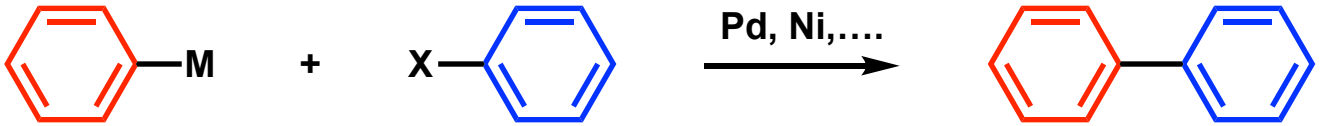
Metal-Catalyzed Asymmetric Cross-Coupling Reactions

181215_LS_Daiki_Kamakura

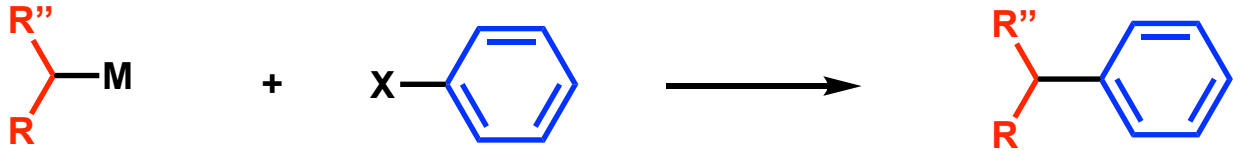
Cross-Coupling Reactions Using sp^3-Substrates

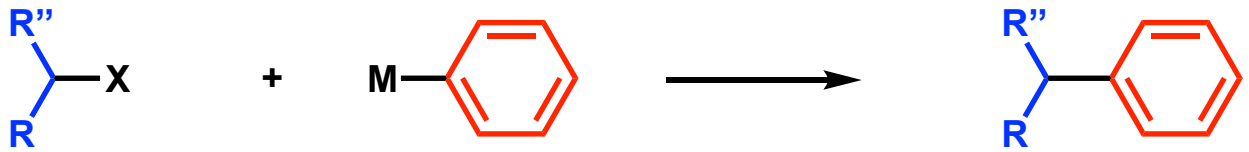
sp^2-sp^2 cross cpupling



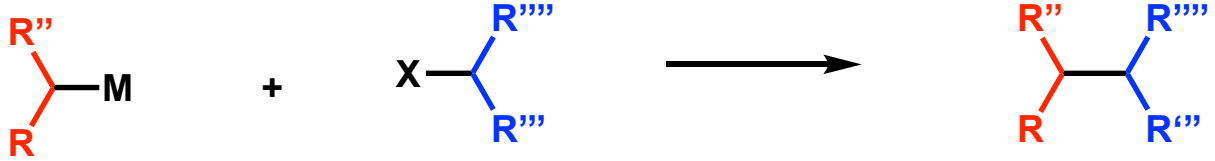
M = BR_2, ZnR, SnR_3, SiR_3,…; X = I, Br, Cl, OTf,….

sp^3-sp^2 cross cpupling

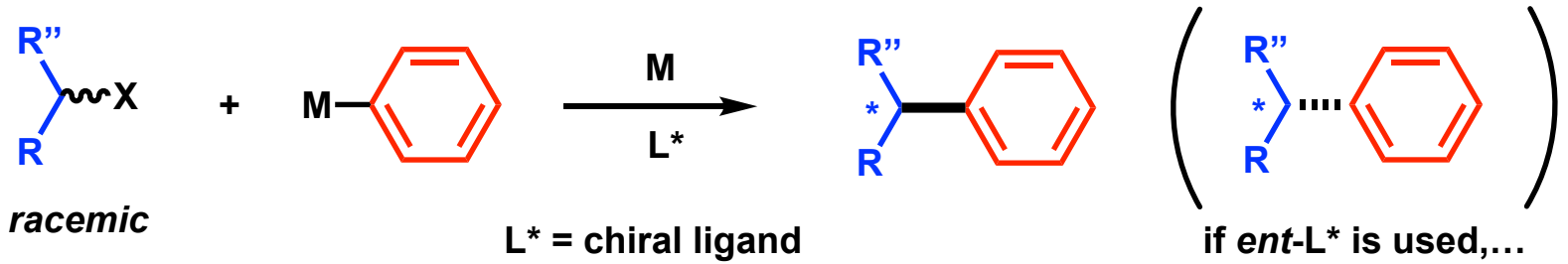


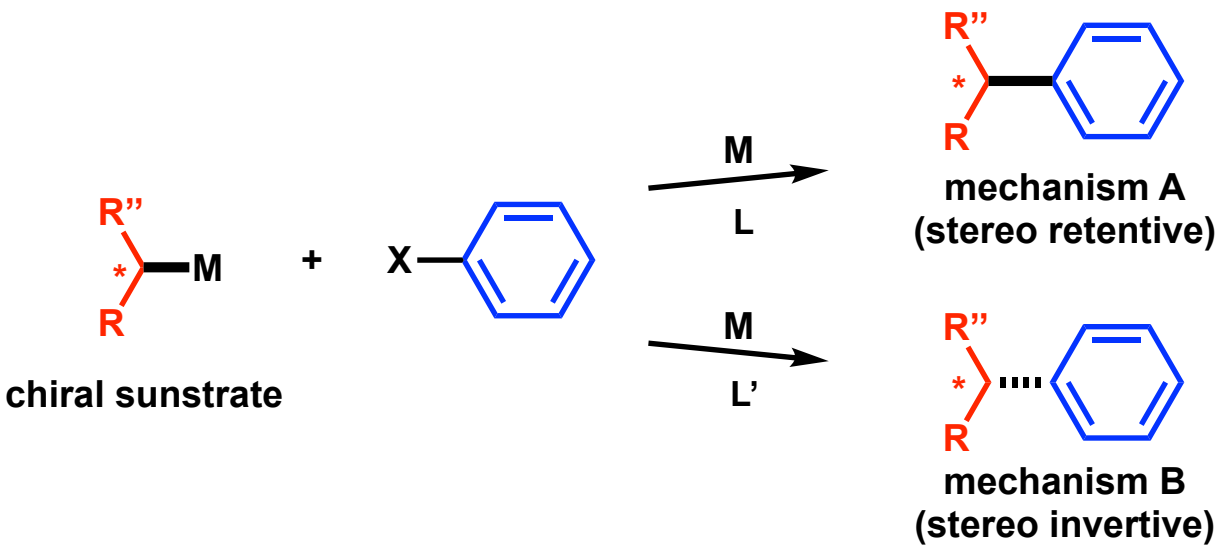


sp^3-sp^3 cross cpupling



Strategies for Asymmetric Cross-Coupling Reactions





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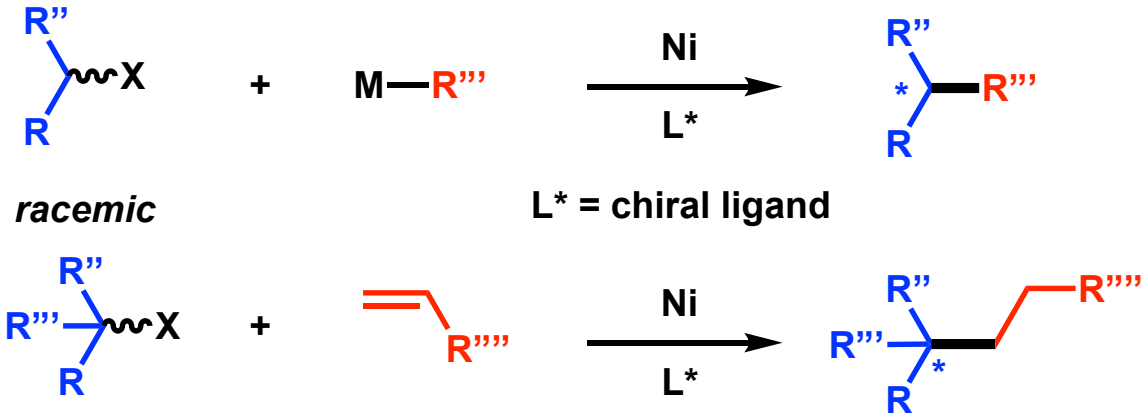
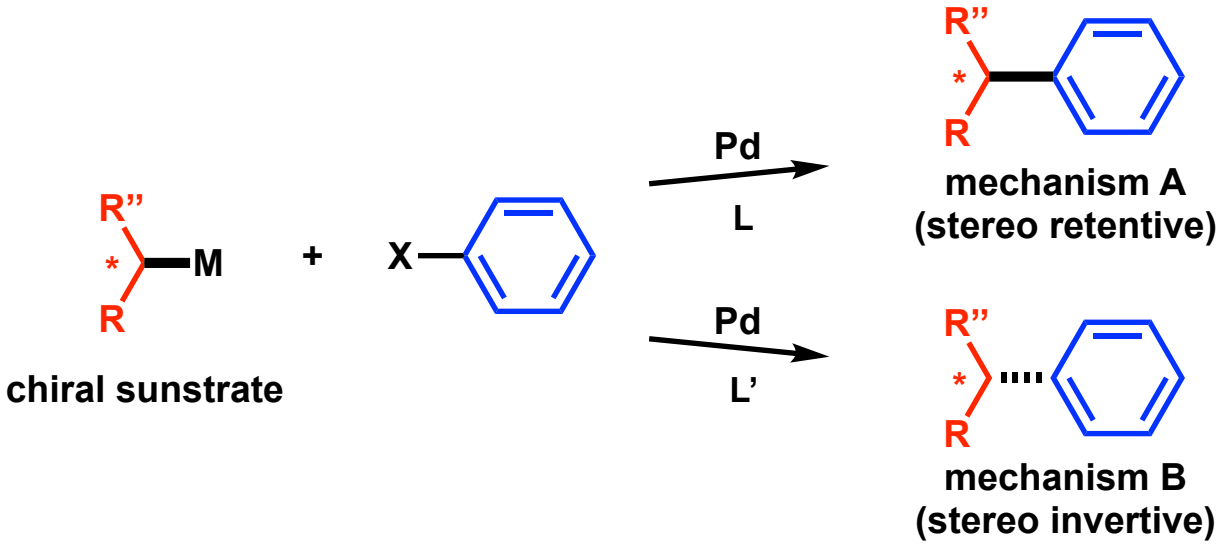


2. **Enantiodivergent Pd-Catalyzed C–C Bond Formation Enabled through Ligand Parameterization (Sigman, Biscoe, 2018)**



Contents

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racemic

L* = chiral ligand

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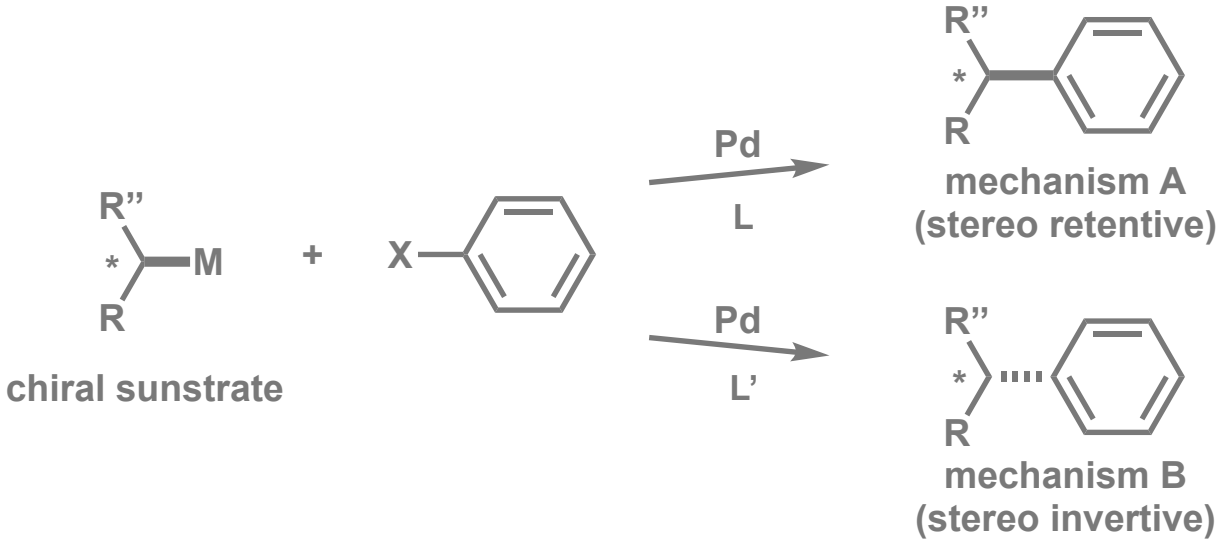
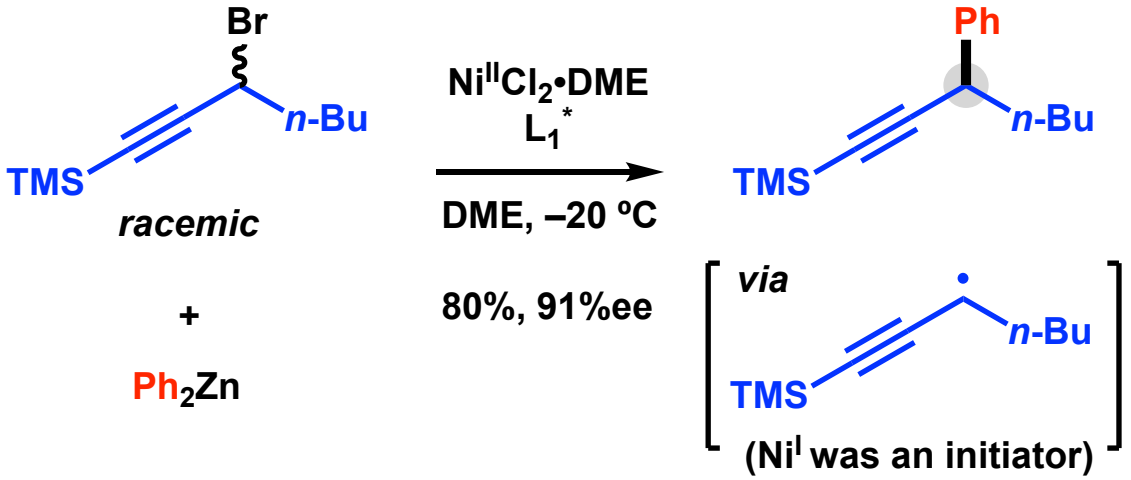
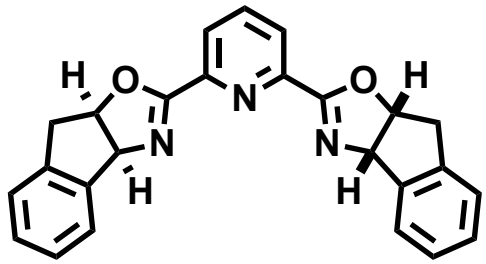


Fu's Previous Works

- **Enantioselective cross coupling of propargyl bromide with diphenylzinc**

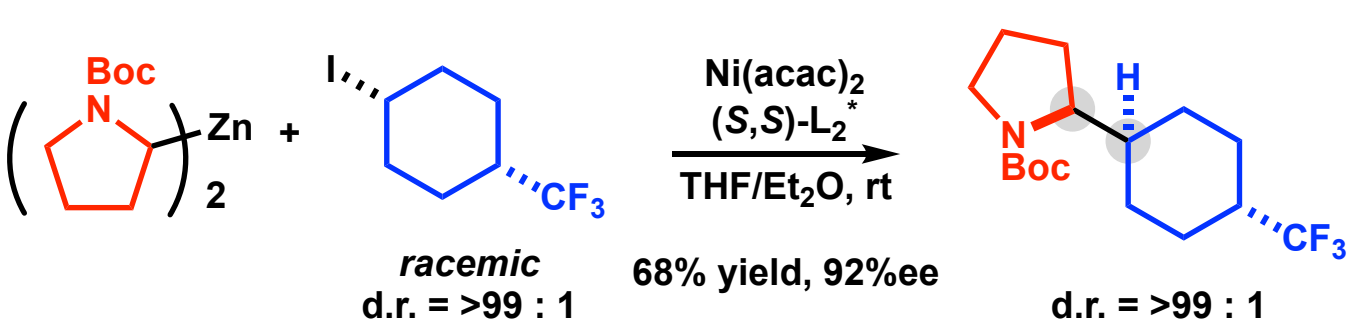


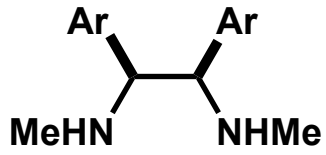


L_1^* = (–)-indenyl-pybox

Smith, S. W.; Fu, G. C. *J. Am. Che. Soc*. **2008**, *130*, 12645.
Schley, N. D.; Fu, G. C. *J. Am. Che. Soc*. **2014**, *136*, 16588.

- **Control of Vicinal Stereocenters through Nickel-Catalyzed Alkyl-Alkyl Cross-Coupling**



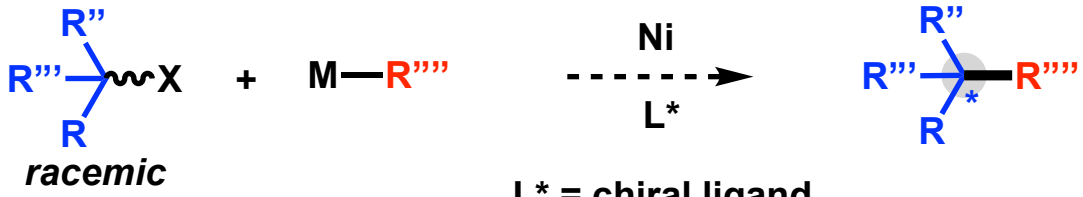


(*S*, *S*)-L_2^*
Ar = 1-Naphthyl

Mu, X.; Shibata, Y.; Makida, Y.; Fu, G. C. *Angew. Chem. Int. Ed.* **2017**, *56*, 5821.

Construction of Quaternary Carbon Center

- **Enantioselective cross coupling of *tert*-haloalkane**

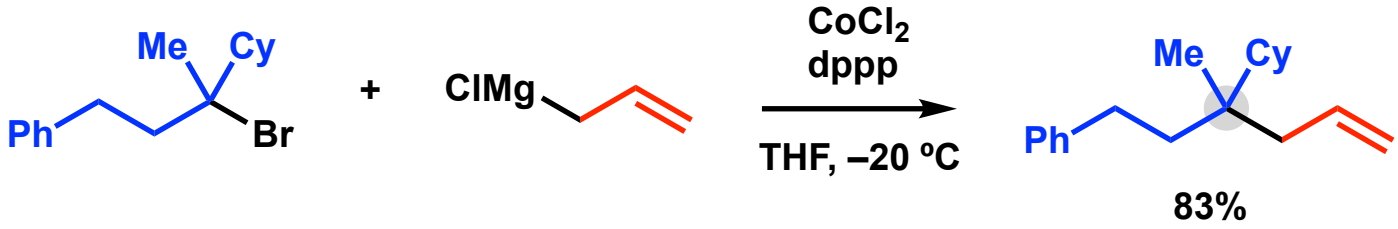


L* = chiral ligand

It is difficult to quaternary carbon center by cross-coupling reaction

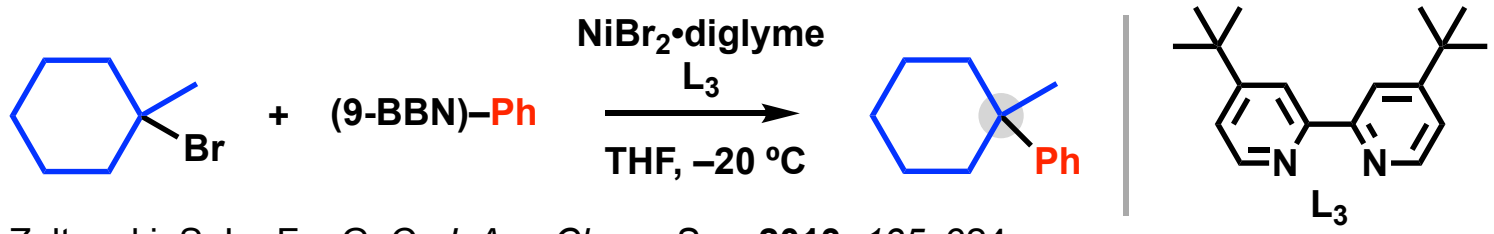
---

- **Reported methods**



83%

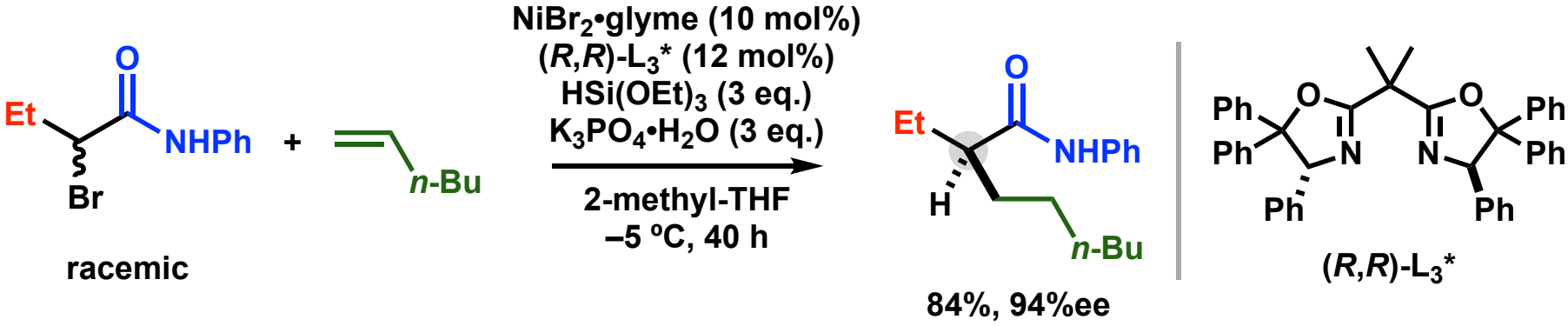
Tsuji, T.; Yorimitsu, H.: Oshima, K. *Angew. Chem. Int. Ed*, **2002**, *41*, 4147.



Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624.

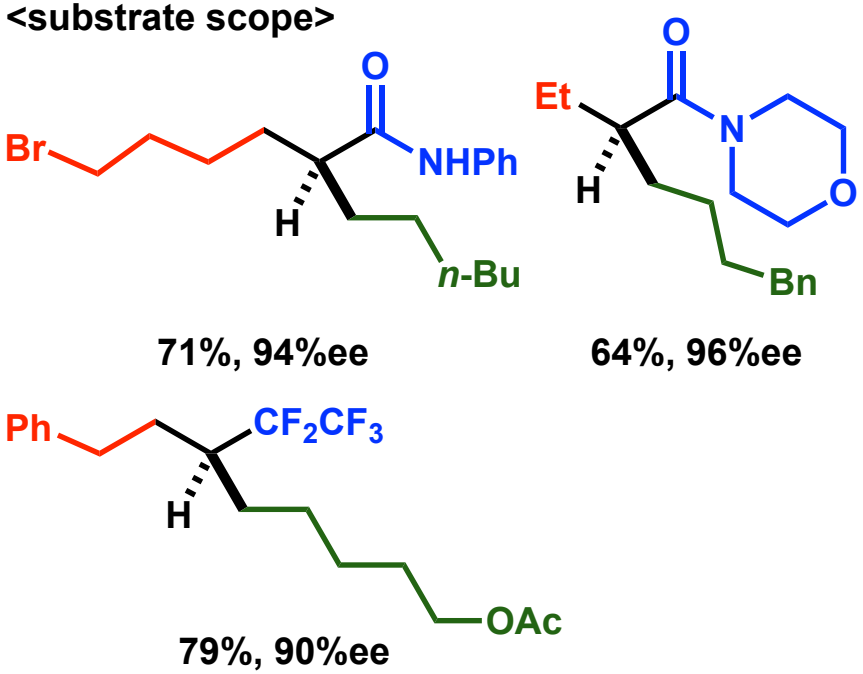
——> Asymmetric construction of quaternary carbon center has not been achieved.

Ni-Catalyzed Reaction of sec-Bromide with Olefin



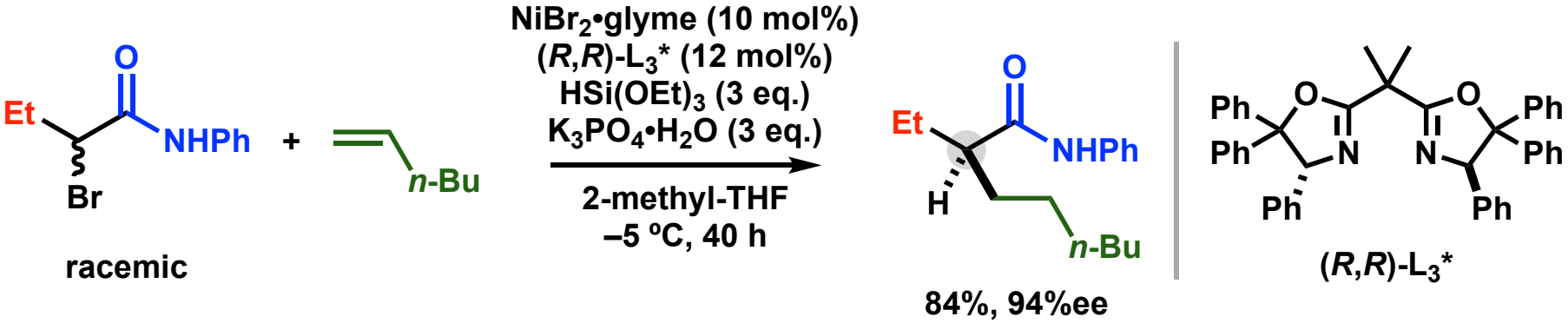
Entry	variation from the "standard conditions"	yield	ee (%)
1	under air	66%	94%
2	with H_2O (1.0 eq.)	78%	95%
3	gram scale	88%	94%

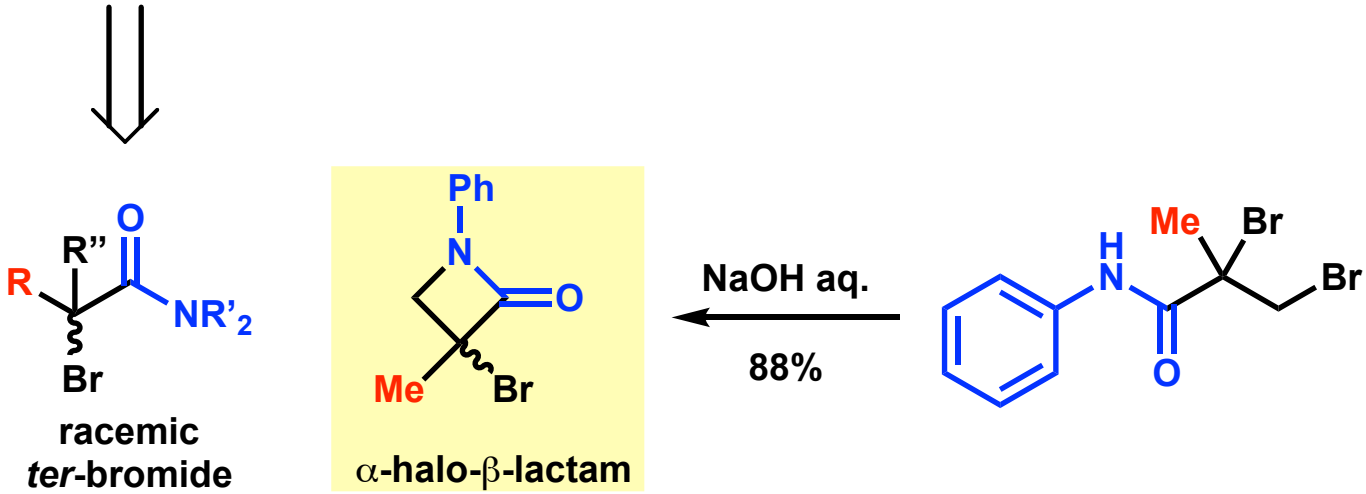
<substrate scope>



Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.

Design of Substrate

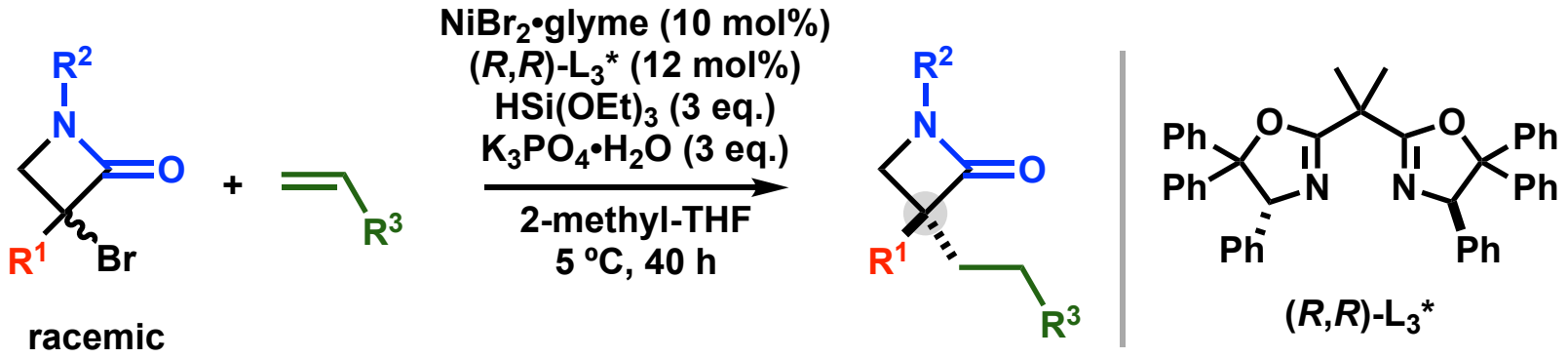


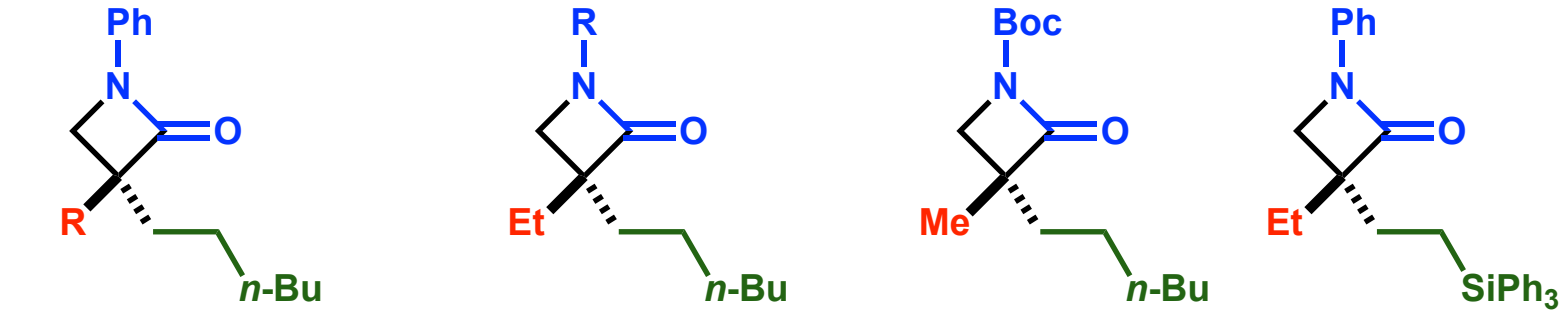


In order to reduce steric hindrance in the vicinity of the reactive site, cyclic substrate was designed.

Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.

Ni-Catalyzed Reaction of tert-Bromide with Olefin





R^1 = Me: 90%, 99%ee
R^1 = Et: 94%, 99%ee
R^1 = Bn: 85%, 98%ee
R^1 = *i*-Pr: 76%, 98%ee

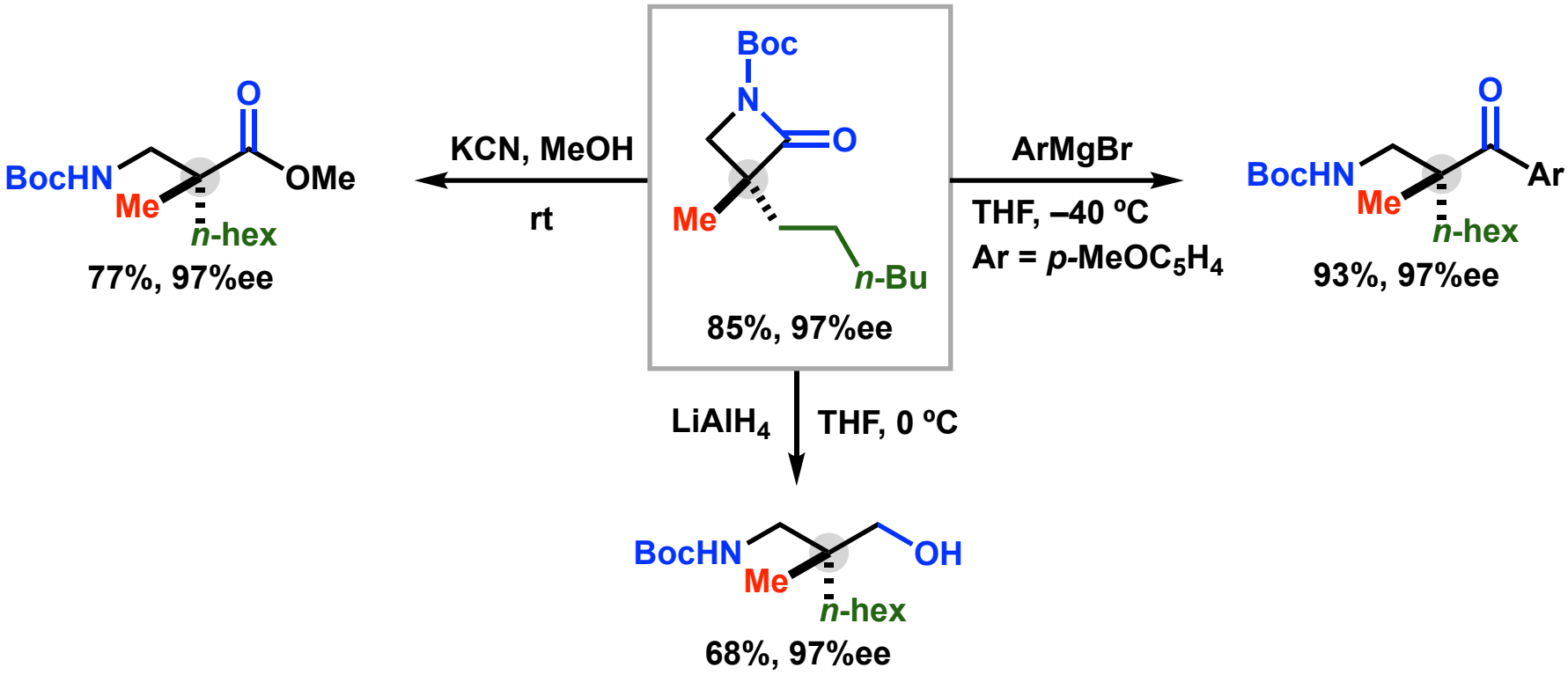
R^2 = *n*-Bu: 92%, 99%ee
R^2 = *c*-hex: 94%, 99%ee
R^2 = $CHPh_2$: 88%, 99%ee
R^2 = OBn: 59%, 97%ee

85%, 97%ee

78%, 95%ee

Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.

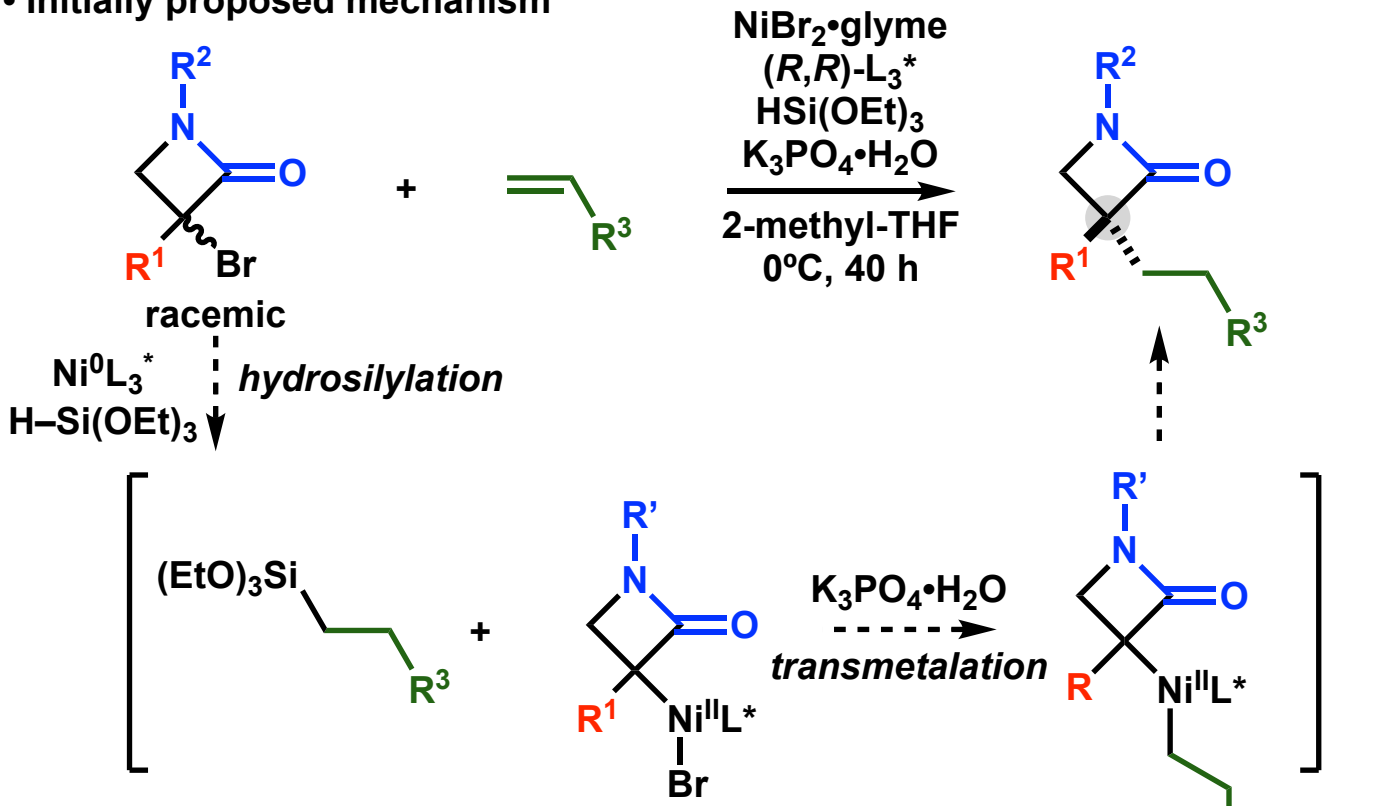
Transformations of Obtained Compound



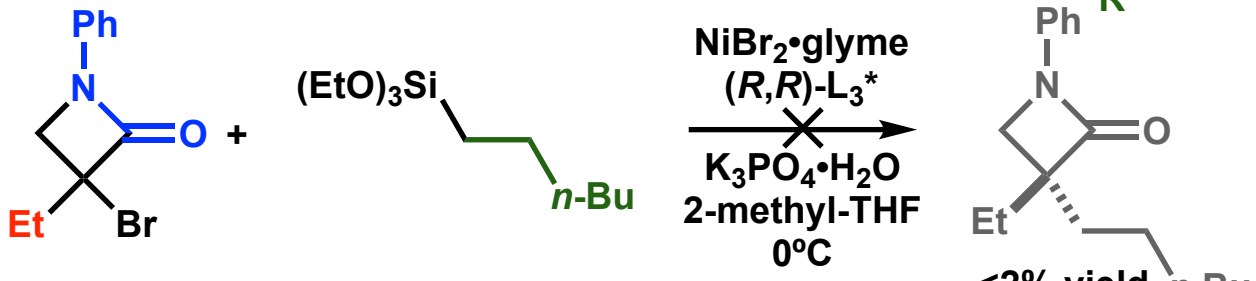
Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.

Initially Proposed Mechanism

- Initially proposed mechanism



- Reaction with alkylsilane

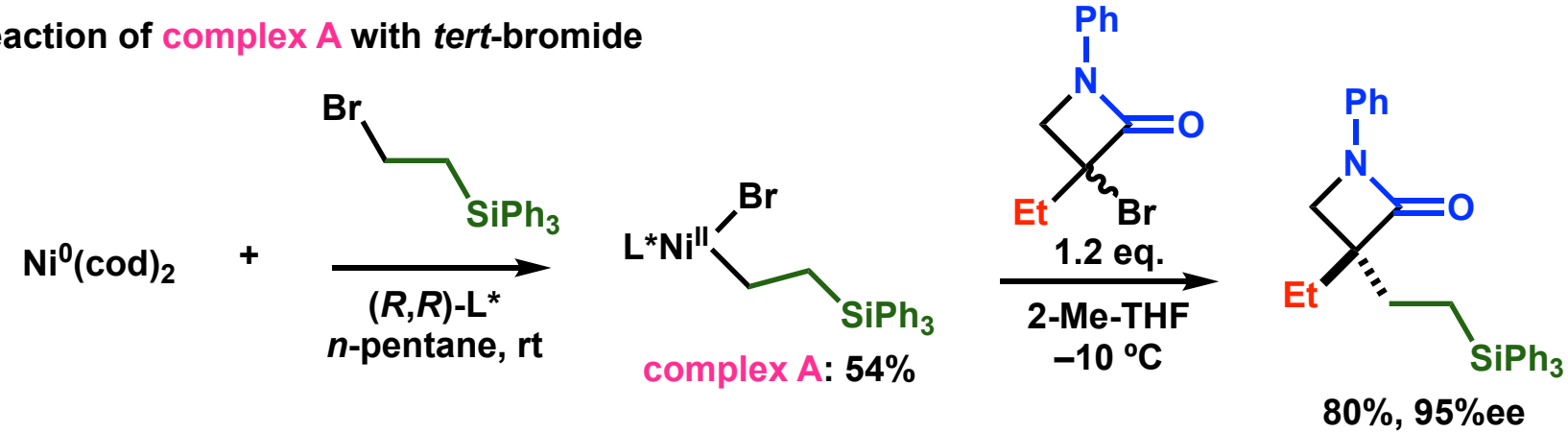


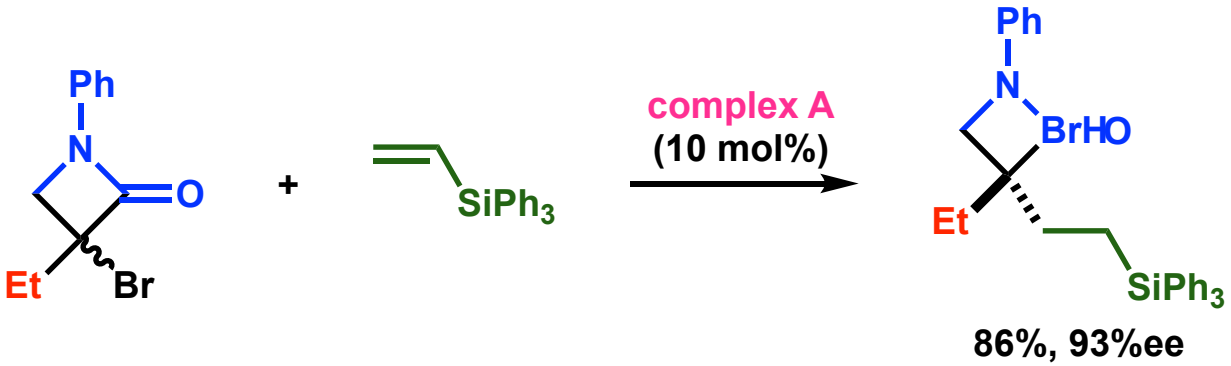
——> Alkylsilane was not reaction intermediate

Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.

Mechanistic Study

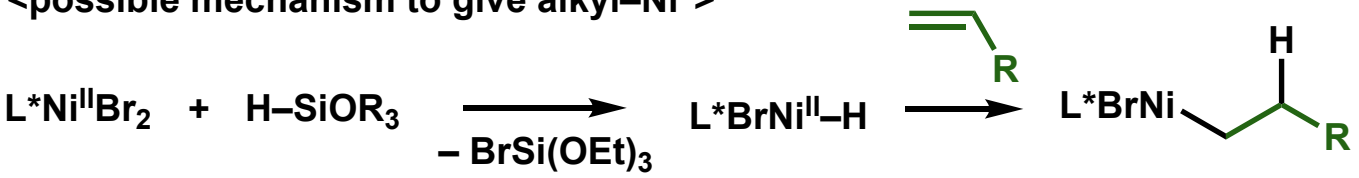
• **Reaction of complex A with *tert*-bromide**





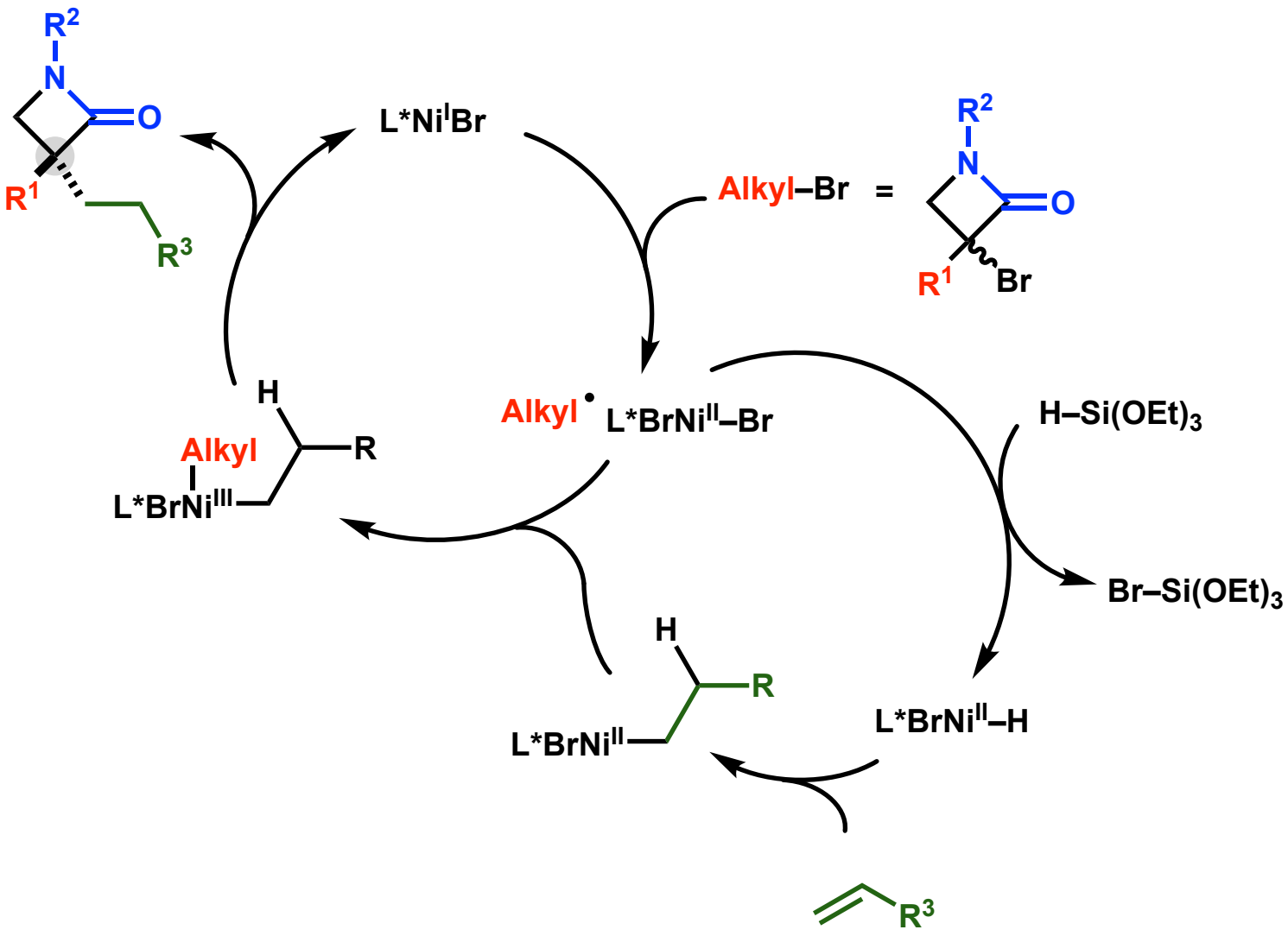
——> **complex A would be the active species of the reaction**

<possible mechanism to give alkyl–Ni^{II}>



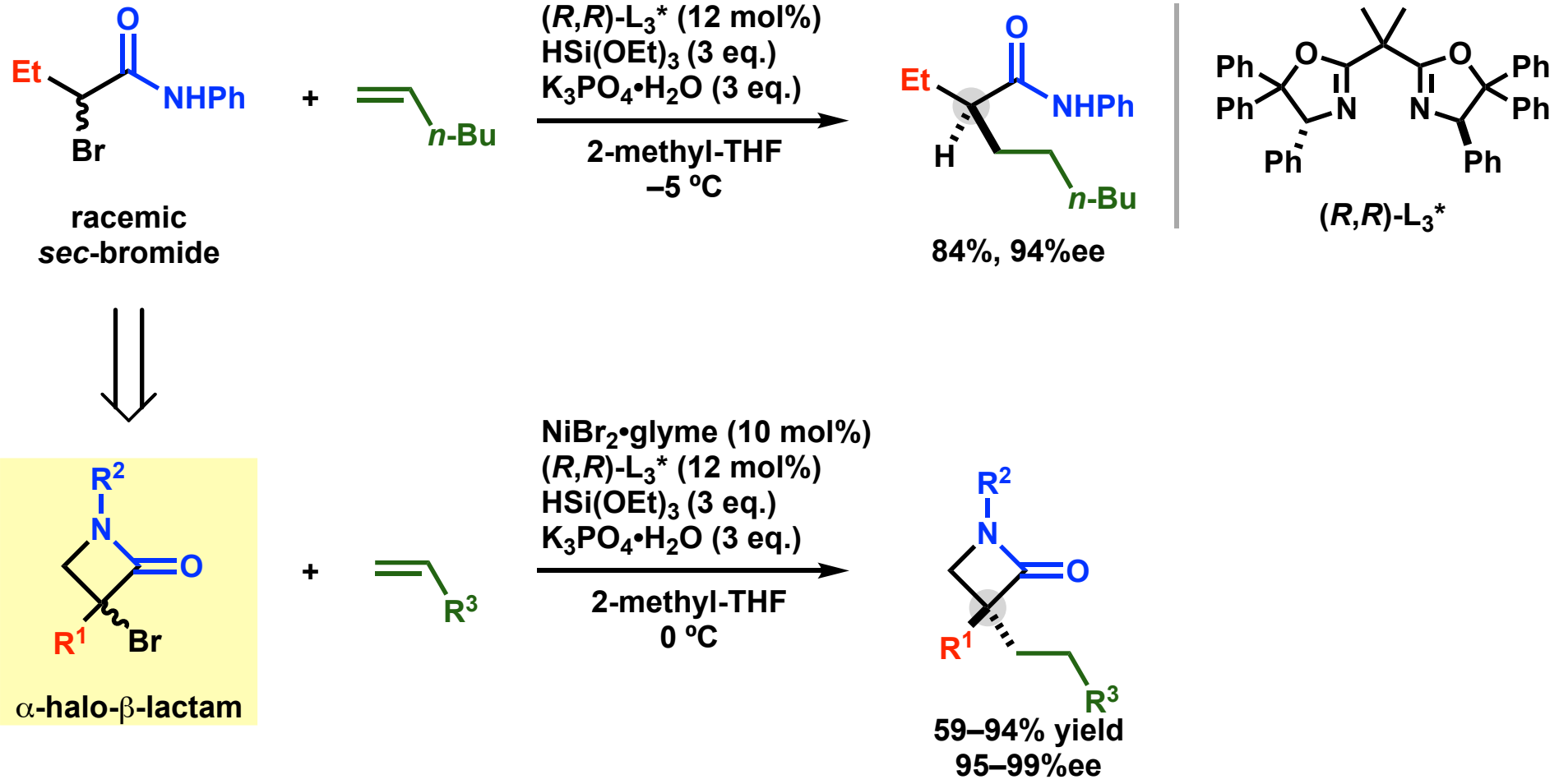
Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.

Proposed Catalytic Cycle



Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.

Short Summary



Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.

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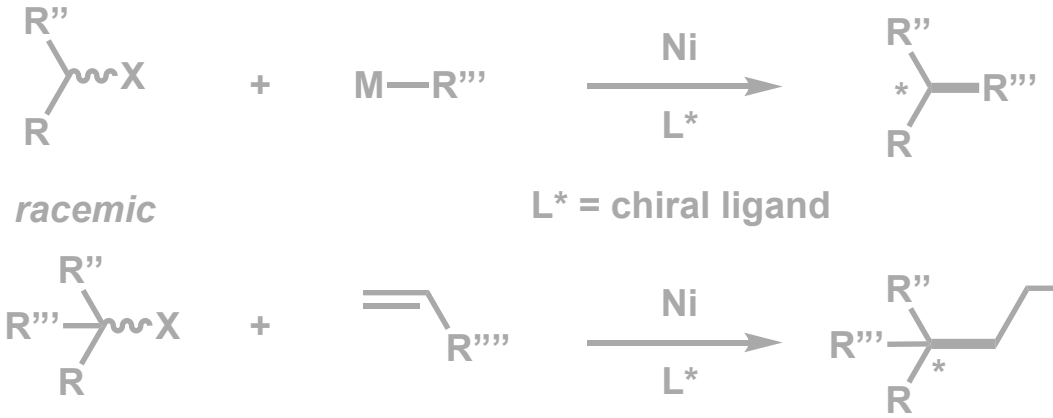

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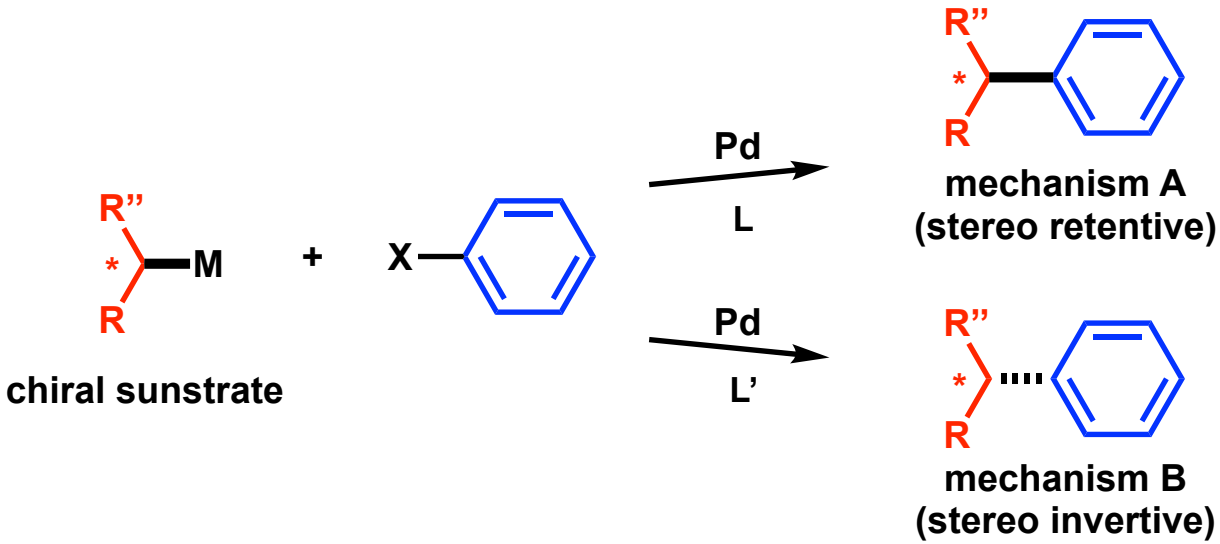
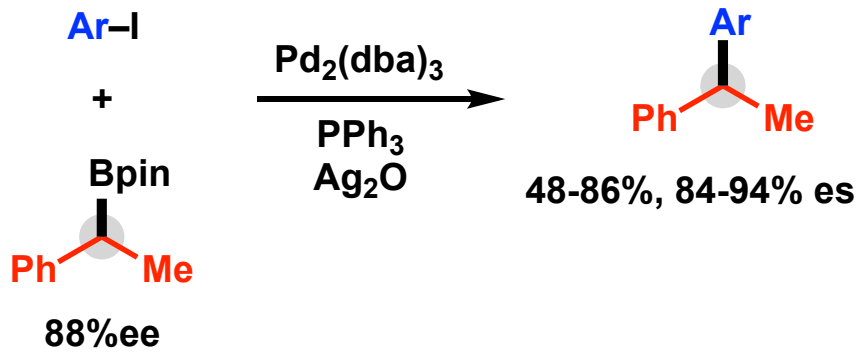


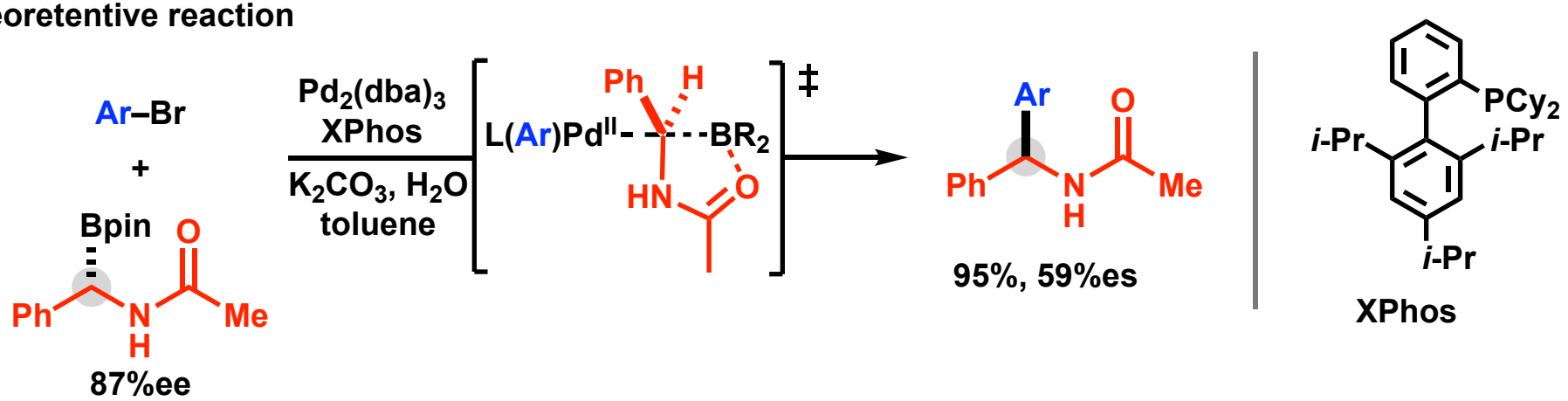
Cross-Coupling of Chiral Boronic Esters

- **Stereoretentive reaction**



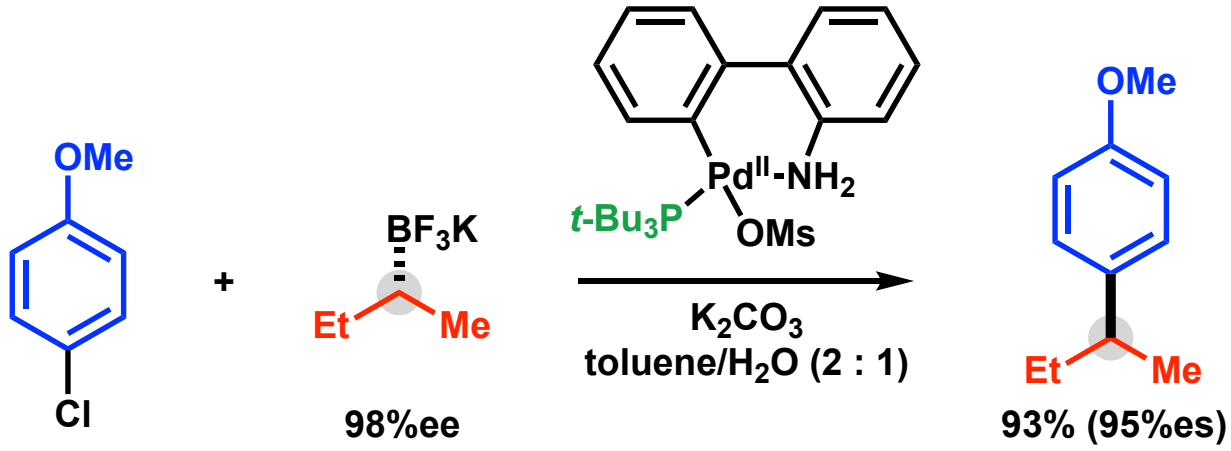
Imao, D,; Veronique, G.; Laberge, S.; Crudden, C. M. *J. Am. Chem. Soc*. **2009**, *131*, 5024.

- **Stereoretentive reaction**



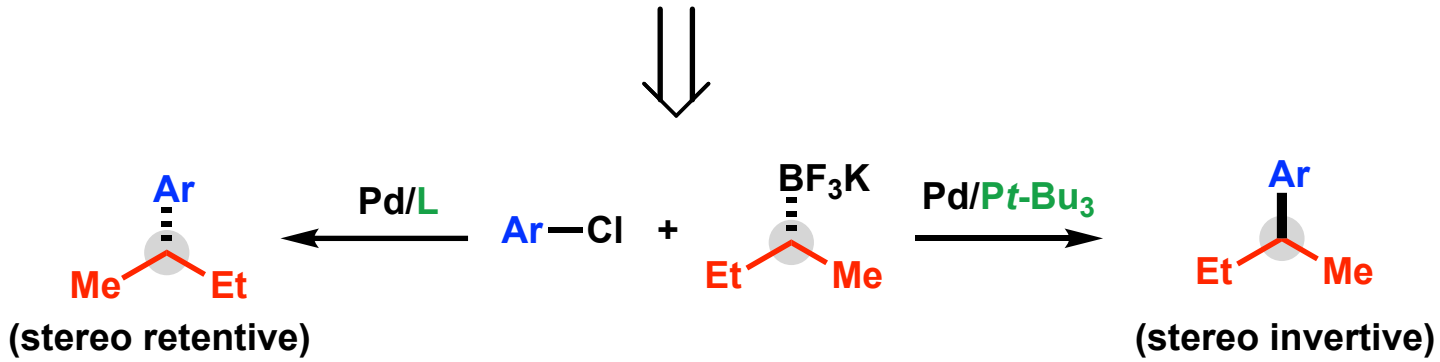
Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132,* 13191.

Cross-Coupling of Chiral Boronic Esters



Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* ***2014***, 136, 14027.

The factors controlling the dominant mechanism of transmetallation are not understood.

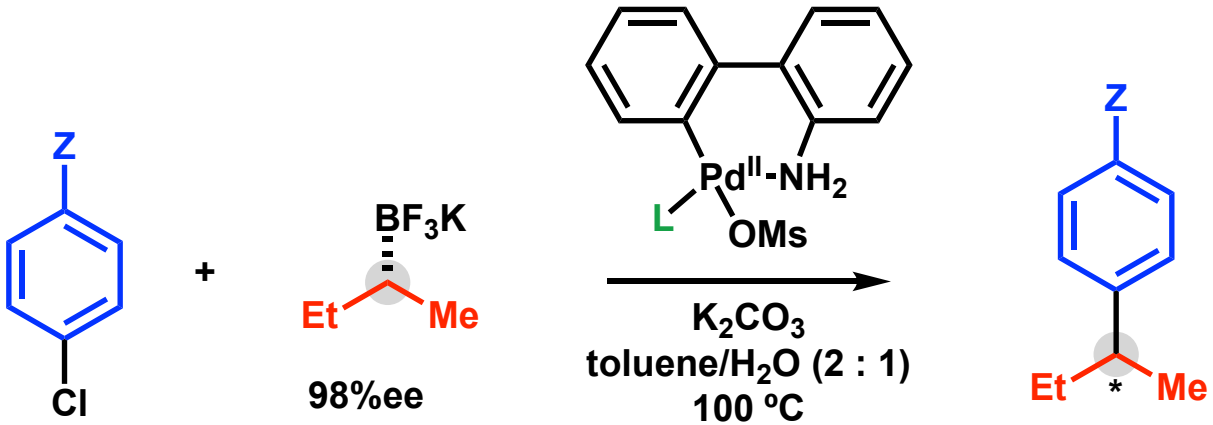


Aim of this research:

- **Development of the ligand-controlled enatiodivergent cross-coupling reaction**
- **To reveal the factors that control the the transfer of stereochemistry**

Wang, Z.; Yin, H.; u, G. C. *Science*, **2018**, *563*, 379.

Effects of the Substituent and Ligand



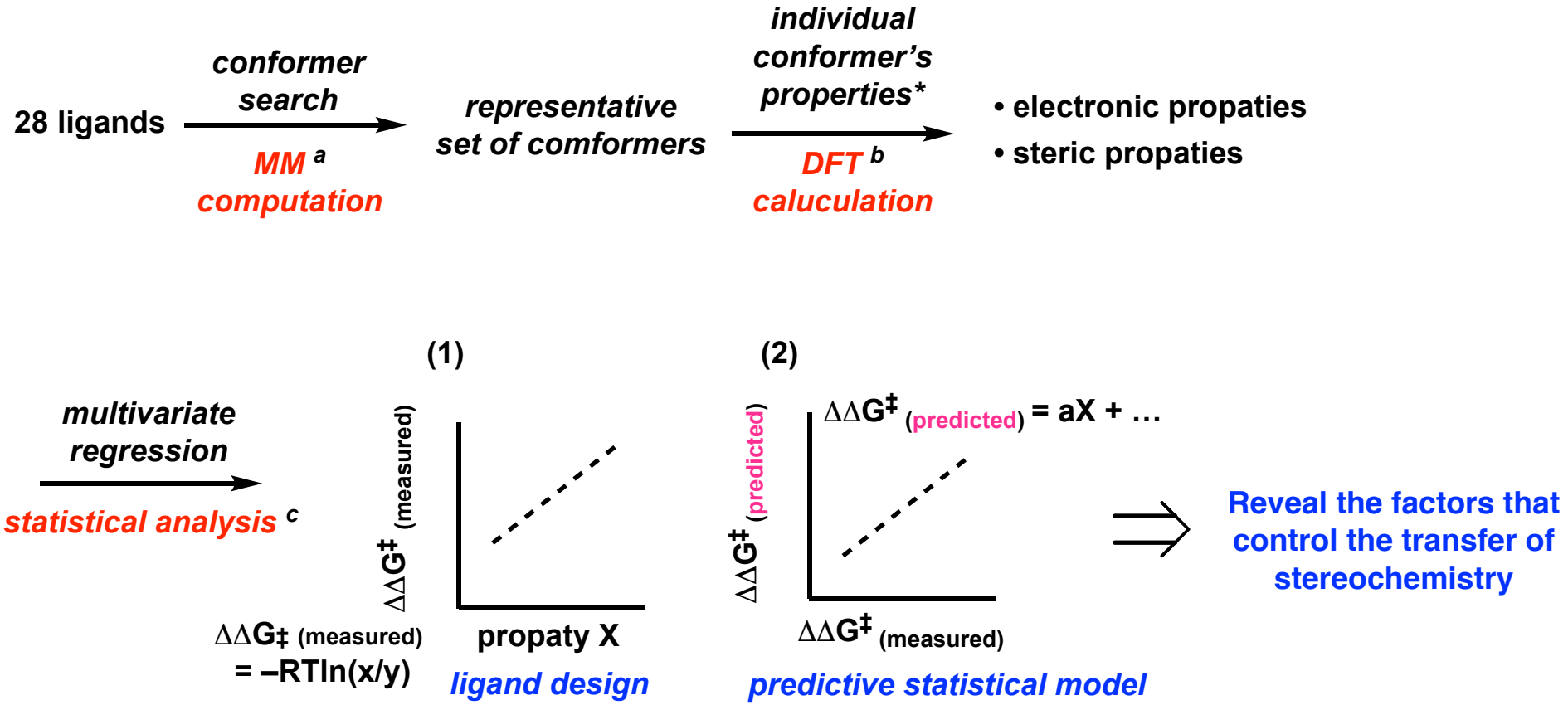
Z	σ_{para}	ee (L = P*t*-Bu$_3$)	L	*solid angle*	ee (Z = CO_2Et)
OMe	–0.27	–91%	P*t*-Bu$_3$	150º	–79%
Me	–0.17	–89%	PAd$_2$*n*-Bu	150º	+4%
CO_2Et	0.45	–79%	PPh_3	126º	+12%
CF_3	0.54	–72%	P*t*-Bu$_2$Ph	145º	+21%
CN	0.66	–67%	Po-tol$_3$	153º	+65%

Ad = adamantyl

——> No obvious correation was observed between these results and the steric properties (solid angle).

Xhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. *Science*, **2018**, *362*, 670.

General Scheme of Model Development



[a] A conformational search was performed for all phosphines using OPLS3 force field and low frequency-mode conformational search. Conformers within 15kcal/mol were considered for further computations.

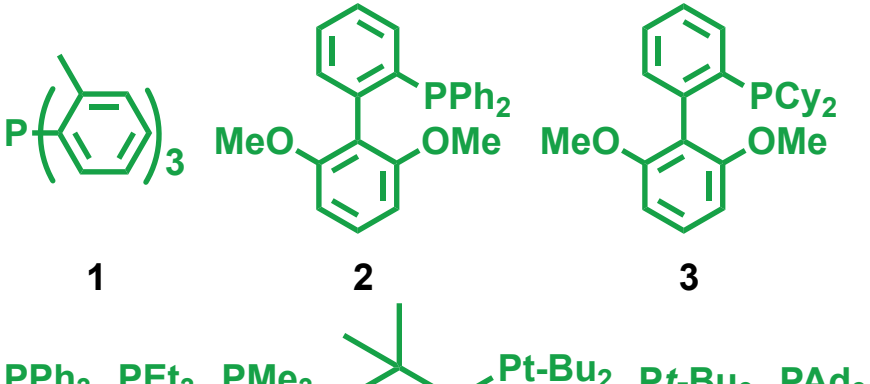
[b] All structures were fully optimized at the PBE0/6-31+G(d) level and frequency analysis was performed at the same level.

[c] Multivariate model development was performed using MATLAB R2017a with forward stepwise linear regression.

Xhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. *Science*, **2018**, *362*, 670.

Experimental Workflow

28 ligands



+ other 19 phosphines

R–BF_3K
Ar–Cl, Pd

experiments

R–Ar
xx%ee

correlation?

MM, DFT caluculation

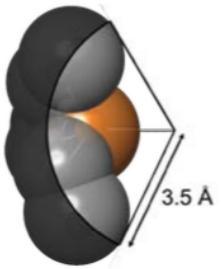
electronic propaties
- P chemical shift
- P lone pair and P–C antibonding orbital energies
- P partial charge
- P lone pair electrostatic potential

steric propaties
- percent buried volume
- Sterimol values
- Solid angle

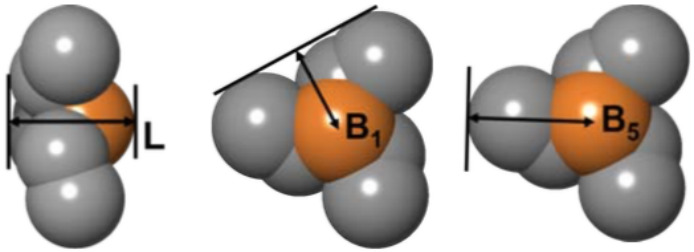
* obtaine four kinds of values (min, max, Boltz, MC)with one propaty

<*steric propaties*>

%V_{bur}

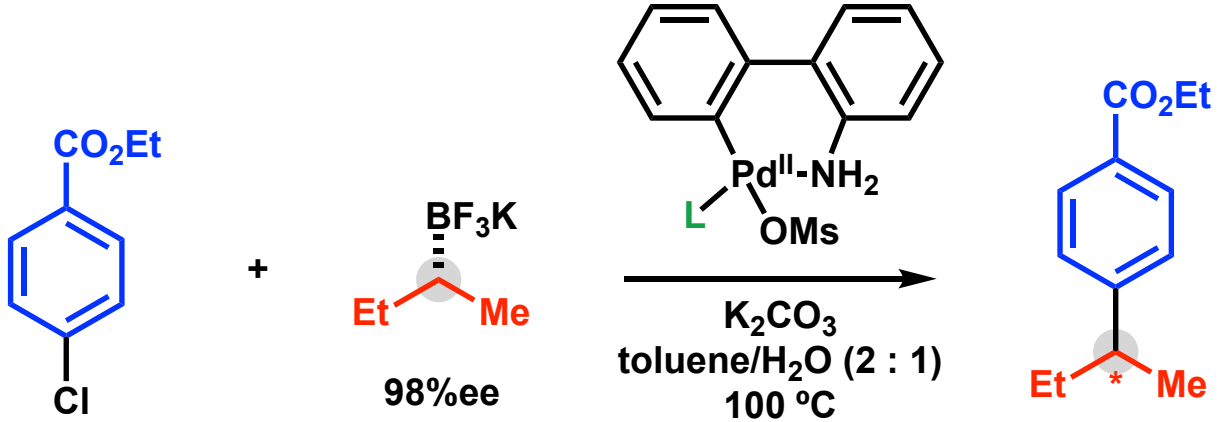


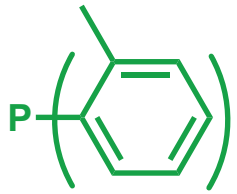
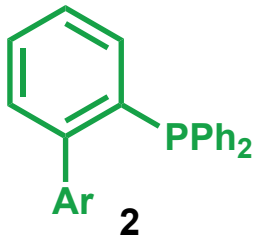
Sterimol values



Xhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. *Science*, **2018**, *362*, 670.

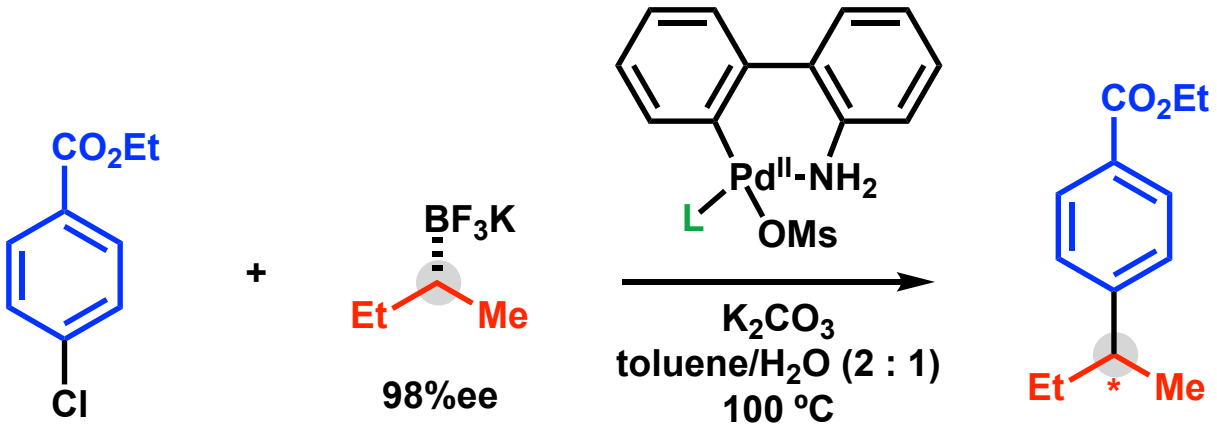
Initial Investigations



L	ee	L	ee
 1	65%	 7	–68%
 2 Ar = 2, 6-di-MeOC$_6$H$_3$	52%	P*t*-Bu$_3$ 8	–79%
		PAd$_3$ 9	–93%

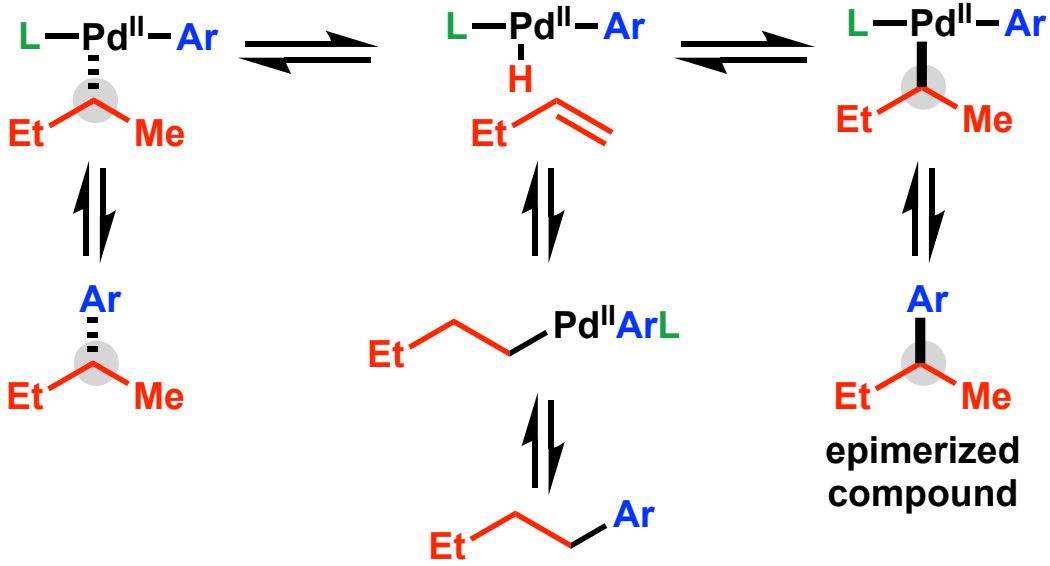
Xhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. *Science*, **2018**, *362*, 670.

Epimerization via β-Hydride Elimination



L	ee
PEt_3 5	9%
PMe_3 6	6%

<proposed epimerized pathway>



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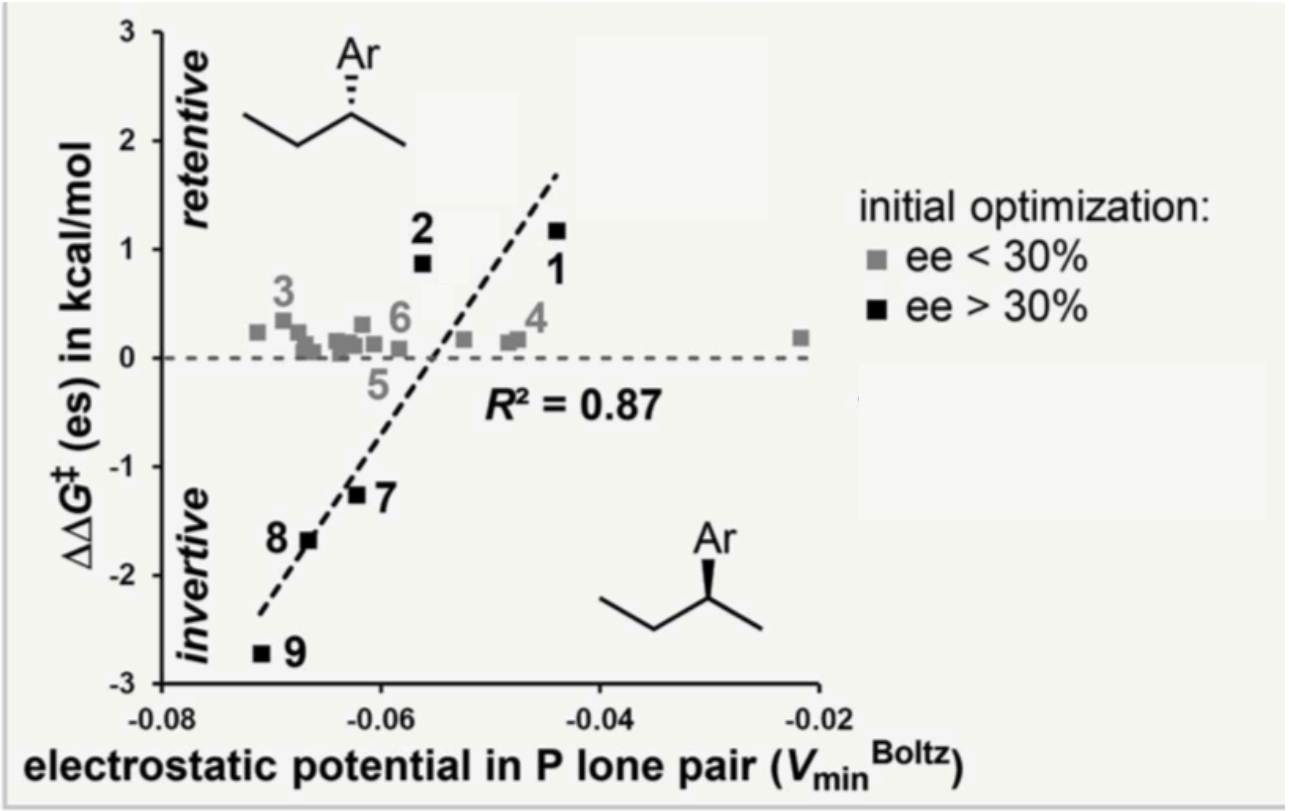
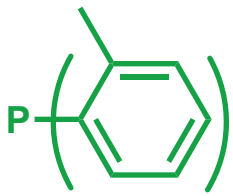
Enantiospecificity Trend



only ligands providing high selectivity were further investigated (>30%ee)

⇓

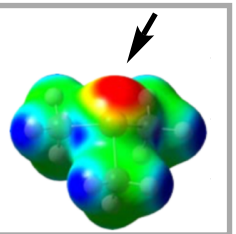
A correlation between enantioselectivity and V_{min} was observed



1

PAd_3
9

V_{min}^{Boltz}: Minimum of the molecular electrostatic potential in the phosphorus lone pair region



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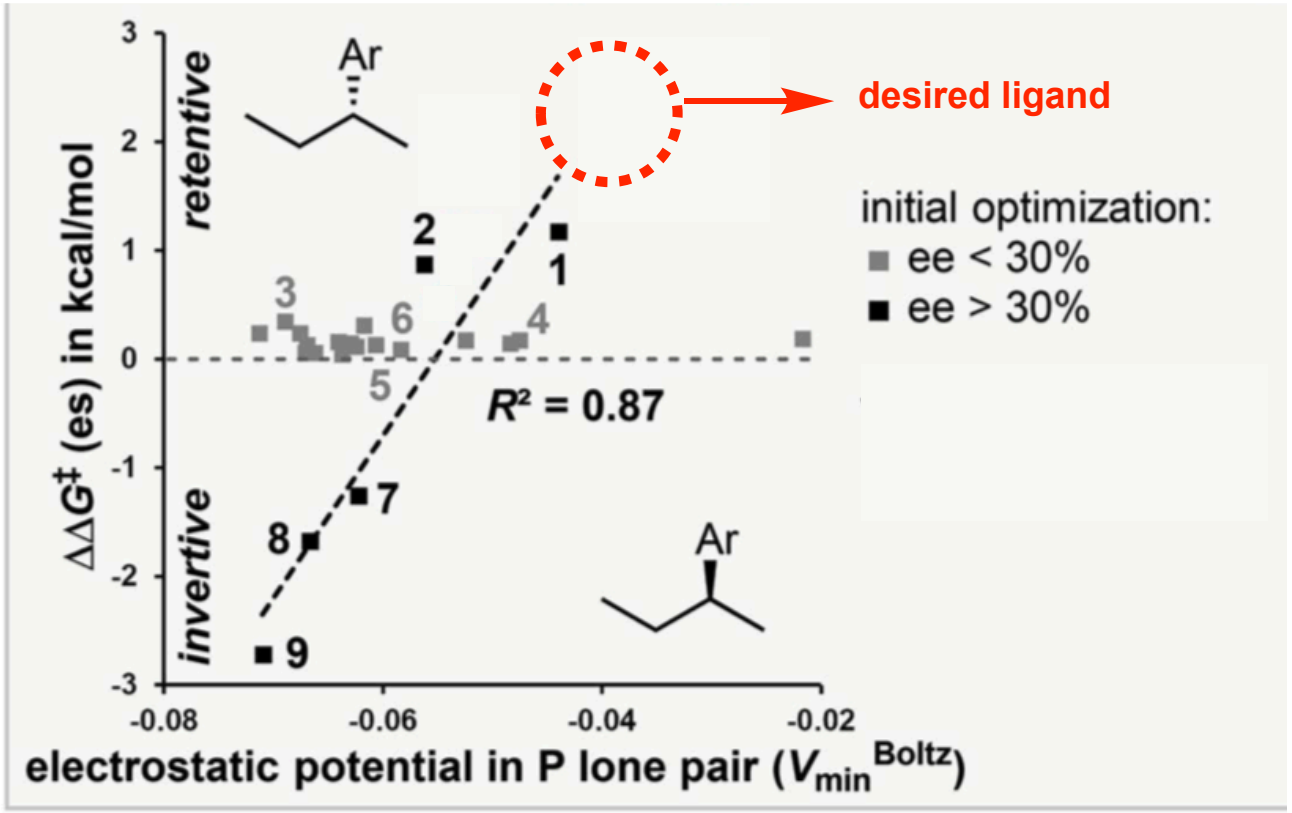
Enantiospecificity Trend



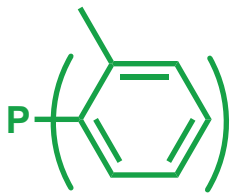
only ligands providing high selectivity were further investigated (>30%ee)

⇓

A correlation between enantioselectivity and V_{min} was observed

⇓

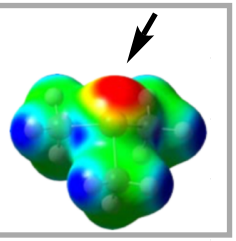
New Ligands were designed



1

PAd_3
9

V_{min}^{Boltz}: **Minimum of the molecular electrostatic potential in the phosphorus lone pair region**



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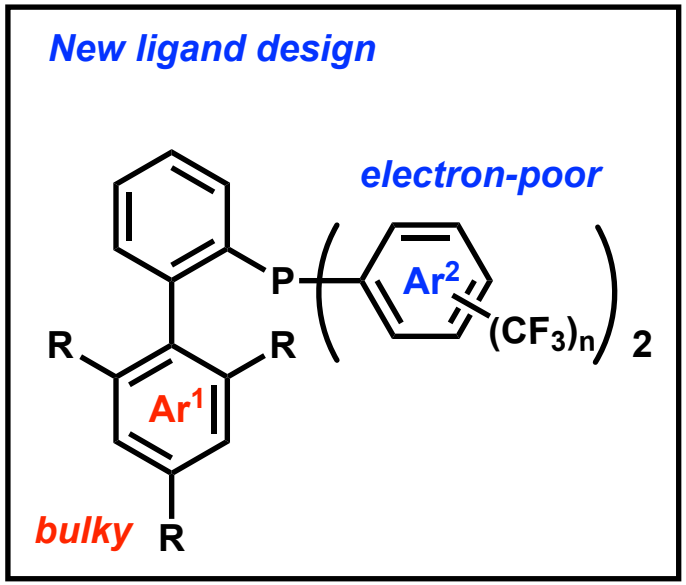
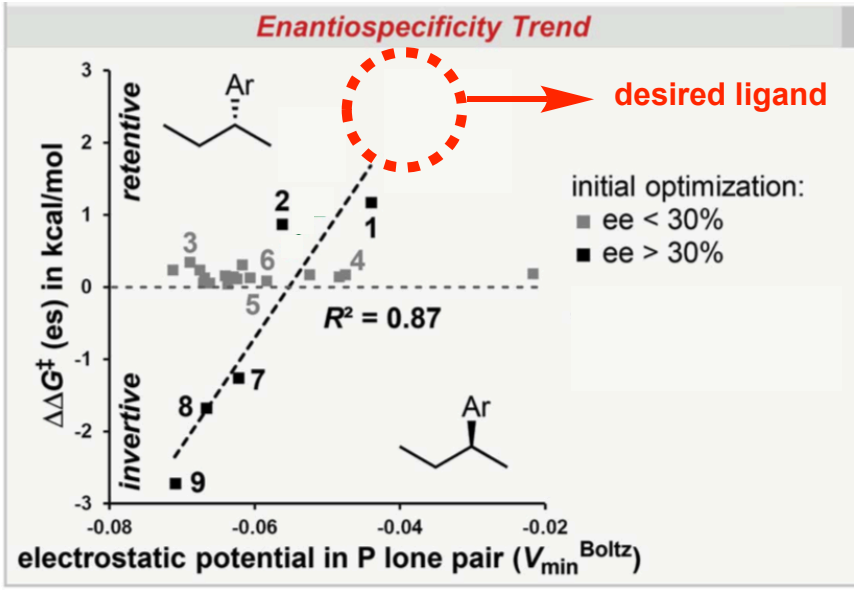
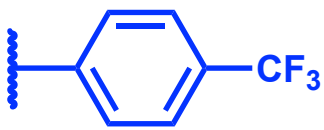
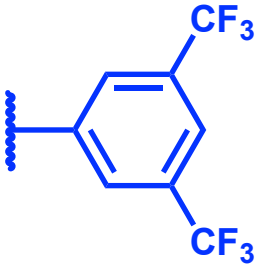
New Ligand Design

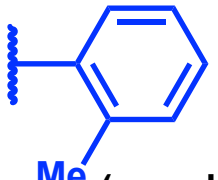




Ar^2 =







(as validation)

Ar^1 = 2,6-di-MeOC$_6$H$_3$	**10** V_{min}^{Bolz} = –0.040	**11** –0.030	**12** –0.055
Ar^1 = 2,4,6-tri-*i*-PrC$_6$H$_2$	**13** –0.038	**14** –0.029	**15** –0.052

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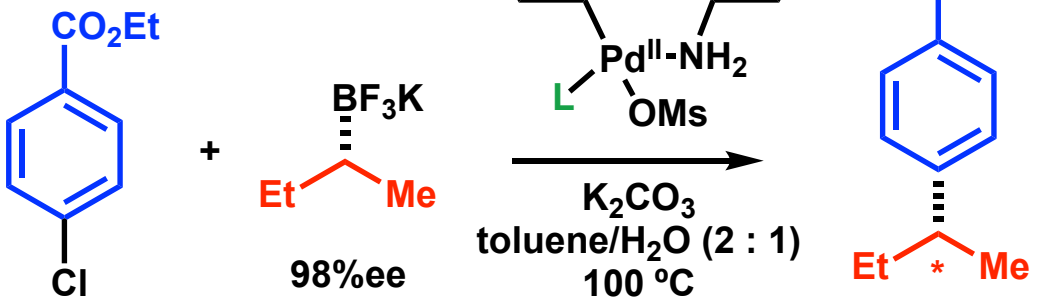
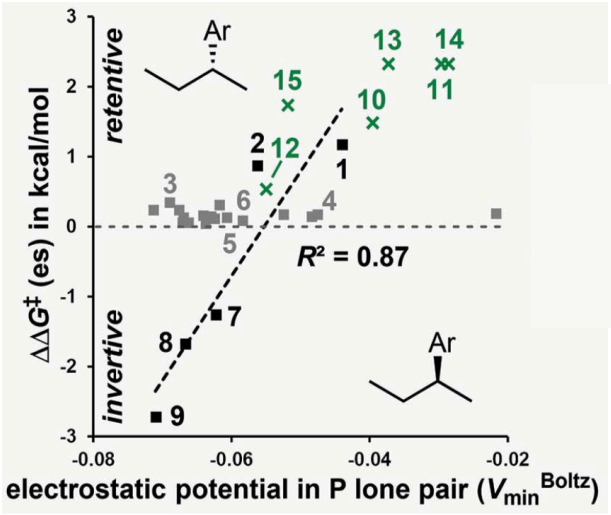
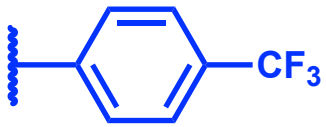
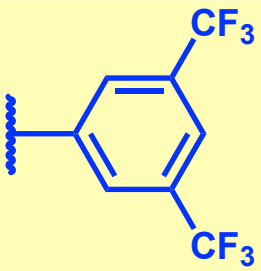
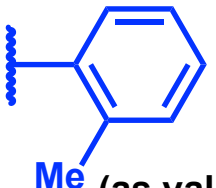
Effects of New Ligands





	Ar^2 = 		 (as validation)
Ar^1 = 2,6-di-$MeOC_6H_3$	10 V_{min}^{Bolz} = –0.040 75%ee 7.4 : 1 (*b*: *l*)	11 –0.030 90%ee 45 : 1 (*b*: *l*)	12 –0.055 35%ee 1 : 2.1 (*b*: *l*)
Ar^1 = 2,4,6-tri-*i*-PrC_6H_2	13 –0.038 90%ee 43 : 1 (*b*: *l*)	14 –0.029 90%ee 69 : 1 (*b*: *l*)	15 –0.052 81%ee (11 :1 *b*: *l*)

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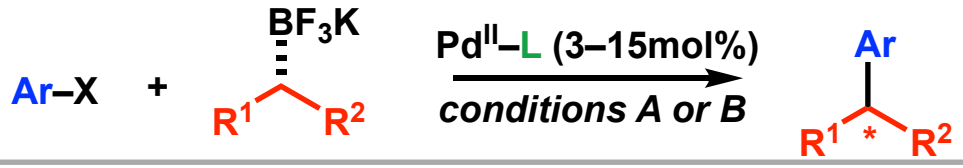
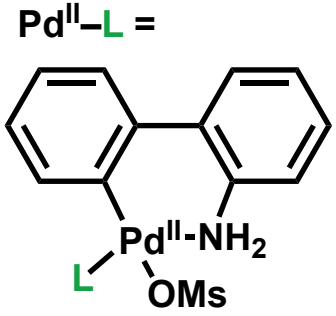
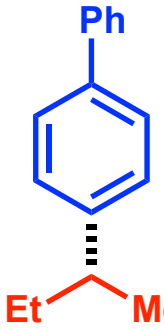
Substrate Scope

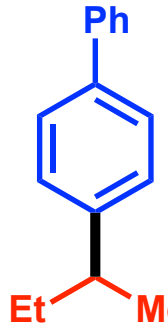


conditions A1	conditions A2	conditions B
L = 11, Cs_2CO_3	L = 14, K_2CO_3	L = PAd_3 (9), K_2CO_3
toluene/H_2O = 1 : 1	toluene/H_2O = 1 : 1	toluene/H_2O = 2 : 1

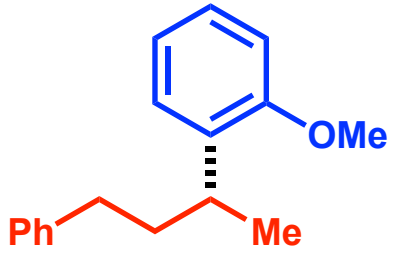




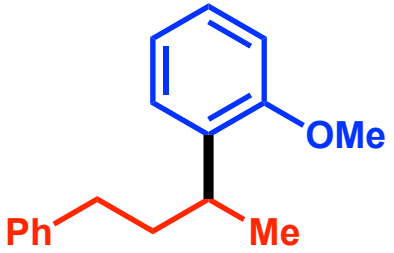
X = Cl, conditions A2
90%yield, 92%es



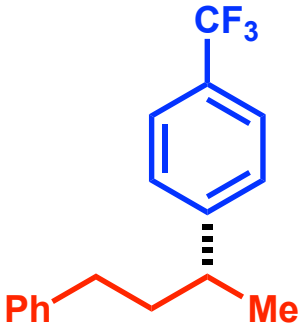
X = Cl, conditions B
92%yield, 98%es



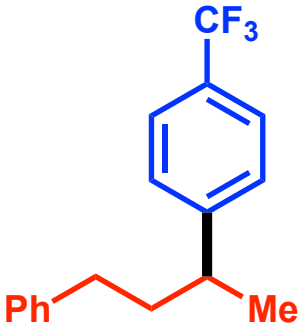
X = Cl, conditions A2
87%yield, 97%es



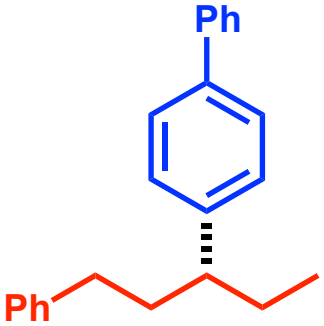
X = Cl, conditions B
90%yield, 99%es



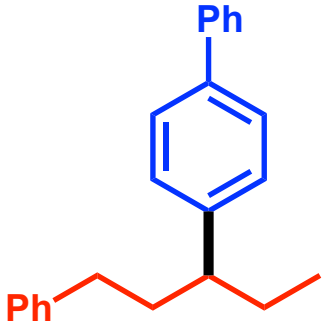
X = Br, conditions A1
81%yield, 95%es



X = Cl, conditions B
84%yield, 91%es



X = Cl, conditions A1
77%yield, 99%es



X = Cl, conditions B
78%yield, 77%es

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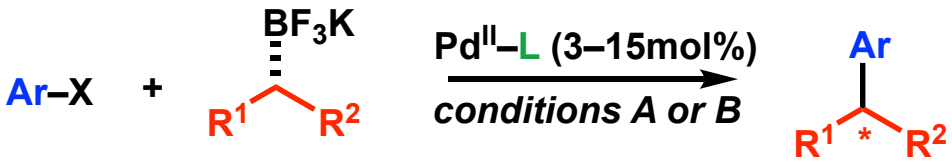
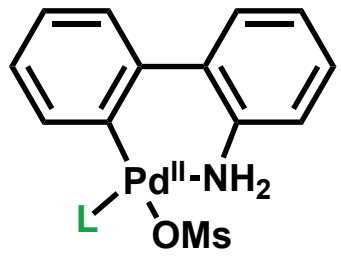
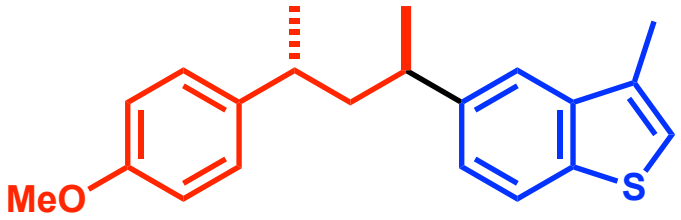
Limitation of the Reaction



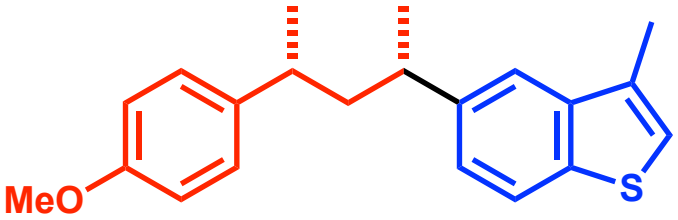
conditions A1	conditions A2	conditions B
L = 11, Cs_2CO_3	L = 14, K_2CO_3	L = PAd_3 (9), K_2CO_3
toluene/H_2O = 1 : 1	toluene/H_2O = 1 : 1	toluene/H_2O = 2 : 1

Pd^{II}–L =

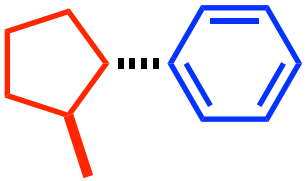




X = Cl, conditions A2
86%, d.r. = 30 : 1

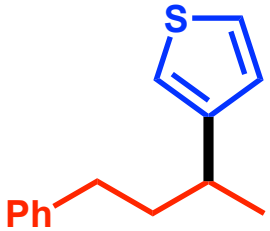


X = Cl, conditions B
65%, d.r. = 5 : 1

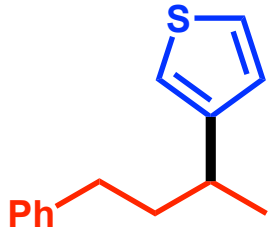


X = Cl, conditions A2
71% yield*

*conditions B results in low conversion of SM.



X = Br, conditions B
52% yield, 95%es



X = Br, conditions B
43% yield, 94%es

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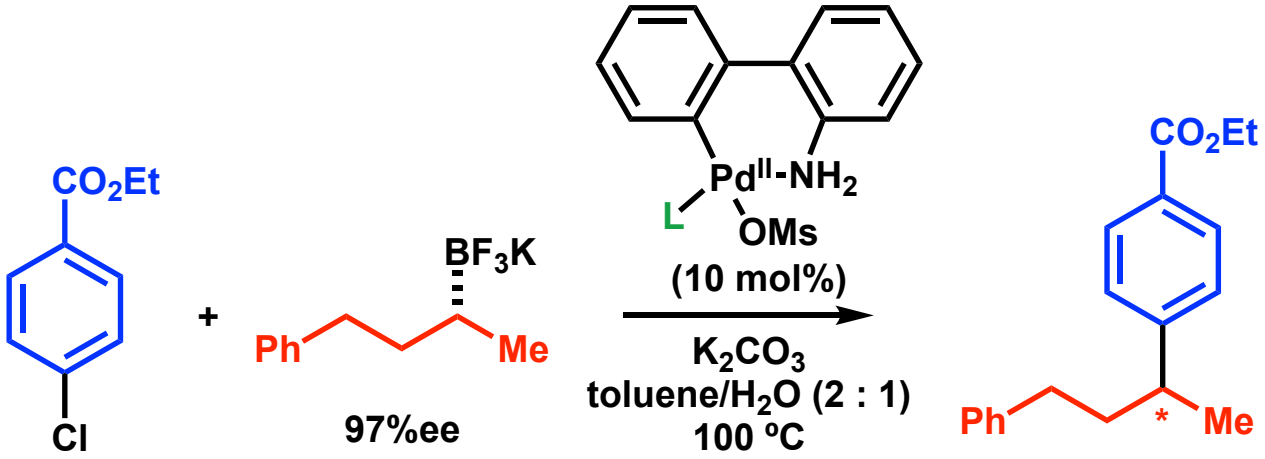
Multivariate Regression Analysis



Additionally, 24 ligands were tested

17 training sets

+

7 varidations

⟹ **–90% ~ +98%ee**

$\Delta\Delta G^{\ddagger}$ range: 5.5 kcal/mol

⟹ ***omit smaller 4 ligands (B_1^{Boltz}<4)***

Multivariate linear regression

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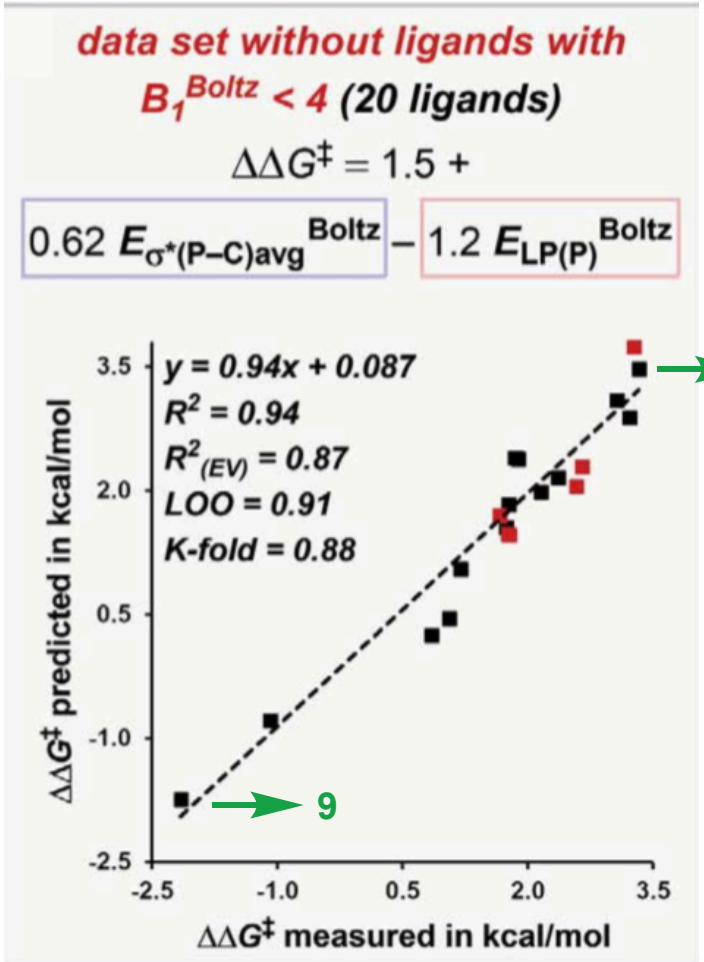
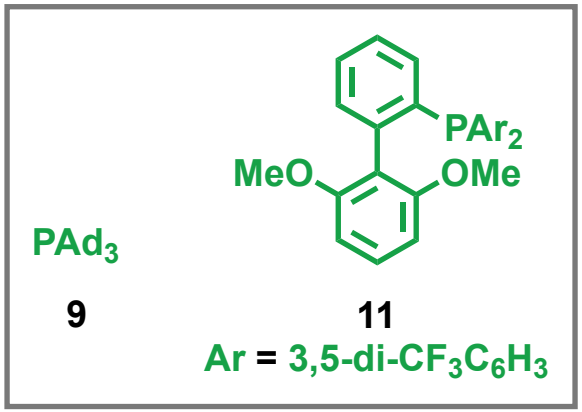
Results of Multivariate Linear Regression



Eσ*(P–C)ave ••• The average energy of the P–C antibonding (σ*) orbitals

ELP(P) ••• the energy of the lone pair orbital of phosphorus

It was found that enantioselectivity depends on the electrical properties of the ligands



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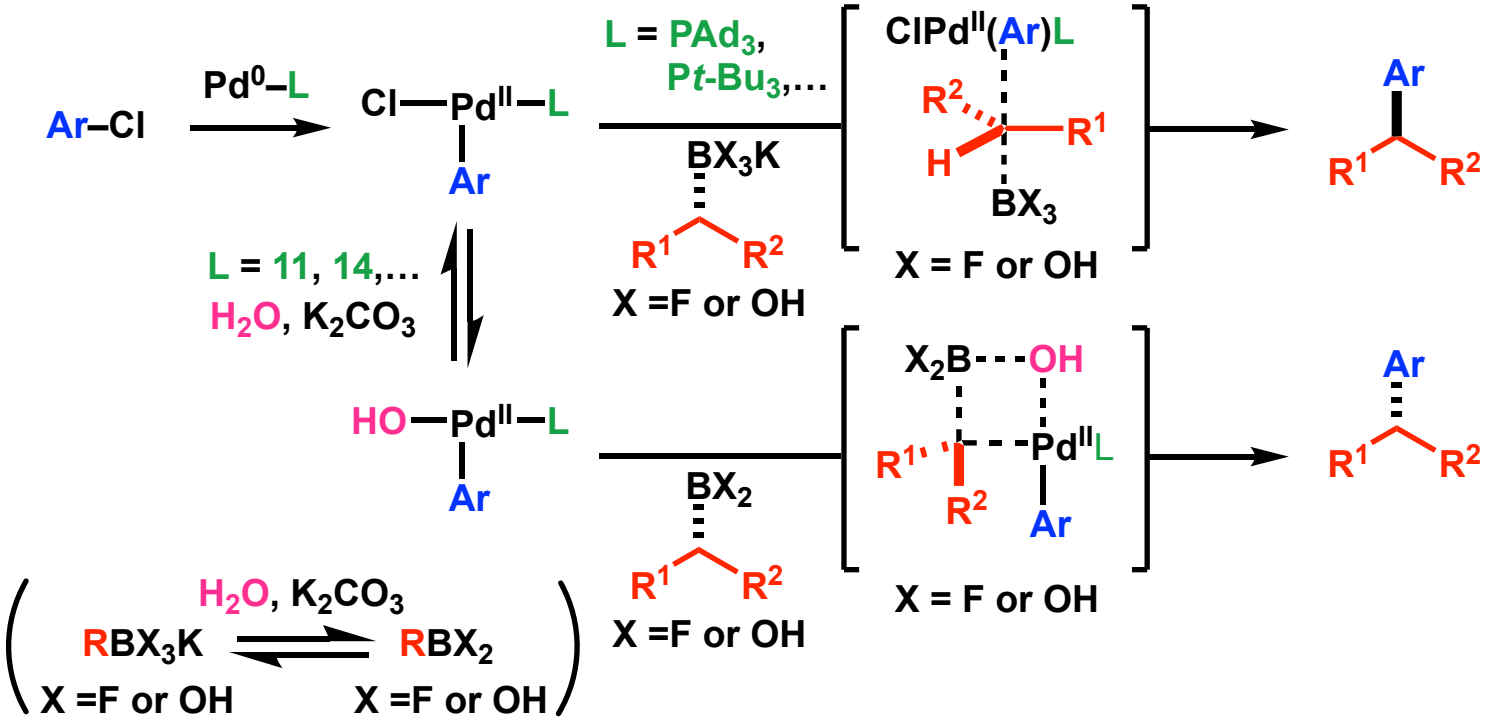
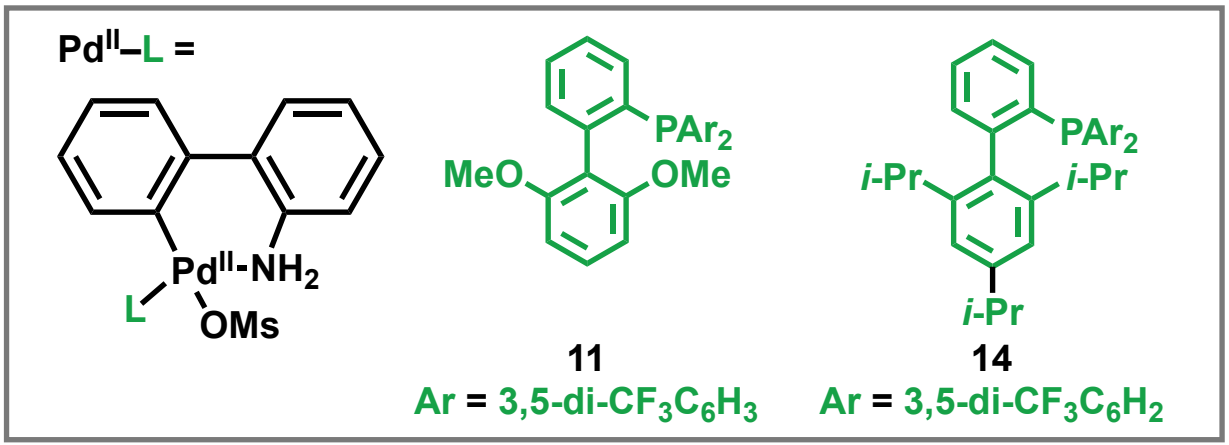
Proposed Reaction Mechanism





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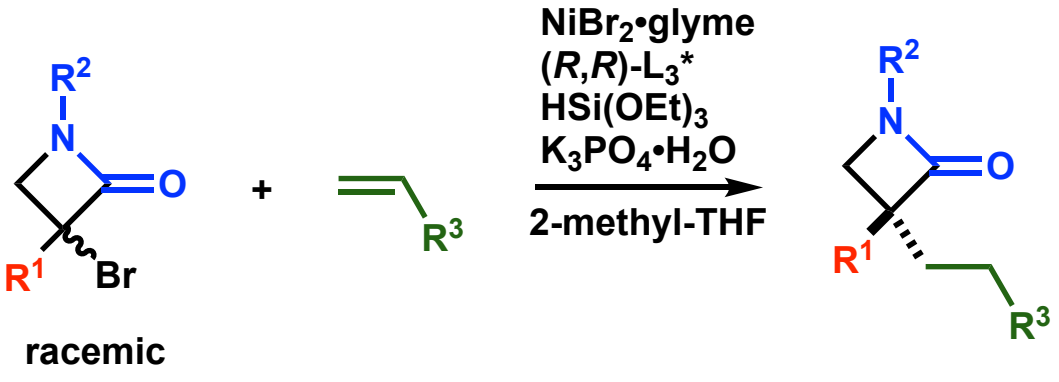
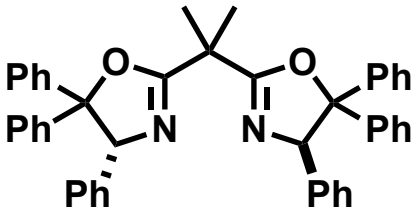
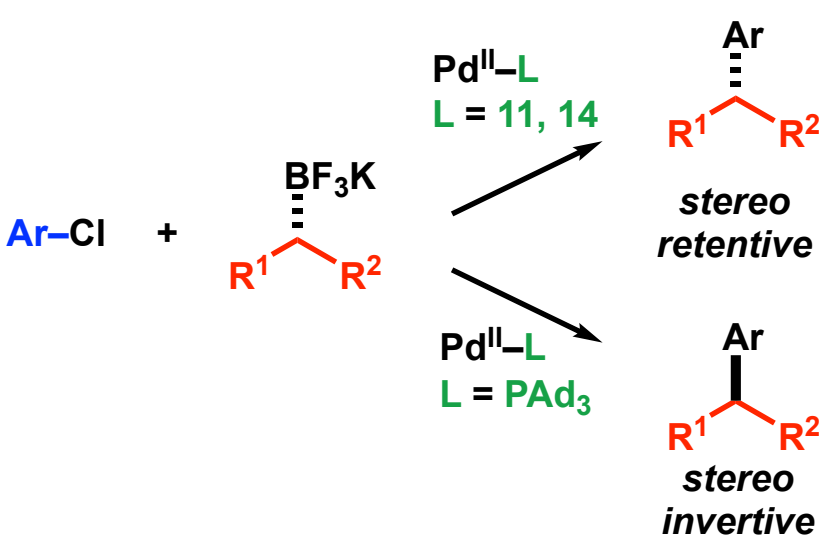
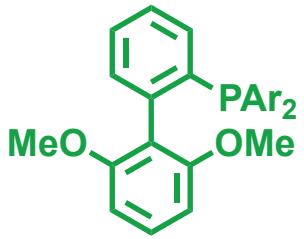
Summary

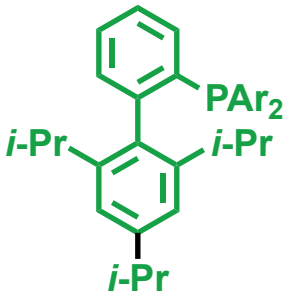








11
Ar = 3,5-di-$CF_3C_6H_3$



14
Ar = 3,5-di-$CF_3C_6H_2$

$\Delta\Delta G^{\ddagger} = 1.5 + 0.62E_{\sigma^*(P\text{-}C)ave}^{Boltz} - 1.2E_{LP(P)}^{Bolz}$

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Appendix

Branched : linear ratio

Branched:linear ratios and yields for ligands used in Figure 2. (see S46 for ligands)

ligand	yield (%)	branched/linear	ligand	yield (%)	branched/linear
1	62	2.5	**S1**	54	2.0
2	24	2.5	**S2**	97	27.8
3	75	1.1	**S3**	78	1.5
4	17	1.1	**S4**	12	2.1
5	27	0.09	**S5**	19	1.6
6	12	0.09	**S6**	17	1.1
7	41	2.2	**S7**	46	1.0
8	67	20.2	**S8**	11	1.1
9	87	190	**S9**	69	0.8
10	57	7.4	**S10**	14	0.6
11	63	45	**S11**	70	0.8
12	25	0.5	**S12**	24	0.07
13	63	43	**S13**	67	3.6
14	50	69	**S14**	77	0.3
15	53	11	**S15**	97	0.1
			S16	50	69

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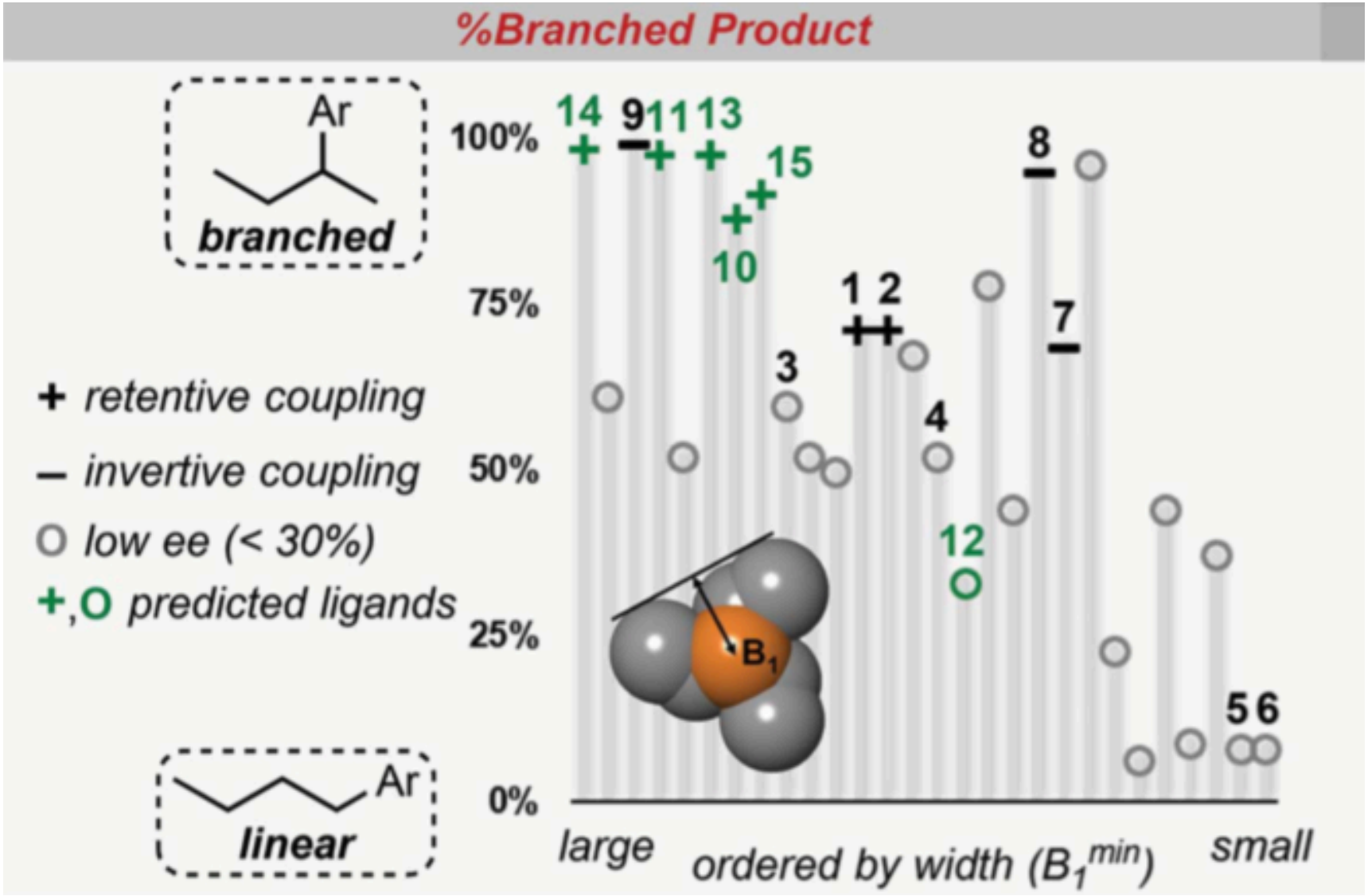
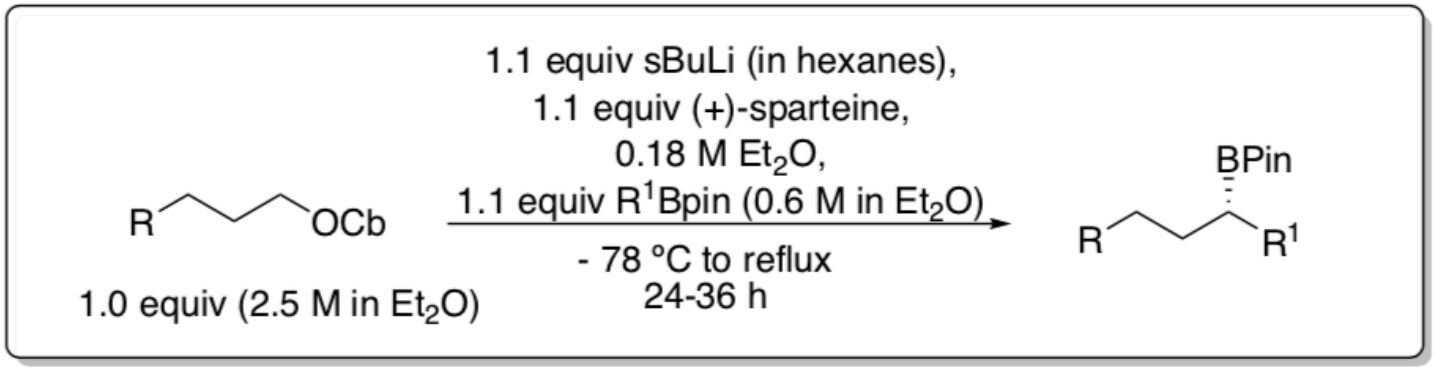
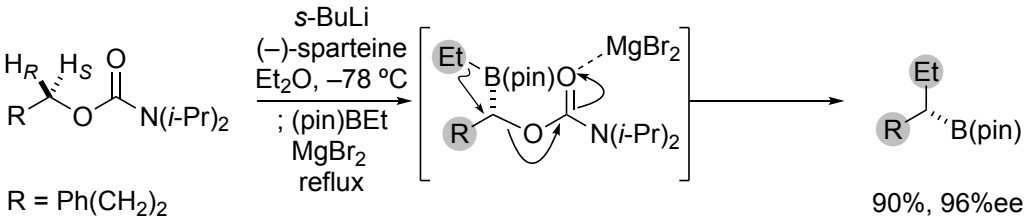
The Ratio of Branched Compounds



Xhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. *Science*, **2018**, *362*, 670.

Preparation of Substrates





R = $Ph(CH_2)_2$

90%, 96%ee

Stymiest, J. L.; Dutheuil, G. D.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491.
Homologation reaction using lithiated carbamate: 140614_LS_Keiichiro_Fukushima

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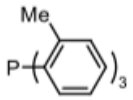
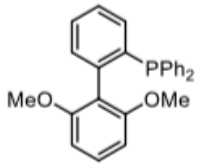
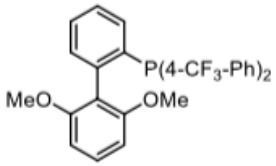
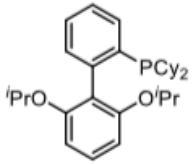
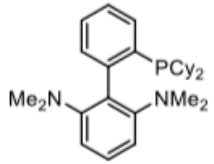
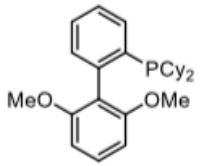
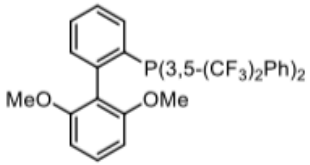
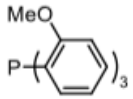
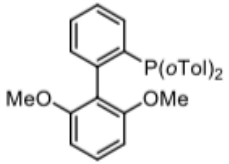
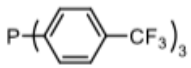
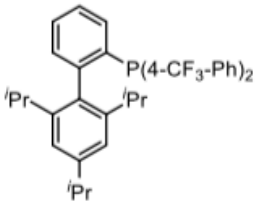
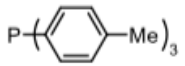
Ligand Set (1)

1		**9**	 PAd$_3$	**S2**	P^{t}Bu$_2$Ph	**S10**	PBnPh$_2$
2		**10**		**S3**	 RuPhos	**S11**	 CPhos
3	 SPhos	**11**	 di-CF$_3$PhSPhos	**S4**		**S12**	P^{n}Bu$_3$
4	PPh$_3$	**12**	 *o*TolSPhos	**S5**		**S13**	PAd$_2$^{n}Bu
5	PEt$_3$	**13**		**S6**		**S14**	PCy$_3$

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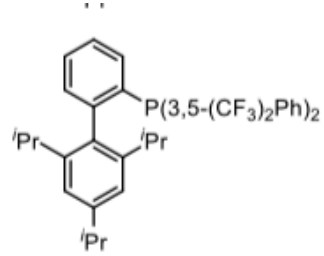
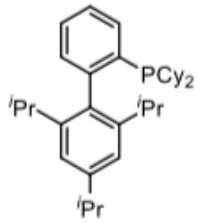
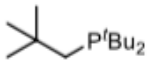
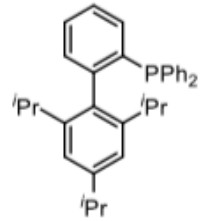
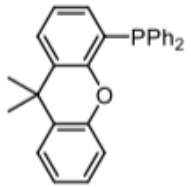
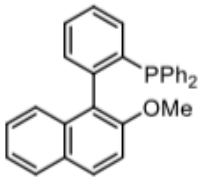
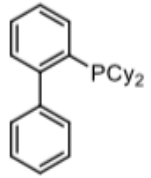
Ligand Set (2)

6	PMe_3	**14**	 di-CF_3PhXPhos	**S7**	 XPhos	**S15**	P^tBu_2Me
7		**15**	 PhXPhos	**S8**	 monoXanthphos	**S16**	P^tBuCy_2
8	P^tBu_3	**S1**		**S9**	 CyJohnPhos	**S17**	P^tBu_2Cy

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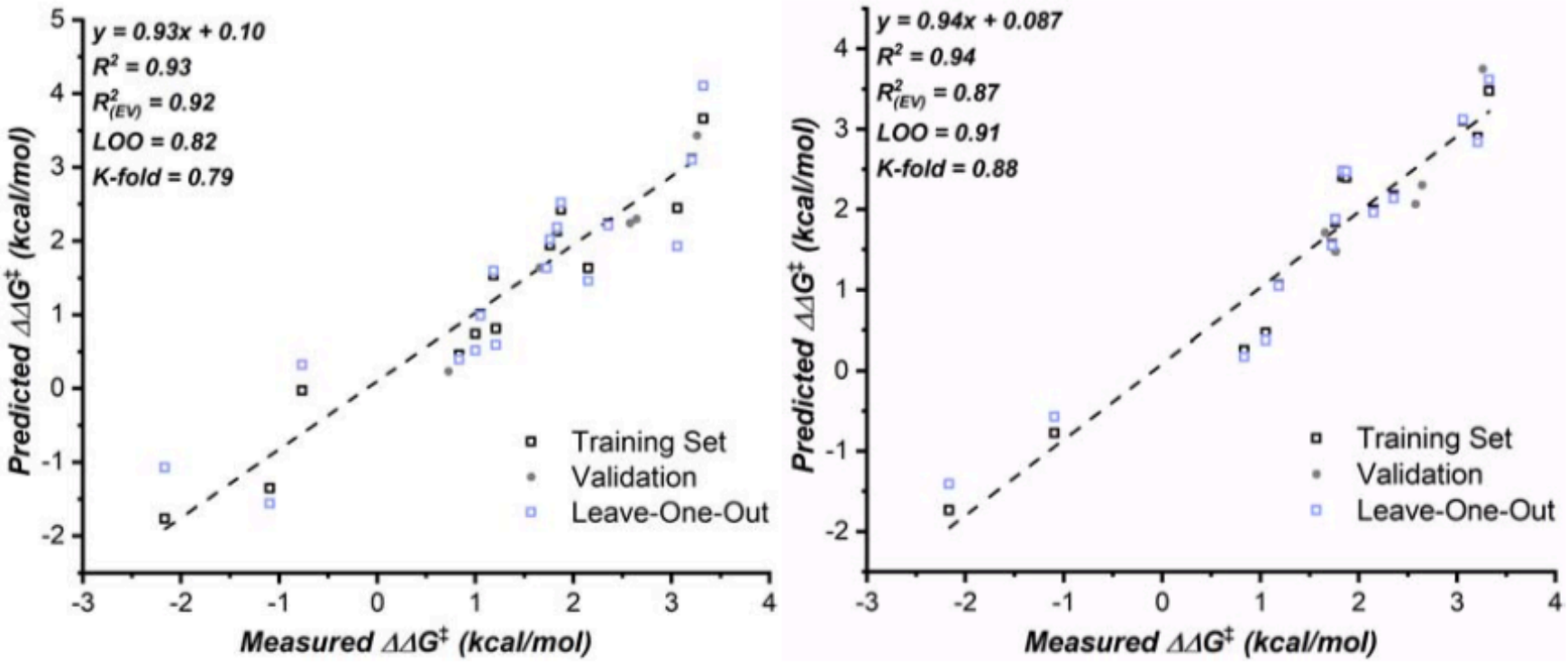
Data Set

Figure S1. Left: "Full data set" model from Figure 4B. Right: "20 ligand set" from Figure 4D.



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Parameters (1)

Table S4. Parameters describing steric properties of the ligands.

No.	Ligand	%V_{bur} in %				Sterimol B_1				Sterimol B_5				Sterimol L				*SolidA.*
		Boltz	MC	Min	Max	Boltz	MC	Min	Max	Boltz	MC	Min	Max	Boltz	MC	Min	Max	Boltz
1	P*o*Tol$_3$	41.1	41.1	33.3	41.1	4.47	4.47	4.32	4.47	6.35	6.35	6.35	6.65	6.99	6.98	6.98	7.88	153
2	PhSPhos	51.8	51.8	30.6	51.8	4.32	4.32	4.32	4.61	7.16	7.16	6.83	7.16	7.29	7.29	7.29	9.90	179
3	SPhos	55.0	55.9	32.9	60.3	4.52	4.38	4.33	4.93	7.24	7.30	6.55	7.30	7.72	7.72	7.70	10.3	192
4	PPh$_3$	28.8	28.8	28.8	28.8	4.27	4.27	4.27	4.27	6.34	6.34	6.34	6.34	7.12	7.12	7.12	7.12	126
5	PEt$_3$	27.4	27.6	25.6	28.0	3.25	3.39	2.98	3.39	4.81	4.80	4.77	4.87	5.93	5.74	5.74	6.73	124
6	PMe$_3$	22.3	22.3	22.3	22.3	2.96	2.96	2.96	2.96	3.47	3.47	3.47	3.47	5.74	5.74	5.74	5.74	106
7	P^{t}Bu$_2$neopentyl	40.8	40.8	34.7	40.8	3.99	3.99	3.93	3.99	6.18	6.18	5.56	6.18	6.64	6.64	6.64	7.88	158
8	P^{t}Bu$_3$	36.6	36.6	36.6	36.6	4.04	4.04	4.04	4.04	4.87	4.87	4.87	4.87	6.62	6.62	6.62	6.62	150
9	PAd$_3$	37.2	37.2	37.2	37.2	5.21	5.21	5.21	5.21	6.88	6.88	6.88	6.88	7.34	7.34	7.34	7.34	157
10	CF$_3$PhSPhos	51.9	51.9	29.6	51.9	4.59	4.59	4.59	5.24	7.99	7.99	7.99	8.17	7.96	7.96	7.96	9.44	180
11	di-CF$_3$PhSPhos	50.7	52.6	30.7	52.6	5.17	5.16	5.16	5.30	7.74	7.74	7.68	7.74	8.77	8.65	8.65	10.0	187
12	*o*TolSPhos	59.6	59.7	39.6	62.2	4.47	4.47	4.22	4.71	7.17	7.17	6.57	7.43	7.21	7.20	7.20	9.95	196
13	CF$_3$PhXPhos	55.6	55.6	31.5	55.6	5.41	5.41	4.89	5.41	8.03	8.03	8.03	8.19	7.94	7.94	7.94	11.5	198
14	di-CF$_3$PhXPhos	56.8	56.8	31.1	56.8	5.92	5.92	5.68	5.92	7.76	7.76	7.76	7.81	8.89	8.89	8.89	11.5	206
15	PhXPhos	55.7	56.0	32.1	58.2	4.36	4.36	4.36	4.69	7.45	7.45	7.30	7.64	7.33	7.33	7.33	11.3	199
S1	3-C9	51.3	51.2	30.5	51.8	4.32	4.30	4.30	4.57	7.23	6.89	6.89	8.13	7.31	7.27	7.27	9.85	178
S2	P^{t}Bu$_2$Ph	35.7	35.7	35.7	35.7	3.93	3.93	3.93	3.93	6.43	6.43	6.43	6.43	7.46	7.46	7.46	7.46	145
S3	RuPhos	57.2	59.7	52.4	59.7	4.59	4.35	4.34	4.95	8.50	8.78	8.12	8.78	7.72	7.74	7.54	7.75	203
S4	P(2-OMe-Ph)$_3$	37.2	37.4	33.2	42.3	4.98	5.07	4.28	5.07	6.38	6.36	6.36	6.57	7.09	6.92	6.92	8.74	149
S5	P(4-CF$_3$-Ph)$_3$	28.8	28.8	28.8	28.8	5.31	5.31	5.30	5.31	8.04	8.04	8.04	8.04	7.70	7.88	7.51	7.88	127
S6	P*p*Tol$_3$	28.8	28.8	28.8	28.8	4.91	4.91	4.91	4.91	7.45	7.45	7.45	7.45	7.28	7.28	7.28	7.28	126
S7	XPhos	57.4	57.2	55.7	62.9	4.90	4.97	4.32	4.97	7.52	7.50	7.34	7.87	7.66	7.67	7.57	7.71	205
S8	monoXantphos	32.4	32.4	30.3	32.4	4.21	4.21	4.11	4.21	8.67	8.70	7.02	8.70	7.35	7.29	7.29	11.5	140
S9	CyJohnPhos	47.9	47.6	34.6	54.7	4.40	4.39	4.08	4.44	6.75	6.75	6.69	6.78	7.75	7.73	7.73	10.2	173
S10	PBnPh$_2$	30.7	30.7	27.2	32.1	3.34	3.36	3.25	3.40	7.33	7.38	6.46	7.47	7.72	7.52	7.52	9.96	134
S11	CPhos	56.9	59.7	50.9	63.0	4.89	4.97	3.47	5.00	7.69	7.88	7.25	7.97	7.64	7.66	7.62	7.86	207
S12	P^{n}Bu$_3$	26.4	26.1	25.6	33.3	3.60	3.53	3.53	4.16	7.21	7.35	6.33	7.35	8.52	8.75	6.88	8.75	121
S13	PAd$_2$^{n}Bu	35.8	34.7	33.4	42.4	4.67	4.64	4.11	4.98	7.15	7.42	6.81	7.42	7.48	7.48	7.46	8.59	150
S14	PCy$_3$	32.3	32.1	30.8	42.9	4.41	4.41	3.87	4.62	6.75	6.77	6.45	6.83	7.66	7.71	7.38	7.82	139
S15	P^{t}Bu$_2$Me	31.9	31.9	31.9	31.9	3.31	3.31	3.31	3.31	4.87	4.87	4.87	4.87	6.63	6.63	6.63	6.63	135
S16	P^{t}Bu$_2$Cy	36.1	36.1	35.1	40.5	3.97	3.97	3.97	4.06	6.56	6.56	5.89	6.78	7.45	7.45	6.67	7.45	147
S17	P^{t}BuCy$_2$	33.9	33.6	32.9	43.4	4.06	3.99	3.85	4.24	6.74	6.80	6.02	6.80	7.51	7.51	6.71	7.61	144

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Parameters (2)

Table S5. Parameters describing electronic properties of the ligands, Pt. 1.

No.	Ligand	E_{HOMO} in Hartree				E_{LUMO} in Hartree				V_{min} in kcal/mol				$\sigma(^{31}P)$ in ppm			
		Boltz	MC	Min	Max	Boltz	MC	Min	Max	Boltz	MC	Min	Max	Boltz	MC	Min	Max
1	P*o*Tol$_3$	-0.258	-0.258	-0.258	-0.250	0.000	0.000	-0.006	0.000	-27.6	-27.6	-32.9	-27.6	343	343	306	343
2	PhSPhos	-0.253	-0.253	-0.253	-0.213	0.004	0.004	-0.019	0.004	-35.3	-35.3	-35.3	-35.1	325	325	302	325
3	SPhos	-0.251	-0.251	-0.256	-0.247	0.014	0.012	0.011	0.017	-43.3	-43.4	-44.7	-41.2	325	325	284	355
4	PPh$_3$	-0.265	-0.265	-0.265	-0.225	0.000	0.000	-0.024	0.000	-29.9	-29.9	-29.9	-29.9	320	320	320	320
5	PEt$_3$	-0.269	-0.271	-0.271	-0.267	0.061	0.063	0.058	0.063	-38.1	-37.6	-38.9	-37.5	341	338	338	345
6	PMe$_3$	-0.274	-0.274	-0.274	-0.274	0.065	0.065	0.065	0.065	-36.6	-36.6	-36.6	-36.6	384	384	384	384
7	P^{t}Bu$_2$neopentyl	-0.259	-0.259	-0.259	-0.219	0.052	0.052	0.035	0.052	-39.1	-39.1	-43.2	-39.1	301	301	266	301
8	P^{t}Bu$_3$	-0.255	-0.255	-0.255	-0.255	0.059	0.059	0.059	0.059	-41.9	-41.9	-41.9	-41.9	256	256	256	256
9	PAd$_3$	-0.247	-0.247	-0.247	-0.247	0.038	0.038	0.038	0.038	-44.6	-44.6	-44.6	-44.6	253	253	253	253
10	CF$_3$PhSPhos	-0.271	-0.271	-0.271	-0.228	-0.025	-0.025	-0.047	-0.025	-25.0	-25.0	-25.0	-24.1	324	324	308	324
11	di-CF$_3$PhSPhos	-0.281	-0.281	-0.285	-0.281	-0.041	-0.041	-0.041	-0.041	-18.8	-18.9	-18.9	-17.9	322	323	308	323
12	*o*TolSPhos	-0.250	-0.250	-0.256	-0.210	0.005	0.005	-0.018	0.005	-34.7	-34.7	-36.2	-31.7	341	341	315	345
13	CF$_3$PhXPhos	-0.276	-0.276	-0.278	-0.276	-0.032	-0.031	-0.033	-0.031	-23.6	-23.6	-23.6	-21.5	331	331	294	331
14	di-CF$_3$PhXPhos	-0.286	-0.286	-0.289	-0.286	-0.047	-0.047	-0.048	-0.047	-18.1	-18.1	-18.1	-14.9	330	330	296	330
15	PhXPhos	-0.260	-0.260	-0.260	-0.256	-0.008	-0.007	-0.010	-0.007	-32.8	-32.8	-35.7	-32.1	331	331	293	332
S1	3-C9	-0.249	-0.250	-0.251	-0.206	-0.016	-0.016	-0.038	-0.015	-36.1	-37.1	-37.1	-33.6	329	330	302	330
S2	P^{t}Bu$_2$Ph	-0.263	-0.263	-0.263	-0.263	0.005	0.005	0.005	0.005	-38.8	-38.8	-38.8	-38.8	278	278	278	278
S3	RuPhos	-0.251	-0.251	-0.255	-0.249	0.015	0.014	0.009	0.018	-44.7	-44.6	-46.1	-43.6	326	326	324	337
S4	P(2-OMe-Ph)$_3$	-0.245	-0.244	-0.250	-0.204	0.011	0.011	-0.015	0.011	-42.4	-42.7	-42.7	-37.2	351	352	330	353
S5	P(4-CF$_3$-Ph)$_3$	-0.297	-0.297	-0.297	-0.254	-0.038	-0.038	-0.060	-0.038	-13.6	-13.6	-13.6	-13.6	320	320	320	320
S6	P*p*Tol$_3$	-0.256	-0.256	-0.256	-0.217	0.006	0.006	-0.018	0.006	-32.9	-32.9	-32.9	-32.9	323	323	323	323
S7	XPhos	-0.257	-0.257	-0.262	-0.217	0.002	0.003	-0.026	0.004	-40.2	-40.1	-41.9	-38.2	329	329	329	343
S8	monoXantphos	-0.258	-0.258	-0.261	-0.221	-0.002	-0.001	-0.032	-0.001	-32.6	-32.6	-32.6	-31.9	328	328	309	328
S9	CyJohnPhos	-0.257	-0.256	-0.262	-0.256	0.000	0.000	-0.001	0.000	-39.5	-39.3	-40.7	-39.3	333	333	285	345
S10	PBnPh$_2$	-0.268	-0.269	-0.269	-0.229	0.000	0.001	-0.023	0.001	-30.4	-30.7	-30.9	-28.7	322	323	310	323
S11	CPhos	-0.250	-0.249	-0.255	-0.248	0.005	0.005	0.004	0.008	-42.0	-40.6	-45.8	-40.6	323	323	314	337
S12	P^{n}Bu$_3$	-0.266	-0.265	-0.269	-0.264	0.054	0.054	0.051	0.061	-39.2	-39.3	-39.6	-37.5	350	350	346	366
S13	PAd$_2$^{n}Bu	-0.255	-0.255	-0.255	-0.250	0.043	0.042	0.040	0.044	-42.1	-42.3	-43.8	-39.5	293	291	285	312
S14	PCy$_3$	-0.258	-0.258	-0.261	-0.252	0.054	0.054	0.049	0.058	-41.6	-41.7	-43.9	-39.0	306	304	285	341
S15	P^{t}Bu$_2$Me	-0.262	-0.262	-0.262	-0.262	0.057	0.057	0.057	0.057	-40.0	-40.0	-40.0	-40.0	309	309	309	309
S16	P^{t}Bu$_2$Cy	-0.254	-0.254	-0.256	-0.253	0.056	0.056	0.055	0.057	-42.2	-42.2	-42.7	-40.5	268	268	268	294
S17	P^{t}BuCy$_2$	-0.257	-0.258	-0.259	-0.253	0.054	0.054	0.051	0.056	-41.7	-41.5	-43.0	-39.2	290	292	277	323

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Parameters (3)

Table S6. Parameters describing electronic properties of the ligands, Pt. 2.

No.	Ligand	*NBO(P)*				$E_{LP(P)}$ in Hartree		$E_{\sigma^*(P-C)min}$ in Hartree		$E_{\sigma^*(P-C)avg}$ in Hartree	
		Boltz	MC	Min	Max	Boltz	MC	Boltz	MC	Boltz	MC
1	P*o*Tol$_3$	0.819	0.819	0.819	0.836	-0.398	-0.398	0.261	0.261	0.261	0.261
2	PhSPhos	0.841	0.841	0.837	0.841	-0.398	-0.398	0.262	0.262	0.263	0.263
3	SPhos	0.829	0.831	0.764	0.831	-0.396	-0.394	0.241	0.242	0.251	0.252
4	PPh$_3$	0.829	0.829	0.829	0.829	-0.406	-0.406	0.254	0.254	0.254	0.254
5	PEt$_3$	0.764	0.762	0.758	0.768	-0.421	-0.425	0.234	0.235	0.235	0.235
6	PMe$_3$	0.764	0.764	0.764	0.764	-0.424	-0.424	0.243	0.243	0.243	0.243
7	P^{t}Bu$_2$neopentyl	0.788	0.788	0.788	0.794	-0.400	-0.400	0.212	0.212	0.221	0.221
8	P^{t}Bu$_3$	0.785	0.785	0.785	0.785	-0.387	-0.387	0.207	0.207	0.207	0.207
9	PAd$_3$	0.839	0.839	0.839	0.839	-0.369	-0.369	0.220	0.220	0.220	0.220
10	CF$_3$PhSPhos	0.852	0.852	0.847	0.852	-0.417	-0.417	0.243	0.243	0.244	0.244
11	di-CF$_3$PhSPhos	0.863	0.864	0.849	0.864	-0.431	-0.432	0.226	0.226	0.229	0.229
12	*o*TolSPhos	0.834	0.834	0.827	0.841	-0.393	-0.393	0.266	0.266	0.268	0.268
13	CF$_3$PhXPhos	0.854	0.854	0.844	0.854	-0.422	-0.422	0.237	0.237	0.238	0.238
14	di-CF$_3$PhXPhos	0.865	0.865	0.853	0.865	-0.437	-0.437	0.220	0.220	0.223	0.223
15	PhXPhos	0.843	0.843	0.839	0.849	-0.404	-0.403	0.253	0.253	0.257	0.257
S1	3-C9	0.843	0.843	0.838	0.843	-0.400	-0.400	0.258	0.258	0.260	0.260
S2	P^{t}Bu$_2$Ph	0.804	0.804	0.804	0.804	-0.388	-0.388	0.211	0.211	0.229	0.229
S3	RuPhos	0.827	0.830	0.789	0.837	-0.396	-0.394	0.241	0.242	0.251	0.251
S4	P(2-OMe-Ph)$_3$	0.890	0.892	0.851	0.892	-0.393	-0.394	0.269	0.269	0.269	0.269
S5	P(4-CF$_3$-Ph)$_3$	0.841	0.841	0.841	0.841	-0.436	-0.436	0.224	0.224	0.224	0.224
S6	P*p*Tol$_3$	0.829	0.829	0.829	0.829	-0.400	-0.400	0.261	0.261	0.261	0.261
S7	XPhos	0.827	0.829	0.783	0.829	-0.403	-0.402	0.231	0.231	0.242	0.242
S8	monoXantphos	0.848	0.848	0.836	0.848	-0.405	-0.405	0.252	0.252	0.257	0.257
S9	CyJohnPhos	0.822	0.825	0.793	0.825	-0.403	-0.401	0.233	0.234	0.243	0.243
S10	PBnPh$_2$	0.827	0.829	0.822	0.829	-0.420	-0.421	0.217	0.217	0.240	0.240
S11	CPhos	0.837	0.846	0.793	0.846	-0.398	-0.398	0.238	0.240	0.247	0.248
S12	P^{n}Bu$_3$	0.786	0.786	0.772	0.792	-0.412	-0.411	0.238	0.238	0.239	0.239
S13	PAd$_2$^{n}Bu	0.838	0.841	0.822	0.843	-0.388	-0.387	0.229	0.230	0.234	0.234
S14	PCy$_3$	0.812	0.814	0.761	0.823	-0.397	-0.396	0.231	0.231	0.236	0.236
S15	P^{t}Bu$_2$Me	0.794	0.794	0.794	0.794	-0.402	-0.402	0.213	0.213	0.223	0.223
S16	P^{t}Bu$_2$Cy	0.808	0.808	0.765	0.808	-0.384	-0.384	0.215	0.215	0.221	0.221
S17	P^{t}BuCy$_2$	0.806	0.804	0.746	0.817	-0.393	-0.397	0.214	0.213	0.227	0.227

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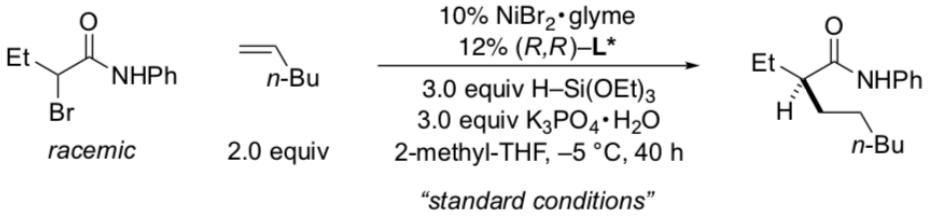
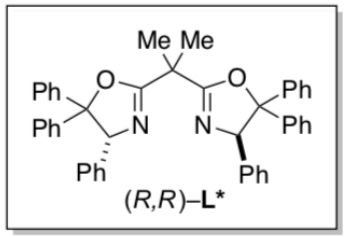
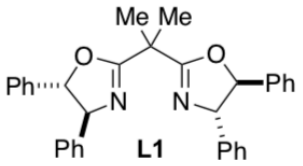
Initial Investigations

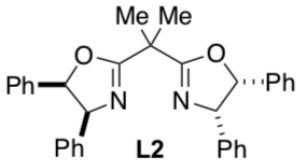
Table S-1. Effect of Reaction Parameters.

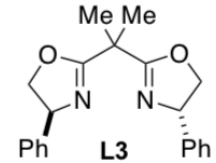


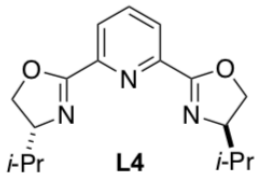
Entry	Variation from the "standard conditions"	ee (%)	Yield (%)
1	none	94	84
2	no $NiBr_2$•glyme	–	<1
3	no (*R,R*)–**L***	–	<1
4	no K_3PO_4•H_2O	–	<1
5	**L1**, instead of (*R,R*)–**L***	–92	84
6	**L2**, instead of (*R,R*)–**L***	–69	26
7	**L3**, instead of (*R,R*)–**L***	–49	33
8	**L4**, instead of (*R,R*)–**L***	–	12
9	H–$SiMe(OEt)_2$, instead of H–$Si(OEt)_3$	94	72
10	5% $NiBr_2$•glyme, 6% (*R,R*)–L*	94	75
11	1.5 equiv 1-hexene	94	70
12	2.0 equiv H–$Si(OEt)_3$, 2.0 equiv K_3PO_4•H_2O	94	76
13	r.t., instead of –5 °C	89	74
14	24 h, instead of 40 h	95	62
15	THF, instead of 2-methyl-THF	94	70
16	toluene, instead of 2-methyl-THF	92	82
17	1.0 equiv H_2O added	95	78
18	under air (balloon)	94	66











Wang, Z.; Yin, H.; Fu, G. C. *Science*, **2018**, *563*, 379.