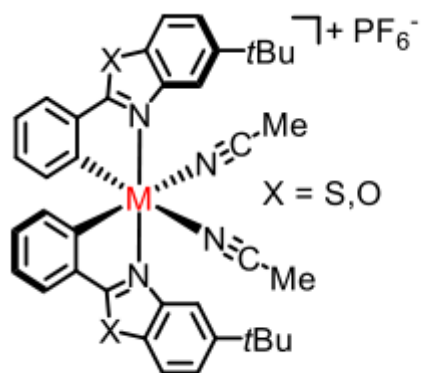
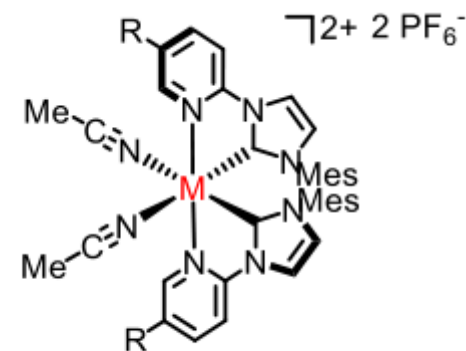
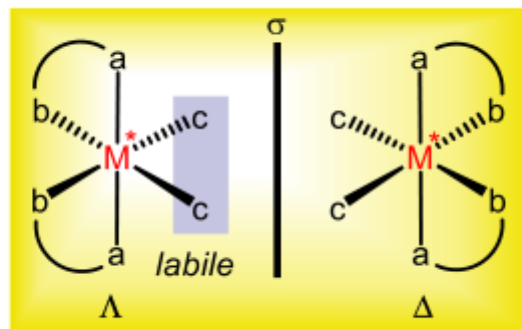


“Chiral-at-Metal” Transition Metal Catalysts



Rhodium & Iridium



Iron & Ruthenium

汇报人：张丹

时间：2023/7/14

Character introduction



Prof. Dr. Eric Leif Meggers

➤ 教育和研究经历

1995 波恩大学 学士学位

1995-1999 巴塞尔大学 博士学位 (Bernd Giese教授)

1999-2002 Scripps研究所 博士研究生 ([Peter G. Schultz](#)教授)

2002-2007 宾夕法尼亚大学 助理教授

2007-至今 德国马尔堡大学 教授

2011-至今 厦门大学 教授

➤ 研究方向

- 手性金属催化剂设计
- 铁的可持续催化
- 立体控制有机光化学
- 立体控制电化学
- 对映选择性氮烯化学



Contents

□ 01 Background

□ 02 “Chiral-at-metal” catalysts

✓ Ir-catalyzed reactions

✓ Rh-catalyzed reactions

✓ Ru-catalyzed reactions

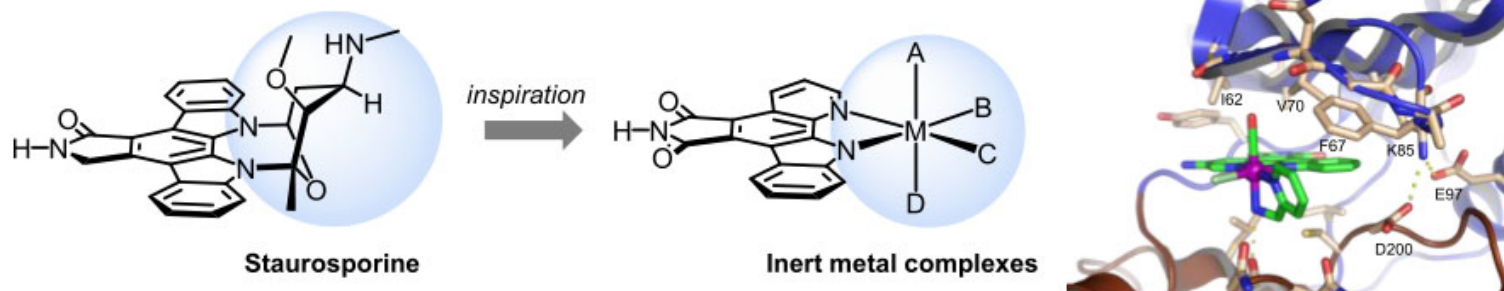
✓ Fe-catalyzed reactions

□ 03 proposal

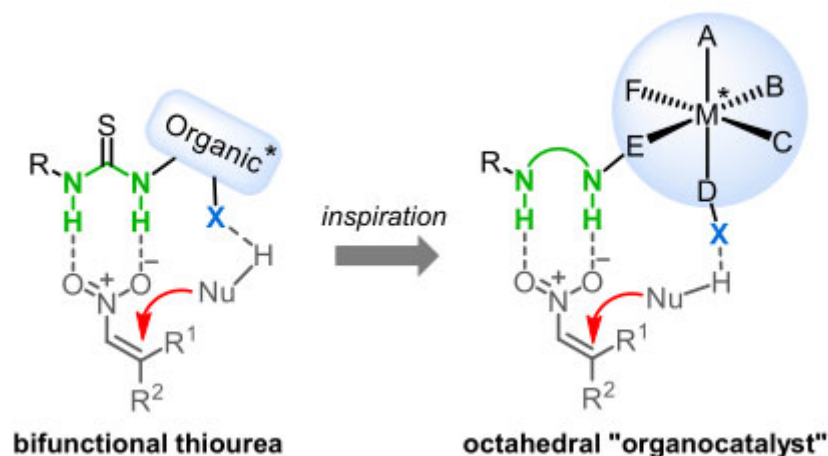


01 The research content of this group

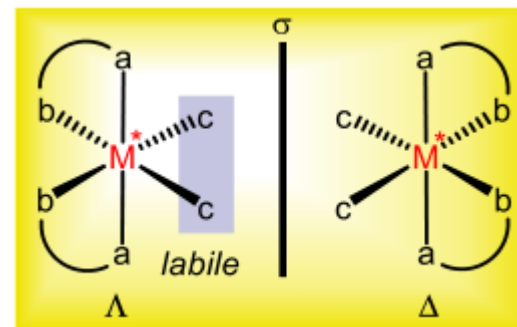
- ❑ Other Previous Projects: Biased towards biochemistry.
(PhD research and postdoctoral research)
- ❑ Inert Metal Complexes as Enzyme Inhibitors



- ❑ Metal-Templated Asymmetric Organocatalysis



- ❑ "Chiral-at-Metal" Transition Metal Catalysts



Stereogenic Metal Center & Achiral Ligands

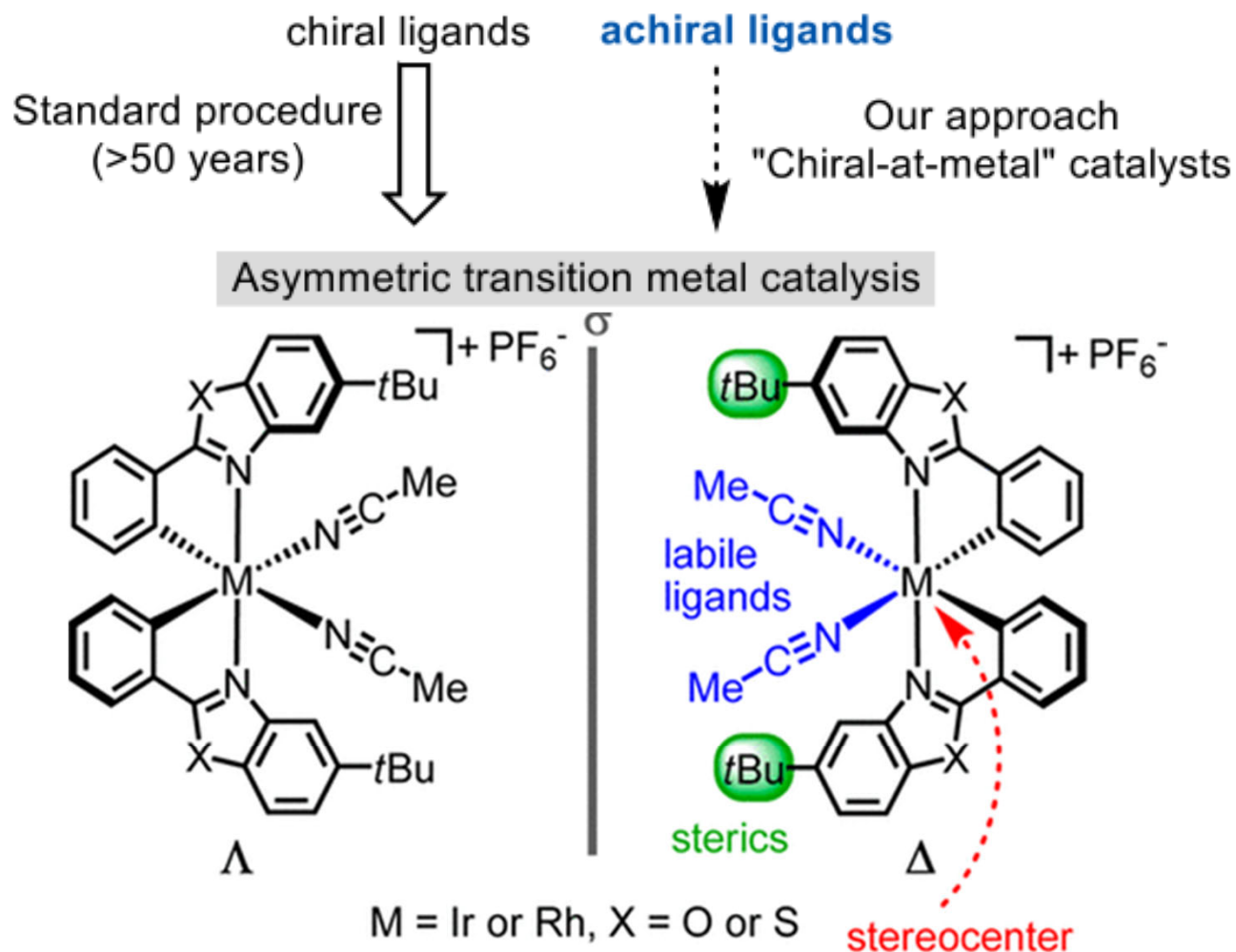


Part 01

Background



01 Background

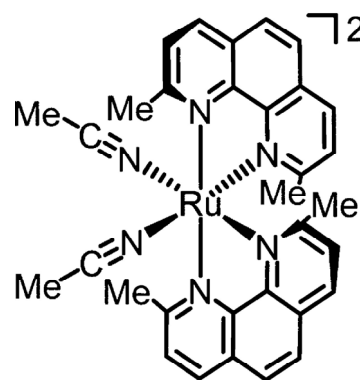


Features:

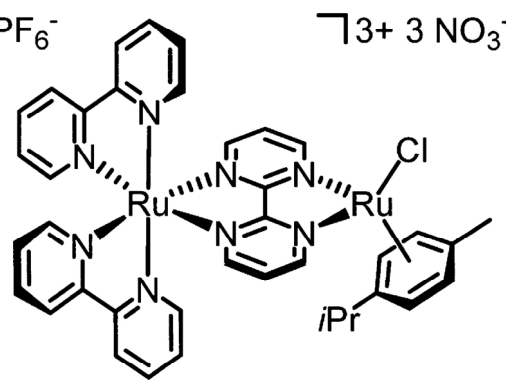
- Exclusive metal-centered chirality (structural function)
- Activation by metal coordination (catalytic function)
- Optional activation by visible light (photoredox function)

03 Background

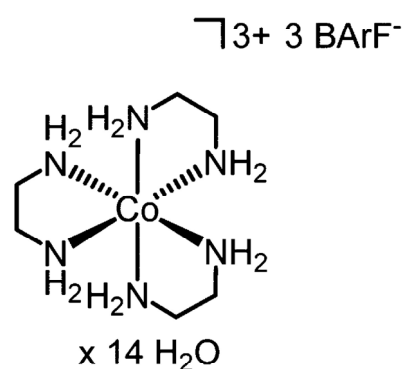
Previous work on octahedral chiral-at-metal catalysts with exclusively achiral ligands.



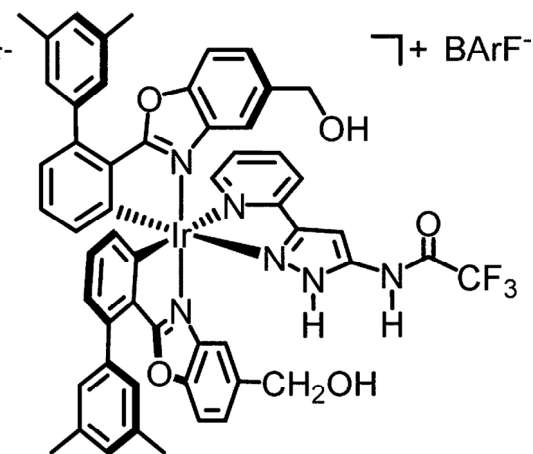
Fontecave (2003)
Oxidation of sulfides
18% ee (2 mol% cat)



Fontecave (2007)
Transfer hydrogenation
26% ee (0.5 mol% cat)



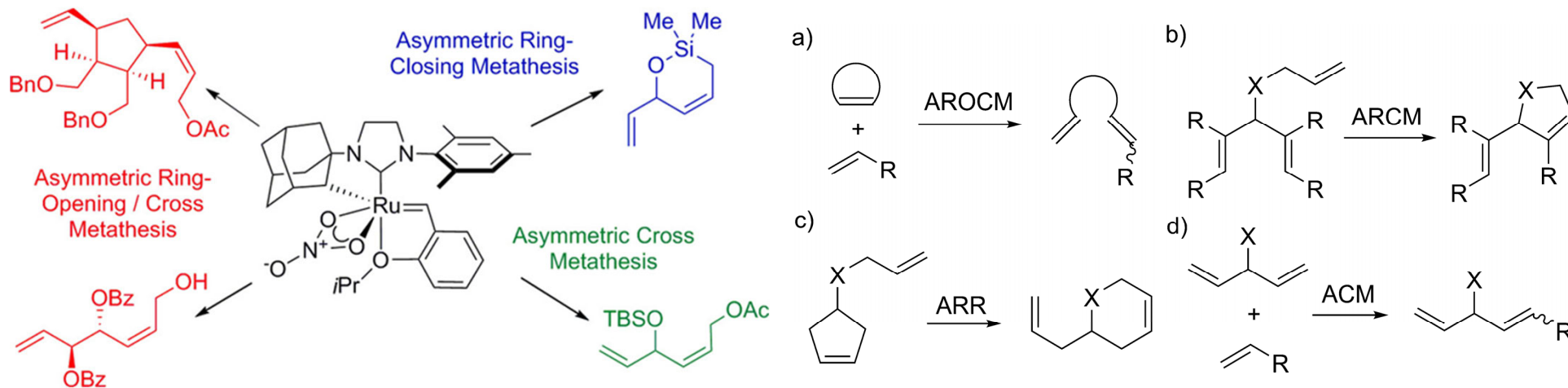
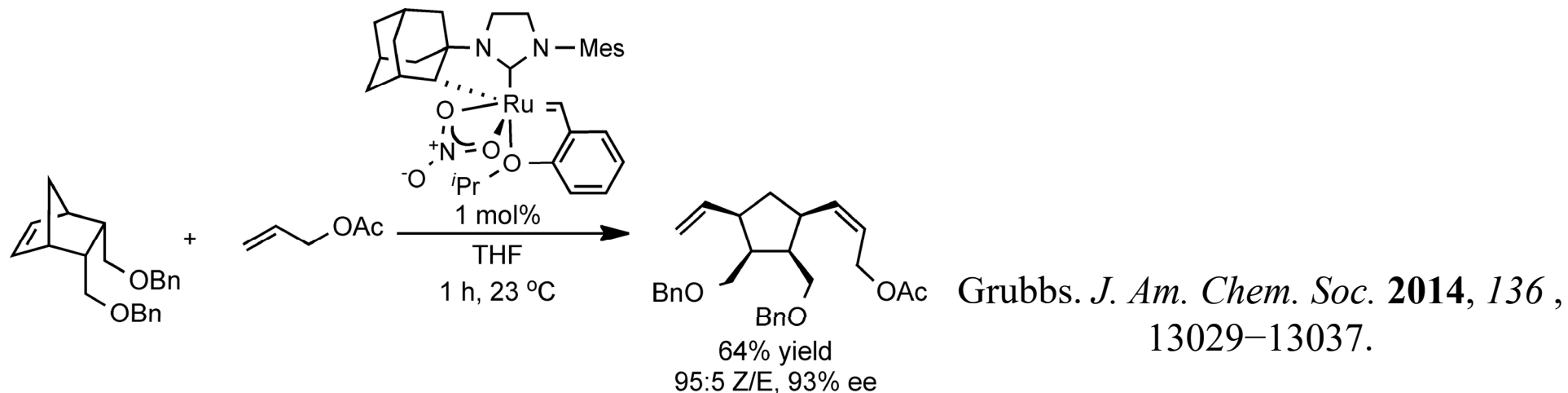
Gladysz (2008)
Michael addition
33% ee (9 mol% cat)



Meggers & Gong (2013)
Transfer hydrogenation
94% ee (0.1 mol% cat)

01 Background

Previous work on octahedral chiral-at-metal catalysts with exclusively achiral ligands.

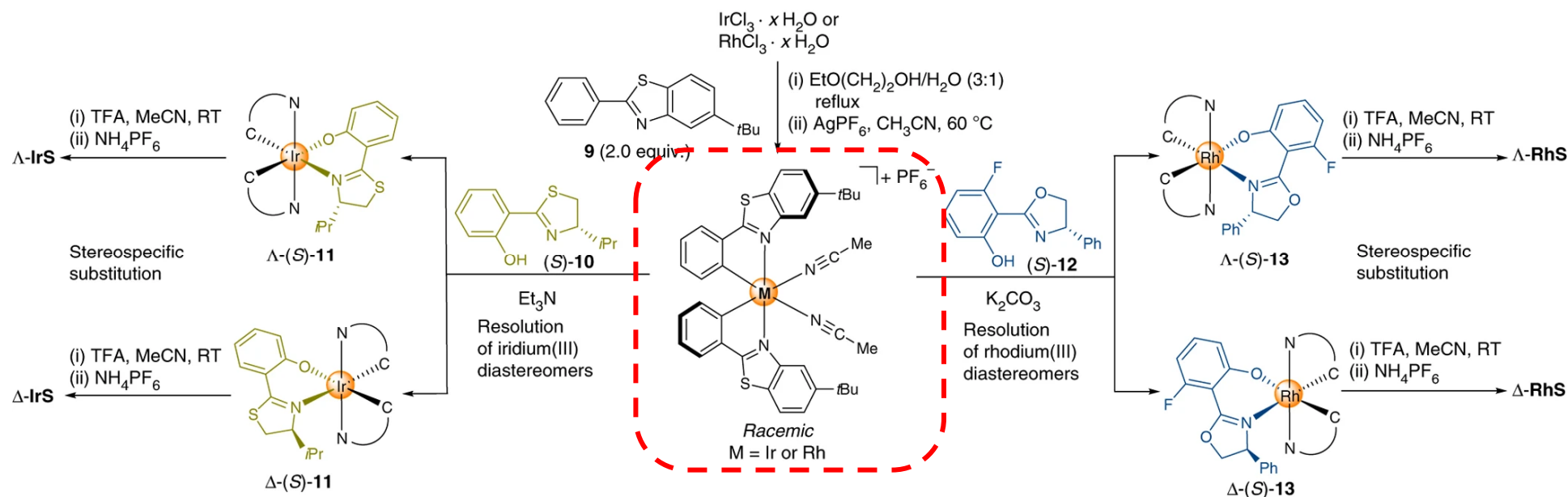
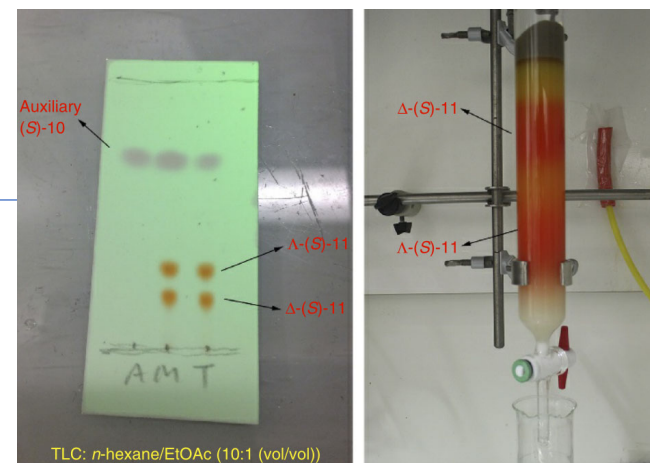


Grubbs. *J. Am. Chem. Soc.* **2013**, *135*, 28, 10183-10185.

01 Background

Challenges

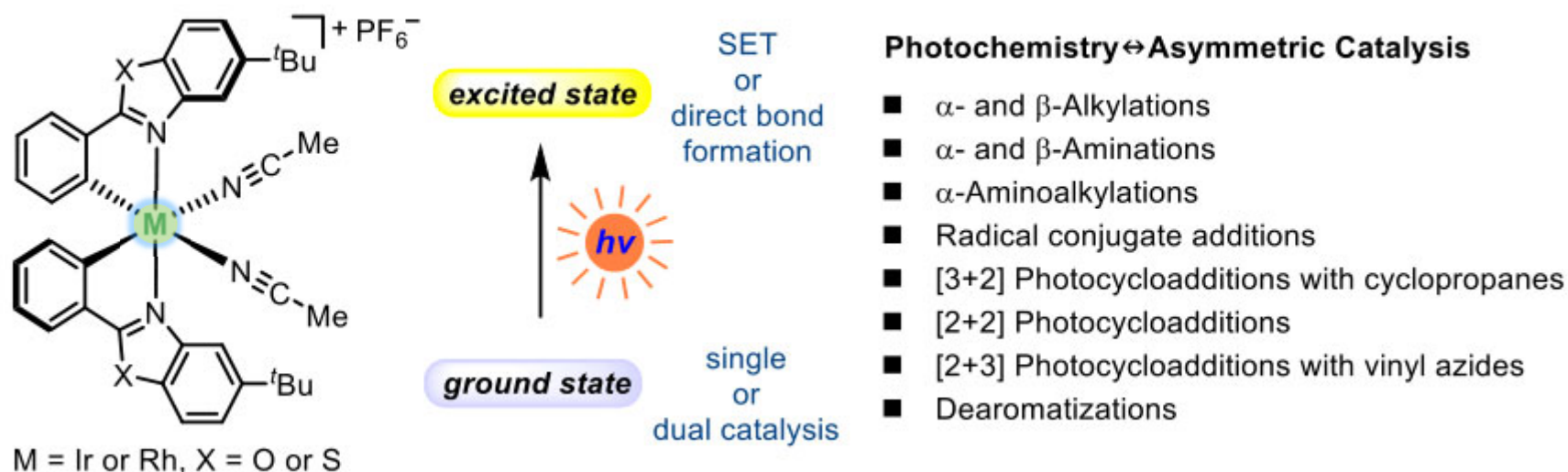
- ✓ 简便的合成方法
- ✓ 合适的金属络合物骨架，必须在结构上完全惰性才能保留中心金属的手性信息
- ✓ 除了产生空位的不稳定配体外，这些配体还用于试剂底物的催化活化



Ma, J. J. *Am. Nat. Protoc.* **2018**, *13*, 605–632.

01 Background

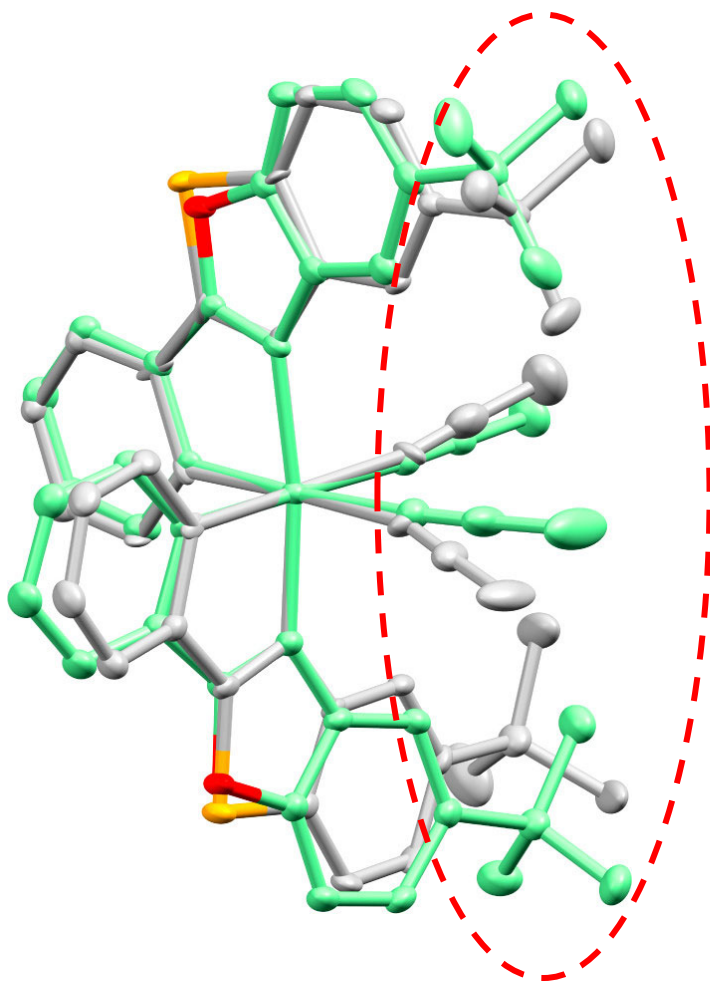
(1) Asymmetric photocatalysis: Bis-cyclometalated iridium(III) or rhodium(III) complexes. 将光活化与不对称催化相结合



Advantages

- ✓ 通过柱层析即可以高收率获得两种非对映异构体
- ✓ 具备合适的金属络合物骨架（强 σ -供体苯基配体产生了强配体场和高配体活化能），在结构上完全惰性，保持催化剂的手性。仅使用非手性配体构建金属手性中心，避免可将光照射下导致金属络合物的快速外消旋化。
- ✓ 除了产生空位的不稳定配体外，这些配体还用于试剂底物的催化活化。

01 Background



Superimposed crystal structure

Δ -RhS (gray) Δ -RhO (green)

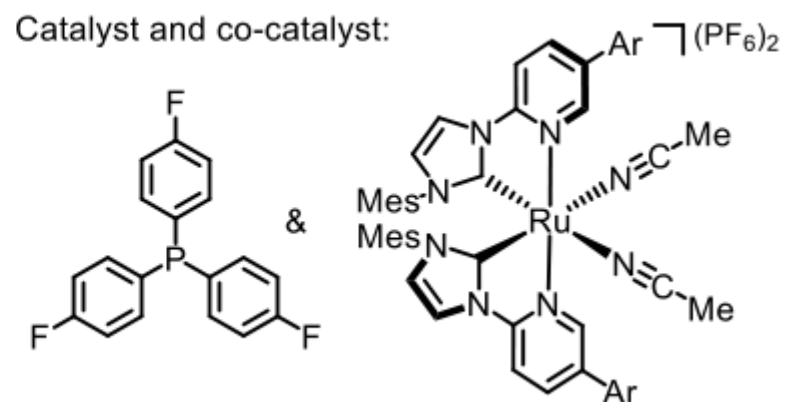
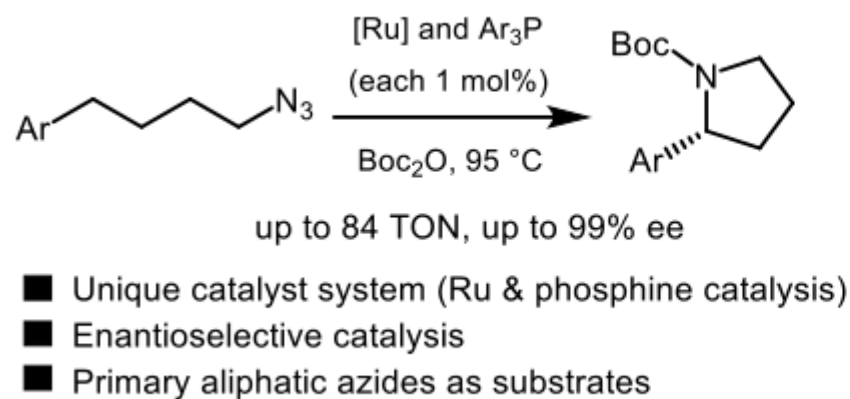
$$d(\text{C-S}) > d(\text{C-O})$$

- 位阻效应：苯并噻唑络合物比苯并噁唑络合物提供更高的立体选择性，是更优异的不对称催化剂

Ir cata.	Rh cata.
构型稳定性更高，允许高温反应（70-80°C）	配体交换动力学更快，允许低温反应
催化剂坚固 许多反应，无需严格排除空气与水分	

01 Background

(2) Asymmetric Nitrene-Mediated C-H Aminations and Oxygenations: the chiral-at-metal ruthenium complexes & iron complexes





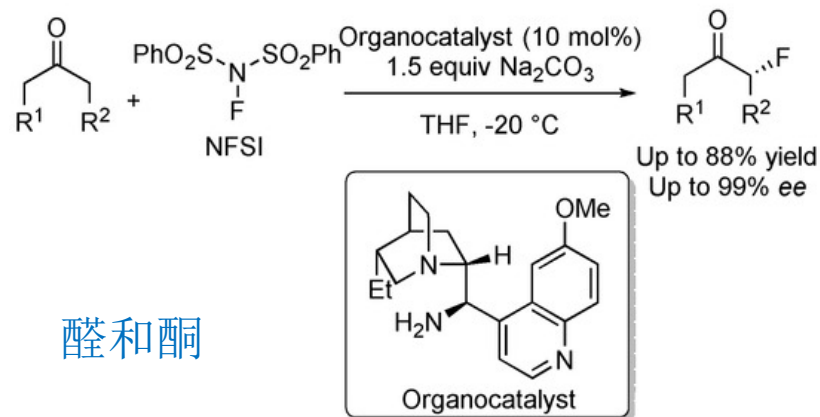
Part 02

“Chiral-at-metal” catalysts



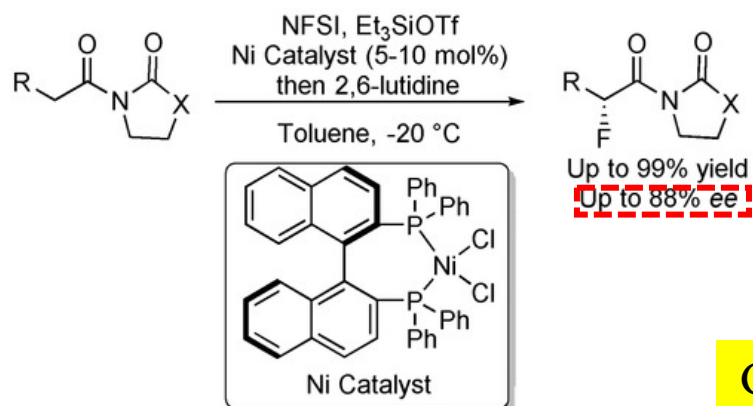
α -Fluorination Reaction

a) MacMillan^[14]: Enantioselective Organocatalytic α -Fluorination of Cyclic Ketones



局限：羰基 α 位无支链的高度活化的羰基化合物无法实现

b) Sodeoka^[11a]: Asymmetric Fluorination of α -Aryl Acetic Acid Derivatives



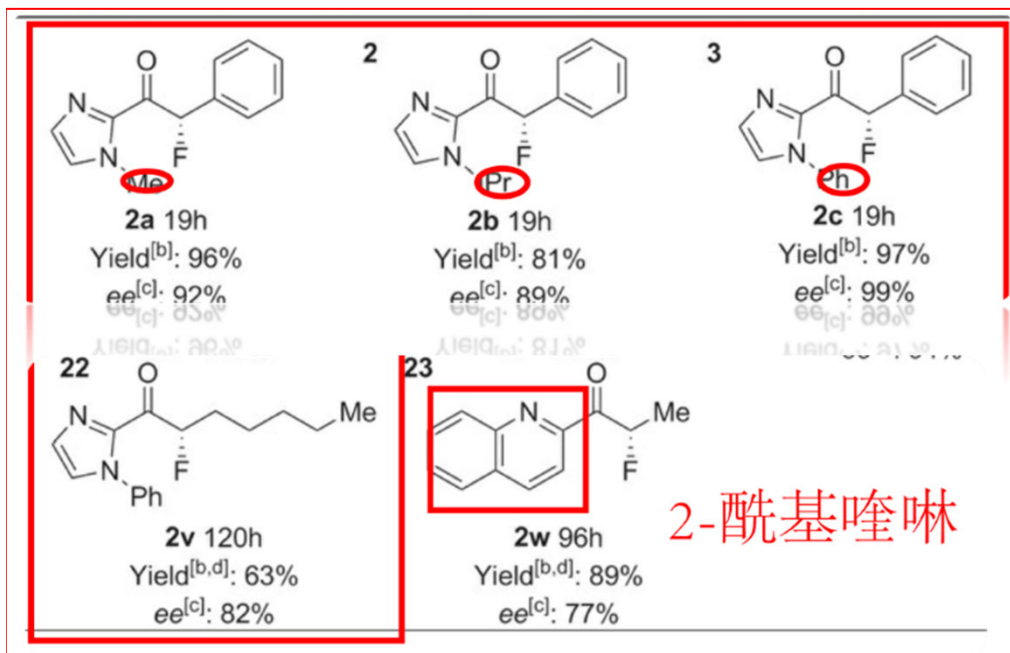
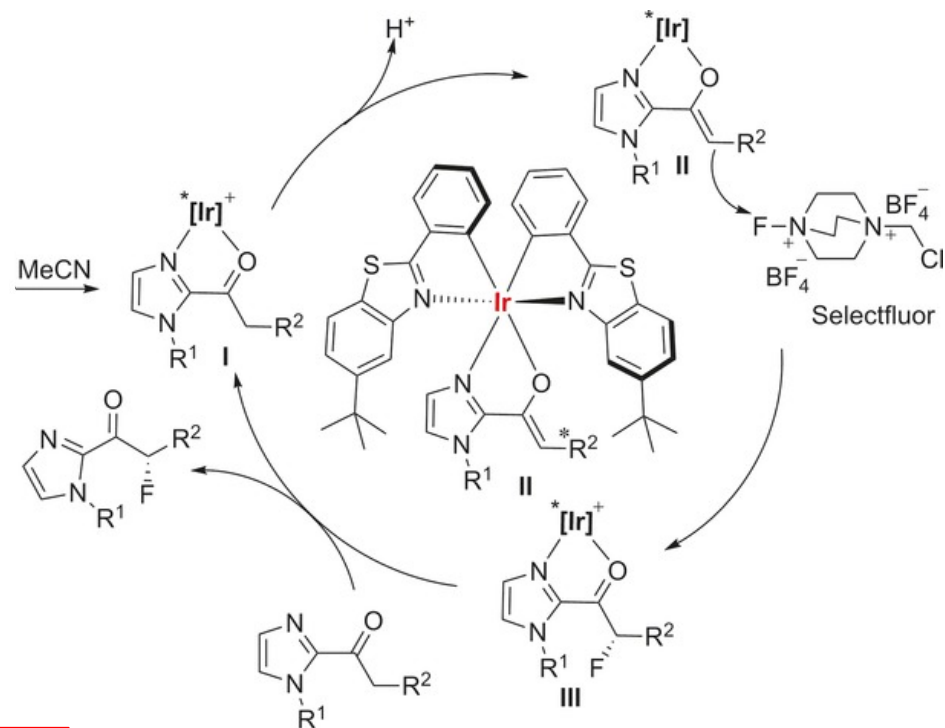
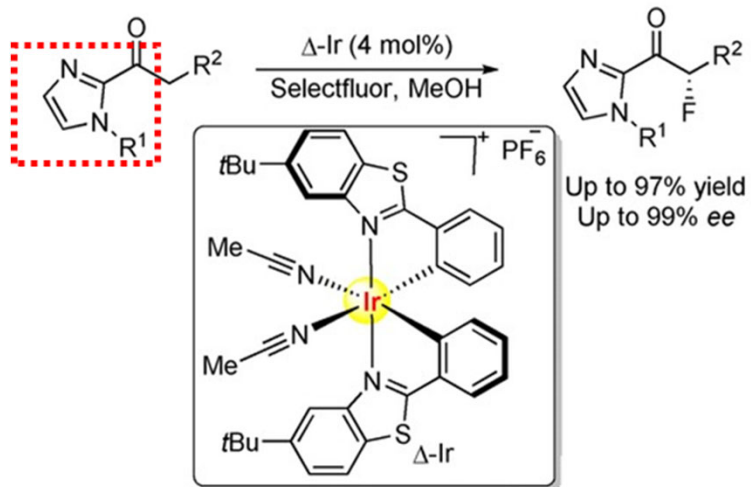
局限：相应的手性氟产物由于其烯醇化能力而容易外消旋，ee值不够理想

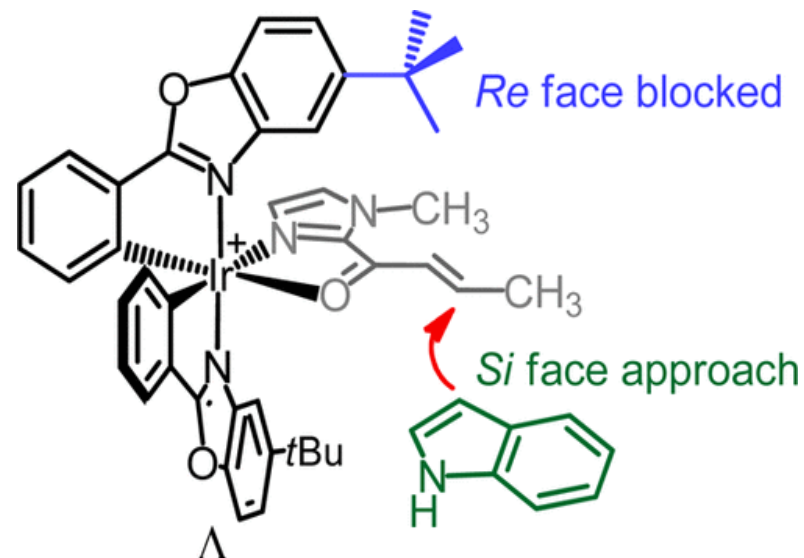
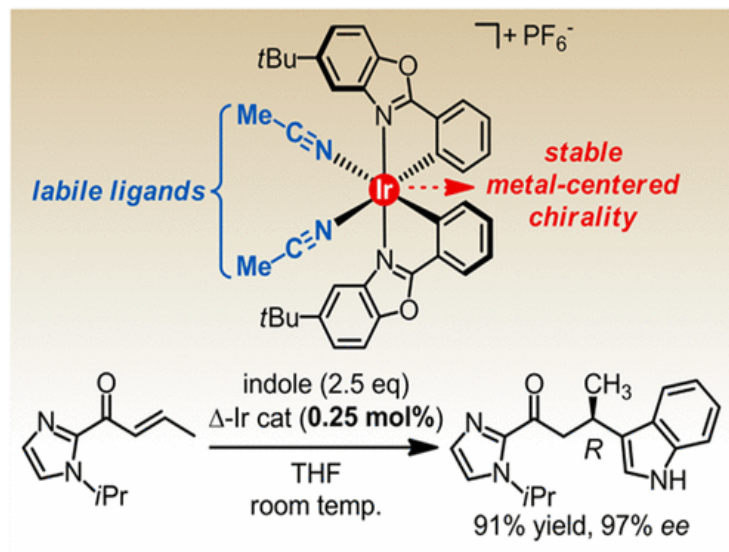
Guo-Qiang Xu. *Chem. Asian J.* 2016, 11, 3355 – 3358.

α -芳基乙酸衍生物（羰基 α 位无支链的高度活化的羰基化合物）

α -Fluorination Reaction

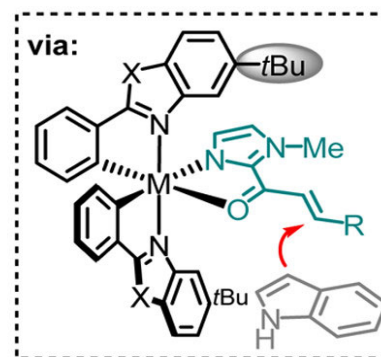
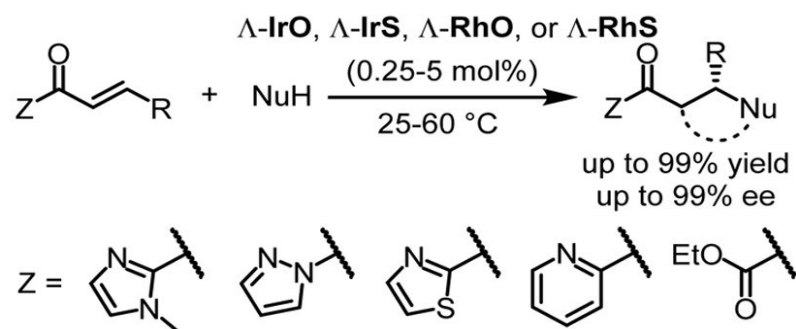
c) This work: Asymmetric Fluorination of 2-Acetic imidazole Derivatives



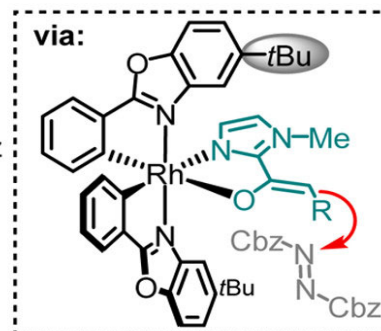
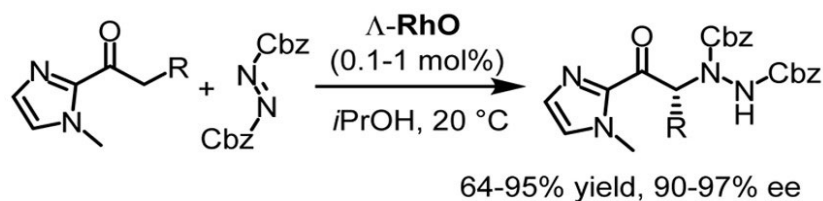


Haohua Huo. *J. Am. Chem. Soc.* **2014**, *136* (8), 2990-2993.

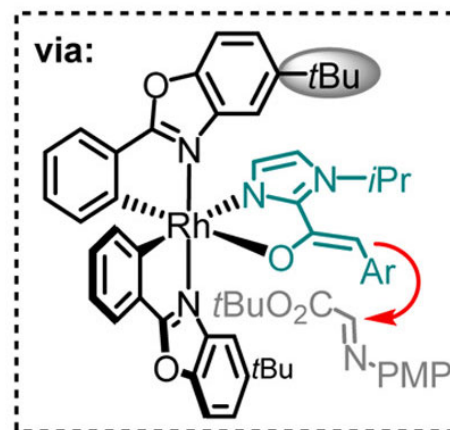
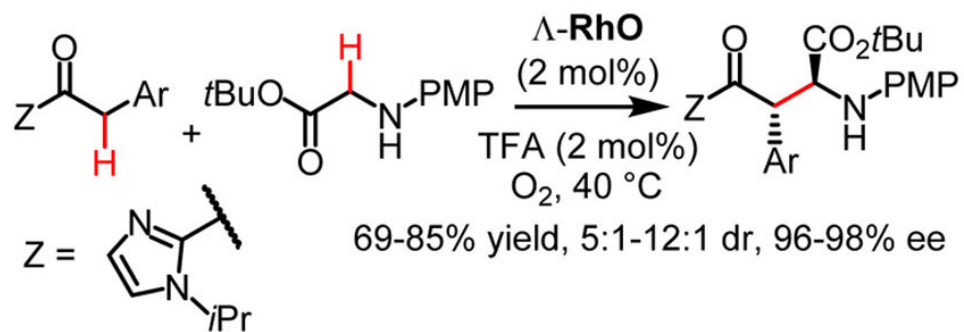
a) **Asymmetric Friedel-Crafts reactions, Michael additions, cycloadditions**



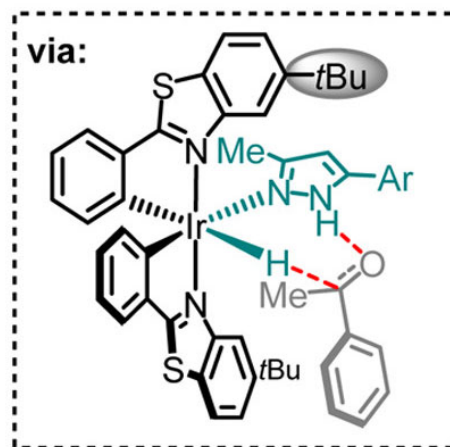
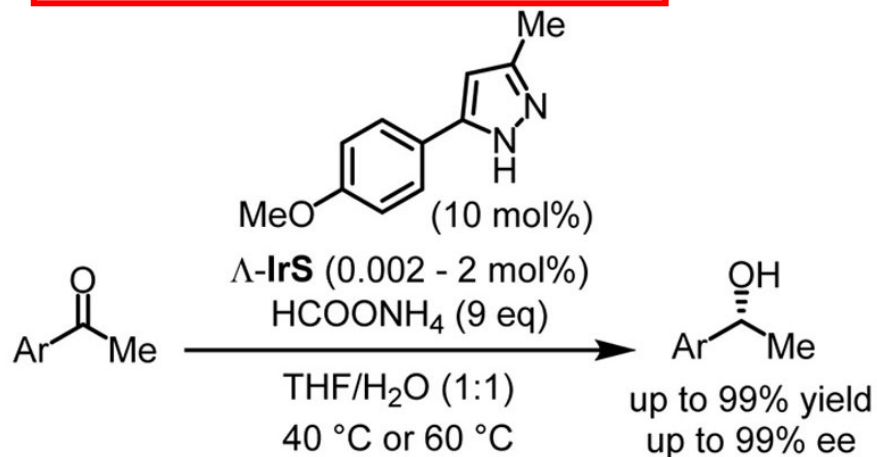
b) **Enantioselective α -amination**

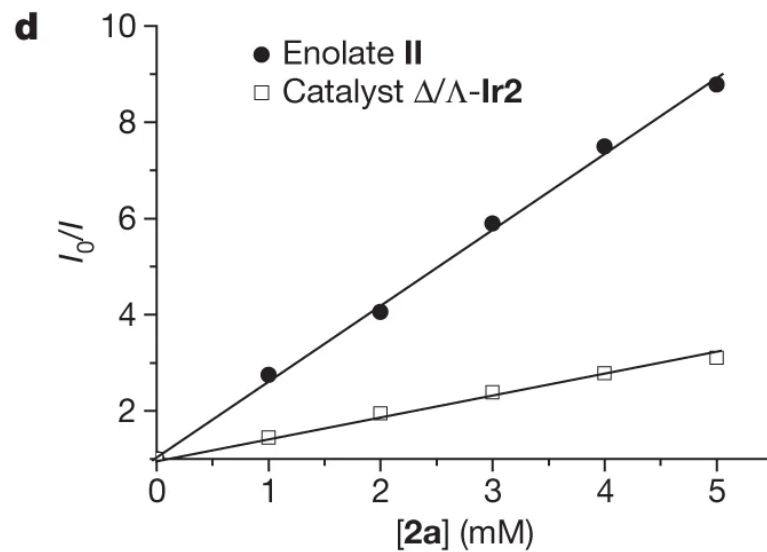
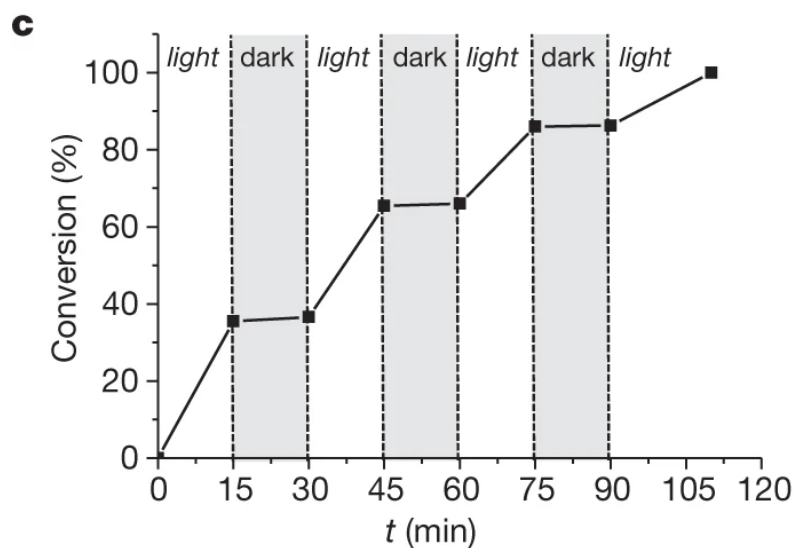
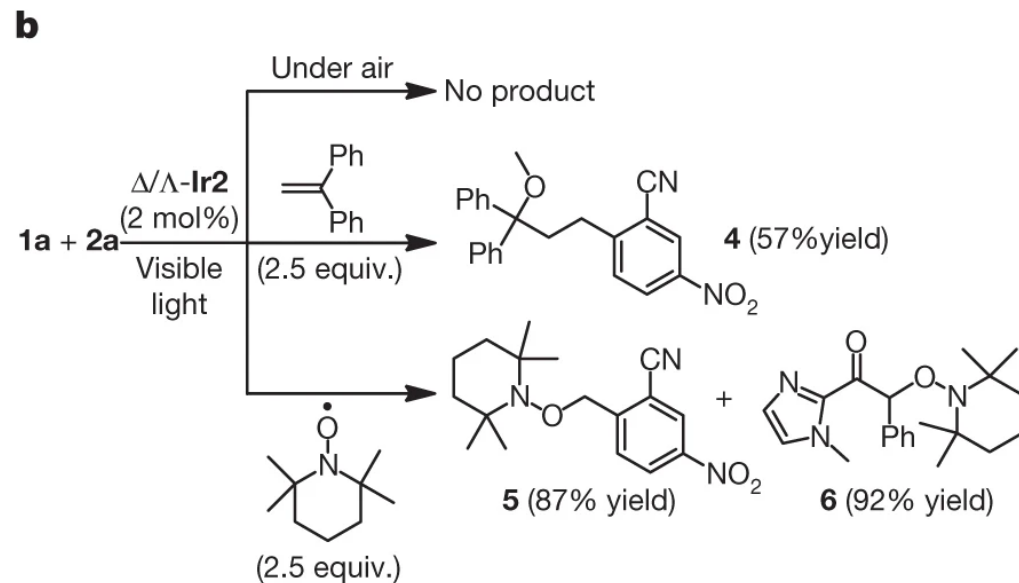
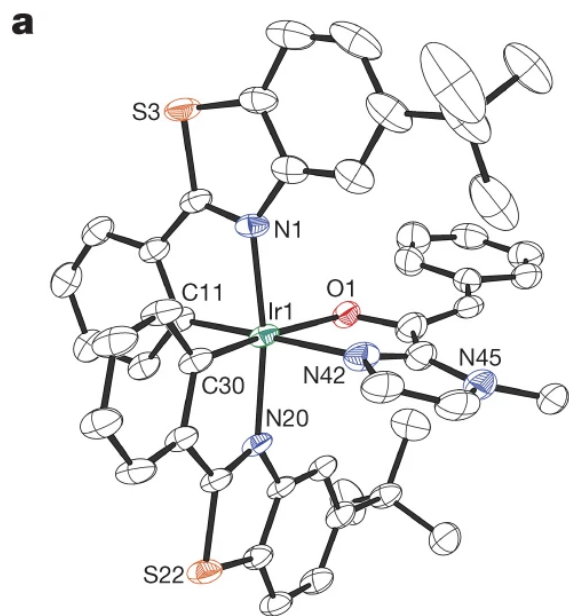


c) **Asymmetric cross-dehydrogenative coupling**



d) **Asymmetric transfer hydrogenation**

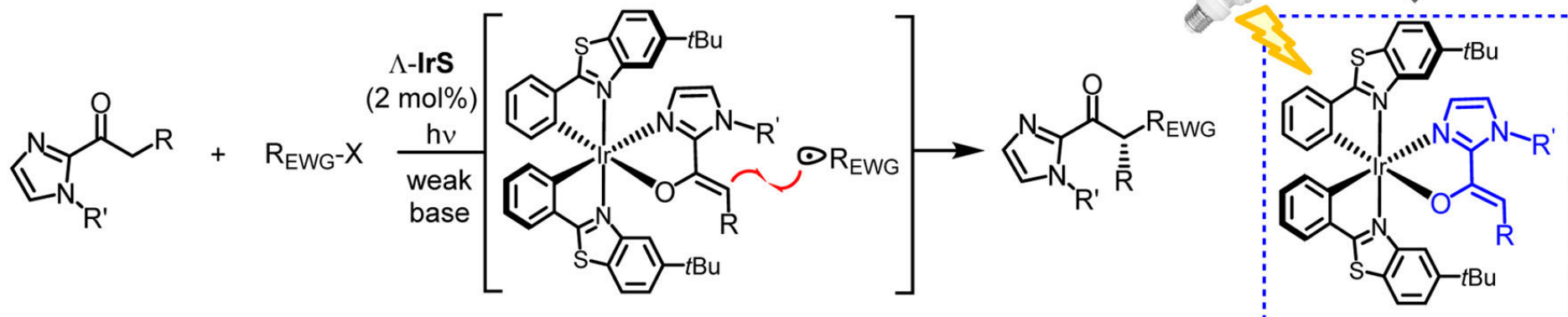




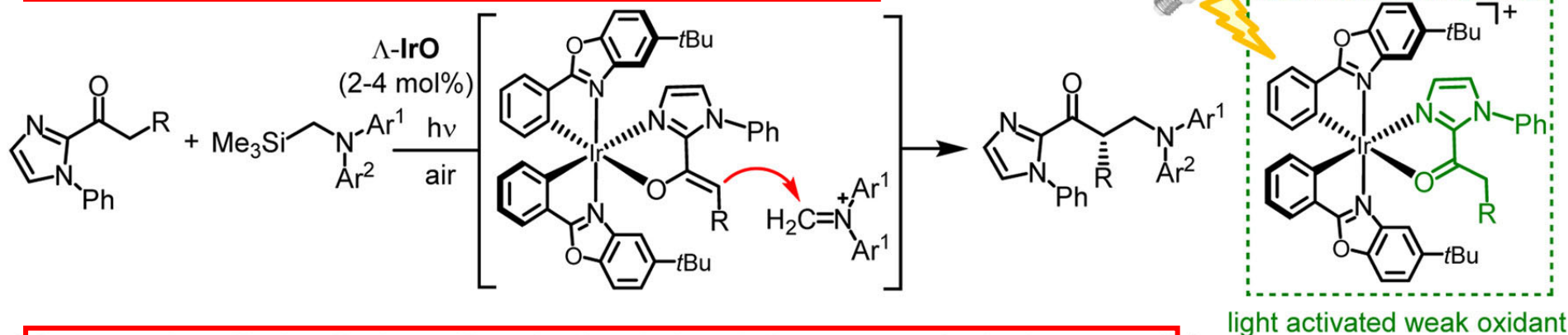
e

Complex	Absorbance λ_{\max}	Emission λ_{\max} (E^{00})	$E_{1/2}(\text{PS}^+/\text{PS})$	$E_{1/2}(\text{PS}^+/\text{PS}^*)$
Δ/Λ -Ir2	425 nm	560 nm (2.21 eV)	> +1.5 V	> -0.71 V
Enolate II	440 nm	550 nm (2.25 eV)	+0.51 V	-1.74 V

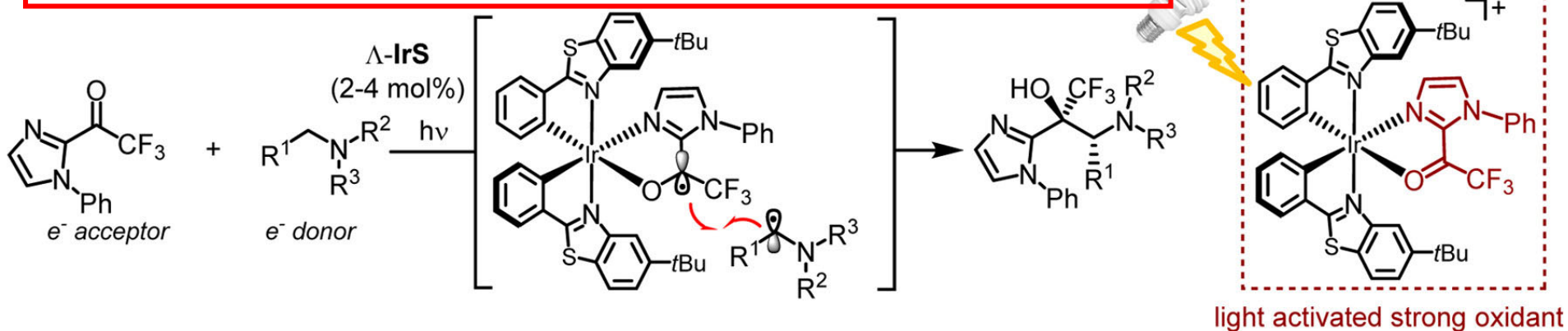
a) Enantioselective alkylation via photoreductive activation (redox neutral)



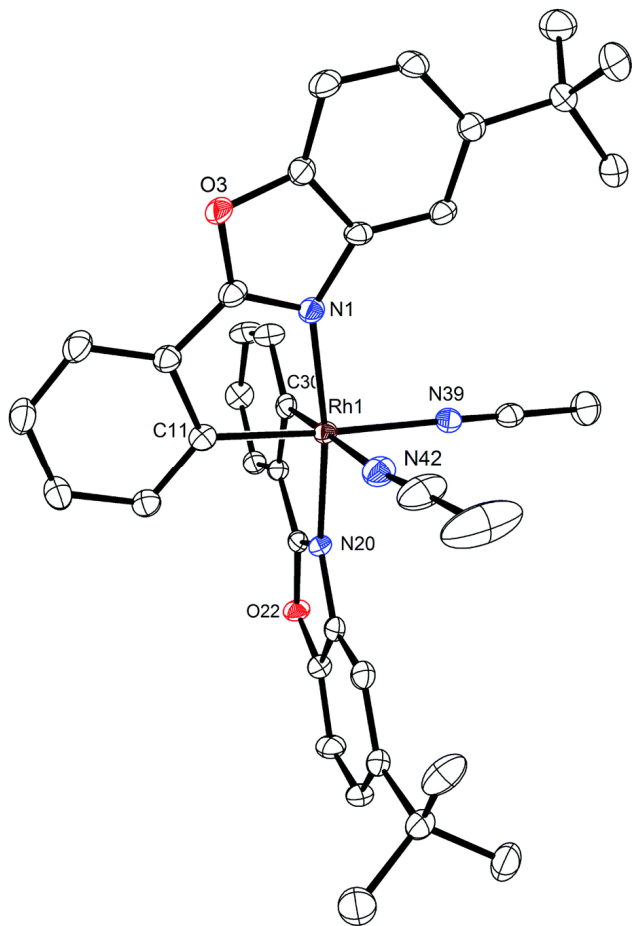
b) Enantioselective α-aminoalkylation via photoinduced oxidation



c) Asymmetric radical-radical coupling via photoinduced electron transfer (redox neutral)



02 Rh-catalyzed reactions



Crystal structure of the propeller-shaped catalyst Δ -**Rh**.

镧系元素收缩

39 钇	40 锆	41 铌	42 钼	43 锝	44 钌	45 铑
Y	Zr	Nb	Mo	Tc	Ru	Rh
88.906	91.22	92.9064	95.94	99	101.07	102.906
71 镧	72 铪	73 钽	74 钨	75 铼	76 锇	77 铱
Lu	Hf	Ta	W	Re	Os	Ir
174.96	178.4	180.947	183.8	186.207	190.2	192.2

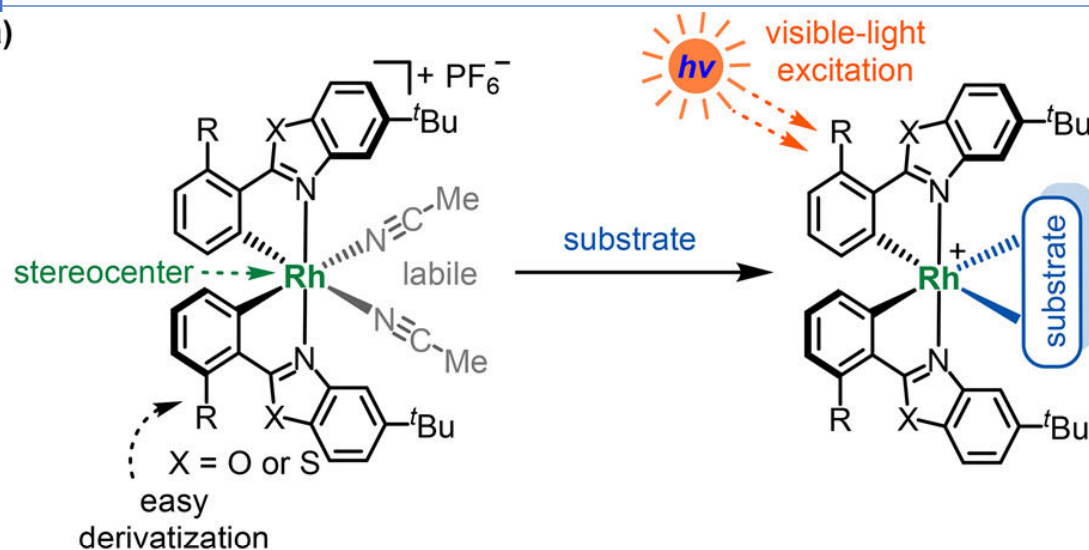
Δ -Rh、 Δ -Ir: 几乎相同的结构

铑催化剂优于铱催化剂

更快的配体交换动力学，允许更高的周转频率和周转数

02 Rh-catalyzed reactions

a)



■ Ground state

Activation of substrate towards redox & radical chemistry

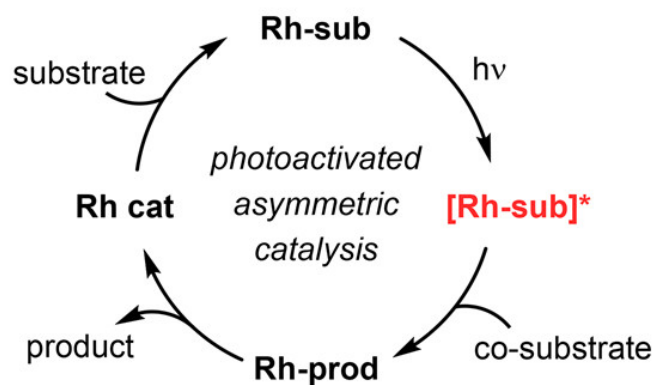
■ Primary photochemistry

[Rh-sub]* as intermediate in asymmetric catalysis cycle

■ Secondary photochemistry

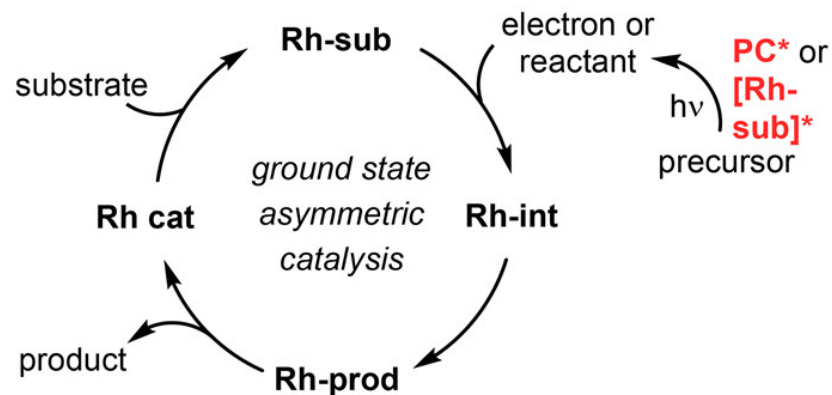
- i) **[Rh-sub]*** induces chain process or generates reactant
- ii) Dual catalysis with add. photocat

b) PRIMARY ASYMMETRIC PHOTOCATALYSIS



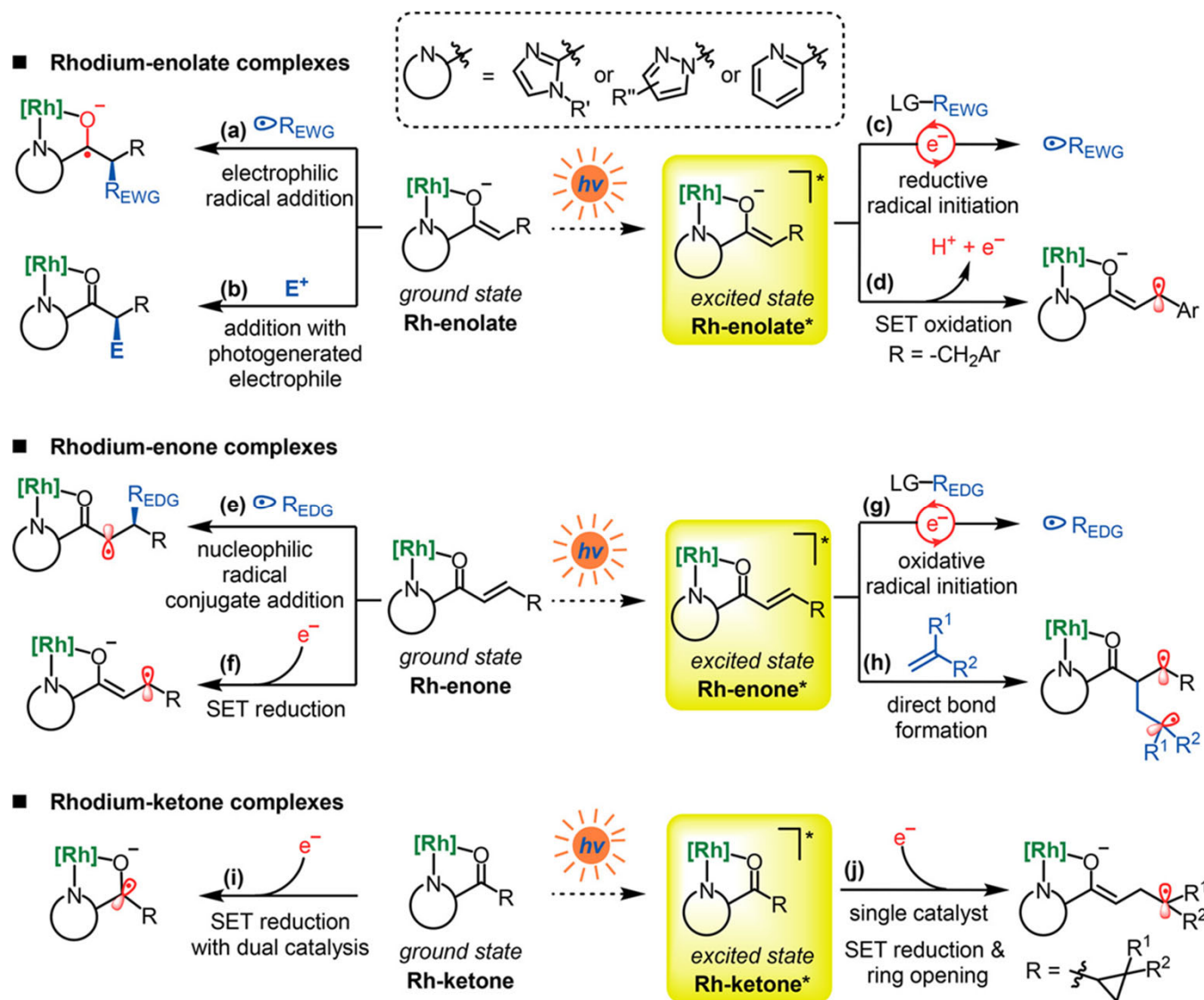
直接从光激发态形成立体控制键

SECONDARY ASYMMETRIC PHOTOCATALYSIS



不对称光氧化还原过程

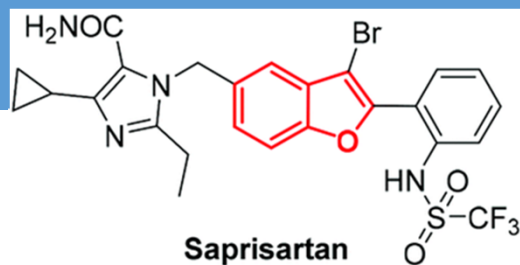
02 Rh-catalyzed reactions



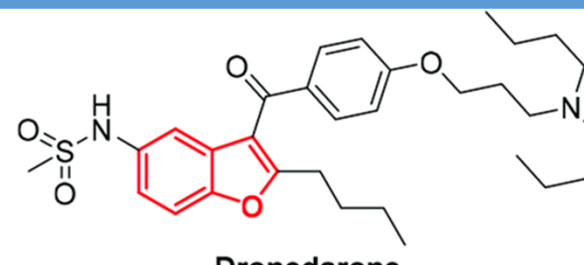
Summary of the multiple reaction modes of the intermediate bis-cyclometalated rhodium-substrate complexes.

Ground state

Michael加成

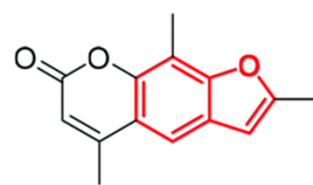


Used in the treatment of hypertension and heart failure

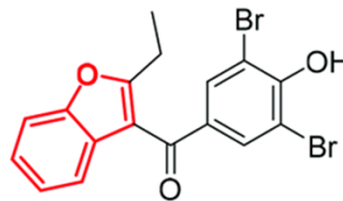


Antiarrhythmic agent

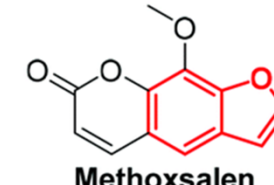
E型模式



Increase skin tolerance to sunlight and enhance pigmentation



Used in the treatment of gout

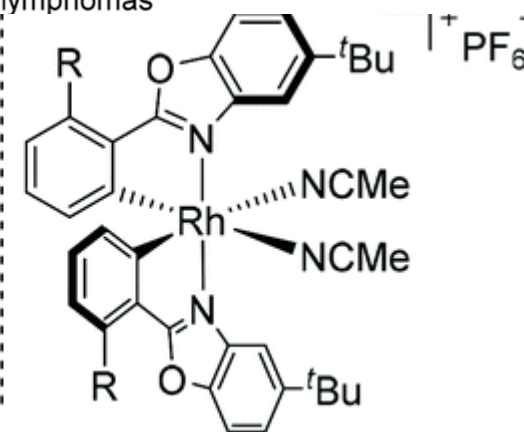


Used in the treatment of psoriasis, eczema, vitiligo and cutaneous lymphomas

c) This work

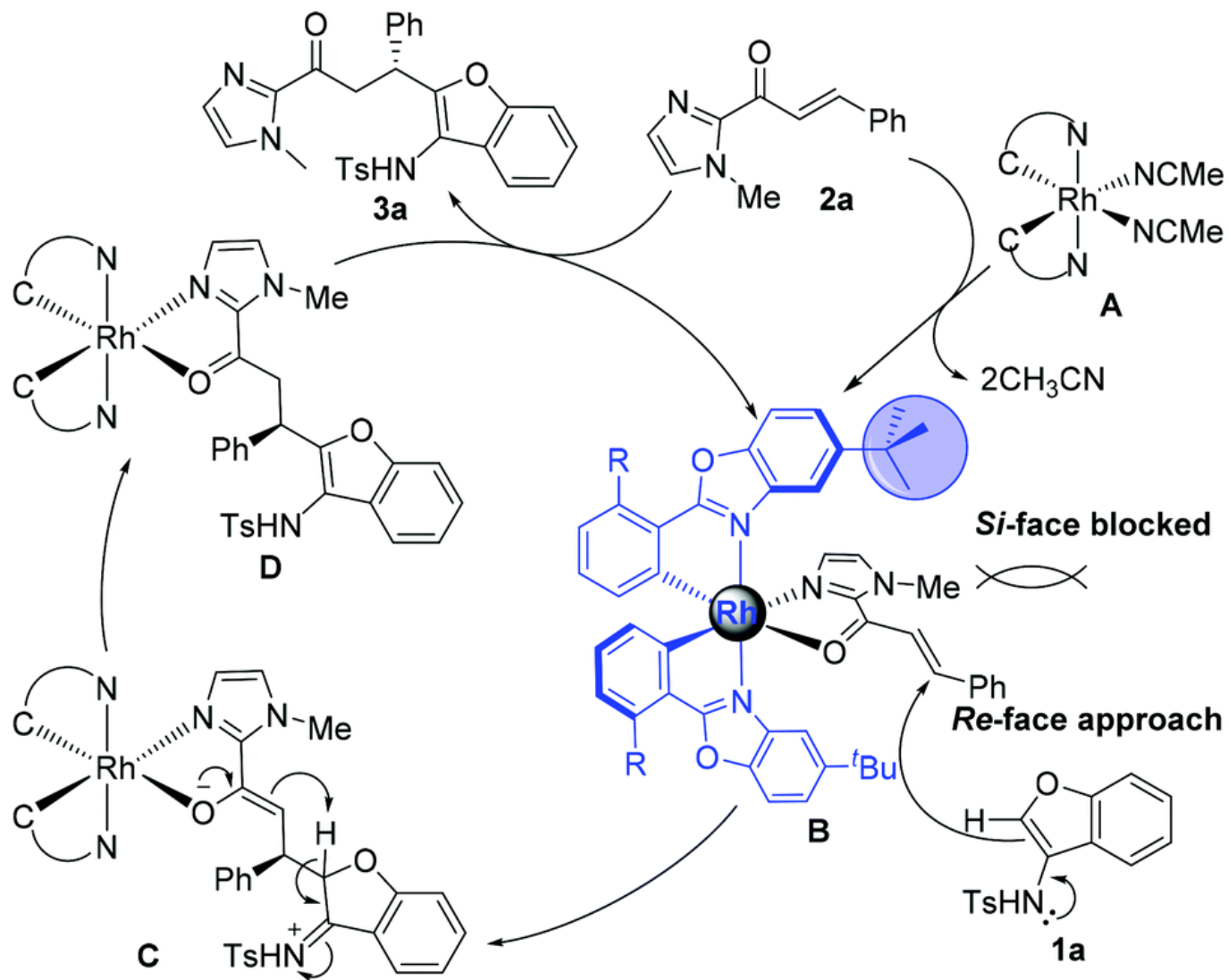


- low catalyst loading
- high enantioselectivity



Haoran Zhang. *Org. Chem. Front.* **2019**, 6, 3683–3687.

Mechanism

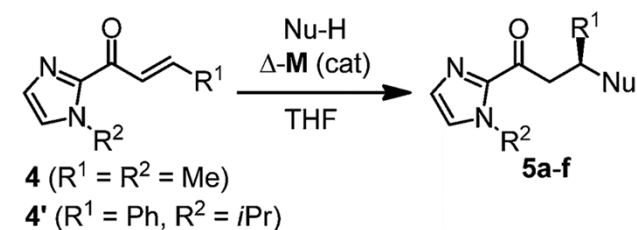


β -二羰基化合物的Michael加成

Rh催化剂 提供了较高的对映选择性

E型模式

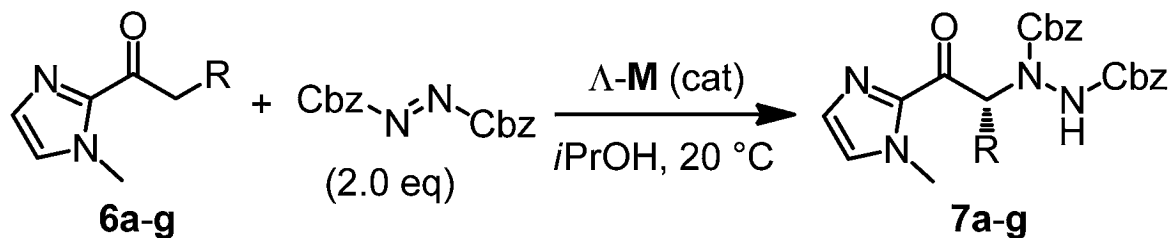
Entry	Nucleophile	Product	Catalyst ^b	T ^c (°C)	Yield (%)	ee ^{d,e} (%)
1			Δ -Ir (1.0)	Rt (20 h)	97	96
			Δ -Rh (1.0)	Rt (40 h)	94	95
2	NC-CH ₂ -CN		Δ -Ir (1.0)	Rt (16 h)	96	89
			Δ -Rh (1.0)	Rt (16 h)	96	92 ^f
3	NC-CH ₂ -CN		Δ -Ir (1.0)	Rt (96 h)	40	88
			Δ -Rh (1.0)	Rt (28 h)	91	95
4			Δ -Ir (1.0)	Rt (16 h)	99	68
			Δ -Rh (1.0)	Rt (16 h)	99	85
			None	Rt (16 h)	8.5	N.d. ^g
			Δ -Rh (1.0)	5 (16 h)	97	94
			Δ -Rh (2.0)	Rt (6 h)	96	95
5			Δ -Ir (1.0)	Rt (96 h)	41	97 (3 : 1 dr) ^h
			Δ -Rh (1.0)	Rt (48 h)	83	99 (4 : 1 dr)
6			Δ -Ir (1.0)	Rt (72 h)	89	97 (10 : 1 dr) ^h
			Δ -Rh (1.0)	Rt (20 h)	92	96 (14 : 1 dr)



Guo-Qiang Xu. *Chem. Sci.* **2015**, *6*, 1094–1100.

α -Aminations Reaction

A型模式



Entry	Starting Cpds	Product	Catalyst (mol%)	Time (h)	Yield ^b (%)	ee ^c (%)
1	R = Ph (6a)	(R)-7a	$\Lambda\text{-Ir}$ (2.0)	3	86	92 (>99.5)
			$\Lambda\text{-Rh}$ (0.2)	4	88	96 (>99.5)
			$\Lambda\text{-Rh}$ (0.1)	15	83	94 (>99.5)
			None	11	4	N.d. ^d
2	R = 2-MePh (6b)	(R)-7b	$\Lambda\text{-Ir}$ (2.0)	5	81	91 (>99.5)
			$\Lambda\text{-Rh}$ (0.2)	4	84	94 (>99.5)
3	R = 4-MeOPh (6c)	(R)-7c	$\Lambda\text{-Ir}$ (2.0)	4	87	95 (99)
			$\Lambda\text{-Rh}$ (0.2)	6	85	97 (99)
4	R = 4-ClPh (6d)	(R)-7d	$\Lambda\text{-Ir}$ (2.0)	5	82	79 (84)
			$\Lambda\text{-Rh}$ (0.5)	8	83	95 (97)
5	R = 2-Naph (6e)	(R)-7e	$\Lambda\text{-Ir}$ (2.0)	4	83	90 (>99.5)
			$\Lambda\text{-Rh}$ (0.2)	6	86	96 (99)
6	R = 3-thienyl (6f)	(R)-7f	$\Lambda\text{-Ir}$ (2.0)	8	71	80 (94)
			$\Lambda\text{-Rh}$ (0.2)	12	64	90 (97)
7	R = Me (6g)	(R)-7g	$\Lambda\text{-Ir}$ (2.0)	16	85	91
			$\Lambda\text{-Rh}$ (1.0)	22	95	92

^a Reaction conditions: to **6a-g** (0.20 mmol) in anhydrous *i*PrOH (0.10 mL, 2.0 M) was added the catalyst, stirred at room temperature for 30 min, before dibenzyl azodicarboxylate (0.40 mmol) was added and the reaction was stirred for the indicated time at 20 °C. ^b Isolated yields.

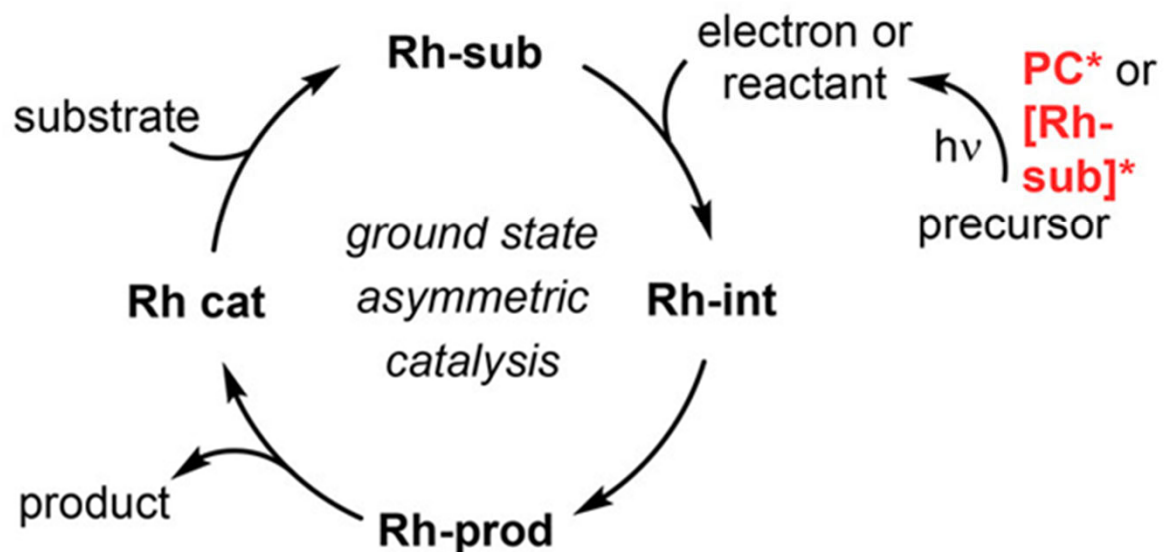
^c Enantiomeric excess determined by HPLC on chiral stationary phase. Enantiomeric purities after washing with Et₂O/*n*-hexane (1 : 4) are provided in brackets. ^d Not determined.

➤ 通过用Et₂O/正己烷（1:4）洗涤产物，可提高ee值，进而几乎完全实现对映纯度。

Secondary asymmetric photocatalysis

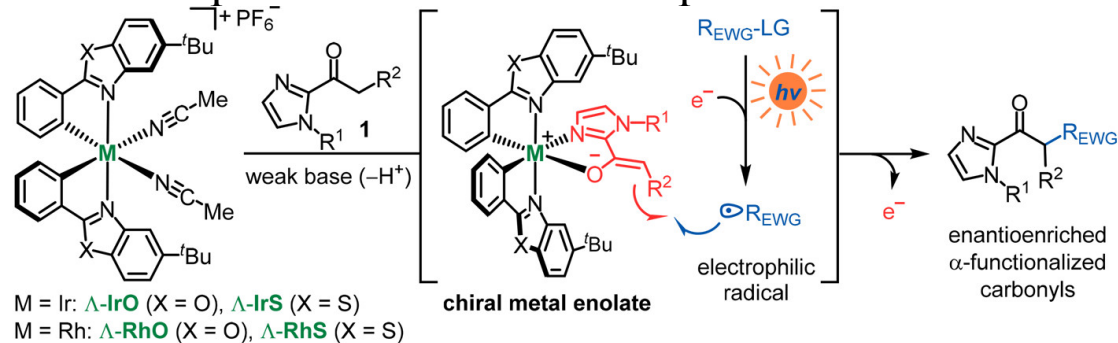
Rhodium–substrate complexes react with photogenerated reactive intermediates

SECONDARY ASYMMETRIC PHOTOCATALYSIS

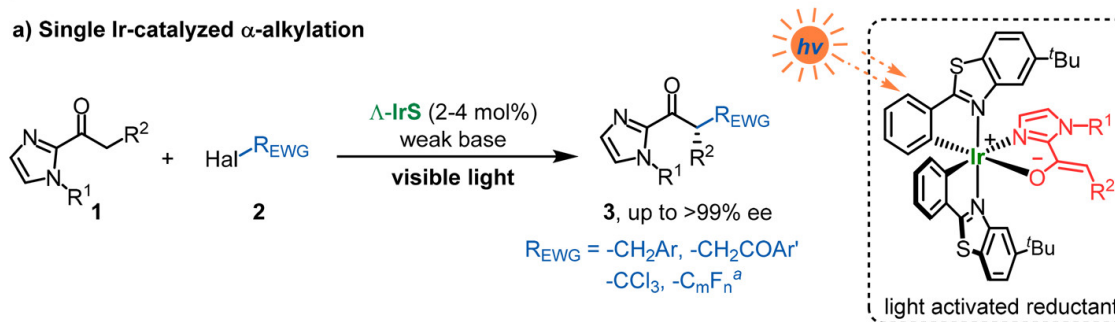


C型模式

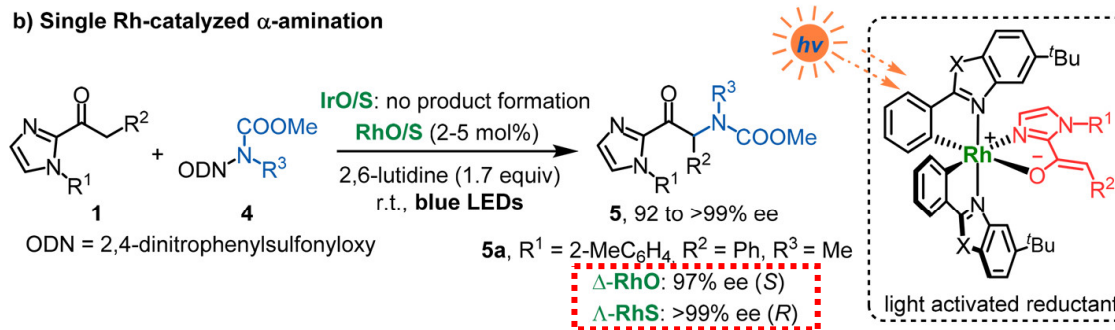
✓ Rhodium enolate complexes react with electrophilic radicals



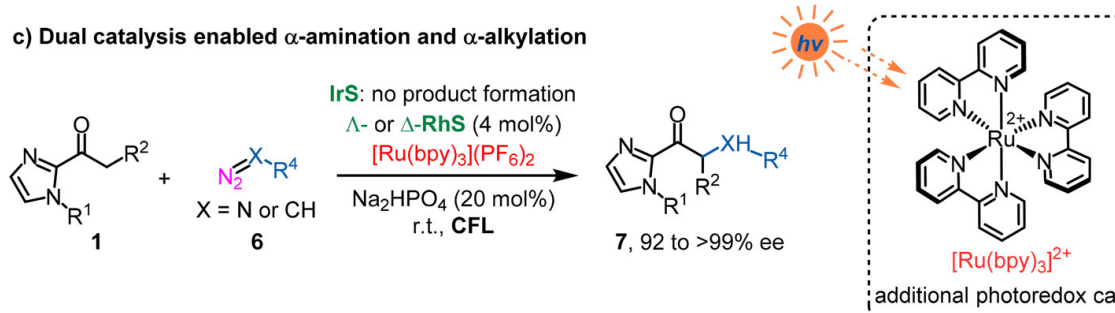
a) Single Ir-catalyzed α -alkylation



b) Single Rh-catalyzed α -amination

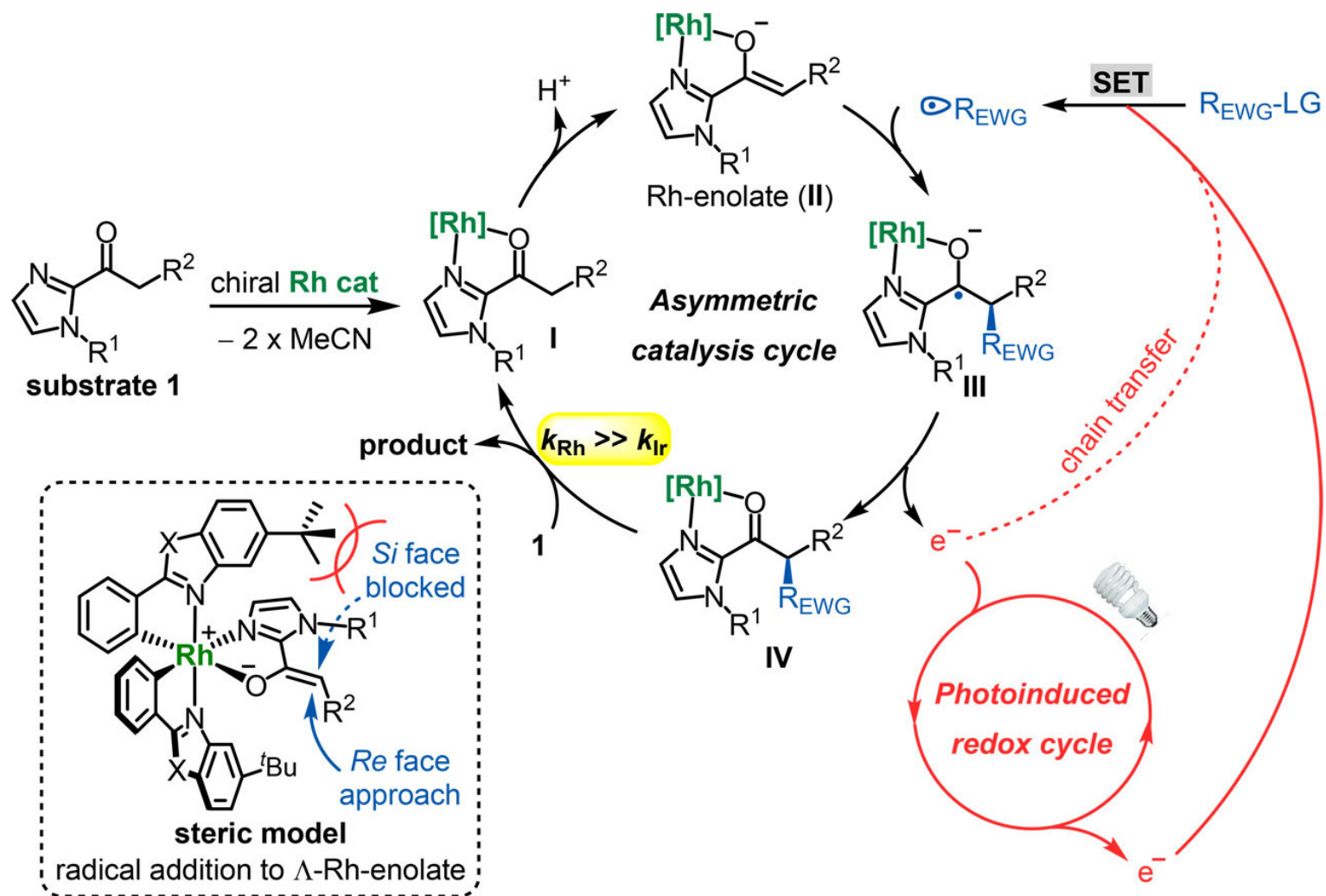


c) Dual catalysis enabled α -amination and α -alkylation



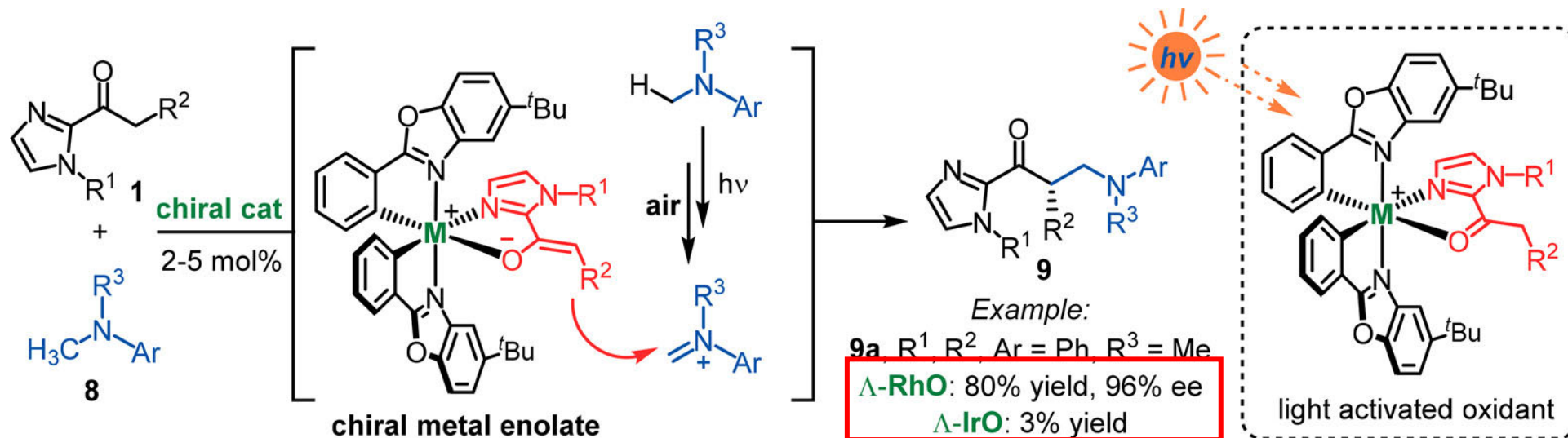
ODN=2,4-二
硝基苯基磺
酰氧基做自
由基源

Mechanism



B型模式

✓ Rhodium enolate complexes react with iminium ions



烯醇化物作为亲核试剂与光氧化生亚氨基离子（亲电试剂）反应

亲电试剂由来：由烯酮铑中间体所具有的氧化性，对不利于与烯醇铑中间体反应富电子的 α -氨基烷基化合物进行氧化，生成亚胺离子中间体，以促进催化循环。

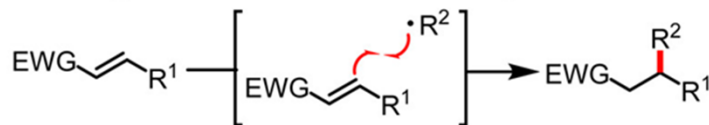
E型模式

✓ Rhodium enone complexes react with nucleophilic radicals

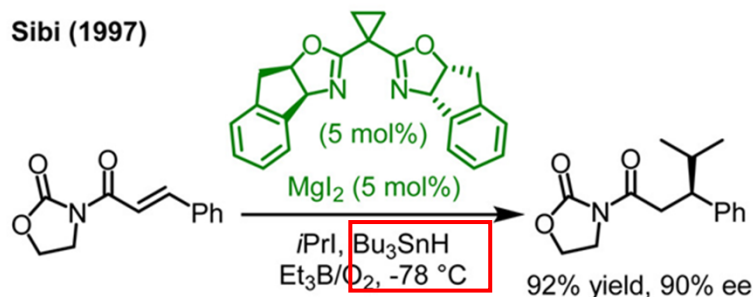
Enantioselective conjugate radical additions (Giese反应)

Enantioselective & Catalytic Free Radical Addition to Alkenes

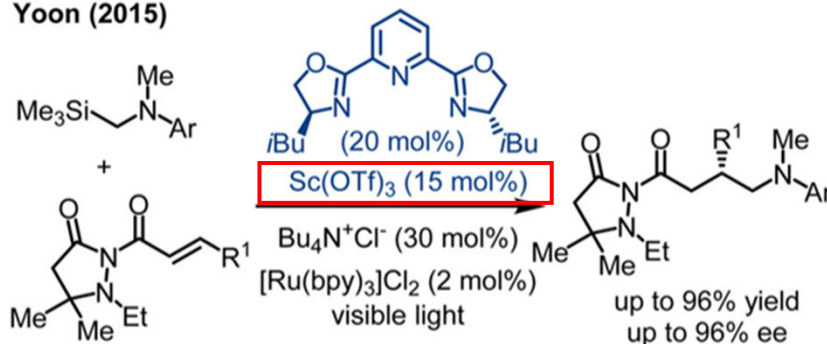
Challenge:
Fast background radical reaction due to high radical reactivity



Sibi (1997)

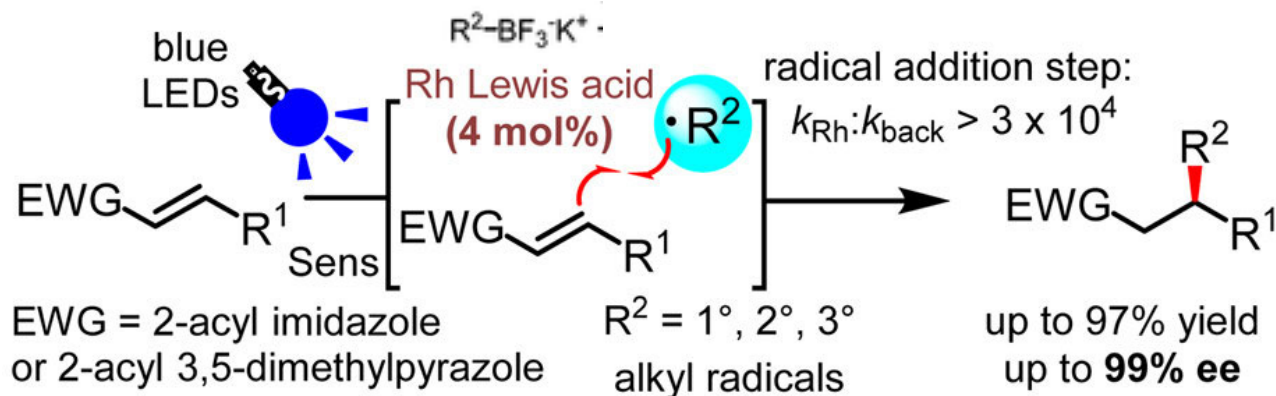


Yoon (2015)

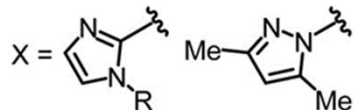


Sibi局限: 等摩尔量有毒锡烷 & -78°C

Yoon局限: 底物范围窄 (α 位有胺的硅烷) & 高催化剂负载量



highly efficient chiral Lewis acid catalyzed radical reaction



Haohua Huo. *J. Am. Chem. Soc.* **2016**, 138, 6936–6939.

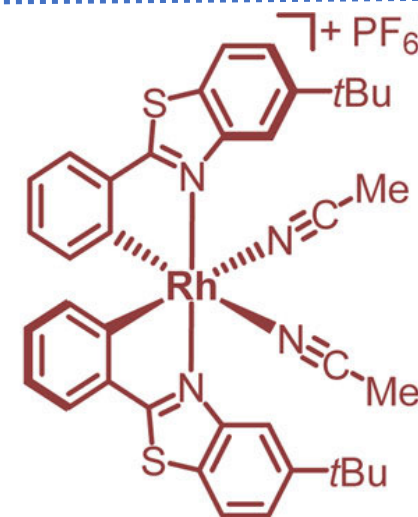
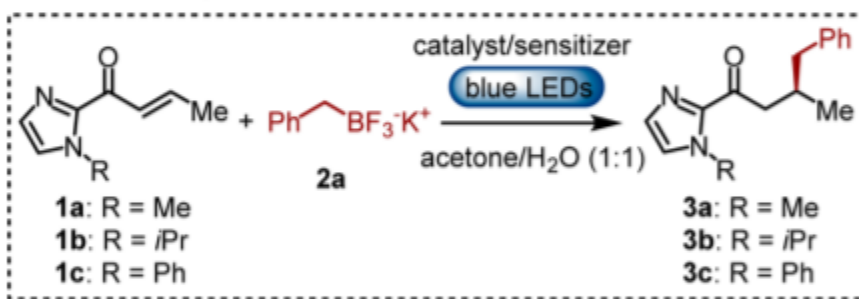
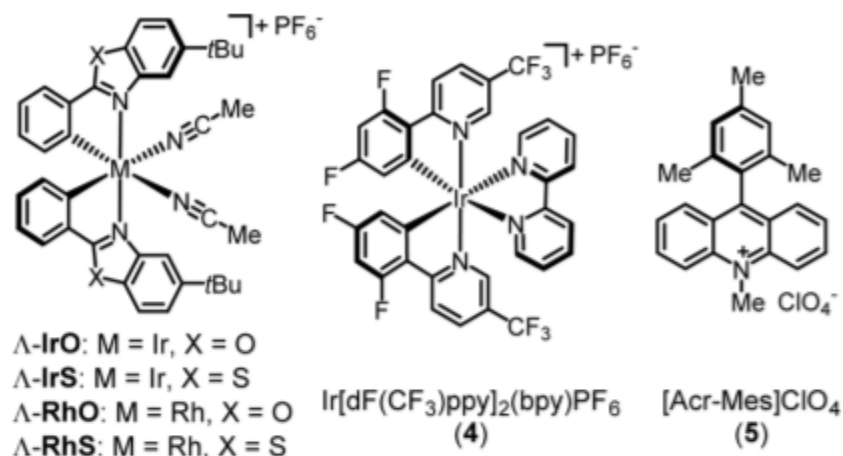
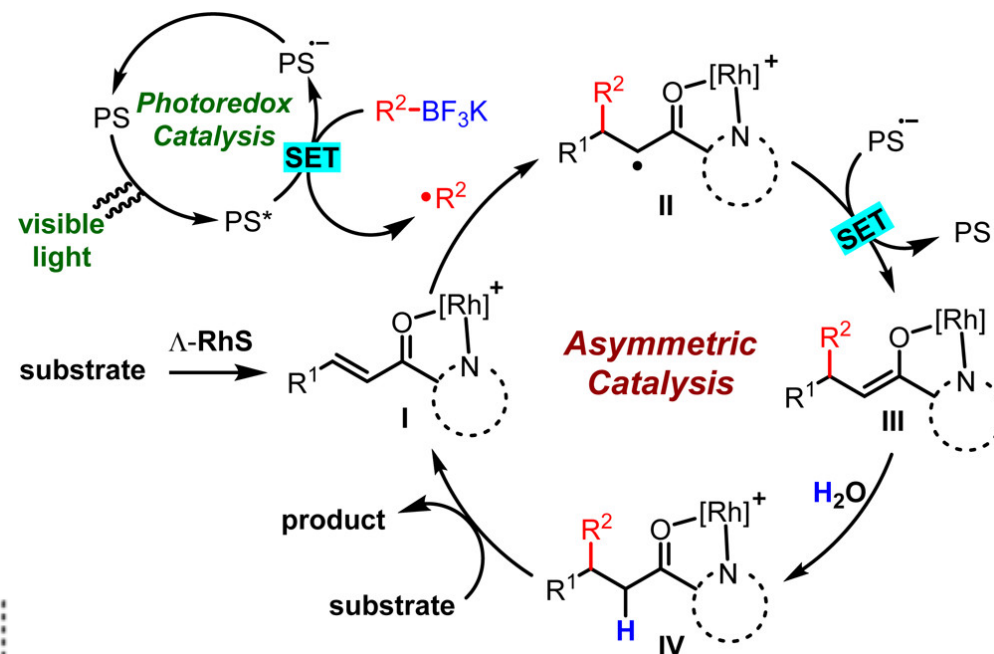


Table 1. Initial Experiments To Identify an Optimal Catalyst/Sensitizer Combination^a



entry	catalyst	sensitizer	$h\nu^b$	substrate	yield (%) ^c	ee (%) ^d
1	Δ -IrO	none	yes	1a	0	n.a.
2	Δ -IrS	none	yes	1a	0	n.a.
3	Δ -IrS	4	yes	1a	<5	n.d.
4	Δ -RhO	4	yes	1a	43	79
5	Δ -RhS	4	yes	1a	67	88
6	Δ -RhS	4	yes	1b	66	93
7	Δ -RhS	4	yes	1c	73	94
8	Δ -RhS	5	yes	1c	73	96
9	Δ -RhS	4	no	1c	0	n.a.
10	Δ -RhS	none	yes	1c	0	n.a.
11	none	4	yes	1c	29	0



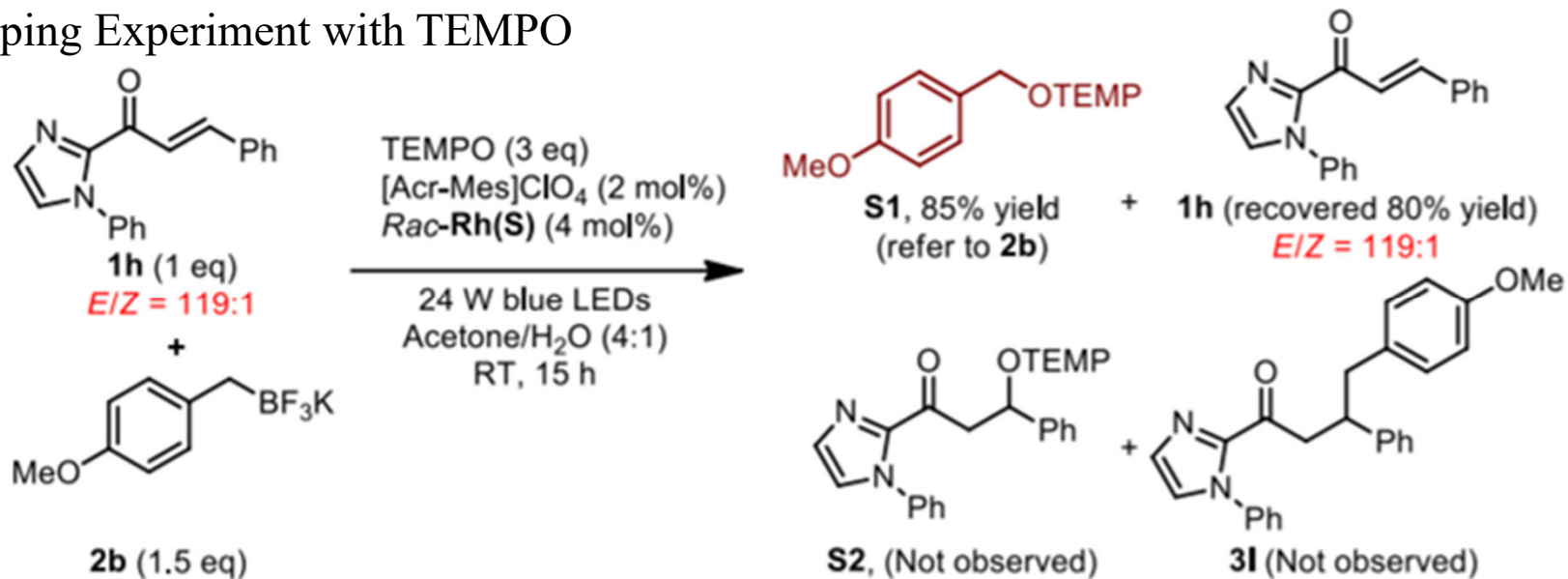
- 在没有手性路易斯酸 Δ -RhS的情况下，自由基加成产物3c仍然以29%的产率产生（外消旋混合物）。
- Δ -RhS必须强烈加速自由基的加成，以克服主要的外消旋副反应。

双催化剂:

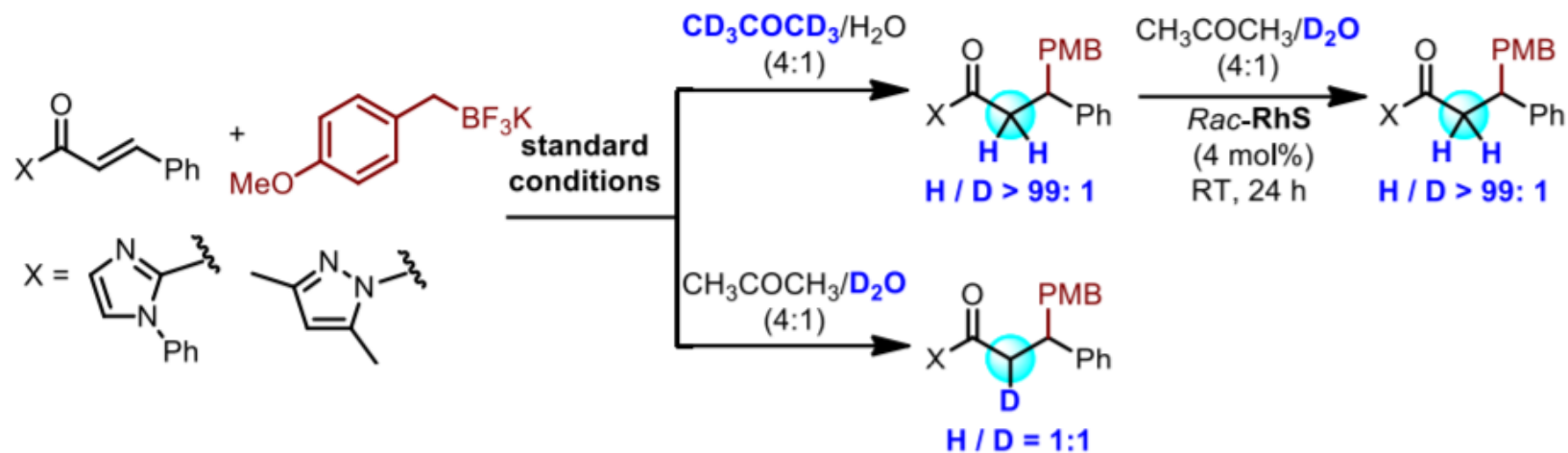
- ✓ 铑催化过程中优异的周转频率
- ✓ 补偿铑体系的有限光化学性质

Mechanistic Experiments

Trapping Experiment with TEMPO

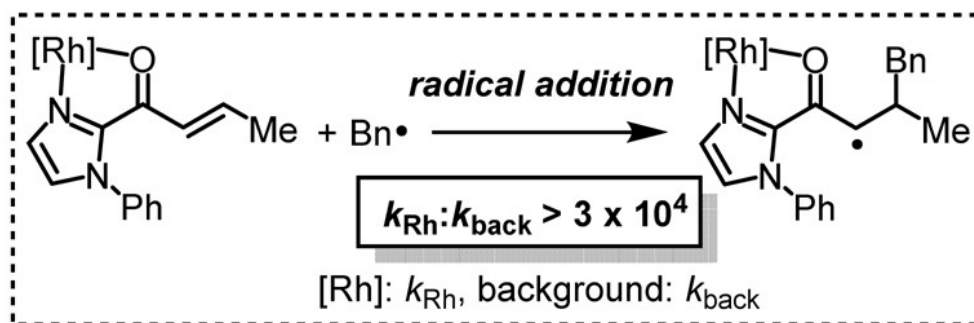
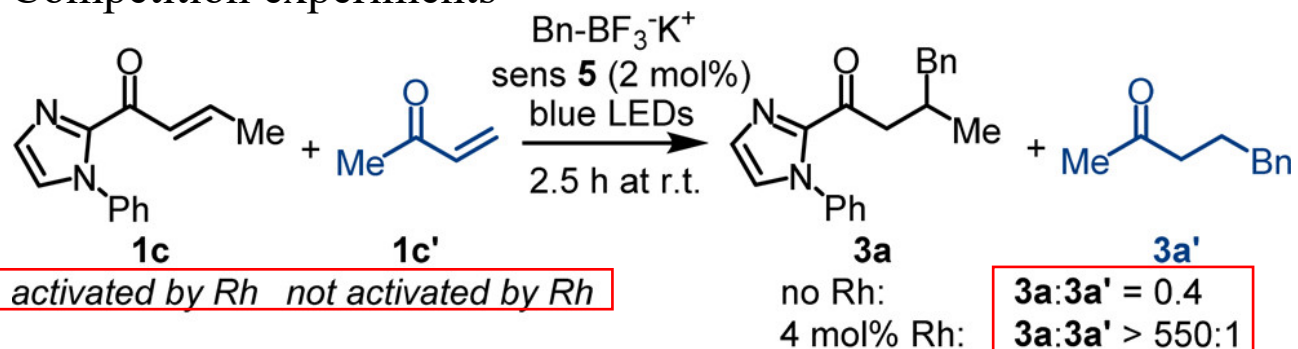


Control experiments in deuterated solvent



Mechanistic Experiments

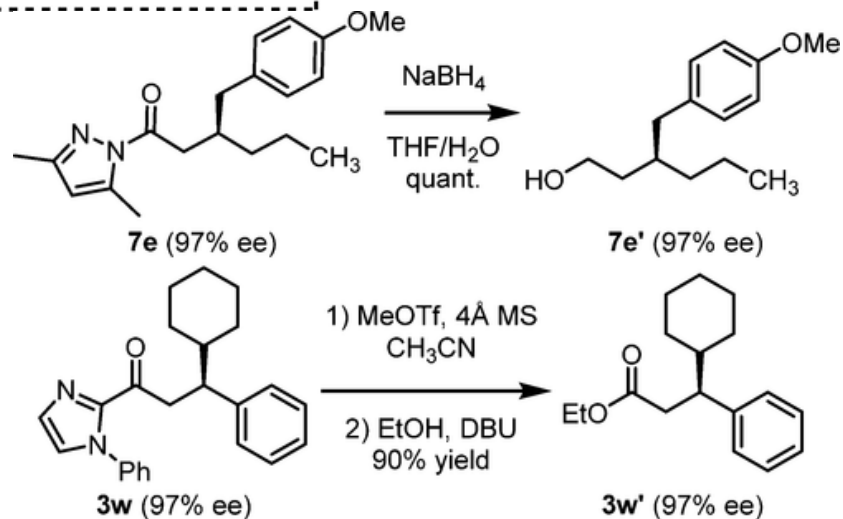
Competition experiments



- 立体控制极好
- 自由基加成步骤加速4-5个数量级

Transformation of selected products.

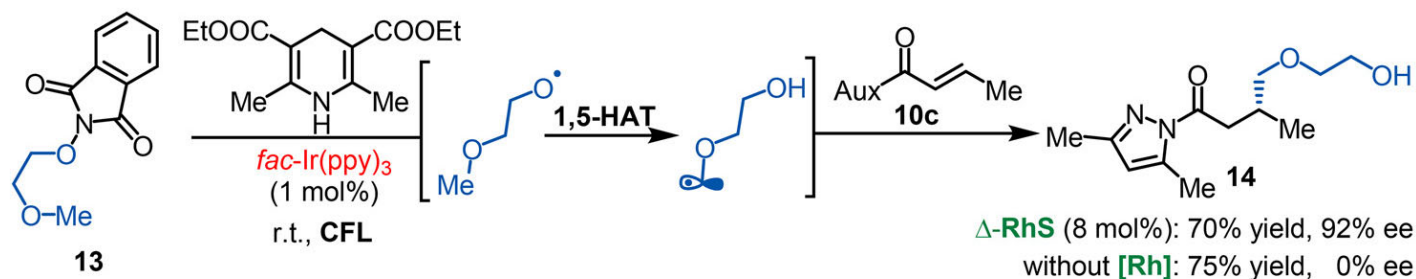
ee值不损失



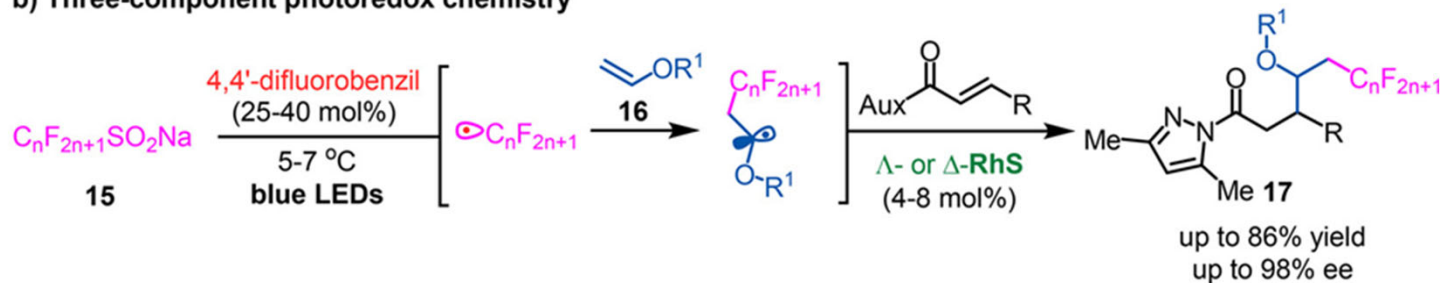
A set of reactions based on the above method

E型模式

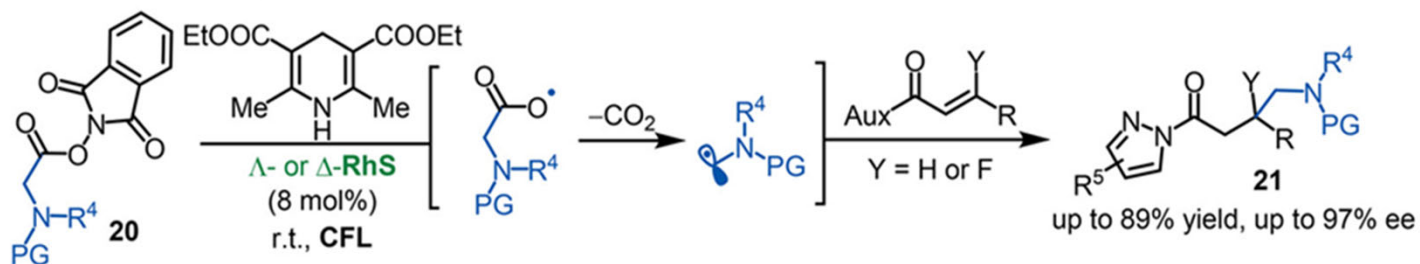
a) Radical translocation



b) Three-component photoredox chemistry

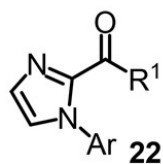


d) Decarboxylative generation of radical



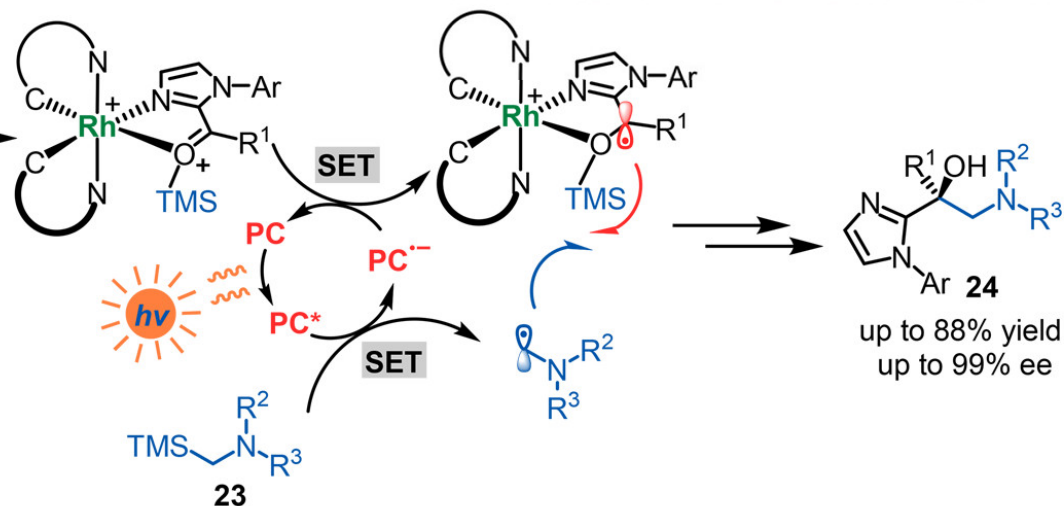
I型模式+额外光催化

a) Imidazolyl ketones

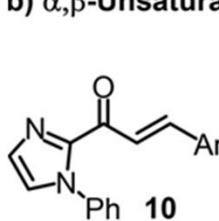


R¹ = aryl or alkyl
Ar = 2-(C₆H₅)C₆H₄

PC: [Ru(bpy)₃](PF₆)₂
(1 mol%)



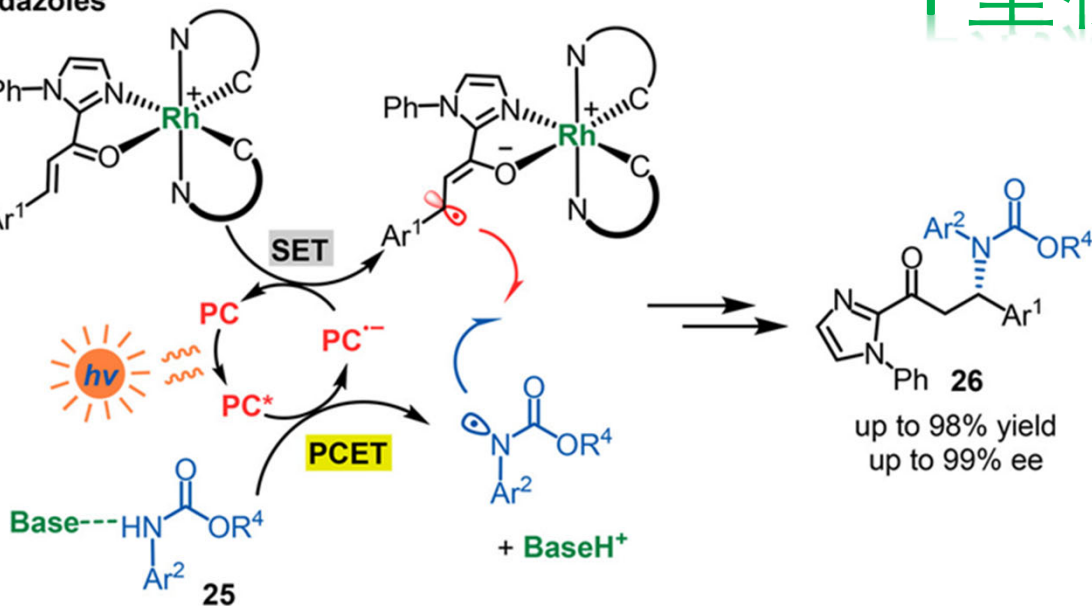
b) α,β-Unsaturated 2-acyl imidazoles



10b, Ar¹ = Ph

PC: [Ir(dFCF₃ppy)₂(5,5'-di-CF₃-bpy)](PF₆) (2 mol%)

Base: PhO-P(=O)(OPh)₂⁻ N(ⁿBu)₄⁺
(20 mol%)

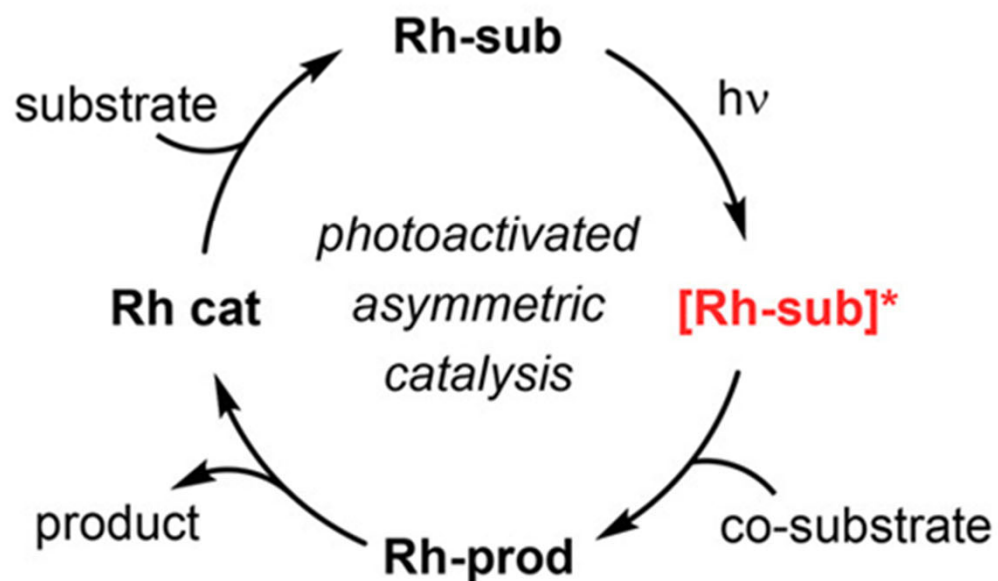


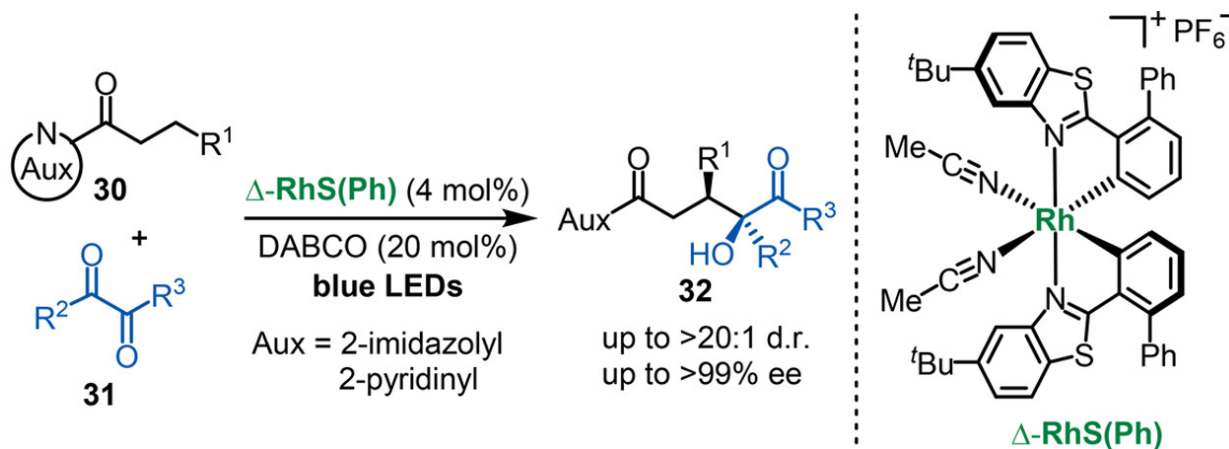
F型模式

Primary asymmetric photocatalysis

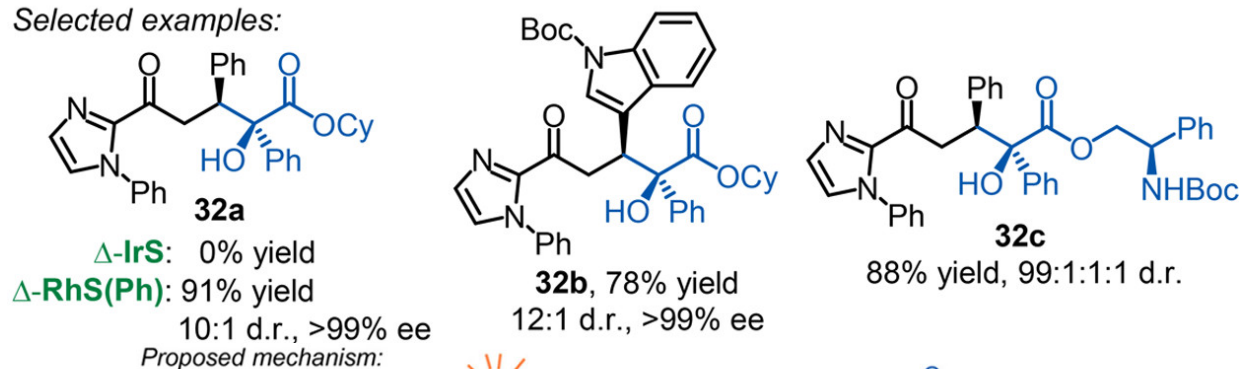
Photoexcited Rhodium–substrate complexes are part of the asymmetric catalytic cycle

b) PRIMARY ASYMMETRIC PHOTOCATALYSIS

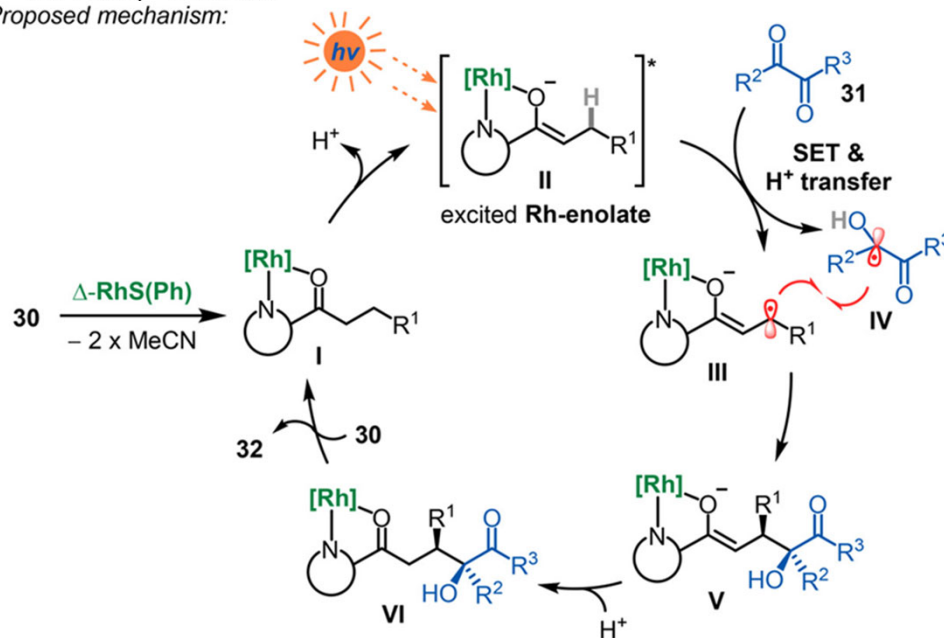




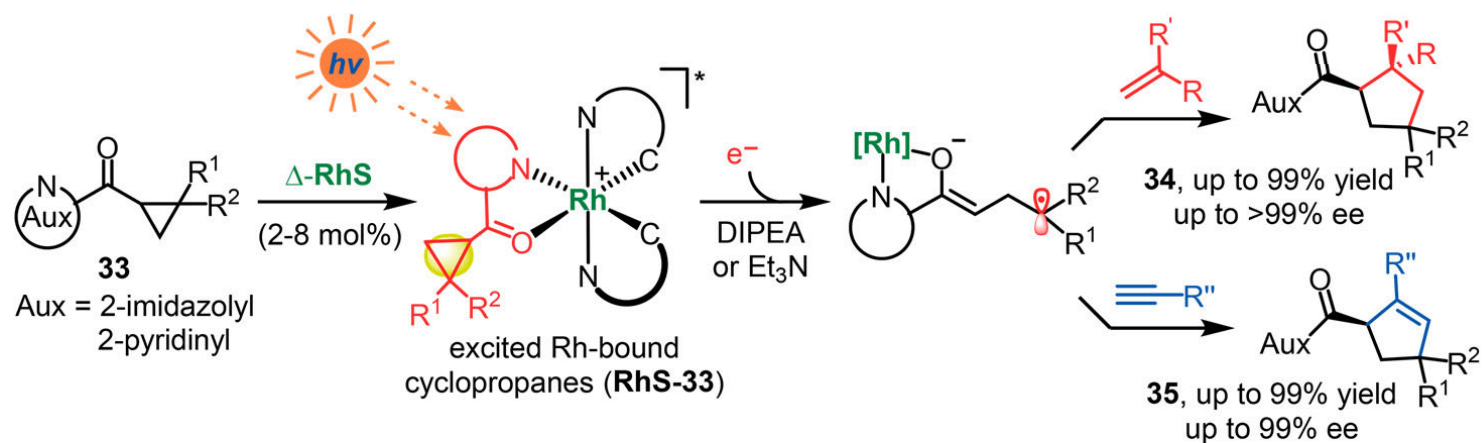
Selected examples:



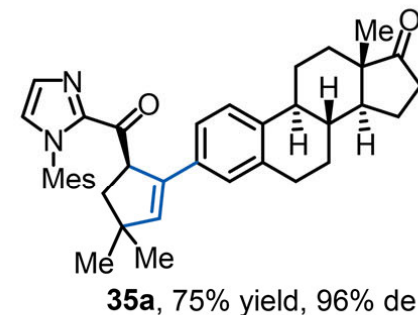
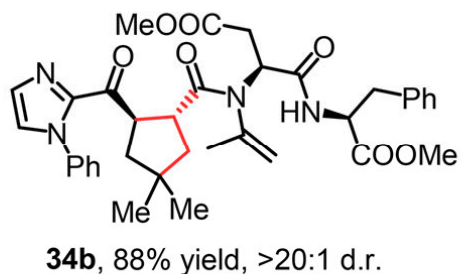
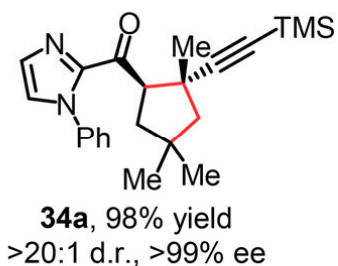
D型模式



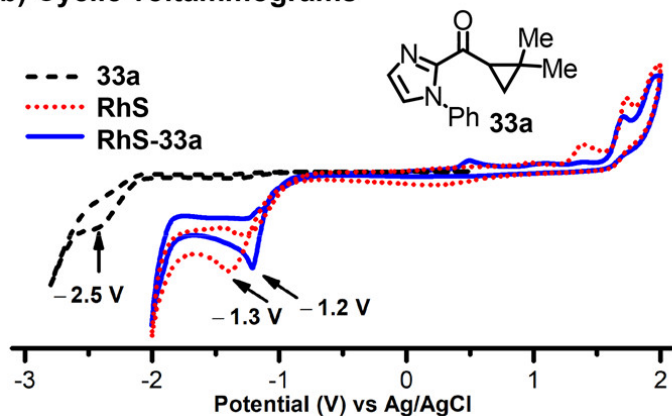
J型模式



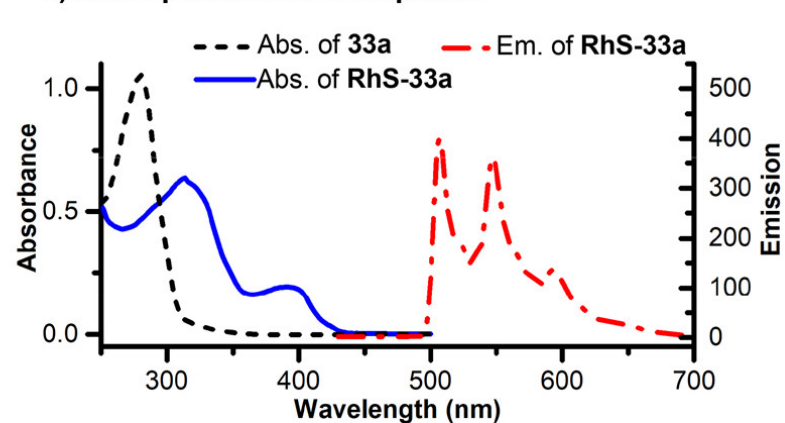
a) Selected examples



b) Cyclic voltammograms

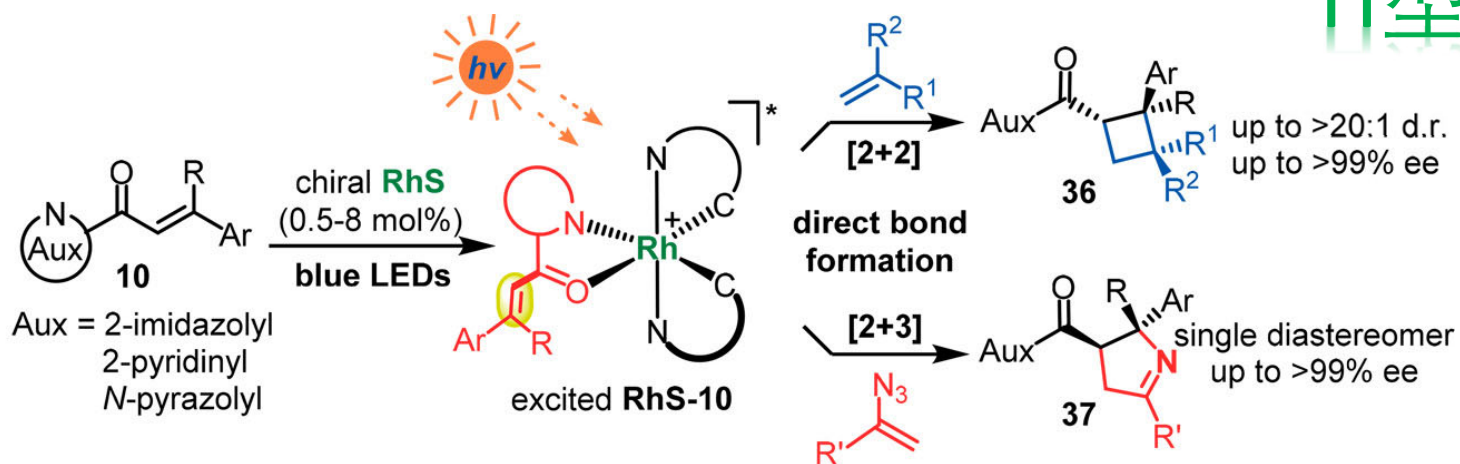


c) Absorption/emission spectra

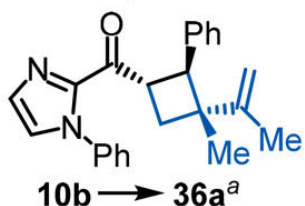


✓ Stereoselective direct bond formations of photoexcited rhodium–substrate complexes

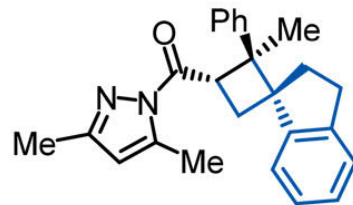
H型模式



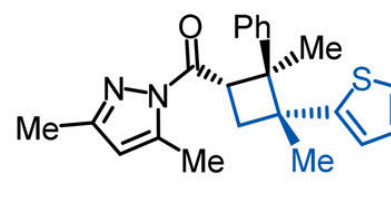
Selected examples:



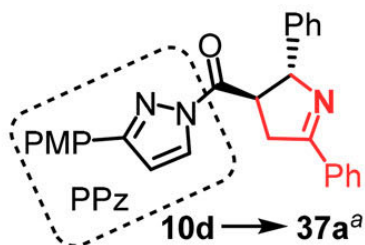
Δ -RhS: 99% yield, 14:1 d.r., 99% ee
 Δ -IrS: 63% yield, 5:1 d.r., 0% ee
 none: 19% yield, 6:1 d.r., 0% ee



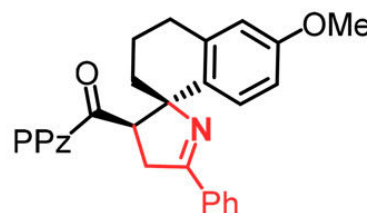
96% yield
>20:1 d.r., 99% ee



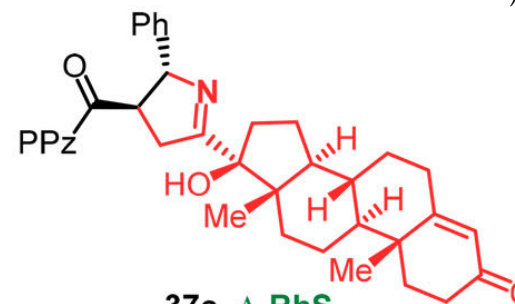
99% yield
17:1 d.r., 99% ee



Δ -RhS: 92% yield, 94% ee
 Δ -IrS: 50% yield, 0% ee
 none: 7% yield

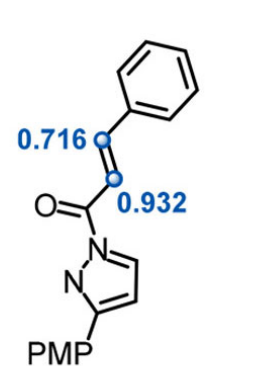
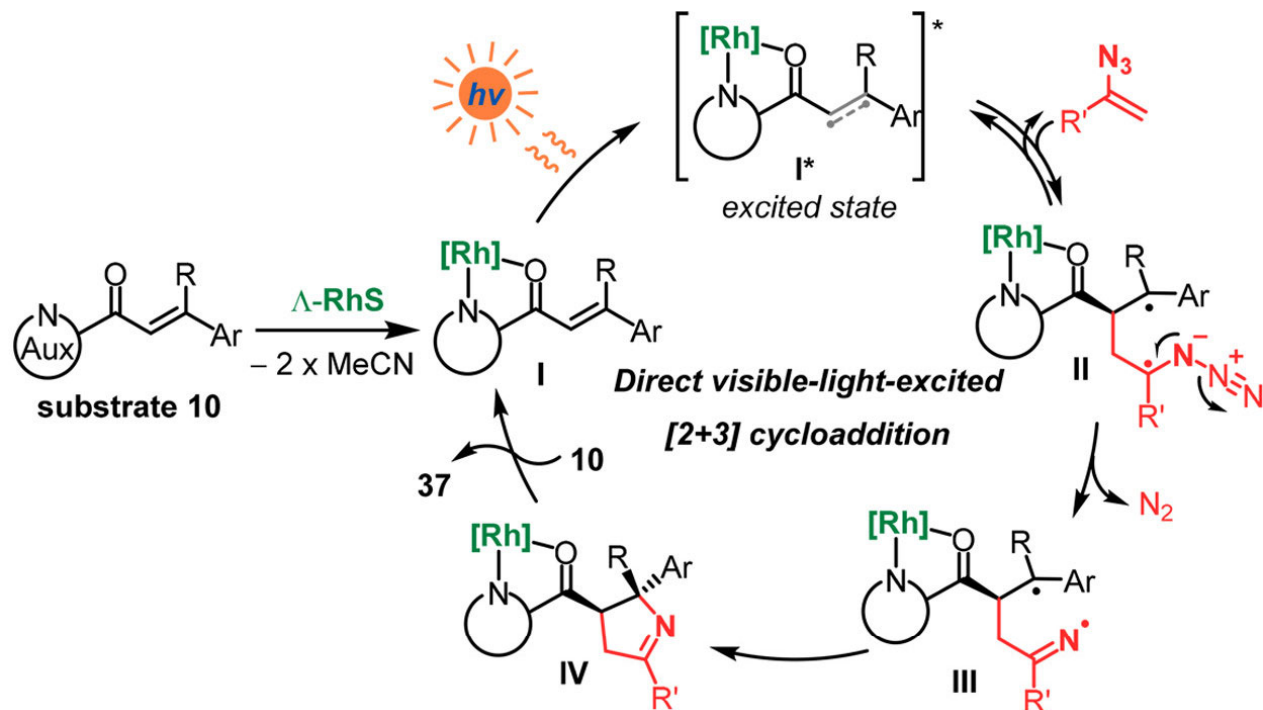


94% yield, >99% ee

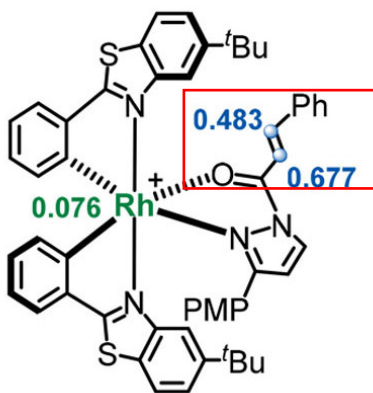


86% yield, >20:1 d.r.

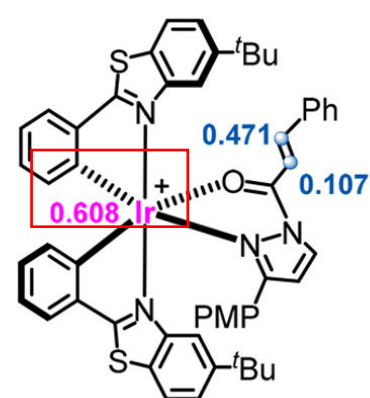
- 单一手性催化剂RhS
- 直接从可见光激发态进行立体控制的成键反应



10d in T_1
 $E_T = 212.4 \text{ kJ/mol}$



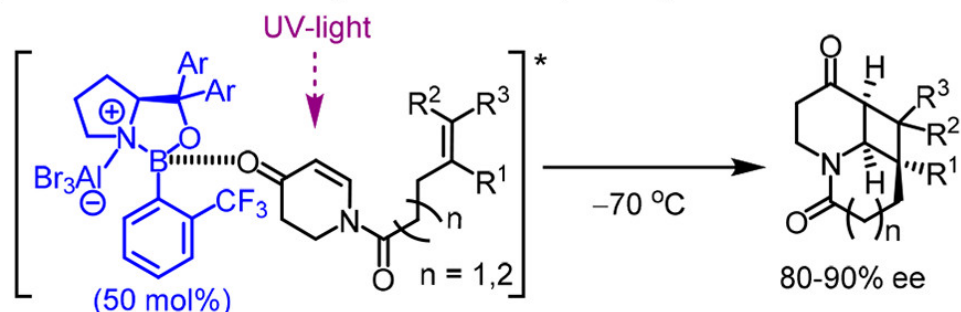
RhS-10d in T_1
 $E_T = 209.5 \text{ kJ/mol}$



IrS-10d in T_1
 $E_T = 209.5 \text{ kJ/mol}$

Intermolecular [2+2] Photocycloadditions

a) Chiral Lewis acid catalysis activated by UV-light

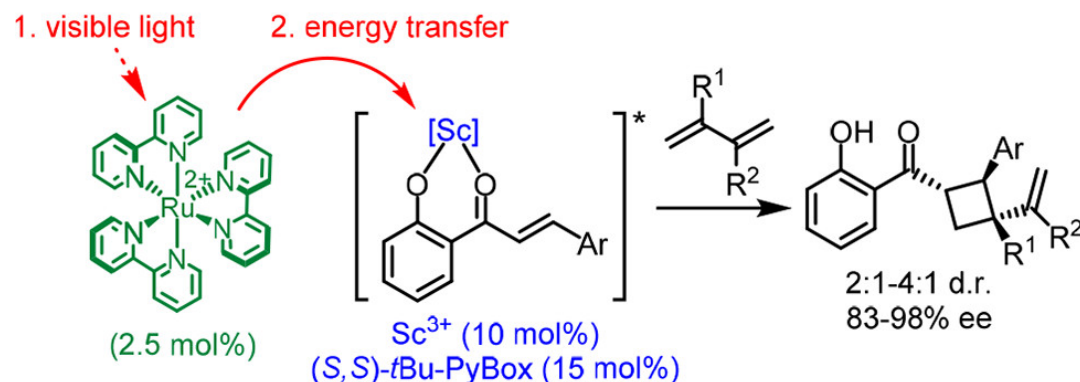


Role of Lewis acid: Red-shift of UV-absorption of substrate

H型模式

Bach局限: 紫外线、低温和高催化剂负载量

b) Chiral Lewis acid / photosensitizer dual catalysis activated by visible light

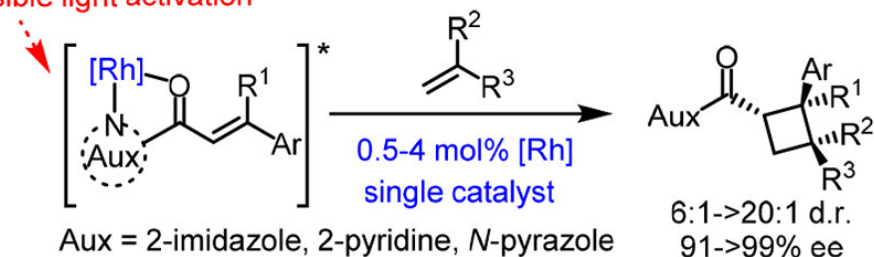


Role of Lewis acid: Lowering of triplet energy of Sc-coordinated substrate

Yoon局限: 两种催化剂、底物范围有限
2'-hydroxychalcones (2-羟基查尔酮, 黄酮类化合物的一种重要中间体)

c) Chiral Lewis acid catalysis activated by visible light (*this work*)

direct visible light activation



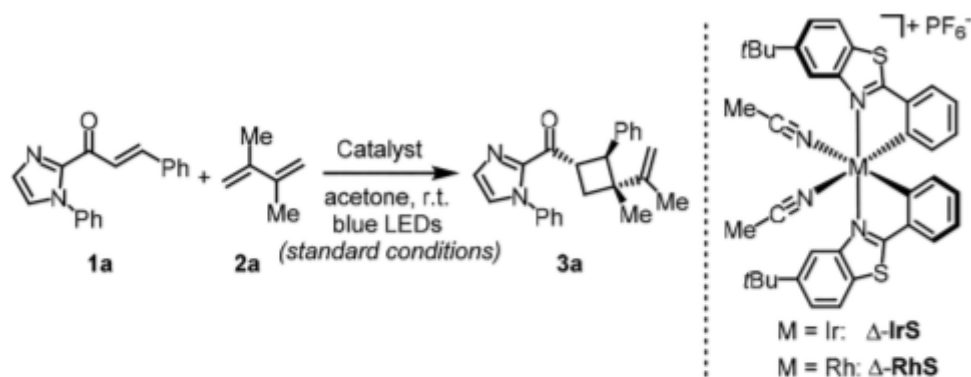
Role of Lewis acid: Direct visible light excitation of Rh-substrate complex

Xiaoqiang Huang. *J. Am. Chem. Soc.* **2017**, 139, 9120–9123.

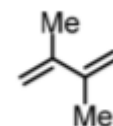
- 单一催化剂
- 底物/手性路易斯酸 (CLA) 复合物被可见光直接活化

Condition optimization and substrate range

Table 1. Visible-Light-Activated Asymmetric [2+2] Cycloaddition Using a Single Catalyst^a



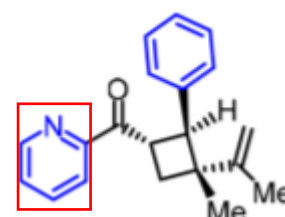
entry	catalyst ^b	conditions ^c	t (h)	yield (%) ^d	d.r. ^e	ee (%) ^f
1	Δ -IrS (2.0)	standard	16	63	5:1	0
2	Δ -RhS (2.0)	standard	16	99 (97) ^g	14:1	99
3	Δ -RhS (0.5)	standard	24	98	12:1	96
4	Δ -RhS (2.0)	air	16	97	14:1	99
5	Δ -RhS (2.0)	air, 1% H ₂ O	24	96	13:1	99
6	Δ -RhS (2.0)	DMF solvent	16	95	13:1	98
7	Δ -RhS (2.0)	CH ₂ Cl ₂ solv.	16	99	14:1	99
8	Δ -RhS (2.0)	no light	16	0	n.a. ^h	n.a.
9	no catalyst	standard	16	19	6:1	0



二烯



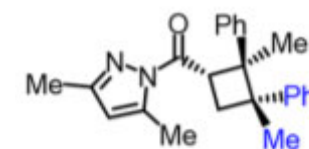
单烯



3k^b

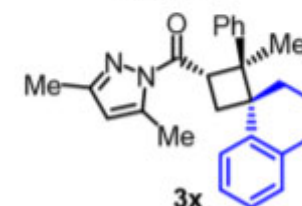
72% yield, 8:1 d.r.
95% ee

咪唑→吡啶



3u

94% yield, >20:1 d.r.
99% ee



3x

97% yield, >20:1 d.r.
99% ee

- **Unique:** 以分子间方式安装两个相邻的全碳四元立体中心（含螺中心）

Mechanism

铑/底物复合物RhS-1a: 根据基态的氧化还原电势和计算 S_0-T_1 间隙

	RhS-1a (II)	底物2
OX	+0.88	+2.05
RED	-0.78	-2.91

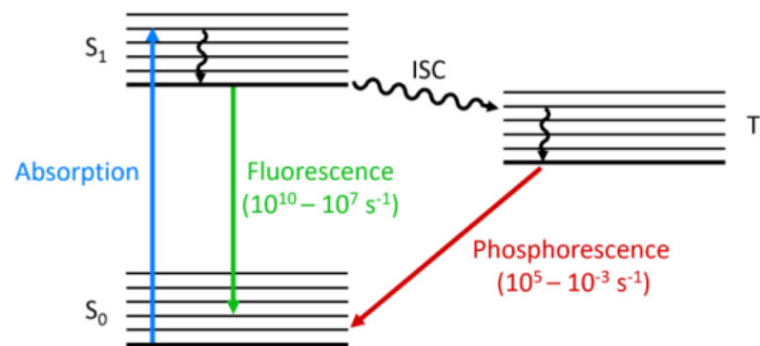
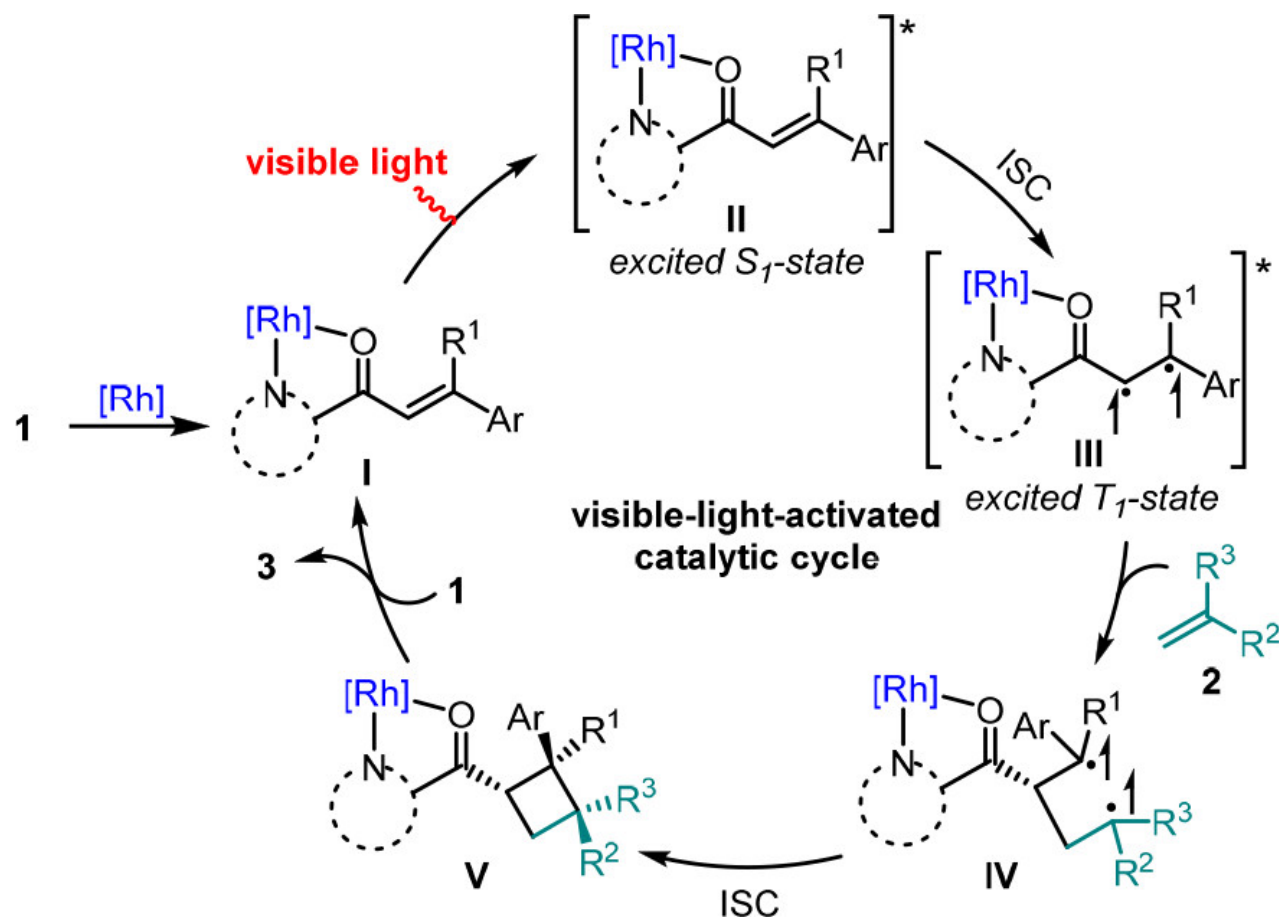


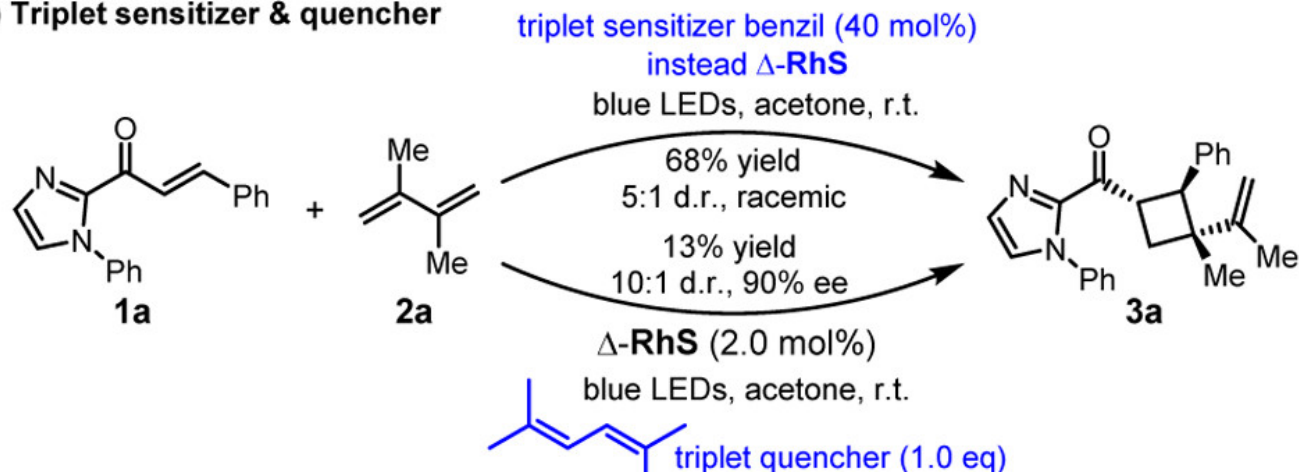
图1荧光和磷光发生过程的电子能级转换示意图

S_0 为基态单重态
 S_1 属于激发单重态
 T_1 属于激发三重态

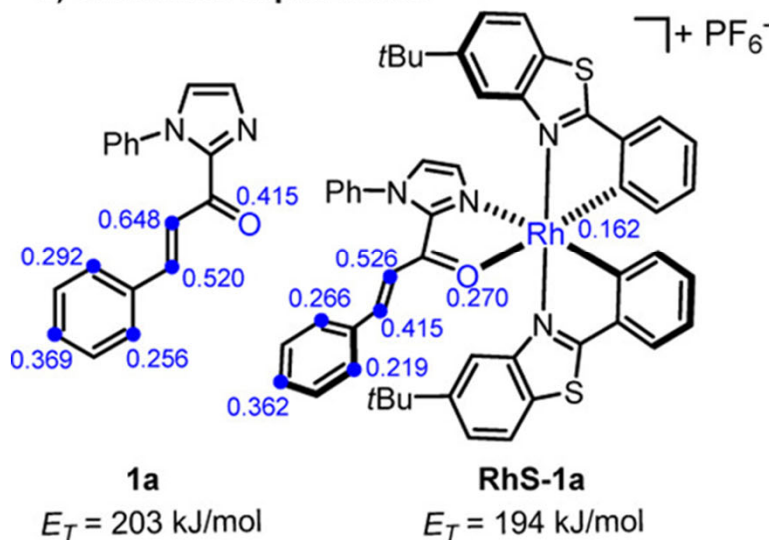


Mechanistic Experiments

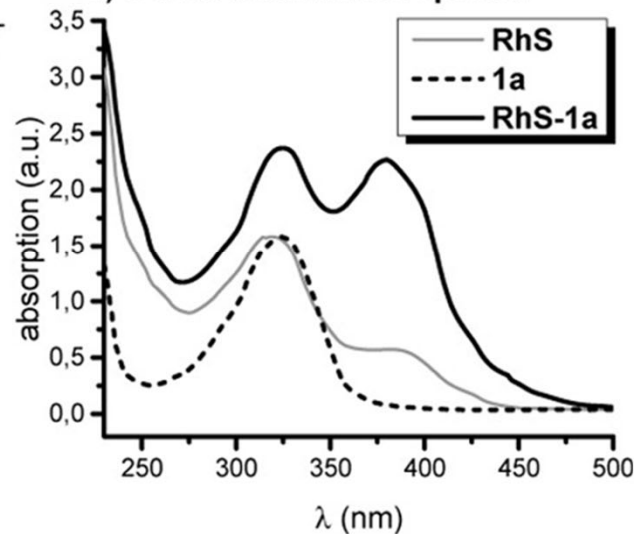
a) Triplet sensitizer & quencher



c) Calculated triplet states

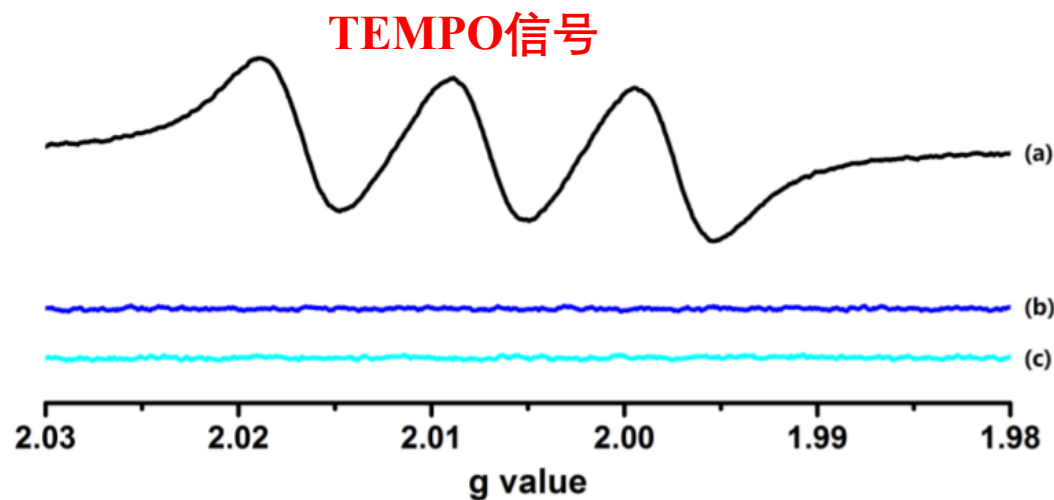
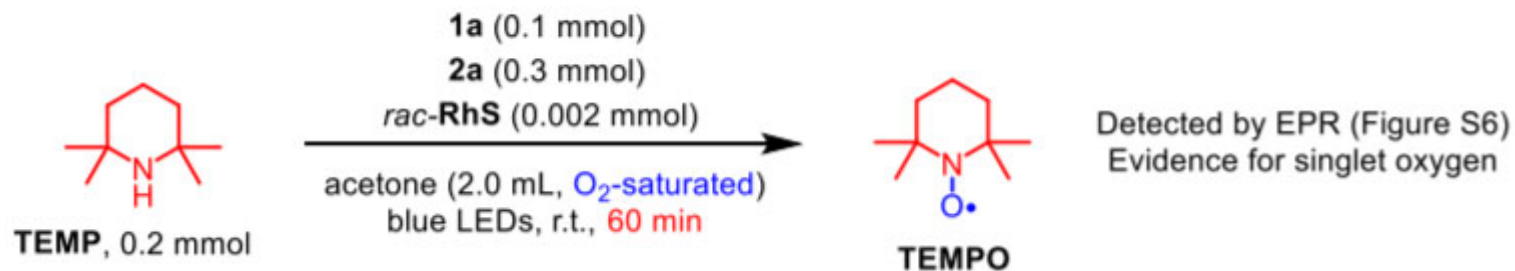


d) UV/Vis absorbance spectra

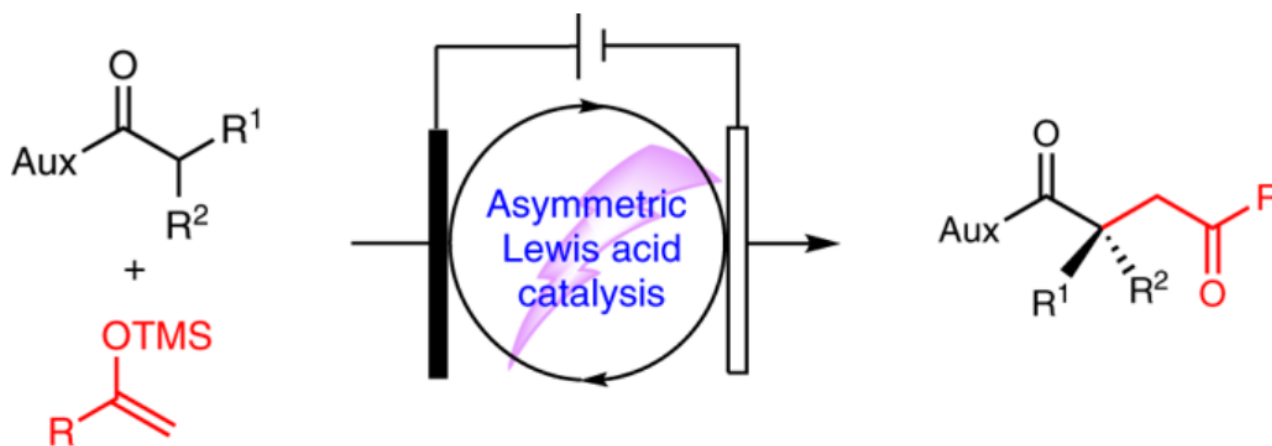


Mechanistic Experiments

b) Substrate diastereomers



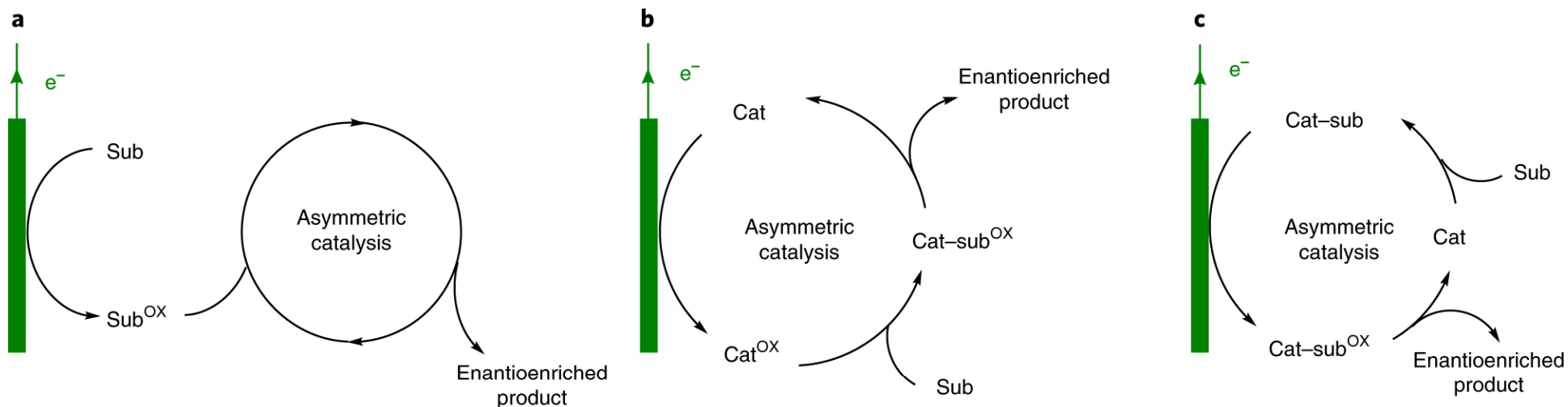
Electricity-driven asymmetric Lewis acid catalysis



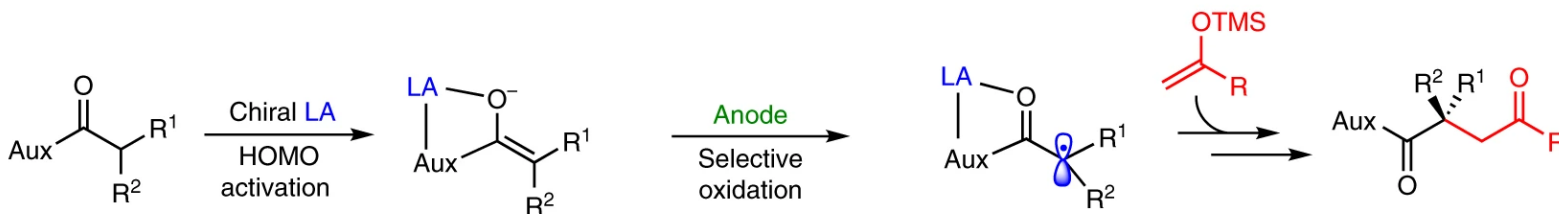
- Electricity-driven asymmetric catalysis
- Green cross-coupling of enolates
- All-carbon quaternary centres
- 38 examples, 90 to >99% e.e.

Xiaoqiang Huang. *Nat Catal.* **2019**, 2, 34–40.

Strategies for electrochemical asymmetric catalysis with anodic processes.



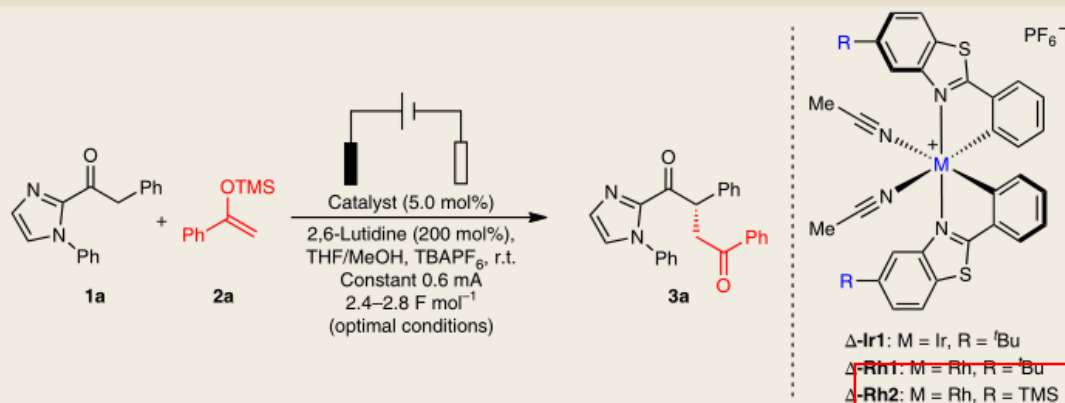
d



- Catalytic asymmetric electrochemistry
- Green oxidative cross-coupling of enolates

- Access to all-carbon quaternary stereocentres
- 38 examples, 42–91% yields, 90 to >99% e.e.

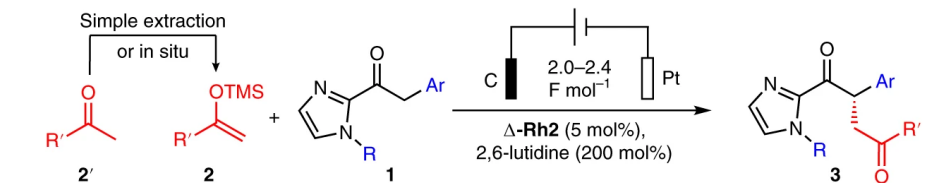
- 手性胺催化剂和烯胺中间体的氧化敏感性，底物受限
- 活性不对称催化剂由电化学产生,与电极的直接相互作用需要氧化还原手性催化剂，因此得到较低的对映选择性，必须使用额外的氧化还原介质以提高对映选择性
- 使用单一催化剂，该催化剂不仅提供不对称诱导，而且通过一种底物的活化促进电化学过程

Table 1 | Electrochemical asymmetric enolate cross-coupling

Entry	Catalyst	Electrodes	Deviations from optimal conditions	Yield (%) ^a	e.e. (%) ^b
1	$\Delta\text{-Ir1}$	BDD-Pt	None	27	98
2	$\Delta\text{-Rh1}$	BDD-Pt	None	45	97
3	$\Delta\text{-Rh2}$	BDD-Pt	None	82	97
4	$\Delta\text{-Rh2}$	Pt-Pt	None	<10	ND
5	$\Delta\text{-Rh2}$	RVC-Pt	None	80	93
6	$\Delta\text{-Rh2}$	Graphite-Pt	None	82 (79) ^c	97
7	$\Delta\text{-Rh2}$	Graphite-Pt	LiClO ₄ instead of TBAPF ₆	79	95
8	$\Delta\text{-Rh2}$	Graphite-Pt	TBABF ₄ instead of TBAPF ₆	44	95
9	$\Delta\text{-Rh2}$	Graphite-Pt	Constant 1.5 mA	80	96
10 ^d	$\Delta\text{-Rh2}$	Graphite-Pt	Constant 0.8 V vs Ag/AgCl	72	97
11 ^e	None	Graphite-Pt	None	0	NA
12	$\Delta\text{-Rh2}$	Graphite-Pt	Without 2,6-lutidine	46	96
13 ^f	$\Delta\text{-Rh2}$	None	O ₂ (balloon), 21 W CFL without electricity and electrolyte	11	86
14 ^g	$\Delta\text{-Rh2}$	None	CAN (2.0 equiv.) without electricity and electrolyte	8	81

Reaction conditions: in an ElectroSyn 2.0 cell, **1a** (0.10 mmol), **2a** (0.60 mmol), catalyst (5.0 mol%), 2,6-lutidine (0.20 mmol) and TBAPF₆ (0.30 mmol) in THF/MeOH (1.0/2.0 ml) were electrolysed under a constant current of 0.6 mA with an electricity consumption of 2.4–2.8 F mol⁻¹. ^aNuclear magnetic resonance yields. ^be.e. was determined by high-performance liquid chromatography analysis on a chiral stationary phase. ^cIsolated yield indicated in the parentheses. ^dAn Ag/AgCl reference electrode was applied with the consumption of 1.8 F mol⁻¹ of current. ^eHomocoupling of **2a** was the major side reaction. ^fConversion of 27% with the formation of 1-phenyl-2-(1-phenyl-1*H*-imidazol-2-yl)ethane-1,2-dione in 9% yield. ^gDecomposed. CAN, ceric ammonium nitrate; CFL, compact fluorescent lamp; ND, not determined; NA, not applicable; r.t., room temperature; BDD, boron-doped diamond; RVC, reticulated vitreous carbon; TBAPF₆, tetrabutylammonium hexafluorophosphate; TBABF₄, tetrabutylammonium tetrafluoroborate.

13和14这些结果突出了电化学在催化不对称杂环方面在转化率、产率和对映选择性方面的独特优势。电子的受控电化学递送确保了在温和的氧化还原条件下的清洁转化，而不会形成在光氧化还原条件或用化学氧化剂观察到的不期望的副产物。



Imidazoles

$\text{R}^1 = 4\text{-OMe}$

3b, 68% yield, 97% e.e.

4-Me

3c, 88% yield, 97% e.e.

4-Cl

3d, 67% yield, 95% e.e.

3-Cl

3e, 88% yield, 96% e.e.

2-Cl

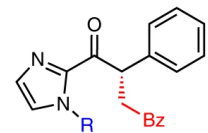
3f, 76% yield, 94% e.e.

4-Br

3g, 83% yield, 97% e.e.

4-CF₃

3h, 87% yield, 95% e.e.



$\text{R} = \text{Mes}$

3j, 50% yield, >99% e.e.

PMP

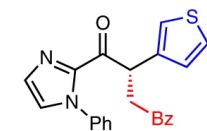
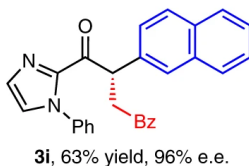
3k, 55% yield, 96% e.e.

4-FC₆H₄

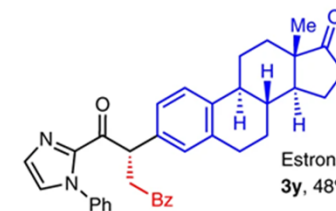
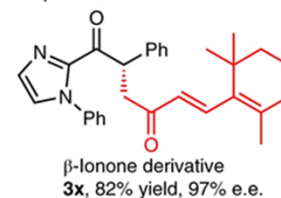
3l, 52% yield, 96% e.e.

Me

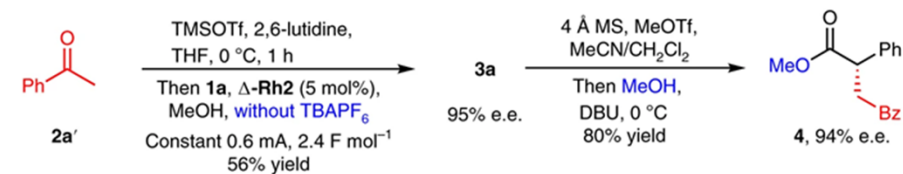
3m, <10% yield



Complex molecules



One-pot procedure and cleavage of imidazolyl group



Silyl enol ethers

$\text{R}^2 = 4\text{-OMe}$

3o, 91% yield, 94% e.e.

3-OMe

3p, 76% yield, 97% e.e.

2-OMe

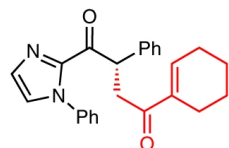
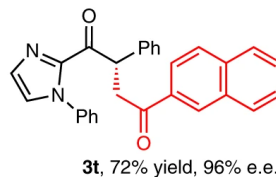
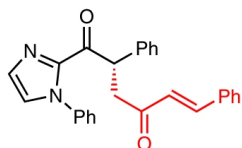
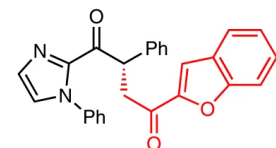
3q, 80% yield, 94% e.e.

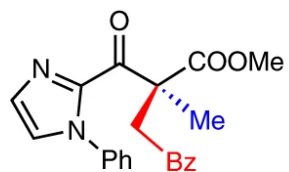
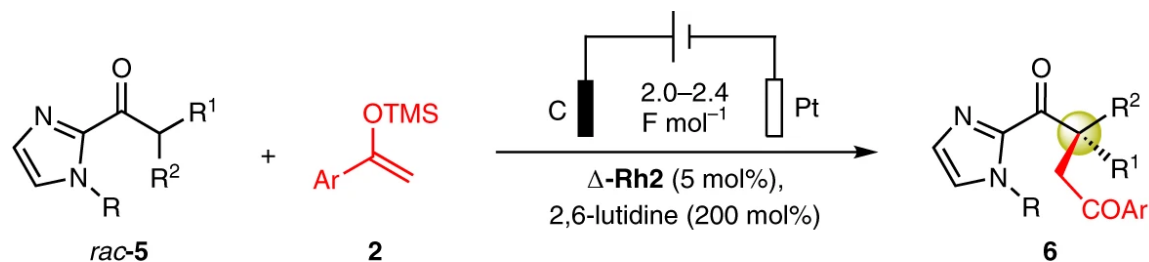
3-CF₃

3r, 47% yield, 98% e.e.

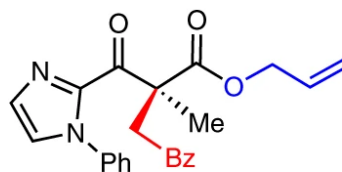
4-COOMe

3s, 73% yield, 98% e.e.

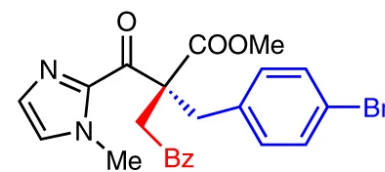




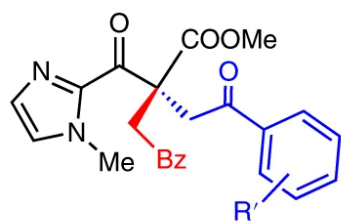
6a, 83% yield, 96% e.e.



6b, 75% yield, 95% e.e.



6c, 84% yield, 93% e.e.^a



$\text{R}' = 4\text{-Cl}$

6d, 46% yield, 87% e.e.

91% yield, 96% e.e.^a

4-Br

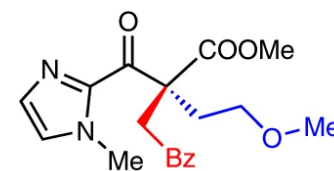
6e, 70% yield, 93% e.e.^a

3-OMe

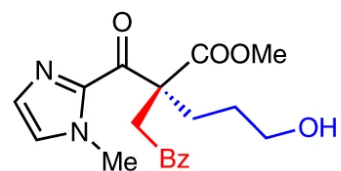
6f, 81% yield, 95% e.e.^a

2-CF₃

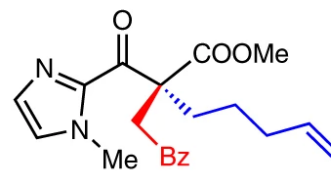
6g, 79% yield, 93% e.e.^a



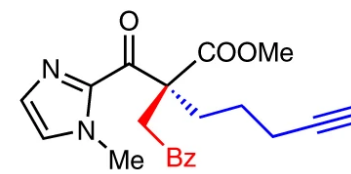
6h, 75% yield, 96% e.e.



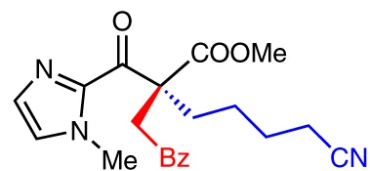
6i, 69% yield, 96% e.e.^a



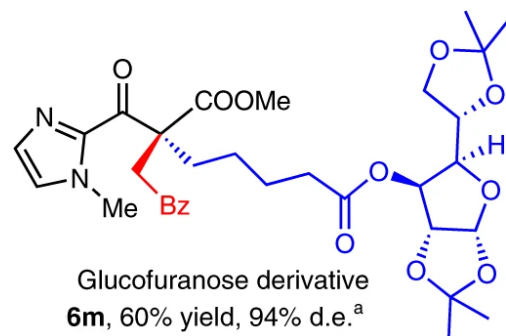
6j, 55% yield, 94% e.e.^a



6k, 69% yield, 90% e.e.

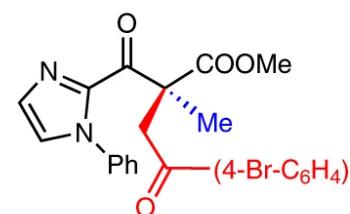


6l, 55% yield, 91% e.e.^a

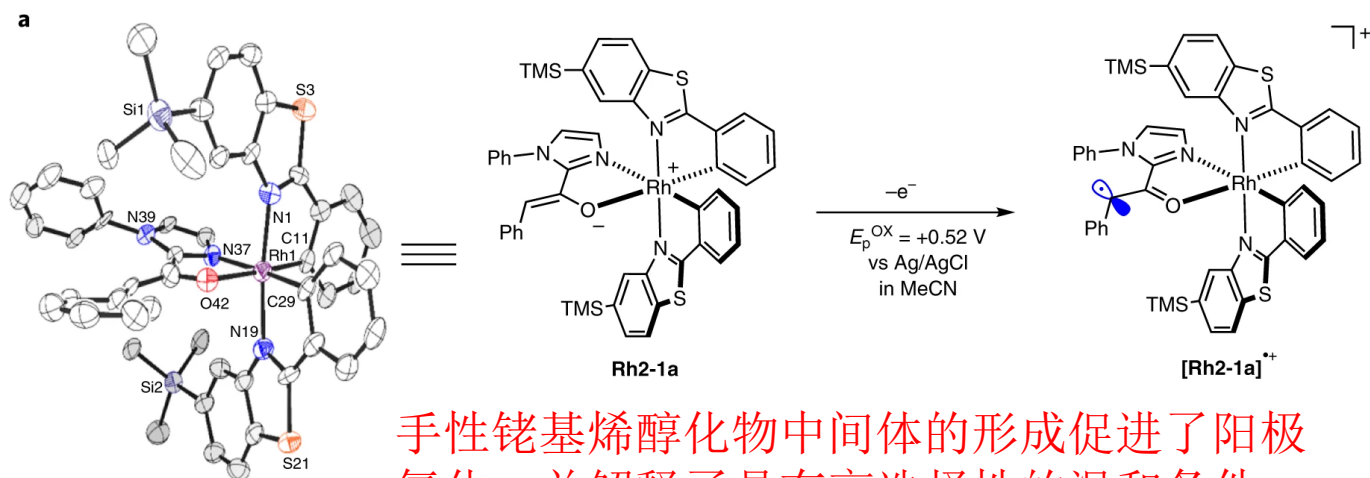


Glucufuranose derivative

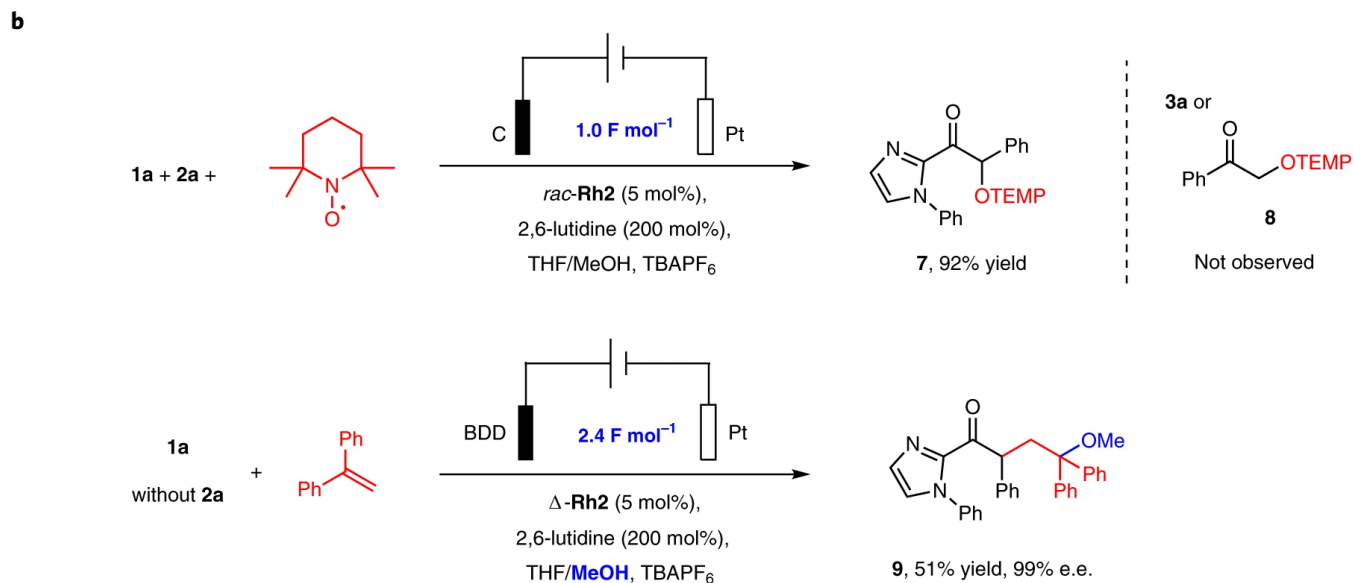
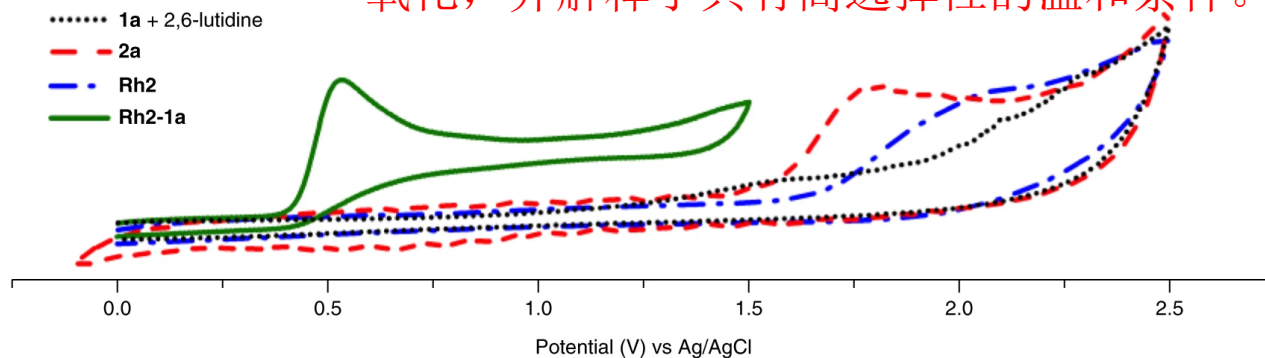
6m, 60% yield, 94% d.e.^a



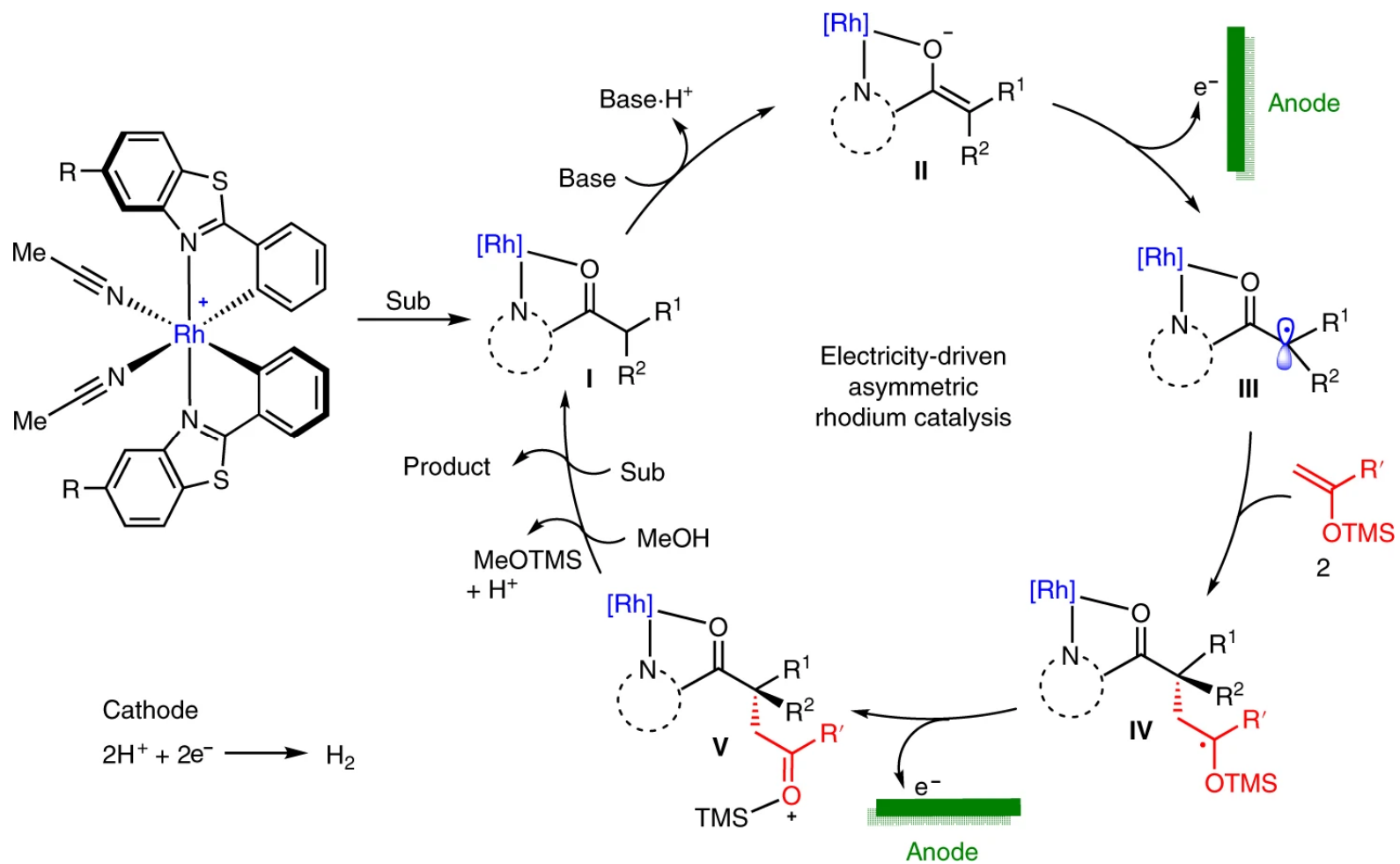
6n, 82% yield, 97% e.e.



手性铑基烯醇化物中间体的形成促进了阳极氧化，并解释了具有高选择性的温和条件。

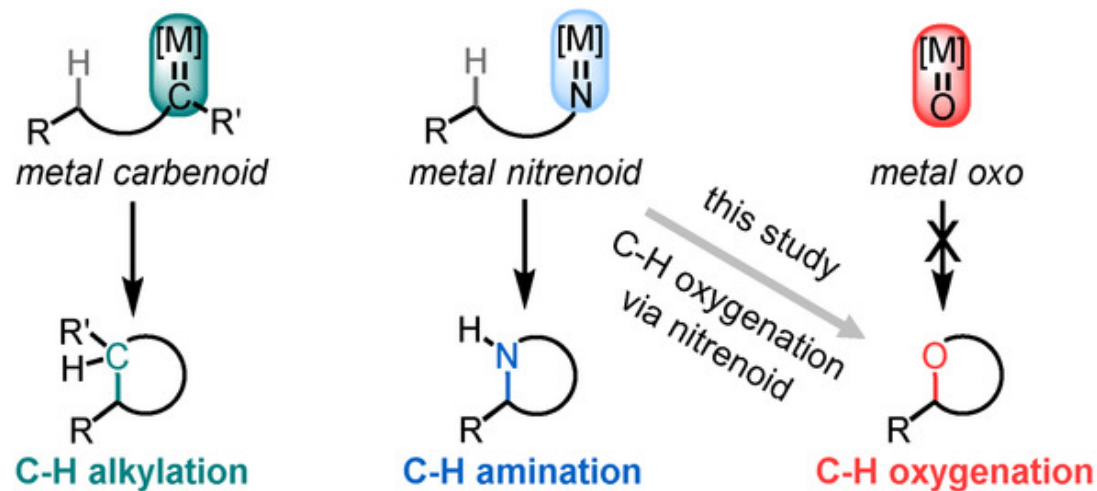


Mechanism

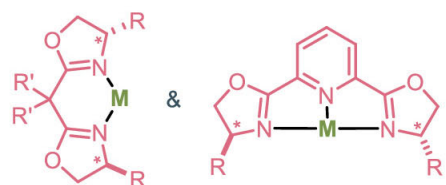


02 Ru-catalyzed reactions

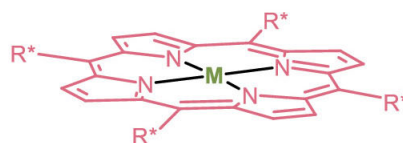
Intramolecular C-H insertion via carbenoids and nitrenoids



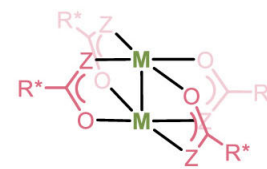
b) Privileged chiral transition metal catalysts for asymmetric nitrene C(sp³)-H insertions



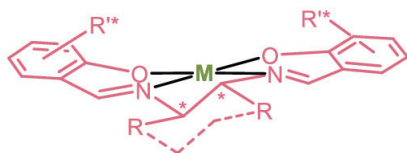
Chiral metal-bisoxazoline complexes
 $M = Ru^{II}, Ag^I$



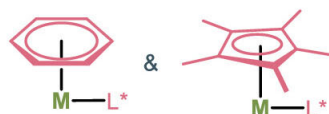
Chiral metal-porphyrin complexes
 $M = Ru^{II}, Mn^{III}, Co^{II}$



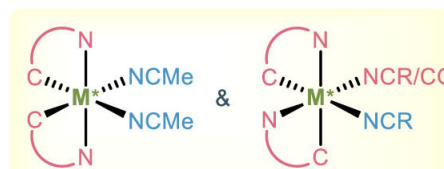
(Z = O, N)
Chiral paddle-wheel complexes
 $M_2 = Rh^{II}-Rh^{II}, Ru^{II}\equiv Ru^{II}$



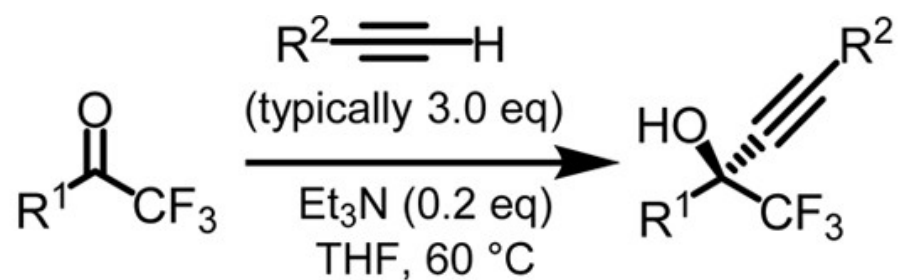
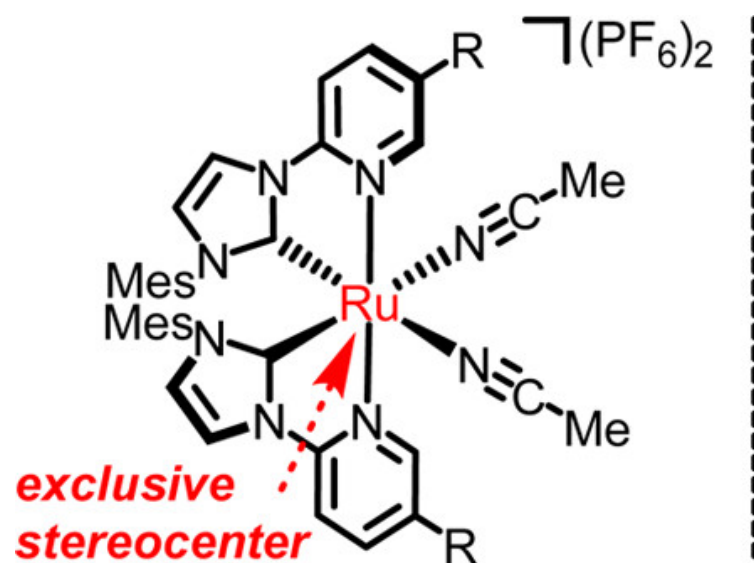
Chiral metal-salen complexes
 $M = Ru^{II}, Mn^{III}, Ir^{III}$



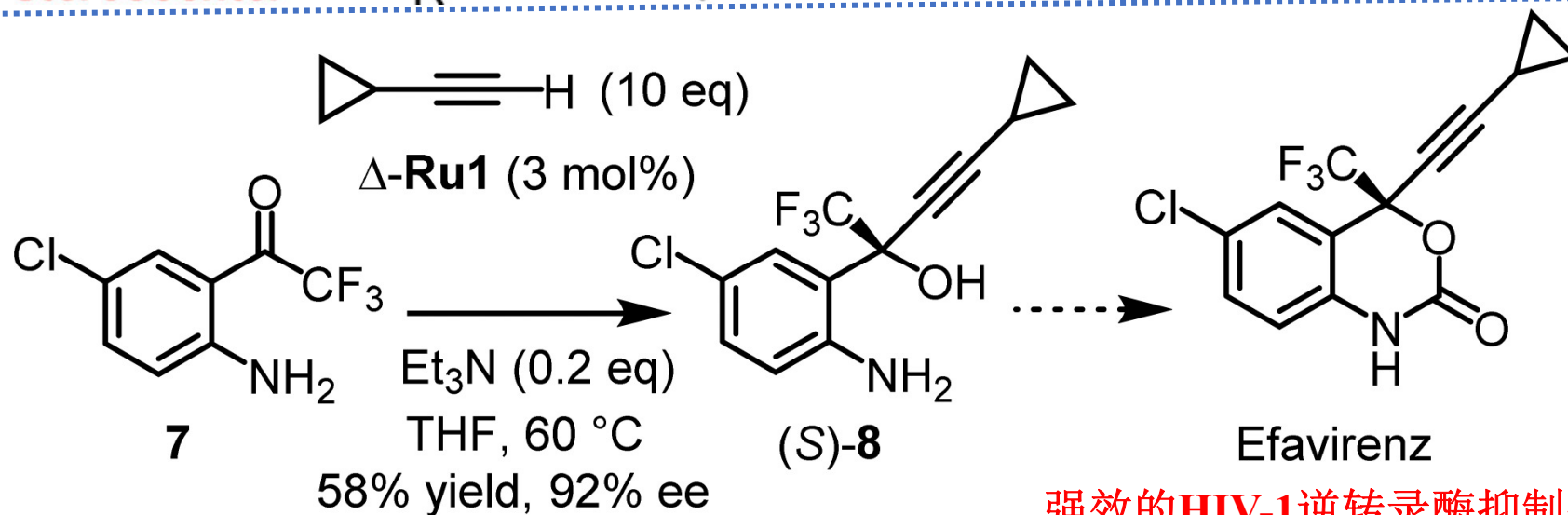
Chiral half-sandwich complexes
 $M = Ru^{II}, Ir^{III}, Rh^{III}$



Chiral-at-metal complexes
 $M^* = Ru^{II}, Os^{II}$

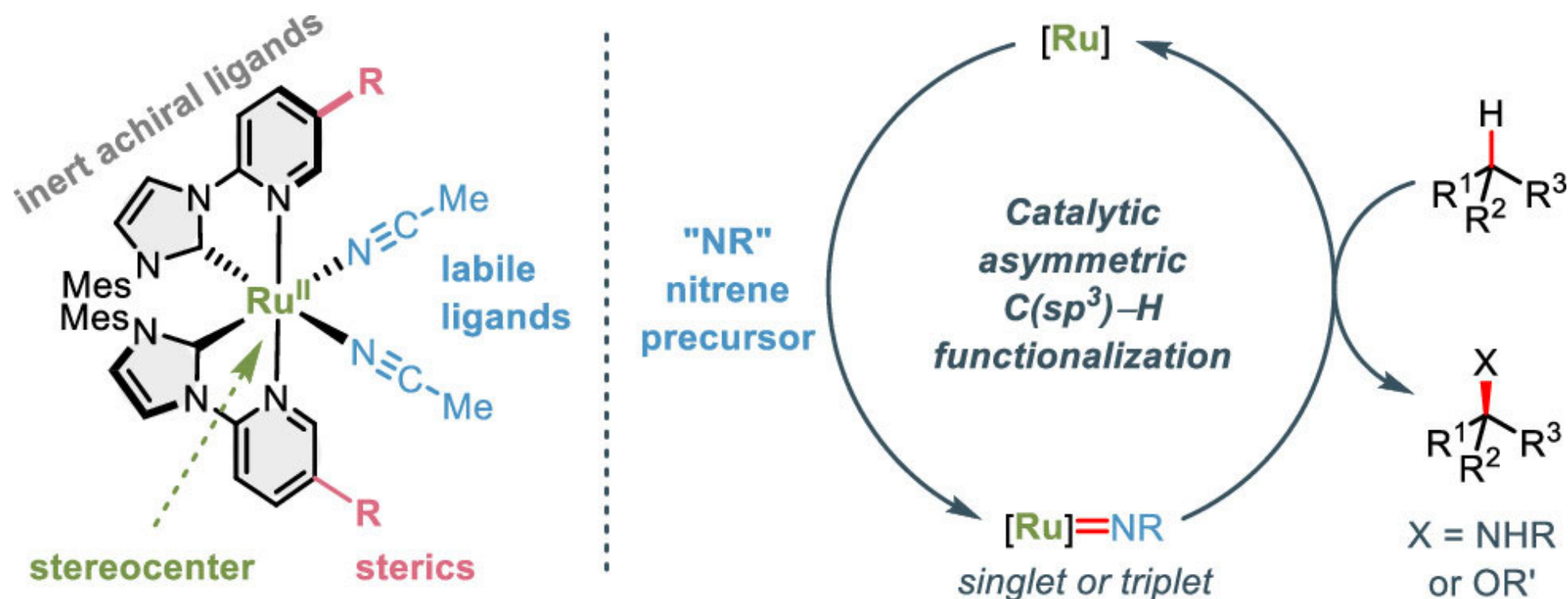


- catalyst loading down to 0.2 mol%
- high yields (up to 99%)
- high enantioselectivity (up to >99% ee)

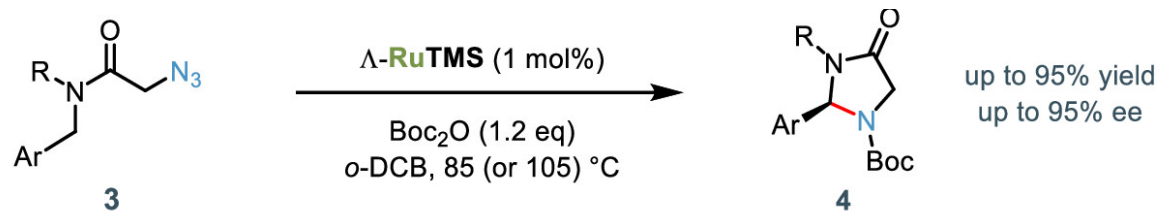


强效的HIV-1逆转录酶抑制剂

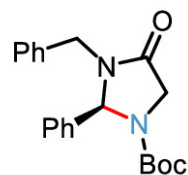
Chiral-at-ruthenium catalysts for nitrene-mediated asymmetric C–H functionalizations



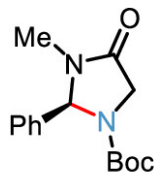
Chen-Xi Ye. *Acc. Chem. Res.* **2023**, 56, 1128–1141.



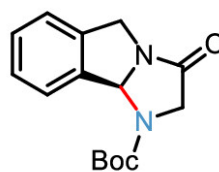
Selected examples:



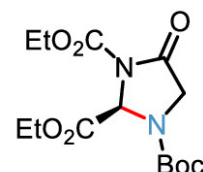
4a, 80% yield
97% ee



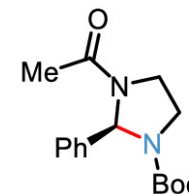
4b, 51% yield
95% ee



4c, 74% yield
94% ee

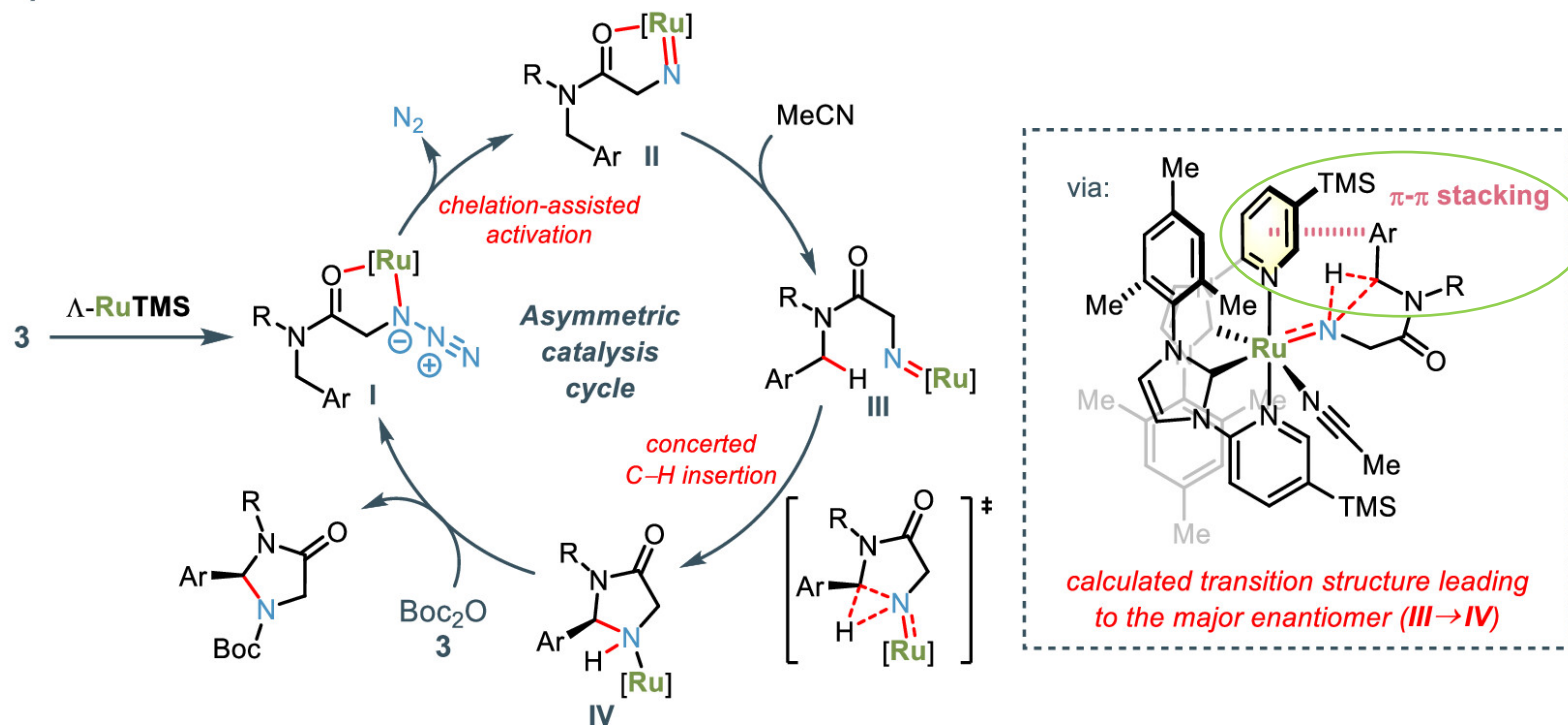


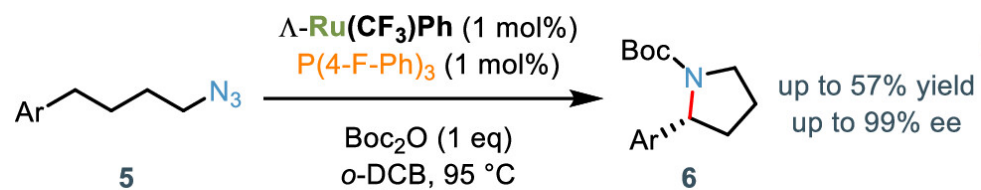
4d, 73% yield
32% ee



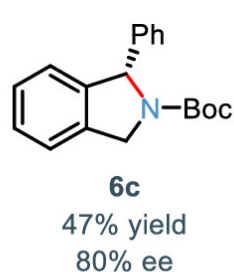
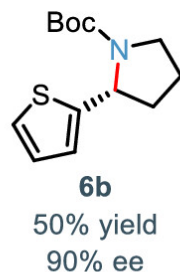
4e, <5% yield
no chelation effect

Proposed mechanism:

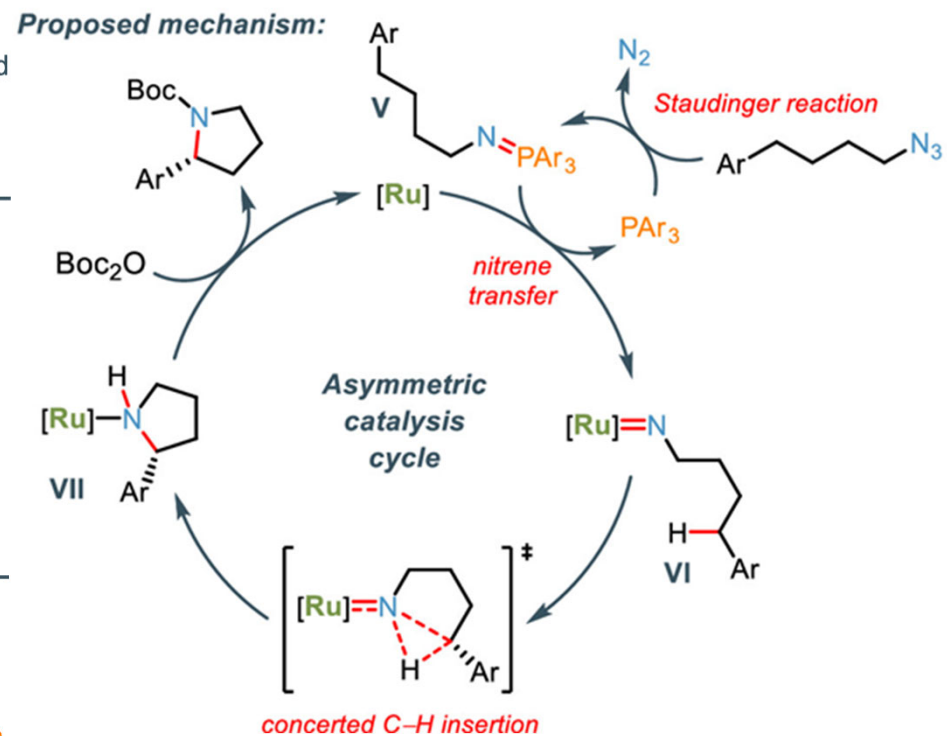
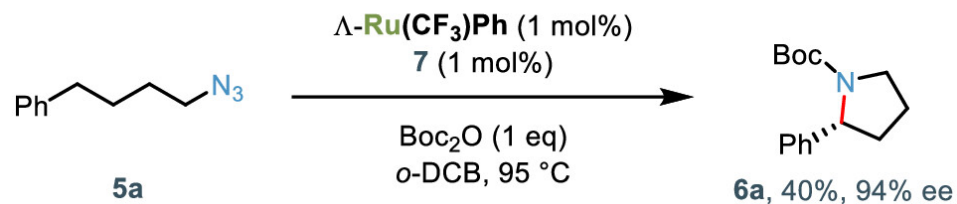
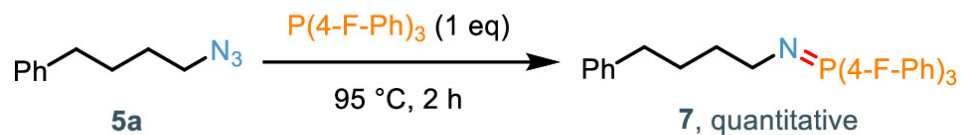




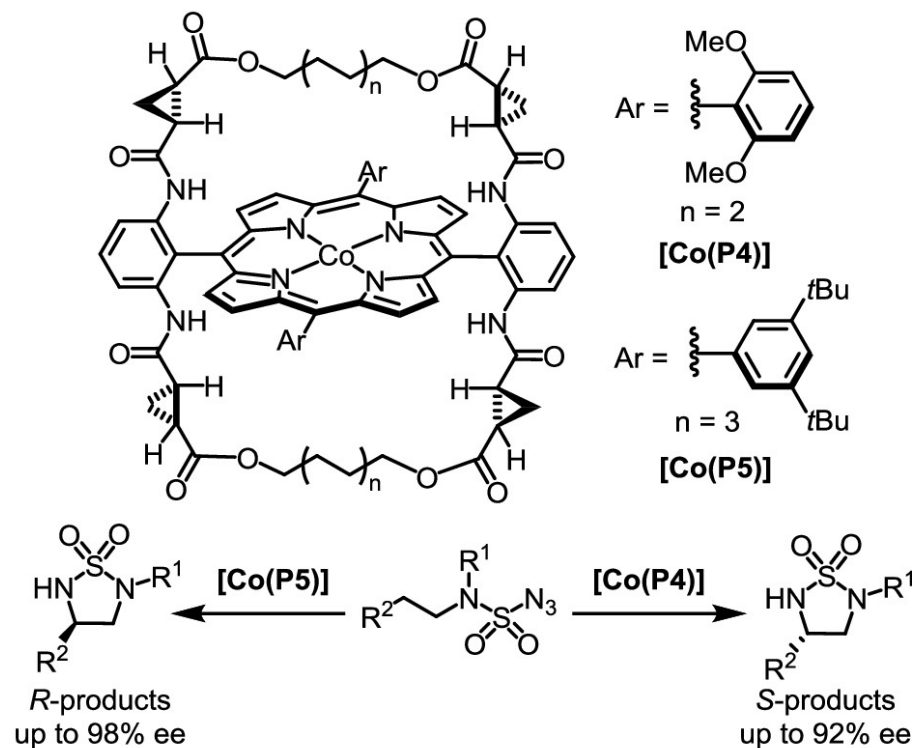
Selected examples:



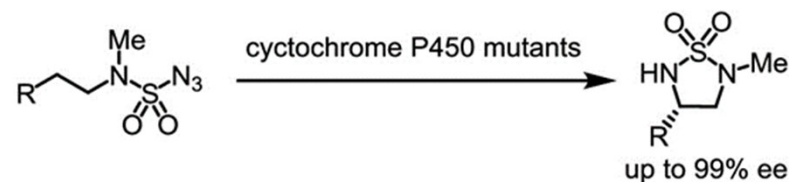
Probing the role of phosphine co-catalyst:



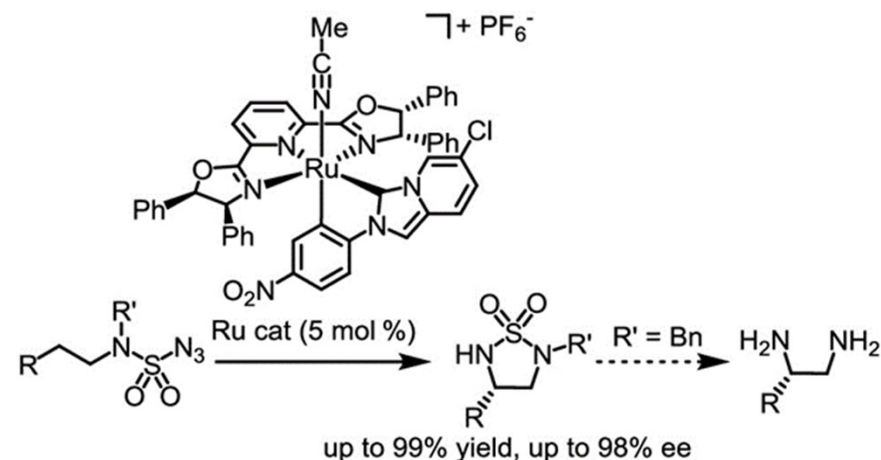
(a) Chiral cobalt porphyrin catalysis: Zhang, 2019



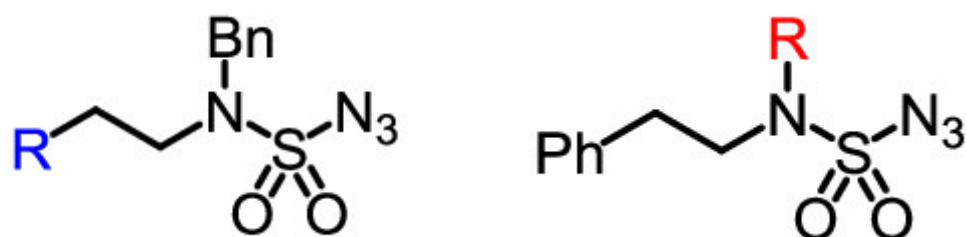
(b) Enzymatic catalysis: Arnold, 2019



(c) Chiral ruthenium pybox catalysis: *This work*



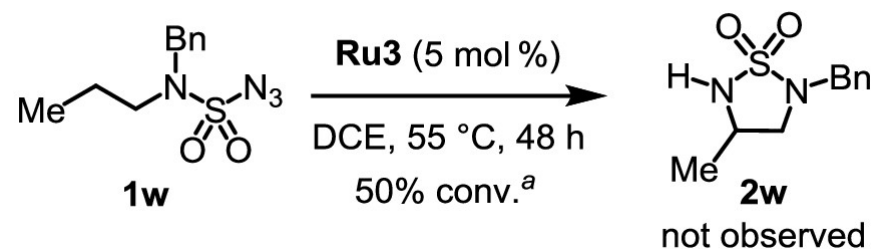
Features: ■ Simple Pybox-Ru catalyst ■ Access to chiral 1,2-diamines



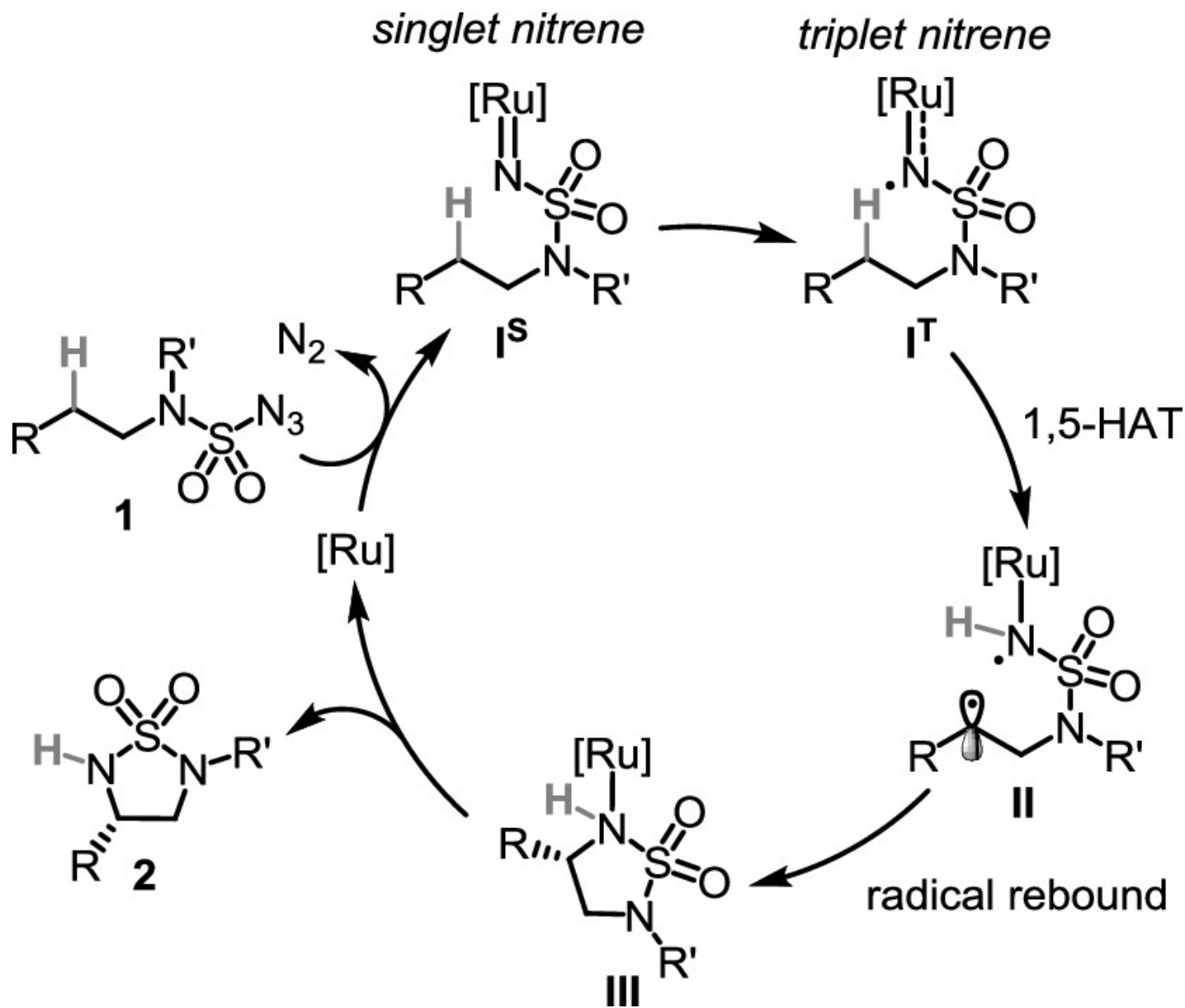
- R: 各种不同电性取代的各种位置的苯基 & 杂芳环*烯基&炔基
- R: 烷基&烯基&炔基

R不能是脂肪族侧链

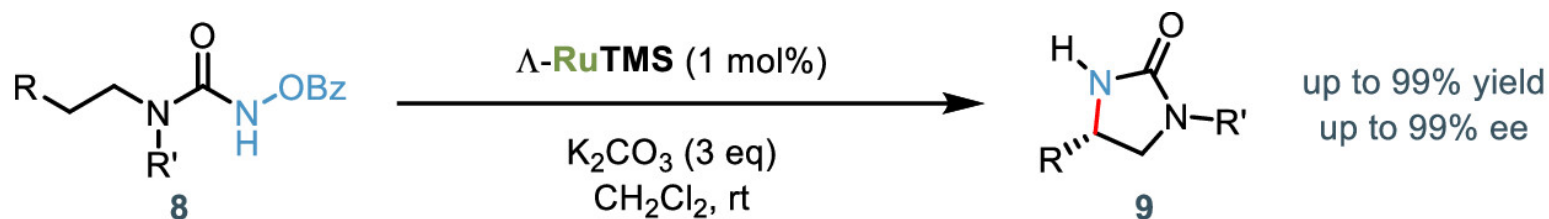
(a) C-H-amination of non-activated C-H groups



Mechanism

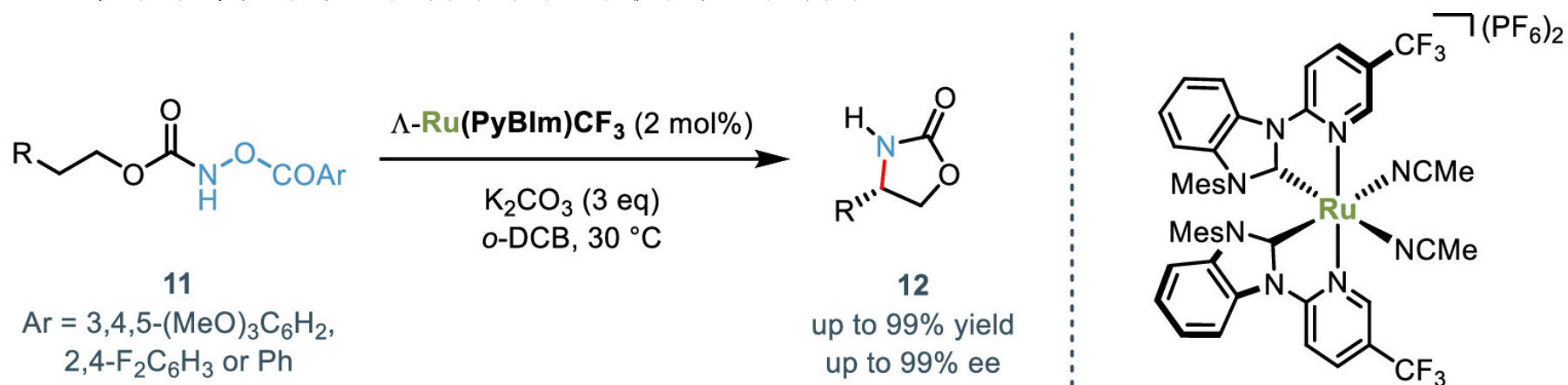


➤ N-苯甲酰氧基脲手性2-咪唑烷酮

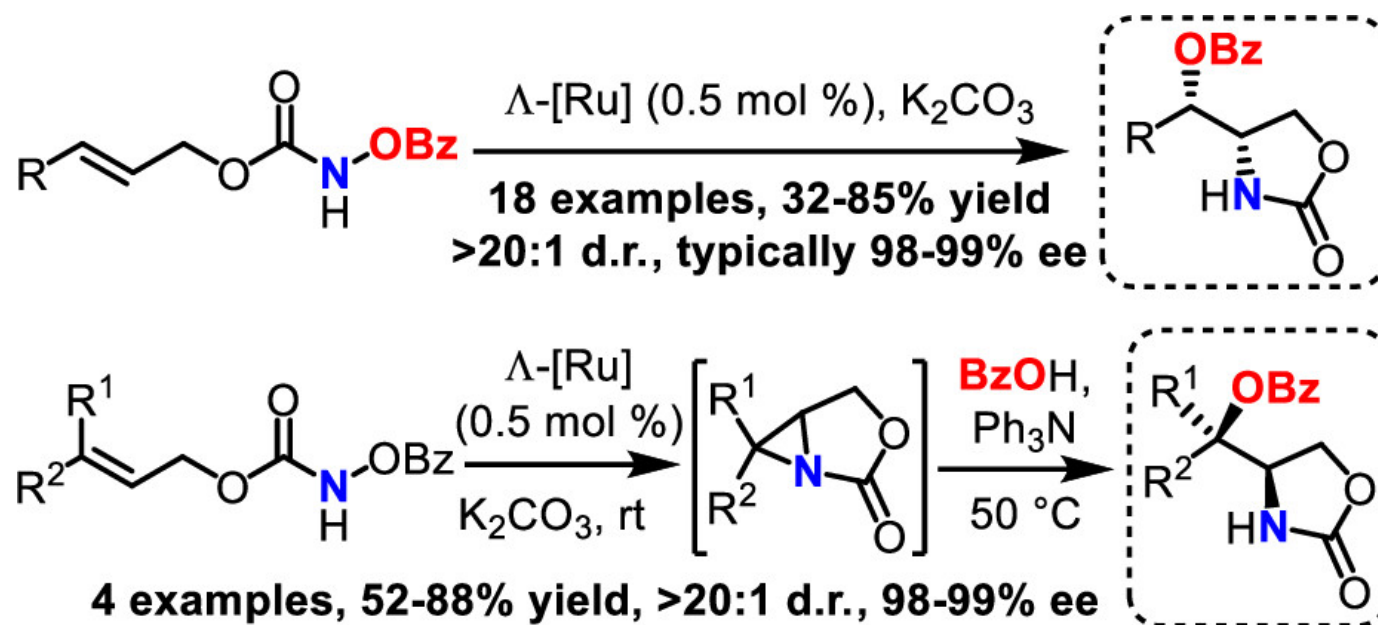


Zijun Zhou. *Chem.* **2020**, *6*, 2024–2034.

➤ N-苯甲酰氧基氨基甲酸酯手性环状氨基甲酸酯



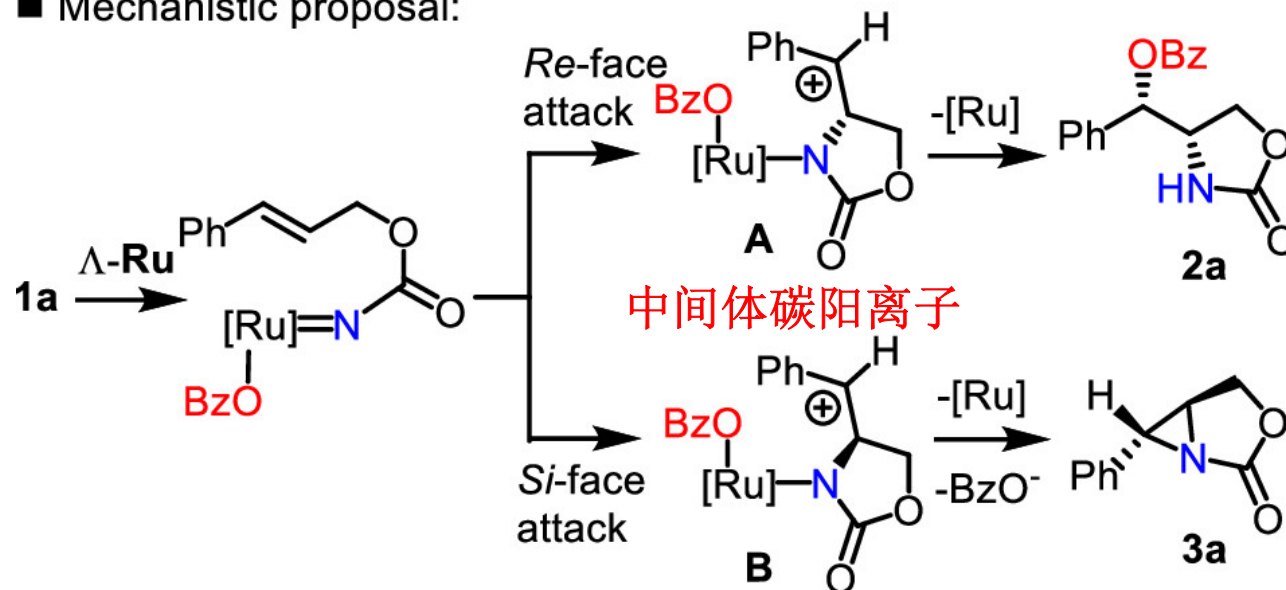
烯烃与邻苯甲酰氧基氨基甲酸酯的闭环氨基氧化反应



Yuqi Tan. *Org. Lett.* 2020, 22, 6653–6656.

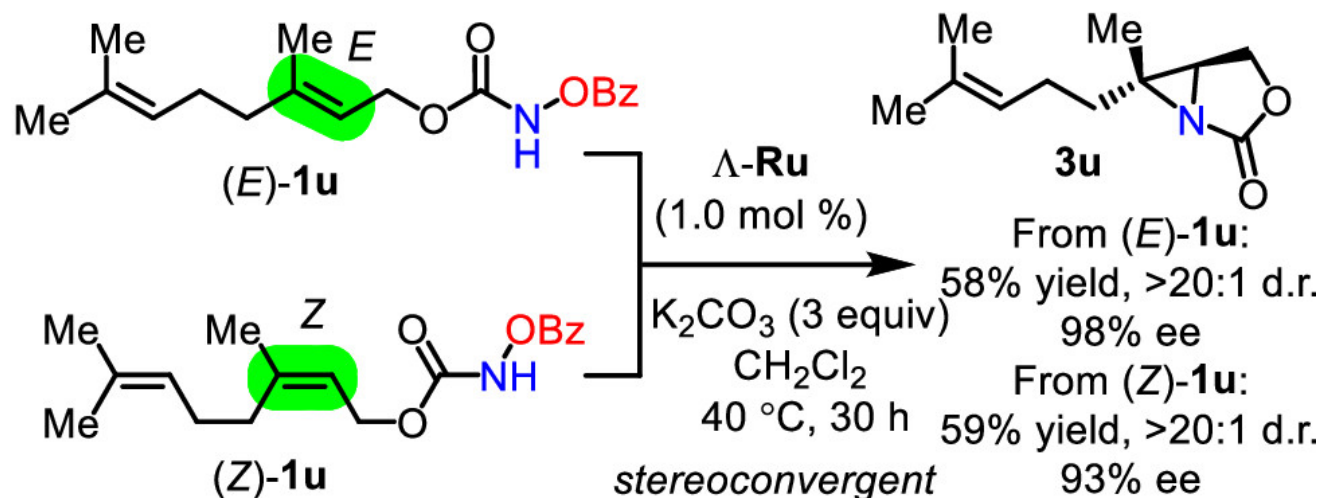
Mechanistic Experiments

■ Mechanistic proposal:

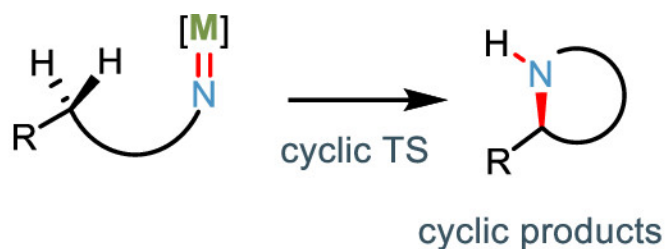


■ Support for carbenium ion intermediate:

验证：中间体碳阳离子机制



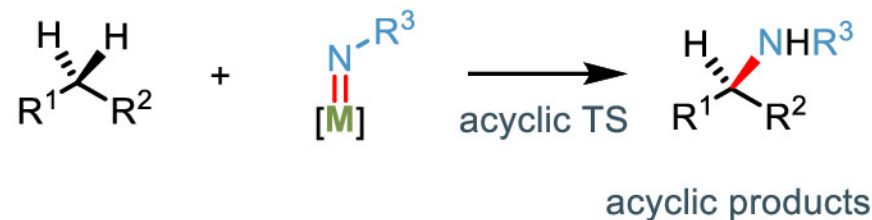
非环状产物的不对称C-H胺化反应



Intramolecular

- (+) High regio- & stereocontrol
- (-) Limited to cyclic products

vs.

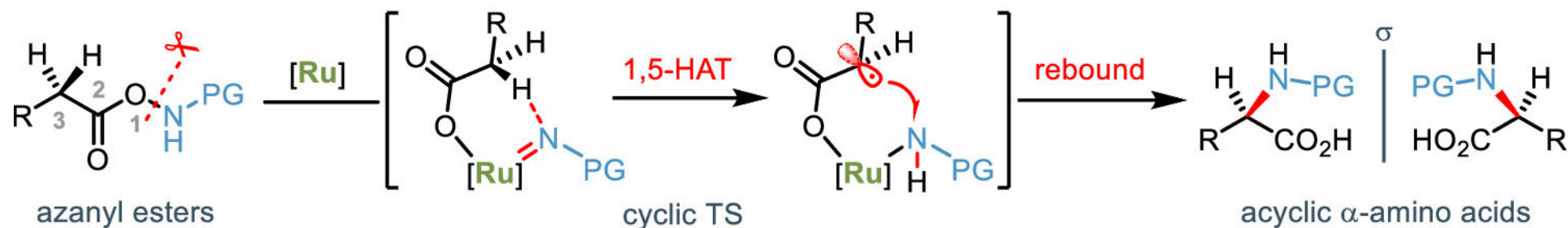


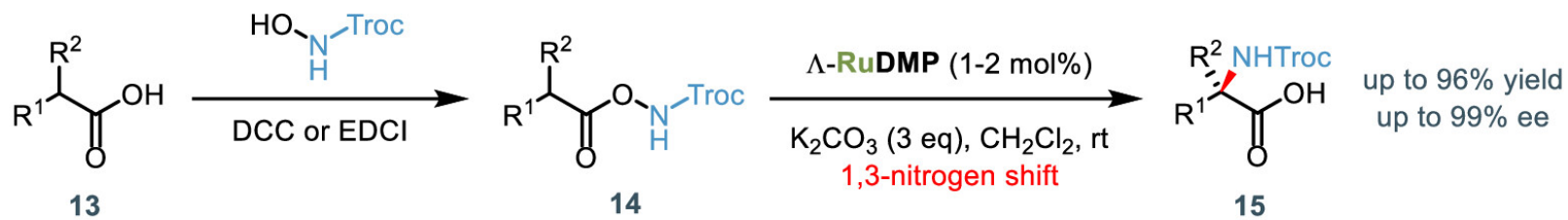
Intermolecular

- (+) Very general
- (-) Challenging regio- & stereocontrol

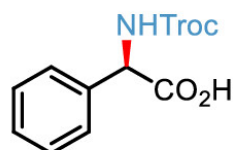
1,3-Nitrogen Shift

- ✓ Cyclic TS: high regio- and stereocontrol
- ✓ No ring-closing: acyclic product

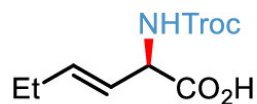




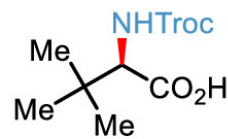
Selected examples:



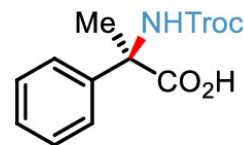
15a, 91% yield
95% ee



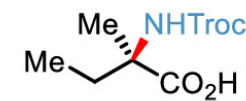
15b, 83% yield
84% ee



15c, 20% yield
90% ee^a



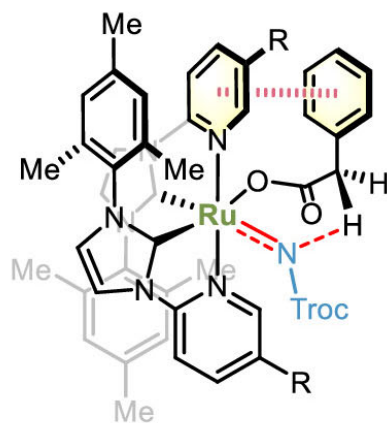
15d, 91% yield
98% ee^b



15e, 57% yield
86% ee^{a,b}

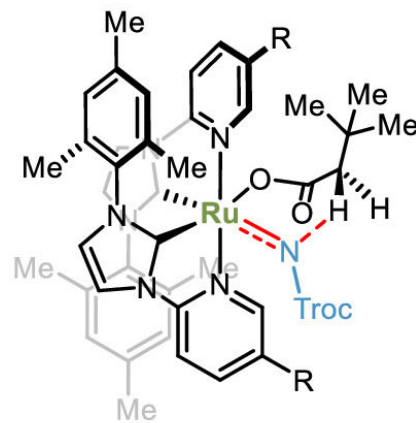
Origin of stereocontrol (calculated transition structures):

a) π - π stacking



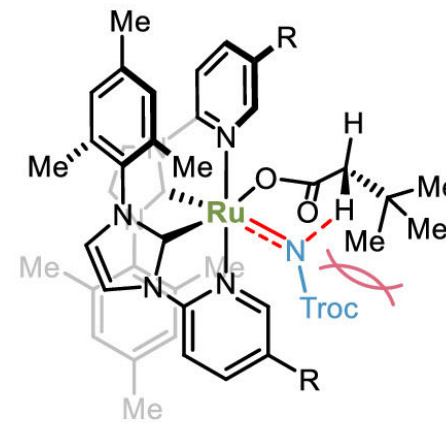
TS-I

b) steric repulsion



TS-II (favored)

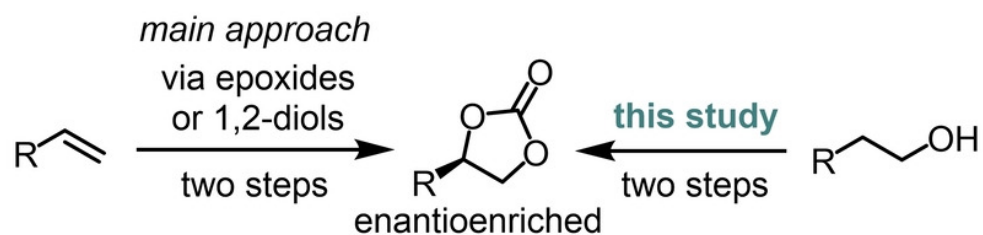
vs.



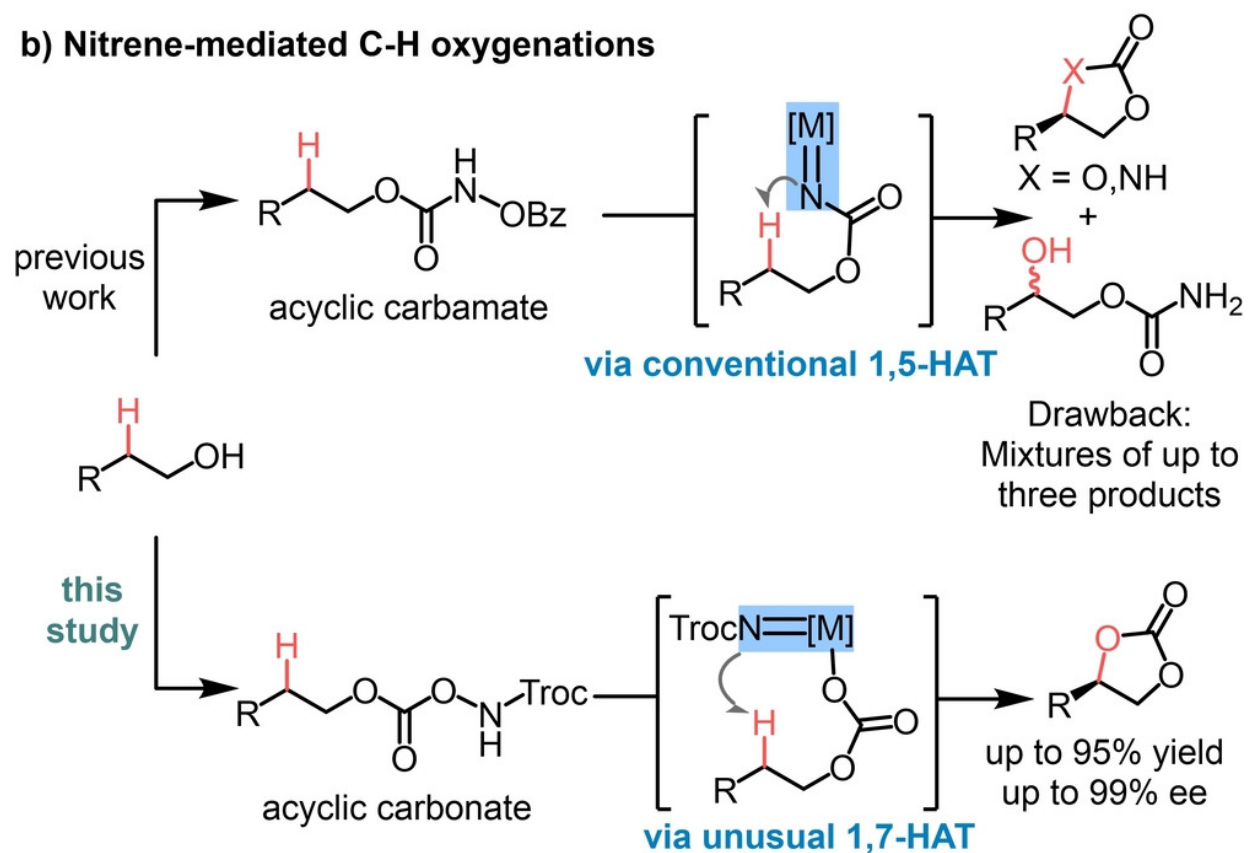
TS-II' (disfavored)

Asymmetric C–H oxygenation

a) Synthesis of enantioenriched cyclic carbonates



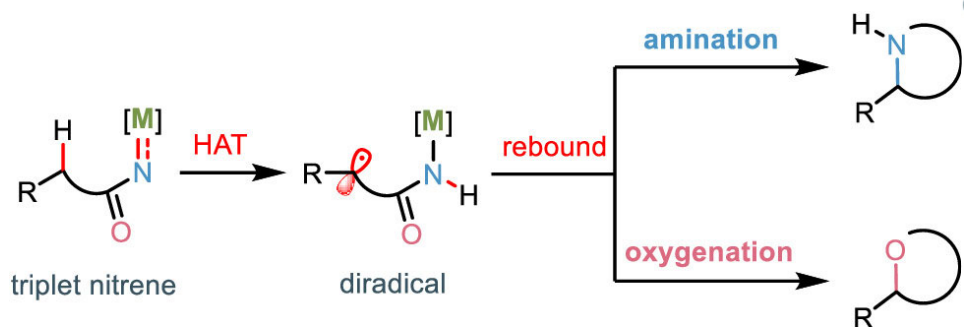
b) Nitrene-mediated C-H oxygenations



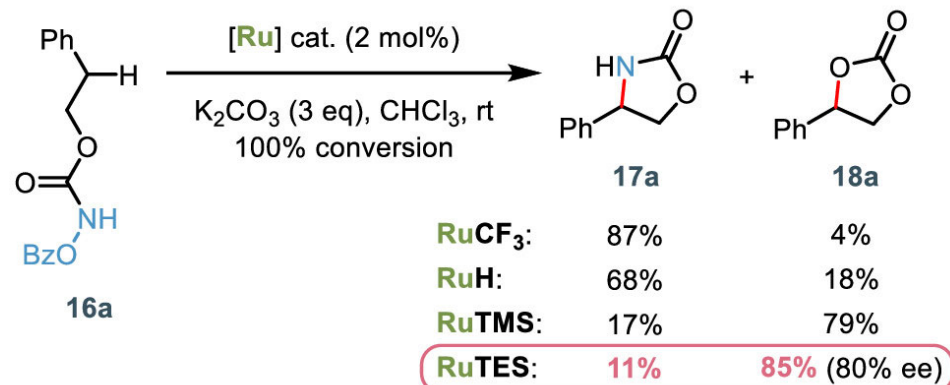
Xin Nie. *Angew. Chem. Int. Ed.* **2022**, 61, e202211971.

Previous work

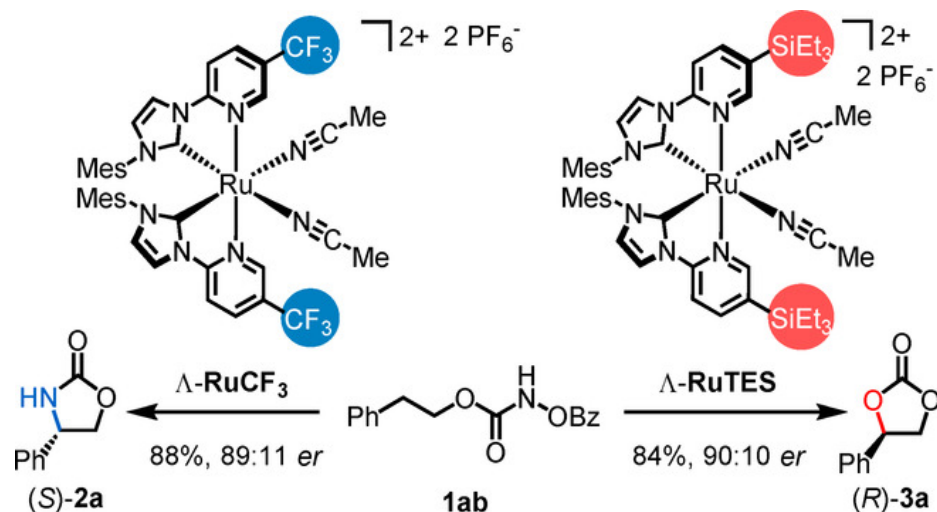
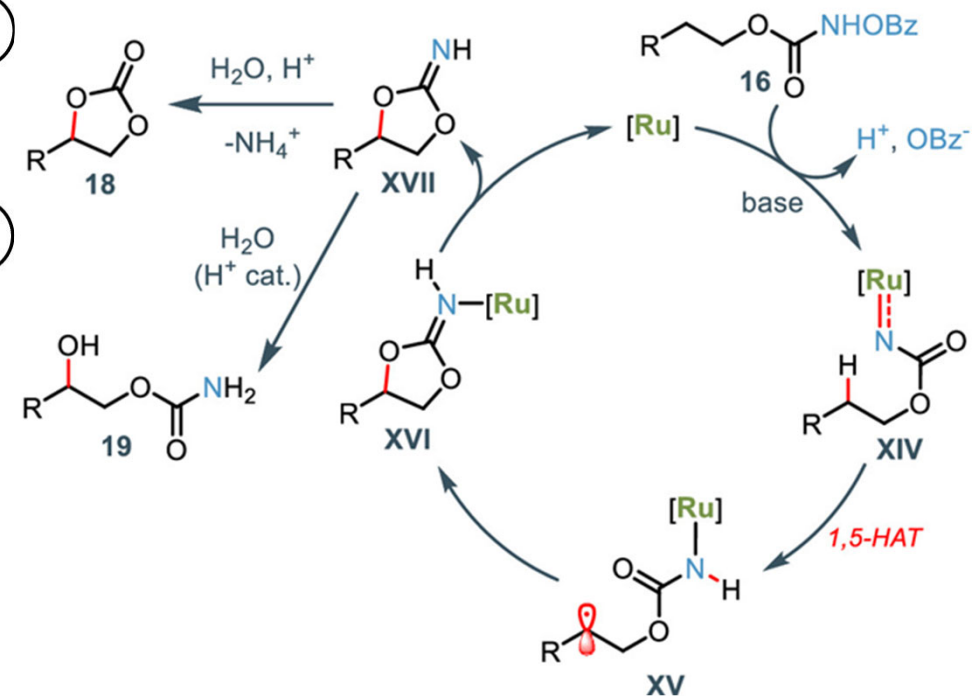
a) Ring-closing C–H oxygenation through metal nitrene species



b) Reaction development



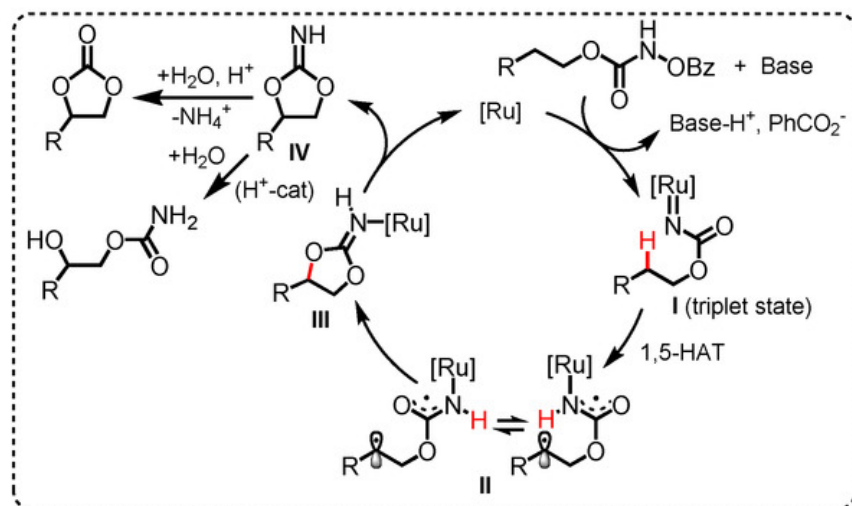
c) Mechanism for nitrene-mediated C–H oxygenation



Yuqi Tan. *Angew. Chem. Int. Ed.*
2020, 59, 21706–21710.

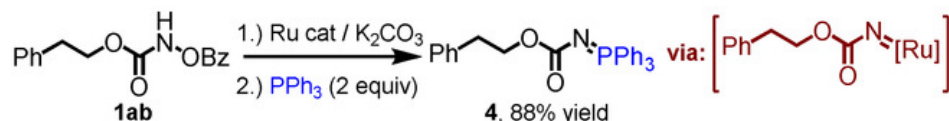
Mechanistic Experiments

Proposed mechanism



Supporting experiments

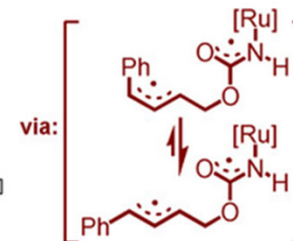
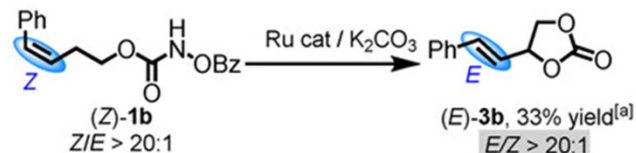
a) Nitrene trapping with PPh_3



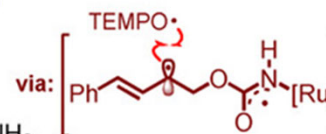
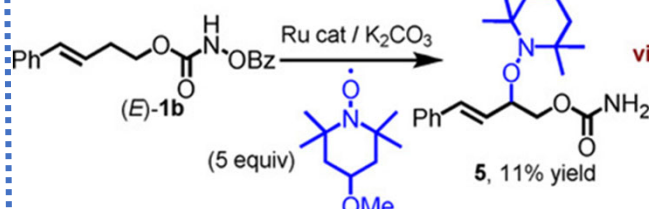
a) 存在氮宾

b) 自由基机制：基本完全异构化，生成稳定的E式结构

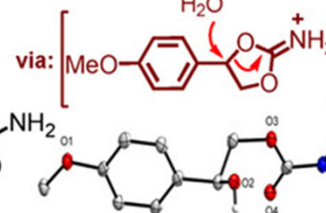
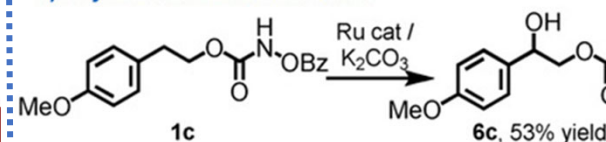
b) Olefin isomerization



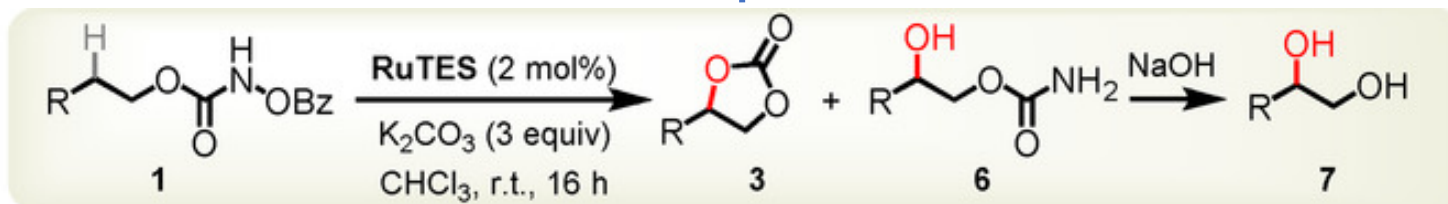
c) Radical trapping with TEMPO



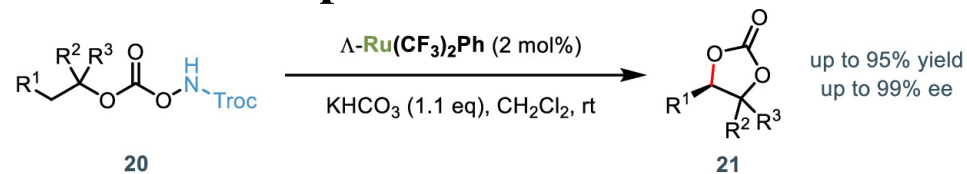
d) Acyclic carbamate formation



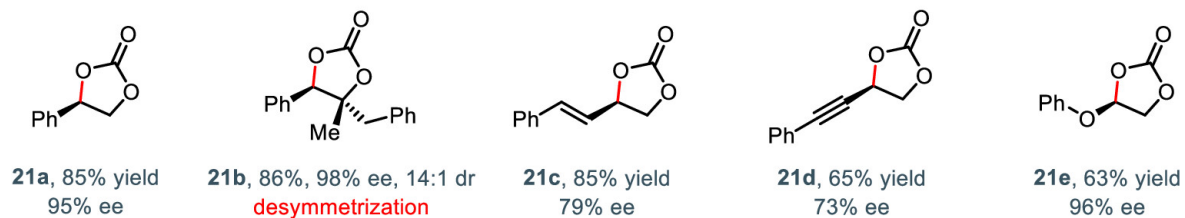
c) 自由基机制：TEMPO成功捕获C自由基



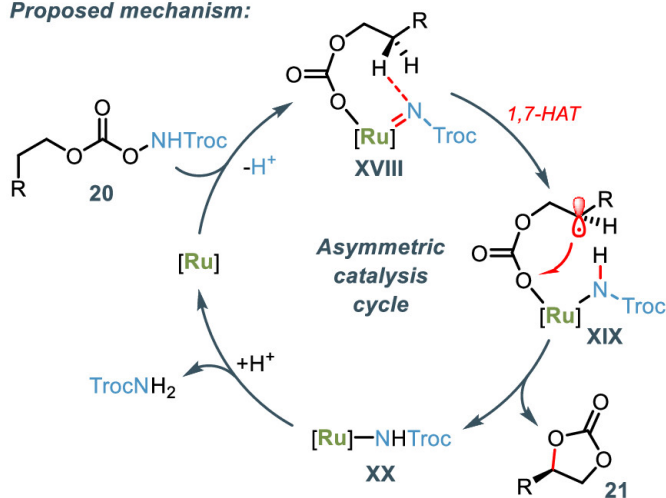
Improvement methods



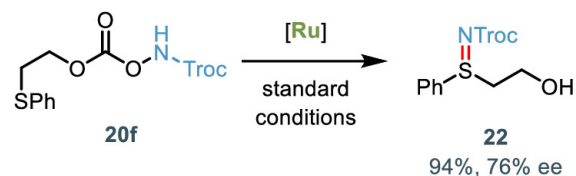
Selected examples:



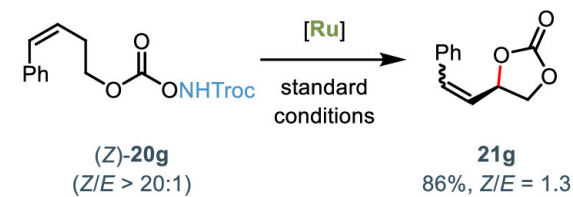
Proposed mechanism:



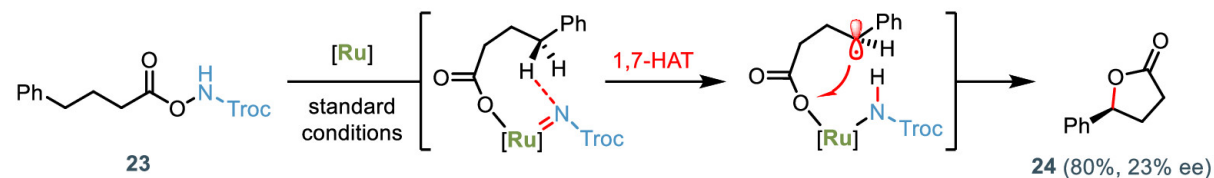
Nitrene trapping by thioether:

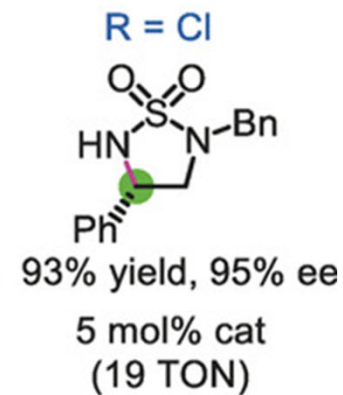
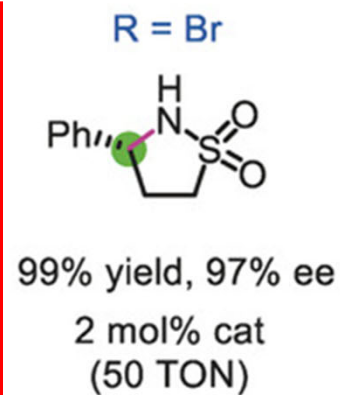
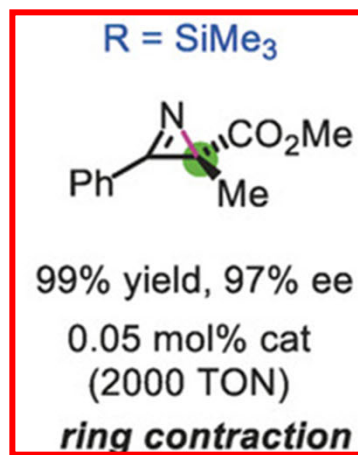
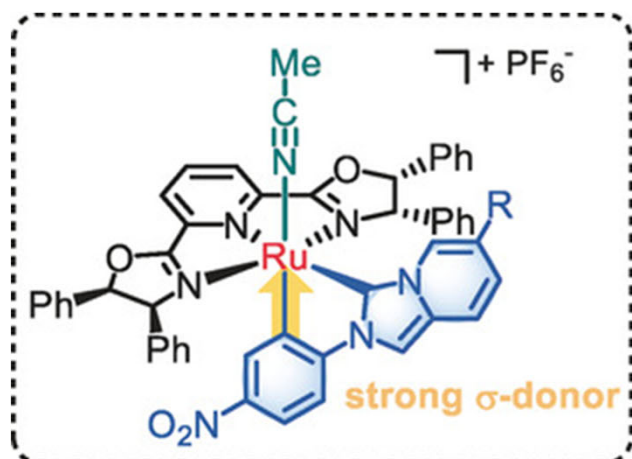


Alkene isomerization: C-H的活化、提取是立体决定步骤

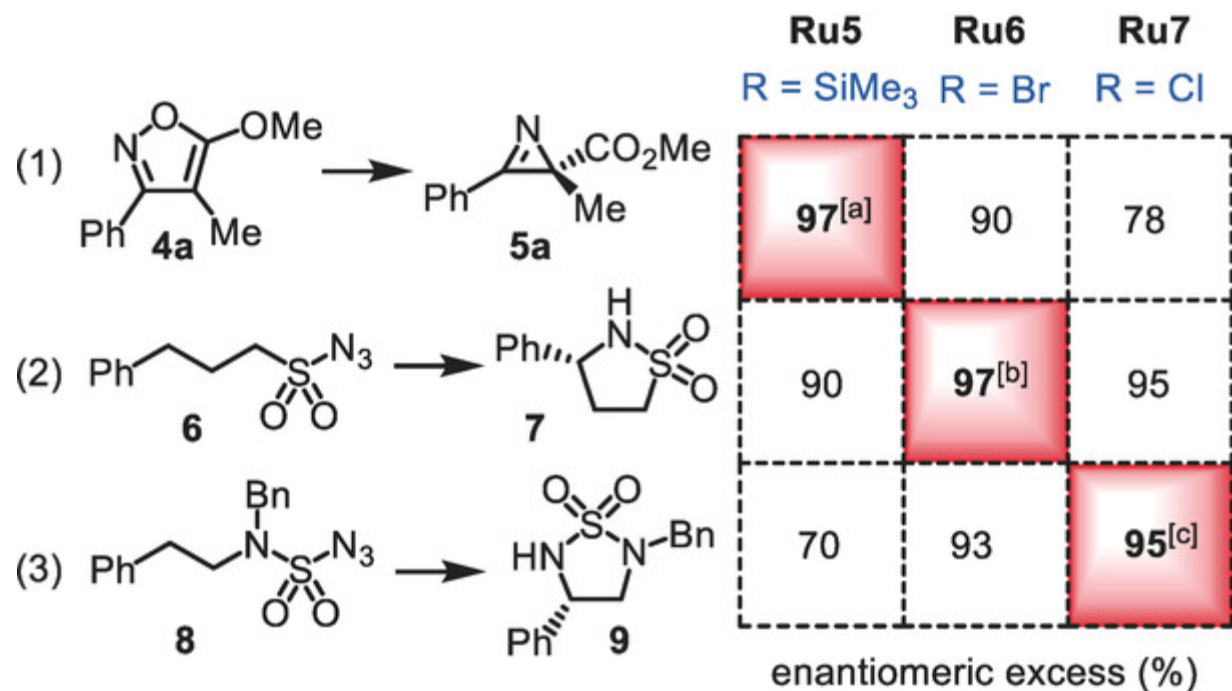


C(sp³)-H oxygenation for accessing chiral lactones:



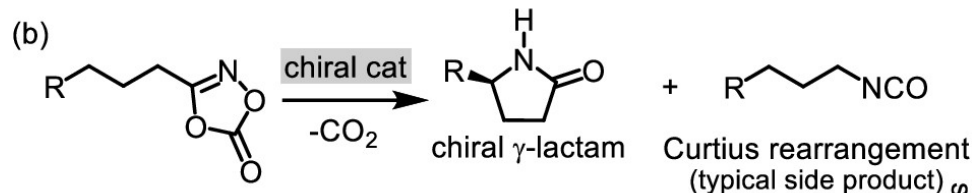
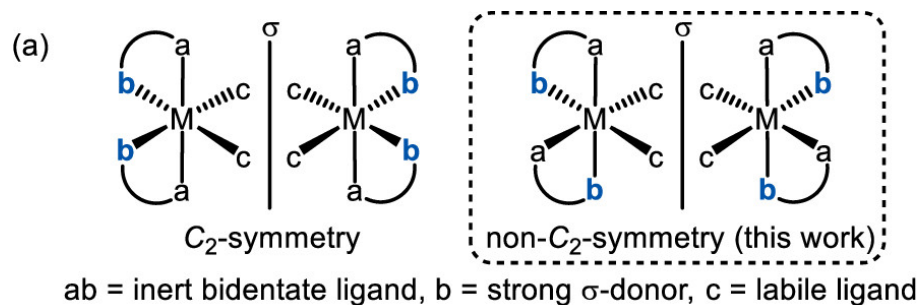


C(sp³)-H aminations

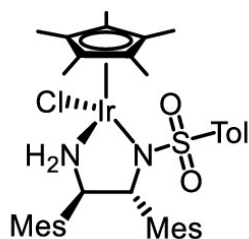


Long Li. *Angew. Chem. Int. Ed.* **2020**, *59*, 12392 – 12395.

Non-C₂-Symmetric Chiral-at-Ruthenium Catalyst

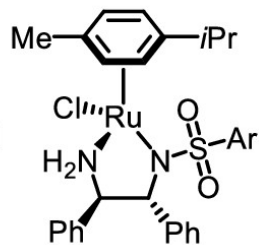


Chang, 2019:



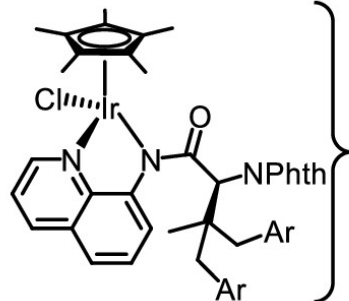
up to 99:1 e.r.
TON = 19

Yu, 2019:



up to 99:1 e.r.
TON = 9

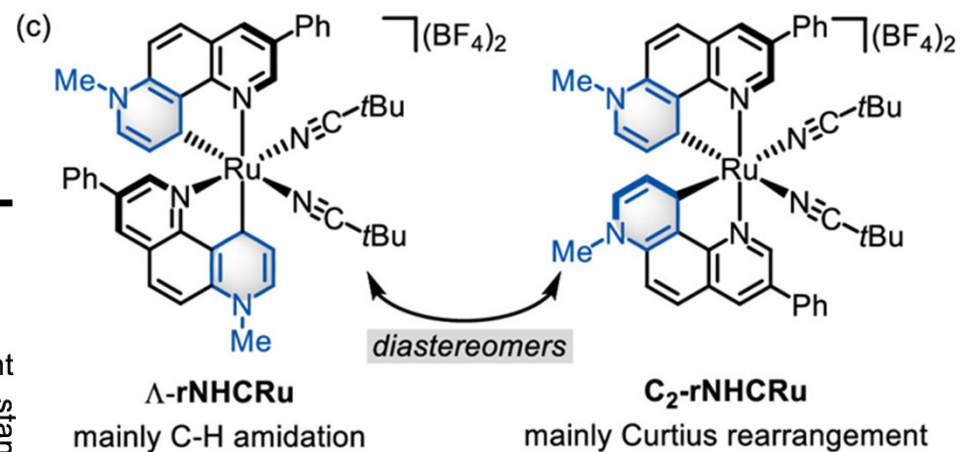
Chen, 2019:



up to 99:1 e.r.
up to TON = 100

standard half-sandwich scaffolds

This work: Novel cat. Λ -rNHCRu, up to 99:1 e.r., up to TON = 11200



Zijun Zhou. *J. Am. Chem. Soc.*
2019, 141, 19048–19057.

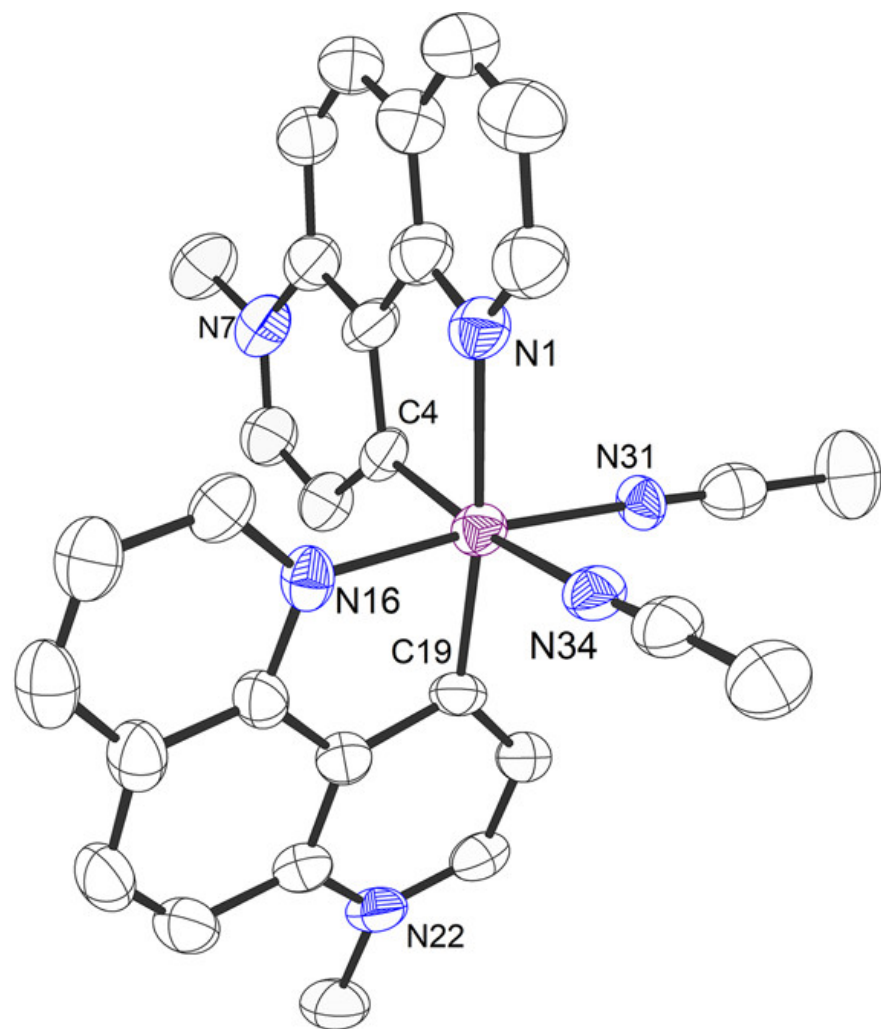
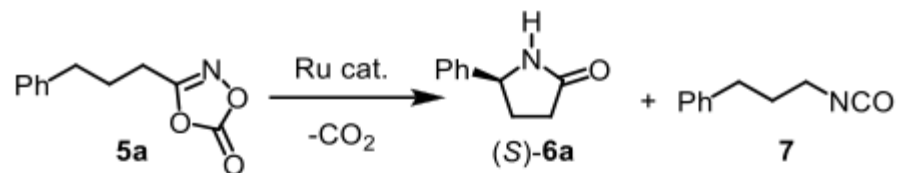
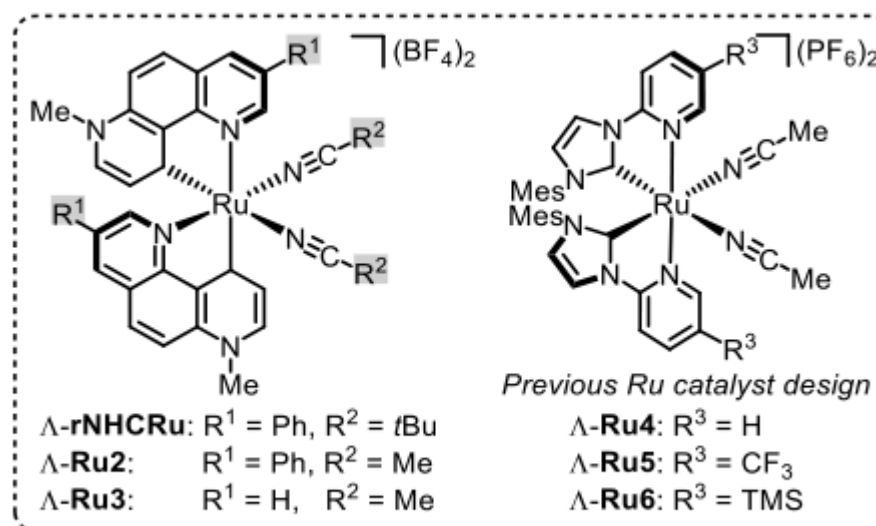


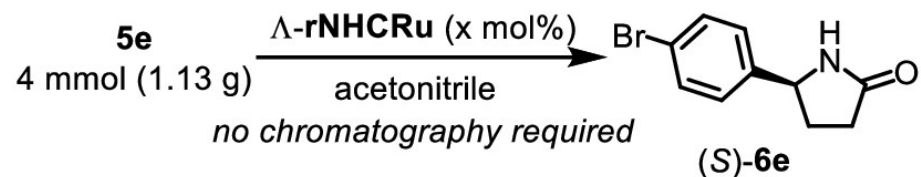
Table 1. Comparison of Different Ruthenium Catalysts^a



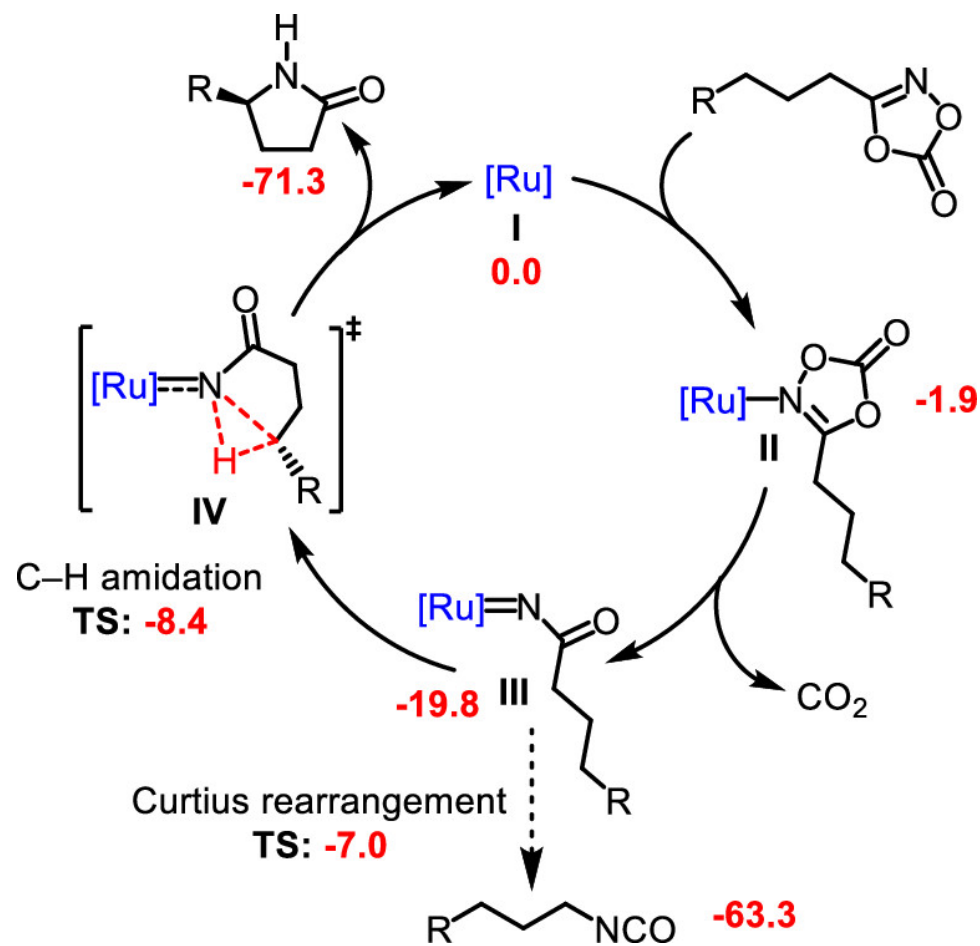
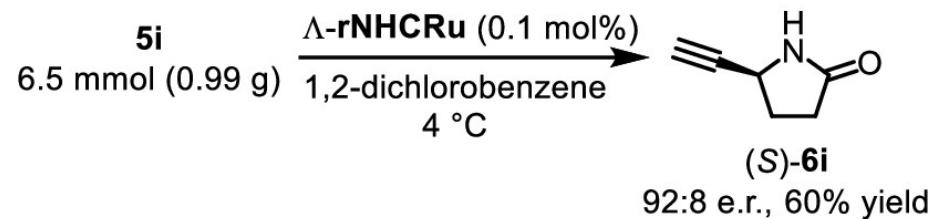
entry	catalyst	loading (mol %)	T (°C)	yield (%) ^b		er ^c
				6a	7	
1	Λ -rNHCRu	0.5	rt	93 (92) ^d	6	95:5
2	Λ -Ru2	0.5	rt	92 (91) ^d	7	94:6
3	Λ -Ru3	0.5	rt	84 (82) ^d	15	92:8
4	Λ -Ru4	0.5	rt		>99	
5	Λ -Ru5	0.5	rt		>99	
6	Λ -Ru6	0.5	rt		>99	
7	Λ -rNHCRu	0.5	4	95 (95) ^d	5	96:4
8 ^e	Λ -rNHCRu	0.1	4	95 (95) ^d	5	96:4
9 ^f	Λ -rNHCRu	0.05	4	93 (93) ^d	7	95:5

Mechanism

(a) Gram-scale synthesis of (S)-6e and (S)-6i:

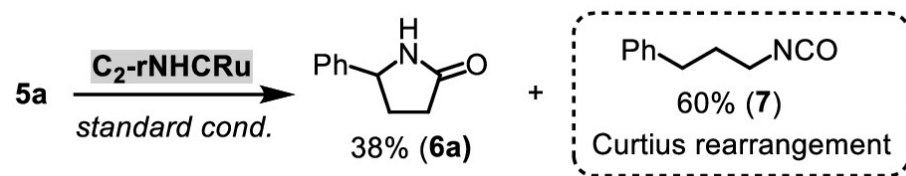


Cond. A: 0.02 mol% cat. at r.t. >99:1 e.r., 74% yield
Cond. B: 0.005 mol% cat. at 40 °C >99:1 e.r., 56% yield

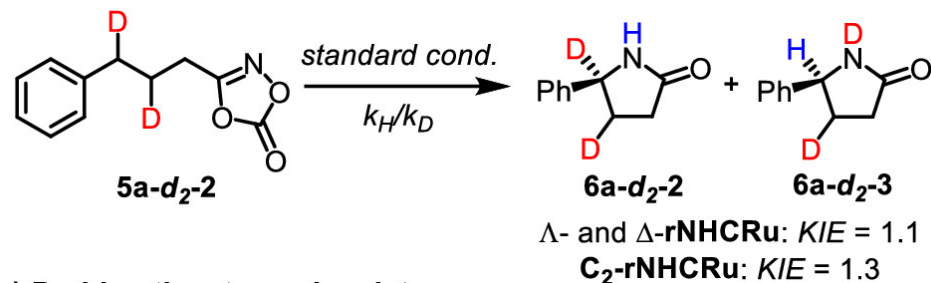
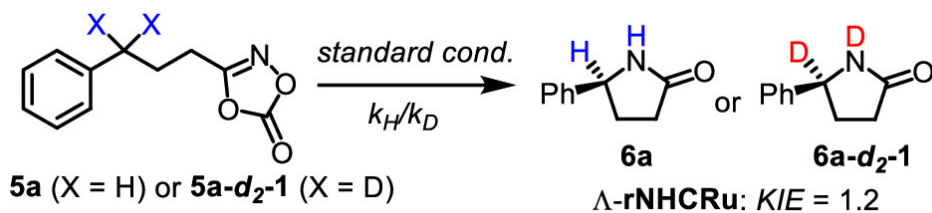


Mechanistic Experiments

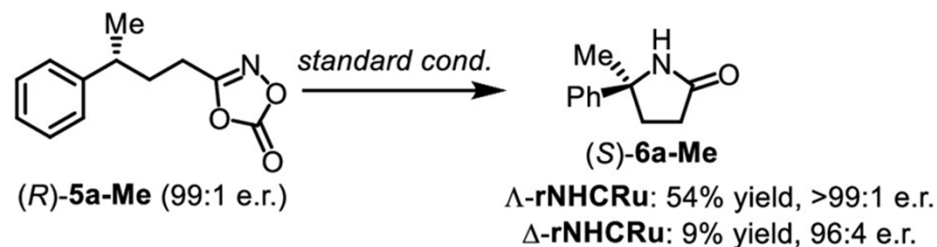
(a) Control experiment with C₂-symmetric rNHCRu:



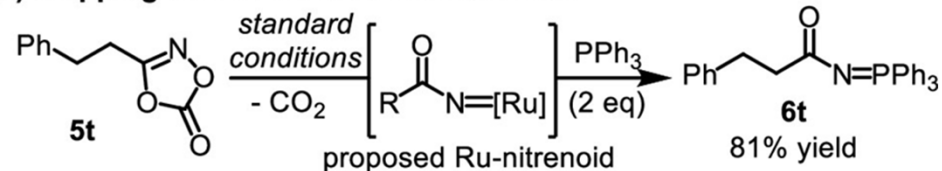
(b) Kinetic isotope effects:



(c) Probing the stereochemistry:



(d) Trapping of Ru-nitrenoid intermediate:



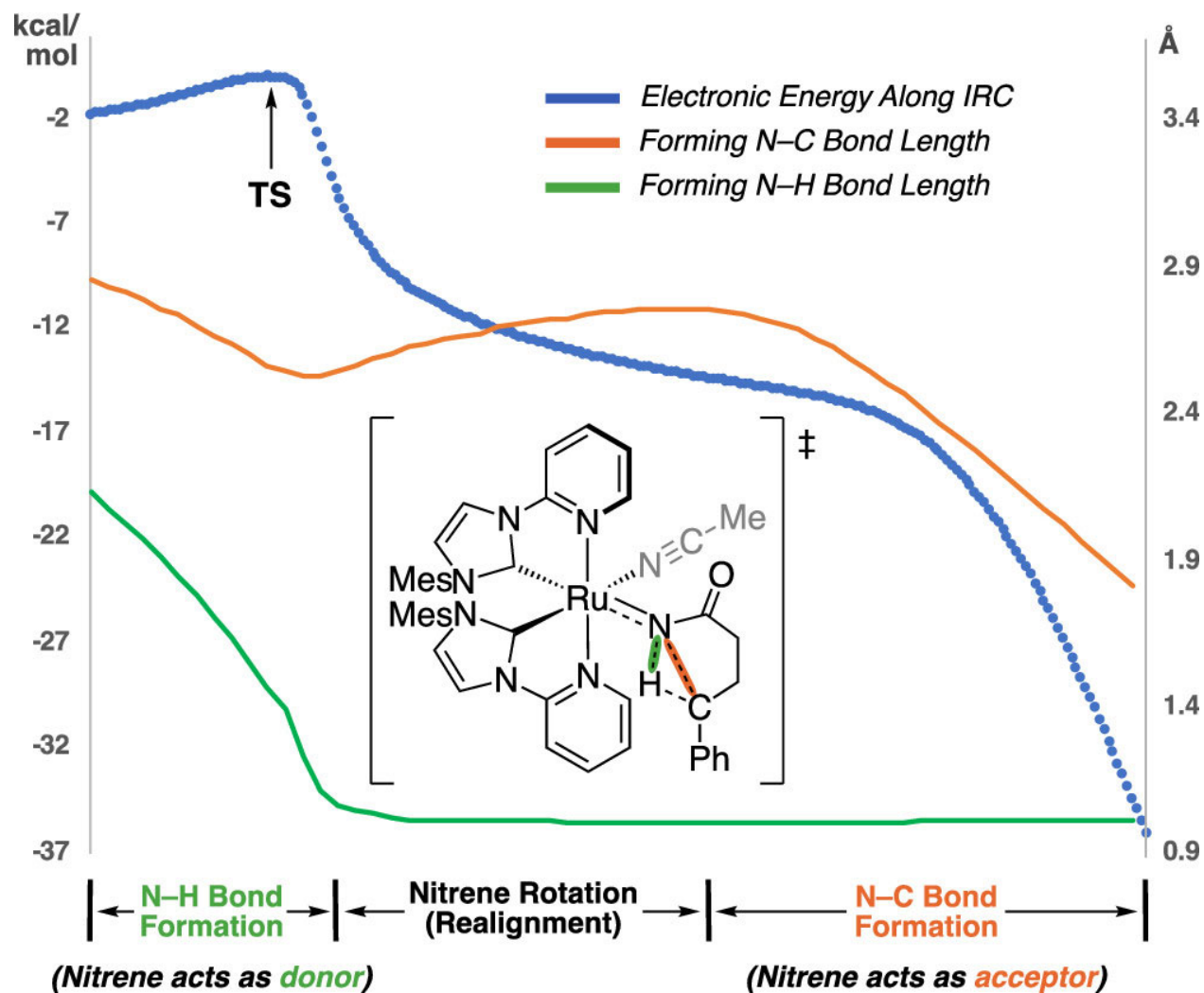
a) C₂对称催化剂有利于Curtius副产物

b) KIE: 单重态氮宾插入具有协同的N-C 和N-H 形成途径

c) 两个对映体C-H键之间的高度立体化学区别, 两种不同催化剂对产率影响较大

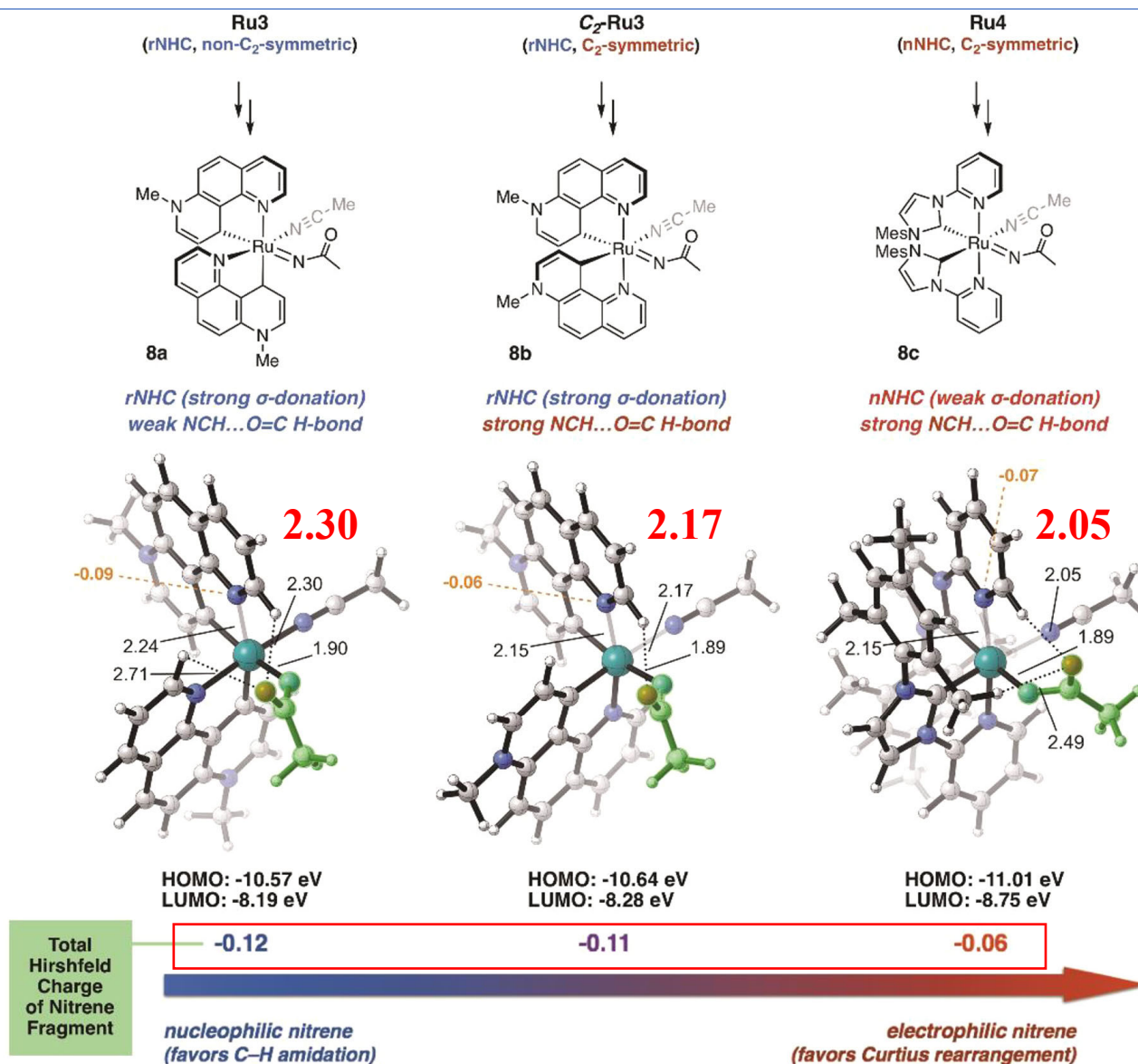
d) PPh₃成功捕获氮宾中间体

Mechanistic Experiments



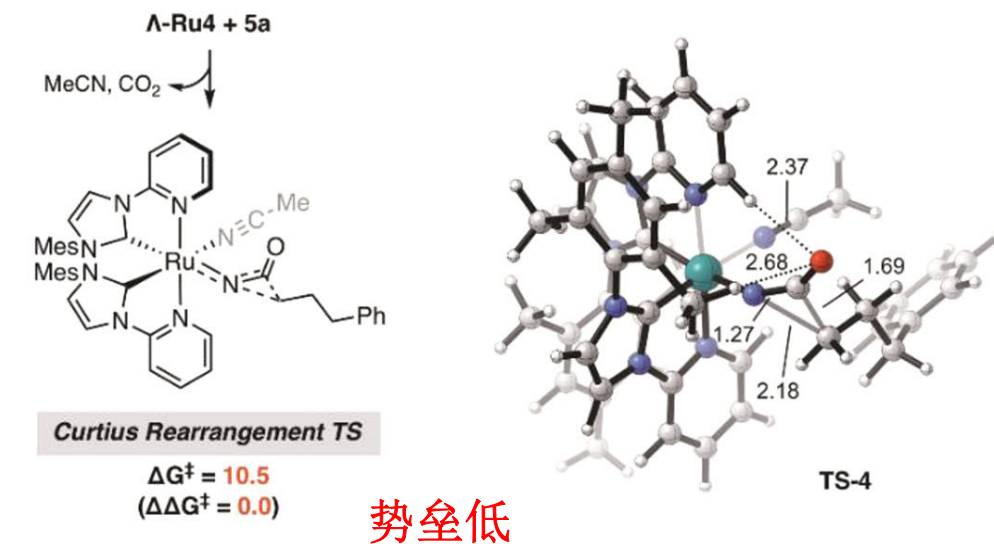
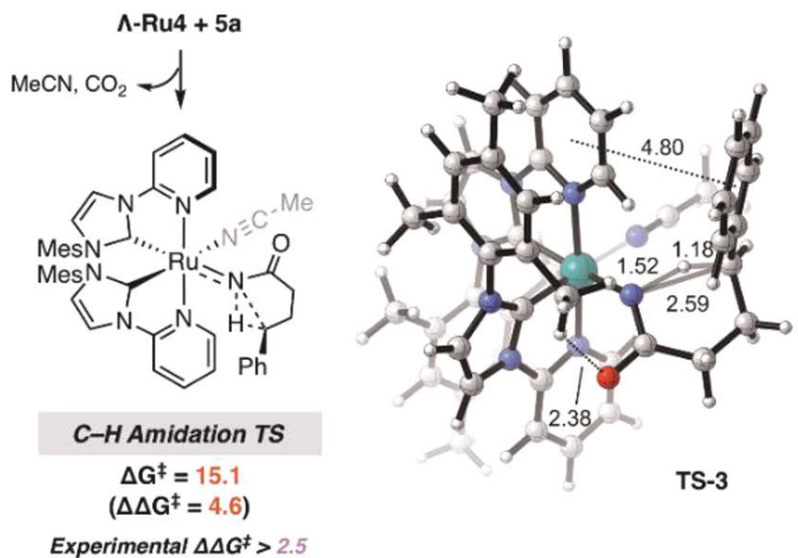
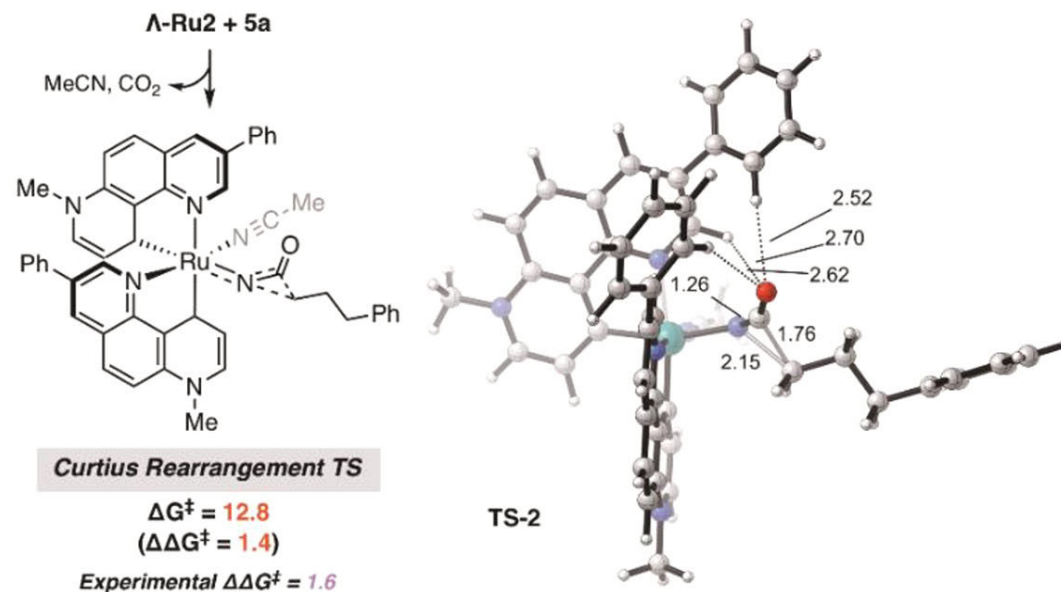
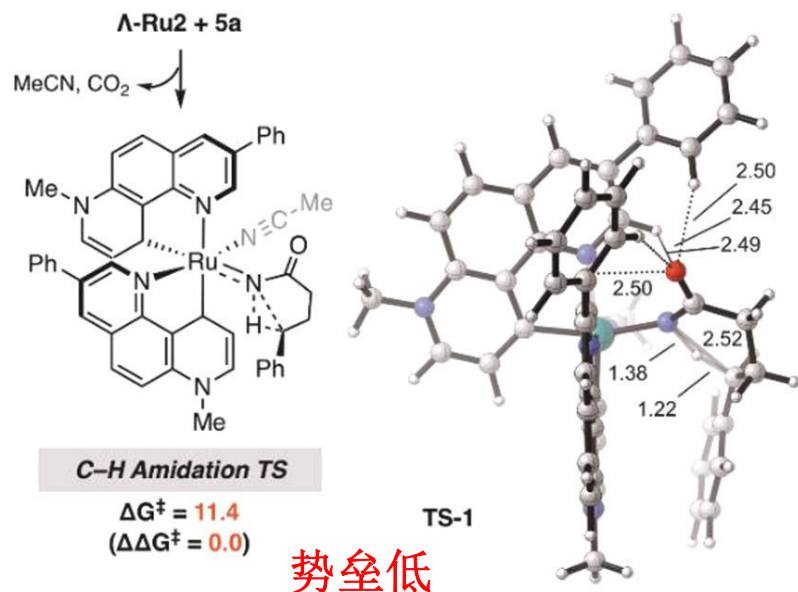
C₂-对称催化剂

Mechanistic Experiments

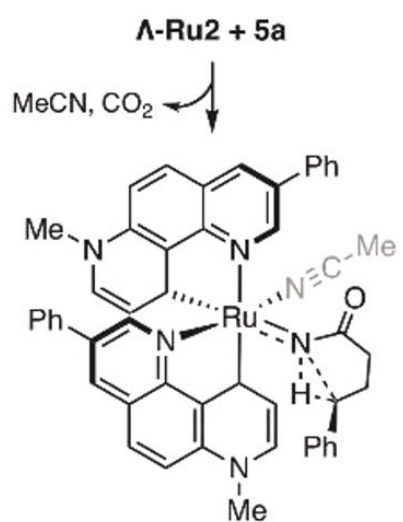


rNHC比nNHC配体更高的 σ 供体能力

Mechanistic Experiments

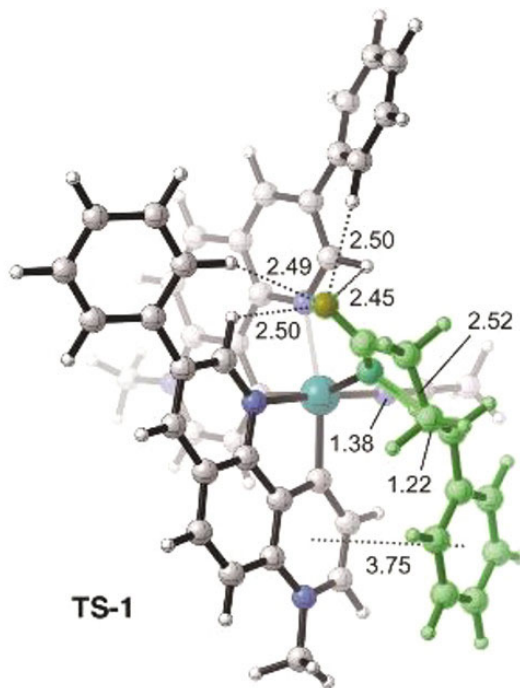


Mechanistic Experiments

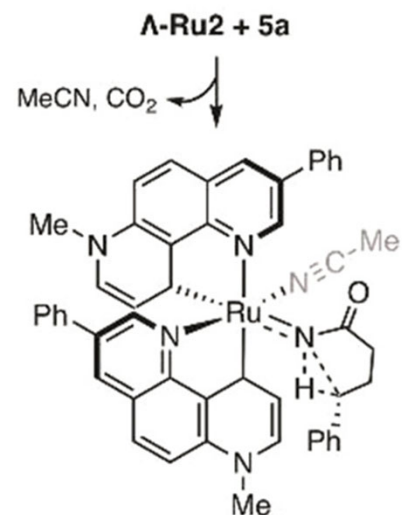


C-H Amidation TS (Major)

$$\Delta G^\ddagger = 11.4$$
$$(\Delta\Delta G^\ddagger = 0.0)$$



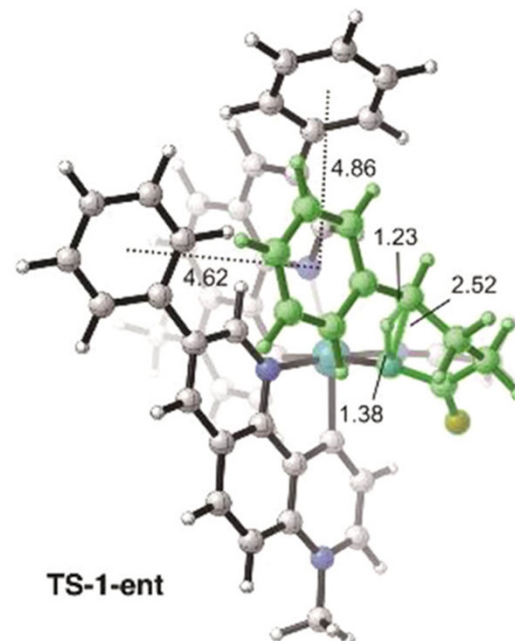
π - π 堆积相互作用



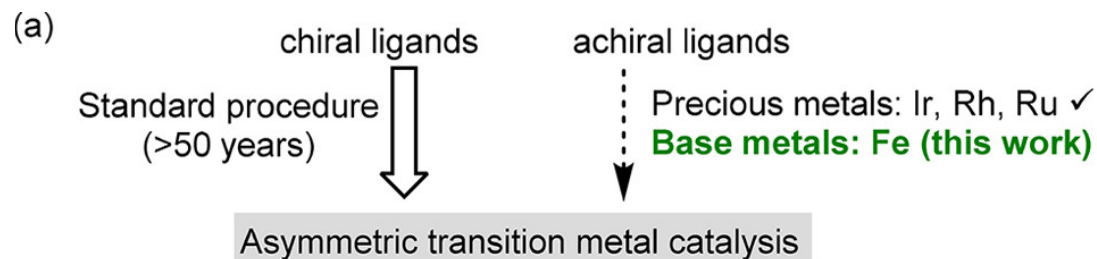
C-H Amidation TS (Minor)

$$\Delta G^\ddagger = 13.2$$
$$(\Delta\Delta G^\ddagger = 1.8)$$

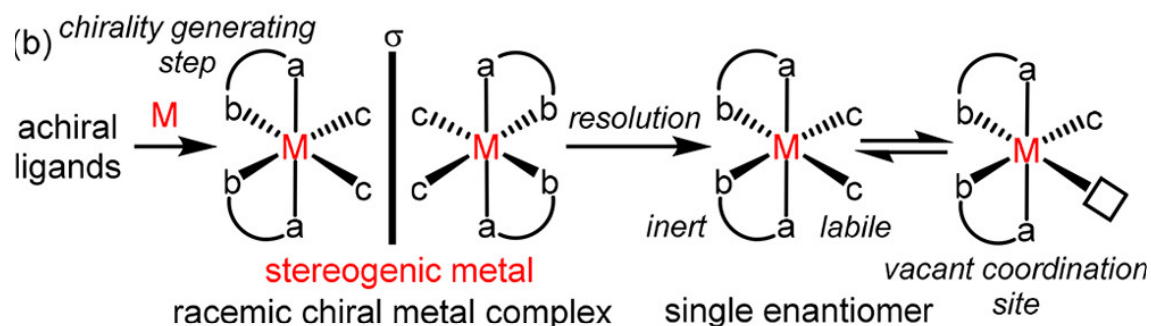
Experimental $\Delta\Delta G^\ddagger = 1.6$



02 Fe-catalyzed reactions



4d、5d → 3d金属



Challenge for 3d metals: Configurational stability and reactive metal!

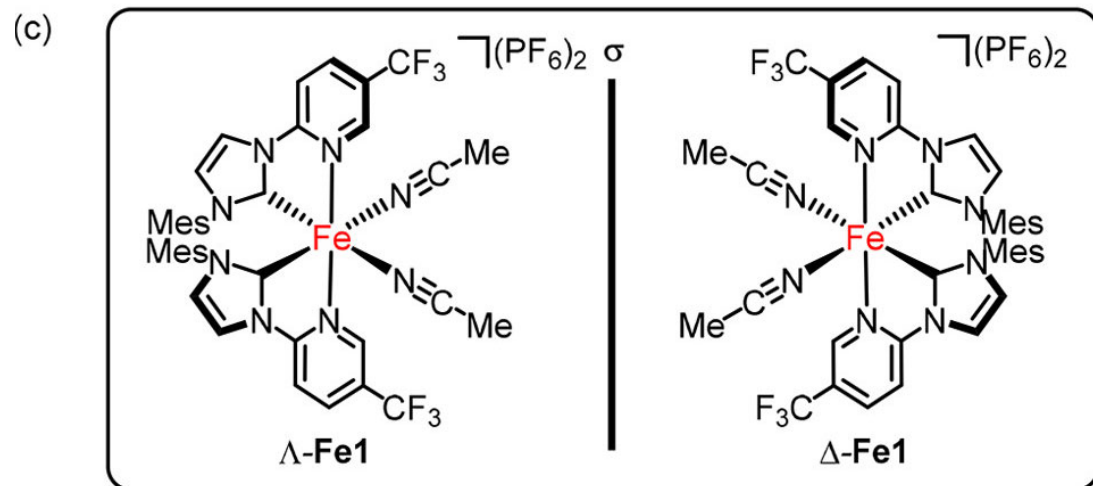


Table 1. Enantioselective Intramolecular Cannizzaro Reaction Catalyzed by Λ - or Δ -Fe1^{4a}

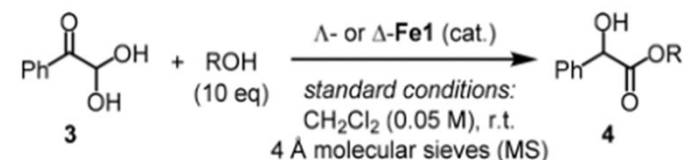
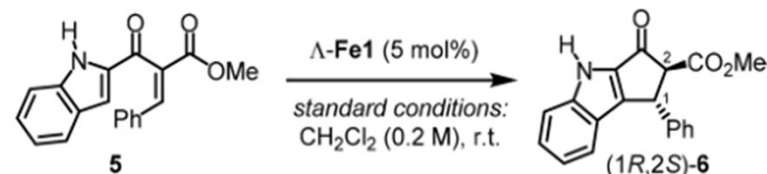
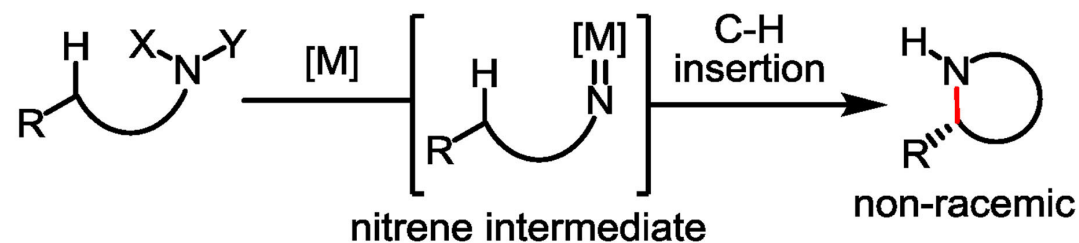


Table 2. Asymmetric Nazarov Cyclization Catalyzed by Fe1^{4a}



Yubiao Hong. *J. Am. Chem. Soc.* **2019**, 141, 4569–4572.

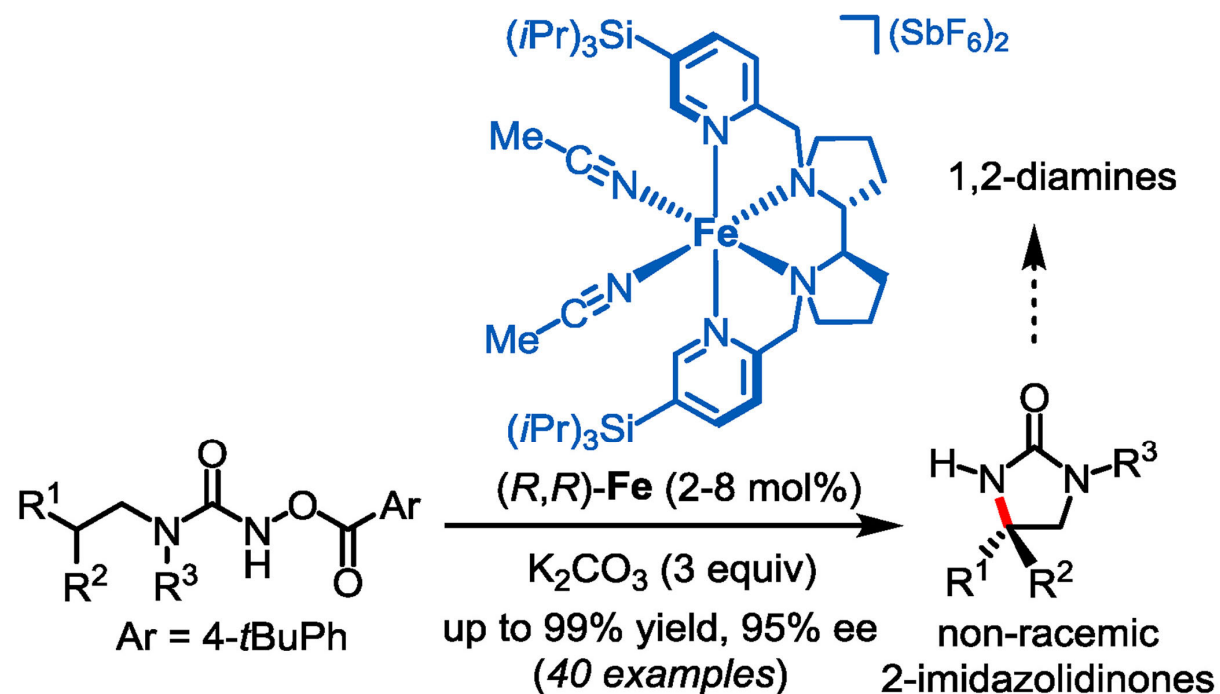
a) Enantioselective ring-closing nitrene insertion

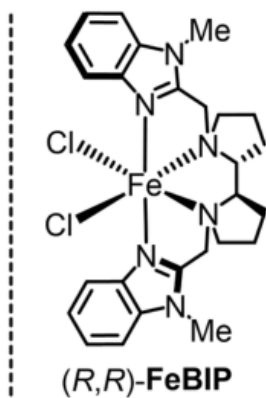
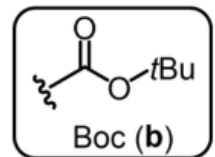
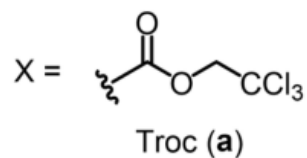
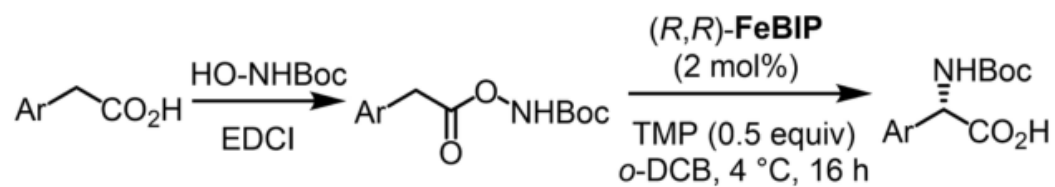
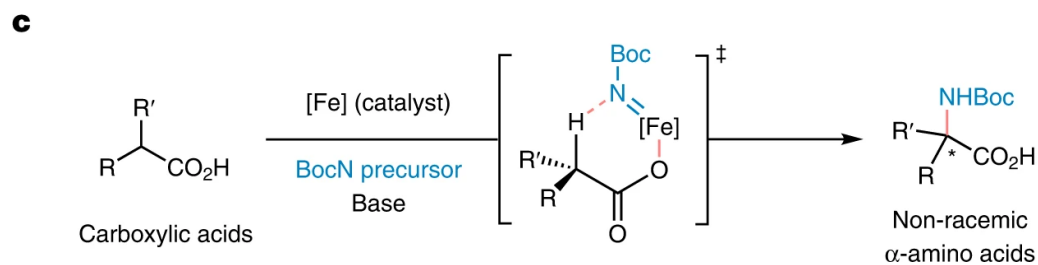
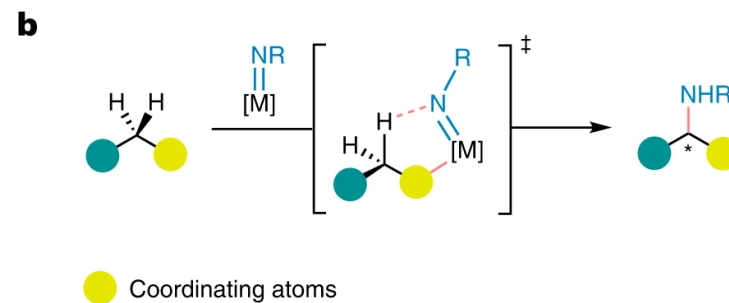
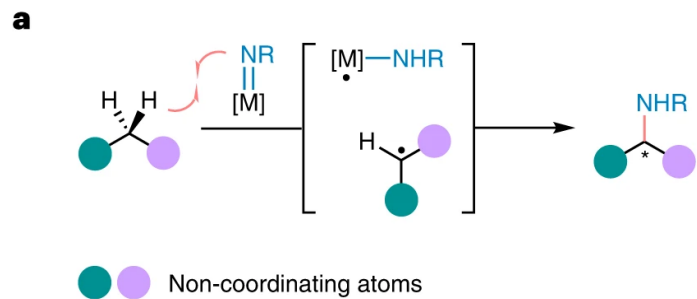


Established: M = Ru, Ir, Os, Pd, Co, etc.

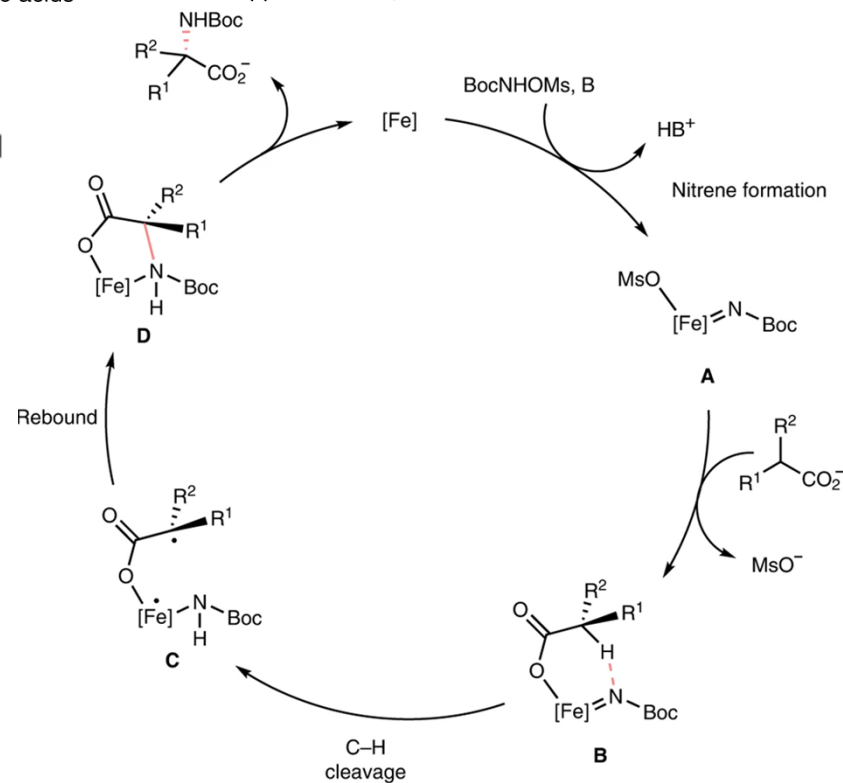
This work: Synthetic Fe catalyst

b) This work: Enantioselective & enantioconvergent Fe catalysis





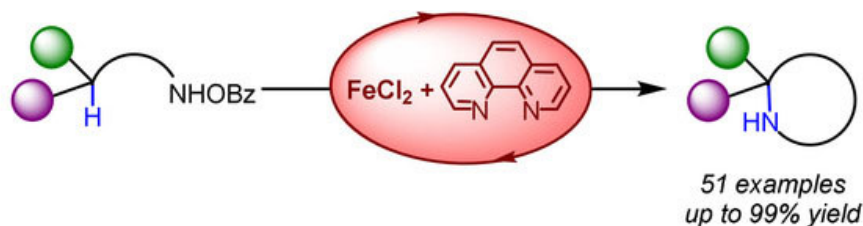
- Most efficient α -amino acid synthesis
- Enantioselective iron catalysis
- Abundant carboxylic acid feedstocks
- Desirable protection group scheme
- Applicable to α,α -disubstituted α -amino acids



Ye, CX. *Nat. Synth.* 2023.

a.) Desirable features for C-H functionalization methods

- (1) Avoiding noble metals
- (2) Cheap, nontoxic and readily available catalyst
- (3) Functionalization of non-activated C(sp³)-H bonds



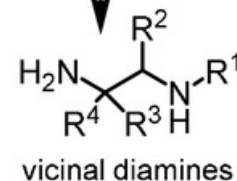
- ✓ Inexpensive and commercially available catalytic system
- ✓ Open flask and mild reaction conditions
- ✓ Broad scope of aminated C-H bonds

b.) This work: Efficient C-H amination with simple Fe catalyst

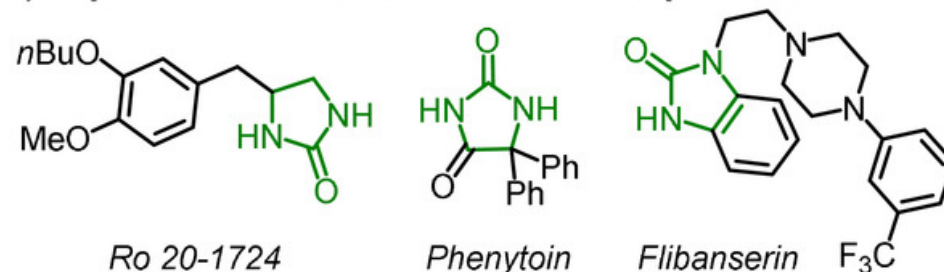


Broad scope of C-H bonds:

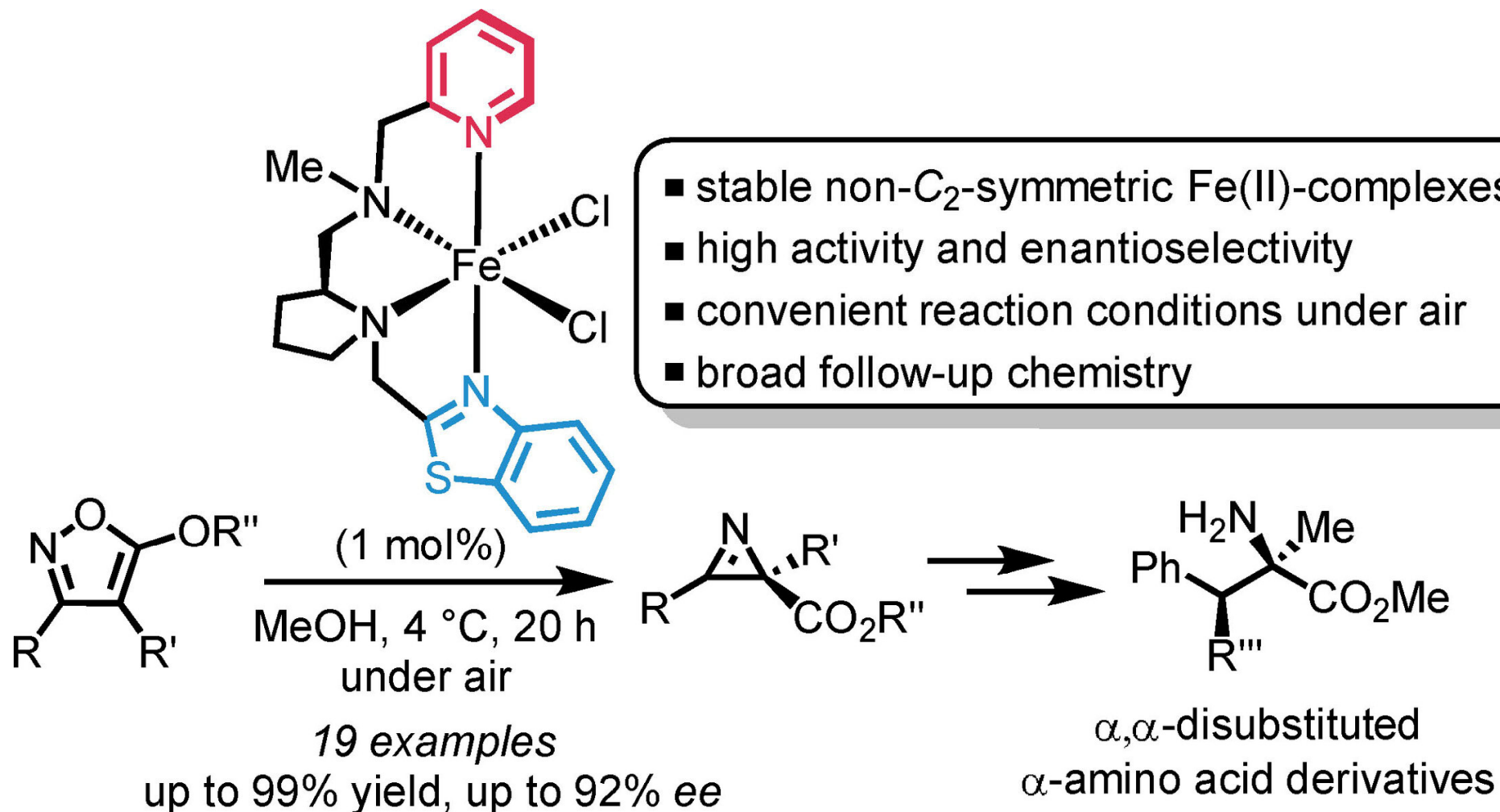
- ✓ Aliphatic, benzylic, allylic, and propargylic
- ✓ Secondary and tertiary
- ✓ C(sp³)-H and C(sp²)-H bonds



c.) Representative imidazolidinone-based pharmaceuticals

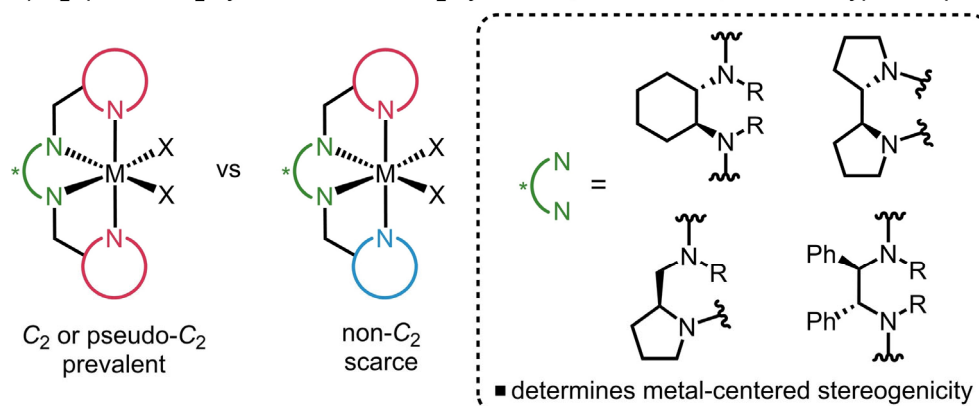


不对称催化四齿非C₂-对称Fe(II)-配合物中立体诱导的对称性

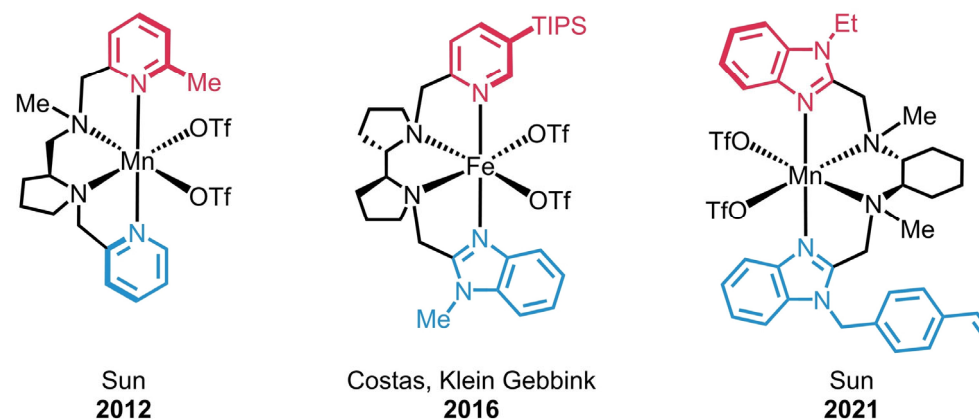


Philipp S. Steinlandt. *Eur. J. Org. Chem.* **2023**, e202300296.

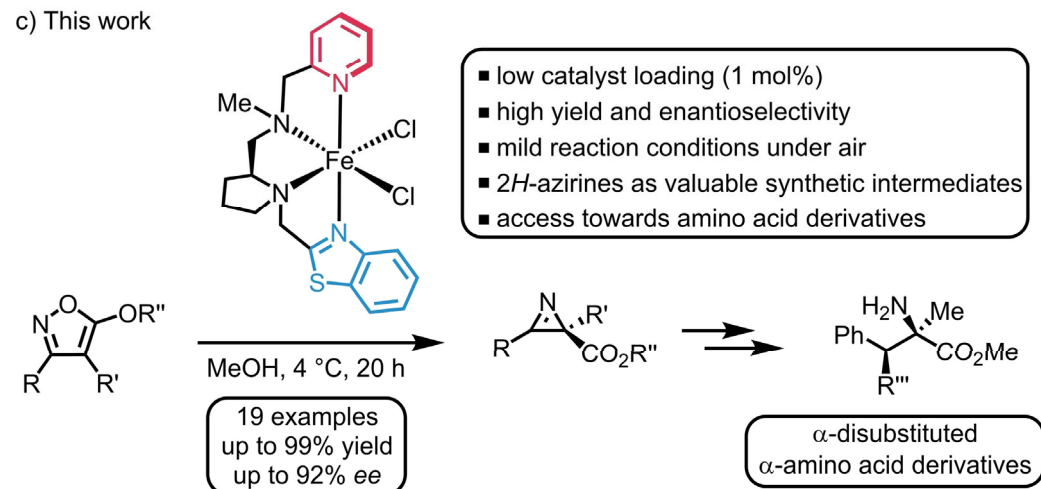
a) C_2 -/pseudo- C_2 -symmetric vs non- C_2 -symmetric, tetradentate, linear N4-type complexes

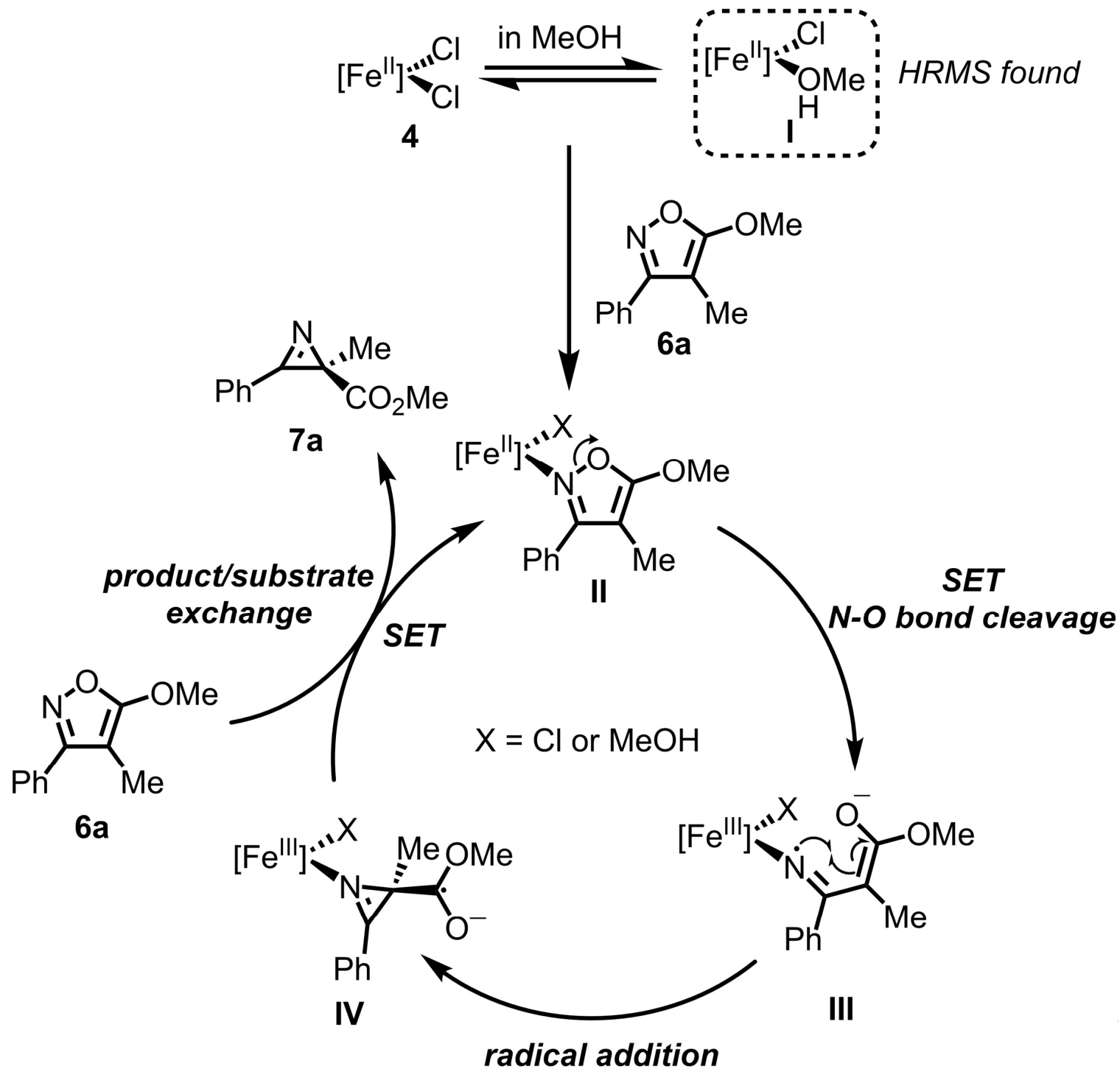


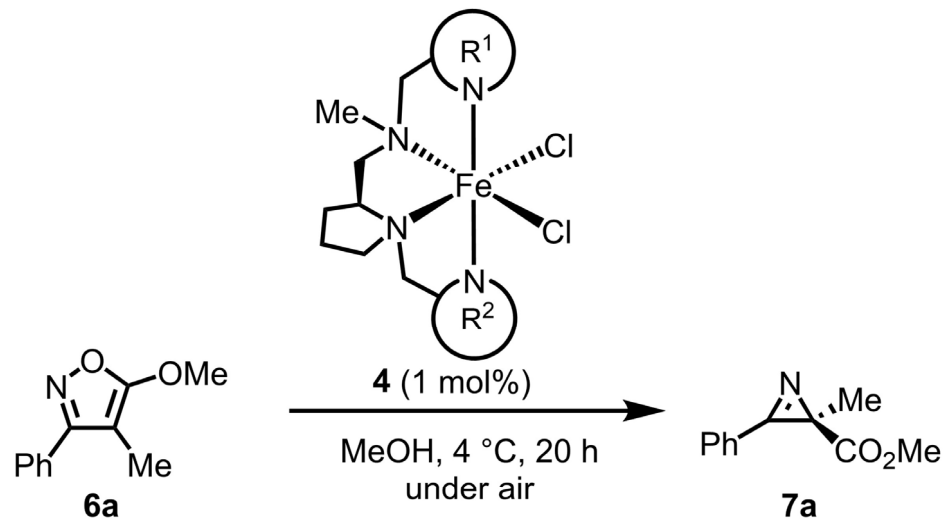
b) Selected examples of linear, N4-type, non- C_2 -symmetric catalysts

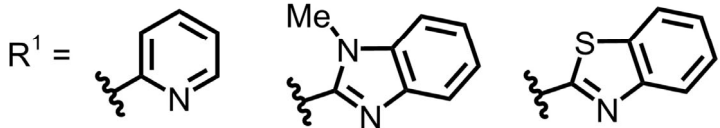


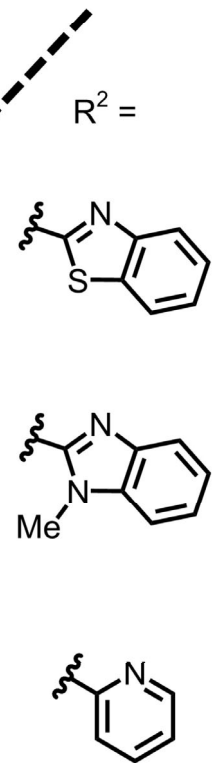
c) This work





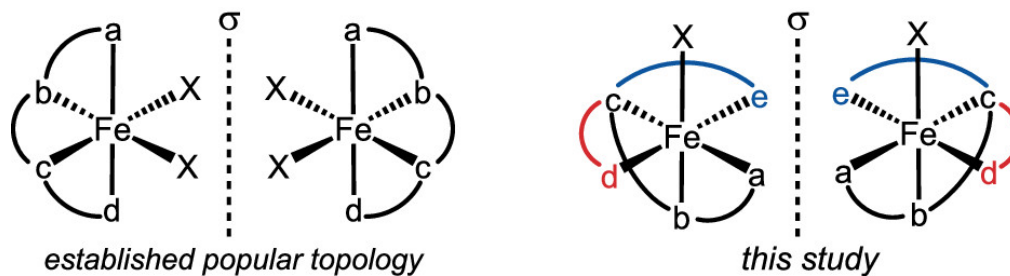


R¹ = 

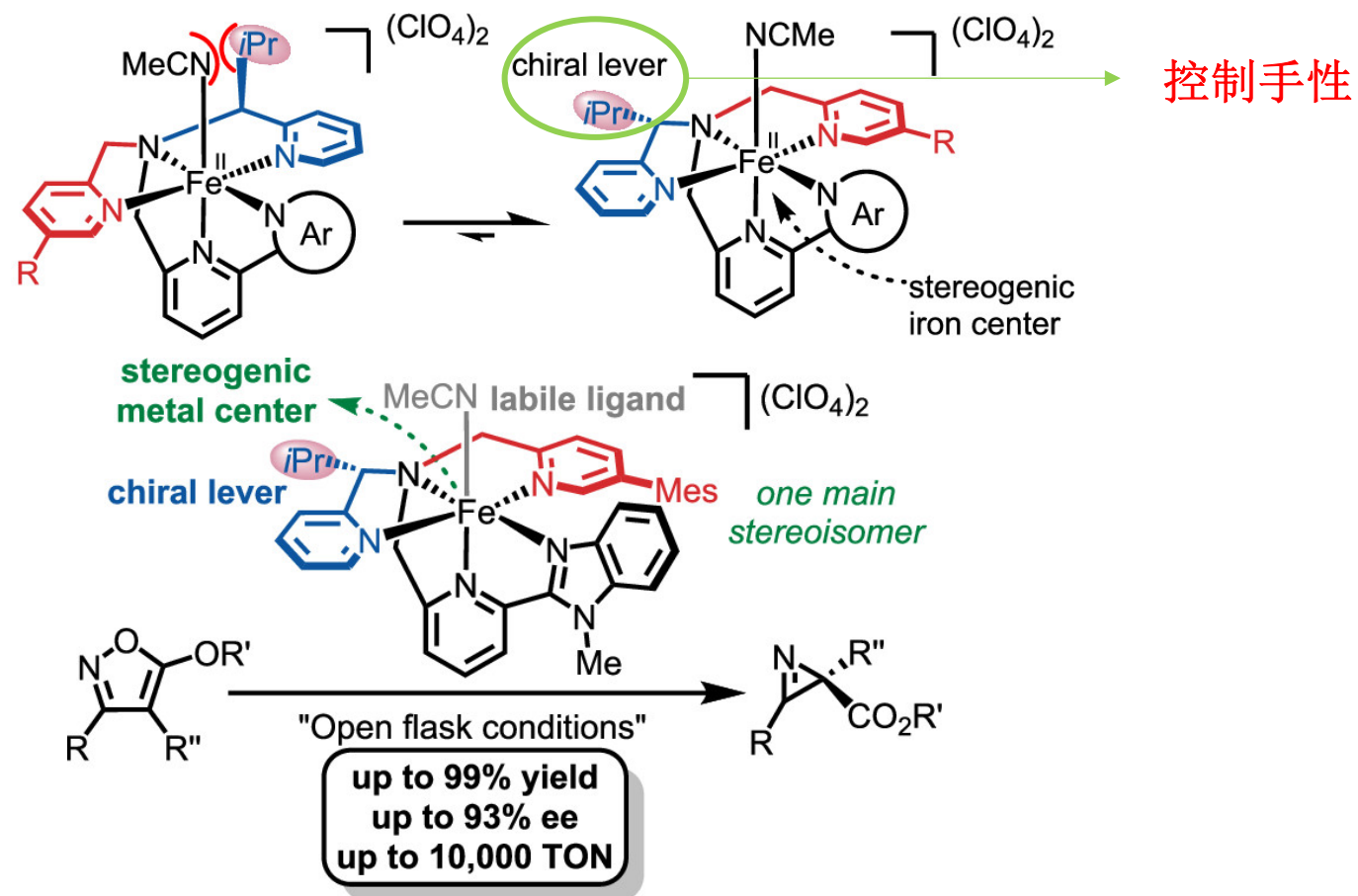
R² = 

4a 90% ee (99%)	4b 69% ee (75%)	4c 76% ee (30%)
4d 7% ee (64%)	4e 12% ee (18%)	4f 55% ee (66%)
4g 69% ee (99%)	4h 58% ee (48%)	4i 73% ee (85%)

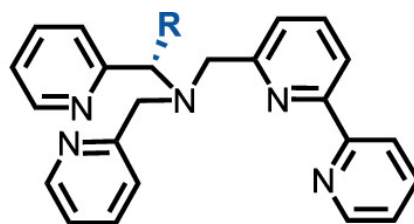
a) Linear tetradentate helical chirality vs tripodal pentadentate chirality



b) Realization: Controlling stereocenter with chiral lever group

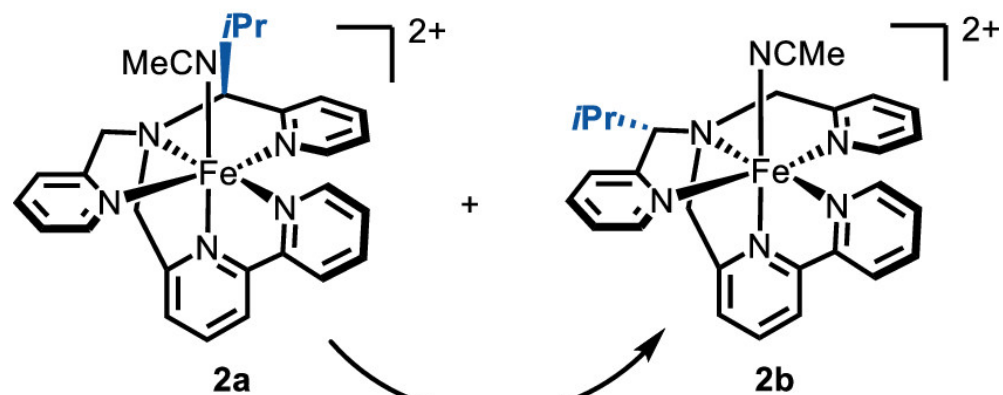
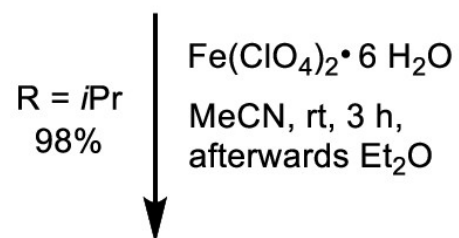


Philipp S. Steinlandt. *ACS Catal.* **2021**, 11, 7467–7476.



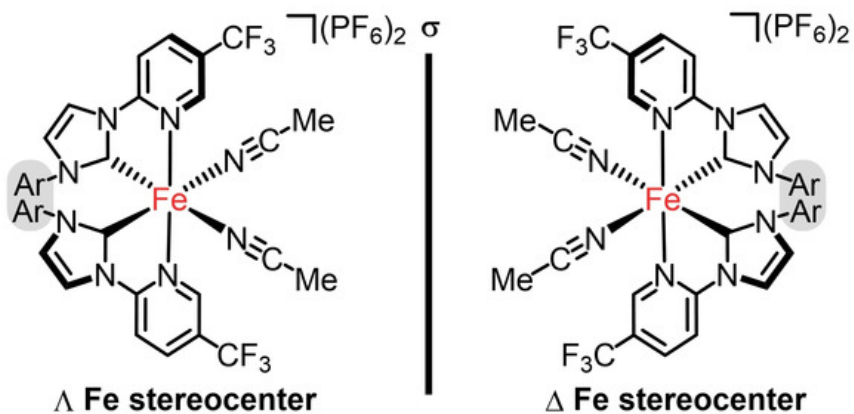
R = H: BPAbipy

R = *i*Pr: **1**

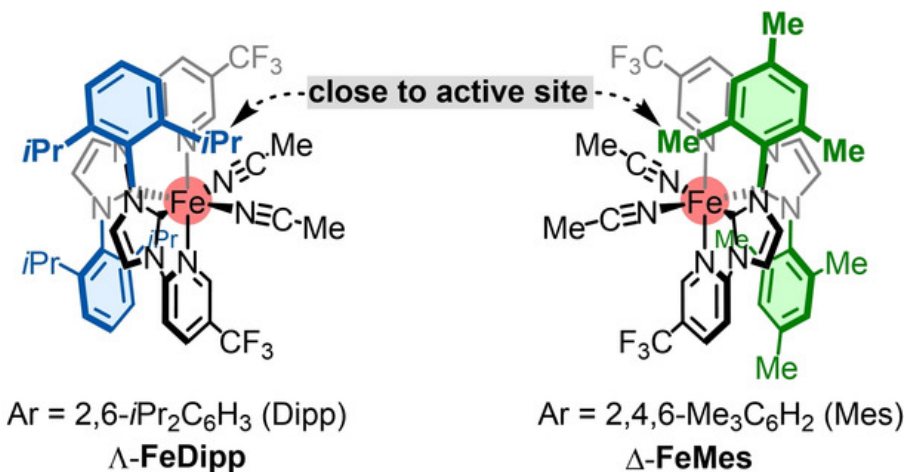


MeCN, 70 °C, 16 h
isomerization to **2b** (>20:1 dr)
99%

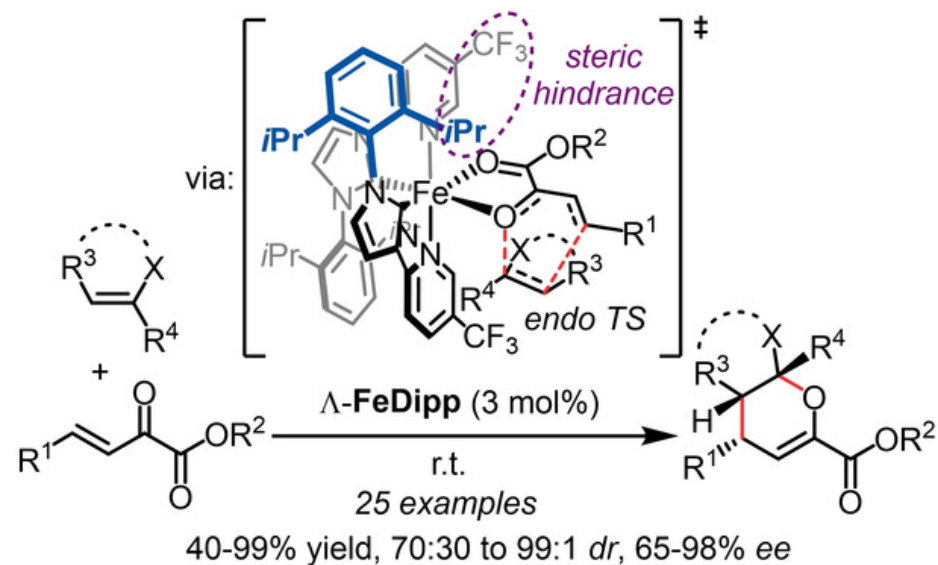
a.) Chiral-at-iron catalyst scaffold



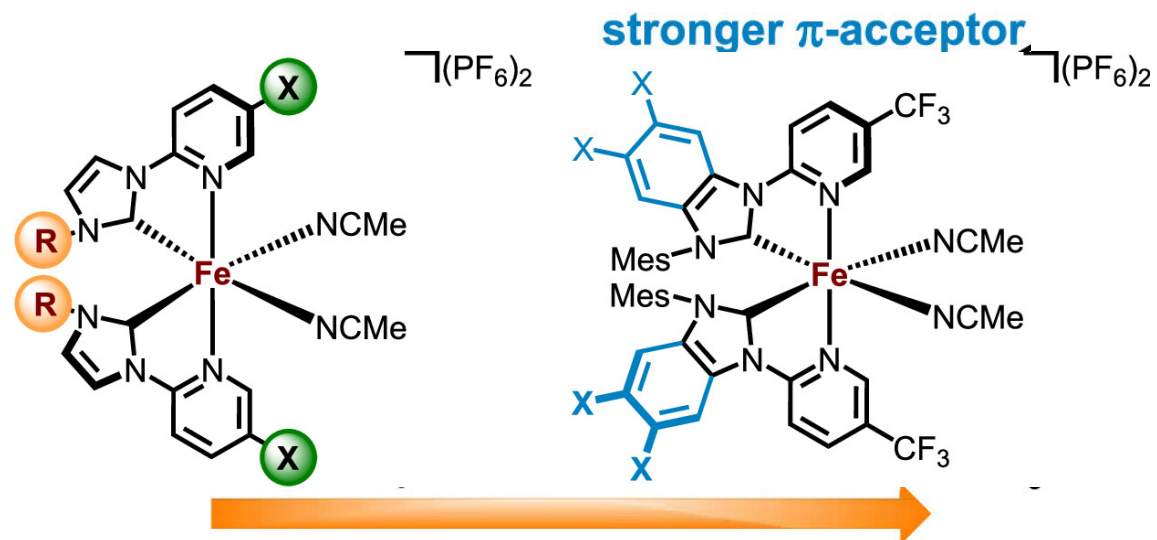
b.) *This work*: Influence of NHC substituents on enantioselectivity



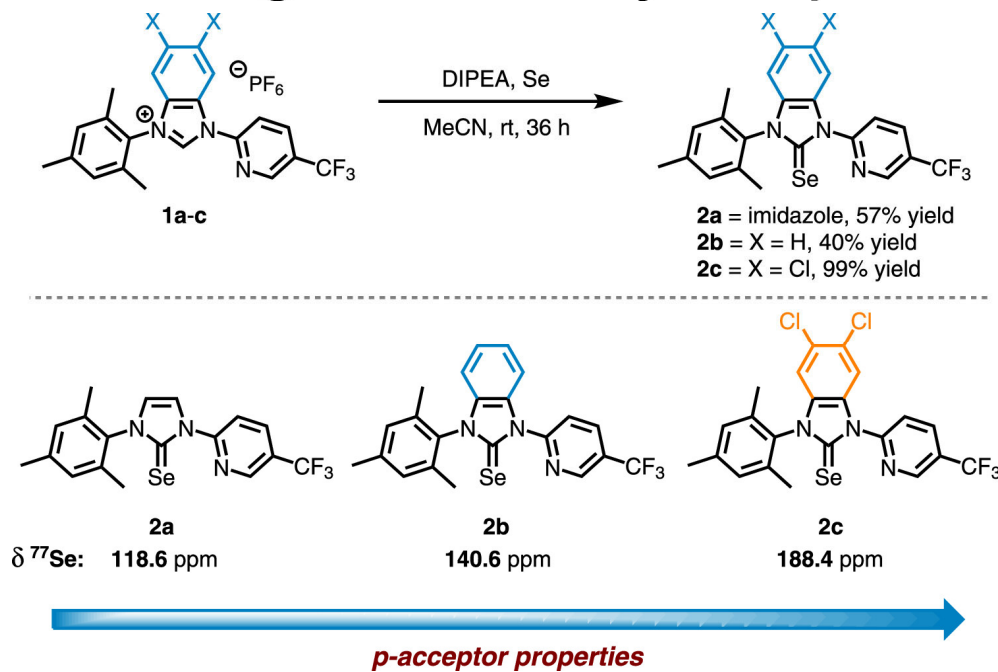
c.) Chiral-at-iron catalyzed asymmetric hetero-Diels-Alder reaction



Yubiao Hong. *Chem. Eur. J.* **2021**, *27*, 8557–8563.

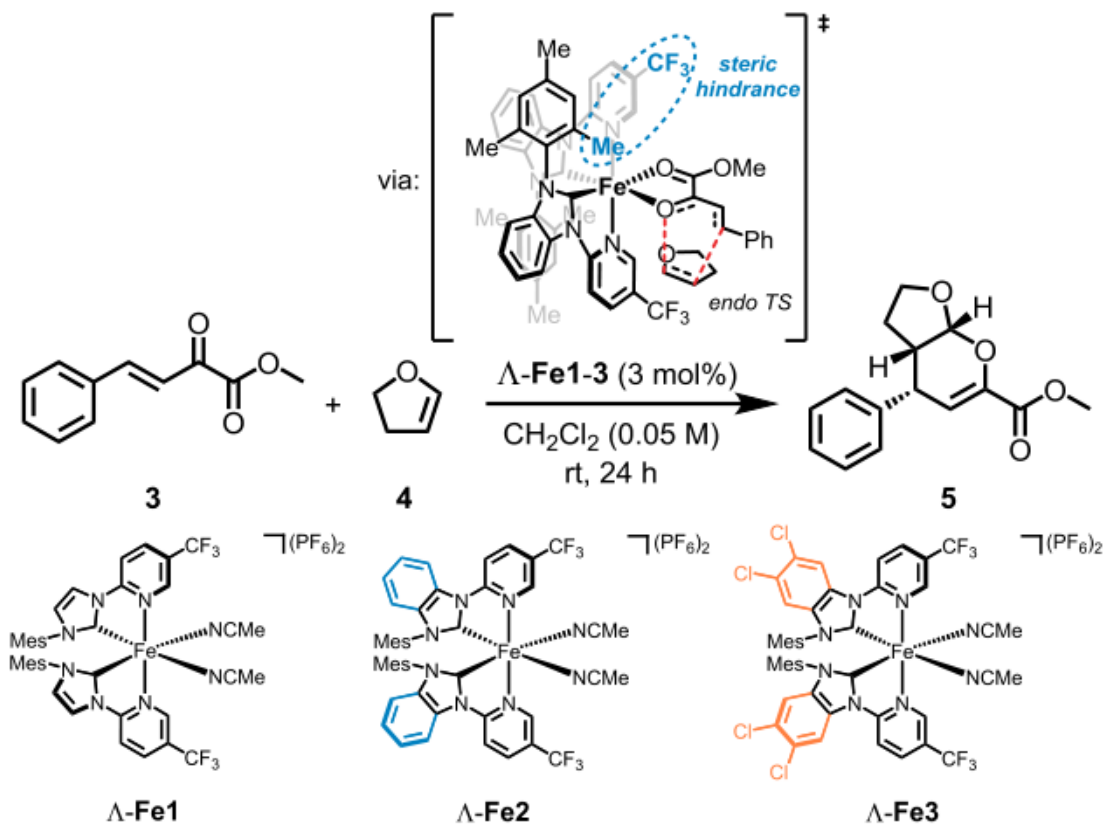


Enhanced configurational stability & cat. performance



Nemrud Demirel. *Organometallics*. 2022, 41, 3852–3860.

Table 1. Comparison of Different Chiral-at-Iron Catalysts in a Hetero-Diels–Alder Reaction^a

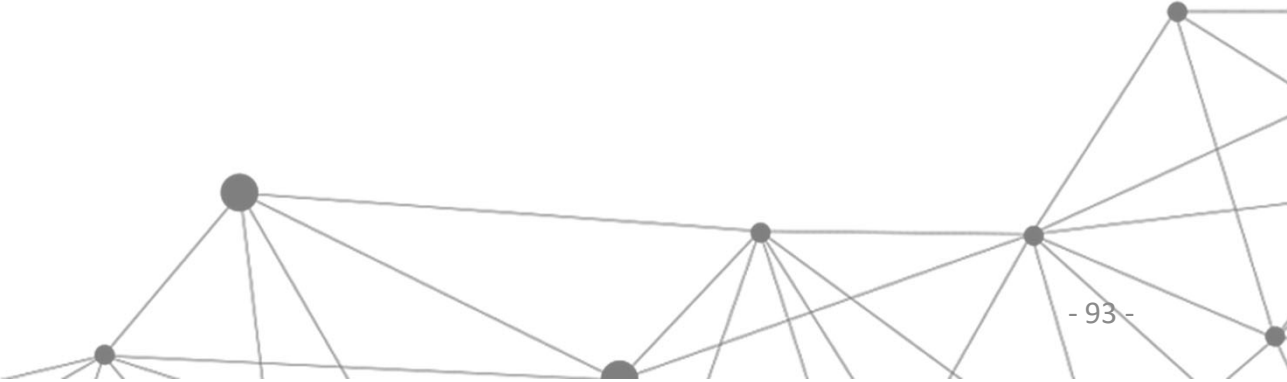


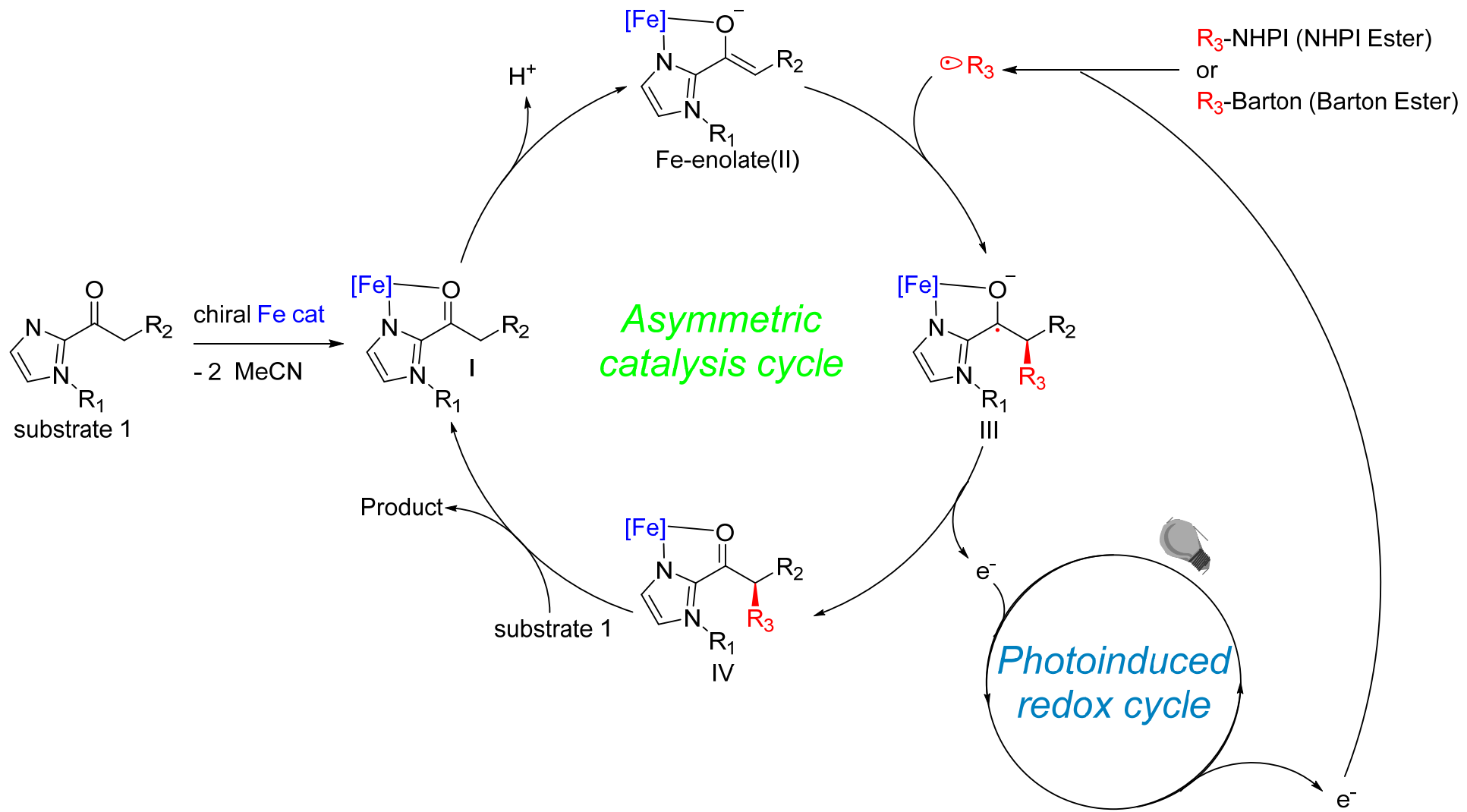
entry	catalyst	conditions	yield (%) ^b	dr ^c	ee (%) ^c
1	Δ -Fe1	N_2	88	97:3	89.4
2	Δ -Fe1	Air	71	97:3	89.6
3	Δ -Fe1	$\text{N}_2 + \text{H}_2\text{O}$ (10 equiv)	78	97:3	74.6
4	Δ -Fe1	Air + H_2O (10 equiv)	67	98:2	81.2
5	Δ -Fe2	N_2	83	97:3	91.4
6	Δ -Fe2	Air	77	97:3	91.6
7	Δ -Fe2	$\text{N}_2 + \text{H}_2\text{O}$ (10 equiv)	83	98:2	93.6
8	Δ -Fe2	Air + H_2O (10 equiv)	61	98:2	93.8
9	Δ -Fe3	N_2	64	95:5	70.8
10	Δ -Fe3	Air + H_2O (10 equiv)	38	99:1	89.0
11 ^d	Δ -Fe2	Air + H_2O (10 equiv)	75	98:2	93.9
12	Δ -Fe2	Air + H_2O (20 equiv)	63	98:2	-94.1



Part 03

Proposal







Thanks for your listening

