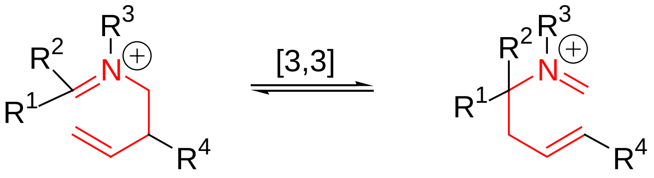
Stereocontrolled Synthesis of Angularly Substituted 1-Azabicyclic Rings by Cationic 2-Aza-Cope Rearrangement



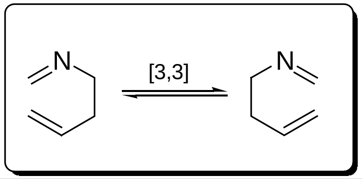
Cationic 2-aza-Cope rearrangement

Zachary D. Aron and Larry Overman

Department of Chemistry, University of California-Irvine

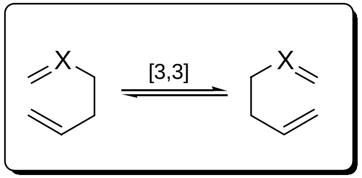
Organic Letters **2005**, *ASAP*

Topic Outline

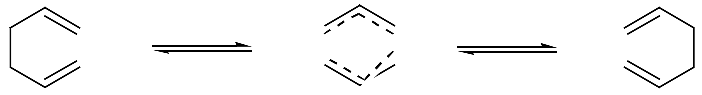


- Introduction to "cationic" aza-Cope [3,3]-sigmatropic rearrangement
- Preparation of iminium ions
- Methods to derive "cationic" aza-Cope [3,3]-sigmatropic rearrangement to a single product
- Developments and applications of "cationic" aza-Cope [3,3]-sigmatropic rearrangement
- Stereocontrolled synthesis of angularly substituted 1-azabicyclic rings via "cationic" aza-Cope [3,3]-sigmatropic rearrangement
- Summary

Rearrangements of Charged Intermediates

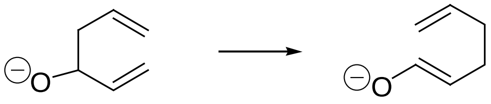


Classical Cope-rearrangement



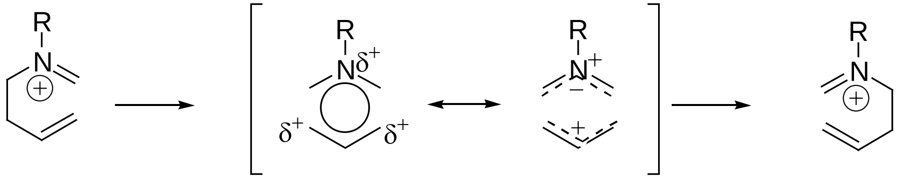
- concerted process
- 6-membered TS

Reactions accelerated by charged atom



oxy-Cope rearrangement

up to 10^{17} relative to Cope rearrangement of 1,5-hexatriene

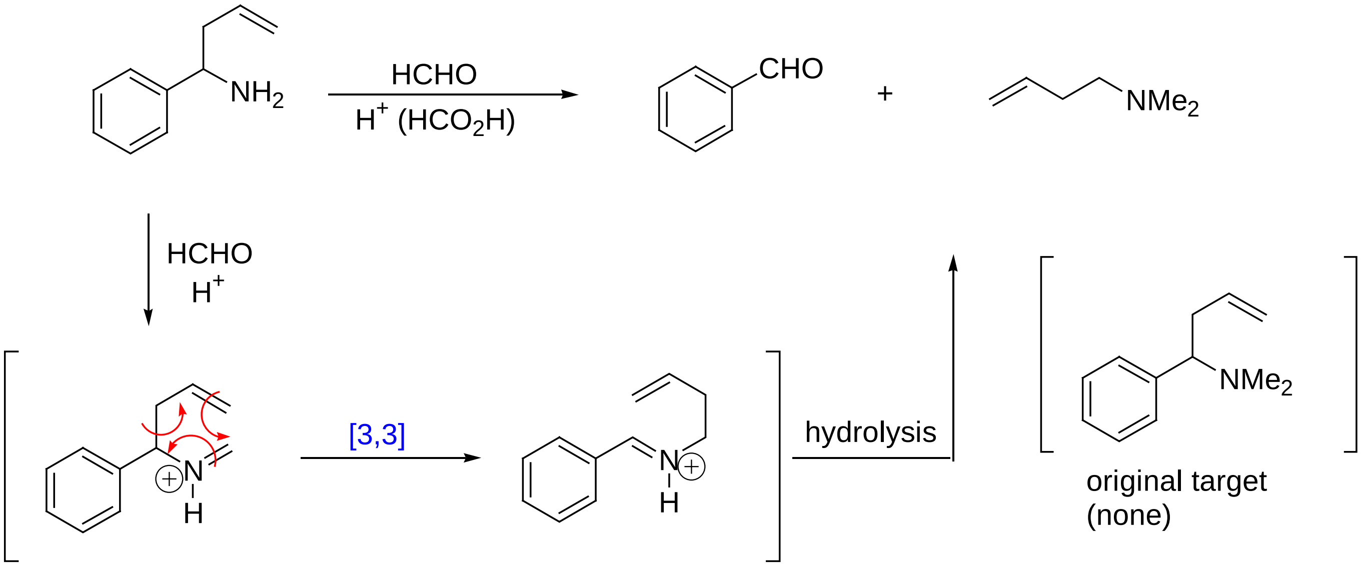


aza-Cope rearrangement

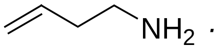
up to 10^{10}

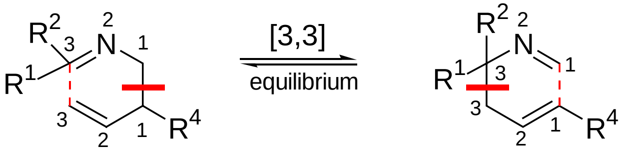
- highly polarized
- free energy of activation is lowered
- concerted mechanism is distorted
- milder reaction conditions (typically 100-200 ^{o}C below Cope rearrangement)
- higher selectivity in bond formation

First Reported Aza-Cope [3,3]-Sigmatropic Rearrangement



Cationic 2-aza-Cope rearrangement

⇨ *Absence of formic acid gave PhCHO and*  .

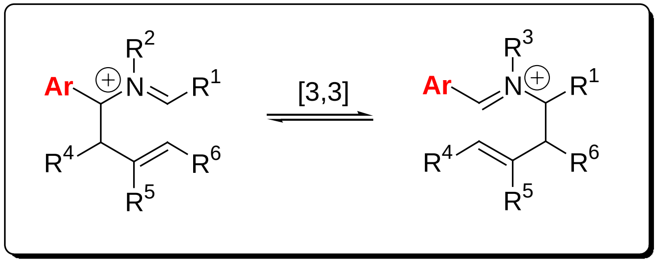


Nitrogen is inserted into the 1,5-diene system

R. M. Horowitz and T. A. Geissman *JACS* **1950**, *72*, 1518

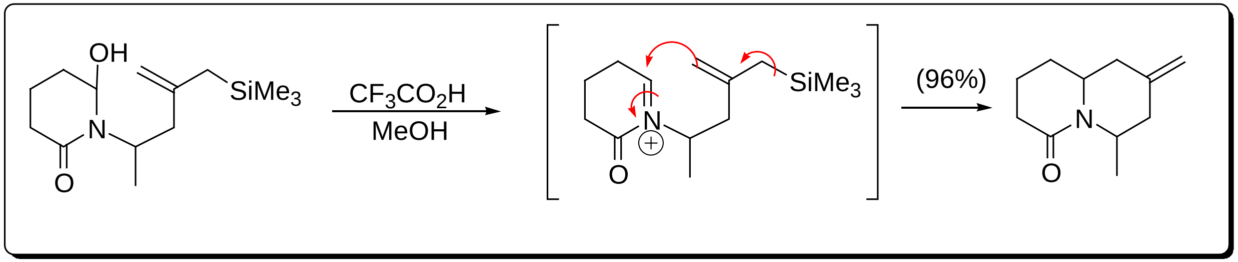
Methods for Driving Aza-Cope Rearrangement to a Single Product

- Drive the rearrangement by aryl conjugation of the iminium ion.



M. Geisel, C. A. Grob, and R. A. Wohl, *Helv. Chim. Acta.* **1969**, *52*, 2206.
J. A. Marshall and J. H. Babler, *J. Org. Chem*. **1969**, *34*, 4186.
C. A. Grob, W. Kunz, and P. R. Marbet*, TL*. **1975**, 2613.

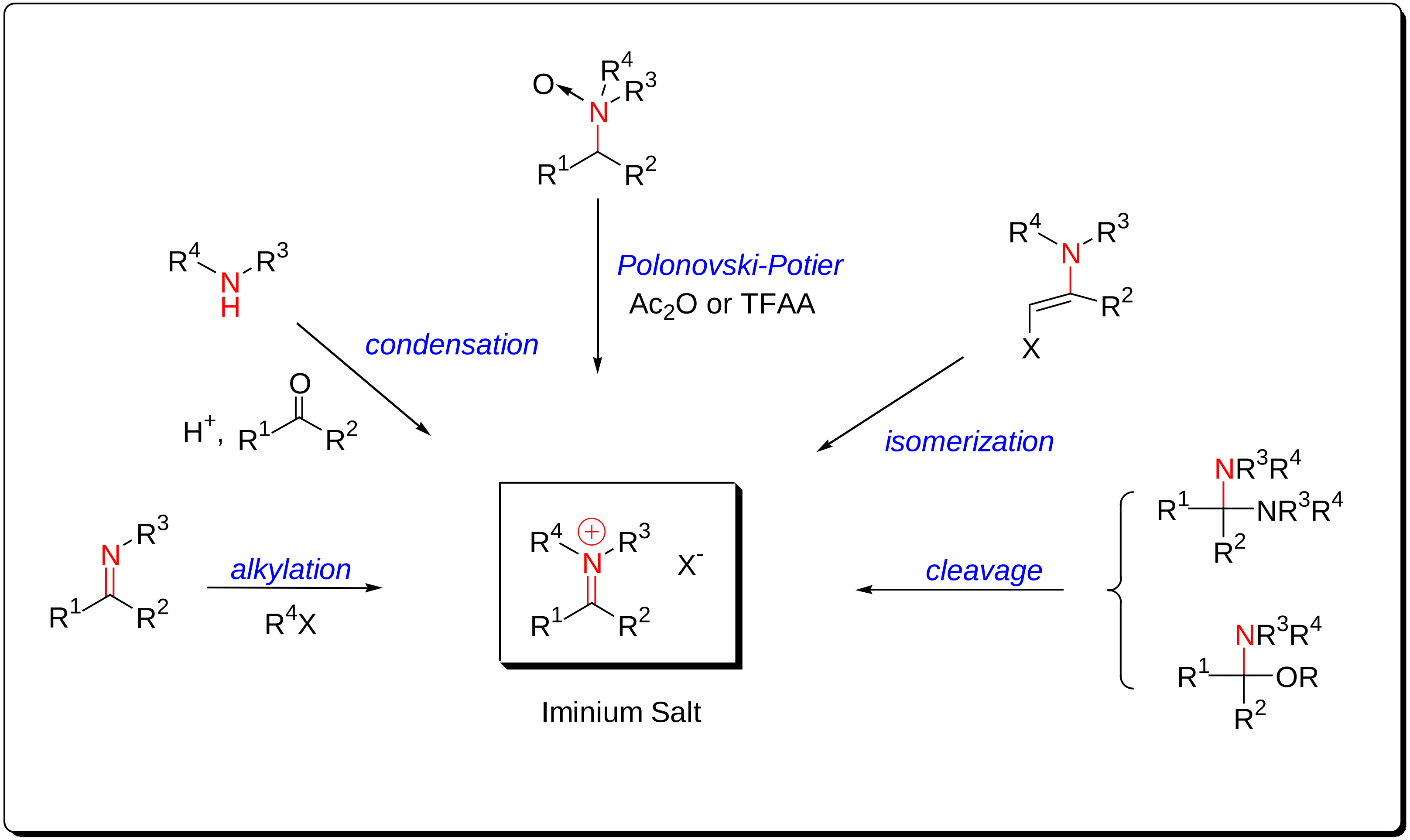
- Intramolecular trapping of the iminium ion with an incorporated nucleophile (eg. ene cyclization).



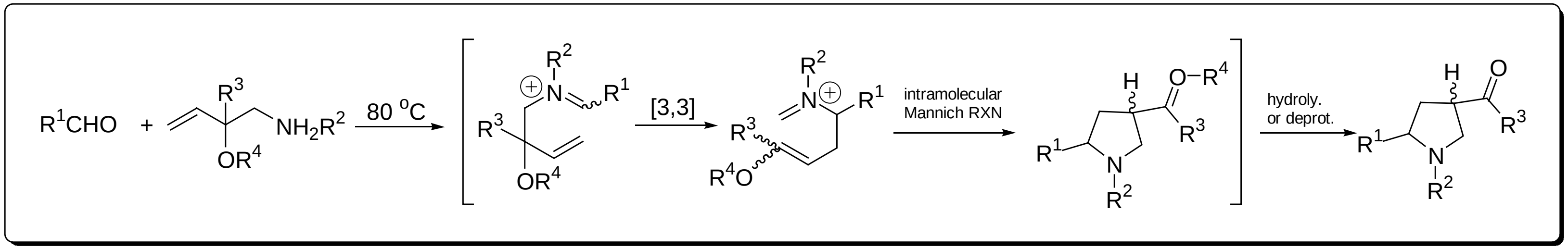
Y. Gelas-Mialhe, J-C. Gramain, A. Louvet, and R. Remuson, *TL* **1992**, *33,* 73.

- *Trapping one iminium ion by Mannich reaction (aza-Cope-Mannich reaction).*

Preparation of Iminium Ions



Directed 2-Azonia-[3,3]-Sigmatropic Rearrangements Pyrrolidine Synthesis



L. A. Overman and M. Kakimoto, *JACS* **1979**, *101*, 1310.

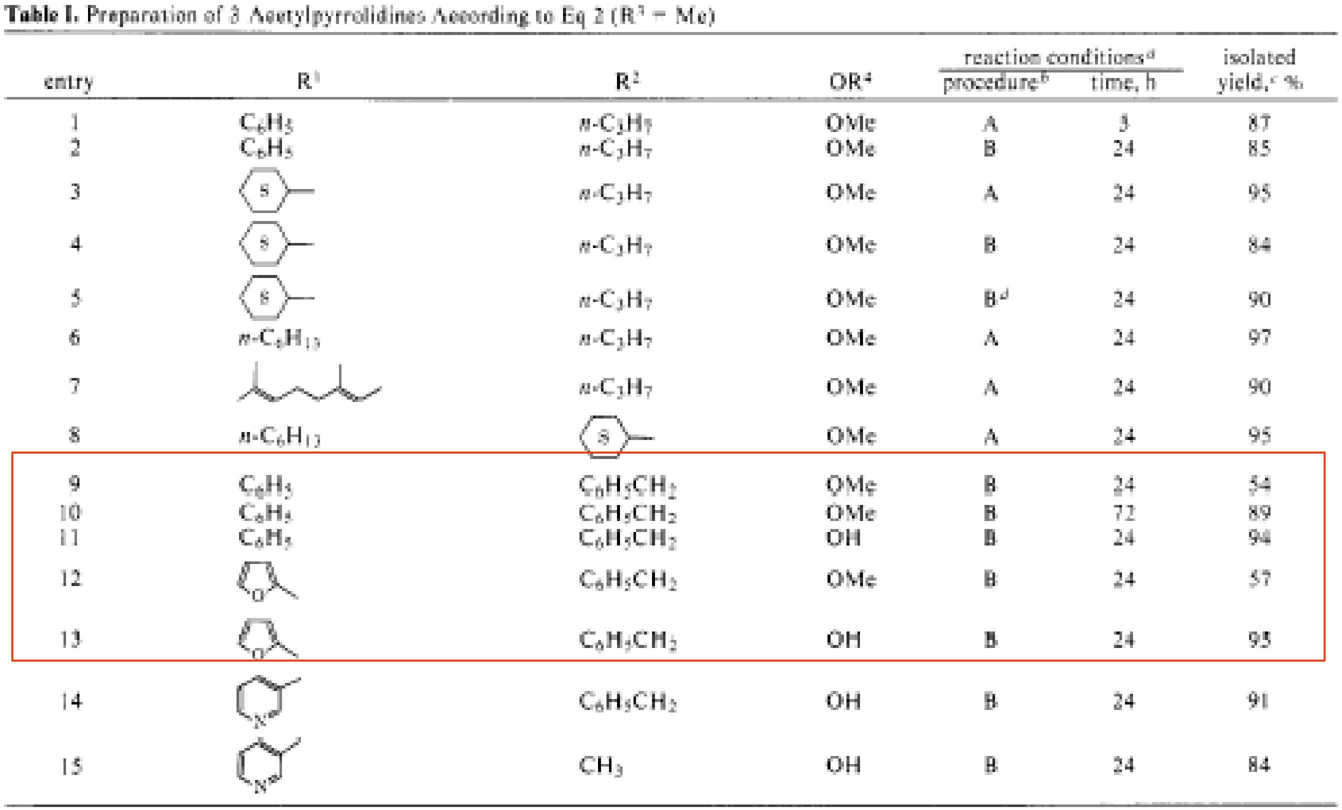


Table I. Preparation of 3-Acetylpyrrolidines According to Eq 2 (R^3 = Me)

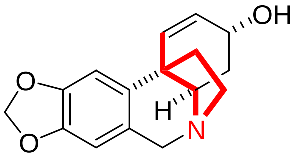
entry	R^1	R^2	OR^4	reaction conditions[a] procedure[b]	time, h	isolated yield,[c] %
1	C_6H_5	$n\text{-}C_3H_7$	OMe	A	3	87
2	C_6H_5	$n\text{-}C_3H_7$	OMe	B	24	85
3	S	$n\text{-}C_3H_7$	OMe	A	24	95
4	S	$n\text{-}C_3H_7$	OMe	B	24	84
5	S	$n\text{-}C_3H_7$	OMe	B[d]	24	90
6	$n\text{-}C_6H_{13}$	$n\text{-}C_3H_7$	OMe	A	24	97
7		$n\text{-}C_3H_7$	OMe	A	24	90
8	$n\text{-}C_6H_{13}$	S	OMe	A	24	95
9	C_6H_5	$C_6H_5CH_2$	OMe	B	24	54
10	C_6H_5	$C_6H_5CH_2$	OMe	B	72	89
11	C_6H_5	$C_6H_5CH_2$	OH	B	24	94
12	O	$C_6H_5CH_2$	OMe	B	24	57
13	O	$C_6H_5CH_2$	OH	B	24	95
14	N	$C_6H_5CH_2$	OH	B	24	91
15	N	CH_3	OH	B	24	84

---

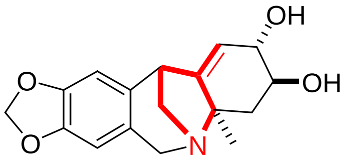
[a] A benzene solution of the amine salt (0.6 M) and the aldehyde (1.1 equiv) were heated at reflux for the indicated time. Twenty-four hours was taken as a convenient standard time and many of the reactions were done much sooner. [b] A, the crystalline amine tetrafluoroborate salt was used; B, the free amine plus 0.9 equiv of *d*-10-camphorsulfonic acid was used. [c] All pyrrolidines were a mixture of acetyl epimers.[11] [d] 0.1 equiv of *d*-10-camphorsulfonic acid was employed.

Representative Alkaloid Syntheses Accomplished Using the aza-Cope-Mannich Reaction as the Key Synthetic Step

Amaryllidaceae alkaloids

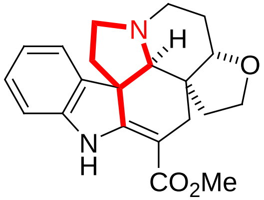


(-)-crinine

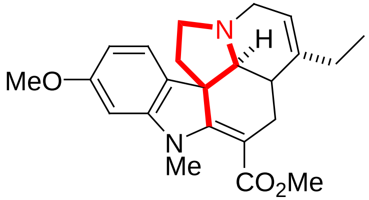


(+/-)-pancracine

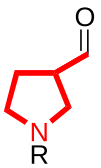
Aspidosperma alkaloids



(+/-)-deoxoapodine

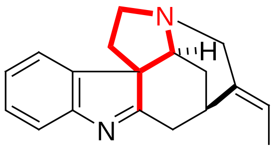


(+/-)-16-methoxytabersonine

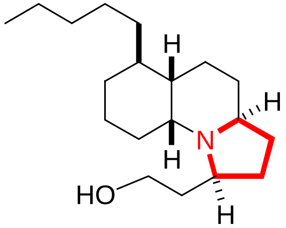


3-Acylpyrrolidine

Strychnos alkaloids

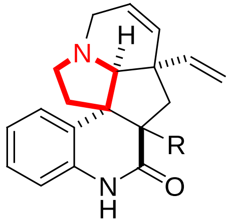


(+/-)-dehydrotubifoline



(+/-)-perhydrigephyrotoxin

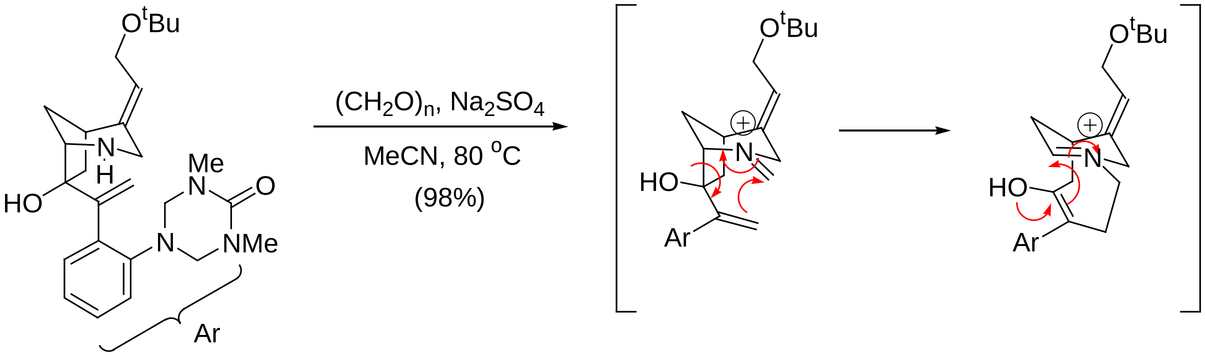
Dendrobatid alkaloids



(+/-)-meloscine C-16 β-H
(+/-)-epimeloscine C-16 α-H

Melodinus alkaloids

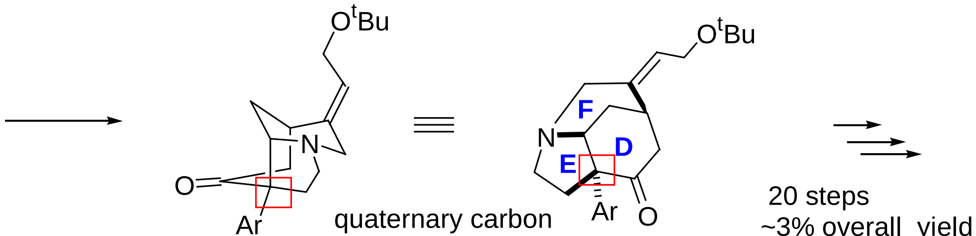
Application of Tandem Aza-Cope-Mannich Reaction
Total Synthesis of (-)-Strychnine



$(CH_2O)_n$, Na_2SO_4

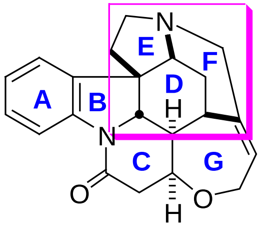
MeCN, 80 ^{o}C

(98%)



quaternary carbon formation

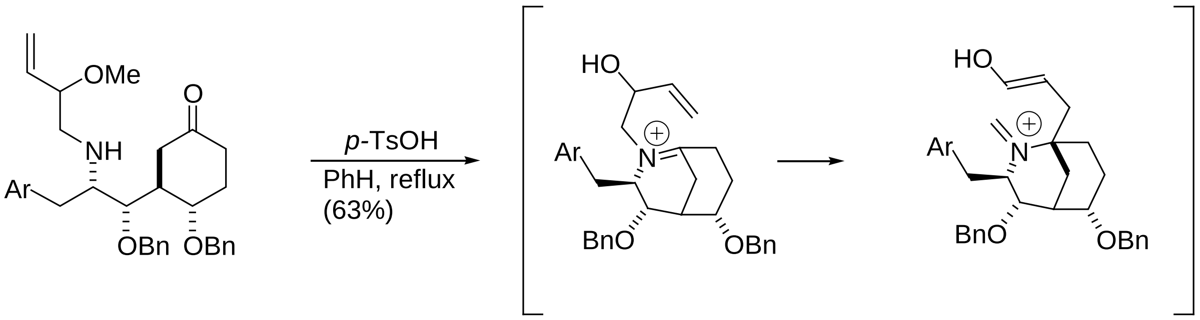
20 steps
~3% overall yield



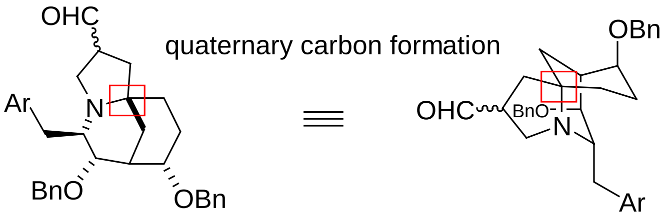
(-)-Strychnine(plant alkaloid)
Isolated in 1818 from *Strychnos ignatii*
Structure was elucidated in 1946
First total synthesis in 1954 by Woodward
First asymmetric total synthesis in 1993 by Overman

S. D. Knight, L. A. Overman and G. Pairaudeau, *JACS* **1993**, *115*, 9293.

Application of Tandem Aza-Cope-Mannich Reaction
Total Synthesis of (-)-FR901483

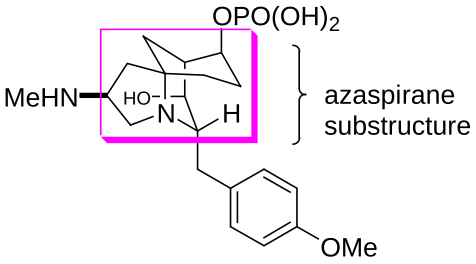


p-TsOH
PhH, reflux
(63%)



quaternary carbon formation

18 steps
2.5% overall yield

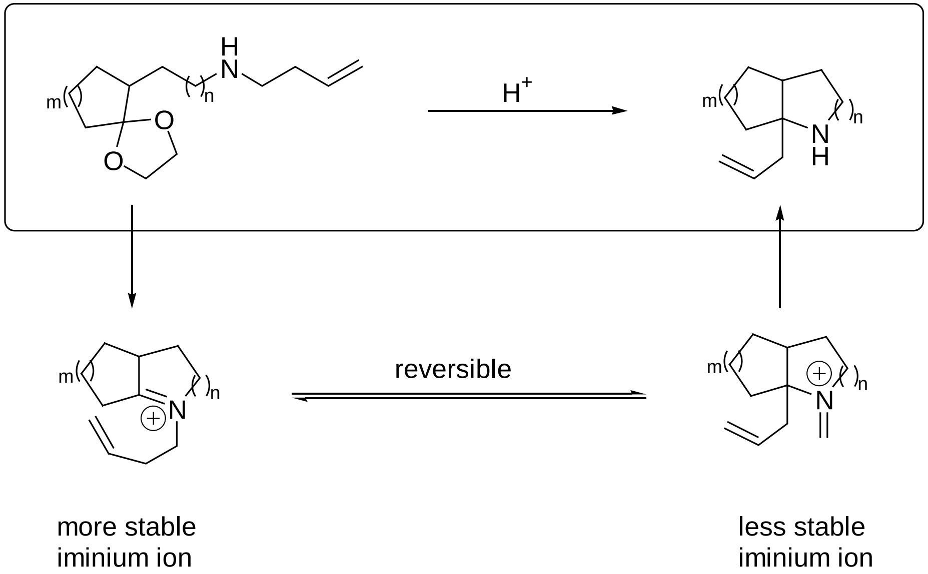


azaspirane substructure

(-)-FR901483
Isolated in 1996 from the fermentation broth of *Cladobotrym sp.* No. 11231
Immunosuppressants

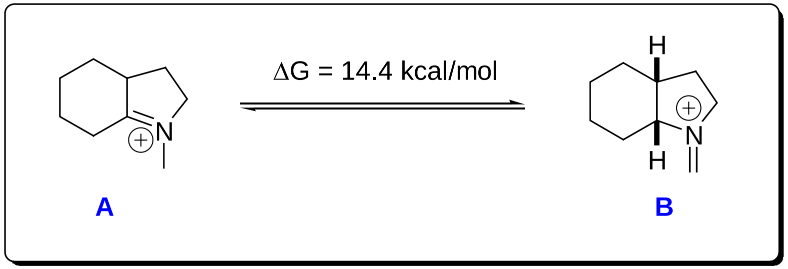
K. M. Brummond and S-p Hong, *JOC* **2005**, *70,* 907.

Stereocontrolled Synthesis of Angularly Substituted 1-Azabicyclic Ring by Cationic 2-Aza-Cope Rearrangement



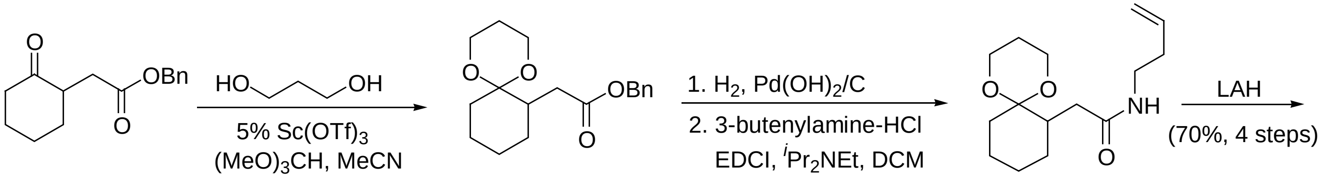
***Challenge*: To develope an efficient method to trap the methylene unit of the less stable iminium ion.**

Model study *- the rearrangement is calculated to be endothermoic from* ***A*** → ***B*** *by 14.4 kcal/mol*
(ab initio calculations using DFT/B3LYP/6-21G as conducted in the Spartan 2002)*



Z. A. Aron and L. E. Overman, *OL* **2005**, *ASAP*

Stereocontrolled Synthesis of Angularly Substituted 1-Azabicyclic Ring by Cationic 2-Aza-Cope Rearrangement



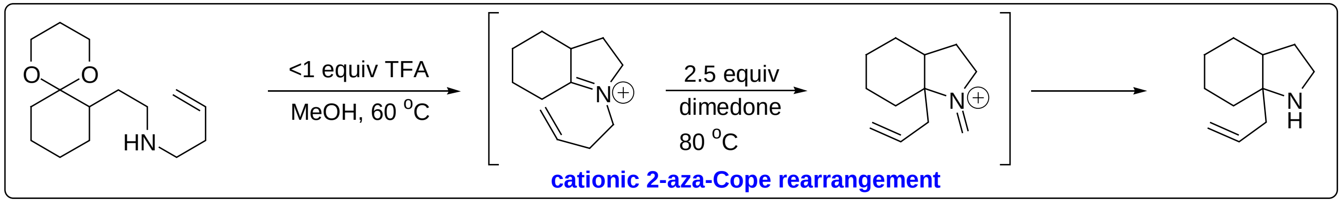
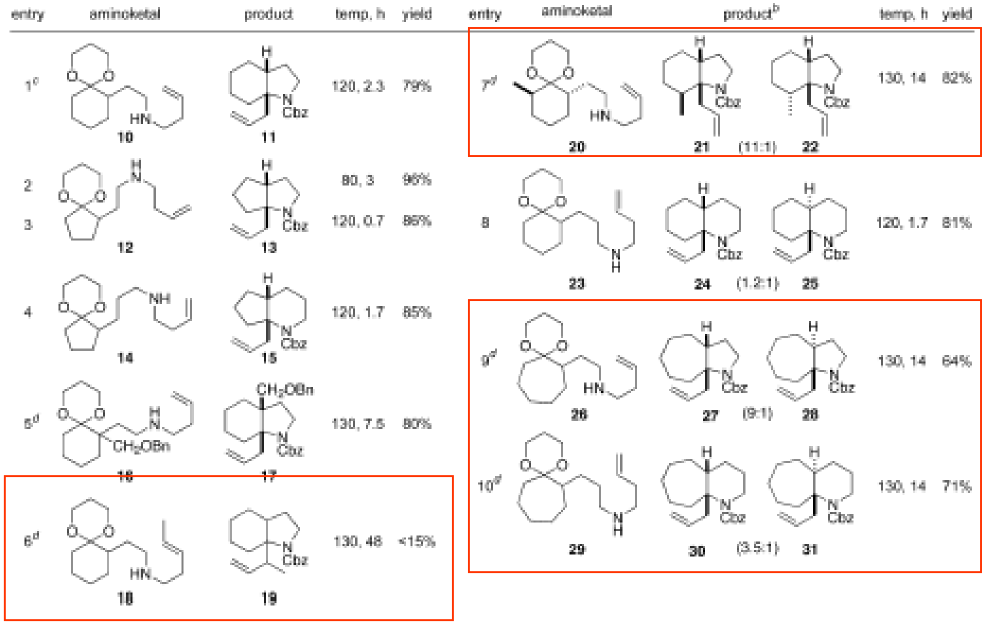


Table 1. Synthesis of Angularly Substituted 1-Azabicyclic Rings by Methylene Transfer-Driven Cationic 2-Aza-Cope Rearrangements[a]



entry	aminoketal	product	temp, h	yield
1[c]	**10**	**11**	120, 2.3	79%
2	**12**	**13**	80, 3	96%
3			120, 0.7	86%
4	**14**	**15**	120, 1.7	85%
5[d]	**16**	**17**	130, 7.5	80%
6[d]	**18**	**19**	130, 48	<15%

entry	aminoketal	product[b]	temp, h	yield
7[d]	**20**	**21** (11:1) **22**	130, 14	82%
8	**23**	**24** (1.2:1) **25**	120, 1.7	81%
9[d]	**26**	**27** (9:1) **28**	130, 14	64%
10[d]	**29**	**30** (3.5:1) **31**	130, 14	71%

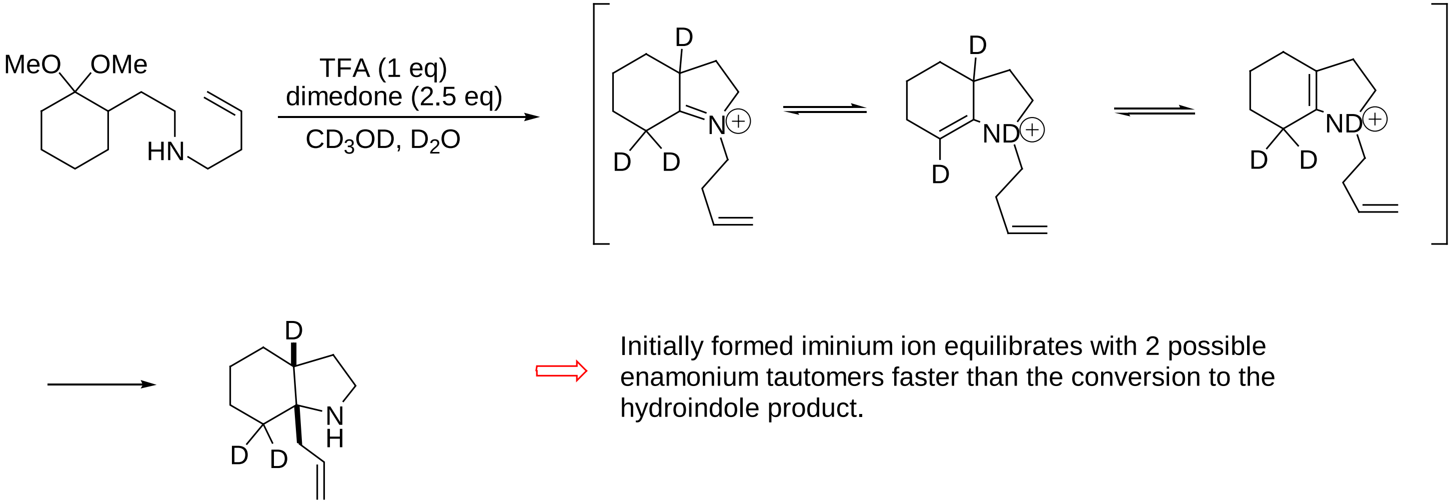
[a] Typical reaction conditions: TFA (1.0 equiv), morpholine (0.1 equiv), dimedone (2.5 equiv), followed by reaction of the crude product in chloroform with benzyl chloroformate (2.5 equiv) and Na_2CO_3. [b] Product ratios were determined from yields of pure products; these ratios were confirmed by analysis of ^1H NMR spectra of the crude reaction product. [c] As demonstrated by ^1H NMR analysis using an internal standard, a 78% yield was obtained when the reaction was conducted at 2 M in toluene in a sealed reaction vessel at 120 °C for 2.7 h. [d] Performed with portionwise addition of 4.0 equiv of dimedone over 4 h.

Trends

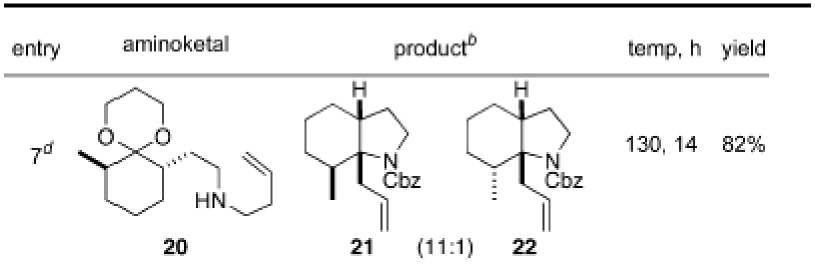
- Reaction rate is dependent on the size of the pre-existing ring (5 and 6-membered ring > 7-membered ring, entries 9/10).
- Introduction of an additional substituent on either side of the acetal carbon decelerated the reaction (entry 7).
- Products are formed with high *cis* stereoselectivities (the allylic hydrogens of the angular allyl group and the angular hydrogen).
- Observed diastereoselectivies are consistent with formation of thermodynamic products.

Z. A. Aron and L. E. Overman, *OL* **2005**, *ASAP*

Mechanistic Insight - Equilibrium between the Initially Formed Iminium Ion and Its Enamine Tautomers



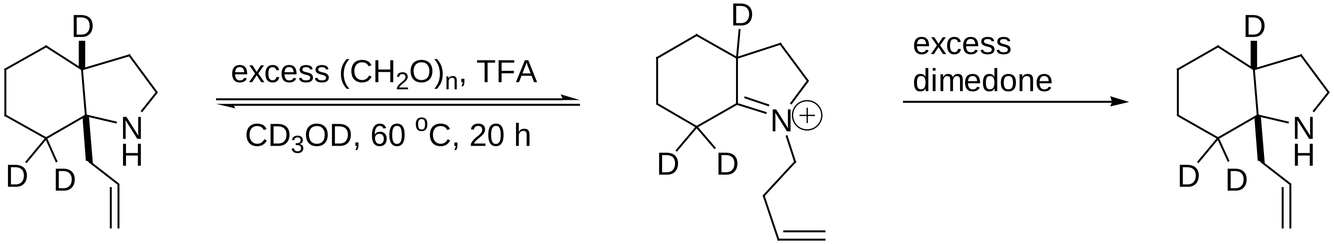
⇨ Initially formed iminium ion equilibrates with 2 possible enamonium tautomers faster than the conversion to the hydroindole product.



entry	aminoketal	product^b	temp, h	yield
7^d	**20**	**21** (11:1) **22**	130, 14	82%

Z. A. Aron and L. E. Overman, *OL* **2005**, *ASAP*

The Reversibility of Cationic 2-Aza-Cope Rearrangement

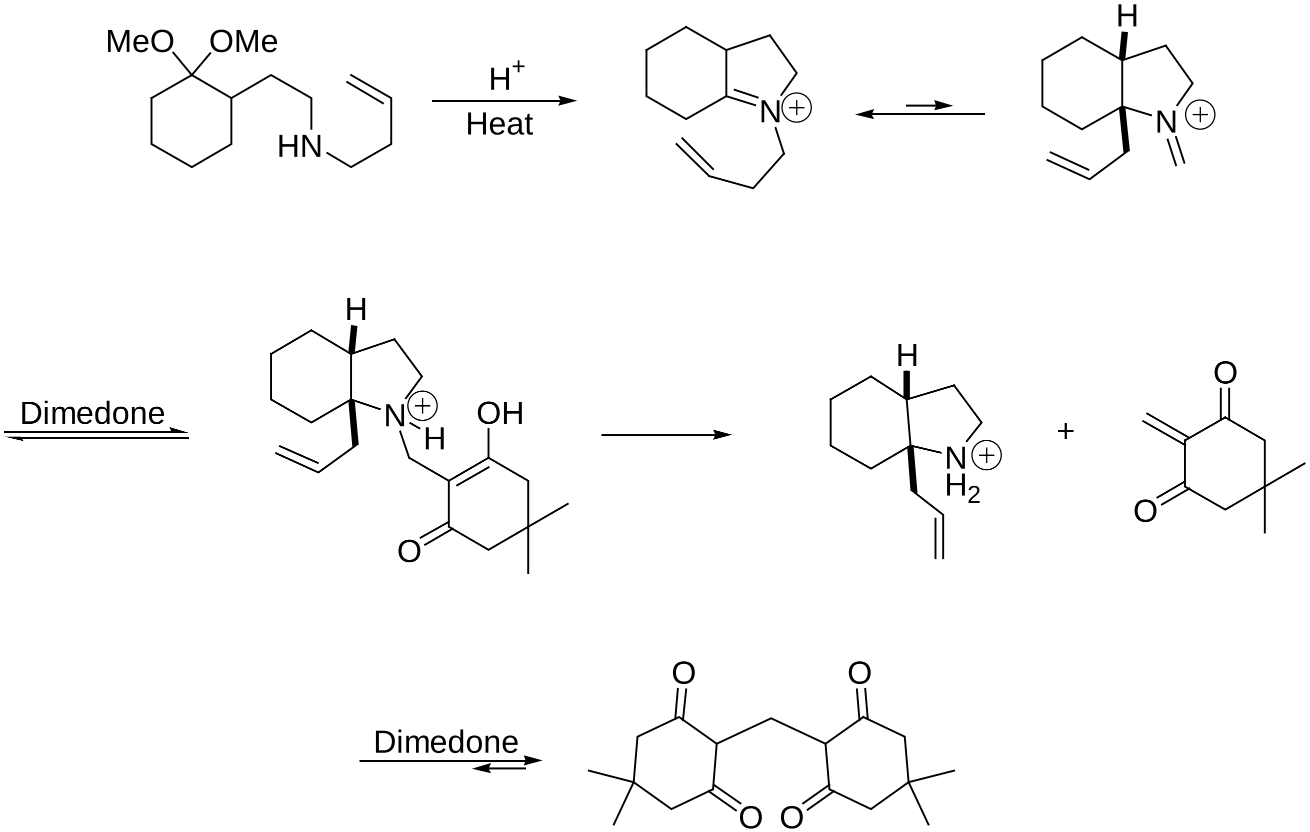


observed by ^1H NMR

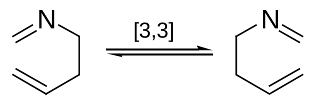
⇨ Thereby confirming the reversibility of cationic aza-Cope rearrangement

Z. A. Aron and L. E. Overman, *OL* **2005**, *ASAP*

Plausible Mechanism for Cationic 2-Aza-Cope Rearrangements



Z. A. Aron and L. E. Overman, *OL* **2005**, *ASAP*



Summary

- Highly endothermic cationic 2-aza-Cope rearrangement of *ketone-derived* iminium ions directed by subsequent Mannich reaction has been reported for the first time.
- Reaction performs with high stereocontrol and affords a wide range of angularly substituted 1-azabicyclic ring systems.
- This chemistry introduced vicinal quaternary carbon centers (carbon adjacent to nitrogen).
- The development of the asymmetric version of this methodology is under investigation.

Relevent reviews

N. M. Przheval'skii and I. I. Grandberg "The Cope Aza-rearrangement in Organic Synthesis." *Russ. Chem. Rev.* **1987**, *56*, 71-82.

S. Blechert "The hetero-Cope Rearrangement in Organic Synthesis." *Synthesis* **1989**, 71-82.

L. E. Overman "Charge as a Key Component in Reaction Design. The Invention of Cationic Cyclization Reactions of Importance in Synthesis." *Acc. Chem. Rev.* **1992**, *25*, 352-359.