

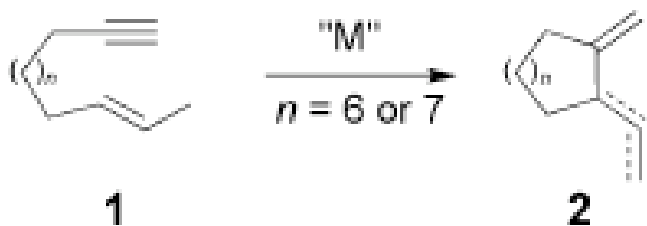


# Asymmetric Cycloisomerization of 1,6- and 1,7-Enynes by Transition- Metal Catalysts

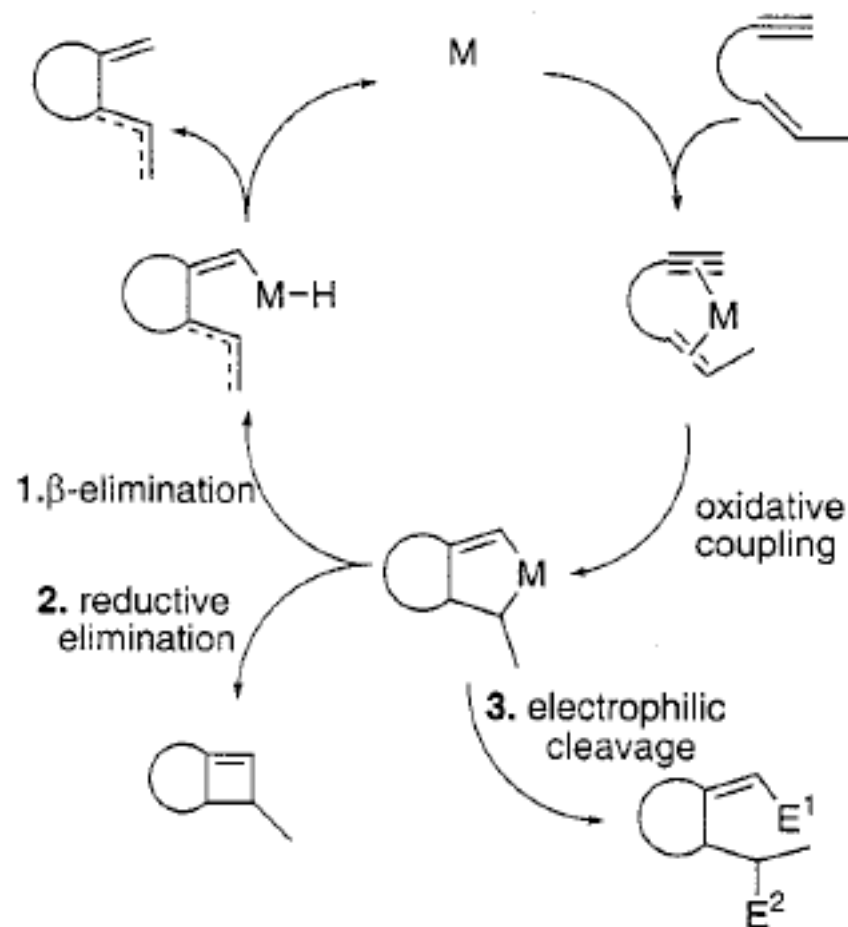
Fairlamb, Ian J. S. *Angew. Chem. Int. Ed* **2004**, 43, 1048-1052

**Chunrui Wu**  
**March 4th, 2004**

# Introduction

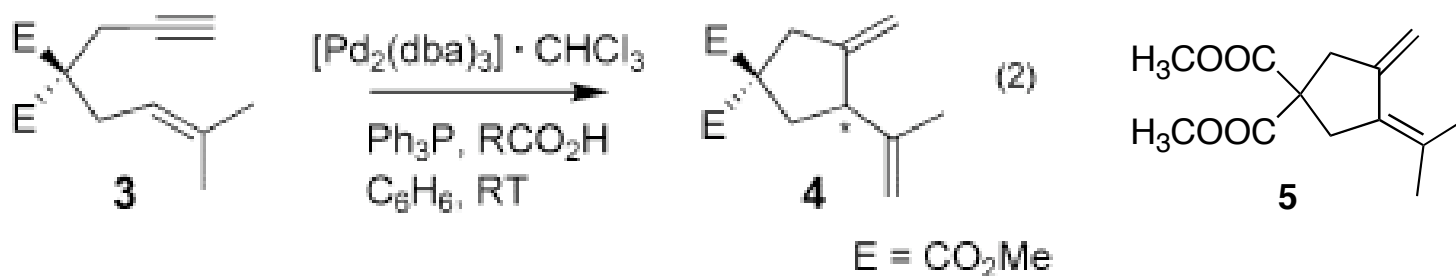


M = Ti, Ru, Co, Rh, Ni-Cr,  
Pd and Pt



# Asymmetric Pd-Catalyzed Cycloisomerization

## First example by Trost



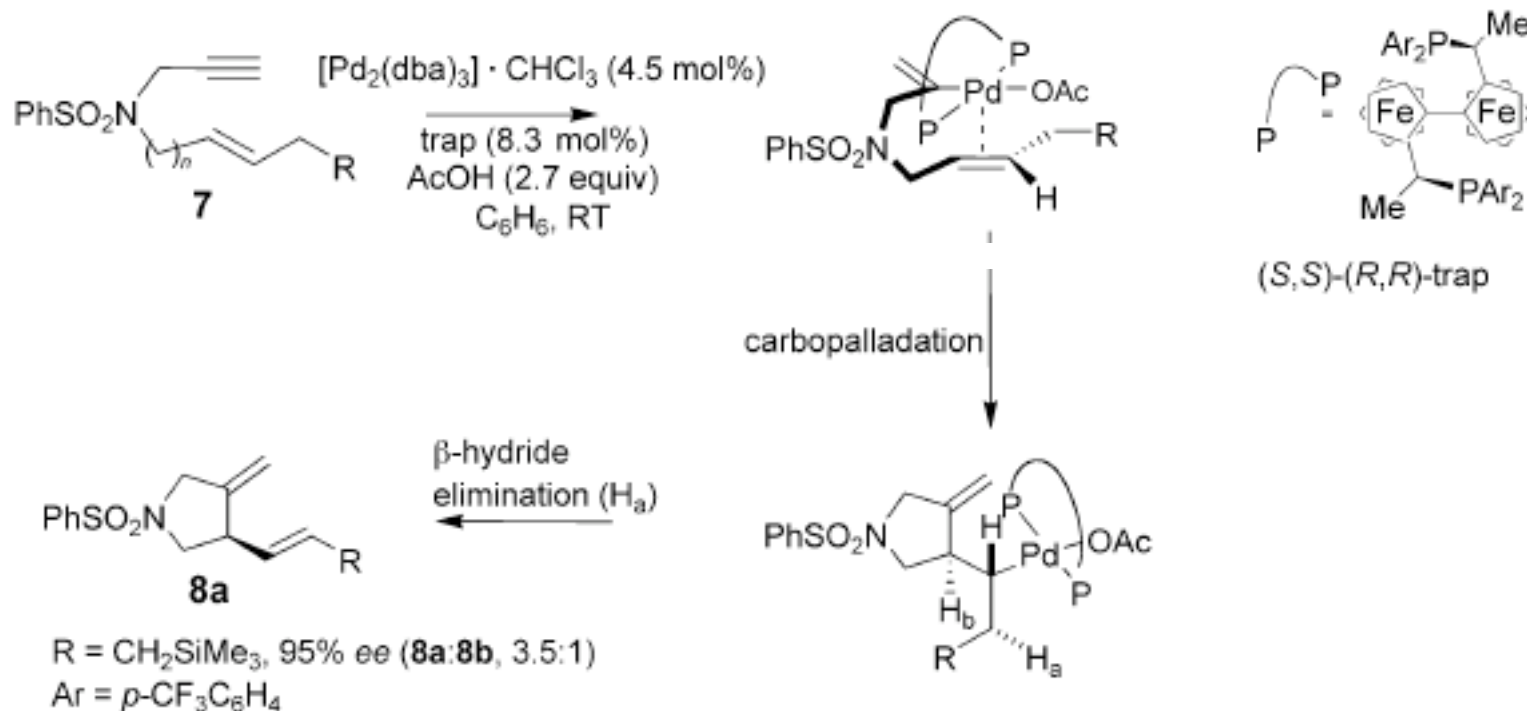
Generation of the active catalytic species



*S*-(-)-binaphthoic acid 61 % 33% ee, 3: 1 ( **4**: **5** )

Trost, B. M., Lee, D. C., Rise, F. *Tetrahedron Lett.* **1989**, 30, 651.

## More efficient bidental ligands

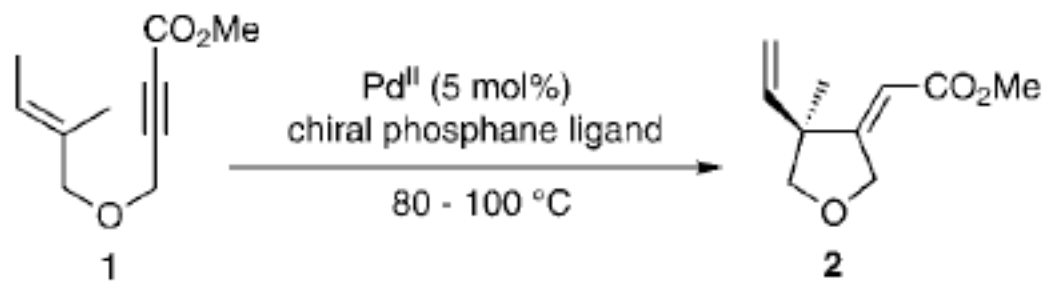


Substrate sensitive: R=aryl, alkyl, low ee  
*E*-olefin, *R*-product; *Z*-olefin, *S*-Product

Chiralphos, diop gave poor selectivities (6-15% ee)  
Binap, no conversion at 80°C

Ito, Y., Goeke, A., Sawamura, M. Kuwano, R. *Angew. Chem. Int. Ed.* **1996**, 35, 662.

# Improvements for Pd-BINAP system



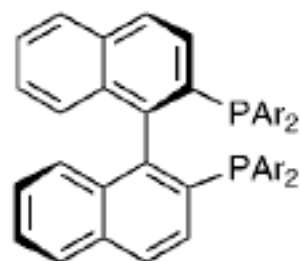
Entry	Pd species (mol %)	Solvent	Reaction time [h]	Yield [%]	<i>ee</i> [%] <sup>[b]</sup> (Config.)
1	Pd(OAc) <sub>2</sub> (5)	C <sub>6</sub> D <sub>6</sub>	72	68	11 ( <i>S</i> )
2 <sup>[c]</sup>	[Pd <sub>2</sub> (dba) <sub>3</sub> ] · CHCl <sub>3</sub> (2.5)/AcOH (12)	C <sub>6</sub> D <sub>6</sub>	96	18	77 ( <i>S</i> )
3 <sup>[c]</sup>	[Pd <sub>2</sub> (dba) <sub>3</sub> ] · CHCl <sub>3</sub> (2.5)/TFA (12)	C <sub>6</sub> D <sub>6</sub>	96	25	84 ( <i>S</i> )
4	Pd(OCOCF <sub>3</sub> ) <sub>2</sub> (5)	C <sub>6</sub> D <sub>6</sub>	24	> 99	93 ( <i>S</i> )
5 <sup>[c,d]</sup>	Pd(OCOCF <sub>3</sub> ) <sub>2</sub> (5)	C <sub>6</sub> D <sub>6</sub>	80	> 99	94 ( <i>S</i> )
6 <sup>[c]</sup>	Pd(OCOCF <sub>3</sub> ) <sub>2</sub> (5)	DMSO	16	> 99	72 ( <i>S</i> )
7 <sup>[c]</sup>	[(MeCN) <sub>4</sub> Pd](BF <sub>4</sub> ) <sub>2</sub> (5)	DMSO	6	> 99	73 ( <i>S</i> )

[a] Reactions were carried out in thoroughly degassed solvents at 100 °C with 5 mol% of Pd catalyst and 10 mol% of (*R*)-BINAP as a chiral ligand unless otherwise noted.

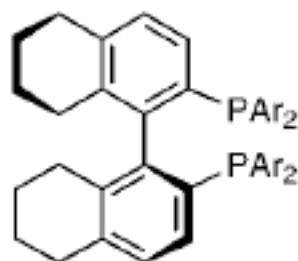
[b] The *ee* value was based on chiral GC analysis of **2**. [c] Reactions were carried out at 80 °C. [d] 5.5 mol% of (*R*)-BINAP was used.

Mikami, K., Terada, M., Hatano, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 249

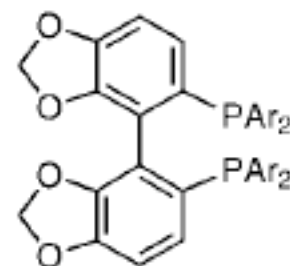
Table 2. Ene-type carbocyclization of **1** catalyzed by Pd(OCOCCF<sub>3</sub>)<sub>2</sub>/C<sub>6</sub>D<sub>6</sub> or [(MeCN)<sub>4</sub>Pd](BF<sub>4</sub>)<sub>2</sub>/DMSO with modified BINAP ligands.



(*R*)-BINAP (Ar = Ph)  
(*R*)-tol-BINAP  
(Ar = *p*-MeC<sub>6</sub>H<sub>4</sub>)



(*S*)-H<sub>8</sub>-BINAP (Ar = Ph)  
(*S*)-xylyl-H<sub>8</sub>-BINAP  
(Ar = 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)

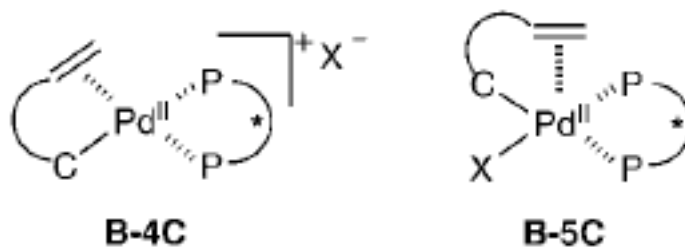


(*R*)-SEGPHOS (Ar = Ph)  
(*S*)-xylyl-SEGPHOS  
(Ar = 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)

Entry	System <sup>[a]</sup>	Ligand	Reaction time [h]	Yield [%]	<i>ee</i> [%] (Config.)
1	Pd(OCOCCF <sub>3</sub> ) <sub>2</sub> /C <sub>6</sub> D <sub>6</sub>	( <i>R</i> )-tol-BINAP	43	> 99	94 ( <i>S</i> )
2	Pd(OCOCCF <sub>3</sub> ) <sub>2</sub> /C <sub>6</sub> D <sub>6</sub>	( <i>S</i> )-H <sub>8</sub> -BINAP	48	> 99	95 ( <i>R</i> )
3	Pd(OCOCCF <sub>3</sub> ) <sub>2</sub> /C <sub>6</sub> D <sub>6</sub>	( <i>S</i> )-xylyl-H <sub>8</sub> -BINAP	20	> 99	12 ( <i>R</i> )
4	Pd(OCOCCF <sub>3</sub> ) <sub>2</sub> /C <sub>6</sub> D <sub>6</sub>	( <i>R</i> )-SEGPHOS	37	> 99	> 99 ( <i>S</i> )
5	[(MeCN) <sub>4</sub> Pd](BF <sub>4</sub> ) <sub>2</sub> /DMSO	( <i>R</i> )-SEGPHOS	6	> 99	90 ( <i>S</i> )
6	[(MeCN) <sub>4</sub> Pd](BF <sub>4</sub> ) <sub>2</sub> /DMSO	( <i>S</i> )-xylyl-H <sub>8</sub> -BINAP	12	> 99	94 ( <i>R</i> )
7	[(MeCN) <sub>4</sub> Pd](BF <sub>4</sub> ) <sub>2</sub> /DMSO	( <i>S</i> )-xylyl-SEGPHOS	14	> 99	96 ( <i>R</i> )

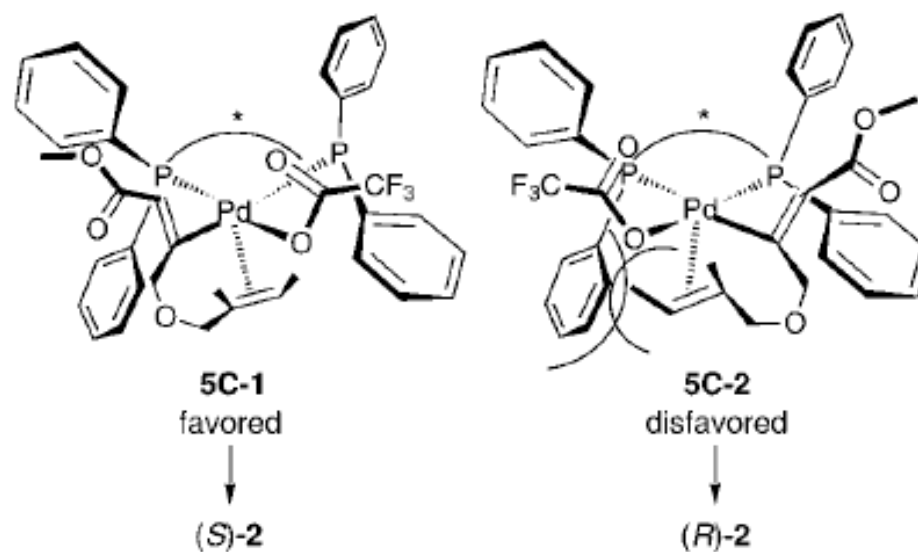
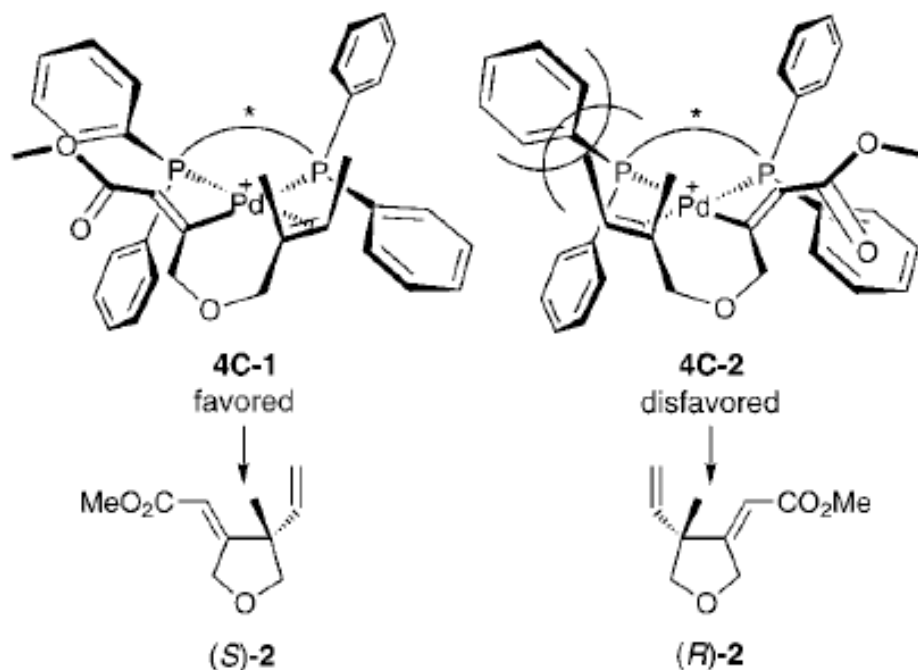
[a] Reactions were carried out with 5 mol % of Pd catalyst and 10 mol % of chiral ligand in thoroughly degassed solvents at 100 °C in the Pd(OCOCCF<sub>3</sub>)<sub>2</sub>/C<sub>6</sub>D<sub>6</sub> system or at 80 °C in the [(MeCN)<sub>4</sub>Pd](BF<sub>4</sub>)<sub>2</sub>/DMSO system.

# Solvent and Ligand Effects



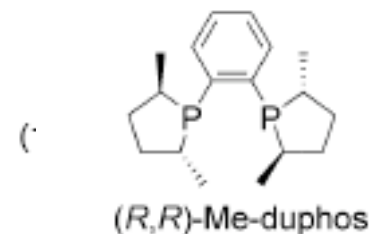
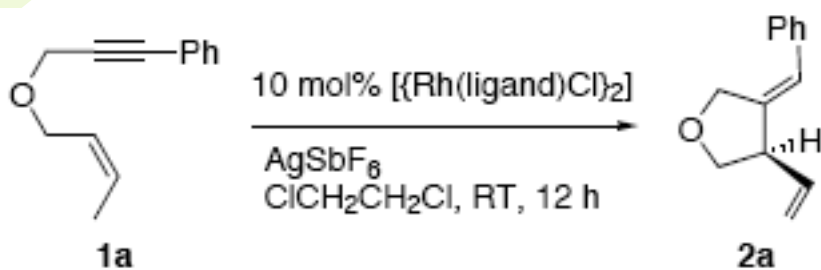
polar condition: *four*-coordination

less polar condition: *five*-coordination

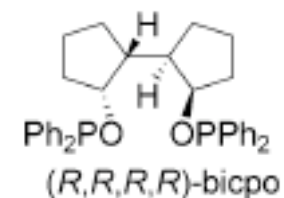
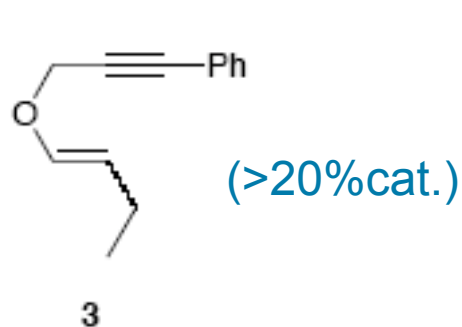
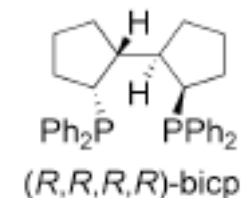


Mikami, K., Terada, M., Hatano, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 249

# Rh-Catalyzed Enyne Cycloisomerization

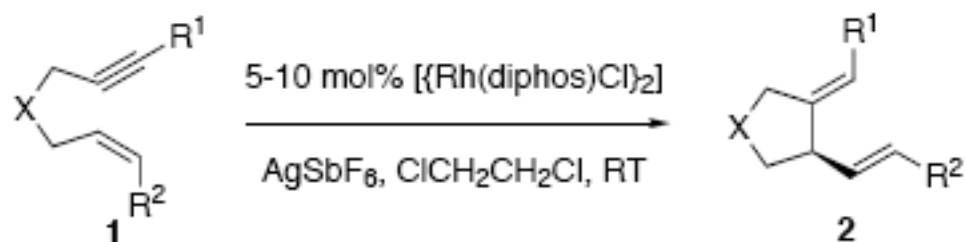


Entry	Ligand	Conversion [%] <sup>[b]</sup>	ee [%] <sup>[d]</sup>
1	Me-DuPhos	100	95
2	Et-DuPhos	<5	63
3	BICP	100	74
4	Me-PennPhos	100	71
5	BINAP	0	–
6	Et-BPE	<5	5



Zhang, X., Cao, P. *Angew. Chem. Int. Ed.* **2000**, 39, 4104.

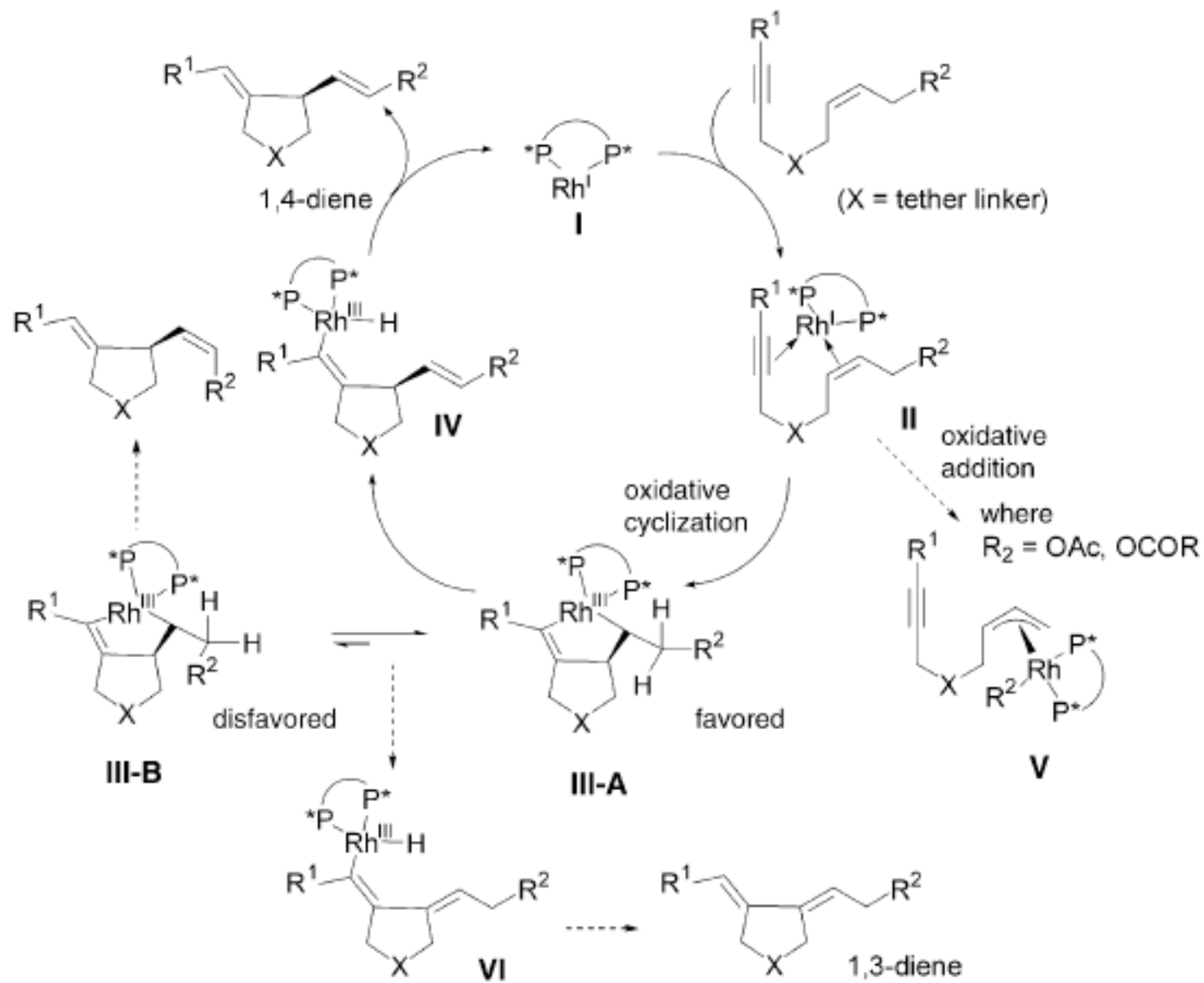




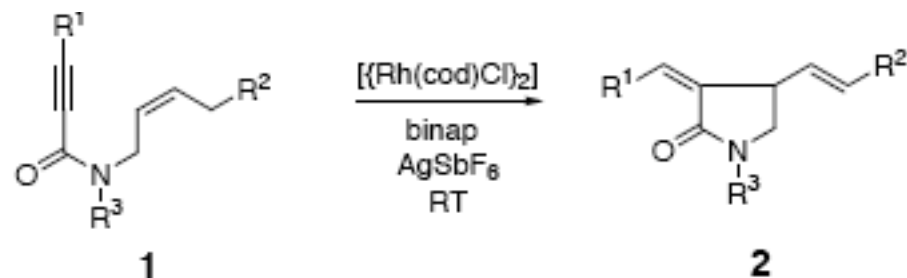
Entry	X	R <sup>1</sup>	R <sup>2</sup>	Ligand	Ca [mol %]	Yield [%]	ee [%] (config.)
1	O	Ph	Me	( <i>R,R</i> )-Me-DuPhos	5	62	96 (–)
2				( <i>R,R,R,R</i> )-BICP	5	73	74 (–)
3				( <i>R,R,R,R</i> )-BICPO	10	81	65 (+)
4	O	C <sub>6</sub> H <sub>4</sub> ( <i>p</i> -Me)	Me	( <i>R,R</i> )-Me-DuPhos	10	38	77 (–)
5				( <i>R,R,R,R</i> )-BICP	10	58	87 (–)
6	O	C <sub>6</sub> H <sub>4</sub> ( <i>p</i> -Cl)	Me	( <i>R,R</i> )-Me-DuPhos	5	60	95 (–)
7				( <i>R,R,R,R</i> )-BICP	10	24	83 (–)
8	O	C <sub>6</sub> H <sub>4</sub> ( <i>m</i> -Cl)	Me	( <i>R,R</i> )-Me-DuPhos	10	68	93 (–)
9				( <i>R,R,R,R</i> )-BICP	10	39	79 (–)
10	O	C <sub>6</sub> H <sub>4</sub> ( <i>p</i> -CF <sub>3</sub> )	Me	( <i>R,R</i> )-Me-DuPhos	5	60	96 (–)
11				( <i>R,R,R,R</i> )-BICP	10	47	91 (–)
12	O	cyclopentyl	Me	( <i>R,R</i> )-Me-DuPhos	10	–	–
13				( <i>R,R,R,R</i> )-BICP <sup>el</sup>	5	43	95 (–)
14	O	C <sub>4</sub> H <sub>9</sub>	Me	( <i>R,R</i> )-Me-DuPhos	10	–	–
15				( <i>R,R,R,R</i> )-BICP	5	67	98 (–)
16	PhSO <sub>2</sub> N	Me	Me	( <i>R,R,R,R</i> )-BICPO	3	98	82 (–)
17	PhSO <sub>2</sub> N	Et	Me	( <i>R,R,R,R</i> )-BICPO	3	99	80 (–)
18	PhSO <sub>2</sub> N	Me	Et	( <i>R,R,R,R</i> )-BICPO	3	99	69 (–)

Zhang, X., Cao, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4104.

# Mechanism for Ru-cat Enantioselective Enyne Cycloisomerization



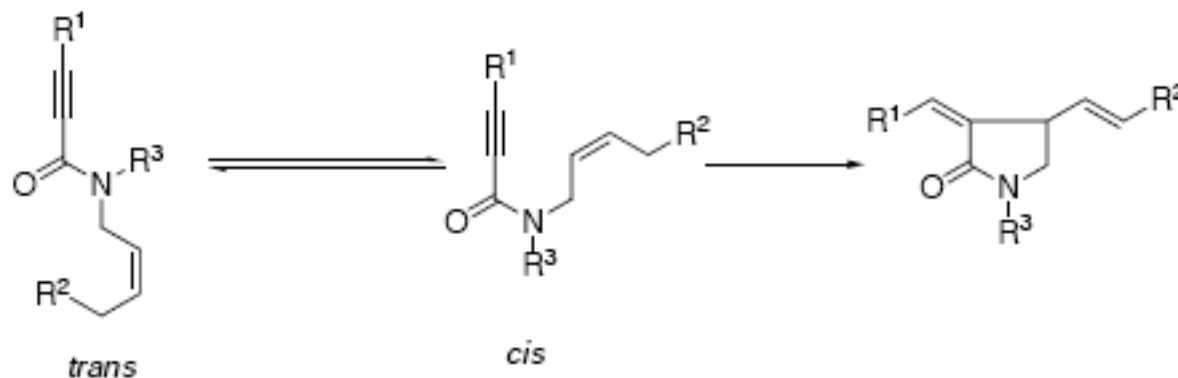
# Rh-Catalyzed Enyne to Prepare Lactams



Entry	Substrate					Product	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
	1	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	binap			
1	<b>1a</b>	Ph	Et	Bn	( <i>S</i> )	(+)- <b>2a</b>	95	> 99
2	<b>1a</b>	Ph	Et	Bn	( <i>R</i> )	(-)- <b>2a</b>	96	> 99
3	<b>1b</b>	Ph	H	Bn	( <i>S</i> )	(+)- <b>2b</b>	90	> 99
4	<b>1c</b>	Ph	Me	Bn	( <i>S</i> )	(+)- <b>2c</b>	91	> 99
5	<b>1d</b>	Me	H	Bn	( <i>R</i> )	(-)- <b>2d</b>	91	> 99
6	<b>1d</b>	Me	H	Bn	( <i>S</i> )	(+)- <b>2d</b>	92	> 99
7	<b>1e</b>	Me	H	Me	( <i>S</i> )	(+)- <b>2e</b>	91	> 99
8	<b>1f</b>	Me	Me	Bn	( <i>S</i> )	(+)- <b>2f</b>	96	> 99
9	<b>1g</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	H	Bn	( <i>S</i> )	(+)- <b>2g</b>	93	> 99
10	<b>1h</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	Me	Bn	( <i>S</i> )	(+)- <b>2h</b>	91	> 99
11	<b>1i</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	Et	Bn	( <i>S</i> )	(+)- <b>2i</b>	92	> 99
12	<b>1j</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	Et	Bn	( <i>S</i> )	(+)- <b>2j</b>	90	> 99

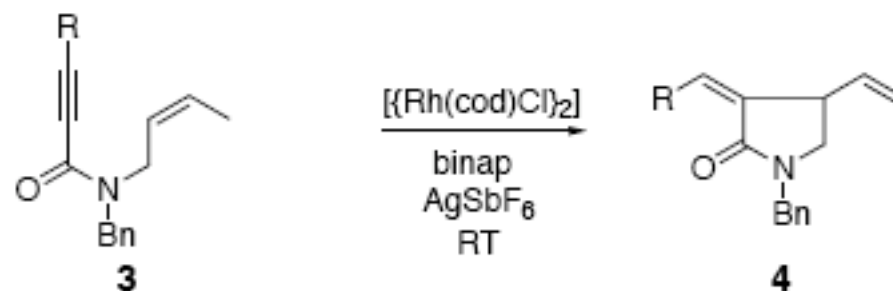
Zhang, X., Lei, A., Waldkirch, J. P., He, M., *Angew. Chem. Int. Ed.* **2002**, *41*, 4526.

$R^3=H$ , no cyclization product and S.M. recovered



Scheme 1. Effect of *trans/cis*-isomers in the Rh-catalyzed Alder-ene reaction.

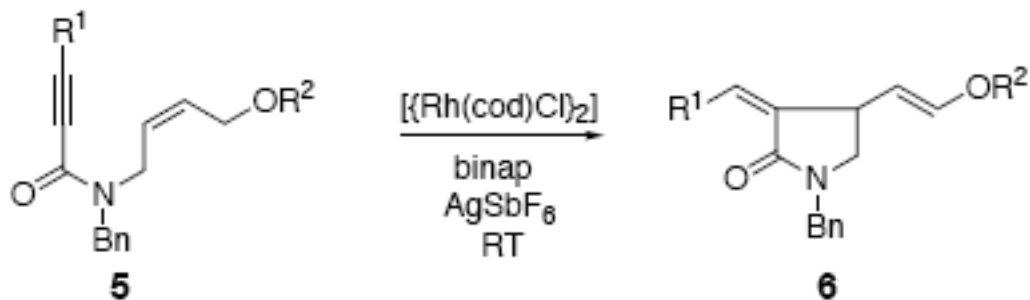
## Functionalized alkynyl derivatives



R = $\text{CH}_2\text{OMOM}$	<b>3a</b>	( <i>S</i> )-binap	(+)- <b>4a</b>	87%	>99% <i>ee</i>
	<b>3a</b>	( <i>R</i> )-binap	(-)- <b>4a</b>	88%	>99% <i>ee</i>
R = $\text{CH}_2\text{OTBDMS}$	<b>3b</b>	( <i>S</i> )-binap	(+)- <b>4b</b>	82%	>99% <i>ee</i>
	<b>3b</b>	( <i>R</i> )-binap	(-)- <b>4b</b>	84%	>99% <i>ee</i>
R = $\text{CH}_2\text{OBn}$	<b>3c</b>	( <i>S</i> )-binap	(+)- <b>4c</b>	92%	>99% <i>ee</i>

Zhang, X., Lei, A., Waldkirch, J. P., He, M., *Angew. Chem. Int. Ed.* **2002**, *41*, 4526.

# Functionalized vinyl derivatives



R<sup>1</sup> = Ph, R<sup>2</sup> = Me

**5a** (*S*)-binap

(+)-**6a** 87% >99% ee

**5a** (*R*)-binap

(-)-**6a** 88% >99% ee

R<sup>1</sup> = Ph, R<sup>2</sup> = Bn

**5b** (*S*)-binap

(+)-**6b** 89% >99% ee

R<sup>1</sup> = *n*-C<sub>5</sub>H<sub>11</sub>, R<sup>2</sup> = Me

**5c** (*S*)-binap

(+)-**6c** 92% >99% ee

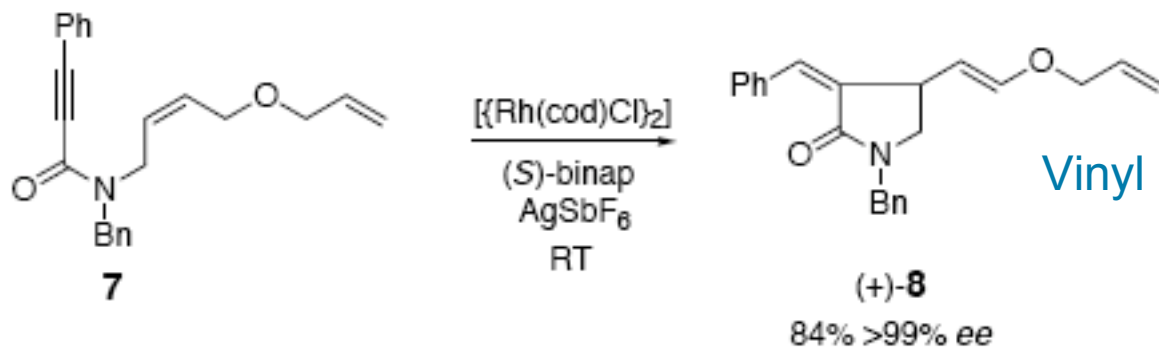
R<sup>1</sup> = Ph, R<sup>2</sup> = Ac

**5d** (*S*)-binap

(+)-**6d** 89% >99% ee

Vinyl ether

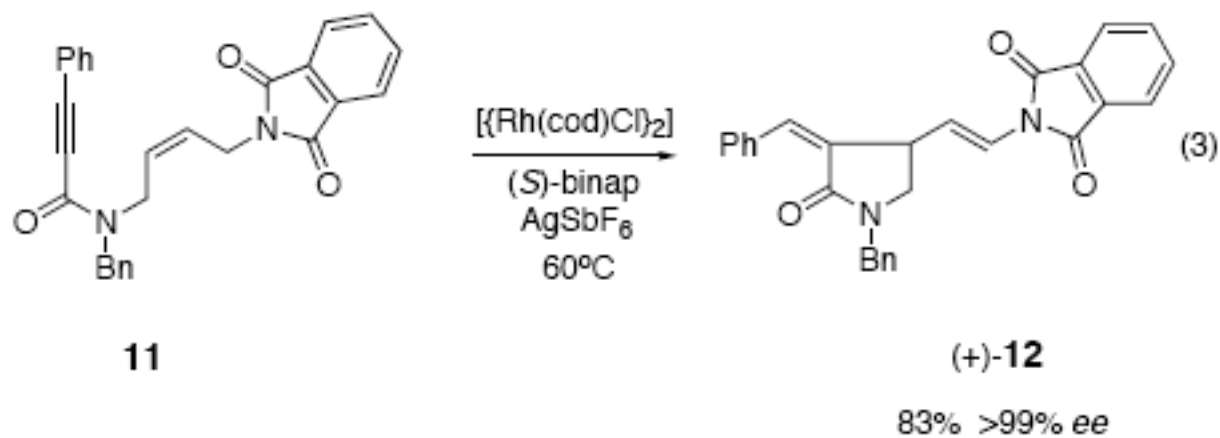
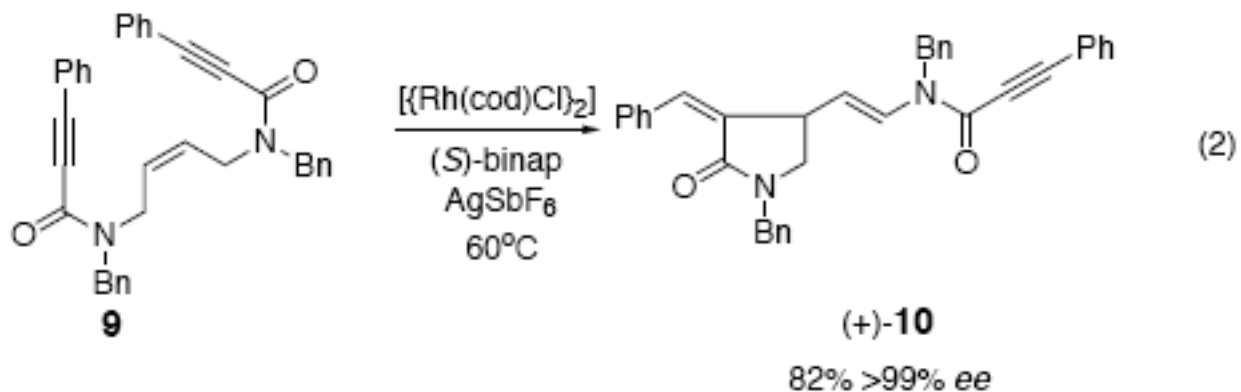
Vinyl acetate



Vinyl allylic ether

Zhang, X., Lei, A., Waldkirch, J. P., He, M., *Angew. Chem. Int. Ed.* **2002**, *41*, 4526.

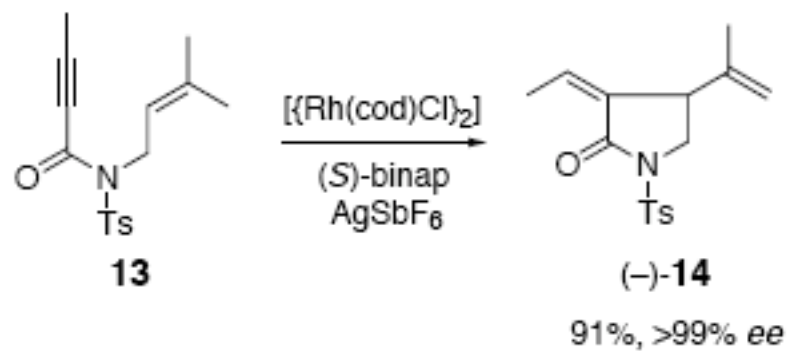
## Other functionalized vinyl derivatives



Zhang, X., Lei, A., Waldkirch, J. P., He, M., *Angew. Chem. Int. Ed.* **2002**, *41*, 4526.

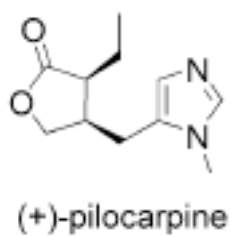


## Trisubstituted olefin



Bn-substituted substrates failed to yield the 1,4-diene.

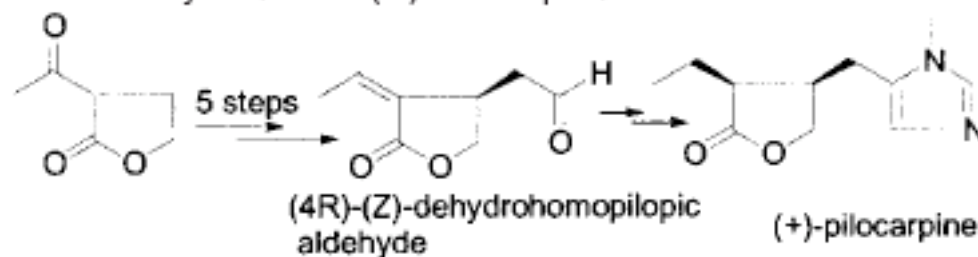
# Application in Synthesis of (+)-Pilocarpine



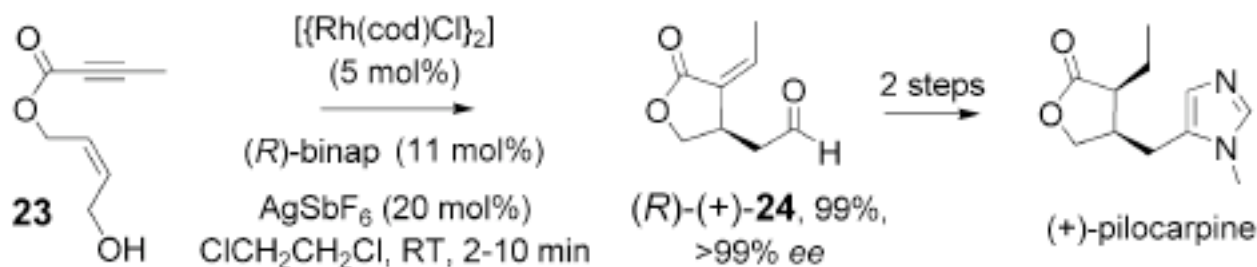
Isolated in 1875

Therapeutic agent for glaucoma

*Scheme 1.* Synthesis of (+)-Pilocarpine



92% ee, 20% yield

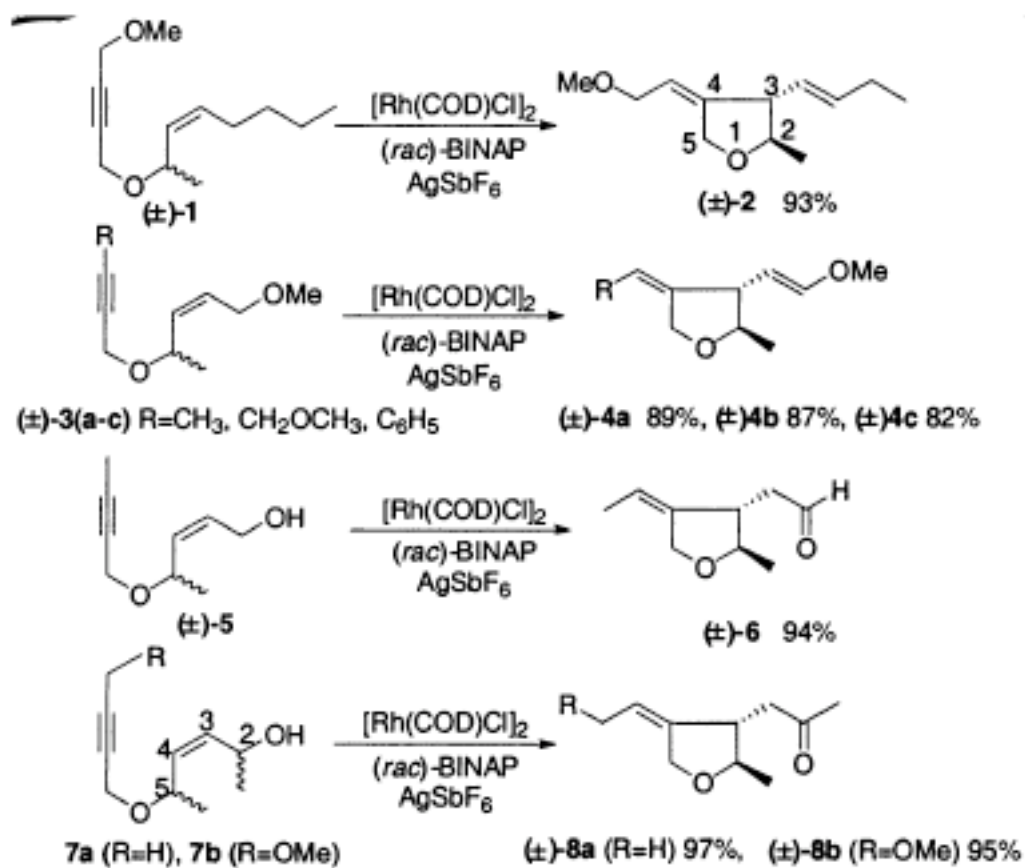


Zhang, X., Lei, A., He, M., *J. Am. Chem. Soc.* **2002**, *124*, 8198-8199

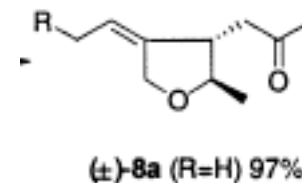
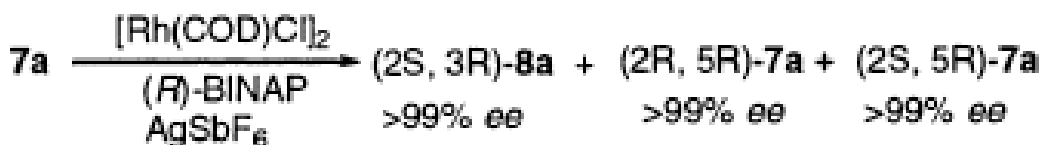
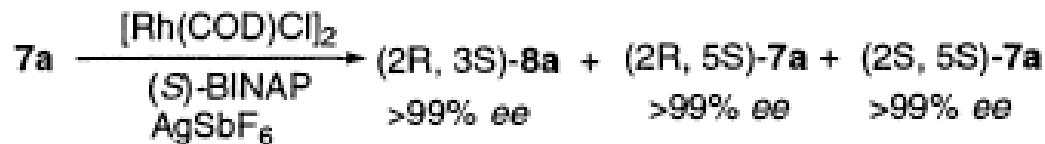
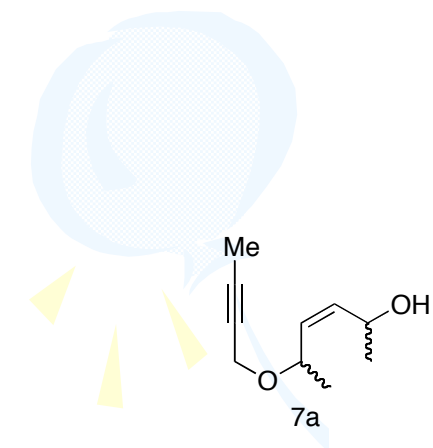
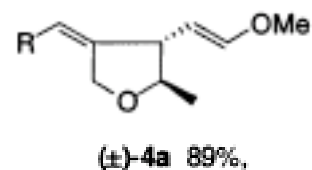
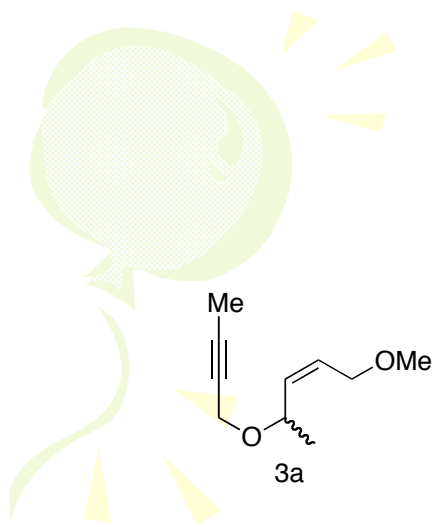
Horne, D. a., Fugnann, B., Yakushijin, K., Buchi, G., *J. Org. Chem.* **1993**, *58*, 62.



## Further Application: Stereoselective Kinetic Resolution of Enynes

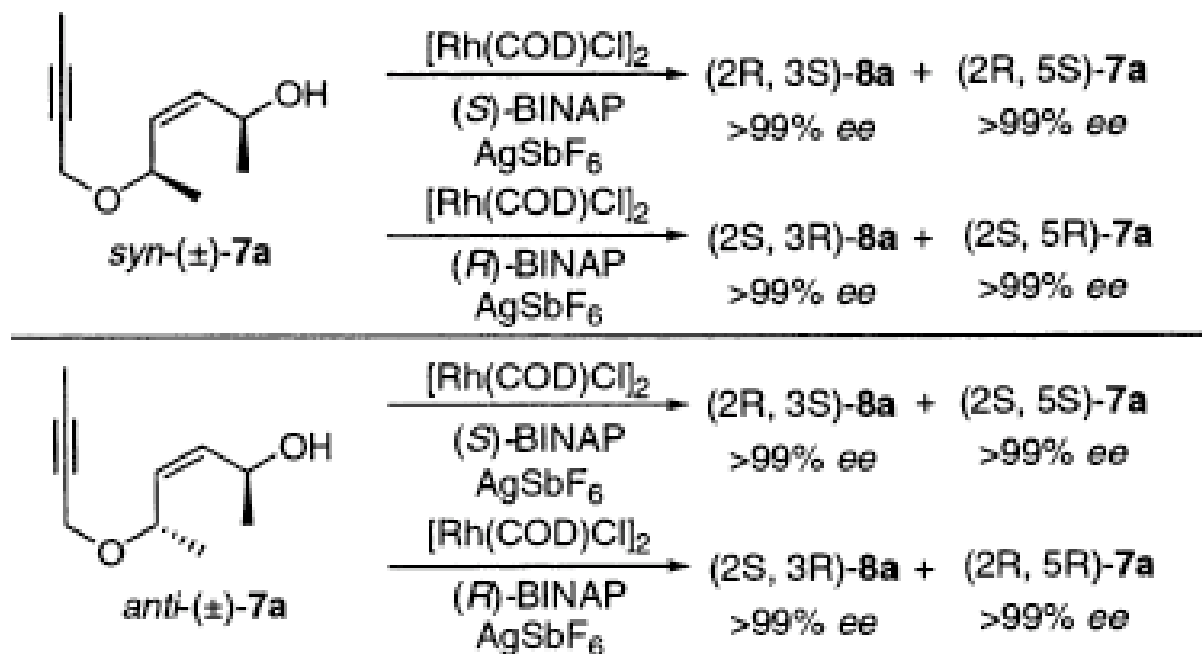


Zhang, X., Lei, A., He, M., *J. Am. Chem. Soc.* **2003**, *125*, 11472-3



Zhang, X., Lei, A., He, M., *J. Am. Chem. Soc.* **2003**, *125*, 11472-3

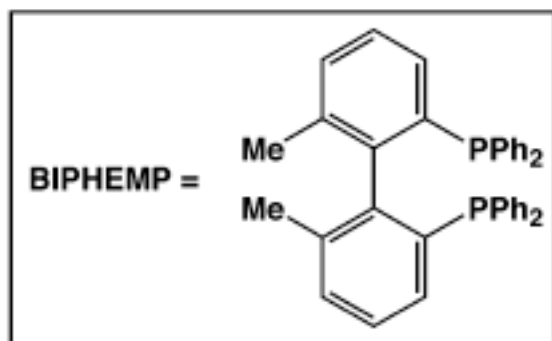
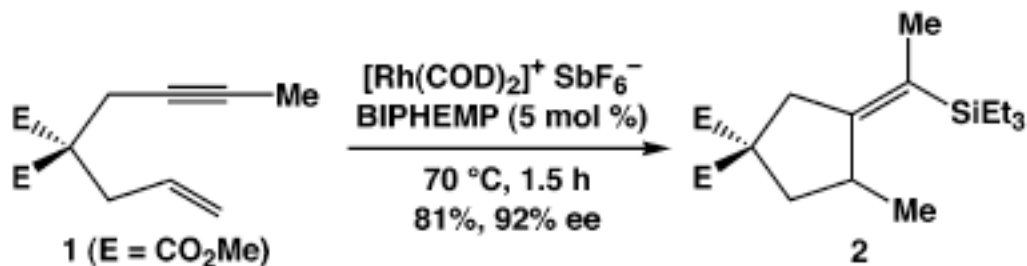
## Control reactions



(*R*)-substrate matches (*S*)-BINAP

Zhang, X., Lei, A., He, M., *J. Am. Chem. Soc.* **2003**, *125*, 11472-3

# Enantioselective Cyclization/hydrosilylation of 1,6-Enyne



BINAP not effective

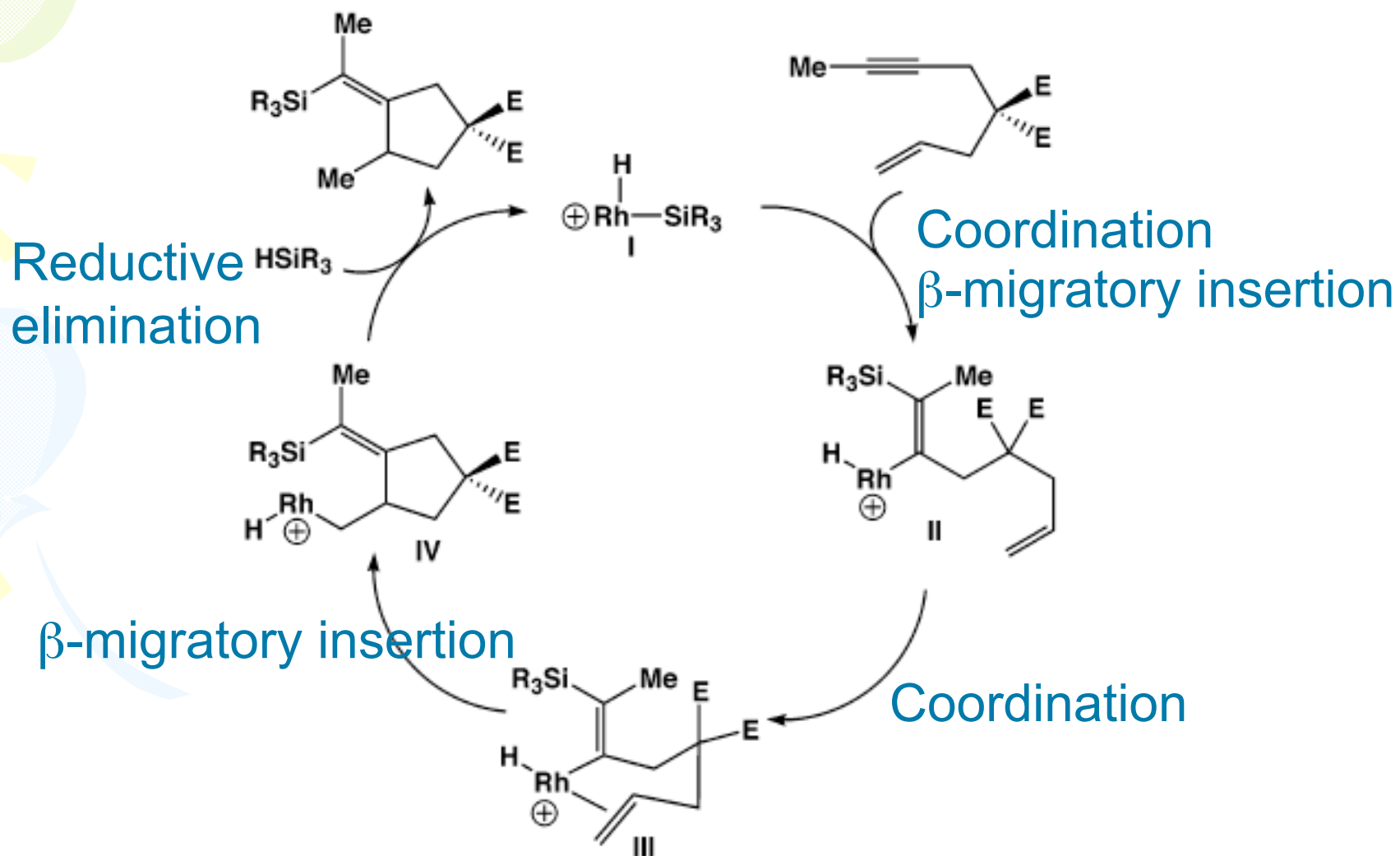
E=CH<sub>2</sub>OMe, CH<sub>2</sub>OAc, CH<sub>2</sub>COEt etc

Silane= HSiMe<sub>2</sub>Bn, HSiMe<sub>2</sub>Ph, HSiEt<sub>3</sub> etc

Yield: 48-81%, ee: 77-92%

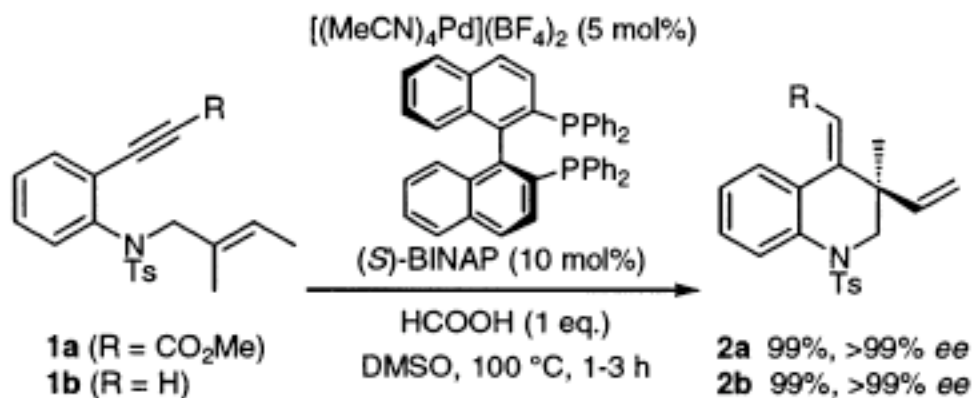
Widenhoefer, R. A., Liu, C., Chakrapani, H., *Org. Lett.* **2003**, *5*, 157

# Proposed Mechanism

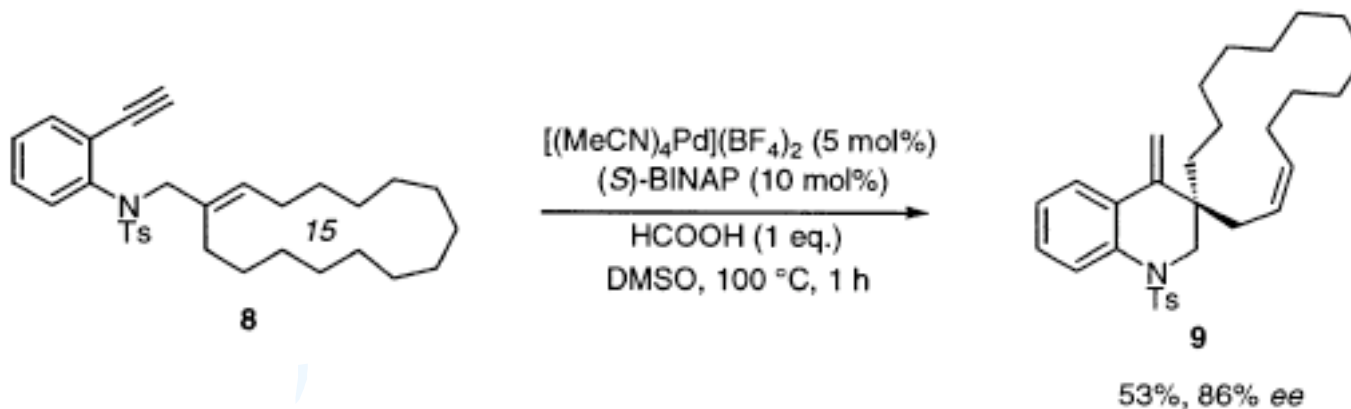


Widenhoefer, R. A., Liu, C., Chakrapani, H., *Org. Lett.* **2003**, *5*, 157

# Pd-cat Enantioselective Cyclization of 1, 7-Enynes



The *ortho*-substituted benzene skeleton is essential.



Mikami, K., Hatano, M., *J. Am. Chem. Soc.* **2003**, *125*, 4704