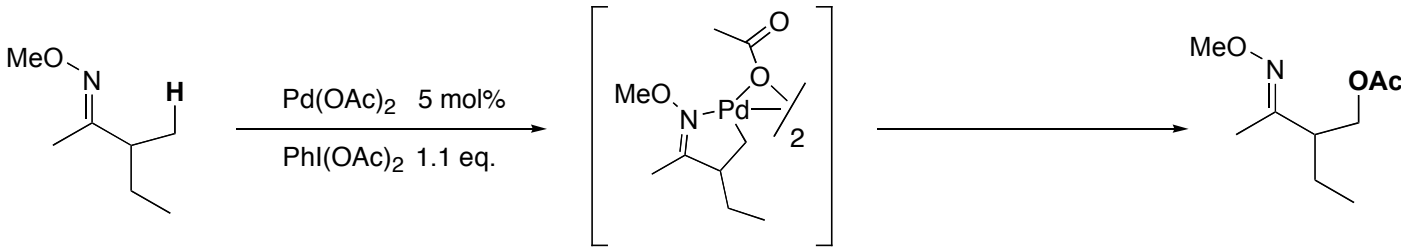
Palladium-Catalyzed Oxygenation of Unactivated sp^3 C-H Bonds



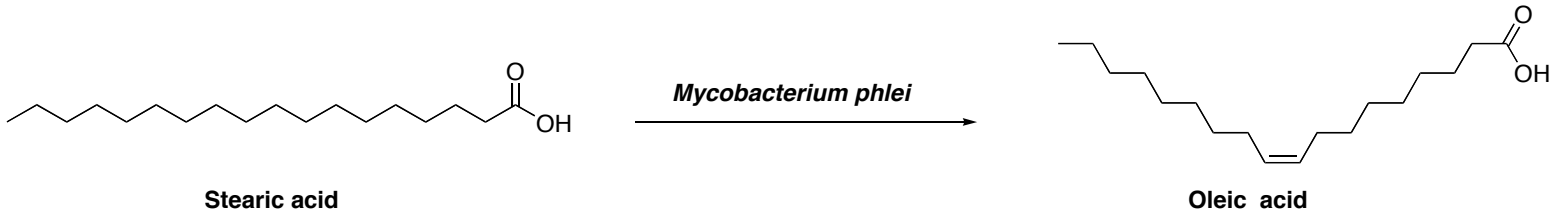
Desai, L. P.; Hull, K. L.; Sanford*, M. S.
University of Michigan

J. Am. Chem. Soc. **2004**, *126*, ASAP (Web Release 16th July 2004)

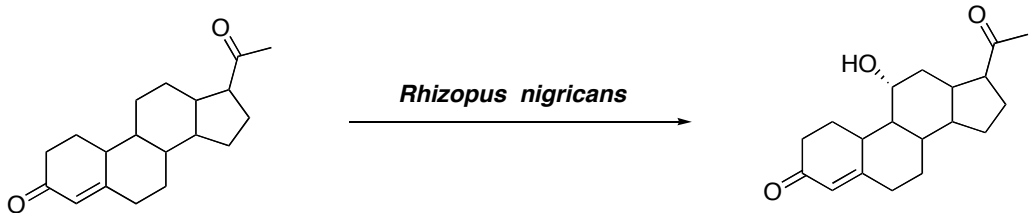
Oxidation of Unactivated sp^3 C-H Bonds: A Challenge in Organic Synthesis…

- **REACTIVITY** **(C-H bond dissociation energy in methane 104 kcal mol^{-1})**
- **SELECTIVITY** **(C-H bond dissociation energy in methanol: 93 kcal mol^{-1})**

…. while in Nature…



Stearic acid **Oleic acid**



Chemical Routes for the Intramolecular Oxidative Functionalization of Unactivated sp^3 C-H Bond

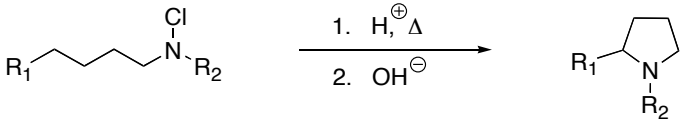
a) Reactions based on heteroatom centered radicals

b) Reactions based on Rhodium-mediated carbene and nitrene sp^3 C-H bond insertions

c) Reactions based on transition metal-mediated sp^3 C-H bond activation

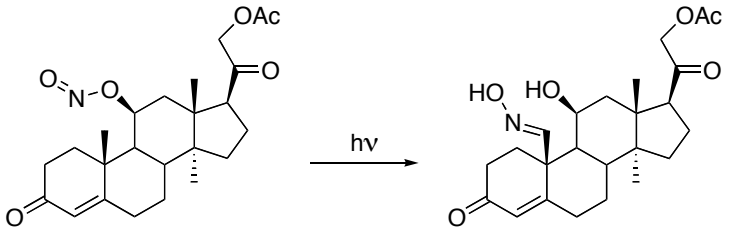
Reactions Based on Heteroatom-Centered Radicals

Hoffmann-Loeffler-Freytag Reaction



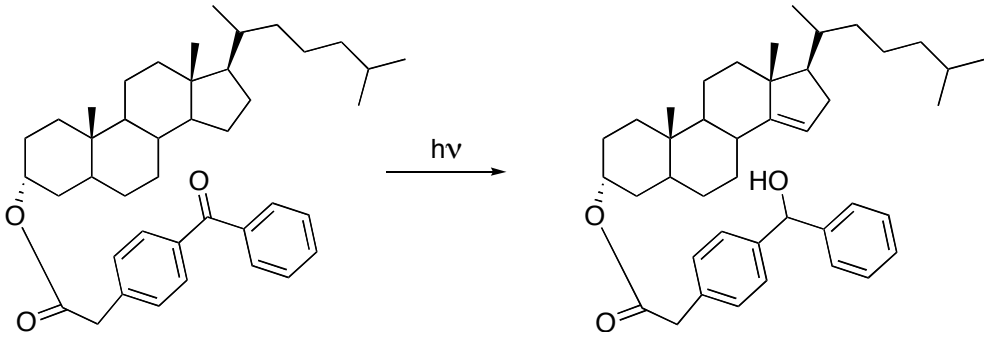
Hoffmann, A. W. *Ber.* **1883**, *16*, 558.
Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1958**, *80*, 2903.
Arigoni, D. *and coworkers J.Am. Chem. Soc.* **1958**, *80*, 2905.

Barton`s Nitrite Photolysis



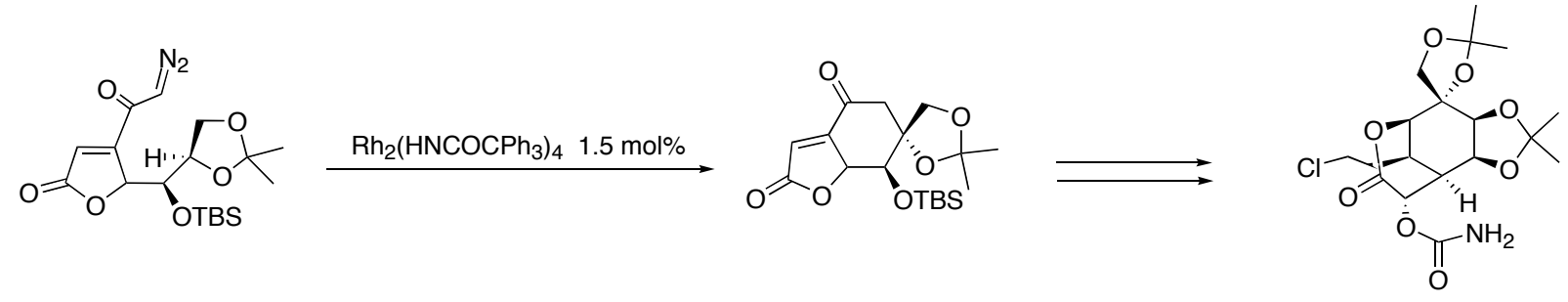
Barton, D. H. R. *and coworkers J.Am. Chem. Soc*. **1960**, *82*, 2640

Breslow`s Remote Oxidation

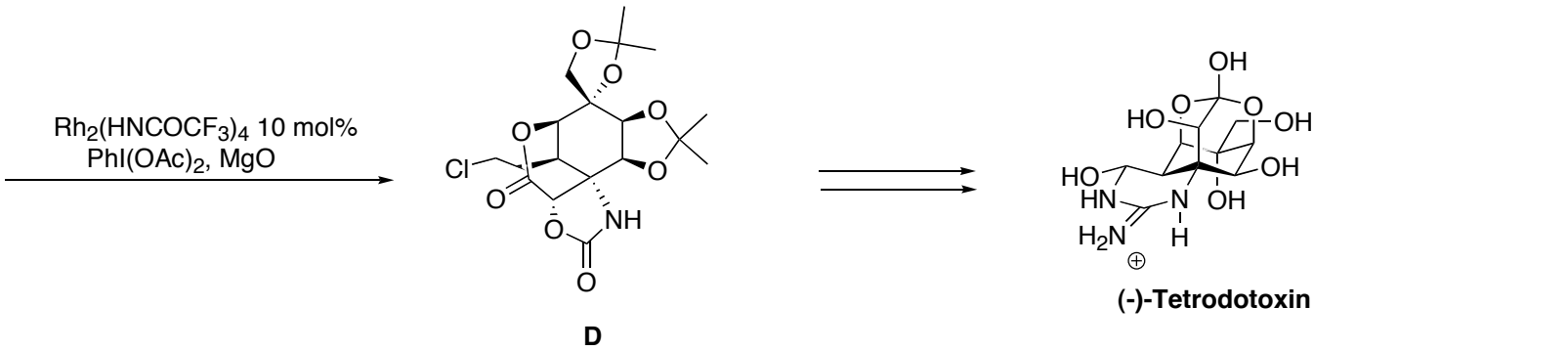


Breslow, R. *and coworkers J. Am. Chem.* **1973**, *95*, 3251
Jung, M. E.: Johnson, T. W. *J. Am. Chem. Soc.* **1997**, *119*, 12412

Reactions Based on Rhodium-Mediated Carbene and Nitrene sp^3 C-H Bond Insertions



A B C

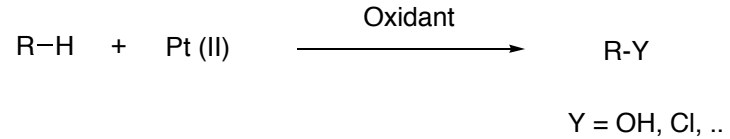


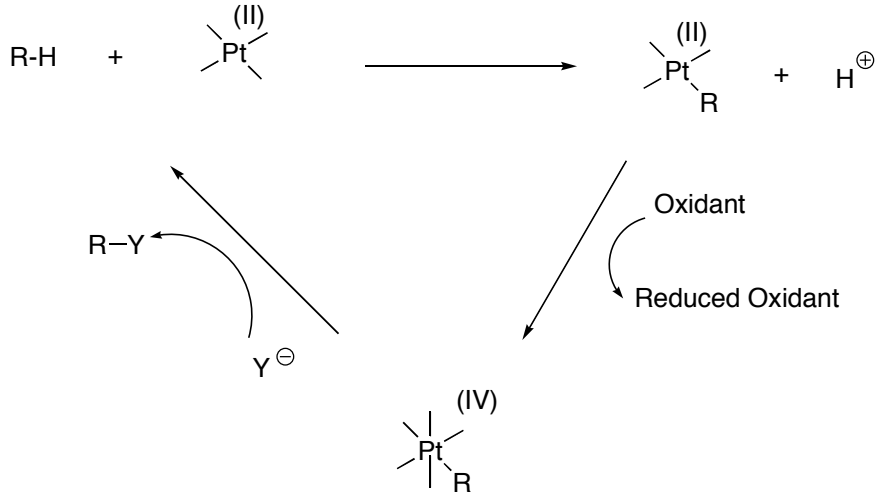
D (-)-Tetrodotoxin

Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.
Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598.

For a Review on the Use of Rh-Mediated Intramolecular C-H Insertion in Natural Products Syntheses see:
Taber, D. F.; Stiriba, S.-E. *Chem. Eur. J.* **1998**, *4*, 990 and references therein.

Reactions Based on Transition Metal-Mediated sp^3 C-H Bond Activation: the Shilov Reaction





Shilov, A. E.; Shul`pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.
Stahl, S. S. *and coworkers Angew. Chem., Int. Ed.* **1998**, *37*, 2180.
Sen, A. *and coworkers J. Am. Chem. Soc.* **2001**, *123*, 1000.

Unactivated sp^3 C-H Bond Oxidative Functionalization by Group 10 Metals

PROBLEMS:

a) Harsh reaction conditions: no applications to complex organic molecules

b) Low TON

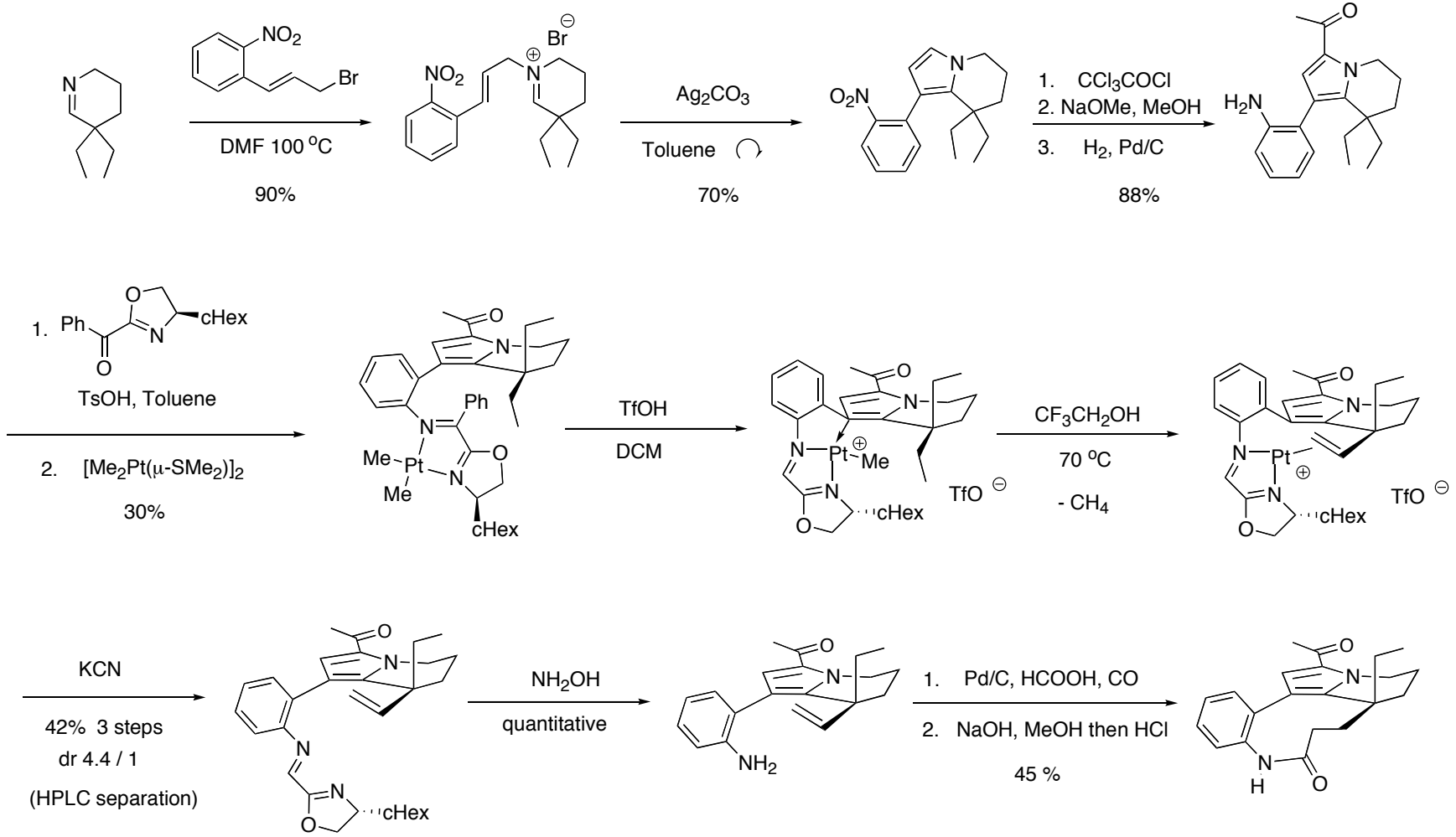
c) Low functional group tolerance

d) Low level of regioselectivity

THE KEY:

The use of substrates containing coordinating functional groups that can bind the metal catalyst and direct the oxidation process to a specific sp^3 C-H bond within the molecule.

Unactivated sp^3 C-H Bond Oxidative Functionalization by Group 10 Metals: Stoichiometric Version



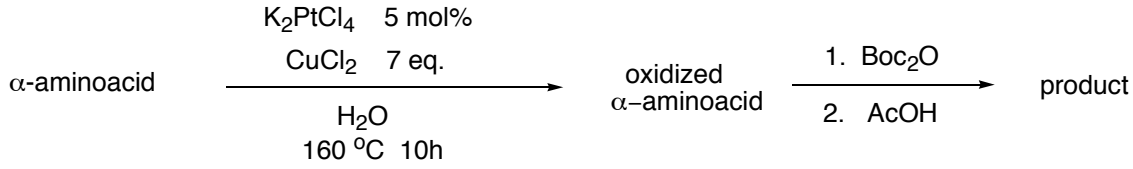
Sames, D. *and coworkers J. Am. Chem. Soc.* **2002**, *124*, 6900.

(-)-Rhazinilam

For other Stoichiometric Examples see:

Sames, D. *and coworkers J. Am. Chem. Soc.* **2002**, *124*, 11856.
Gribble, G. W. *and coworkers J. Org. Chem.* **2000**, *65*, 6278.

Unactivated sp^3 C-H Bond Oxidative Functionalization by Group 10 Metals: Catalytic Version



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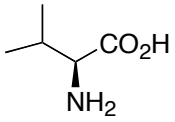
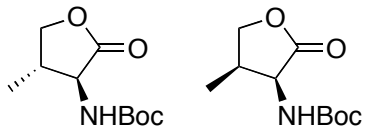
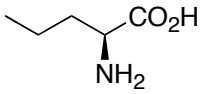
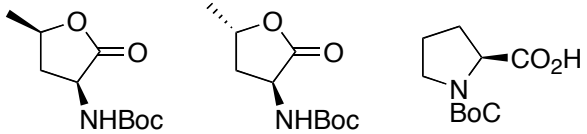
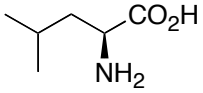
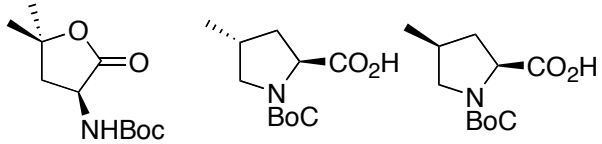
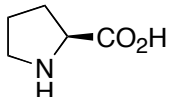
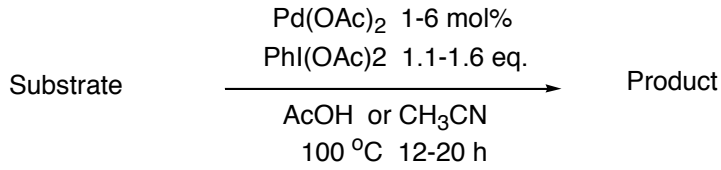
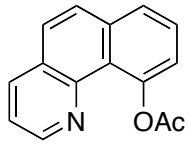
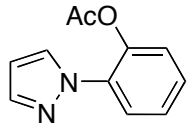
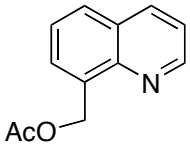
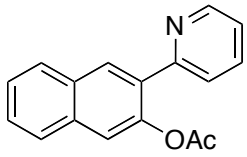
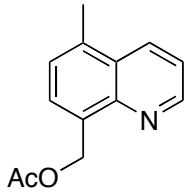
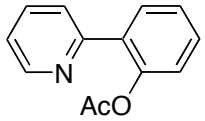
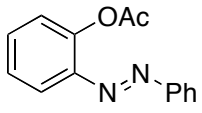
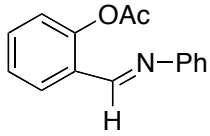
1	L-Valine 	 3 1	—	27
2	L-Norvaline 	 2 1 1	3	21
3	L-Leucine 	 22 4 1	4.5	15
4	L-Proline 	NO REACTION	—	—

Sames, D. and coworkers *J. Am. Chem. Soc.* **2001**, *123*, 8149.

For an another Catalytic example see: Sames, D. *and coworkers J. Am. Chem. Soc.* **2002**, *124*, 13372.

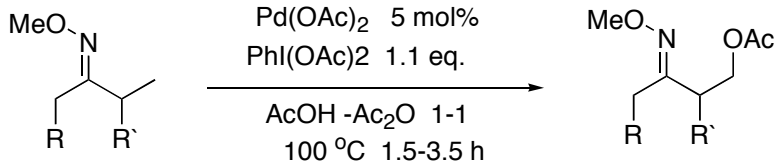
Authors Precedent Paper: A Highly Selective Catalytic Method for the Oxidative Functionalization of C-H Bonds



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		86	5		54
2		88	6		72
3		80	7		52
4		62	8		47

Sanford, M. S. *and coworkers J. Am. Chem. Soc.* **2004**, *126*, 2300.

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



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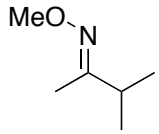
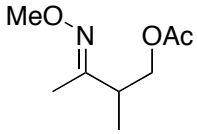
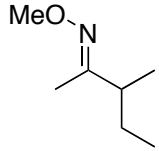
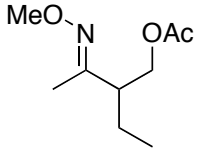
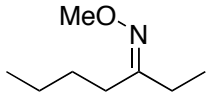
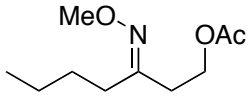
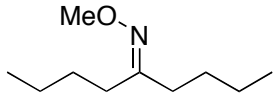
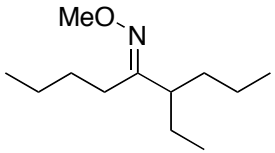
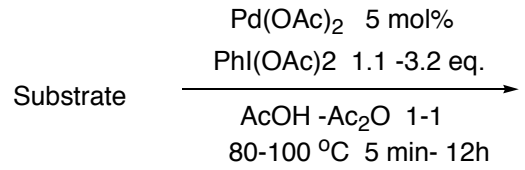
1			74
2			78
3			39
4		NO REACTION	—
5		NO REACTION	—

Sanford, M. S. *and coworkers J. Am. Chem. Soc.* **2004**, *126*,ASAP.

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



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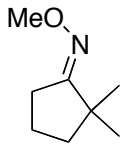
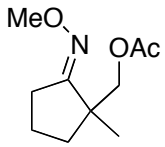
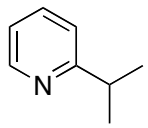
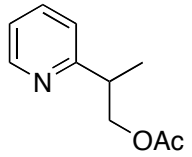
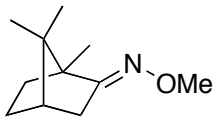
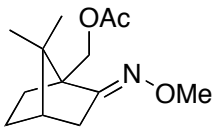
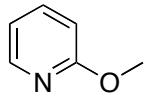
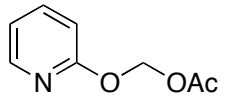
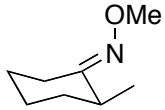
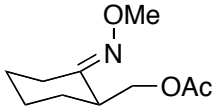
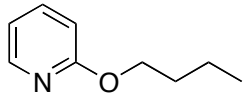
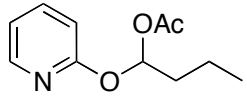
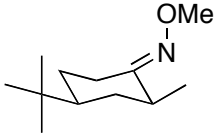
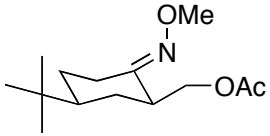
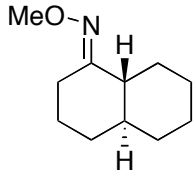
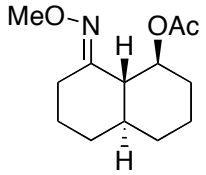
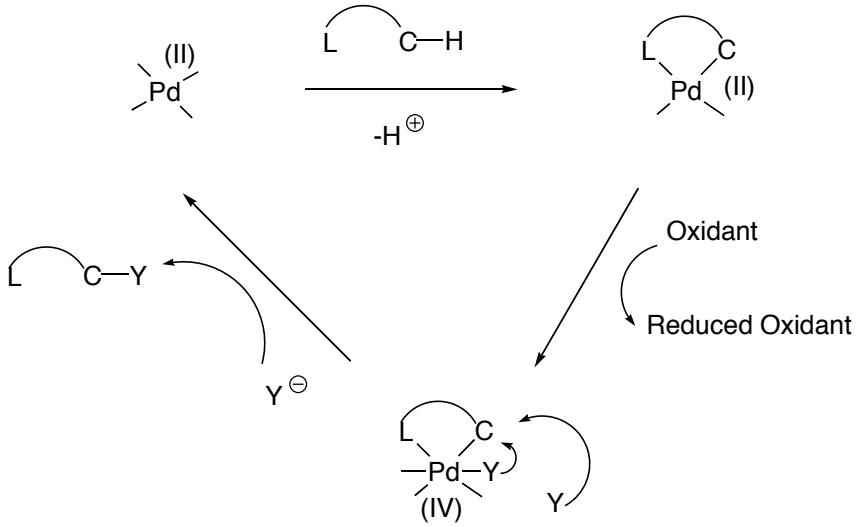
1			61	5			42
2			75	6			66
3			81	7			44
4			86	8			81

Sanford, M. S. *and coworkers J. Am. Chem. Soc.* **2004**, *126*,ASAP.

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

Hypothesized Mechanism



Summary

- **An efficient and highly β selective sp^3 C-H bond oxidative functionalization for *O*-methyl oximes and pyridines have been described.**

- **The level of regioselectivity displayed by the described methodology is unprecedented.**

- **The mild reaction conditions used along with the selectivity displayed, make the methodology a significant potential synthetic tool.**

- **Future work aimed to elucidate the scope and the mechanism of the transformation described would be of particular interest for the synthetic community.**