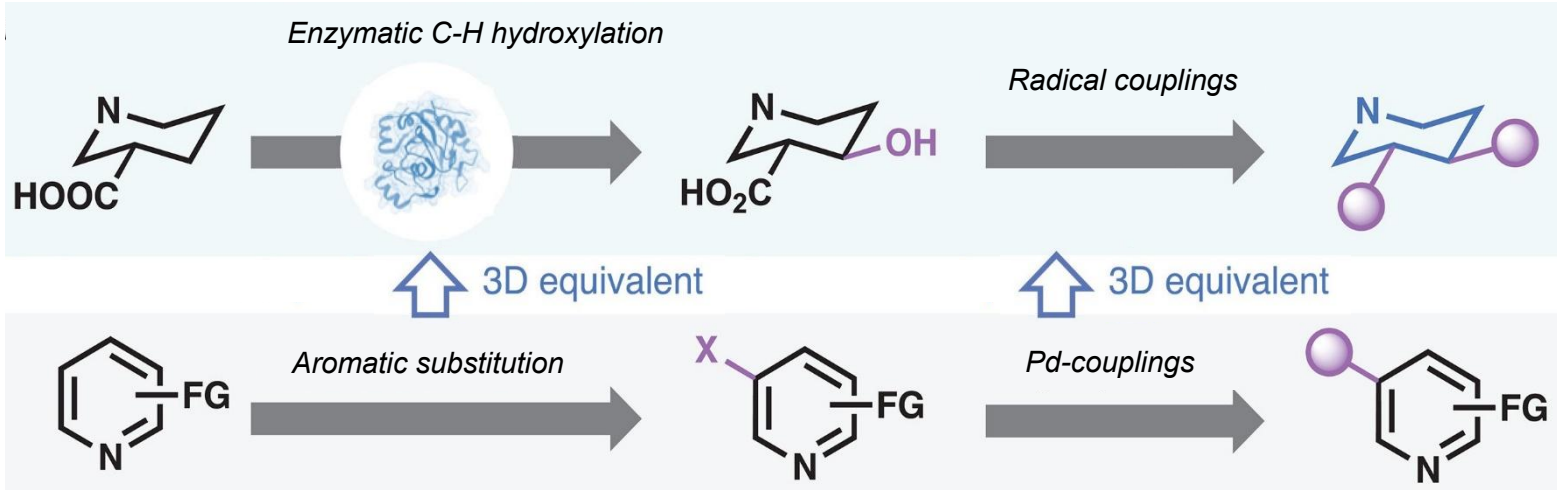
# Biocatalytic C–H oxidation meets radical crosscoupling
# Simplifying complex piperidine synthesis




**Yongle Luo**

**1/18/2025**

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B.S. New York University, 1997

Ph.D. The Scripps Research Institute, 2001

Postdoctor, Harvard University, E.J. Corey

Associate Professor, Scripps Institute, 2003

Professor, Scripps Institute, 2008-present

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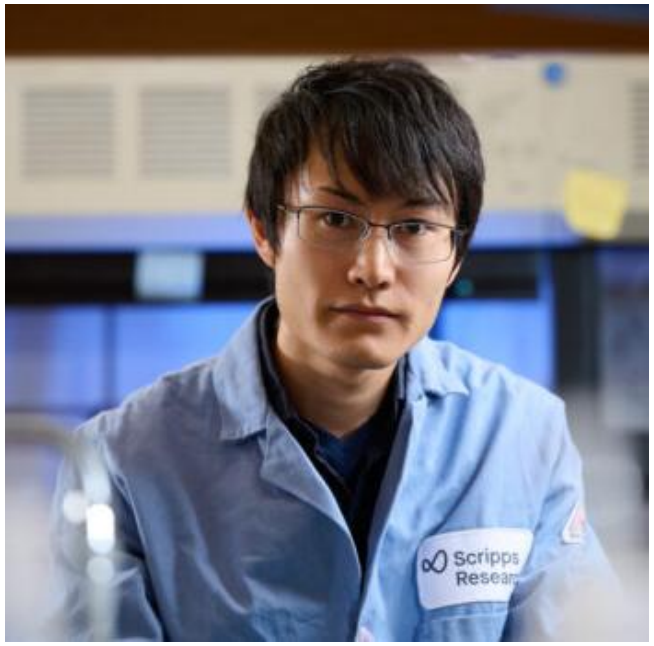
B.S. Columbia University, 2008

Ph.D. The Scripps Research Institute, 2013

Postdoctor, Caltech, Frances Arnold

Investigator, Scripps Institute, 2016

Associate Professor, Rice University, 2022-present



## Yu Kawamata

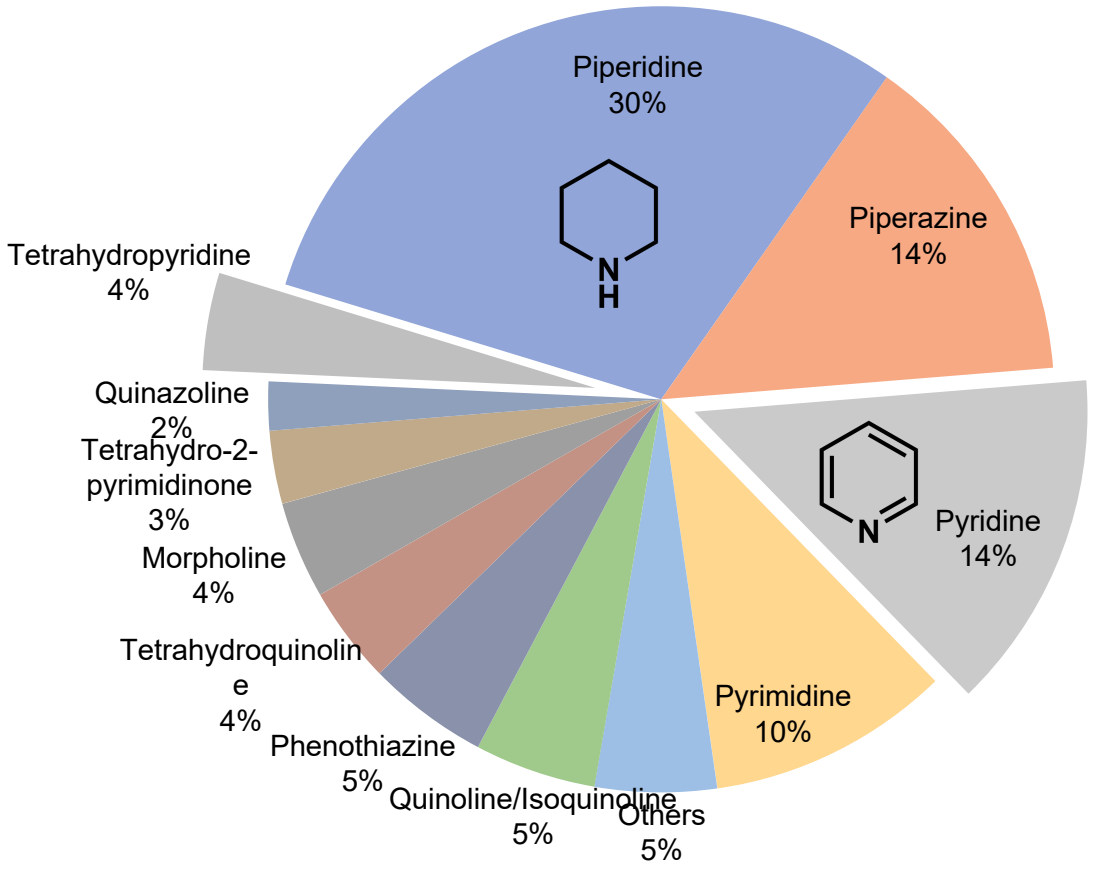
Institute investigator
Scripps Research Institute

B.S. Kyoto University, 2011

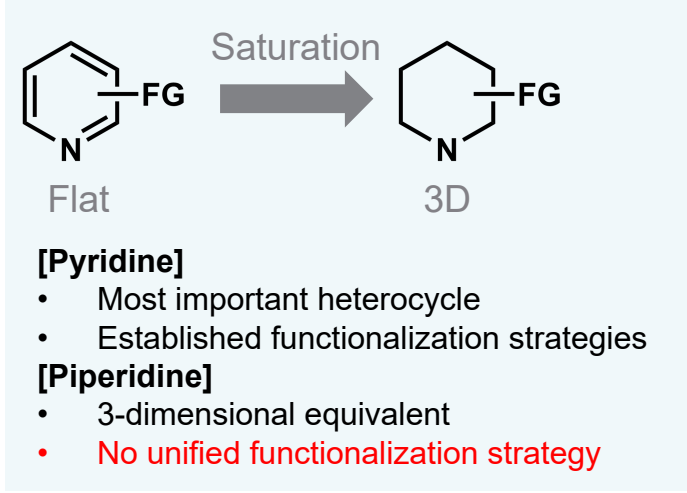
B.S. Kyoto University, 2013

Ph.D. Kyoto University, 2016

# Piperidine is a representative motif in drugs and natural products

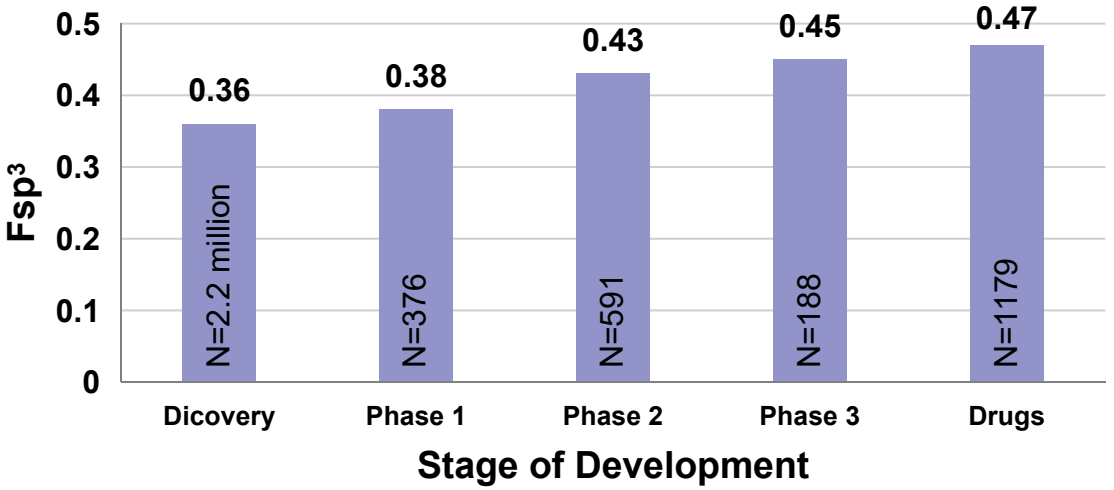



**Distribution of *N*-heterocyclic drugs in the FDA database**




**[Pyridine]**
- Most important heterocycle
- Established functionalization strategies

**[Piperidine]**
- 3-dimensional equivalent
- No unified functionalization strategy

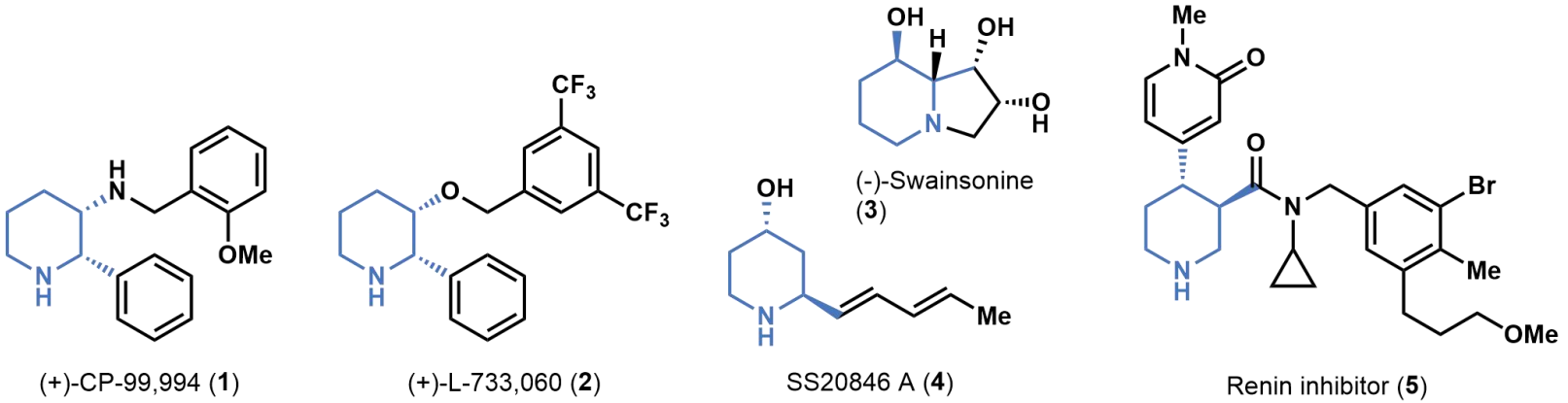


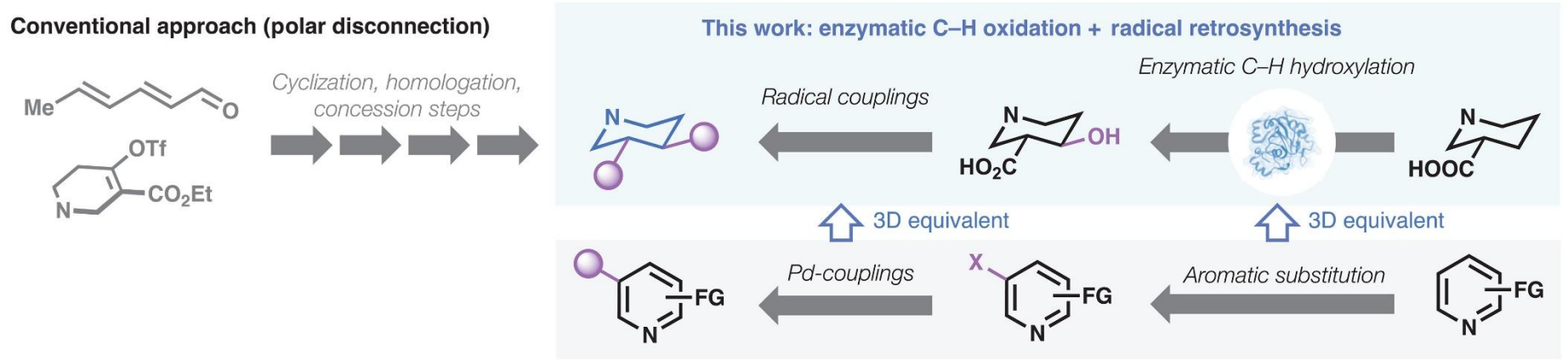

$Fsp^3$ = (number of $sp^3$ hybridized carbons/total carbon count)

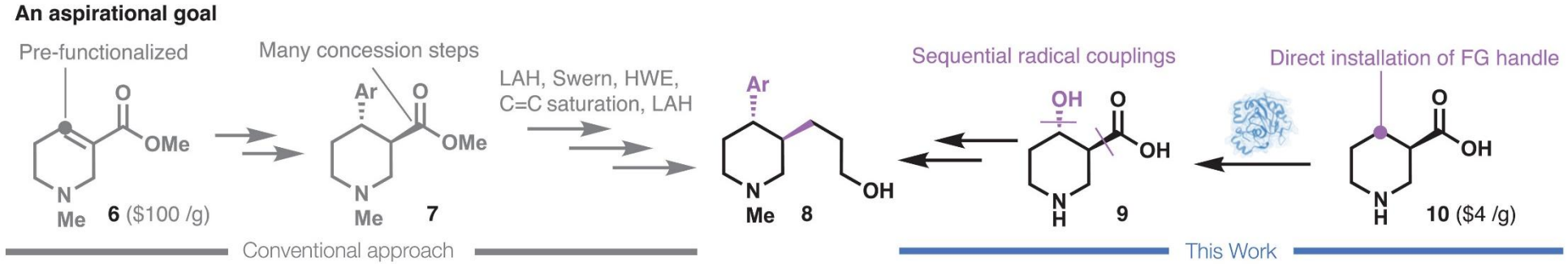
Wang, Y. et al. *DDDT* **2021**, *Volume 15*, 4289–4338.

Humblet, C. et al. *J. Med. Chem.* **2009**, *52* (21), 6752–6756.

# Two stage elaboration of 3D scaffolds analogous to “flatland” strategies

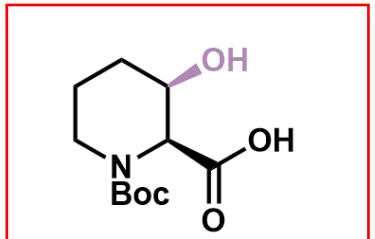


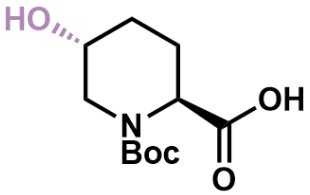
# Scalable, biocatalytic synthesis of hydroxylated piperidines

## Preparative scale production of enantiopure piperidine building blocks



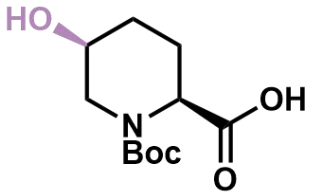

14

82% over 2 steps*
$1,737/g (ChemScene)



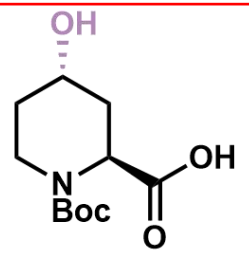

15

78% over 2 steps
$1,028/g (ChemScene)



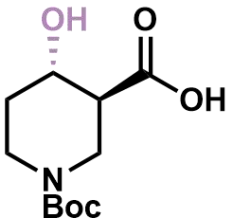

16

67% over 2 steps
$773/g (ChemScene)



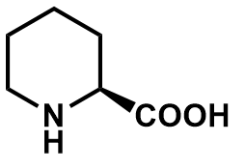

17

99% over 2 steps**
$1,241/g (ChemScene)



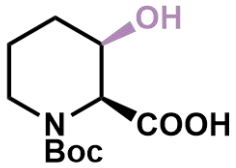

18

78% over 2 steps
Not commercial



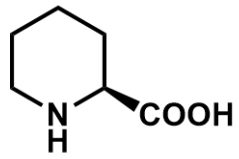

11

1. GetF, $O_2$, αKG, $Fe^{2+}$
2. $Boc_2O$
74% yield over 2 steps
(500 mg scale)



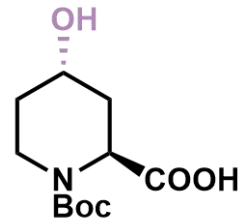

14

Renata, H. et al. *J. Am. Chem. Soc.* **2021**, *143* (3), 1673–1679.




11

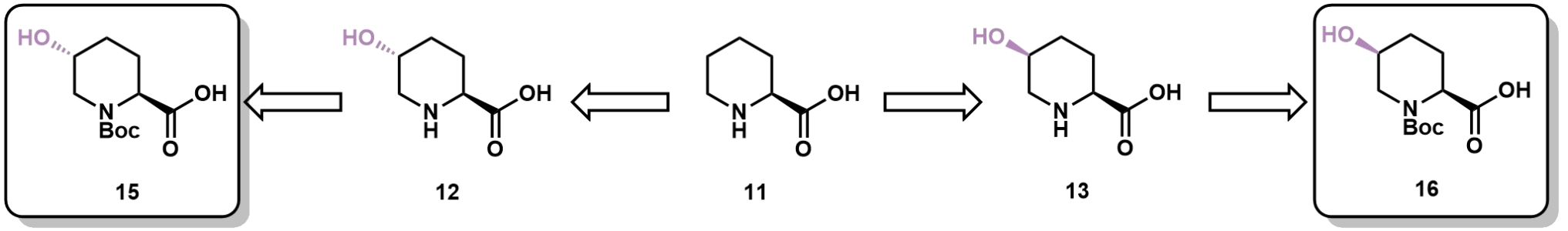
1. FoPip4H, $O_2$, αKG, ascorib acid
2. $Boc_2O$, NaOH, EtOH
100% yield over 2 steps
(multi-aram scale)

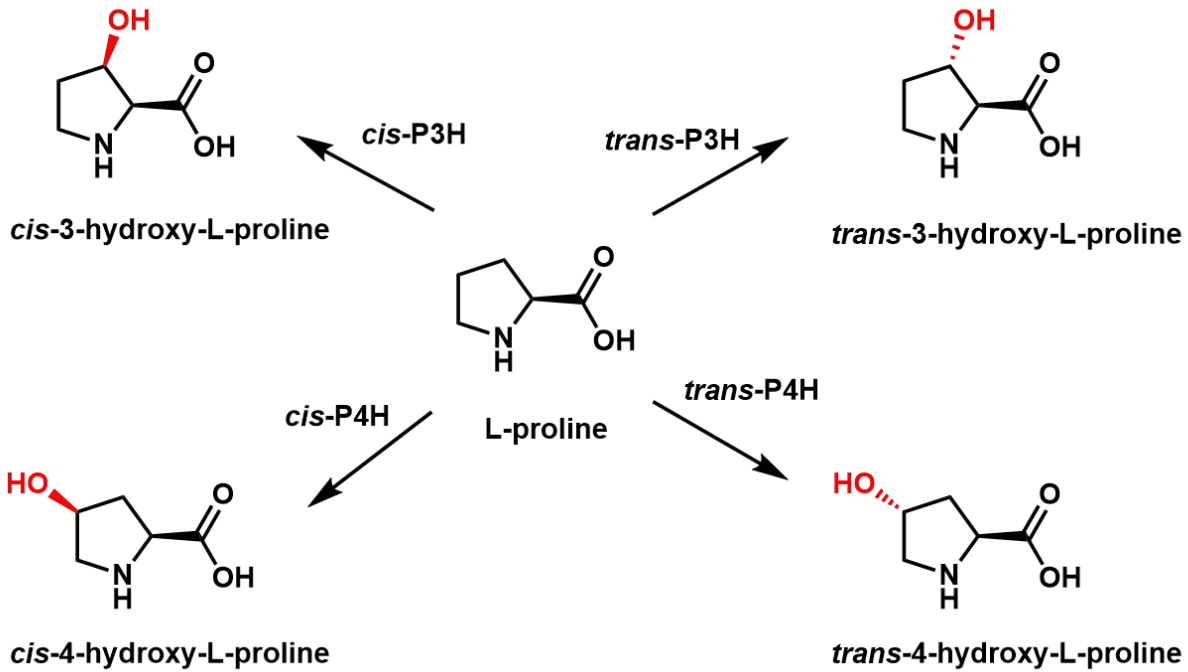


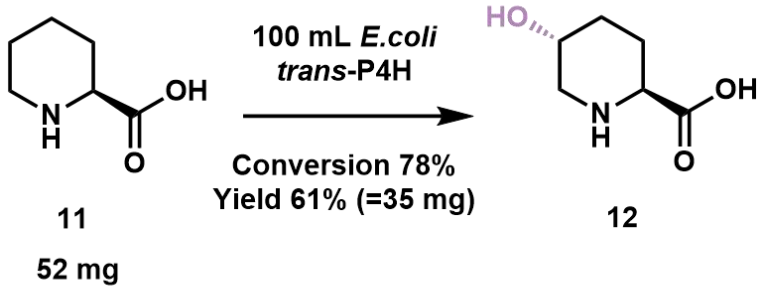

17

Renata, H. et al. *ACS Cent. Sci.* **2023**, *9* (2), 239–251.

# Enzyme discovery for building block construction



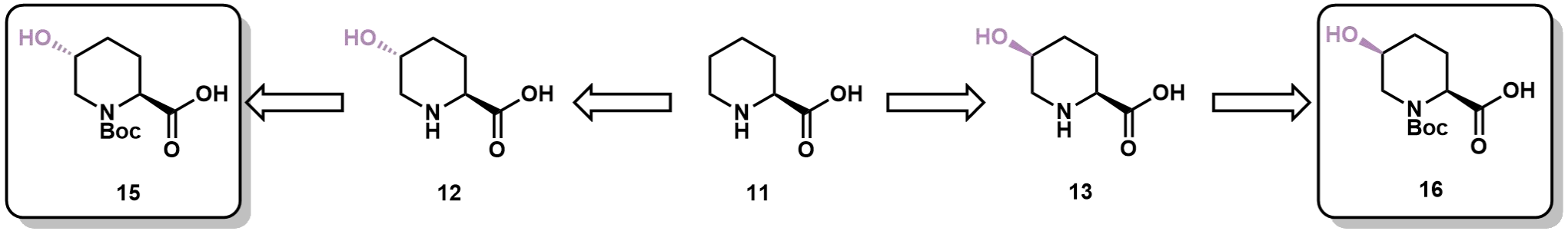




Eluted in a fraction together with 13 mg trans-4-hydroxyproline.
Product concentrations were determined by HPLC.

Hüttel, W. et al. *Adv Synth Catal* **2011**, *353* (8), 1375–1383.

# Enzyme discovery and optimization for building block construction

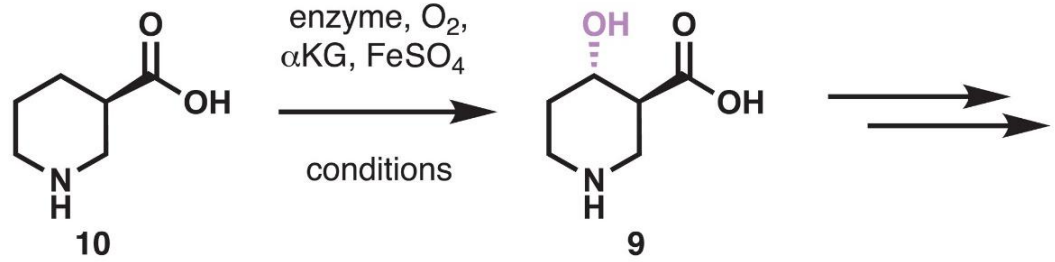


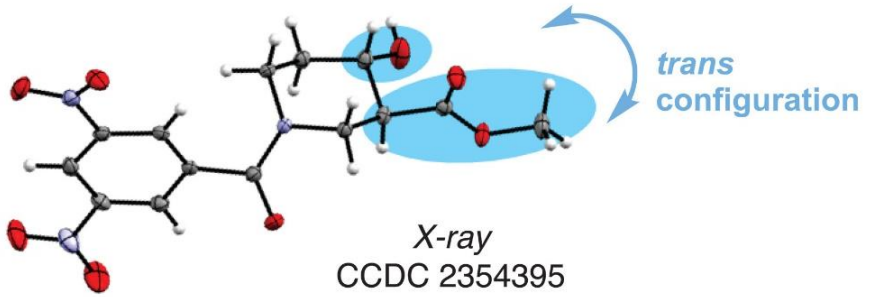


| [Substrate] (mM) | αKG equiv. | $Fe^{2+}$ equiv. | Headspace (volume %) | Buffer pH | Conversion ($^1$H NMR) |
|---|---|---|---|---|---|
| 4.0 | 2.0 | 0.25 | 80 | 6.5 | 39% |
| 4.0 | 2.0 | 0.25 | 80 | 7.0 | 50% |
| 4.0 | 2.0 | 0.25 | 80 | 8.0 | 45% |
| 4.0 | 5.0 | 0.50 | 80 | 7.0 | 86% |
| 8.0 | 5.0 | 0.25 | 90 | 7.0 | 100% |
| 15 | 5.0 | 0.13 | 90 | 7.0 | 100% |

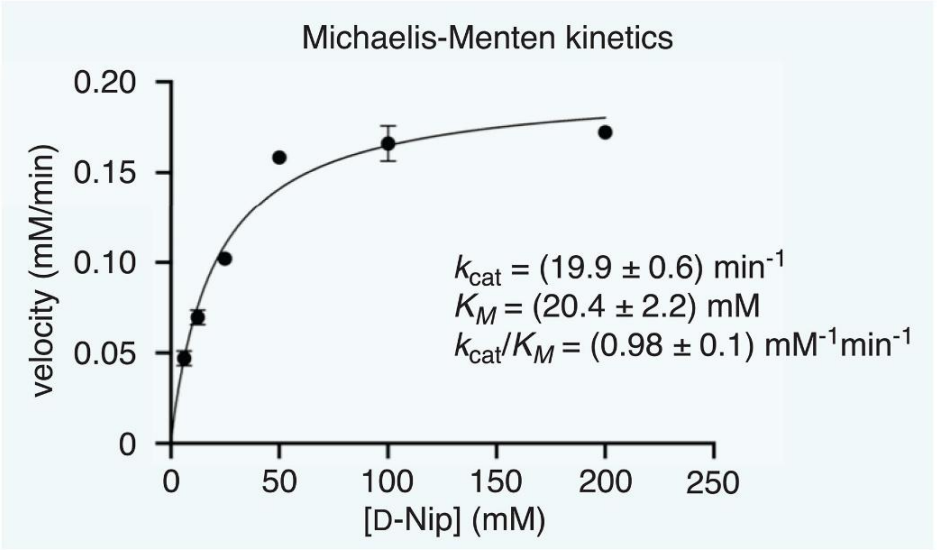
| [Substrate] (mM) | Enzyme | αKG equiv. | $Fe^{2+}$ equiv. | Buffer pH | Conversion ($^1$H NMR) |
|---|---|---|---|---|---|
| 20 | XdPH YR | 2.0 | 0.05 | 6.5 | 0% |
| 20 | XdPH YR | 2.0 | 0.10 | 6.5 | 0% |
| 20 | P4H810 | 2.0 | 0.10 | 6.5 | 80% |
| 10 | P4H810 | 2.0 | 0.20 | 6.5 | 89% |
| 10 | P4H810 | 2.0 | 0.20 | 7.0 | 70% |
| 10 | P4H810 | 2.0 | 0.20 | 8.0 | 100% |

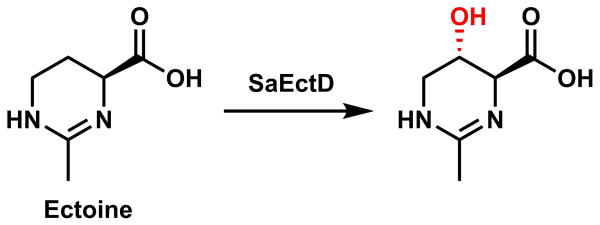
# Enzyme discovery and optimization for building block construction




| [Substrate] (mM) | Enzyme | αKG equiv. | $Fe^{2+}$ equiv. | Buffer pH | Conversion ($^1$H NMR) |
|---|---|---|---|---|---|
| 8.0 | *trans*-P4H | 5.0 | 0.25 | 7.0 | 0% |
| 10 | P4H810 | 2.0 | 0.20 | 8.0 | 0% |
| 10 | *Fo*Pip4H | 2.5 | 0.10 | 7.5 | 0% |
| 10 | *Sa*EctD | 2.5 | 0.10 | 7.5 | 94% |
| 10 | *Sa*EctD | 5.0 | 0.10 | 7.5 | 100% |
| 15 | *Sa*EctD | 5.0 | 0.07 | 7.5 | 100% |

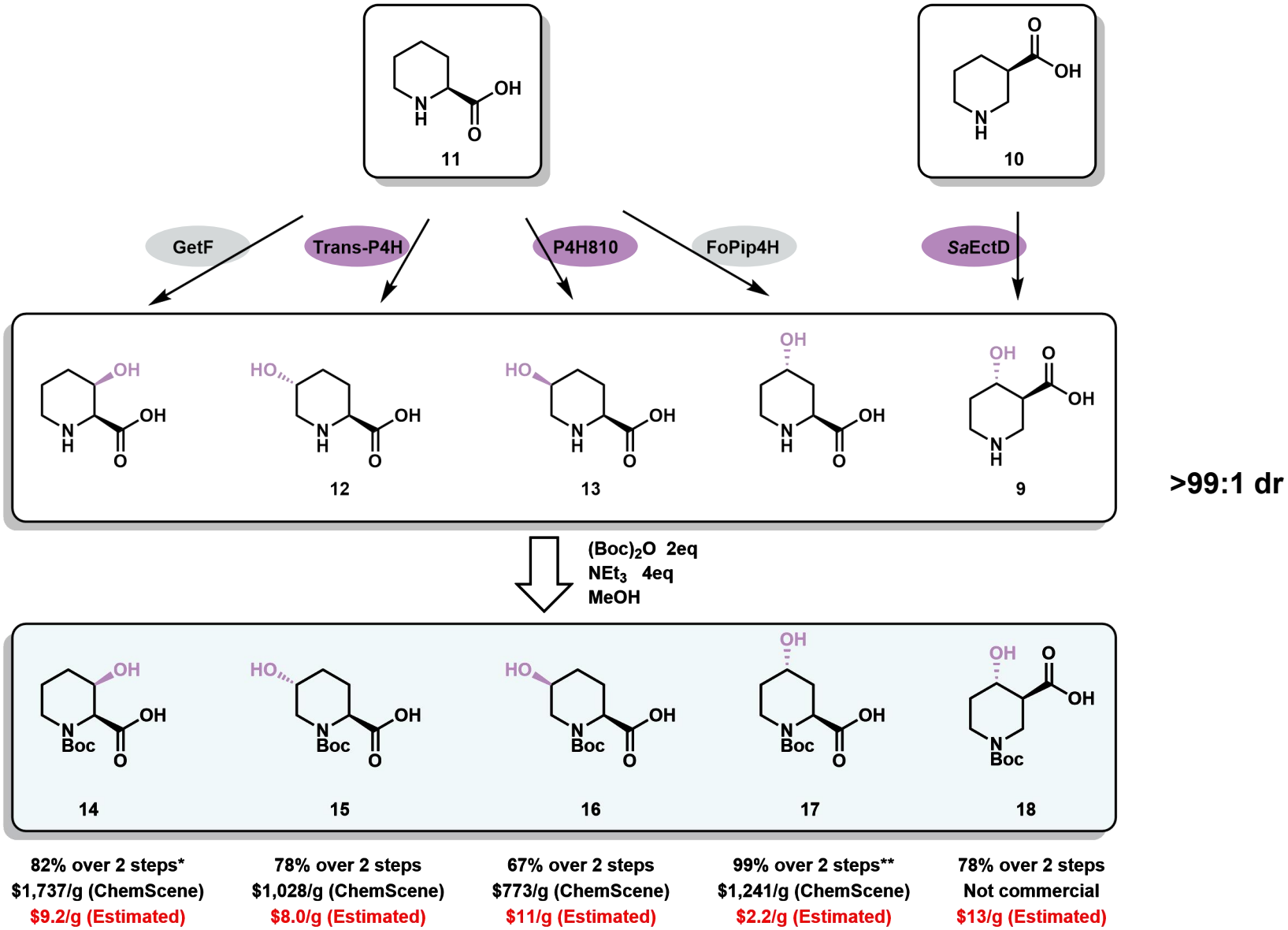


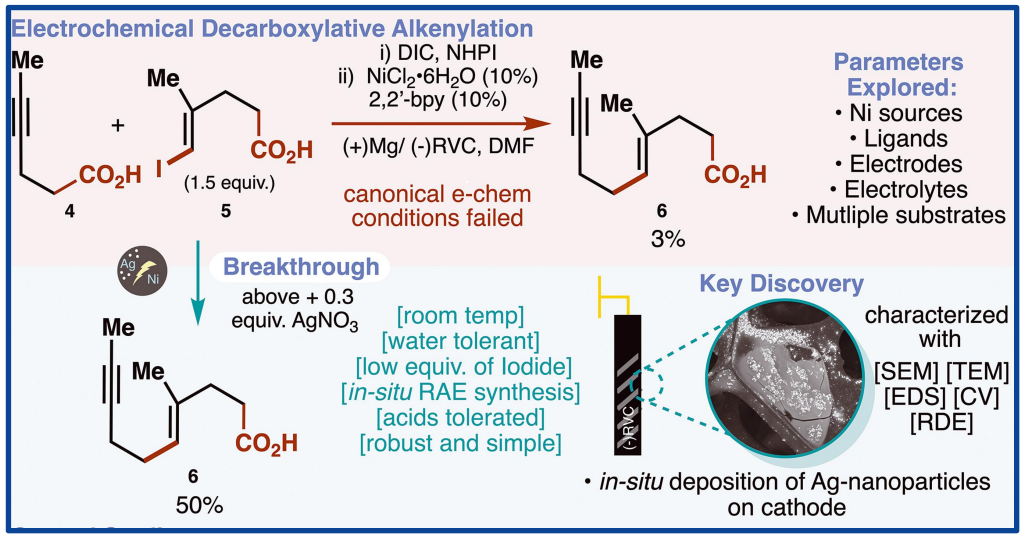

SaEctD was identified from *Sphingopyxis alaskensis*

Vargas, C. et al. *J Bacteriol* **2006**, *188* (11), 3774–3784.

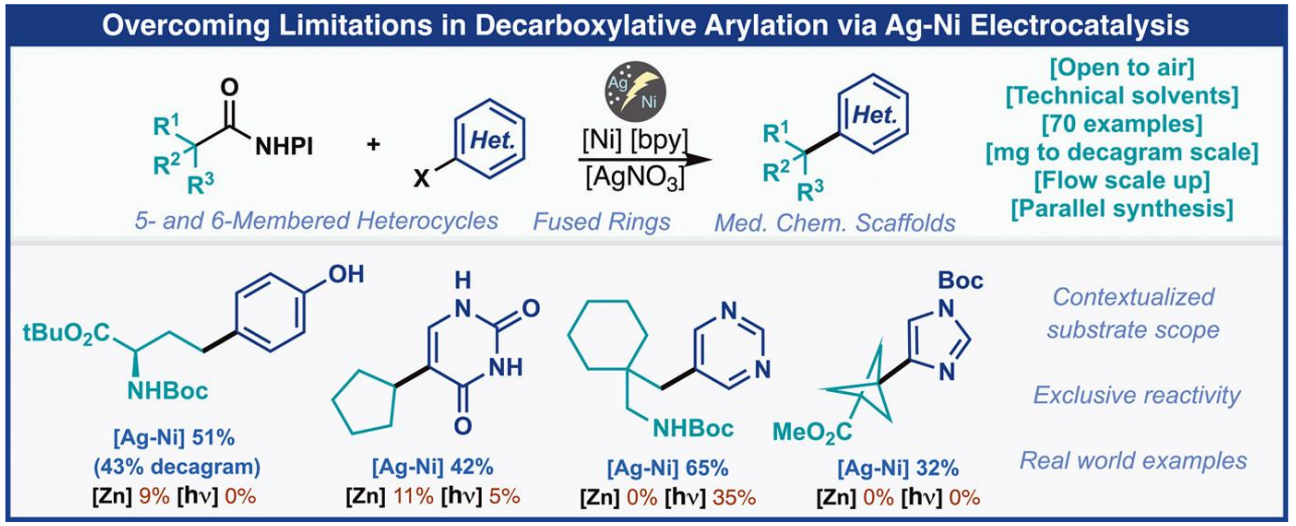
# Preparative scale production of enantiopure piperidine building blocks



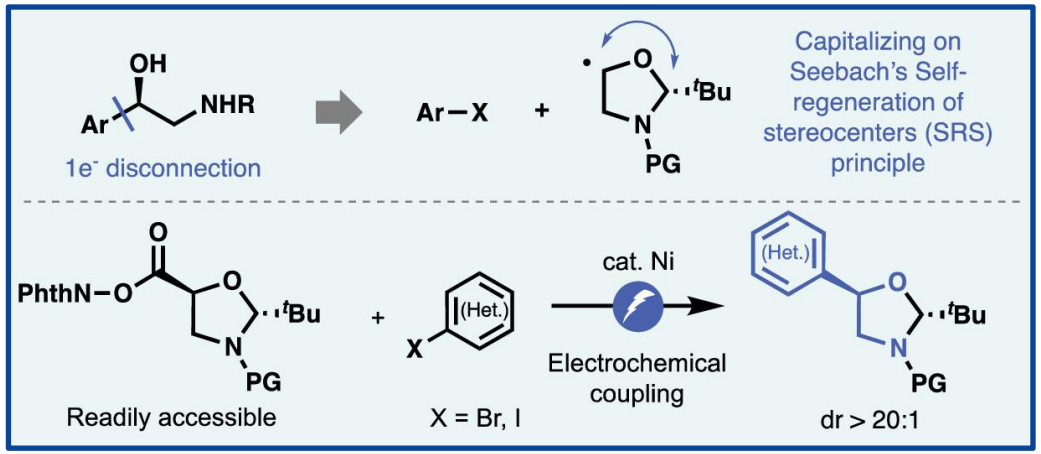
# Radical cross-coupling



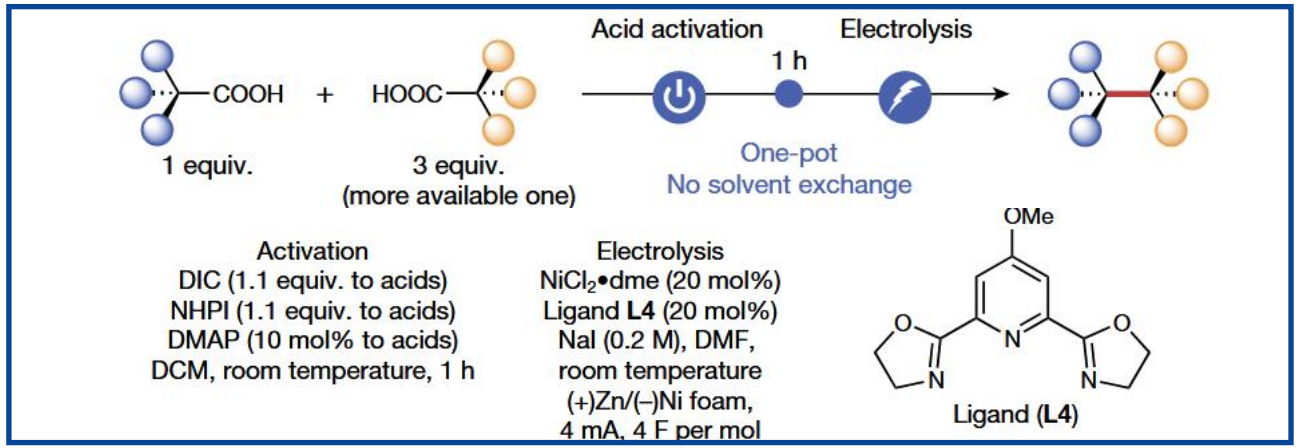

Baran, P. S. et al. *Science* **2022**, *375* (6582), 745–752.




Baran, P. S. et al. *J. Am. Chem. Soc.* **2022**, *144* (38), 17709–17720.



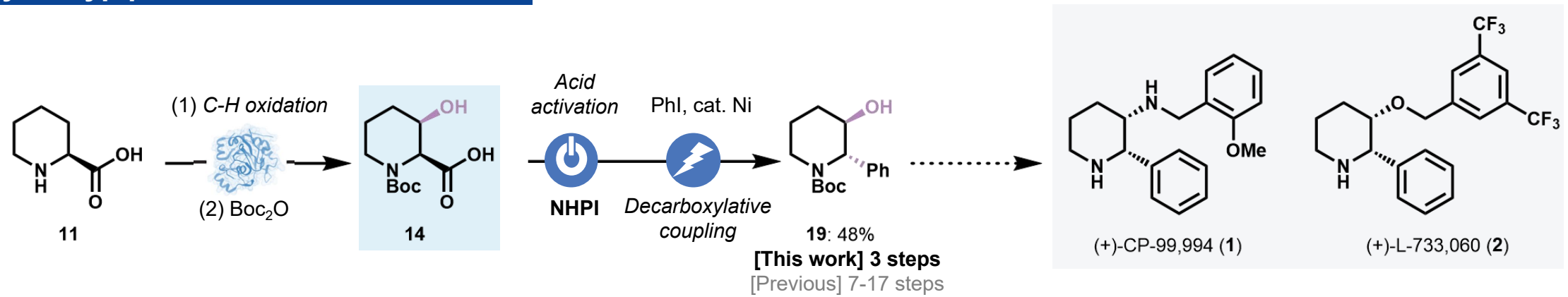

Baran, P. S. et al. *J. Am. Chem. Soc.* **2024**, *146* (9), 6209–6216.



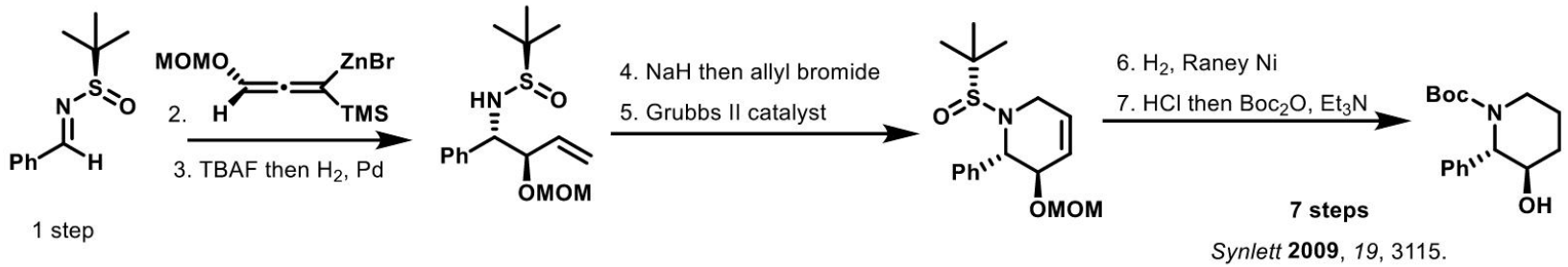

Baran, P. S. *Nature* **2022**, *606* (7913), 313–318.

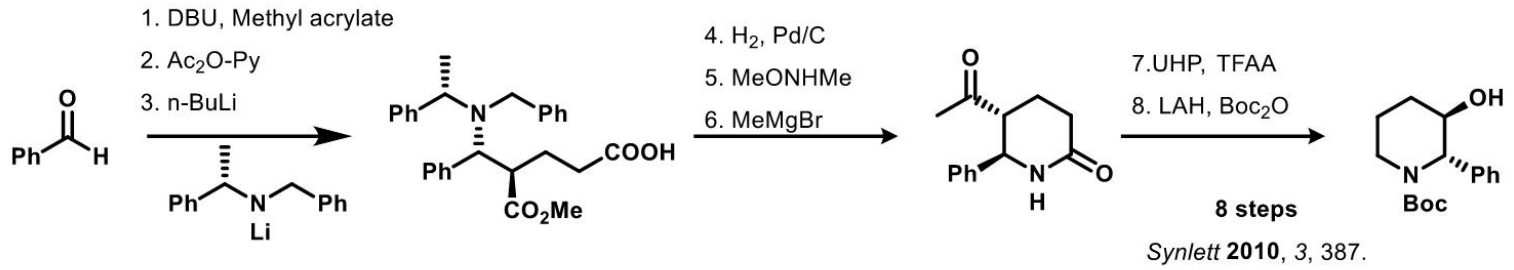
# Modular radical cross-coupling to simplify complex piperidine synthesis

## 3-Hydroxypipecolic acid diversification



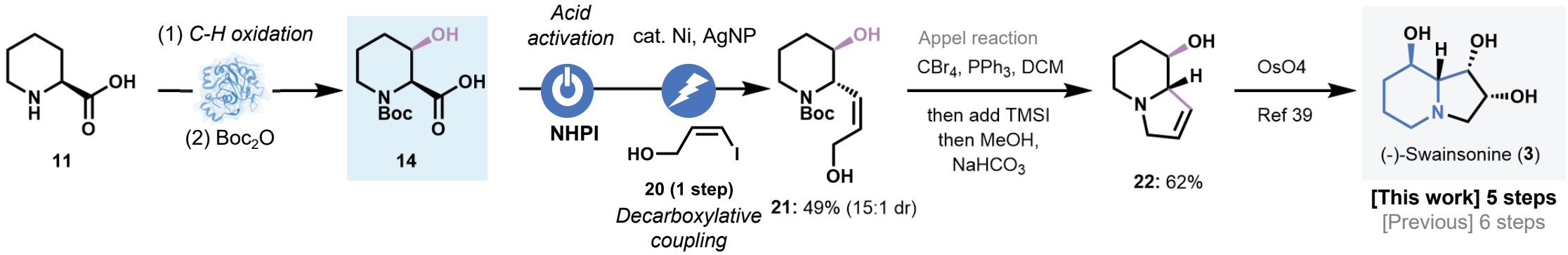

Previous works



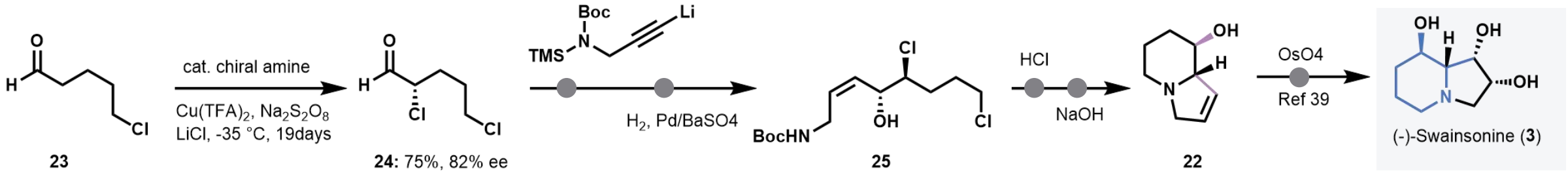



# Modular radical cross-coupling to simplify complex piperidine synthesis

## 3-Hydroxypipecolic acid diversification



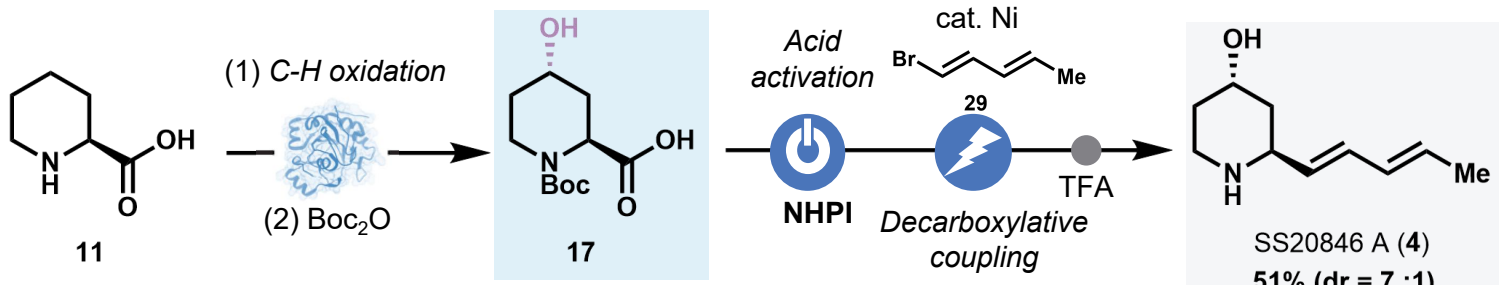

Previous works




Britton, R. et al. *Org. Lett.* **2013**, *15* (8), 1914–1917.

# Modular radical cross-coupling to simplify complex piperidine synthesis

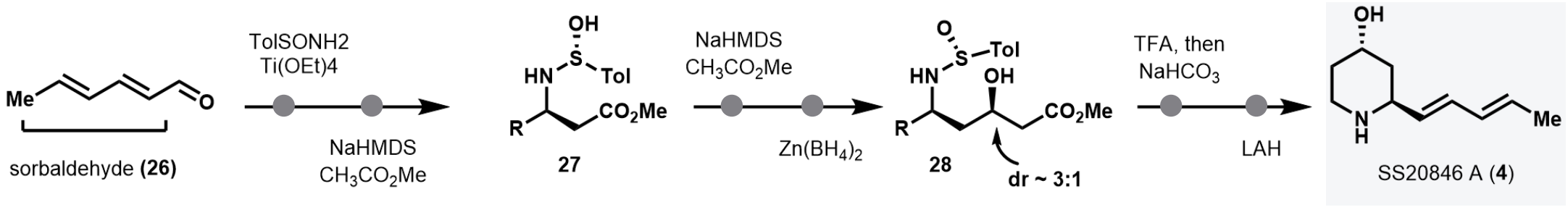
## 4-Hydroxypipecolic acid diversification




**[This work] 3 steps**

[Previous] 6 steps

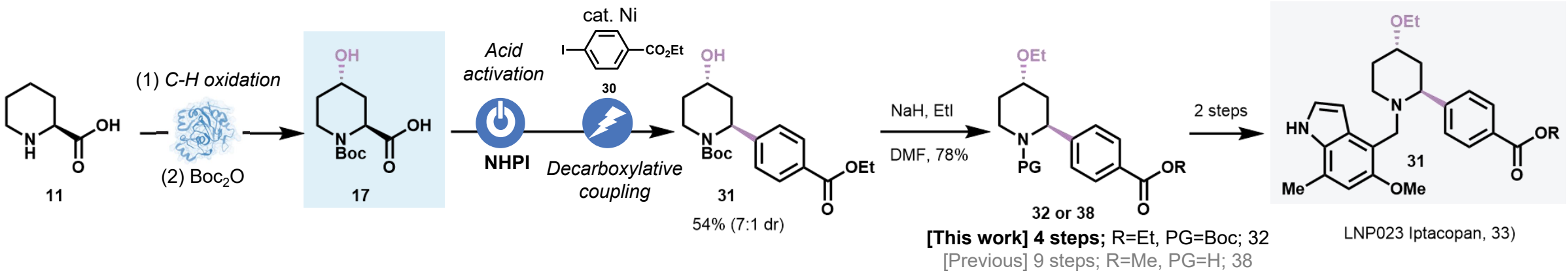
Previous works



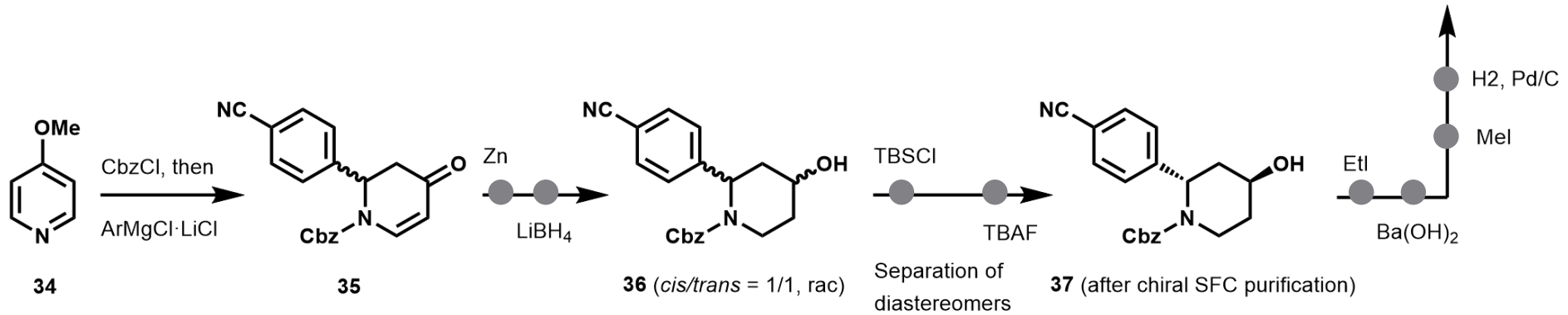

Szewczyk, J. M. et al. *Org. Lett.* **2000**, *2* (8), 1041–1043.

# Modular radical cross-coupling to simplify complex piperidine synthesis

## 4-Hydroxypipecolic acid diversification



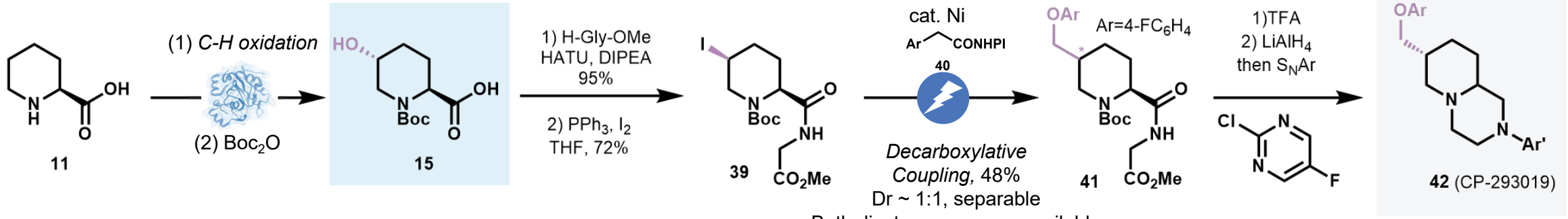

Previous works




Adams, C. M. et al. *J. Med. Chem.* **2020**, *63* (11), 5697–5722.

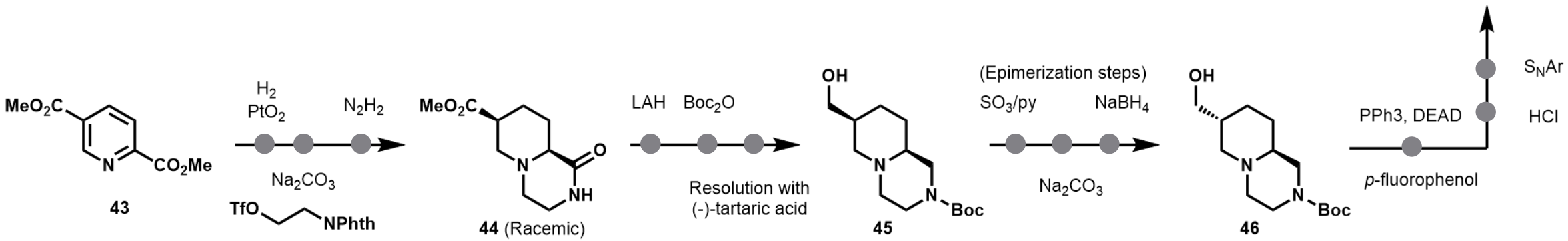
# Modular radical cross-coupling to simplify complex piperidine synthesis

## 5-Hydroxypipecolic acid diversification




**[This work] 7 steps**
[Previous] 12 steps

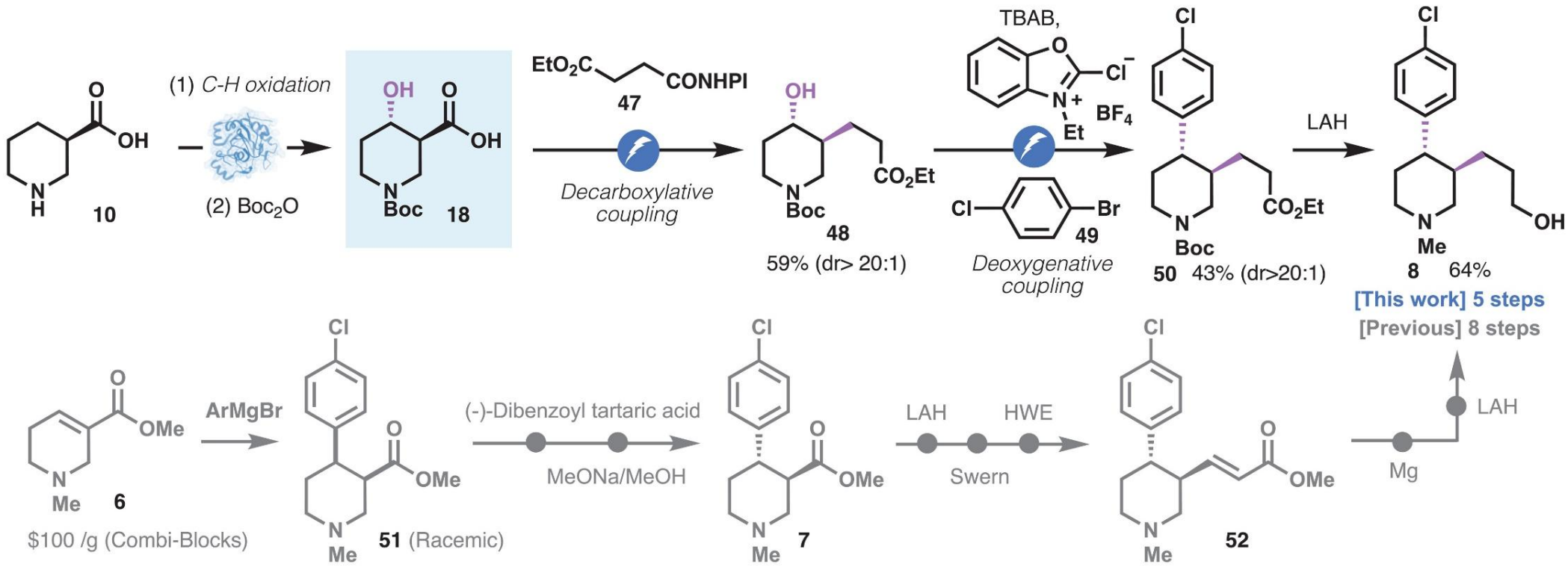
Previous works




Each diastereomer was prepared separated

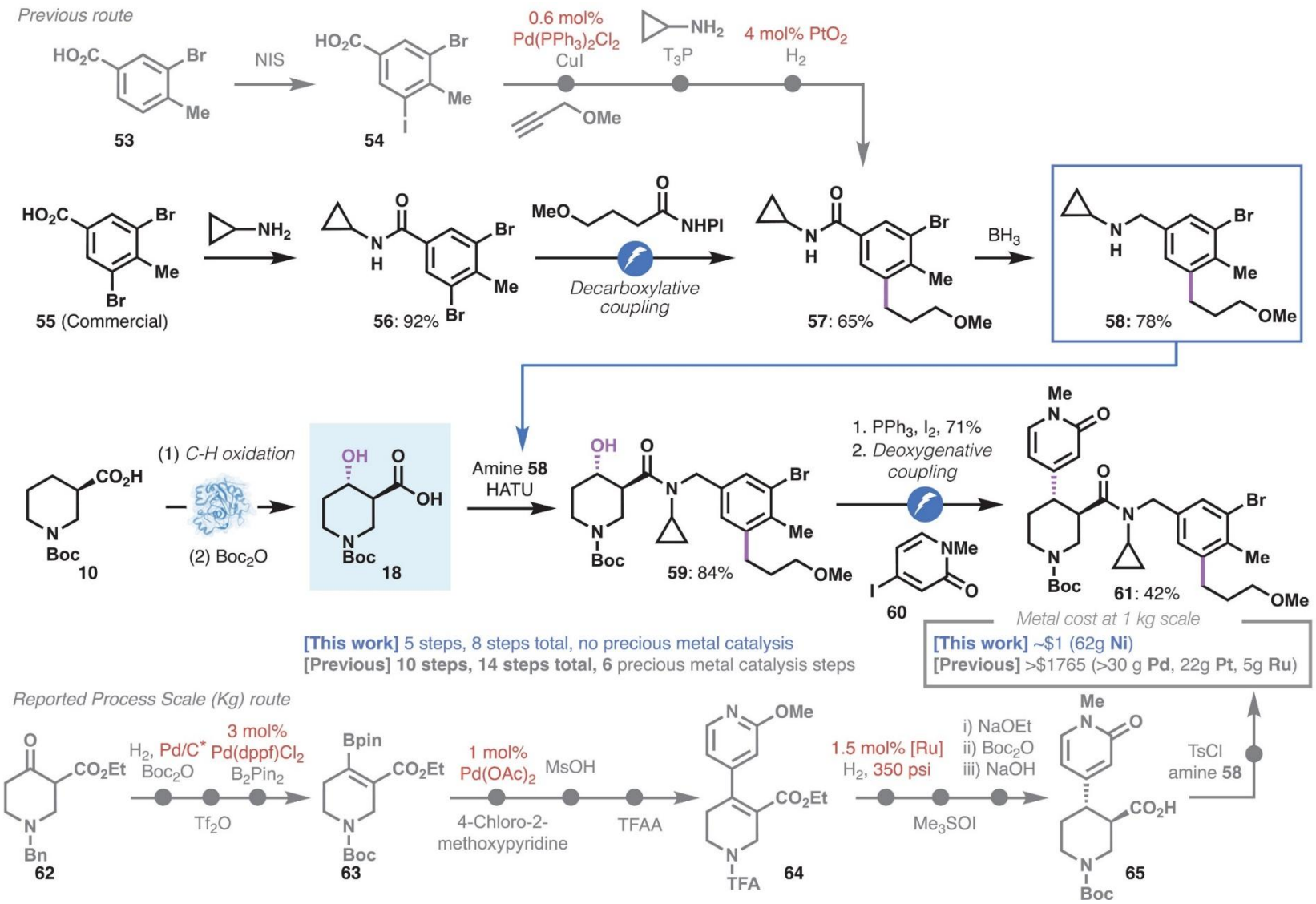
# Modular radical cross-coupling to simplify complex piperidine synthesis

## 4-Hydroxynipecotic acid diversification



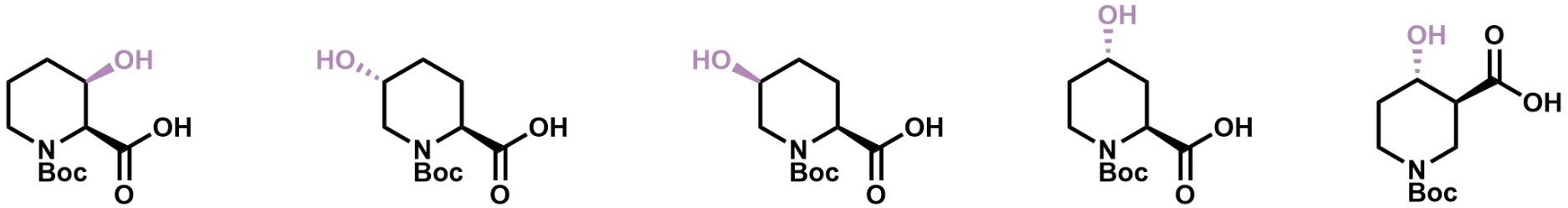
# Modular radical cross-coupling to simplify complex piperidine synthesis

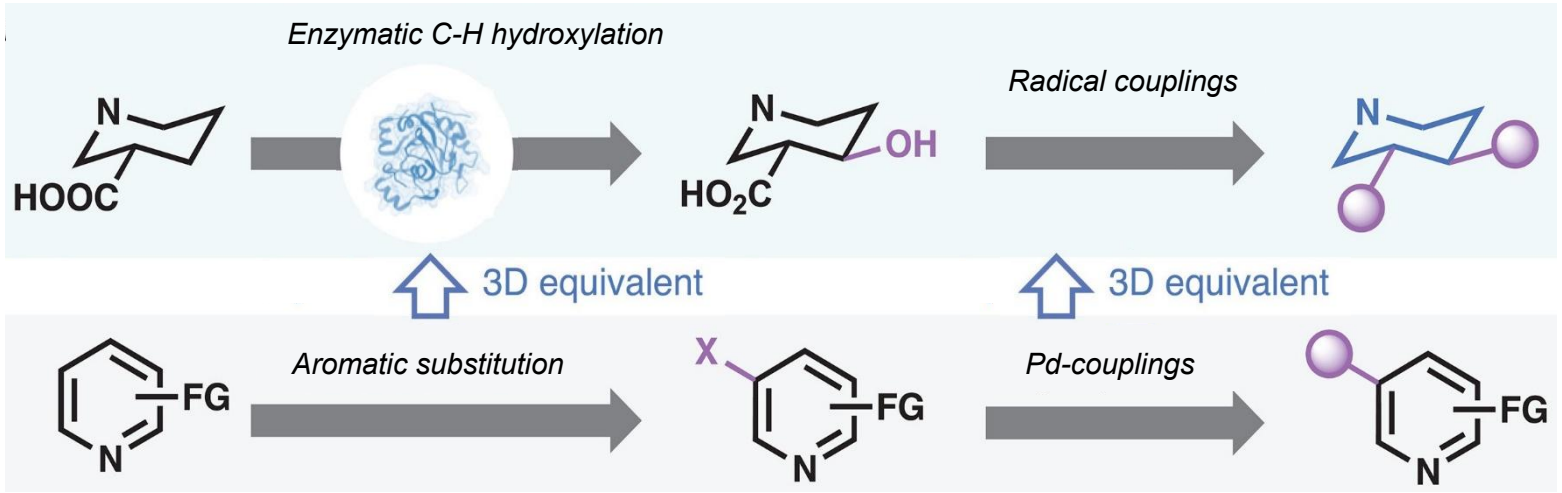
## 4-Hydroxynipecotic acid diversification



# Summary

**Preparative scale production of enantiopure piperidine building blocks**



# Thanks