Functionalization Reactions: Oxidation, Amination, Isotopes

Outline:

- I. Introduction and Background
    1. The purpose of these group meetings
    2. How did we decide on what to include?
    3. Late-stage functionalization strategies
- II. Oxidation Reactions
    1. Polonovski Reaction
    2. Oxime-directed oxidation
    3. Copper-catalyzed γ-hydroxylation
    4. Oxaziridine-mediated oxidation
    5. Transition metal-catalyzed undirected sp^3 C-H oxidation
    6. Transition metal-catalyzed allylic oxidation
    7. Electrochemical sp^3 C-H oxidation
    8. Leaving group installation
    9. Alcohol-directed sp^3 C-H silylation/oxidation
- III. Amination/Azidation Reactions
    1. Intermolecular amination of unactivated sp^3 C-H bonds
    2. Intermolecular allylic amidation
    3. Intramolecular amidation
    4. Amination at tertiary centers
    5. Undirected sp^3 C-H azidation
    6. C-H azidation mediated by photoredox catalysis
- IV. Isotope Incorporation
    1. The Shilov system
    2. Pt/Pd extensive deuterium incorporation
    3. Bergman's iridium system
    4. Isotope exchange at vinylic positions
    5. Site-selective labeling of heteroaromatics
    6. Selective labeling of benzylic positions
    7. Labeling of *ortho*-positions
    8. Labeling of *meta*/*para*-positions
    9. Photoredox-mediated labeling

I. Introduction and Background

1. The purpose of these group meetings

To create a resource for late-stage functionalization reactions that can be applied to complex settings. These are reactions we believe can be applied to pharmaceuticals for medicinal chemistry investigations.

We will present each strategy in a consistent manner: discussing the substrate scope, mechanism, and any examples of their application (or that of highly related reactions).

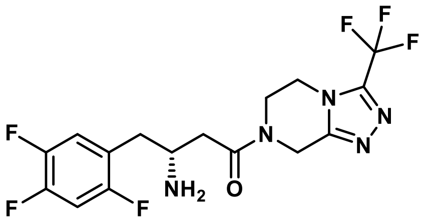
2. How did we decide on what to include?

Each paper we chose, and many more that we did not choose, were put through an evaluation of whether the transformation could be applied to more complex settings than those presented.

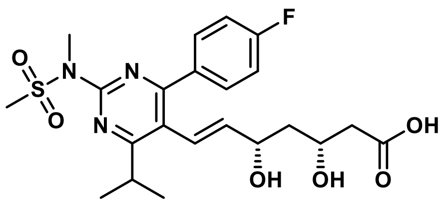
This was determined by the choice of three top-selling pharmaceuticals with varying functionalities present (*vide infra*) as the model systems. If the reaction was believed to be applicable to any of the three, then we included it here. However, if we did not think it could be applied then we excluded it. **This does not have any reflection on the relative merits of the papers chosen or those not chosen as all the papers reviewed were significant andvances in their own respective fields.**

Furthermore, if there were multiple transformations that could be applied, but their conditions were highly similar, we chose the paper that was published first. We often tried to incroporate the seminal reports rather than the follow-up papers, as the later papers can be easily found through the seminal report.

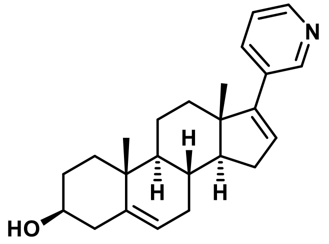
In no way is this collection the comprehensive overview of the reactions discussed, as each section can (and should) be a group meeting itself.



januvia



crestor



zytiga

3. Late-stage functionalization strategies.

This week:

Oxidation reactions
Amination/azidation reactions
Isotope incorporation

Next time:

Borylation reactions
Olefin functionalizations

Final presentation:

Halogenation reactions
Perfluoroalkylation reactions
Arylation reactions
Alkylation reactions

Functionalization Reactions: Oxidation, Amination, Isotopes

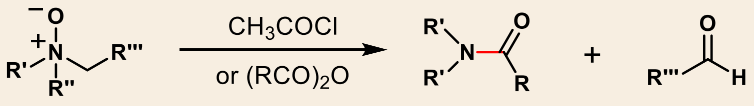
II. Oxidation reactions

The field of C-H functionalization has been extensively reviewed:
Godula, K., Sames, D. *Science*, **2006**, *312*, 67.
Newhouse, T., Baran, P. S. *Angew. Chem. Int. Ed.*, **2011**, *50*, 3362.
Hartwig, J. F., Larsen, M. A. *ACS Cent. Sci.*, **2016**, *2*, 281.

The oxidation of alkanes can be traced back to the Shilov process. However, the conditions required can be quite vigorous, and require a stoichiometric platinum reoxidant. Shilov, A. E., Shul'pin, G. E. *Chem. Rev.*, **1997**, *97*, 2879.

1. Polonovski Reaction

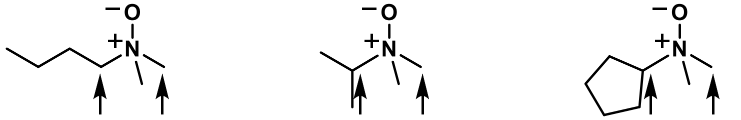
Polonovski 1927



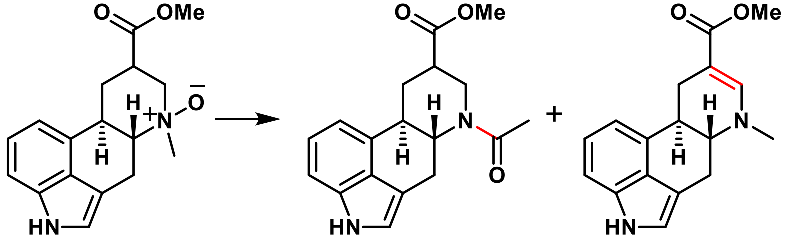
Polonovski, M., Polonovski M. *Bull. Soc. Chim.*, **1927**, *41*, 1190.

Originally employed for the demethylation of tertiary amines. More thermodynamically stable iminium ion formed when TFAA used, and with Ac_2O iminium forms with more kinetically acidic proton. Stronger base required wiht Ac_2O conditions.

A = Ac_2O
B = TFAA (Polonovski-Portier)



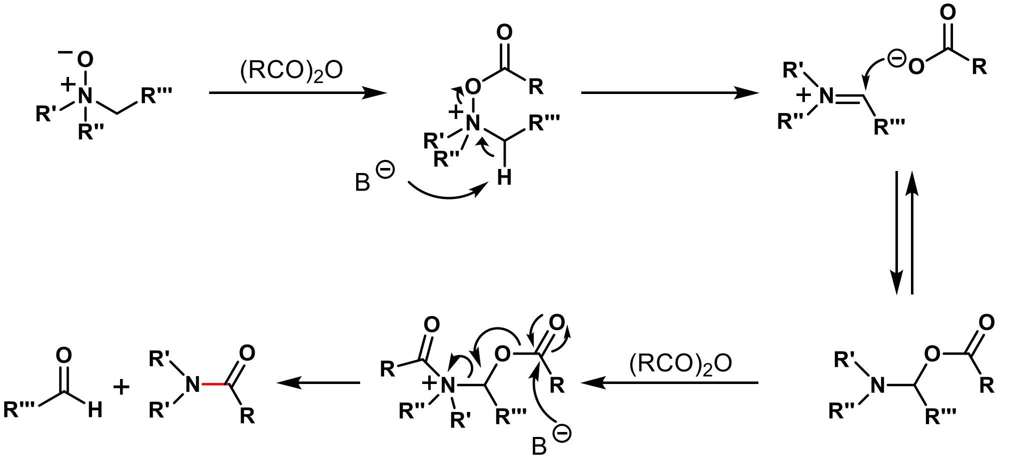
A	(13%)	(87%)	**A**	(50%)	(50%)	**A**	(68%)	(32%)
B	(37%)	(63%)	**B**	(80%)	(20%)	**B**	(99%)	(1%)



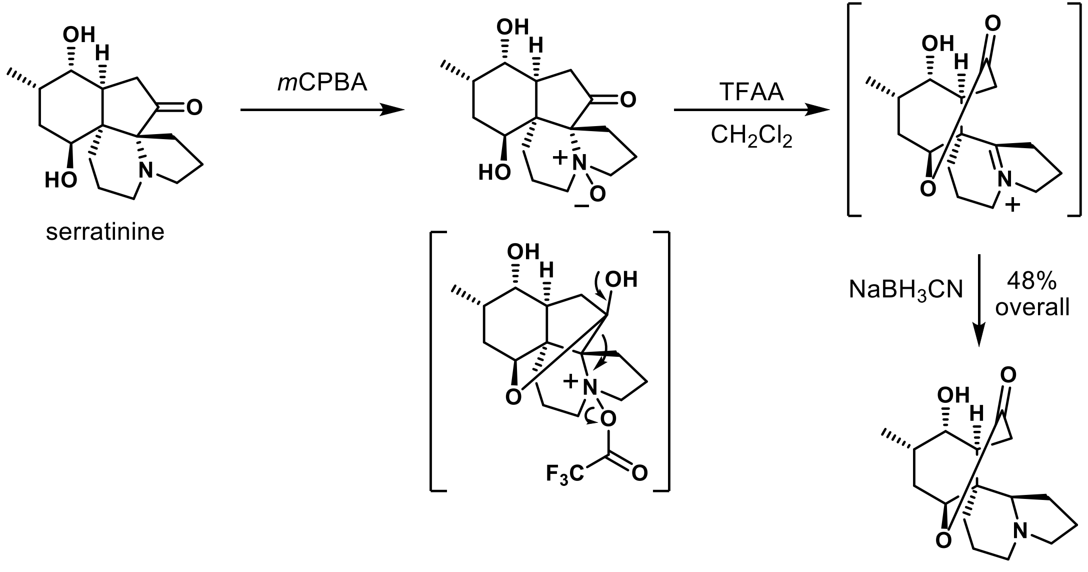
A	(10%)	(24%)
B	(3%)	(45-50%)

Grierson, D. *Org. React.*, **1990**, *39*, 85.

Mechanism



Application in Total Synthesis



serratinine

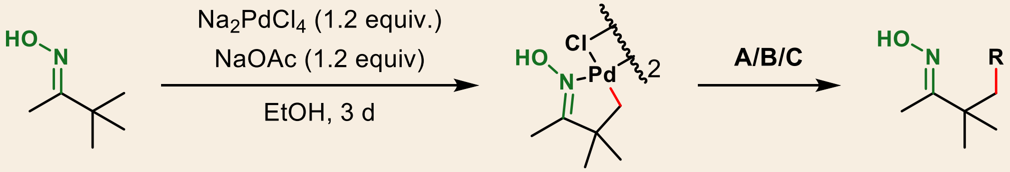
serratezomine A

Morita, H., Kobayashi, J. *J. Org. Chem.*, **2002**, *67*, 5378.

Functionalization Reactions: Oxidation, Amination, Isotopes

2. Oxime-directed oxidation

In 1985, Baldwin and coworkers explored the reactivity of a stoichiometrically generated palladacycle directed by an oxime.

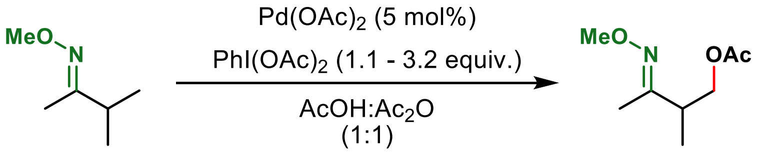


Na_2PdCl_4 (1.2 equiv.)
NaOAc (1.2 equiv)
EtOH, 3 d

Conditions	R	Yield
A: 1) Cl_2, CCl_4 2) $NaBH_3CN$	Cl	64
B: 1) Py., *then* $Pb(OAc)_4$ 2) $NaBH_4$	OAc	quant.
C: 1) $NaBD_3CN$	D	41

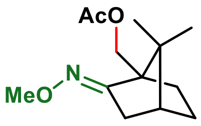
Baldwin. J. E., Jones, R. H., Najera, C., Yus, M. *Tetrahedron*, **1985**, *41*, 699.

Then, in 2004, the Sanford group made the conditions catalytic.

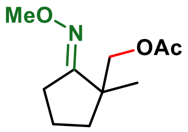


$Pd(OAc)_2$ (5 mol%)
$PhI(OAc)_2$ (1.1 - 3.2 equiv.)
$AcOH:Ac_2O$
(1:1)
100 °C

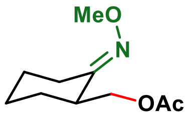
74%



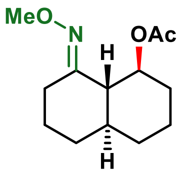
75%



61%



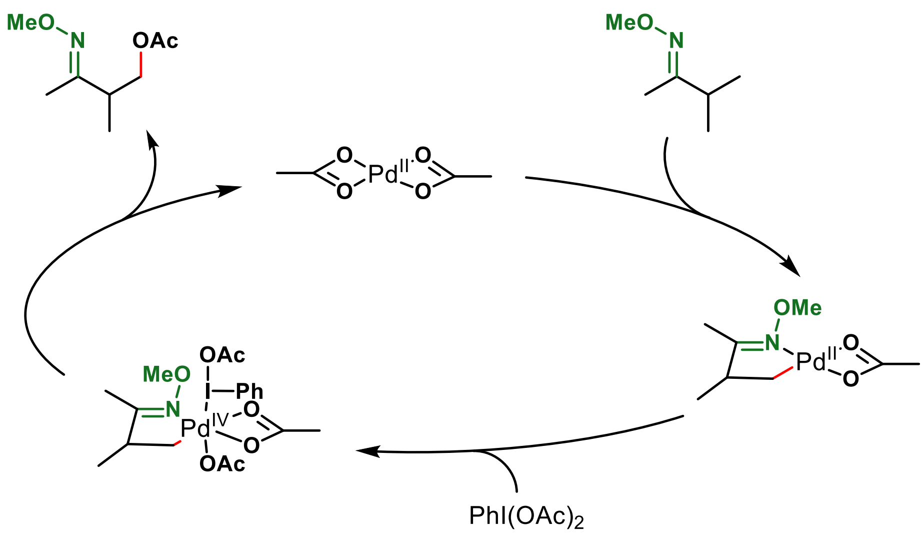
81%



81%

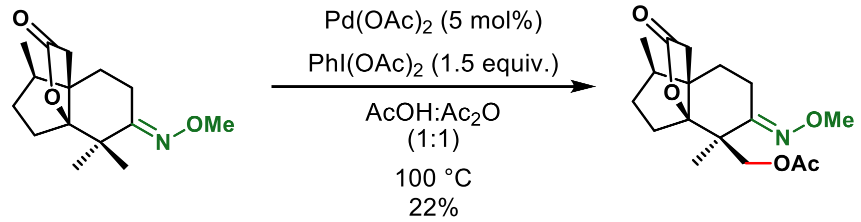
Desai, L. V., Hull, K. L., Sanford, M. S. *J. Am. Chem. Soc.*, **2004**, *126*, 9542.

Mechanism

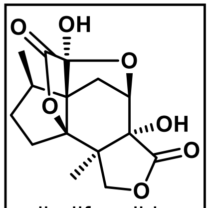


$PhI(OAc)_2$

Application in Total Synthesis



$Pd(OAc)_2$ (5 mol%)
$PhI(OAc)_2$ (1.5 equiv.)
$AcOH:Ac_2O$
(1:1)
100 °C
22%



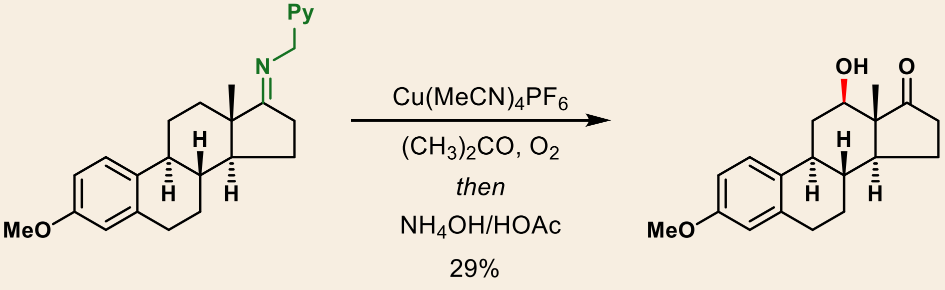
jiadifenolide

Siler, D. A., Mighion, J. D., Sorensen, E. J. *Angew. Chem. Int. Ed.*, **2014**, *53*, 5332.

Functionalization Reactions: Oxidation, Amination, Isotopes

3. Copper-catalyzed γ-hydroxylation

First reported by Schönecker, the aerobic oxidation of C-H bonds by copper directed by iminomethyl pyridines was achieved in low yields.



$Cu(MeCN)_4PF_6$

$(CH_3)_2CO$, O_2

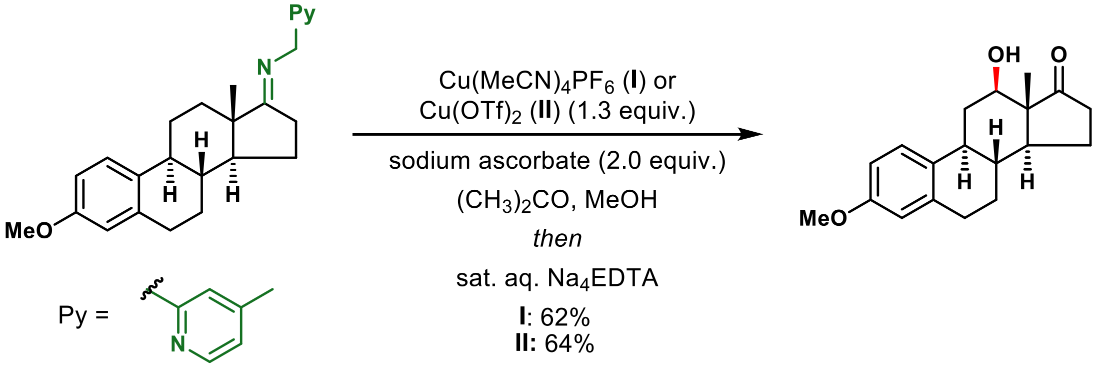
then

$NH_4OH/HOAc$

29%

Schönecker, B. *et al. Chem. Eur. J.*, **2004**, *10*, 6029.

Then in 2015, the Baran group improved on the transformation and investigated the substrate scope.



$Cu(MeCN)_4PF_6$ (**I**) or

$Cu(OTf)_2$ (**II**) (1.3 equiv.)

sodium ascorbate (2.0 equiv.)

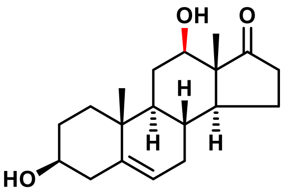
$(CH_3)_2CO$, MeOH

then

sat. aq. Na_4EDTA

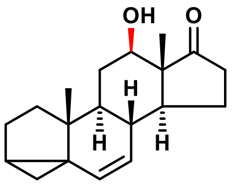
I: 62%

II: 64%



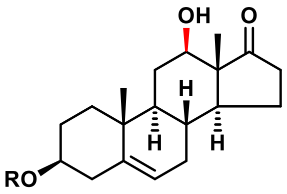
I: 90%

II: 68%



I: 90%

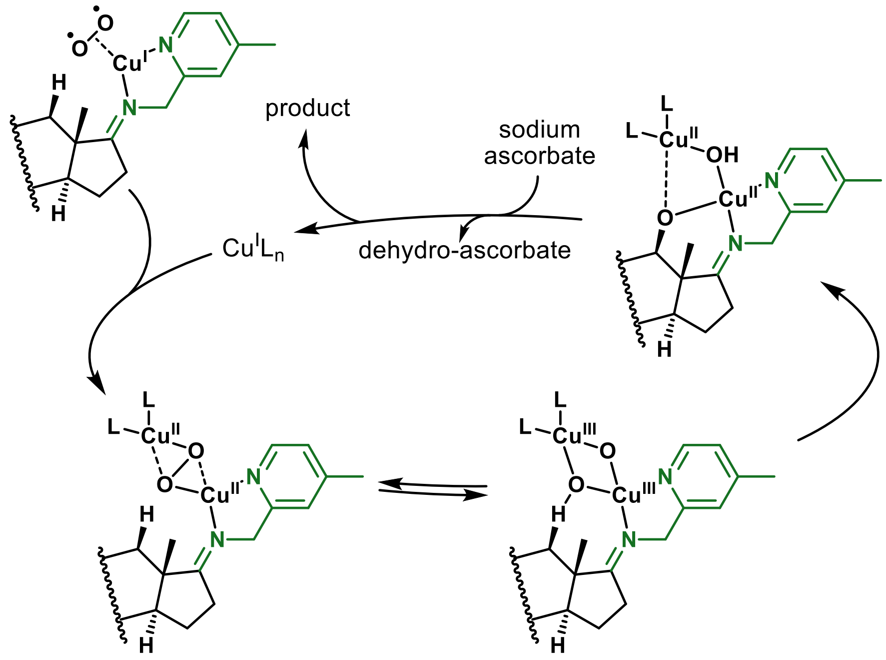
II: 68%



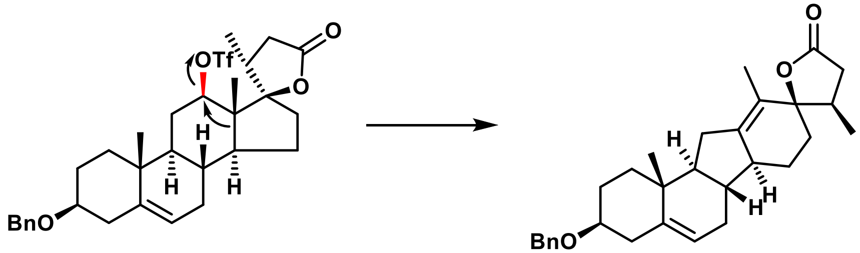
R = OBn	**I**: 55% **II**: 73%
R = OTBS	**I**: 52% **II**: 51%
R = OAc	**I**: 46% **II**: 61%

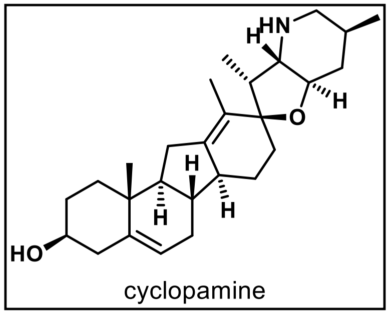
See, Y. Y., Herrmann, A. T., Aihara, Y., Baran, P. S. *J. Am. Chem. Soc.*, **2015**, *137*, 13776.

Mechanism



Application in Total Synthesis





cyclopamine

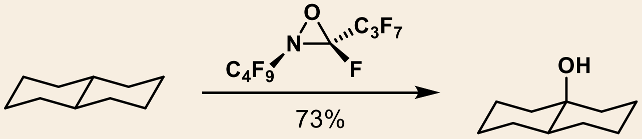
Giannis, A. *et al. Angew. Chem. Int. Ed.*, **2009**, *48*, 7911.

Functionalization Reactions: Oxidation, Amination, Isotopes

4. Oxaziridine/oxirane-mediated oxidation

For a review on polyfluorinated oxaziridines: *Chem. Rev.*, **1996**, *96*, 1809.

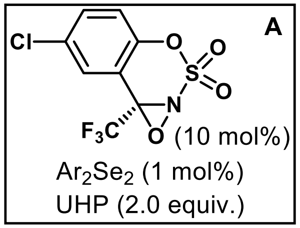
In 1993, DesMarteau and coworkers investigated the stoichiometric oxidation of alkanes mediated by perfluorinated oxaziridines. They found that the selectivities followed the same trends as their dioxirane counterparts.



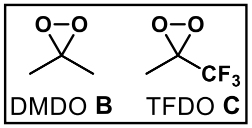
DesMarteau, D. D. *et al. J. Am. Chem. Soc.*, **1993**, *115*, 4897.

Du Bois and coworkers showed the reaction could be made catalytic through the use of a selenium shuttle for the oxidant.

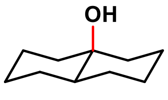
The dioxiranes DMDO and TFDO have also been shown for the oxidation of alkanes, with both stoichiometric and catalytic conditions.



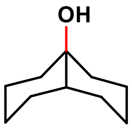
(10 mol%)
Ar_2Se_2 (1 mol%)
UHP (2.0 equiv.)



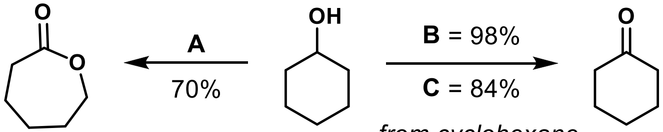
DMDO **B** TFDO **C**



A = 63%

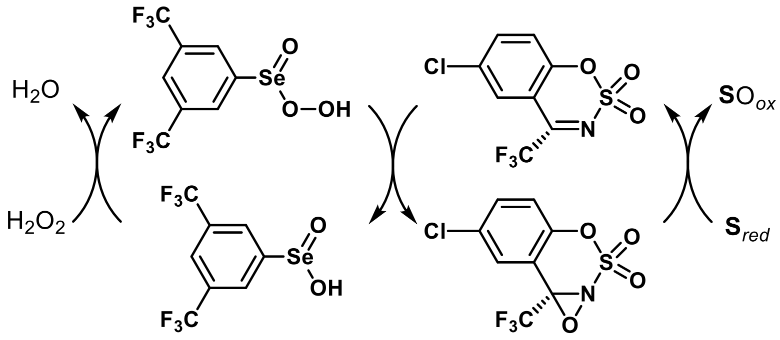


B = 98%
C = 84%

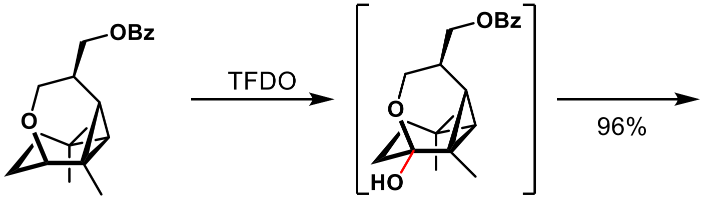


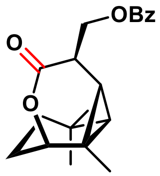
from cyclohexane

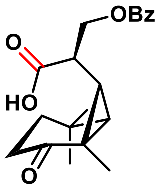
Mechanism

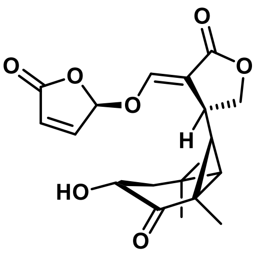


Application in Total Synthesis



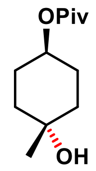




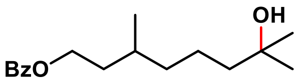


avenaol

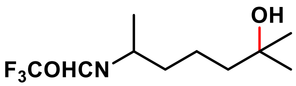
Yasui, M., Ota, R., Tsukano, C., Takemoto, Y. *Nature Comm.*, **2017**, *8*, 674.



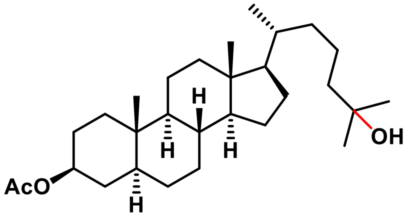
A = 36%



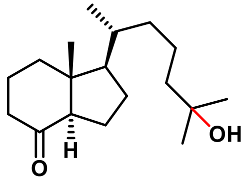
A = 43%



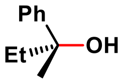
A = 39%



C = 80 - 85%



C = 86%

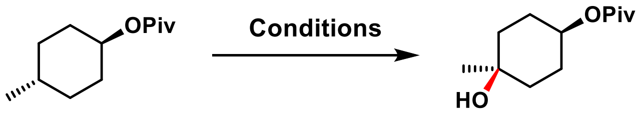


C = > 95%
> 99% es

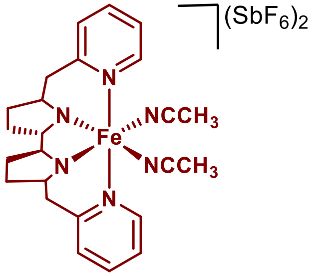
Brodsky, B. H., Du Bois, J. *J. Am. Chem. Soc.*, **2005**, *127*, 15391. Curci, R., D'Accolti, L., Fusco, C. *Acc. Chem. Res.*, **2006**, *39*, 1.

Functionalization Reactions: Oxidation, Amination, Isotopes

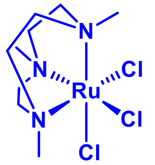
5. Transition metal-catalyzed undirected sp^3 C-H oxidation



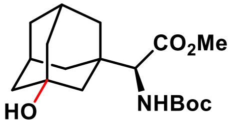
A	**B**	**C**
Fe(*S*,*S*-PDP) (5 mol%) H_2O_2 (1.2 equiv.) AcOH, MeCN, rt 51%	[(Me$_3$tacn)RuCl$_3$] (1 mol%) $AgClO_4$ (4 mol%) $(NH_4)_2Ce(NO_3)_6$ (6.0 equiv) *t*BuOH/H_2O 52%	$RuCl_3$ (5 mol%) $KBrO_3$ (3.0 equiv.) Py (10 mol%) MeCN/H_2O 57%



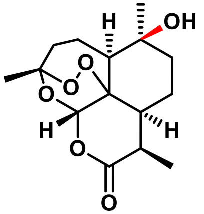
Fe(*S*,*S*-PDP)



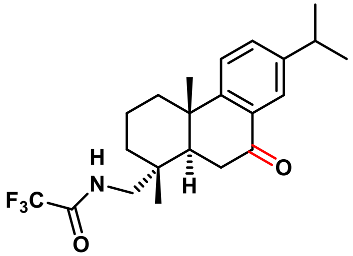
[(Me$_3$tacn)RuCl$_3$]



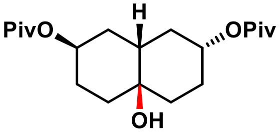
C = 57%



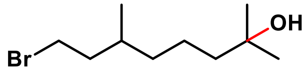
A = 52%



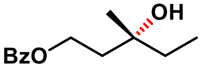
B = 72%



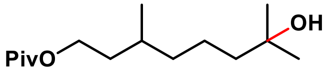
C = 41%



A = 39%



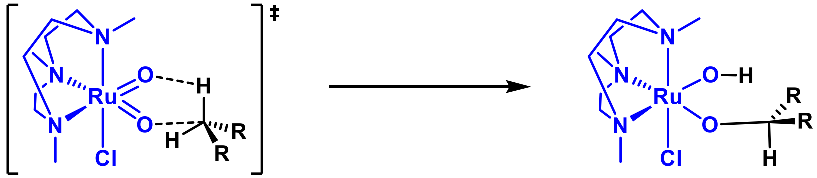
B = 34%
> 99% es



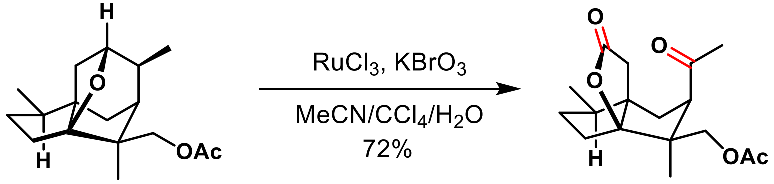
C = 44%

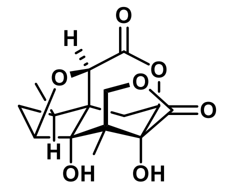
Chen, M. S., White, M. C. *Science*, **2007**, *318*, 783.
McNeill, E., Du Bois, J. *Chem. Sci.*, **2012**, *3*, 1810.
McNeil, E., Du Bois, J. *J. Am. Chem. Soc.*, **2010**, *132*, 10202.

Mechanism



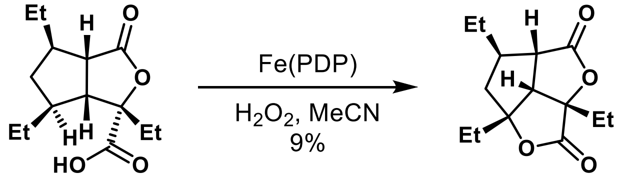
Application in Total Synthesis





(-)-jiadifenoxolane A

Condakes, M. L., Hung, K., Harwood, S. J., Maimone, T. J. *J. Am. Chem. Soc.*, **2017**, *139*, 17783.



gracilioether F

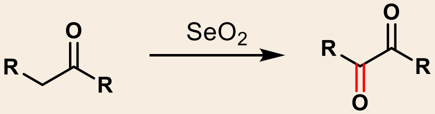
The Brown group employed the conditions developed by Prof. White for C-H oxidation in their synthesis of gracilioether F. While they ended up using alternative conditions, these were one of only three conditions to give the natural product. The conditions used to achieve the natural produt gave a 15% isolated yield.

Rasik, C. M., Brown, M. K. *Angew. Chem. Int. Ed.*, **2014**, *53*, 14522.

Functionalization Reactions: Oxidation, Amination, Isotopes

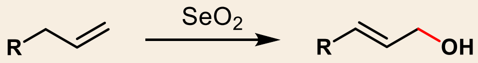
6. Transition metal-catalyzed allylic oxidation

Riley 1932

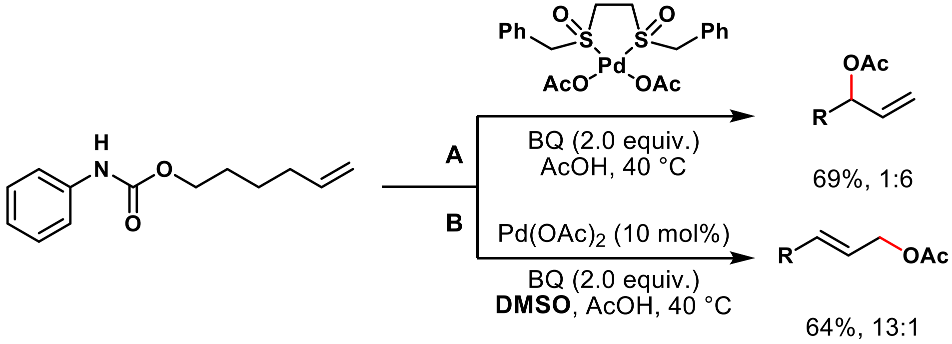


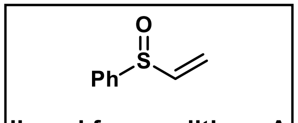
Riley, H. L. *et. al. J. Chem. Soc.*, **1932**, 1875.

Guillemonat 1939

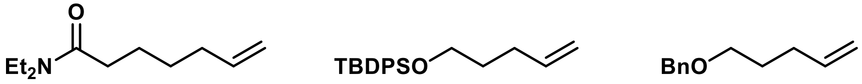


Guillemonat, A. *Annali di Chimica Applicata*, **1939**, *11*, 143.





ligand for conditions A



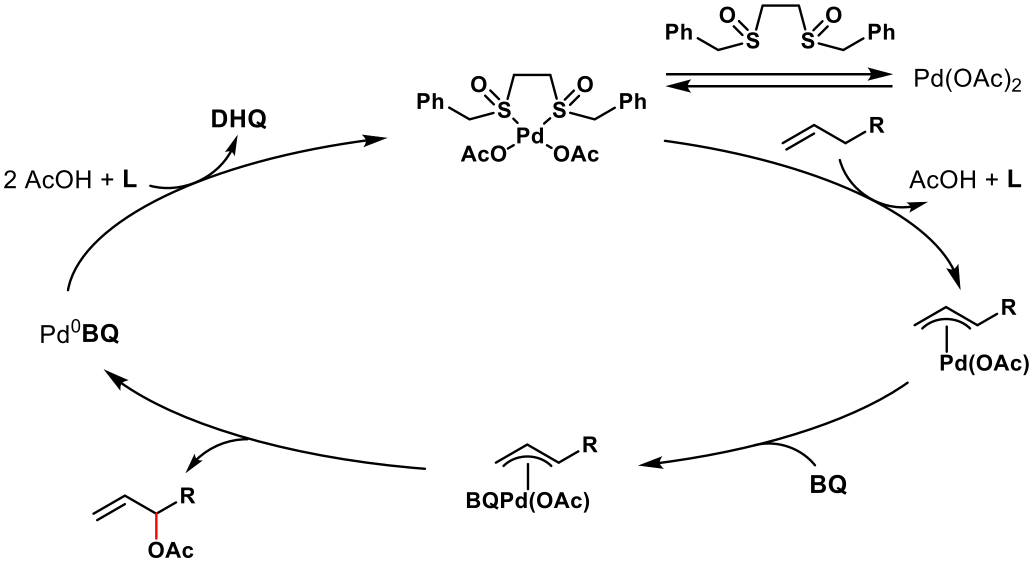
A = 56%, 18:1
B = 62%, 23:1

A = 72%, 16:1
B = 50%, 31:1

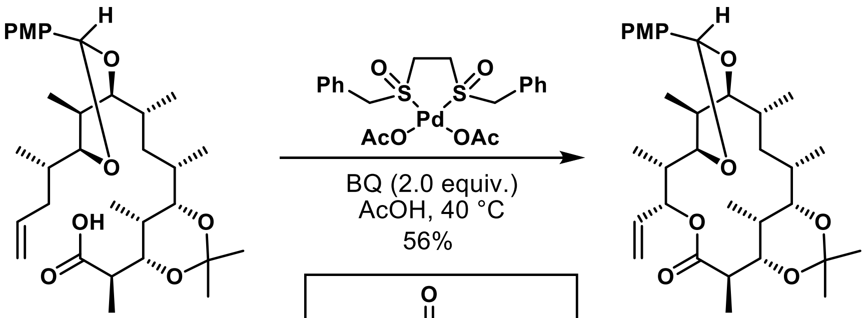
A = 59%, 18:1
B = 57%, 31:1

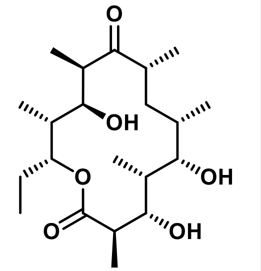
Chen, M. S., White, M. C. *J. Am. Chem. Soc.*, **2004**, *126*, 1346.
Chen, M. S. *et al. J. Am. Chem. Soc.*, **2005**, *127*, 6970.
Electrochemical Example: Baran, P. S. *Nature*, **2016**, *533*, 77.

Mechanism



Application in Total Synthesis



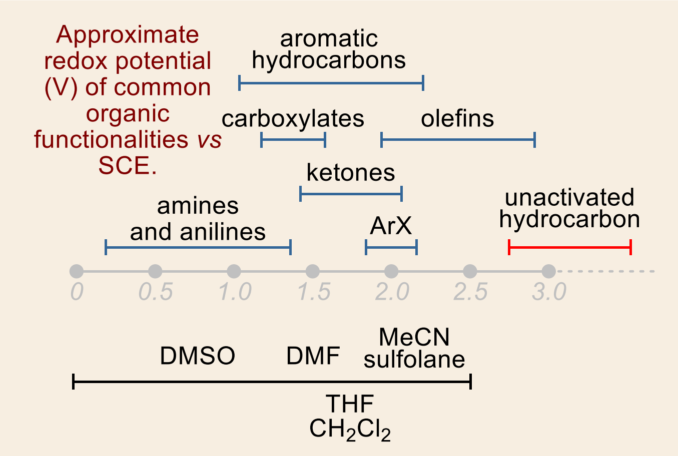


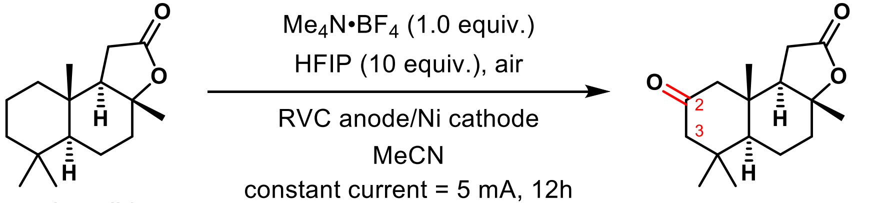
6-deoxyerythronolide B

Stang, E. M., White, M. C. *Nat. Chem.*, **2009**, *1*, 547.

Functionalization Reactions: Oxidation, Amination, Isotopes

7. Electrochemical sp^3 C-H oxidation



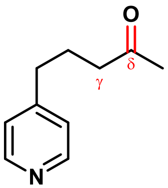


sclareolide

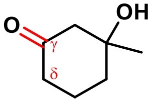
quinuclidine (1.0 equiv.)
$Me_4N•BF_4$ (1.0 equiv.)
HFIP (10 equiv.), air

RVC anode/Ni cathode
MeCN
constant current = 5 mA, 12h

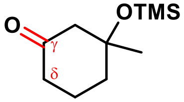
51%, C2:C3 (4.6:1)



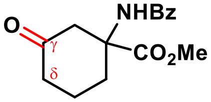
44% (γ:δ 2:1)



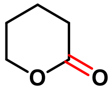
80% (γ:δ 4:1)



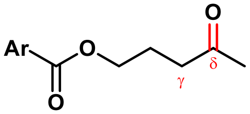
52% (γ:δ 2.4:1)



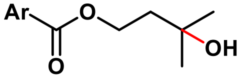
63% (γ:δ 2.4:1)



65%



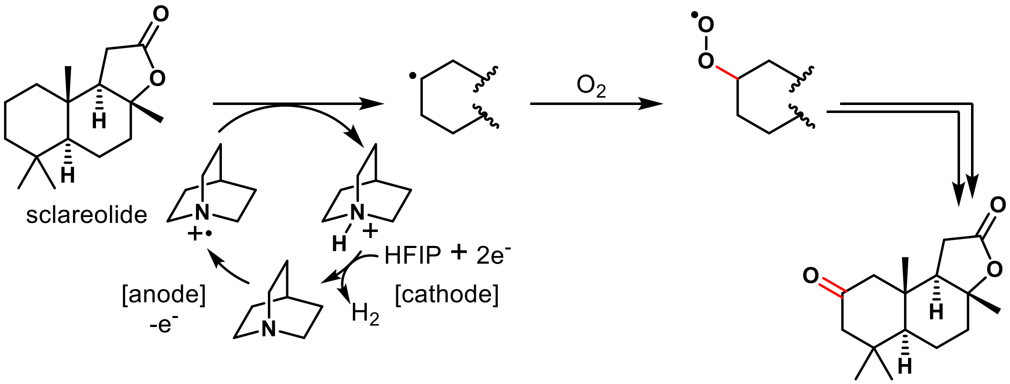
Ar = 4-ClC_6H_4
52% (γ:δ 1:3)



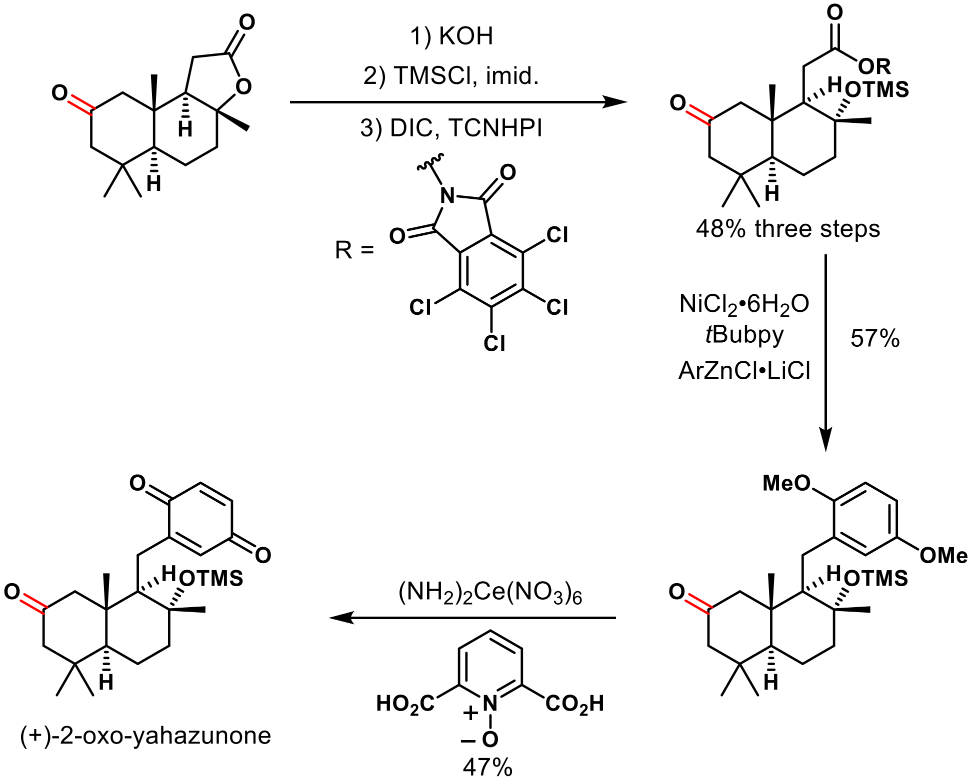
Ar = 4-ClC_6H_4
62%

Baran, P. S. *J. Am. Chem. Soc.*, **2017**, *139*, 7448.

Mechanism



Application in Total Synthesis



1) KOH
2) TMSCl, imid.
3) DIC, TCNHPI

48% three steps

$NiCl_2•6H_2O$
*t*Bubpy
ArZnCl•LiCl

57%

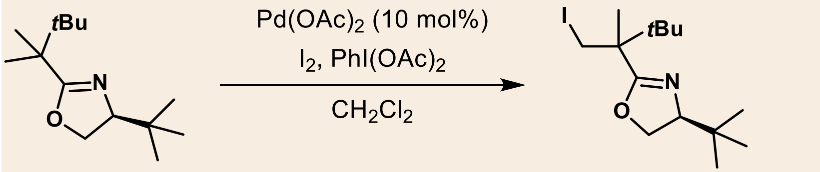
$(NH_2)_2Ce(NO_3)_6$

47%

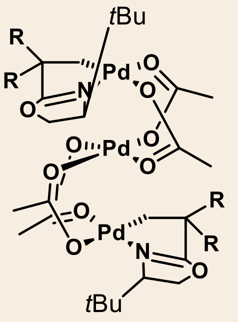
(+)-2-oxo-yahazunone

8. Leaving group installation

Yu 2005

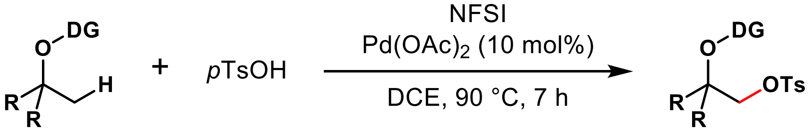


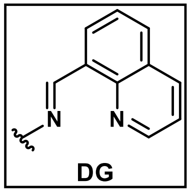
stereochemistry not defined
83%, 91:9 dr



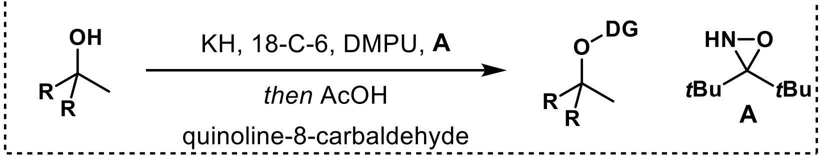
stereochemical model

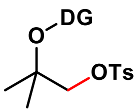
Giri, R., Chen, X., Yu, J.-Q. *Angew. Chem. Int. Ed.*, **2005**, *44*, 2112.

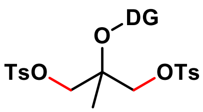




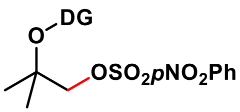
*installation of **DG***



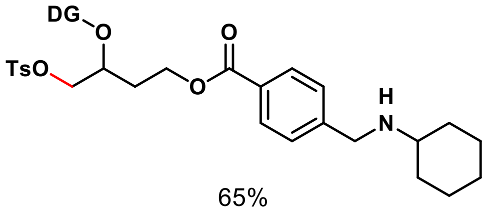




44%, 2:1

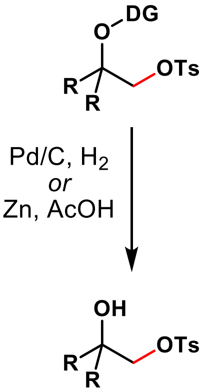


64%



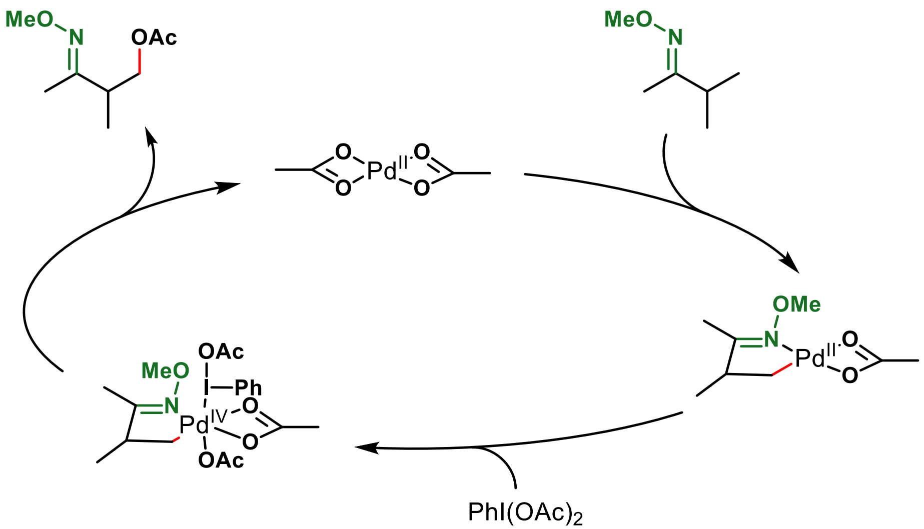
65%

*Removal of **DG***



Dong, G. *Nat. Chem.*, **2015**, *7*, 829.

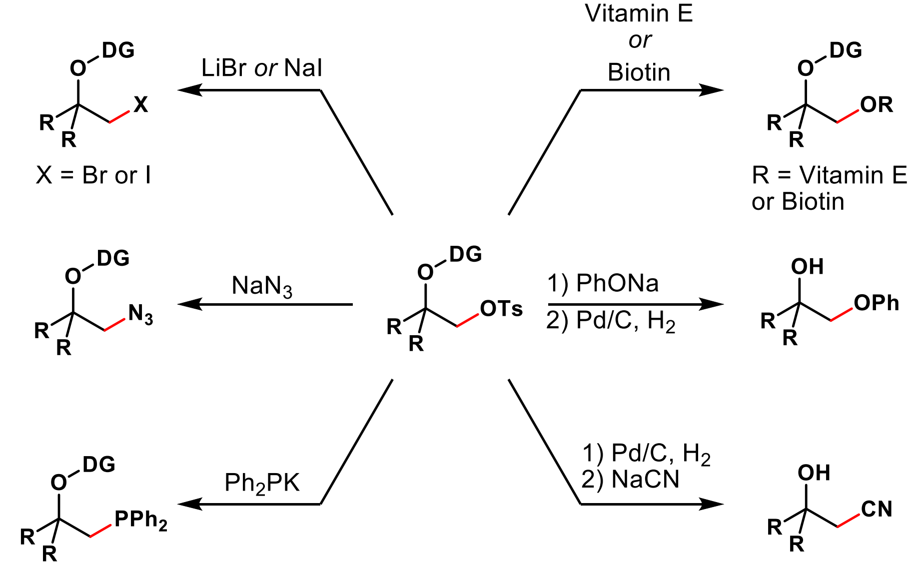
Mechanism



While the Dong group has not investigated the mechanism of this transformation, they suggested it may be similar to that proposed by Sanford and coworkers.

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

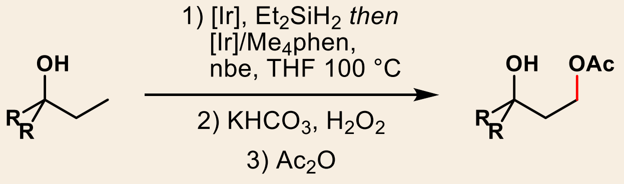
Diversification of OTs products



Functionalization Reactions: Oxidation, Amination, Isotopes

9. Alcohol-directed sp^3 C-H silylation/oxidation

Hartwig 2012



1) [Ir], Et_2SiH_2 *then* [Ir]/Me_4phen, nbe, THF 100 °C

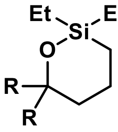
2) $KHCO_3$, H_2O_2

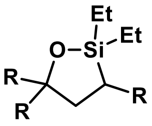
3) Ac_2O

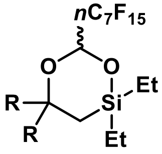
selective for the synthesis of 1,3-diols at terminal carbons

Simmons, E. M., Hartwig, J. F. *Nature*, **2012**, *483*, 70.

A	**B**	**C**
1,4-diols	*1,3-diols*	*1,2-diols*
1) $[Ir(cod)OMe]_2$ Et_2SiH_2 *then* RhCl(Xantphos) nbe, THF, 100 °C 2) KH, TBHP TBAF, NMP	1) $[Ir(cod)OMe]_2$ Et_2SiH_2 *then* $[Ir(cod)OMe]_2/Me_4Phen$ nbe, THF, 120 °C 2) TBHP, $CsOH•H_2O$ TBAF, DMF	1) $nC_7F_{15}COCl$ 2) $[Ir(cod)OMe]_2$ Et_2SiH_2 3) $[Ir(cod)OMe]_2/Me_4Phen$ nbe, THF, 120 °C 4) H_2O_2, $KHCO_3$, KF MeOH
selective for terminal C-H bonds	*can form internal diol if no primary C-H bond available*	*selective for terminal C-H bonds*

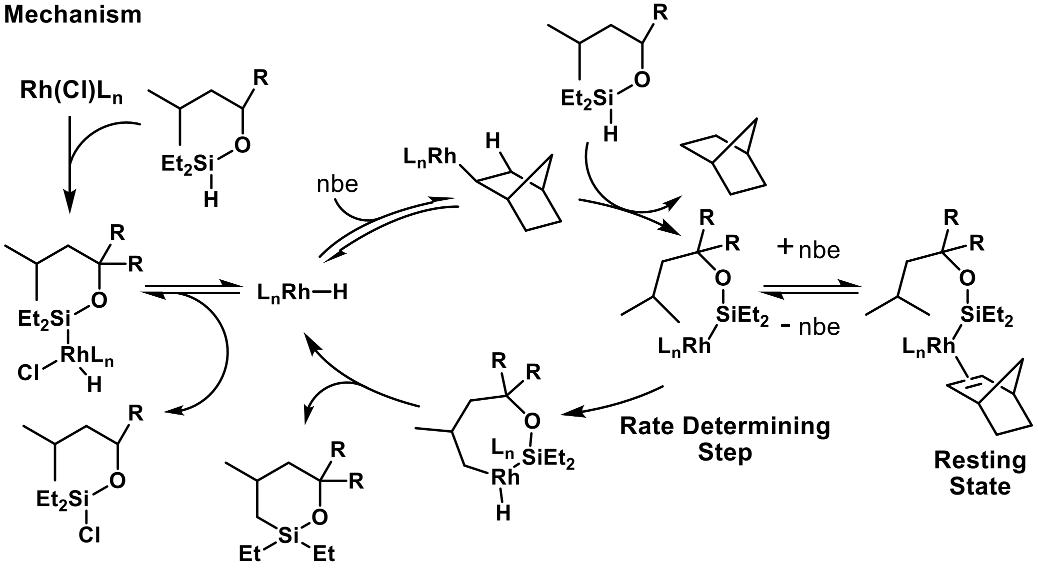






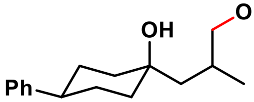
Karmel, C., Li, B., Hartwig, J. F. *J. Am. Chem. Soc.*, **2018**, *140*, 1460.
Li, B., Driess, M., Hartwig, J. F. *J. Am. Chem. Soc.*, **2014**, *136*, 6586.
Bunescu, A., Butcher, T. W., Hartwig, J. F. *J. Am. Chem. Soc.*, **2018**, *140*, 1502.

Mechanism

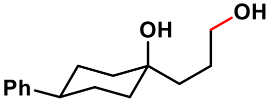


Selected Substrate Scope

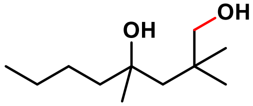
A



76%

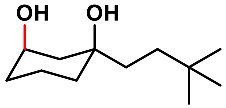


>10%

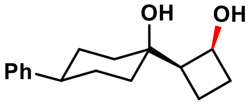


66%

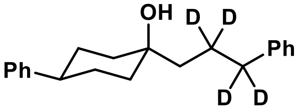
B



76%

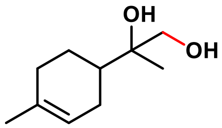


18%
85% silylation

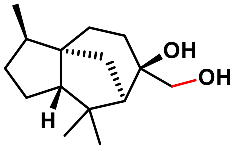


k_H/k_D = 2.0

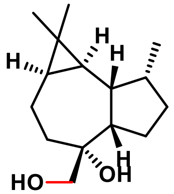
C



36%



25%



21%

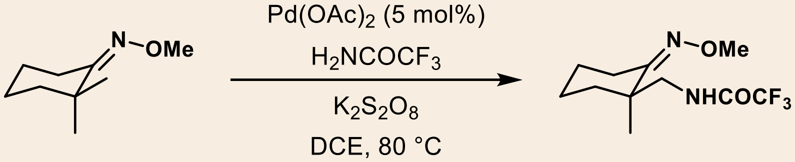
Functionalization Reactions: Oxidation, Amination, Isotopes

III. Amination/Azidaiton Reactions

For an excellent review: Chang, S. *Chem. Rev.*, **2017**, *117*, 9247.

1. Intermolecular amination of unactivated sp^3 C-H bonds

Che 2006

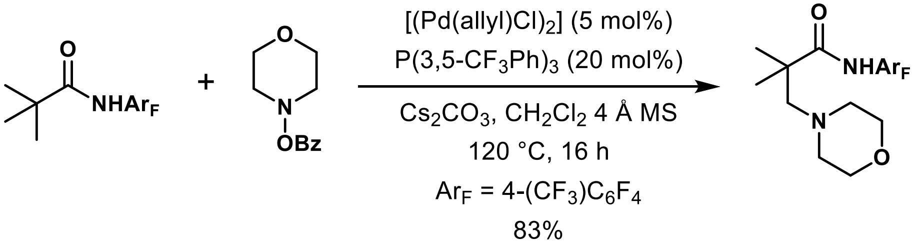


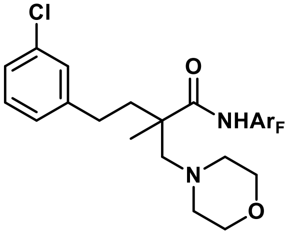
expanding the reactivity reported by Sanford to C-H amidation

Thu, H.-Y., Yu, W.-Y., Che, C.-M. *J. Am. Chem. Soc.*, **2006**, *128*, 9048.

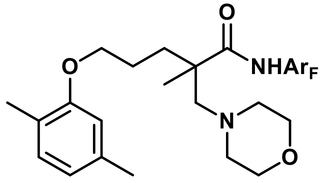
further developed by Chang in 2014

Chang, S. *J. Am. Chem. Soc.*, **2014**, *136*, 4141.

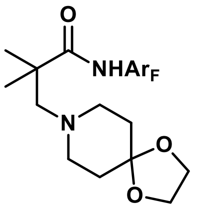




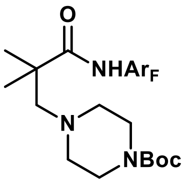
72%



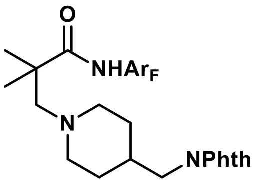
75%



67%



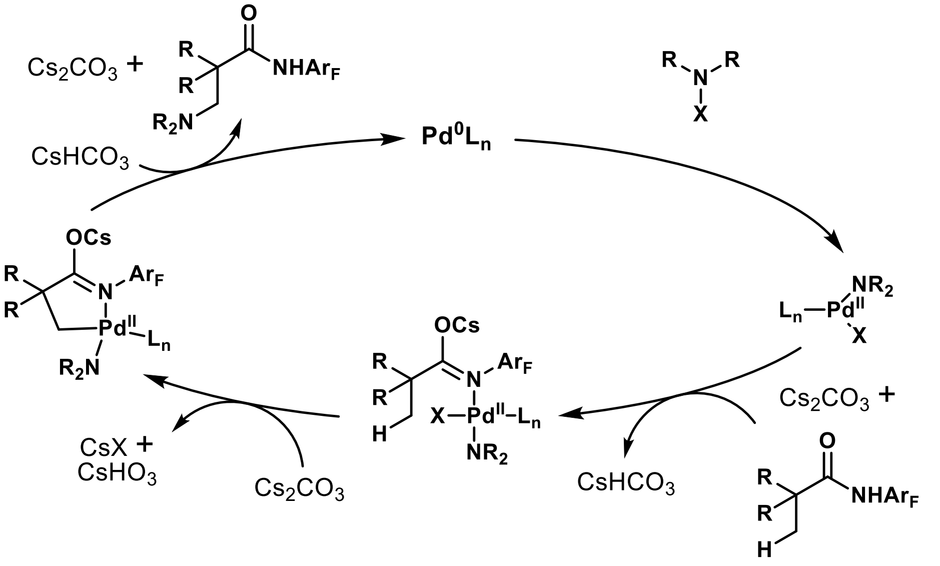
52%



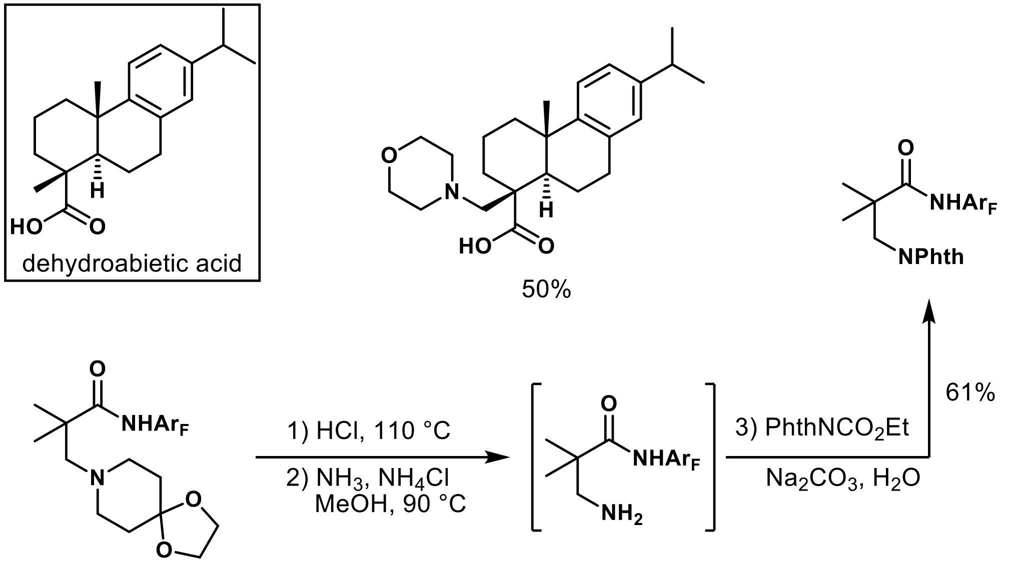
67%

He, J., Shigenari, T., Yu, J.-Q. *Angew. Chem. Int. Ed.*, **2015**, *54*, 6545.

Mechanism



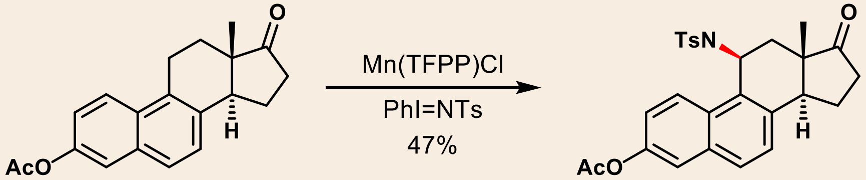
Diversification of Products



Functionalization Reactions: Oxidation, Amination, Isotopes

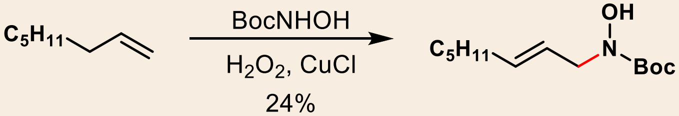
2. Intermolecular allylic amination

Breslow 2000



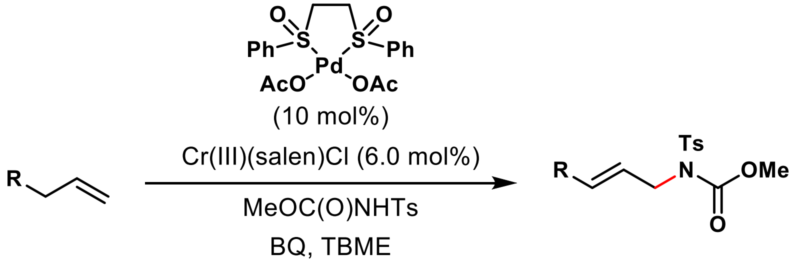
Yang, J., Weinberg, R., Breslow, R. *Chem. Commun.*, **2000**, 531.

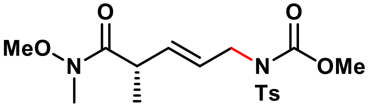
Nicholas 2005



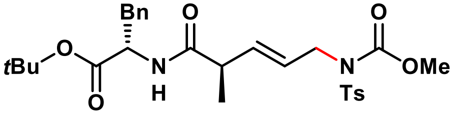
via nitroso-ene reaction

Kalita, B., Nicholas, K. M. *Tetrahedron Lett.*, **2005**, *46*, 1451.

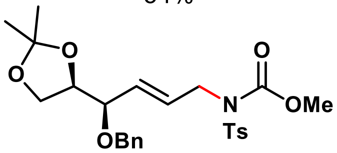




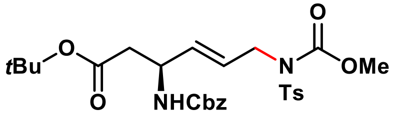
54%



50%



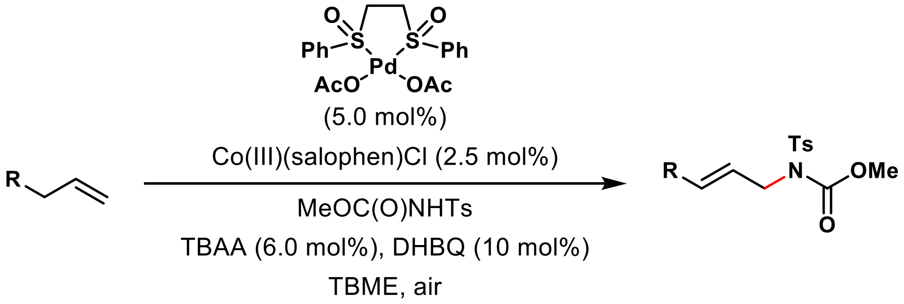
63%



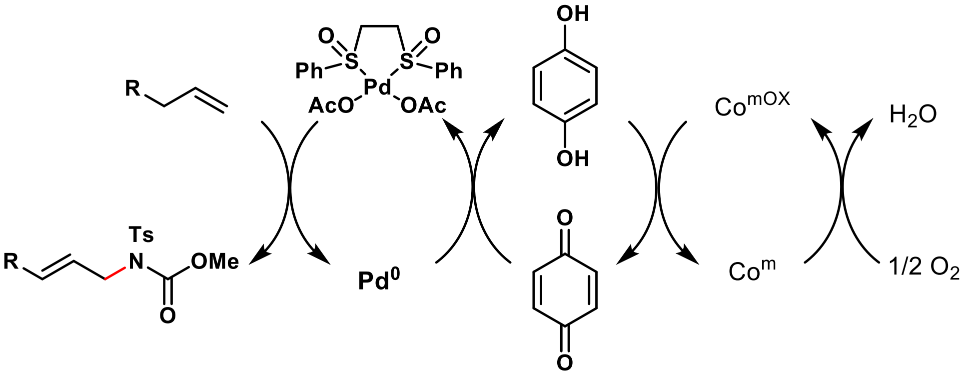
55%

Reed, S. A., White, M. C. *J. Am. Chem. Soc.*, **2008**, *138*, 3316.

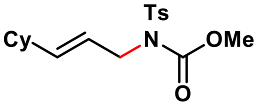
These conditions were made aerobic with oxygen as terminal oxidant.



Mechanism for reoxidation



Inhibition by benzoquinone



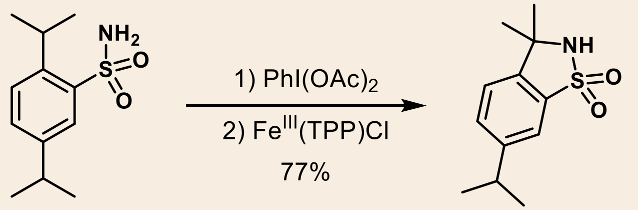
Entry	co-catalyst	BQ equiv.	Yield
1	Co(II)(salophen)	0.1	81%
2	Co(II)(salophen)	0.5	56%
3	Co(II)(salophen)	1.0	50%
4	VO(acac)$_2$	0.1	70%
5	VO(acac)$_2$	0.5	40%
6	VO(acac)$_2$	1.0	25%

White, M. C. *J. Am. Chem. Soc.*, **2016**, *138*, 1265.

Functionalization Reactions: Oxidation, Amination, Isotopes

3. Intramolecular amidation

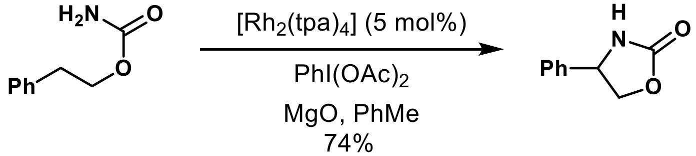
Breslow 1983



stoichiometric pre-generation of imidoiodobenzene

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

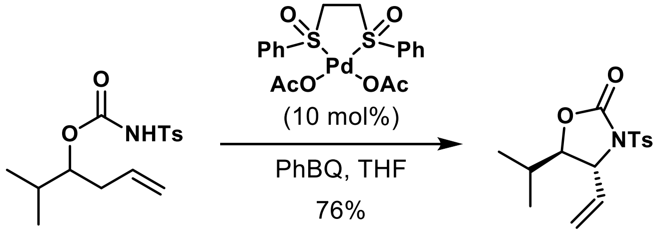
The reaction was then made one-pot by Du Bois in 2001.



Du Bois, J. *Angew. Chem. Int. Ed.*, **2001**, *40*, 598.

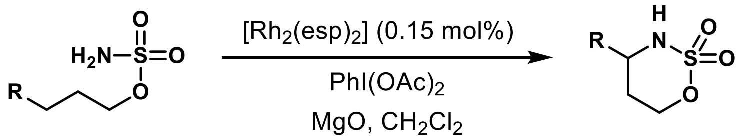
$Rh_2(esp)_2$ urea variant: Du Bois, J. *J. Am. Chem. Soc.*, **2004**, *126*, 15378.

Expanded to allylic systems in 2007 by White.



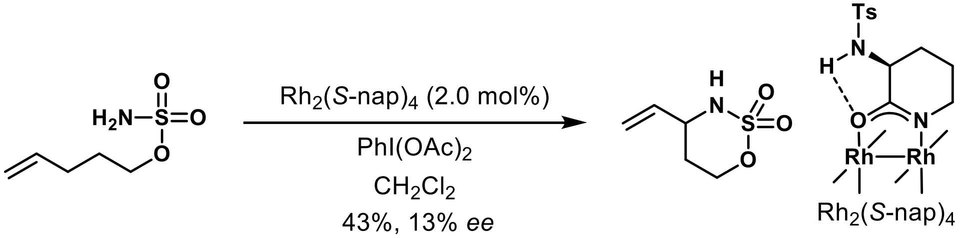
Fraunhoffer, K. J., White, M. C. *J. Am. Chem. Soc.*, **2007**, *129*, 7274.

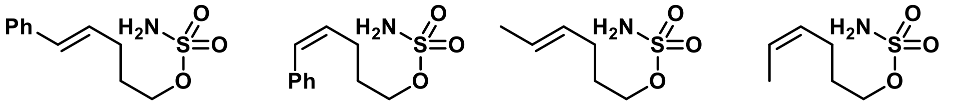
Synthesis of 1,3-amino alcohols through sulfamate esters by Du Bois in 2004.



Du Bois, J. *J. Am. Chem. Soc.*, **2004**, *126*, 15378.

Reaction made enantioselective by Du Bois in 2008.

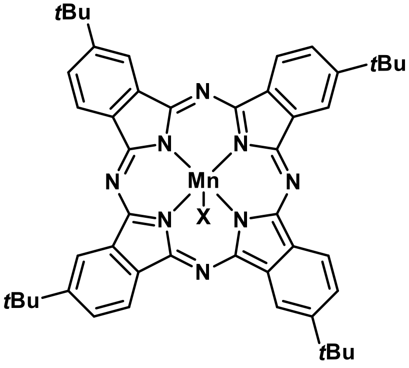




48%, 12% *ee* | 55%, 84% *ee* | 51%, 54% *ee* | 55%, 84% *ee*

Du Bois, J. *J. Am. Chem. Soc.*, **2008**, *130*, 9220.

Catalyst expanded to manganese and iron by White in 2015.

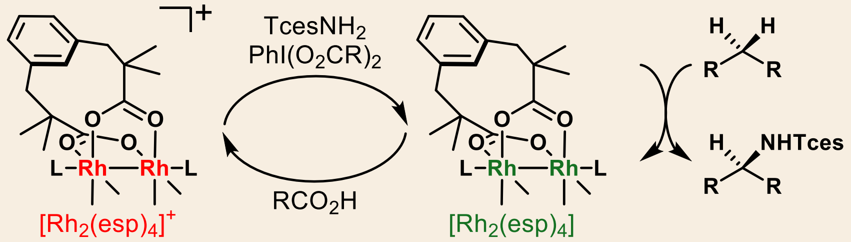


Mn(*t*BuPc)
X = SbF_6

White, M. C. *Nature Chem.*, **2015**, *7*, 987.

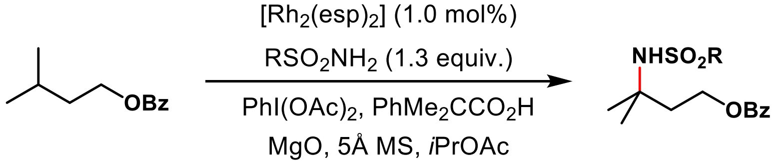
Functionalization Reactions: Oxidation, Amination, Isotopes

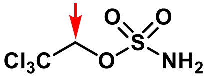
4. Amination at tertiary centers



Through mechanistic studies, the Du Buois group found that the rhodium catalyst was being competitively oxidized to an inactive cationic state. It was observed that the acid derived from the iodine oxidant would reduce the catalyst back to its active state. Therefore, addition of acid to the reaction was found to increase catalytic activity.

Zalatan, D. N., Du Bois, J. *J. Am. Chem. Soc.*, **2009**, *131*, 7558.



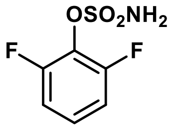


TcesNH$_2$
25%

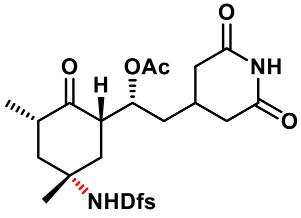
alkoxysulfonamide was observed to be mostly consumed in the reaction despite poor yields

attributed to oxidation of the methylene

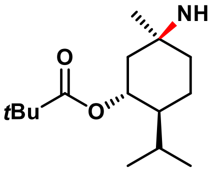
alternative alkoxysulfonamide gave improved results



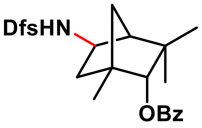
DfsNH$_2$
57%



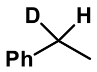
57%



68%



62%

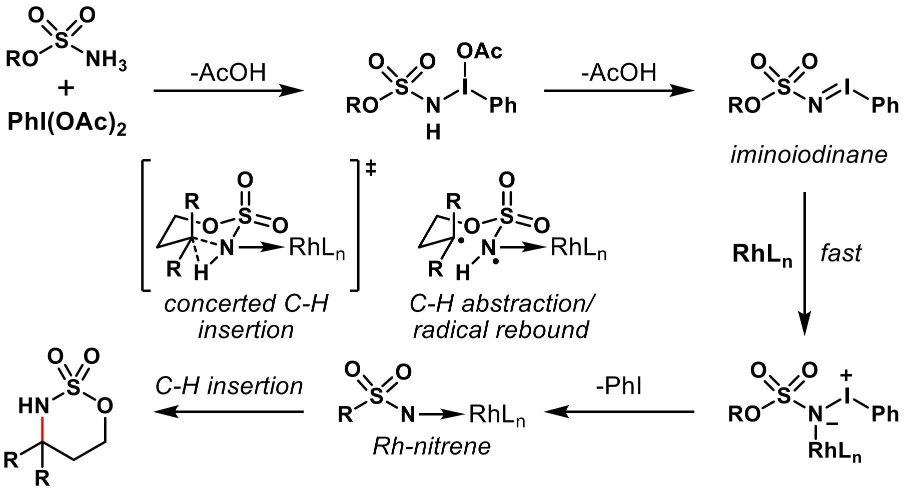


k_H/k_D = 5.2

The observed KIE is "suggestive of a transition structure for intermolecular C–H amination in which extensive C-H bond breaking has occurred"

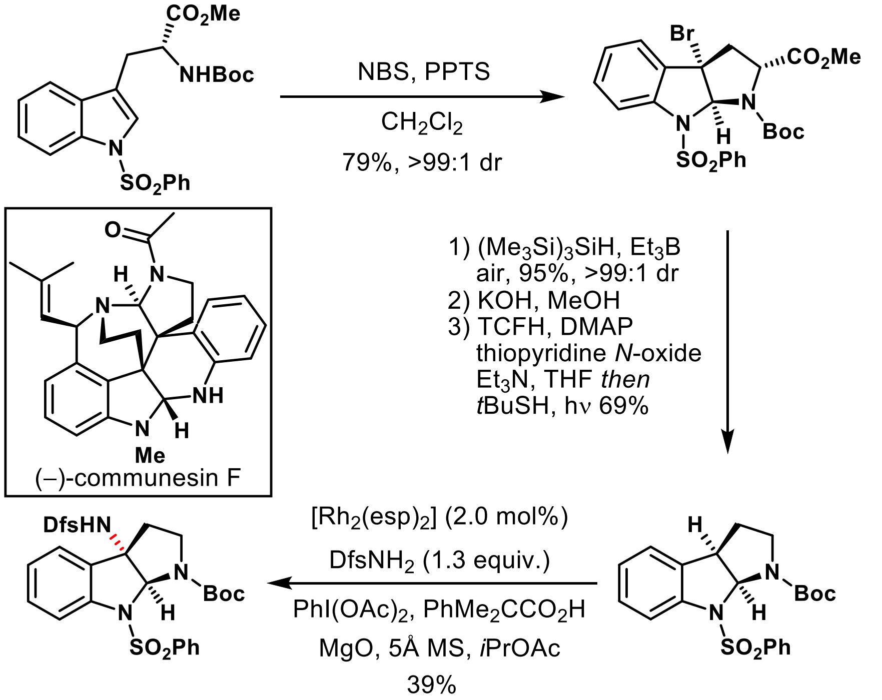
Roizen, J. L., Zalatan, D. N., Du Bois, J. *Angew. Chem. Int. Ed.*, **2013**, *52*, 11343.

Mechanism



Du Bois, J. *Tetrahedron*, **2009**, *65*, 3042.

Application in Total Synthesis



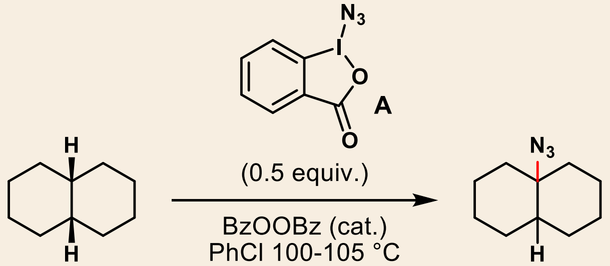
Movassaghi, M. *J. Am. Chem. Soc.*, **2016**, *138*, 7763.

Functionalization Reactions: Oxidation, Amination, Isotopes

5. Undirected sp^3 C-H azidation

Zhdankin 1996

Zhdankin and coworkers reported radical conditions for the azidation of alkanes. The conditions required higher temperatures and had low functional group tolerance due to the readical nature of the reaction.

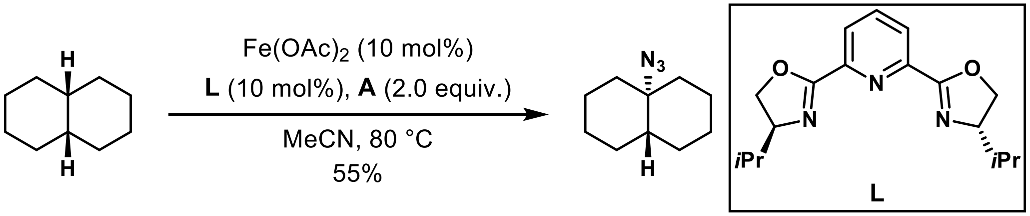


(0.5 equiv.)
BzOOBz (cat.)
PhCl 100-105 °C
62%

stereochemistry not reported
excess alkane required in most cases

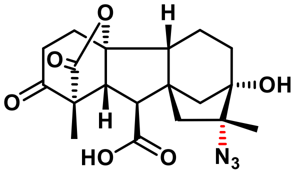
Zhdankin, V. V. *et al. J. Am. Chem. Soc.*, **1996**, *118*, 5192.

In 2015, the Hartwig group showed this reaction could be catalyzed by an Fe-PyBox complex to give products with synthetically useful r.r.s. While still proceeding through a radical mechanism, the tolerated functionality was shown to be quite broad.

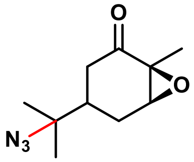


$Fe(OAc)_2$ (10 mol%)
L (10 mol%), **A** (2.0 equiv.)
MeCN, 80 °C
55%

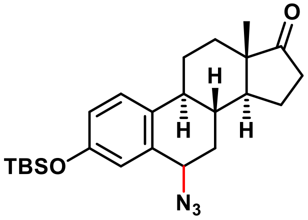
L



75%



50% 11:1:1



24% 5:1

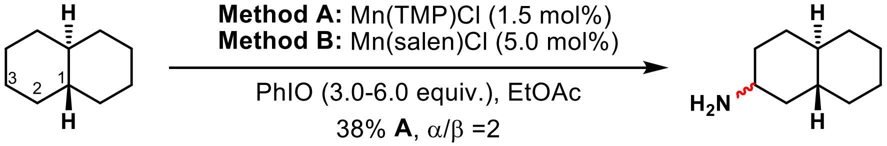
Sharma, A. Hartwig, J. F. *Nature*, **2015**, *517*, 600.

Hartwig made a set of empirical rules for his azidation conditions:

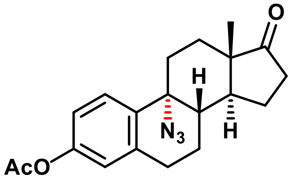
(1) Electron-rich and sterically accessible C-H bonds are the most reactive sites for azidation.
(2) Secondary and tertiary benzylic C-H bonds are more reactive toward this azidation than are alkyl and primary benzylic C-H bonds.
(3) Among alkyl C-H bonds, only the tertiary C-H bonds reacted.
(4) Trisubstituted olefins underwent allylic C-H bond azidation while 1,1-disubstituted olefins underwent alkene diazidation.
(5) The combination of $Fe(OAc)_2$ and PyBox ligand L_1 catalyzes the trifluoromethylazidation of a variety of olefins in complex molecules. 1,1-Disubstituted olefins are the most reactive olefins toward trifluoromethylazidation, and electron-rich olefins underwent trifluoromethylazidation selectively over electron-poor olefins

Further investigation of the scope: Hartwig, J. F. *ACS Cent. Sci.*, **2016**, *2*, 715.

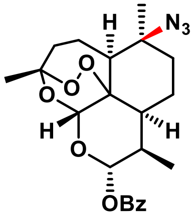
In 2015, Groves showed that through a Mn catalyst, NaN_3 could be employed as the azide source rather than the hypervalent iodine reported by Hartwig. Also, the observed constitutional isomers were often complementary to those reported by Hartwig.



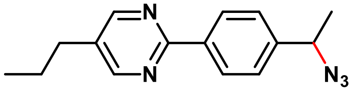
catalyst, NaN_3 (aq., 1.5 M, 4.0 equiv.)
Method A: Mn(TMP)Cl (1.5 mol%)
Method B: Mn(salen)Cl (5.0 mol%)
PhIO (3.0-6.0 equiv.), EtOAc
38% **A**, α/β =2
12% C2, 3% C1



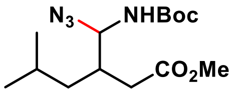
38% **B** (+ 18% diazidation)



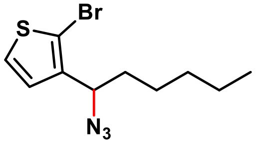
20% **B**



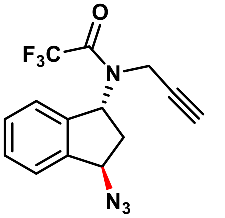
50% **B**



60% **A**



70% **B**



45% **B**

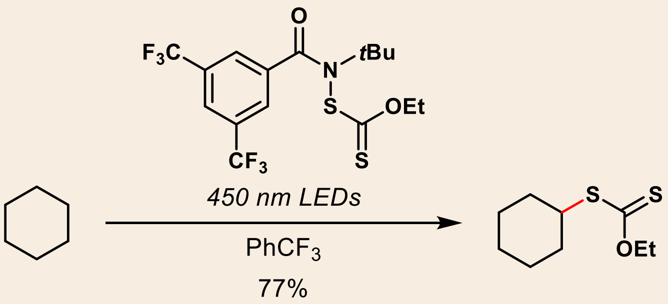
Groves, J. T. *J. Am. Chem. Soc.*, **2015**, *137*, 5300.

Functionalization Reactions: Oxidation, Amination, Isotopes

6. C-H azidation mediated by photoredox catalysis

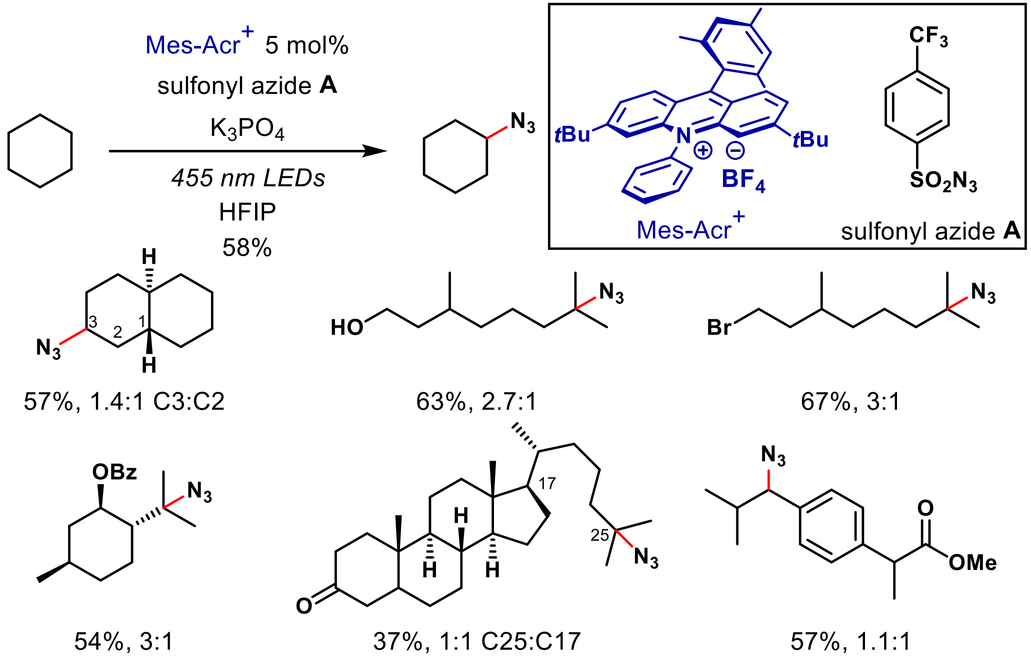
Alexanian 2016

In 2016, the Alexanian lab reported conditions for C-H xanthylation. These compounds could be further derivatized to alkyl, vinyl, azide, deutero, hydroxyl, and thiol products.



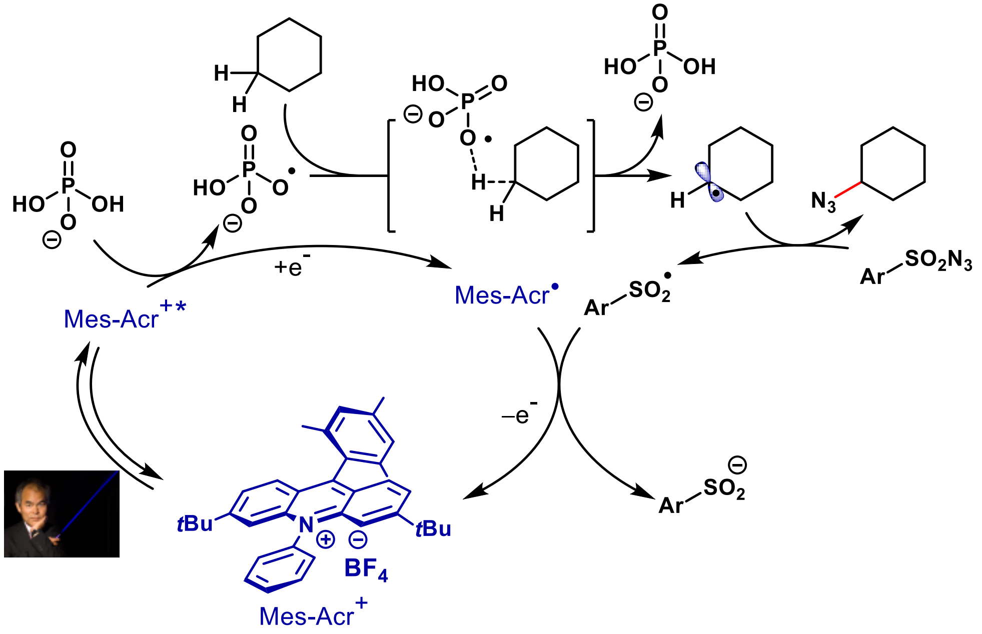
Czaplyski, W. L., Na, C. G., Alexanian, E. J. *J. Am. Chem. Soc.*, **2016**, *138*, 13854.

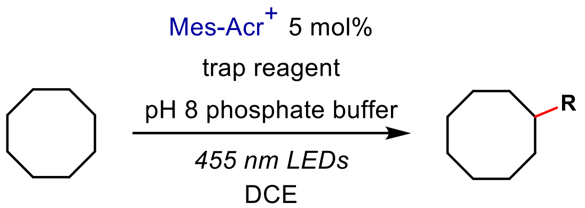
Then, in 2018, a collaborative effort from the Nicewicz and Alexanian labs bypassed the need for xanthylation, and could directly install the desired functionality through organic photoredox catalysis.



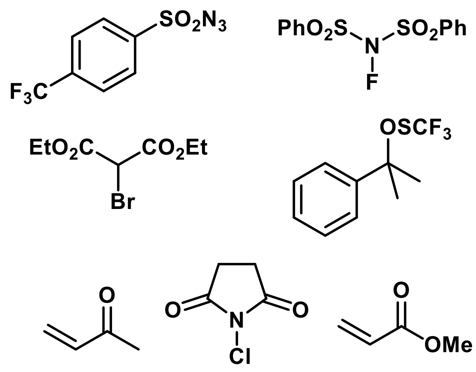
Nicewicz, D. A., Alexanian, E. J. *J. Am. Chem. Soc.*, **2018**, *140*, 4213.

Mechanism





Trap Reagents



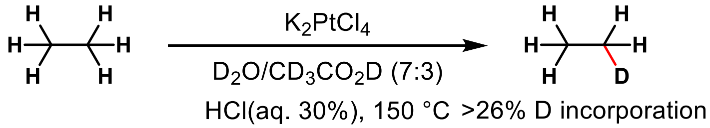
derivative (R=)		yield (%)
N_3	*previous conditions*	70
F		64
Br		60
Cl		32
SCF_3		30
$CH_2CH_2C(O)Me$		76
$CH_2CH_2CO_2Me$		43

IV. Isotope incorporation

The structuring of this section will be slightly altered from the previous two sections. Rather than the format of precedent-improvement-mechanism-application, this section will cover the precedent and its improvement. The mechanism and application will not be discussed in most cases (except for one at the end).

1. The Shilov system

One cannot discuss the incorporation of isotopes into alkanes without first introducing the Shilov system. The conditions reported by Shilov and coworkers in 1969 laid the groundwork for the field of C-H activation of alkanes, as their system was the first example of homogeneous activation of alkanes. By employing platinum salts under acidic conditions at high temperatures, deuterium could be incorporated into methane and ethane.

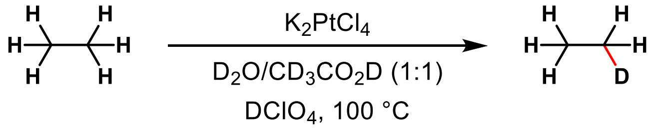

K_2PtCl_4

D_2O/CD_3CO_2D (7:3)

HCl(aq. 30%), 150 °C >26% D incorporation

Shilov, A. E. *Zh. Fiz. Khim.*, **1969**, *43*, 2174.
Shilov, A. E., Shteinman, A. A. *Chem. Rev.*, **1977**, *24*, 97.
Shilov, A. E., Shul'pin, G. B. *Chem. Rev.*, **1997**, *97*, 2879.
Lersch, M., Tilset, M. *Chem. Rev.*, **2005**, *105*, 2471.
Rudakov, E. S., Shul'pin, G. B. *J. Organomet. Chem.*, **2015**, *793*, 4.

Following this seminal report, Hodges verified these conditions in 1971 as well as expanding the scope of alkanes. The purpose of the added acid was to stabilize the homogeneous platinum catalyst, as in the absence platinum black would rapidly crash out. However, this did not fully solve the issue and upon the addition of aromatics, *i.e.* pyrene and benzene, higher catalytic efficiencies could be achieved.


K_2PtCl_4

D_2O/CD_3CO_2D (1:1)

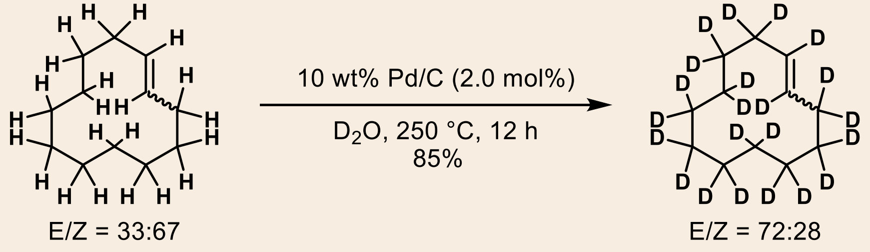
$DClO_4$, 100 °C

Alkane	Time (h)	D found (%)	Me- (%)	-CH_2- (%)	-CH- (%)
Methane	95	25	—	—	—
Ethane	137	91	91	—	—
Pentane	137	75	92	57	—
2-Methylbutane	137	69	83	37	9
Cyclohexane	110	70	—	70	—

Hodges, R. J., *et al. J. Chem. Soc. D.*, **1971**, 462.

2. Pt/Pd extensive deuterium incorporation

Matsubara 2003
Following the pioneering work of Breslow running organic reactions in water, Matsubara showed that cyclododecene could be deuterated in 85% yield under thermal conditions.


10 wt% Pd/C (2.0 mol%)

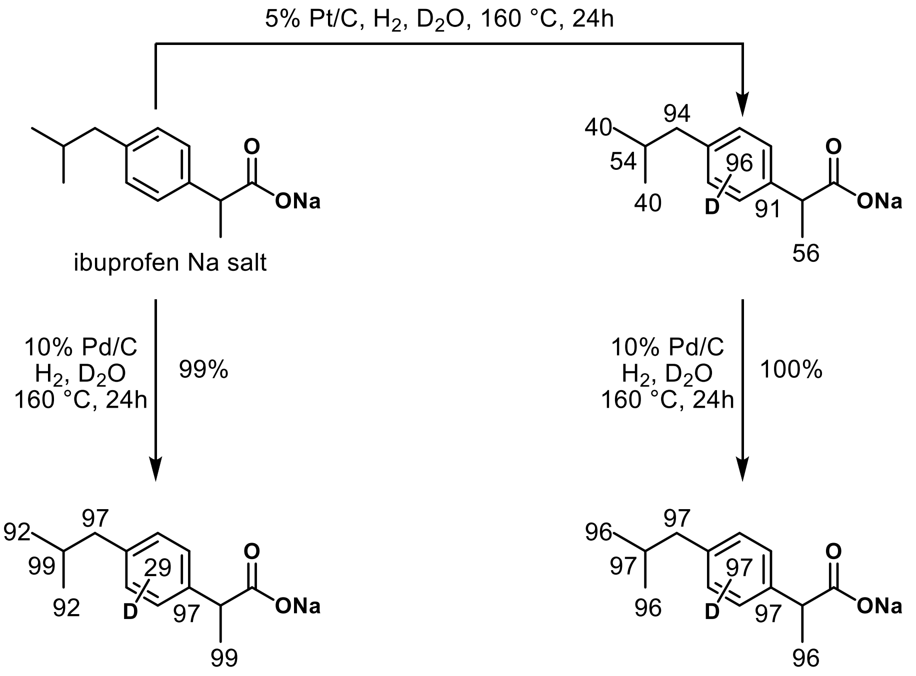
D_2O, 250 °C, 12 h
85%

E/Z = 33:67

E/Z = 72:28

Matsubara, S. *Chem. Lett.*, **2004**, *4*, 294.

Following this, Sajiki and coworkers found an interesting set of complementary conditions for aliphatic/aromatic deuteration in 2005.



% incorporated D represented at each position

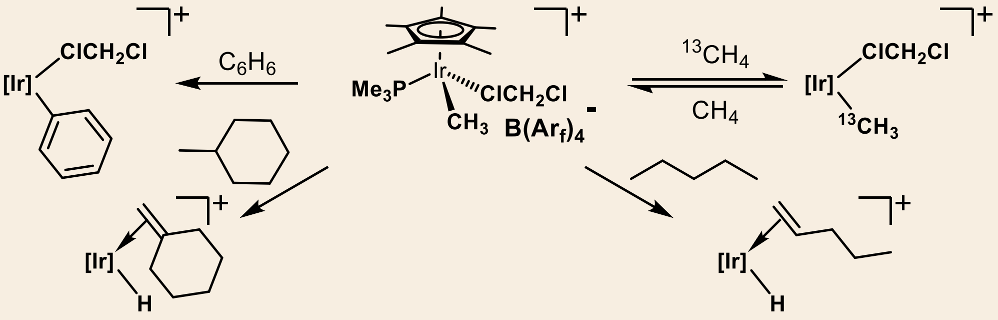
Sajiki, H. *Tetrahedron Lett.*, **2005**, *46*, 6995.

Functionalization Reactions: Oxidation, Amination, Isotopes

3. Bergman's iridium system

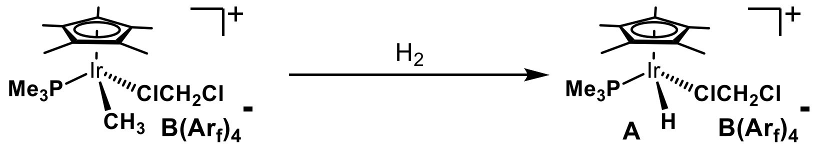
Bergman 1995

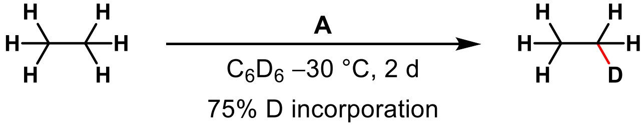
In 1995, Bergman reported a cationic iridium complex that could insert into C-H bonds. It was shown that insertion could occur at temperatures as low as –30 °C.



Arndtsen, B. A., Bergman, R. G. *Science*, **1995**, *270*, 1970.

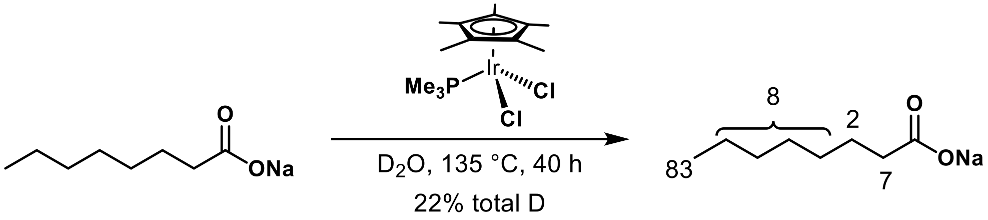
They then showed that these complexes could perform H/D exchange at low temperatures after activation with H_2. C_6D_6 served as solvent and D source.





Bergman, R. G. *J. Am. Chem. Soc.*, **2001**, *123*, 5837.

Following this report, the Bergman group showed that using a less active catalyst allowed for the selective incorporation of D from D_2O as the solvent under thermal conditions.

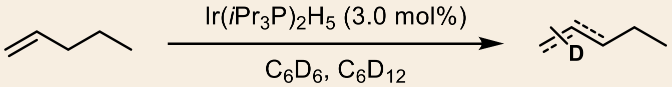


Bergman, R. G. *J. Am. Chem. Soc.*, **2002**, *124*, 2092.

4. Isotope exchange at vinylic positions

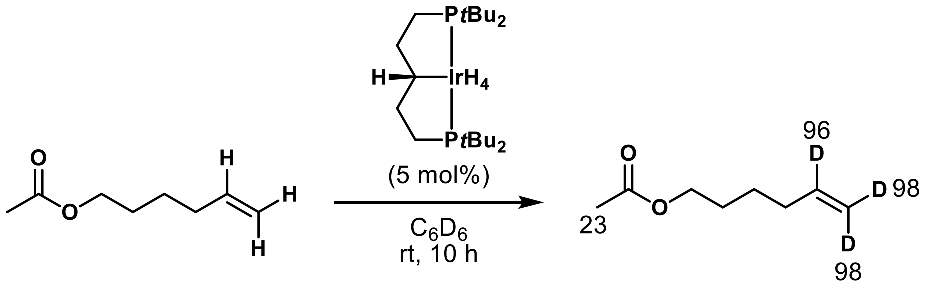
Faller 1989

Previously, it was reported that vinylic positions could undergo H/D exchange. However, this reaction was plagued with isomerization of the olefin to a more thermodynamically favored position.

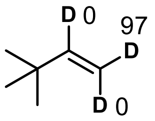


Faller, J. W., Smart, C. J. *Organometallics*, **1989**, *8*, 602.

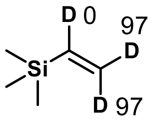
Then, in 2008, Hartwig reported conditions for vinylic deuteration by employing an iridium pincer complex and C_6D_6 as the deuterium source. They found that under these reaction conditions there was no isomerization of the olefin to the more thermodynamically favored position.



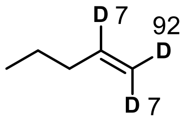
In their substrate scope, they showed that the proton in the *trans* position would be exchanged the fastest. They took advantage of this by carefully controlling reaction time to obtain the level of deuterium incorporation desired.



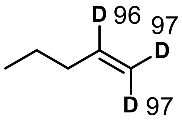
rt, 1 min



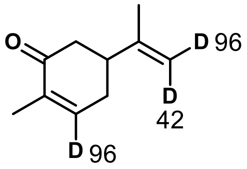
rt, 1 min



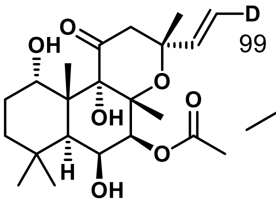
rt, 5 min



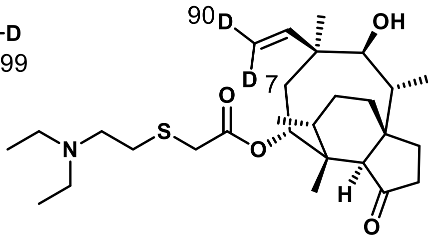
rt, 20 h



rt, 60 h



rt, 5 min



rt, 10 min

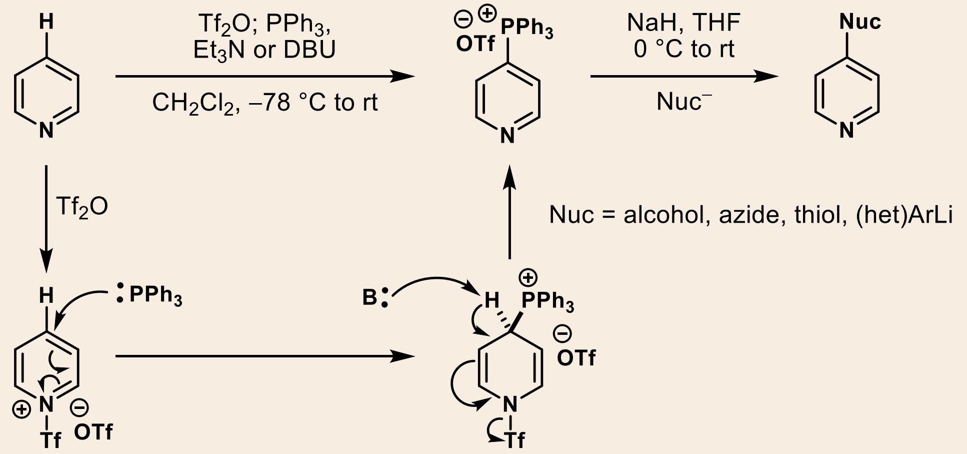
Zhou, J, Hartwig, J. F. *Angew. Chem. Int. Ed.*, **2008**, *47*, 5783.

Functionalization Reactions: Oxidation, Amination, Isotopes

5. Site-selective labeling of heteroaromatics

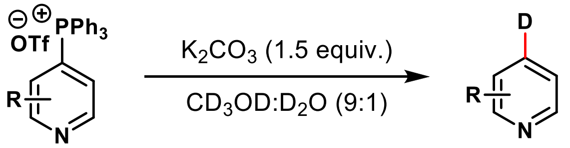
McNally 2016

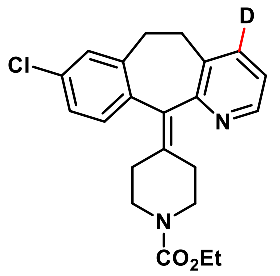
McNally and coworkers showed in 2016 that through the formation of heterocyclic phosphonium salts, site-selective functionalization of heteroaromatics could be achieved. Different nucleophiles could then be introduced, providing a wide range of functionality.



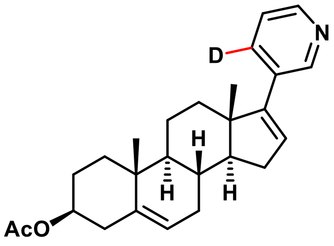
McNally, A. *J. Am. Chem. Soc.*, **2016**, *138*, 13806.

Then in 2018, McNally reported conditions to convert the heterocyclic phosphonium salts to deuterated/tritiated products. They explored the scope on pharmaceuticals and found it to be broad. Yields shown are for salt formation then deuteration.

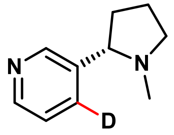




88%, 79%



67%, 62%



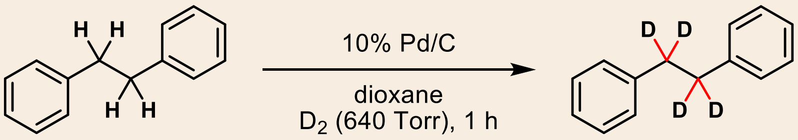
76%, 79%

McNally, A. *J. Am. Chem. Soc.*, **2018**, *140*, 1990.

6. Selective labeling of benzylic positions

Azran 1994

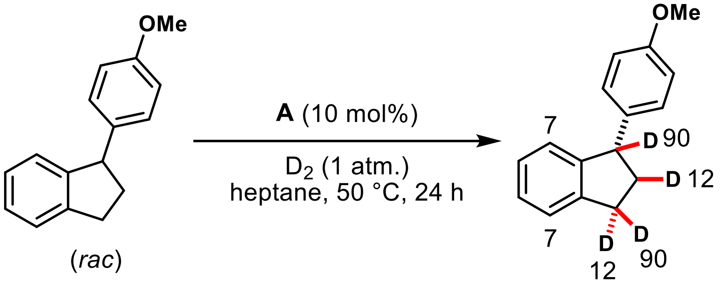
Under a slight vacuum and an atmosphere of D_2, it was found that Pd/C could catalyze the exchange of benzylic hydrogen atoms with deuterium. However, these conditions required multiple activation and pretreatment events for optimal incorporation of the desired isotope.

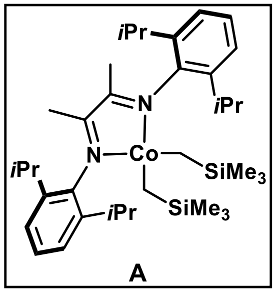


H atoms exchanged = 3.3
%H exchanged = 82.5%

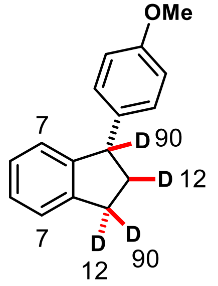
Azran, J., Shimoni, M., Buchman, O. *J. Catal.*, **1994**, *148*, 648.

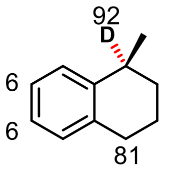
Chirik and coworkers then reported a cobalt-based catalyst that could selectively label benzylic positions. In the presence of pre-existing stereochemical information, it was found that the installation of deuterium was stereoretentive.

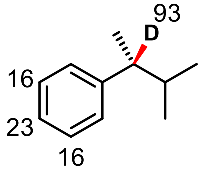


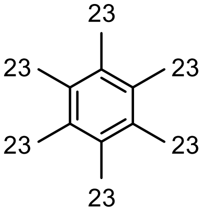


A

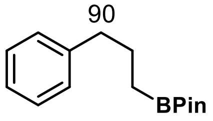








unlabeled:	>98% *ee* (*S*)	92% *ee* (*S*)	72% *ee* (*R*)
labeled:	>98% *ee* (*S*)	92% *ee* (*S*)	72% *ee* (*R*)
retention:	>98% *es*	>98% *es*	>98% *es*



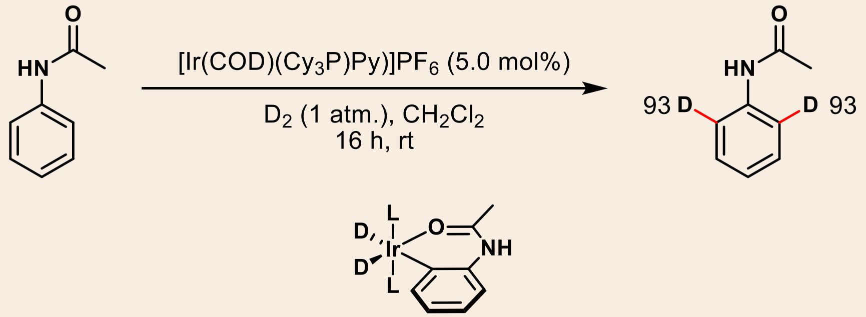
Palmer, W. N., Chirik, P. J. *ACS Catal.*, **2017**, *7*, 5674.

Functionalization Reactions: Oxidation, Amination, Isotopes

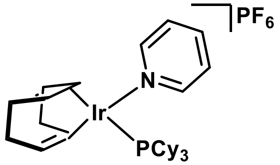
7. Labeling of *ortho*-positions

Evans 1995

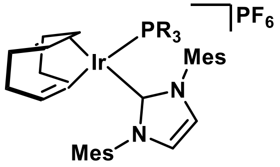
In 1995, Evans and coworkers showed that Crabtree's catalyst could be employed for the exceptionally mild and selective *ortho*-deuteration of acetanilides. The high selectivity was attributed to the coordination of the acetamide to the catalyst, directing C-H insertion.



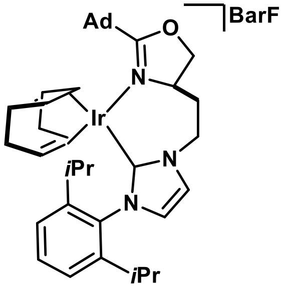
Hesk, D., Das, P. R., Evans, B. *J. Labelled Comp. Radiopharm.*, **1995**, *36*, 497.



Crabtree's catalyst

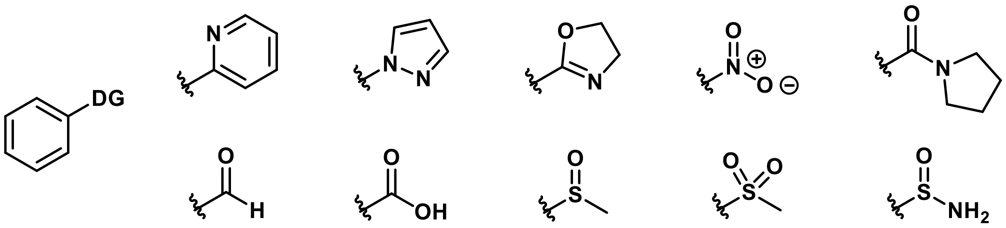


Kerr's catalyst



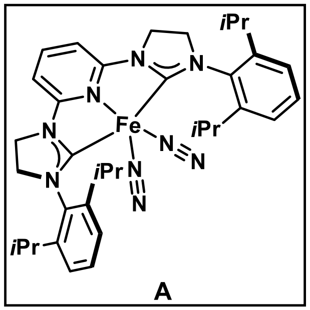
Burgess' catalyst

With the advent of Burgess' catalyst, the scope of directing groups was significantly expanded.



Derdau, V. *J. Labelled Comp. Radiopharm.*, **2017**, *60*, 343.

8. Labeling of *meta*/*para*-positions



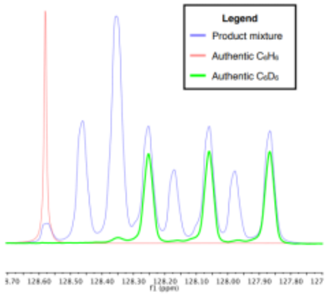
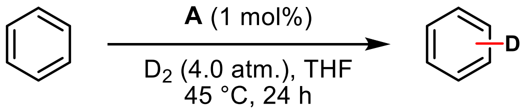
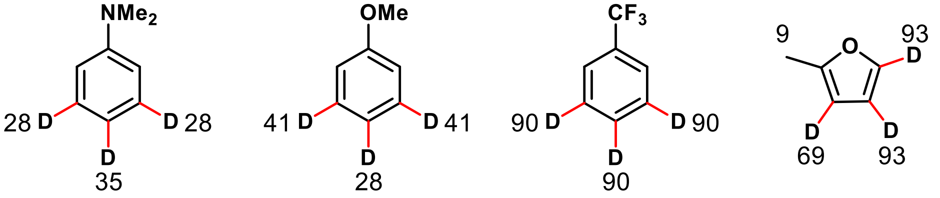
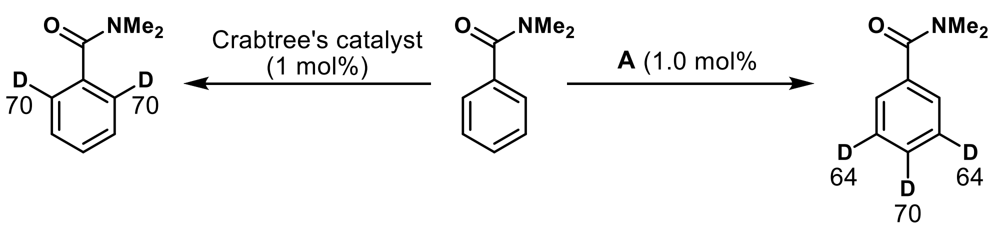


Figure S1 Stacked $^{13}C\{^{1}H\}$ NMR spectra of deuteration of benzene (blue), authentic C_6H_6 (pink) and authentic C_6D_6 (green)



During the studies of the catalytic hydrogenation capibilities of iron complex **A**, the Chirik group found that isotope exchange was occuring on the benzene solvent. They decided to investigate the selectivity and scope of this transformation.





Adapted by permission from Springer Nature: Springer Nature
Iron-catalysed tritiation of pharmaceuticals, Yu, R. P., Hesk, D., Rivera, N., Pelczer, I., Chirik, P. J. *Nature*, **2016**, *529*, 195. Copyright 2016.