Case Studies of Ionic Interactions in Transition-Metal Catalyzed Processes

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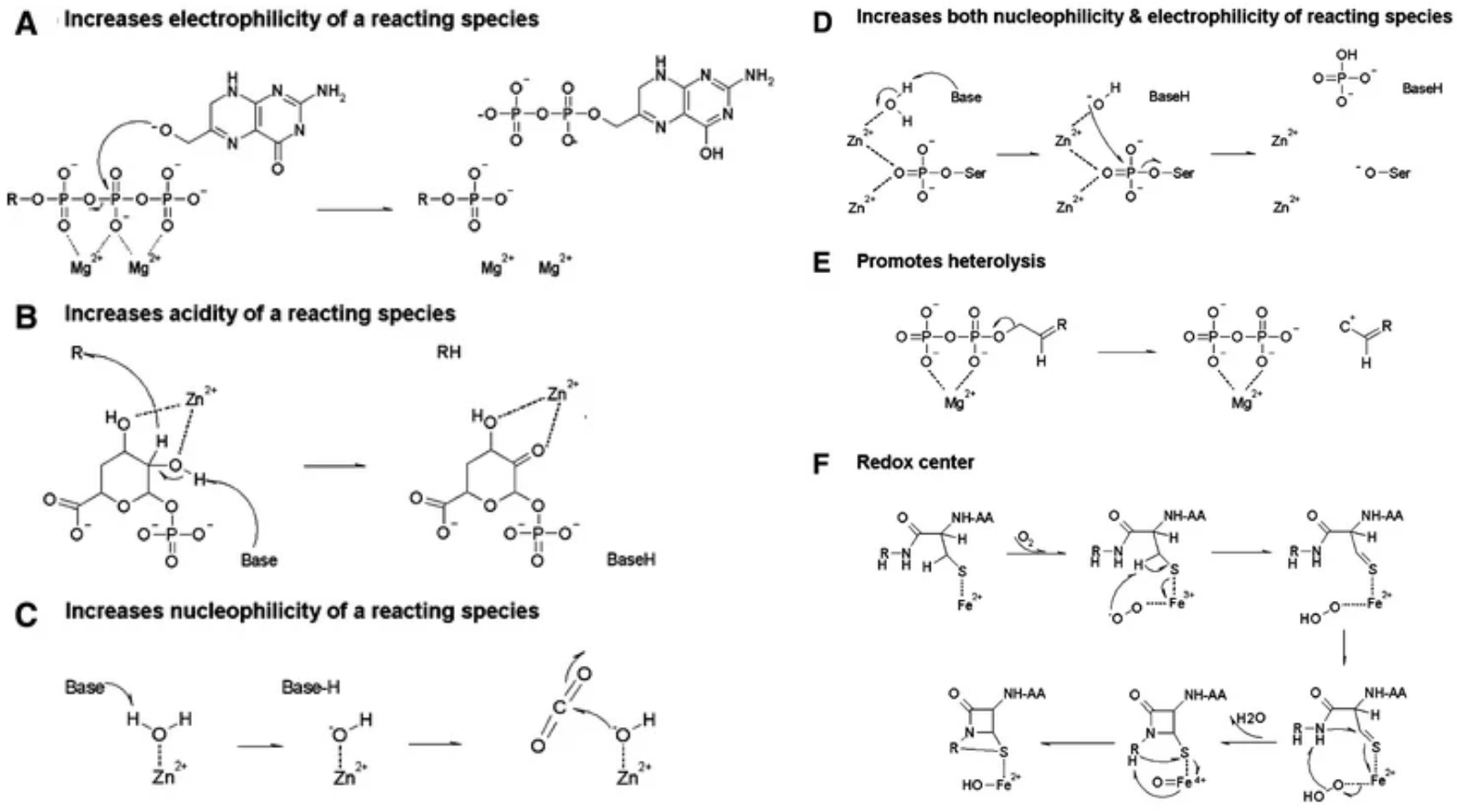
Denmark Group Meeting
April 29th, 2025

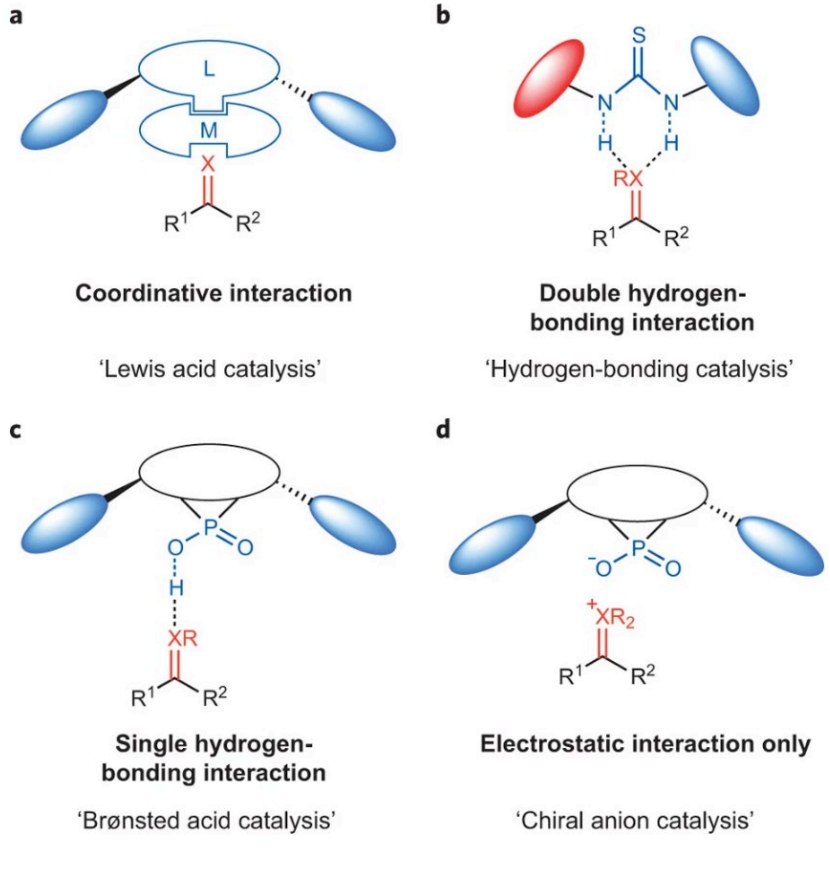
Introduction

In Nature, enzymes use metals in tandem with attractive noncovalent interactions at the active site to precisely position the substrate for a desired transformation. In general, all forms of reactivity: chemo, site, and enantioselectivity are optimized for the substrate.

Metal Ions in Enzymatic Catalysis:

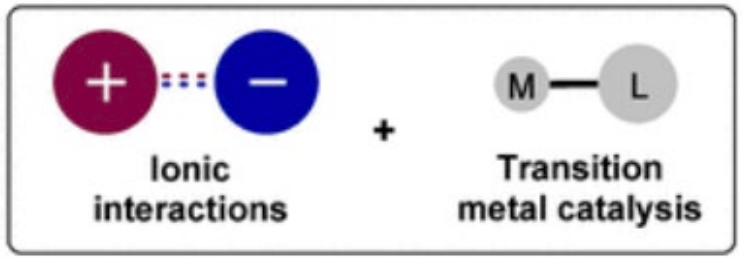


Representative Modes of Catalysis:

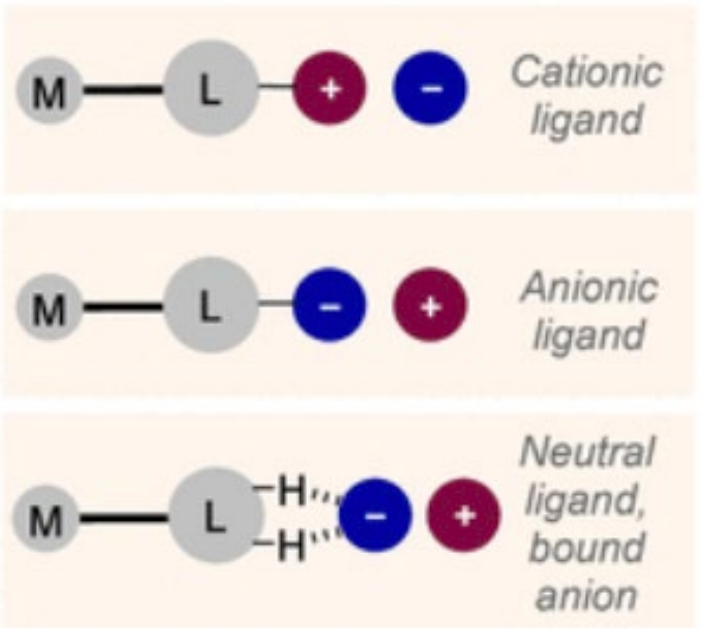


J Biol Inorg Chem. ***2008***, 13, 1205-1218.
Nature Chem. ***2012***, 4, 603-614.

Overview



Covered:

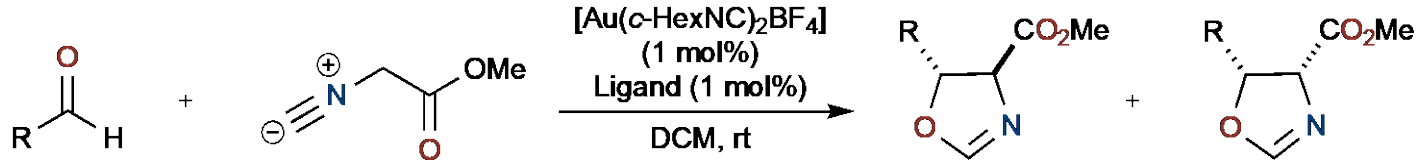


Not Covered:

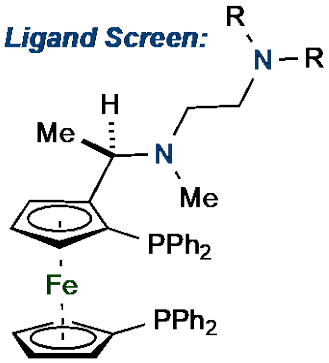
Chem Rev. ***2025***, 125, 2846-2907.

Ito and Hayashi's Gold-Catalyzed Aldol:

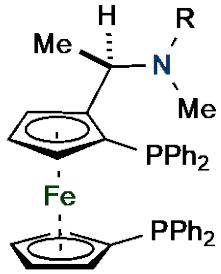
Seminal Report: Ito and Hayashi
Gold-catalyzed Asymmetric Aldol Reaction



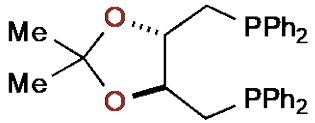
Ligand Screen:



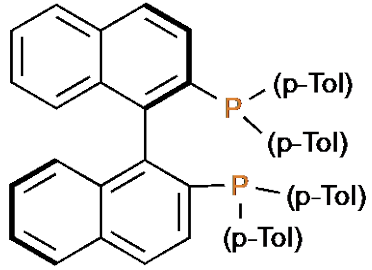
R = Et, ***2a***
Me, ***2b***



R = Me
$CH_2CH_2CH_2NEt_2$

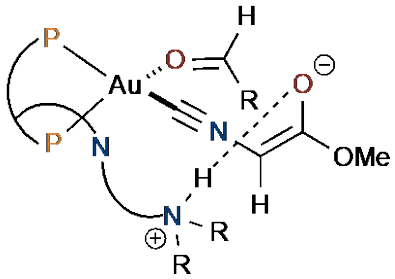


only racemic product obtained



only racemic product obtained

Ito and Hayashi's Proposed Interaction:



Substrate Scope:

Aldehyde	yield (%)	*trans*:*cis*	*ee* (%)
PhCHO	98%	89:11	96%
MeCHO	100%	84:16	72%
i-PrCHO	99%	98:2	92%
c-HexCHO	95%	97:3	90%
t-BuCHO	100%	100:0	97%

Major Conclusions invoked by Hayashi:

1. Gold (I) is undergoing tetra-coordination
2. Enolate formation is driven by the pendant amino-linker
3. The reactive pi-face of the enolate formed is determined by the possible hydrogen bonding

Pastor's Rebuttal: X-Ray Diffraction of Gold Complex

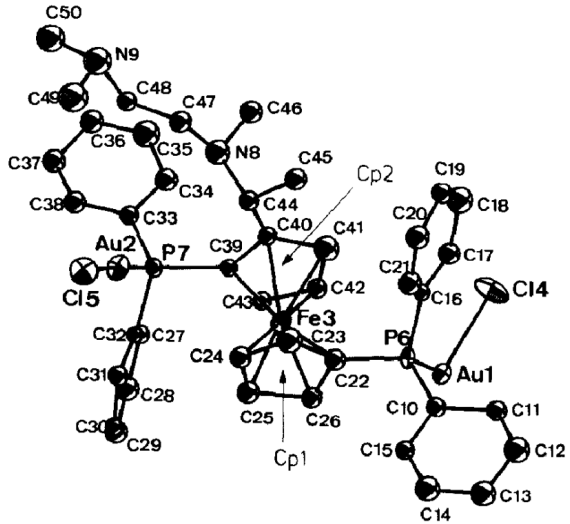
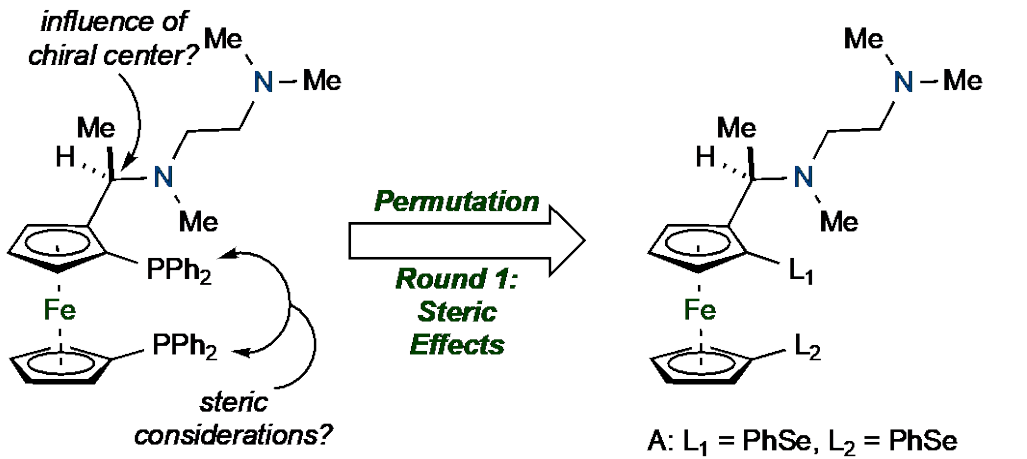


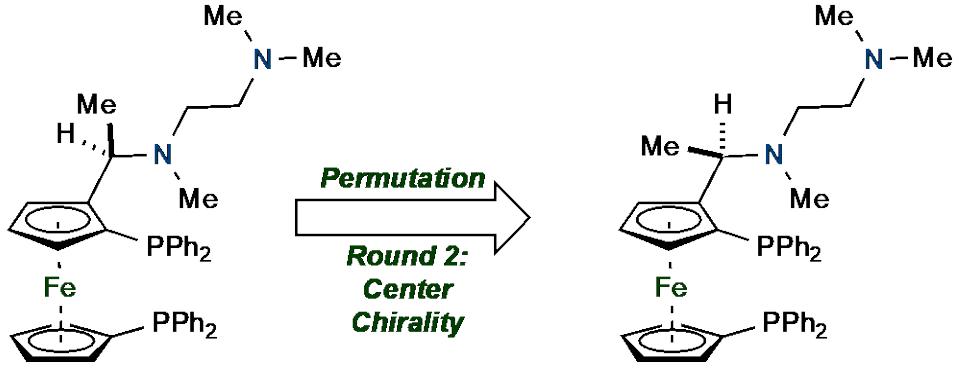
Fig. 1. ORTEP-view [8] of complex **7** showing one of the two symmetry related units and the atom numbering scheme; thermal ellipsoids are at the 20% probability level. Relevant bonding parameters: Au(1)–Cl(4) 2.52(3), Au(1)–P(6) 2.31(2), Au(2)–Cl(5) 2.28(2) and Au(2)–P(7) 2.20(2) Å; P(6)–Au(1)–P(6′) 134(2), P(6)–Au(1)–Cl(4) 113(2) and P(7)–Au(2)–Cl(5) 177(2).

J. Am. Chem. Soc. ***1986***, 108, 6405-6406.
Journal of Organometallic Chemistry. ***1990***, 381, C21-C25.

Pastor's Studies on the Gold-Catalyzed Aldol:

Pastor's Independent Mechanistic Interrogation:



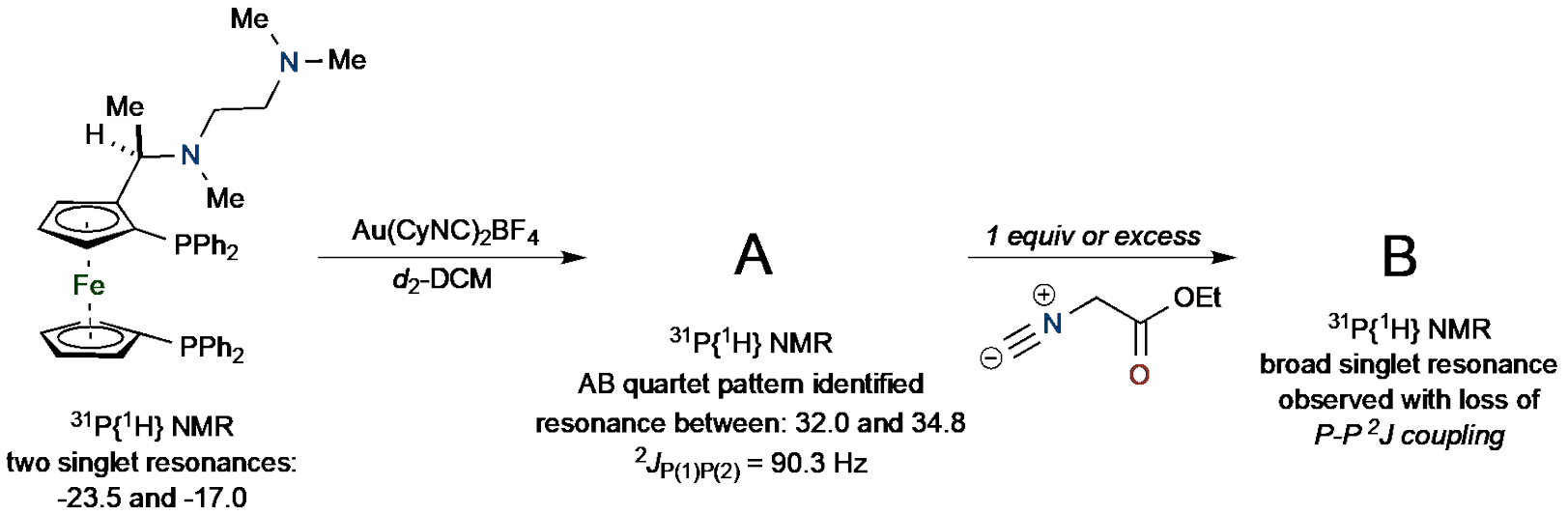


entry	ligand	aldehyde	ester	% trans (ee) 5	% cis (ee) 6
1[f]	(*R*)-(*S*)-**4**	**1a**	**2a**	90 (91 [4*S*,5*R*]) **5a**	10 (7 [4*S*,5*S*]) **6a**
2[f]	(*S*)-(*R*)-**4**	**1a**	**2a**	90 (90 [4*R*,5*S*]) **5a**	10 (12 [4*R*,5*R*]) **6a**
3[f]	(*S*)-(*S*)-**4**	**1a**	**2a**	84 (41 [4*R*,5*S*]) **5a**	16 (20 [4*S*,5*S*]) **6a**
4	(*S*)-(*R*)-**18**	**1a**	**2a**	74 (21 [4*R*,5*S*]) **5a**	26 (4 [4*R*,5*R*)] **6a**
5	(*R*)-(*S*)-**4**	**1b**	**2b**	91 (78) **5b**	9 (9) **6b**
6	(*R*)-(*S*)-**18**	**1b**	**2b**	77 (16) **5b**	23 (1) **6b**
7[g]	(*R*)-(*S*)-**4**	**1a**	**2b**	89 (93) **5c**	11 (18) **6c**
8	(*R*)-(*S*)-**4**	**1c**	**2b**	86 (87) **5d**	14 (7) **6d**
9	(*R*)-(*S*)-**4**	**1d**	**2b**	68 (32) **5e**	32 (83) **6e**
10	(*R*)-(*S*)-**4**	**1e**	**2b**	88 (75) **5f**	12 (78) **6f**
11	(*R*)-(*S*)-**4**	**1f**	**2b**	88 (79) **5g**	12 (62) **6g**
12	(*R*)-(*S*)-**4**	**1g**	**2b**	75 (6) **5h**	25 (84) **6h**
13	*h*	**1g**	**2b**	78 (0) **5h**	22 (0) **6h**
14	*i*	**1g**	**2b**	74 (0) **5h**	26 (0) **6h**
15	*j*	**1g**	**2b**	94 (0) **5h**	6 (0) **6h**
16	(*S*)-(*R*)-**4**	**1h**	**2a**	95 (51) **5i**	5 (59) **6i**
17	(*S*)-(*R*)-**4**	**1i**	**2b**	85 (85) **5j**	15 (57) **6j**
18	(*S*)-(*R*)-**4**	**1j**	**2b**	81 (84) **5k**	19 (62) **6k**
19	(*S*)-(*R*)-**4**	**1k**	**2b**	84 (88) **5l**	16 (86) **6l**
20	(*S*)-(*R*)-**4**	**1l**	**2b**	93 (92) **5m**	7 (21) **6m**

Pastor invokes the principle of double stereodifferentiation. Where both the central and planar chirality of the ligand is controlling enantioselectivity of the process as both a matched and mismatched case.

Pastor's Studies on the Gold-Catalyzed Aldol:

Mode of Gold Coordination and the Rate-Determining Step: Possible Coordination Modes



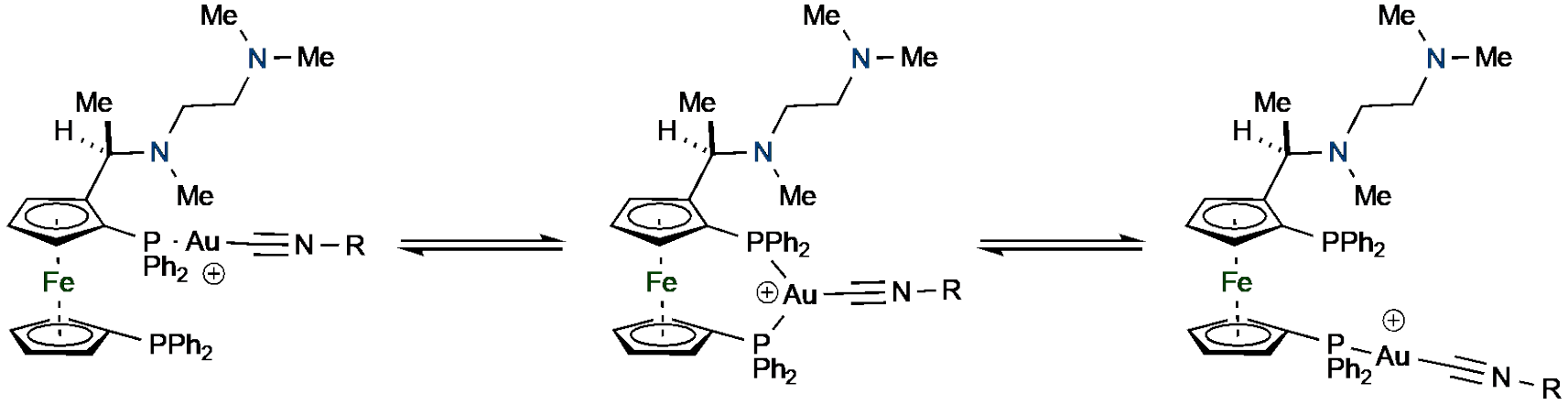
$^{31}P\{^{1}H\}$ NMR
two singlet resonances:
-23.5 and -17.0

$^{31}P\{^{1}H\}$ NMR
AB quartet pattern identified
resonance between: 32.0 and 34.8
$^{2}J_{P(1)P(2)}$ = 90.3 Hz

$^{31}P\{^{1}H\}$ NMR
broad singlet resonance
observed with loss of
P-P ^{2}J *coupling*

Addition of benzaldehyde to complex A resulted in no observable change to the spectrum. This could provide evidence against any prior coordination of the aldehyde to gold as suggested by Hayashi.

Possible Equilibrating States:



1. ***Observation of complex A with a coupling hints at the complexation of both phosphorous atoms with Au.***
2. ***Addition of excess isocyanide resulting in loss of coupling could indicate a dynamic process involving a rapid exchange of the phosphorous atoms.***

Pastor's Studies on the Gold-Catalyzed Aldol:

Further Interrogation: Hammett Plot

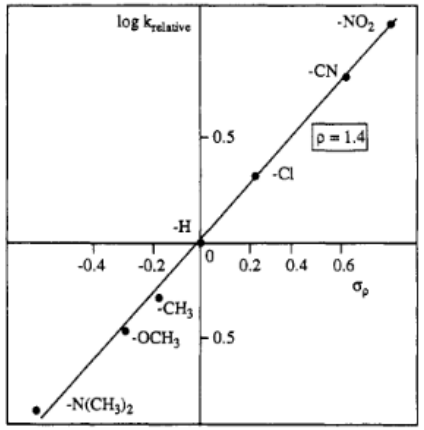
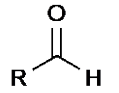


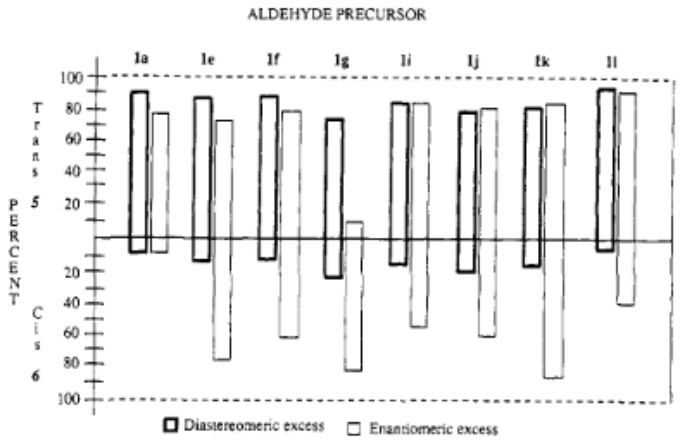
Figure 4. A Hammett plot of the reaction of para-substituted benzaldehydes with **2b**.

Positive slope indicates build-up of increased electron density on the carbonyl carbon atom in the RDS. The RDS of the reaction is strongly suggested to be the electrophilic attack of the aldehyde by the enolate pi-face.

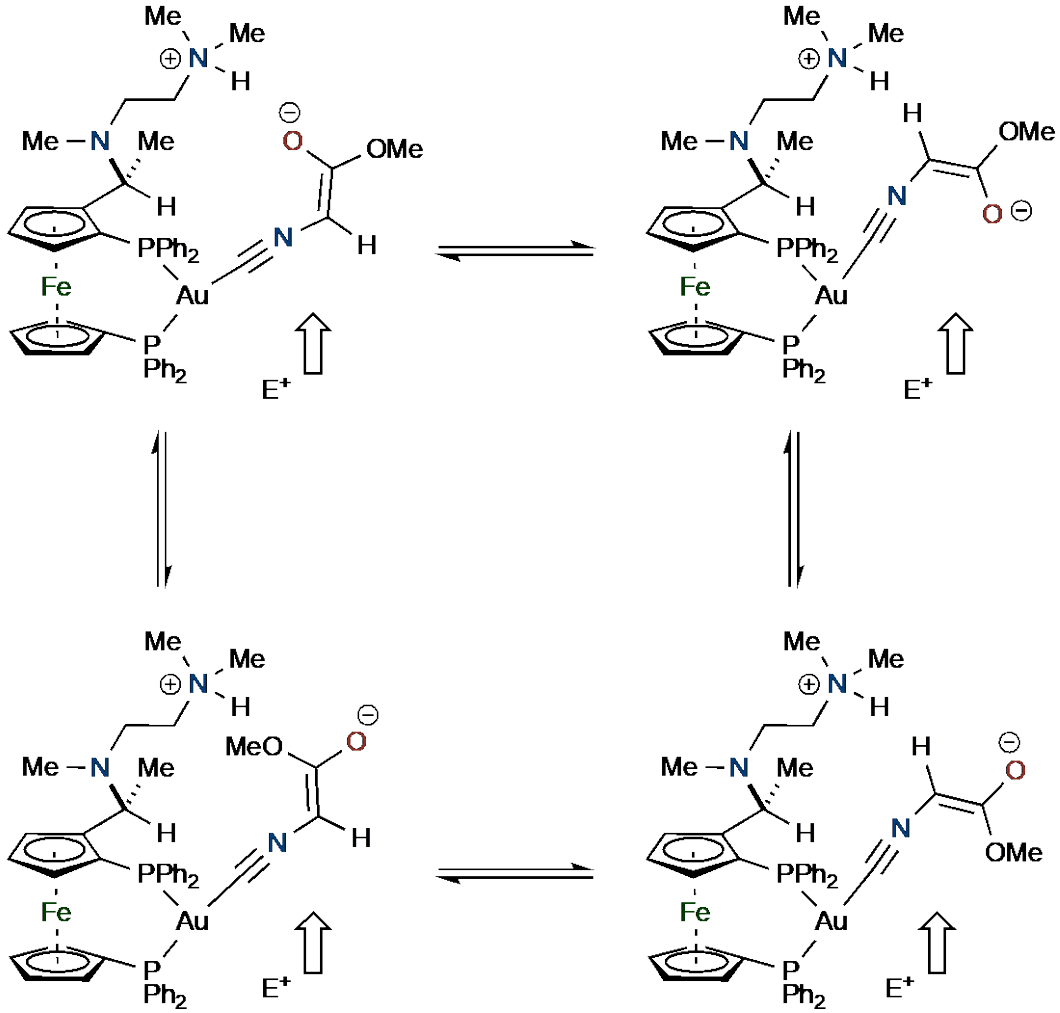
Further Interrogation: Electronic Effects



a. R = Ph
b. R = 1-Methylethenyl
c. R = 3-Furyl
d. R= 2-Furyl
e. R= 4-Pyridinyl
f. R = 3-Pyridinyl
g. R = 2-Pyridinyl
h. R = 1,1-(Ethylenedioxy)ethyl
i. R = 4-CF_3-C_6H_4
j. R = 3-CF_3-C_6H_4
k. R = 2-CF_3-C_6H_4
l. R = 2-CH_3-C_6H_4



Pastor's Proposed Transition States:

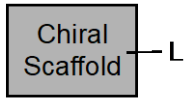


J. Org. Chem. ***1990***, 55, 1649-1664.

Ooi's Palladium-Catalyzed Allylic Alkylation:

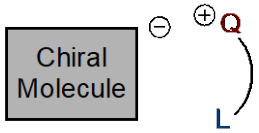
Ooi's Hypothesis: Separation of the Chiral Backbone and Cationic Component

Conventional Approach:

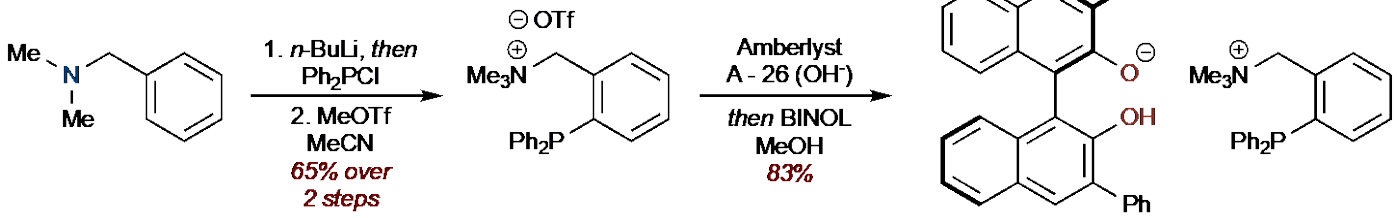


Single chiral molecule constructed by covalent bond

Ion-paired chiral ligand:



Simple chiral molecule and achiral ligand with built in electrostatic interaction
Q = quaternary onium cation
L = coordinating group

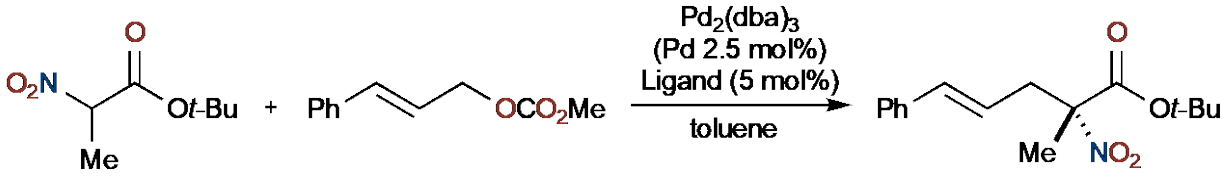


rapid synthesis and highly modular combinations available

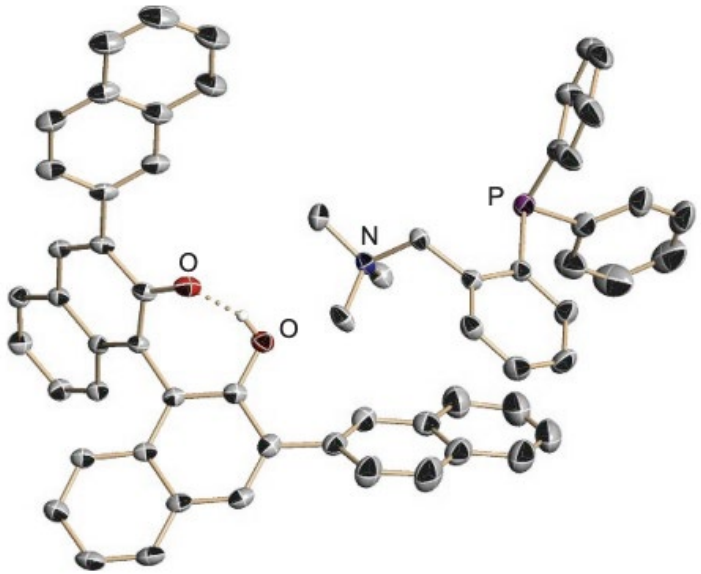
Application of the Concept: Asymmetric Allylic Alkylation

Reaction Selection Rationale:

1. ***Control of C over O alkylation.***
2. ***Stereochemical control in the attack of a prochiral nucleophile on a pi-allyl metal complex by a chiral ligand.***
3. ***Asymmetric reactions involving anionic nucleophiles are not controllable by the chiral anion strategy.***

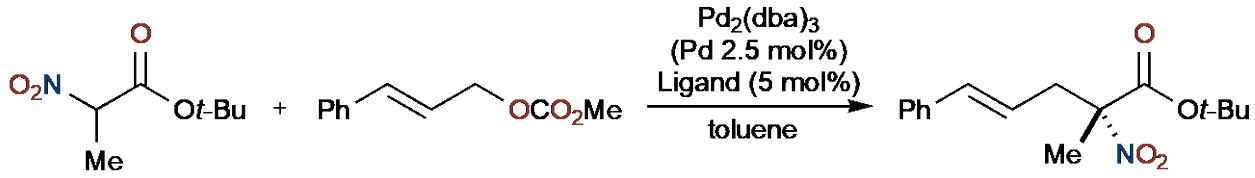


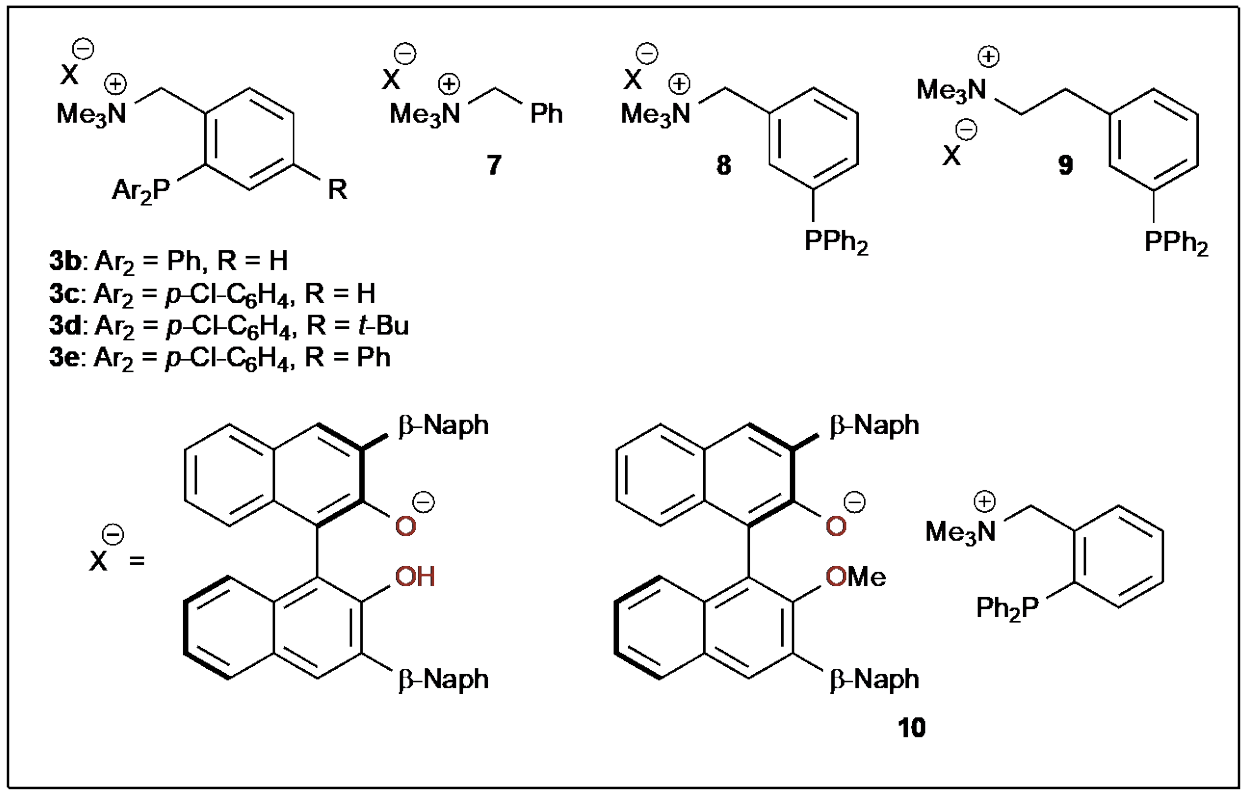
Ligand Structure:



Ooi's Palladium-Catalyzed Allylic Alkylation:

Ligand Diversity and Initial Screening:





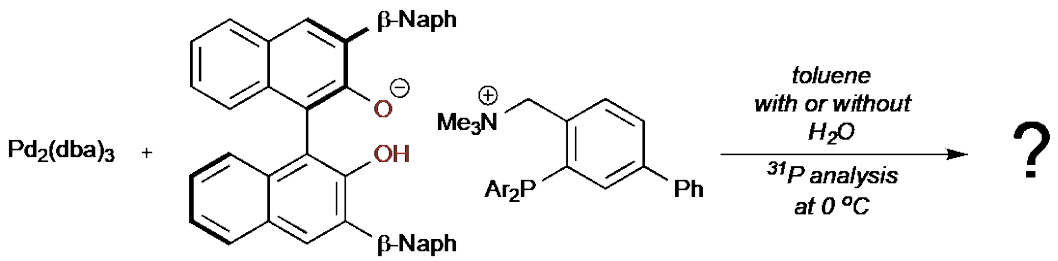
Entry	Ligand	Conditions	Yield (%)*	e.e. (%)†
1	**3a**	r.t., 5 h	56	38
2	**3b**	r.t., 5 h	78	68
3	PPh_3	With **7** (5 mol%), r.t., 5 h	99	<1
4	**1**·Br	With **2b** (5 mol%), r.t., 5 h	85	<1
5	**8**	r.t., 5 h	99	<1
6	**9**	r.t., 5 h	83	<1
7	**10**	r.t., 5 h	92	−3
8	**3c**	r.t., 5 h	99	73
9	**3d**	r.t., 5 h	99	75
10	**3e**	r.t., 5 h	99	83
11	**3e**	0 °C, 24 h	78	88
12	**3e**	Toluene/H_2O (20:1. v/v), 0 °C, 12 h	97	94

Preliminary Observations:

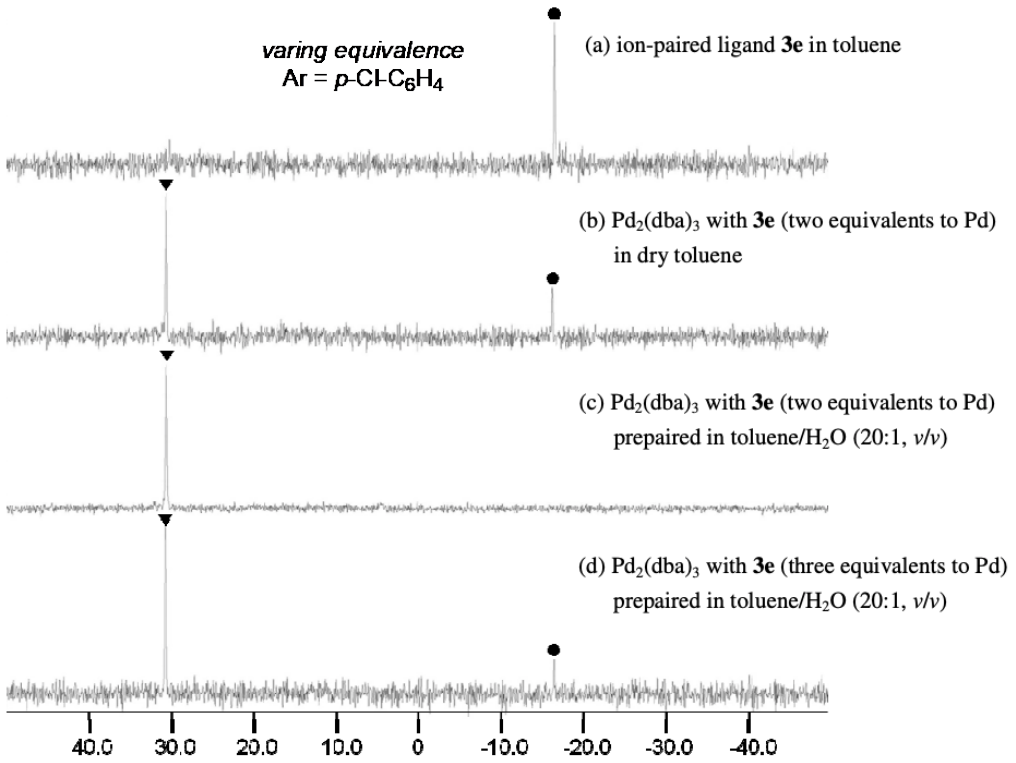
1. ***Presence of proximal phosphine binding site and quaternary ammonium entity is crucial for enantioselectivity.***
2. ***Aryl phosphine switch to p-chlorophenyl and introduction of distal steric-inducing substituent also increases e.e.***
3. ***Addition of water causes strange increase in performance.***

Ooi's Palladium-Catalyzed Allylic Alkylation:

Mechanistic Investigation of the Water Effect: NMR Experiments



Pd$_2$(dba)$_3$ +



Mechanistic Investigation: Asymmetric Amplification

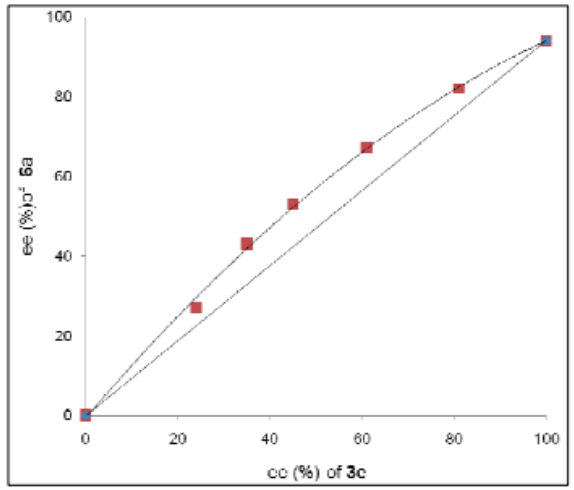
First-Round of Observations:

1. ***Palladium catalyst and two equivalents of ligand in toluene do not result in complete complexation except upon addition of water.***
2. ***It could be possible for water to be facilitating the ligand exchange process.***
3. ***Live analysis of the reaction via spectroscopy (^{1}H and ^{31}P) only displayed the active 30.7 ppm signal with no other entities.***

(C) Nonlinear Effect

4a + **5a** → (Pd$_2$(dba)$_3$ (Pd 2.5 mol%), **3e** (24-100% ee, 5 mol%), toluene/H$_2$O (20:1), 0 °C, 12 h) → **6a**

entry	ee (%) of **3e**	yield (%) of **6a**	ee (%) of **6a**
1	24	99	27
2	35	99	43
3	45	97	53
4	61	96	67
5	81	93	82
6	100	97	93



A modest positive nonlinear effect is identified which may indicate the presence of more than one ion-paired ligand in the stereo-determining step.

Nature Chem. ***2012***, 4, 473-477.

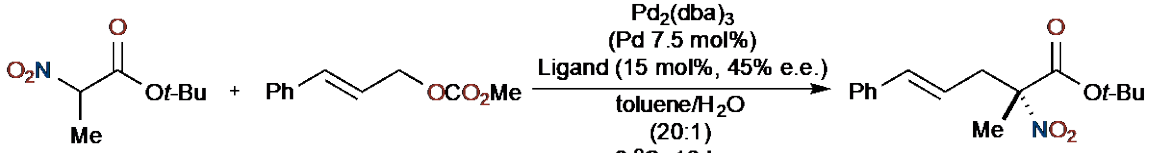
Ooi's Palladium-Catalyzed Allylic Alkylation:

Mechanistic Investigation: Asymmetric Amplification

Two possible scenarios possible:

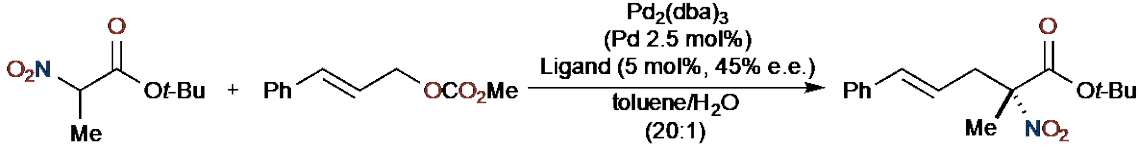
1. ***Reservoir effect: catalyst molecules are aggregating in the resting state, but not the stereodetermining step.***
2. ***Catalyst-product interaction***

Reservoir Examination:



no change in e.e. despite higher catalyst loading

Catalyst-Product Interaction:



quenching reaction early results in the same e.e. but inferior yield

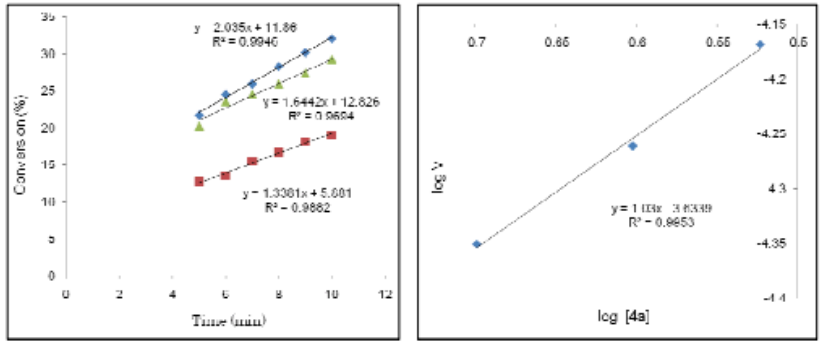
Despite ruling out the possibilities of a reservoir or catalyst-product interaction, more detail is required. The authors turn to kinetics.

Mechanistic Investigation: Kinetic Analysis

Kinetics Data

Kinetics on Nitropropionate 4a:

[**4a**] = 0.2 ~ 0.3 M, [Pd] = 0.005 M, [**3e**] = 0.01 M, [**5a**] = 0.2 M, [$PhMe_3Si$] = 0.033 M.



initial rate

0.2 M: 4.46×10^{-5} Ms^{-1}

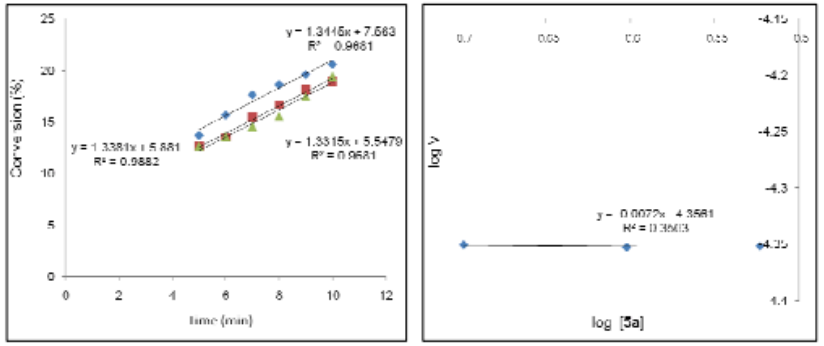
0.25 M: 5.48×10^{-5} Ms^{-1}

0.3 M: 6.78×10^{-5} Ms^{-1}

Figure S7. Kinetics on Nitropropionate **4a**

Kinetics on Cinnamyl Carbonate 5a:

[**5a**] = 0.2 ~ 0.3 M, [Pd] = 0.005 M, [**3e**] = 0.01 M, [**4a**] = 0.2 M, [$PhMe_3Si$] = 0.033 M.



initial rate

0.2 M: 4.46×10^{-5} Ms^{-1}

0.25 M: 4.43×10^{-5} Ms^{-1}

0.3 M: 4.45×10^{-5} Ms^{-1}

Figure S8. Kinetics on Cinnamyl Carbonate **5a**

Zero order dependence on cinnamyl carbonate **5a**

RDS – nucleophilic addition of nitronate to π-allyl Pd(II)

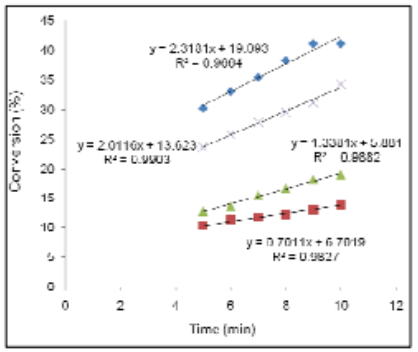
Nature Chem. ***2012***, 4, 473-477.

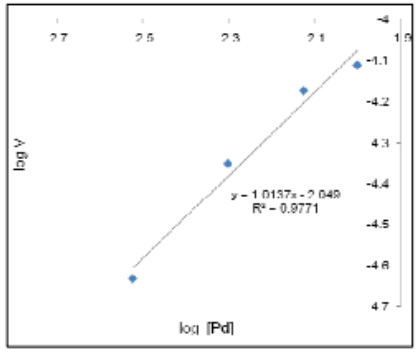
Ooi's Palladium-Catalyzed Allylic Alkylation:

Mechanistic Investigation: Kinetic Analysis

Kinetics on Pd catalyst (Pd/3e = 1:2 mixture):

[Pd] = 0.003 ~ 0.01 M, [**3e**] = 0.006 ~ 0.02 M, [**4a**] = 0.2 M, [**5a**] = 0.2 M, [$PhMe_3Si$] = 0.033 M.





initial rate

0.003 M: 2.34×10^{-5} Ms^{-1}

0.005 M: 4.46×10^{-5} Ms^{-1}

0.0075 M: 6.71×10^{-5} Ms^{-1}

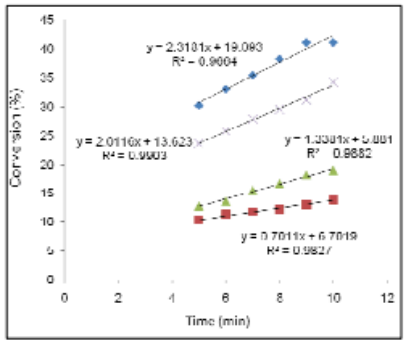
0.01 M: 7.73×10^{-5} Ms^{-1}

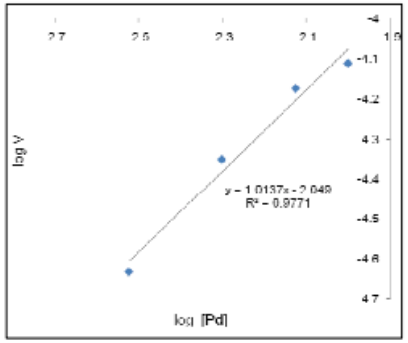
Figure S9. Kinetics on Pd Catalyst

First order dependence indicates a monomeric Pd complex in RDS

Kinetics on Pd catalyst (Pd/3e = 1:2 mixture):

[Pd] = 0.003 ~ 0.01 M, [**3e**] = 0.006 ~ 0.02 M, [**4a**] = 0.2 M, [**5a**] = 0.2 M, [$PhMe_3Si$] = 0.033 M.





initial rate

0.003 M: 2.34×10^{-5} Ms^{-1}

0.005 M: 4.46×10^{-5} Ms^{-1}

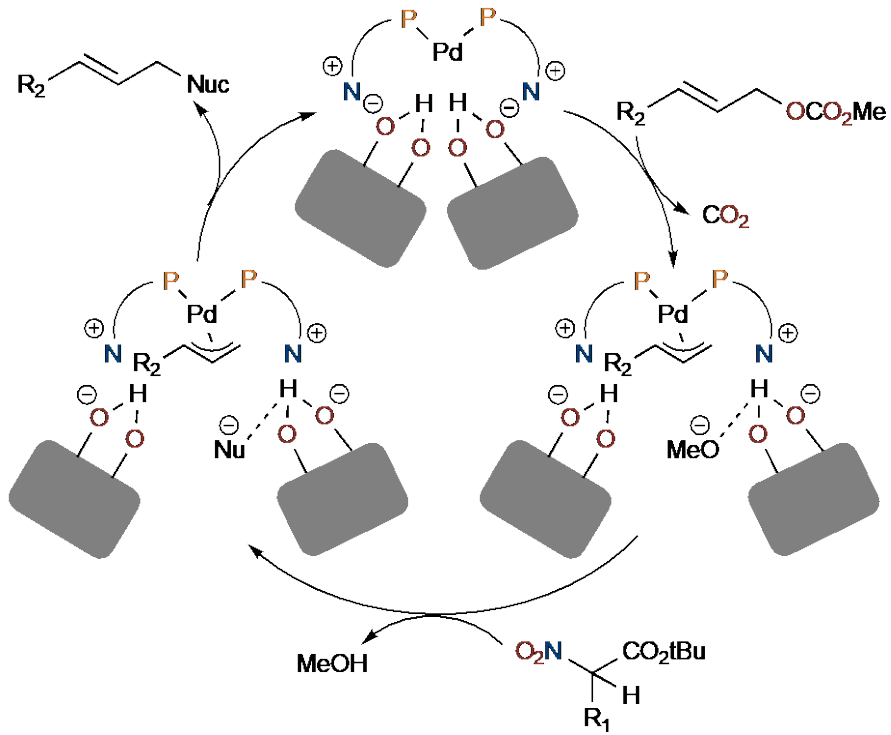
0.0075 M: 6.71×10^{-5} Ms^{-1}

0.01 M: 7.73×10^{-5} Ms^{-1}

Figure S9. Kinetics on Pd Catalyst

Second order dependence – two ion-paired ligands in complex

Proposed Mechanism and Scope:



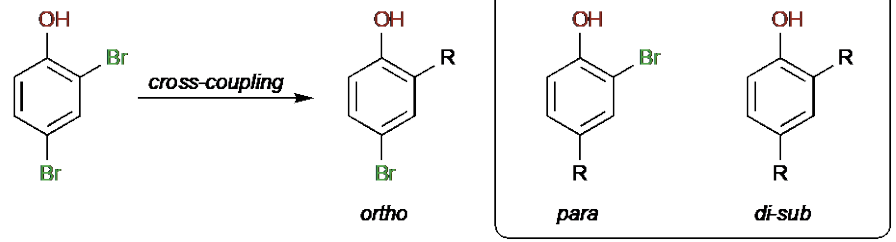
R^1	5	R^2	Product	Time (h)	Yield (%)*	e.e. (%)†
Et	**5a**	Ph	**6b**	24	97	93
CH_2CHMe_2	**5a**	Ph	**6c**	36	96	97
n-Hex	**5a**	Ph	**6d**	30	97	95
CH_2Ph	**5a**	Ph	**6e**	30	94	97
$(CH_2)_2CO_2Me$	**5a**	Ph	**6f**	24	98	93
Me	**5b**	*p*-Cl-C_6H_4	**6g**	18	90	90
Me	**5c**	*p*-Br-C_6H_4	**6h**	24	99	90
Me	**5d**	*p*-MeO-C_6H_4	**6i**	30	99	93
Me	**5e**	2-naphthyl	**6j**	24	98	91
Me	**5f**	2-thienyl	**6k**	48	94	91
Me	**5g**	H	**6l**	12	91	<1

Nature Chem. ***2012***, 4, 473-477.

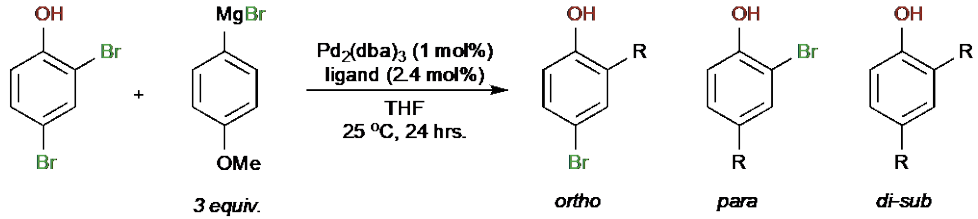
Manabe's Phenol-Directed Cross-Coupling:

Manabe's Attempt at Selective Cross-Coupling:

General Reaction Overview:

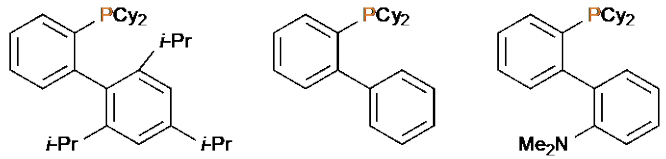


Model System:



Ligands:

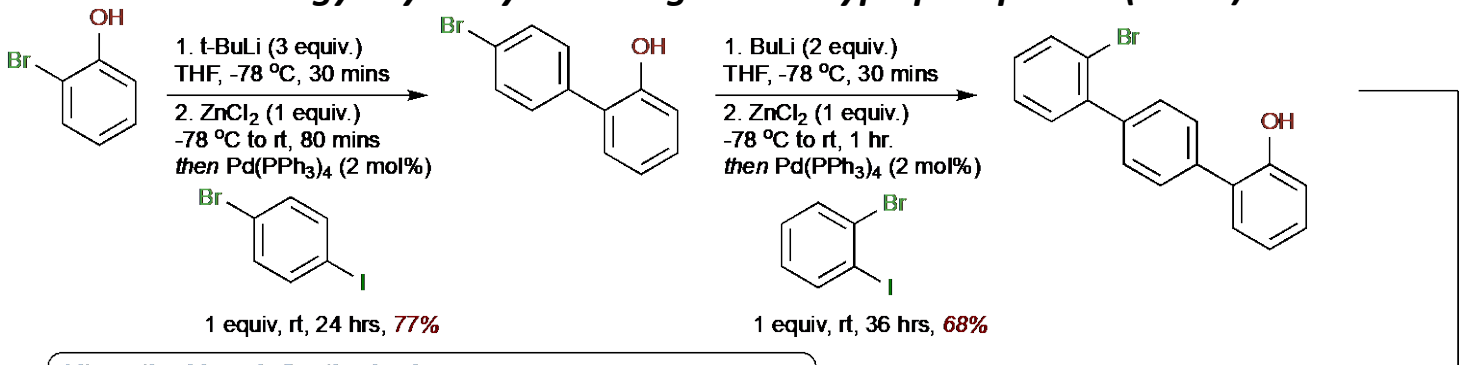
PPh$_3$
PCy$_3$
P(*t*-Bu)$_3$-BF$_4$
DPPF



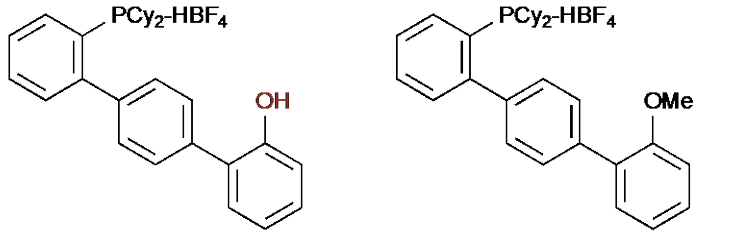
Product Distribution: **Yield (%):**

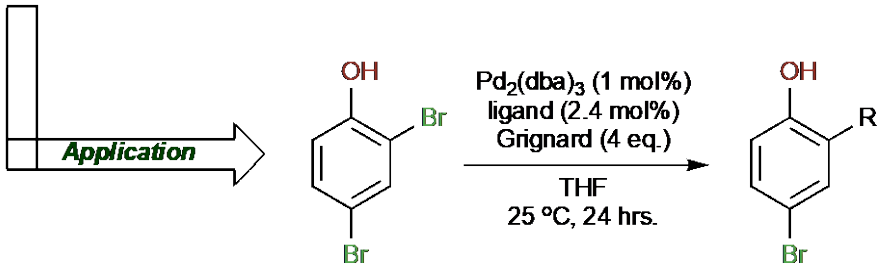
	ortho	*para*	*di-sub*
PPh$_3$	22	16	14
PCy$_3$	21	14	38
P(*t*-Bu)$_3$-BF$_4$	0	40	25
DPPF	1	77	1
6	5	5	1
7	8	12	3
8	2	8	0

Alternative Strategy: Hydroxylated oligoarene-type phosphines (HOPs)



Alternative Ligands Synthesized:





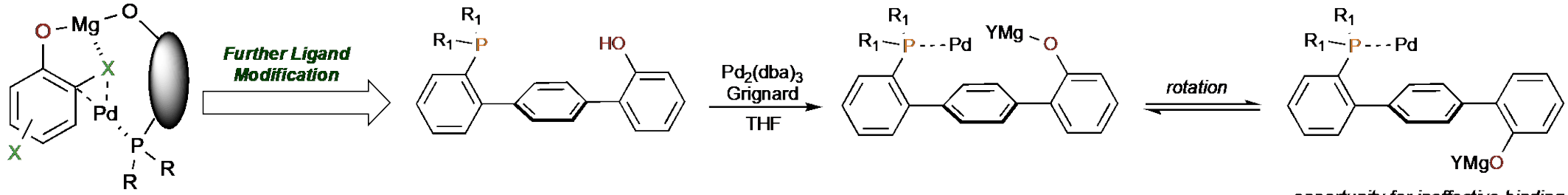
Ligand	Reaction time/h	Yield/% *ortho*	*isomer*	*di*
1	2	60	0	17
10	2	84	0	5
DPPF	24	0	77	8
1	72	66	0	13
10	72	3	0	0
DPPF	19	0	88	4
1	5	55	0	21
10	5	<22[a]	0	29
DPPF	5	0	0	0
1	6	0	0	0

Enhanced selectivity and kinetics are observed

Angew. Chem. Int. Ed. ***2010***, 49, 772-775.

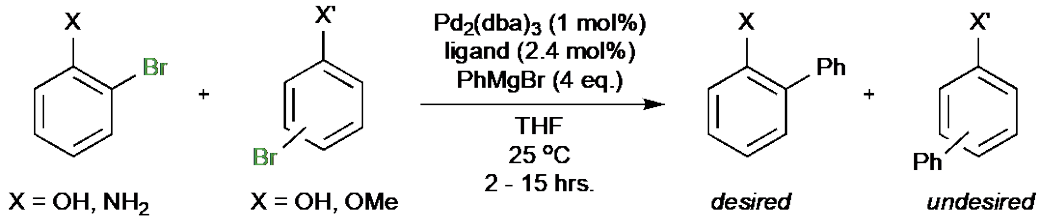
Manabe's Phenol-Directed Cross-Coupling:

Rationale and Further Optimization of Ligand Structure:



Manabe speculates that perhaps a magnesium oxido species is responsible. Although extensive evidence was not provided.

Intermolecular Competition:

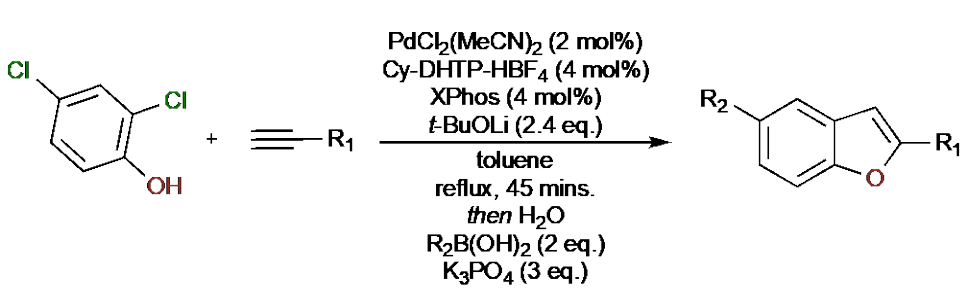


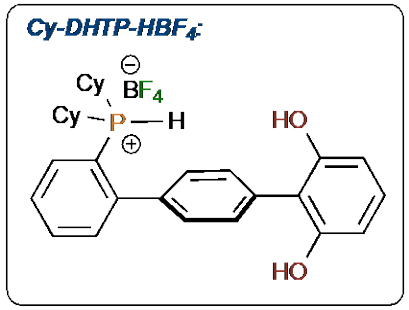
X = OH, NH_2	X = OH, OMe	*desired*	*undesired*
X = OH	X = OH, *p*-Br	86%	0%
X = OH	X = OH, *m*-Br	85%	2%
X = OH	X = OMe, *p*-Br	96%	2%
X = NH_2	X = OH, *p*-Br	88%	1%

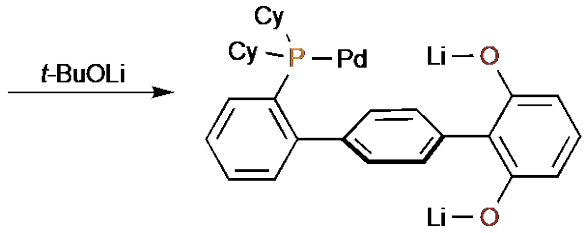
Angew. Chem. Int. Ed. ***2010***, 49, 772-775.

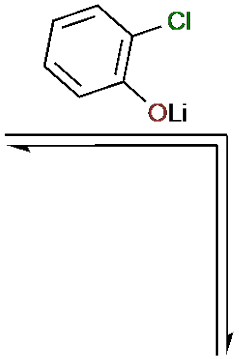
Manabe's Phenol-Directed Cross-Coupling:

Further Application of the Methodology Suspected Intermediates:

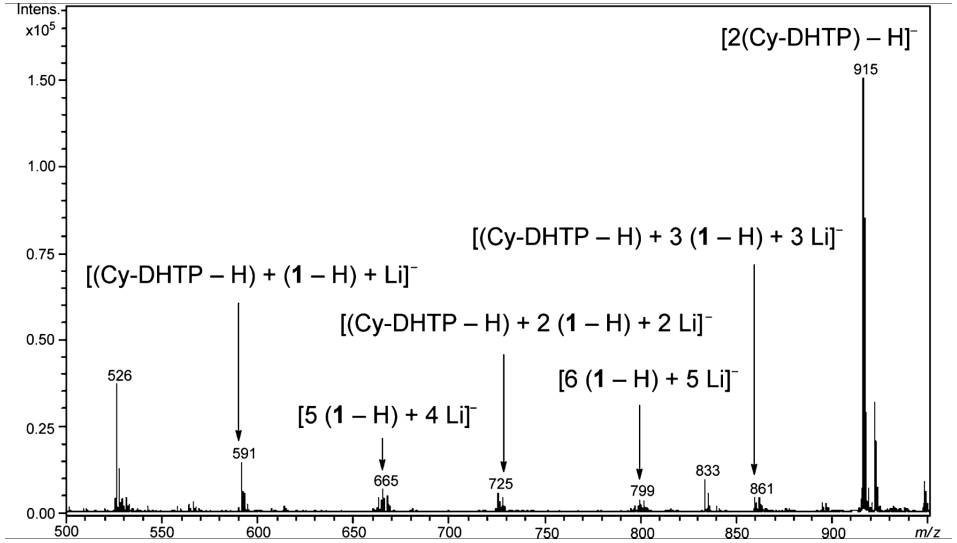


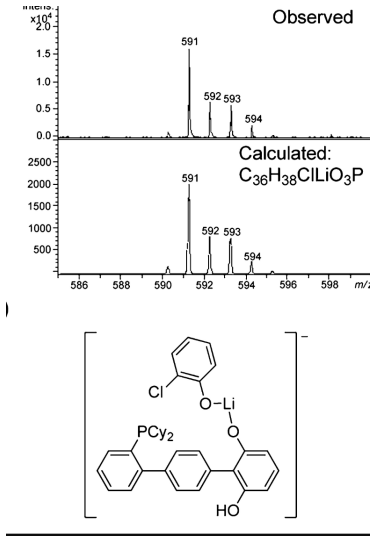




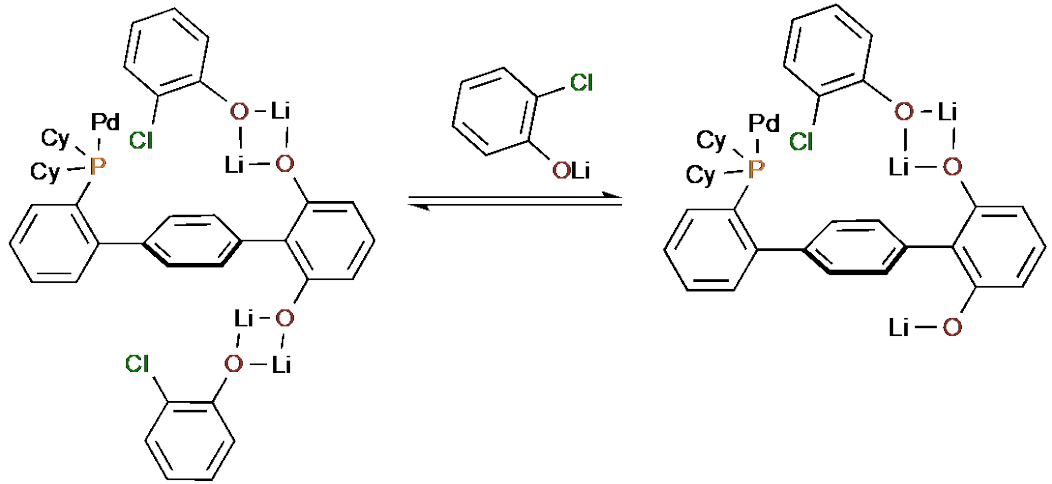


ESI Studies:





Mixture of 2-Chlorophenol and 40 mol% DHTP with 2 eq. t-BuOLi

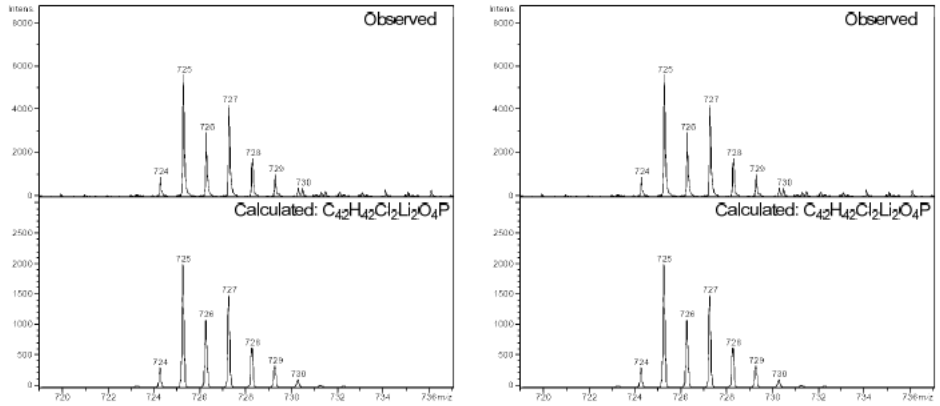


Angew. Chem. Int. Ed. ***2010***, 49, 772-775.
J. Org. Chem. ***2016***, 81, 5450-5463.

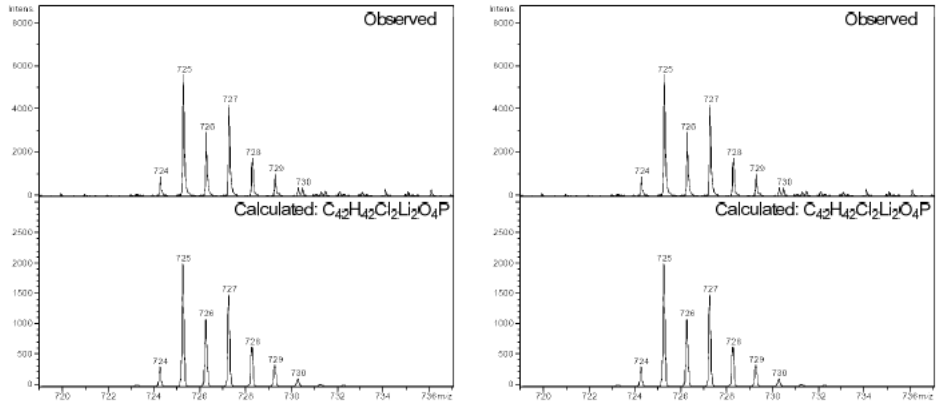
Manabe's Phenol-Directed Cross-Coupling:

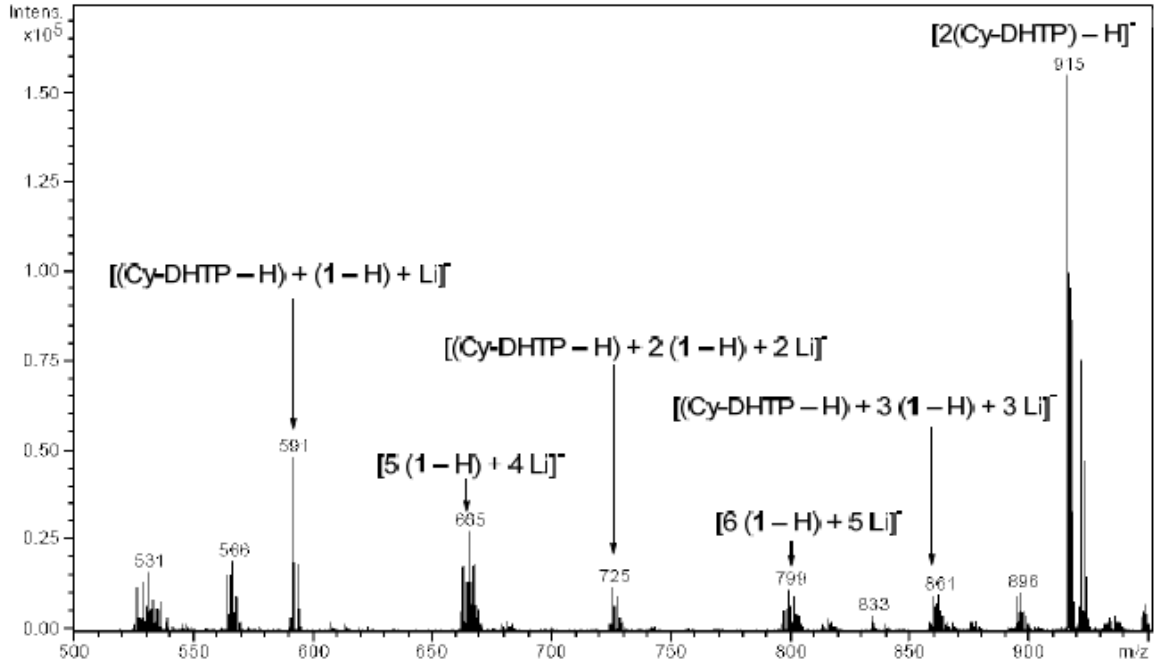
Further ESI Studies: Heteroaggregate formation of lithium phenoxides between Cy-DHTP and 2-Chlorophenol

Isotopic Distribution for masses m/z: 725 and 861



Isotopic Distribution for masses m/z: 665 and 799





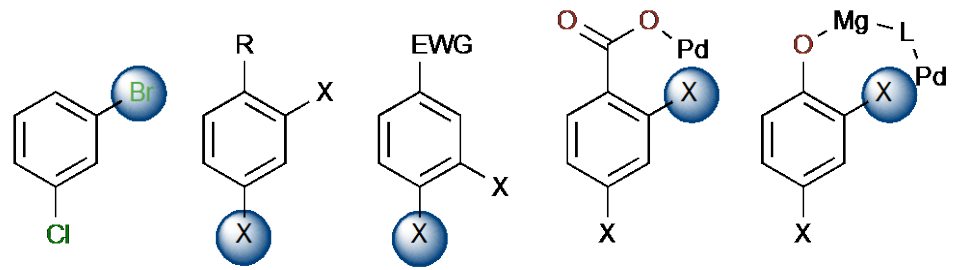
ESI analysis of previous mixture with 0.4 eq.* Xphos in the presence of *1 eq. t-BuOLi in the negative mode.

Angew. Chem. Int. Ed. ***2010***, 49, 772-775.
J. Org. Chem. ***2016***, 81, 5450-5463.

Phipp's Directed Cross-Coupling:

Phipps Remote Functionalization of Dihalogenated Arenes:

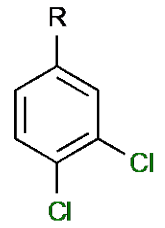
Prior Functionalization Tactics:



Bond Dissociation Energy | *Sterics* | *Electronics* | *Substrate coordination to catalyst* | *Substrate coordination to ligand*

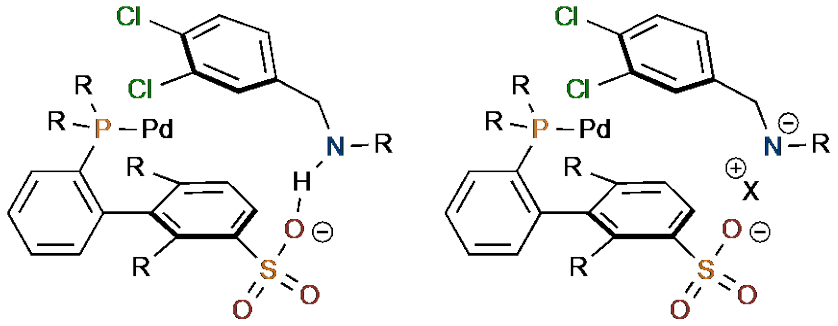
Problem Identification

Problem:

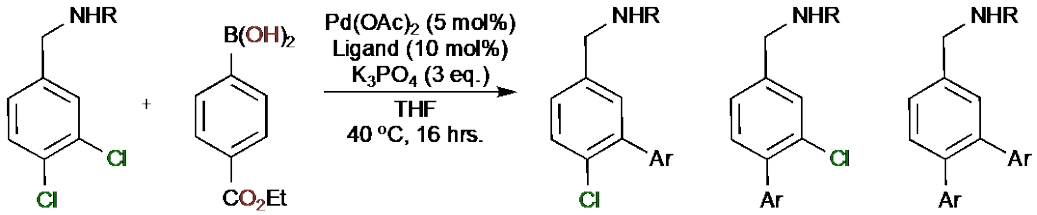


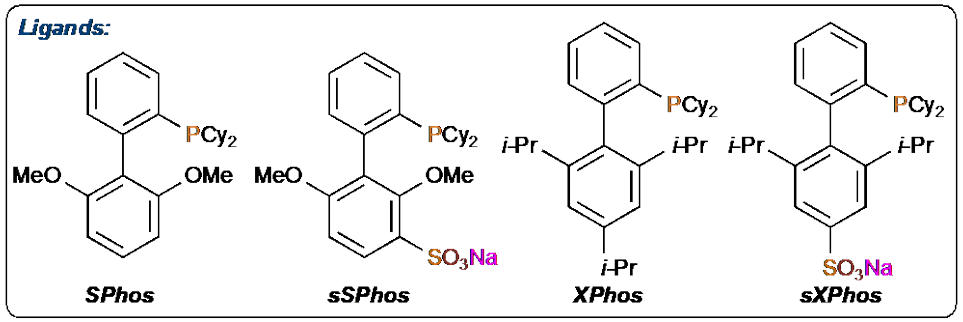
Remote undifferentiated chlorides

Hypothesis:



Phipps Remote Functionalization of Dihalogenated Arenes:



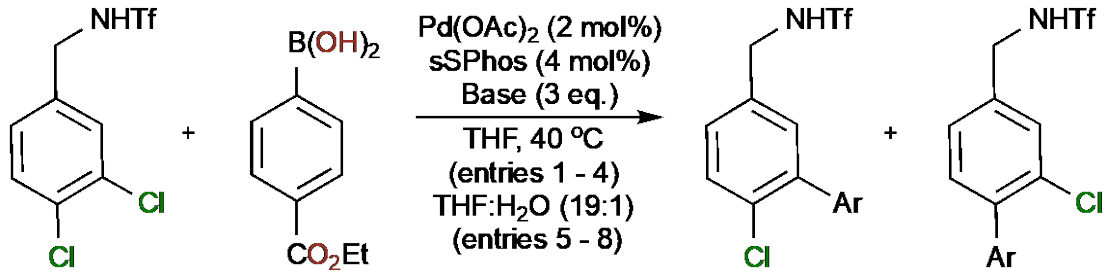


R	ligand	yield (%) 2	3	4	2:3	% conv.
Ac (1a)	SPhos	19	18	17	1.1:1	65
Ac	XPhos	41	32	10	1.3:1	100
Ac	sSPhos	38	10	5	3.8:1	54
Ac	sXPhos	42	22	6	1.8:1	70
TFA (1b)	sSPhos	39	20	14	1.9:1	73
Boc (1c)	sSPhos	17	11	8	1.5:1	34
Ts (1d)	sSPhos	48	6	4	7.5:1	53
*p*Ns (1e)	sSPhos	48	2	<1	>20:1	50
Tf (1f)	sSPhos	78	<1	9	>20:1	91
Tf	sSPhos	63	<1	31	>20:1	100
Tf	sSPhos	60	<1	31	>20:1	100
Tf	sSPhos	88 (82)	<1	11	>20:1	100
Tf	SPhos	30	19	30	1.6:1	75
Tf	sXPhos	67	9	10	7:1	91
Tf	XPhos	40	33	22	1.2:1	88

J. Am. Chem. Soc. ***2018***, 140, 13570-13574.

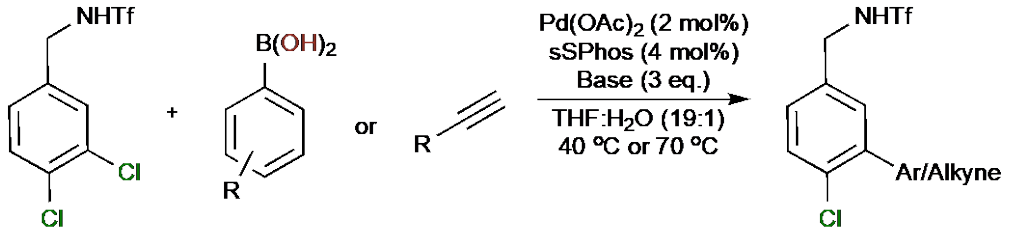
Phipp's Directed Cross-Coupling:

Effect of Crown Ethers and Cationic Radius:

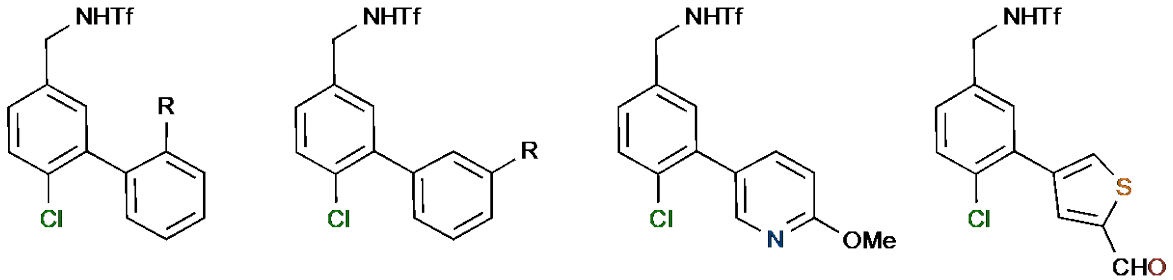


Entry	Additive (3 eq.)	Base	Selectivity (*m*/*p*)	% Conv.
1	None	K_3PO_4	>20:1	89
2	18-Crown-6	K_3PO_4	1.5:1	60
3	15-Crown-5	K_3PO_4	3.5:1	51
4	12-Crown-4	K_3PO_4	>20:1	88
5	None	Li_2CO_3	1.8:1	38
6	None	Na_2CO_3	3.8:1	68
7	None	K_2CO_3	>20:1	77
8	None	Cs_2CO_3	>20:1	60

Reaction Scope:



Arylation Scope:



R = CF_3, > 20:1, 92%
R = OH, > 20:1, 75%

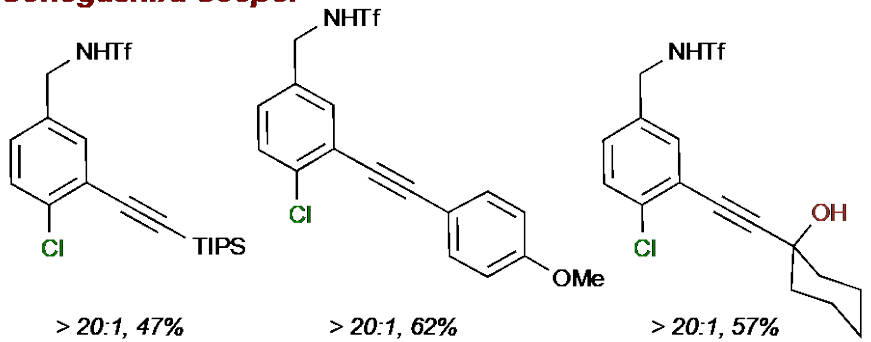
R = $COCH_3$, > 20:1, 84%
R = NH_2, > 20:1, 64%
R = NHAc, > 20:1, 73%

> 20:1, 88%

> 20:1, 73%

Sonogashira and Buchwald-Hartwig Expansion:

Sonogashira Scope:

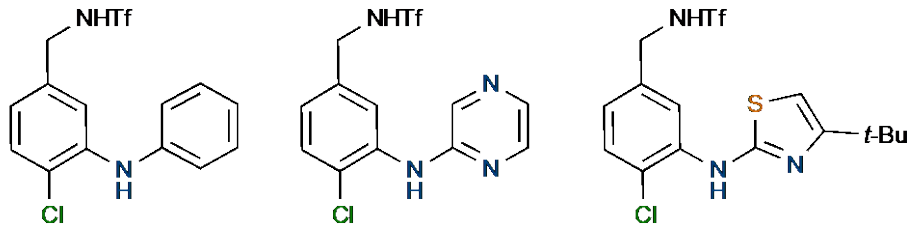


> 20:1, 47%

> 20:1, 62%

> 20:1, 57%

Buchwald-Hartwig Scope:



> 20:1, 89%

> 20:1, 45%

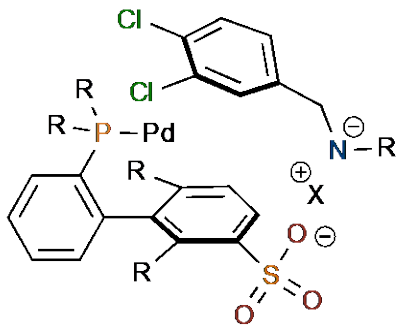
> 20:1, 55%

J. Am. Chem. Soc. ***2018***, 140, 13570-13574.

Phipp's Resolution of Sulfonated Ligands:

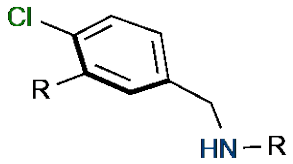
Expanding the Boundaries of Selectivity: Phipps Resolution of Ligands

Previous Achievement:

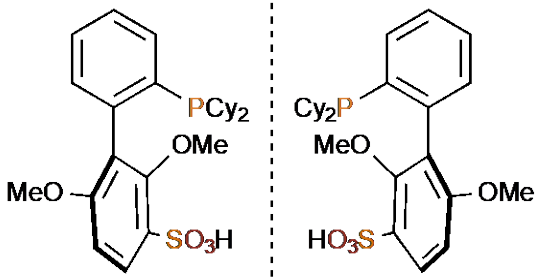


racemic ligand implemented

various coupling platforms

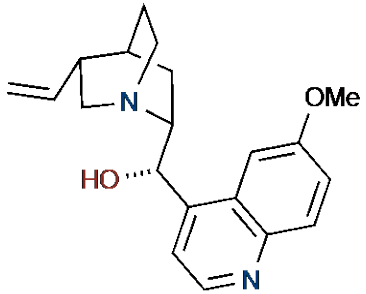


Excellent site-selectivity. What about enantioselectivity?



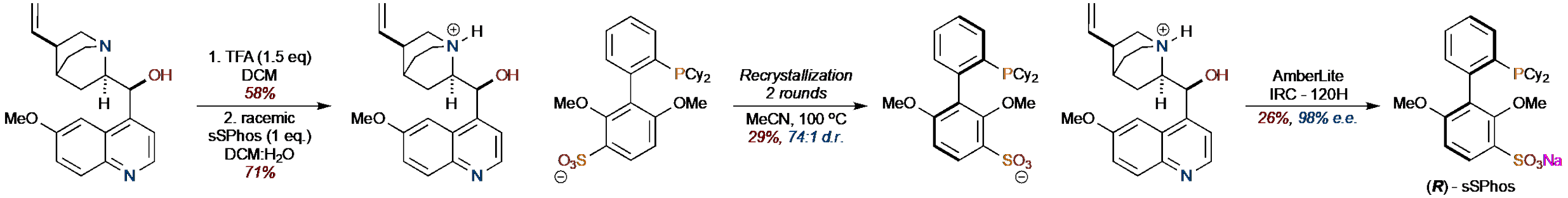
readily available in 1 step from SPhos. Resolution would be most convenient.

Chiral Pool Trace



Quinidine
25g ~ $ 50.00

Resolution Procedure:



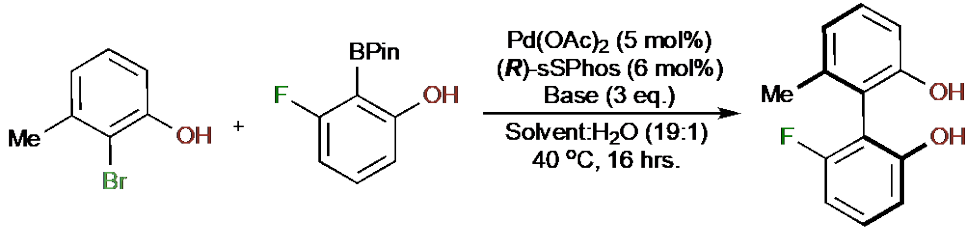
(***R***) - sSPhos

Rapid access to wide variety of enantioenriched ligands which enable screening of a variety of processes for enantioselective processes.

J. Am. Chem. Soc. ***2022***, 144, 15026-15032.

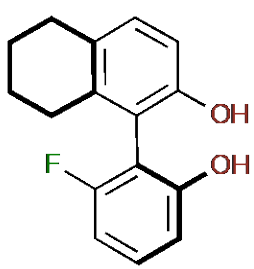
Phipp's Atroposelective Suzuki-Coupling:

Application to Standard Palladium-Catalyzed Processes: Atroposelective Suzuki-Coupling

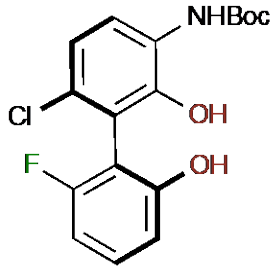


Base	*Solvent*	*yield (%), e.e. (%)*
K_3PO_4	*THF*	*19, 81*
K_3PO_4	*MeCN*	*5, 74*
K_3PO_4	*toluene*	*18, 95*
K_2CO_3	*toluene*	*40, 90*
Cs_2CO_3	*toluene*	*16, 90*
Na_2CO_3	*toluene*	*67, 88*
Na_3PO_4	*toluene*	*73, 92*

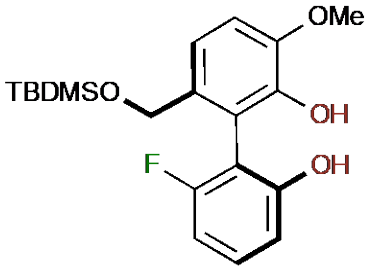
Selected Scope:



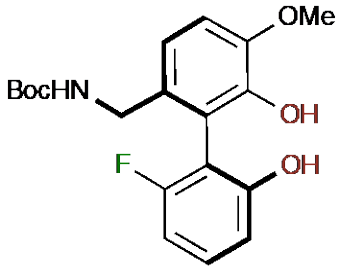
66%, 93 % e.e.



55%, 93 % e.e.



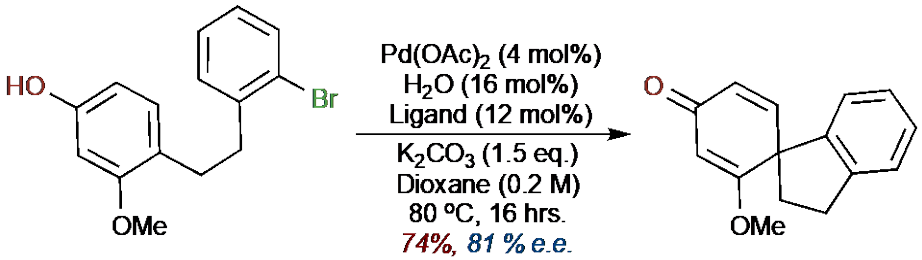
89%, 98 % e.e.

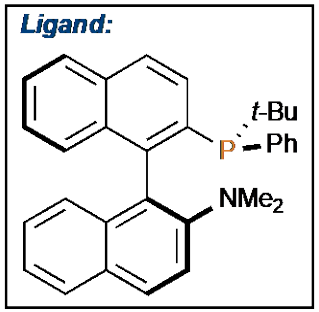


82%, 87 % e.e.

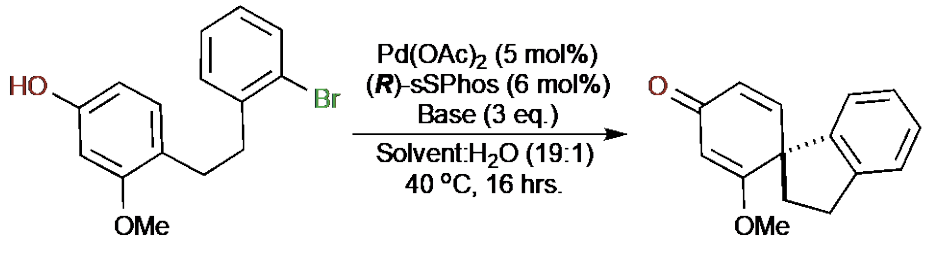
Second Application: Palladium-Catalyzed Dearomatization of Phenols

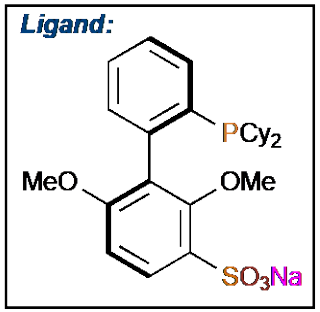
Buchwald's Precedent:





Phipp's Design:



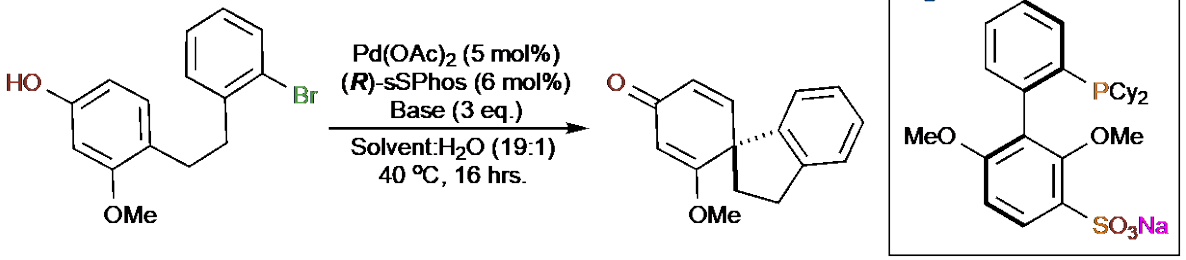


J. Am. Chem. Soc. ***2022***, 144, 15026-15032.
J. Am. Chem. Soc. ***2023***, 145, 25553-25558.

Phipp's Dearomatization of Phenols:

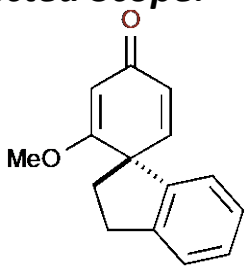
Optimization of Palladium-Catalyzed Dearomatization of Phenols

Phipp's Design:

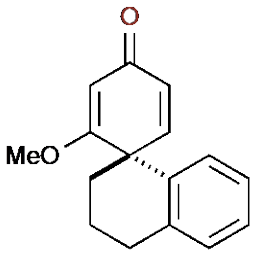


Pd source	base	solvent	yield (%)[a]	ee (%)[b]
$[PdCl(cinnamyl)]_2$	K_2CO_3	dioxane	76	44
$[PdCl(allyl)]_2$	K_2CO_3	dioxane	48	34
$Pd(OAc)_2$	K_2CO_3	dioxane	13	27
Pd_2dba_3	K_2CO_3	dioxane	81	63
Pd_2dba_3	KOH	dioxane	48	84
Pd_2dba_3	KOH	$PhCF_3$	41	83
Pd_2dba_3	KOH	PhMe	60	83
Pd_2dba_3	KOH	dioxane/H_2O (10:1)	66	89
Pd_2dba_3	KOH	$PhCF_3$/H_2O (10:1)	91	91
Pd_2dba_3	KOH	PhMe/H_2O (10:1)	99 (98)	92
Pd_2dba_3	KOH	PhMe/H_2O (10:1)	95	91
Pd_2dba_3	LiOH	PhMe/H_2O (10:1)	84	95
Pd_2dba_3	NaOH	PhMe/H_2O (10:1)	98	92
Pd_2dba_3	CsOH	PhMe/H_2O (10:1)	87	95

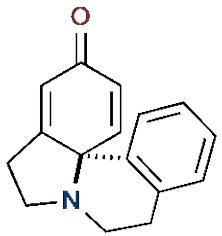
Selected Scope:



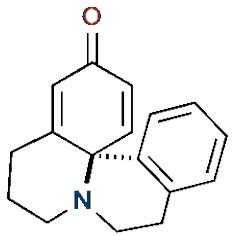
98%, 92%



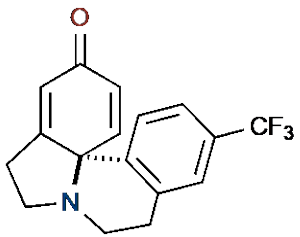
77%, 93% e.e.



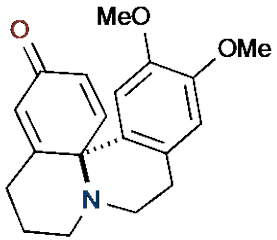
64%, 93% e.e.



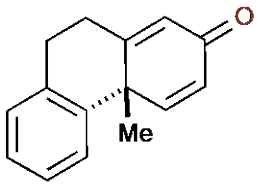
71%, 97% e.e.



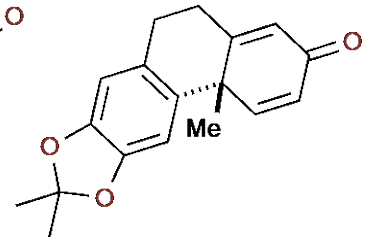
74%, 92% e.e.



62%, 91% e.e.



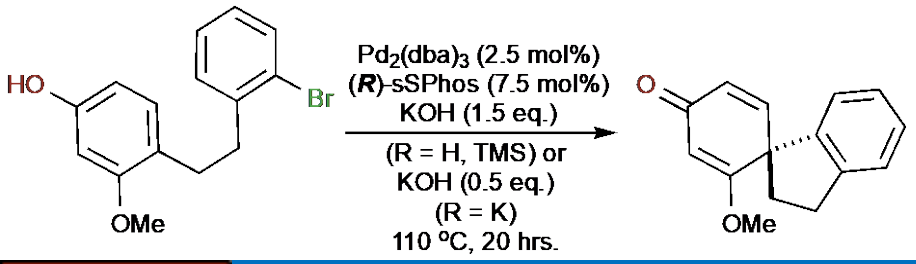
59%, 93% e.e.



53%, 90% e.e.

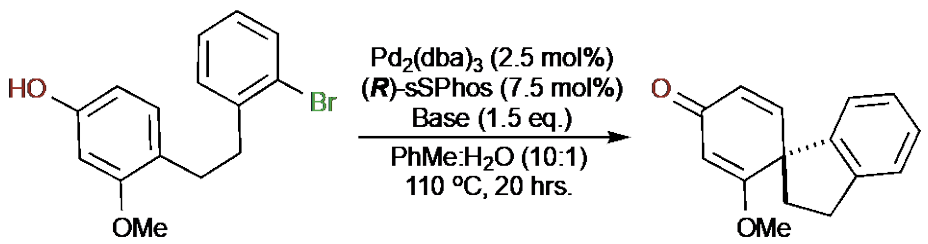
Control Experiments to Probe Ligand-Substrate Interactions:

Exclusion of Hydrogen-Bonding:



R	Yield	% ee
H	60	83
TMS	46	83
K	53	92

Use of quaternary onium cations:

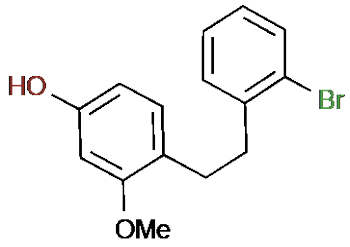


Base	Yield	% ee
KOH	99	92
Bu_4NOH	11	57
Bu_4POH	11	70
Me_4NOH	82	88

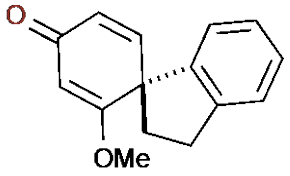
J. Am. Chem. Soc. ***2022***, 144, 15026-15032.
J. Am. Chem. Soc. ***2023***, 145, 25553-25558.

Transition from Palladium to Iridium:

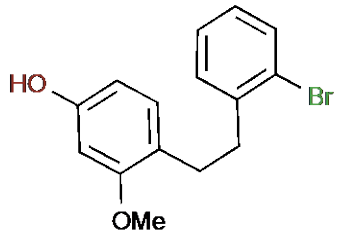
Crown Ether Experiments (no water co-solvent) and use of neutral, alkylated ligand:



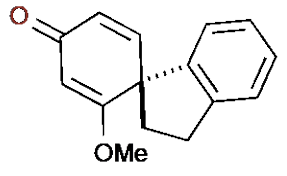
$Pd_2(dba)_3$ (2.5 mol%)
(*R*)-sSPhos (7.5 mol%)
Additive (1.5 eq.)
KOH (1.5 eq.)
toluene (entries 1 - 4)
dioxane (entries 5 - 8)
110 °C, 20 hrs.



ıtry	Additive	% ee
1	None	83
2	12-Crown-4	81
3	15-Crown-5	61
4	18-Crown-6	70
5	None	84
6	12-Crown-4	84
7	15-Crown-5	63
8	18-Crown-6	63

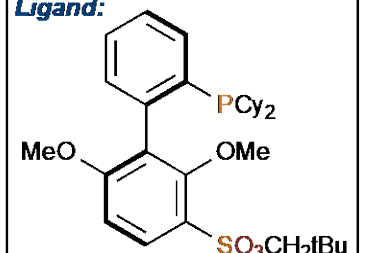


$Pd_2(dba)_3$ (2.5 mol%)
(*R*)-sSPhos-Np
(7.5 mol%)
KOH (1.5 eq.)
PhMe:H_2O (10:1)
110 °C, 20 hrs.



89%, -6% e.e.

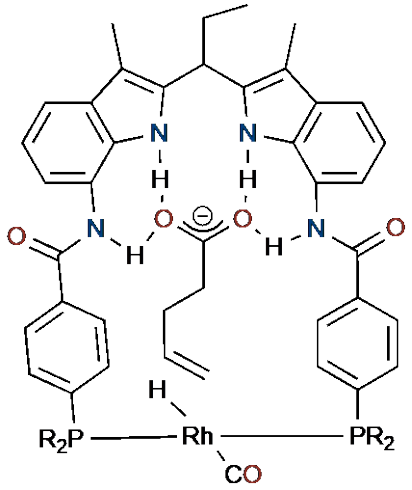
Ligand:



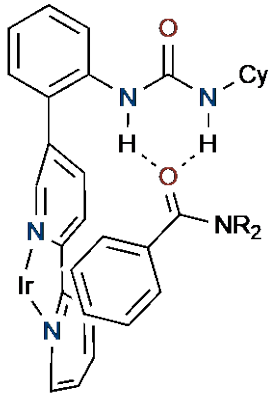
(*R*) - sSPhos-Np

Incorporation of Sulfate Group into a different ligand scaffold:

Prior Work:

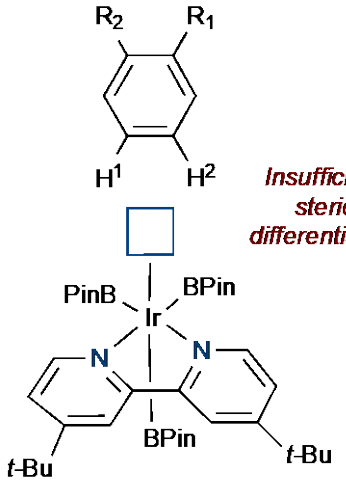


Hydroformylation of Unsaturated Acids (Reek)



Meta-Selective Arene Borylation (Kuninobu, Kanai)

Conventional Approach:

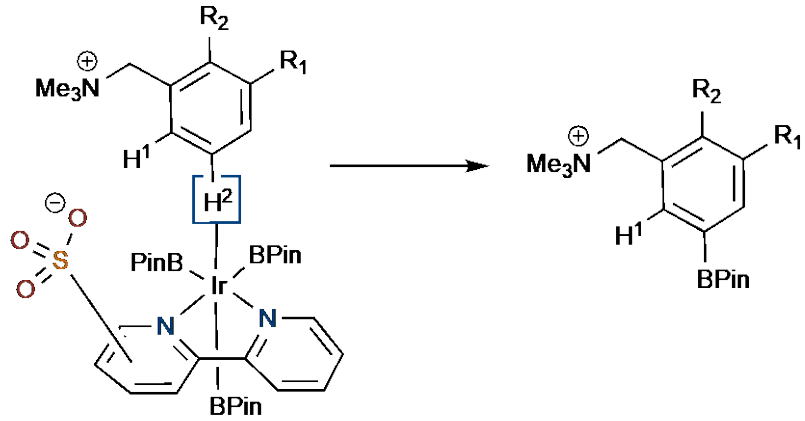


Insufficient steric differentiation

Poor selectivity on 1,2-disubstituted aromatics

Ligand Augmentation and Substrate Modification

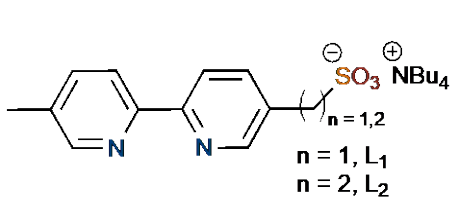
Hypothesis:

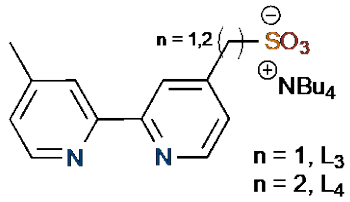


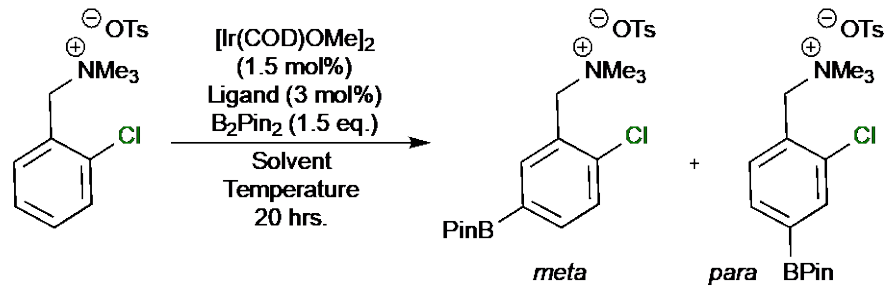
J. Am. Chem. Soc. ***2016***, 138, 12759-12762.
J. Am. Chem. Soc. ***2023***, 145, 25553-25558.

Phipp's Meta-Selective Iridium-Catalyzed Borylation:

Ligand Augmentation and Screening:



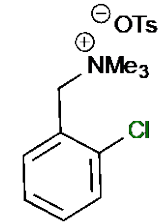




solvent	ligand	*T*	conv.[a]	meta:para[a]
cyclohexane	**dtbpy**	50	24	1.1:1
THF	**dtbpy**	50	98	1:2.4
THF	**L1**	50	96	10:1
THF	**L2**	50	100	3.5:1
THF	**L3**	50	100	1.8:1
THF	**L4**	50	100	1.1:1
cyclohexane	**L1**	70	<5	–

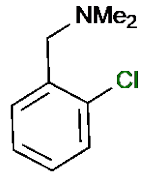
Control Experiments:

Cationic Substrate:

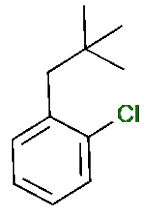


m:p = 10:1

Neutral Substrates:



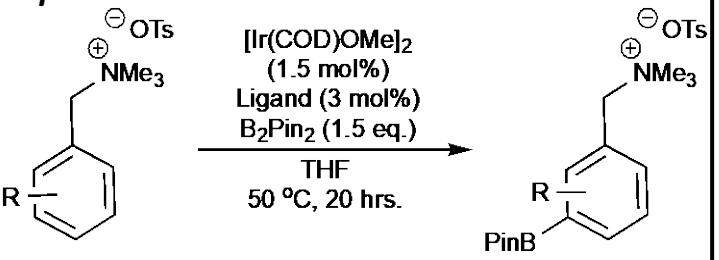
m:p = 1:1



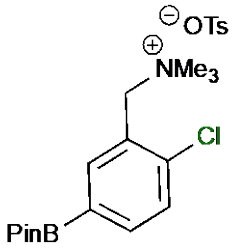
m:p = 11:1

optimized parameters: L_1 in THF
Additional amounts of Bu_4NOTs led to decrease in selectivity potentially due to excess cation displacing the substrate as ligand counterion.

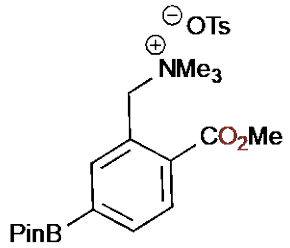
Optimized Conditions:



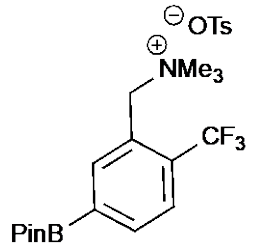
Selected Scope:



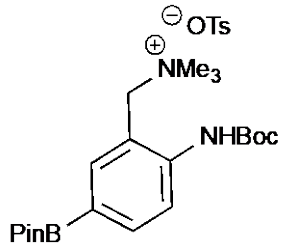
L_1, THF: 11:1, *77%*
dtbpy, THF: 1:2, 80%



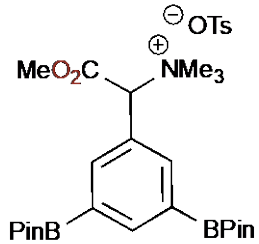
L_1, THF: 13:1, 71%
dtbpy, THF: 1.5:1, 100%



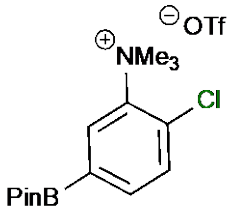
L_1, THF: 8:1, 78%
dtbpy, THF: 1:1.4, 63%



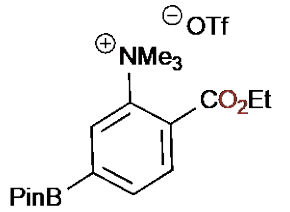
L_1, THF: 20:1, 59%
dtbpy, THF: 1.5:1, 52%



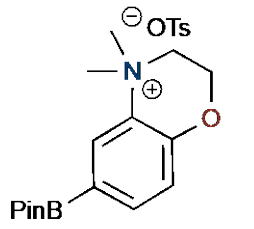
L_1, THF: 20:1, 52%
dtbpy, THF: 5:1, 92%



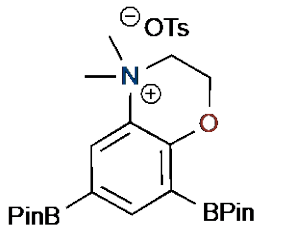
L_1, THF: 8:1, 88%
dtbpy, THF: 1:2, 91%



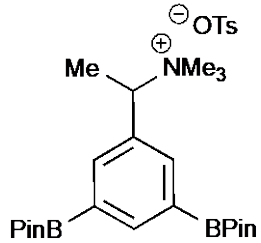
L_1, THF: 7:1, 91%
dtbpy, THF: 1:1, 98%



L_1, THF: 20:1, 80%
dtbpy, THF: 2.1:1, 67%



L_1, THF: 20:1, 89%
dtbpy, THF: 1.4:1, 73%



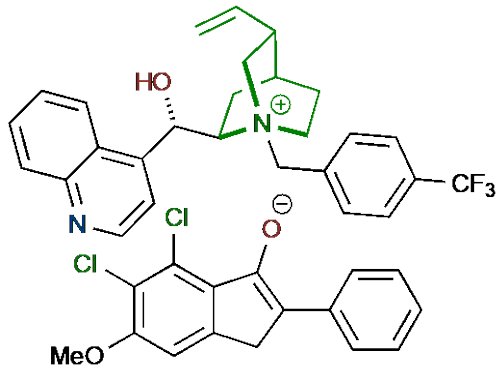
L_1, THF: 20:1, 96%
dtbpy, THF: 5:1, 94%

J. Am. Chem. Soc. ***2016***, 138, 12759-12762.

Enantioselective Iridium-Catalyzed Borylation:

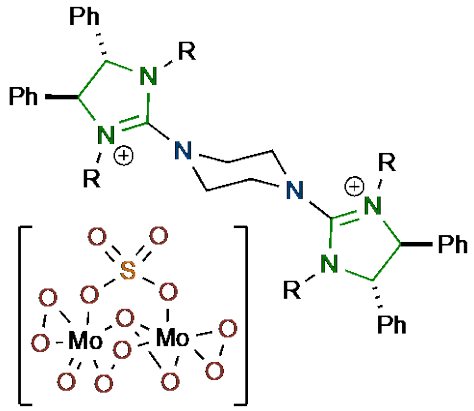
Upgrading to Enantioselectivity: Phipp's Utilization of a Chiral Cation

Asymmetric Phase Transfer Catalyst



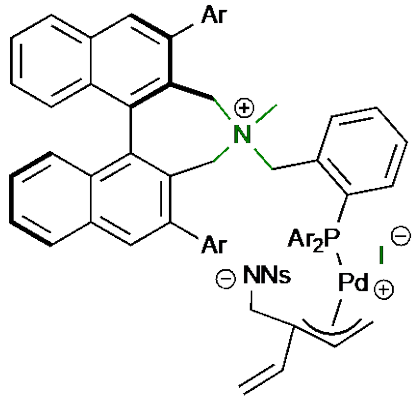
Dolling and co-workers (1984)
Subsequent contributions from numerous groups

Paired with transition metal 'ate' complexes



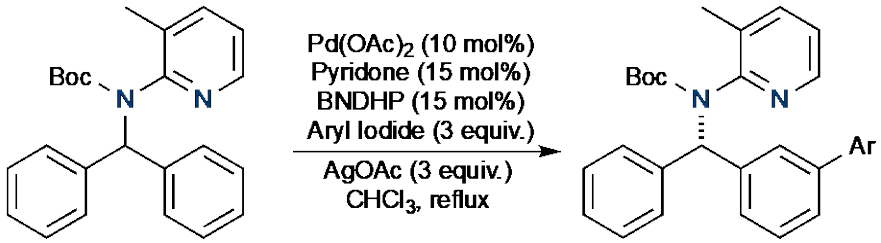
Tan and co-workers (2016)

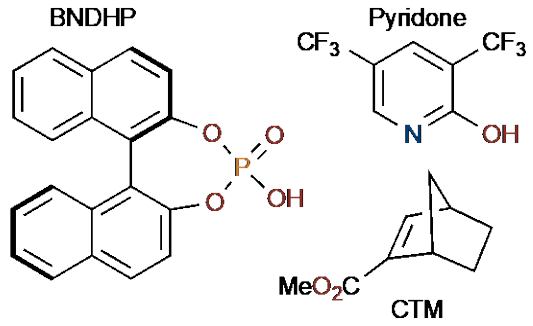
Integrated into ligand scaffold for asymmetric Pd catalysis



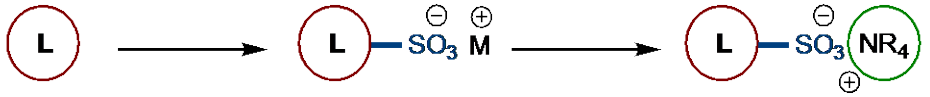
Ooi and co-workers (2014)

Prior Work:





Conceptualization:

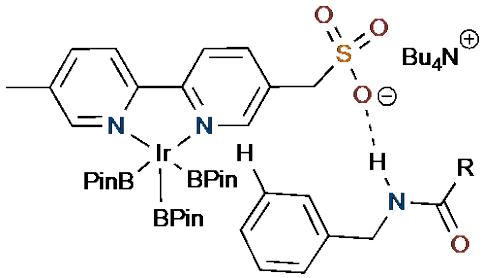


Common ligand scaffold used in TM catalysis

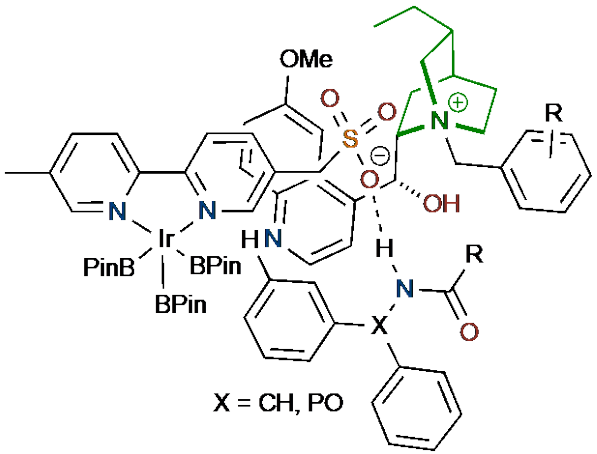
Incorporation of anionic handle

Exchange with chiral cation

Previous System (Racemic):



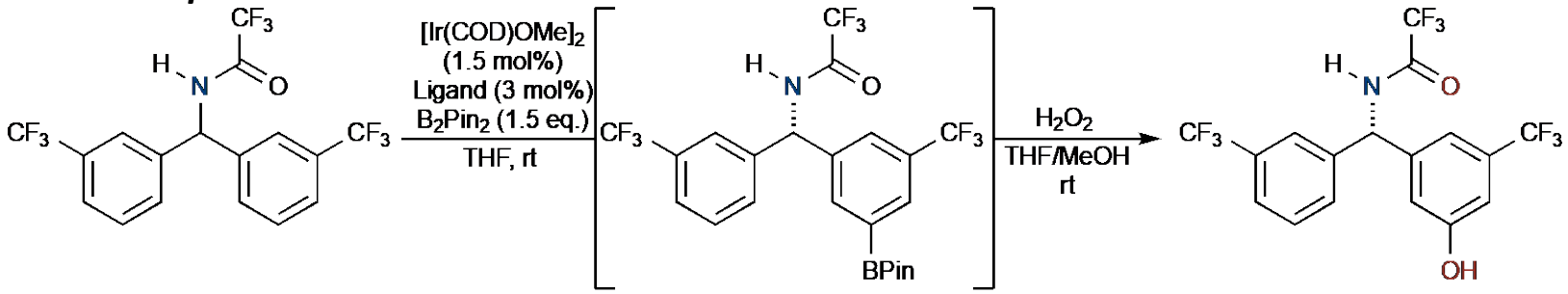
New System:



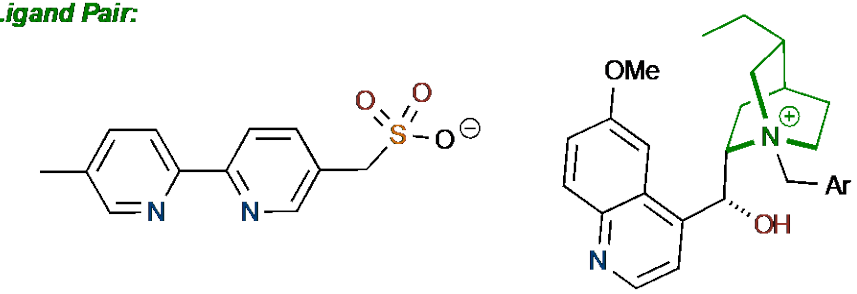
J. Am. Chem. Soc. ***2016***, 138, 12759-12762.
Nature Chem. ***2015***, 7, 712-717.
Science. ***2020***, 367, 1246-1251.

Enantioselective Iridium-Catalyzed Borylation:

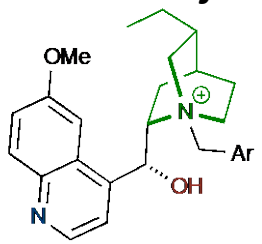
Reaction Optimization:



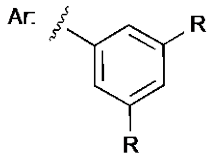
Ligand Pair:



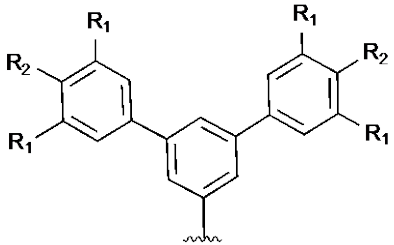
Quinine Modification: Aryl Substituent



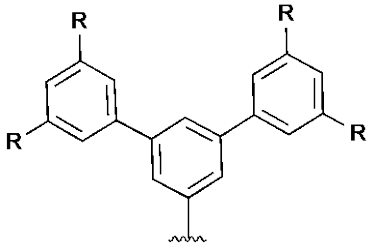
Group, Designation, *(%) e.e.*



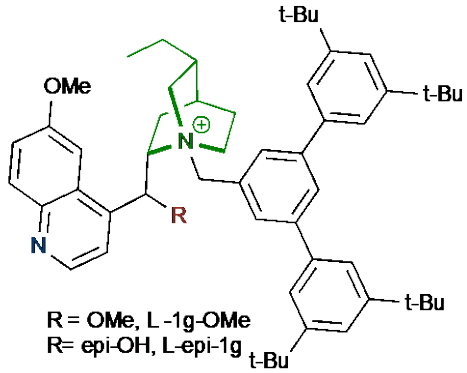
R = OMe, L-1a, 31%
R = *t*-Bu, L-1b, 30%



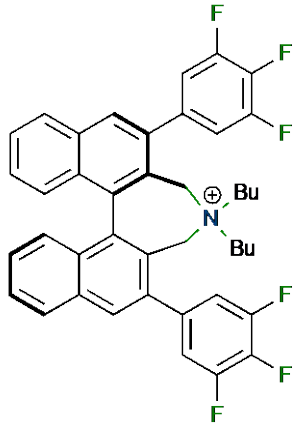
R_1 = H, R_2 = CF_3, L-1c, 39%
R_1 = F, R_2 = F, L-1d, 52%



R = CF_3, L-1e, 60% R = *t*-Bu, L-1g, 73%
R = OMe, L-1f, 60% R = Mes, L-1h, 55%
R = CF_3-Mes, L-1i, 26%



R = OMe, L-1g-OMe
R= epi-OH, L-epi-1g

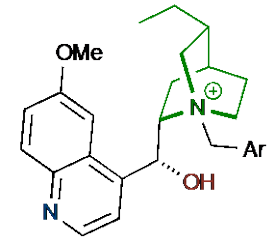


Ligand	Solvent	Temp / °C	Time	NMR Yield 3a' / %†	NMR Yield 4a' / %†	NMR Yield Overall / %†	3a':4a'	%ee 3a'‡
L•1k§	THF	50	16 h	36	64	100	1:1.8	0
L•1l§	THF	50	16 h	41	59	100	1:1.4	24
L•1a§	THF	50	16 h	51	49	100	1:1	20
L•1a	THF	rt	16 h	59	41	100	1.5:1	31
L•1b	THF	rt	16 h	73	27	100	2.7:1	30
L•1c	THF	rt	16 h	77	16	93	4.8:1	39
L•1d	THF	rt	16 h	65	32	97	2:1	52
L•1e	THF	rt	16 h	80	20	100	4:1	60
L•1f	THF	rt	16 h	65	35	100	1.9:1	60
L•1g	THF	rt	16 h	73	27	100	2.7:1	73
L•1h	THF	rt	16 h	50	2	52	>20:1	55
L•1e	THF	rt	16 h	67	28	95	2.4:1	26
L•Mar	THF	rt	16 h	63	37	100	1.7:1	0
L•1g§	Cyclo-hexane	30	16 h	37	5	42	7.4:1	15
L•1g§	Hexane	30	16 h	76	11	87	6.7:1	9

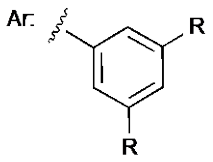
Science. ***2020***, 367, 1246-1251.

Enantioselective Iridium-Catalyzed Borylation:

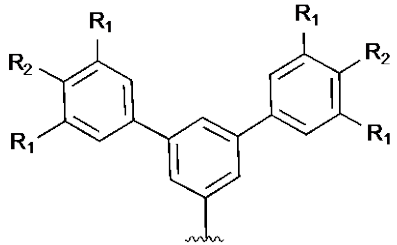
Further Screening: Solvent Effects



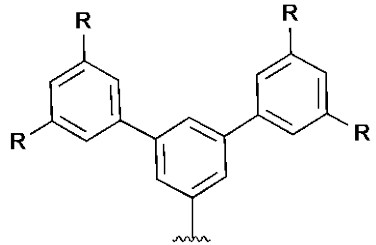
Group, Designation, *(%) e.e.*



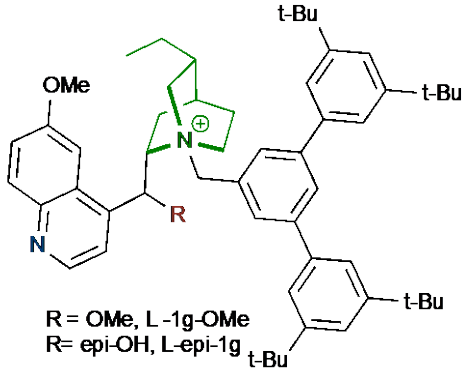
R = OMe, L-1a, 31%
R = *t*-Bu, L-1b, 30%



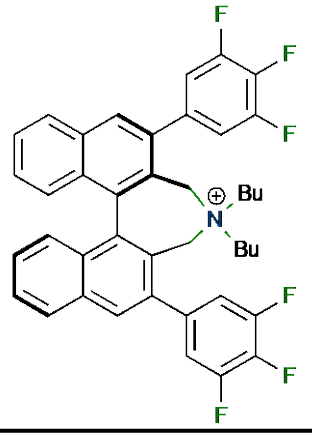
R_1 = H, R_2 = CF_3, L-1c, 39%
R_1 = F, R_2 = F, L-1d, 52%



R = CF_3, L-1e, 60% R = *t*-Bu, L-1g, 73%
R = OMe, L-1f, 60% R = Mes, L-1h, 55%
R = CF_3-Mes, L-1i, 26%



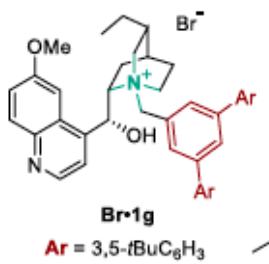
R = OMe, L-1g-OMe
R= epi-OH, L-epi-1g



Ligand	Solvent	Temp / °C	Time	NMR Yield 3a' / %†	NMR Yield 4a' / %†	NMR Yield Overall / %†	3a':4a'	%ee 3a'‡
L•1g§	*p*-Xylene	30	16 h	77	5	82	14.6:1	76
L•1g§	EtOAc	30	16 h	80	7	87	11:1	73
L•1g§	Acetone	30	16 h	5	1	6	5:1	14
L•1g§	1,4-Dioxane	30	16 h	76	21	97	3.6:1	66
L•1g§	CPME	30	16 h	52	48	100	1.1:1	83
L•1g§	Et_2O	30	16 h	33	67	100	1:2	86
L•1g§,¶	Et_2O	-10	21 h	-	-	-	n.r	n.r
L•1g¶,#	CPME	-10	48 h	75 (72)	25	100	3.0:1	97 (96)
L•1g-OMe¶,#	CPME	-10	48 h	57	3	60	19:1	72
L•*epi*-1g¶	CPME	-10	24h	76	10	86	7.6:1	11

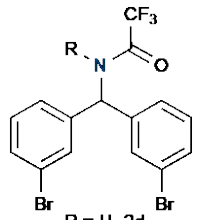
***Final optimized conditions with* L•1g:**
2 equiv. B_2Pin_2, *Temp*: -10 °C, *Solvent:* CPME
3a isolated in 72% yield with 96% *ee*

Ligand-Cation Interaction Probing:



Br•1g
Ar = 3,5-*t*BuC$_6$H$_3$

L•NBu$_4$



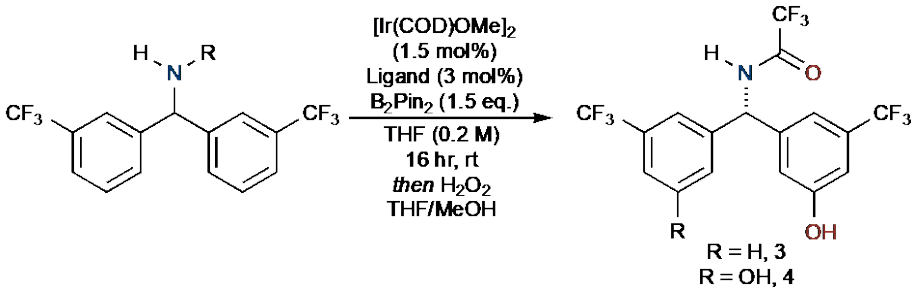
R = H, 2d
R = Me, 2x

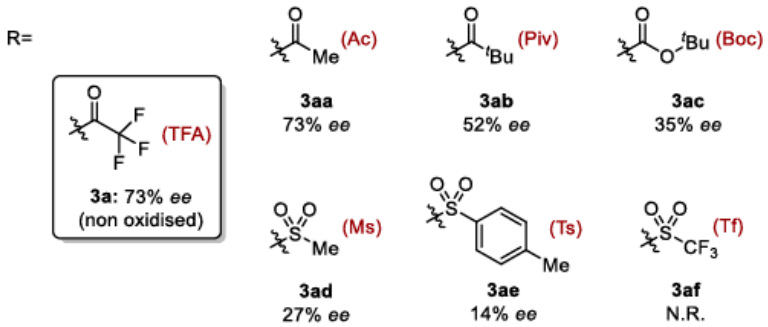
Additives (3 mol% each)	2a / %	3a' / %	4a' / %	3a':4a'	% *ee* 3a'
Br Salt Br•1g Neutral Ligand 8	87	10	<1	>20:1	0
Br Salt Br•1g Anionic ligand L•NBu$_4$	32	59	3	19:1	58

	Temp. (°C)	% conv.	%ee
2d	-10	91	91
2x	-10	0	-
2d	10	>95	73
2x	10	>95	8

Enantioselective Iridium-Catalyzed Borylation:

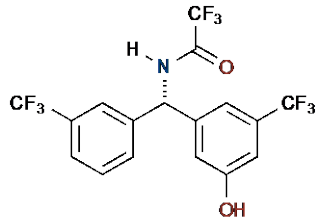
Evaluation of Nitrogen-Protecting Group:

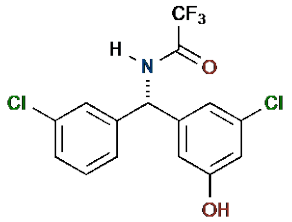


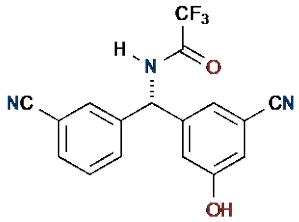


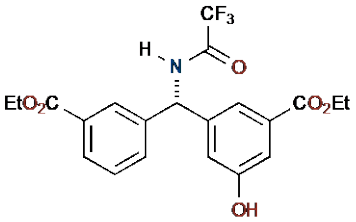
R	NMR Yield 3 / %†	NMR Yield 4 / %†	NMR Yield Overall / %†	3:4	%ee 3‡
TFA	73	27	100	2.7:1	73
Ac	81	11	92 (70)	7.4:1	73
Piv	75	24	99 (64)	3.1:1	52
Boc	69	4	73 (67)	17:1	35
Ms	69	25	94 (68)	2.8:1	27
Ts	77	10	87 (75)	7.7:1	14
Tf	-	-	No reaction	-	-

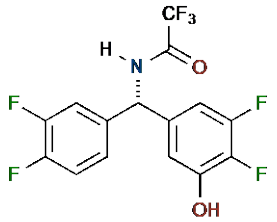
Selected Scope: Enantioselectivity

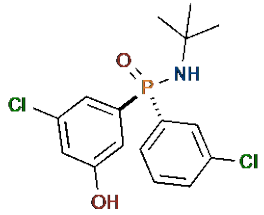

72%, 96% e.e.

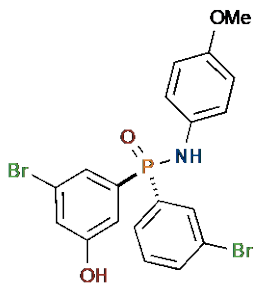

77%, 89% e.e.

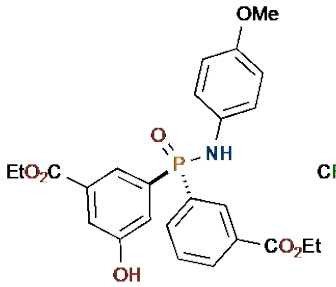

39%, 86% e.e.

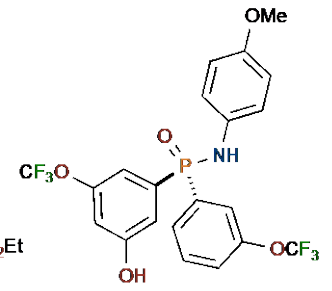

50%, 89% e.e.

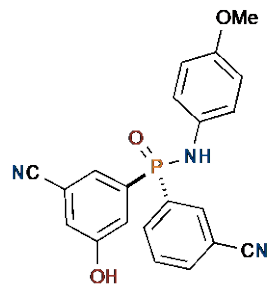

52%, 83% e.e.


67% yield, 95% e.e.

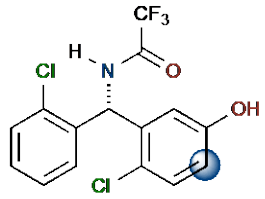

80% yield, 88% e.e.

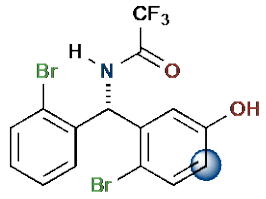

39% yield, 80% e.e.

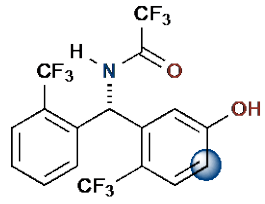

61% yield. 86% e.e.

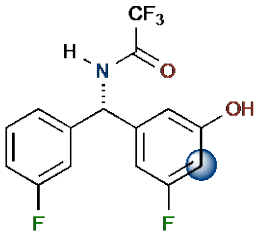

49% yield, 93% e.e.

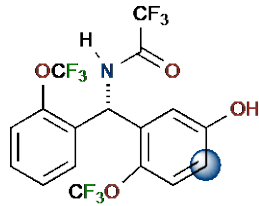
Selected Scope: Enantioselectivity and Regioselectivity


43%, 10:1 rr
85% e.e.


57%, 7:1 rr
79% e.e.


42%, 15:1 rr
79% e.e.


57%, > 20:1 rr
79% e.e.


72%, 8:1 rr
83% e.e.

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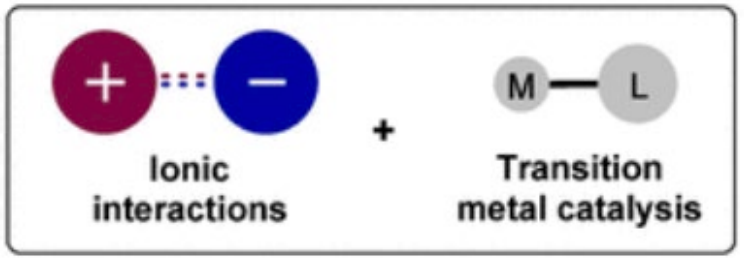
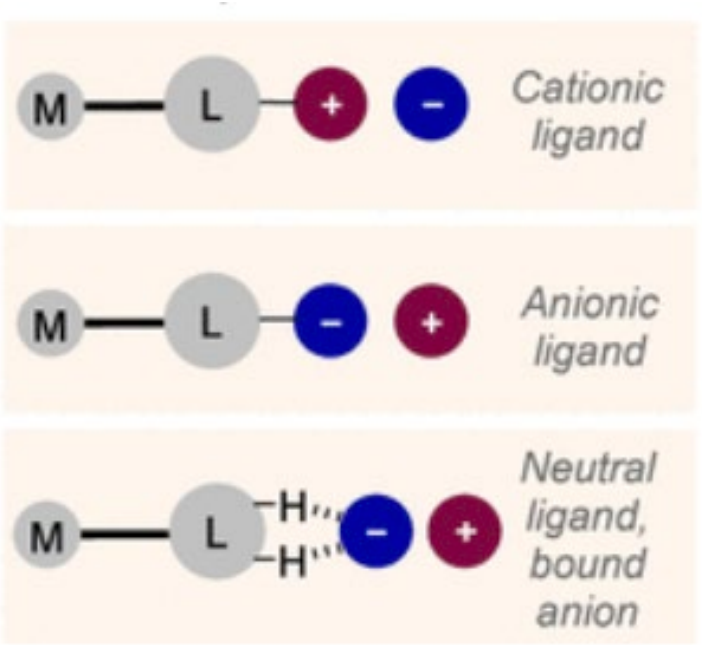
Overview



Covered:



Not Covered:

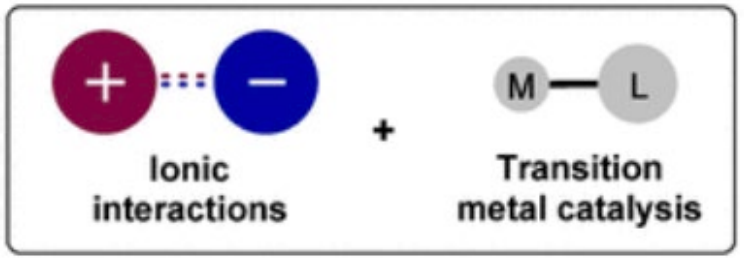
Advantages:

1. **Specific chemical problems can be solved with specific permutations in ionic interactions.**
2. **Higher levels of selectivity can be achieved which are not accessible through traditional catalytic means.**

Disadvantages:

1. **Ligand scaffolds must be simply and readily tunable for expedient implementation.**
2. **Some systems may require highly specific substrates with multiple limitations.**

Overview



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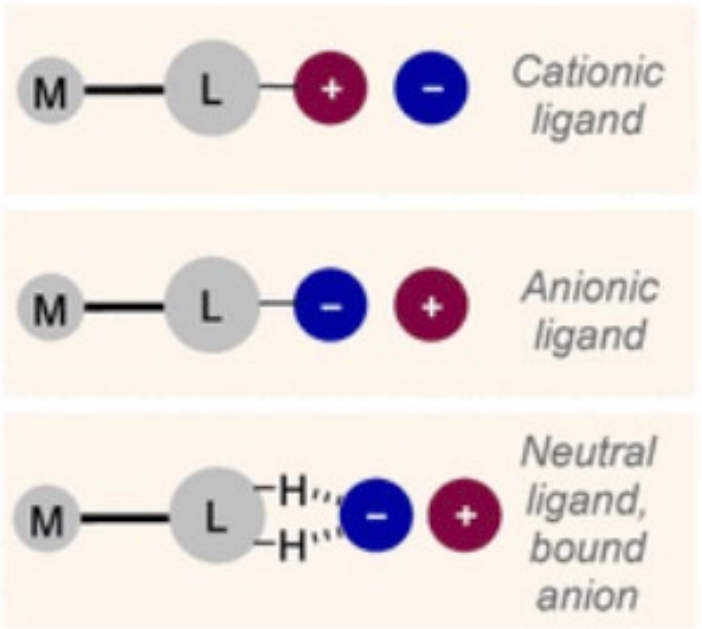

Not Covered:

Questions?