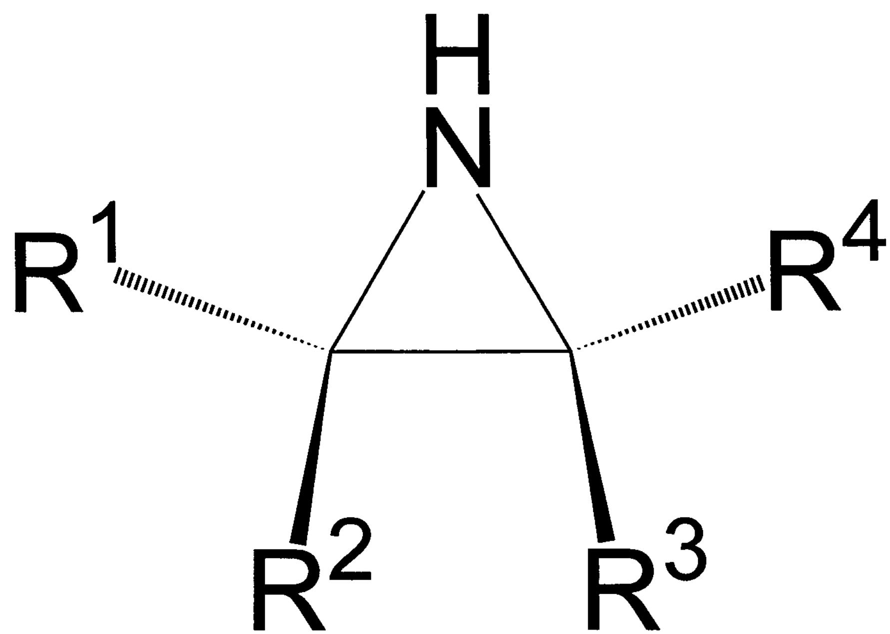
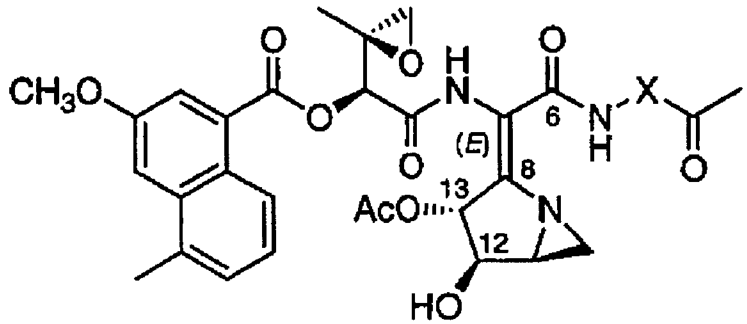
Christy
2-13-01

Catalytic asymmetric aziridination



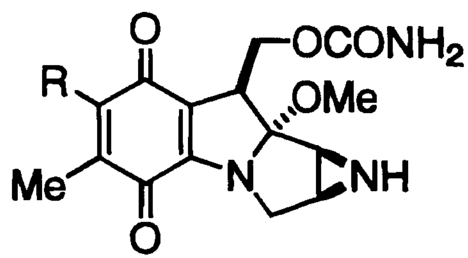
Naturally occuring aziridines



Azinomycin A (X = CH_2) **1a**
Azinomycin B (X = C=CHOH) **1b**

Antitumor activity

J. Am. Chem. Soc. **1999** 9088



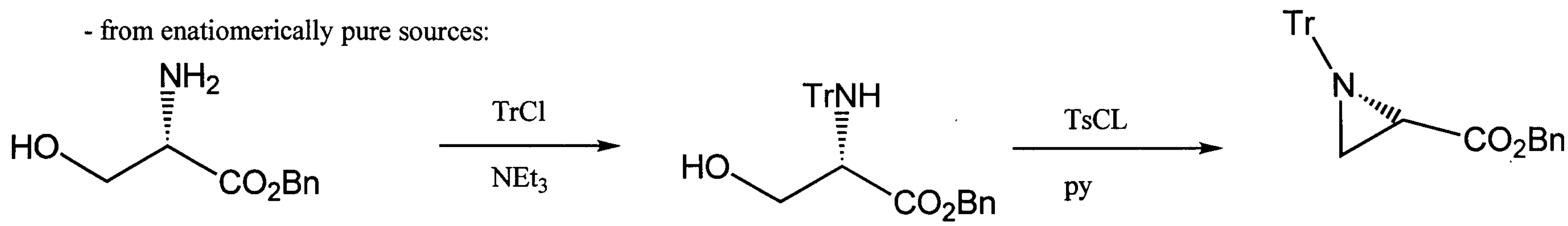
4 R = NH_2 Mitomycin C
5 R = CH_3O Mitomycin A

antibiotic and antitumor activity

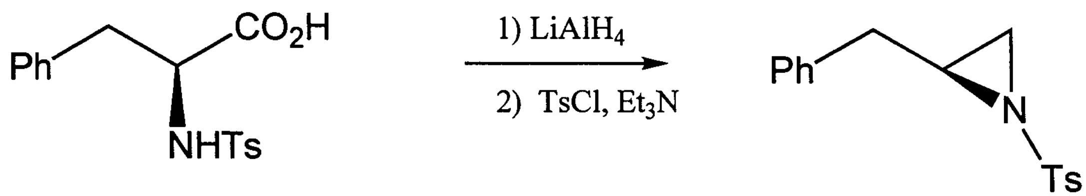
J. Org. Chem. **1999** 8350

Non-catalytic synthetic methods of chiral aziridines

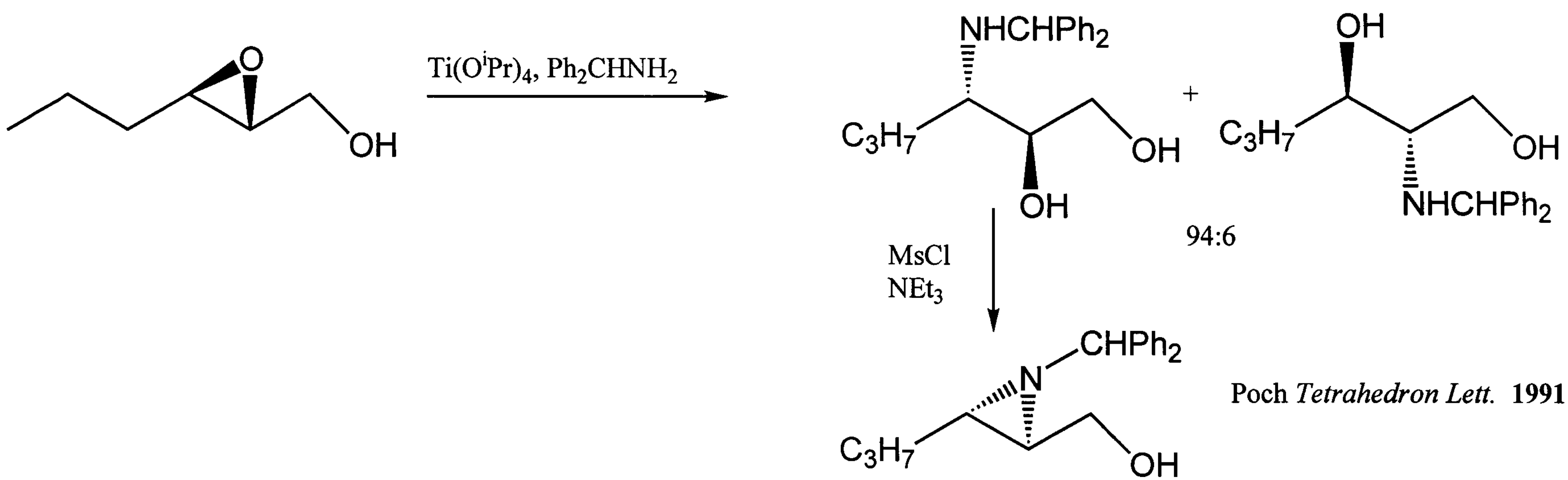
- from enatiomerically pure sources:



Nakajima *Bull. Chem. Soc. Jpn.* **1978** 1577.



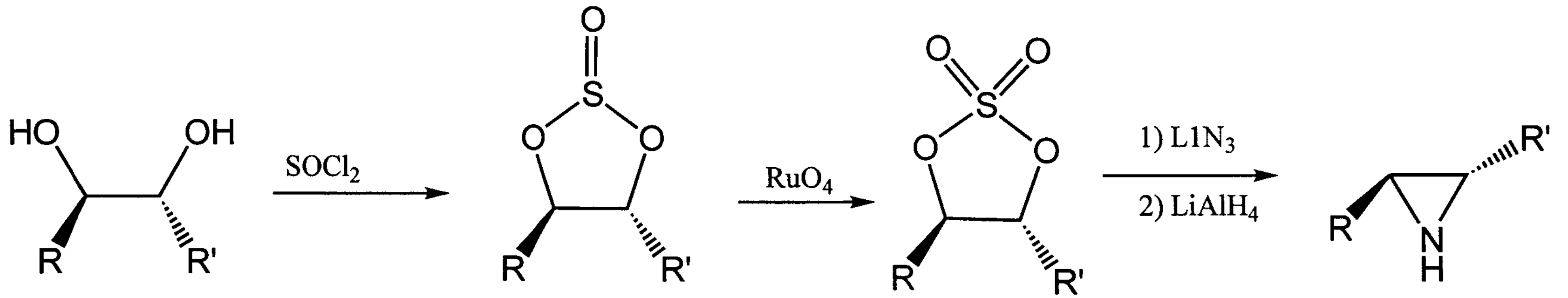
Overman *Tetrahedron* **1988** 3919



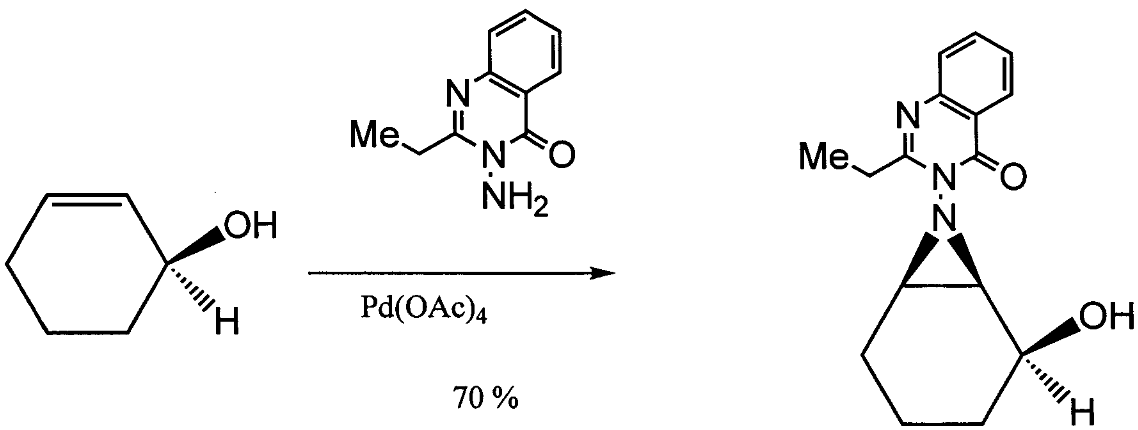
Poch *Tetrahedron Lett.* **1991** 6935

Non-catalytic synthetic methods of chiral aziridines

- from enatiomerically pure sources:

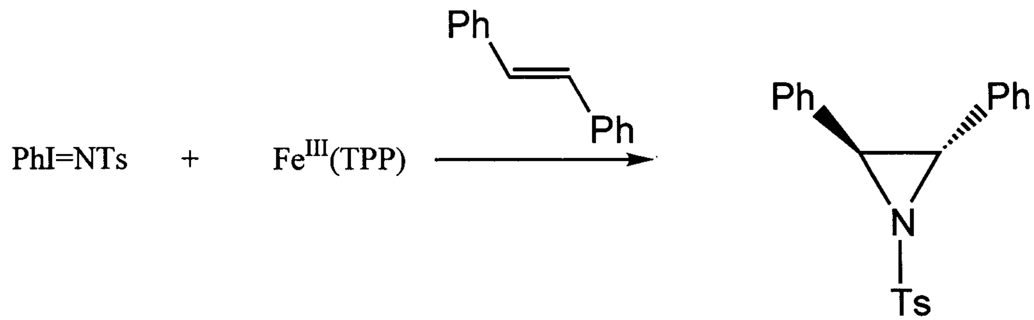


Sharpless *Tetrahedron Lett.* **1989** 2623



Atkinson *J Chem Soc Perkin Trans I* **1989** 1515

First catalytic Aziridination

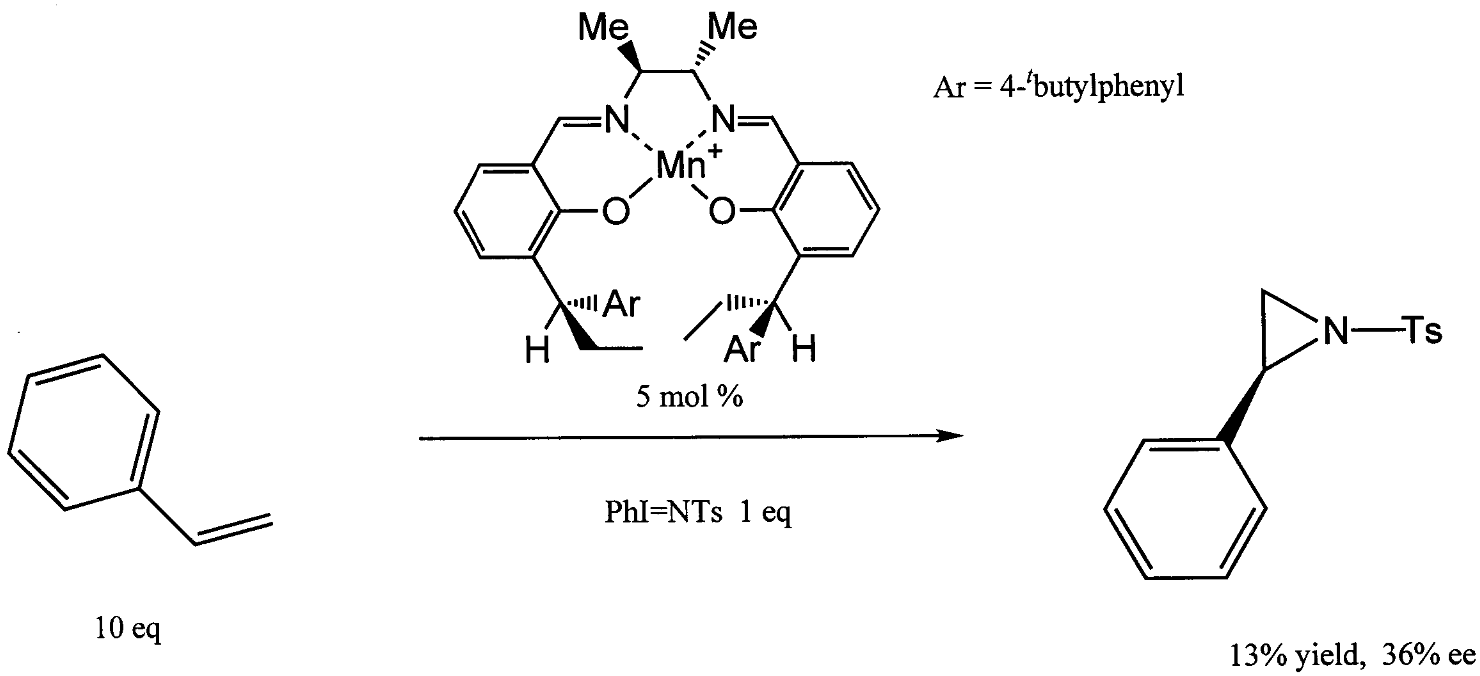


Alkene	Product	Yield (%) Fe(TPP)Cl	Mn(TPP)Cl
styrene	*N*-Tosyl-2-phenlaziridine	55	80
cis-stilbene	*trans*-*N*-Tosyl-2,3-diphenlaziridine	37	20
trans-stilbene	*trans*-*N*-Tosyl-2,3-diphenlaziridine	32	16
1,1-Diphenylethylene	*trans*-*N*-Tosyl-2,2-diphenlaziridine	21	56

Nitrene addintion not stereospecific

Mansuy *J Chem Soc Chem Commun* **1984** 1161

First asymmetric Mn^{III} cat aziridination

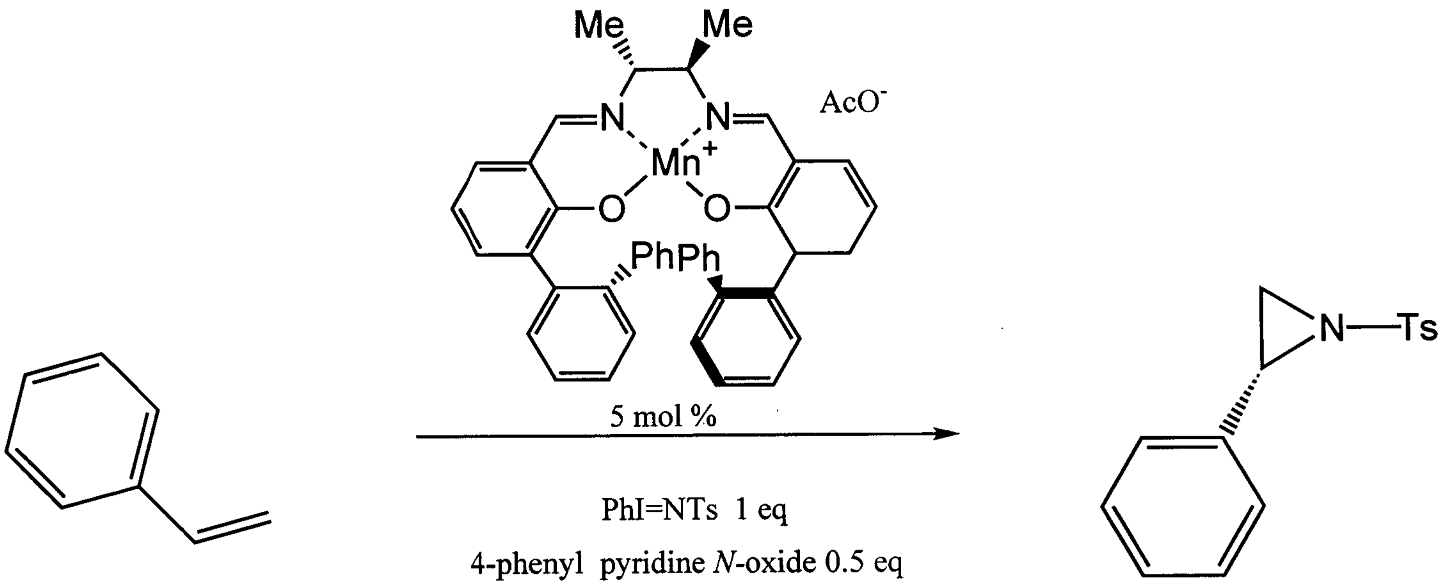


when pyridine *N*-oxide added in 50 mol%
yield was decreased to 9% but enantio selectivity
increased to afford 61% ee

A variety of ligands were tried but all afford poor yields as well as poor ee's

Katsuki *Synlett* **1993** 469

Further study of asymmetric Mn^{III} cat aziridination



5 eq

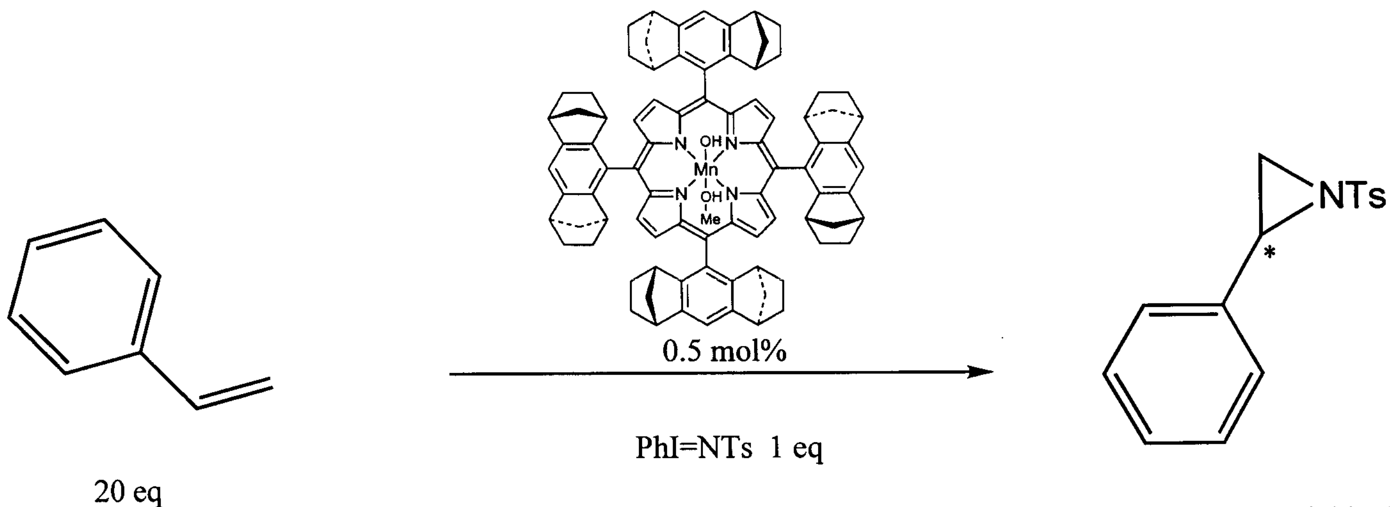
76% yield, 94% ee

substrate	yield	ee
p-chlorostyrene	70	86
p-methylstyrene	75	81

All other ligands tried gave much poorer ee's and yields

Katsuki *Tetrahedron Lett.* **1996** 9245

D_4-Mn^{III} porphyrin catalyst for aziridination



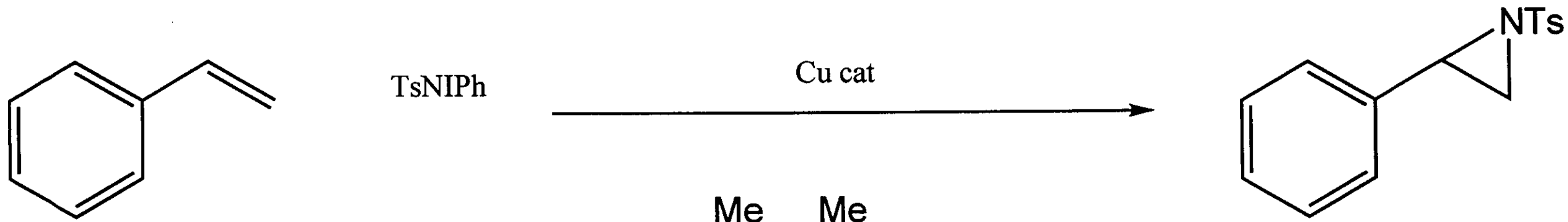
71% yield, 49% ee

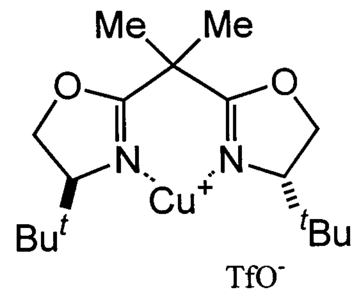
substrate	yield	ee	Turnover
p-chlorostyrene	43	45	86
p-methylstyrene	66	44	132
m-chlorostyrene	49	49	98
o-bromostyrene	44	62	88

Evidence of Mn^{IV} reactive intermediate observed by UV-VIS 433 nm

Che *Chem Commun.* **1997** 2373

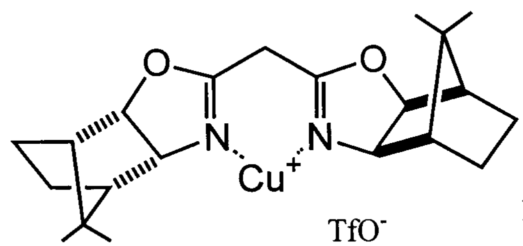
Cu catalyzed asymmetric aziridination





Evans *J Am Chem Soc* **1991** 726

97%
61% ee



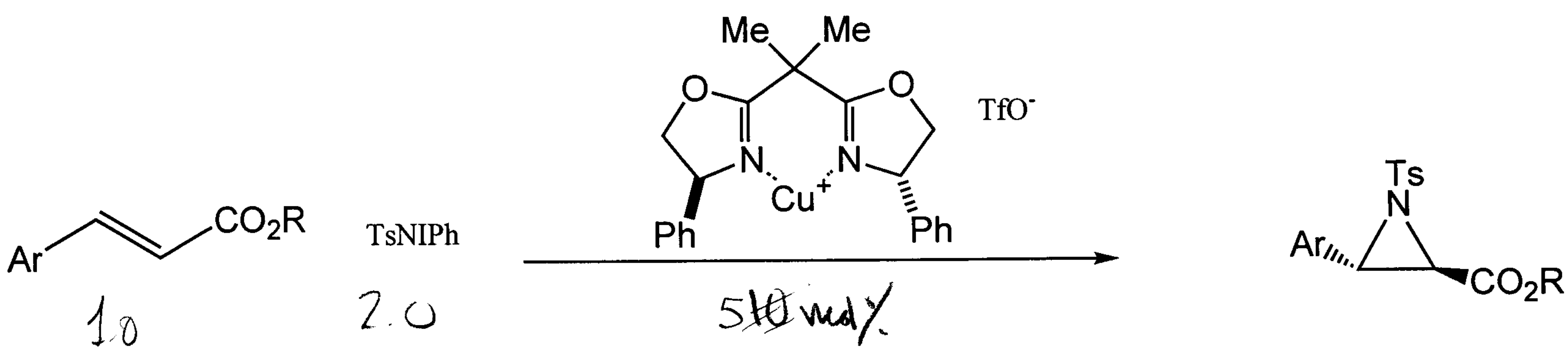
Masamune *Tetrahedromn Lett.* **1991** 7373

1 mol%

91%
88% ee

Both examples were the single aziridination example in papers on cyclopropanation

Cu catalyzed asymmetric aziridination



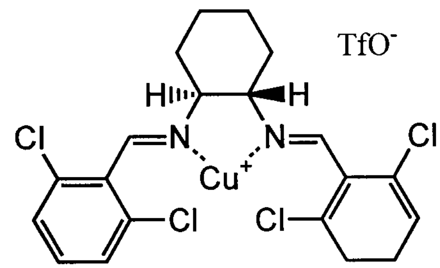
Ar	R	solvent	time	yield %	ee, %
Ph	Me	MeCN	24h (21°C)	21	70
"	"	C_6H_6	"	63	94
"	Ph	"	"	64	97
"	tBu	"	"	60	96
(β)Nap	Me	"	24h (18°C)	73	96
(α)Nap	Me	"	24h (21°C)	76	95
β-methylstyrene		MeCN	3d (-20°C)	62	70

First effective Cu catalyzed aziridination

Evans *J Am Chem Soc* **1993** 5329

Cu catalyzed asymmetric aziridination

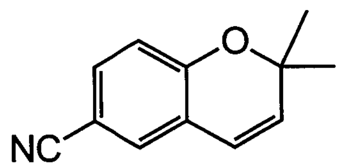
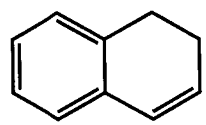
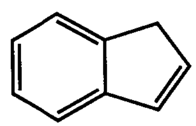
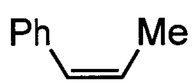
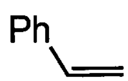
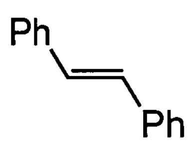
substrate	PhI=NTs
1 eq	1.5 eq



10 mol%

CH_2Cl_2, -78°C

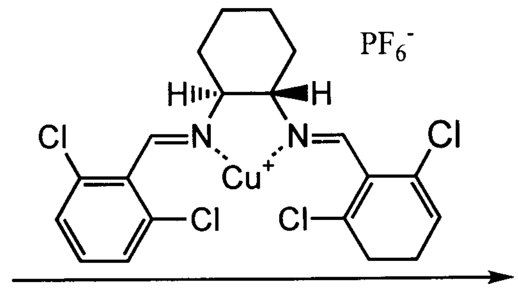
Chiral aziridine

	yield	ee
	75	>98
	70	87
	50	58
	79 (*cis:trans;* 3:1)	67(*cis*) 81(*trans*)
	79	66
	nd	30

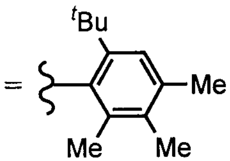
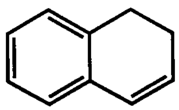
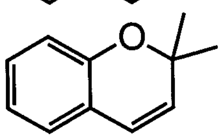
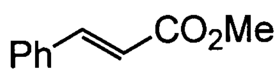
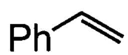
Jacobsen *J Am Chem Soc* **1993** 5326

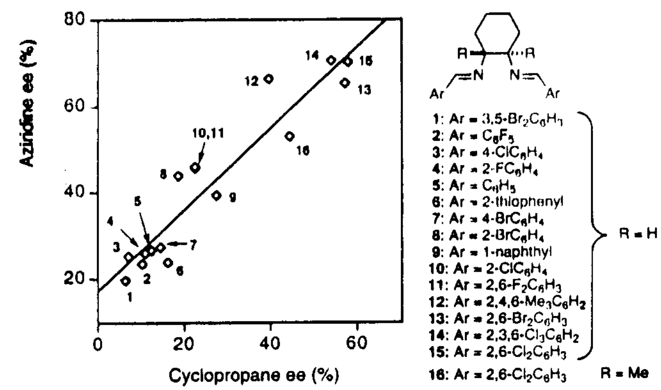
Mechanism of Cu catalyzed asymmetric aziridination

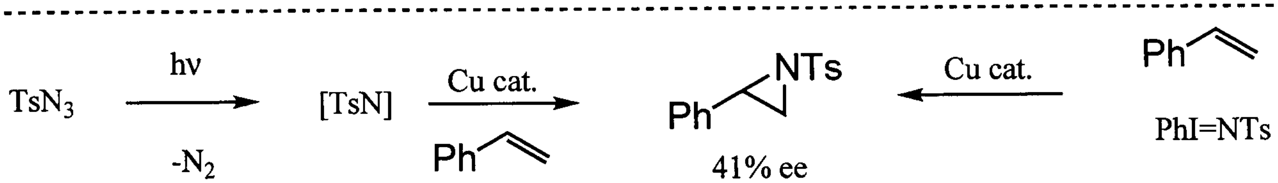
alkene ArI=NTs



aziridine

Alkene	Ar = Ph	Ar = 
	ee, %	
	62	63
	85	84
	71	70
	42	43

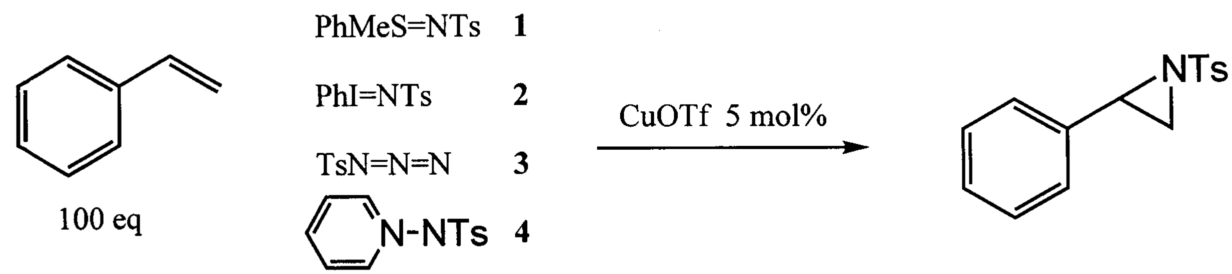




Results support Cu-nitrene intermediate

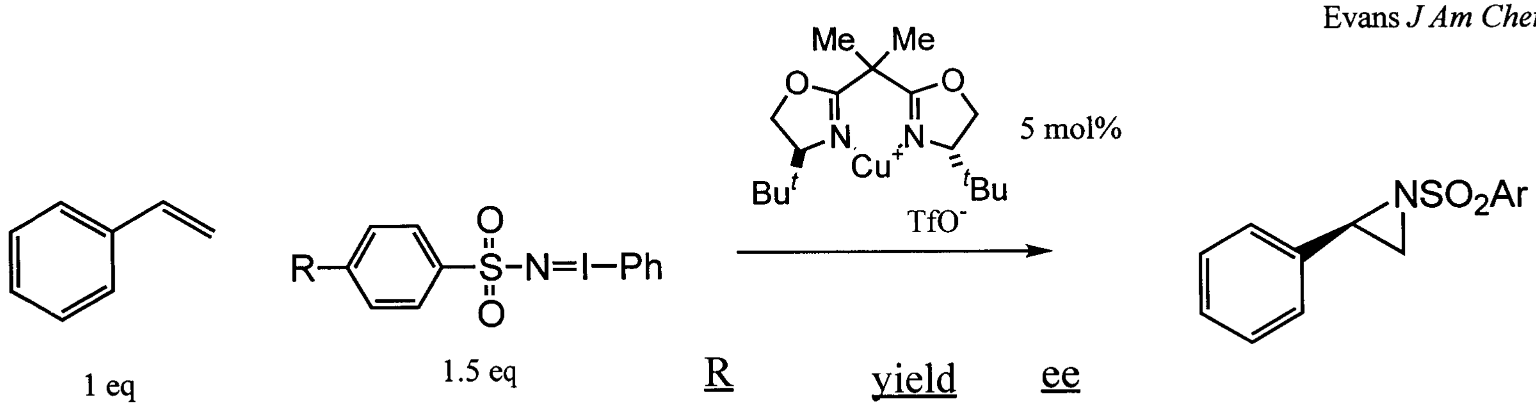
Jacobsen *J Am Chem Soc* **1995** 5889

Nitrene sources for Cu catalyzed asymmetric aziridination



1	NR
2	96% (< 5 min @ 25°C)
3	12% (12 h 65°C)
4	NR

Evans *J Am Chem Soc* **1994** 2742

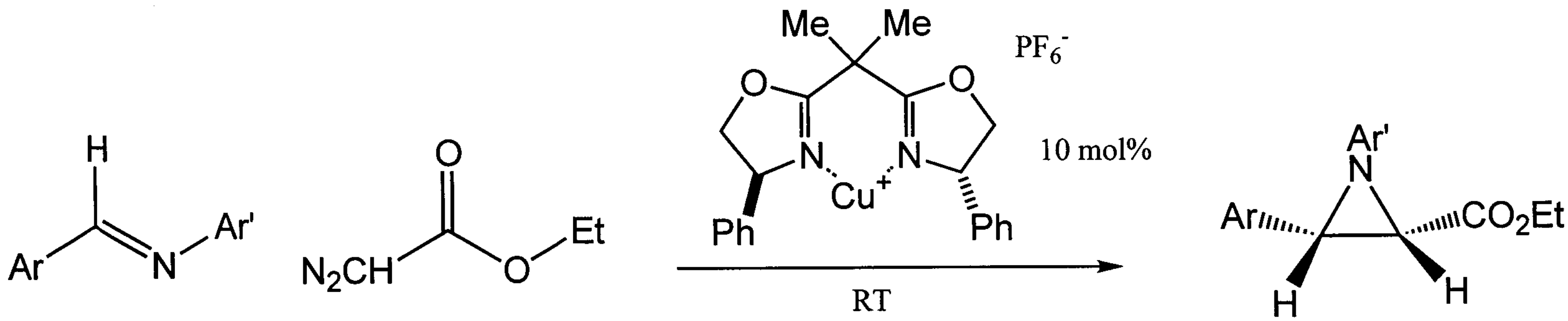


R	yield	ee
Me	77	52
NO_2	94	66
OMe	86	78
F	91	50
CF_3	89	43

Across survey of other olefin substrates *p*-NO_2 substituent gives highest yield and often highest ee

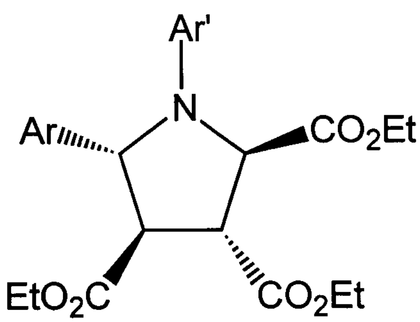
Sodergren *Tetrahedren: Asym* **1997** 3563

Carbene transfer to imines



1 eq   1 eq (over 12.5 h)

Ar	Ar'	*cis/trans*	ee(*cis*)/ee(*trans*)	yield
p-MeC$_0$H$_4$	Ph	9	44/26	17
Ph	*p*-MeOC$_6$H$_4$	9	67/32	23
Ph	*p*-ClC$_6$H$_4$	4	49/22	34

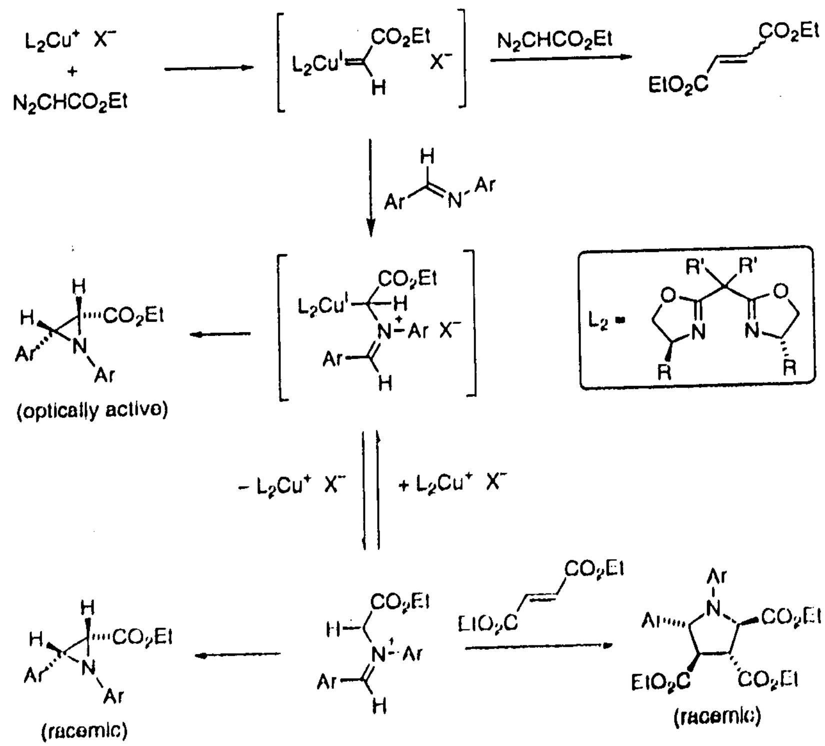


-pyrolidine also formed in all three reactions but at less than 5%

-addition of 2eq dimethylfumarate lead to formation of 3,4-bis(carboxymethyl)pyrolidine exclusively

Jacobsen *Angew Chem Int Ed Engl* **1995** 676

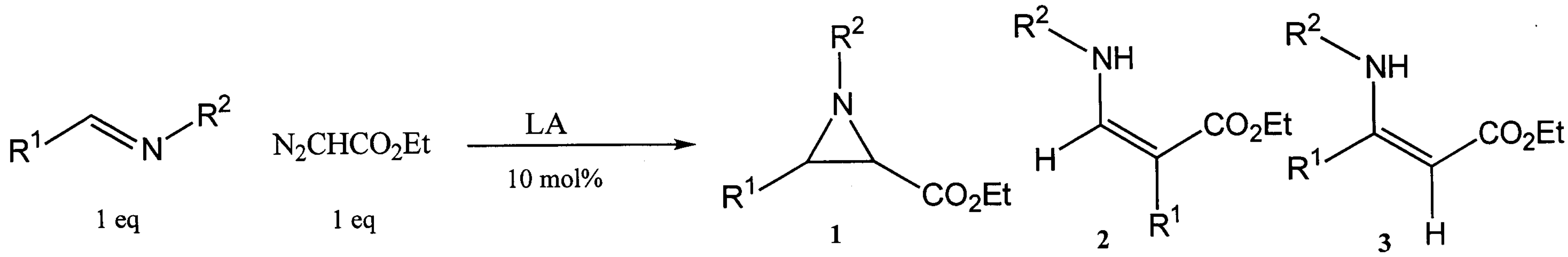
Proposed mechanism for aziridination



Azomethine ylide is the proposed intermidiat that either closes to the aziridine or form the pyrolidine in a [3+2] cycloaddition

Jacobsen *Angew Chem Int Ed Engl* **1995** 676

Lewis acids catalyzed carbene transfer to imine

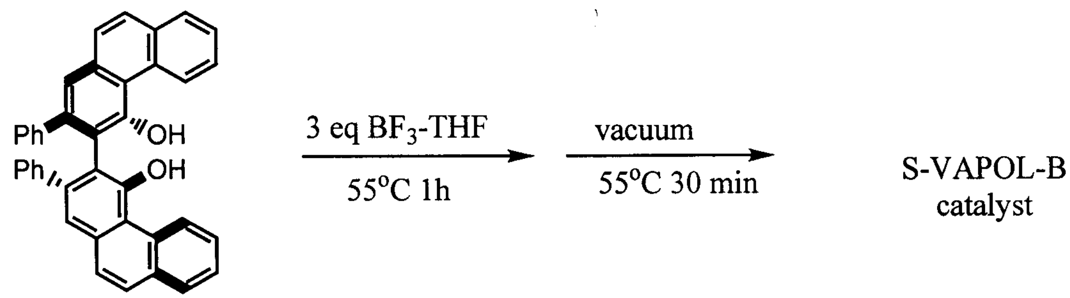


R^1	R^2	LA	solvent	time	**1:(2+3)**	*cis:trans*	yield **1**
Ph	Ph	BF_3	hexane	15 min	94:6	93:7	93
^{t}Bu	"	"	Et_2O	15 min	55:45	38:62	61
Ph	"	$AlCl_3$	CH_2Cl_2	2 h	65:35	98:2	56
^{t}Bu	"	"	Et_2O	15 min	88:12	28:72	58
Ph	"	$TiCl_4$	Et_2O	48 h	63:37	89:11	62
^{t}Bu	"	"	CH_2Cl_2	2 h	90:10	48:52	62

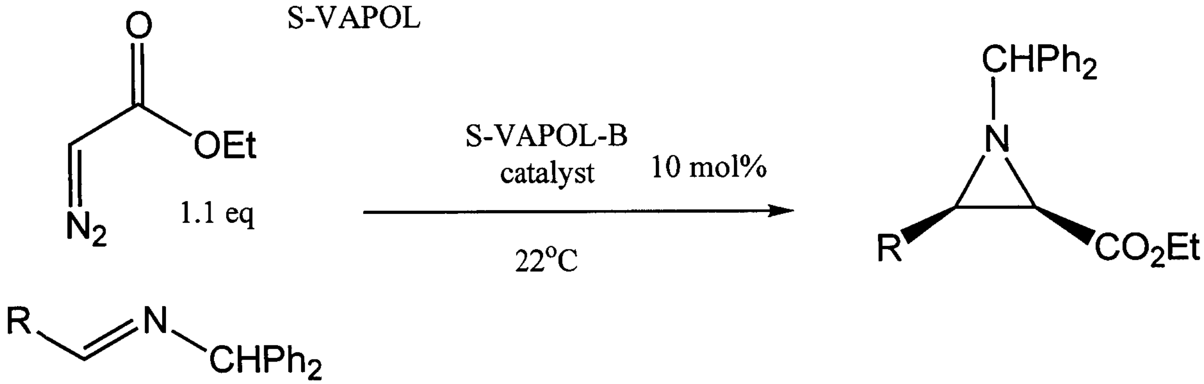
Lewis acids can effectively catalyze aziridination

Templeton *J Org Chem* **1996** 8358

Lewis acids catalysis of asymmetric carbene transfer to imine



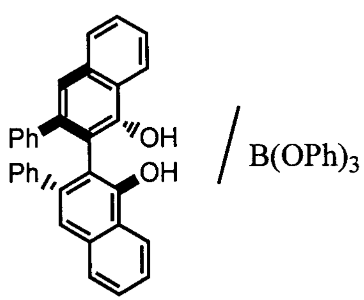
S-VAPOL



1 eq

With R varied between a variety of aryl groups and alkyl groups yields between 55 and 77 with ee's 91 to 97

Wulff *J Am Chem Soc* **1999** 5099

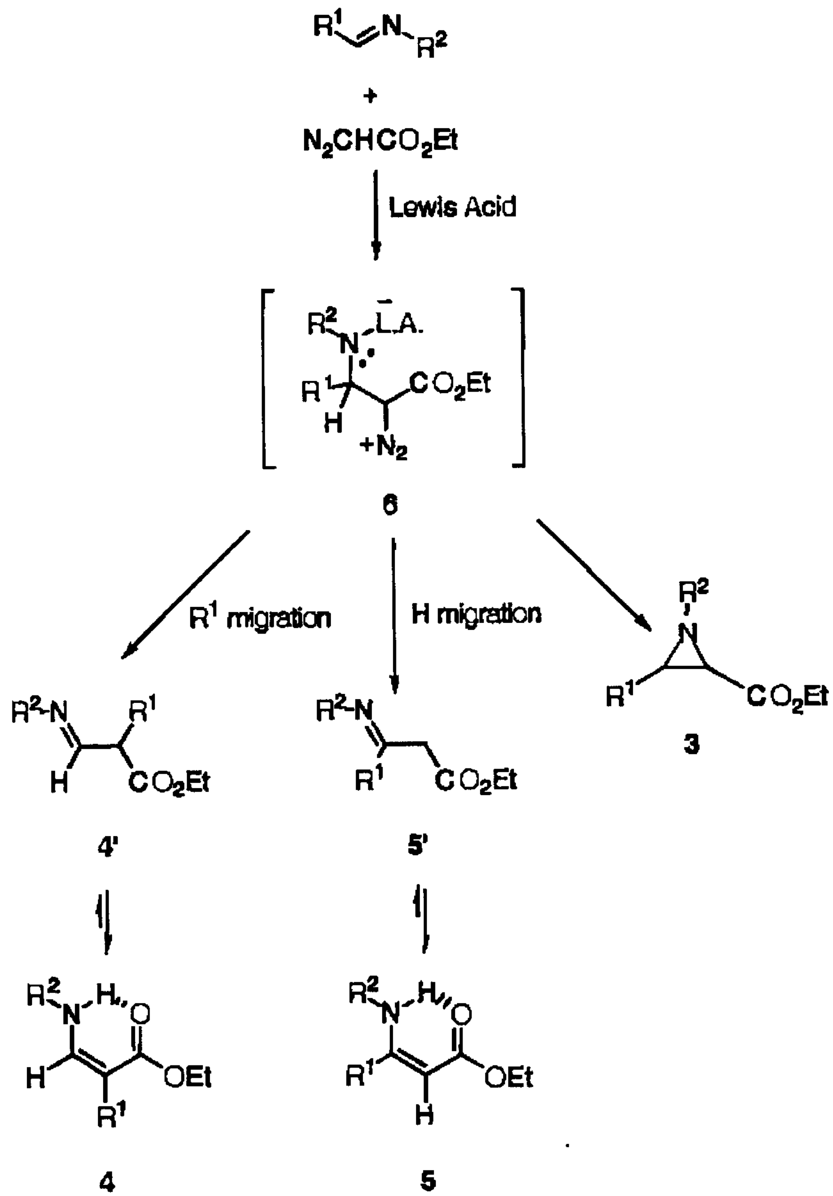


S-VANOL

S-VANOL-B catatlyst can slightly improve yields and ee's over corresponding S-VAPOL-B cat

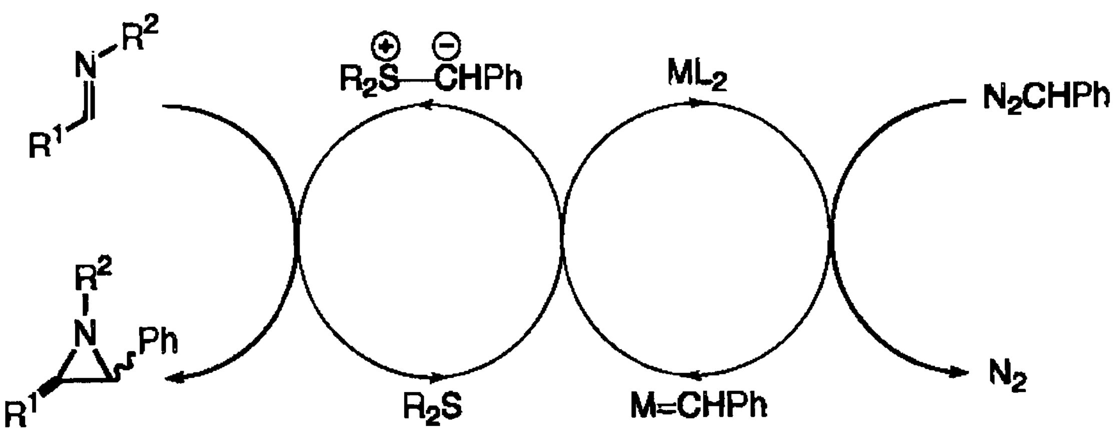
Wulff *Angew Chem Int Ed* **2000** 4518

Proposed mechanism for Lewis acids catalysis

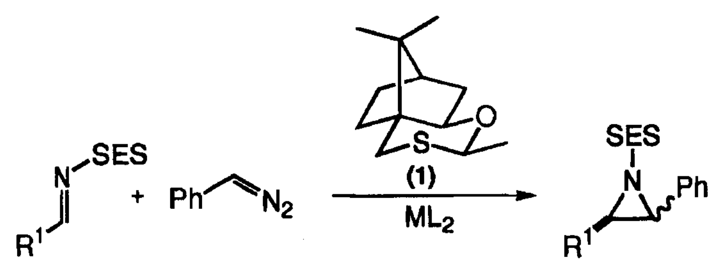


Templeton *J Org Chem* **1996** 8358

Sulfur ylide mediated aziridination

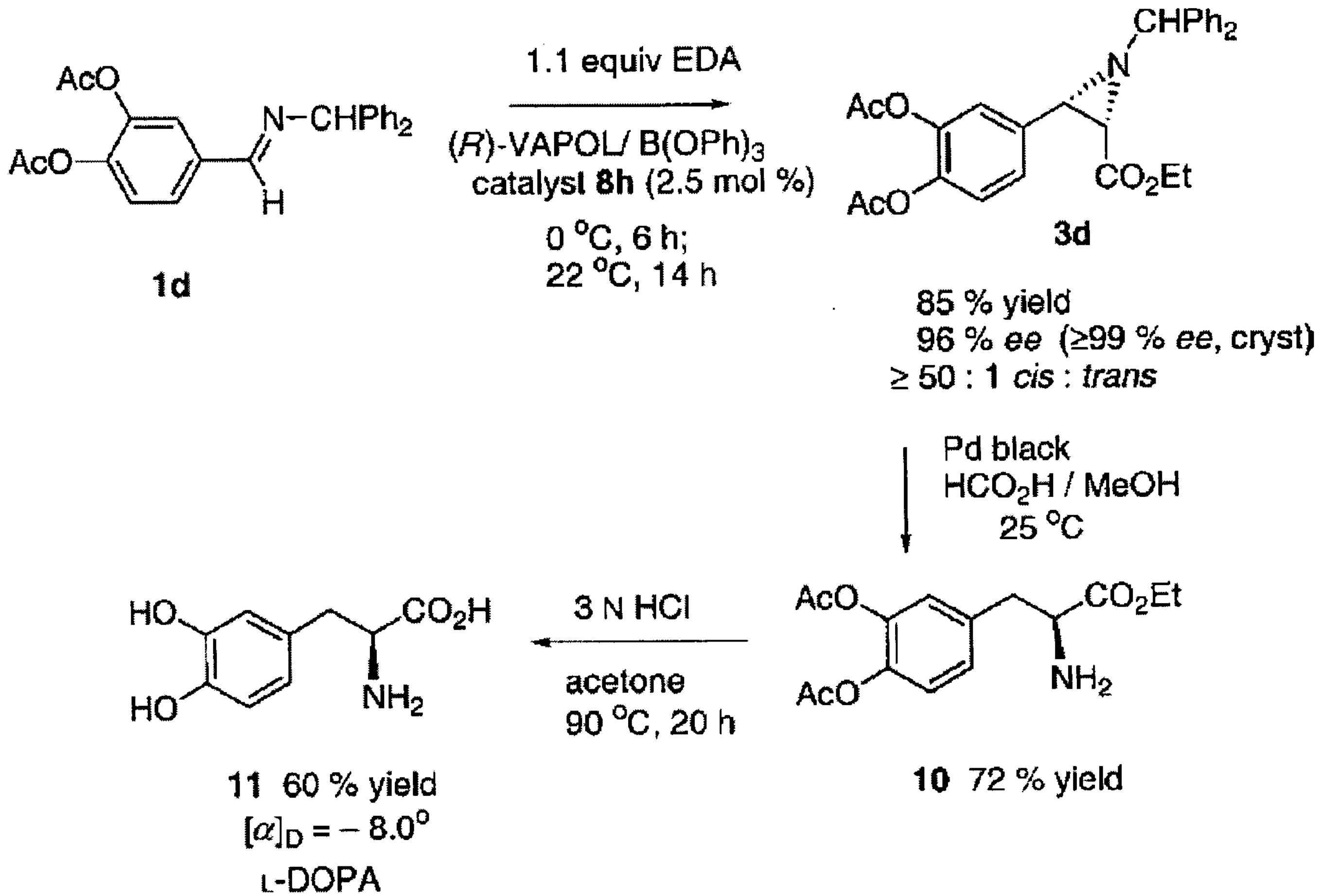


entry	R^1	equiv of **1**	ML_2	yield[a]/%	ratio (*trans:cis*)	ee[b,c]/%
1	Ph	1.0	$Rh_2(OAc)_4$	55	3:1	97 (*R,R*)[d]
2	Ph	1.0	$Cu(acac)_2$	83	3:1	95 (*R,R*)[d]
3	Ph	0.2	$Cu(acac)_2$	62	3:1	90 (*R,R*)[d]
4	*p*-MeC_6H_4	1.0	$Rh_2(OAc)_4$	88	3:1	95 (*R,R*)[e]
5	*p*-MeC_6H_4	0.2	$Cu(acac)_2$	50	3:1	88 (*R,R*)[e]
6	*p*-ClC_6H_4	1.0	$Rh_2(OAc)_4$	70	3:1	88 (*R,R*)[e]
7	*p*-ClC_6H_4	0.2	$Cu(acac)_2$	44	3:1	85 (*R,R*)[e]



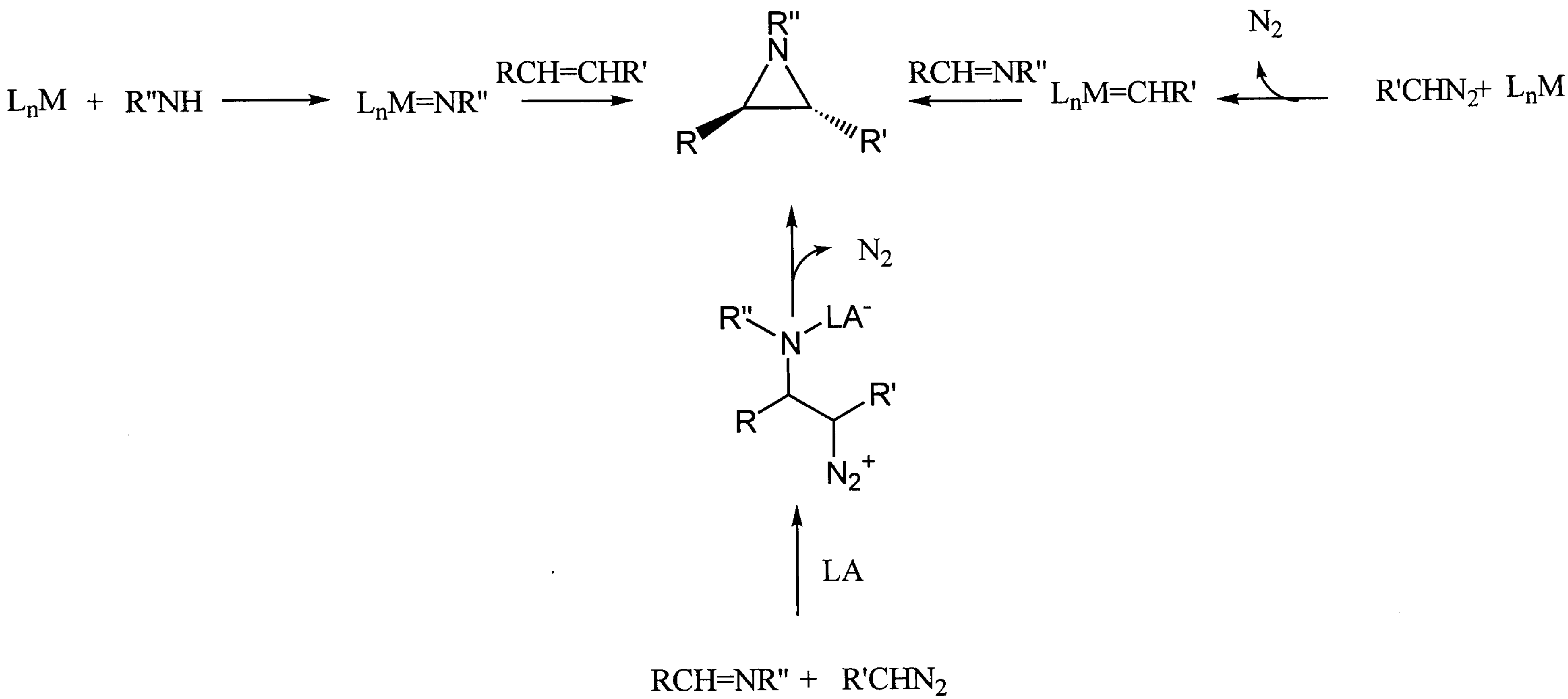
Standen *J Org Chem* **1996** 8368

Short total synthesis using LA cat aziridination



Wulff *Angew Chem Int Ed* **2000** 4518

Summary


LnM + R"NH
LnM=NR"
RCH=CHR'
R"
N
R
R'
RCH=NR"
LnM=CHR'
N2
R'CHN2+ LnM
N2
R"
N
LA-
R
R'
N2+
LA
RCH=NR" + R'CHN2

Additional References:

Aziridine reviews:

Deyrup *Chemistry of Heterocyclic Compounds* **1983** vol 42 p1-214
Sweeney *Tetrahedron: Asymmetry* **1997** 1693
Tanner *Angew Chem Int Ed Engl* **1994** 599

Cu cat nitrene addition to olefin
Tanner *Tetrahedron Letters* **1994** 4631
Hutchings *Chem Commun* **1998** 1601
Knight *Synlett* **1996** 677
Andersson *Organometalllics* **1999** 1281