Cu(I)-Catalyzed Asymmetric Allylation of Ketones

Yong Guan

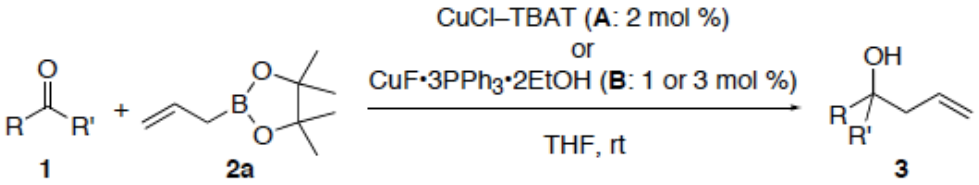
Wulff's group

2010-04-30

Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.

Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl. Chem.* **2008**, *80*, 1055.

Shi, S.-L.; Xu, L.-W.; Oisaki,K.; Kanai,M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, ASAP.



1 2a 3

entry	ketone	catalyst (mol %)	2a (equiv)	h	3 (%)
1	**1a**: R^1, R^2, R^3 = H	**A** (2)	3	6	100
2	**1b**: R^1 = CH_3, R^2, R^3 = H	**B** (1)	1.1	17	100
3	**1c**: R^1, R^3 = H, R^2 = CH_3	**B** (3)	1.1	3	98
4	**1j**: R^1, R^2 = H, R^3 = CH_3	**B** (1)	1.1	17	100
5	**1k**	**B** (3)	1.1	3	98
6	**1d**	**B** (3)	1.2	3	83
7	**1l**	**B** (3)	1.2	4	98
8	**1m**	**B** (1)	1.1	17	81
9	**1h**	**B** (3)	1.2	3	75
10	**1n**	**B** (3)	1.2	3	91
11	**1o**	**A** (2)	3	6	100
12	**1p**	**A** (2)	3	17	64

TBAT (tetrabutylammonium difluorotriphenylsilicate)

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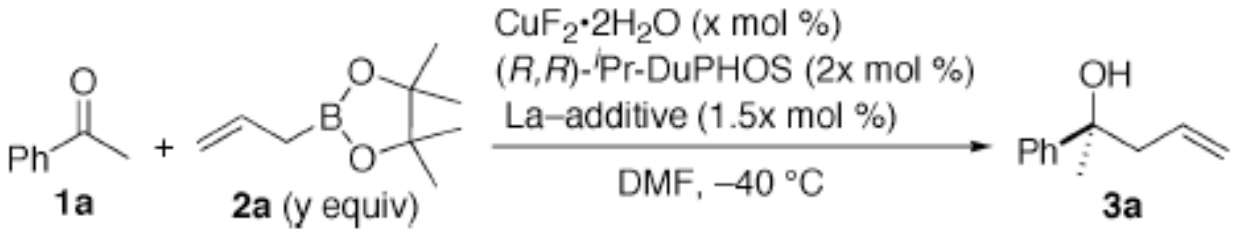
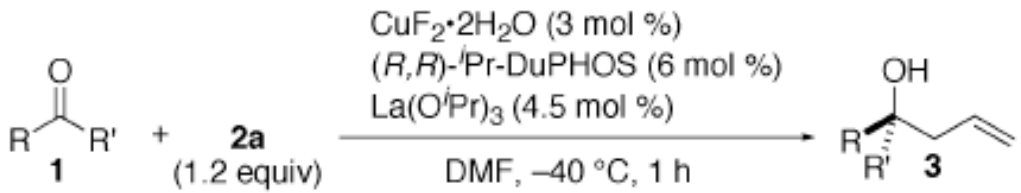
Lanthanide Effect on Allylboration of Ketones



entry	catalyst (*x* mol %)	**2a** (*y* equiv)	La-additive	time (h)	yield[a] (%)	ee[b] (%)
1	15	3	–	20	42	79
2	15	3	$La(O^iPr)_3$	3.5	95	77
3	3	1.2	$La(O^iPr)_3$	1	94	82
4	15	3	(*R*)-BINOL-$La(O^iPr)_3$	20	52	80
5	15	3	(*S*)-BINOL-$La(O^iPr)_3$	20	48	79

Dynamic coordinating nature of lanthanide metals

Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.



entry	substrate	yield (%)[a]	ee (%)[b]
1	**1a**: R^1, R^2 = H	94	82[c]
2	**1b**: R^1 = CH_3, R^2 = H	89	84
3	**1c**: R^1 = H, R^2 = CH_3	83	83
4	**1d**	84	85
5	**1e**	88	84[c]
6	**1f**	87	90
7	**1g**	99	91
8	**1h**	98	84
9	**1i**	96	67[c]

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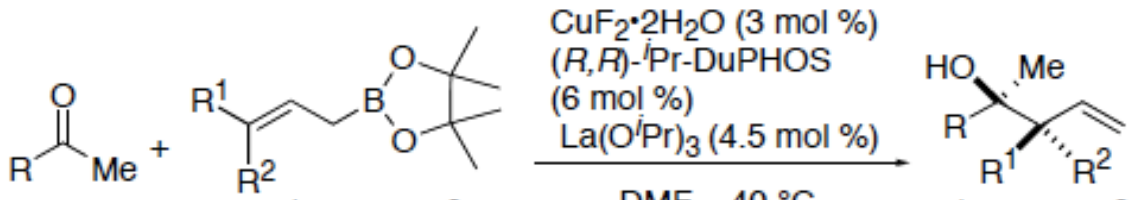
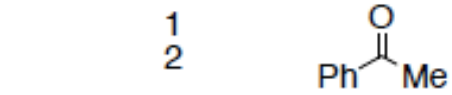
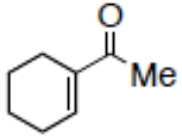
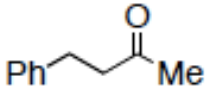
Catalytic Enantioselective Crotylation of Ketones



1

2b: $R^1 = CH_3$, $R^2 = H$
2c: $R^1 = H$, $R^2 = CH_3$

syn: $R^1 = CH_3$, $R^2 = H$
anti: $R^1 = H$, $R^2 = CH_3$

entry	substrate	crotylboronate (1.2 equiv)	time (h)	yield (%)	dr (*syn*/*anti*)	ee (%)
1	 **1a**	**2b**	1	73	30/70	75/90
2		**2c**	5	94	84/16	87/74
3	 **1f**	**2b**	3	80	27/73	90/93
4		**2c**	4	90	38/62	90/92
5	 **1l**	**2b**	4	100	34/66	16/85
6		**2c**	4	100	36/64	21/85

No crotylation proceeded in the absence of La(O*i*Pr)$_3$.
First example of a catalytic enantioselective crotylation of ketones, giving the chiral tetrasubstituted carbons with high enantioselectivity.

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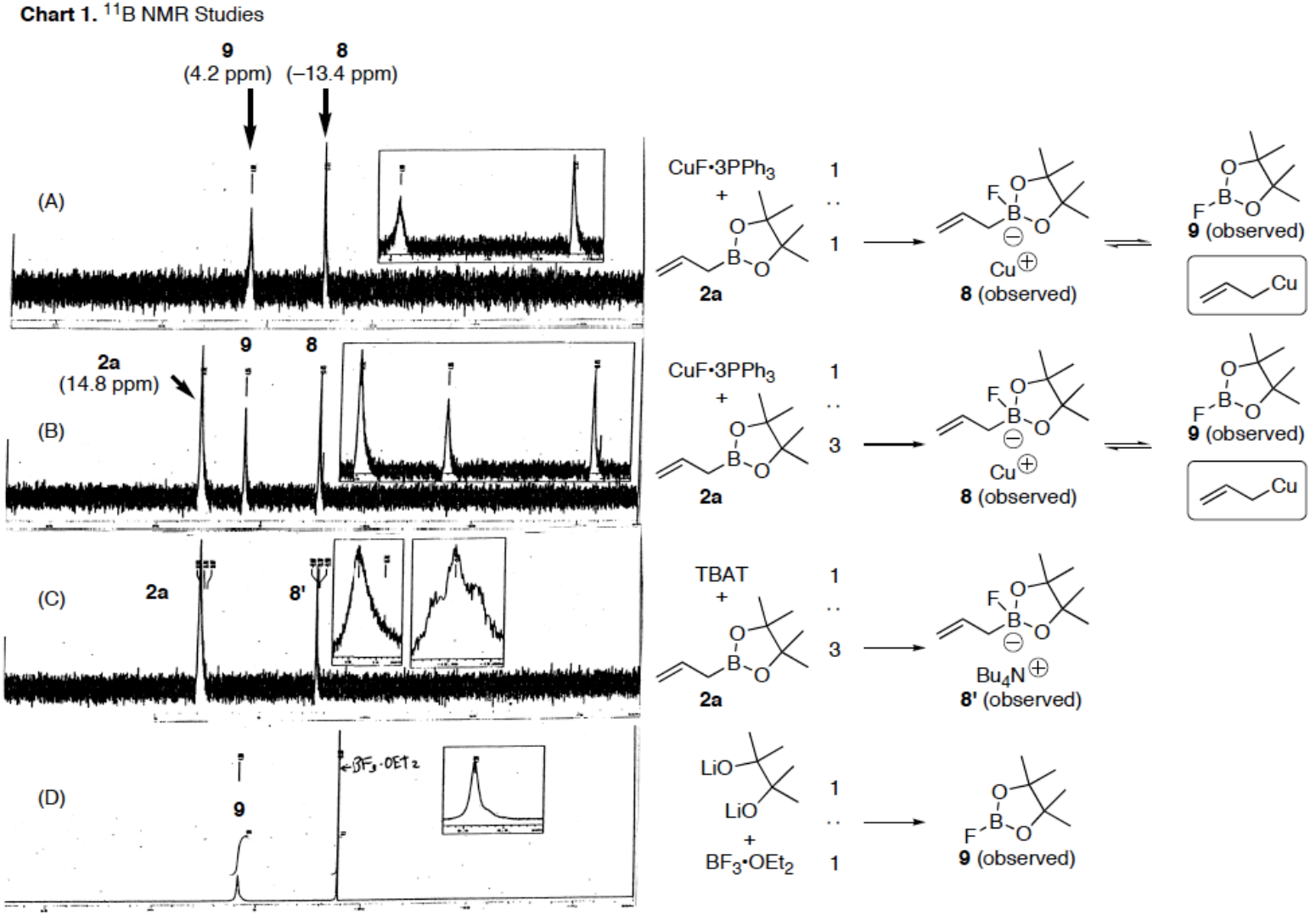
^{11}B NMR Studies



allylation reagents is an allylcopper

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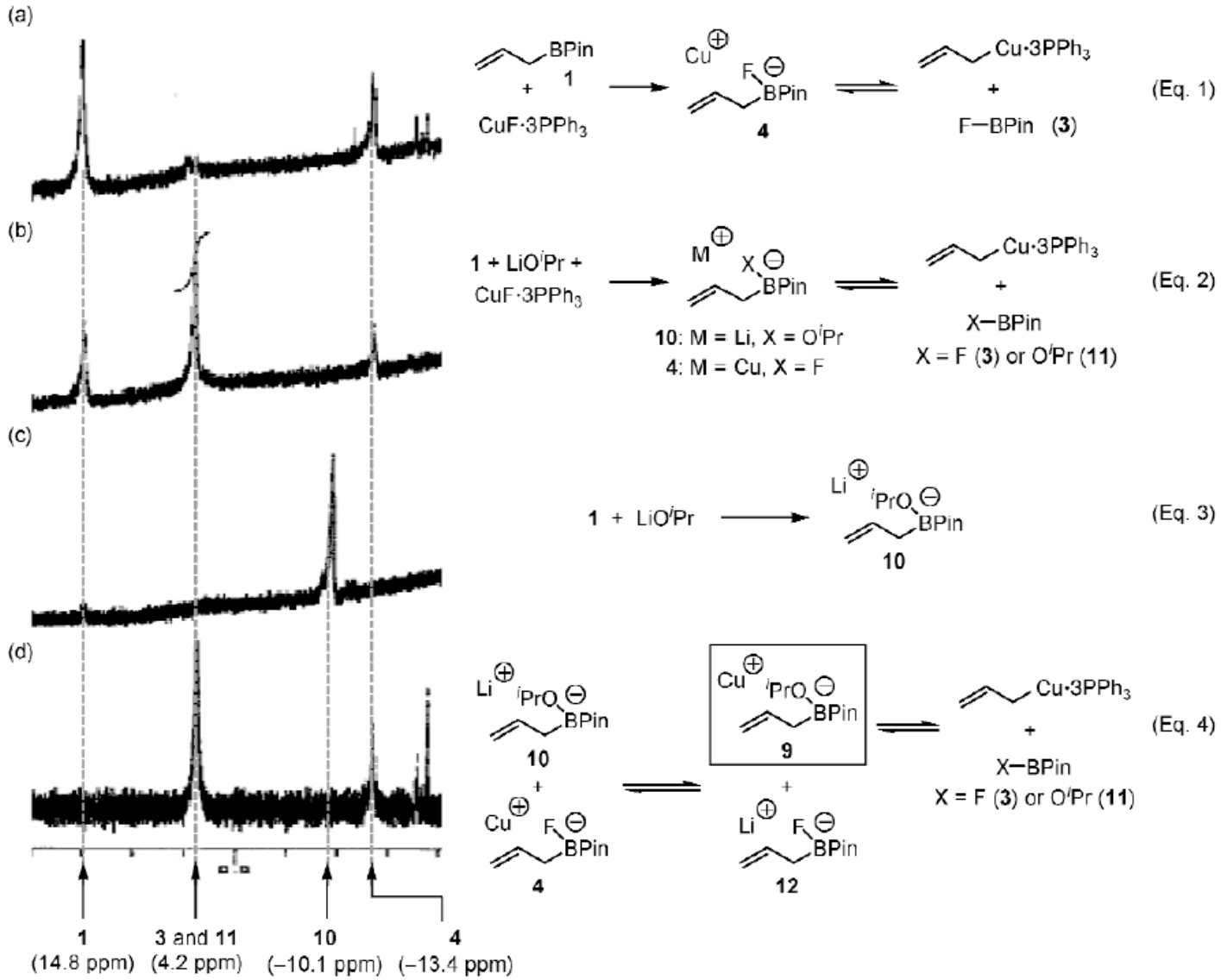
Rate Acceleration of Metal Alkoxide



Kinetic studies

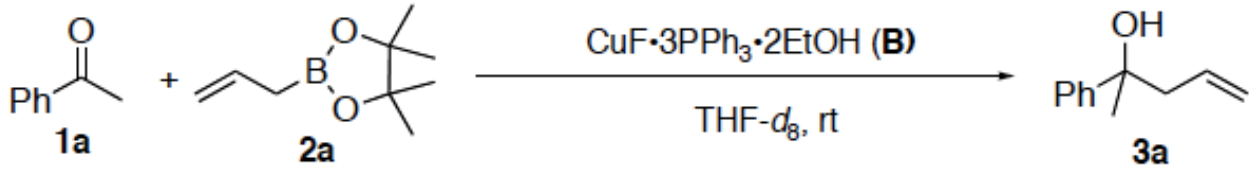


Fig. 2 Order on CuF Catalyst

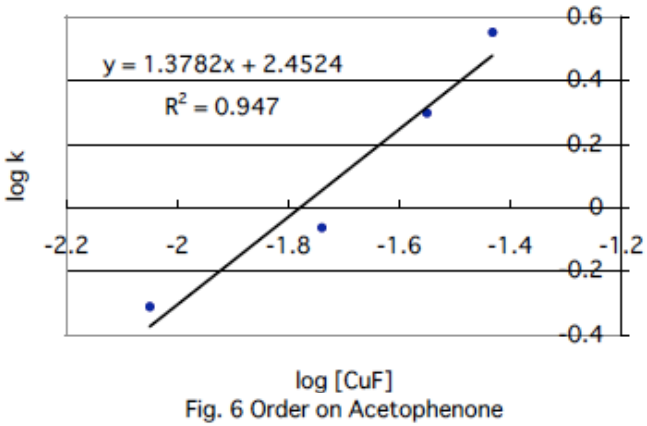


Fig. 4 Order on Allylboronate

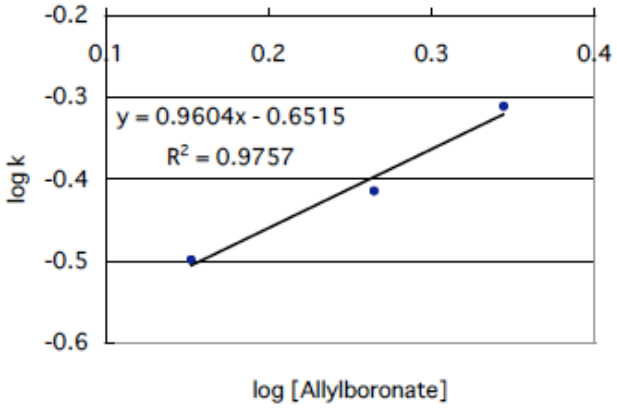
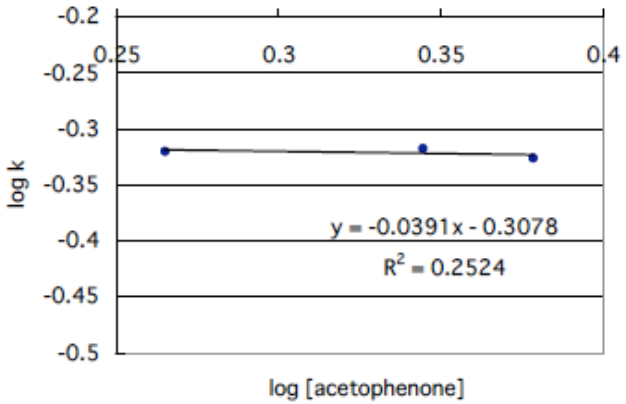


Fig. 6 Order on Acetophenone



the rate-determining step is the generation of the active nucleophile through a ligand exchange between boron and copper atoms, and NOT the addition to a substrate ketone

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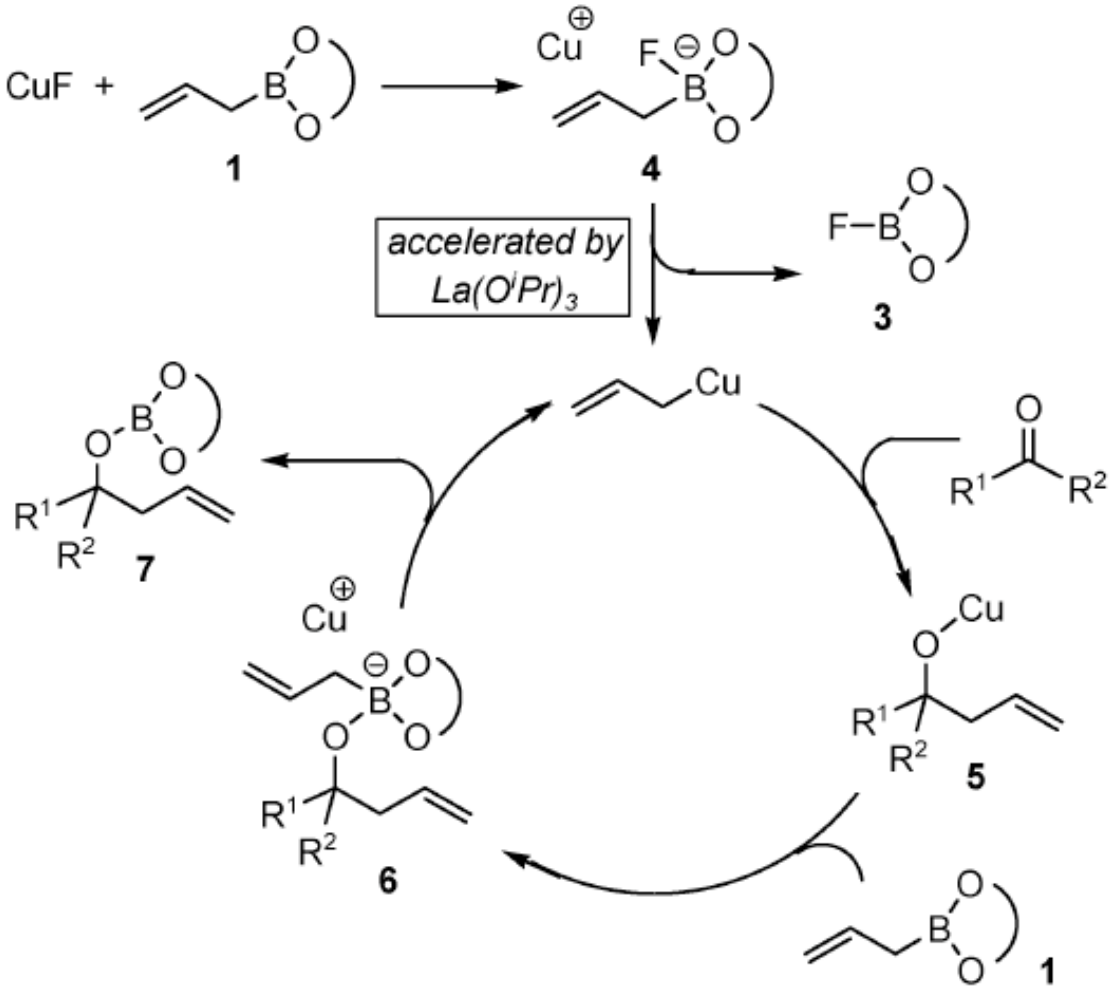
Proposed Catalytic Cycle



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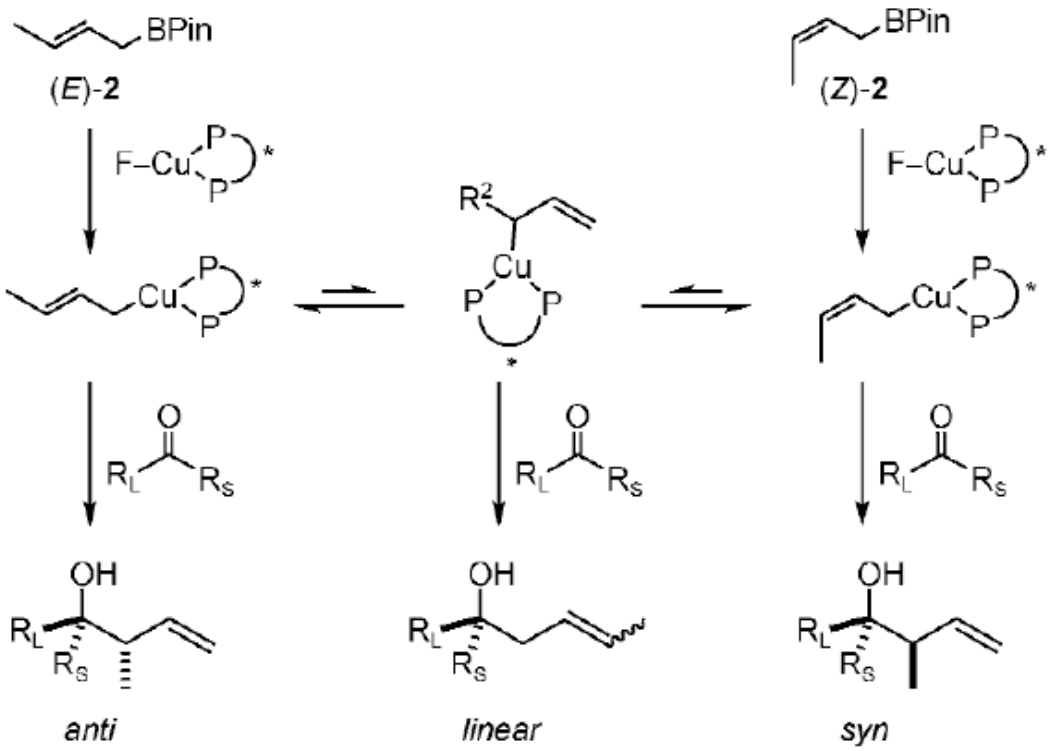
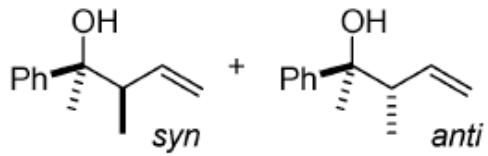
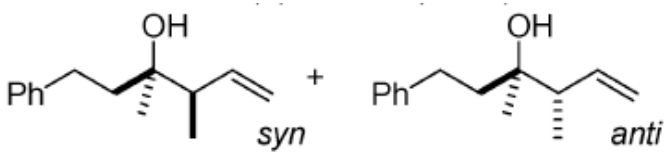
Proposed Model of Crotylation of Ketones





(*E*)-**2**: 73 % (30/70), 75/90 % ee
(Z)-**2**: 94 % (84/16), 87/74 % ee



(*E*)-**2**: 100 % (34/66), 16/85 % ee
(Z)-**2**: 100 % (36/64), 21/85 % ee

The rate of the crotylcopper addition step to aromatic ketones might be faster than that to aliphatic ketones.
The addition could proceed before(*E)/(Z)* equilibrium of crotylcopper in the case of aromatic ketones, whereas the addition proceeded after equilibrium in the case of aliphatic ketones.

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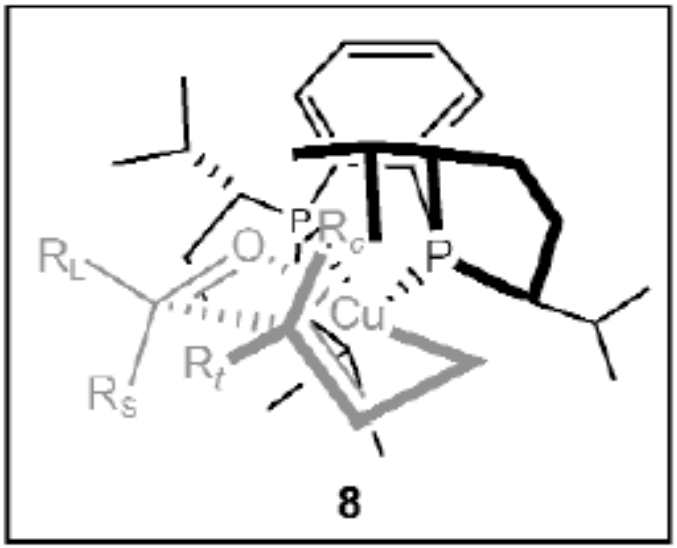
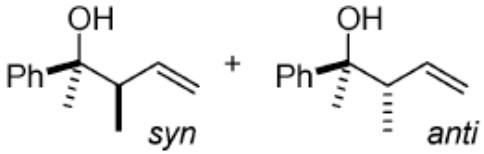
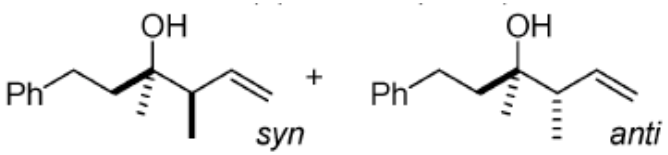
Proposed Model of Crotylation of Ketones



8



(*E*)-**2**: 73 % (30/70), 75/90 % ee
(*Z*)-**2**: 94 % (84/16), 87/74 % ee



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(*Z*)-**2**: 100 % (36/64), 21/85 % ee

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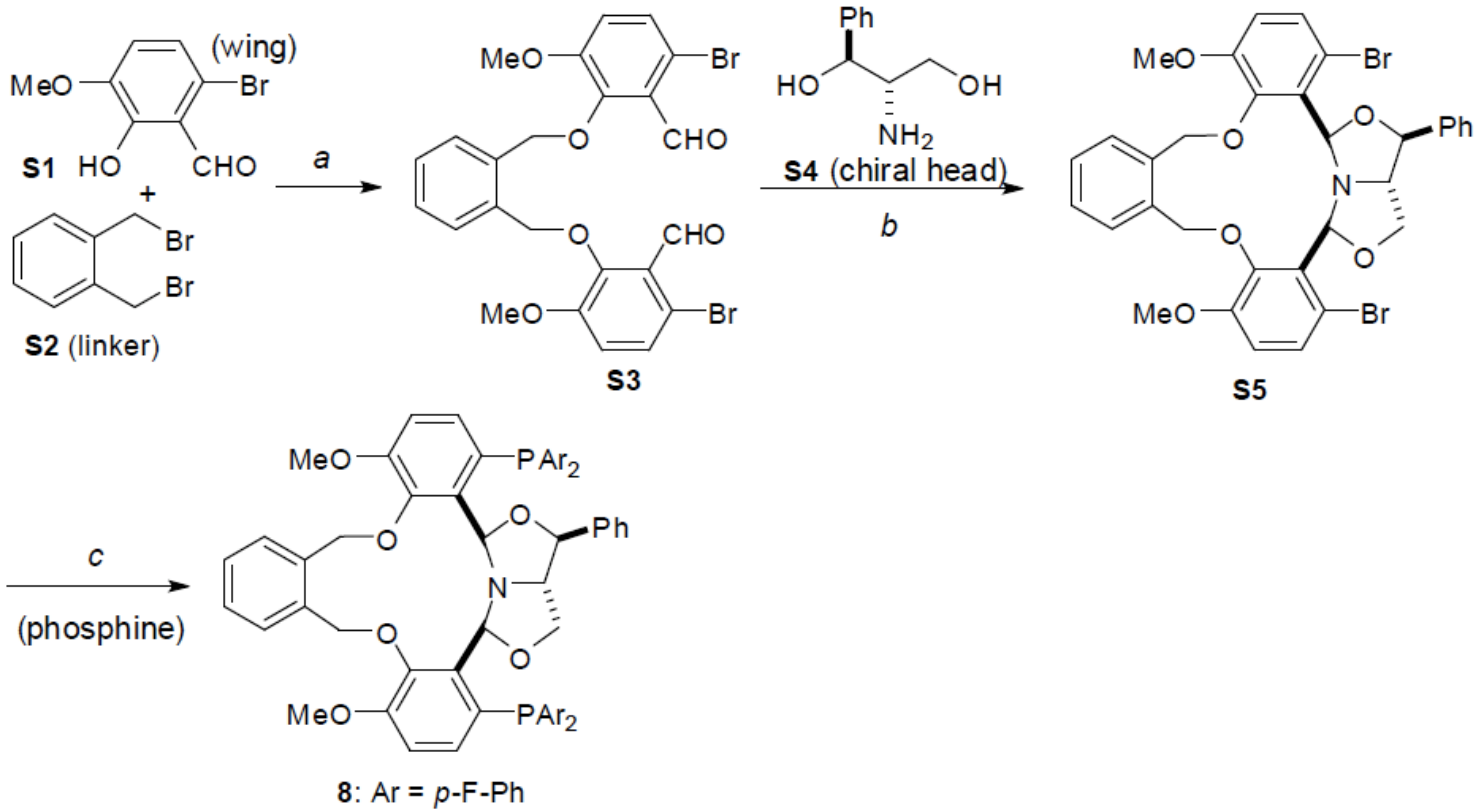
Synthesis of Modular Chiral Bisphosphine



[a] Conditions: (a) K_2CO_3, DMF, 80 °C, overnight; (b) AcOH/$(CH_2)_2Cl_2$ (1/10), 4A MS, 70 °C, 30 h, 85.8% (two steps); (c) ^{n}BuLi, THF, –78 °C, 1 h; $ClPAr_2$, –78 °C to rt, rt overnight, 70%.

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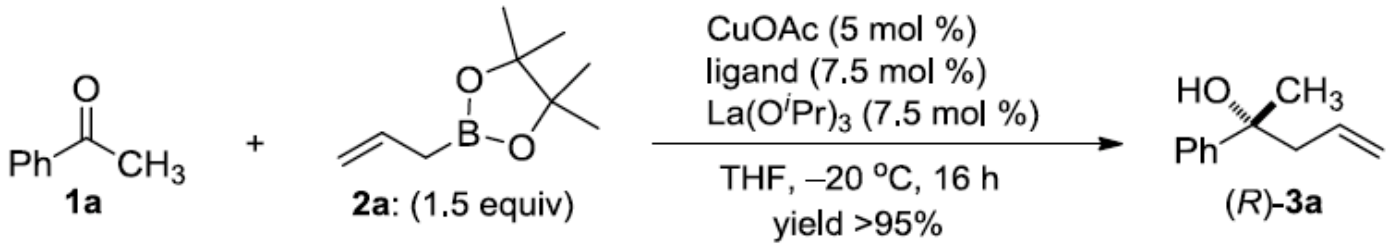
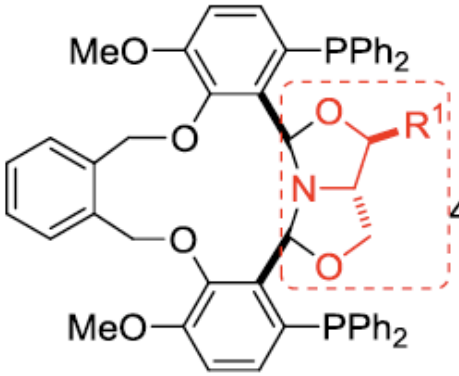
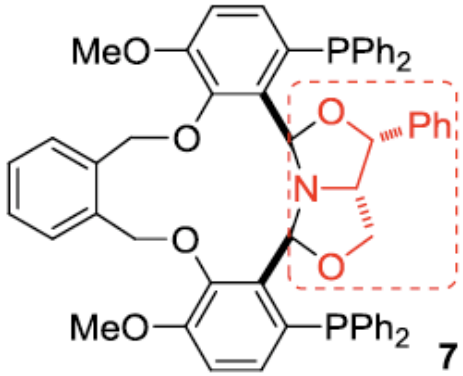
Effects of Chiral Head Structure





R^1 of ligand	ee of (*R*)-**3a** (%)
Ph (**5**)	65
4-MeS-C_6H_4 (**11**)	61
cyclo-Hex (**6**)	9
$Ph(CH_2)_2$ (**12**)	3



7

ee of (*S*)-**3a** (%)

64

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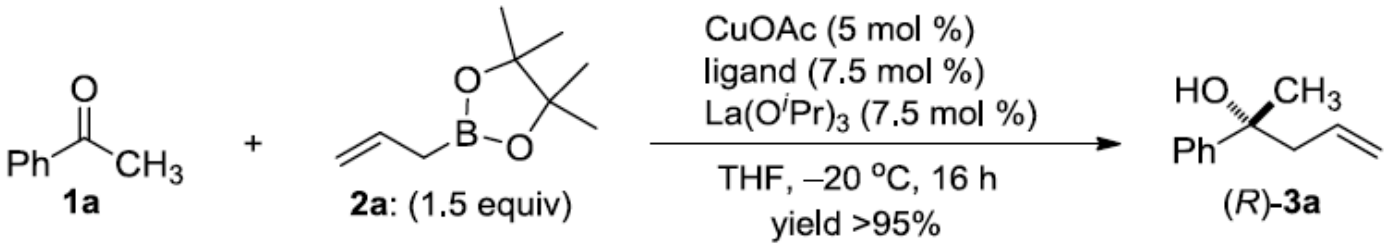
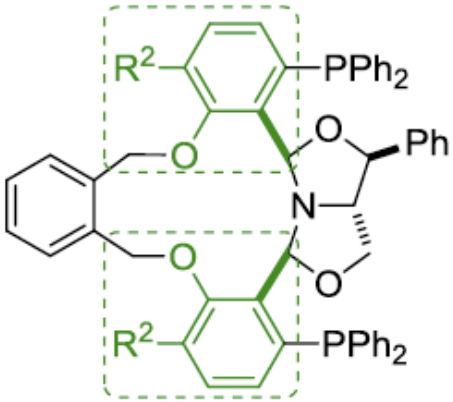
Effects of Wing Structure





R^2 of ligand	ee of (*R*)-**3a** (%)
MeO (**5**)	65
H (**13**)	34
^{i}PrO (**14**)	59

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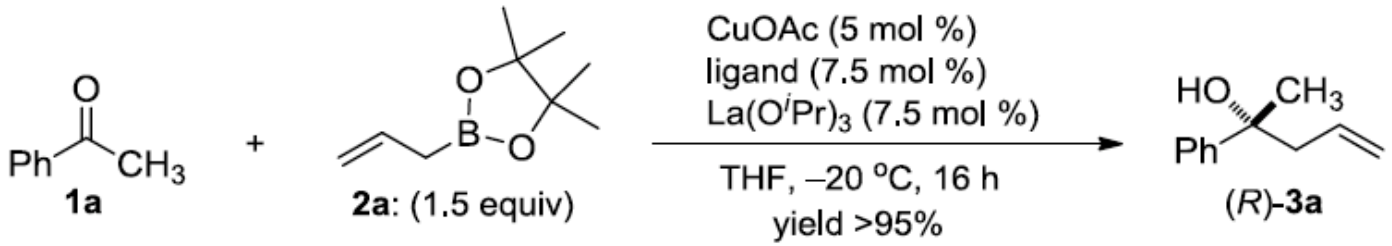
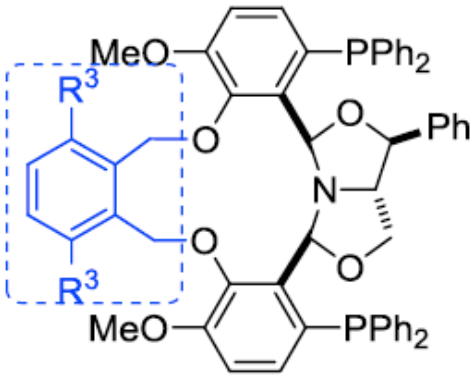
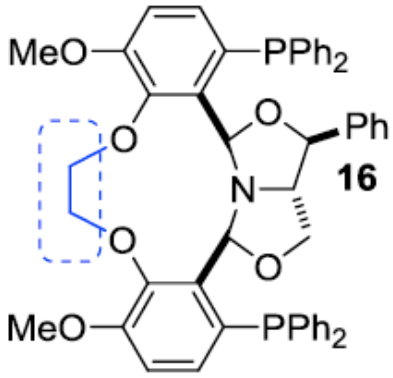
Effects of Linker Structure





R^3 of ligand	ee of (*R*)-**3a** (%)
H (**5**)	65
MeO (**15**)	33



16

ee of (*R*)-**3a** (%)

17

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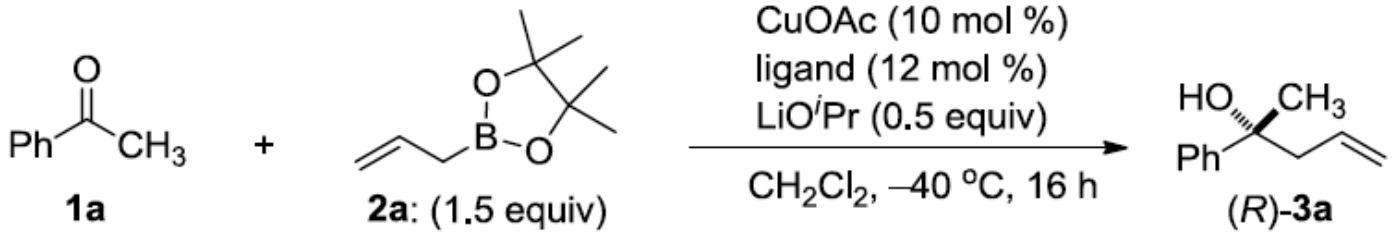
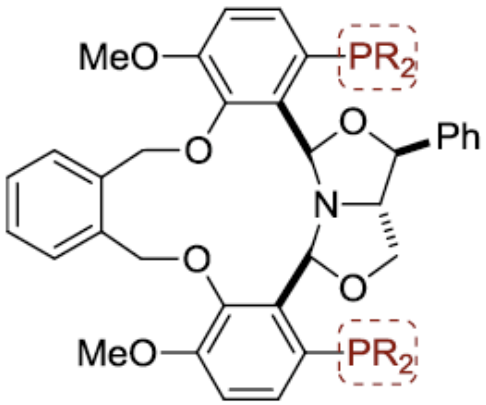
Effects of Phosphine Part





R of phosphine	yield of (*R*)-**3a** (%)	ee of (*R*)-**3a** (%)
Ph (**5**)	>99	76
p-MeO-C_6H_4 (**17**)	>99	76
o-MeO-C_6H_4 (**18**)	5	53
c-Hex (**19**)	60	0
p-F-C_6H_4 (**8**)	>99	81
p-Cl-C_6H_4 (**20**)	99	80
p-CF_3-C_6H_4 (**21**)	>99	78
3,5-$(CF_3)_2$-C_6H_3 (**22**)	46	27

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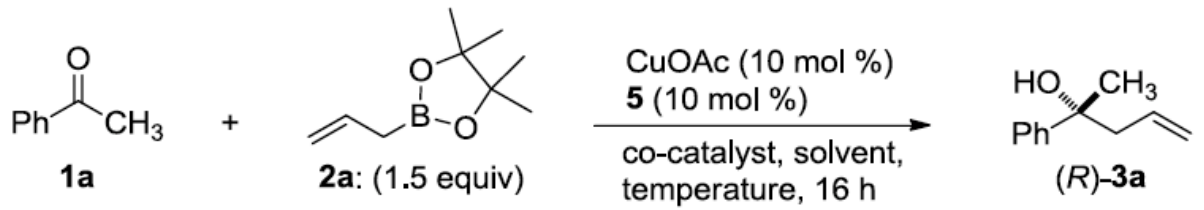
Effects of Solvent, Co-catalyst, and Temperature



entry	co-catalyst	(eq.)	solvent	temp. (°C)	yield(%)	ee (%)
1	$La(O^iPr)_3$	0.15	THF	–20	>99	65
2	$La(O^iPr)_3$	0.15	DMF	–20	70	63
3	$La(O^iPr)_3$	0.15	toluene	–20	>99	64
4	$La(O^iPr)_3$	0.15	CH_2Cl_2	–20	>99	71
5	LiO^iPr	0.5	CH_2Cl_2	–20	>99	72
6	LiO^iPr	0.5	CH_2Cl_2	–40	>99	76
7	LiOMe	1.0	CH_2Cl_2	–40	57	76
8	LiO^tBu	0.5	CH_2Cl_2	–40	99	76
9	$Mg(O^iPr)_2$	0.5	CH_2Cl_2	–40	77	77
10	$Ba(O^iPr)_2$	0.5	CH_2Cl_2	–40	99	77
11	$Ca(O^iPr)_2$	0.5	CH_2Cl_2	–40	38	77

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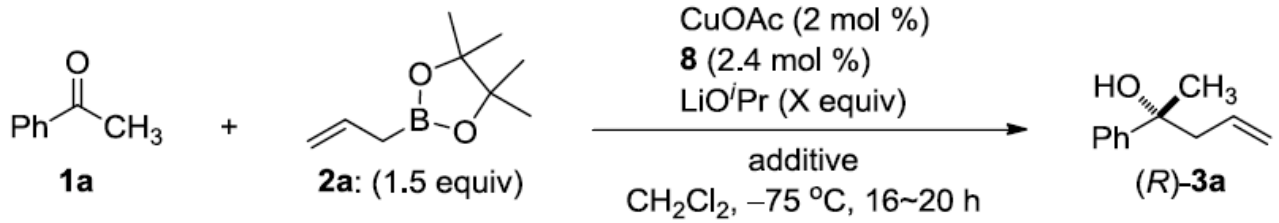
Effects of Protic Addictive



entry	LiO^iPr (X equiv)	additive (1 equiv)	yield (%)	ee (%)
1	2	—	99	89
2	0.5	—	47	84
3	0.5	^{i}PrOH	99	89
4	0.5	MeOH	24	78
5	0.5	^{t}BuOH	46	83

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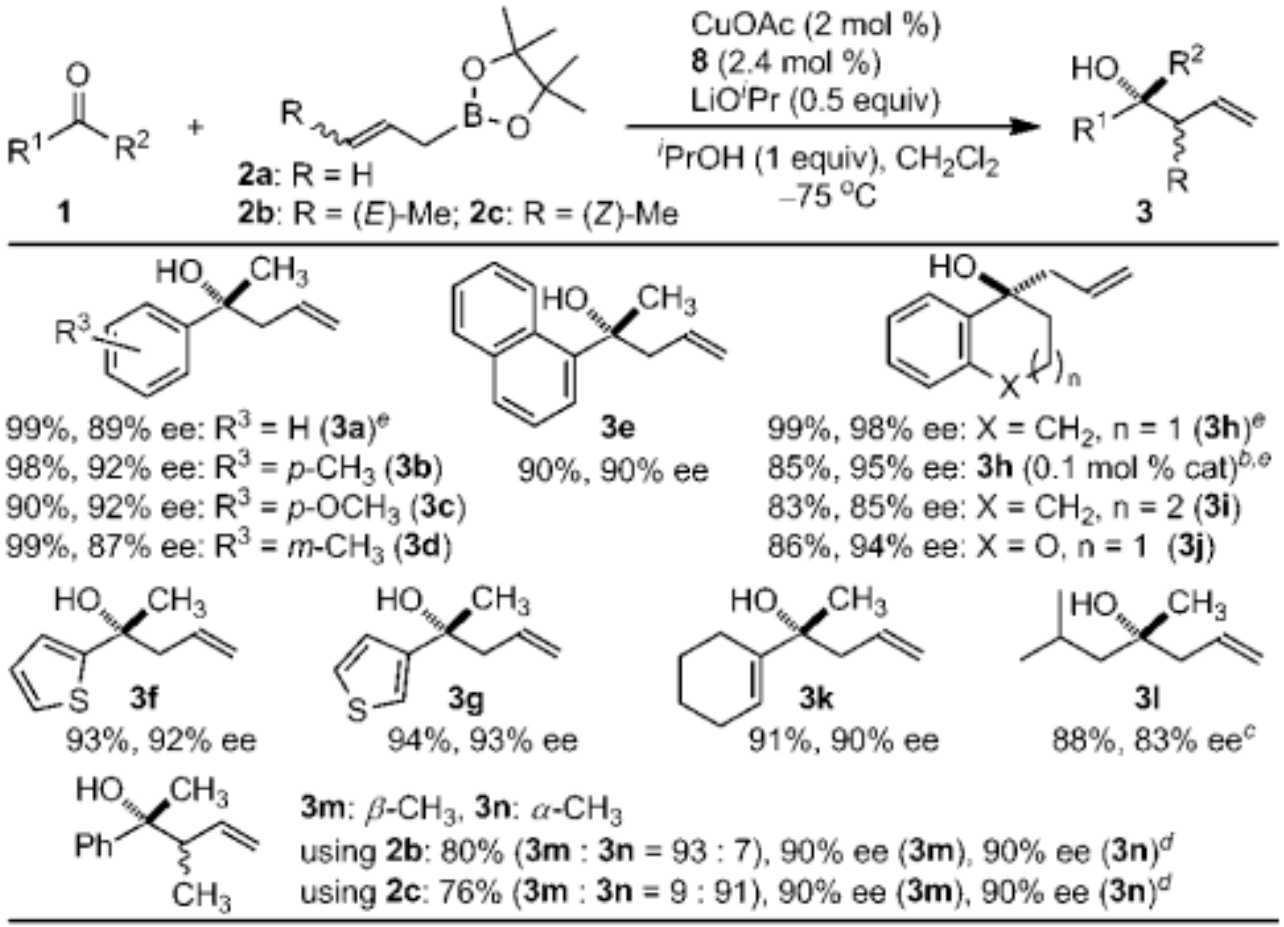
Catalytic Asymmetric Allylation of Ketones



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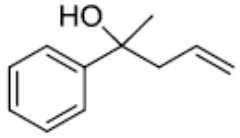
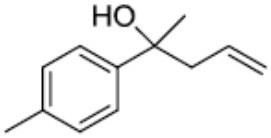
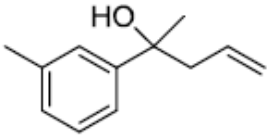
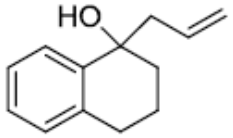
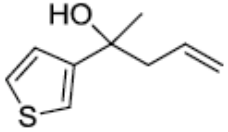
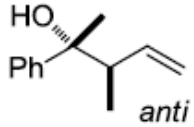
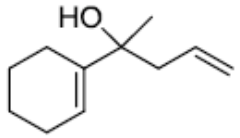
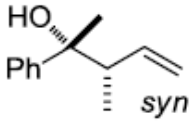
New Ligand vs iPr-DuPHOS

product	**8** [a]	^{i}Pr-DuPHOS [b]	product	**8** [a]	^{i}Pr-DuPHOS [b]
	99% 89% ee	94% 82% ee		98% 92% ee	89% 84% ee
	99% 87% ee	83% 83% ee		99% 98% ee	88% 84% ee
	94% 93% ee	84% 85% ee		**(*E*)-crotylboronate** *anti* : *syn* = 93 : 7 80% 90% ee : 90% ee	**(*E*)-crotylboronate** *anti* : *syn* = 70 : 30 70% 90% ee : 75% ee
	91% 90% ee	87% 90% ee		**(*Z*)-crotylboronate** *anti* : *syn* = 9 : 91 76% 90% ee : 90% ee	**(*Z*)-crotylboronate** *anti* : *syn* = 16 : 84 94% 74% ee : 87% ee

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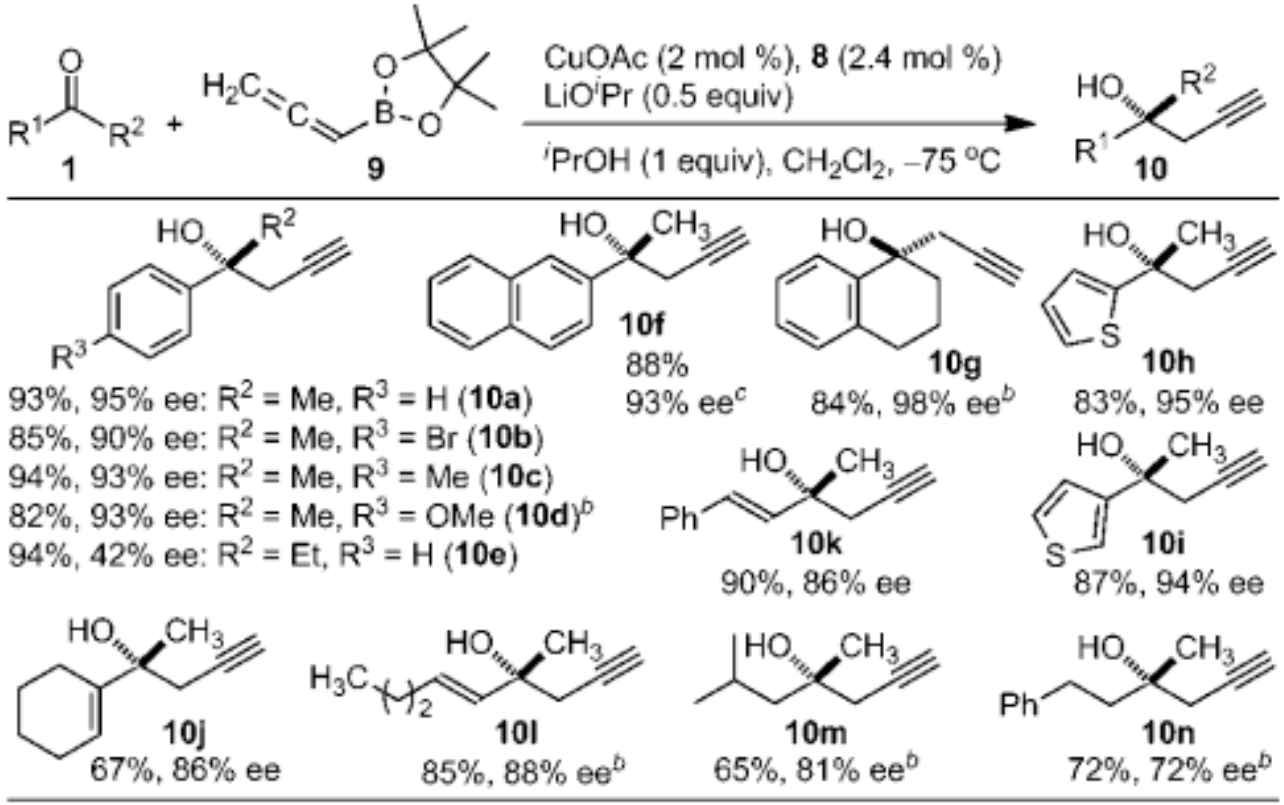
Catalytic Asymmetric Propargylation of Ketones



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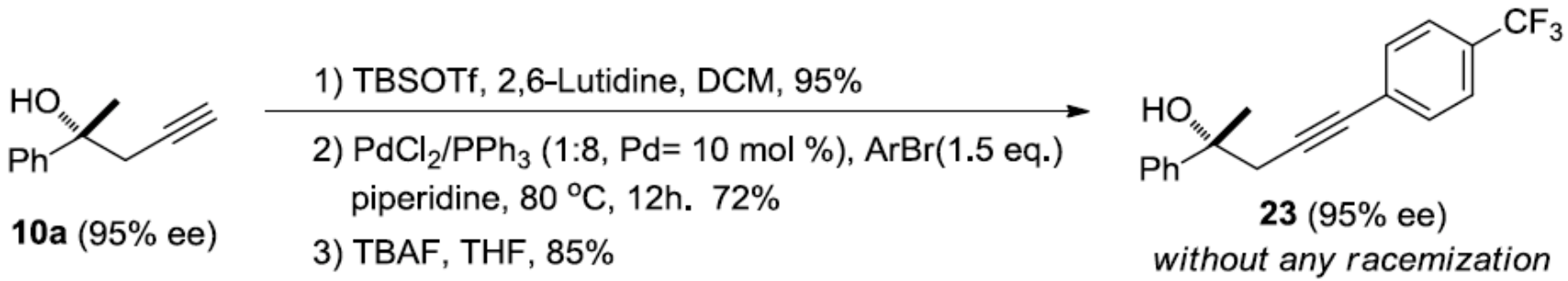
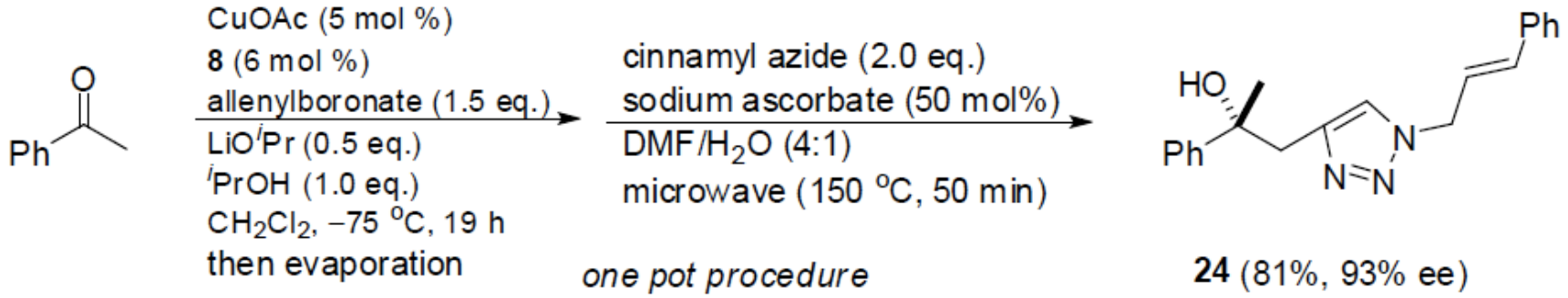
Utility of Homopropargyl Alcohols





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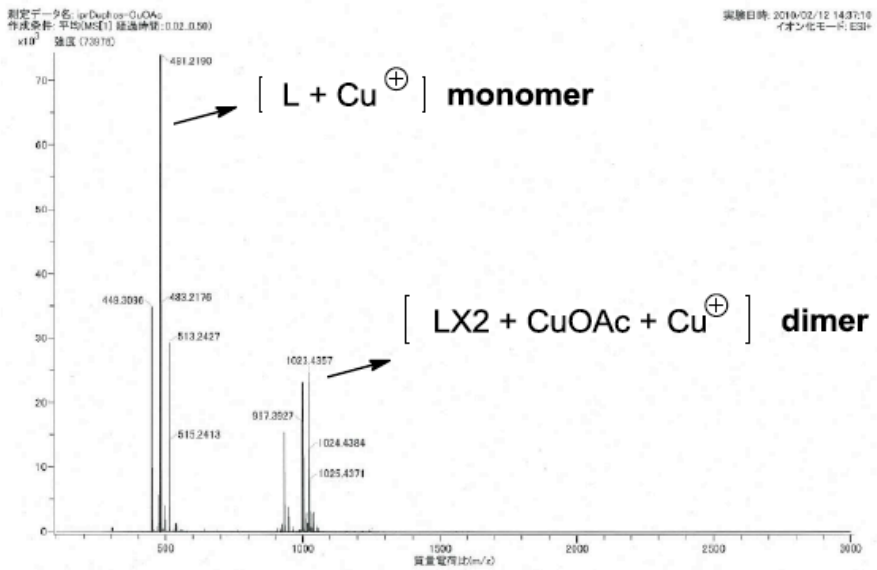
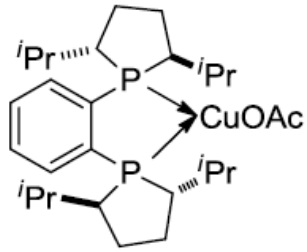
A: CuOAc + ^{i}Pr-DuPHOS (1:1)

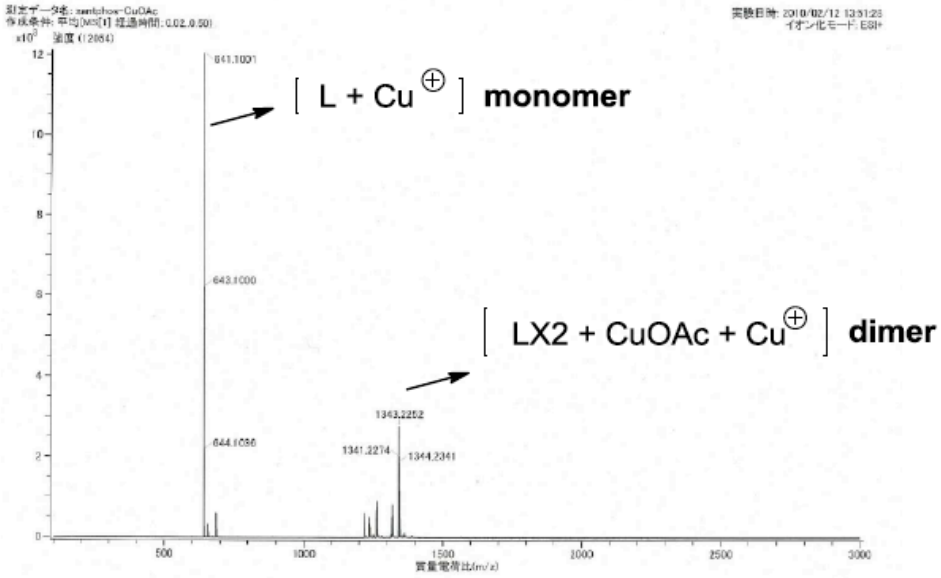


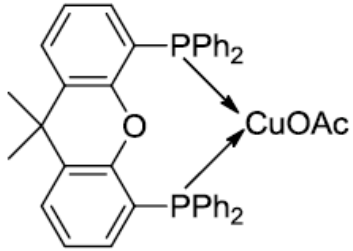


∠ PCuP = 90.2°
(By DFT calculation)

allylation : 4%, 83% ee
propargylation: no reaction

B: CuOAc + Xantphos (1:1)



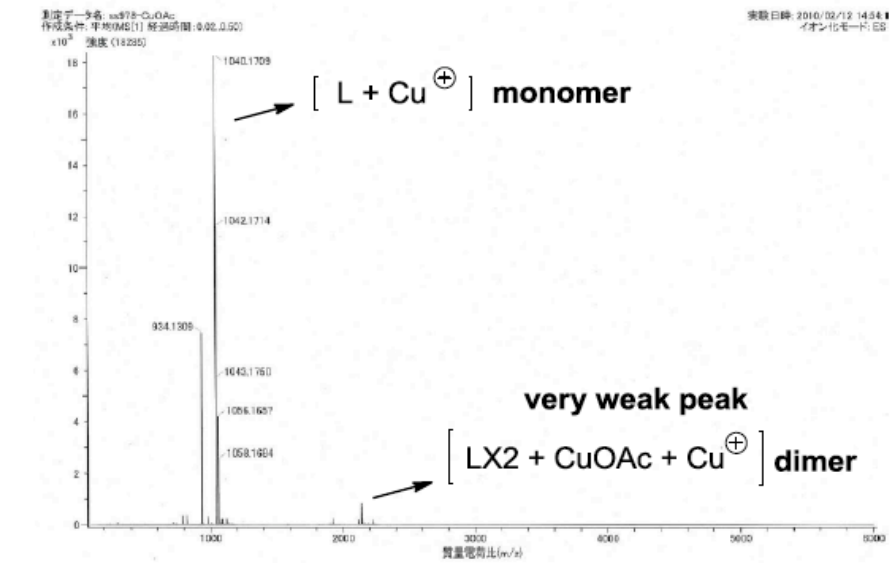


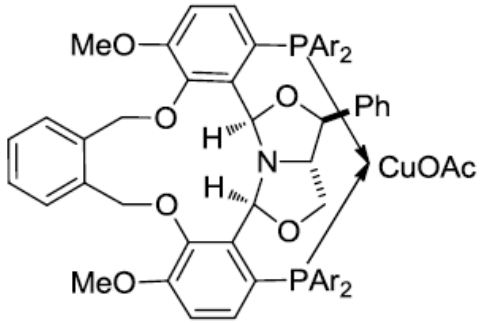
∠ PCuP = 115.2°
(By DFT calculation)

allylation : 2%
propargylation: <2%

Catalyst Activity Rationale

C: CuOAc + **8** (1:1)





8 (Ar = p-F-Ph)

∠ PCuP = 137.8° (By X-ray crystal structure)

∠ PCuP = 134.2° (By DFT calculation)

allylation : 99%, 89% ee
propargylation: 93%, 95% ee

The monomer is the catalytically active species.
The wider bite angle of **8** than ^{i}Pr-DuPHOS and Xantophos, leading to the stablization of the monomeric complex.

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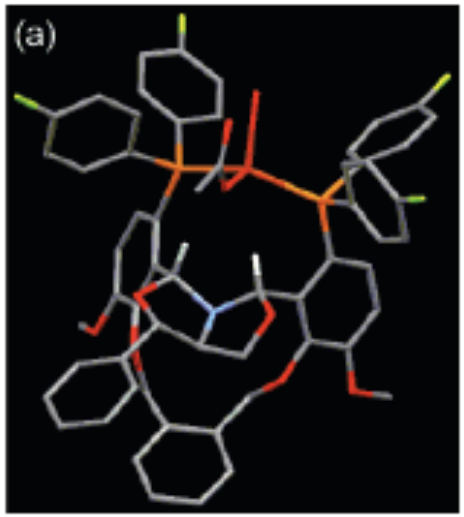
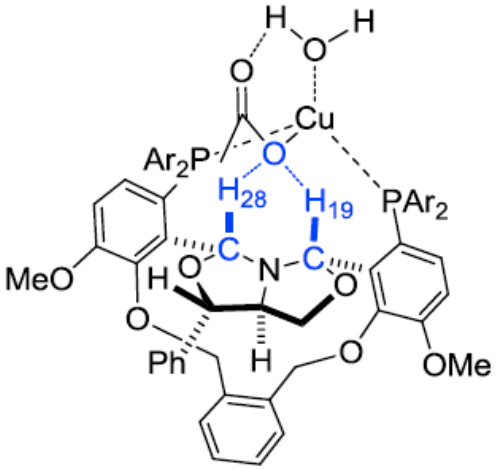
X-ray Crystal Structure





X-ray structure of CuOAc-**8**

H–Bond	H···O (Å)	C···O (Å)	∠CHO (°)	C–H (Å)
typical	≤2.7	3.3–3.8	90–180.0	1.1
C–H_{19}···O (calcd)	2.375	3.298	141.4	1.090
C–H_{19}···O (obsd)	2.538	3.443	150.2	1.001
C–H_{28}···O (calcd)	2.364	3.384	154.1	1.097
C–H_{28}···O (obsd)	2.531	3.486	159.8	1.000

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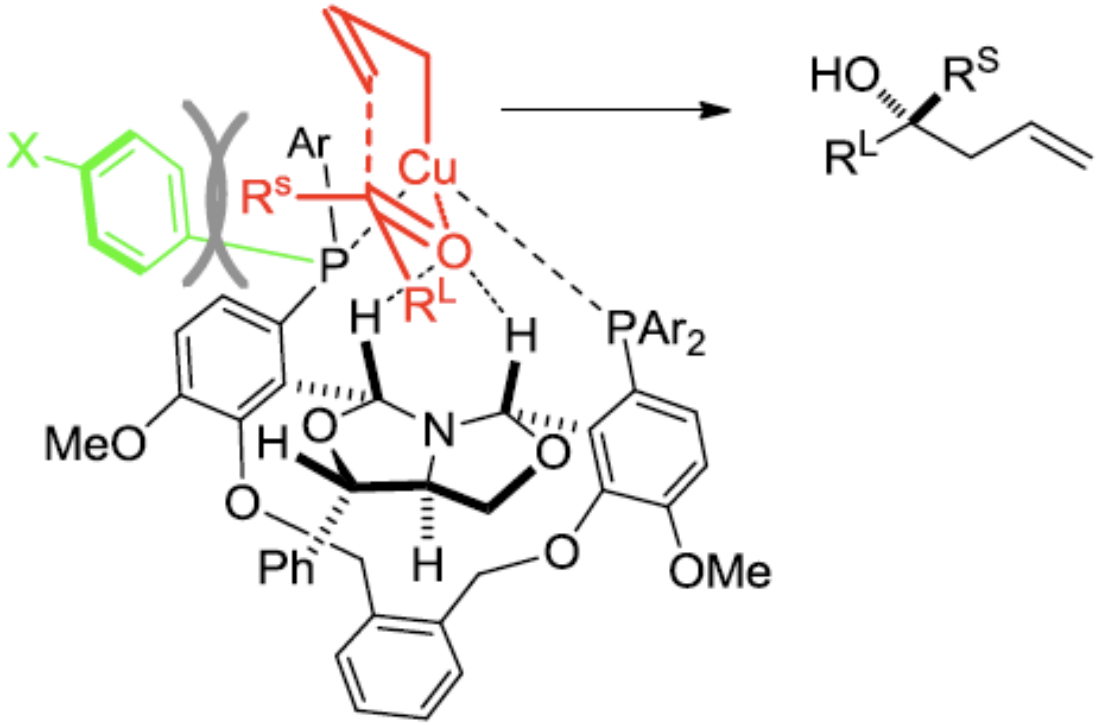
Proposed Transition State



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