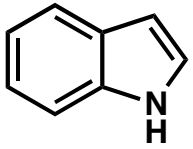
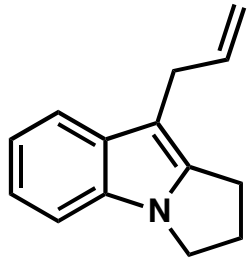
Mechanism Problem



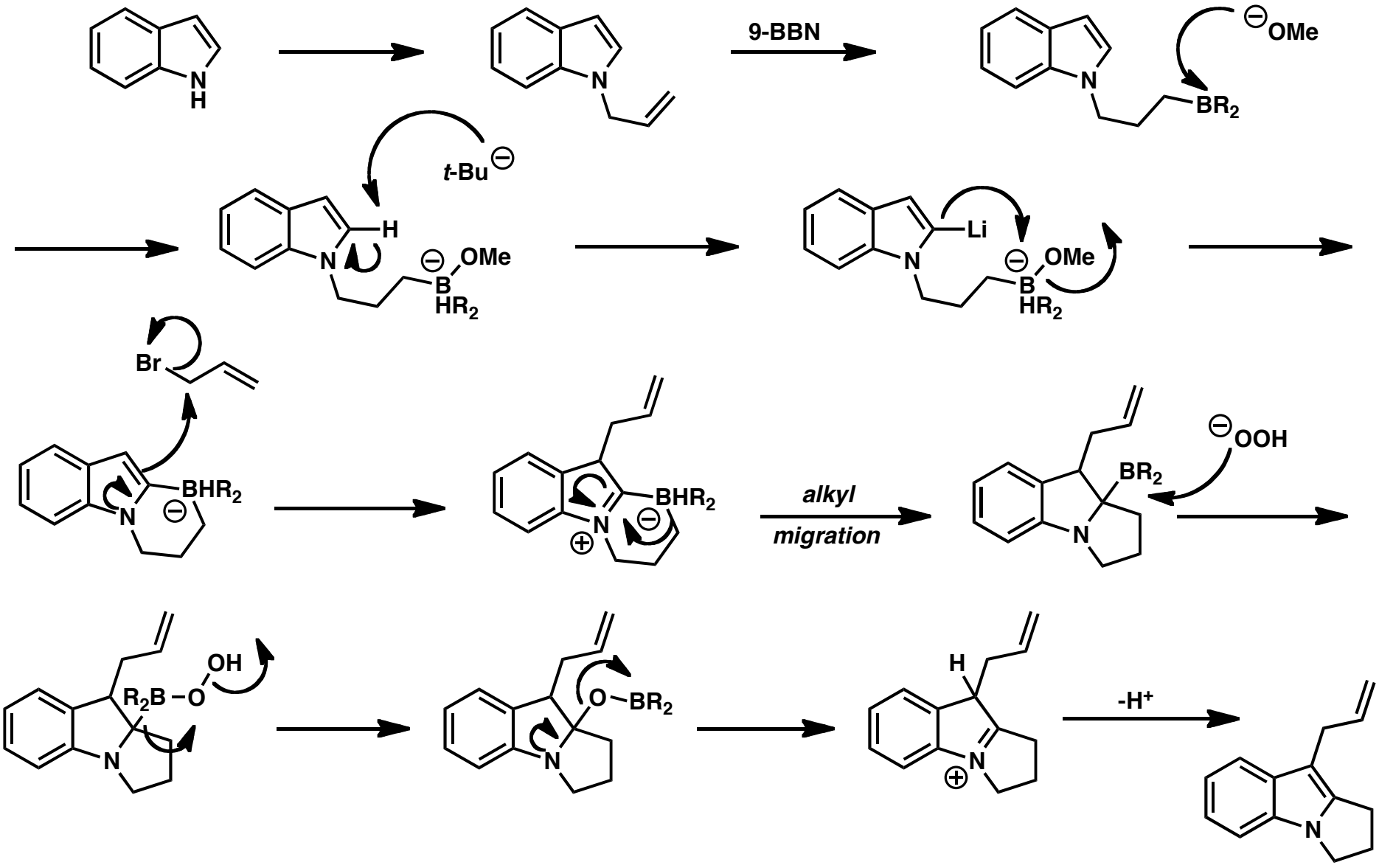
1. NaH
allyl bromide, THF

2. 9-BBN (1.2 equiv), THF, rt;
NaOMe (1.2 equiv);
***t*-BuLi (2.4 equiv), TMEDA (2.4 equiv)**
–30 to rt;
allyl bromide;
30% H_2O_2, aq. NaOH, 0 °C



(58% yield)

Mechanism Problem



Terashima, *TL* **1992**, *33*, 6849-6852.

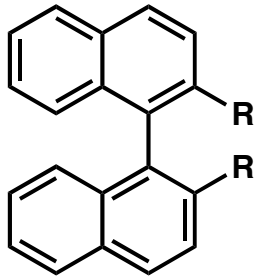
Enantioselection by C_1-Symmetric Ligands

Design and Applications in Asymmetric Catalysis

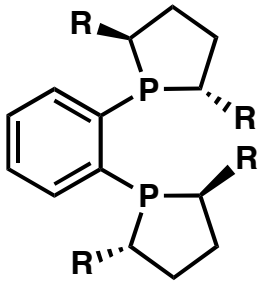
Boram Hong
Stoltz Group
January 10, 2011

Privileged Ligand Structures

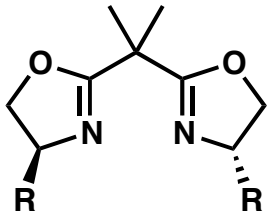
Prevalence of C_2-symmetry



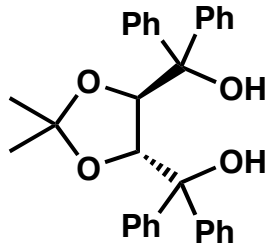
BINOL (R = OH)
BINAP (R = PPh_2)



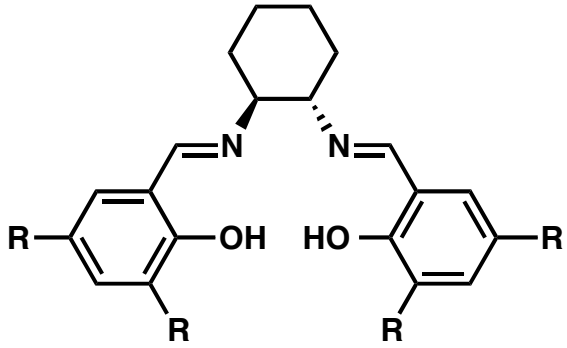
DuPhos



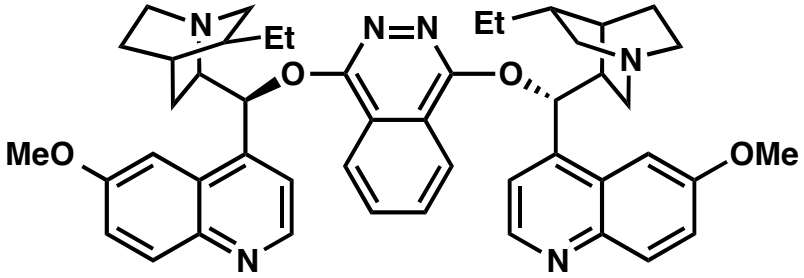
BOX



TADDOL



SALEN



Cinchona alkaloid

Diverse applications: Diels-Alder, hydrogenation, Mukaiyama aldol, conjugate additions, cyclopropanation, epoxidation

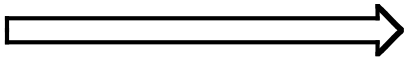
Jacbosen, Science **2003**, *299*, 1691–1693.

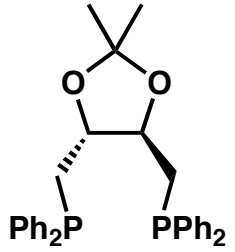
First C_2-symmetric ligands

DIOP & DIPAMP

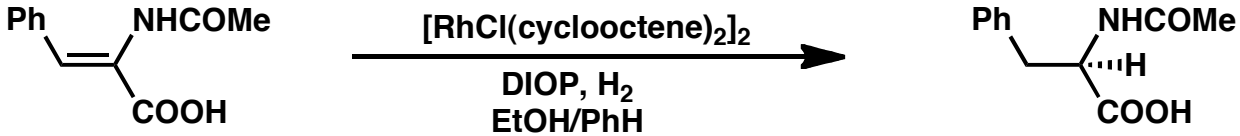
Kagan's DIOP

- **Ligand conformations must have maximum rigidity**
- **Ligands must stay firmly bonded to the metal**
- **Avoid competing, diastereomeric transition states via C_2-symmetry**





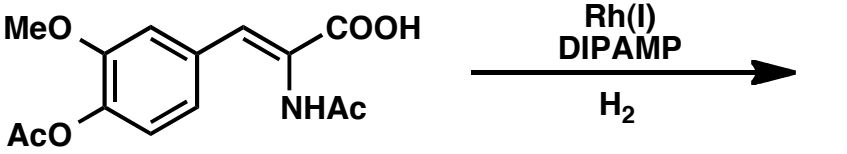
DIOP



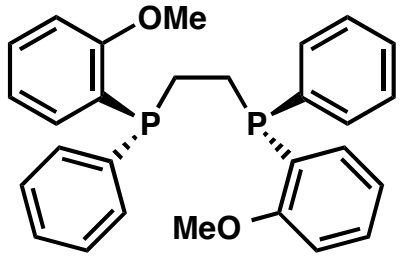
(95% yield)

72% ee

Knowles' DIPAMP



95% ee



DIPAMP

Kagan, *J. Am. Chem. Soc.* **1972**, *94*, 6429-6433.
Knowles, *Adv. Synth. Catal.* **2003**, *345*, 3-13.

Rational Design of C_1-symmetric Bisphosphine Ligand

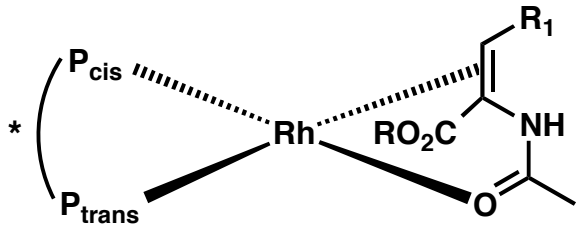
Electronic and Steric Asymmetry

– Mechanism of asymmetric hydrogenation of dehydroamino acids reported by Halpern

– Oxidative addition of H_2 is rate-determining step

– Important interactions: occupied d_{yz} of Rh and σ^* of hydrogen

d-π^* back-donation from Rh to olefin



P_{cis} : steric control (enantioselection)

P_{trans} : electronic control

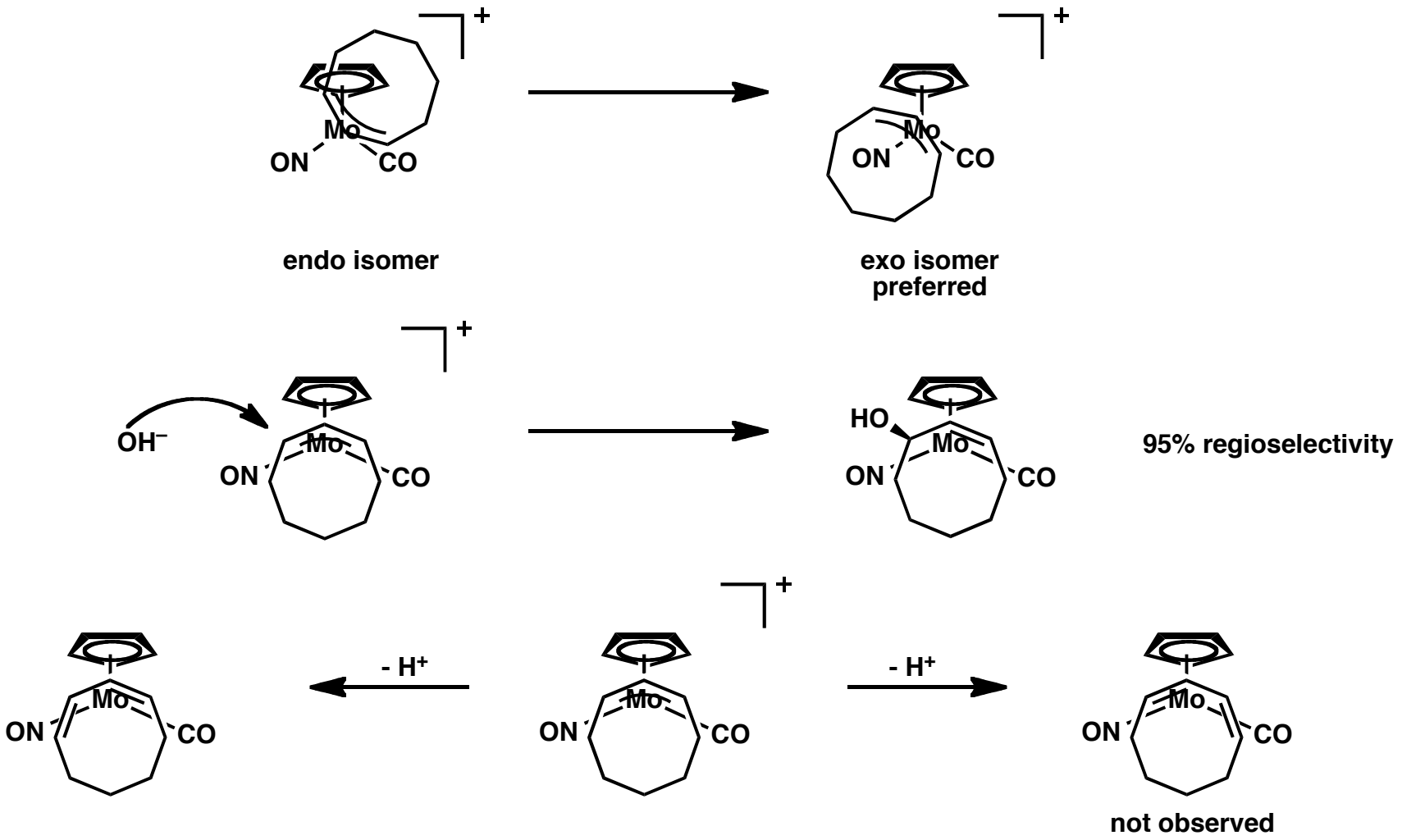
– Distinct roles; need to optimize each phosphine group individually

Achiwa, *Synlett* **1992**, 169-178.

Electronic Desymmetrization

Controlling Regioselectivity

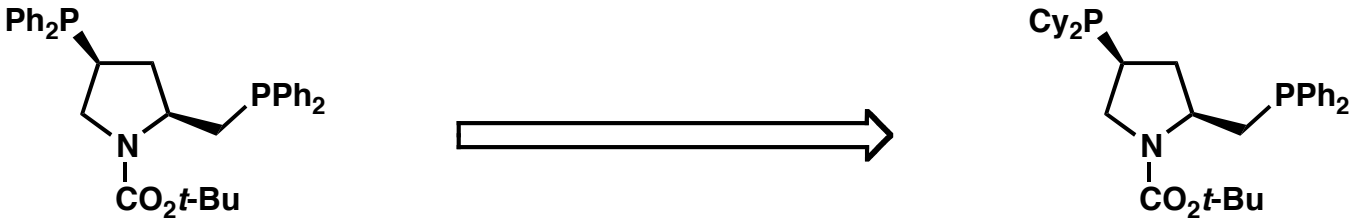
– Faller studied nucleophilic addition reactions on unsaturated ligands bound to Mo



Faller, *J. Am. Chem. Soc.* **1984**, *3*, 1231-1240.

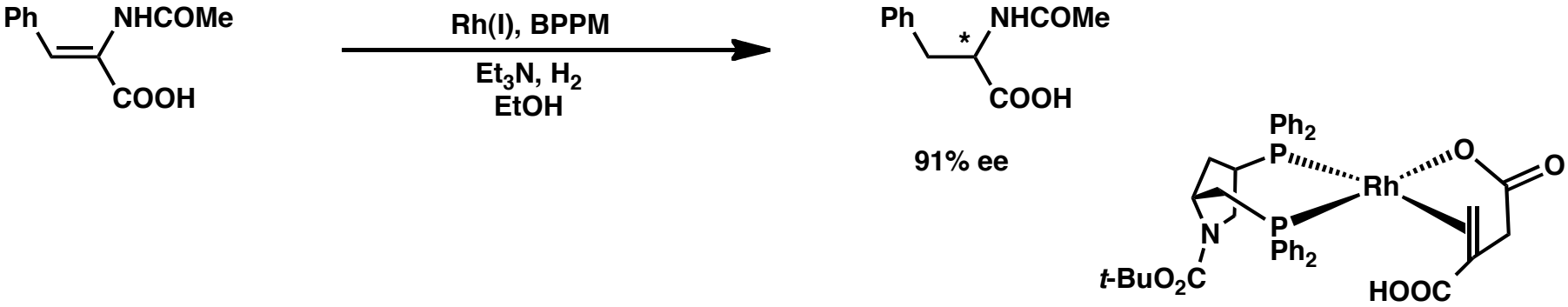
Rational Design of C_1-Symmetric Bisphosphine Ligand

Electronic and Steric Asymmetry



BPPM
(2*S*, 4*S*)-*N*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine

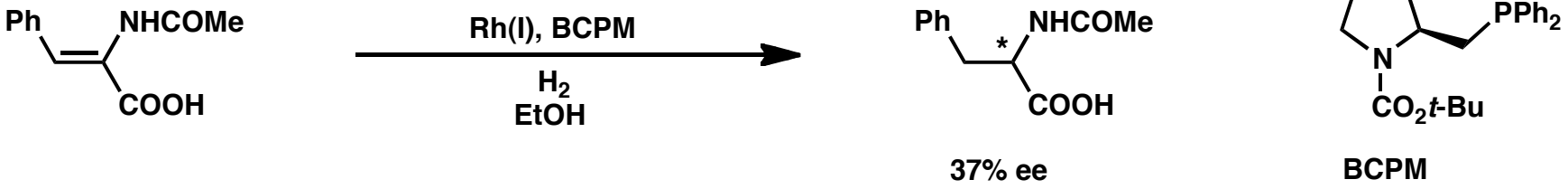
BCPM

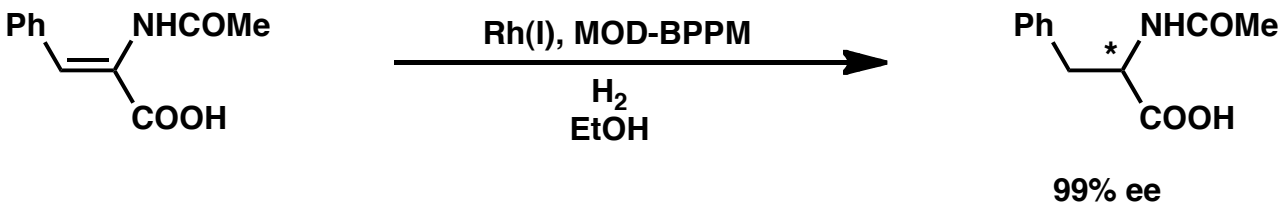


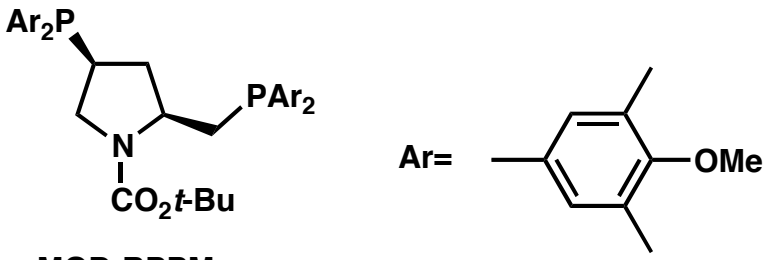
Achiwa, *J. Am. Chem. Soc.* **1976**, *98*, 8265.
Achiwa, *Synlett* **1992**, 169-178.

Rational Design of C_1-Symmetric Bisphosphine Ligand

Electronic and Steric Asymmetry

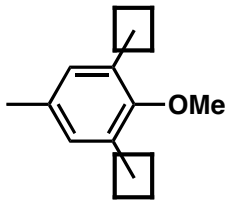






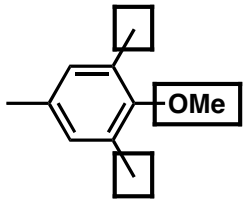
cis **(enantioselecting function)**

steric effect of m-methyl groups



trans **(rate-acceleration)**

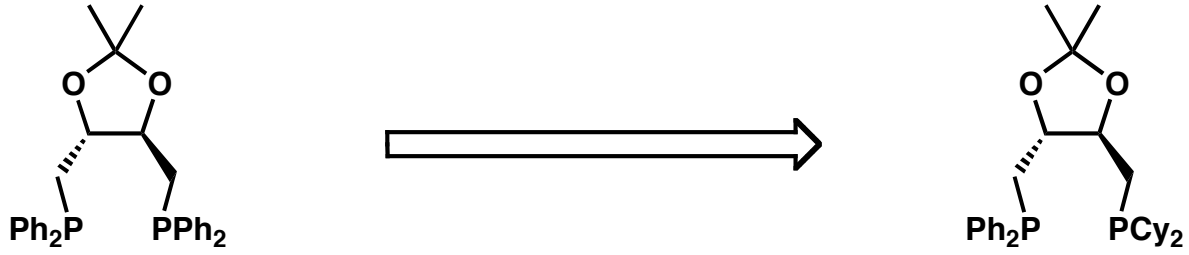
electron-donating effect



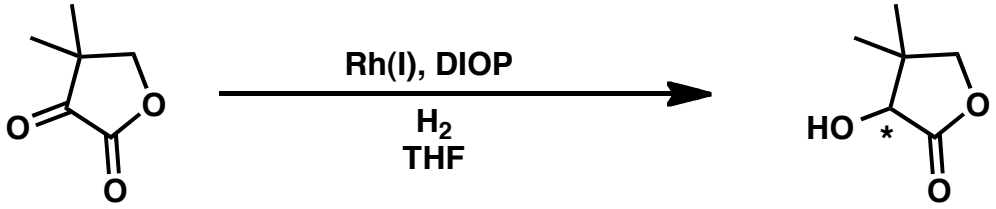
Achiwa, *Synlett* **1992**, 169-178.

Rational Design of C_1-Symmetric Bisphosphine Ligand

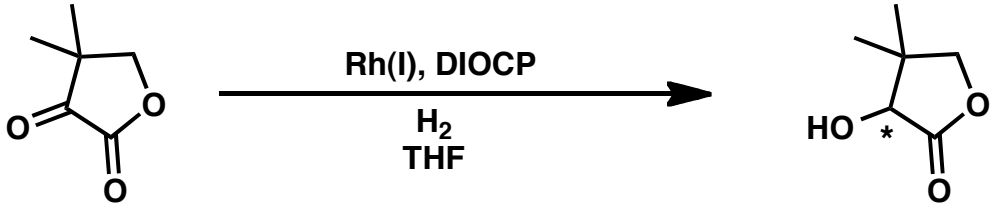
Development of Modified DIOP ligand



DIOP **DIOCP**



52% ee



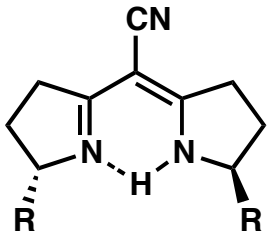
75% ee

– activity and enantioselectivity of catalyst enhanced by desymmetrization of DIOP

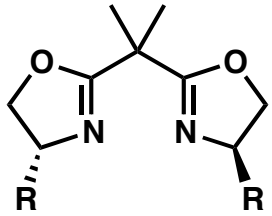
Achiwa, *Synlett* **1992**, 169-178.

From C_2-Symmetric to Nonsymmetrical Ligands

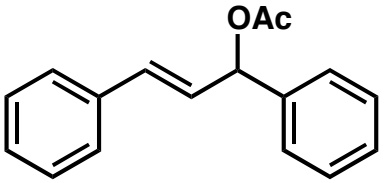
BOX to PHOX



Semicorrins

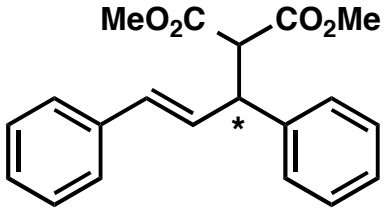


BOX

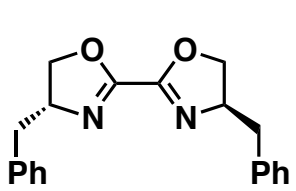


$[Pd(C_3H_5)Cl]_2$ (1 mol%)

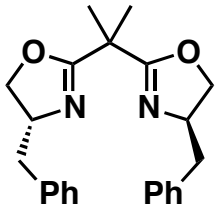
L* (2.5 mol%)



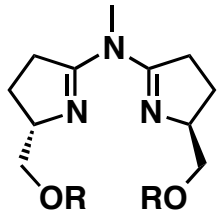
Ligand	Conditions	% yield	% ee
1	$NaCH(CO_2Me)_2$, THF, 50 °C	86	77
2	$CH_2(CO_2Me)_2$, BSA, KOAc CH_2Cl_2, 23 °C	97	88
3	"	99	95
4	"	97	97



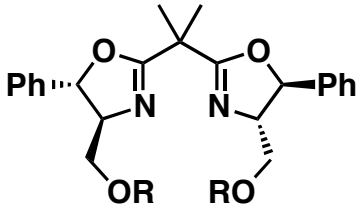
1



2



3



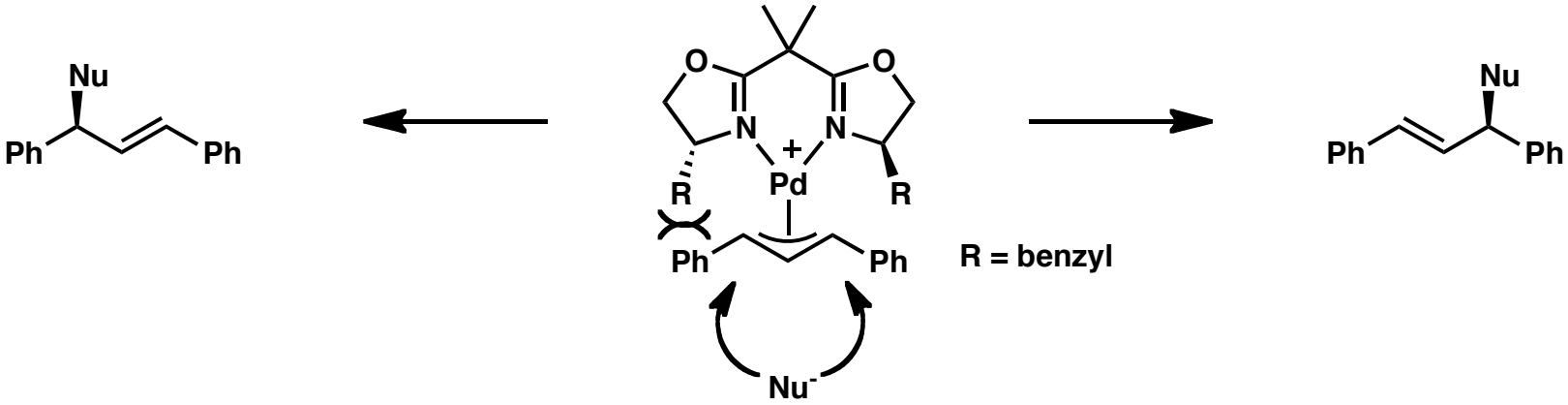
4

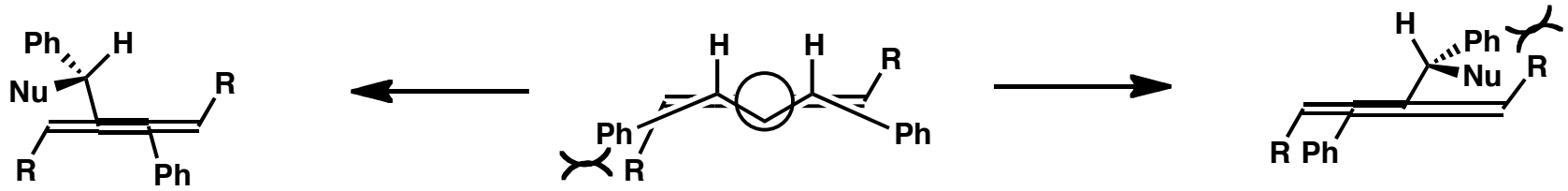
R= $SiMe_2$*t*-Bu

Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339-345.

From C_2-Symmetric to Nonsymmetrical Ligands

BOX to PHOX





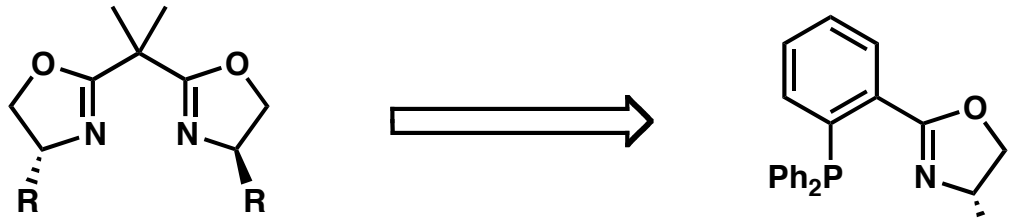
– steric repulsion between allylic phenyl group and benzyl substituent

– nucleophile attacks the longer, more strained Pd–C bond: strain release

Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339-345.

Controlling Regioselectivity via Electronic Differentiation

PHOX

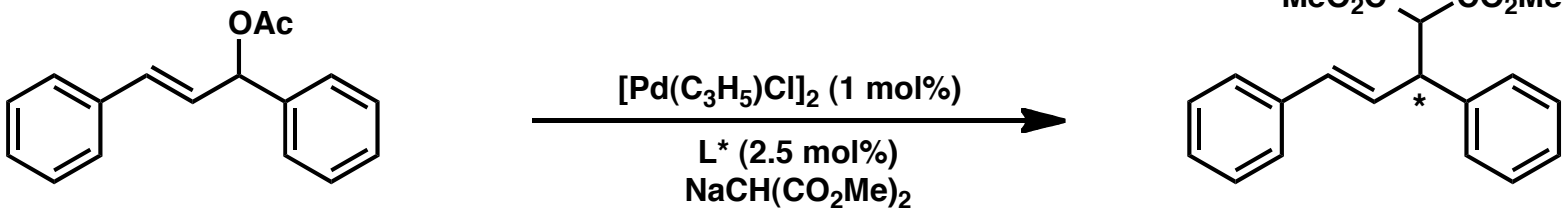


BOX **PHOX**

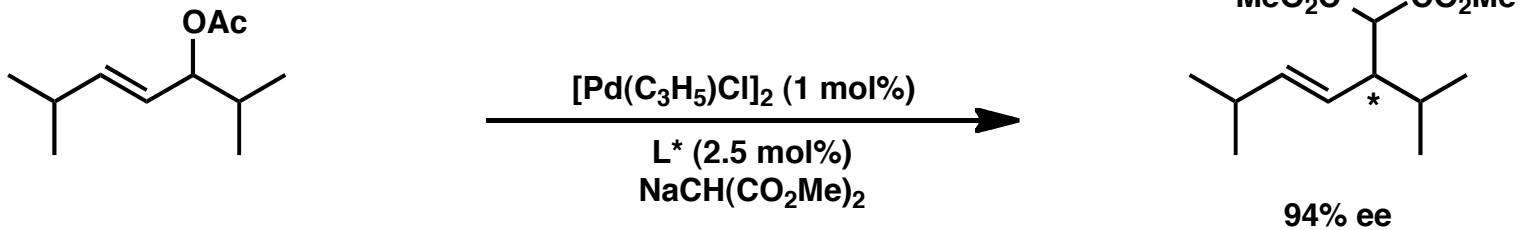
– Desymmetrize N,N-ligand to mixed donor P,N-ligand

– "soft" P-ligand (π–acceptor) and "hard" N-ligand (σ–donor)

– exploit trans influence of P atom



98.5% ee

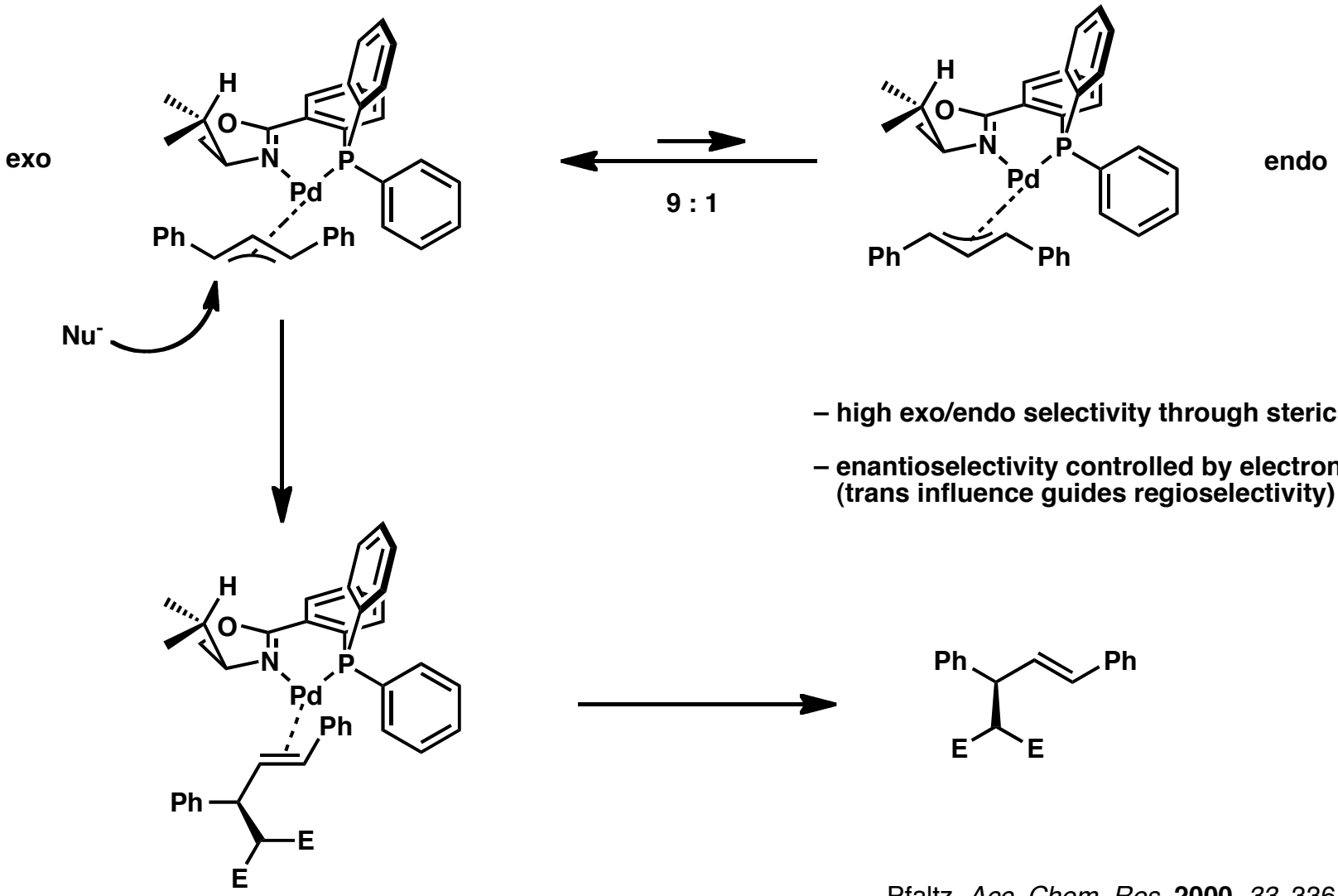


94% ee

Pfaltz, *Proc. Natl. Acad. Sci*. **2004**, *101*, 5723-5726.
Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336-345.

Controlling Regioselectivity via Electronic Differentiation

PHOX



– high exo/endo selectivity through sterics

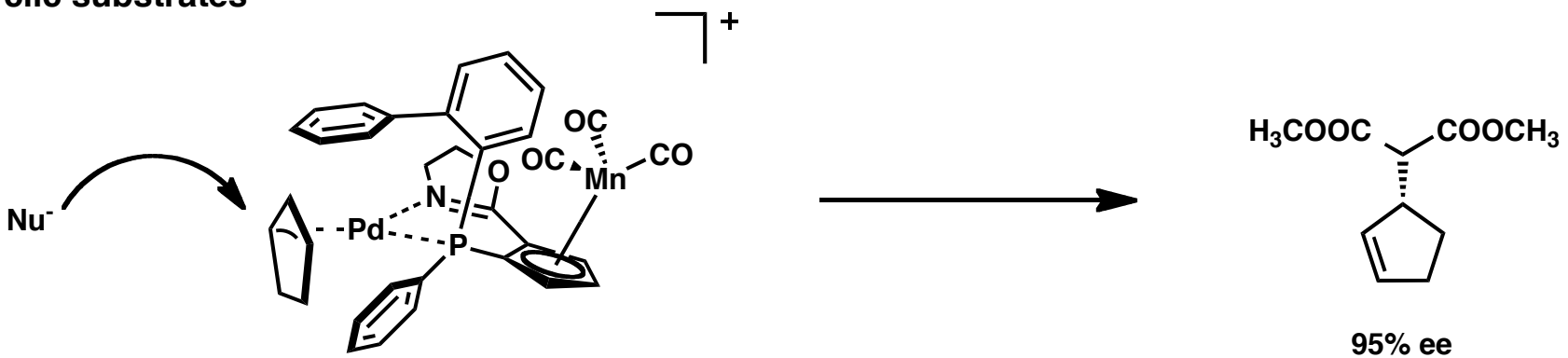
– enantioselectivity controlled by electronics (trans influence guides regioselectivity)

Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336-345.

Controlling Regioselectivity via Electronic Differentiation

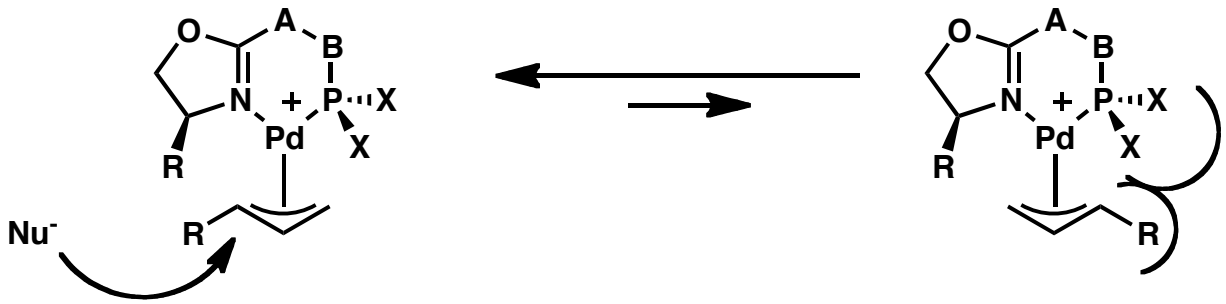
PHOX

Cyclic substrates



95% ee

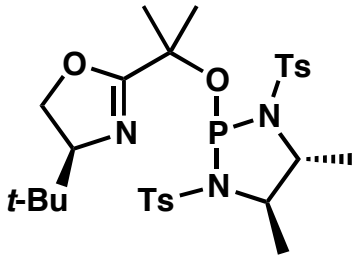
Nonsymmetrical substrates



Nu⁻ = $NaCH(CO_2Me)_2$

84	**:**	**16**	**94% ee (R = phenyl)**
98	**:**	**2**	**98% ee (R = 1-naphthyl)**

L =

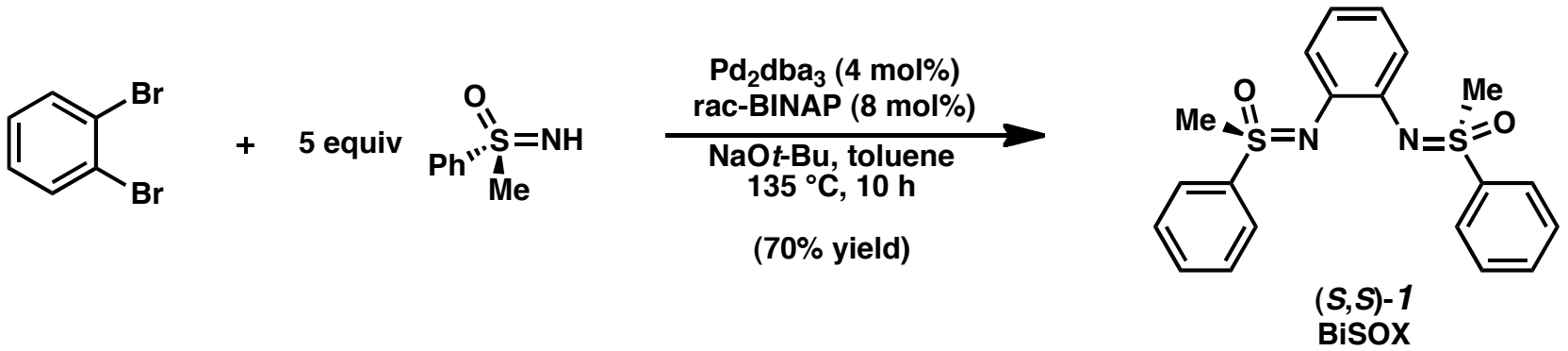


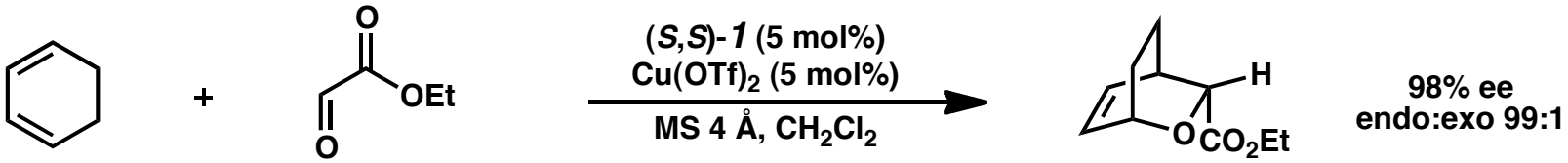
– Usually Pd complexes favor linear products
– More cationic Pd and bulky phosphine favors branched products

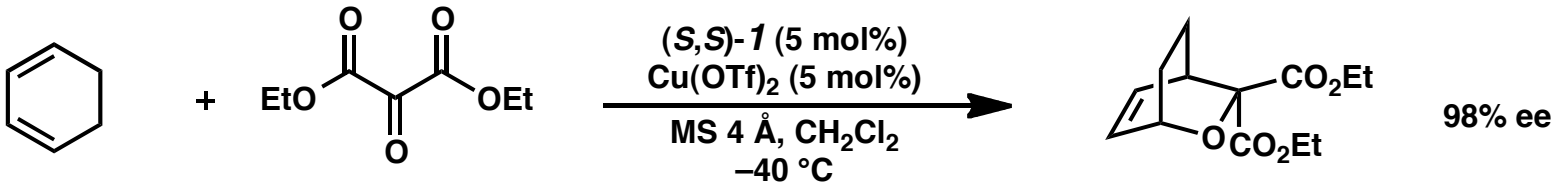
Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336-345.

C_2-Symmetric N,N-ligands

Sulfoximines





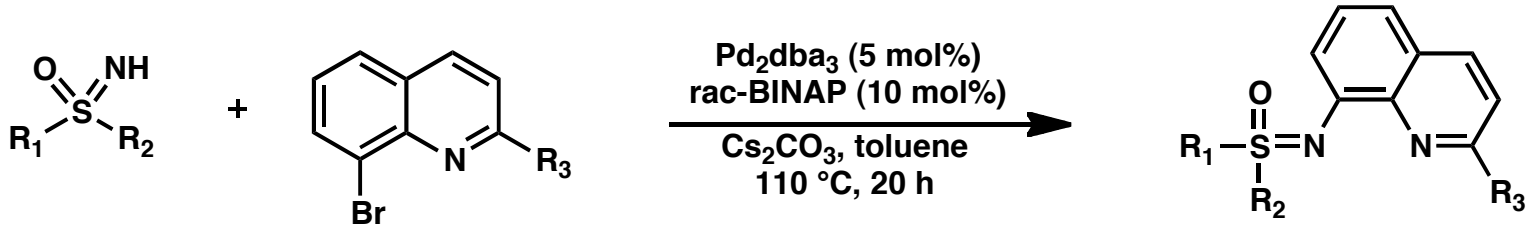


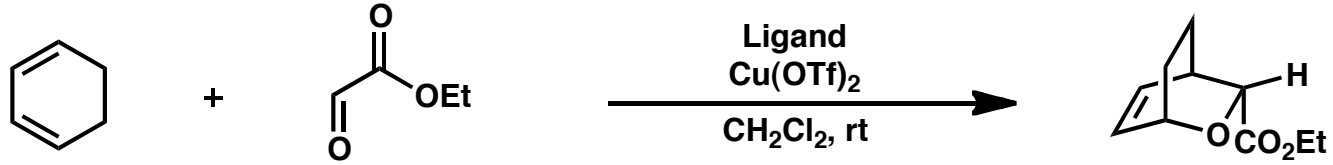
Bolm, *J. Am. Chem. Soc.* **2001**, *123*, 3830-3831.

From C_2- to C_1-Symmetric Sulfoximines

– **Spectroscopic investigations of BiSOX Cu(II) complexes revealed distorted, nonsymmetric square pyramidal geometry**

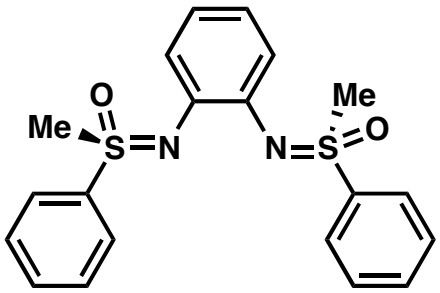
– **Two coordinating sulfoximine nitrogens occupy non-equivalent positions**



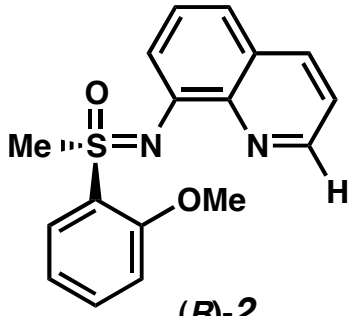


entry	ligand	% yield	%ee	endo:exo
1	1	62	99	99:1
2	2	98	91	98:2
3*	2	65	96	99:1

*with $Cu(ClO_4)_2$, –10 °C



(*S,S*)-*1*
BiSOX

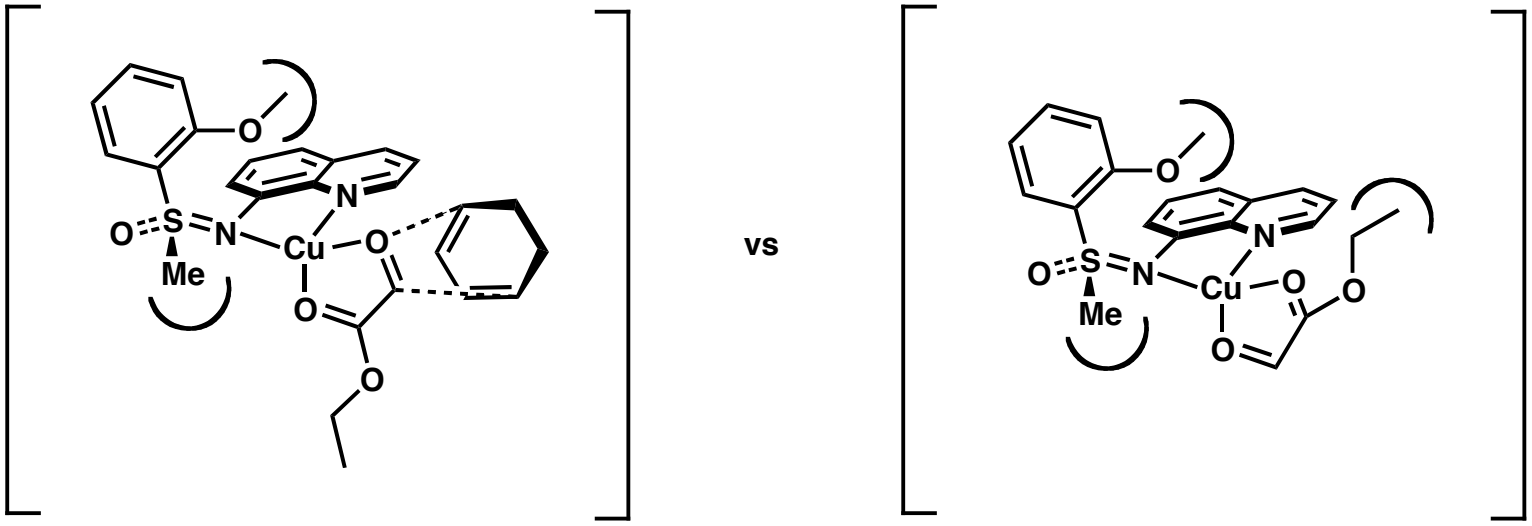


(*R*)-*2*

Bolm, *J. Am. Chem. Soc.* **2003**, *125*, 6222-62227.
Bolm, *Chem. Commun.* **2003**, 2826-2827.

From C_2- to C_1-Symmetric Sulfoximines

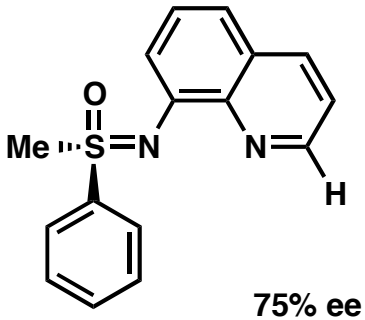
Mechanistic Model



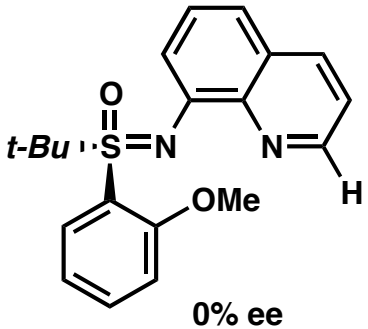
A
favored

B

– Enantioselectivity of the reaction is determined by the coordination mode of substrate



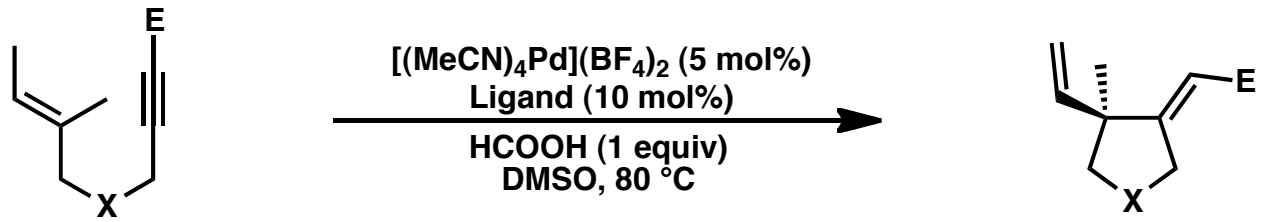
75% ee



0% ee

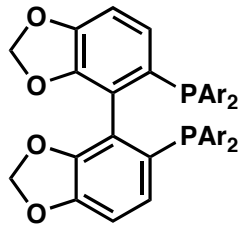
Bolm, *Chem. Commun.* **2003**, 2826-2827.

C_1-Symmetric P,N-ligand in Enyne Cyclization

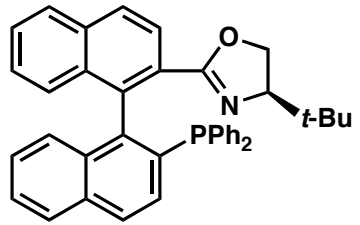


X = $C(CO_2Et)_2$, E = $CONMe_2$

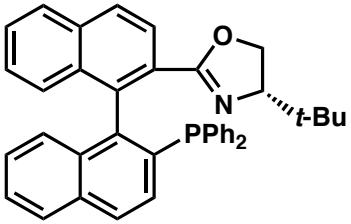
ligand	time	% yield	% ee	config.
1	3	>99	6	*S*
2	24	42	81	*S*
3	9	>99	86	*S*
4	24	9	50	*R*



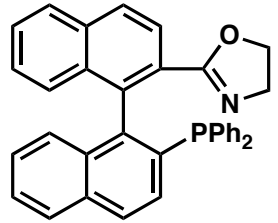
1



2



3



4

– C_1 symmetry yields better enantioselectivities than C_2 symmetry

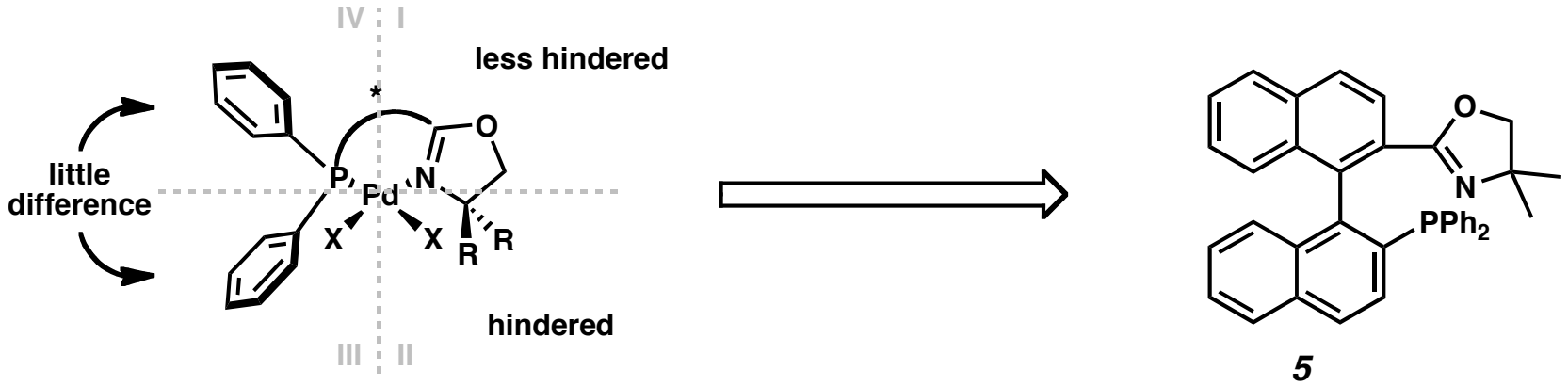
– Sense of chirality does does not matter

Mikami, *Eur. J. Org. Chem.* **2003**, 2552-2555.

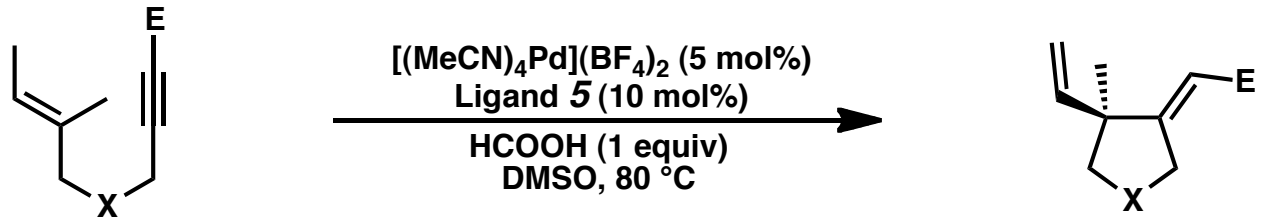
C_1-Symmetric P,N-ligand in Enyne Cyclization

Rational Design of Optimized Ligand

X-ray analyses reveals:



5



X = $C(CO_2Et)_2$, E = $CONMe_2$

(>99% yield)

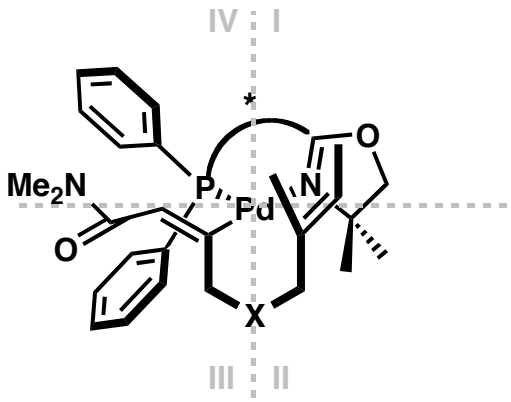
95% ee

previous best 86% ee (with *t*-Bu ligand)

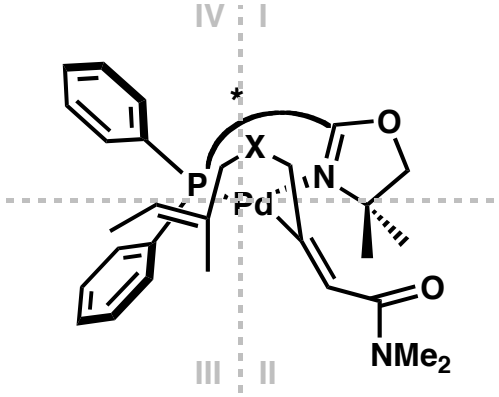
Mikami, *Eur. J. Org. Chem.* **2003**, 2552-2555.

C_1-Symmetric P,N-ligand in Enyne Cyclization

Transition State Analysis



A



B

favored

Steric factors:

– A: steric repulsion between terminal Me groups of substrate and dimethyl substituents of oxazoline

– B: terminal akenyl Me groups cannot fully differentitate the two Ph groups

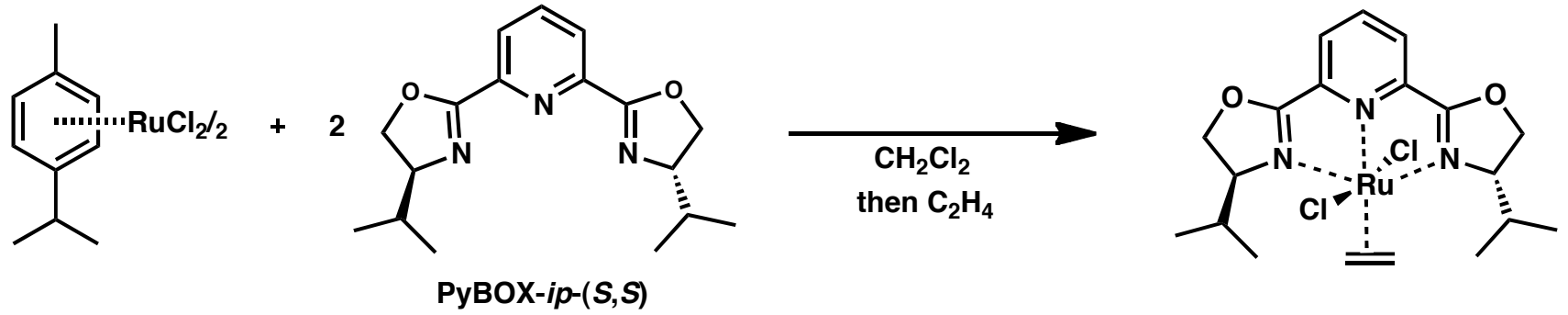
Electronic factor:

– π-coordination of olefin *trans* to P is favored (*trans* influence)

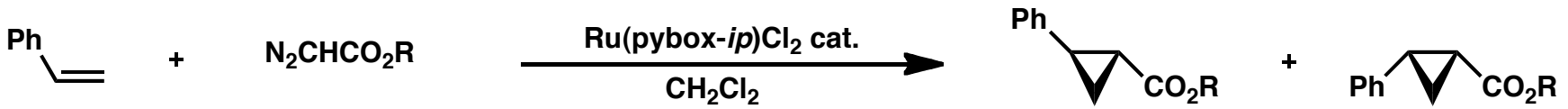
Mikami, *Eur. J. Org. Chem.* **2003**, 2552-2555.

Asymmetric Cyclopropanation of Olefins with Diazoacetates

PyBOX



PyBOX-*ip*-(*S*,*S*)



up to 98:2 *trans*:*cis*

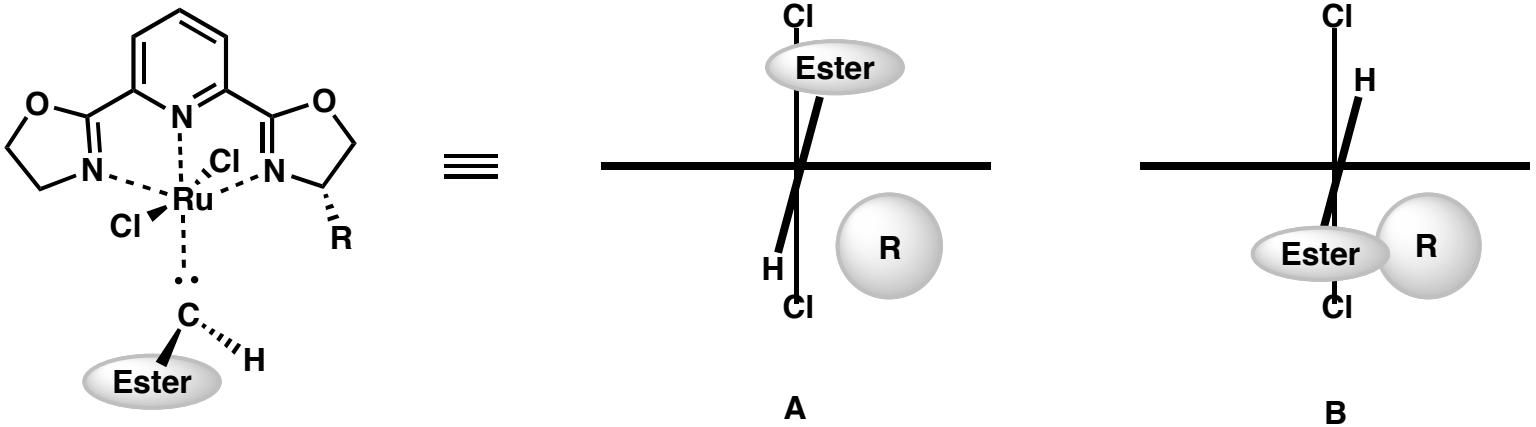
up to 97% ee

Nishiyama, *J. Am. Chem. Soc.* **1994**, *116*, 2223-2224.

Asymmetric Cyclopropanation of Olefins with Diazoacetates

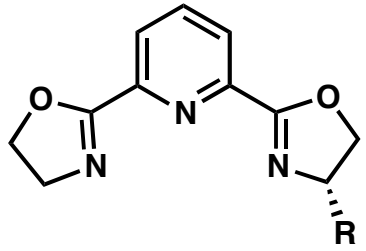
Single-Chiral PyBOX

– Analysis of transition states reveals C_2-symmetry may not be necessary



A
favored

B

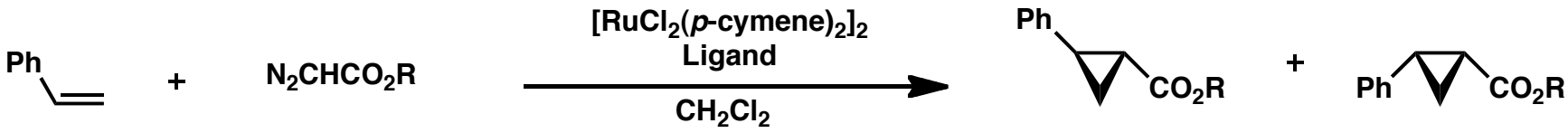


R = *t*-Bu

Nishiyama, *Tetrahedron: Asymmetry* **1998**, *9*, 2865-2869.

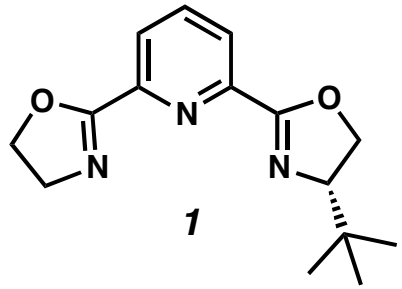
Asymmetric Cyclopropanation of Olefins with Diazoacetates

Single-Chiral PyBOX

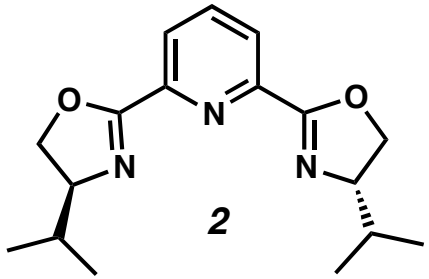


trans ***cis***

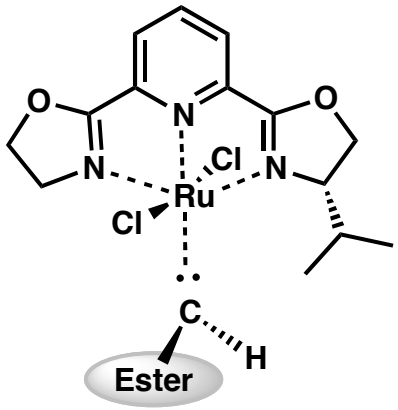
entry	Pybox	N_2CHCO_2R, R=	% yield	*trans*:*cis*	% ee (*trans*)	% ee (*cis*)
1	***1***	Me	88	83:17	86	63
2	***2***	Me	82	89:11	92	97
3	***1***	Et	93	89:11	90	66
4	***1***	*i*-Pr	80	92:8	90	68
5	***1***	*l*-Menthyl	84	99:1	94	64

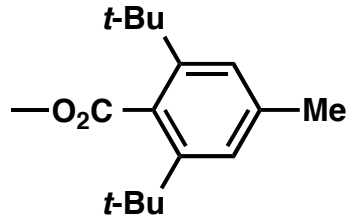


1



2



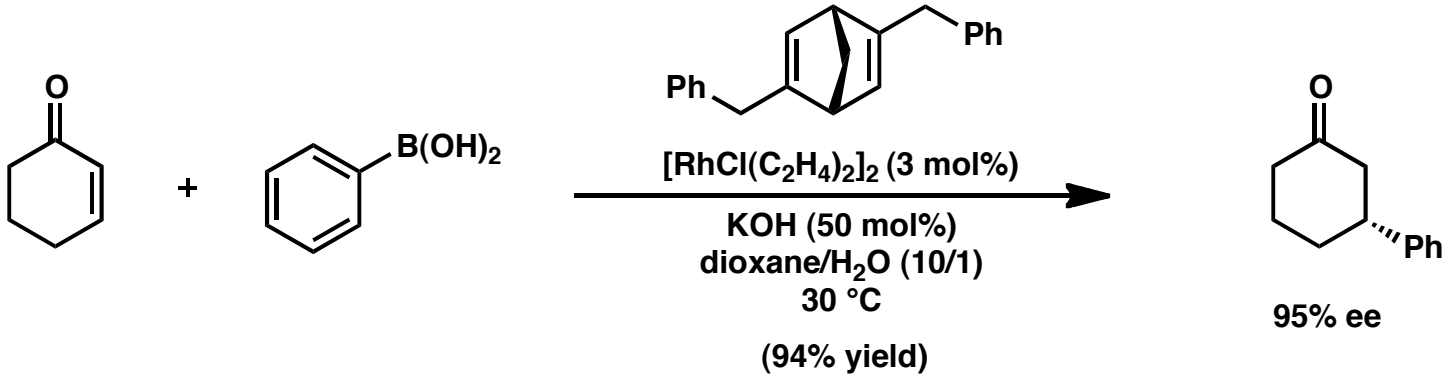
Ester = 

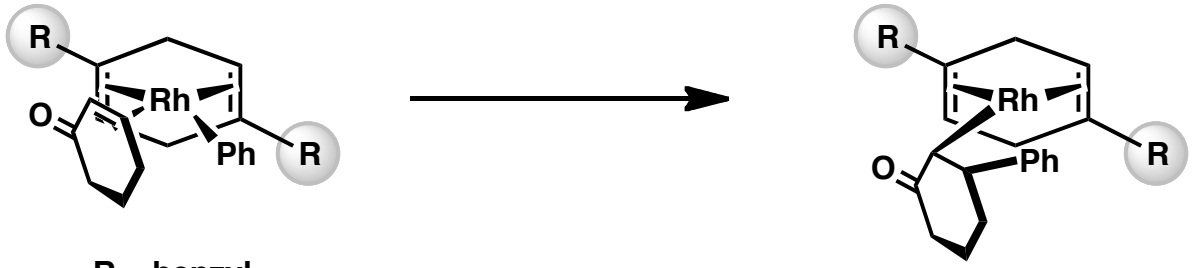
– Only one isomer detected by NMR analysis

Nishiyama, *Tetrahedron: Asymmetry* **1998**, *9*, 2865-2869.

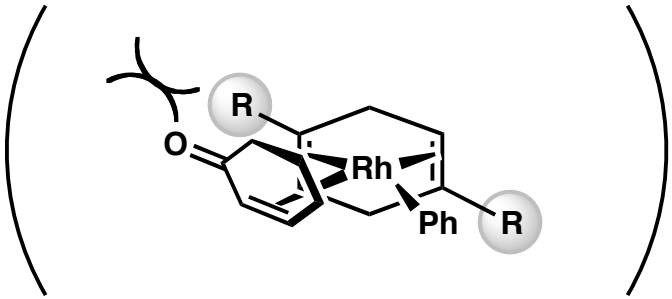
Asymmetric 1,4-Additions of Organoboron Reagents

C_2-Symmetric Dienes





R = benzyl

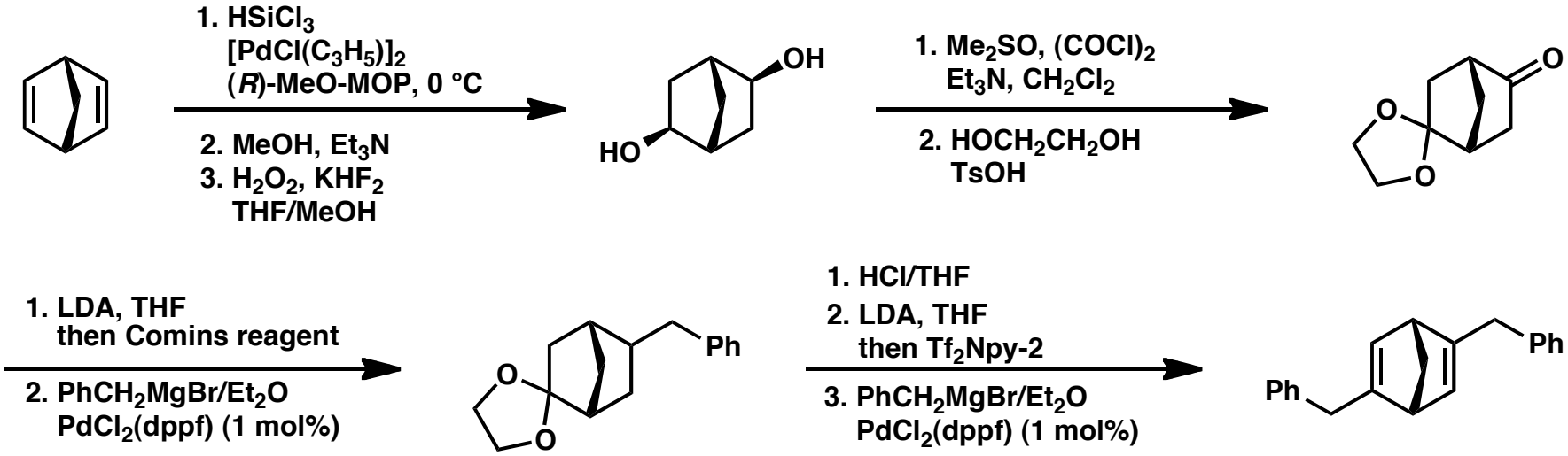


Hayashi, *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509.

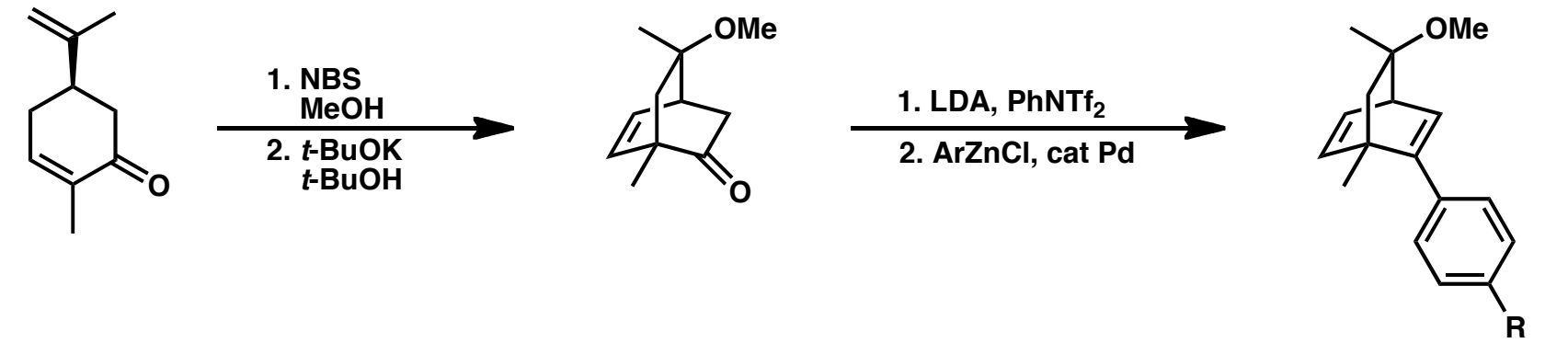
Asymmetric 1,4-Additions of Organoboron Reagents

Ligand Synthesis

Hayashi's ligand synthesis



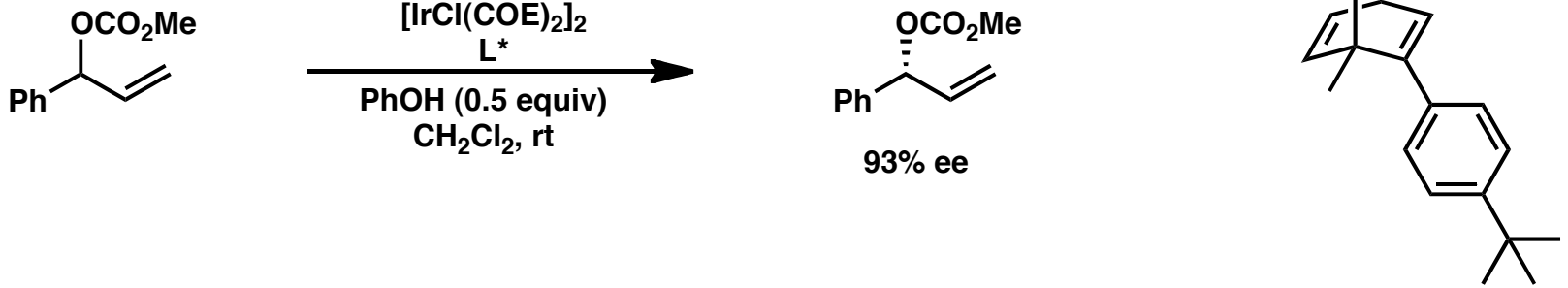
Carreira's ligand synthesis

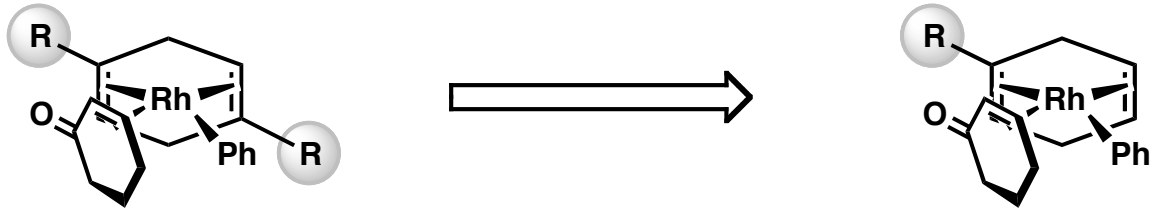


Hayashi, *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509.
Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629.

Asymmetric 1,4-Additions of Organoboron Reagents

Rationale Behind Application of C_1-Symmetric Diene





– Assume coordination of unsaturated substrate to rhodium occurs after transmetalation of the organoborane

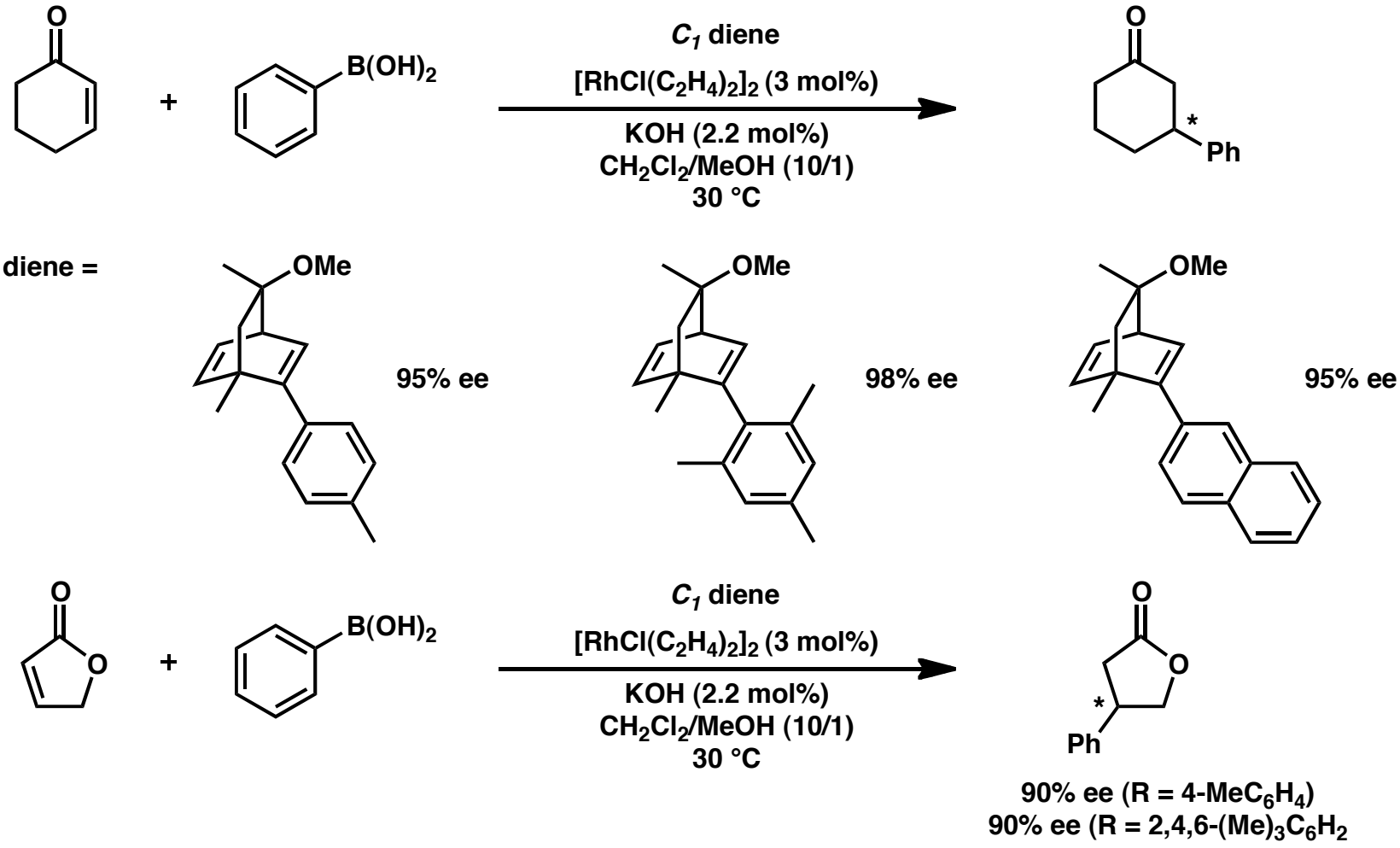
– Aryl group would block one of the R substituents

– Therefore, only one substituent would be sufficient for chiral recognition of enantiotopic faces

Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629.
Darses, *Angew. Chem. Int. Ed.* **2008**, *47*, 7669-7672.

Asymmetric 1,4-Additions of Organoboron Reagents

Application of C_1-Symmetric Diene



90% ee (R = 4-MeC_6H_4)
90% ee (R = 2,4,6-$(Me)_3C_6H_2$

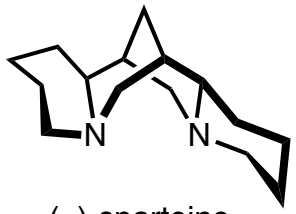
– high ee's (up to 98% ee) with a wide range of boronic acids (electron-rich, -deficient)

Darses, *Angew. Chem. Int. Ed.* **2008**, *47*, 7669-7672.

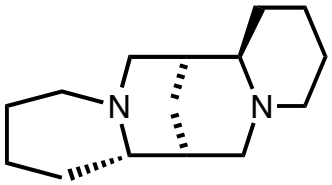
Oxidative Kinetic Resolution of Secondary Alcohols

Sparteine, a C_1-Symmetric Ligand

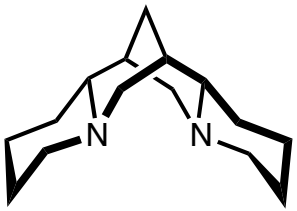
C_1



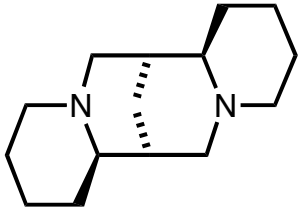
(–)-sparteine



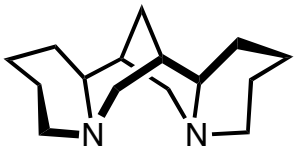
C_2



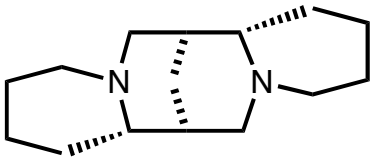
(–)-α-isosparteine



C_2



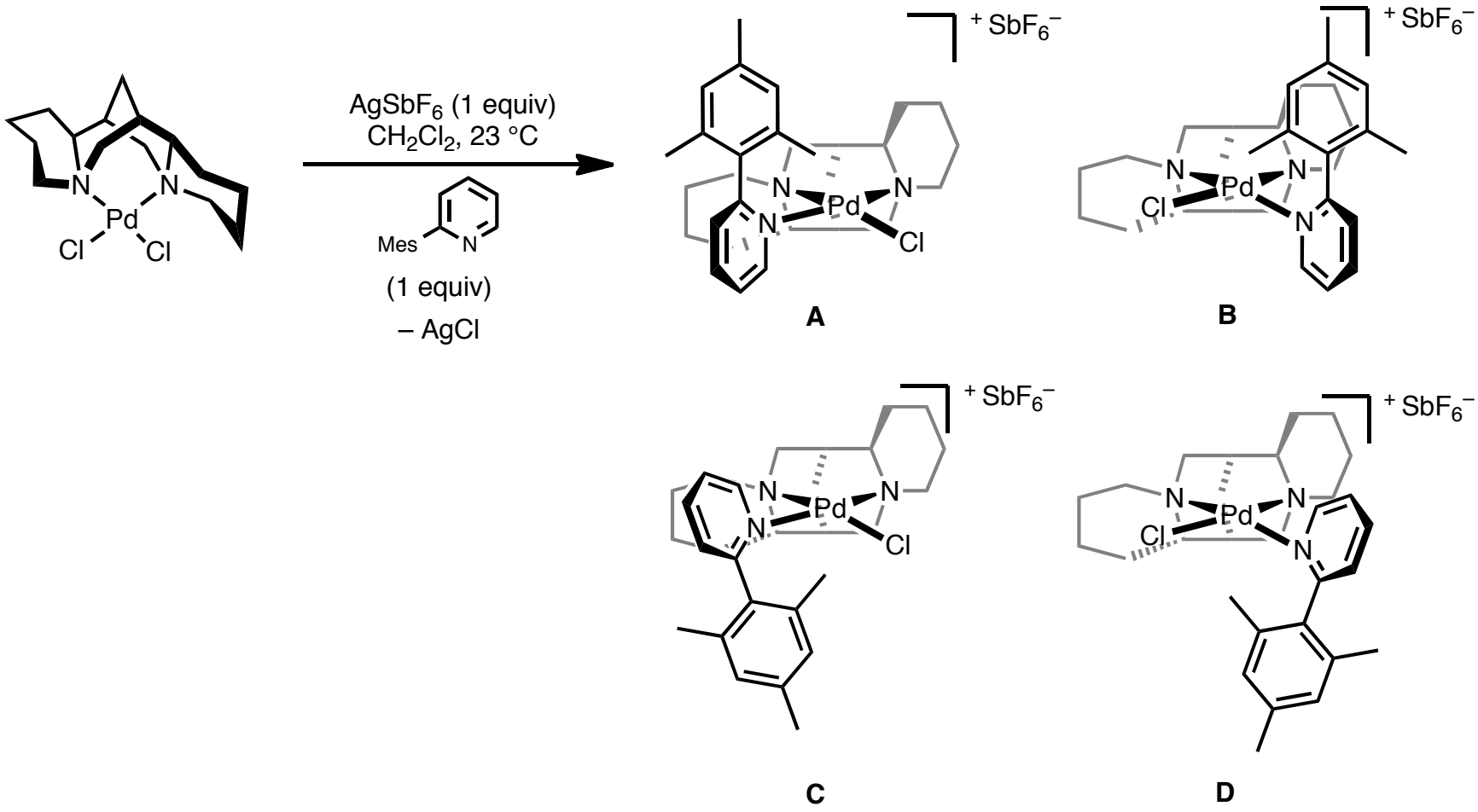
(+)-β-isosparteine



Stoltz *J. Am. Chem. Soc.* **2008**, *130*, 15957-15966.

Oxidative Kinetic Resolution of Secondary Alcohols

Regioselectivity by Sparteine

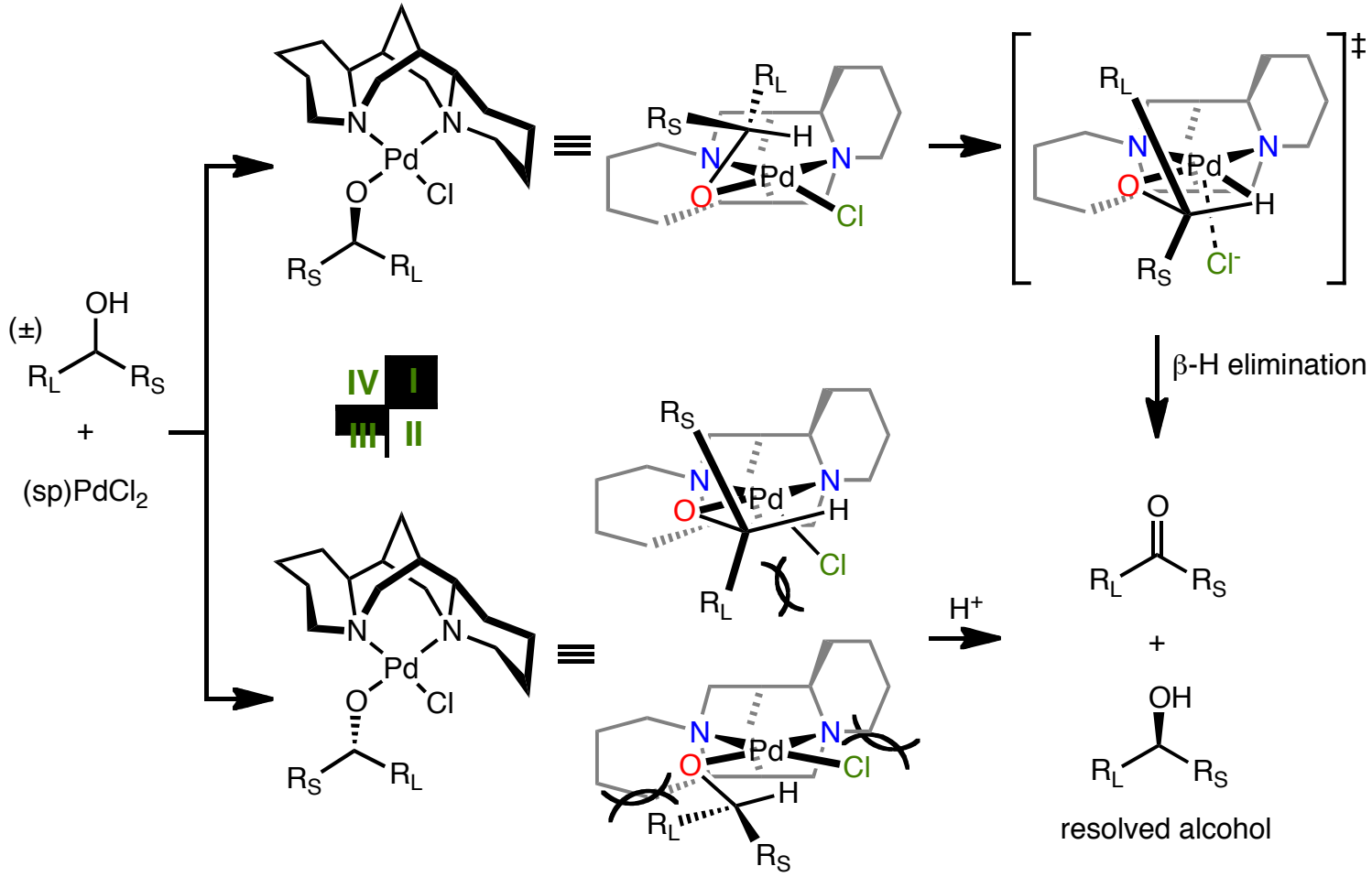


– Only A observed with bulk of substrate oriented toward vacant quadrant IV

Stoltz *J. Am. Chem. Soc.* **2008**, *130*, 15957-15966.

A Proposed Model for the Observed Stereochemistry

Sparteine and C_1-Symmetry



Stoltz *J. Am. Chem. Soc.* **2008**, *130*, 15957-15966.

Summary

– C_2-symmetry is still a dominant structural motif

– Advantage of C_2-symmetry: reduced number of possible, competing diastereomeric structures

– Careful consideration of transition states showed that C_2-symmetry is not always necessary

– C_1-symmetric ligands allow the application of steric and electronic differentiation

– C_1-symmetric ligands also offer the possibility of creating a single site of reactivity via desymmetrization of transition states

– With the continuous discovery of new "privileged" frameworks, C_1-symmetric ligands are likely to play an increasing role in the development of asymmetric catalysis