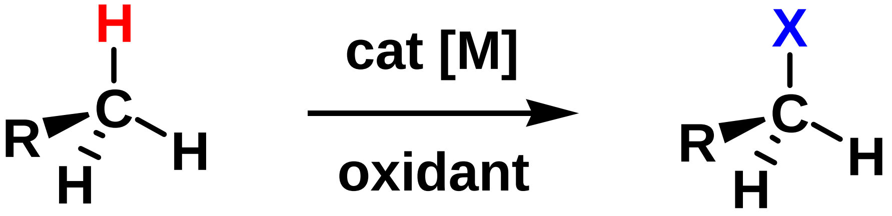
Recent Advances in Directed and Intramolecular Transition Metal Catalyzed Oxidative Functionalizations of Carbon-Hydrogen Bonds

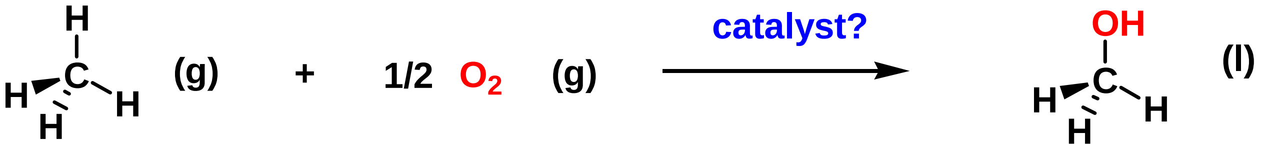
1 step



X = NR_2, OR, halogen

John Heemstra Jr.
April 18, 2006

Oxidative Functionalization of Alkanes

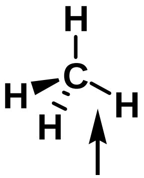


ΔH^o = -30.7 kcal/mol

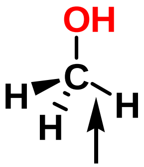
However, two major problems:

Chemoselectivity: product more reactive toward oxidant than starting alkene

if oxidation involves abstraction of H atom, overoxidation to CO_2 will be observed



104 kcal/mol



93 kcal/mol

Regioselectivity: radical and electrophilic reagents oxidize $3^o>2^o>1^o$

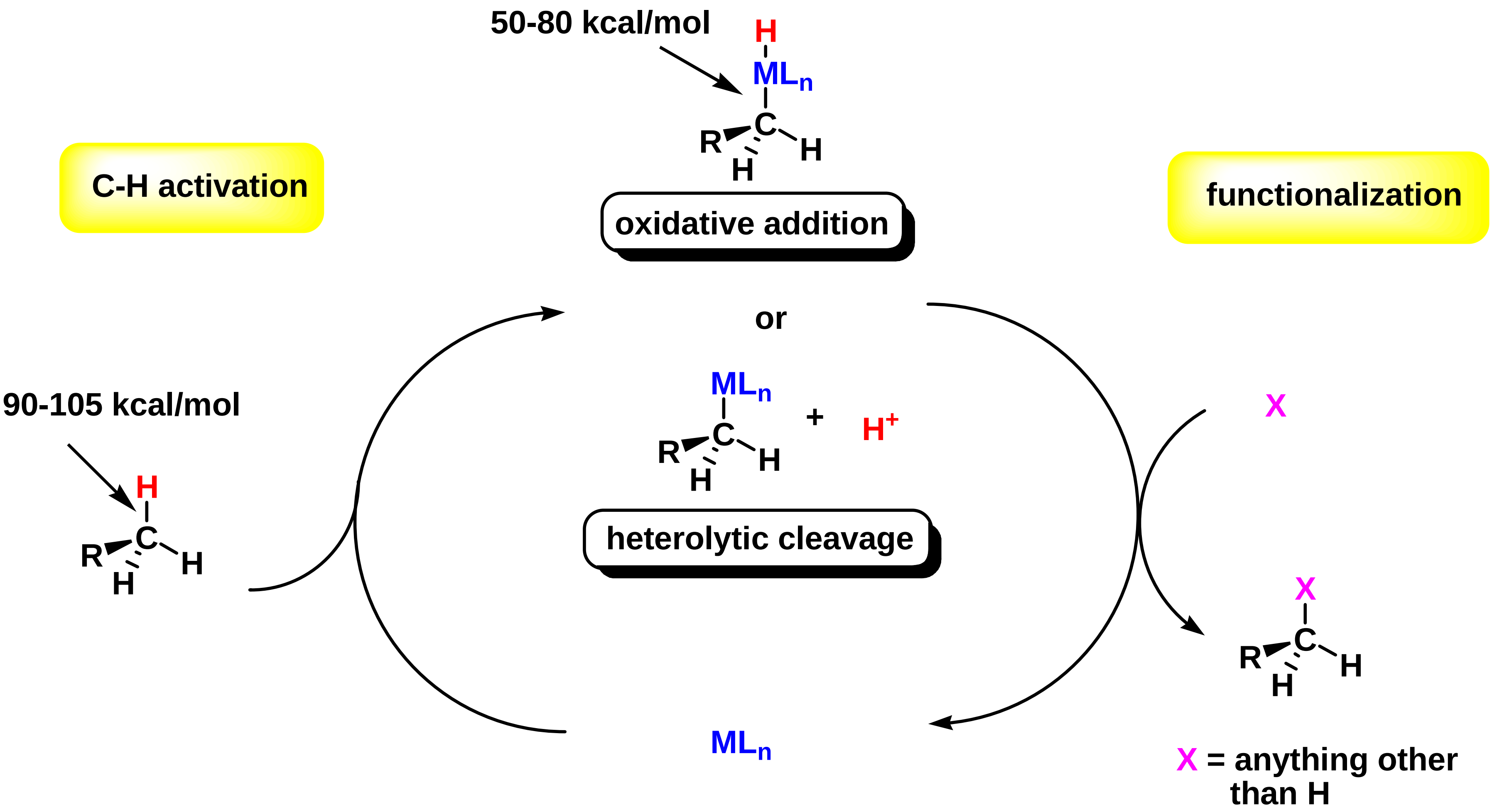
However, the selectivity is often not high

R	**R-H -> R + H**
Me	104.9
Et	101.1
i-Pr	98.6
t-Bu	96.5

Stahl, S.S.; Labinger, J.A.; Bercaw, J.E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180

C-H Functionalization via the ‘Inner-Sphere’ Mechanism

(alternatively termed ‘organometallic’)



50-80 kcal/mol

C-H activation

oxidative addition

or

heterolytic cleavage

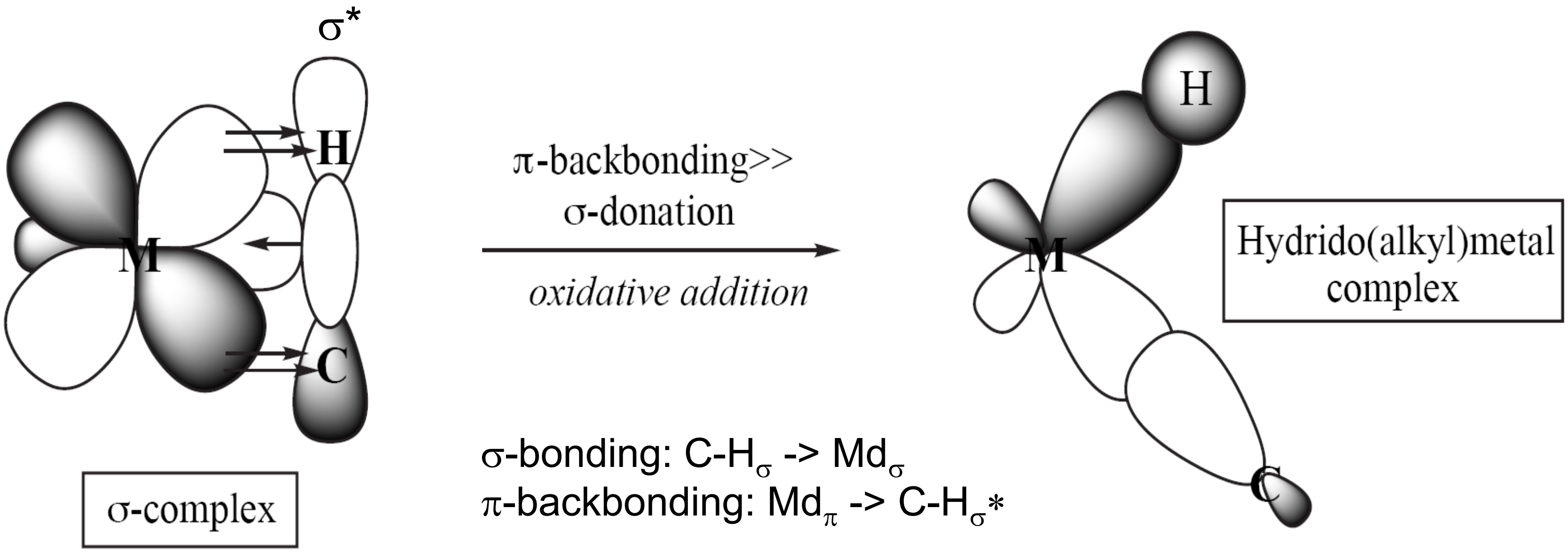
functionalization

90-105 kcal/mol

X = anything other than H

Selectivity: kinetic and thermodynamic preference to form the less sterically hindered C-M intermediate (1^o sp^3 > 2^o sp^3 >>> 3^o sp^3)

C-H Activation Via Late, Nucleophilic Complexes

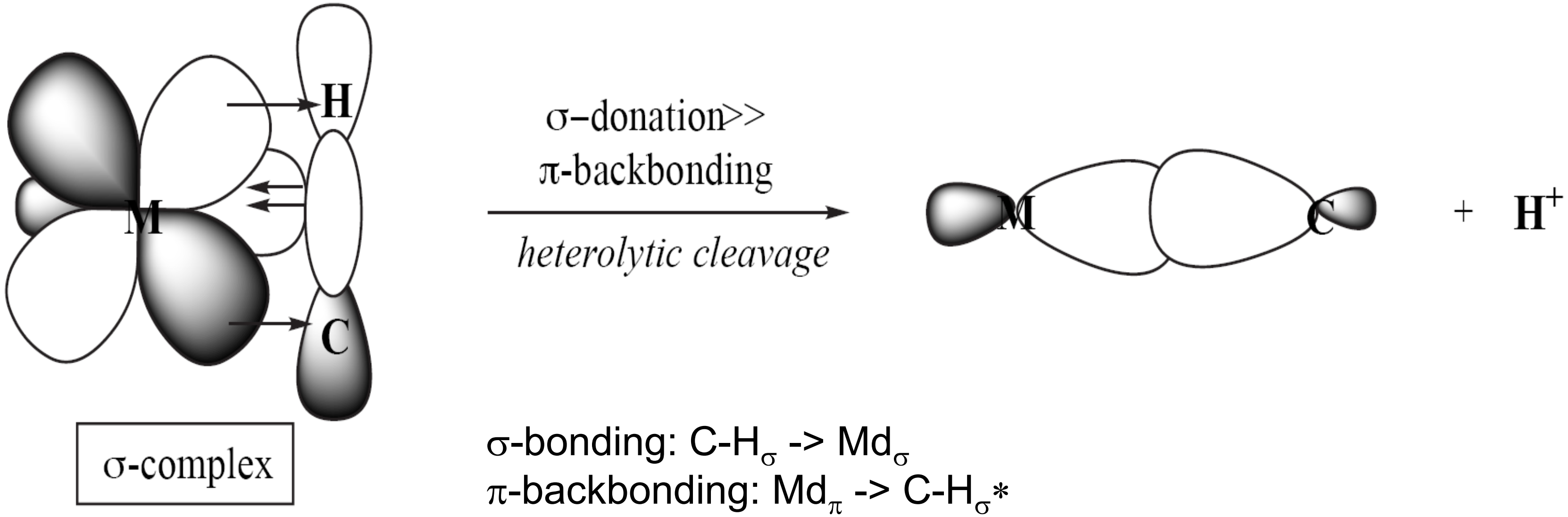


σ-bonding: C-H$_{\sigma}$ -> Md$_{\sigma}$
π-backbonding: Md$_{\pi}$ -> C-H$_{\sigma}$*

- Typically involves coordinatively and electronically unsaturated Rh(I) and Ir(I) intermediate complexes

- Prone to non-productive reductive elimination in the presence of oxidants and non-productive protonolysis in the presence of protic reagents.

C-H Activation Via Late, Electrophilic Complexes



σ-bonding: C-H_σ -> Md_σ
π-backbonding: Md_π -> C-H_σ*

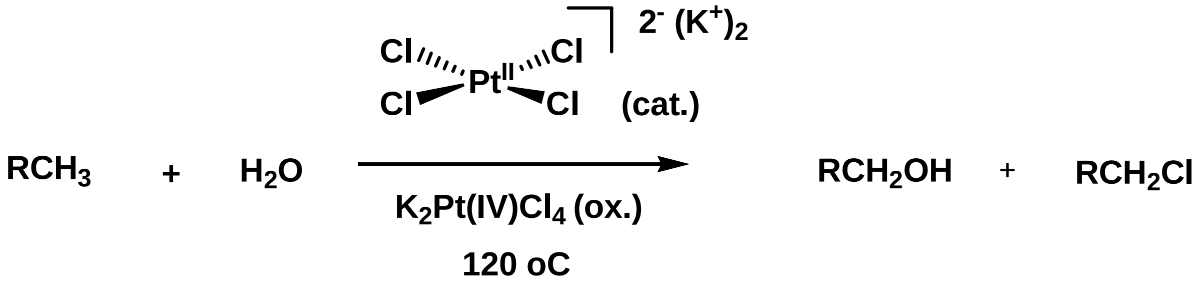
- Heterolytic cleavage results in no oxidation state change in metal.

- Electrophilic complexes in their highest stable oxidation state are typically used (eg. Pt^{II} and Pd^{II})

- Compatible with oxidants (including O_2) and provide a route to oxidative functionalization.

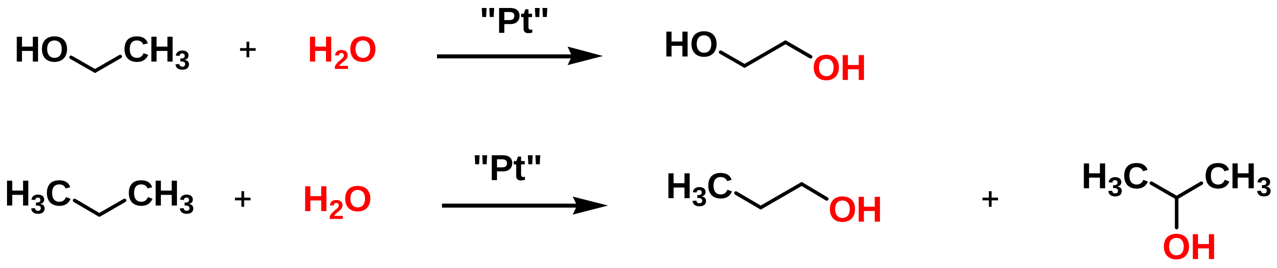
The Shilov System

First reported by Shilov and coworkers In 1972…….a paradigm shift



1° > 2° > 3°

> “Even though these results were mostly ignored or met with disbelief at first, they are now seen as the origin of the organometallic class of alkene oxidations.”
>
> Robert Crabtree



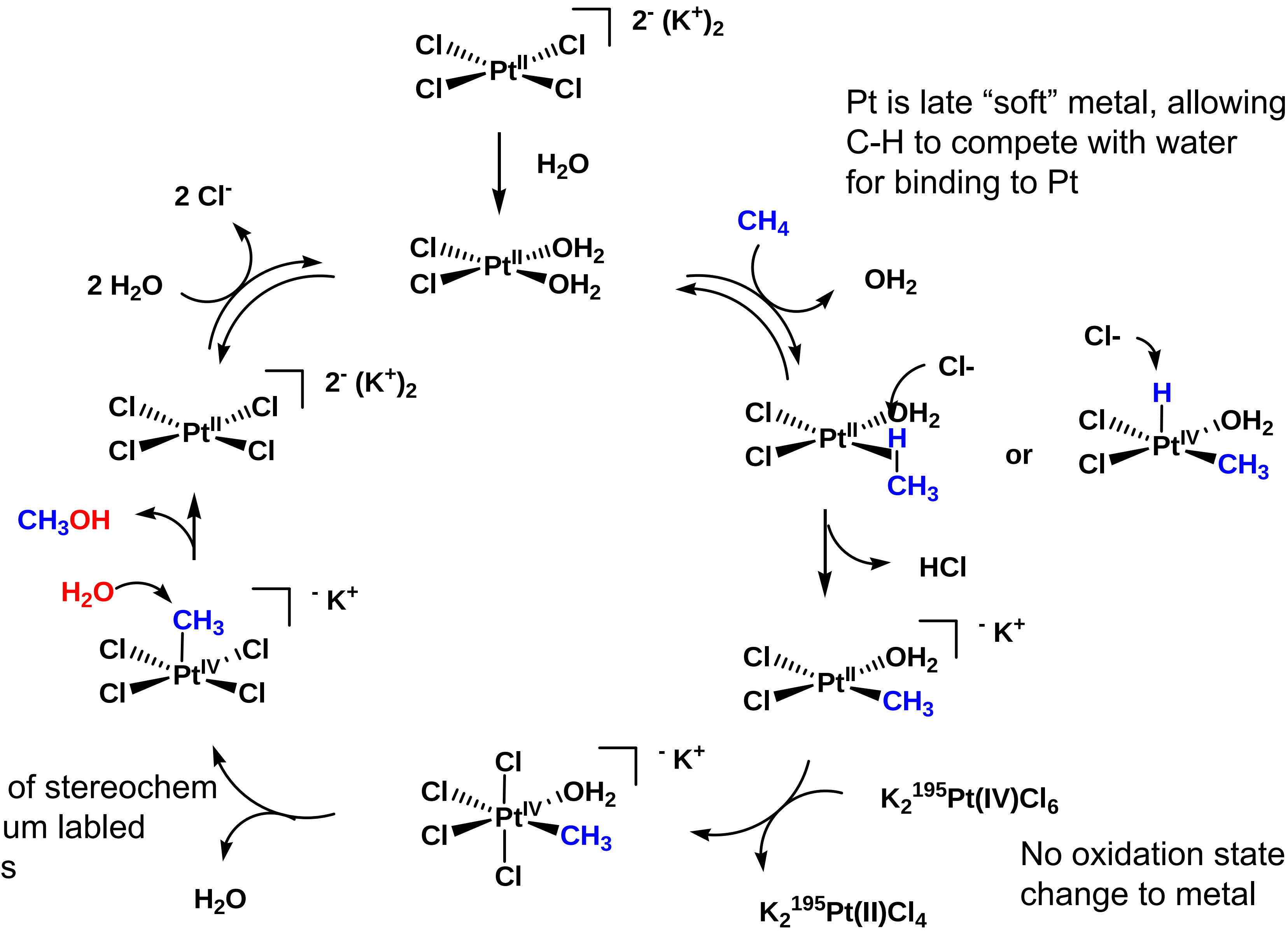
3

1

Although excellent chemioselectivity is observed, only modest regioselectivities have been obtained for unfunctionalized alkanes.

Stahl, S.S.; Labinger, J.A.; Bercaw, J.E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180

The Shilov System



Pt is late "soft" metal, allowing C-H to compete with water for binding to Pt

Inversion of stereochem of deuterium labled substrates

No oxidation state change to metal

Stahl, S.S.; Labinger, J.A.; Bercaw, J.E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180

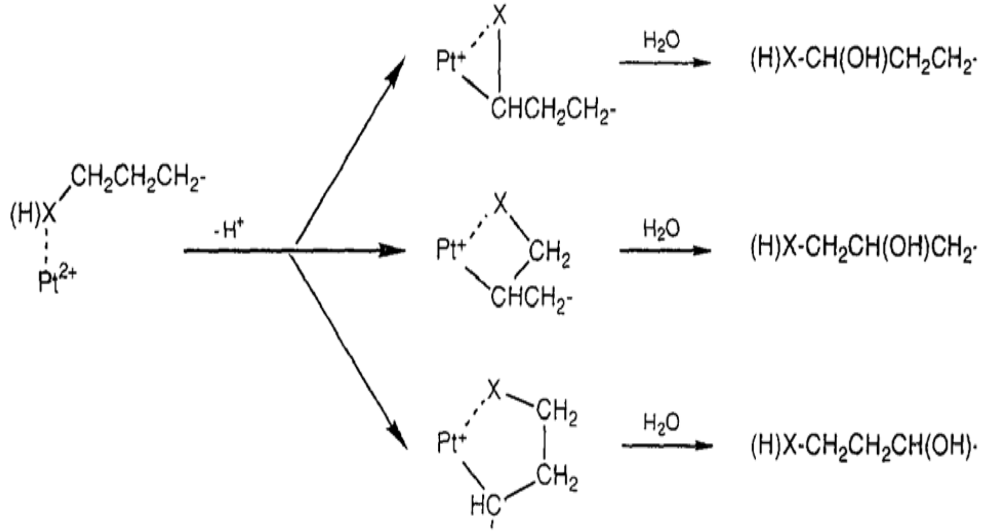
Chelate-Directed C-H Bond Functionalizations

Substrate	Product	Yield
1-Propanol	1,3-Propanediol	84%
2-Butanol	1,3-Butanediol	114%
1-Butanol	1,3-Butanediol	19%
	1,4-Butanediol	38%
	Tetrahydrofuran	32%

[b] Yield with respect to Pt^{II} present initially.

Conditions:
17 mol% $K_2Pt(II)Cl_4$, 50 mol% $K_2Pt(IV)Cl_6$, D_2O, 110-120 °C, 3 days

Tetrahydrofuran 32% → Kinetic product formed by reductive elim.?



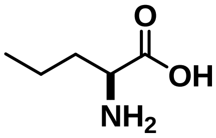
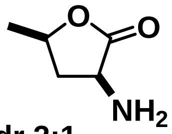
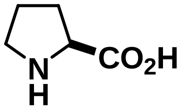
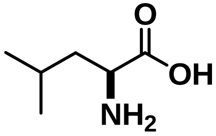
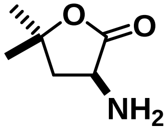
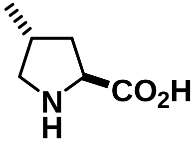
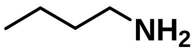
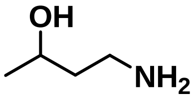
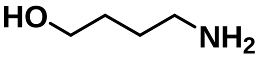
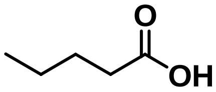
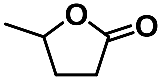
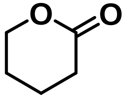
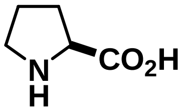
Selectivity arises form the tendence to form the metallacycle with the least ring strain

For alcohols:
α-CH << β-CH < γ-CH ≤ δ-CH

Trend also observed for carboxylic acids, Sulfonic acids, and phosphonic acids

Basickes, N.; Sen, A. *Polyhedron* **1995**, *14*, 202

Chelate-Directed C-H Bond Functionalizations

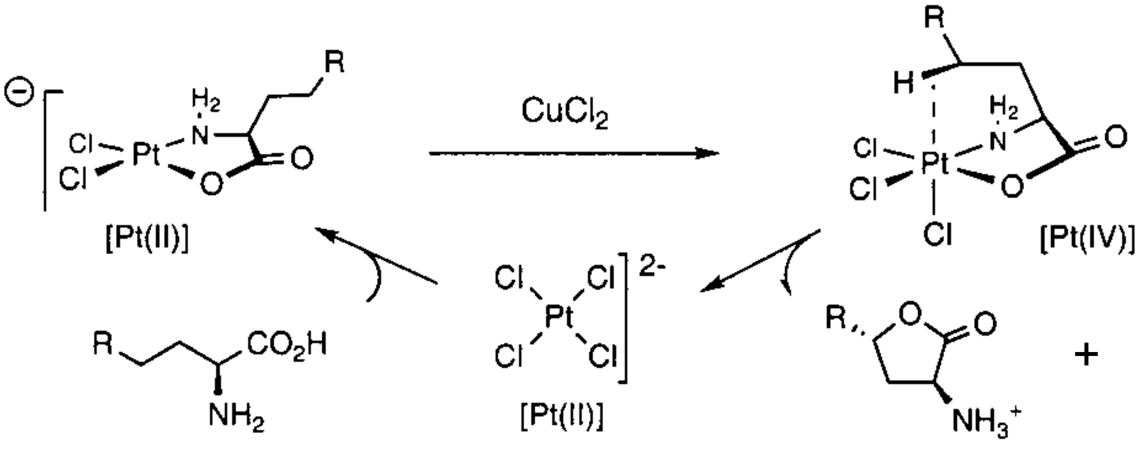
substrate	products			γ– / δ– products	isolated yield,%
	 dr 2:1	+		4 : 1	21
		+	 dr 2:1	4.5 : 1	15
		+		1:3	24
		+		2 : 3	nd
	no reaction				

conditions: 0.05 equiv K_2PtCl_4, 7 equiv $CuCl_2$, H_2O, 160 ^{o}C, 10h

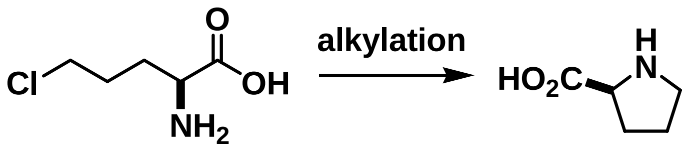
The chelation effect in amino acids can override the inherent selectivity of the C-H activation step.

Dangel, B.D.; Johnson, J.A.; Sames, D.S. *J. Am. Chem. Soc.* **2001**, *123*, 8149

Proposed Catalytic Cycle

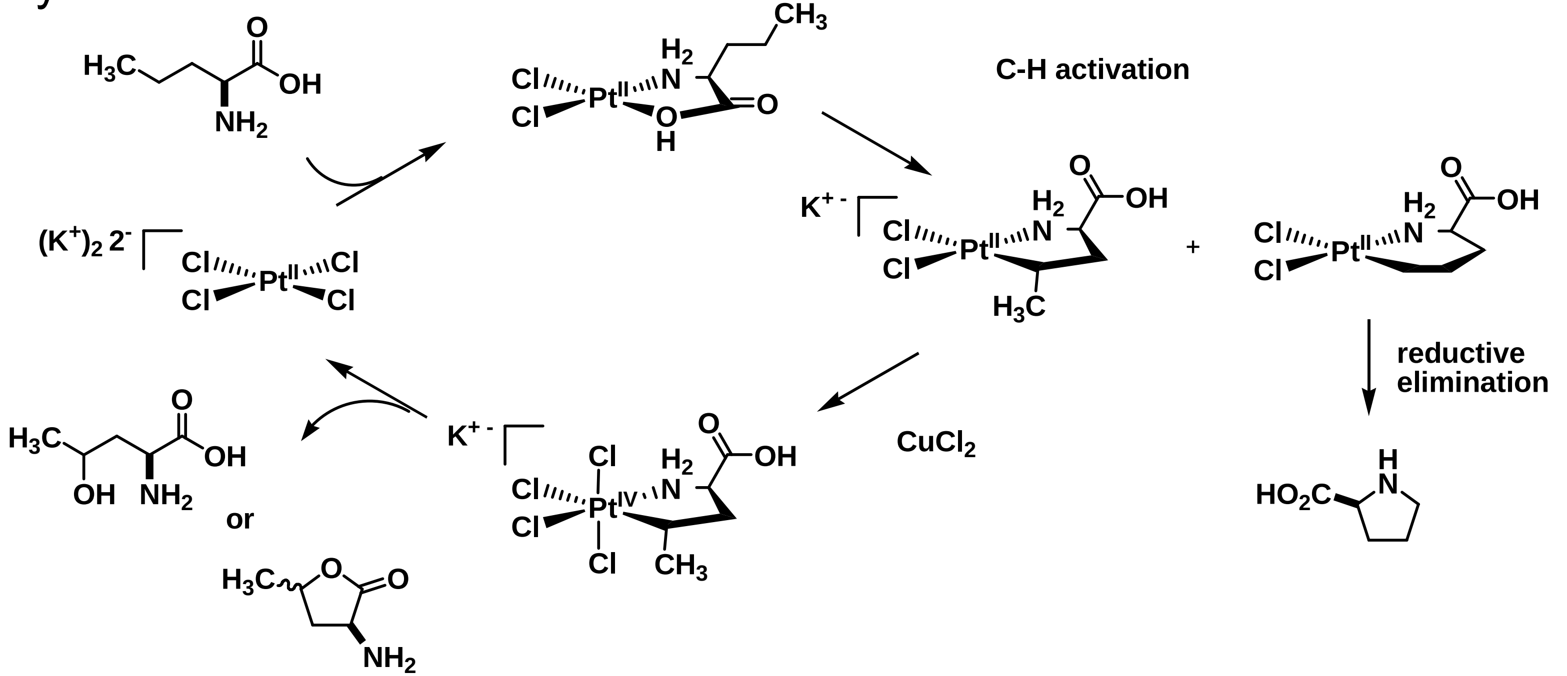


γ-selective pathway = oxygenation
δ-selective pathway = chlorination

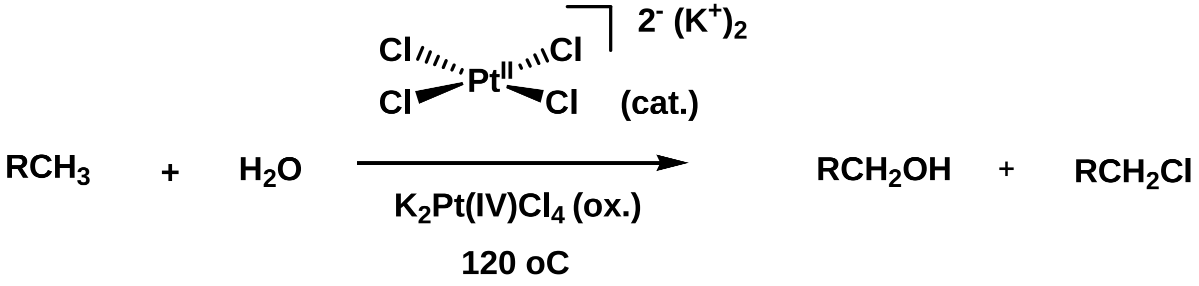


Dangel, B.D.; Johnson, J.A.; Sames, D.S. *J. Am. Chem. Soc.* **2001**, *123*, 8149

Alternatively….



Summary of Platinum Mediated Alkane Oxidations



- Has been instrumental in the understanding of mechanistic and selectivity issues related to alkane oxidation by homogeneous transition metal complexes

- Moderate to excellent regioselectivity can be achieved in the oxidation of functionalized alkanes (eg. alcohols and acids) via the chelate effect

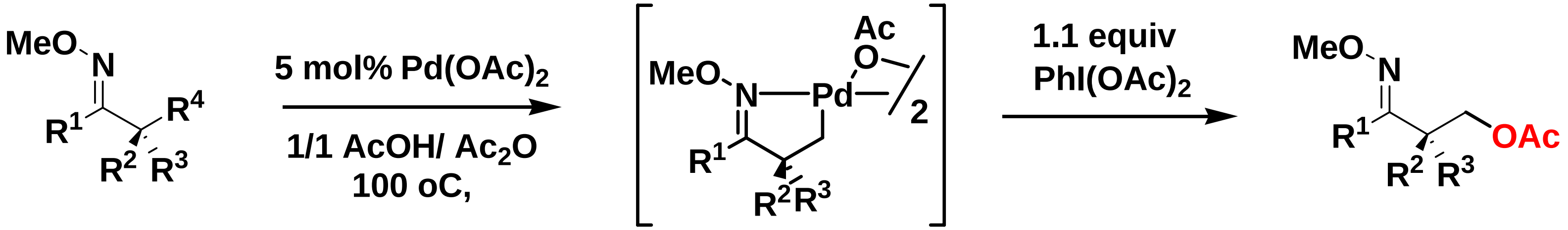
- However, the platinum mediated chemistry is plagued by low catatyst turnover numbers.

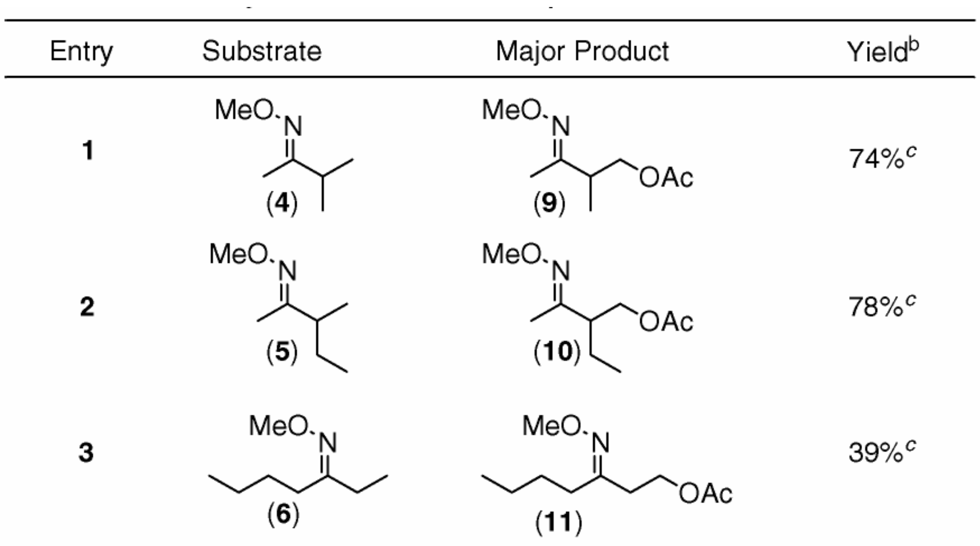
- Pt(IV) is not a practical stoichiometric oxidant (cost) and attempts at replacing it with other oxidants have afforded decreased chemoselectivity.

- Deposition of platinum metal erodes selectivities and the oxidation of Pt(0) tends to be difficult. Palladium on the other hand……..

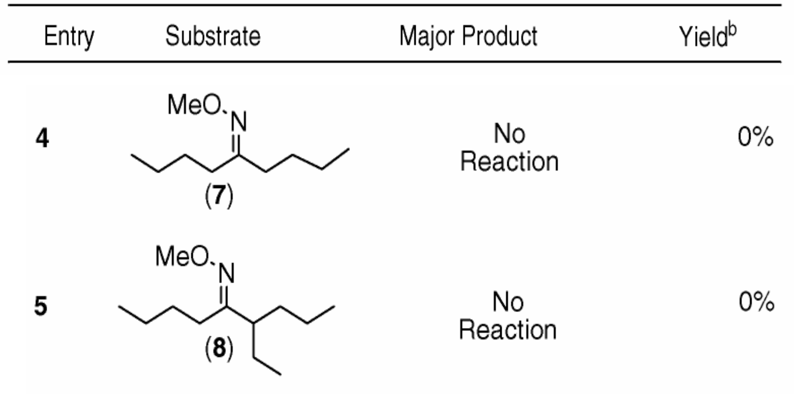
Stahl, S.S.; Labinger, J.A.; Bercaw, J.E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180

Palladium-Catalyzed Oxygenation of Unactivated sp^3 C-H Bonds





Entry	Substrate	Major Product	Yield^b
1	(4)	(9)	74%^{c}
2	(5)	(10)	78%^{c}
3	(6)	(11)	39%^{c}



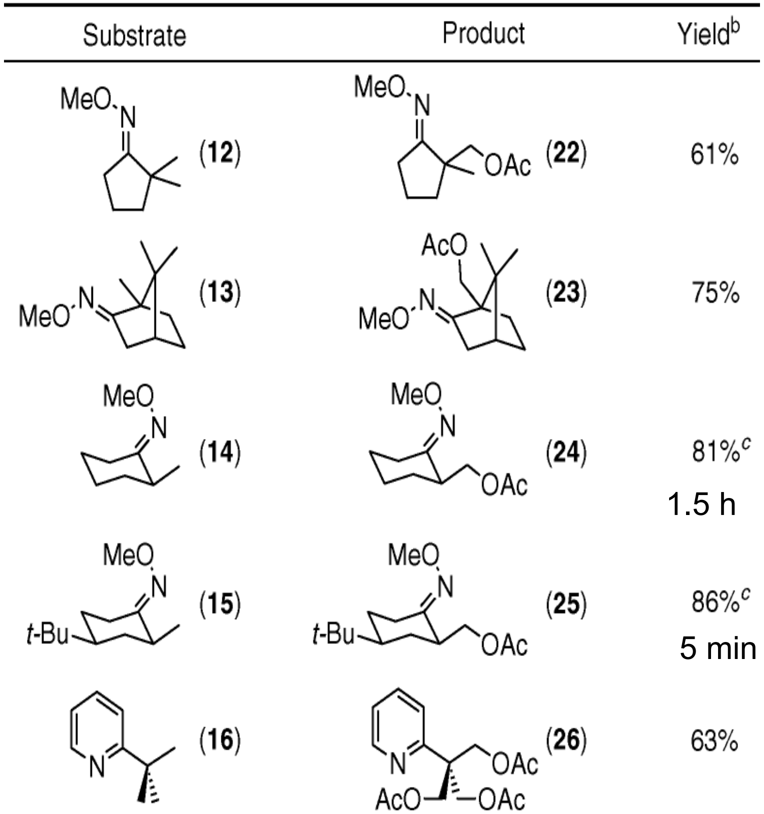
Entry	Substrate	Major Product	Yield^b
4	(7)	No Reaction	0%
5	(8)	No Reaction	0%

Unlike Pt(II), only 1^0 β-C-H bonds undergo functionalization!

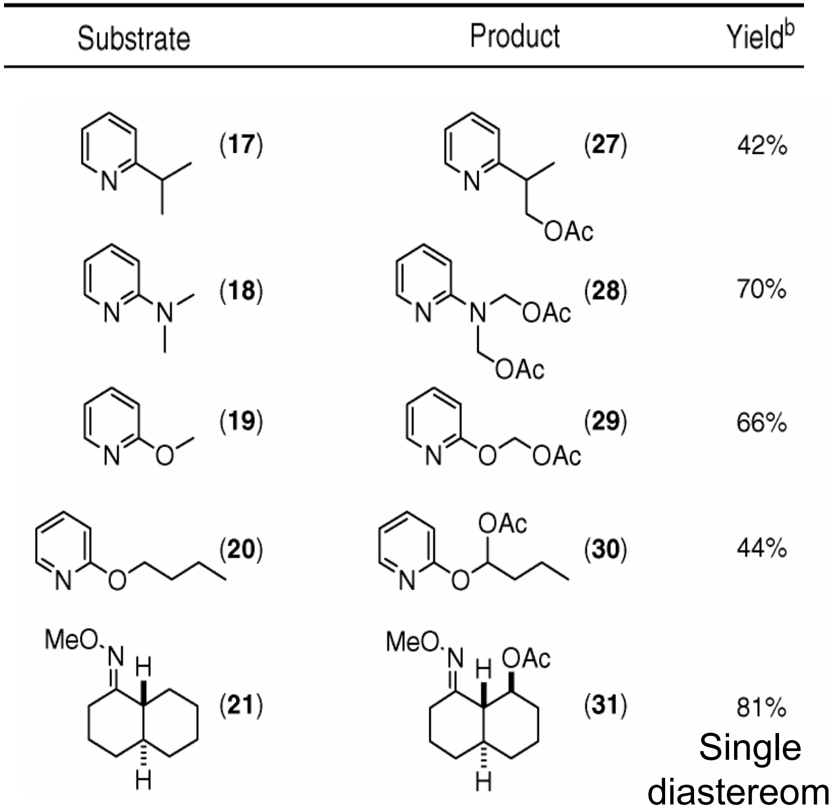
- The chelating group believed to both direct and accelerate unactivated sp^3 C-H activation
- High reactivity for 1º β–C-H likely reflects preference for forming 5-membered palladacycles and strong steric preference for formation less hindered 1º Pd-alkyls.

Desai, L.D.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, *126*, 9542

Palladium-Catalyzed Oxygenation of Unactivated sp^3 C-H Bonds



Substrate	Product	Yield[b]
(12)	(22)	61%
(13)	(23)	75%
(14)	(24)	81%[c] 1.5 h
(15)	(25)	86%[c] 5 min
(16)	(26)	63%



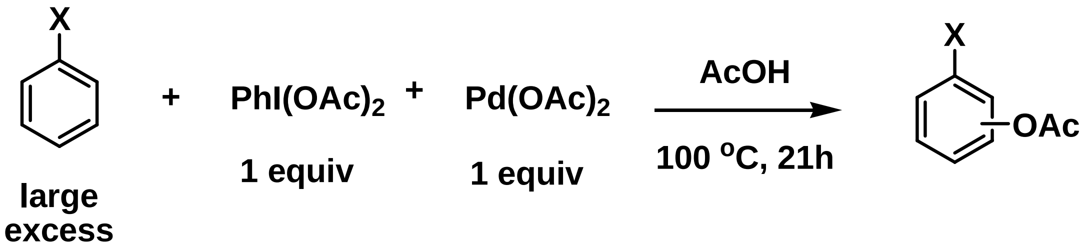
Substrate	Product	Yield[b]
(17)	(27)	42%
(18)	(28)	70%
(19)	(29)	66%
(20)	(30)	44%
(21)	(31)	81% Single diastereomer

[a] 1 equiv of substrate (0.12 M), 1.1−3.2 equiv of $PhI(OAc)_2$, 5 mol % $Pd(OAc)_2$, in AcOH, 50% AcOH/50% Ac_2O, or CH_2Cl_2, 80−100 °C, 5 min−12 h. [b] Isolated yields. [c] Isolated as a mixture of oxime E/Z isomers.

These Pd-catalyzed reactions typically proceed under significantly milder conditions, with higher TON (often ≥50) and with broader substrate scope than those with Pt catalysts

Desai, L.D.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, *126*, 9542

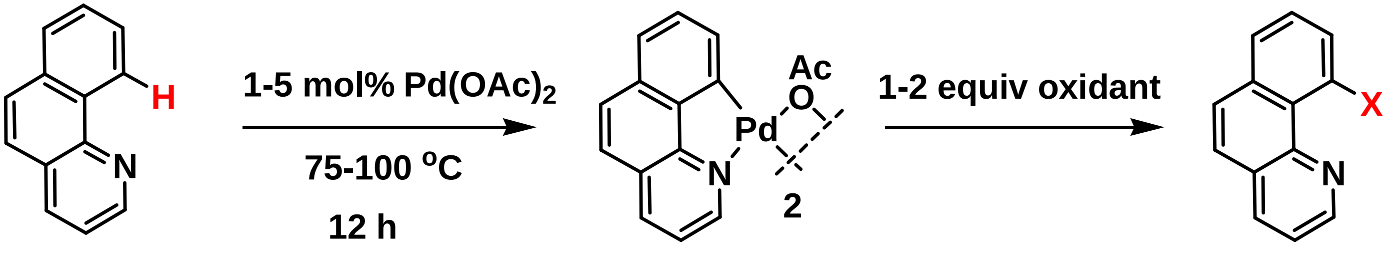
Palladium-Catalyzed Oxygenation of Unactivated sp^2 C-H Bonds

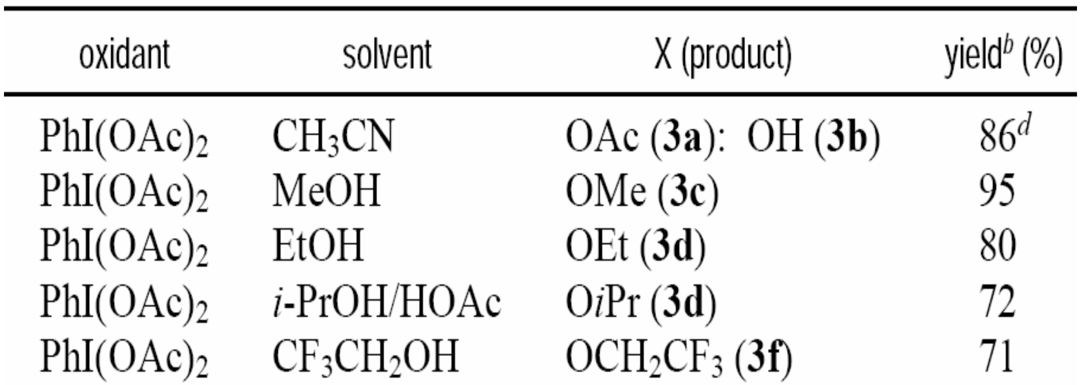


Substrate	yield	o:m:p
Benzene	39	
Anisole	40	44:5:51
Toluene	39	43:26:31

Low levels of regioselectivity observed

Yoneyama, T.; Crabtree, R.S. *J. Mol. Catal. A* **1996**, *108*, 35



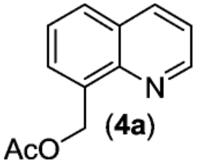


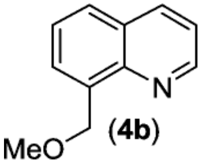
oxidant	solvent	X (product)	yield[b] (%)
PhI(OAc)$_2$	CH_3CN	OAc (**3a**): OH (**3b**)	86[d]
PhI(OAc)$_2$	MeOH	OMe (**3c**)	95
PhI(OAc)$_2$	EtOH	OEt (**3d**)	80
PhI(OAc)$_2$	*i*-PrOH/HOAc	O*i*Pr (**3d**)	72
PhI(OAc)$_2$	CF_3CH_2OH	OCH_2CF_3 (**3f**)	71

Dick, A.R.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, *126*, 2300

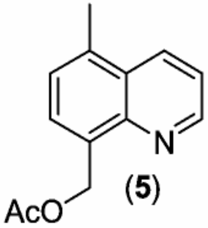
Chelate-Directed Oxidation of sp^2 and sp^3 C-H Bonds

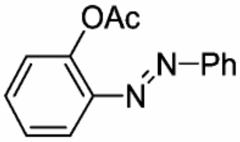
Monooxidation of substrates: Conditions: 1.1-1.6 equiv of $PhI(OAc)_2$, 1-6 mol% $Pd(OAc)_2$, 100 °C, 12-20 h, CH_3CN

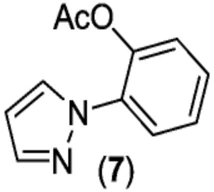

(**4a**) 88%

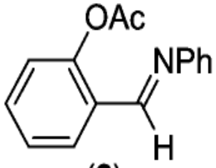

(**4b**) 77%

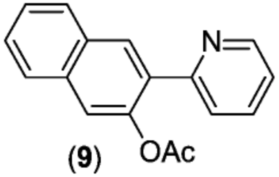
in MeOH

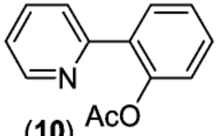

(**5**) 80%


(**6**) 62%

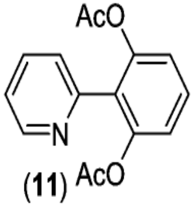

(**7**) 54%

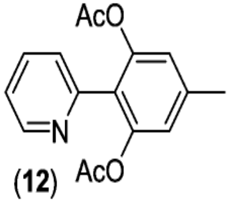

(**8**) 47%[d]

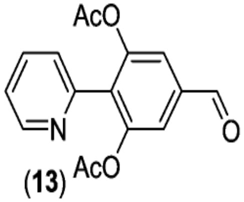

(**9**) 72%


(**10**) 52%

Dioxidation of substrates: Conditions: 2.3 equiv of $PhI(OAc)_2$, 6-8 mol% $Pd(OAc)_2$, 100 °C, 12h, CH_3CN

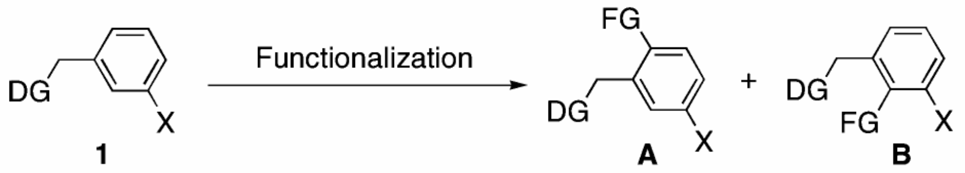

(**11**) 83%


(**12**) 78%


(**13**) 58%

Dick, A.R.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, *126*, 2300

Palladium-Catalyzed Acetoxylation of *Meta*-Substituted Aryl pyridines



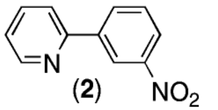
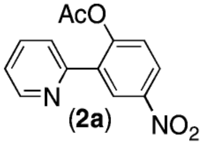
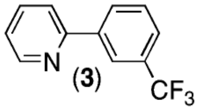
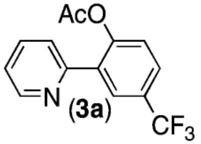
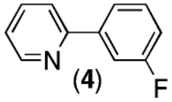
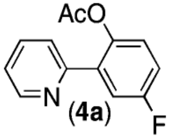
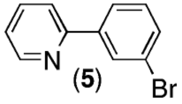
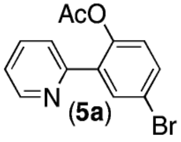
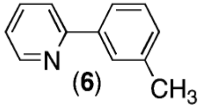
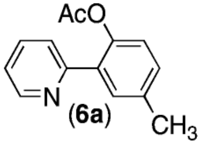
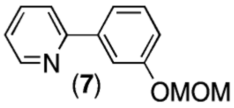
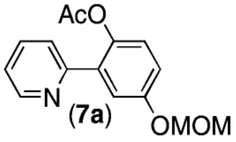
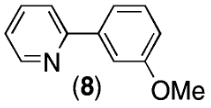
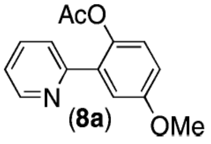
DG = Directing Group, FG = Functional Group

X = OMe, OMOM, CH_3, Br, F, CF_3, Ac, oxime, NO_2, etc.

Conditions:

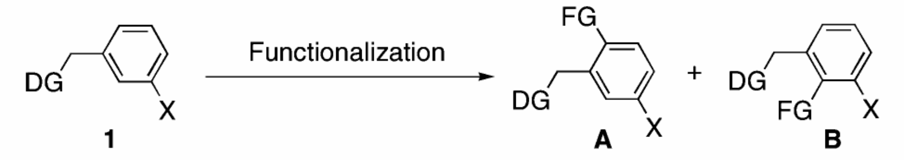
5 mol% $Pd(OAc)_2$, 1.1-3.0 equiv $PhI(OAc)_2$, AcOH, C_6H_6 or C_6H_6/Ac_2O, 100 °C, 0.5-4 h

Unlike directed ortho-lithiation and Ru-catalyzed C-H activation reactions, OMe, OMOM, and F Did not exhibit secondary directing effects

entry	starting material	major product	yield	ratio of **A**:B
1			60%	>20:1[b]
2			81%	>20:1[b]
3			59%	6:1[c]
4			83%	>20:1[b]
5			77%	27:1[d]
6			76%	>20:1[b]
7			78%	60:1[d]

Kalyani, D.; Sanford, M.S. *Org Lett.* **2005**, *19*, 4149

Palladium-Catalyzed Acetoxylation of Aryl Pyrrolidinones

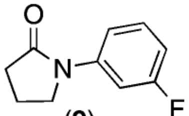
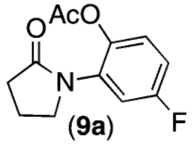
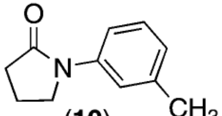
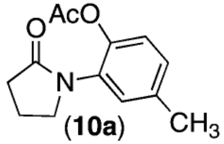
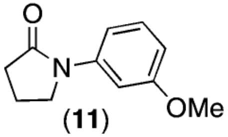
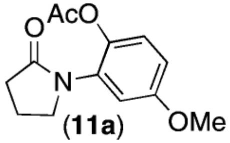
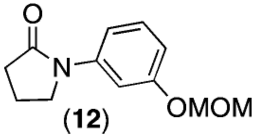
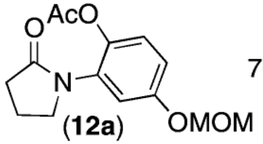


DG = Directing Group, FG = Functional Group

X = OMe, OMOM, CH_3, Br, F, CF_3, Ac, oxime, NO_2, etc.

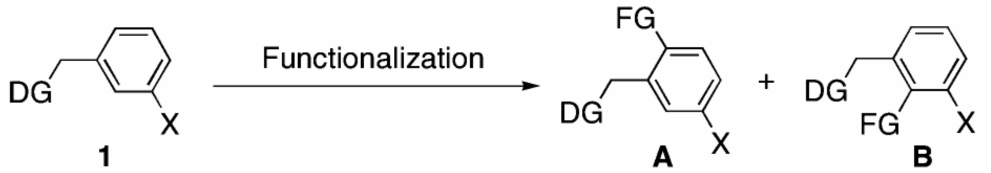
Conditions:
5 mol% $Pd(OAc)_2$, 1.1-2.2 equiv $PhI(OAc)_2$, AcOH, AcOH/Ac_2O, 100 ^oC, 3-12 h

Selectivity for **A** may be general over many classes of directing groups in PdII-catalzed C-H activation/oxidative functionalizations.

entry	starting material	major product	yield	ratio of **A**:**B**
1	 (**9**)	 (**9a**)	88%[b]	14:1[c]
2	 (**10**)	 (**10a**)	74%	>20:1[d]
3	 (**11**)	 (**11a**)	73%	>20:1[d]
4	 (**12**)	 (**12a**)	70%	>20:1[d]

Kalyani, D.; Sanford, M.S. *Org Lett.* **2005**, *19*, 4149

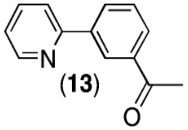
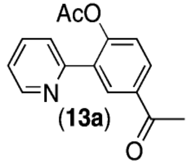
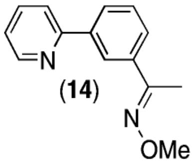
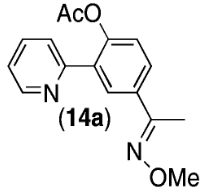
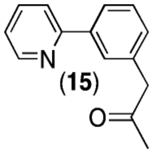
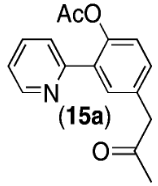
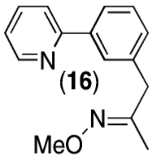
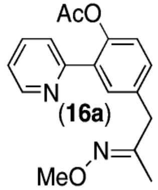
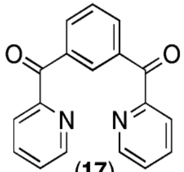
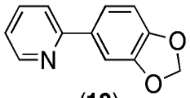
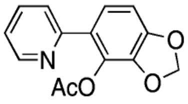
Palladium-Catalyzed Acetoxylation of Substrates with Potential Dual Chelating Groups

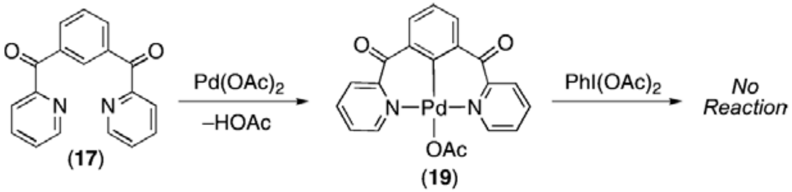


DG = Directing Group, FG = Functional Group

X = OMe, OMOM, CH_3, Br, F, CF_3, Ac, oxime, NO_2, etc.

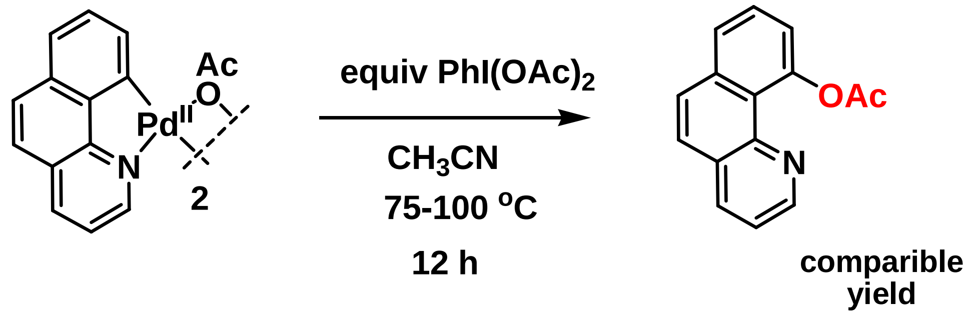
Conditions:
5 mol% $Pd(OAc)_2$, 1.5-1.8 equiv $PhI(OAc)_2$,
C_6H_6 or C_6H_6/Ac_2O, 100 ^oC

entry	starting material	major product	yield	ratio of **A**:**B**
1	 (**13**)	 (**13a**)	82%	>20:1[b]
2	 (**14**)	 (**14a**)	81%	>20:1[b]
3	 (**15**)	 (**15a**)	83%	>20:1[b]
4	 (**16**)	 (**16a**)	78%	>20:1[b]
5	 (**17**)	***No Reaction***		
6	 (**18**)	 (**18b**)	29%[d]	1:2[c]



Kalyani, D.; Sanford, M.S. *Org Lett.* **2005**, *19*, 4149

Proposed Catalytic Cycle for Palladium-Catalyzed Acetoxylation of Benzo[*h*]quinone



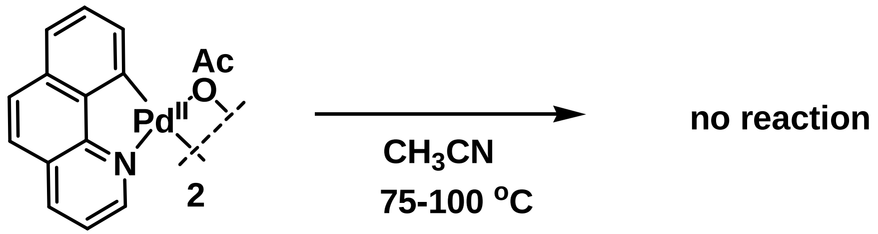
equiv PhI(OAc)$_2$

CH$_3$CN

75-100 ^{o}C

12 h

comparible yield

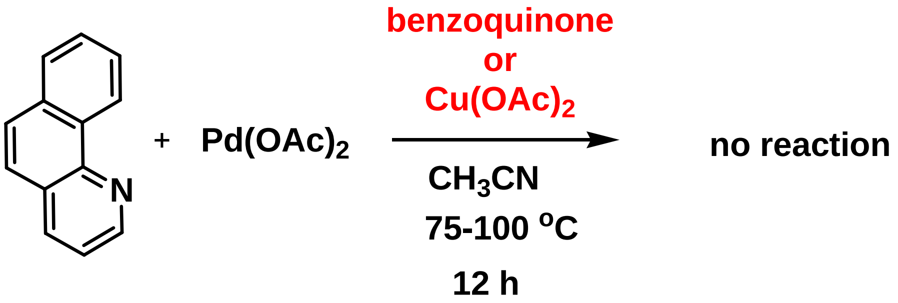


CH$_3$CN

75-100 ^{o}C

12 h

no reaction



Pd(OAc)$_2$

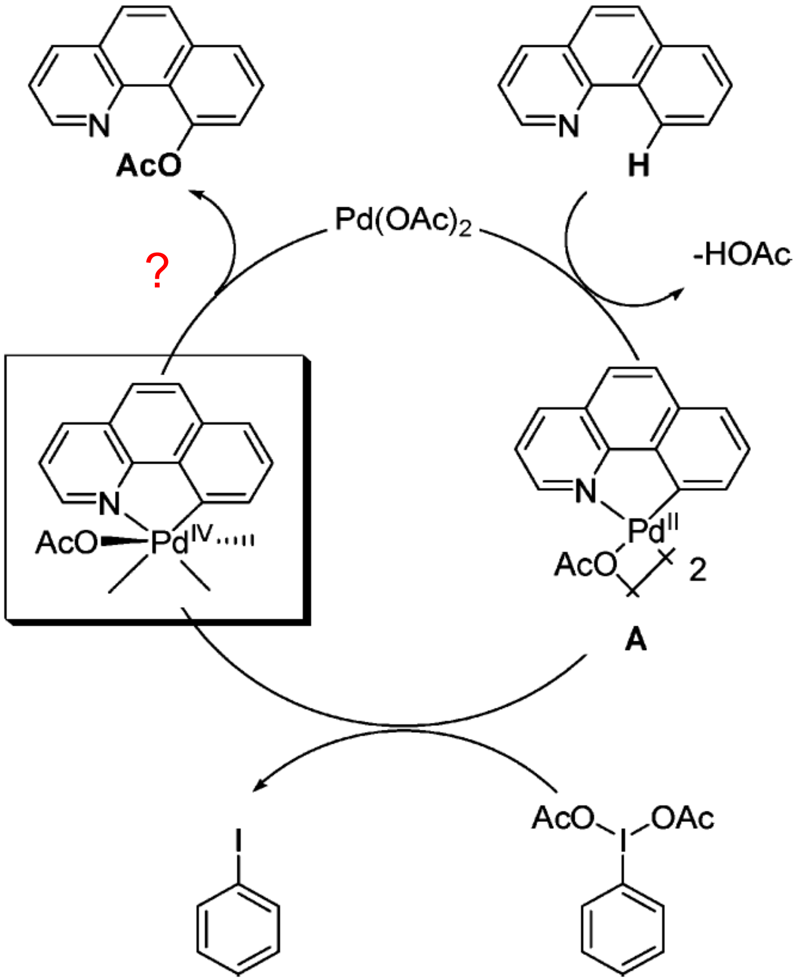
benzoquinone
or
Cu(OAc)$_2$

CH$_3$CN

75-100 ^{o}C

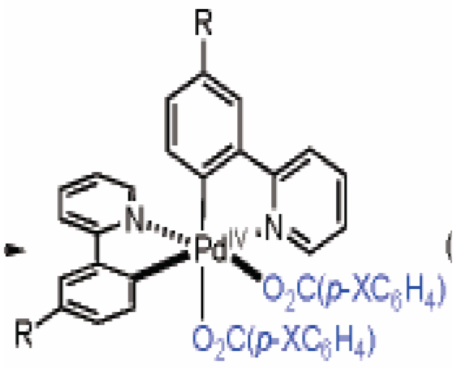
12 h

no reaction

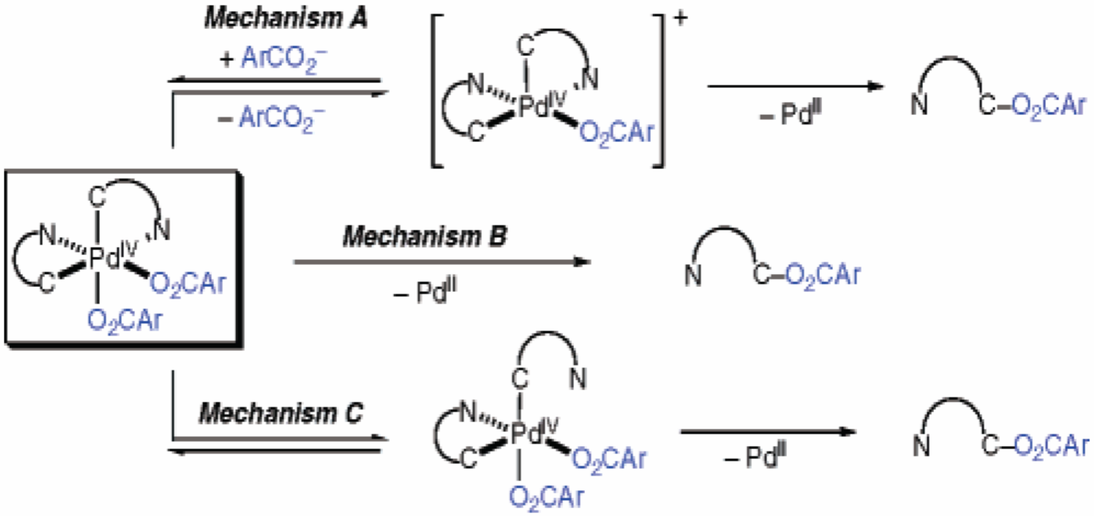


Dick, A.R.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, *126*, 2300

Mechanistic Investigations of C-O Bond-Forming Reductive Elimination of Pd(IV) Complexes



Stable at rt



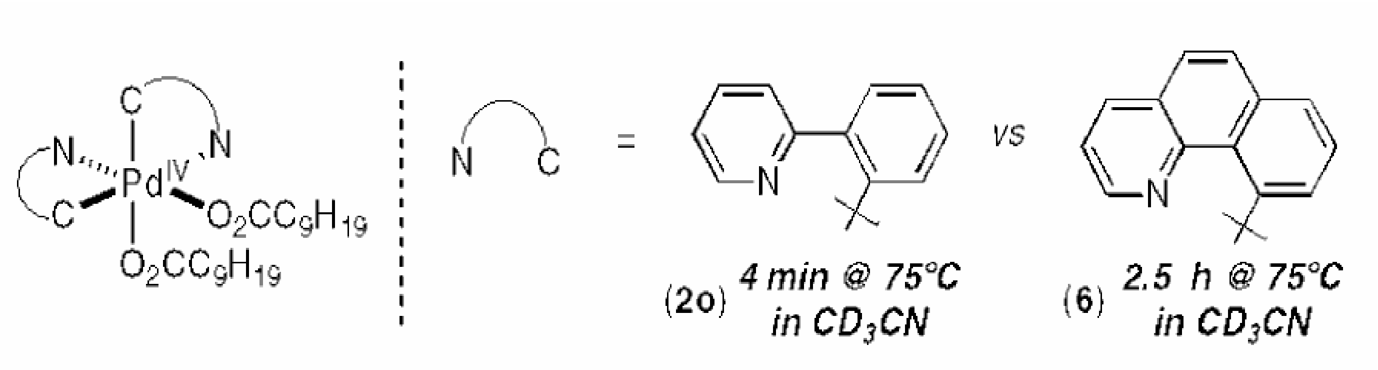
Expected **mechanism A** most likely by analogy to C-O bond-forming reactions with Pt^{IV}
However….

- no observed rate acceleration in more polar solvents and no correlation with solvent dielectric constant
- ΔS = +4.2 ± 1.4 and -1.4 ± 1.9 eu in d_6 DMSO and $CDCl_3$ respectively (ionic reductive eliminations typically show highly negative values of ΔS).
- ρ = -1.36 ± 0.04 (Pt^{VI} C-O bond forming reductive elimination ρ = +1.44)
- Thermolysis in the presence of 5 equiv NBu_4OAc resulted less than 5% incorporation of the acetate in $CHCl_3$ or DMSO

What experiments would you perform to distinguish between Mech. B and C?

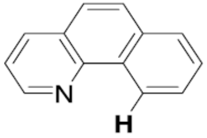
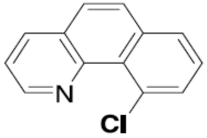
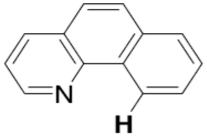
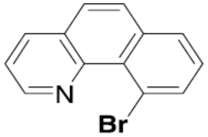
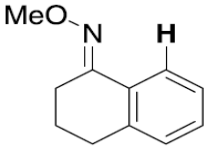
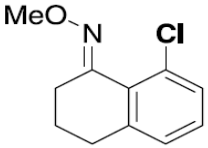
Dick, A.R.; Kampf, J.W.; Sanford, M.S. *J. Am. Chem. Soc.* **2005**, *127*, 12790

Mechanistic Investigations of C-O Bond-Forming Reductive Elimination of Pd(IV) Complexes



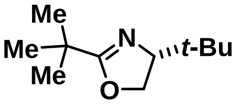
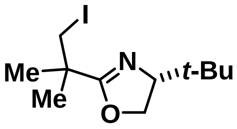
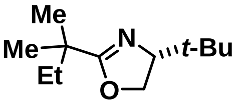
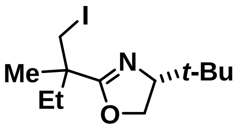
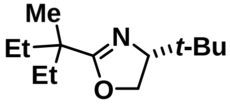
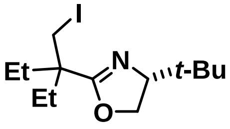
Sanford and co-worker currently favor mechanism C

Selective C-H Activation/Halogenation catalyzed by $Pd(OAc)_2$

Substrate	Product	Yield (%)
		95
		93
		86

Conditions:
1 mol% $Pd(OAc)_2$, 1.1 equiv of N-Halosuccinamide, MeCN, 100 °C, 24-72 h

Dick, A.R.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, *126*, 2300

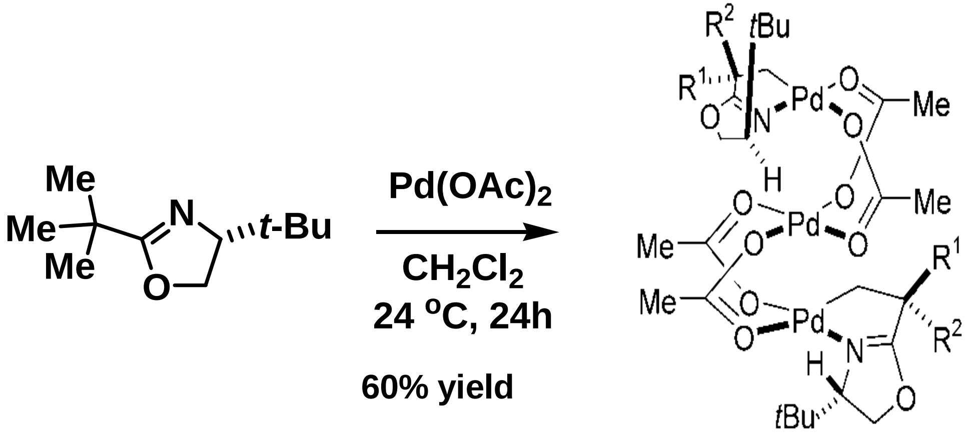
Substrate	Product	Yield (%)
		92
		91 (63:37 dr)
		88

Conditions:
10 mol% $Pd(OAc)_2$, I_2 (1 equiv) $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 48-72 h

Ethanolamine, 2-methyl-2-amino-propanol, or valinol derived oxazolines proceed at much slower rate

Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112

Selective C-H Activation/Halogenation catalyzed by Pd(OAc)$_2$



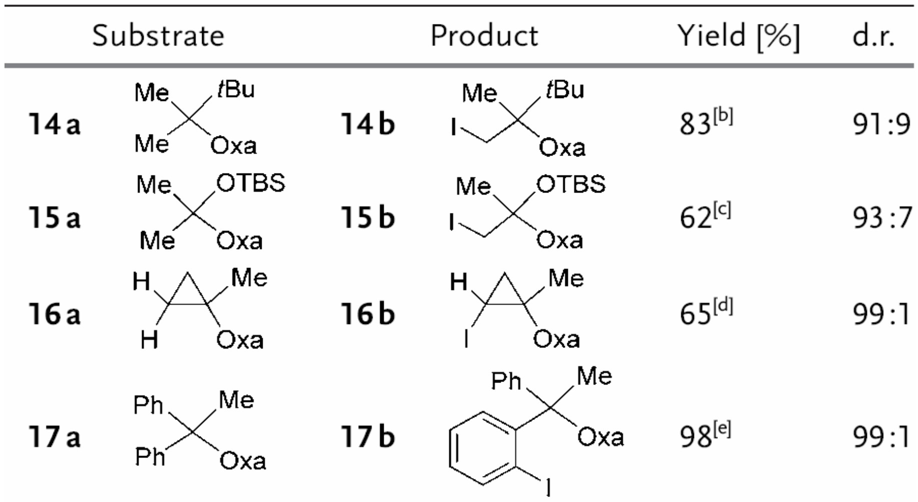
Pd(OAc)$_2$

CH$_2$Cl$_2$

24 °C, 24h

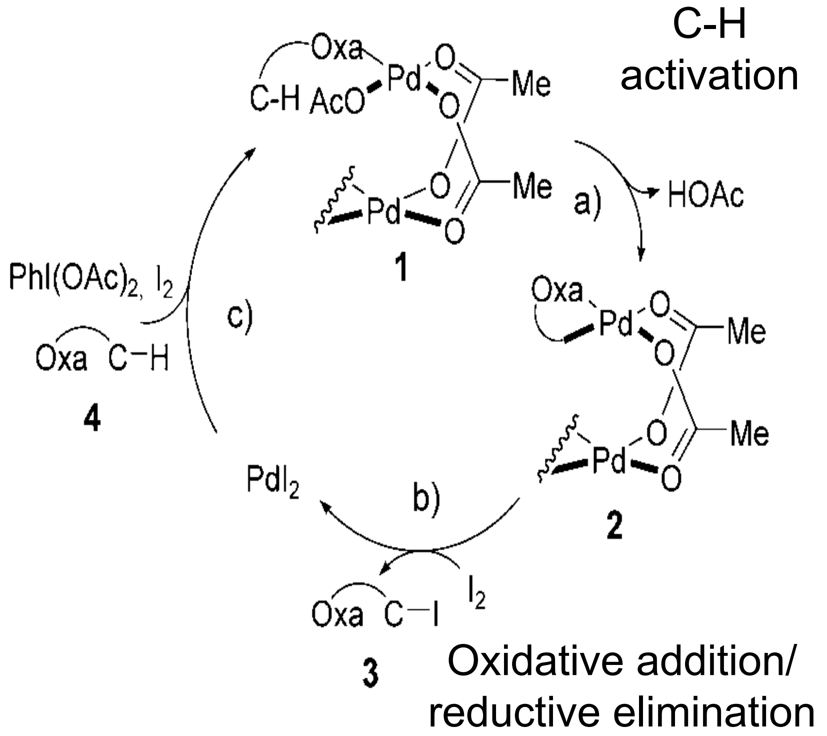
60% yield

2a: R^1 = R^2 = Me



Substrate	Product	Yield [%]	d.r.
14a	14b	83[b]	91:9
15a	15b	62[c]	93:7
16a	16b	65[d]	99:1
17a	17b	98[e]	99:1

[a] Reaction conditions: Pd(OAc)$_2$ (10 mol%), I$_2$ (1 equiv), PhI(OAc)$_2$ (1 equiv), CH$_2$Cl$_2$. [b] 24 °C, 30 h. [c] 50 °C, 48 h. [d] 24 °C, 96 h. [e] 24 °C,



C-H activation

Oxidative addition/ reductive elimination

$$\mathrm{PdI_2} \xrightarrow[\mathrm{CH_2Cl_2,\ 24\ h}]{\mathrm{PhI(OAc)_2\ (1\ equiv)}\quad \mathrm{I_2\ (1\ equiv)}} \mathrm{Pd(OAc)_2}$$

Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112

Summary of the Palladium Catalyzed sp^3 and sp^2 C-H bond Oxidative Functionalization

- Unactivated sp^3 and sp^2 C-H bonds of oximes, pyridine, pyrazole, imine, and azo-benzene substrates undergo highly regio- and chemoselective Pd(II) catalyzed oxygenations with $PhI(OAc)_2$ as a stoichiometric oxidant.

- C-H bonds can also be replaced with ether functionality or halides when reaction are performed in alcohol solvants or in the presence of N-halosuccinamides, or I_2.

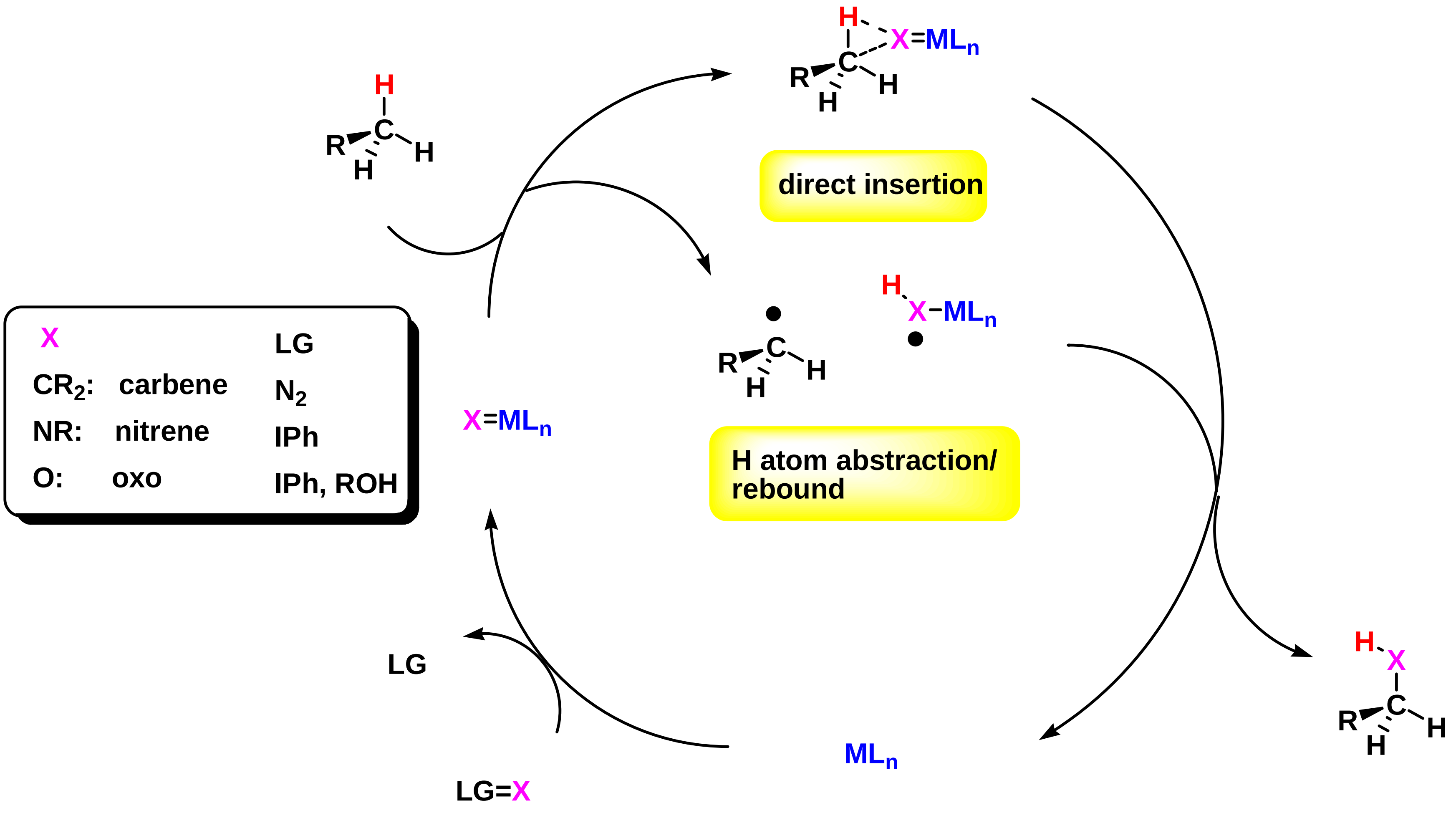
- Pd-catalyzed chelate-directed acetoxylation of *meta*-substituted arene substrates exhibit high regioselectivity for functionalization at the less substituted *ortho*-position

- These Pd-catalyzed reactions typically proceed under significantly milder conditions, With higher TON (often ≥50) and with broader substrate scope than those with Pt catalysts.

- The almost exclusive selectivity for 1^o C-H bonds is a could be a limitation if one wanted to develop a stereospecific or enantioselective process.

C-H Functionalization via the ‘Outer-Sphere’ Mechanism

(alternatively termed ‘coordination’)

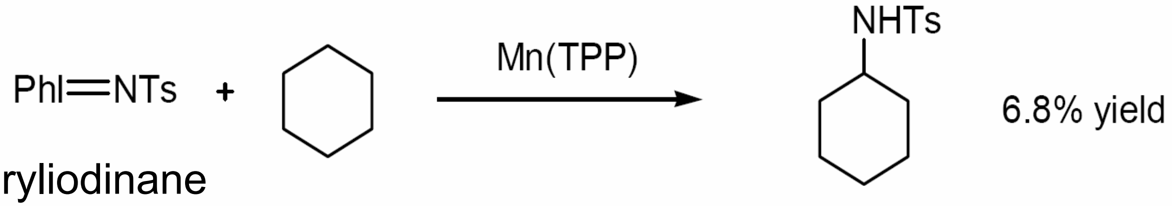


X		LG
CR$_2$:	carbene	N$_2$
NR:	nitrene	IPh
O:	oxo	IPh, ROH

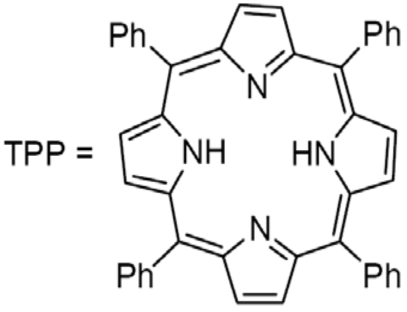
Selectivity: involves buildup of radical and/or cationic character at carbon and shows selectivity for weaker C-H bonds: benzylic, allylic, 3°, or α to heteroatoms.

C-H Bond Amination via the ‘Outer-Sphere’ Mechanism

First example of an intermolecular C-H amination

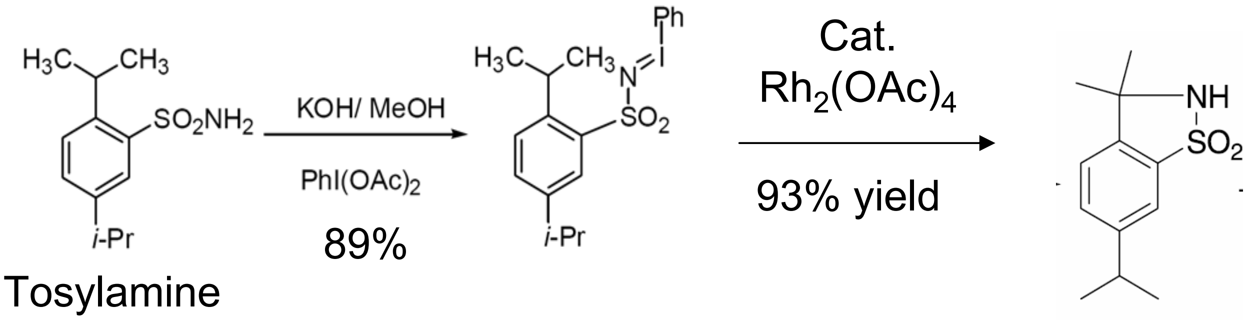


aryliodinane



Breslow. R; Gellman, S.H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400

First example of an intramolecular C-H amination



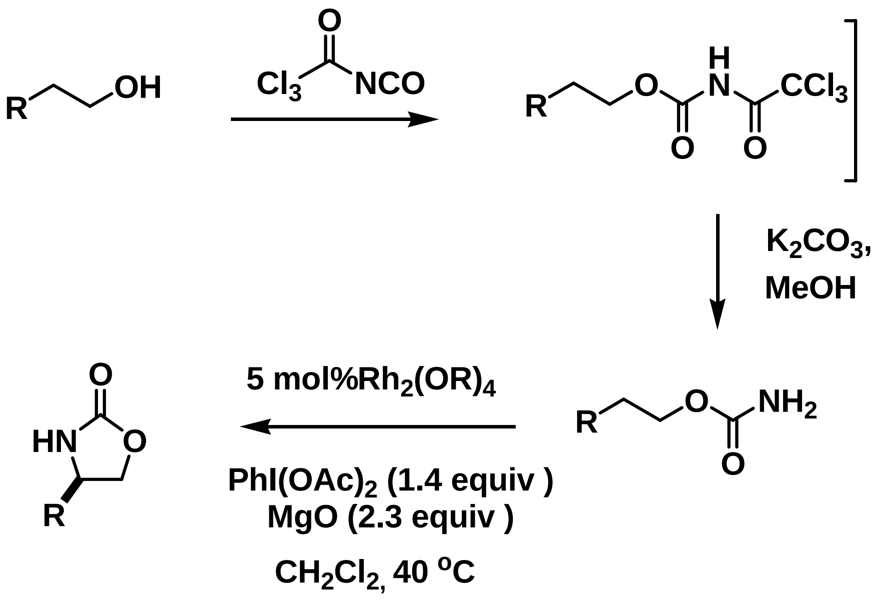
Tosylamine

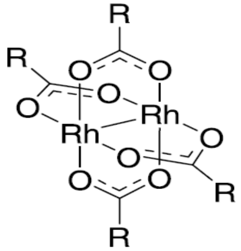
Aryliodinane intermediates have poor shelf life

First demonstration of the use of the oxidant $PhI(OAc)_2$ and Rh catalyst system

Breslow. R; Gellman, S.H. *J. Am. Chem. Soc.* **1983**, *105*, 6728

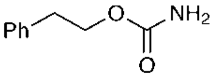
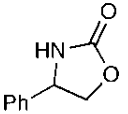
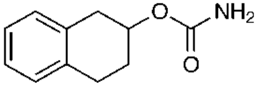
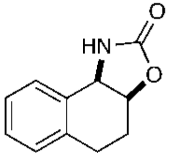
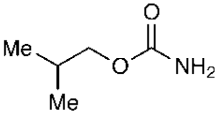
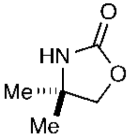
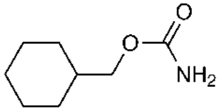
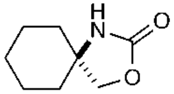
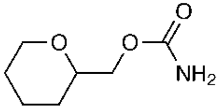
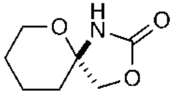
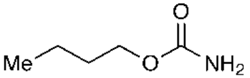
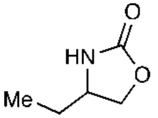
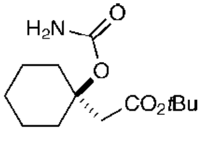
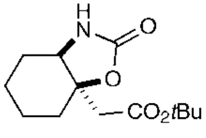
Rhodium-Catalyzed Oxidative C-H Insertion Reaction for Oxazolidinone Synthesis





A = $Rh_2(OAc)_4$

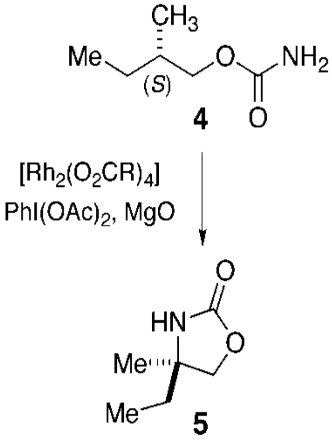
B = $Rh_2(tpa)_4$

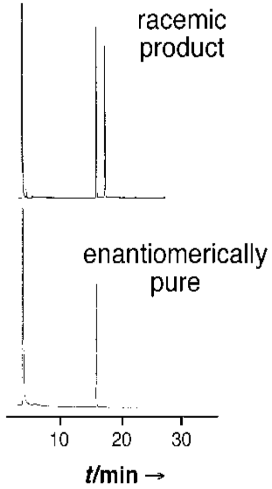
Substrate	Product	Catalyst[a]	Yield[b
		**B**	74
		**B**	77[c]
		**A**	83
		**A**	77
		B	79
		**A**	82
		B	84
		**B**	44
		**A**	82

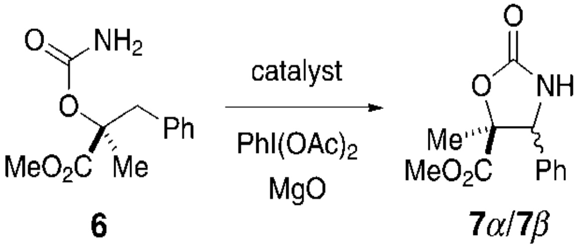
One-pot procedure for formation of aryliodinane and insertion of metallonitrenoids in C-H bond

Espino, C.G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598

Mechanism of Oxazolidinone Formation

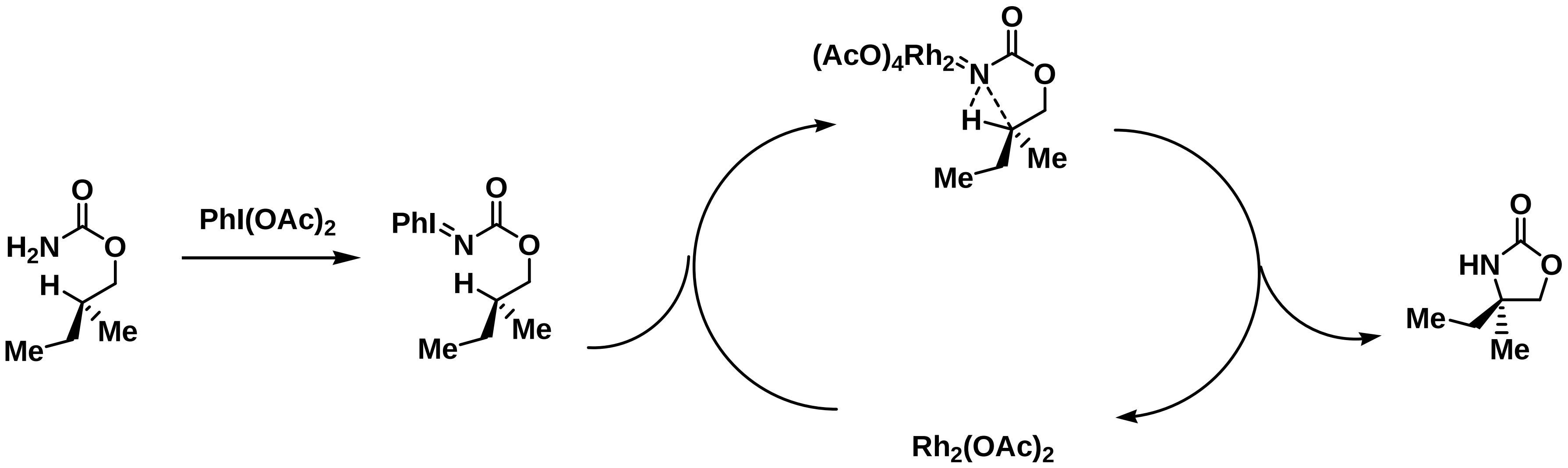






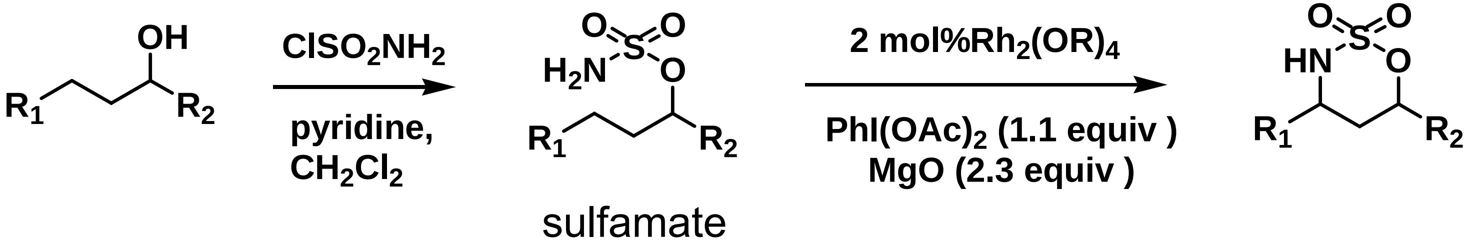
	7α:7β
$[Rh_2(OAc)_4]$	2:1
$[Rh_2(tpa)_4]$	1:2.6

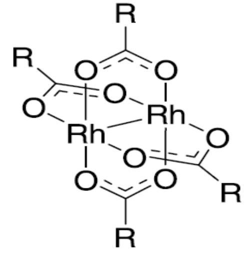
Data suggests a concerted, metal-directed N-atom insertion process



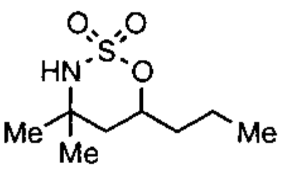
Espino, C.G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598

Rhodium-Catalyzed Oxidative C-H Insertion Reaction for Oxathiazinane Synthesis

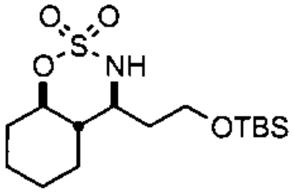




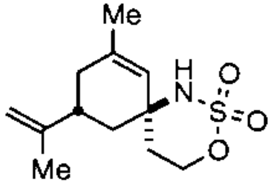
A = $Rh_2(OAc)_4$
B = $Rh_2(oct)_4$



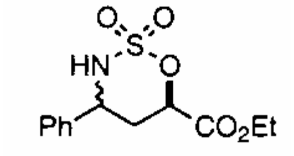
90% (A)



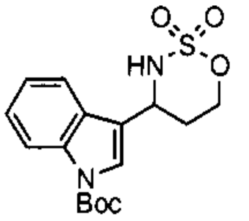
75% (B)
single isomer



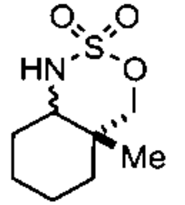
80% (A)
single isomer



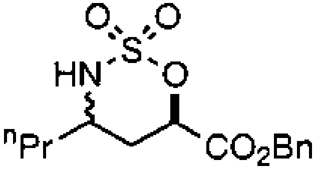
91% (B)
13/1 syn/anti



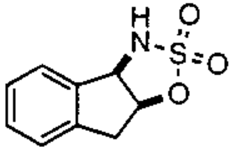
78% (A)



85% (A)
8/1 cis/trans



78% (B)
4/1 cis/anti



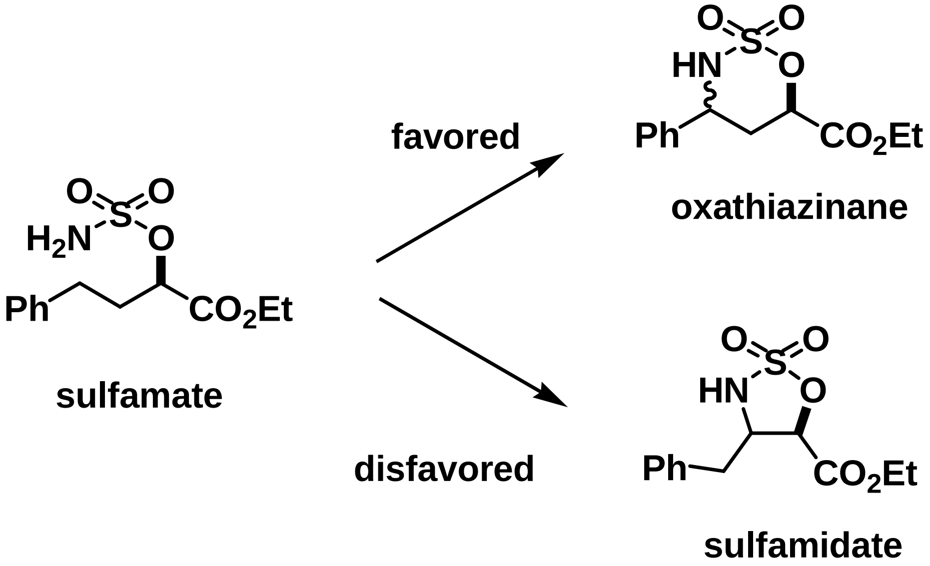
60% (A)

Espino, C.G.; Wehn P.M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935

Rhodium-Catalyzed Oxidative C-H Insertion Reaction for Oxathiazinane Synthesis

S-O and S-N bond lengths of 1.58 A

N-S-O angle of 103°



sulfamate

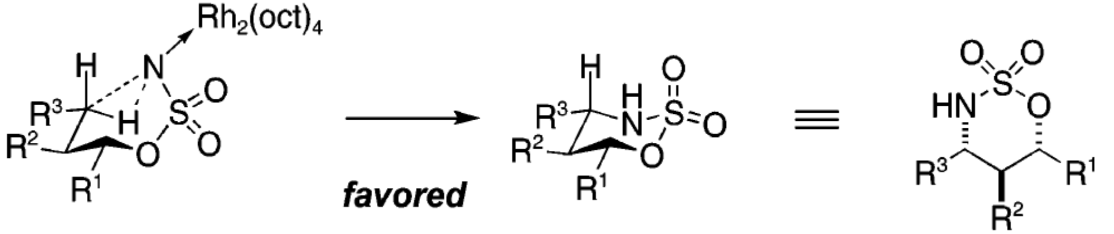
oxathiazinane

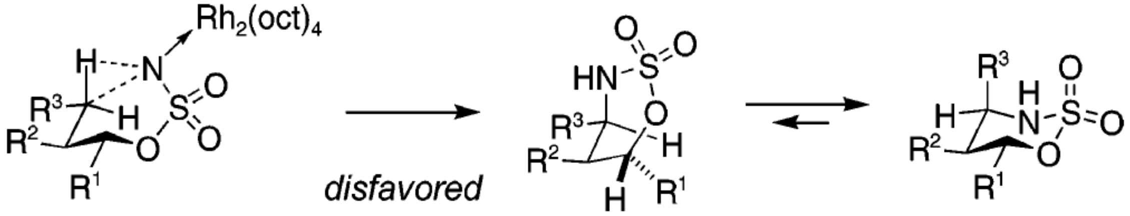
sulfamidate

S-O and S-N bond lengths of 1.59 A

N-S-O angle of 105°

N-S-O angle of 95°

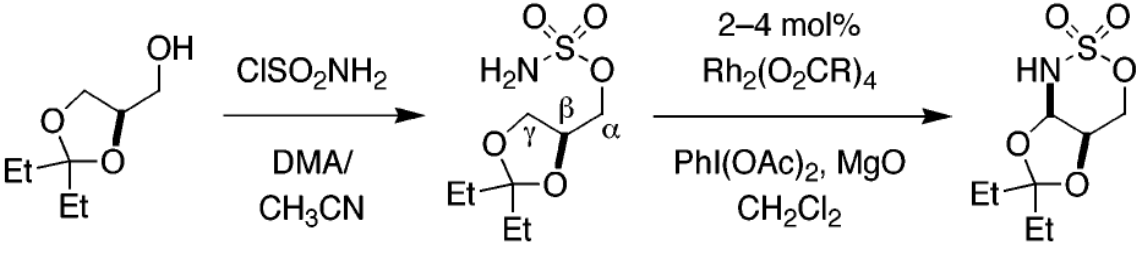




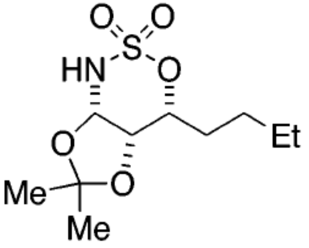
Torsional strain induced in developing product

Wehn P.M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823

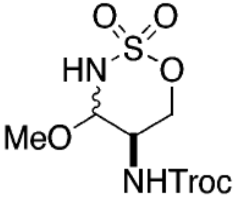
Rhodium-Catalyzed Amidation of Ethereal C^{α}-H Bonds



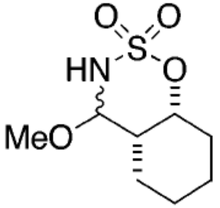
1 92%



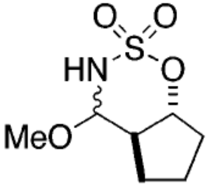
2 91%



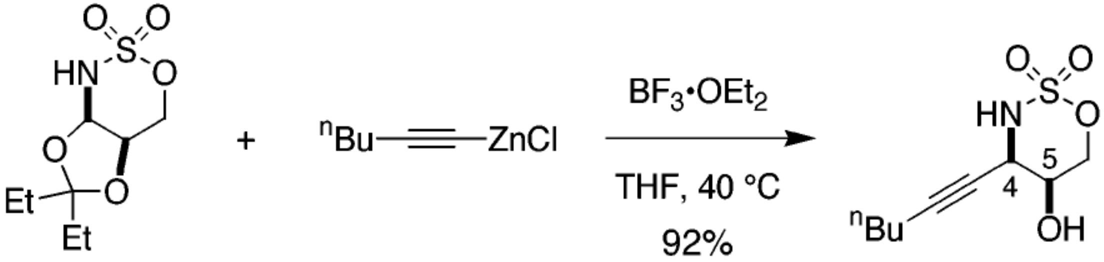
3 75%



4 78%



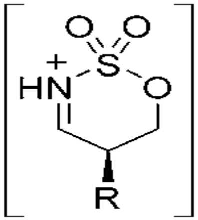
5 90%



92%

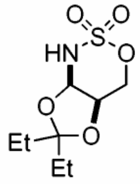
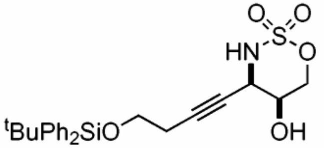
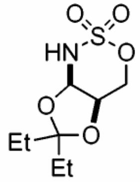
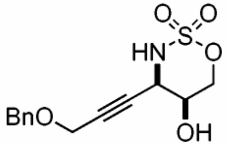
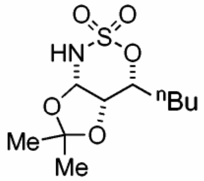
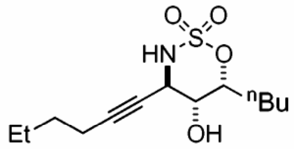
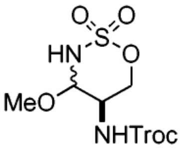
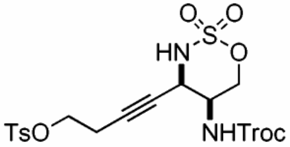
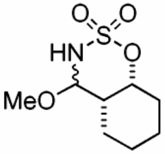
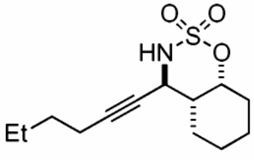
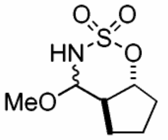
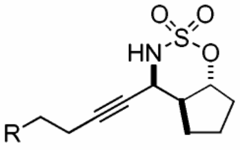
single diastereomer

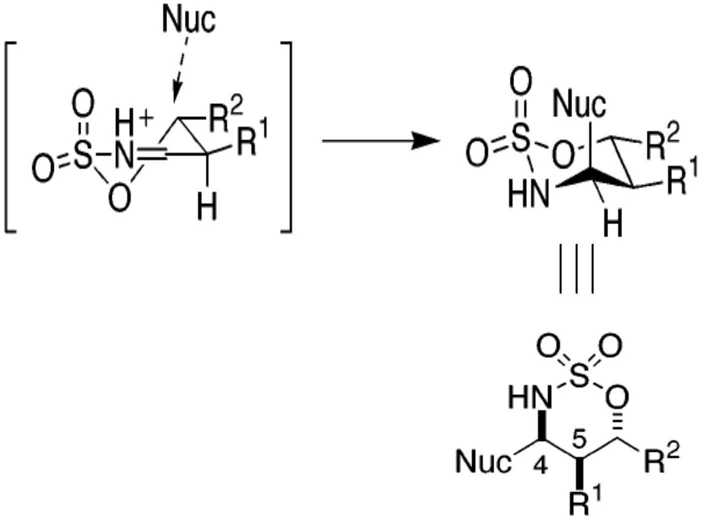
1 **6**



Fleming, J.J.; Fiori, K.W.. Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028

Alkynlzinc Addition Reactions with N,O-Acetals

Entry	Substrate	Major isomer[a]		Selectivity[b]	Yield[c]
1				**20:1**	**85**
2				**20:1**	**82**
3				**12:1**	**71**
4				**8:1**	**70**
5				**20:1**	**76**
6			R = Et	**6:1**	**80**
			= OP	**6:1**	**63**[d]

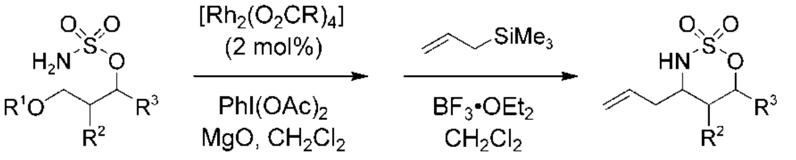


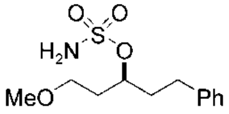
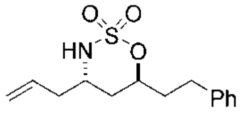
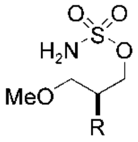
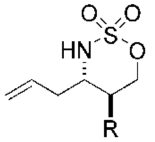
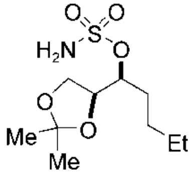
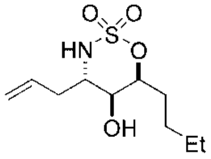
- When C6 unsubstituted, 4,5-*syn* favored

- When C6 substituted, 4,6-*anti* favored regardless of C5 configuration

Fleming, J.J.; Fiori, K.W.. Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028

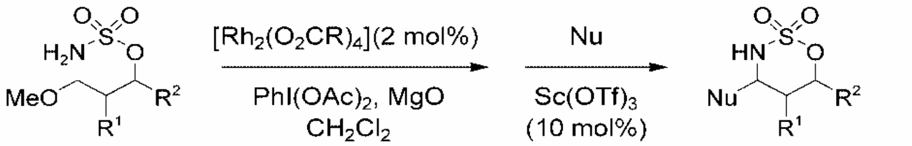
Tandem Rhodium C-H Amination, Iminium Ion Coupling Reactions

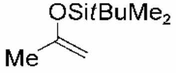
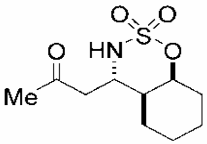
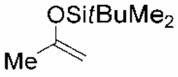
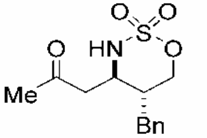
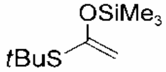
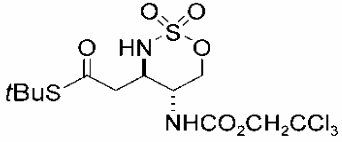


Entry	Substrate	Major product		d.r.[b]	Yield [%][c]
1 a				20:1	71[d]
2 a			R = Bn = *i*Pr = NHP	20:1 10:1 20:1	75[d,e] 60 60[d,f]
3 b				20:1	78[d]

a R = Me b R = CPh$_3$

R = Me



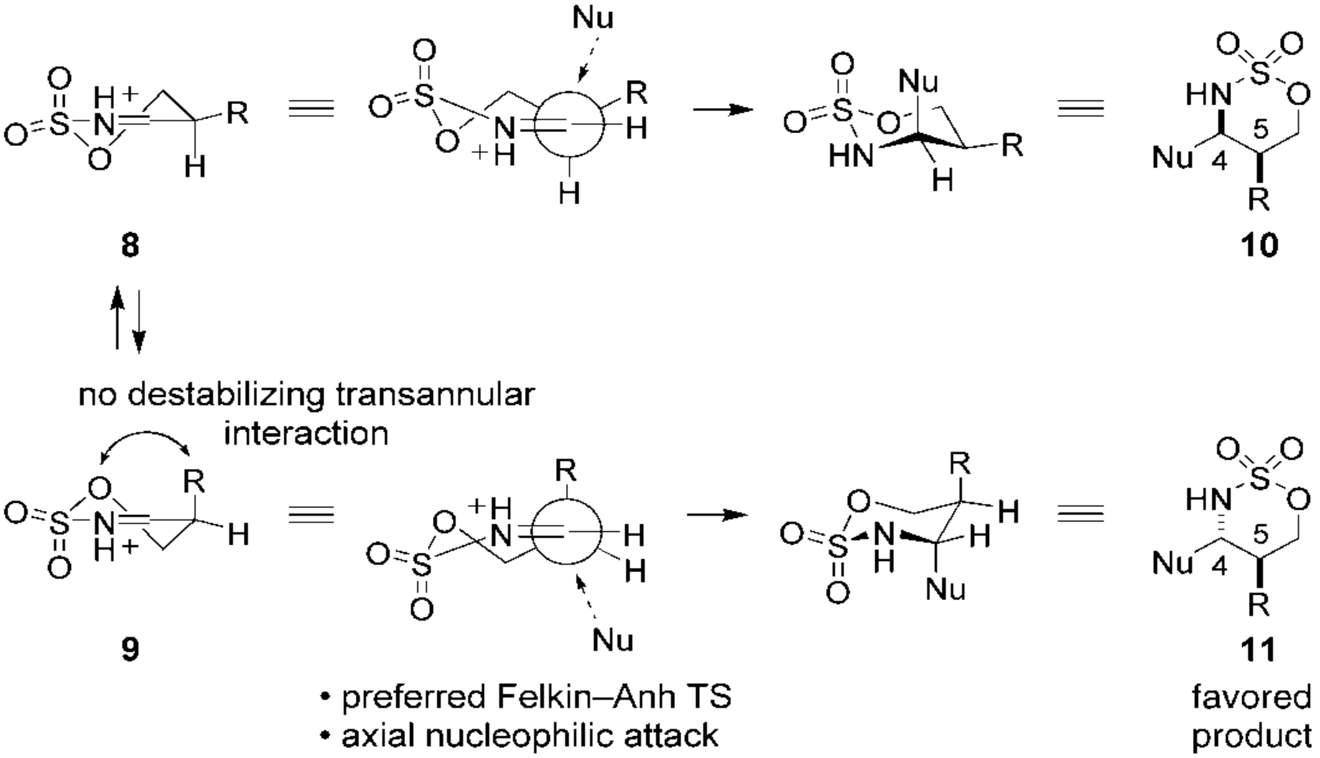
Entry	Nucleophile	Major product	d.r.[b]	Yield [%][c]
1			20:1	80
2			20:1	68[d]
3			20:1	60[d]

Ketene acetals can also be employed

One-pot procedure: rxn mixture filtered to remove MgO and then treated with either 1.5 equiv BF$_3$ OEt$_2$ and 4 equiv allyltrimethyl silane or 0.1 equiv Sc(OTf)$_3$ and 4 equiv of silyl enol ether

Fiori, K.W.; Fleming, J.J. Du Bois, J.*Angew. Chem. Int. Ed.* **2004**, *43*, 4349

Stereochemical Models for Iminium Ion Additions



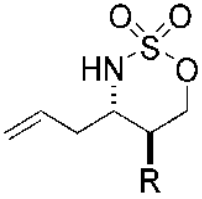
no destabilizing transannular interaction

- preferred Felkin–Anh TS
- axial nucleophilic attack

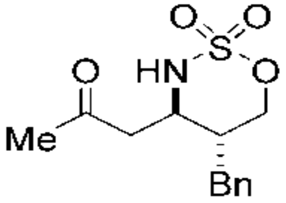
favored product

Model for alkylzinc Reagents

Model for allylsilanes and silyl enol ethers



R = Bn	20:1	75
= *i*Pr	10:1	60
= NHP	20:1	60

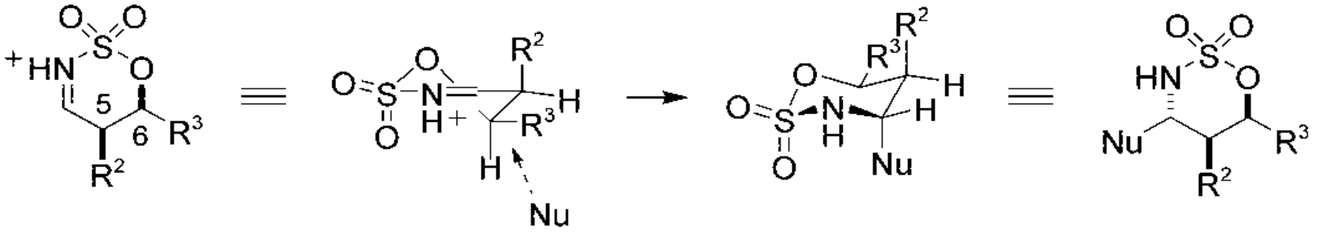


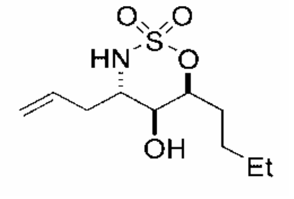
20:1 68[d]

Fiori, K.W.; Fleming, J.J. Du Bois, J.*Angew. Chem. Int. Ed.* **2004**, *43*, 4349

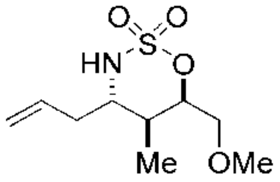
Stereochemical Models for Iminium Ion Additions

Highly selective additions to 5,6-syn-substituted iminium ions



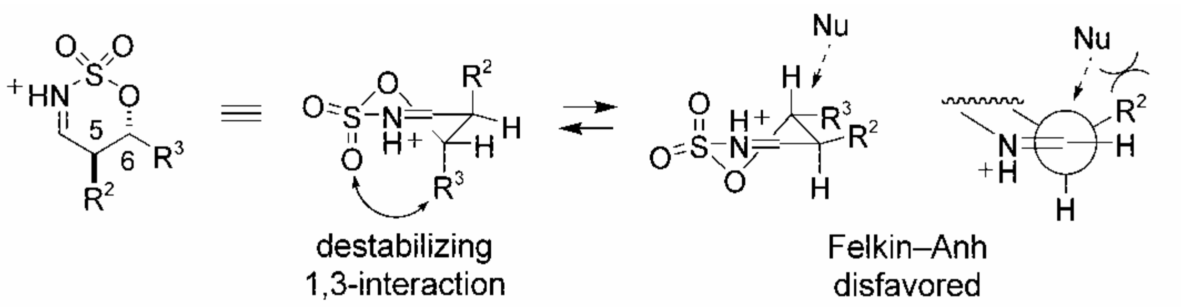


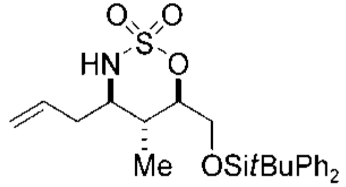
78%
20:1



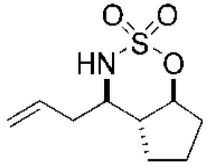
72%
20:1

Selectivity erodes with 5,6-*anti*-configured substrates





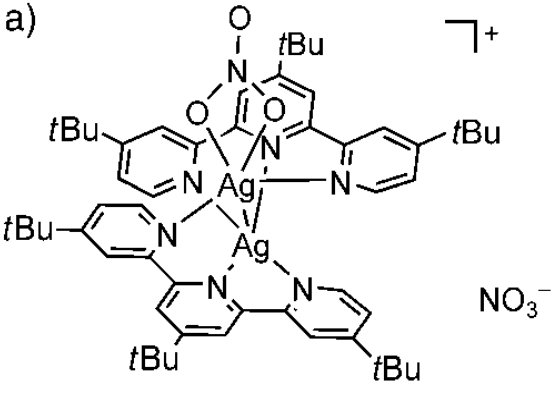
81%
1.5:1



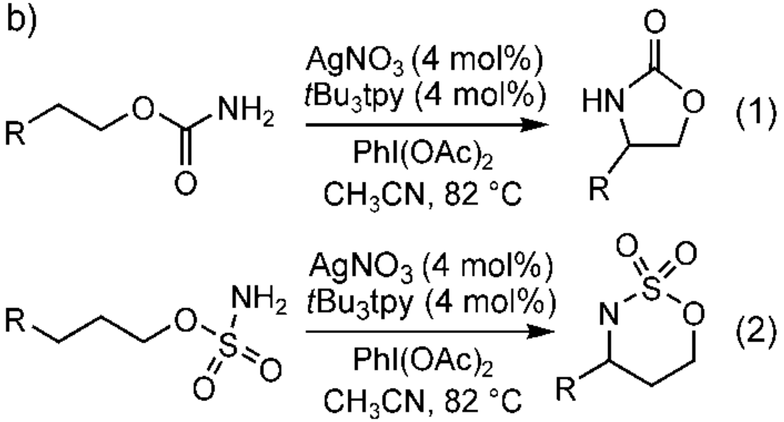
82%
2.5:1

Fiori, K.W.; Fleming, J.J. Du Bois, J.*Angew. Chem. Int. Ed.* **2004**, *43*, 4349

A Silver-Catalyzed Oxidative C-H Insertion Reaction for Oxazolidinone and Oxathiazinane Synthesis



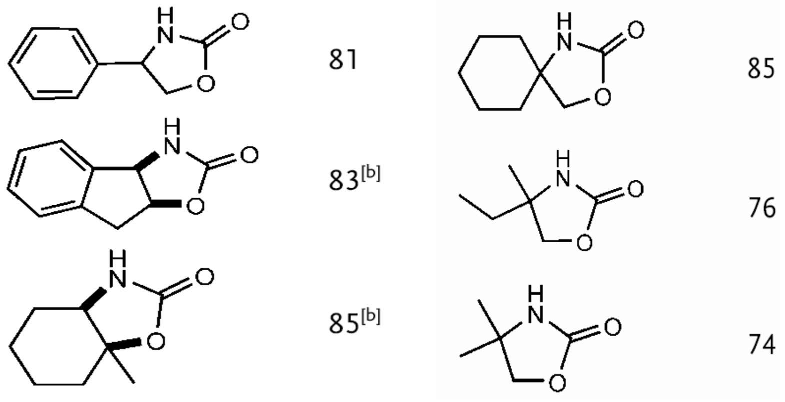
1

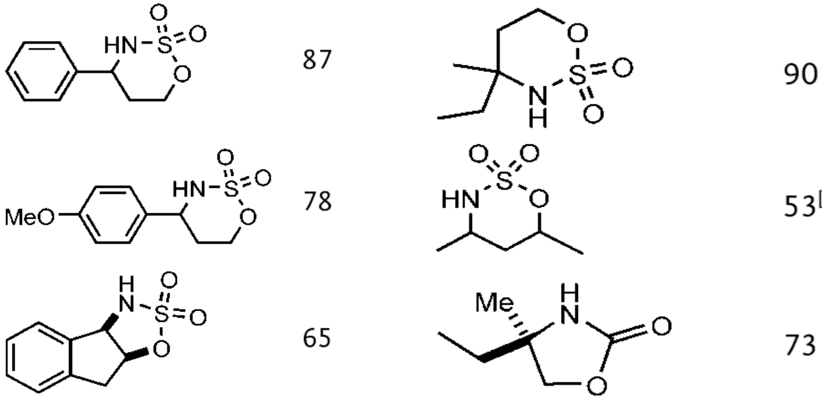


Both ligand and Ag Salt commercially available

Carbamate C-H insertions

sulfamate C-H insertions



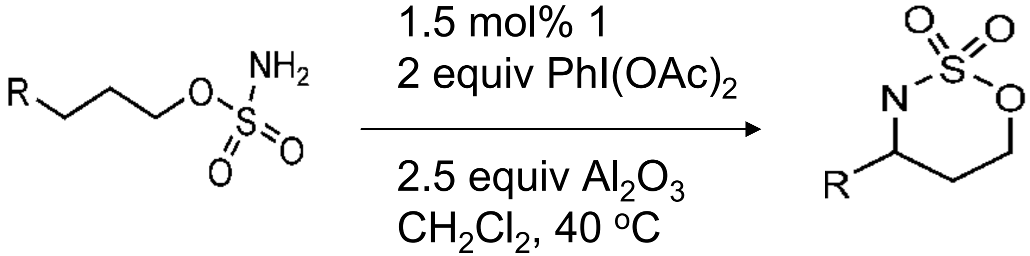


stereospecific

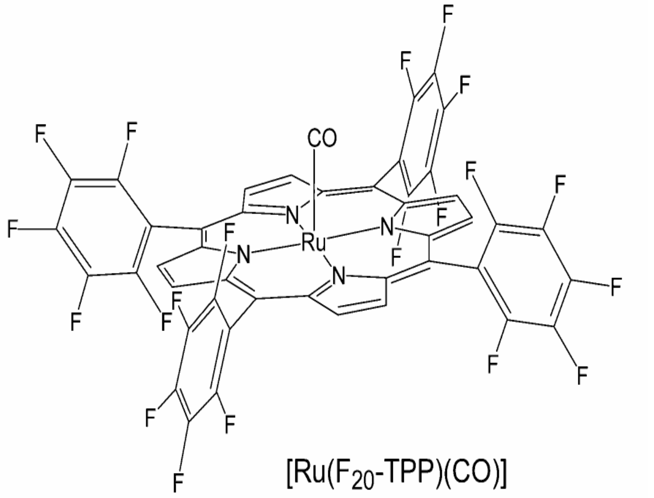
Similar yields; however, Rh-catalyzed process proceeds at 40 ^{o}C

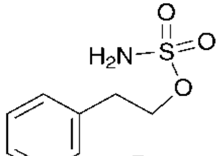
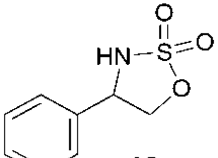
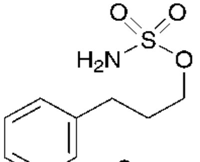
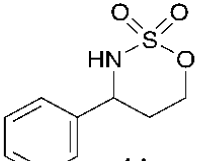
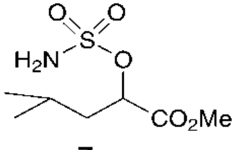
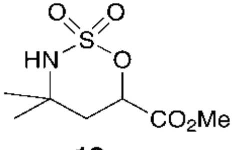
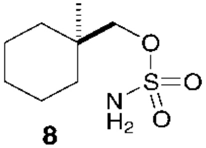
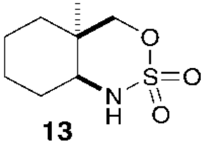
Cui, Y.; He, C. *Angew. Chem. Int. Ed.* **2004**, *5*, 4210

Intramolecular C-N Bond Formations Reactions Catalyzed By a Ruthenium Porphyrin


1.5 mol% 1
2 equiv $PhI(OAc)_2$

2.5 equiv Al_2O_3
CH_2Cl_2, 40 °C


[Ru(F_{20}-TPP)(CO)]

 **5**	 **10**	56
 **6**	 **11**	77
 **7**	 **12**	76
 **8**	 **13**	88

Single isomer*

Fe and Mn metalloporphyrins afforded lower yields

Highly robust catalyst featuring
up to 59 catalytic turnovers at 1.5 mol%,
and up to 300 at 0.1 mol% catalyst loadings

*Dirhodium complex afforded 8:1 cis:trans

Liang, J.-L.; Yuan, S.-X.; Huang, J.S.; Yu, W.Y.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610

Intramolecular C-N Bond Formations Reactions Catalyzed By Ruthenium Porphyrins

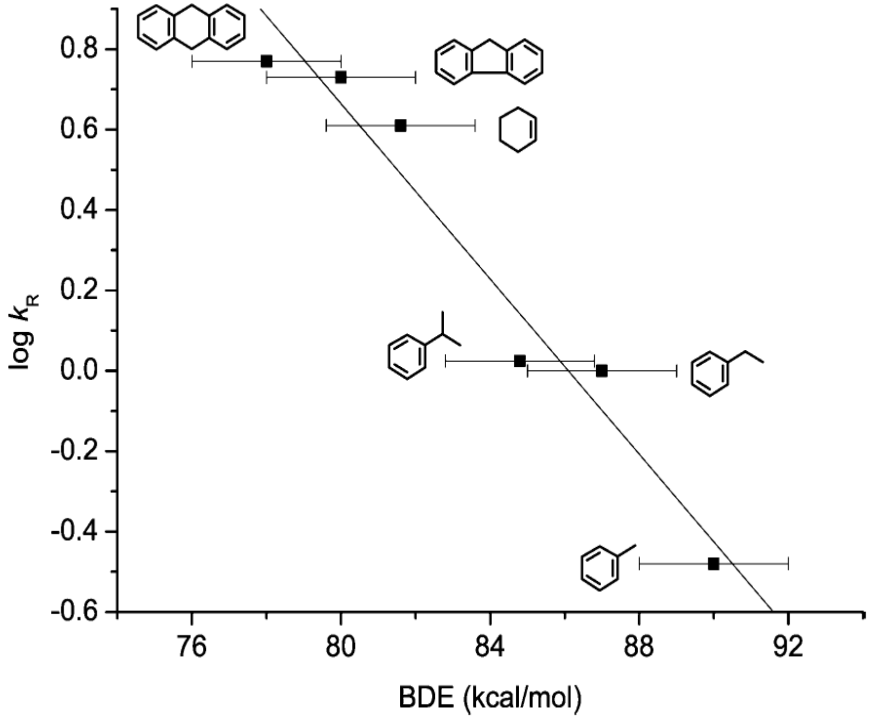
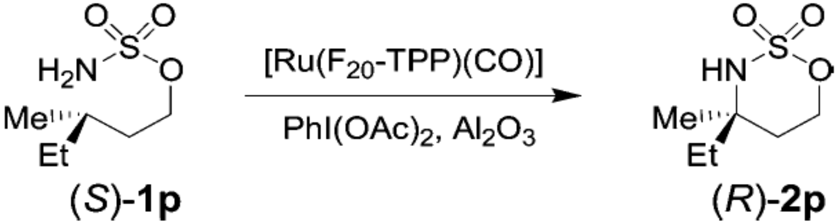


FIGURE 2. Correlation between relative amidation rates (log k_R) and C−H bond dissociation energies (BDE) for the intermolecular amidation of hydrocarbons with "$PhI(OAc)_2 + NH_2$-SO_2-*p*-$C_6H_4NO_2$" catalyzed by [Ru(F_{20}-TPP)(CO)].

Data for intermolecular reaction supports H-atom abstraction mechanism

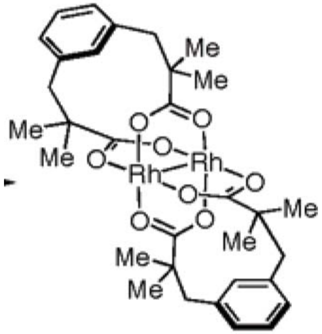


However, intramolecular C-H amination is stereospecific!

a) Carboradical is too shortlived to undergo configuration inversion
b) Nonsynchronous concerted mechanism bearing significant hydrogen abstraction character

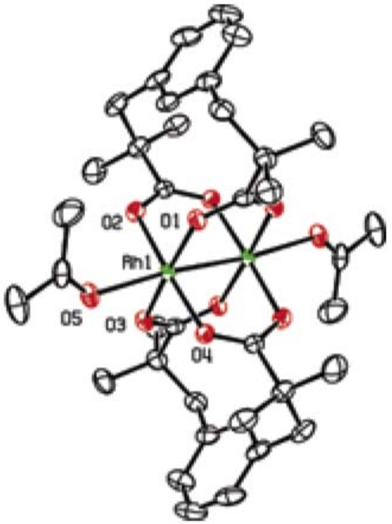
Liang, J.-L.; Yuan, S.-X.; Huang, J.S.; Yu, W.Y.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610

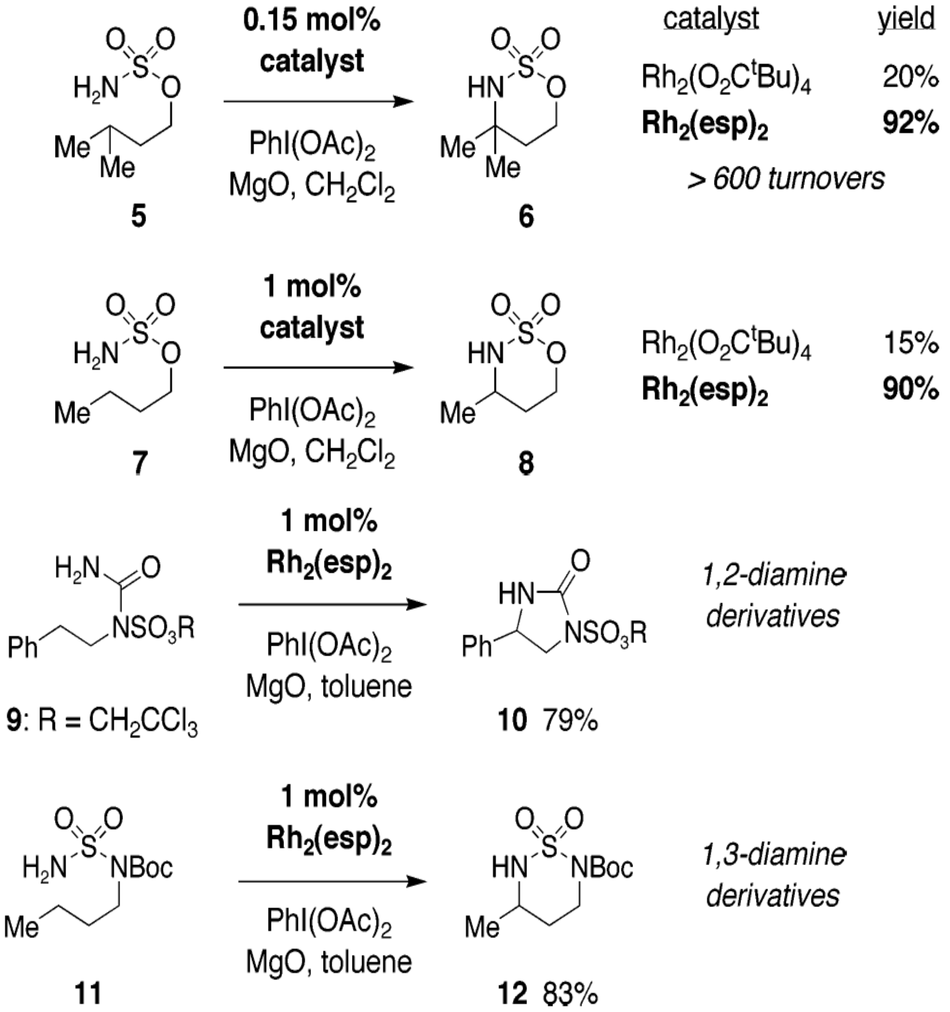
Expanding the Scope of C-H Amination Through Catalyst Design



$Rh_2(esp)_2$

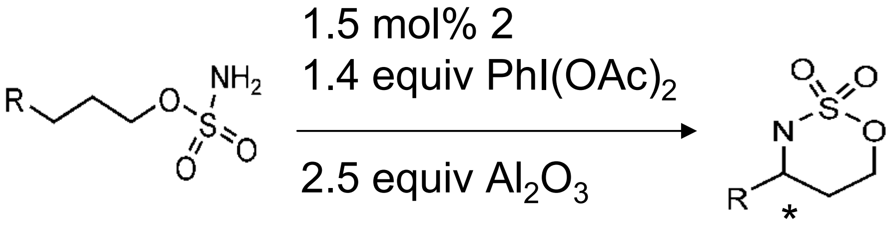
Chelate effect should disfavor complete ligand dissociation from metal center and confer added stability to complex





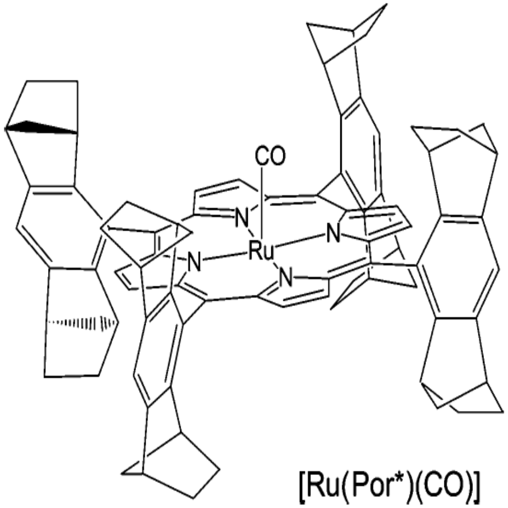
Espino, C.G.; Fiori,K.W.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378

Intramolecular C-N Bond Formations Reactions Catalyzed By a Chiral Ruthenium

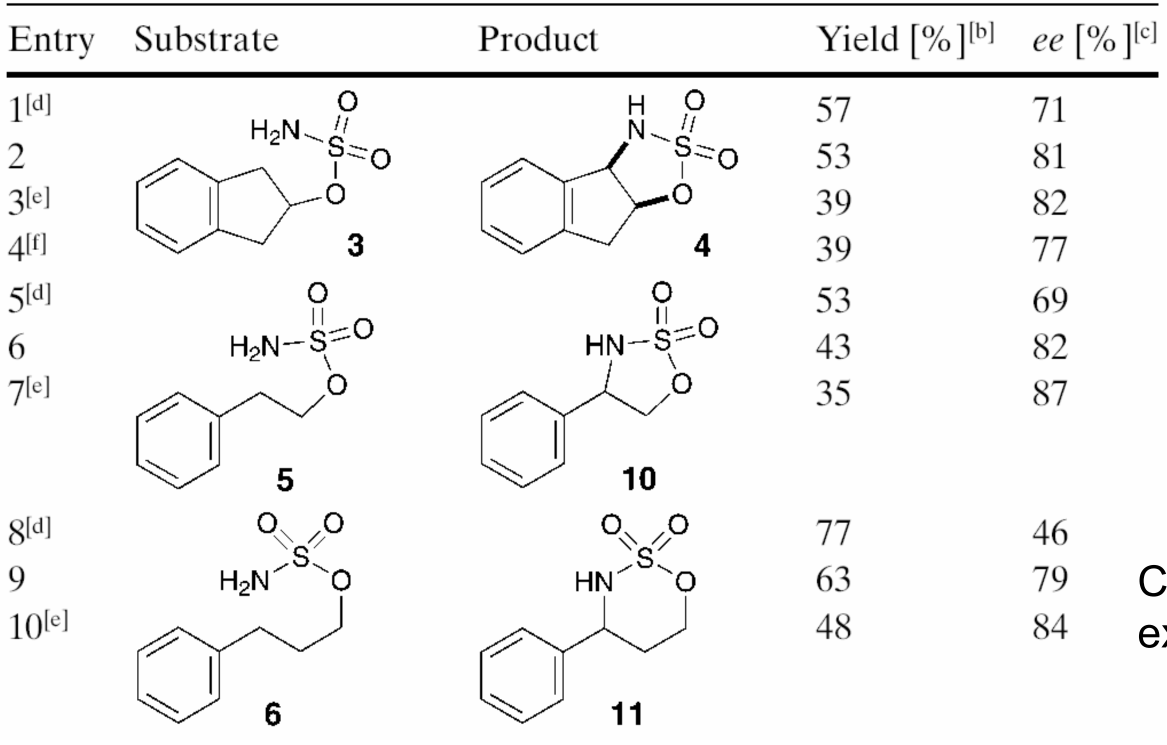


1.5 mol% 2
1.4 equiv $PhI(OAc)_2$

2.5 equiv Al_2O_3



[Ru(Por*)(CO)]



Entry	Substrate	Product	Yield [%][b]	*ee* [%][c]
1[d]	**3**	**4**	57	71
2			53	81
3[e]			39	82
4[f]			39	77
5[d]	**5**	**10**	53	69
6			43	82
7[e]			35	87
8[d]	**6**	**11**	77	46
9			63	79
10[e]			48	84

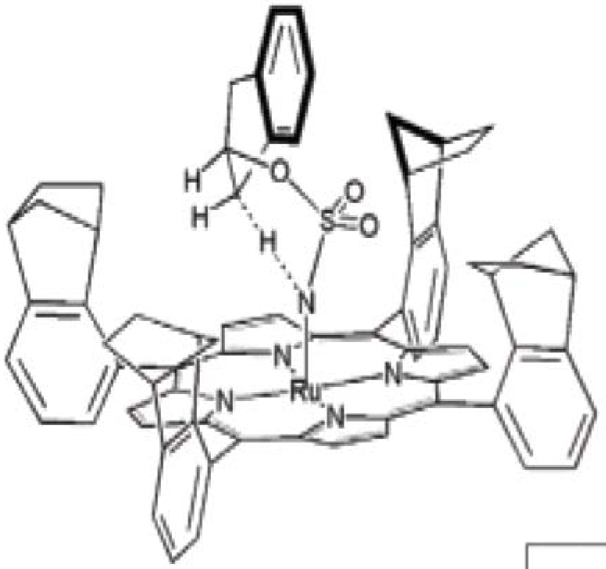
[d] in CH_2Cl_2 at 40 °C
[e] in CH_2Cl_2 at 5 °C
[f] in toluene at 0 °C

Chiral porphyrin ligand is both expensive and difficult to synthesize

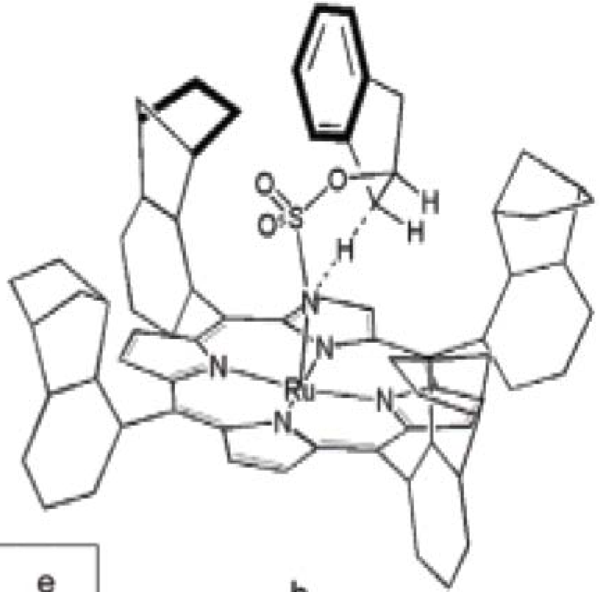
Liang, J.-L.; Yuan, S.-X.; Huang, J.S.; Yu, W.Y.; Che, C.-M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3465

Intramolecular C-N Bond Formations Reactions Catalyzed By a Chiral Ruthenium Porphyrin

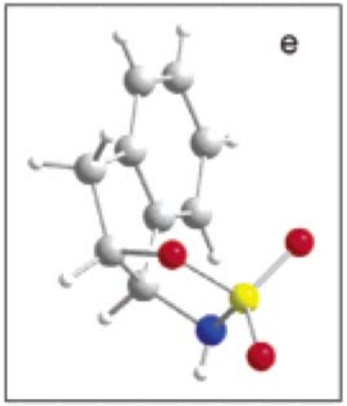
Imido phenyl group points toward the smaller methano-bridge



a



b

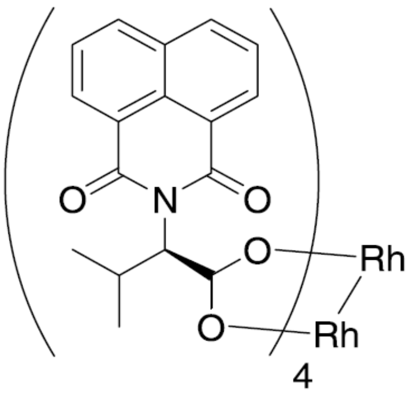


e

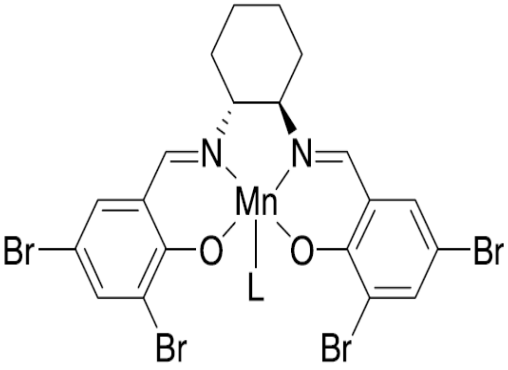
X-ray structure of the major enantiomer

Liang, J.-L.; Yuan, S.-X.; Huang, J.S.; Yu, W.Y.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610

Intramolecular C-N Bond Formations Reactions Catalyzed By Rhodium and Manganese complexes

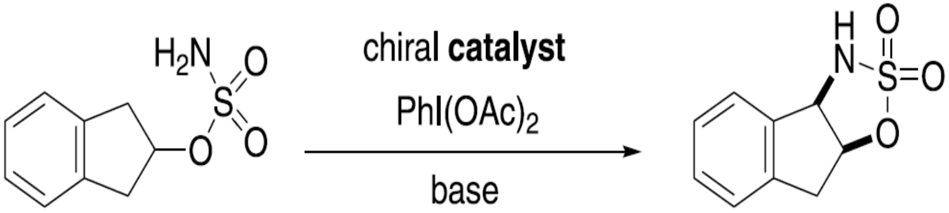


A



L = Cl

B



JRH1

Catalyst	yield	er
A	55%	65:35
B	48%	76:24

More readily accessible and cheaper
However low selectivity obtained

Fruit, C.; Muller, P. *Helv. Chim. Acta* **2004**, *87*, 1607
Zhang, J.; Chan, P.W.H.; Che, C.-M. *Tetrahedron Lett.* **2005**, *46*, 5403

Slide 42

JRH1 John R Heemstra Jr, 4/17/2006

Summary of Intramolecular C-H Aminations via the ‘Outer-Sphere’ Mechanism

- The intramolecular C-H amination reaction is now a highly dependable and predictable transformation and has found application in the preparation of a variety of natural products.

- The intramolecular insertion of metallonitrenoids (M = Ag, Rh, Ru) into C-H bond is a stereospecific process.

- The new $Rh_2(esp)_2$ catalysts now allows very low catalyst loadings and extremely high catalyst TON (>600)

- Enantioselective methods are still in their infancy and a method that provides high selectivity is still lacking