# *Aziridines*

## *- Overview and Recent Advancements -*

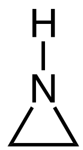
Jan Streuff

Stoltzgroup - Literature Seminar

01-26-2009, 8pm
147 Noyes

# *Some Properties of Aziridine*

Physical Properties:



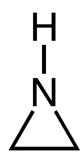
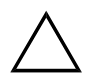
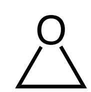
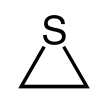
*bp = 57°C*
*pKa (of conjug. acid) = 7.98*

*possibly carcinogenic*

*absorbed through skin*

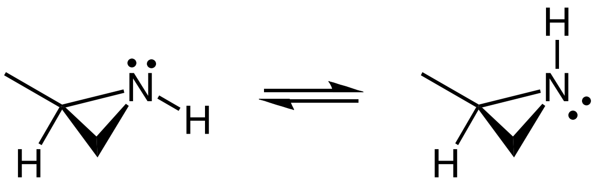
*potential mutagen: interacts with DNA nucleobases*

Strain energy:

| |  |  |  |  |
|---|---|---|---|---|
| *experimental :* | *26.7 kcal/mol* | *27.5 kcal/mol* | *26.3 kcal/mol* | *-* |
| *(calculated) :* | *(26.2 kcal/mol)* | *(27.3 kcal/mol)* | *(24.6 kcal/mol)* | *(18.9 kcal/mol)* |

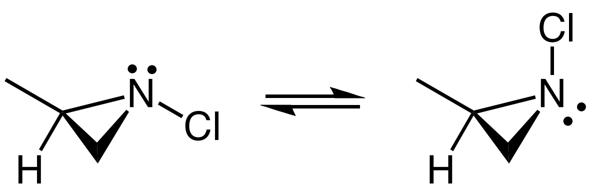
J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247.
R. D. Bach, O. Dmitrenko, *J. Org. Chem.* **2002**, *67*, 3884.

# *Inversion Barrier*



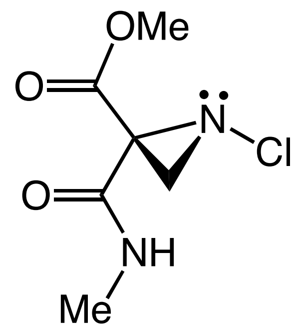

*$\Delta G^{\ddagger}$ = 16.7 kcal/mol*

*(inversion at 25°C)*

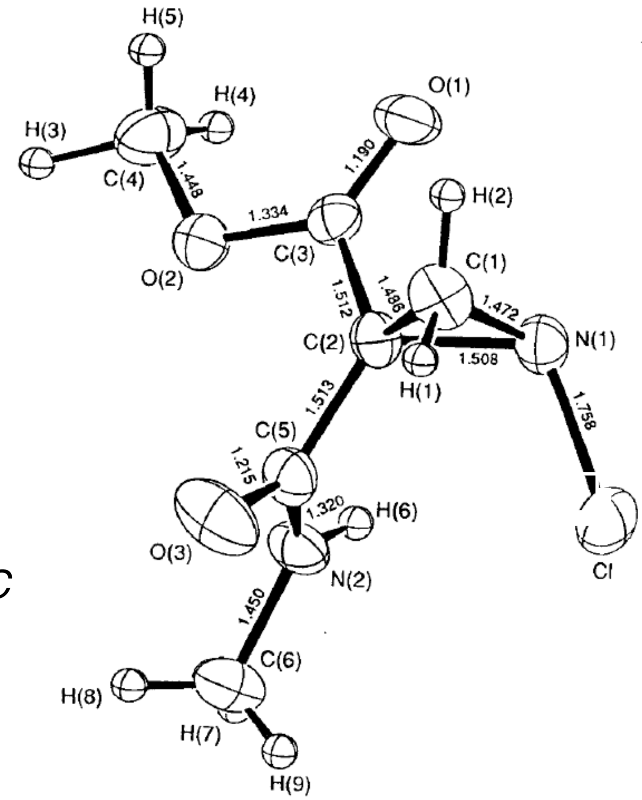



*$\Delta G^{\ddagger}$ = 26.8 kcal/mol*

*(diastereomers isolable at 25°C)*

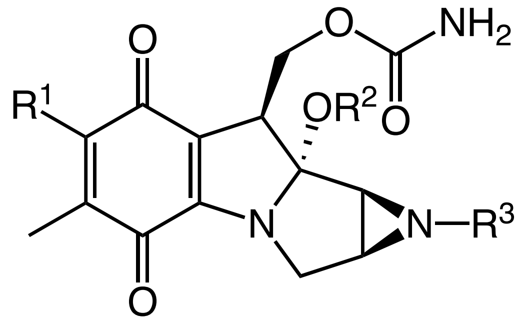


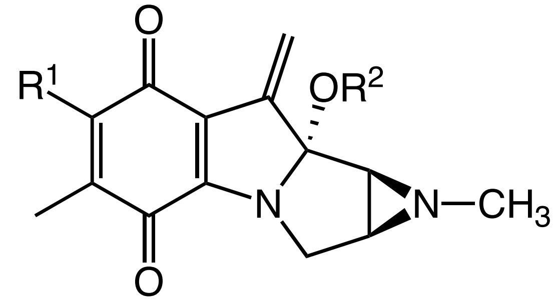

*no inversion at 50°C*




J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247.

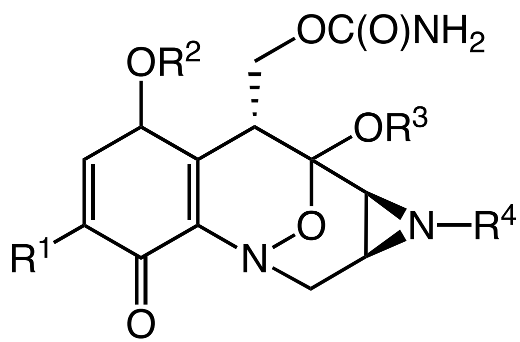
*DNA Interaction of Aziridines*




| | |
|---|---|
| *Mitomycin A* | *$R^1$ = OMe, $R^2$ = Me, $R^3$ = H* |
| *Mitomycin B* | *$R^1$ = OMe, $R^2$ = H, $R^3$= Me* |
| *Mitomycin C* | *$R^1$ = $NH_2$, $R^2$ = Me, $R^3$ = H* |
| *Porfiromycin* | *$R^1$ = $NH_2$, $R^2$ = Me, $R^3$ = Me* |

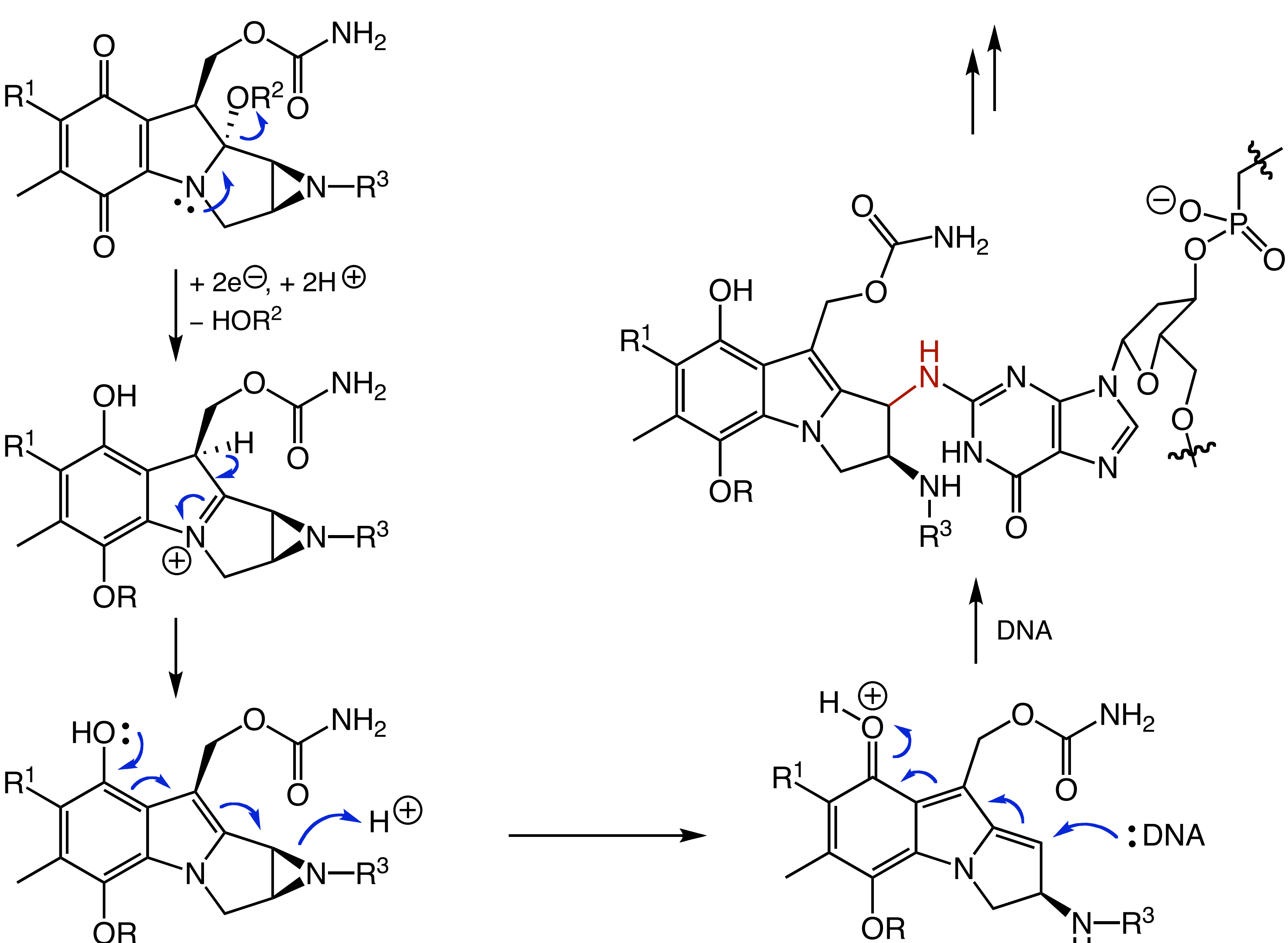
| | |
|---|---|
| *Mitomycin G* | *$R^1$ = $NH_2$, $R^2$ = Me* |
| *Mitomycin H* | *$R^1$ = OMe, $R^2$ = H* |
| *Mitomycin K* | *$R^1$ = OMe, $R^2$ = Me* |




| | |
|---|---|
| *FR-900482* | *$R^1$ = CHO, $R^2$ = $R^3$ = $R^4$ = H* |
| *FR-66979* | *$R^1$ = $CH_2OH$, $R^2$ = $R^3$ = $R^4$ = H* |
| *FR-70496* | *$R^1$ = CHO, $R^2$ = Me, $R^3$ = H, $R^4$ = Ac* |
| *FK-973* | *$R^1$ = CHO, $R^2$ = $R^3$ = $R^4$ = Ac* |
| *FK-317* | *$R^1$ = CHO, $R^2$ = Me, $R^3$ = Ac* |

J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247.

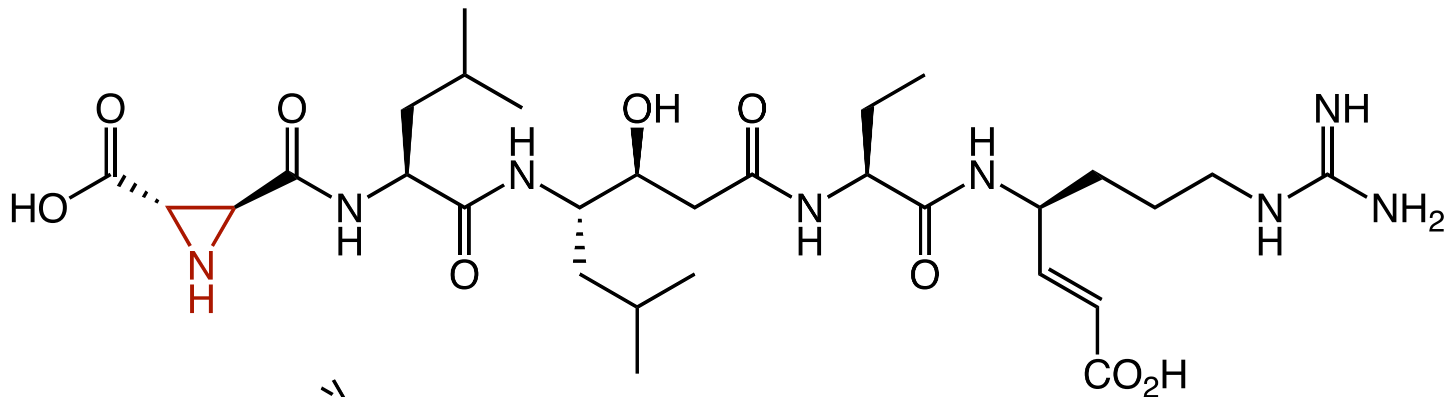
# *DNA Interaction of Aziridines*



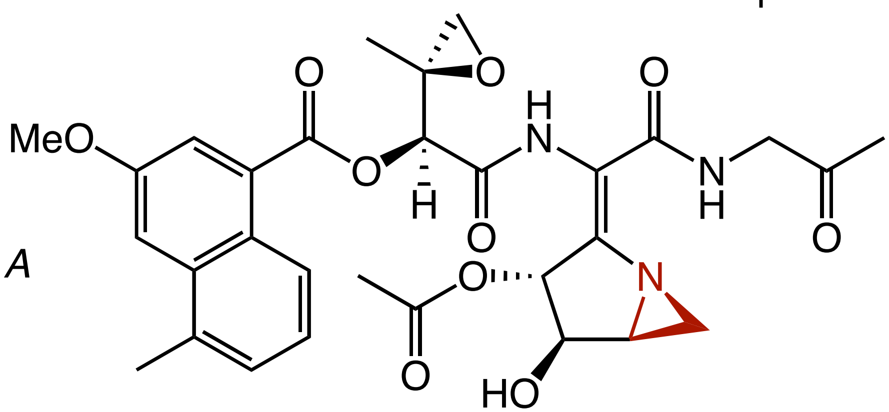

J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247.

# *Other Natural Products Containing Aziridines*

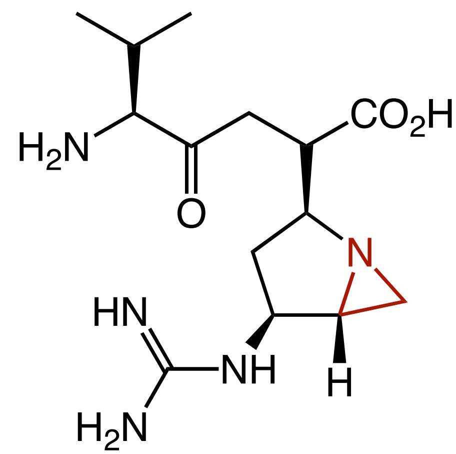
*Miraziridine*

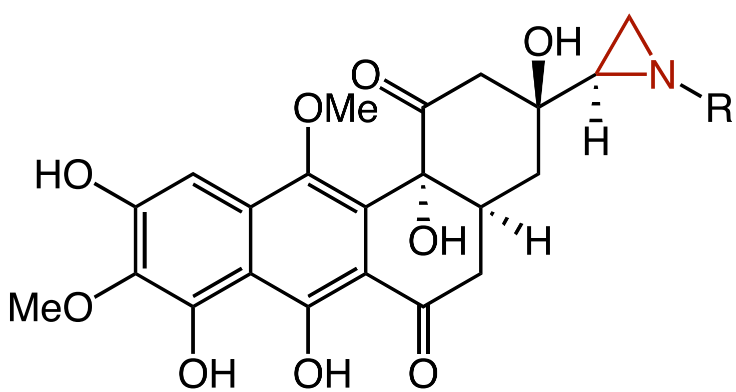


*Azinomycin A*

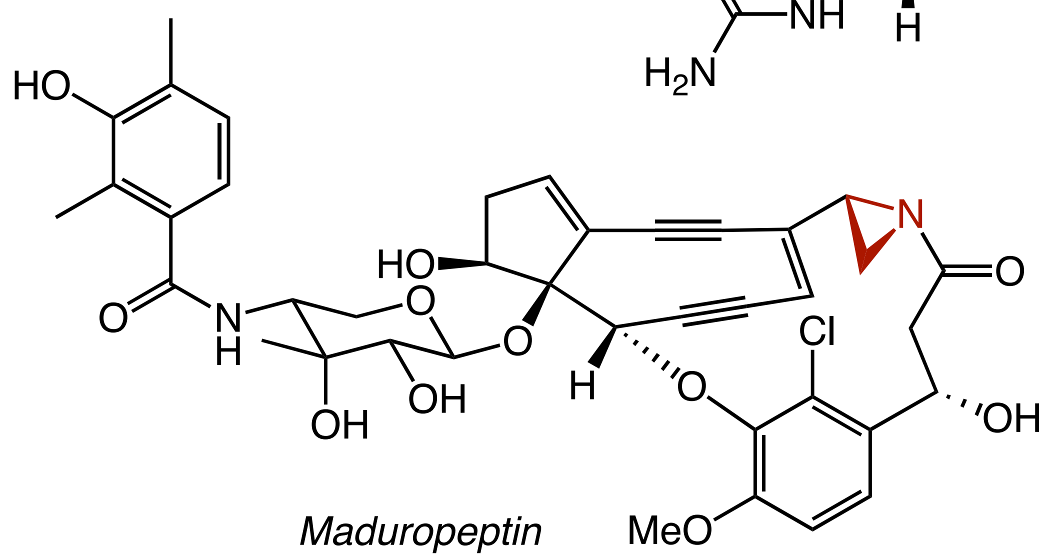


*Ficellomycin*





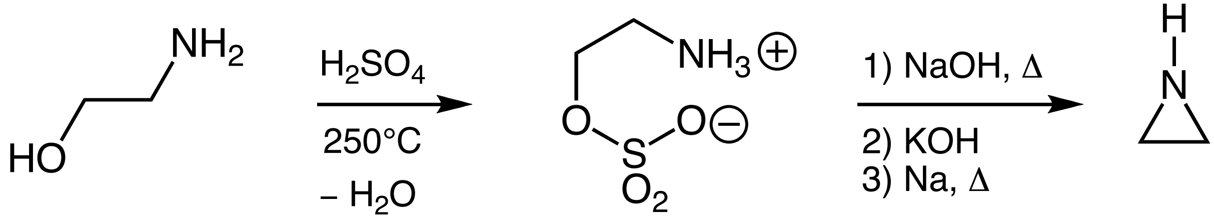
*Azicemicin A: R = H*
*Azicemicin B: R = Me*



*Maduropeptin*

# *Classic Aziridine Syntheses*

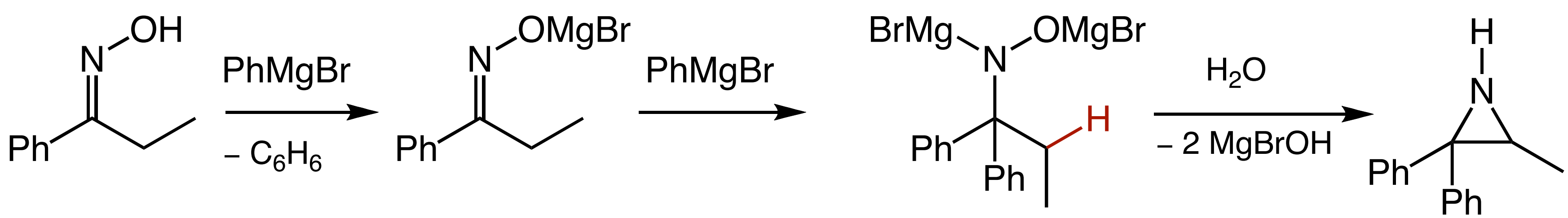
Wenker's Synthesis (1935):




610 g | 71% | 27%

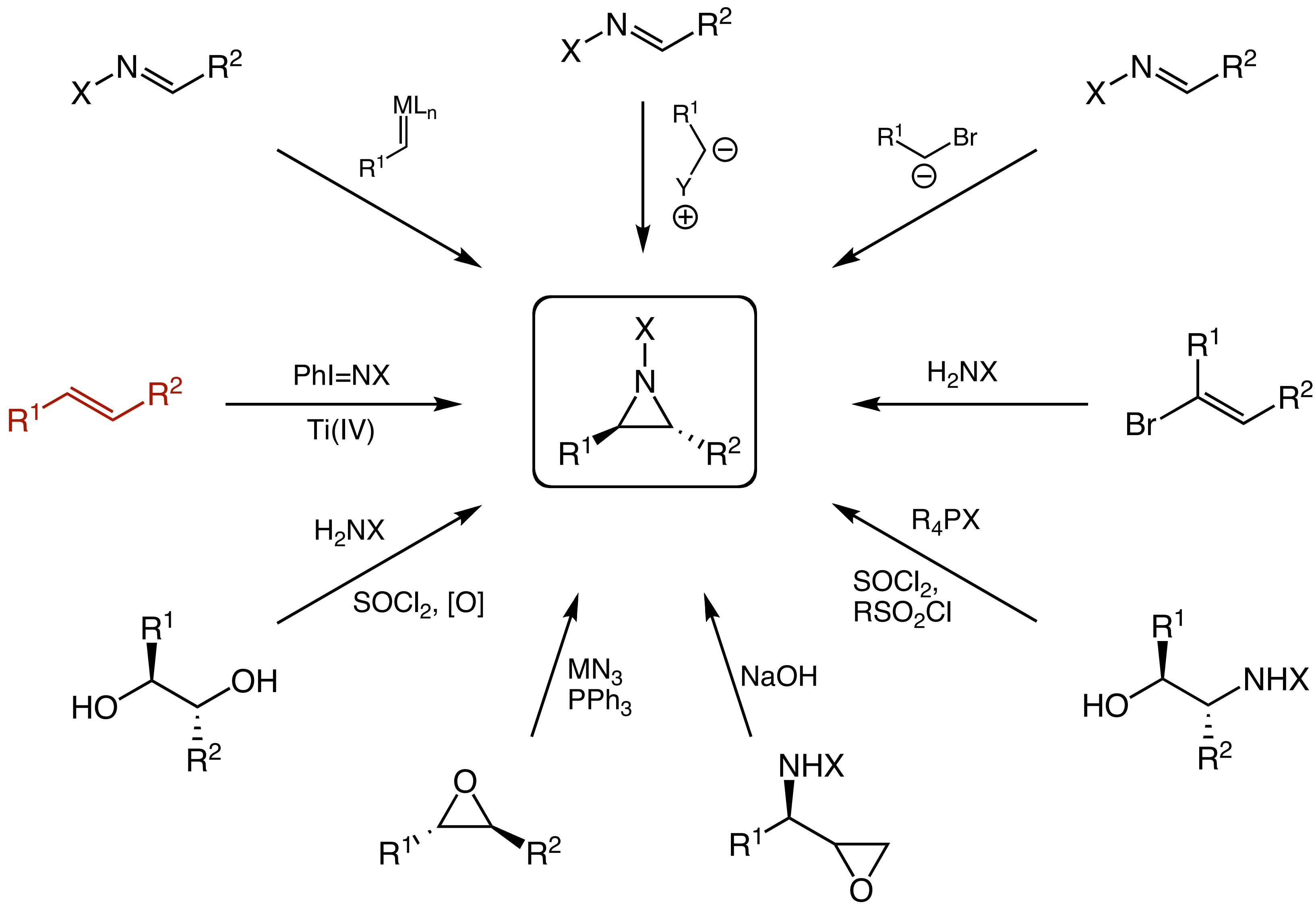
H. Wenker, *J. Am. Chem. Soc.* **1935**, *57*, 2328.

Hoch-Campbell Synthesis (1934):




J. Hoch, *Compt. Rend.* **1934**, *198*, 1865
K. N. Campbell, B. K. Campbell, J. F. McKenna, E. P. Chaput, *J.Org. Chem.* **1943**, *8*, 103.

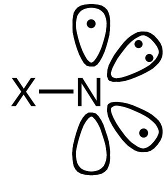
*Aziridine Synthesis - Overview*

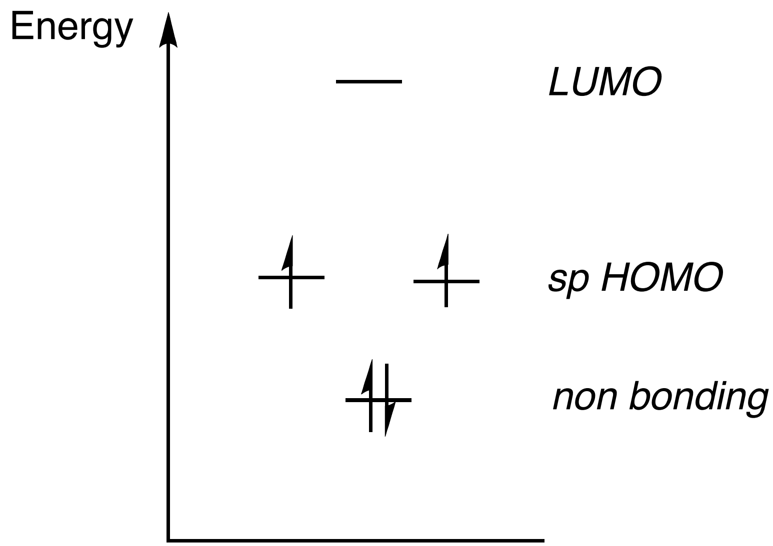


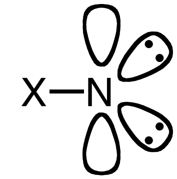


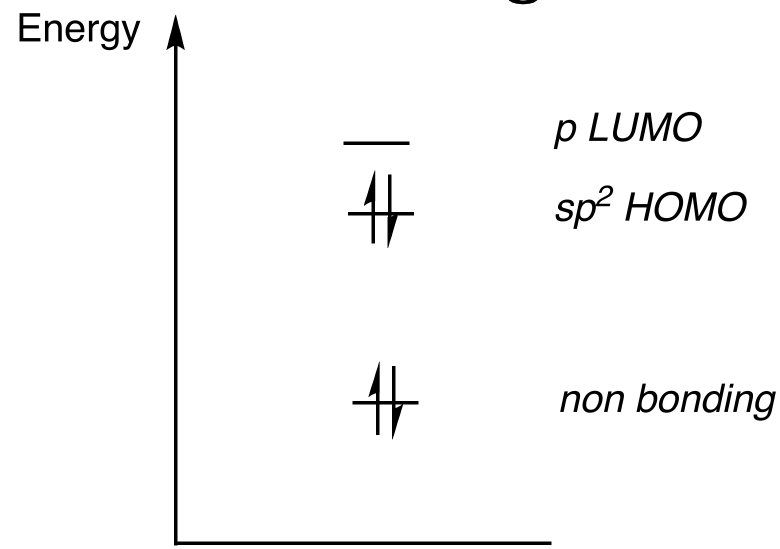
I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.
T. Ibuka, *Chem. Soc. Rev.* **1998**, *27*, 145.

# *A Brief Introduction to Nitrenes*

Triplet nitrene: 


Singlet nitrene: 


*slightly higher energy*
*stabilized by electrondonating substituents*

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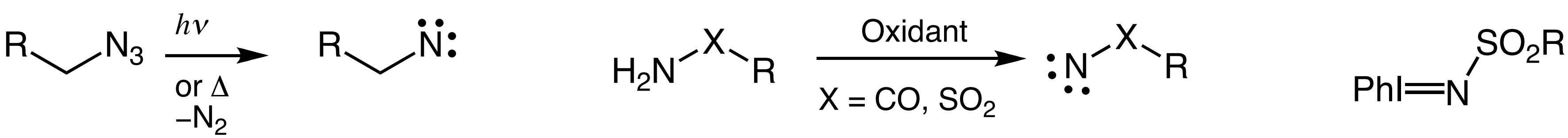
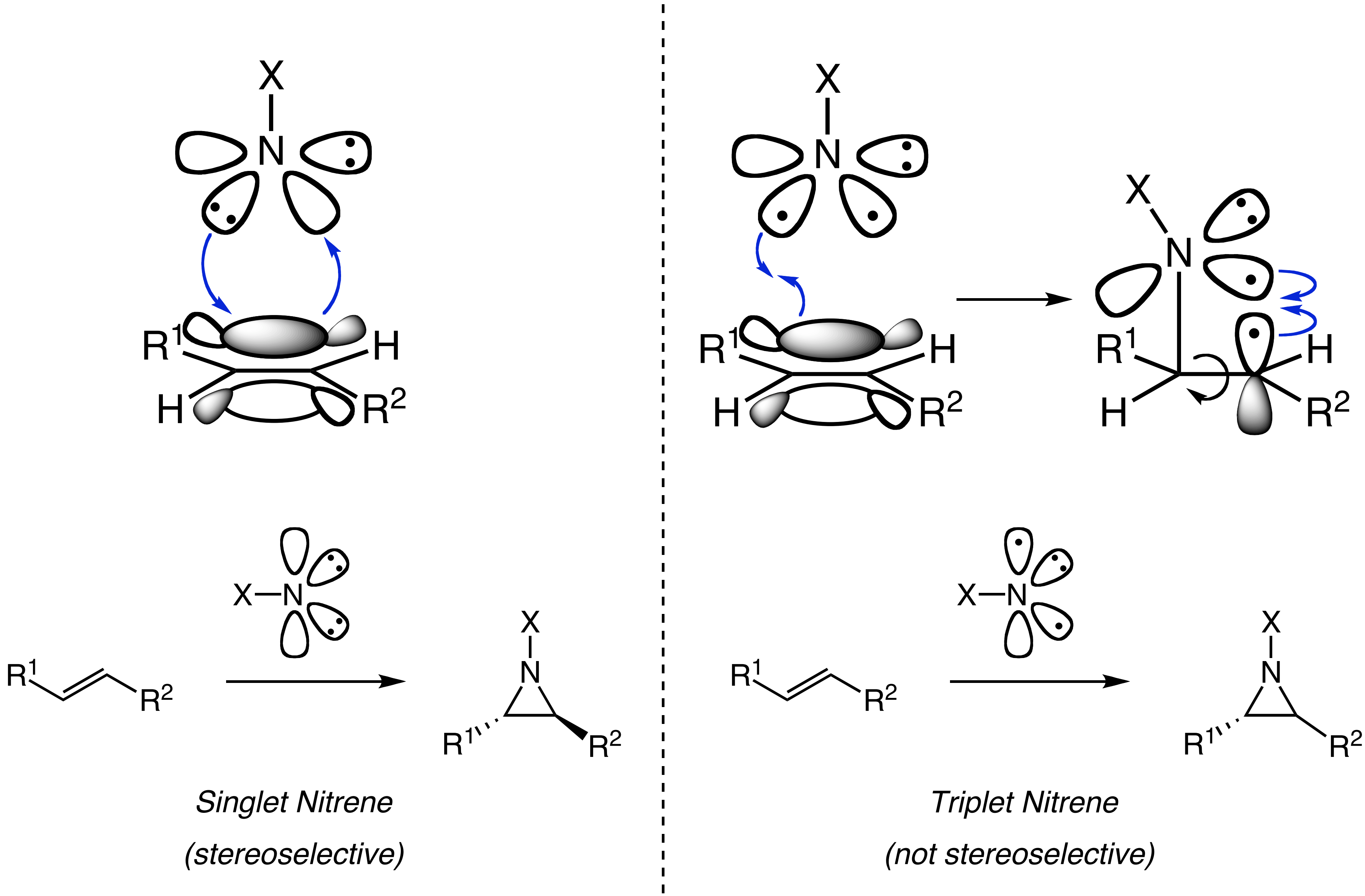
Common nitrene precursors:



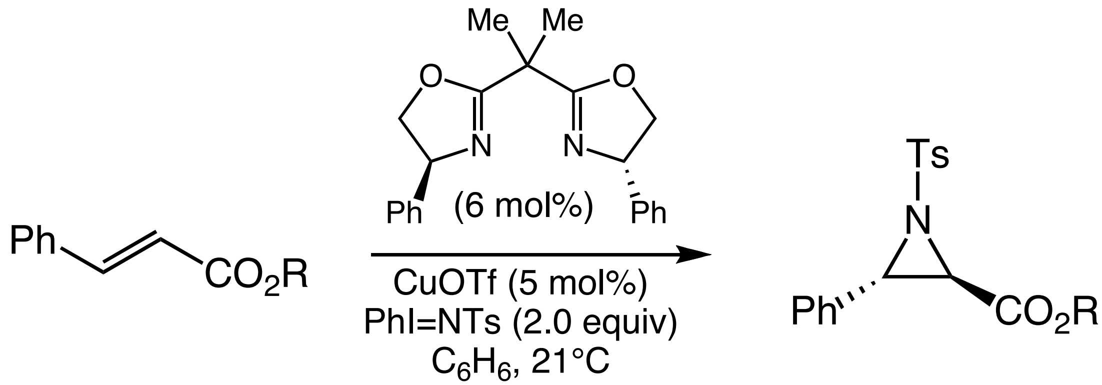

W. Schoeller, A. B. Rozhenko, *Eur. J. Org. Chem.* **2001**, 845.
W. Lwowski in *Nitrenes* (Ed.: W. Lwowski), Interscience, New York, **1970**, pp. 1-11.

# *Selected Examples for the Synthesis of Aziridines from Alkenes*



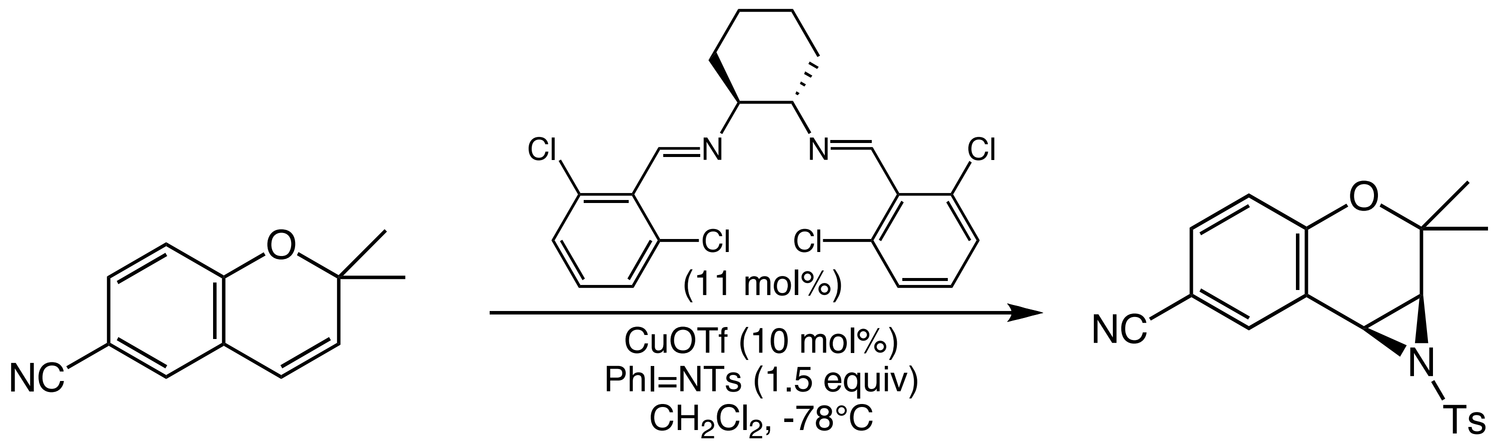

J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247.

# *Copper Catalyzed Aziridinations*




*R = Me   63% i.y., 94% ee*
*R = Ph   64% i.y., 97%ee*

D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328.
D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Am. Chem. Soc.* **1994**, *116*, 2742.




*75% i.y., >98% ee*

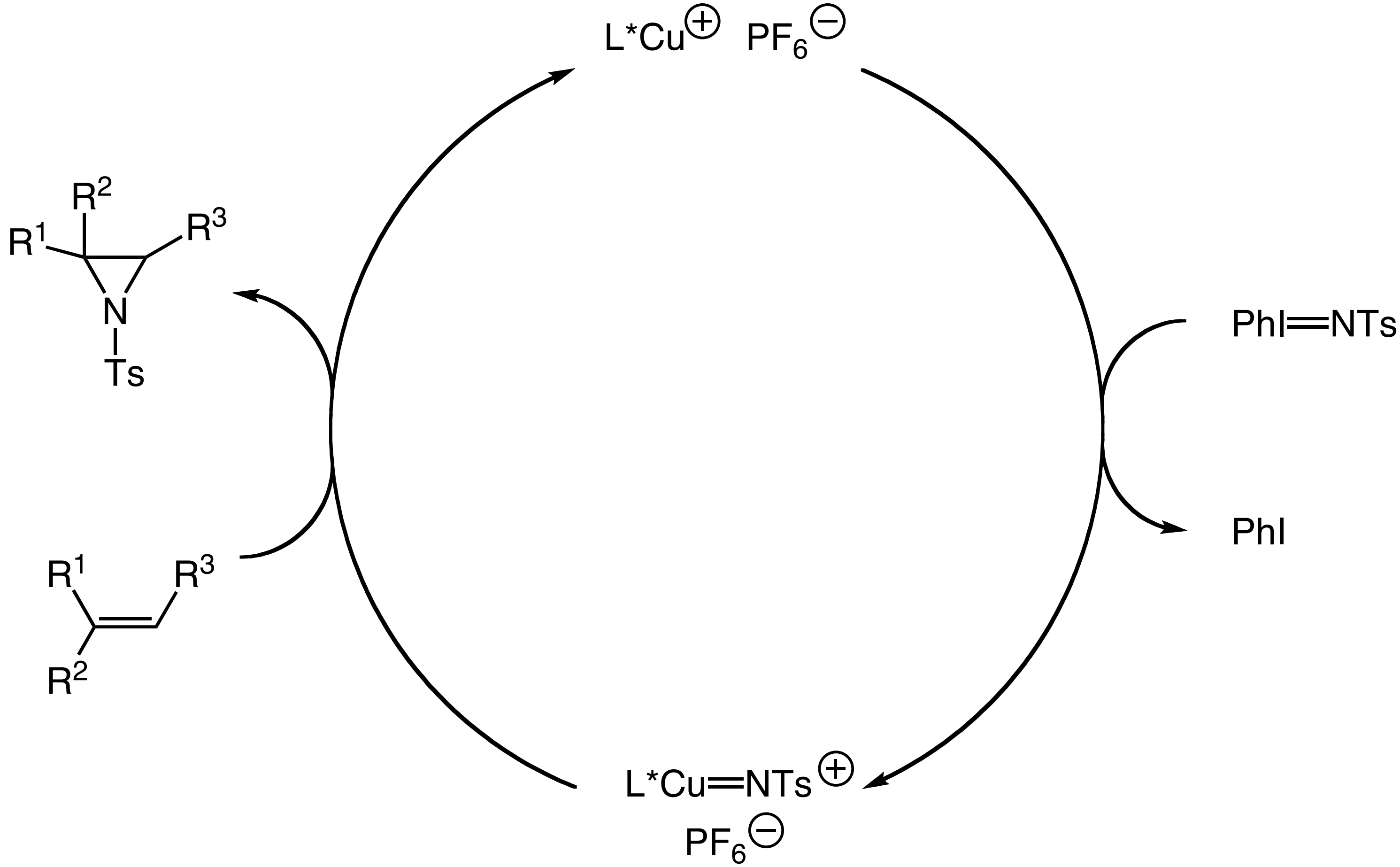
Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.* **1993**, *115*, 5326.
Z. Li, R. W. Quan, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5889.

Via copper nitrene species:

L*Cu═NTs  OTf

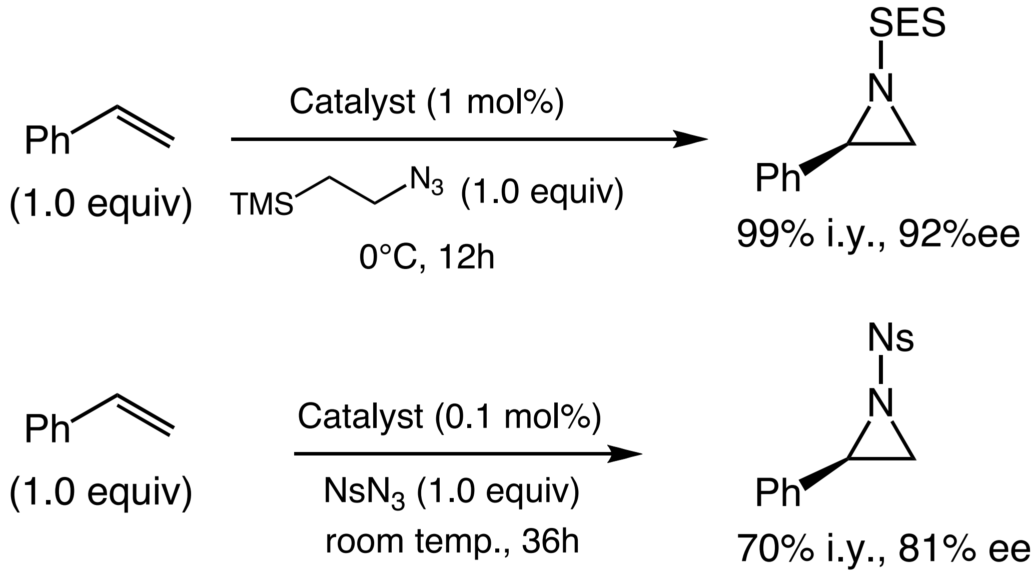
*Drawbacks:  Limited substrate scope*
*Often an excess of the alkene required*

# *Copper Catalyzed Aziridination - Catalytic Cycle*

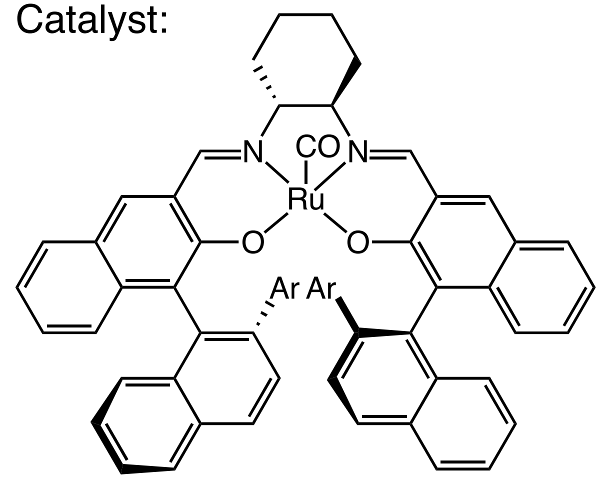



Z. Li, R. W. Quan, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5889.

# *Aziridinations with Ruthenium and Rhodium*

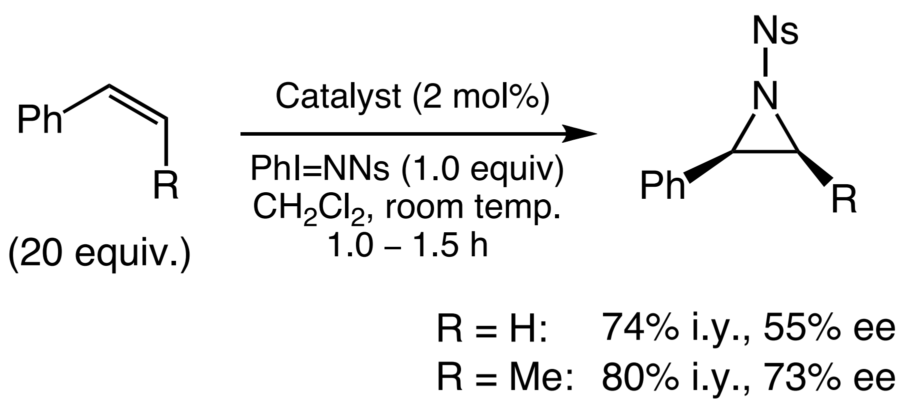



Catalyst:

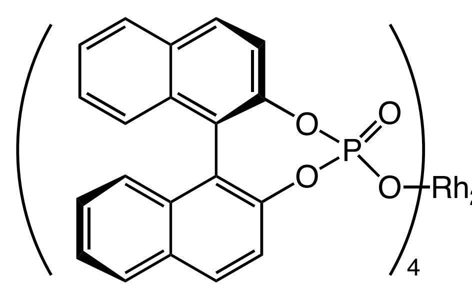



*Ar = 3,5-$Cl_2$-4-$(CH_3)_3SiC_6H_2$*

H. Kawabata, K. Omura, T. Katsuki, *Tetrahedron Lett.* **2006**, *47*, 1571.

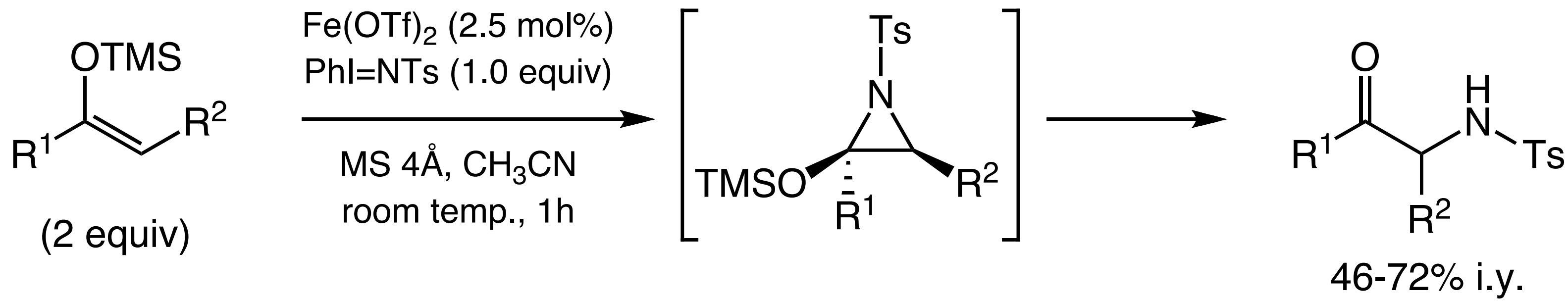



Catalyst:

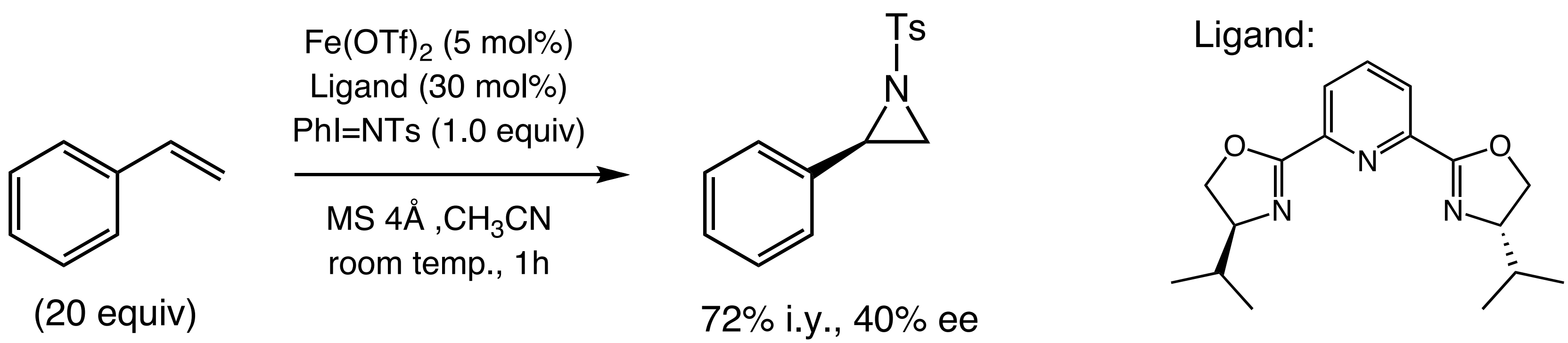



P. Müller, C. Baud, Y. Jacquier, *Can. J. Chem.* **1998**, *76*, 738.
M. C. Pirrung, J. Zhang, *Tetrahedron Lett.* **1992**, *33*, 5987.
P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905.

# *Iron Catalyzed Aziridination*

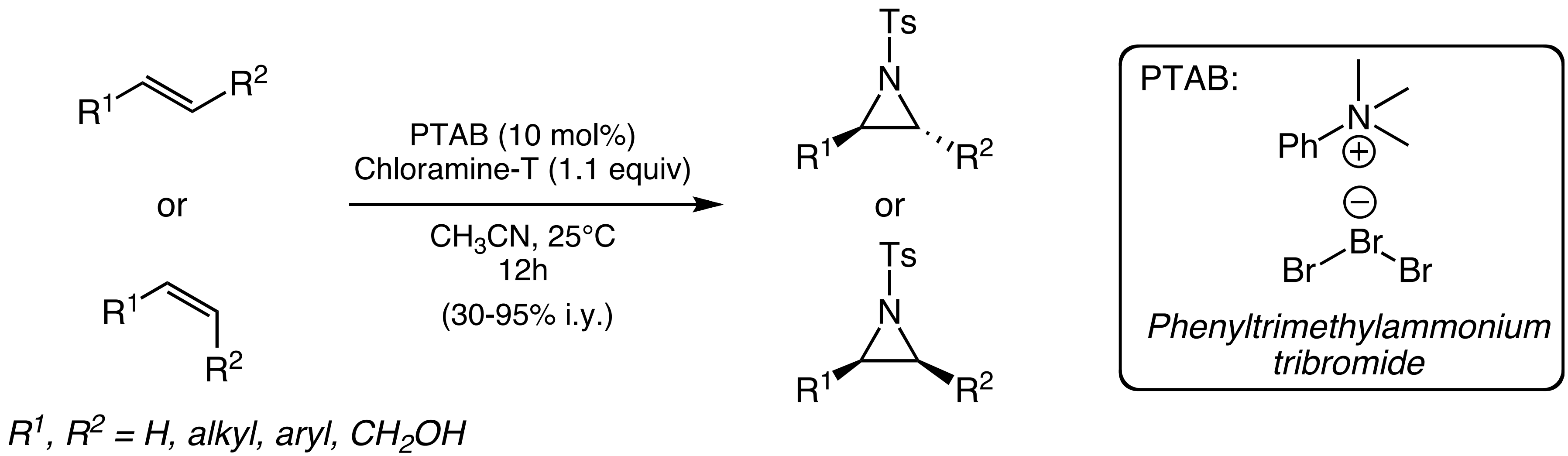


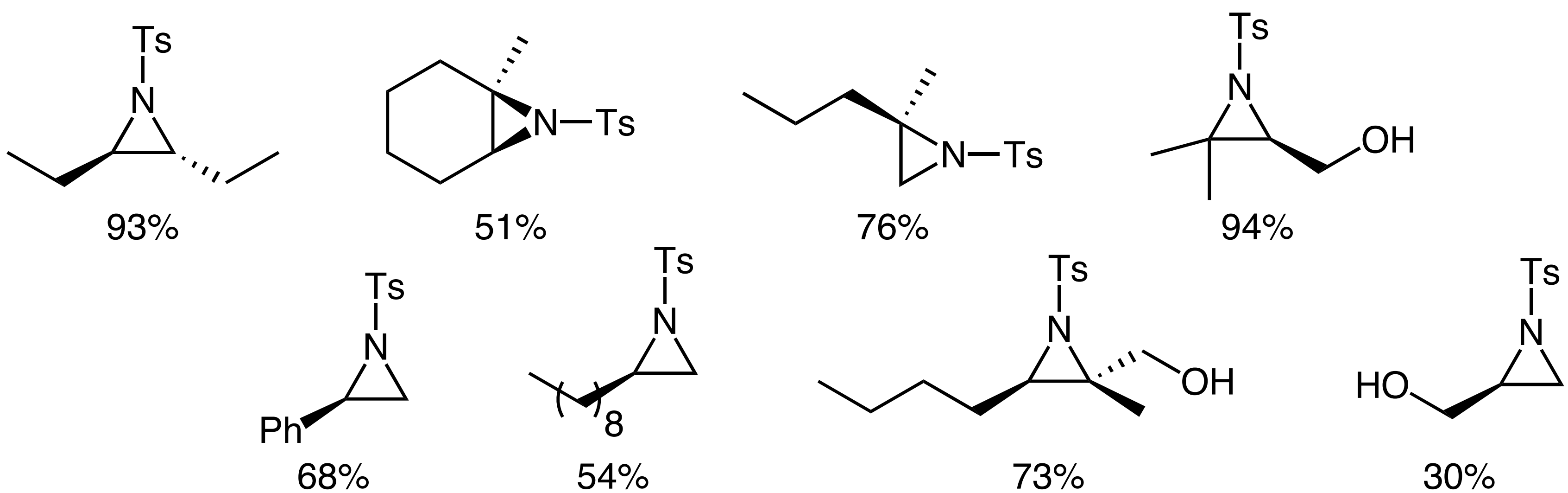

*$R^1$ = aryl, alkyl*
*$R^2$ = H, alkyl*




M. Nakanishi, A.-F. Salit, C. Bolm, *Adv. Synth. Catal.* **2008**, *350*, 1835.

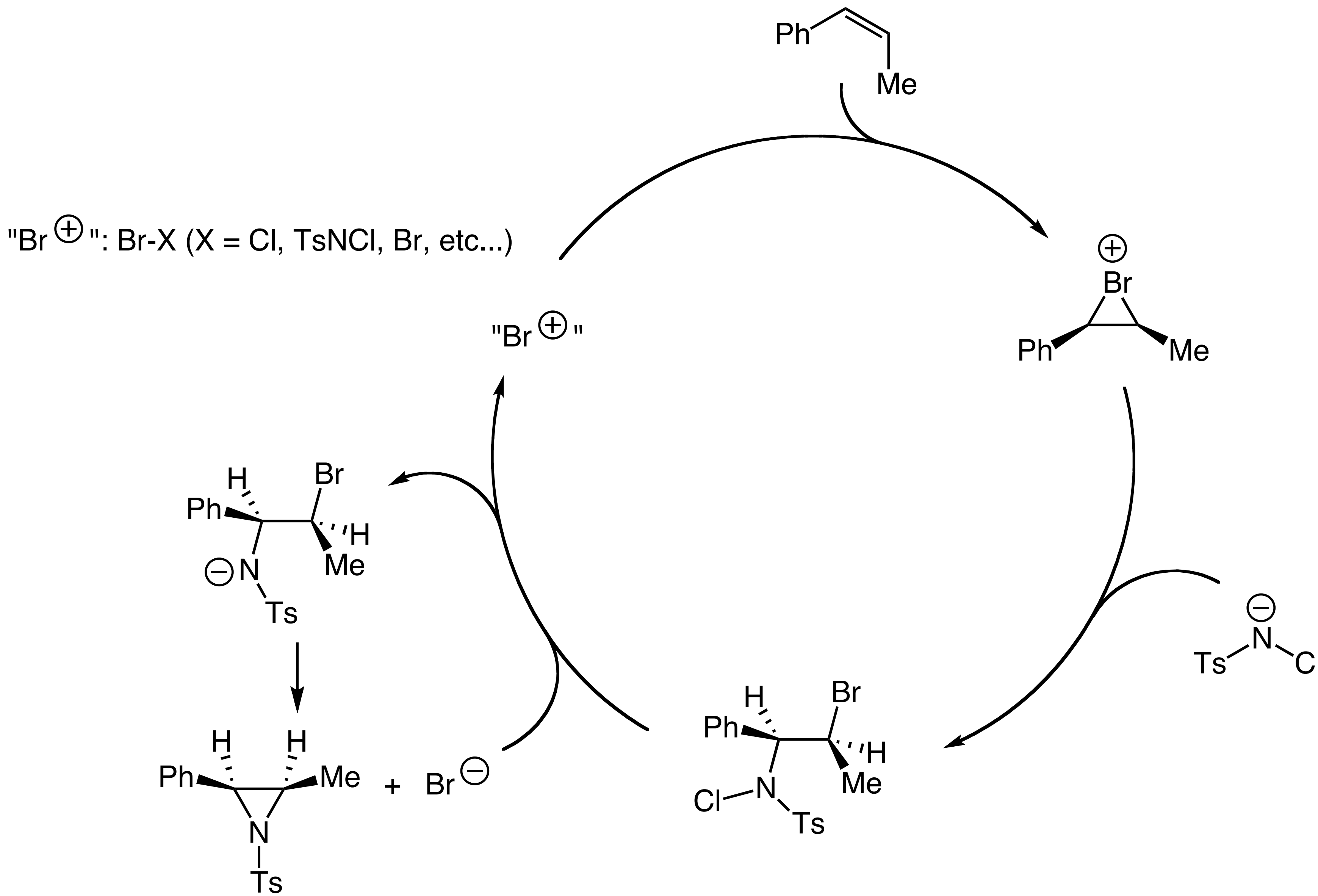
# *Main Group Element Catalyzed Aziridination*




J. U. Jeong, B. Tao, I. Sagasser, H. Henniges, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, *120*, 6844.
J. U. Jeong, K. B. Sharpless, U.S. Patent number 5,929,252, **1999**.

## *Main Group Element Catalyzed Aziridination*




J. U. Jeong, B. Tao, I. Sagasser, H. Henniges, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, *120*, 6844.

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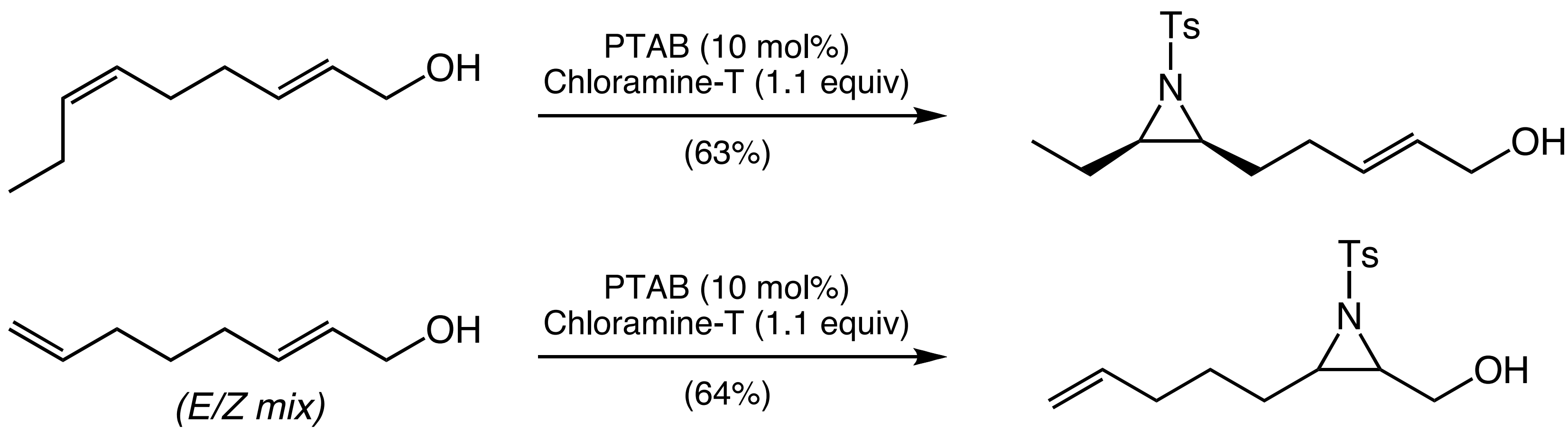
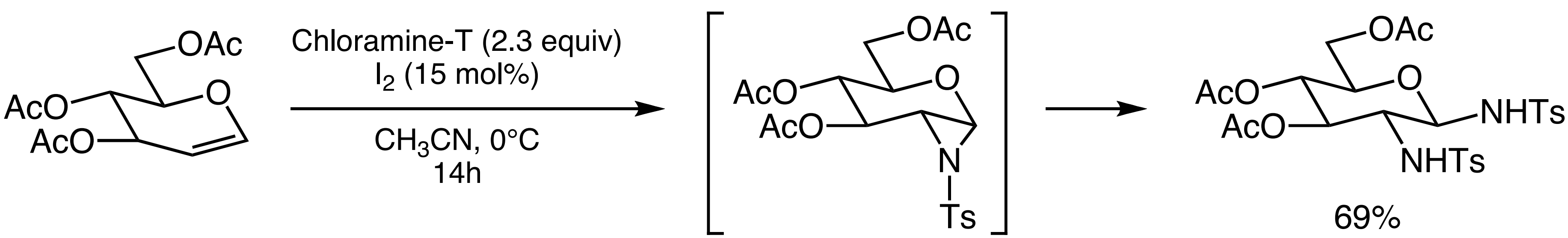


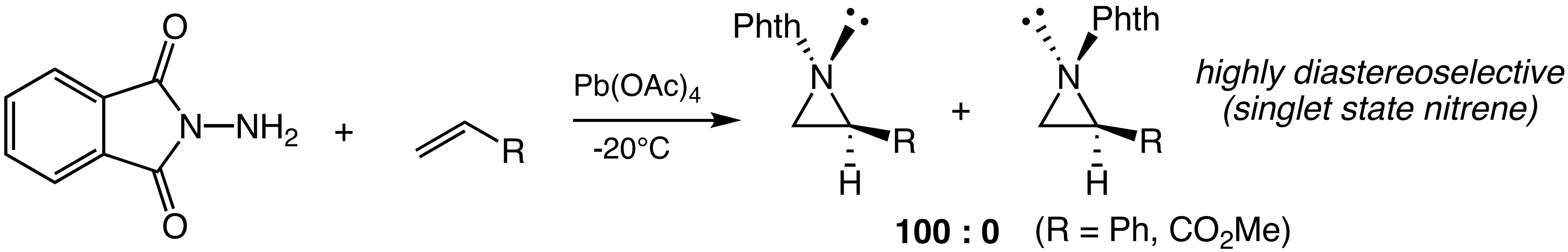

J. U. Jeong, B. Tao, I. Sagasser, H. Henniges, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, *120*, 6844.
J. U. Jeong, K. B. Sharpless, U.S. Patent number 5,929,252, **1999**.




V. Kumar, N. G. Ramesh, *Chem. Commun.* **2006**, 4952.

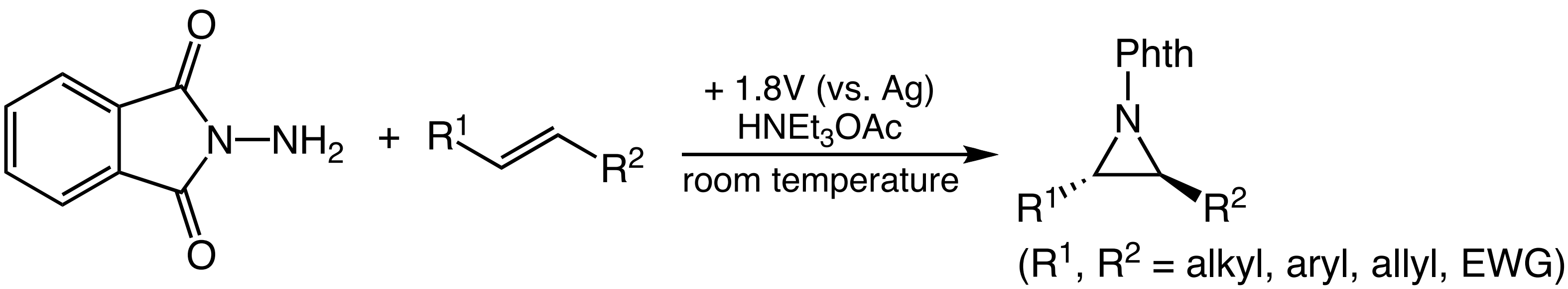
# *Aziridination with Hydrazines*

With $Pb(OAc)_4$ as oxidant:



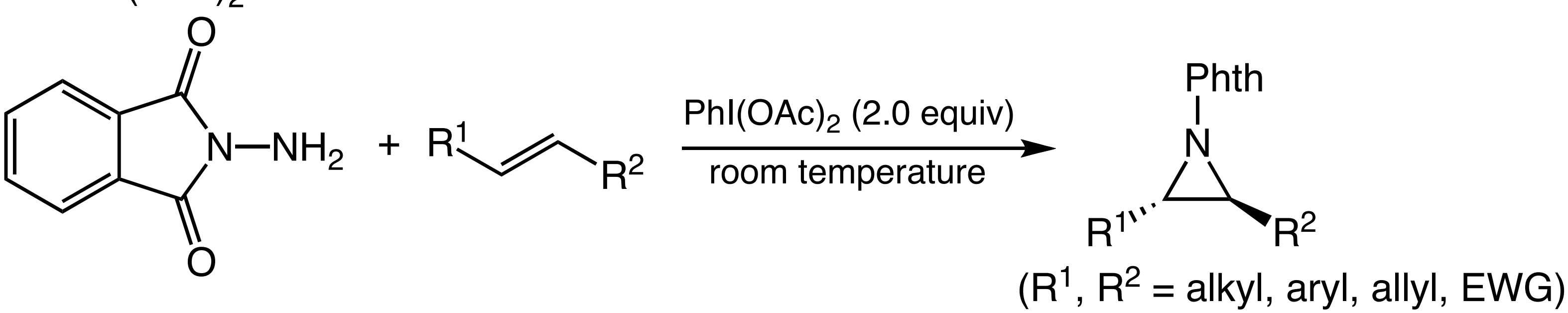

R. S. Atkinson, M. J. Grimshire, B. J. Kelly, *Tetrahedron* **1989**, *45*, 2875.
R. S. Atkinson, D. W. Jones, B. J. Kelly, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1344.

Electrochemically (platinum electrodes):



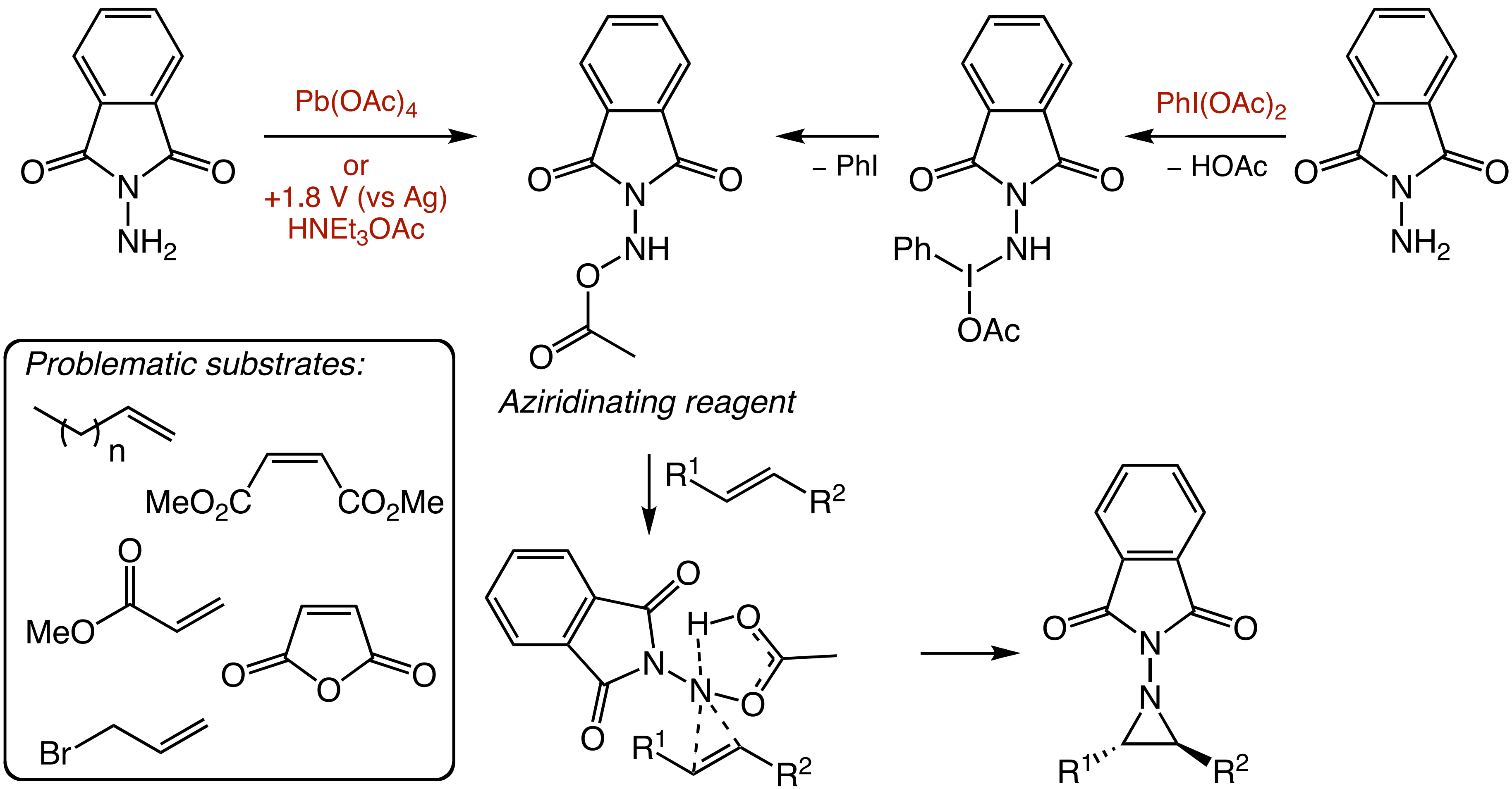

T. Siu, A. K. Yudin, *J. Am. Chem. Soc.* **2002**, *124*, 530.

With $PhI(OAc)_2$ as oxidant:

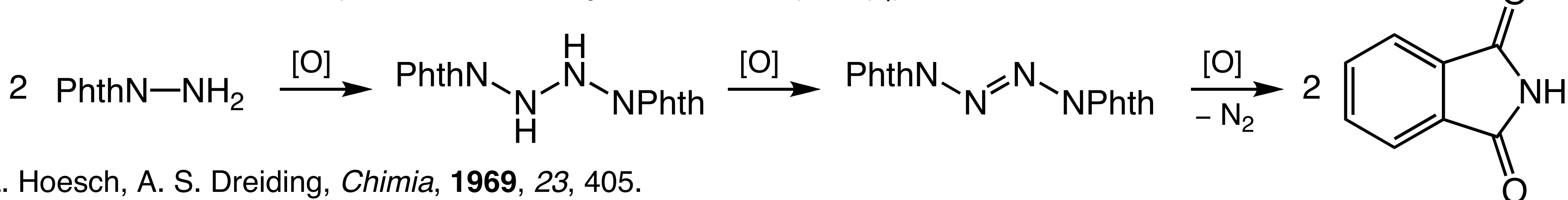



L. B. Krasnova, R. M. Hili, O. V. Chernoloz, A. K. Yudin, *ARKIVOC* **2005**, *4*, 26.

# *Aziridination with Hydrazines*



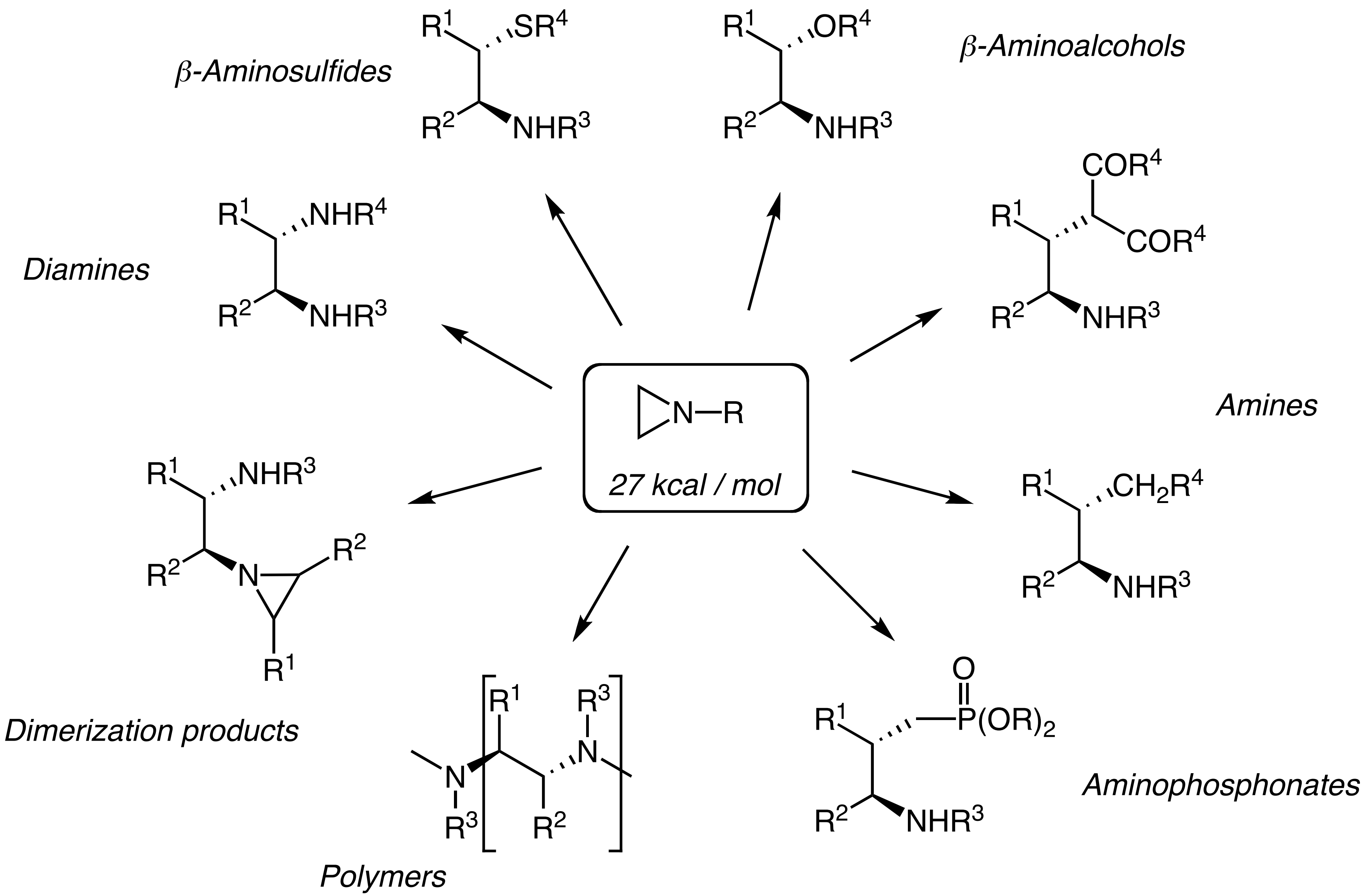

Observed sidereaction (electrochemically and with $Pb(OAc)_4$):





L. Hoesch, A. S. Dreiding, *Chimia*, **1969**, *23*, 405.
I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.

# *Aziridine Transformations - Ring Opening*

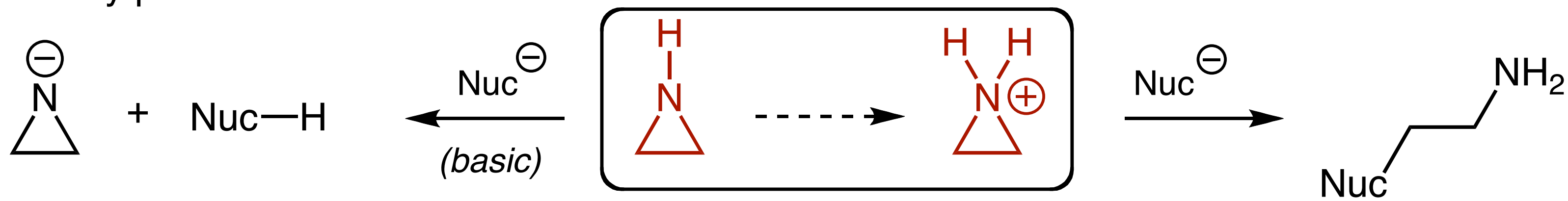




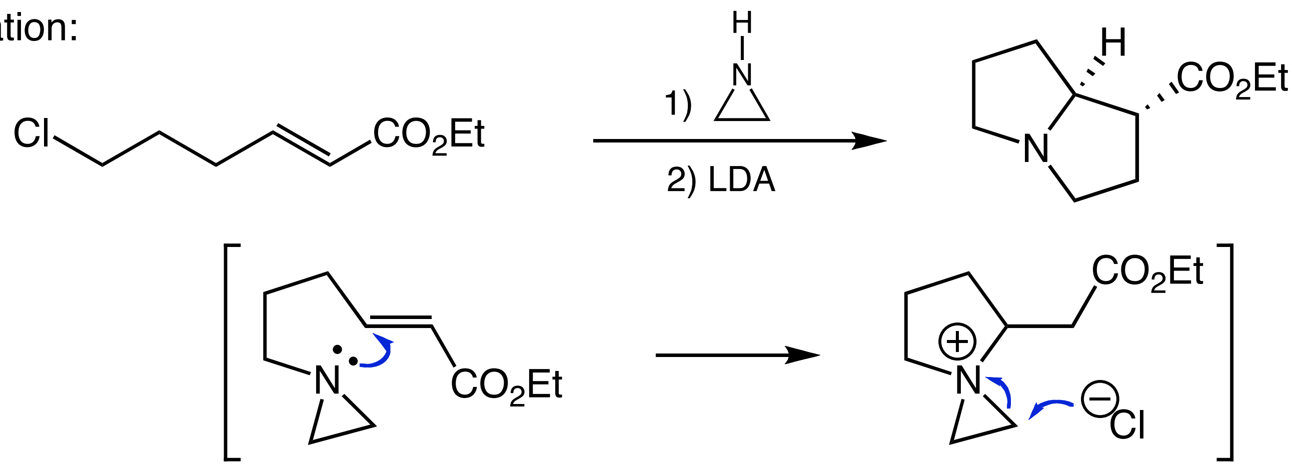
I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.
T. Ibuka, *Chem. Soc. Rev.* **1998**, *27*, 145.

## *Concepts for the Activation of Aziridines*

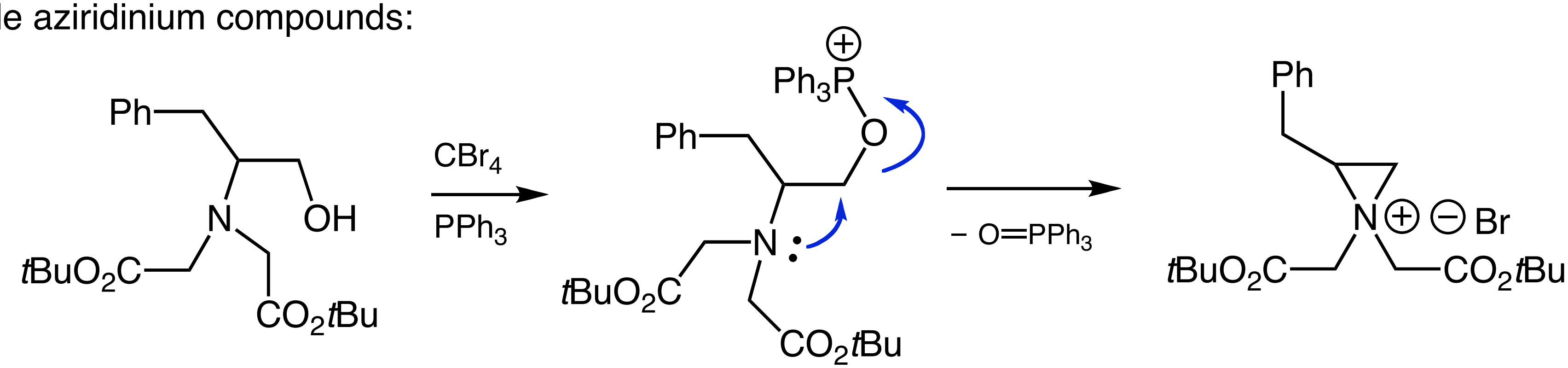
Activation by protonation:




Activation by alkylation:



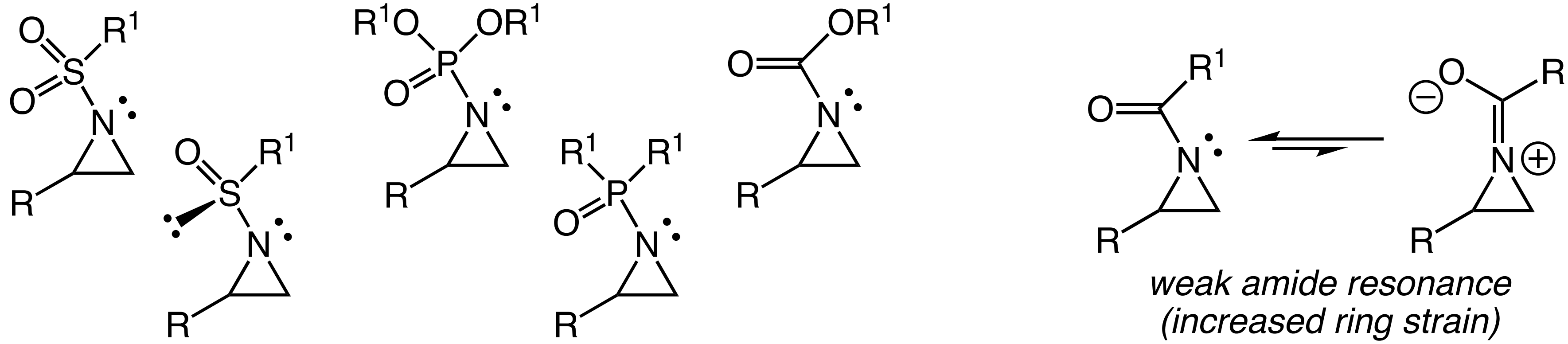

Isolable aziridinium compounds:




H. A. Song, M. Dadwal, Y. Lee, E. Mick, H.-S. Chong, *Angew. Chem. Int. Ed.* **2009**, *early view.*

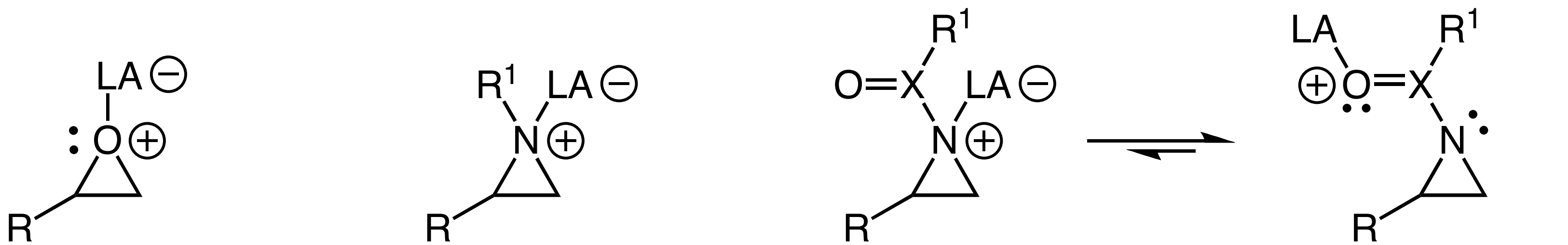
## *Concepts for the Activation of Aziridines*

Activation with substituents:



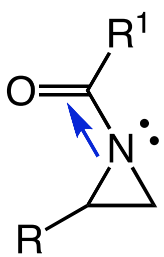

*weak amide resonance*
*(increased ring strain)*

Activation with Lewis acids:

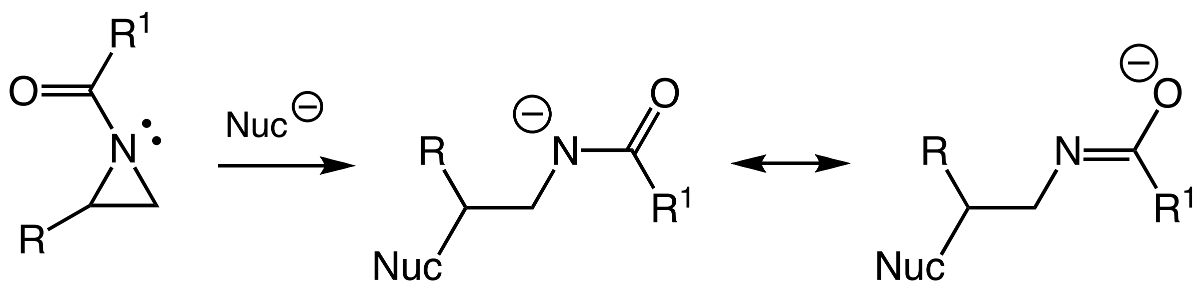



*(R1 = H, alkyl)* *(indirect interaction)*

Kinetic activation: Thermodynamic activation:

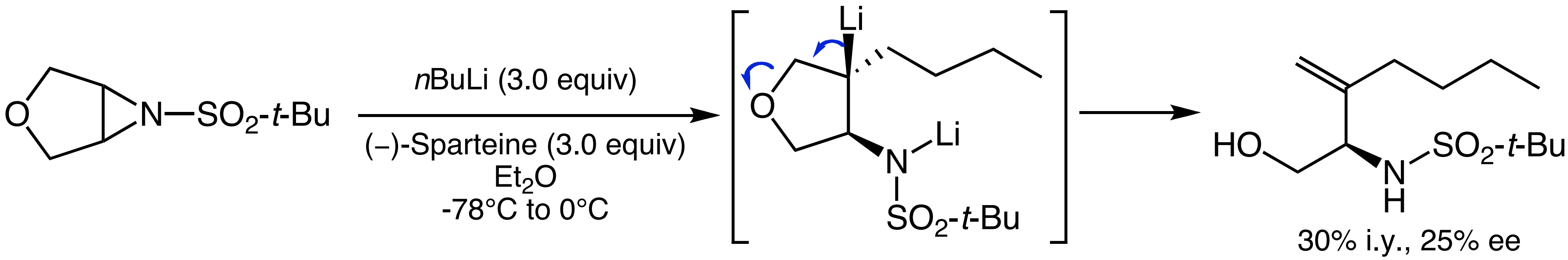



*(polarization)*

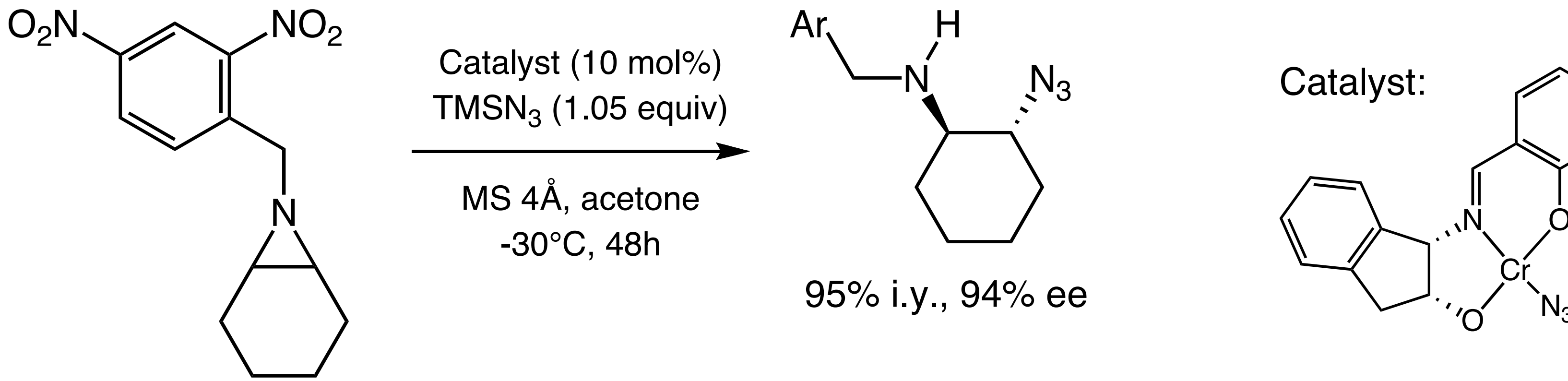



*(stabilization)*

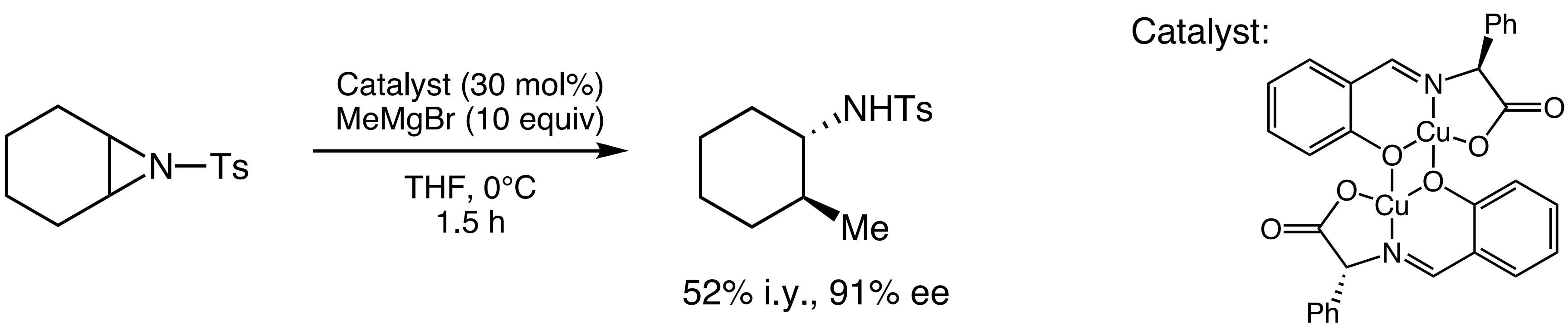
# *Enantioselective Opening of Aziridines*




D. M. Hodgson, B. Stefane, T. J. Miles, J. Witherington, *Chem. Commun.* **2004**, 2234.

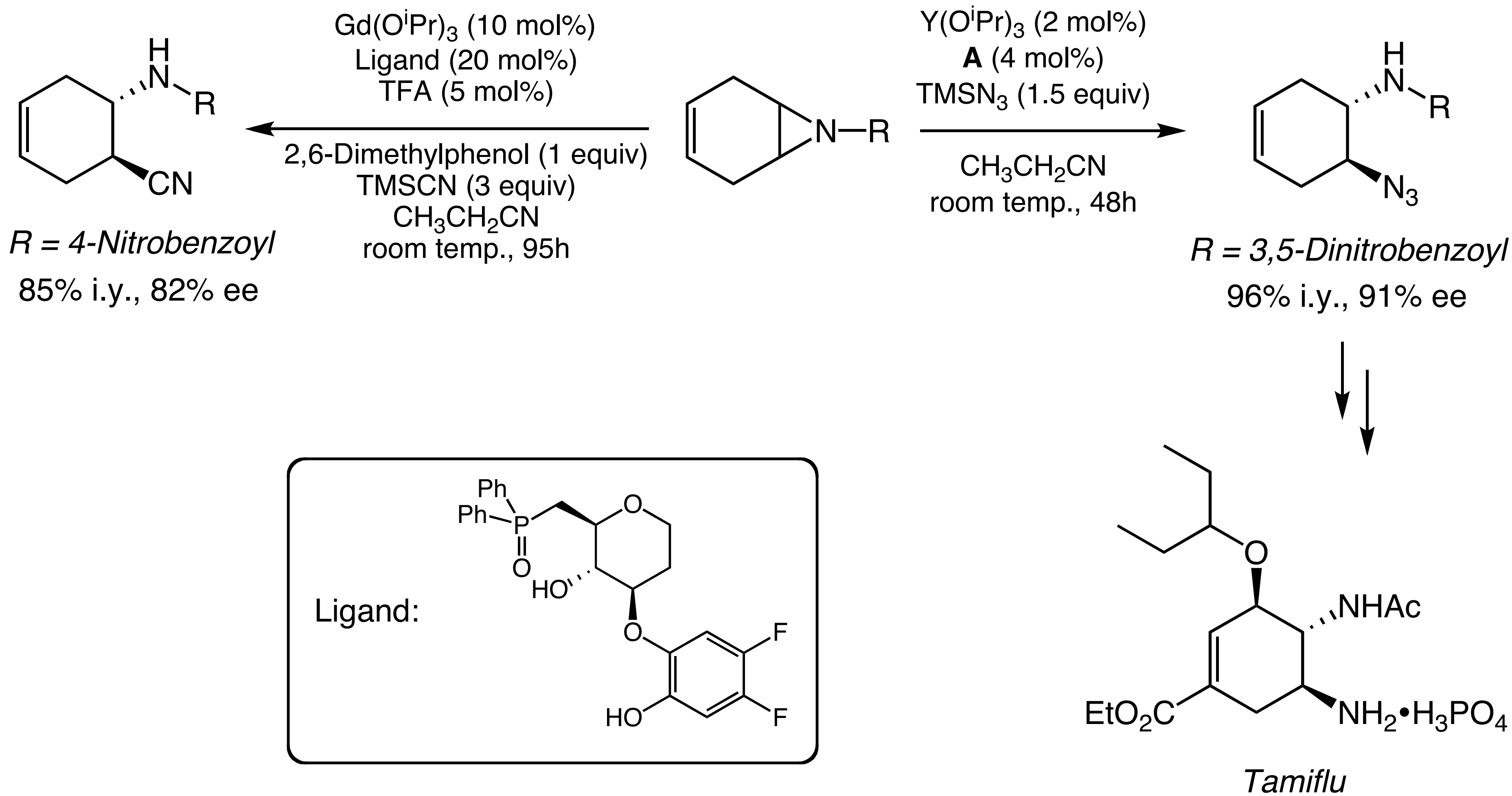



Z. Li, M. Fernández, E. N. Jacobsen, *Org. Lett.* **1999**, *1*, 1611.



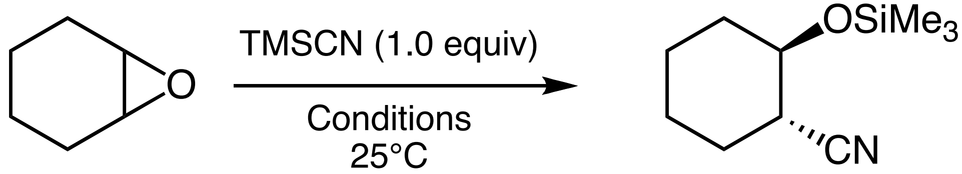

P. Müller, P. Nury, *Org. Lett.* **1999**, *1*, 439.

# *Catalytic Enantioselective Opening of Aziridines*



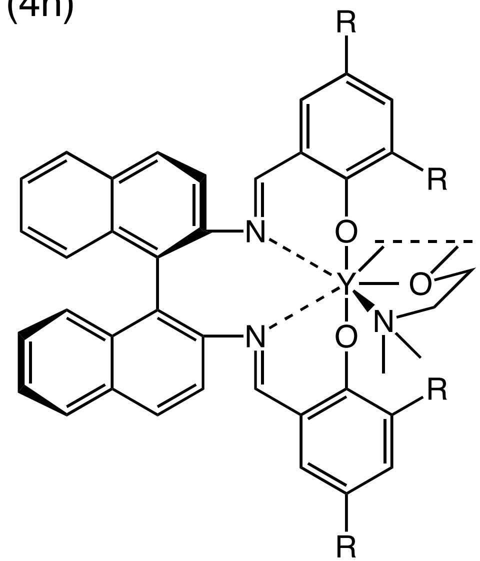

Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312.
T. Mita, I. Fujimori, R. Wada, J. Wen, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 11252.

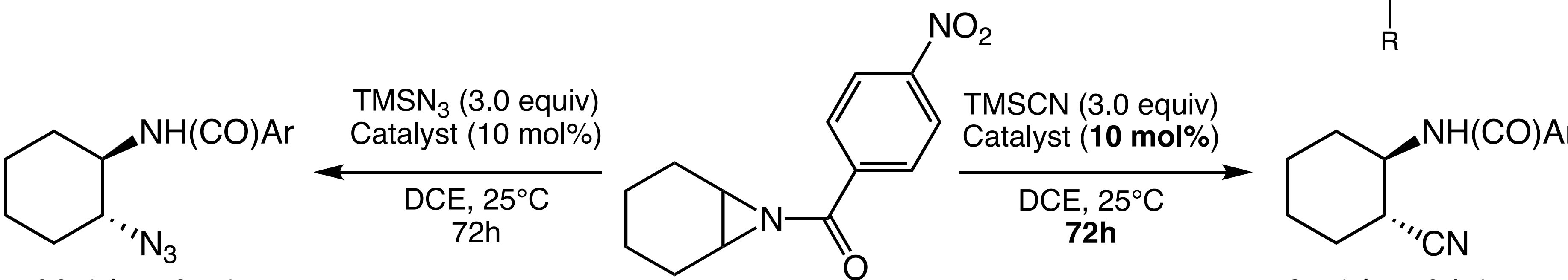
# *Enantioselective Opening of Aziridines*




2 mol% Catalyst, $CH_2Cl_2$ : 100% conv., 77% ee (2h)
0.01 mol% Catalyst, neat : 100% conv., 56%ee (4h)

Catalyst (dimer):



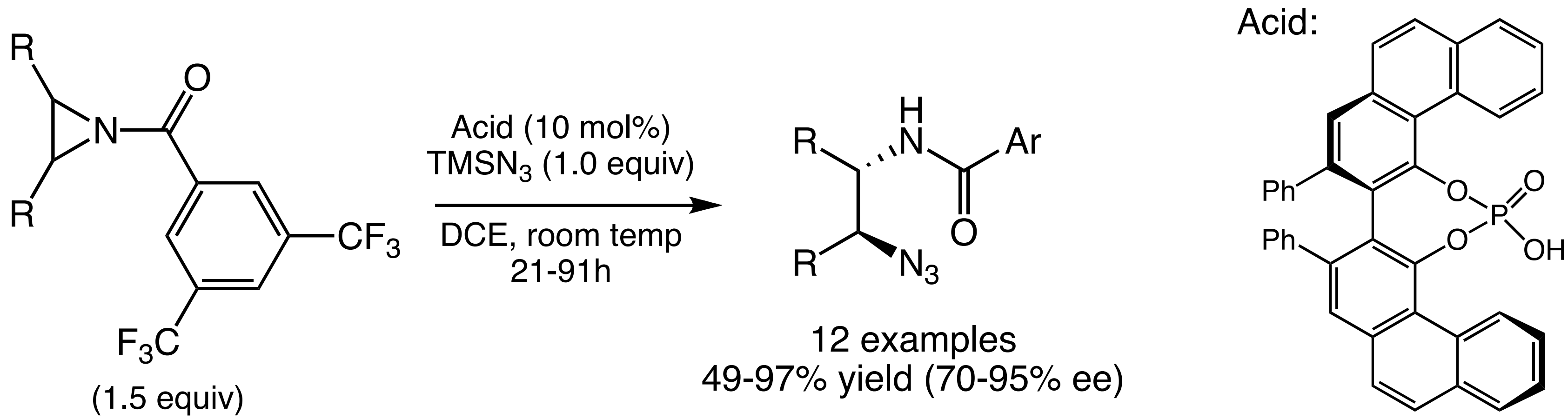




99% i.y., 97% ee

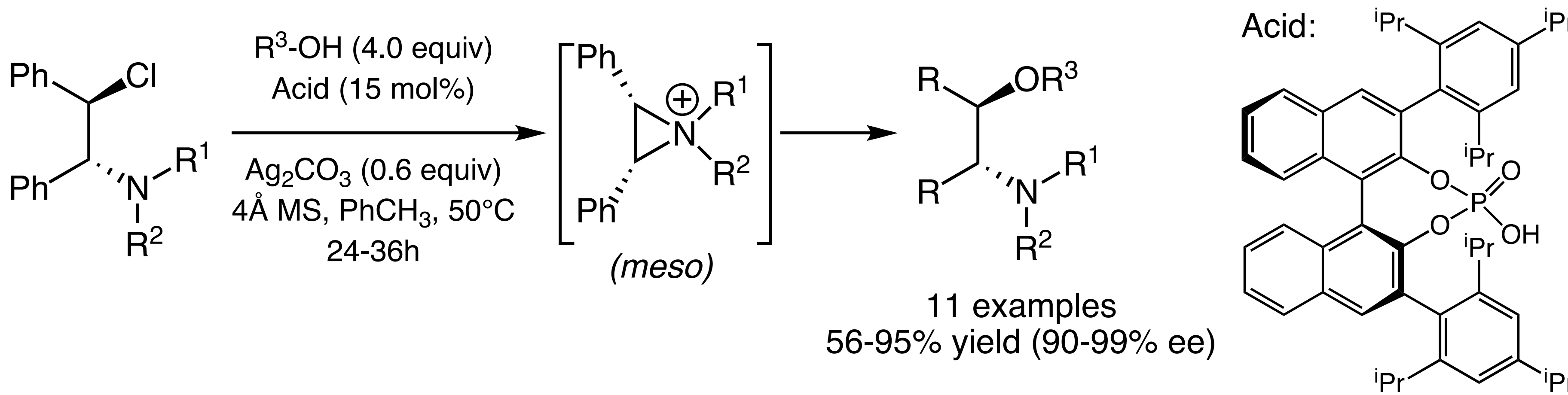
87% i.y., 94% ee

B. Saha, M.-H. Lin, T. V. RajanBabu, *J. Org. Chem.* **2007**, *72*, 8648.
B. Wu, J. C. Gallucci, J. R. Parquette, T. V. RajanBabu, *Angew. Chem. Int. Ed.* **2009**, *early view.*

# *Asymmetric Opening of Aziridines with chiral Acids*



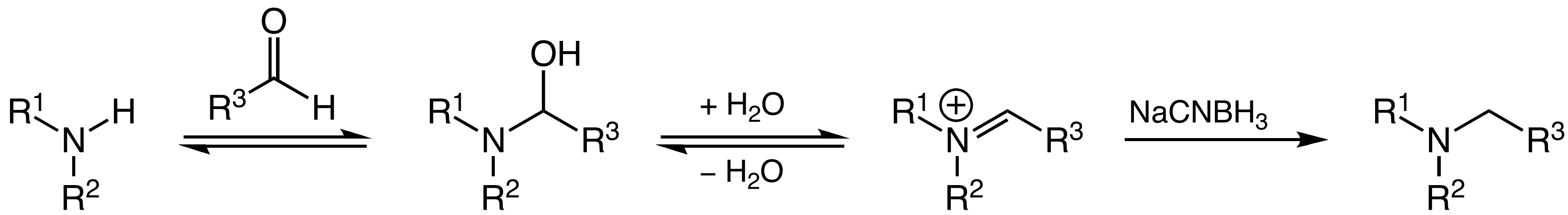

E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 12084.



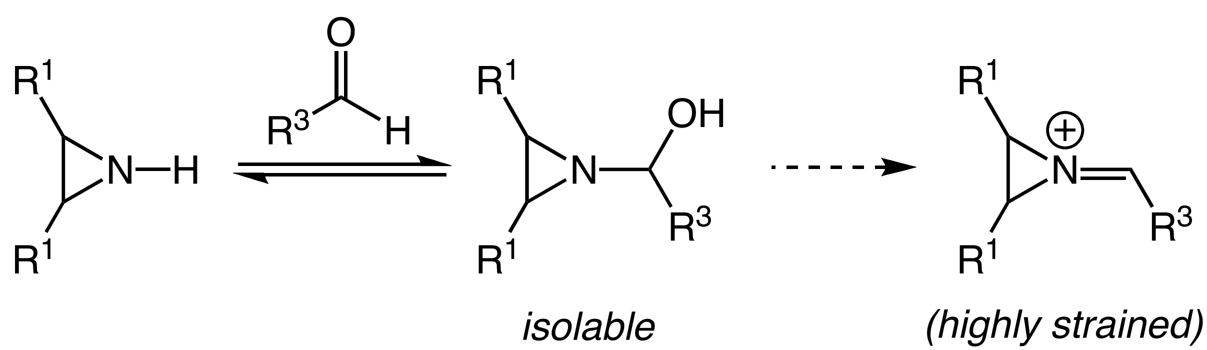

G. L. Hamilton, T. kanai, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 14984.

# *N-Functionalization of Aziridines*

Reactivity of Amines:

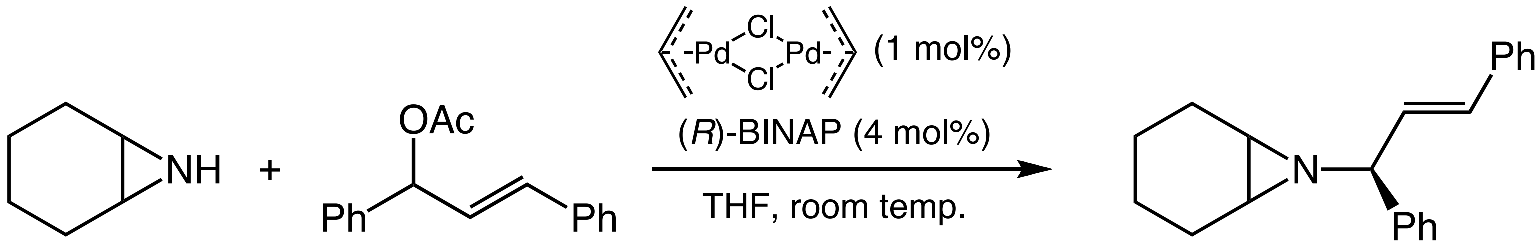



Reactivity of Aziridines:



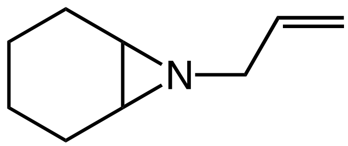

I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.

## *Palladium Catalyzed Allylation of Aziridines*

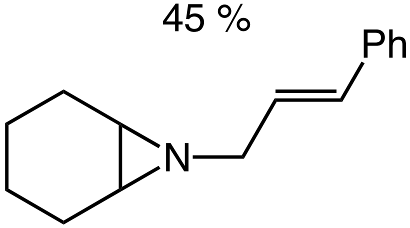



97% i.y., 97% ee

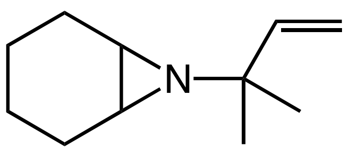
Results obtained with $PPh_3$ as ligand (ratio = linear : branched) :



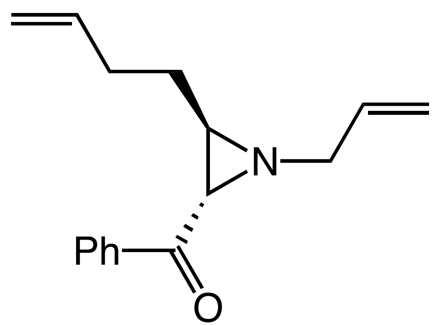

45 %



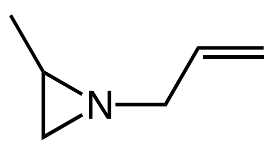

99% (92:8)



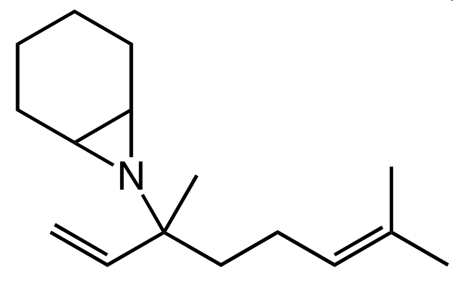

89% i.y. (0:100)



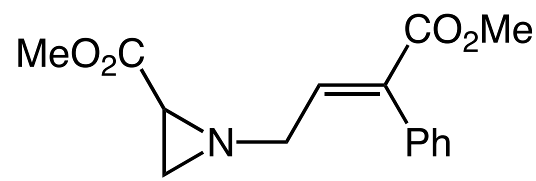

79%




64%



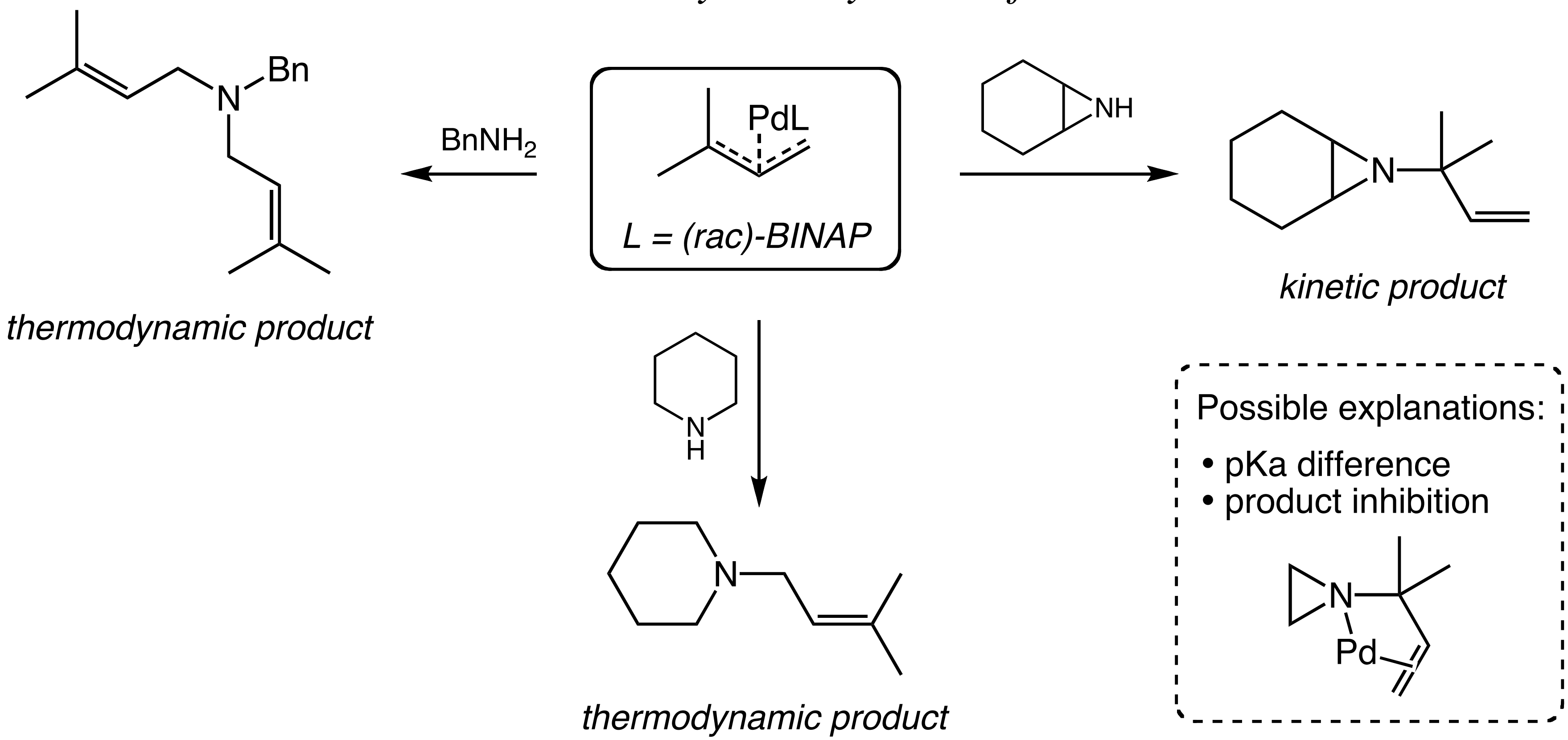

80% (12:88)



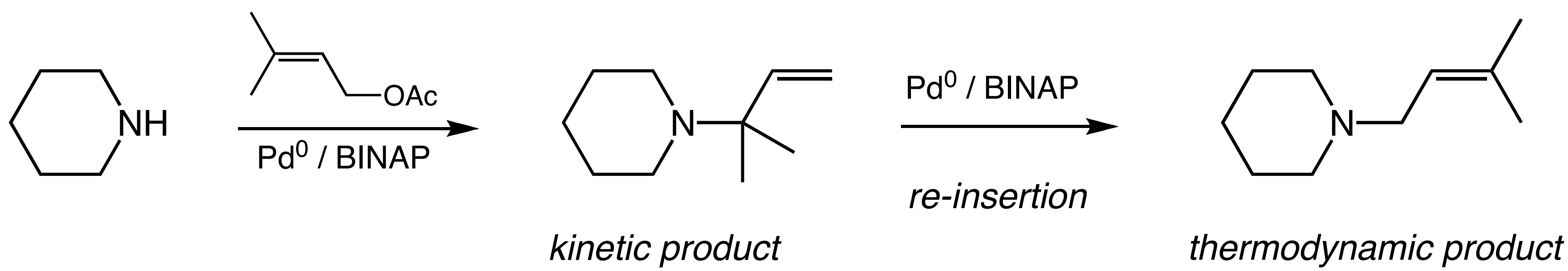

84%

I. D. G. Watson, S. A. Styler, A. K. Yudin, *J. Am. Chem. Soc.* **2004**, *126*, 5086.

# *Palladium Catalyzed Allylation of Aziridines*



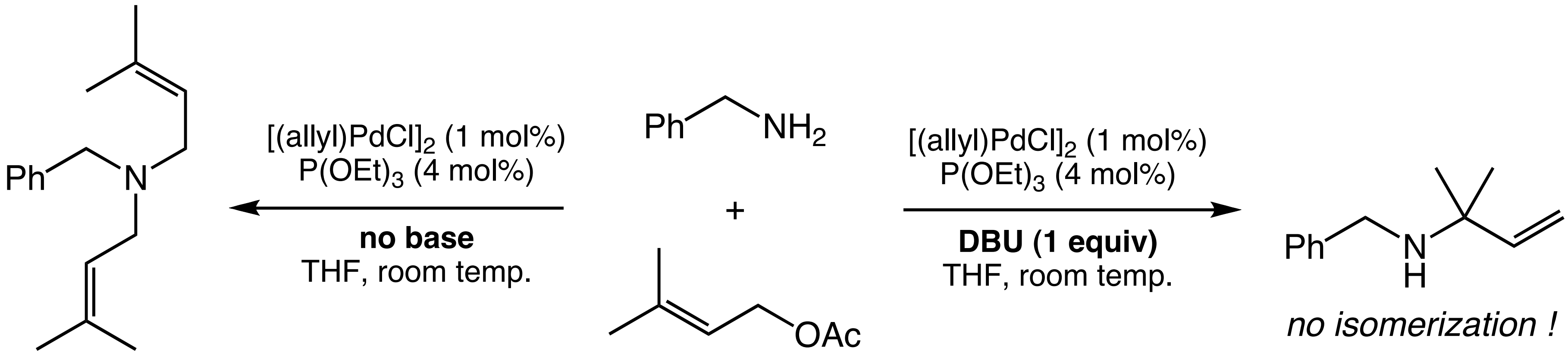

Monitoring the reaction over time:

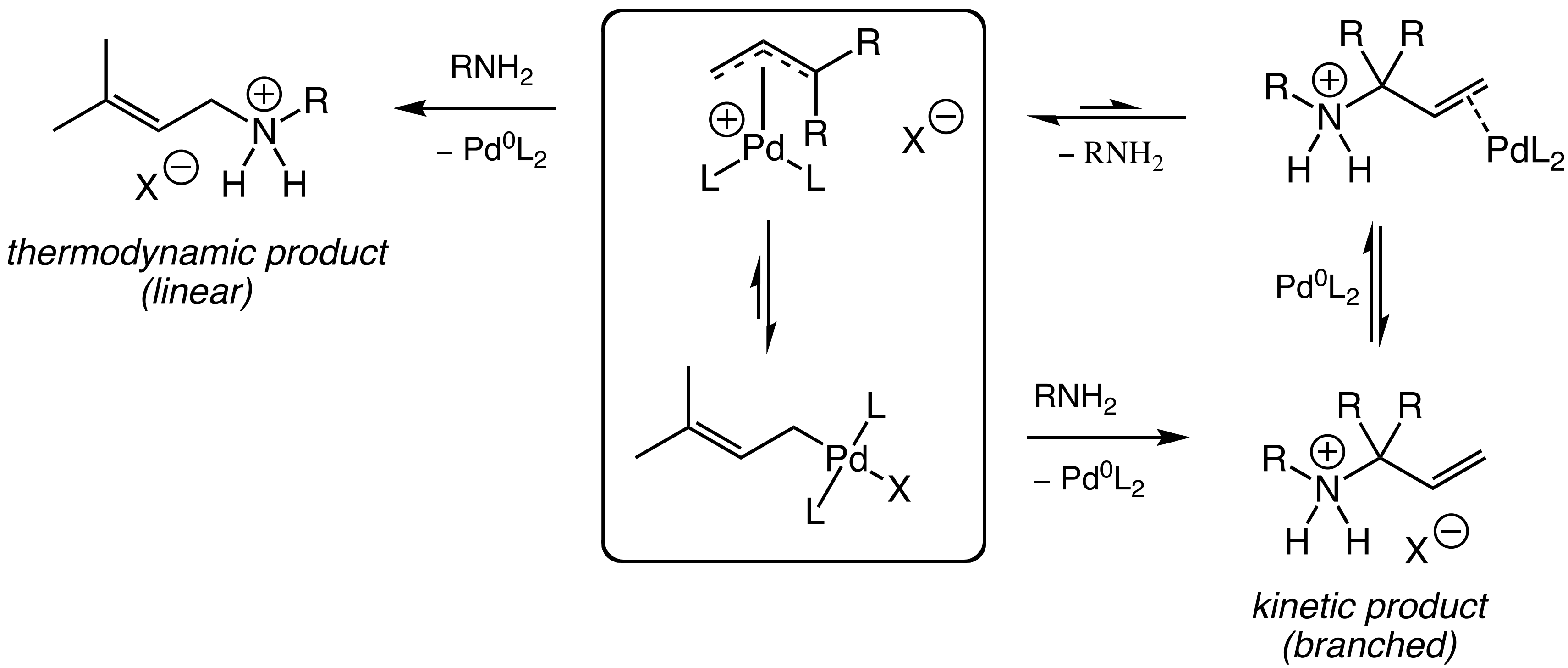




I. D. G. Watson, S. A. Styler, A. K. Yudin, *J. Am. Chem. Soc.* **2004**, *126*, 5086.
I. D. G. Watson, A. K. Yudin, *J. Am. Chem. Soc.* **2005**, *127*, 17516.

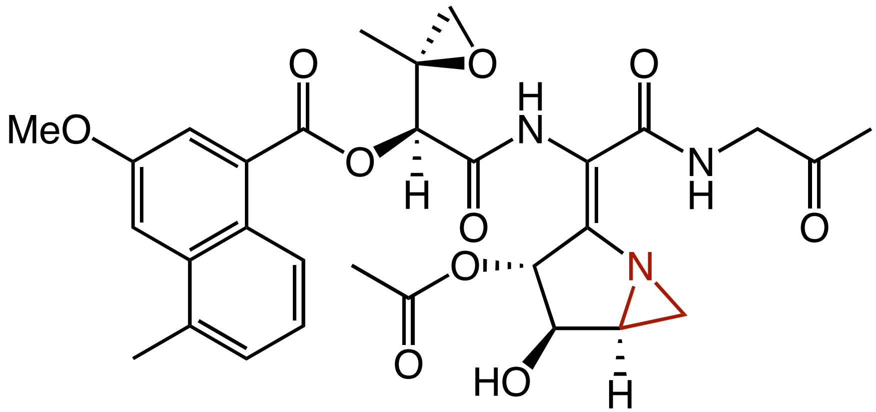
*Palladium Catalyzed Allylic Amination*



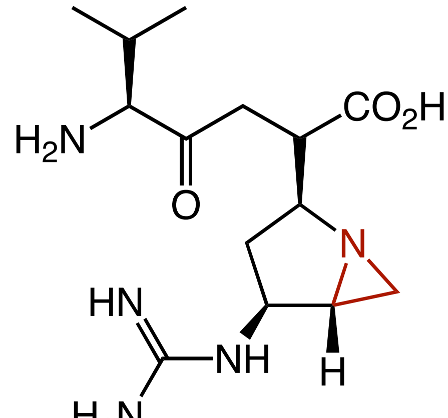




I. Dubovyk, I. D. G. Watson, A. K. Yudin, *J. Am. Chem. Soc.* **2007**, *129*, 14172.

# *Cycloamination Reactions of Aziridines*



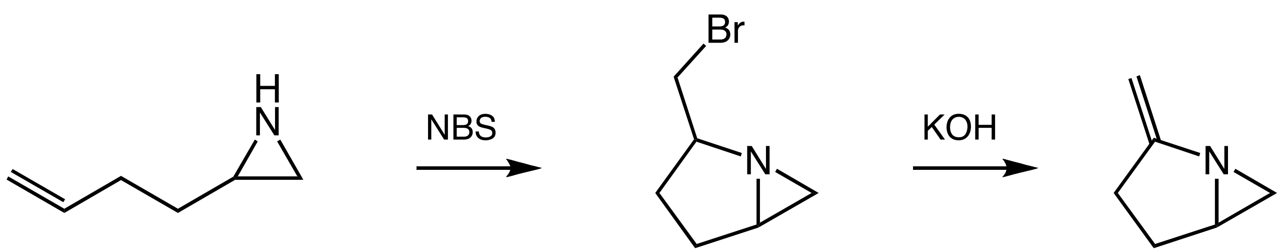
*Azinomycin A*



*Ficellomycin*

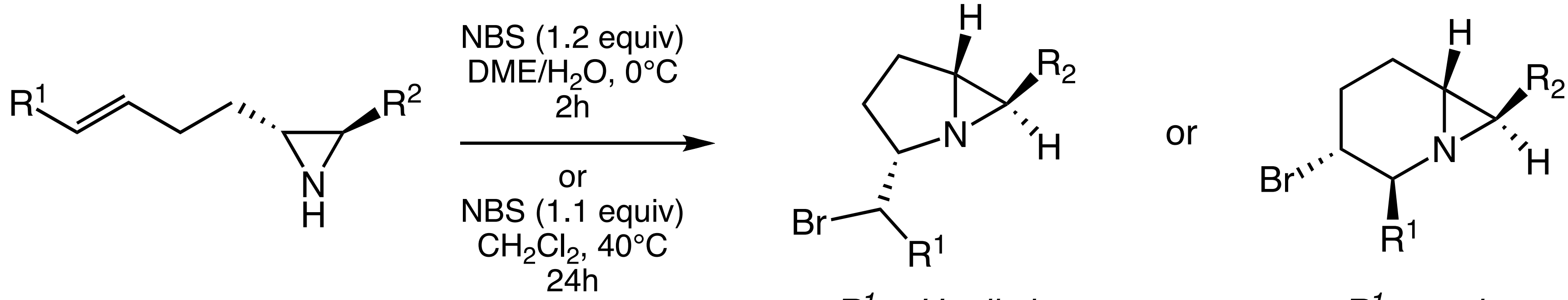
---

Concept: Cycloamination

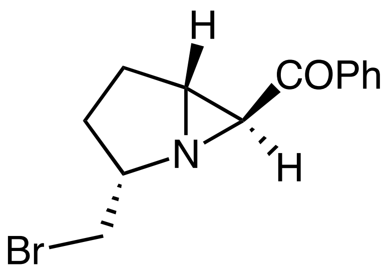



G. Chen, M. Sasaki, X. Li, A. K. Yudin, *J. Org. Chem.* **2006**, *71*, 6067
I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.

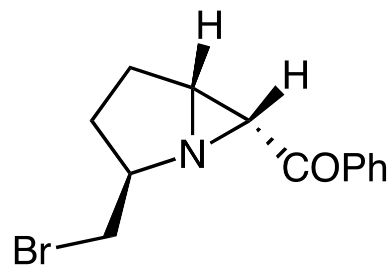
# *Cycloamination Reactions of Aziridines*



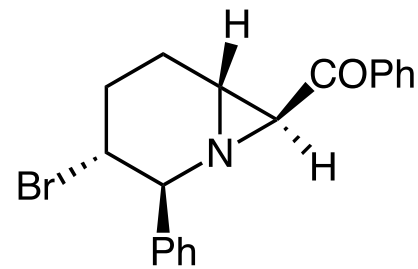

*$R^1$ = H, alkyl*    *$R^1$ = aryl*



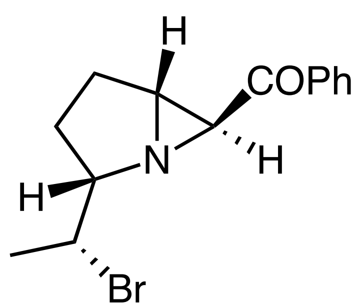
98% (d.r.: 74:26)



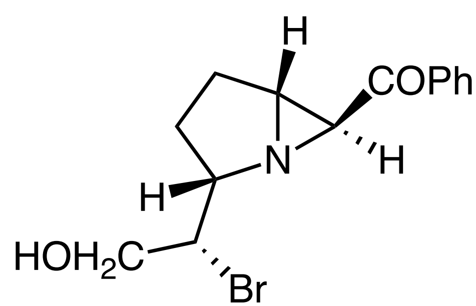
68% (d.r.: > 99:1)



67% (d.r.: 81:19)



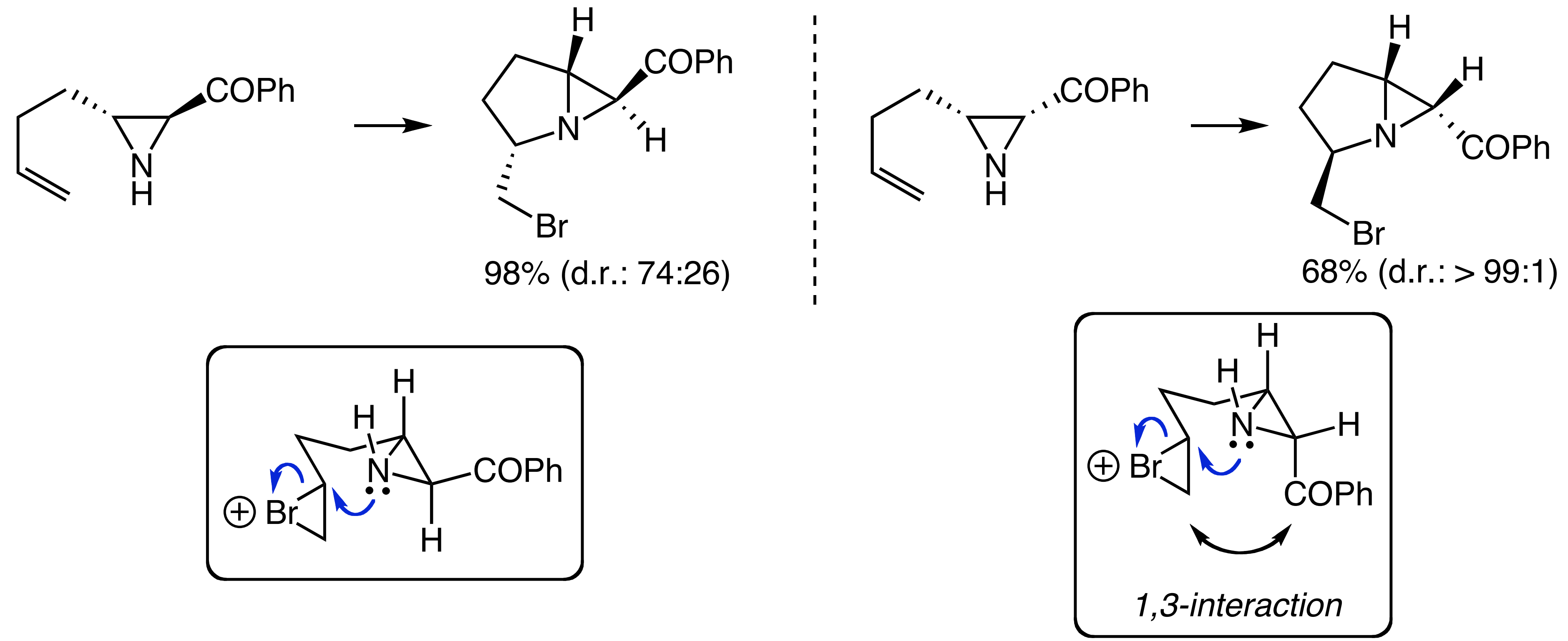
51% (d.r.: 67:33)

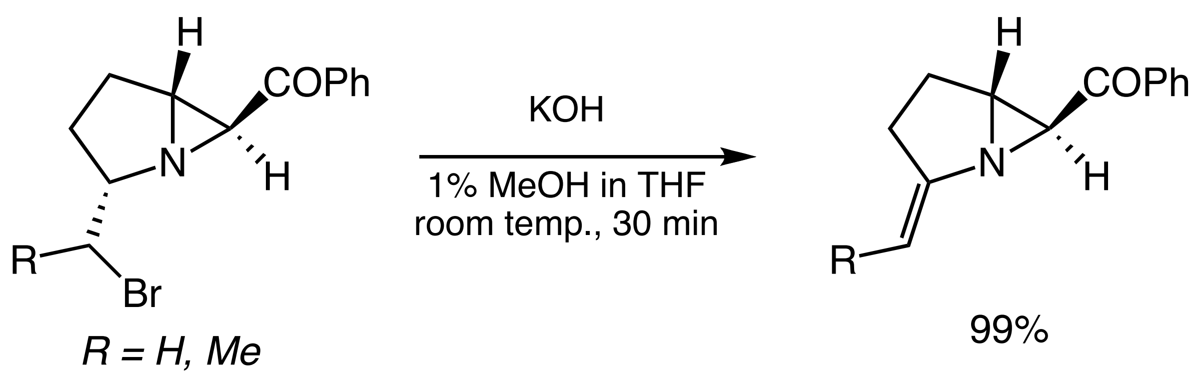


51% (d.r.: 67:33)


G. Chen, M. Sasaki, X. Li, A. K. Yudin, *J. Org. Chem.* **2006**, *71*, 6067

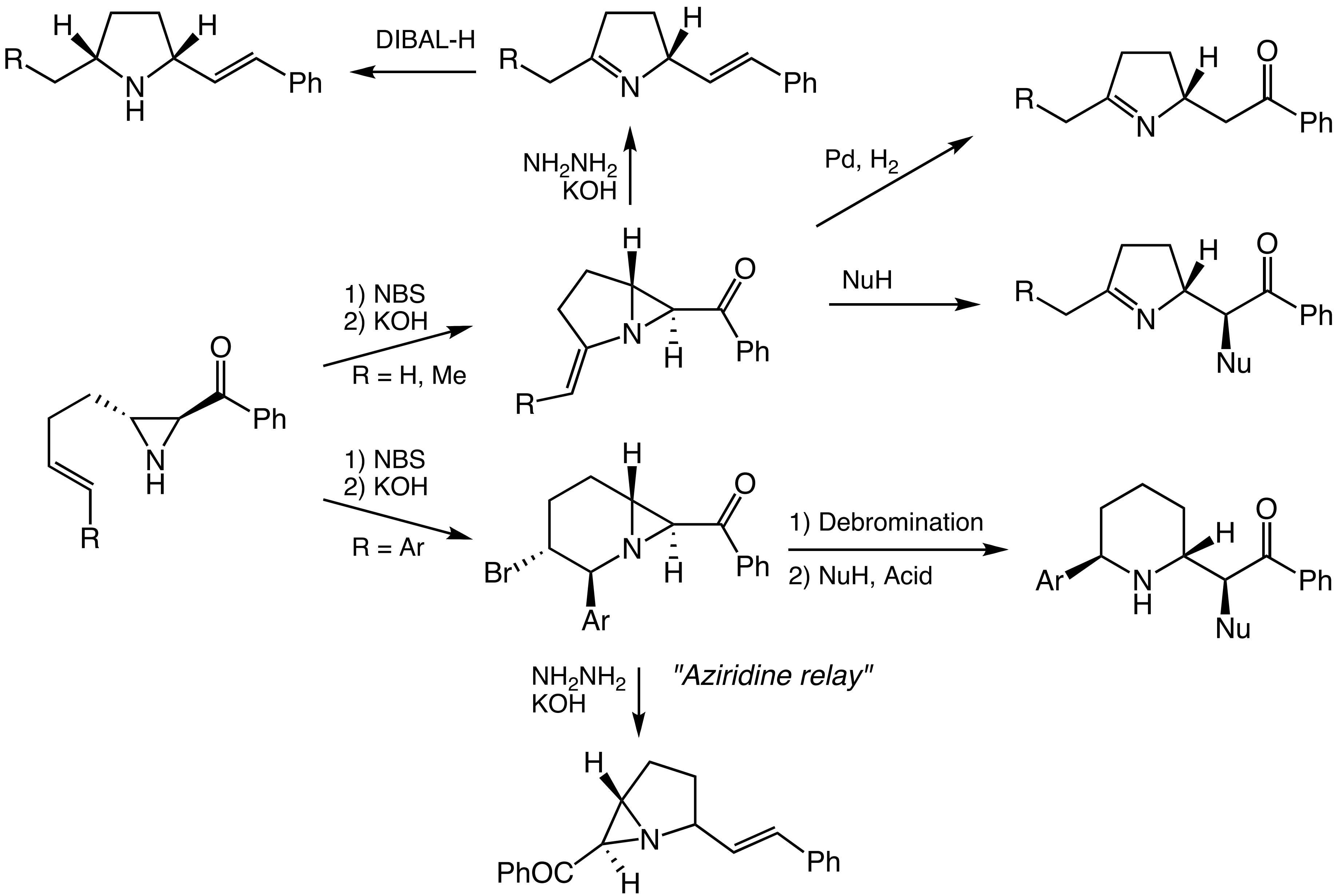
*Cycloamination Reactions Transition State*



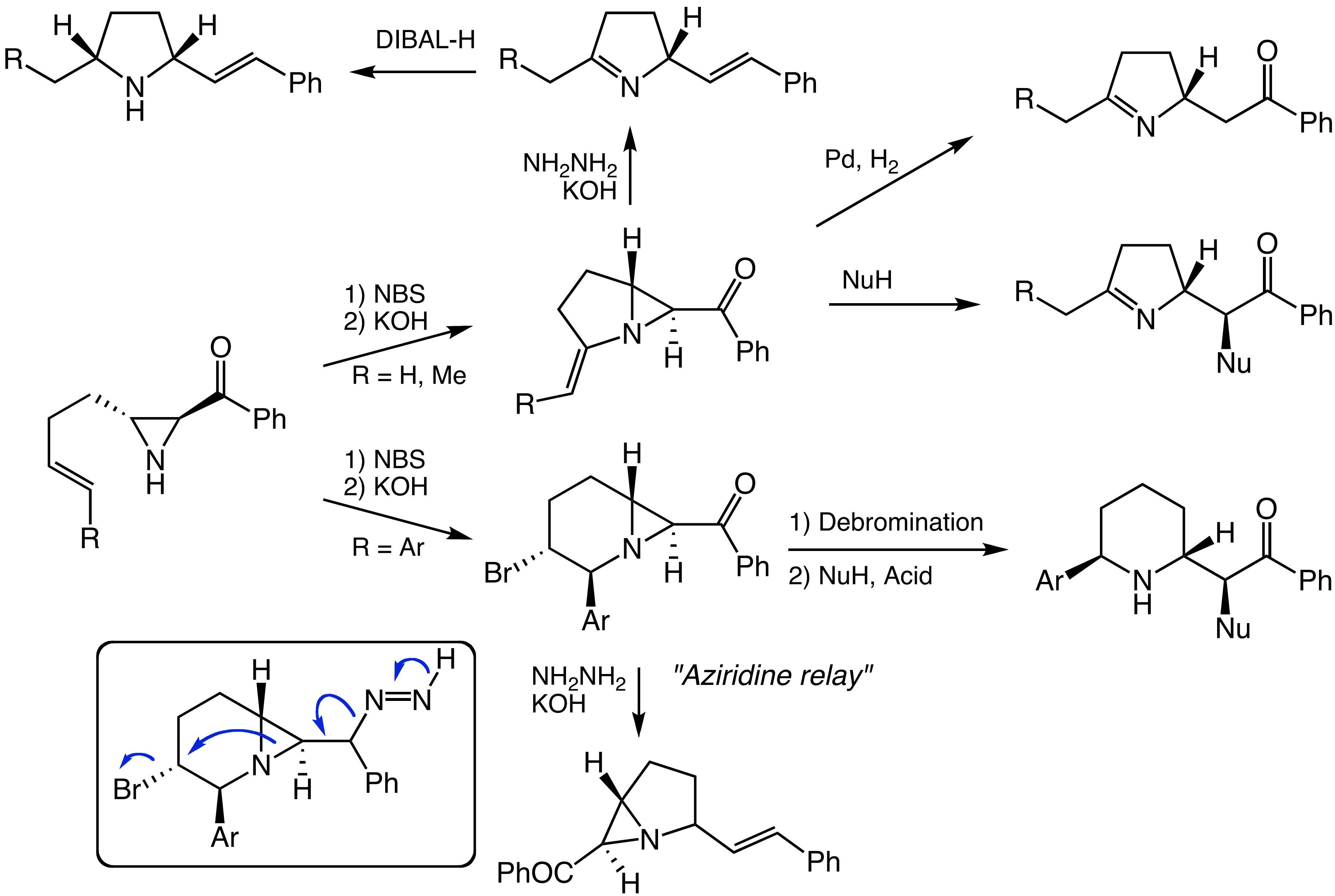

G. Chen, M. Sasaki, X. Li, A. K. Yudin, *J. Org. Chem.* **2006**, *71*, 6067

# *Cycloamination Reactions and Follow-Up Chemistry*



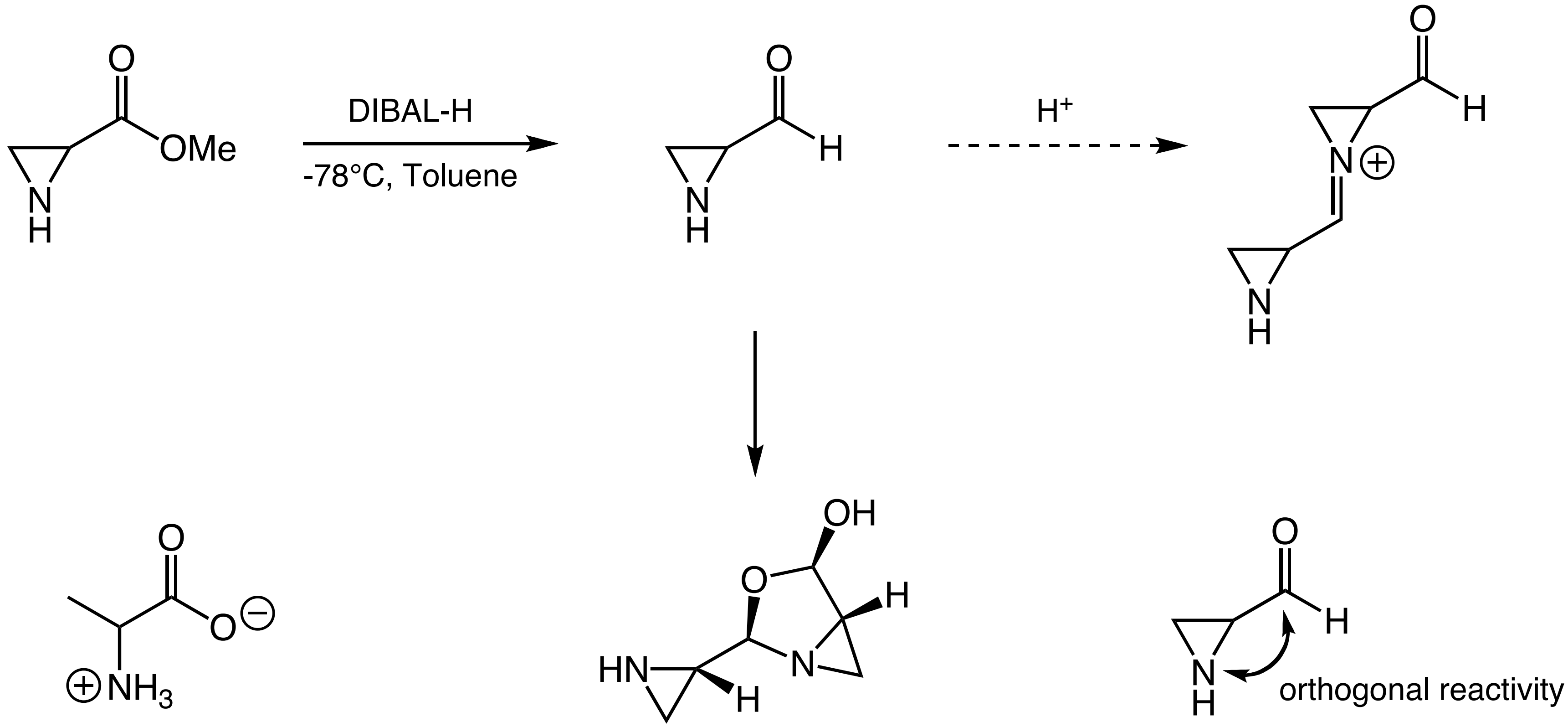

I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.

*Cycloamination Reactions and Follow-Up Chemistry*




I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.

# *Aziridinoaldehydes - Kinetic Amphoters*




*thermodynamic amphoter (zwitterionic)*

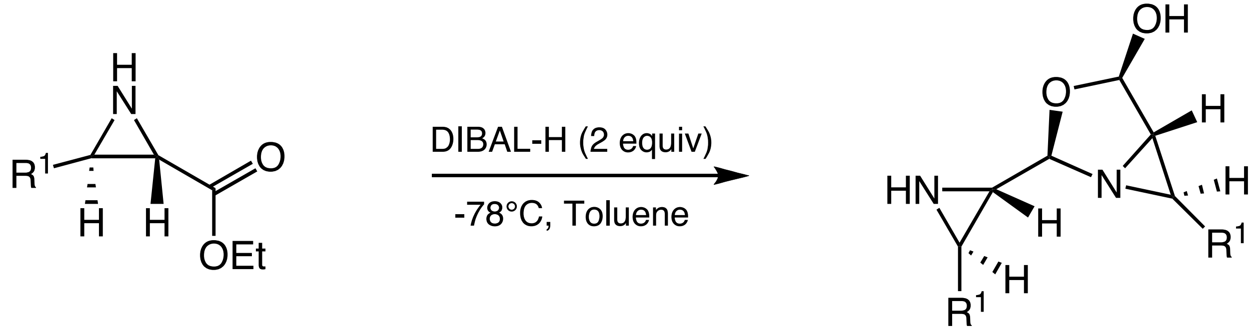
76% i.y.

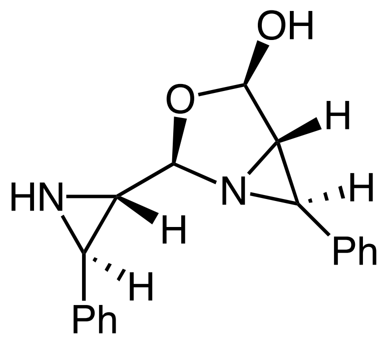
- *stable to racemization*
- *water-soluble*

*kinetic amphoter*

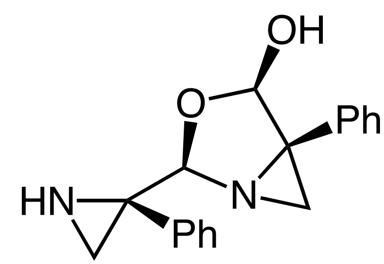

R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772.
A. K. Yudin, R. Hili, *Chem. Eur. J.* **2007**, *13*, 6538.

# *Aziridinoaldehydes - Kinetic Amphoters*

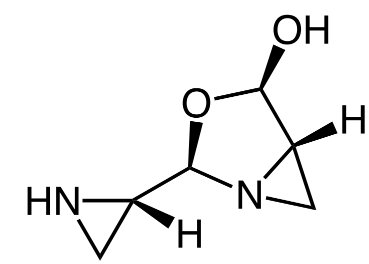


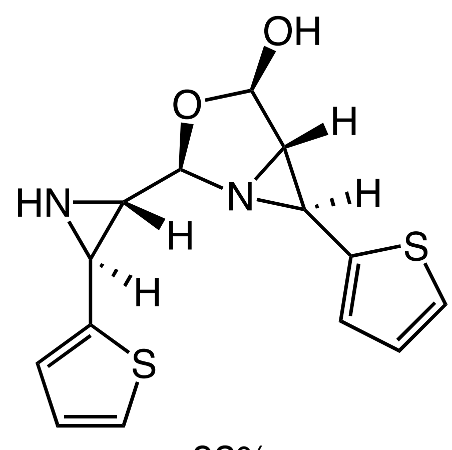
83%



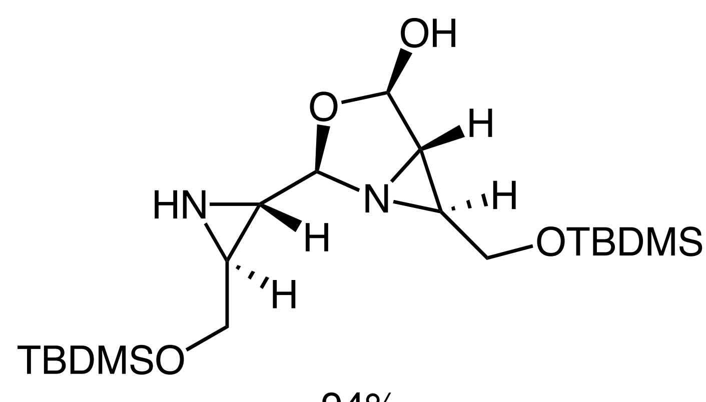
81%



76%



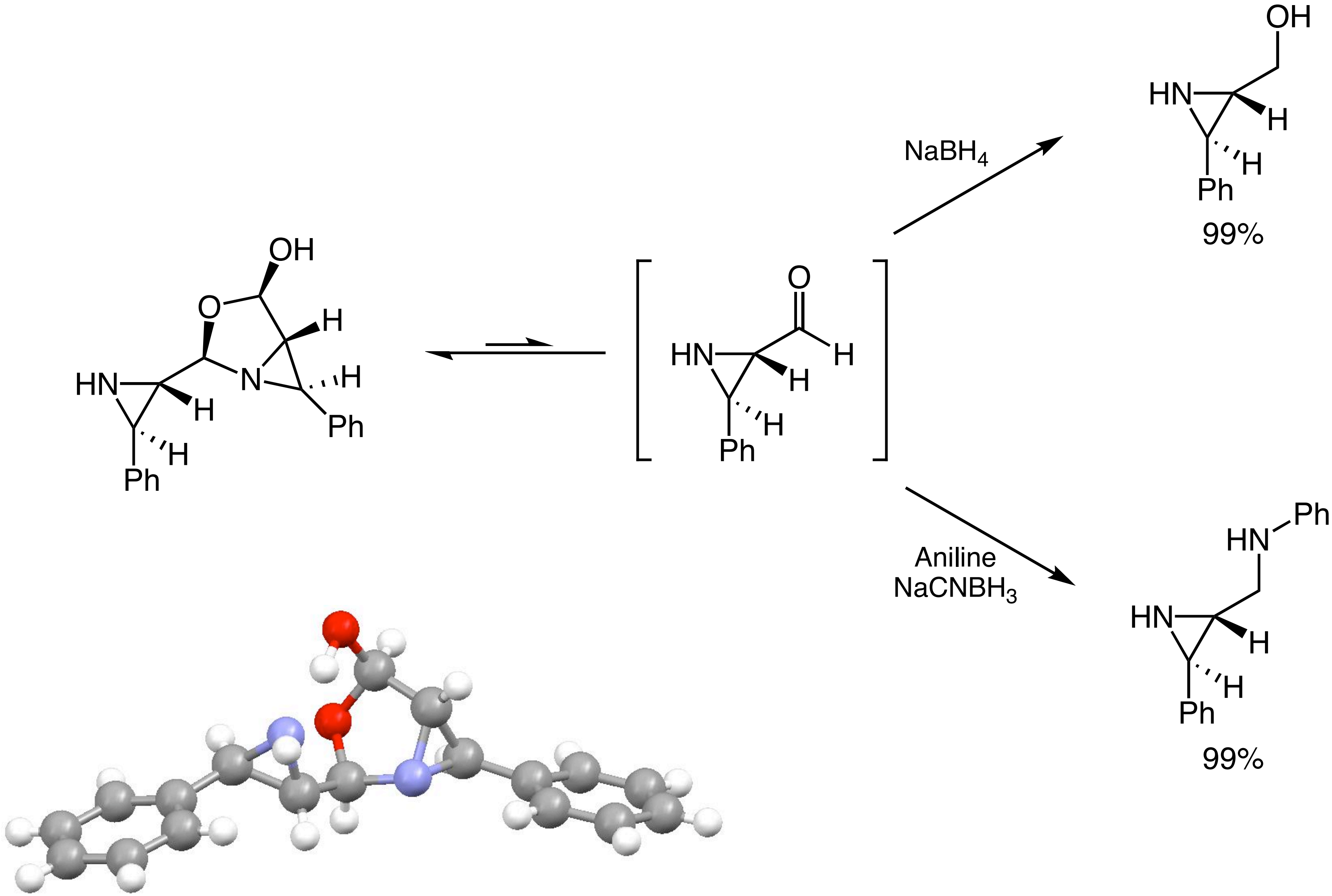
92%



94%

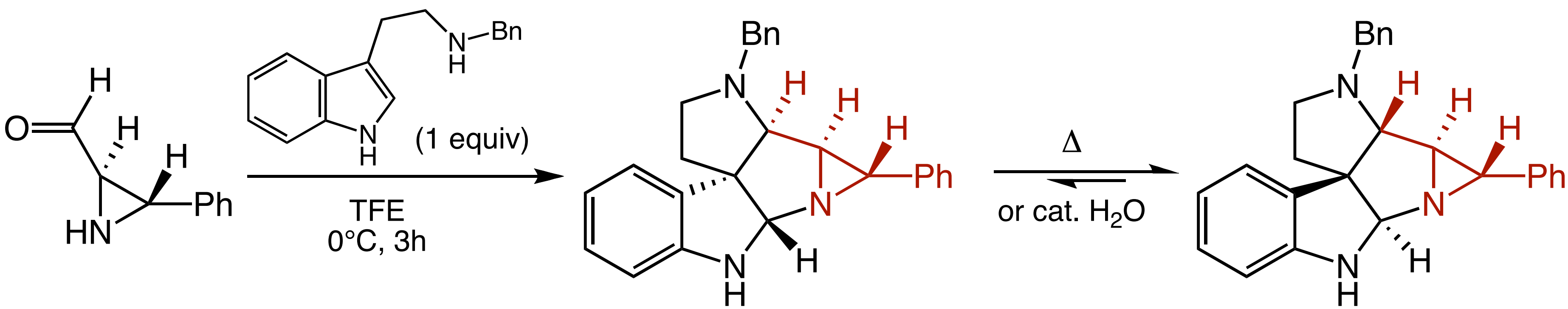
R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772.

# *Aziridinoaldehydes - Reactivity*




R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772.

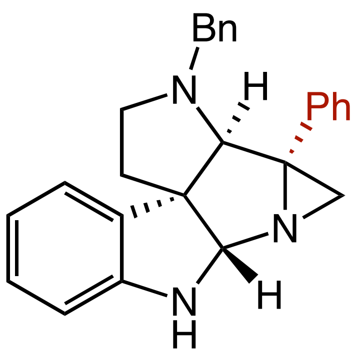
# *Aziridinoaldehydes - Polyheterocycle Synthesis*



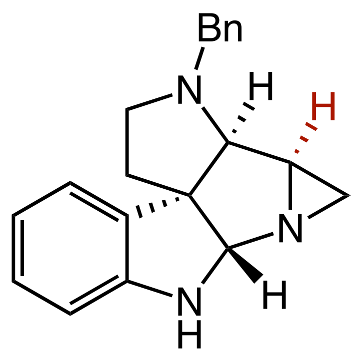

(Dimer) (syn) (anti)

0°C: 97%, (syn/anti = 8:1)
–20°C: 94%, (syn/anti = 20:1)

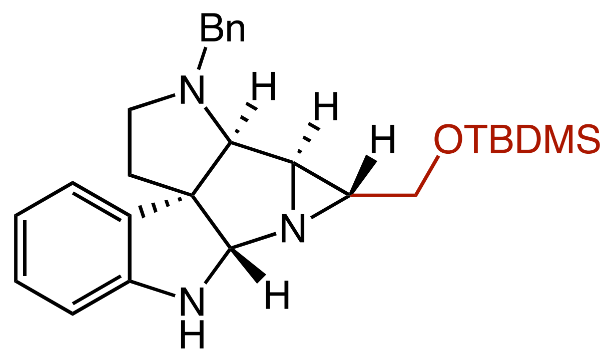
---



81%, (syn/anti = 2:1)



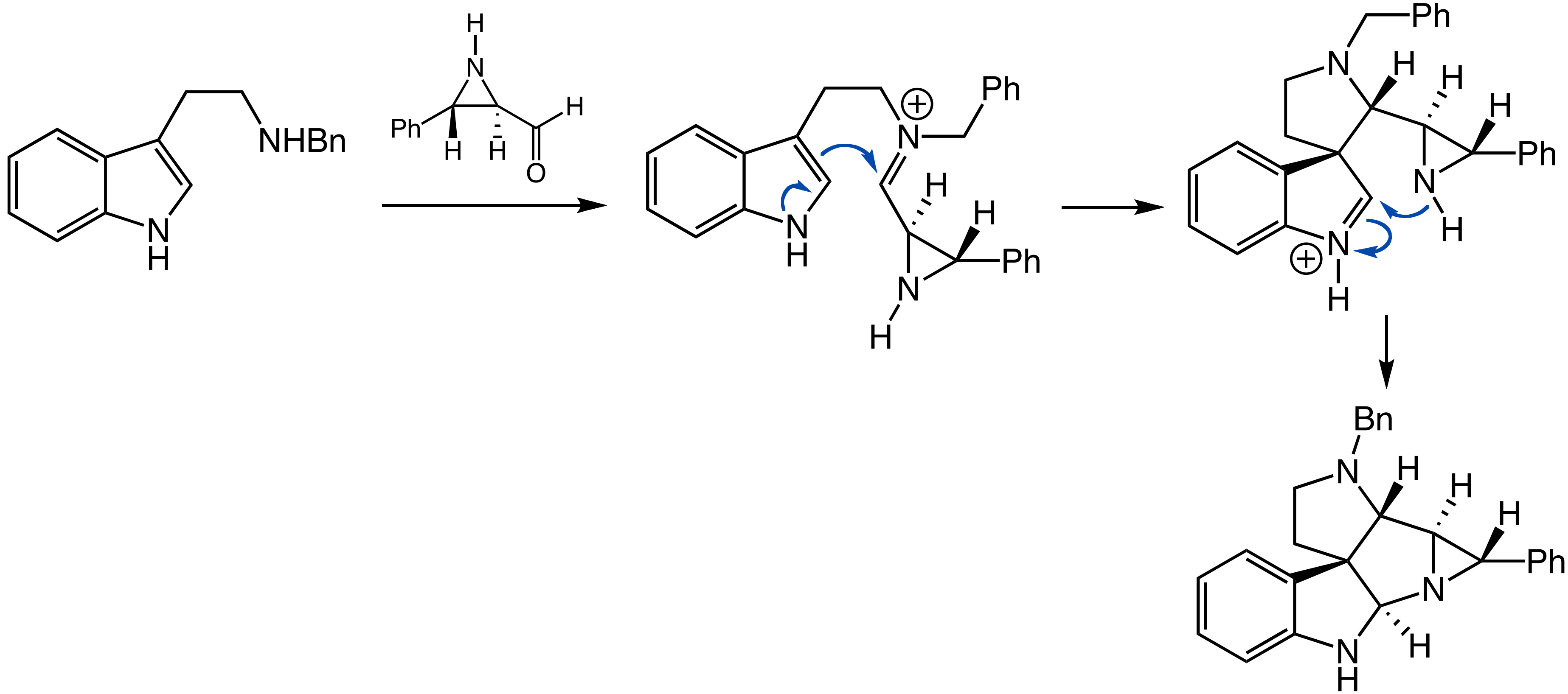
74%, (syn/anti = 1.5:1)

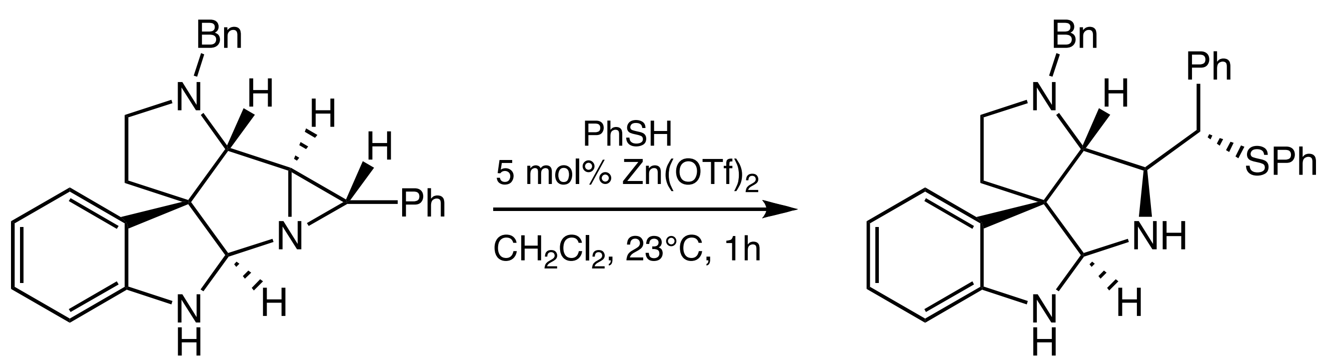


94%, (syn/anti = 3:1)


R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772.

*Polyheterocycle Formation - Mechanism*




R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772.
A. K. Yudin, R. Hili, *Chem. Eur. J.* **2007**, *13*, 6538.

# *Conclusion*

- *The direct aziridination of olefins is more difficult than the corresponding epoxidation*
- *A general solution towards an enantioselective ring-opening of aziridines does not exist*
- *Partial solutions have been discovered over the past 10 years but they are very specific*

- *Aziridines react different than amines in N-allylation reactions (under the same conditions)*
- *Cycloamination of aziridines leads to building blocks for heterocycle chemistry and natural products*
- *Aziridinoaldehydes are kinetic amphoters with unique reactivity*

*Literature:*


*Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin),Wiley-VCH, Weinheim, **2006.**
A. K. Yudin, R. Hili, *Chem. Eur. J.* **2007**, *13*, 6538.
I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.
M. Pineschi, *Eur. J. Org. Chem.* **2006**, 4979.
A. Padwa, S. S. Murphree, *ARKIVOC* **2006**, *3*, 6.
J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247.
H. M. I. Osborn, J. Sweeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1693.
D. Tanner, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.