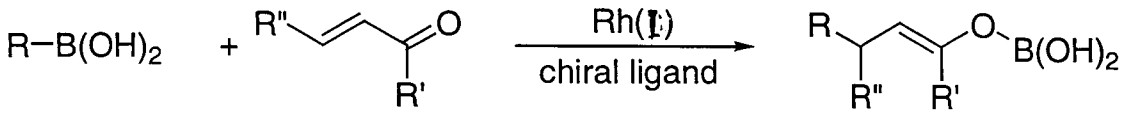
1,4-Conjugate Additions Using Organoboron Compounds



Shinji Fujimori
Denmark Group Meeting
6/12/01

Conjugate Additions

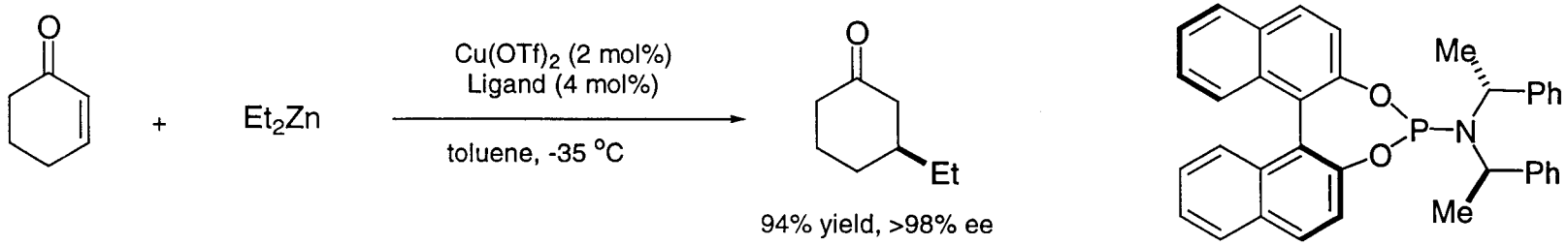
1. Carbon-Carbon bond formation
   - found in many natural product syntheses (steroids, terpenes, prosteglandines)

2. Variety of Donors and Acceptors
   - C, H, N, O, S, etc.
   - Enone, enal, enoate, enamide, nitroalkene, etc.

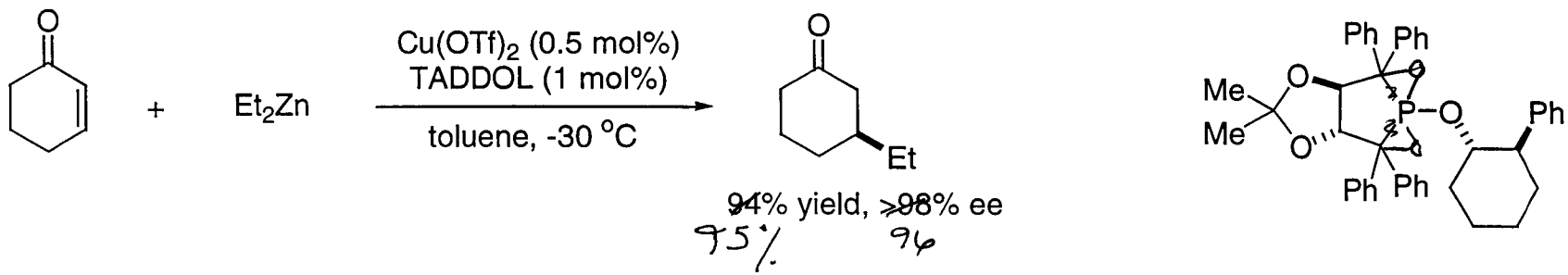
3. Transition metal catalysis
   - Cu, Ni, Pd, Al
   - chiral ligands => stereoselective reactions

Reviews:
Sibi, M. P. and Manyem, S. *Tetrahedron*, **2000**, *56*, 8033.
Krause, N. and Hoffmann-Roder, A. *Synthesis*, **2001**, 171.
Rossiter, B. E. and Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

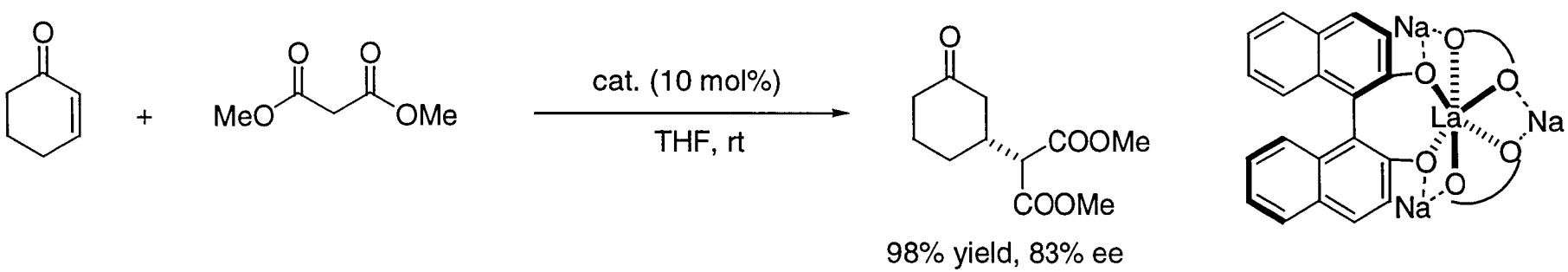
Recent Development in Catalytic Enantioselective Conjugate Additions



Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.



Alexakis, A. *et. al. Tetrahedron Lett.*, **1998**, *39*, 7869.



Shibasaki, M. *et. al. J. Am. Chem. Soc.* **1995**, *117*, 6194

Organoboron Reagents

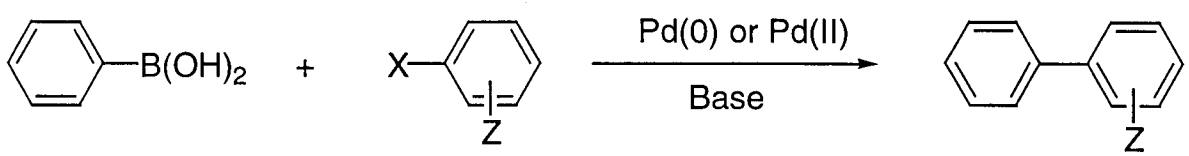
Stable in protic / aqueous media

Stable toward oxygen

Boronic acids and esters are compatible to many functionalities

Transmetallation to other metals

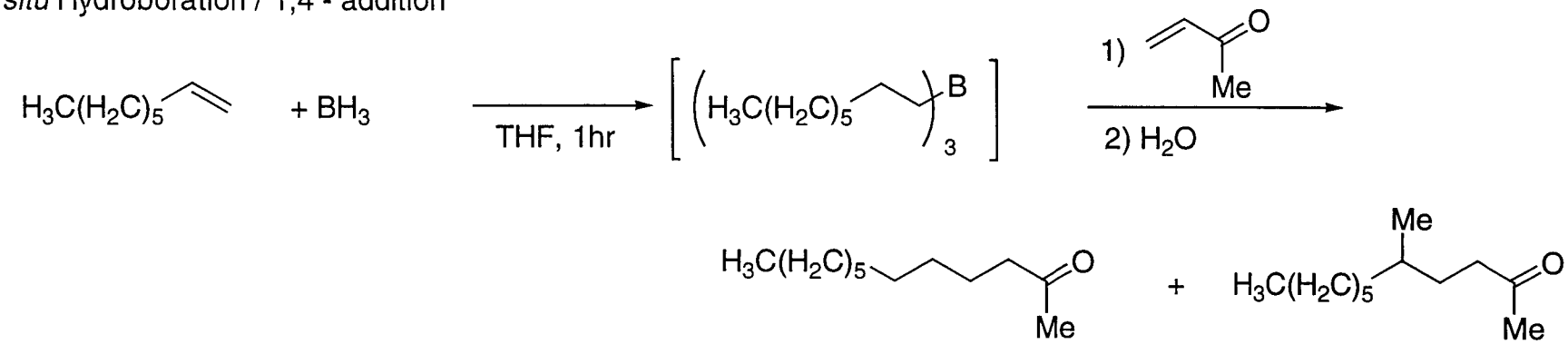
Ag(I), Mg(I), Zn(II), Al(II), Sn(IV), Cu(I), Hg(II) halides are known
to Pd very well-known



Miyaura, N. and Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

Conjugate Addition of Alkyl and Alkynyl Boranes

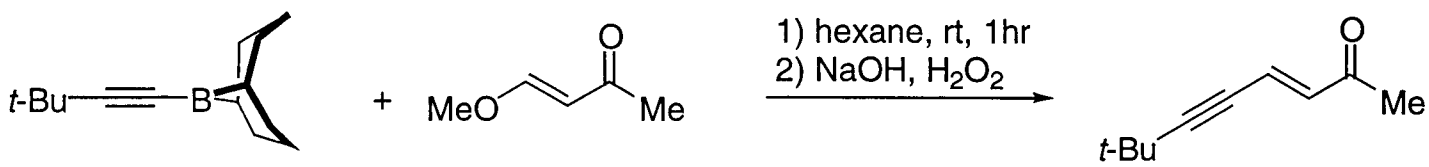
in situ Hydroboration / 1,4 - addition



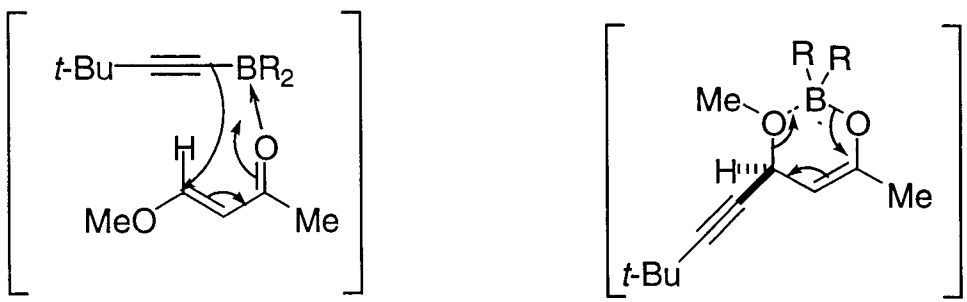
86/14 mixture, 93% yield

Suzuki, A.; Brown, H. C. *et. al. J. Am. Chem. Soc.* **1967**, *89*, 5708.

Alkynyl, alkenyl 9-BBN addition to enones

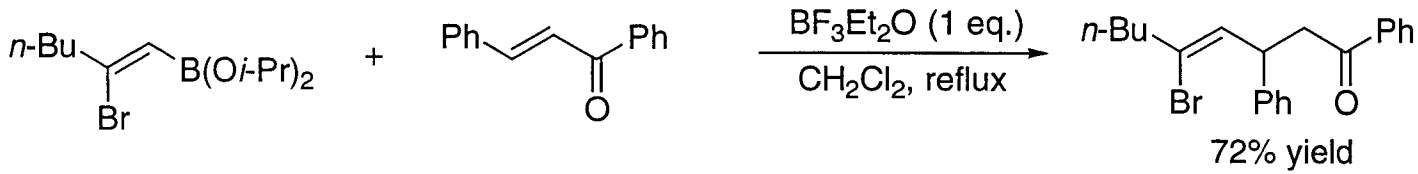


E - only, 98% yield

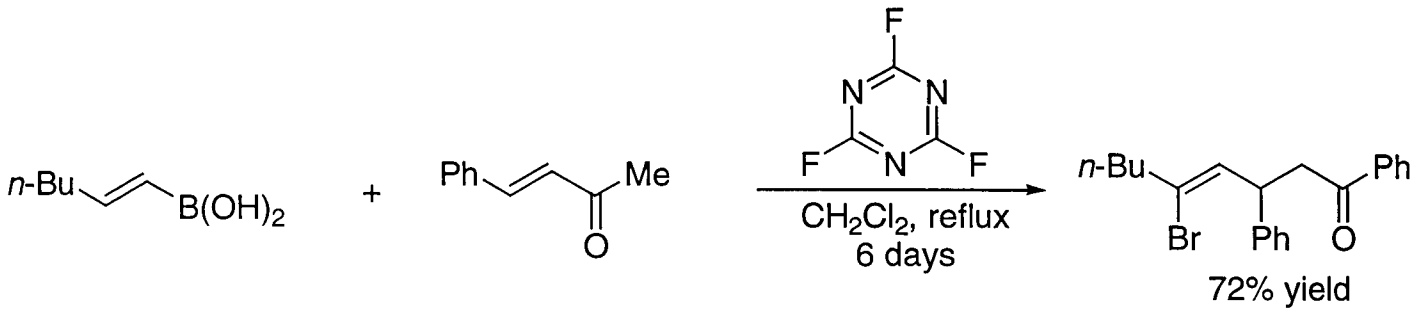


Brown, H. C. and Molander, G. A. *J. Org. Chem.* **1977**, *42*, 3106.

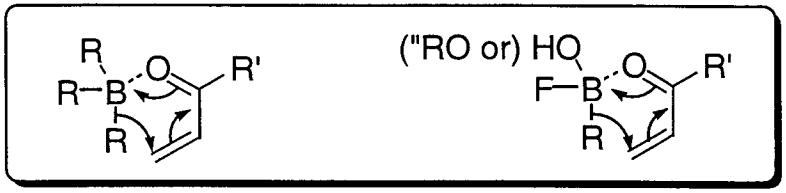
Additions of Dialkoxy Boranes and Boronic Acids



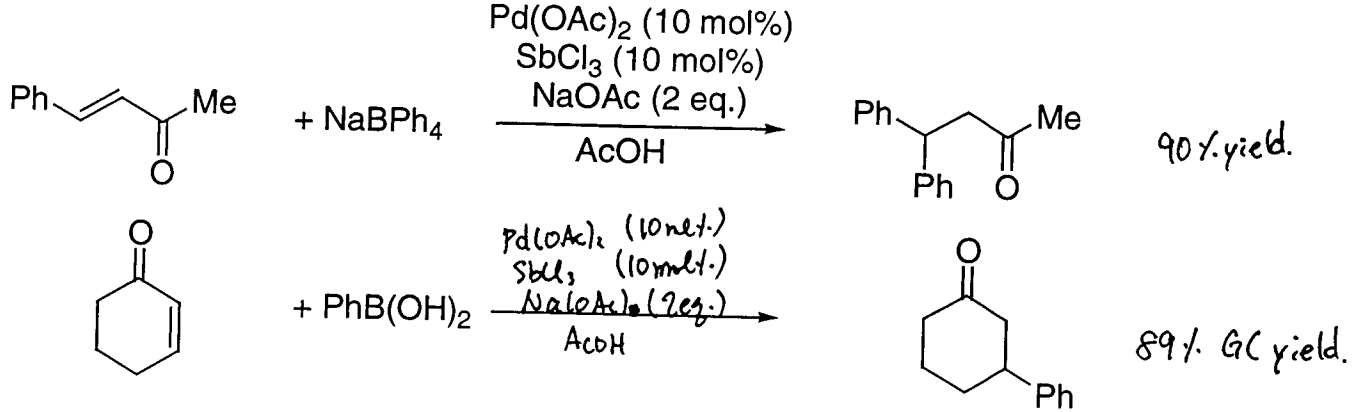
Suzuki, A. *et. al. Tetrahedron Lett.* **1990**, *31*, 247.



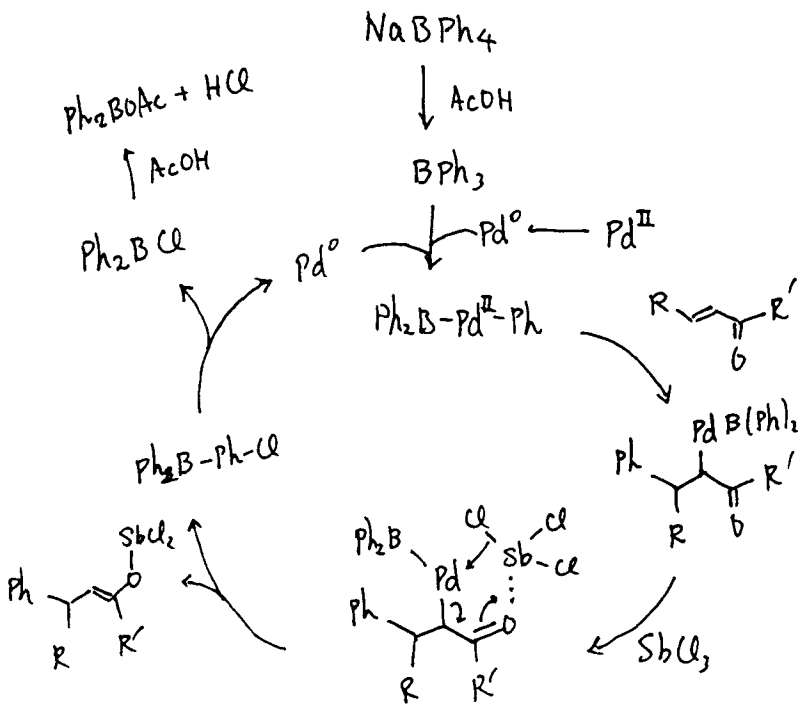
Suzuki, A. *et. al. Synlett.* **1996**, 993.



Palladium-Catalyzed Addition of Arylboron Compounds



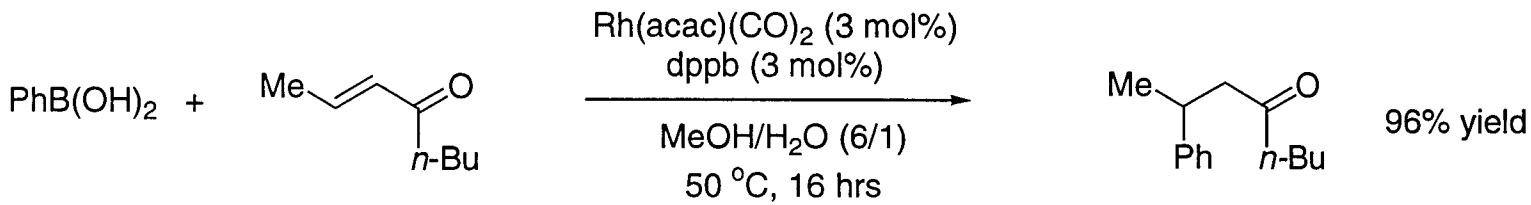
Proposed Catalytic Cycle:



Uemura, S. *et. al. J. Organomet. Chem.* **1994**, *465*, 85.
Uemura, S. *et. al. J. Org. Chem.* **1995**, *60*, 883.

- Heck-type process was proposed.

Rhodium-Catalyzed Addition of Boronic Acids



Solvent Effect

enone	DMF/H_2O (6/1)	cyclohexane/H_2O (6/1)	MeOH/H_2O (6/1)
MVK	82 (99)	(90)	(99)
2-octen-4-one	28	60, 74 *	96 *
cyclohexenone	trace	52 *	trace

() = GC yield
* = 2 eq. of boronic acid

Reaction do not proceed without added water.

Addition of various bases retarded the rate. (NaOH, NaOAc, triethylamine)

Subsitution on arylboronic acid

substituent	yield in DMF/water (6/1)
4-MeO	84
2-MeO	68
4-MeCO	94
2,4,6-$(Me)_3$	(44), (80) *

Miyaura, N. *et al. Organometallics*, **1997**, *16*, 4229

Rhodium-Catalyzed Addition of Boronic Acids (Cont.)

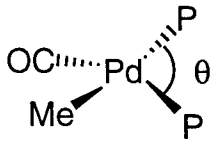
Effect of Phosphines

phosphine	yield in DMF/water (6/1) MVK	2-octen-4-one	P-Pd-P anlgle
PBu_3	93		
PPh_3	83	0	
TFP	94	12	
dppe	70	0	85.8
dppp	97	19	90.6
dppb	99	28	94.51

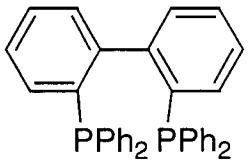
Miyaura, N. *et al. Organometallics*, **1997**, *16*, 4229

Possible relationship with P-RhP angle
rate acceleration as the angle increases

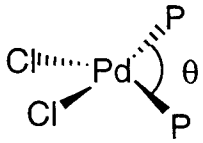
The rate of Pd-catalyzed carbonylation



van Leeuwen, P. W. N. M.
Organometallics, **1992**, *11*,1598.



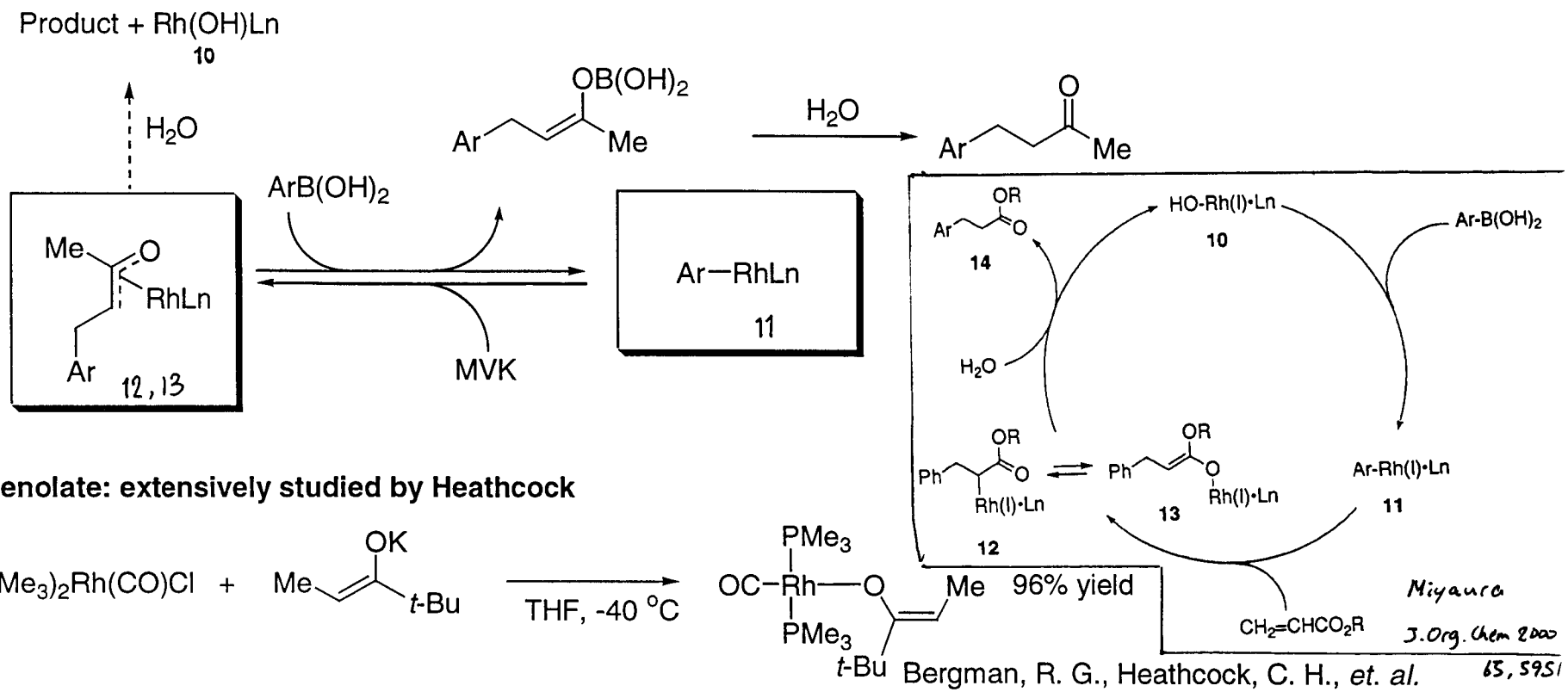
dpbp found to increase the rate
of cojugate addition



P-Pd-P 92.24 (smaller than dppb)
Cl-Pd-Cl 88.21 (smaller than dppb)

Hayashi, T. *et. al. Organometallics.* **2000**, *19*, 1567.

Proposed Catalytic Cycle



Miyaura J. Org. Chem 2000 65, 5951

Rh-enolate: extensively studied by Heathcock

Bergman, R. G., Heathcock, C. H., *et. al.* *J. Am. Chem. Soc.* **1989**, *111*, 938.

Alkyl/Aryl Rh(I) species

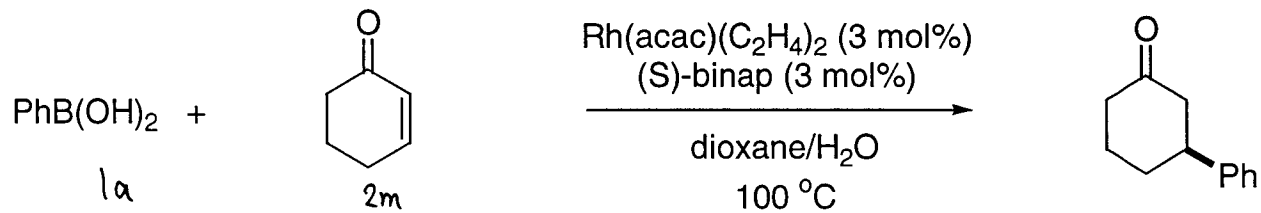
$RhCl(CO)(PPh_3)_2$ + PhLi $\xrightarrow{\text{THF,-78 °C}}$ $Rh(Ph)(CO)(PPh_3)_2$

Hegedous, L. S. *et. al*. *J. Am. Chem. Soc.* **1973**, *95*, 3040.

$(PPh_3)_3RhCl$ + PhMgBr $\xrightarrow{\text{Ether, rt}}$ $PhRh(PPh_3)_3$ 90% yield

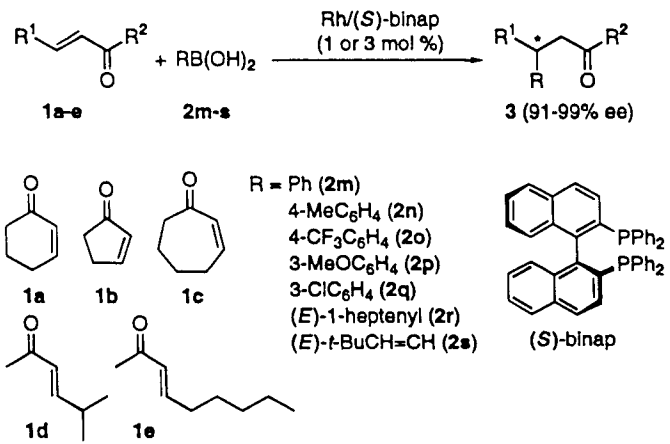
Keim, W. *J. Organomet. Chem.* **1968**, *14*, 179.

Asymmetric Addition of Boronic Acid to Enones



64% yield
97% ee

Scheme 1



- Rh (acac) $(CO)_2$ 15% yield ; 43% ee
- excess boronic acid greatly improved yield.

equiv of 2m (to 1)	yield
1.4	64%
2.5	93%
5.0	99%

- higher temp required (1.4eq of 2m to 1a)

temp(°C)	yield	ee
40	<2%	97%
60	3%	97%
80	42%	97%
120	59%	97%

- substitution on aryl did not affect yield or selectivity significantly
- alkenyl boronic acids also added w/ high enantioselectivity

Hayashi, T.; Miyaura, N. *et al. J. Am. Chem. Soc.*, **1998**, *120*, 5579

Catalytically Active Species

NMR study

$$Rh(acac)(C_2H_4)_2 + (S)\text{-binap} \xrightarrow[THF]{} Rh(acac)(S)\text{-binap}$$

quantitatively formed
H, P-NMR analysis
elemental analysis
consistent with the precedented Rh-bisphoshine complex

$$Rh(acac)(COD) + \text{bisphosphine} \xrightarrow[THF]{} Rh(acac)\text{bosphosphine} + COD$$

Budzelaar, P. H. M. *J. Organomet. Chem.* **1990,** *393*, 287.

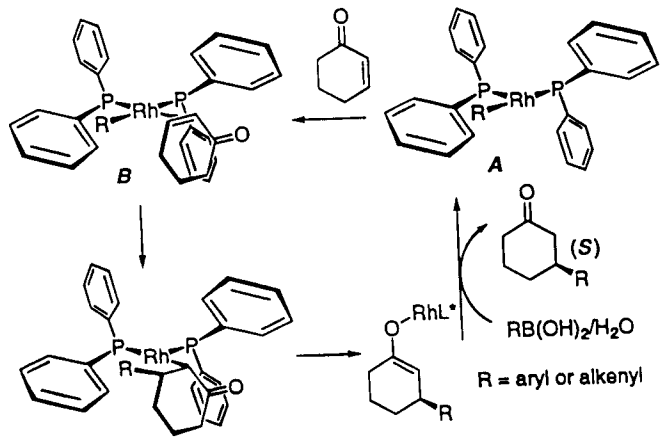
$$Rh(acac)(CO)_2 + (S)\text{-binap} \xrightarrow[THF]{} Rh(acac)(S)\text{-binap} + \text{complex mixture}$$

low catalytic activity/stereoselectivity are probably due to the formation of complex mixture of Rh species.

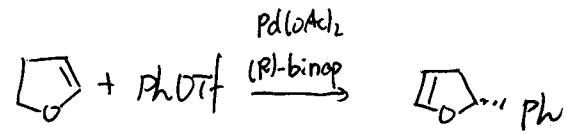
Hayashi, T.; Miyaura, N. *et al. J. Am. Chem. Soc.*, **1998**, *120*, 5579

Origin of Selectivity

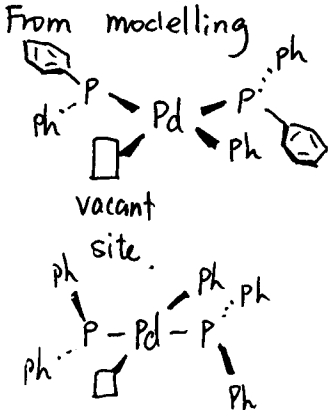
Scheme 2[a]



[a] The binaphthylene moiety in (*S*)-binap is omitted for clarity.



From modelling



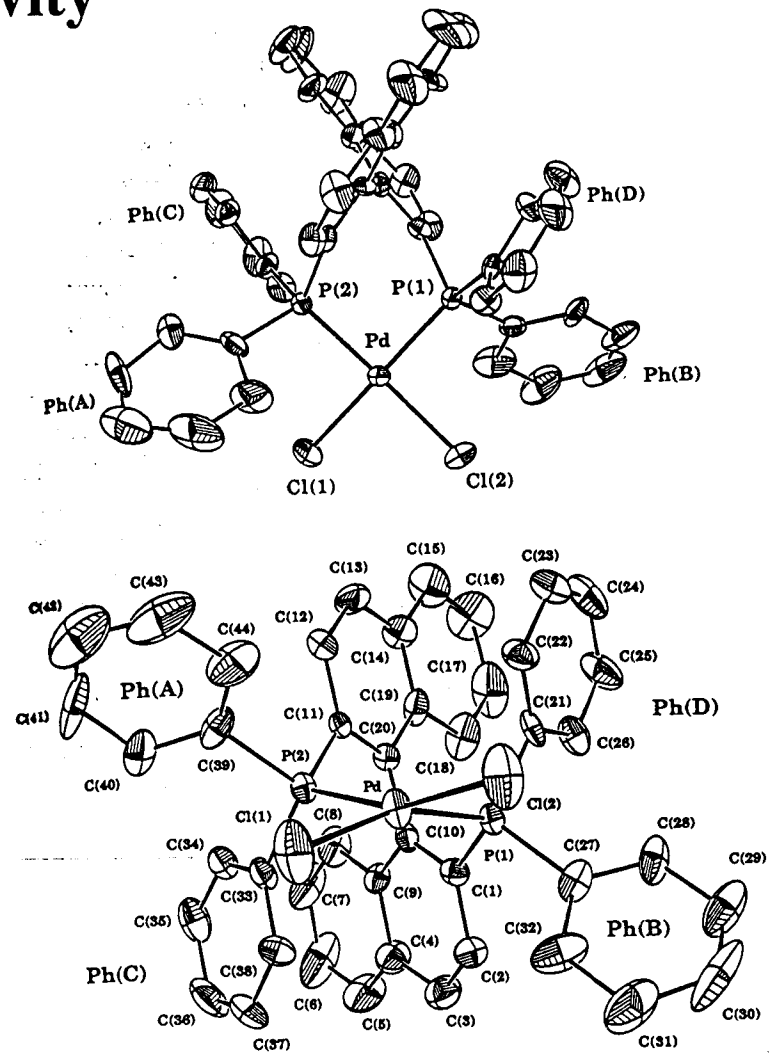


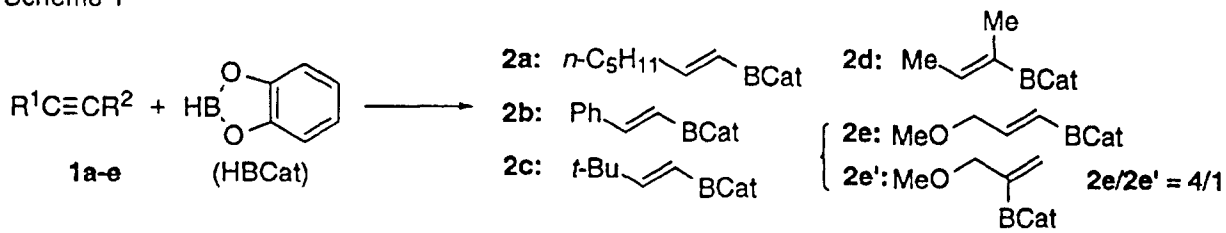
Figure 1. ORTEP diagrams of $PdCl_2\{(R)\text{-BINAP}\}$. The ellipsoids are drawn at the 30% probability level.

Hayashi, T.; Miyaura, N. *et. al .J. Am. Chem. Soc.* **1998**, *120*, 5579.
Ozawa, F.; Hayashi, T. *et. al. Organometallics.* **1993**, *12*, 4188.

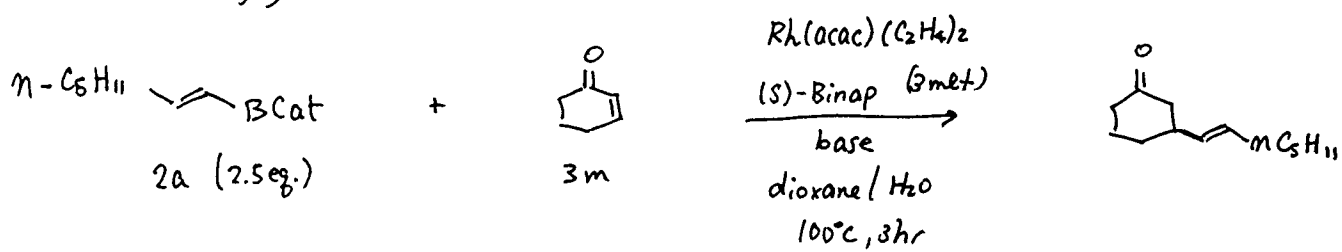
Addition of Alkenylboronate

- preparation of alkenylboronate

Scheme 1



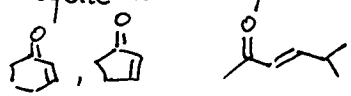
- effect of base in conjugate addition



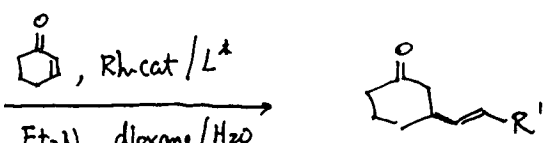
base	yield	%ee
none	29	94
Et_3N (5eq.)	78	95
iPr_2NEt (•)	29	94
NaOH (•)	26	94
Et_3N (10eq)	92*	96

* 10eq. of 2a was used.

- 2a-e were added to cyclic and acyclic enones. (68~92% yield; 81~99% ee)



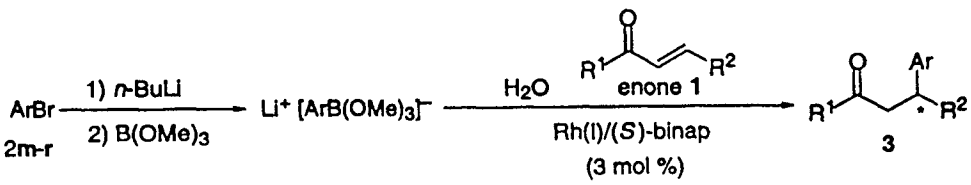
- one-pot hydroboration / 1.4-addition



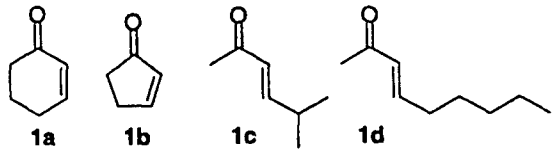
R' = nC5H11 85% yield, 95% ee
tBu 75% yield, 92% ee

Hayashi, T. *et. al* . *Tetrahedron Lett.* **1998**, *39*, 8479.

Addition of Arylborate

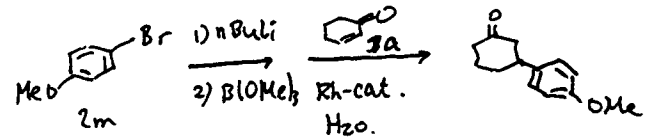


Ar = 4-$MeOC_6H_4$ (2m)
Ph (2n)
4-MeC_6H_4 (2o)
4-$CF_3C_6H_4$ (2p)
2-naphthyl (2q)
3,5-Me_2-4-$MeOC_6H_2$ (2r)



Scheme 2.

- amount of H_2O affect the yield.

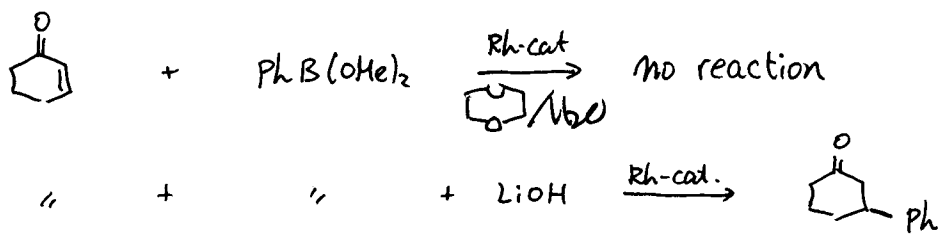


(2.5 equiv)

H_2O (equiv to 2m)	yield	% ee
10	19	98
2	51	98
1	80	98
0.5	74	98
none	4	97

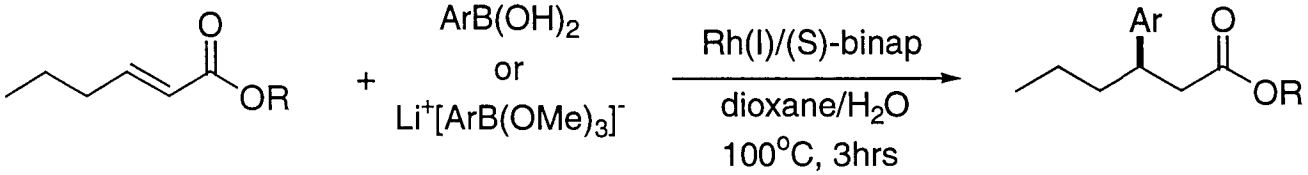
- Excellent yields and selectivities. (75~99% yield ; 91~99% ee)

- $Li[PhB(OMe)_3]$ + 1 eq. H_2O ⟶ $Li[PhB(OMe)_2(OH)]$ or $PhB(OMe)(OLi)$ are the reactive species.



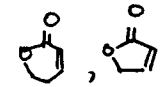
Hayashi, T. *et. al* .*Tetrahedron Lett.* **1999**, *40*, 8479.

Additions to α,β-Unsaturated Esters



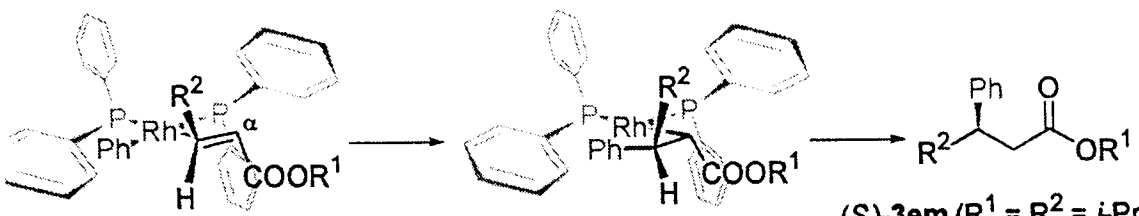
Dependence on the size of R

R	Using $PhB(OH)_2$	Using $[PhB(OMe)_3]^{\ominus}$
Me	94% yield, 86% ee	>99% yield, 89% ee
Et	>99 ", 90 "	>99% yield, 91% ee
iPr	42 ", 94 "	96 ", 95 "
tBu	21 ", 95 "	92 ", 96 "

- For cyclic lactones 

$PhB(OH)_2$ was better arylating reagent
96~98% ee's were obtained.

Stereochemistry

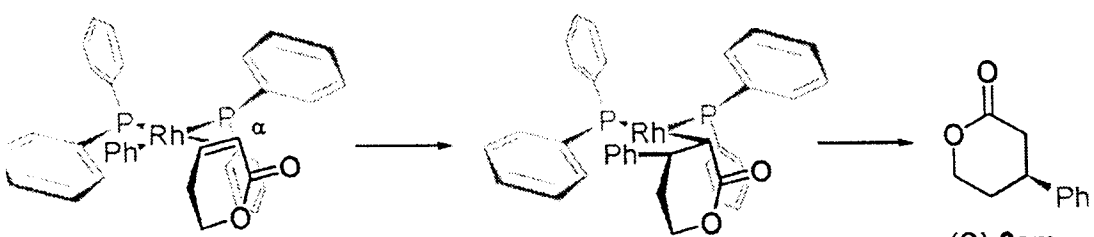


α-*si* face

(*S*)-**3em** ($R^1 = R^2 = i$-Pr)
(*R*)-**3fm** ($R^1 = i$-Pr, $R^2 = n$-Bu)

Z-enoate gives an enantiomeric product

ester	yield	%ee
pure (E), R=tBu	92%	98
E/Z (97/3), R=tBu	86%	93



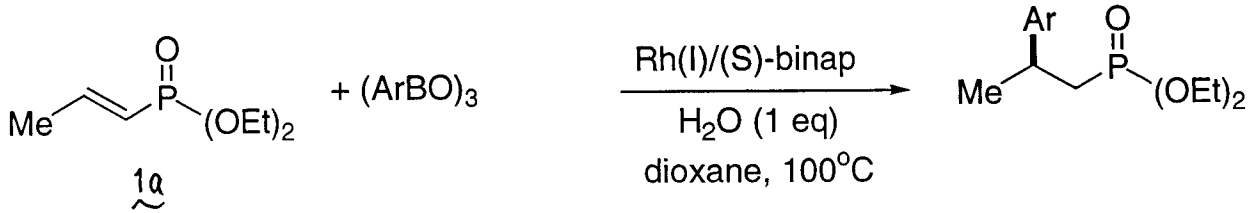
α-*si* face

(*S*)-**6am**

Hayashi, T. *et. al* .*Tetrahedron Asymmetry.* **1999**, *10*, 4047.
Miyaura, N. *et. al* .*J. Org. Chem.* **2000**, *65*, 5951.

Scheme 4. The binaphthylene moiety in (*S*)-binap is omitted for clarity

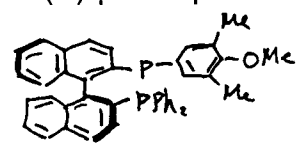
Additions to Other Acceptors



Arylboroxines are better substrate.

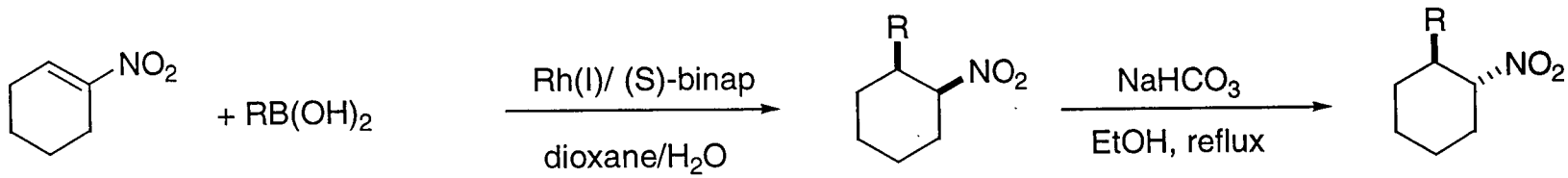
Boron	yield	% ee
$PhB(OH)_2$	44%	84 (S)
$(PhBO)_3$	94%	96 (S)
$(PhBO)_3$	5%	— (w/o H_2O)

Use of (S)-μ-binap



	phosphine	phosphonate	yield	% ee
	binap	(Z)-1a	96%	89 (R)
	μ-binap	(Z)-1a	98%	92 (R)
Ar = 2-naphthyl	binap	(E)-1a	89%	89
	μ-binap	(E)-1a	92%	90

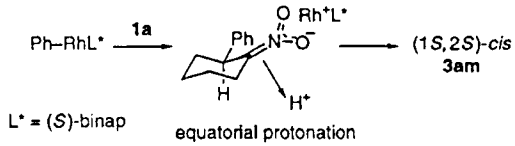
Hayashi, T.*et. al. J. Am. Chem. Soc.* **1999**, *121*, 11591.



R = Ph; 89% yield
cis/trans = 87/13
98.5% ee

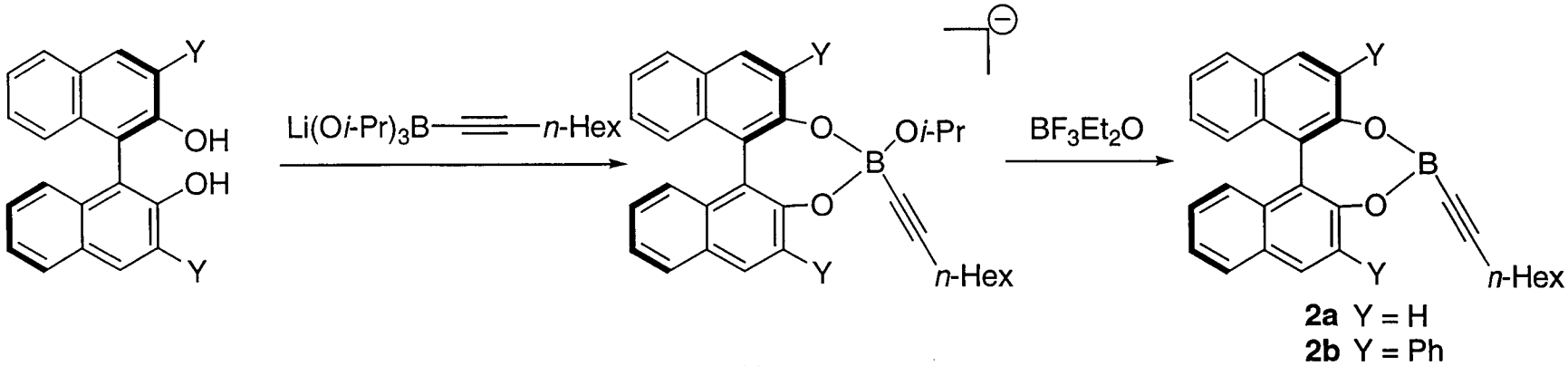
R = Ph;
cis/trans = 3/97
98.5% ee

Scheme 2

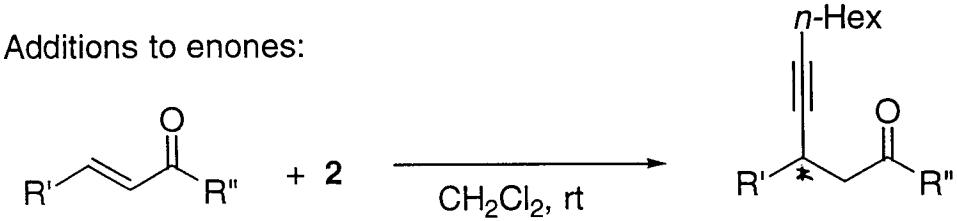


Hayashi, T.*et. al. J. Am. Chem. Soc.* **2000**, *122*, 10716.

Asymmetric Additions of Alkynylboronates

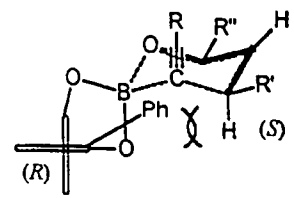


Additions to enones:

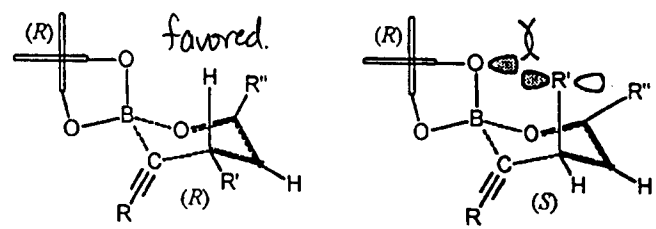


6a : R' = R" = Ph
6b : R' = Ph, R" = Me
6c : R' = 2furyl, R" = Ph

enone	boronate	yield	% ee
6a	2a	90	31
6a	2b	88	85
6b	2a	38	31
6b	2b	50	85
6c	2b	91	>98



10



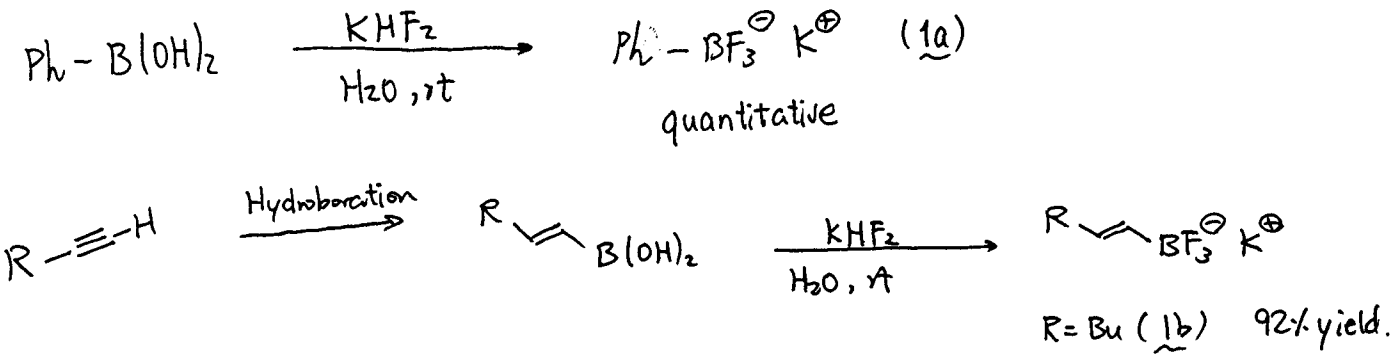
11*R* **11*S***

Figure 1. Cyclic 6-membered chair-transition states.

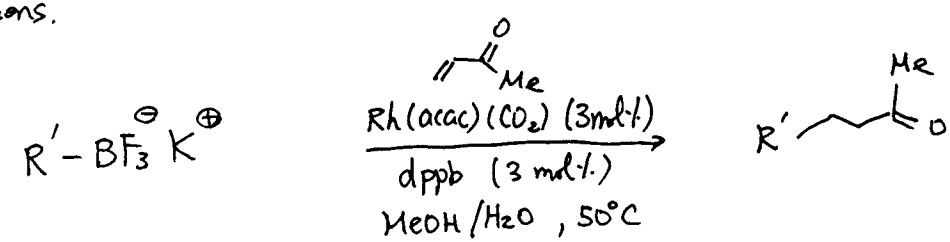
Chong, J. M. *et. al .J. Am. Chem. Soc.* **2000**, *122*, 1822.

Use of Aryltrifluoroborates

- Preparation of Aryl and alkenyl trifluoroborates



- conjugate additions.

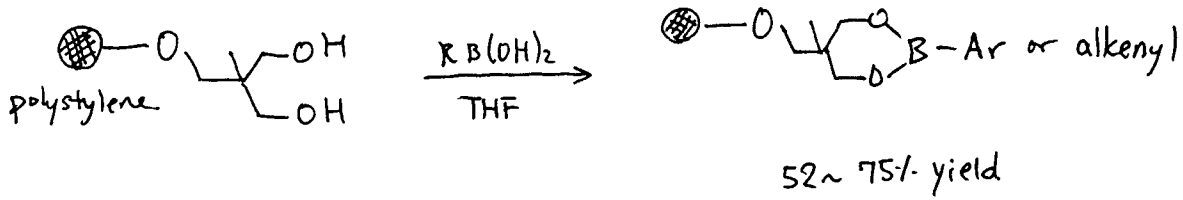


borate	R′	yield
1a	Ph	85%
1b	Bu	90%

Batey, R. A. *et. al. Org. Lett.* **1999**, *1*, 1683.

Boronic Acids on Solid-Support

- synthesis of polymer-bound boronic acids



52~75% yield

- the Suzuki Coupling is also possible using this Solid supported boronic acids

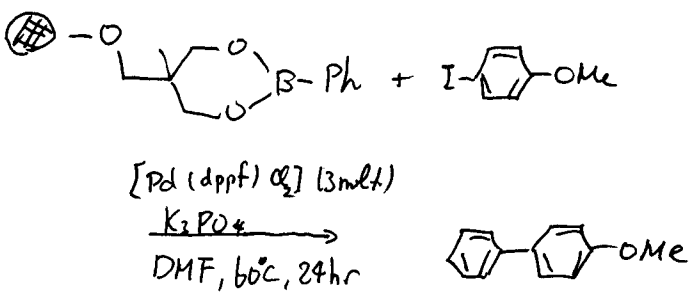
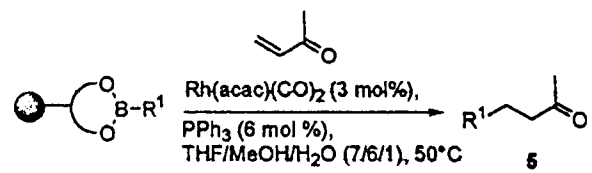


Table 3. Conjuguate Arylation and Alkenylation of MVK with Supported Boronic Acids

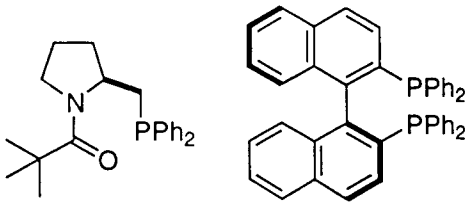


entry	R^1	MVK (equiv)	ketone	yield (%)[a]	purity (%)[b]
1	Ph	1.2	**5a**	50	>95
2	Ph	5	**5a**	60	>95
3	4-MeC_6H_4	5	**5b**	47	>95
4	1-hexenyl	5	**5c**	55	>95

[a] Yields of isolated products based on the loading of the resin **1** (1 mmol/g). All compounds were purified by flash chromatography on silica gel. [b] Determined by ^1H NMR (apart from triphenylphosphine oxide).

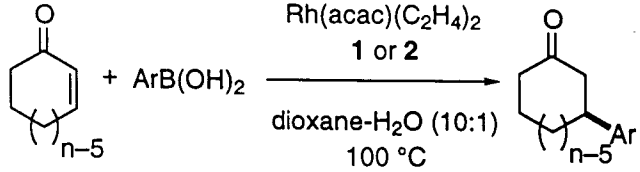
Carreaux, F.; Carboni, B. *et. al. Org. Lett.* **2001**, *3*, 803.

Chiral Amidomonophosphine Ligand



(*S*)-(–)-**1** (*S*)-(–)-BINAP **2**

Figure 1. Chiral phosphine ligands **1** and **2**.



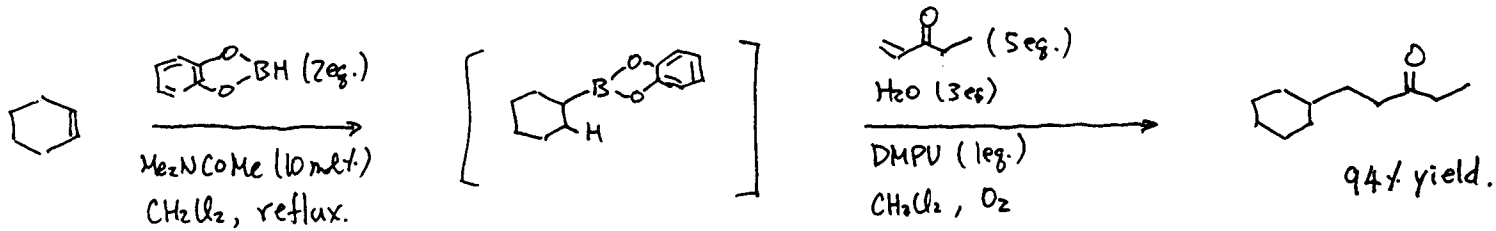
Scheme 1. Asymmetric 1,4-addition of arylboronic acids to cycloalkenones controlled by chiral phosphines **1** and **2**.

- Ligand 1 behaves like a bidentate ligand. (entry 1 and 5)
- recyclable ligand.
- structural feature of Rh-1 complex not clear

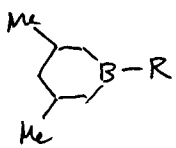
Ar	n	ligand	Rh cat.	time	yield	% ee
Ph	6	1 (1.3 eq.)	1 mol%	1 hr	99%	96
Ph	6	2 (1 eq.)	3 mol%	3 hr	99%	97
Ph	5	1 (1.3 eq.)	1 mol%	6 hr	90%	83
Ph	7	1 (1 eq.)	1 mol%	24 hr	95%	91
Ph	6	1 (3 eq.)	1 mol%	1 hr	80%	94

Tomioka, K. *et. al. Tetrahedron. Lett.* **2001**, *42*, 921.

Radical Conjugate Addition of Alkylborane



- The reaction was inhibited by the addition of TEMPO and galvinyl oxide
- similar reactions are known using



but yields, generalities are not great.

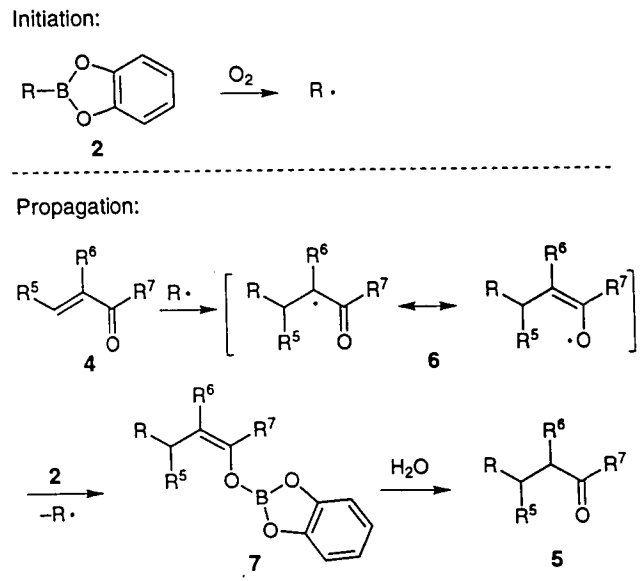


Figure 1. Possible mechanism for the formation of **5**.

Renand, P. *et. al. Chem. Eur. J.* **1999**, *5*, 1468.

Conclusion

Organoboron compounds can be used in conjugate additions.

Efficient transmetallation to rhodium catalysts have been demonstrated by Miyaura and Hayashi.

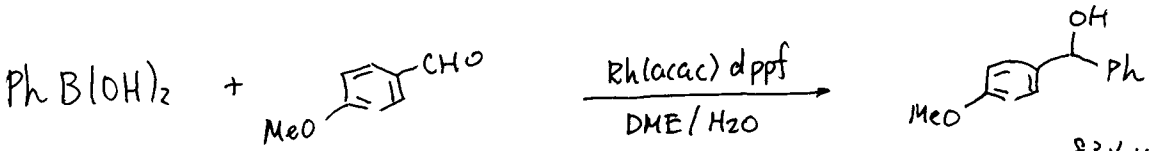
Chiral phosphine ligands allowed high enantioselectivities in the Addition products

Generality of the reaction was sufficiently expanded\

More stable boron reagents have been developed

Additional References.

- organoboronic acid · additions to aldehydes.
  (not enals)



83% yield.

Miyaura, N. et. al. Angew. Chem. Int. Ed. 1998, 37, 3279

also, " , J. Org. Chem. 2000, 65, 4450.

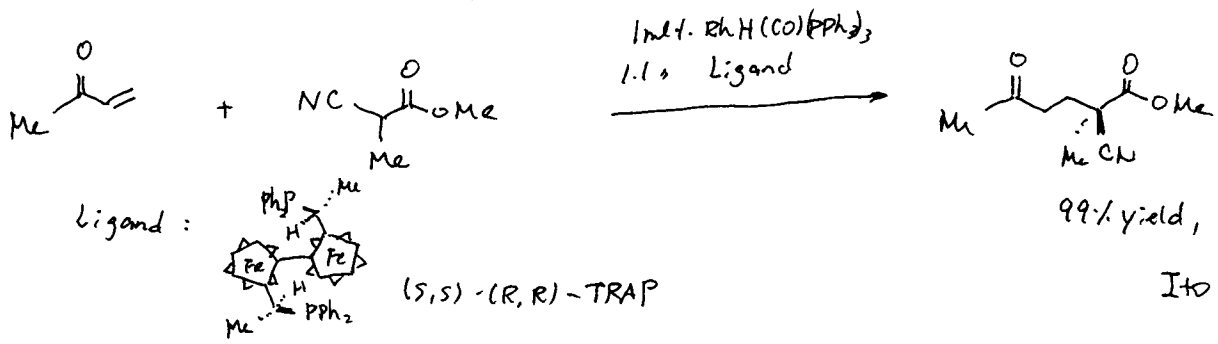
use of imidazol carbene as ligand

Fürstner, A. Adv. Synth. Catal. 2001, 343

addition to aldimines

Miyaura, N. Synlett. 2000, 1637.

- addition of active methylene compounds to enones



(S,S)-(R,R)-TRAP

99% yield, 72% ee

Ito, Y. et. al. J. Am. Chem. Soc. 1992, 114, 8295
Tetrahedron, 1994, 50, 4439