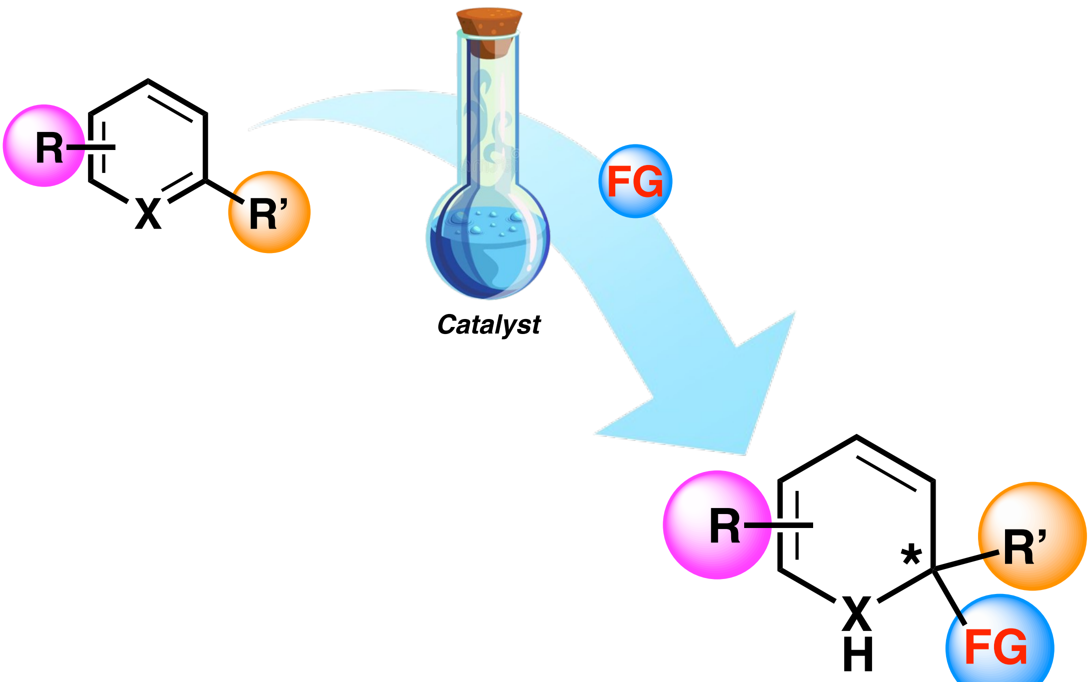
Dearomatization reactions and their applications



2023.12.23. (Sat.)

LIANG Yaohan (梁 耀涵)

Contents

1. Introduction

1-1. The discovery of benzene

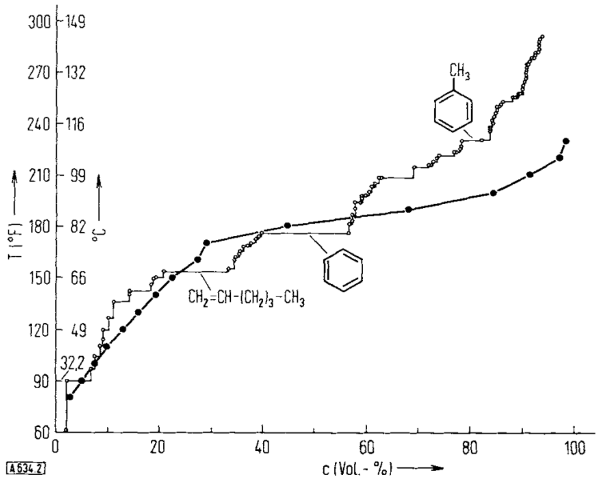
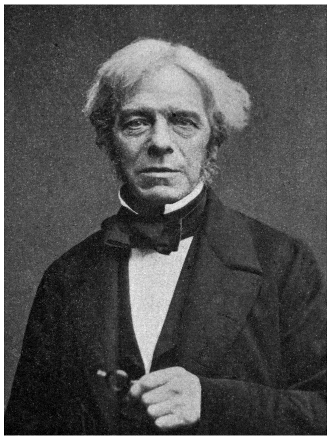


Fig. 2. Boiling curves from *Faraday*'s data (—•—•—) and from the gas-chromatographic analysis (—o—o—).

portable gas lamp



Michael Faraday (1791-1867)

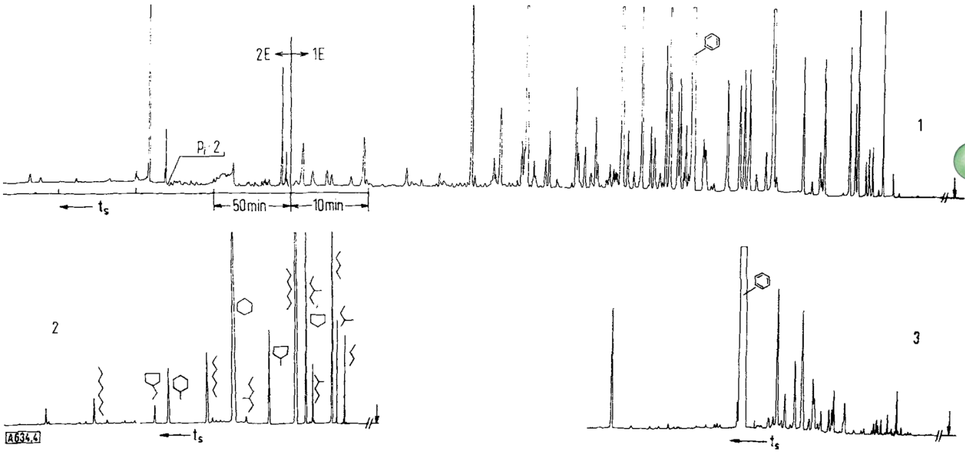
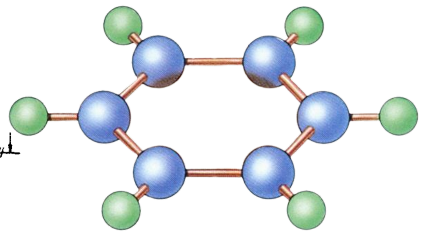


Fig. 4. Chromatogram 1: Capillary chromatogram of the pyrolysis condensate having b.p. 20–120 °C, temperature-programmed and partly pressure-programmed, shown with modified chart drive. Steel thin film capillary, p_i = 2.2 atm N_2.

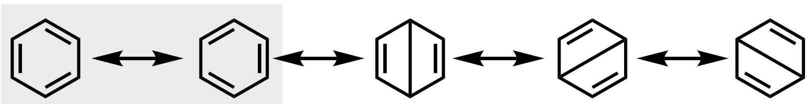
Chromatogram 2: Capillary chromatogram of the hydrogenated pyrolysis condensate.

Chromatogram 3: Capillary chromatogram of the "hydrocarbon C_2H_3", which was found to be the mother liquor of the crystallizing benzene.

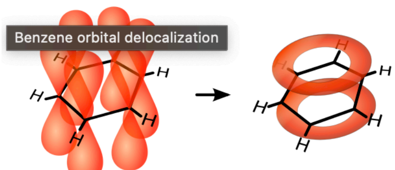


"Bicarburet of Hydrogen"

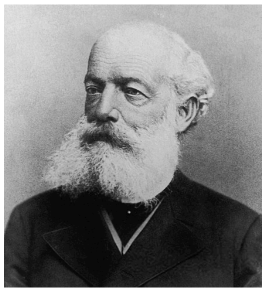
1-2. Aromaticity



i **ii** **iii** **iv** **v**



6 p-orbitals delocalized



Friedrich August Kekulé (1829-1896)

Characteristics:

1. Bond length **averaging**
2. Large **delocalization** energy
3. Structural **stability**

Hückel's rule:

1. A delocalized **conjugated** π **system**, most commonly an arrangement of alternating single and double bonds
2. Coplanar structure, with all the contributing atoms **in the same plane**
3. Contributing atoms arranged in one or more **rings**
4. A number of π delocalized electrons that is even, but not a multiple of 4. That is, **(4*n* + 2)** π**-electrons**, where n = 0, 1, 2, 3, and so on.

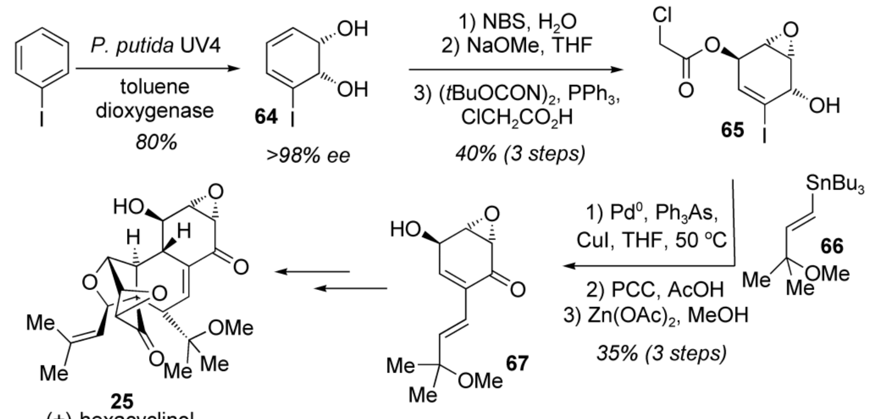
Erich Hückel (1896-1980)

Reference
R. Kaiser. *Angew*. Chem. internat. Edit. **1968**, *7*, 345.
Hua, Y.; Zhang, H.; Xia, H. *Chin. J. Org. Chem.* **2018**, *38*, 11

1. Introduction

1-3. Dearomative strategies in total synthesis

(+)-Hexacyclinol



Scheme 1. Preparation of epoxyquinl synthons by enzymatic dihydroxylation of iodobenzene and elaboration to hexacyclinol

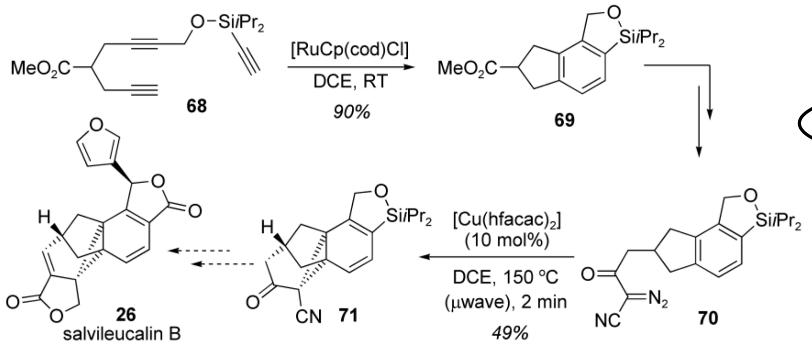
antiproliferative

antibacteria

antitumor

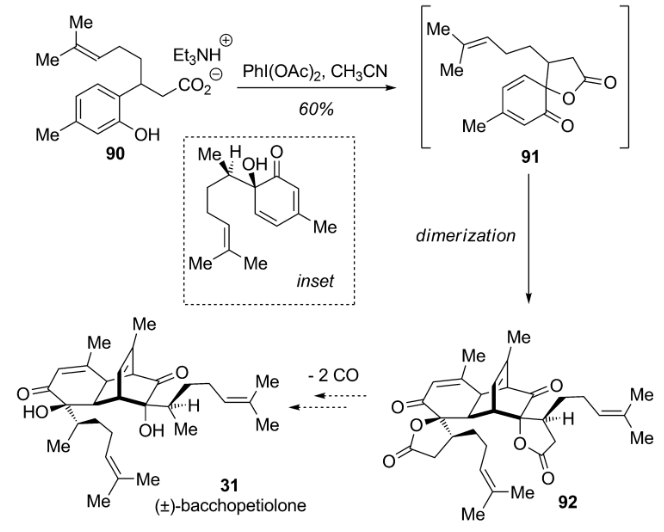
anticancer

Salvileucalin B



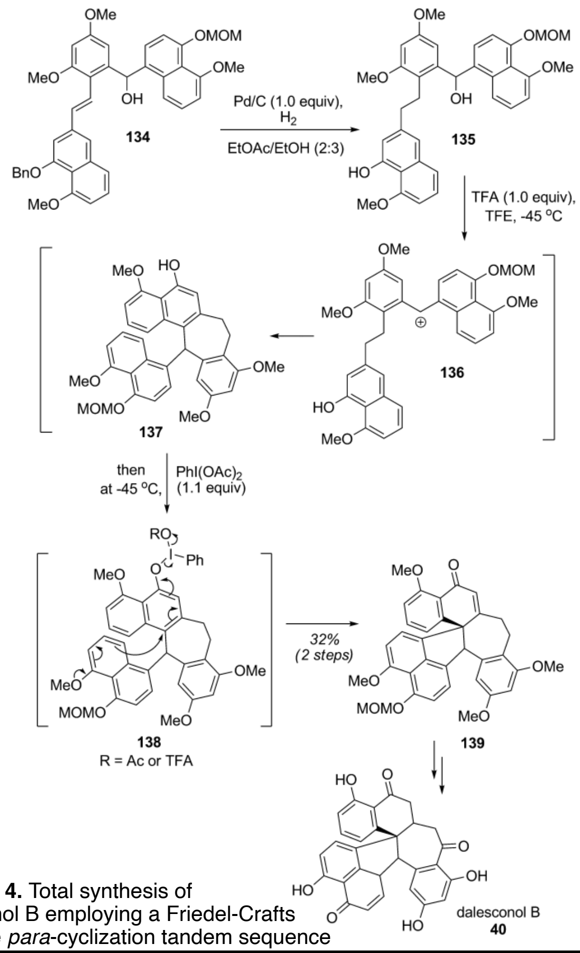
Scheme 2. Approach to salvileucalin B:
Preparation of the pentacyclic framework by Buchner dearomatization

(+)-Bacchopetiolone



Scheme 3. Approach to bacchopetiolone employing oxidative spirolactonization

Dalesconol B



Scheme 4. Total synthesis of dalesconol B employing a Friedel-Crafts oxidative *para*-cyclization tandem sequence

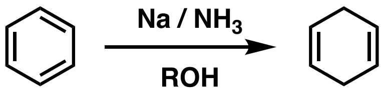
Reference

Roche, S-P.; Jr Porco, J-A*. *Angew, Chem. Int. Ed.* **2011**, *50*, 4068-4093.

Franklin, J-L*. *J. Am. Chem. Soc.* **1950**, *72*, 4378-4280.

2. Symmetric Dearomatization Reactions

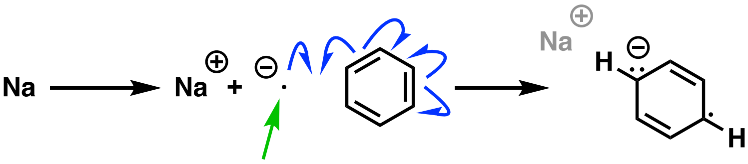
2-1. Birch reduction



Arthur Birch
(1915-1995)

2-1-1. Birch reduction Mechanism

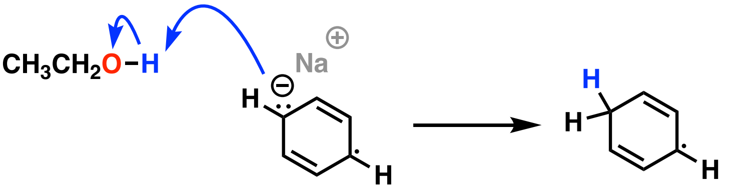
Step 1: Reduction of Benzene to the benzene "radical anion"



"solvated electron"

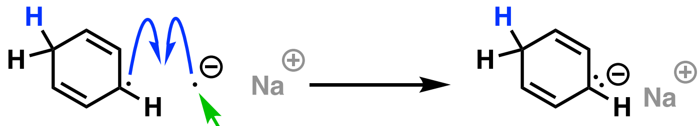
Benzene "radical anion"
· Seven π electrons
· Only one resonance form shown

Step 2: Protonation of the benezene "radical anion"



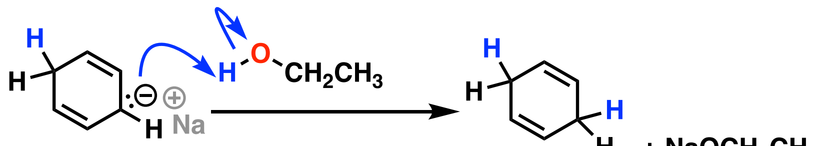
pentadienyl radical
(only one resonance form shown)

Step 3: Reduction of the radical to an anion by the electron



Radical — *Pentadienyl radical*; *electron*; *Anion* — *Pentadienyl anion*

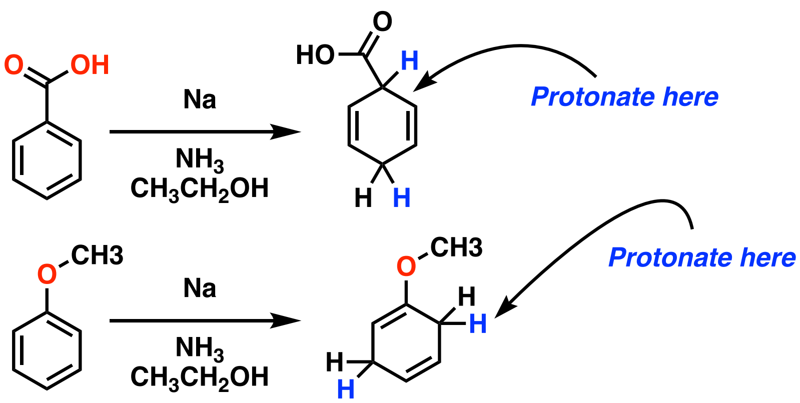
Step 4: Protonation of the anion by alcohol



Anion
Pentadienyl anion

Alcohol is absolutely required for this step (NH_3 is not acidic enough!)

2-1-2. Substituent Effects in the Birch reduction



Since "nucleophlie" here is free electrons (e^-), the reaction is **faster** on aromatic rings with **EWG**, and **slower** on aromatic rings with **EDG**

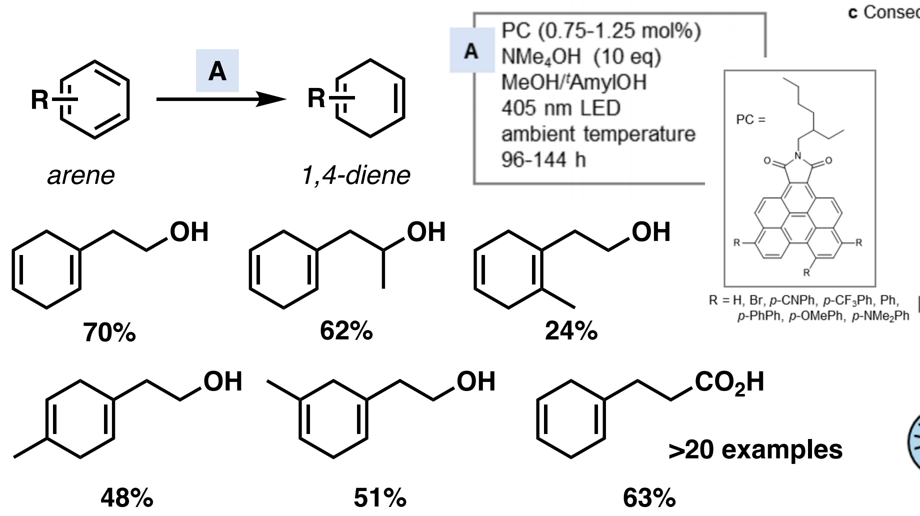
When a substituent is present, the **formation of the first C–H bond** determines which product will form. This, in turn, depends on **the site where the most stable anion will form.**

Reference
Arthur J. Birch. *J. Chem. Soc.* **1944**, 430-436.
Peter W. R.; Marcinow; Zbigniew. *Org. React.* **1992**, *42*, 1-334.

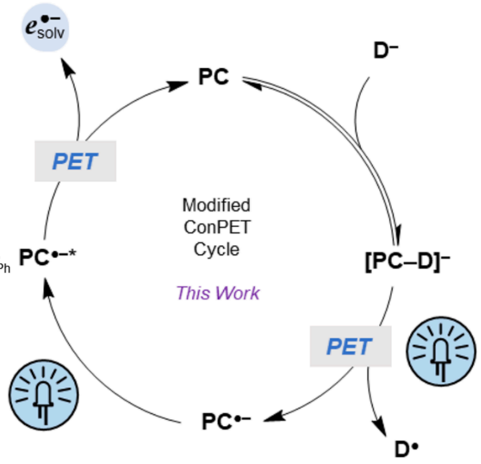
2. Symmetric Dearomatization Reactions

2-1-3. The application of Birch reduction

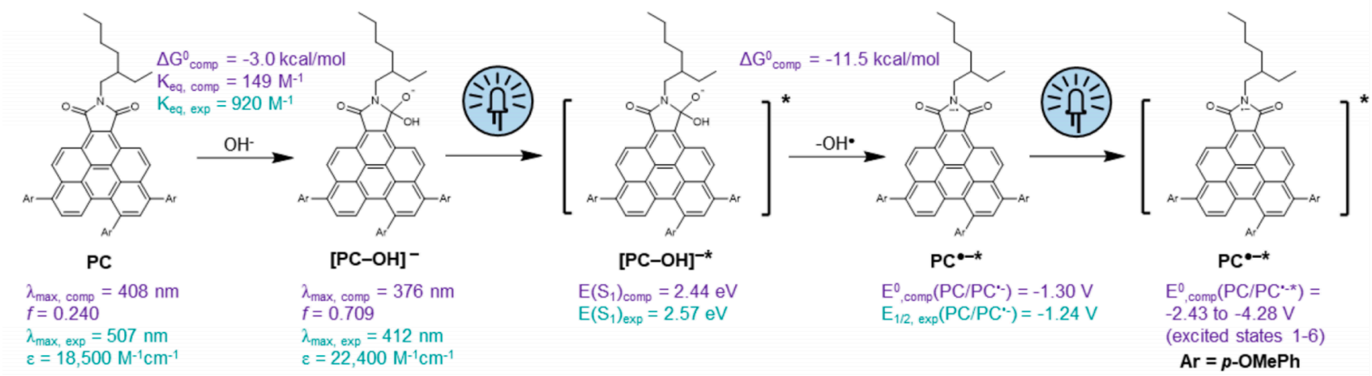
Organocatalyzed Birch Reduction Driven by Visible Light



c Consecutive Photoinduced Electron Transfer (ConPET)



a Plausible Mechanism for Consecutive Photoinduced Electron Transfer

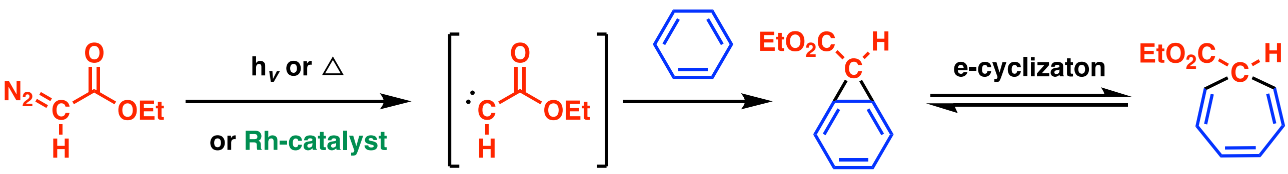


2-2. Buchner ring-expansion

Eduard Buchner (1860-1917)

The Nobel Prize in Chemistry 1907

"For his biochemical researches and his discovery of cell-free fermentation"



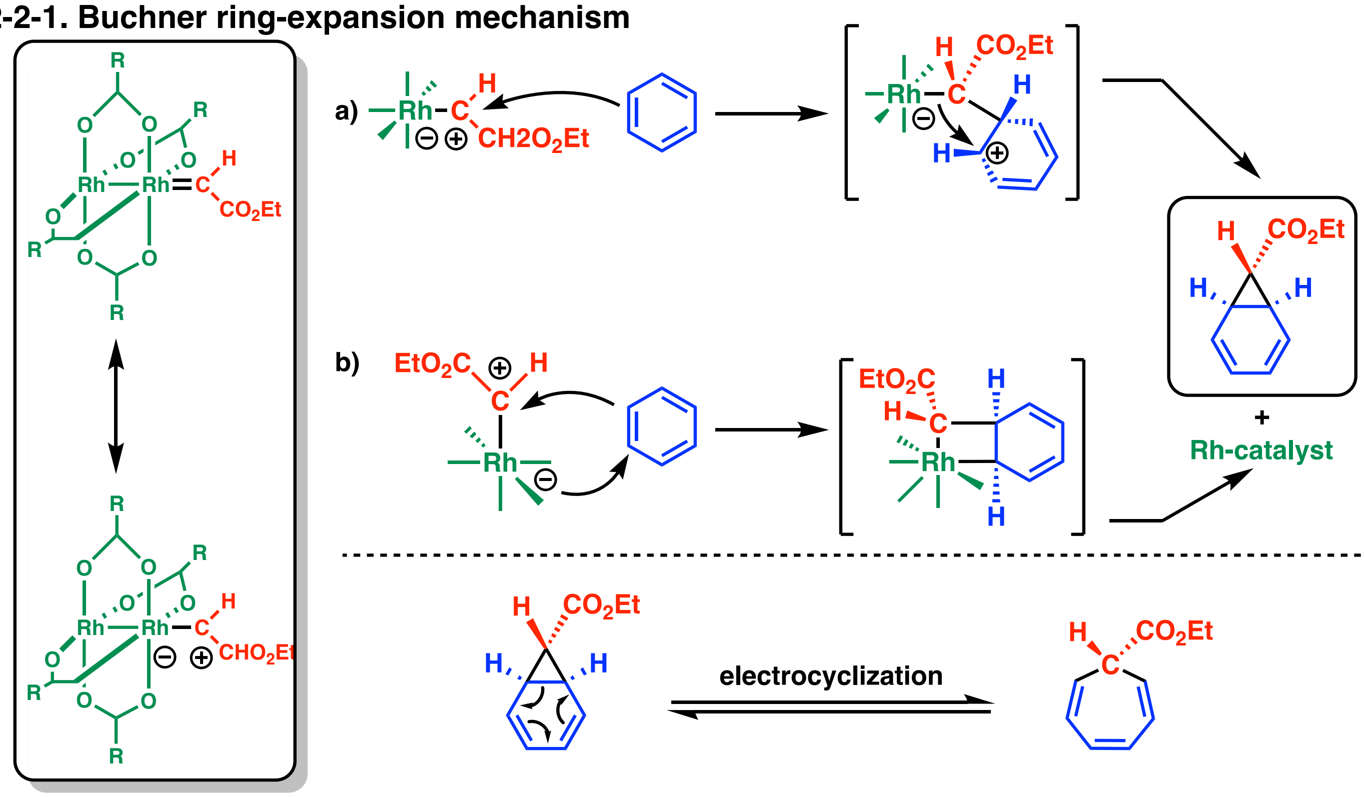
Reference

Buchner, E.; Curtius, T.; *Berichte der deutschen chemischen Gesellschaft*. **1885**, *18*, 2371-2377.

Buchner, E.; Curtius, T.; *Berichte der deutschen chemischen Gesellschaft*. **1885**, *18*, 2377-2379.

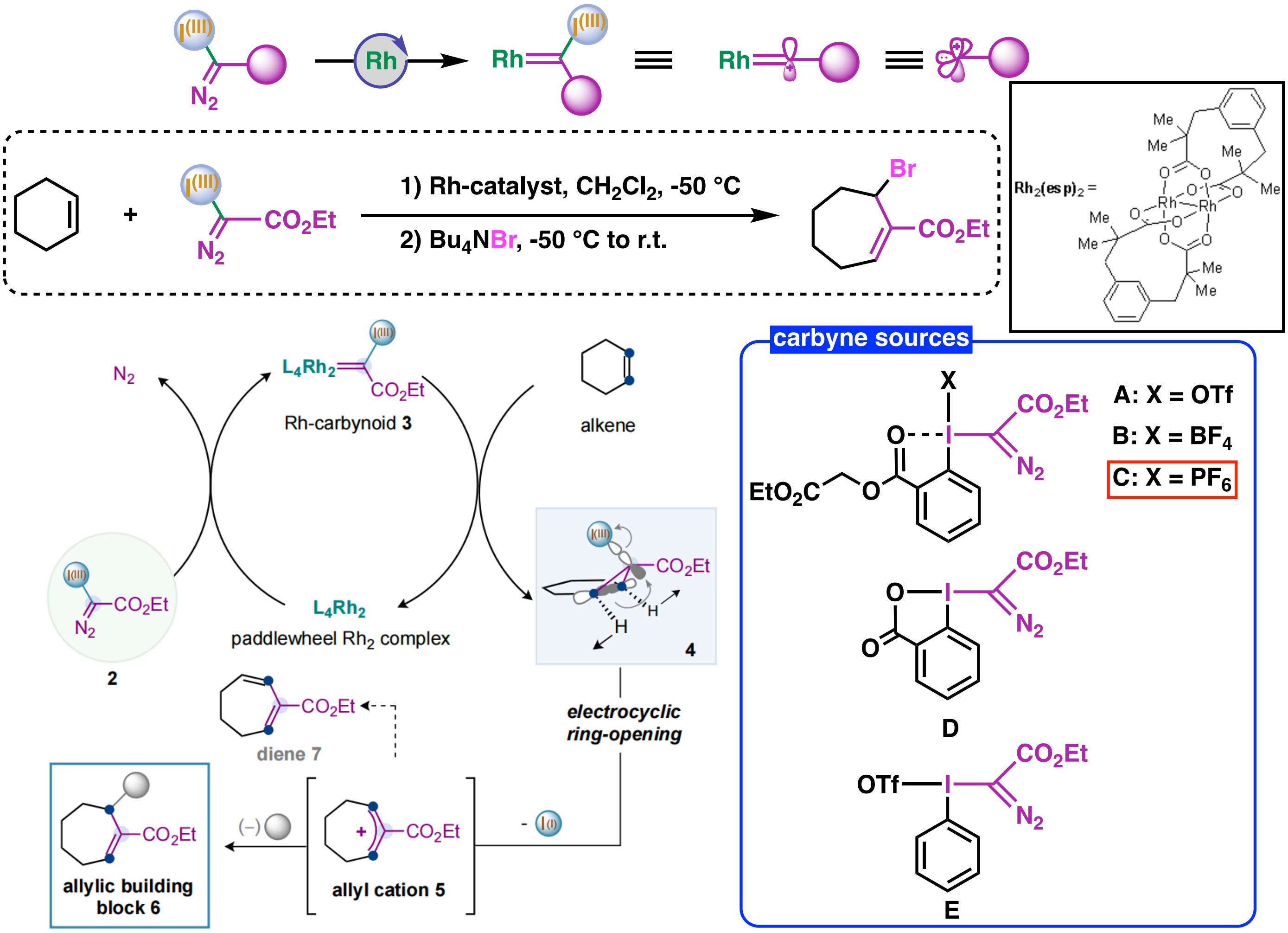
2. Symmetric Dearomatization Reactions

2-2-1. Buchner ring-expansion mechanism



2-2-2. The application of Buchner ring-expansion

Catalytic cleavage of C(sp^2)–C(sp^2) bonds with Rh-carbonoids



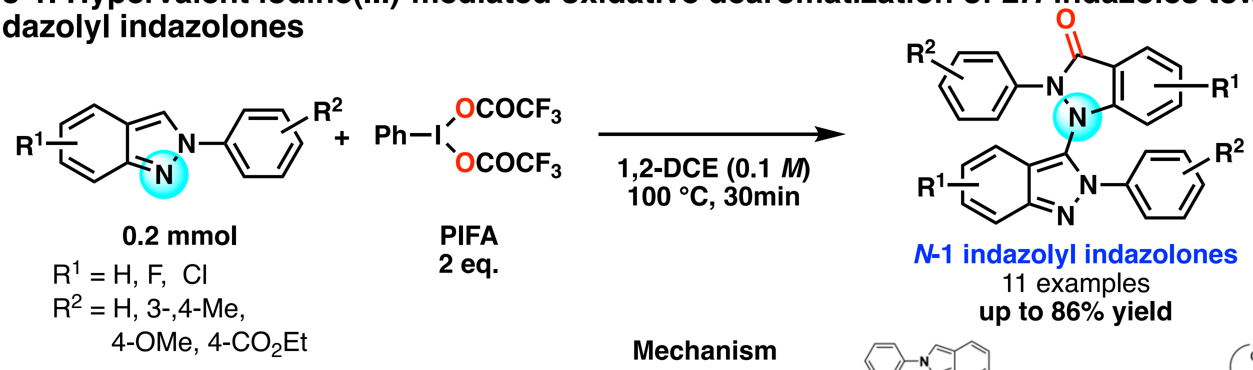
Reference

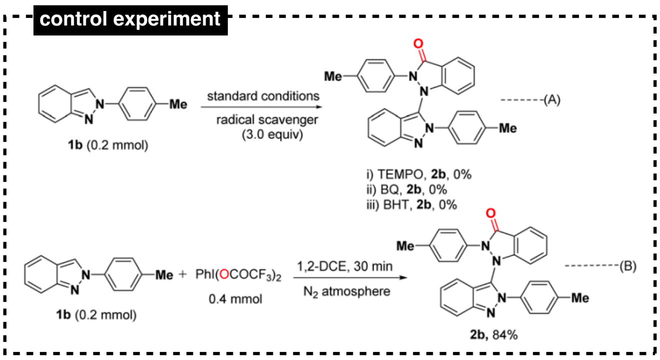
Ramachandran, K. et al. *Helv. Chim. Acta.* **1987**, *70*, 1429-1438.
Suero, M. G. et al. *J. Am. Chem. Soc.* **2019**, *39*, 15509-15514.

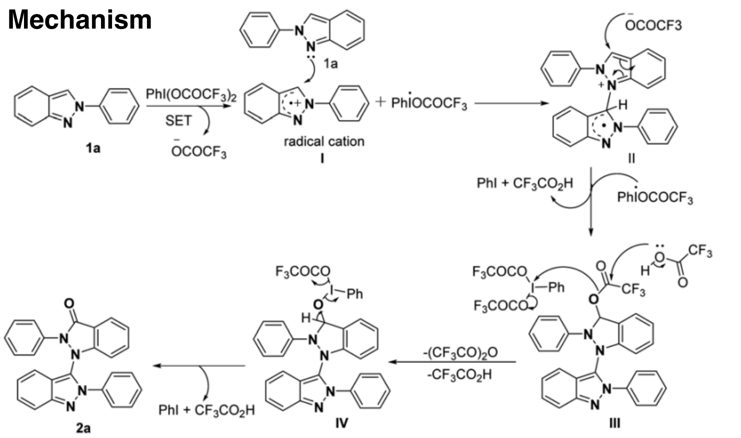
2. Symmetric Dearomatization Reactions

2-3. Hypervalent Iodine-promoted intramolecular reaction

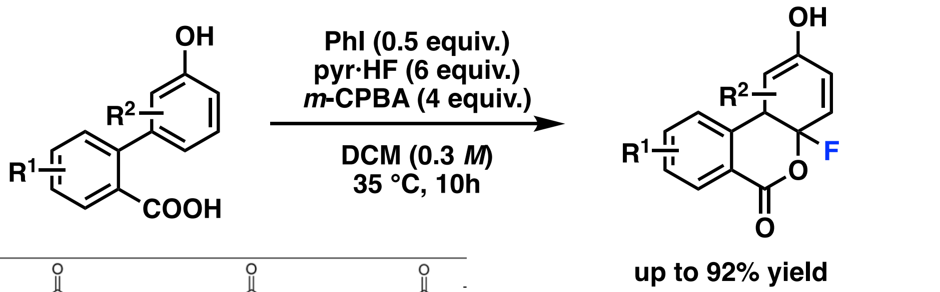
2-3-1. Hypervalent iodine(III)-mediated oxidative dearomatization of 2*H*-indazoles towards indazolyl indazolones

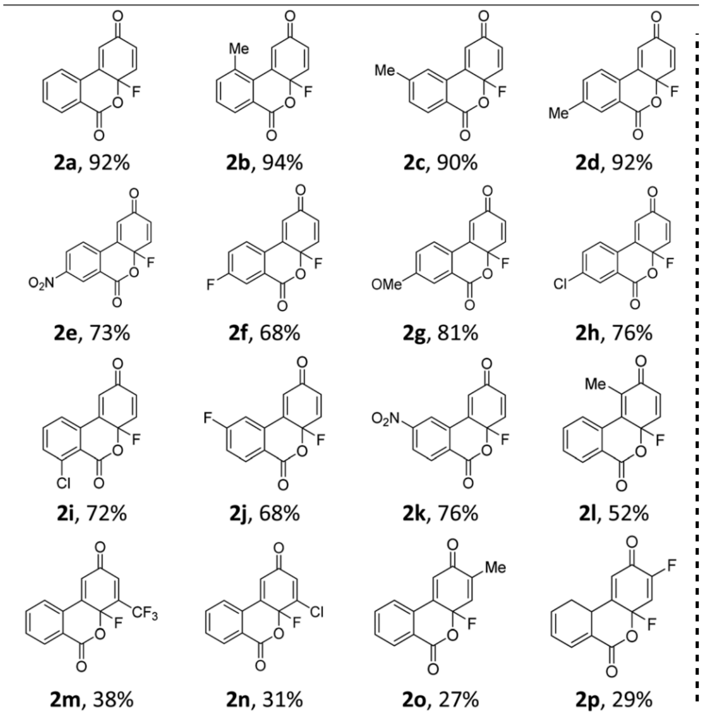






2-3-2. Synthesis of fluorinated polycyclic dehydroaltenusin analogs through hypervalent iodine-catalyzed dearomatization





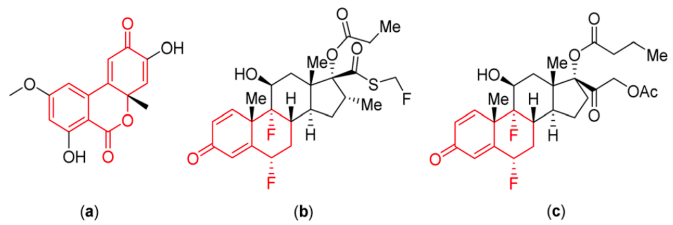
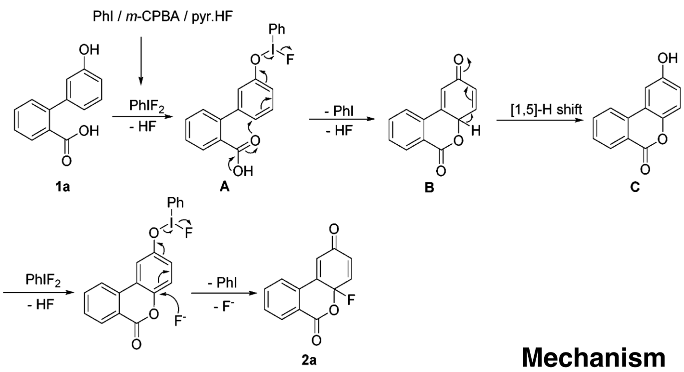


Fig. 1 Dehydroaltenusin (a) and fluorine-containing drugs (b and c).



Reference

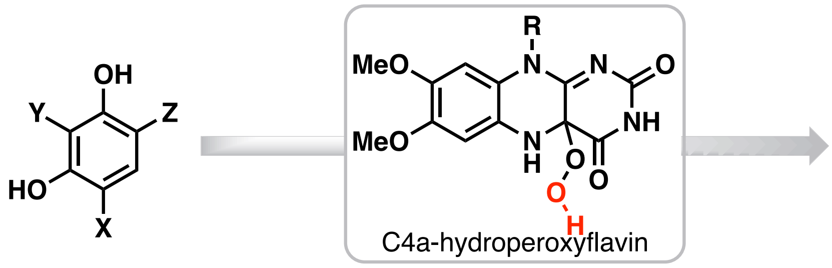
Bhattacharjee, S.; Laru, S.; Hajra, A. *Org. Biomol. Chem.*, **2022**, *20*, 8893-8897.

Xiong, Y. et al. *Org. Biomol. Chem.*, **2022**, *20*, 8104-8107.

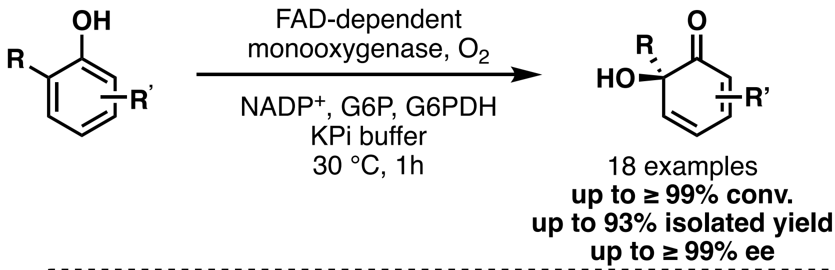
3. Dearomatization strategy in Biochemistry

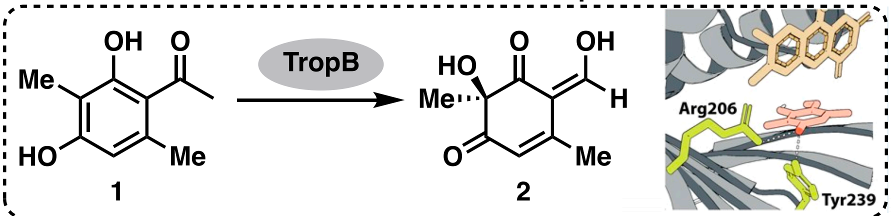
3-1. Enzyme-catalyzed transformations

Biocatalytic site- and enantioselective oxidative dearomatization of phenols



Alison R. H. Narayan
(1984-)
University of Michigan





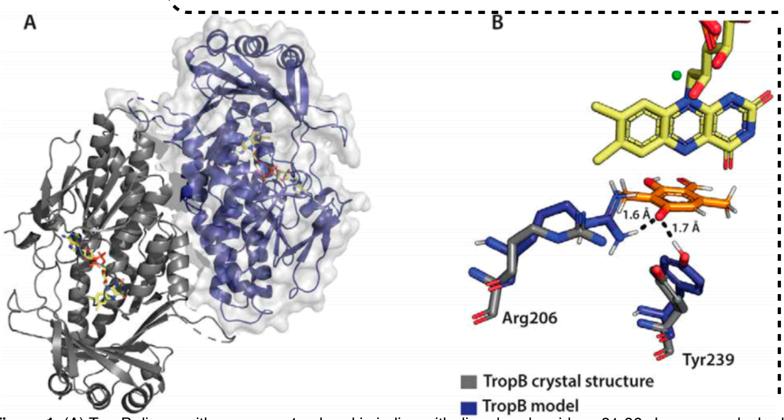


Figure 1. (A) TropB dimer, with monomer 1 colored in indigo with disordered residues 81-86 shown as a dashed line and monomer 2 shown in gray. (B) TropB crystal structure overlaid with the TropB QM/MM model with substrate 1.

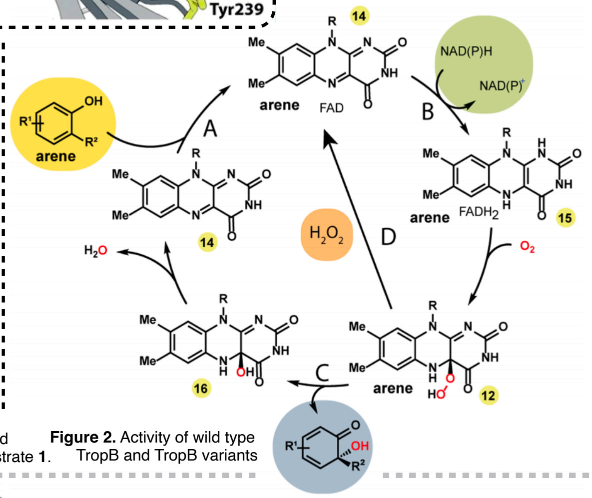


Figure 2. Activity of wild type TropB and TropB variants

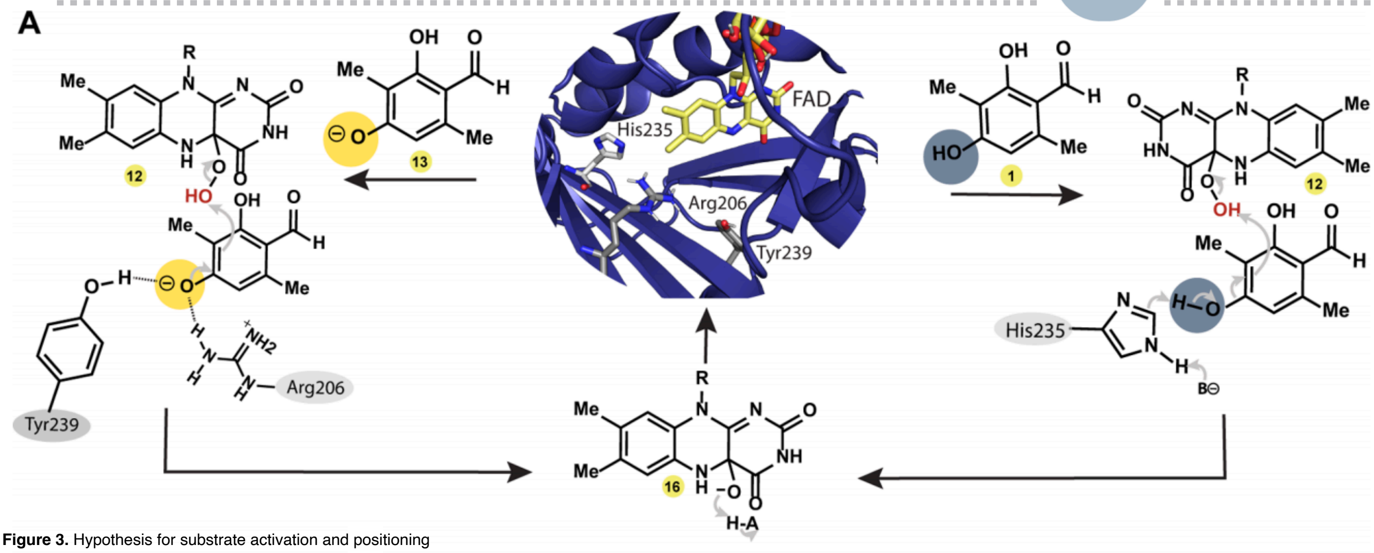


Figure 3. Hypothesis for substrate activation and positioning

Reference

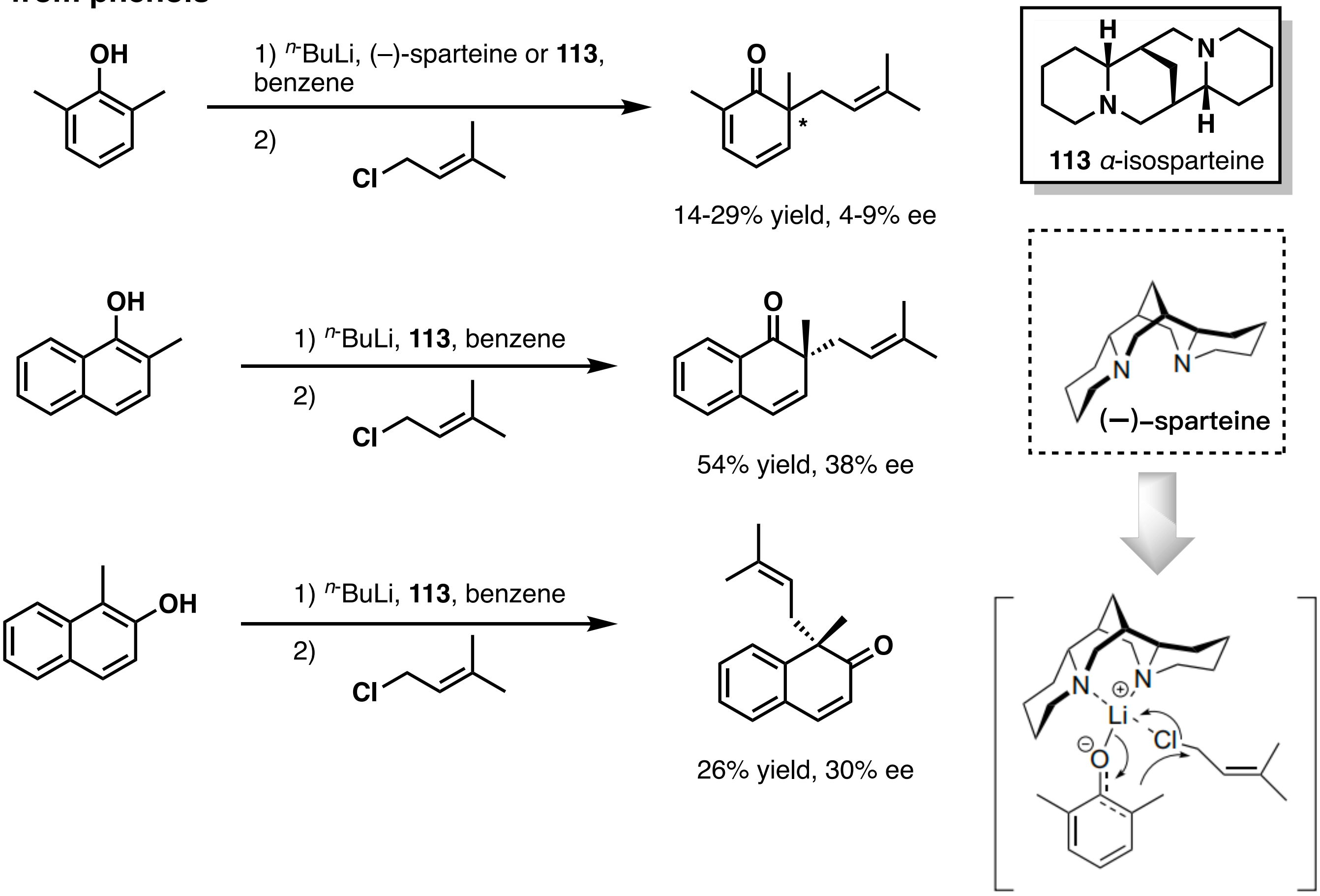
Dockrey, S.; Lukowski, A.; Becker, M.; Naratan, A*. *Nat. Chem.* **2018**, *10*, 119-125.

Narayan, A.* et al. *ACS, Catal.* **2019**, *9*, 3633-3640.

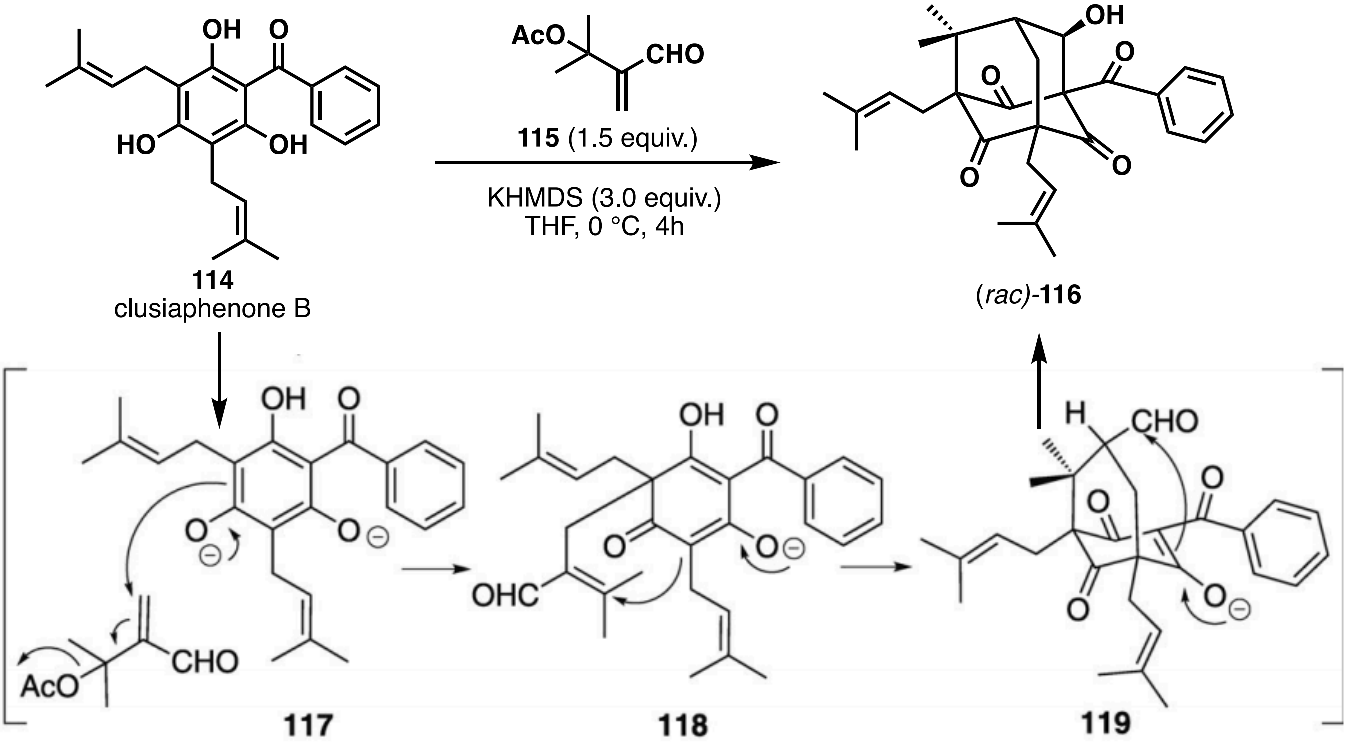
4. Catalytic Asymmetric Dearomatization (CADA) Reactions

4-1. Alkylative Dearomatization Reactions

4-1-1. Stereoselective syntheisis of cyclohexa-2,4-dien-1-ones and cyclohex-2-en-1-ones from phenols



4-1-2. Enantioselective Alkylation Dearomatization–Annulation in Total Synthesis

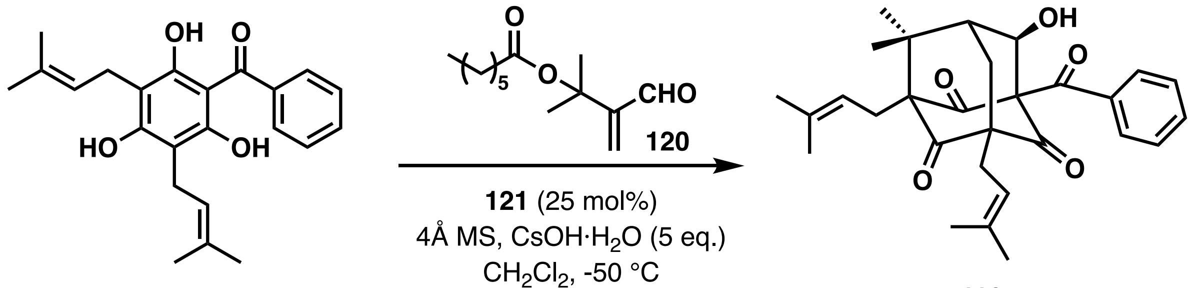


Reference
Fráter, G. et al. *Tetrahedron: Asymmetry*. **2006**, *17*, 1693-1699.
Porco, J. et al. *J. Am. Chem. Soc.* **2010**, *132*, 13642-13644.

4. Catalytic Asymmetric Dearomatization (CADA) Reactions

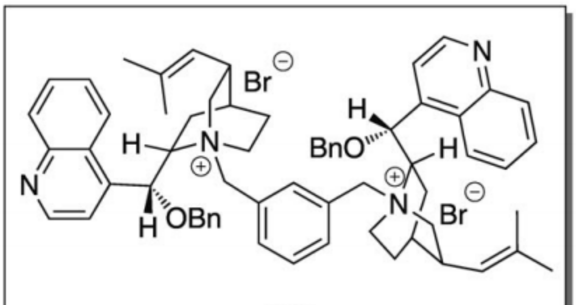
4-1. Alkylative Dearomatization Reactions

4-1-2. Enantioselective Alkylation Dearomatization–Annulation in Total Synthesis

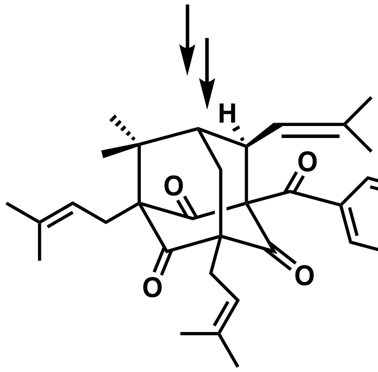


114
clusiaphenone B

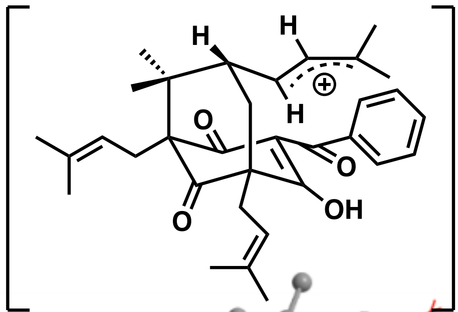
116
71% yield, 90% ee



121



(–)-hyperibone K



13

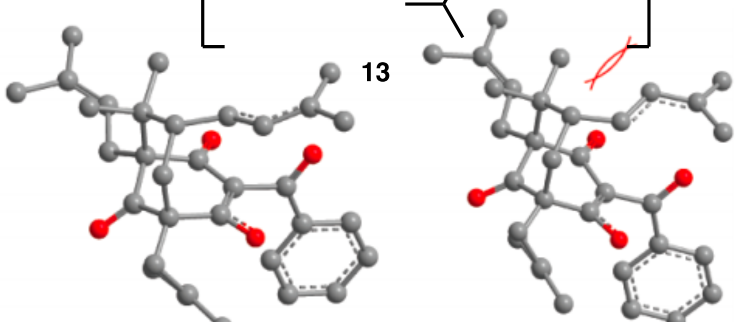
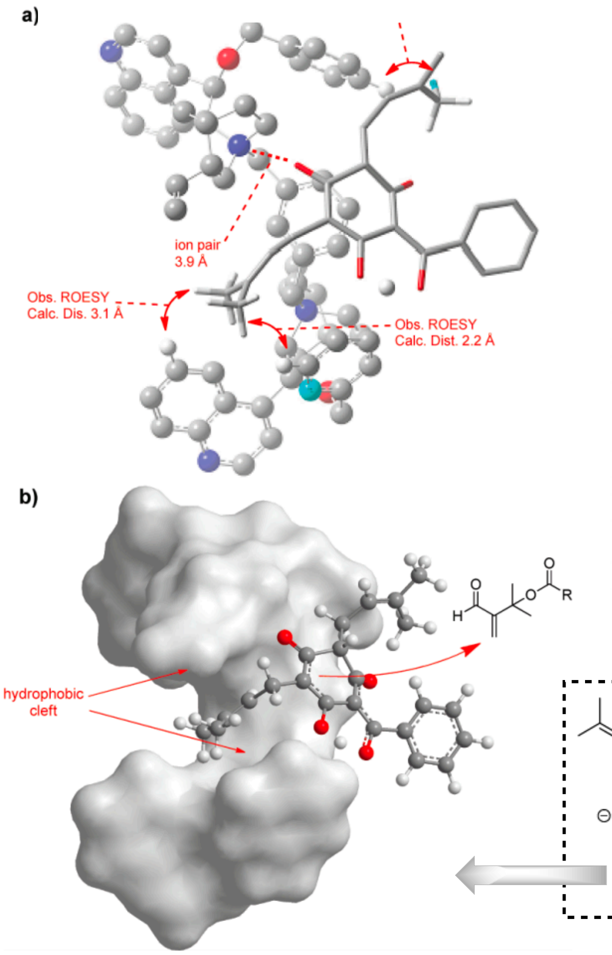


Figure 1. Allylic cation intermediate **13**



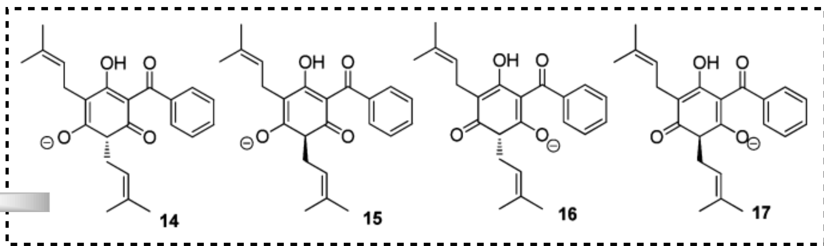


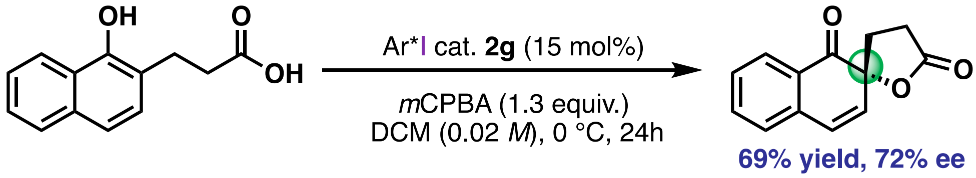
Figure 2. Proposed Binding Model of Catalyst **121** and **15**.
(a) Key interactions of **121** and **15**. (b) 1.4 Å Connolly surface.

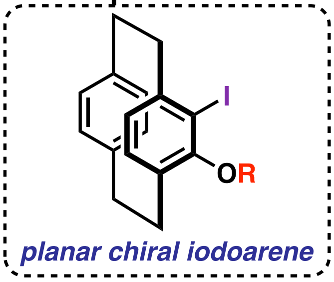
Reference
Porco, J. et al. *J. Am. Chem. Soc.* **2007**, *129*, 12682-12683.
Porco, J. et al. *J. Am. Chem. Soc.* **2010**, *132*, 14212-14215.

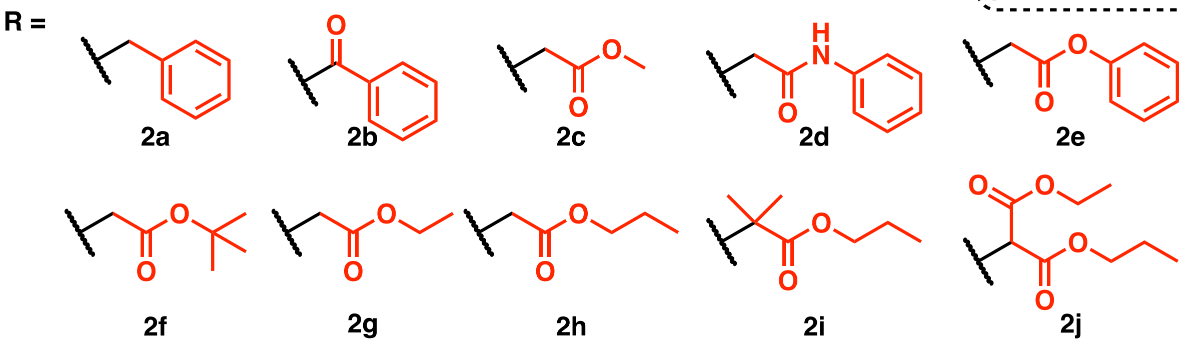
4. Catalytic Asymmetric Dearomatization (CADA) Reactions

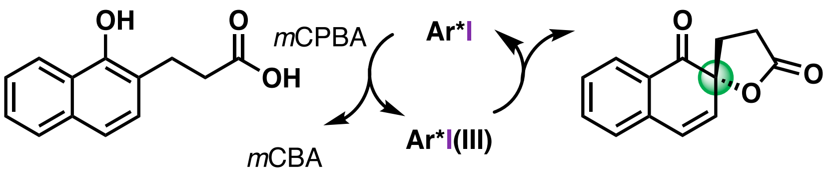
4-2. Oxidative Dearomatization Reactions

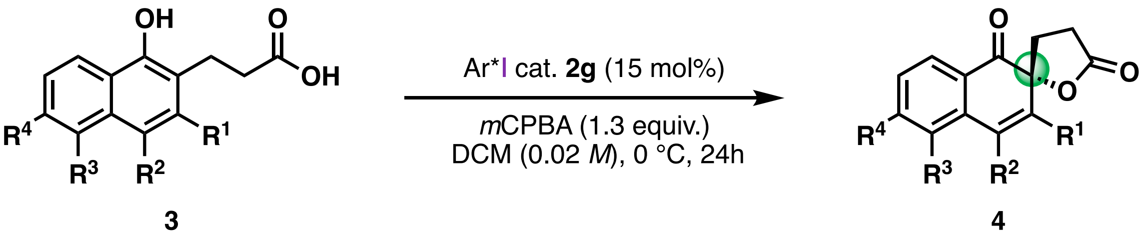
4-2-1. Enantioselective Intramolecular Dearomative Lactonization of Naphthols Catalyzed by Planar Chiral Iodoarene











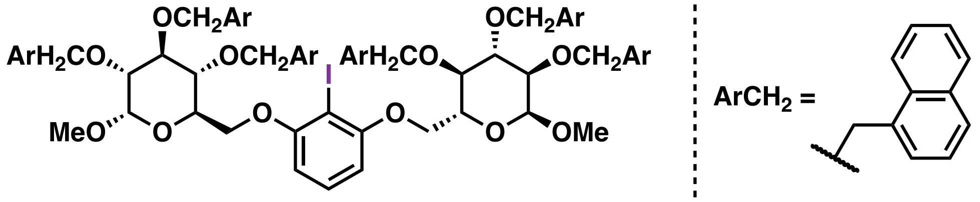
Entry	Substrate	R[1]	R[2]	R[3]	R[4]	Product	Yield (%)[b]	ee (%)[c]
1	**3a**	H	H	H	H	**4a**	69	72
2	**3b**	OMe	H	H	H	**4b**	1	58
3	**3c**	H	Cl	H	H	**4c**	42	38
4	**3d**	H	Br	H	H	**4d**	66	54
5	**3e**	H	Ph	H	H	**4e**	53	54
6	**3f**	H	Ac	H	H	**4f**	37	8
7	**3g**	H	H	OMe	H	**4g**	54	64
8	**3h**	H	H	OBn	H	**4h**	49	56
9	**3i**	H	H	H	OMe	**4i**	41	60

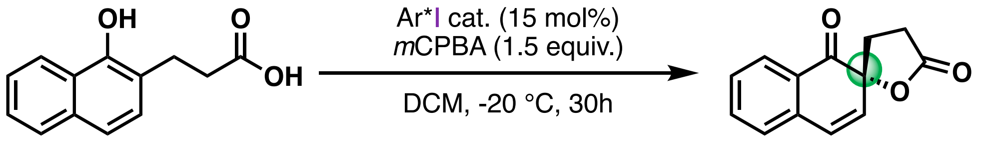
Reference
Shi, X. et al. *Chin. J. Org. Chem.* **2023**, *43*, 1-29.
Zheng, W. et al. *Synthesis*, **2019**, *51*, 3675-3682.

4. Catalytic Asymmetric Dearomatization (CADA) Reactions

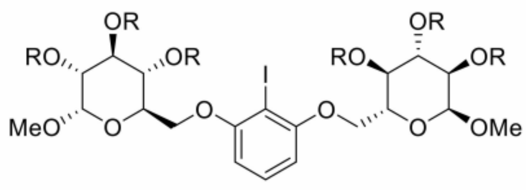
4-2. Oxidative Dearomatization Reactions

4-2-2. Carbohydrate based chiral iodoarene catalysts for enantioselective dearomative spirocyclization





75% yield, 76% ee



8
8a: R= Ac
8b: R= Bz
8c: R= Me
8d: R= Bn

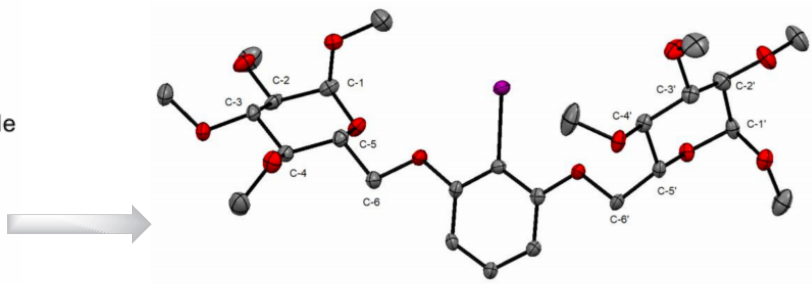
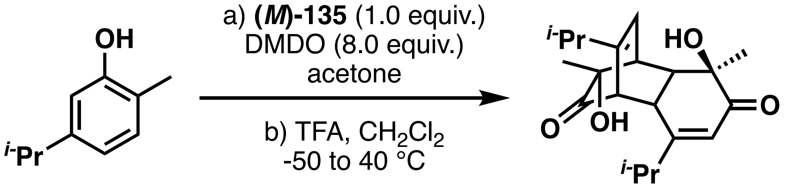
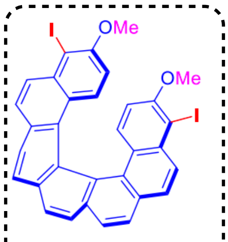


Figure 1. Molecular structure of **8c**. Ellipsoids are given at the 50% probability level; hydrogens are omitted for better clarity. Grey: carbon, red: oxygen, purple: iodine.

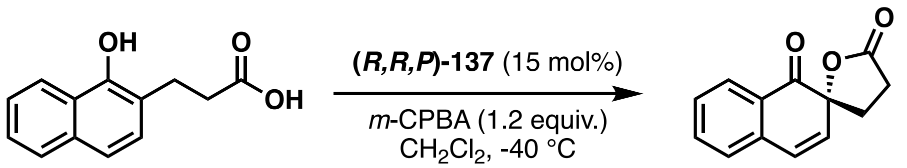
4-2-3. Synthesis of [7]Helicene Enantiomers and Exploratory Study of Their Conversion into Helically Chiral Iodoarenes and Iodanes



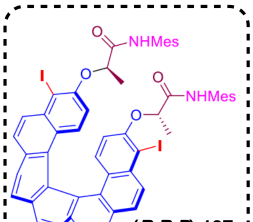
18% yield, 64% ee



(*M*)-135



90% yield, 56% ee



(*R,R,P*)-137

a)

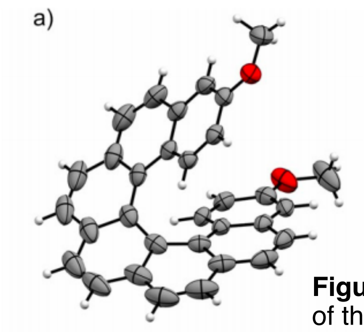


Figure 1. ORTEP drawing of the crystal structure of **(*M*)-135**

c)

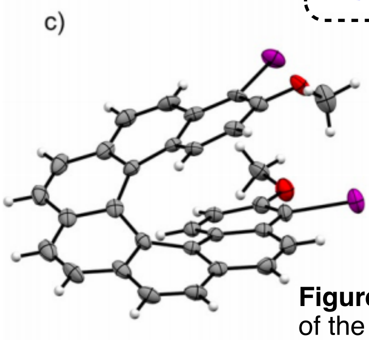


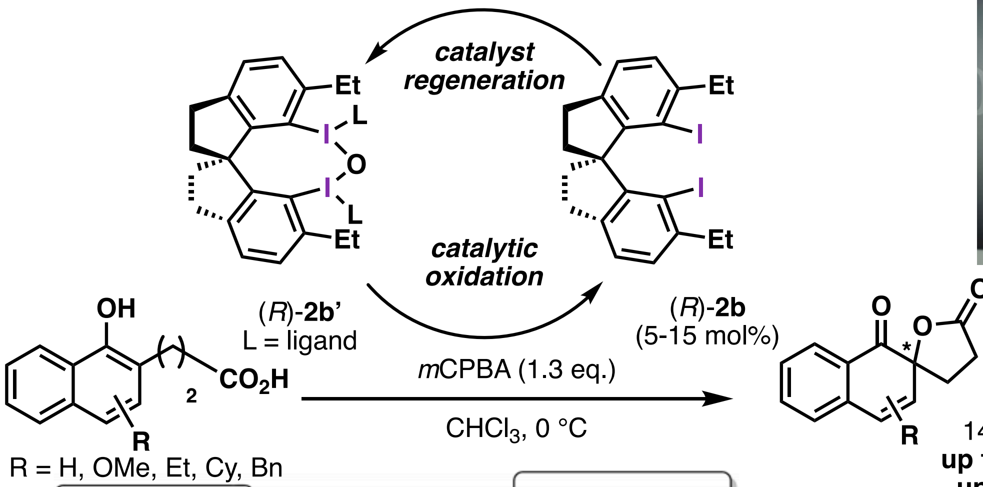
Figure 2. ORTEP drawing of the crystal structure of **(*R,R,P*)-137**

Reference
Ziegler T. et al. *Molecules*. **2019**, *24*, 3833.
Quideau, S. et al. *Chem. Eur. J.* **2019**, *25*, 2852-2858.

4. Catalytic Asymmetric Dearomatization (CADA) Reactions

4-2. Oxidative Dearomatization Reactions

4-2-4. Asymmetric Dearomatizing Spirolactonization of Naphthols Catalyzed by Spirobiindane-Based Chiral Hypervalent Iodine Species



Yasuyuki Kita
(1945-)
Ritsumeikan University

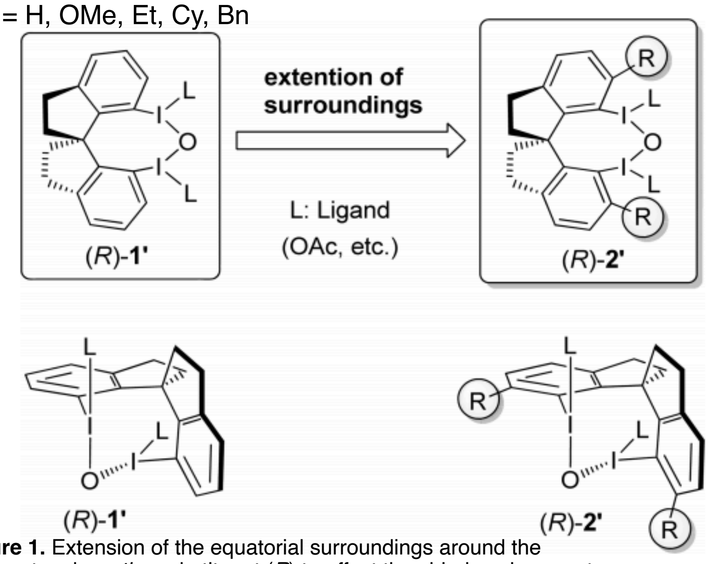


Figure 1. Extension of the equatorial surroundings around the iodine atom by *ortho*-substituent (*R*) to affect the chiral environment

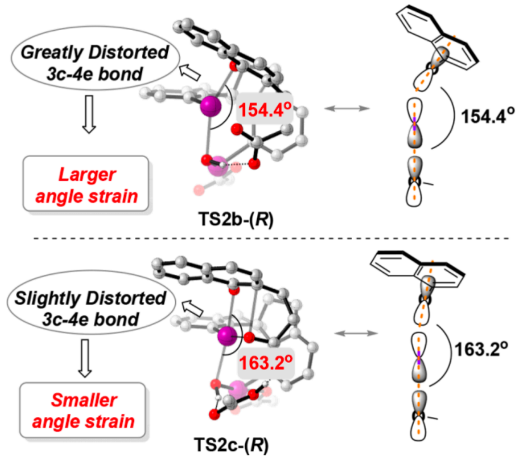
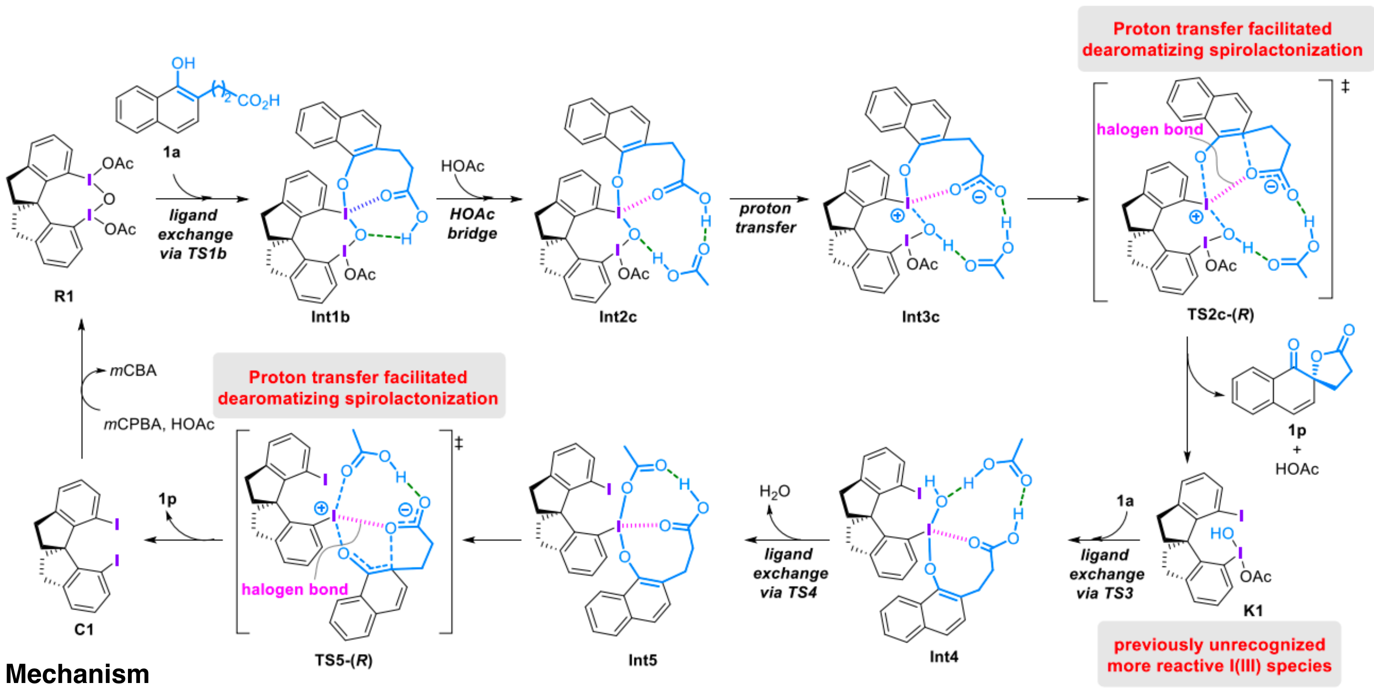


Figure 2. Angle of the breaking O—I(III)—O 3-center-4-electron bond in **TS2b-(*R*)** and in **TS2c-(*R*)**



Mechanism

Referencew

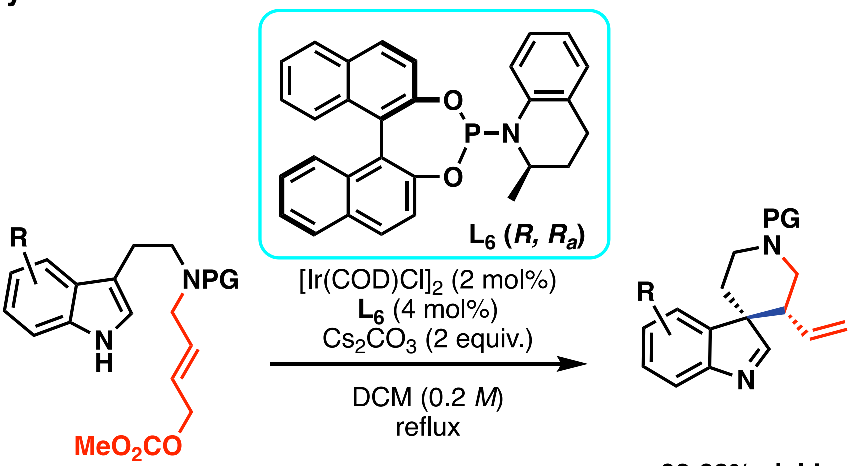
Kita, Y*. et al. *J.Am. Chem. Soc.* **2013**, *135*, 4558-4566.

Zheng, H-L.; Sang, Y-Q.; Houk, K*.; Xue, X-S*.; Cheng, J-P*. *J. Am. Chem. Soc.* **2019**, *141*, 16046-16056.

4. Catalytic Asymmetric Dearomatization (CADA) Reactions

4-3 Transition-Metal-Catalyzed Dearomatization Reactions

4-3-1. Enantioselective Construction of Spiroindolenines by Ir-Catalyzed Allylic Alkylation Reactions

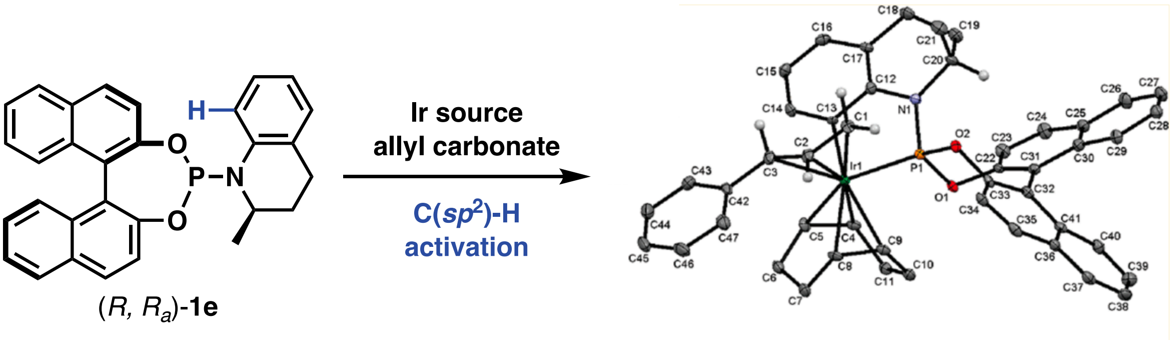


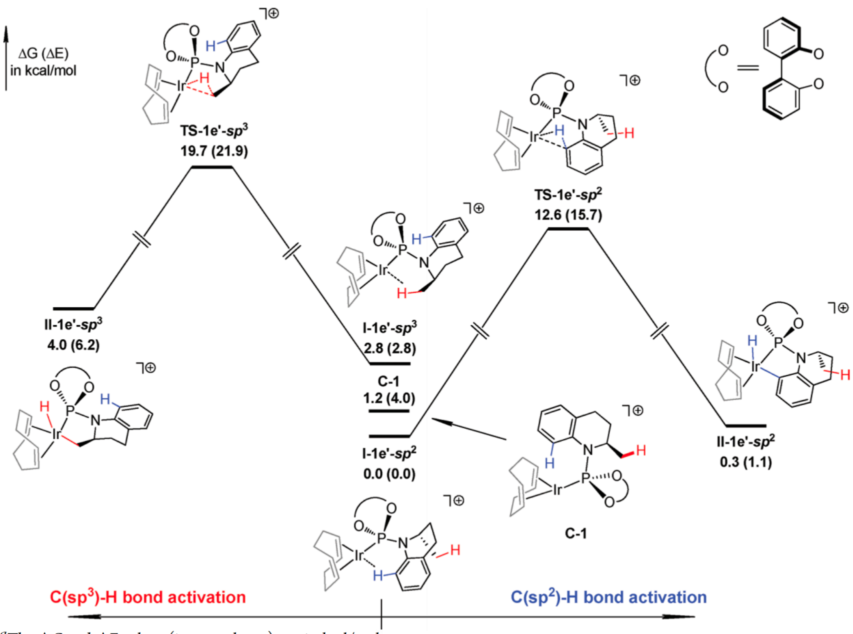
R = H, Bn, *p*-Br-$C_6H_4CH_2$, F, Me, OMe, allyl

92-98% yield
up to >99/1 *dr*
97% ee

Shu-Li You
(1975-)
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences

Iridium-Catalyzed Allylic Alkylation Reaction with *N*-Aryl Phosphoramidite Ligands





^{a}The ΔG and ΔE values (in parentheses) are in kcal/mol.

Figure 1. Possible C–H Bond Activation Pathways in the Preparation of the Active Catalytic Species with Model Ligand 1e' Calculated at the M06-2X/SDD/6-31G(d,p) Level of Theory

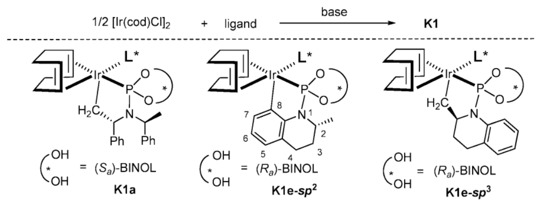
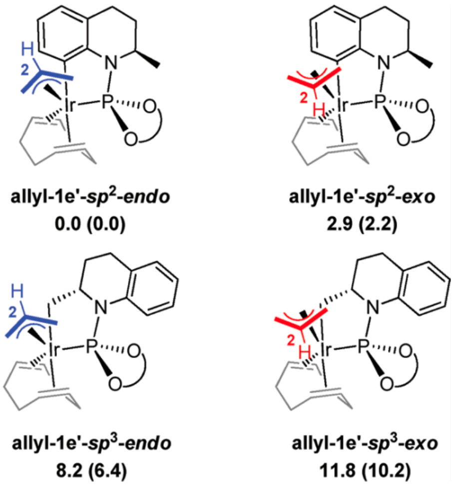


Figure 2. Cyclometalated Ir Complexes



^{a}The ΔG and ΔE values (in parentheses) are in kcal/mol.

Figure 3. Possible (*π*-Allyl)-Ir Complexes with Model Ligand 1e'

Reference

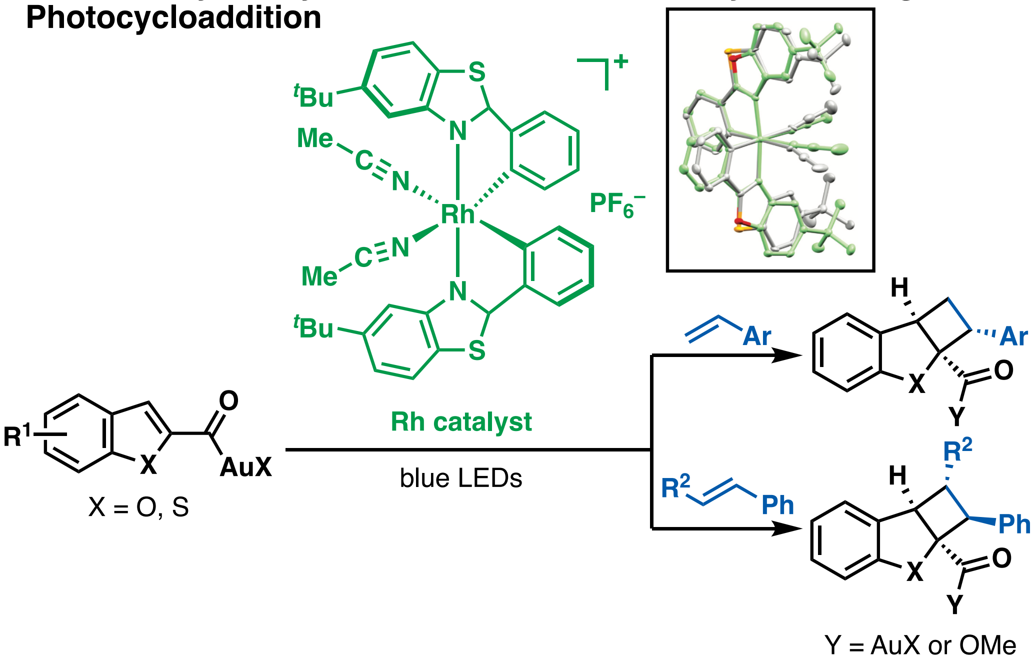
You, S-L.; Wu, Q-F.; He, H.; Liu, W-B. *J. Am. Chem. Soc.* **2010**, *132*, 11418-11419.

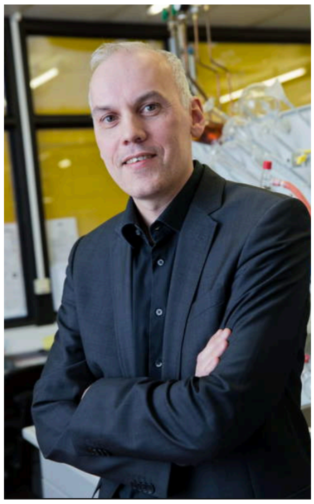
You, S-L. et al. *J. Am. Chem. Soc.* **2012**, *134*, 4812-4821.

4. Catalytic Asymmetric Dearomatization (CADA) Reactions

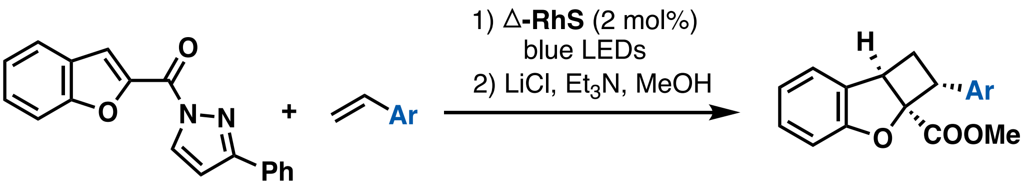
4-3 Transition-Metal-Catalyzed Dearomatization Reactions

4-3-2. Catalytic Asymmetric Dearomatization by Visible-Light-Activated [2+2] Photocycloaddition

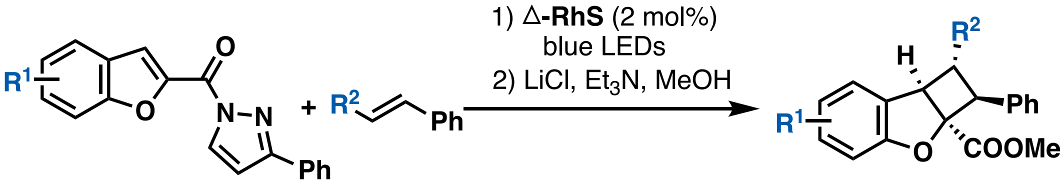




Eric Meggers
(1968-)
Philipps University Marburg
(Germany)



9 examples
up to 88% yield,
98% ee



9 examples
up to 93% yield,
99% ee

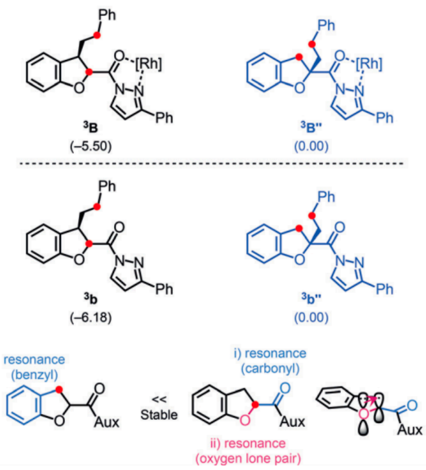
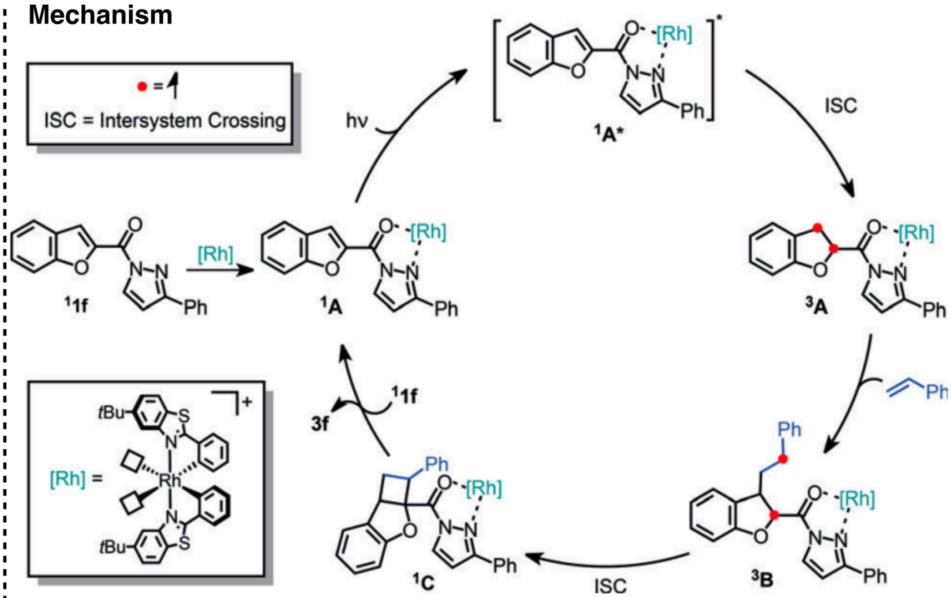


Figure 1. up) Energy differences of two analogous 1,4-biradical intermediates down)Schematic illustrationsof the radical stabilizations



Reference

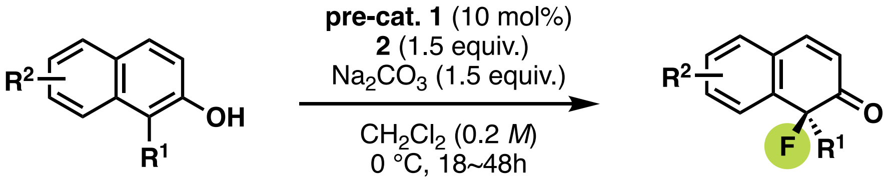
Meggers, E. et al. *Angew. Chem. Int. Ed.* **2018**, *57*, 6242-6246.

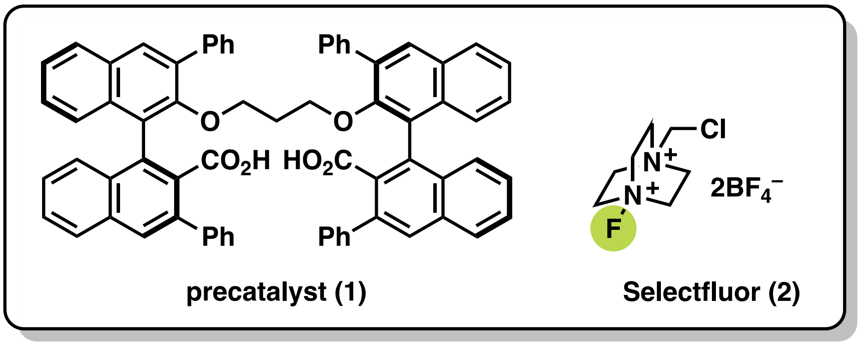
Meggers, E. et al. *Dalton Trans.* **2016**, *45*, 8320-8323.

4. Catalytic Asymmetric Dearomatization (CADA) Reactions

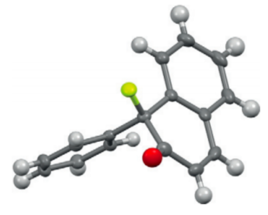
4-4 Asymmetric Dearomative Halogenation

Asymmetric Dearomative Fluorination of 2-Naphthols with a Dicarboxylate Phase-Transfer Catalyst

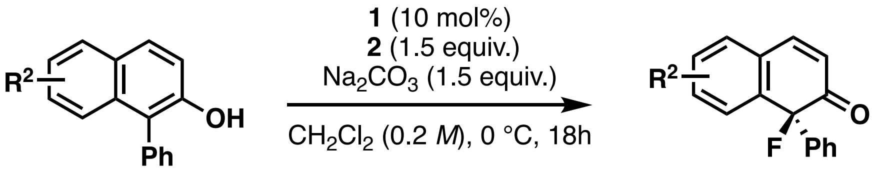




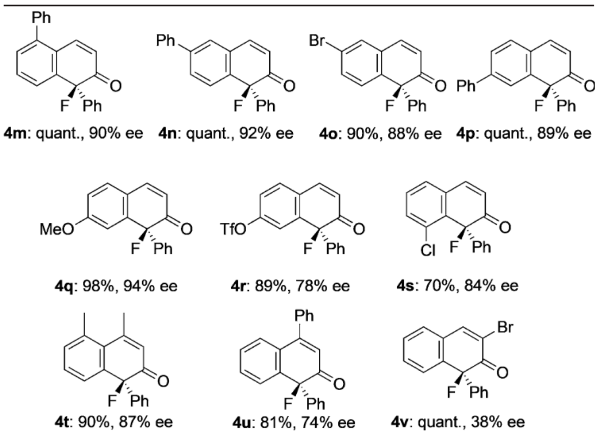
Yoshitaka HAMASHIMA
(1974-)
University of Shizuoka

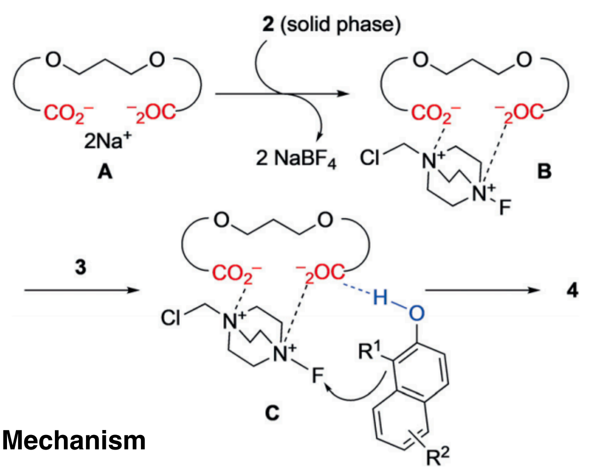


X-ray structure of **4a**
(R^2 = H)



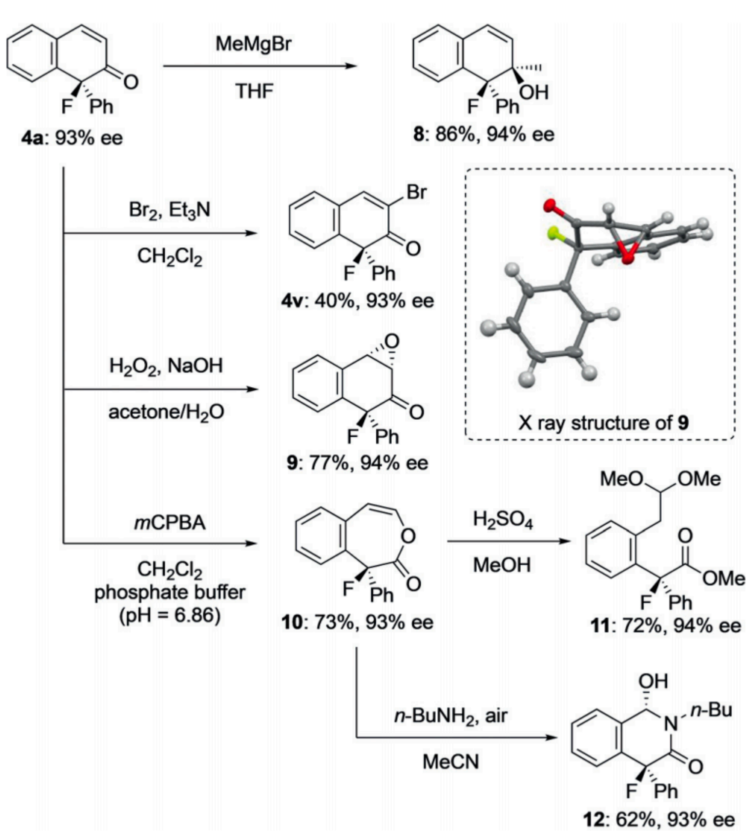
3 **4**





Mechanism

Transformation of **4a**

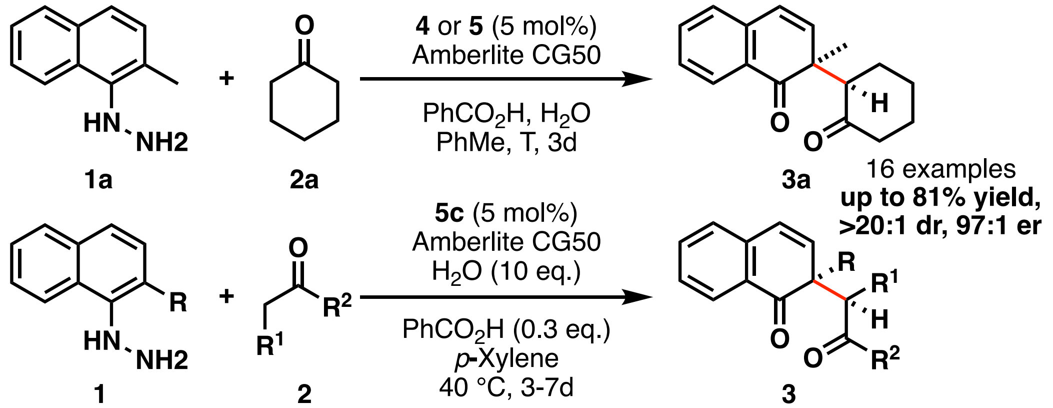


Reference
Hamashima, Y. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 14101-14105.
Müller, K.; Faeh, C.; Diederich, F. *Science*, **2007**, *317*, 1881-1886.

4. Catalytic Asymmetric Dearomatization (CADA) Reactions

4-5 Brønsted acid–catalyzed Asymmetric Dearomatization

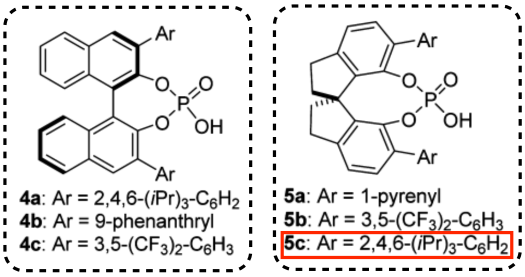
4-5-1. Catalytic Asymmetric Dearomatizing Redox Cross Coupling of Ketones with Aryl Hydrazines Giving 1,4-Diketones

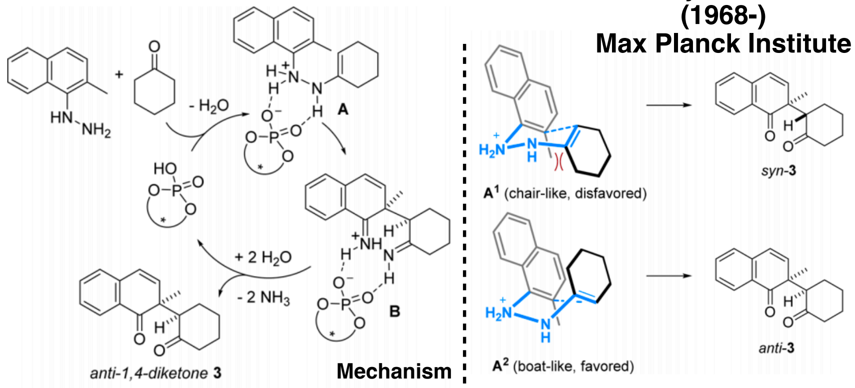


Benjamin List
(1968-)
Max Planck Institute

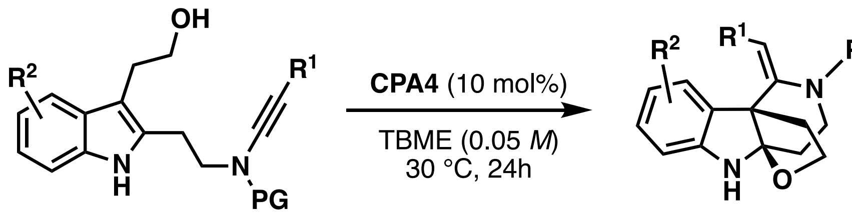
R = alkyl

R^1, R^2 = alkyl, cycloaliphatic halogen cycloaliphatic



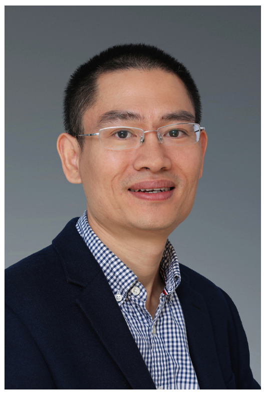


4-5-2. Brønsted acid-catalyzed asymmetric dearomatization of indolyl ynamides: Practical and enantio-selective synthesis of polycyclic indolines

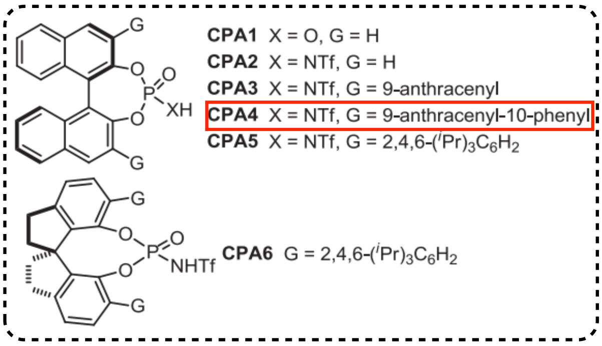


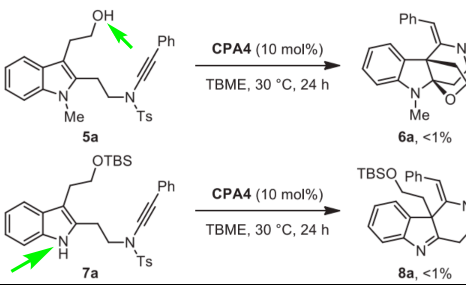
R^1 = alkyl, aryl, halogen, OMe, OBn
R^2 = H, Me

28 examples
up to 75% yield,
95:5 dr, 94% ee

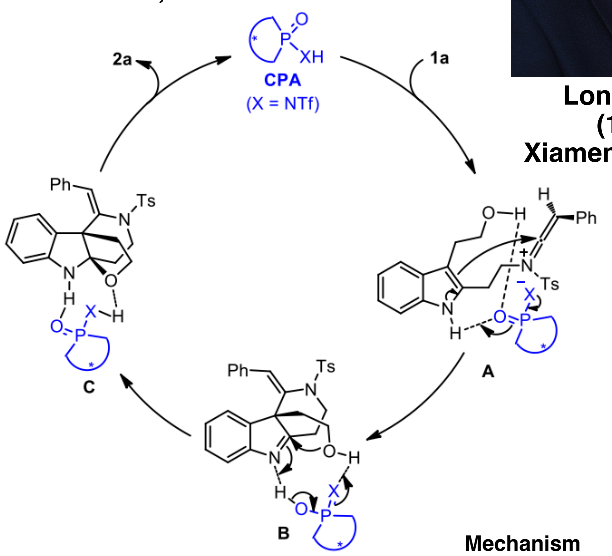


Long-Wu Ye
(1981-)
Xiamen University





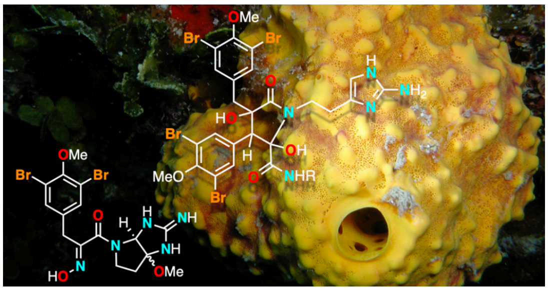
Control experiment



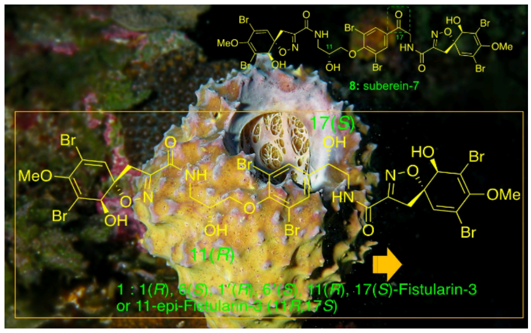
Mechanism

Reference
Huang, S.; Kötzner L.; De, C-K.; List, B. *J. Am. Chem. Soc.* **2015**, 137, 3446-3449.
Ye, L-W. *Chinese Chemical Letters.* **2023**. *34*, 107647.

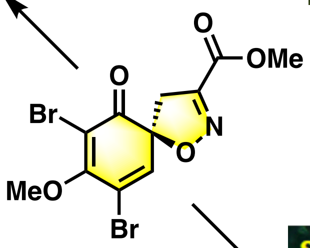
5. Asymmetric Synthesis of Spiroisoxazolines



Bromotyrosine alkaloid-
Aiolochroiamides

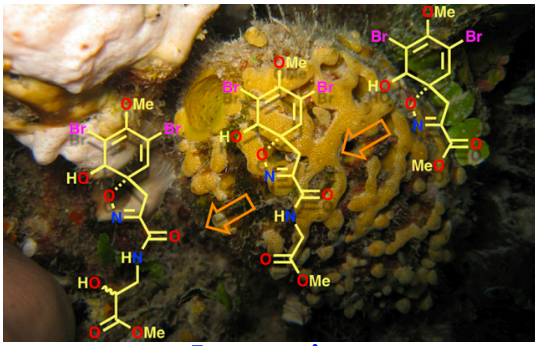


11-deoxyfistularin-3

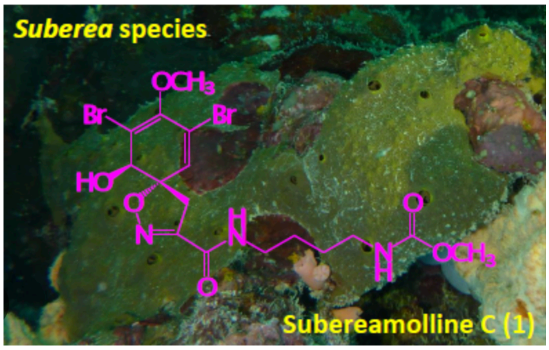


"Spiroisoxazoline"

Antibacterial, Antiviral,
Anticancer, Antitumor…



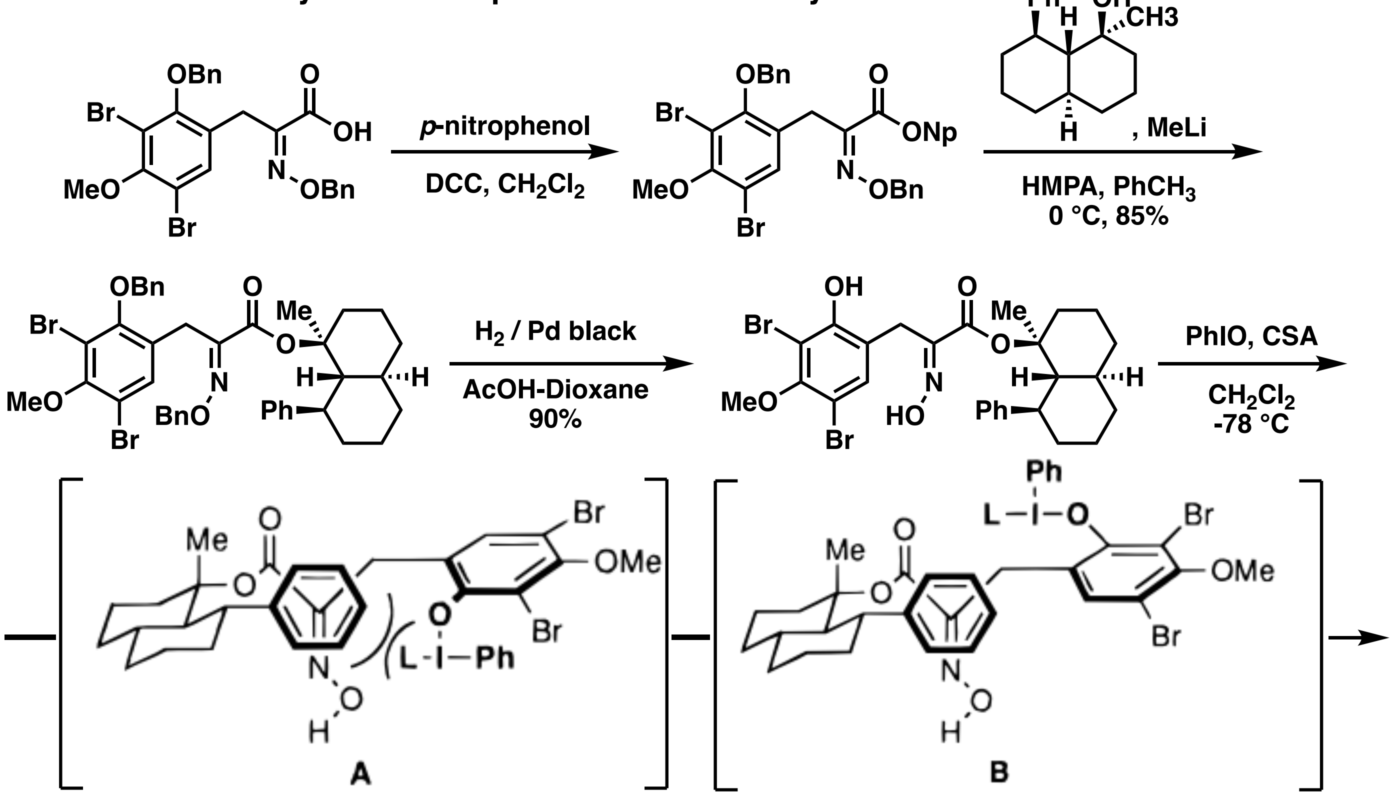
Lacunosins



Subereamolline C

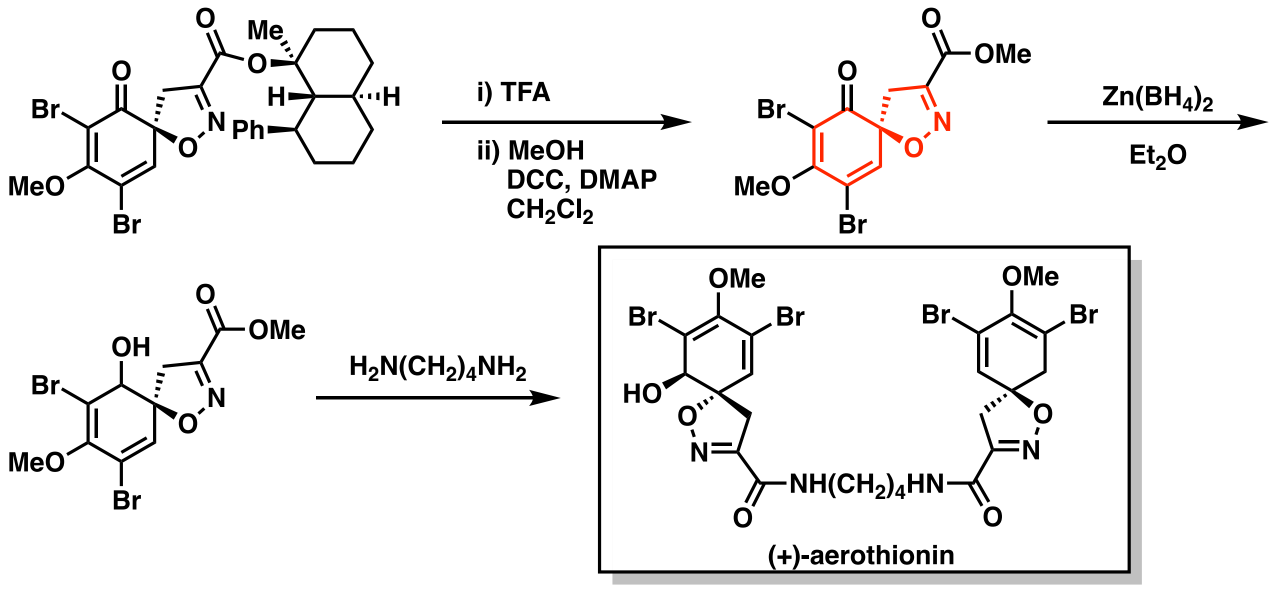
5-1. Synthesis of Spiroisoxazoline via Oxidative Cyclization

Asymmetric Oxidative Cyclization of *o*-Phenolic Oxime-Esters: First Synthesis of Enantiomerically Enriched Spiroisoxazoline Methyl Esters



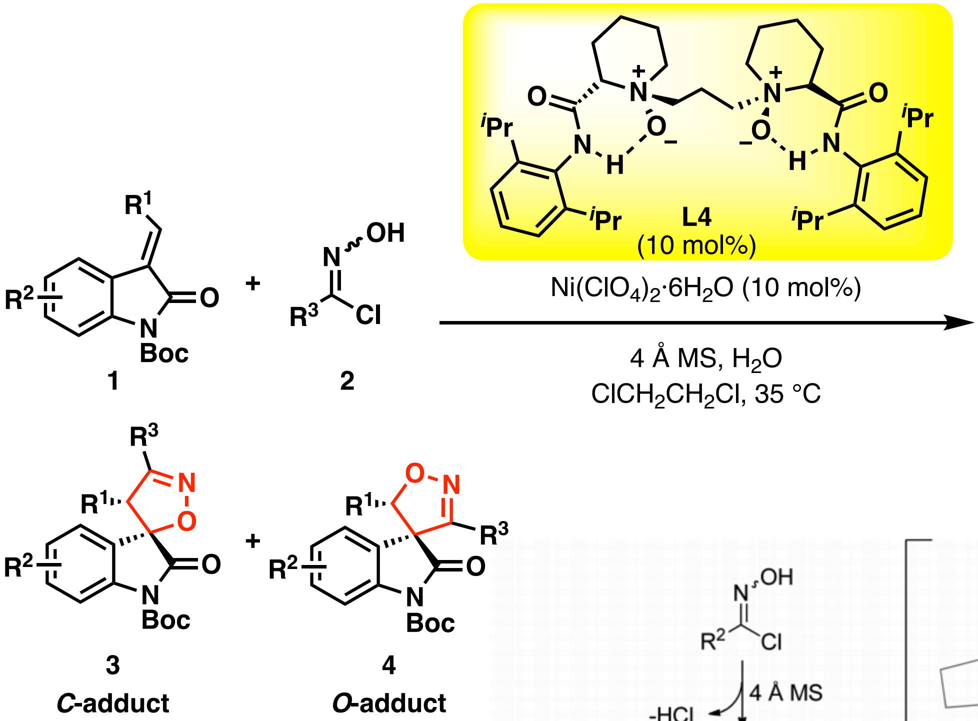
Reference
Das, P.; Valente, E-J.; Hamme II, A-T*. *Eur. J. Org. Chem.* **2014**, *13*, 2659-2663.
Murakata, M.; Tamura, M.; Hoshino, O*. *J. Org. Chem.* **1997**, *62*, 4428-4433.

5. Asymmetric Synthesis of Spiroisoxazolines



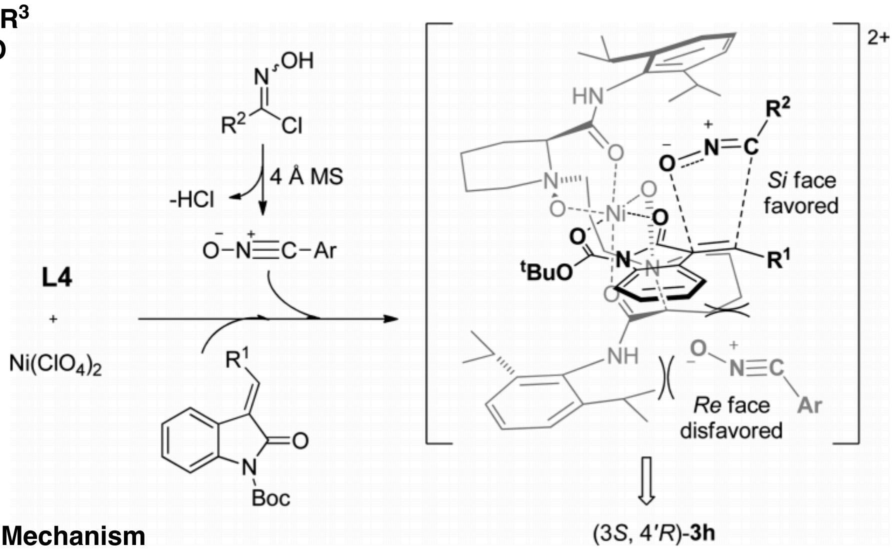
5-2. Synthesis of Spiroisoxazoline via 1,3-Dipolar Cycloaddition

Asymmetric Synthesis of Spiro[isoxazolin-3,3'-oxindoles] via the Catalytic 1,3-Dipolar Cycloaddition Reaction of Nitrile Oxides



27 examples
***C* : *O* = ≤99:1**
≤65% yield, ≤99% ee

Xiao-Ming Feng
(1963-)
Sichun University



Mechanism

Reference
Nishiyama, S.; Yamamura, S*. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3453-3456.
Lian, X-J.; Guo, S-S.; Wang, G.; Lin, L-L.; Liu, X-H.; Feng, X-M*. *J. Org. Chem.* **2014**, *79*, 7703-7710.