ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

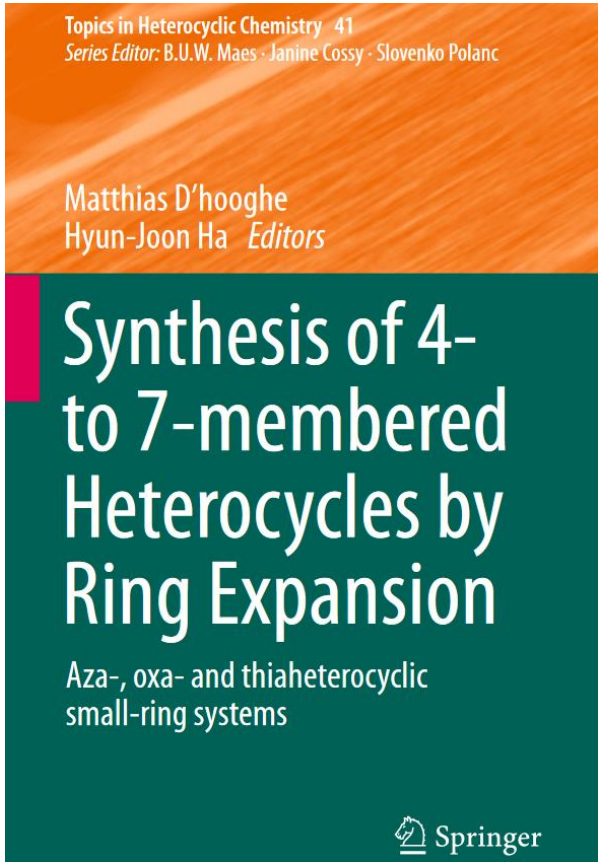
Group Seminar

Alexandre Leclair

ISIC - LSPN

Ring expansion of aziridines and azetidines for the synthesis of 5-membered azacycles

Important literatures



In this book:

F. Couty, O. R. P. David,

Ring Expansions of Nonactivated Aziridines and Azetidines, p 1-47

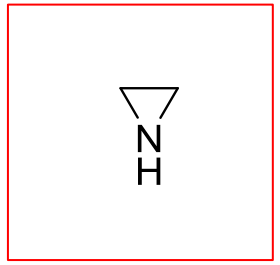
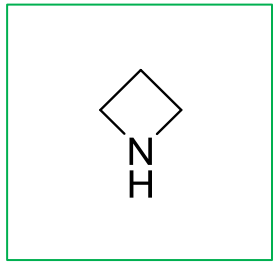
M. K. Ghoraj, A. Bhattacharyya, S. Das, N. Chauhan,

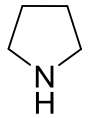
Ring Expansions of activated Aziridines and Azetidines, p 49-142

F. Couty, O.R.P. David, Ring Expansions of Nonactivated Aziridines and Azetidines, D'hooghe M., Ha HJ. (eds) Synthesis of 4- to 7-membered Heterocycles by Ring Expansion. Topics in Heterocyclic Chemistry, Vol. 41. Springer, Cham, 2015, p 1-47

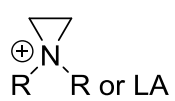
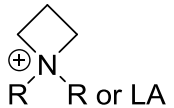
Table of contents

I. Introduction

Extensively studied ⇦   ⇨ Far less studied

- Calculated ring strain: (kcal.mol^{-1}) 27.3 25.2 In comparison:  27.4
- pKa (in water): 7.98 11.3 In comparison:  11.3

⇨ High ring strain energy / Basic: **Two key parameters for their reactivity**

Usually, activation through:  **Aziridinium**  **Azetidinium**

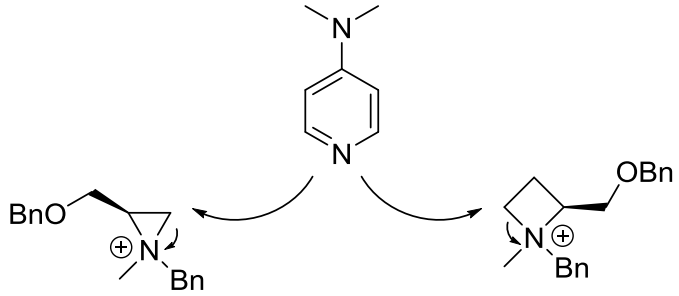
F. Couty, B. Drouillat, G. Evano, O. David, *Eur. J. Org. Chem.* **2013**, *11*, 2045-2056
J. D. Dill, A. Greenberg, J. F. Liebman, *J. Am. Chem. Soc.* **1979**, *101*, 6814-6826

I. Introduction

High ring strain energy / Basic: **BUT** not the only one

$\Delta E_{ring\ strain}$= 2.1 kcal.mol^{-1}

- Ring opening with DMAP:

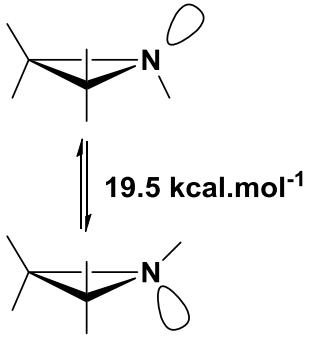


1,7.10^4 times slower

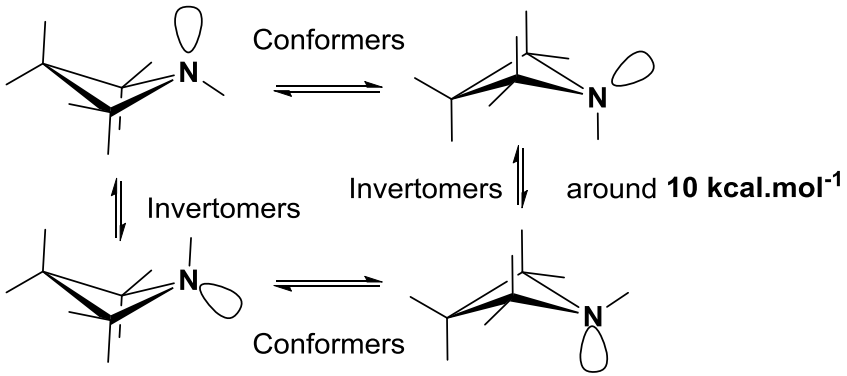
From this rate difference:
→ $\Delta\Delta G^{\#}$= 5.6 kcal.mol^{-1}

⇨ **Ring strain not the only important factor**

- Nitrogen inversion energy barrier:



Invertomers
Often observable by NMR at rt

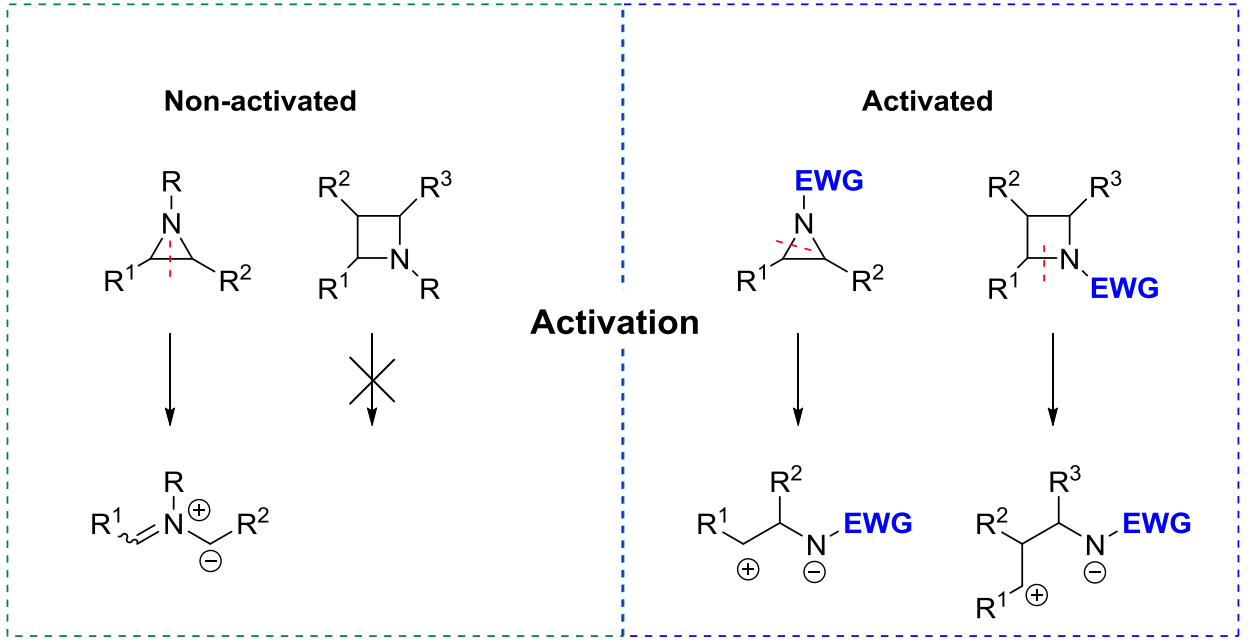


Not distinguishable in NMR at rt

N. De Rycke, O. David, F. Couty, *Org. Lett.* **2011**, *13*, 1836-1839

I. Introduction

Important to differentiate activated and non-activated substrates:



N rich in electron
Nucleophilic substrates

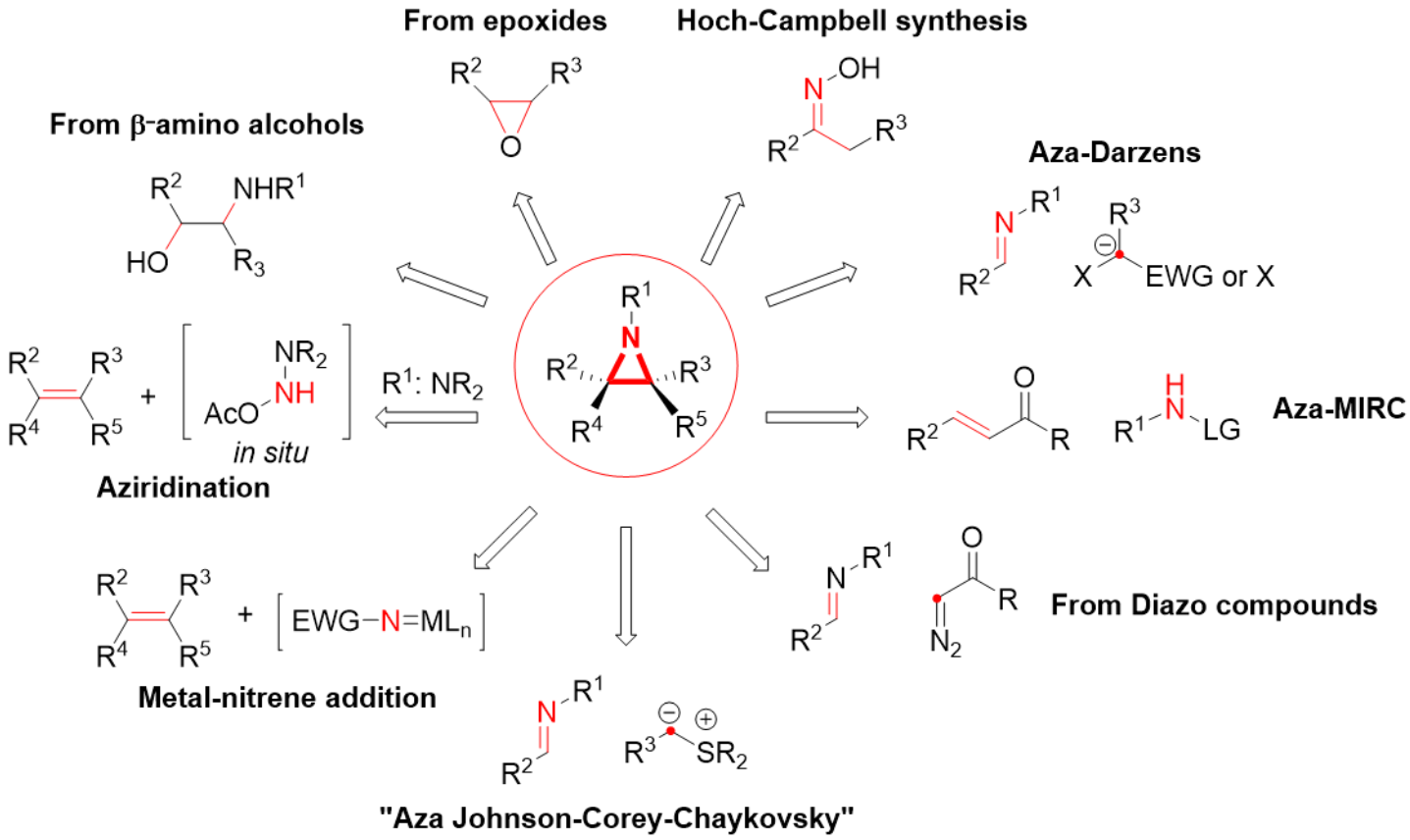
EWG on the nitrogen
Electrophilic substrates

Special case:
Donor-acceptor aziridine

Difference of reactivities

II. Synthesis of aziridine and azetidine

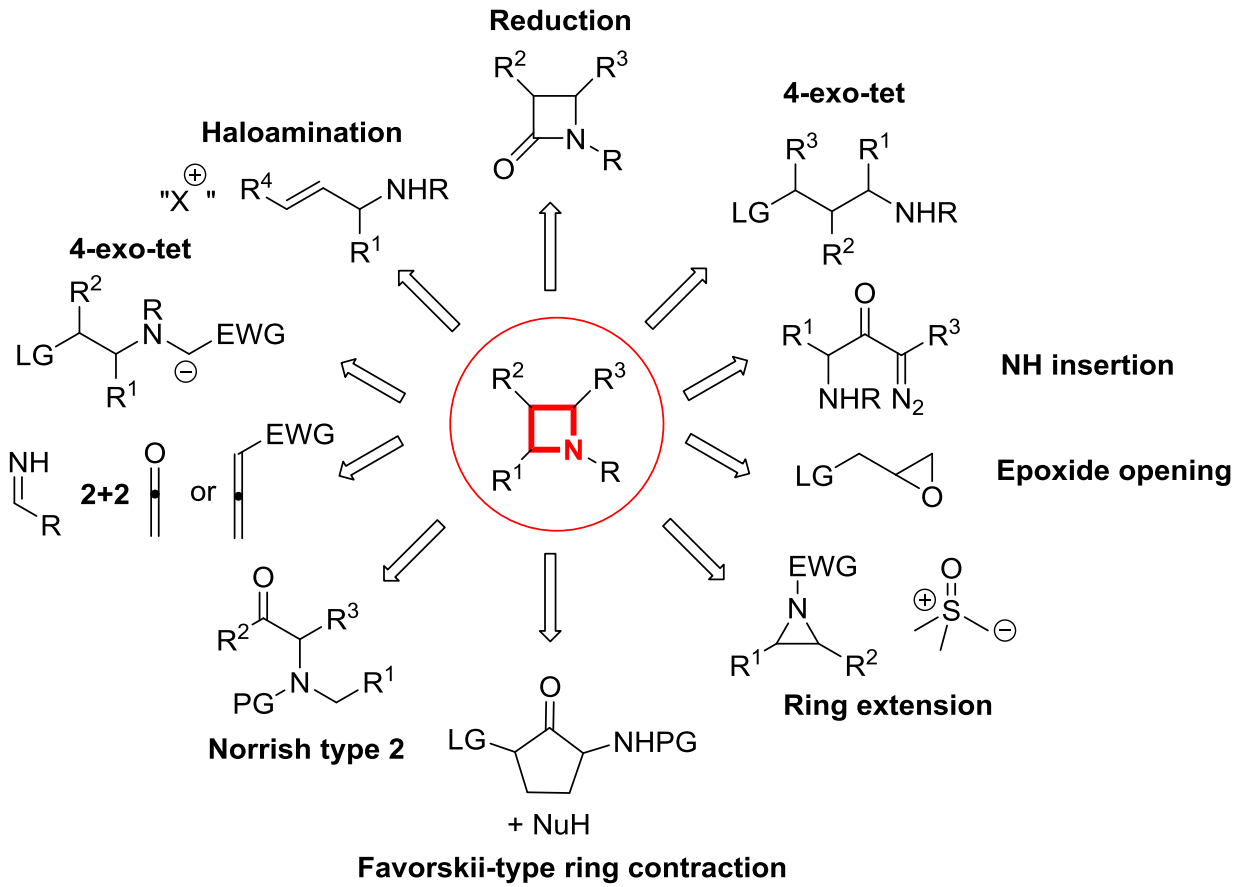
- Easy access to aziridines



To learn more about stereoselective synthesis of aziridines:
L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881−7929

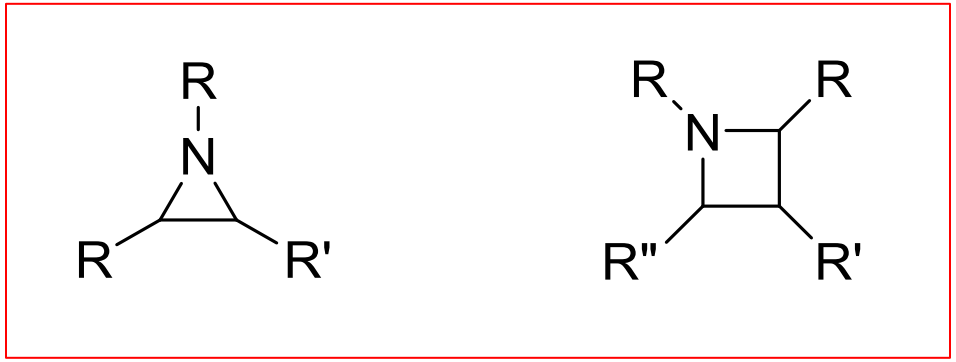
II. Synthesis of aziridine and azetidine

- Several methods for the synthesis of azetidine



For a more intensive look to the synthesis of azetidine:
A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988-4035

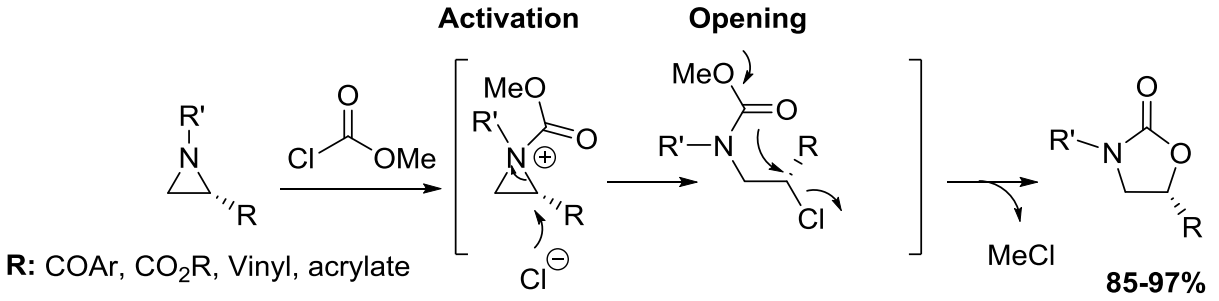
III. Reactivity of non-activated aziridines and azetidines



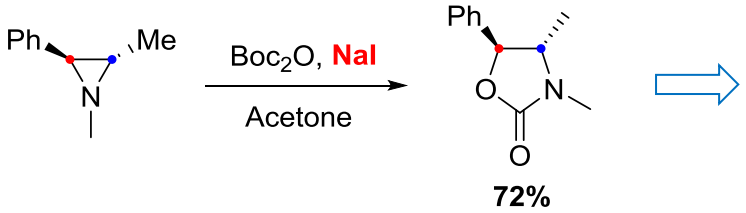
III. Reactivity of non-activated aziridines and azetidines

Ring expansion with "CX_2 inclusion":

- Double S_N2 inversion process



- Require an external nucleophile for other precursors:



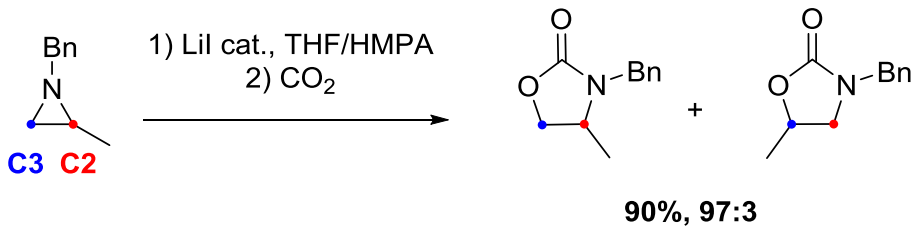
The released carbonate not sufficiently nucleophile
→ Halogen salt added to open the aziridinium

T. B. Sim, S. H. Kang, K. S. Lee, W. K. Lee, H. Yun, Y. Dong, H-J. Ha, *J. Org. Chem.* **2003**, *68*, 104-108
L. Testa, M. Akssira, E. Zaballos-Garcia, P. Arroyo, L. R. Domingo, J. Sepulveda-Arques, *Tetrahedron* **2003**, *59*, 677-683

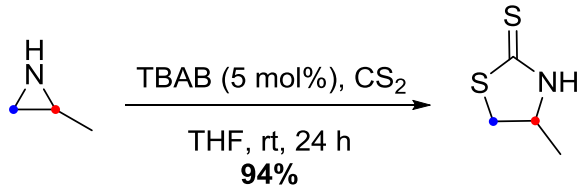
III. Reactivity of non-activated aziridines and azetidines

Ring expansion with "CX_2 inclusion":

- Allow the trapping of $CO_{2\,(g)}$



- Other heteroatoms can be introduced: CS_2



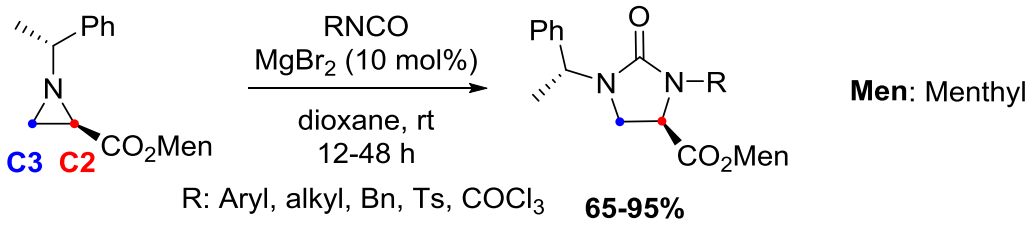
⇨ When only alkyl substituents: C3 opening → On the less hindered carbon

M. T. Hancock. A. R. Pinhas, *Tetrahedron Letters* **2003**, *44*, 5457-5460
A. Sudo, Y. Moriaka, E. Koizumi, F. Sanda, T. Endo, *Tetrahedron Letters* **2003**, *44*, 7889-7891

III. Reactivity of non-activated aziridines and azetidines

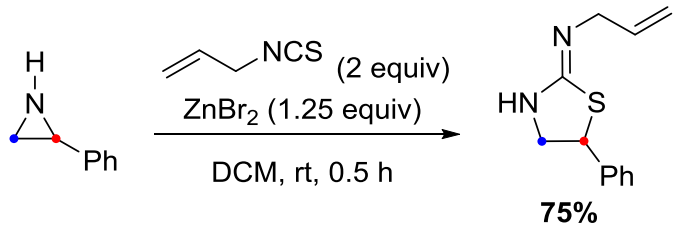
Ring expansion with "CX_2 inclusion":

- Isocyanates upon activation can be used:



Men: Menthyl

- But also thioisocyanates



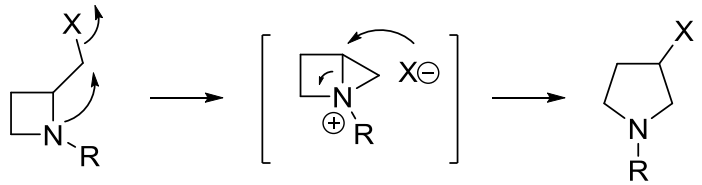
⇨ If Aryl or Ester substituted aziridine: C2 opening → On the most substituted carbon
(Between Ph and CO_2R → opening at Ph position favored)

M. S. Kim, Y-W. Kim, H. S. Hahm, J. W. Jang, W. K. Lee, H-J. Ha, *Chem. Commun.* **2005**, *25*, 3062-3064
R. A. Craig, N. R. O'Connor, A. F. G. Goldberg, B. M. Stoltz, *Chem. Eur. J.* **2014**, *20*, 4806 – 4813
S. Stankovic, M. D'Hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe, H-J. Ha, *Chem. Soc. Rev.* **2012**, *41*, 643-665

III. Reactivity of non-activated aziridines and azetidines

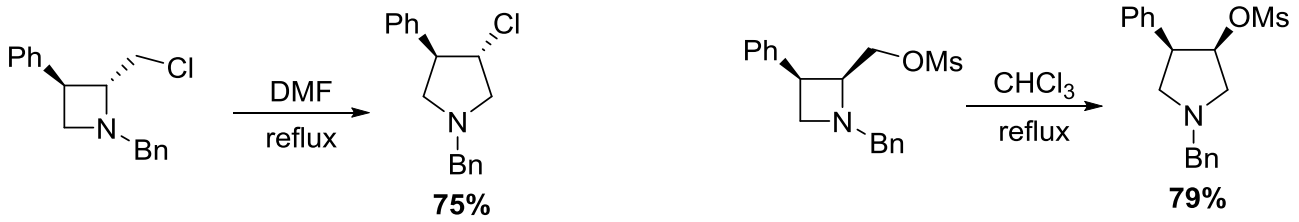
Ring expansion of 2-haloalkyl azetidines

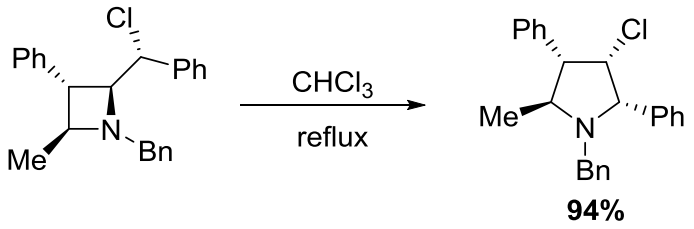
- Proposed mechanism:



⇨ Calculations tend to favor this bicyclic intermediate in DMSO

Stereospecific:
→ Retention via double S_N2



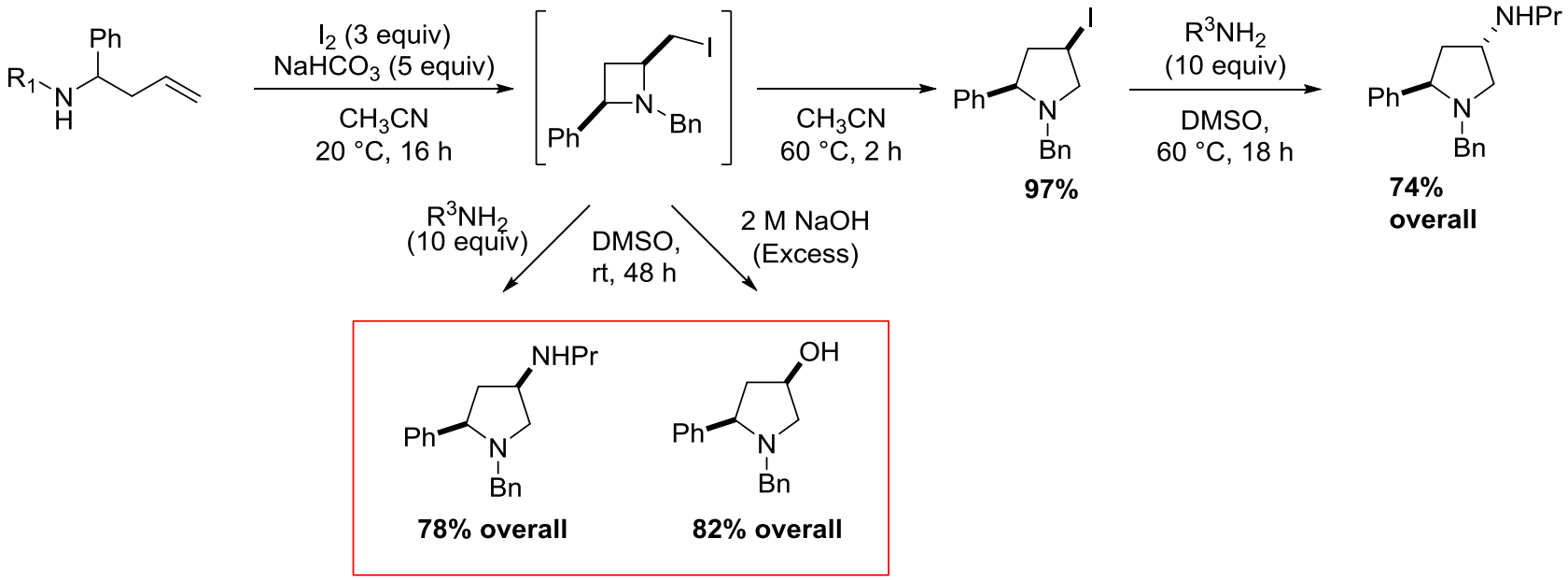


F. Couty, M. Kletskii, *J. Mol. Struct. THEOCHEM* **2009**, *908*, 26–30
F. Couty, F. Durrat, D. Prim, *Tetrahedron Letters* **2003**, *44*, 5209-5212

III. Reactivity of non-activated aziridines and azetidines

Ring expansion of 2-haloalkyl azetidines

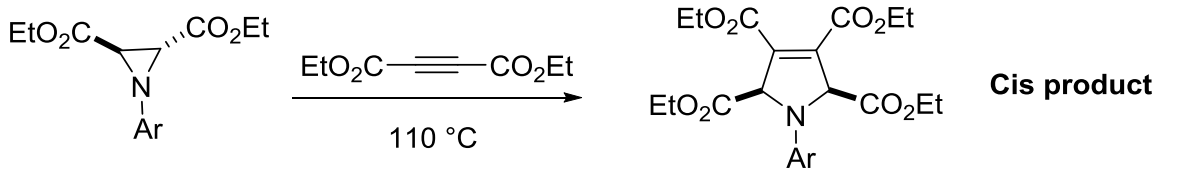
- Possible ring expansion of iodo-azetidine in presence of another nucleophiles



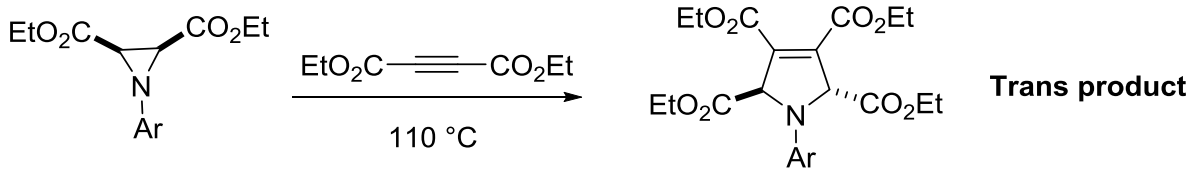
A. Feula, S. S. Dhillon, R. Byravan, M. Sangha, R. Ebanks, M. A. Hama Salih, N. Spencer, L. Male, I. Magyary, W-P. Deng, F. Müller, J. S. Fossey, *Org. Biomol. Chem*. **2013**, *11*, 5083-5093

III. Reactivity of non-activated aziridines and azetidines

Huisgen et al., 1967: 1,3-dipolar cycloadditions via azomethine ylides



Cis product

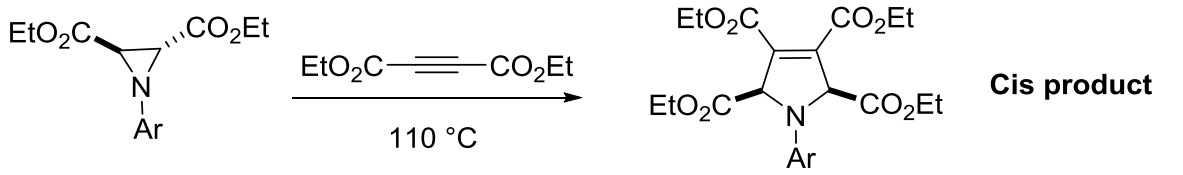


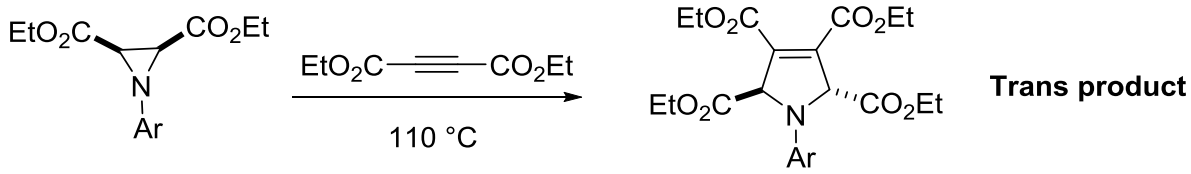
Trans product

R. Huisgen, W. Scheer, H. Huber *J. Am. Chem. Soc.* **1967**, 89, 1753-1755

III. Reactivity of non-activated aziridines and azetidines

Huisgen et al., 1967: 1,3-dipolar cycloadditions via azomethine ylides





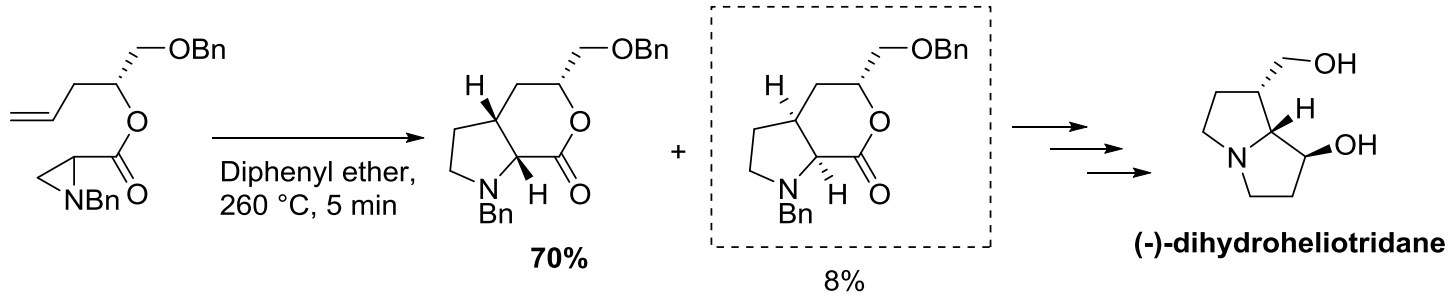
Question 1: How can you explain the stereoselectivity of these 2 examples?

R. Huisgen, W. Scheer, H. Huber *J. Am. Chem. Soc.* **1967**, 89, 1753-1755

III. Reactivity of non-activated aziridines and azetidines

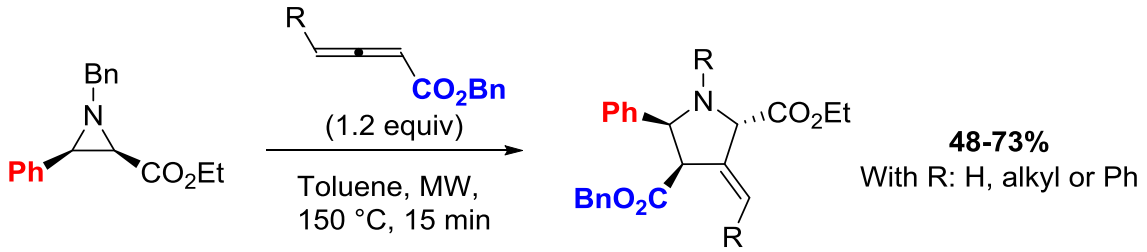
1,3-dipolar cycloadditions via azomethine ylides

- With non polarized alkenes



⇨ Intramolecular + require very high temperature

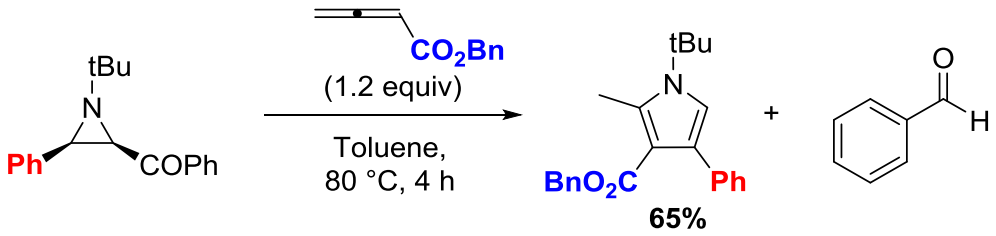
- With allenoates



48-73%
With R: H, alkyl or Ph

+ Presence of pyrrole
(Formal 3+2)

- Interestingly if N protected with *t*Bu or Cy:
Formal 3+2 major

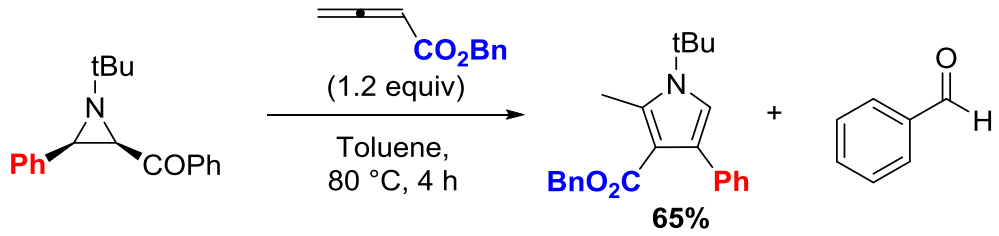


K. Hashimura, S. Tomita, K. Hiroya, K. Ogasawara, *J. Chem. Soc., Chem. Commun*. **1995**,*22*, 2291-2292
F. M. Ribeiro Laia, A. L. Cardoso, A. M. Beja, M. R. Silva, T. M.V.D. Pinho e Melo, *Tetrahedron* **2010**, *66*, 8815-8822

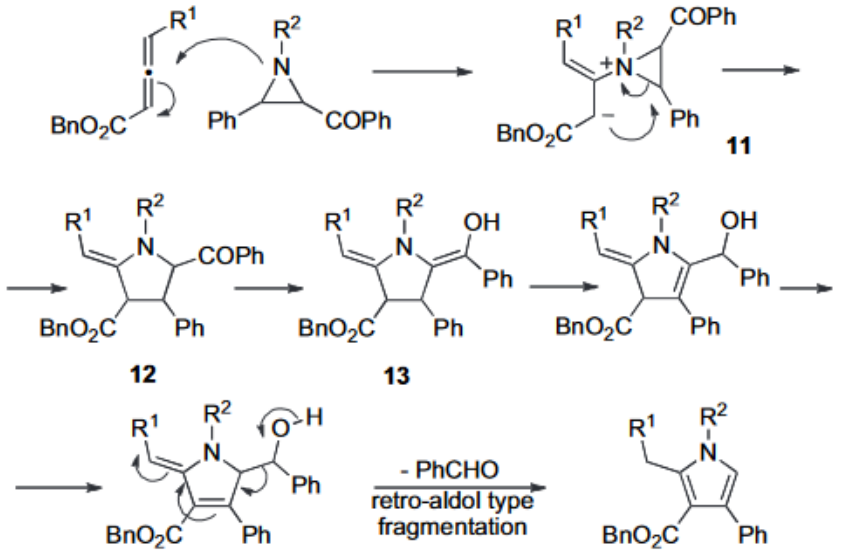
III. Reactivity of non-activated aziridines and azetidines

1,3-dipolar cycloadditions via azomethine ylides

- Interestingly if N protected with *t*Bu or Cy:



Formal 3+2 major



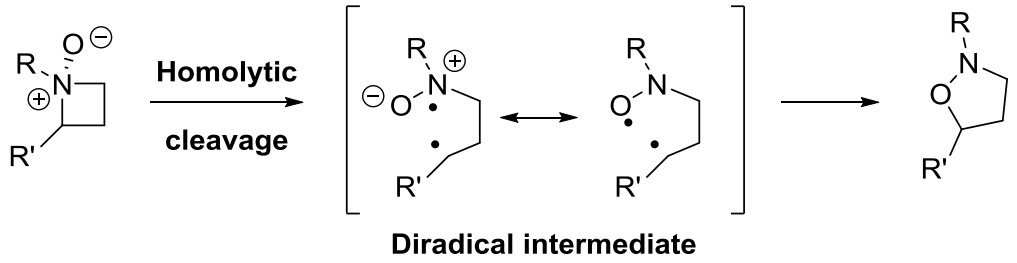
Scheme 4. Mechanism proposal of the formal [3+2] cycloaddition of aziridines and allenoates.

F. M. Ribeiro Laia, A. L. Cardoso, A. M. Beja, M. R. Silva, T. M.V.D. Pinho e Melo, *Tetrahedron* **2010**, *66*, 8815-8822

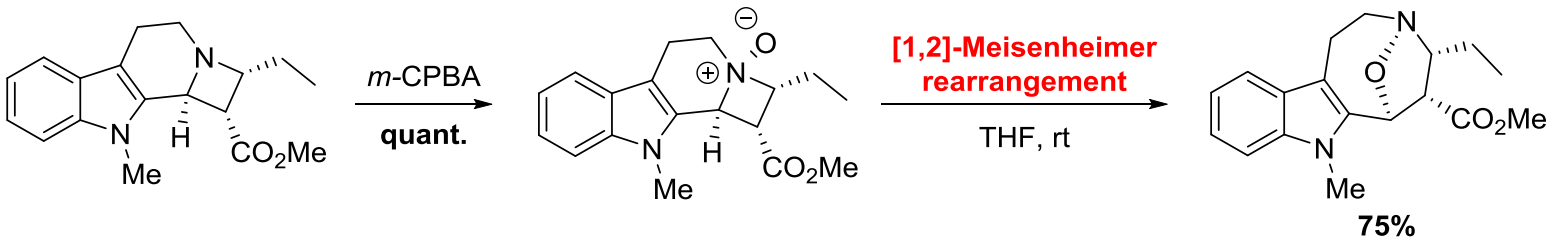
III. Reactivity of non-activated aziridines and azetidines

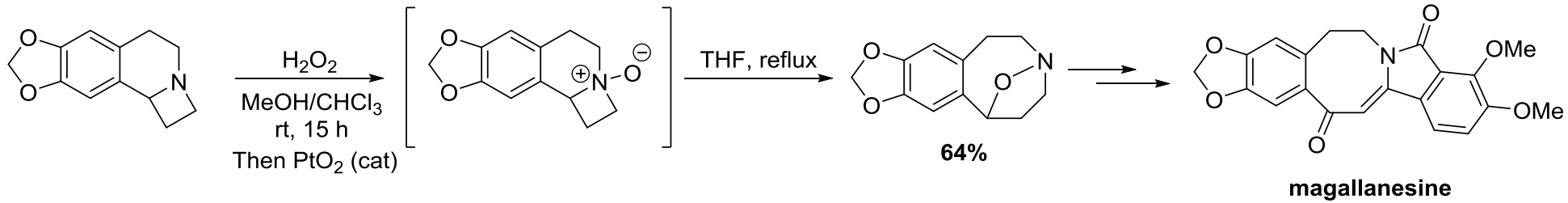
[1,2]-Meisenheimer rearrangement with N-oxide of azetidines

[1,2]-Meisenheimer rearrangement:



- Kurihara et al. 1993 and 1996:



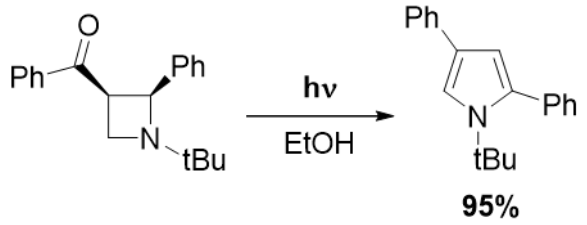


More details about mechanism: L. Menguy, B. Drouillat, J. Marrot, F. Couty, *Tetrahedron Letters* **2012**, *53*, 4697-4699
T. Kurihara, Y. Sakamoto, M. Takai, K. Ohuchi, S. Harusawa, R. Yoneda, *Chem. Pharm. Bull*. **1993**, *41*, 1221-1225
R. Yoneda, Y. Sakamoto, Y. Oketo, S. Harusawa, T. Kurihara, *Tetrahedron* **1996**, *46*, 14563-14576

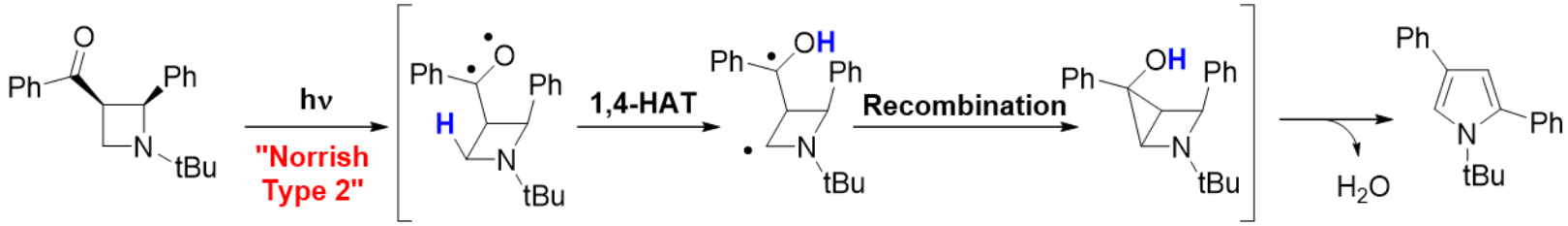
III. Reactivity of non-activated aziridines and azetidines

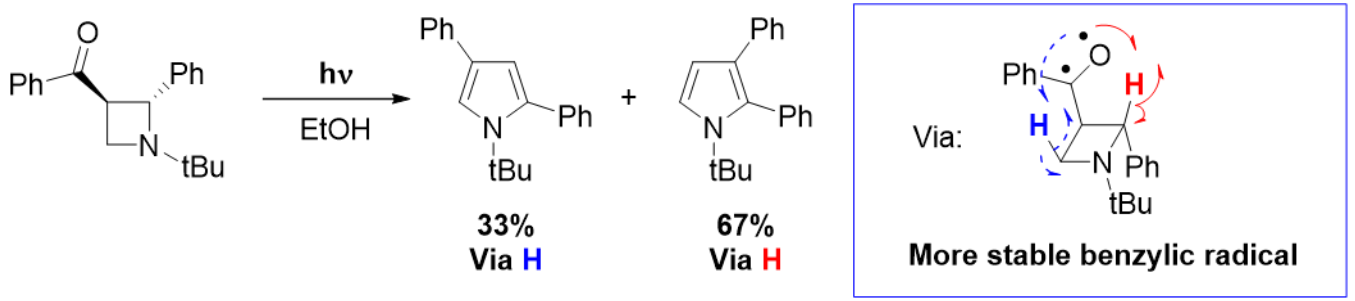
Photo-rearrangement of 3-benzoyl azetidine

- Padwa et al., 1967:



- Proposed mechanism:



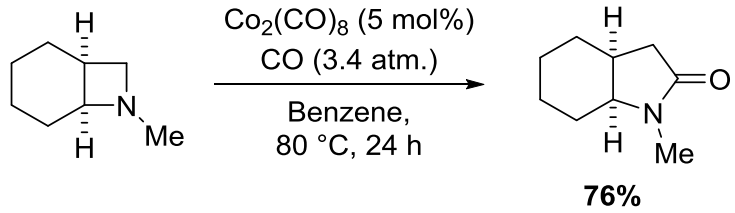


A. Padwa, R. Gruber, L. Hamilton, *J. Am. Chem. Soc.* **1967**, *89*, 3077-3078
A. Padwa, R. Gruber, *J. Am. Chem. Soc.* **1968**, *90*, 4456-4458

III. Reactivity of non-activated aziridines and azetidines

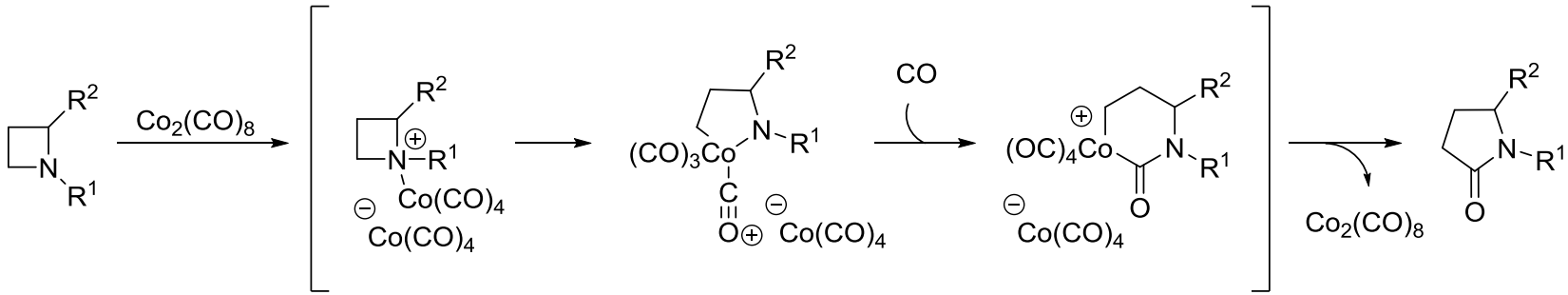
Cobalt-catalyzed carbonylation of azetidine

- Alper and Roberto, 1989



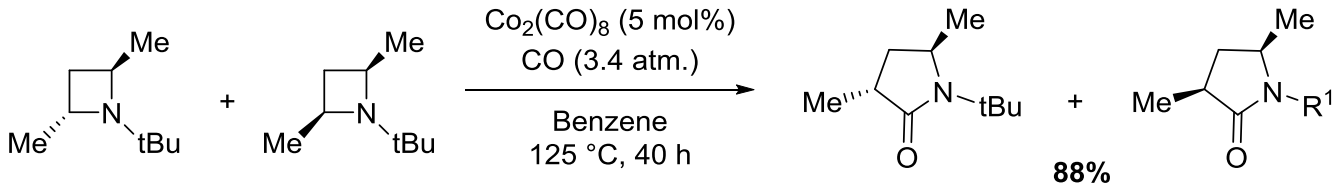
76%

- Proposed mechanism:



⇨ Insertion in the less substituted C-N bond

- Stereospecific process:

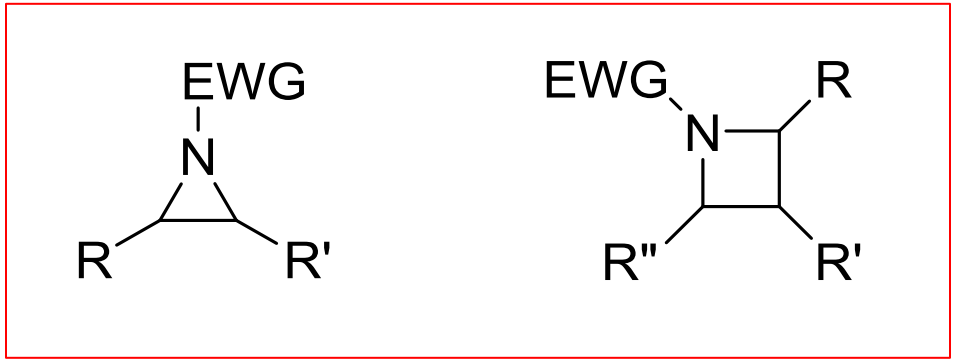


Ratio 3/1

88%
Ratio 3/1

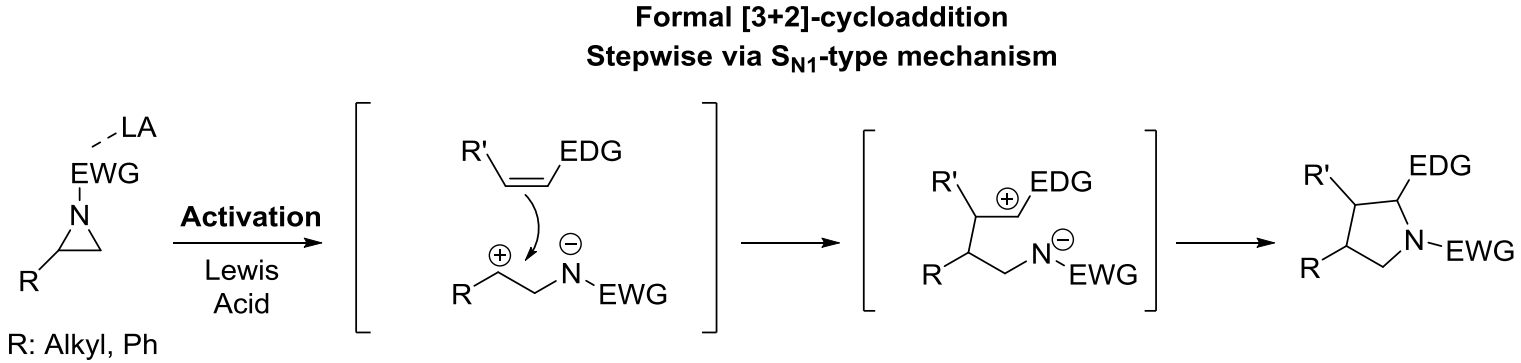
D. Roberto, H. Alper, *J. Am. Chem. Soc.* **1989**, *111*, 7539-7543

IV. Reactivity of activated aziridines and azetidines

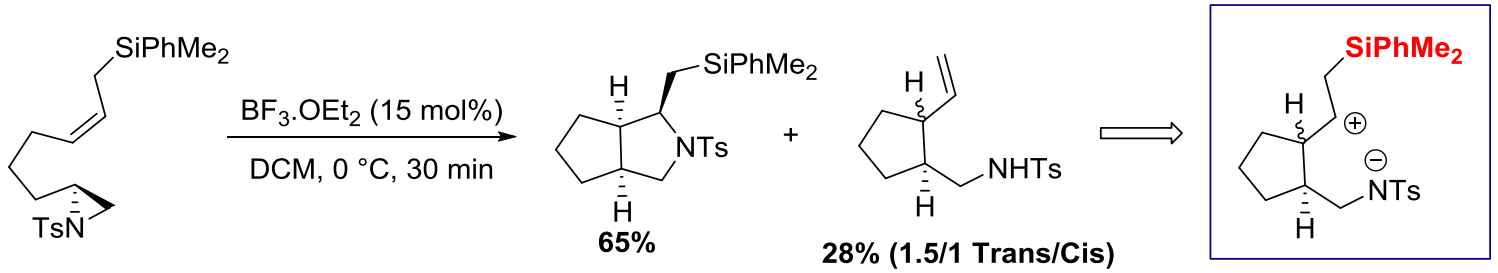


IV. Reactivity of activated aziridines and azetidines

- Formal [3+2] cycloaddition:



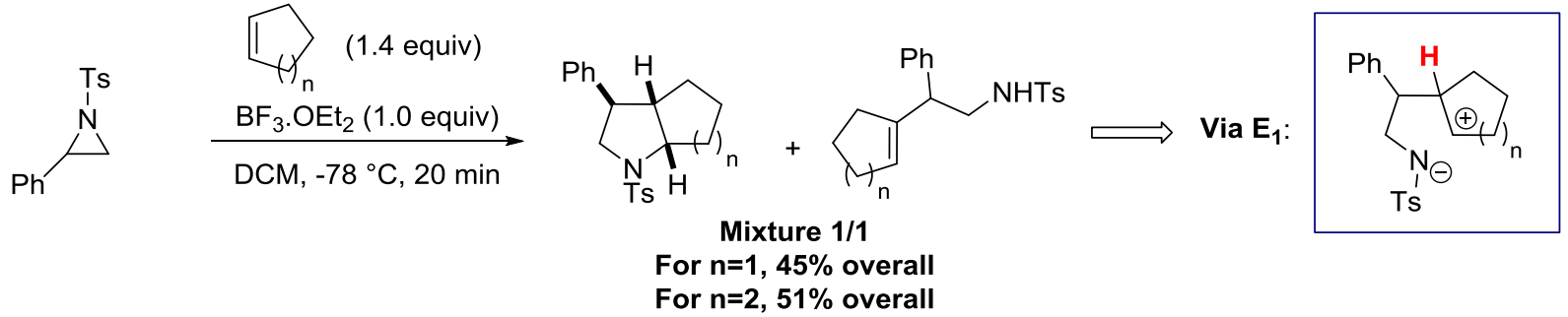
- Evidence: Presence of eliminated products



S.C. Bergmeier, S. L. Fundy, P. P. Seth, *Tetrahedron* **1999**, *55*, 8025-8038

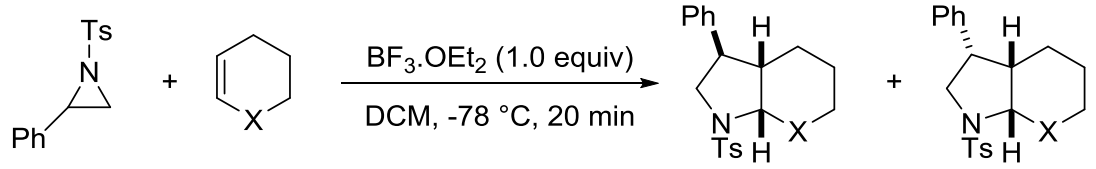
IV. Reactivity of activated aziridines and azetidines

- Same observation without silylated moiety:



Mixture 1/1
For n=1, 45% overall
For n=2, 51% overall

- With electron-enriched alkenes → no opened product BUT mixture exo/endo

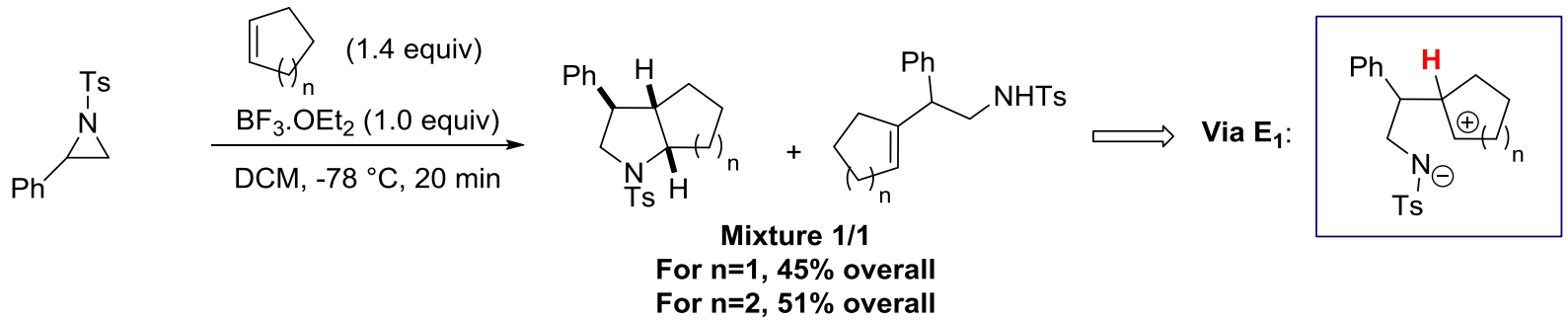


Exo / endo: 1 / 1
X= O, 80%
X=NTs, 90%

I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed.* **2000**, *39*, 4615-4617
I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Tetrahedron Letters* **2001** *42* 6087-6091

IV. Reactivity of activated aziridines and azetidines

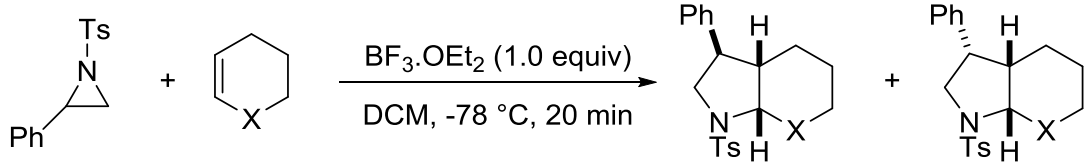
- Same observation without silylated moiety:



Mixture 1/1
For n=1, 45% overall
For n=2, 51% overall

Question 2: How can you explain this difference between these two examples ?

- With electron-enriched alkenes → no opened product BUT mixture exo/endo



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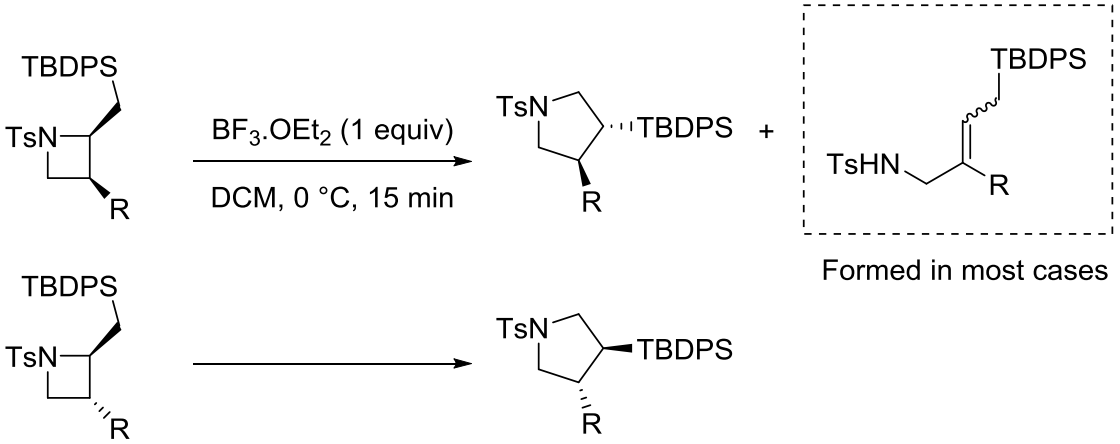
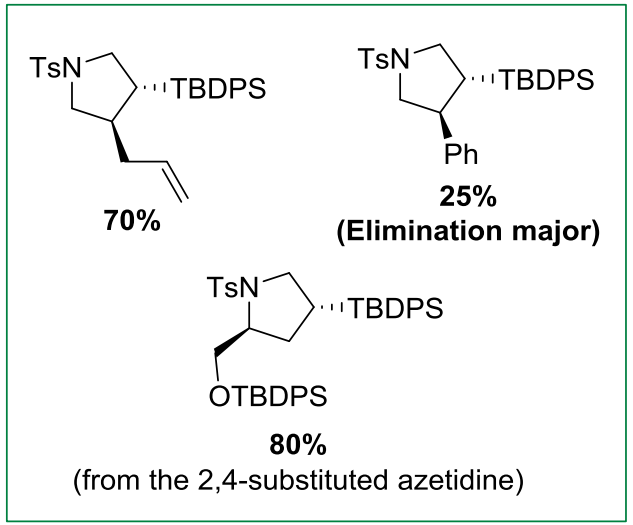
I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed.* **2000**, *39*, 4615-4617
I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Tetrahedron Letters* **2001** *42* 6087-6091

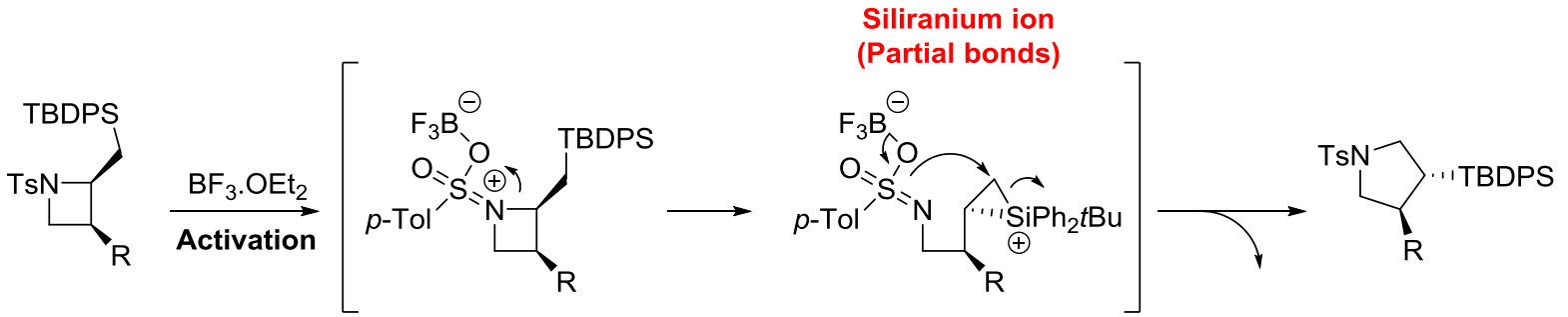
IV. Reactivity of activated aziridines and azetidines

- **Yadav et al., 2012**: Ring-expansion of 2-TBDPS methyl azetidine:





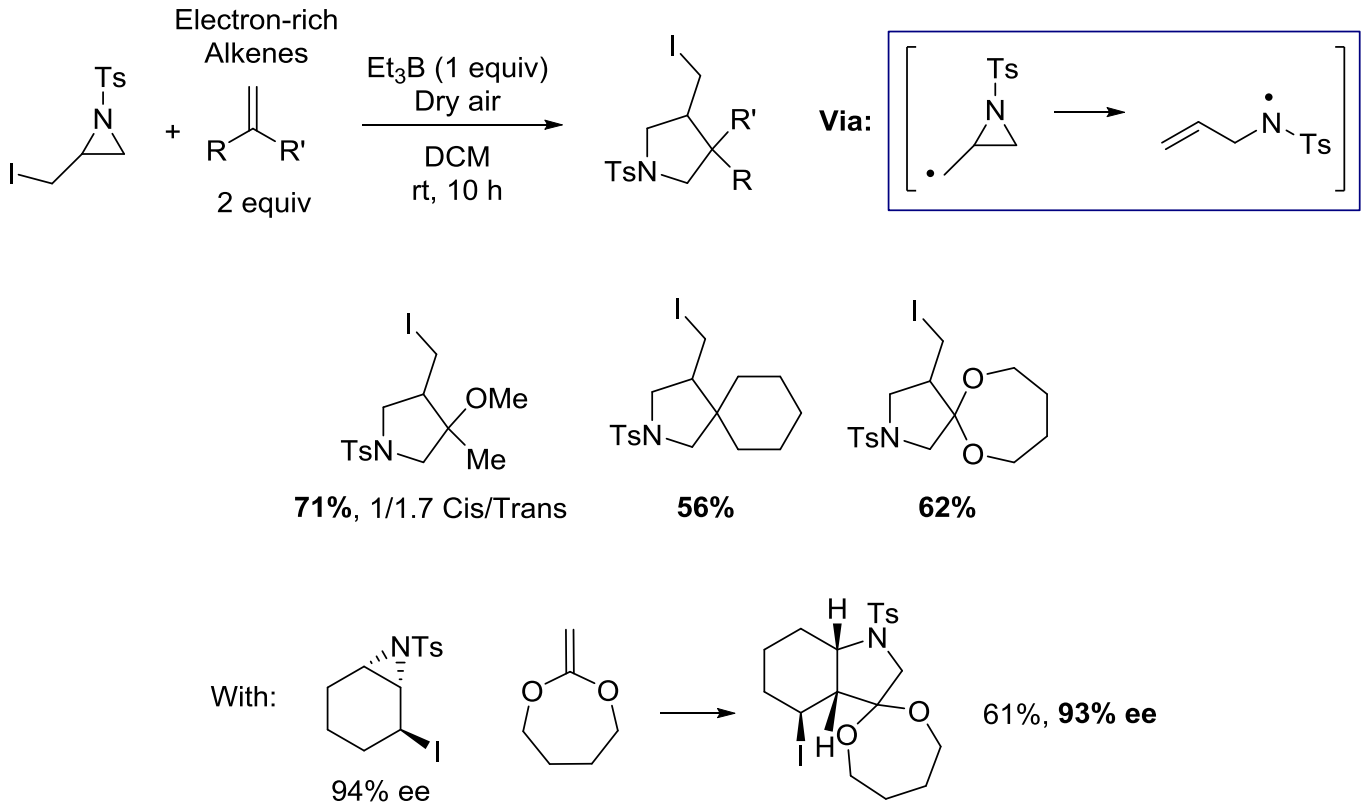
- Mechanism: Siliranium ion invariably trans to R substituent



B. D. Narhe, V. Sriramurthy, V. K. Yadav, *Org. Biomol. Chem.* **2012**, *10*, 4390–4399

IV. Reactivity of activated aziridines and azetidines

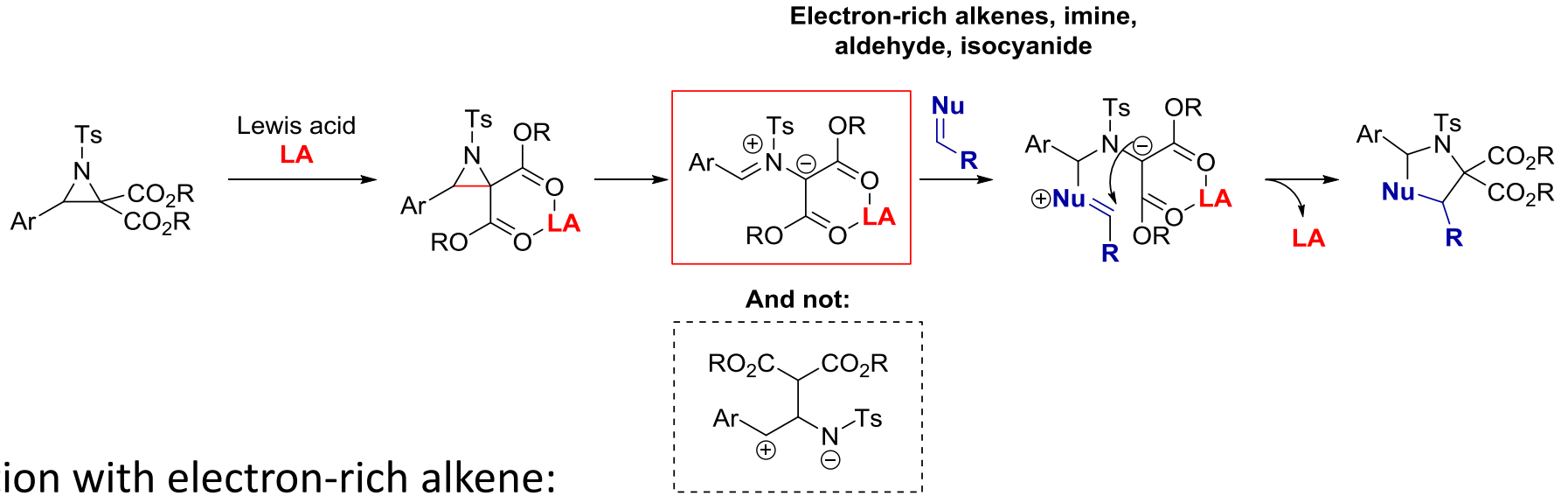
- **Taguchi et al., 2003**: Radical [3+2] cycloaddition via Iodine Atom Transfer:



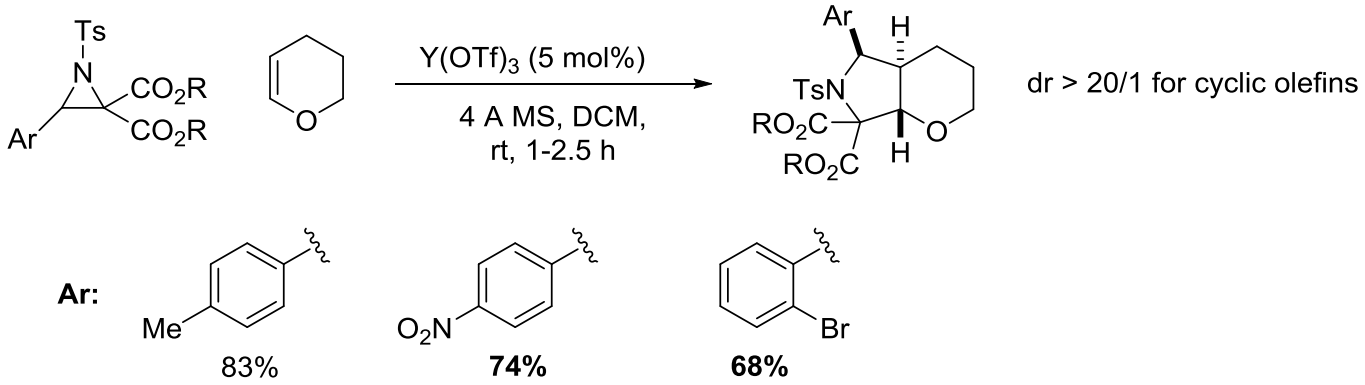
O. Kitagawa, S. Miyaji, Y. Yamada, H. Fujiwara, T. Taguchi, *J. Org. Chem.* **2003**, *68*, 3184-3189

IV. Reactivity of activated aziridines and azetidines

- **Non-activated aziridine reactivity** using donor-acceptor activated aziridines:



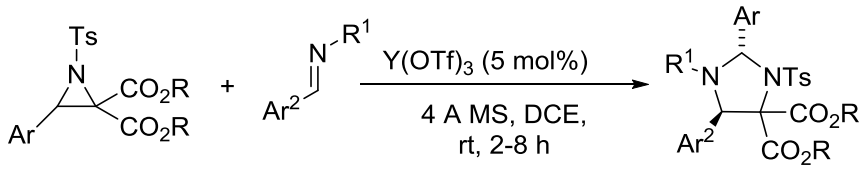
- Reaction with electron-rich alkene:



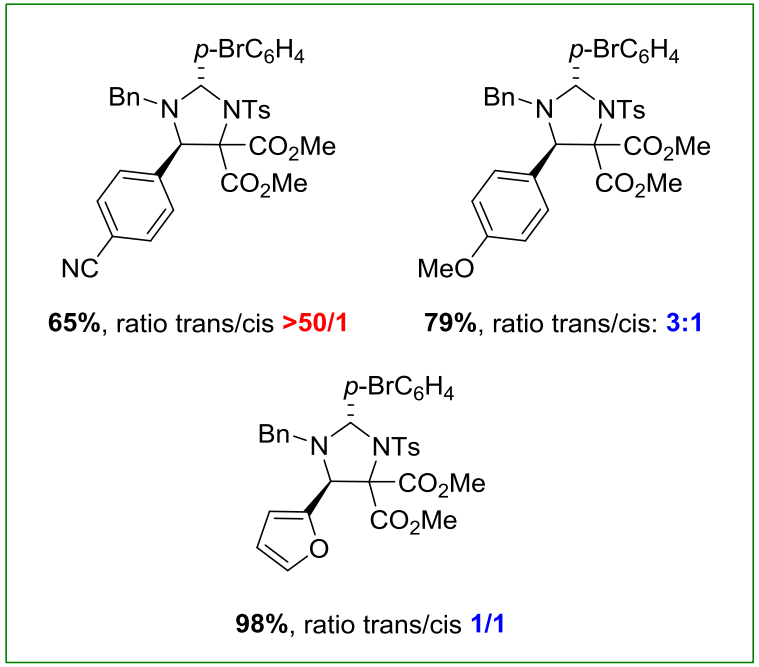
L. Li, X. Wu, J. Zhang, *Chem. Commun.* **2011**, *47*, 5049-5051

IV. Reactivity of activated aziridines and azetidines

- Reaction with aromatic imine :



65-98%
dr trans/cis up to >50/1

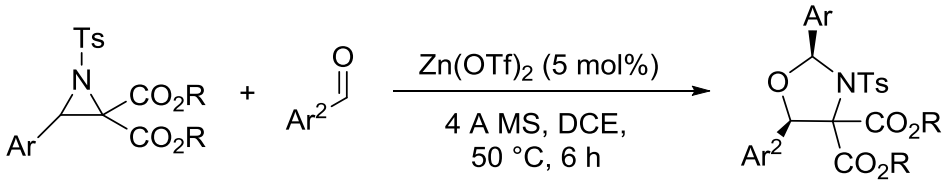


65%, ratio trans/cis **>50/1**

79%, ratio trans/cis: **3:1**

98%, ratio trans/cis **1/1**

- Reaction with aromatic aldehyde:



Both electron-rich and
poor aromatic aldehyde

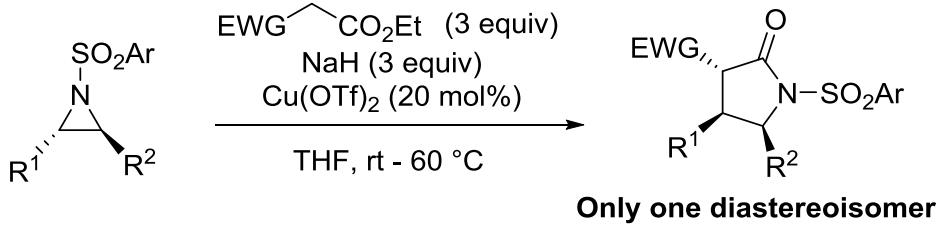
52-97%
Most cases:
Only **cis** diastereoisomer

X. Wu, J. Zhang, *Synthesis* **2012**, *44*, 2147-2154
Z. Jiang, J. Wang, P. Lu, Y. Wang, *Tetrahedron* **2011**, *67,* 9609-9617

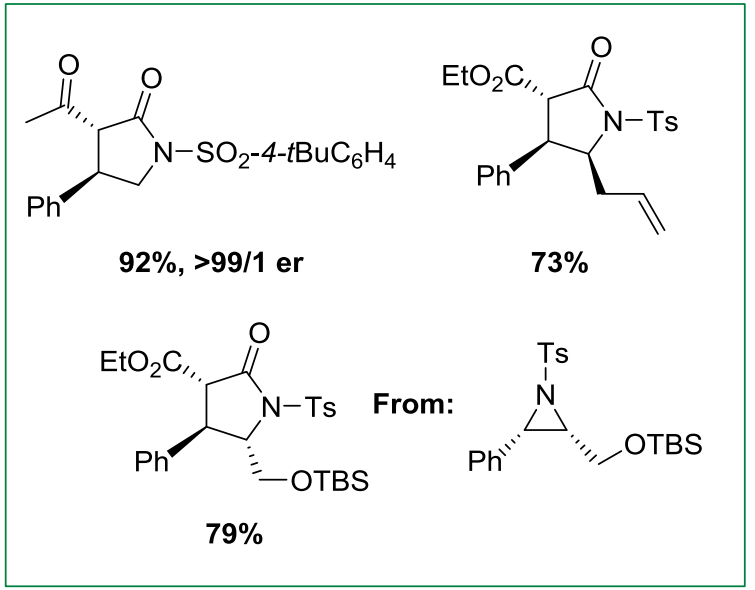
IV. Reactivity of activated aziridines and azetidines

- S_N2-type ring opening-cyclization:

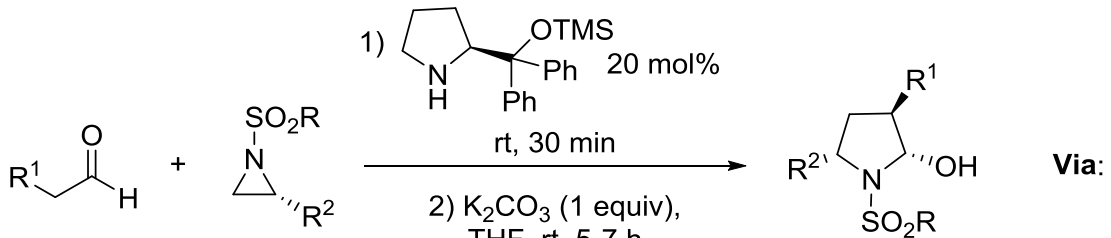
With enolates:



Only one diastereoisomer

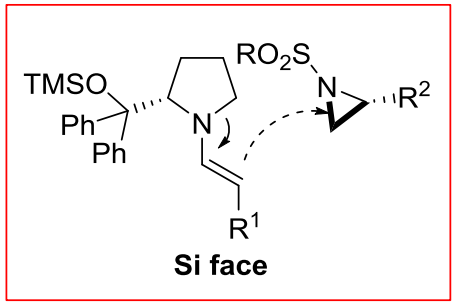


With enamine:



78-90%
Single diastereoisomer

Via:

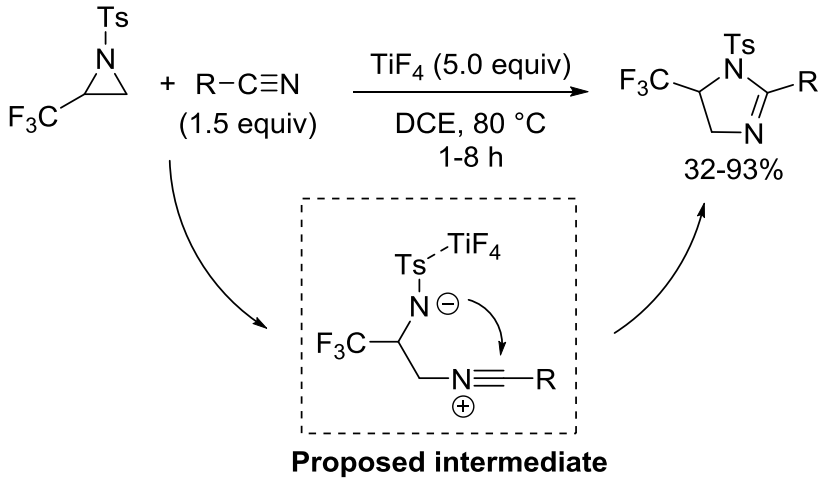


M. K. Ghorai, D. P. Tiwari, *J. Org. Chem*. **2010**, *75*, 6173–6181
A. Rai, D. S. Yadav, *Tetrahedron Letters* **2013**, *54*, 3127-3131

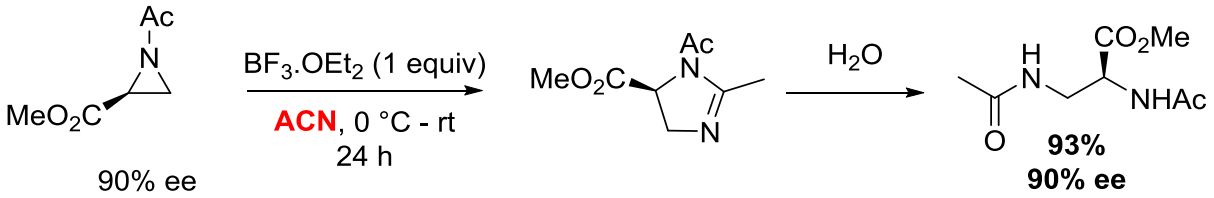
IV. Reactivity of activated aziridines and azetidines

- S_N2-type ring opening-cyclization:

Even with nitriles:



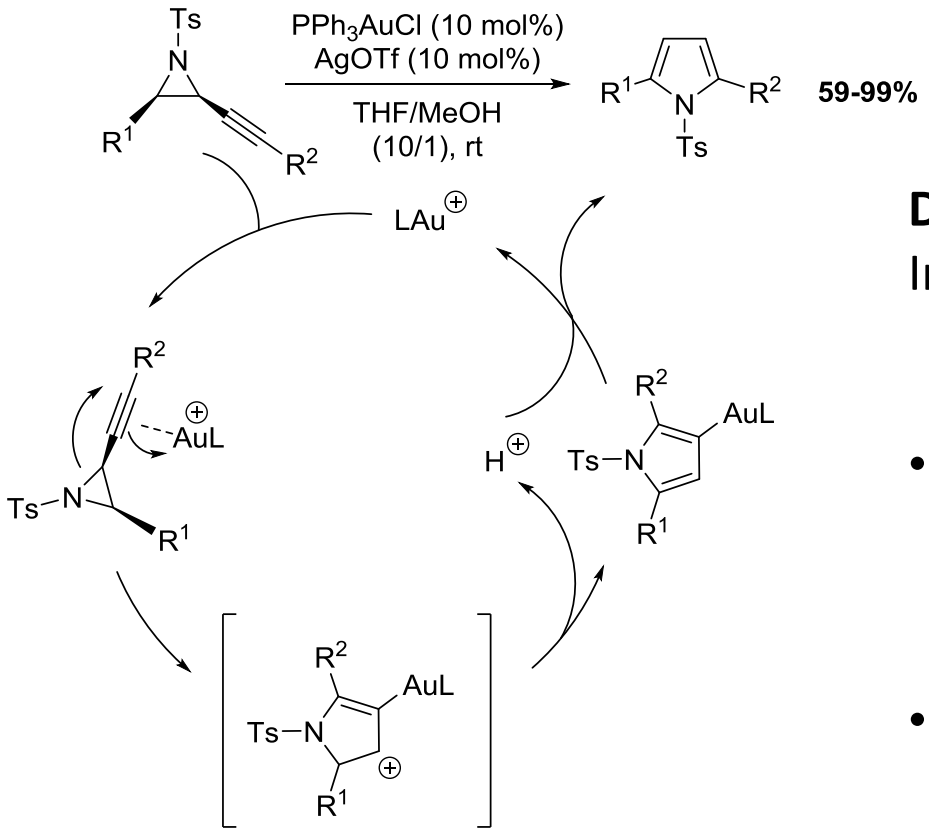
Retention of the stereochemistry:



M. Yoshiki, R. Ishibashi, Y. Yamada, T. Hanamoto, *Org. Lett.* **2014**, *16*, 5509-5511
M. Bucciarelli, A. Forni, I. Moretti, F. Prati, G. Torre, *Tetrahedron: Asymmetry* **1995**, *6*, 2073-2080

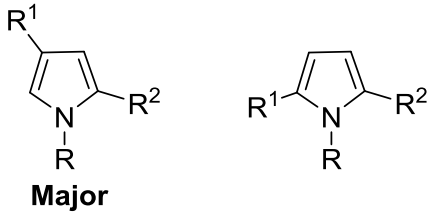
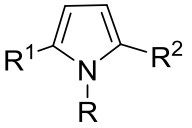
IV. Reactivity of activated aziridines and azetidines

- **Hou and Davies groups, 2009**: Gold-catalyzed ring expansion:



Davies et al.:

In apolar solvents: Ag**X** play on the regioselectivity

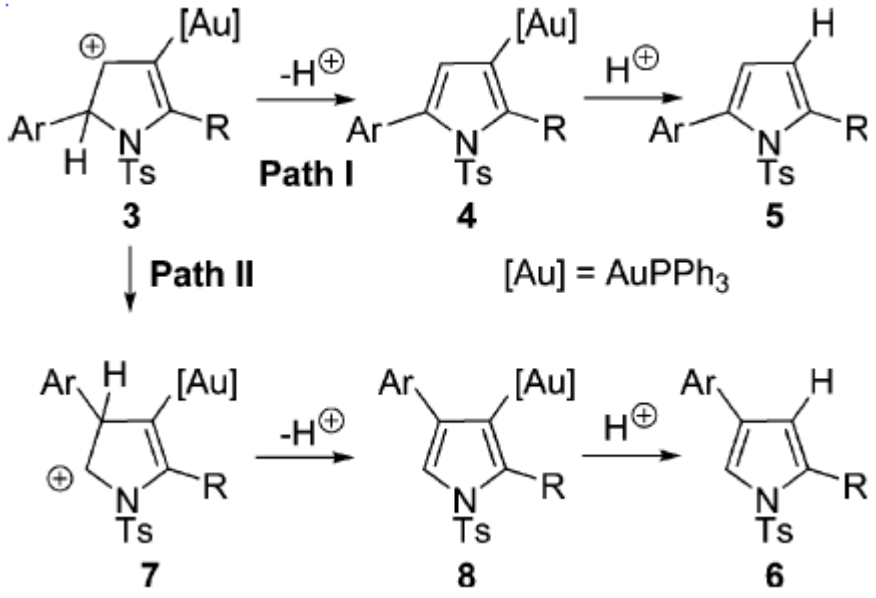
- AgOTf in DCM →  **Major**
- AgOTs in DCM → Only prod. 

D-D. Chen, X-L. Hou, L-X. Dai, *Tetrahedron Letters* **2009**, *50*, 6944-694

P. W. Davies, N. Martin, *Org. Lett.* **2009**, *11*, 2293-2296

IV. Reactivity of activated aziridines and azetidines

- **Hou and Davies groups, 2009**: Gold-catalyzed ring expansion:



Davies *et al.*:
In apolar solvents: Ag**X** play on the regioselectivity

→ If neither the solvent or X is enough basic to promote the elimination → Migration predominant

Hou *et al.*:
With polar solvent: THF/MeOH and AgOTf

→ No migration

D-D. Chen, X-L. Hou, L-X. Dai, *Tetrahedron Letters* **2009**, *50*, 6944-694
P. W. Davies, N. Martin, *Org. Lett.* **2009**, *11*, 2293-2296

V. Conclusion

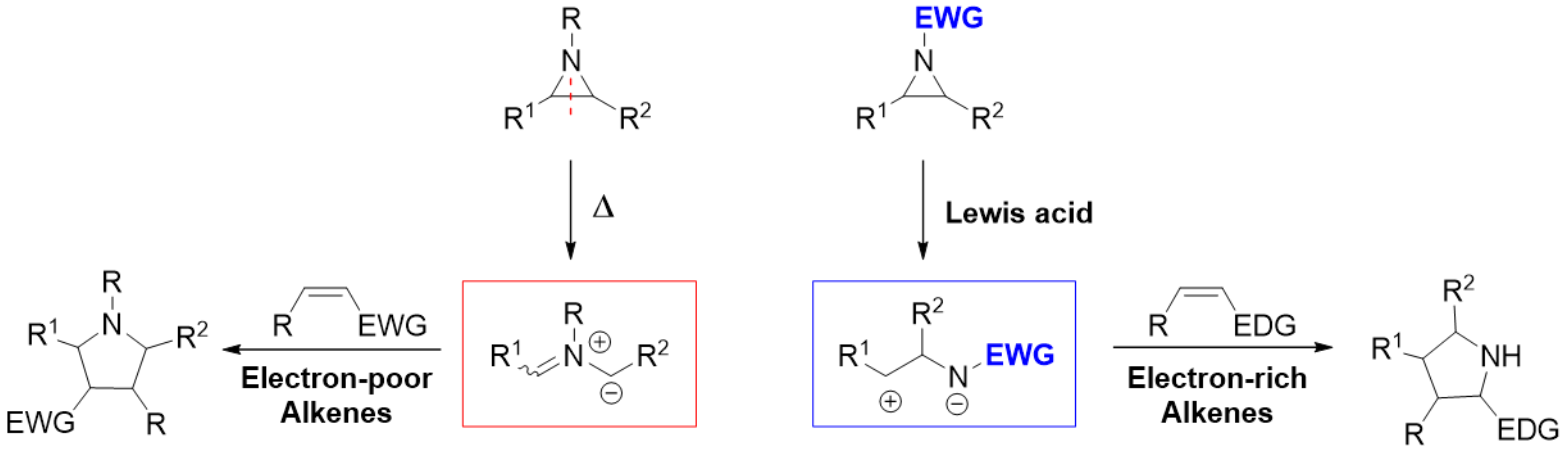
- Activated and non-activated aziridines/azetidines:

⇨ **Opposite reactivity**

Non-activated: Act as a **nucleophile** then ring-expansion

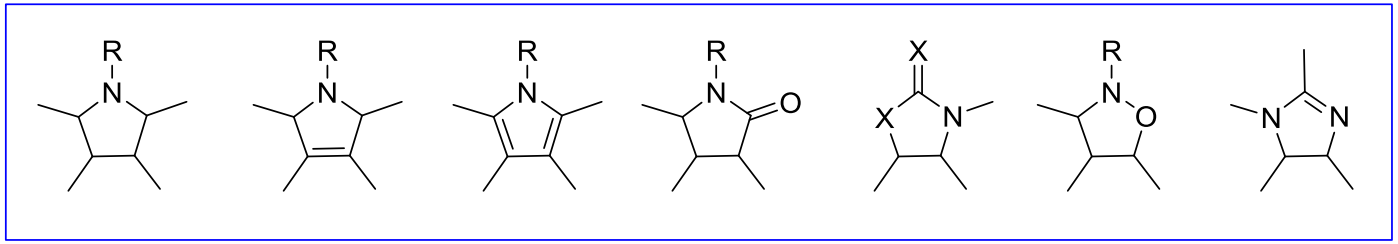
Activated: Act as an **electrophile** then ring-expansion

- Upon activation, regioselectivity of the 1,3-dipole different:



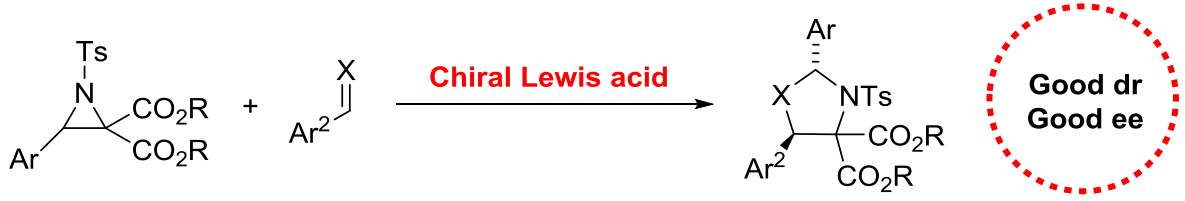
V. Conclusion

- Allow the synthesis of a diversity of 5-membered azacycles



- In many cases: good regio and stereoselectivity for the ring-expansions

- Still not much efficient enantioselective catalysis for the formal [3+2]

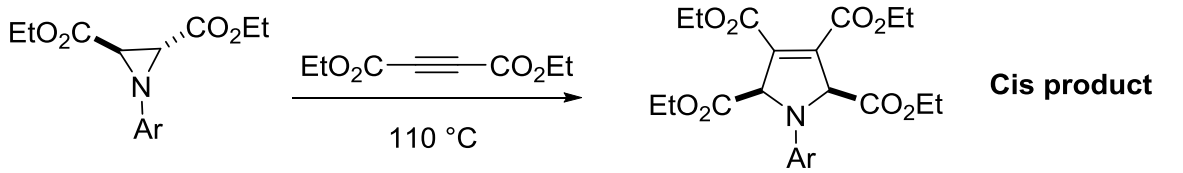


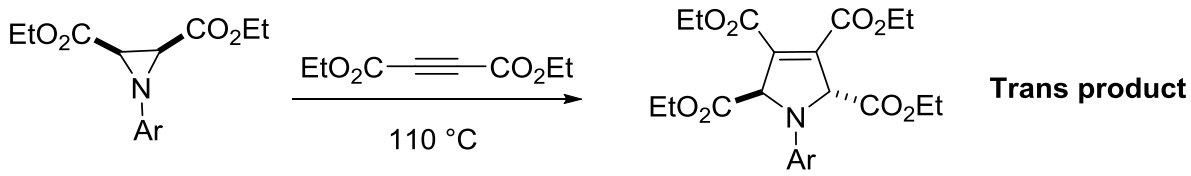
Thank you for your attention

Questions

III. Reactivity of non-activated aziridines and azetidines

Huisgen et al., 1967: 1,3-dipolar cycloadditions via azomethine ylides





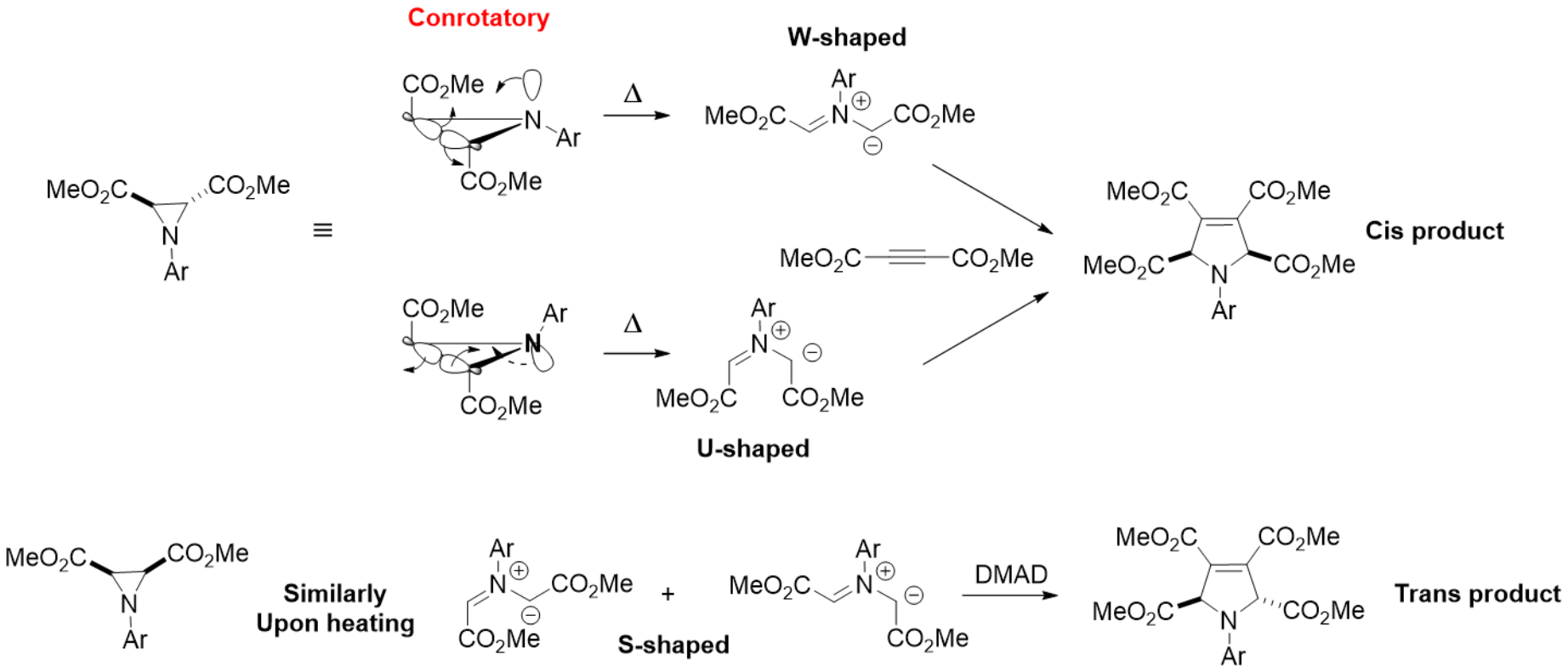
Question 1: How can you explain the stereoselectivity of these 2 examples?

R. Huisgen, W. Scheer, H. Huber *J. Am. Chem. Soc.* **1967**, 89, 1753-1755

Questions

Question 1: How can you explain the relative stereoselectivity of these 2 examples?

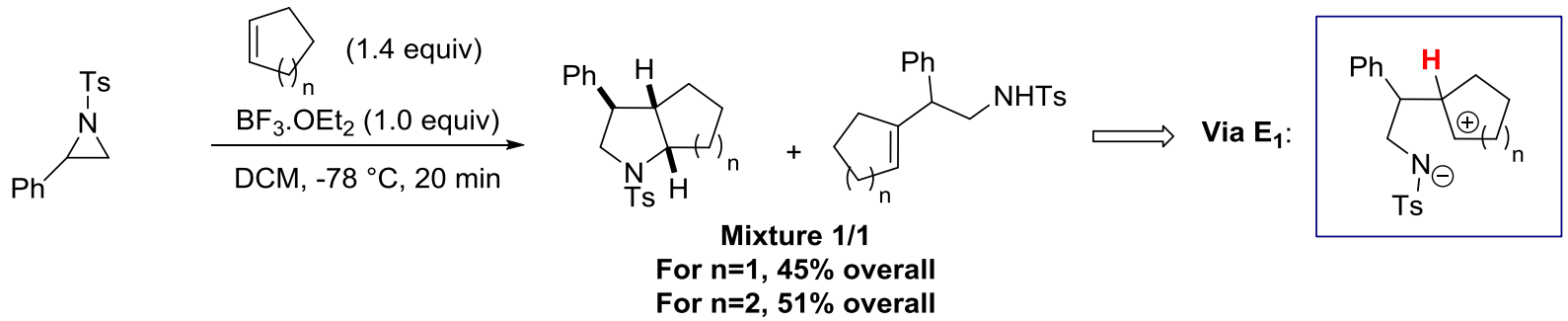
→ Using Woodward-Hoffmann rules: 4n electrocyclic opening in a thermal process: **Conrotatory**



R. Huisgen, W. Scheer, H. Huber *J. Am. Chem. Soc.* **1967**, 89, 1753-1755

IV. Reactivity of activated aziridines and azetidines

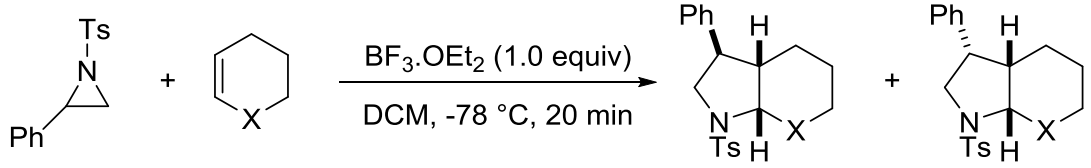
- Same observation without silylated moiety:



Mixture 1/1
For n=1, 45% overall
For n=2, 51% overall

Question 2: How can you explain this difference between these two examples ?

- With electron-enriched alkenes → no opened product BUT mixture exo/endo

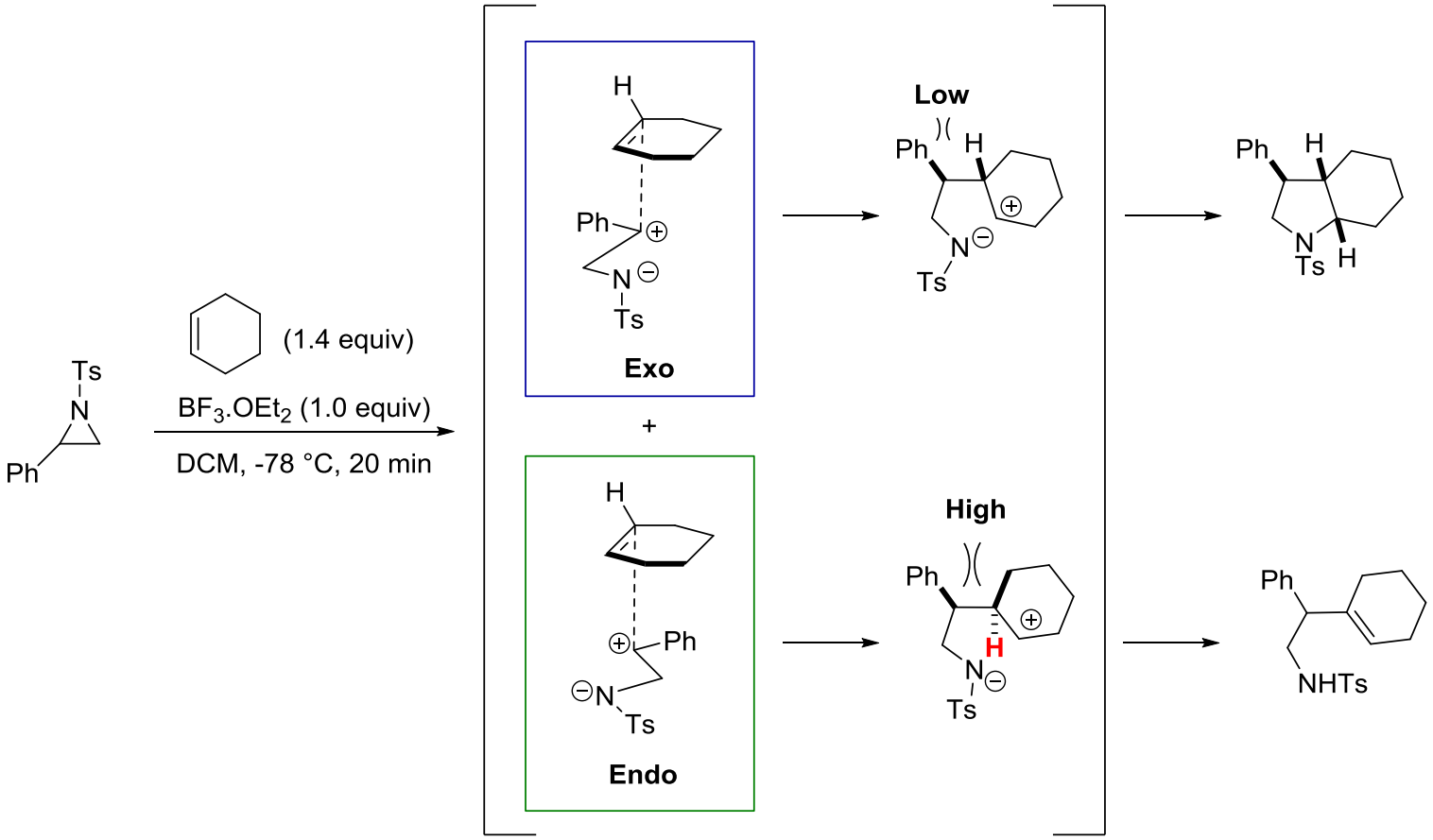


Exo / endo: 1 / 1
X= O, 80%
X=NTs, 90%

I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed.* **2000**, *39*, 4615-4617
I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Tetrahedron Letters* **2001** *42* 6087-6091

Questions

Question 2: How can you explain this difference between these two examples ?



I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed.* **2000**, *39*, 4615-4617

Questions

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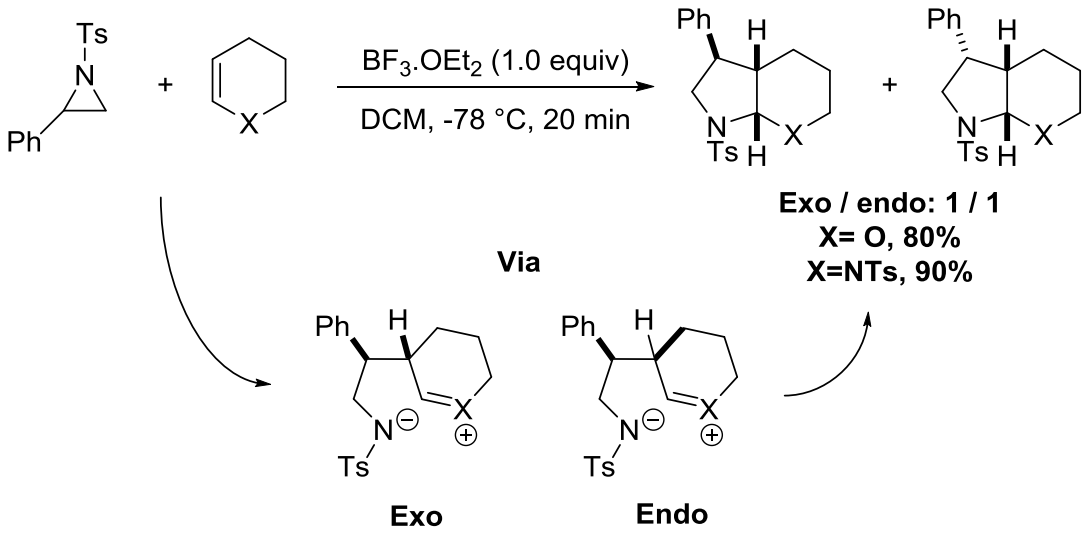
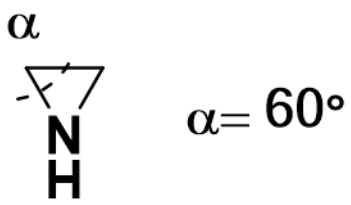


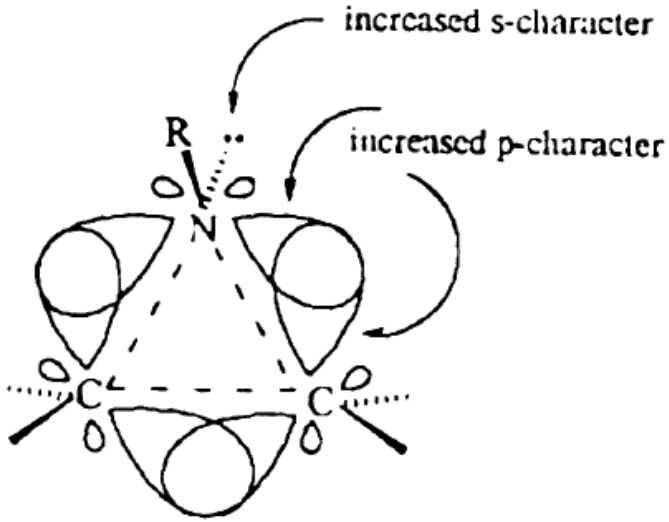
I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Tetrahedron Letters* **2001,** *42,* 6087-6091

I. Introduction – pKa explanation



(See Walsh diagram)

- pKa (in water): **7.98**
- Not simple covalent bond: C-C-N bond angle ≈ 60 ° (<< 109.5° expected for sp3 C)



⇨ Possible with increased **p**-character of the cycle bonds → Bend bonds

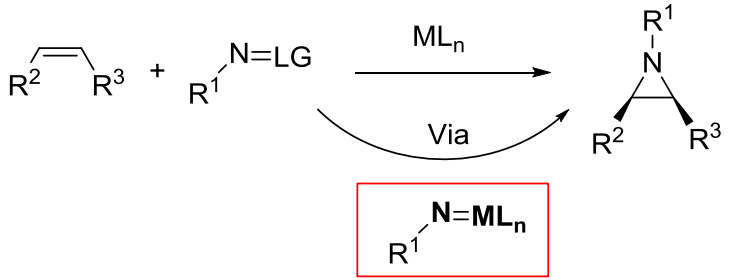
⇨ Results in an increased **s**-character of the nitrogen lone pair

Decrease in the basicity of the nitrogen
Increase inversion energy barrier

K. B. Wiberg, *Acc. Chem. Res.* **1996**, *29*, 229-234
Picture from: C. K. Meades, Diene-Derived N-(3,4-Dihydro-4-oxoquinazolin-3-yl)aziridines: Preparation and Reactivity, Ph.D. Thesis, The University of Leicester, March 2000

II. Synthesis of aziridine and azetidine

- Addition of Metal-nitrenes to olefins



From: PhI=N(EWG) , N_3–EWG , TsO–N(H)–CO_2R , NH_2–EWG + Oxidant

ML_n: Cu, Co, Ru, Rh, Mn, Fe, Ag

Two possible pathways: