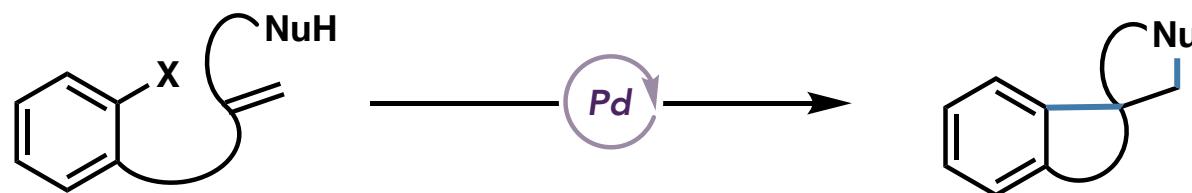


Palladium Cascade Cyclizations in Natural Product Synthesis

Selected Recent Examples

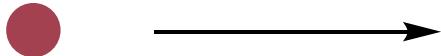


Nicholas A. Falcone
Literature Group Meeting
April 8th, 2022

Palladium-Catalyzed Cascades



Palladium-Catalyzed Cascades



Initiation

Oxidative addition

Nucleophilic palladation

Palladium-Catalyzed Cascades



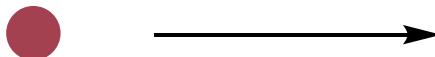
Initiation

Oxidative addition

Nucleophilic palladation



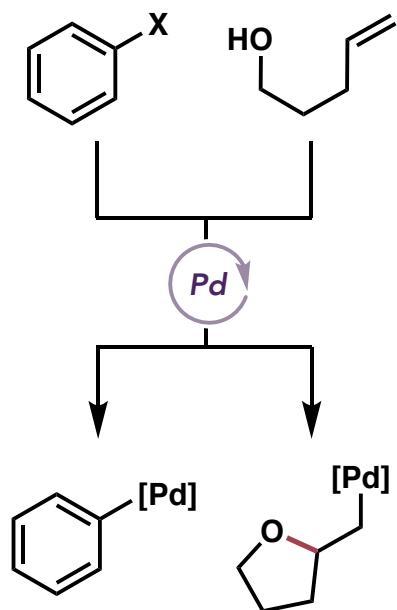
Palladium-Catalyzed Cascades



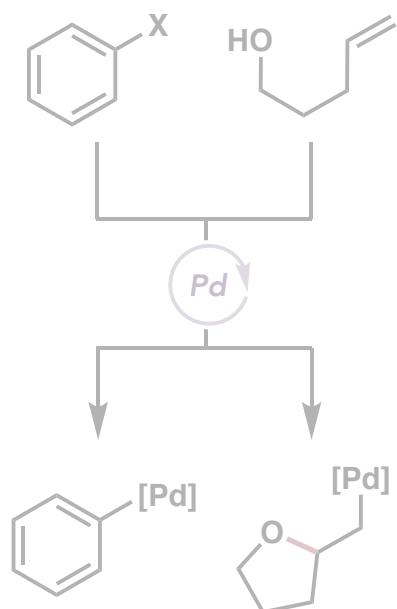
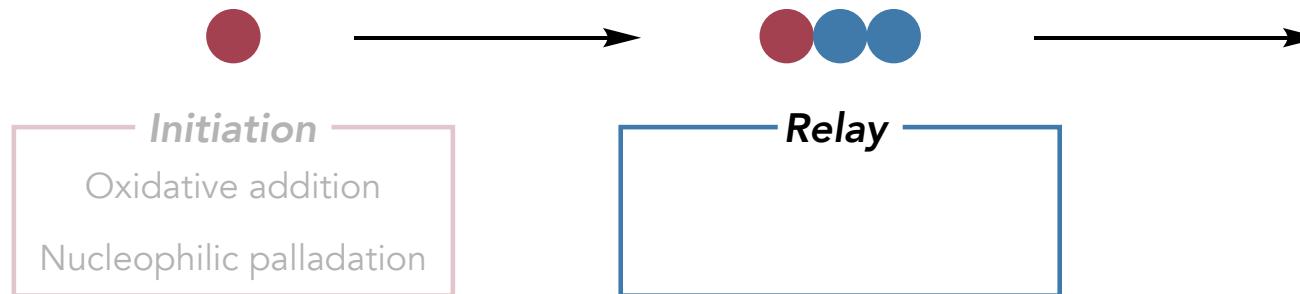
Initiation

Oxidative addition

Nucleophilic palladation



Palladium-Catalyzed Cascades



Palladium-Catalyzed Cascades



Initiation

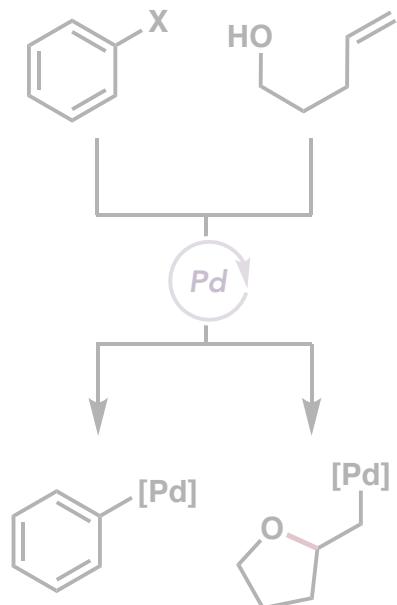
Oxidative addition

Nucleophilic palladation

Relay

Carbopalladation

Carbonylation



Palladium-Catalyzed Cascades



Initiation

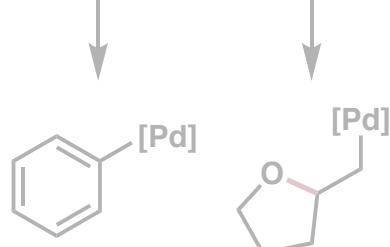
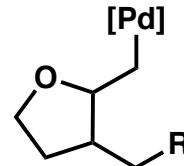
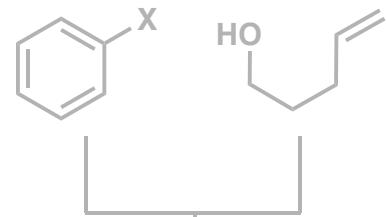
Oxidative addition

Nucleophilic palladation

Relay

Carbopalladation

Carbonylation



Palladium-Catalyzed Cascades



Initiation

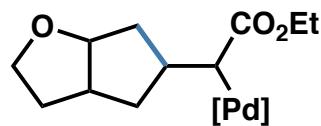
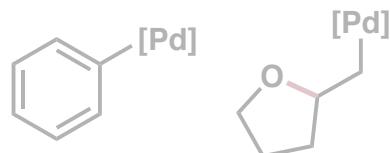
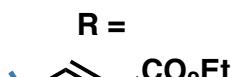
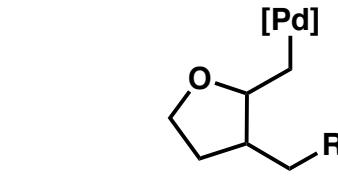
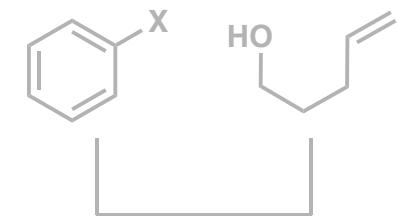
Oxidative addition

Nucleophilic palladation

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Carbonylation



Palladium-Catalyzed Cascades



Initiation

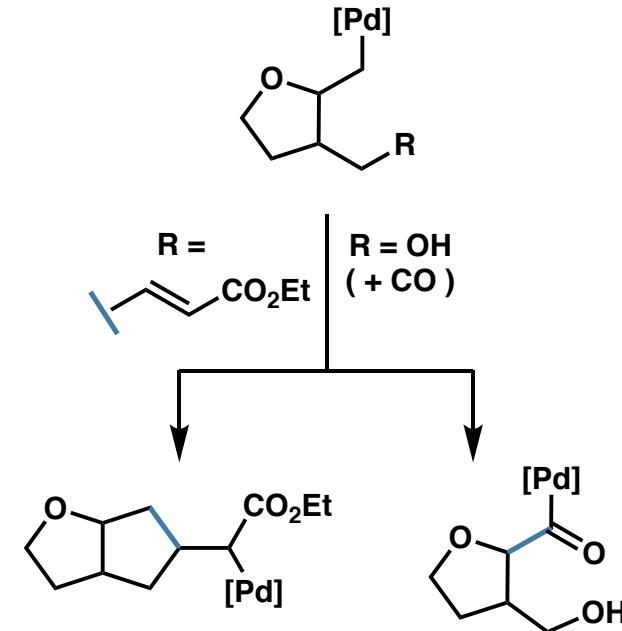
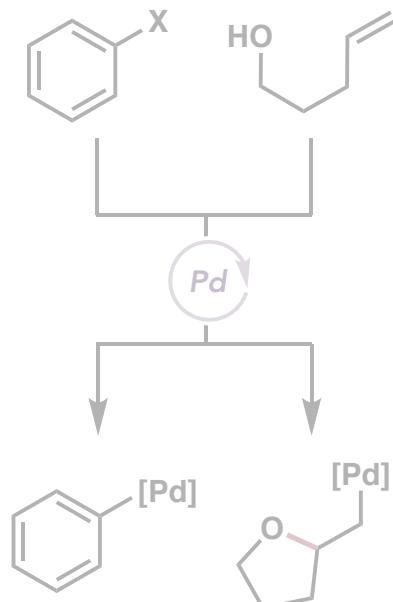
Oxidative addition

Nucleophilic palladation

Relay

Carbopalladation

Carbonylation



Palladium-Catalyzed Cascades



Initiation

Oxidative addition

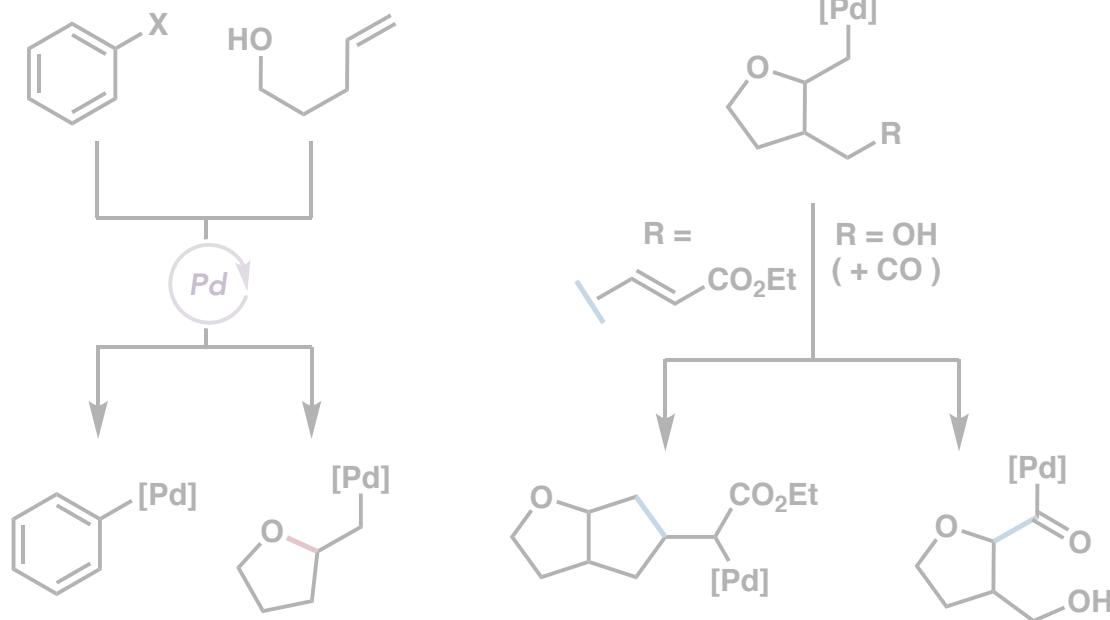
Nucleophilic palladation

Relay

Carbopalladation

Carbonylation

Termination



Palladium-Catalyzed Cascades



Initiation

Oxidative addition

Nucleophilic palladation

Relay

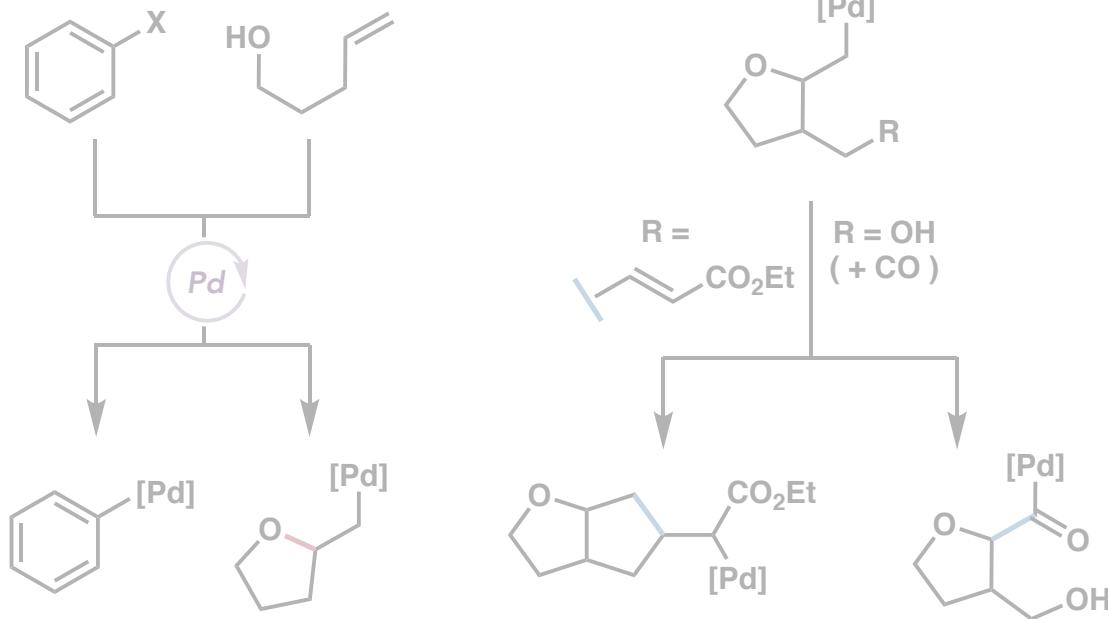
Carbopalladation

Carbonylation

Termination

β -hydride elimination

Nucleophilic capture



Palladium-Catalyzed Cascades



Initiation

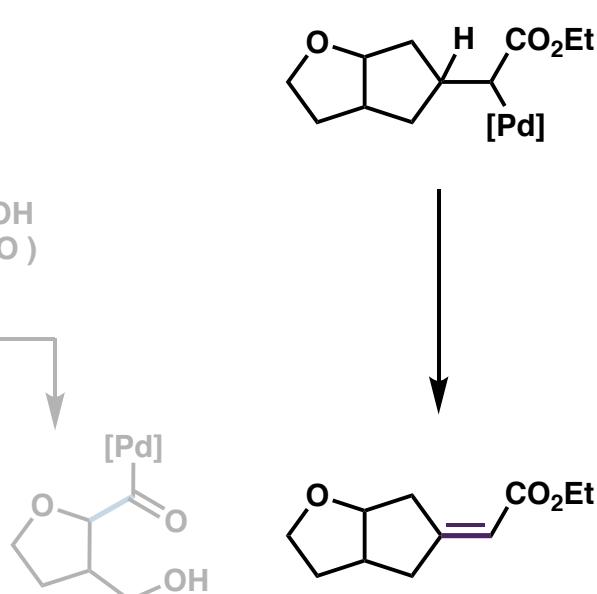
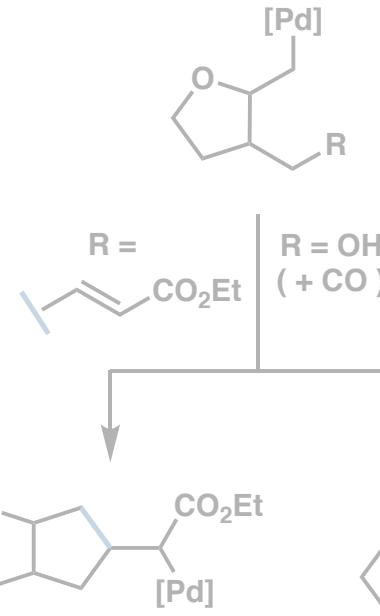
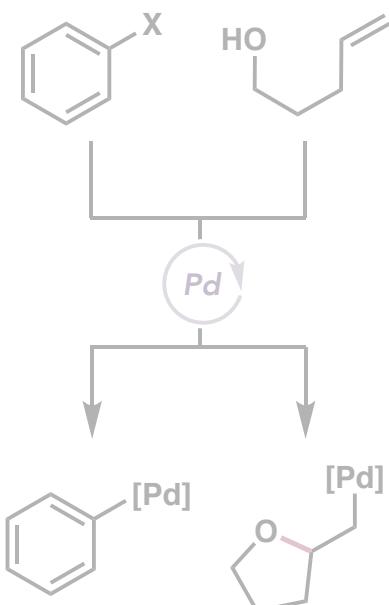
Oxidative addition
Nucleophilic palladation

Relay

Carbopalladation
Carbonylation

Termination

β -hydride elimination
Nucleophilic capture



Palladium-Catalyzed Cascades



Initiation

Oxidative addition

Nucleophilic palladation

Relay

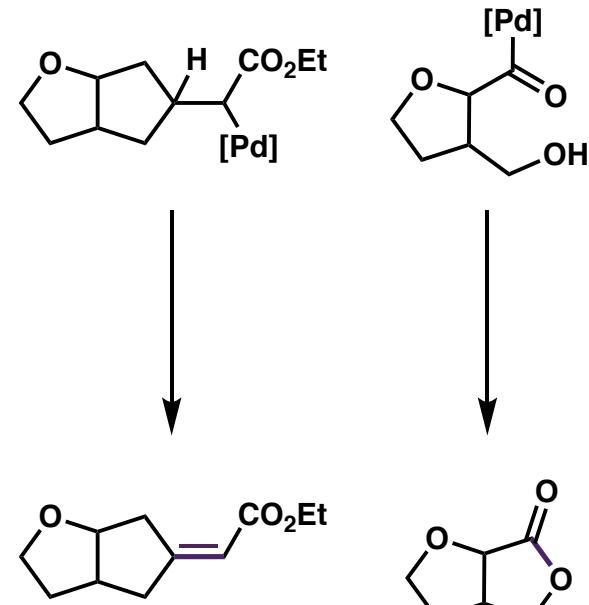
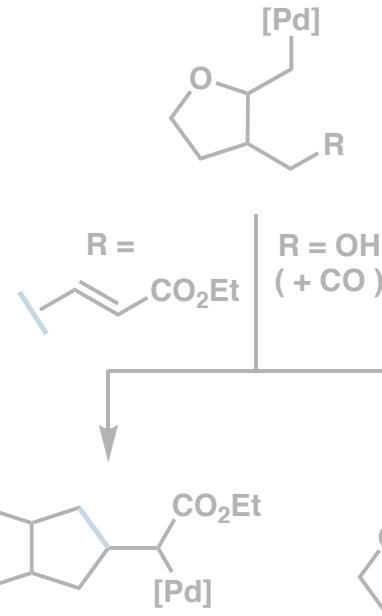
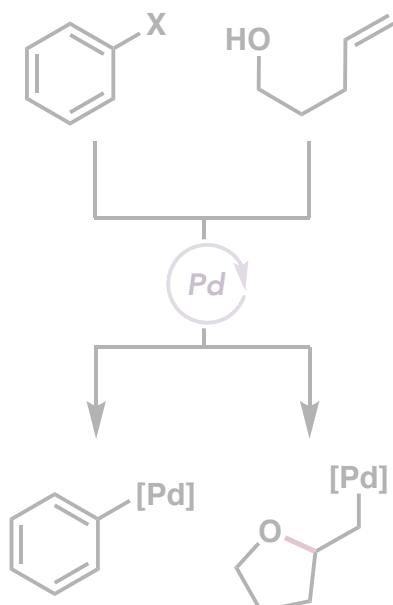
Carbopalladation

Carbonylation

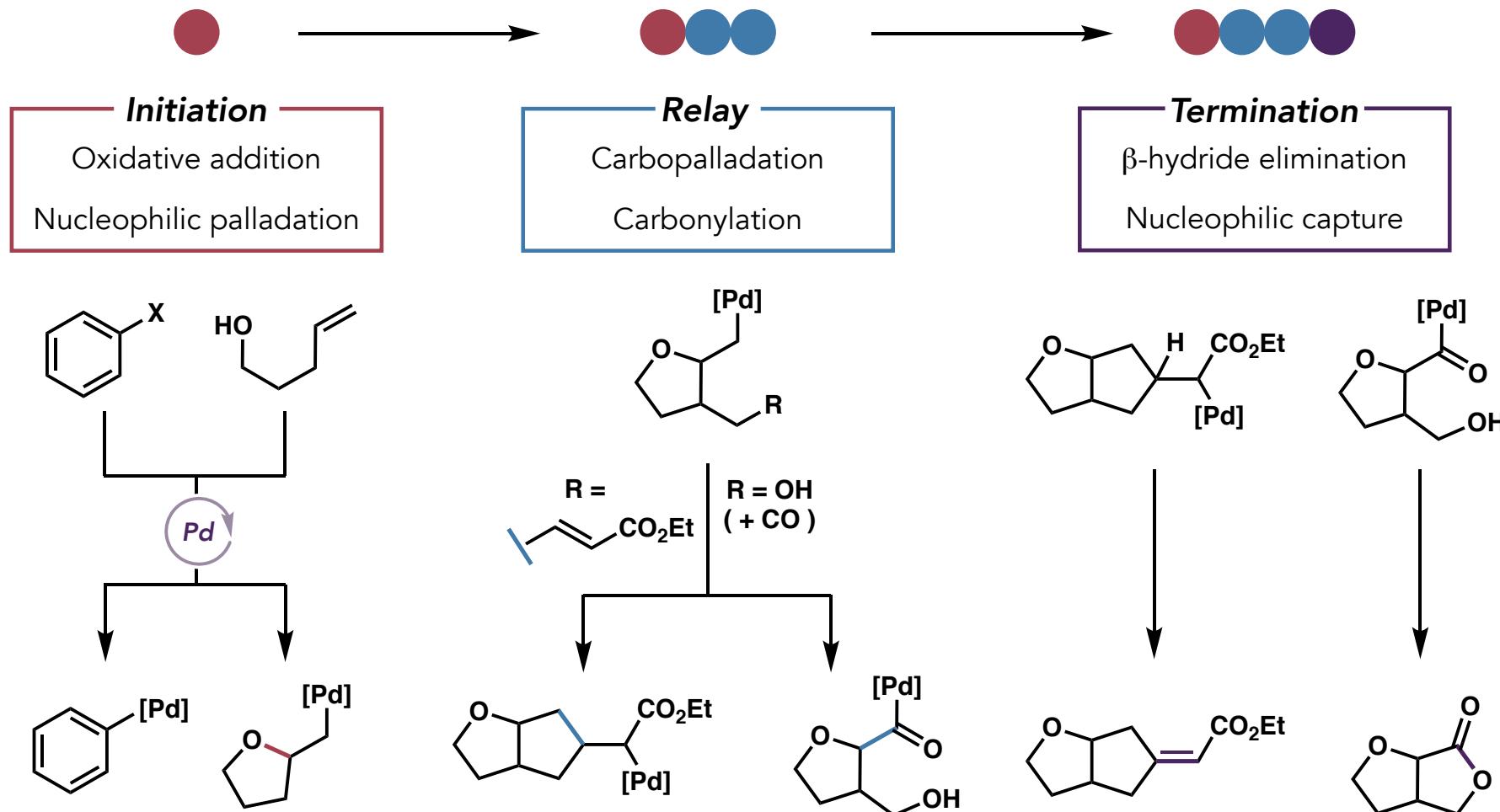
Termination

β -hydride elimination

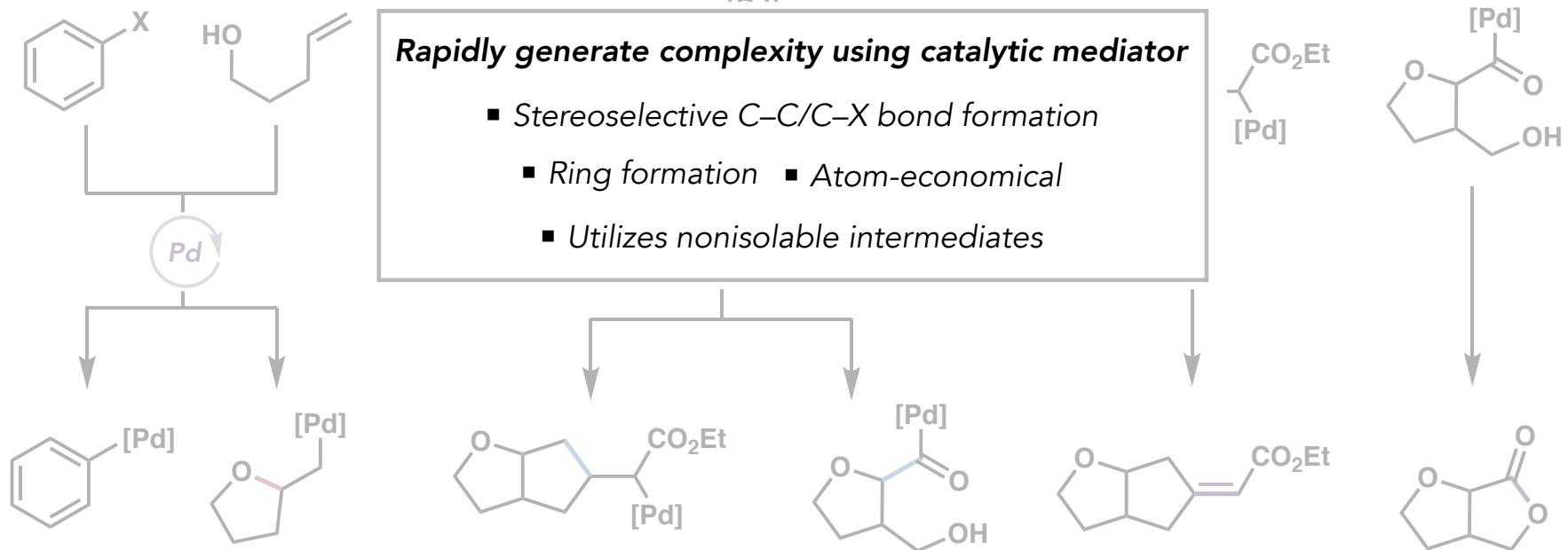
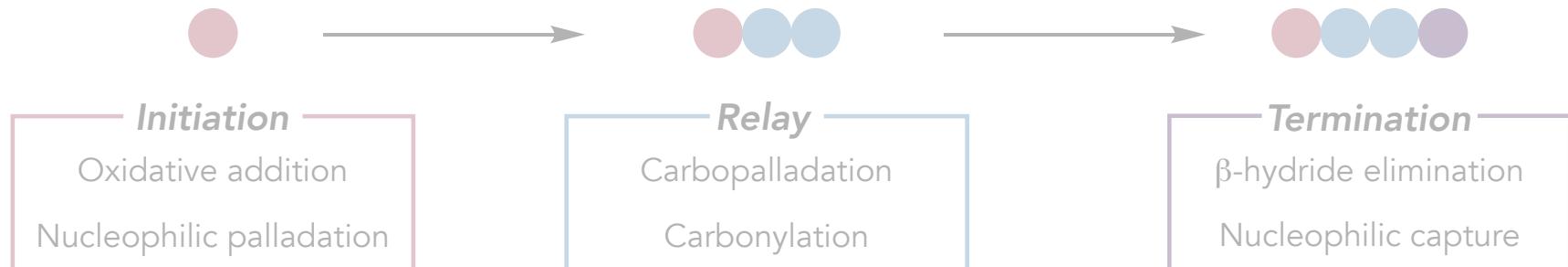
Nucleophilic capture



Palladium-Catalyzed Cascades



Palladium-Catalyzed Cascades



Palladium-Catalyzed Cascades



Initiation

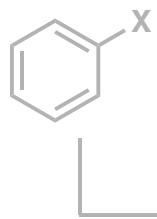
Oxidative addition
Nucleophilic palladation

Relay

Carbopalladation
Carbonylation

Termination

β -hydride elimination
Nucleophilic capture



[Pd] Recent Reviews

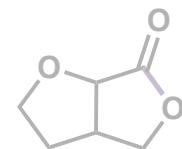
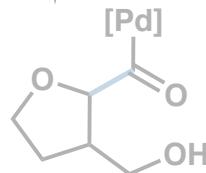
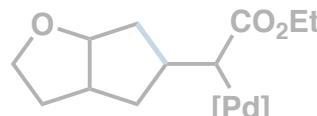
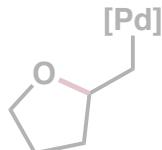
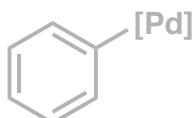
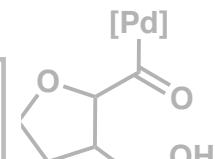
Brief History of Pd-catalyzed reactions: Tsuji, J. *Tetrahedron*, **2015**, 71, 6330–6348.

Cyclic carbopalladation: Negishi, E.-I. et al. *Chem. Rev.* **1996**, 96, 365–393.

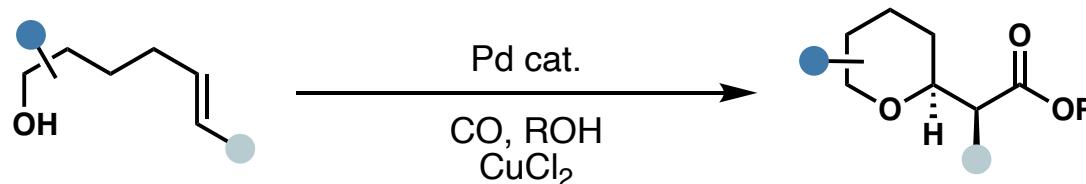
Palladium Cascades in Synthesis: Reisman, S. E. et al. *Chem. Soc. Rev.* **2021**, 50, 7891–7908.

Palladium Cascade Cyclizations: Biemolt, J.; Ruijter, E. *Adv. Synth. Catal.* **2018**, 360, 3821–3871.

Cascade reactions in total synthesis: Nicolaou, K. C. et al. *ACIE* **2006**, 45, 7134–7186.

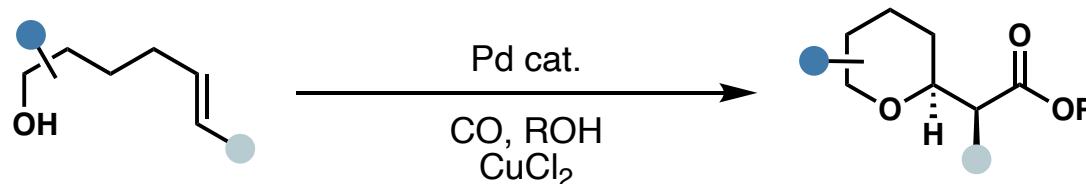


Semmelhack Reaction: Intramolecular Alkoxy carbonylation



Early reports of alkoxy carbonylation: James, D. E.; Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1806.
Bodurow, C.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1984**, *106*, 1496.
Baum, M.; Bodurow, C.; Semmelhack, M. F. *Tetrahedron Lett.*, **1984**, *25*, 3171.

Semmelhack Reaction: Intramolecular Alkoxy carbonylation



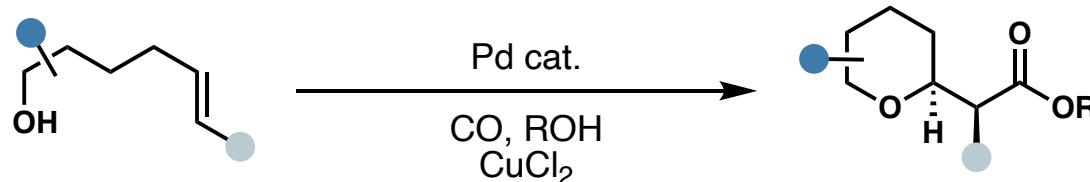
- Alkoxy carbonylation
- Substituted THF and THP rings
- Internal nucleophiles generate fused systems

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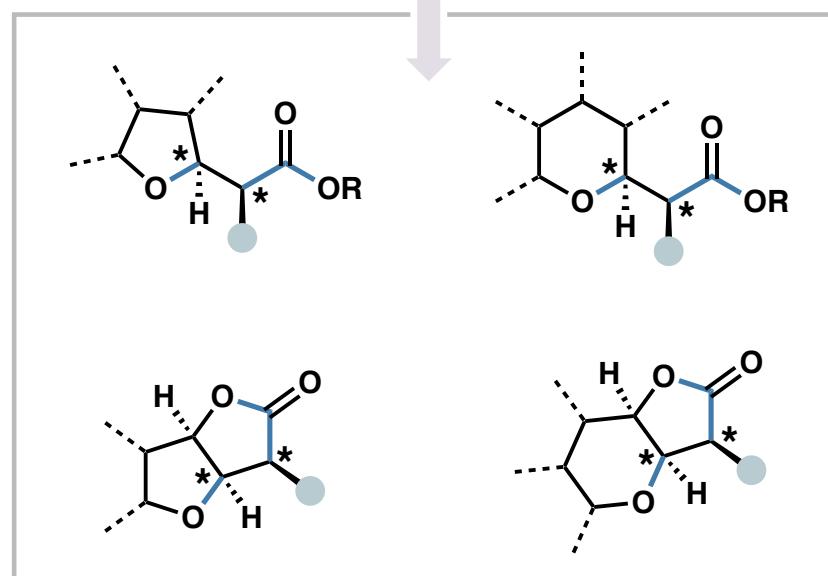
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Semmelhack Reaction: Intramolecular Alkoxy carbonylation



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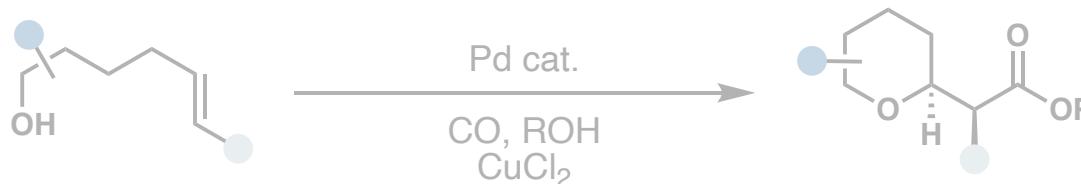


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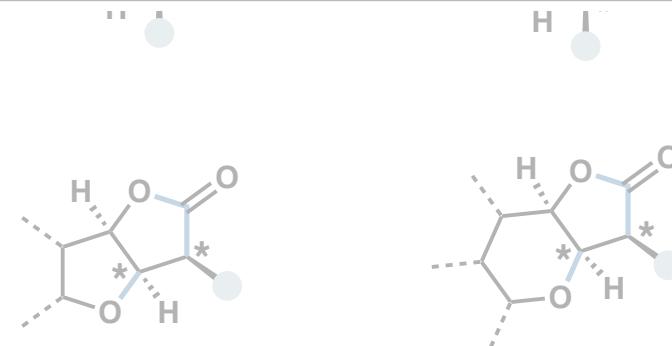
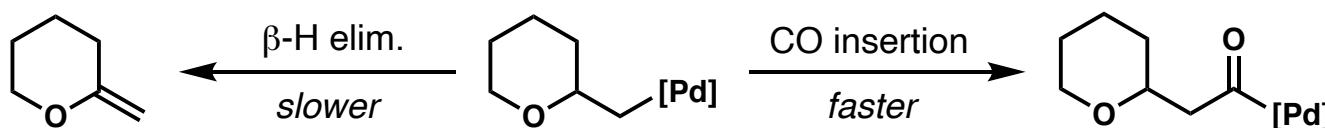
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Semmelhack Reaction: Intramolecular Alkoxy carbonylation



■ Alkoxy carbonylation

■ Substituted THF and THP rings

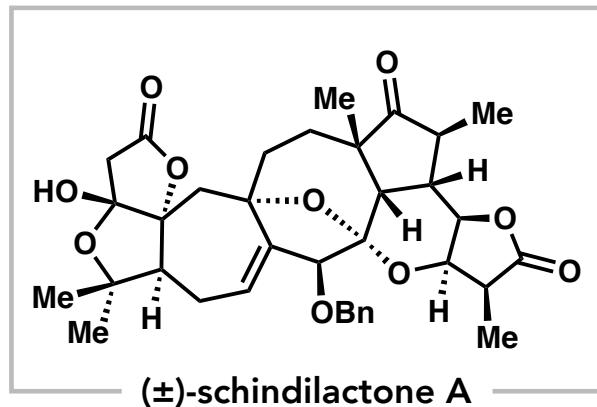


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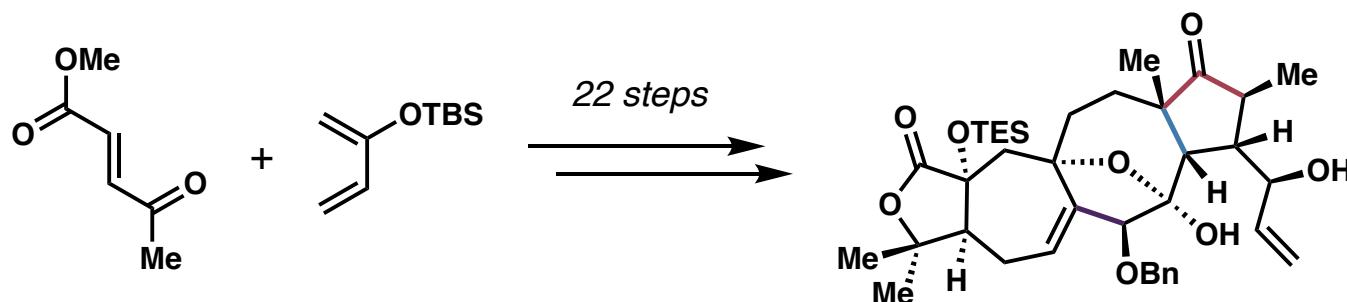
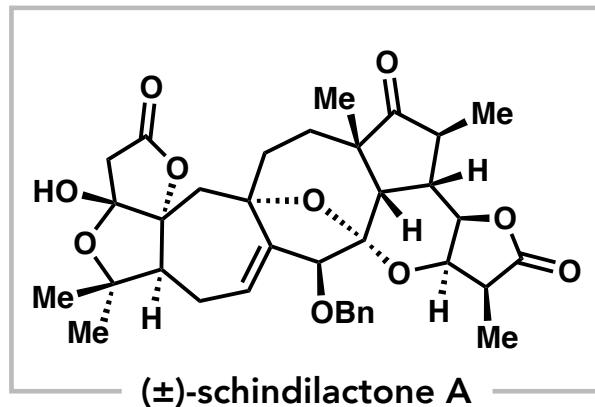
Bodurow, C.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1984**, *106*, 1496.

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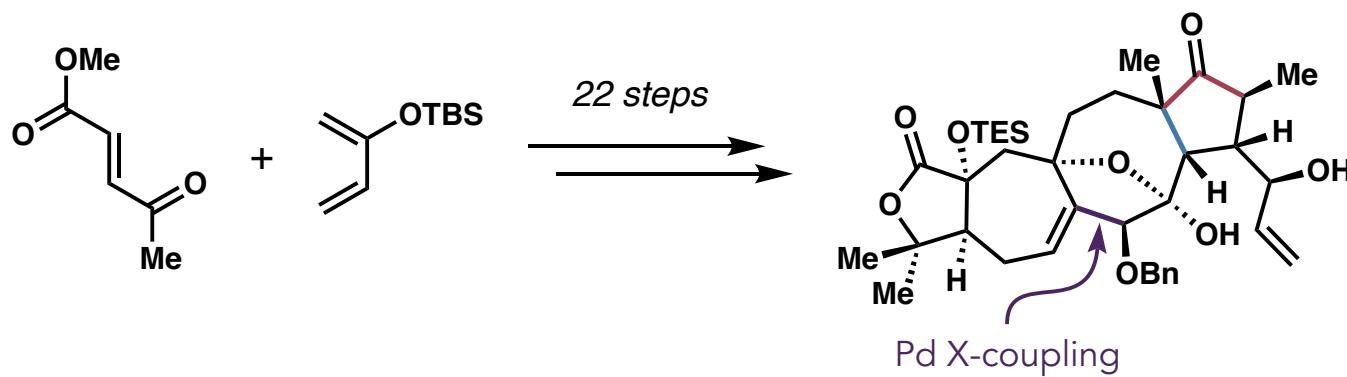
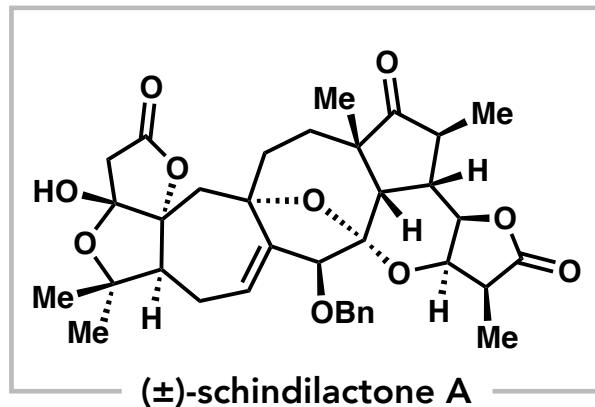
Yang's Synthesis of Schindilactone A



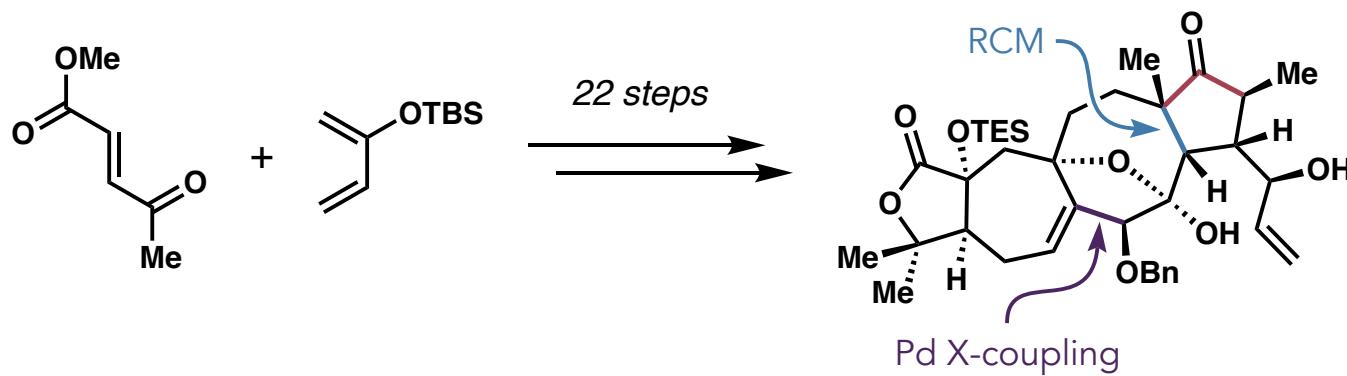
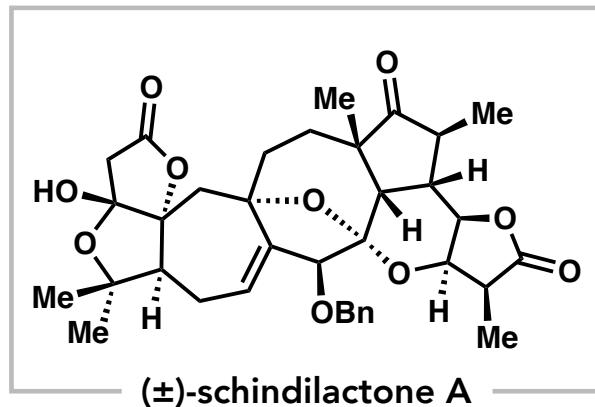
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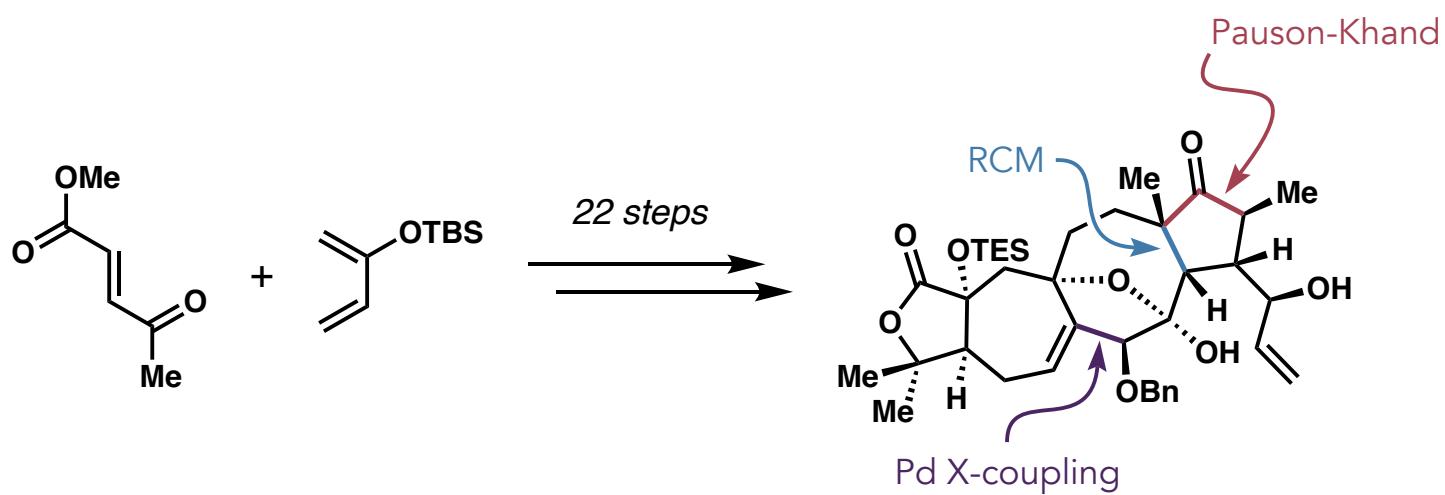
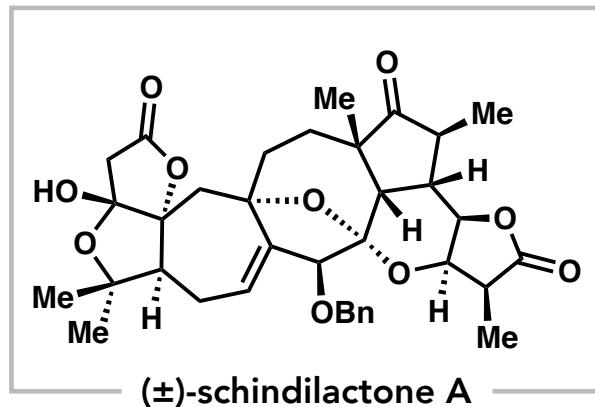
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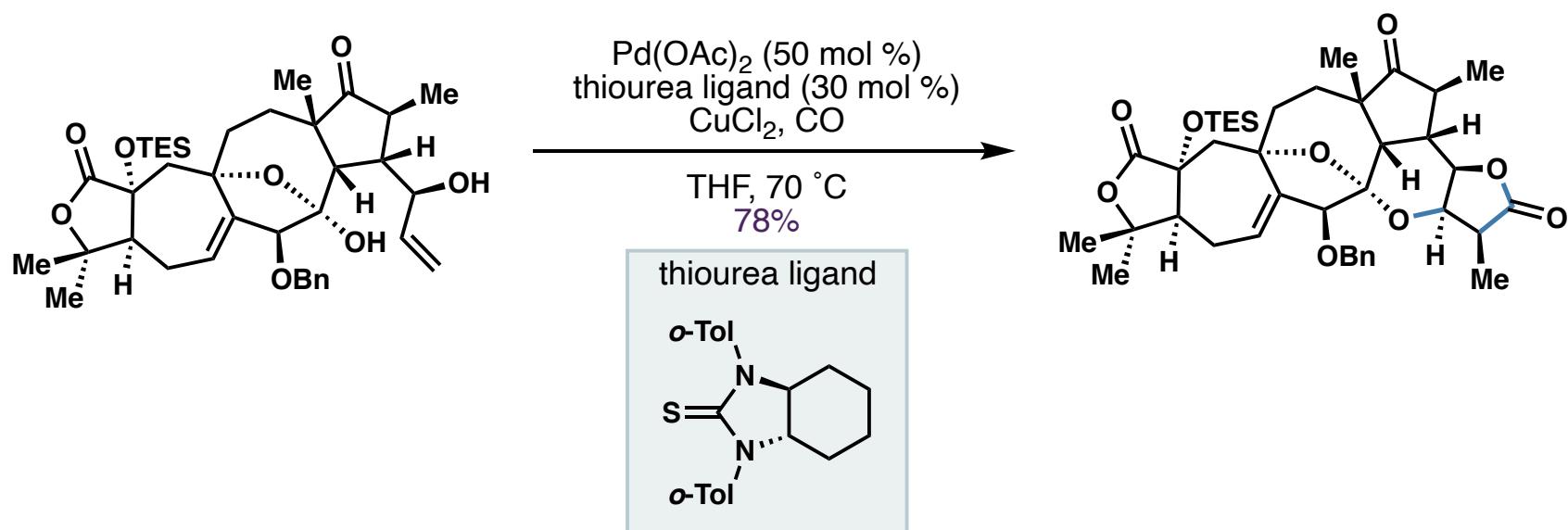
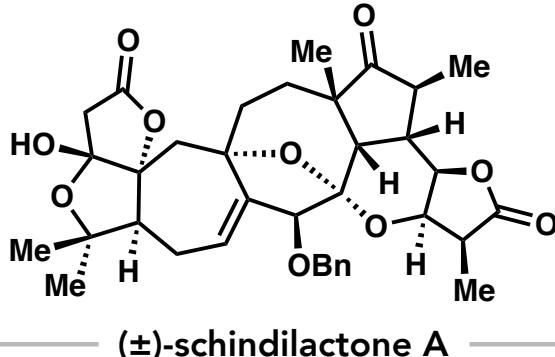
Yang's Synthesis of Schindilactone A



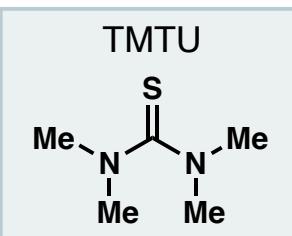
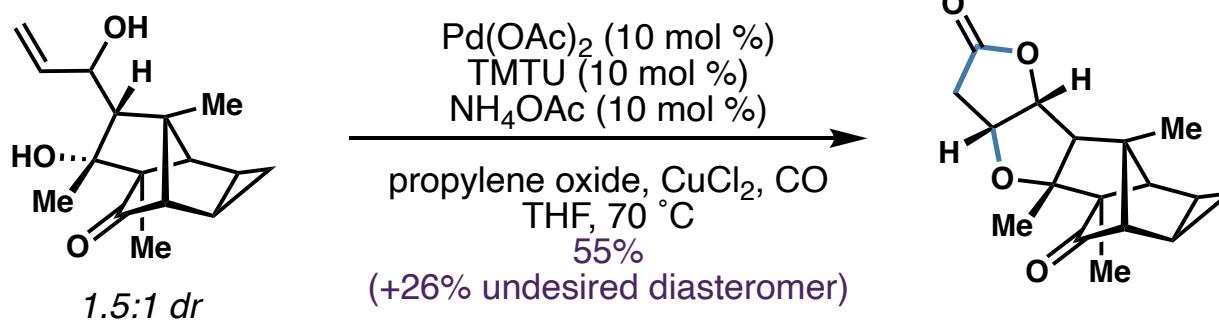
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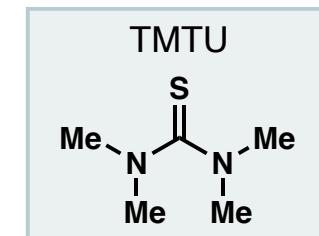
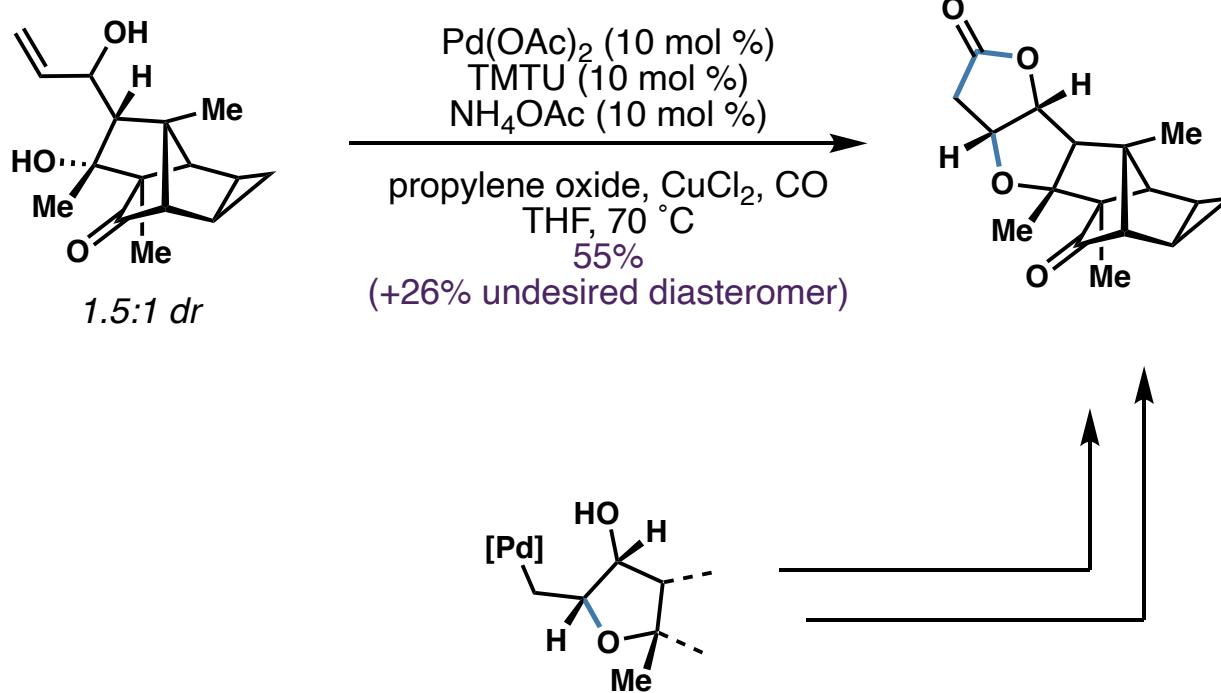
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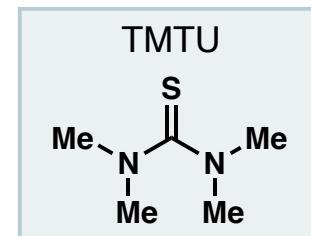
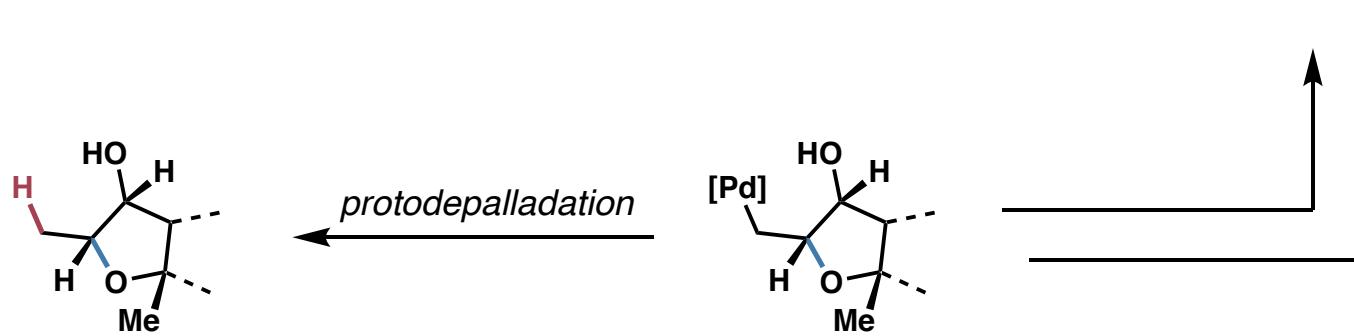
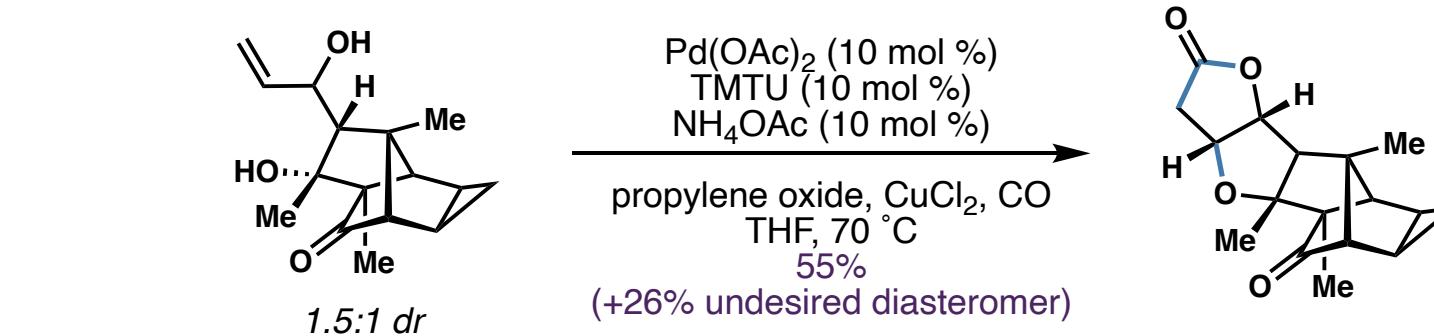
Carreira's Syntheses of Pallambins A & B



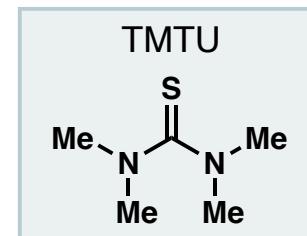
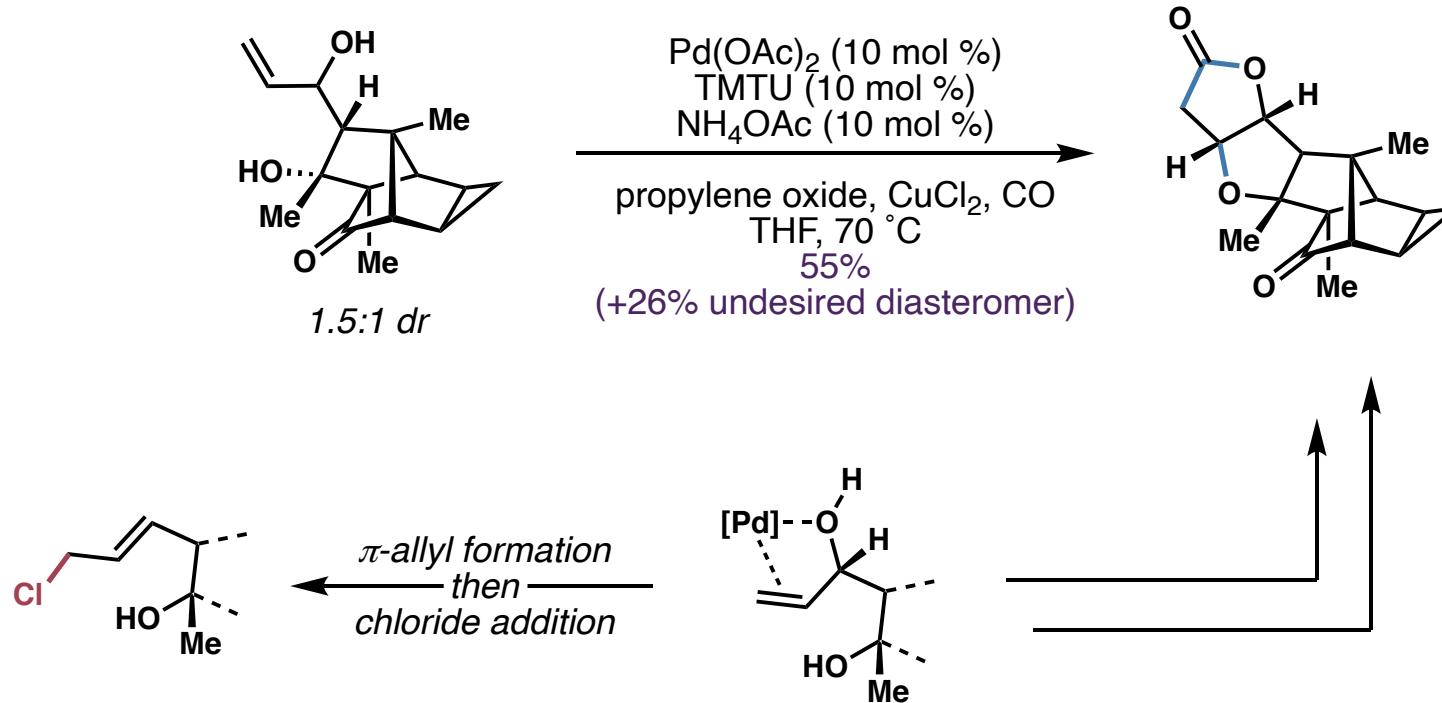
Carreira's Syntheses of Pallambins A & B



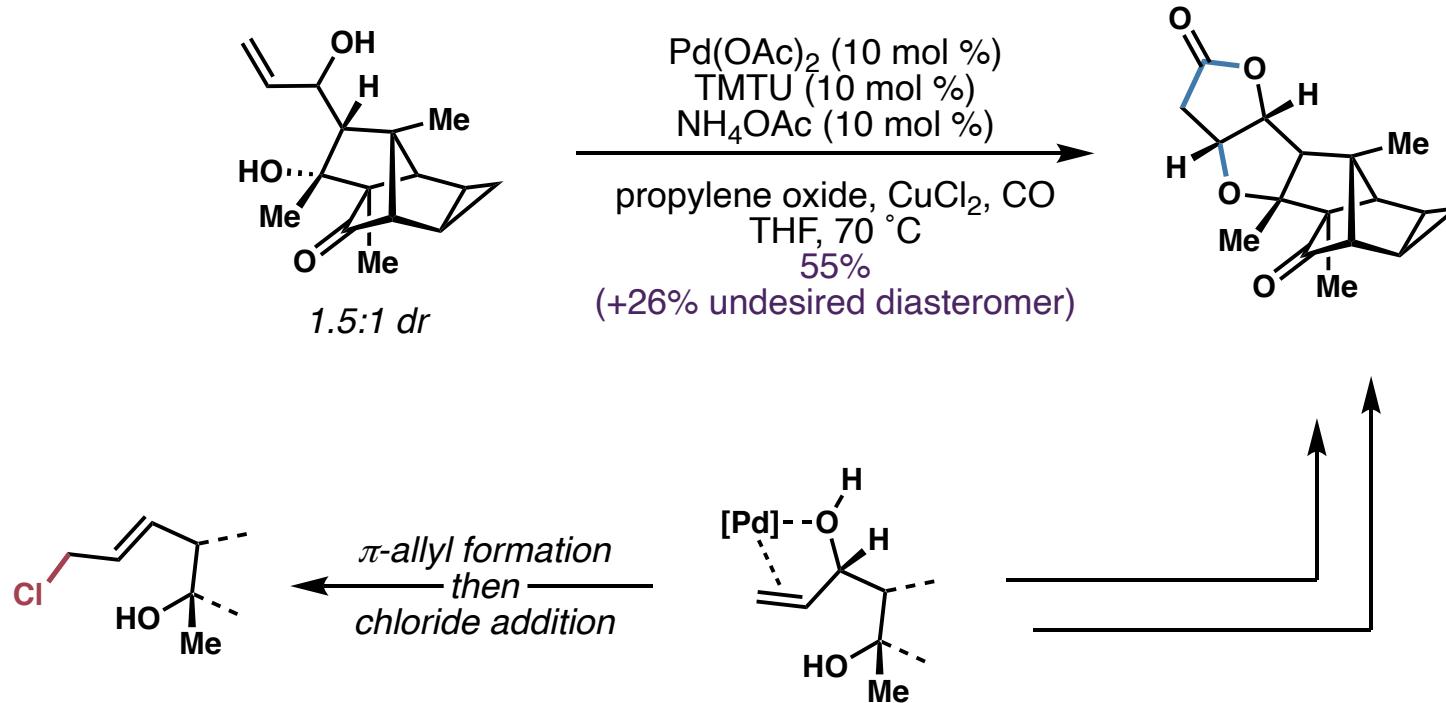
Carreira's Syntheses of Pallambins A & B



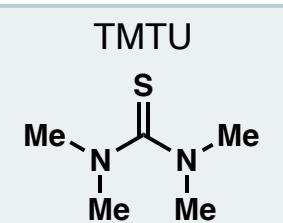
Carreira's Syntheses of Pallambins A & B



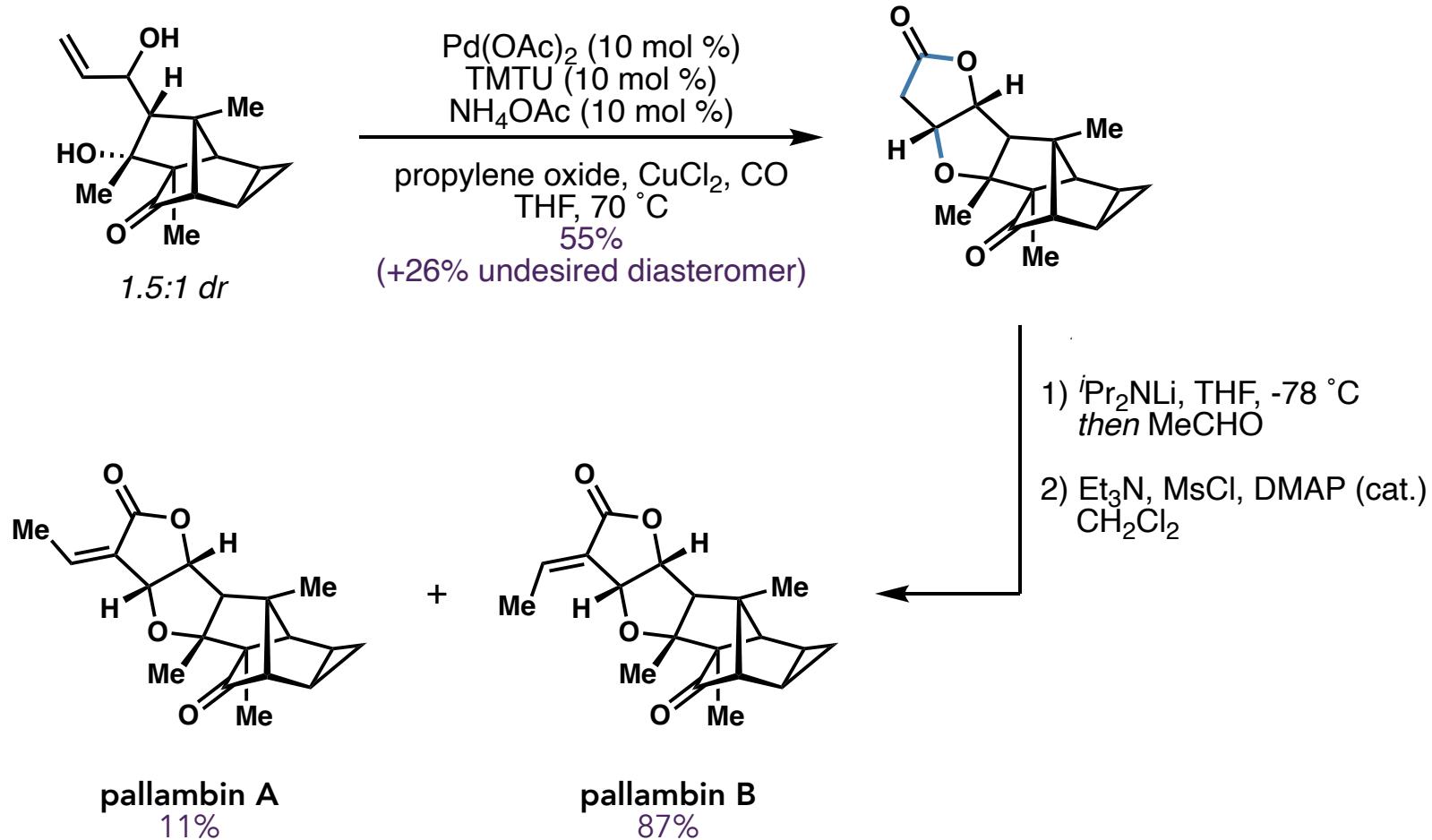
Carreira's Syntheses of Pallambins A & B



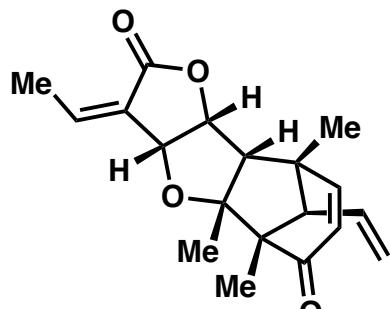
- NH₄OAc inhibits protodepalladation
- Propylene oxide scavenges Cl⁻



Carreira's Syntheses of Pallambins A & B

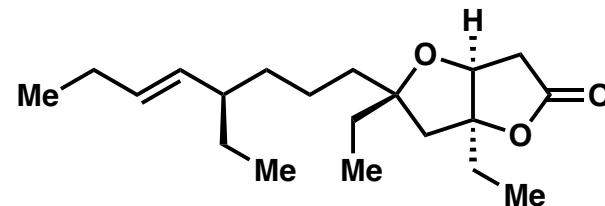
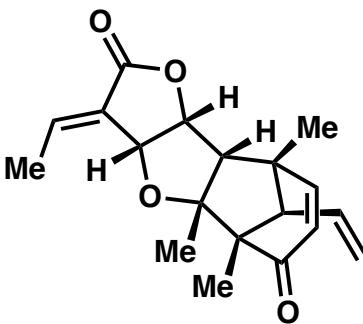


Additonal Examples of the Semmelhack Reaction



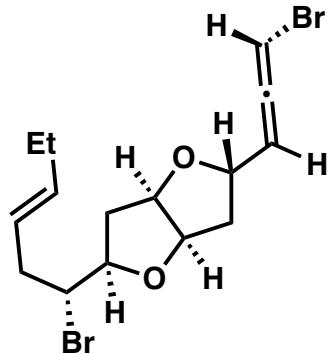
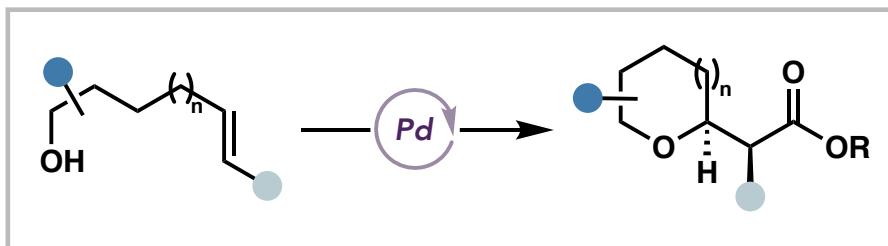
pallambins C & D

Wong, H. N. C. et al. *Chem. Commun.*, 2012, 48, 8517.



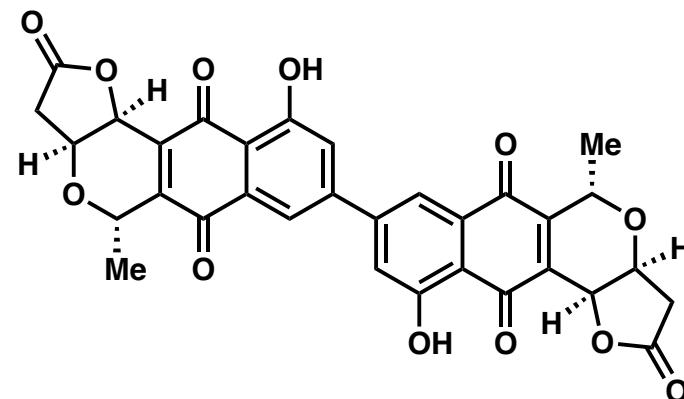
plakortone D

Hayes, P. Y.; Kitching, W. *JACS*, 2002, 124, 9718.



(-)-kumausallene

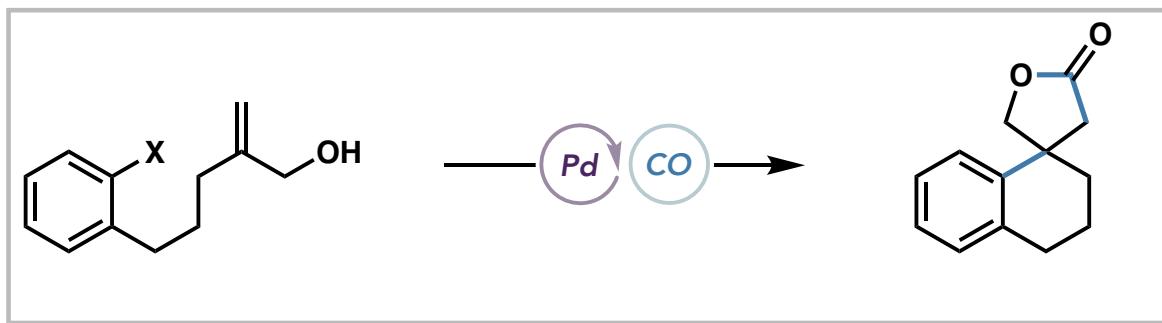
Werness, J. B.; Tang, W. *Org. Lett.*, 2011, 13, 3664.



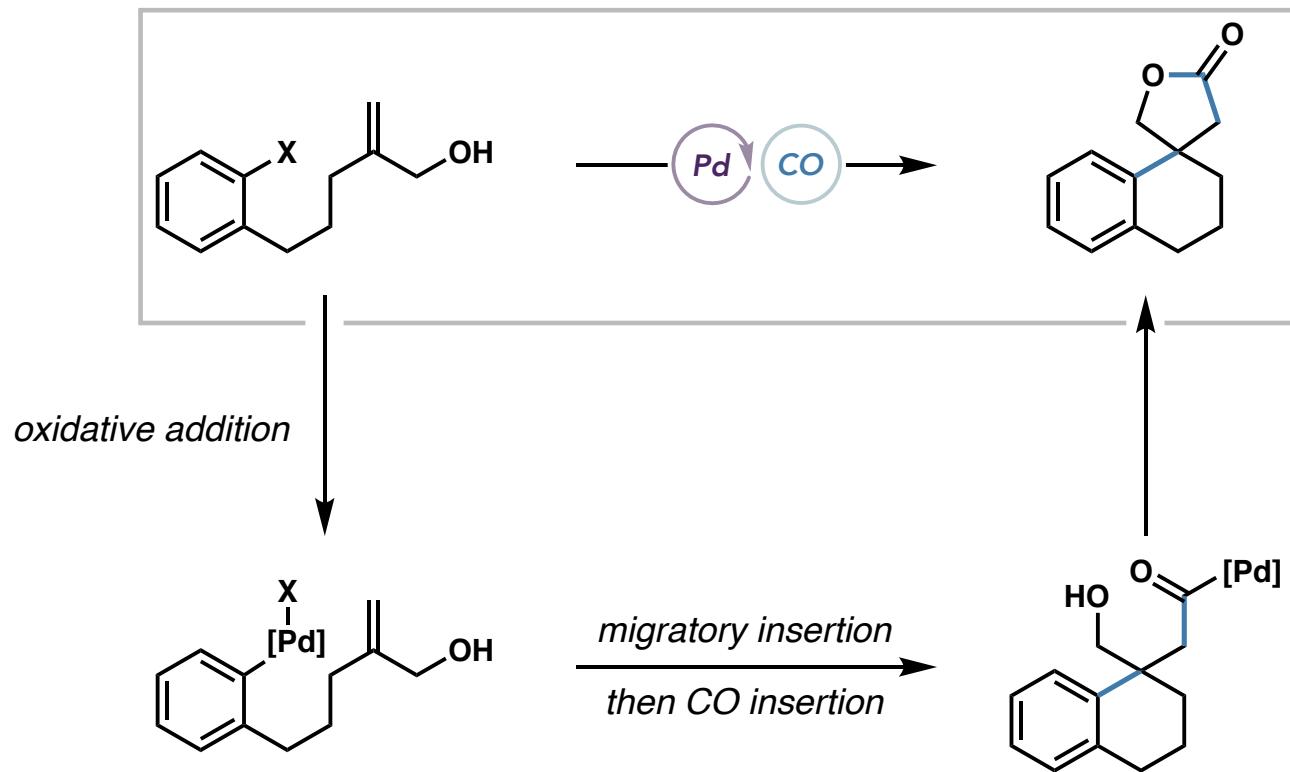
(\pm)-crisamicin A

Yang, Z. et al. *Org. Lett.*, 2008, 10, 3017.

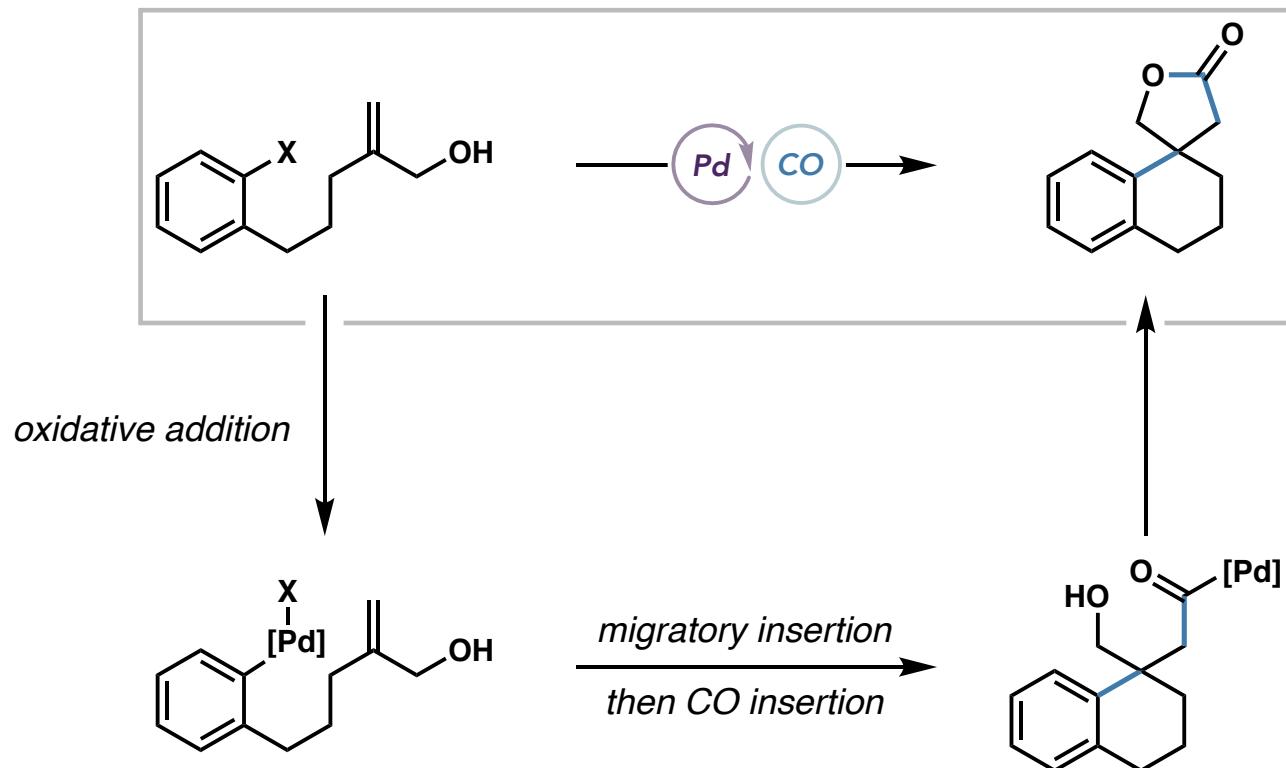
Carbopalladation/Carbonylative Lactonization



Carbopalladation/Carbonylative Lactonization

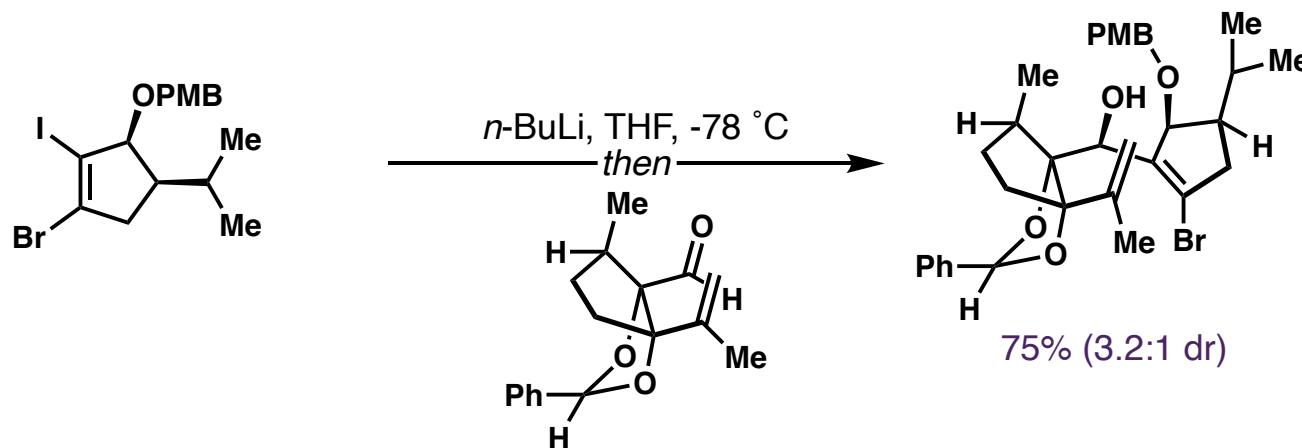


Carbopalladation/Carbonylative Lactonization

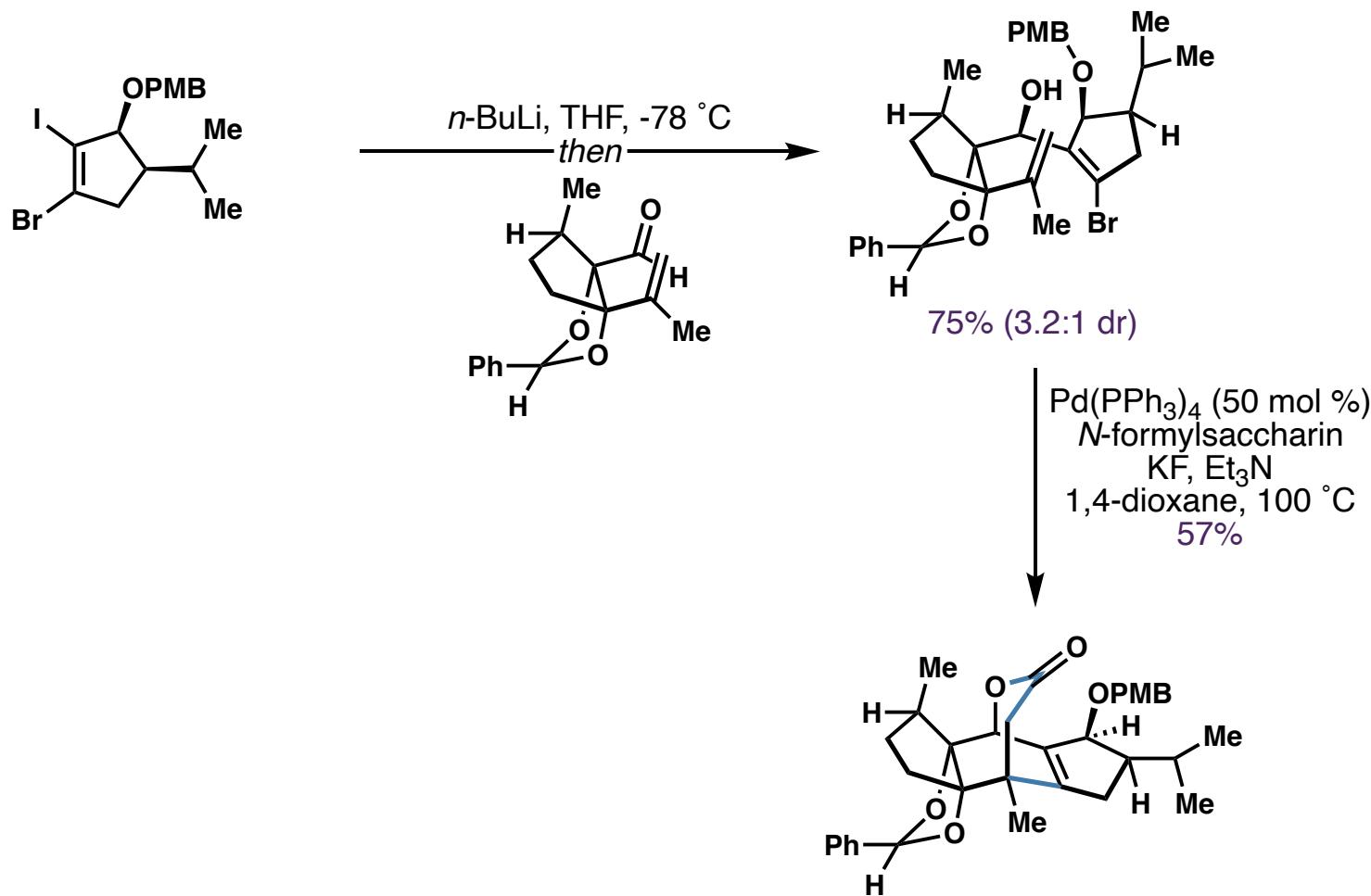


- Heck-type reactivity
- Multiple C–C bonds
- Fused lactone/carbocyclic systems

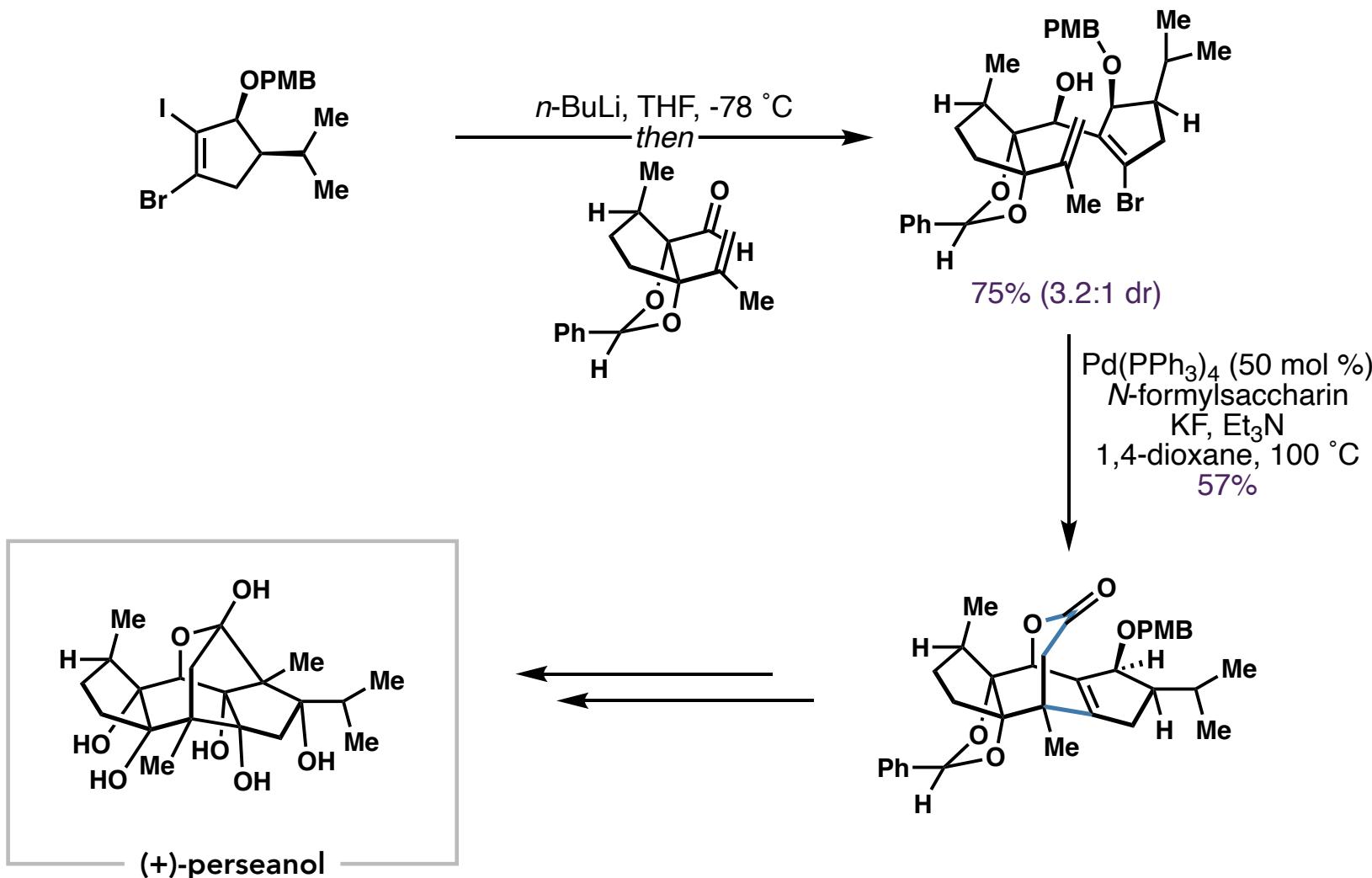
Reisman's Convergent Perseanol Synthesis



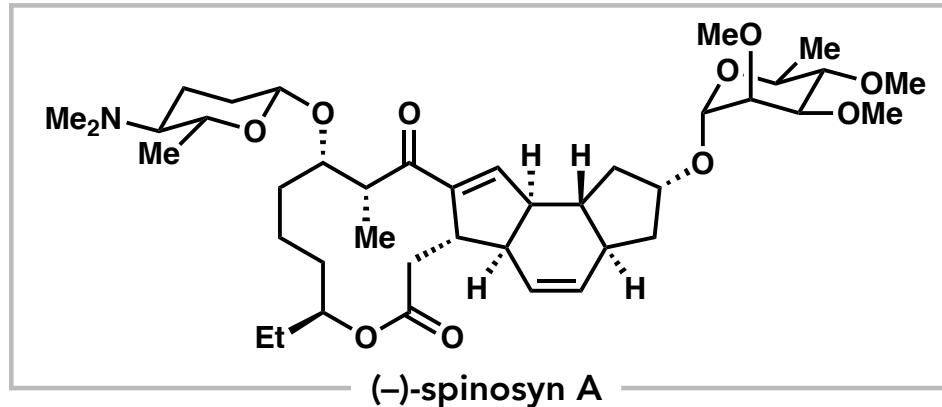
Reisman's Convergent Perseanol Synthesis



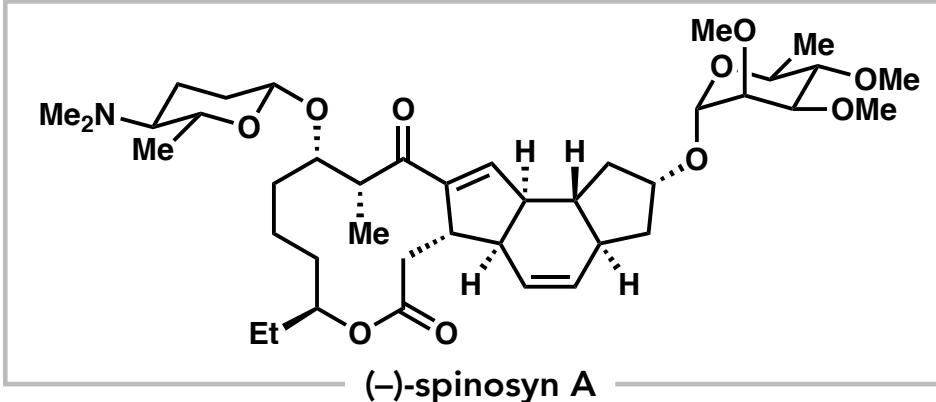
Reisman's Convergent Perseanol Synthesis



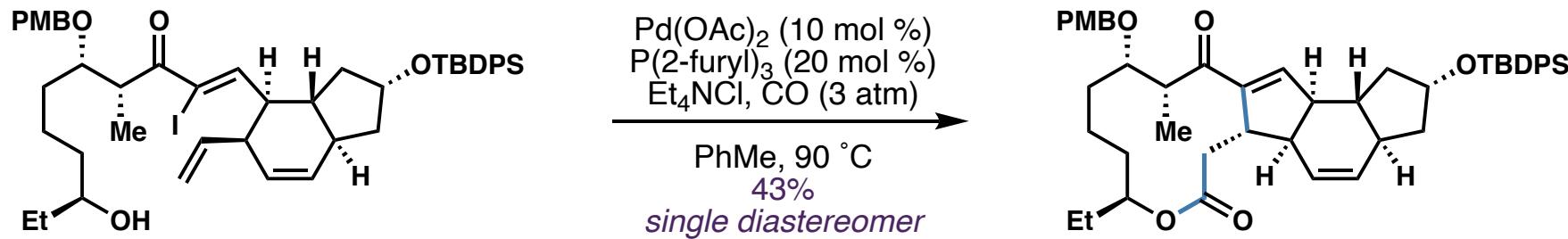
Macrolactonization Cascade Towards Spinosyn A



Macrolactonization Cascade Towards Spinosyn A

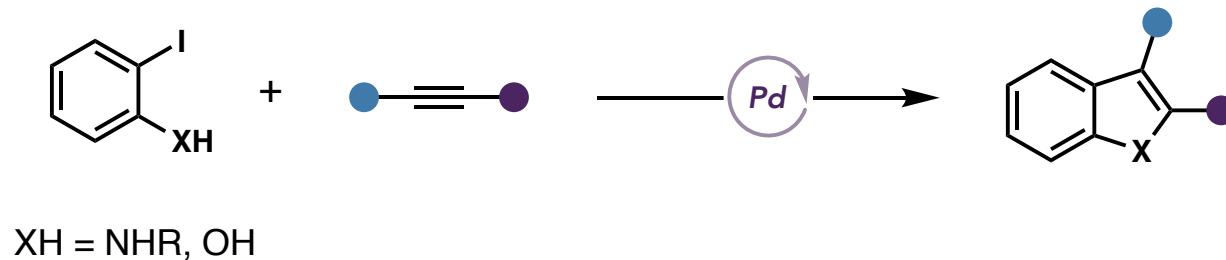


($-$)-spinosyn A



11 steps from commercial

Larock Heteroannulations

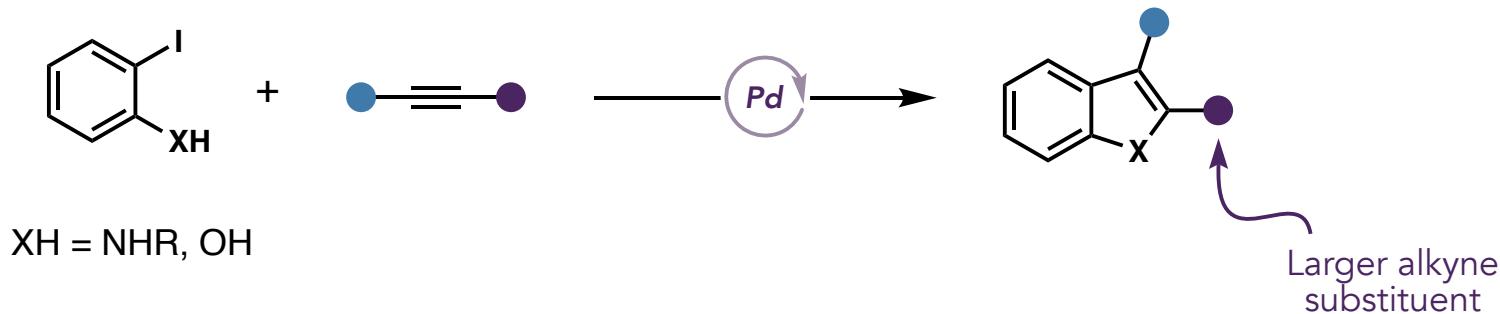


Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

Shibasaki, M. et al. *J. Org. Chem.* **1996**, *61*, 4876.

Jia, Y. et al. *Org. Lett.* **2017**, *19*, 3323.

Larock Heteroannulations

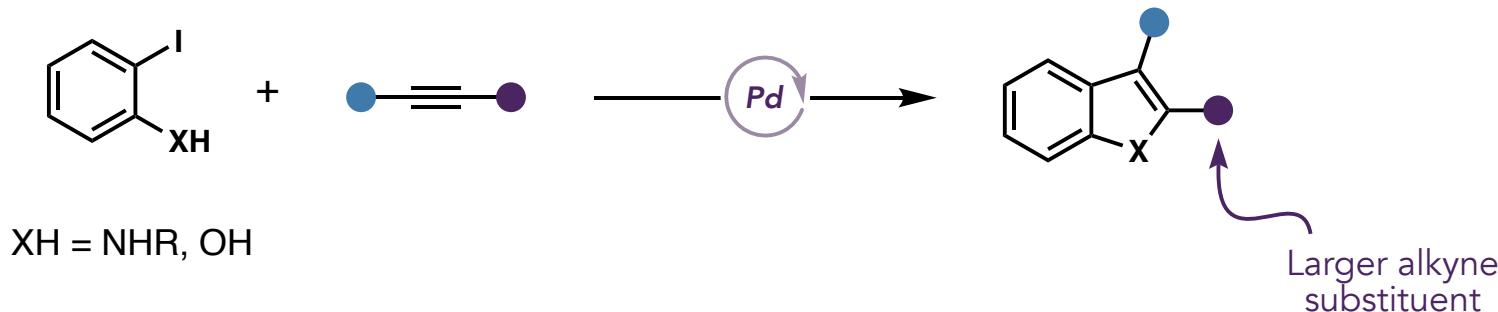


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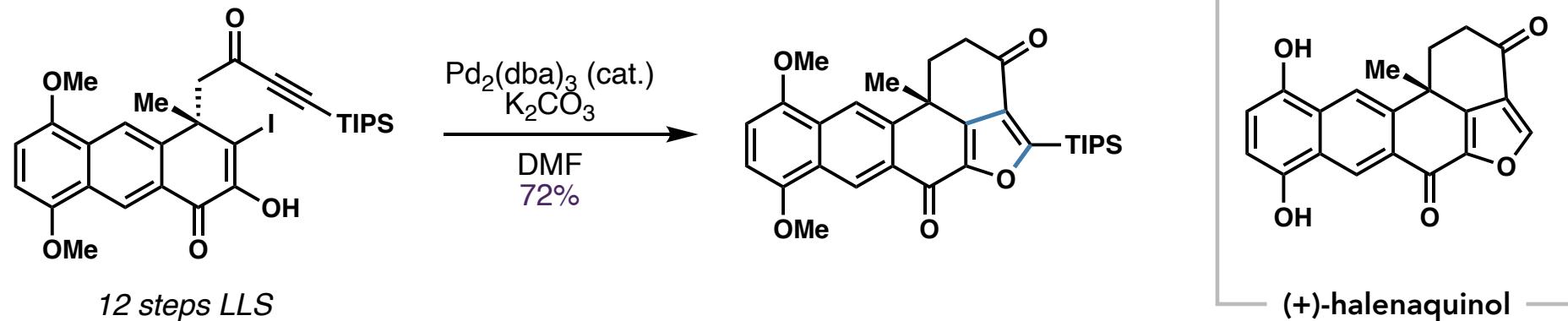
Shibasaki, M. et al. *J. Org. Chem.* **1996**, *61*, 4876.

Jia, Y. et al. *Org. Lett.* **2017**, *19*, 3323.

Larock Heteroannulations



First Example of Intramolecular Larock:

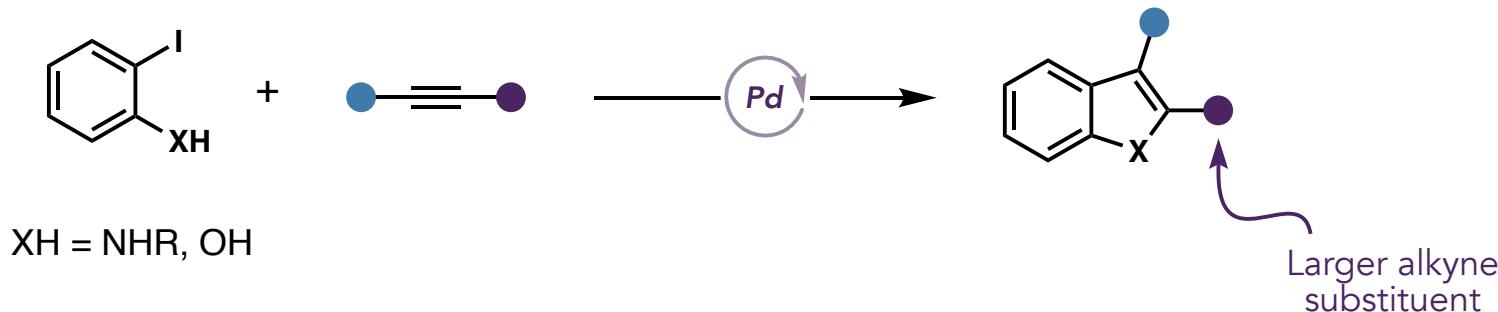


Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

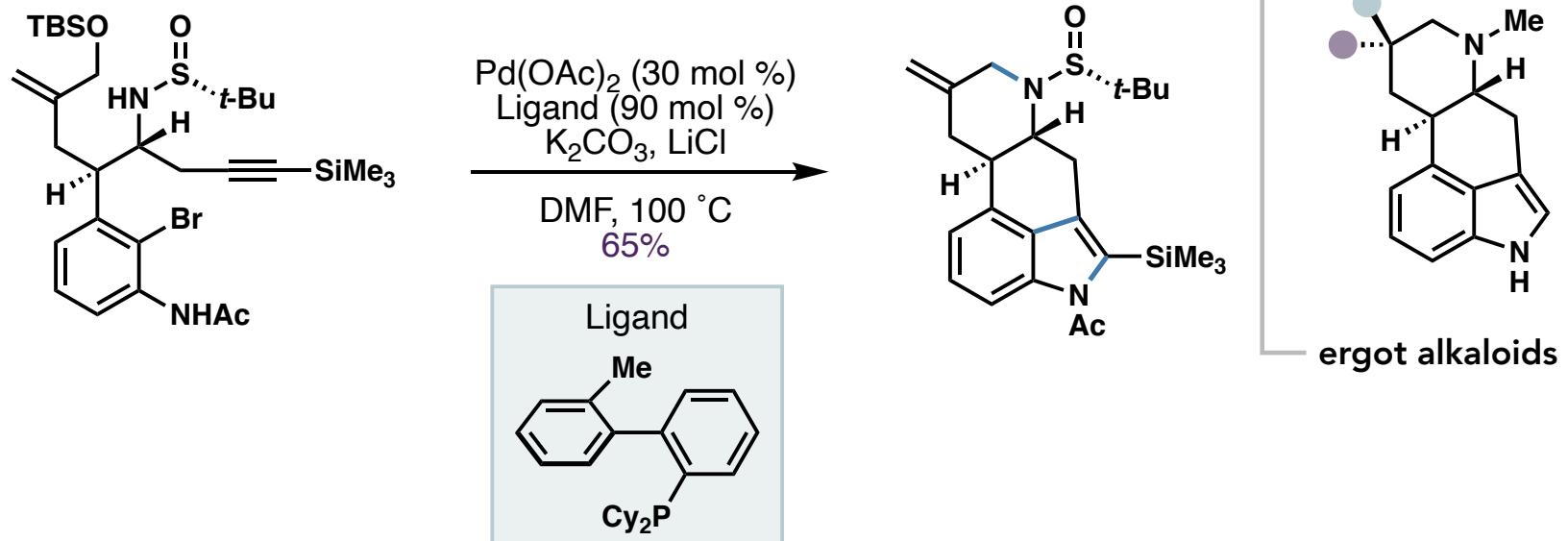
Shibasaki, M. et al. *J. Org. Chem.* **1996**, *61*, 4876.

Jia, Y. et al. *Org. Lett.* **2017**, *19*, 3323.

Larock Heteroannulations



One-pot Larock heteroannulation/Tsuji-Trost:

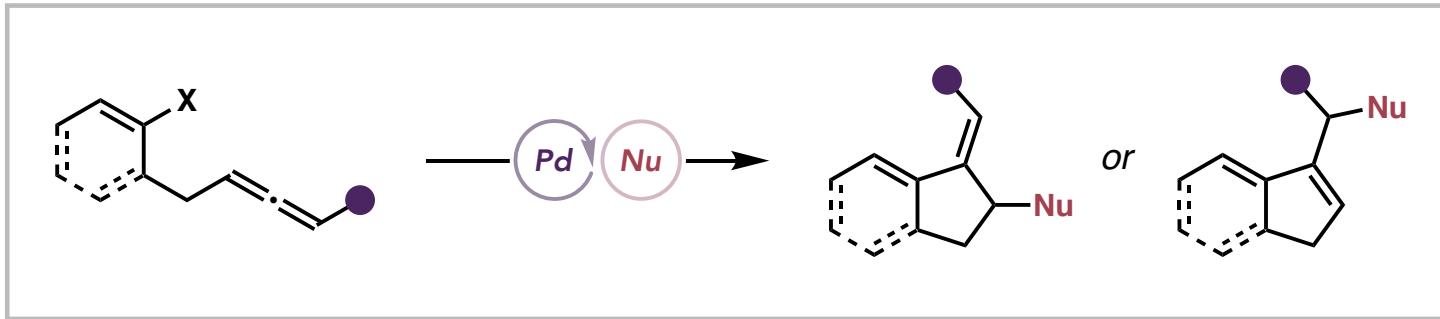


Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

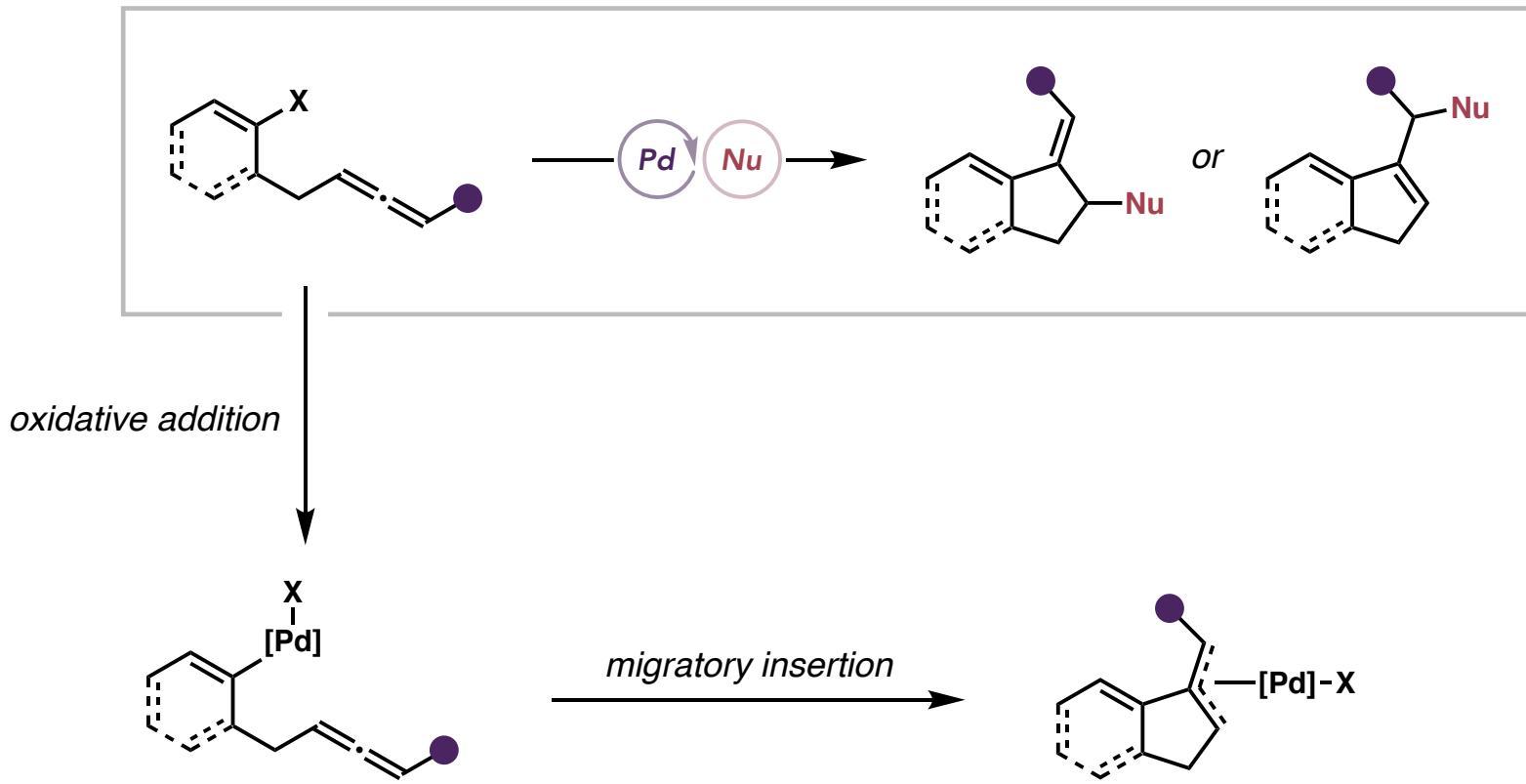
Shibasaki, M. et al. *J. Org. Chem.* **1996**, *61*, 4876.

Jia, Y. et al. *Org. Lett.* **2017**, *19*, 3323.

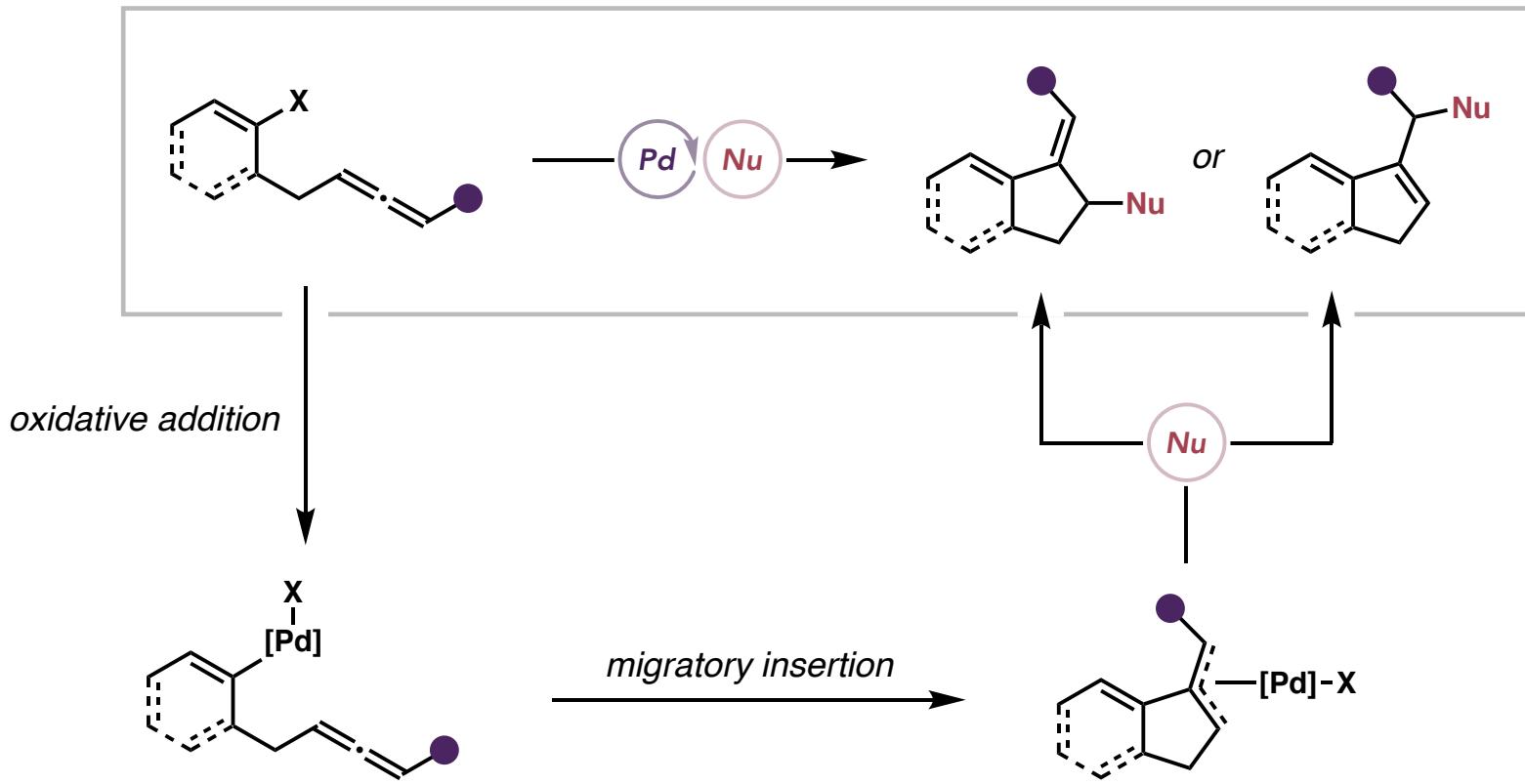
Carbopalladation/π-allyl Capture Cascades



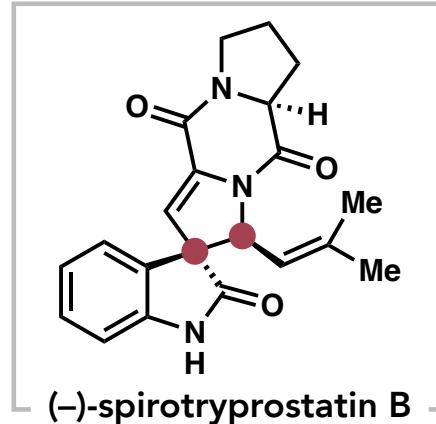
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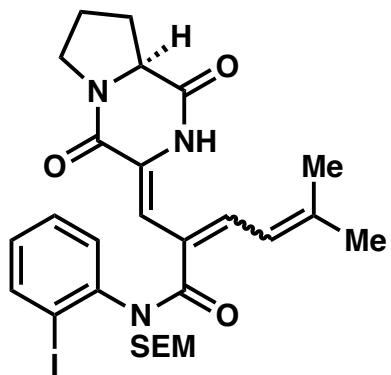
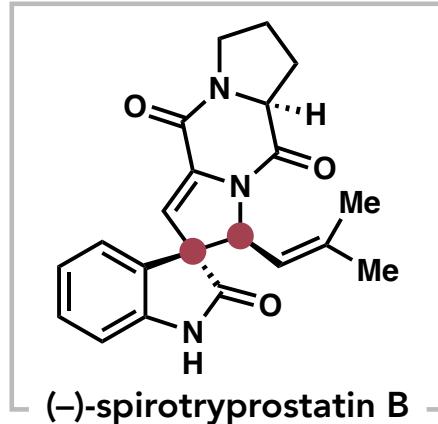
Carbopalladation/π-allyl Capture Cascades



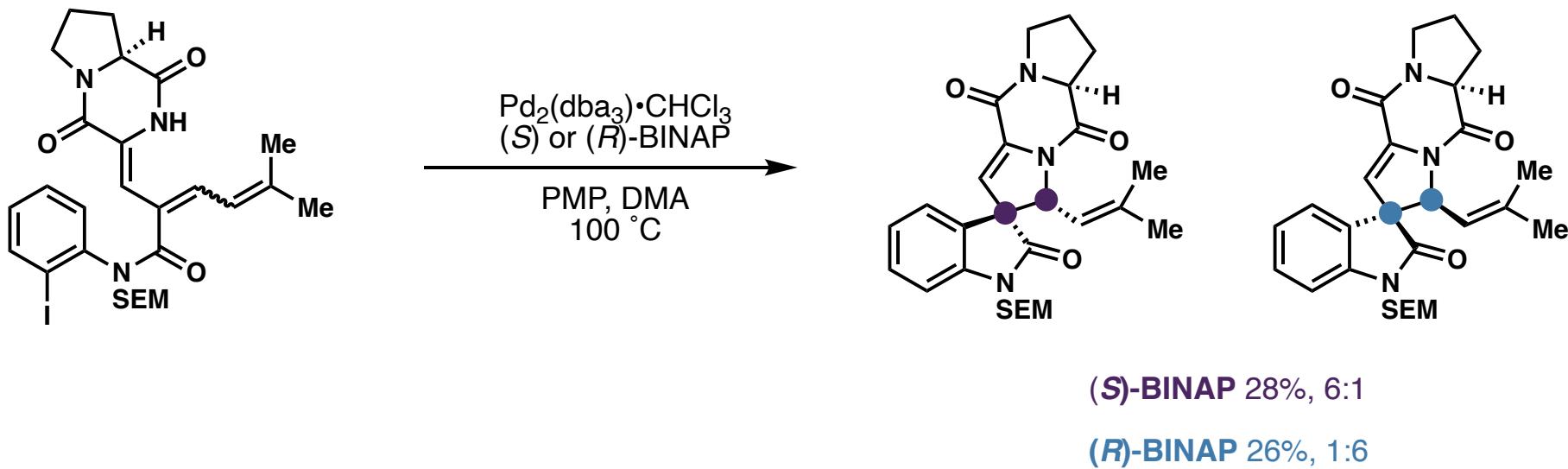
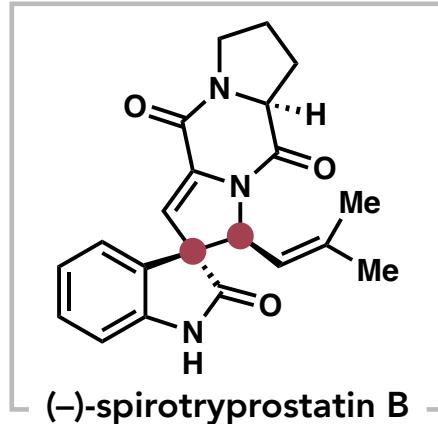
Overman's Diastereoselectivity Debacle



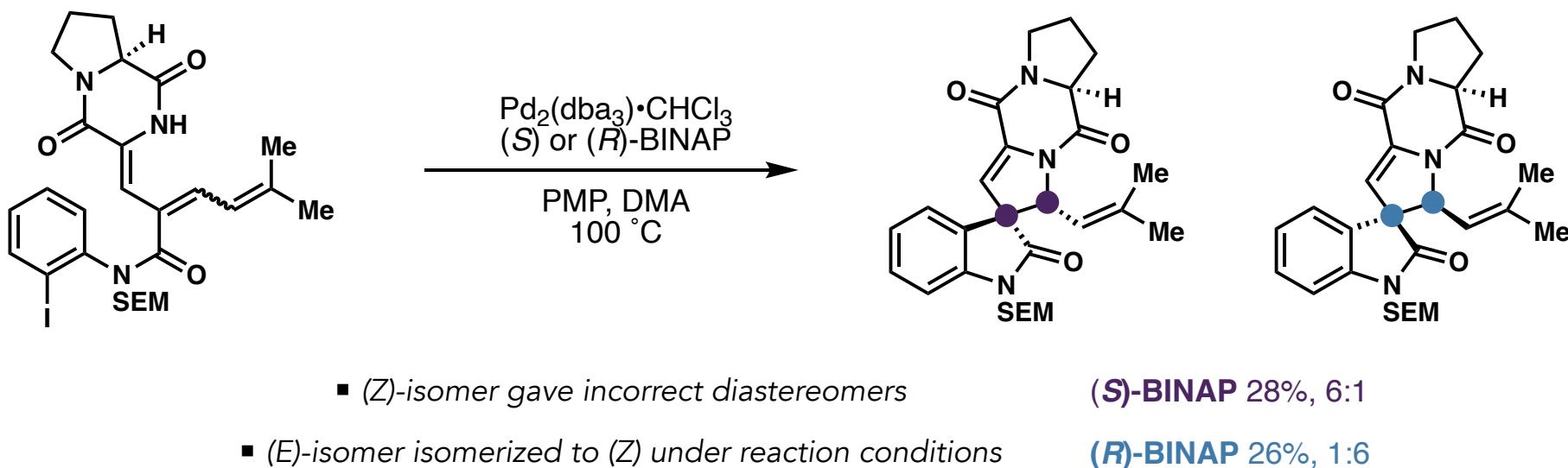
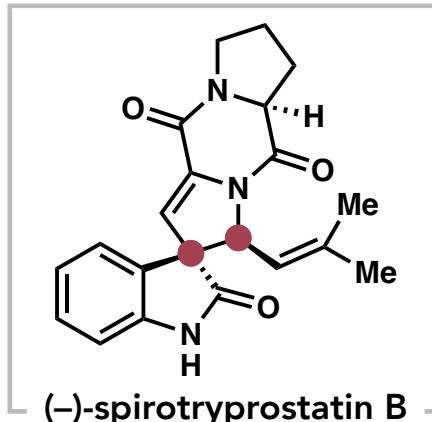
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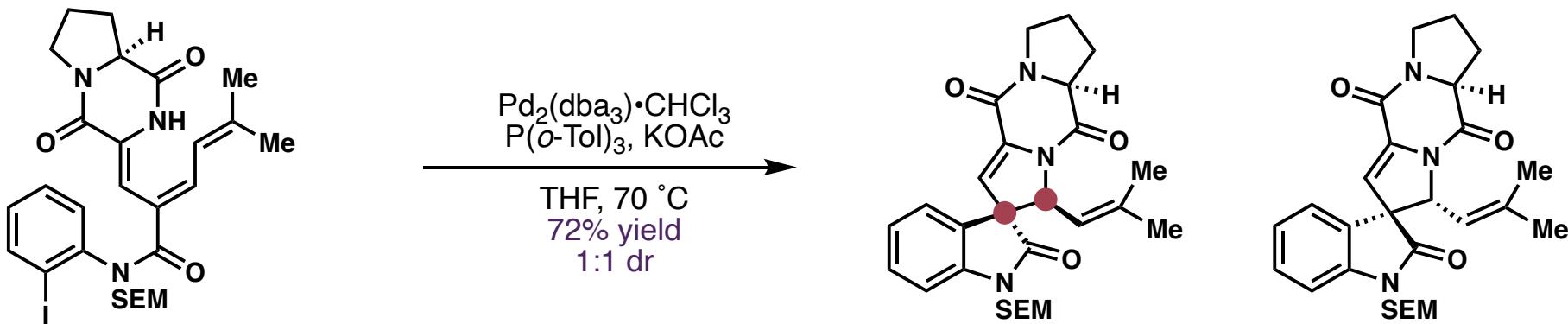
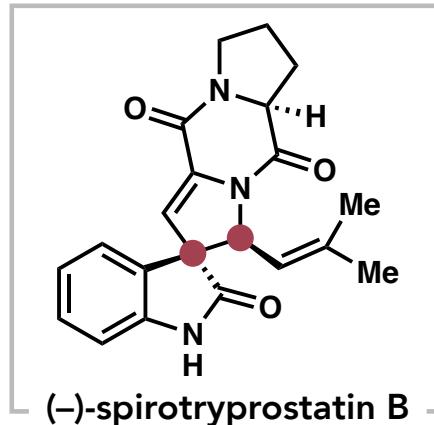
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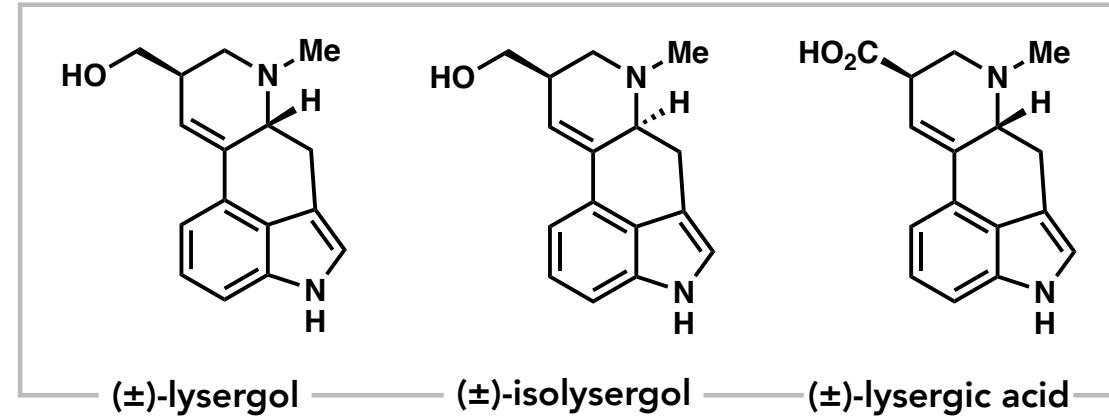
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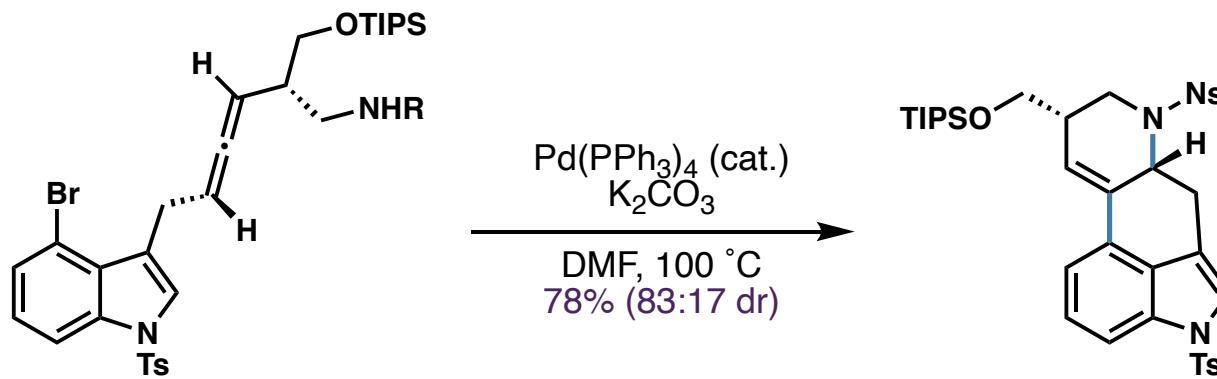
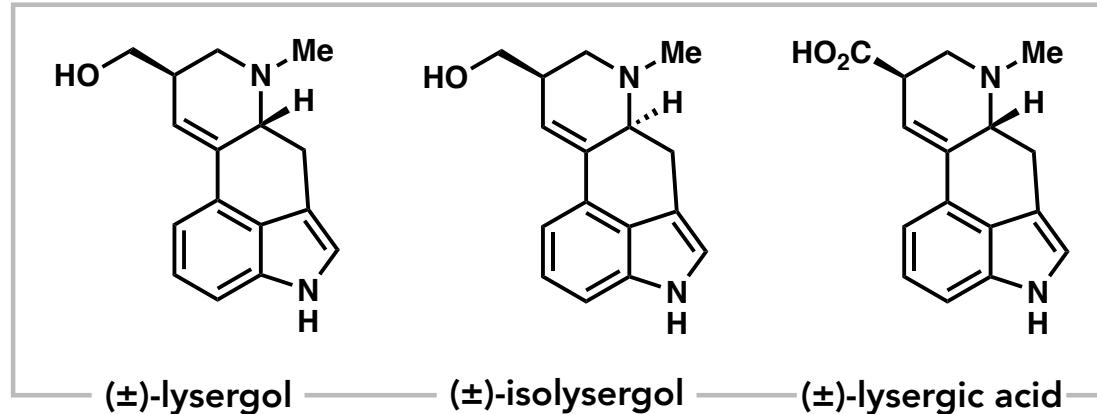
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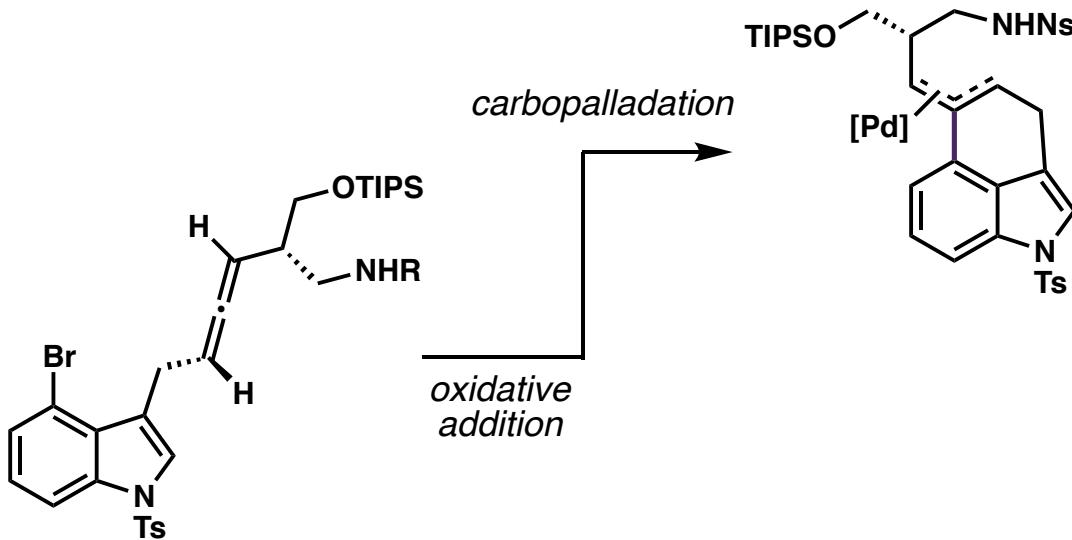
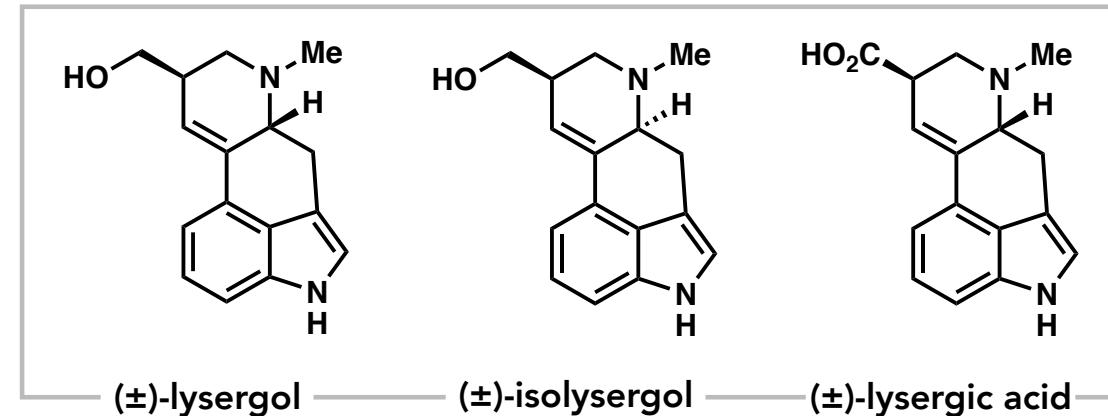
Ohno and Fujii's Syntheses of Ergot Alkaloids



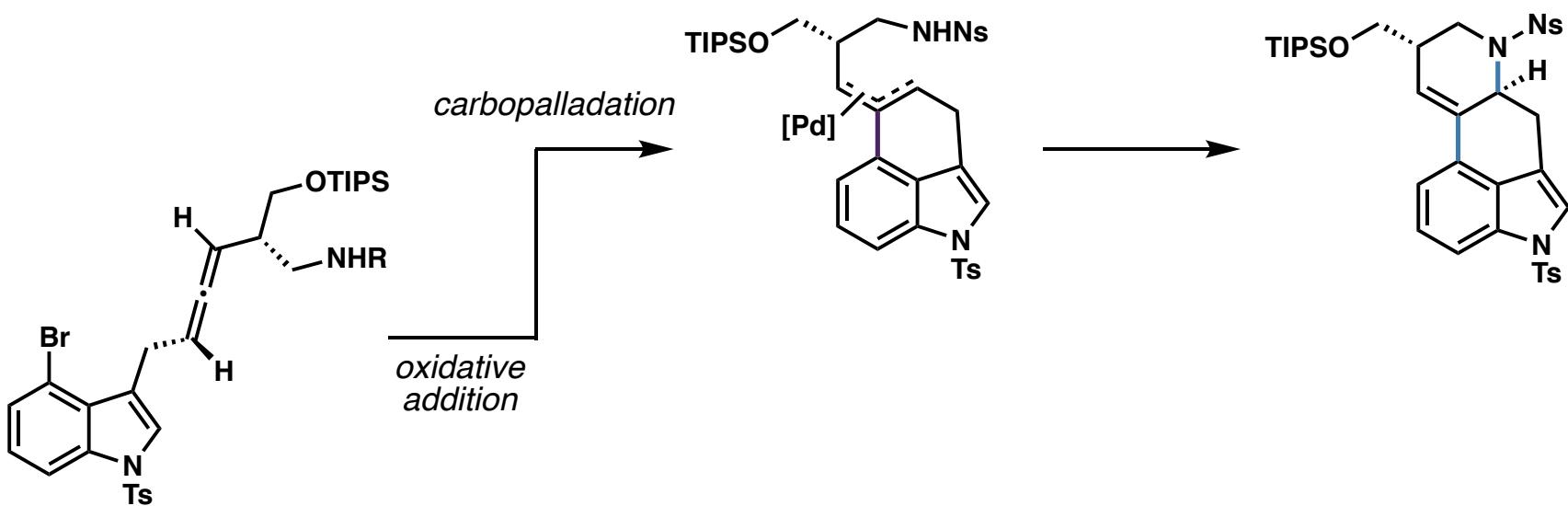
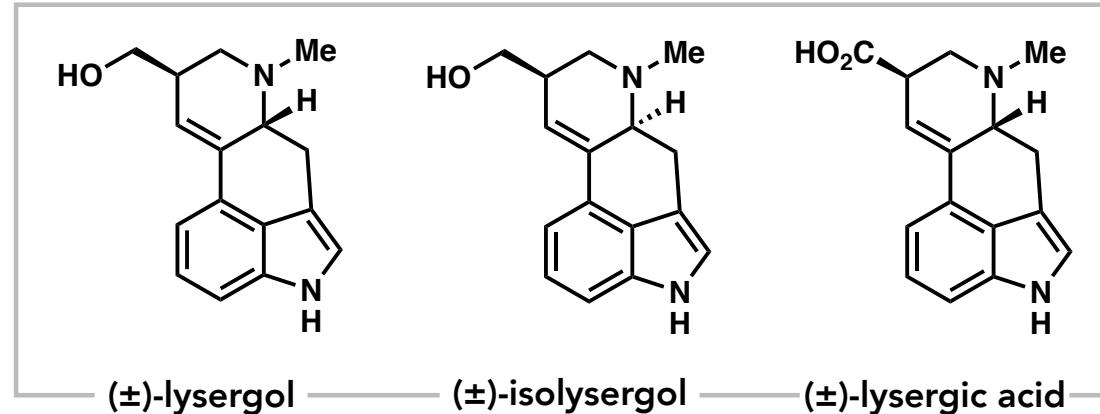
Ohno and Fujii's Syntheses of Ergot Alkaloids



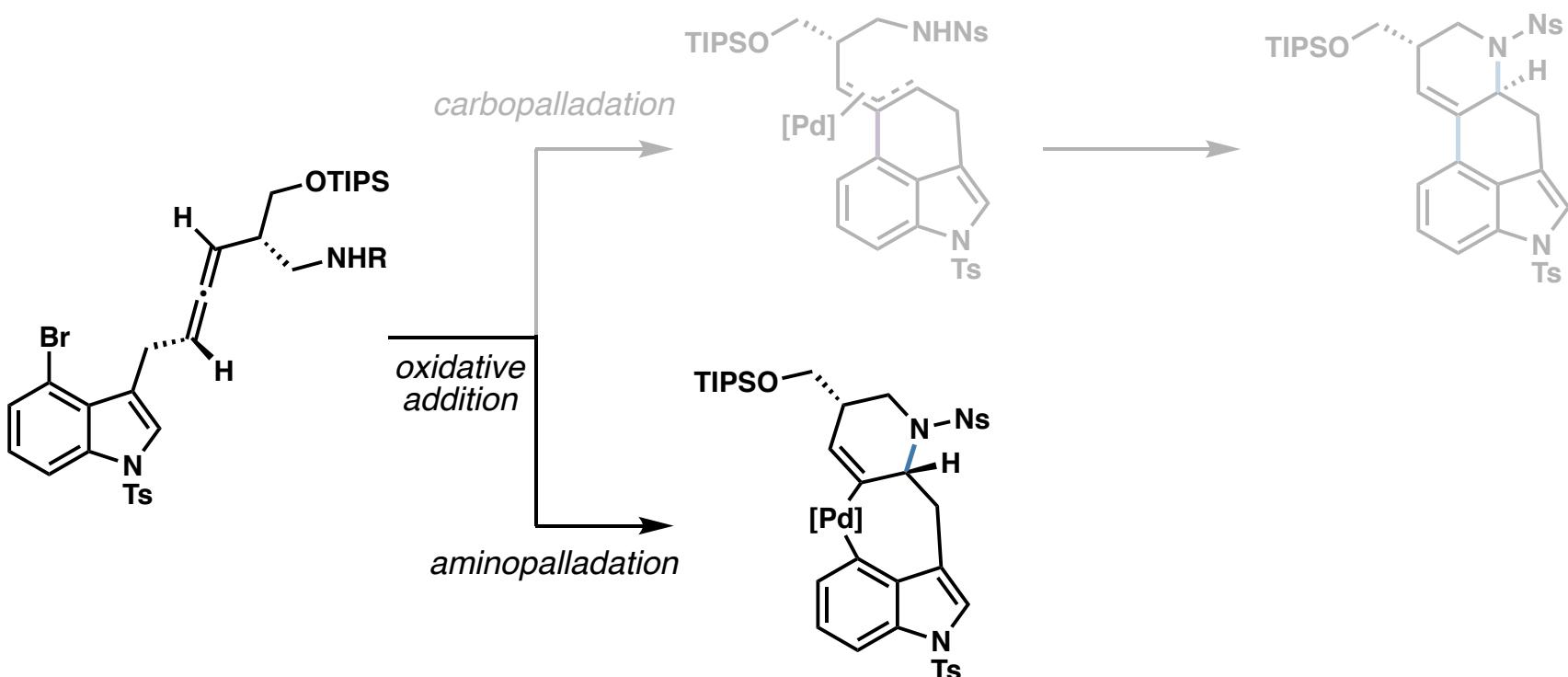
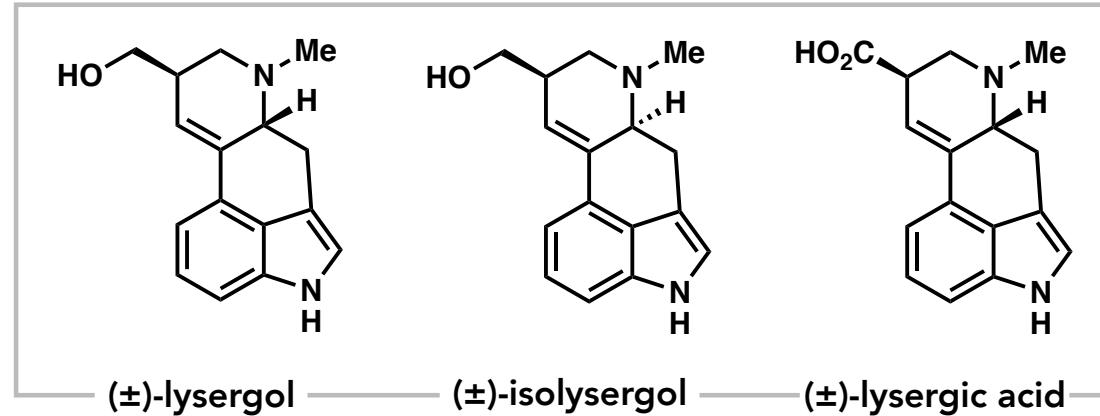
Ohno and Fujii's Syntheses of Ergot Alkaloids



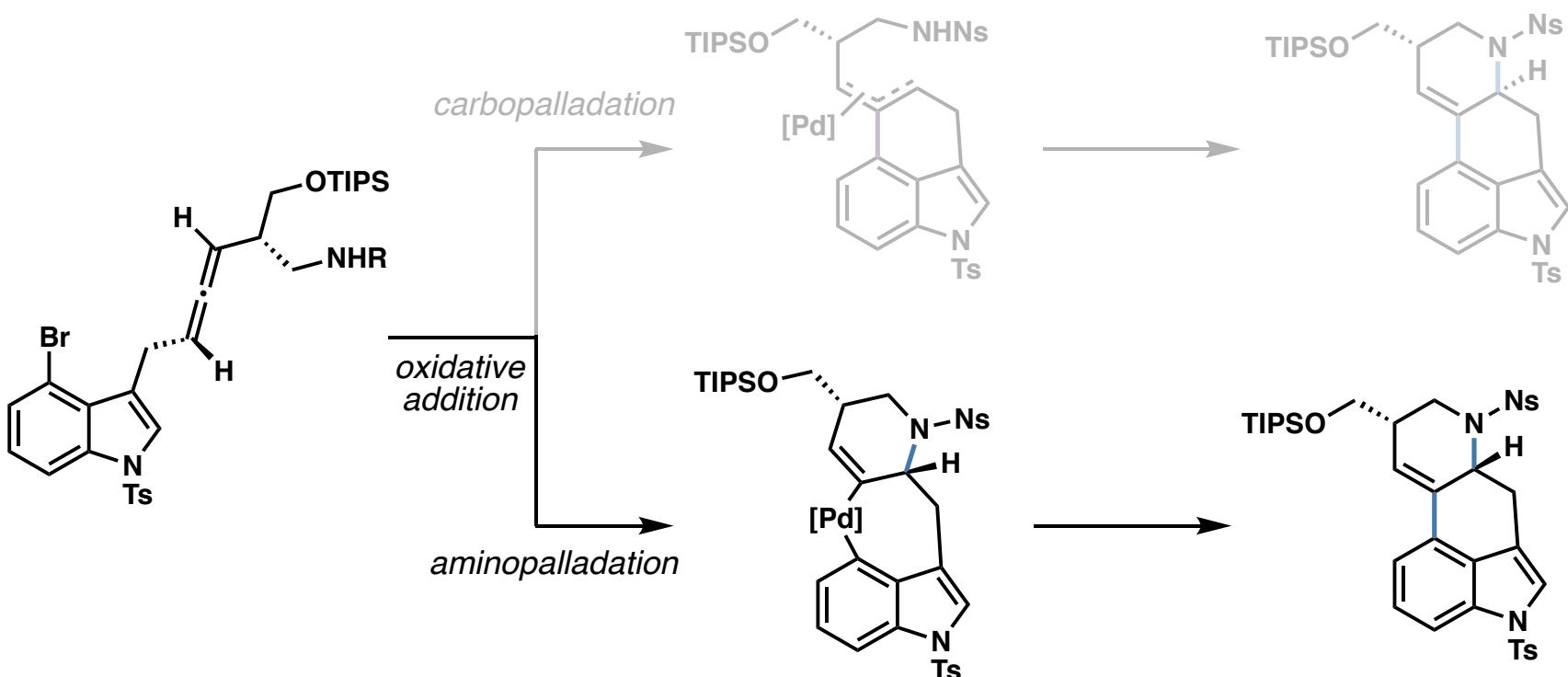
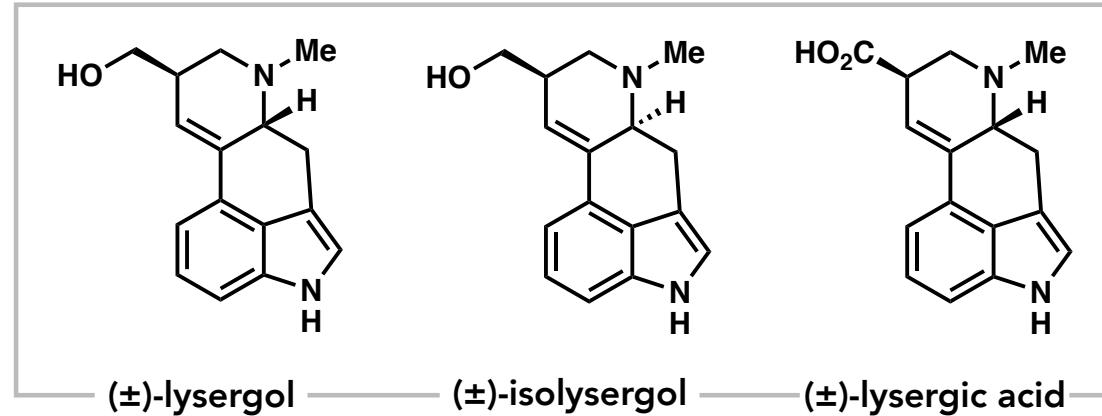
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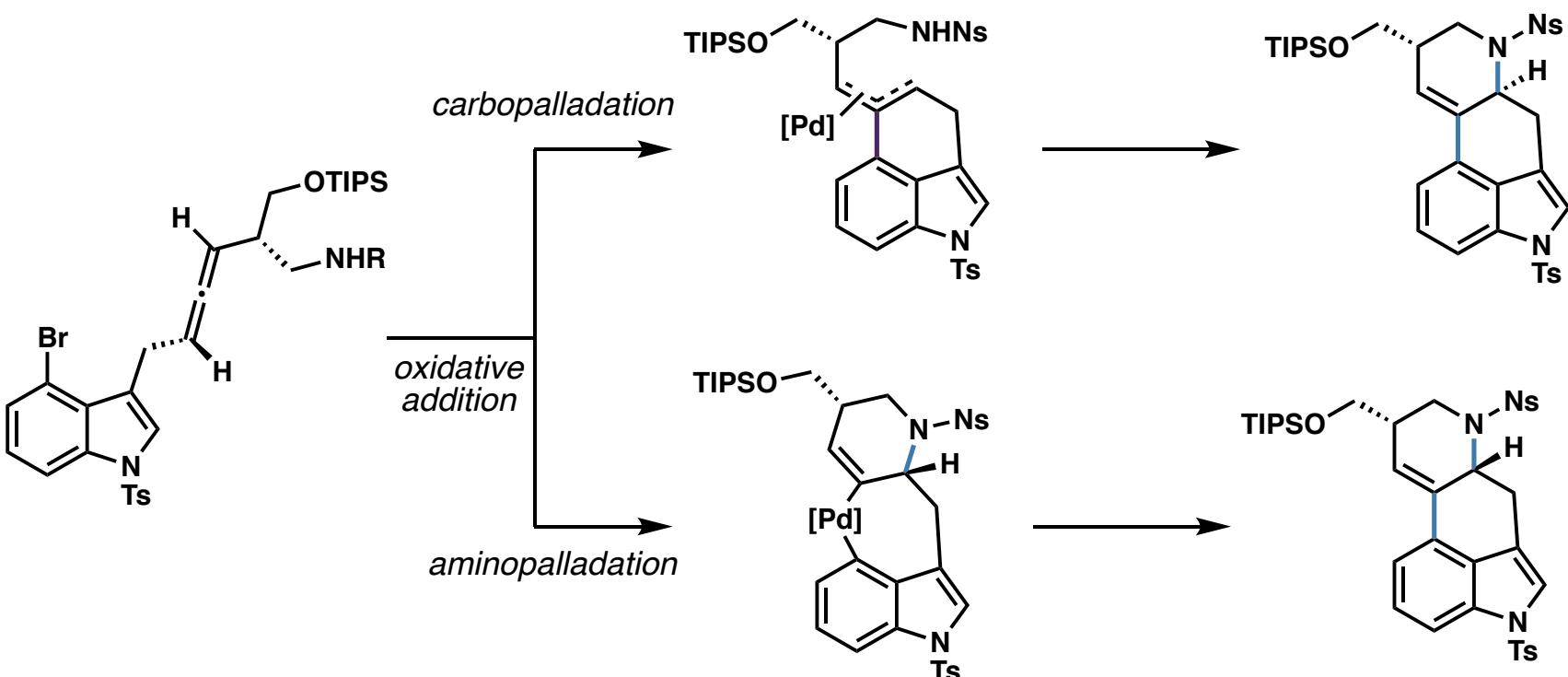
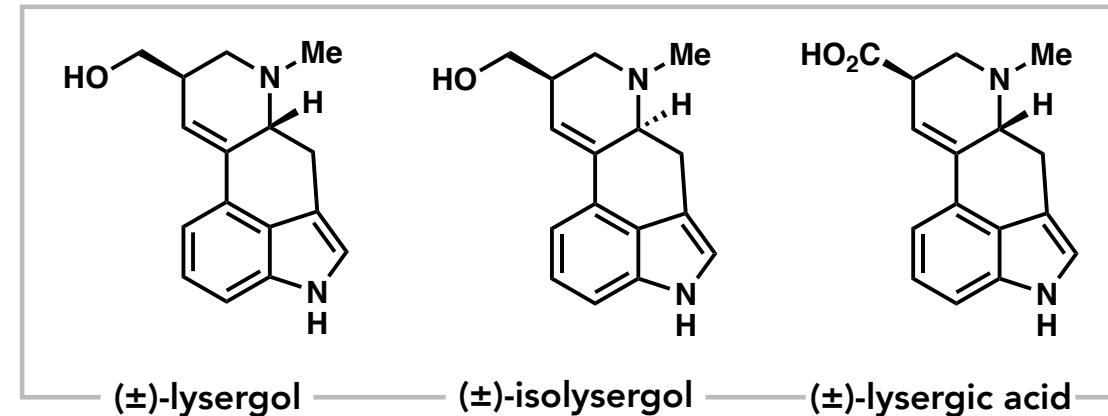
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Ohno and Fujii's Syntheses of Ergot Alkaloids



Ohno and Fujii's Syntheses of Ergot Alkaloids



Palladium-Catalyzed Cascades

