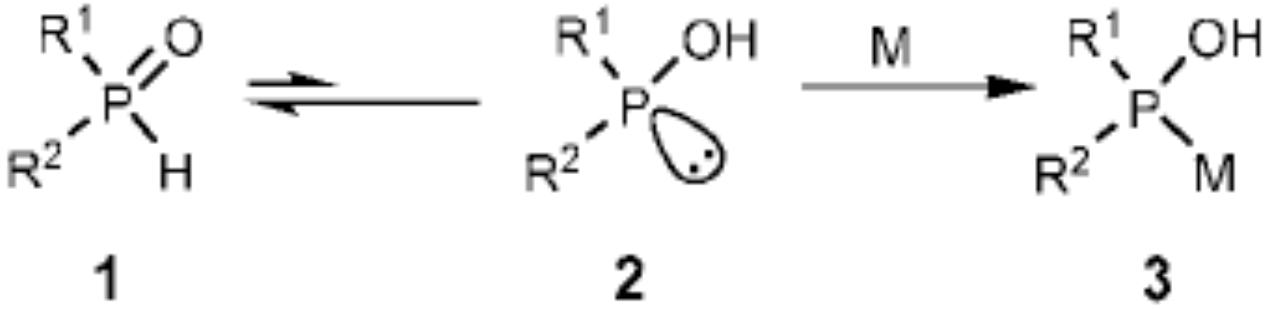
Chiral Phosphine Oxide Preligands (SPO's)



Cory A. Newman

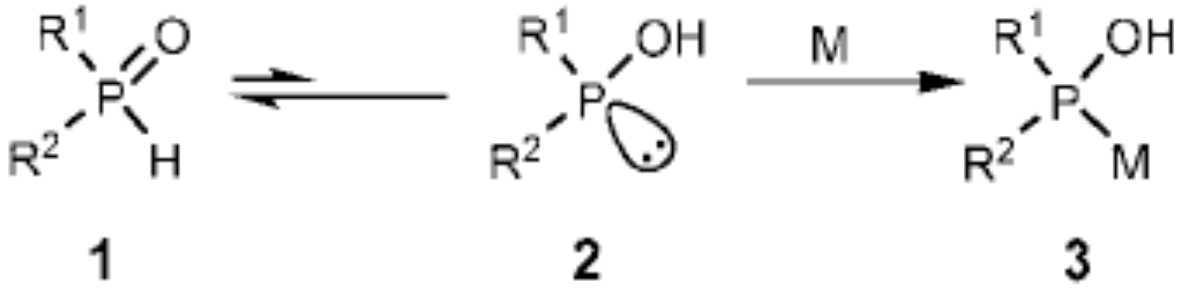
Literature Presentation

January 13, 2005

Dubrovina, N. V.; Borner, A. *Ang. Chem. Int. Ed.* **2004**, 43, 5883-5886
Yasumasa Hamada, et al. *J. Am. Chem. Soc.* **2004**, 126, 3690-3691
Ferringa, B. L.; de Vries, J. G.; et al. *Org. Lett.* **2003**, 5, 1503-1506

What is a Preligand?

*Something that is not exclusively in a form that will coordinate to a metal, but when added to solution containing a metal will become exclusively a ligand.



Heaton, B.T; Chatt, J. *J. Am. Chem. Soc*. **1968** 2745-2757

Why is this Needed?

*This is needed because certain ligands are not stable to air or moistrue, whereas in preligand form are stable to ambient conditions.

*Phosphorus compounds are subject to oxidation (so need to be protected).

$P\text{-}BH_3$, P=O

$P\text{-}BH_3$

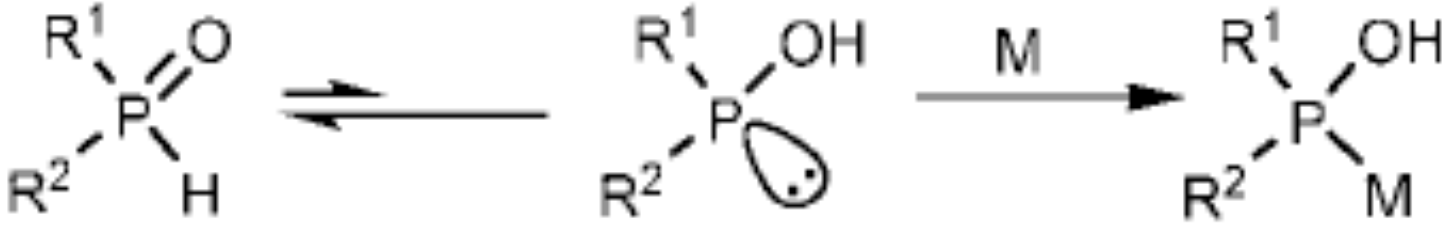
$P\text{-}BH_3$ is unstable towards many acids and Lewis bases.
And…basic amines used to remove $\text{-}BH_3$ can also attack hydrolyzable P-O bonds.

P=O

"oxygen protective group" is removed by reductive conditions
-usually with silanes prior to catalysis.
-oxidation problem delayed not solved

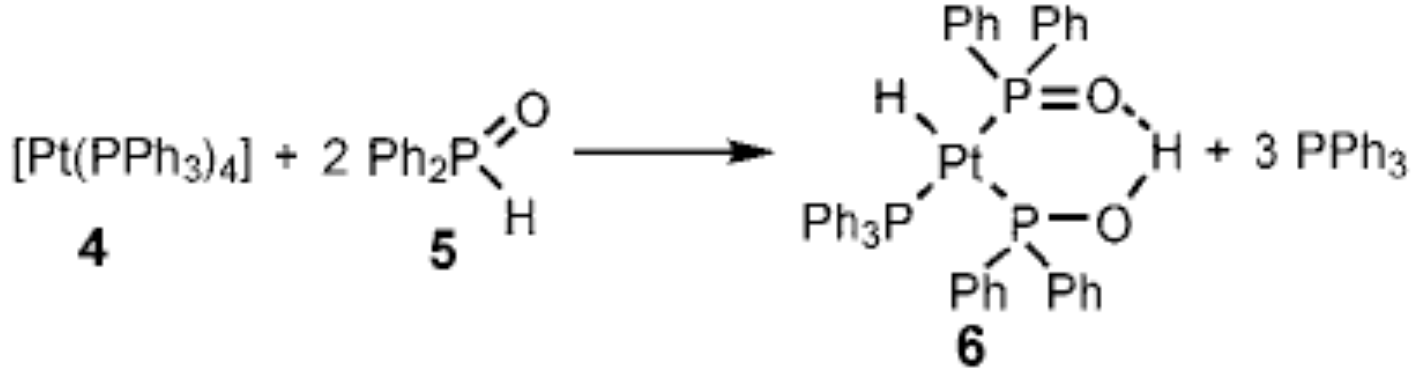
SO…

Phosphine Oxides



1 2 3

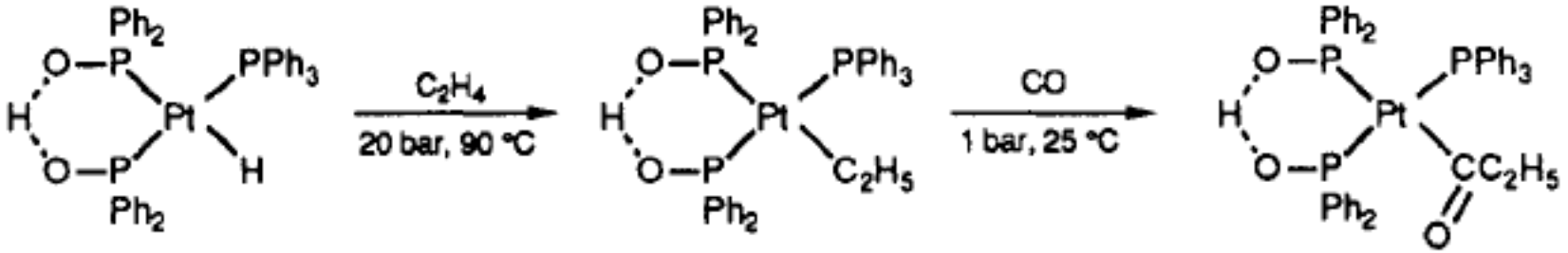
-Easilly prepared by P-C coupling reaction with phosphine halides followed by hydrolysis of the remaining P-X bond.
-Stable to oxidation and inert to water
-The tautomerization leads to the ligand.
-Often abreviated "SPO" --> secondary phosphine oxides and sometimes POP to describe equilibrium between P=O and P cmpds



4 5 6

Heaulieu, W. B.; Rauchfuss, T. B.; Roundhill, D. M. *Inorg. Chem.* **1975**, 14, 1732-1734

Hydroformylation



Pt-H + alk-1-ene $\rightleftharpoons$ Pt-n-alkyl

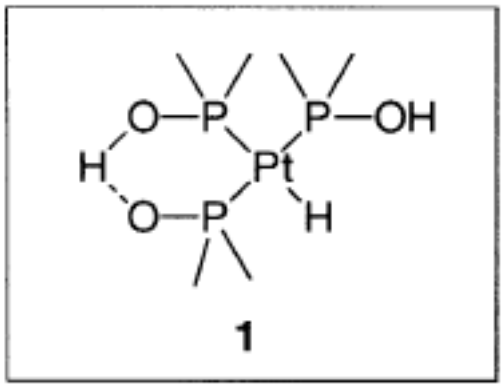
Pt-n-alkyl + CO $\rightleftharpoons$ Pt-acyl

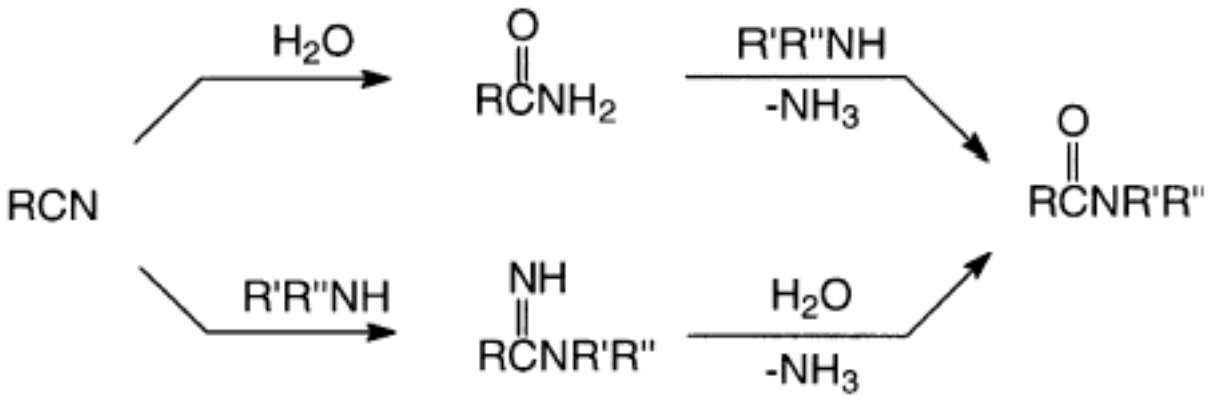
Pt-acyl + H_2 $\longrightarrow$ Pt-H + aldehyde

Roobeek, C. F.; Wife, R. L.; Frijns, J. H. G.; van Leeuwen, P. W. N. M. *J. Chem. Soc.Chem. Comm.* **1986**, 31-33

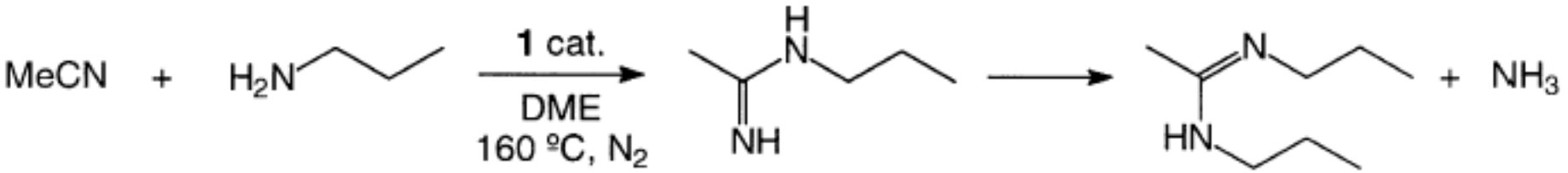
Roobeek, C. F.; Frijns, J. H. G.; van Leeuwen, P. W. N. M. *Organomet.* **1990**, 9, 1211-1222

Hydrolysis of Nitriles

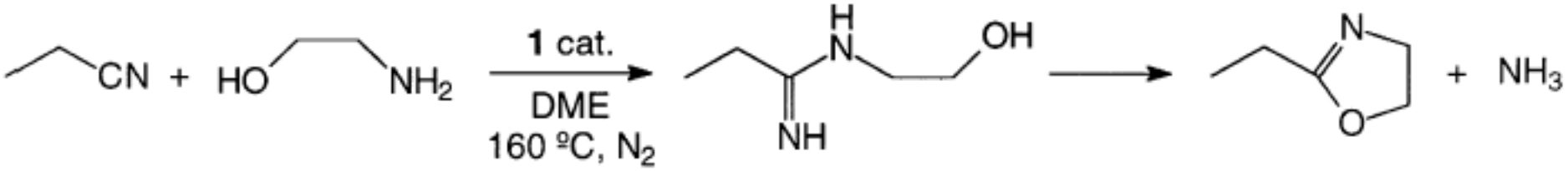




In absence of water

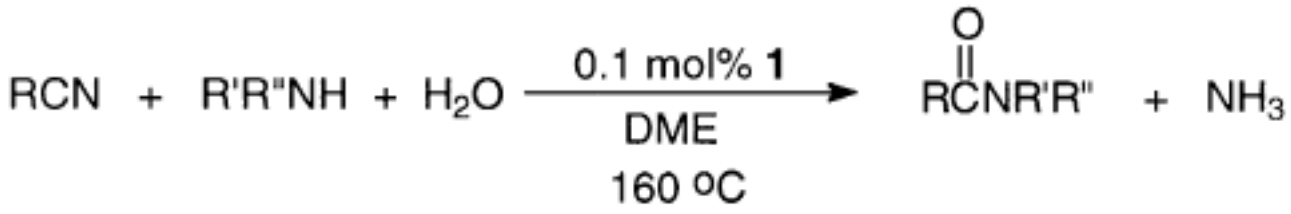


Intra/intermolecular



Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett*. **1995**, 36, 8657-8660
Cobley, C. J.; van den Heuvel, M.; Abbadi, A.; de Vries, J. G. *Tetrahedron Lett*. **2000**, 2467-2470

Hydrolysis of Nitriles

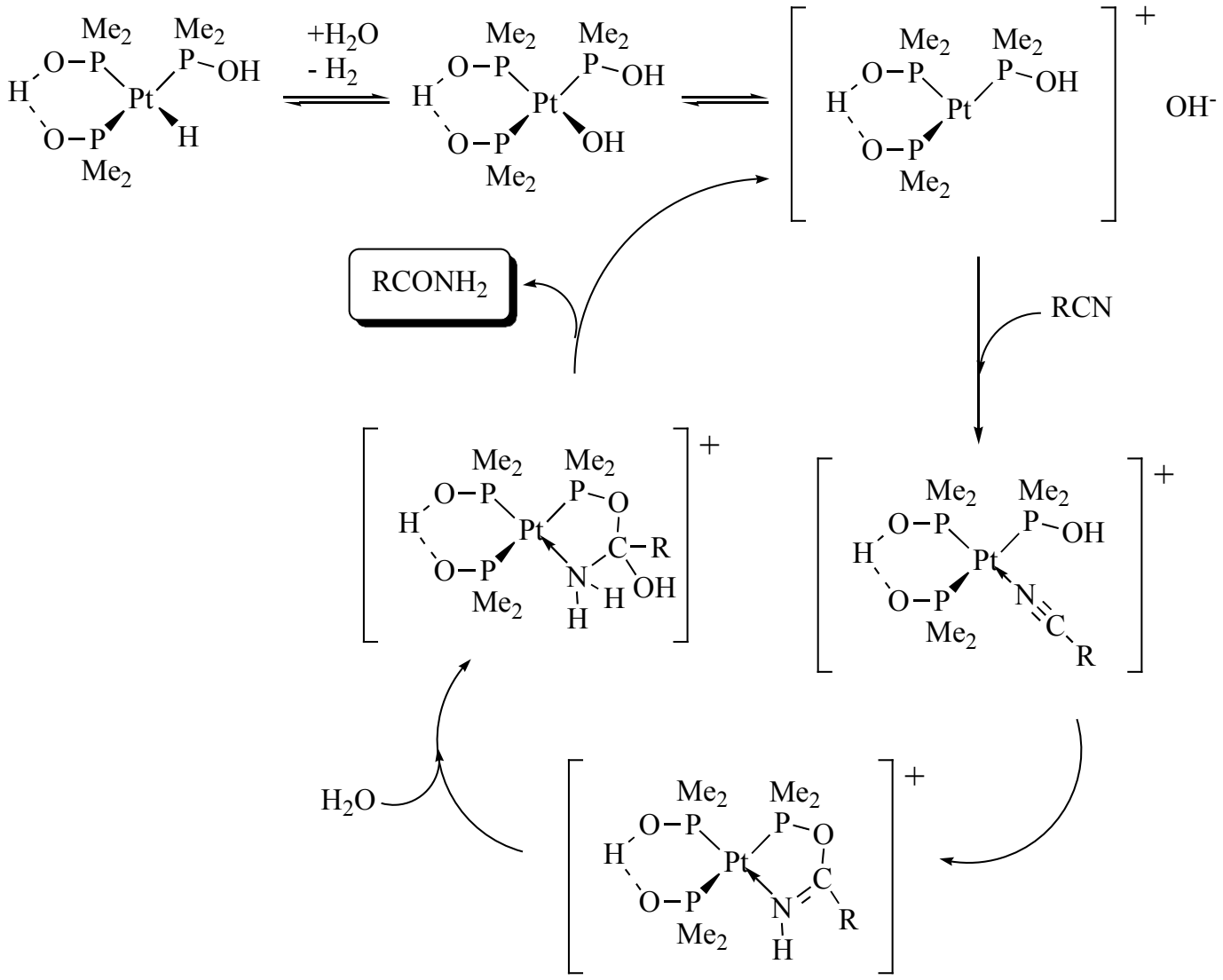


Entry	Nitrile	Amine	Time (h)	Isolated Yield of *N*-subst. Amide (%)
1	CH_3CN	*n*-Pr-NH_2	24	57
2	CH_3CN	$C_6H_5CH_2NH_2$	24	73
3	CH_3CN	$C_6H_5NH_2$	70	63
4[a]	CH_3CN	Pyrrolidine	39	66
5	CH_3CN	Piperidine	24	62
6	CH_3CN	Morpholine	60	60
7	C_6H_5CN	*n*-Pr-NH_2	24	0
8	*n*-Hex-CN	*n*-Pr-NH_2	18	63
9	*n*-Hex-CN	$C_6H_5CH_2NH_2$	18	83
10	*n*-Hex-CN	Pyrrolidine	18	71
11	Succinonitrile	*n*-Pr-NH_2	18	51[b]
12	Succinonitrile	$C_6H_5CH_2NH_2$	18	61[b]
13	Succinonitrile	Pyrrolidine	18	89[b]

[a] This experiment was performed using only 0.023 mol% of catalyst **1**.

[b] Resulted in the formation of the *N*-substituted *bis*amide.

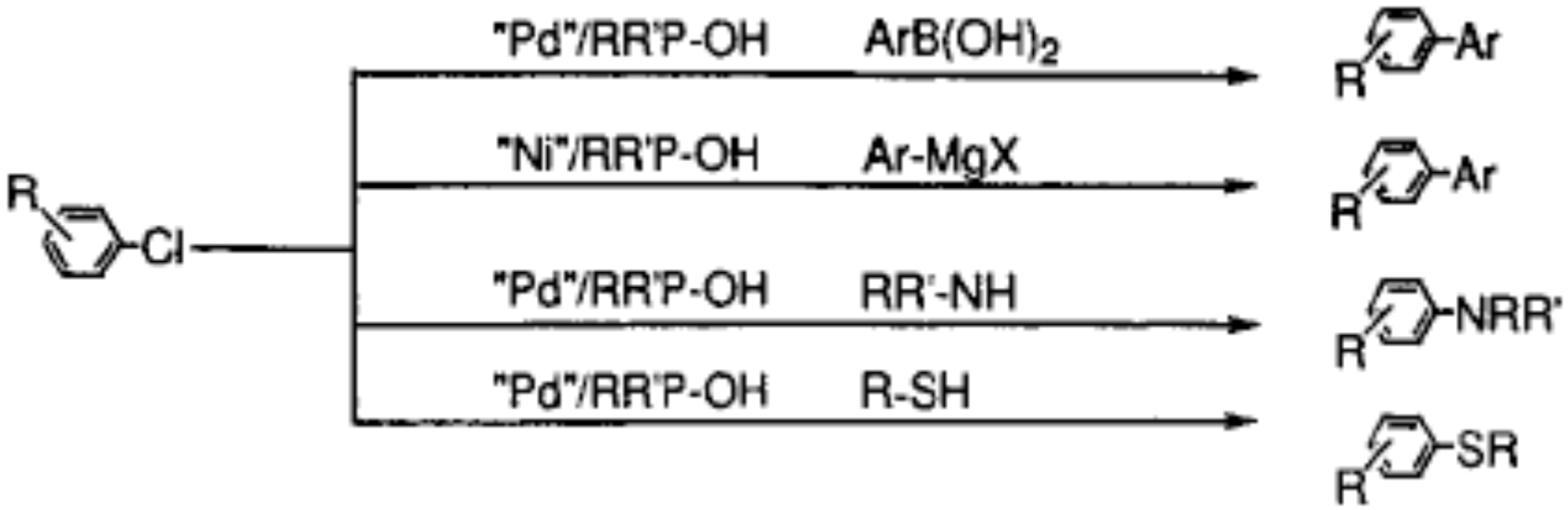
Hydrolysis of Nitriles…Mechanism



Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, 36, 8657-8660

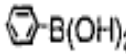
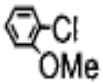
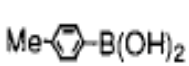
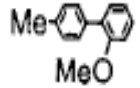
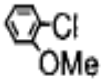
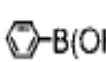
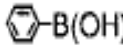
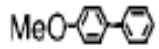
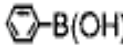
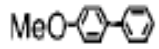
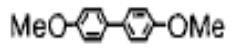
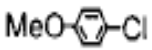
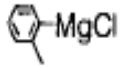
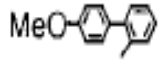
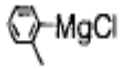
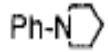
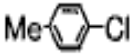
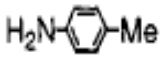
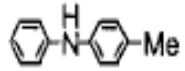
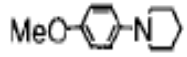
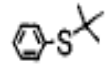
Cross-Coupling Reactions

with non-activated aryl chlorides



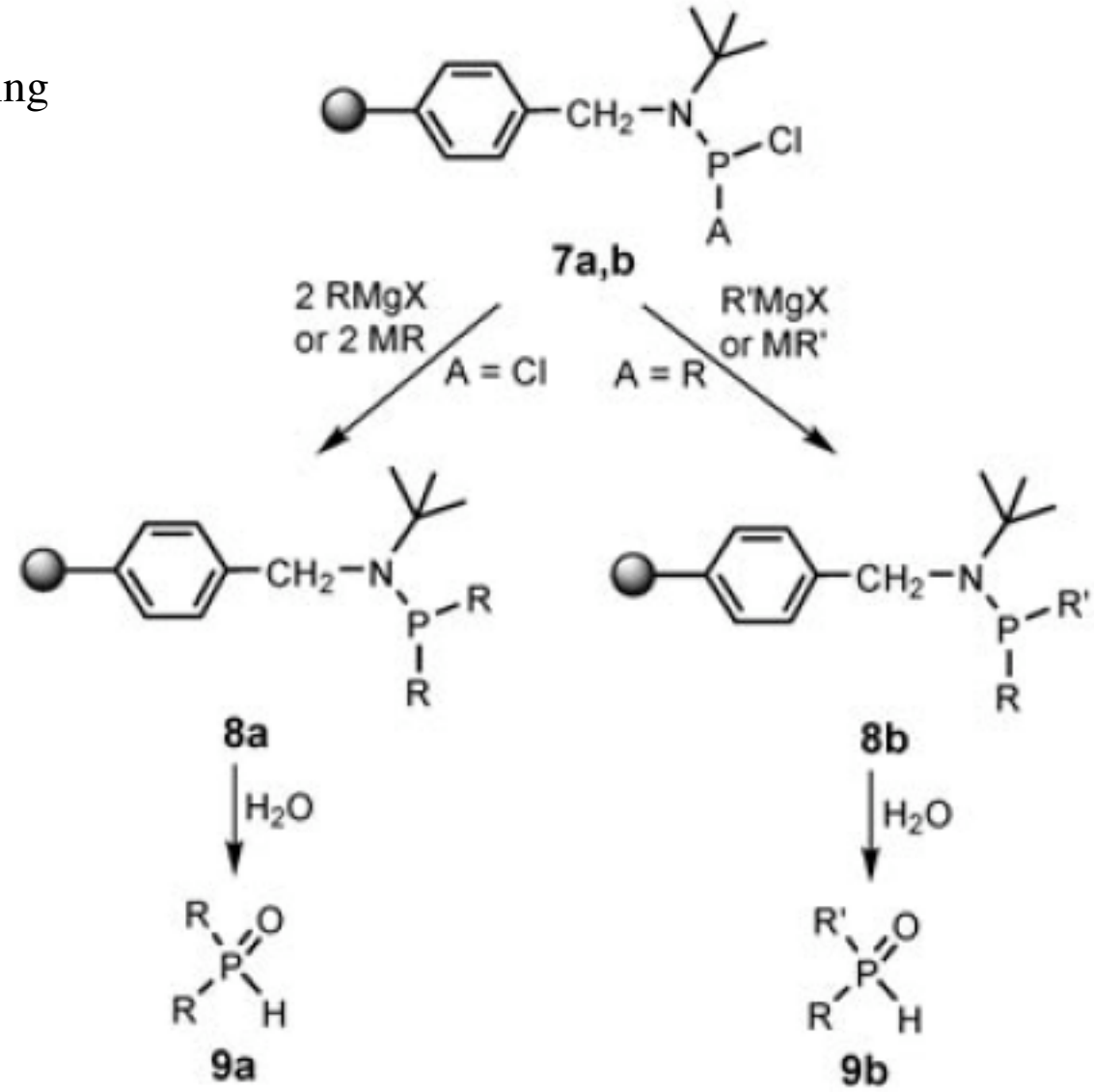
1-5 mol% catalyst

Li, G. Y. *Ang. Chem. Int. Ed.* **2001**, 40, 1513-1516

Halide	Coupling partner	Base	Temp [°C]	Time [h]	Product	Yield [%] (i
		$CsCO_3$	100	12		88[b]
		CsF	100	12		83[b]
		CsF	100	12		91[c]
		CsF	100	12		97[b]
		CsF	100	12		99[c]
		CsF	100	12		99[b,d]
		none	RT	12		93[e]
		none	RT	12		96[e]
		NaO*t*Bu	100	12		51[b]
		NaO*t*Bu	100	12		61[b]
		NaO*t*Bu	100	12		44[b]
		NaO*t*Bu	100	12		67[b]
		NaO*t*Bu	100	24		26[f]
		NaO*t*Bu	RT	24		49[f]

Solid Supported Preparation of Ligands

Use in constructing libraries

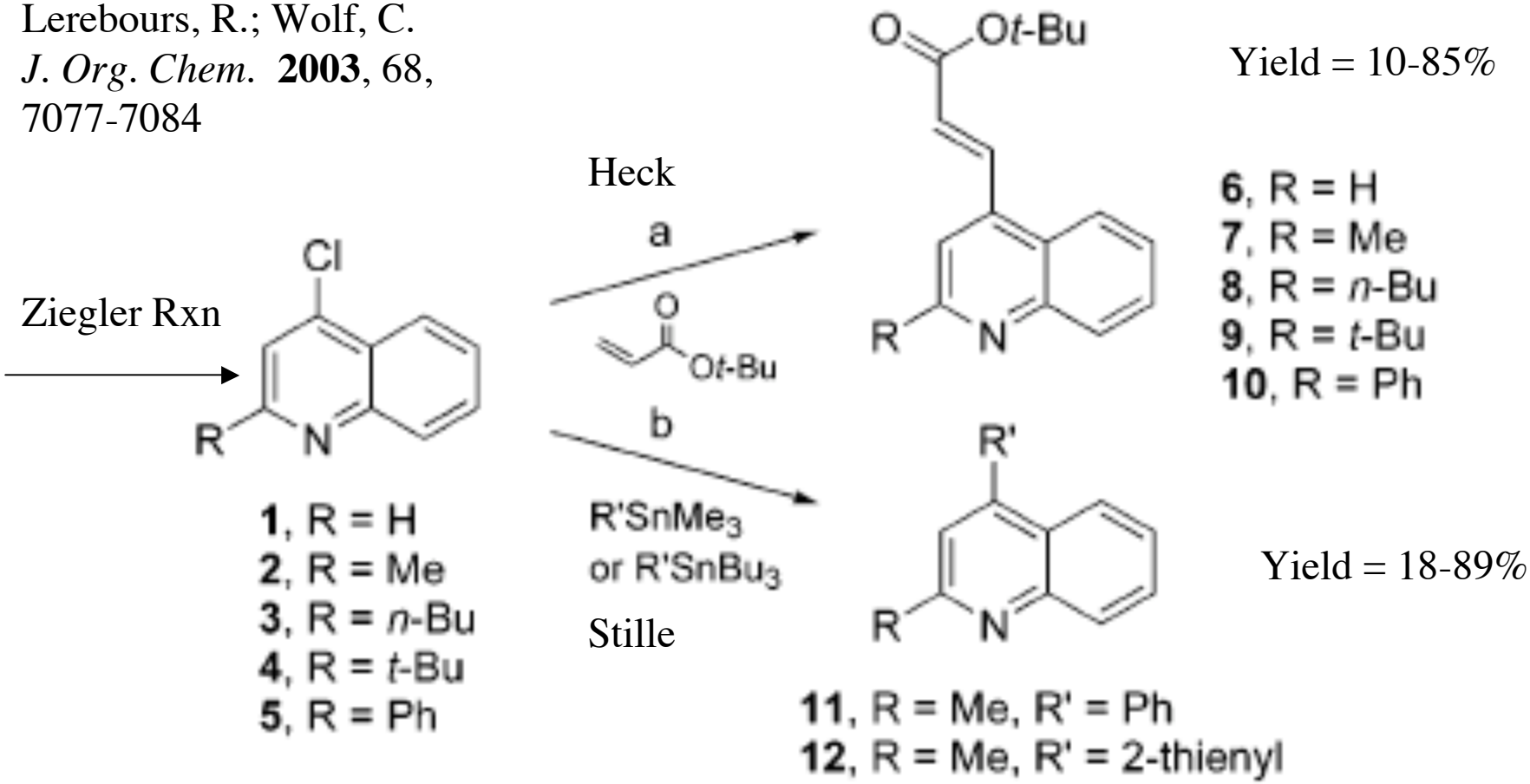


Li, G. Y. *Ang. Chem. Int. Ed.* **2001**, 40, 1513-1516

Cross-Coupling Reactions

Stille and Heck reactions of Chloroquinolines

Lerebours, R.; Wolf, C.
J. Org. Chem. **2003**, 68, 7077-7084



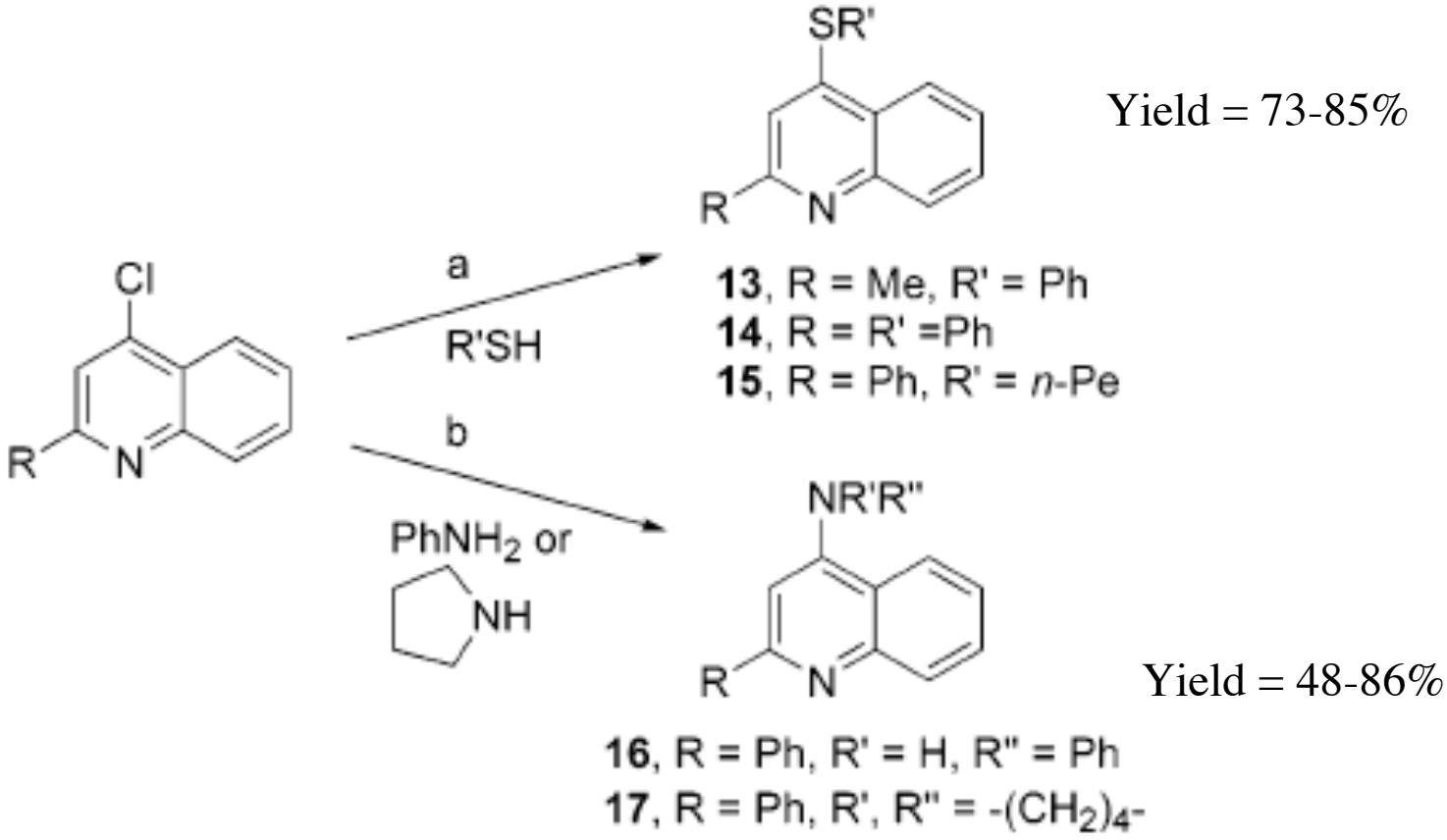
Yield = 10-85%

Yield = 18-89%

[a] Reagents and conditions: (a) 6 mol % POPd, 5 equiv of *tert*-butyl acrylate, 1.2 equiv of base, DMF, 135 °C, 24 h. (b) 6 mol % POPd, 1.3 equiv of Rm′$SnMe_3$ (R′$SnBu_3$), 1.1 equiv of Cy_2NMe, DMF, 135 °C, 24 h.

Cross Coupling Reactins

Amination and thiation reactions of Chloroquinolines

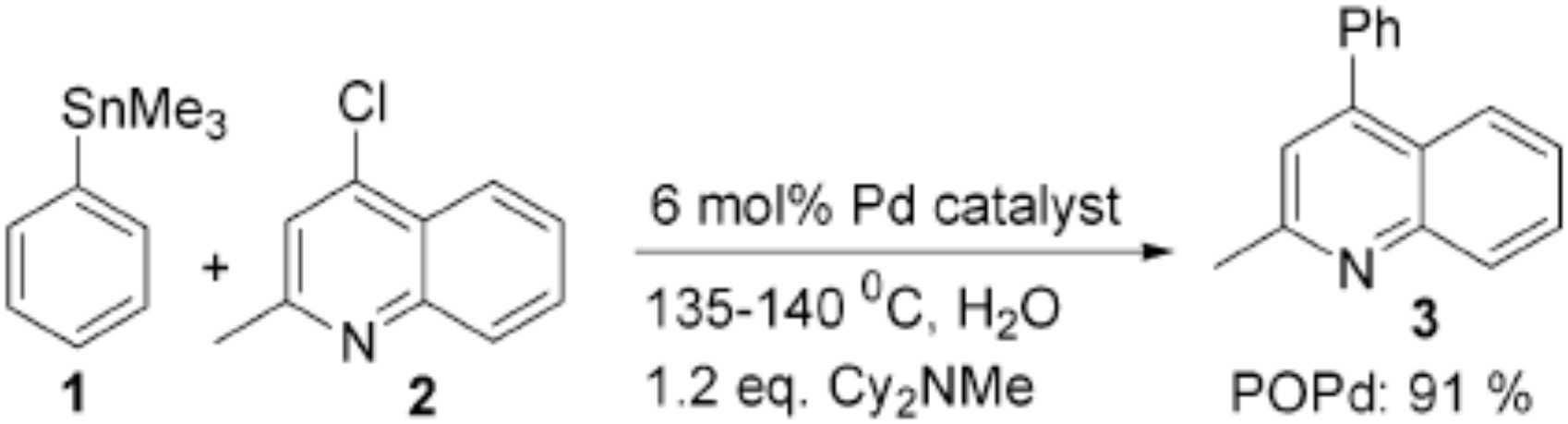


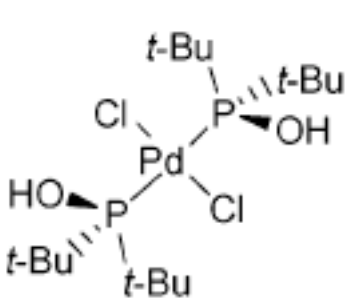
[a] Reagents and Conditions: (a) 1.6 equiv of R′SH, 1.1 equiv of base, DMF, 135 °C, 24 h. (b) 1.1 equiv of R″NH_2/R″$_2$NH, 1.1 equiv of. *t*-BuOK/*t*-BuOH, DMF, 135 °C, 24 h.

Lerebours, R.; Wolf, C. *J. Org. Chem.* **2003**, 68, 7077-7084

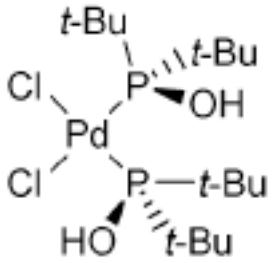
Cross Coupling Reactions

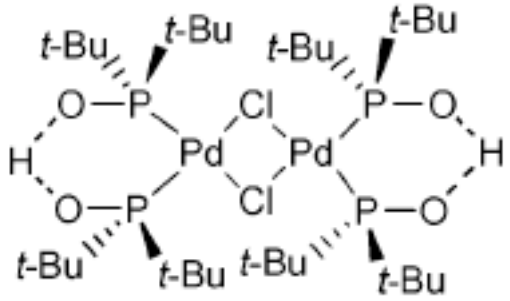
Stille Coupling in Water



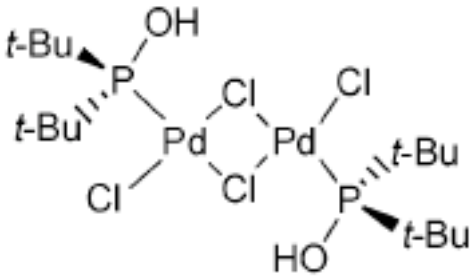


POPd





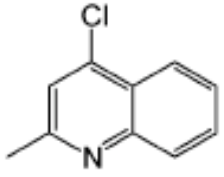
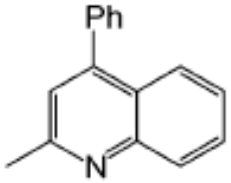
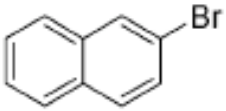
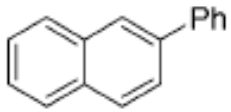
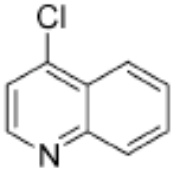
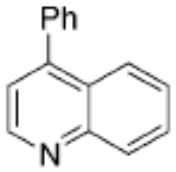
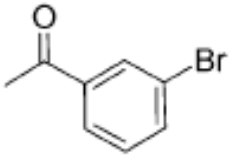
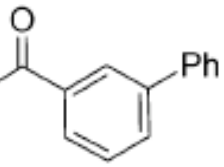
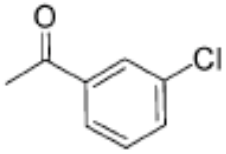
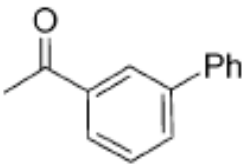
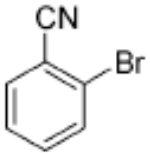
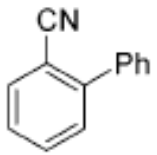
POPd1

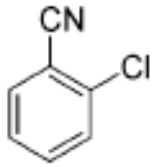
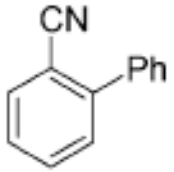
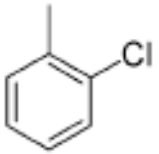
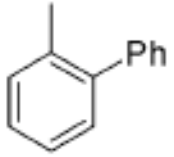
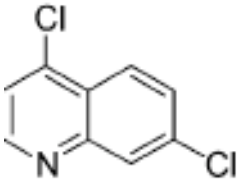
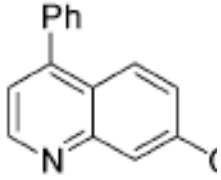
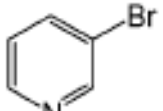
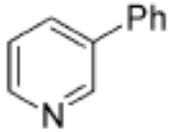
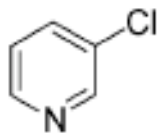
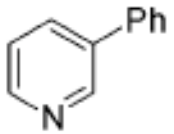
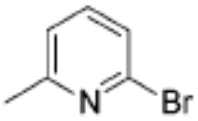
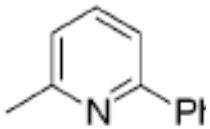


POPd2

Lerebours, R.; Wolf, C. *J. Org. Chem.* **2003**, 68, 7551-7554

Stille Couplings in Water

aryl halide	product	yield (%)
	 **3**	91
	 **4**	80
	 **5**	80
	 **6**	91
	 **6**	88
	 **7**	87

aryl halide	product	yield (%)
	 **7**	62
	 **8**	60
	 **9**	76[b]
	 **10**	96
	 **10**	61
	 **11**	61

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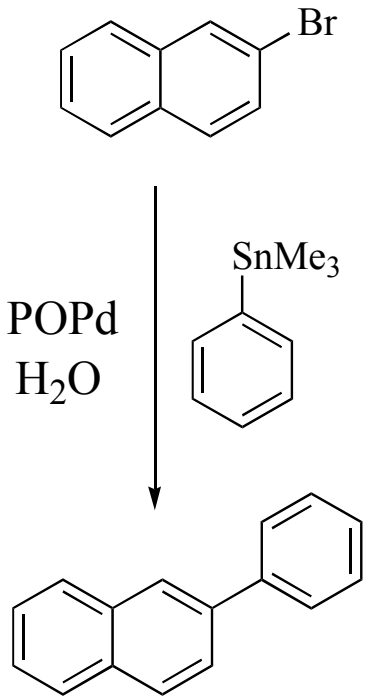
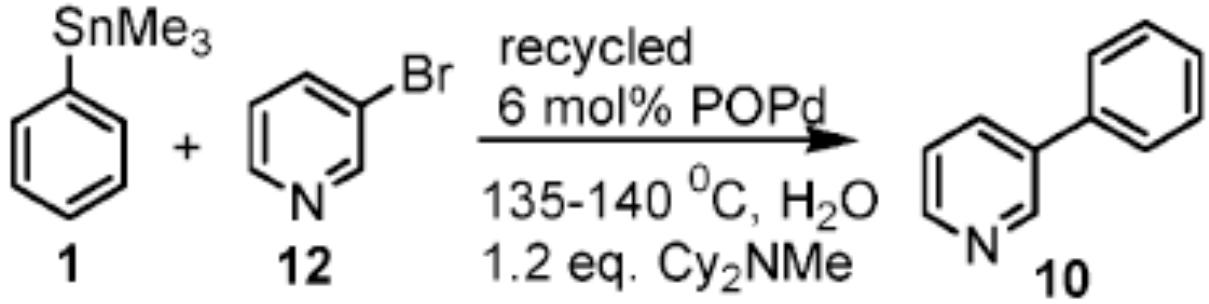
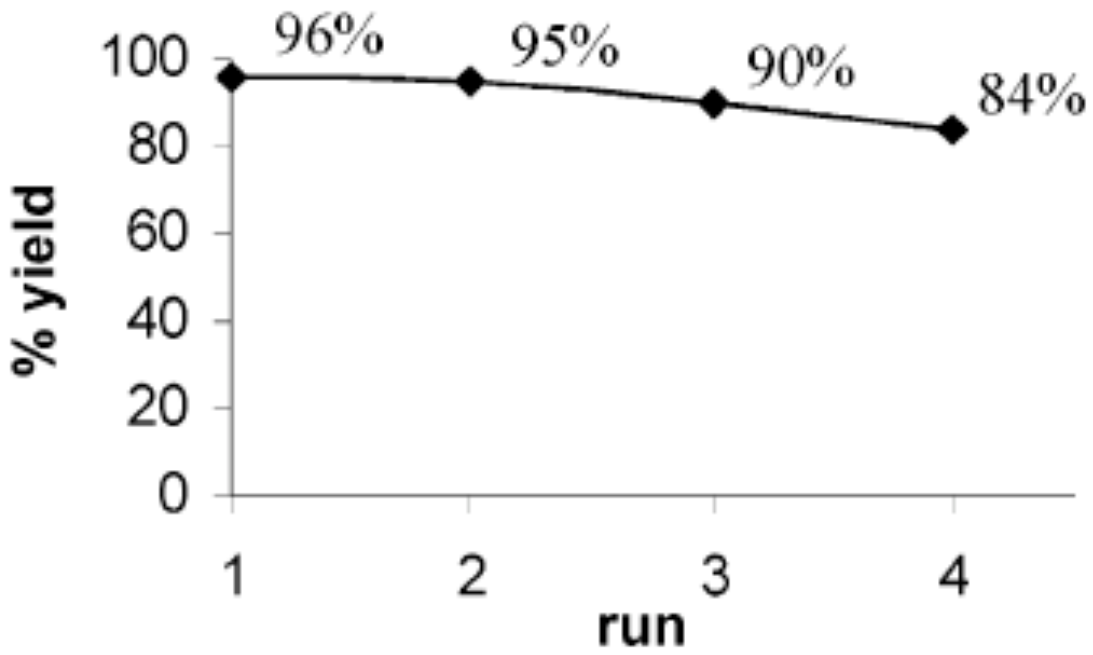
Stille Couplings in Water

Scale up and recyclable catalyst



0.5 mmol = 80% yield
5.0 mmol = 79% yield
(1 gram)





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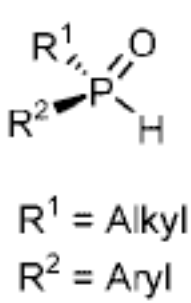
Chiral Phosphorus Preligands

- Highly stable to epimerization
- Two methods of preparation
  1. Formation by the diastereoselective generation of the stereogenic phosphorus atom (with chiral alcohols-BINOL and mandelic acid) followed by resolution of the racemate[1].
  2. Separation of enantiomers on preparative chiral HPLC columns[2].



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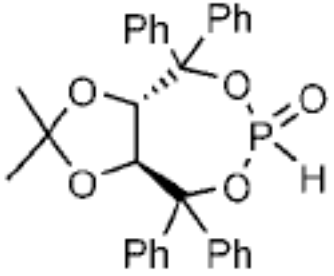

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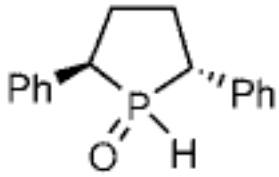
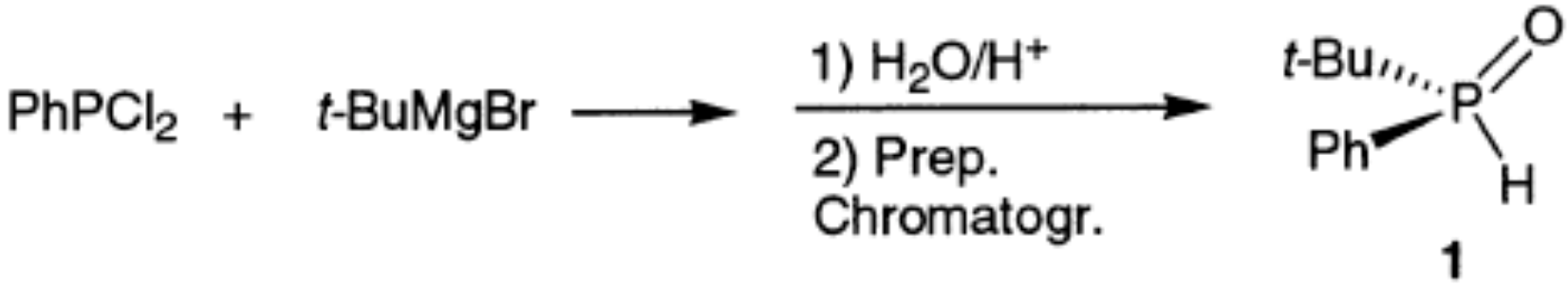


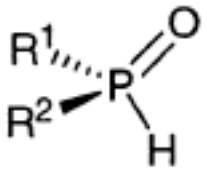
12

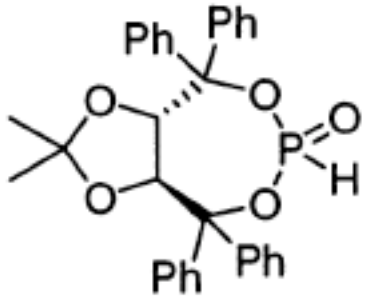
1.Drabowicz, J.; Lyzwa, P.; Omelanczuk, J.; Pietrusiewicz, K. M.; Mikilajczyk, M. *Tetrahedron Assym*. **1999**, 10, 2757-2763

2.Jiang, X.; Minnaard, A. J.; Hessen, B.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; Ferringa, B. L.; de Vries, J. G. *Org*. *Lett*. **2003**, 5, 1503-1506

Applications of Chiral SPO's







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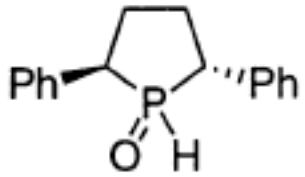


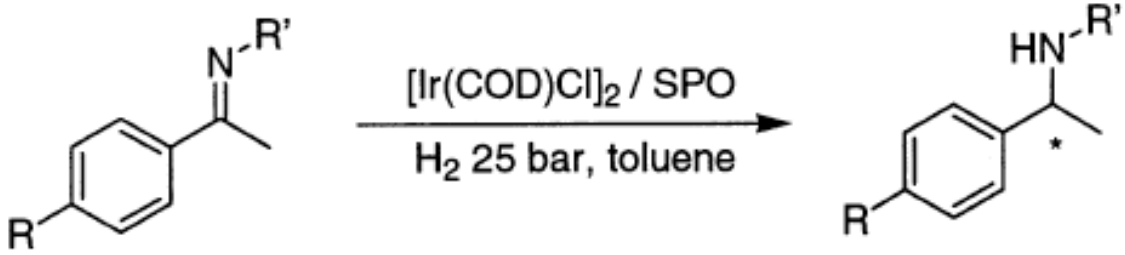
9

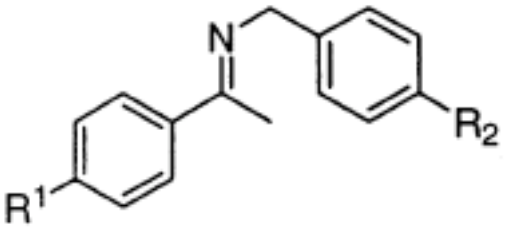
1 R^1= *t*-Bu, R^2=Ph
2 R^1= *i*-Pr, R^2=Ph
3 R^1= *t*-Bu, R^2=2-Naphthyl
4 R^1= *t*-Bu, R^2=2-MeOPhenyl
5 R^1= *t*-Bu, R^2=3,5-di-MePhenyl
6 R^1= *t*-Bu, R^2=2,4,6-tri-MePhenyl
7 R^1= Ph, R^2=2-Naphthyl

Jiang, X.; Minnaard, A. J.; Hessen, B.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; Ferringa, B. L.; de Vries, J. G. *Org. Lett.* **2003**, 5, 1503-1506

Applications of Chiral SPO's

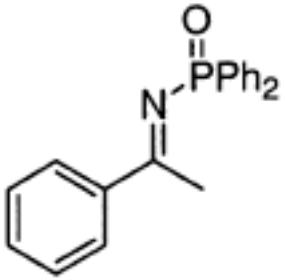
Iridium/SPO-Catalyzed Imine Hydrogenation





10-->R1=R2=H

11-->R1=Ome, R2=H



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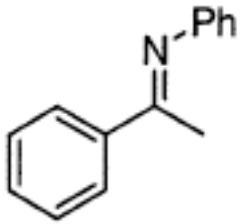

17

entry	imine	ligand	t (h)	conversion (%)[b]	ee (%)[c]
1[d]	**10**	**1** (*R*)	0.8	100	10 (*S*)
2[e]	**10**	**1** (*R*)	24	75	45 (*S*)
3	**10**	**1** (*R*)	51	>95	69 (*S*)
4[f]	**10**	**1** (*R*)	72	100	4 (*S*)
5[g]	**10**	**1** (*R*)	114	89	70 (*S*)
6	**10**	**6**	24	100	7
7	**10**	**7**	24	100	2
8	**10**	**8**	48	>95	9
9	**11**	**9**	24	>95	51
10[h]	**15**	**1** (*R*)	24	100	70
11	**17**	**1** (*R*)	24	100	0
12[i]	**10**	**1** (*R*)	168	100	76 (*S*)

F_3C-toluene

1 bar H2

[a] General conditions: $[Ir(COD)Cl]_2$/SPO/imine = 2.5:10:100, 25 bar H_2, toluene, room temperature. [b] Conversion was determined by ^1H NMR ($CDCl_3$). [c] Ee was determined by HPLC (chiralpak AD or OD, heptane/2-propanol = 95/5 or 90/10) on the *N*-acetyl derivatives. Configuration is unknown when none is shown. [d] CH_2Cl_2 as solvent, Ir/**1** =1:1. [e] CH_2Cl_2 as solvent. [f] $[Ir(COD)_2]BF_4$ as a precursor. [g] $CF_3C_6H_5$ as a solvent. [h] Temperature = 40 °C. [i] H_2 (1 bar; balloon).

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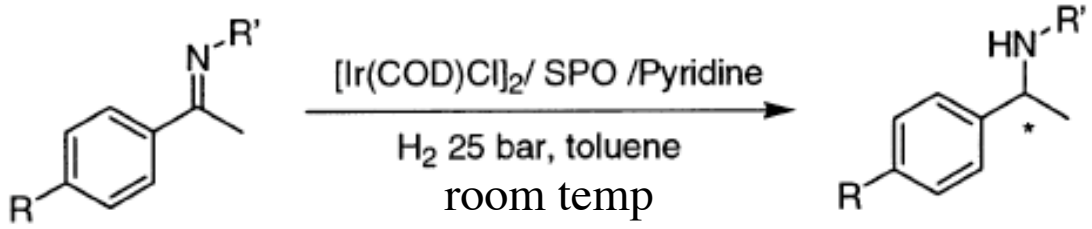
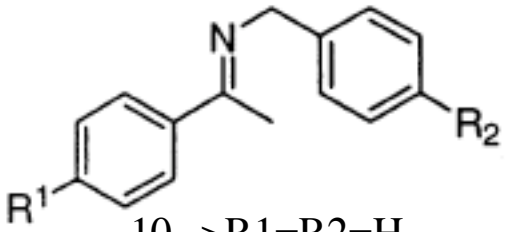


entry	imine	ligand	*t* (h)	conversion (%)[b]	ee (%)[c]
1	**10**	**1** (*R*)	24	100	78 (*S*)
2[d]	**10**	**1** (*R*)	24	>98	78 (*S*)
3	**11**	**1** (*R*)	24	100	**80**
4[e] **0 °C**	**10**	**1** (*R*)	120	75	**82** (*S*)
5[e]	**11**	**1** (*R*)	120	80	**83**
6	**12**	**1** (*R*)	24	85	76
7	**13**	**1** (*R*)	24	75	77
8	**14**	**3**	17	76	62
9	**15**	**1** (*R*)	139	85	12
10[f]	**16**	**1** (*R*)	48	50	57
11[f]	**10**	**1** (*R*)	48	100	73 (*S*)
12[g]	**10**	**1** (*R*)	24 cyclohexane	30	68 (*S*)
13[h]	**11**	**1** (*R*)	72	100	76
14[i]	**11**	**1** (*R*)	10	100	73
15	**11**	**2**	17	>95	33
16	**11**	**3**	17	>95	68
17	**11**	**4**	17	60	70
18	**10**	**5**	17	>95	66 (*S*)
19	**10**	**6**	24	100	7 (*S*)
20	**10**	**7**	24	100	4 (*S*)
21[j]	**10**	**8**	48	100	1 (*S*)
22	**10**	**9**	24	>95	23 (*S*)



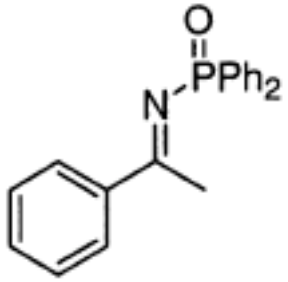
10-->R1=R2=H

11-->R1=OMe, R2=H

12-->R1=H, R2=OMe

13-->R1=H, R2=Cl

14-->R1=Cl, R2-H



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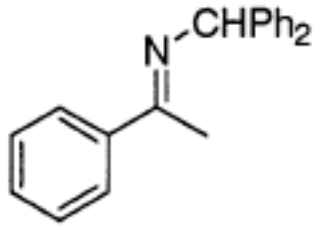

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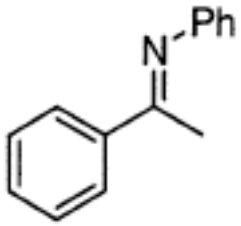

17

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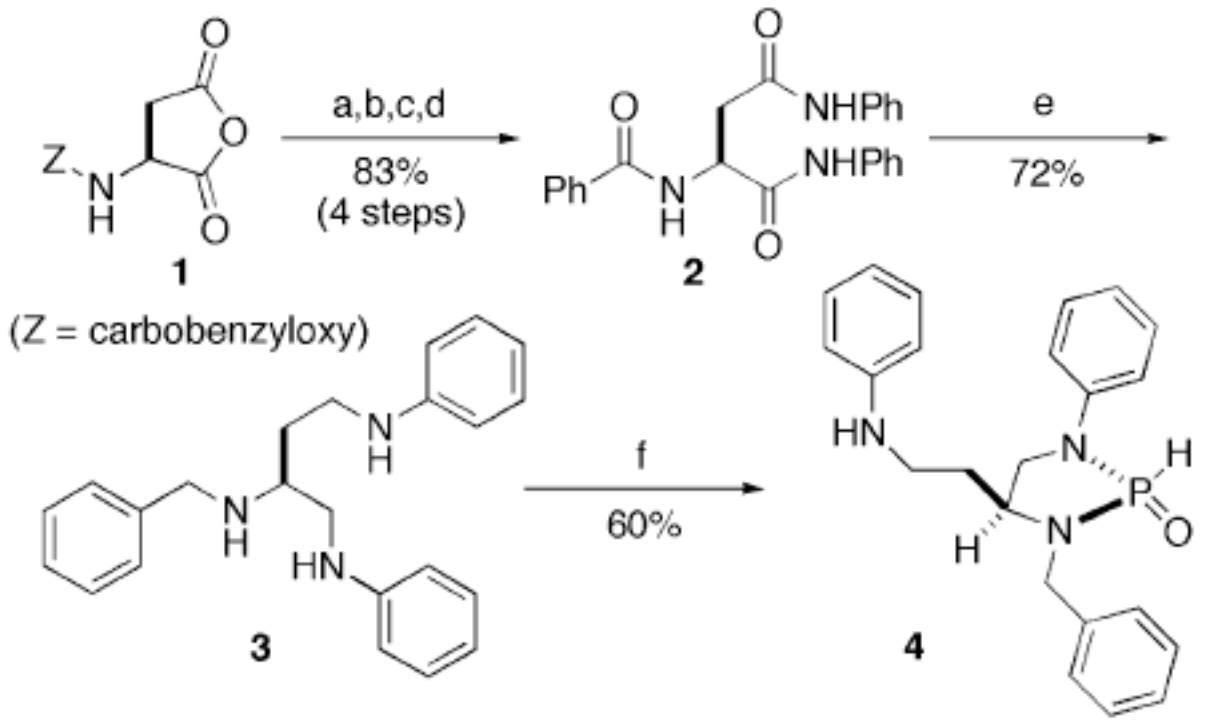
P-Chirogenic Diaminophosphine Oxide

Scheme 1. Synthesis of Diaminophosphine Oxide **4**[a]



[a] Reagents and conditions: (a) aniline, DMSO, room temperature, 1 h; (b) aniline, WSCI, DMF, room temperature, 24 h; (c) Pd−C (2 mol %), H_2, 2-propanol−DMF, room temperature, 6 h; (d) benzoyl chloride, NEt_3, THF, room temperature, 1 h; (e) $LiAlH_4$, THF, reflux, 13 h; (f) PCl_3, NEt_3, toluene, −78 °C to room temperature, 16 h, then SiO_2, H_2O, AcOEt, room temperature, 18 h.

Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y.
J. Am. Chem. Soc. **2004**, 126, 3690-3691

P-Chirogenic Diaminophosphine Oxide

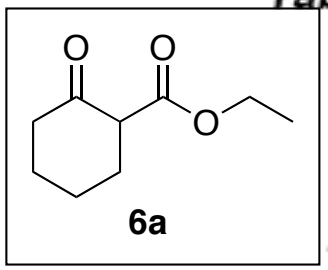
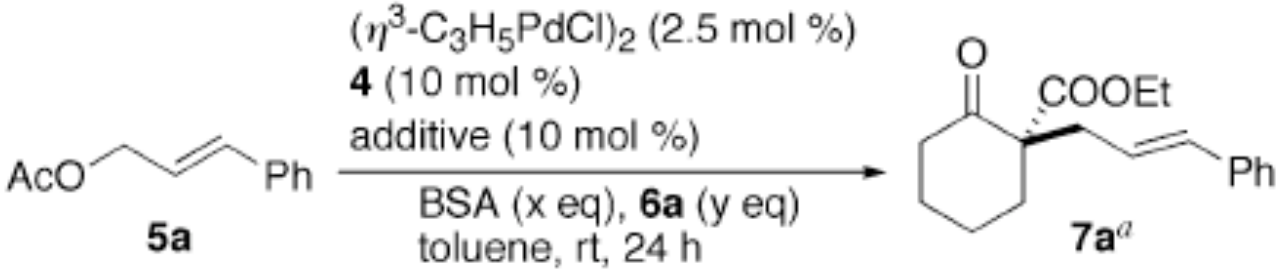


Table 1. Asymmetric Allylic Substitution of **5a** with **6a**



run	additive	*x* (equiv)	*y* (equiv)	yield[b]	ee[c]
1		3.0	1.25	10%	53% ee
2	LiOAc	3.0	1.25	53%	8% ee
3	$Mg(OAc)_2 \cdot 4H_2O$	3.0	1.25	99%	66% ee
4	$Zn(OAc)_2 \cdot 2H_2O$	3.0	1.25	81%	89% ee
5	$Zn(OAc)_2$	3.0	1.25	80%	91% ee
6	$Zn(OAc)_2$	3.0	1.5	86%	91% ee
7	$Zn(OAc)_2$	4.0	1.5	99%	92% ee

[a] The absolute configuration was determined to be *S*; see the Supporting Information for details. [b] Isolated yield. [c] Determined by HPLC analysis.

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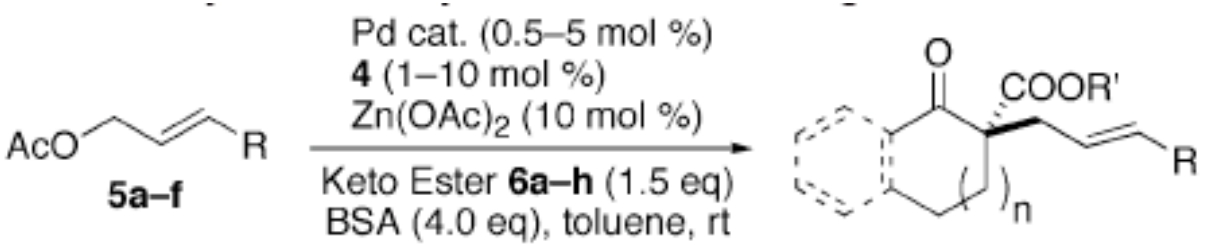
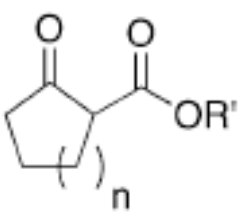
Allylic Substitution of Various Substrates

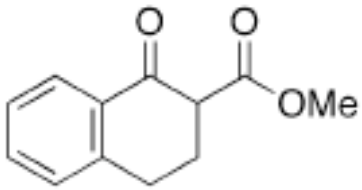


5a: R = C_6H_5 **5d**: R = 2-naphthyl
5b: R = 4-Me-C_6H_4 **5e**: R = $CH_2CH_2C_6H_5$
5c: R = 4-Cl-C_6H_4 **5f** : R = C_6H_{11}

run	acetates	keto esters	products	time (h)	yield[a] (%)	ee[b] (%)
1[c]	**5a**	**6a** (n = 2, R' = Et)	**7a**	16	99	93(*S*)[i]
2[d]	**5a**	**6a** (n = 2, R' = Et)	**7a**	20	98	92
3[e]	**5a**	**6a** (n = 2, R' = Et)	**7a**	32	85	93
4[c]	**5a**	**6b** (n = 2, R' = Bn)	**7b**	15	99	91(*S*)[i]
5[c]	**5a**	**6c** (n = 2, R' = Me)	**7c**	20	93	94
6[f]	**5a**	**6d** (n = 1, R' = Me)	**7d**	24	75	85(*S*)[i]
7[c,g]	**5a**	**6e** (n = 3, R' = Me)	**7e**	24	85	78
8[c,g]	**5a**	**6f** (n = 4, R' = Me)	**7f**	20	97	72
9[c]	**5a**	**6g**	**7g**	8	99	93(*S*)[i]
10[d]	**5a**	**6g**	**7g**	12	96	93
11[c]	**5b**	**6g**	**7h**	10	98	92
12[c]	**5c**	**6g**	**7i**	7	99	91
13[c]	**5d**	**6g**	**7j**	6	91	91
14[f]	**5e**	**6g**	**7k**	24	74	82
15[f,h]	**5f**	**6g**	**7l**	20	83	80



6a–f



6g

[a] Isolated yield. [b] Determined by HPLC analysis. [c] 2 mol % of the Pd catalyst was used. [d] 1 mol % of the Pd catalyst was used. [e] 0.5 mol % of the Pd catalyst was used. [f] 5 mol % of the Pd catalyst was used. [g] Xylenes was used as a solvent. [h] 12.5 mol % of **4** was used. [i] See the Supporting Information for details.

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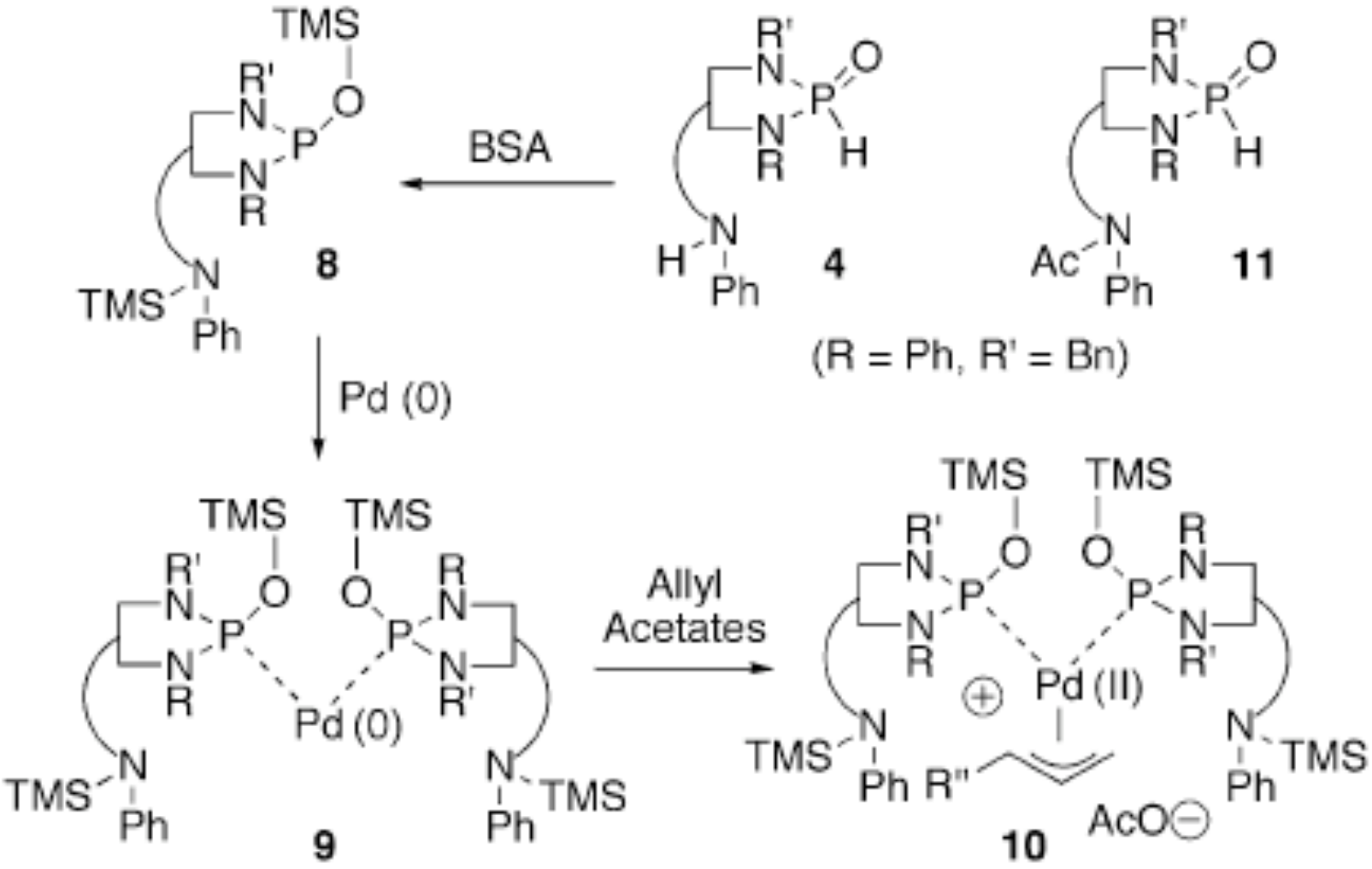
Proposed Structure of Active Species



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Conclusions