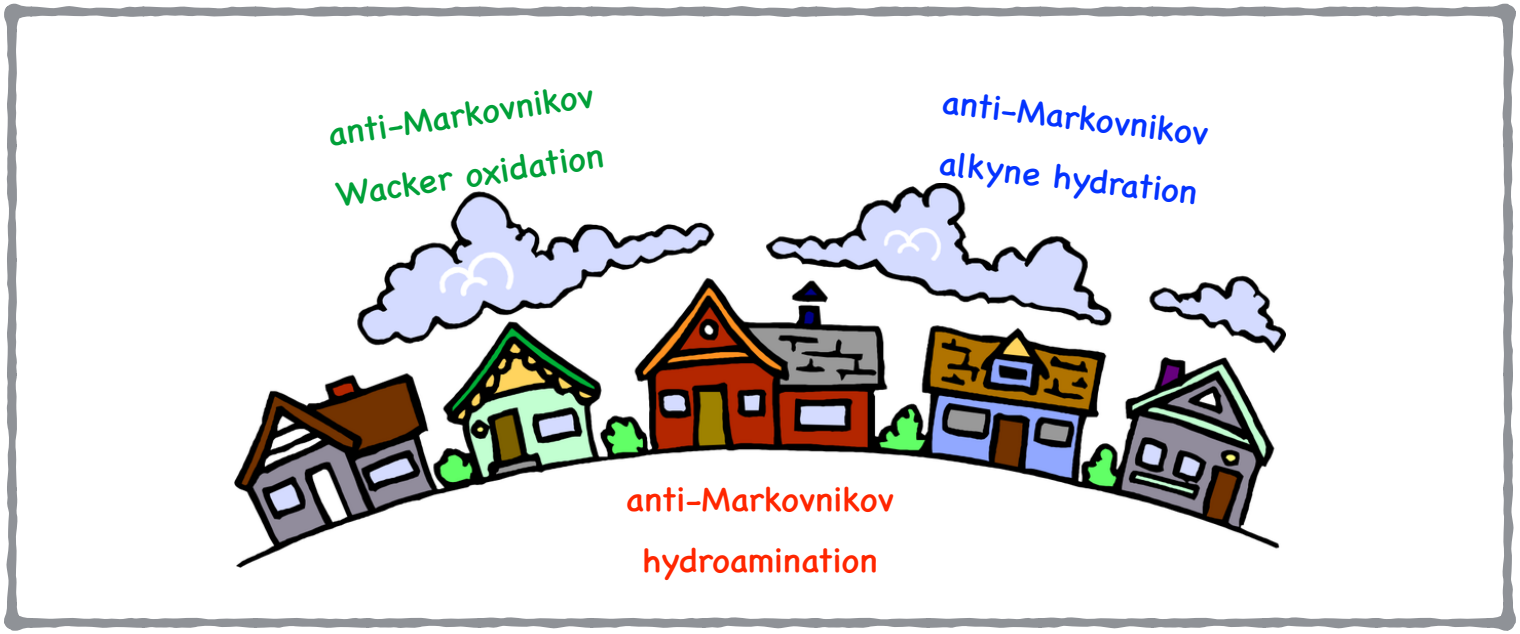
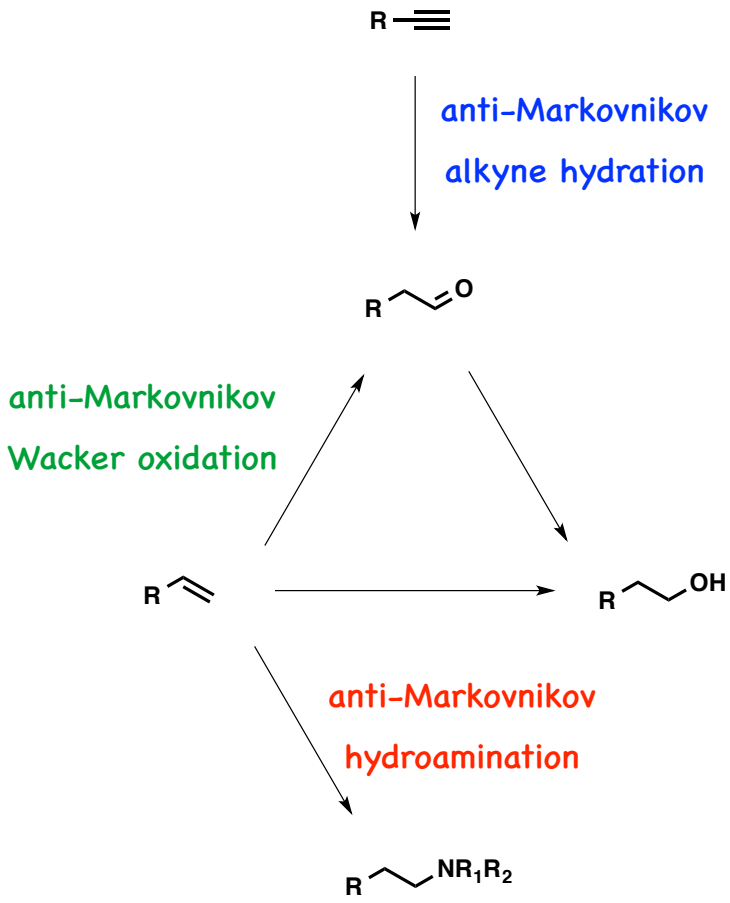
Neighbors of Catalytic anti-Markovnikov Olefin Hydration:

A Mechanistic Review



Scope of today's talk



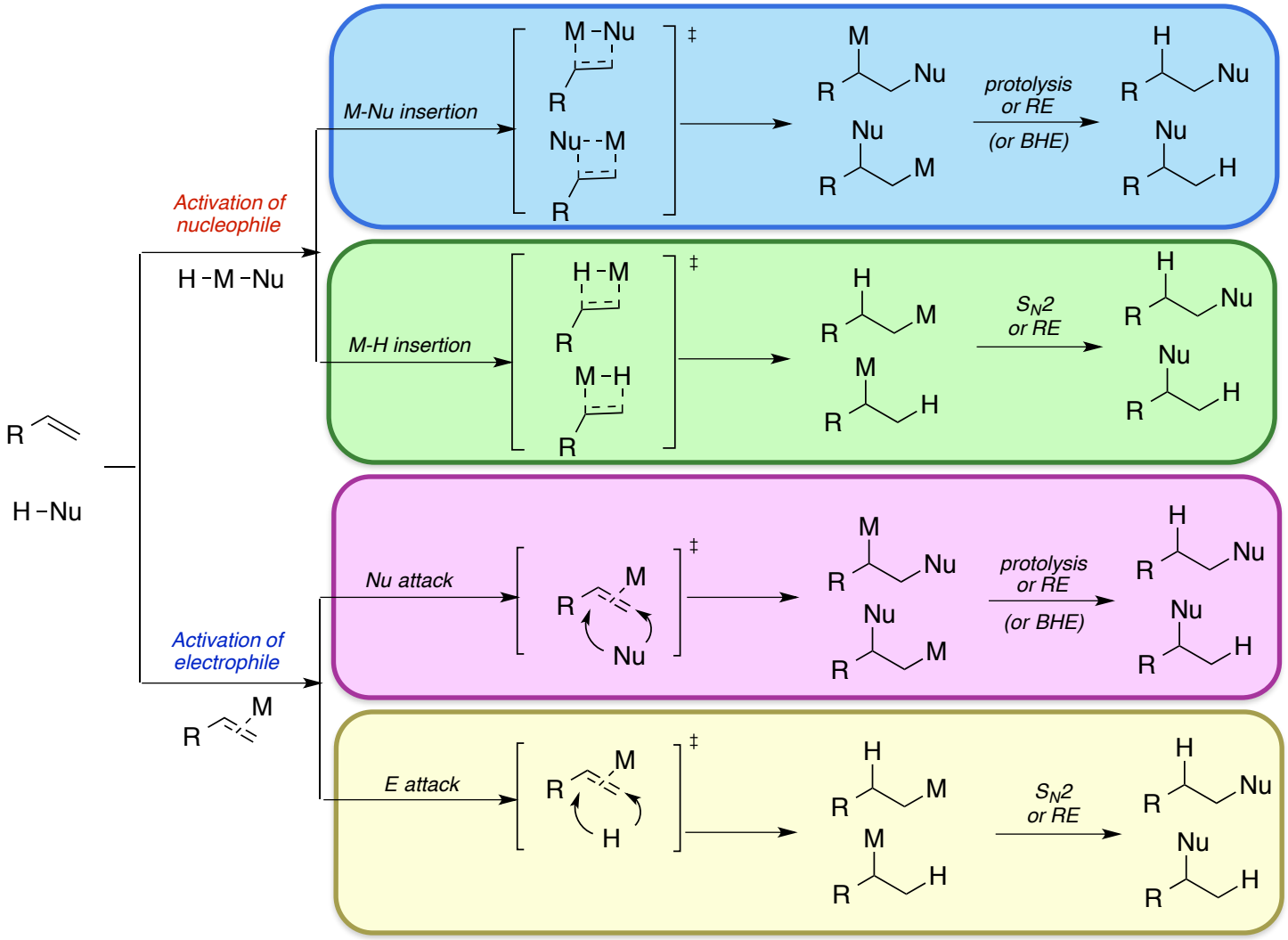
✓ Key questions for reactivity

What is the mechanism for each reaction?
What is the RDS?
How to improve the reactivity?

✓ Key question for selectivity

What is the origin of AM selectivity?

Contents: sorted by mechanism



- ✓ Wacker oxidation
- ✓ hydroamination (Ln, Ir)

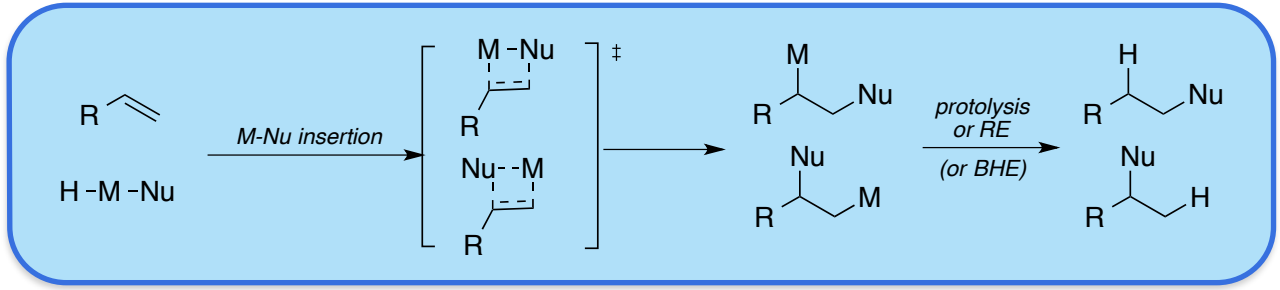
- ✓ No literature

- ✓ alkyne hydration (Au)
- ✓ hydroamination (Rh, Ir, Pd, Ru)

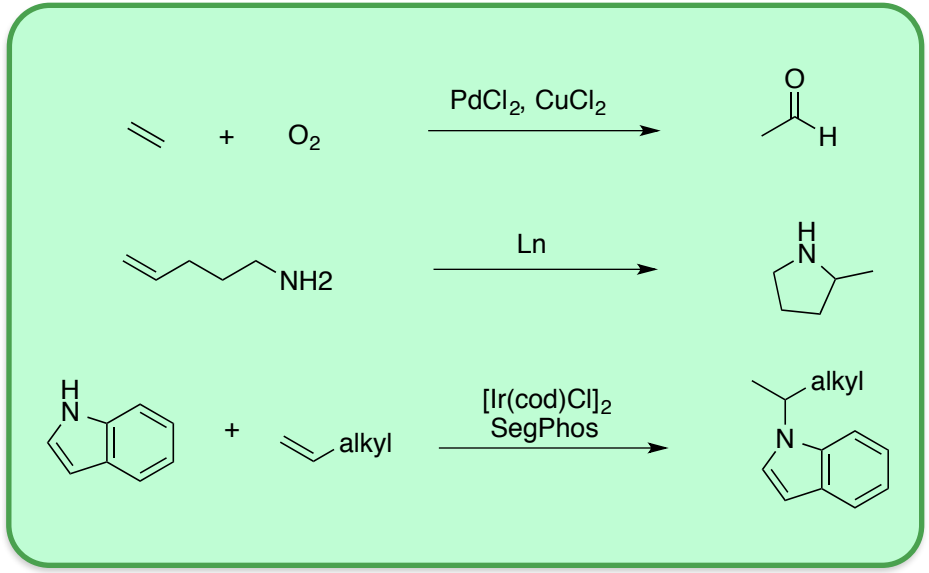
- ✓ alkyne hydration (Ru)
- ✓ hydroamination (Pd)

Overview of M-Nu insertion pathway

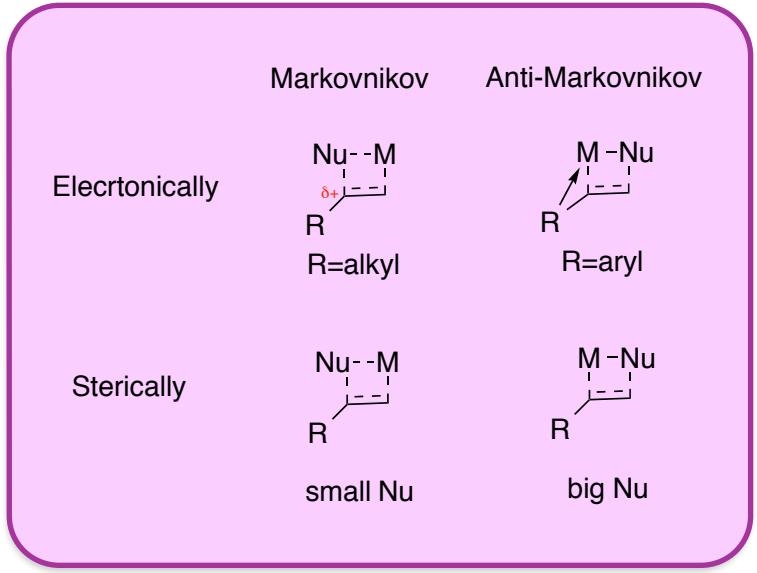
✓ Simplified reaction mechanism



✓ Three examples

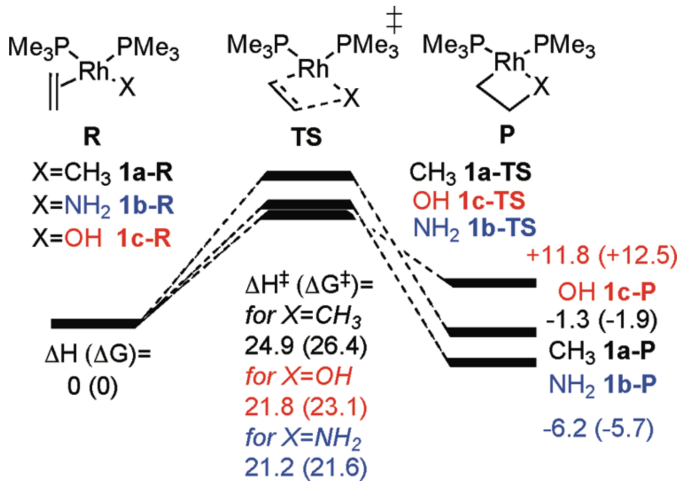


✓ Regioselectivity

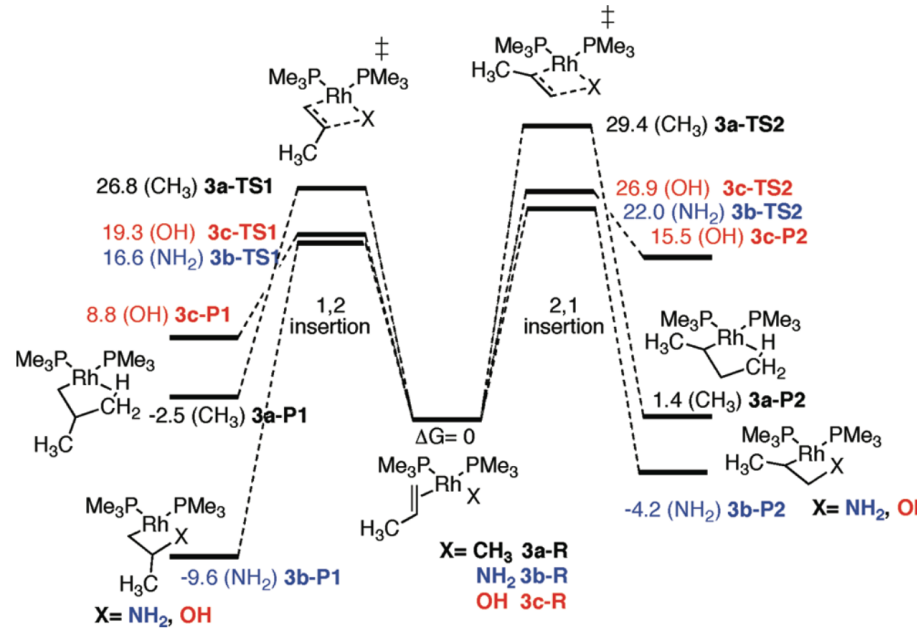


Migratory insertion of M-N and M-O bond

✓ Reactivity



✓ Selectivity



Conclusions:

✓ Rate: Rh-N > Rh-O >> Rh-C

✓ Reason: Rh-N and Rh-O dative bond in the TS

Conclusions:

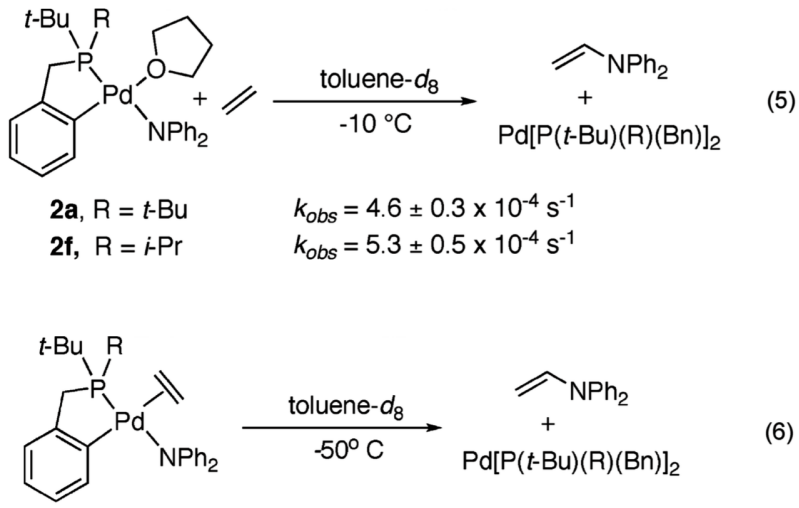
✓ Enhanced Markovnikov selectivity for M-N and M-O insertion

✓ Growing positive charge on carbon

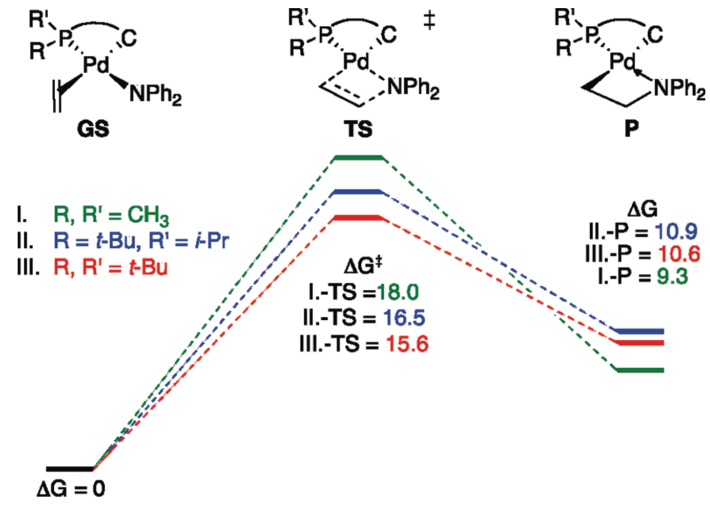
Tye, J. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009,** *131,* 14703.

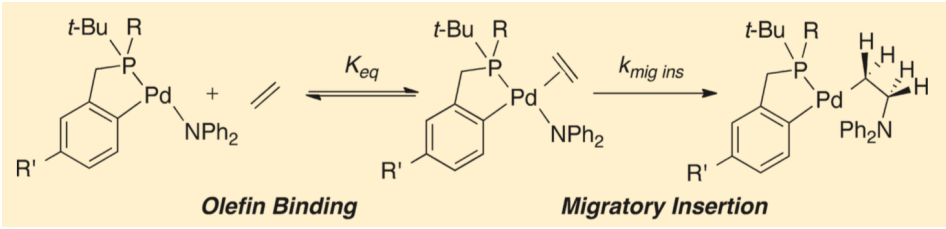
How to accelerate migratory insertion?

✓ Experiments about steric effect



✓ Computational result





Conclusions:

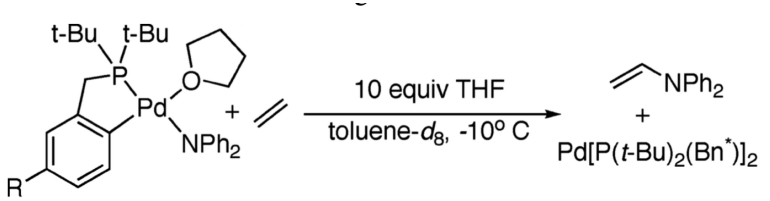
✓ Bigger steric accelerates insertion

✓ However, it also slows down binding

Hanley, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 15661.

How to accelerate migratory insertion?

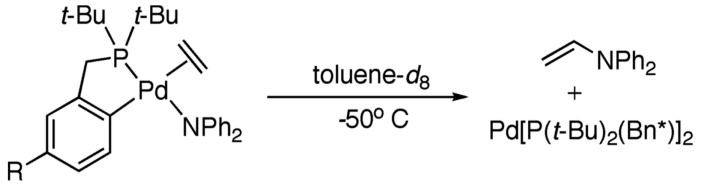
✓ Experiments about electronic effect



2h, R = CF_3 $k_{obs} = 1.0 \pm 0.04 \times 10^{-3}\ s^{-1}$

2a, R = H $k_{obs} = 4.6 \pm 0.3 \times 10^{-4}\ s^{-1}$

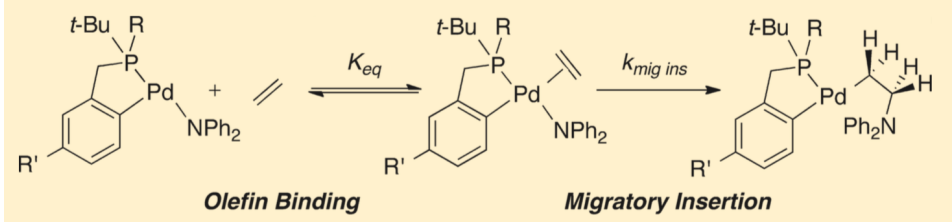
2g, R = OCH_3 $k_{obs} = 3.9 \pm 0.2 \times 10^{-4}\ s^{-1}$



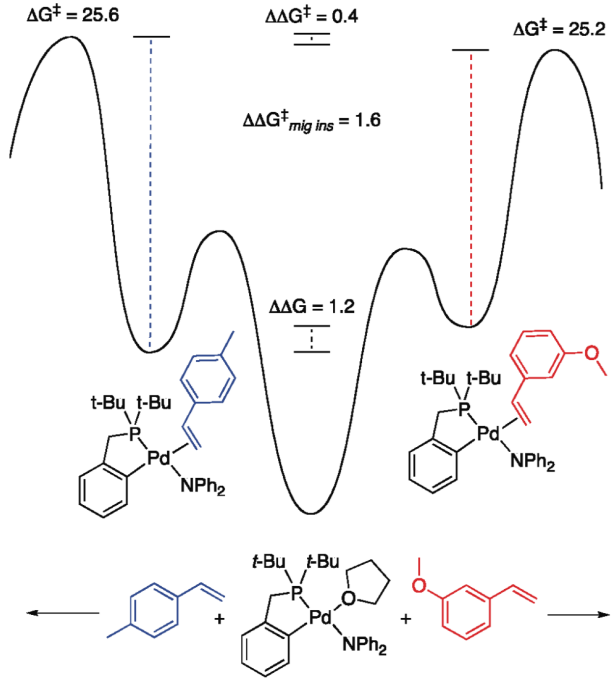
3h - ethylene adduct, R = CF_3 $k_{mig\ ins} = 2.6 \pm 0.2 \times 10^{-3}\ s^{-1}$

3a - ethylene adduct (**8**), R = H $k_{mig\ ins} = 8.7 \times 10^{-4}\ s^{-1}$

3g - ethylene adduct, R = OCH_3 $k_{mig\ ins} = 3.8 \times 10^{-4}\ s^{-1}$



✓ Computational result



Conclusions:

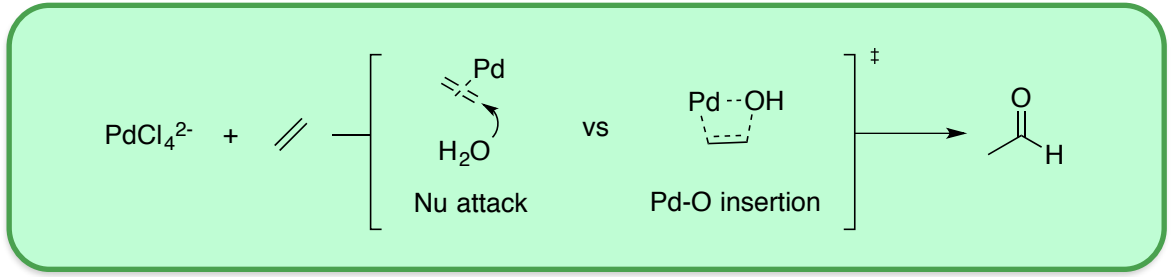
✓ EWG on ligand accelerates insertion

✓ Electron-poor olefin: insert faster but bind badly

Hanley, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 15661.

Wacker Oxidation

✓ Key question: syn or anti attack?



✓ Determination of the rate law

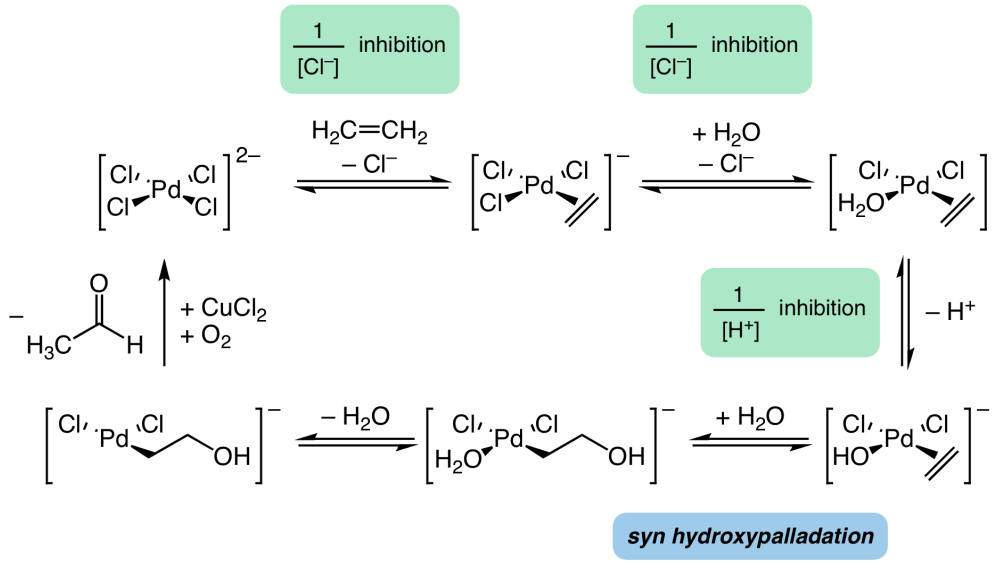
$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[C_2H_4]}{[Cl^-]^2\,[H^+]}$$

Conclusions:

✓ First order acid inhibition

✓ Deprotonation happens *before* RDS

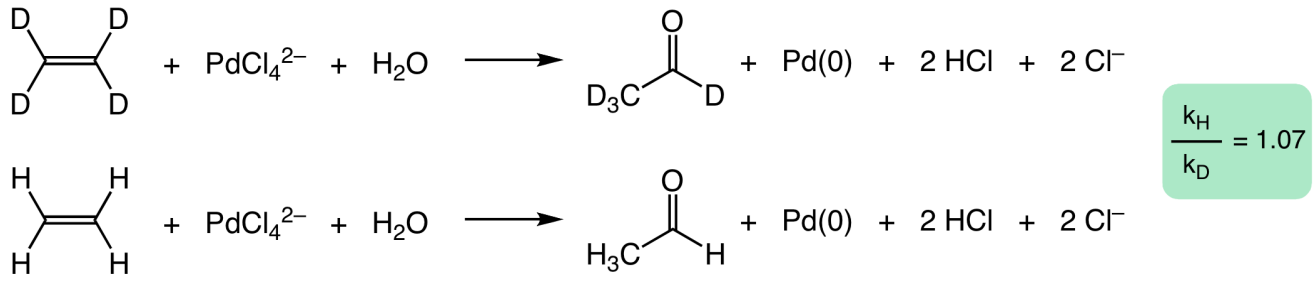
✓ Syn attack mechanism

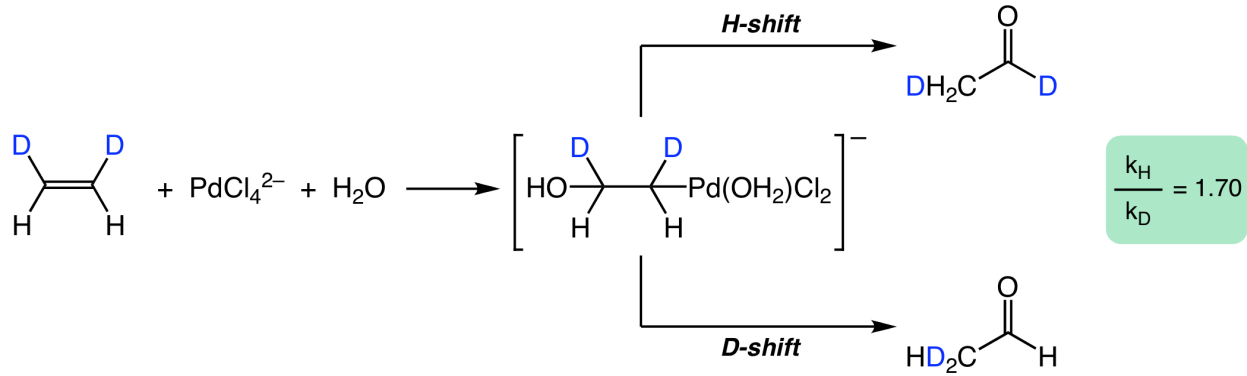


For a detailed review on this 45-year debate, see: Keith, J. A.; Henry, P. M. *Angew. Chem. Int. Ed.* **2009,** *48,* 9038.

Wacker Oxidation

✓ KIE experimental result





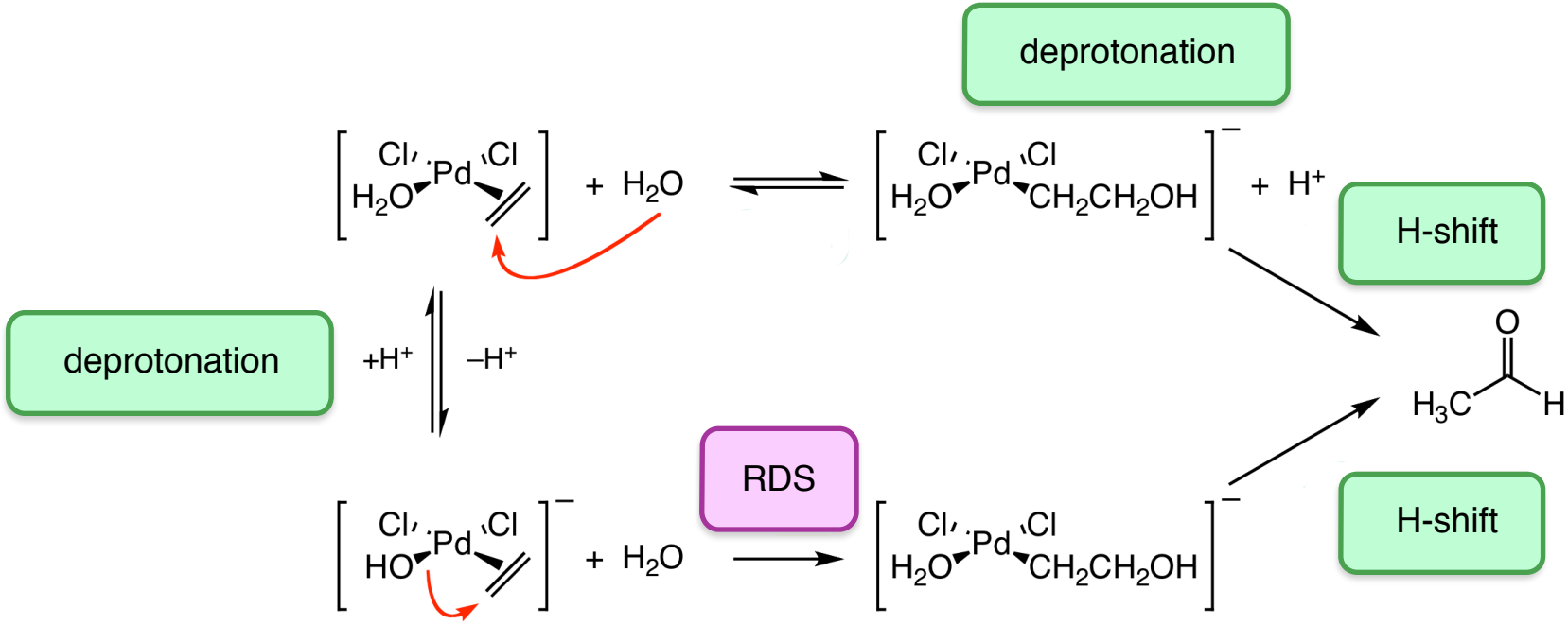
Conclusions:

✓ No KIE but primary competitive KIE

✓ H-shift happens *after* RDS!

Wacker Oxidation

✓ Combining the two kinetic information



Key information:

✓ Deprotonation happens *before* RDS

✓ H-shift happens *after* RDS!

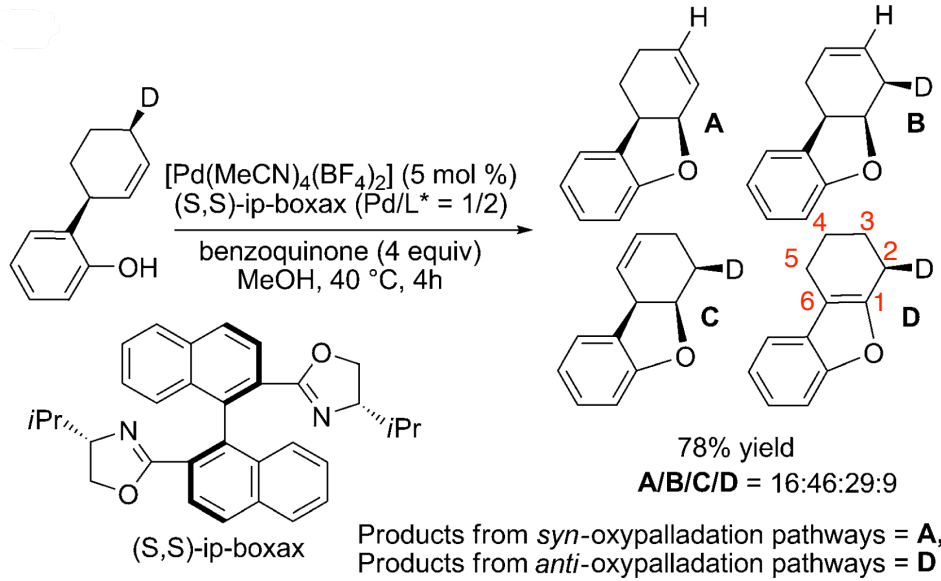
✓ OH^- attack is impossible, considering its concentration

Conclusion:

✓ Pd-O insertion is the correct mechanism under Wacker condition

Wacker Oxidation

✓ Syn or anti attack is also distinguishable from stereochemistry experiment



Question 01:

Hayashi did an isotope experiment in 2004 to distinguish between *syn* and *anti* attack. Assume that Pd-O insertion is RDS, while beta-hydrogen elimination and re-insertion are facile.

(1) Which of four products come(s) from *syn* attack? Please also draw the key intermediate(s).

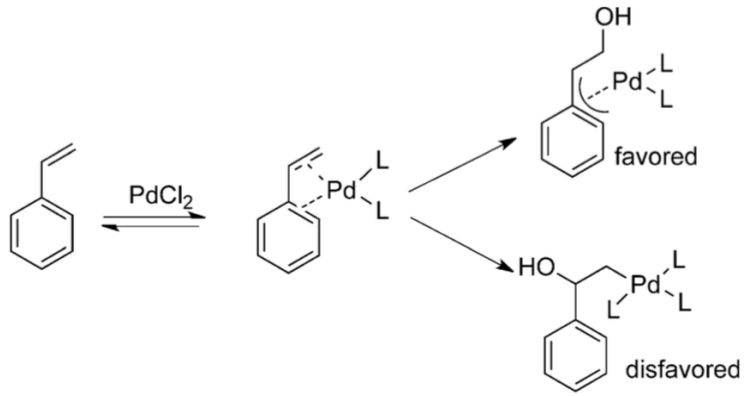
(2) The picture above is captured from a review paper by Hartwig. The authors claimed that *syn* : *anti* = 91:9 based on this experiment. Compare your result with their claim.

(3) Given that **D** is also 5% deuterated at 3-position (95% at 2-position), calculate an approximate ratio of *syn* : *anti*.

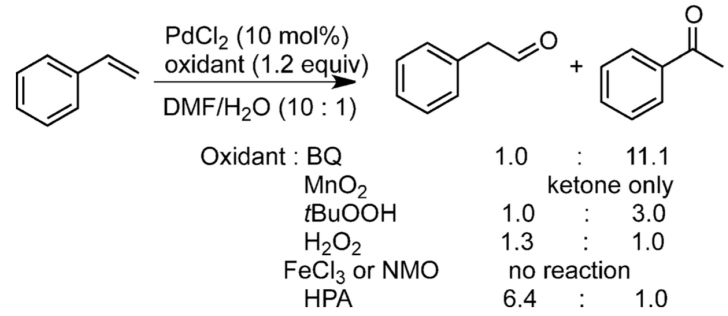
Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036;
Hanley, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 8510.

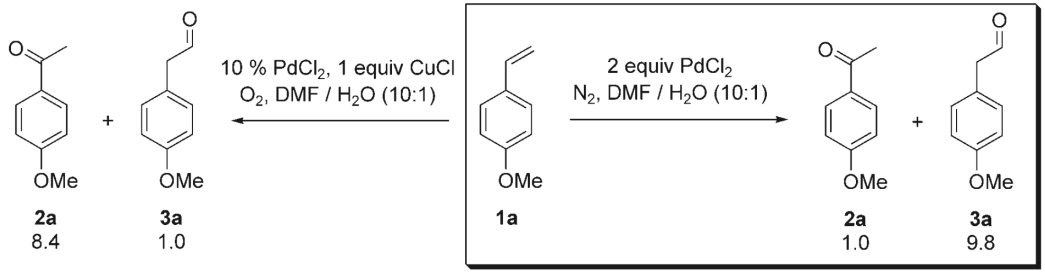
Anti-Markovnikov Wacker Oxidation

✓ AM selectivity is favored for styrene in stoichimetric reaction



✓ Choice of oxidant changes selectivity





Conclusions:

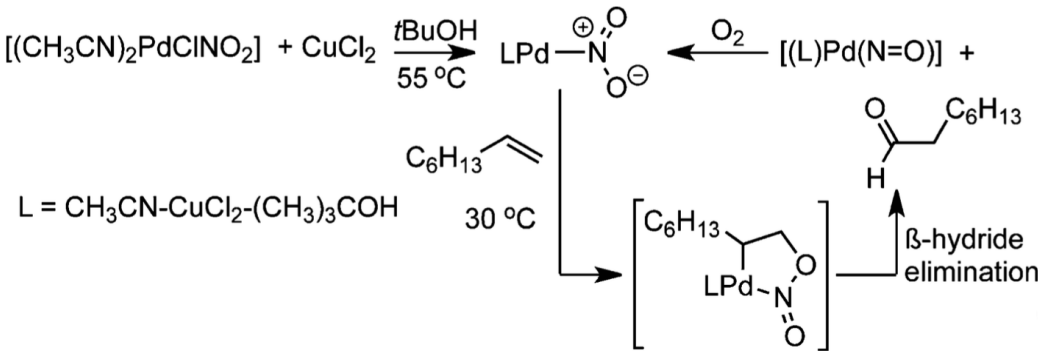
✓ Oxidant does NOT just involve in innocent Pd(II) re-oxidization

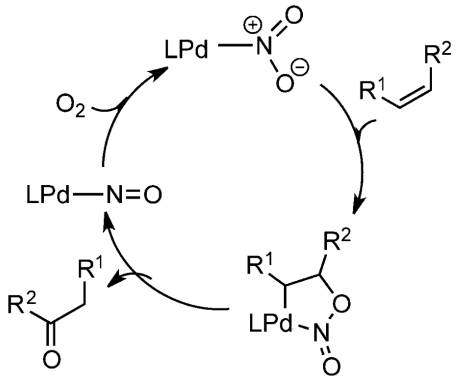
✓ At least, it changes the position of RDS

Wright, J. A.; Gaunt, M. J.; Spencer, J. B. *Chem. Eur. J.* **2006**, *12*, 949.

Anti-Markovnikov Wacker Oxidation

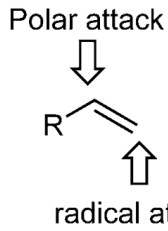
✓ Pd(NO2) system gives some preference

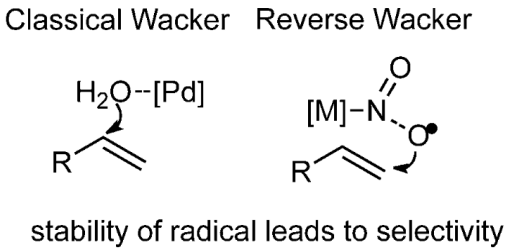




For decene, aldhyde:ketone = 3:2

✓ Their rational for this system





stability of radical leads to selectivity

✓ Big Nu improves the selectivity

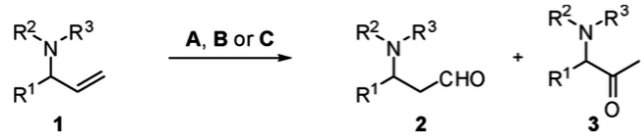
Choice of ^{t}BuOH as solvent (nucleophile)

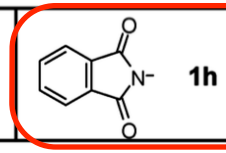
Selectivity is a very bad!

Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1986**, 909.

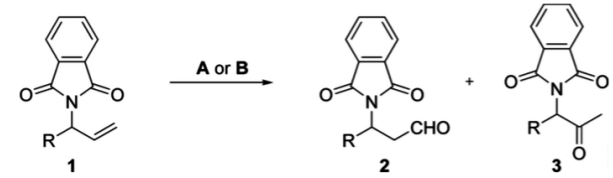
Anti-Markovnikov Wacker Oxidation

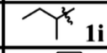
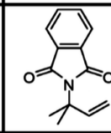
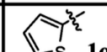
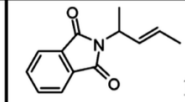
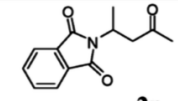
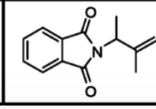
✓ Screening of protecting group (directing group)



entry	substrate	cat	conversion %	2 : 3[c]
1	R^1=Ph, R^2=PMP, R^3=H **1a**	A[b]	0	-
2	**1a**	B	0	-
3	R^1=Ph, R^2=Cbz, R^3=H **1b**	A[b]	100	60:40
4	**1b**	B	100	70:30
5	R^1=Ph, R^2=Ts, R^3=H **1c**	A[b]	100	45:55
6	**1c**	B	100	3:97
7	R^1=Ph, R^2=Boc, R^3=H **1d**	A[b]	10	35:65
8	**1d**	B	0	-
9	R^1=Me, R^2=Bz, R^3=H **1e**	A[b]	12	77:23
10	**1e**	B	100	80:20
11	R^1=Me, R^2=*o*-Ns, R^3=H **1f**	B	100	4:96
12	R^1=Me, R^2=*o*-Ns, R^3=Boc **1g**	C	0	-
13	R^1=Me  **1h**	A[d]	100	96:4
14	**1h**	B	100	>99:1
15	**1h**	C	80	94:6

✓ Substrate scope



entry	substrate	cat	2 : 3[a]	Isolated yield %
1	R = CH_3 **1g**	B	>99:1	94
2	R = C_5H_{11} **1h**	B	>99:1	91
3	 **1i**	A	>99:1	93
4	 **1k**	A	94:6	74[b]
5	R = Bn **1l**	B	>99:1	94
6	R = $BnOCH_2$ **1m**	B	>99:1	93
7	R = Ph **1n**	B	>99:1	95
8	 **1o**	B	>99:1	77
9	 **1p**	A	>1:99	89  **2p**
10	 **1q**	A B	- -	0 0

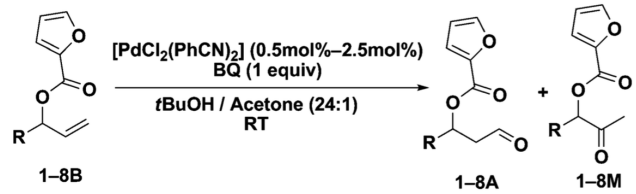
[a] A: $Pd(MeCN)_2Cl(NO_2)$ (1−5 mol %), $CuCl_2$ (5−20 mol %), *tert*-BuOH, O_2; 16 h. B: $PdCl_2$ (10 mol %), CuCl (1.0 equiv), DMF/H_2O (7:1). O_2; 3 d. C: $PdCl_2$ (10 mol %), $CuCl_2$ (50 mol %), DMF/H_2O (4:1), O_2; 3 d. [b] 5 mol % Pd-cat, 20 mol % $CuCl_2$. [c] Determined by ^1H NMR. [d] 1 mol % Pd-cat, 5 mol % $CuCl_2$.

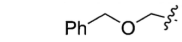
Weiner, B.; Baeza, A.; Jerphagnon, T.; Feringa, B. L. *J. Am. Chem. Soc.* **2009**, *131*, 9473.

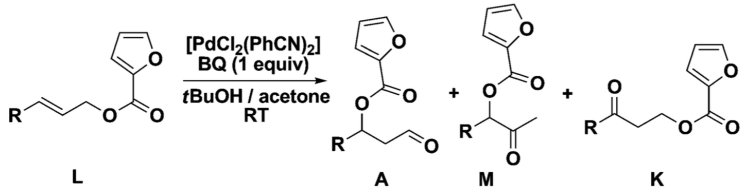
Anti-Markovnikov Wacker Oxidation

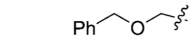
✓ Substrate scope

BQ as oxidant

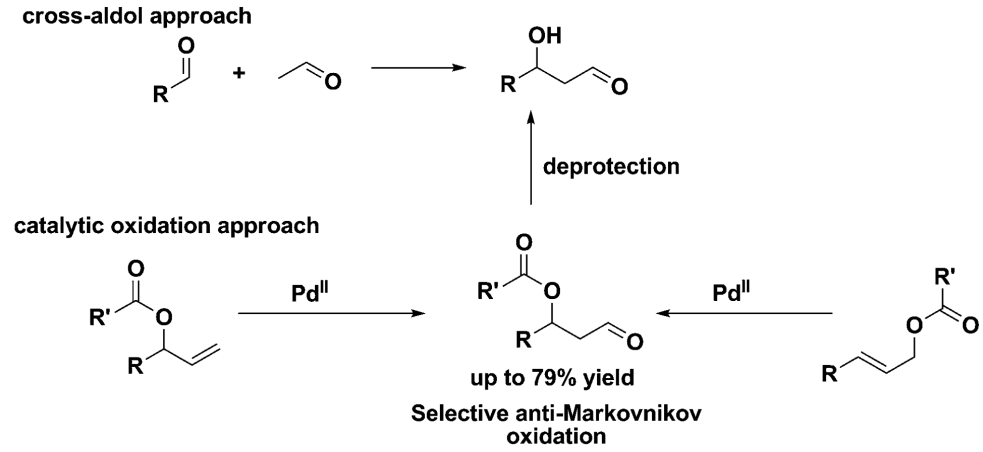


Entry	R	B	Conv.	A/M	A	Yield [%][b]
1[c]	H	**1B**	full	11:1	**1A**	78
2[d]	CH_3	**2B**	full	7:1	**2A**	71
3[d]	C_2H_5	**3B**	full	20:1	**3A**	79
4[e]	C_5H_{11}	**4B**	full	20:1	**4A**	73
5[e,f]		**5B**	95%	20:1	**5A**	45
6[c]		**6B**	full	20:1	**6A**	71
7[e,f]	Ph	**7B**	full	20:1	**7A**	52
8[e,g]	Bn	**8B**	95%	20:1	**8A**	64



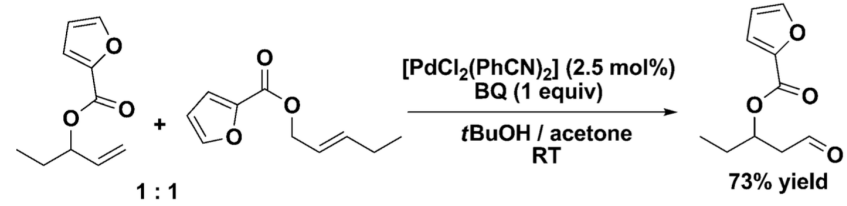
Entry	R	L	Conv.[a,b]	A/M	A	Yield [%][b]
1[c]	CH_3	**2L**	full	7:1	**2A**	70
2[d]	C_2H_5	**3L**	full	16:1	**3A**	74
3[d]	C_5H_{11}	**4L**	95%	15:1	**4A**	72
4[c]		**6L**	full	20:1	**6A**	71
5[e,f]	Bn	**8L**	85%	10:1	**8A**	43

✓ The application of Anti-Markovnikov Wacker oxidation



Allylic rearrangement is a pre-equilibrium before oxidation

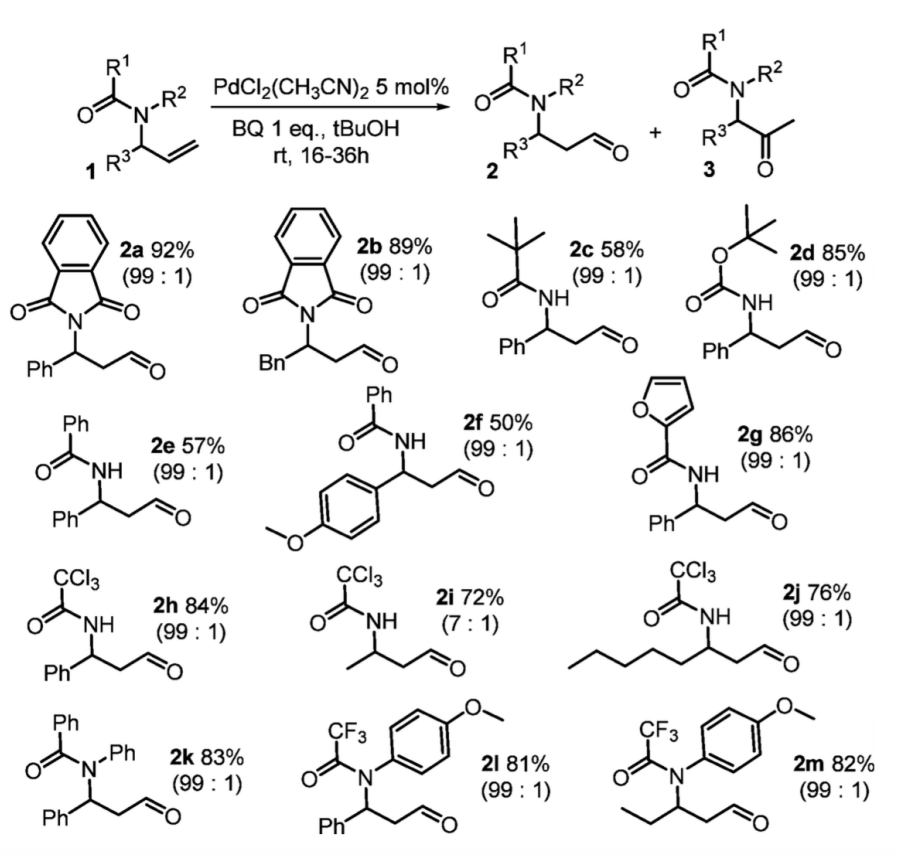
✓ Convergent synthesis (like Zhe's chemistry)



Dong, J. J.; Fañanás-Mastral, M.; Alsters, P. L.; Browne, W. R.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 5561.

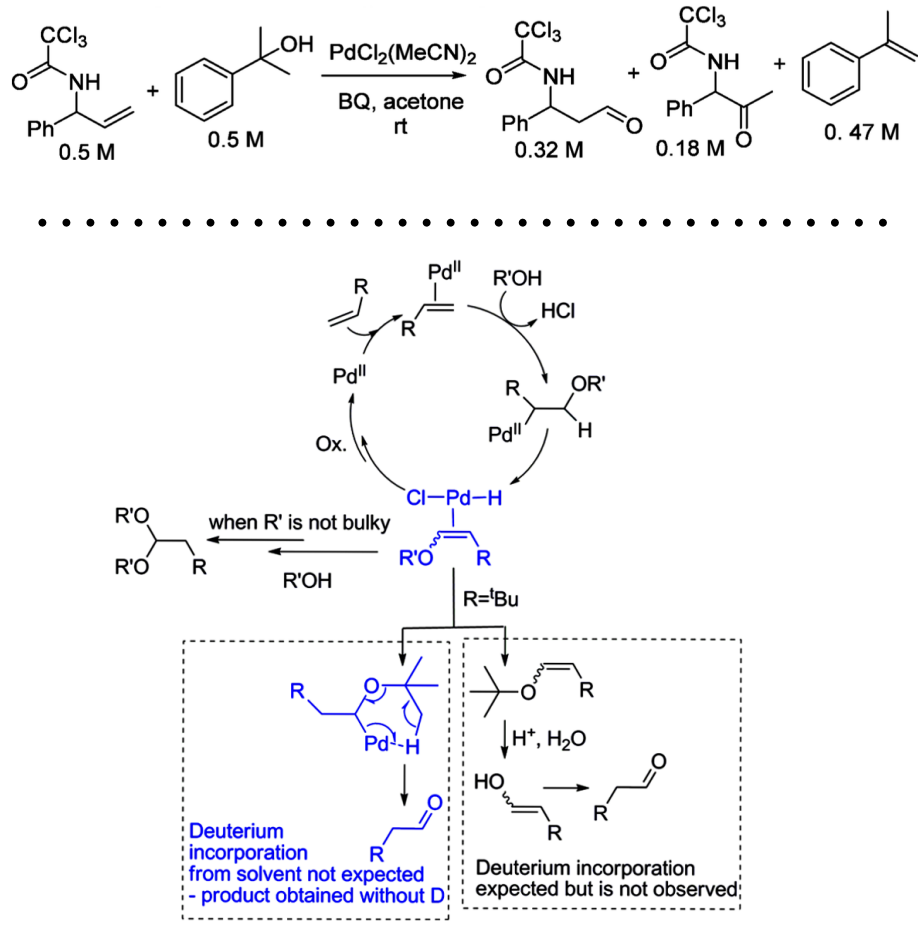
Anti-Markovnikov Wacker Oxidation

✓ Various protecting group scope



BQ as oxidant

✓ Mechanism study



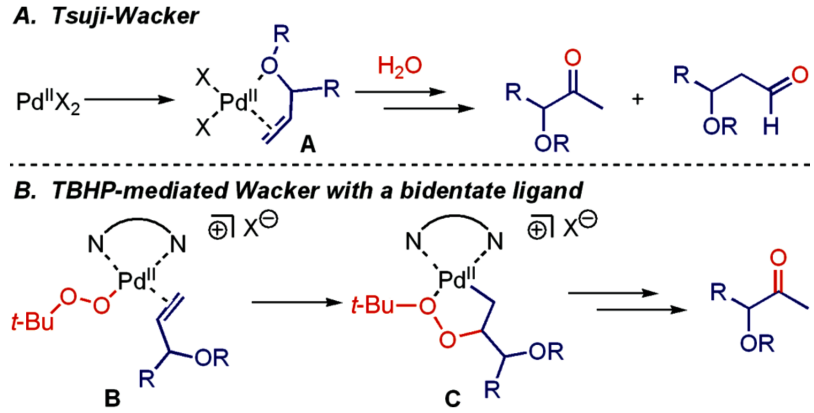
Their mechanism

Grubbs' mechanism

Dong, J. J.; Harvey, E. C.; Fañanás-Mastral, M.; Browne, W. R.; Feringa, B. L. *J. Am. Chem. Soc.* **2014**, *136*, 17302.

Markovnikov Wacker Oxidation

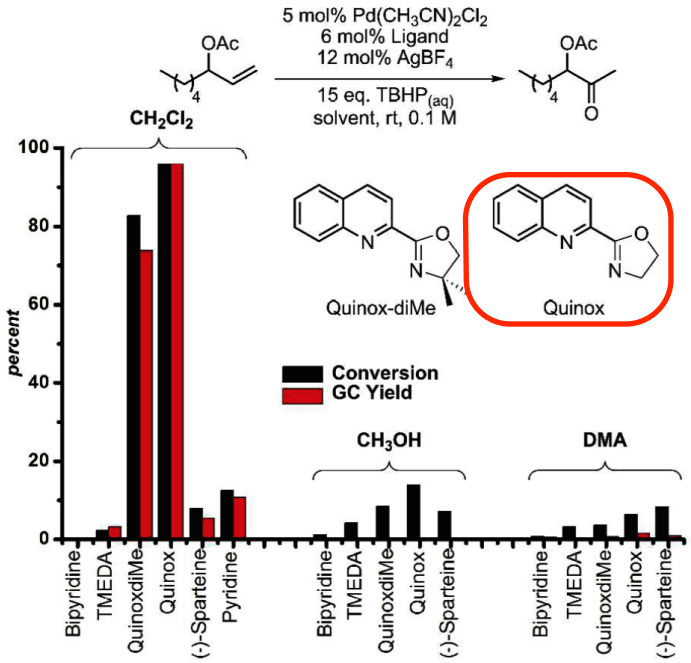
✓ Directing group *usually* gives a mixture: Markovnikov is also difficult!



Key design: bidentate ligand to avoid substrate chelation

Substrate control to catalyst control (albeit Markovnikov)

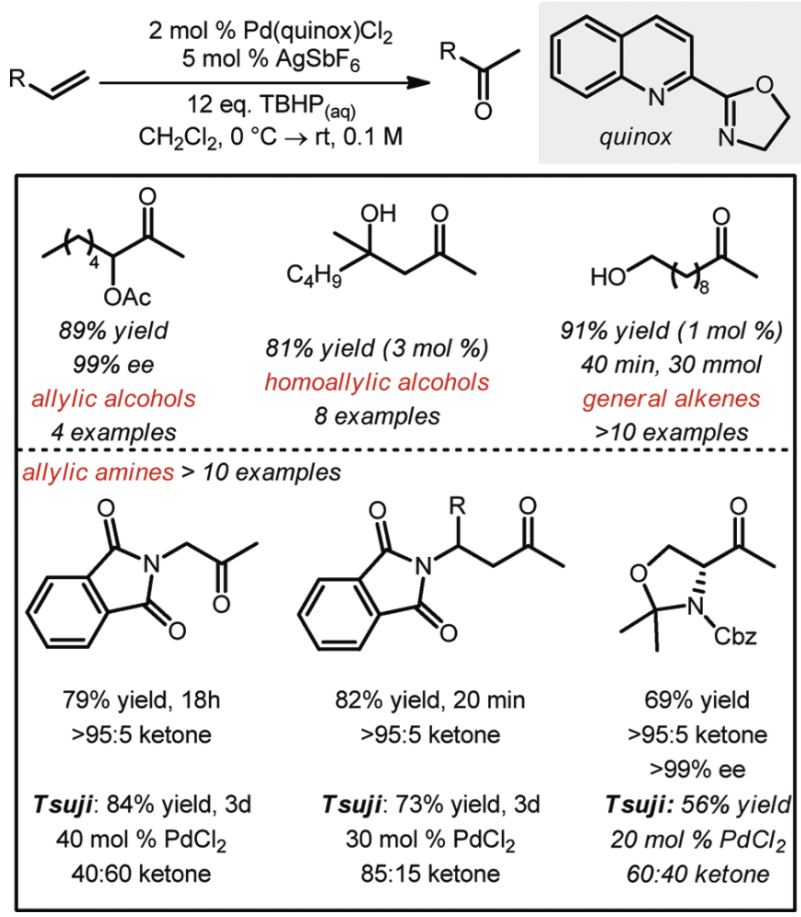
✓ Ligand screening



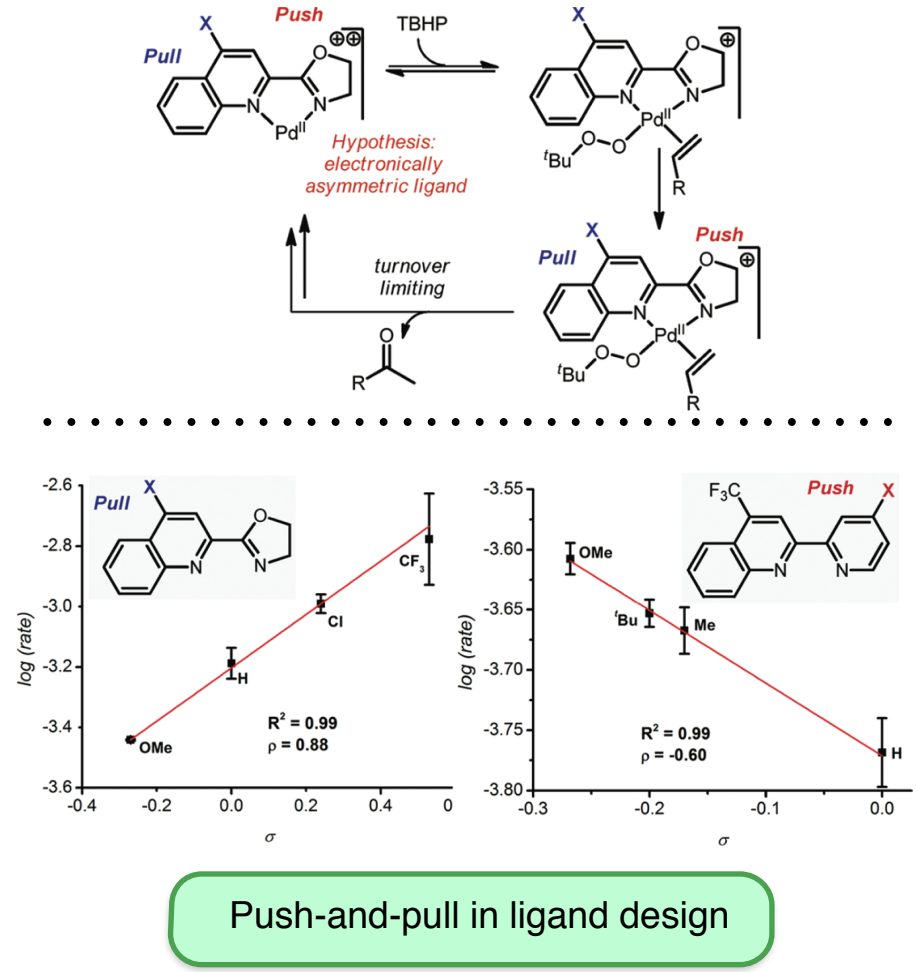
Michel, B. W.; Camelio, A. M.; Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 6076.

Markovnikov Wacker Oxidation

✓ Substrate scope and comparison



✓ Electronic effect of ligands

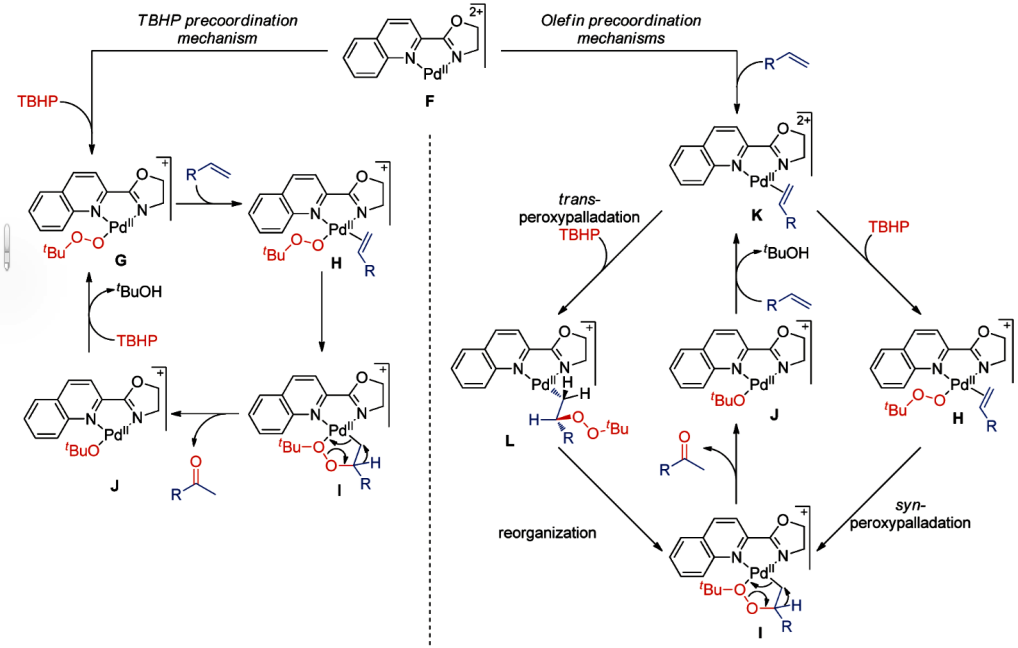


Push-and-pull in ligand design

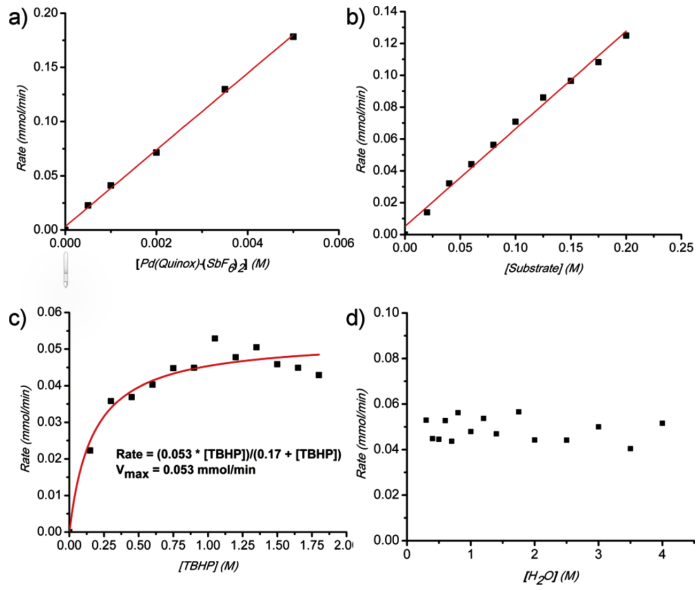
Michel, B. W.; Camelio, A. M.; Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 6076;
Michel, B. W.; McCombs, J. R.; Winkler, A.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 7312;
Sigman, M. S.; Werner, E. W. *Acc. Chem. Res.* **2012**, *45*, 874.

Markovnikov Wacker Oxidation

✓ Proposed three mechanisms



✓ Kinetic experiment



Question 02: (Math-free question!)

Sigman proposed three mechanisms for their reaction. The main difference is whether TBHP coordinates first (path: F-G-H-I-J) or olefin coordinates first (path: F-K-H-I-J or F-K-L-I-J). The rate law is: first order on Pd and olefin, but *saturation kinetics on TBHP*.

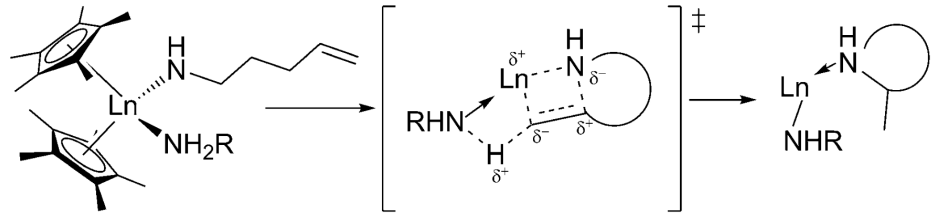
(1) Forget about three mechanisms. It is fair to assume that peroxypalladation is RDS, while olefin and TBHP coordination is a pre-equilibrium. Based on this assumption, what would you expect for the reaction order for TBHP?

(2) Now look at their mechanisms closely. Actually, pre-coordination means the coordination step is *NOT* involved in the catalytic cycle. Don't try to derive the rate law! Please choose the right mechanism and *qualitatively* explain why.

Michel, B. W.; Steffens, L. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 8317.

Lanthanide-catalyzed hydroamination

✓ The originally proposed mechanism (the TS is weird)



Key findings:

✓ Primary KIE: 2.7 - 5.2

✓ Rate law: first order on Ln, zero order on substrate

✓ $\Delta H^{\neq}$ = 12.7 ± 1.4 kcal/mol

✓ $\Delta S^{\neq}$ = - 27.0 ± 4.6 cal/mol˙T

Conclusions:

✓ Zero-order: resting state directly undergoes RDS without pre-association or dissociation

✓ But it can also mean similar inhibition by product

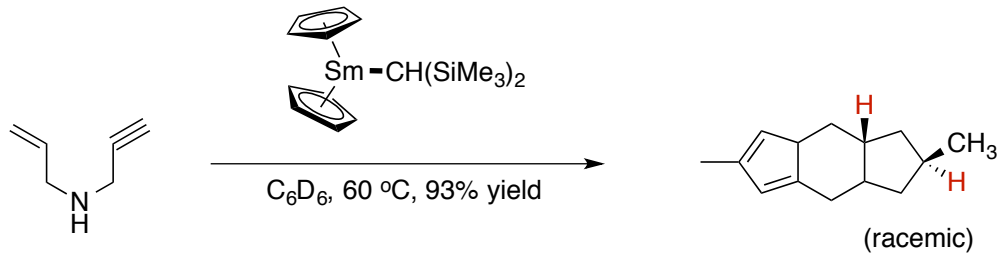
✓ Significant N-H breaking during RDS

✓ Large negative $\Delta S^{\neq}$: highly ordered TS

Gagne, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.

Lanthanide-catalyzed hydroamination

✓ Application for fused ring synthesis: evidence for Ln-C species

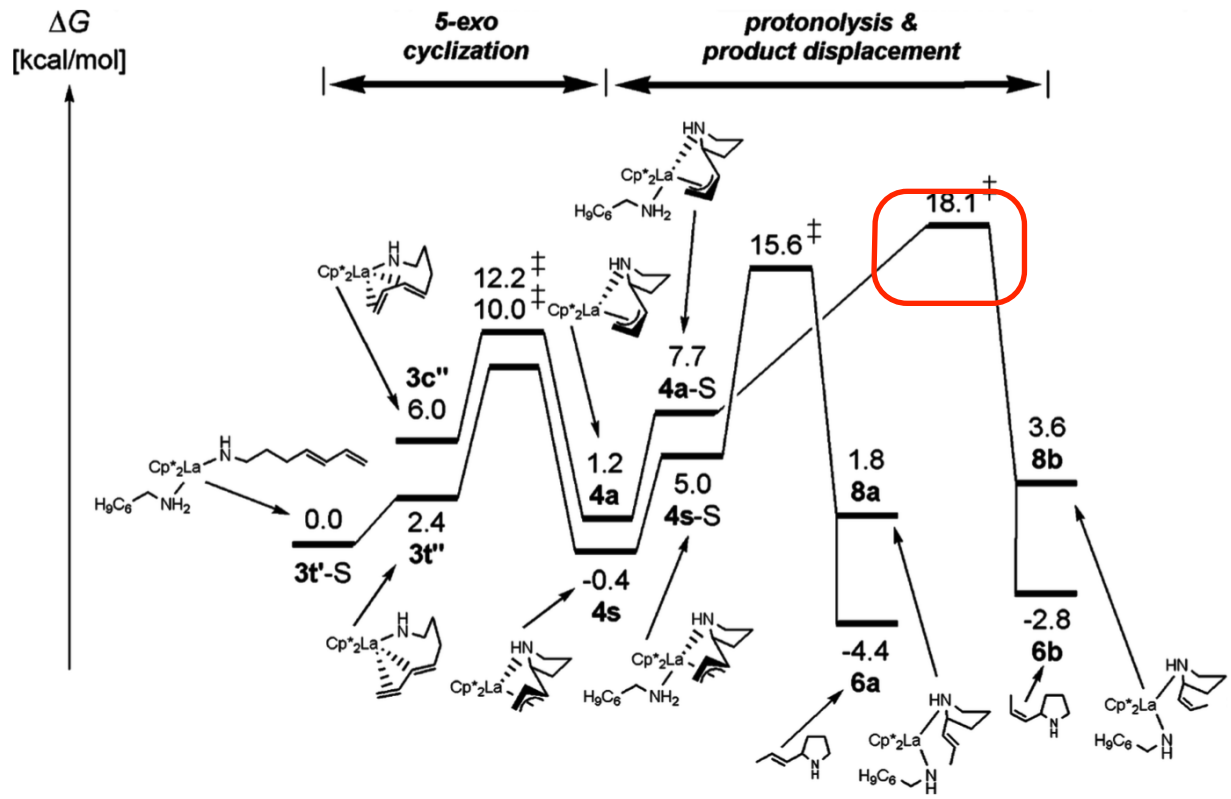


Question 03:
In 1998, Marks showed that his Ln-catalyzed hydroamination chemistry can be used to quickly prepare tricyclic fused ring system. Although we knew it might not be that useful considering the poor functional group tolerance, the success of tricyclic fused ring demonstrates the lifetime of Sm-C species.
(1) Propose a mechanism for the above transformation. Remember that syn attack is the right mechanism and obviously alkyne is more active than alkene in hydroamination.
(2) The reaction is also diastereoselective, please draw the *last* hydroamination step in a chair form and explain why two highlighted hydrogens are *trans* to each other.

Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757.

Lanthanide-catalyzed hydroamination

✓ Calculation does not support the original proposal



Key findings:

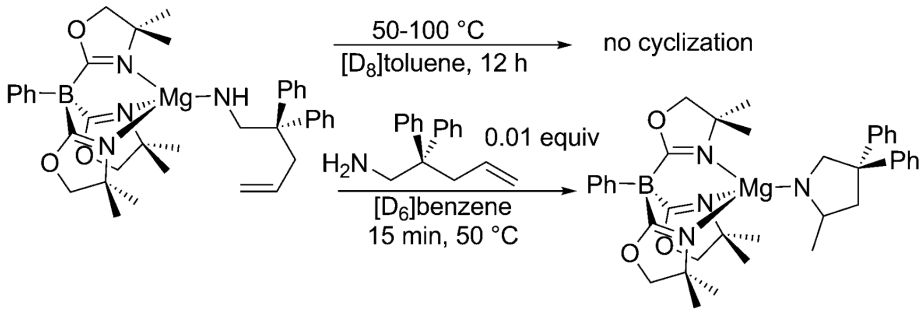
✓ Protonolysis is RDS: primary KIE

✓ $\Delta S^{\neq}$ is relative to resting state: cyclization would result in positive entropy because of releasing binding substrate

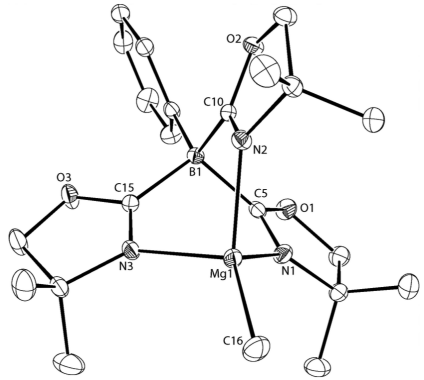
Tobisch, S. *J. Am. Chem. Soc.* **2005**, *127*, 11979.

Lanthanide-catalyzed hydroamination

✓ Experimental result: need additional substrate



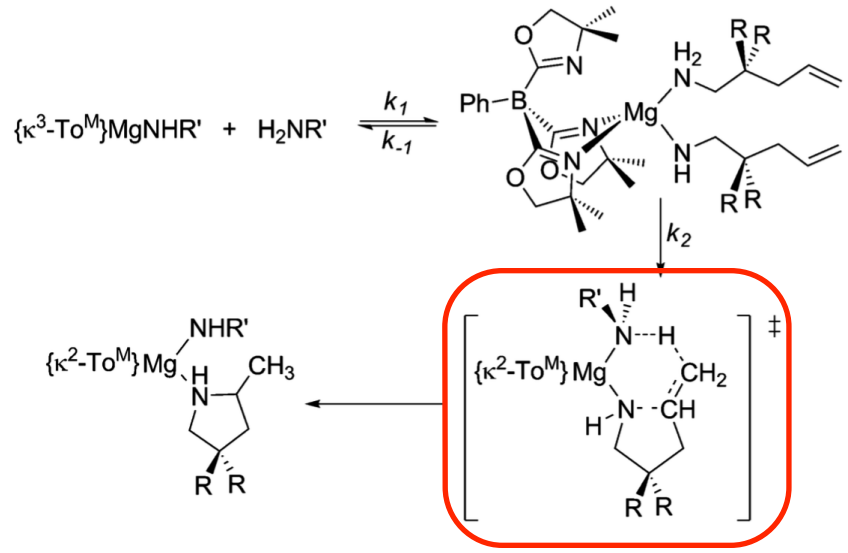
✓ Catalyst precursor structure that they obtained



✓ Kinetic experiment

KIE = 4.6

✓ Their proposed mechanism

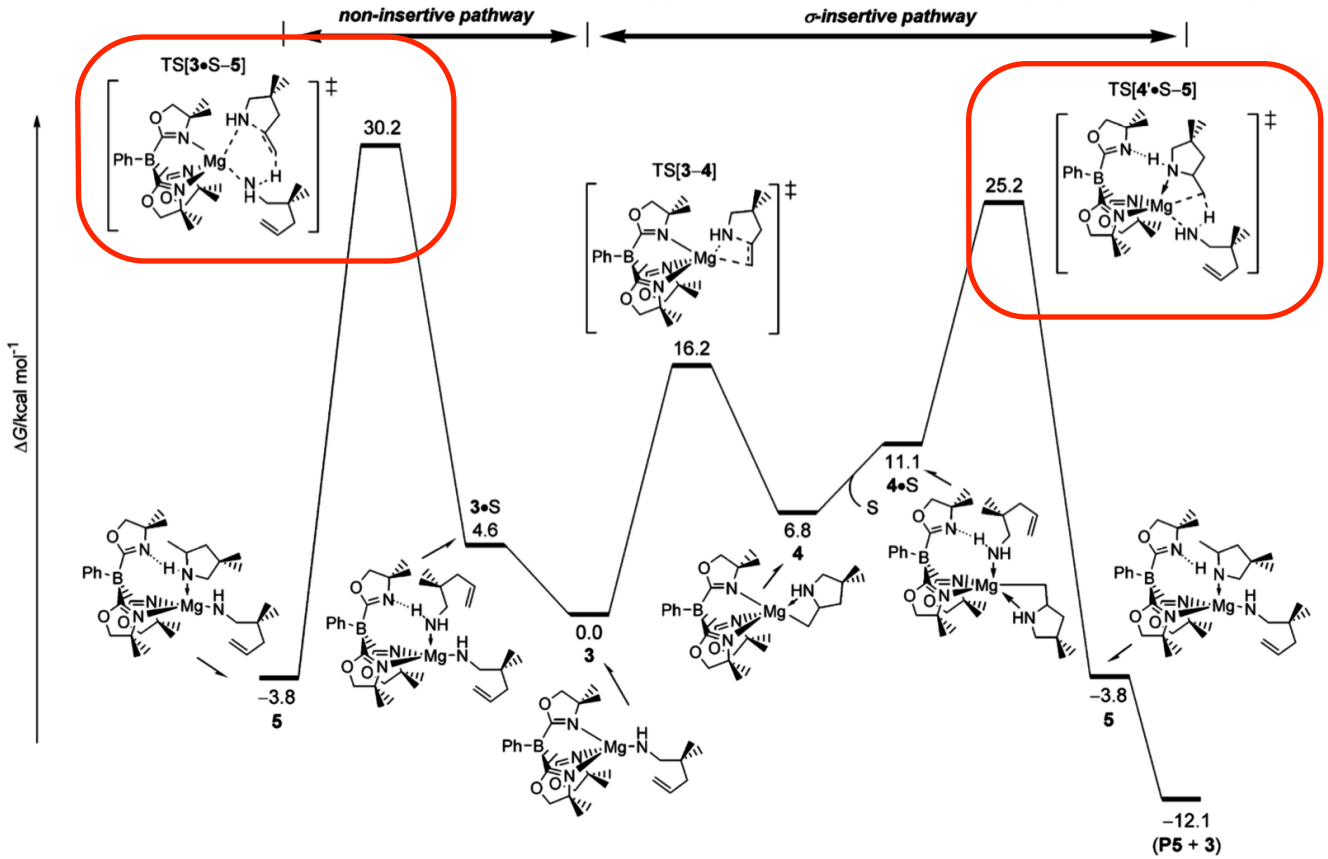


"It seems possible that the mechanism of lanthanide-catalyzed hydroamination occurs through a related six-membered transition state."

Dunne, J. F.; Fulton, D. B.; Ellern, A.; Sadow, A. D. *J. Am. Chem. Soc.* **2010**, *132*, 17680;
Hanley, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 8510.

Lanthanide-catalyzed hydroamination

✓ However, this fancy mechanism is not appreciated by computational chemists



How it explains:

✓ Additional substrate just help protonolysis

✓ Insertion is facile but product is higher in energy

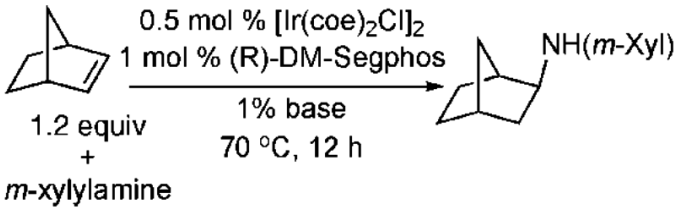
Conclusion:

✓ More evidence is needed

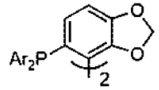
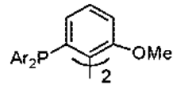
Tobisch, S. *Chem. Eur. J.* **2011**, *17*, 14974.

Iridium-catalyzed hydroamination

✓ Discovery of the reaction



Base	Yield (%)	*ee* (%)
None	6	37
KHMDS	63	96
KNHXyl	61	96

Entry	Ligand	Ar[a]	Dihedral Angle[b]	Yield (%)	*ee* (%)
1	(*R*)-Ar-BINAP	Ph	86°	2	90
2		DM		26	85
3	(*R*)-Ar-Segphos	Ph	67°	19	99
4		DM		63	96
5	(*R*)-Ar-Segphos= 	DTBM		96	97
6	(*R*)-Ar-MeOBIPHEP	Ph	72°	7	96
7		DM		46	93
8	(*R*)-Ar-MeOBIPHEP= 	DTBM		90	97

[a] DM = 3,5-dimethylphenyl; DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl. [b] Values from Jeulin, S.; de Paule, S. D.; Ratovelomanana-Vidal, V.; Genet, J. P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5799.

Key findings:

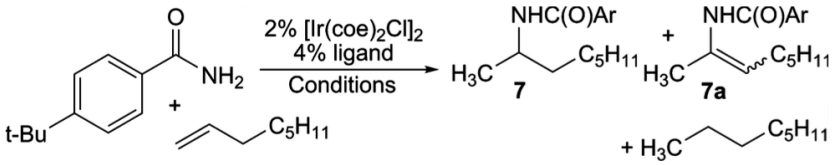
✓ Small bite angle with big steric gives better yield (facilitate insertion?)

✓ Limitation: only strained olefin

Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

Iridium-catalyzed hydroamination

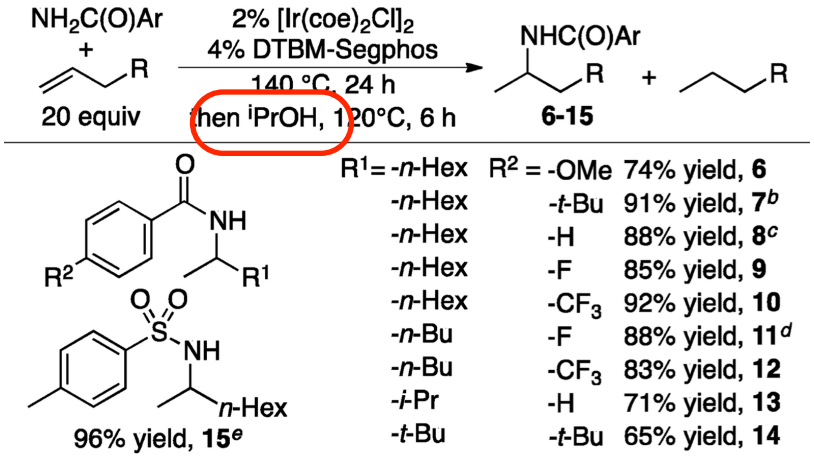
✓ An unstrained version



entry	ligand	equivs of 1-octene	temp (°C)	% yield of 7 + 7a[b]	ratio 7:7a
1	dcpm[c]	5	120	8	12:1
2	(*R*)-DM-BINAP	5	120	2	4.1:1
3	(*R*)-DM-MeOBIPHEP	5	120	12	1.8:1
4	(*S*)-DM-SEGPHOS[d]	5	120	18	2.0:0
5	(*R*)-DTBM-MeOBIPHEP	5	120	28	1.9:1
6	(*S*)-DTBM-SEGPHOS[e]	5	120	44	1.9:1
7	(*S*)-DTBM-SEGPHOS	1	120	13	3.3:1
8	(*S*)-DTBM-SEGPHOS	20	120	74	1.3:1
9	(*S*)-DTBM-SEGPHOS	20	100	47	1.8:1
10	(*S*)-DTBM-SEGPHOS	20	140	96	1.4:1

[a]Reactions were performed neat in 1-octene with 0.1 mmol of 4-*tert*-butylbenzamide. [b]Yields and conversions were determined by GC analysis with dodecane as an internal standard. [c]dcpm = bis-(dicyclohexylphosphino)methane. [d]DM = 3,5-dimethylphenyl. [e]DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl.

✓ Substrate scope



Key finding:

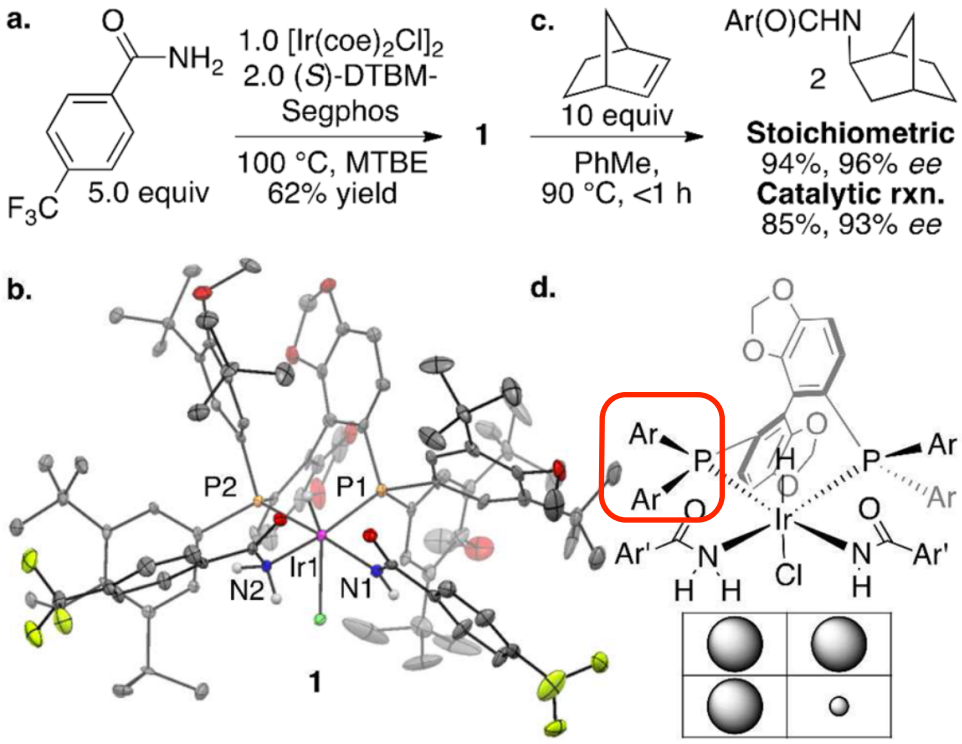
✓ Small bite angle with big steric gives better yield

✓ Work up with ^{i}PrOH

Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 11960.

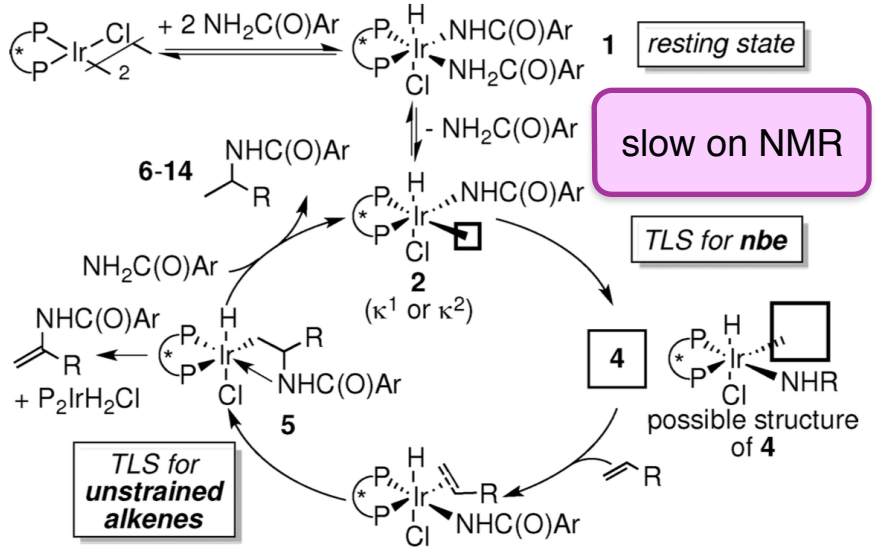
Iridium-catalyzed hydroamination

✓ Mechanism study: isolation of resting state



The ligand is actually asymmetric in terms of steric

✓ Proposed mechanism



Hint in ligand design (maybe wrong):

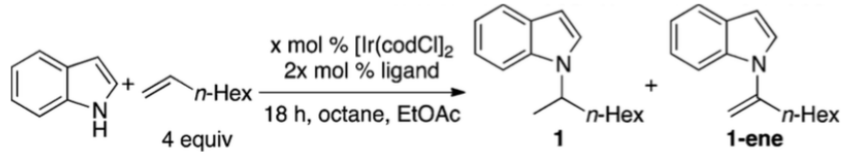
✓ Asymmetric steric might help insertion

✓ Axial steric that helps insertion but allows binding is good

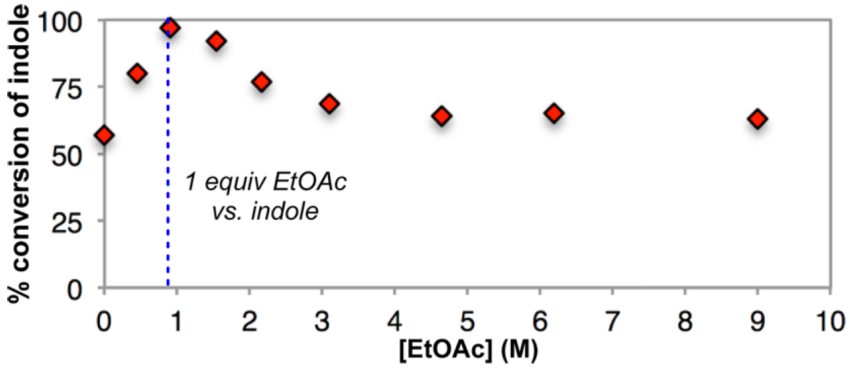
Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 11960.

Iridium-catalyzed hydroamination

✓ Another unstrained version



entry	ligand	*x* mol % $[Ir(cod)Cl]_2$	temp (°C)	EtOAc (equiv)	% **1**	% **1-ene**	**1/1-ene**
1	(*S*)-SEGPHOS	1	150	0	9	7	1.3
2	(*S*)-DM-SEGPHOS	1	150	0	15	5	3.0
3	(*S*)-DTBM-SEGPHOS	1	150	0	74[b]	23	3.2
4	(*S*)-DTBM-SEGPHOS	2	120	0	72	20	3.6
5	(*S*)-DTBM-SEGPHOS	2	100	0	45	11	4.1
6	(*S*)-DTBM-SEGPHOS	2	100	10	50	13	3.8
7	(*S*)-DTBM-SEGPHOS	2	100	5	52	13	4.0
8	**(*S*)-DTBM-SEGPHOS**	**2**	**100**	**1**	**76**[c]	**18**	**4.2**
9	(*S*)-DTBM-SEGPHOS	2	100	0.5	63	16	3.9
10[d]	(*S*)-DTBM-SEGPHOS	4	80	1	65[e]	12	5.4

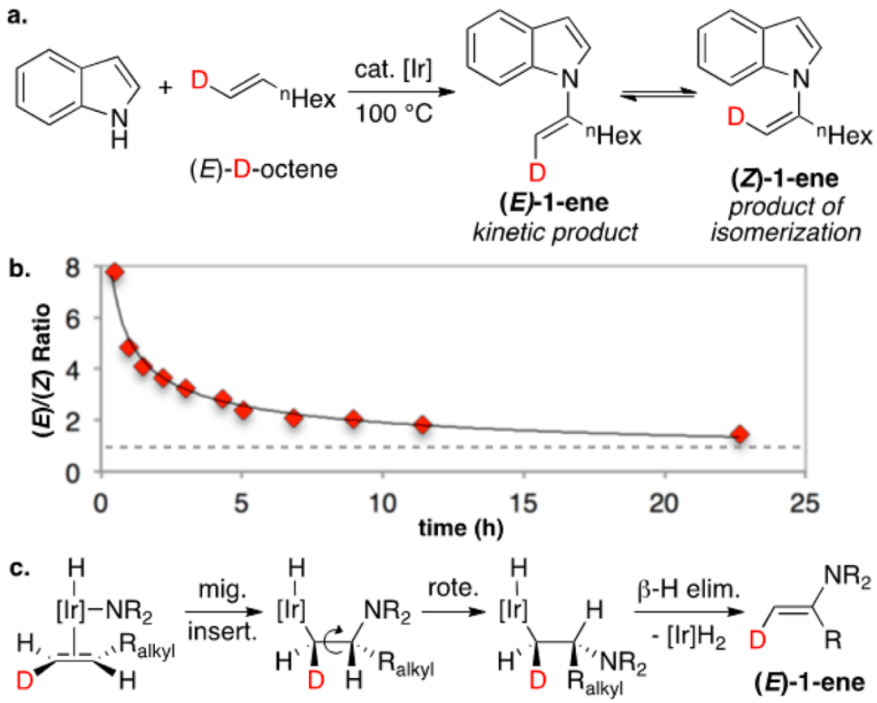


Unclear role of EtOAc

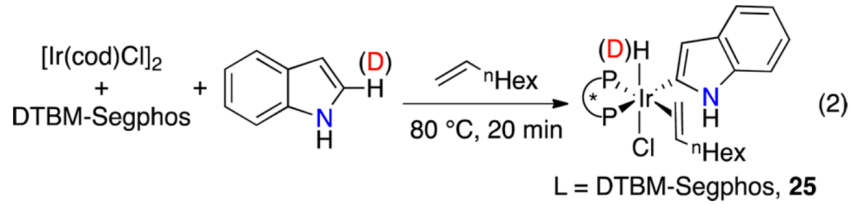
Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 3200.

Iridium-catalyzed hydroamination

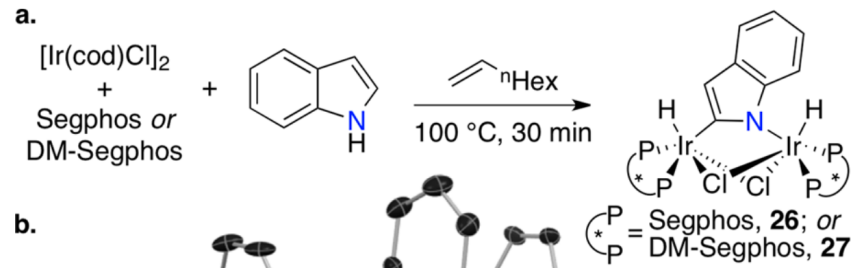
✓ Syn or anti attack?

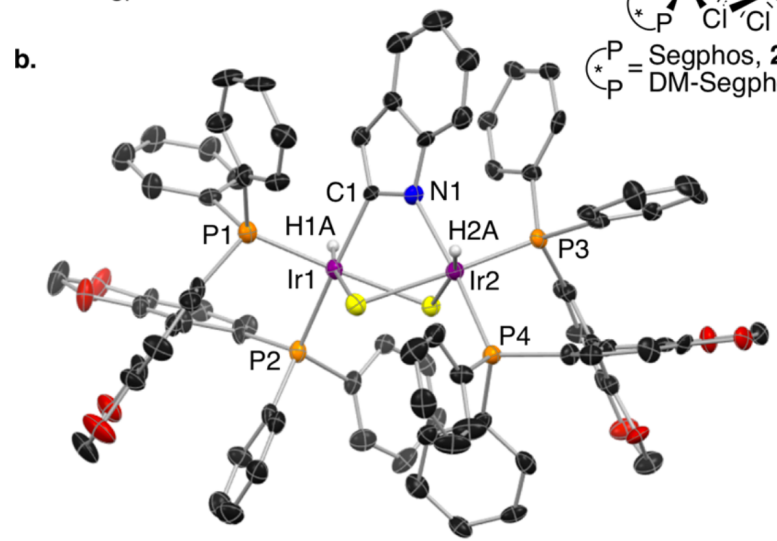


✓ Resting state



(2)





Conclusions:

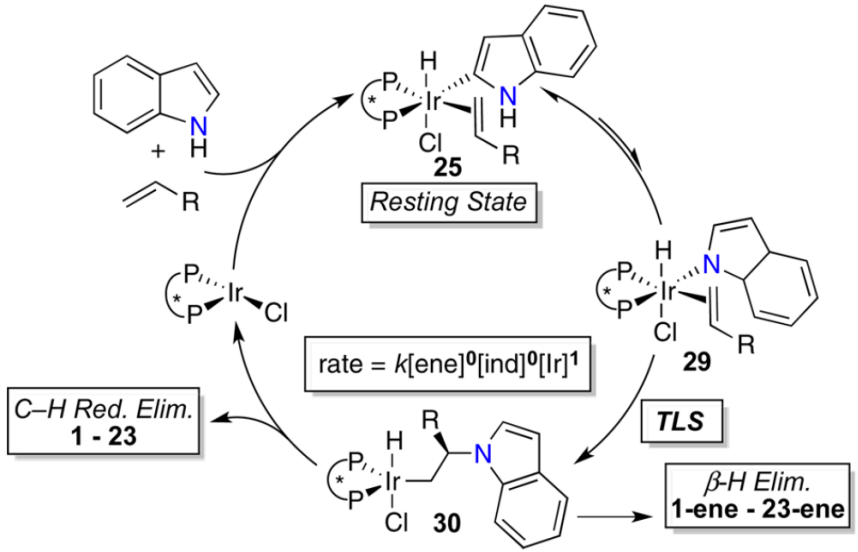
✓ Syn attack is the mechanism

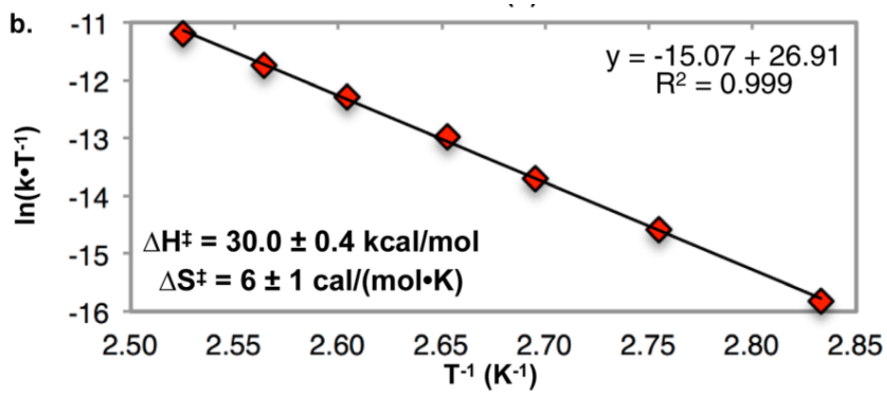
✓ C-H activation is resting state

Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 3200.

Iridium-catalyzed hydroamination

✓ Proposed mechanism





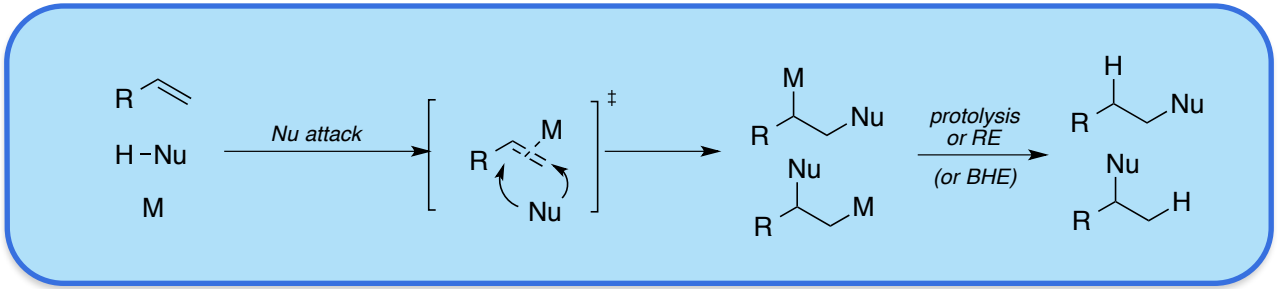
Key findings:

- ✓ KIE = 1.7, a little bit bigger than secondary KIE (my understanding is a result of thermodynamic isotope effect: Ir-H vs N-H)
- ✓ Rate law: zero order on substrate
- ✓ $\Delta H^{\neq}$ = 30.0 ± 0.4 kcal/mol
- ✓ $\Delta S^{\neq}$ = 6 ± 1 cal/mol˙T
- ✓ Preference to insert Ir-N over Ir-C is confirmed by DFT

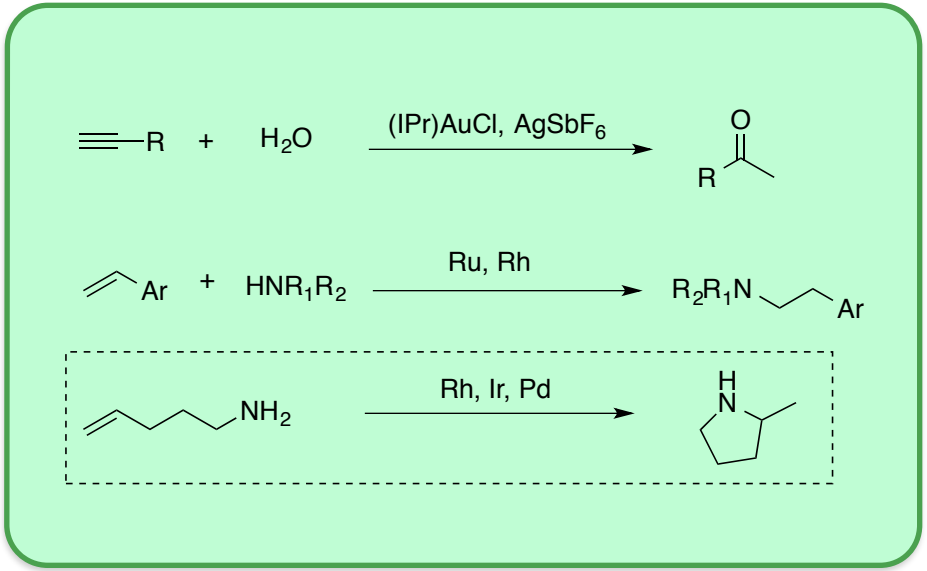
Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 3200.

Overview of Nu attack pathway

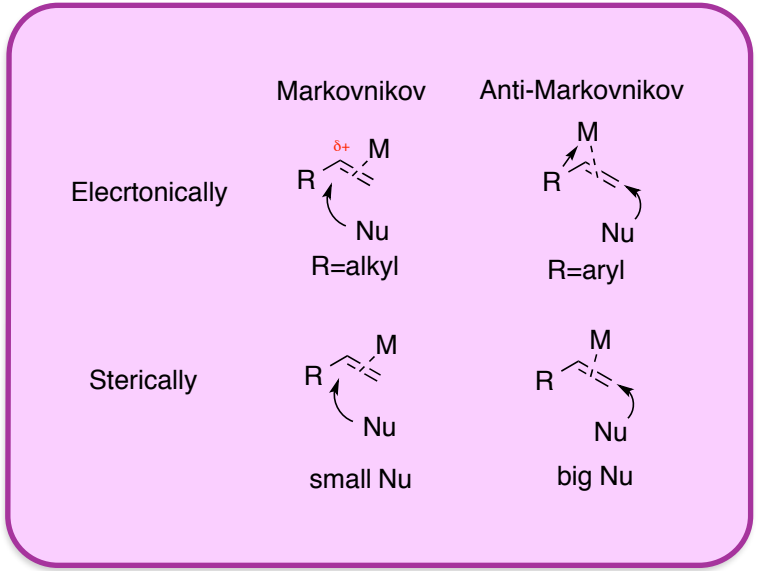
✓ Simplified reaction mechanism



✓ Three examples

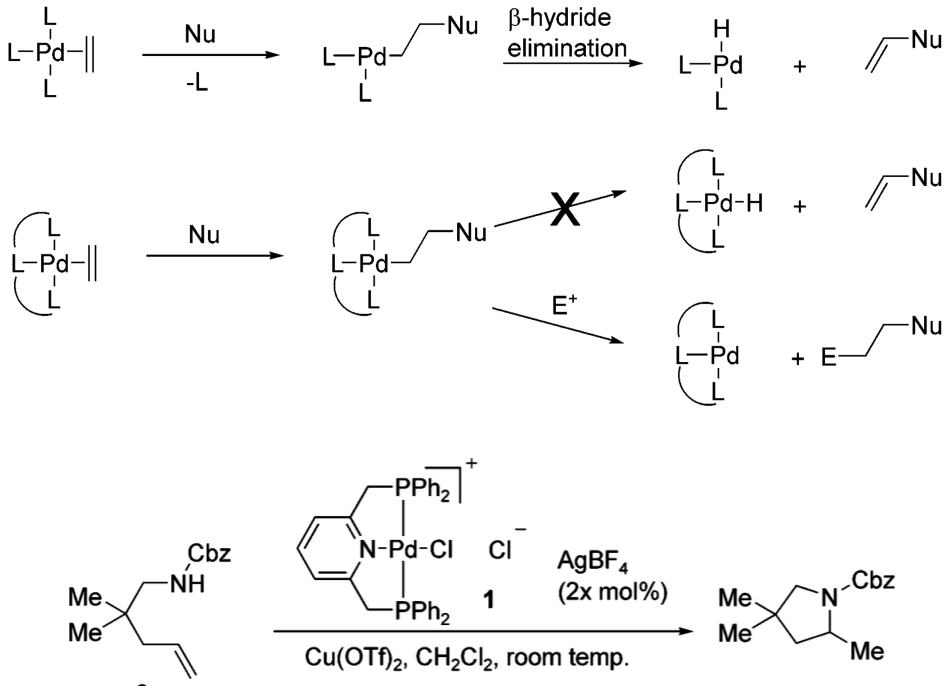


✓ Regioselectivity

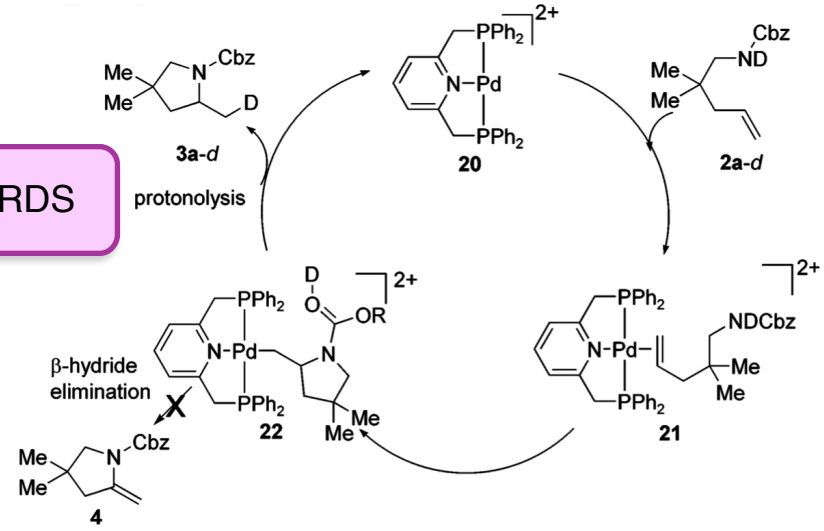


Palladium-catalyzed hydroamination

✓ Tridentate ligand avoids open coordination site



✓ Proposed mechanism



Key findings:

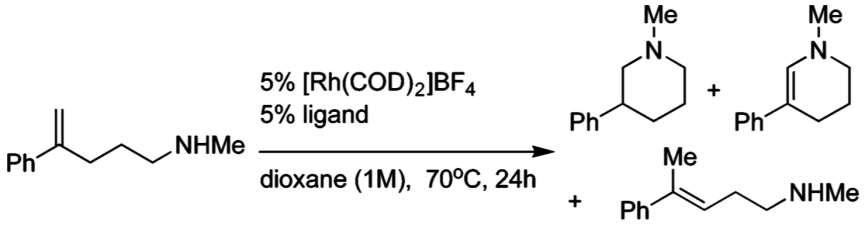
✓ At low temperature and with acid, cyclization is reversible

✓ Acid promotes the reaction

Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246;
Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786.

Rhodium-catalyzed hydroamination

✓ Anti-Markovnikov selectivity

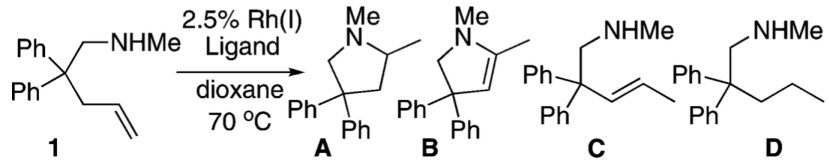


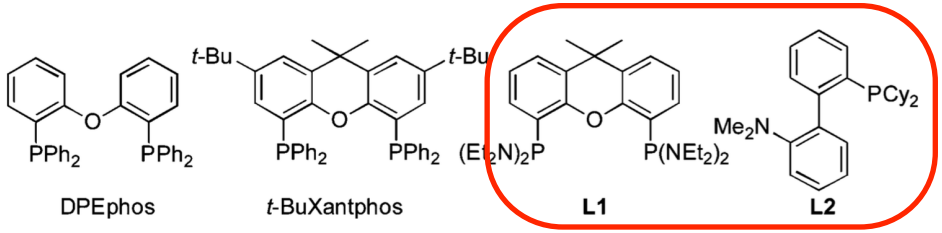
entry	ligand	yields: amine[a] (%)	enamine[b] (%)	isomerized olefin[b] (%)
1	DPEphos[c]	10	12	10
2	BINAP[d]	14	3	*i*
3	DPPF[e]	44	16	trace
4	Xantphos[g]	trace	5	41
5	DPPP[h]	*i*	*i*	*i*
6	DPPB[f]	84	7	trace
7	PPh_3	*i*	23	58
8	$PEtPh_2$	*i*	16	33

✓ It seems that the reaction outcomes depends highly on the substrate

✓ No further comment on this

✓ Markovnikov selectivity



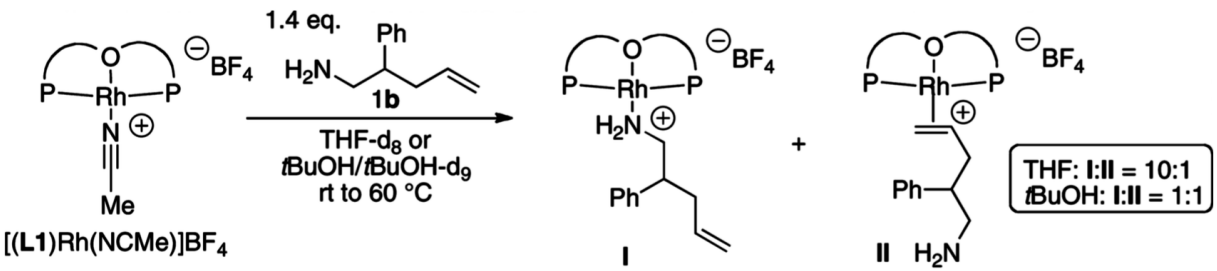


entry	catalyst	ligand[b]	%A[c]	%B[c]	%C[c]	%D[c]
1	$[Rh(COD)_2]BF_4$	DPEphos	0	0	93	0
2	$[Rh(COD)_2]BF_4$	DPPB	10	40	10	30
3	$[Rh(COD)_2]BF_4$	PPh_3	0	0	92	0
4	$[Rh(COD)_2]BF_4$	PCy_3	0	30	30	30
5	$[Rh(COD)_2]BF_4$	DPPF	20	30	10	30
6	$[Rh(COD)_2]BF_4$	*t*-BuXantphos	60	10	10	10
7	$[Rh(COD)_2]BF_4$	L1	86	0	0	0
8	$[Rh(COD)_2]BF_4$	L2	93	0	0	0
9	$[Rh(MeCN)_2(COD)]BF_4$	L2	92	0	0	0
10[d]	$[Rh(COE)_2Cl]_2$	L2	28	0	0	0
11[d]	$[Rh(COD)Cl]_2$	L2	9	0	0	0
12	5% $HBF_4 \cdot OEt_2$	L2	0	0	0	0

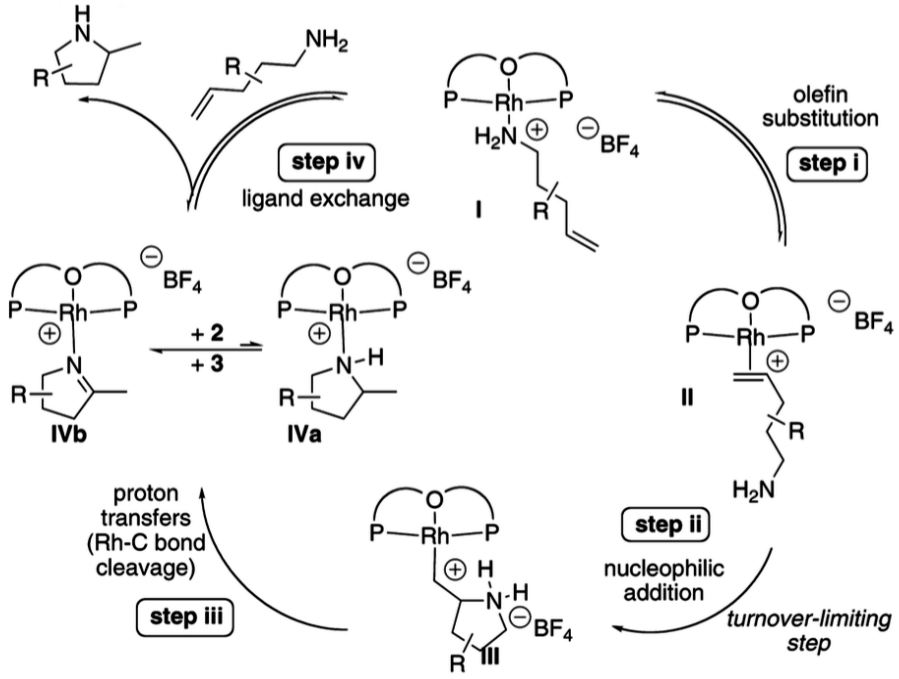
Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042;
Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570.

Rhodium-catalyzed hydroamination

✓ Determination of the resting state (by ^{31}P NMR)



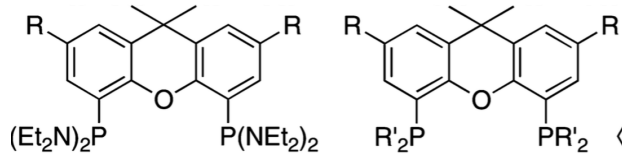
✓ Proposed mechanism



✓ KIE experiment

KIE = 1.16

✓ Ligand comparison



L1; R = *t*Bu
L1'; R = H

L2; R = *t*Bu; R' = Ph
L2'; R = H; R' = Ph
L3; R = H; R' = Cy

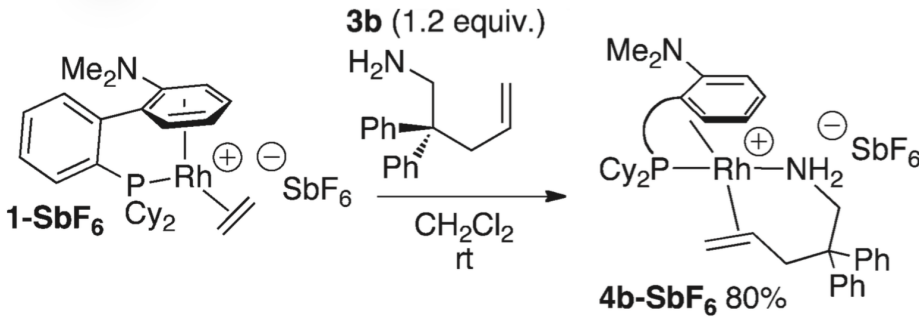
Key findings:

- ✓ Small KIE means no breaking of N-H at RDS, so portionless is not RDS
- ✓ Tridentate ligand design
- ✓ The nitrogen on phosphine might act as a proton shuttle

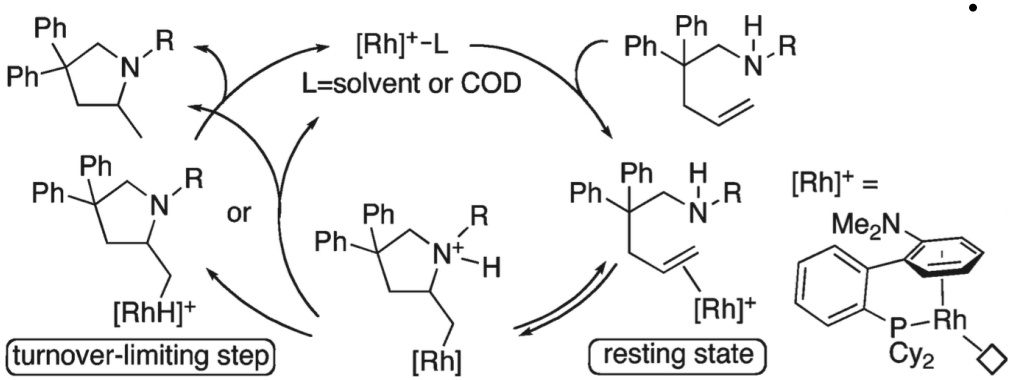
Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 13813.

Rhodium-catalyzed hydroamination

✓ Determination of the resting state (by X-Ray)



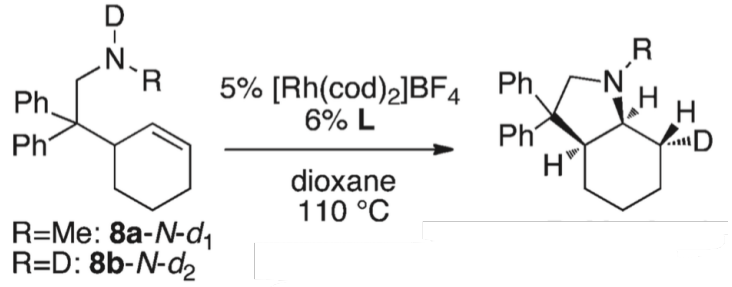
✓ Proposed mechanism



✓ KIE experiment

KIE = 2.5

✓ Anti attack



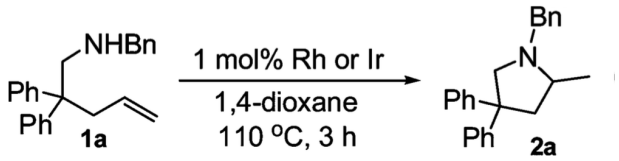
Key findings:

- ✓ Primary KIE means breaking of N-H at RDS
- ✓ Ligand with no open coordination site
- ✓ Different ligands have different mechanisms!

Liu, Z.; Yamamichi, H.; Madrahimov, S. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2772.

[Ir(cod)]$_2$-catalyzed hydroamination

✓ Screening the metal source



entry	catalyst precursor	conversion to **2a**[b]
1−1	$[Ir(COD)Cl]_2$	>95
1−2	$[Ir(COE)_2Cl]_2$	10
1−3	$[Ir(COD)OMe]_2$	7
1−4	$[(\eta^5\text{-}C_5Me_5)IrCl_2]_2$	<5
1−5	$[Rh(COD)Cl]_2$	<5
1−6	$[Ir(COD)_2]BF_4$	<5
1−7	$[Ir(MeCN)_2(COD)]BF_4$	28[c]
1−8	$[Ir(COD)PCy_3(py)]PF_6$	10[c]
1−9	none	<5

Key findings:

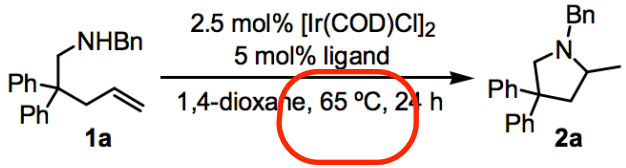
✓ The metal alone gives good yield

✓ Addition of NnBu4Cl, LiOTf, AgBF4, or LiB(C6F5)4 · 2.5OEt2 all give worse yield

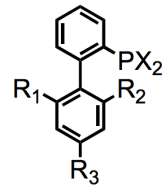
Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413.

[Ir(cod)]$_2$-catalyzed hydroamination

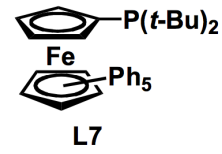
✓ Screening the ligand



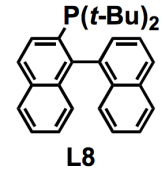
Entry	Ligand	% Conversion[b] (% Yield 2a)
S2-1	-	60
S2-2	2,2'-bipyridine	<5
S2-3	Terpyridine	<5
S2-4	PPh_3	<5
S2-5	PCy_3	34
S2-6	P(*t*-Bu)$_3$	62
S2-7	DPPE[c]	>95 (<5)
S2-8	DCPE[d]	90 (<5)
S2-9	DPPB[e]	<5
S2-10	Xantphos[f]	<5
S2-11	DPEphos[g]	<5
S2-12	DPPF[h]	>95 (<5)
S2-13	DiPPF[i]	45 (<5)
S2-14	**L1**	<5
S2-15	**L2**	>95
S2-16	**L3**	7
S2-17	**L4**	>95
S2-18	**L5**	6
S2-19	**L6**	58
S2-20	**L7**	>95
S2-21	**L8**	>95



X= Cy, R^1= R^2= R^3= H **L1**
X= *t*-Bu, R^1= R^2= R^3= H **L2**
X= Cy, R^1= NMe_2, R^2= R^3= H **L3**
X= *t*-Bu, R^1= NMe_2, R^2= R^3= H **L4**
X= Cy, R^1= R^2= R^3= *i*-Pr **L5**
X= *t*-Bu, R^1= R^2= R^3= *i*-Pr **L6**



L7



L8

Key findings:

✓ Some ligands did improve reactivity

✓ But, concentration of ligands is an inverse order to the rate

✓ The effect of ligand is to stabilize the Ir center, and the real catalyst is [Ir(cod)Cl]$_2$

Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413.

[Ir(cod)]$_2$-catalyzed hydroamination

✓ Kinetic studies

Key findings:

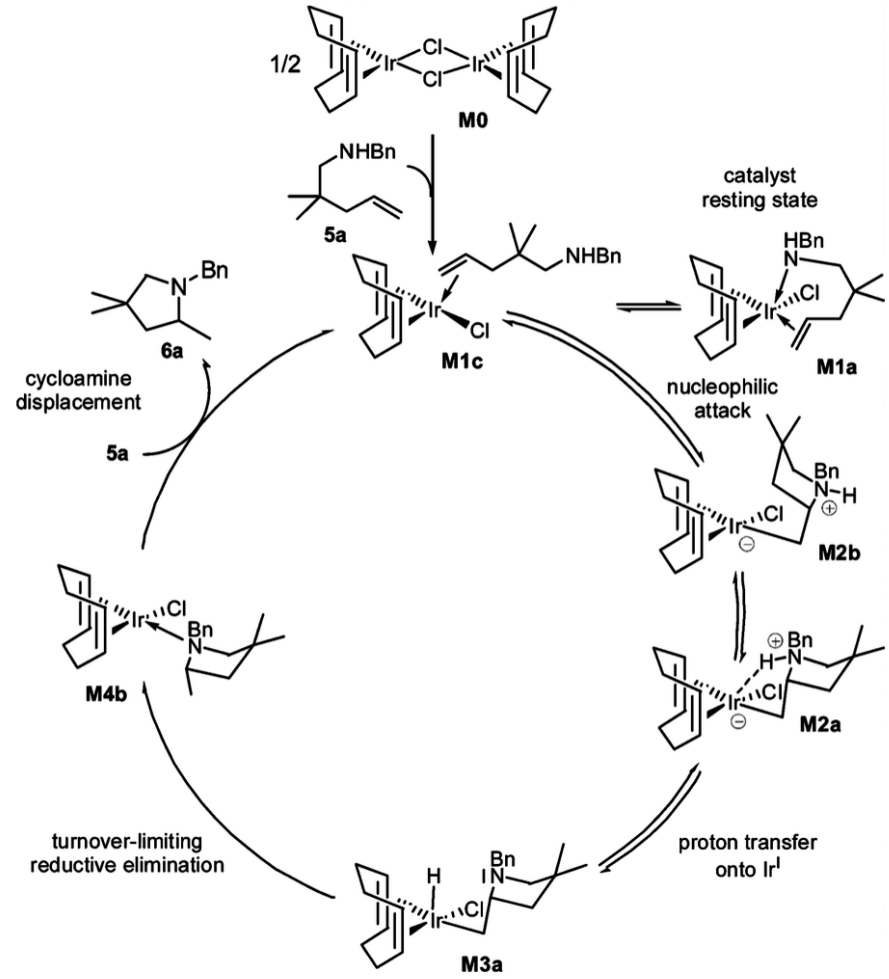
- ✓ KIE = 3.4
- ✓ Rate law: first order on [Ir], monomeric
- ✓ $\Delta H^{\neq}$ = 20.9 ± 0.3 kcal/mol, $\Delta S^{\neq}$ = -23.1± 0.8 cal/mol˙T, $\Delta G^{\neq}$ = 21.6 ± 0.3 kcal/mol
- ✓ Hammett plot: electron-rich amine is faster

✓ DFT studies

Key findings:

- ✓ Oxidative addition of N-H is inaccessible, 38.3 kcal/mol
- ✓ Calc'd $\Delta G^{\neq}$ = 24.6 kcal/mol
- ✓ Proton transfers to Ir then RE, instead of direct protonolysis
- ✓ Higly ordered RE is RDS

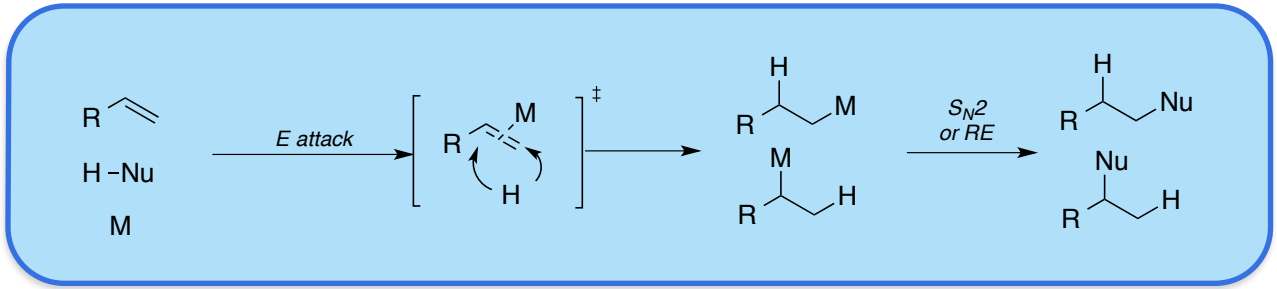
✓ Proposed Mechanism



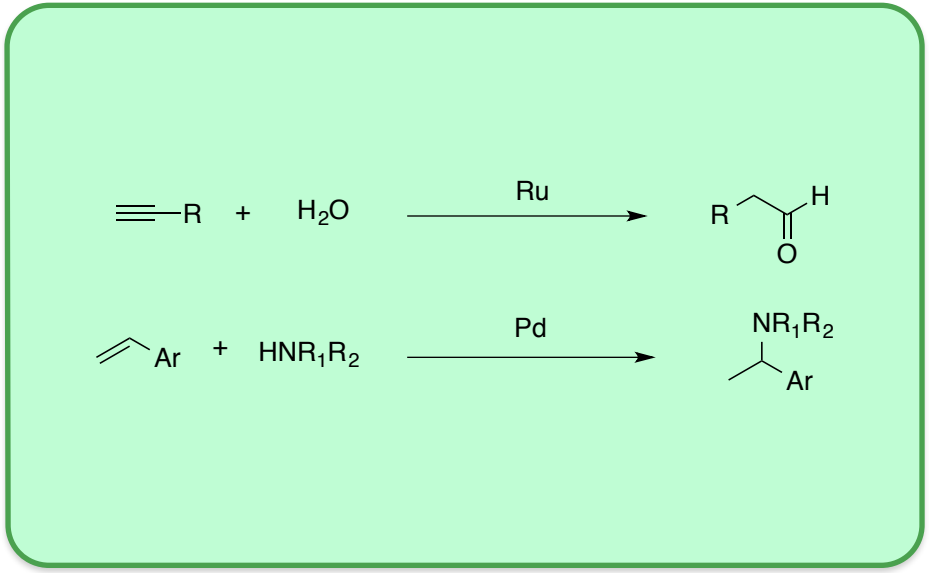
Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413.

Overview of E attack pathway

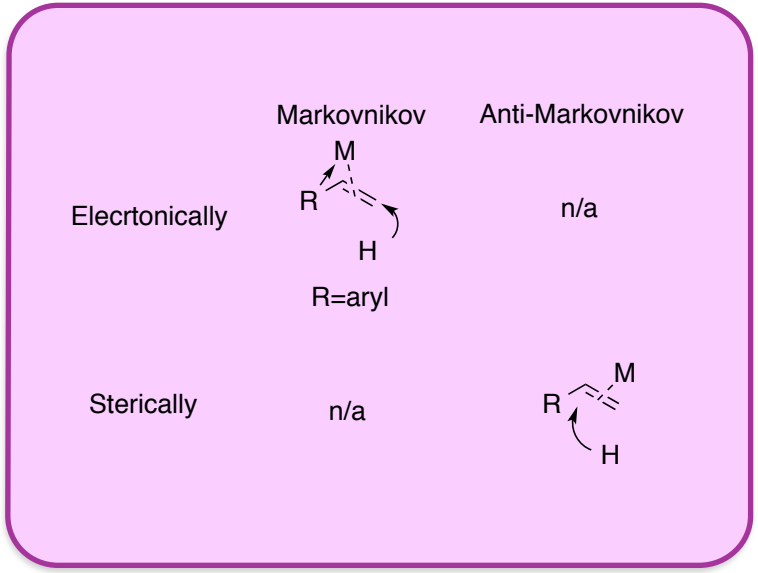
✓ Simplified reaction mechanism



✓ Two examples

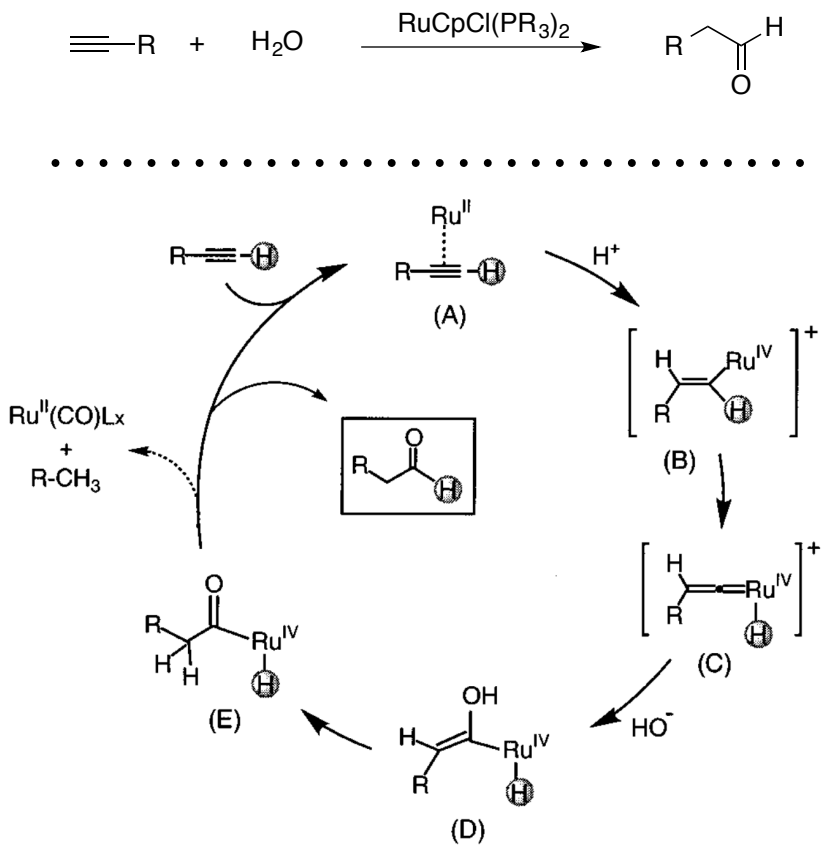


✓ Regioselectivity

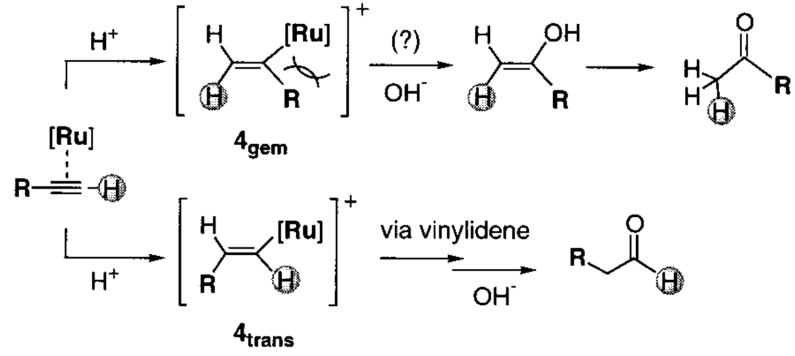


Ruthenium-catalyzed alkyne hydration

✓ The reaction mechanism



✓ The rational for selectivity



Key findings:

✓ Selectivity is dictated by the first step: irreversible protonation

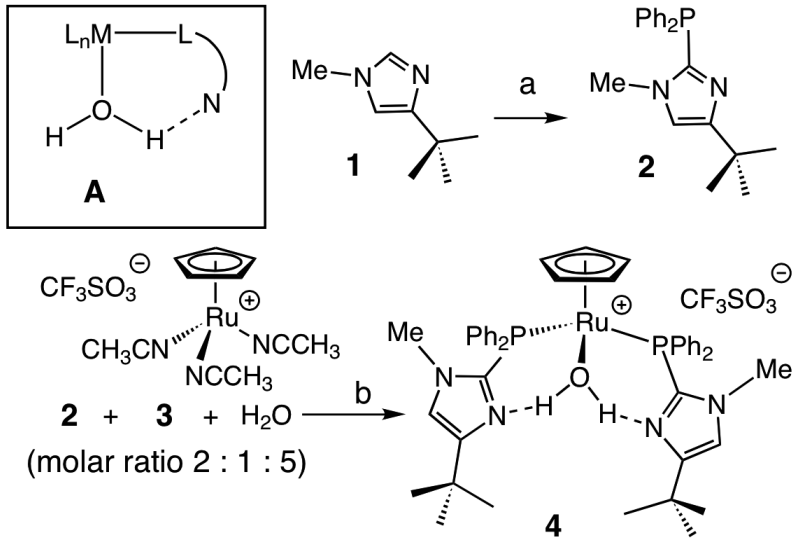
✓ Electronically, Markovnikov favors

✓ Selectivity comes from steric concern

Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11917.

Ruthenium-catalyzed alkyne hydration

✓ Proton shuttle strategy



Key finding:

✓ The imidazole functions as a proton shuttle that speeds up the reaction

✓ Substrate scope

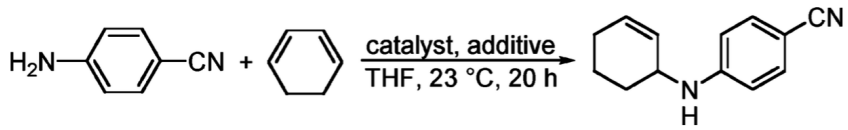
entry	alkyne	aldehyde yields 1 h	3 h	later (time)
1	$CH_3(CH_2)_6C{\equiv}CH$	55.0	**99.9**	nd
2[b]	$CH_3(CH_2)_6C{\equiv}CH$	nd	30.2[b]	**98.6** (48 h)
3	$C_6H_5C{\equiv}CH$	11.8	33.1	**99.8** (20 h)
4	4-$MeOC_6H_4C{\equiv}CH$	14.0	42.7	**99.8** (24 h)
5	4-$O_2NC_6H_4C{\equiv}CH$	0.31[d]	nd	nd
6	$N{\equiv}C(CH_2)_3C{\equiv}CH$	3.6	12.0	**97.8** (96 h)
7	$HC{\equiv}C(CH_2)_4C{\equiv}CH$	47.7[c]	nd	**71.2**[c] (8 h)
8	$THPOCH_2C{\equiv}CH$	26.1	76.2	**98.0** (9 h)
9	$TsNHCH_2CH_2C{\equiv}CH$	nd	97.0[e]	**98.1**[e] (6 h)
10	$CH_3C{\equiv}CSi(CH_3)_3$	6.7[f]	24.3[f]	**100**[f] (66 h)
11	$(CH_3)_2C(OH)C{\equiv}CH$	nd	nd	**80.7**[g] (168 h)
12	1-ethynylcyclohexene	nd	nd	**41.0**[g,h](168 h)

[a] Unless otherwise specified, using **6** (2 mol %), H_2O (5 equiv), acetone, 70 °C, initial alkyne concentration 0.50 M. [b] Room-temperature reaction with 5 mol % catalyst; 30.2% after 5.5 h. [c] Yields of dialdehyde and ynal (double and single hydration products) at 1 and 8 h = 27.9 + 19.8 and 51.6 + 19.6%, respectively. [d] In addition, 2.1% of corresponding alkane and deactivated catalyst. No further reaction seen. [e] Product formed as 1:8 mixture of aldehyde and its cyclized form (*N*-tosyl-2-hydroxypyrrolidine). [f] Product is propanal. [g] Room-temperature reaction. [h] 34.2 and 6.9% β,γ- and isomerized α,β-unsaturated aldehydes, respectively.

Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 4323;
Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232.

Palladium-catalyzed hydroamination

✓ Screening of the ligand



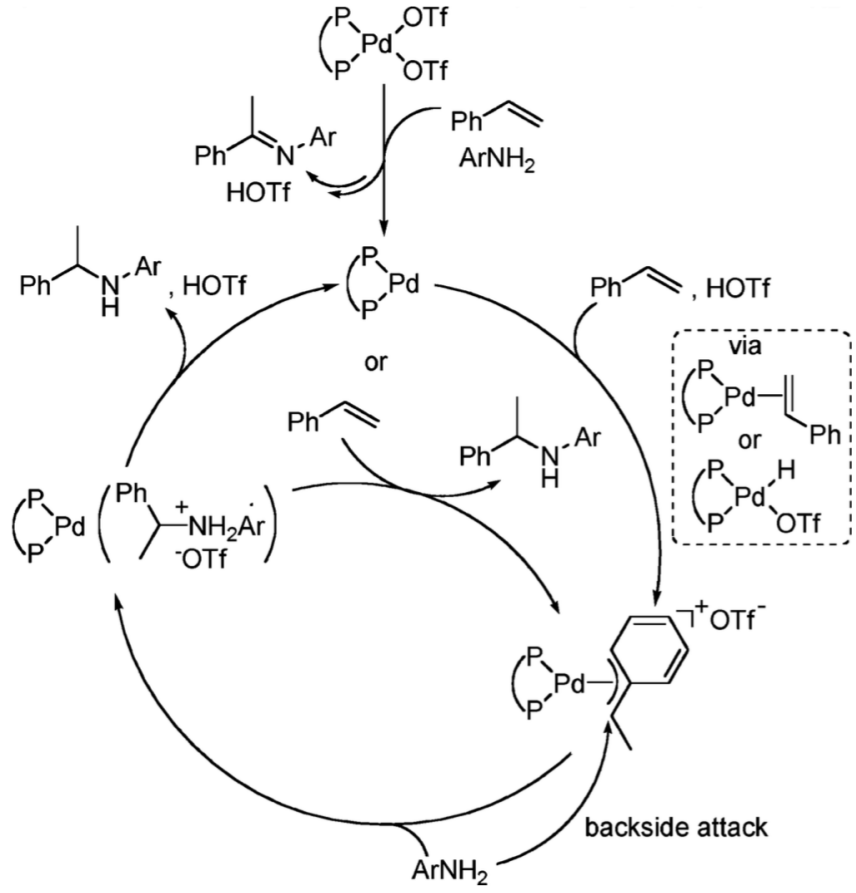
entry	Pd precursor	ligand	additive	yield[b]
1	1% [Pd(η^3-allyl)Cl]$_2$	2% Xantphos	-	99
2	1% [Pd(η^3-allyl)Cl]$_2$	2% Xantphos	2% AgOTF	3
3	2% [(Xantphos)Pd-(η^3-allyl)]OTf	-	-	2
4	1% [Pd(η^3-allyl)Cl]$_2$	2% Xantphos	10% HCl	87
5	1% [Pd(η^3-allyl)Cl]$_2$	2% DPEphos	-	7
6	1% [Pd(η^3-allyl)Cl]$_2$	2% DPPF	-	2
7	1% [Pd(η^3-allyl)Cl]$_2$	2% BINAP	-	0
8	1% [Pd(η^3-allyl)Cl]$_2$	2% DPPPent	-	0
9	1% [Pd(η^3-allyl)Cl]$_2$	4% PPh_3	-	0
10	2% $Pd(PPh_3)_4$	-	10% TFA	22
11[c]	2% $Pd(PPh_3)_4$	-	10% TFA	11
12	-	-	10% TfOH	0
13	-	-	10% HBF_4[d]	0
14	-	-	10% HCl[e]	0

Key findings:

✓ Resting state is Pd-allyl complex

✓ Large bite-angle facilitates Nu attack (unclear reason)

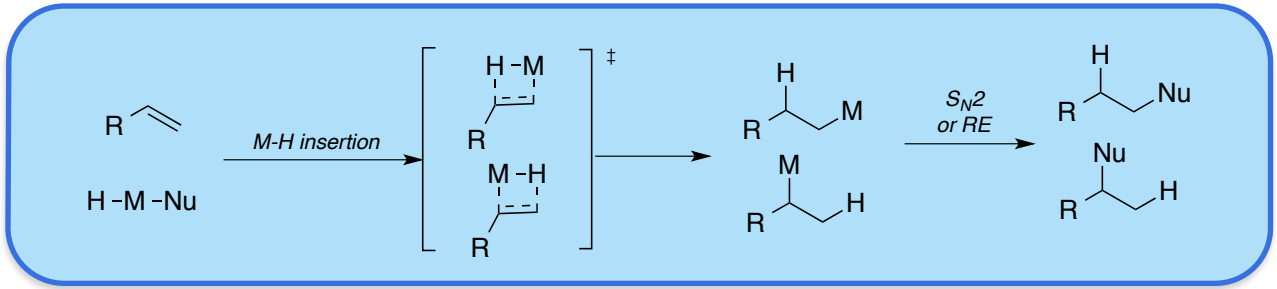
✓ Proposed mechanism



Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828.

Overview of M-H insertion pathway

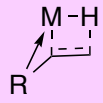
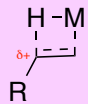
✓ Simplified reaction mechanism



✓ No literature example

Oops… 404 not found…

✓ Regioselectivity

	Markovnikov	Anti-Markovnikov
Elecrtonically	 R=aryl	 R=alkyl
Sterically	n/a	

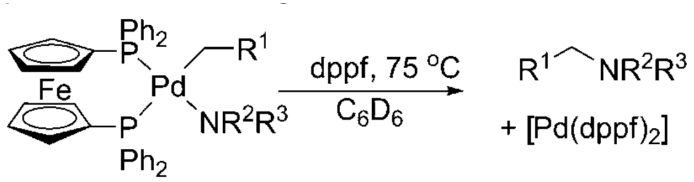
sp³ C-N reductive elimination?

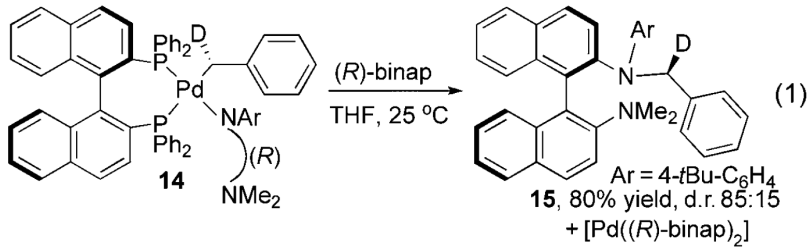
✓ Two challenges

M-H insertion over M-N insertion

C-N reductive elimination

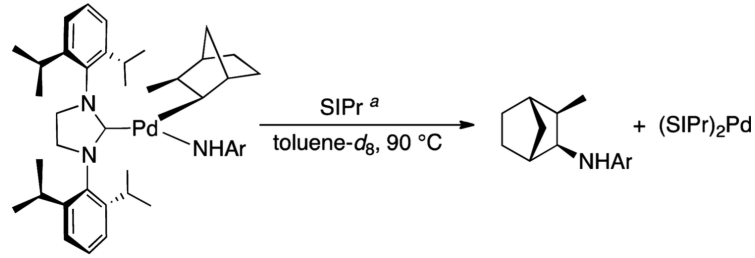
✓ Stepwise reductive elimination (inversion)



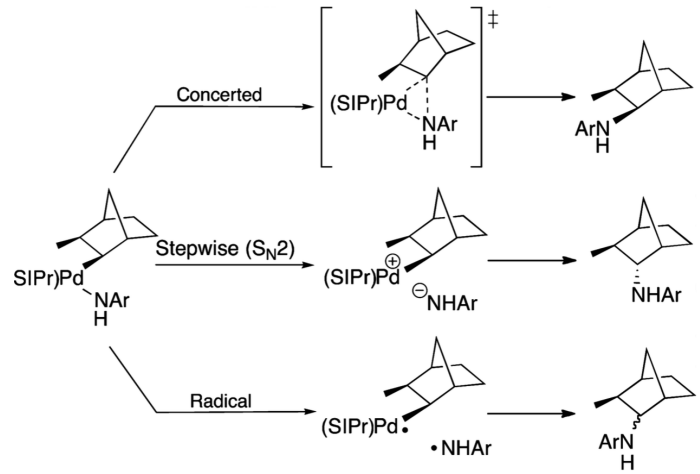


Possible but challenging

✓ Concerted reductive elimination (retention)



entry	complex	yield[b] (%)	k_{obs} ($\times 10^{-4}$ s^{-1})
1	**2a**; Ar = 4-$CH_3C_6H_4$	85	11 ± 1
2	**2b**; Ar = 4-$OCH_3C_6H_4$	77	18
3	**2c**; Ar = 3-CF_3C_6H	70	1.2 ± 0.1
4	**2d**; Ar = 2-$CH_3C_6H_4$	79	2.4 ± 0.2
5	**2e**; Ar = 2,6-$(CH_3)_2C_6H_3$	84	7.2 ± 0.5
6	**2f**; Ar = 2,4-$(CH_3)_2C_6H_3$	95	4.8



Marquard, S. L.; Rosenfeld, D. C.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2009**, *49*, 793;
Hanley, P. S.; Marquard, S. L.; Cundari, T. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 15281.

Summary

Reaction	Metal	Mechanism	RDS	Selectivity	Scope
Wacker oxidation	Pd	Pd-O insertion	Pd-O insertion	M or AM	AM: styrene or PG
Hydroamination	Ln, Cp	Ln-N insertion	protonolysis?	M	intra
Hydroamination	Ir, DTBM-Segphos	Ir-N insertion	Ir-N insertion	M	hexene, indole
Hydroamination	Ru, DPPPent	Nu attack	Nu attack	AM	styrene
Hydroamination	Pd, PNP ligand	Nu attack	protonolysis	M	intra
Hydroamination	Rh, Xantphos	Nu attack	protonolysis	M	intra
Hydroamination	Rh, P-Ar ligand	Nu attack	Nu attack	M	intra
Hydroamination	$[Ir(cod)Cl]_2$	Nu attack	reductive elimination	M	intra
Alkyne hydration	Ru, PN ligand	H^+ attack	unclear	AM	alkyl alkyne is better
Hydroamination	Pd, Xantphos	H^+ attack	Nu attack	M	styrene

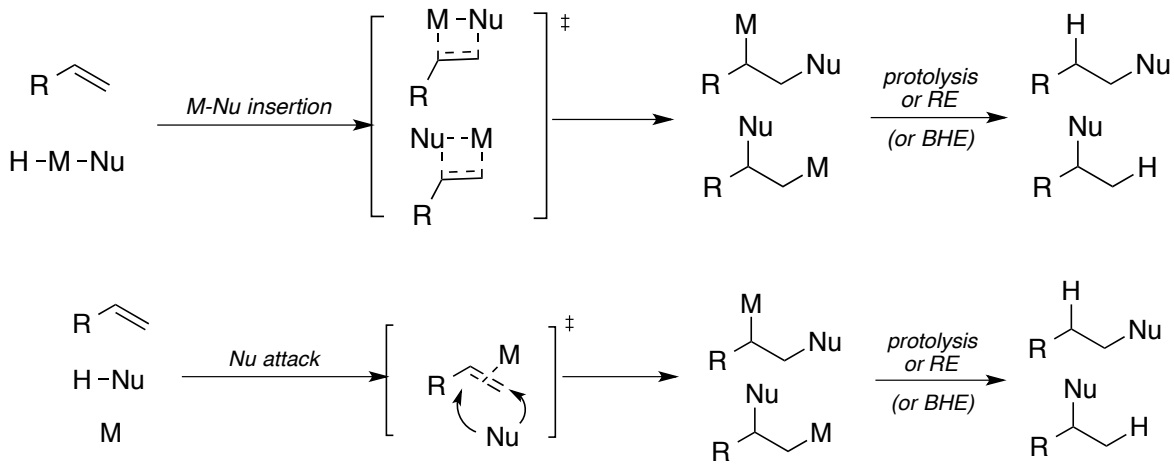
Some (misleading?) clues on ligand choice

✓ Migratory insertion mechanism

Open site for olefin coordination
Proper steric (axial?)
Bidentate is better?
Asymmetric ligand (electronic, steric)

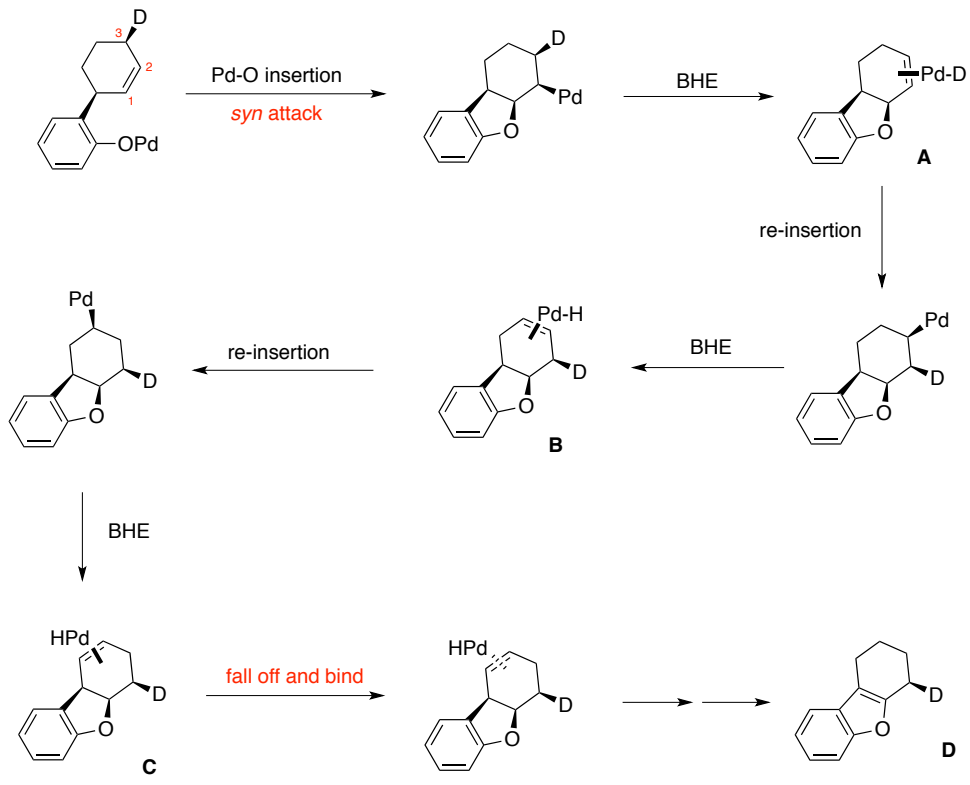
✓ Nucleophilic attack mechanism

No available site for coordination
Lewis acid/base moiety
Bite angle is important



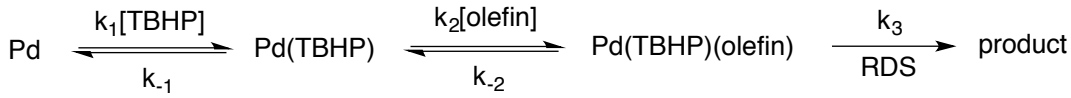
Take a bus and meet our interesting neighbor!

Answer to Question 1



- ✓ All of them come from syn attack because only syn attack can move D from 3-position to 2-position
- ✓ The result in this review is a typo
- ✓ 2-deuterated **D** comes from anti attack, thus anti ratio is only 9% x 5% = 0.45%

Answer to Question 2



$$\text{rate} = \frac{k_1 k_2 k_3 [\text{TBHP}][\text{olefin}]}{k_1 k_2 [\text{TBHP}][\text{olefin}] + k_2 k_3 [\text{olefin}] + k_{-1} k_{-2}}$$

Pre-equilibrium means: $k_{-1}k_{-2}$ is big

$$\text{rate} = \frac{k_1 k_2 k_3 [\text{TBHP}][\text{olefin}]}{k_{-1} k_{-2}}$$

- ✓ First order
- ✓ The concentration of TBHP does not matter as long as there is enough to bind the Pd center. (The wrong assumption we made is steady-state approximation on Pd(TBHP), but actually it is the resting state.)

Answer to Question 3