Asymmetric Aziridination

2009/05/20 Literature Seminer Shinsuke Mouri (D1 part)

General Reference: Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.
Metal Catalyzed Aziridinations: Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.
Aziridines and Epoxides in Asymmetric Synthesis; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, **2006**

How are they different from other secondary amines?

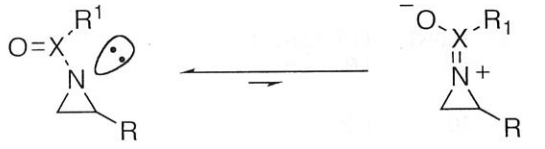
- Weaker basicity than alkylamines but stronger than arylamines (aziridinium ion has a pKa of 7.98)
- Bond strain gives a higher barrier of inversion at N than in acylic amines preventing racemization at RT.
  most acylic amines ~20 kJ mol^{-1} for N-inversion
  2-methylaziridines is ~70 kJ mol^{-1}
  1-chloro-2 methyl aziridine (N-substitution with an EWG) is 112 kJ mol^{-1}

How are they different from other epoxides?

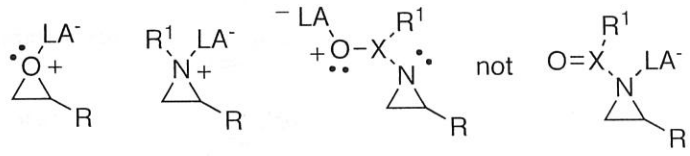
- Epoxides and aziridines are both three-membered heterocycles with comparable Baeyer strain (111kJ mol-1)
- Difference lies in the additional valency and less electronegative heteroatom in aziridines make them less reactive in corresponding reactions for epoxides

Feature of the N-substituent

- Activated aziridines refer to substitution with an EWG, protonation, or addition of a Lewis acid to mask the N- H bond in simple aziridines.



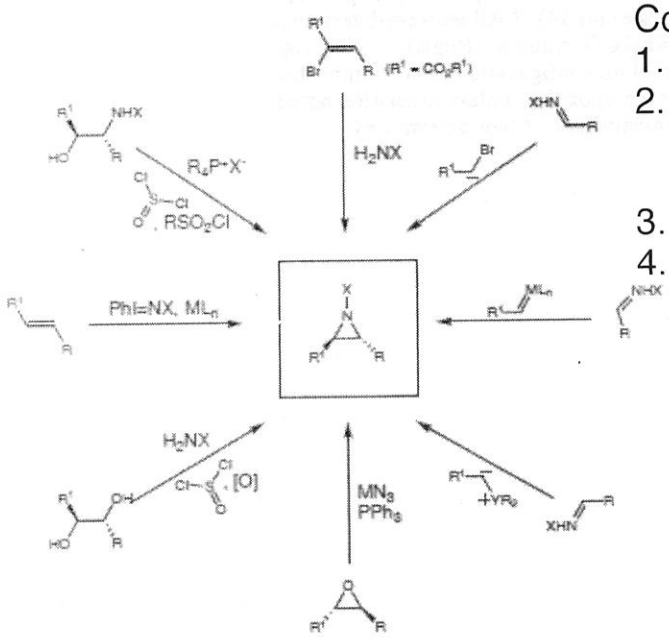
ring strain prevents resonance interactions



not

R^1= H, alkyl

Summary of Methods Used to Access Asymmetric Aziridines



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

Contents

2. C_2+N_1 : Cu-catalyzed aziridination

2.1. Jacobsen's method

Jacobsen *et. al* (J. Am. Chem. Soc., **1993**, *115*, 5326)

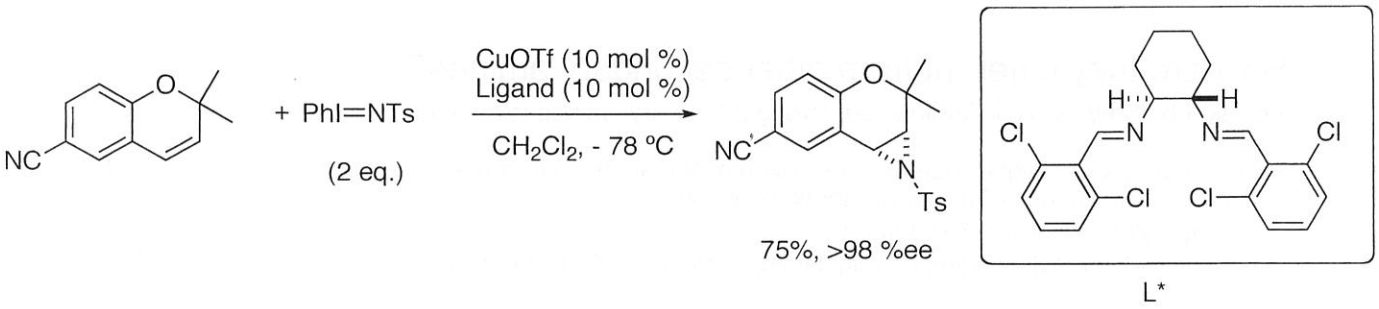
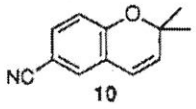
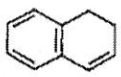
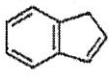
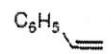
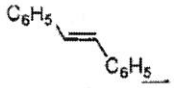


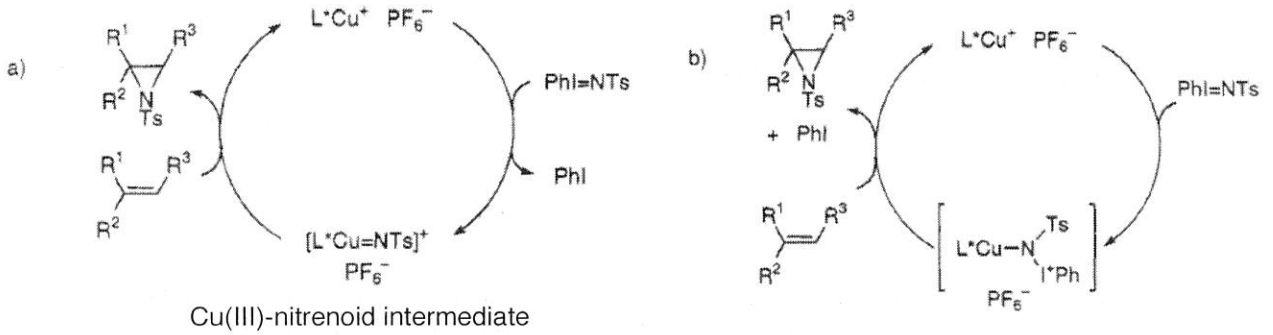
Table II. Asymmetric Aziridination of Alkenes Catalyzed by (*S*,*S*)-**8**/CuOTf

substrate	aziridine yield (%)[a]	ee (%)[b]	aziridine config[c]
 **10**	75	>98	(3*R*,4*R*)-(+)
	70	87	(1*R*,2*S*)-(+)
	50	58	(1*R*,2*S*)-(−)
	79	67 (cis)	(1*R*,2*S*)-(−)
	(cis = trans, 3:1) 79	81 (trans) 66	(1*S*,2*S*)-(−) (*R*)-(−)[d]
	nd[e]	30	nd[e]

[a] Reactions were carried out on 0.5 mmol scale of substrate with 10 mol% catalyst; yields are based on alkene and correspond to pure products isolated by flash chromatography (see note 14). [b] All ees were determined by HPLC on a commercial Whelk-O column (Regis). [c] The sign corresponds to that of $[\alpha]_D$. Absolute configurations were established by correlation to the corresponding epoxides, unless otherwise noted. [d] Correlated with (*R*)-(−)-2-phenylglycinol. [e] Not determined.

<Mechical insights>

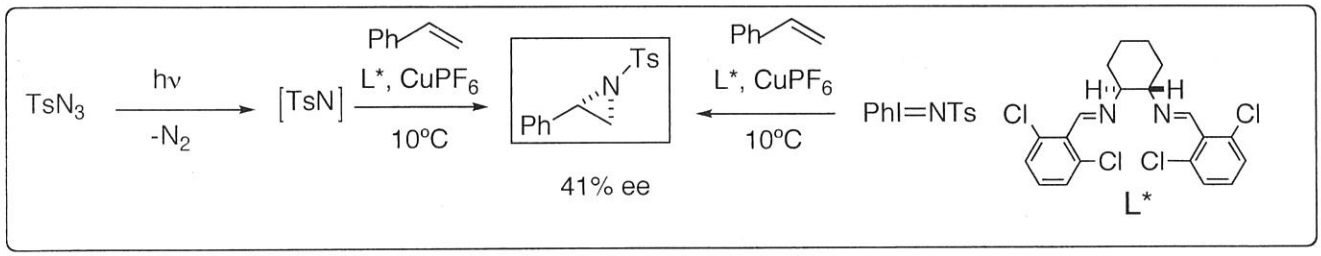
Jacobsen *et. al* .*J. Am. Chem. Soc.* **1995**,*117*, 5889
J. Am. Chem. Soc..**1996**, *118*, 8156



Cu(III)-nitrenoid intermediate

redox mechanism **Lewis acid mechanism**

1.



2.

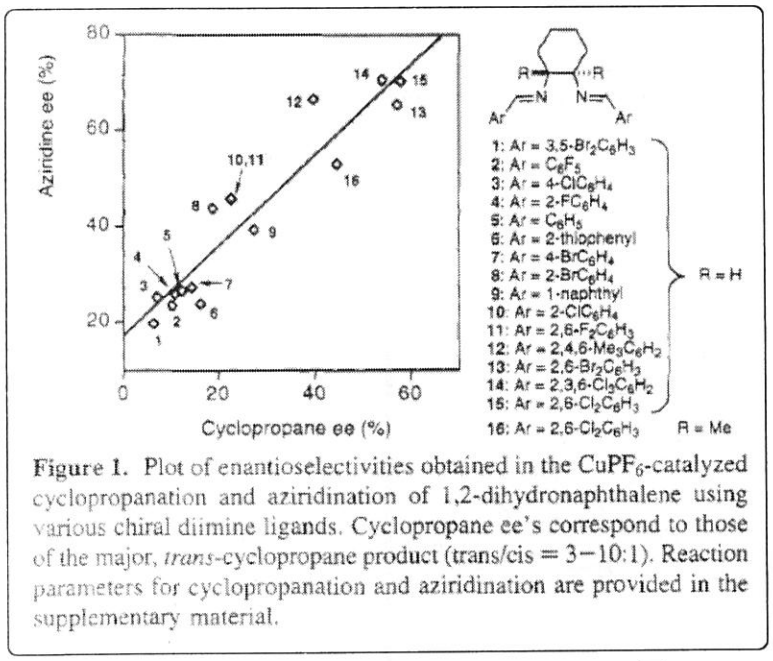
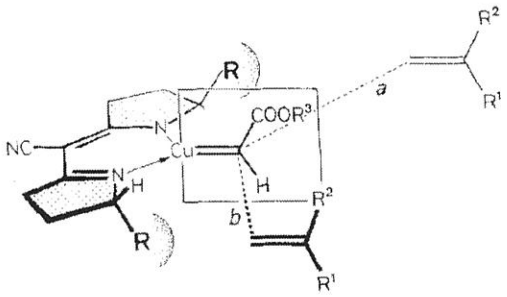
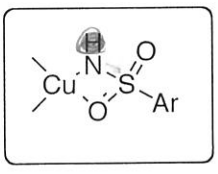


Figure 1. Plot of enantioselectivities obtained in the $CuPF_6$-catalyzed cyclopropanation and aziridination of 1,2-dihydronaphthalene using various chiral diimine ligands. Cyclopropane ee's correspond to those of the major, *trans*-cyclopropane product (trans/cis = 3−10:1). Reaction parameters for cyclopropanation and aziridination are provided in the supplementary material.



Pfaltz *et. al* . *Helv. Chin. Acta.* **1988**, *71*, 1553

Redox mechanism may be supported.

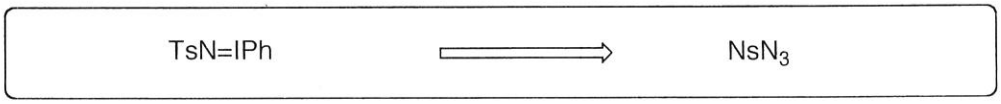


DFT studies support a copper-bound sulfonyl nitrene and additional oxygen coordination in the reactive intermediate

Norrby, *et.al.* J. *Am. Chem. Soc.* **2000,** *122*, 8013.

Katsuki's method

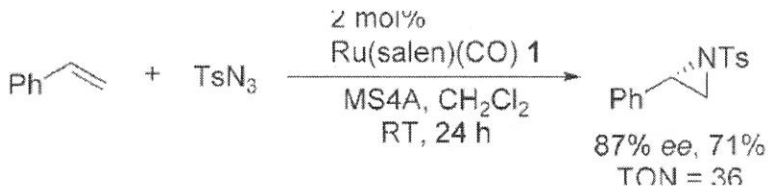
•Alternative nitrene source

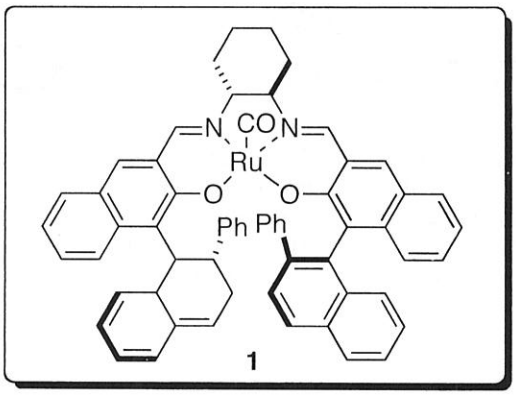


problems : PhI should be produced.
To remove Ts group harsh condition is needed.
High costs

merit : easy to removal of Ns
problem : In most cases Δ or hν needed.

Katsuki *et. al. Chem. Asian J.* **2007**, 2, *248*

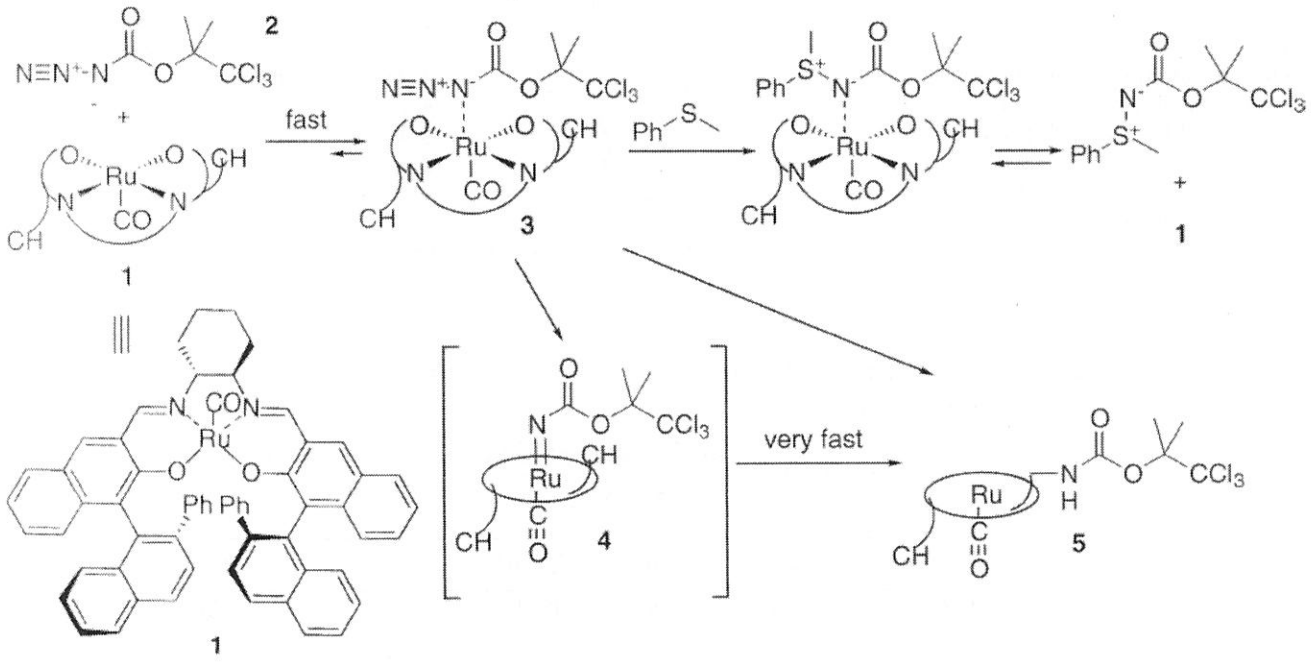




Scheme 1. Asymmetric nitrene-transfer reactions with the Ru(salen)-(CO)/TsN_3 system. MS4A = 4-Å molecular sieves.

Problems: Low TON
Catalyst decompose

katsuki *et al. Tetrahedron Letters,* 44, **2003**, 7965.



<structural determination of **5**>

•NMR 1H the chemical shifts of some aromatic protons in the 1H NMR spectrum of **1** shifted slightly.
13C (DEPT) The new complex showed that onemethine or aromatic proton disappeared in the complex.

•HRFABMS analysis [m/z 1171.1854] of which revealed its molecularformula, $C_{66}H_{50}Cl_3N_3O_5Ru$

one aromatic carbon was oxidized by intramolecular nitrene insertion to an aromatic C H bond during the reaction.

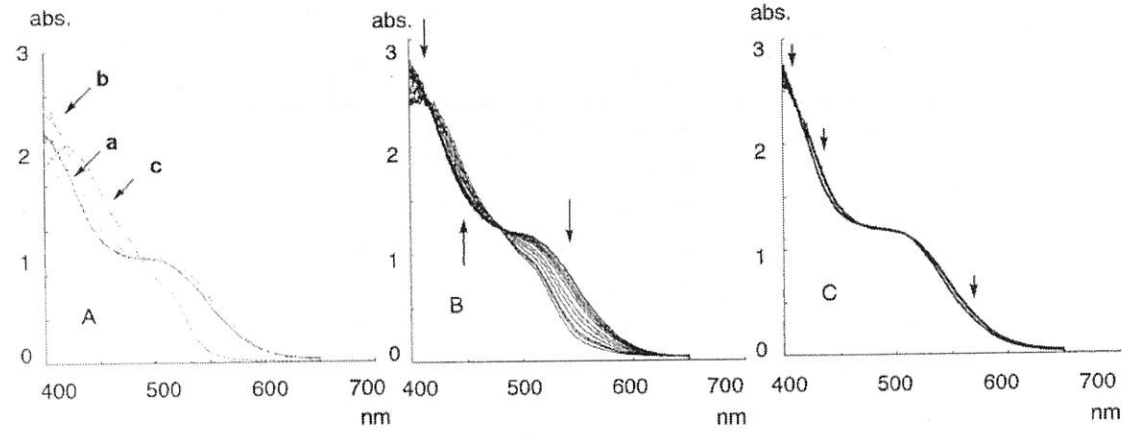
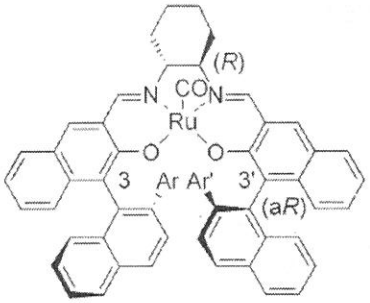


Figure 1. A, line a: visible spectrum of Ru(CO)-salen **1**; line b: visible spectrum of a mixture of **1** and **2**, immediately after the mixing; line c: visible spectrum of complex **5**. B, spectral change of the reaction of **1** and **2** (for 24 h). C, spectral change of the reaction of **1**, **2**, and PhSMe (for 24 h).

catalyst design

1) steric protection ofthe m-carbon atoms by introducing a bulky substituent such as the tert-butyldimethylsilyl or tert butyldiphenylsilyl groupat the p-carbon atom of the phenyl group.

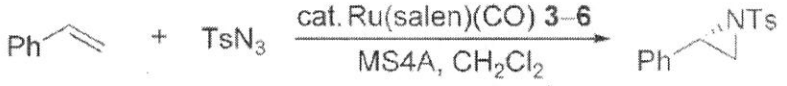
2) substitutionof the m-hydrogen atom with an inert atom such as halogen.



1: Ar = Ar' = Ph
2: Ar = Ph, Ar' = $Cl_3CCMe_2OCONHC_6H_4$
3: Ar = Ar' = 4-*t*BuMe$_2$SiC_6H_4
4: Ar = Ar' = 4-*t*BuPh$_2$SiC_6H_4
5: Ar = Ar' = 3,5-F_2-4-MeC_6H_2
6: Ar = Ar' = 3,5-Cl_2-4-Me$_3$SiC_6H_2

Scheme 1. Asymmetric nitrene-transfer reactions with the Ru(salen)-(CO)/TsN_3 system. MS4A = 4-Å molecular sieves.

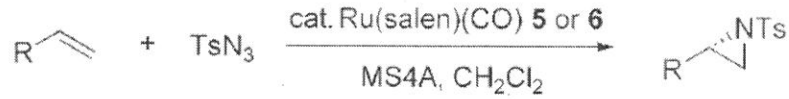
Table 1. Asymmetric aziridination of styrene with Ru(salen)(CO) complexes **3**–**6** and TsN_3.



Entry	Catalyst	*T*	*t* (h)	Yield[a]	*ee*[b]	TON[a]
0	**1** (0.1)	RT	24	~~48~~ 13	87	130
1	**3** (0.1)	RT	24	41	87 (*S*)	410
2	**4** (0.1)	RT	24	23	87	230
3	**5** (0.09)	RT	24	78	85	867
4	**6** (0.1)	RT	12	93[c]	86	982
5	**6** (0.1)	0	12	92	90	920
6	**6** (0.1)	−15	12	30	91	–
7	**6** (0.1)	−30	12	19	92	–

[a] Calculated according to ^{1}H NMR spectroscopic analysis. [b] Determined by HPLC analysis. [c] Yield of isolated product after silica-gel column chromatography.

Table 2. Asymmetric aziridination of various olefins with TsN_3 in the presence of Ru(salen)(CO) complex **5** or **6**.



Entry	R or substrate	Catalyst [mol %]	*T* [°C]	*t* [h]	Yield[a] [%]	*ee*[b] [%]	TON[a]
1	4-BrC_6H_4	**5** (0.09)	RT	24	79	90	878
2	4-BrC_6H_4	**6** (0.1)	RT	12	91	90	910
3	4-BrC_6H_4	**6** (0.1)	0	12	90	93	900
4	2-$C_{10}H_7$	**6** (0.1)	RT	12	99	82	990
5	2-$C_{10}H_7$	**6** (0.1)	0	12	69	91	960
6	PhC≡C	**6** (0.1)	0	12	76	98	690
7	*n*-C_6H_{13}	**6** (2.0)	0	38	64	84	32
8	*n*-C_6H_{13}	**5** (2.0)	RT	24	20	86	10
9	indene	**6** (2.0)	RT	38	48	>99	24

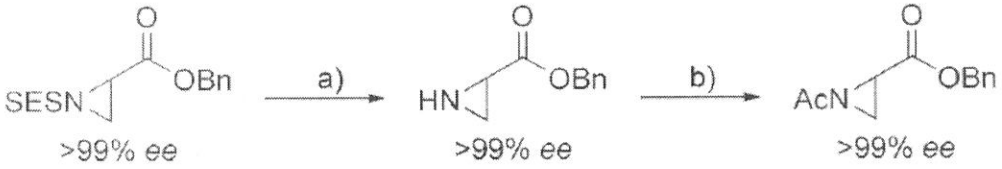
[a] Calculated according to ^{1}H NMR analysis. [b] Determined by HPLC analysis. [c] Yield of isolated product after silica-gel column chromatography.

Table 3. Asymmetric aziridination of various olefins with *p*-NsN_3, *o*-NsN_3, or $SESN_3$ catalyzed by Ru(salen)(CO) complex **5** or **6**.

Entry	Azide	Catalyst [mol %]	Substrate	*T* [°C]	*t* [h]	Yield[a] [%]	*ee*[b] [%]	TON[c]
1	*p*-NsN_3	**1** (4.0)	styrene	RT	24	22	84	5
2	*p*-NsN_3	**5** (1.0)	styrene	RT	24	34	84	34
3	*p*-NsN_3	**6** (0.1)	styrene	RT	38	70	81	746
4	*o*-NsN_3	**6** (0.1)	styrene	RT	12	62	73	660
5	$SESN_3$	**5** (1.0)	styrene	RT	12	67	88 (*S*)	67
6	$SESN_3$	**6** (0.1)	styrene	RT	12	26	91 (*S*)	260
7	$SESN_3$	**6** (1.0)	styrene	0	12	99	92 (*S*)	99
8	$SESN_3$	**6** (1.0)	4-BrC_6H_4-CH=CH_2	0	12	76	92	98
9	$SESN_3$	**6** (1.0)	PhC≡C-CH=CH_2	0	12	50	>99	51
10	$SESN_3$	**6** (5.0)	1-octene	reflux	38	28[c]	77[d]	6
11	$SESN_3$	**6** (5.0)	indene	reflux	38	65	98	13
12	$SESN_3$	**6** (2.0)	CH_2=$CHCO_2$Bn	RT	24	81	>99 (*R*)	41
13	$SESN_3$	**6** (2.0)	CH_2=CHCON(OMe)Bn	RT	24	85	>99	43

[a] Yield of isolated product after silica-gel chromatography, unless otherwise noted. [b] Determined by HPLC analysis. [c] Calculated according to ^{1}H NMR analysis. [d] Determined by chiral HLPC analysis after conversion into the 2-naphthylsulfide derivative.[24]

<Transformation>



Reagents and conditions: a) tris(dimethylamino)sulfonium difluorotrimethylsilicate, DMF, room temperature, 70%; b) Ac_2O, pyridine,dichloromethane, 0 °C, 81%.

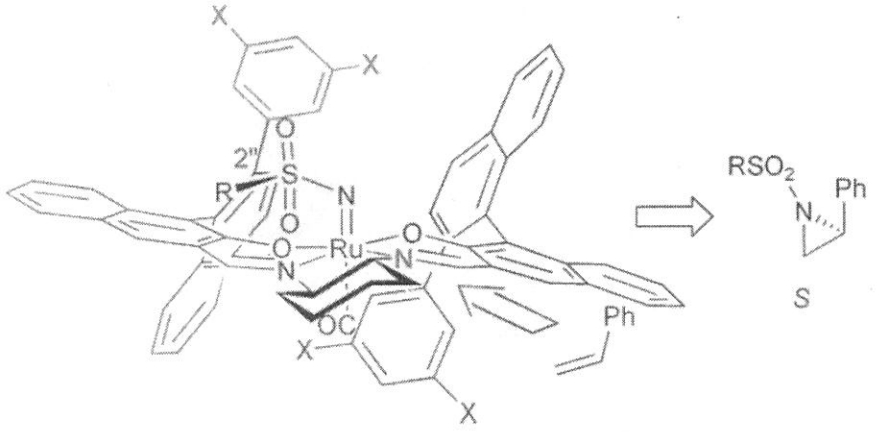


Figure 1. Schematic explanation of the proposed mechanism of asymmetric induction by Ru(salen)(CO) complexes.

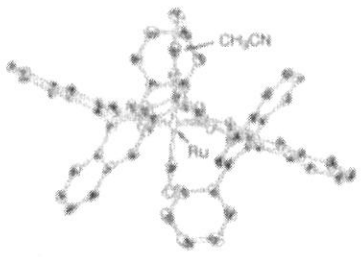
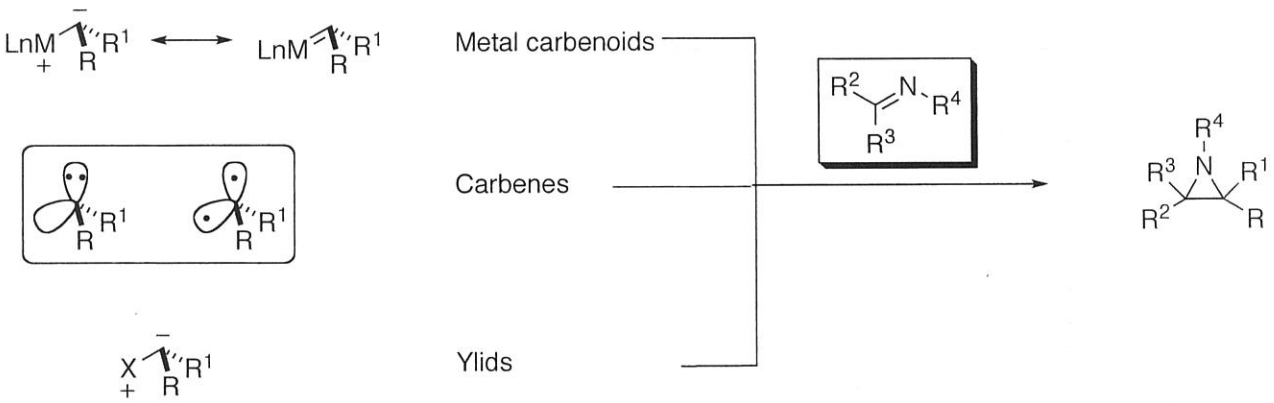


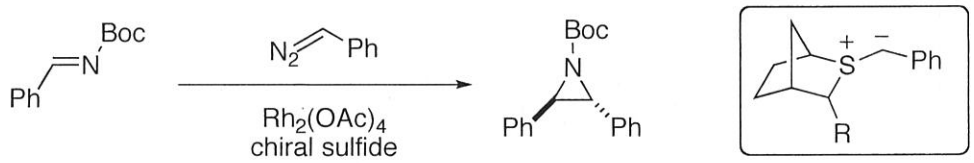
Fig. 1 An ORTEP diagram for the X-ray structure of **1**. The hydrogen atoms and solvent molecules are omitted for clarity.

Katsuki et. al. *Chem . Commun* ., **2004** , 2060.

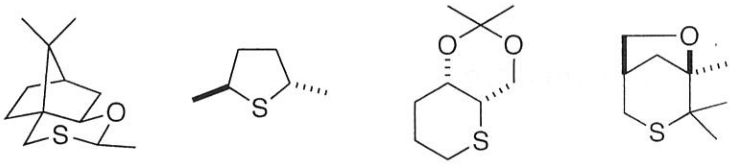
Carbene Methodology



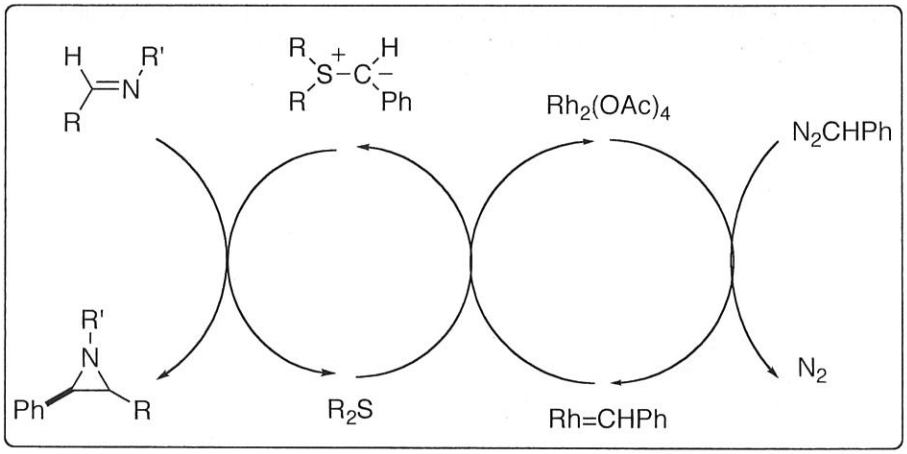
3-2. Carbene transfer to imines vis chiral sulfonium ylides

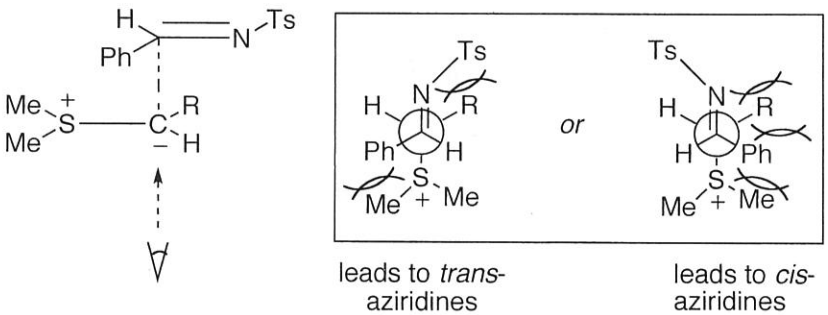


Chiral sulfides:



47%	34%	36%	24%
95% ee	95% ee	79 % ee	77 % ee
cis:trans=1:3	cis:trans=1:3	cis:trans=1:3	cis:trans=2:4





leads to *trans*-aziridines (major isomer)

leads to *cis*-aziridines

- Observed diastereoselectivity varies with N-substitution: Larger bulky groups on N leads to reduced trans selectivity (sulfonyl or phoshinyl groups)
- Smaller groups on N leads to increased trans selectivity (alkoxycarbonyl groups)

Addition of sulfure ylides to imine

Aggarwal, *et. al.* J. Org. Chem. **1996,** 61, 8368.

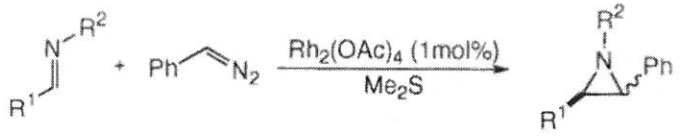
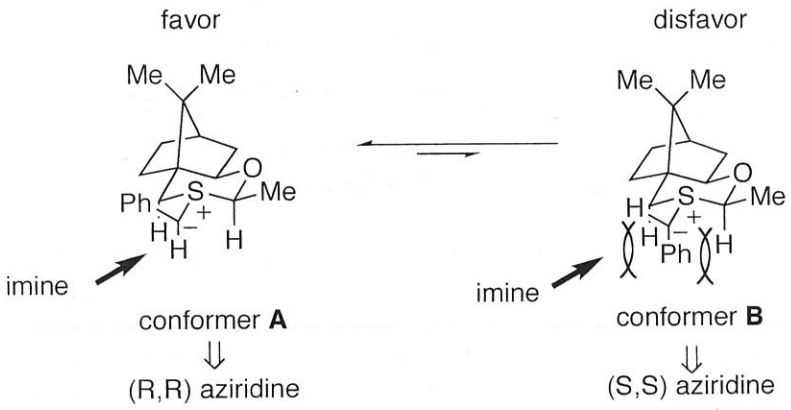


Table 1. Preparation of Aziridines from Imines and Phenyldiazomethane

entry	R^1	R^2	equiv of Me_2S	yield[a]/%	ratio *(trans:cis)*
1	Ph	Ts	1.0	90	4:1
2	Ph	Ts	0.2	91	4:1
3	Ph	DPP	0.2	83	3:1
4	Ph	SES	0.2	92	3:1
5	*p*-ClC_6H_4	SES	0.2	88	3:1
6	*p*-MeC_6H_4	SES	0.2	96	3:1

[a] The yield refers to the total yield of *trans* and *cis* isomers.

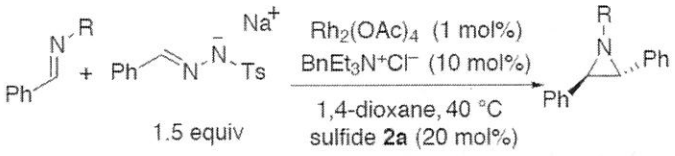
Aggarwal, V. K., *et. al. J. Chem. Soc. Perkin Trans.* 1, **2001**, 1635.



Asymmetric Aziridination-*in situ* prep of diazocompounds

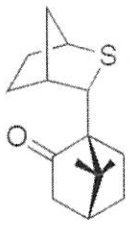
Aggarwal, *et. al. Angew. Chem. Int. Ed.* **2001**, *40*,1433

Table 1. Effect of the nitrogen substituent on the yield, diastereoselectivity, and enantioselectivity.[a]



Entry	R	Yield [%][b]	d.r.[c] (*trans*:*cis*)	*ee* [%][d]
1	SES	75	2.5:1	94
2	Ts	68	2.5:1	98
3	$SO_2C_{10}H_7$	70	3:1	97
4	Boc	33[e,f]	8:1	89
5	TcBoc	71	6:1	90
6[g]	SES	66	2.5:1	95

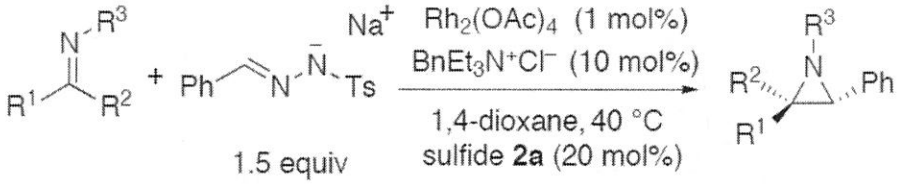
[a] Tosylhydrazone salt (1.5 equiv), imine (1.0 equiv), phase-transfer catalyst (PTC, 0.1 equiv), $Rh_2(OAc)_4$ (0.01 equiv), 1,4-dioxane (0.33 M), chiral sulfide **2a** (0.2 equiv), 40 °C. [b] Yield of isolated product. [c] The *trans*:*cis* ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess values were determined on a Chiralcel OD column; the absolute configuration was 1*R*,2*R*. [e] 0.05 equiv of PTC were used. [f] *trans*-stilbene oxide was obtained as the main side product. [g] 5 mol% of sulfide was used. Ts = tosyl = toluene-sulfonyl.



2a

Asymmetric Aziridination- *application to a Range of Imines*

Table 2. Asymmetric aziridination of a range of imines.[a]



Entry	R^1	R^2	R^3	Yield [%][b]	d.r.[c]	*ee* [%] (*trans*:*cis*)[d]
1	*p*-ClC_6H_4	H	TcBoc	56	6:1	94:90
2	*p*-ClC_6H_4	H	SES	82	2:1	98:81
3	C_6H_{11}	H	SES	50	2.5:1	98:89
4	*t*Bu	H	Ts	53	2:1	73:95
5	*trans*-PhCH=CH	H	SES	59	8:1	94
6	*p*-$MeOC_6H_4$	H	SES	60	2.5:1	92:78
7	3-furfuryl	H	Ts	72	8:1	95
8	Ph	Ph	$SO_2C_8H_7$	50	–	84

[a] Tosylhydrazone salt (1.5 equiv), imine (1.0 equiv), PTC (0.1 equiv), $Rh_2(OAc)_4$ (0.01 equiv), 1,4-dioxane (0.33 M), chiral sulfide **2a** (0.2 equiv), 40 °C. Bn = benzyl. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess values were determined on a Chiralcel OD column. See the Supporting Information.

4. Conclusions and outlook

1967 Kahn Cu(I)/ TsN_3

1974 Baret Cu powder ethyl diazoacetate

1982 Breslow and Gellman Fe or Mn porphyrins or $[Rh_2(OAc)_4]$ using TsN=IPh

Groves and Takahashi (porphyrine)Mn-imido complex

1984 Mansuy Catalytic Fe or Mn porphyrins

1991 Evans Catalytic Enantioselective [bis(oxazoline)]Cu complex

1992 Pirrung Catalytic Enantioselective Rh(II) Complex

1993 Jacobsen Catalytic Enantioselective Diimine-Cu complex

1995 Jacobsen Catalytic Enantioselective [bis(oxazoline)]Cu complex and diazoacetate

1996 Templeton and Brookhart LA and diazoacetate

1999 Wulff Catalytic Enantioselective LA-VAPOL complex with diazoacetate

Che Ru(VI) and Ru(II)

2003 He Catalytic Disilver(I) Complex

2008 maruoka organocatlyst