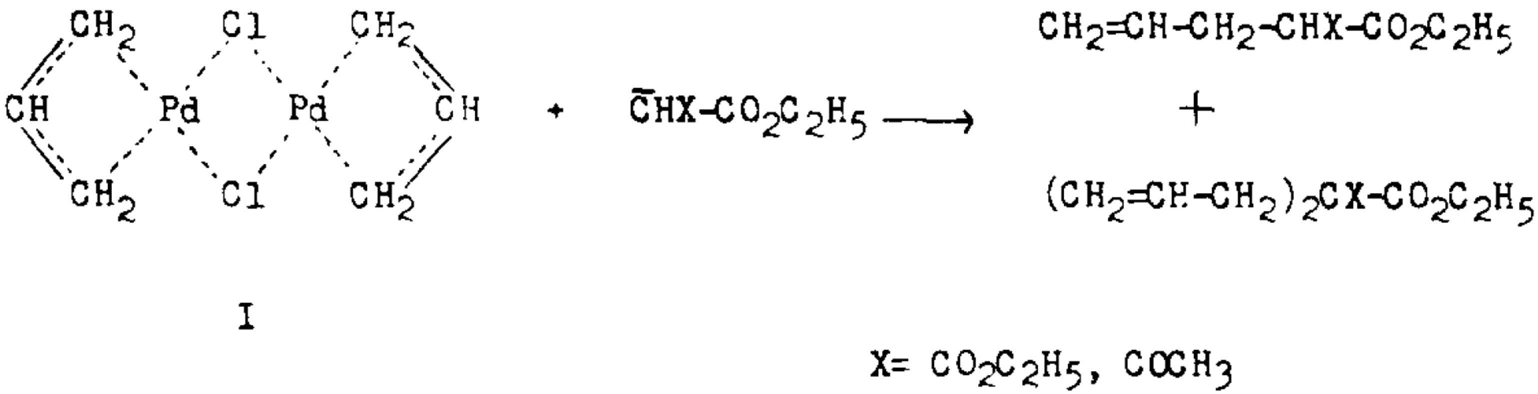
Iridium-Catalyzed Selective Allylic Substitution

2017/5/20 (Sat.)

Literature Seminar

Taiki Fujita (M1)

Introduction



Tsuji, J., *et al. tetrahedron lett.* **1965**, 4387.

Prof. Tsuji found that π-allyl Pd complex reacts with malonate anion.

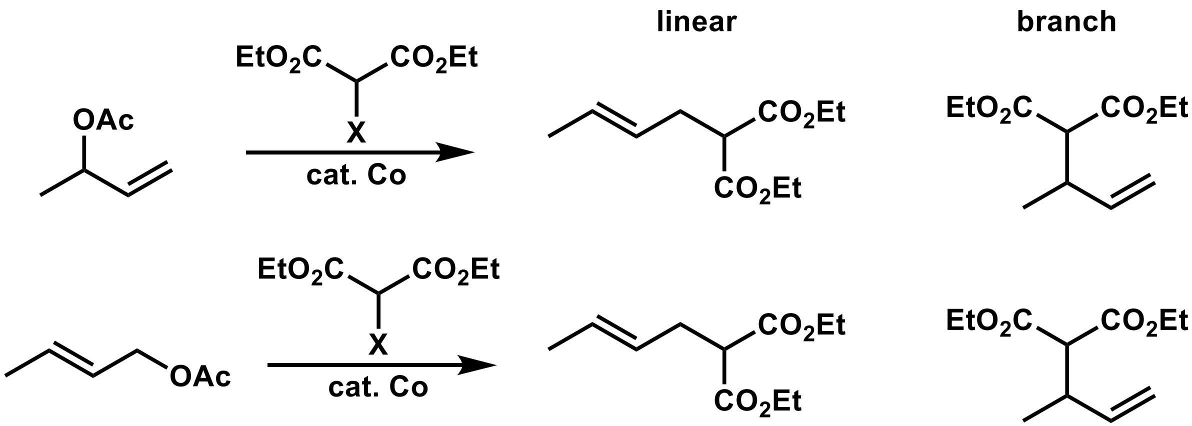
Even today, allylic substitution via π-allyl metal complex is used widely.

allylation → Total synthesis

allylation → Reaction development

Other Metals

Co

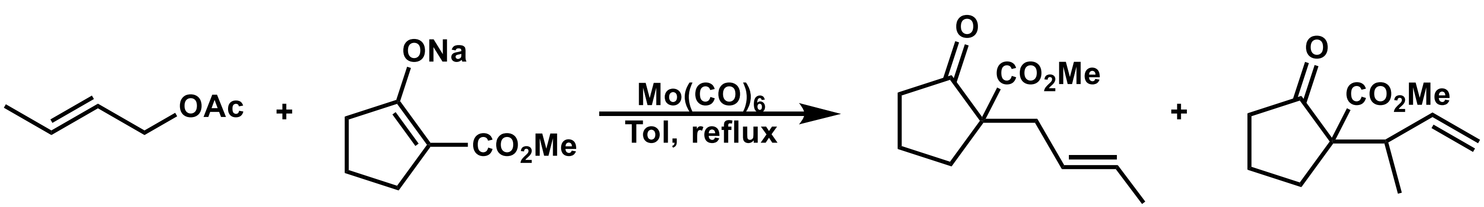


79% conversion
linear/ branch= 9/ 91

90% conversion
linear/ branch= 95/ 5

Roustan, J. L., *et al. tetrahedron lett.* **1979**. 3721.

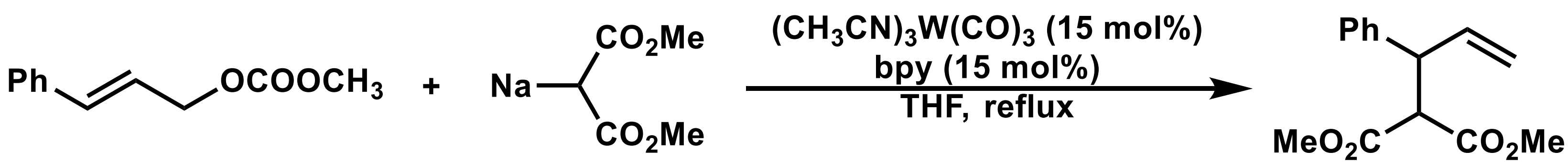
Mo



DME	**1**	**:**	**6**	**84% yield**
$PhCH_3$	**19**	**:**	**1**	**84% yield**

Trost, B. M. *et al. J. Am. Chem. Soc.* **1982**, *104,* 5543.

W

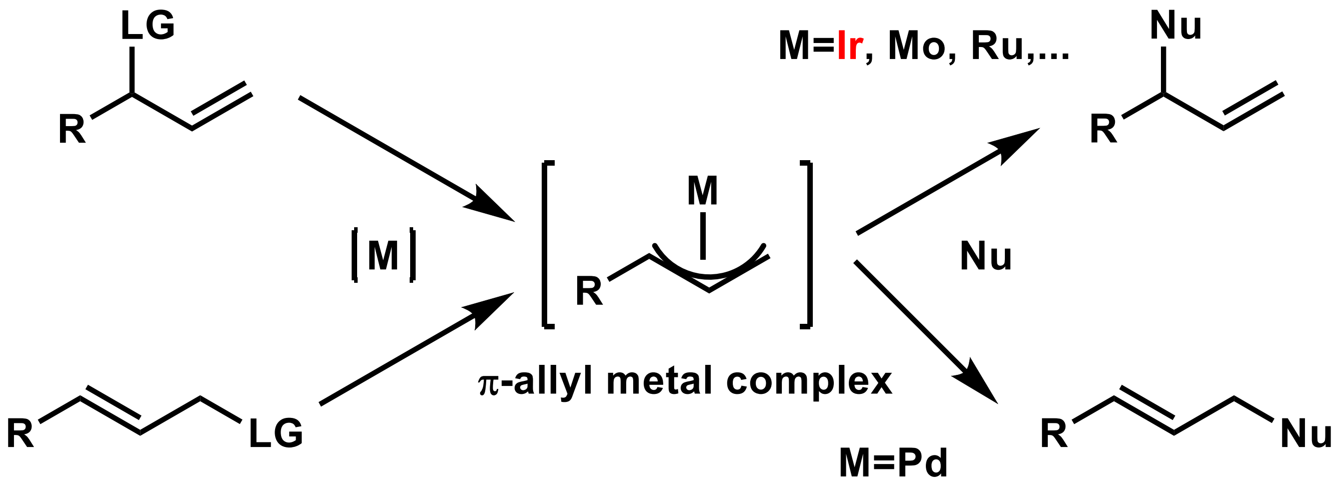


91% yield

Ir, Ru, Rh…..

Trost, B. M. *et al. J. Am. Chem. Soc.* **1983**, *105,* 7757.

Regioselectivity



controlling selectivity

retention or inversion of configuration

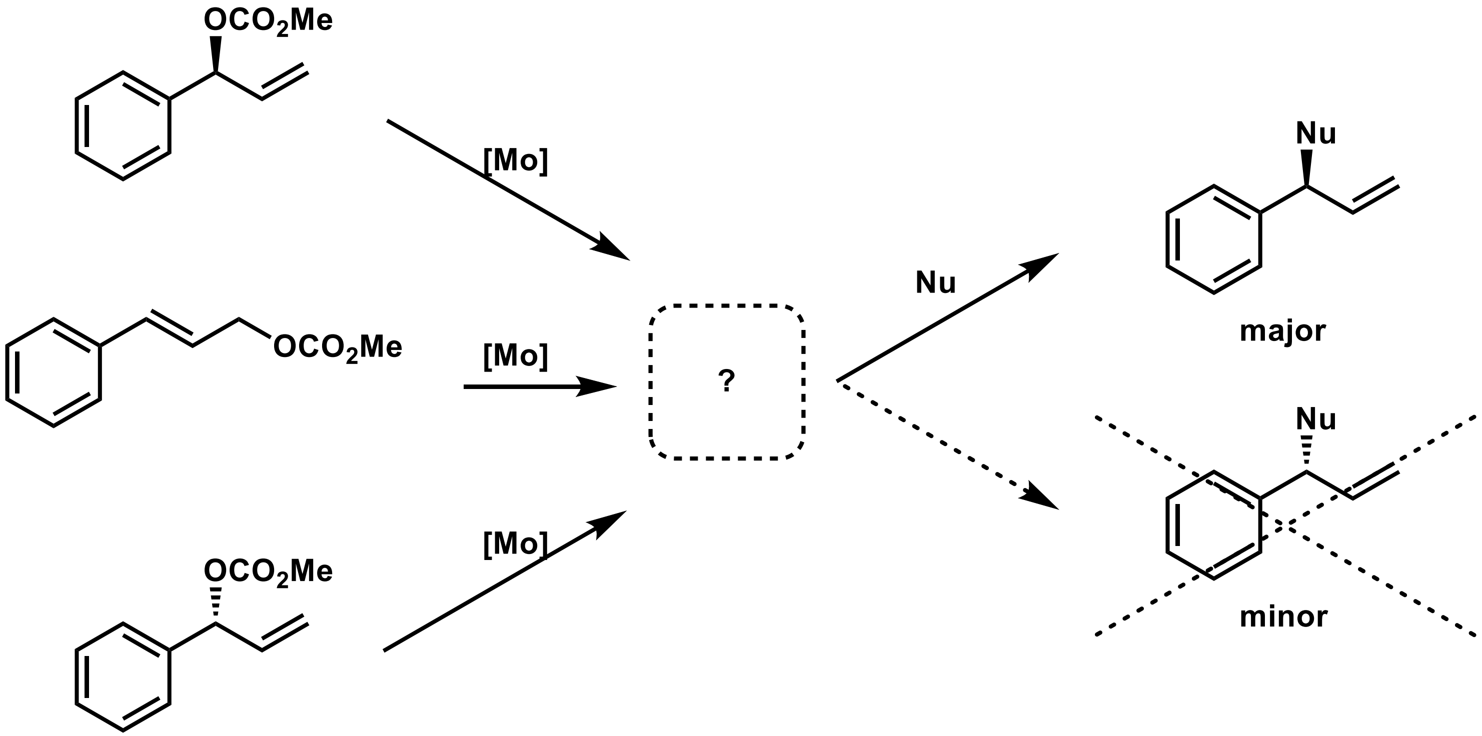
oxidative addition

memory effect

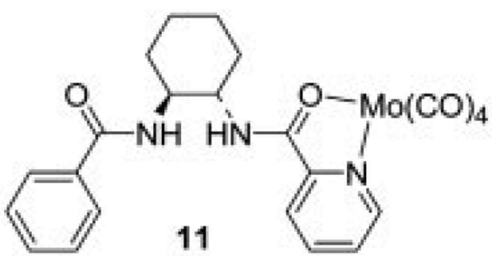
nucleophilic addition

ligand

First Mechanistic Studies

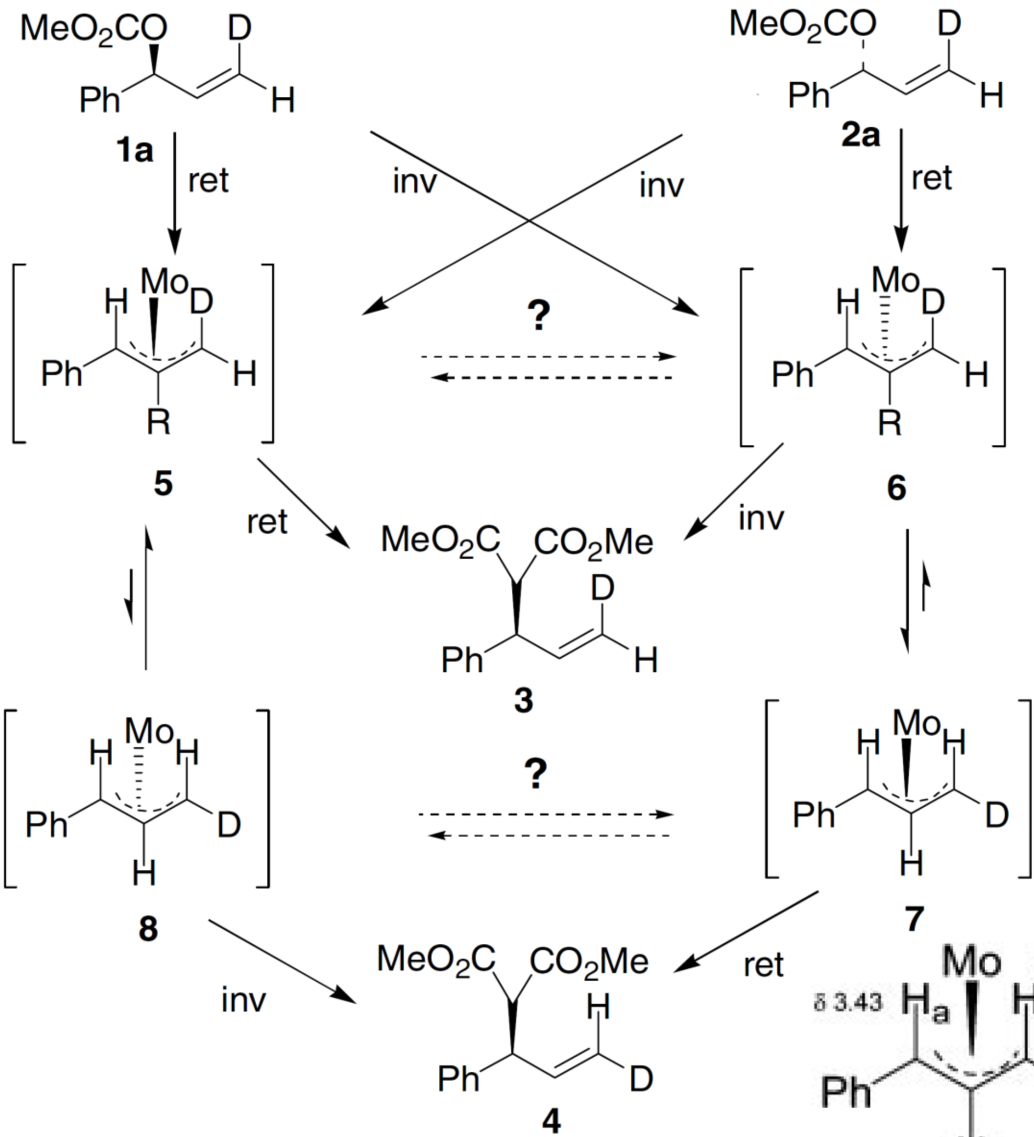


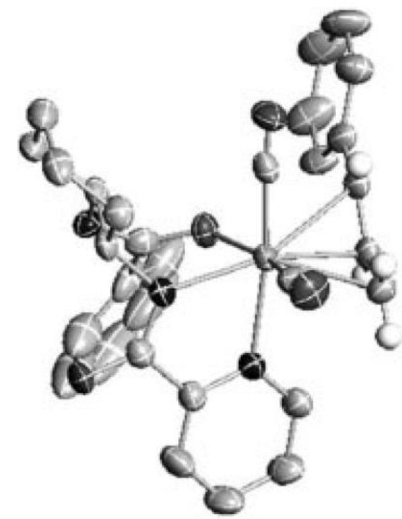
[Mo]=

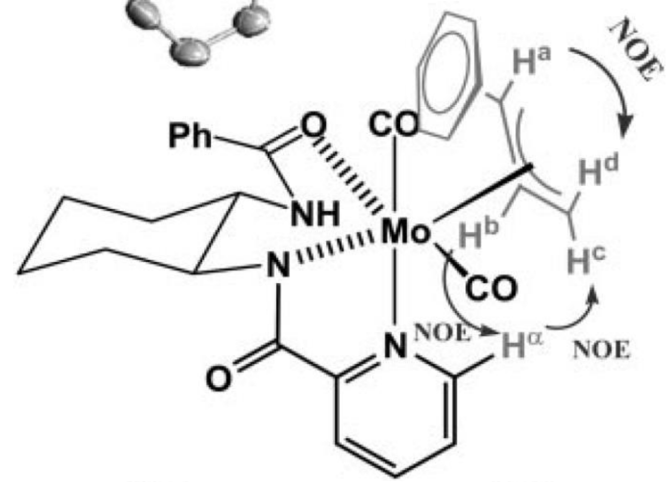


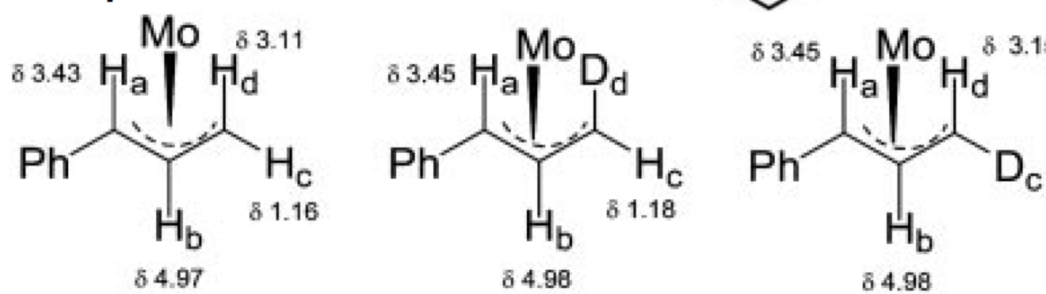
Lloyd-Jones, G. C., Reamer, R. A. *et al. J. Am. Chem. Soc.* **2004**, *126,* 702.
Lloyd-Jones, G. C., Reamer, R. A. *et al. Proc. Natl. Acad. Sci. USA.* **2004**, *101,* 5379.

Deuterated Substrate



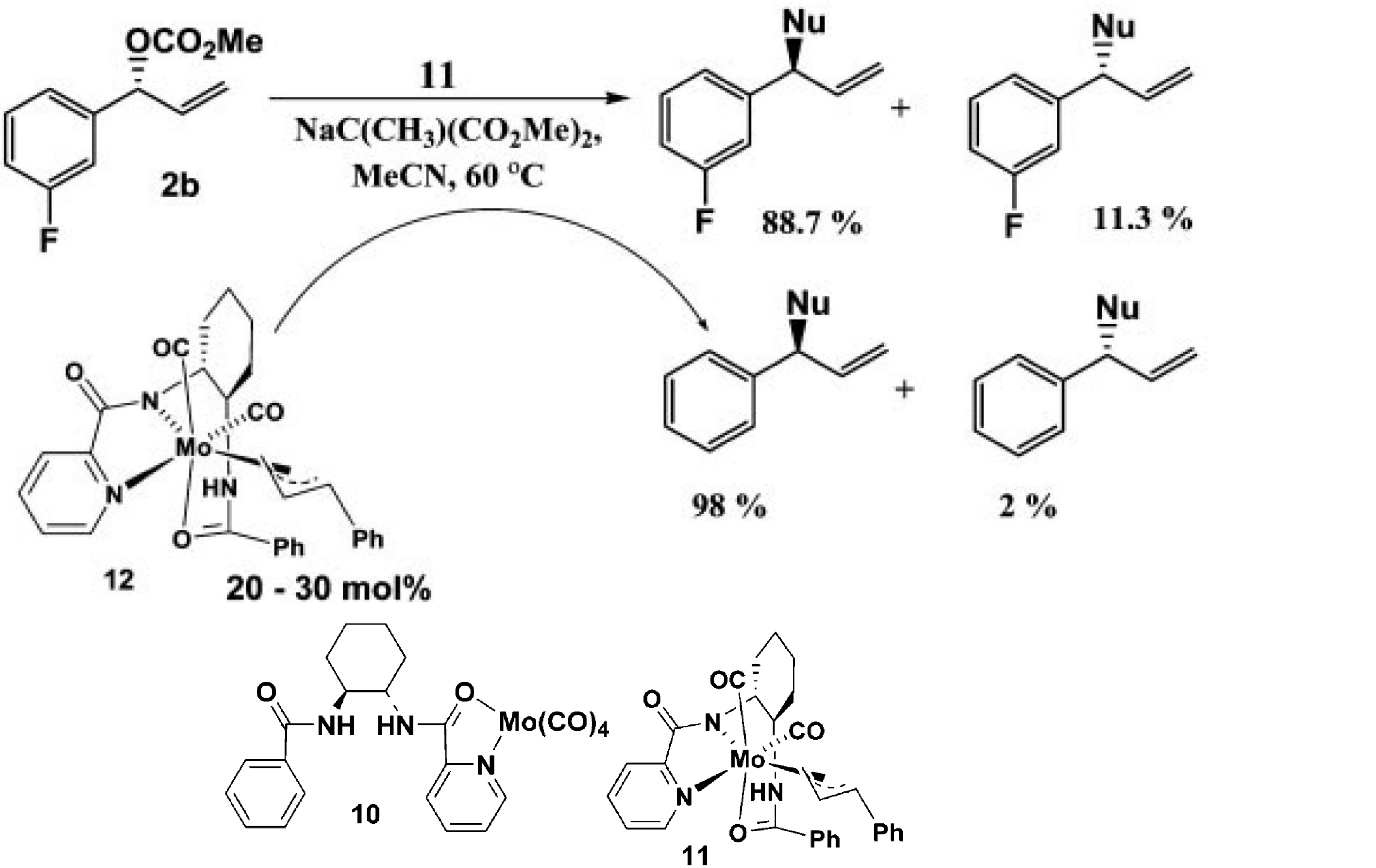






Lloyd-Jones, G. C., Reamer, R. A. *et al. J. Am. Chem. Soc.* **2004**, *126,* 702.
Lloyd-Jones, G. C., Reamer, R. A. *et al. Proc. Natl. Acad. Sci. USA.* **2004**, *101,* 5379.

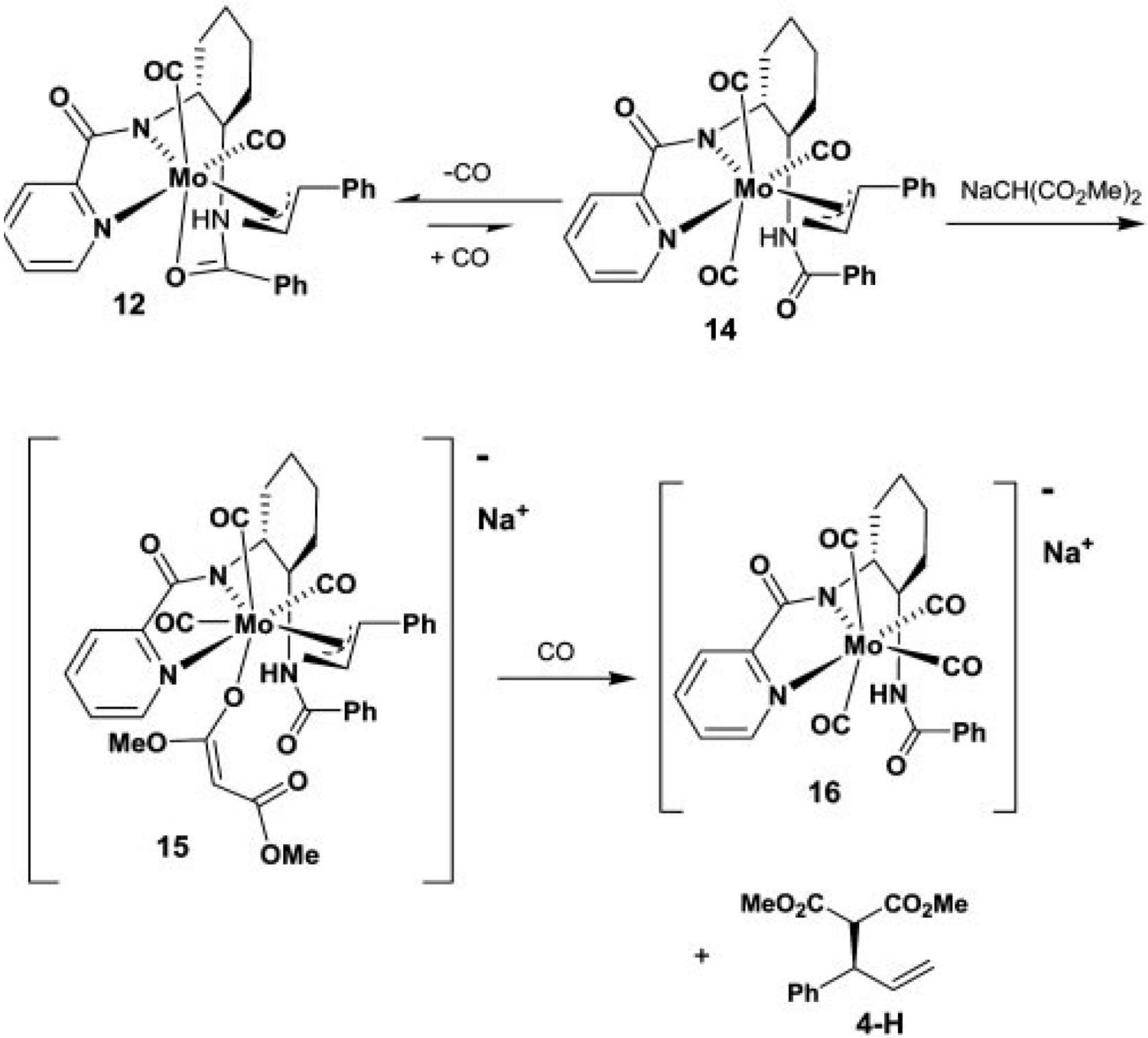
Competition Experiment



Lloyd-Jones, G. C., Reamer, R. A. *et al. J. Am. Chem. Soc.* **2004**, *126,* 702.

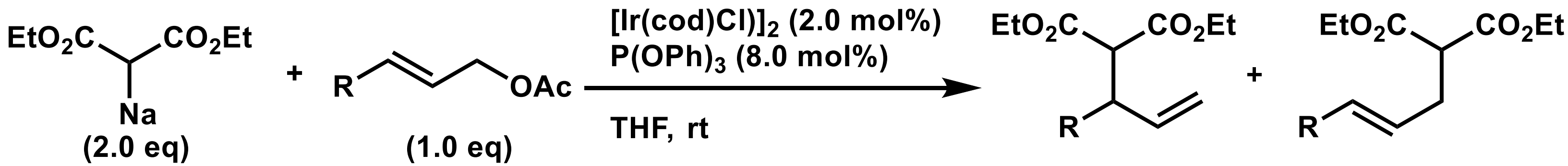
Lloyd-Jones, G. C., Reamer, R. A. *et al. Proc. Natl. Acad. Sci. USA.* **2004**, *101,* 5379.

Nucleophilic Attack with Retention of Conversion



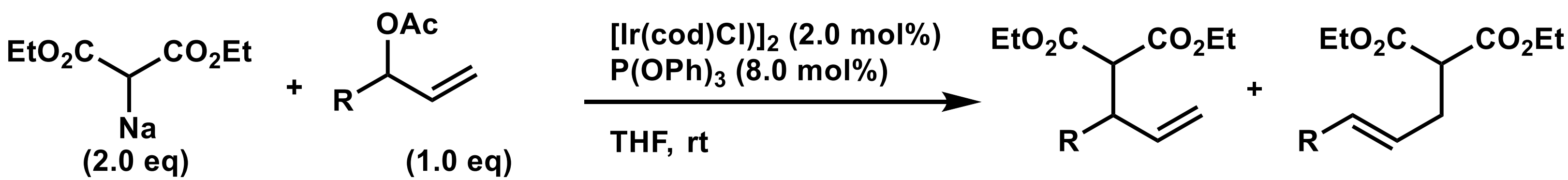
Lloyd-Jones, G. C., Reamer, R. A. *et al. Proc. Natl. Acad. Sci. USA.* ***2004***, *101,* 5379.

Introduction of Iridium



R= ^{n}Pr: 89% yield, branch/ linear= 96/ 4

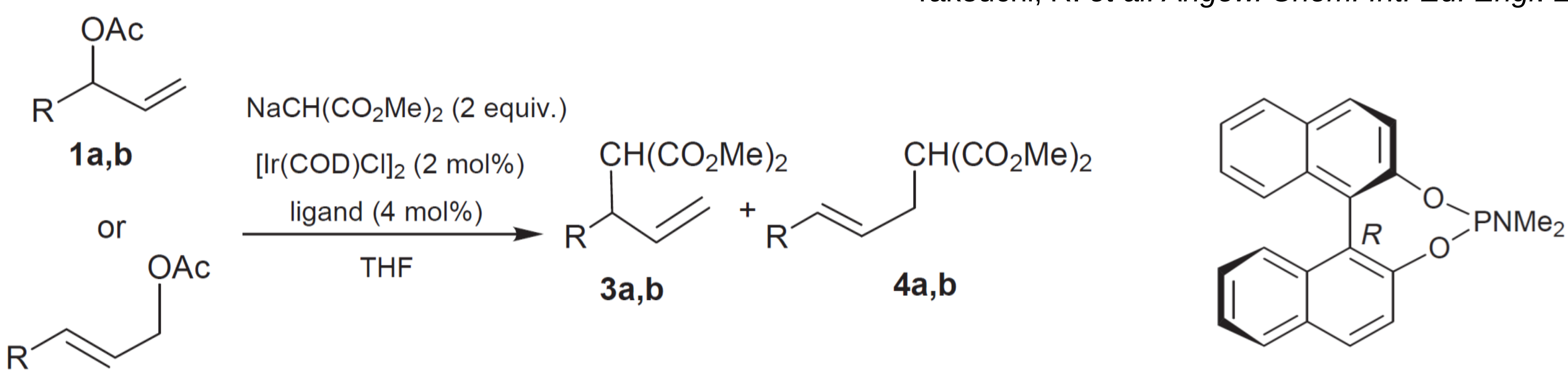
R= Ph: 98% yield, branch/ linear= 99/ 1



R= ^{n}Pr: 86% yield, branch/ linear= 95/ 4

R= Ph: 99% yield, branch/ linear= 99/ 1

Takeuchi, R. *et al. Angew. Chem. Int. Ed. Engl*. **1997**, *36,* 263.



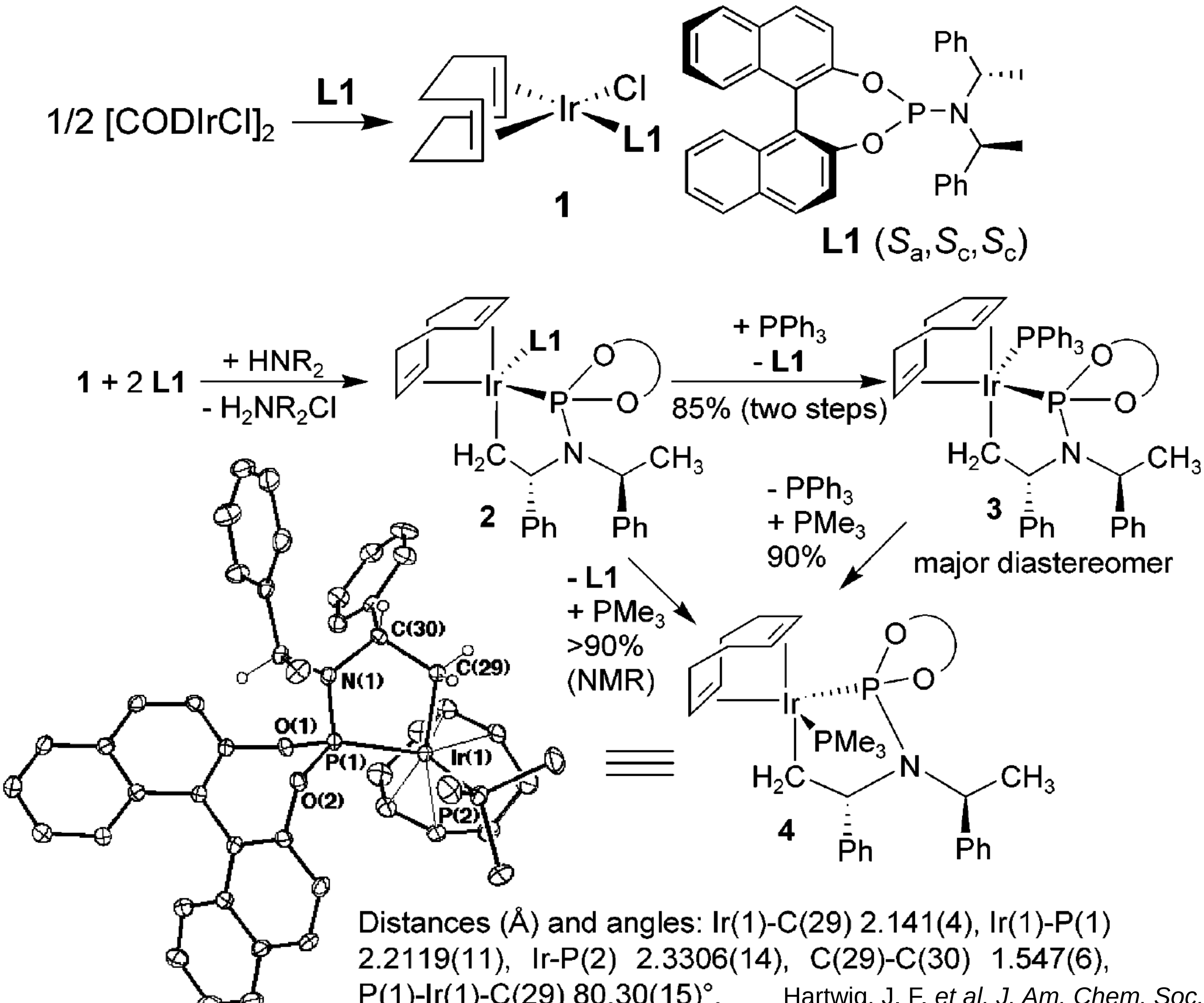
2a,b

a R = CH_2CH_2Ph **b** R = Ph

rac-1a 92% yield, branch/ linear= 98/2, 69% ee (*R*)
rac-2a 54% yield, branch/ linear= 95/5, 43% ee (*R*)

Helmchen, G. *et al. Chem. Commun.* **1999**, 741.

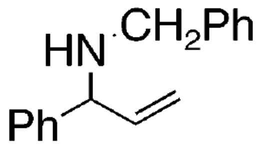
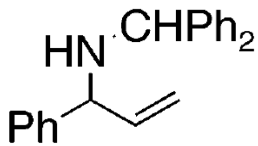
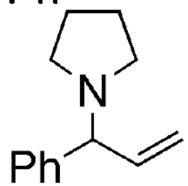
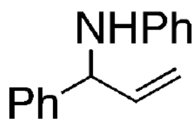
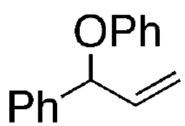
Iridacycle

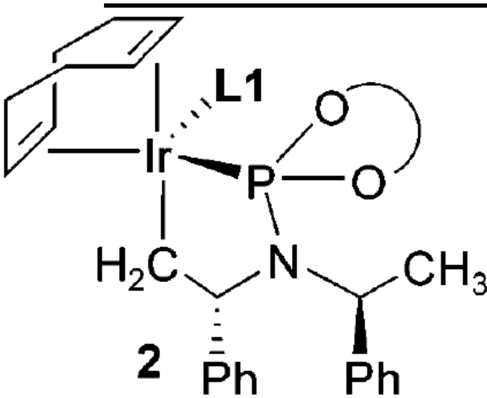


Distances (Å) and angles: Ir(1)-C(29) 2.141(4), Ir(1)-P(1) 2.2119(11), Ir-P(2) 2.3306(14), C(29)-C(30) 1.547(6), P(1)-Ir(1)-C(29) 80.30(15)°.

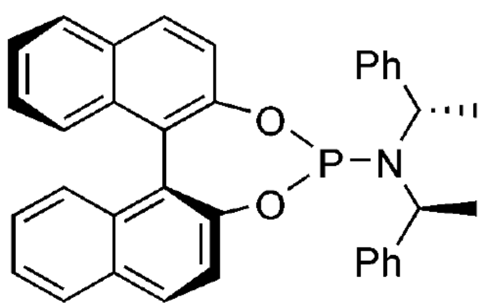
Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2003**, *125*, 14273.

Iridacycle

Entry	Product	Catalyst	Time (h)	b / l	yield[a]	ee
1		1% **2** + $[Ir(COD)Cl]_2$	2	98/2	81%	97%
2		2% **L1** + $[Ir(COD)Cl]_2$	12	98/2	84%	95%
3		1% **2** + $[Ir(COD)Cl]_2$	10	97/3	85%	98%
4		2% **L1** + $[Ir(COD)Cl]_2$	10	–	11%[b]	–
5		0.1% **2** + $[Ir(COD)Cl]_2$	10	99/1	81%	98%
6		0.2% **L1** + $[Ir(COD)Cl]_2$	16	99/1	64%	97%
7		1% **2** + $[Ir(COD)Cl]_2$	2	99/1	81%	97%
8		2% **L1** + $[Ir(COD)Cl]_2$	24	–	<1%	–
9[c]		1% **2** + $[Ir(COD)Cl]_2$	2	95/5	75%	94%
10[c]		2% **L1** + $[Ir(COD)Cl]_2$	35	99/1	76%	94%



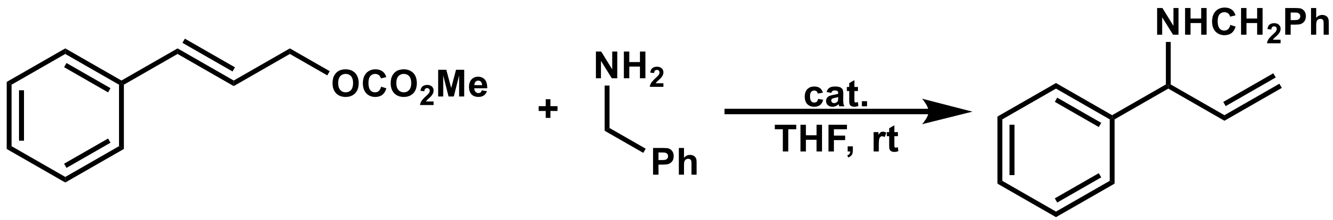
2

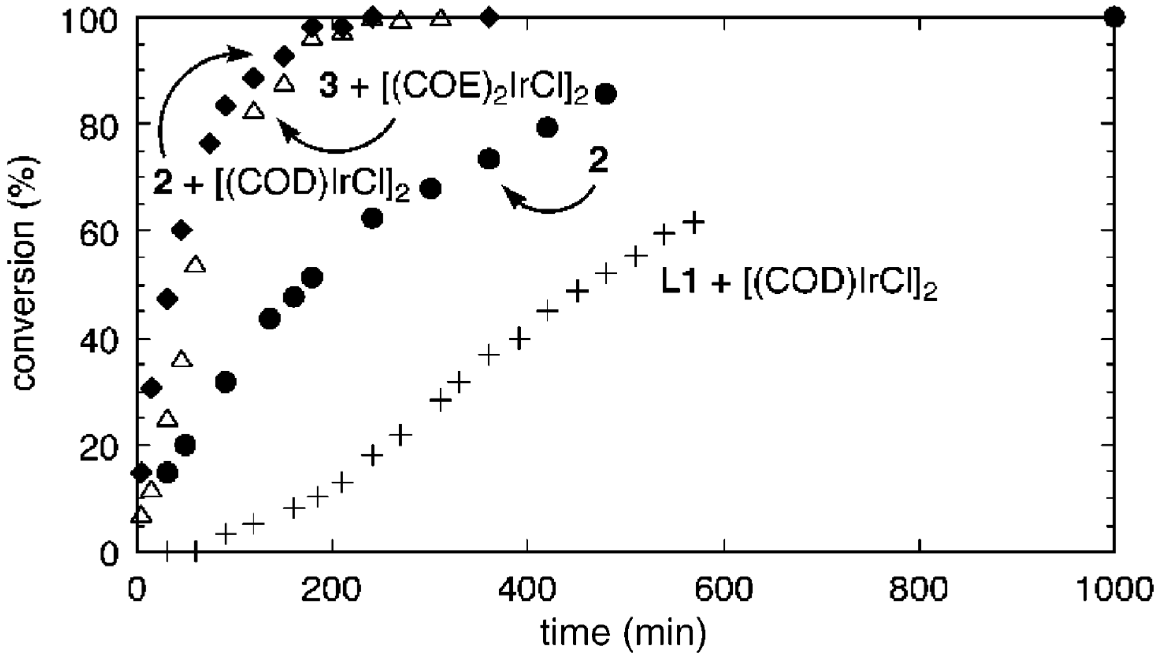


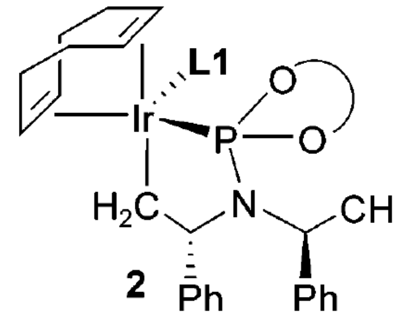
L1 (S_a,S_c,S_c)

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2003**, *125*, 14273.

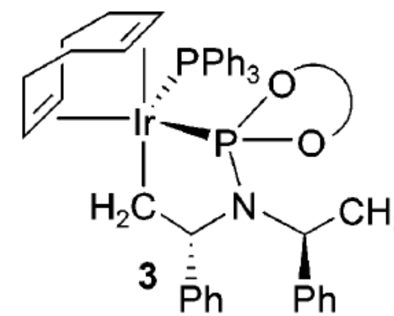
Reactivity



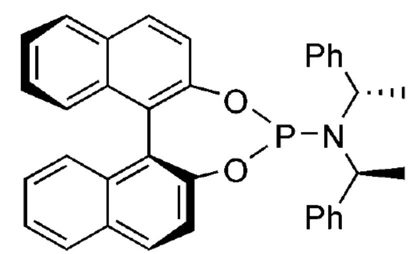




2



3

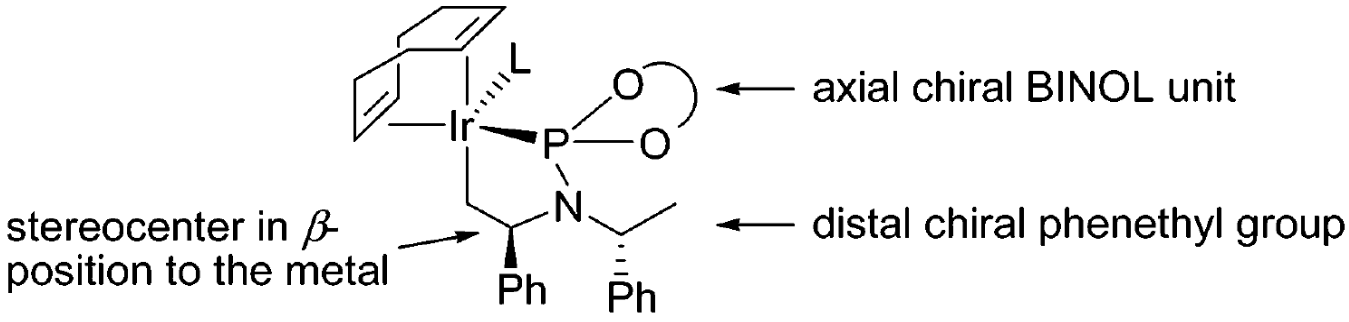


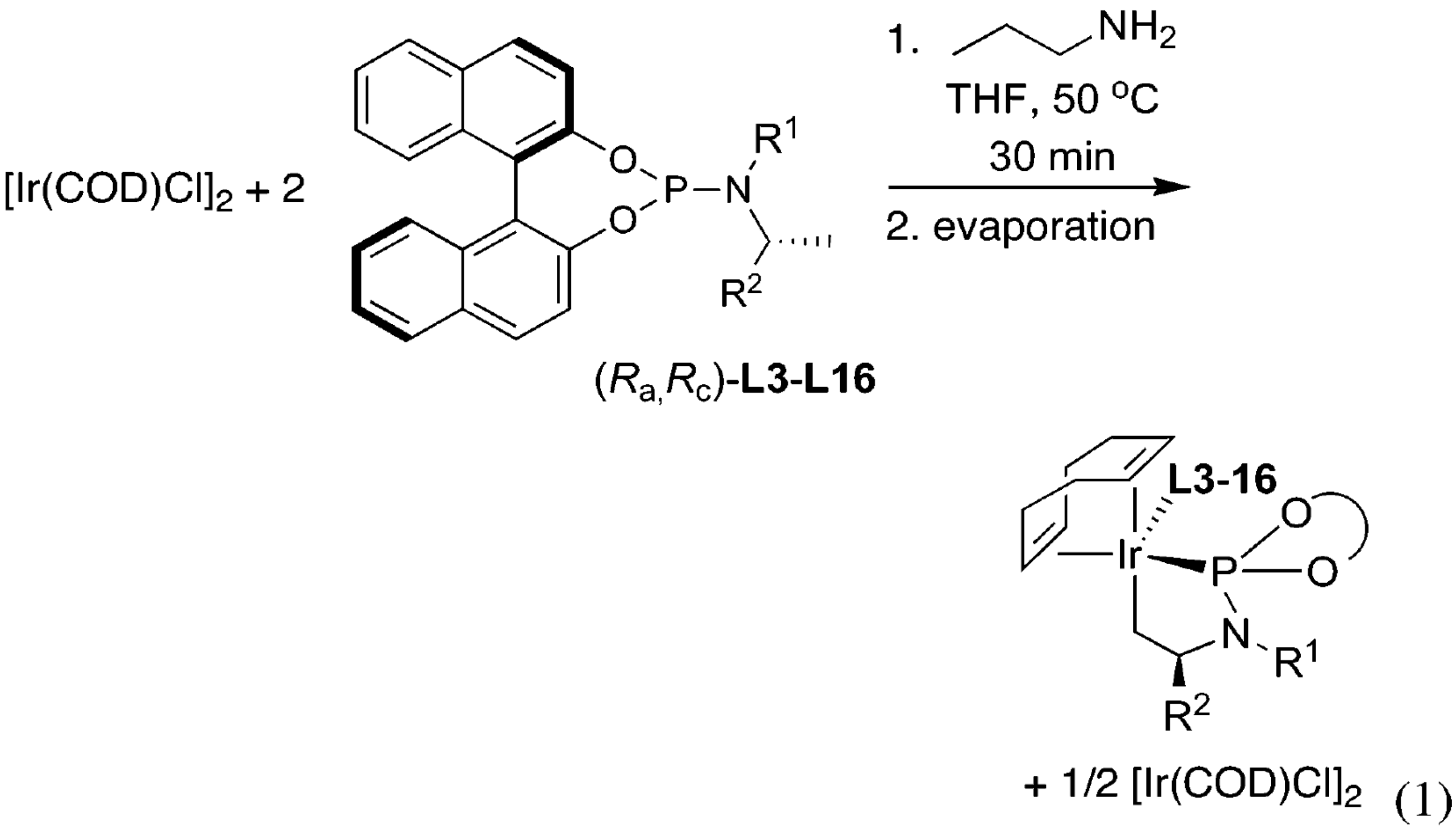
L1 (S_a,S_c,S_c)

Figure 1. A comparison of the reactions of a series of iridium-phosphoramidite catalysts for the amination of cinnamyl carbonate with benzylamine in THF solvent at room temperature. Catalysts: ◆, 1 mol % **2** + 0.5 mol % [Ir(COD)Cl]$_2$; △, 1 mol % **3** + 0.5 mol % [Ir(COE)$_2$Cl]$_2$; ●, 1 mol % **2**; +, 2 mol % **L1** + 1 mol % [Ir(COD)Cl]$_2$. Reactions catalyzed by **2** and **3** occurred in 97% ee, and the reaction catalyzed by **L1** and [Ir(COD)Cl]$_2$ occurred in 95% ee.

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2003**, *125*, 14273.

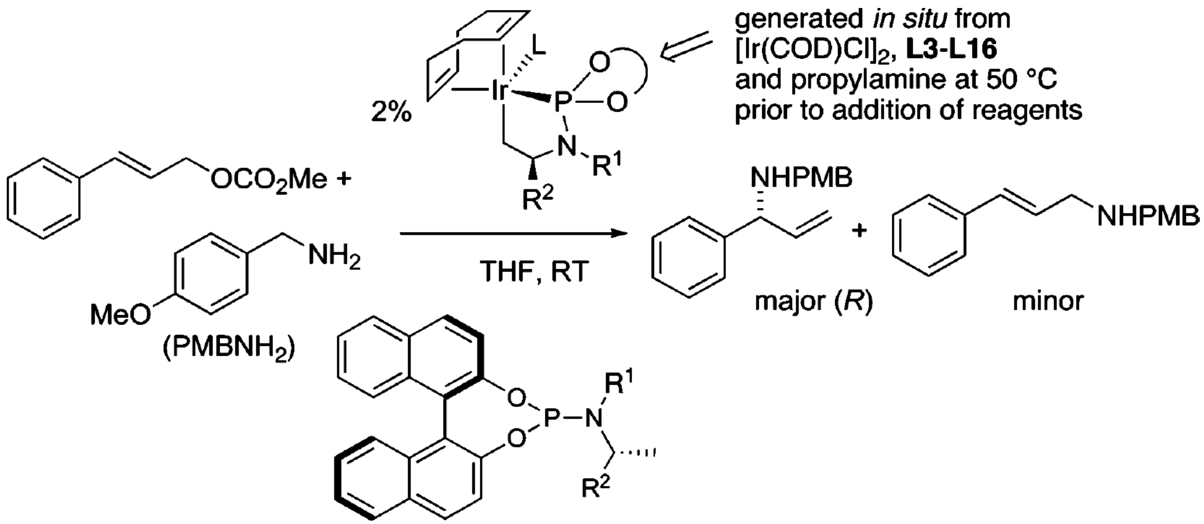
Which position is critical for enantio selectivity



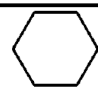
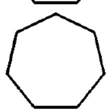
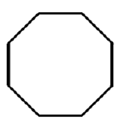
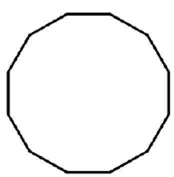
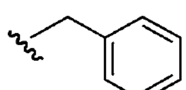


Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2005**, *127,* 15509.

Achiral Alkyl Group



(R_a,R_c)-**L3-L16**

entry	R^1	R^2	ligand	ee[b] (%)	b/l[c]	reaction time (h)[d]
1		Ph	**L3**	78	95:5	4
2		Ph	**L4**	91	95:5	3
3		Ph	**L5**	94	96:4	4
4		Ph	**L6**	96	95:5	1.5
5		Ph	**L7**	91	94:6	24

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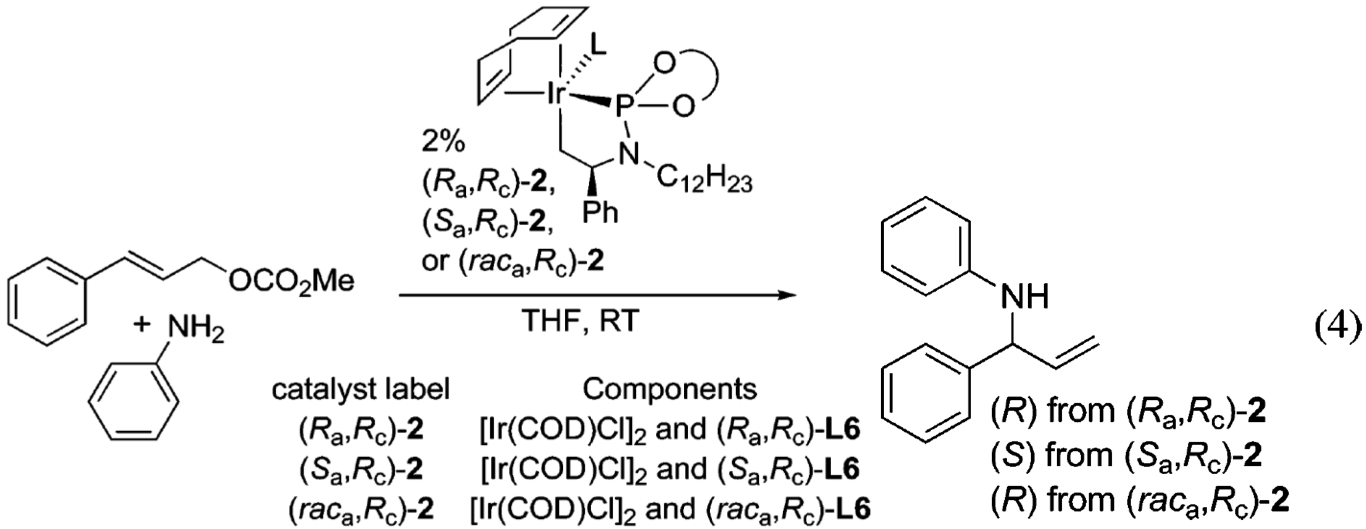
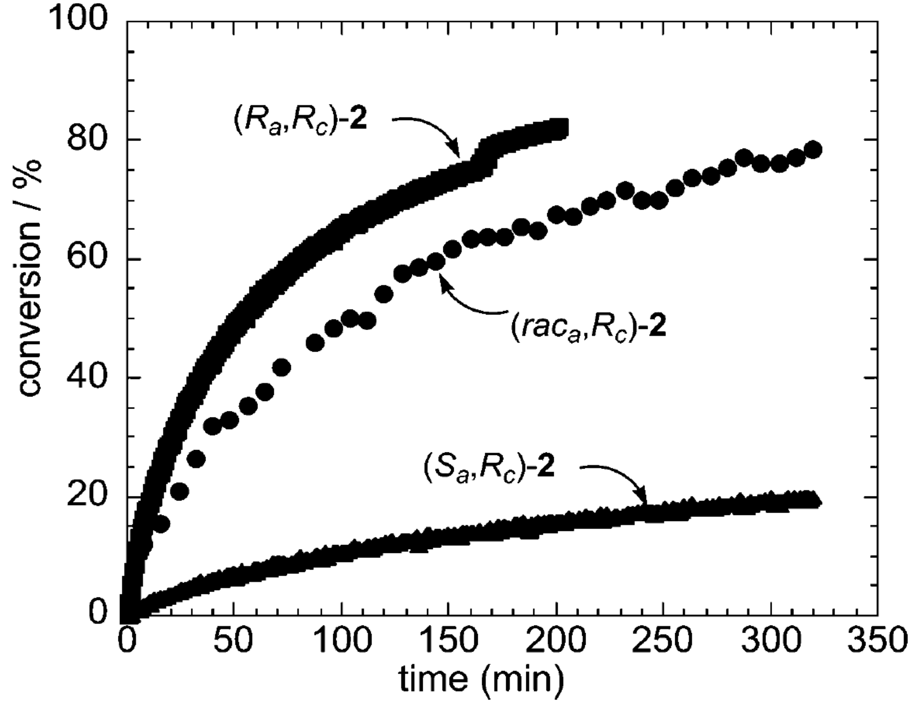
Axial Chirality



catalyst label	Components
(R_a,R_c)-**2**	$[Ir(COD)Cl]_2$ and (R_a,R_c)-**L6**
(S_a,R_c)-**2**	$[Ir(COD)Cl]_2$ and (S_a,R_c)-**L6**
(rac_a,R_c)-**2**	$[Ir(COD)Cl]_2$ and (rac_a,R_c)-**L6**



(R_a, R_c) 96% ee
(rac_a, R_c) 90% ee

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The Rate of Generating Iridacycle

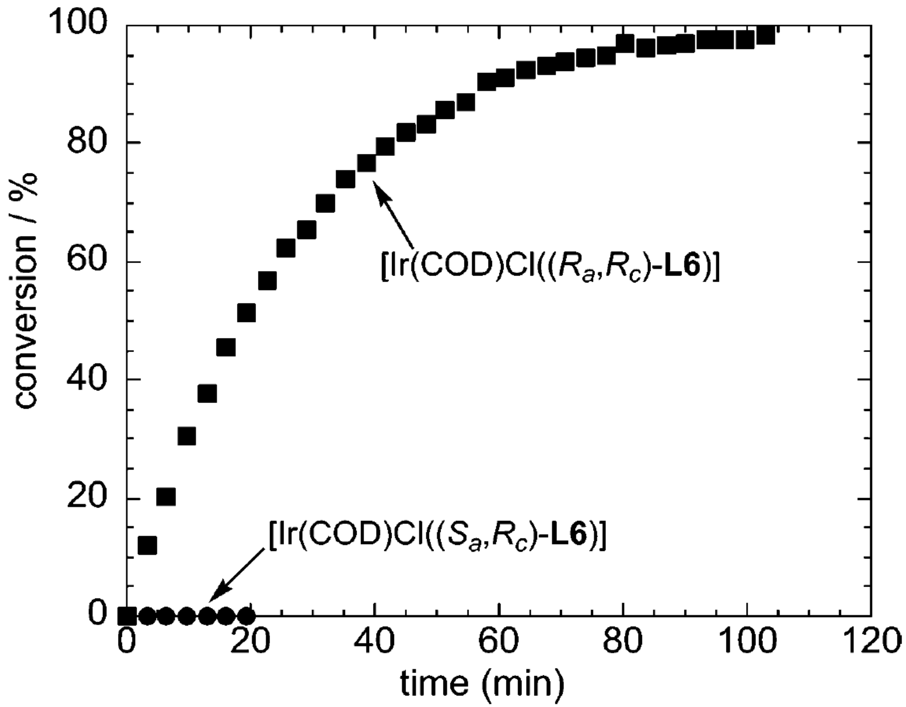
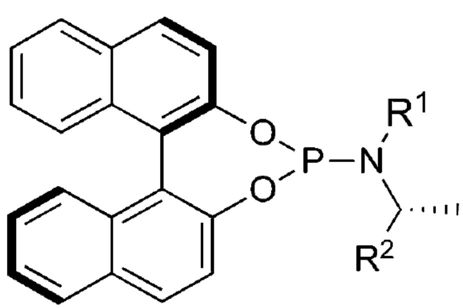


Figure 5. Relative rates of cyclometalation of [Ir(COD)Cl((R_a,R_c)-**L6**)] and [Ir(COD)Cl((S_a,R_c)-**L6**)] in the presence of propylamine at room temperature monitored by ^{31}P NMR spectroscopy.



(R_a,R_c) -**L6**

R^1=$C_{12}H_{23}$
R^2=Ph

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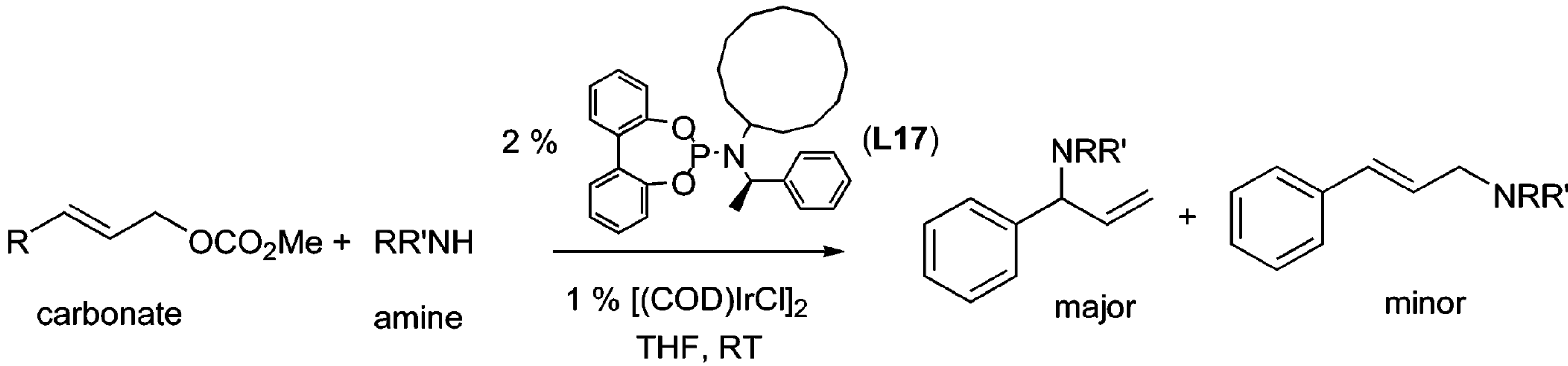
Biphenyl Type



entry	carbonate	amine	yield[b] (%)	ee (%)	b/l
1	Ph OCO_2Me	NH_2	86	94 (*R*)	98:2
2	Ph OCO_2Me	S NH_2	83	94	97:3
3	Ph OCO_2Me	O NH_2	84	93	99:1
4	Ph OCO_2Me	$HNEt_2$	72	97	98:2
5	Ph OCO_2Me	O NH	85	95	98:2
6	Ph OCO_2Me	NH_2	93	94	99:1
7	Ph OCO_2Me	MeS NH_2	81	94	99:1
8	OCO_2Me	NH_2	75	95	95:5
9	OCO_2Me	NH_2	72	94	99:1

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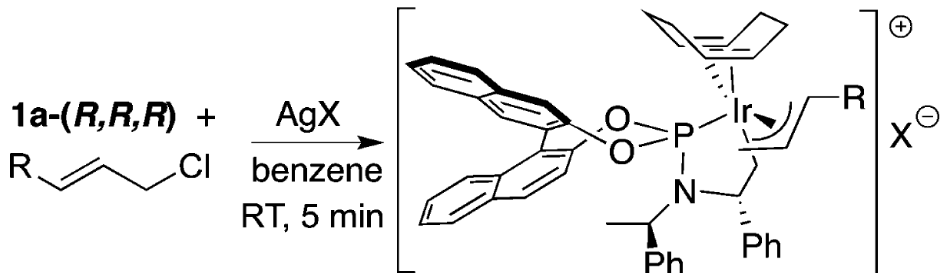
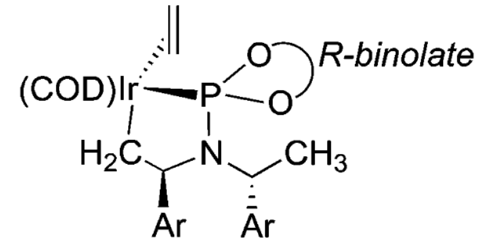
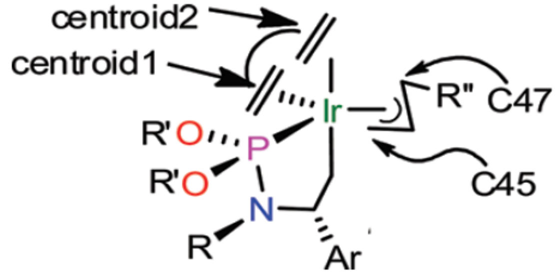
The Length of Iridium-Carbon



2a: R=H
X=⁻OTf
2b: R=Me
X=SbF_6^-



Ar = Ph: **1a-(*R,R,R*)**
Ar = 2-(OMe)Ph: **1b-(*R,R,R*)**

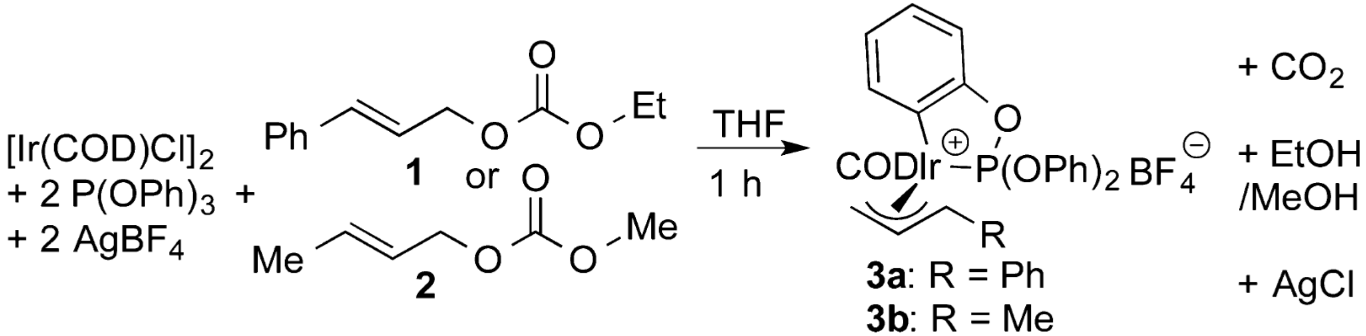


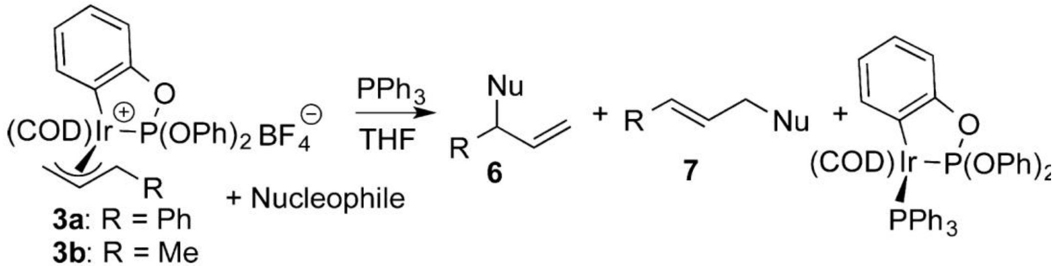
2a: R" = H, Ar = Ph
2b: R" = Me, Ar = Ph
2c: R" = Ph, Ar = Ph
2d: R" = 2,6-difluorophenyl, Ar = Ph
2e: R" = 2-bromophenyl, Ar = Ph
3a: R" = Me, Ar = 2-(OMe)-C_6H_4

	2a	2b	2c	2d
distances, Å				
Ir−P	2.2685(6)	2.280(3)	2.2582(14)	2.2611(18)
Ir−C45	2.204(3)	2.240(10)	2.190(5)	2.191(6)
Ir−C47	2.274(3)	2.377(11)	2.461(5)	2.460(7)
Ir−C21	2.125(3)	2.114(15)	2.120(5)	2.111(6)
Ir−cent1	2.099	2.097	2.099	2.104
Ir−cent2	2.244	2.215	2.263	2.258
C45−C46	1.407(4)	1.414(16)	1.409(7)	1.395(9)
C46−C47	1.405(4)	1.39(2)	1.387(7)	1.368(9)

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2012**, *134*, 8136.

Branch Selectivity with Phosphite Ligand



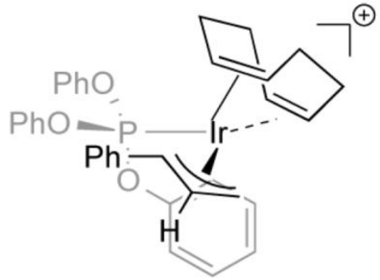


perfect selectivity

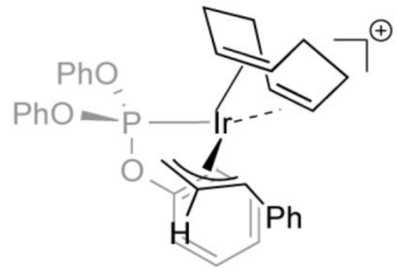
	allyliridium complex	nucleophile	solvent	**6**:**7**	yield (%)
1	**3a**	$NaCH(COOMe)_2$	THF	99:1	100
2	**3a**	$NaCMe(COOMe)_2$	THF	97:3	96
3	**3a**	$NaCH(COOMe)_2$	EtOH	95:5	70
4	**3a**	KOPh	THF	94:6	100
5	**3a**	$OctylNH_2$	THF	97:3	100
6	**3a**	$OctylNH_2$	EtOH	99:1	100
7	**3a**	$PhNH_2$/TEA	THF	97:3	60
8	**3b**	$NaCH(COOMe)_2$	THF	99:1	80
9	**3b**	$NaCMe(COOMe)_2$	THF	99:1	96
10	**3b**	KOPh	THF	99:1	70
11	**3b**	$OctylNH_2$	THF	99:1	70

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2015**, *137*, 14968.

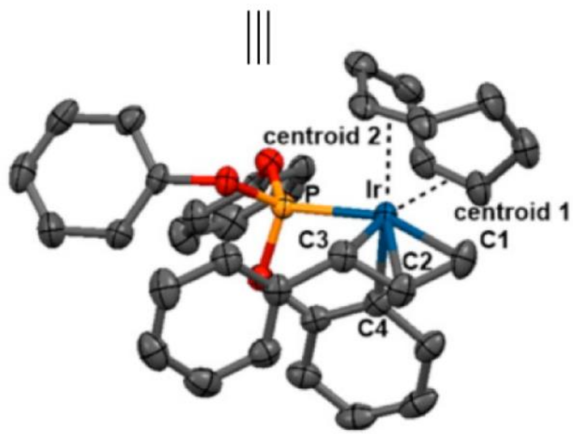
The Length of Iridium-Carbon

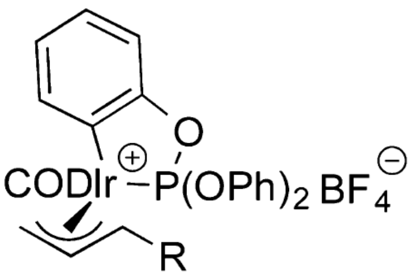


a: major isomer



a: minor isomer





3a: R = Ph

distances (Å)		angles (deg)			
Ir–P	2.256	P–Ir–C3	92.2	cent2–Ir–C1	94.1
Ir–C1	2.285	P–Ir–cent1	104.1	cent2–Ir–cent1	77.7
Ir–C2	2.220	cent1–Ir–C1	99.1	C4–Ir–P	78.0
Ir–C3	2.281	C1–Ir–C3	65.5	C4–Ir–cent1	90.3
Ir–C4	2.092	cent2–Ir–P	97.7	C4–Ir–C1	93.3
Ir–cent1	2.239	cent2–Ir–C3	91.5	C4–Ir–C3	97.3
Ir–cent2	2.356				

same length…

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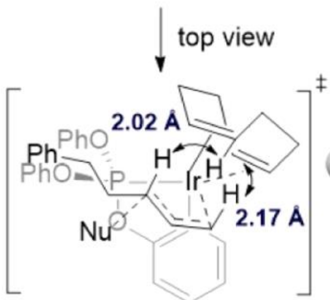
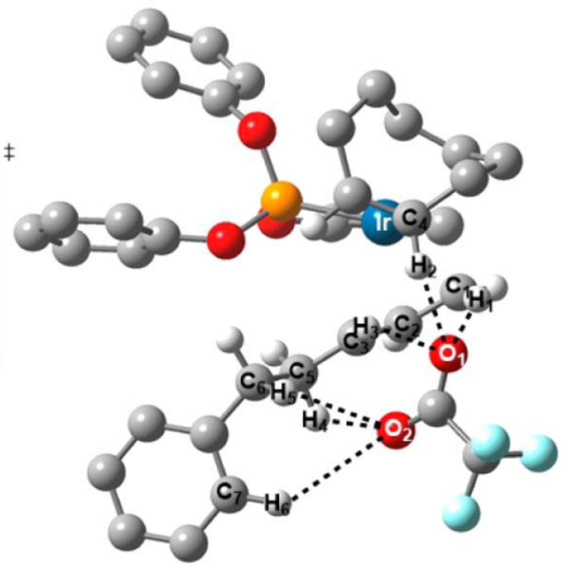
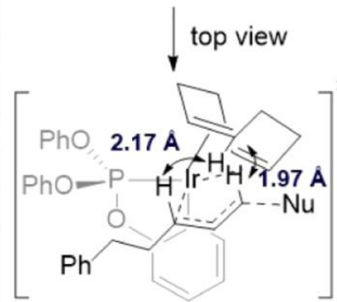
NBO Calculation



TS-branched-major

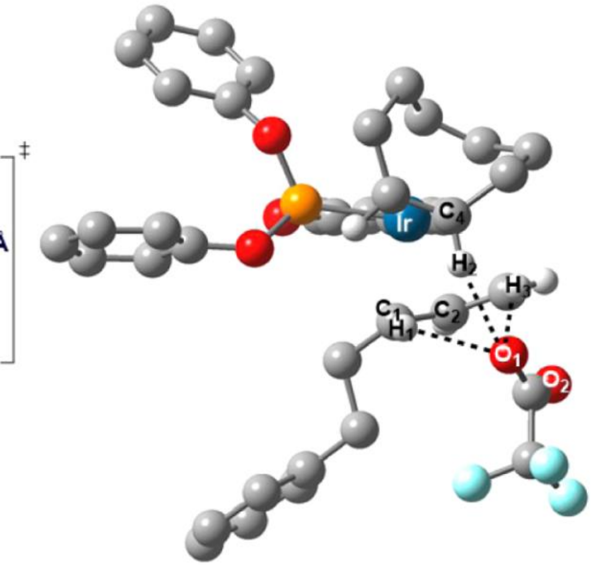
$\Delta\Delta G^{\ddagger}_{THF\ 298\ K}$ 0.0
($\Delta\Delta G^{\ddagger}_{gas\ 298\ K}$) (0.0)
[$\Delta\Delta H^{\ddagger}_{gas\ 298\ K}$] [0.0]
in kcal/mol





TS-linear-major

4.5
(5.0)
[4.9]

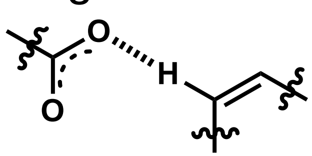


C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O) (in Å)	d(O–H) (in Å)	∠(C–H–O)
C3–H3···O1	2.25	3.10	2.27	132.4°
C1–H1···O1	1.01	3.25	2.37	137.3°
C4–H2···O1	9.44	3.12	2.05	167.9°
C5–H4···O2	0.23	2.94	2.64	94.9 °
C6–H5···O2	0.90	3.24	2.57	118.4°

C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O) (in Å)	d(O–H) (in Å)	∠(C–H–O)
C4–H2···O1	4.81	3.27	2.23	159.9°
C1–H1···O1	0.15	3.38	2.61	127.7°
C3–H3···O1	4.49	2.91	2.13	128.7°

difference in C–H···O interaction: branched-linear = 4.4 kcal/mol. $\Delta\Delta G^{\ddagger}_{THF\ 298\ K}$(branched-linear) = 4.5 kcal/mol.

Regioselectivity can be well explained by ***NBO calculation.***



CH…O interaction is very important.

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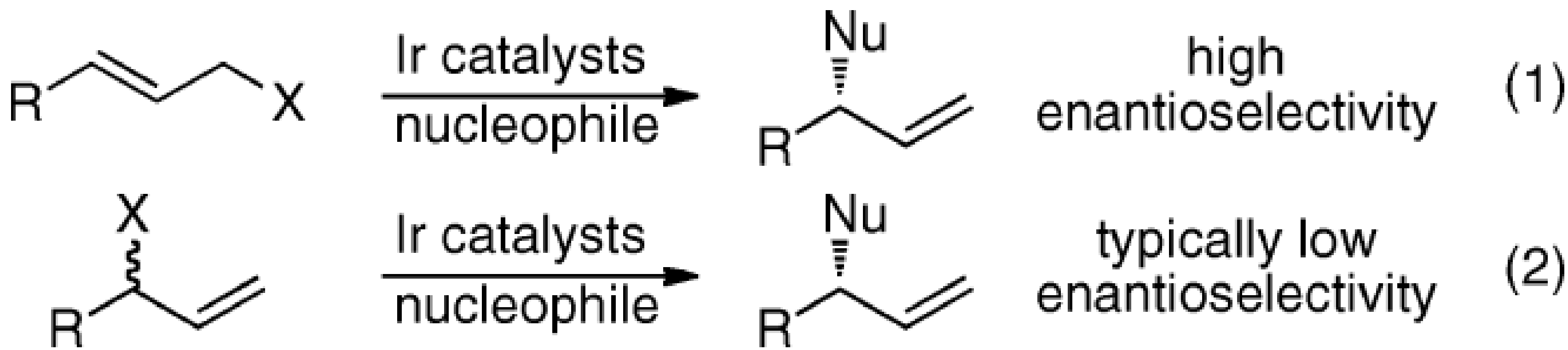
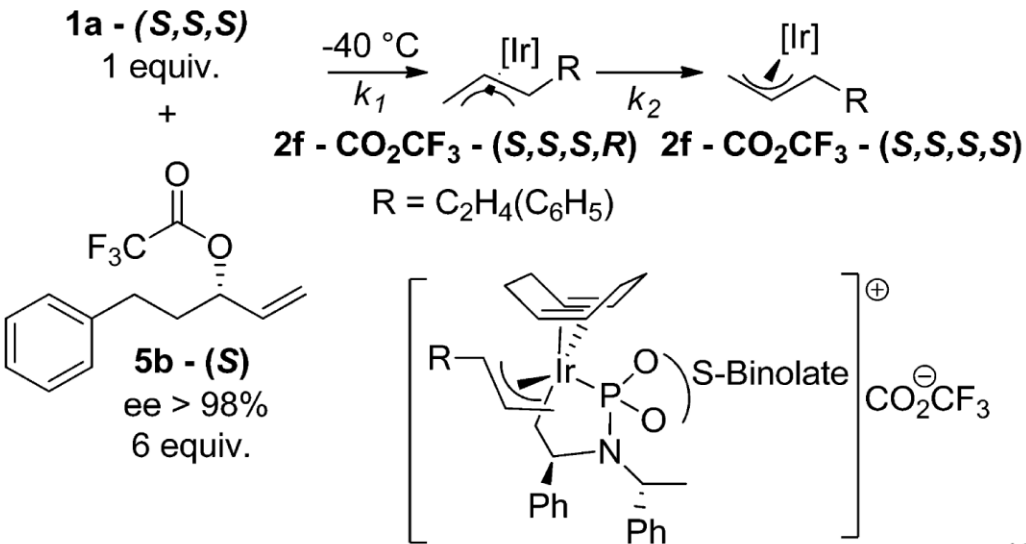
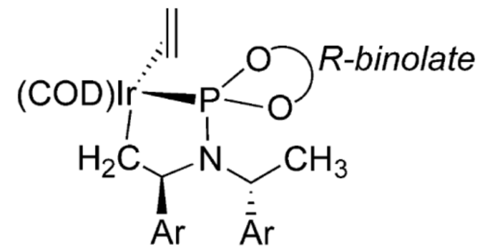
Enantioselectivity



Kinetic and Thermodynamic Control

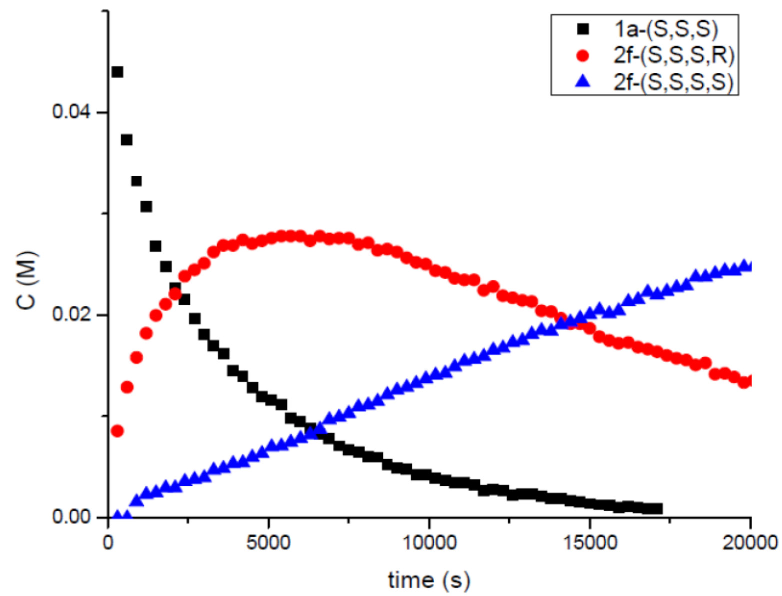


2f: R = CH_2CH_2Ph



Ar = Ph: **1a-(*R,R,R*)**
Ar = 2-(OMe)Ph: **1b-(*R,R,R*)**

at -40℃



Thermodynamically (*S,S,S,R*) is *less stable* than (*S,S,S,S*).

k_2=5.4*10^{-5}

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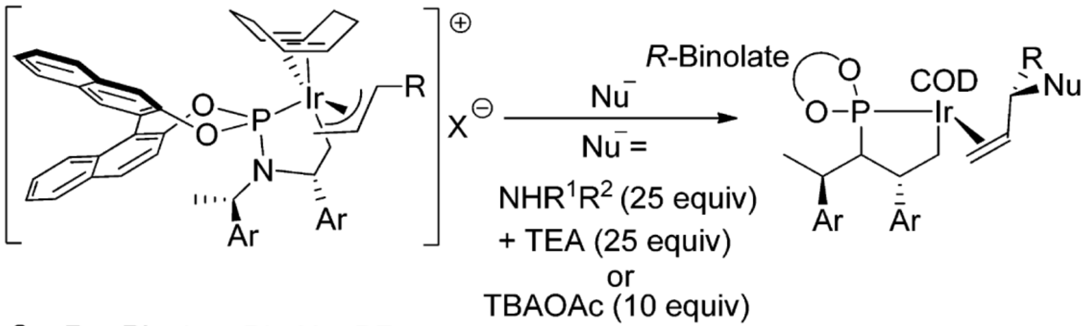
Nucleophilic Addition is Very Fast Step

Table 2. Rate Constants of Nucleophilic Attack on Allyliridium Complexes 2c,d,f and 3b



2c: R = Ph; Ar = Ph; X = BF_4^-
2d: R = 2,6-difluorophenyl; Ar = Ph; X = BF_4^-
3b: R = Ph; Ar = 2-(OMe)Ph; X = ClO_4^-
2f-(*S*,*S*,*S*,*S*): R = $(CH_2)_2Ph$; Ar = Ph; X = $CO_2CF_3^-$
2f-BF$_4$: R = $(CH_2)_2Ph$; Ar = Ph; X = BF_4^-

entry	complex[a] (M)	NHR^1R^2 or TBAOAc	solvent	T, °C	k_{obs}, s^{-1}
1	**2c** (0.030)	$PhNH_2$	CH_2Cl_2	−30	6.0×10^{-4}
2	**2c** (0.043)	$PhNH_2$	THF	−40	3.4×10^{-3}
3	**2c** (0.030)	$PrNH_2$	THF	−60	too fast to measure
4	**2d** (0.030)	$PhNH_2$	CH_2Cl_2	−30	2.8×10^{-4}
5	**2d** (0.043)	PhNH(Me)	CH_2Cl_2	−30	2.0×10^{-4}
6	**3b** (0.030)	$PhNH_2$	THF	−40	9.9×10^{-4}
7	**2c** (0.030)	TBAOAc	THF	−60	too fast to measure
8	**2f-TFA** (0.046)	$PhNH_2$	THF	−40	2.5×10^{-3}

Nucleophilic addition is *much faster* than the conversion of the minor to major.

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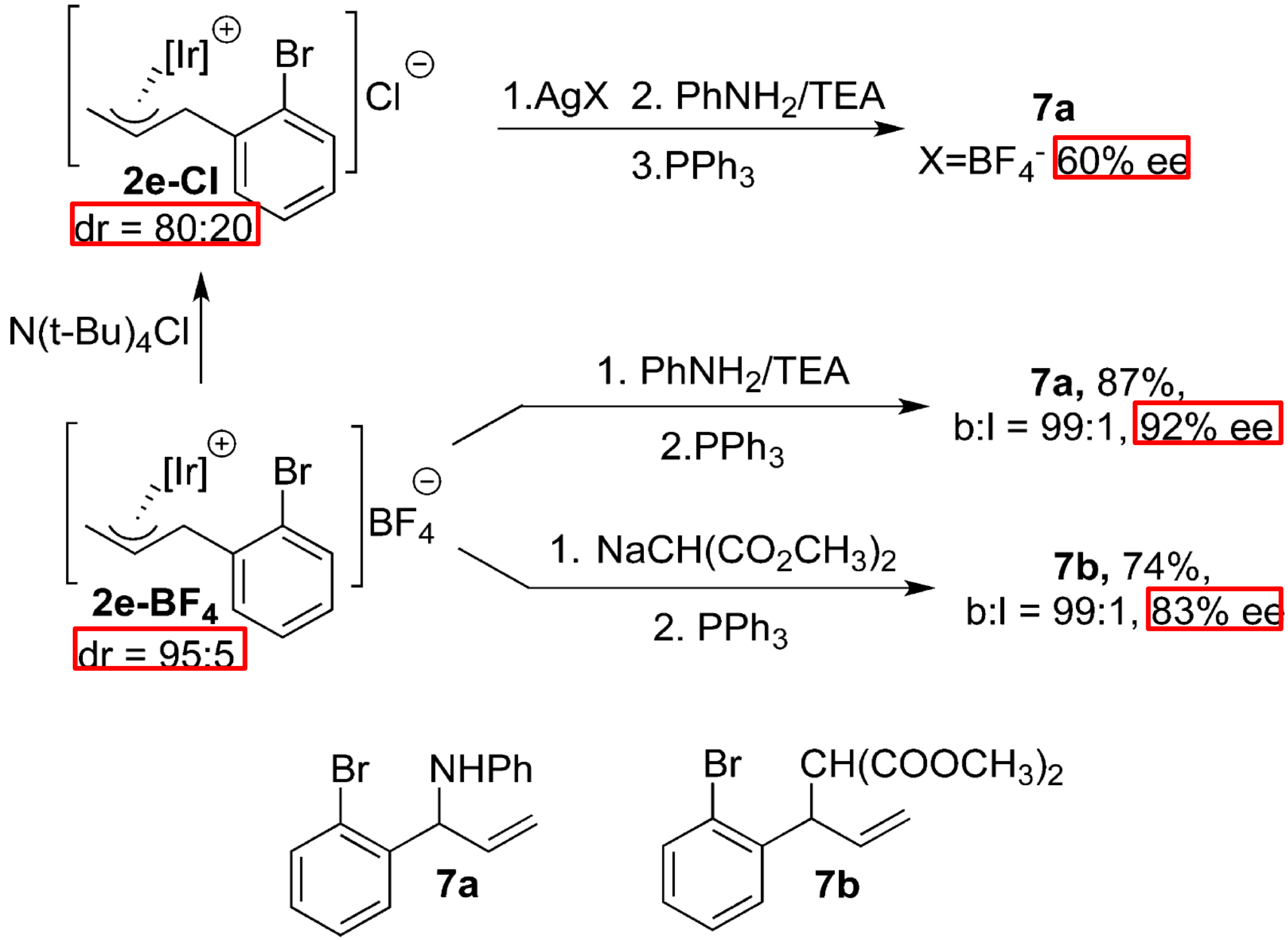
Compare dr with ee of TM

Scheme 4. Stoichiometric Reactions of 2e



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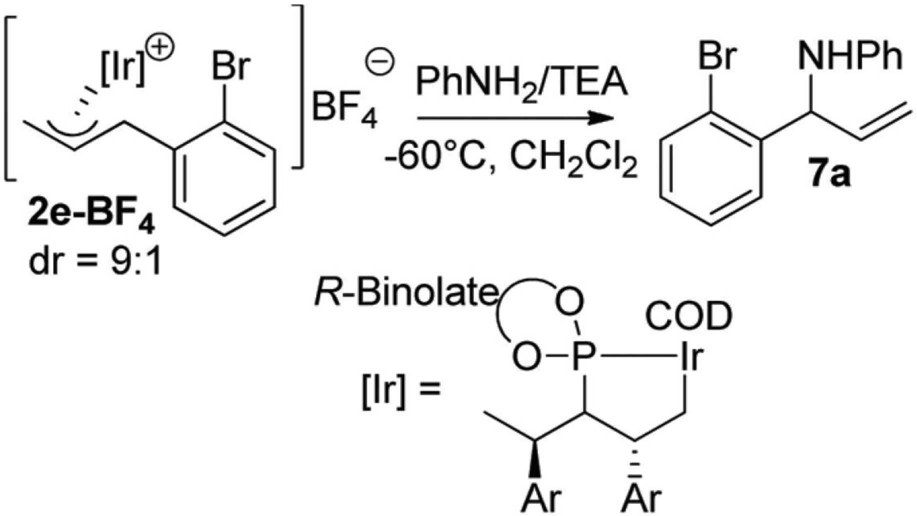
The Importance of Oxidative Addition Step

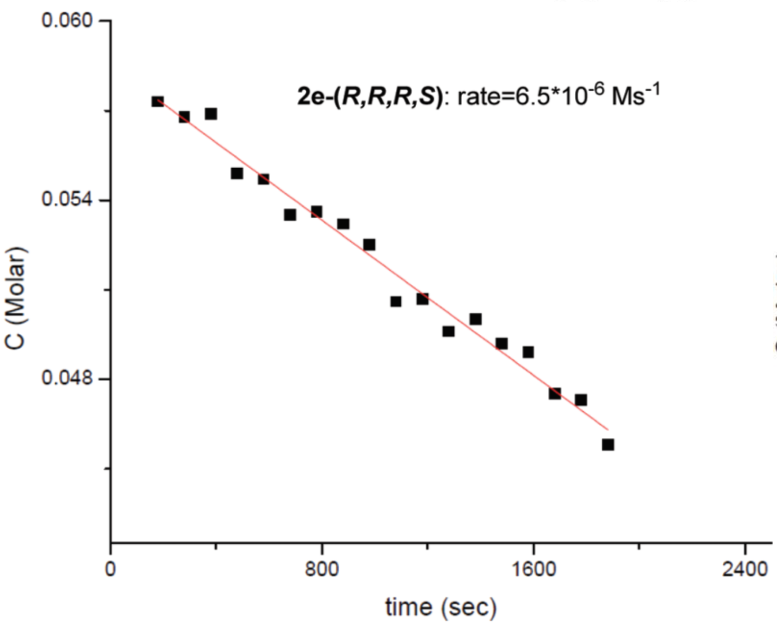
At -60°C the conversion does *not occurred*.

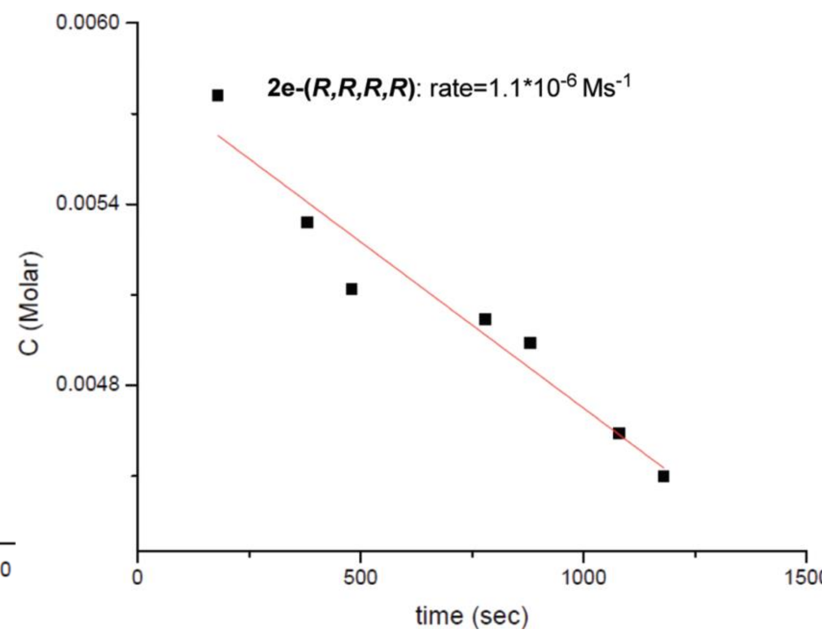


Major=(*R*,*R*,*R*,*S*)
Minor=(*R*,*R*,*R*,*R*)

k_{major}=1.2*10^{-4} s^{-1}
k_{minor}= 2.0*10^{-4} s^{-1}

oxidative addition *must be critical* for enantio selectivity.





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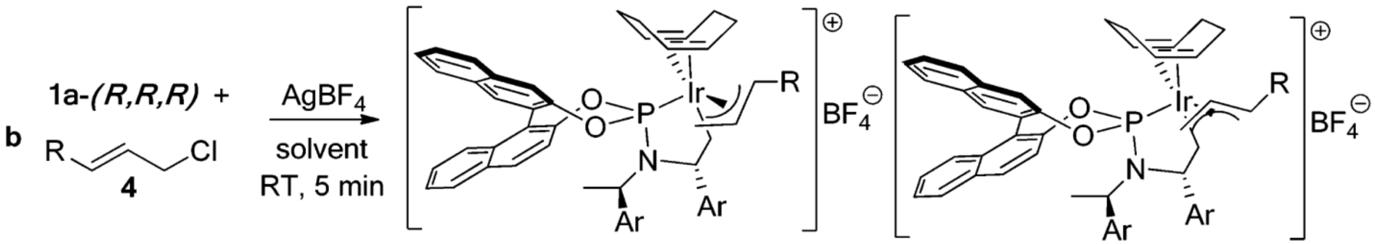
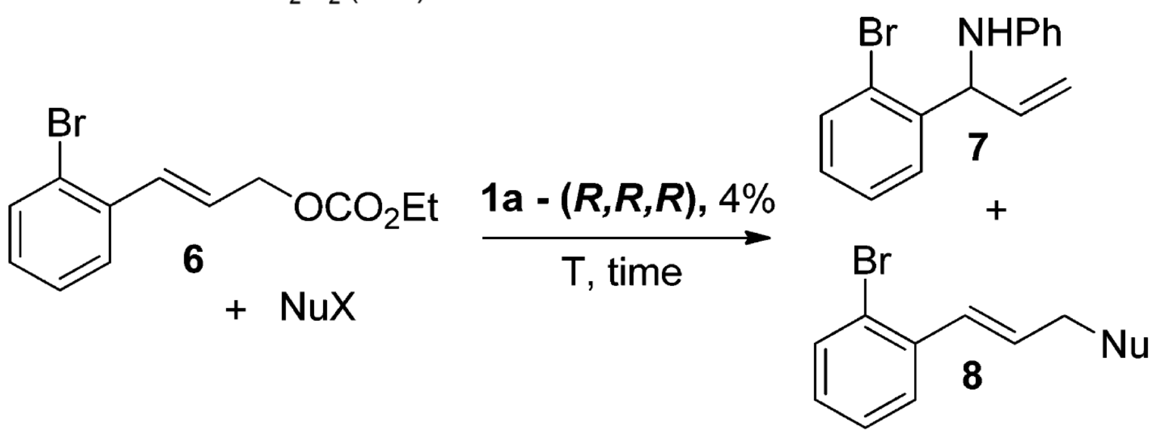
Oxidative Addition Step



4d: R = 2-bromophenyl

2e: R = 2-bromophenyl, Ar = Ph

	2e-(*R,R,R,S*)	**2e (*R,R,R,R*)**
benzene (60%):	60	40
THF (50%):	80	20
CH_2Cl_2 (55%):	90	10



nucleophile (product)	yield, %	7/8	ee, %	*T*, °C	time, h
$PhNH_2$ (**7a**)	26	99:1	29	50	12
$(CH_3CO_2)_2CHNa$ (**7b**)	90	99:1	25	RT	12
PhOLi (**7c**)	53	99:1	26	50	0.5

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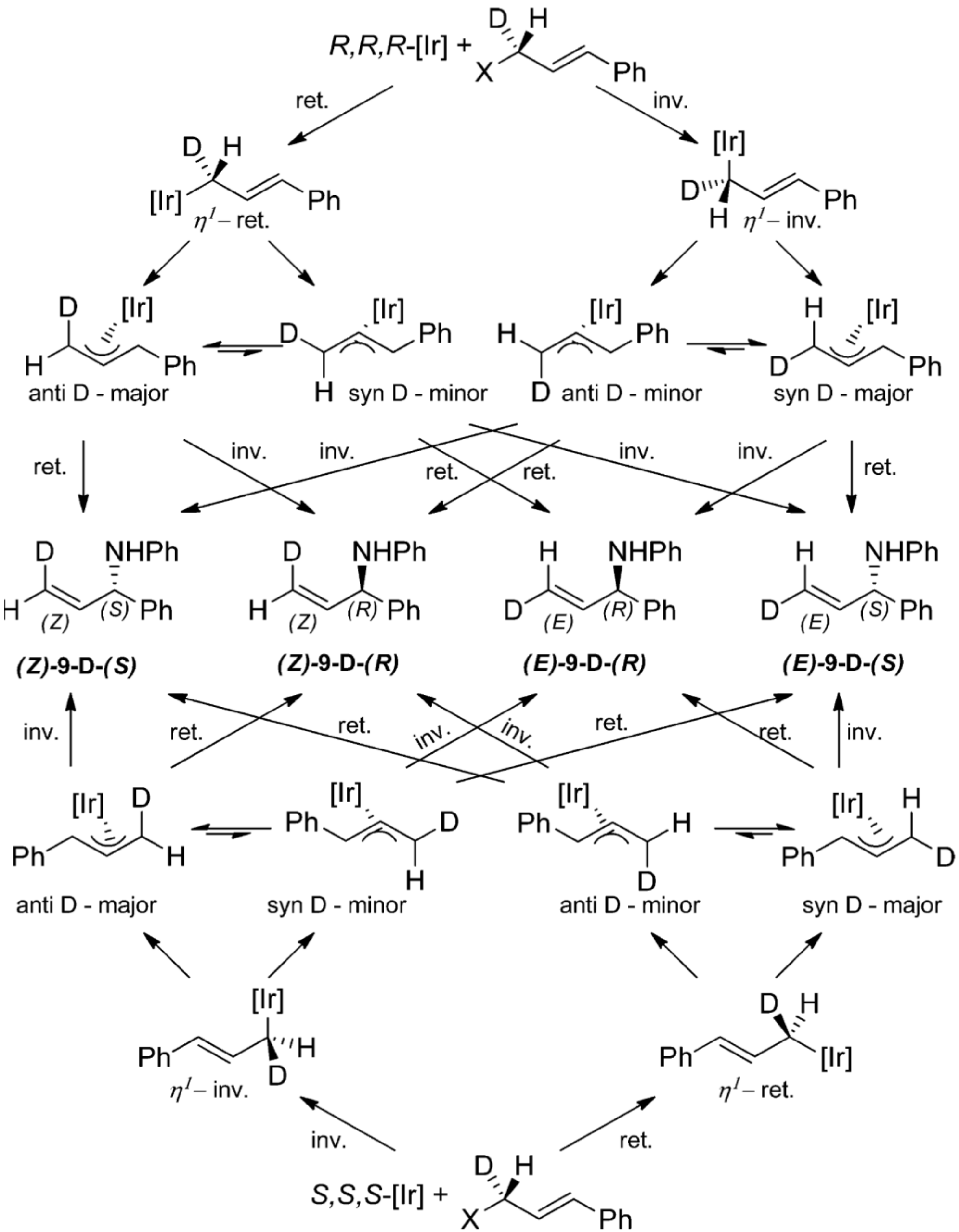
Retention or Inversion?



oxidative addition is *inversion* of configuration.

✚

nucleophilic addition is *inversion* of configuration.

⇩

Toally, allylation is *retention* of configuration.

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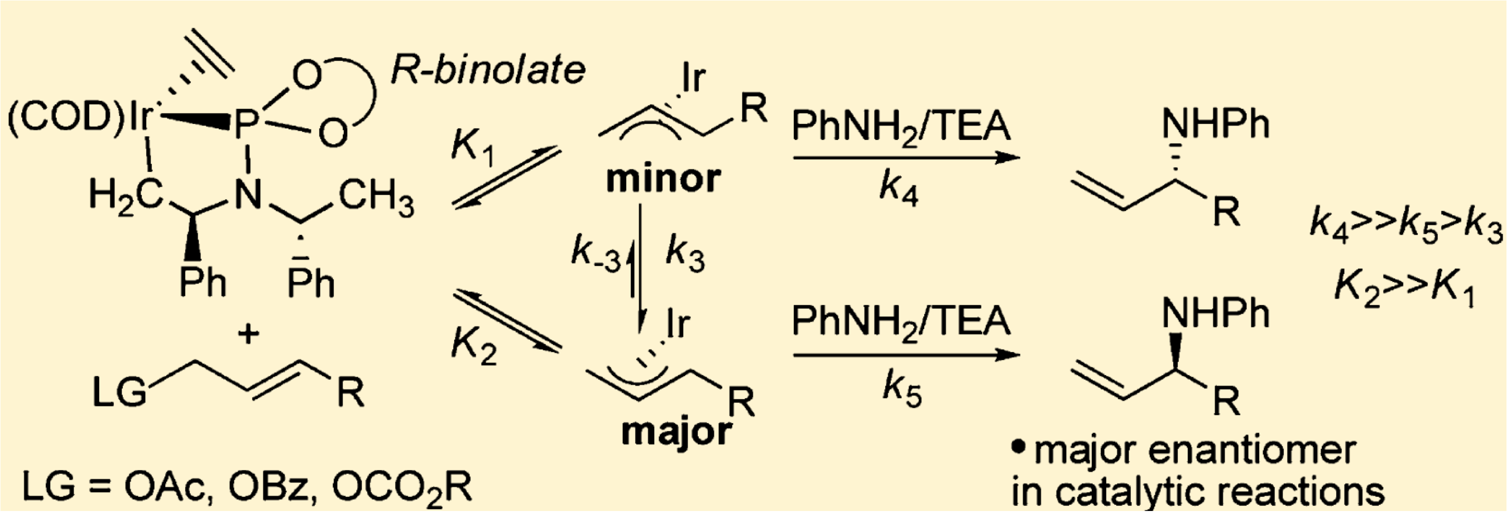
Short Summary



The stereoselectivity of Ir-catalyzed allylic substitution originates from *oxidative addition*.

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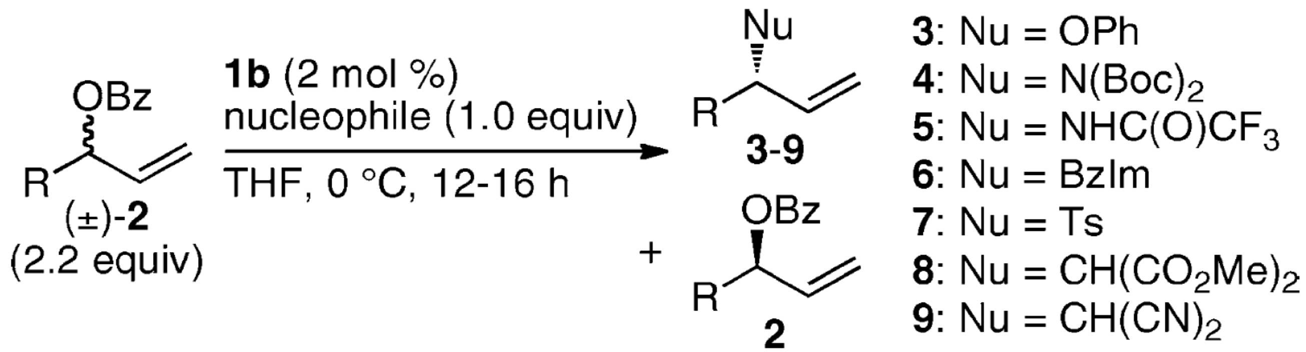
Kinetic Resolution



entry	R (**2**)	nucleophile	product	yield (%)[b]	ee (%)[c]
1	$BnCH_2$ (**2a**)	NaOPh	**3a**	83	95
2	*n*-Pr (**2b**)	NaOPh	**3b**	86	92
3	*i*-Pr (**2c**)	NaOPh	**3c**	76	98
4	Cy (**2d**)	NaOPh	**3d**	86	96
5[d]	*t*-Bu (**2e**)	NaOPh	**3e**	88	96
6	$BnCH_2$ (**2a**)	$LiN(Boc)_2$	**4a**	96	93
7	$BnCH_2$ (**2a**)	$KNHC(O)CF_3$	**5a**	74	98
8	$BnCH_2$ (**2a**)	NaBzIm	**6a**	84	97
9	$BnCH_2$ (**2a**)	NaTs	**7a**	80	94
10	$BnCH_2$ (**2a**)	$NaCH(CO_2Me)_2$	**8a**	82	94
11	$BnCH_2$ (**2a**)	$NaCH(CN)_2$	**9a**	77	88

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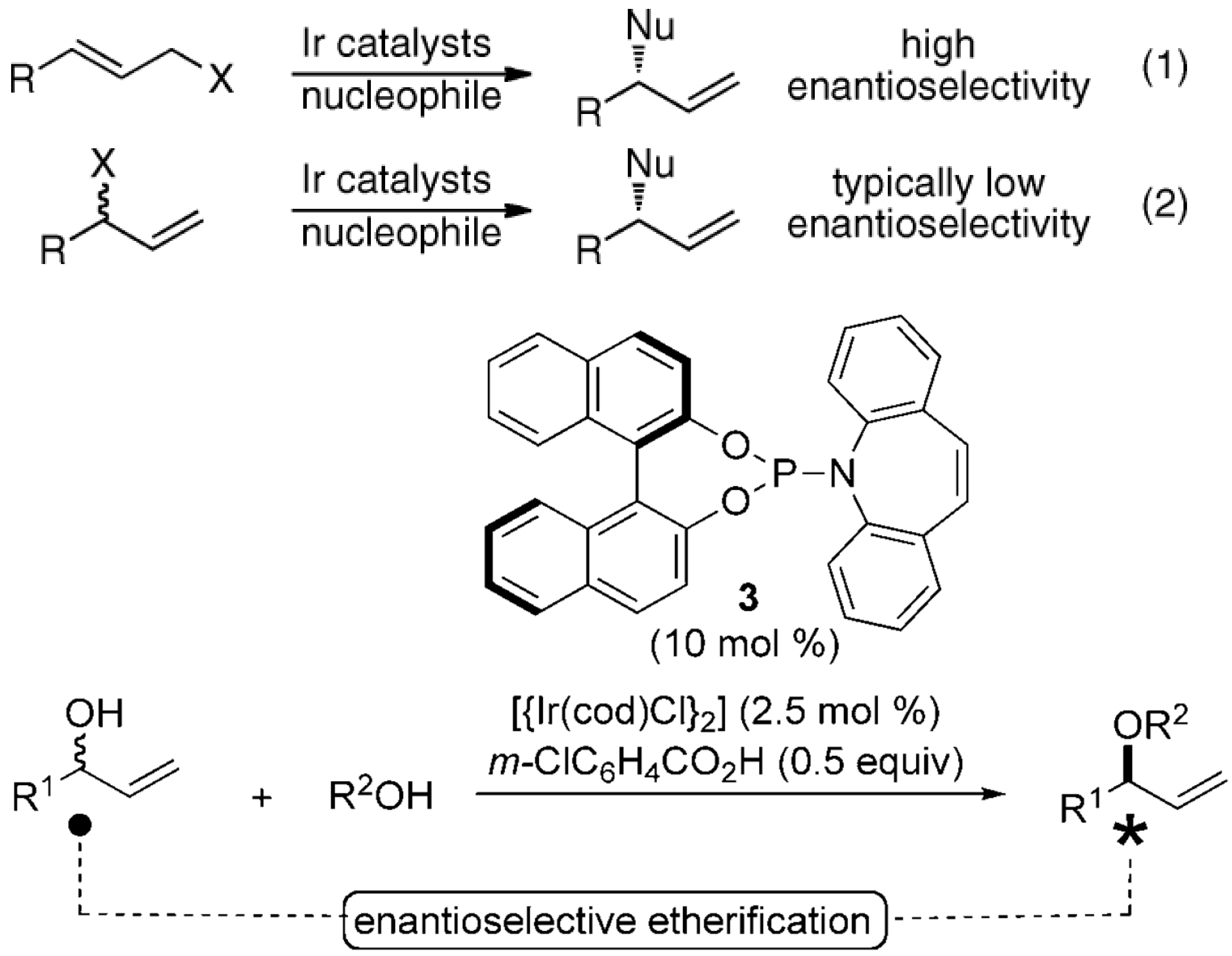
Etherification



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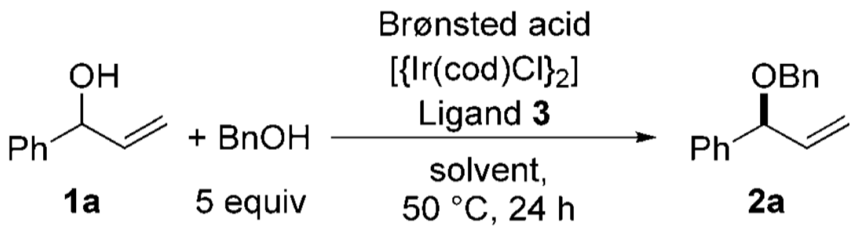
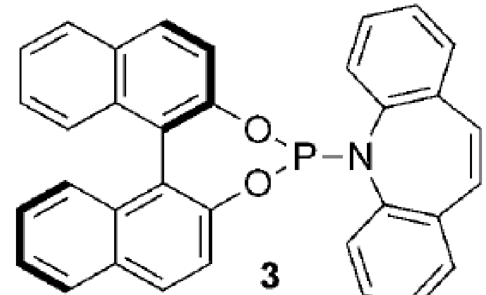
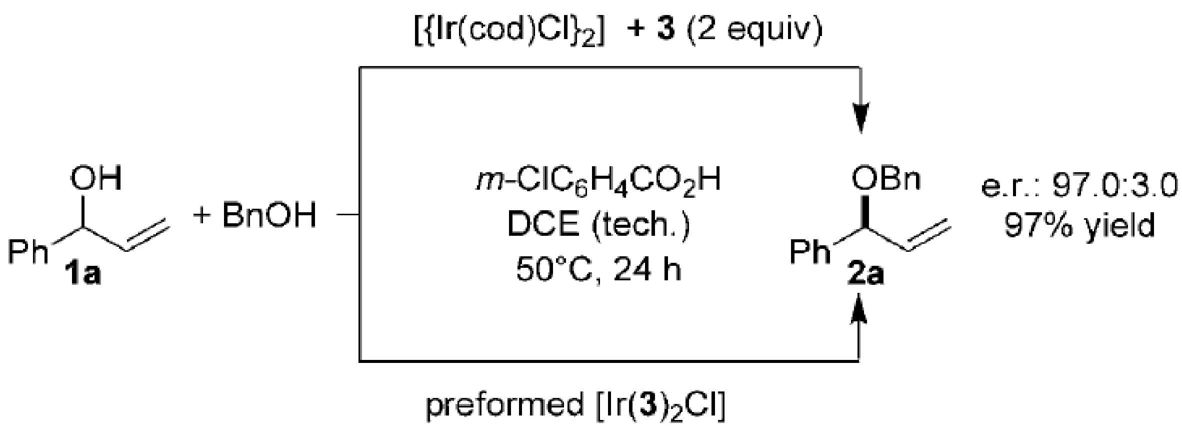
Brønsted Acid Plays Critical Role





3
(10 mol %)

Entry	Acid	Solvent	Conv (%)[b]	e.r.
1	$MeCO_2H$	toluene	< 10	–
2	$PhCO_2H$	toluene	0	–
3	CSA[c]	toluene	0	–
4	HCO_2H	toluene	60	92.5:7.5
5	HCO_2H	THF	50	81.5:18.5
6	HCO_2H	DCE	73	87.0:13.0
7	*p*-$NO_2C_6H_4CO_2H$	DCE	74	89.5:10.5
8	***m*-$ClC_6H_4CO_2H$**	**DCE**	**> 95**	**98.5:1.5**
9	*m*-$ClC_6H_4CO_2H$	BnOH, DCE[d]	0	–



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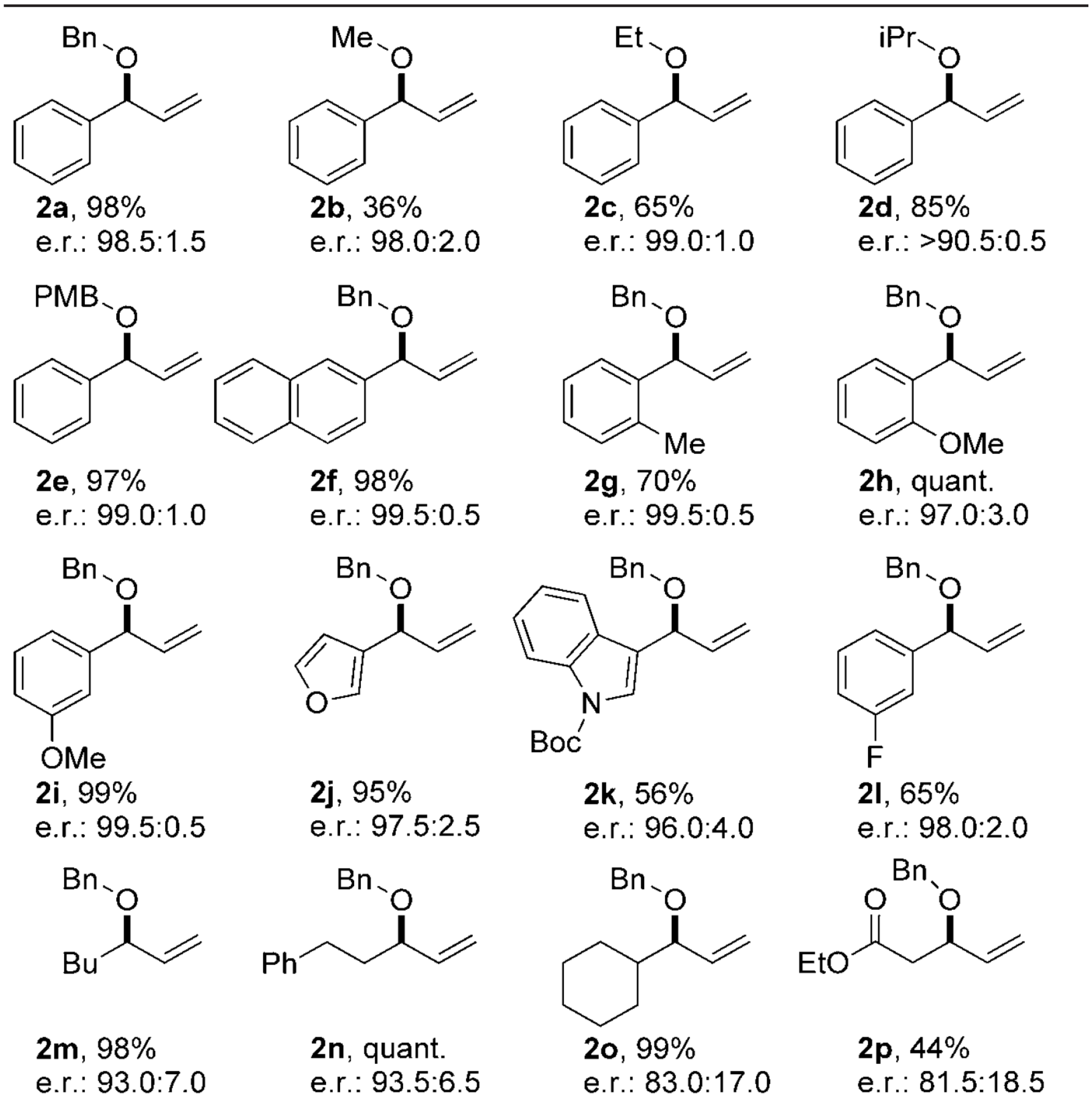
Substrate Scope



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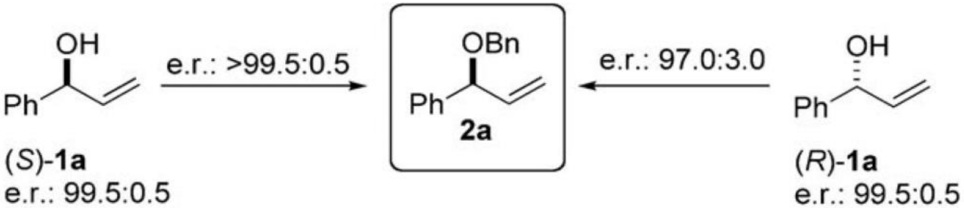
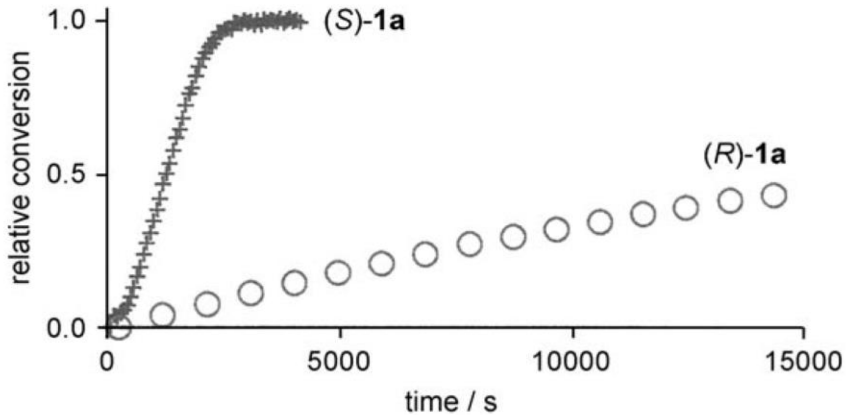
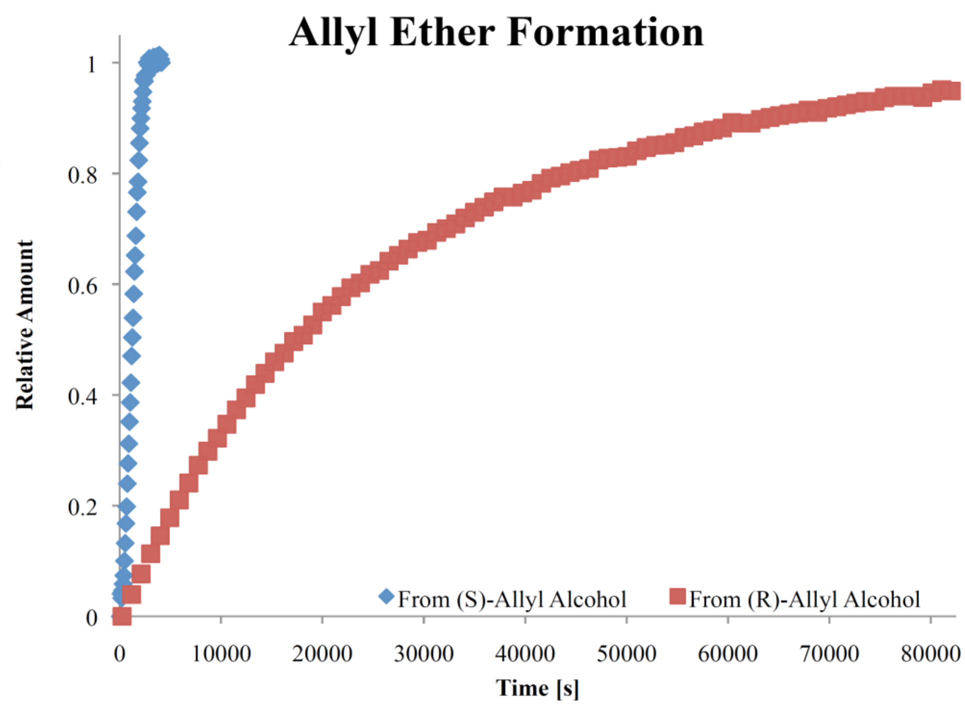
Both Enantiomers







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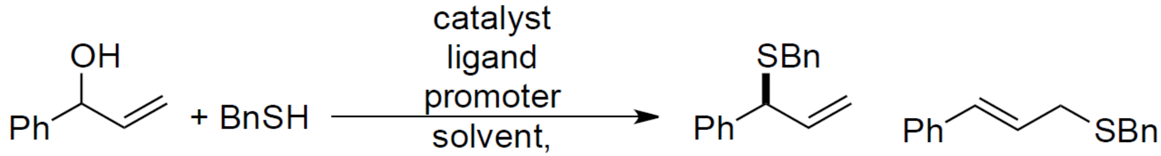
Thioetherification



1a 1.2 equiv. 50 °C, 24 h **2a** **2a'**

Table S2. Promoter screen.

Entry	Promoter	Conv. (%)	**2a/4a**	e.r. **2a**
1	No additive	60	83/17	96.5:3.5
2	*m*Cl-$C_6H_4CO_2H$	>95	60/40	86.5:13.5
3	*p*-NO_2-BzOH	70	80/20	93.0:7.0
4	Formic Acid	60	85/15	96.0:4.0
5	ClH_2CCO_2H	>95	86.	88.0:12.0
6	Cl_2HCCO_2H	>95	65/35	93.0:7.0
7	$CeCl_3$	80	>95/5	88.0:12.0
9	$Ti(^iPrO)_4$	75	>95/5	90.0:10.0
10	$AlCl_3$	decomp.	n/a	n/a
11	$ZnCl_2$	>95	30/70	45.0:55.0
12	$ScTf_3$	>95	25/75	64.5:35.5

. Phosphorus promoter screen.

Entry	Promoter	Conv. (%)	**2a/4a**	e.r.
1	$P(O)(OEt)_2Cl$	>95	92/8	92.5:7.5
2	$P(O)(OPh)_3$	60	95/5	93.5:6.5
3	$P(O)(OC_{16}H_{33})_2OH$	>95	97/3	90.0:10.0
4	$P(O)(OPh)_2OH$	>95	64/36	91.0:9.0
5	P(O)(*S*-BINOL)$_2$OH	>95	91/9	95.0:5.0
6	**$P(O)(OBu)_2OH$**	**>95**	**96/4**	**95.0:5.0**

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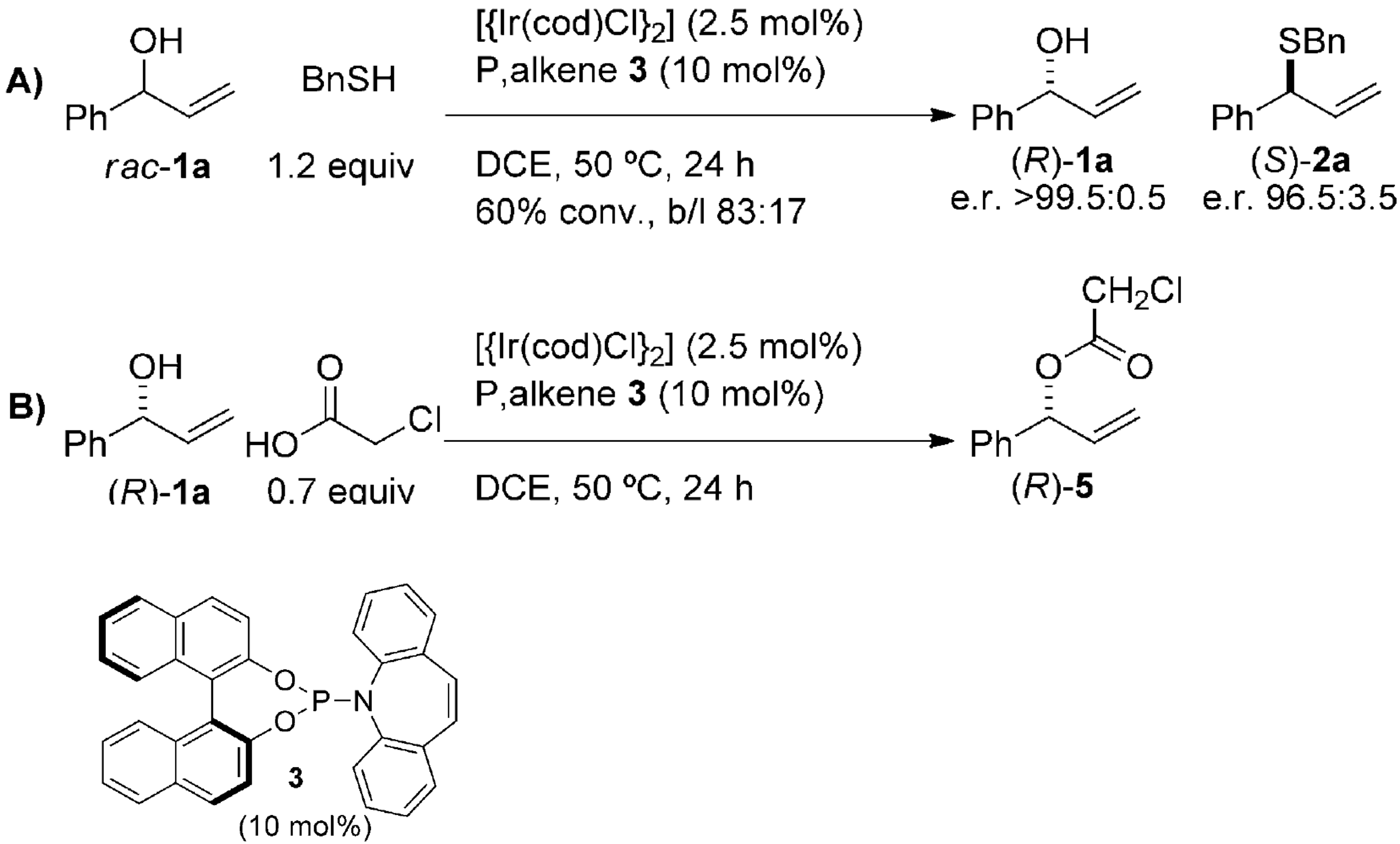
Kinetic Resolution?



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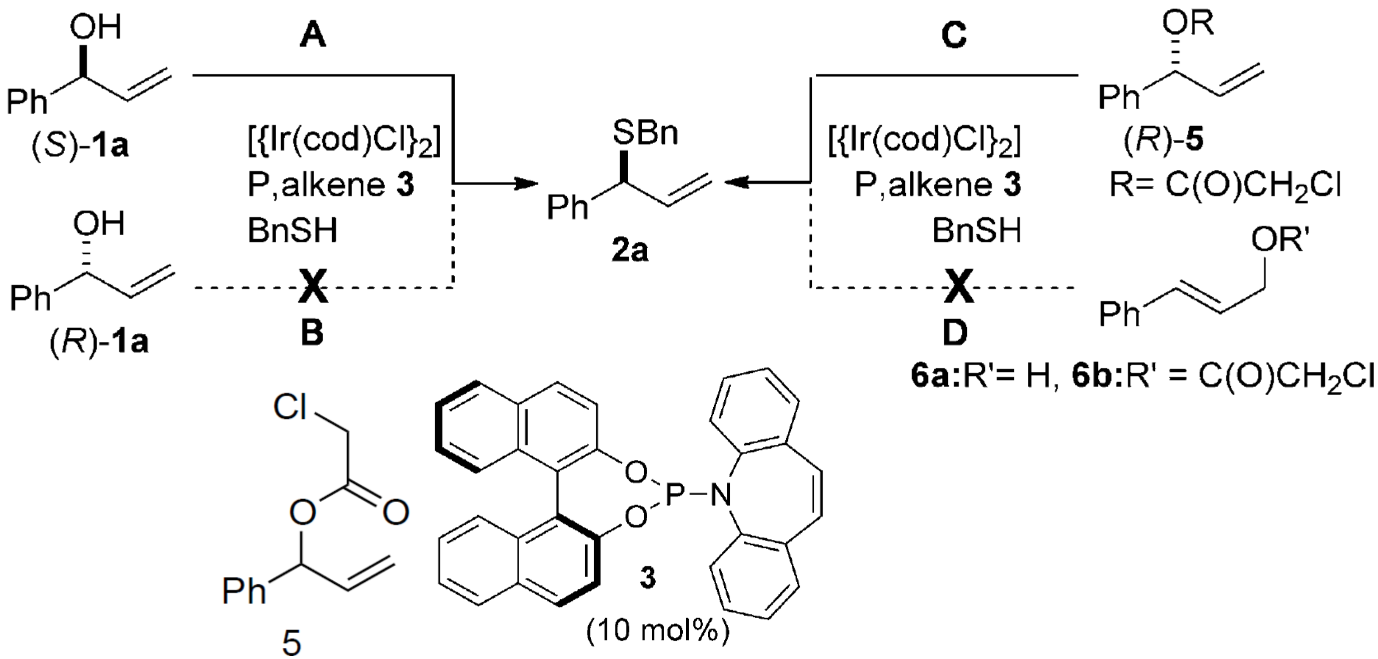
Substrate



Entry	Substrate	Reagents	Conv. (%)[b]	Products[b]	e.r.[c]
1	(*rac*)-**1a**	[{Ir(cod)Cl}$_2$], **3**, BnSH	60	**2a**, 50%; **4a**, 10%	96.5:3.5 (*S*) [>99.5:0.5 (*R*)-**1a**]
2[d]	(*S*)-**1a** (>99.5:0.5)	[{Ir(cod)Cl}$_2$], **3**, BnSH	>95	**2a**, >99%; **4a**, <1%	>99.5:0.5 (*S*)
3	(*R*)-**1a** (97.5:2.5)	[{Ir(cod)Cl}$_2$], **3**, BnSH	40	**2a**, 38%; **4a**, 2%	64.0:36.0 (*S*)
7	(*S*)- **5(c)** (99.0:1.0)	[{Ir(cod)Cl}$_2$], **3**, BnSH	>95	**2a**, 96%; **4a**, 4%	94.5:5.5 (*S*)
8	(*R*)- **5(c)** (97.6:2.4)	[{Ir(cod)Cl}$_2$], **3**, BnSH	>95	**2a**, 85%; **4a**, 15%	86.0:14.0 (*S*)

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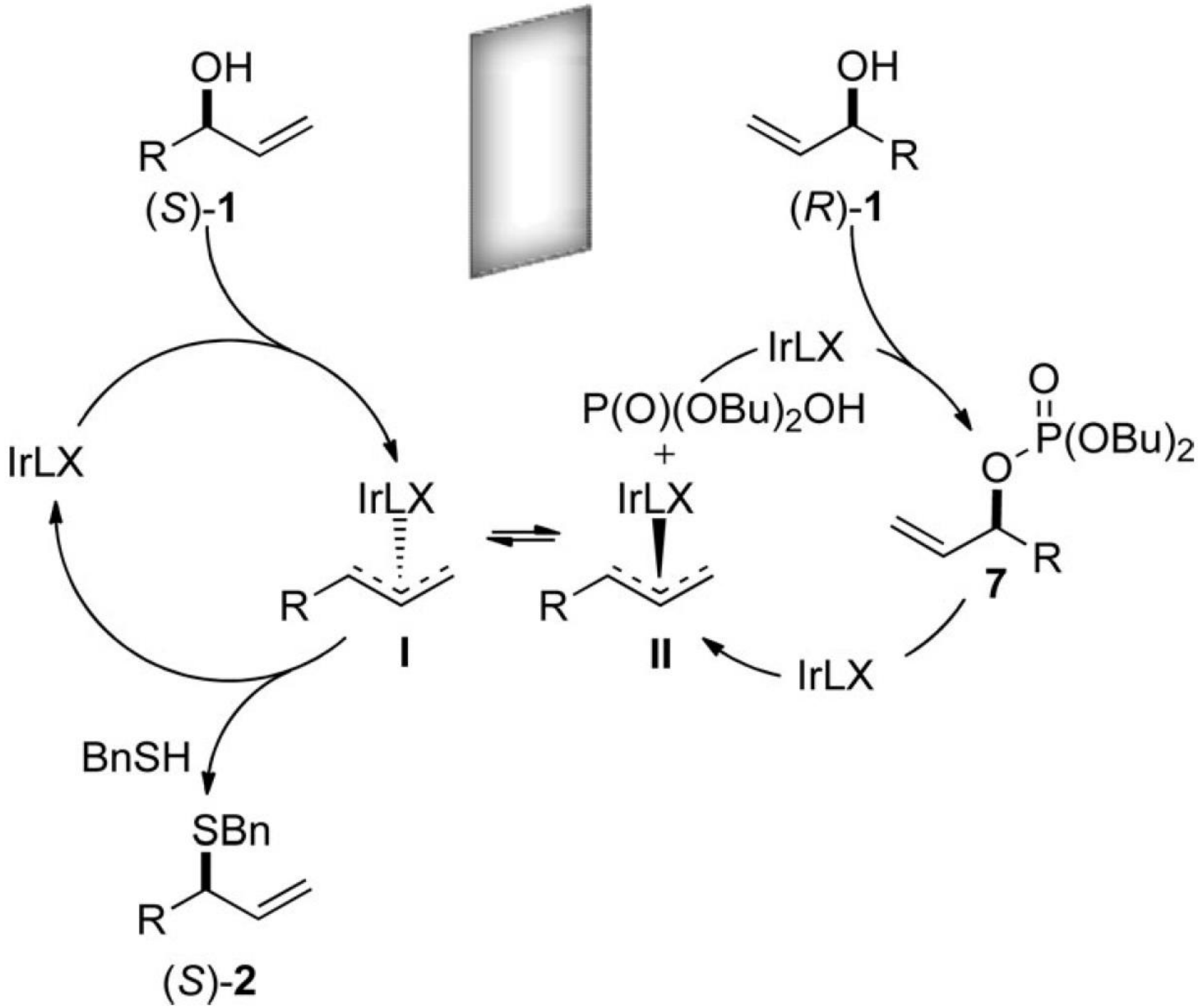
Proposed Mechanism



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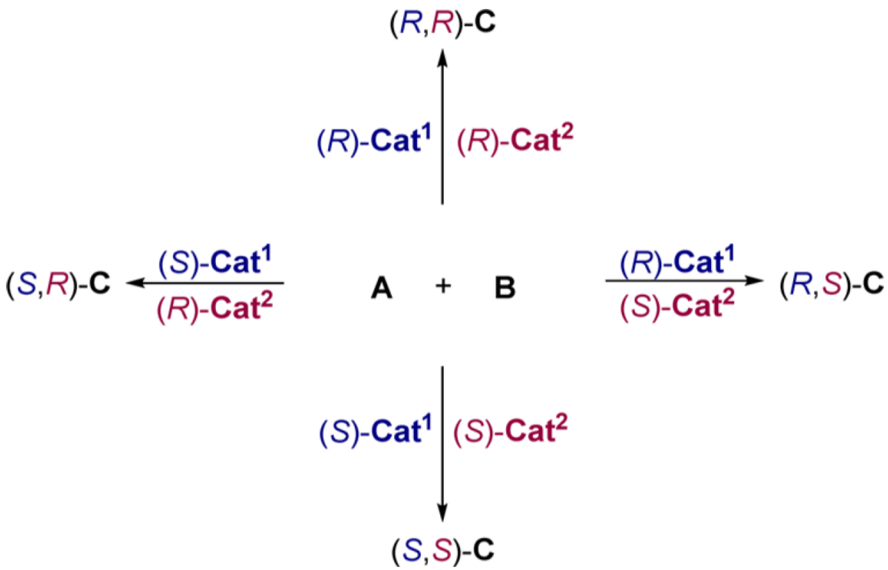
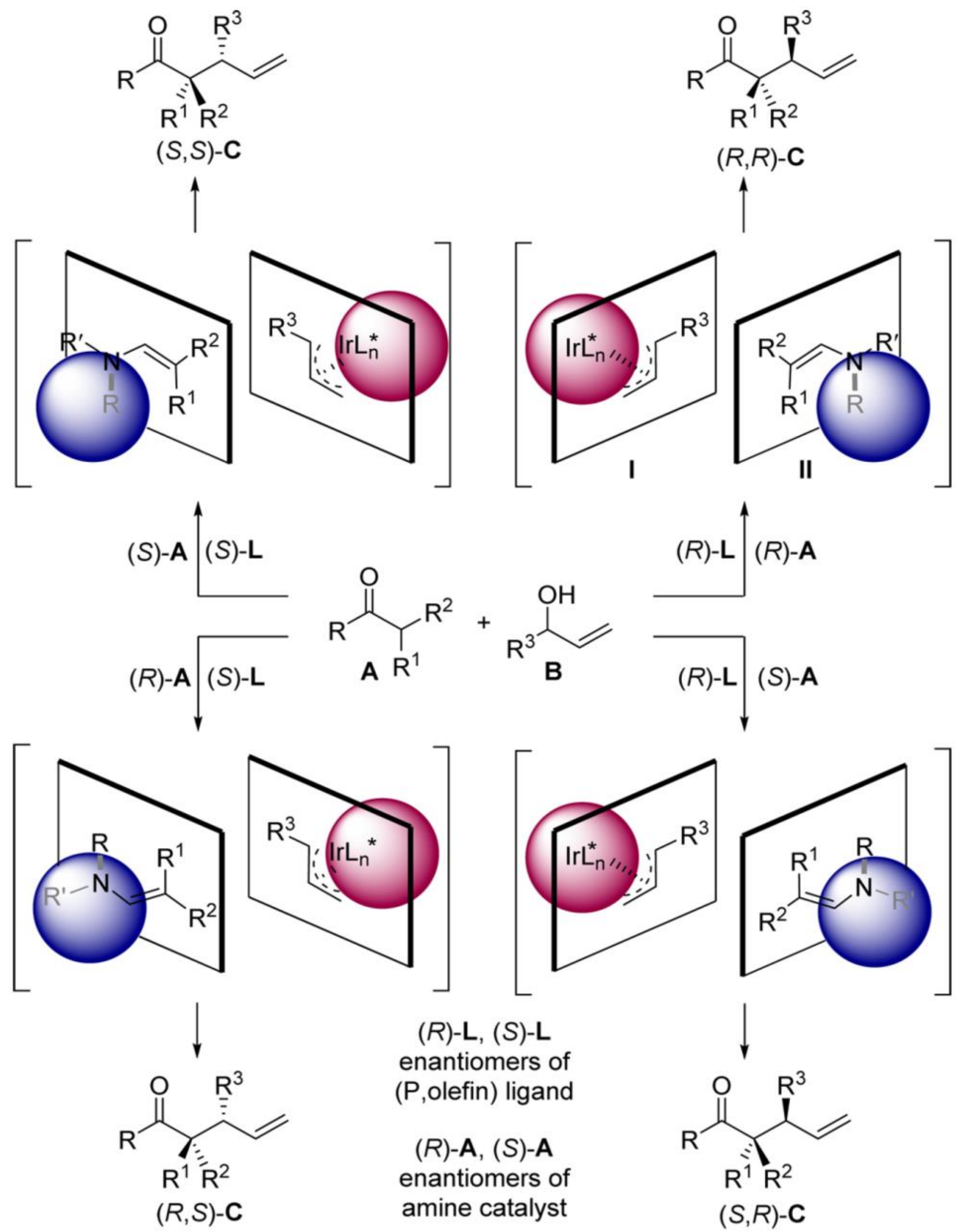
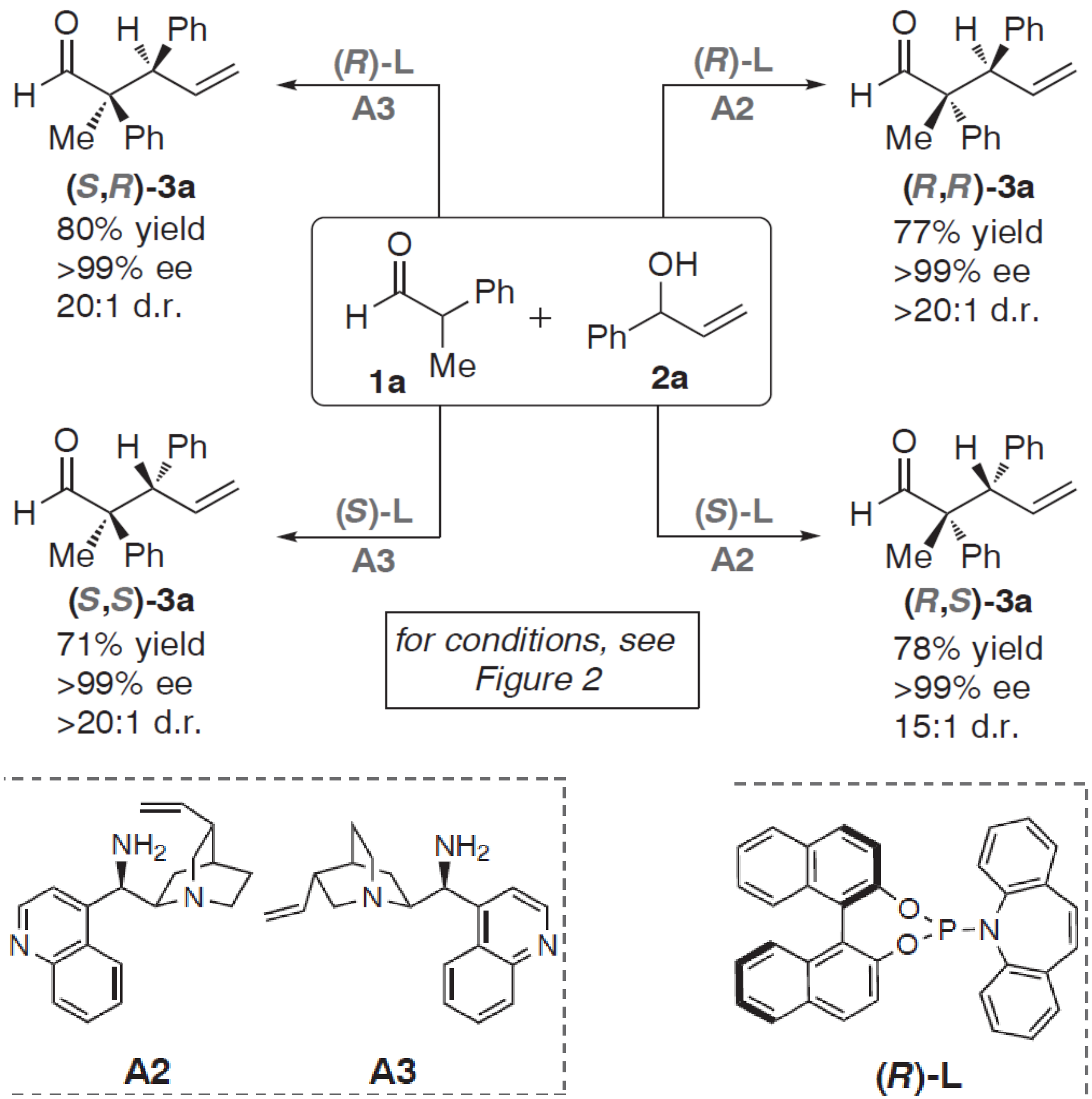
Dual Catalysis





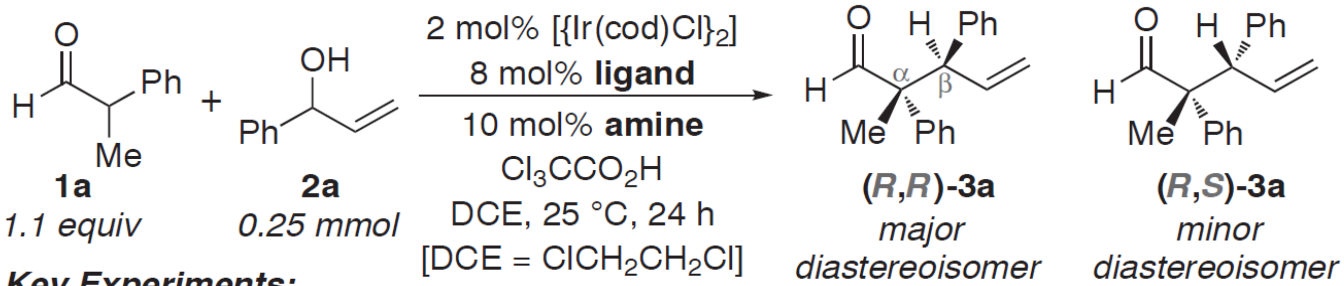
Carreira, E. M. *et al. J. Am. Chem. Soc.* **2017**, *51*, 8652.
Carreira, E. M. *et al. Science.* **2013**, *340*, 1065.

Four Isomers



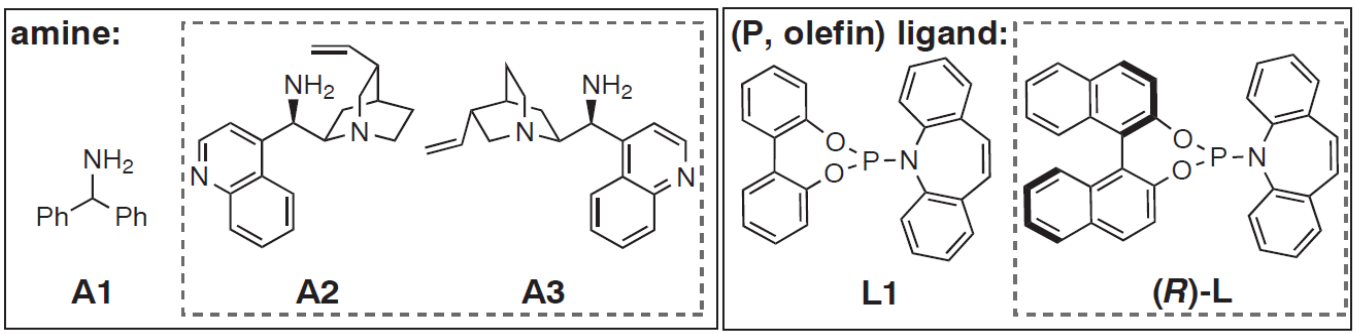
Carreira, E. M. *et al. Science.* **2013**, *340*, 1065.

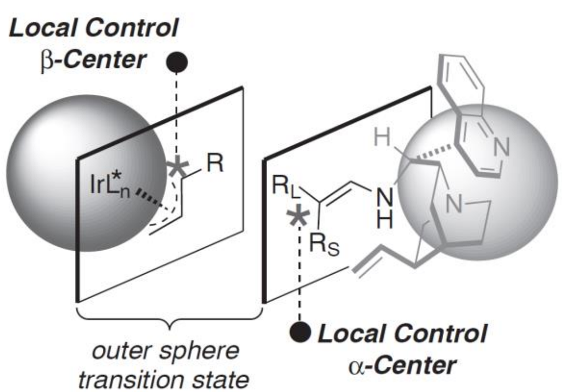
Controlling Two Stereo Centers



Key Experiments:

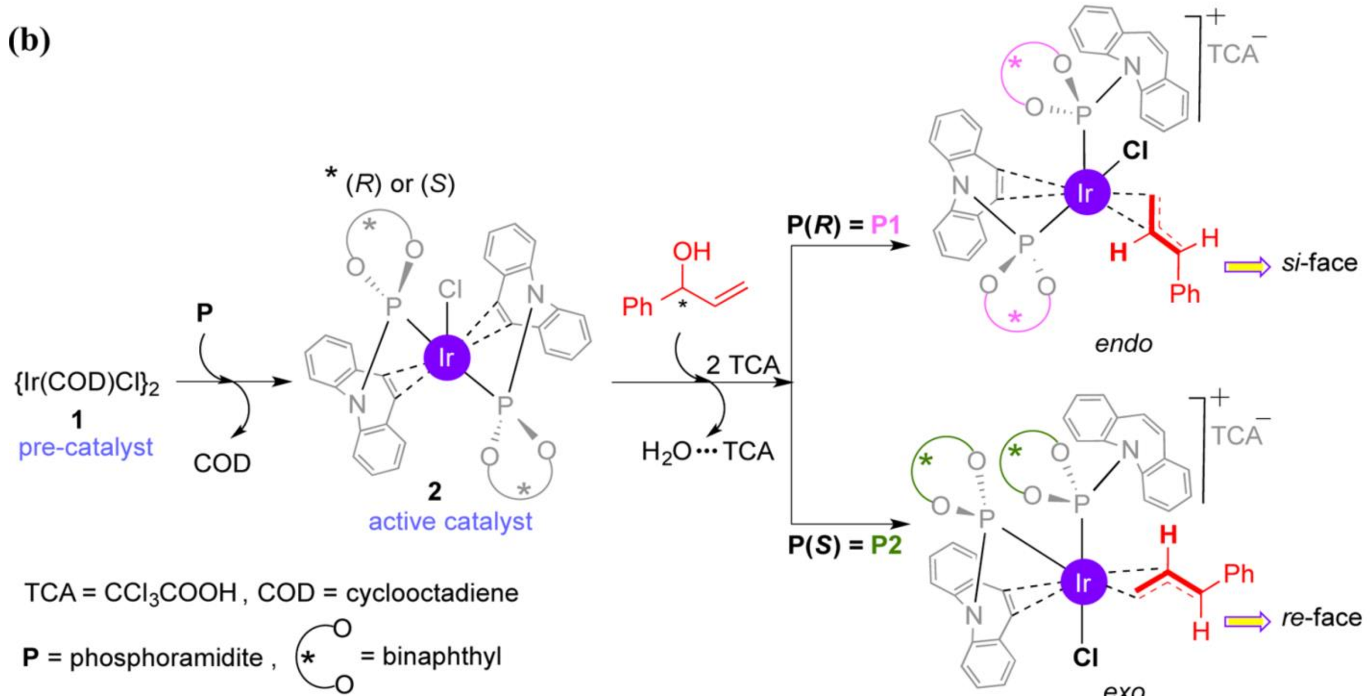
#1	#2	#3	#4
(*R*)-L + **A1**	**L1** + **A2**	**L1** + **A1**	(*R*)-L + **A2**
69%, 3:1 d.r.	69%, 1.3:1 d.r.	71%, 3:1 d.r.	77%, >20:1 d.r.
99% ee	68% ee/92% ee		99% ee
(*R*)-L: β-control	**A2**: α-control		(*R*)-L + **A2**: α & β-control



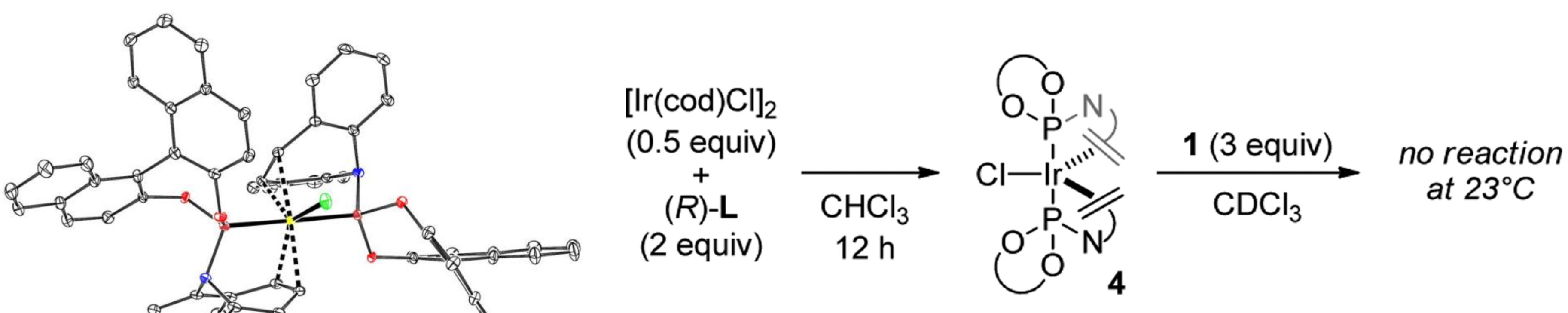


Carreira, E. M. *et al. Science.* **2013**, *340*, 1065.

Mechanistic Study



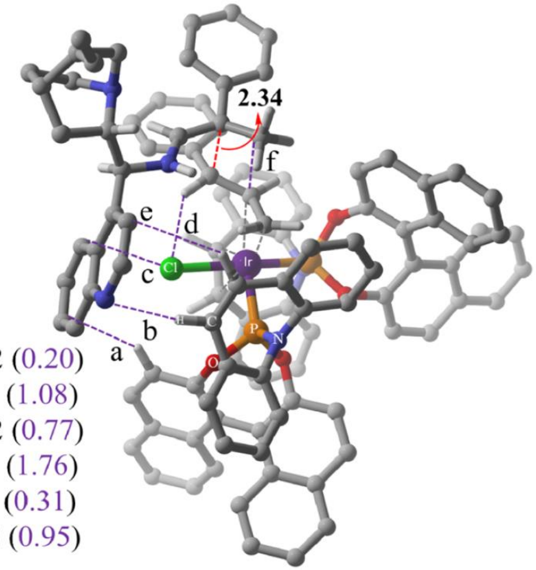
Sunoj, R. B. *et al. J. Am. Chem. Soc.* **2015**, *137,* 151722.



Carreira, E. M. *et al. J. Am. Chem. Soc.* **2017**, *139,* 3603.

Diastereo Selectivity

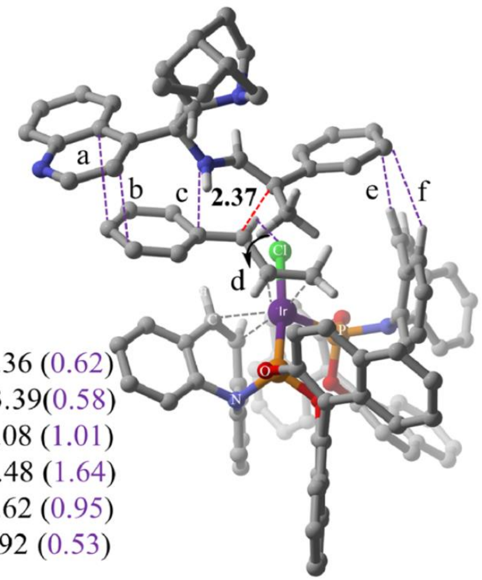
si-si



a= 3.32 (0.20)
b=2.44 (1.08)
c= 3.32 (0.77)
d=2.45 (1.76)
e=3.17 (0.31)
f= 3.08 (0.95)

P1-C2

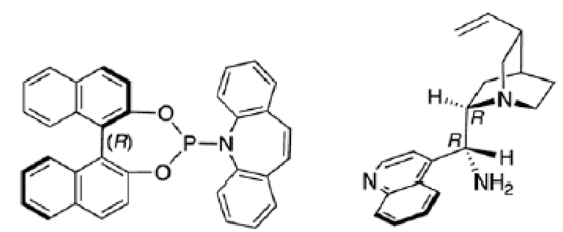
si-re



a=3.36 (0.62)
b= 3.39(0.58)
c=3.08 (1.01)
d=2.48 (1.64)
e=2.62 (0.95)
f=2.92 (0.53)

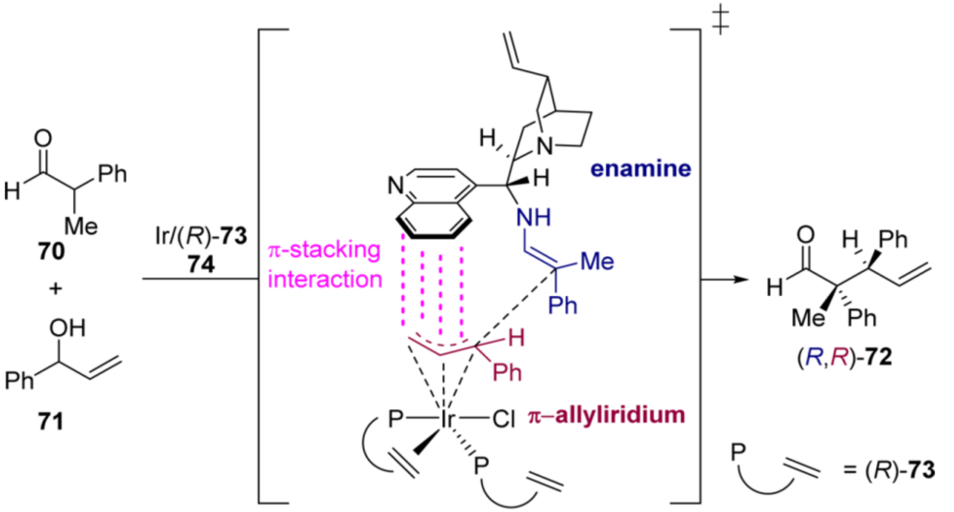
P2-C2

Major



P1 = phosphoramidite **C1** = cinchona amine

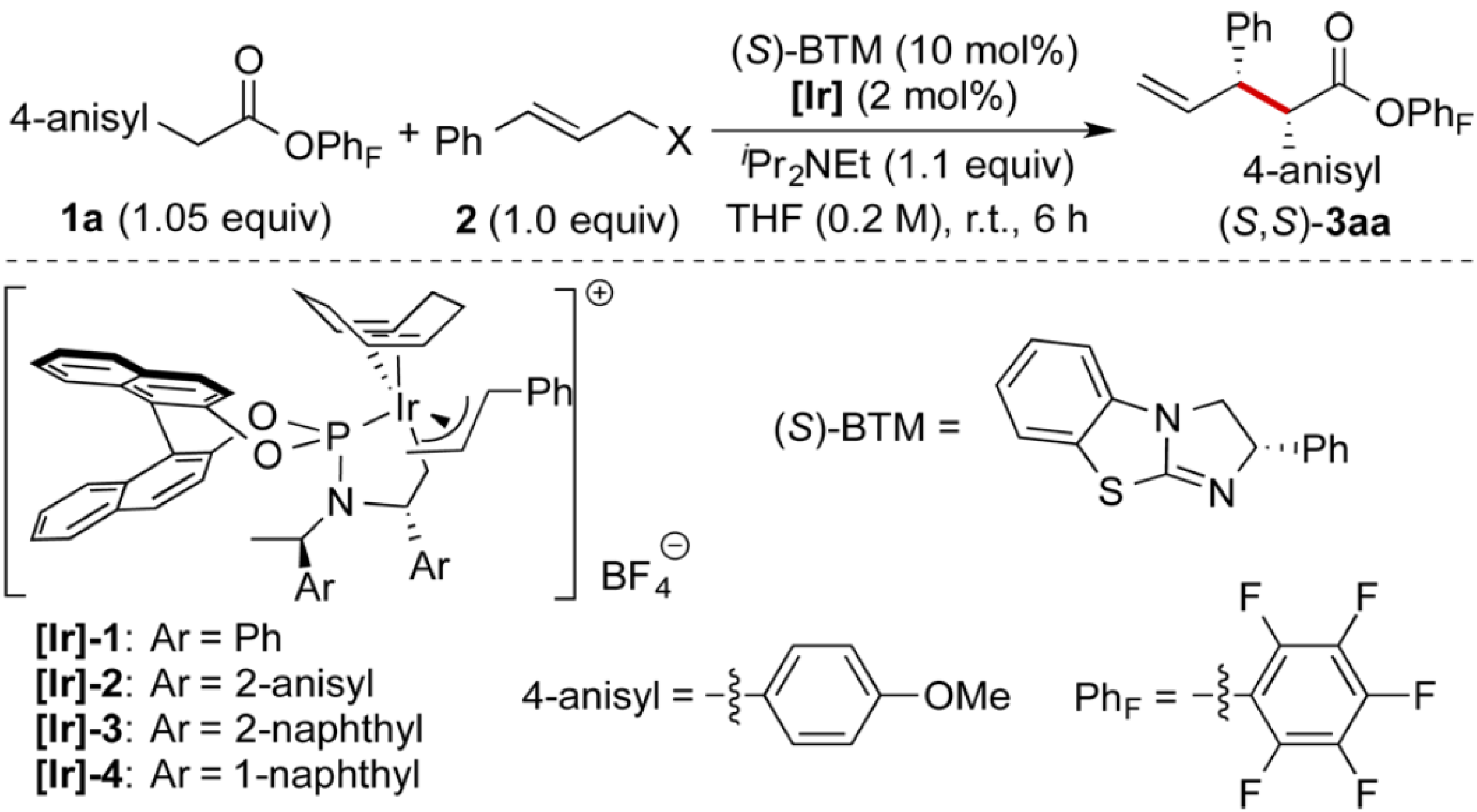
Sunoj, R. B. *et al. J. Am. Chem. Soc.* **2015**, *137,* 151722.



diastereocontrolling, C-C bond-forming transition state

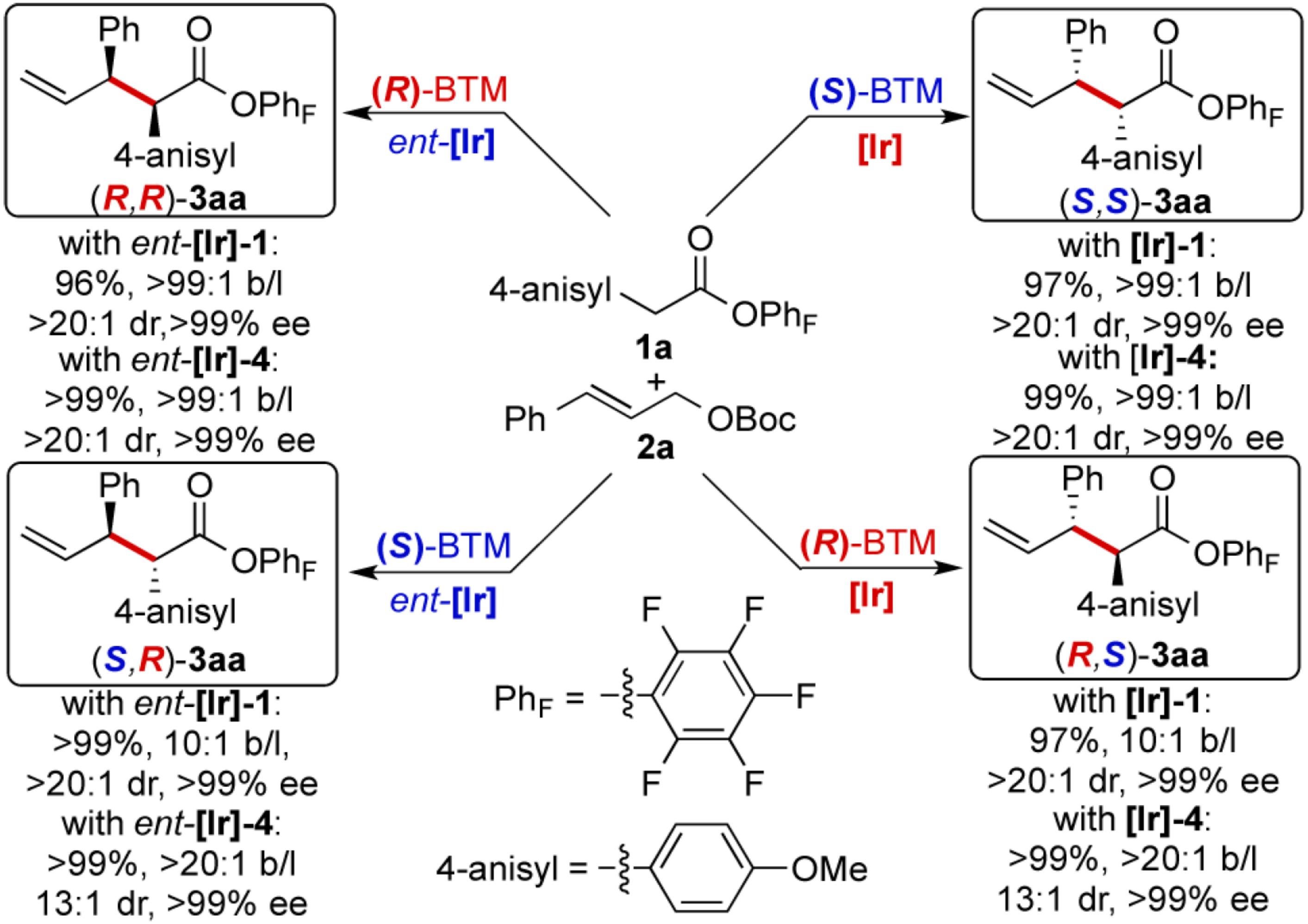
Carreira, E. M. *et al. J. Am. Chem. Soc.* **2017**, *139,* 3603.

Ester Substrate



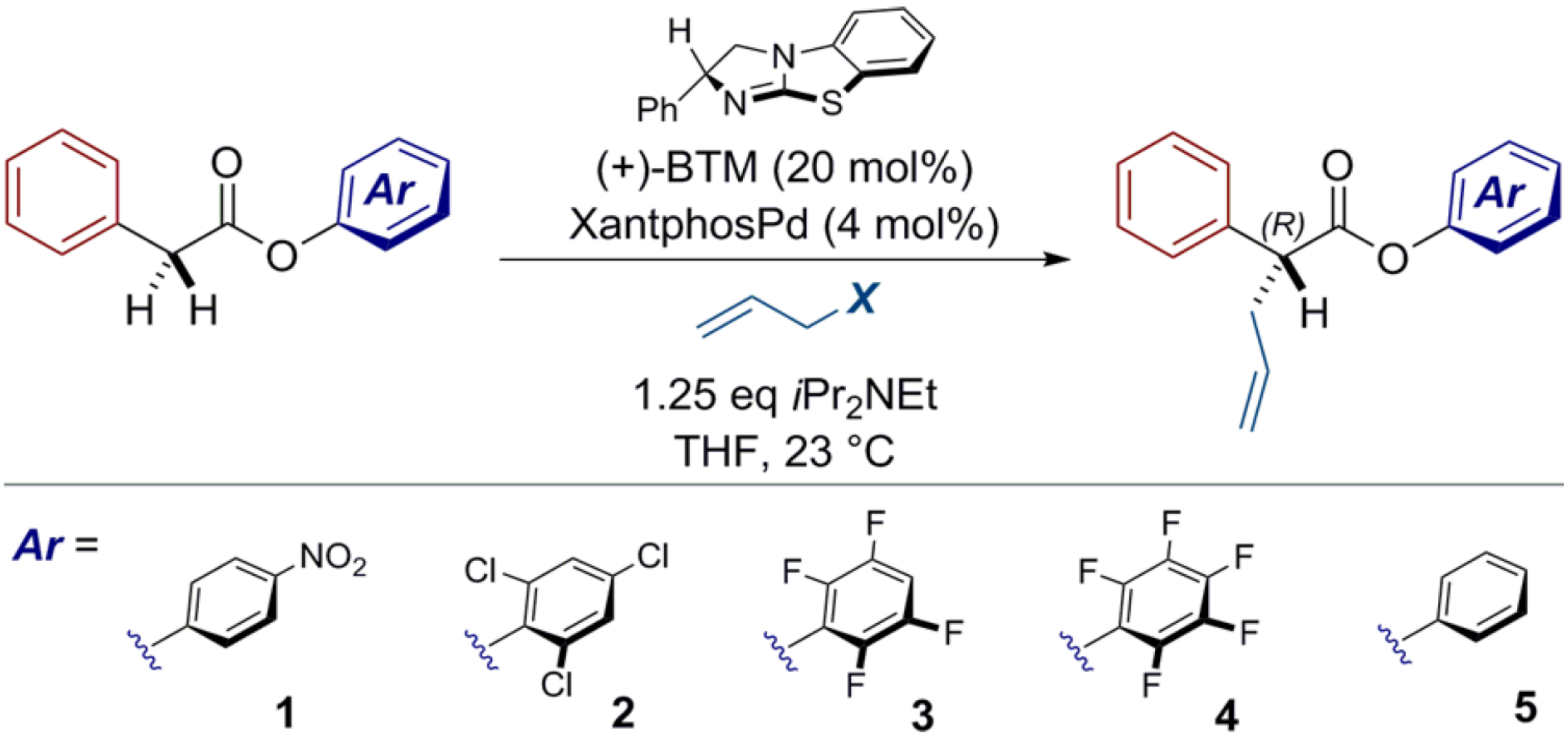
Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2017**, *139*, 87.

Four Isomers



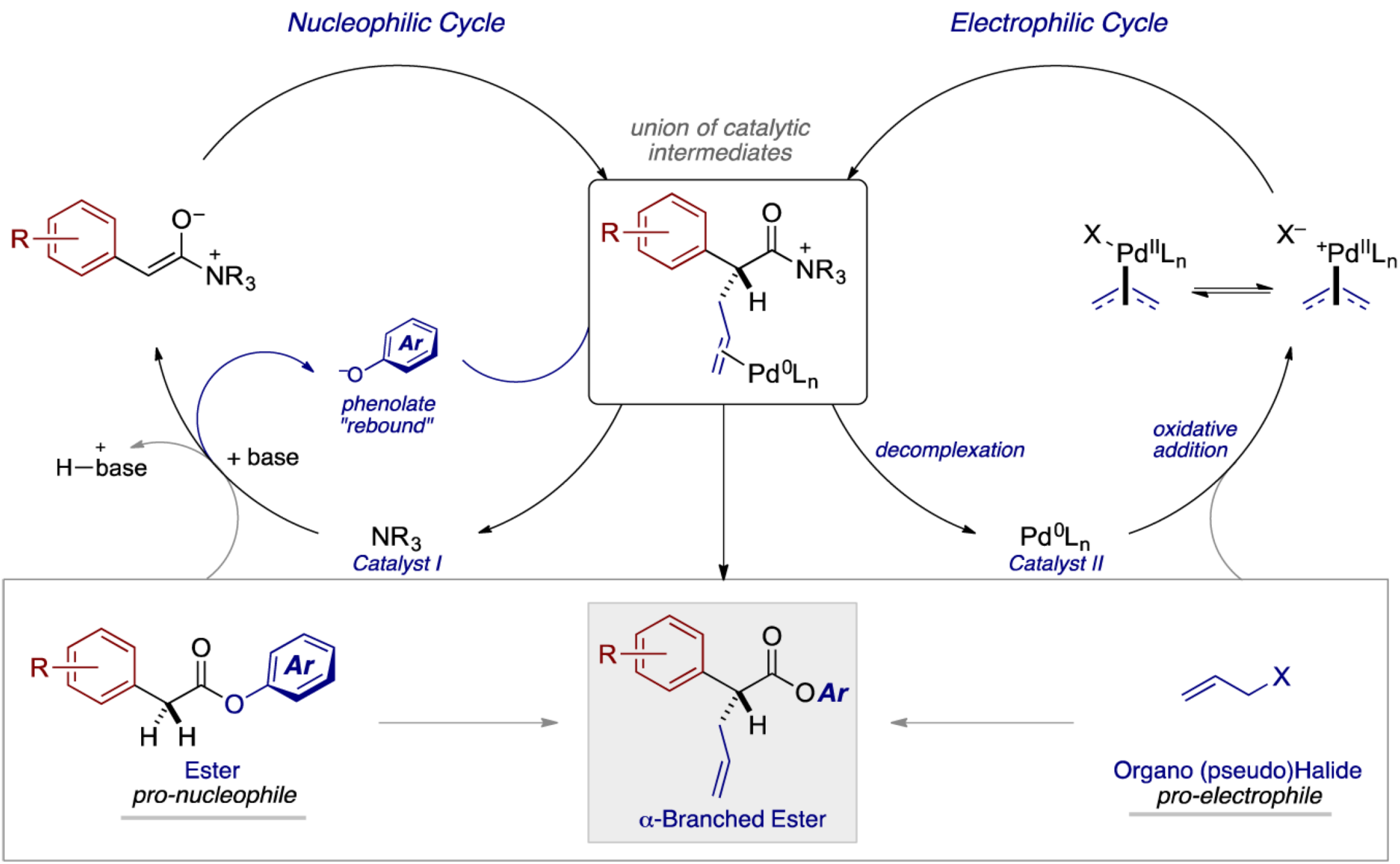
Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2017**, *139*, 87.

Snaddon's Precedent Work



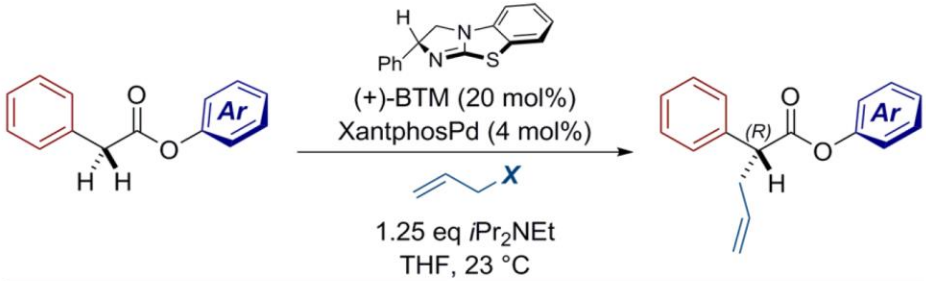
Snaddon, T. N. *et al. J. Am. Chem. Soc.* **2016**, *138,* 5214.

Proposed Mechanism

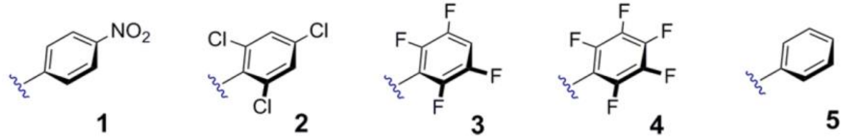


Snaddon, T. N. *et al. J. Am. Chem. Soc.* **2016**, *138,* 5214.

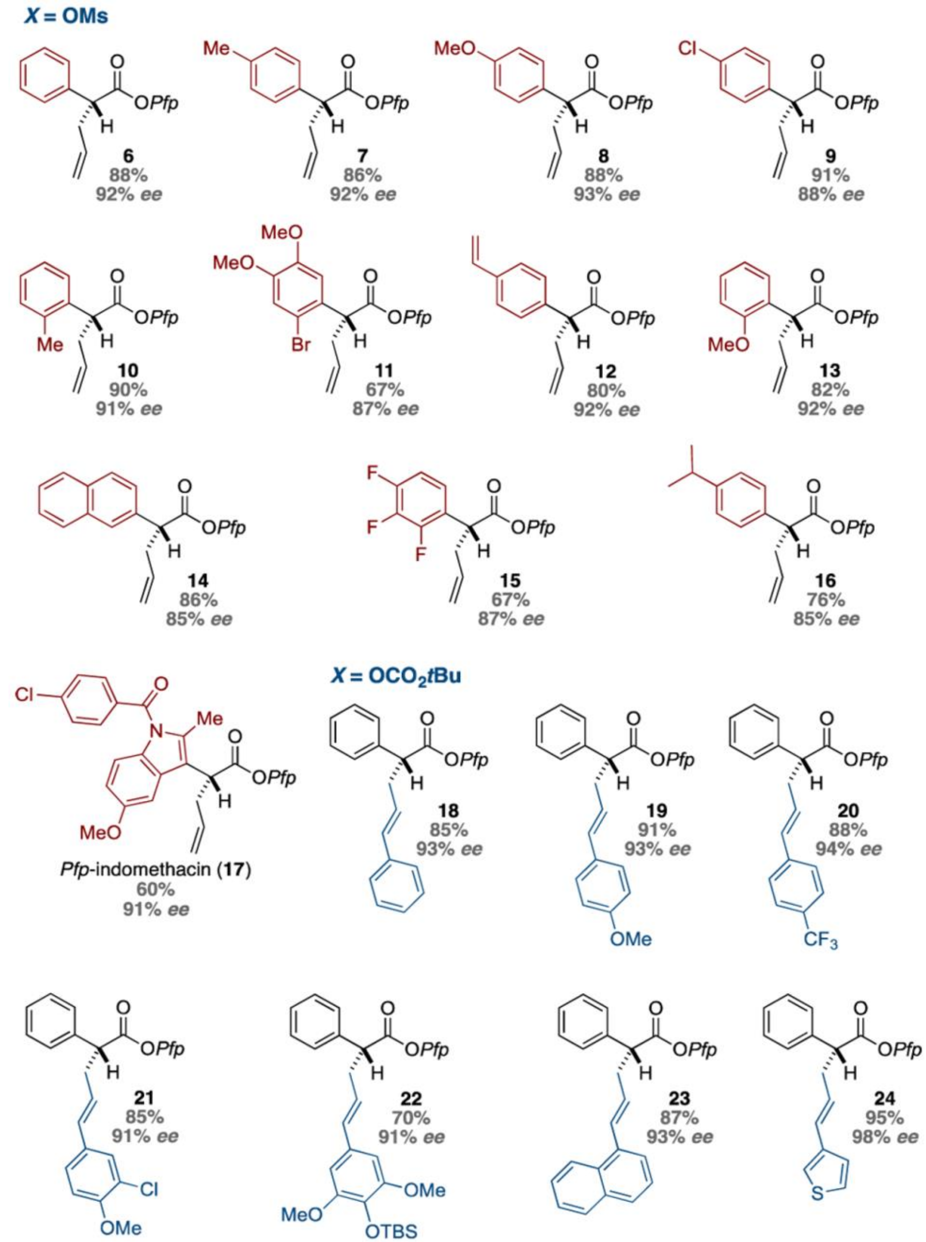
Ester and Substrate Scope



Ar =

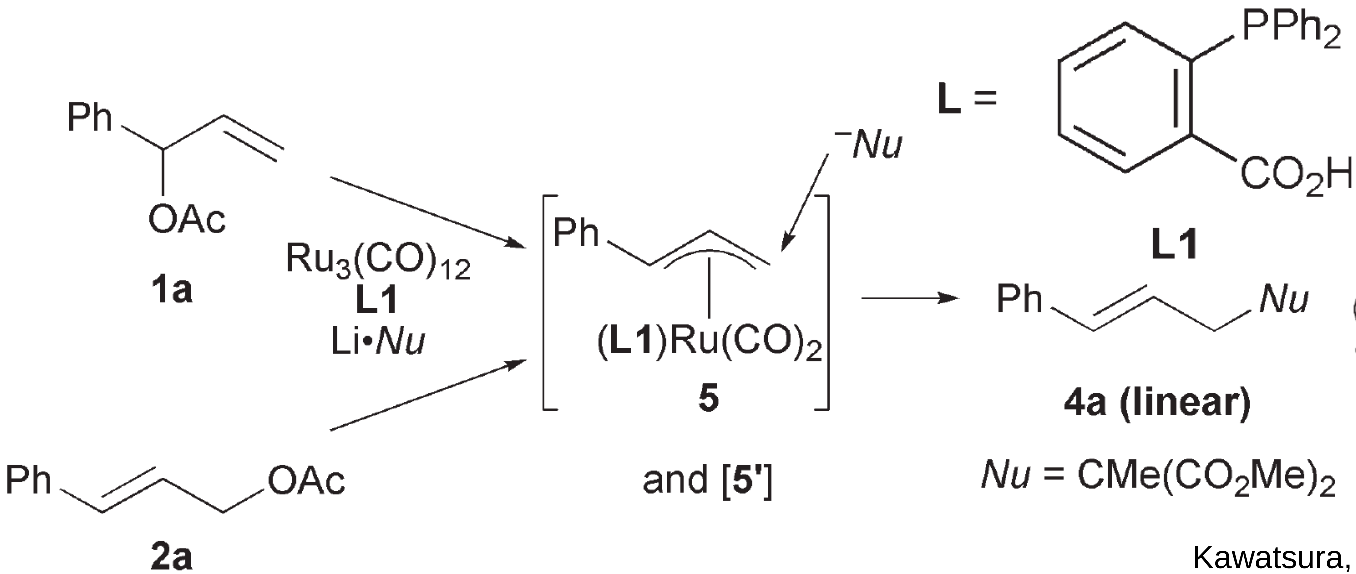


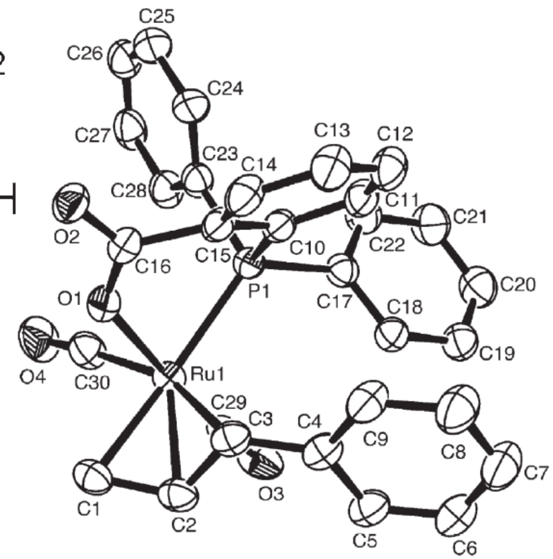
Entry[a]	*Ar*	*X*	Time [h]	Yield [%][b,c]	*ee* [%][d]
1	**1**	OAc	72	50	3
2		OPiv	72	56	5
3		OP(O)(OEt)$_2$	72	20	77
4		OP(O)(OPh)$_2$	72	43	84
5		OCO$_2$*i*Bu	72	80[e]	53
6		OCO$_2$*t*Bu	72	85	52
7		Cl	72	40	38
8		OMs	72	62 (42)	92
9	**2**	OMs	72	37	40
10	**3**	OMs	6	85 (75)	94
11	**4**	OMs	6	91 (88)	92
12	**5**	OMs	72	0	--



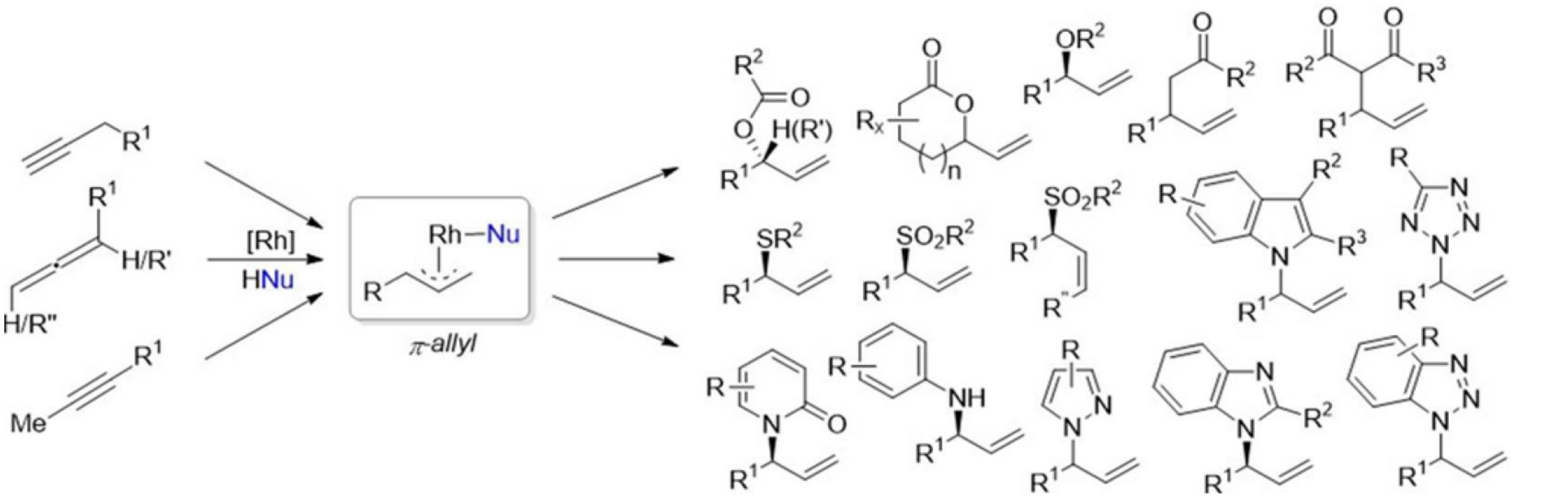
Snaddon, T. N. *et al. J. Am. Chem. Soc.* **2016**, *138,* 5214.

Recent Development





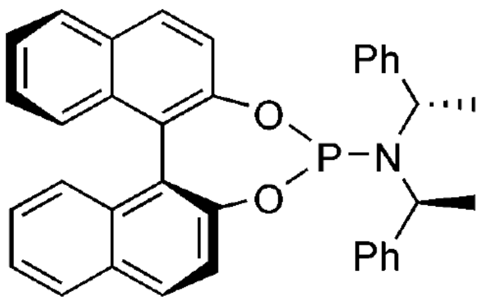
Kawatsura, M. *et al. Chem. Commun.* **2007**, 298.

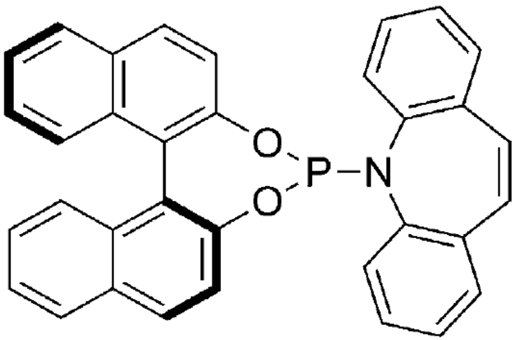


Breit, B. *et al. Acc. Chem. Res.* **2016**, *49,* 1524.

Summary

Ir-catalyzed allylic substitution shows high *enantioselectivity* and *regioselectivity*.



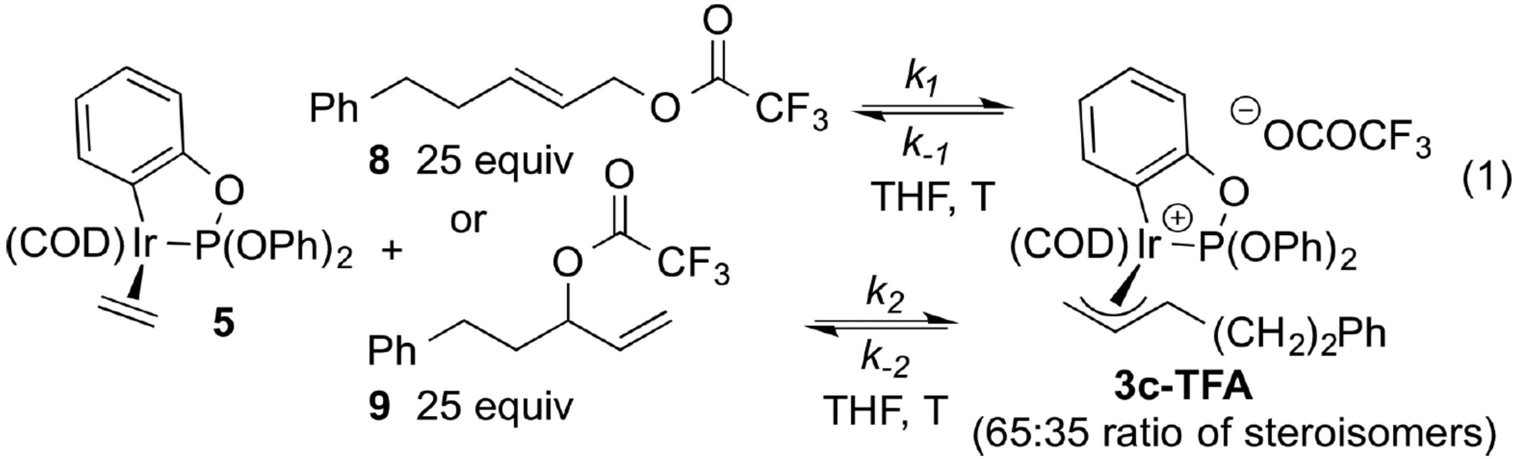


- Basic condition is necessary
- Oxidative addition step is the most critical for enantioselectivity.
- Nucleophilic attack is much faster than oxidative addition
- Linear selectivity can be explained by CH…O weak interaction.
- Only kinetic resolution.

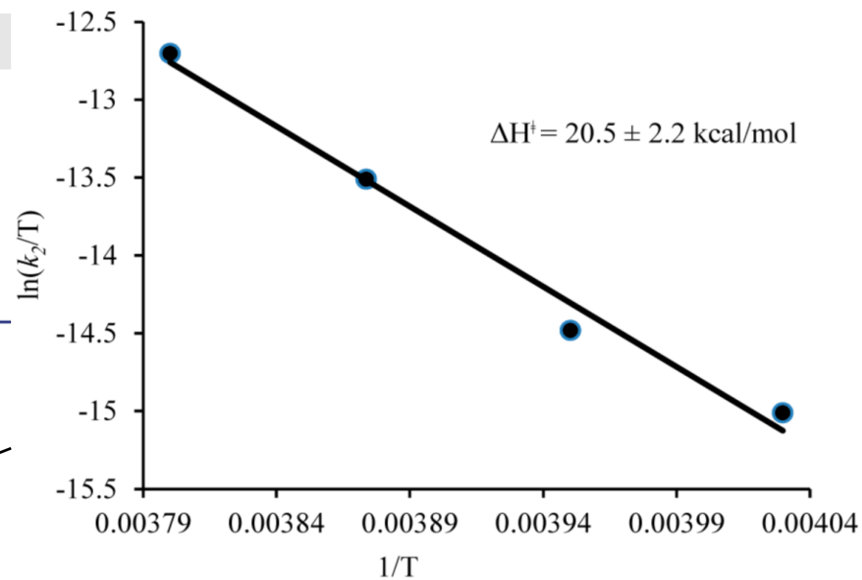
- Acidic condition is necessary。
- Dynamic kinetic resolution can be also used.
- First diastereo- enantio-divergent allylic substitution.

Even today, Ir-catalyzed allylic substitution is *evolving constantly* !

Kinetic Experiment



	8 or **9**	*T* (°C)	k_1 or k_2 (s^-)
1	**9**	−10	8×10^{-4}
2	**9**	−15	3.5×10^{-4}
3	**9**	−20	1.3×10^{-4}
4	**9**	−25	7.5×10^{-5}
5	**8**	20	2.7×10^{-4}

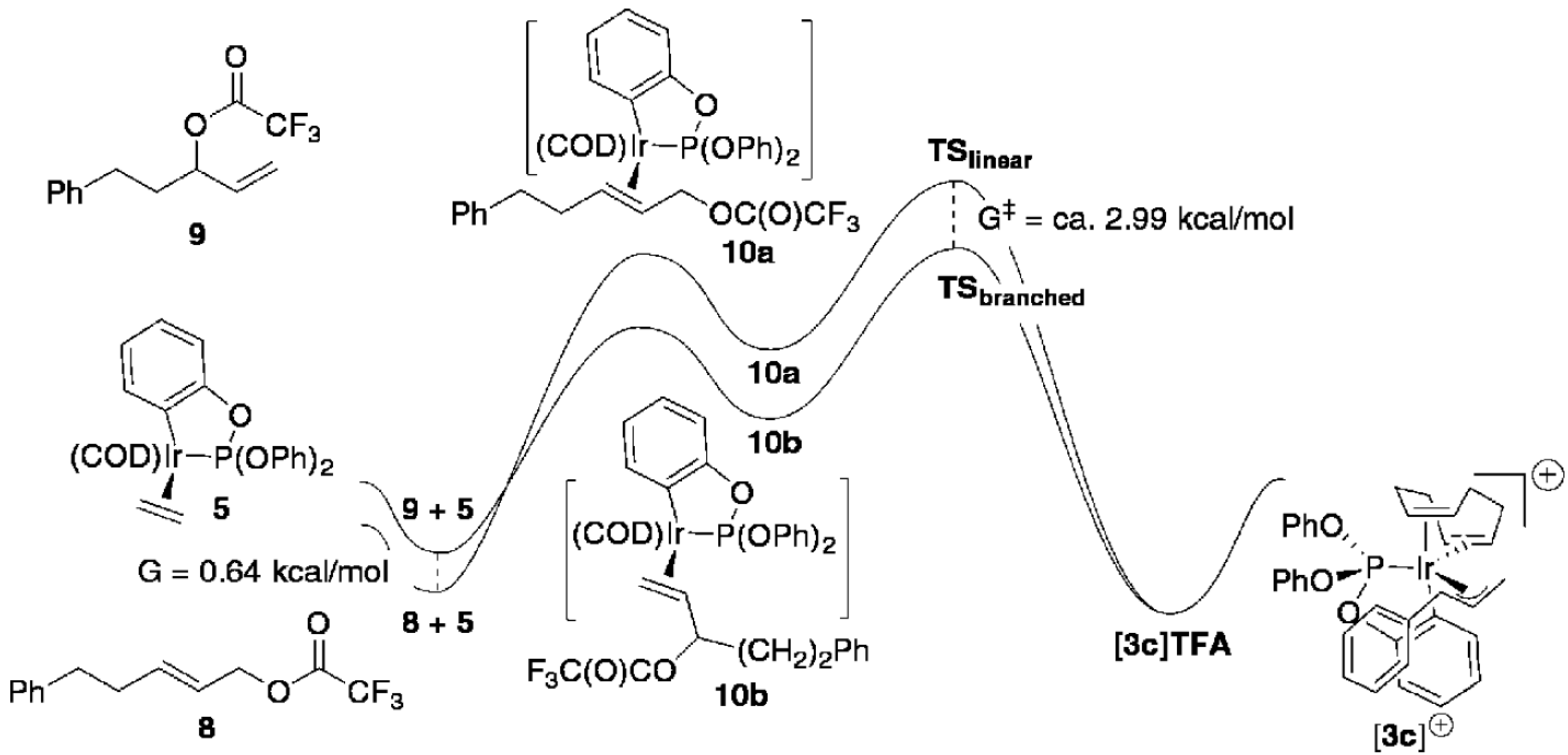


$k_1=2.7*10^{-4}$

$k_2=4.6*10^{-2}$

k_2 is 170 times bigger than k_1. = 3 kcal/ mol

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2015**, *137*, 14968.



O
O
CF3
Ph
9
(COD)Ir
O
P(OPh)2
Ph
OC(O)CF3
10a
TSlinear
G‡ = ca. 2.99 kcal/mol
TSbranched
10a
10b
(COD)Ir
O
P(OPh)2
5
9 + 5
G = 0.64 kcal/mol
8 + 5
(COD)Ir
O
P(OPh)2
F3C(O)CO
(CH2)2Ph
10b
O
Ph
O
CF3
8
[3c]TFA
PhO
PhO
P
Ir
O
[3c]