Progress in the Asymmetric Dearomatization Reactions of Phenols

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Supervisor: Can Zhu (朱灿 青年研究员)

2026.4.24

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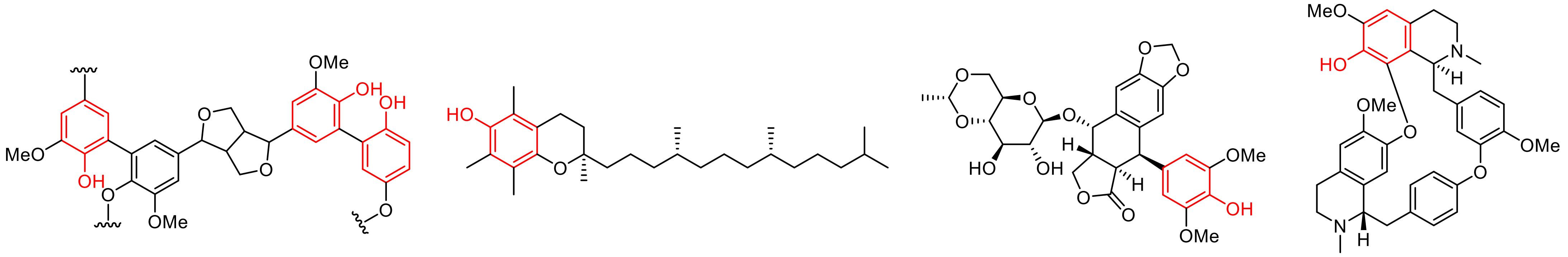
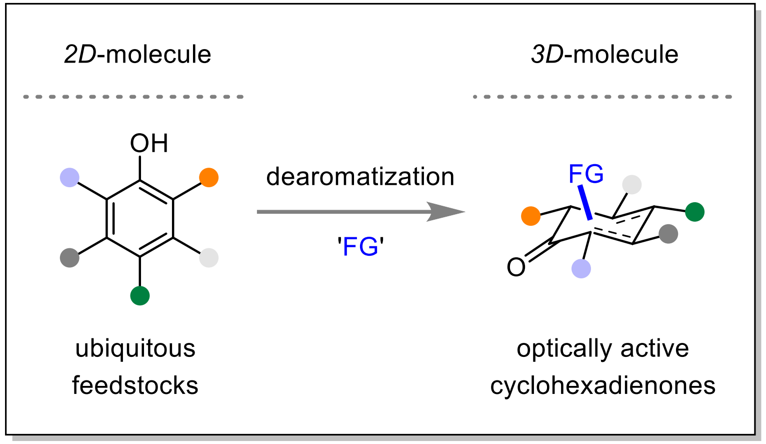
1. Introduction

Representative Natural Products and Pharmaceutical Molecules Bearing Phenol Skeleton



Dearomatization——Escaping from Flatland



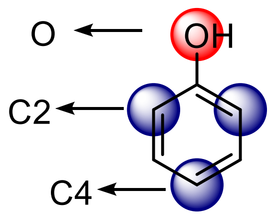
Importance：
- Construction of three-dimensional rigid structures enriched with C(sp³)
- Reducing the toxicity of drug candidates.
- Improving the pharmacokinetic profiles of drug candidates.

J. H. P. Tyman. *Synthetic and Natural Phenols.* Elsevier, **1996**.
S. L. You; et al. *Chem. Soc. Rev.* **2016**, *45*, 1570–1580.
W. Thomas; et al. *Top. Curr. Chem.* **2016**, *373*, 27.
T. Katsuki; et al. *J. Am. Chem. Soc.* **2012**, *134*, 20017–20020.
X. H. Bi; et al. *Nat. Chem.* **2025**, *17*, 215–225.

Content

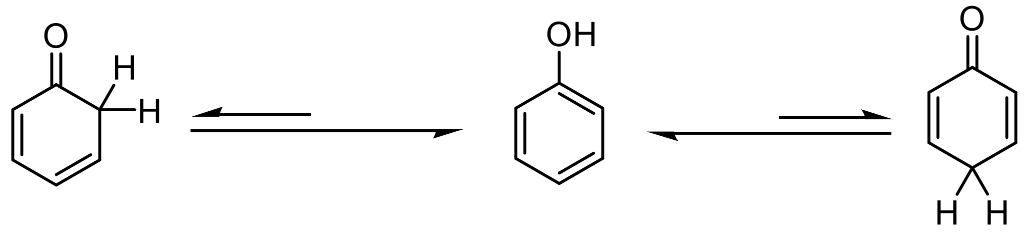
2. Asymmetric Dearomatization of Phenols as Nucleophiles

1. Main challenges

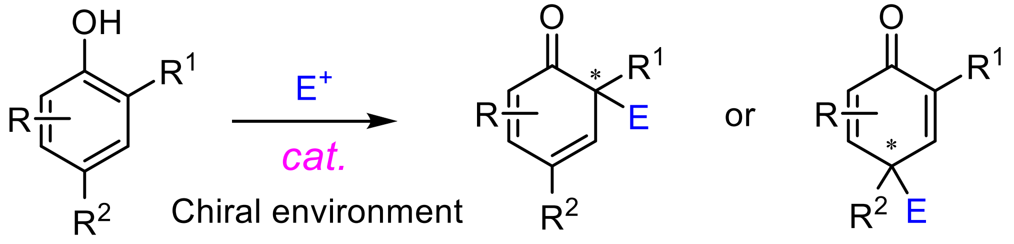


- chemoselectivity
- regioselectivity
- enantioselectivity

intrinsic keto-enol tautomerization



2. Significant progress



Asymmetric Dearomatization of Phenols
- Dearomative Asymmetric Alkylation
- Dearomative Asymmetric Alkenylation
- Dearomative Asymmetric Arylation
- Dearomative Asymmetric Amination
- Dearomative Asymmetric Halogenation

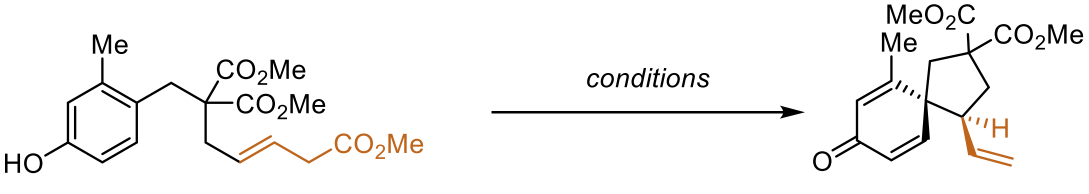
(Alkylation, Alkenylation, Arylation: C–C Bonds)

S. L. You; et al. *Chem. Soc. Rev.* **2016**, *45*, 1570–1580.

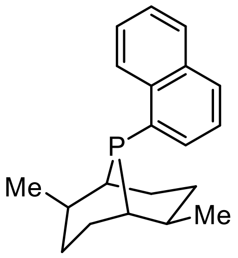
2.1 Asymmetric Dearomatization of Phenols for the Construction of C–C Bonds

2.1.1 Construction of C–C Bonds via Dearomative Asymmetric Allylic Alkylation Reaction

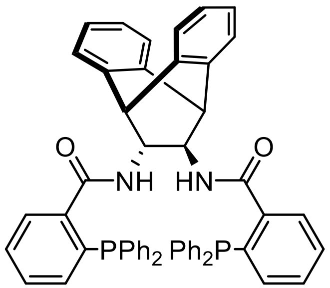
2010, 2012, Hamada



1-1 → 1-4



1-2



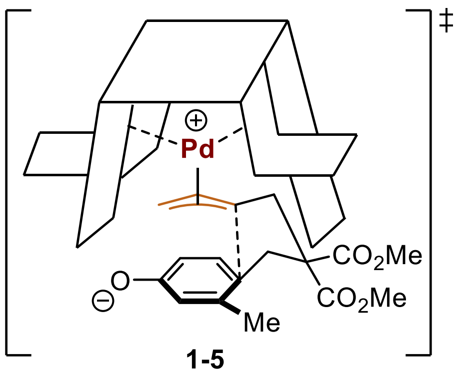
1-3

conditions 1

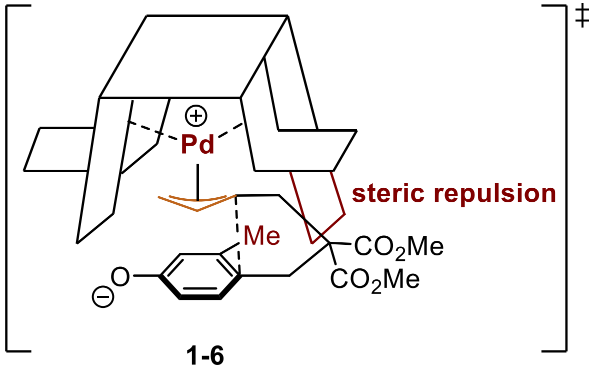
$[AllylPdCl]_2$ (5 mol%)
1-2
NaOAc (1.0 equiv.)
THF (degassed), rt
1-4: 37%, 2.9:1 dr, 93% *ee*

conditions 2

$Pd(dba)_2$ (5 mol%)
1-3
Li_2CO_3 (1.0 equiv.)
MeCN (degassed), 10 °C
1-4: 80%, 9.2:1 dr, 89% *ee*



1-5
favored

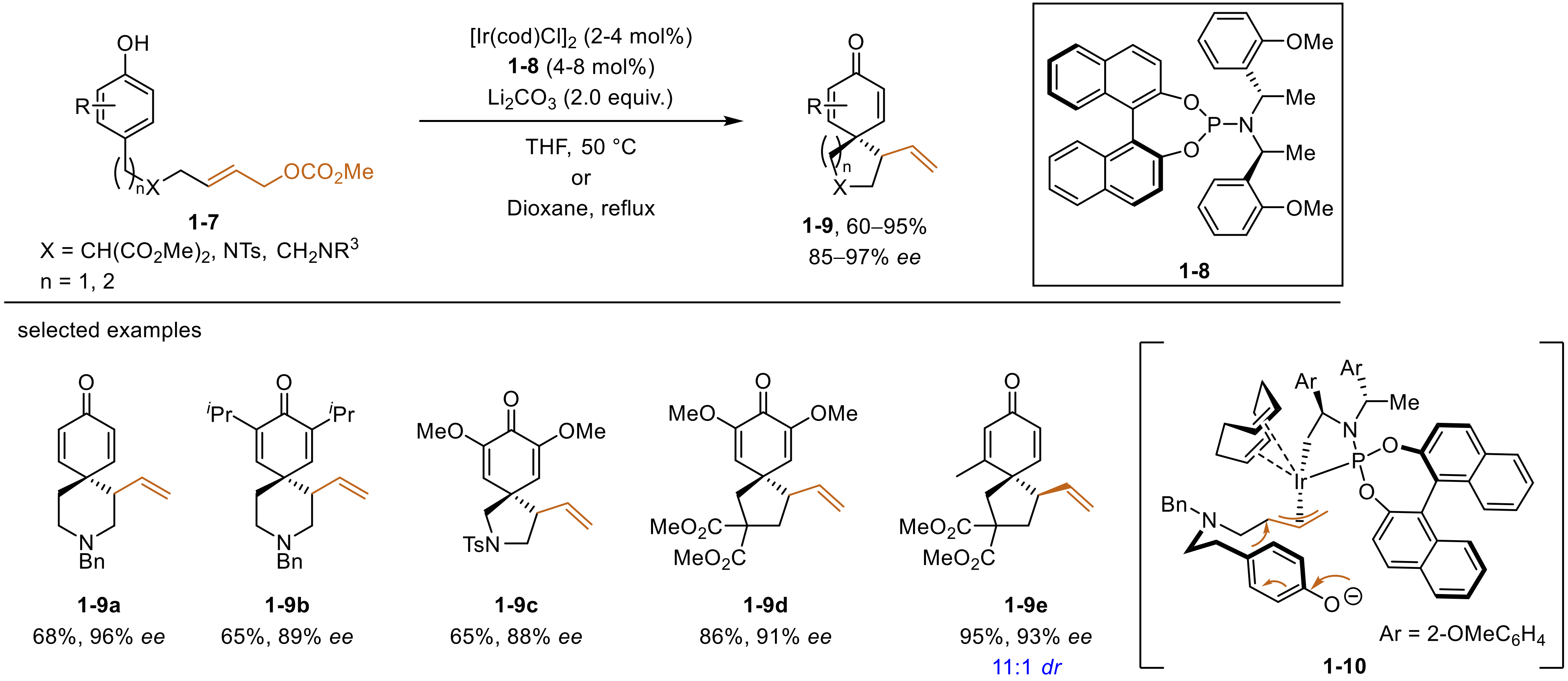


1-6
disfavored

Y. Hamada; et al. *Org. Lett.* **2010**, *12*, 5020−5023. Y. Hamada; et al. *Tetrahedron Asymmetry*, **2012**, *23*, 859−866.

2.1.1 Construction of C–C Bonds via Dearomative Asymmetric Allylic Alkylation Reaction

2011, Shu-Li You

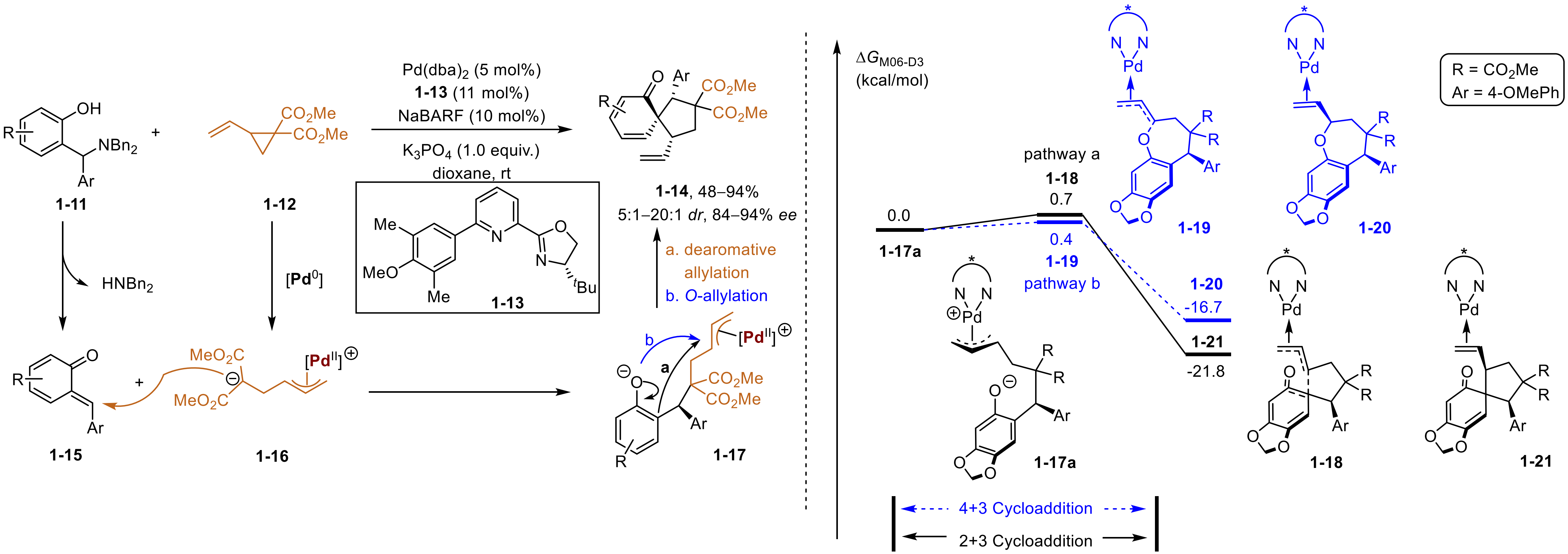


S. L. You; et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455−4458.

2.1 Asymmetric Dearomatization of Phenols for the Construction of C–C Bonds

2.1.1 Construction of C–C Bonds via Dearomative Asymmetric Allylic Alkylation Reaction

2022, Quan-Zhong Liu

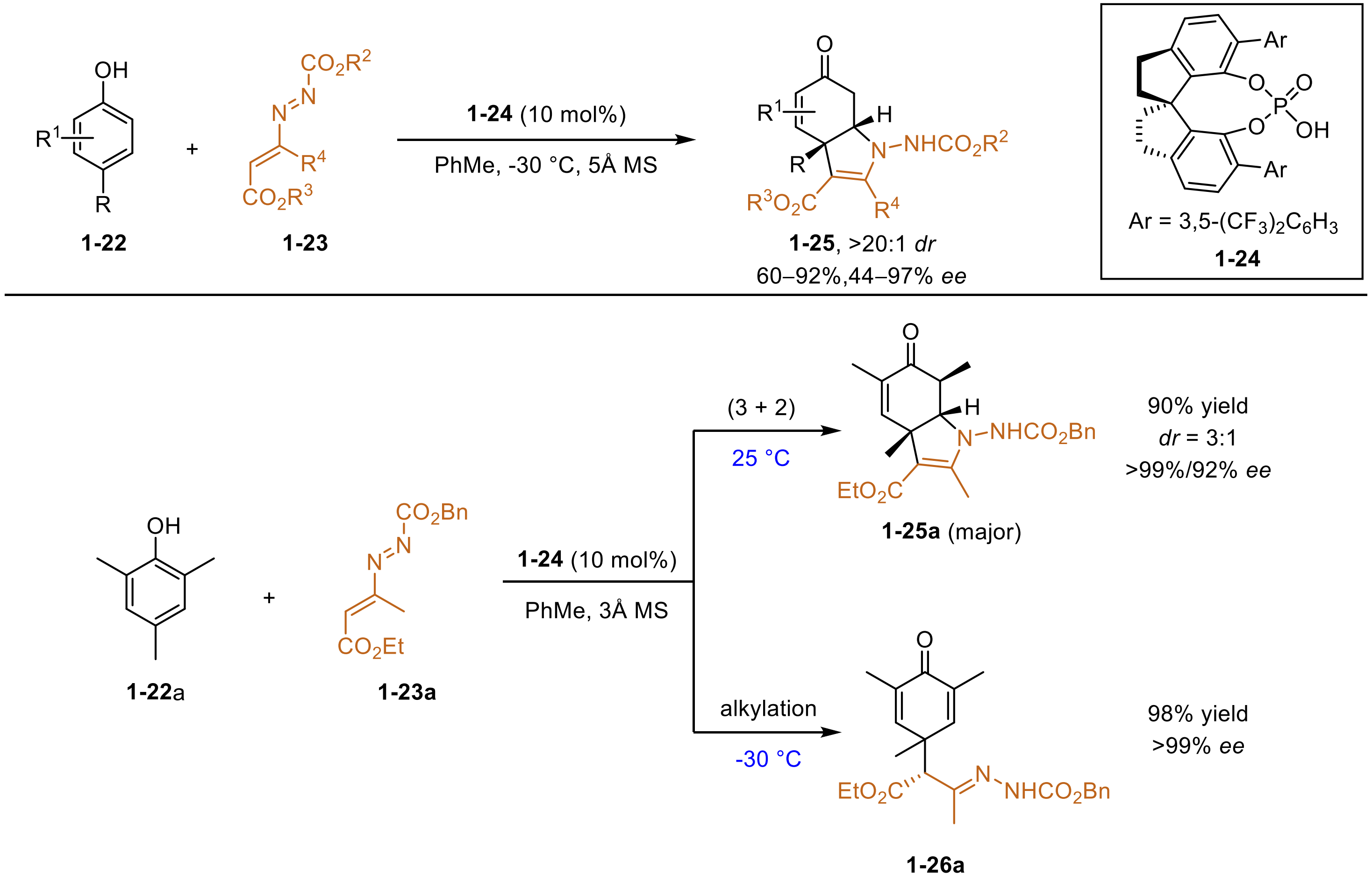


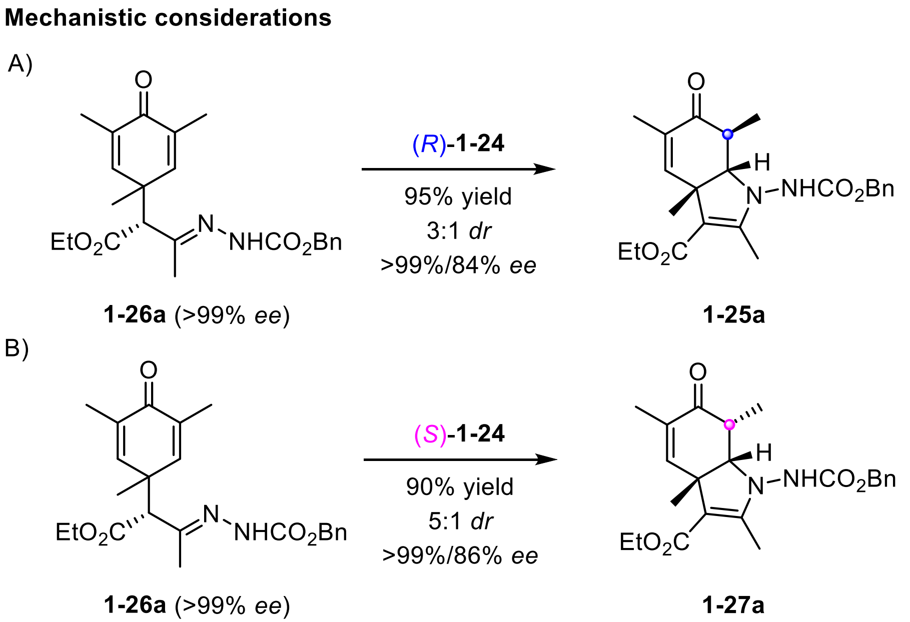
Q. Z. Liu; et al. *Org. Lett.* **2022**, *24*, 4865−4870.

2.1 Asymmetric Dearomatization of Phenols for the Construction of C–C Bonds

2.1.2 Construction of C–C Bonds via Dearomative Asymmetric Alkenylation Reaction

2023, Guang-Jian Mei

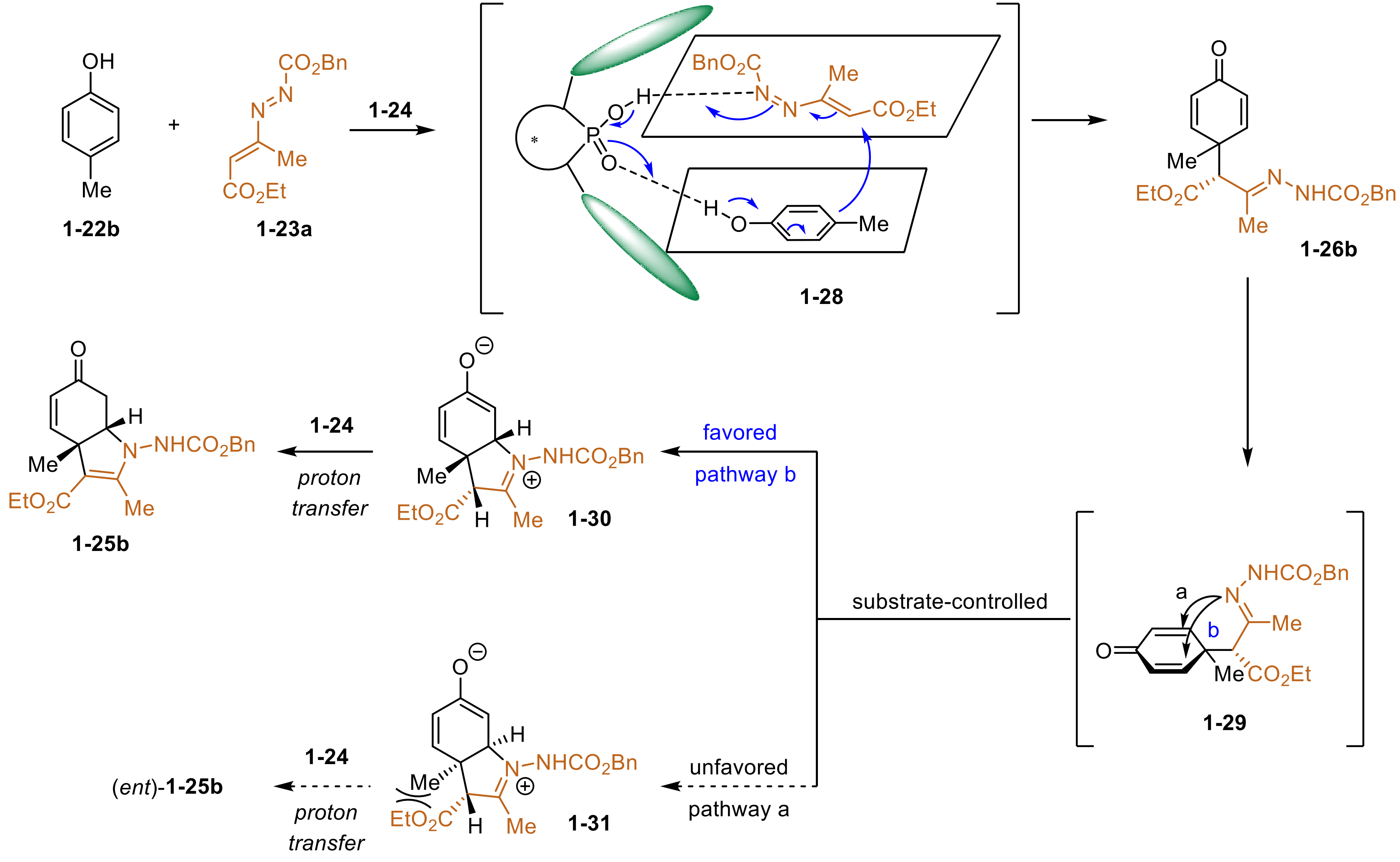




G. J. Mei; et al. *Nat. Commun.* **2023**, *14*, 5189.

2.1.2 Construction of C–C Bonds via Dearomative Asymmetric Alkenylation Reaction

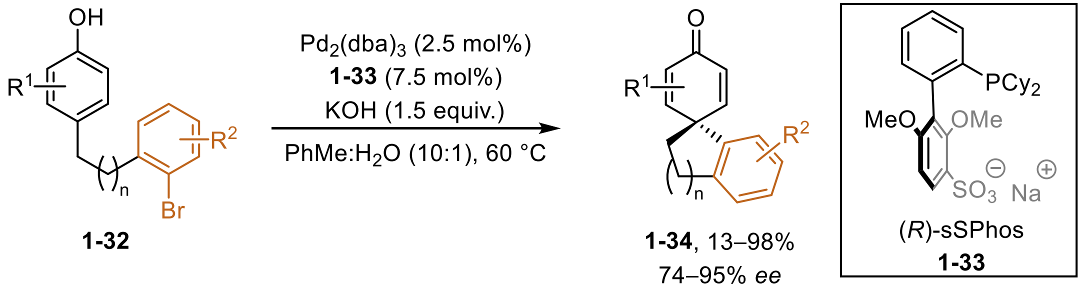
2023, Guang-Jian Mei



G. J. Mei; et al. *Nat. Commun.* **2023**, *14*, 5189.

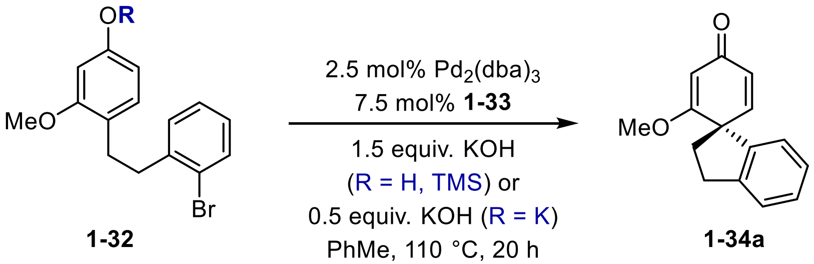
2.1.3 Construction of C–C Bonds via Dearomative Asymmetric Arylation Reaction

2023, Phipps



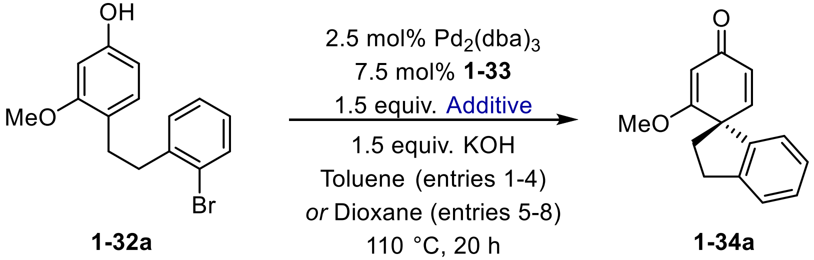
Mechanistic considerations

A) Conditions with no proton source (to exclude hydrogen bonding):



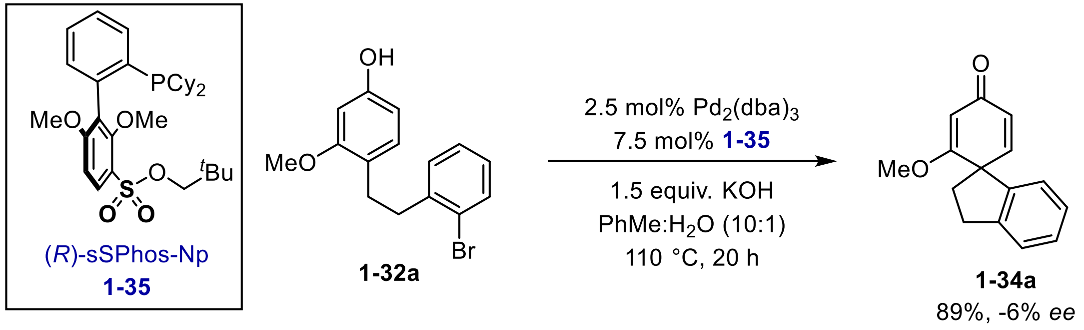
R	Yield	% *ee*
H	60	83
TMS	46	83
K	53	92

B) Crown Ether Experiments (no water co-solvent):

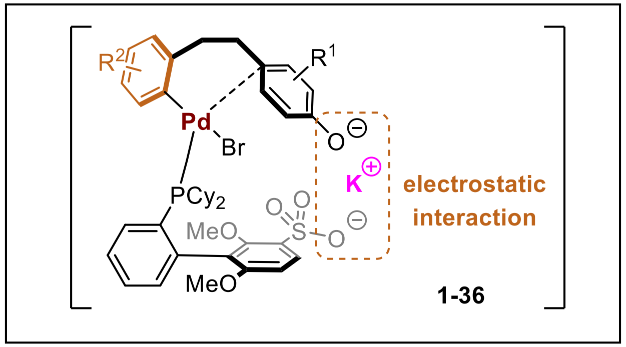


Entry	Additive	% *ee*
1	None	83
2	12-Crown-4	81
3	15-Crown-5	61
4	18-Crown-6	70
5	None	84
6	12-Crown-4	84
7	15-Crown-5	63
8	18-Crown-6	63

C) Use of neutral, alkylated ligand:



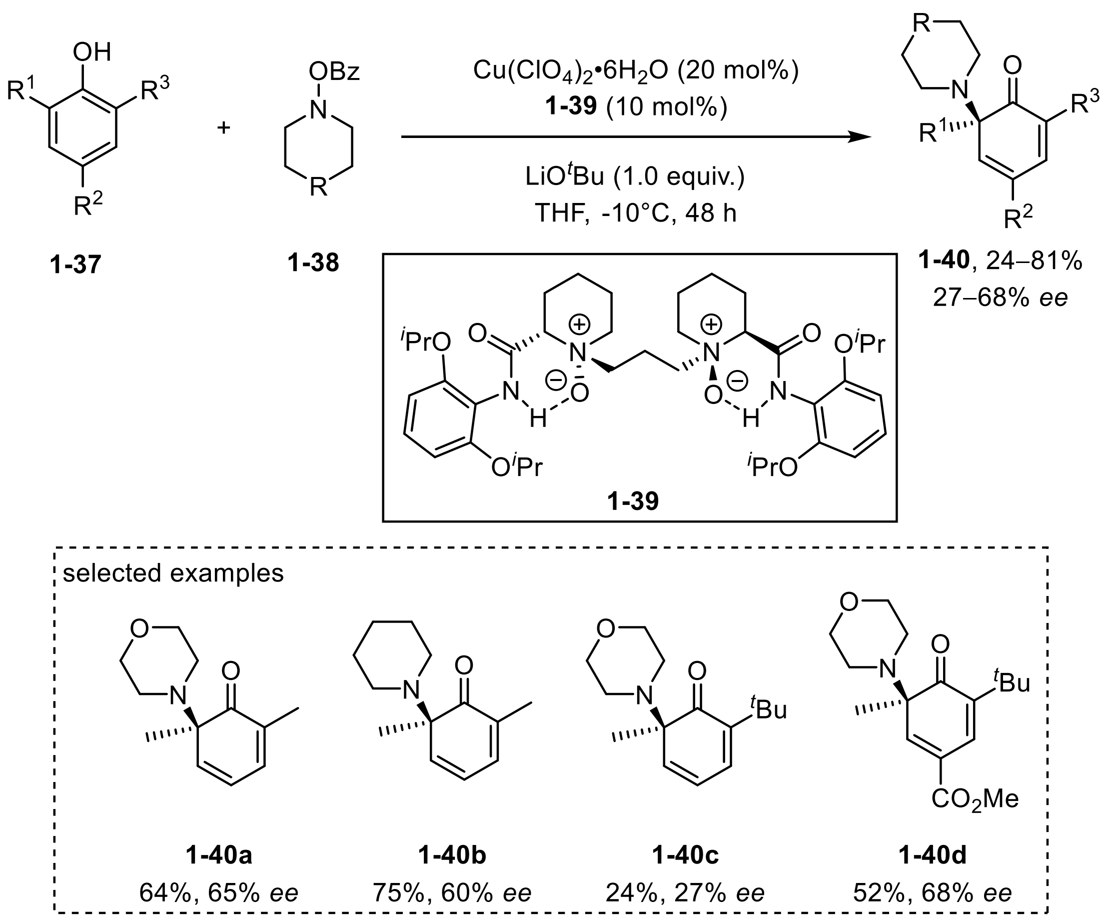
D) Working model

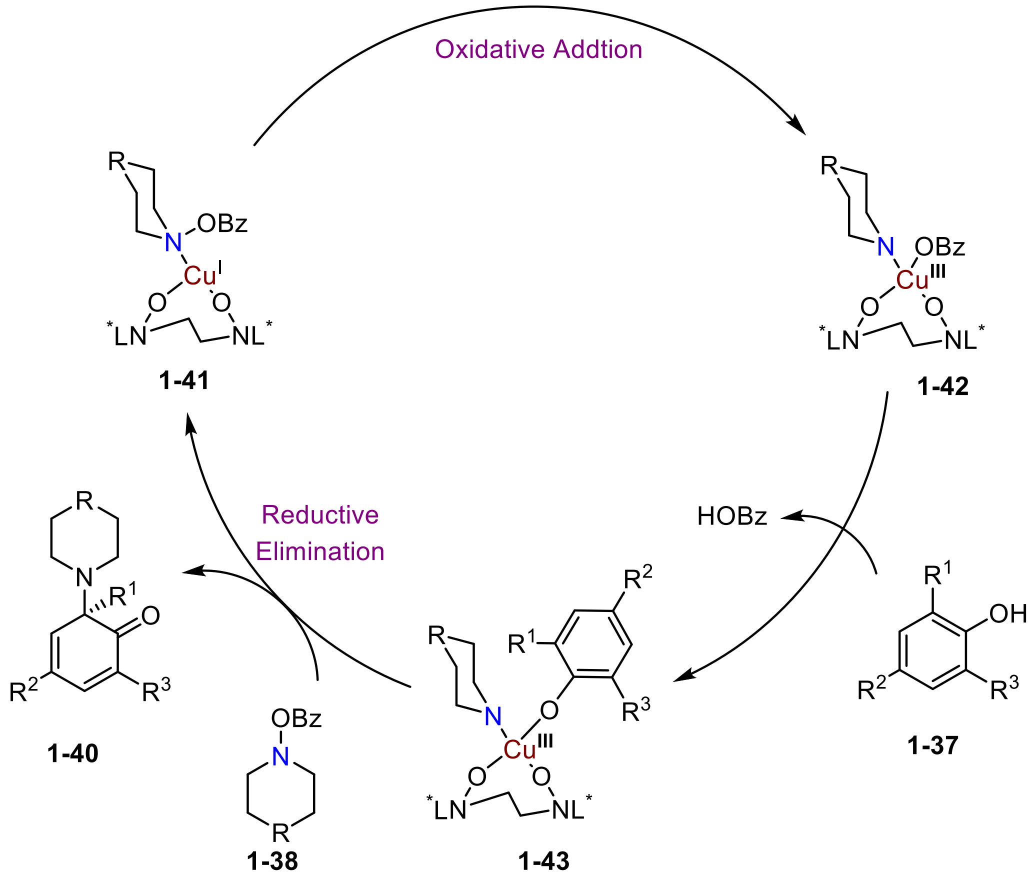


R. J. Phipps; et al. *J. Am. Chem. Soc.* **2023**, *145*, 25553−25558.

2.2 Asymmetric Dearomatization Amination of Phenols

2024, Xiao-Ming Feng



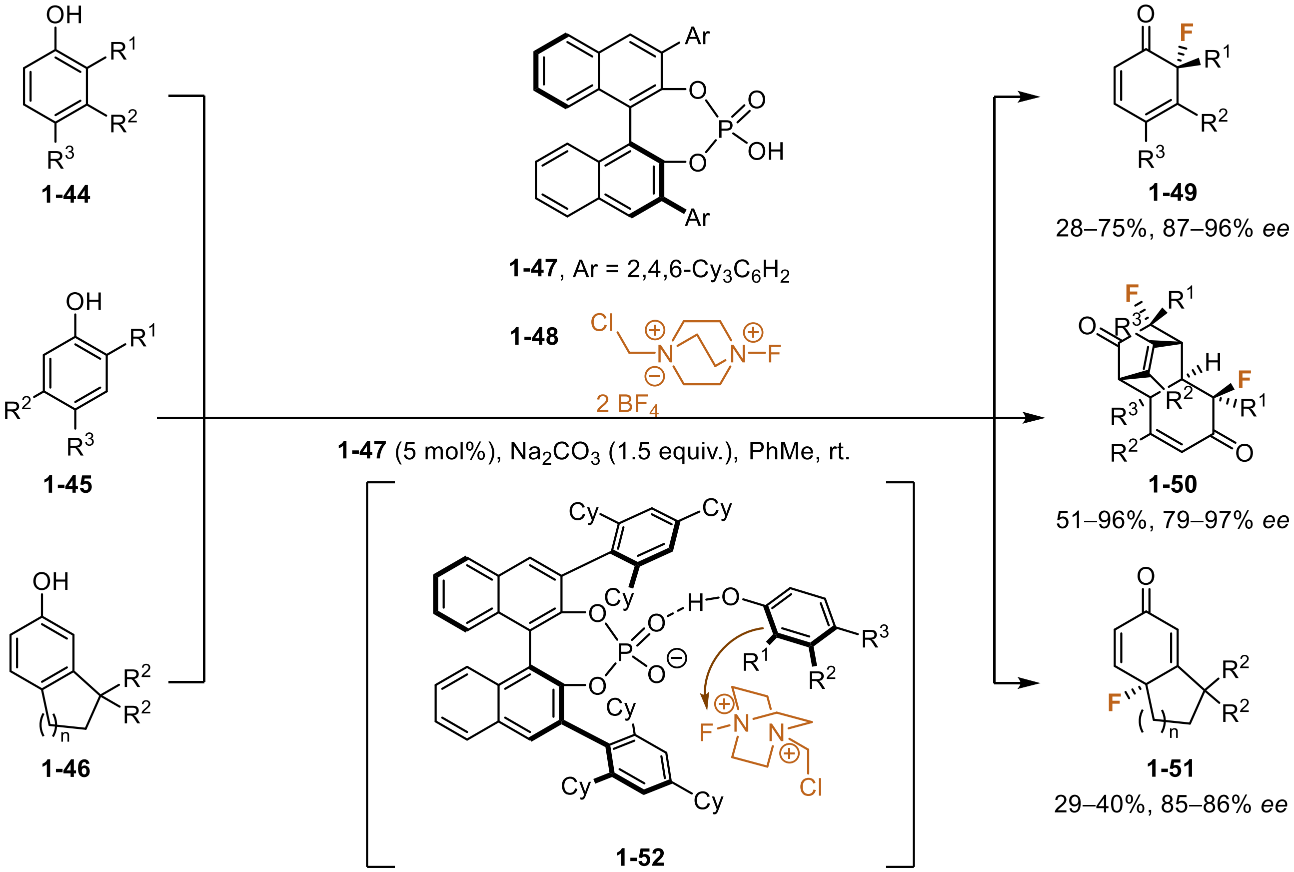


X. M. Feng; et al. *Sci. China Chem.* **2024**, *67*, 2694–2700.

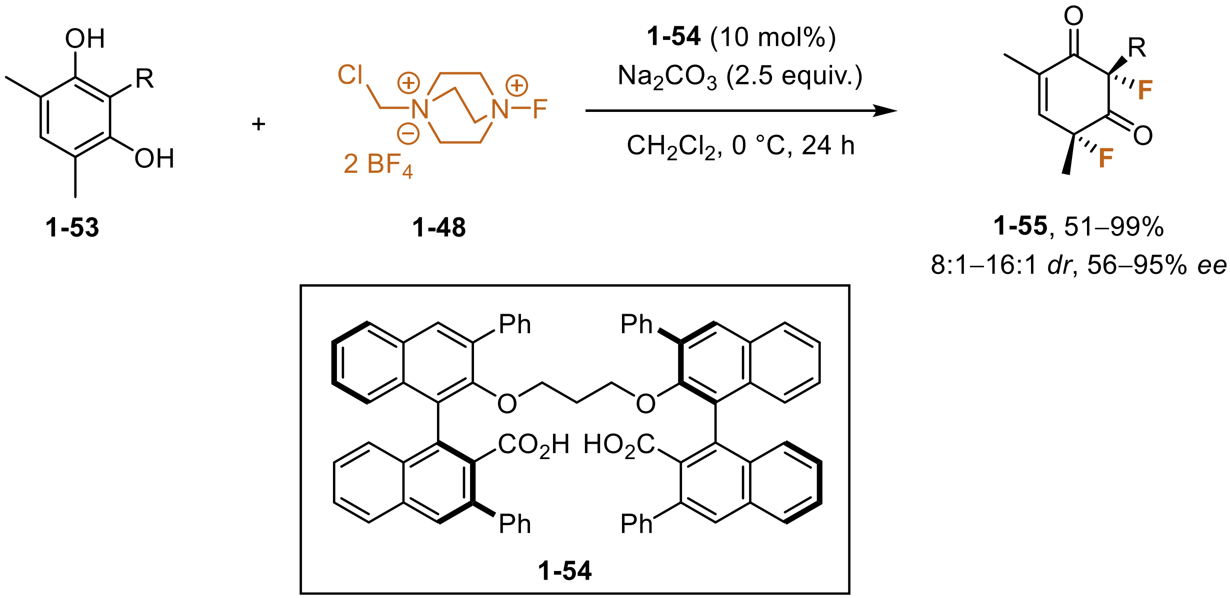
2.3 Asymmetric Dearomatization Fluorination of Phenols

Incorporation of fluorine atoms into organic and pharmaceutical molecules enhances cellular uptake and metabolic stability.

2013, Toste



2021, Hamashima



F. D. Toste; et al. *J. Am. Chem. Soc.* **2013**, *135*, 1268−1271. Y. Hamashima; et al. *Tetrahedron* **2021**, *96*, 132355.

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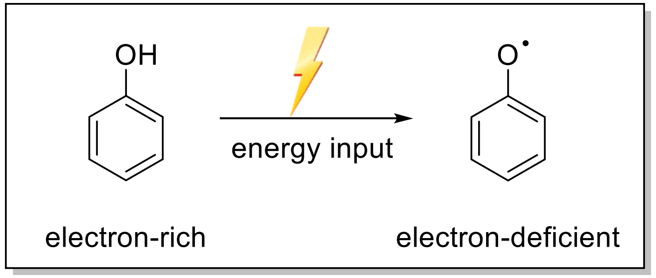
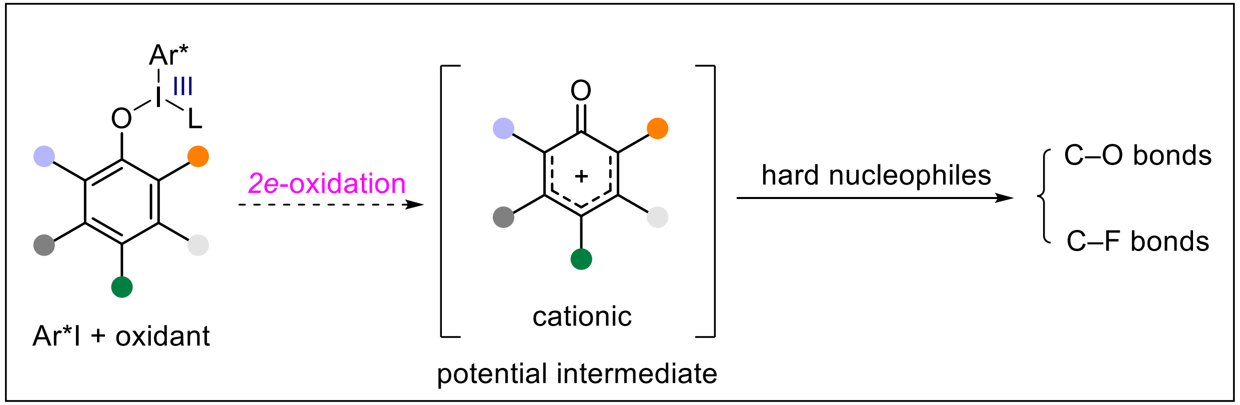
3. Asymmetric Dearomatization of Phenols as Electrophiles

1.Asymmetric oxidative dearomatization of phenols

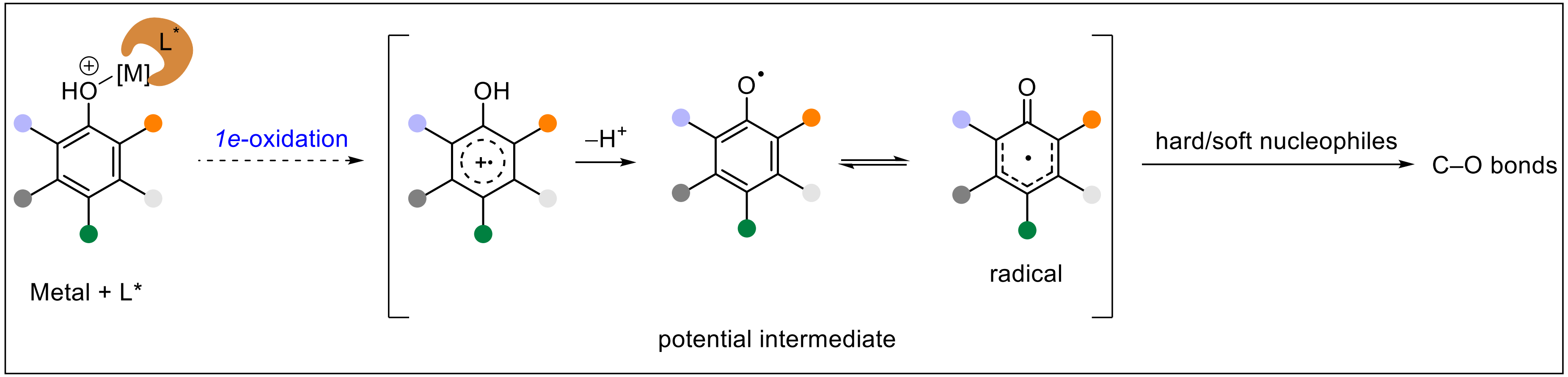


Oxidative Model

Double Electrons Transfer Oxidation Reactions



Single Electron Transfer Oxidation Reactions



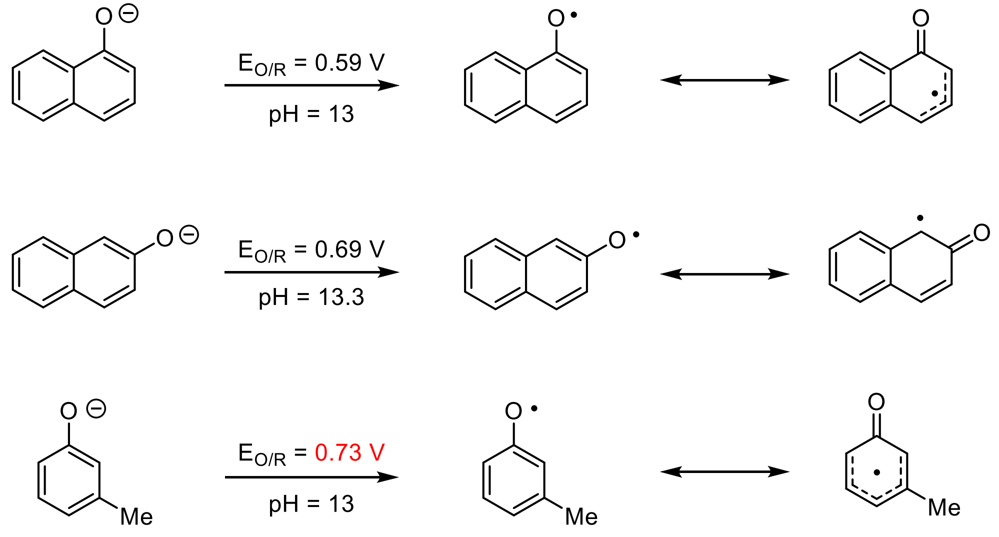
P. Neta; et al. *J. Phys. Chem. A.* **1998**, *102*, 7081–7085.

3. Asymmetric Dearomatization of Phenols as Electrophiles

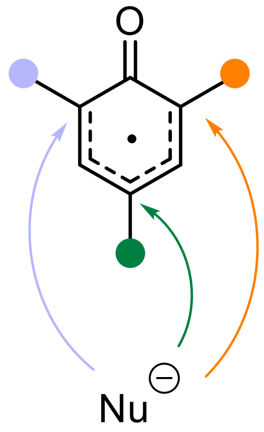
2.Main challenges

- Breaking aromaticity

Oxidation potentials of Naphthoxyl, and 3-Methylphenoxyl anions in aqueous solutions. ($E_{O/R}$ versus NHE)



- Selectivity Control
  - chemoselectivity
  - regioselectivity
  - enantioselectivity

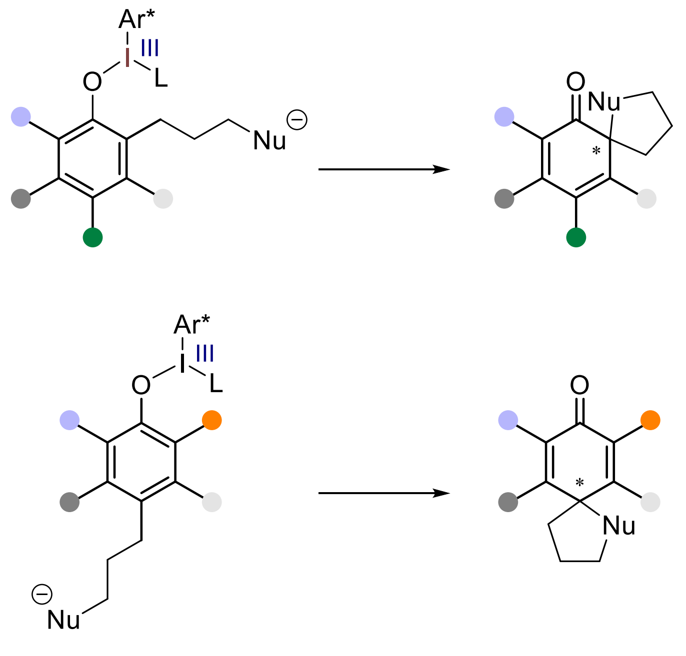


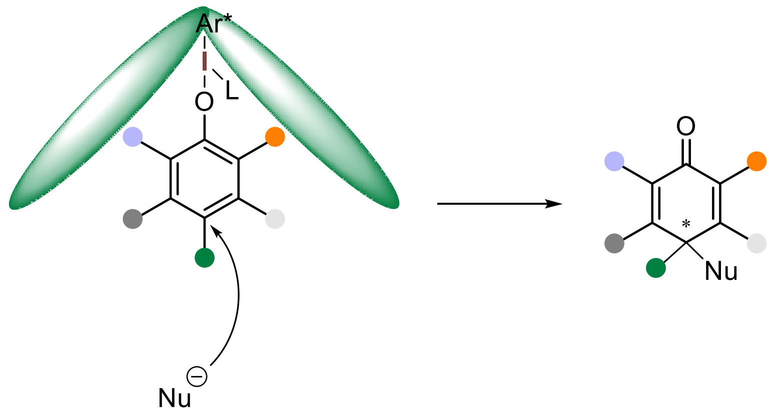
P. Neta; et al. *J. Phys. Chem. A.* **1998**, *102*, 7081–7085.

3. Significant progress

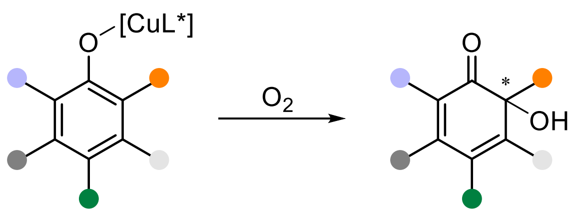
1. Double electrons transfer oxidation reactions

- intramolecular reaction
- intermolecular reaction





2. Single electron transfer oxidation reactions

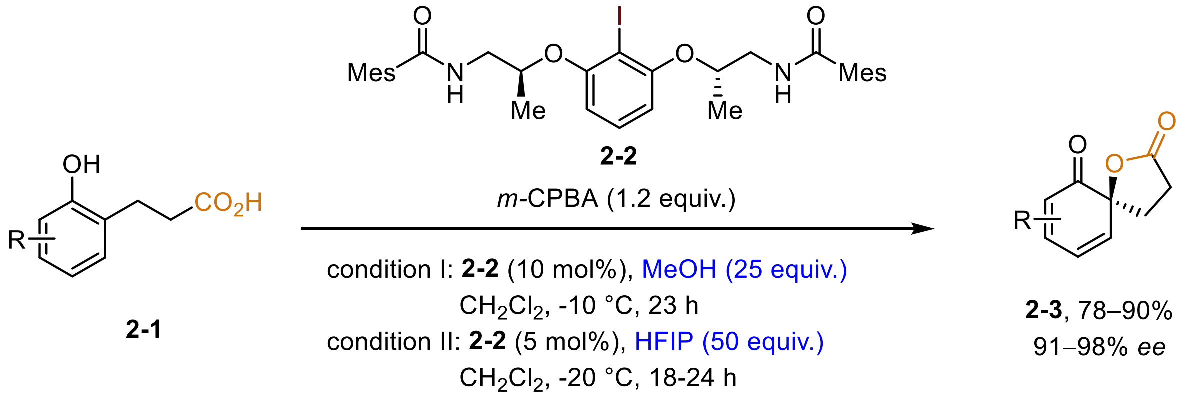


P. Neta; et al. *J. Phys. Chem. A.* **1998**, *102*, 7081–7085.

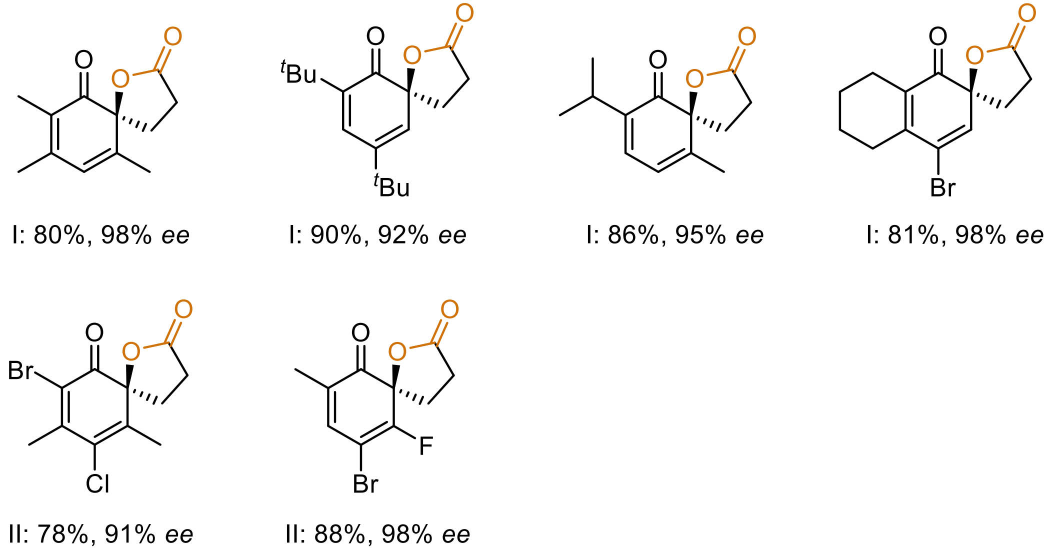
3.1 Double Electrons Transfer Oxidation Reactions

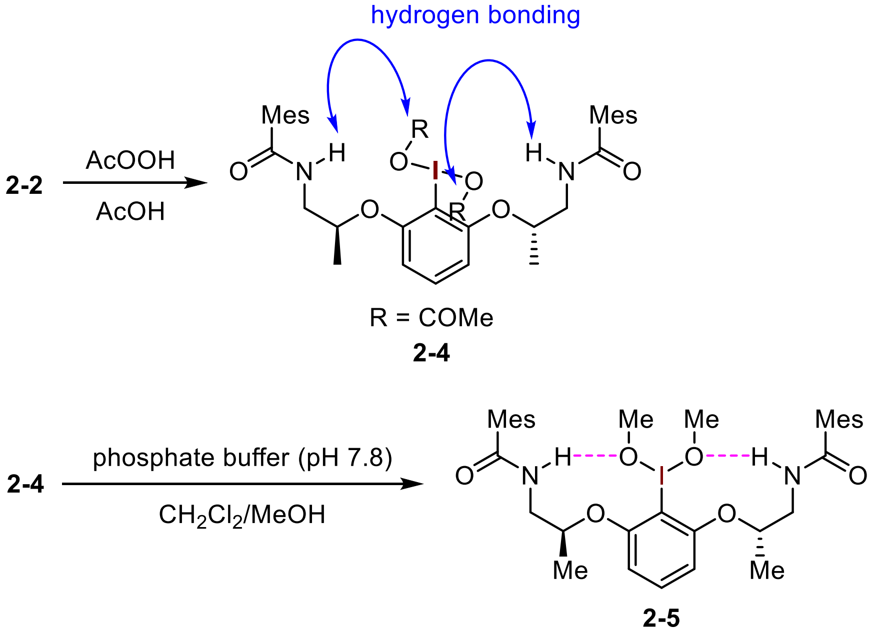
3.1.1 Construction of C–O bonds via intramolecular reactions

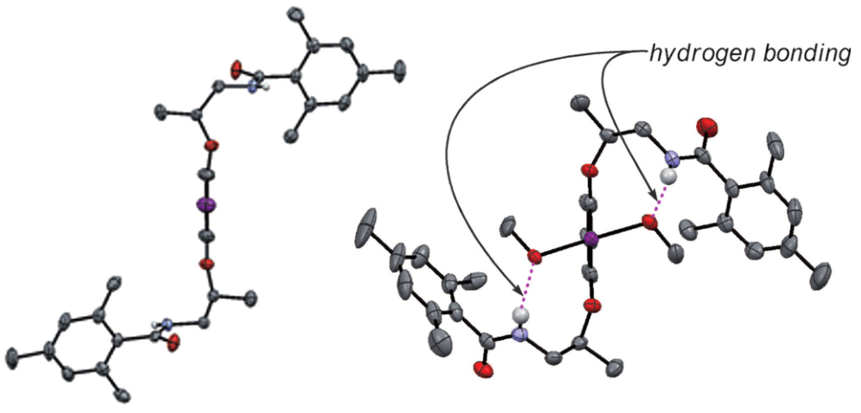
2013, Ishihara



selected examples







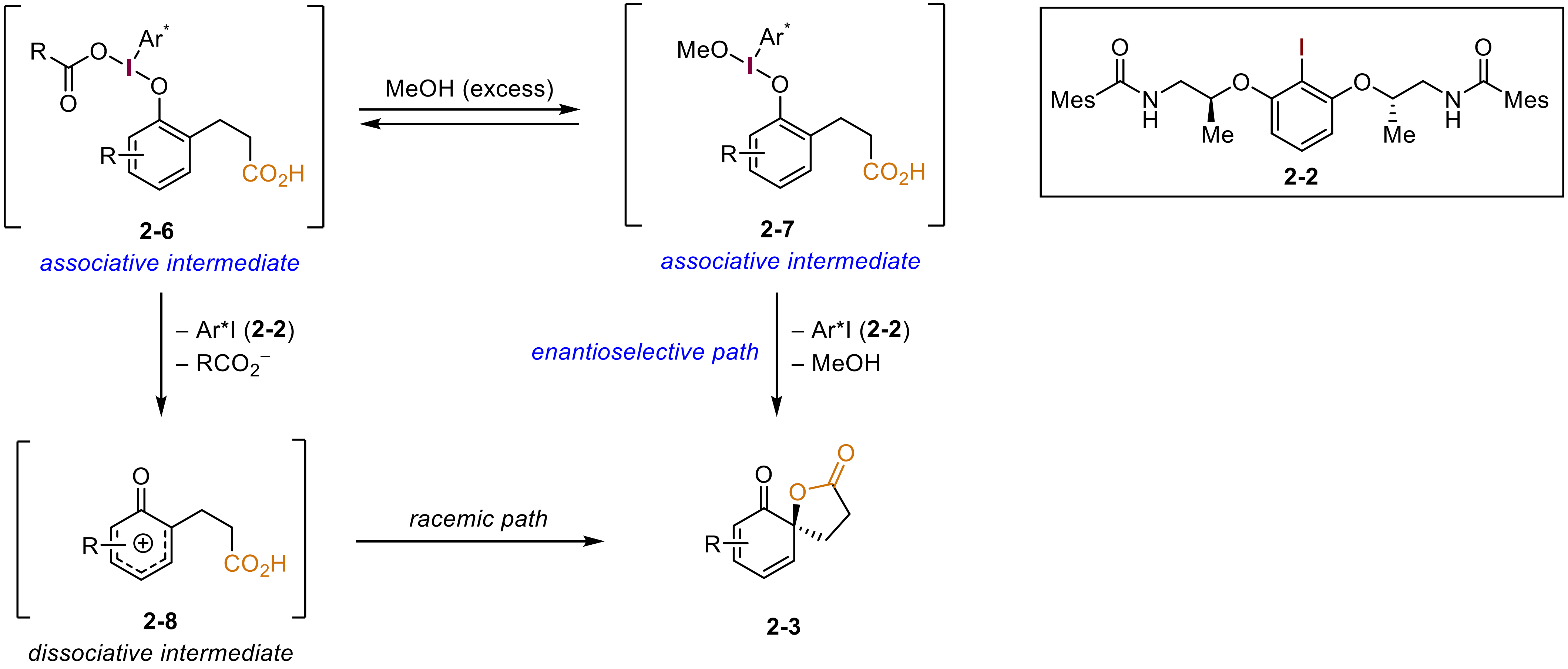
2-2 2-5

K. Ishihara; et al. *Angew. Chem., Int. Ed.* **2013**, *52*, 9215−9218.

3.1 Double Electrons Transfer Oxidation Reactions

3.1.1 Construction of C–O bonds via intramolecular reactions

2013, Ishihara

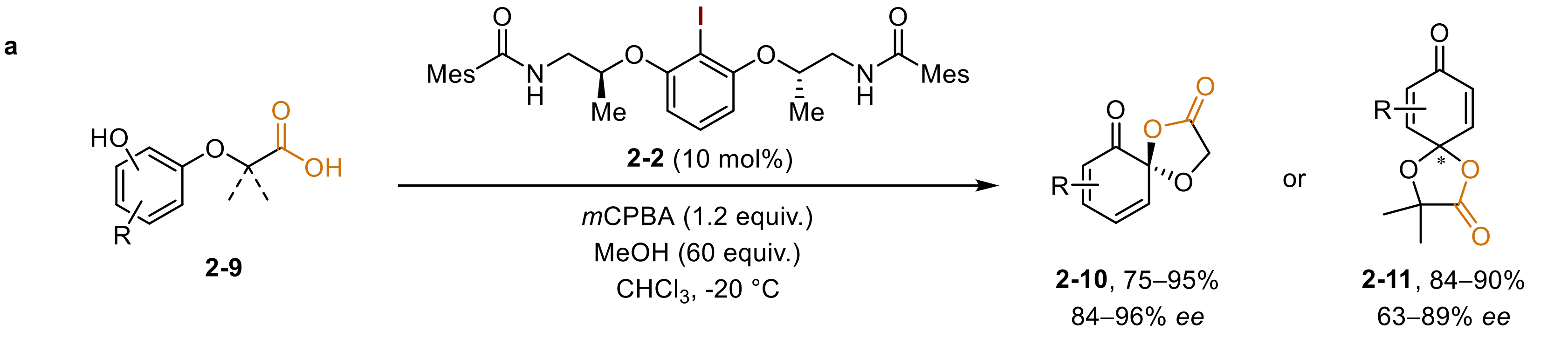


K. Ishihara; et al. *Angew. Chem., Int. Ed.* **2013**, *52*, 9215–9218.

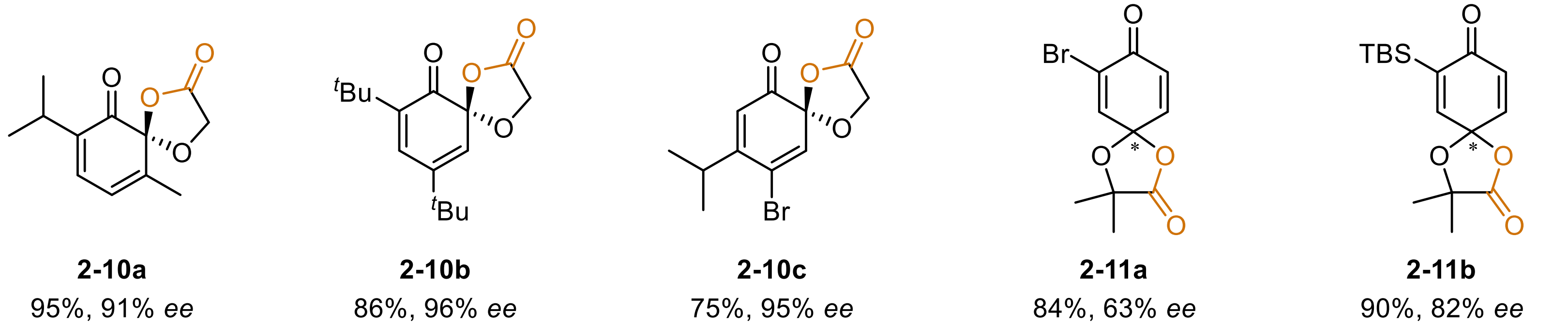
3.1.1 Construction of C–O bonds via intramolecular reactions

2017, Ishihara

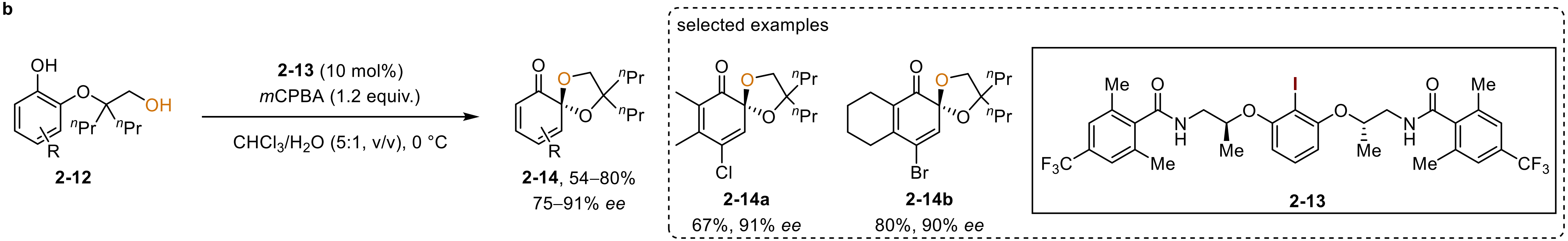
a



selected examples



b

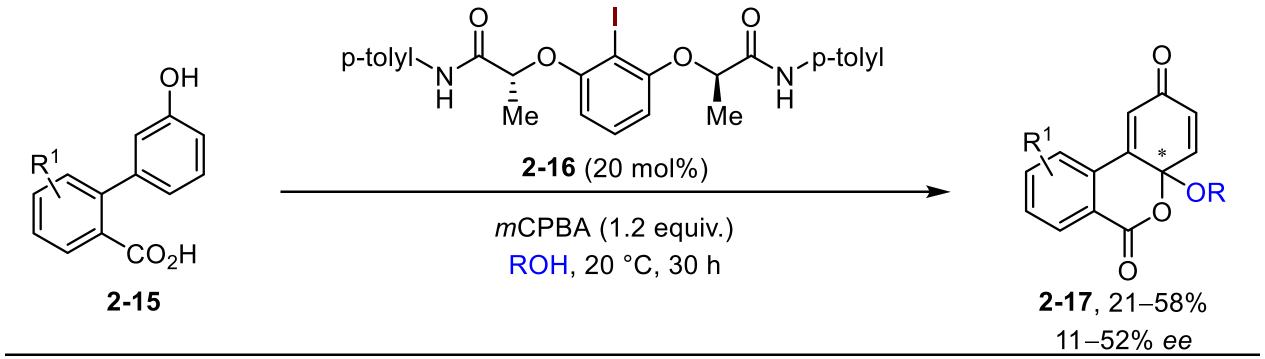


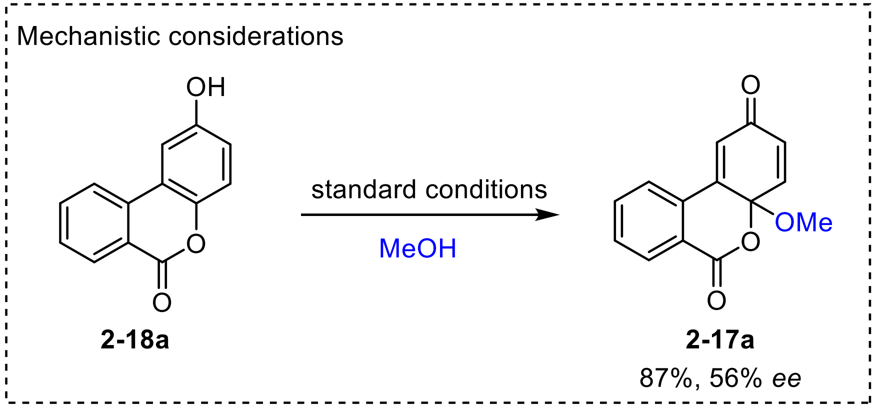
K. Ishihara; et al. *ACS Catal.* **2017**, *7*, 872−876.

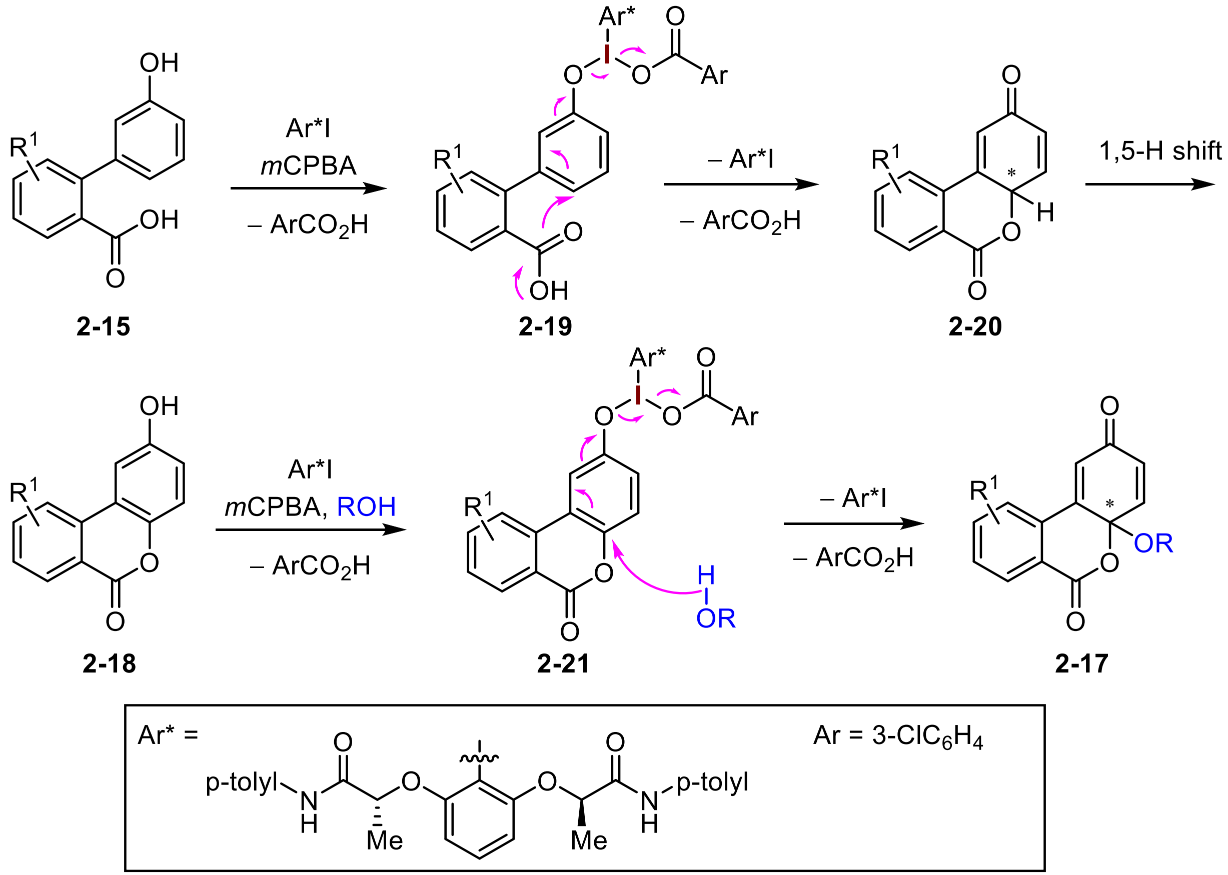
3.1 Double Electrons Transfer Oxidation Reactions

3.1.2 Construction of C–O bonds via intermolecular reactions

2020, Yan Xiong





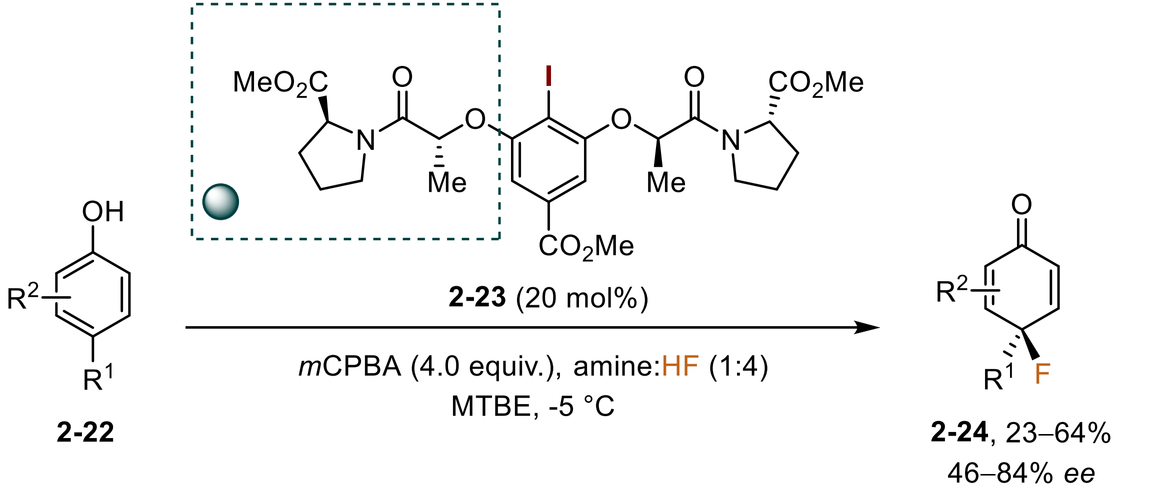


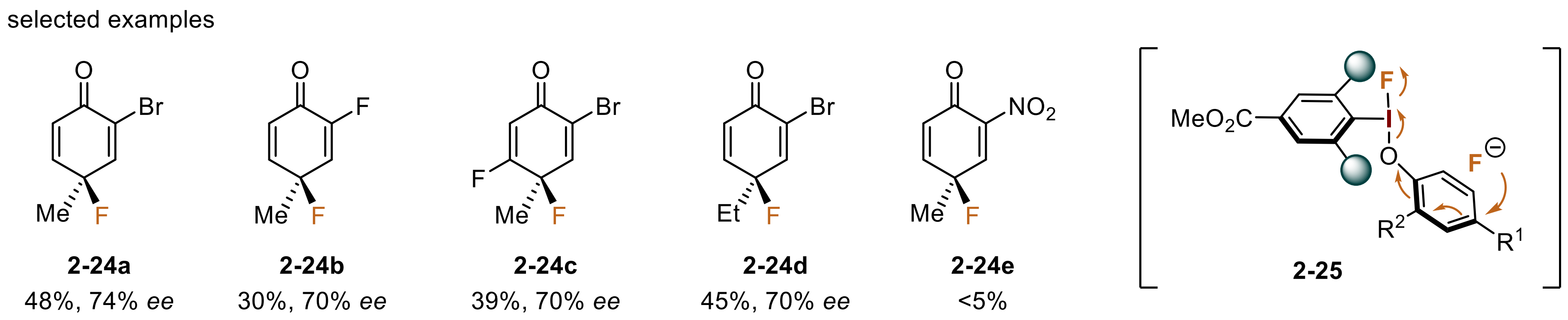
Y. Xiong; et al. *J. Org. Chem.* **2020**, *85*, 3125–3133.

3.1 Double Electrons Transfer Oxidation Reactions

3.1.3 Construction of C–F bonds

2023, Gilmour



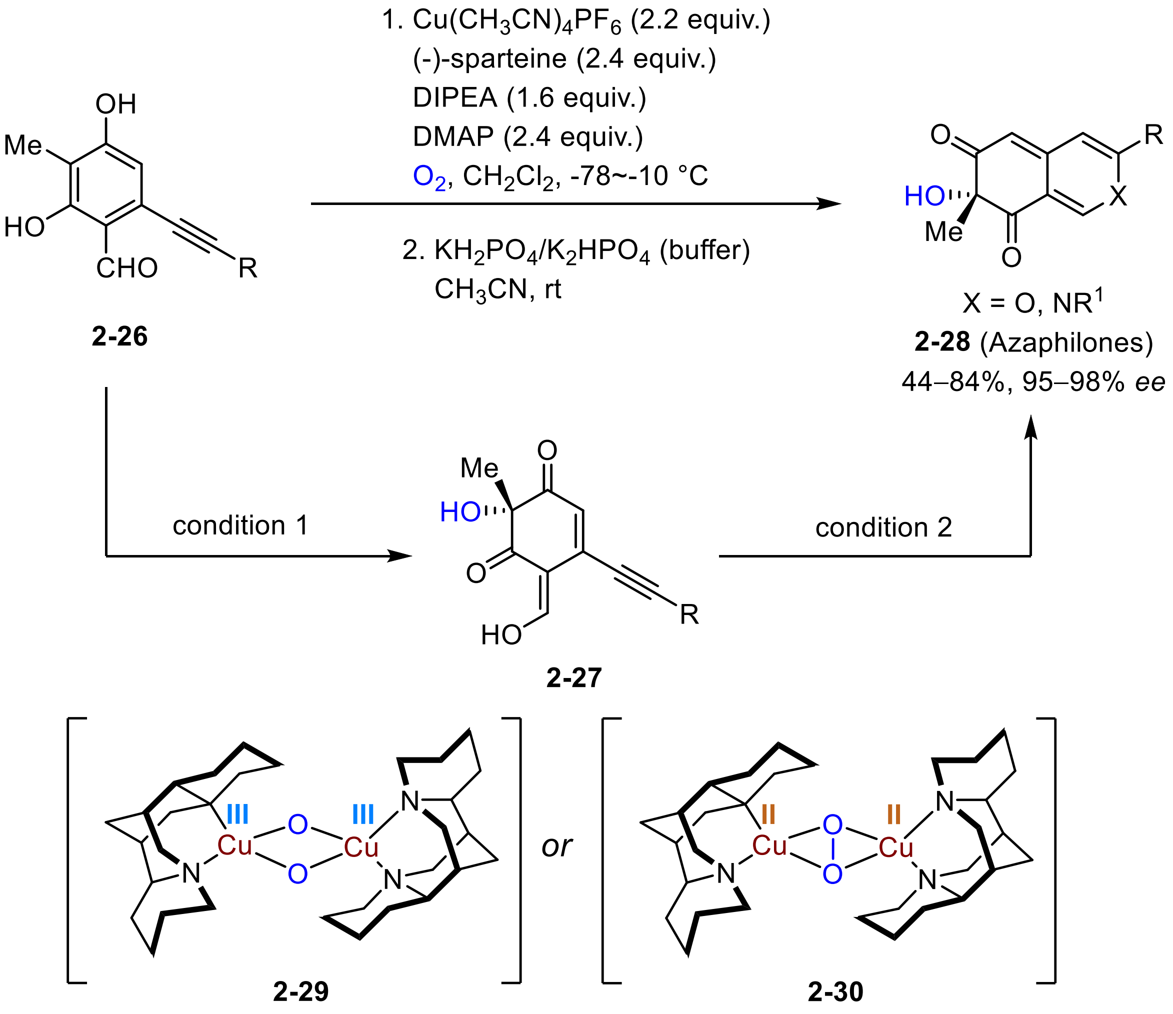


R. Gilmour; et al. *Chem. Sci.* **2023**, *14*, 13574−13580.

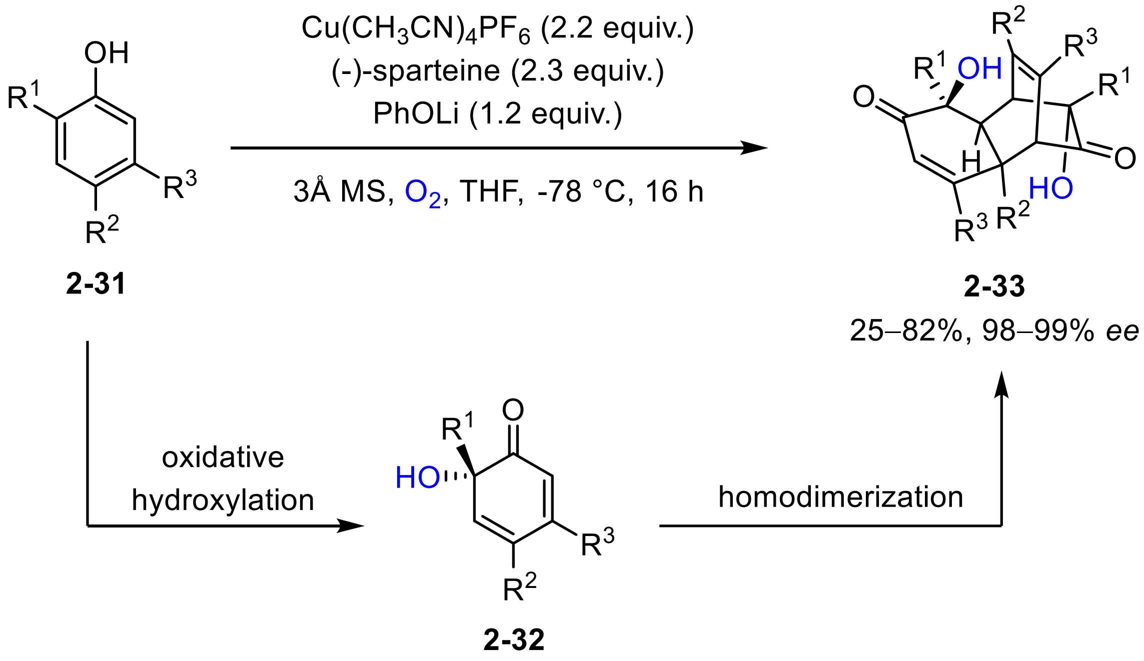
3.2 Single Electron Transfer Oxidation Reactions

Cu-Mediated Asymmetric Oxidative Dearomatization Reactions of Phenols

2005, Porco



2008, Porco



J. A. Porco; et al. *J. Am. Chem. Soc.* **2005**, *127*, 9342−9343.   J. A. Porco; et al. *J. Am. Chem. Soc.* **2008**, *130*, 2738−2739.

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1. Introduction

2. Asymmetric Dearomatization of Phenols as Nucleophiles

   2.1 Asymmetric Dearomatization of Phenols for the Construction of C-C Bonds

   2.2 Asymmetric Dearomatization Amination of Phenols

   2.3 Asymmetric Dearomatization Fluorination of Phenols

3. Asymmetric Dearomatization of Phenols as Electrophiles

   3.1 Double Electrons Transfer Oxidation Reactions

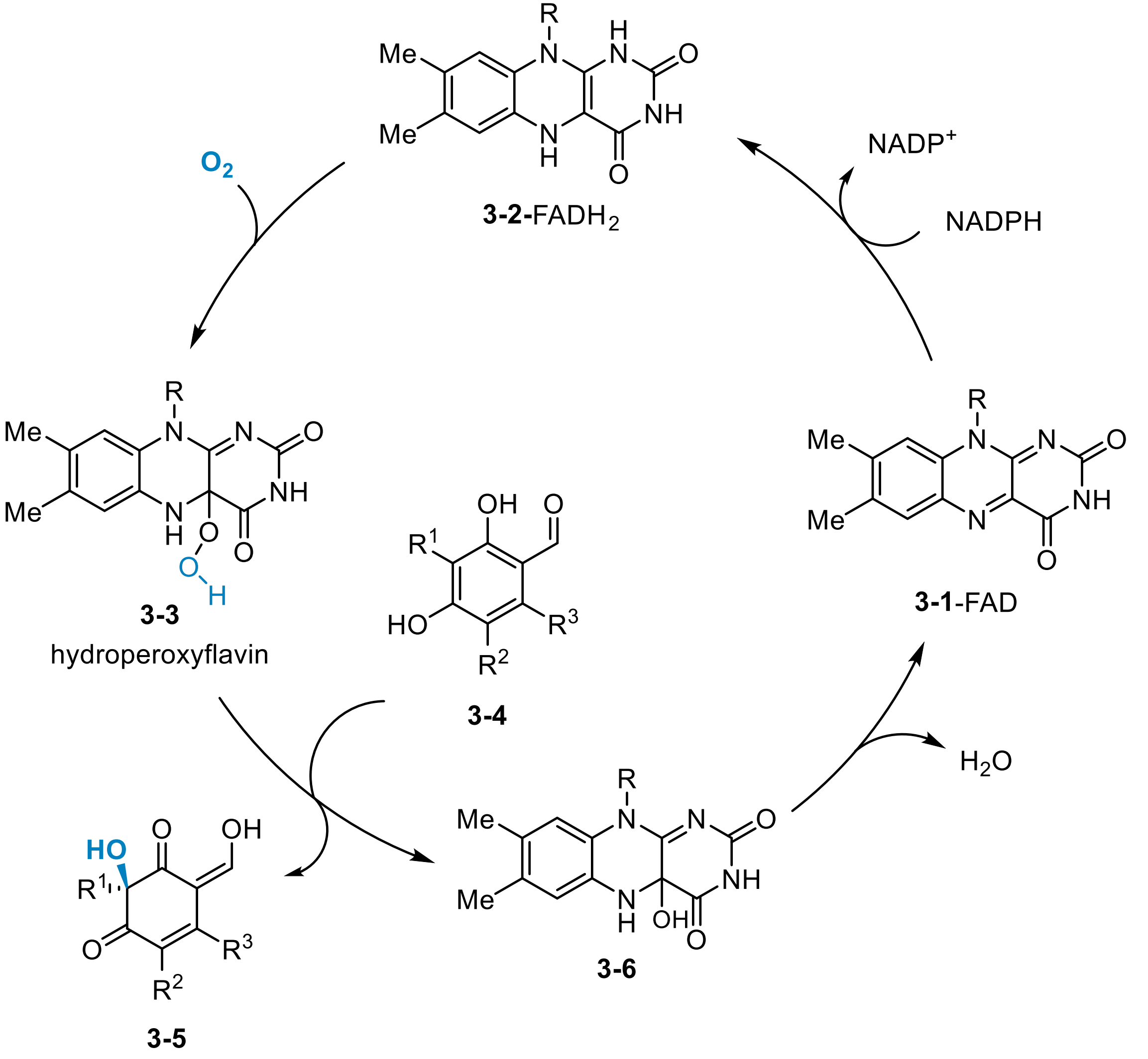
   3.2 Single Electron Transfer Oxidation Reactions

4. Asymmetric Dearomatization of Phenols via Enzyme Catalysis

5. Summary and Outlook

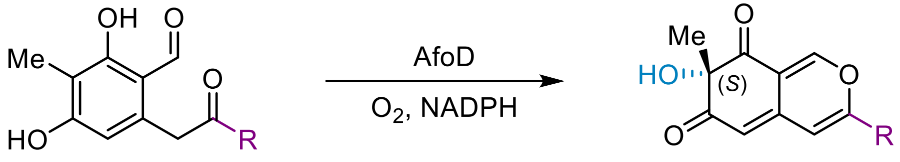
4. Asymmetric Dearomatization of Phenols via Enzyme Catalysis

Flavin-dependent monooxygenases (FDMOs) present an ideal platform for oxidative dearomatization reactions.



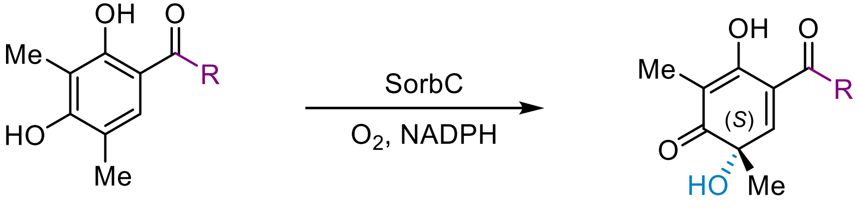
Catalytic mechanism of Flavin-dependent monooxygenases (FDMOs).

2009, Wang



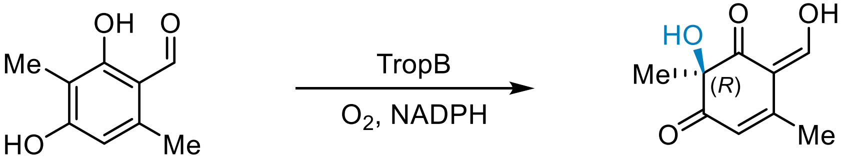
3-1A 3-7

2014, Cox



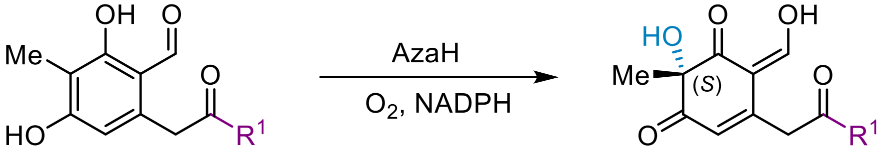
3-1B 3-8

2015, Cox



3-1C 3-9

2019, Narayan



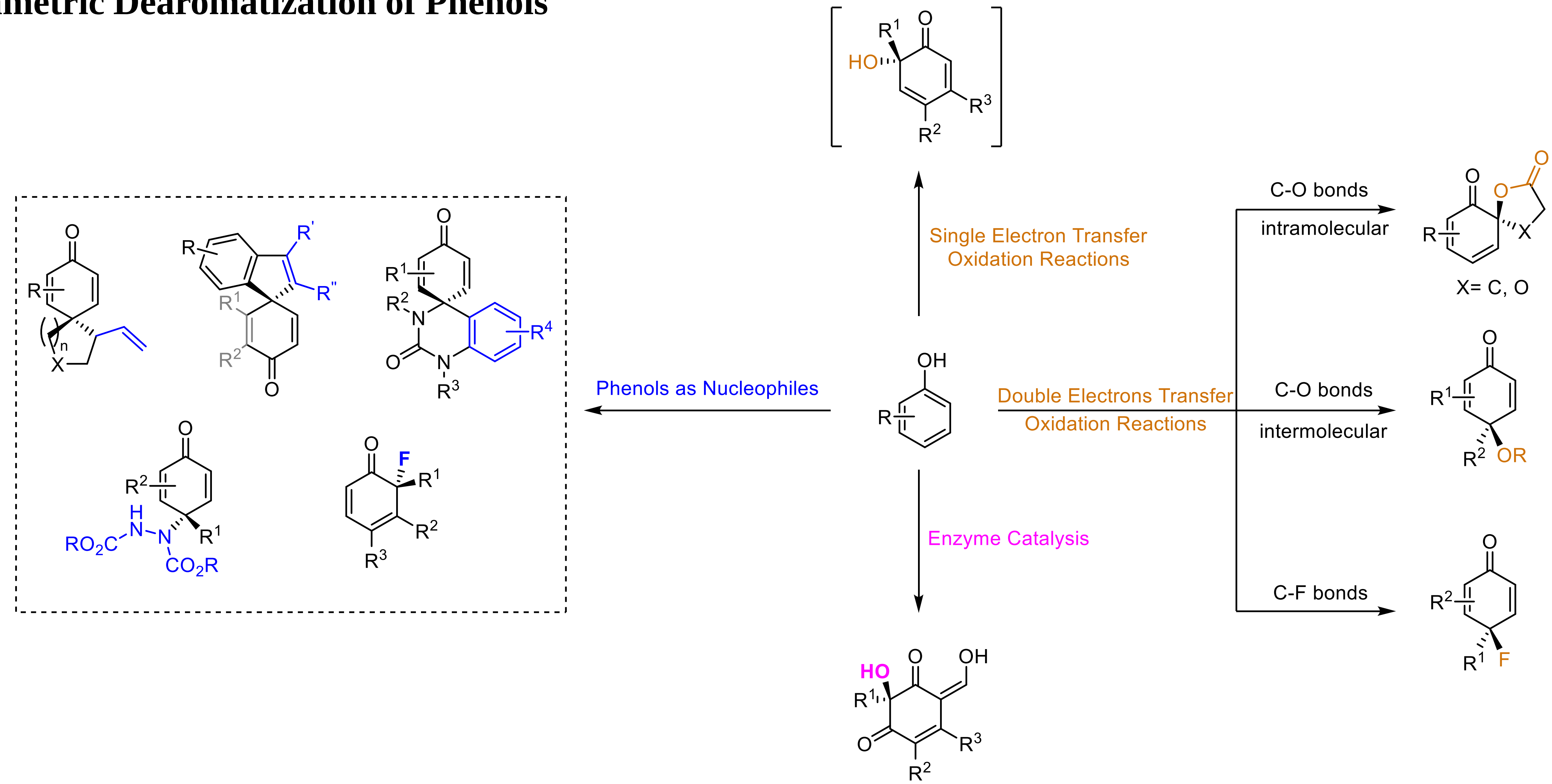
3-1D 3-10

Clay C. C. Wang; et al. *J. Am. Chem. Soc.* **2009**, *131*, 2965−2970. R. J. Cox; et al. *Chem. Sci.* **2014**, *5*, 523−527. R. J. Cox; et al. *RSC Adv.* **2015**, *5*, 49987−49995.
Alison R. H. Narayan; et al. *J. Am. Chem. Soc.* **2019**, *141*, 18551−18559. Alison R. H. Narayan; et al. *J. Am. Chem. Soc.* **2024**, *146*, 44, 30194–30203.

Content

Summary

Asymmetric Dearomatization of Phenols



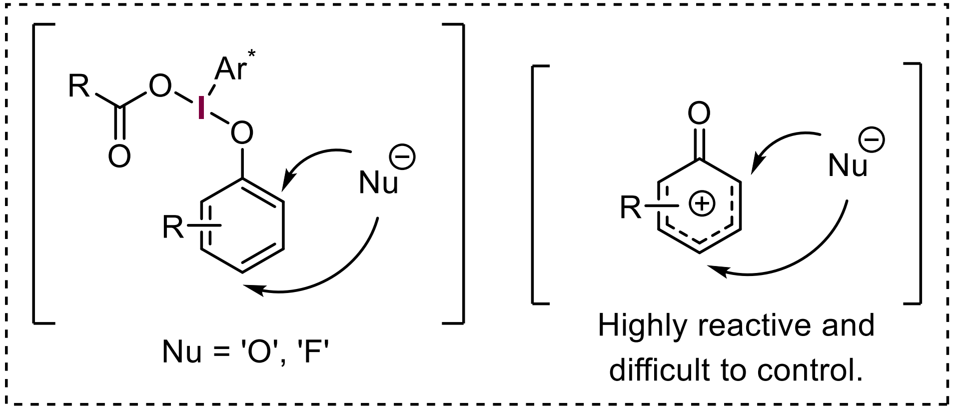
Outlook

There is still great potential for the development of intermolecular oxidative dearomatization of phenols.

1. Improving the enantioselectivity of the reaction and expanding the scope of nucleophiles.

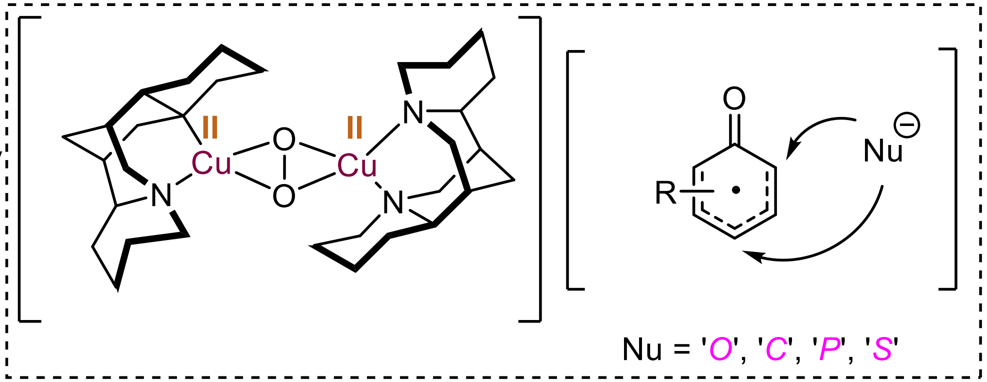
Key issue:

- moderate enantioselectivity
- narrow scope of nucleophiles



New strategy

- exceptional enantioselectivity
- broad scope of nucleophiles

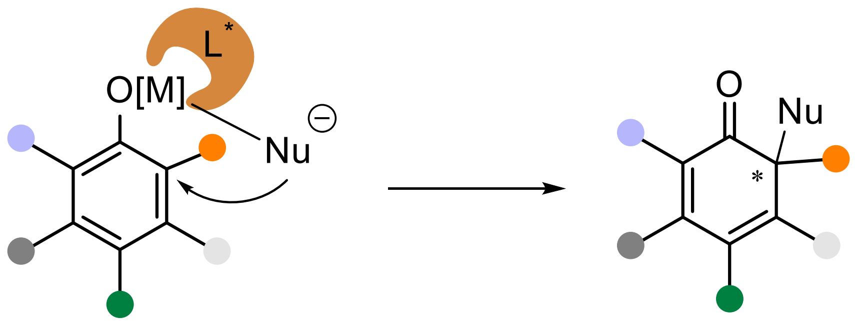


Lowering the reactivity enhances controllability

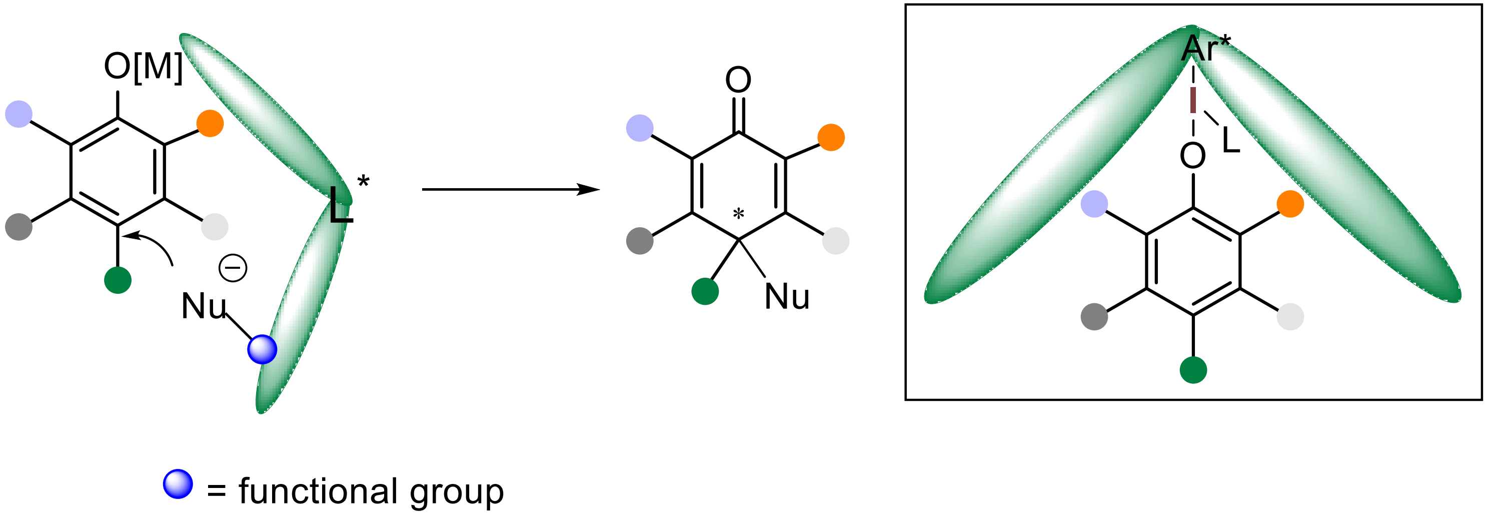
Outlook

2. Achieving complete control over the reaction site.

a. *Ortho*-directing effect via coordination interaction between nucleophiles and metals



b. *Para*-direction achieved by reversible condensation reaction between nucleophiles and ligands



Thank you ！