Frontiers in Chemistry Seminar

Transition Metal-Catalyzed Functionalization of C_{sp3} via C-H bond activation

Presented by: Jared T. Hammill
Wipf Group Meeting
University of Pittsburgh
September 22, 2012

Outline

A. Introduction

B. C_{sp3} C-H Bond Functionalization

   A. C-O Bond Formation

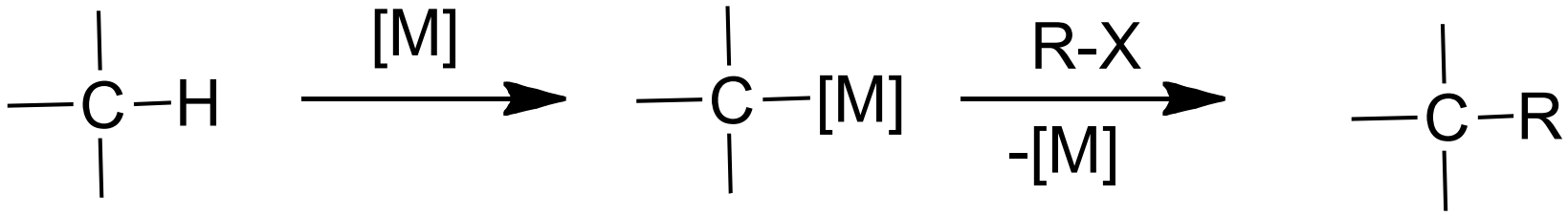
   B. C-N Bond Formation

   C. C-C Bond Formation

   D. C-X Bond Formation

C. Conclusions and Future Directions

What is Transition Metal-Catalyzed C-H activation?



R = C, N, O, S, B, halogen

Definition:

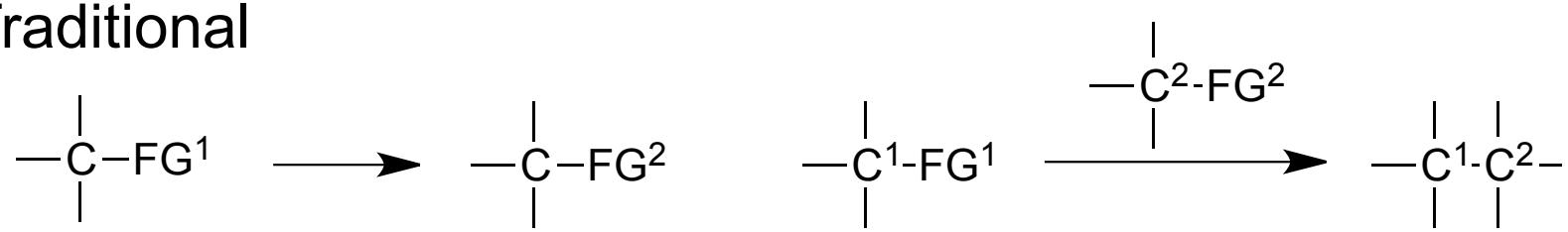
The use of transition metals to increase the reactivity of a C-H bond by replacement of the strong C-H bond with a more readily functionalized C-[M] bond.

Chem. Rev. **1997**, *97*, 2879-2932

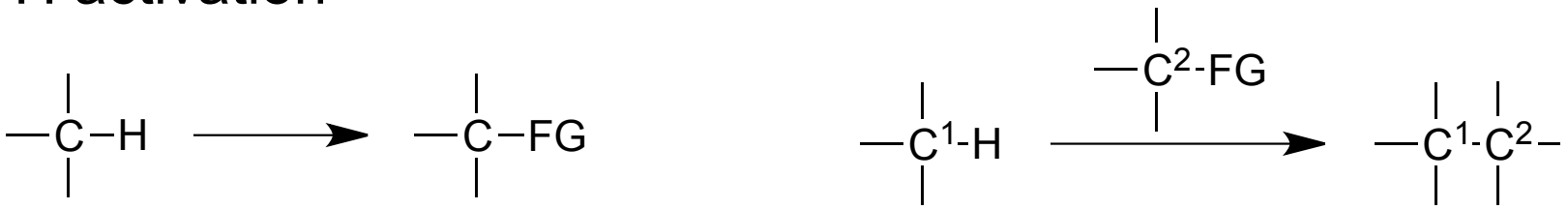
Advantages of C-H activation

Only requires prefunctionalization of one precursor

Traditional



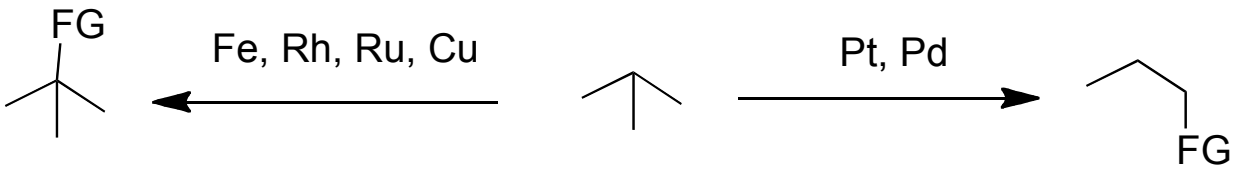
C-H activation



Science, **2006**, *312*, 67-72

Advantages of C-H activation

Transition Metal Cataysis:



Changing Metal we can get reactivity at 1º, 2º, and 3º C-H bonds

While many transition metals have been used today I will focus on Pt, Pd, Fe, Rh, Ru

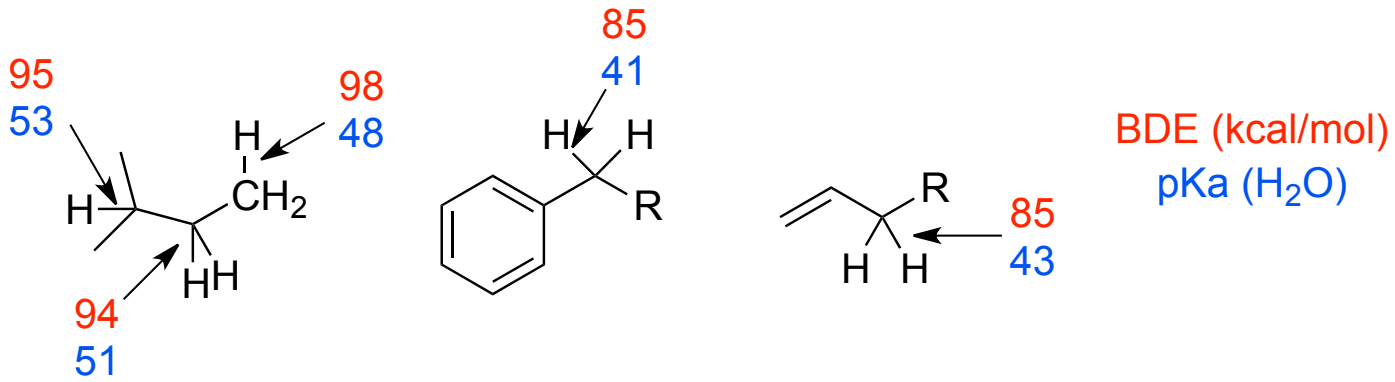
Challenges of C-H activation

"Inertness" of alkanes

Formerly known as "paraffins", derived from the latin *parum affinis* (without affinity), products more reactive than SM

Ubiquitous nature of C-H bonds

Selectivity challenging: little difference in reactivity between C-H bonds



pKa's were reproduced from http://evans.harvard.edu/pdf/evans_pka_table.pdf
BDE's were reproduced based on http://www.q1.fcen.uba.ar/materias/qi1/Tablas/disocia.pdf

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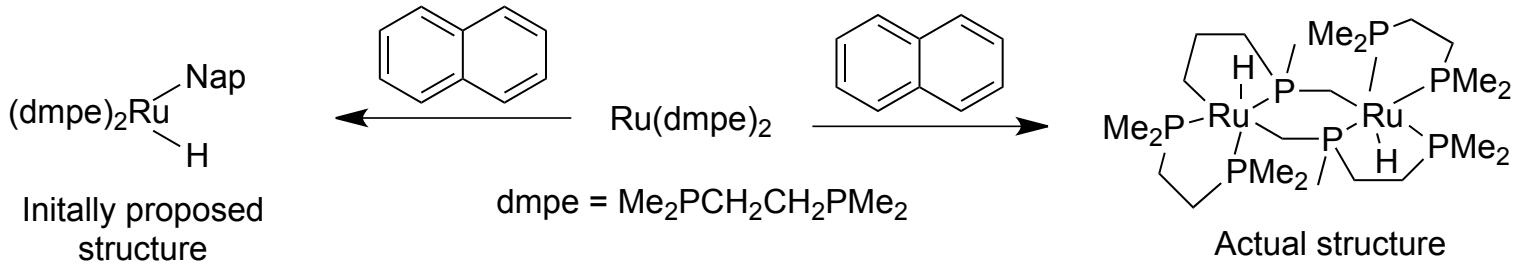
Chem. Rev. **1997**, *97*, 2879-2932

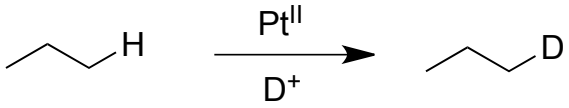
Background C-H Insertion

1962: Chatt



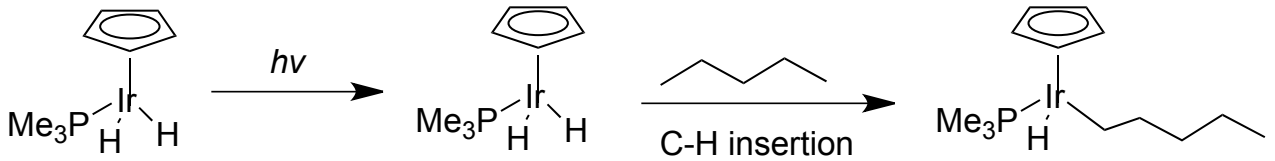
J. Chem. Soc. **1962**, 2545 *J. Organomet. Chem.* **2004**, *689*, 4083-4091

1969: Shilov



J. Phys. Chem. **1969**, *73*, 1525

1982: Bergmann



Science, **1984**, *223*, 902

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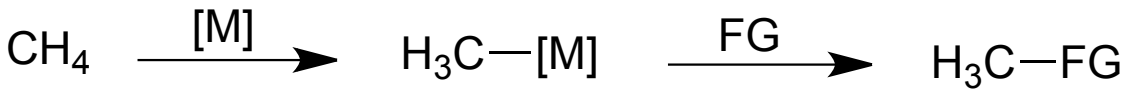
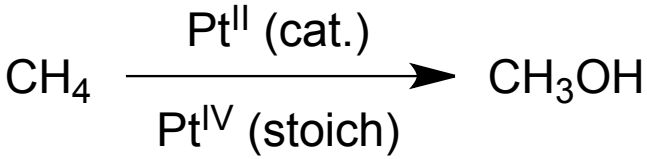
Shilov Chemistry



Functionalization of Methane

- Methane = main constituent of natural gas
- Need way to functionalize for transport (gas → liquid)
- Need to use for synthesis of fine chemicals

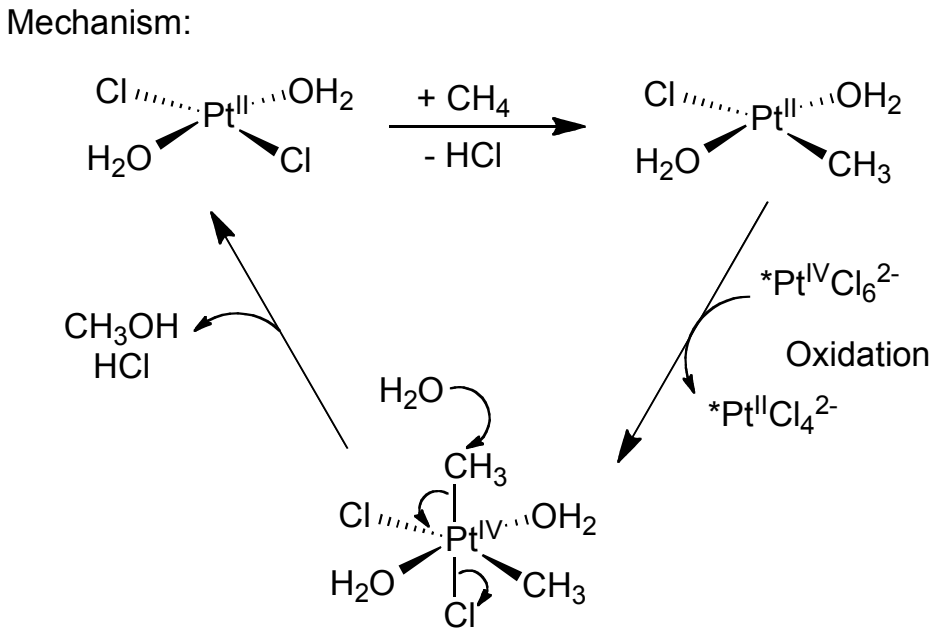
Shilov chemistry



- Methanol = industrial SM for plastics and paints
- Poor efficiency

Nature, **2007**, *446*, 391-594
New J. Chem. **1983**, *7*, 729

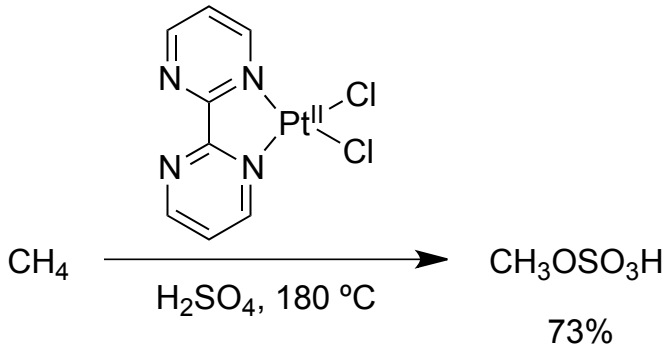
Shilov Chemistry



Key observation:

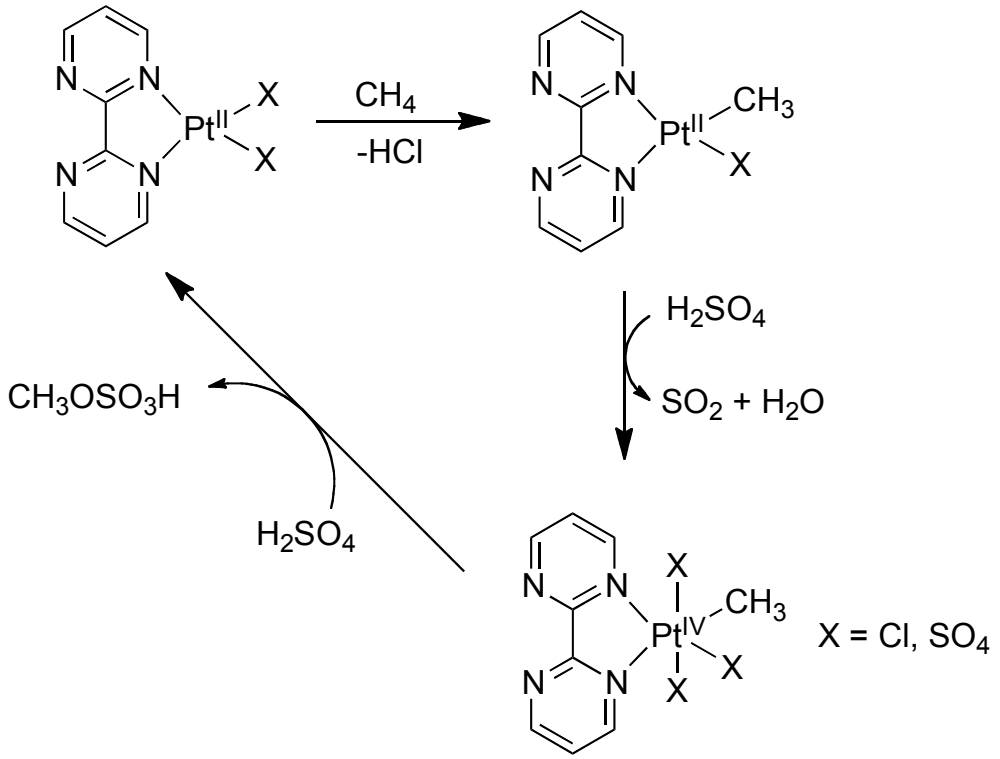
Stoichiometric amount of Pt (needed for oxidation)

Current State of the Art



- Cat. Pt w/H_2SO_4 for Ox.
- Ligand stabilized Pt^{II} In Conc. H_2SO_4 @ 180 ºC >50 h

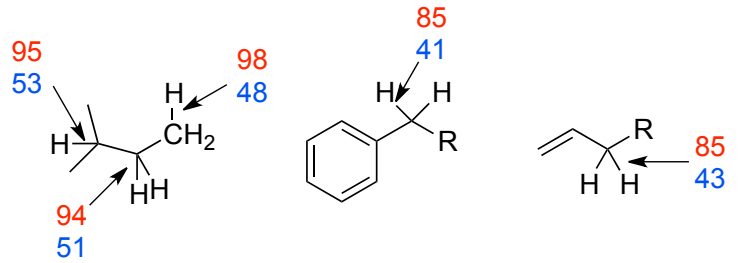
Mechanism:

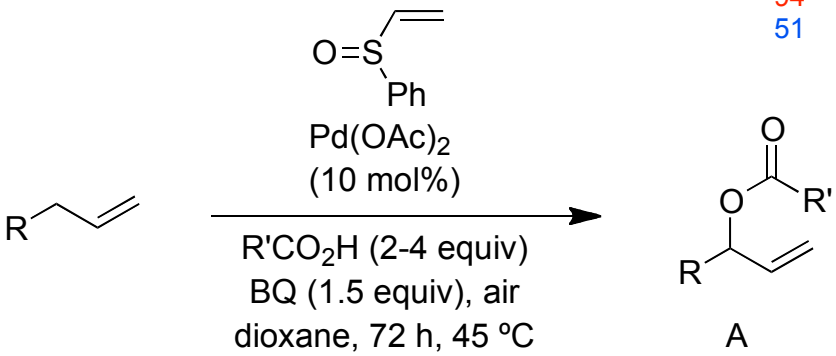


Science, **1998**, *280*, 560

White's Pd^{II} Allylic C-H Activation

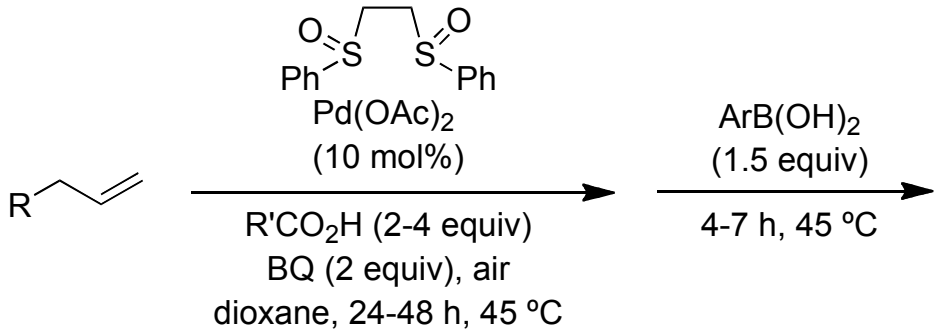
Selective Allylic C-H Insertion:





13 examples:
53-77% yield
16:1 to 46:1 A:B

J. Am. Chem. Soc. **2005,** *127,* 6970



13 examples:
53-77% yield
>20:1 E:Z
>20:1 internal:terminal

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J. Am. Chem. Soc. **2006**, 128, 15076

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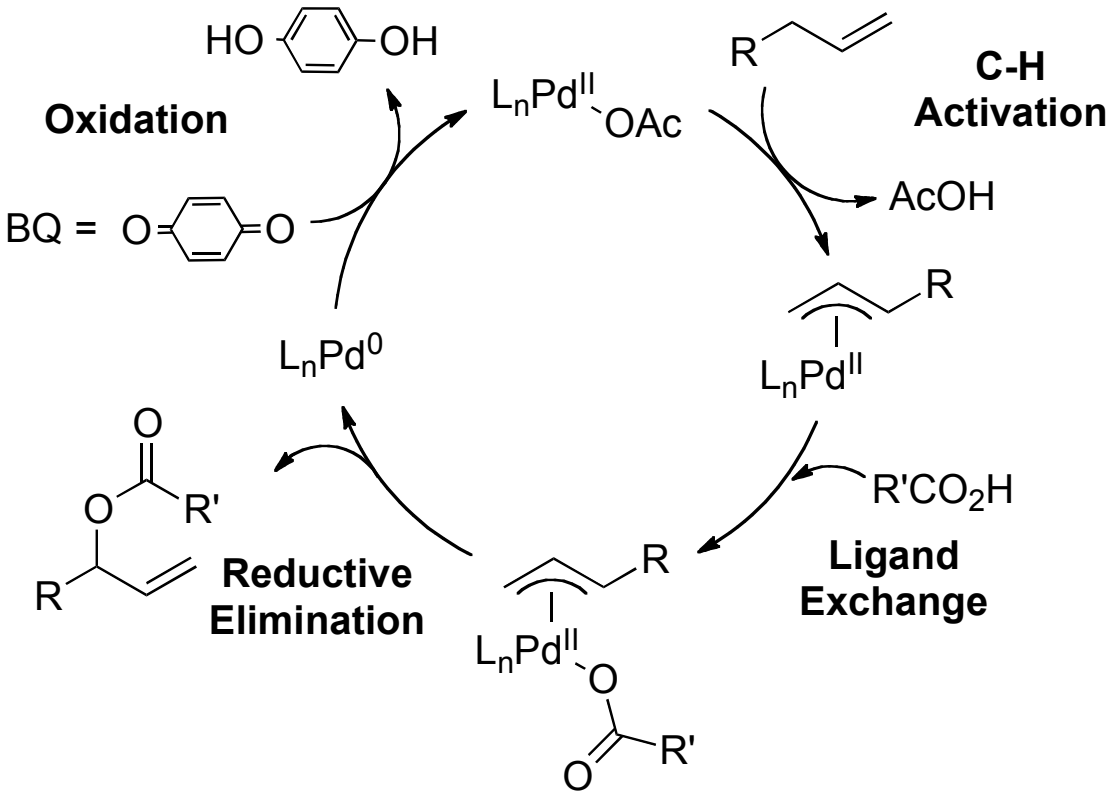
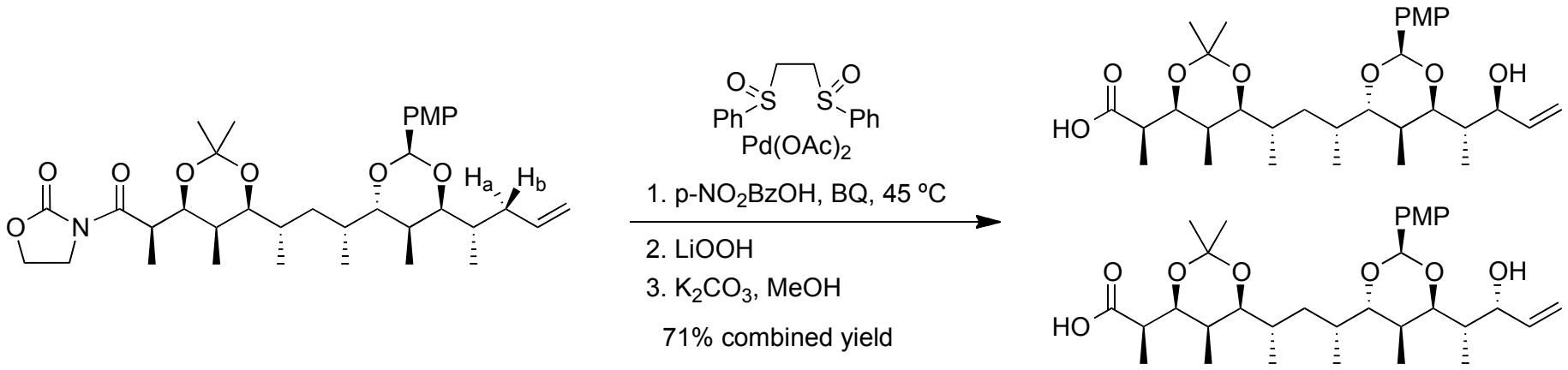
Mechanism of Allylic C-H Activation

Electrophillic Pd^{II}/Pd^{0} Catalysis

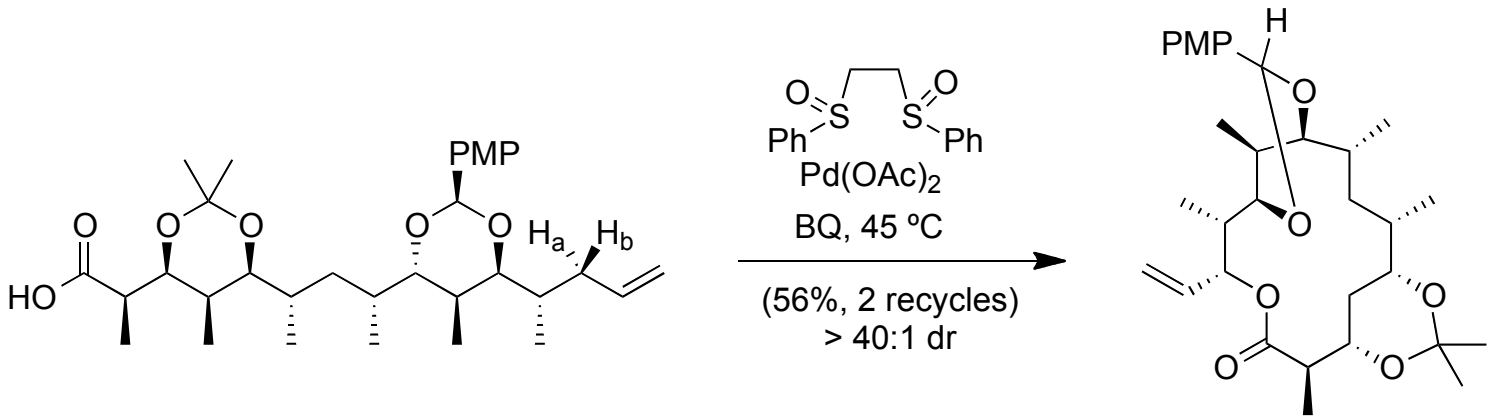


Complex Product Allylic C-H

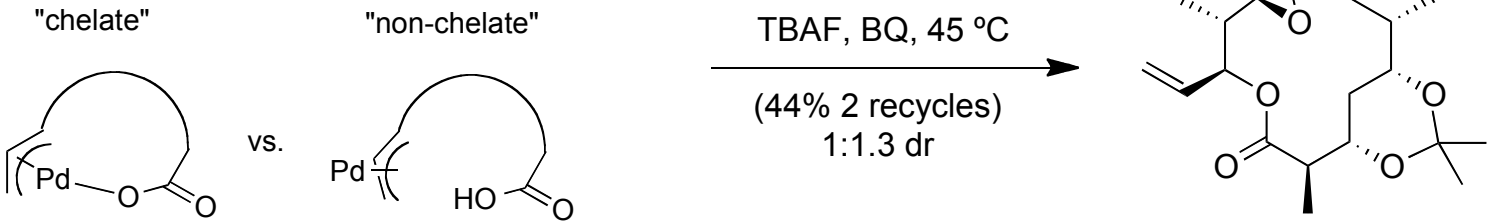


Nat. Chem., **2009**, *1*, 547

6-Deoxyerthronolide B



TBAF breaks chelation to acid
(outer sphere vs. inner sphere)



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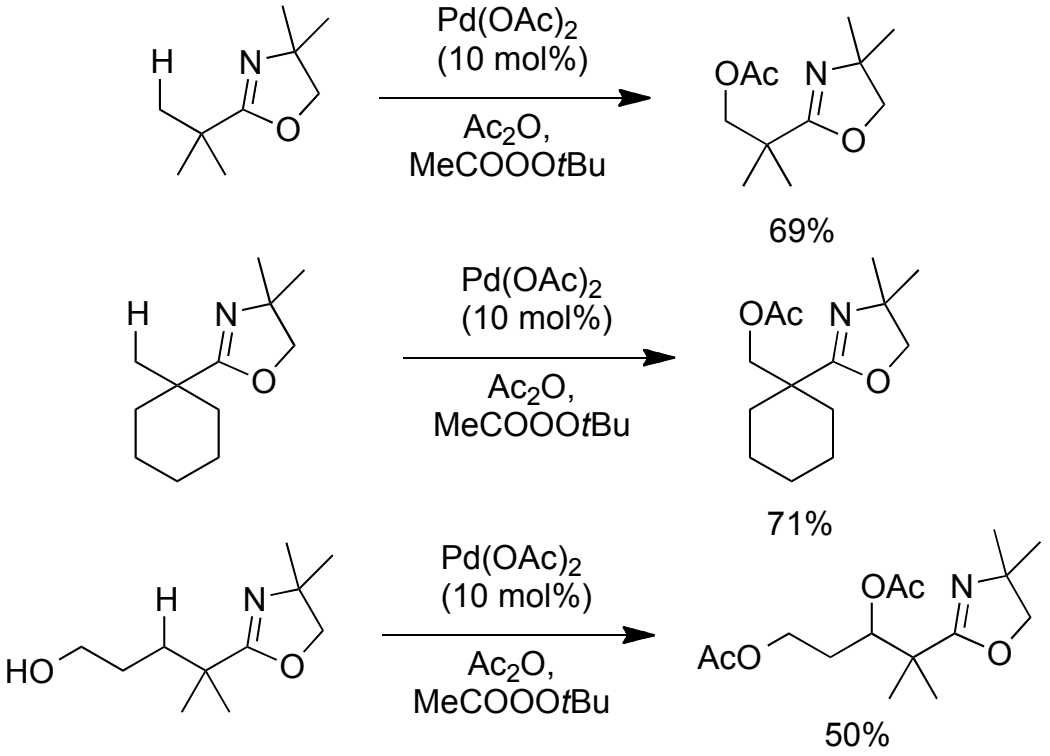
Nat. Chem., **2009**, *1*, 547

Oxazoline Directed C-H activation

Direct the Palladium where to go:



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Angew. Chem. Int. Ed. **2005**, *44*, 7420

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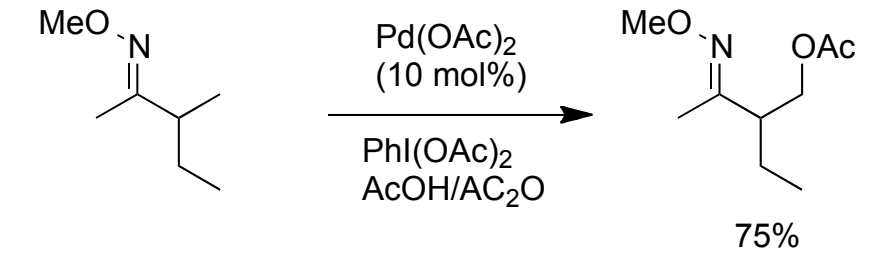
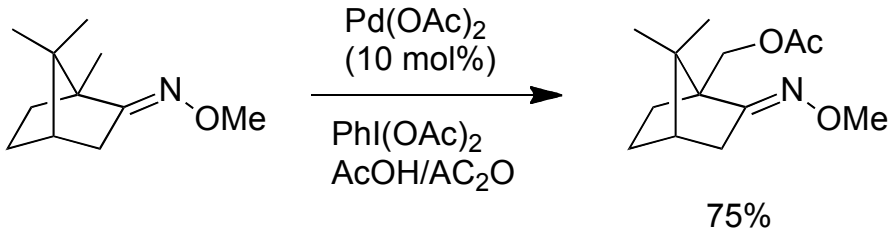
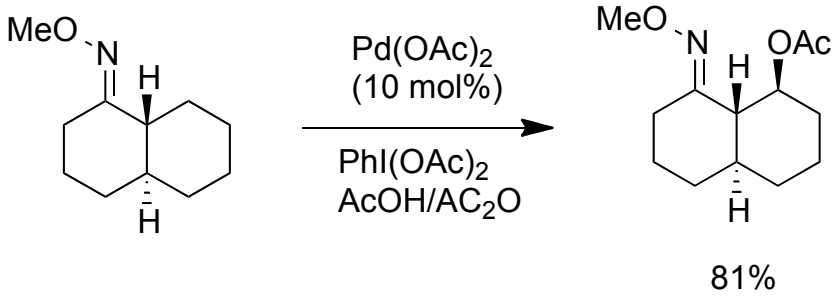
Sanford's Oxime







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J. Am. Chem. Soc. **2004**, *126*, 9542

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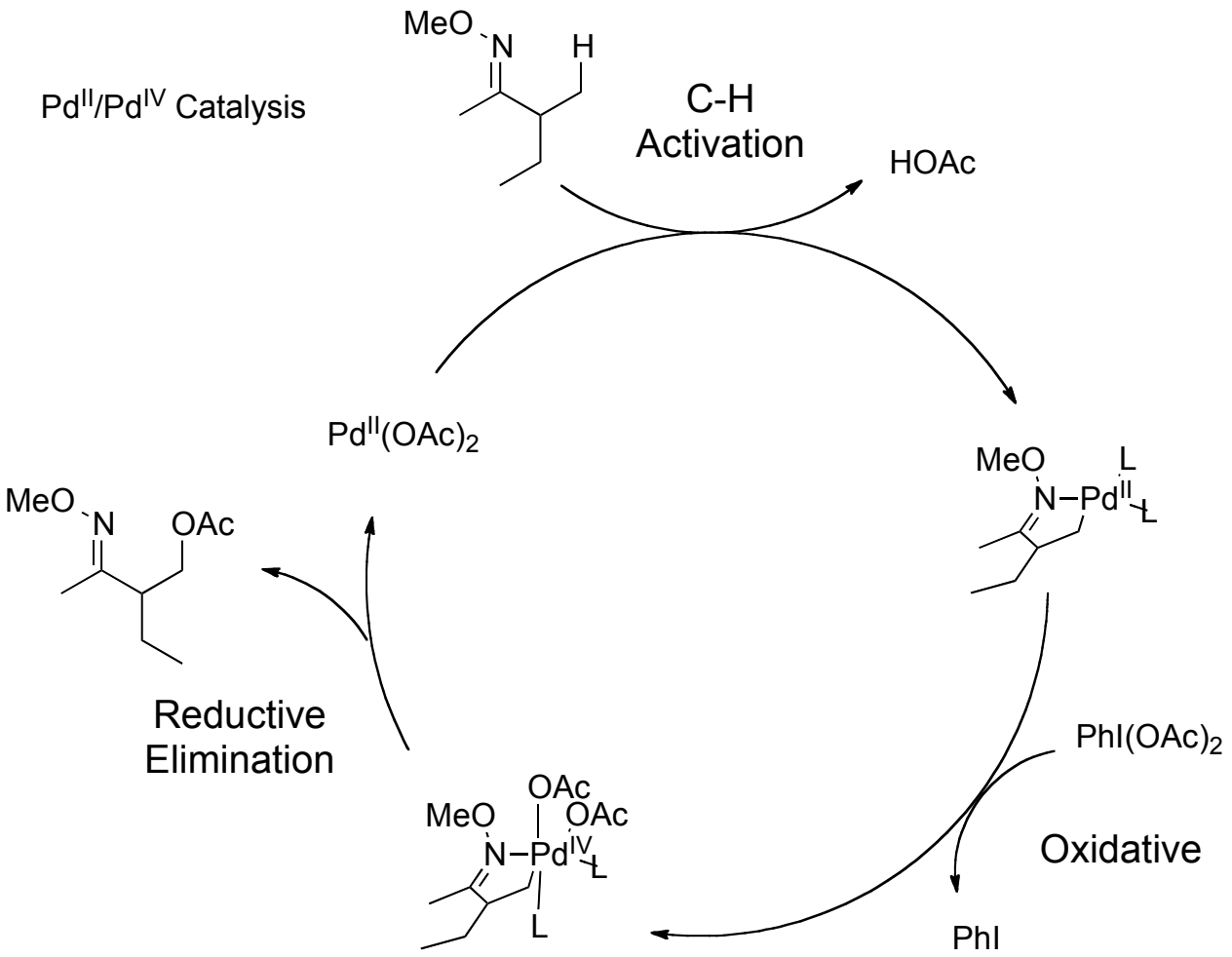
Directed C-H activation



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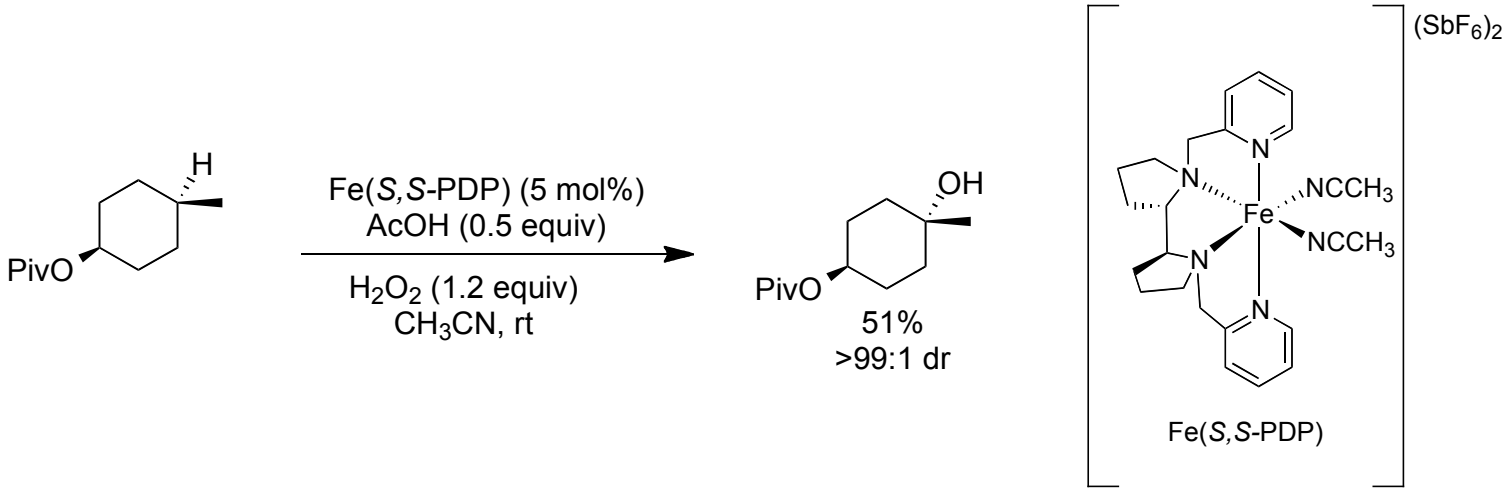
White's Fe C-H activation



Science, **2007**, *318*, 783
Science, **2010**, *327*, 566
Nat. Chem., **2011**, *3*, 216
Science, **2012**, *335*, 807
J. Am. Chem. Soc. **2012**, *143*, 9721

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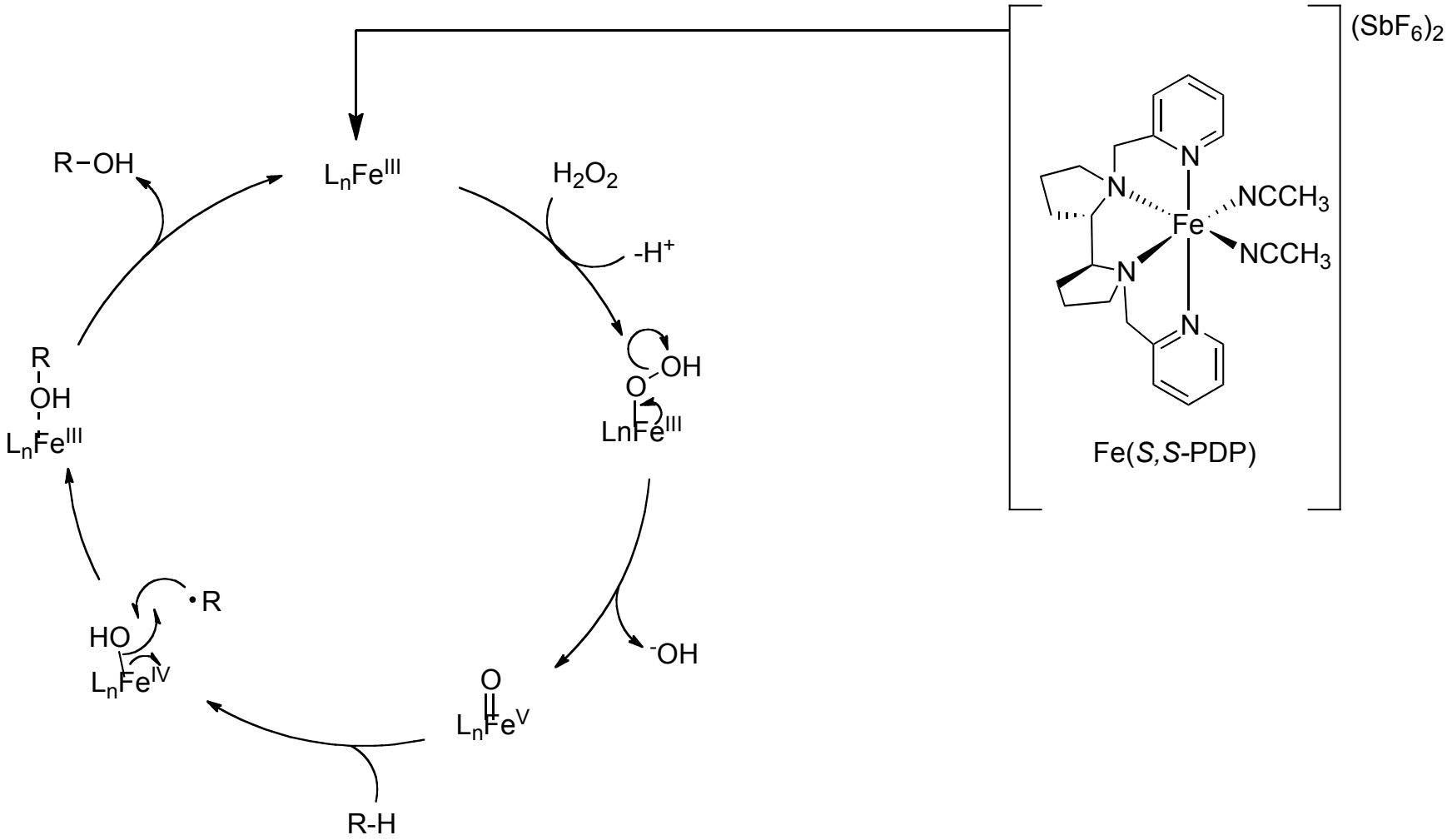
White's Fe C-H activation



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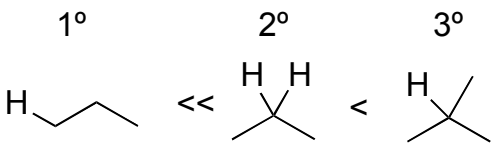
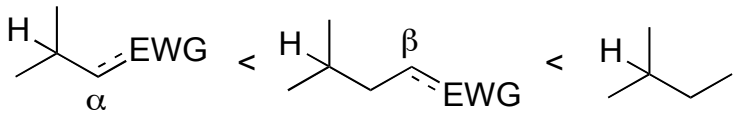
Predictable selectivity

General reactivity trends mirror BDE:





Want: electron rich, 3º C-H bonds

Does it work?

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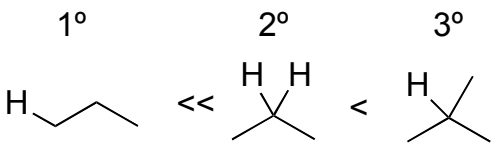
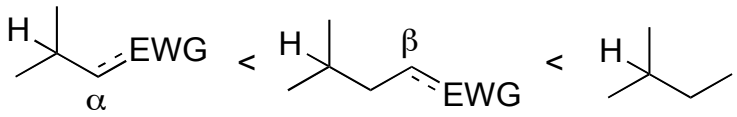
Science, **2007**, *318*, 783

Predictable selectivity

General reactivity trends mirror BDE:





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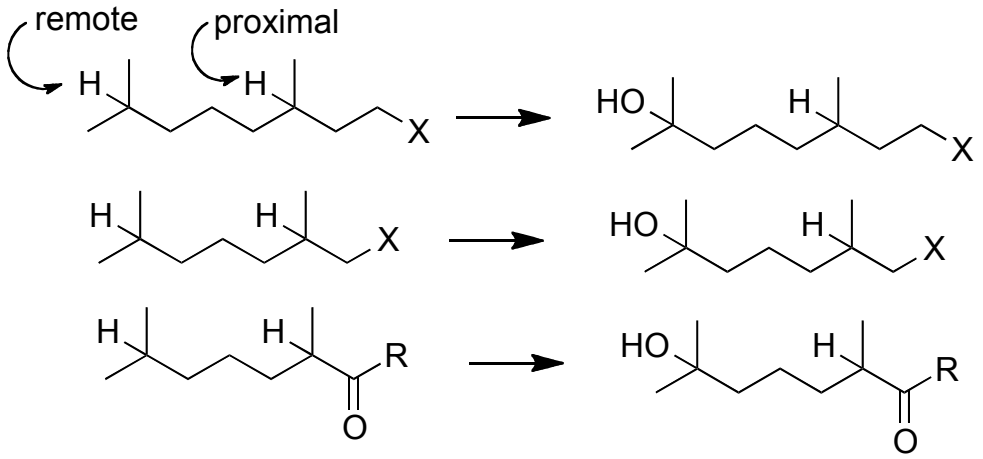

	remote:proximal
X = OAc,	5:1
X = Br,	9:1
X = OAc	29:1
X = Br	20:1
R = CH_3	>99:1
R = OCH_3	>99:1

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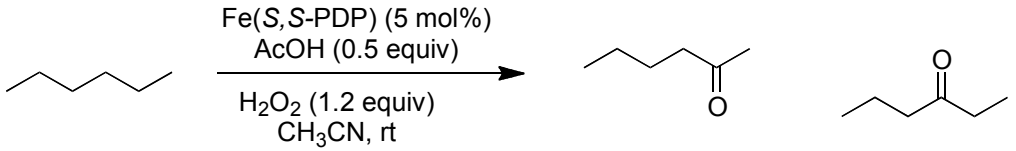
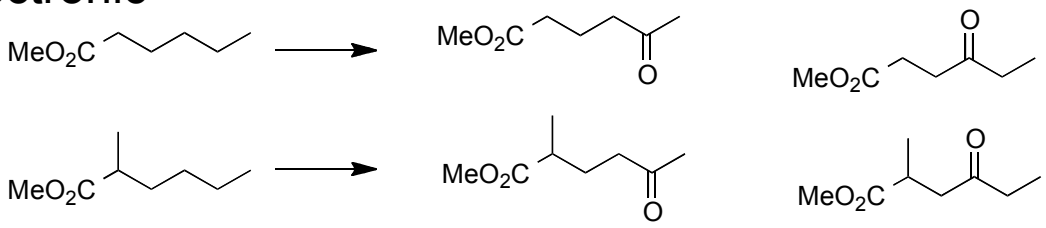
Science, **2007**, *318*, 783

Methylene reactivity selectivity



Yield	Selectivity
56%	1.1:1

Stereoelectronic



72%	2:1	
69%	3.5:1	

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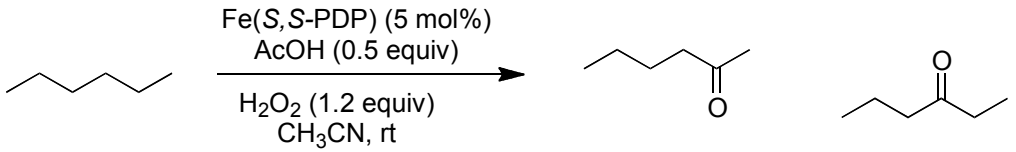
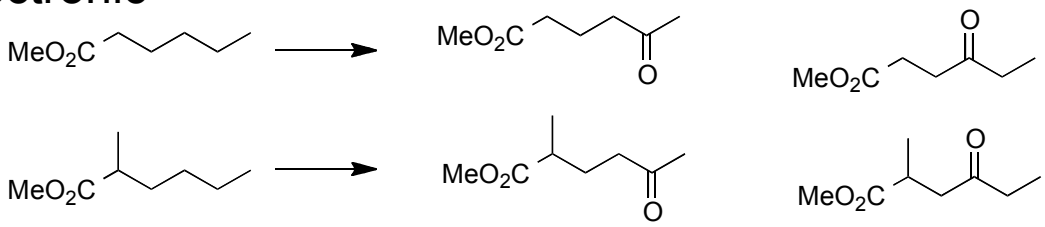
Science, **2010**, *327*, 566

Methylene reactivity selectivity



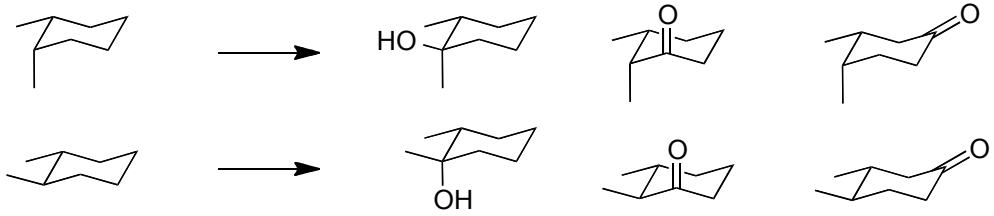
	Yield	Selectivity
	56%	1.1:1

Stereoelectronic



	72%	2:1
	69%	3.5:1

Steric



	70%	10:2:1
	79%	1:1:1

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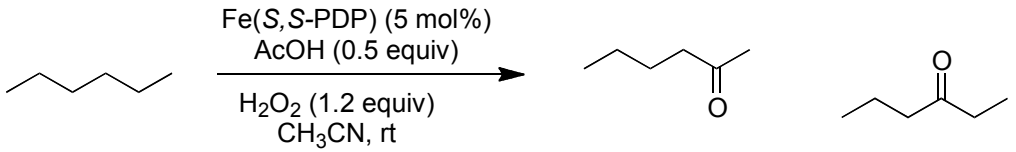
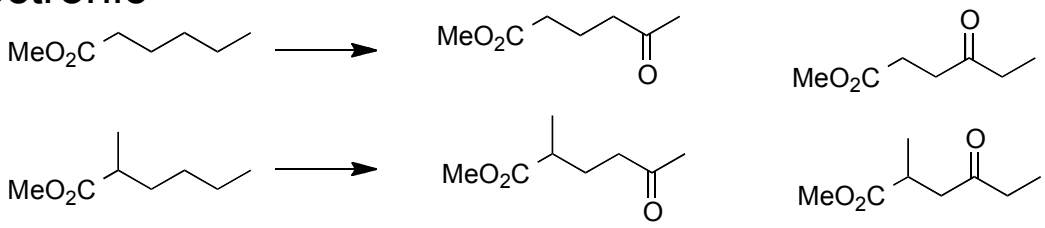
Science, **2010**, *327*, 566

Methylene reactivity selectivity



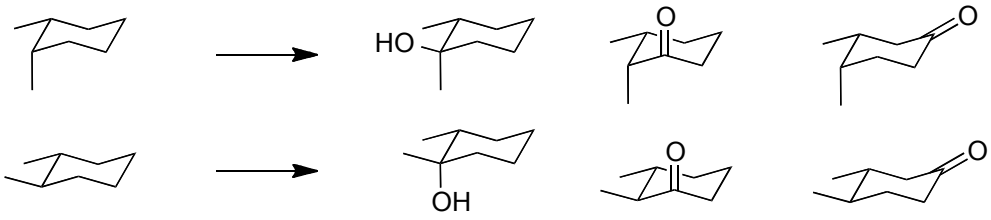
	Yield	Selectivity
	56%	1.1:1

Stereoelectronic



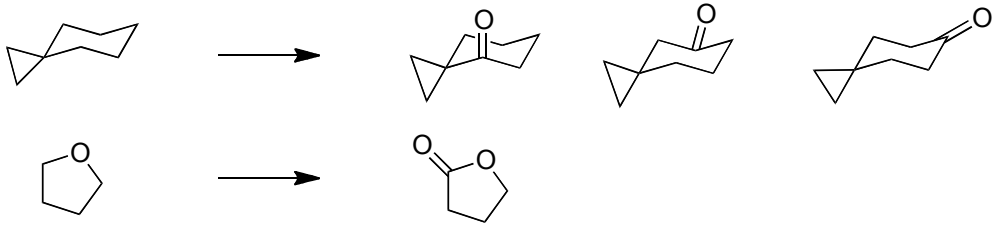
	72%	2:1
	69%	3.5:1

Steric



	70%	10:2:1
	79%	1:1:1

Electronic



	62%	9:1:1
	41%	

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Science, **2010**, *327*, 566

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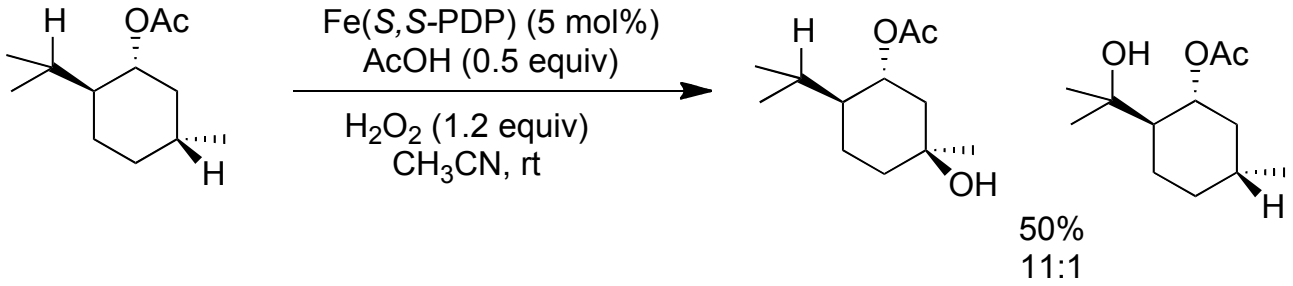
Methylene reactivity selectivity



DFT calculation → 3º C-H bonds equal electronically
Selectivity comes from sterics

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Science, **2010**, *327*, 566

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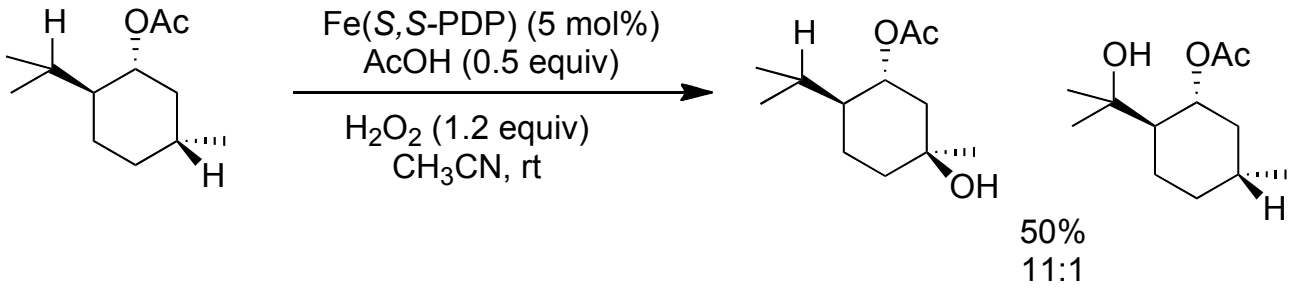
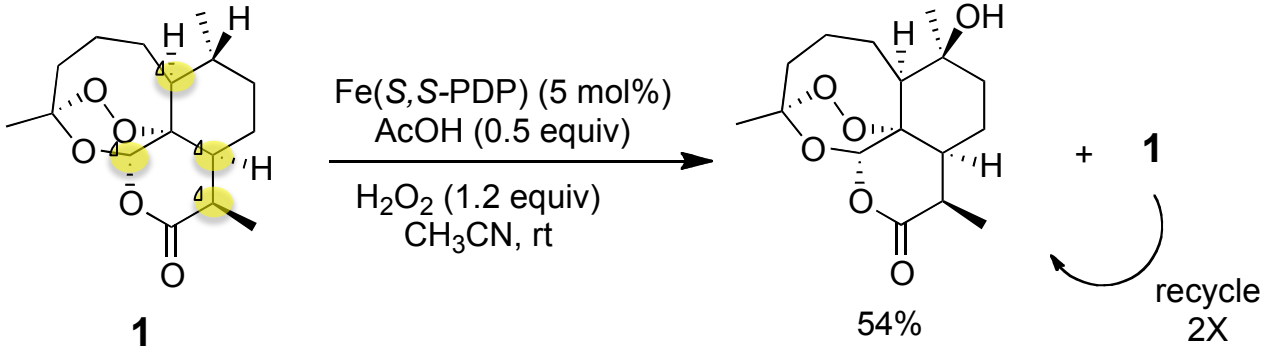
Methylene reactivity selectivity





= sterically or electronically deactivated 3º C-H

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Science, **2010**, *327*, 566

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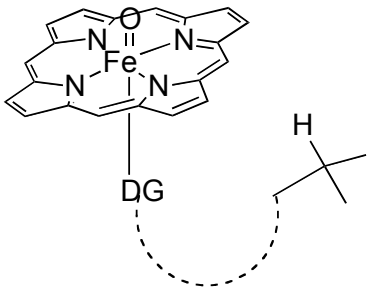
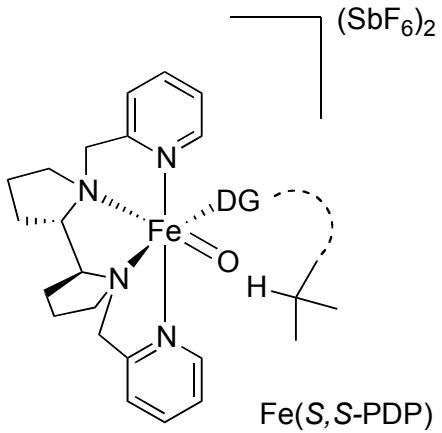
Overriding inherent selectivity

Heme



Non-Heme



Fe(*S,S*-PDP)

General selectivity: E^- rich, sterically accessible, 3º C-H bonds

Can we direct C-H oxidation to less reactive groups?

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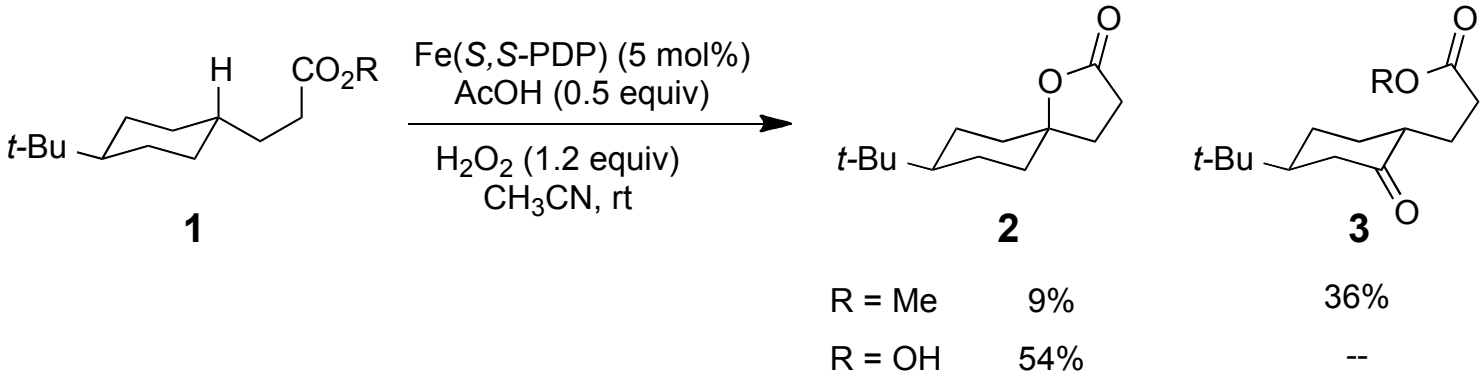
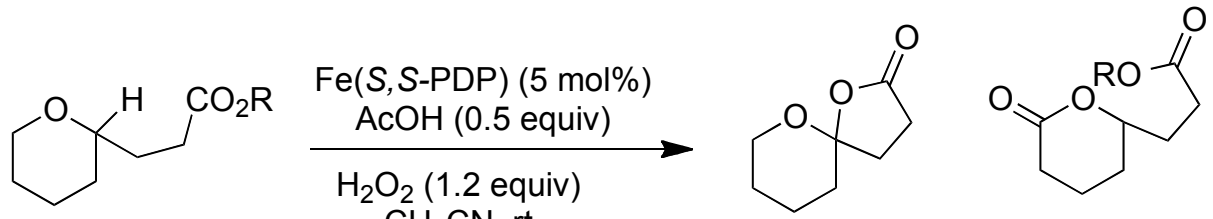
J. Am. Chem. Soc. **2012**, *143*, 9721-9726

Yes we can!



1 **2** **3**

R = Me	9%	36%
R = OH	54%	--



4 **5** **6**

R = Me	2%	22
R = OH	58%	--

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J. Am. Chem. Soc. **2012**, *134*, 9721-9726

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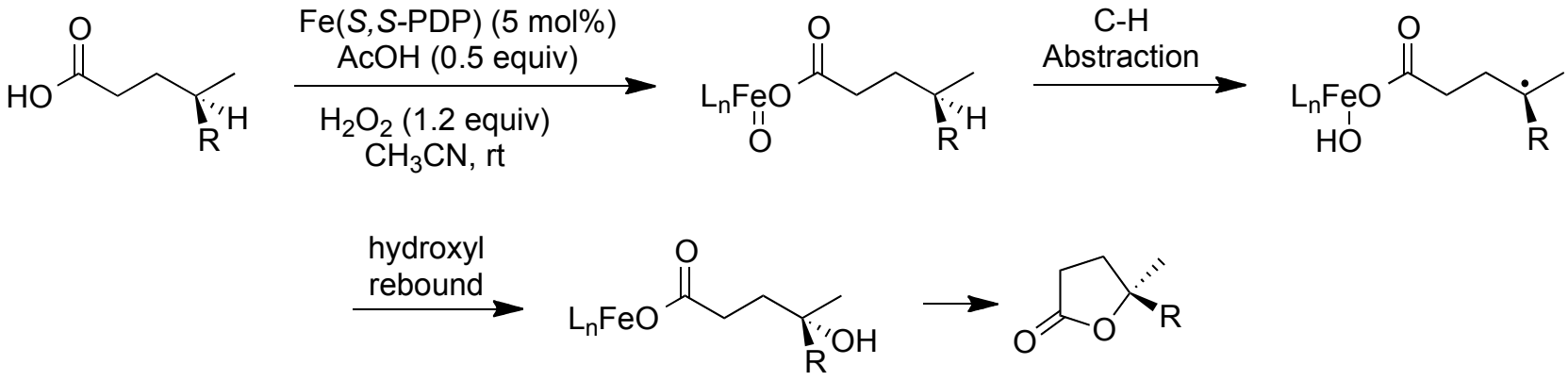
Yes we can!



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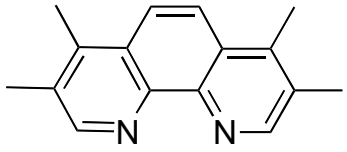
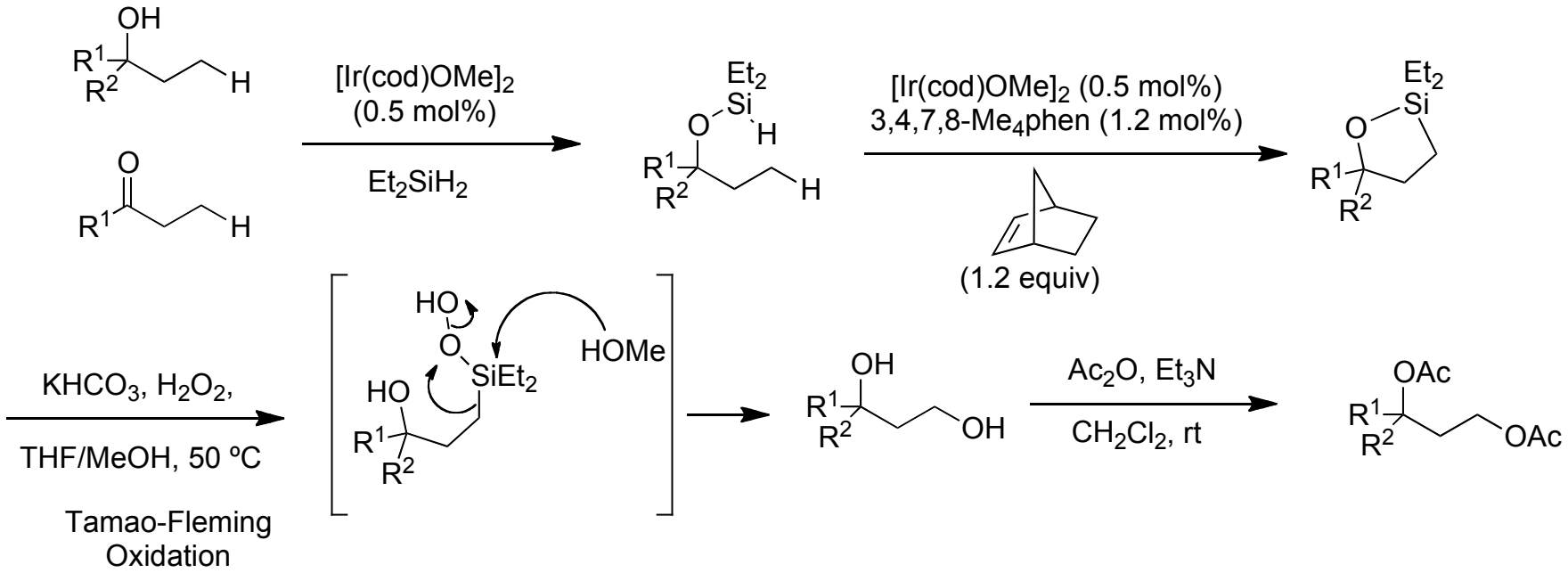
Hartwig's Ir Catalysis

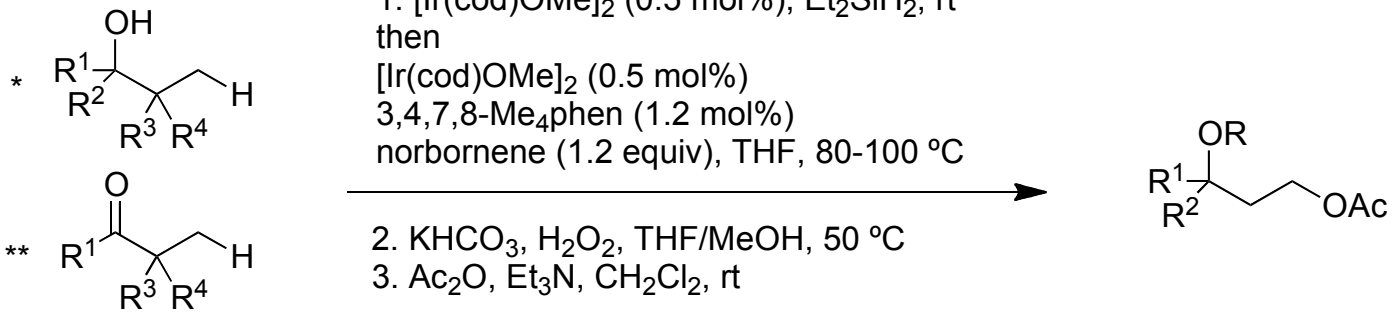


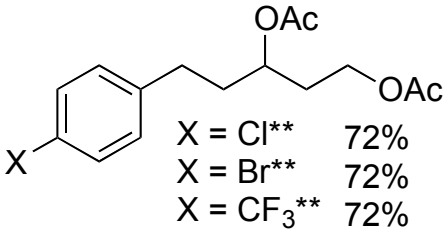
3,4,7,8-Me_4phen

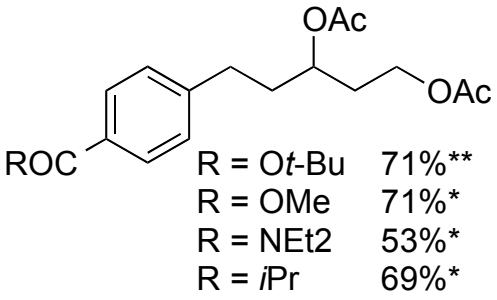


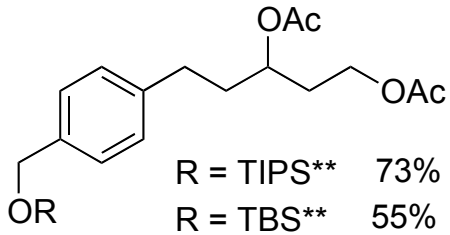
Nature, **2012**, *483*, 70

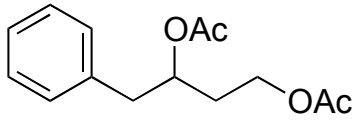
Scope

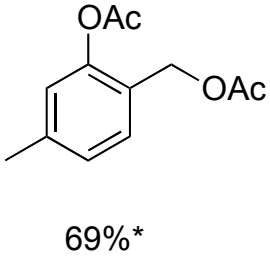












Nature, **2012**, *483*, 70

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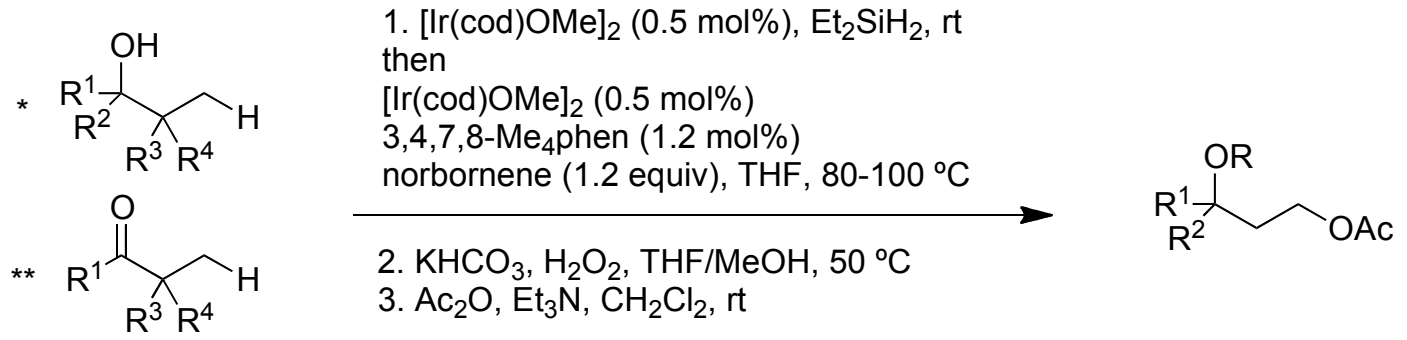
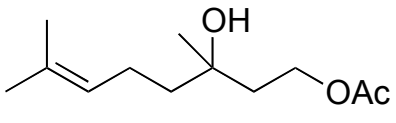
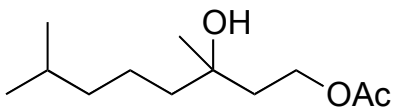
Scope

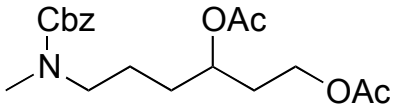




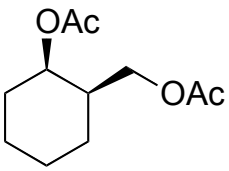
*60%



76%*



70%*



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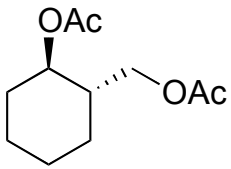

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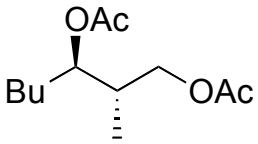

60%** (8:2 dr)

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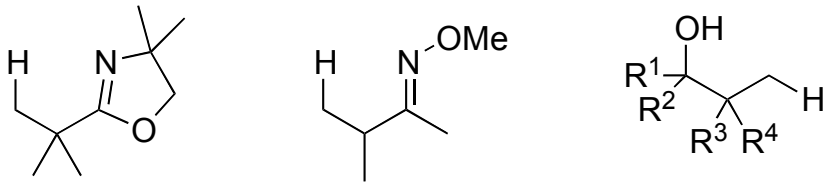
Nature, **2012**, *483*, 70

C-H oxygentaion Summary

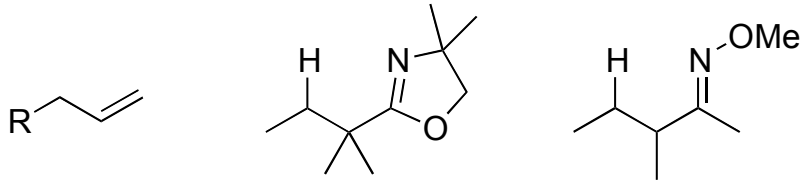
1º C-H Bonds

Directed Pd or Ir catalysis



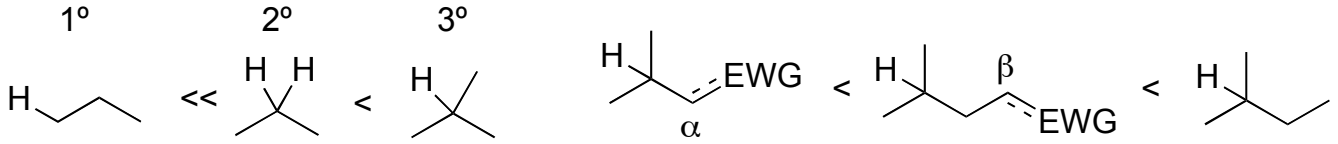
2º C-H Bonds

Allylic or Directed Pd catalysis



3º C-H Bonds

Selective Fe cataylsis



Outline

A. Introduction

B. C_{sp3} C-H Bond Functionalization

   A. C-O Bond Formation

   B. C-N Bond Formation

   C. C-C Bond Formation

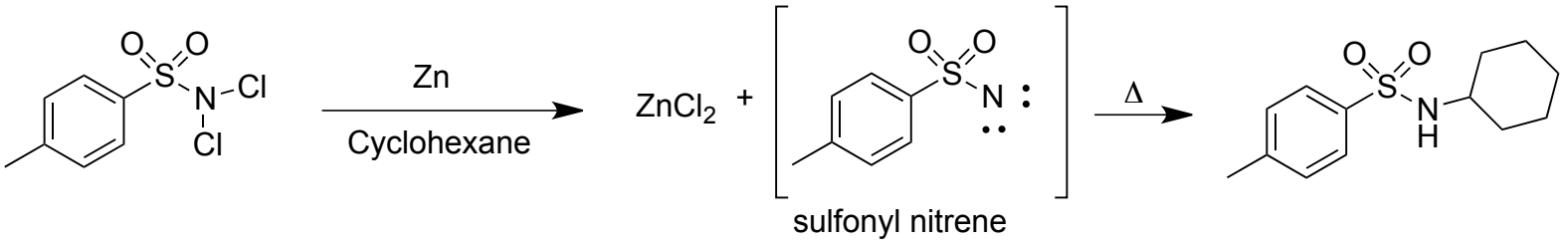
   D. C-X Bond Formation

C. Conclusions and Future Directions

C-N Bond formation

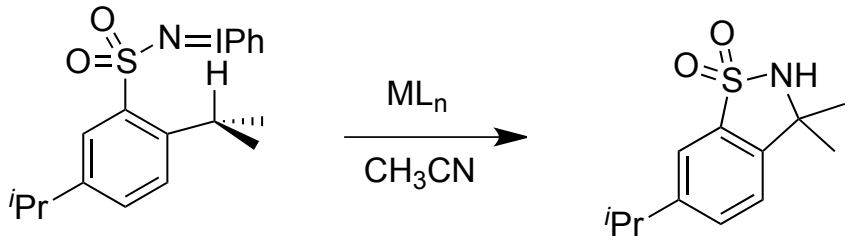
1) Need to preoxidize C-H bond for either displacement or reductive exchange
2) Reliance on protection/deprotection to mask polar/acidic nature of nitrogens

Breslow 1968:



Tet. Lett., **1968**, *51*, 5349

Early work of Gellman and R. Breslow (1968-1983)



MLn =		
	Mn(TPP)Cl	16%
	Fe(TPP)Cl	77%
	$[Fe(cyclam)Cl_2]Cl$	42%
	$FeCl_3$	16%
	$Rh_2(OAc)_4$	**86%**

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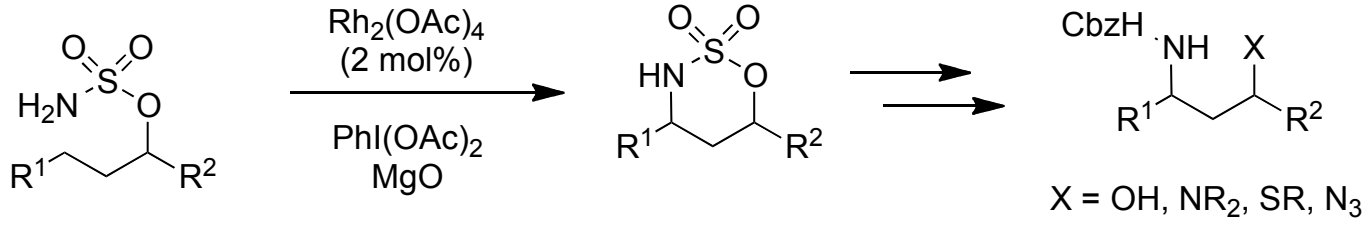
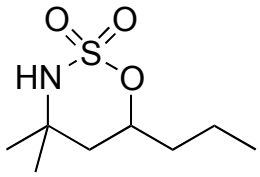
Top Curr. Chem. **2010**, *292*, 347

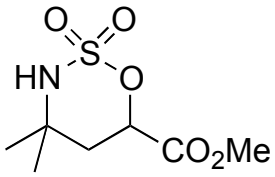
Du Bois's Rh Nitrenoid



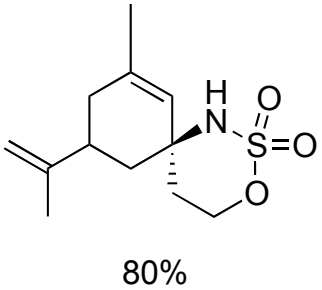
3°



90%

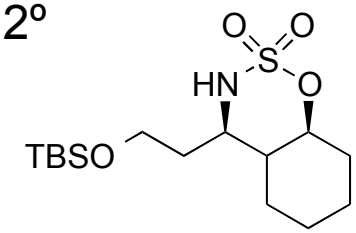


86%

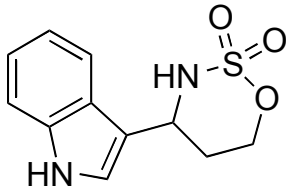


80%

2°

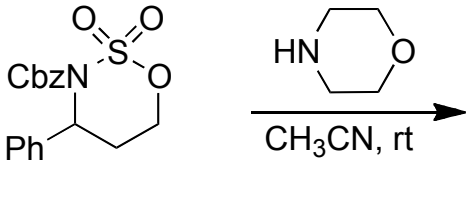


75%

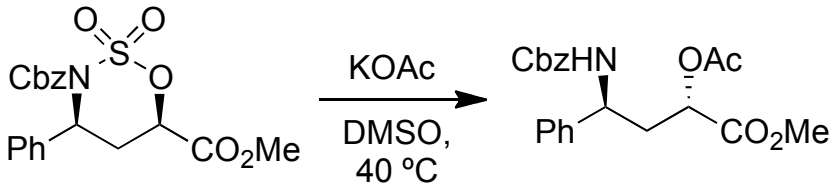


78%

Opening:



88%



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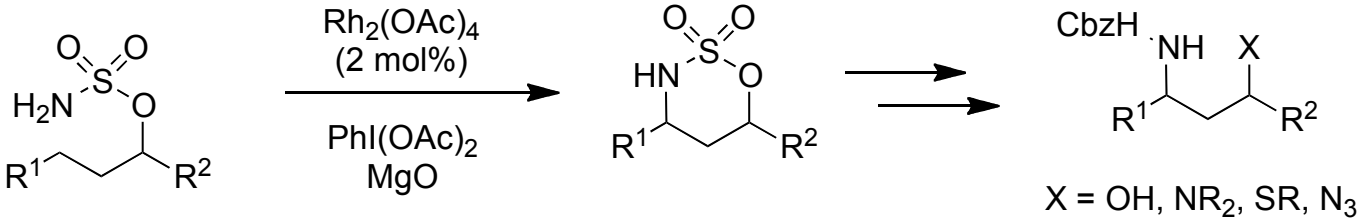
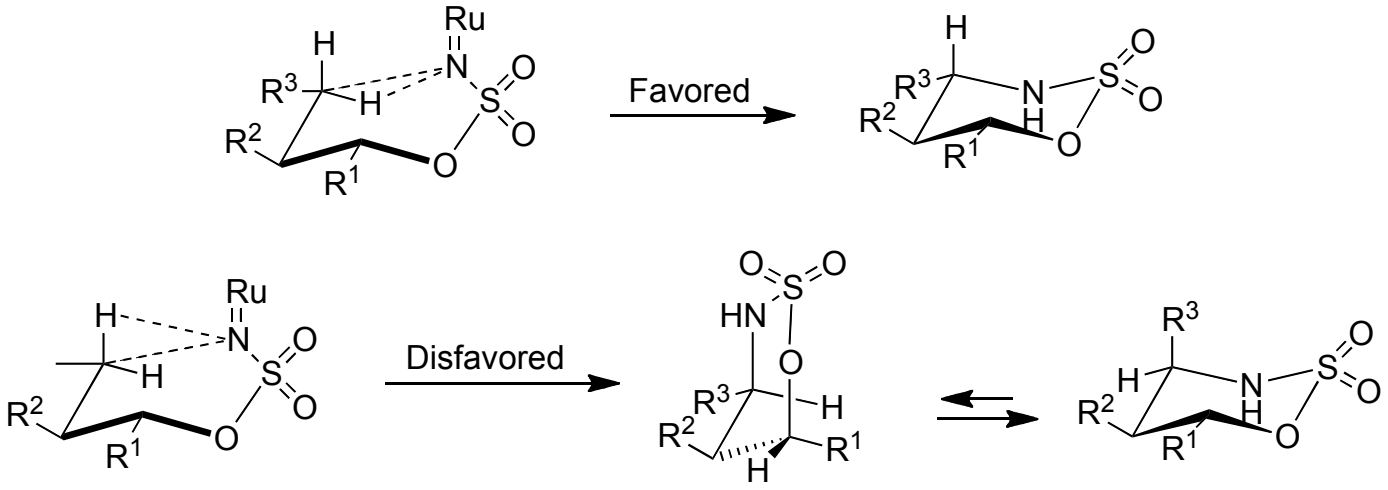
J. Am. Chem. Soc. **2001,** *123,* 6935

Du Bois's Rh Nitrenoid

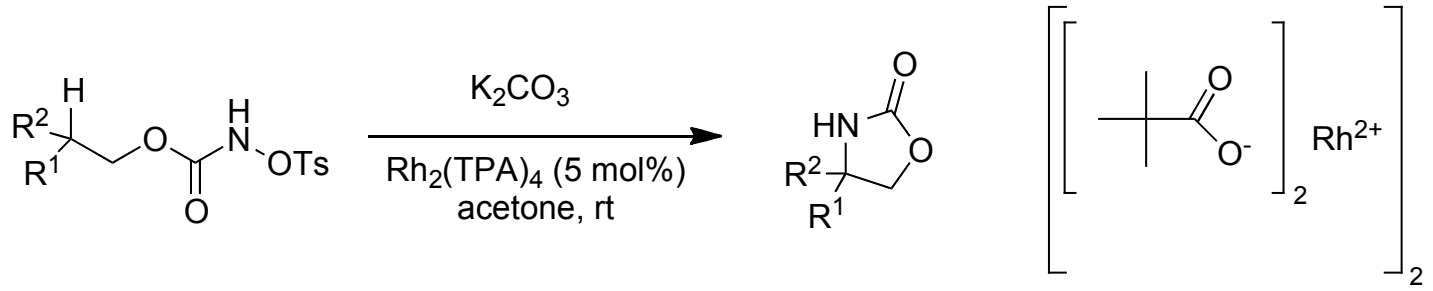


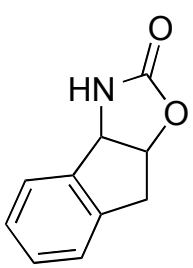
2º C-H Bond selectivity derived from chair-like TS:



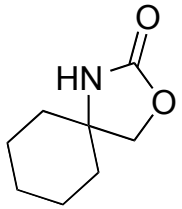
J. Am. Chem. Soc. **2001,** *123,* 6935

Rh Nitrenoid





84%



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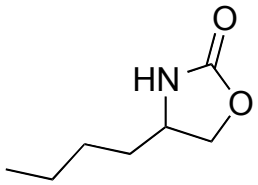
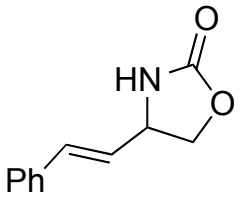
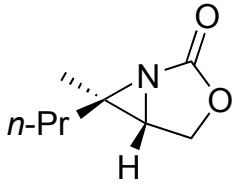


64%

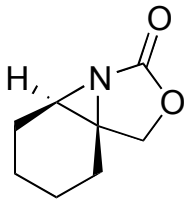


60%

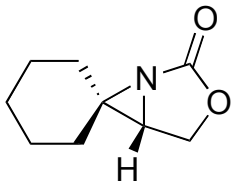
From Allylic Substrates:



67%



79%



62%

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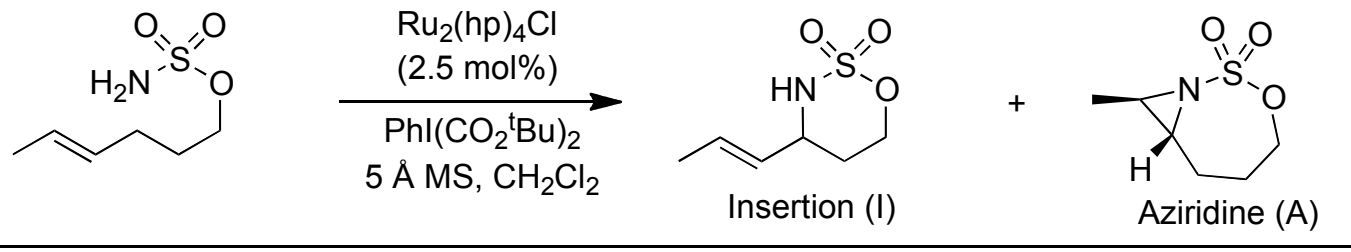
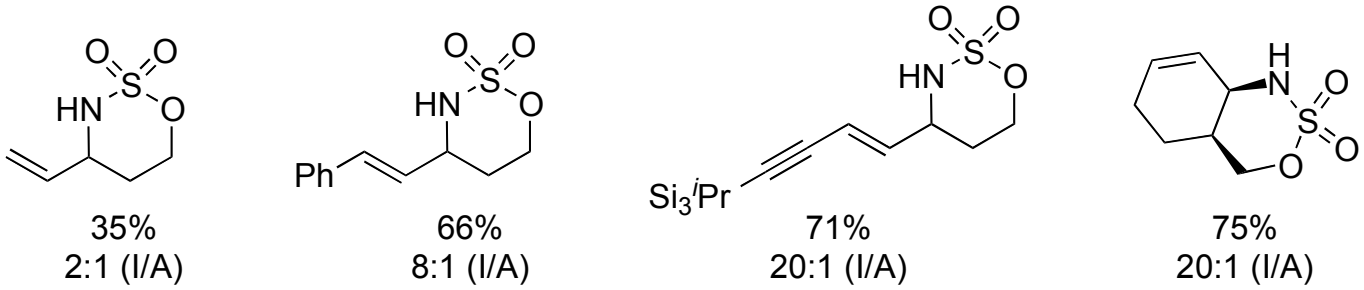
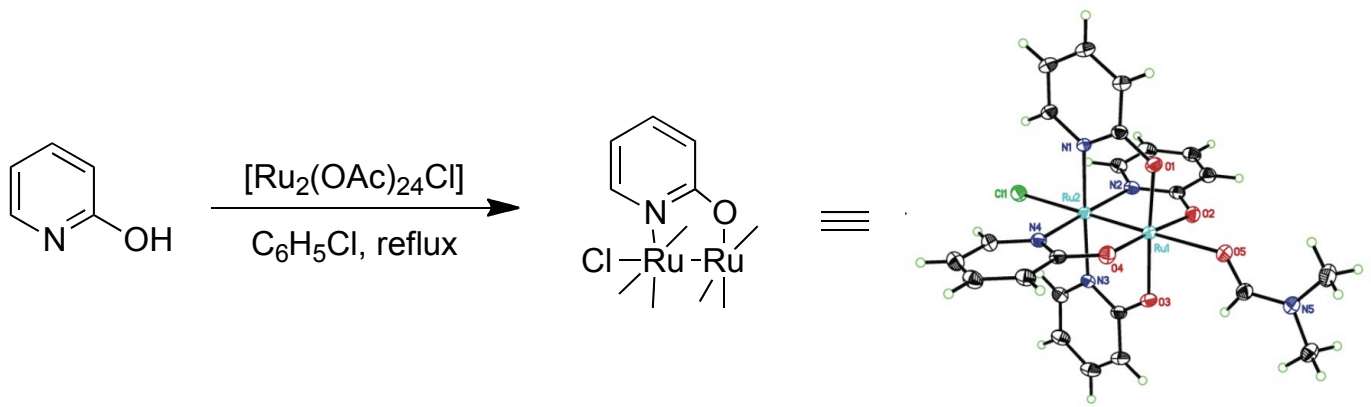
J. Am. Chem. Soc. **2005,** *127,* 14199

39

Du Bois's allylic solution







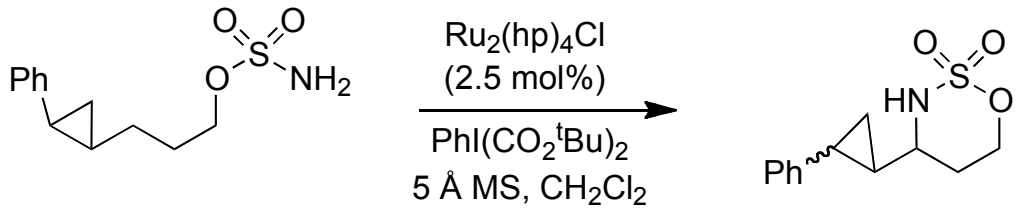
Jared Hammill @ Wipf Group

J. Am. Chem. Soc. **2011**, *133*, 17207

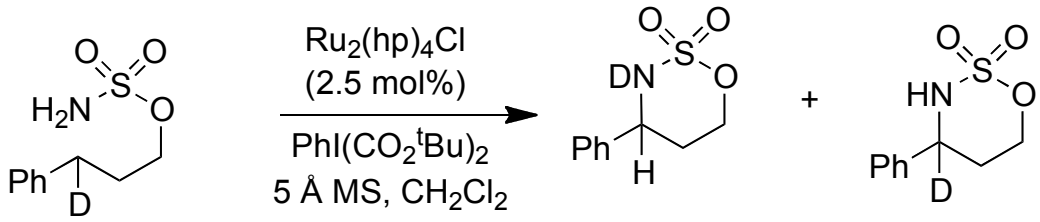
40

Ru Nitrenoid a radical approach

Stepwise biradical formation and recombination:



No ring-opening
2-3% cis-trans isomerization
Picosecond radical lifetime



k_H/k_D = 4.9
Supports radical abstraction
Rebound mechanism

J. Am. Chem. Soc. **2011**, *133,* 17207

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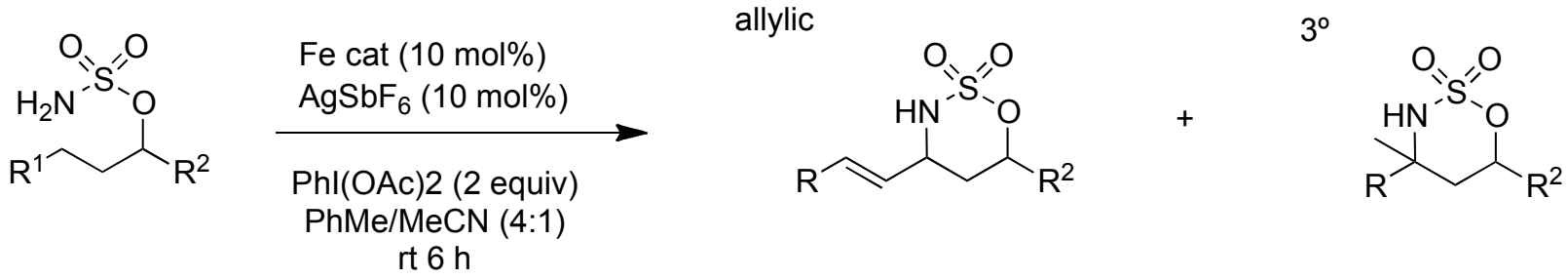
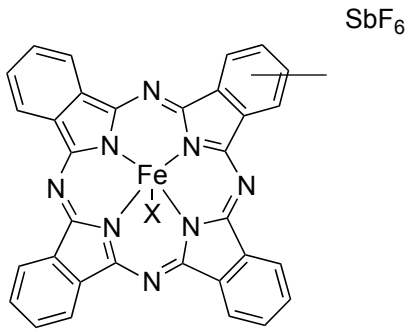
White's Fe Catalysis





[FePc]•SbF_6

Yields superior to $Rh_2(OAc)_4$ and No aziridination observed

Jared Hammill @ Wipf Group

J. Am. Chem. Soc. **2012,** *134,* 2036

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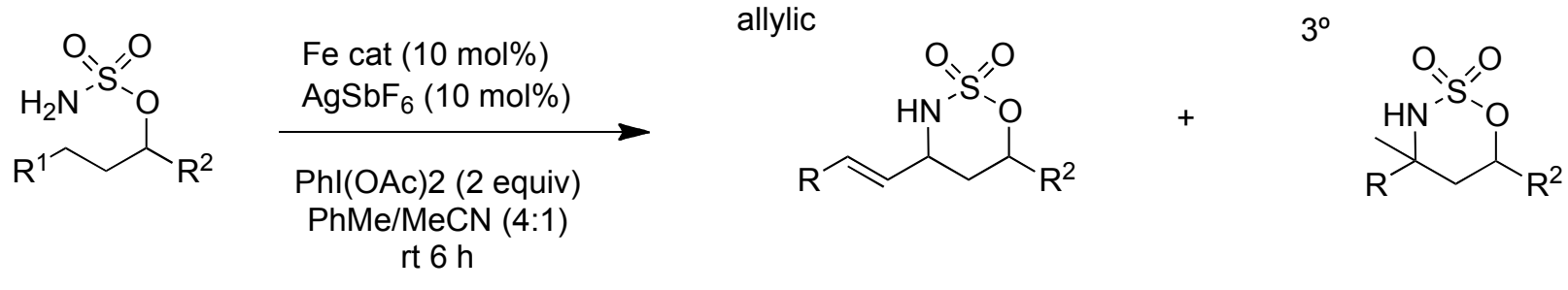
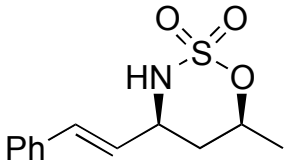
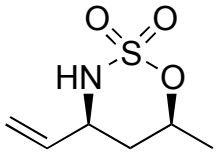
Fe Catalyst Scope

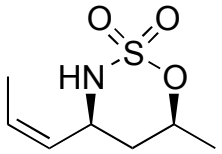




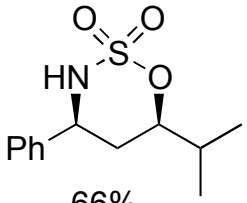
70%
d.r. 3.5:1



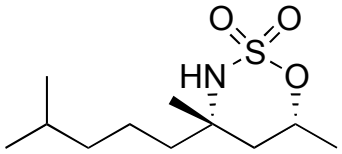
53%
d.r. 3:1



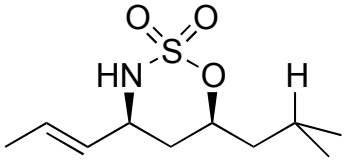
>20:1 E/Z retained



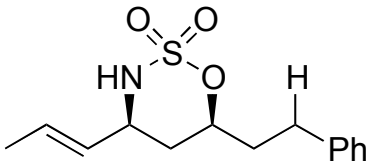
66%
d.r. 17:1



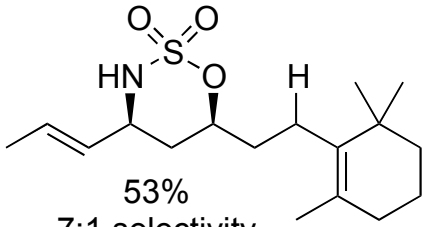
45%
d.r. 97:3



72%
>20:1 (allyl/3º)



62%
5:1 (allyl/benzy)



53%
7:1 selectivity
sterics

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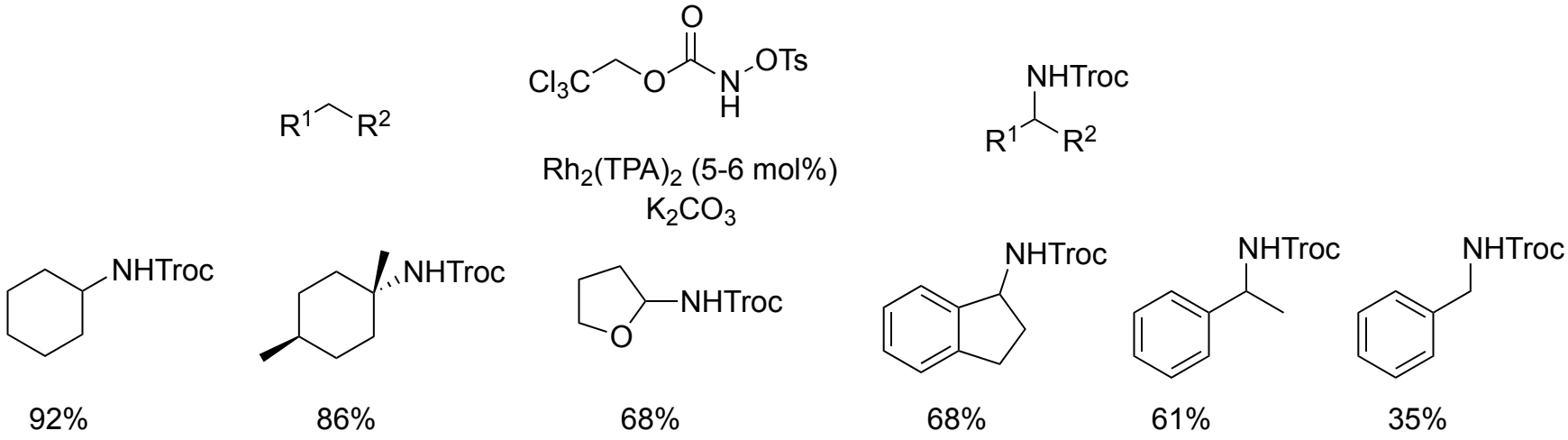
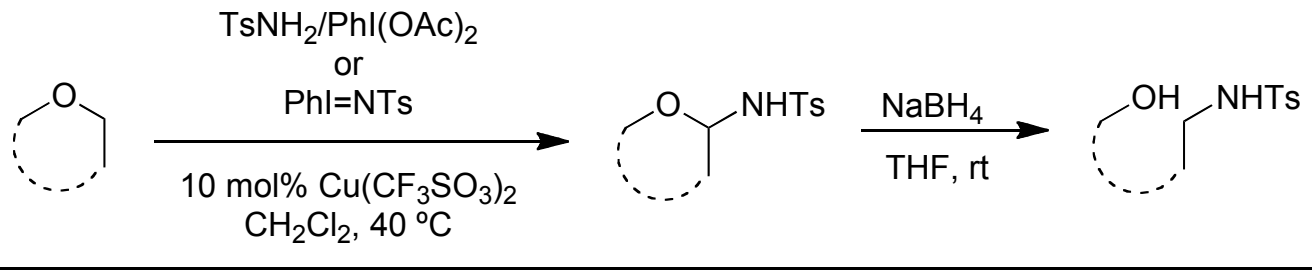
J. Am. Chem. Soc. **2012,** *134,* 2036

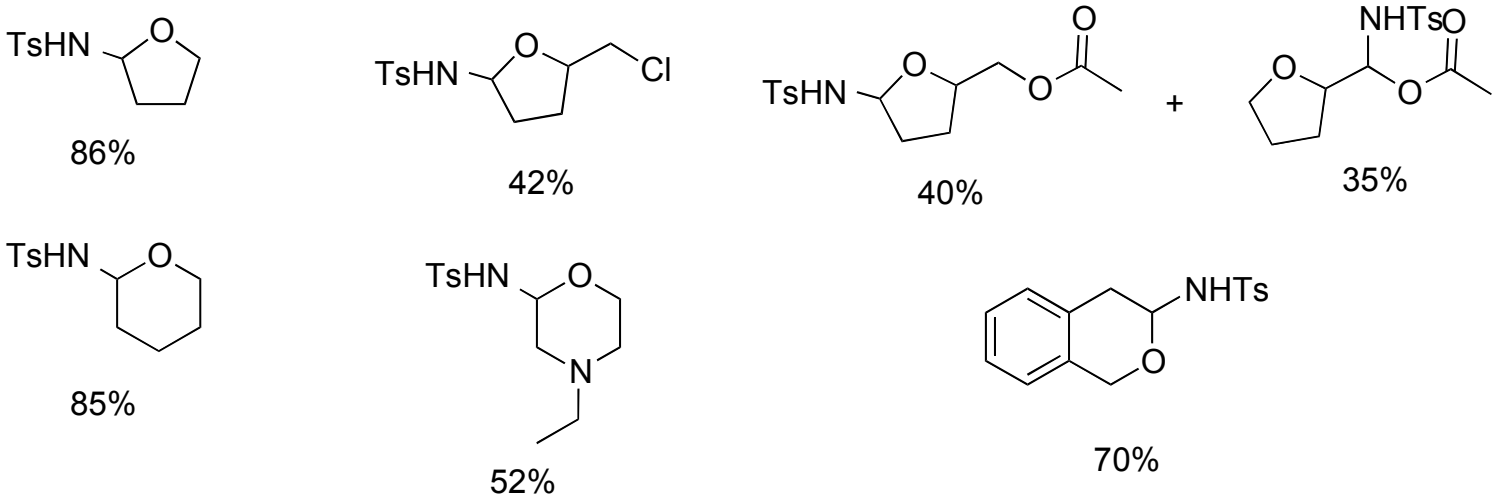
Intermolecular Rh Nitrenoid



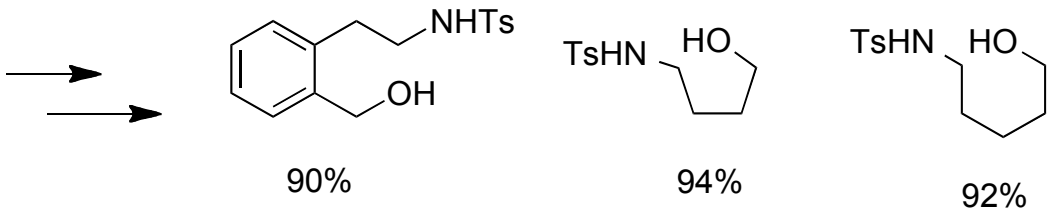
Org. Lett. **2007**, *9*, 639

Cu Catalysis C-N Bond formation





Opening:



45

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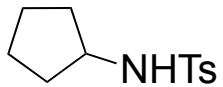
Org. Lett., **2007**, *9*, 2277

Cu Nitrenoid



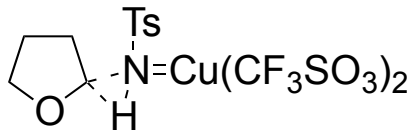
$Cu(CF_3SO_3)_2$

PhI=NTs
or
$PhI(OAc)_2 + TsNH_2$

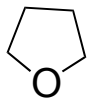
Nitrene Formation

PhI

$TsN=Cu(CF_3SO_3)_2$



Concerted C-H Insertion



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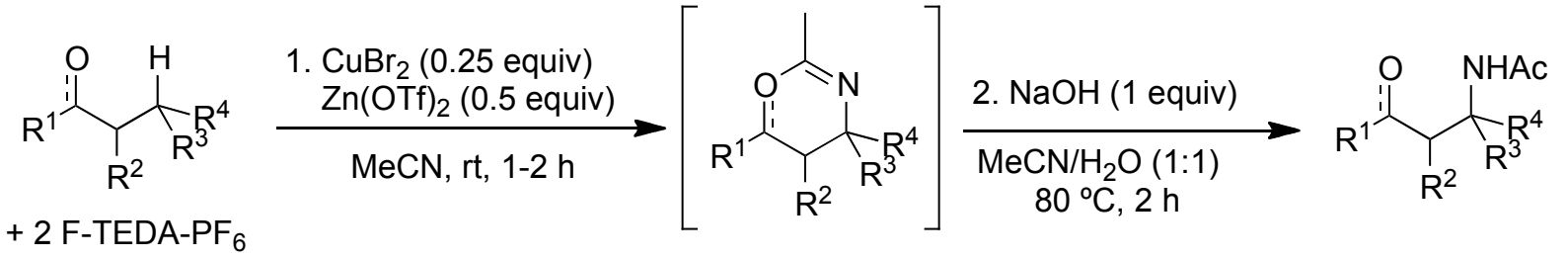
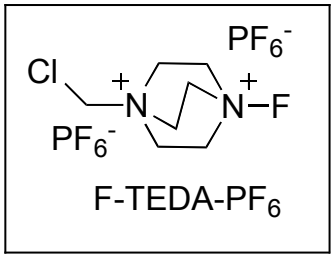
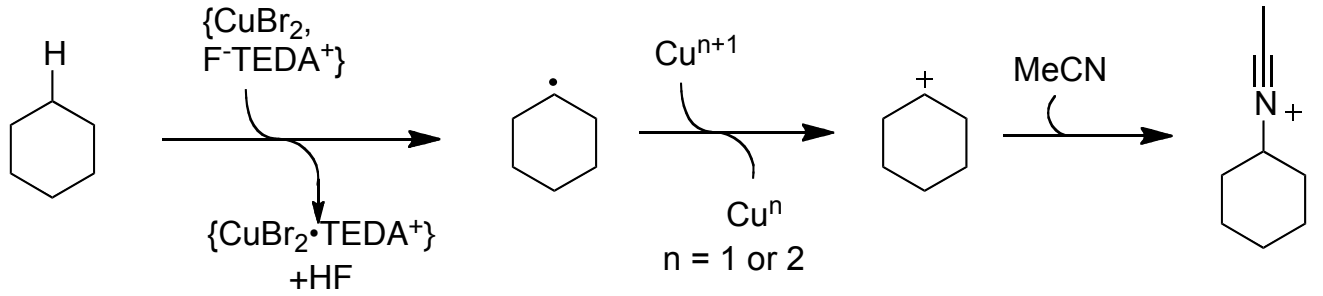
Org. Lett., **2007**, *9*, 2277

Baran's Cu Catalysis "Ritter-Type"





Mechanism (Ritter Rxn):



J. Am. Chem. Soc., **2012**, *134*, 2547

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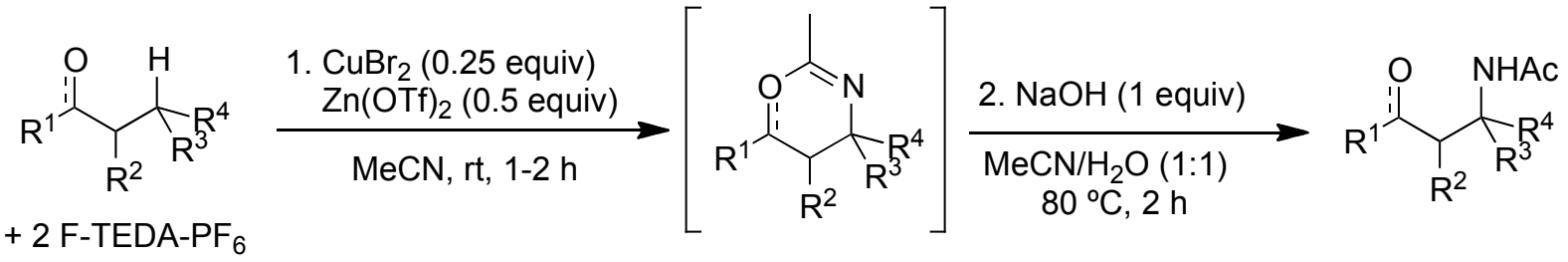
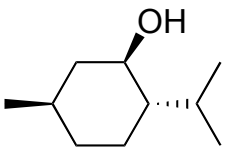
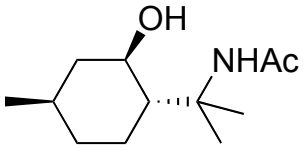
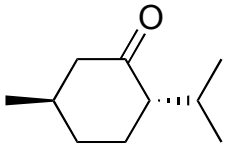
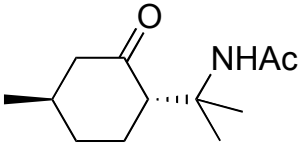
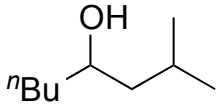
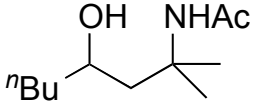
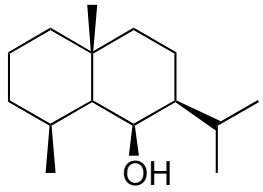
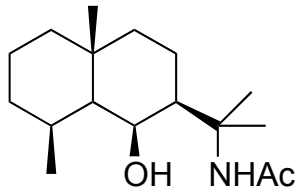
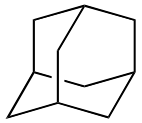
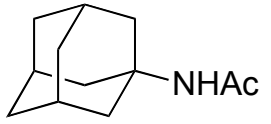
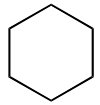
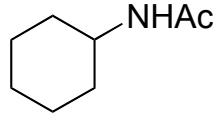
Baran's Cu Catalysis "Ritter-Type"



Scope:

SM	Product (Yield)	
		(91%)
		(61%)
		(53%)

SM	Product (Yield)	
		(65%)
		(90%)
		(51%)

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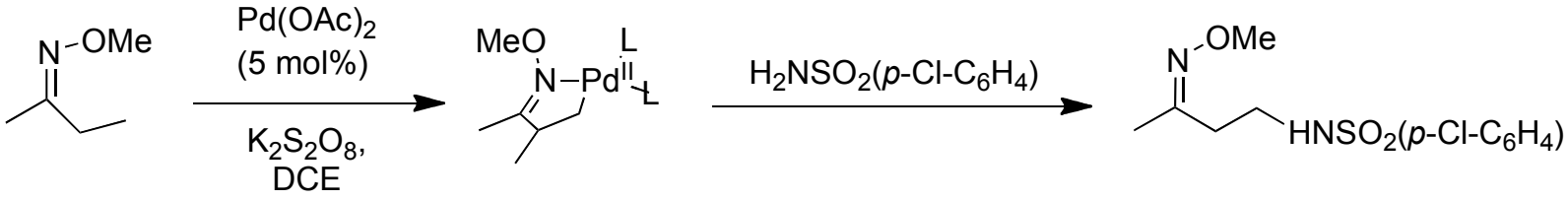
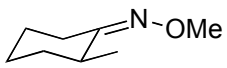
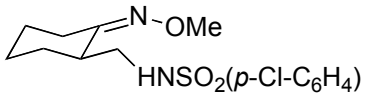
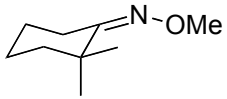
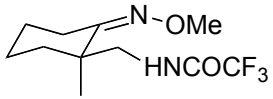
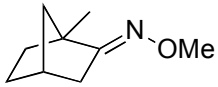
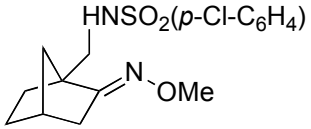
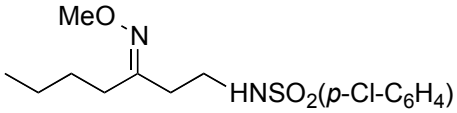
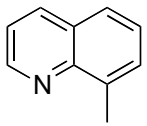
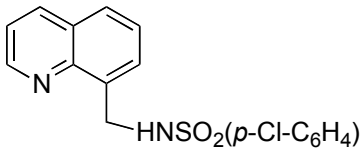
Che's Directed Pd Catalysis



SM	amide	Product	yield
	$H_2NSO_2(p\text{-}Cl\text{-}C_6H_4)$		88%
	H_2NCOCF_3		89%
	$H_2NSO_2(p\text{-}Cl\text{-}C_6H_4)$		93%
	$H_2NSO_2(p\text{-}Cl\text{-}C_6H_4)$		76%
	$H_2NSO_2(p\text{-}Cl\text{-}C_6H_4)$		79%

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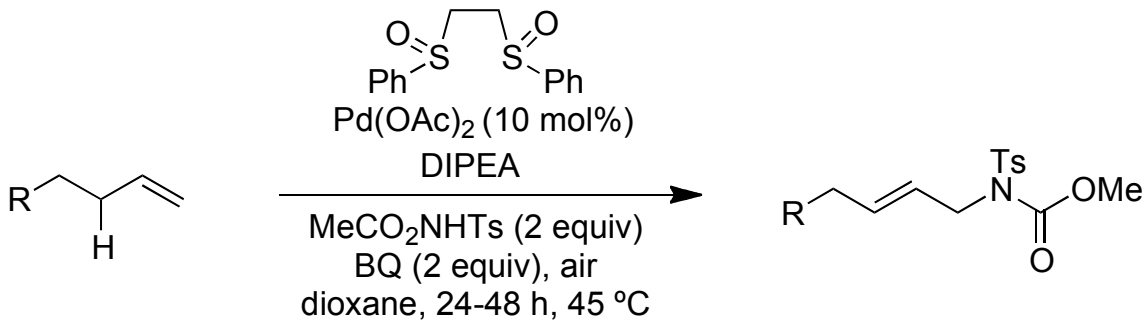
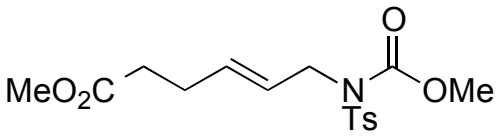
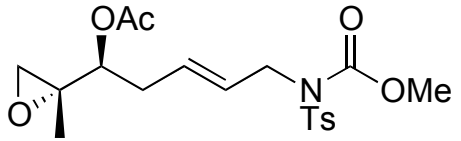
J. Am. Chem. Soc. **2006,** *128,* 9048

White's Pd Catalyst





61%



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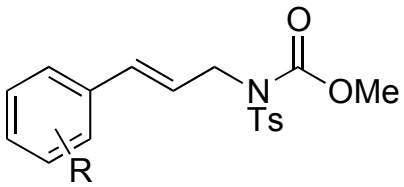
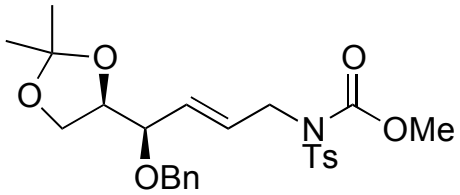
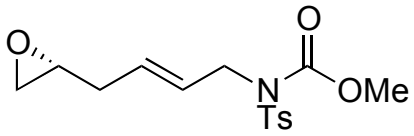


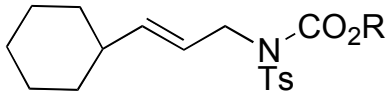
54-89%
R = EWG, EDG



76%



48%



R = Me	84%
R = Bn	87%
R = *t*-Bu	69%
R = Fm	55%

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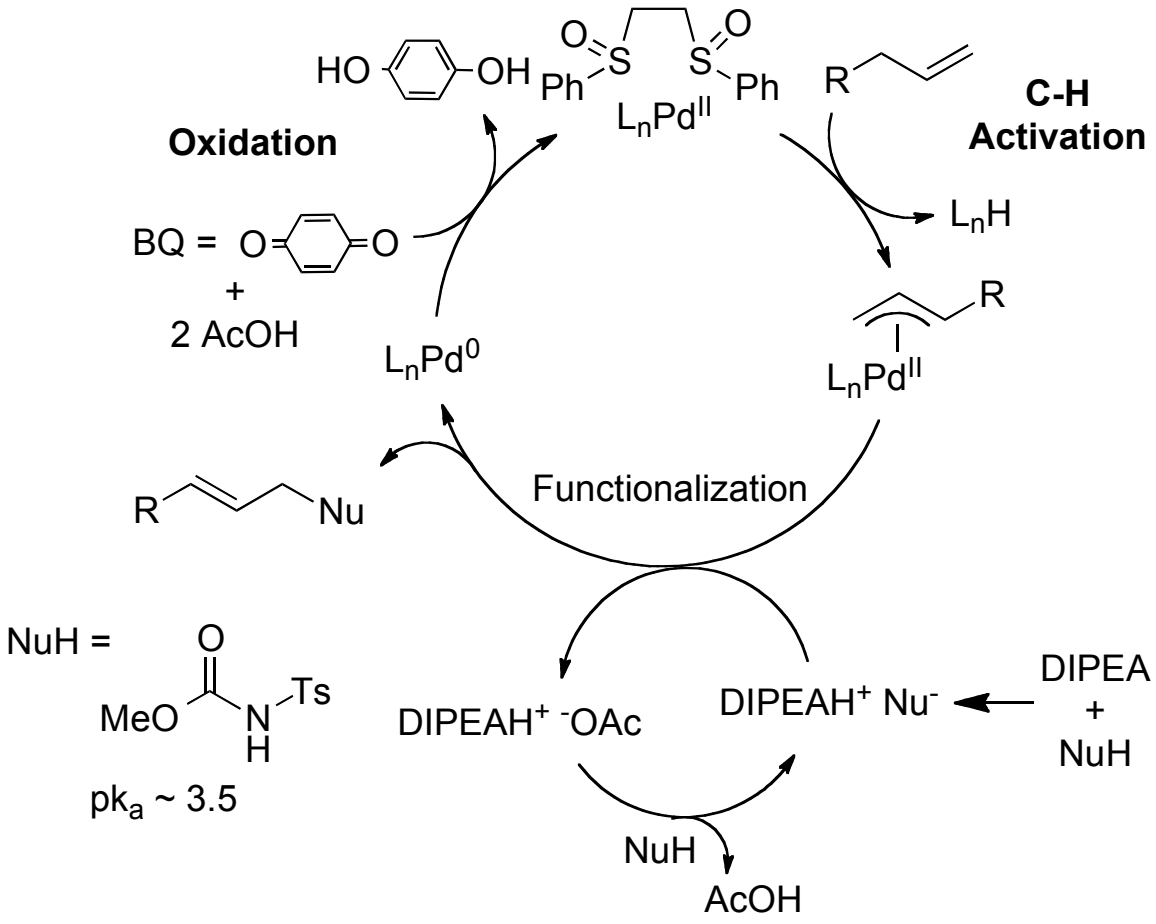
J. Am. Chem. Soc. **2009,** *131,* 11701

Allylic C-H Mechanism

Electrophillic Pd^{II}/Pd^{0} Catalysis



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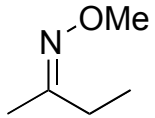
J. Am. Chem. Soc. **2009,** *131,* 11701

C-H Amination Summary

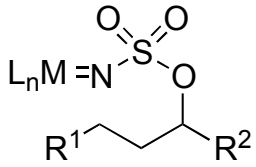
1º C-H Bonds

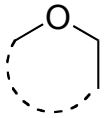
Directed Pd catalysis

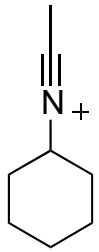


2º C-H Bonds

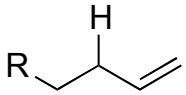
Directed Fe, Rh, Ru, or Cu Catalysis





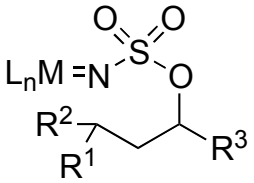


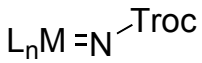
Allylic Rh, Ru, Pd Catalysis



3º C-H Bonds

Directed Fe, Rh, Ru, or Cu Catalysis





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Outline

A. Introduction

B. C_{sp3} C-H Bond Functionalization

   A. C-O Bond Formation

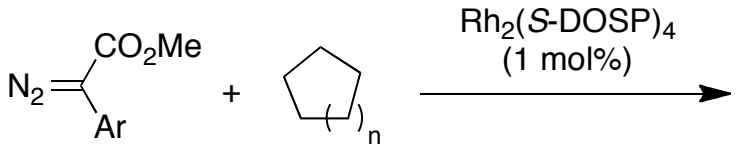
   B. C-N Bond Formation

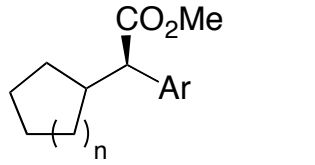
   C. C-C Bond Formation

   D. C-X Bond Formation

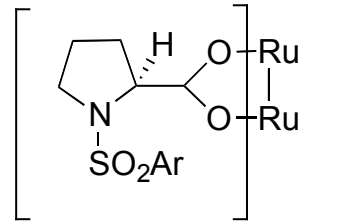
C. Conclusions and Future Directions

Davies's Carbenoid Approach



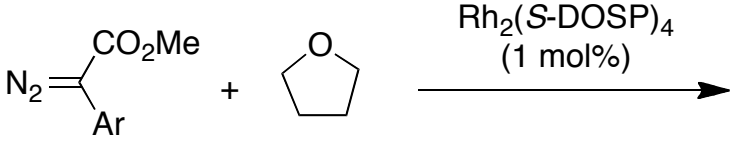


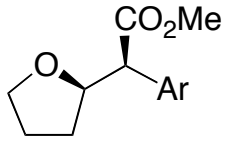
n = 1 72%, 96% ee
n = 2 80%, 95% ee



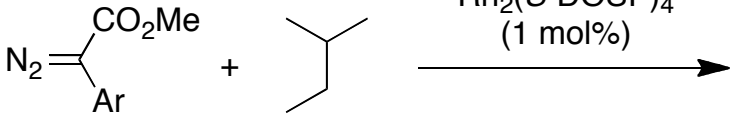
Ar = p-($C_{11\text{-}13}H_{23\text{-}27}$)$C_6H_4$

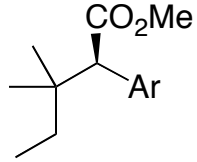
Rh_2(*S*-DOSP)$_4$





74%, 98% ee





60%, 68% ee

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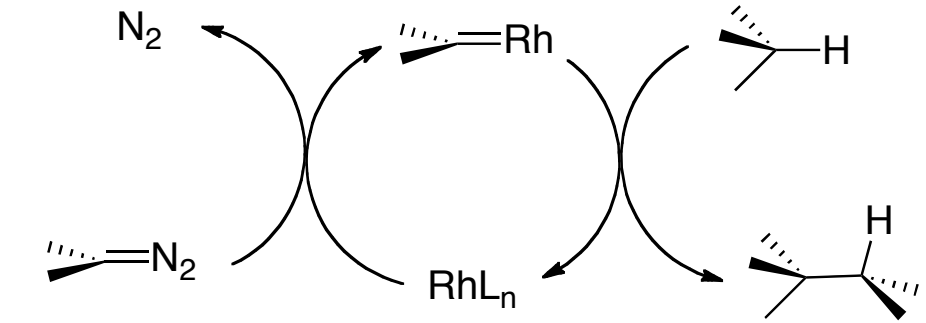
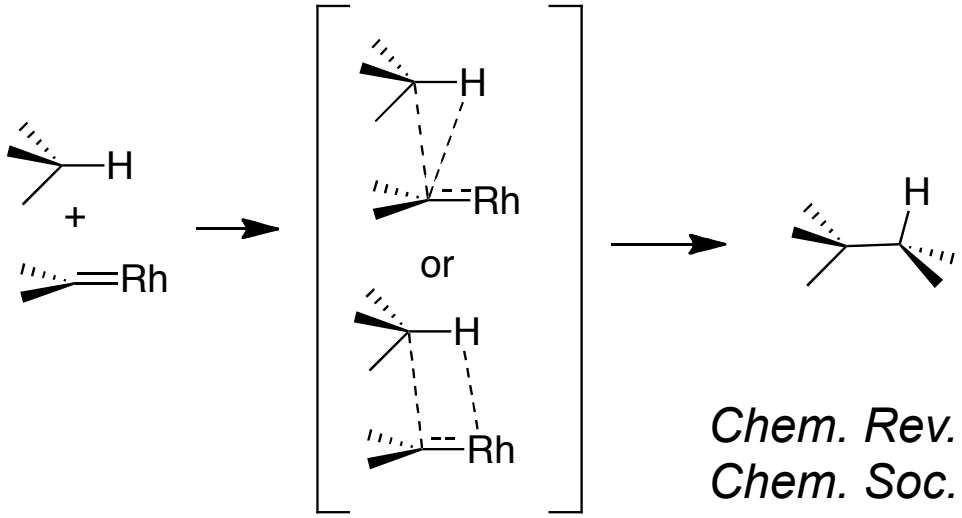
J. Am. Chem. Soc. **2000,** *122,* 3063

54

C-H carbon bond formation



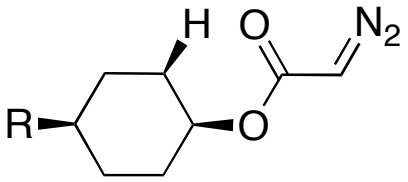


Chem. Rev. **2010,** *110,* 704
Chem. Soc. Rev. **2011**, *40*, 1857

Jared Hammill @ Wipf Group

55

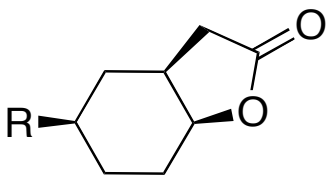
C-H carbon bond formation



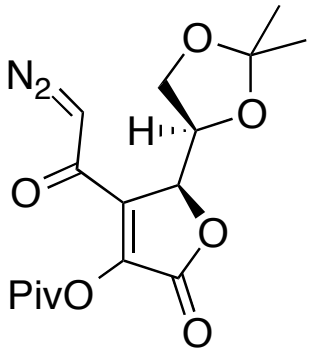
R = Me, ^{t}Bu

$Rh_2(4S\text{-MEOX})_4$

CH_2Cl_2, 71%

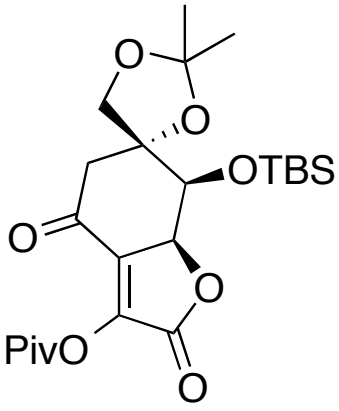


R = Me, ^{t}Bu

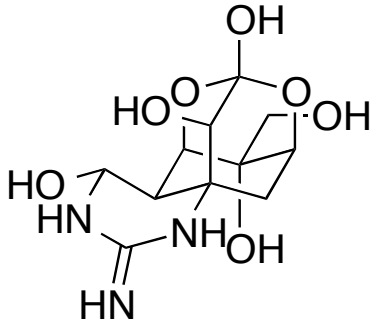


$Rh_2(HNCOCPh_3)_4$

CCl_4



>75%



(-)-tetrodotoxin

Science **2006**, *312*, 67
J. Am. Chem. Soc. **2003**, *125*, 11510
Chem. Eur. J. **1998**, *6*, 990

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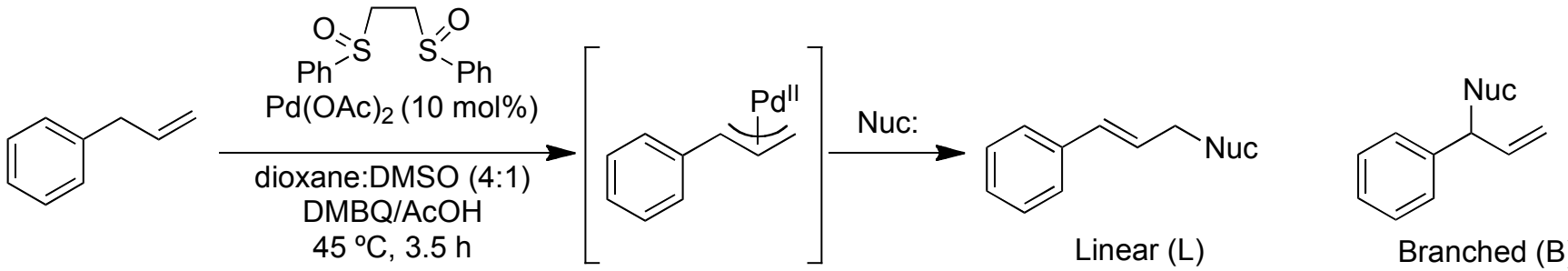
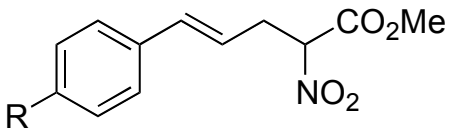
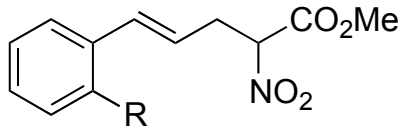
White's C-H C-C formation

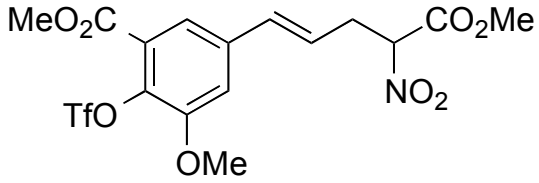




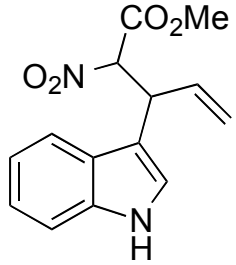
R = OMe 50% 1.7:1 (L:B)
R = Me 61% 3:1 (L:B)
R = CO_2Me 61% 10:1 (L:B)
R = CF_3 65% 12:1 (L:B)



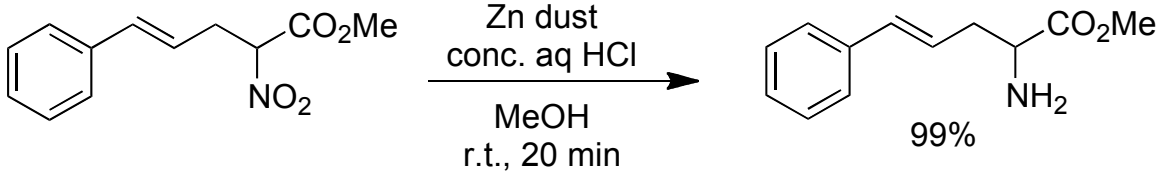
R = OTBS 62% 5:1 (L:B)
R = Me 58% 3:1 (L:B)
R = CF_3 59% >20:1 (L:B)



63% 7:1 (L:B)



42% 1:5 (L:B)



99%

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J. Am. Chem. Soc. **2008,** *130,* 14090

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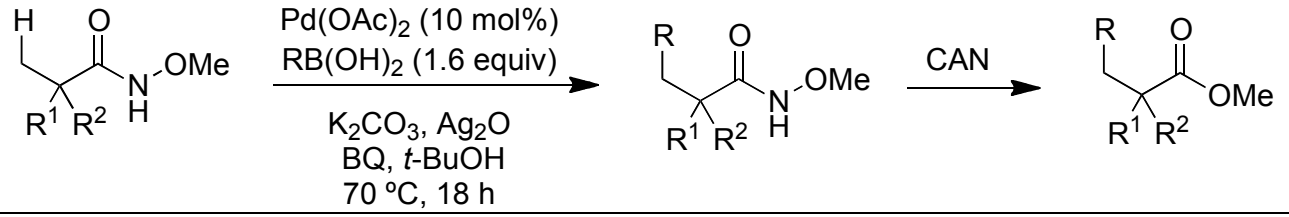
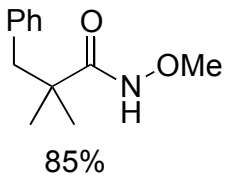
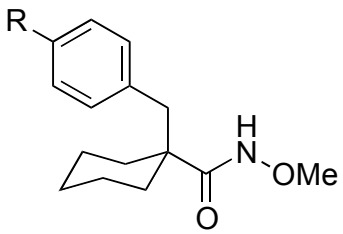
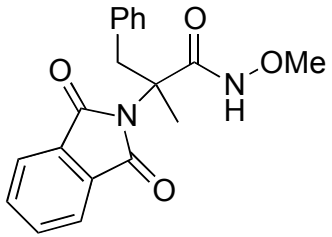
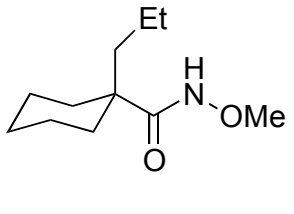
Yu's C-H C-C formation

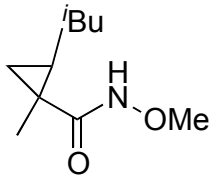




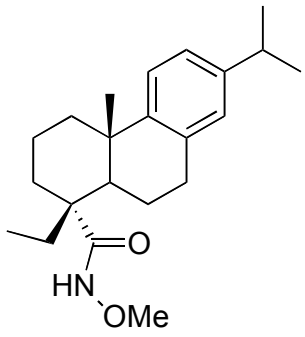


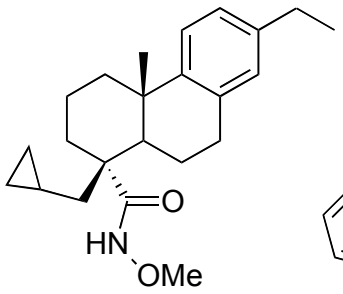


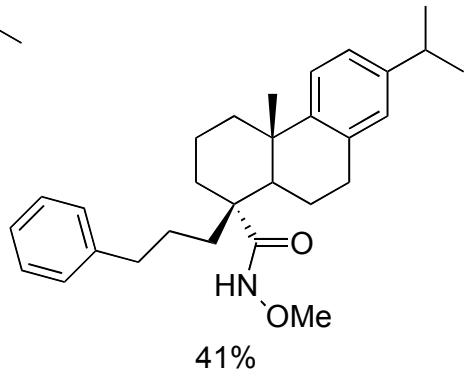




Can use air in place of Ag_2O







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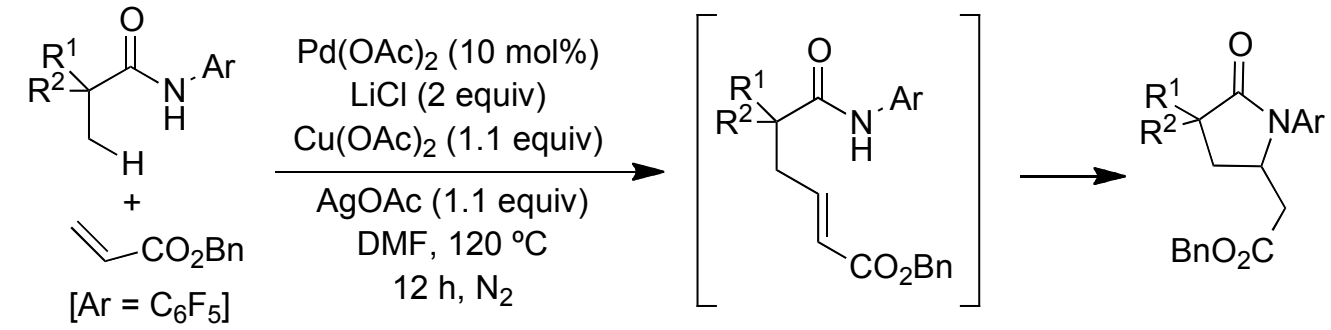
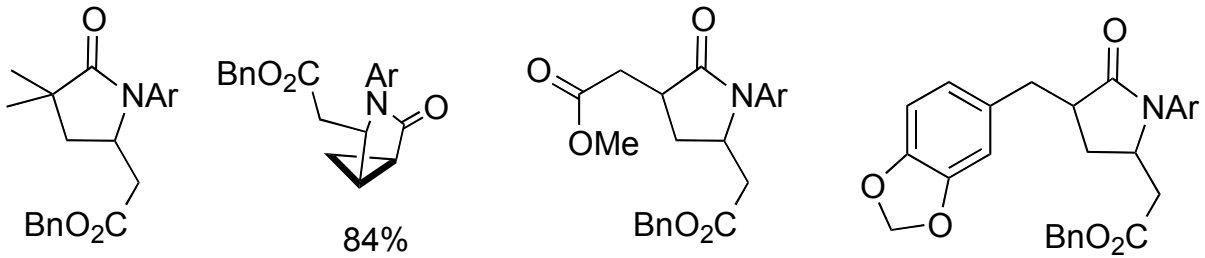
J. Am. Chem. Soc. **2008,** *130,* 7190

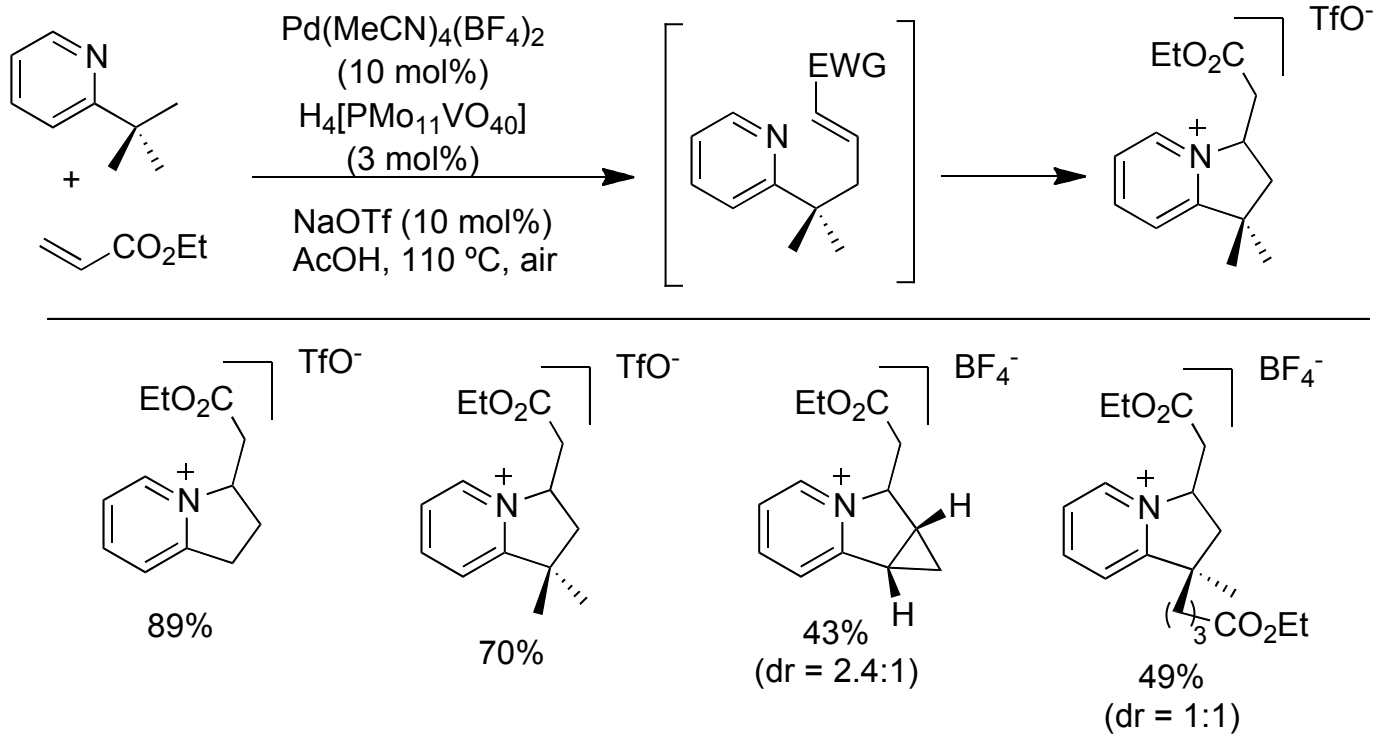
Yu's C-H C-C formation





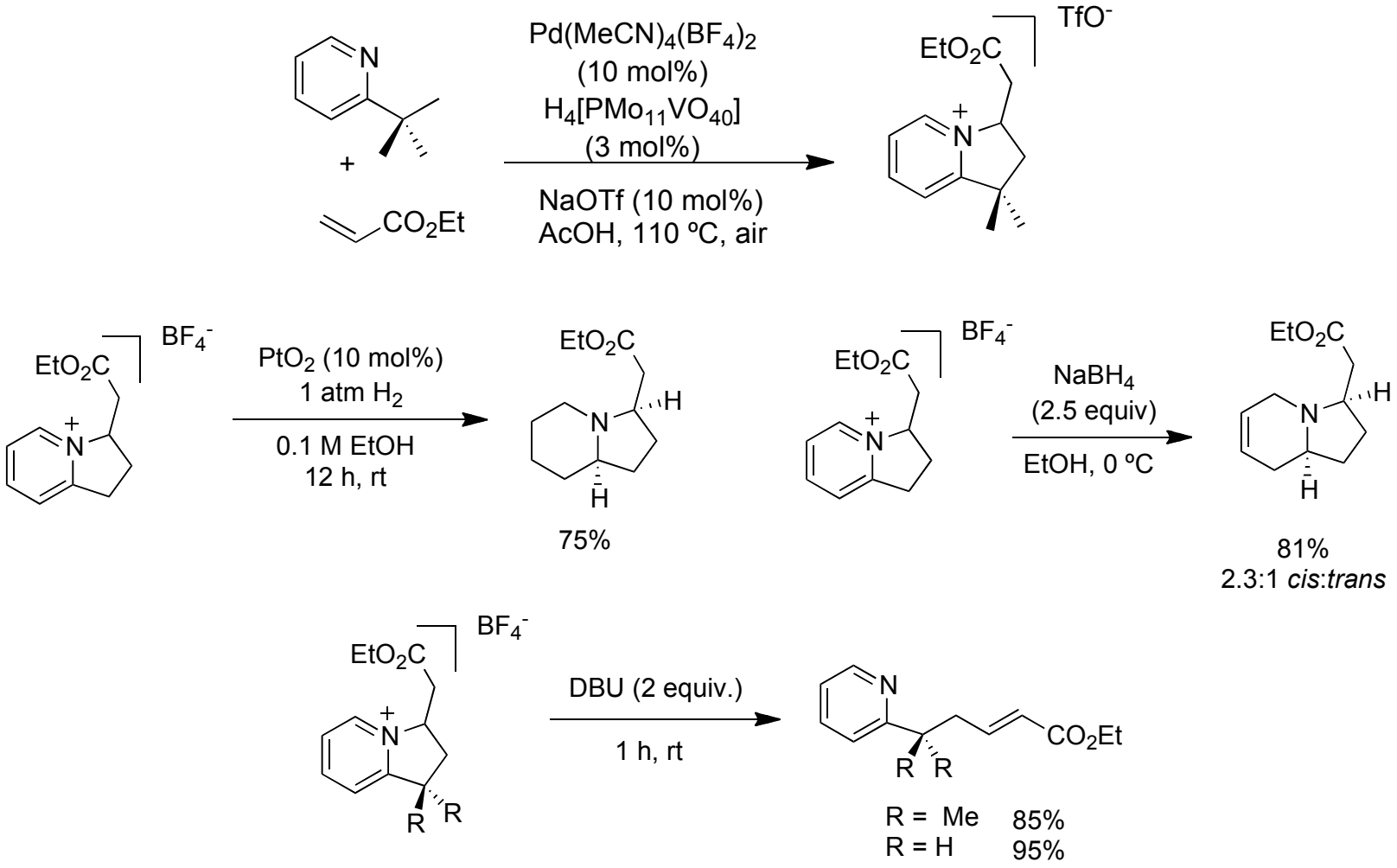
J. Am. Chem. Soc. **2010,** *132,* 3680

Sanford's C-H C-C formation



J. Am. Chem. Soc. **2011,** *133,* 6541

Sanford's C-H C-C formation



Jared Hammill @ Wipf Group

J. Am. Chem. Soc. **2011,** *133,* 6541

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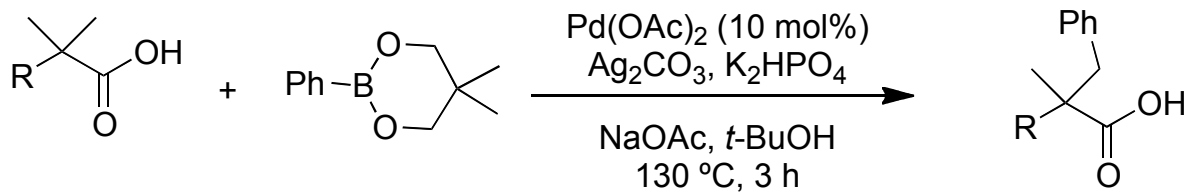
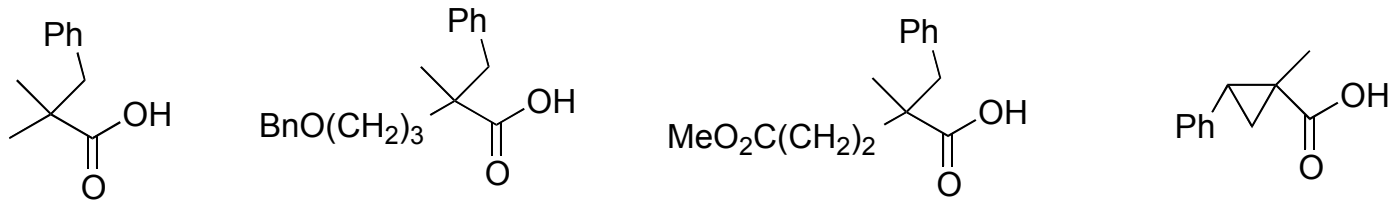
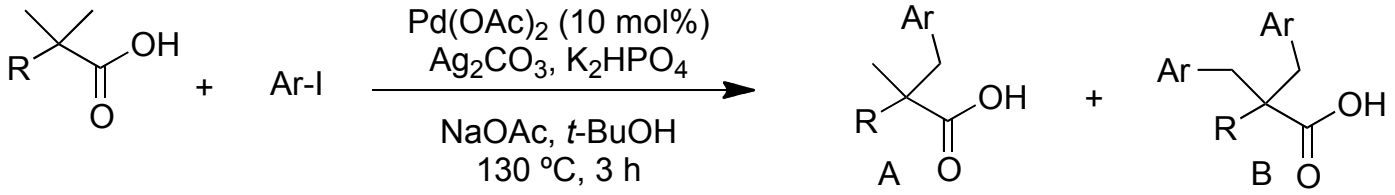
Yu's C-H C-C formation





38% 30% 30% 20%



R = Me Ar = Ph	70% 5:2 (A:B)	R = $(CH_2)_3OBn$ Ar = Ph	45% 5:1 (A:B)	R = ^{i}Bu Ar = Ph	62% 4:1 (A:B)	R = $(CH_2)_2CO_2Me$ Ar = Ph	42% 5:1 (A:B)

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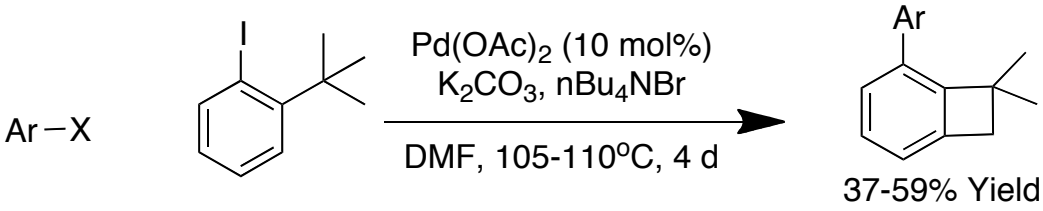
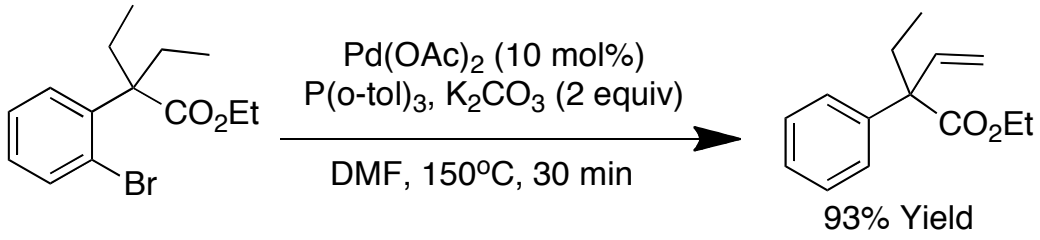
J. Am. Chem. Soc. **2007,** *129,* 3510

62

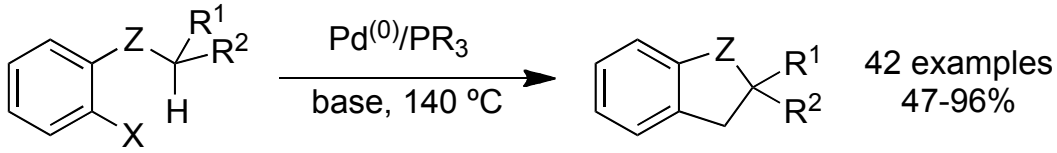
Halogen Directed C-H C-C Formation



Angew. Chem. Int. Ed. **2003**, *33*, 103



Angew. Chem. Int. Ed. **2003**, *42*, 5736



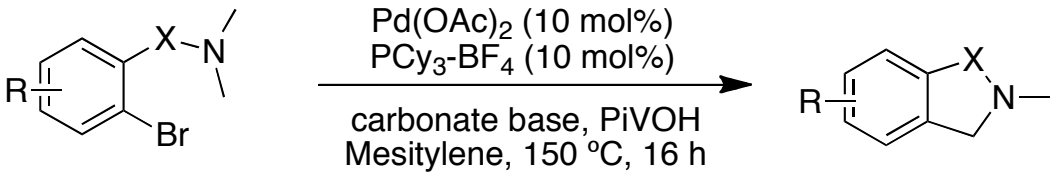
X = Cl, Br Z = no atom, CR_2, N-R, C=O

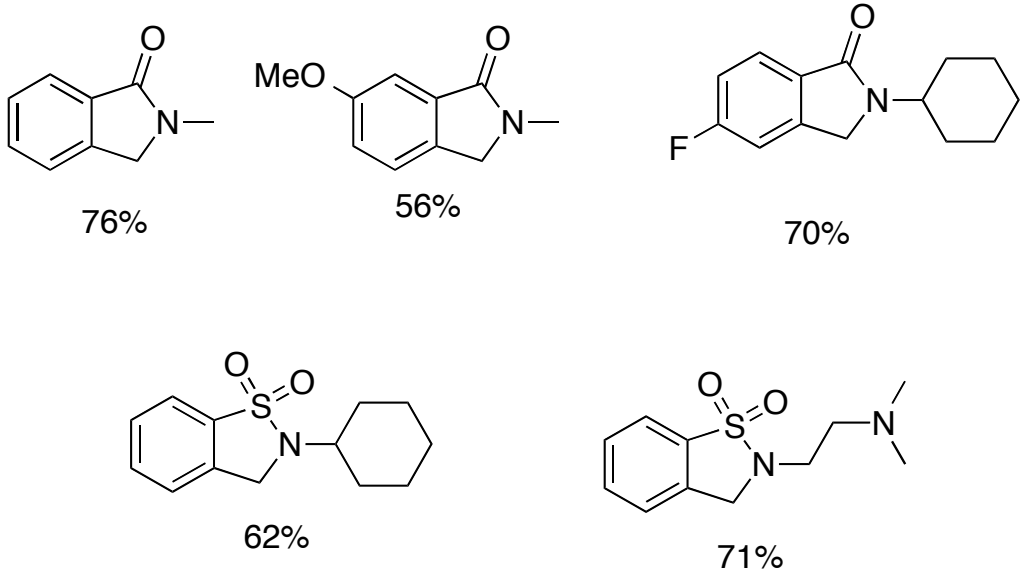
R^1 = alkyl R^2 = H, CO_2Me, CN

J. Am. Chem. Soc. **2010**, *132*, 10706

Jared Hammill @ Wipf Group

Fagnou's C-H C-C formation



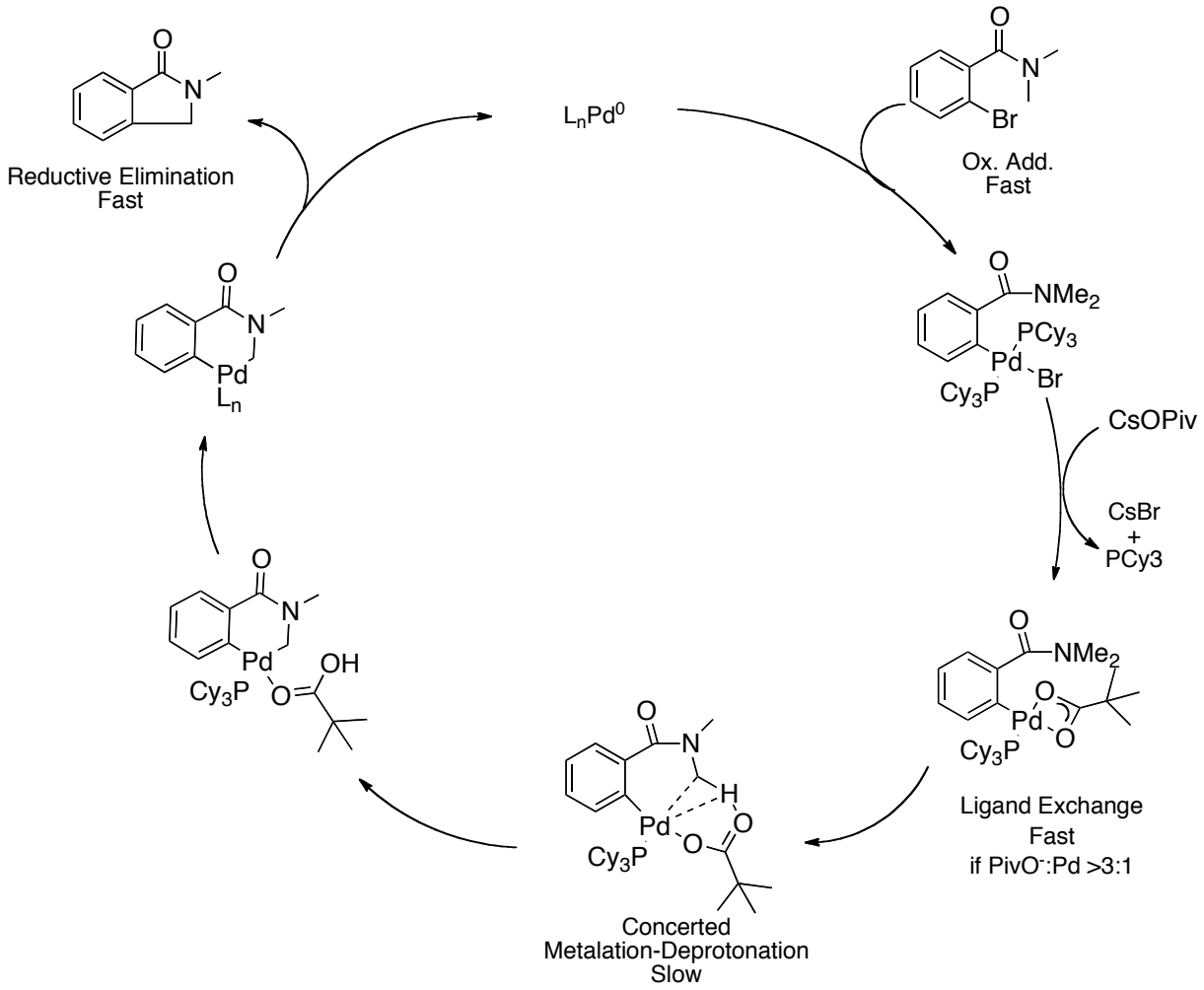


Jared Hammill @ Wipf Group

J. Am. Chem. Soc. **2010,** *132,* 10692

64

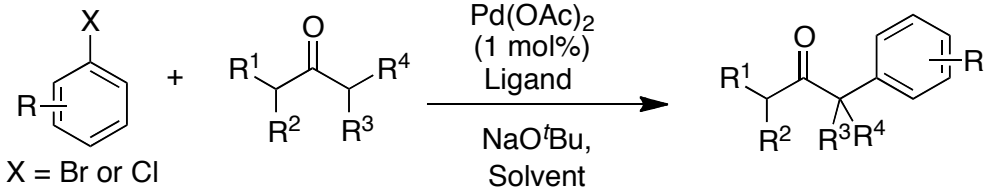
C-H C-C formation



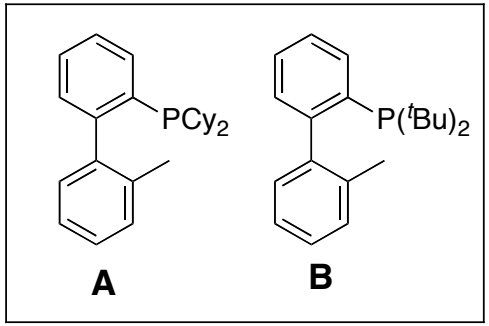
Jared Hammill @ Wipf Group

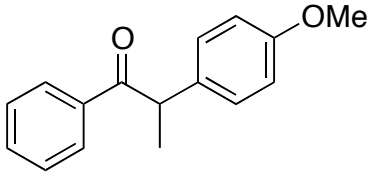
J. Am. Chem. Soc. **2010,** *132,* 10692

Buchwald's C-H C-C formation

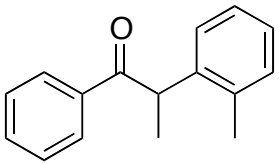


Typical solvents: toluene, THF, dioxane
Typical rxn temperatures: 80-120 °C

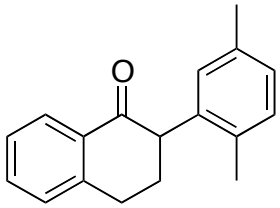




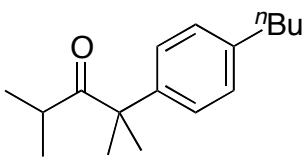
No Ligand
93%



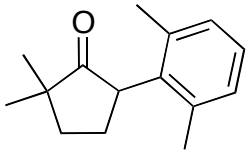
No Ligand
46%



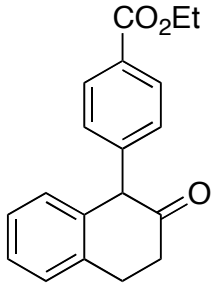
A
93%



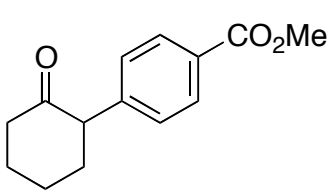
A
61%



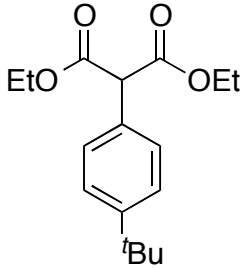
A
64%



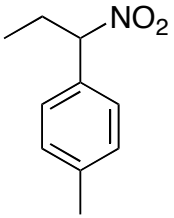
A
85%



A
70%



B
92%

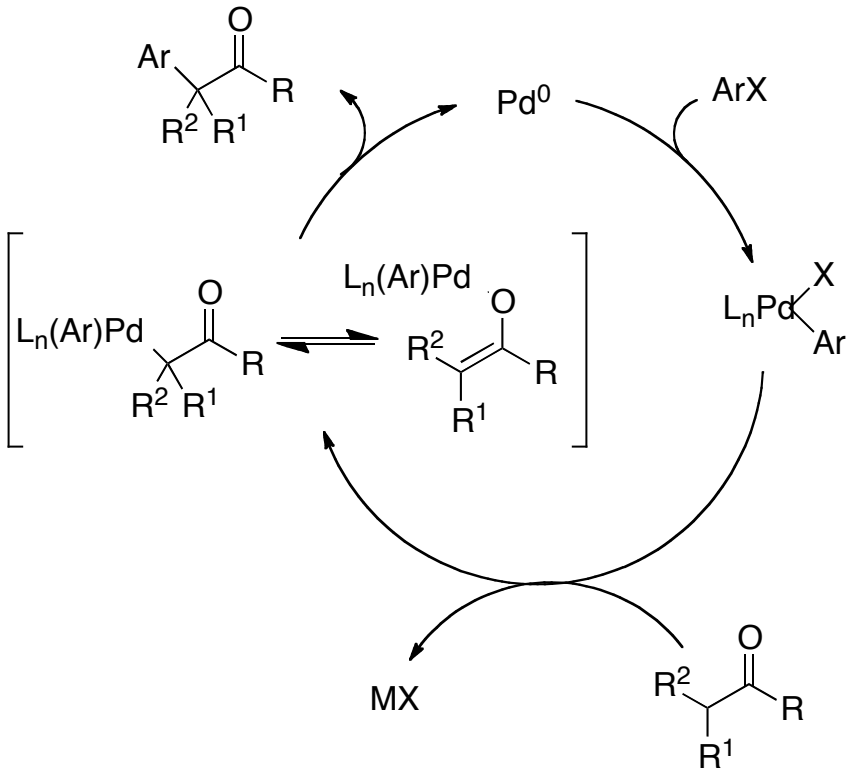


B
76%

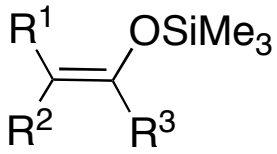
Jared Hammill @ Wipf Group

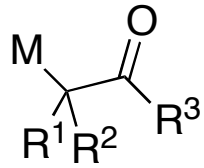
J. Am. Chem. Soc. **2000,** *122,* 1360

C-H C-C formation



Enolate equivalents work too:





M = Zn, Cu

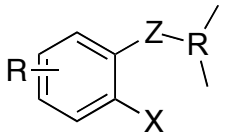
Chem Rev. **2010,** *132,* 1360
Angew. Chem. Int. Ed. **2010,** *49,* 676

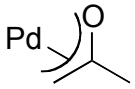
Jared Hammill @ Wipf Group

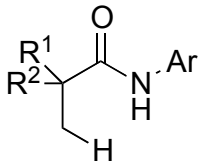
C-C bond formation summary

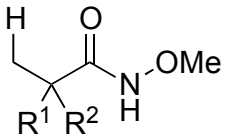
1º C-H Bonds

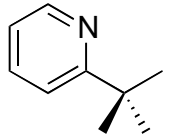
Directed Pd catalysis

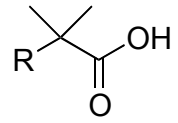






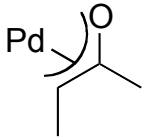


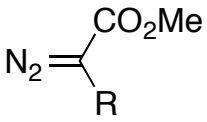




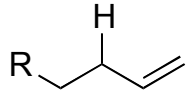
2º C-H Bonds

Directed Pd or Rh Catalysis



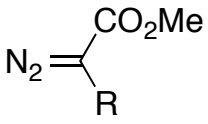


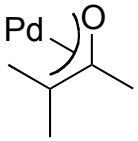
Allylic, Pd Catalysis



3º C-H Bonds

Directed Pd, Rh, Catalysis





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Outline

A. Introduction

B. C_{sp3} C-H Bond Functionalization

   A. C-O Bond Formation

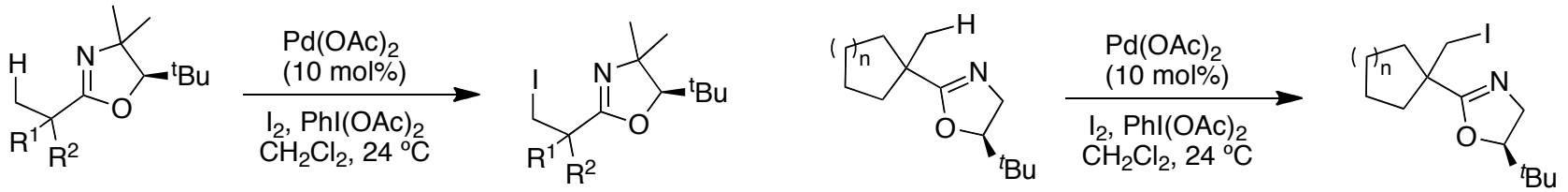
   B. C-N Bond Formation

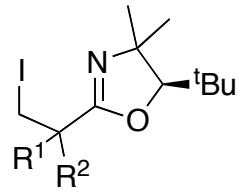
   C. C-C Bond Formation

   D. C-X Bond Formation

C. Conclusions and Future Directions

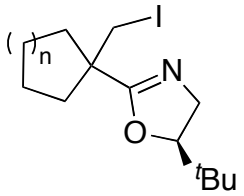
Yu's C-H C-I formation





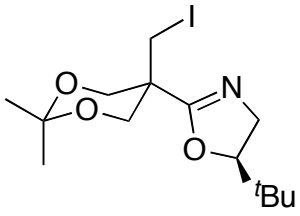
R^1, R^2 = Me or Et

88-92%

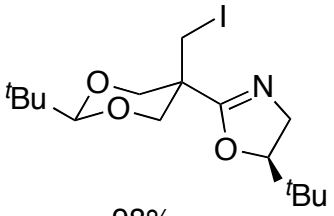


n = 1-3

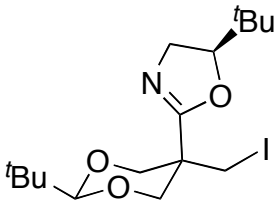
81-97%



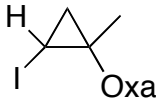
67%



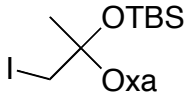
98%



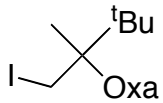
32%



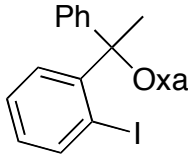
65%
99:1 dr



62%
93:7 dr



83%
91:9 dr



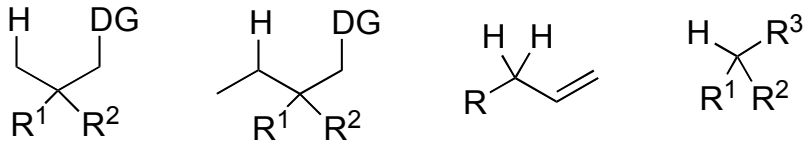
98%
99:1 dr

Angew. Chem. Int. Ed. **2005**, *44*, 2112

Summary

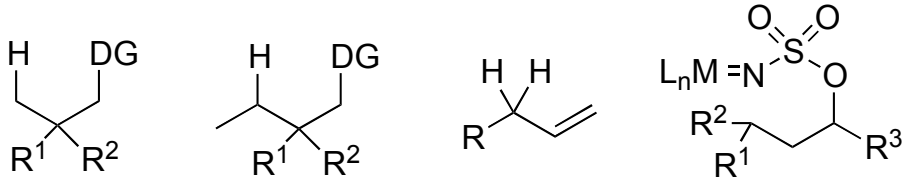
C-H Oxygenation

Pt, Pd, Fe, Ir



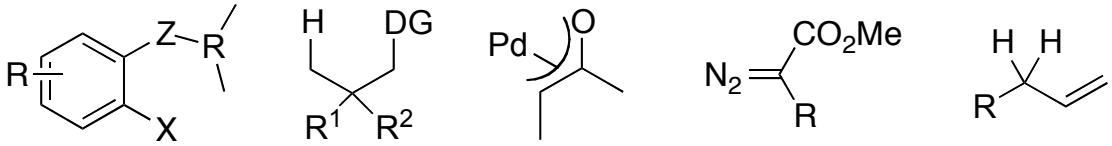
C-H Amination

Cu, Rh, Ru Pd, Fe



C-H C-C Formation

Pd, Rh



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Conclusion and Future Directions

Hot Topic

>600 journal articles (not reviews) published since 2000

- Ground work has been laid
- Continued mechanistic elucidation → rational catalyst design
  - New catalysts/ligands
    - Higher levels of predictable selectivity
- Implementation in complex molecule synthesis

"If we can find ways to use C-H bonds as versatile functional groups we can revolutionize the rules that have influenced our strategies for assembling molecules over the last 100 years."

Jared Hammill @ Wipf Group

Chem. Soc. Rev. **2011**, *40*, 1885

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Transition Metal-Catalyzed Functionalization of C_{sp3} C-H bond activation

Thanks for your attention!

Questions?