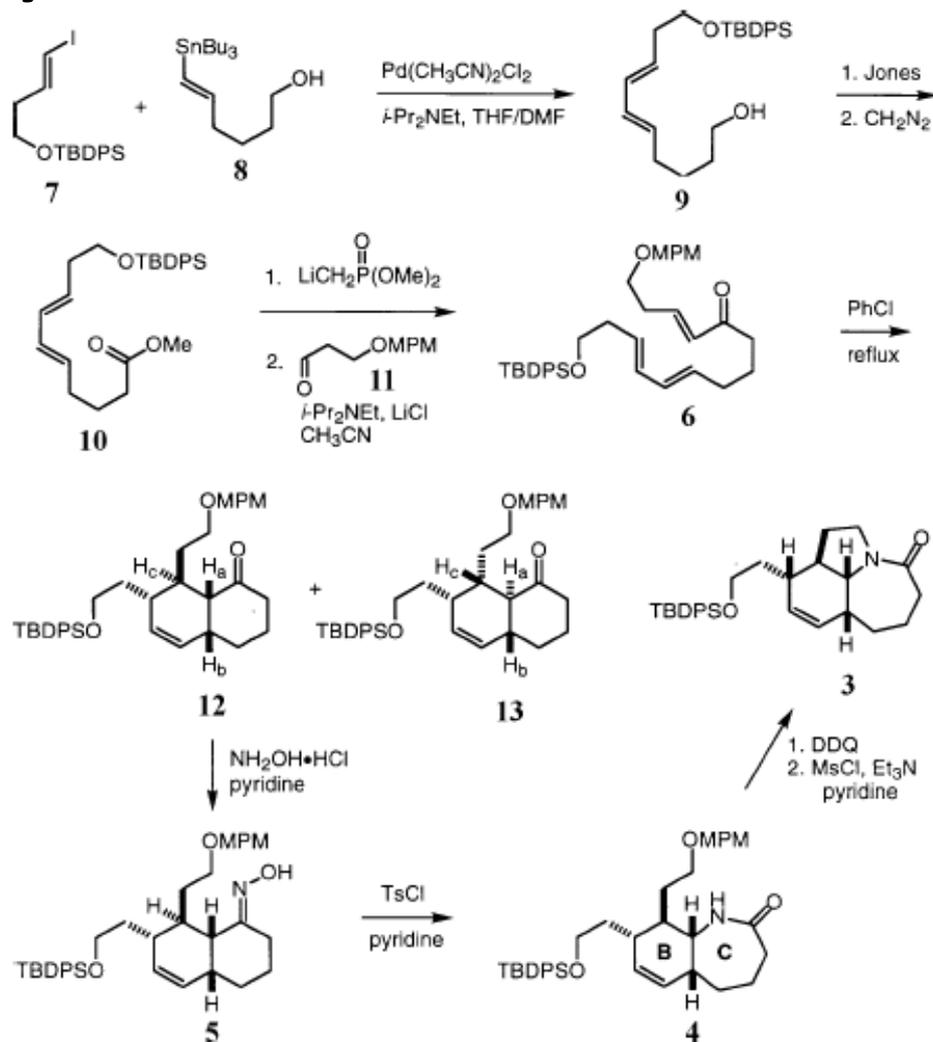
- 15 steps to reach key intermediate 6
  - Greater step count than Stork, but Aubé's route is enantioselective

# (±)-Stenine

- *A formal synthesis* from Aubé
- Numerous other syntheses of the core structure exist (Hart, Wipf, Morimoto, Padwa, Sun Hoh Jung)



# Synthetic Route: Jung

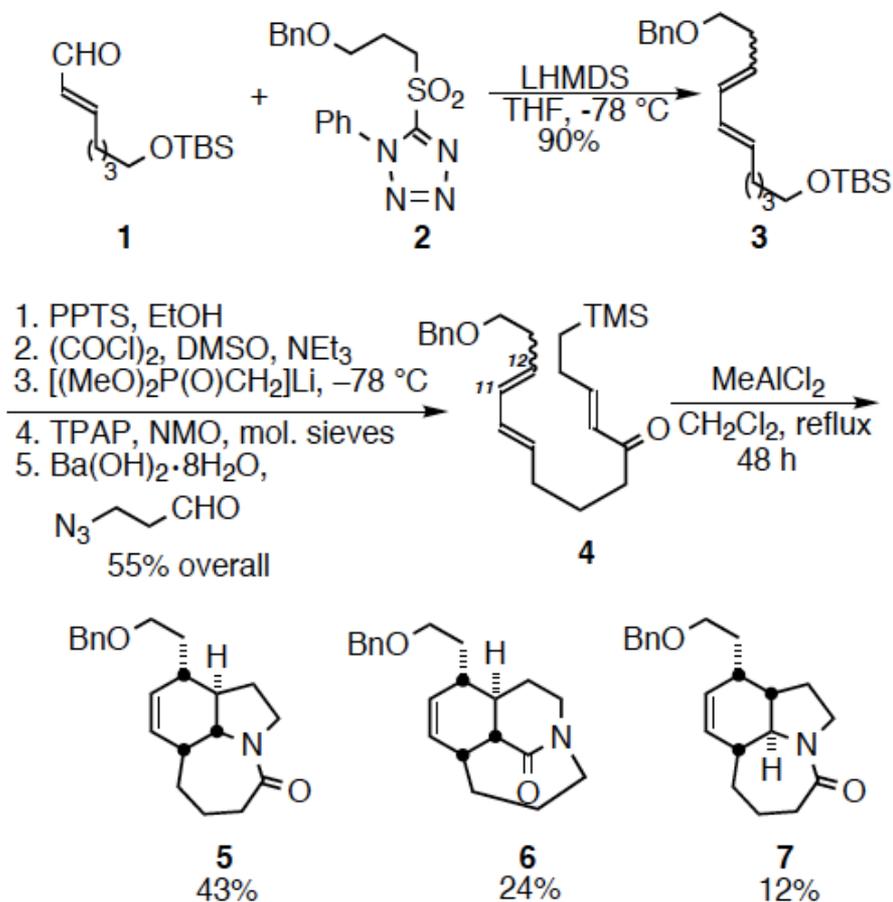


# Summary of Jung's Synthesis

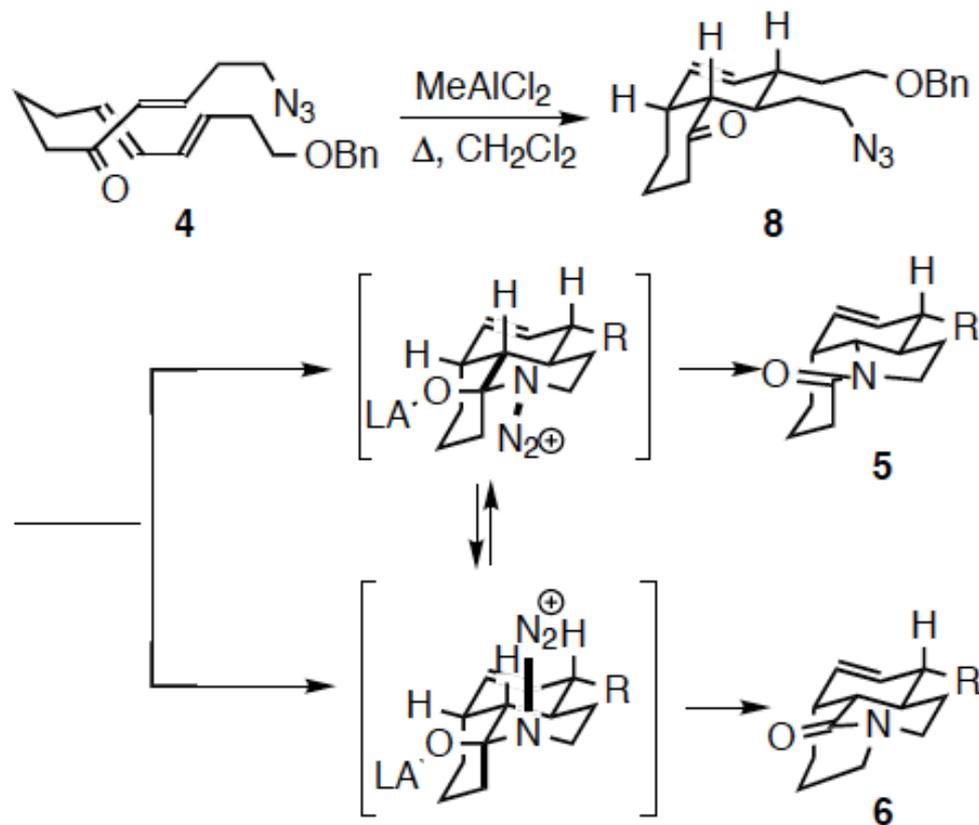
- 10 steps to reach key intermediate 3

# Synthetic Route: Aubé

- 12 steps to reach key intermediate 5 (5 is equivalent to Jung's "3").

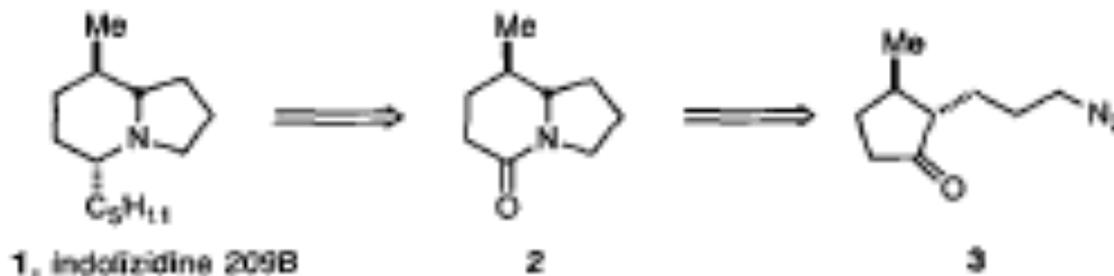


# Review of Key Migration

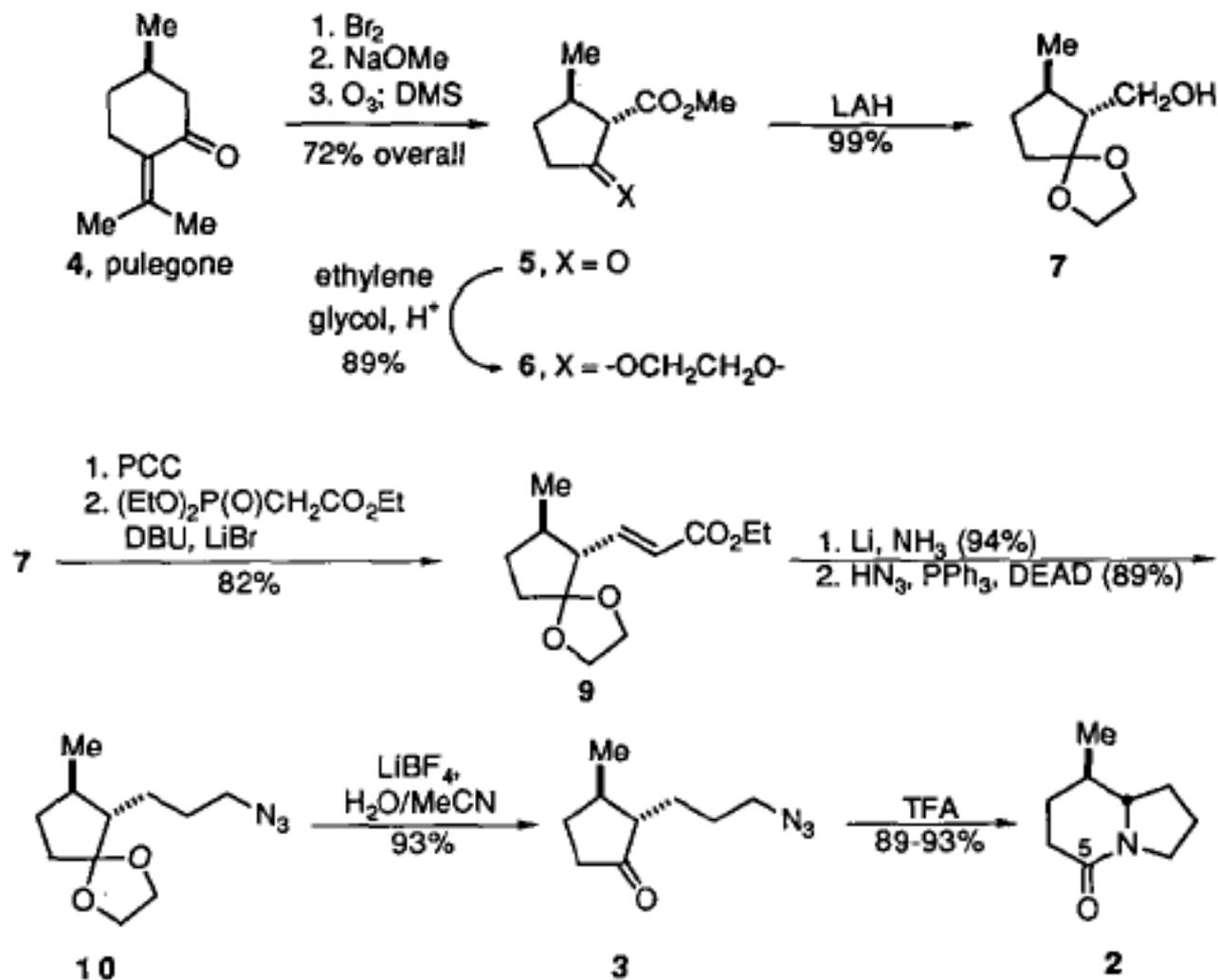


# (-)-Indolizidine 209B

- First non-auxiliary-based endeavor
- Clever use of the chiral pool (pulegone, 4) to carry out a diastereoselective Favorskii rearrangement



# Synthetic Route: (-)-Indolizidine 209B



# Conclusions

- Methodology toward understanding strained amides is of theoretical and practical interest
  - Understanding cis/trans isomerization of amides in peptides
  - Insight into intermediates: enzymatic cleavages, amide addition reactions
- Natural Products
  - Schmidt methodology often contrived
  - More steps, often circuitous transformations
- Reaction Scope
  - Impressive selectivity for bridged versus fused in many cases
  - Tether length is a major limitation
- Overall, a good lesson on choosing a research problem
  - Curiosity versus applications-driven research