

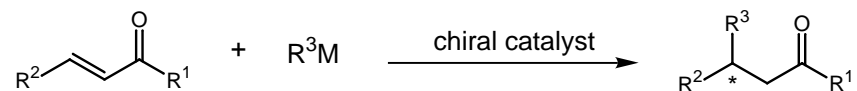
# Recent Advances in Catalytic Asymmetric Conjugate Addition

An Evans Group Evening Seminar

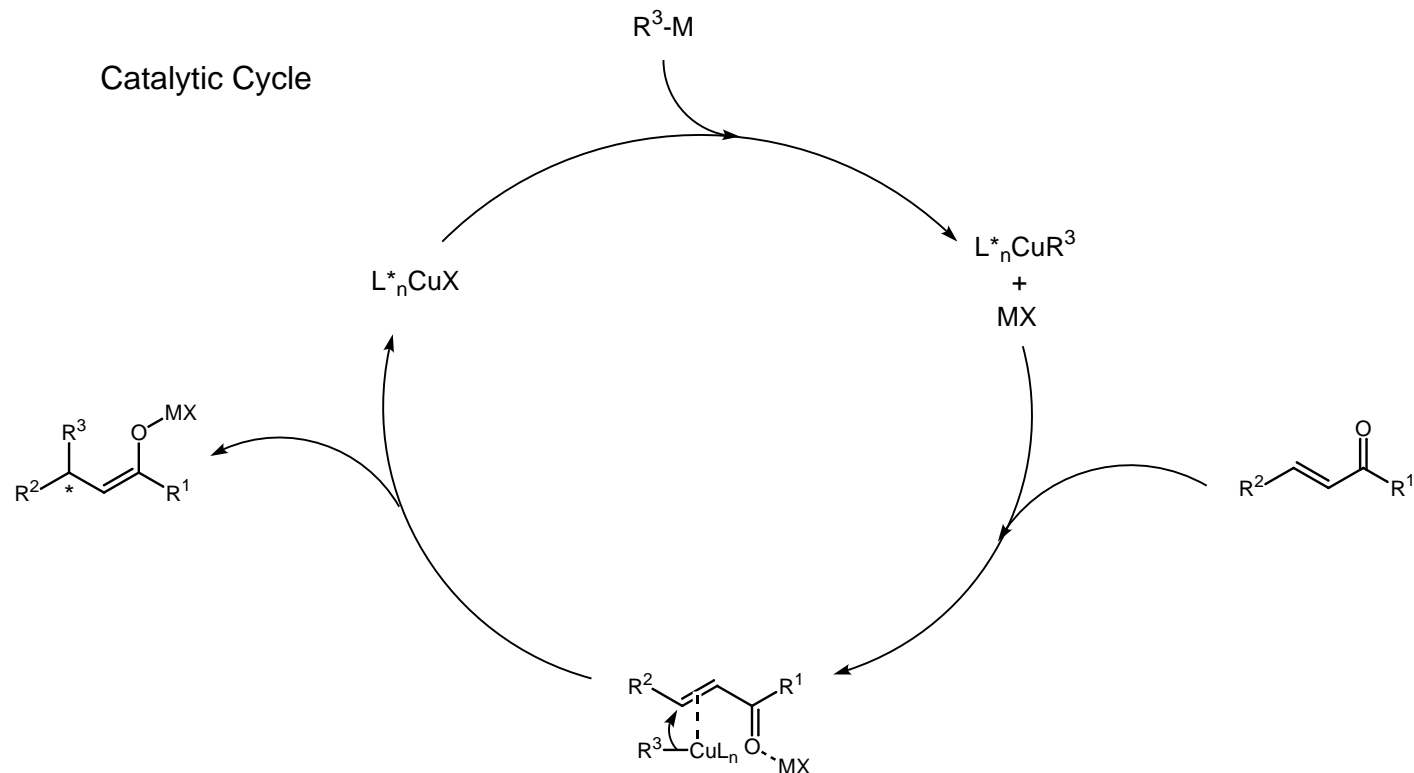
Wade Downey

Friday, March 3, 2000

# Catalytic Asymmetric Conjugate Addition



- Typical nucleophiles: RMgX, R<sub>2</sub>CuLi, R<sub>2</sub>Zn, R<sub>3</sub>Al



## Reviews:

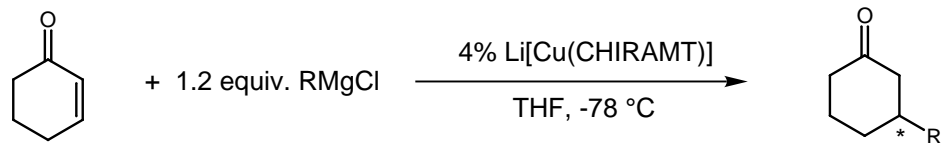
Rossiter, B.; Swingle, N. *Chem. Rev.* **1992**, 92, 771.

Feringa, B. *Advances in Catalytic Processes, Vol 1* (Ed.: M. Doyle), JAI Press, Connecticut, **1995**, p. 151.

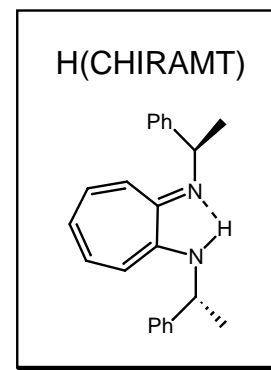
Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 283.

Evans, D.; Rovis, T. forthcoming

## Lippard: The Beginning

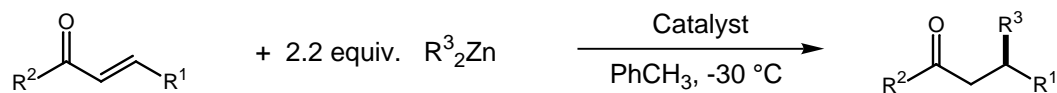


R	% ee (S)
Ph	4
Bu	14

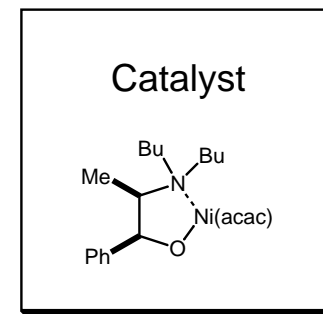


Lippard S. *J. Am. Chem. Soc.* **1988**, 110, 3175.

## Soai: Catalytic Nickel

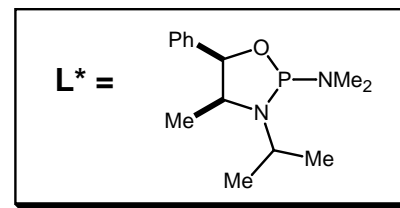
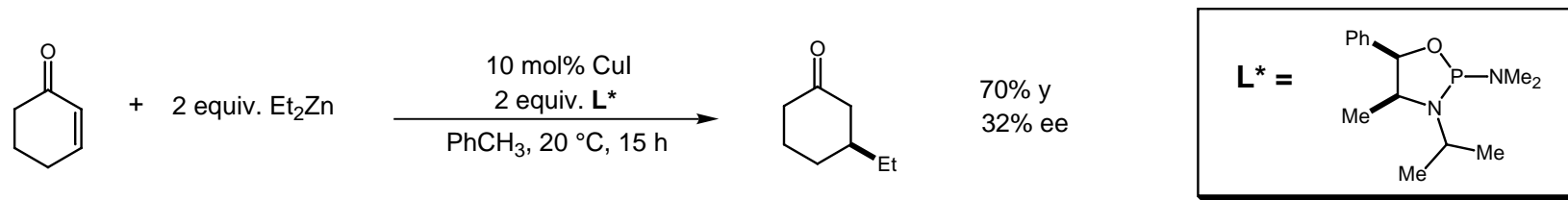


R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	% Cat	ee
Ph	Ph	Me	60	40
Ph	Ph	Et	50	45
Ph	Ph	Et	6	20
Ph	Me	Et	60	12
Me	Ph	Et	50	44

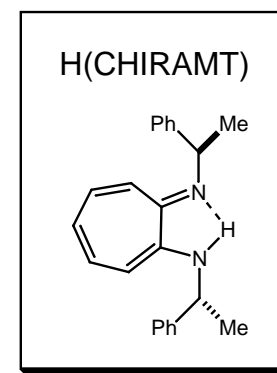
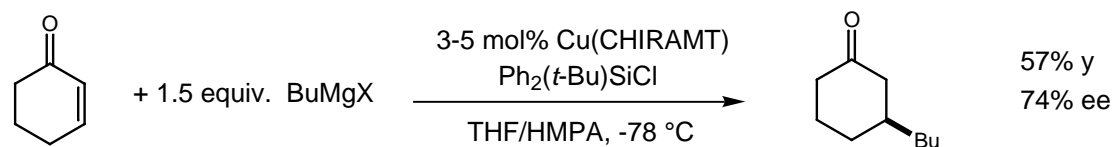


Soai, K. *J. Org. Chem.* **1988**, 53, 4148.

## 1993: Cyclohexenone Additions



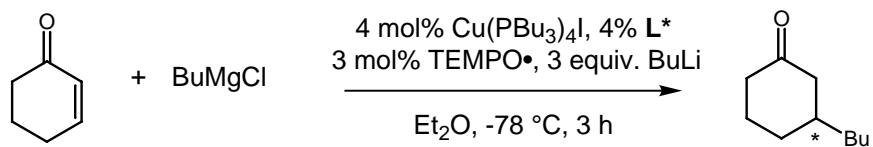
Alexakis, A. *Tetrahedron: Asymmetry* **1993**, 4, 2427.



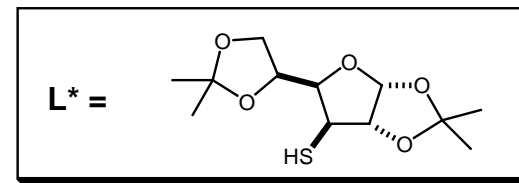
- As of 1993, this is the best result for the addition to cyclohexenone.

Lippard, S. *Organometallics* **1990**, 9, 3178.

## 1993: Cyclohexenone Additions

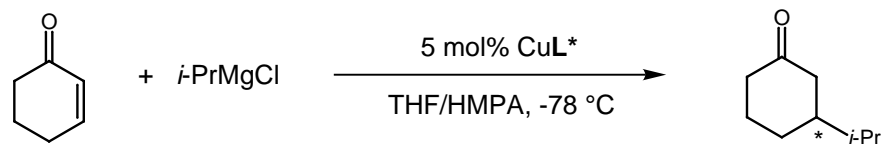


90% y  
58% ee

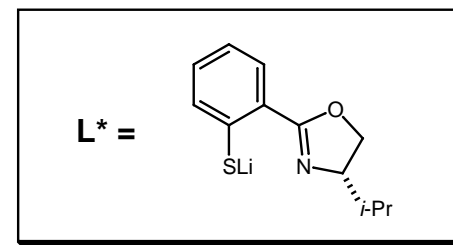


- CuBr and Cu(OTf)<sub>2</sub> produced inferior results.

Spescha, M. *Helv. Chim. Acta* **1993**, 76, 1219.



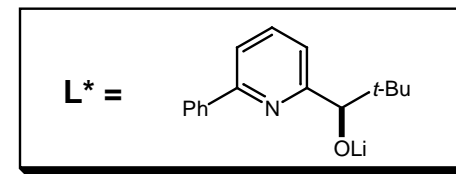
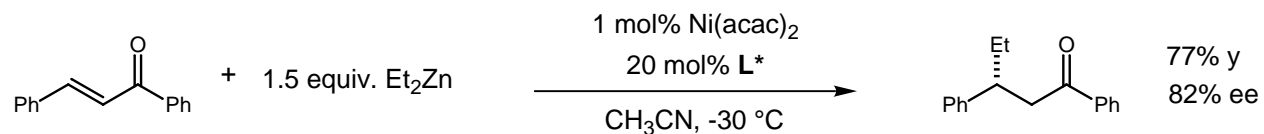
71% y  
72% ee



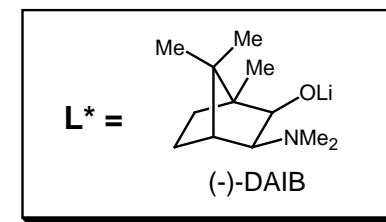
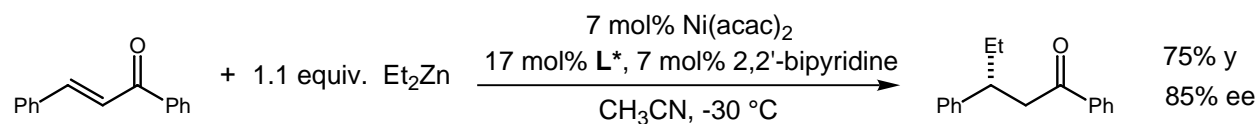
- As of 1993, this is the best result for addition to cyclohexenone.

Pfaltz A., *Tetrahedron Lett.* **1993**, 34, 7725.

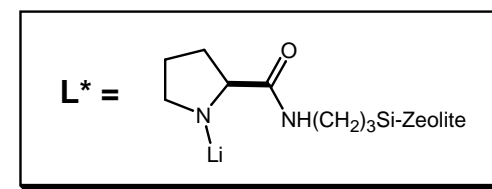
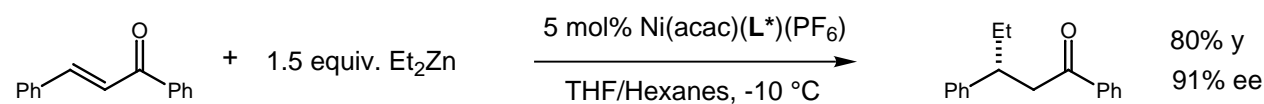
# 1993: Chalcone Additions



Bolm, C. *Tetrahedron: Asymmetry* **1991**, 2, 701.



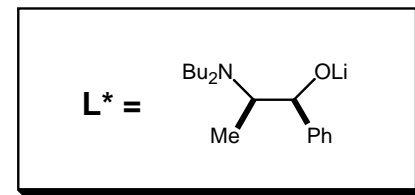
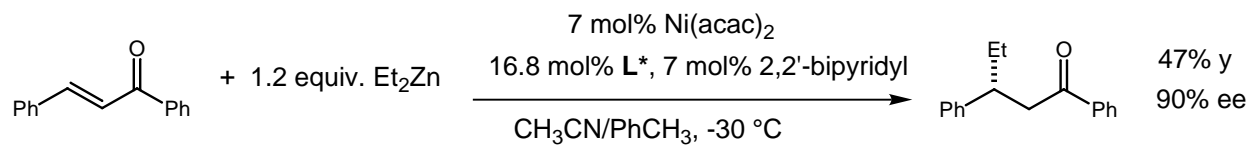
Feringa, B. *Tetrahedron: Asymmetry* **1992**, 3, 581.



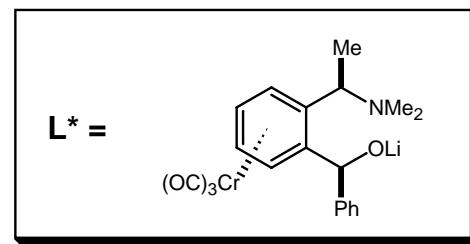
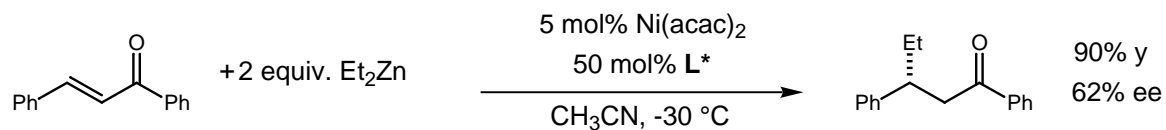
- As of 1993, this is the best result for addition to chalcone.

Sanchez, F. *Tetrahedron: Asymmetry* **1992**, 3, 845.

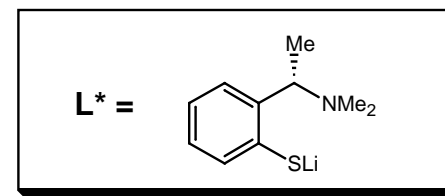
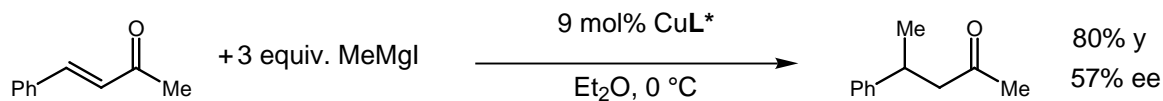
# 1993: Chalcone Additions



Soai, K. *Chem. Commun.* **1989**, 516.

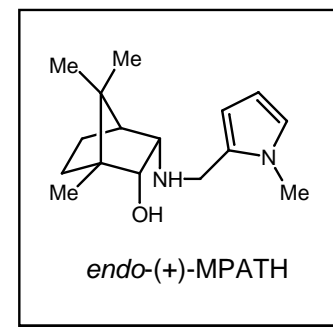
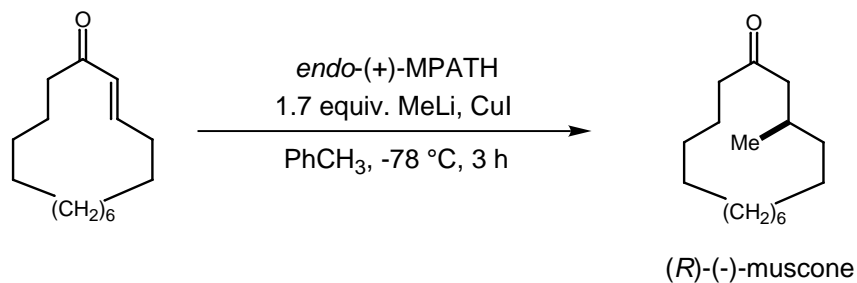


Uemura, M. *J. Org. Chem.* **1993**, 58, 1238.



van Koten, G. *Tetrahedron: Asymmetry* **1991**, 2, 1097.

# Tanaka: Synthesis of (*R*)-(-)-muscone



Additive Optimization

Conc. (M)	Additive (eq)	% yield	% ee
0.056	none	76	54
0.056	THF (10)	79	80
0.112	none	83	68
0.112	THF (10)	78	82
<b>0.112</b>	<b>THF (5)</b>	<b>76</b>	<b>97</b>
<b>0.112</b>	<b>THF (1)</b>	<b>85</b>	<b>99</b>
0.112	TMSCl (5)	72	79

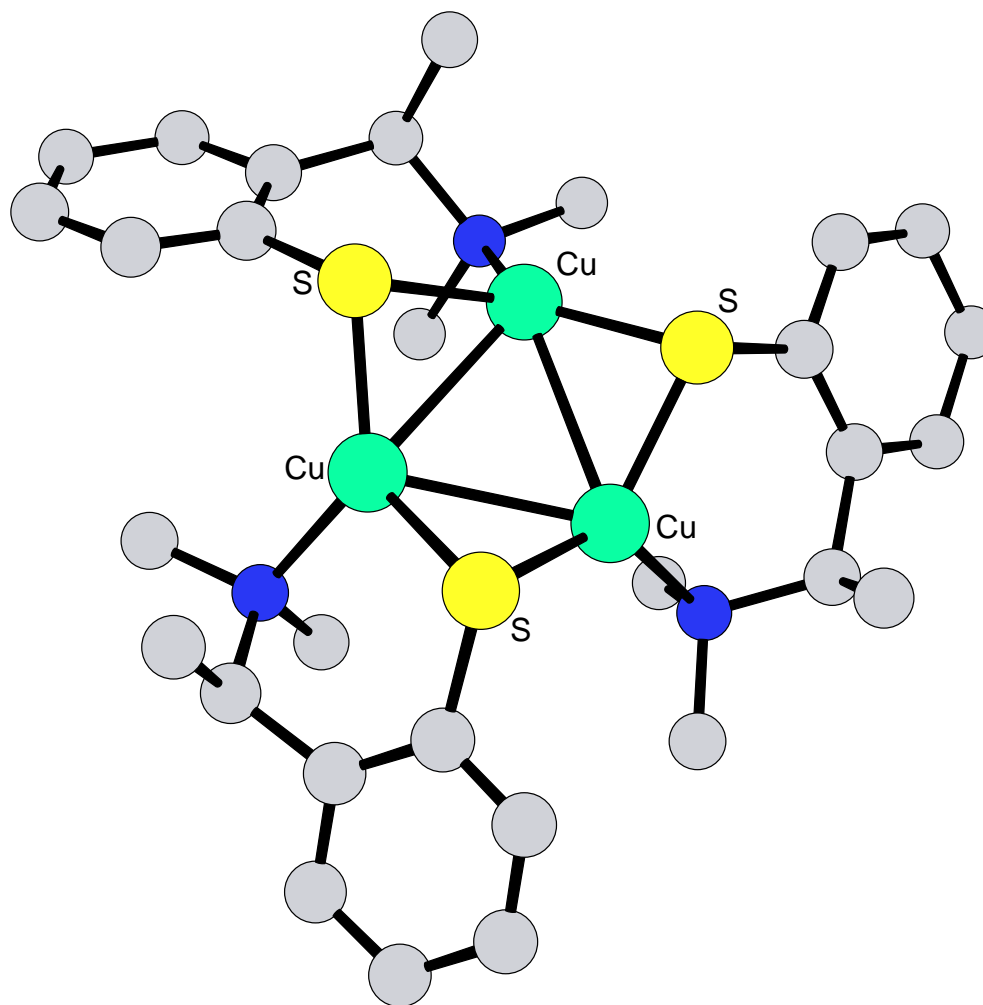
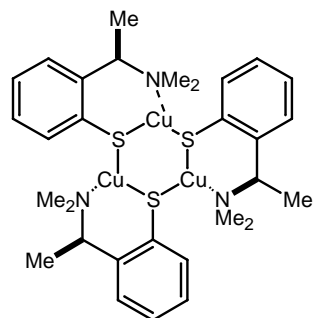
Catalyst Loading

% ligand	% CuI	THF (eq)	% yield	% ee
110	100	5	77	100
55	50	5	79	100
<b>36</b>	<b>33</b>	<b>1</b>	<b>85</b>	<b>99</b>
28	25	5	78	80
28	25	1	82	92
22	20	5	84	70
22	20	1	80	90

- A complicated procedure was necessary to effect high conversion and selectivity: to the ligand (0.33 eq.) was added sequentially 0.33 eq. MeLi, 0.33 eq. CuI, 0.66 eq. MeLi, 1.0 eq. THF, 0.33 eq. substrate, 0.33 eq. MeLi, 0.33 eq. substrate, 0.33 eq. MeLi, and 0.33 eq. substrate.

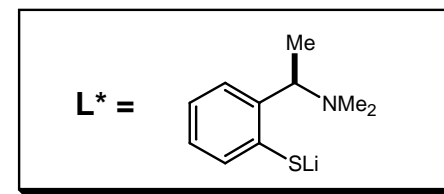
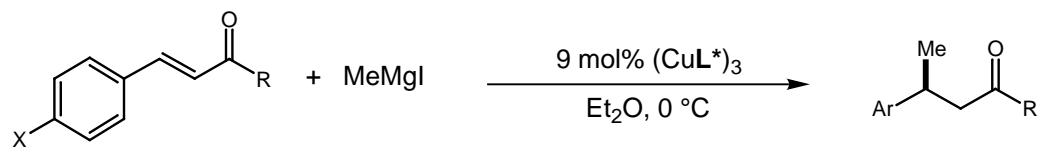


# van Koten: Copper Trimer



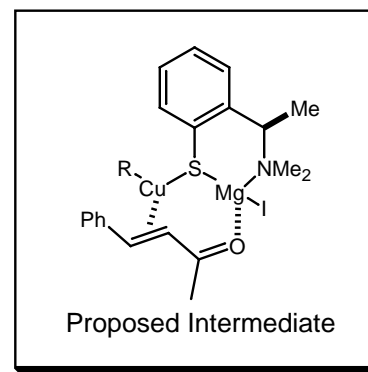
van Koten, G. *Angew. Chem., Int. Ed. Eng.* **1989**, 28, 341.

# van Koten: Arenethiolatacopper(I) Catalyst Scope



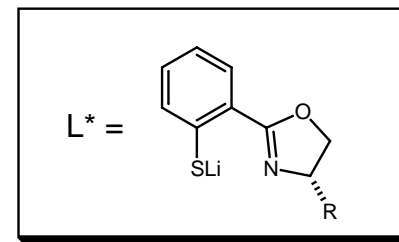
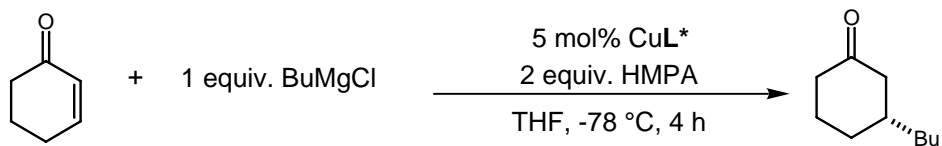
X	R	% yield	% ee
CN	Me	20	13
<b>Cl</b>	<b>Me</b>	<b>&gt;99</b>	<b>69</b>
<b>H</b>	<b>Me</b>	<b>97</b>	<b>76</b>
Me	Me	>99	64
OMe	Me	>99	56
H	<i>i</i> -Pr	98	72
H	<i>t</i> -Bu	>99	45
H	Ph	>99	0

- Electronic effects are more important than steric effects.
- For X = CN, chemoselectivity was also "very low." These data indicate that the anchoring of the double bond to copper is probably more important for the enantioselectivity than for the chemoselectivity of these Michael addition reactions."



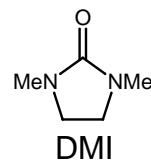
van Koten, G. *Tetrahedron Lett.* **1994**, 35, 6135.

# Pfaltz: Reaction Optimization and Ligand Synthesis

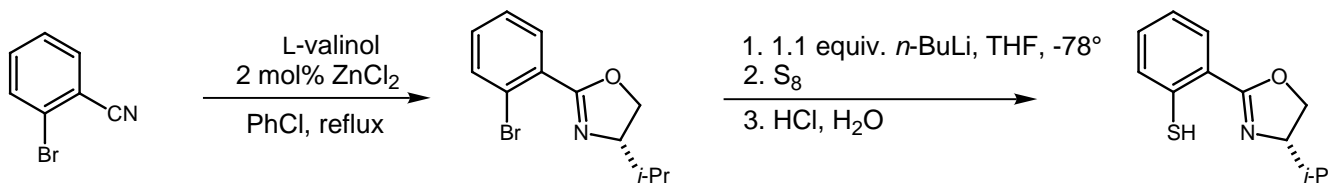


R	% yield	% ee
Me	39	58
<b><i>i</i>-Pr</b>	<b>67</b>	<b>60</b>
<i>t</i> -Bu	46	15
Bn	60	52

- Addition of TMSCl and TBDPSCI resulted in lowered selectivity.
- DMI, TMEDA, and DBU were less effective at increasing yield than HMPA.

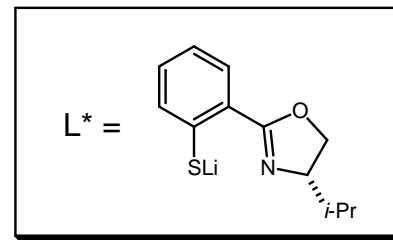
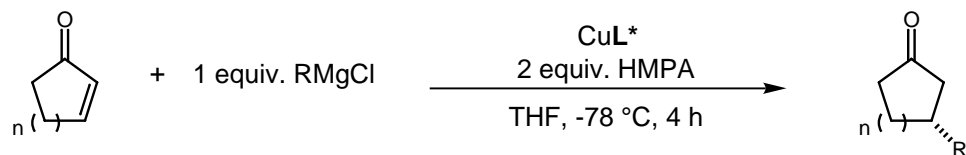


- BuMgBr gave slightly lower yields and selectivities.



Pfaltz, A. *Tetrahedron* **1994**, 50, 4467.

# Pfaltz: Cu-Catalyzed Grignard Addition

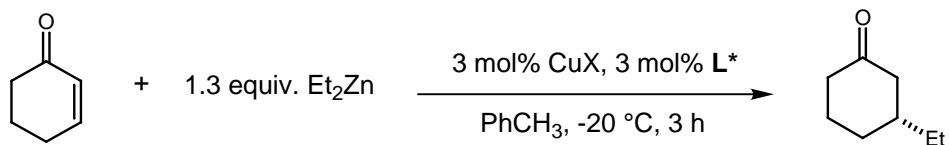


n	% Cu	R	T (°C)	% yield	% ee
1	5	Bu	-78	30	16
1	5	<i>i</i> -Pr	-78	43	37
2	5	Bu	-78	67	60
2	5	<i>i</i> -Pr	-78	71	72
<b>2</b>	<b>5</b>	<b><i>i</i>-Pr</b>	<b>-45</b>	<b>89</b>	<b>68</b>
3	5	Bu	-78	24	83
3	10	Bu	-78	50	83
3	10	<i>i</i> -Pr	-78	55	87
3	10	<i>i</i> -Pr	-45	71	71

- A negative nonlinear effect was observed, but lack of structural information "preclude a straightforward interpretation of the results."
- Ph, Me, and vinyl Grignard reagents "reacted with poor enantioselectivity."

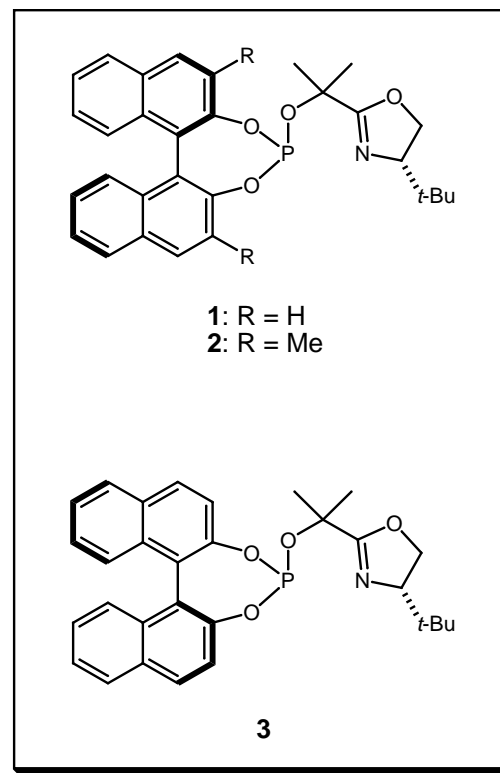
Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467.

# Pfaltz: Chiral Oxazoline-Phosphite Ligands



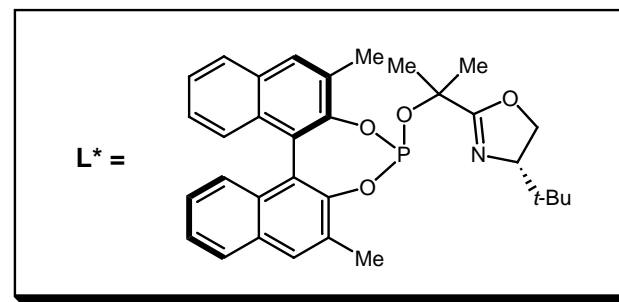
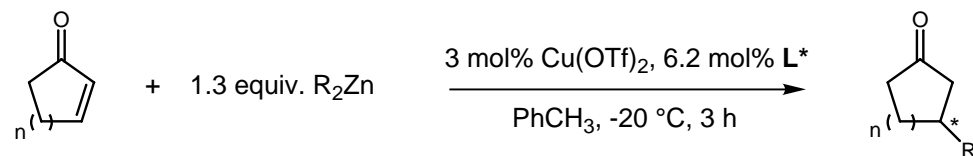
$\text{L}^*$	X	$\text{L}^*:\text{Cu}$	% yield	% ee ( <i>R</i> )
none	$(\text{OTf})_2$	N/A	84	0
<b>1</b>	$(\text{OTf})_2$	1:1	85	52
<b>1</b>	$(\text{OTf})_2$	2:1	91	54
<b>2</b>	OTf	2:1	99	82
<b>2</b>	<b><math>(\text{OTf})_2</math></b>	<b>2:1</b>	<b>96</b>	<b>90</b>
<b>3</b>	$(\text{OTf})_2$	1:1	93	-9

- Ligand 2 was selected for substrate scan.



Pfaltz, A. *Synlett* **1997**, 50, 1431.

# Pfaltz: Chiral Oxazoline-Phosphite Ligand

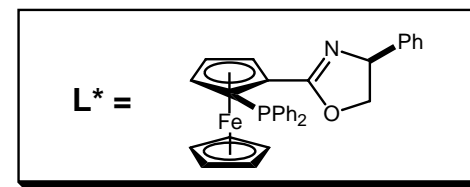
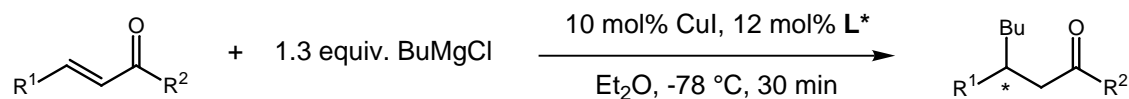


Product	% yield	% ee
	52	72
	<b>66</b>	<b>96</b>
	33	87
	96	87
	41	77

- Reaction of acyclic  $\alpha,\beta$ -unsaturated ketones with 2 mol% catalyst resulted in low yields (<50%) and low selectivities (4-50% ee).

Pfaltz, A. *Synlett* **1997**, 50, 1431.

# Sammakia: Ferrocenyl Phosphine Oxazoline Ligands

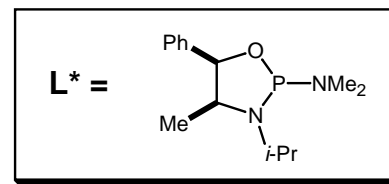
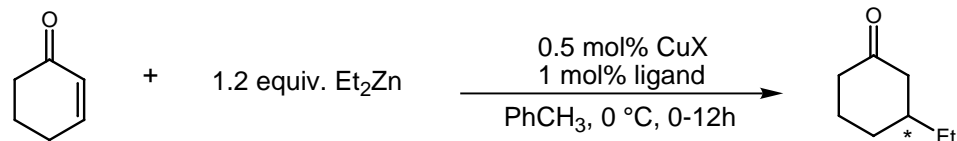


Enone	% CuI	% L*	1,4:1,2	% yield	% ee
	1	1.2	8:1	74	77
	5	6	70:1	90	79
	10	12	>100:1	97	83
	10	12	>100:1	82	65
	<b>10</b>	<b>12</b>	<b>&gt;100:1</b>	<b>82</b>	<b>92</b>
	10	12	80:1	81	61

- Additives such as HMPA, TMSCl, and MeI resulted in no advantages.
- THF or toluene as solvent reduced selectivity.
- Catalyst loadings greater than 10 mol % provided no increase in selectivity.
- Use of other oxazolines either lowered yields (*i*-Pr, Me, *t*-Bu) or resulted in almost identical results (Bn).
- Replacement of the ferrocenyl moiety with a phenyl moiety drastically reduced selectivity.

Sammakia, T. *Tetrahedron* **1997**, 53, 16503.

## Alexakis: Ligand Acceleration



CuX	Ligand	% yield 10 min	% yield 1 h	% yield 5 h	% yield 12 h (RT)
CuCN	none	-	21	77	100
CuCN	$\text{L}^*$	52	88	100 <sup>a</sup>	-
CuCN	$\text{P}(\text{OEt})_3$	20	30	50	100
CuOTf	$\text{P}(\text{OEt})_3$	67	100	-	-
$\text{Cu}(\text{OTf})_2$	none	-	28	78	100
$\text{Cu}(\text{OTf})_2$	$\text{L}^*$	<b>100<sup>b</sup></b>	-	-	-
$\text{Cu}(\text{OTf})_2$	$\text{P}(\text{NMe}_2)_3$	74	94	100	-
$\text{Cu}(\text{OTf})_2$	$\text{PBu}_3$	<b>100</b>	-	-	-
$\text{Cu}(\text{OTf})_2$	$\text{P}(\text{OEt})_3$	<b>100</b>	-	-	-

<sup>a</sup>32% ee. <sup>b</sup>No report of ee was made.

- No report of ee's in the presence of  $\text{L}^*$  was made.

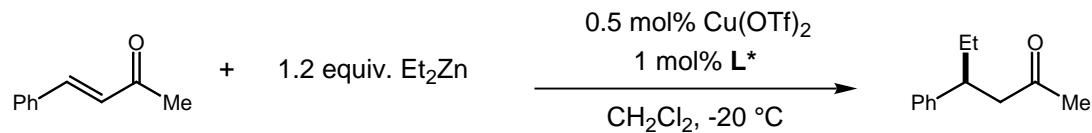
For  $\text{L} = \text{P}(\text{OEt})_3$ :

- $\text{CuI}$ ,  $\text{CuCl}$ , and  $\text{CuCl}_2$  were ineffective.
- $\text{CH}_2\text{Cl}_2$  and  $\text{Et}_2\text{O}$  were equally effective.
- THF and  $\text{CH}_3\text{CN}$  slowed the reaction.

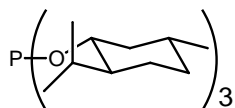
Alexakis, A. *Tetrahedron Lett.* **1997**, *38*, 7745.



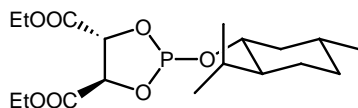
# Alexakis: Phosphite Ligand Scan



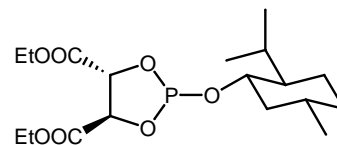
• Note low catalyst loadings.



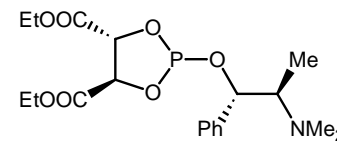
-4% ee  
57% y



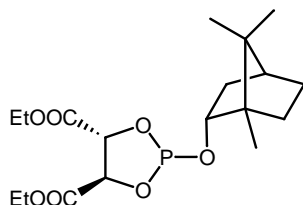
**62% ee**  
**48% y**



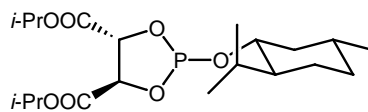
**63% ee**  
**60% y**



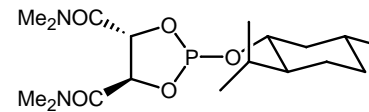
22% ee  
70% y



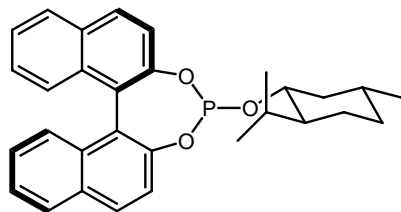
**65% ee**  
**77% y**



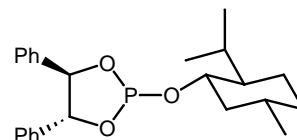
53% ee  
67% y



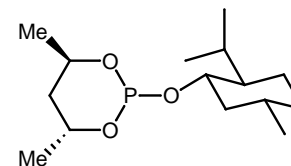
28% ee  
98% y



-4% ee  
52% y



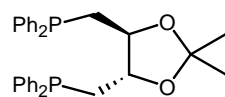
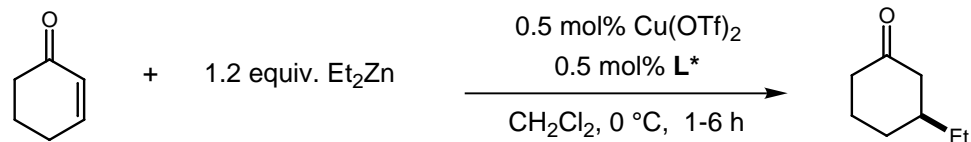
-6% ee  
9% y



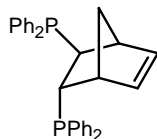
11% ee  
74% y

Alexakis, A. *Tetrahedron: Asymmetry* **1997**, 8, 3193.

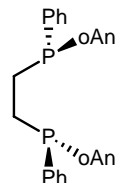
# Alexakis: Diphosphine Ligand Scan



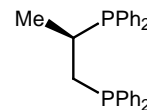
8% ee  
84% y



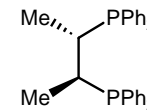
**44% ee**  
**81% y**



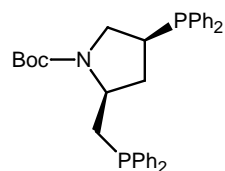
10% ee  
81% y



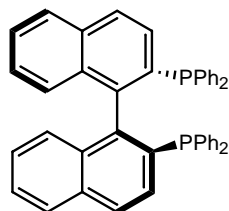
36% ee  
72% y



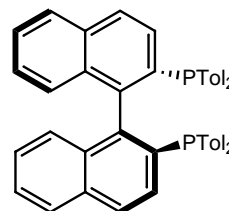
**44% ee**  
**98% y**



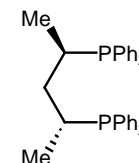
0% ee  
83% y



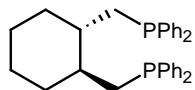
24% ee  
80% y



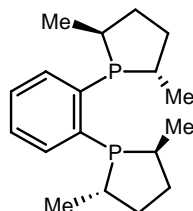
26% ee  
67% y



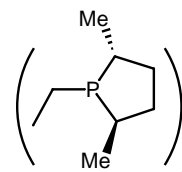
-9% ee  
81% y



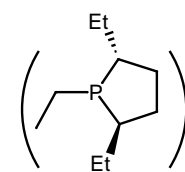
8% ee  
93% y



16% ee  
82% y

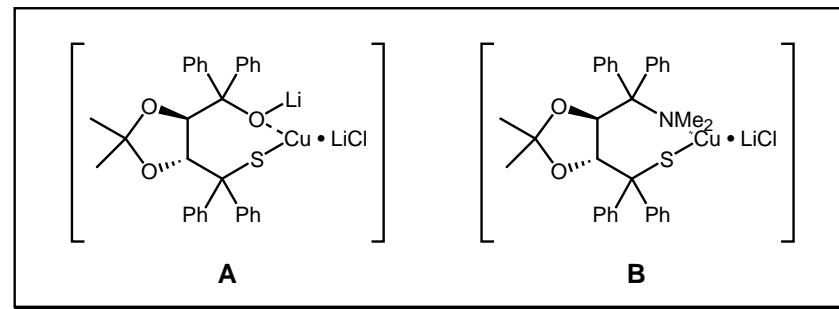
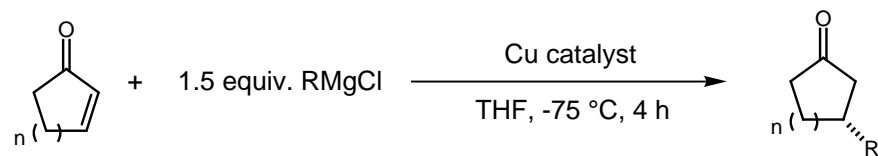


-14% ee  
99% y



-6% ee  
98% y

# Seebach, Jaeschke: Mixed O,S- and N,S-Ligands

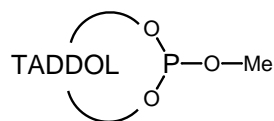
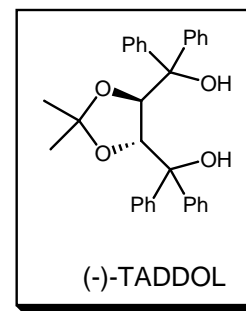
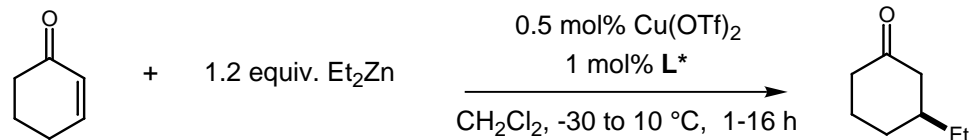


n	catalyst	% cat	R	% yield	% ee
1	<b>A</b>	5	Bu	23	-20
1	<b>B</b>	10	Bu	50	40
2	<b>A</b>	5	Bu	77	-64
2	<b>B</b>	5	Bu	77	78
3	<b>A</b>	5	Bu	81	-74
3	<b>B</b>	5	Bu	77	80
<b>3</b>	<b>B</b>	<b>10</b>	<b>Bu</b>	<b>80</b>	<b>82</b>
3	<b>A</b>	5	Me	68	-64
3	<b>B</b>	5	Me	58	78
3	<b>B</b>	5	Pr	76	80
3	<b>B</b>	5	<i>i</i> -Pr	65	50
<b>4</b>	<b>A</b>	<b>5</b>	<b>Bu</b>	<b>81</b>	<b>-60</b>
<b>4</b>	<b>B</b>	<b>5</b>	<b>Bu</b>	<b>78</b>	<b>52</b>

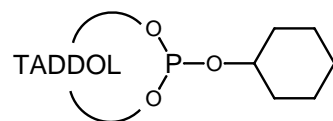
- Selectivity pattern implies that the *trans* influence may be important.
- Additives such as HMPA, DBU, DMPU, TMEDA, TBDPSCI, TMSCl, and 12-crown-4 did not affect selectivity or yield.

Seebach, D.; Jaeschke, G. *Helv. Chim. Acta* **1997**, *80*, 2518.

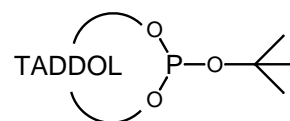
# Alexakis: TADDOL Ligand Scan



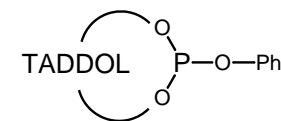
4% ee  
93% y



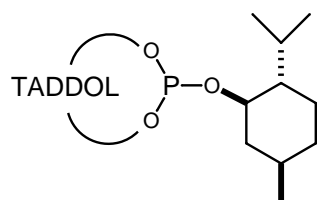
18% ee  
86% y



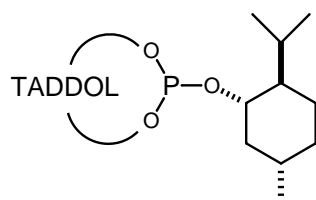
16% ee  
86% y



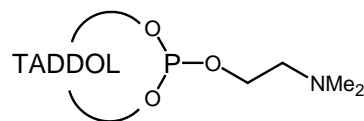
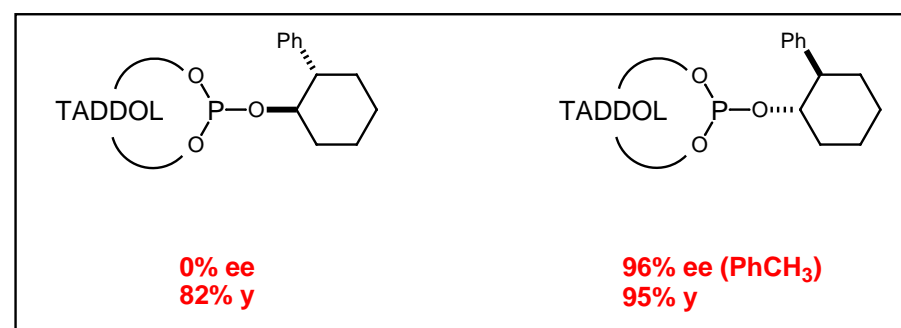
8% ee  
97% y



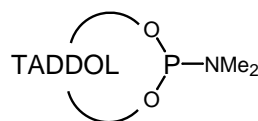
5% ee  
95% y



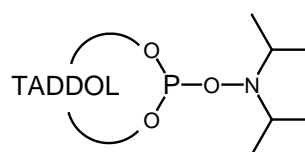
50% ee  
95% y



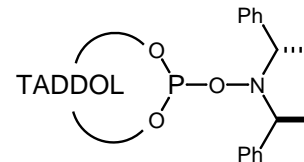
13% ee  
95% y



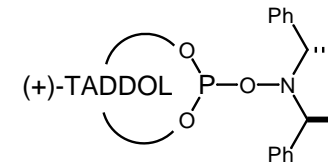
-35% ee  
98% y



17% ee  
94% y



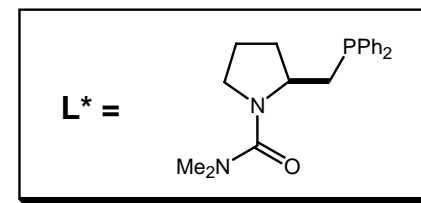
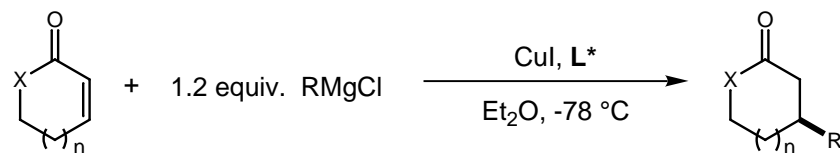
15% ee  
98% y



-17% ee  
98% y

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

# Tomioka: Copper(I) Bidentate Phosphine Ligand Complex



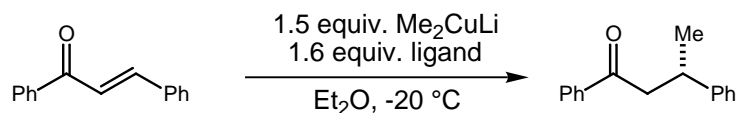
n	X	% CuI	% L*	R	% yield	% ee
<b>1</b>	<b>CH<sub>2</sub></b>	<b>8</b>	<b>32</b>	<b>Bu</b>	<b>92</b>	<b>90</b>
1	CH <sub>2</sub>	2	3	Bu	78	67
1	CH <sub>2</sub>	8	32	Et	83	73
1	CH <sub>2</sub>	8 <sup>a</sup>	32	Pr	77	72
<b>1</b>	<b>CH<sub>2</sub></b>	<b>8<sup>a</sup></b>	<b>32</b>	<b>Hex</b>	<b>90</b>	<b>92</b>
1	CH <sub>2</sub>	8	32	PhCH <sub>2</sub> CH <sub>2</sub>	74	84
2	CH <sub>2</sub>	8	32	Bu	91	81
2	CH <sub>2</sub>	8	32	PhCH <sub>2</sub> CH <sub>2</sub>	70	83
1	O	8 <sup>a</sup>	32	Pr	66	76
<b>1</b>	<b>O</b>	<b>8</b>	<b>32</b>	<b>Bu</b>	<b>70</b>	<b>90</b>
<b>1</b>	<b>O</b>	<b>8<sup>a</sup></b>	<b>32</b>	<b>Hex</b>	<b>70</b>	<b>90</b>

<sup>a</sup>CuI•SMe<sub>2</sub> was used instead of CuI when chemoselectivity was low in the CuI-catalyzed reaction.

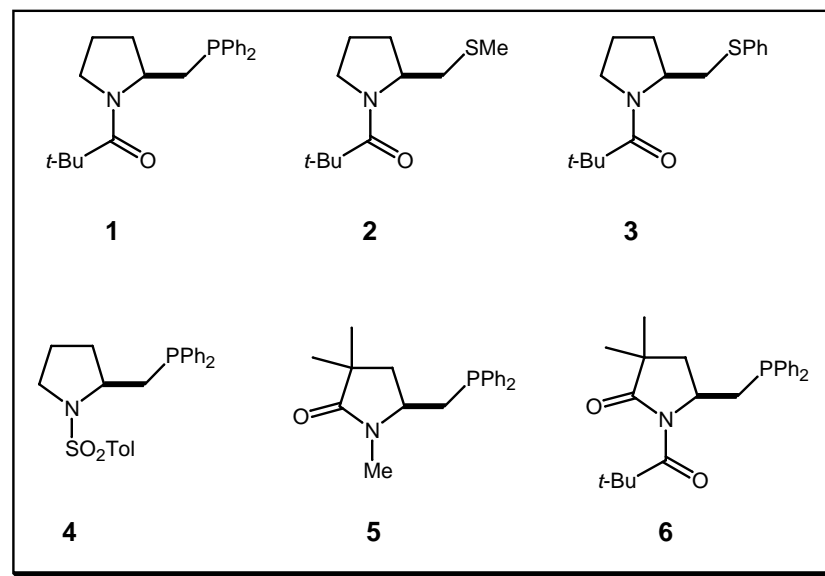
- Substitution of Ph substituents of the phosphine with 4-Me<sub>2</sub>NPh resulted in similar enantioselectivity but much lower yields for BuMgCl addition to cyclohexenone.
- Grignard reagents prepared from alkyl bromides and iodides gave lower ee's and poor yields.
- The copper sources CuCl, CuBr, and CuCN gave comparable ee's but much lower yields.
- Et<sub>2</sub>O, PhCH<sub>3</sub>, and DMS as solvent afforded high ee's and yields (90, 73, 77% ee; 92, 90, 82% yield). No enantioselectivity was observed in THF.
- The phosphine was recovered in 60-99% yield without racemization.

Tomioka, K. *Tetrahedron Lett.*, **1995**, 36, 4275.

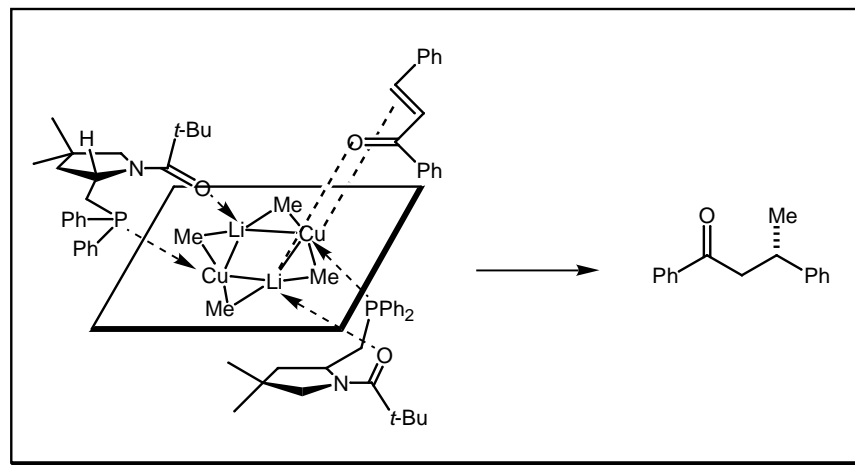
# Tomioka: Design of an Amidophosphine Ligand



ligand	% yield	config	% ee
1	79	S	84
2	99	R	4
3	91	S	4
4	80	S	8
5	90	R	1
<b>6</b>	<b>99</b>	<b>S</b>	<b>90</b>



## Proposed Model:

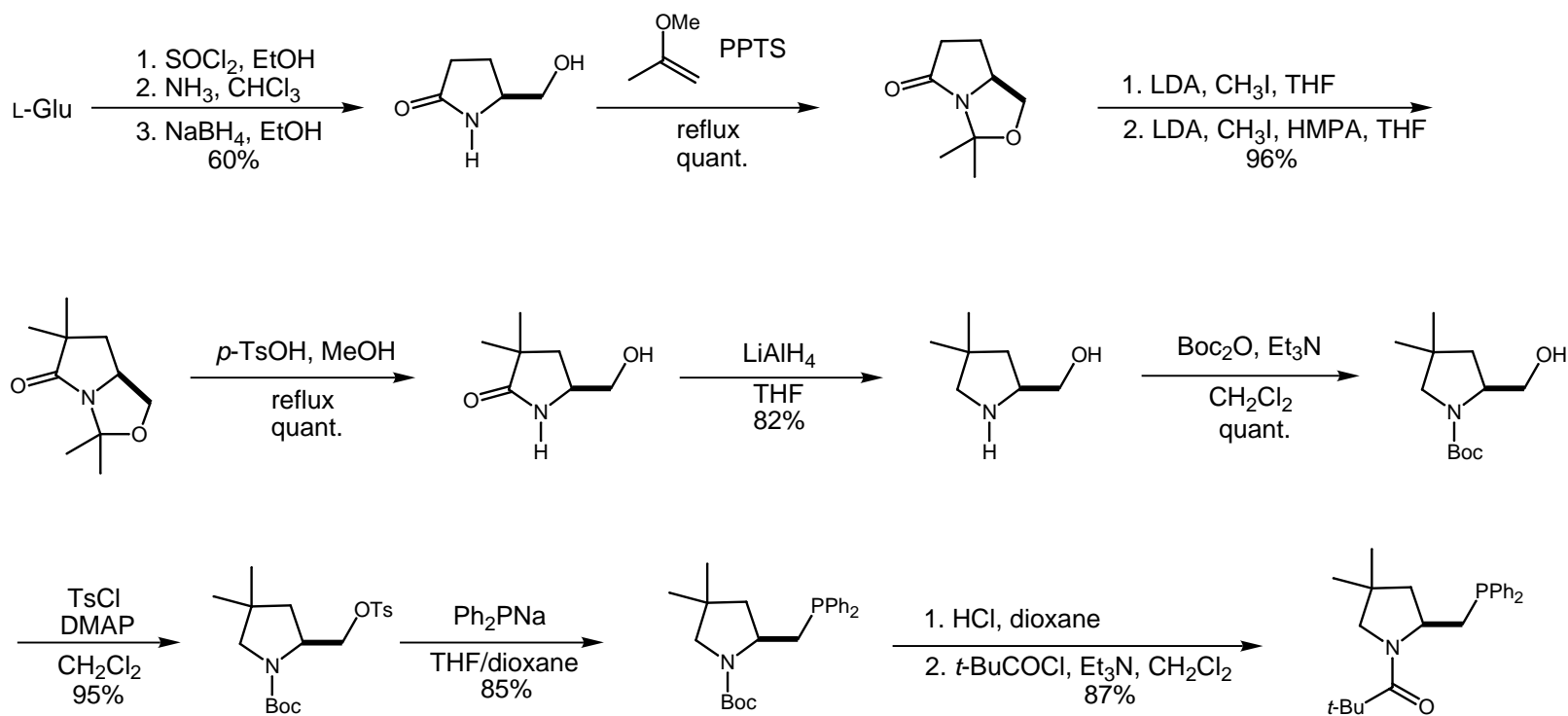
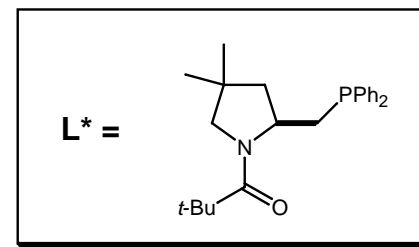


- $^{13}\text{C}$  NMR data for ligand **5** indicates the carbonyl oxygen coordinates exclusively to Li, whereas the phosphorus coordinates exclusively to Cu (1 equiv.  $\text{LiClO}_4$  or  $\text{CuBr}$  was added to the sample).

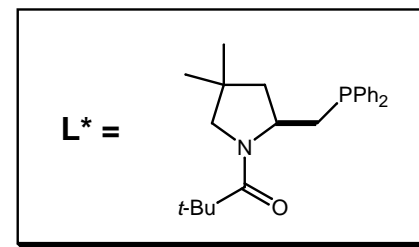
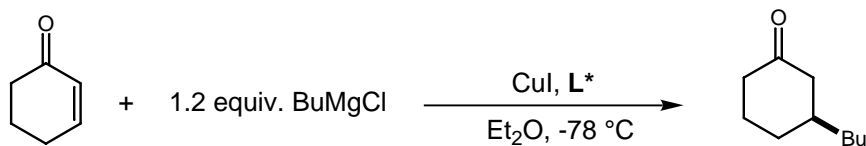
Tomioka, K. *Tetrahedron Lett.* **1996**, 37, 7805.

# Tomioka: Ligand Synthesis

- 13 steps, 33% overall yield



## Tomioka: Amidophosphine Ligand



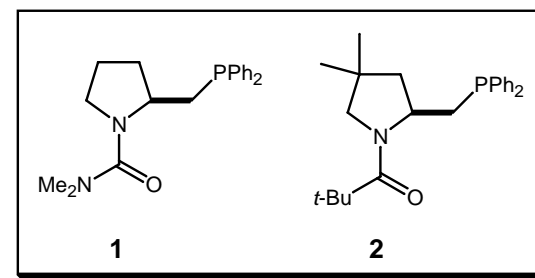
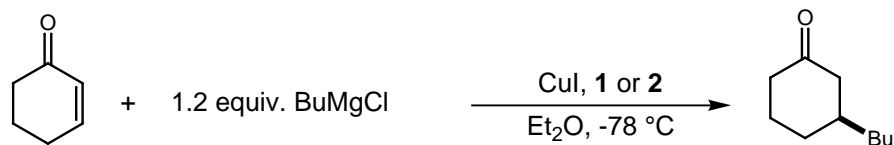
% CuI	% L*	% yield	% ee
120	150	96	96
8	32	82	92
2	3	60	40

- Replacement of the geminal methyl groups on L\* with benzyl groups resulted in lower yield and selectivity (80% y, 75% ee for 8% CuI / 32% L\*).
- Tomioka does not mention any attempts at making the chalcone additions catalytic.
- The stereochemical model for cuprate additions to chalcone does not explain the enantioselectivity for this system.

Tomioka, K. *Tetrahedron* **1998**, *54*, 10295.



# Tomioka: Catalyst Refinement

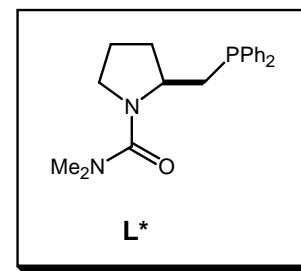
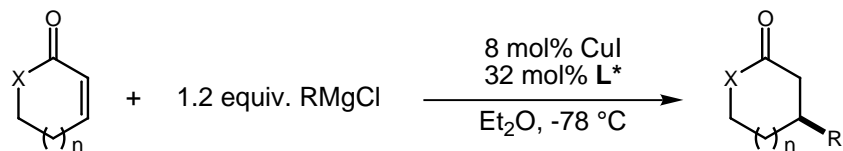


% CuI	ligand	% ligand	% yield	% ee	1,4:1,2
2	1	3	78	67	16:1
2	1	10	69	74	9:1
8	1	10	89	67	65:1
8	1	20	83	80	12:1
<b>8</b>	<b>1</b>	<b>32</b>	<b>92</b>	<b>90</b>	<b>32:1</b>
<b>8</b>	<b>2</b>	<b>32</b>	<b>82</b>	<b>90</b>	<b>18:1</b>

- Use of CuI•SMe<sub>2</sub>, CuCl, CuBr, and CuCN resulted in lower yields (73, 52, 56, 40%) and enantioselectivities (76, 81, 77, 82%).
- Other butylmagnesium species gave much lower 1,4:1,2 ratios: BuMgN(*i*-Pr)<sub>2</sub>, 5:1; Bu<sub>2</sub>Mg, 4:1; BuMgI, 2:1; BuMgBr, 1:1.
- PhCH<sub>3</sub>, DMS, THF, and *i*-Pr<sub>2</sub>O resulted in lower enantioselectivities (73, 77, 0, 18%).

Tomioka, K. *Tetrahedron* **1999**, *55*, 3843.

# Tomioka: The Final Application



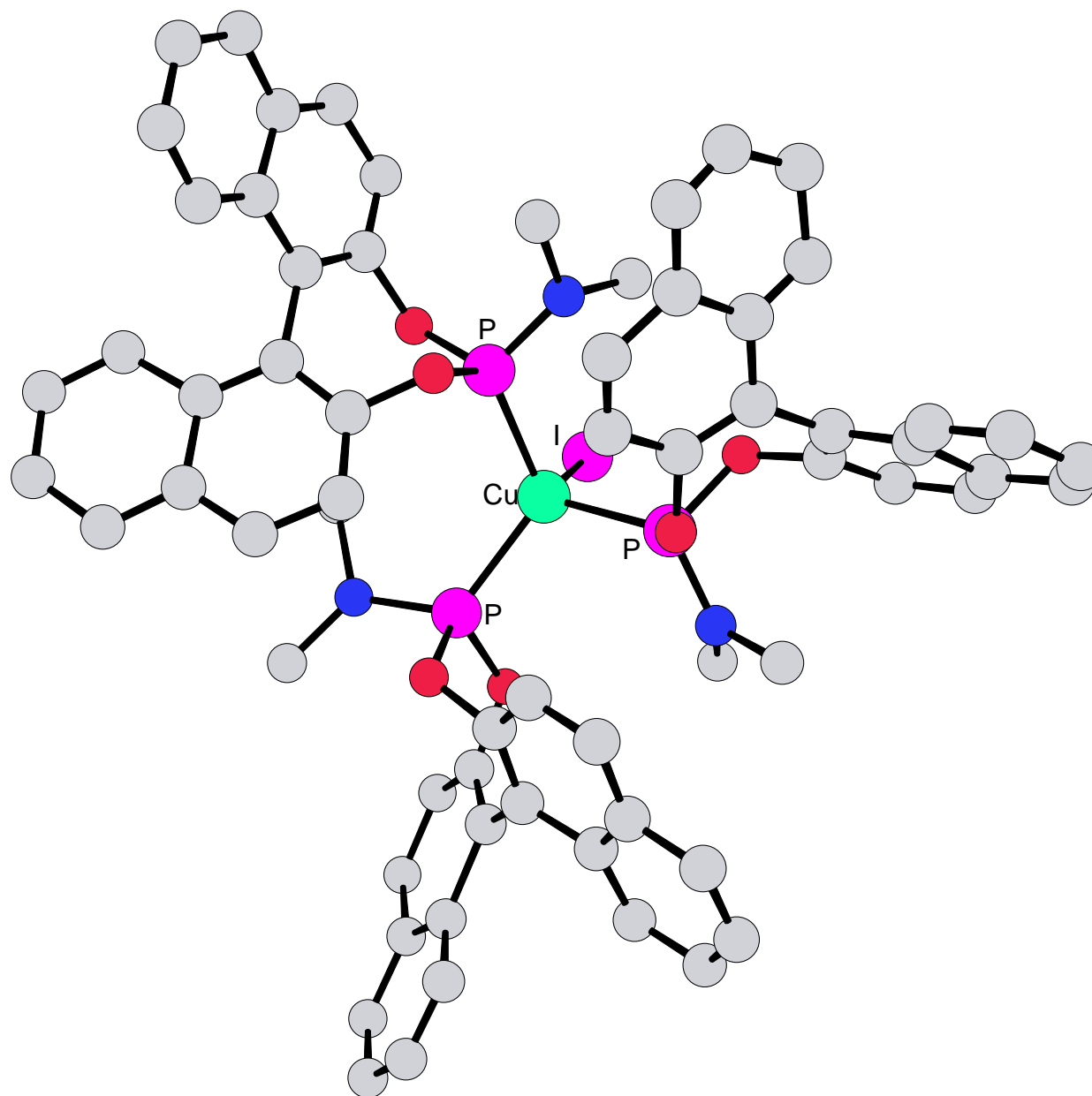
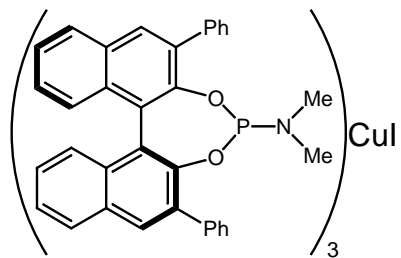
n	X	R	% yield	% ee
1	CH <sub>2</sub>	Me <sup>a</sup>	23	5
1	CH <sub>2</sub>	Et	83	73
1	CH <sub>2</sub>	Pr <sup>b</sup>	77	72
<b>1</b>	<b>CH<sub>2</sub></b>	<b>Bu</b>	<b>92</b>	<b>90</b>
<b>1</b>	<b>CH<sub>2</sub></b>	<b>Hex</b>	<b>90</b>	<b>92</b>
1	CH <sub>2</sub>	PhCH <sub>2</sub>	40	12
<b>1</b>	<b>CH<sub>2</sub></b>	<b>Ph(CH<sub>2</sub>)<sub>2</sub></b>	<b>74</b>	<b>87</b>
1	CH <sub>2</sub>	<i>i</i> -Pr	24	4
1	CH <sub>2</sub>	Ph <sup>a</sup>	10	4
0	CH <sub>2</sub>	Bu	88	42
2	CH <sub>2</sub>	Bu	91	81
2	CH <sub>2</sub>	Ph(CH <sub>2</sub> ) <sub>2</sub>	70	83
1	O	Pr <sup>b</sup>	66	76
<b>1</b>	<b>O</b>	<b>Bu</b>	<b>70</b>	<b>91</b>
<b>1</b>	<b>O</b>	<b>Hex<sup>b</sup></b>	<b>70</b>	<b>90</b>

<sup>a</sup>RMgBr was used. <sup>b</sup>CuI•SMe<sub>2</sub> was used.

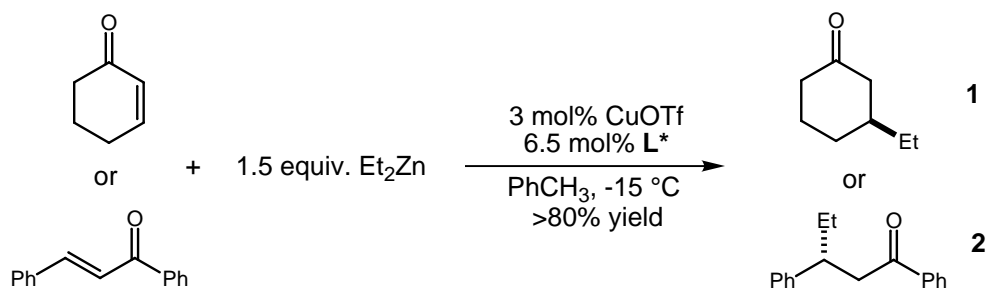
- *n*-alkyl Grignard reagents appear to be optimal for both yield and enantioselectivity.

Tomioka, K. *Tetrahedron* **1999**, *55*, 3843.

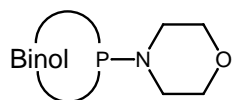
# Feringa: The Beginning



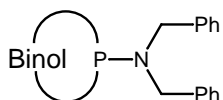
# Feringa: Phosphorus Amidite Ligands



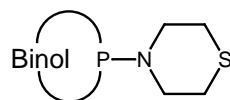
- Complexes generated from CuI gave poor results, presumably due to insolubility.



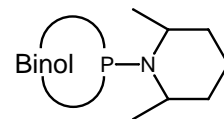
1: 50% ee  
2: 71% ee



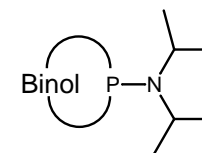
1: 53% ee  
2: 53% ee



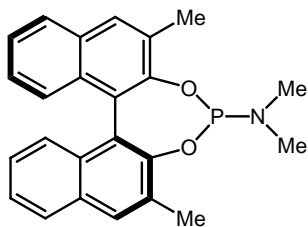
1: 55% ee  
2: 70% ee



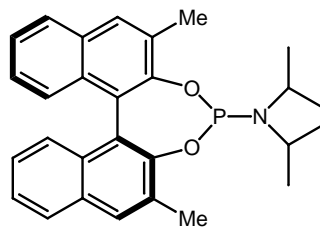
1: 43% ee  
2: 79% ee



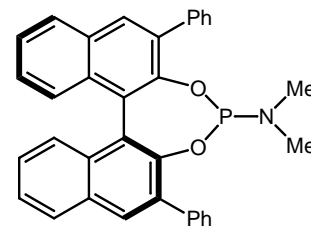
1: 60% ee  
2: 83% ee



1: 56% ee  
2: 52% ee



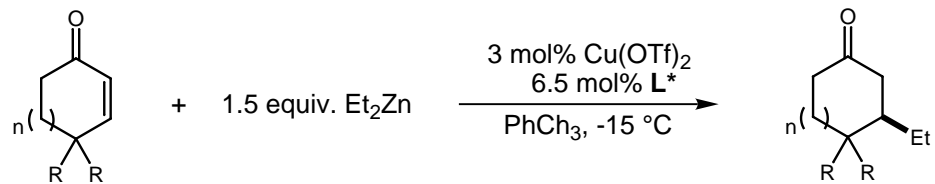
1: 59% ee  
2: 81% ee



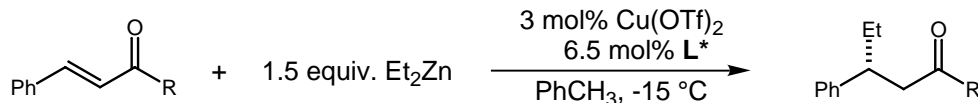
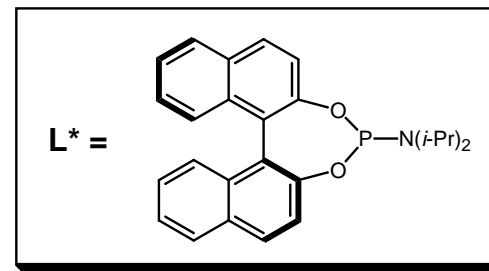
1: 35% ee  
2: <20% ee

Feringa, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374.

## Feringa: Phosphorus Amidite Ligands



**1a:** n = 1, R = H  
**1b:** n = 2, R = H  
**1c:** n = 3, R = Me



**2a:** R = Ph  
**2b:** R = 4-MeOC<sub>6</sub>H<sub>4</sub>  
**2c:** R = 2-pyridyl

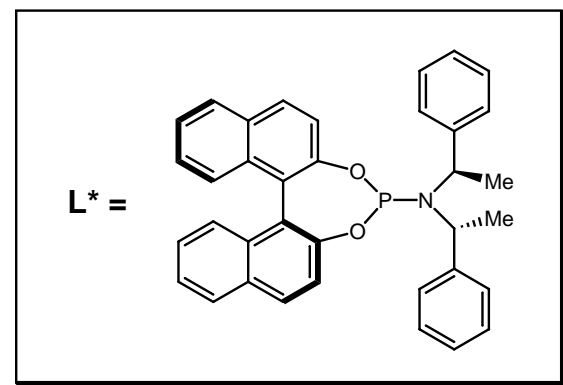
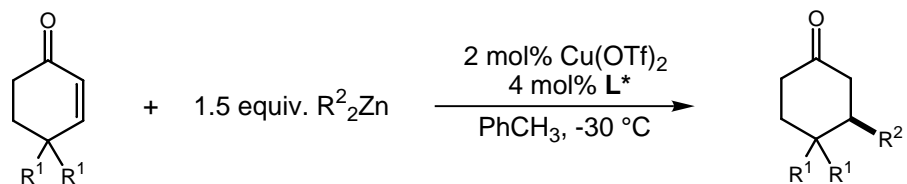
Adduct	% yield	% ee
<b>1a</b>	78	63
<b>1b</b>	76	55
<b>1c</b>	76	81
<b>2a</b>	<b>88</b>	<b>87<sup>a</sup></b>
<b>2a</b>	84	90
<b>2b</b>	85	80

<sup>a</sup>Reaction run at -50 °C

- Cu(OTf)<sub>2</sub> provides higher enantioselectivities than CuOTf. The authors believe a Cu(I) complex, generated by *in situ* reduction, is the active species.
- A linked version of the catalyst afforded very similar ee's when mixed 1:1 with copper, indicating that during reaction two monodentate ligands are bound to the copper ion.
- **2c** was isolated in only 29% ee, perhaps due to competitive binding of the copper catalyst to the pyridine moiety.

Feringa, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374.

# Feringa: Phosphorus Amidite Ligands

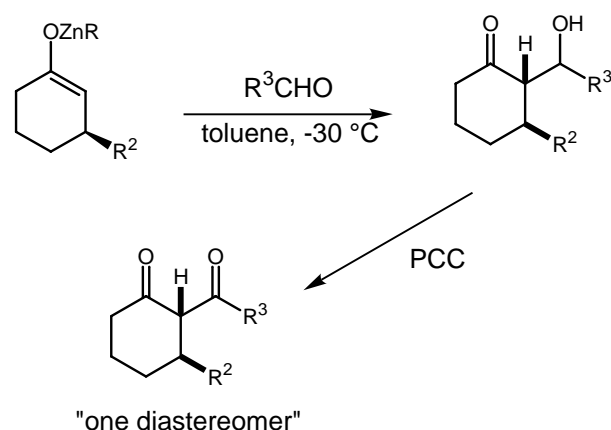


## 1,4-Addition Products:

R <sup>1</sup>	R <sup>2</sup>	% yield	% ee
H	Et	94	>98
Me	Et	74	>98
Ph	Et	93	>98
H	Me	72	>98
Me	Me	68	>98
H	Hep	95	95
H	<i>i</i> -Pr	95	94
H	(CH <sub>2</sub> ) <sub>3</sub> Ph	53	95
<b>H</b>	<b>(CH<sub>2</sub>)<sub>5</sub>OAc</b>	<b>77</b>	<b>95</b>
<b>H</b>	<b>(CH<sub>2</sub>)<sub>3</sub>CH(OEt)<sub>2</sub></b>	<b>91</b>	<b>97</b>
<b>H</b>	<b>(CH<sub>2</sub>)<sub>6</sub>OPiv</b>	<b>87</b>	<b>93</b>

- Addition of Et<sub>2</sub>Zn to cyclopentenone was much less selective (10% ee).

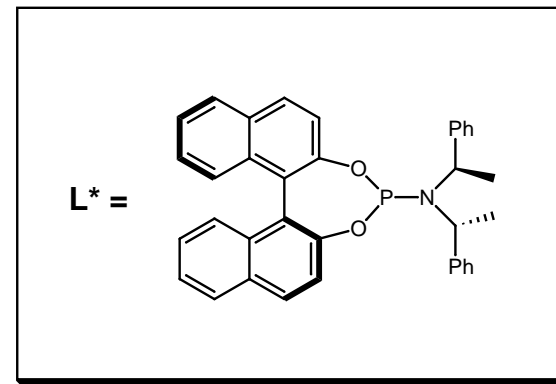
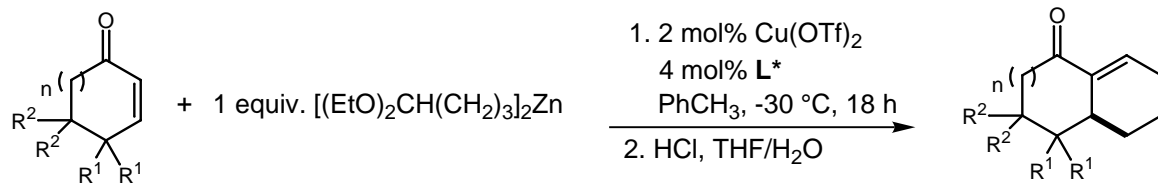
## Caveat:



- The postulated zinc enolate reacted with alkyl, alkenyl, or aryl aldehydes to give mixtures of *erythro* and *threo* products in 67-92% overall yield and 91-99% ee.
- One equivalent of BF<sub>3</sub>•OEt<sub>2</sub> or ZnCl<sub>2</sub>•OEt<sub>2</sub> was necessary to afford good yields of some aldol products.

Feringa, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620.

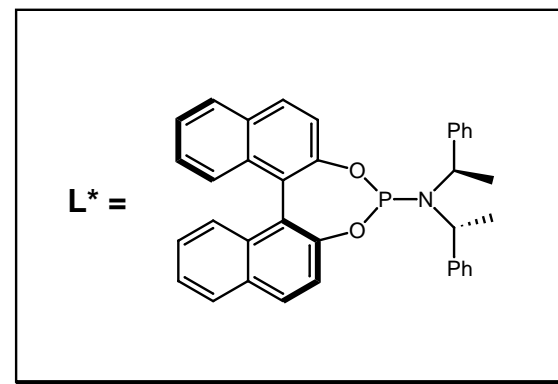
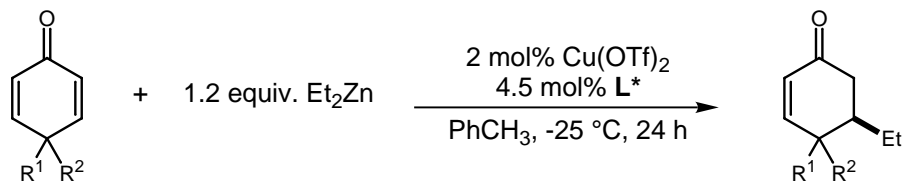
# Feringa: Robinson Annulation



			1,4-adduct		annulation	
$R^1$	$R^2$	$n$	% yield	% ee	% yield	% ee
H	H	1	91	98	62	97
Me	H	1	49	ND	55	>98
H	Me	1	57	ND	56	84
H	H	2	61	ND	50	96
H	H	3	61	ND	42	>98
For $\text{Et}_2\text{Zn}$ addition:						
H	H	2	>95	>98		
H	H	3	>95	97		

- This is the first catalytic annulation protocol that affords 6,6-, 6,7-, and 6,8-annulated ring systems with ee >96%.
- A fused 6,5-version of the annulation is possible *via* a multi-step process (Allylation of Zn enolate, Wacker oxidation, aldol), but the organozinc reagent ( $\text{Et}_2\text{Zn}$ ) is important only to generate the initial enolate. Yields and ee's of the process are comparable to those shown for the 6,6-system.

# Feringa: Dienone Desymmetrization



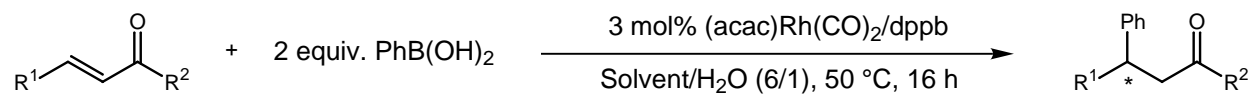
R <sup>1</sup>	R <sup>2</sup>	% yield	dr	% ee major	% ee minor
OMe	OMe	65		97	
OEt	OEt	59		92	
	-OCH <sub>2</sub> CH <sub>2</sub> O-	68		92	
	-OCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O-	62		89	
	-OCH <sub>2</sub> C(Me) <sub>2</sub> CH <sub>2</sub> O-	75		85	
OMe	Me	60	90/10	97	85
OMe	CH <sub>2</sub> Ph	53	97/3	93	ND
<b>OMe</b>	<b>OCH<sub>2</sub>Ph</b>	<b>58</b>	<b>1/1</b>	<b>98</b>	<b>98</b>
	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O-	66	99/1	65	ND

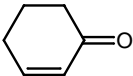
- The reactions were quenched with water or NH<sub>4</sub>Cl solution and extracted immediately with ether to prevent aromatization of the 1,4-adduct to the corresponding phenols.
- NOESY experiments indicate the ethyl substituent is *cis* to the alkoxy group in the major diastereomers.
- Based on the mixed ketal result, the authors argue that the major diastereodifferentiating effect seems to be ketal oxygen-coordination to copper, not steric.

Feringa, B. *Org. Lett.* **1999**, *1*, 623.



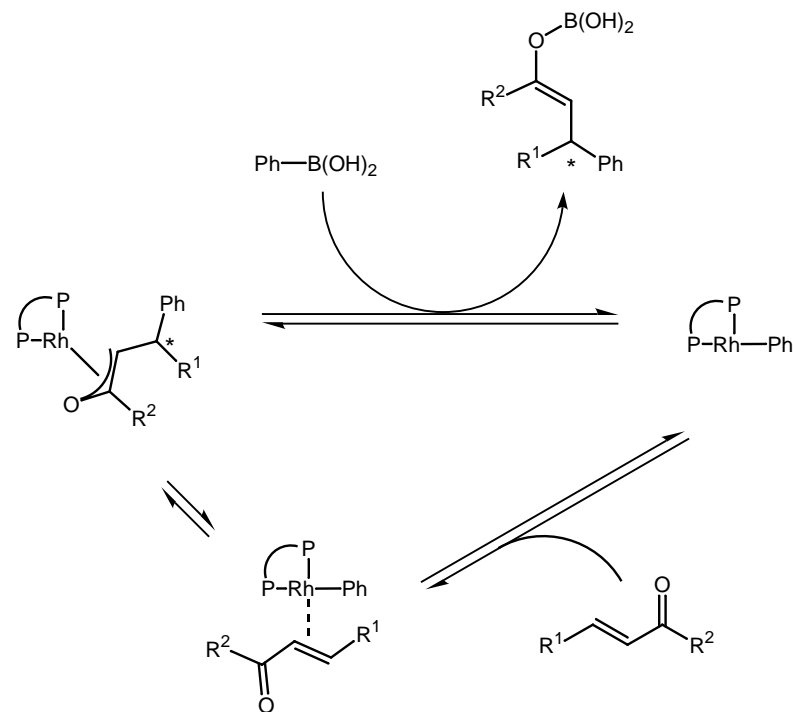
# Miyaura: Rhodium-catalyzed Boronic Acid Addition



enone	% yield, C <sub>6</sub> H <sub>12</sub>	% yield, MeOH
CH <sub>2</sub> =CHCOCH <sub>3</sub>	(90)	(99)
CH <sub>3</sub> CH=CHCOC <sub>4</sub> H <sub>9</sub>	74	96
CH <sub>3</sub> CH=CHCOPh	75	ND
PhCH=CHCOCH <sub>3</sub>	43	99
PhCH=CHCOPh	58	86
	52	trace

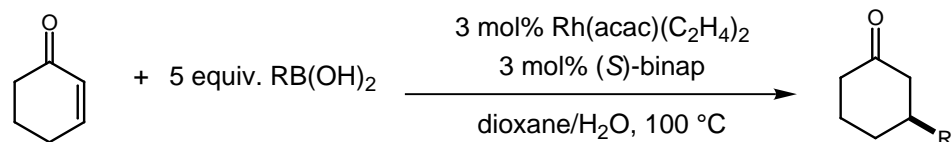
Yields in parentheses are GC yields.

## Proposed Catalytic Cycle:



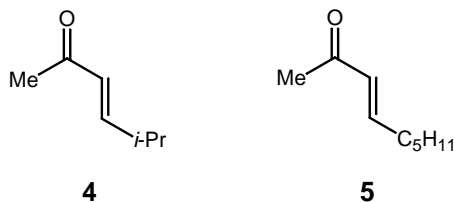
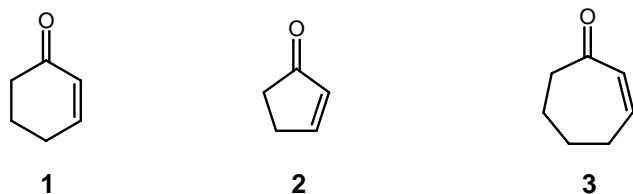
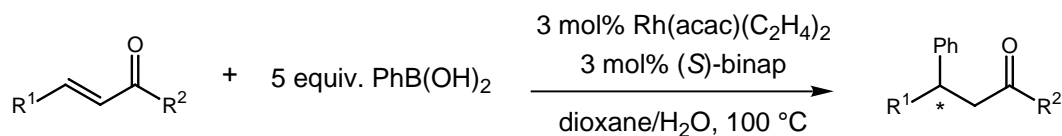
Miyaura, N. *Organometallics* **1997**, 16, 4229.

# Hayashi and Miyaura: Enantioselective Rh-catalyzed Boronic Acid Addition



- Excess arylboronic acid was necessary due to competing hydrolysis to benzene and B(OH)<sub>3</sub>.

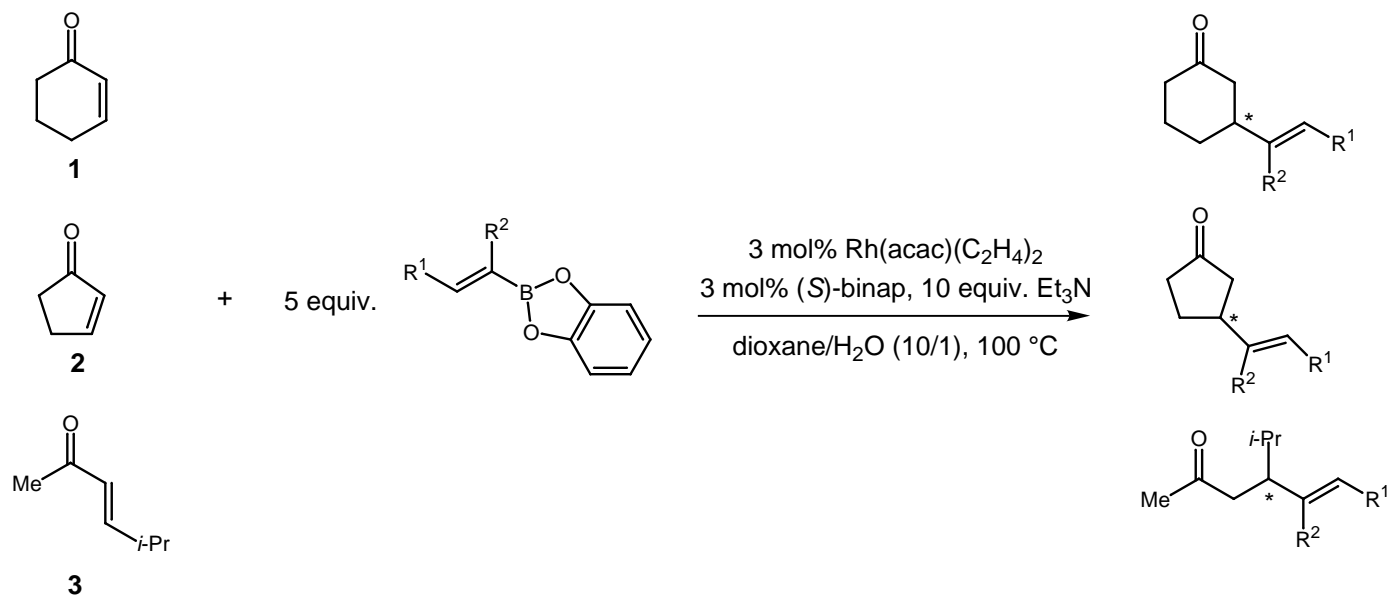
R	equiv	% yield	% ee (S)
Ph	5.0	>99	97
4-MeC <sub>6</sub> H <sub>4</sub>	5.0	>99	97
4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	2.5	70	99
3-MeOC <sub>6</sub> H <sub>4</sub>	5.0	97	96
3-ClC <sub>6</sub> H <sub>4</sub>	5.0	94	96
(E)-heptenyl	2.5	88	94
(E)- <i>t</i> -BuCH=CH	5.0	76	91



enone	equiv PhB(OH) <sub>2</sub>	% yield	%ee
1	5.0	>99	97 (S)
2	1.4	93	97 (S)
3	1.4	51	93
4	5.0	82	97
5	2.5	88	92

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

# Hayashi: Enantioselective Rh-Catalyzed Boronic Ester Addition

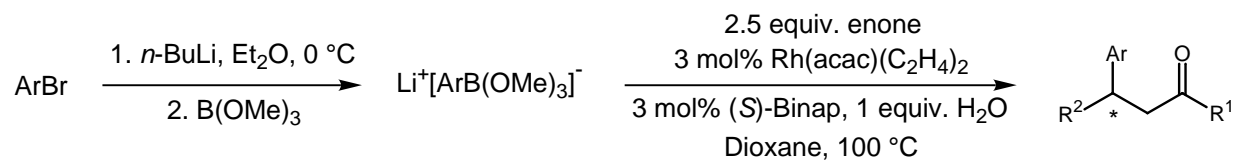


enone	R <sup>1</sup>	R <sup>2</sup>	yield (%)	% ee
<b>1</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	H	92	96 (S)
<b>1</b>	Ph	H	76	92 (S)
<b>1</b>	<i>t</i> -Bu	H	77	91
<b>1</b>	Me	Me	82	99
<b>1</b>	<b>CH<sub>2</sub>OMe<sup>a</sup></b>	<b>H<sup>a</sup></b>	<b>89</b>	<b>94</b>
<b>2</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	H	83	98
<b>2</b>	Me	Me	81	95
<b>3</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	H	68	81

<sup>a</sup>Boronic ester consisted of a 4:1 mixture of regioisomers.

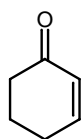
- Boronic esters were generated from catecholborane and alkynes.
- A one-pot procedure for boronic ester generation/conjugate addition was successful for *t*-Bu (75% y, 92% ee) and *n*-pentyl (85% y, 95% ee) acetylene.
- Triethylamine was used to prevent acid-catalyzed hydrolysis of the boronic esters.

# Hayashi: One-pot Procedure from Aryl Bromides

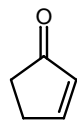


enone	Ar	yield (%)	%ee
1	4-MeOC <sub>6</sub> H <sub>4</sub>	80	98 (S)
1	Ph	>99	99 (S)
1	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	>99	99 (S)
2	Ph	>99	97 (S)
3	Ph	75	97
4	Ph	>99	91

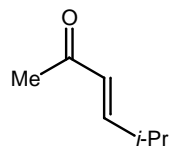
- Higher yielding procedure
- Easier manipulation of reactants
- Other aryl (4-MeC<sub>6</sub>H<sub>4</sub>, 2-naphthyl, and 3,5-Me<sub>2</sub>-4-MeOC<sub>6</sub>H<sub>2</sub>) groups gave similar yields and selectivities.
- Use of 2 equiv. H<sub>2</sub>O resulted in 51% yield, whereas 0.5 equiv. resulted in only 74% yield. Reaction was very sluggish in the absence of water (4% yield).



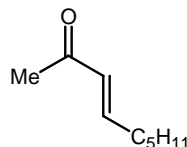
1



2



3



4

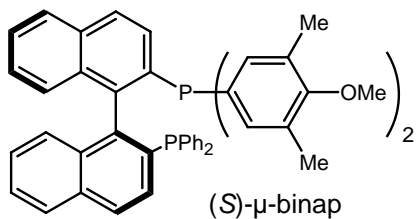
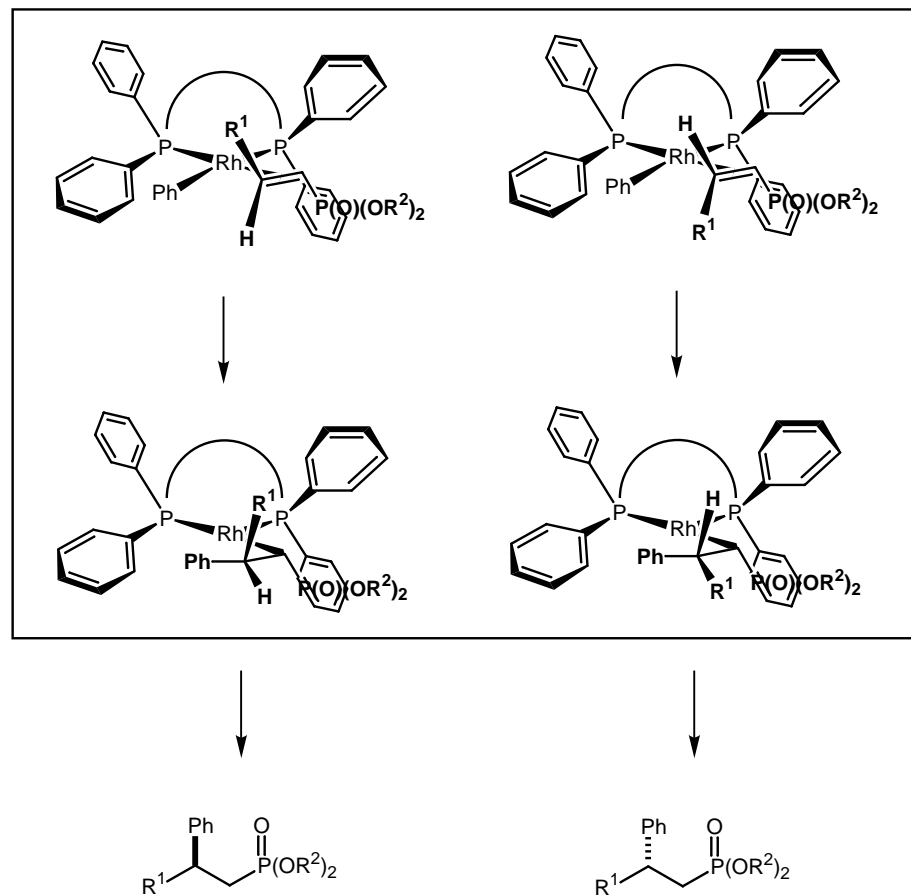
# Hayashi: Addition to 1-Alkenylphosponates



## The Model

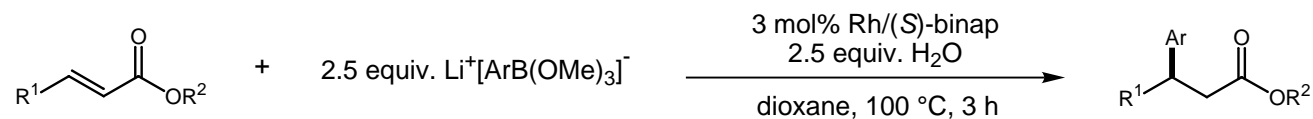
R <sup>1</sup>	R <sup>2</sup>	Ar	%yield	%ee
Me	Et	Ph	94	96
Me	Et	4-MeC <sub>6</sub> H <sub>4</sub>	84	95
Me	Et	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	64	96
Me	Et	2-naphthyl	89	89
<b>(Z)-Me</b>	<b>Et</b>	<b>Ph</b>	<b>96</b>	<b>-89</b>
<b>Pr</b>	<b>Et</b>	<b>Ph</b>	<b>39</b>	<b>99</b>
Me	Me	Ph	96	94
Me	Ph	Ph	95	91

- The resultant diethyl phosphonate esters were converted to diphenyl phosphonate esters, which underwent Horner-Emmons olefination.
- Substitution of (*S*)- $\mu$ -binap resulted in 2-3% gains in yield and enantioselectivity for three trial cases.



Hayashi, T. *J. Am. Chem. Soc.* **1999**, *121*, 11592.

# Hayashi: Addition to (*E*)- $\alpha,\beta$ -Unsaturated Esters

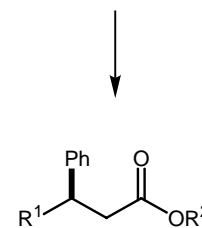
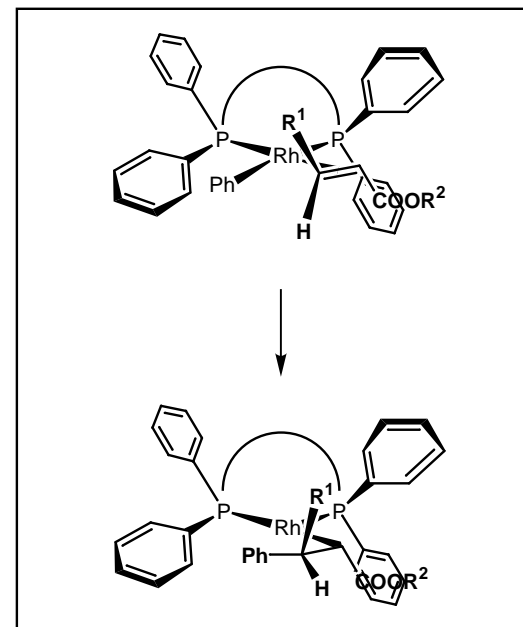


R <sup>1</sup>	R <sup>2</sup>	Ar	%yield	%ee
<b>Pr</b>	<b>Me</b>	<b>Ph</b>	<b>&gt;99</b>	<b>86</b>
Pr	Et	Ph	>99	91
Pr	<i>i</i> -Pr	Ph	96	95
<b>Pr</b>	<b><i>t</i>-Bu</b>	<b>Ph</b>	<b>92</b>	<b>96</b>
<b>Pr<sup>a</sup></b>	<b><i>t</i>-Bu</b>	<b>Ph</b>	<b>86</b>	<b>93</b>
<i>i</i> -Pr	<i>i</i> -Pr	Ph	64	98
Bu	<i>i</i> -Pr	Ph	91	95
Pr	<i>i</i> -Pr	4-ClC <sub>6</sub> H <sub>4</sub>	95	97
Pr	<i>i</i> -Pr	4-MeC <sub>6</sub> H <sub>4</sub>	88	97
Pr	<i>i</i> -Pr	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	98	96
Pr	<i>i</i> -Pr	3-MeOC <sub>6</sub> H <sub>4</sub>	83	94
Pr	<i>i</i> -Pr	2-naphthyl	96	93

<sup>a</sup>A 97:3 *E/Z* mixture was used.

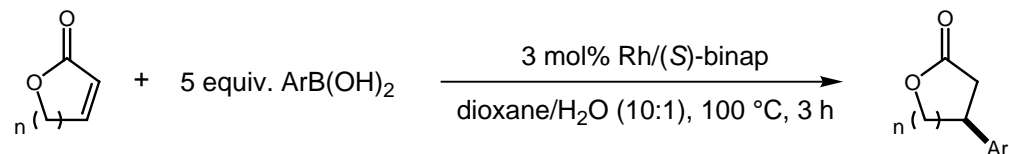
- Use of 5 equiv. of boronic acid in place of the lithium borate resulted in significantly lower yields.

## The Model



Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.

# Hayashi: Addition to Cyclic $\alpha,\beta$ -Unsaturated Esters

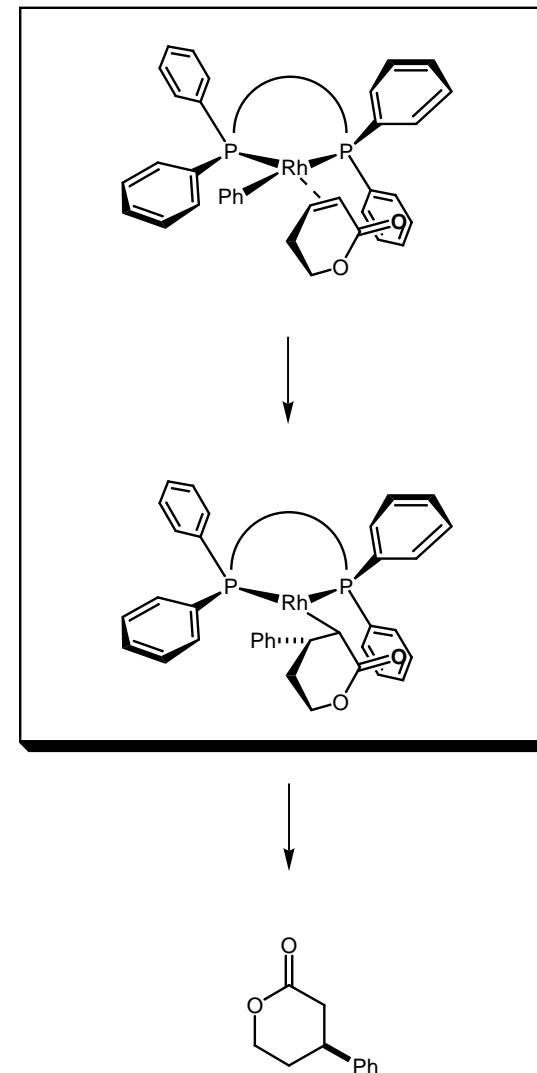


n	Ar	%yield	%ee
2	Ph	94	98
<b>2</b>	<b>Ph<sup>a</sup></b>	<b>38</b>	<b>98</b>
2	4-ClC <sub>6</sub> H <sub>4</sub>	95	97
2	4-MeC <sub>6</sub> H <sub>4</sub>	91	97
2	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	75	97
2	3-MeOC <sub>6</sub> H <sub>4</sub>	91	98
2	2-naphthyl	93	98
<b>1</b>	<b>Ph</b>	<b>33</b>	<b>96</b>

<sup>a</sup>2.5 equiv. Li<sup>+</sup>[PhB(OMe)<sub>3</sub>]<sup>-</sup> was used in place of PhB(OH)<sub>2</sub>.

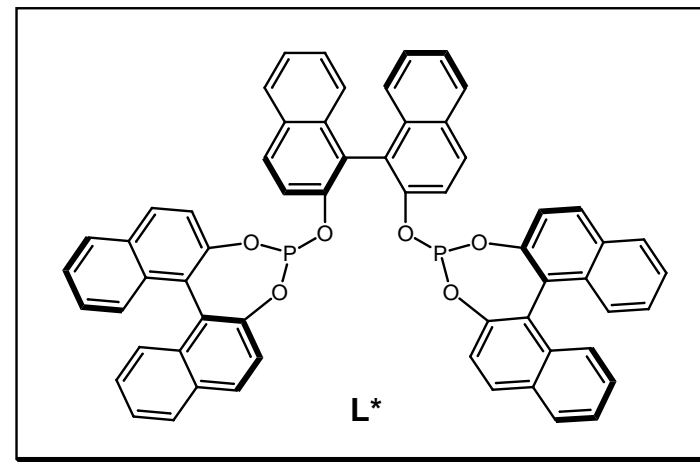
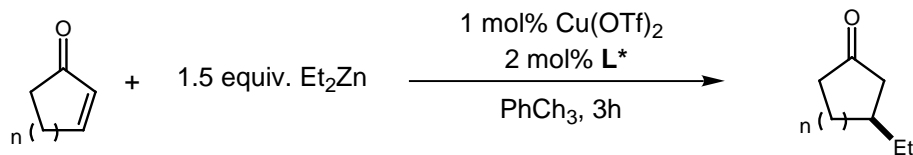
"At this moment, we cannot rationalize the difference of the reactivity between linear esters and cyclic esters."

## The Model



Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.

# Chan: Cu Catalysis with a Binol-derived Diphosphite Ligand



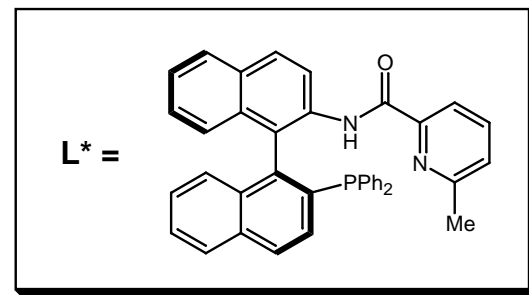
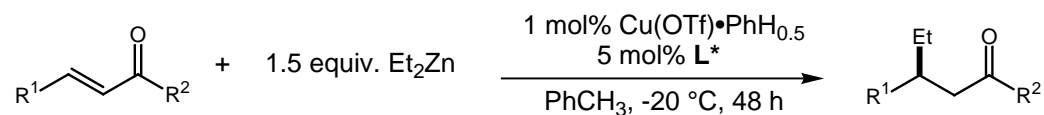
n	mol% Cu	L*:Cu	T (°C)	% Conv.	% ee (S)
2	1	4	0	82	88
<b>2</b>	<b>1</b>	<b>2</b>	<b>0</b>	<b>100</b>	<b>90</b>
2	1	1	0	100	83
2	1	2	40	100	71
2	1	2	20	100	88
2	1	2	-20	100	85
2	1	2	-40	24	39
<b>1</b>	<b>?</b>	<b>?</b>	<b>0</b>	<b>100</b>	<b>-76</b>
3	?	?	0	40	56?

- THF and CH<sub>3</sub>CN lowered conversion and selectivity.
- Substitution of Et<sub>2</sub>Zn with EtMgCl resulted in racemic product.
- <sup>31</sup>P NMR indicates a 1:1:1 L\*:Cu(I):Et complex.
- Mismatched binol ligands led to lower selectivity.
- Both lowering and raising the catalyst loading resulted in lower enantioselectivity.

Chan, A. *Chem. Commun.* **1999**, 11.



## Zhang: Acyclic Control



R <sup>1</sup>	R <sup>2</sup>	additive	% yield	% ee
Ph	Ph	none	72	94
<b>Ph</b>	<b>Ph</b>	<b>EtCl<sub>2</sub></b>	<b>85</b>	<b>96</b>
Ph	4-MeOC <sub>6</sub> H <sub>4</sub>	none	10	90
Ph	4-MeOC <sub>6</sub> H <sub>4</sub>	EtCl <sub>2</sub>	69	97
<b>4-MeOC<sub>6</sub>H<sub>4</sub></b>	<b>Ph</b>	<b>EtCl<sub>2</sub></b>	<b>97</b>	<b>98</b>
<i>i</i> -Pr	Me	none	53	86

- These are by far the best results for alkyl carbanion addition to acyclic substrates.
- Removal of the methyl group from the pyridine moiety of the ligand resulted 92% yield but only 83% ee for chalcone.
- THF and CH<sub>2</sub>Cl<sub>2</sub> resulted in lower enantioselectivity.
- Cu(OTf)<sub>2</sub> gave lower selectivity. Use of [Cu(CH<sub>3</sub>CN)<sub>4</sub>]BF<sub>4</sub> required removal of CH<sub>3</sub>CN for increased conversion and selectivity.
- The authors speculate that the substrates are more soluble when EtCl<sub>2</sub> is a cosolvent.

Zhang, X. *Angew. Chem., Int. Ed. Eng.* **1999**, *38*, 3518.

# Grand Summary

- Almost no progress had been made in additions of alkyl carbanions to acyclic enones (e.g. chalcone) since Sanchez's report in 1992 until Zhang's system in late 1999.

## The Tomioka System

- Works fairly well for n-alkyl Grignard addition to cyclic substrates (70-92% y, 70-92% ee)
- 8 mol % CuI and 32 mol % ligand are necessary.
- Lengthy ligand synthesis

## The Feringa System

- Best overall for alkyl carbanion addition to cyclic substrates
- Good yields (68-95%) and excellent selectivities (>98% ee) for simple dialkylzinc nucleophiles
- Good selectivity for functionalized nucleophiles (93-97% ee)
- The initial 1,4-adduct can be trapped with internal or external electrophiles.
- Application to acyclic systems, however, resulted in only 88% yield and 89% ee.
- The system has been applied with some success to nitro olefins, (*Z*)- $\alpha,\beta$ -unsaturated nitroacetates, and vinyl and propargyl epoxides.

## The Hayashi System

- Best for addition of alkenyl or aryl carbanions.
- Compatible with a variety of electrophiles: cyclic esters, (*E*)- $\alpha,\beta$ -unsaturated esters, alkenylphosphonates, cyclic and acyclic enones
- Selectivities consistently greater than 95% ee
- Requires of 2.5 to 5 equivalents of either the boron nucleophile or the enone to effect high yields

UNC Kenan Laboratories



Professor Michael "The Boss" Crimmins

