Chiral Phosphine…The Nucleophilic Trigger

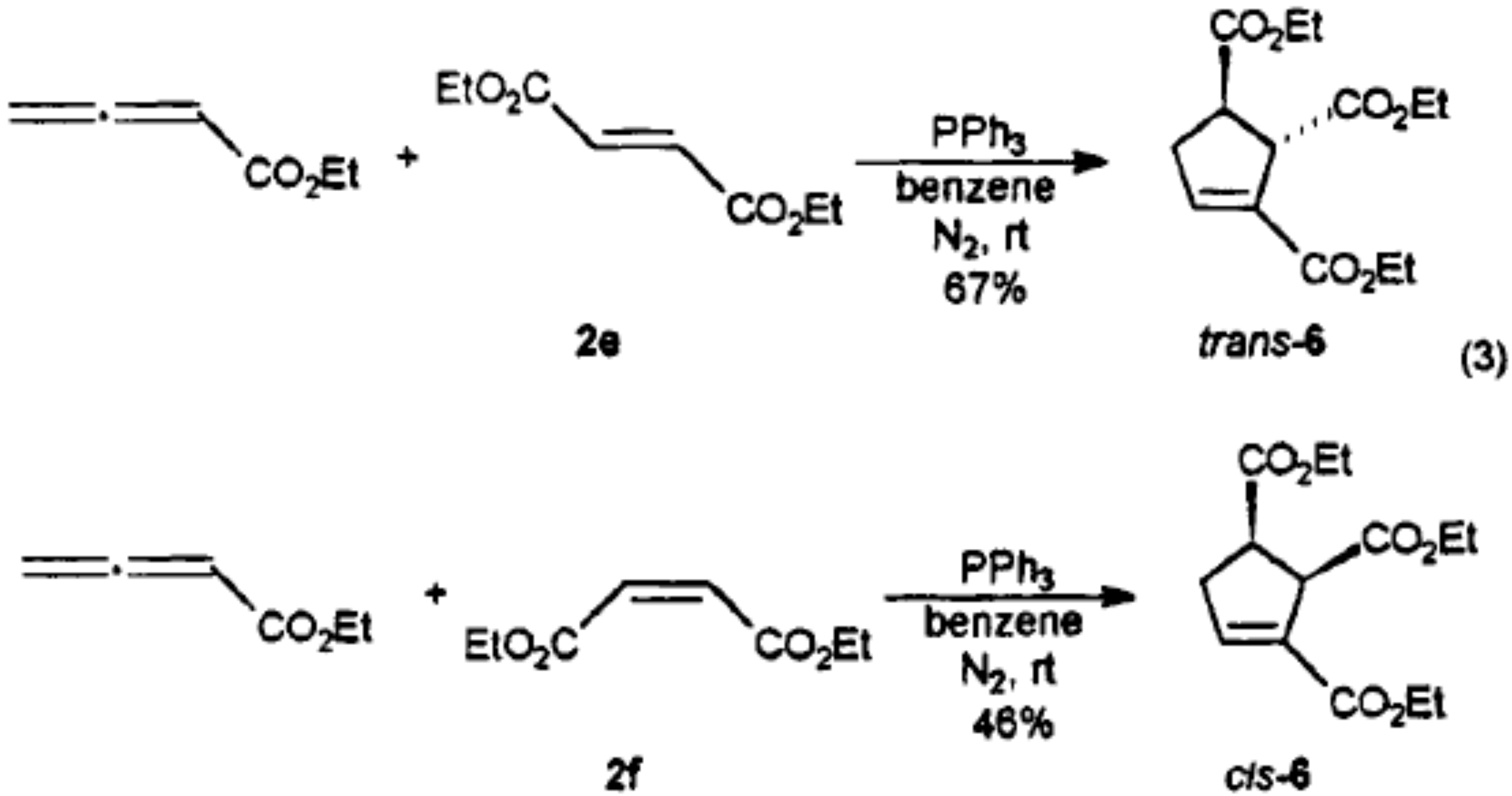
3+2 Cycloaddition

4+2 Annulation

Wilson, J. E.; Fu, G. C. *Angew*. *Chem*. *Int*. *Ed*. **2006**, 45, 1426-1429 (3+2)
Wurz, R. P.; Fu, G. C. *J*. *Am*. *Chem*. *Soc*. **2005**, 127, 12234-12235 (4+2)

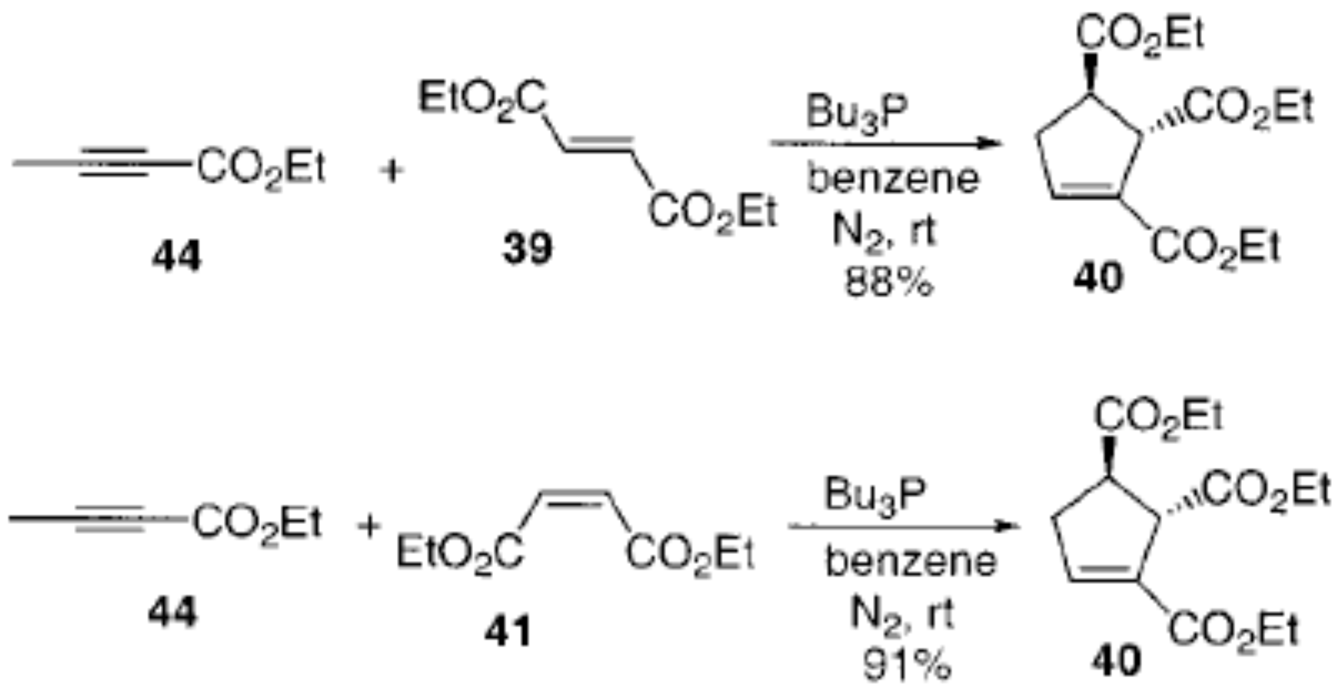
Cory Newman
February 17, 2006

3+2 Cycloaddition Reaction



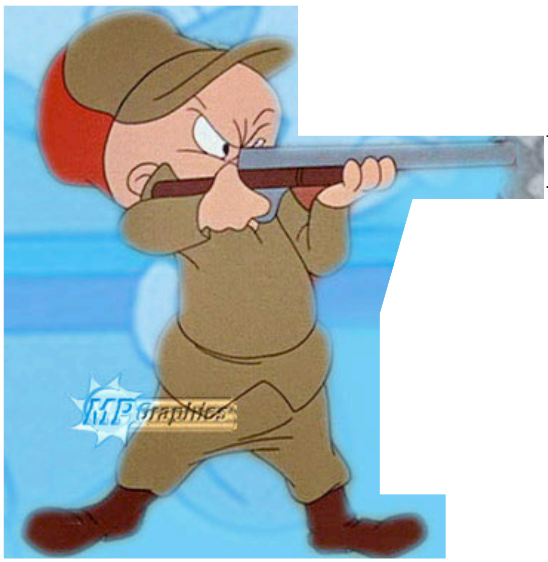
Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, 60, 2906-2908

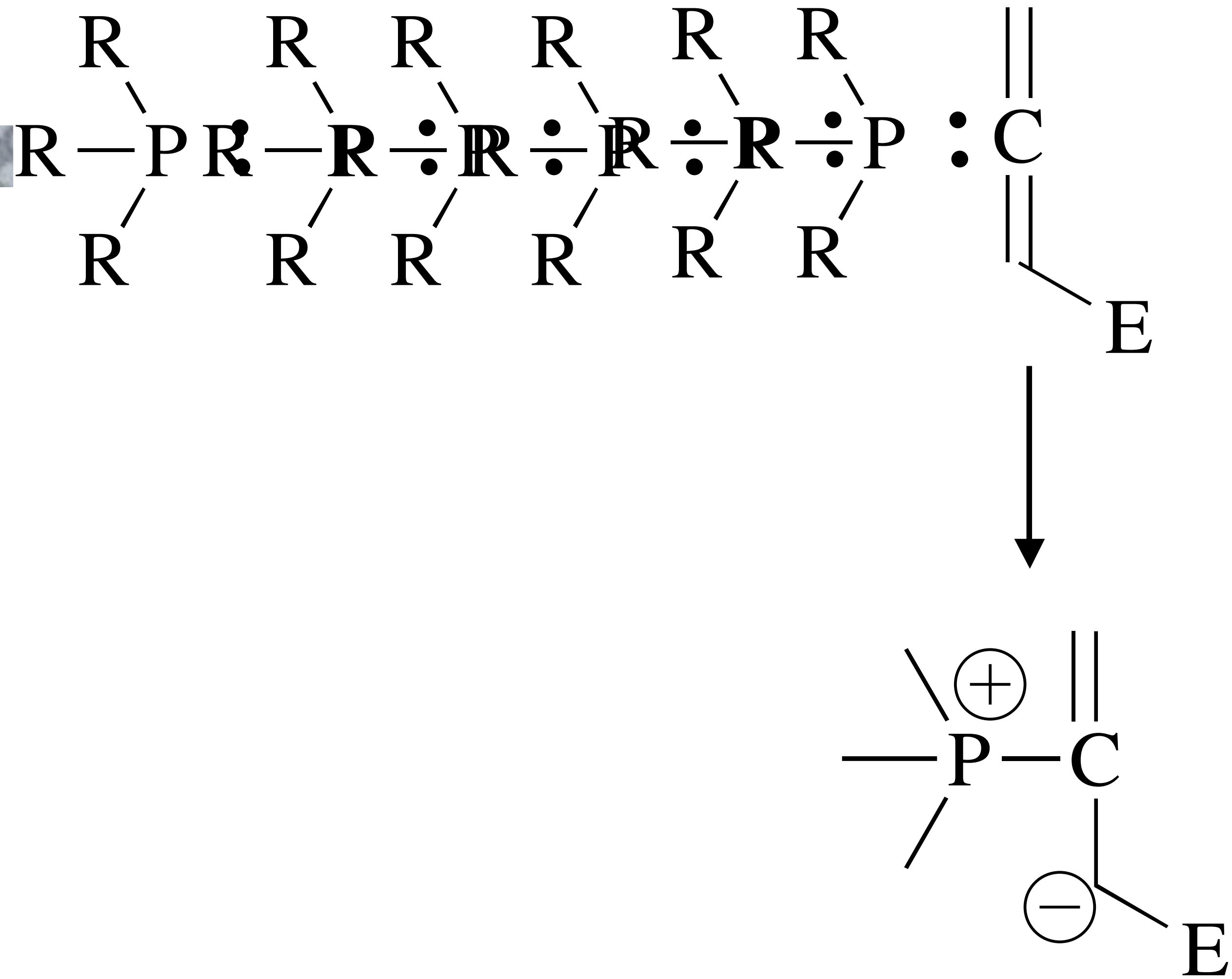
3+2 Cycloaddition using Alkynoates



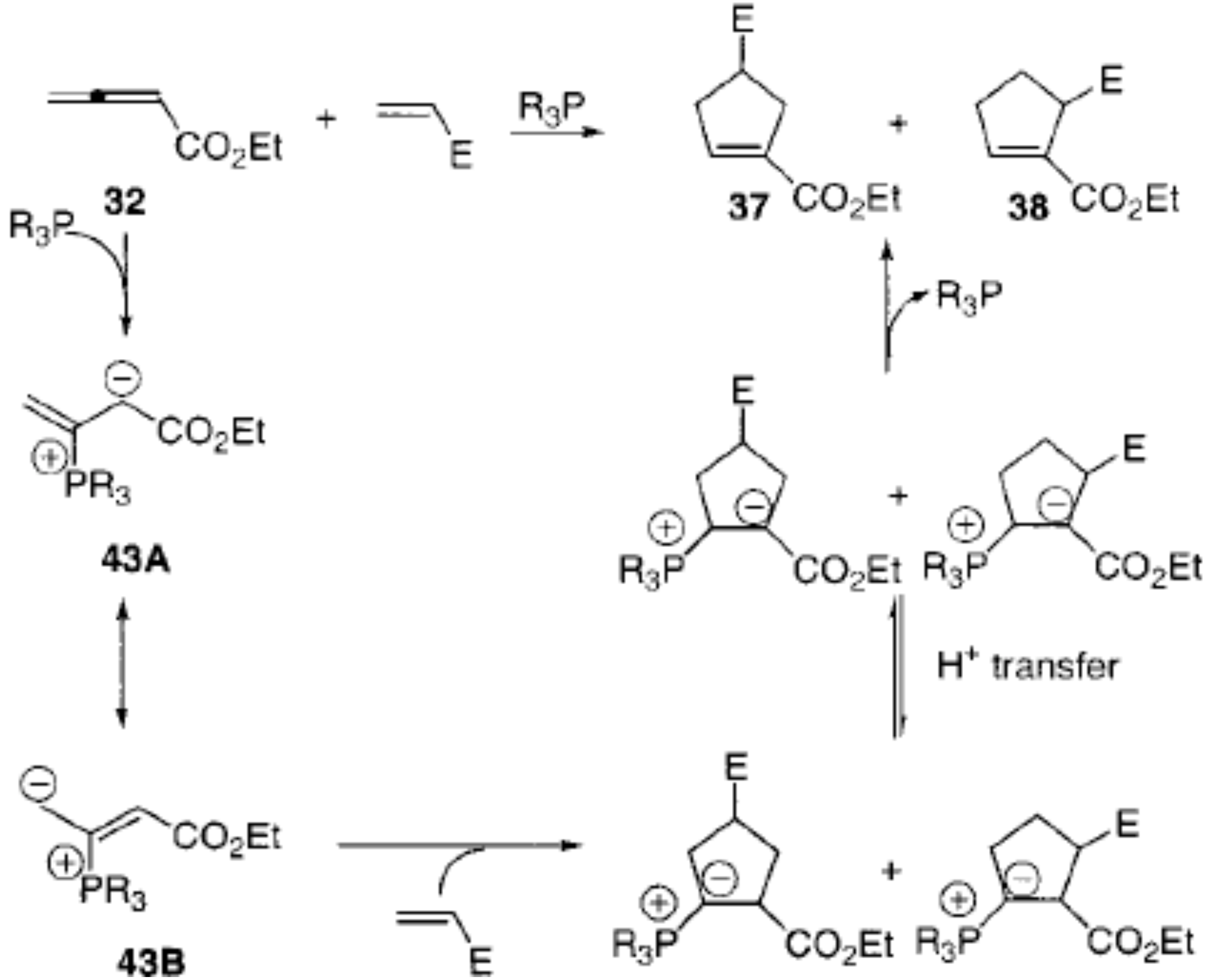
Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, 34, 535-544

Nucleophilic Trigger



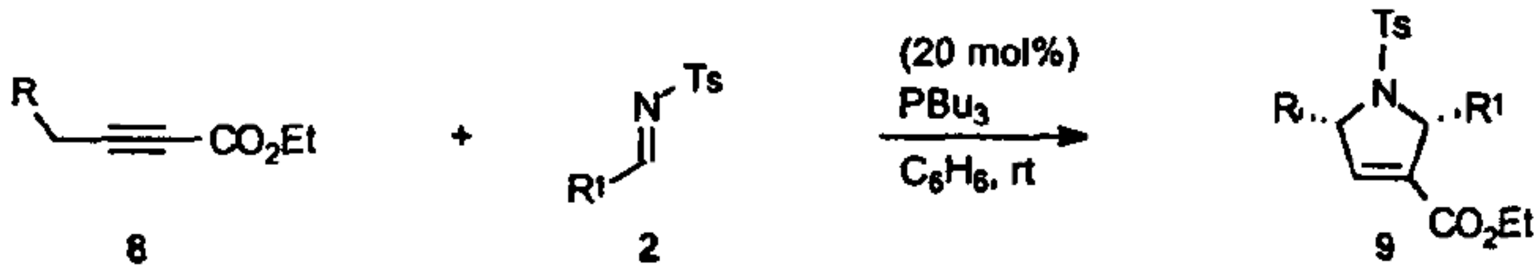


3+2 Cycloaddition Mechanism



Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, 34, 535-544

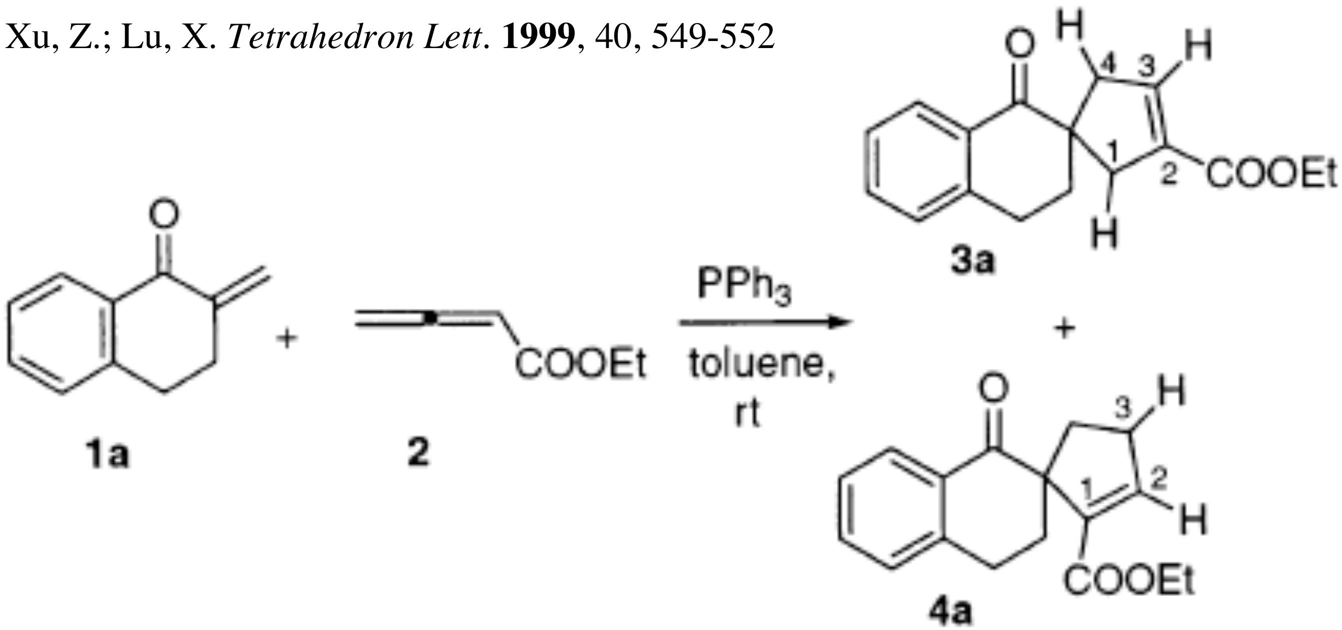
Uses of non-Chiral Phosphorus

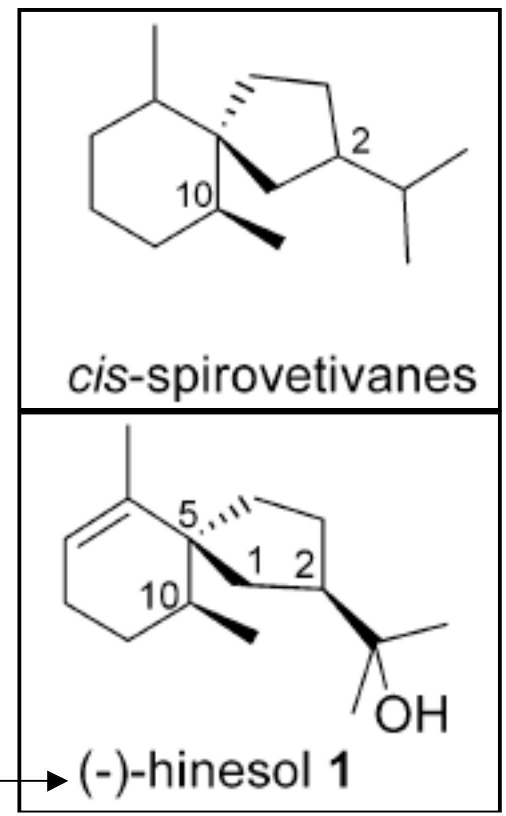


a) R = *n*-Pr, R¹ = Ph, 63% c) R = *n*-Pr, R¹ = 2-furyl, 33%

b) R = Et, R¹ = piperonyl, 65% d) R = THPO(CH_2)$_7$, R¹ = 1-naphthyl, 75%

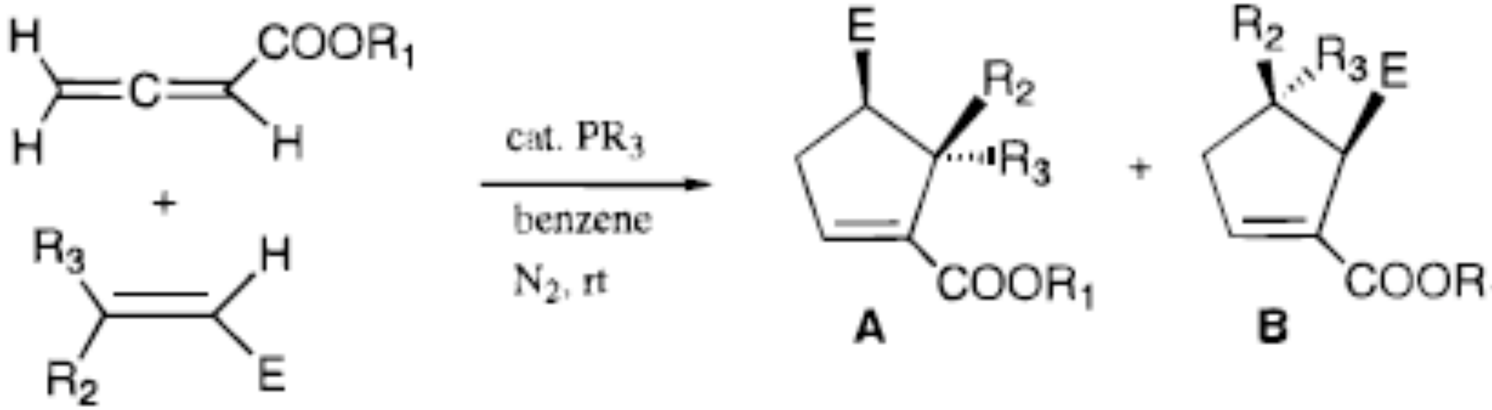
Xu, Z.; Lu, X. *Tetrahedron Lett*. **1999**, 40, 549-552



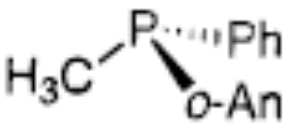


Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, 67, 8901-8905.
Du, Y.; Lu, X. *J. Org. Chem.* **2003**, 68, 6463-6465.

First Example of Chiral Phosphorus



Cat. PR$_3$



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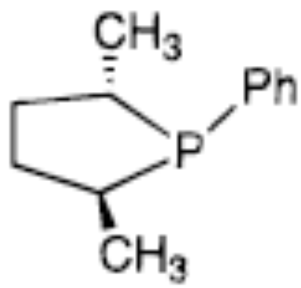

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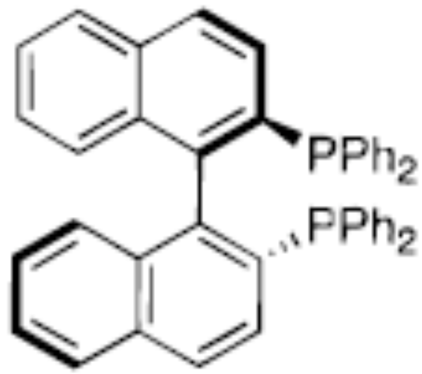

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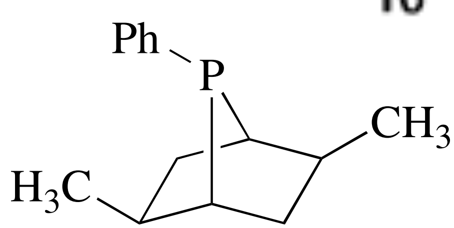

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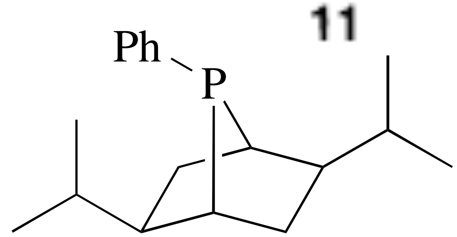
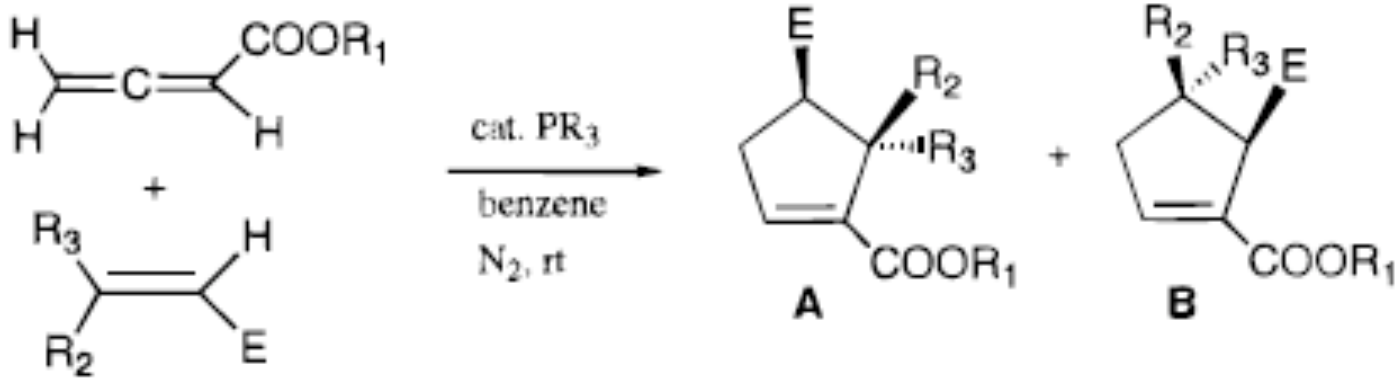


8

Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, 119, 3836-3837

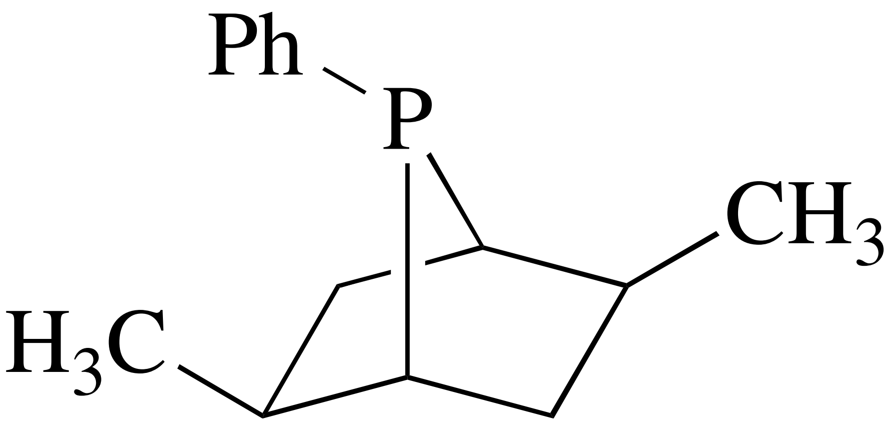
And the Best Chiral Phosphorus is……



phosphine	E	R_1	R_2	R_3	solvent	*T* (°C)[c]	yield (%)	**A**:**B**[b]	% ee of **A**[b]
7	COOEt	Et	H	H	benzene	rt	66	95:5	81
8	COOEt	Et	H	H	benzene	rt	76	97:3	81
9	COOEt	Et	H	H	benzene	rt	80	80:20	56
10	COOEt	Et	H	H	benzene	rt	83	72:29	6
11	COOEt	Et	H	H	benzene	rt	33	73:27	12
7	COO^{i}Bu	Et	H	H	benzene	rt	46	100:0	86
7	COO^{t}Bu	Et	H	H	benzene	rt	69	95:5	89
7	COO^{t}Bu	Et	H	H	toluene	0	42	97:3	93
8	COOMe	Et	H	H	benzene	rt	87	96:4	79
8	COO^{i}Bu	Et	H	H	benzene	rt	92	100:0	88
8	COO^{i}Bu	Et	H	H	toluene	0	**88**	**100**:0	**93**
8	COO^{t}Bu	Et	H	H	benzene	rt	75	95:5	88
7	COOEt	^{t}Bu	H	H	benzene	rt	13	97:3	89
8	COOEt	^{t}Bu	H	H	benzene	rt	84	94:6	69
8	COOEt	Et	COOEt	H	toluene	0	49		79
8	COOMe	Et	H	COOMe	benzene	rt	84		36

Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, 119, 3836-3837

And the Best Chiral Phosphorus is……



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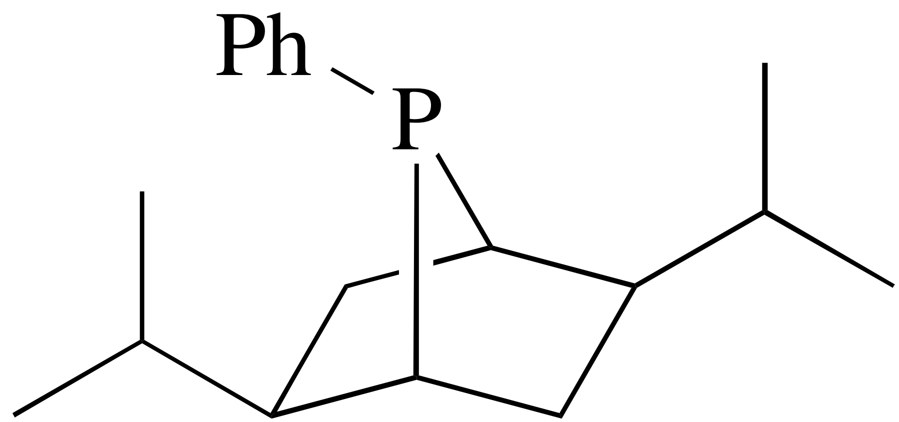

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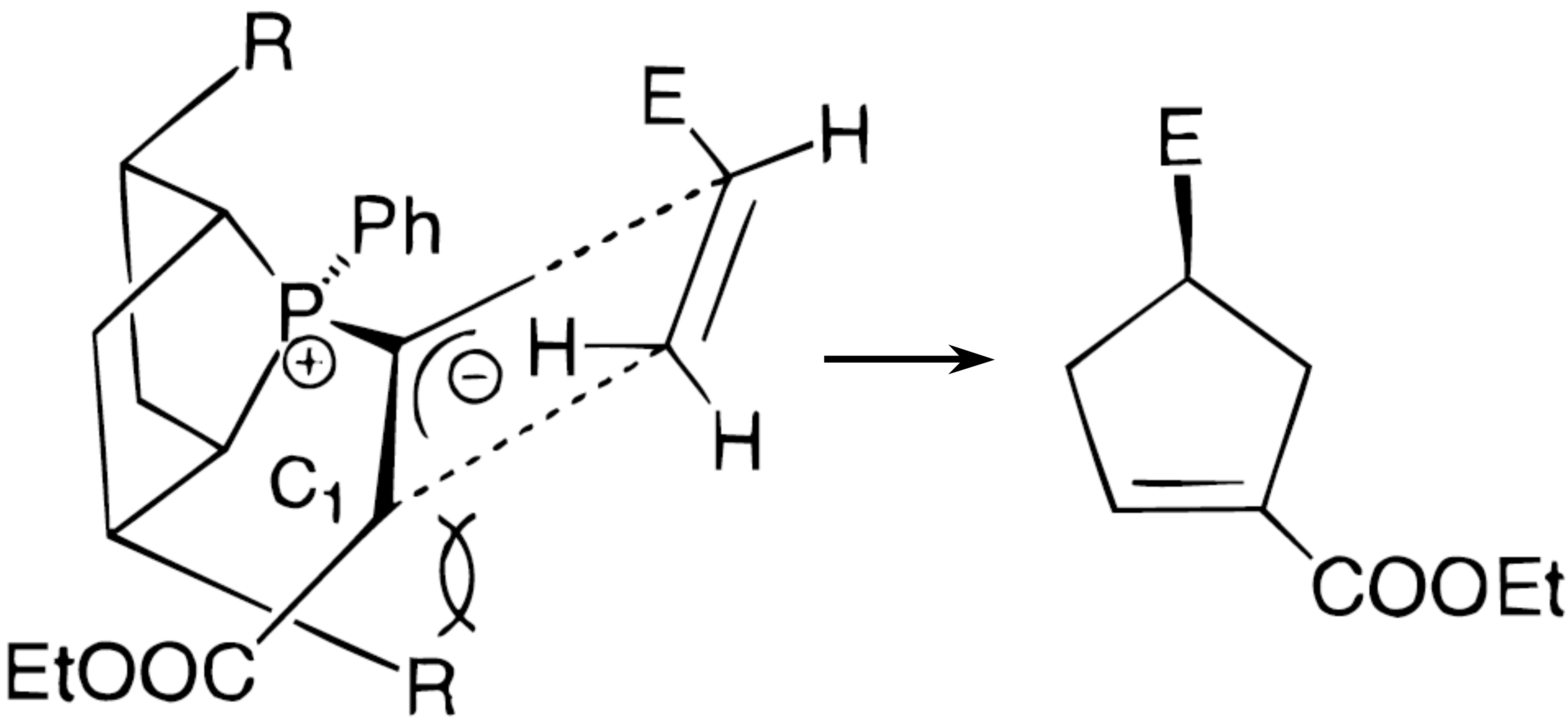
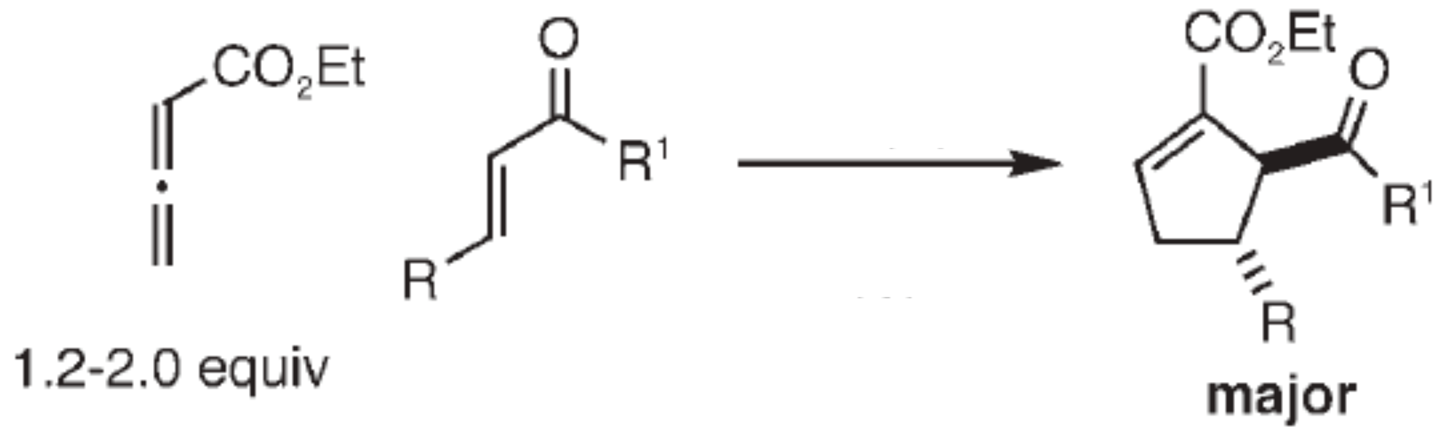
Proposed Transition State



3+2 Cycloaddition of Allenes & Enones



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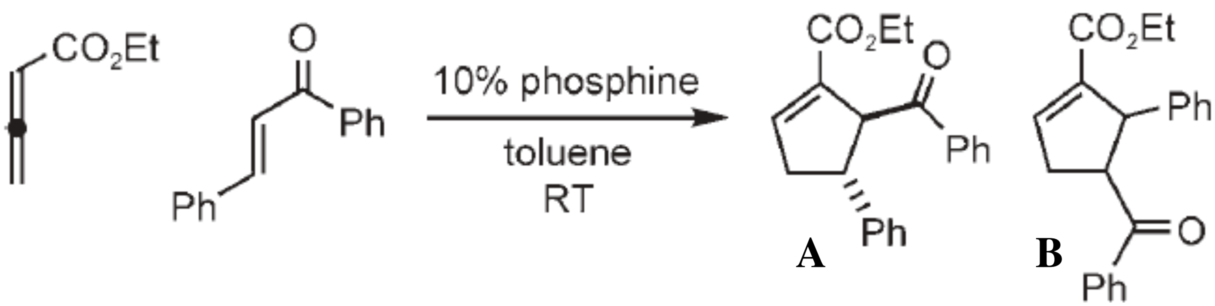
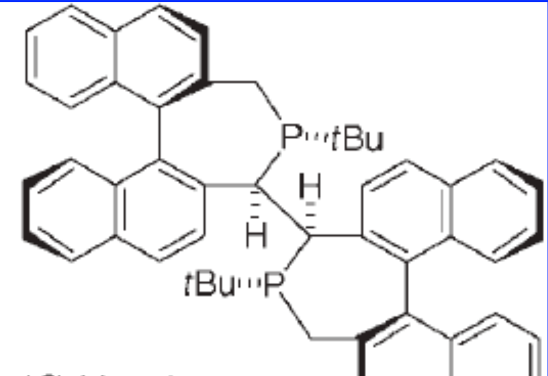
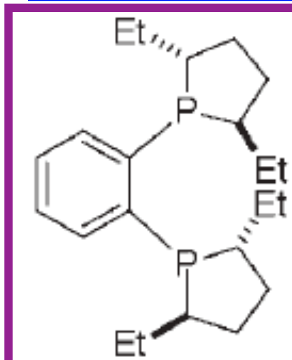
Survey of Chiral Phosphorus



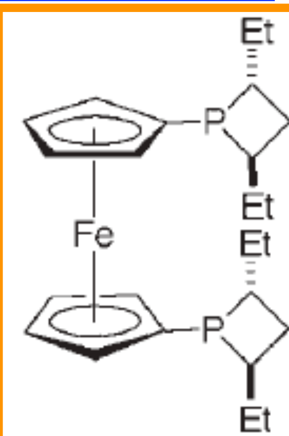
Phosphine[b]	Yield [%][c]	*ee* [%][d]	**A**:**B**
(*R*)-**2**	64	88	13:1
(*S*)-binapine	0	–	–
(*R*)-binap	2	50	>20:1
(*R*)-nmdpp	4	−4	11:1
(*R*,*R*)-Me-bpe	61	−4	6:1
(*R*,*R*)-ferrotane	64	11	7:1
(*R*,*R*)-Et-DuPhos	61	58	7:1



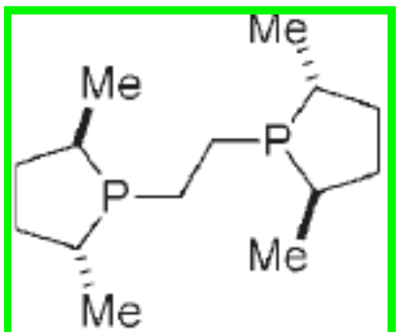
(*S*)-binapine



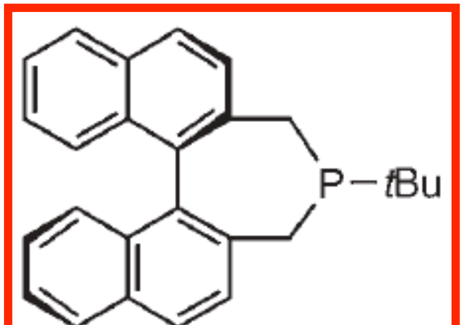
(*R*,*R*)-Et-DuPhos



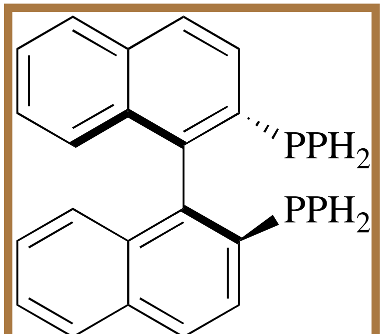
(*R*,*R*)-ferrotane



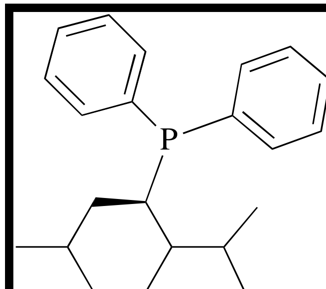
(*R*,*R*)-Me-bpe



(R)-2

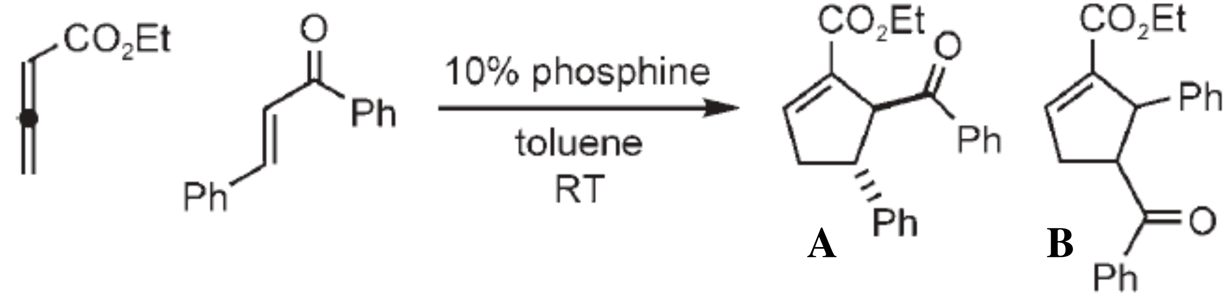


(*R*)-BINAP

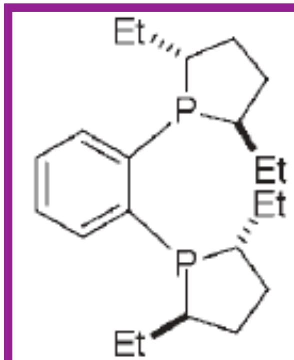


(R)-nmdpp

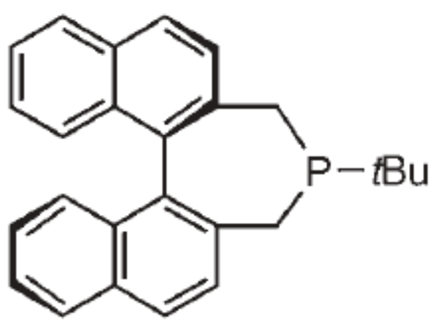
Survey of Chiral Phosphorus



Phosphine[b]	Yield [%][c]	*ee* [%][d]	**A**:**B**
(*R*)-**2**	64	88	13:1
(*S*)-binapine	0	–	–
(*R*)-binap	2	50	>20:1
(*R*)-nmdpp	4	−4	11:1
(*R*,*R*)-Me-bpe	61	−4	6:1
(*R*,*R*)-ferrotane	64	11	7:1
(*R*,*R*)-Et-DuPhos	61	58	7:1

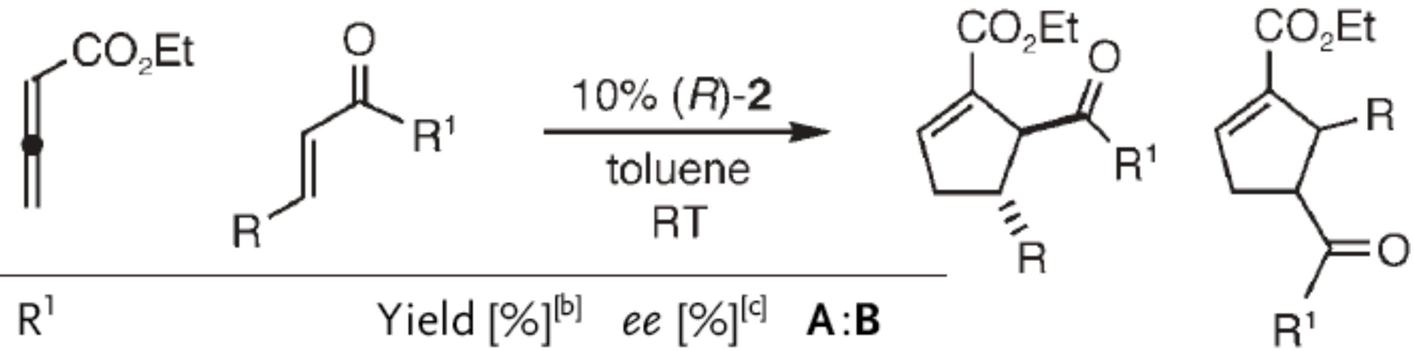


(*R*,*R*)-Et-DuPhos



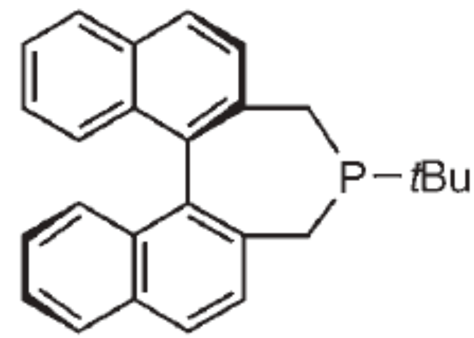
(R)-2

Scope



A B

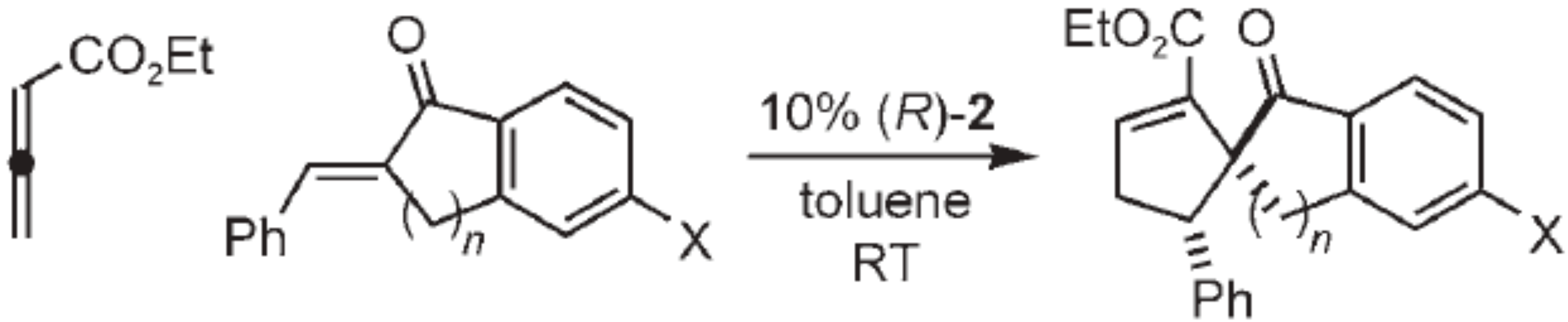
Entry	R	R^1	Yield [%][b]	*ee* [%][c]	**A**:**B**
1	Ph	Ph	64	88	13:1
2	Ph	4-chlorophenyl	76	82	7:1
3	Ph	4-methylphenyl	61	87	20:1
4	Ph	4-methoxy-phenyl	54	88	>20:1
5	4-chlorophenyl	Ph	74	87	9:1
6	4-methoxy-phenyl	Ph	67	87	10:1
7	2-furyl	Ph	69	88	3:1
8[d]	2-quinolyl	Ph	52	88	20:1
9[d]	4-chlorophenyl	2-(5-methyl-furyl)	54	89	>20:1
10	Ph	2-thienyl	74	90	6:1
11	$C{\equiv}CC_5H_{11}$	Ph	65	85	6:1
12	$C{\equiv}CTES$	Ph	70	87	>20:1
13	C_5H_{11}	Ph	39[e]	75	>20:1



(R)-2

Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, 45, 1426-1429

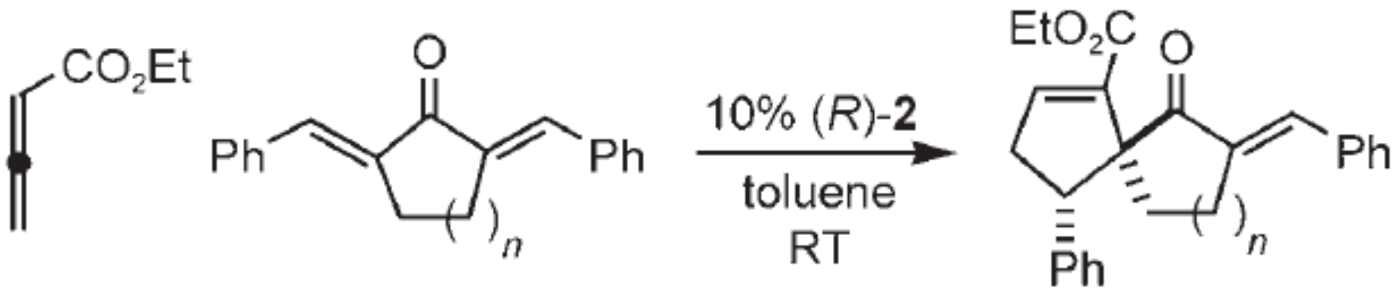
Spiro Example



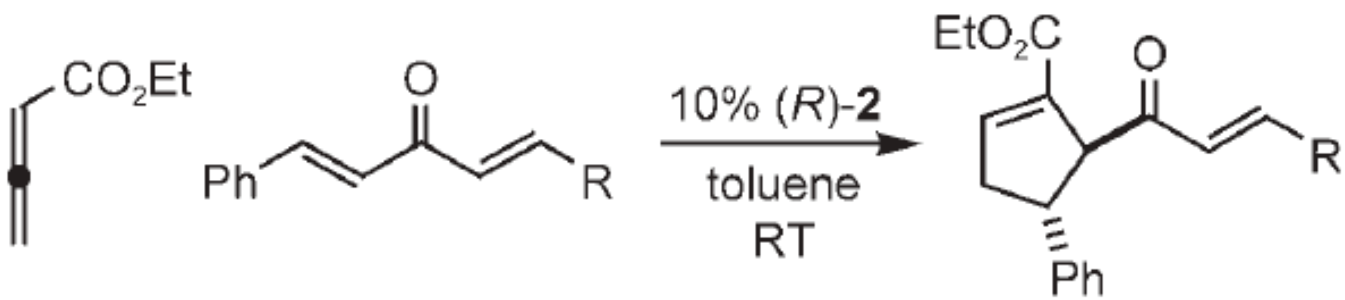
n	X	yield (%)	*ee* (%)
1	Br	97	89
2	H	32	95

Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, 45, 1426-1429

Dienones



n	yield (%)	*ee* (%)
1	81	89
2	57	93



R	yield (%)	*ee* (%)
Ph	75	89
2,6-dichlorophenyl	68	73

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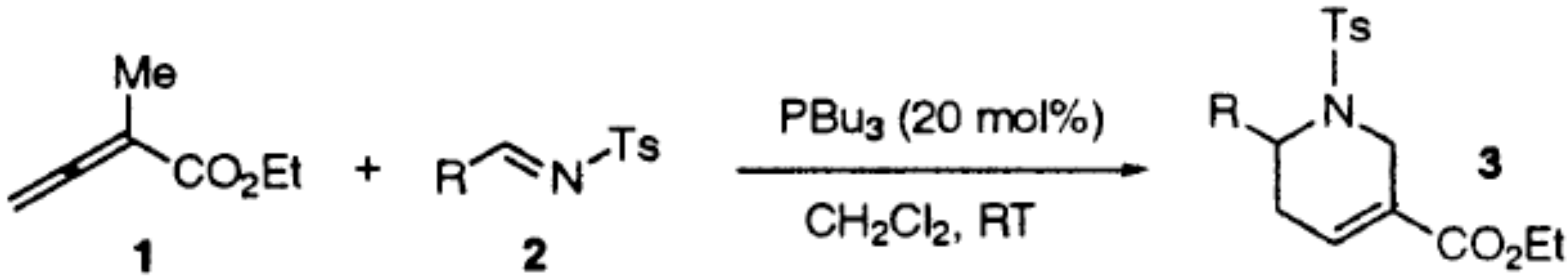
4+2 Cycloaddition Reaction…

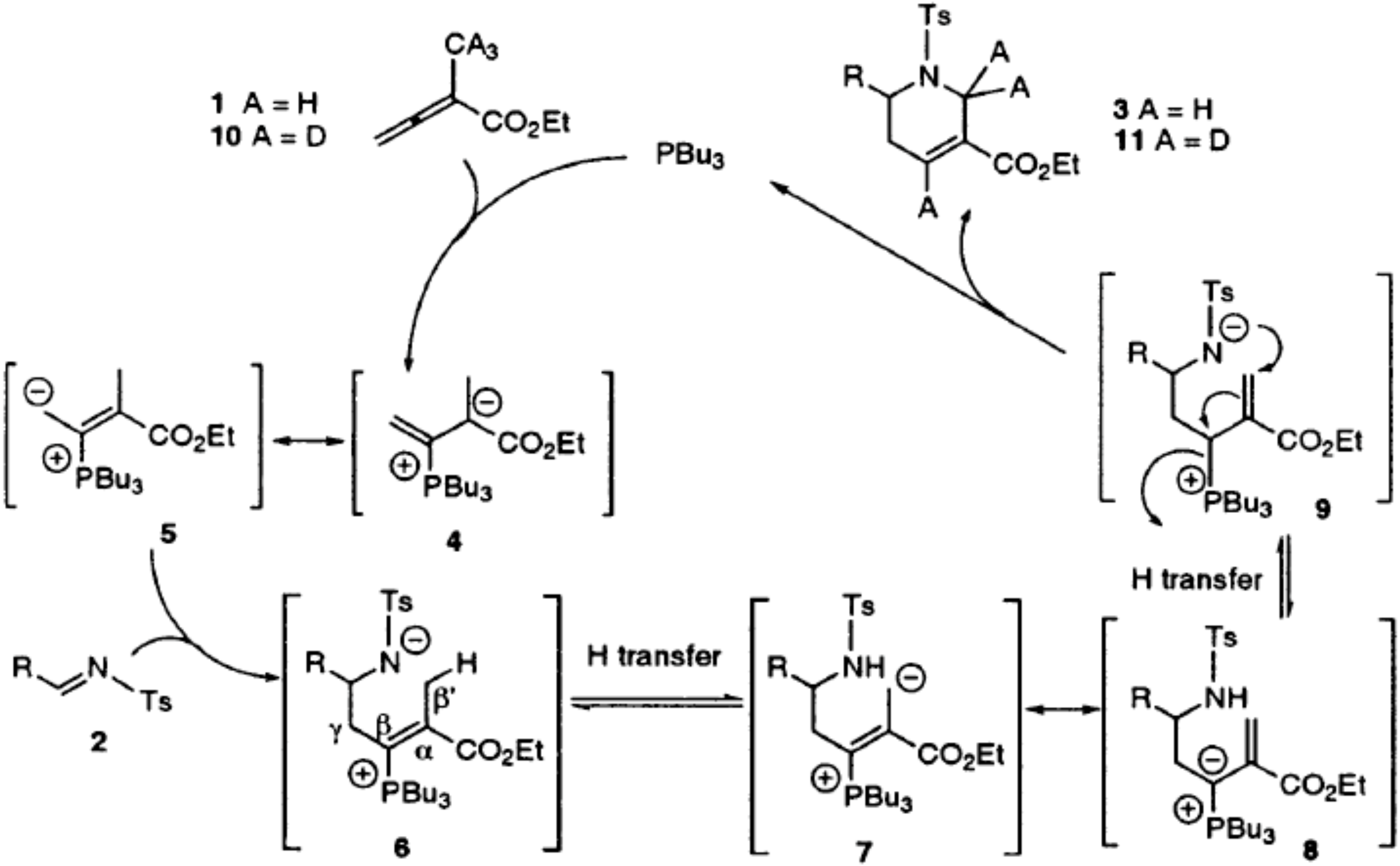
Kwon Reaction



R	product	yield (%)[b]	R	product	yield (%)[b]
Ph (**2a**)	**3a**[c]	98	4-pyridyl (**2k**)	**3k**	92[d]
4-$OMeC_6H_4$ (**2b**)	**3b**	99	4-$NO_2C_6H_4$ (**2l**)	**3l**	86
4-MeC_6H_4 (**2c**)	**3c**	95	2-OHC_6H_4 (**2m**)	**3m**	0
3-ClC_6H_4 (**2d**)	**3d**	96	2-$OTBSC_6H_4$ (**2n**)	**3n**	93
2-ClC_6H_4 (**2e**)	**3e**	93	2-pyrrolyl (**2o**)	**3o**	0
4-FC_6H_4 (**2f**)	**3f**	95	*N*-Boc-2-pyrroyl (**2p**)	**3p**	99
4-CNC_6H_4 (**2g**)	**3g**	98	*trans*-styrenyl (**2q**)	**3q**	trace[e]
2-$CF_3C_6H_4$ (**2h**)	**3h**	98	*t*-butyl (**2r**)	**3r**	86[f]
1-naphthyl (**2i**)	**3i**	96	*n*-propyl (**2s**)	**3s**	0[g]
2-furyl (**2j**)	**3j**	97	2-furyl (**2j**)	**3j**	97

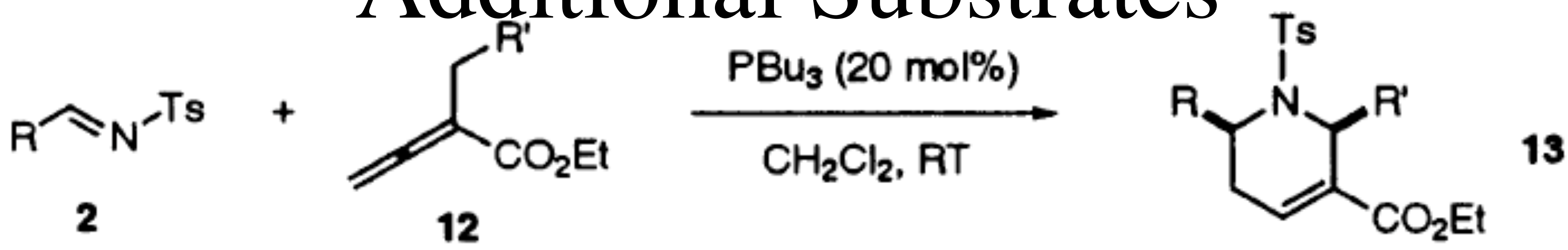
Zhu, X.; Lian, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, 125, 4716-4717

4+2 Cycloaddition Mechanism



Zhu, X.; Lian, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, 125, 4716-4717

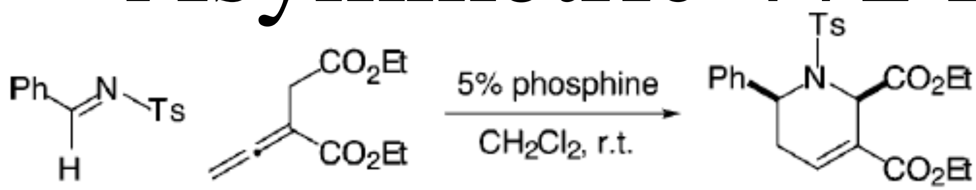
Additional Substrates



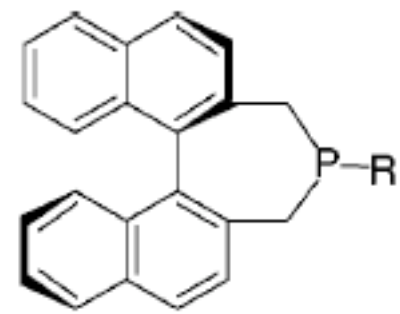
entry	R	R′	product	yield (%)[b]	dr[c]
1	Ph (**2a**)	4-CNC_6H_4 (**12a**)	**13a**	99	98:2
2	Ph (**2a**)	2-FC_6H_4 (**12b**)	**13b**	99	97:3
3	Ph (**2a**)	3-$OMeC_6H_4$ (**12c**)	**13c**	99	98:2
4	Ph (**2a**)	2-MeC_6H_4 (**12d**)	**13d**	82	88:12
5	Ph (**2a**)	Ph (**12e**)	**13e**[d]	99	98:2
6	4-$OMeC_6H_4$ (**2b**)	Ph (**12e**)	**13f**	99	97:3
7	4-$NO_2C_6H_4$ (**2l**)	Ph (**12e**)	**13g**	90	95:5
8	3-ClC_6H_4 (**2d**)	4-CNC_6H_4 (**12a**)	**13h**	99	98:2
9	2-$CF_3C_6H_4$ (**2h**)	4-CNC_6H_4 (**12a**)	**13i**	80	90:10
10	2-ClC_6H_4 (**2e**)	3-$OMeC_6H_4$ (**12c**)	**13j**	96	83:17
11	4-MeC_6H_4 (**2c**)	3-$OMeC_6H_4$ (**12c**)	**13k**	99	98:2

Zhu, X.; Lian, J.; Kwon, O. *J. Am. Chem. Soc*. **2003**, 125, 4716-4717

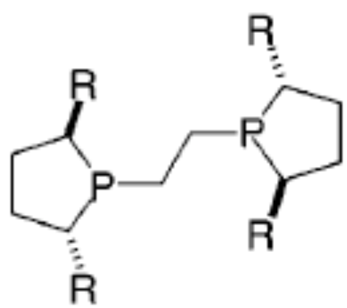
Asymmetric 4+2 Reaction



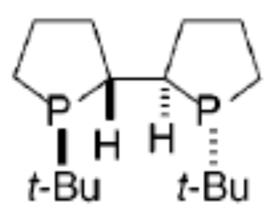
entry	phosphine	ee (%)[b]	cis:trans	isolated yield (%)
1	Me-BPE	−72	72:28	94
2	Et-BPE	−87	66:34	99
3	TANGPHOS	−44	34:66	99
4	**2**	−21	74:26	80
5	**3**	−7	75:25	99
6	**4**	−62	72:28	53
7	**5**	0	70:30	46
8	**6**	51	69:31	99
9	**1**	98	91:9	93
10	BINAPINE	–	–	0



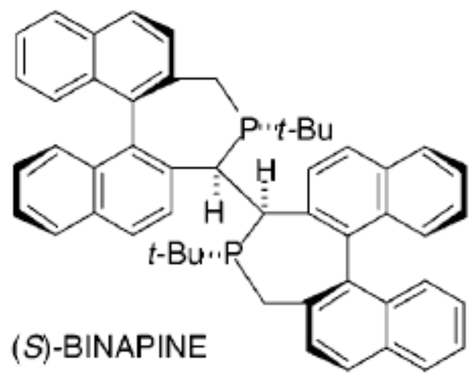
R = Ph ((*R*)-**2**)
R = 4-MeO-C_6H_4 ((*R*)-**3**)
R = NEt_2 ((*R*)-**4**)
R = Et ((*R*)-**5**)
R = *i*-Pr ((*R*)-**6**)
R = *t*-Bu ((*R*)-**1**)



R = Me: (*R*,*R*)-Me-BPE
R = Et: (*R*,*R*)-Et-BPE



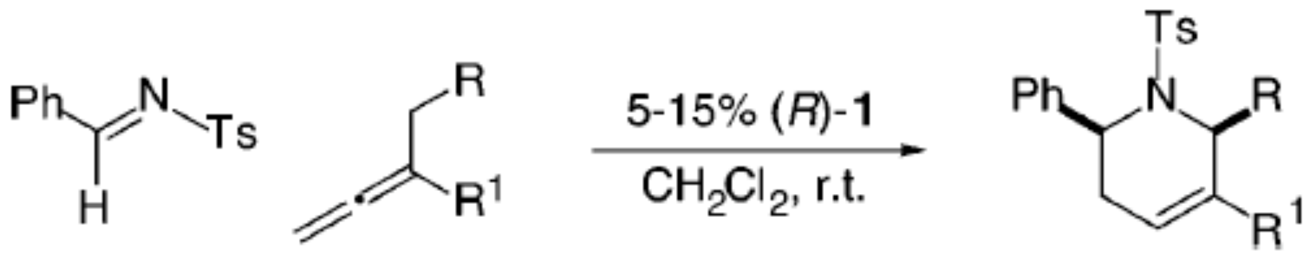
(*S*,*S*,*R*,*R*)-TANGPHOS



(*S*)-BINAPINE

Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, 127, 12234-12235

Allene Scope



entry	R	R[1]	ee (%)[b]	cis:trans	isolated yield (%)
1	CO_2Et	CO_2Et	98	91:9	93
2	Ph	CO_2Et	87	99:1	78
3	4-(CF_3)C_6H_4	CO_2Et	88	99:1	81
4	H	CO_2Et	68	–	72
5	H	COPh	76	–	97

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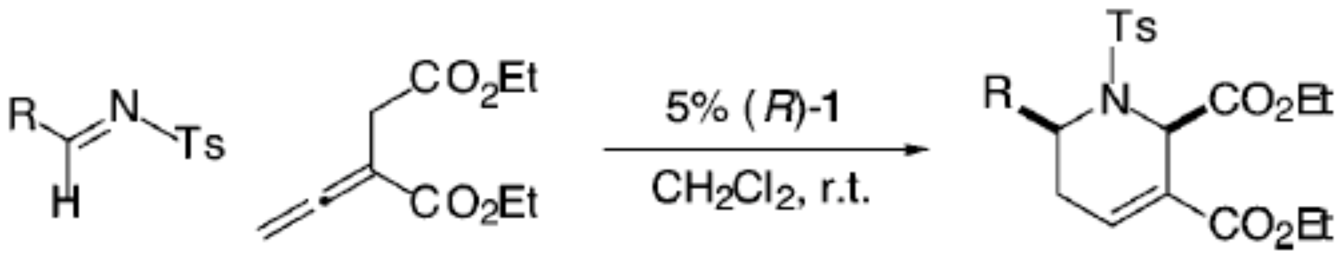
Imine Scope



entry	R	ee (%)[b]	cis:trans	isolated yield (%)
1	Ph	98	91:9	93
2	3-MeC_6H_4	98	93:7	98
3	3,4,5-$(MeO)_3C_6H_2$	96	96:4	86
4	4-$(MeO)C_6H_4$	98	93:7	42
5	4-ClC_6H_4	96	91:9	99
6	3-BrC_6H_4	99	89:11	98
7	2-$(NO_2)C_6H_4$	68	96:4	98
8	2-ClC_6H_4	60	79:21	75
9	2-naphthyl	99	93:7	96
10	2-furyl	97	87:13	98
11	3-pyridyl	97	91:9	76

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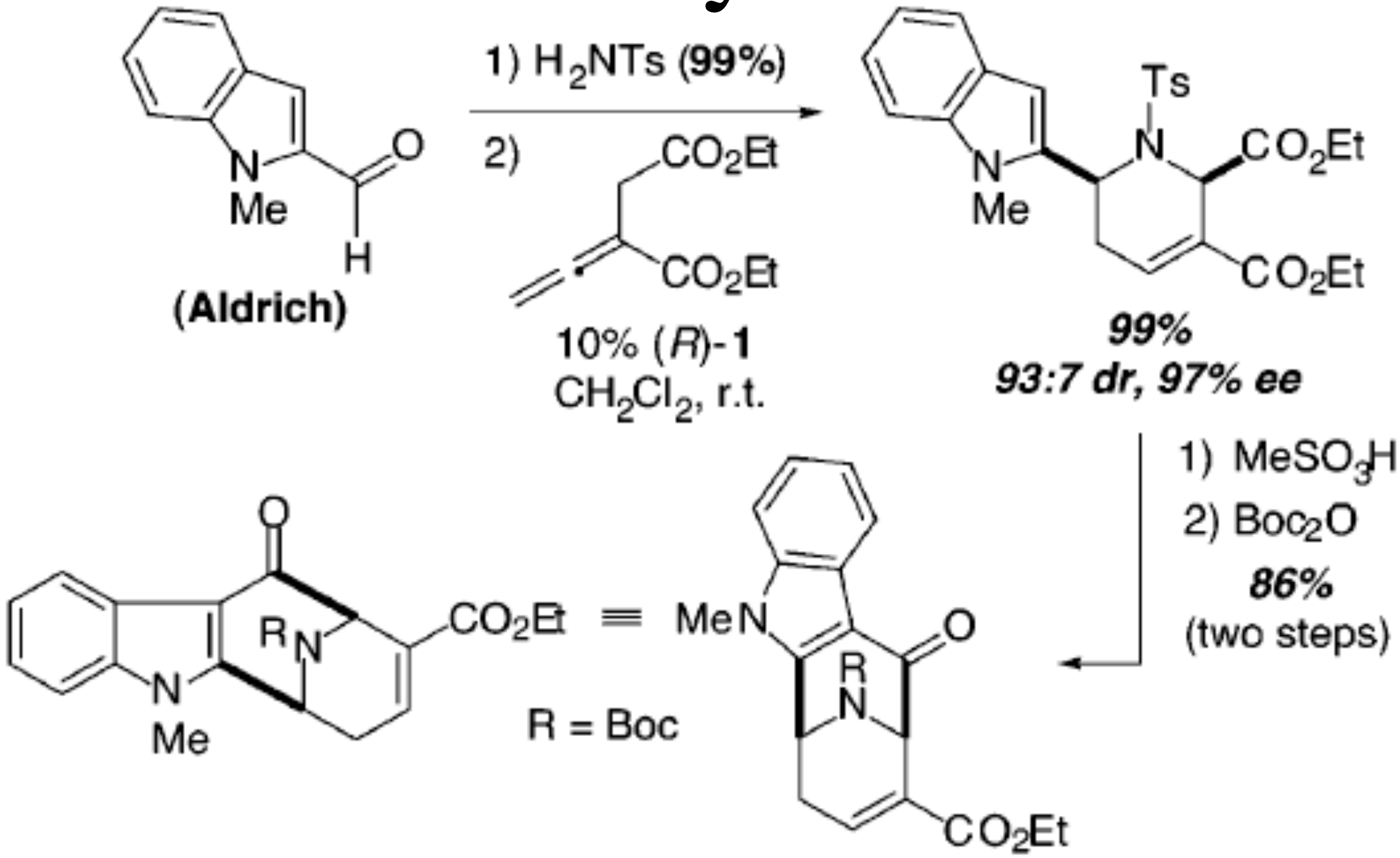
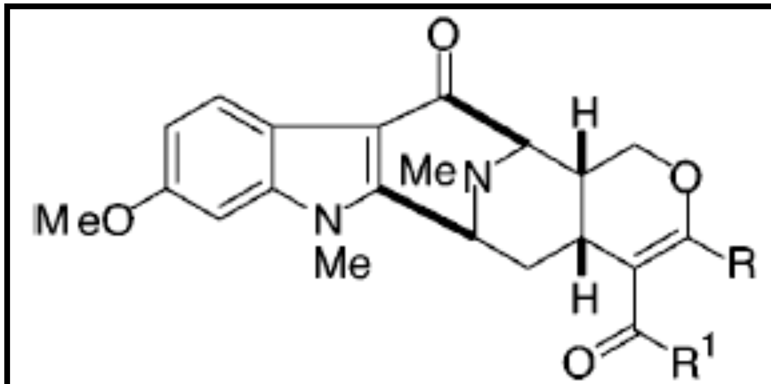
Use in Synthesis





R = Me, R[1] = H: 6-oxoalstophyllal
R = H, R[1] = Me: 6-oxoalstophylline

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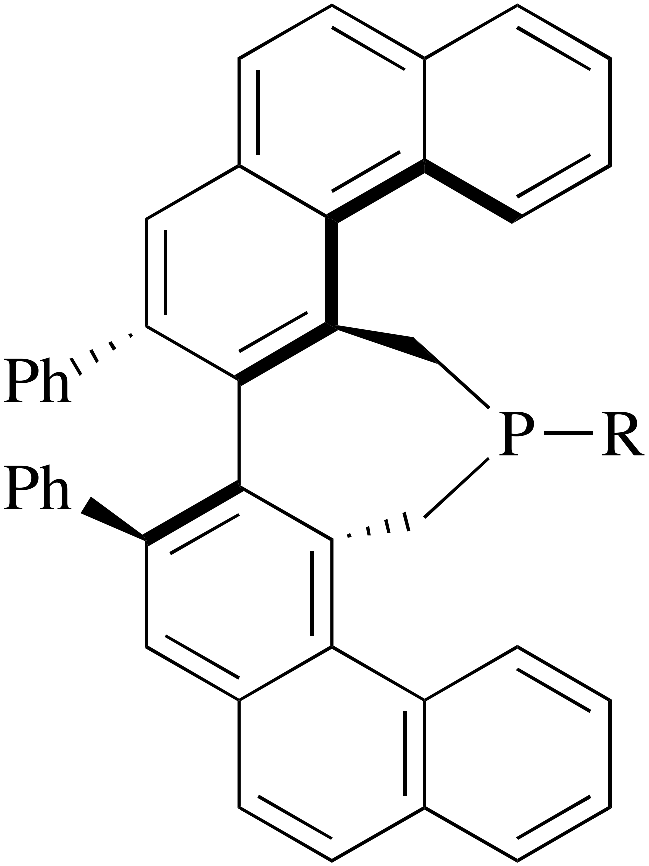
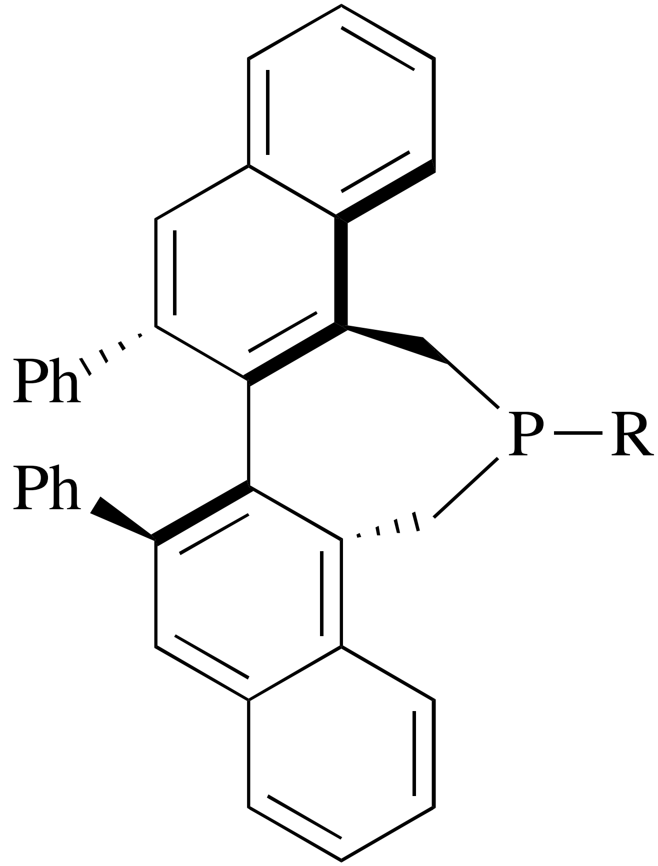
Thanks for the input!

Why Not…


Thanks for the input!


Ph
Ph
P
R

OR


Ph
Ph
P
R


Thanks for the input!


Thanks for the input!