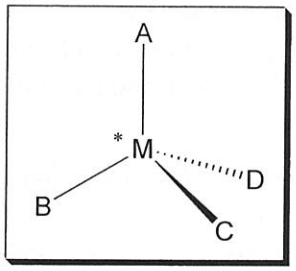
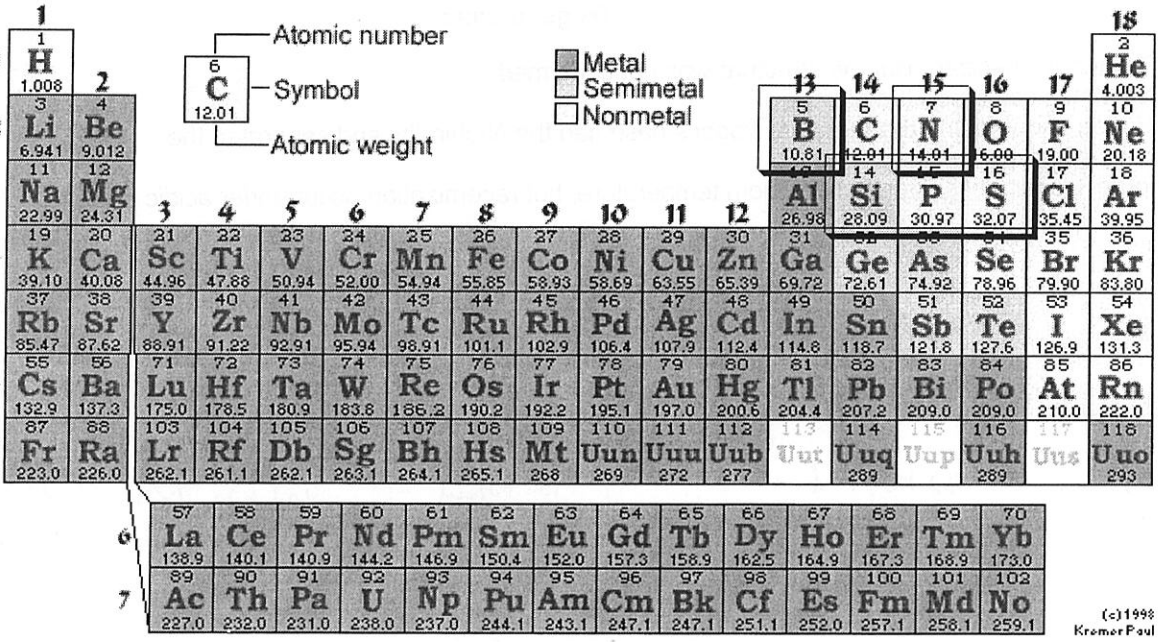
Stereogenic centers on Heteroatoms

contents

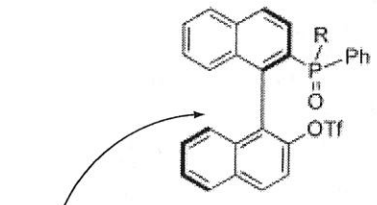


M = heteroatoms

1) Introduction



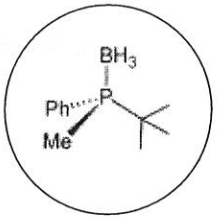
The theme is restricted within ...
1) Molecules containing chiralities on only heteroatoms.
2) Tetrahedral chiralities.
3) Although stereogenic centers on other heteroatoms (e.g. As, Se, Te...) have been reported, I will cover *B*-, *N*-, *Si*-, *P*-, *S*-chiral centers.

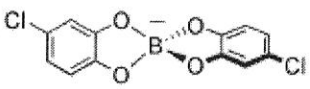


R = Me, *o*-An

Not covered

axial chirality

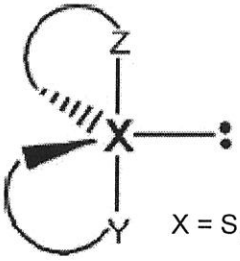




(*R*)-**9**

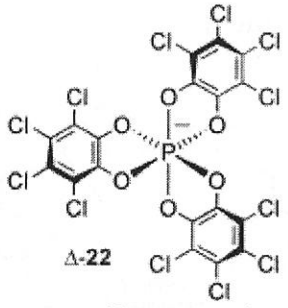
Not covered

axial chirality



X = S, Se...

Not covered



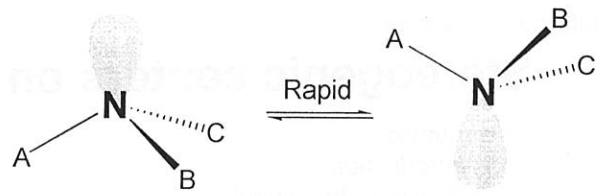
Δ-**22**

Not covered

2) Group-2 atom chirality

2-1) *N*-chirality

Characters of Nitrogen atom



1) Rate of inversion is 5 x 10^5 s^{-1} , 25 °C. (17~30 kJ/mol)

2) Rapid inversion can be prevented by ...

a) Construction of rigid ring structure around nitrogen atom.

b) Lowering *s*-character of nitrogen lone pair. (inversion occur through sp^2 hybridised orbital transition state.)

c) Cordinating to metal.

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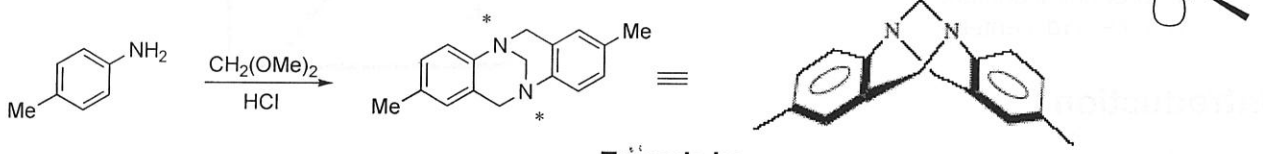
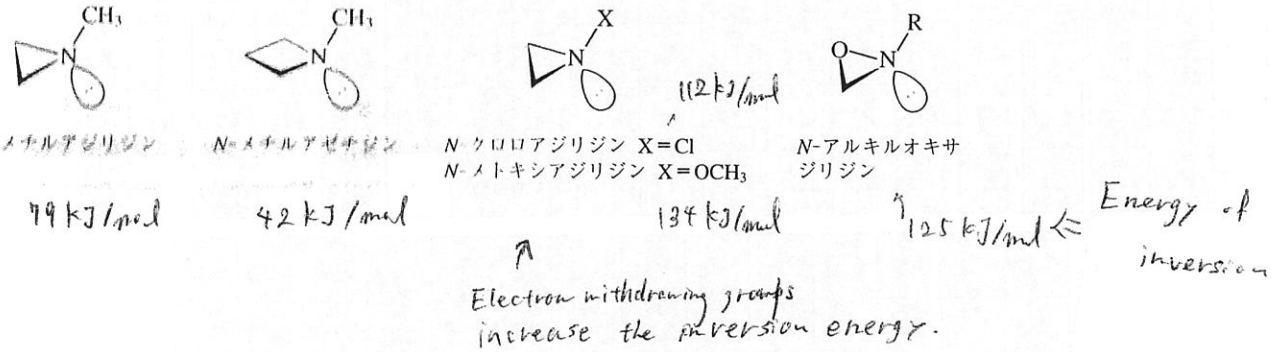
a) Tröger's base... first separated *N*-chiral center.



Tröger's base

+ In 1887, Tröger synthesized. But the structure was not confirmed.
+ In 1935, Spielman confirmed the structure.
+ In 1944, Prelog and Wieland thought that Tröger's base had the *N*-chirality and separated the enantiomers by chiral column.
+ Optically pure Tröger's base is stable at room temperature, but racemization occur under acidic condition.

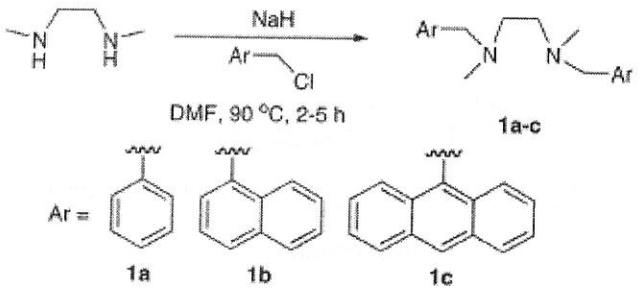
b)



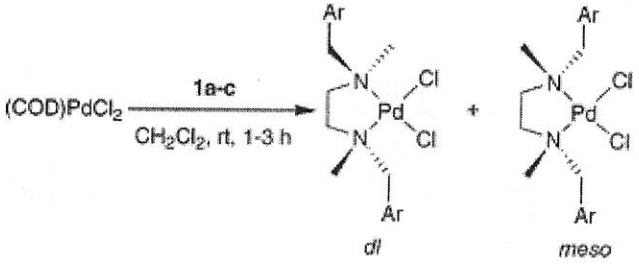
c) Persistent N-Chirality as the Only Source of Asymmetry in Nonracemic N2PdCl2 Complexes

Gagne et. al. *Organometallics* **2004**, *23*, 3210.

Scheme 1

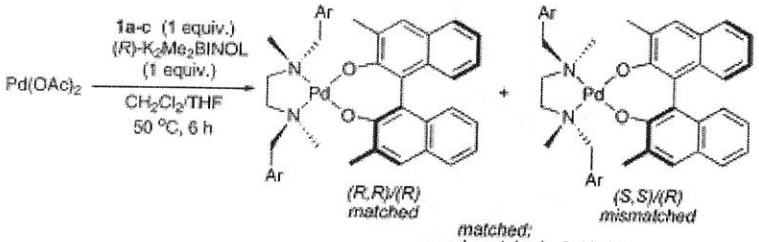


Scheme 2

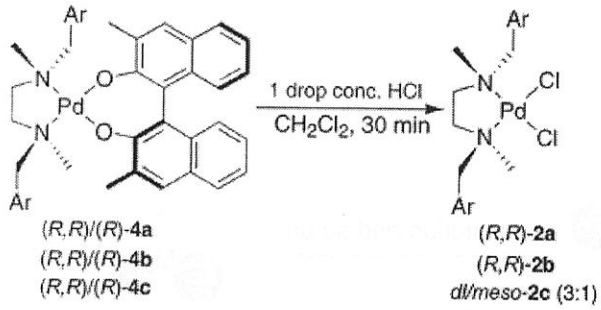


2a-c	dl:meso	% Yield
2a	2:1	95%
2b	2:1	93%
2c	3:1	96%

Scheme 3



	matched: mismatched	% Yield
4a	5:1	95%
4b	8:1	60%
4c	9:1	61%



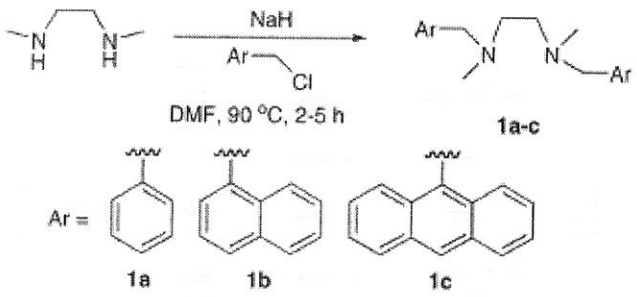
(2)

(*R*,*R*)/(*R*)-**4a**
(*R*,*R*)/(*R*)-**4b**
(*R*,*R*)/(*R*)-**4c**

(*R*,*R*)-**2a**
(*R*,*R*)-**2b**
dl/*meso*-**2c** (3:1)

Racemization of **4c** occured.

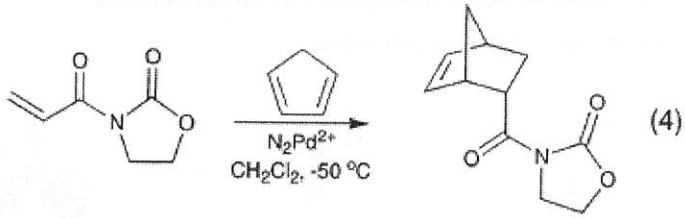
Scheme 1



+ The reason of low ee was thought to be...
a) Racemization of *N*-chirality at high temperture.

→ Compared entry 1 (high temperature) and 2 (low temperature), there was no change of ee. This suggested that no racemization had occured.

Table 2. Application of *N*-Chiral Catalysts to the Diels–Alder Reaction (eq 4)



(4)

entry	catalyst[a]	activation temp[b]	% conversion (h)[c]	*endo*:*exo*	*endo* % ee[d]
1	**1a**-Pd(OTf)$_2^{2+}$	rt	98 (5)	97:3	21
2	**1a**-Pd(OTf)$_2^{2+}$	−78	80 (20)	96:4	23
3	**1b**-Pd(OTf)$_2^{2+}$	rt	100 (4)	95:5	17
4	**1b**-Pd(OTf)$_2^{2+}$	−78	100 (22)	93:7	20
5	**1c**-Pd(OTf)$_2^{2+}$	rt	87 (6)	77:23	9
6	**1c**-Pd(OTf)$_2^{2+}$	−78	100 (12)	93:7	25
7	(*R*,*R*)-**2a**/$AgSbF_6$	rt	96 (6)	96:4	18
8	(*R*,*R*)-**2a**/$AgSbF_6$	−78	98 (6)	95:5	17
9	(*R*,*R*)-**2b**/$AgSbF_6$	rt	75 (6)	95:5	9
10	*dl*/*meso*-**2c**/$AgSbF_6$	rt	95 (6)	90:10	15

[a] The ditriflate catalysts were obtained by first treating the N_2Pd(3,3′-Me_2BINOL) complex with HOTf (1.9 equiv) at the indicated temperature and then cooling to −50 °C to carry out the reaction. [b] Activation was carried out for 15 min prior to preequilibrating at −50 °C and adding CpH. [c] Conversion was monitored by passing an aliquot through a plug of silica gel, eluting with EtOAc to remove the catalyst, then assaying by HPLC. [d] Chiracel OD-H.

b) Racemization of *N*-chirality during preparation of active catalyst.

→ After addition of brine to active catalyst (*R*,*R*)-**2a**/$AgSbF_6$ and (*R*,*R*)-**2b**/$AgSbF_6$, **2a** and **2b** were recovered free of the meso isomer, suggesting that N-epimerization had not occurred.

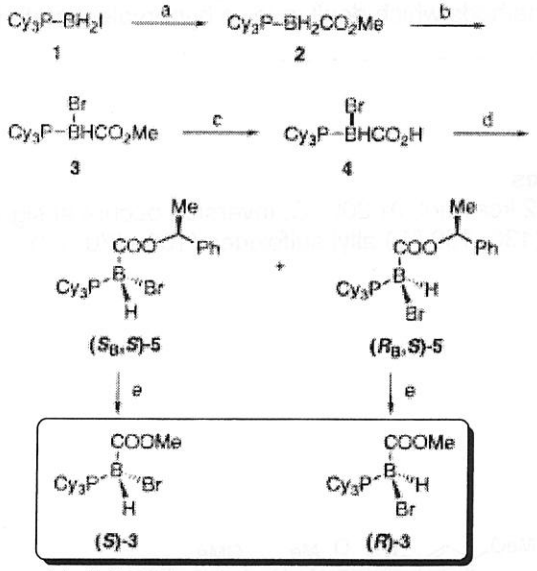
⇩ conclusion

c) A poor stereochemical transfer of information.

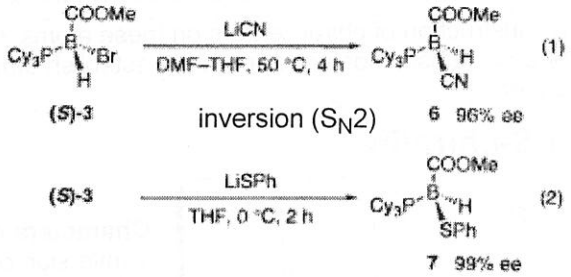
2-2) *B*- Chirality

Imamoto et. al. *J. Am. Chem. Soc.* **2000**, *122*, 6329.

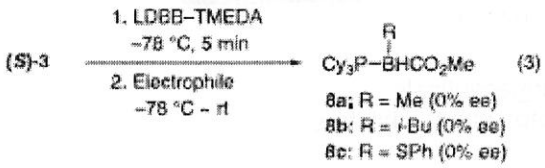
Scheme 1[a]



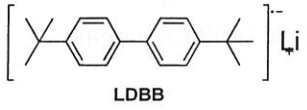
[a] Conditions: (a) (i) LDBB (2.5 equiv)−TMEDA, THF, −78 °C. (ii) $(MeO)_2CO$, 66%. (b) Br_2, MeOH, 0 °C to room temperature, 88%. (c) aq 48% HBr, THF, room temperature, 12 h, 57% after recrystallization from AcOEt. (d) (*S*)-(−)-1-Phenylethanol, 120 °C, 10 min, fractional recrystallization from hexane, (S_B,*S*)-5, 24%; (R_B,*S*)-5, 24%. (e) H_2SO_4 (cat.), MeOH−THF, room temperature, 4 h, 96−98%.



+ Absolute configulation was determined by X-ray analyssis.
+ ee of **6** and **7** were determined by chiral HPLC analysis.
+ **7** of abslute configulation was not determined.



+ It was considered that racemization occured due to the generation of radical or dianionic intermediate.

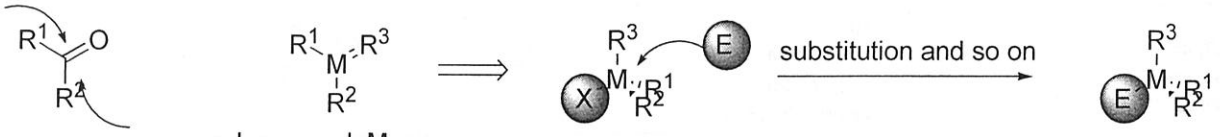


LDBB

3) Group 3 atom chirality

Back ground for construction of chiral centers

1) Low overlap of s- and p-orbitals



Face selective reactions give chiral centers.

In general, M containg double bonds are unstable.

Tetracoodinated state

M = Si, S, P...

2) Generation of hypervalent compounds

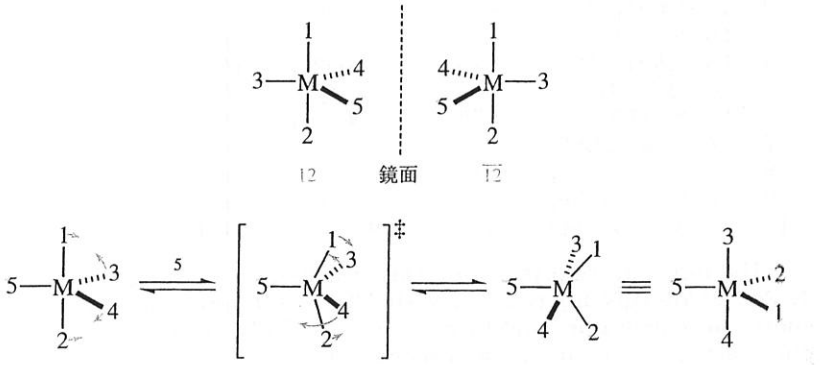


図 8・33　5配位化合物のエナンチオマー，絶対配置の表記法および位置異性化の擬回転機構
矢印の上の数字は擬回転で位置の変化しない軸配位子を意味する．

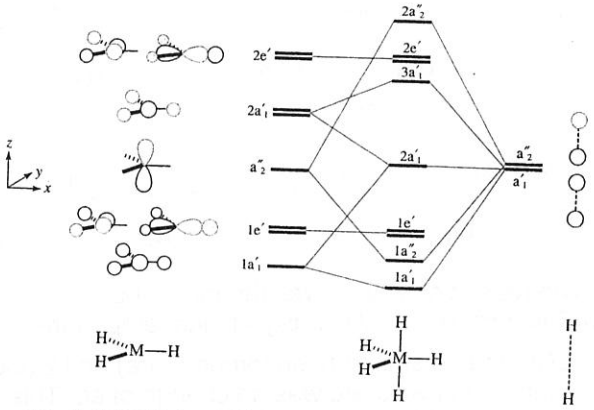
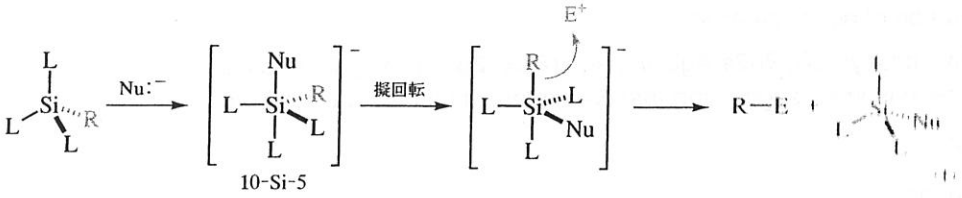


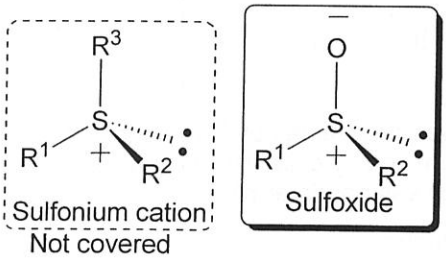
図 8・32　平面の MH_3 と H_2 から構成した三方両錐構造の MH_5(10-M-5)の分子軌道



Apicophilicity: more electronegative atoms tend to stay apical position.

In construction of chiral centers on these atoms, determining retention or invertion configulation is necessary for each substitution condition, or to establish other reliable methods which don't involve hypervalent state is reqired.

3-1) *S*-chirality



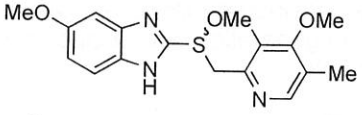
Characters of Sulfoxides

+ Inversion energy 35~42 kcal/mol. At 200 °C, inversion occurs at significant rate. (Benzyl sulfoxides (130~150 °C) allyl sulfoxides (150~170 °C))

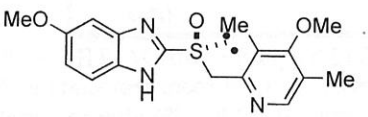
Utility

a) Pharmaceuticals

ex. Proton pump inhibitors



Omeprazole (Astra Zeneca)



Esomeprazole (Astra Zeneca)

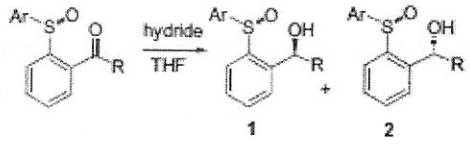
b) Chiral auxiliaries (Review: *Tetrahedron* **2006**, *62*, 5559.)

i) Coordination of the oxygen atom of a sulfoxide to a metal ion or a proton.

ii) Electronic and steric repulsions between nucleophiles and the substituents of a sulfoxide.

iii) As an electron-withdrawing group--activation of a carbon–carbon double bond for conjugate addition and stabilisation of the corresponding α-carbanion.

Toru et. al. *Tetrahedron* **2001**, *57*, 8469.



Ar	R	Hydride	Yield (%)	Ratio 1:2
Tol	Ph	$LiAlH_4$	80	47:53
Tol	Ph	DIBAL	80	15:85
Tol	Me	$LiAlH_4$	84	51:49
Tol	Me	DIBAL	85	37:63
Mes	Ph	$LiAlH_4$	82	21:79
Mes	Ph	DIBAL	92	2:98
Mes	Me	$LiAlH_4$	94	56:44
Mes	Me	DIBAL	94	16:84
Tip	Ph	$LiAlH_4$	81	35:65
Tip	Ph	DIBAL	96	2:98
Tip	Ph	L-selectride	86	11:89
Tip	Ph	Superhydride	86	11:89
Tip	Ph	DIBAL/LiBr	88	16:84
Tip	Ph	DIBAL/$Yb(OTf)_3$	81	19:81
Tip	Ph	DIBAL/$ZnCl_2$	92	85:15
Tip	Me	DIBAL	96	3:97
Tip	Allyl	DIBAL	94	2:98

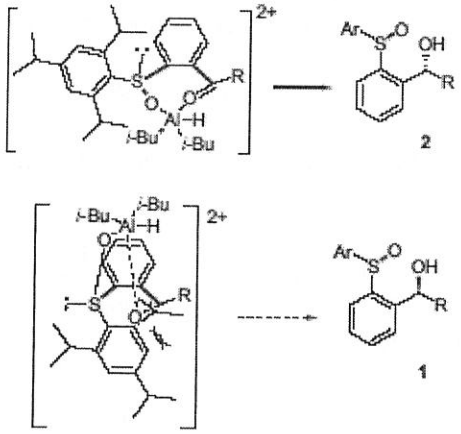


Figure 2. Assumed transition states in DIBAL reduction of 2-(arylsulfinyl)-phenyl ketones.

+ Addition of $ZnCl_2$ reversed the stereochemistry of the product, indicating that $ZnCl_2$ would form a chelate in place of DIBAL, and reduction occurred from the outside of the chelate.

Scheme 12. Stereoselective reduction of 2-(arylsulfinyl)phenyl ketones.

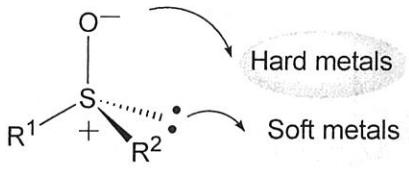
c) Chiral ligands

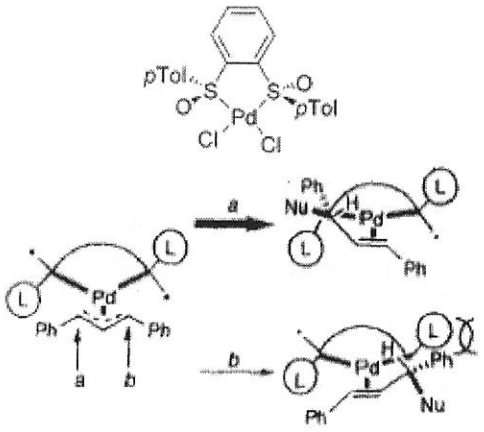
i) Sulfur -- poor σ-donor and poor π-acceptor. (phosphine ligands are better σ-donors and π-acceptors.

ii) Sulfur of the trans-effect is lower than that of the phosphine, but higher than nitrogen and oxygen.

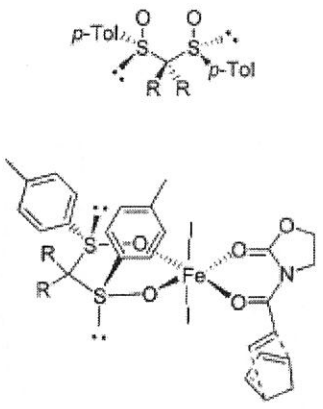
iii) Easily available and stable compared to phosphine.

iv) Sulfoxide ligands have two coordination modes, *O*- and *S*- coordination modes. It is influenced by the hardness or softness of metals. *S*-coordination mode seems to be favored in d^6 and d^8 transition metal ion complexes. (Rh, Ru, Pt...) But steric factors also work. Bulky ligands favor *O*-coodination mode.

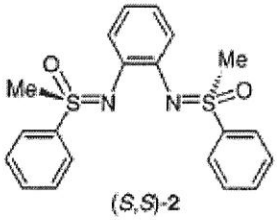




Allylic substitution using *S* coordinating catalyst
Shibasaki et. al.
Terrahedron Lerters **1995**, *36*, 8035.



Diels-Alder reaction using *O* coordinating catalyst
Khiar et. al.
Tetrahedron Letters **1993**, *34*, 123.



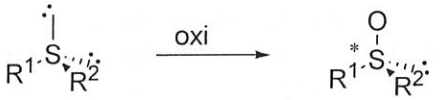
(*S*,*S*)-2
BISOX
+ $Cu(OTf)_2$

Hetero-Diels-Alder reaction using *N* coordinating catalyst
Bolm et. al.
J. Am. Chem. Soc. **2001**, *123*, 3830.

Construction of *S*-chirality (Review: *Chem. Rev.* 2003, *103*, 3651.)

1) Enantioselective sulfoxidations

a) Enzyme-catalyzed -- Walsh et. al. (1982)



b) Metal catalyzed -- Kagan et. al. (1984)

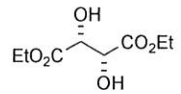
+ The condition was Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/H_2O (1:2:1) and TBHP.

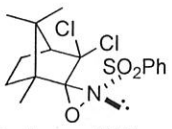
+ Ti(O*i*-Pr)$_4$ was stoichiomeric.

+ Later, It was reduced to 10 mol % under modified condition Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH (1:4:4) and MS 4Å..

c) By chiral oxaziridines -- Davis et. al. (1988)

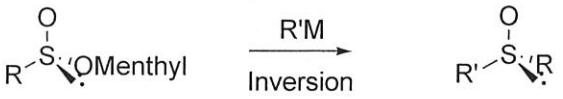

TBHP


DET

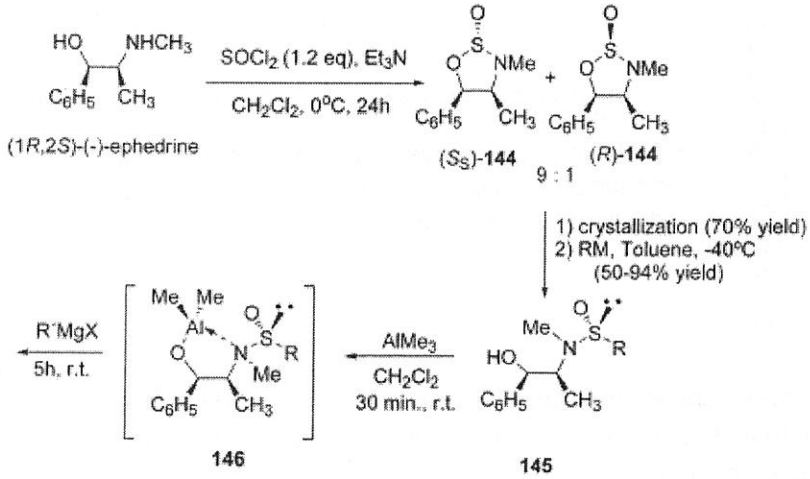

chiral oxaziridine

2) Nucleophilic substitution on diastereomerically pure chiral sulfur derivatives

a) Anderson (1962)



b) Wudl and Lee (1973)

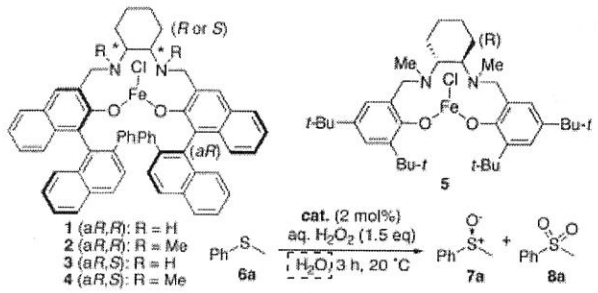


Recent advance on asymmetric sulfoxidation

Fe(salan)-Catalyzed Asymmetric Oxidation of Sulfides with Hydrogen Peroxide in Water

Katsuki et. al. *J. Am. Chem. Soc.* **2007**, *129*, 8941.

Table 1. Oxidation of Methyl Phenyl Sulfide Using Fe(salan) Complexes as Catalyst[a]



entry	cat.	yield of 7a[b] (%)	yield of 8a[b] (%)	ee of 7a[c] (%)
1	none	4	0	
2	**1**	30	2	10 (*R*)[d]
3	**2**	25	2	10 (*S*)[d]
4	**3**	89	5	88 (*S*)[d]
5	**4**	91	9	96 (*S*)[d]
6[e]	**4**	47	1	95 (*S*)[d]
7[f]	**4**	92 (90)[g]	8	96 (*S*)[d]
8	**5**	21	<1	<5 (*R*)[d]

[a] The reactions were carried out in water on a 0.2 mmol scale in the presence of 30% H_2O_2 and Fe(salan) complexes (2 mol %) at 20 °C, unless otherwise mentioned. [b] Determined by ^{1}H NMR (400 MHz) spectroscopic analysis. [c] Determined by HPLC analysis as reported in Supporting Information. [d] Assigned as reported in Supporting Information. [e] The reaction run for 0.5 h. [f] The reaction run with 1 mol % of **4**. [g] Isolated yield (on a 0.4 mmol scale).

Scheme 1. Oxidation of Racemic Sulfoxide Using the **4**/H_2O_2 System

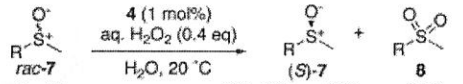
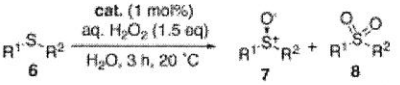


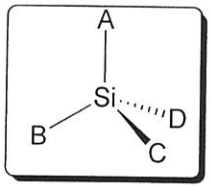
Table 2. Asymmetric Oxidation of Various Sulfides Using **4**[a]



entry	R^1	R^2		yield of 7[b] (%)	yield of 8[b] (%)	ee of 7[c] (%)
1	*p*-MePh	Me	**b**	91 (88)	9	96 (*S*)[d]
2	*p*-MeOPh	Me	**c**	92 (88)	8	95 (*S*)[d]
3	*p*-ClPh	Me	**d**	76 (72)	24	94 (*S*)[d]
4	*o*-ClPh	Me	**e**	97 (86)	<1	96 (*S*)[d]
5	*o*-MeOPh	Me	**f**	99 (90)	<1	95 (*S*)[d]
6[e]	*o*-MeOPh	Me	**f**	80 (77)	<1	93 (*S*)[d]
7	Ph	Et	**g**	78 (73)	22	81 (*S*)[d]
8	$PhCH_2$	Me	**h**	93 (85)	7	87 (*S*)[d]
9	*n*-C_8H_{17}	Me	**i**	82 (73)	18	89 (*S*)[d]
10	*n*-$C_{12}H_{25}$	Me	**j**	82 (79)	18	94 (*S*)[d]
11	*c*-C_6H_{11}	Me	**k**	91 (73)	9	88 (*S*)[d]

[a] The reactions were carried out on a 0.2 mmol scale in water (0.5 mL) in the presence of 30% H_2O_2 (1.5 equiv) and **4** (1 mol %) at 20 °C, unless otherwise mentioned. [b] Determined by ^{1}H NMR (400 MHz) spectroscopic analysis. The values in parenthesis are isolated yields that were obtained on a 0.4 or 0.5 mmol scale. [c] Determined by HPLC analysis as reported in Supporting Information. [d] Assigned as reported in Supporting Information. [e] The reaction run on a 10 mmol scale with 0.01 mol % of **4** for 6 h in the presence of 30% H_2O_2 (1.2 equiv).

3-2) *Si*-chirality

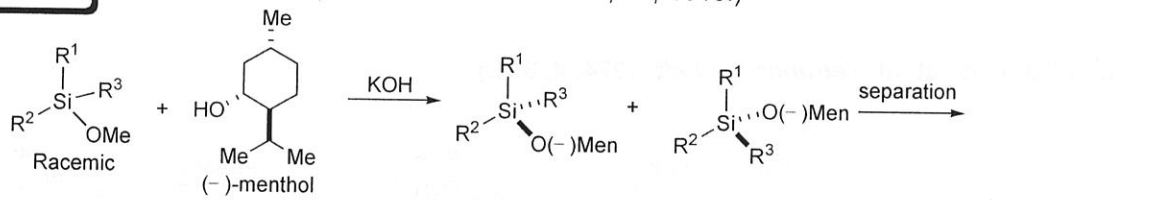


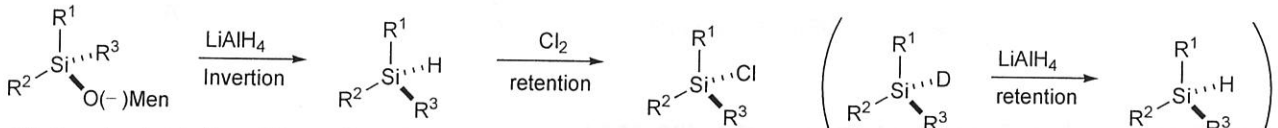
Construction of *Si*-chirality

First synthesis of optically pure *Si*-chiral center -- Kipping et.al. (1907)

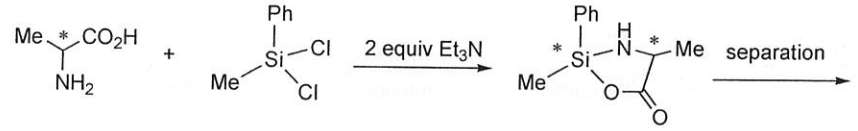
1) Nucleophilic substitution

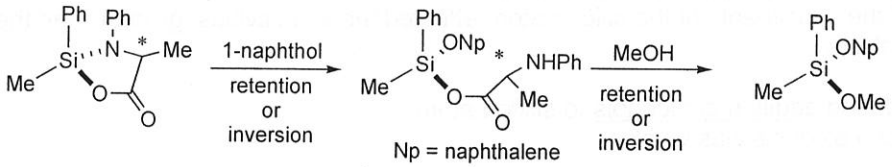
Sommer et. al. (*J. Am. Chem. Soc.* **1959**, *81*, 1013.)





Klebe et. al. (*J. Am. Chem. Soc.* **1968**, *90*, 7255.)





Some racemization occured.

Stereochemistry of nucleophilic substitution at tetracoodinated silicon (Review: *Chem. Rev.* 1990, *90*, 17.)

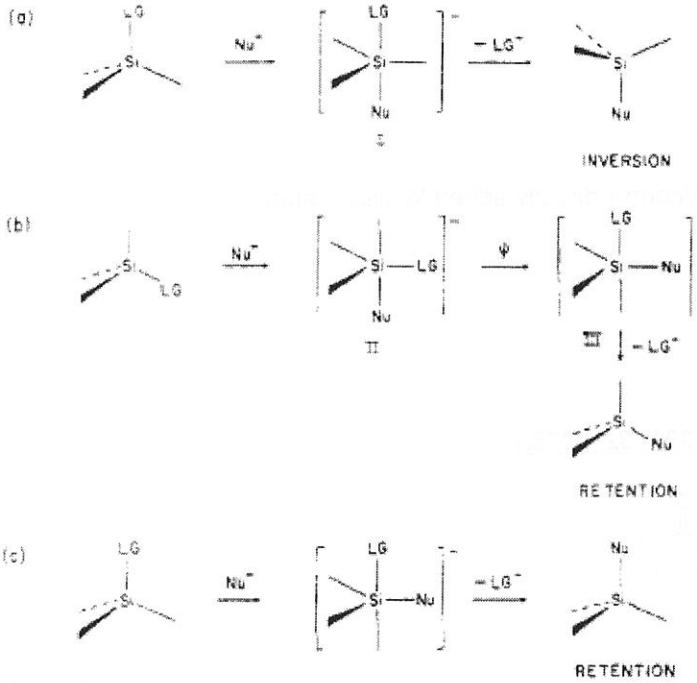


TABLE VIII. Energy Barriers to Retention for $[NucSiH_3(LG)]^-$ (kcal/mol)[15]

Nuc[a]	LG[b]	apicophilicity of LG (ΔE_{12})[c]	pseudorotation barrier (ΔE_{13})[c]	apicophilicity of Nuc (ΔE_{14})[c]
H	Cl	25.6[d]	12.2	
	F	5.6	6.4[d]	
	SH	9.7	12.1[d]	
	OH	4.3	11.7[d]	
	H		7.2[d]	
F	Cl	20.6[d]	12.2	3.7
	F	1.9	4.3[d]	1.9
	SH	7.5	11.5[d]	3.4
OH	Cl	19.9[d]	18.6	6.0
	F	1.9	10.0[d]	2.6
SH	Cl	24.8[d]	24.7	10.2
	F	3.4	11.5[d]	7.5

[a] Nuc = nucleophile. [b] LG = leaving group. [c] ΔE_{12}, ΔE_{13}, and ΔE_{14} are defined in reference to structures 1, 2, 3, and 4. These structures are as follows: (1) TBP, LG, Nuc(axial); (2) TBP, Nuc(axial), LG(equatorial); (3) SP, LG, Nuc(cis basal); (4) TBP, Nuc(equatorial), LG(axial). [d] Determines total barrier height for retention mechanism 1b of Figure 1.

Figure 1. Mechanisms for nucleophilic substitution reactions of silicon: (a) inversion; (b) retention involving axial attack and pseudorotation to give axial departure; (c) retention involving equatorial attack and axial departure. ψ symbolizes a pseudorotational process.

a) Apicophilicity -- Cl > SH > F > OH

b) Leaving group (LG)

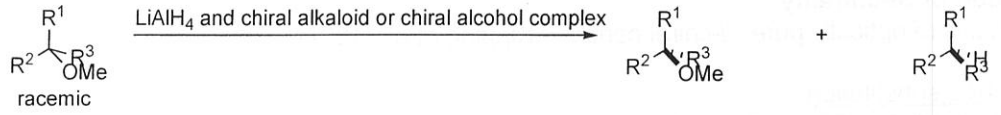
Inversion: Cl > SH, F > OH > H : Retention

c) Nucleophile effect on apicophilicity of LG

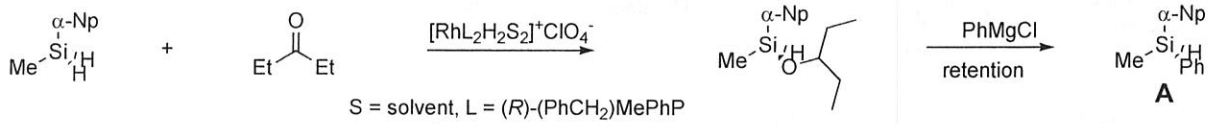
Softer nucleophiles tend to promote an inversion process and harder nucleophiles tend toward retention of configuration.

d) The reactivity of an electronegative leaving group is increased when the equatorial positions are occupied by ligands of low electronegativity and, of the atoms studied, the opposite apical position is occupied by an electronegative atom (Cl > F).

Kinetic resolution (Holt et. al. *J. Chem. Soc., Perkin Trans.* 2 1973, 114.)



2) Metal catalyzed
Hydrosilylation (Kumada et. al. *Tetrahedron Lett.* 1974, *4*, 331.)



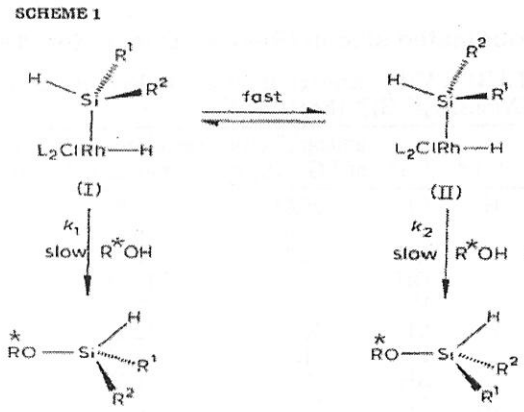
Alcoholysis (Corriu et. al. *J. Organomet. Chem.* 1976, *120*, 337.)

+ Utilisation of enantiopure ligands gave no improvement of selectivity.
+ The configulations of alcohols and the subsituents of the silicon atom effected tne selectivities, greater than the influence of the structures of the catalysts .

⇓

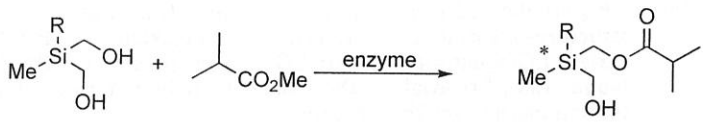
+ Stereochemistry was determined during addition of alcohols to silicon atom.
+ Interaction between the catalysts and alcohols was weak.

SCHEME 1



Alcohols directly added to silicon atom.

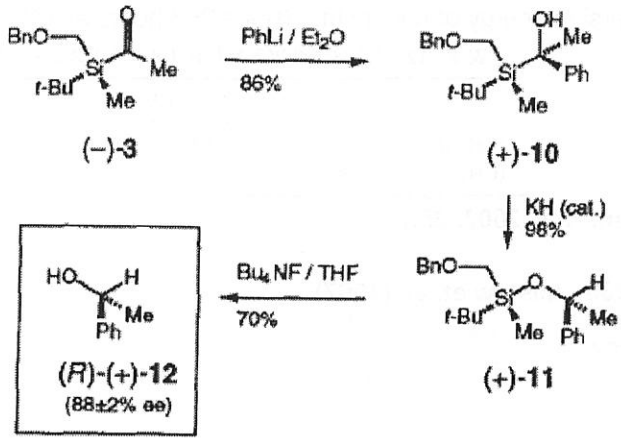
3) Enzymatic esterification (Blanco et. al. *Tetrahedron Lett.* **1991**, *32*, 6325.)



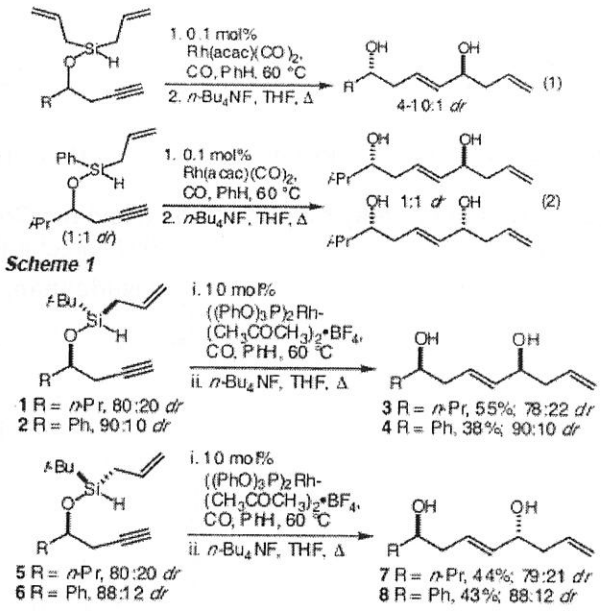
Application

Chiral auxiliaries

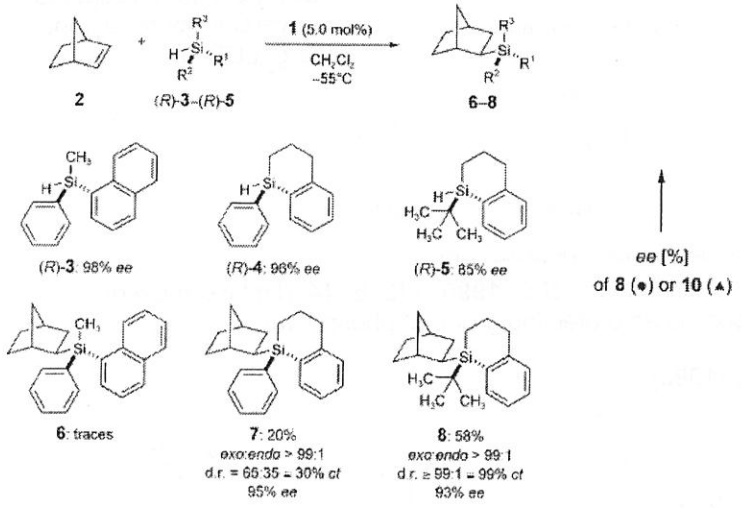
Bienz et. al. *Tetahedron: Asymmetry* **1996**, *7*, 69.



Leighton et. al. *J. Am. Chem. Soc.* **2003**, *125*, 1190.



Oestreich et.al. *Angew. Chem. Int. Ed.* **2005**, *44*, 1661.



Scheme 1. Silicon-to-carbon chirality transfer in the hydrosilylation of norbornene (**2**).

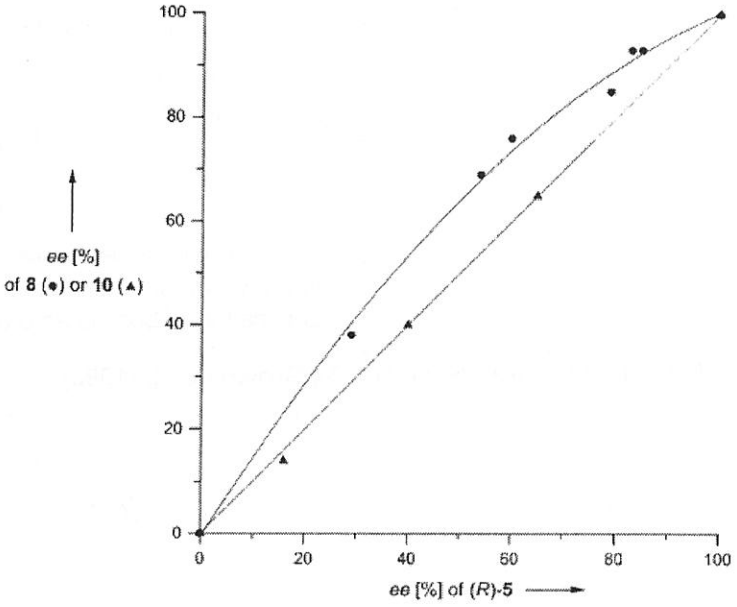
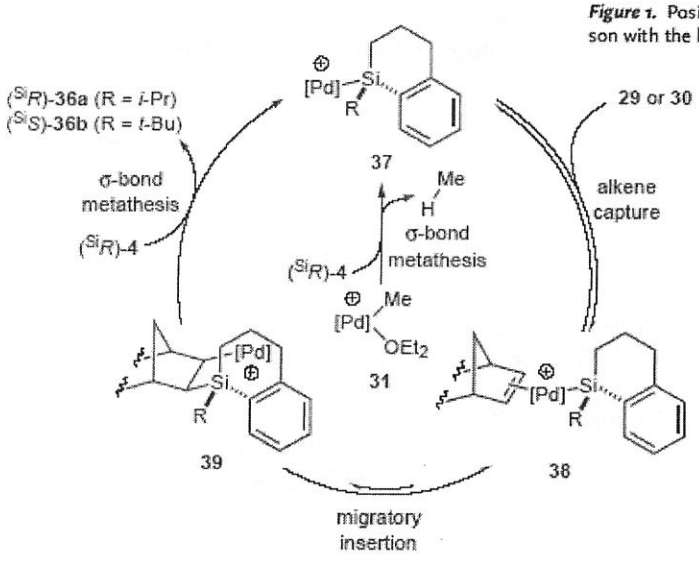
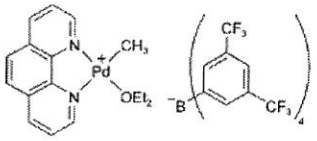


Figure 1. Positive nonlinear effect in the hydrosilylation of **2** with (*R*)-**5** (•) in comparison with the hydrosilylation of **9** with (*R*)-**5** (▲).



Positive nonlinear effect

⇒ Two silicons are involved.

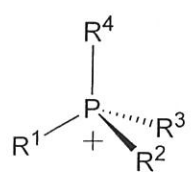


[(phen)Pd(Me)(OEt2)]+[BAr4]−

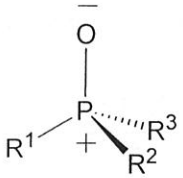
1

Scheme 14 A two-silicon cycle for the palladium-catalyzed hydrosilylation

3-3) *P*-chirality



Phosphonium cation



Phosphine oxide

Phosphine

Characters

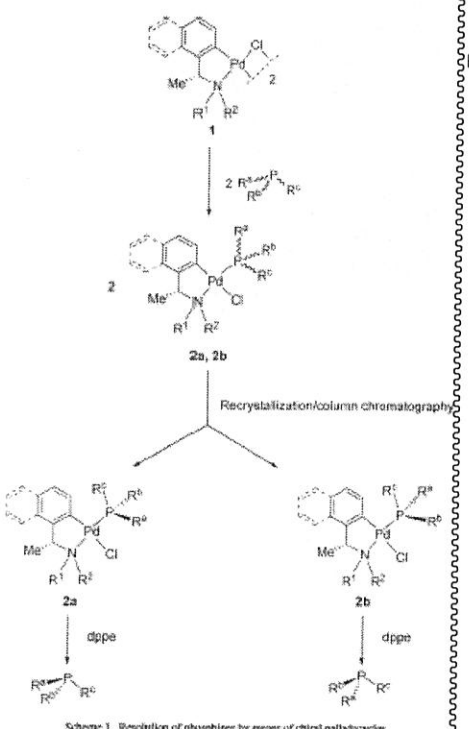
+ Small overlap between s and p orbitals give high inversion energy of phosphine. ($t_{1/2}$ = 2~3 hours at 115 °C)

表 8・12　トリメチルアミンとトリメチルホスフィンの比較

	IP_1, eV	共役酸の pK_a	反転障壁, kJ mol^{-1}
$(CH_3)_3N$	8.44	9.76	34
$(CH_3)_3P$	8.60	8.65	133

Construction of chirality on phosphine (Review: *Coord. Chem. Rev.* 2007, 25.)

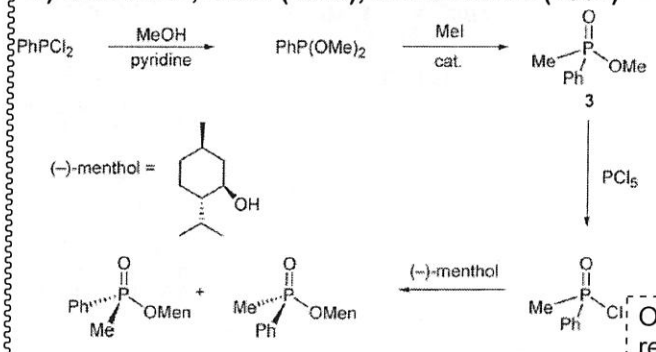
1) Resolution



Scheme 1. Resolution of phosphines by means of chiral palladacycles.

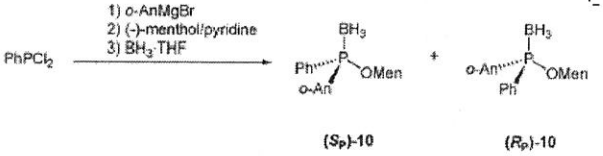
2) Using chiral auxiliary

a) Nudelman, Cram (1968), Mislow et. al. (1967)



Scheme 2. Synthesis of menthylphosphinates.

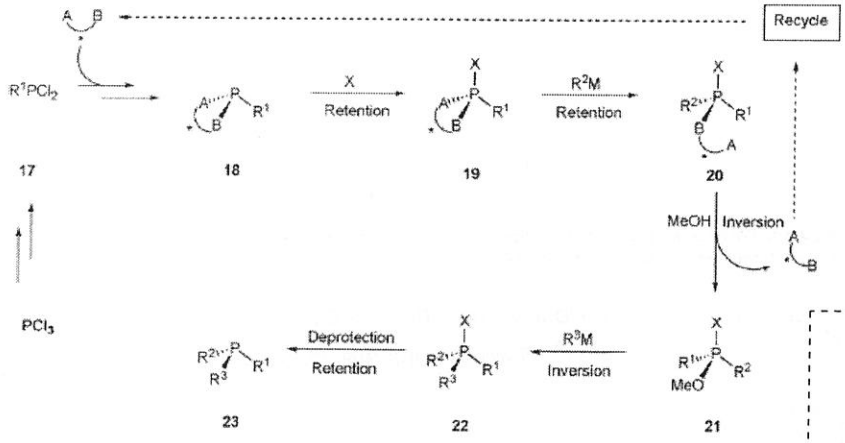
OMen group can be removed by substitution using Grignard reagents (inversion) or reductants (e.g. LDBB).



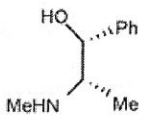
Equation 1. Synthesis of menthylphosphinite-boranes.

Imamoto et. al. *J. Am. Chem. Soc.* **1990**, *112*, 5244. (first example of application of borane as protecting group of phosphine)

b) Juge et. al. (1990), Corey et. al. (1993), Brown et. al. (1993)

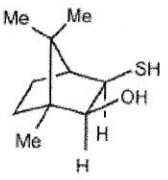


Scheme 7. Preparation of *P*-stereogenic phosphines using a chiral bifunctional auxiliary.

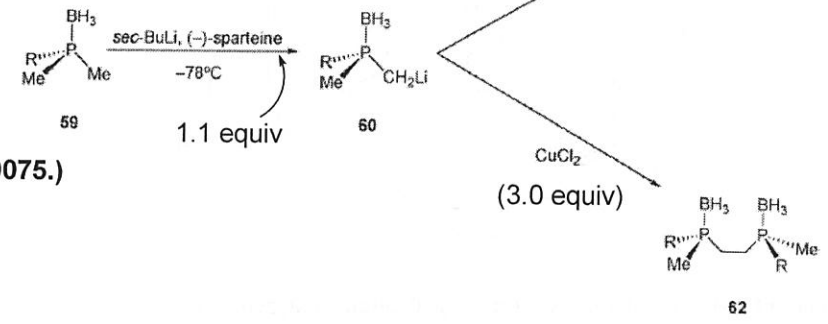


(1*R*,2*S*)-(−)-ephedrine

Juge, Brown

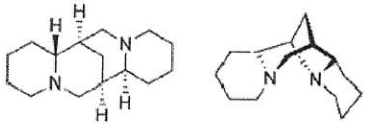


Corey



Scheme 16. Stereoselective deprotonation of an enantiotopic methyl group.

c) Enantioselective Deprotonation
(Evans et. al. *J. Am. Chem. Soc.* 1995, *117*, 9075.)



(−)-sparteine

d) Dynamic resolution
(Livinghouse et. al. *J. Am. Chem. Soc.* 1998, *120*, 5116.)

Scheme 1

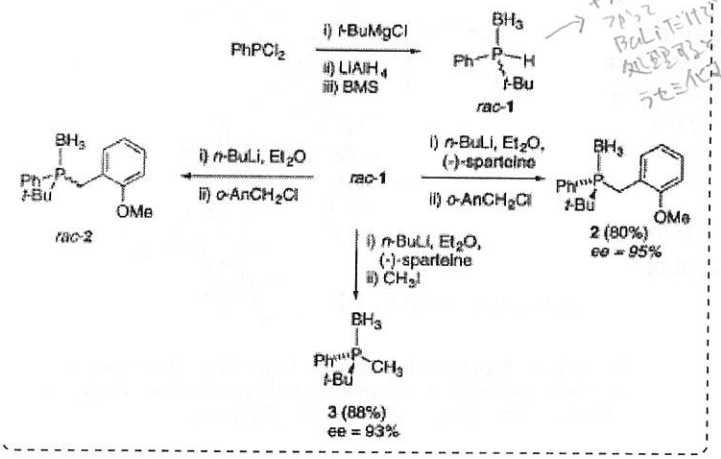
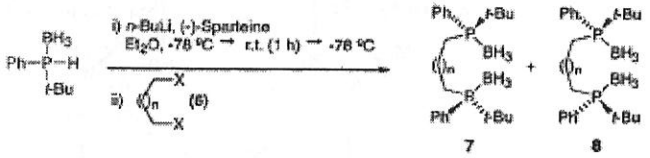


Table 2. Bisalkylations Involving Dynamically Resolved *tert*-Butylphenylphosphine–Borane



Electrophile (6)	Product (7)	7:8[a]	m.p. of 7 (°C)[b]	$[\alpha]_D$ (c) of 7	yield (%)[b]	% ee[c]
a		15.0:1	141-145	-22° (0.99, CH_2Cl_2)	67	d
b		21.7:1	183-190 (decomp.)	+438° (1.03, CH_2Cl_2)	68	>99
c		11.3:1	191-198 (decomp.)	-35° (1.01, CH_2Cl_2)	71	>99
d		18.4:1	210-220 (decomp.)	+39° (1.03, CH_2Cl_2)	76	>99
e		11.8:1	218-229 (decomp.)	+101° (1.01, $CDCl_3$)	73	>99

[a] Diastereomeric ratios were determined by NMR. [b] Melting points and yields determined after recrystallization or chromatography. [c] Percent ee determined before recrystallization by HPLC fitted with a CHIRALPAK AD column. [d] No resolution could be obtained by HPLC fitted with a CHIRALPAK AD column.

3) Metal catalyzed

Glueck et. al.

Using phosphine-boranes

J. Am. Chem. Soc. **2003**, *125*, 1180.

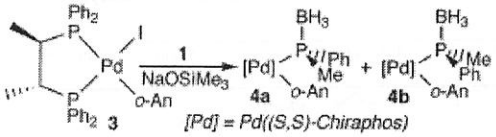
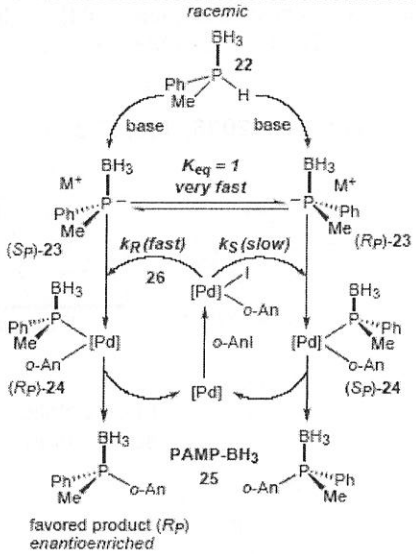


Table 1. Stereochemistry of Pd–P Bond Formation (Transmetalation) in the Reaction of 3 with 1 and $NaOSiMe_3$ in THF-d_8

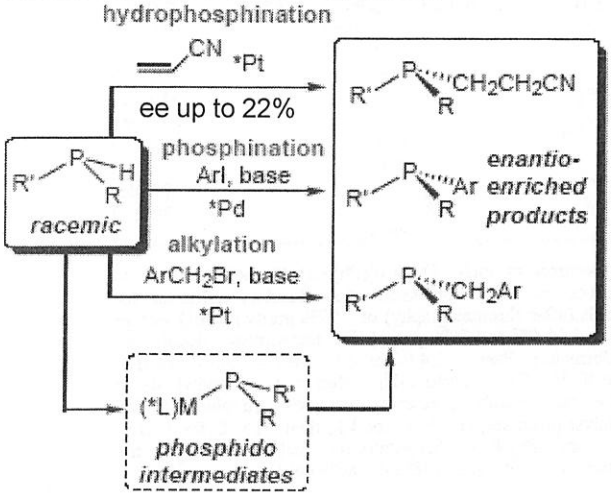
entry	temperature (°C)	ee of 1[a] (%)	de of 4[b] (%)
1	−78	95 (*R*)	94 (*S*, 4a)[c]
2	−78	99 (*S*)	94 (*R*, 4b)
3	21	95 (*R*)	86 (*S*, 4a)[d]
4	21	97 (*S*)	63 (*R*, 4b)
5	21	0	23 (*S*, 4a)[d]

[a] From chiral HPLC (Chiralcel OJ-H). [b] From integration of the ^1H NMR spectrum; the ee and de values obtained at −78 °C (entries 1−2) are the same, within experimental error. [c] Average of two runs. [d] Average of three runs.



Scheme 12 Proposed mechanism of the palladium-catalyzed asymmetric cross-coupling of a secondary phosphine–borane with an aryl iodide {[Pd] = Pd(diphos*), M^+ = counterion, such as Na^+ or amine·H^+, *o*-An = *o*-anisyl}

Phosphido intermediates strategy



Characters of phosphido

+ Barriers of P-inversion is low (10 to 16 kcal/mol, phosphine - 30 kcal/mol)
+ nucleophilic

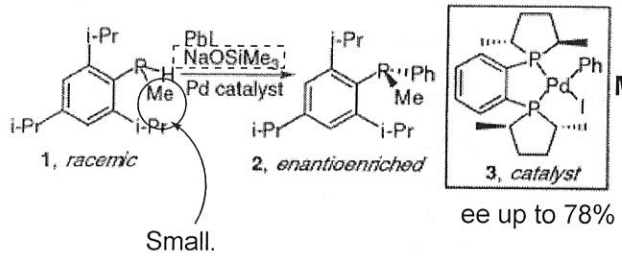
Merits

+ Bulky substituents are thought to be introduced to P atom.

Hurdles for developing these reactions

1) The background reaction of a secondary phosphine with an electrophile must be much slower than the metal-catalyzed reaction.
2) The equilibrium ratio of phosphido diastereomers and their relative reactivities with the electrophile must be controlled.
3) Product inhibition must be avoided.
4) The chiral ancillary ligand must resist displacement from the metal by the excess phosphine substrate and products.

Phosphination (*J. Am. Chem. Soc.* **2002**, *124*, 13356.)

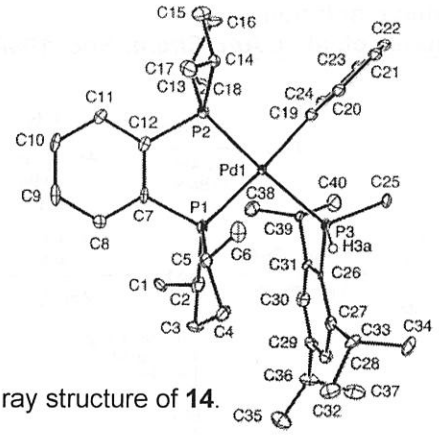


Me-Duphos
Rigit structure overcome the hurdle (4).

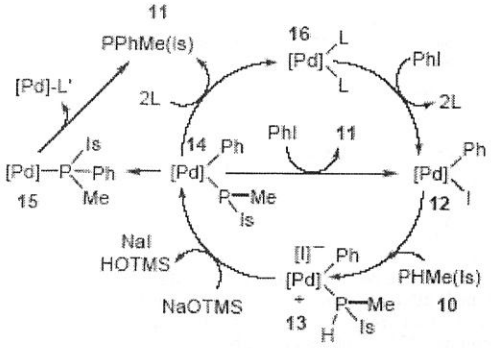
ee up to 78%

Small.

+ $NaOSiMe_3$ was chosen to minimize the concentration of the free phosphido anion [PMeIs]-, which might reduce the Pd catalyst or undergo other side reactions.

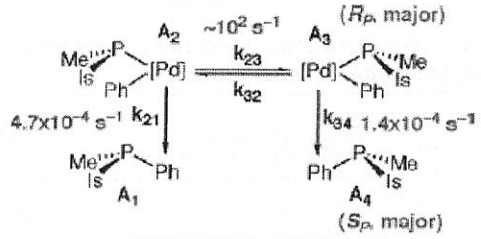


X ray structure of **14**.



Scheme 8 Proposed mechanism for the palladium-catalyzed asymmetric cross-coupling of a secondary phosphine {[Pd] = Pd[(*R*,*R*)-Me-Duphos], L = PHMe(Is) (**10**), L′ = (*R*,*R*)-Me-Duphos}

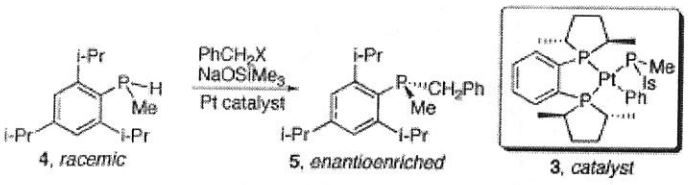
Scheme 8. Approximate Rate and Equilibrium Constants for Inversion and Reductive Elimination of 5a (A_3) and 5b (A_2) at −10 °C in THF ([Pd] = Pd((*R*,*R*)-Me-Duphos))

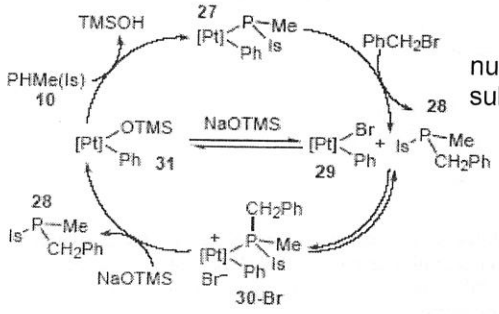


$$K_{eq} = \frac{k_{23}}{k_{32}} = \frac{[A_3]}{[A_2]} = 27$$

$$P = \frac{[A_4]}{[A_1]} = K_{eq}\frac{k_{34}}{k_{21}} = 8$$

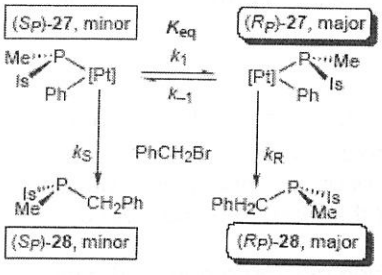
Alkylation (*J. Am. Chem. Soc.* **2006**, *128*, 2788.)





nucleophilic substitution

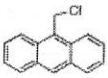
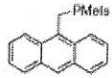
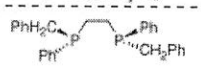
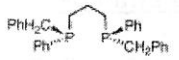
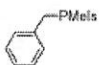
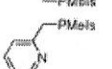
Scheme 15 Proposed mechanism of the platinum-catalyzed asymmetric alkylation of a secondary phosphine {[Pt] = Pt[(*R*,*R*)-Me-Duphos]}



Scheme 16 Proposed origin of enantioselectivity in the platinum-catalyzed asymmetric alkylation of a secondary phosphine {[Pt] = Pt[(*R*,*R*)-Me-Duphos)]

bidentate ligand

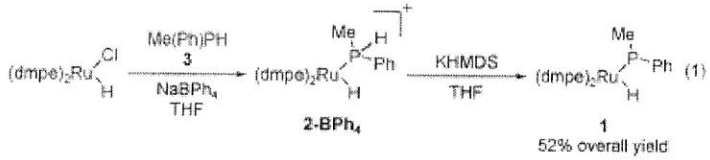
Table 2. Pt-Catalyzed Asymmetric Phosphination of Benzylic Substrates[a]

entry	substrate	product	yield (%)	ee (%)
1			88	55
2			86	50
3[b]			77	66
4	$PhCH_2Br$	$PMe(Phes)(CH_2Ph)$	86	81
5	$PhCH_2Br$	$PMe(Mes)(CH_2Ph)$	86	69
6	$PhCH_2Br$	$PMe(Ph)(CH_2Ph)$	84	35
7	$PhCH_2Br$	$PMe(Men)(CH_2Ph)$	87	56% de
8	$PhCH_2Br$	$PPh(o\text{-}An)(CH_2Ph)$	85	9
9	$PhCH_2Br$	$PPh(Cy)(CH_2Ph)$	93	48
10	$PhCH_2Br$	$PPh(t\text{-}Bu)(CH_2Ph)$	90	42
11[c]	$PhCH_2Br$		81	47% de 91% ee
12	$PhCH_2Br$		87	59% de 93% ee
13[b]			86	55% de 69% ee
14[b]			90	17% de 72% ee

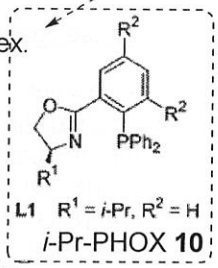
[a] Catalyst precursor = Pt(Me-Duphos)(Ph)(Cl) (5 mol %), base = $NaOSiMe_3$, solvent = THF, room temperature. Product yields are for isolated materials (after chromatography) of >97% purity (NMR), except for entries 13 and 14 (87 and 90% purity). For experimental details, see Supporting Information. Phes = 2,4,6-$Ph_3C_6H_2$, Mes = 2,4,6-$Me_3C_6H_2$, *o*-An = *o*-$MeOC_6H_4$, Cy = cyclo-C_6H_{11}, Men = (−)-menthyl, de = diastereomeric excess. [b] Catalyst precursor = complex **3**, in toluene. [c] With 2.5 mol % catalyst precursor, at −5 °C for 4 h, then −15 °C for 4 days. The catalyst precursor Pt(*i*-Pr-Duphos)(Ph)(Cl) (5 mol %, 21 °C) gave the opposite enantiomer in 98% yield (48% de, 86% ee).[10]

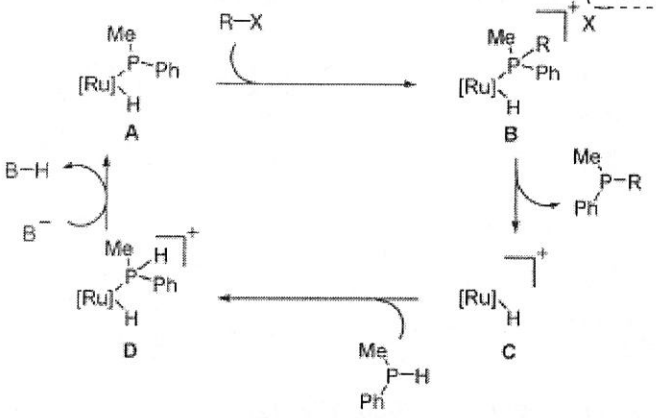
Toste et. al

Alkylation (*J. Am. Chem. Soc.* **2006**, *128*, 2786.)



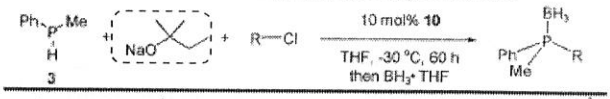
+ sodium *tert*-amyloxide was selected as the most suitable base with regard to two critical criteria:
1) Its ability to regenerate a Ru phosphido complex.
2) Its noncompetitive background reaction.

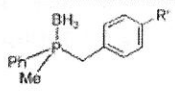
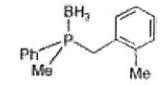
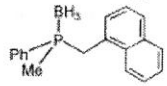
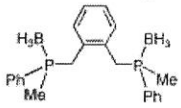
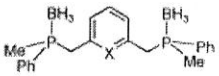
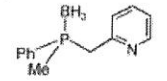
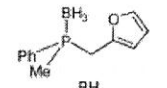
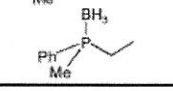




Proposed mechanism

Table 2. Enantioselective Alkylation with Alkyl Chlorides



entry	product		% yield[a]	% ee[b]
1		R' = H (**9**)	91	75 (92[c])
2		R' = Cl	96	41
3		R' = Me	80	83
4		R' = OMe	85	85
5			92	57
6			96	59
7			87	74[d]
8		X = CH	86	95[e]
9		X = N	89	84[f]
10			94	48
11			80	68
12			70	57[g]

[a] Isolated yields. [b] Measured by chiral HPLC. [c] The % ee after a single recrystallization. [d] A 33:67 mixture of C_2:meso diastereomers determined by HPLC. [e] A 74:26 C_2:meso dr. [f] A 58:42 C_2:meso dr. [g] Reaction with ethyl bromide.

Arylation of Silylphosphines (*J. Am. Chem. Soc.* **2007**, *129*, 15122.)

Scheme 1. Proposed Catalytic Cycle

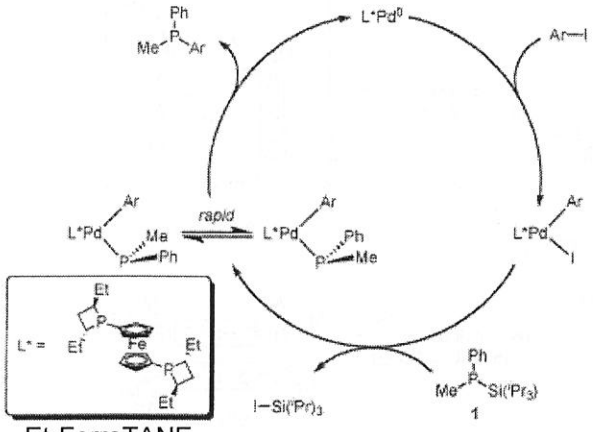
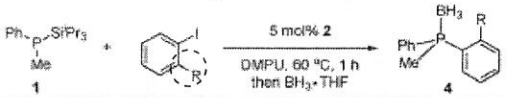
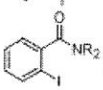
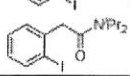


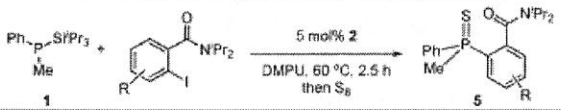
Table 1. Enantioselective Arylation with Iodoarenes

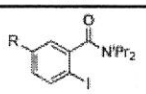
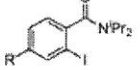
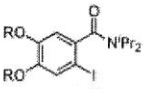
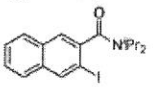
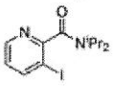
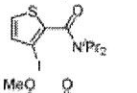
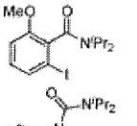
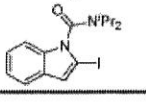


entry	Ar-I		product	% yield[a]	% ee[b]
1		R = OMe	**4a**	74	55 (*R*)
2		R = SMe	**4b**	73	63 (*R*)
3		R = NMe_2	**4c**	77	43
4		R = ^{t}Bu	**4d**	83	78
5		R = 2,6-Me_2-Ph	**4e**	76	82
6		R = 2,6-$^i Pr_2$-Ph	**4f**	77	75
7		R = Me(OMe)	**4g**[c]	65	81
8		R = Et	**4h**[c]	63	79
9		R = ^{i}Pr	**4i**[c]	53	98
10			**4j**[c]	82	32

[a] Isolated yield of the protected phosphine. [b] Measured by chiral HPLC. [c] Phosphine protected as the sulfide after heating at 60 °C for 2.5 h.

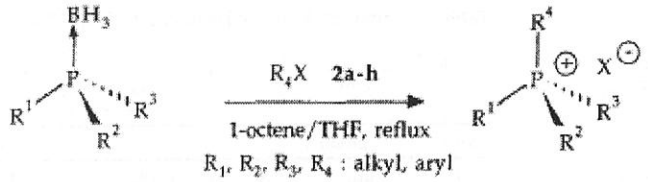
Table 2. Enantioselective Arylation with Iodobenzamides



entry	Ar-I		product	% yield[a]	% ee[b]
1		R = Me	**5a**	61	97
2		R = Cl	**5b**	83	97
3		R = OMe	**5c**	55	97
4		R = CF_3	**5d**	79	97
5		R = Cl	**5e**	80	95
6		R = Me	**5f**[c]	67	97
7		R = -CH_2-	**5g**[c]	66	97
8			**5h**	89	93
9			**5i**	75	94
10			**5j**[d]	44	92
11			**5k**	52	93
12			**5l**	62	86

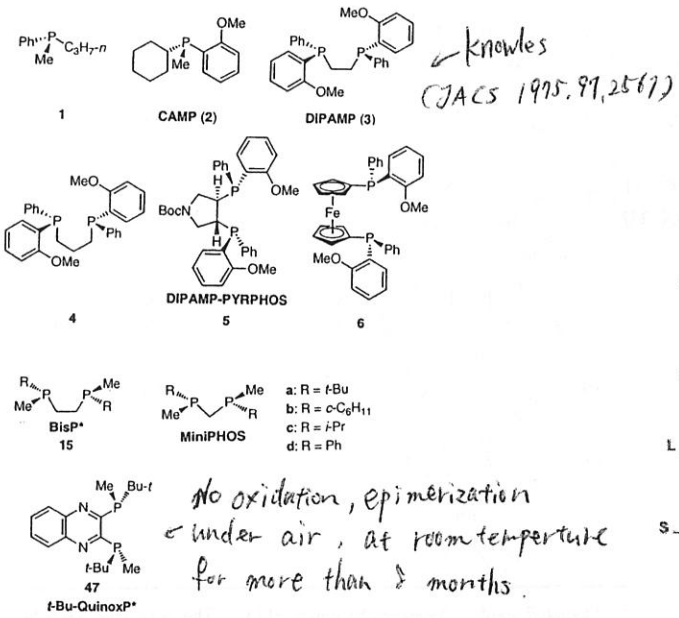
[a] Isolated yield of the phosphine sulfide. [b] Measured by chiral HPLC. [c] Reaction mixture heated at 60 °C for 4.5 h. [d] Reaction proceeded to completion after 8 h at 60 °C.

Construction of chirality on phosphonium salt (Juge et. al. *Tetrahedron Lett.* 1997, *38*, 3405.)



Application of *P*-chiral phosphine or phosphine oxide

1) Chiral ligands



knowles
(JACS 1975, 97, 2567)

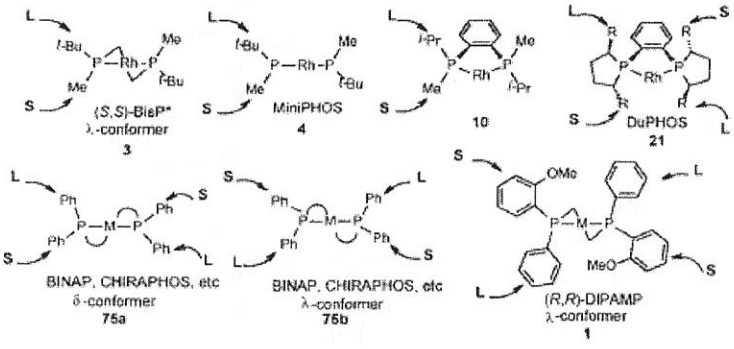
No oxidation, epimerization under air, at room temperture for more than 3 months.

These ligands are useful in mechanistic study.

⇑

+ The different substituents at phosphorus atoms can be easily distinguished in the NMR spectra of the intermediates.

+ The stereochemical assignment of any intermediate complexes is a much easier task compared to that of the complexes of tetraphenyl-substituted ligands.



2) Hydrogen-bonded self-assembled molecules (Imamoto et. al. *J. Am. Chem. Soc.* **2000**, *122*, 12659.)

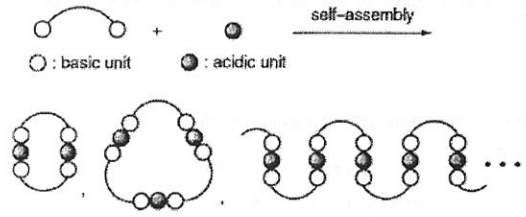


Figure 1. Concept of acid–base interacted supramolecules.

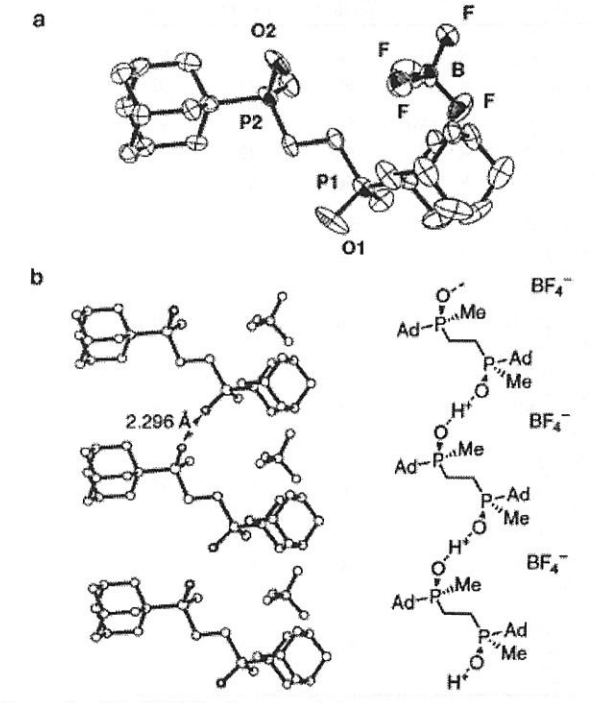
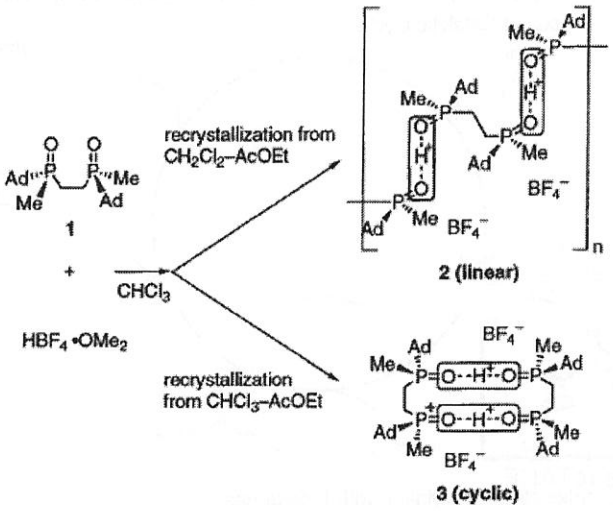


Figure 2. (a) ORTEP diagram of 2, showing 30% probability ellipsoids. The solvent molecule (CH_2Cl_2) is omitted for clarity. Selected bond lengths (Å): P1–O1 = 1.558(7), P2–O2 = 1.529(6). (b) Packing diagram of complex 3 looking down the *c* axis. The distance between two intermolecular oxygen atoms is 2.296(9) Å.

Scheme 1



Scheme 2