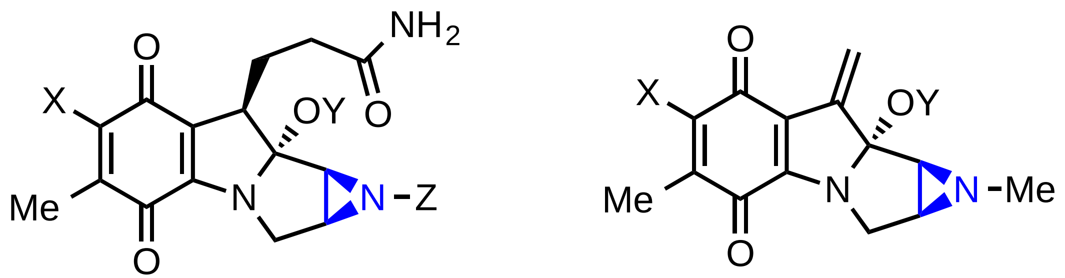
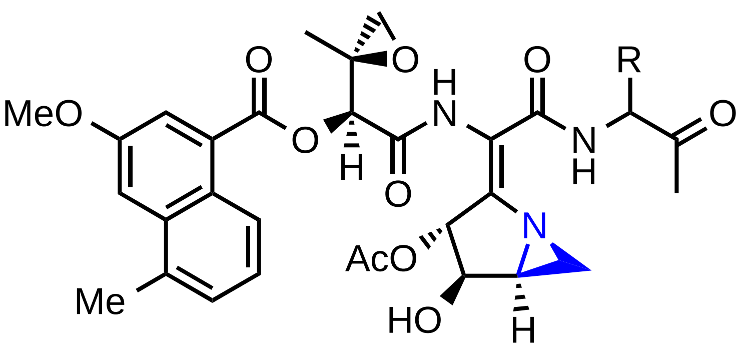
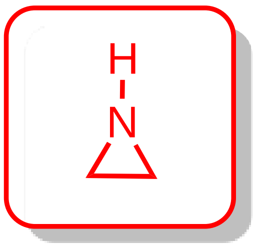
Syntheses of Aziridines

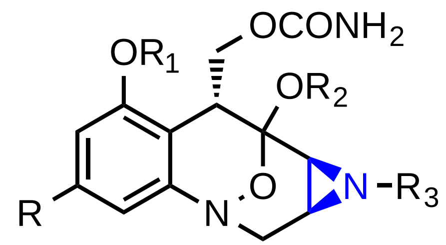


Mitomycin

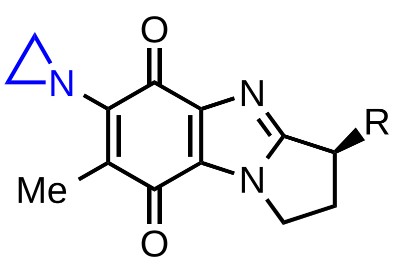


Azinomycin





FR-xxxx



PBI-xxxx

2014. 03. 05

Haye Min Ko

Contents

1. *Physical properties*

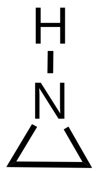
2. *Biological properties*

3. *Reactions of aziridines (for organic chemists)*

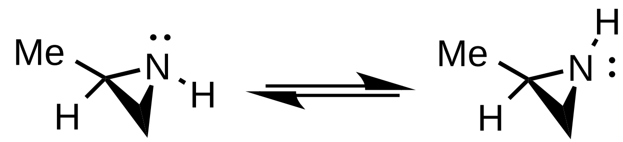
4. *Syntheses of aziridines from olefins*
   - *Nitrene methods*
   - *Cu*
   - *Rh*
   - *Other metals*
   - *Carbene and ylide methods*

5. *Conclusion*

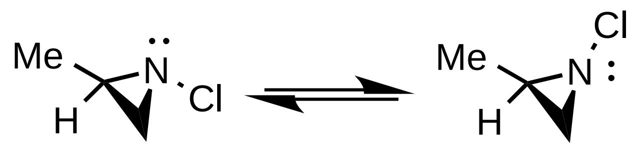
Physical Properties



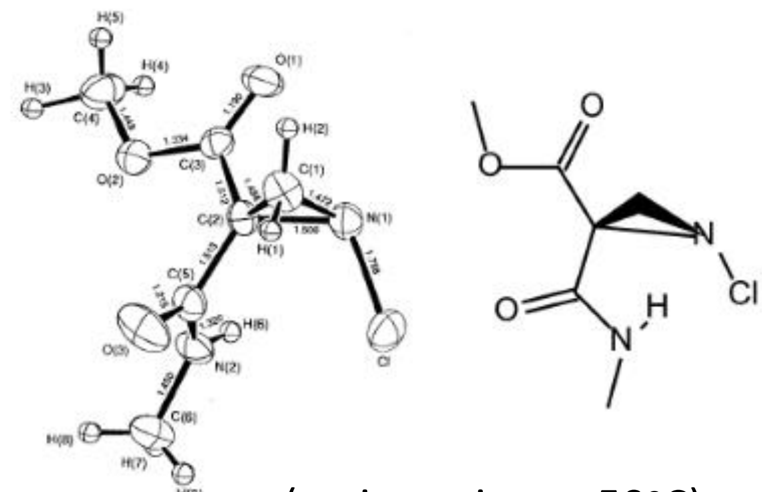
ethyleneimine
water-soluble,
colorless, distillable
liquid
b.p. 57°C
pKa 7.98



E=70kj/mol
(inversion at 25°C)



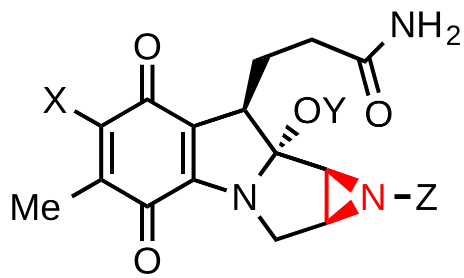
E=112kj/mol
(isolation at 25°C)



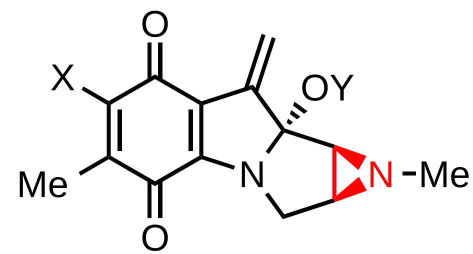
(no inversion at 50°C)

J. B. Sweeney, *Chem. Soc. Rev.*, **2002**, *31*, 247–258

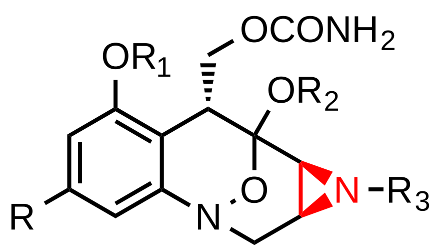
Biological Properties (Natural Products)



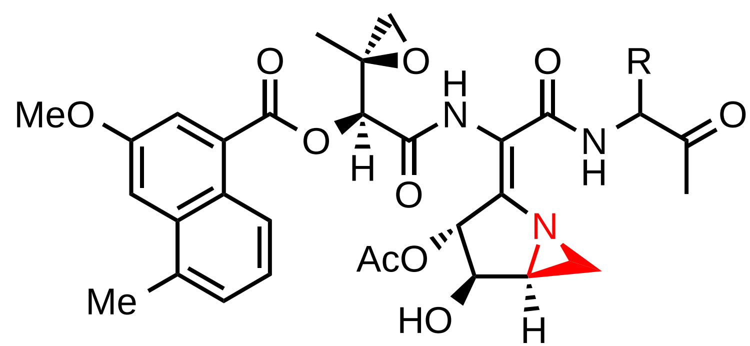
Mitomycin A X=OMe, Y=Me, Z=H
Mitomycin B X=OMe, Y=H, Z=Me
Mitomycin C X=NH_2, Y=Me, Z=H



Mitomycin G X=NH_2, Y=Me
Mitomycin H X=OMe, Y=H
Mitomycin K X=OMe, Y=Me



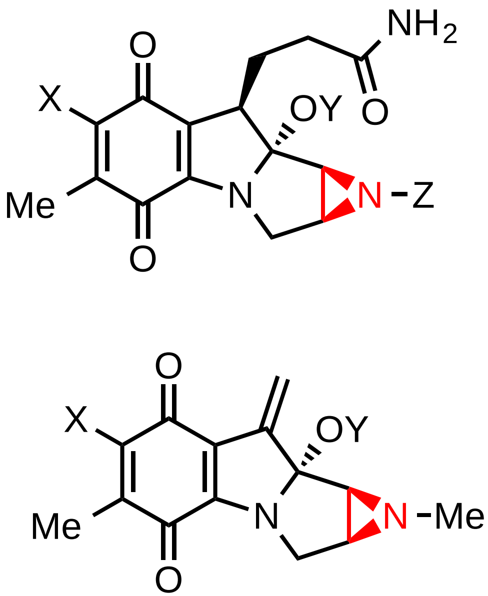
FR-900482 R=CHO, R_1, R_2, R_3=H
FR-66979 R=CH_2OH, R_1, R_2, R_3=H
FR-70496 R=CHO, R_1=Me, R_2=H, R_3=Ac
FK-973 R=CHO, R_1, R_2, R_3=Ac
FK-317 R=CHO, R_1=Me, R_2=Ac



Azinomycin A R=H
Azinomycin B R=CHO

J. B. Sweeney, *Chem. Soc. Rev.*, **2002**, *31*, 247–258

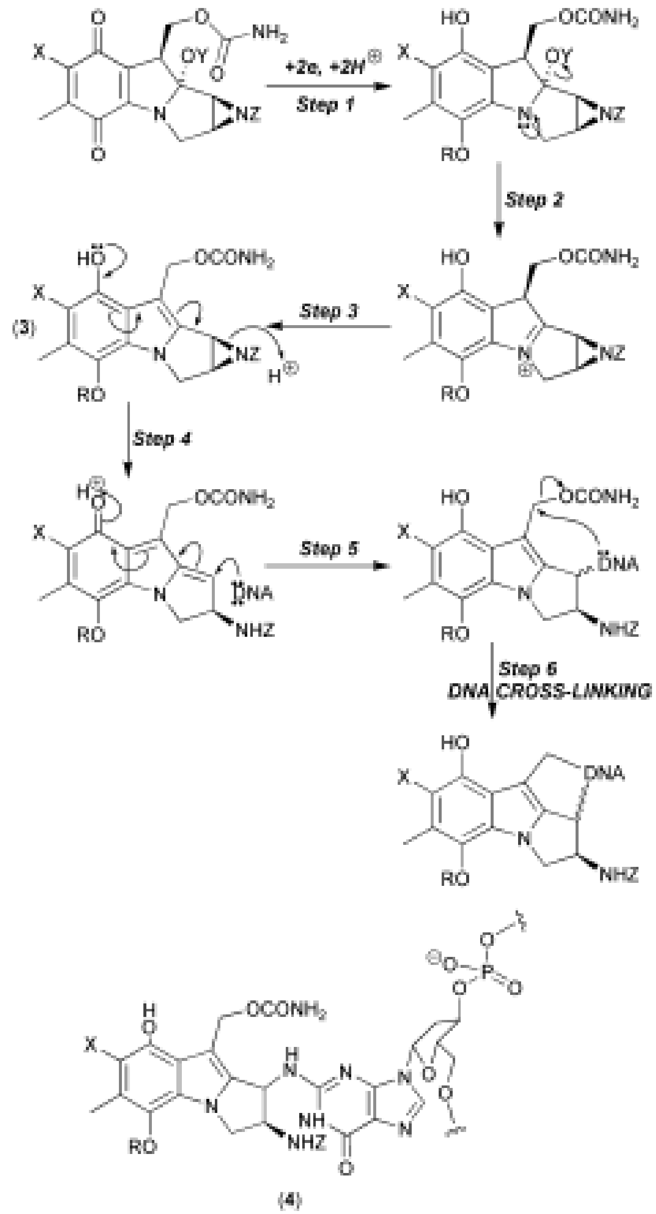
Biological Properties(DNA interaction of aziridines)



Mitosanes

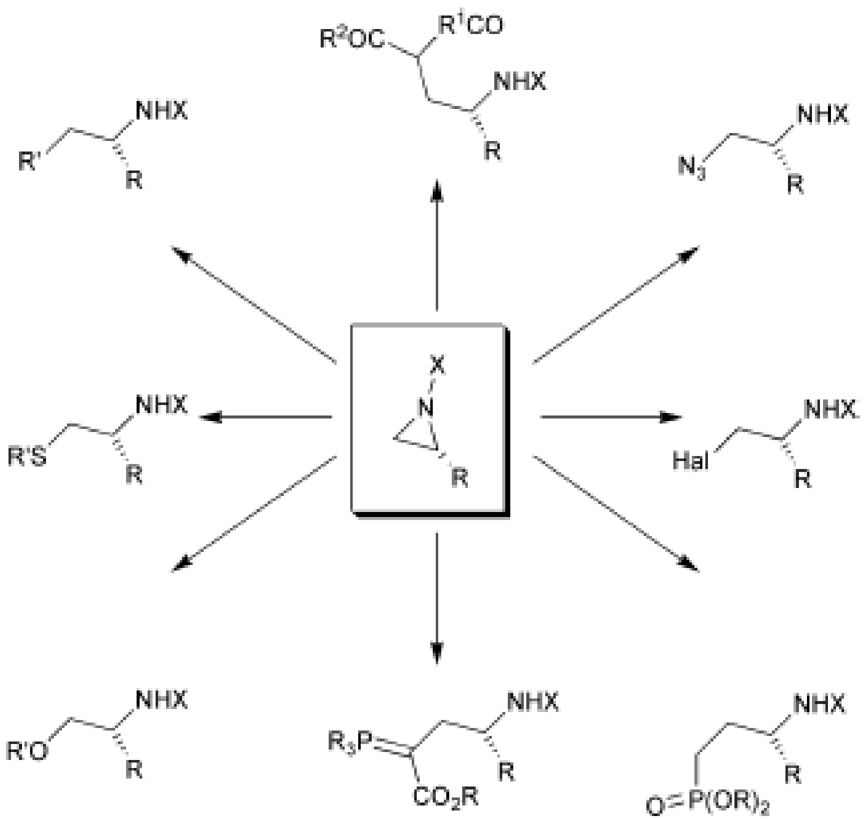
Streptomyces verticillatus
anti-tumour
antibiotic activity

J. B. Sweeney, *Chem. Soc. Rev.*, **2002**, *31*, 247–258

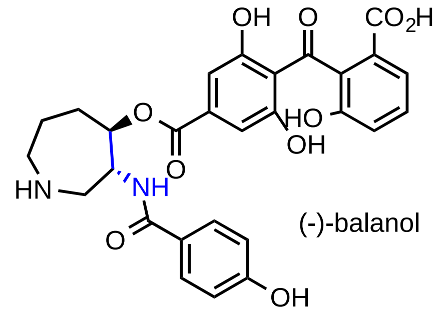


Scheme 1 Mode of action of Mitosanes.

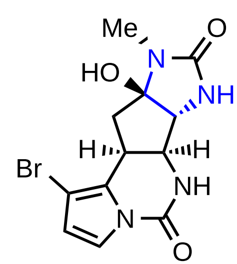
Reactions of Aziridines(Ring opening processes)



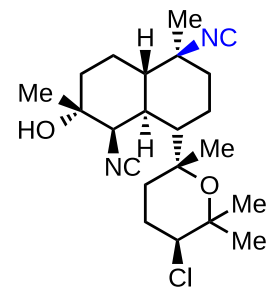
Scheme 6



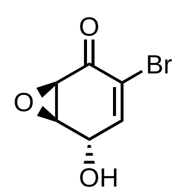
(-)-balanol



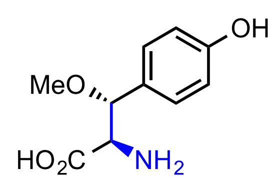
(+)-agelastatin A



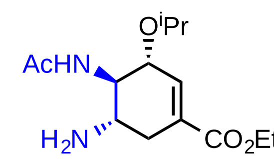
(+)-kalihinol A



(+)-bromoxone



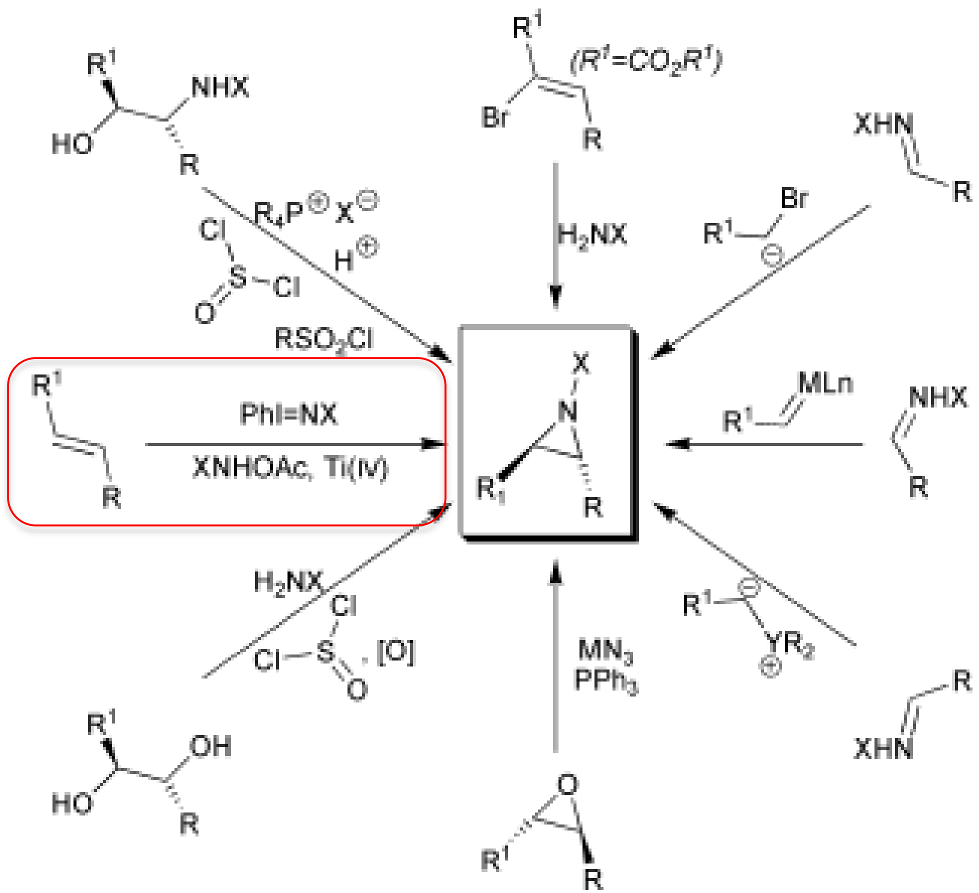
(R,R)-B-methoxytyrosine



(-)-oseltamivir

J. B. Sweeney, *Chem. Soc. Rev.*, **2002**, *31*, 247–258
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

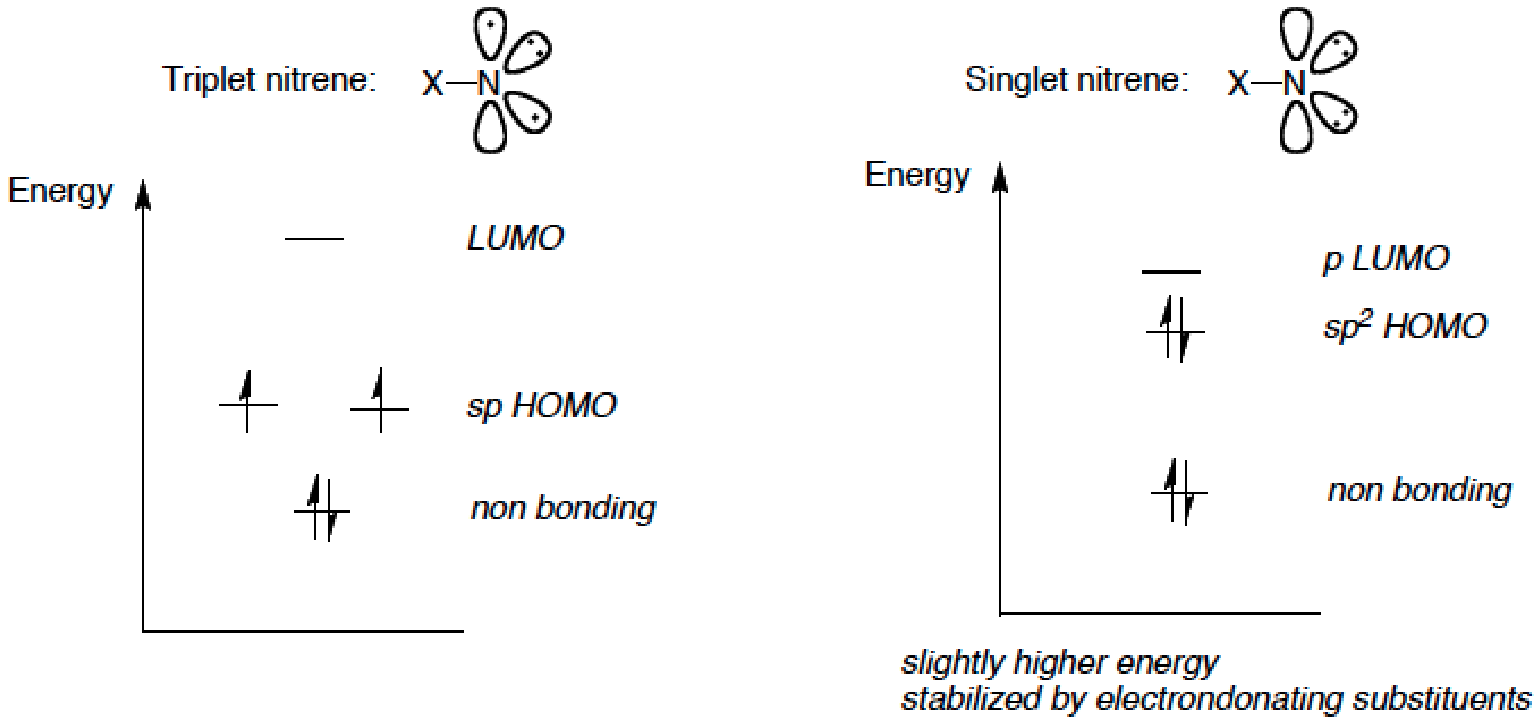
Syntheses of Aziridines(Overview)

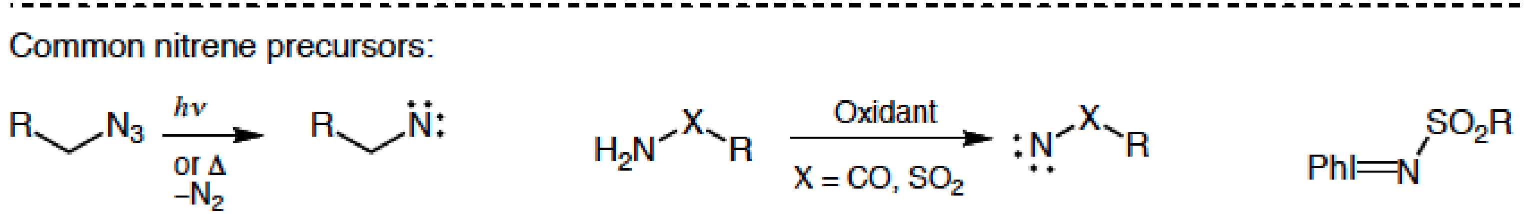


Scheme 19

J. B. Sweeney, *Chem. Soc. Rev.*, **2002**, *31*, 247–258
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Introduction of nitrenes



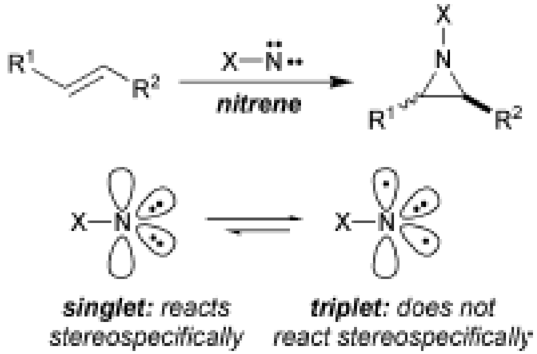


J. B. Sweeney, *Chem. Soc. Rev.*, **2002**, *31*, 247–258

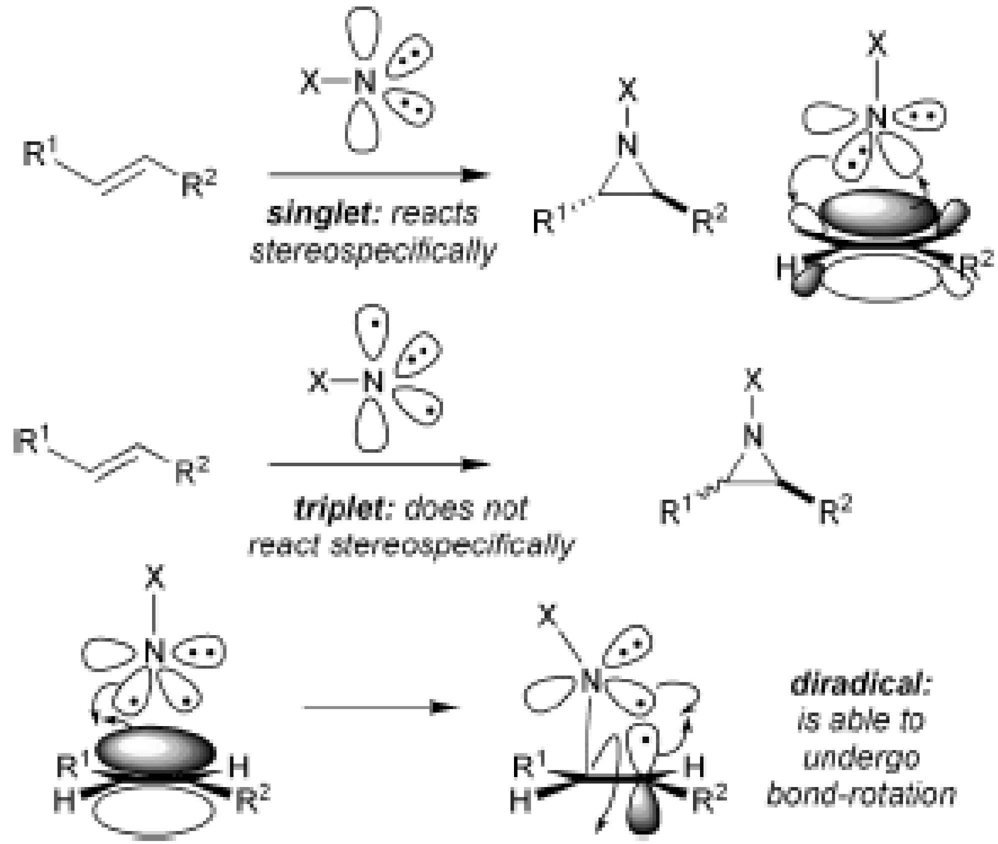
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

W. Schoeller, A. B. Rozhenko, *Eur. J. Inorg. Chem*. **2001**, 845-850.

Stereoselectivity of nitrenes



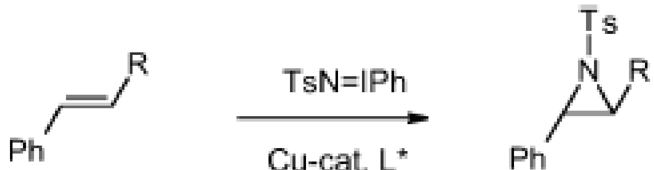
Scheme 21



Scheme 22

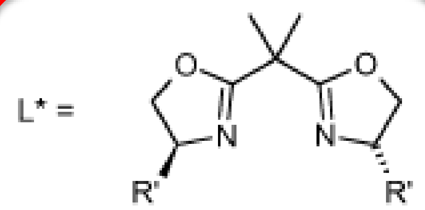
J. B. Sweeney, *Chem. Soc. Rev.*, **2002**, *31*, 247–258

Cu-catalyzed aziridinations(Evans)



1 2

a R = COOMe
b R = COOPh
c R = COO^{t}Bu
d R = Me
e R = H



3a R' = Ph
3b R' = *t*-Bu

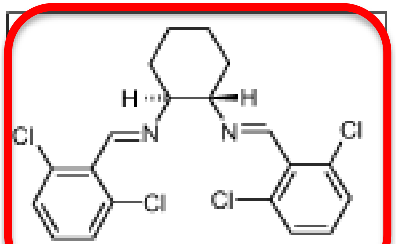
Table 1. Aziridination of Olefins with Bis(oxazoline)−Copper Complexes

olefin	cat.	solvent, conditions	yield, %	ee, %	conf.
methyl cinnamate (**1a**)	**3a**	C_6H_6 (24 h, 21 °C)	63	94	(*S*)
phenyl cinnamate (**1b**)	**3a**	C_6H_6 (24 h, 21 °C)	64	97	(*S*)
t-butyl cinnamate (**1c**)	**3a**	C_6H_6 (24 h, 21 °C)	60	96	(*S*)
trans-*β*-methylstyrene (**1d**)	**3b**	MeCN (3 d, −20 °C)	62	70	(*S*)
styrene (**1e**)	**3b**	styrene (2.5 h, 0°C)	89	63	(*R*)

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.
J. B. Sweeney, *Chem. Soc. Rev*., **2002**, *31*, 247–258
P. Muller, C. Fruit, *Chem. Rev*. **2003**, *103*, 2905-2919

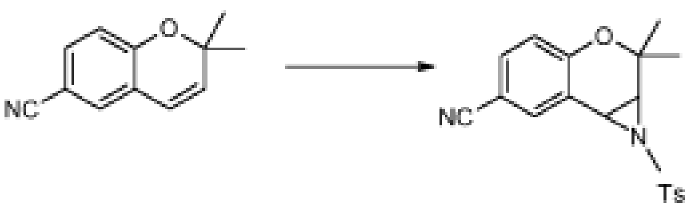
Cu-catalyzed aziridinations(Jacobsen)

1 **2**



9

e R = R' = H
f R = H, R' = Me
g 1,2-dihydronaphthalene
h Indene
i 6-cyano-2,2-dimethylchromene



1i

2i 75%, >98 % ee

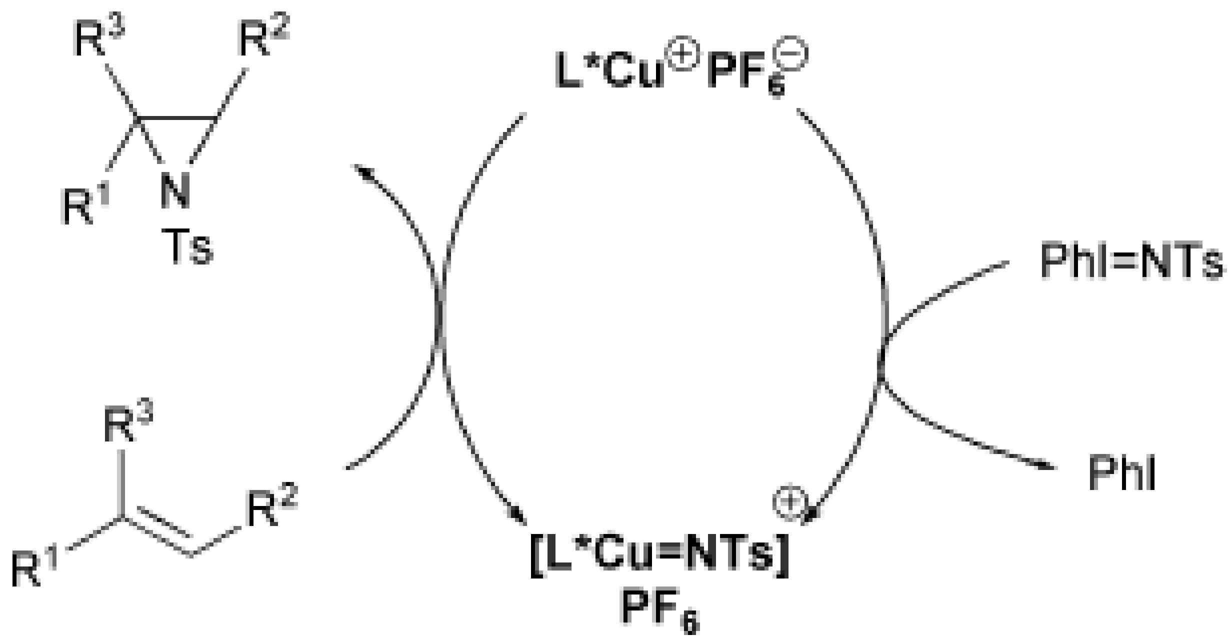
Table 2. Cu-Catalyzed Aziridination of Olefins with Jacobsen's Ligand 9[a]

olefin	aziridine, yield, %	ee, %	abs. conf.
styrene (**1e**)	79	66	(*R*)
cis-*β*-methylstyrene (**1f**)	79 (*d*:*t* = 3:1)	67 (cis)	(1*R*,2*S*)
		81 (trans)	(1*S*,2*S*)
1,2-dihydronaphthalene (**1g**)	70	87	(1*R*,2*S*)
indene (**1h**)	50	58	(1*R*,2*S*)
6-cyano-2,2-dimethyl-chromene (**1i**)	75	>98	(3*R*,4*R*)

[a] −40 to −78 °C, CH_2Cl_2, 4 Å sieves, 5–10 mol % of Cu, 6–12 mol % of **9**.

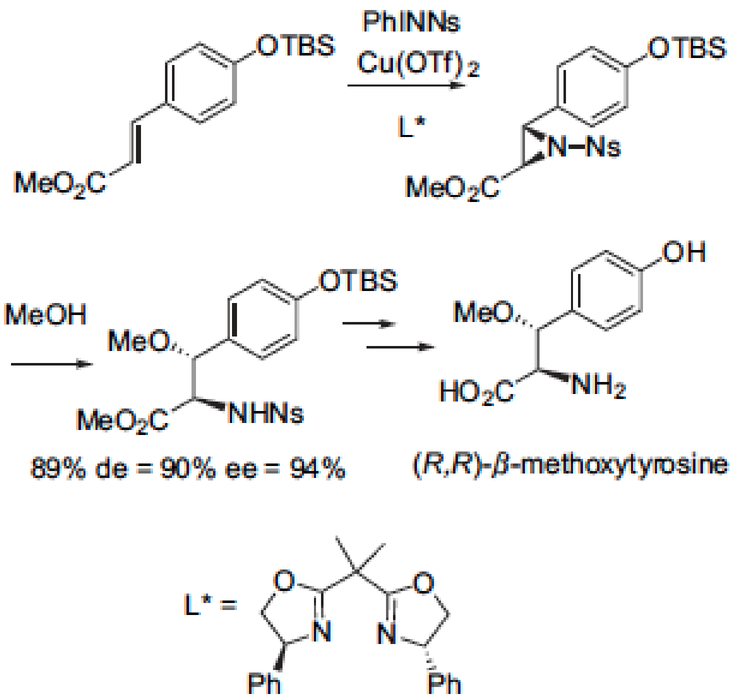
Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc*. **1993**, *115*, 5326.
Z. Li, R. W. Quan, E. N. Jacobsen, *J. Am. Chem. Soc*. **1995**, *117*, 5889.
J. B. Sweeney, *Chem. Soc. Rev*., **2002**, *31*, 247–258
P. Muller, C. Fruit, *Chem. Rev*. **2003**, *103*, 2905-2919

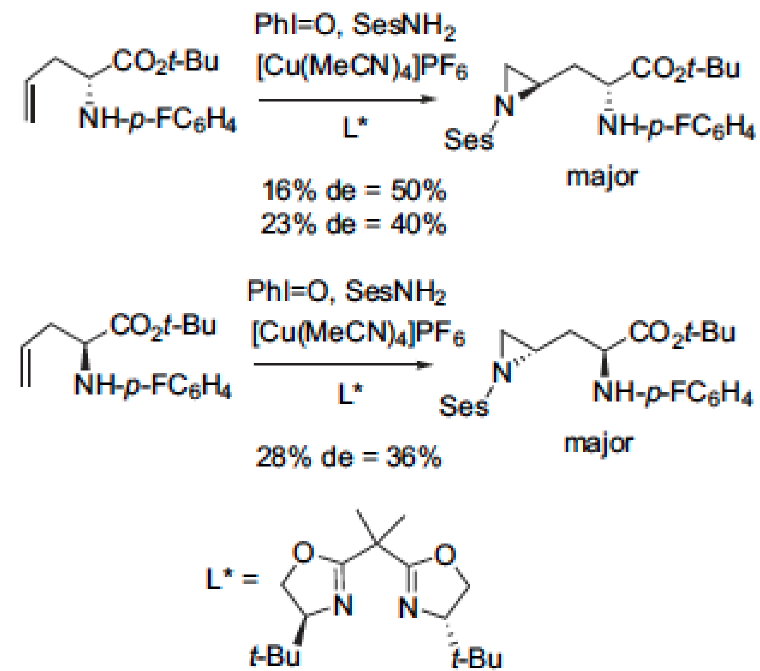
Proposed Mechanism (Jacobsen)



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.

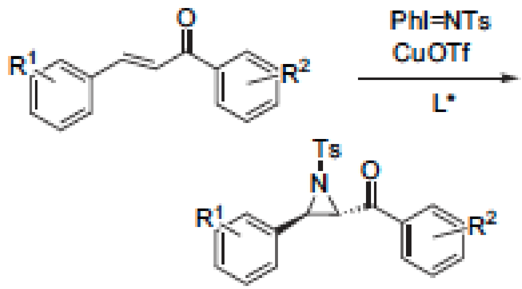
Cu-catalyzed aziridinations(nitrenes)

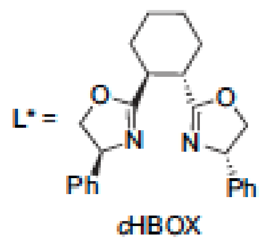


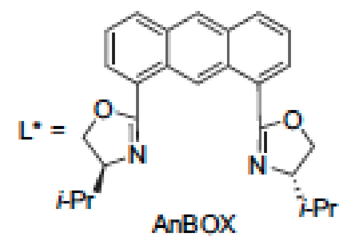


Cranfill, D. C.; Lipton, M. A. *Org. Lett*. **2007**, *9*, 3511–3513.
Leman, L.; Sanie` re, L.; Dauban, P.; Dodd, R. H. *ARKIVOC* **2003**, *vi*, 126–134.
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Cu-catalyzed aziridinations(ligands)





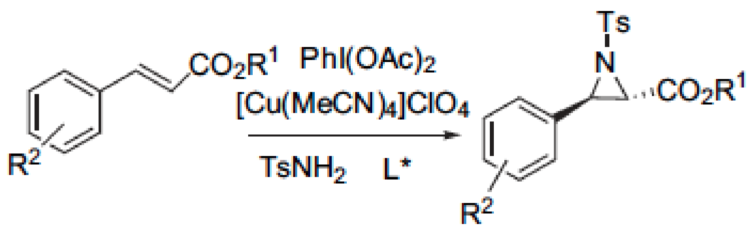


$R^1 = R^2$ = H: 56% ee = 91%
R^1 = *p*-Me, R^2 = H: 62% ee = 94%

$R^1 = R^2$ = H: 80% ee = 96%
R^1 = *p*-Me, R^2 = H: 86% ee = 98%

Ma, L.; Du, D.-M.; Xu, J. *J. Org. Chem*. **2005**, *70*, 10155–10158.
Xu, J.; Ma, L.; Jiao, P. *Chem. Commun*. **2004**, 1616–1617
Ma, L.; Jiao, P.; Zhang, Q.; Xu, J. *Tetrahedron: Asymmetry* **2005**, *16*, 3718–3734.
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Cu-catalyzed aziridinations(ligands)



R^1 = *t*-Bu, R^2 = H: 49% ee = 96%

R^1 = *t*-Bu, R^2 = 4-F: 55% ee = 95%

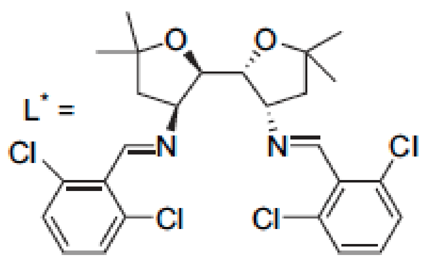
R^1 = *t*-Bu, R^2 = 4-Cl: 45% ee = 95%

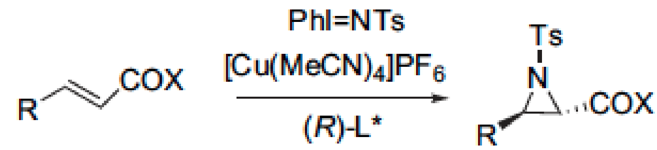
R^1 = *t*-Bu, R^2 = 4-Me: 39% ee = 88%

R^1 = *t*-Bu, R^2 = 4-MeO: 41% ee = 74%

R^1 = *t*-Bu, R^2 = 2-NO_2: 19% ee = 97%

L* =





from (*R*)-BINIM-DC:

R = *p*-ClC_6H_4, X = OMe: 82% ee = 81% (2*S*,3*R*)

R = 1-Naph, X = OMe: 74% ee = 77% (2*S*,3*R*)

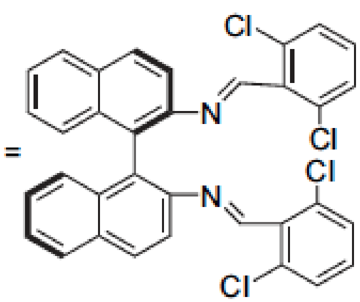
R = 2-Naph, X = OMe: 74% ee = 68% (2*S*,3*R*)

R = Ph, X = OPh: 48% ee = 89% (2*S*,3*R*)

R = Ph, X = O*t*-Bu: 57% ee = 98% (2*S*,3*R*)

R = X = Ph: 87% ee = 84% (2*S*,3*R*)

L* =

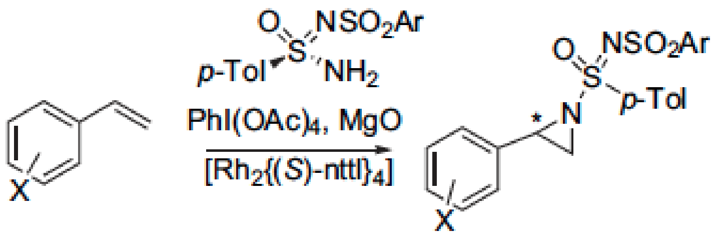


Wang, X.; Ding, K. *Chem.-Eur. J.* **2006**, *12*, 4568–4575.

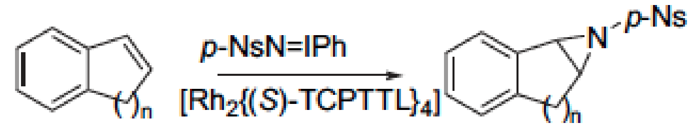
Suga, H.; Kakehi, A.; Ito, S.; Ibata, T.; Fudo, T.; Watanabe, Y.; Kinoshita, Y. *Bull. Chem. Soc. Jpn*. **2003**, *76*, 189–199

H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

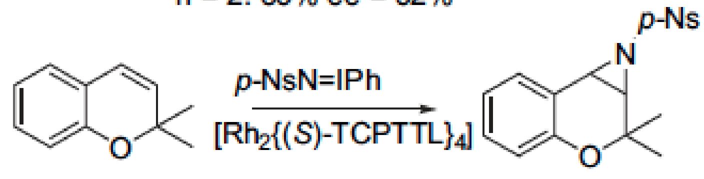
Rh-catalyzed aziridinations



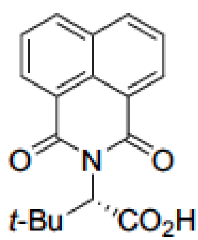
Ar = *p*-Tol, X = H: 63% ee = 80%
Ar = *p*-$NO_2C_6H_4$, X = H: 29% ee = 61%
Ar = *p*-Tol, X = 4-Br: 59% ee = 82%



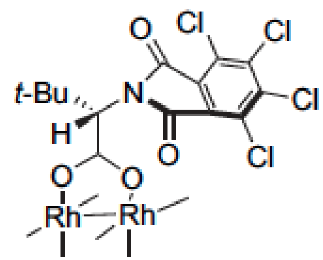
n = 1: 54% ee = 15%
n = 2: 83% ee = 32%



98% ee = 94%



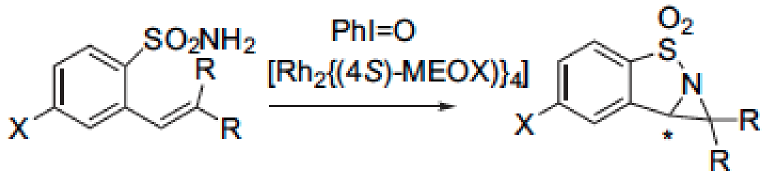
{(*S*)-nttl}



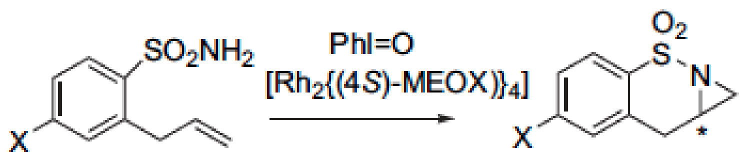
[Rh_2{(*S*)-TCPTTL}$_4$]

Fruit, C.; Robert-Peillard, F.; Bernardinelli, G.; Muller, P.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3484–3487.
Yamawaki, M.; Tanaka, M.; Abe, T.; Anada, M.; Hashimoto, S. *Heterocycles* **2007**, *72*, 709–721
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

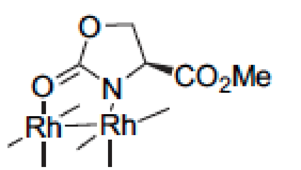
Rh-catalyzed intramolecular aziridinations



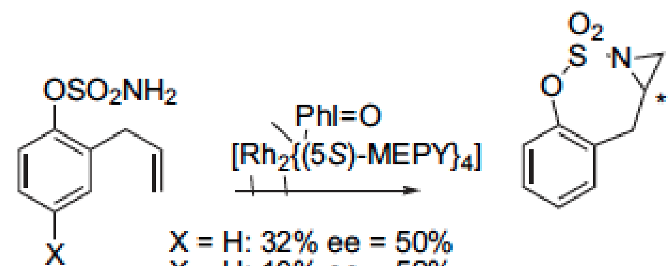
X = R = H: 90% ee = 76%
X = Me, R = H: 71% ee = 74%
X = Br, R = H: 74% ee = 75%
X = H, R = Me: 81% ee = 64%
X = Cl, R: 95% ee = 63%



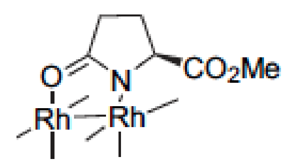
X = Me: 73% ee = 55%
X = Cl: 68% ee = 67%
X = H: 71% ee = 57%



[Rh_2{(4*S*)-MEOX)}$_4$]



X = H: 32% ee = 50%
X = H: 10% ee = 52%
X = F: 63% ee = 17%
X = OMe: 18% ee = 39%



[Rh_2{(5*S*)-MEPY}$_4$]

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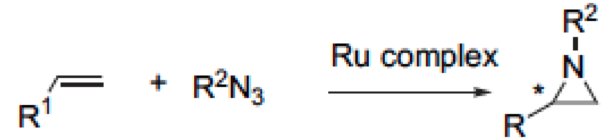
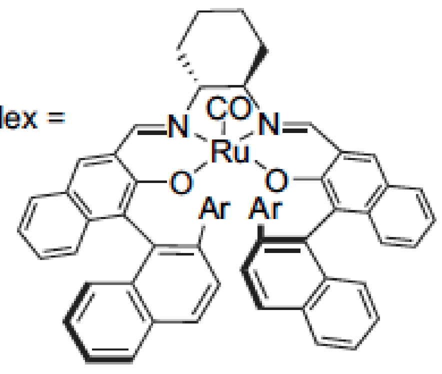
Hayes, C. J.; Beavis, P. W.; Humphries, L. A. *Chem. Commun*. **2006**, 4501–4502.
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Ru-catalyzed aziridinations



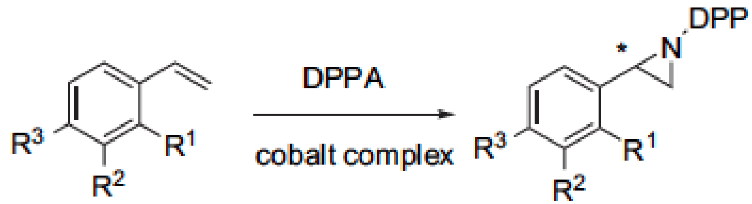
R^1 = Ph, R^2 = *p*-Ns, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
90% ee = 87%
R^1 = *p*-BrC_6H_4, R^2 = *p*-Ns, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
93% ee = 83%

Ru complex =



Kawabata, H.; Omura, K.; Katsuki, T. *Tetrahedron Lett*. **2006**, *47*, 1571–1574
Kawabata, H.; Omura, K.; Uchida, T.; Katsuki, T. *Chem. Asian. J.* **2007**, *2*, 248–256
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Co-catalyzed aziridinations



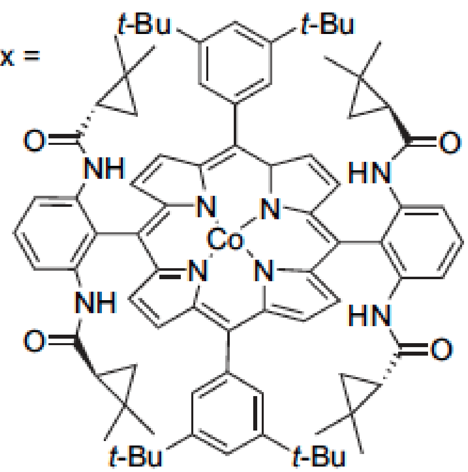
$R^1 = R^2 = R^3 = H$: 88% ee = 37%

$R^1 = Me$, $R^2 = R^3 = H$: 35% ee = 46%

$R^1 = R^3 = H$, $R^2 = Me$: 52% ee = 44%

$R^1 = R^2 = H$, $R^3 = Me$: 58% ee = 37%

cobalt complex =



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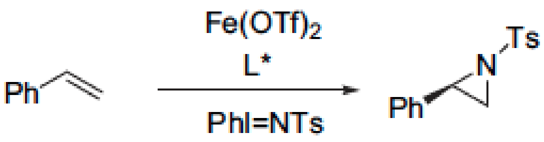
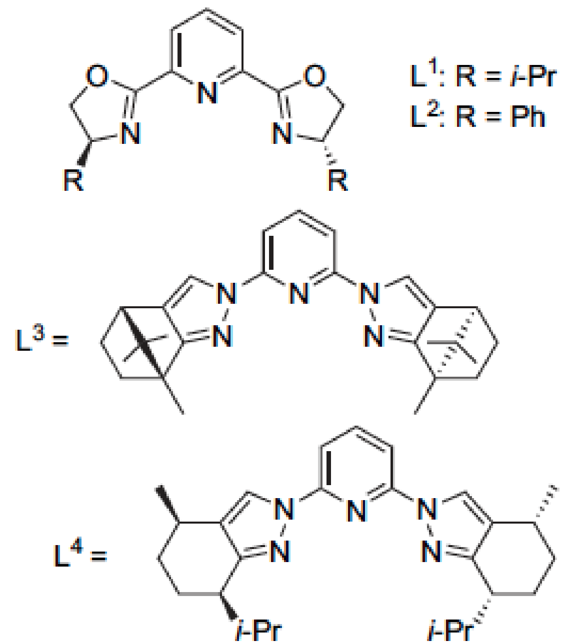
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Fe-catalyzed aziridinations



L* = L[1]: 72% ee = 40%
L* = L[2]: 51% ee = 25%
L* = L[3]: 60% ee = 20%
L* = L[4]: 40% ee = 6%



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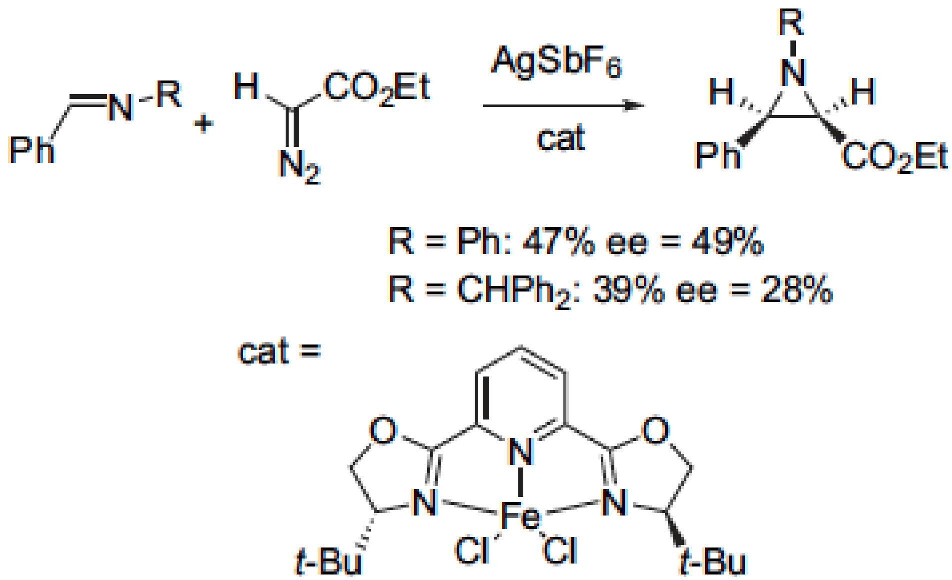
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Carbene methods



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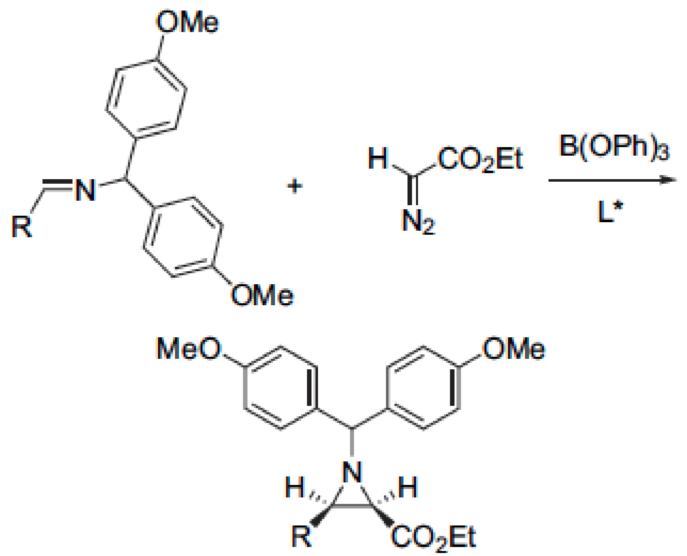
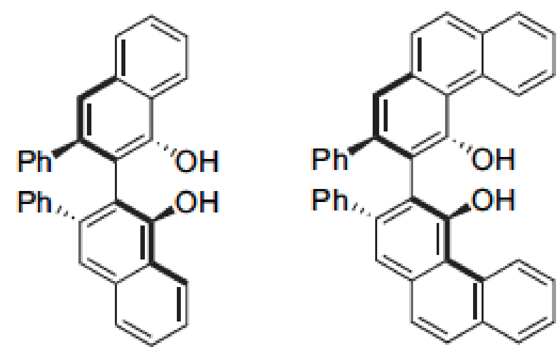
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Carbene methods



with L* = VAPOL:
R = Cy: 86% *cis:trans* = 97:3 ee = 84%
R = *t*-Bu: 70% *cis:trans* = 98:2 ee = 75%

with L* = VANOL:
R = Cy: 69% *cis:trans* = 98:2 ee = 77%
R = *t*-Bu: 77% *cis:trans* = 98:2 ee = 87%



(*S*)-VANOL (*S*)-VAPOL

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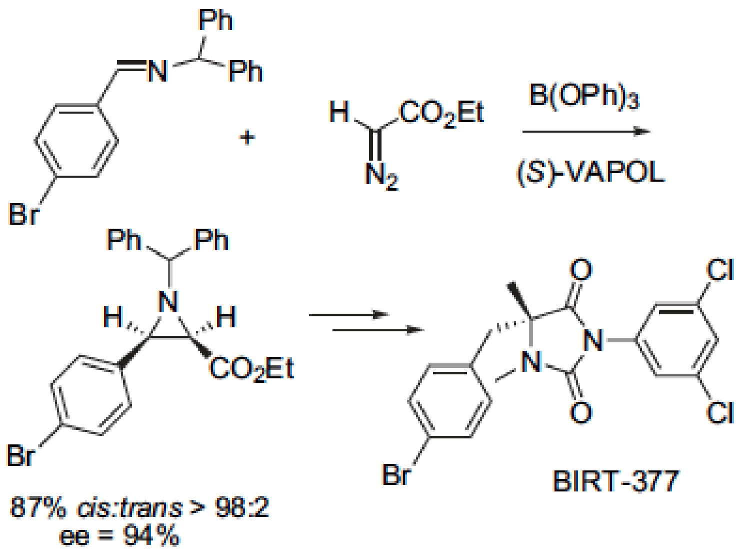
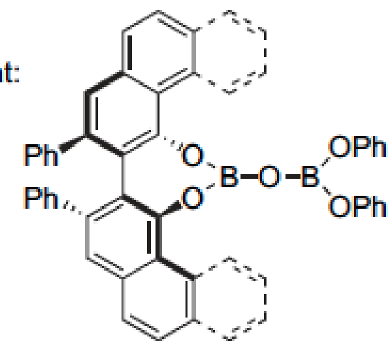
Zhang, Y.; Desai, A.; Lu, Z.; Hu, G.; Ding, Z.;Wulff,W. D. *Chem.-Eur. J*. **2008**, *14*, 3785–3803.
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Carbene methods

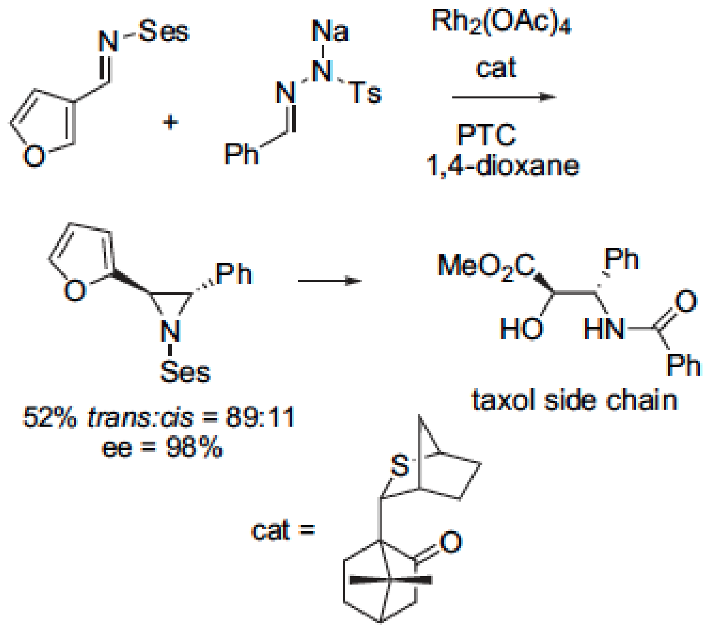


active cat:



Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc*. **2007**, *129*, 7185–7194
Zhang, Y.; Desai, A.; Lu, Z.; Hu, G.; Ding, Z.;Wulff,W. D. *Chem.-Eur. J*. **2008**, *14*, 3785–3803.
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Sulfur ylide-mediated methods



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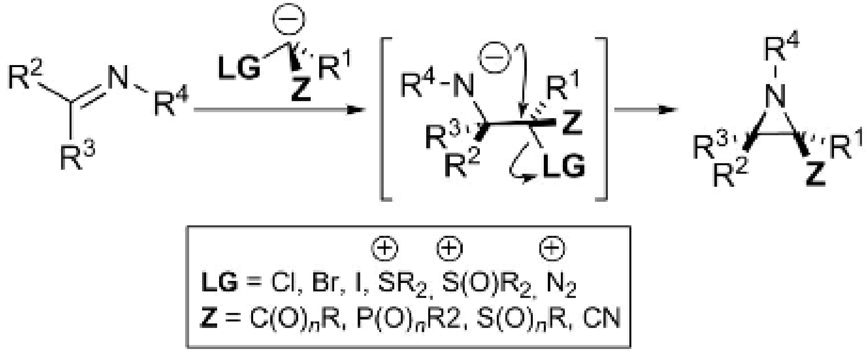
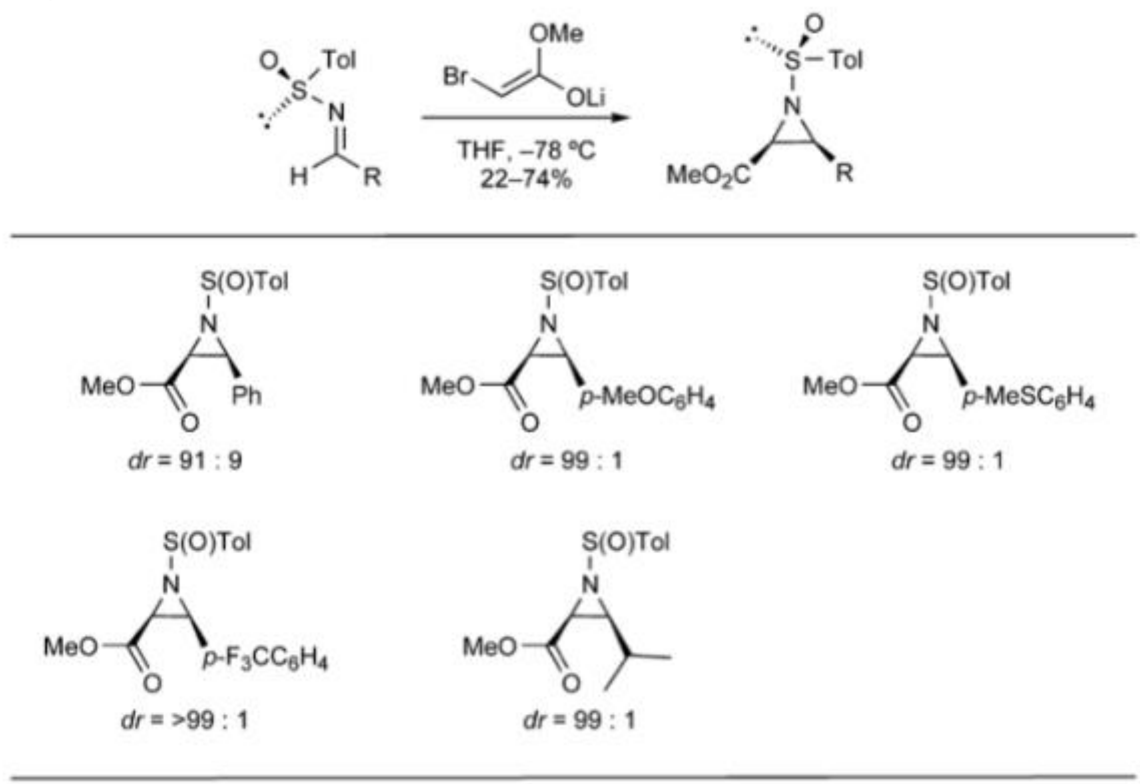
H. Pellissier, *Tetrahedron*, **2010**, *66*, 1509-1555

Aza-Darzens Reaction





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J. B. Sweeney, *Eur. J. Org. Chem.* **2009**, 4911–4919

Conclusion

- Aziridines leads to building blocks for heterocycle chemistry and natural products.

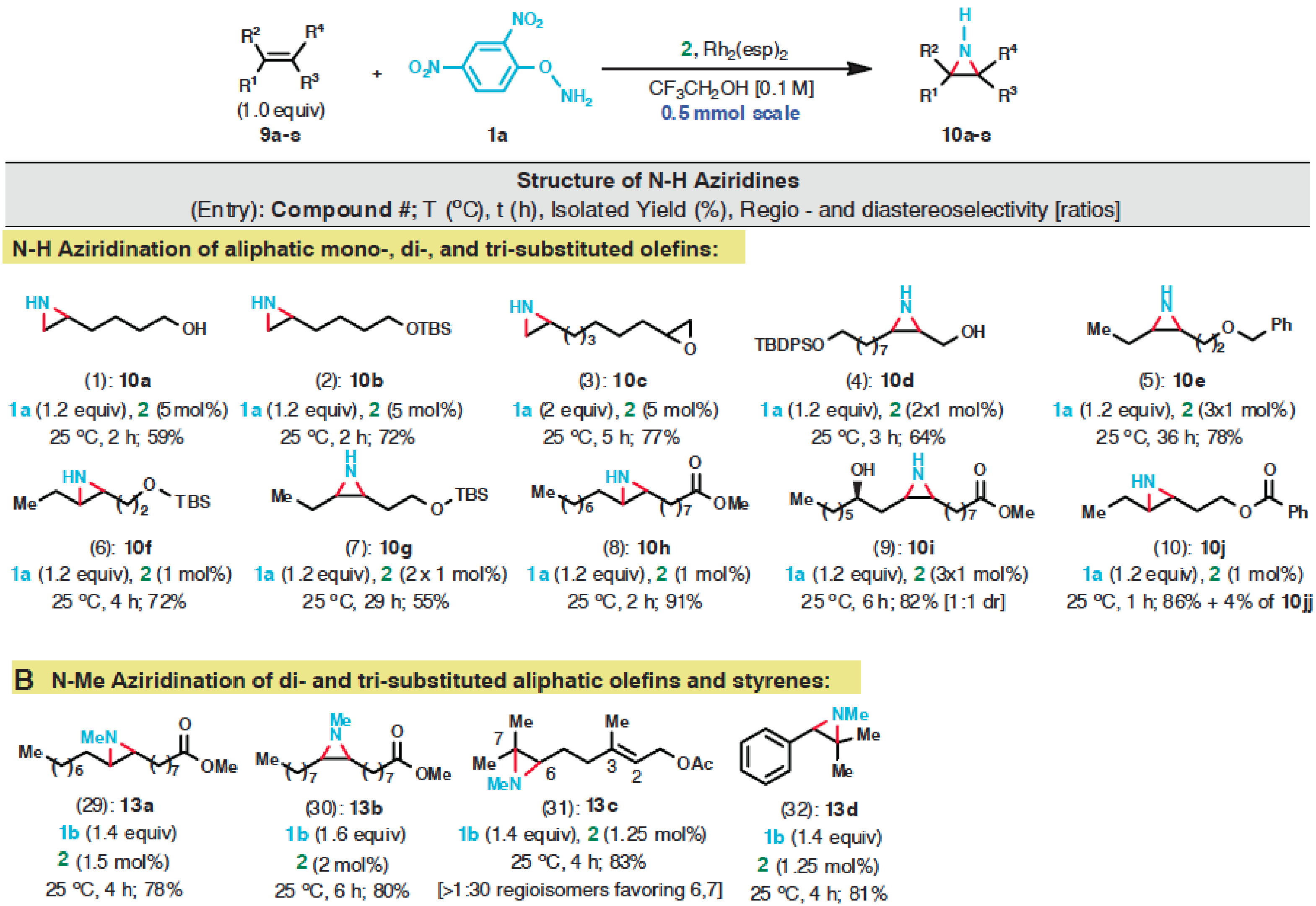
- The direct aziridination of olefins is more difficult than the corresponding epoxidation.

- Most of these methods rely either on the transfer of substituted nitrenes to the C=C bond of olefins or the transfer of substituted carbenes to the C=N bond of imines.

- Normally, the result is an aziridine bearing a strongly electron-withdrawing N-protecting group (e.g., Ts:para-toluenesulfonyl; Ns: para-nitrophenylsulfonyl).

- In addition, the high reactivity of N-protected nitrenes might give rise to nonproductive allylic C-H amination products, as well as the loss of stereospecificity.

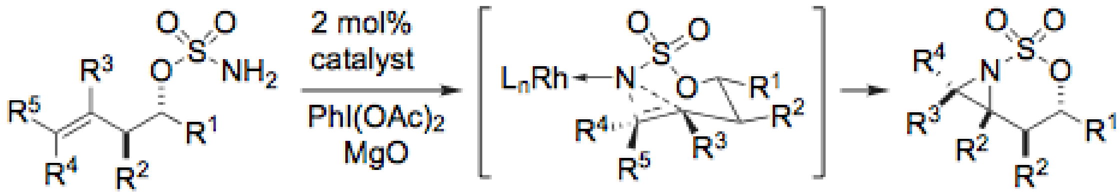
Why

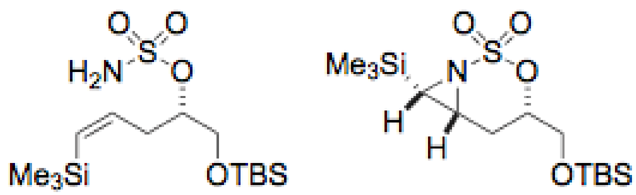


J. L. Jat, M. P. Paudyal, H. Gao, Q. –L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kürti, John R. Falck
SCIENCE, **2014**, *343*, 61

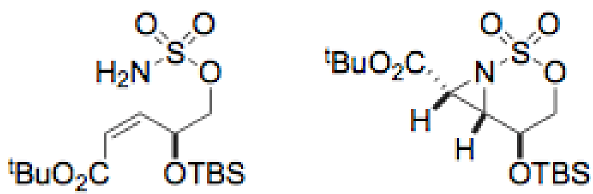
Thank you

Quiz !



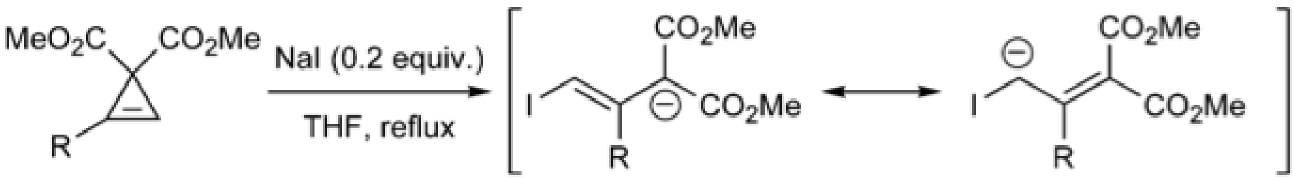


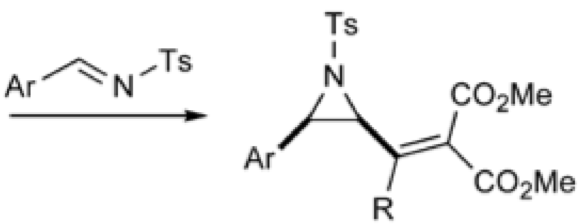
15:1 69

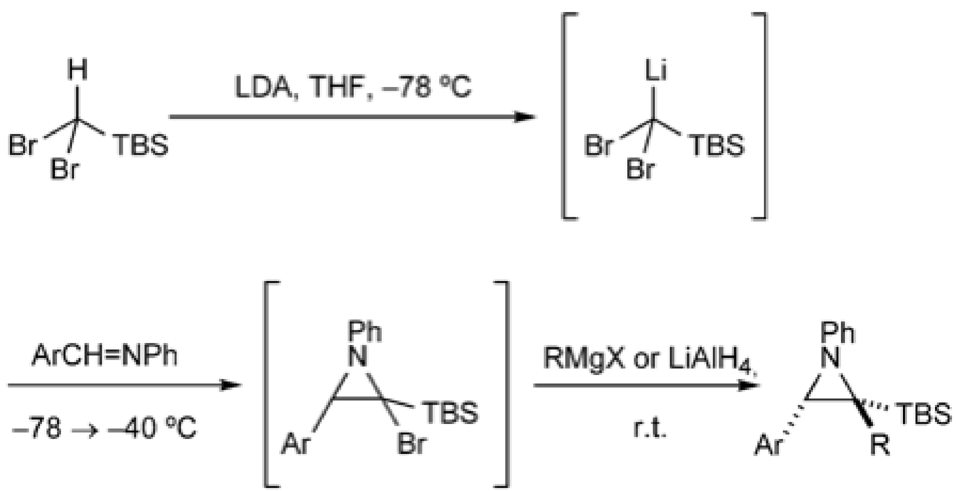


20:1 87

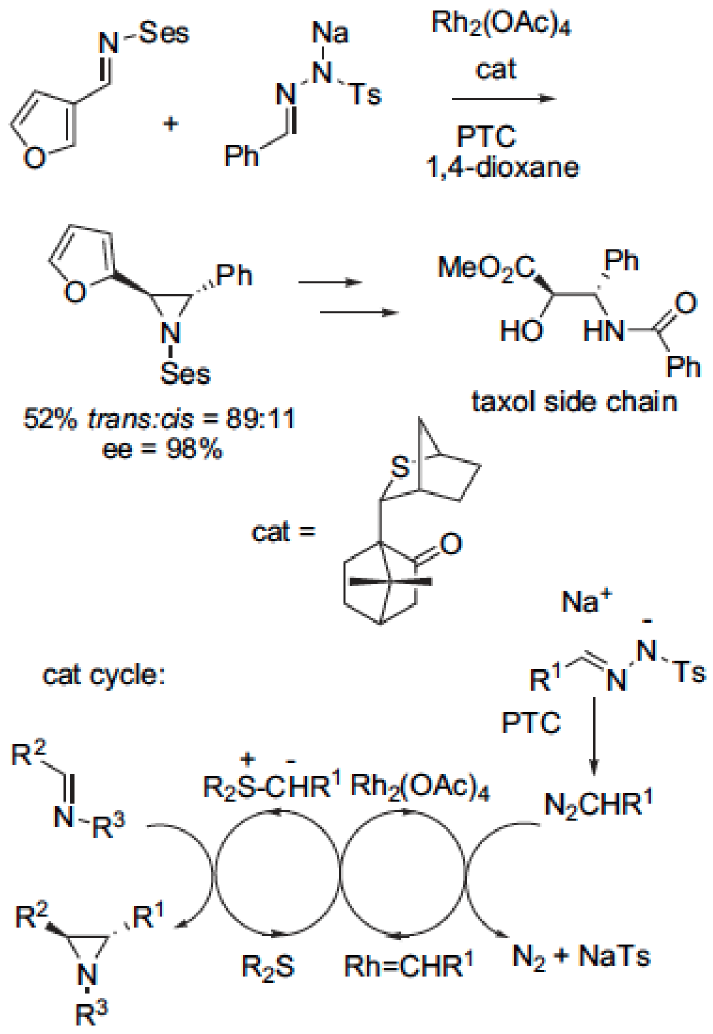
Quiz !


MeO2C
CO2Me
R
NaI (0.2 equiv.)
THF, reflux
CO2Me
I
R
CO2Me
CO2Me
I
R
CO2Me


Ar
N
Ts
Ts
N
Ar
R
CO2Me
CO2Me


H
Br
Br
TBS
LDA, THF, –78 °C
Li
Br
Br
TBS
ArCH=NPh
–78 → –40 °C
Ph
N
Ar
Br
TBS
RMgX or LiAlH4,
r.t.
Ph
N
Ar
R
TBS

Quiz !


N-Ses
O
+
Na
N
N
Ts
Ph
Rh2(OAc)4
cat
PTC
1,4-dioxane
O
Ph
N
Ses
MeO2C
Ph
O
HO
HN
Ph
taxol side chain
52% trans:cis = 89:11
ee = 98%
cat =
S
O
Na+
-
N
Ts
R1
N
PTC
cat cycle:
R2
N-R3
R2S-CHR1
Rh2(OAc)4
N2CHR1
R2
R1
N
R3
R2S
Rh=CHR1
N2 + NaTs