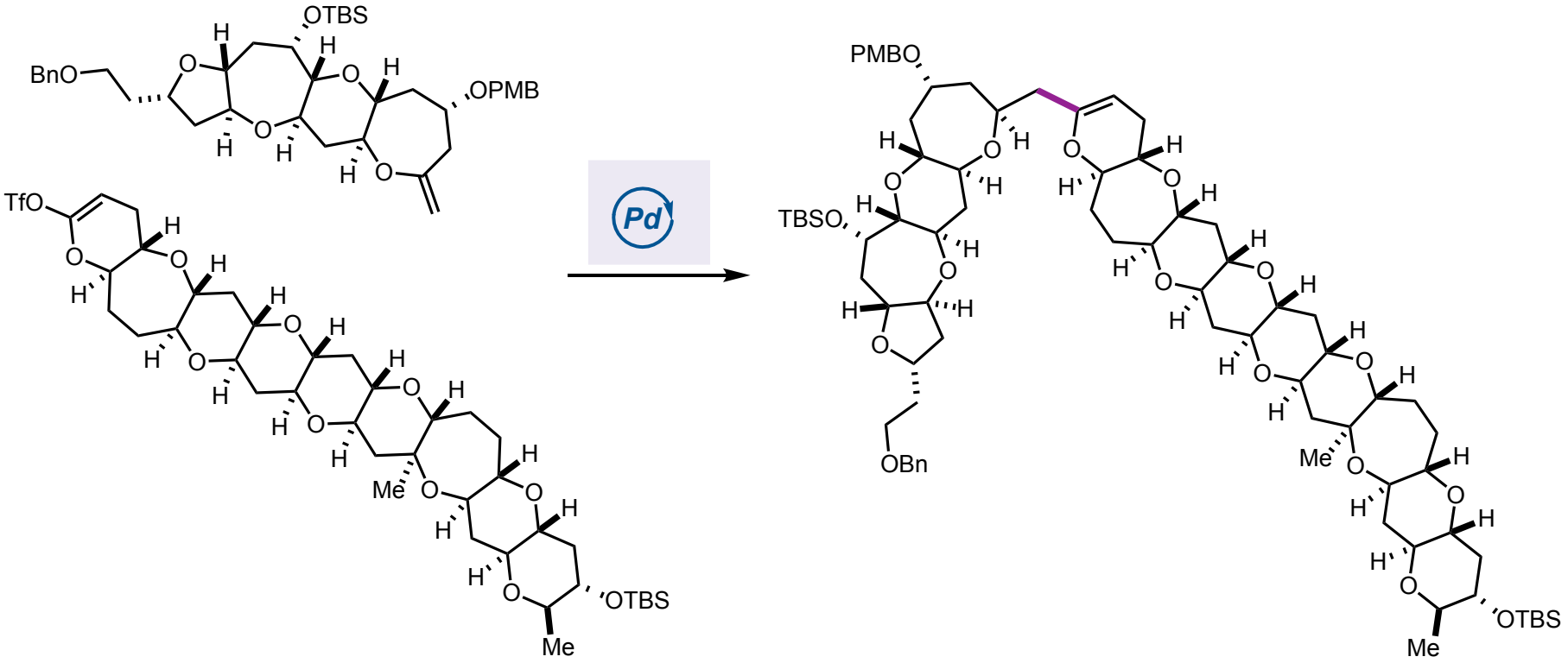
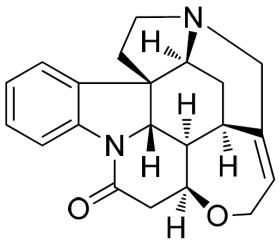
Total Synthesis Enabled by Cross-Coupling

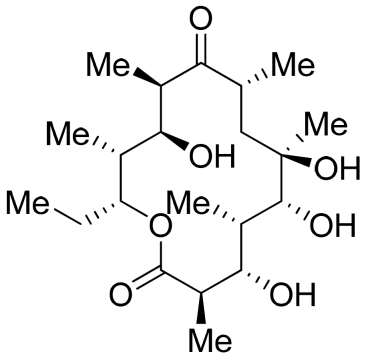


Xiaheng Zhang
MacMillan Group Meeting
May 30th, 2019

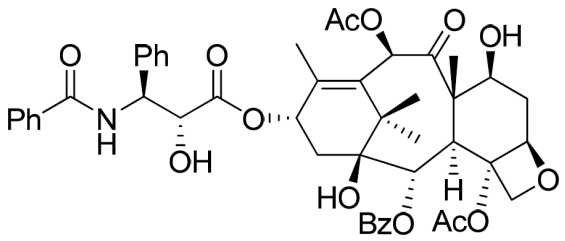
Why Do People Care About Total Synthesis



Strychnine
(Woodward, 1954)



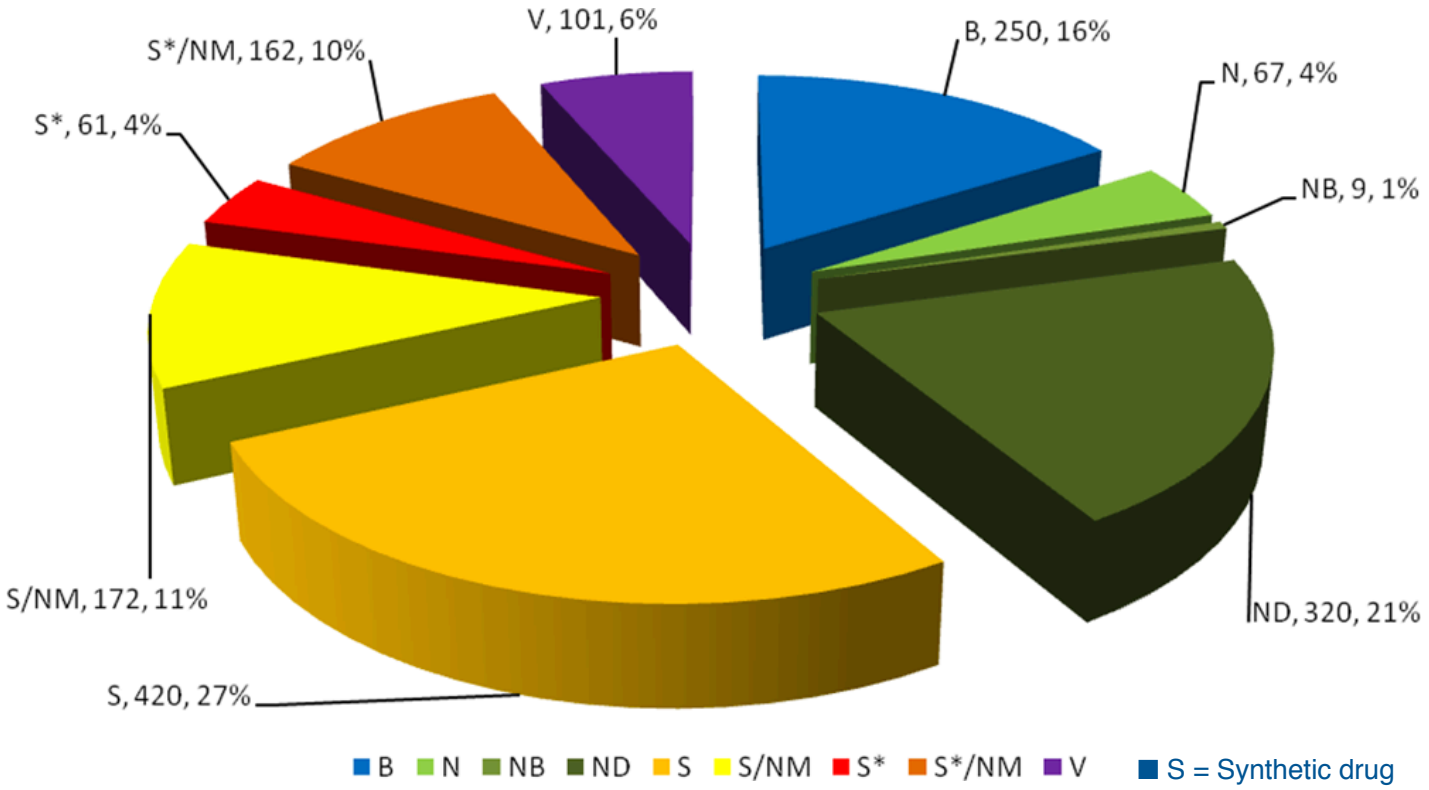
Erythronolide B
(Corey, 1978)



Taxol
(Nicolaou, 1994)

- **invent, test and develop new methodology**
- **produce bioactive molecules**
- **prepare analogs for drug discovery**
- **foundamental study cases for process chemistry**

Why Do People Care About Total Synthesis

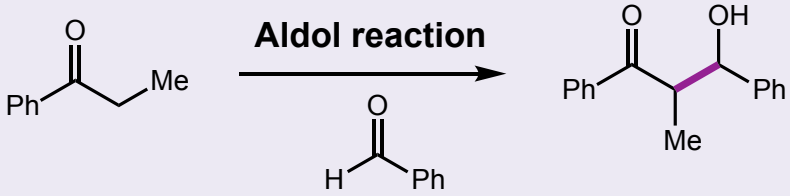


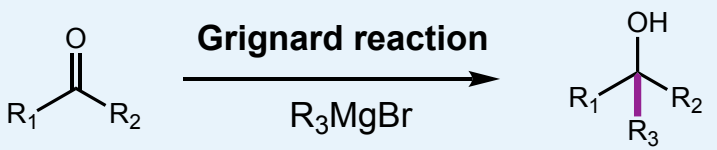
All new approved drugs 1981–2014

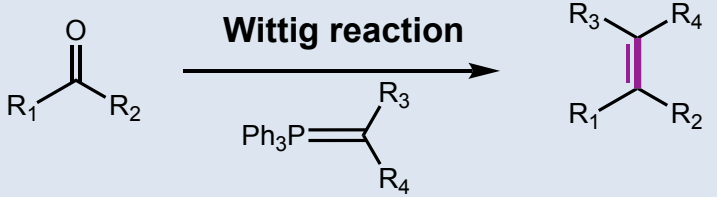
■ More than 50% approved drugs are synthetic drugs

Cragg, G. M.; Newman, D. J. *J. Nat. Prod.* **2016**, *79*, 629.

The Most Common Synthetic Tools in the Total Synthesis







What's next? Cross-Coupling Reaction

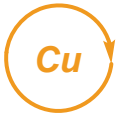
Total Synthesis Enabled by Cross-Coupling

Outline

Palladium-Catalyzed Cross-Coupling in Total Synthesis

Iron-Catalyzed Cross-Coupling in Total Synthesis

Copper-Catalyzed Cross-Coupling in Total Synthesis



Nickel-Catalyzed Cross-Coupling in Total Synthesis

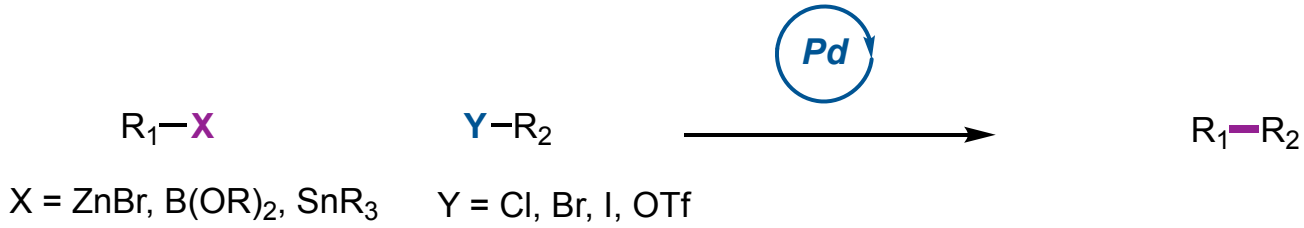
Total Synthesis Enabled by Cross-Coupling

Outline

Palladium-Catalyzed Cross-Coupling in Total Synthesis

Palladium-Catalyzed Cross-Coupling in Total Synthesis

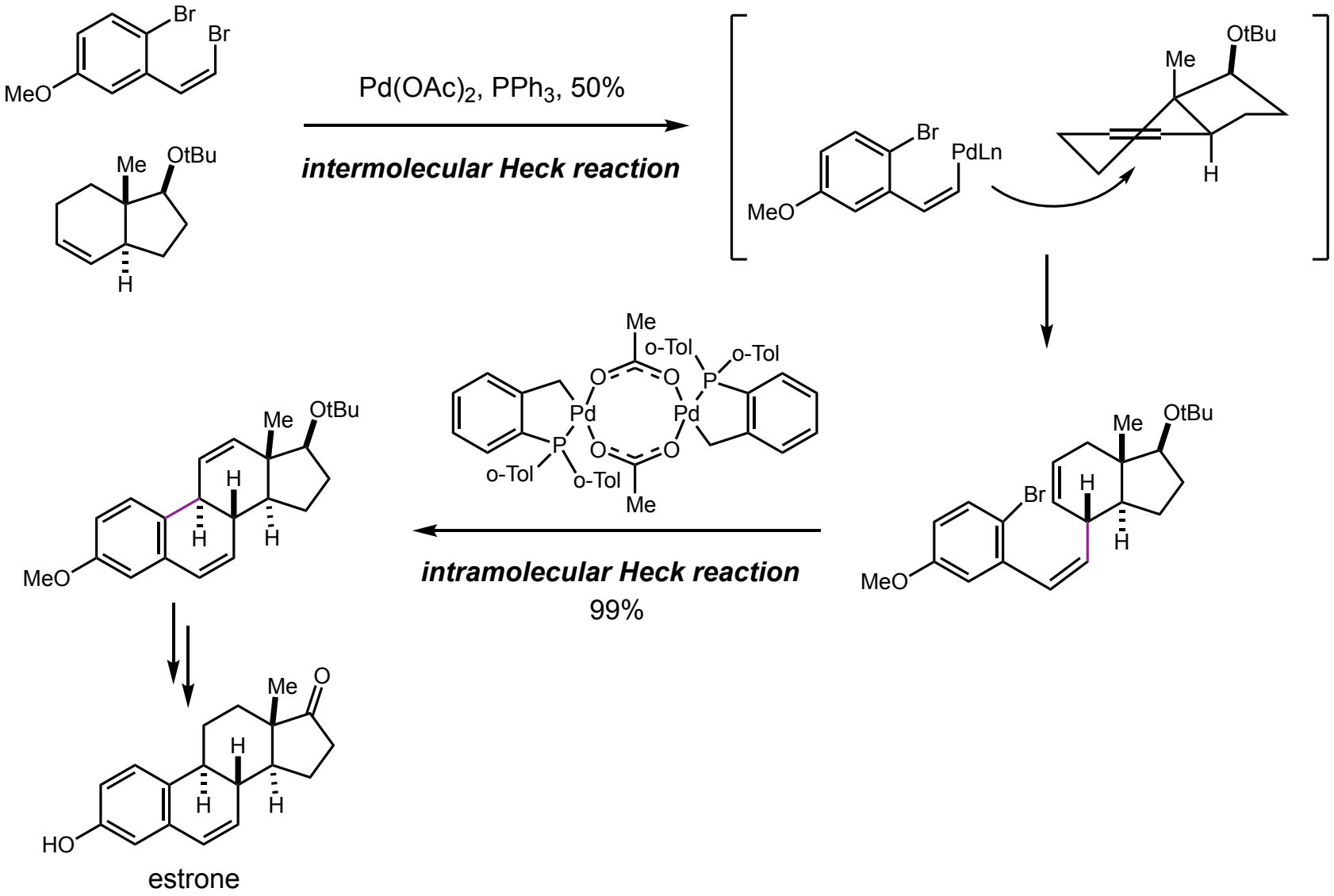
Suzuki, Stille, Negishi reaction



Heck reaction

Sonogashira reaction

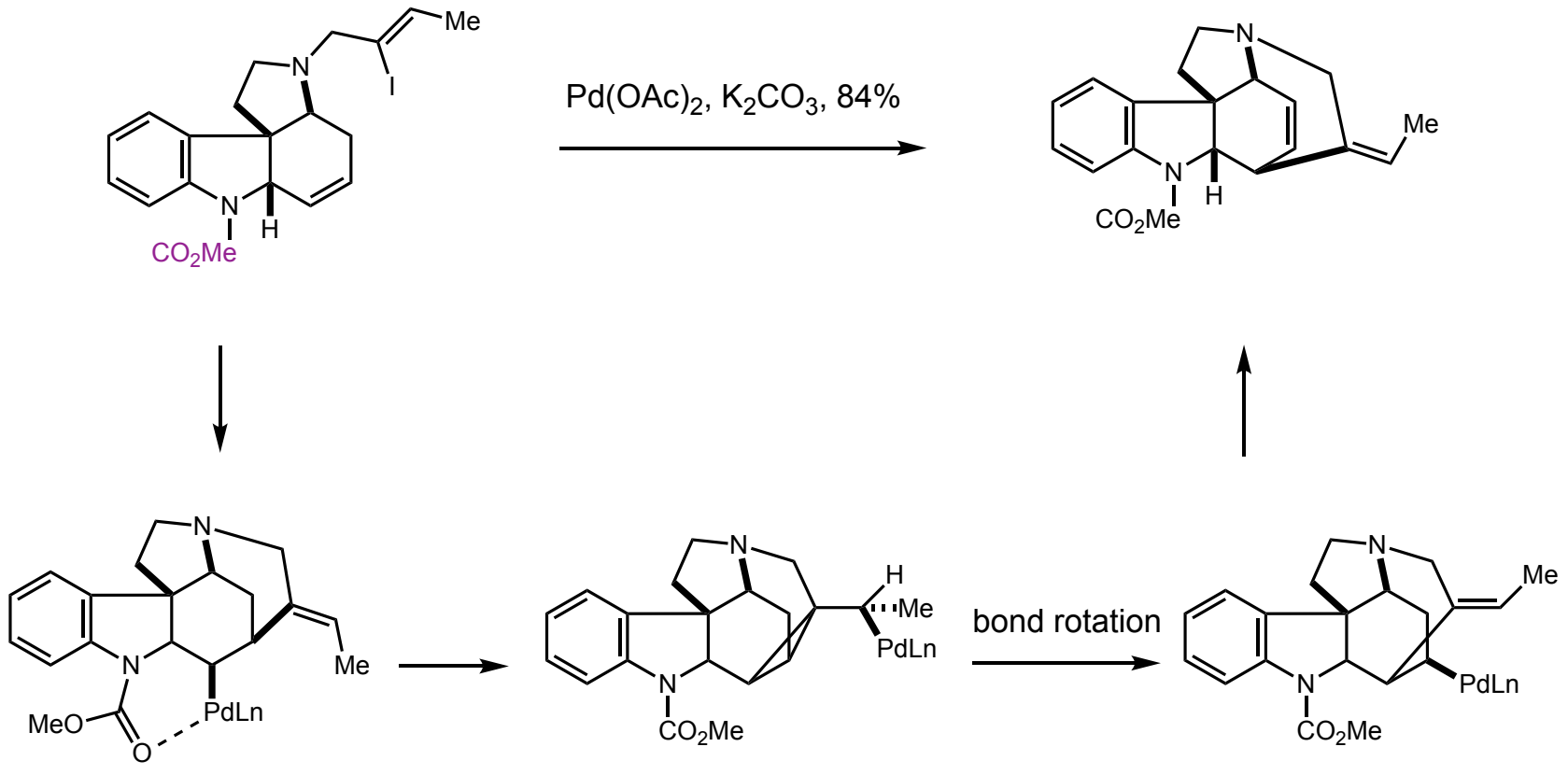
Sequential Heck Reactions in the Enantioselective Synthesis of Estrone



estrone

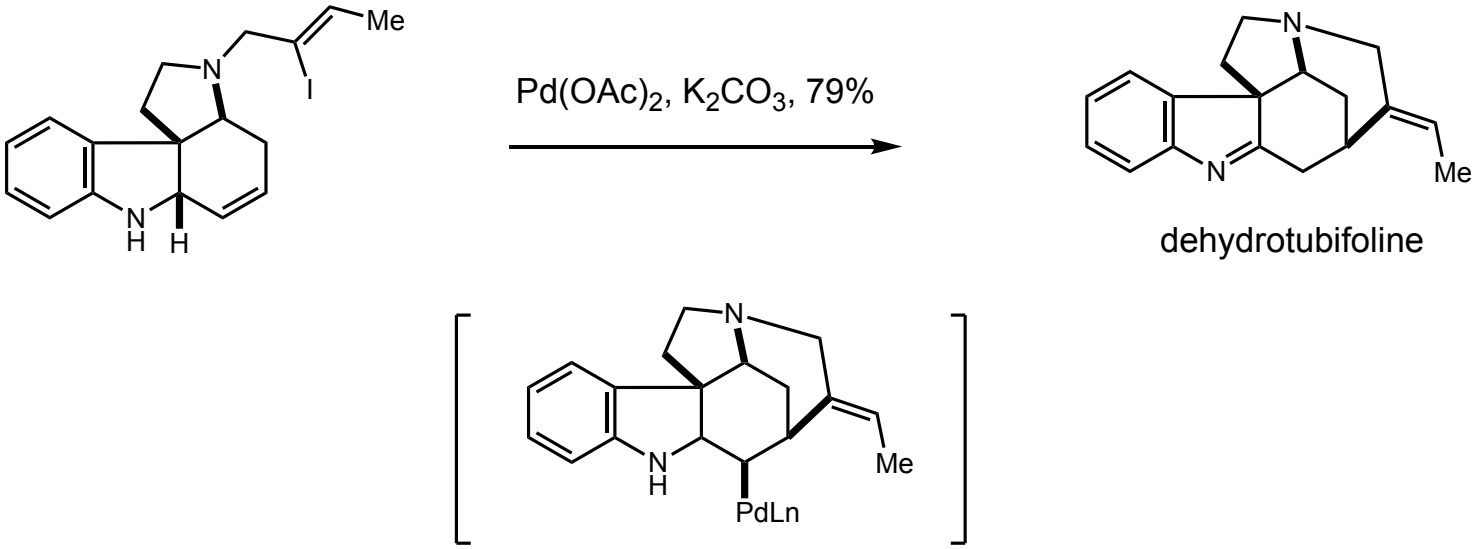
L. F. Tietze, T. NVbel, M. Spescha, *J. Am. Chem. Soc.* **1998**, *120*, 8971.

Intramolecular Heck Reactions in the Total Synthesis of Dehydrotubifoline



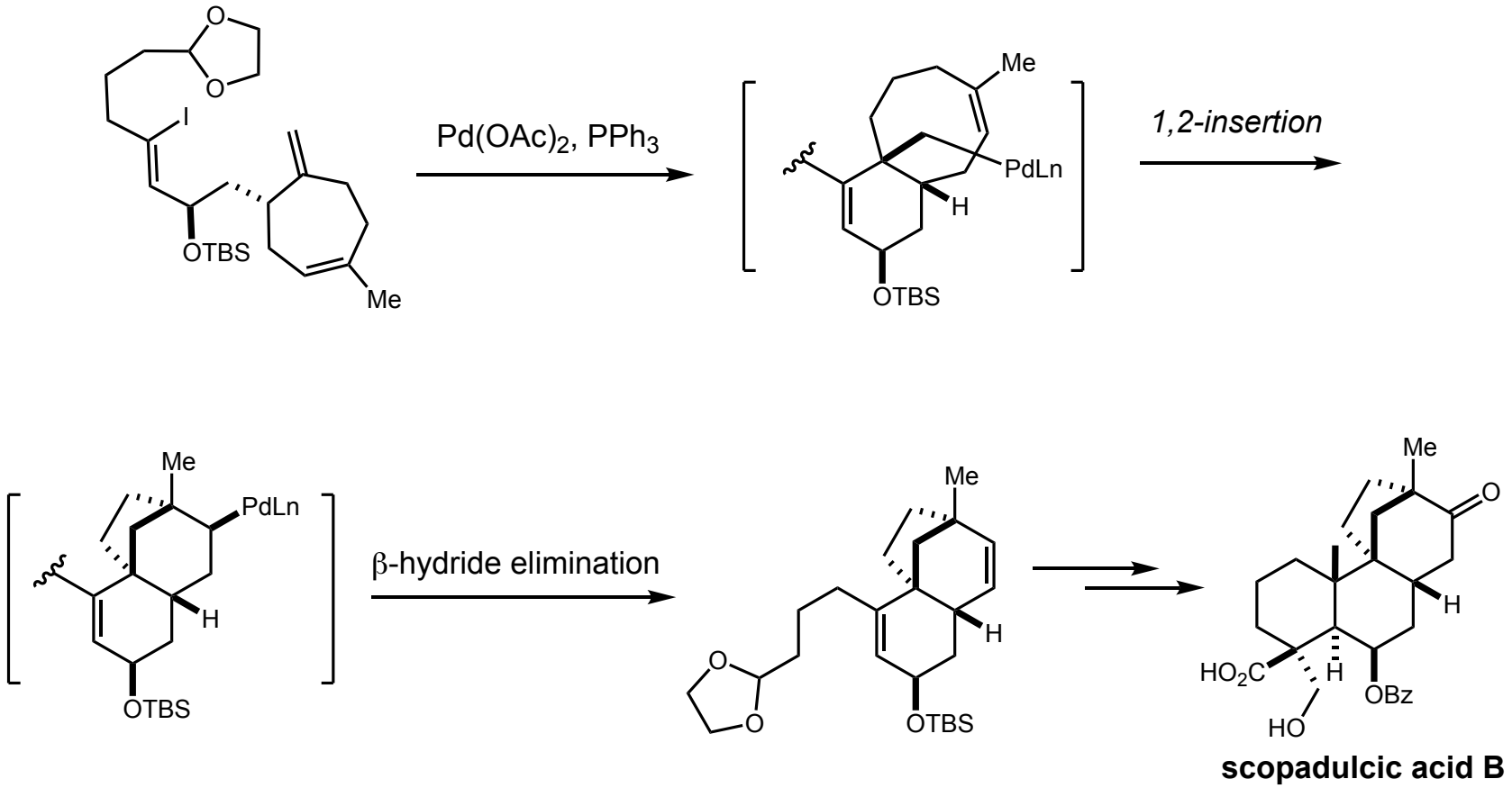
V. H. Rawal, C. Michoud, R. F. Monestel, *J. Am. Chem. Soc*. **1993**, *115*, 3030.

Intramolecular Heck Reactions in the Total Synthesis of Dehydrotubifoline



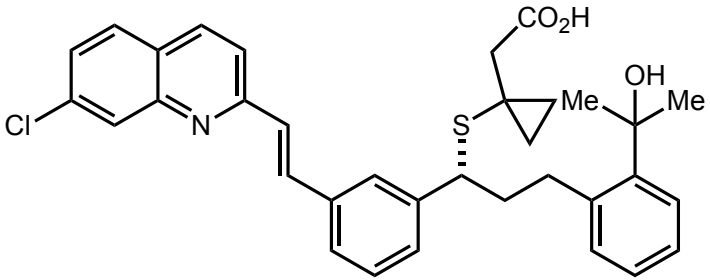
V. H. Rawal, C. Michoud, R. F. Monestel, *J. Am. Chem. Soc*. **1993**, *115*, 3030.

Intramolecular Heck Cascade for the Total Synthesis of Scopadulcic Acid B



L. E. Overman, D. J. Ricca, V. D. Tran, *J. Am. Chem. Soc.* **1993**, *115*, 2042.

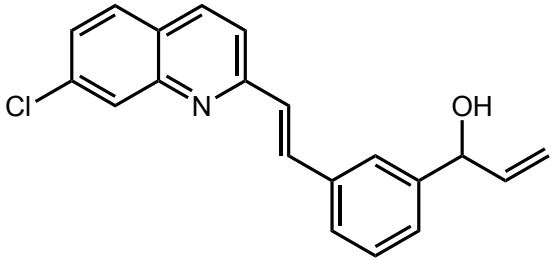
The Use of Heck Reaction in the Commercial Synthesis of Singulair

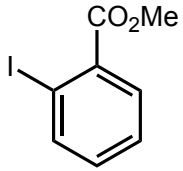


Singulair, by Merck

prevent asthma attacks

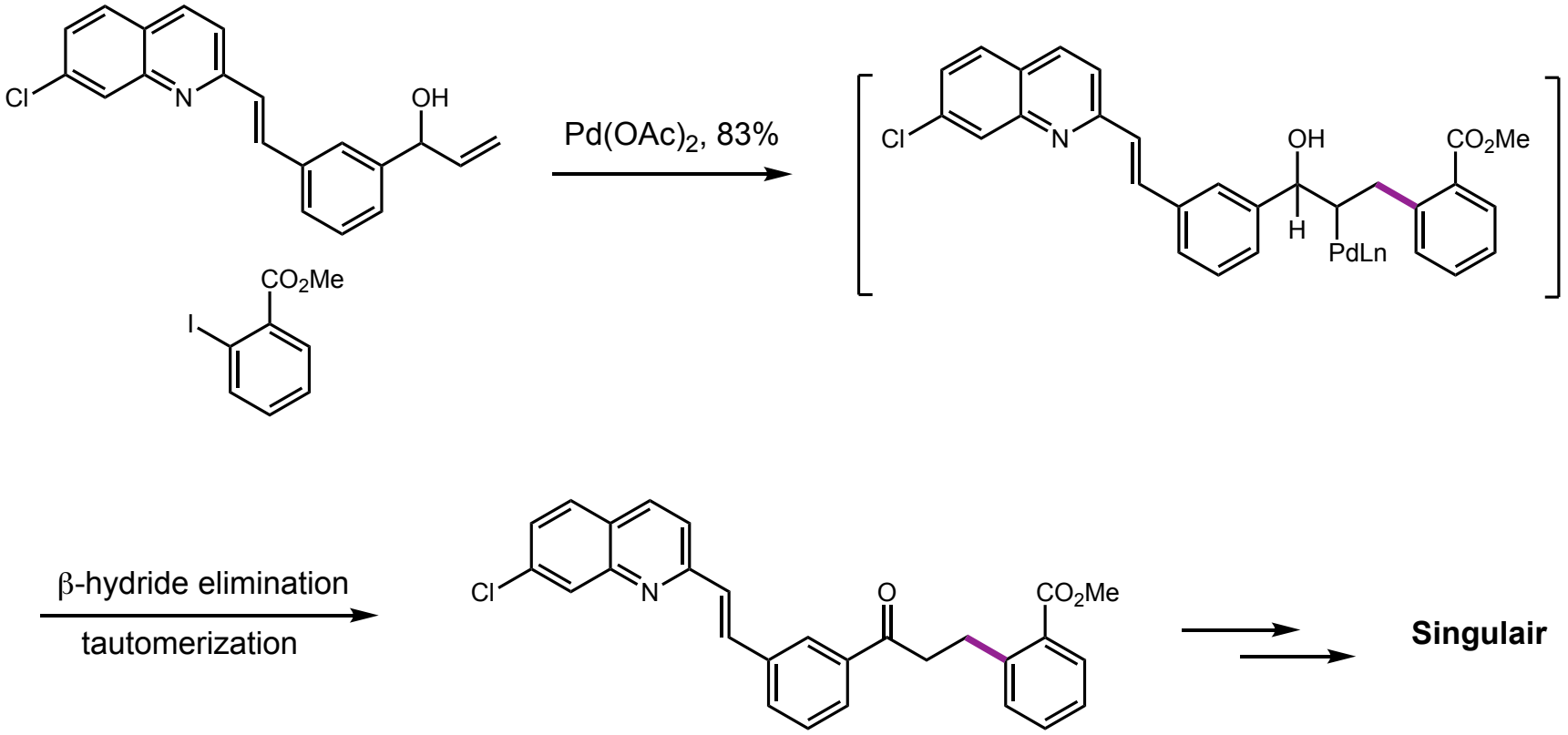
intermolecular Heck





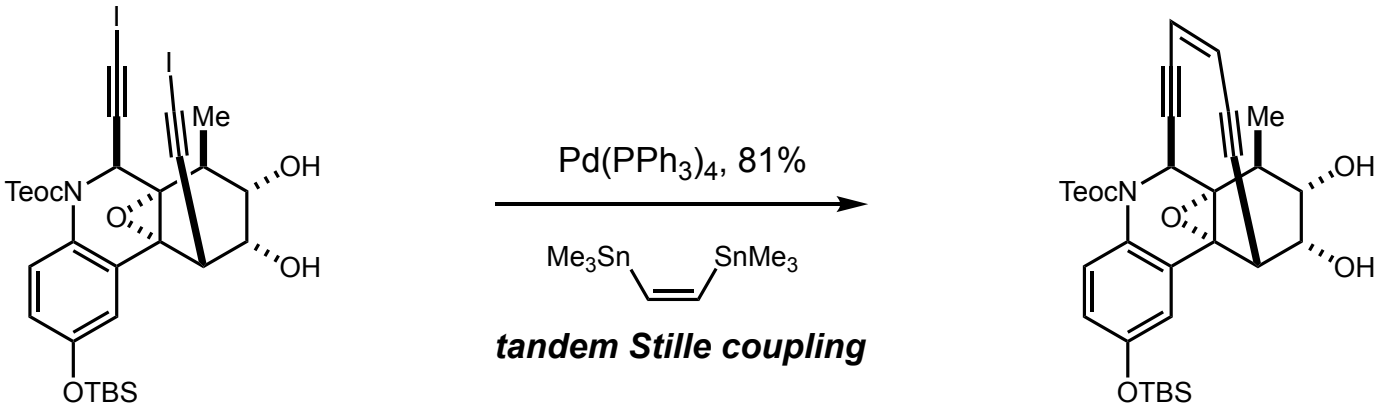
Merck Team. *J. Org. Chem*. **1993**, *58*, 3731.
Merck Team. *J. Org. Chem.* **1996**, *61*, 3398.

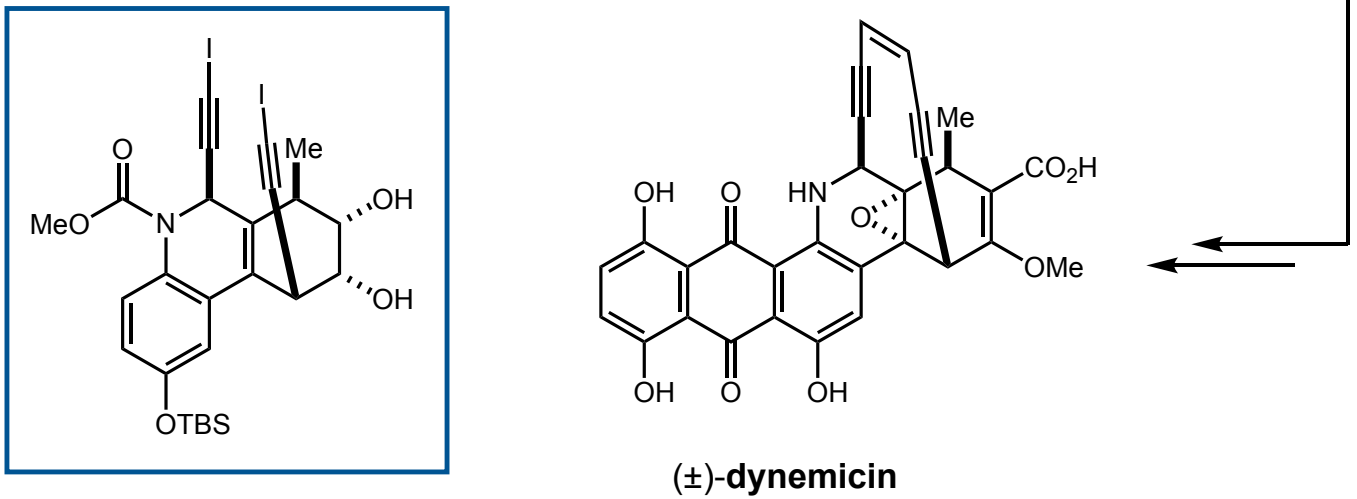
The Use of Heck Reaction in the Commercial Synthesis of Singulair



Merck Team. *J. Org. Chem.* **1993**, *58*, 3731.
Merck Team. *J. Org. Chem.* **1996**, *61*, 3398.

'Stitching Cyclization' Route to the Enediyene Core Synthesis

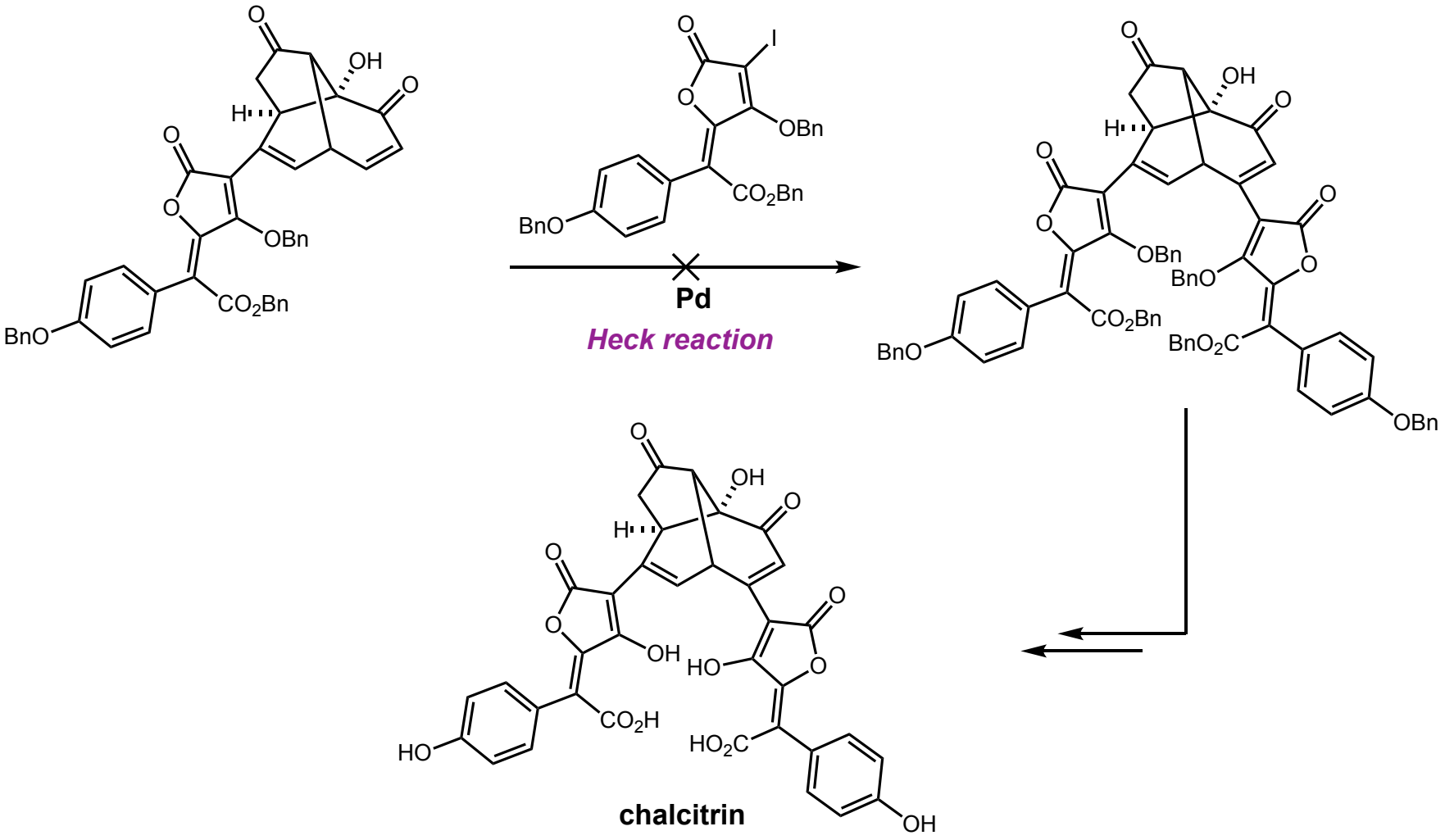




(±)-dynemicin

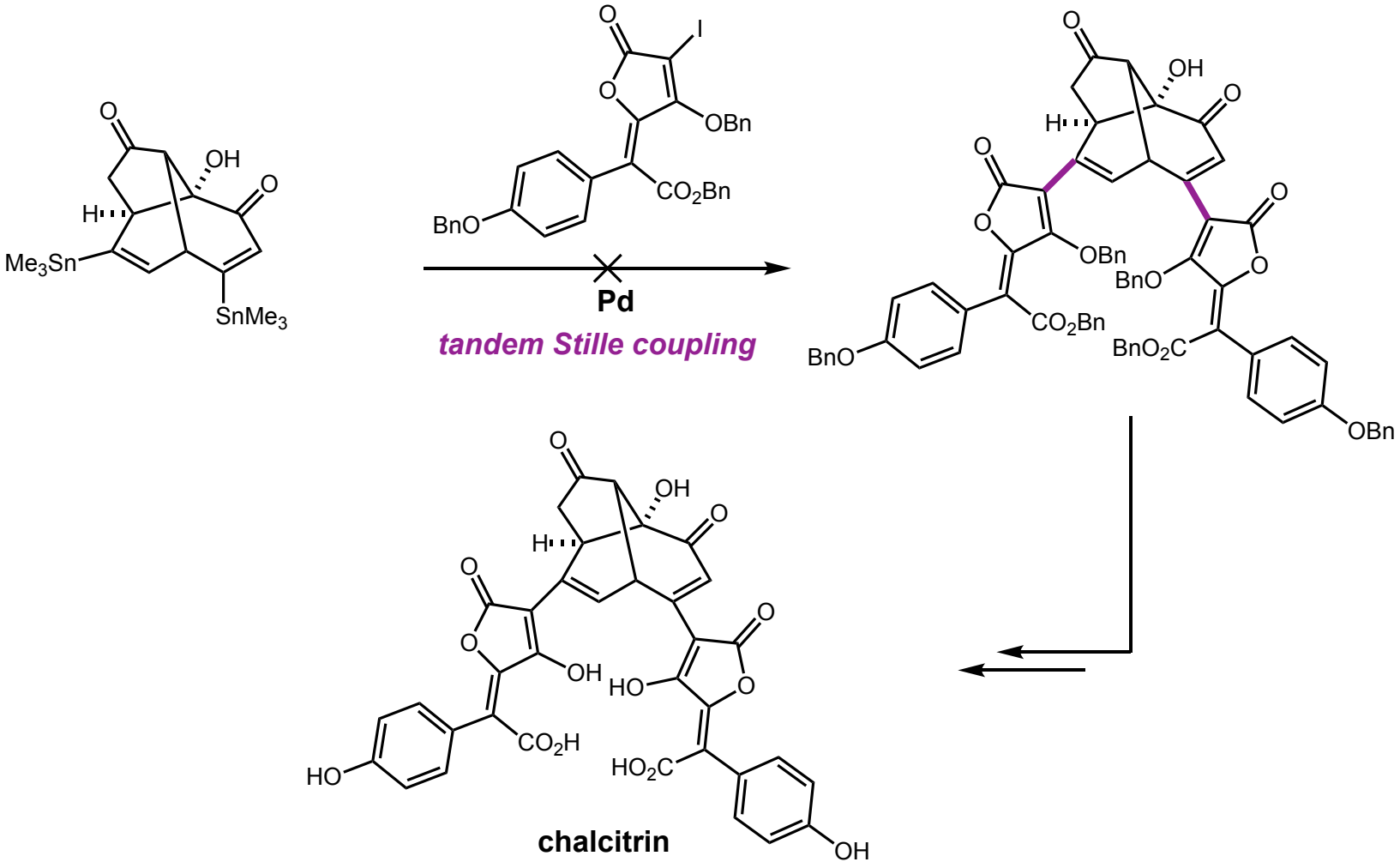
M. D. Shair, T.-Y. Yoon, K. K. Mosny, T. C. Chou, S. J. Danishefsky, *J. Am. Chem. Soc.* **1996**, *118*, 9509.
M. D. Shair, T.-Y. Yoon, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **1995**, *34*, 1721.

Palladium-Catalyzed Cross-Coupling in the Total Synthesis of Chalcitrin



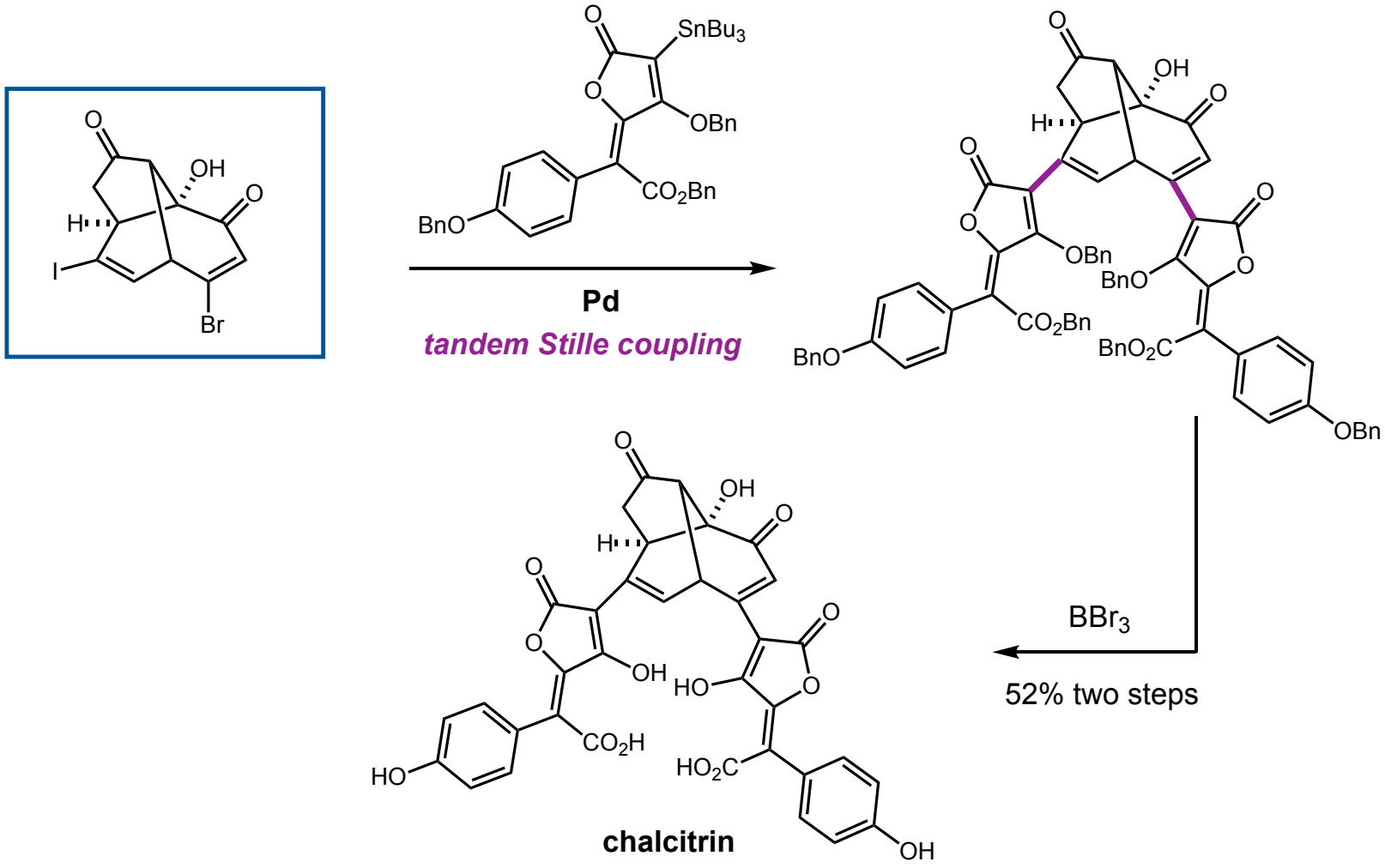
Yang, M.; Yin, F.; Fujno, H.; Snyder, S. *J. Am. Chem. Soc.* **2019**, *141*, 4515.

Palladium-Catalyzed Cross-Coupling in the Total Synthesis of Chalcitrin



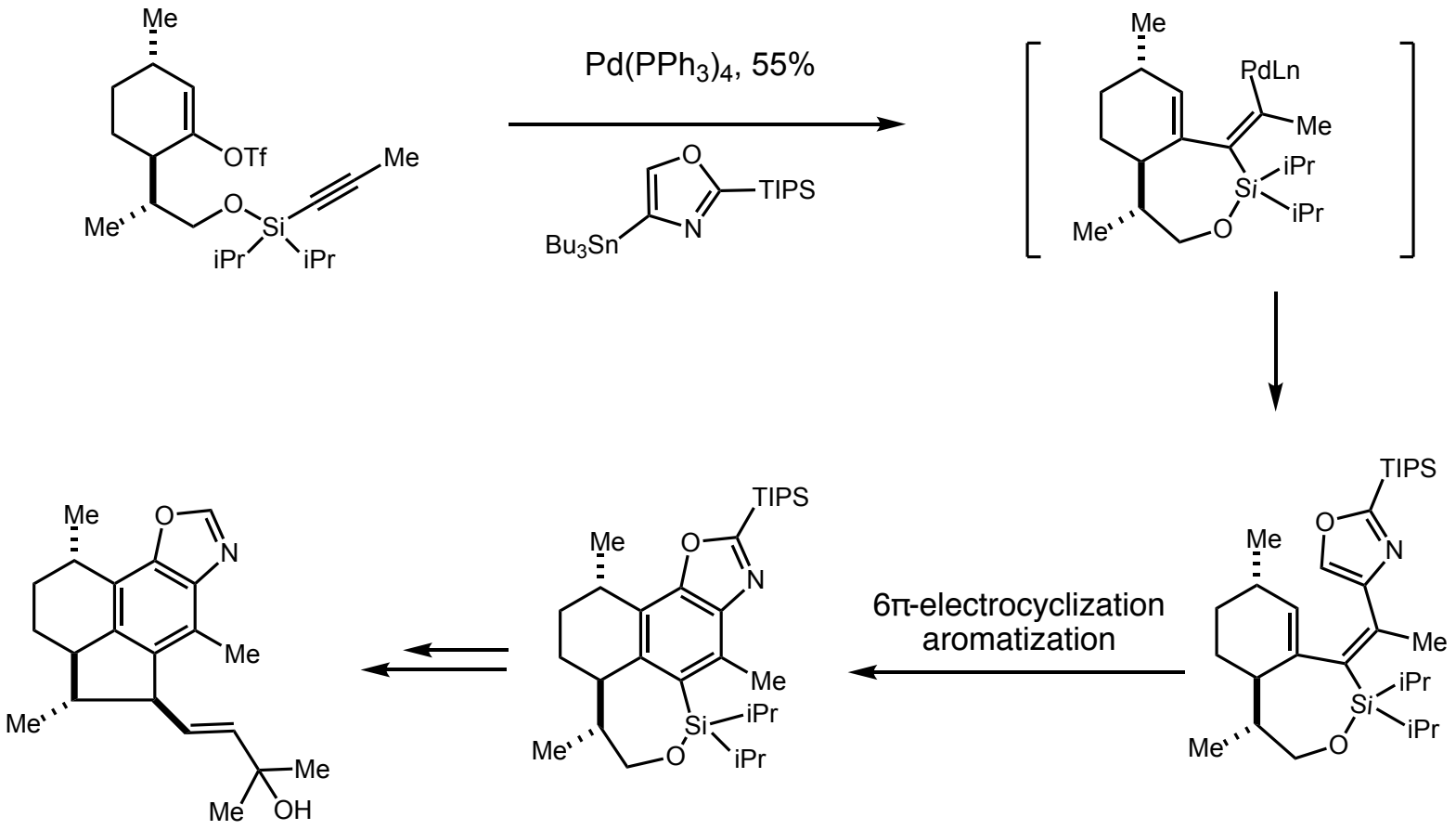
Yang, M.; Yin, F.; Fujno, H.; Snyder, S. *J. Am. Chem. Soc.* **2019**, *141*, 4515.

Palladium-Catalyzed Cross-Coupling in the Total Synthesis of Chalcitrin



Yang, M.; Yin, F.; Fujno, H.; Snyder, S. *J. Am. Chem. Soc.* **2019**, *141*, 4515.

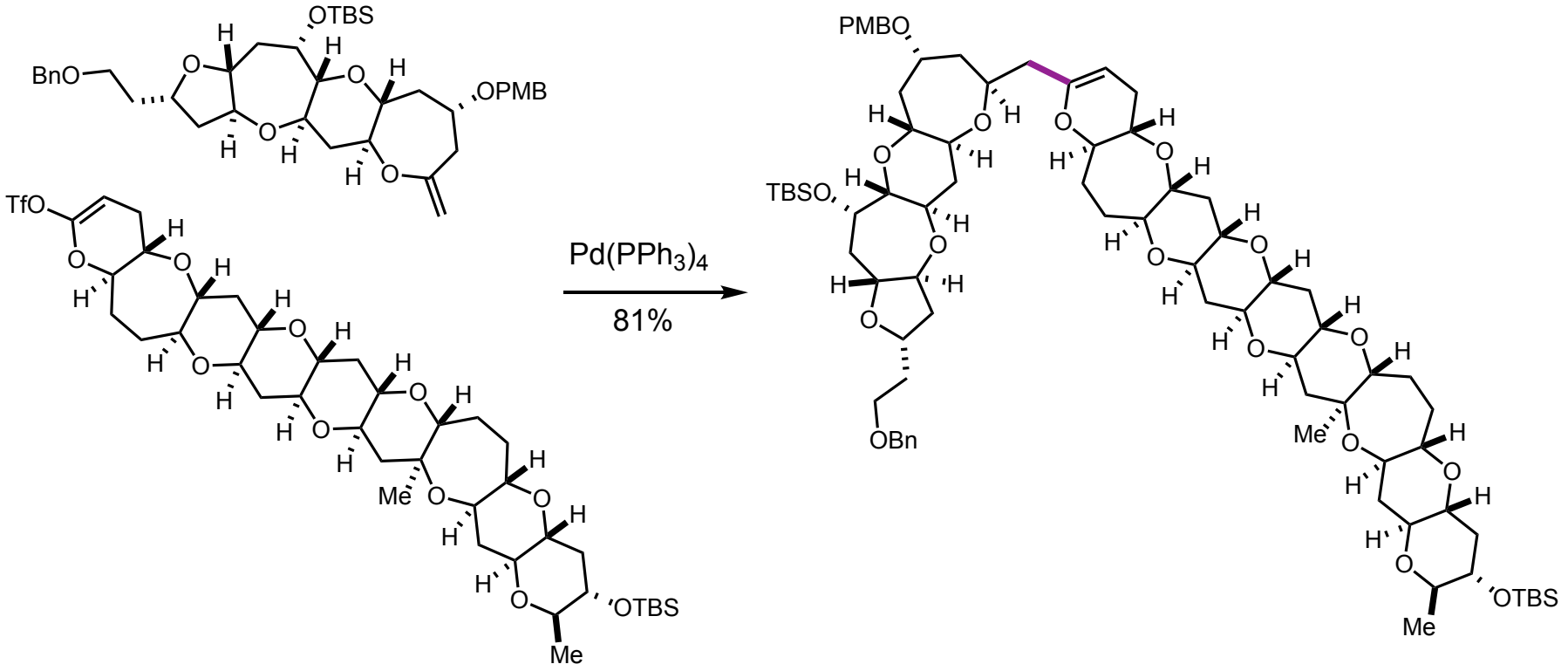
Carbopalladation/Stille Coupling Cascade for the Synthesis of Ileabethoxazole



Ileabethoxazole

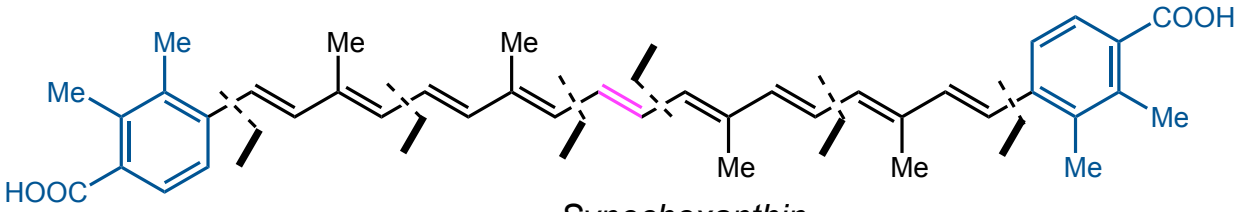
Yang, M.; Yang, X.; Sun, H.; Li, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 2851.

Suzuki-Miyaura Coupling in the Total Synthesis of Gymnocin A

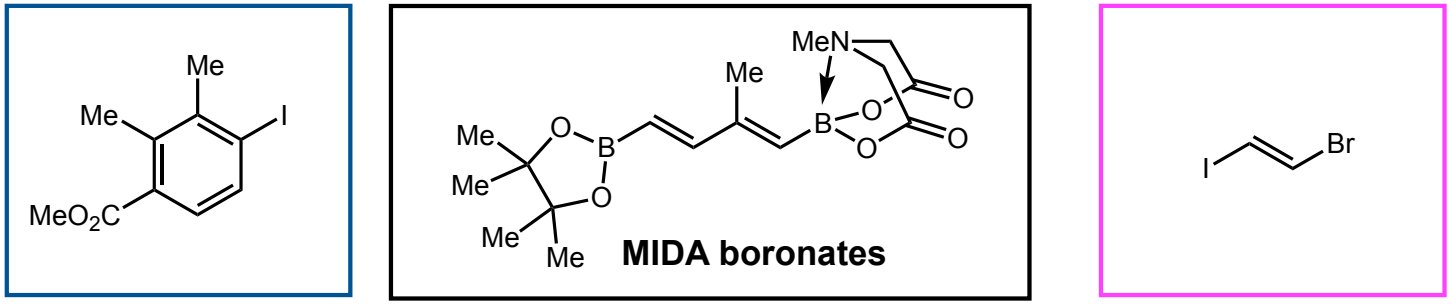


Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 14294.

Iterative Cross-Coupling in the Total Synthesis of Synechoxanthin

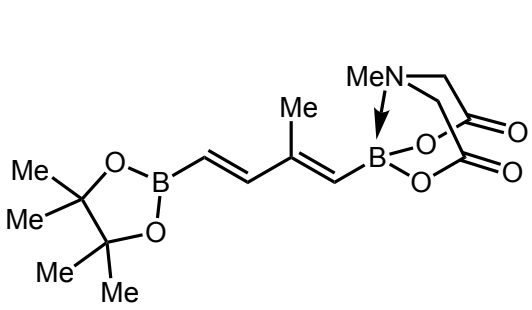


Synechoxanthin

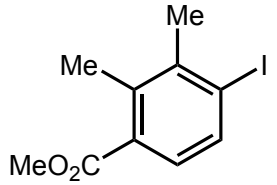


Fujii, S.; Chang, S. Y.; Burke, M. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7862.

Iterative Cross-Coupling in the Total Synthesis of Synechoxanthin

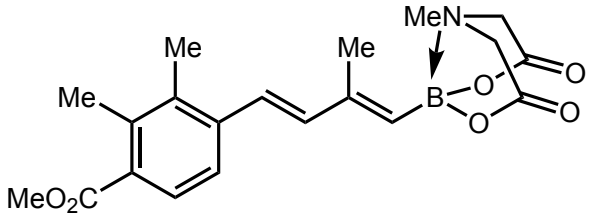


MIDA boronates



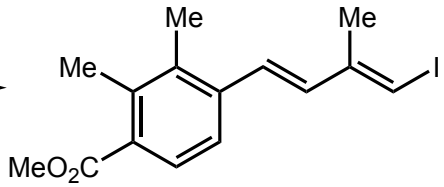
$PdCl_2dppf$, K_3PO_4

70%



NaOMe, I_2

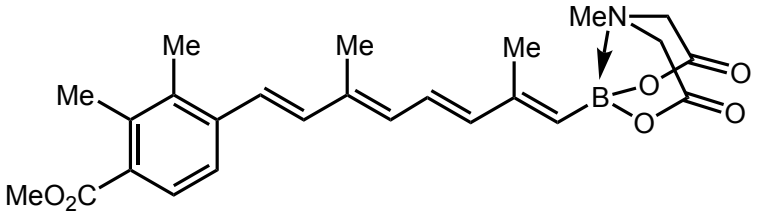
99%



MIDA boronates

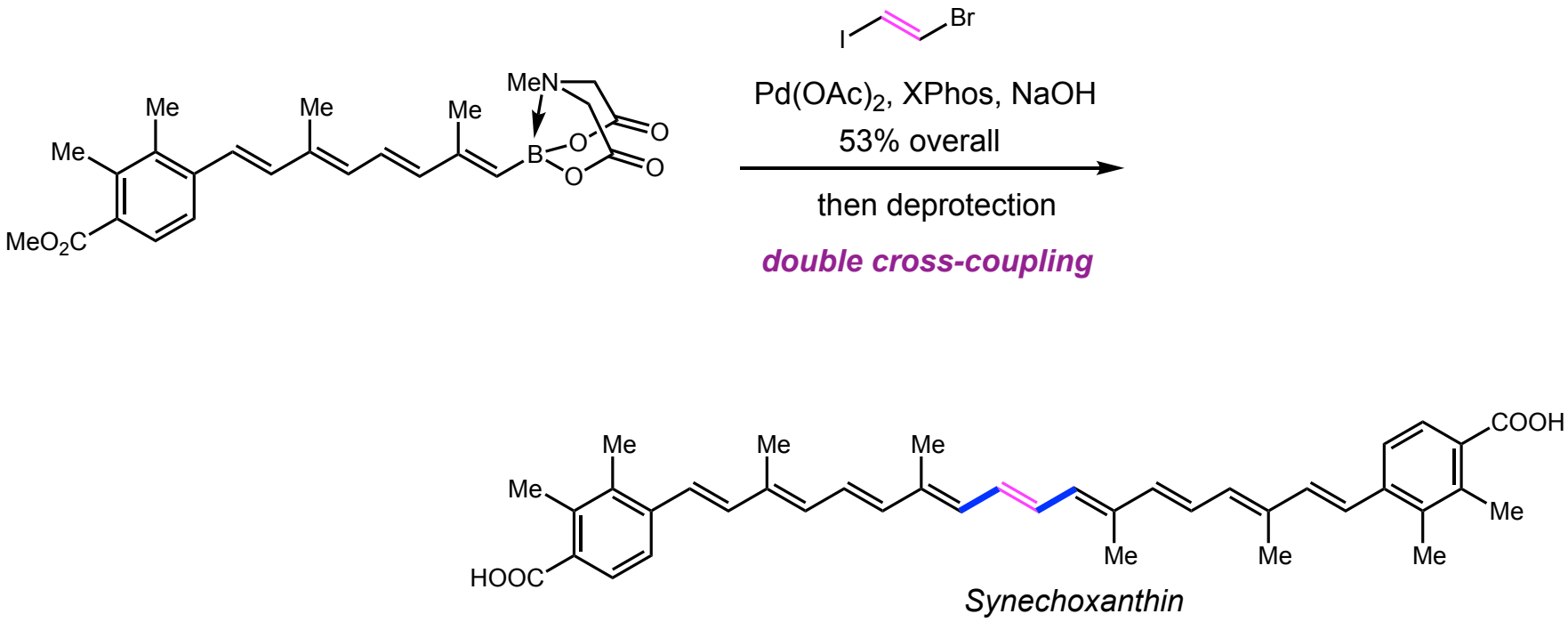
$PdCl_2dppf$, K_3PO_4

65%



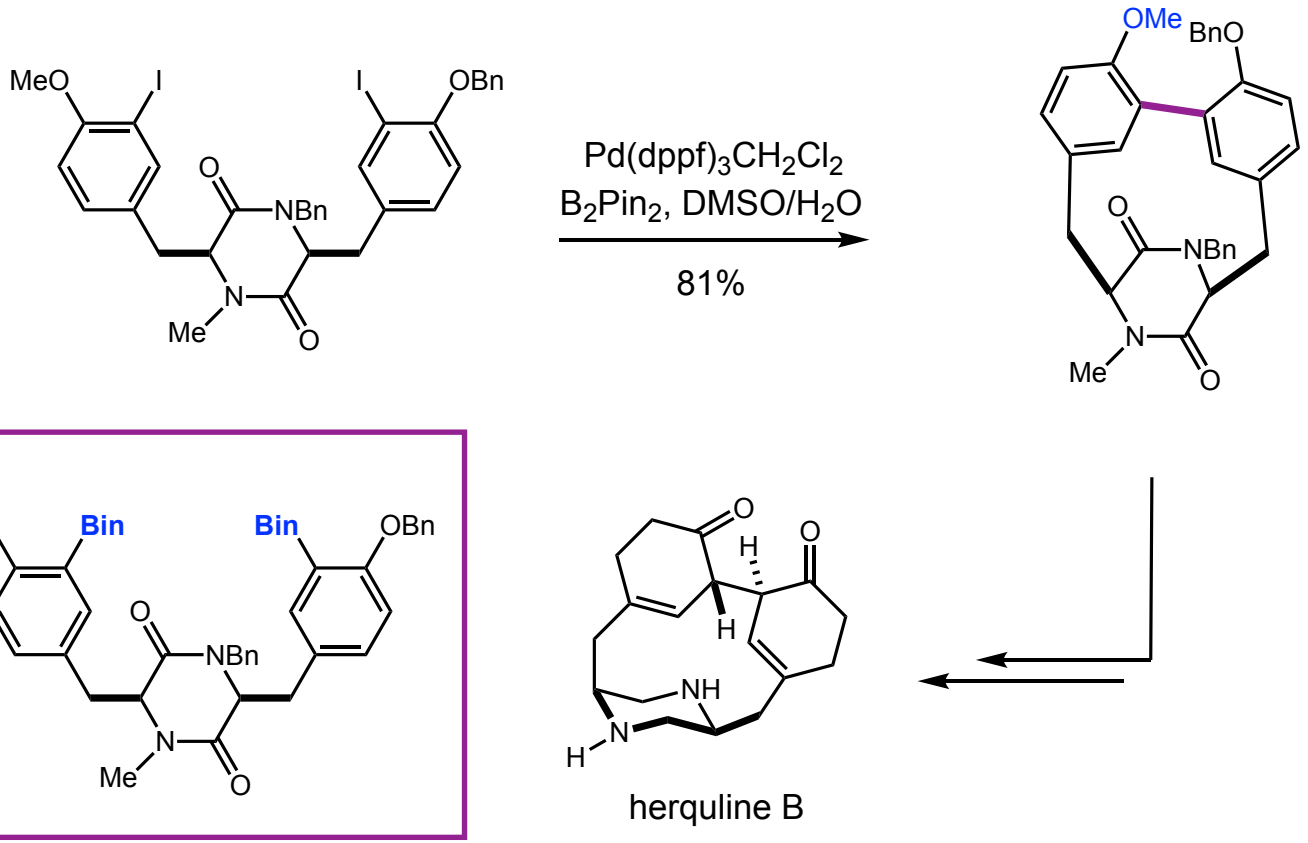
Fujii, S.; Chang, S. Y.; Burke, M. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7862.

Iterative Cross-Coupling in the Total Synthesis of Synechoxanthin



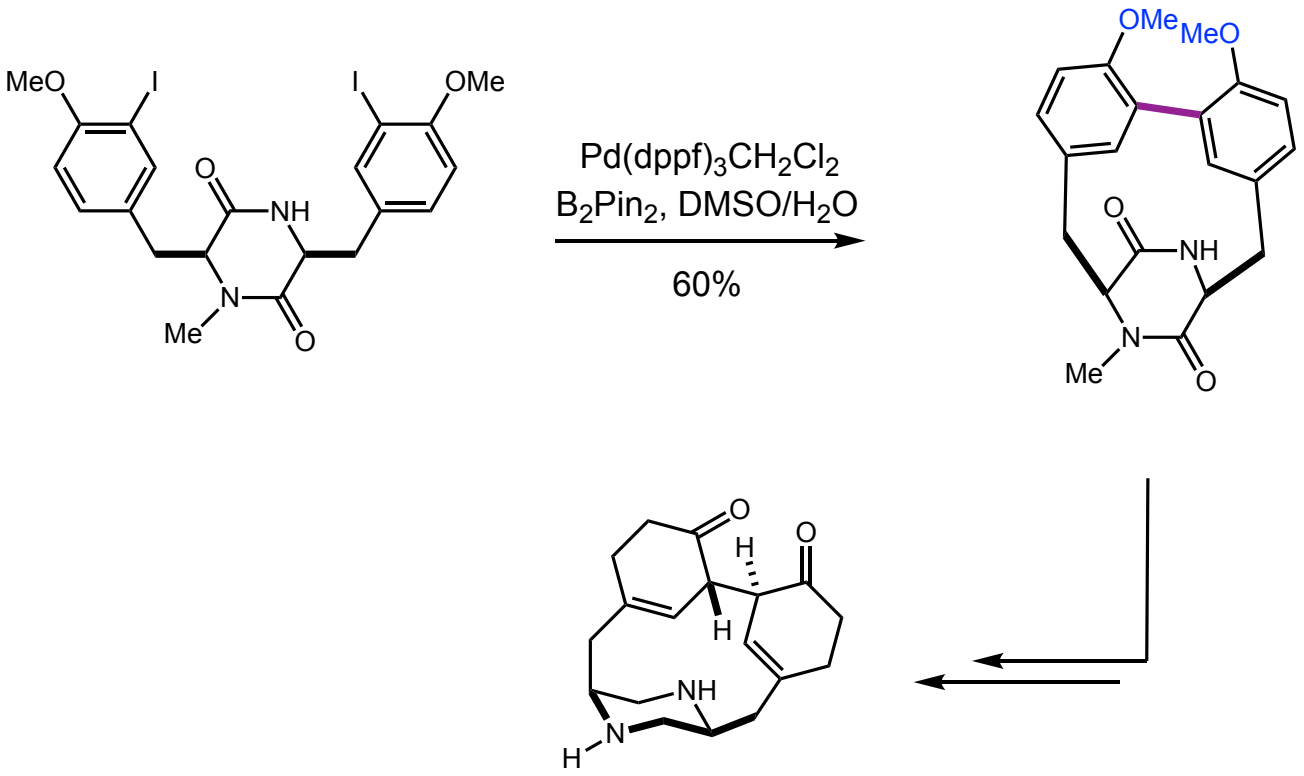
Fujii, S.; Chang, S. Y.; Burke, M. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7862.

Palladium-Catalyzed Macrocyclization in Total Synthesis



Zhu, X.; McAtee, C. C.; Schindler, C. S. *Org. Lett.* **2018**, *20*, 2862.
Zhu, X.; McAtee, C. C.; Schindler, C. S. *J. Am. Chem. Soc.* **2019**, *141*, 3409.

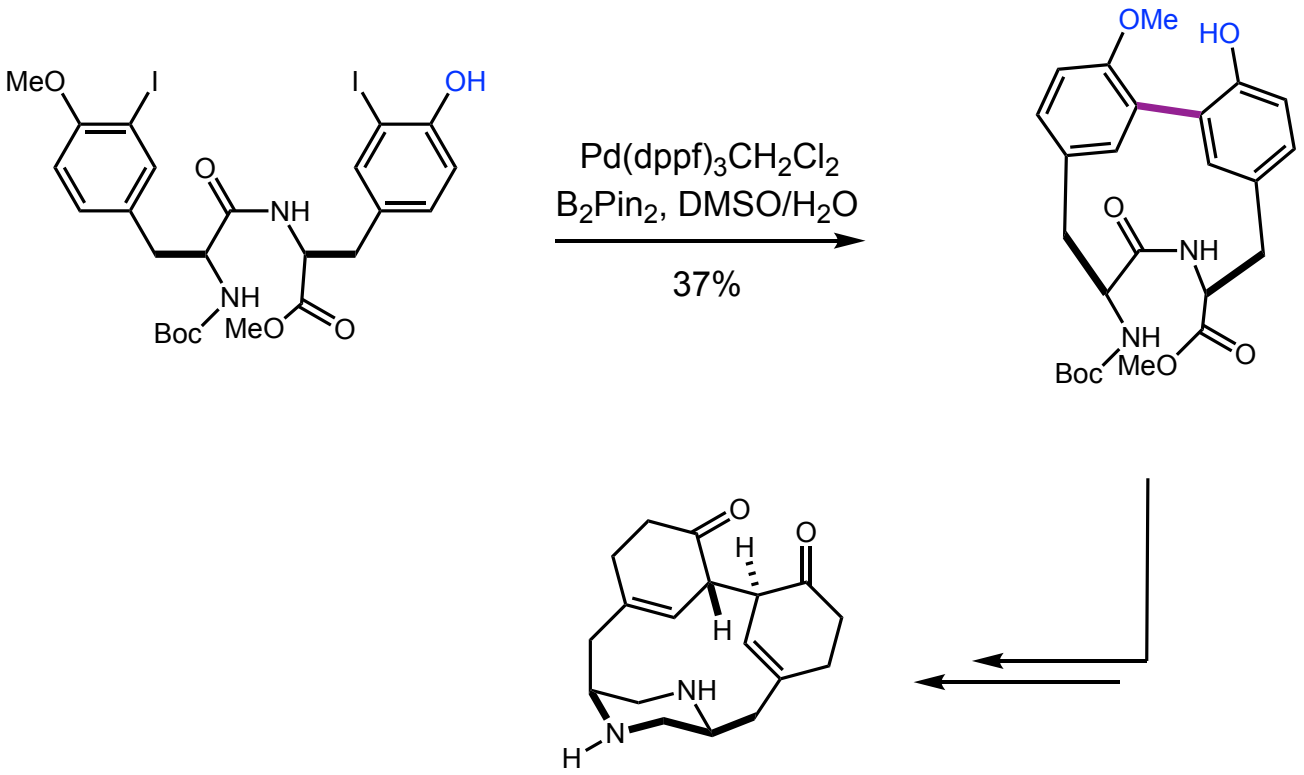
Palladium-Catalyzed Macrocyclization in Total Synthesis



herquline B

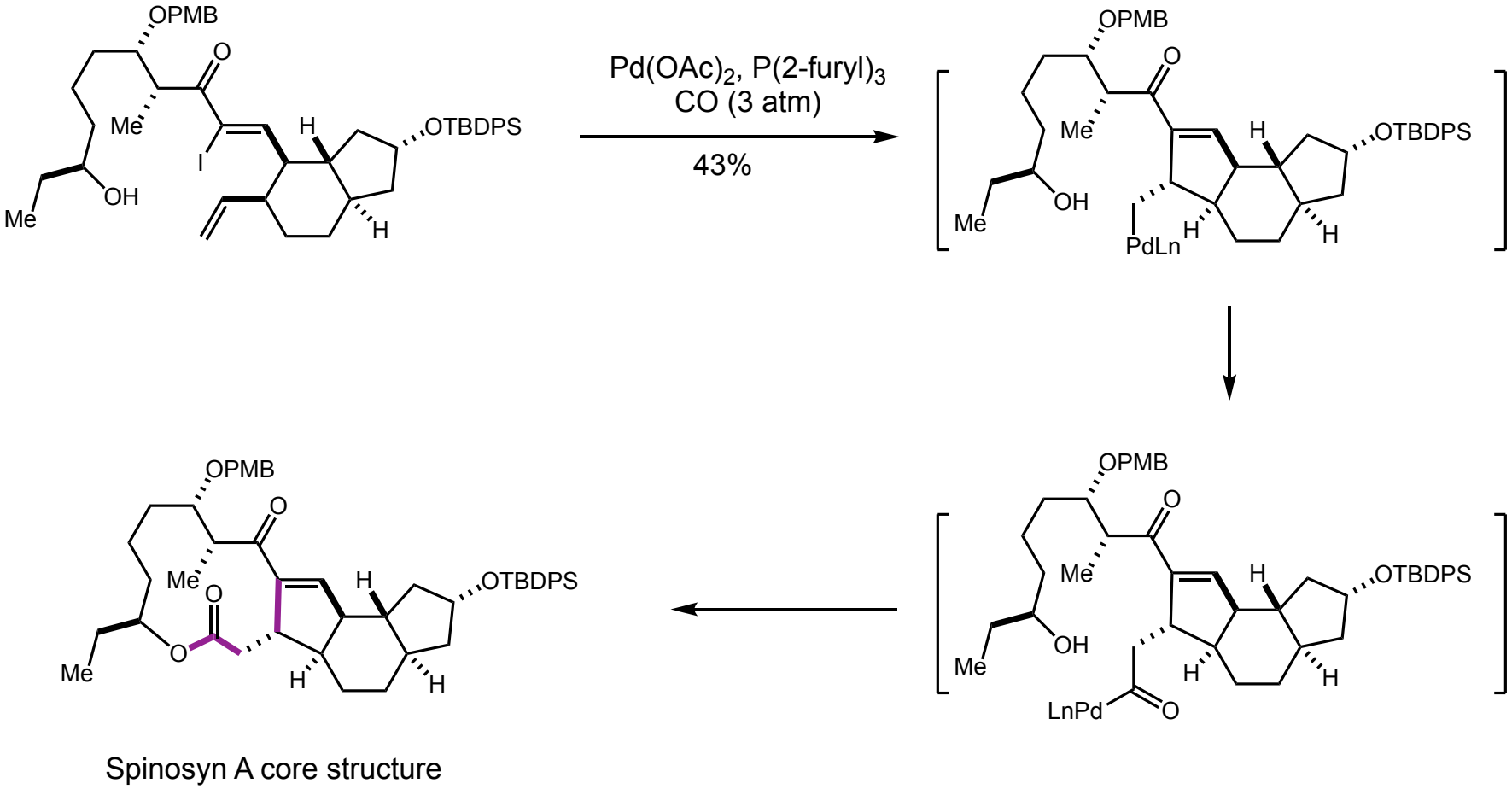
He, C.; Stratton, T. P.; Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 29.

Palladium-Catalyzed Macrocyclization in Total Synthesis



Cox, J. B.; Kimishima, Aoi.; Wood, J. L. *J. Am. Chem. Soc.* **2019**, *141*, 25.

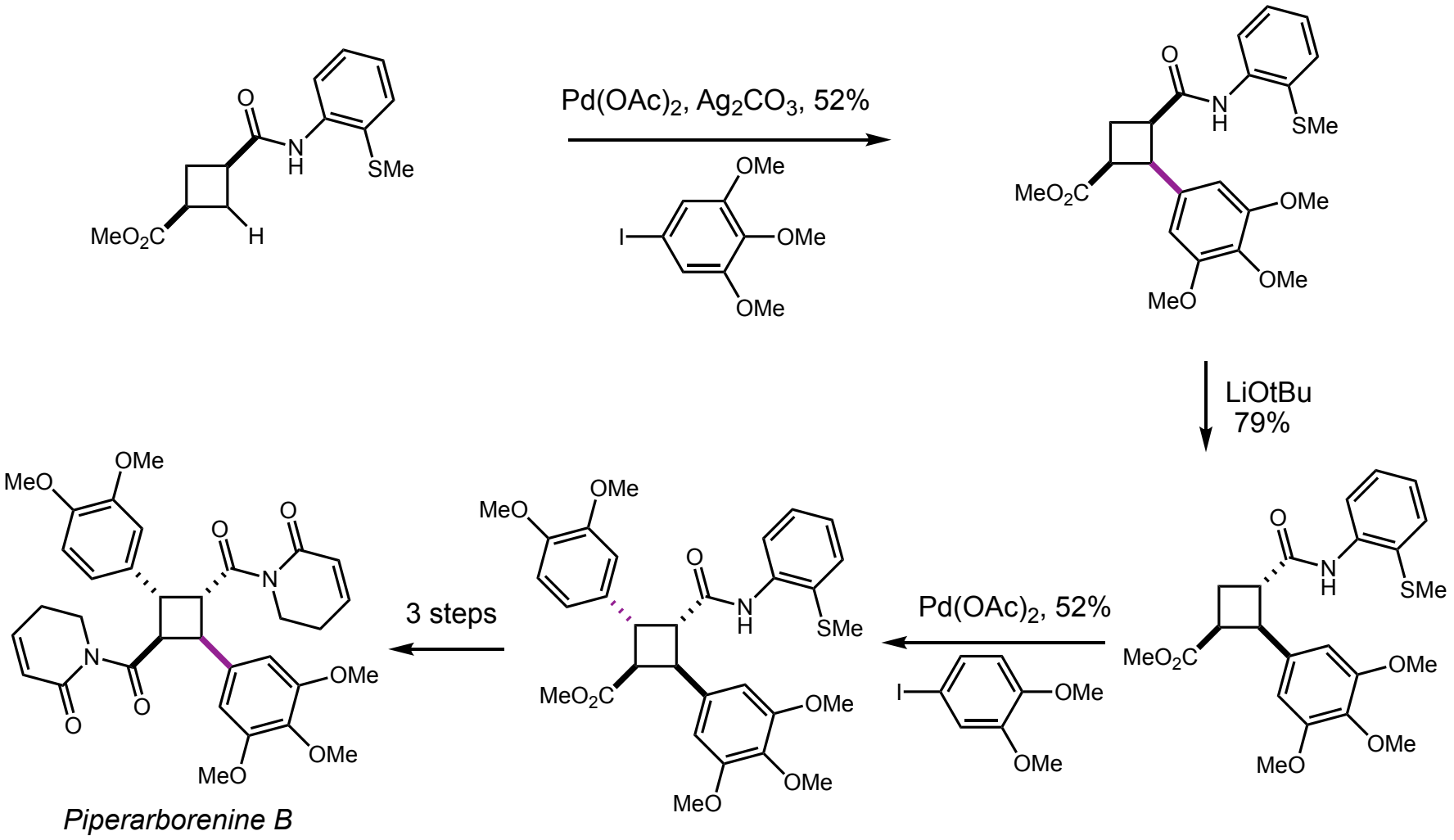
Palladium-Catalyzed Carbonylation in the Total Synthesis



Spinosyn A core structure

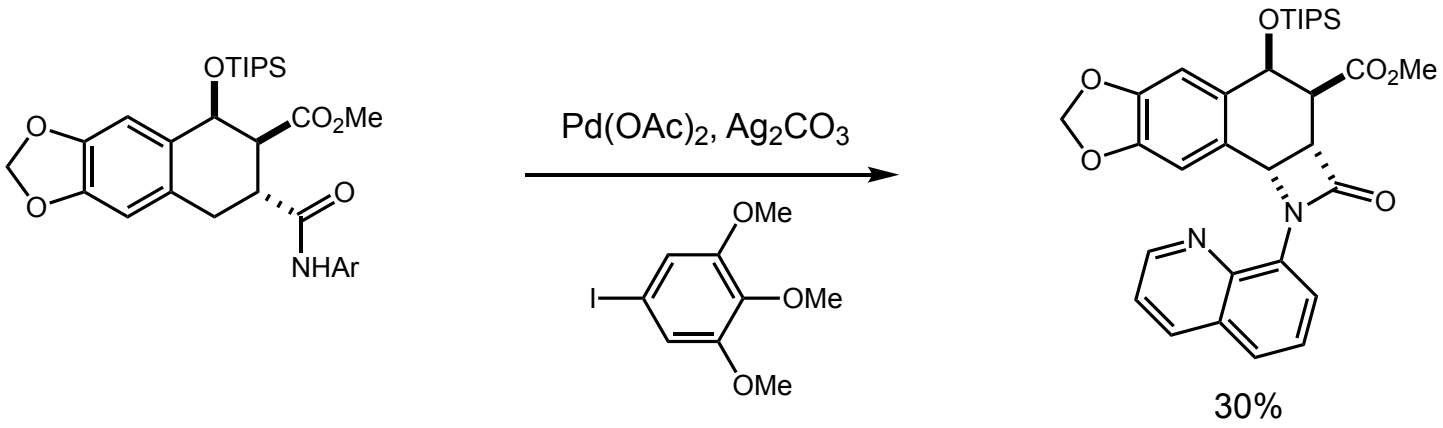
Bai, Y.; Shen, X.; Li, Y.; Dai, M. *J. Am. Chem. Soc.* **2016**, *138*, 10838.

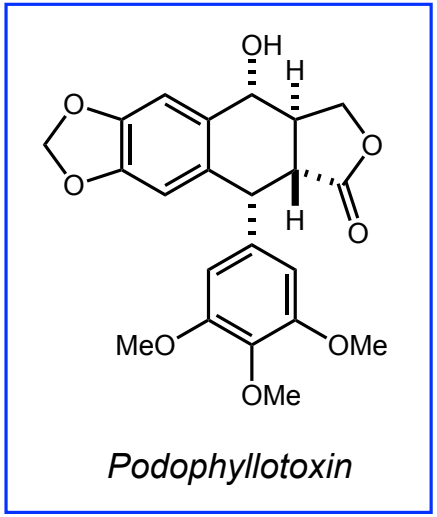
C-H Arylation in the Total Synthesis of Piperarborenine B

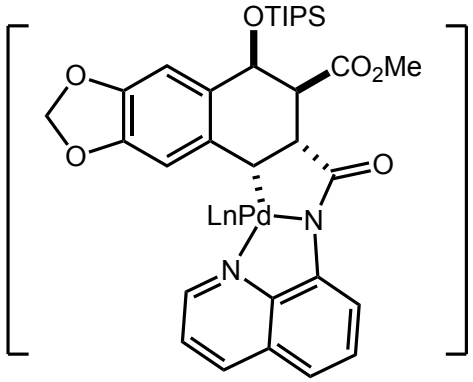


Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.
Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076.
Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7507.

C-H Arylation in the Total Synthesis of Podophyllotoxin

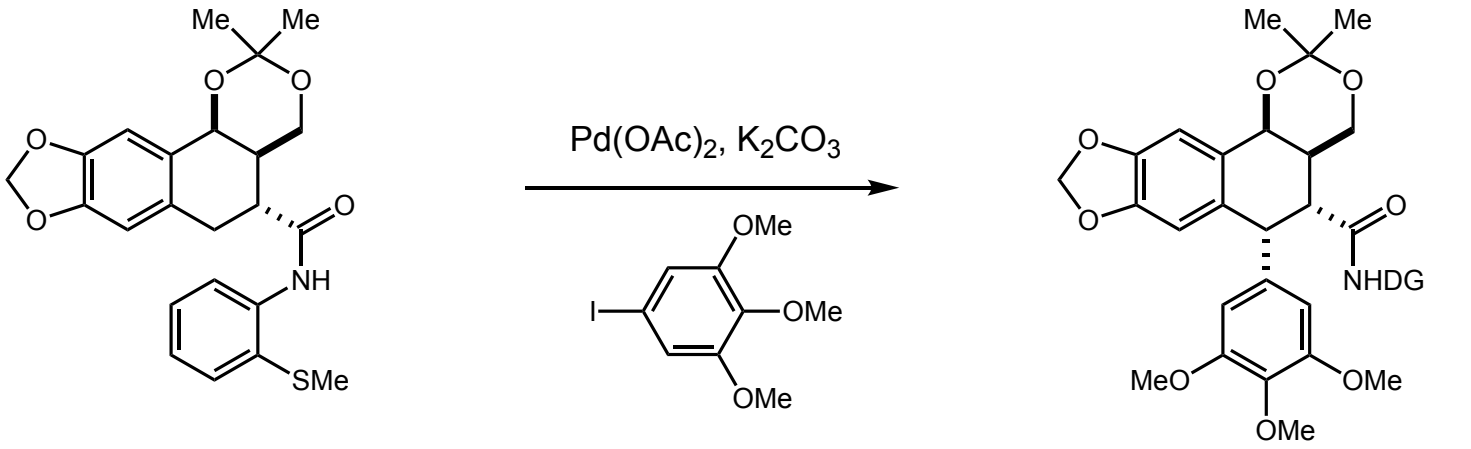




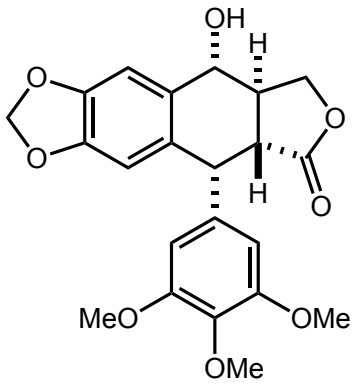


Ting, C. P.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3115.

C-H Arylation in the Total Synthesis of Podophyllotoxin



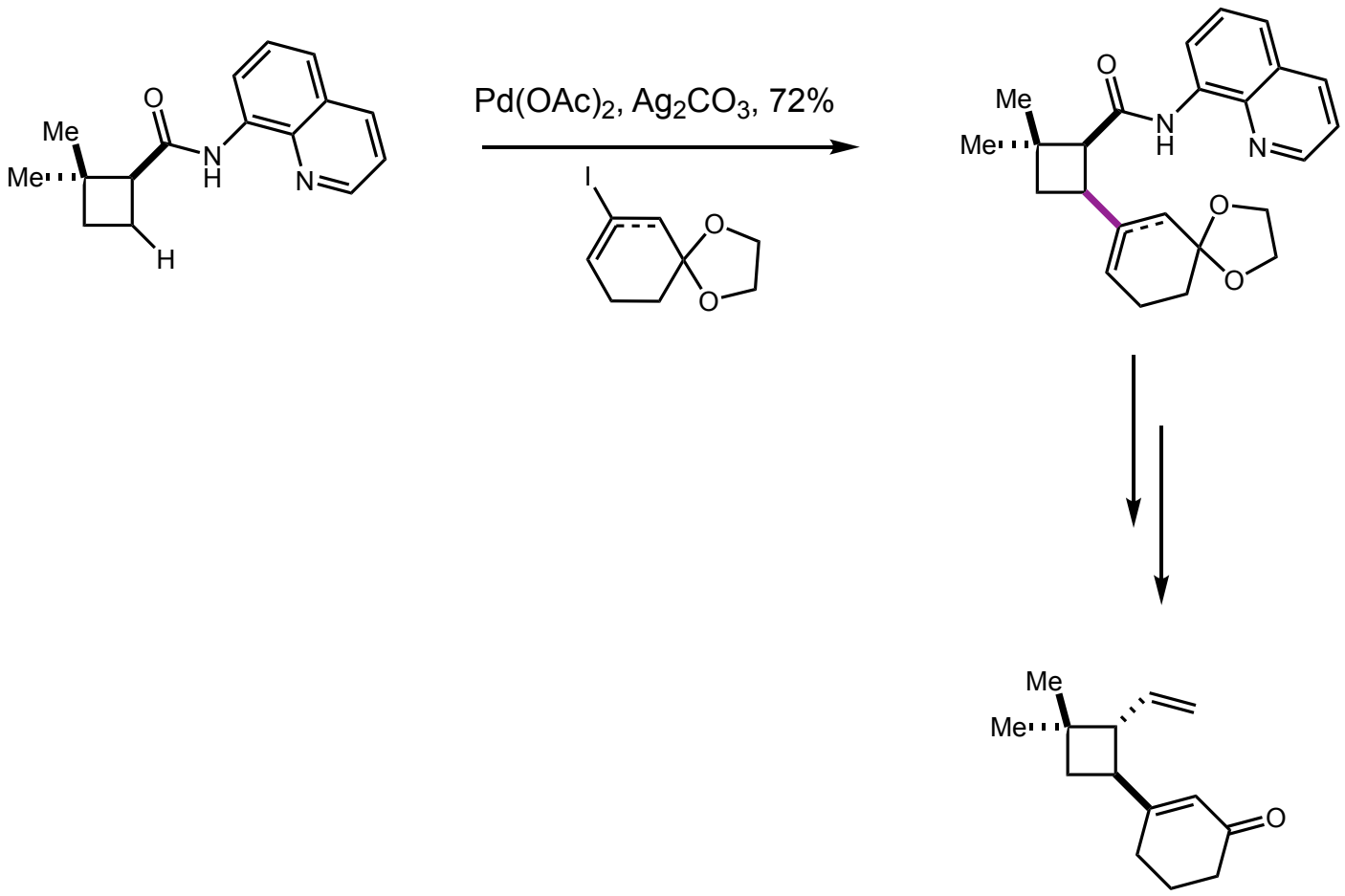
45% single diastereomer



Podophyllotoxin

Ting, C. P.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3115.

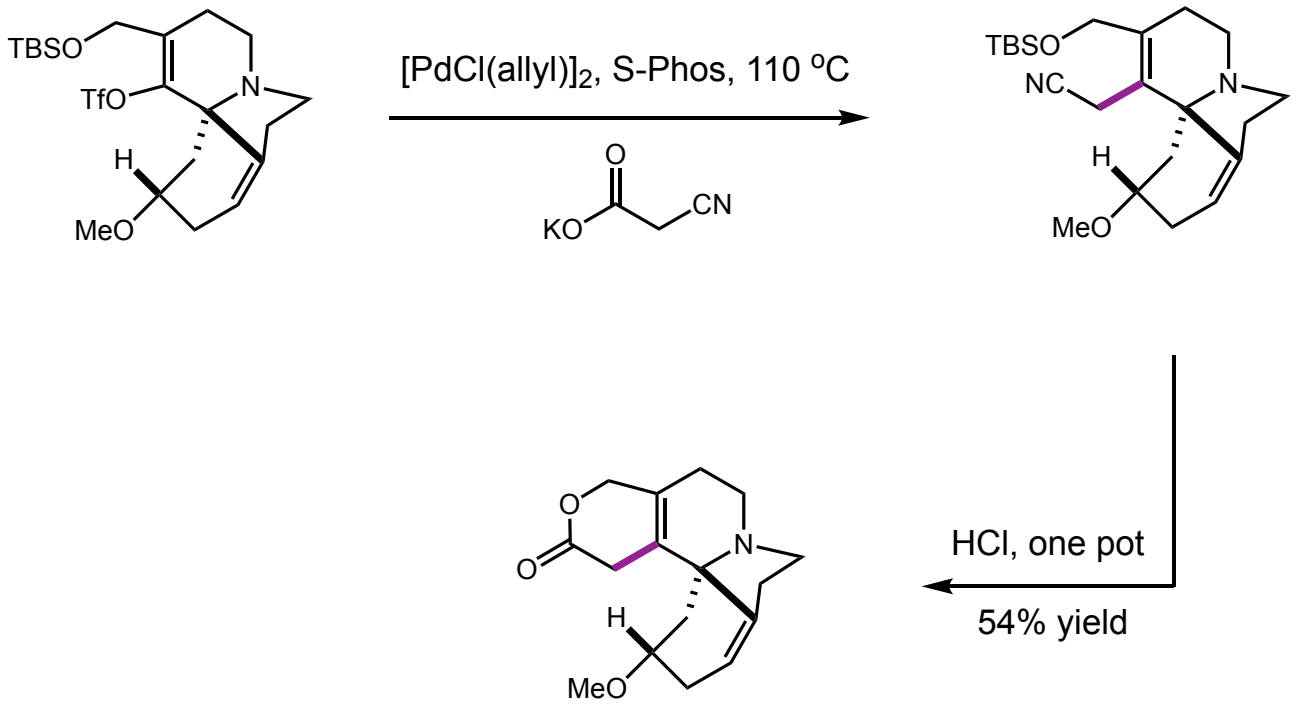
C-H Alkenylation in the Total Synthesis of Psiguadial



Key structure of psiguadial

Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. *J. Am. Chem. Soc.* **2016**, *138*, 9803.

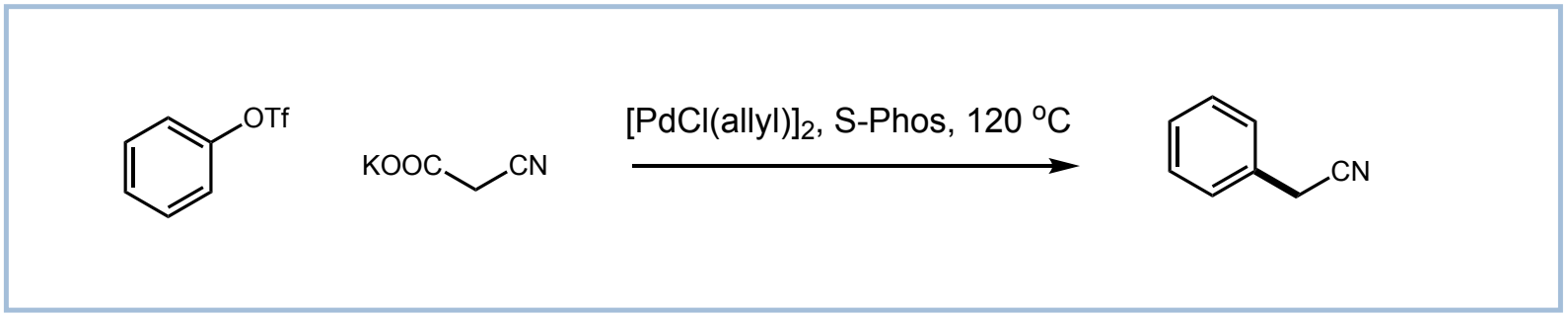
Decarboxylative Alkenylation in the Total Synthesis of (+)-Dihydro-β-erythroidine

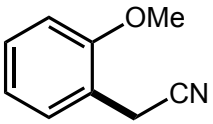


(+)-Dihydro-β-erythroidine

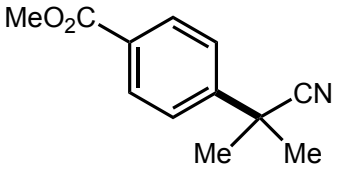
Clementson, S.; Jessing, M.; Pedersen, H.; Vital, P.; Kristensen, J. L. *J. Am. Chem. Soc.* **2019**, *ASAP*

Palladium-Catalyzed Decarboxylative Coupling of Cyanoacetate Salts with ArX

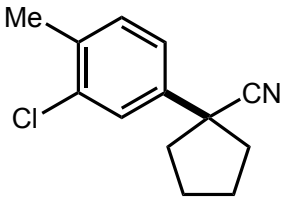




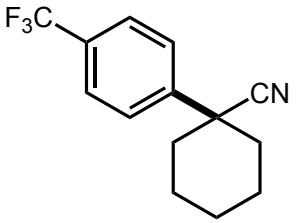
83% yield



82% yield



71% yield



85% yield

Shang, R.; Ji, D.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 4470.

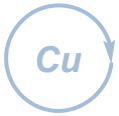
Total Synthesis Enabled by Cross-Coupling

Outline

Palladium-Catalyzed Cross-Coupling in Total Synthesis

Iron-Catalyzed Cross-Coupling in Total Synthesis

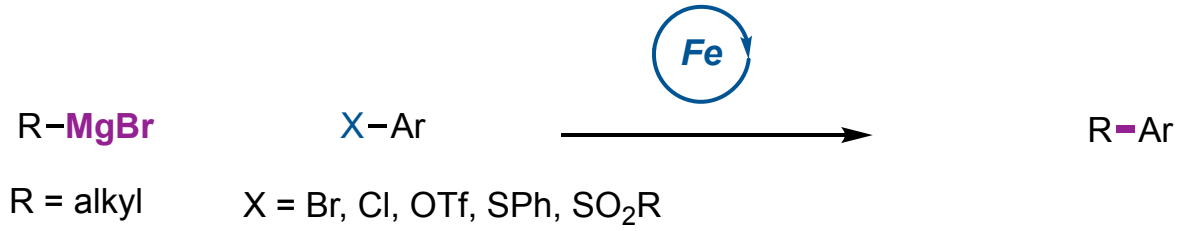
Copper-Catalyzed Cross-Coupling in Total Synthesis



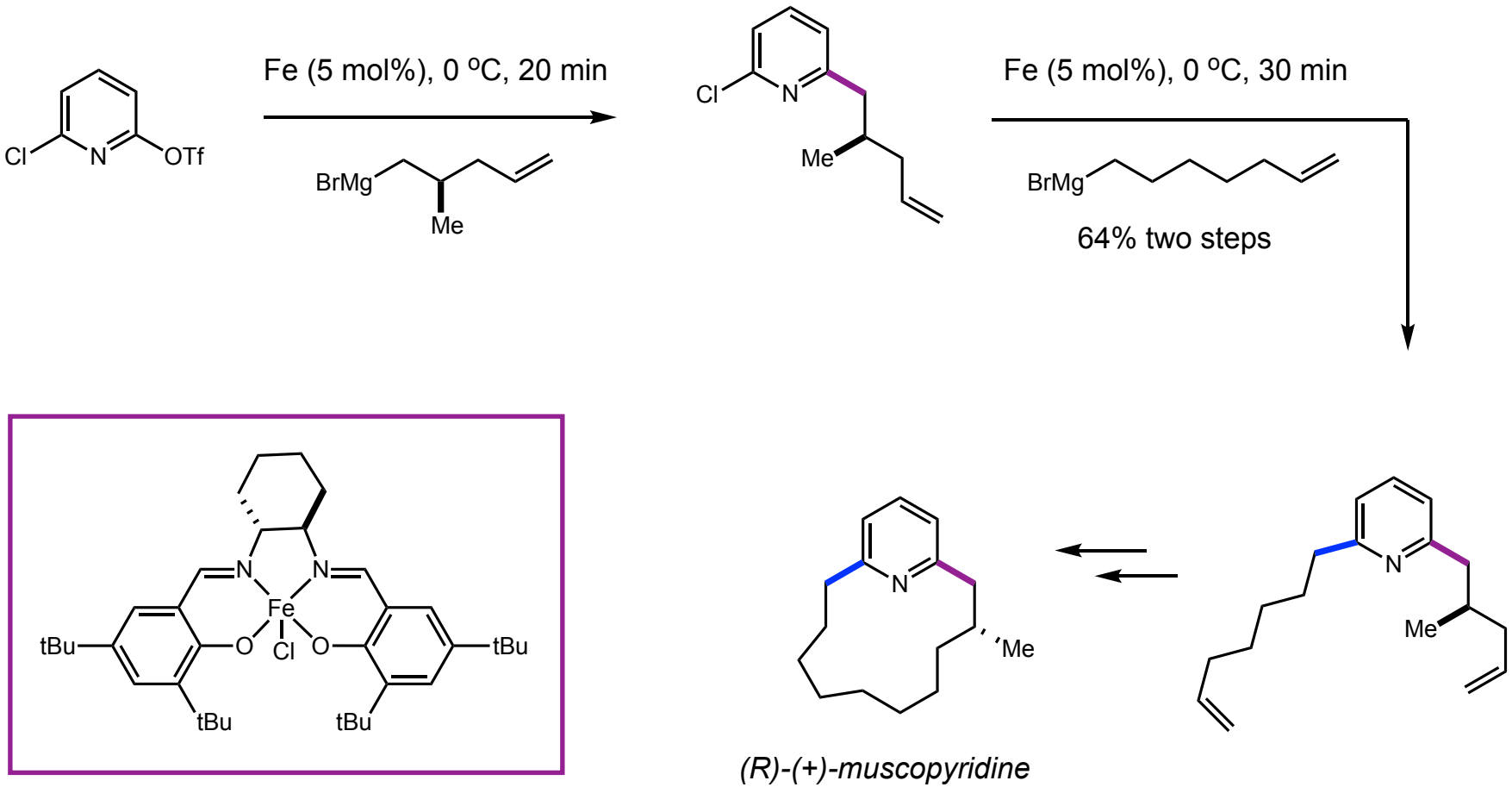
Nickel-Catalyzed Cross-Coupling in Total Synthesis

Iron-Catalyzed Cross-Coupling in Total Synthesis

Kumada type coupling



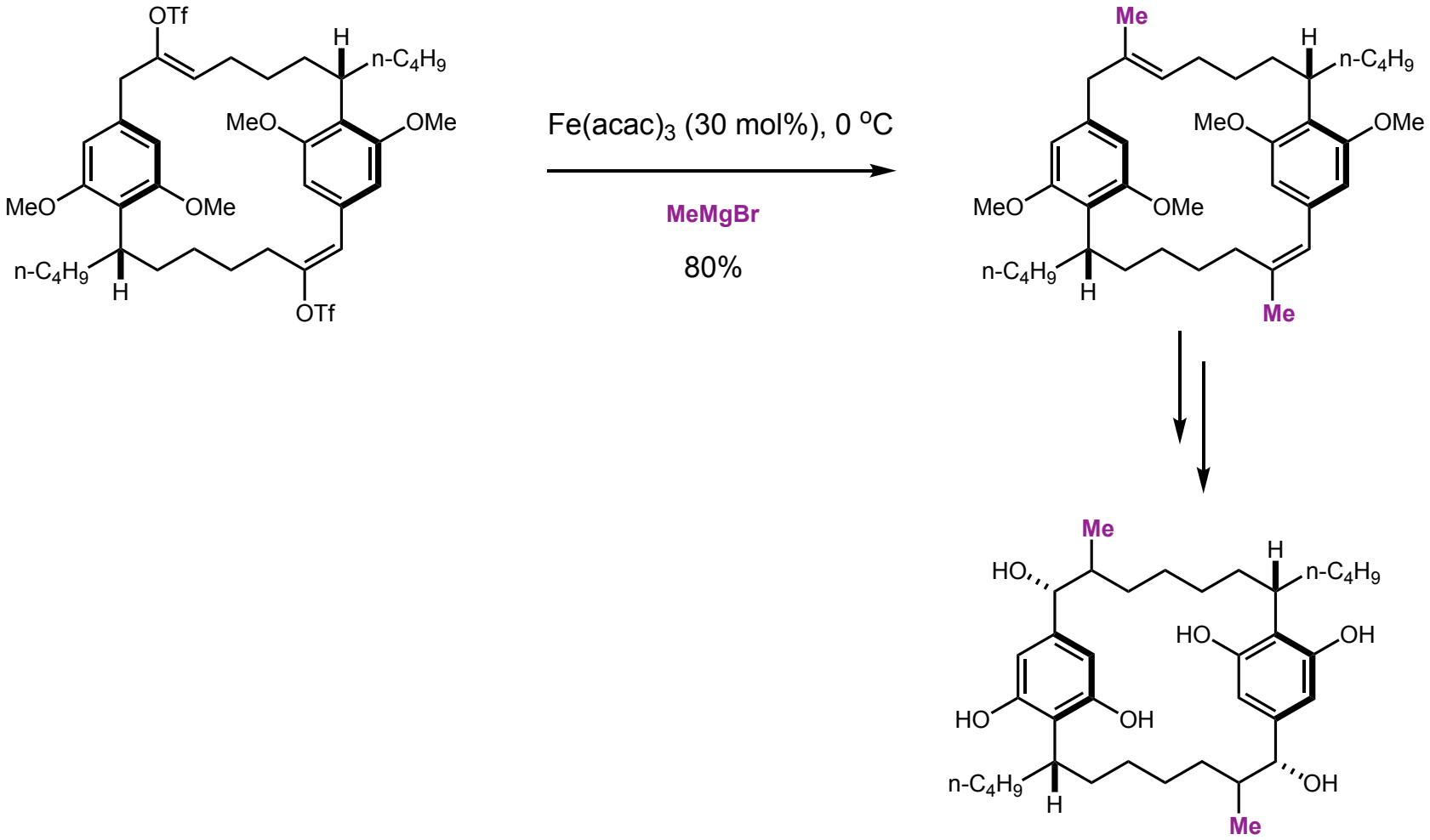
Iron-Catalyzed Cross-Coupling in the Total Synthesis of (R)-(+)-muscopyridine



(R)-(+)-muscopyridine

Scheiper, B.; Glorius, F.; Leitner, A.; Furstner, A. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 11960.
Furstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308.

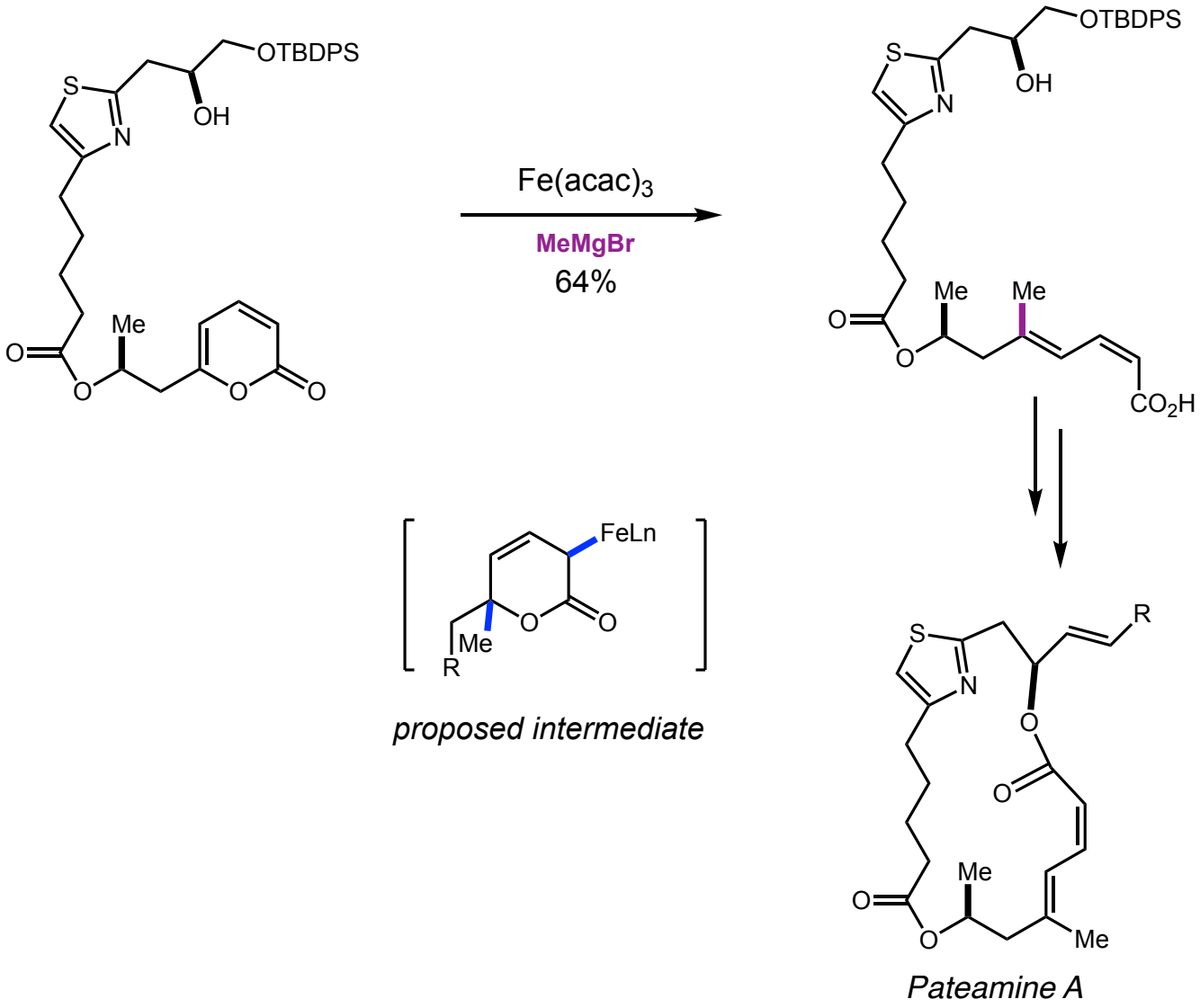
Iron-Catalyzed bis-Methylation in the Total Synthesis of Cylindrocyclophane A



Cylindrocyclophane A

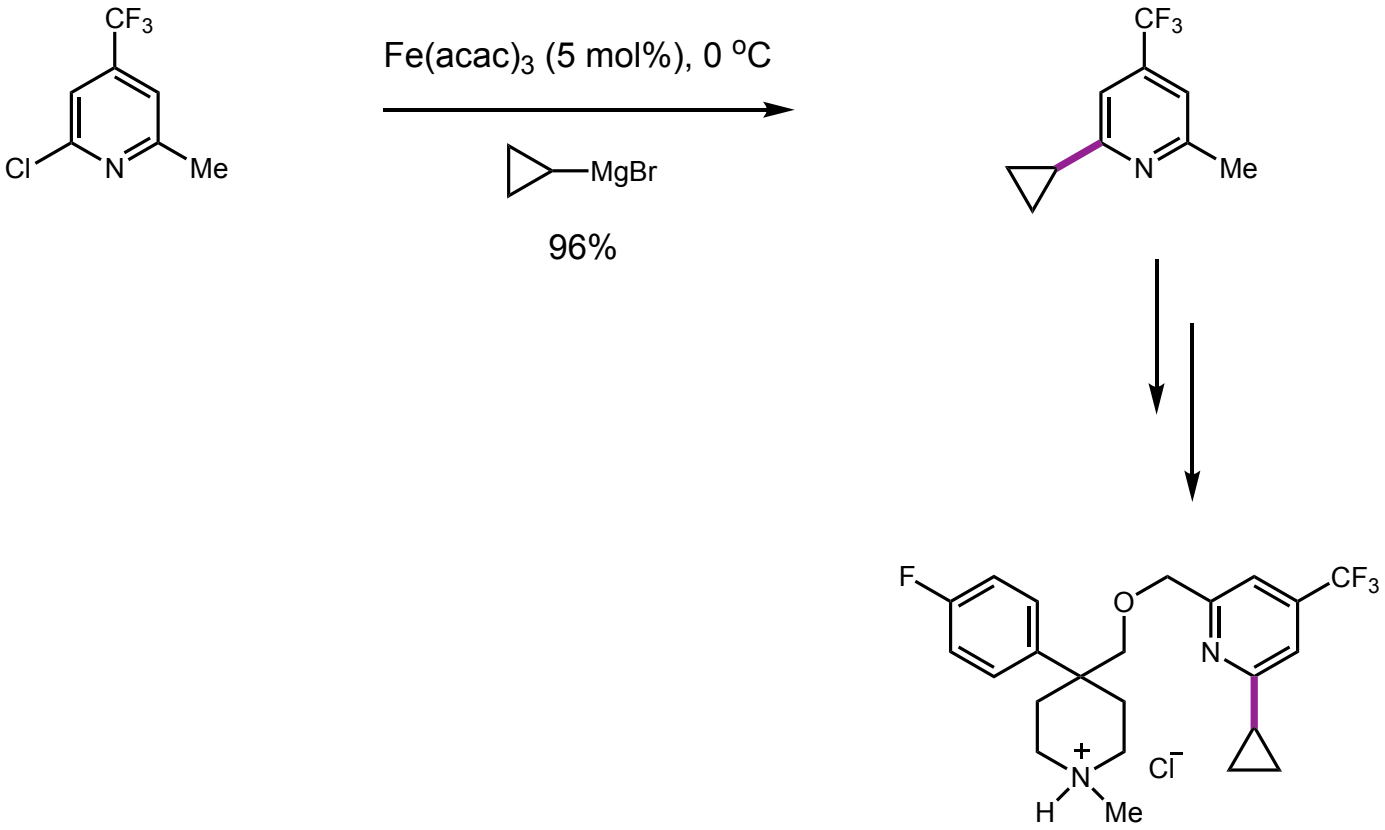
K. C. Nicolaou, Y.-P. Sun, H. Korman, D. Sarlah, *Angew. Chem., Int. Ed.* **2010**, *49*, 5875.

Iron-Catalyzed Ring-Opening/Cross-Coupling in the Synthesis of Pateamine A



Sun, C.-L.; Fürstner, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13071.
Zhuo, C.-X.; Fürstner, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 6051.
Zhuo, C.-X.; Fürstner, A. *J. Am. Chem. Soc.* **2018**, *140*, 10514.

Iron-Catalyzed Cyclopropylation in the Synthesis of Pharmaceutical Ingredient



NK1/serotonin receptor antagonist

BMS

C. Risatti, K. J. Natalie, Z. Shi and D. A. Conlon, *Org. Process Res. Dev.* **2013**, *17*, 257.

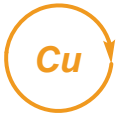
Total Synthesis Enabled by Cross-Coupling

Outline

Palladium-Catalyzed Cross-Coupling in Total Synthesis

Iron-Catalyzed Cross-Coupling in Total Synthesis

Copper-Catalyzed Cross-Coupling in Total Synthesis



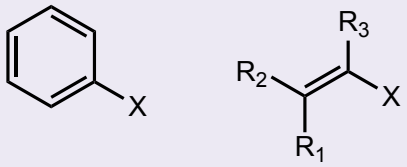
Nickel-Catalyzed Cross-Coupling in Total Synthesis

Copper-Catalyzed Cross-Coupling in Total Synthesis

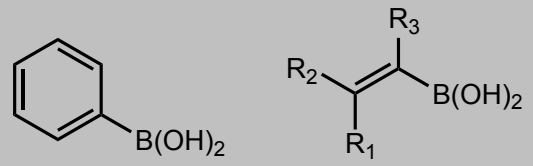
Copper catalysis C-X bond formation

X = Cl, Br, I, $B(OH)_2$

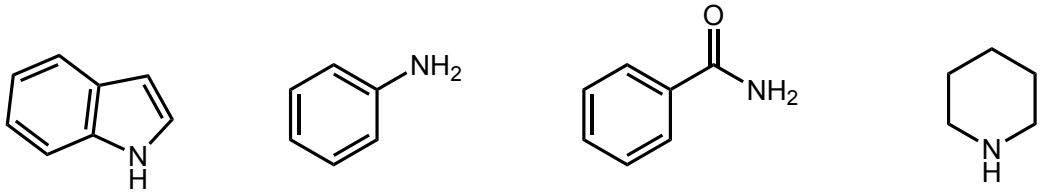
Ullmann-type Coupling



Chan-Lam-Evans-type Coupling



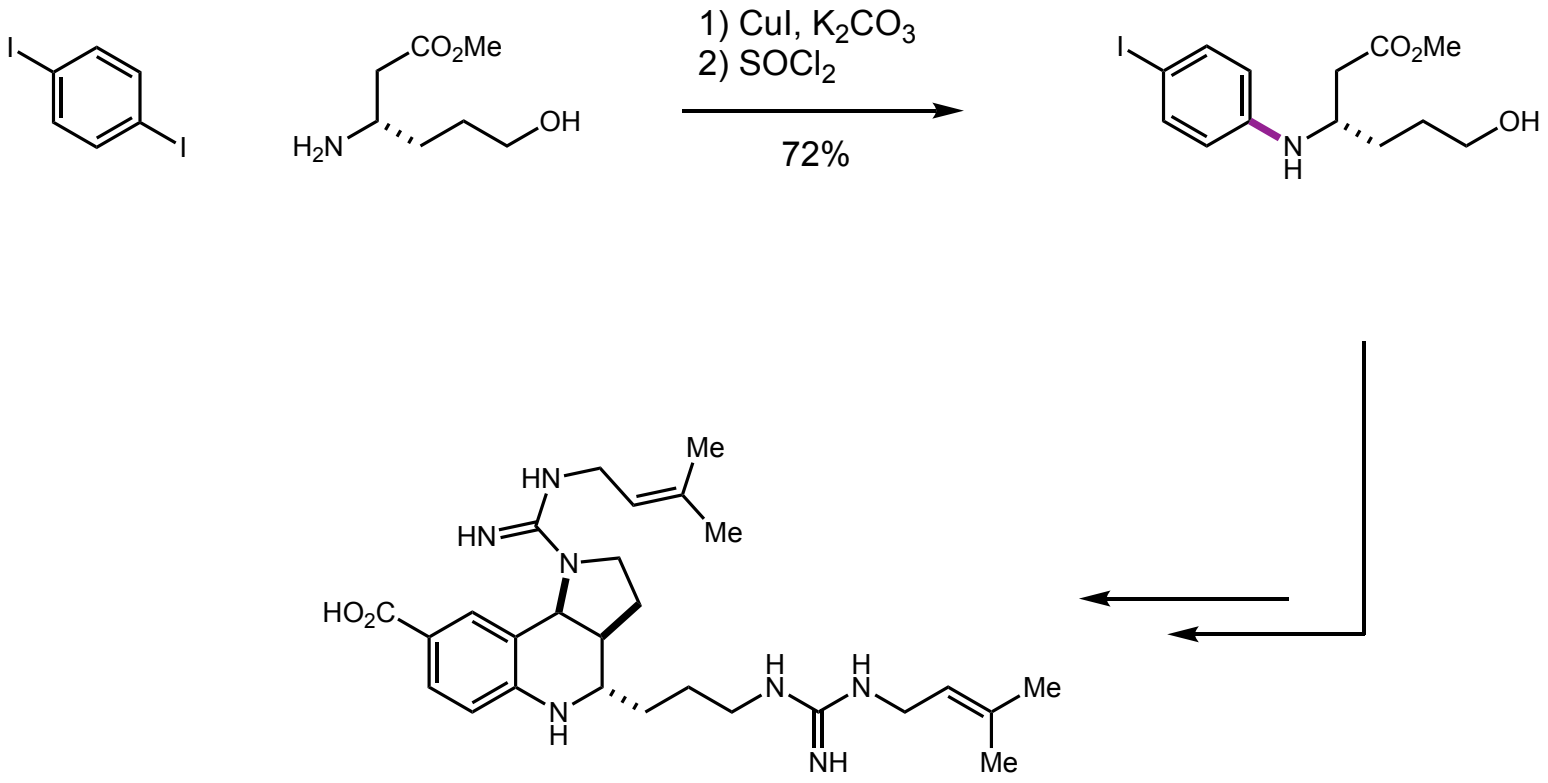
N-nucleophile



O-nucleophile ROH ArOH RCOOH

other-nucleophile RSH ArSH $\ominus CF_3$ $\ominus CN$

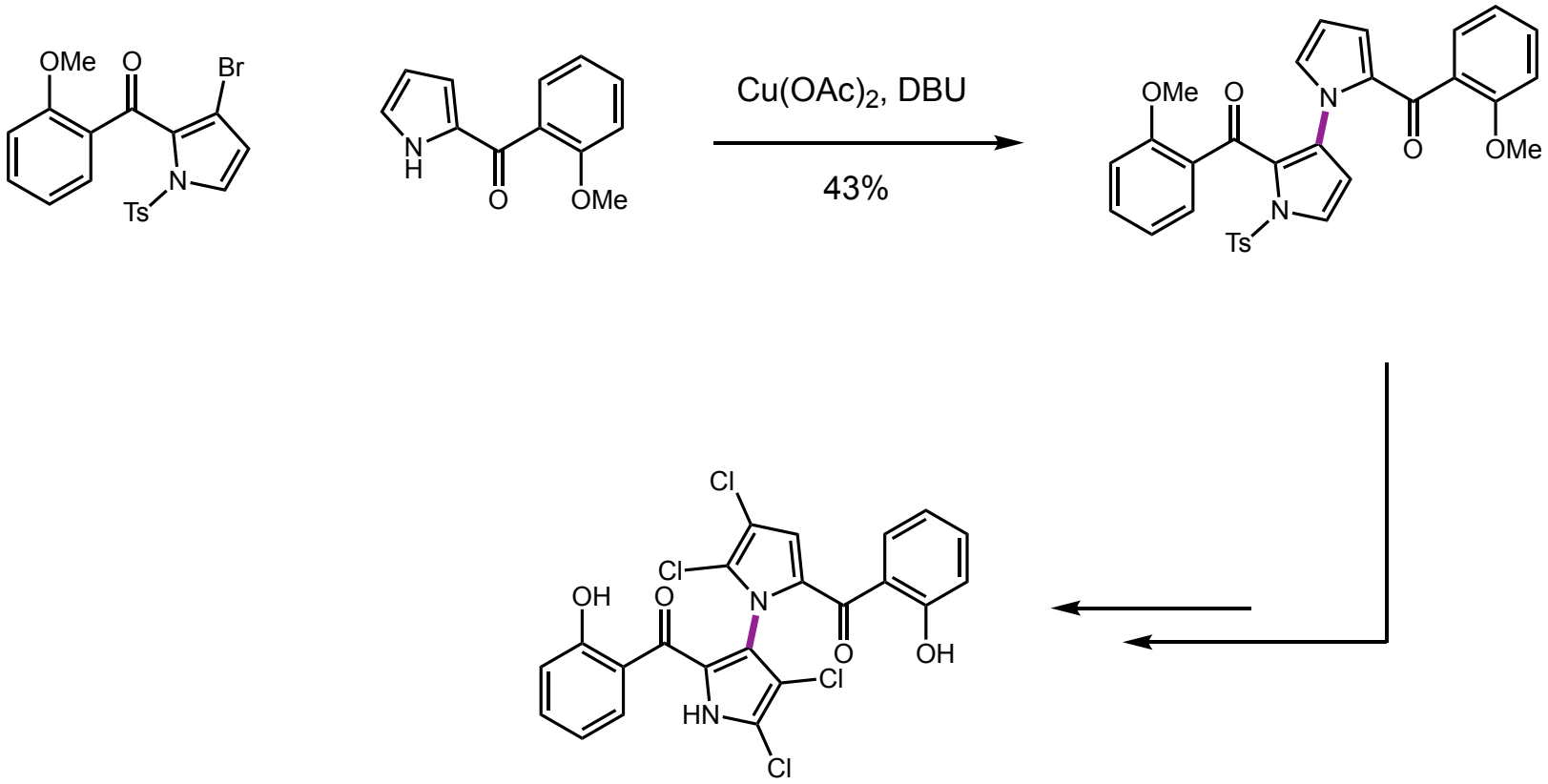
Copper-Catalyzed Cross-Coupling in Total Synthesis



martinellic acid

Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459
Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189;

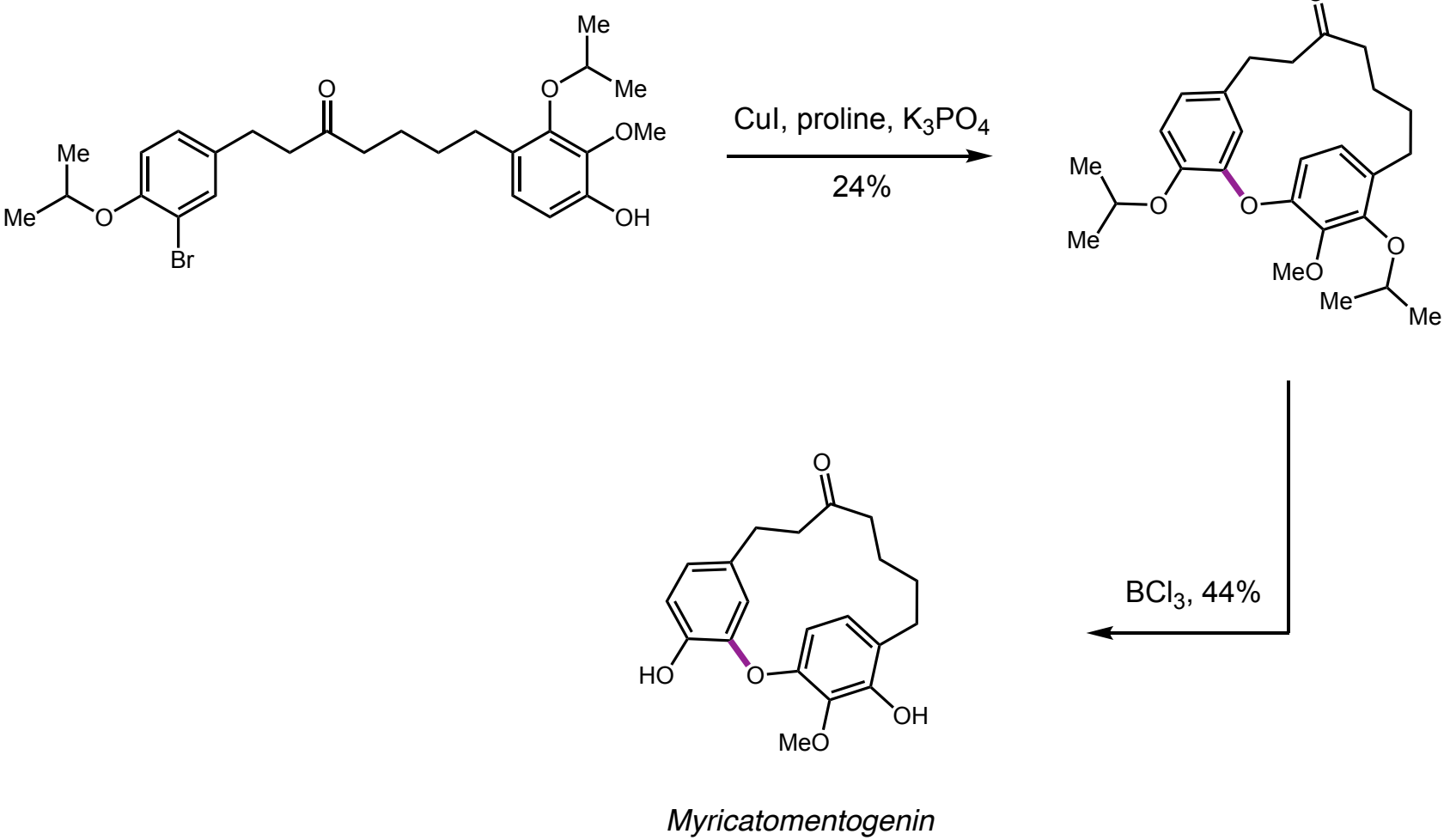
Copper-Catalyzed Cross-Coupling in Total Synthesis



Marinopyrrole A

Kanakis, A. A.; Sarli, V. *Org. Lett.* **2010**, *12*, 4872.

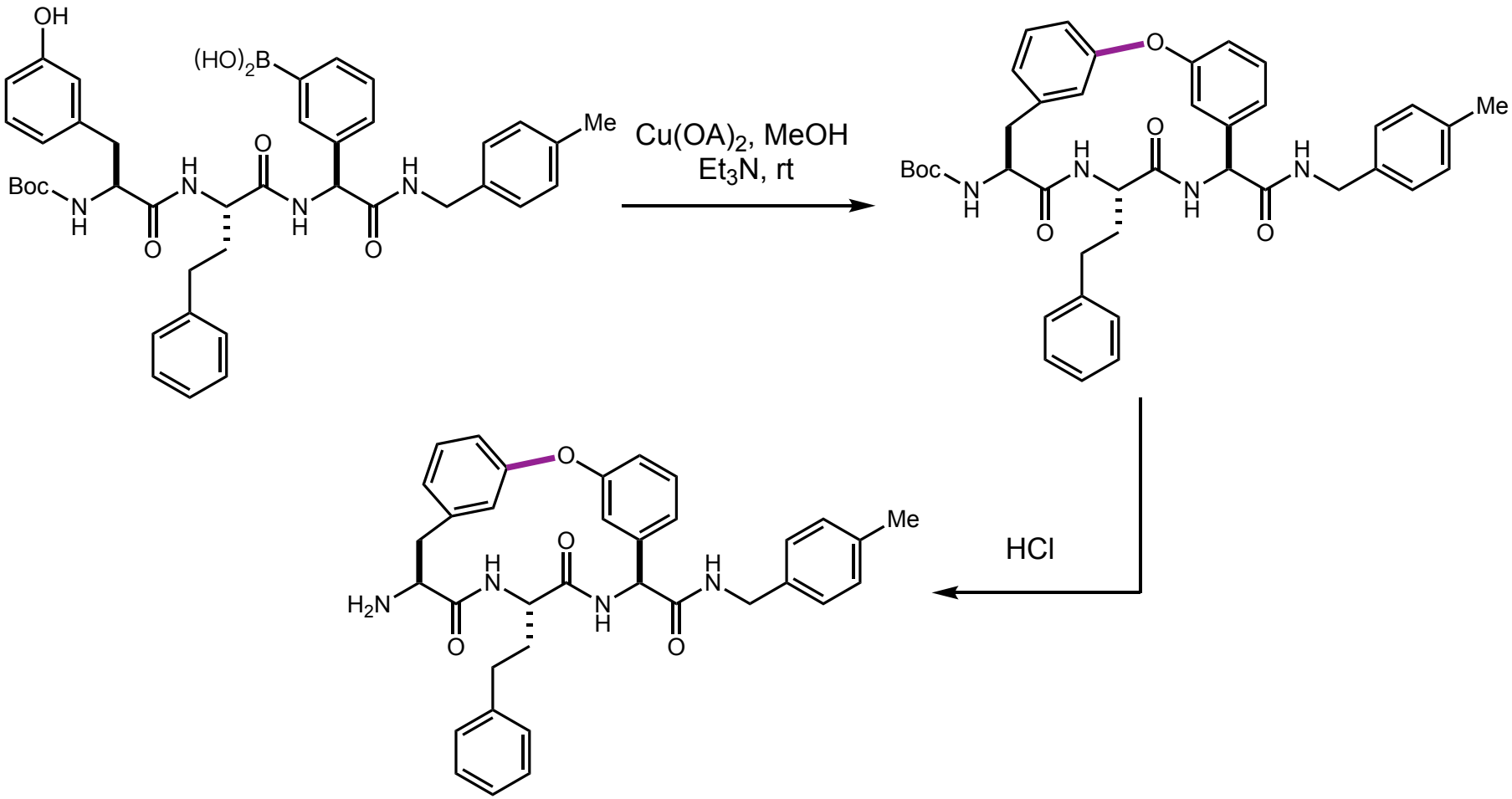
Copper-Catalyzed Cross-Coupling in Total Synthesis



Myricatomentogenin

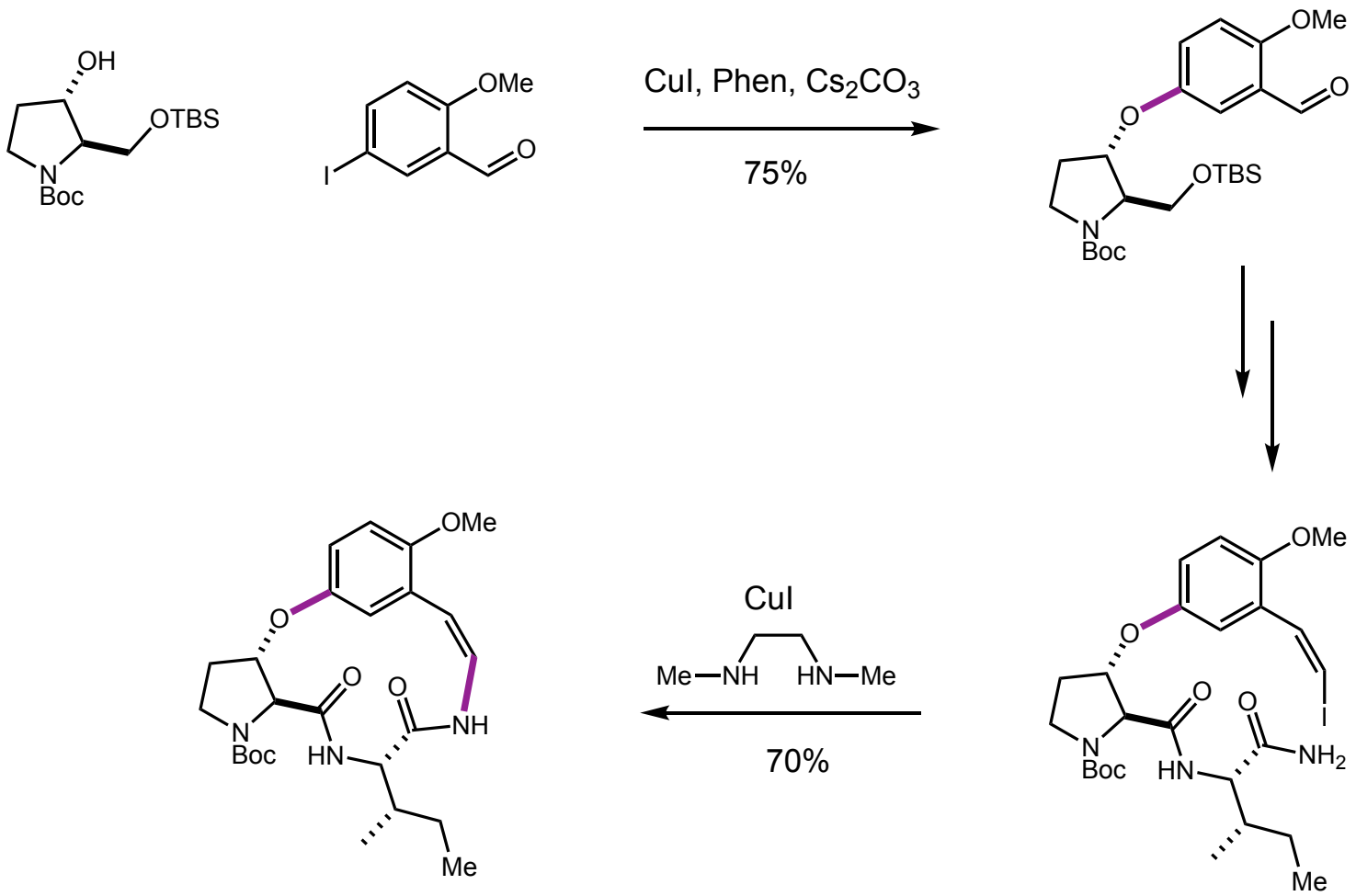
Salih, M. Q.; Beaudry, C. M. *Org. Lett.* **2013**, *15*, 4540.

Copper-Catalyzed Cross-Coupling in Total Synthesis of Peptides



Li, H.; Tsu, C.; Blackburn, C.; Li, G.; Hales, P.; Dick, L.; Bogyo, M. *J. Am. Chem. Soc.* **2014**, *136*, 13562.

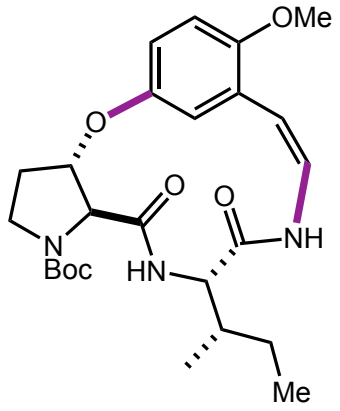
Copper-Catalyzed Cross-Coupling in the Total Synthesis of Paliurine F



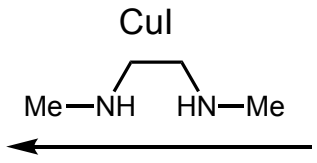
Core structure of Paliurine F

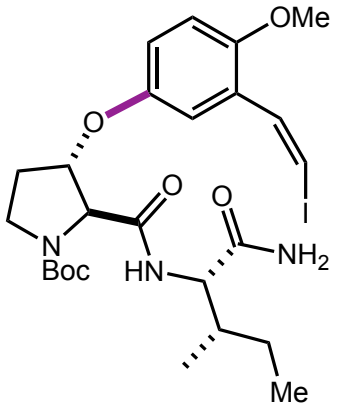
M. Toumi, F. Couty and G. Evano, *Angew. Chem., Int. Ed.* **2007**, *46*, 572.

Copper-Catalyzed Cross-Coupling in the Total Synthesis of Paliurine F

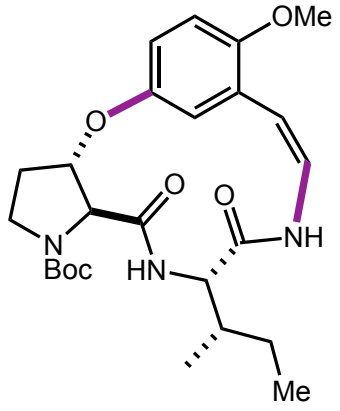


Core structure of Paliurine F

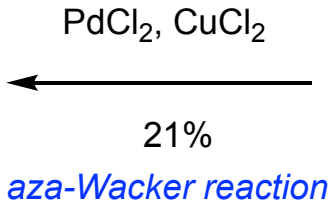


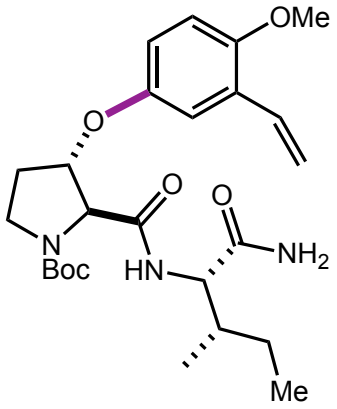


Previous route



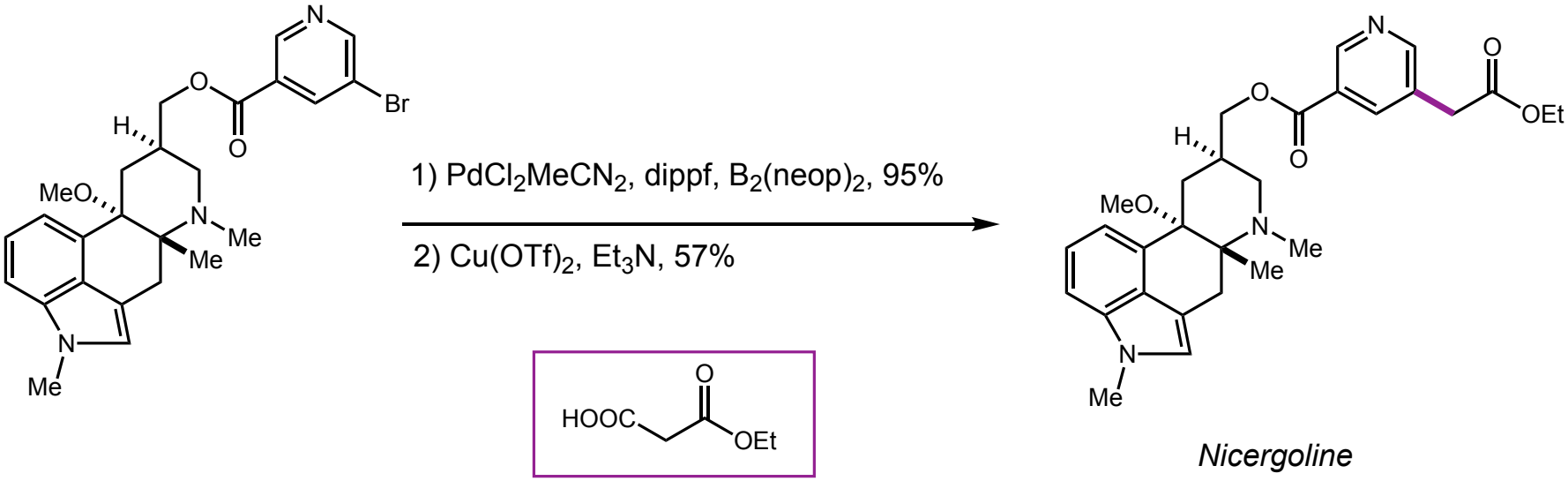
Core structure of Paliurine F





M. Toumi, F. Couty and G. Evano, *Angew. Chem., Int. Ed.* **2007**, *46*, 572.

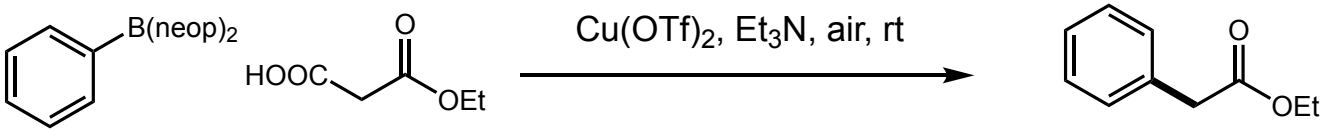
Copper-Catalyzed Cross-Coupling in the Synthesis of Nicergoline

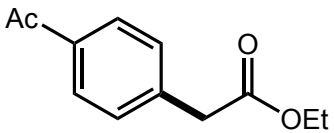


Copper-catalyzed decarboxylative C-C bond formation

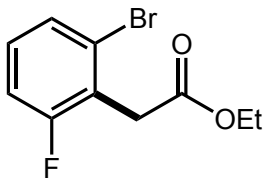
Moon, P. J.; Yin, S. K.; Lundgren, R. J. *J. Am. Chem. Soc.* **2016**, *138*, 13826.

Copper-Catalyzed Decarboxylative Arylation of Malonate

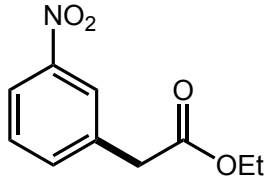




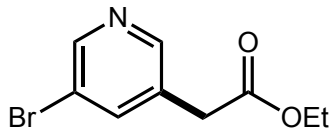
75% yield



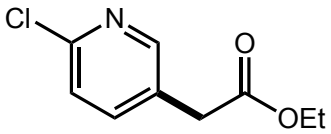
54% yield



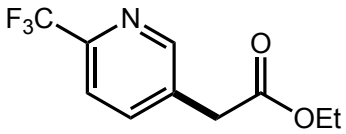
68% yield



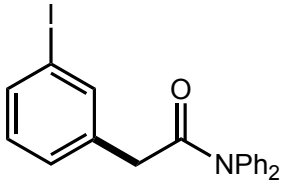
47% yield



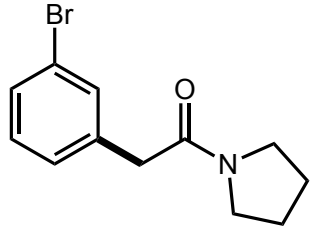
67% yield



77% yield



84% yield



58% yield

Moon, P. J.; Yin, S. K.; Lundgren, R. J. *J. Am. Chem. Soc.* **2016**, *138*, 13826.

Total Synthesis Enabled by Cross-Coupling

Outline

Palladium-Catalyzed Cross-Coupling in Total Synthesis

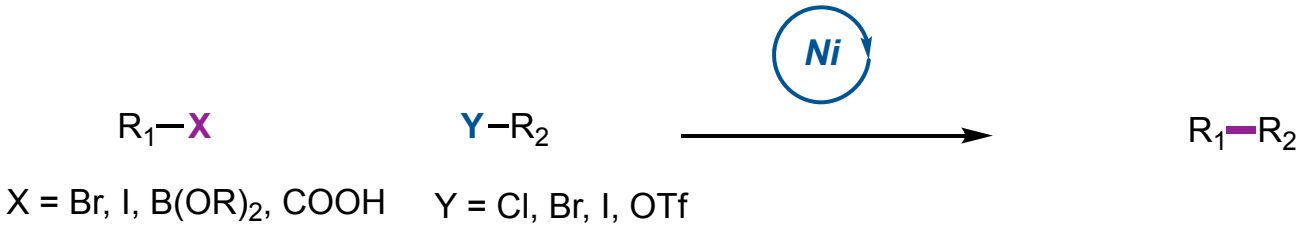
Iron-Catalyzed Cross-Coupling in Total Synthesis

Copper-Catalyzed Cross-Coupling in Total Synthesis

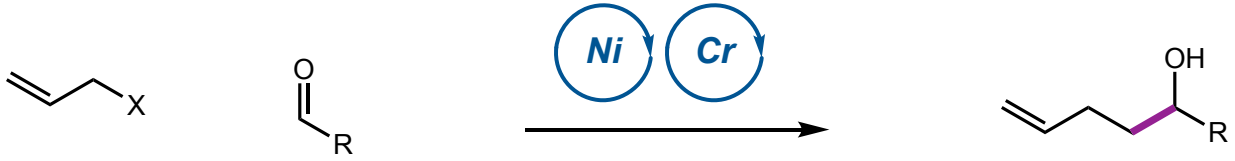
Nickel-Catalyzed Cross-Coupling in Total Synthesis

Nickel-Catalyzed Cross-Coupling in Total Synthesis

C-C bond formation

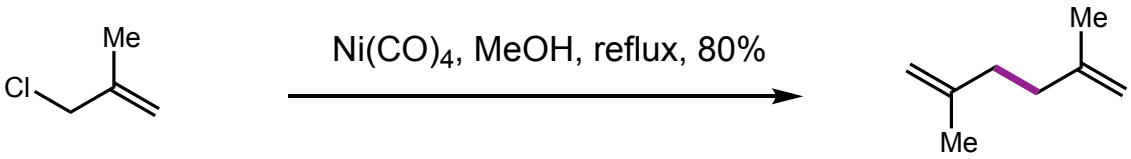


Nozaki-Hiyama-Kishi reaction



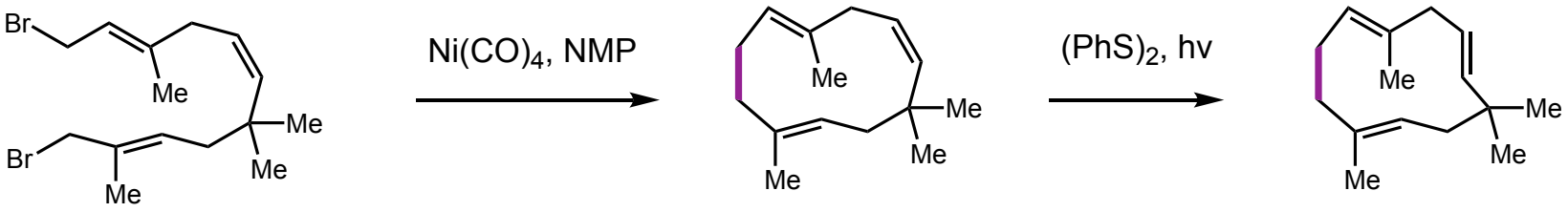
Nickel-Catalyzed Cross-Coupling in Total Synthesis

- First Nickel-mediated reductive coupling—Farben, 1943



I.G. Farben. Belgian Patent 448884. February 27, **1943**; *Chem. Abstr.* **1947**, *41*, 6576.

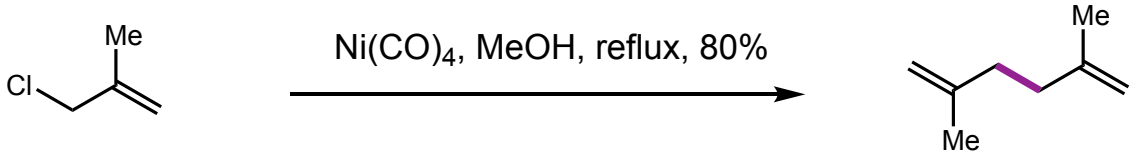
- Corey's synthesis of Humulene



Corey, E. J.; Hamanaka, E. *J. Am. Chem. Soc.* **1964**, *86*, 1641.
Corey, E. J.; Hamanaka, E. *J. Am. Chem. Soc.* **1967**, *89*, 2758.

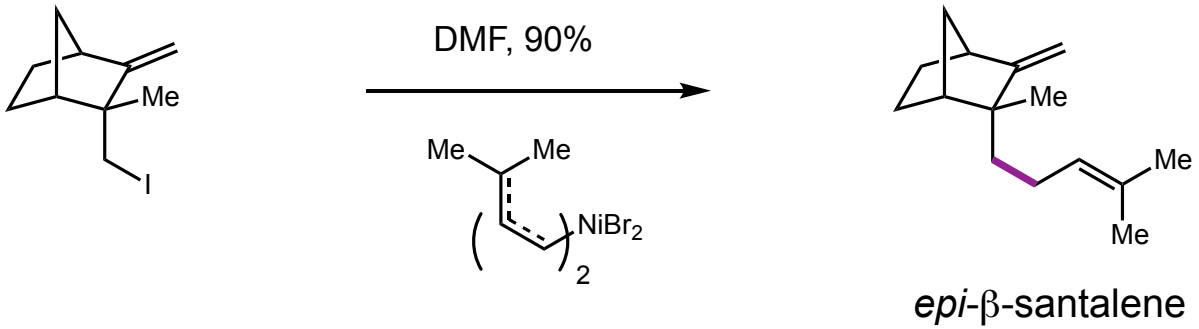
Nickel-Catalyzed Cross-Coupling in Total Synthesis

- First Nickel-mediated reductive coupling—Farben, 1943



I.G. Farben. Belgian Patent 448884. February 27, **1943**; *Chem. Abstr.* **1947**, *41*, 6576.

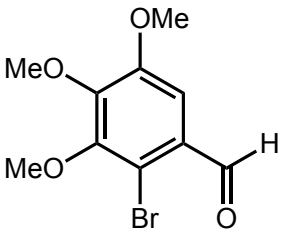
- Corey's synthesis of *epi*-β-santalene



epi-β-santalene

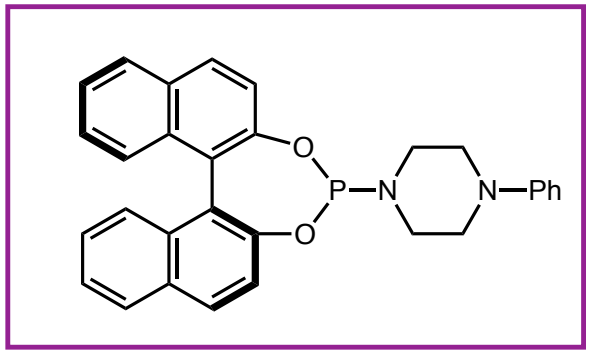
Corey, E. J.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1967**, *89*, 2755.

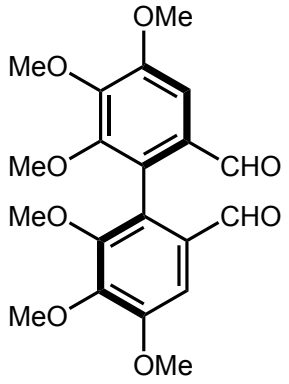
Nickel-Catalyzed Cross-Coupling in Total Synthesis

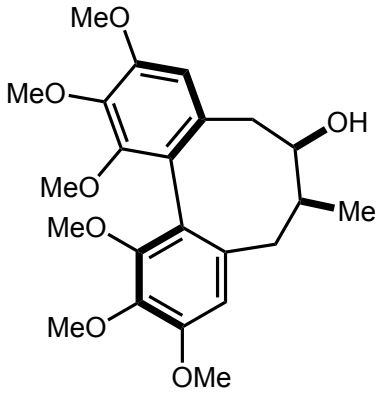


$NiCl_2(PPh_3)_2$, Bu_4Ni, Zn

67%, 68% ee



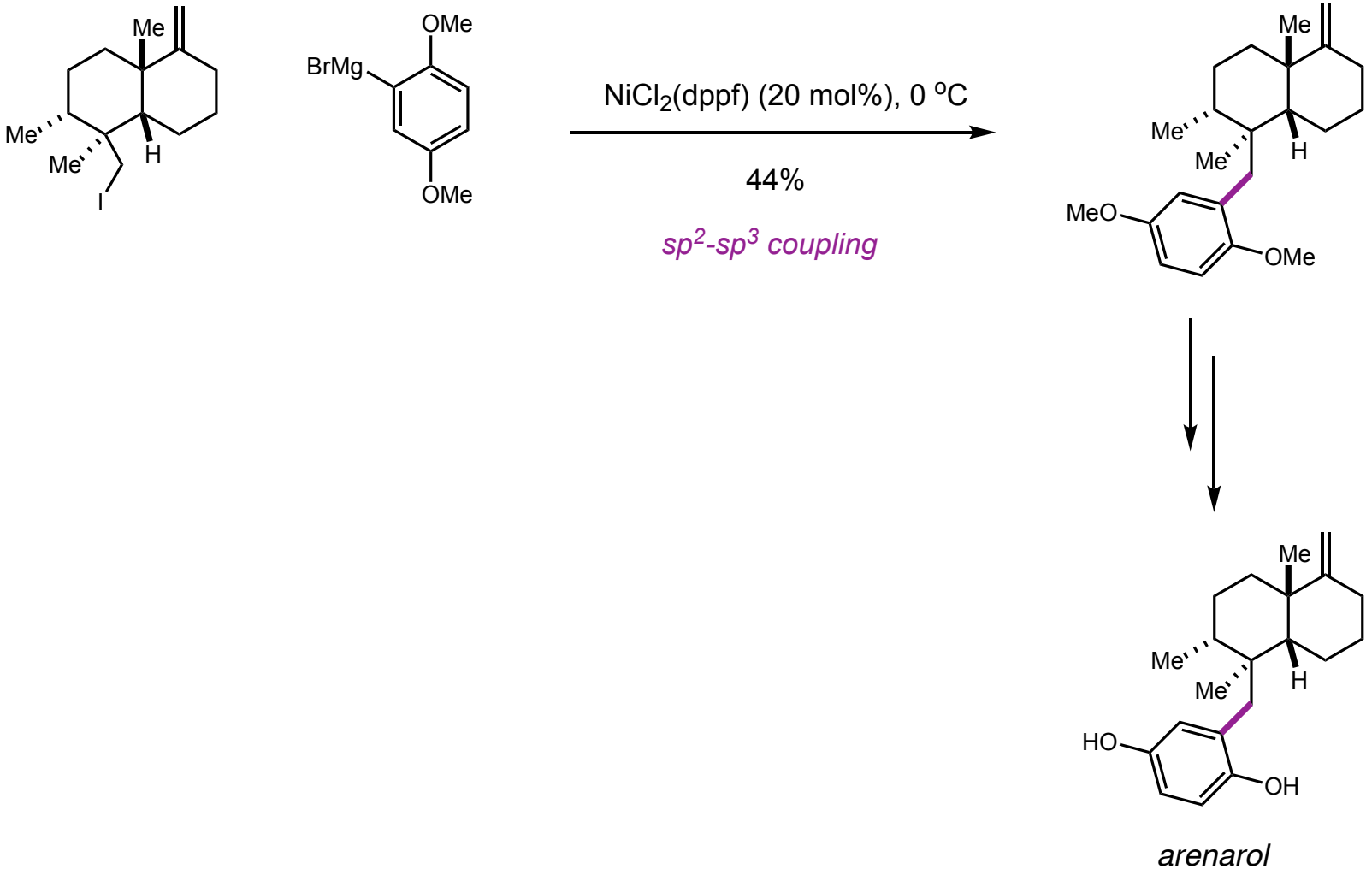




isoschizandrin

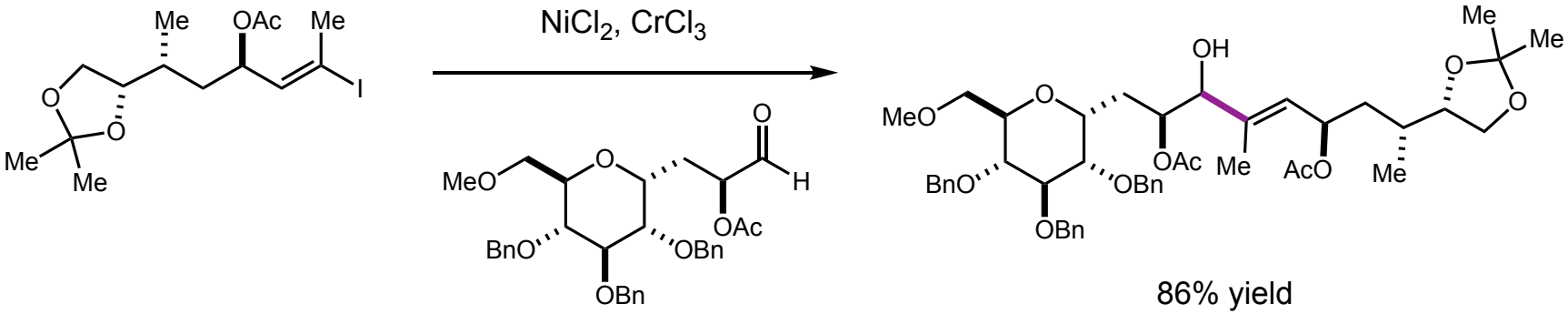
Chen, W.-W.; Zhao, Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 1072.

Nickel-Catalyzed Cross-Coupling in Total Synthesis



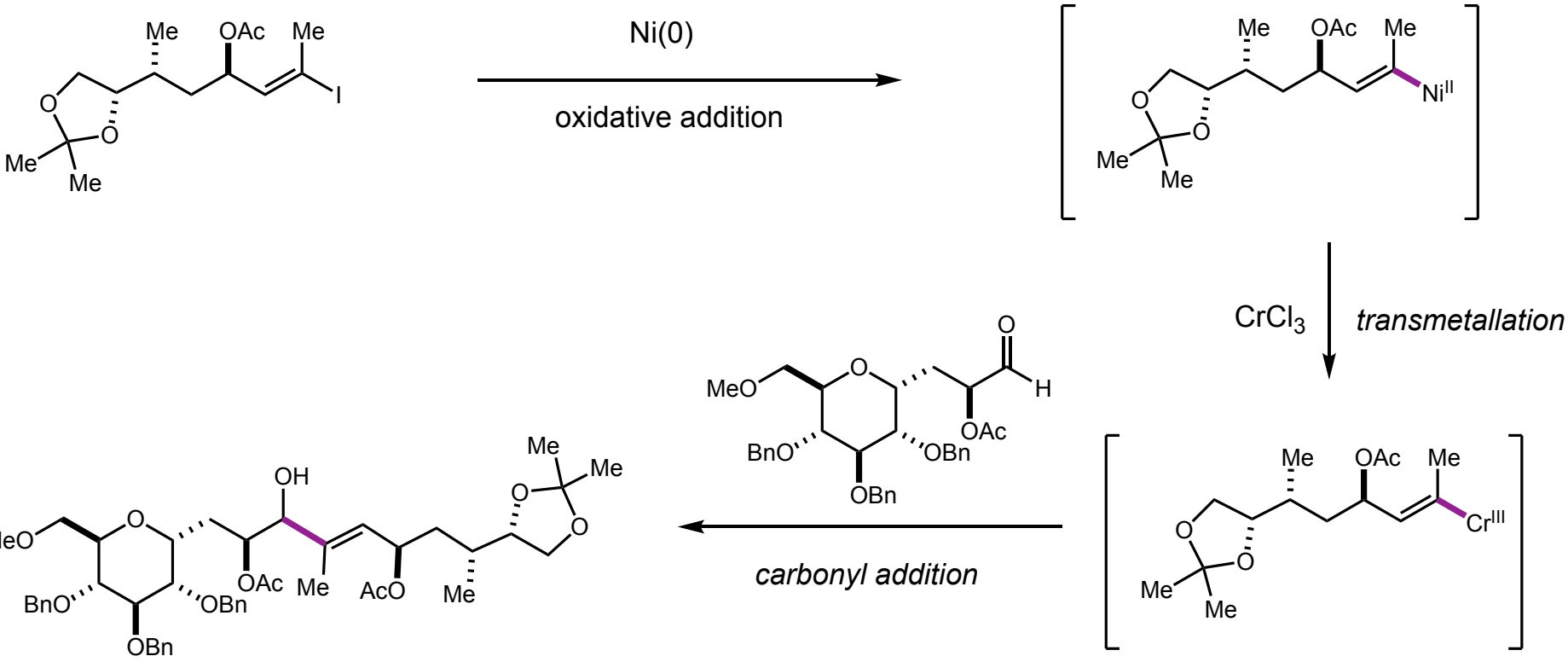
Watson, A. T.; Park, K.; Wiemer, D. F.; Scott, W. J. *J. Org. Chem.* **1995**, *66*, 5102.

Nozaki-Hiyama-Kishi Reaction in the Total Synthesis of Palytoxin



Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644

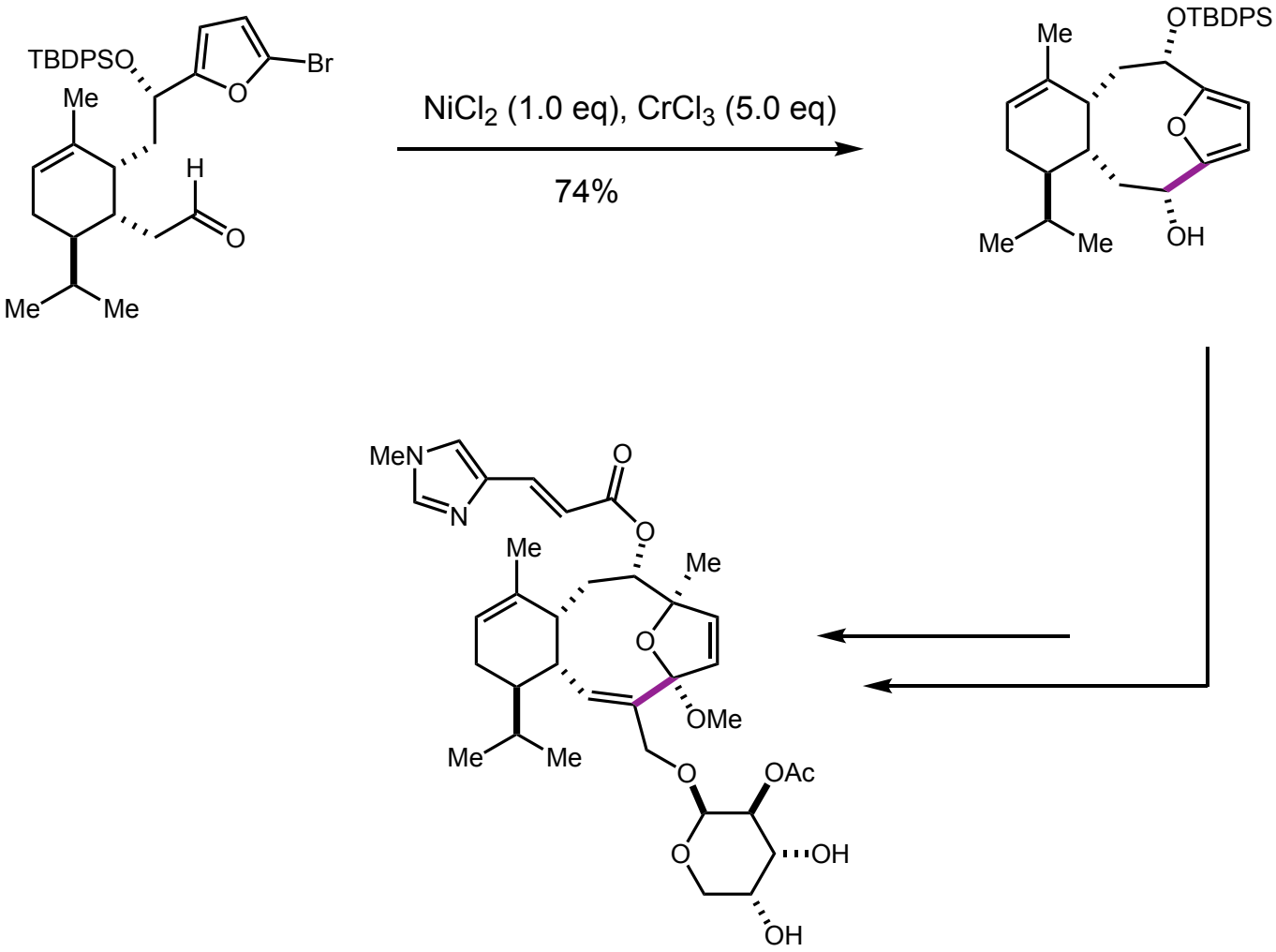
Nozaki-Hiyama-Kishi Reaction in the Total Synthesis of Palytoxin



86% yield

Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644

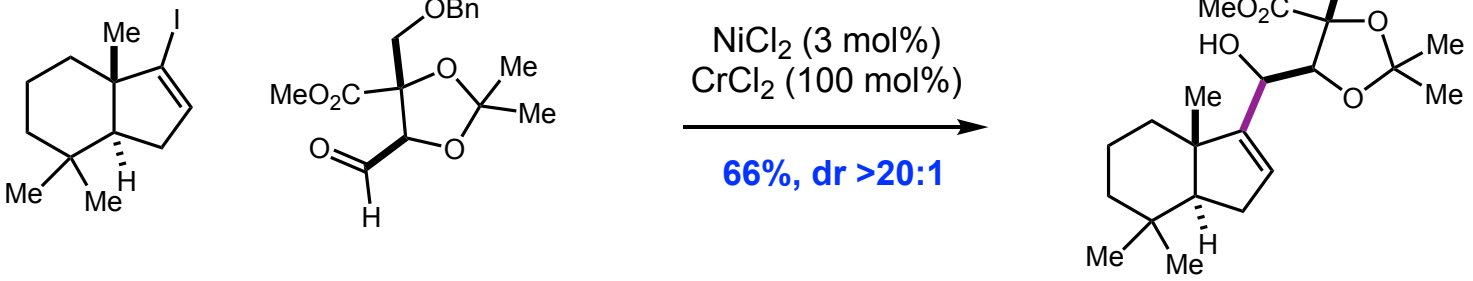
Nozaki-Hiyama-Kishi Reaction in the Total Synthesis of Eleutherobin



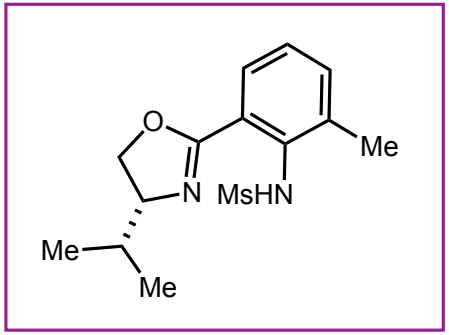
Eleutherobin

Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563.

Nozaki-Hiyama-Kishi Reaction in the Total Synthesis of Chromodorolide

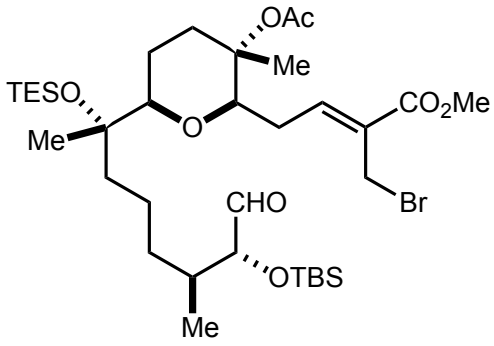


Core structure of *chromodorolide*



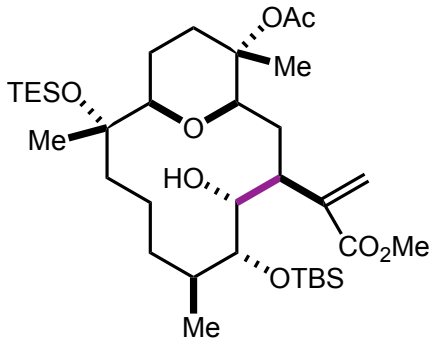
Tao, D. J.; Stutskyy, Y.; Overman, L. E. J. *J. Am. Chem. Soc.* **2016**, *138*, 2186.

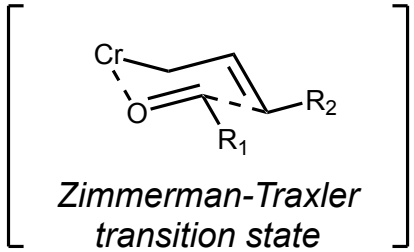
Nozaki-Hiyama-Kishi Allylation in Total Synthesis



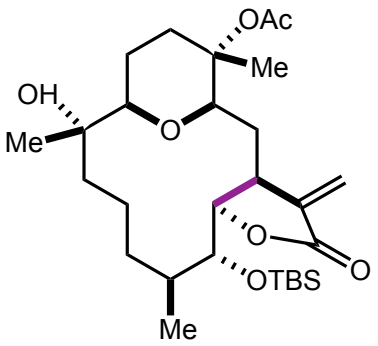
$CrCl_2$ (20 eq)

95%, single isomer





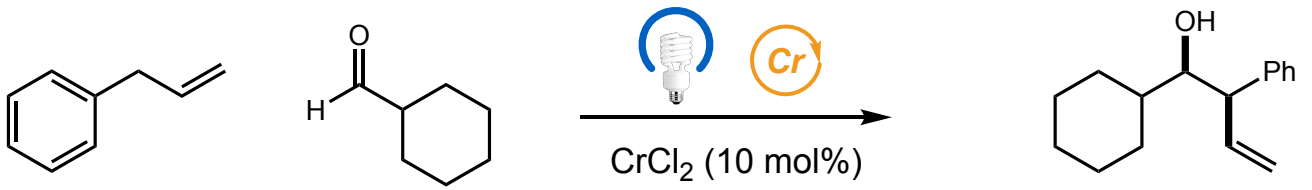
Zimmerman-Traxler transition state



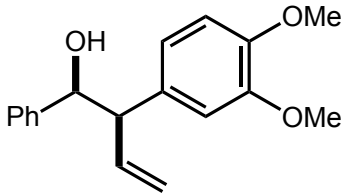
uprolide F

Zhu, L.; Tong, R. *Org. Lett.* **2015**, *17*, 1966.

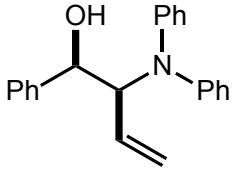
Diastereoselective Allylation of Aldehydes



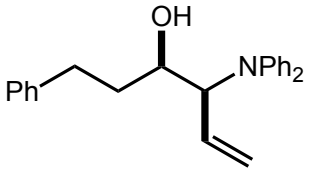
homoallylic alcohol



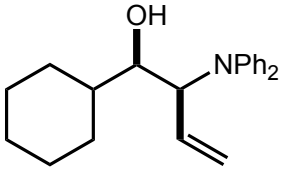
95% yield, dr >19:1



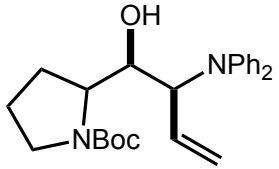
85% yield, dr >19:1



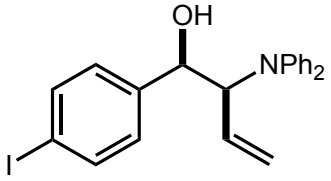
90% yield, dr >19:1



56% yield, dr >19:1



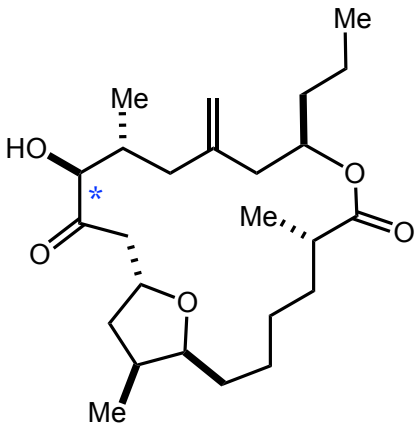
82% yield, dr >19:1



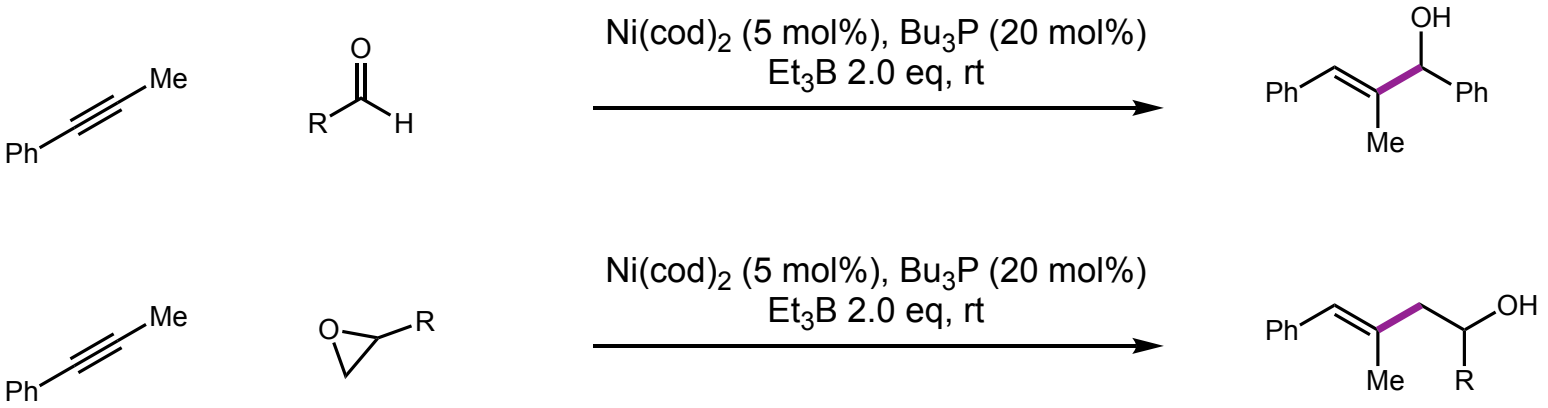
86% yield, dr >19:1

Schwarz, J. L.; Schafë rs, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F. *J. Am. Chem. Soc.* **2018**, *140*, 12705.

Nickel-Catalyzed Alkyne-Aldehyde Reductive Coupling in Total Synthesis

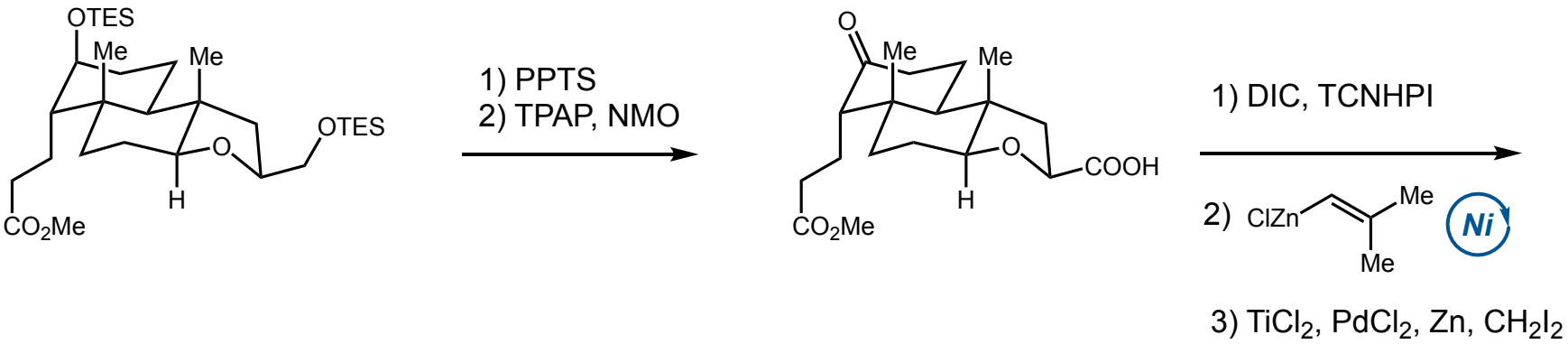


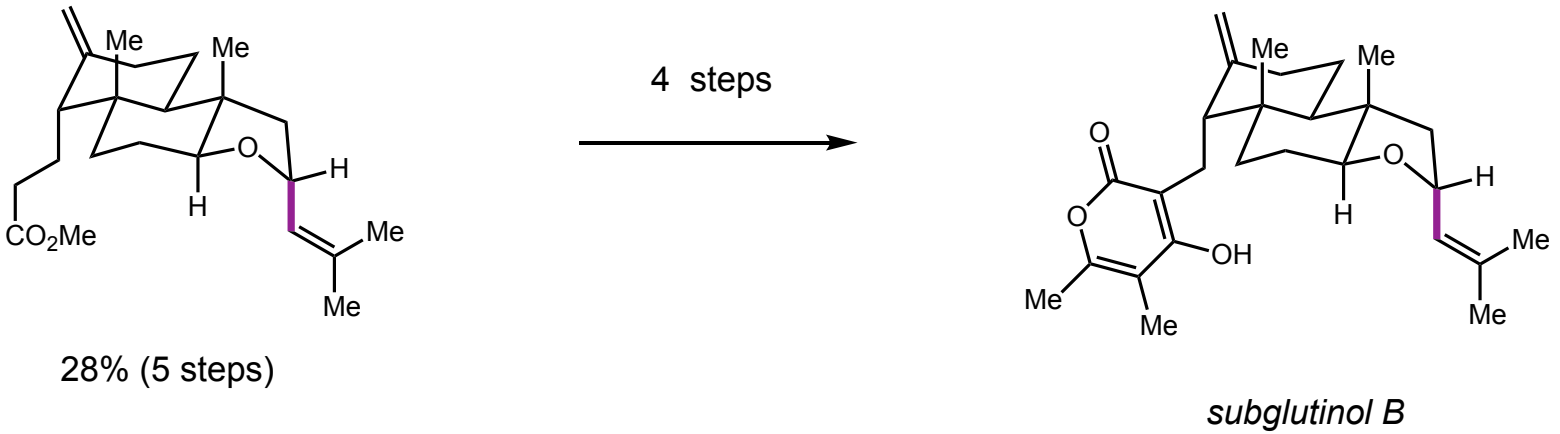
amphidinolide T1



Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998
Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297

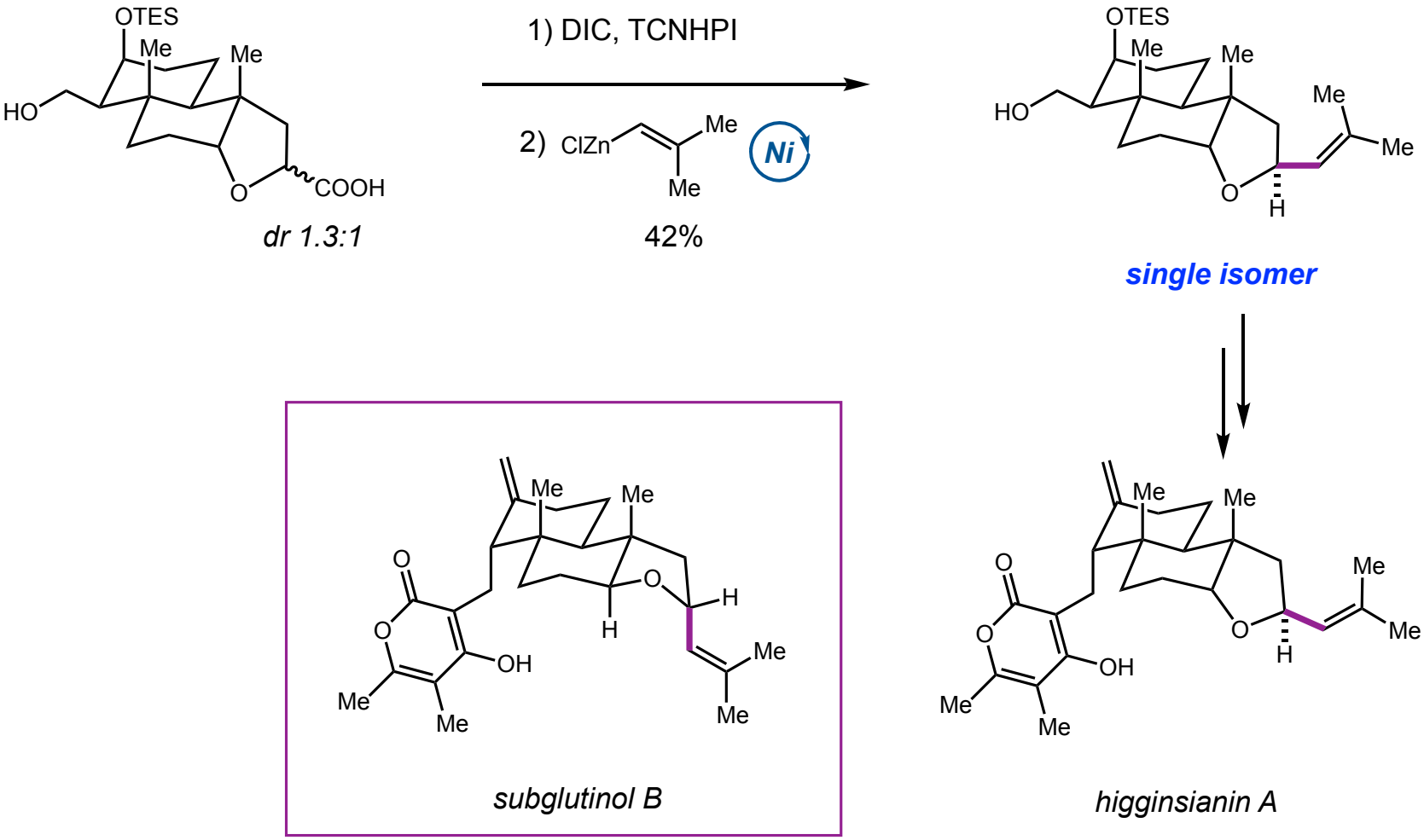
Decarboxylative Coupling via Nickel Catalysis in Total Synthesis





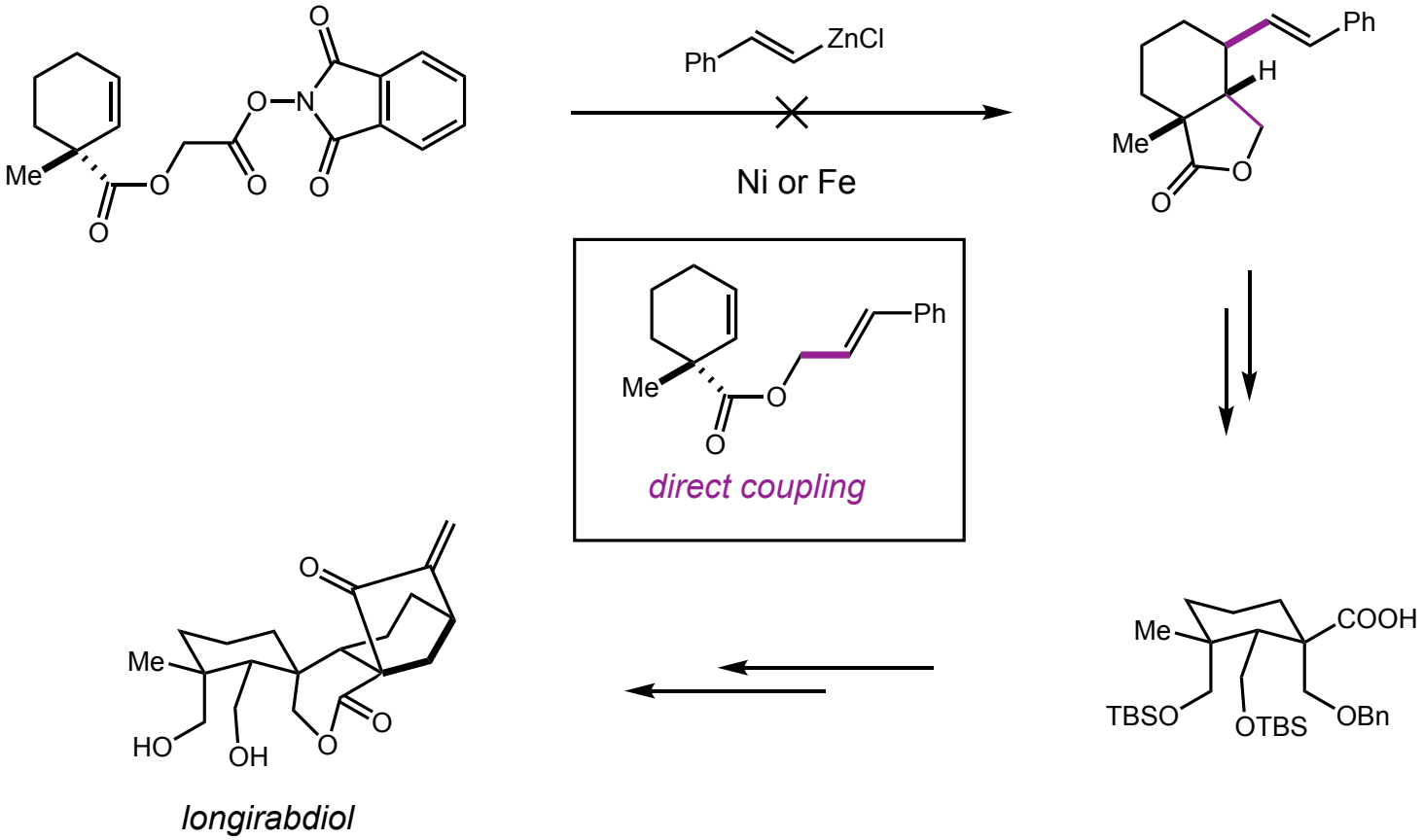
Merchant, R. R.; Oberg, K. M.; Lin, Y.; Novak, A. J. E.; Felding, J.; Baran, P. S *J. Am. Chem. Soc.* **2018**, *140*, 7462.

Decarboxylative Coupling via Nickel Catalysis in Total Synthesis



Merchant, R. R.; Oberg, K. M.; Lin, Y.; Novak, A. J. E.; Felding, J.; Baran, P. S *J. Am. Chem. Soc.* **2018**, *140*, 7462.

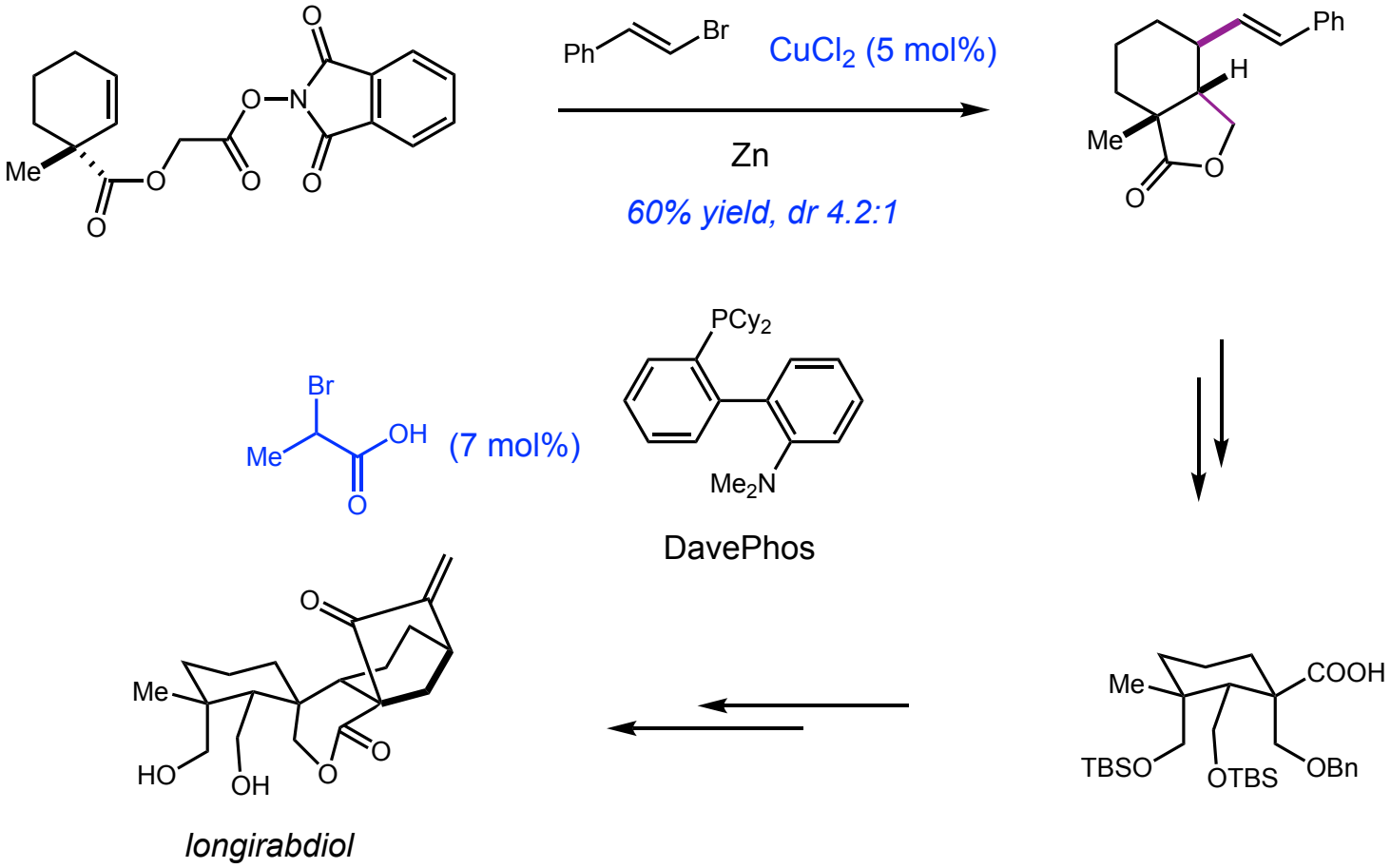
Decarboxylative Coupling via Nickel Catalysis in Total Synthesis



longirabdiol

Zhang, J.; Li, Z.; Zhuo, J.; Cui, Y.; Han, T.; Li, C. *J. Am. Chem. Soc.* **2019**, *141*, 8372.

Decarboxylative Coupling via Nickel Catalysis in Total Synthesis



Zhang, J.; Li, Z.; Zhuo, J.; Cui, Y.; Han, T.; Li, C. *J. Am. Chem. Soc.* **2019**, *141*, 8372.