

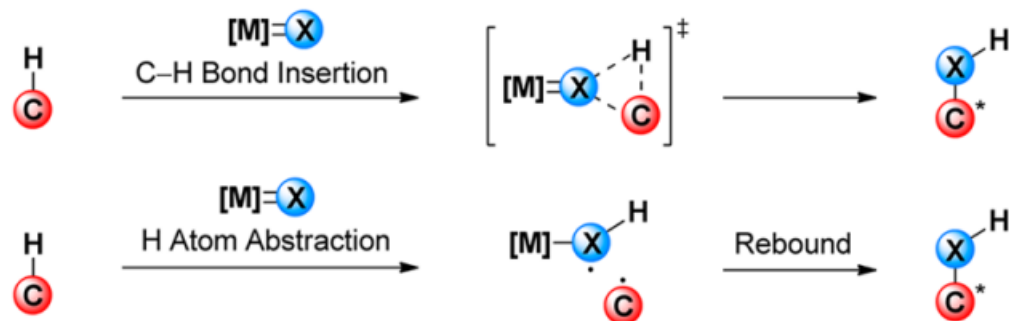
Enantioselective C(sp³)–H bond activation by chiral transition metal catalysts

Reporter: He Zhiqi
Supervisor: Prof. Yong Huang
2018.03.05

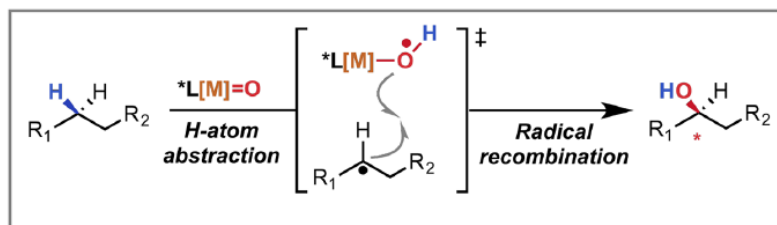
Yu. J.-Q., *et al.* *Science* **2018**, DOI: [10.1126/science.aao4798](https://doi.org/10.1126/science.aao4798)

1. Overview of mechanistic differentiation in TM mediated enantioselective C-H functionalization

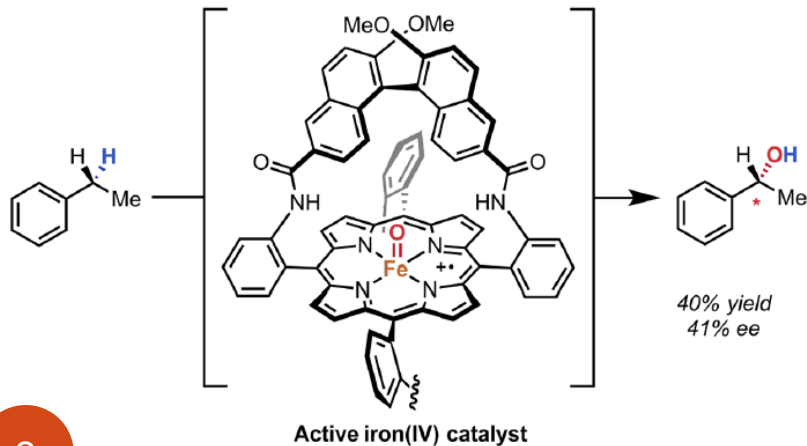
Outer-sphere Mechanism



A Biomimetic approaches/metal-oxo H-atom abstraction

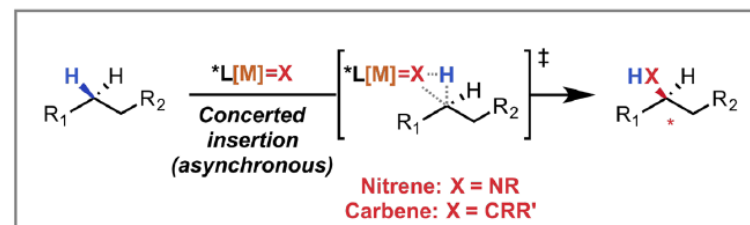


Representative example: intermolecular enantioselective hydroxylation

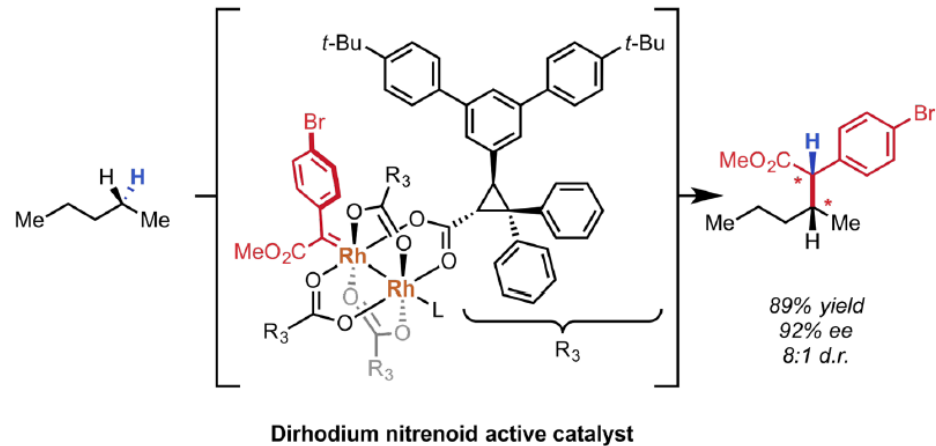


J. Am. Chem. Soc. **1989**, *111*, 8538

B Metallonitrene and metallocarbene insertion into C-H bonds



Representative example: intermolecular carbene insertion



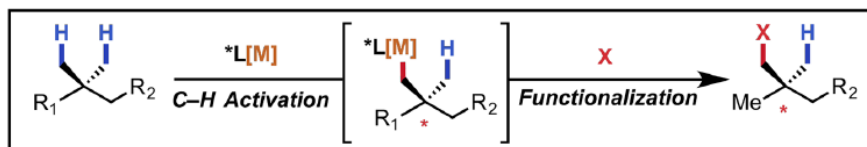
Nature **2016**, *533*, 230

Inner-sphere Mechanism

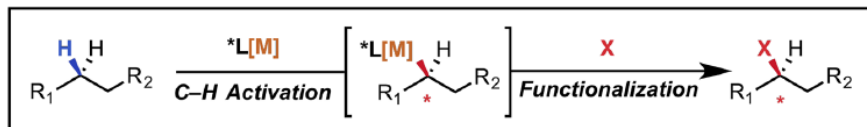


C Transition metal C-H activation (focus of this review)

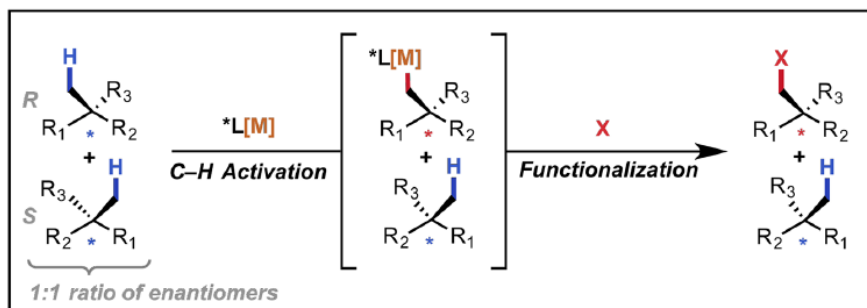
C-H Activation/desymmetrization



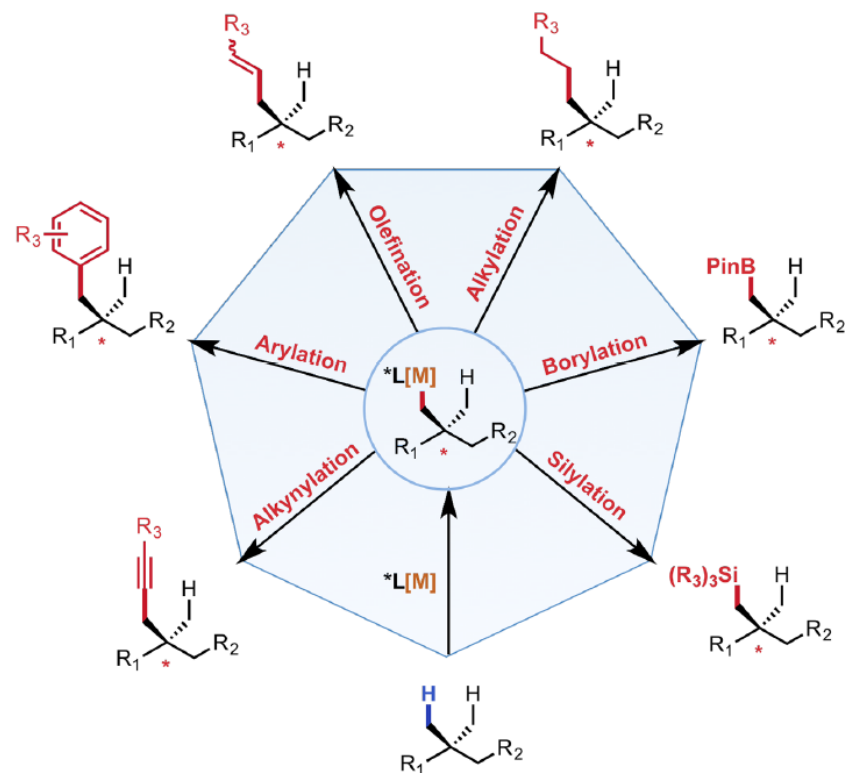
Enantioselective methylene C-H activation



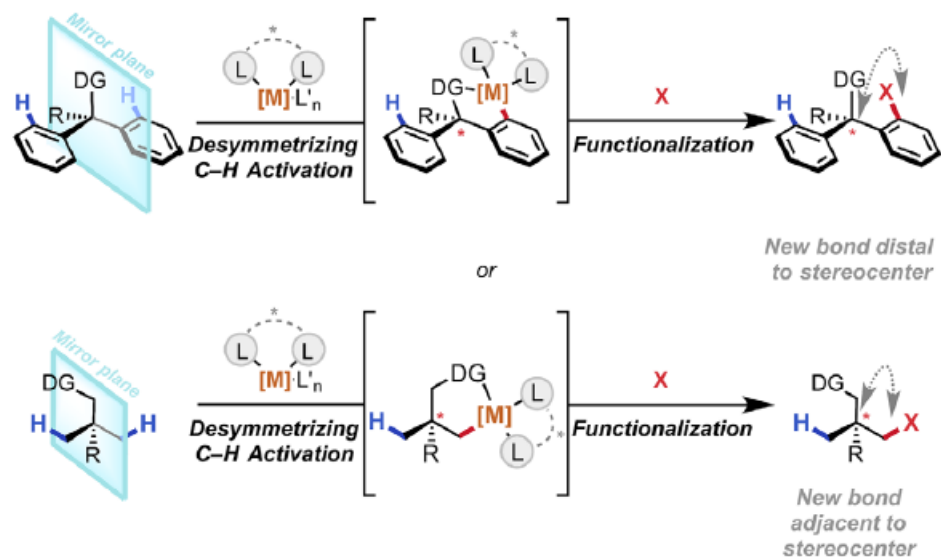
Kinetic resolution



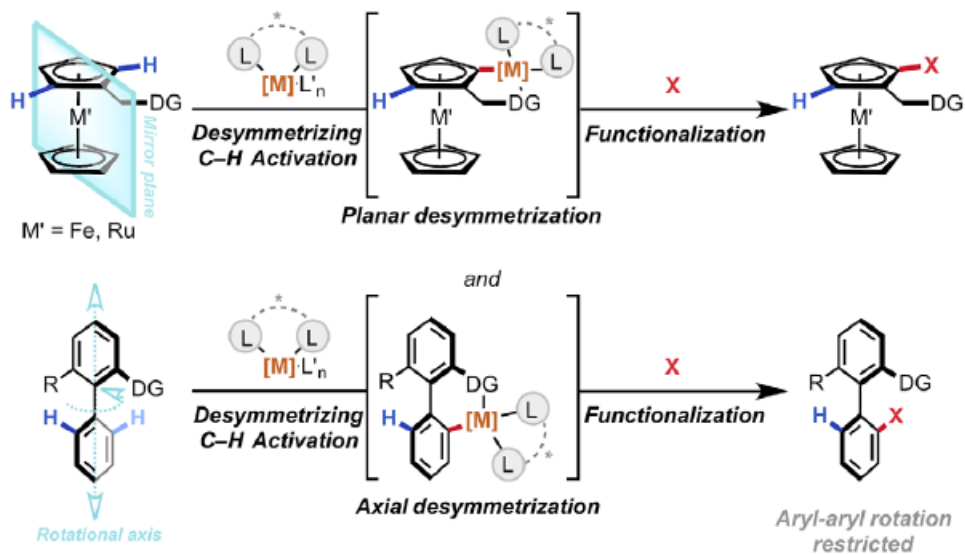
D Diverse transformations enabled by enantioselective C-H activation



A Overview of point desymmetrization C-H activation: C(sp²)-H and C(sp³)-H

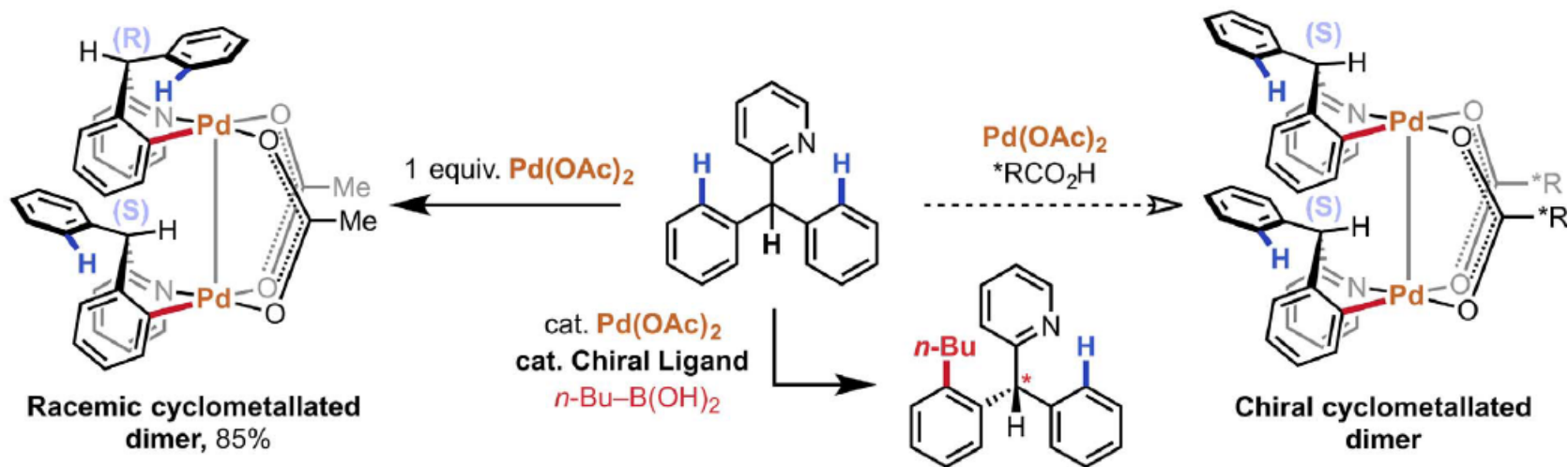


B Overview of planar and axial desymmetrization C-H activation: C(sp²)-H only



2. Enantioselective C-H activation through desymmetrization

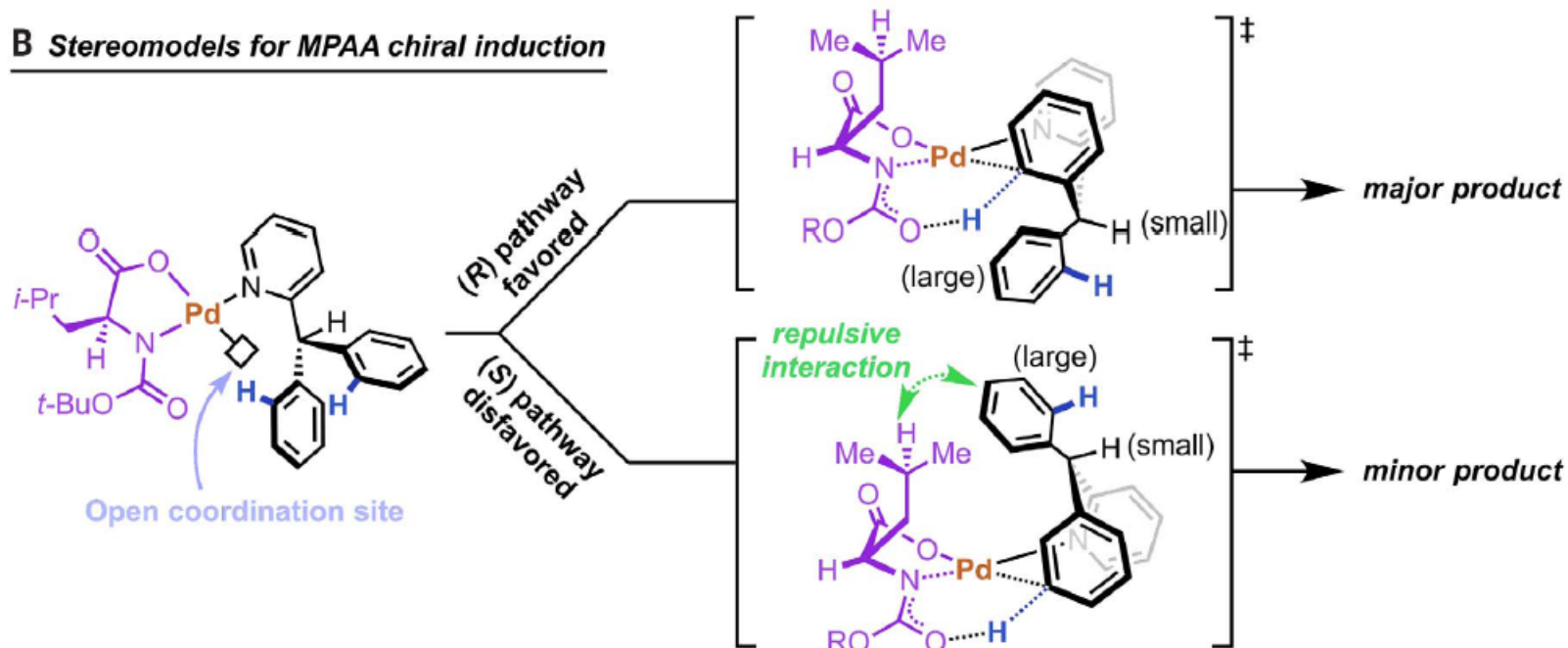
A Initial discovery of chiral mono-N-protected amino acid (MPAA) ligands for enantioselective C-H activation



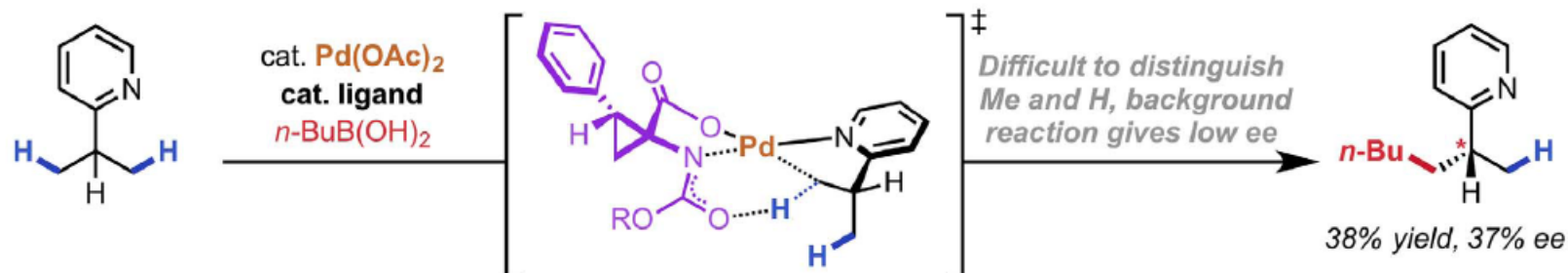
Entry	1	2	3	4	5	6	7
Chiral Ligand							
Yield (%)	n.r.	74	63	86	46	58	91
ee (%)	--	7	90	0	46	0	87

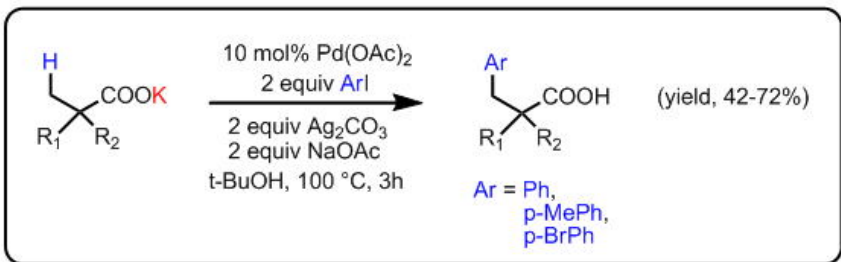
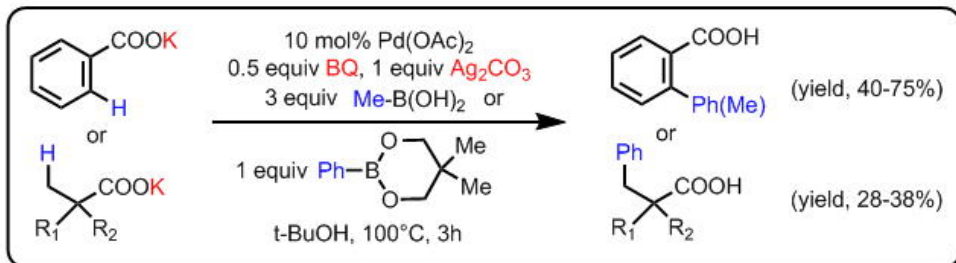
Angew. Chem. Int. Ed. **2008**, *47*, 4882.

B Stereomodels for MPAA chiral induction

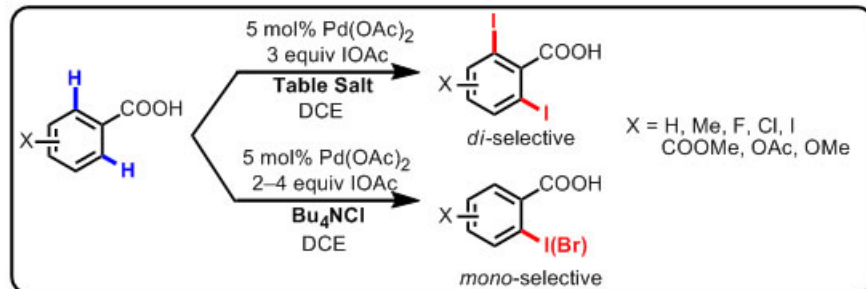


C Preliminary results on enantioselective $C(sp^3)$ -H activation with strong directing groups

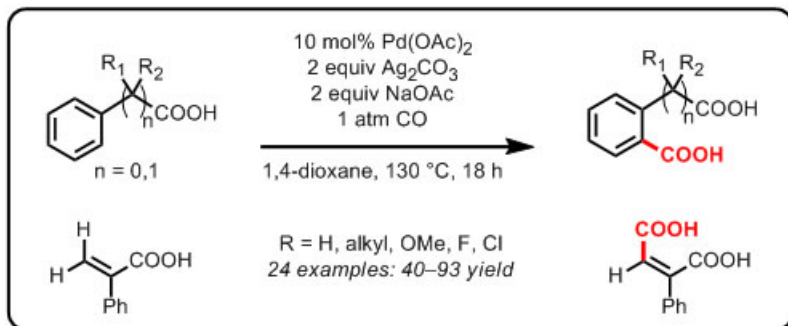




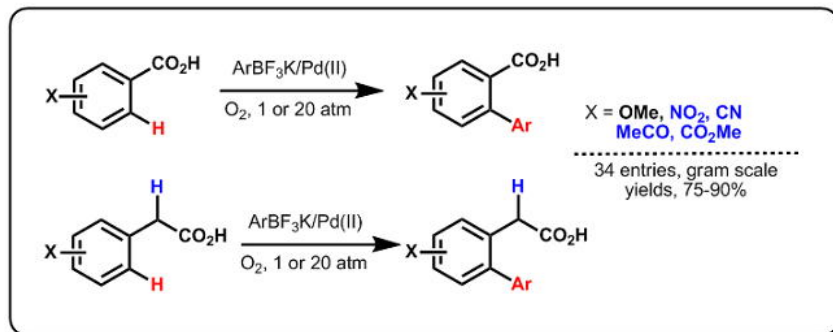
J. Am. Chem. Soc **2007**, *129*, 3510



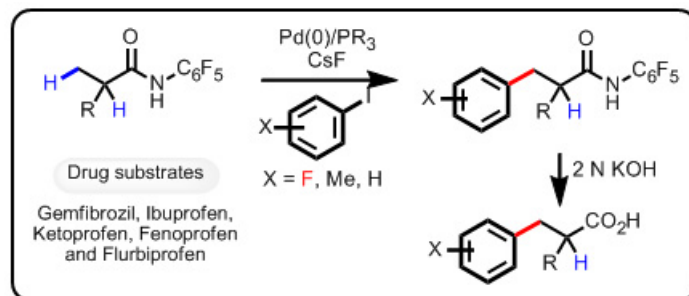
Angew. Chem. Int. Ed. **2008**, *47*, 5215.



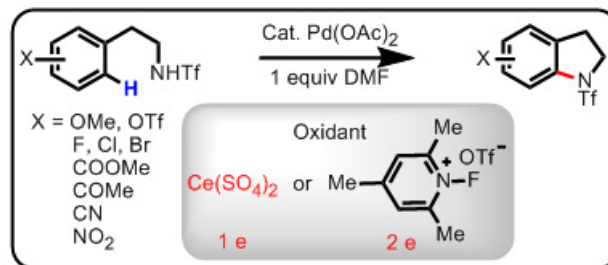
J. Am. Chem. Soc **2008**, *130*, 14082



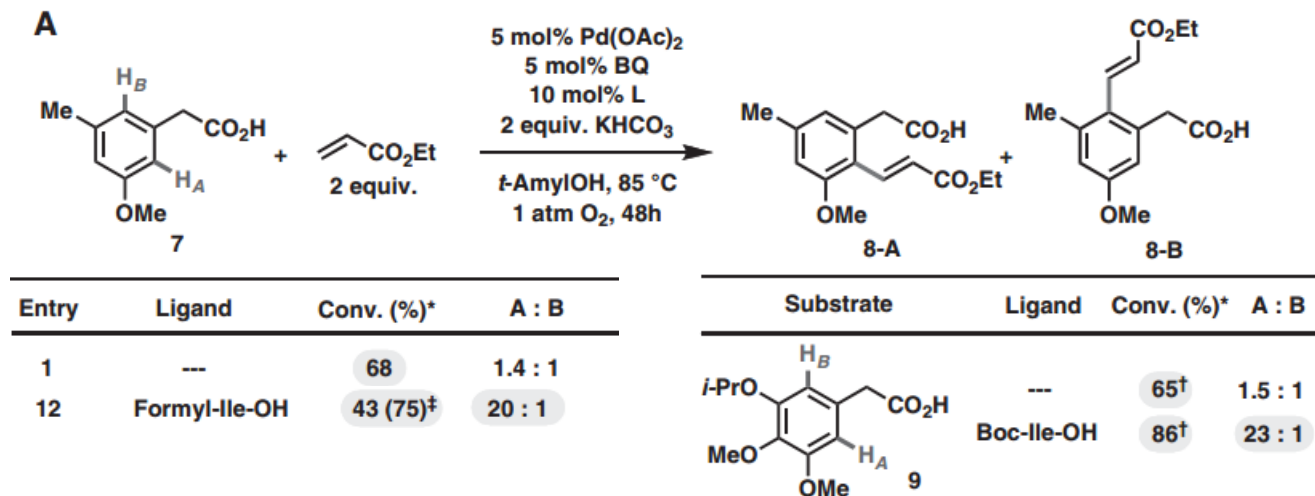
J. Am. Chem. Soc **2008**, *130*, 17636



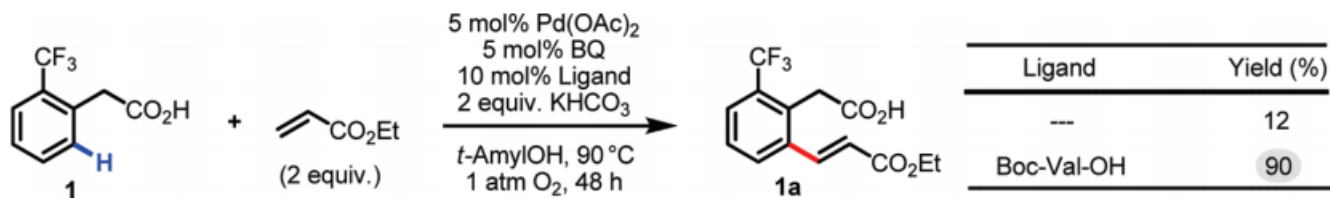
J. Am. Chem. Soc. **2009**, *131*, 9886.



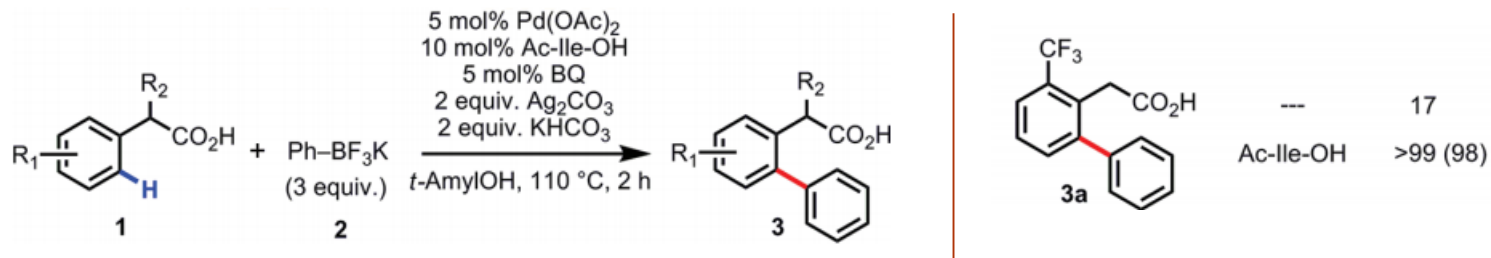
J. Am. Chem. Soc. **2009**, *131*, 10806.



Science **2010**, 327, 315

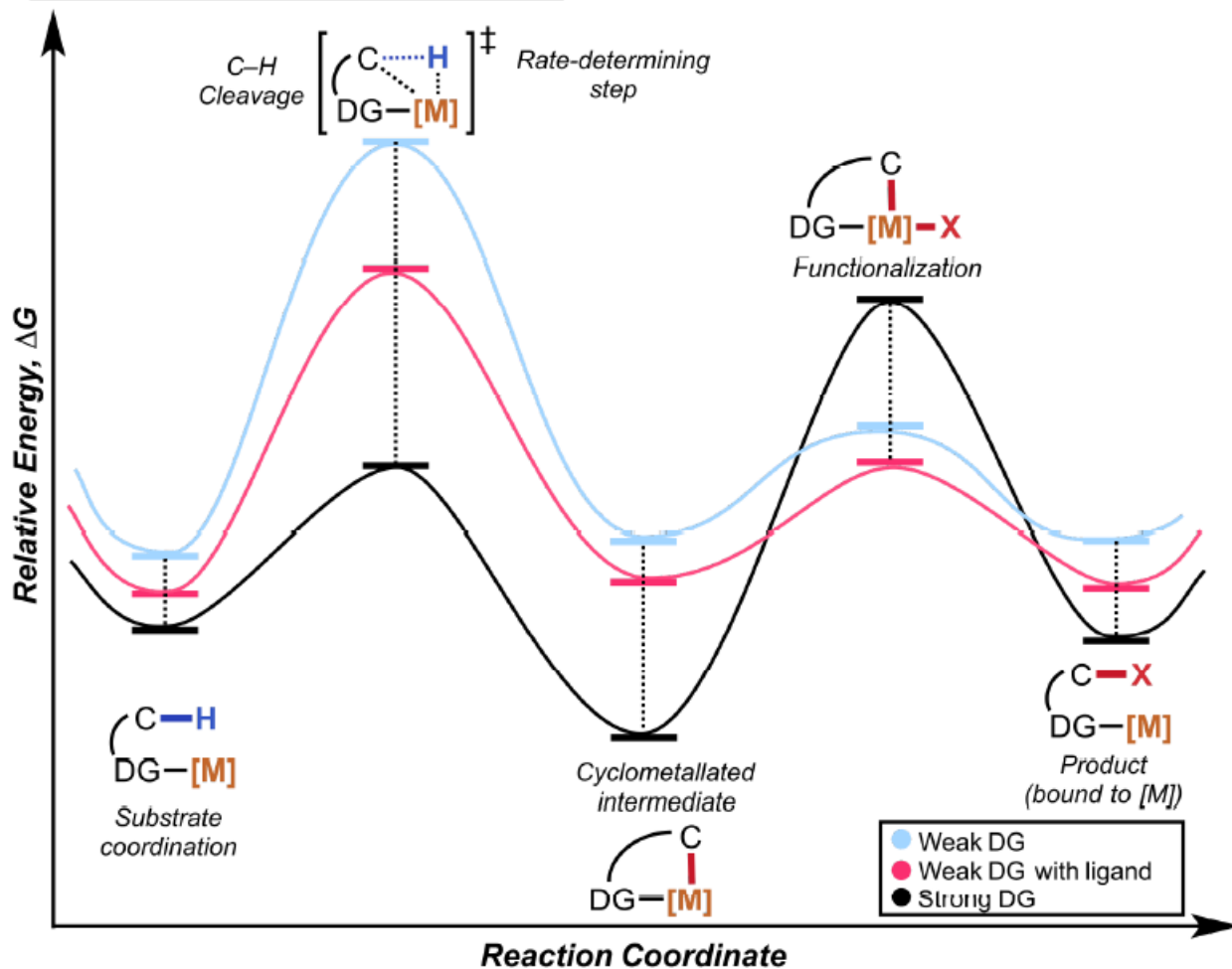


J. Am. Chem. Soc. **2010**, 132, 14137

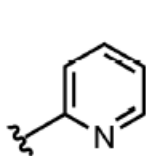


J. Am. Chem. Soc. **2011**, 133, 18183

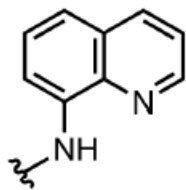
A Comparative reaction coordinate



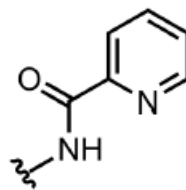
B Typical strong directing groups



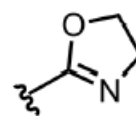
Pyridine



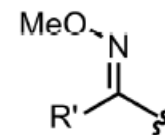
8-Amino quinoline



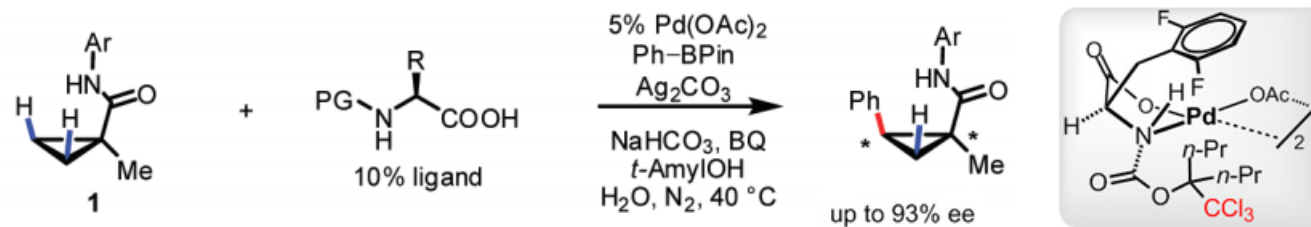
2-Picolinamide



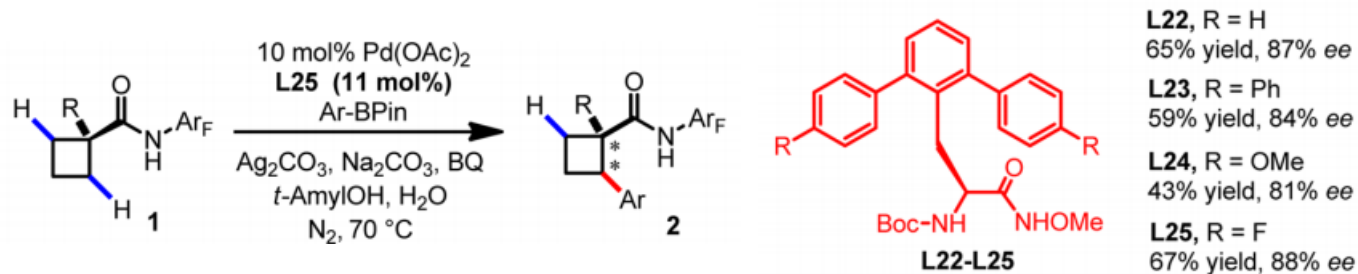
Oxazolines



Oxime Ethers

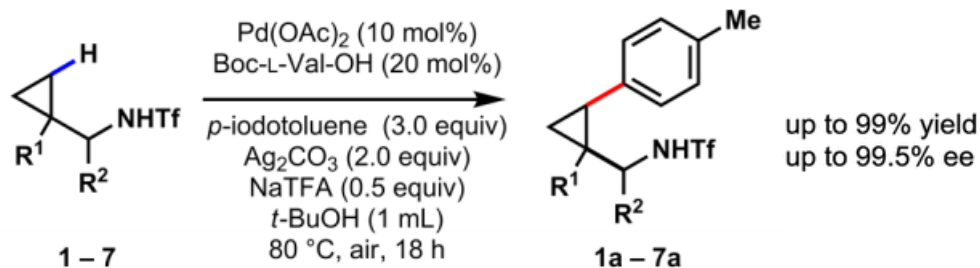
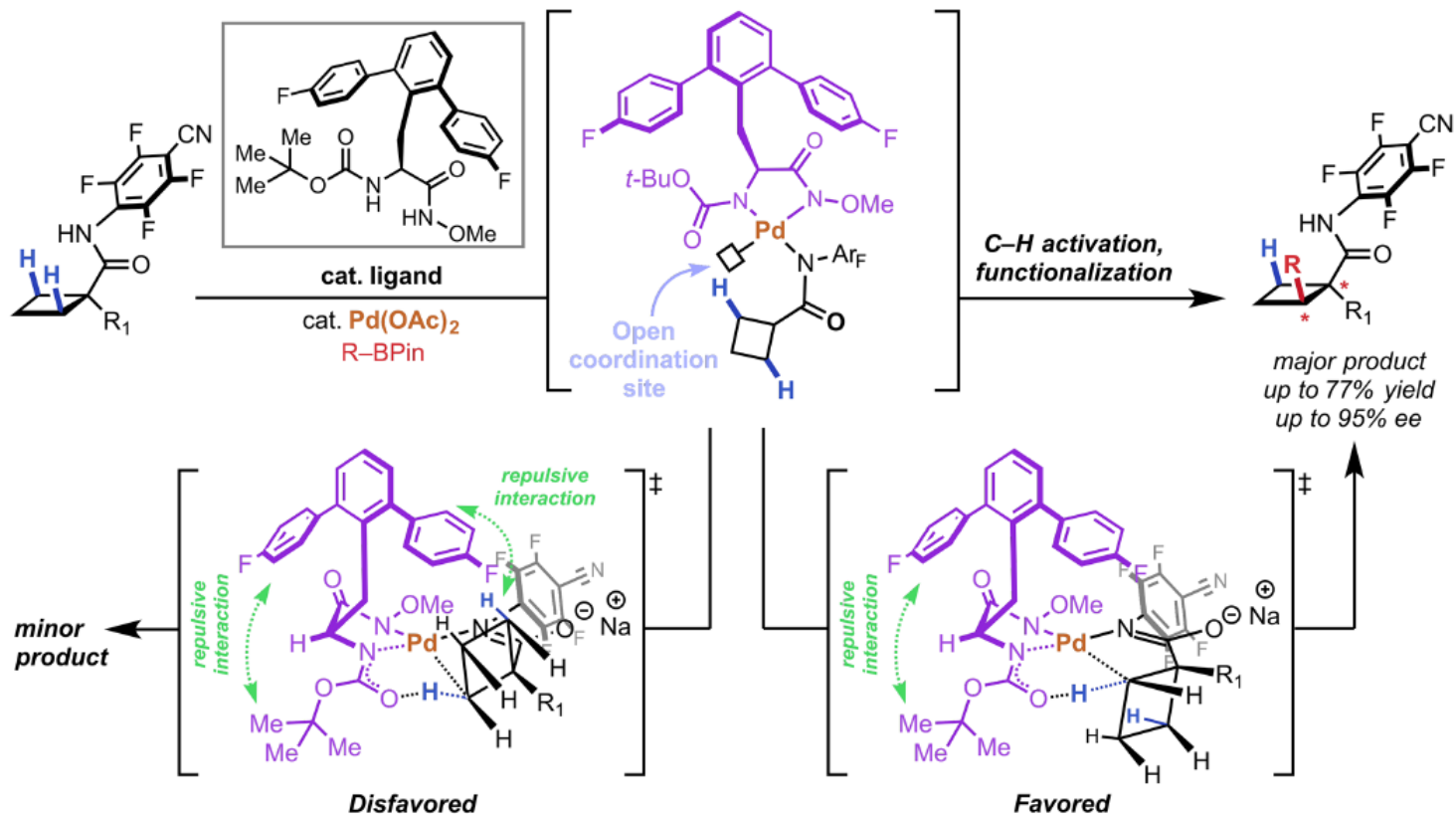


J. Am. Chem. Soc. **2011**, *133*, 19598

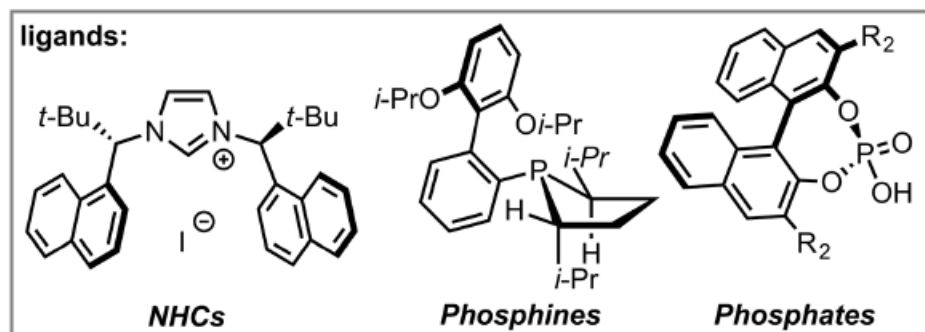


J. Am. Chem. Soc. **2014**, *136*, 8138

A Amino acid-derived ligand-enabled desymmetrization of cyclobutyl compounds: Pd(II)/Pd(0) Catalysis



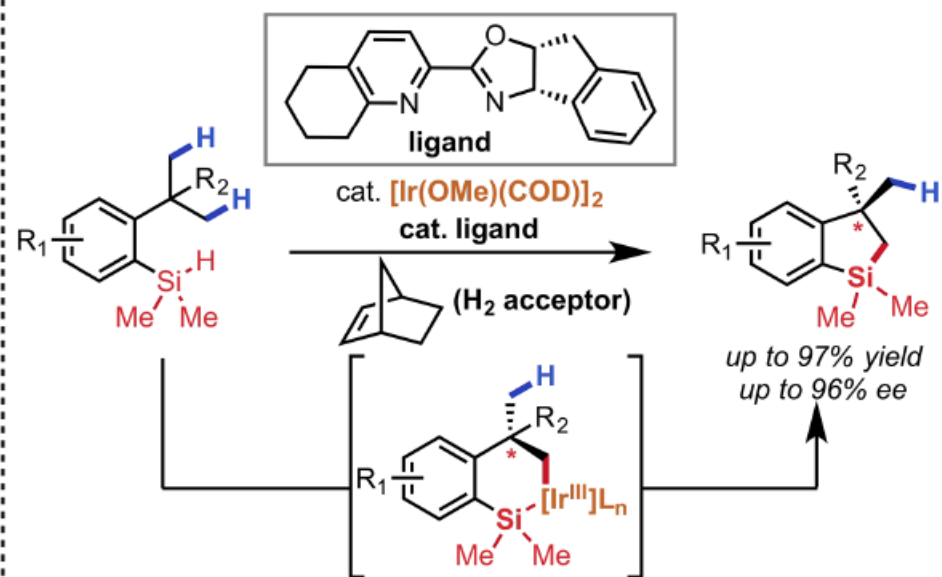
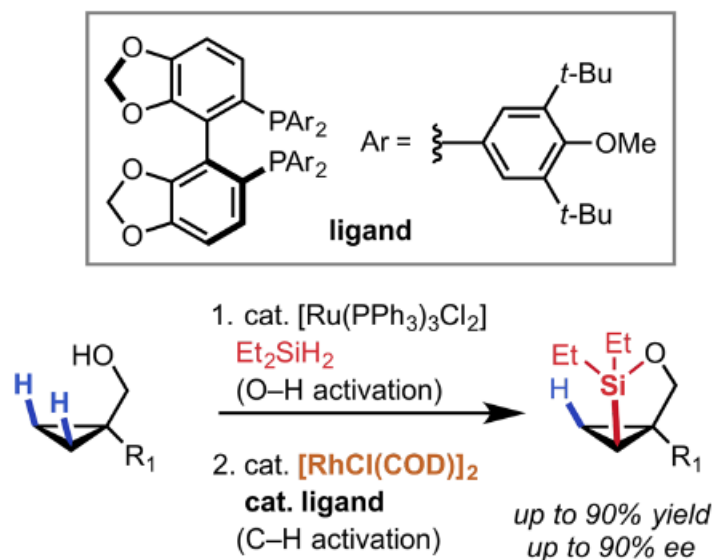
B Summary of Pd(0)/Pd(II) intramolecular enantioselective C–H cyclization:



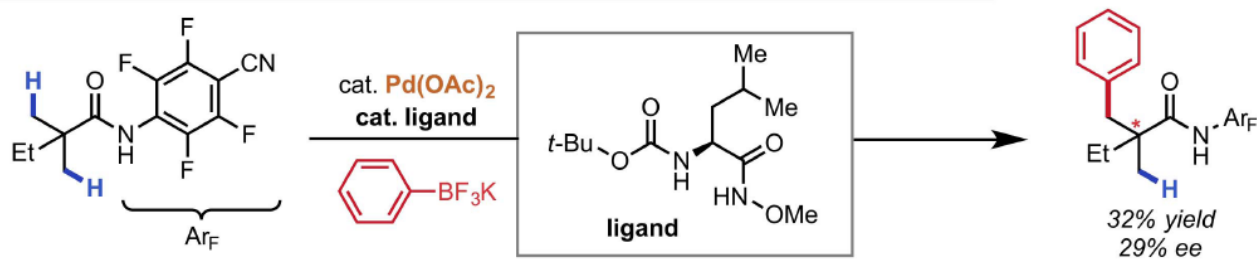
Chem. Sci. **2013**, *4*, 1995

ACS Catal., **2015**, *5*, 4300

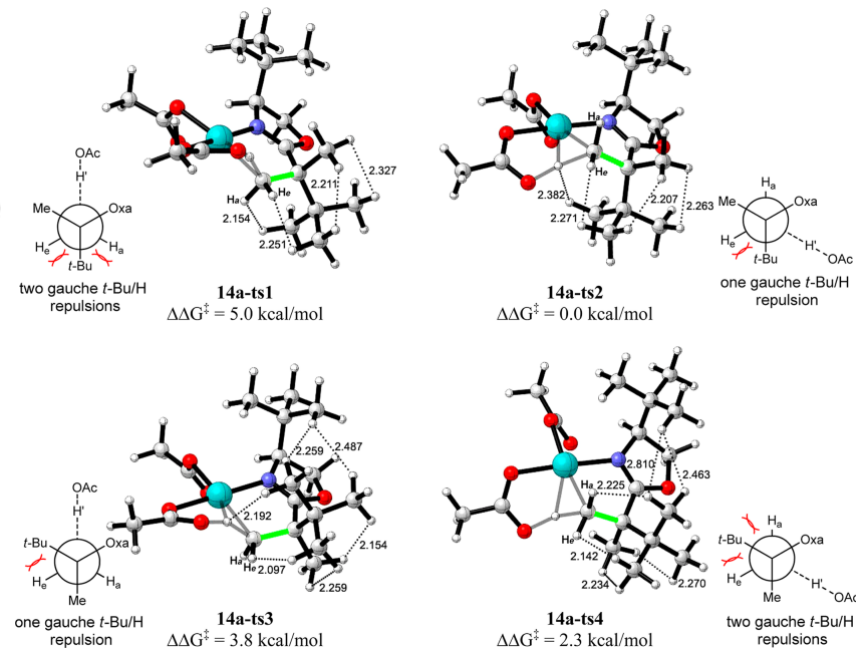
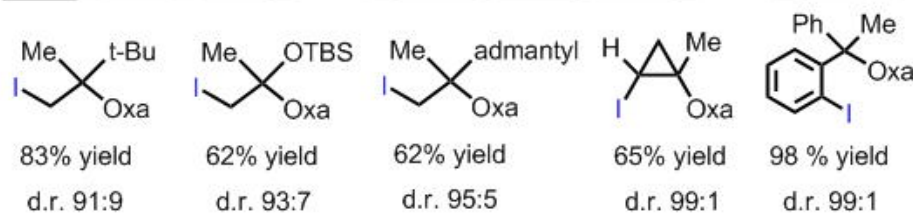
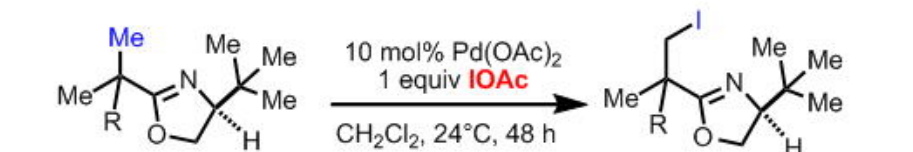
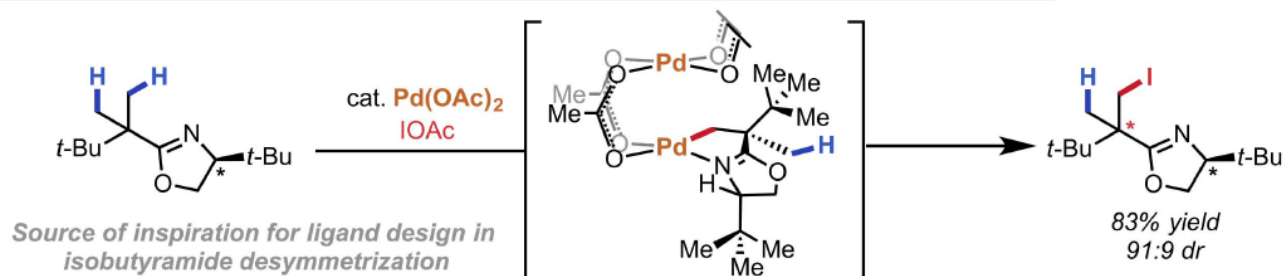
C Representative examples of Rh(I)/Rh(III) and Ir(I)/Ir(III) intramolecular enantioselective C–H cyclization:



A Challenges in intermolecular desymmetrization C(sp³)-H activation: acyclic systems

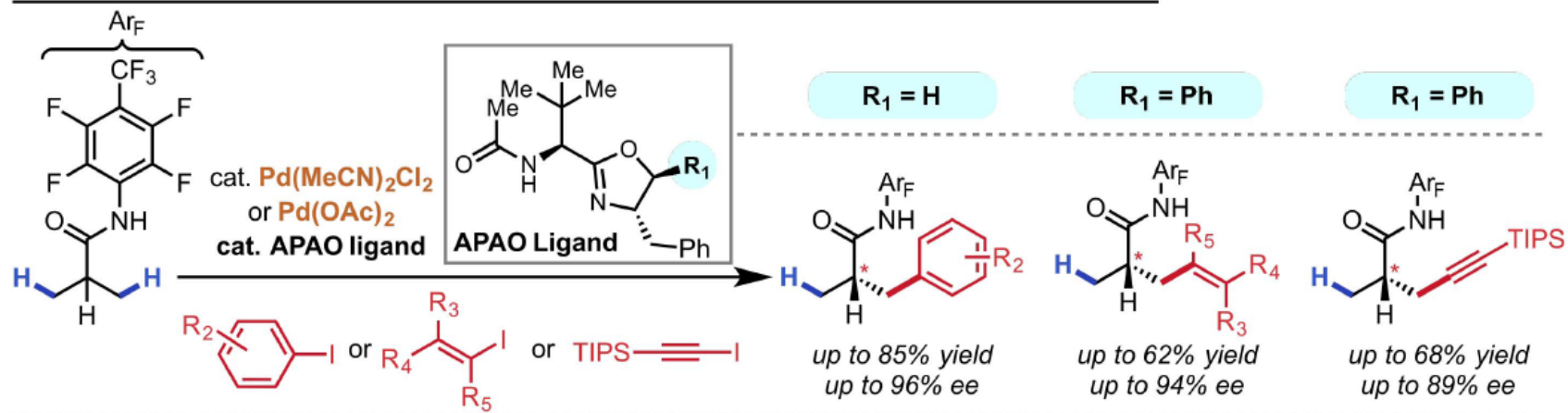


B Inspiration for desymmetrization of geminal dimethyls: diastereoselective model

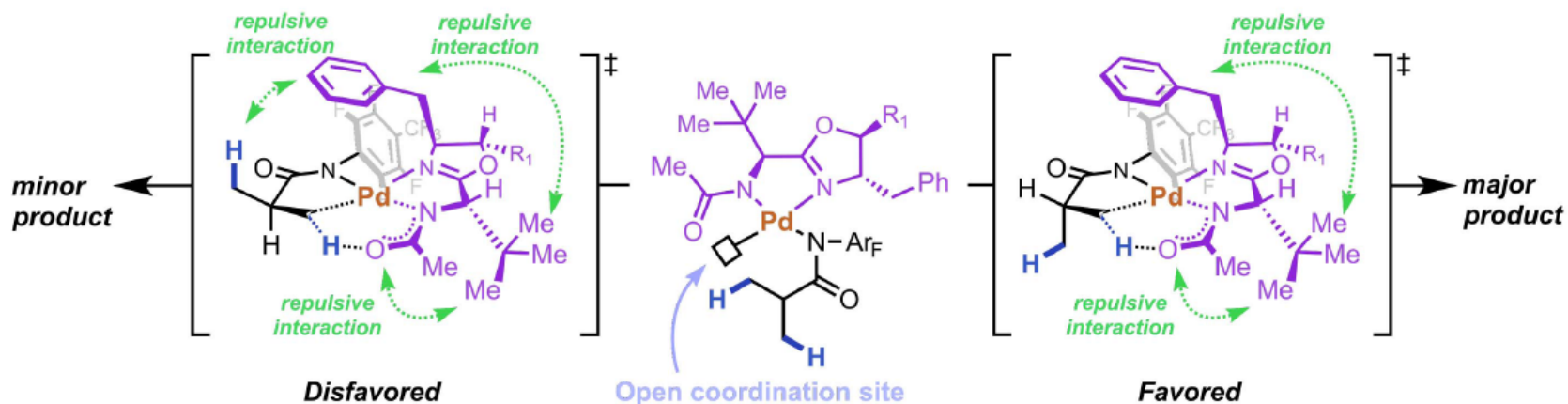


J. Am. Chem. Soc. **2014**, *136*, 8138
Angew. Chem. Int. Ed. **2005**, *44*, 2112.
J. Am. Chem. Soc. **2012**, *134*, 14118

C Enantioselective C–H activation of geminal dimethyls enabled by bidentate APAO ligands



D Proposed stereomodel for the desymmetrization of geminal dimethyl amides

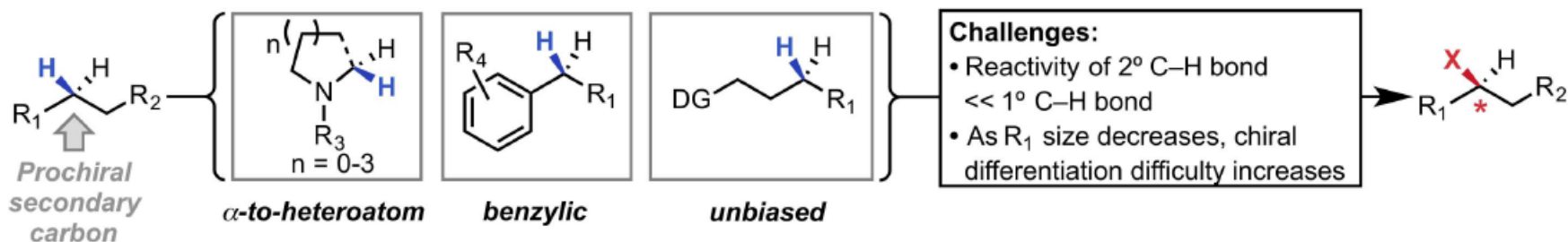


Science **2017**, 355, 499

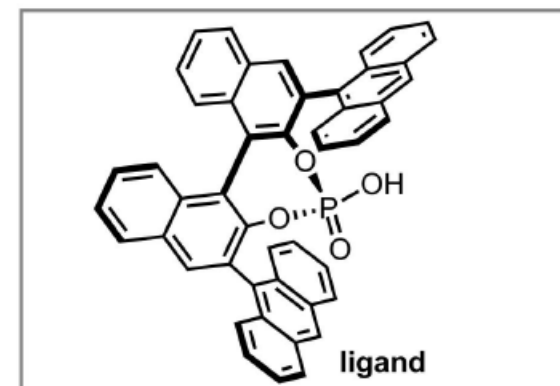
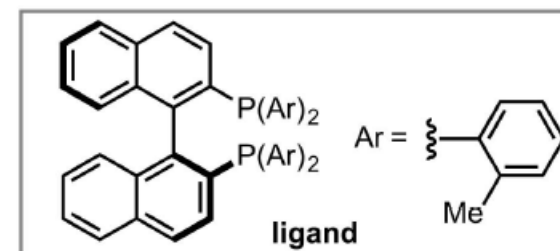
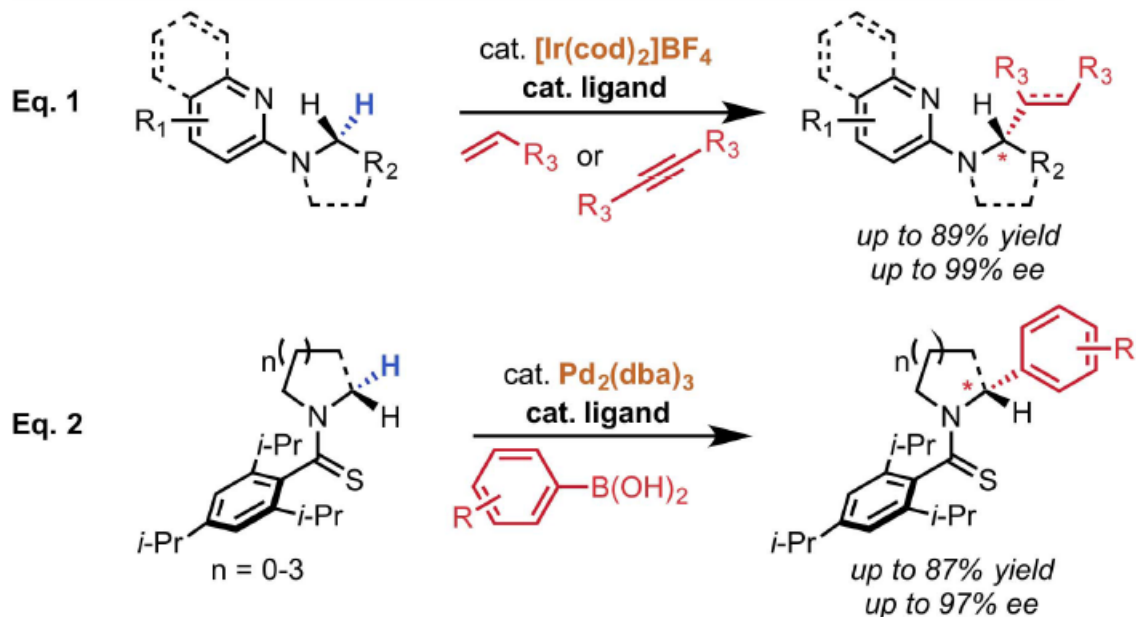
J. Am. Chem. Soc. **2017**, 139, 3344

3. Enantioselective methylene C-H activation

A Overview of enantioselective methylene C-H activation

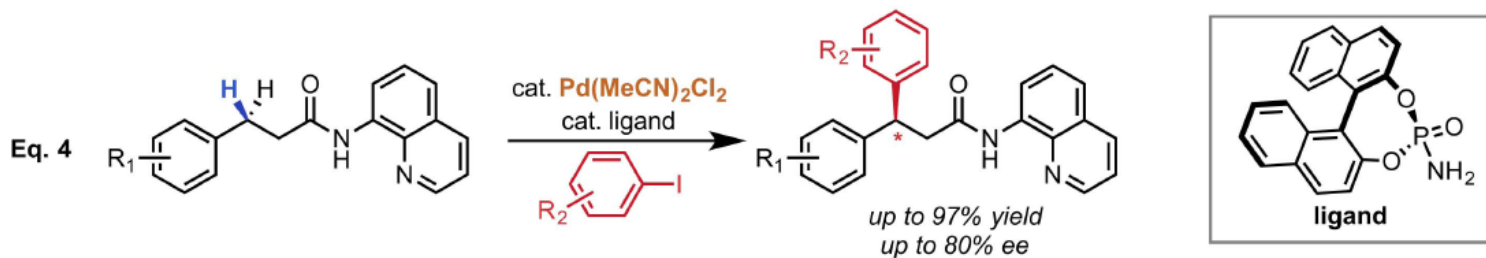
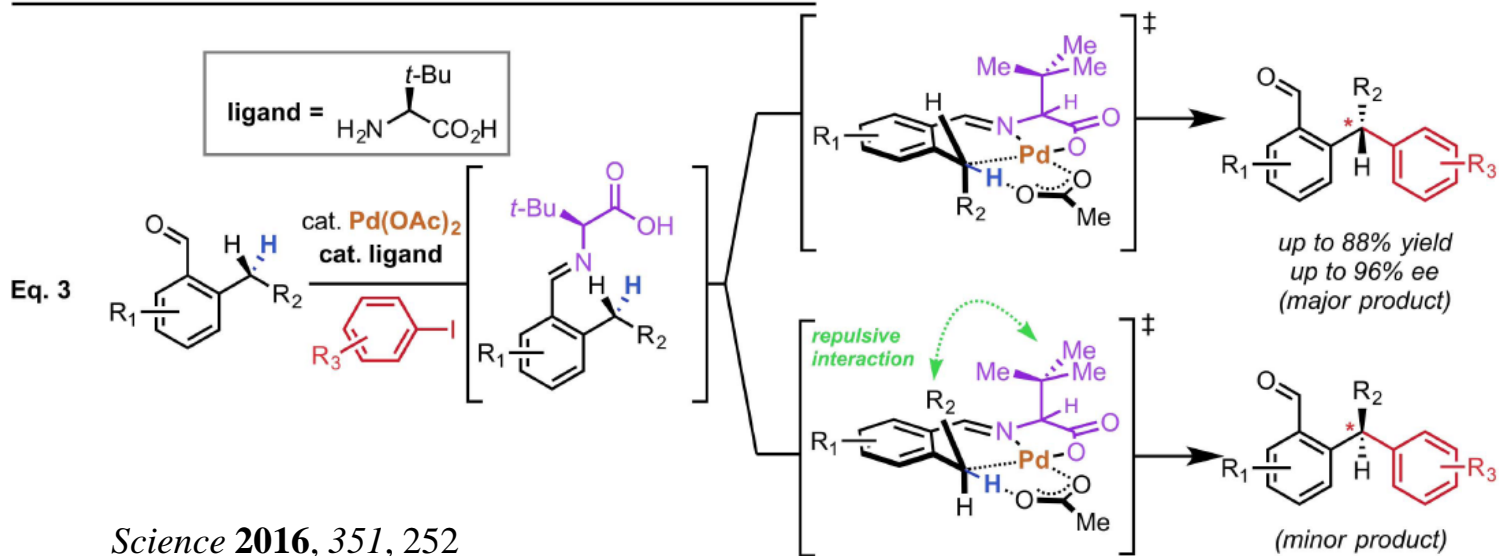


B Examples of enantioselective methylene C-H activation α -to-heteroatom

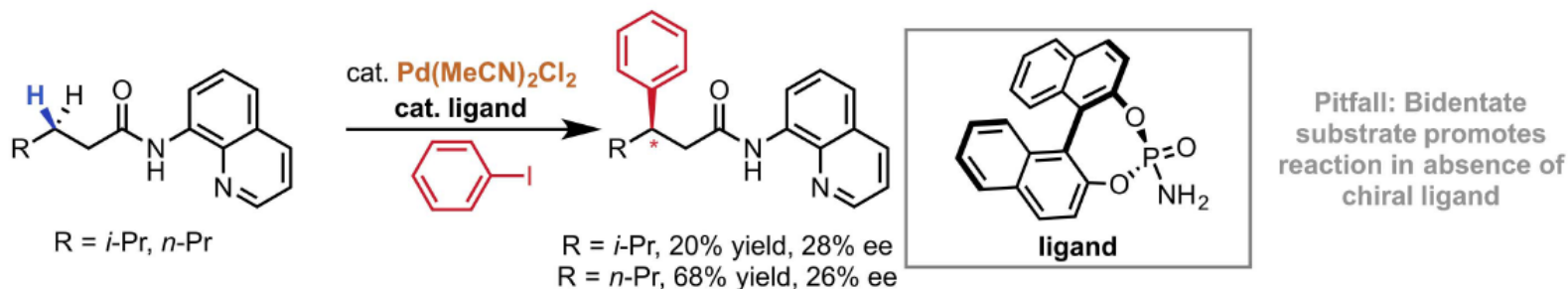


Nat. Chem. **2016**, 353, 1023.

C Examples of enantioselective benzylic methylene C–H activation



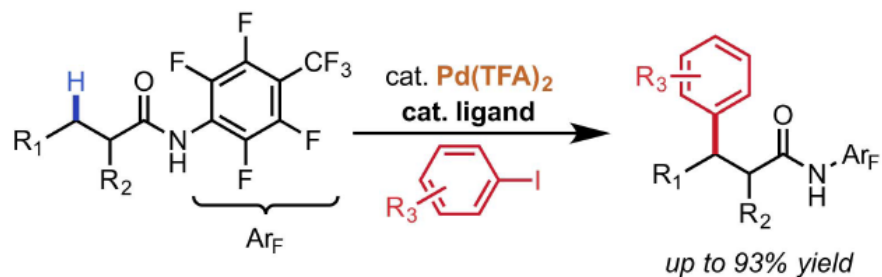
A Bidentate directing group/monodentate ligand for electronically unbiased methylene C–H activation



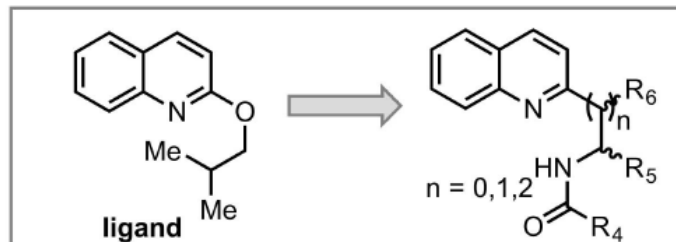
Org. Lett., **2015**, 17, 2458

Angew. Chem. Int. Ed. **2016**, 55, 15387

B Inspiration for bidentate chiral ligands for enantioselective methylene C–H activation

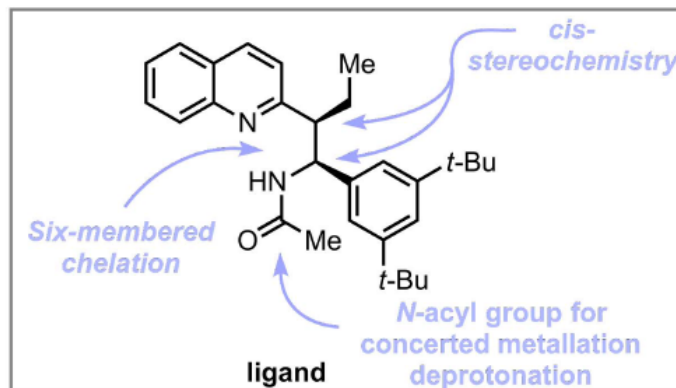
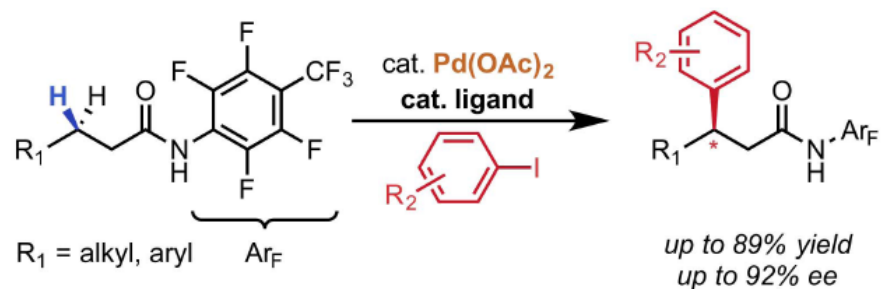


J. Am. Chem. Soc. **2012**, *134*, 18570.

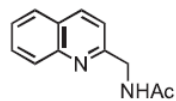


Source of inspiration for bidentate chiral ligand design for unbiased methylene C–H activation

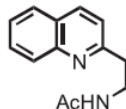
C Monodentate directing group/bidentate ligand for electronically unbiased methylene C–H activation



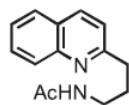
Science **2016**, *353*, 1023



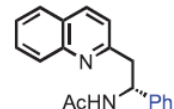
L6, N.R.



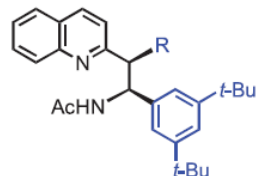
L9, 46% yield



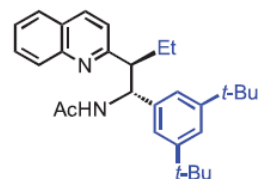
L10, 58% yield



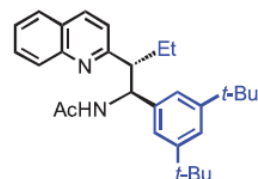
L17, 76% yield, 29:71 er



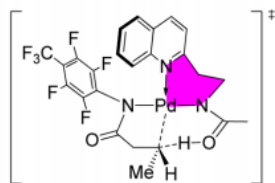
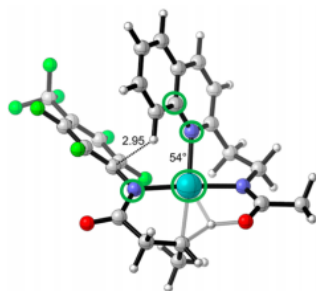
R = Me	L34, 86% yield, 90:10 er
Et	L35, 82% yield, 92.5:7.5 er
n-Pr	L36, 71% yield, 90.5:9.5 er
i-Pr	L37, 48% yield, 78:22 er
OMe	L38, 69% yield, 84:16 er
Bn	L39, 75% yield, 88:12 er



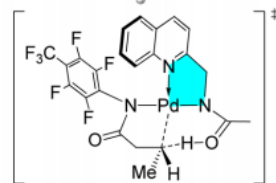
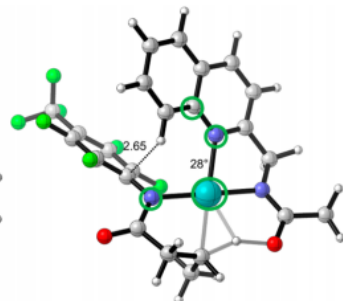
L40, 13% yield, 31:69 er



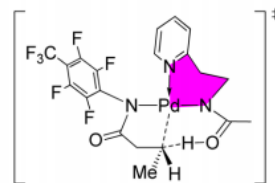
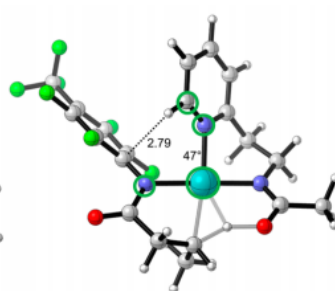
L41, 15% yield, 68:32 er



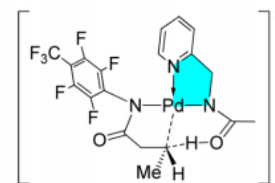
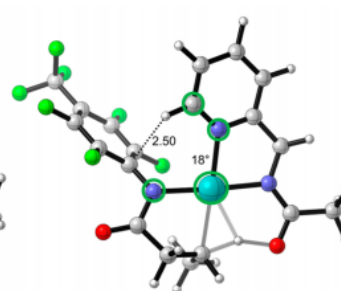
26
20.8 kcal/mol
22.1 kcal/mol



27
26.5 kcal/mol
29.8 kcal/mol

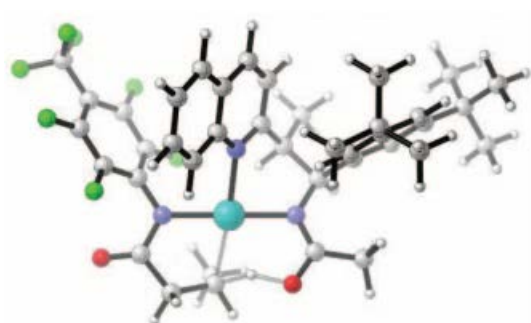
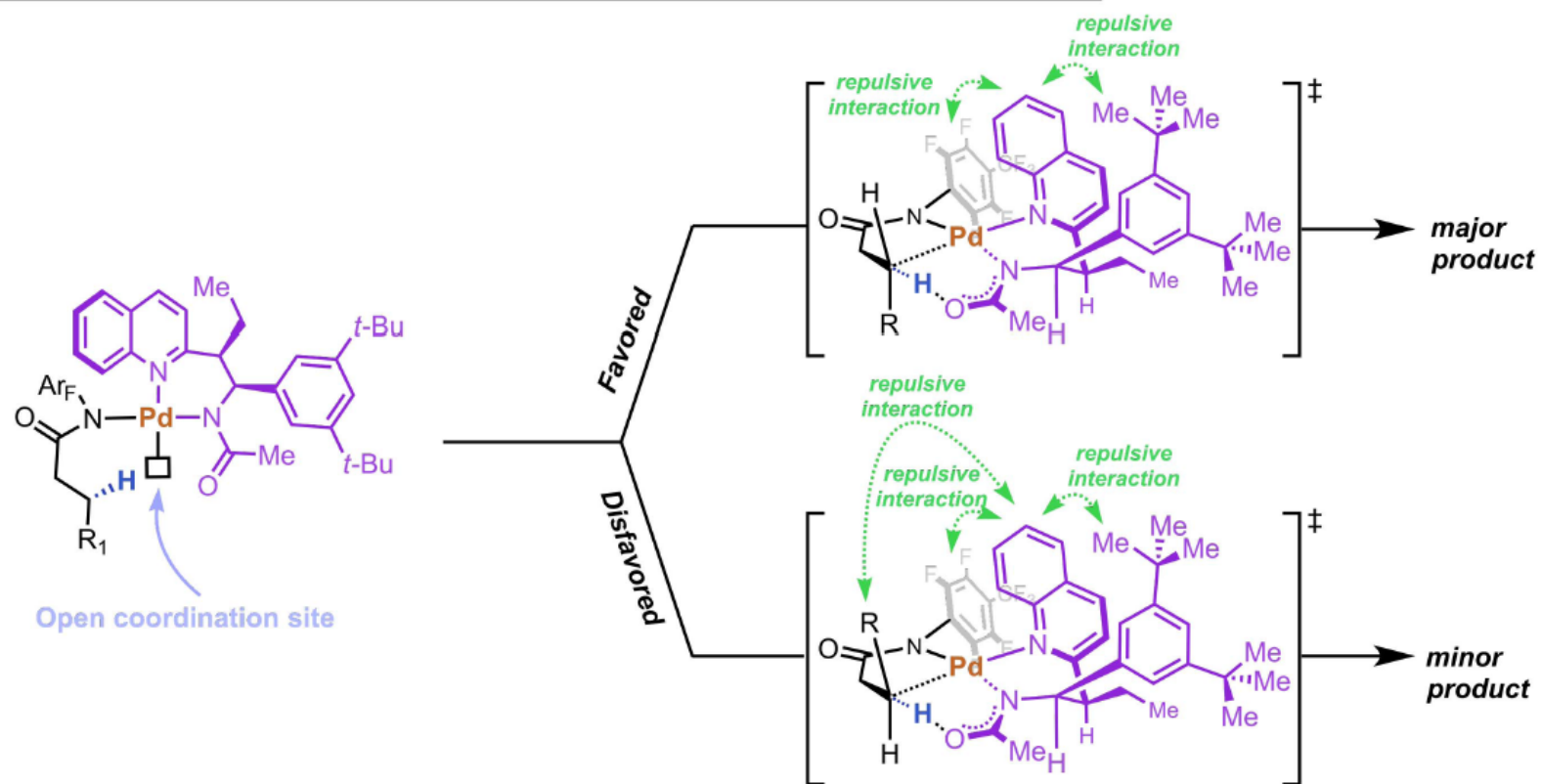


28
20.0 kcal/mol
22.8 kcal/mol

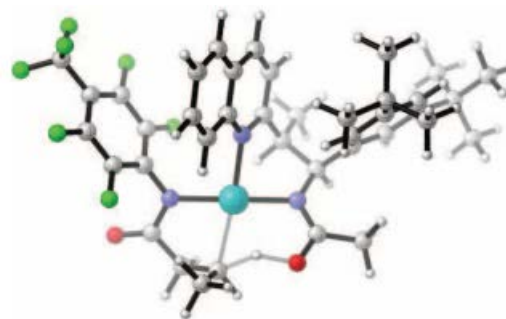


29
22.6 kcal/mol
29.3 kcal/mol

D Proposed stereomodel for APAQ-enabled enantioselective methylene C–H activation



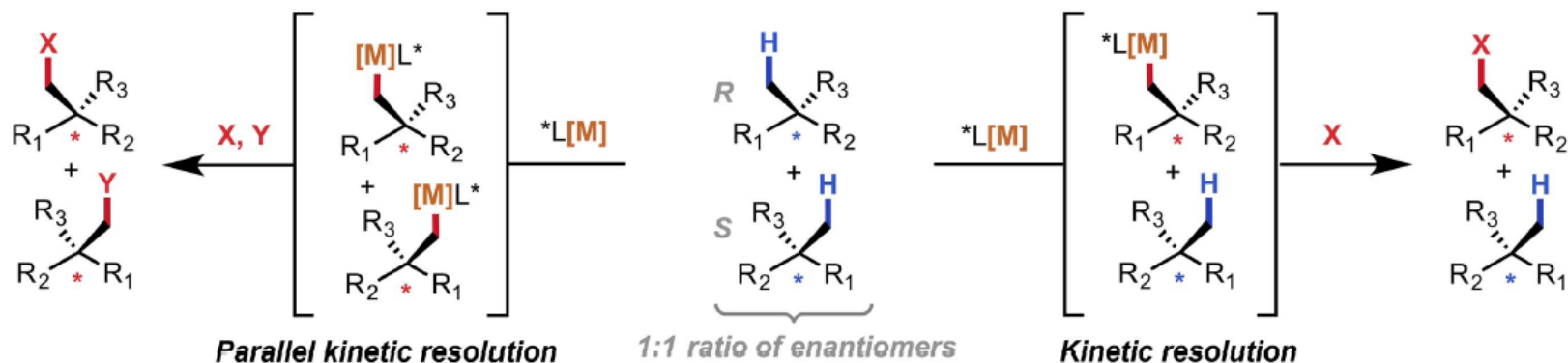
TS_R
 $\Delta\Delta G = 0.0$ kcal/mol



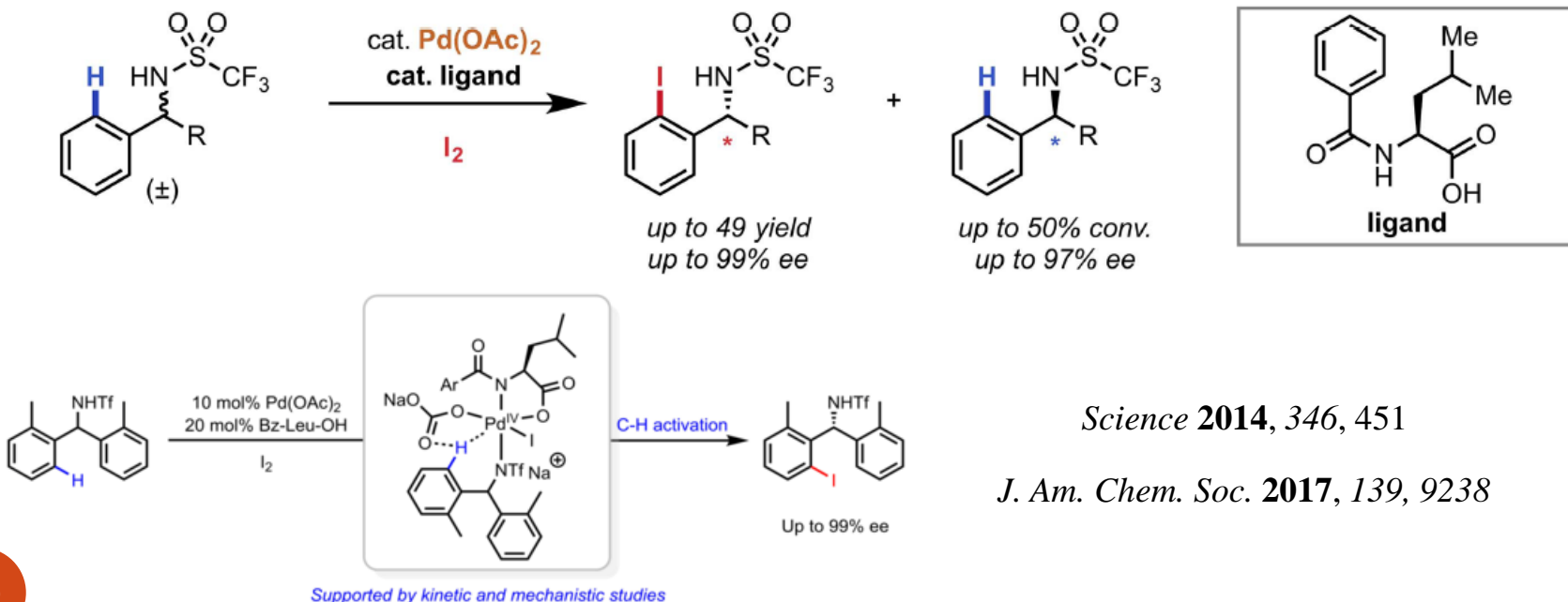
TS_S
 $\Delta\Delta G = 1.2$ kcal/mol

3. Kinetic resolution

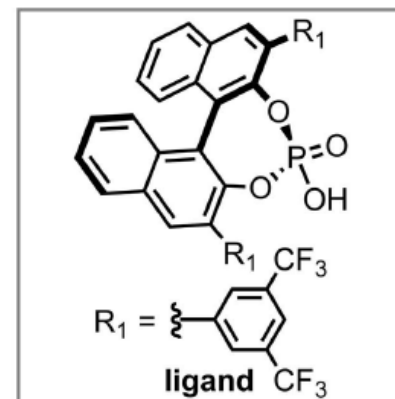
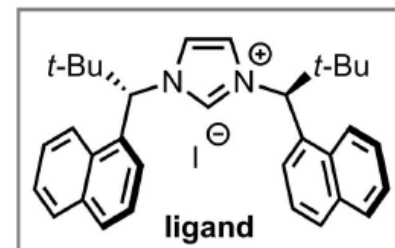
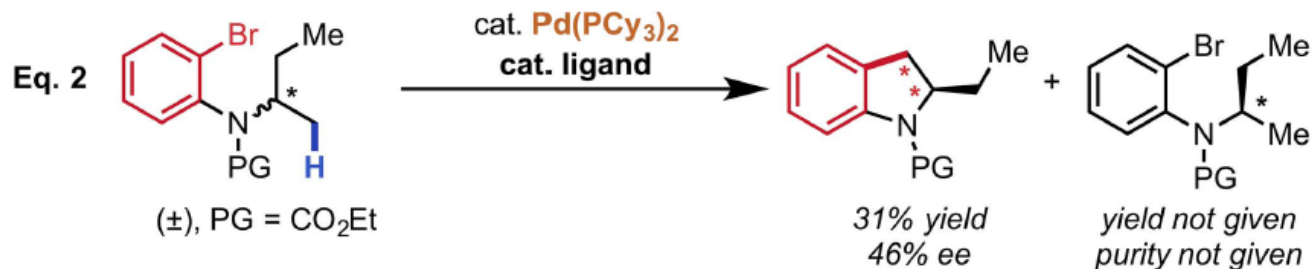
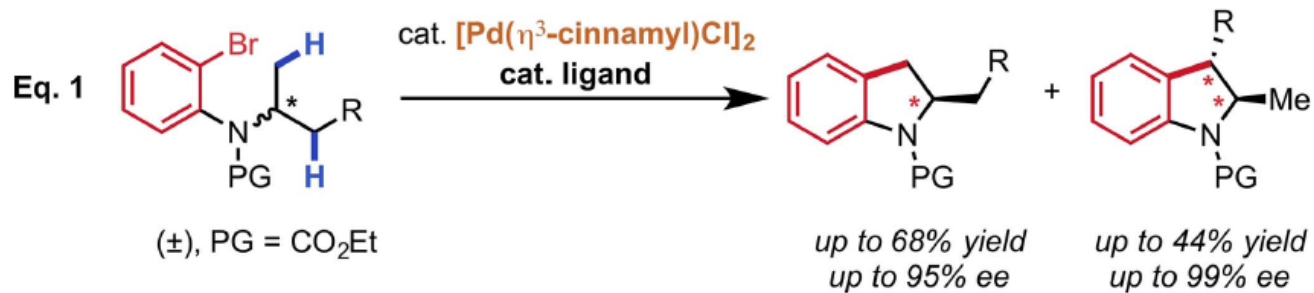
A Kinetic resolution and parallel kinetic resolution



B Initial report of MPAA-enabled $C(sp^2)$ -H kinetic resolution



C Intramolecular Pd(0)/Pd(II) Parallel Kinetic Resolution and Kinetic Resolution



Chem. Sci. **2012**, *3*, 1422

Chem. Sci. **2017**, *8*, 1344

3. Summary and outlook

A. Detailed aspect: more general substrates

B. Transformation aspect: various C-X formation

C. Concept aspect: concept combination

**Thanks for Your
Attention!**