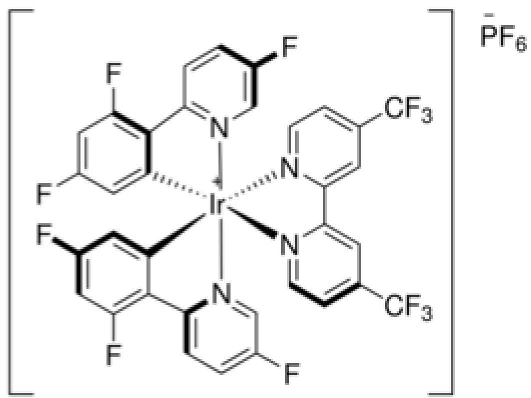
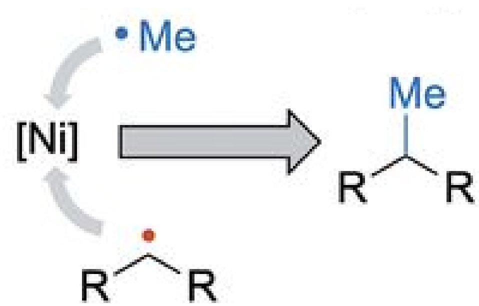
C(sp^3)–H Methylation Enabled by Peroxide Photosensitization and Ni-mediated Radical Coupling



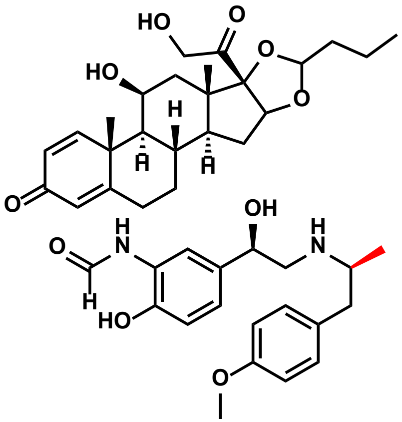


Shannon S. Stahl et al. *Science* **2021**, 372, 398-403

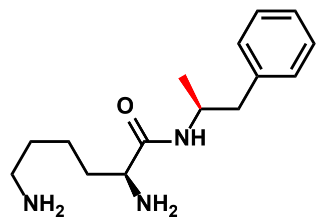
Shoule Han
2022/1/15

Top 200 Phamaceuticals Small Molecule

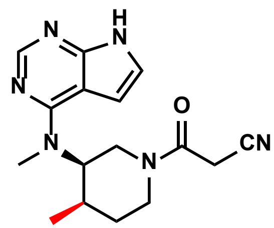
Symbicort



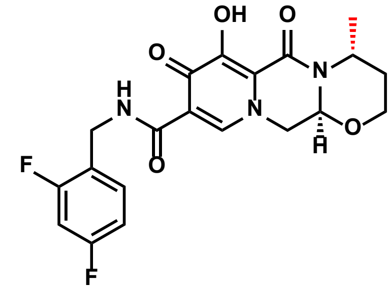
Vyvanse



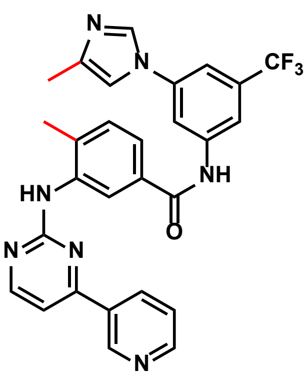
Xeljanz



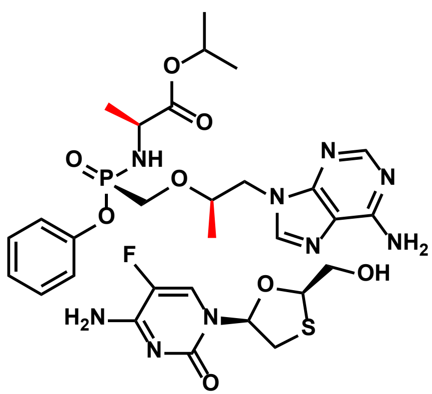
Tivicay



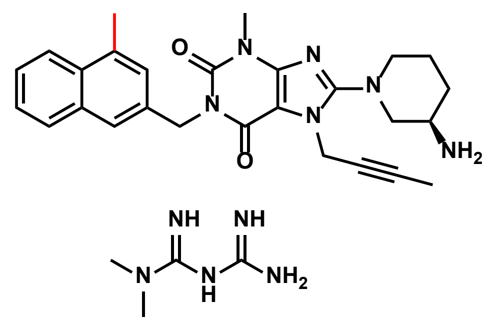
Tasigna



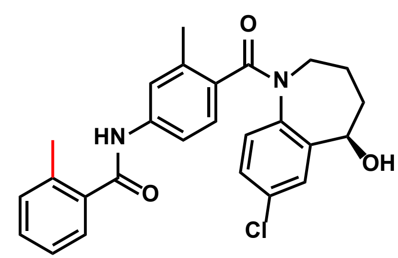
Descovy



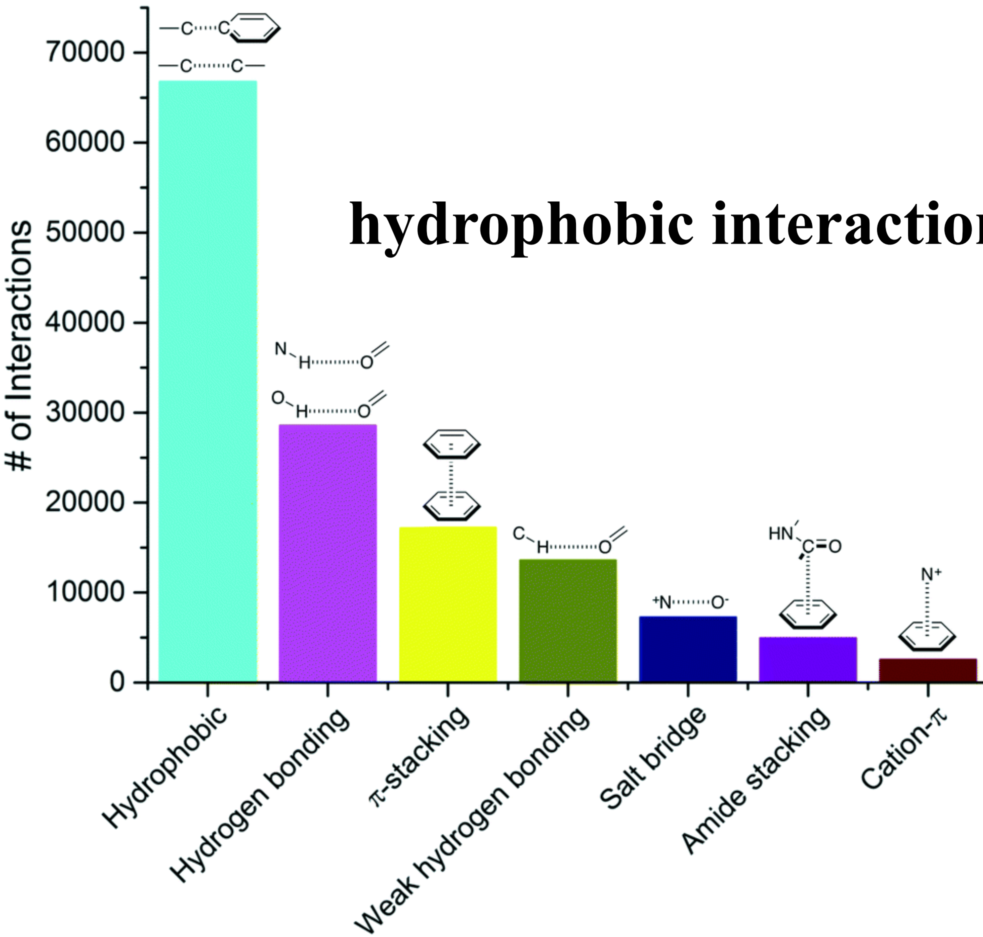
Jentadueto



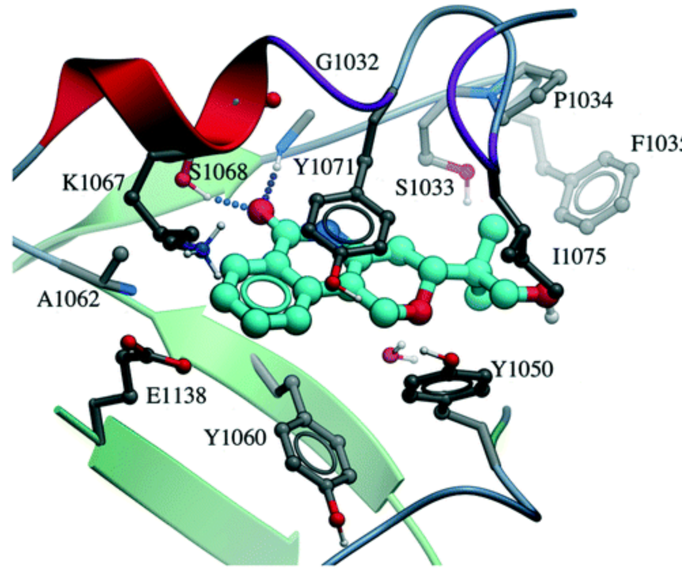
Samsca

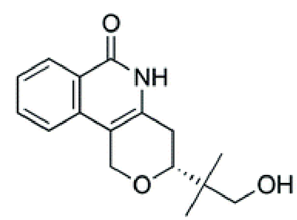


Magic Methyl Effect



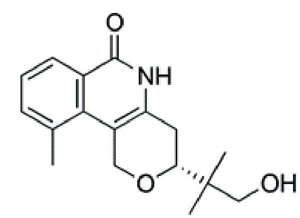
hydrophobic interactions





1

IC_{50} = 341 nM



2

IC_{50} = 7 nM

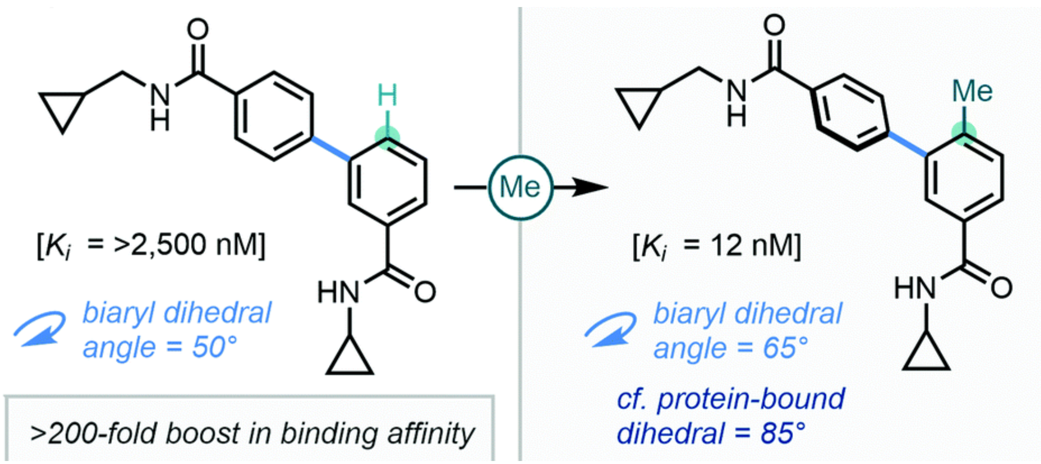
tankyrase-2 (TNKS2) inhibitor

Matthieu Schapira et al. *Med. Chem. Commun.* **2017**, 8, 1970-1981

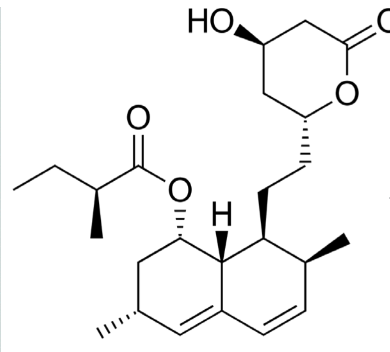
Magic Methyl Effect

conformational effects

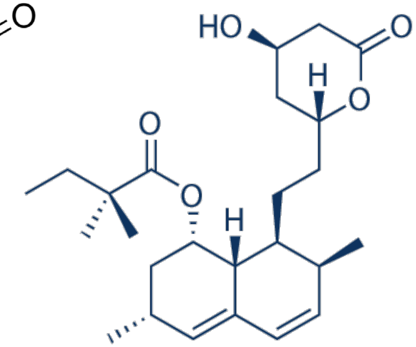
GSK, 2008 p38α MAP3 kinase



Metabolic stability changes



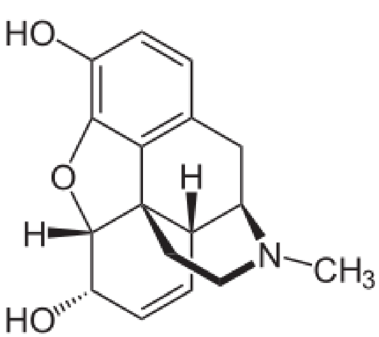
Lovastatin



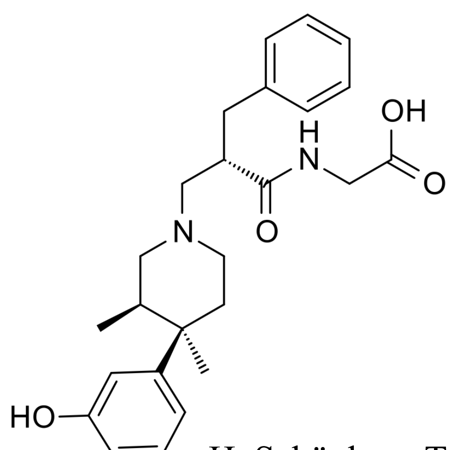
Simvastatin

2-fold increase in $t_{1/2}$

convert an agonist into an antagonist



Morphine



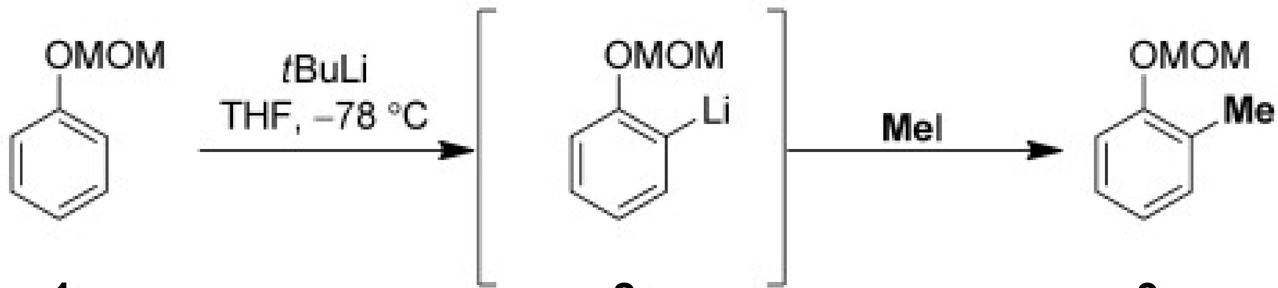
Alvimopan

μ-opioid receptor antagonist

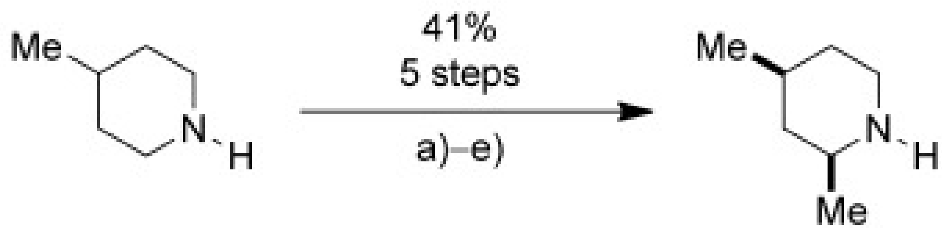
treatment of postoperative ileus

H. Schönherr, T. Cernak, *Angew. Chem. Int. Ed.* **2013**, 52, 12256–12267

C-H Activation



1 **2** **3**

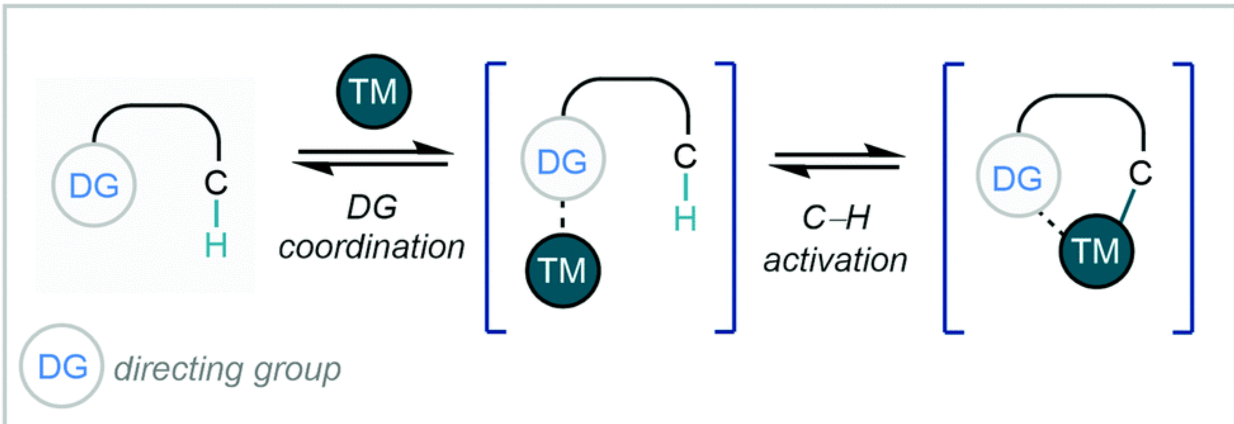


4 **5**

Reagents and conditions: a) Boc_2O, THF/H_2O, NaOH; b) 20 mol % $RuO_2 \cdot x\,H_2O$, $NaIO_4$, EtOAc/H_2O; c) MeMgBr; d) TFA then NaOH; e) $Pd(OH)_2$/C, H_2 (45 psi). Boc=*tert*-butoxycarbonyl, THF=tetrahydrofuran, TFA=trifluoroacetic acid.

L. Zhang et al. *J. Am. Chem. Soc.* **2009**, 131, 8394– 8395

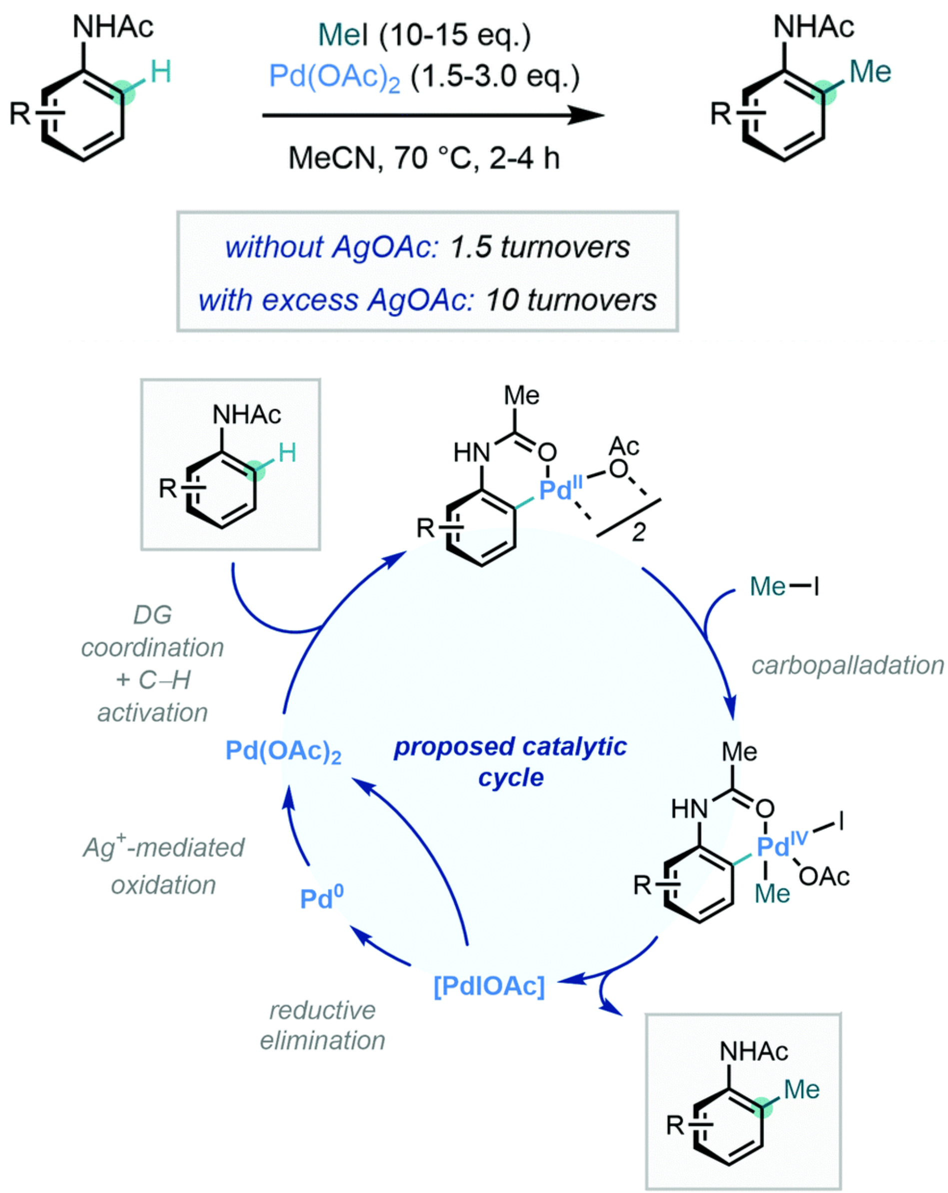
C-H Activation



4d transition metals: Pd, Rh, and Ru

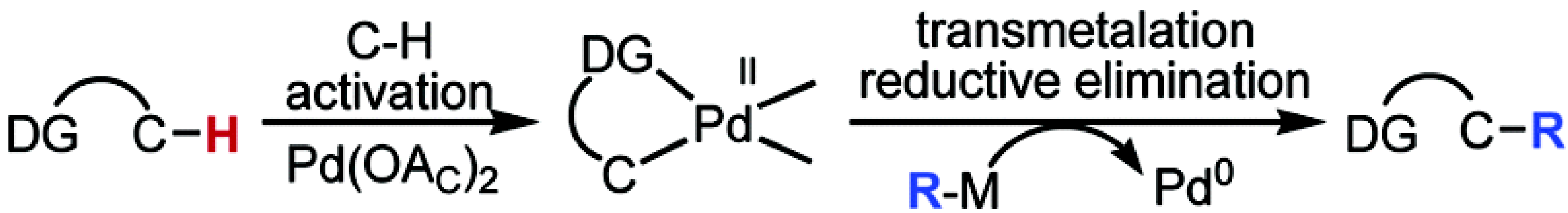
Darren J. Dixon et al. *Chem. Soc. Rev.* **2021**, 50, 5517-5563

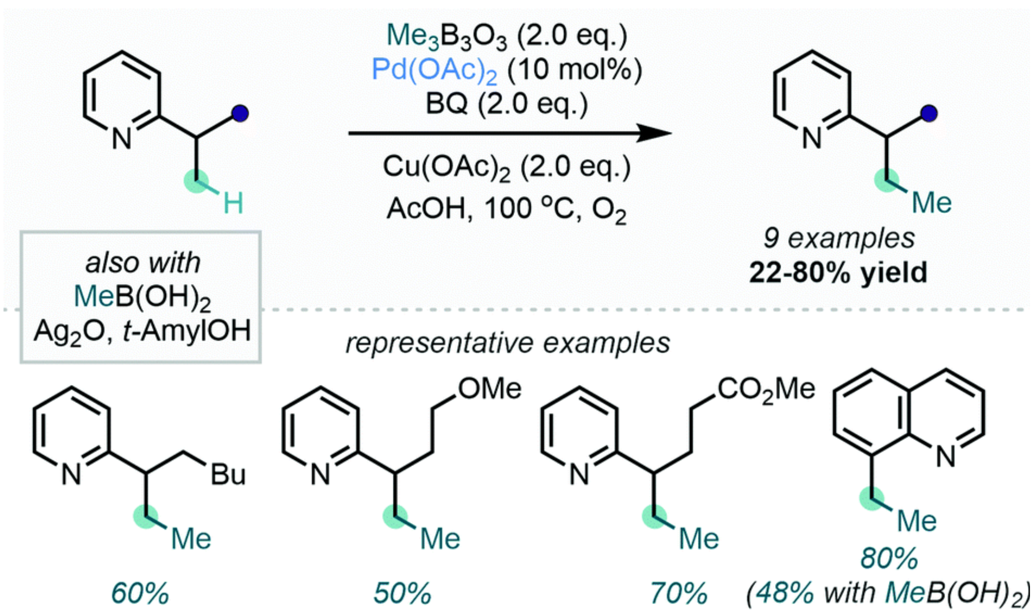
C-H Activation



S. J. Tremont and H. U. Rahman , *J. Am. Chem. Soc.* **1984**, 106, 5759 —5760

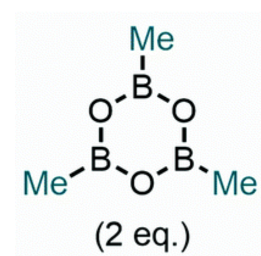
C-H Activation





pyridyl-directed C–H activation by Pd

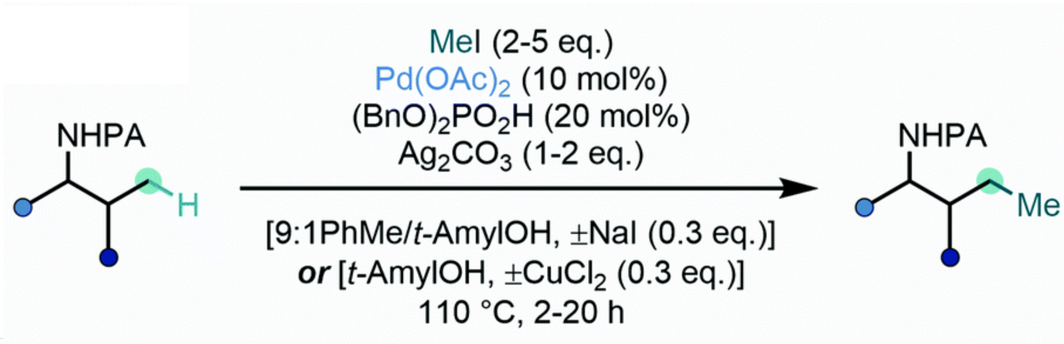
efficient transmetalating agents

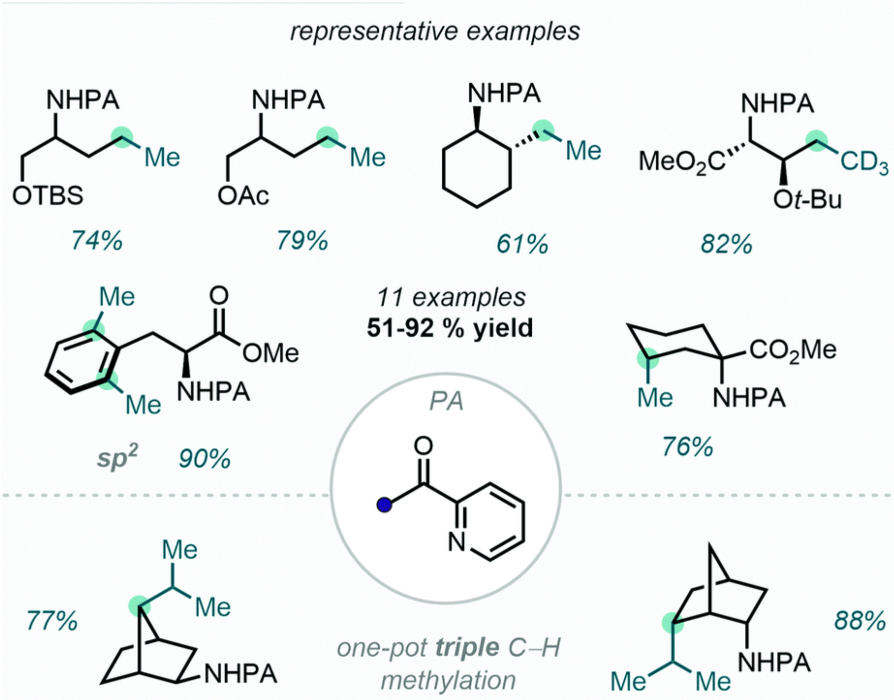


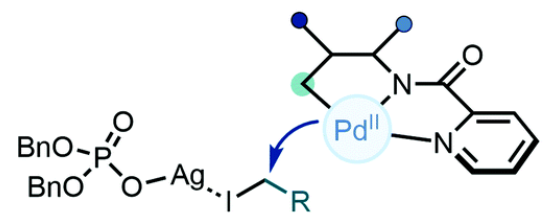
J.-Q. Yu et al. *J. Am. Chem. Soc.* **2006**, 128, 1, 78–79

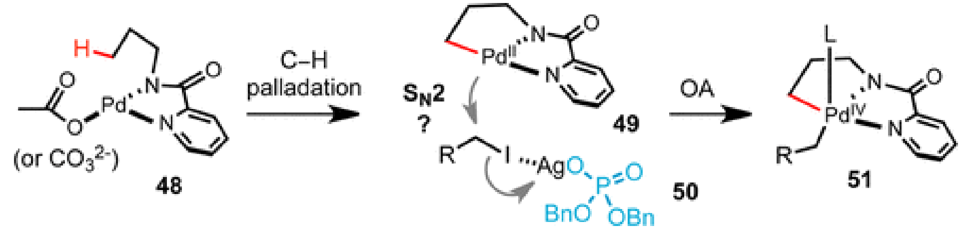
J.-Q. Yu et al. *J. Am. Chem. Soc.* **2006**, 128, 12634 —12635

Directed C(sp3)-H Methylation





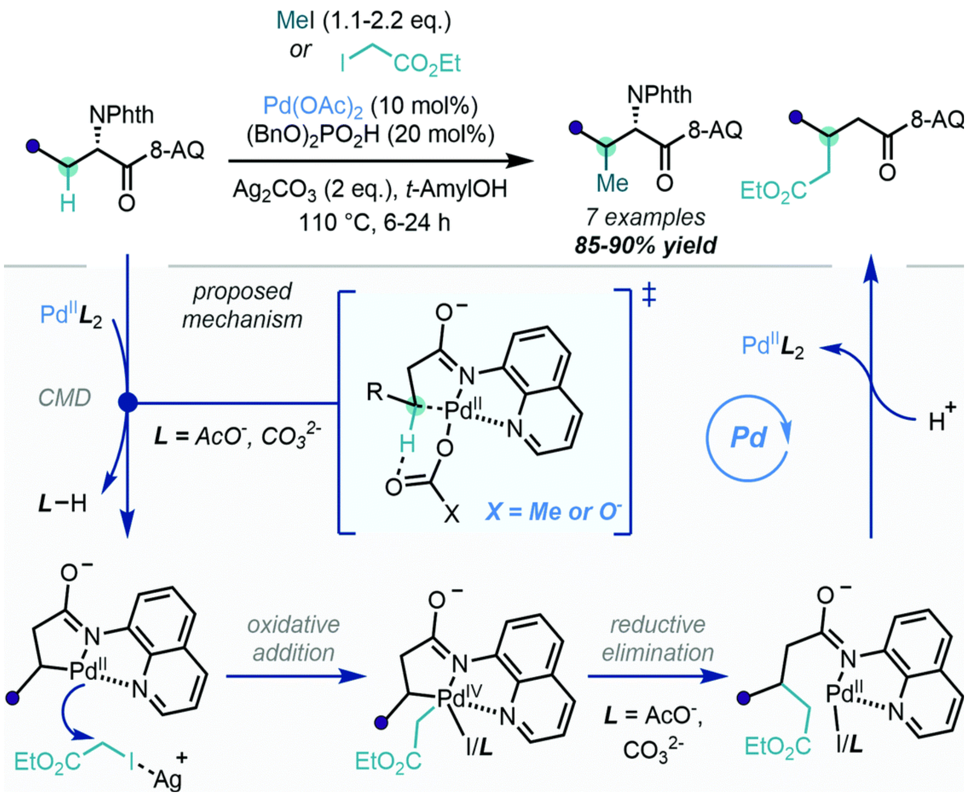


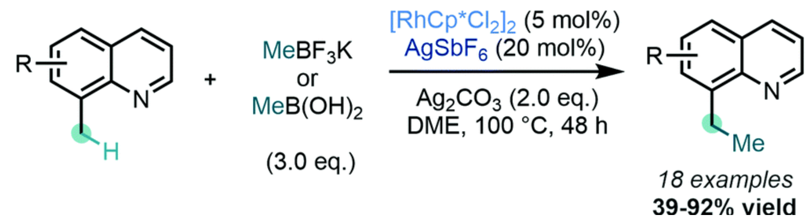


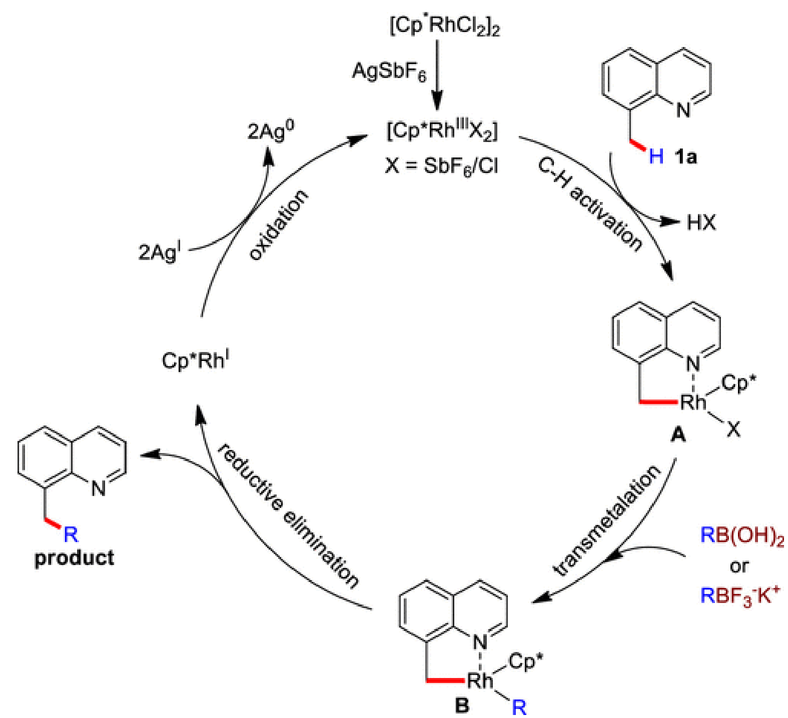
Dibenzyl phosphate as solid-to-solution phase transfer catalyst for Ag+

Gong Chen et al. *J. Am. Chem. Soc.* **2013**, 135, 2124–2127

Directed C(sp3)-H Methylation



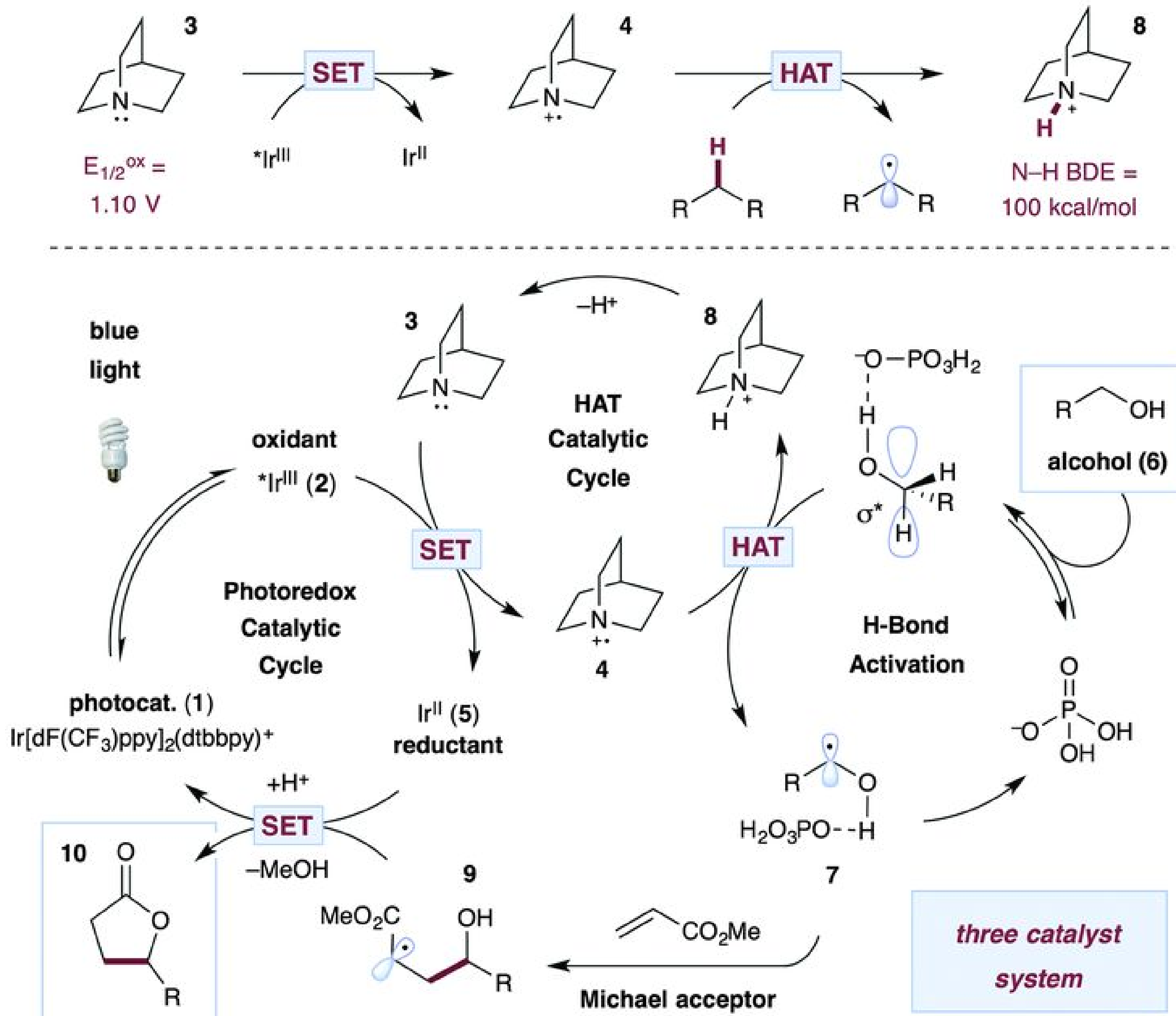




Concerted metalation-deprotonation mechanism

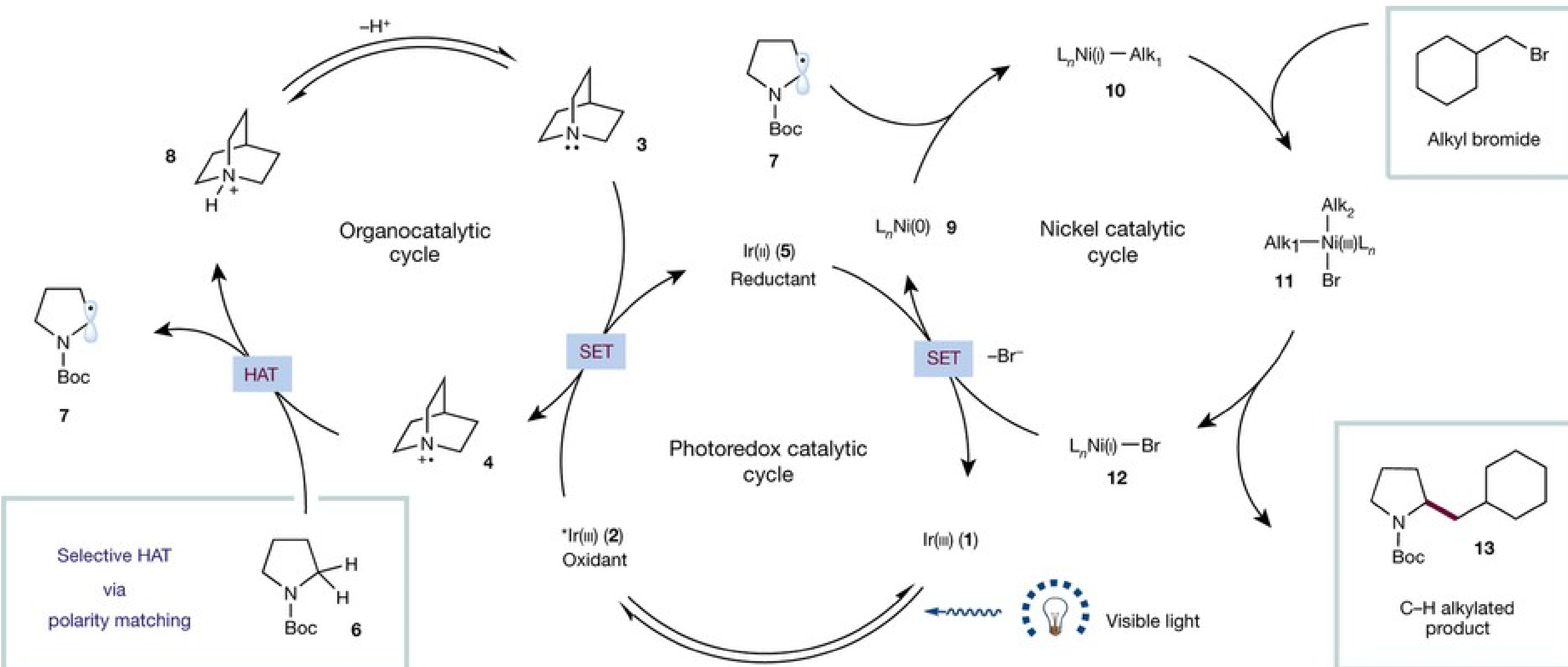
Gong Chen et al. *J. Am. Chem. Soc.*, **2013**, 135 , 12135 —12141
B.-F. Shi et al. *Chem. Sci.*, **2013**, 4 , 3906 —3911
U. Sharma et al. *Org. Lett.*, **2020**, 22, 305 —309

Oxidative C(sp3)-H Activation



David W. C. MacMillan et al. *Science* **2015**, 349, 1532–1536

Oxidative C(sp3)-H Methylation

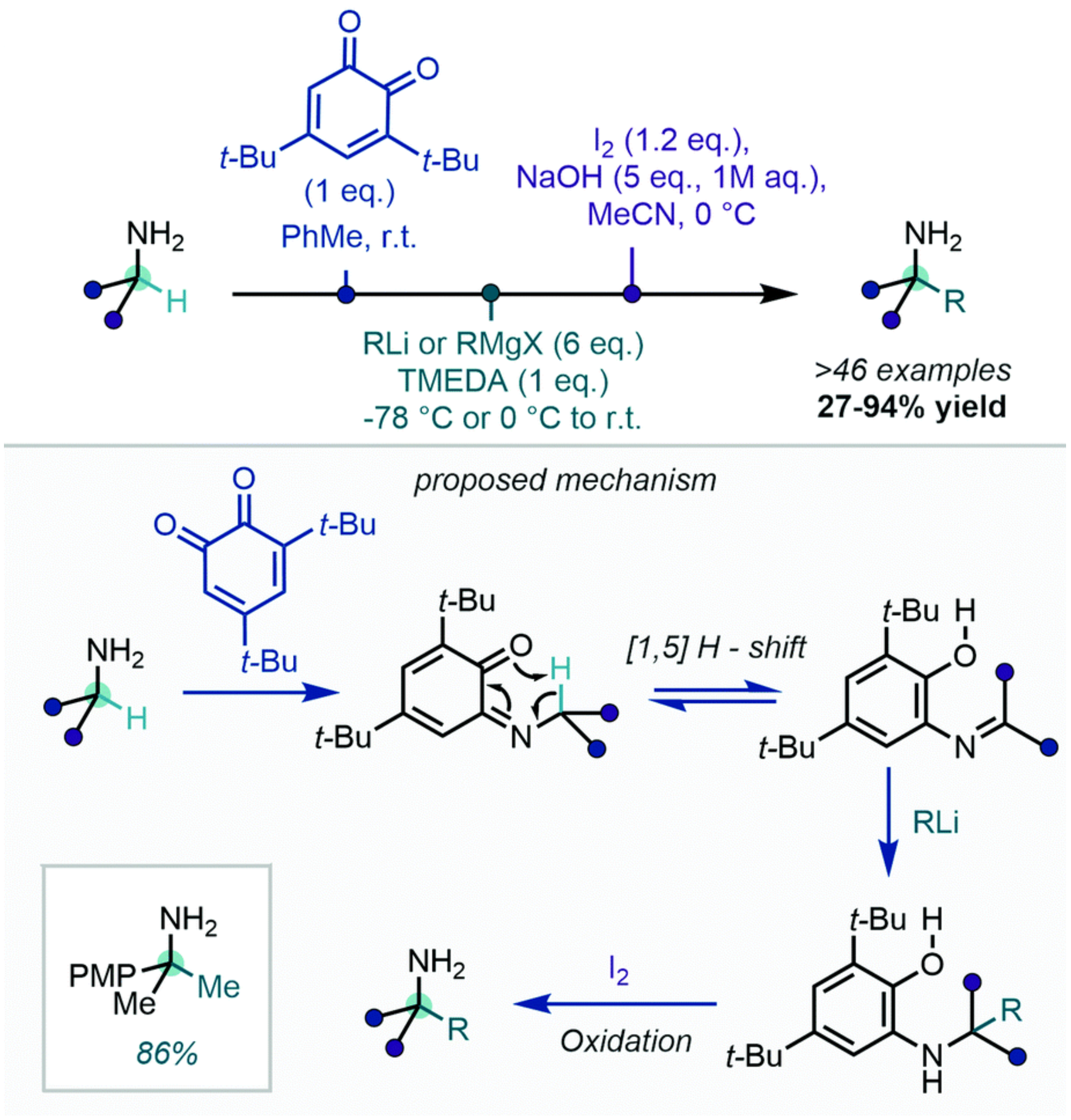


combined photoredox, polarity-matched HAT, and nickel catalytic cycles

high positional selectivity is determined *via* polarity-matched HAT

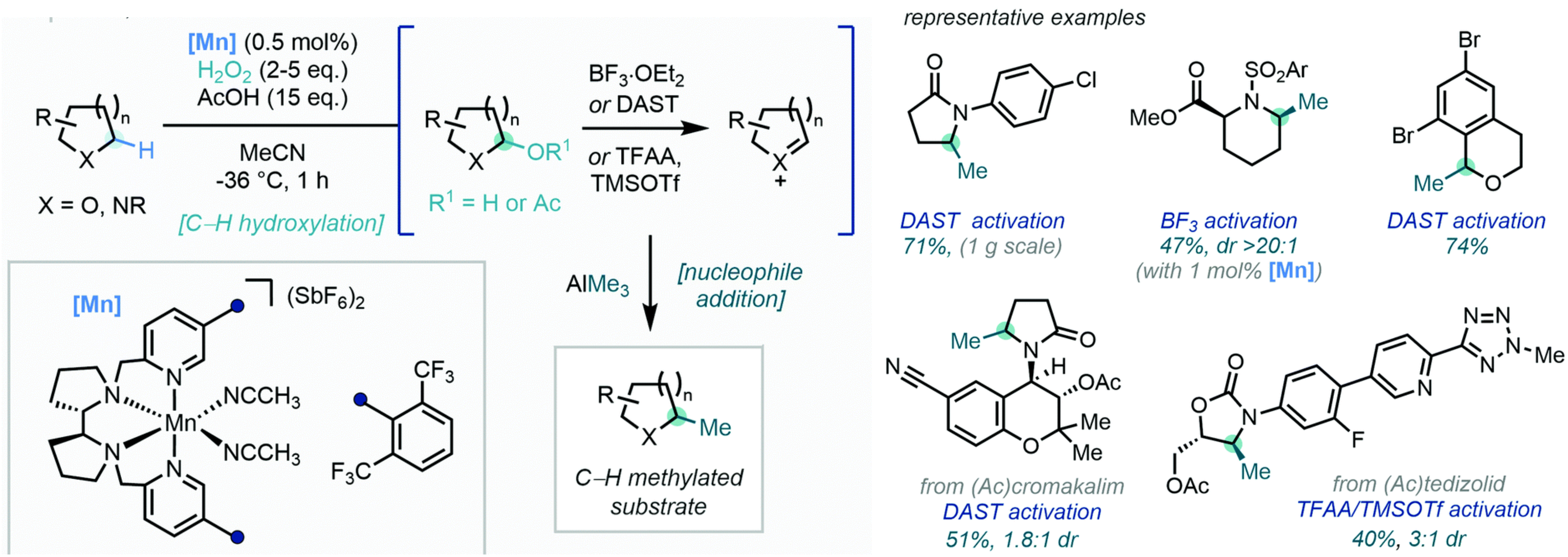
David W. C. MacMillan et al. *Nature* **2017**, 547, 79-83

Oxidative C(sp3)-H Methylation



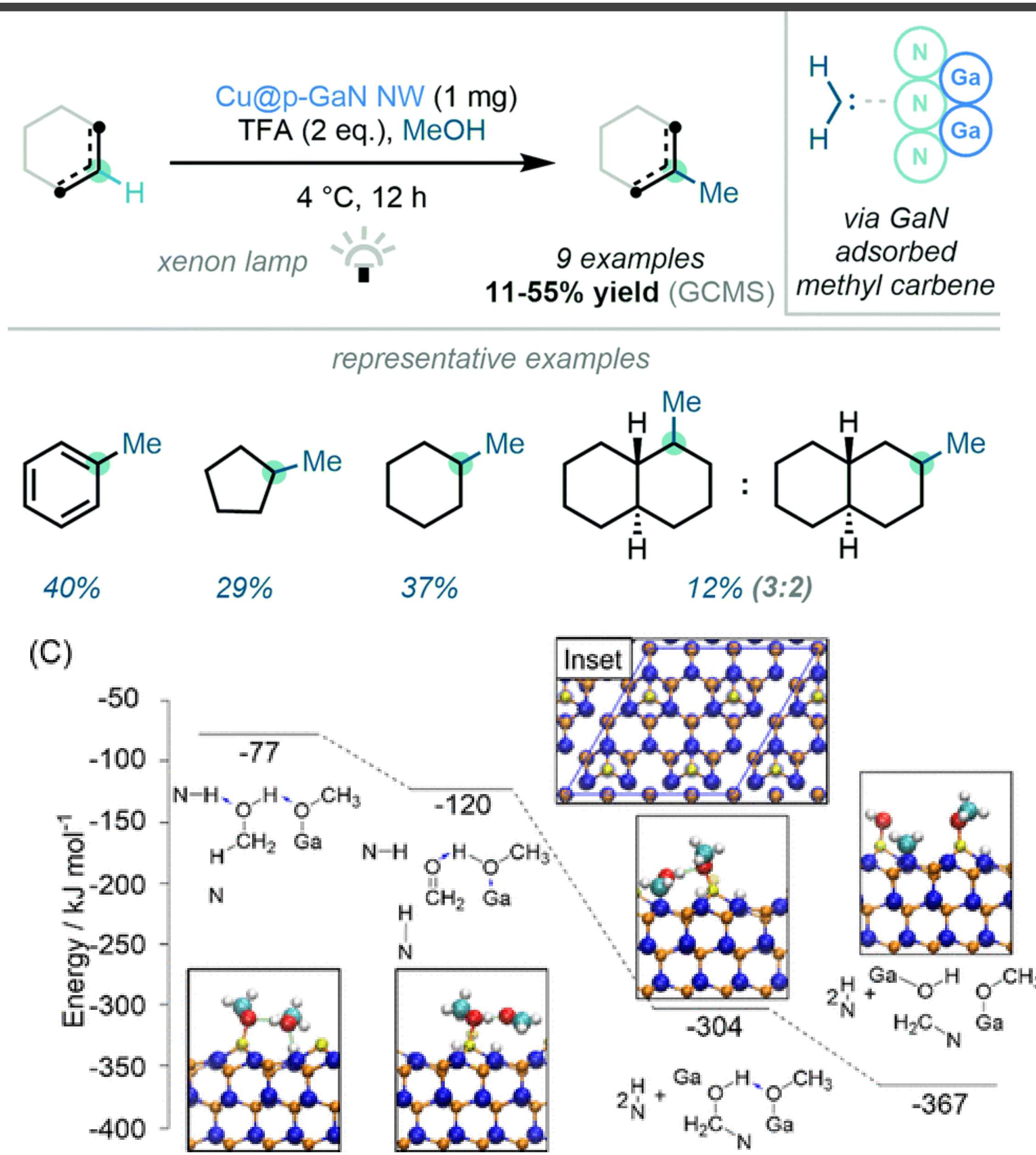
A. Paul and D. Seidel , *J. Am. Chem. Soc*. **2019**, 141, 8778 —8782

Oxidative C(sp3)-H Methylation



M. Christina White et al. *Nature* **2020**, 580, 621–627

C(sp3)-H Methylation



C.-J. Li et al. *ACS Catal.* **2020**, 10, 6248–6253

Shannon S. Stahl

B.S. Chemistry (1992)

University of Illinois Urbana-Champaign

Ph.D. Chemistry (1997)

California Institute of Technology 1891

Postdoctoral (1997---1999)

Massachusetts Institute of Technology

Advisor: Professor Stephen J. Lippard
Thesis: Mechanistic Enzymology of Soluble Methane Monooxygenase

Professor of Chemistry

Wisconsin University of Wisconsin–Madison

Advisor: Professor John E. Bercaw
Thesis: Mechanistic Studies of Alkane Activation by Platinum(II) Complexes

Palladium or Copper Catalyzed Aerobic Oxidation

Developing new heterogeneous catalysts for organic synthesis

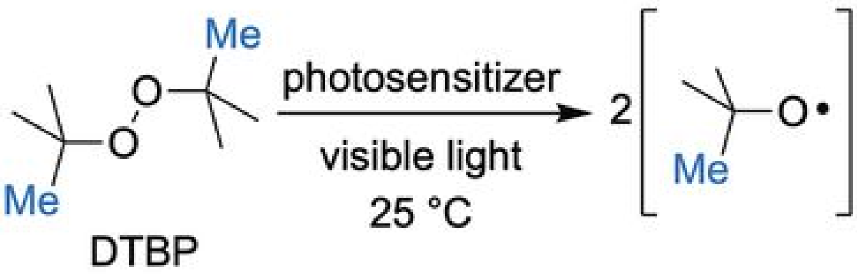
Electrocatalysis and Electrochemical Organic Synthesis

Energy Storage and Conversion

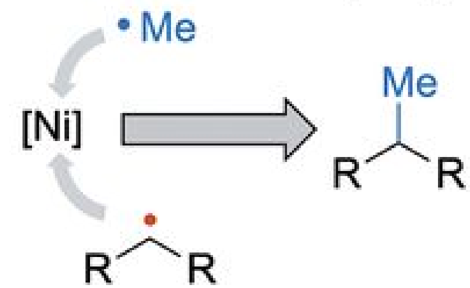
Directed C(sp3)-H Methylation

Three fundamental reactivity concepts:

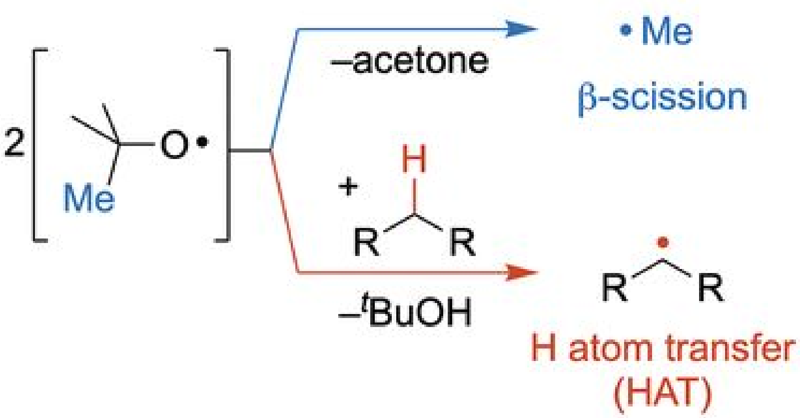
(i) Triplet-sensitized peroxide O–O homolysis



(iii) Nickel-mediated radical coupling



(ii) Oxyl radical reactivity to generate methyl radical and/or promote H-atom transfer

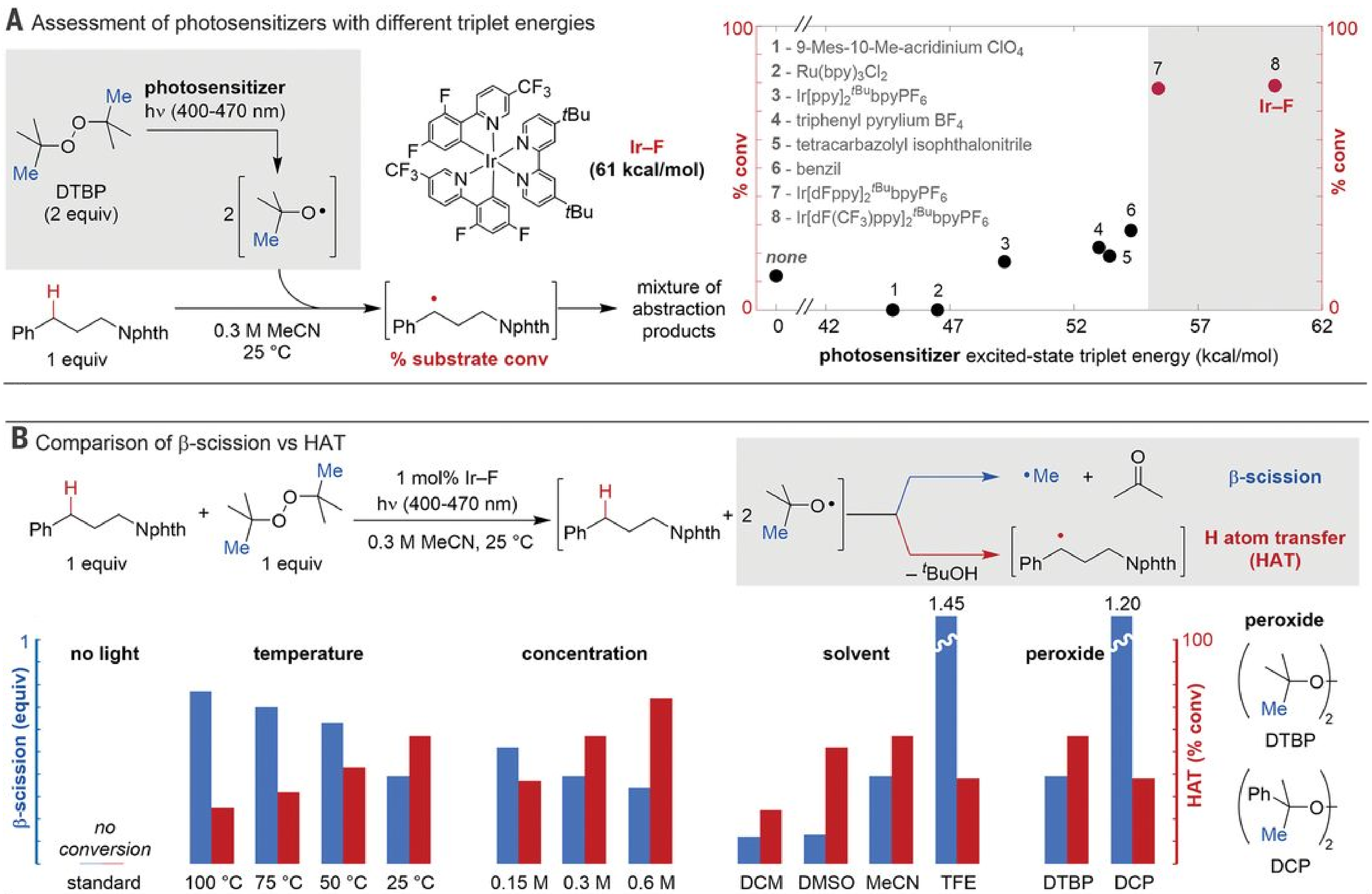


competition between HAT and β-methyl scission

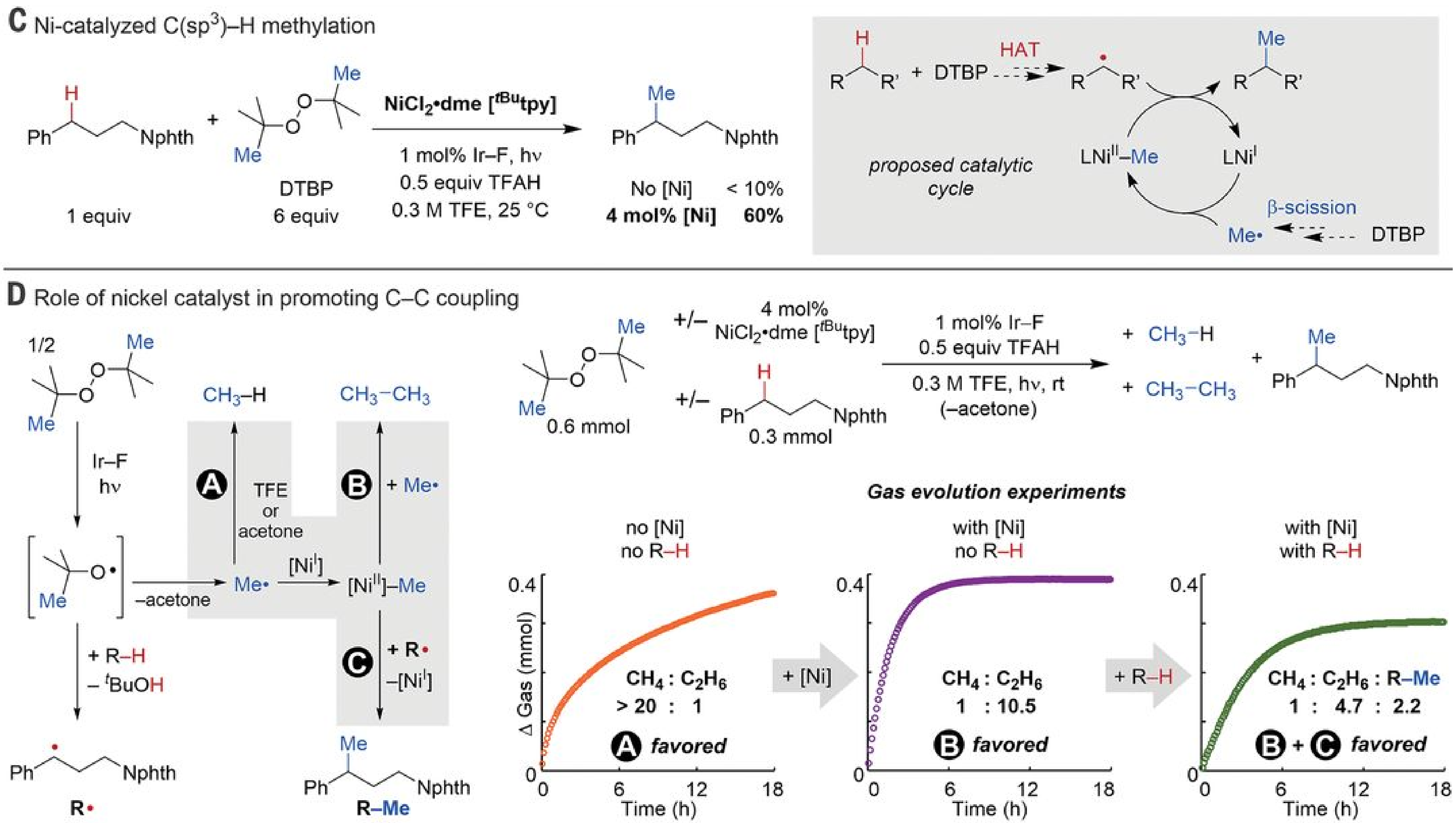
elevated temperatures: β-methyl scission

lower temperatures: HAT

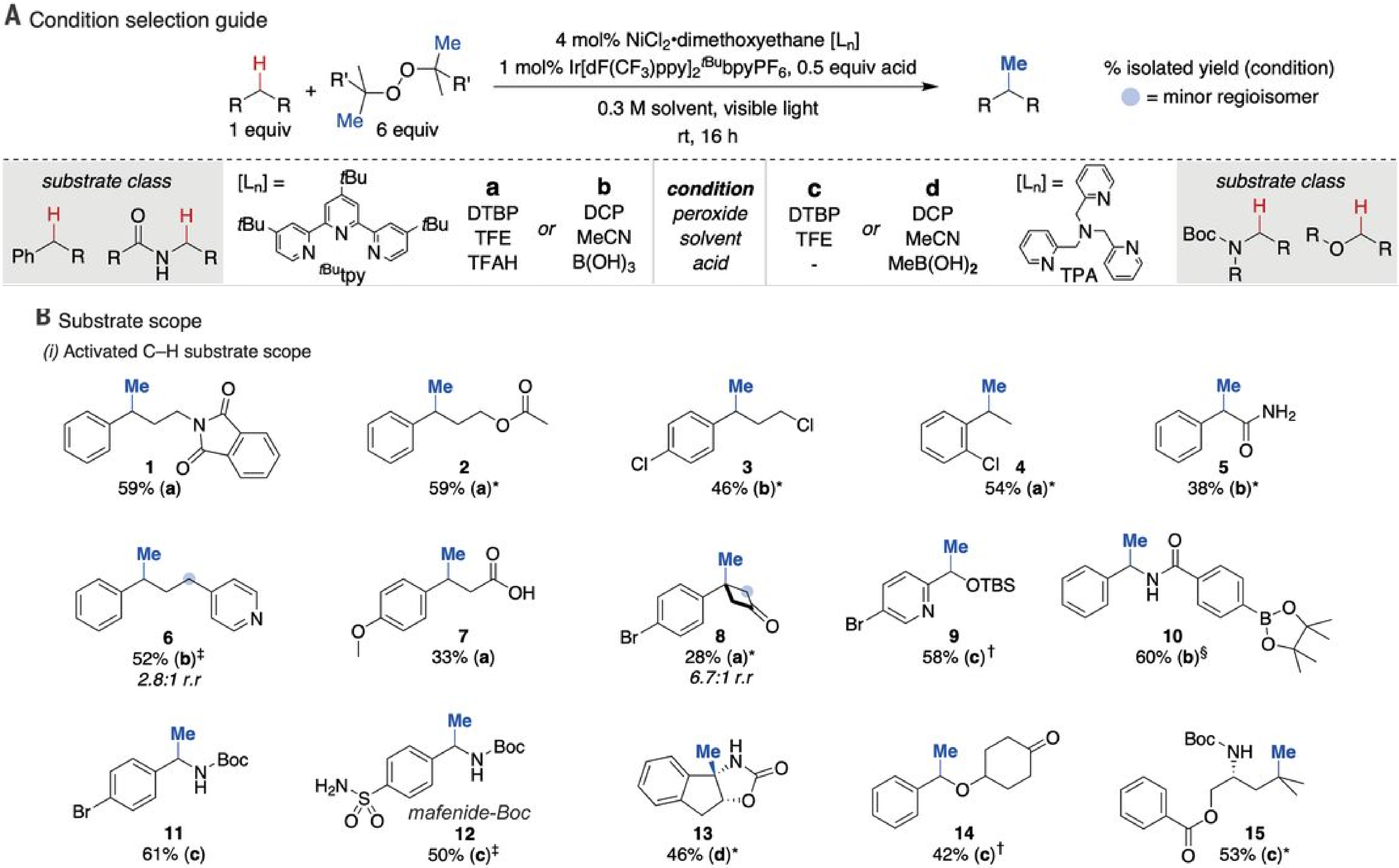
Directed C(sp3)-H Methylation



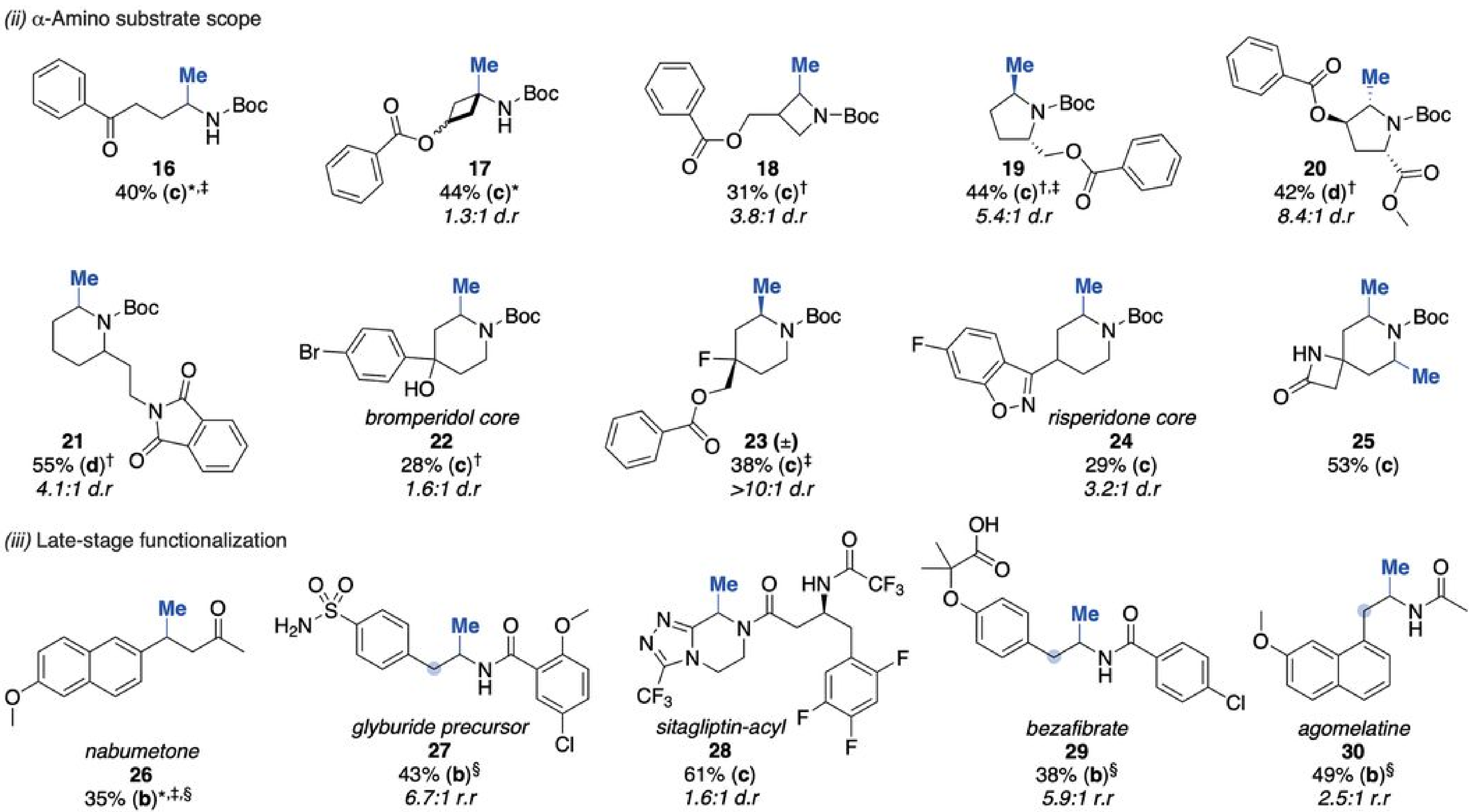
Directed C(sp3)-H Methylation

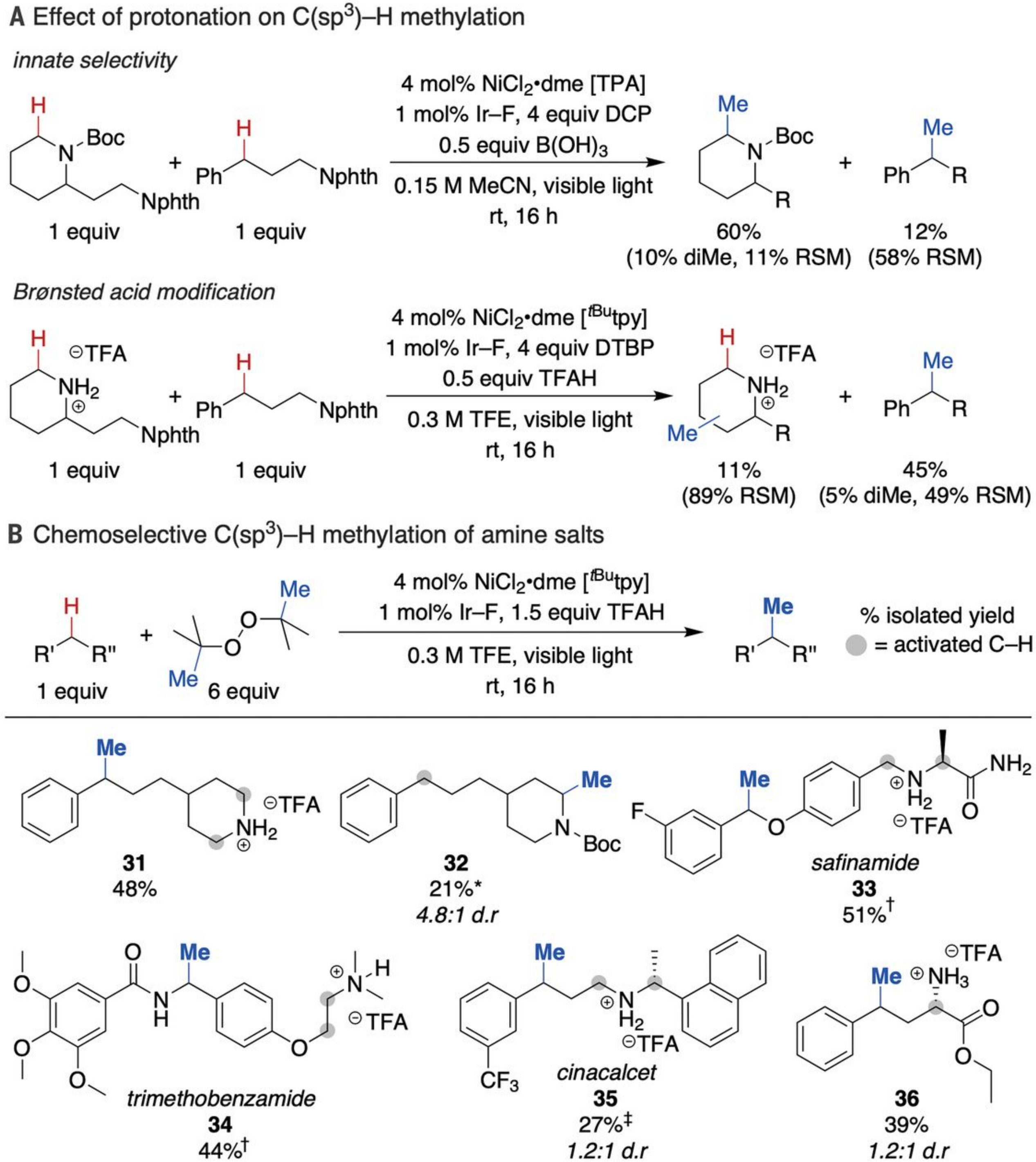


Directed C(sp3)-H Methylation

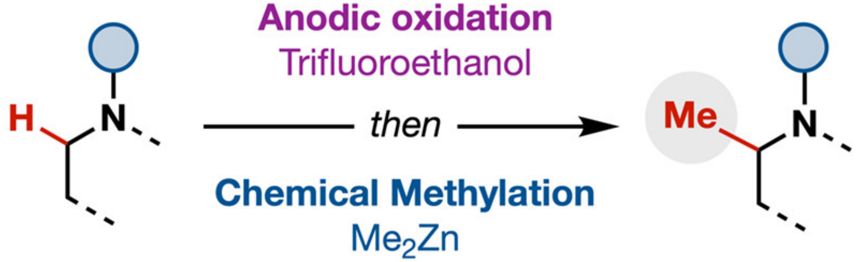


Directed C(sp3)-H Methylation



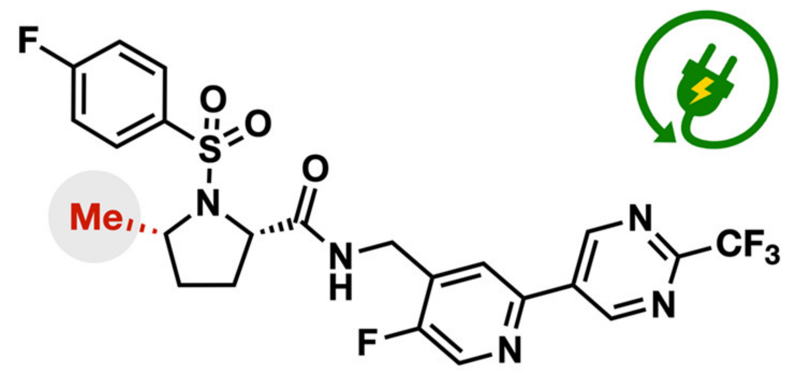

A Effect of protonation on C(sp3)–H methylation
innate selectivity
4 mol% NiCl2•dme [TPA]
1 mol% Ir–F, 4 equiv DCP
0.5 equiv B(OH)3
0.15 M MeCN, visible light
rt, 16 h
1 equiv
1 equiv
60%
(10% diMe, 11% RSM)
12%
(58% RSM)
Brønsted acid modification
4 mol% NiCl2•dme [tButpy]
1 mol% Ir–F, 4 equiv DTBP
0.5 equiv TFAH
0.3 M TFE, visible light
rt, 16 h
1 equiv
1 equiv
11%
(89% RSM)
45%
(5% diMe, 49% RSM)
B Chemoselective C(sp3)–H methylation of amine salts
4 mol% NiCl2•dme [tButpy]
1 mol% Ir–F, 1.5 equiv TFAH
0.3 M TFE, visible light
rt, 16 h
1 equiv
6 equiv
% isolated yield
= activated C–H
31
48%
32
21%*
4.8:1 d.r
safinamide
33
51%†
trimethobenzamide
34
44%†
cinacalcet
35
27%‡
1.2:1 d.r
36
39%
1.2:1 d.r

Oxidative C(sp3)-H Methylation



- *Late-stage methylation: compatible with basic nitrogens*
- *Simple operation: commercial vessels and reagents*
- *Broad scope: tolerates substrates with high E_{ox}*

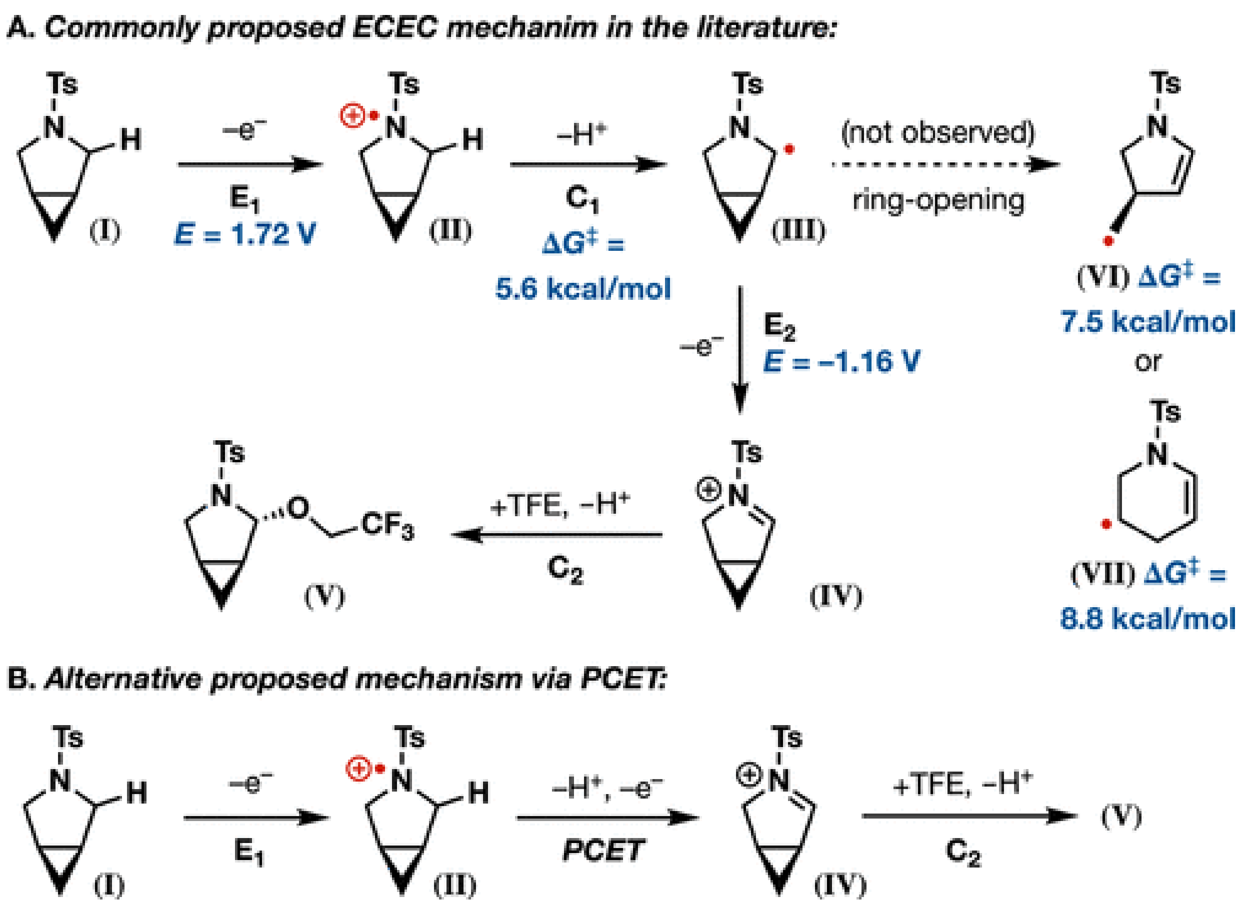
Late Stage C(sp^3)–H methylation



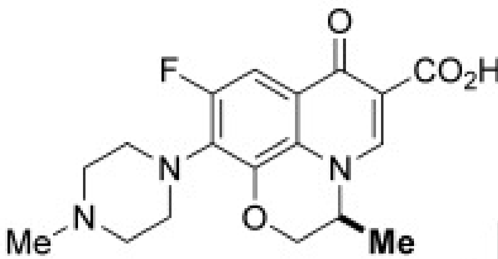
TRPA1 antagonist (vs. 7-step de novo synthesis)

Song Lin et al. *J. Am. Chem. Soc.* **2022**, https://doi.org/10.1021/jacs.1c09412

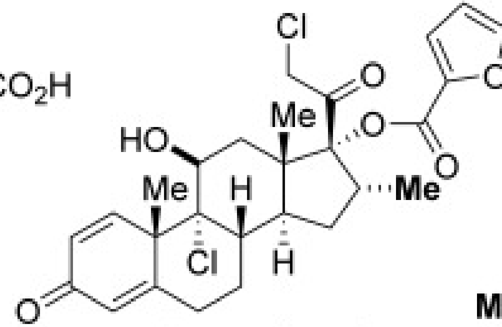
Thanks for Attention



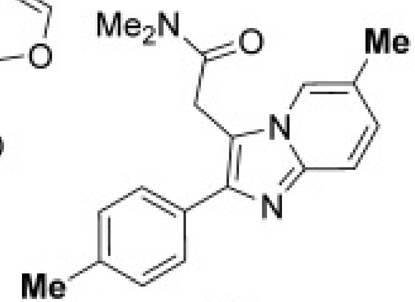
J. Am. Chem. Soc. 2022, https://doi.org/10.1021/jacs.1c09412



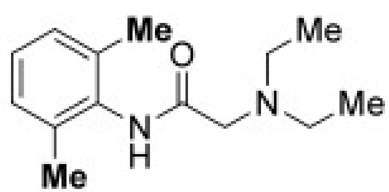
levofloxacin



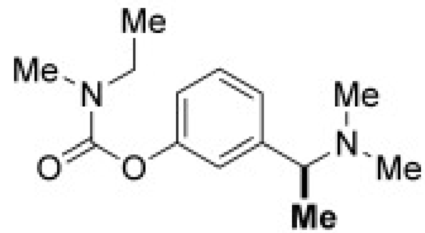
mometasone furoate



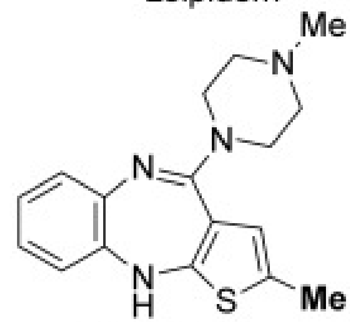
zolpidem



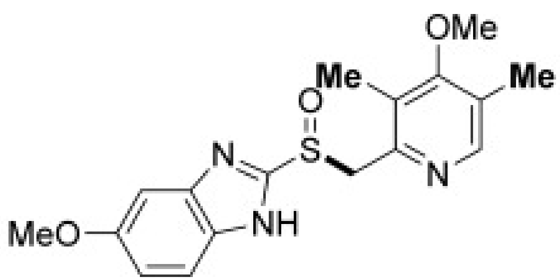
xylocaine



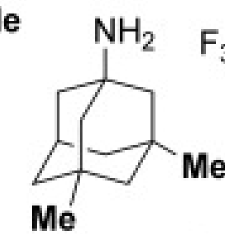
rivastigmine



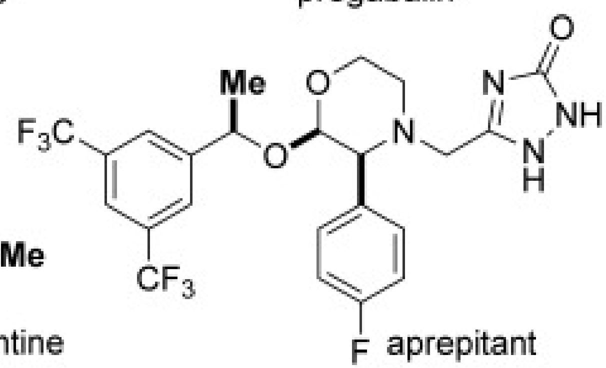
pregabalin



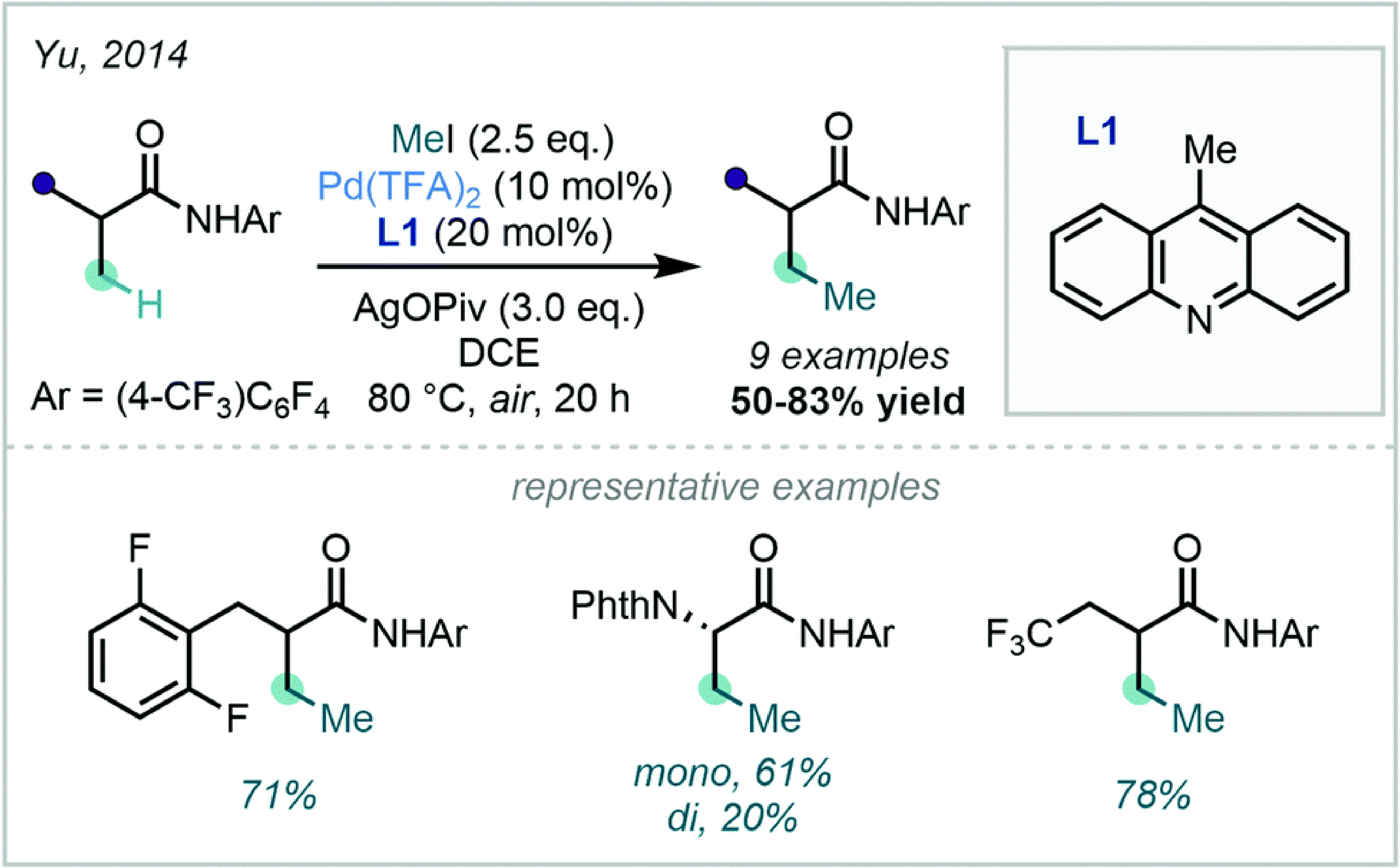
esomeprazole



memantine



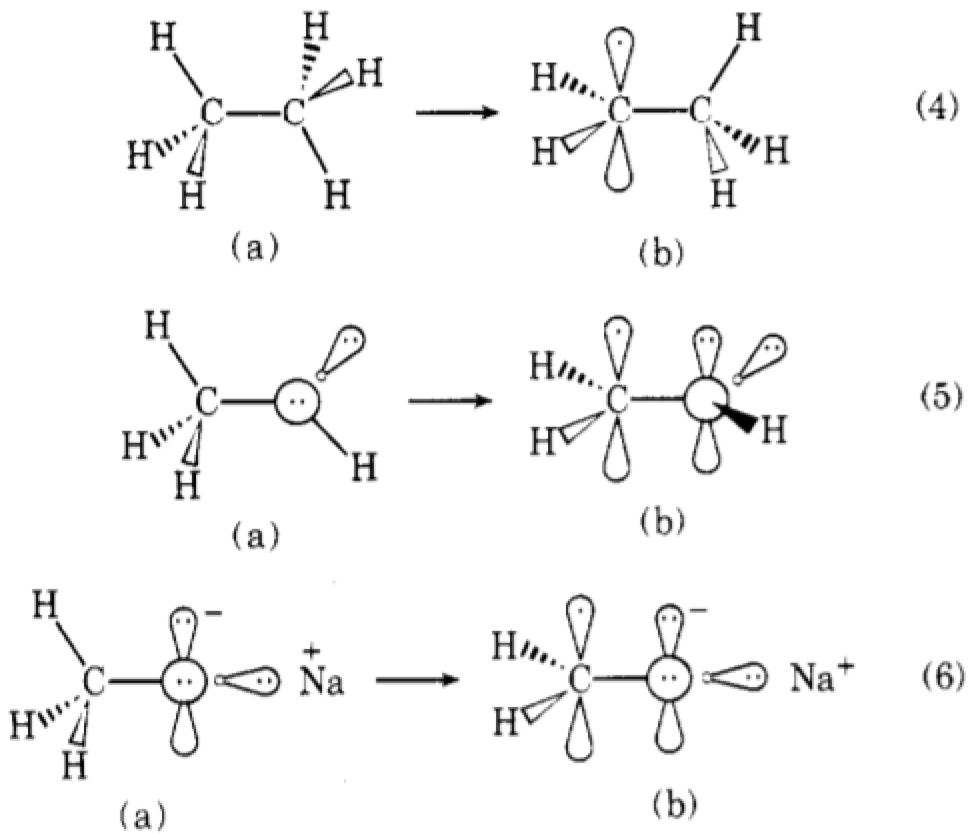
aprepitant



9-Methylacridine(9-甲基吖啶) was identified as a generally effective ligand to promote a Pd(II)-catalyzed C(sp^3)–H and C(sp^2)–H alkylation of simple amides with various alkyl iodides.

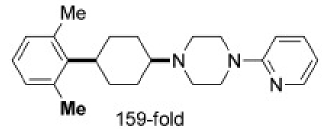
J.-Q. Yu et al. *J. Am. Chem. Soc.*, 2014, **136** , 13194 —13197

Theoretical Studies of the Oxy Anionic Substituent Effect

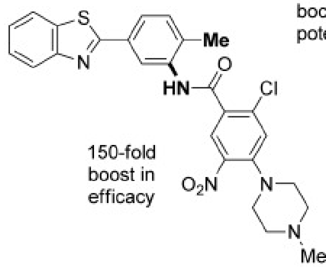


David A. Evans et al. *J. Am. Chem. Soc.* ***101***, 1994–1997 (1979).

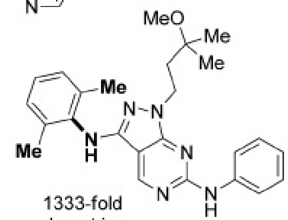
a) *ortho* substitution



159-fold boost in potency

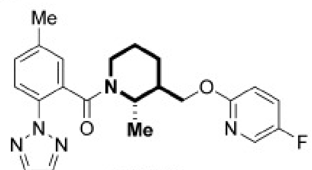


150-fold boost in efficacy

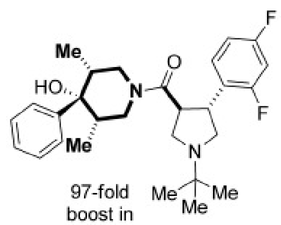


1333-fold boost in potency

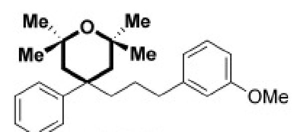
b) on substituted rings



480-fold boost in potency

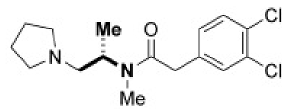


97-fold boost in potency

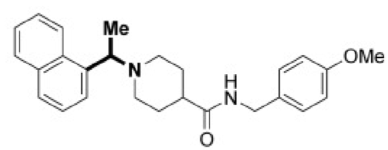


598-fold boost in potency

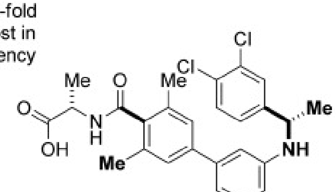
c) between two freely rotatable bonds



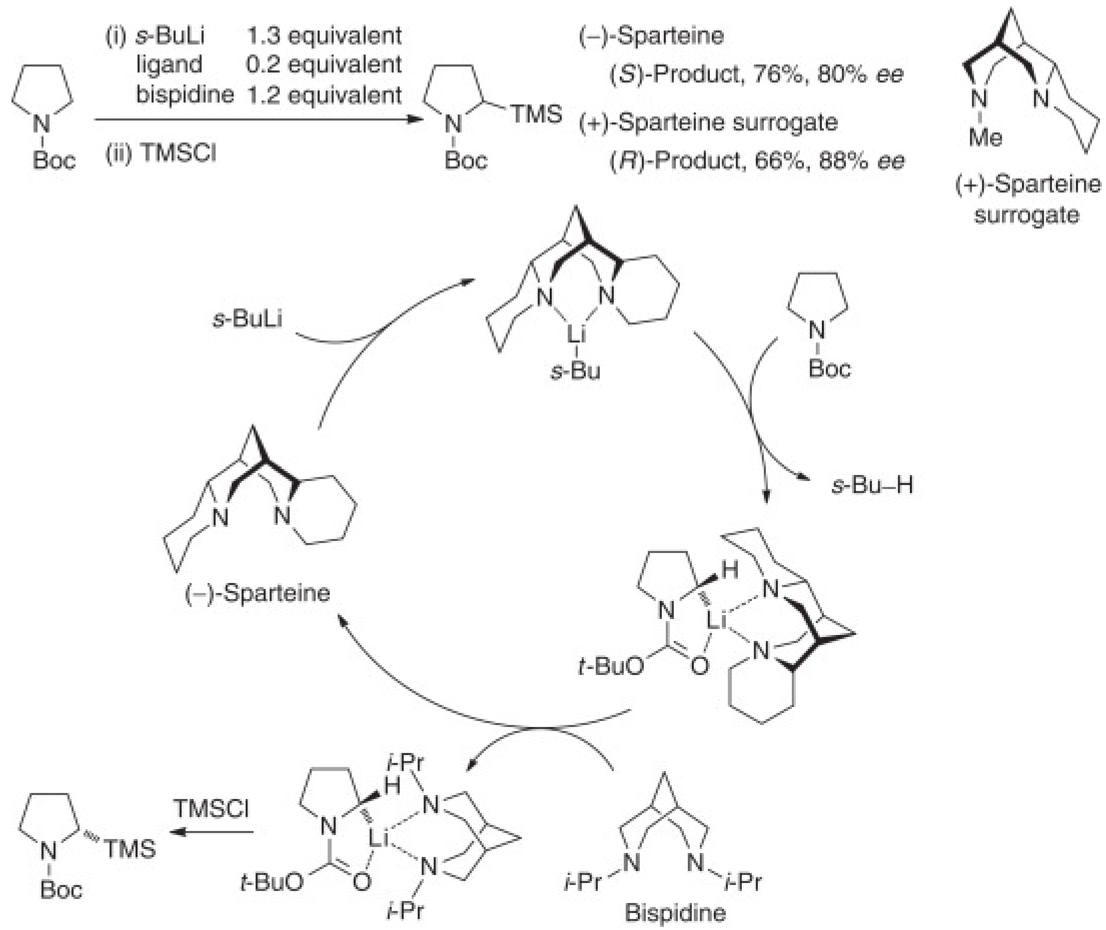
480-fold boost in potency

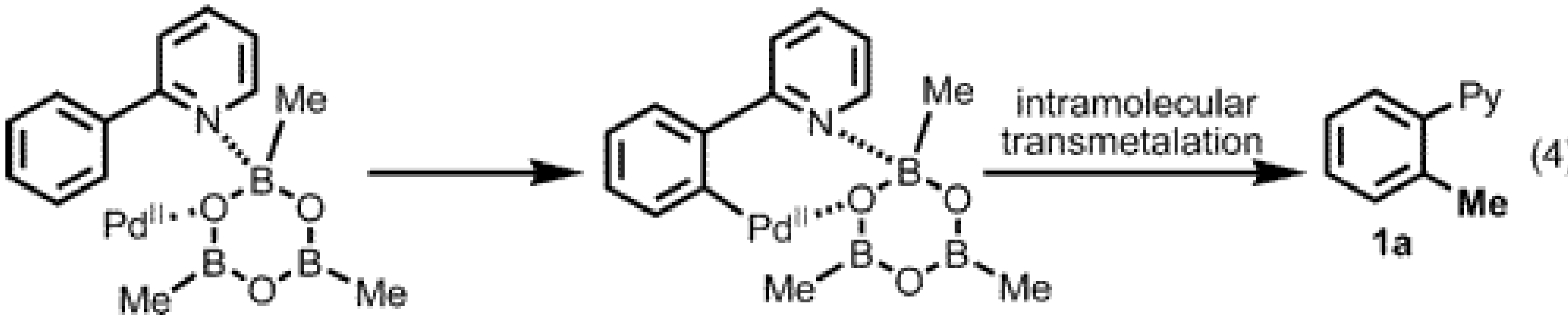


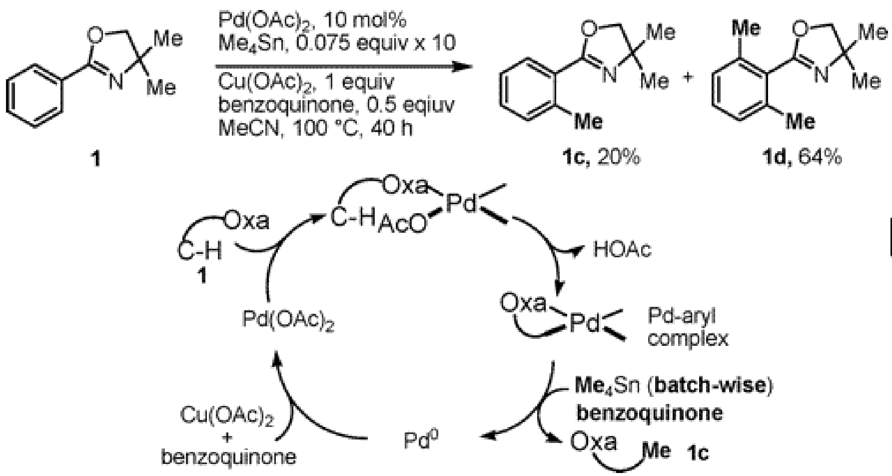
174-fold boost in potency

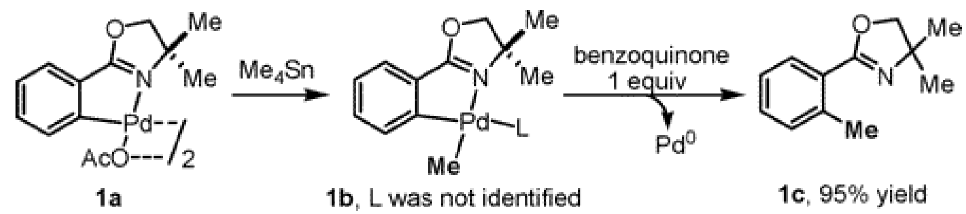


2135-fold boost in potency


(i) s-BuLi 1.3 equivalent
ligand 0.2 equivalent
bispidine 1.2 equivalent
(ii) TMSCl
Boc
TMS
(–)-Sparteine
(S)-Product, 76%, 80% ee
(+)-Sparteine surrogate
(R)-Product, 66%, 88% ee
Me
(+)-Sparteine surrogate
s-BuLi
Li
s-Bu
s-Bu–H
(–)-Sparteine
t-BuO
i-Pr
TMSCl
Bispidine


Me
N
B
Pd^{II}
O
O
B
B
Me
O
Me
intramolecular
transmetalation
Py
Me
1a
(4)


Pd(OAc)$_2$, 10 mol%
Me$_4$Sn, 0.075 equiv x 10
Cu(OAc)$_2$, 1 equiv
benzoquinone, 0.5 eqiuv
MeCN, 100 °C, 40 h
1
1c, 20%
1d, 64%
Oxa
C-H
1
C-H
AcO
Pd
HOAc
Oxa
Pd
Pd-aryl
complex
Pd(OAc)$_2$
Me$_4$Sn (batch-wise)
benzoquinone
Cu(OAc)$_2$
+
benzoquinone
Pd^0
Oxa
Me
1c


Pd
AcO
2
1a
Me$_4$Sn
Pd—L
Me
1b, L was not identified
benzoquinone
1 equiv
Pd^0
1c, 95% yield