Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

Research Center for Molecular Recognition and Synthesis

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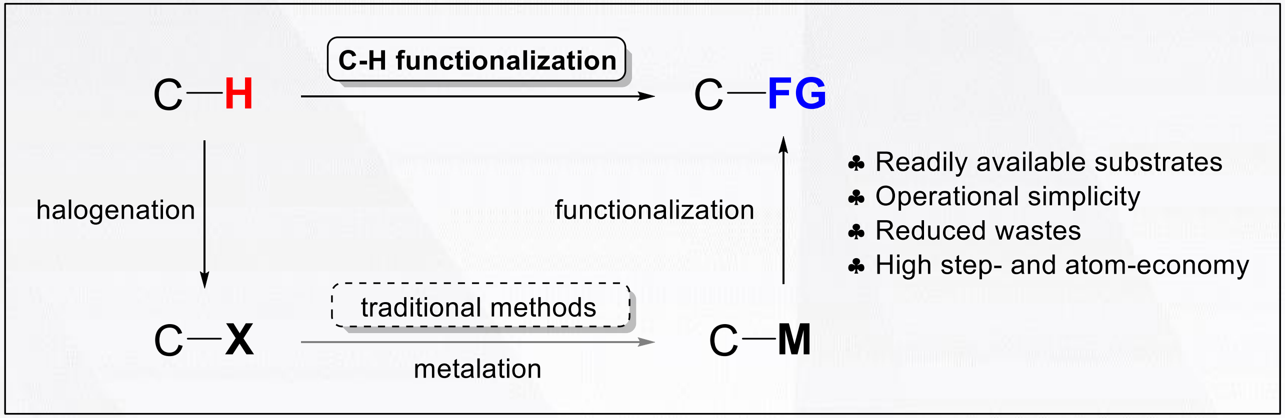
Achiral $Cp^xM(III)$-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

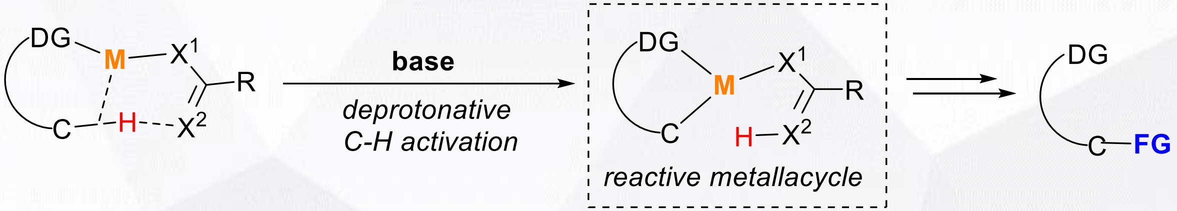
Background

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

C-H functionalization and its development in transition metal catalysis



Directing-Group-Assisted C-H Activation via base-assisted deprotonation:



M = Pd^{II}, Ru^{II}, Co^{III}, Rh^{III}, Ir^{III}, etc.

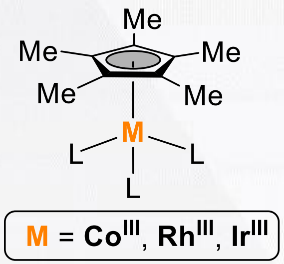
- Macgregor, S. A. et al. *Chem. Rev.* **2017**, *117*, 8649-8709.
- Wencel-Delord, J. et al. *Chem. Soc. Rev.* **2016**, *45*, 2900-2936.
- Li, X. et al. *Acc. Chem. Res.* **2015**, *48*, 1007-1020.

Background

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

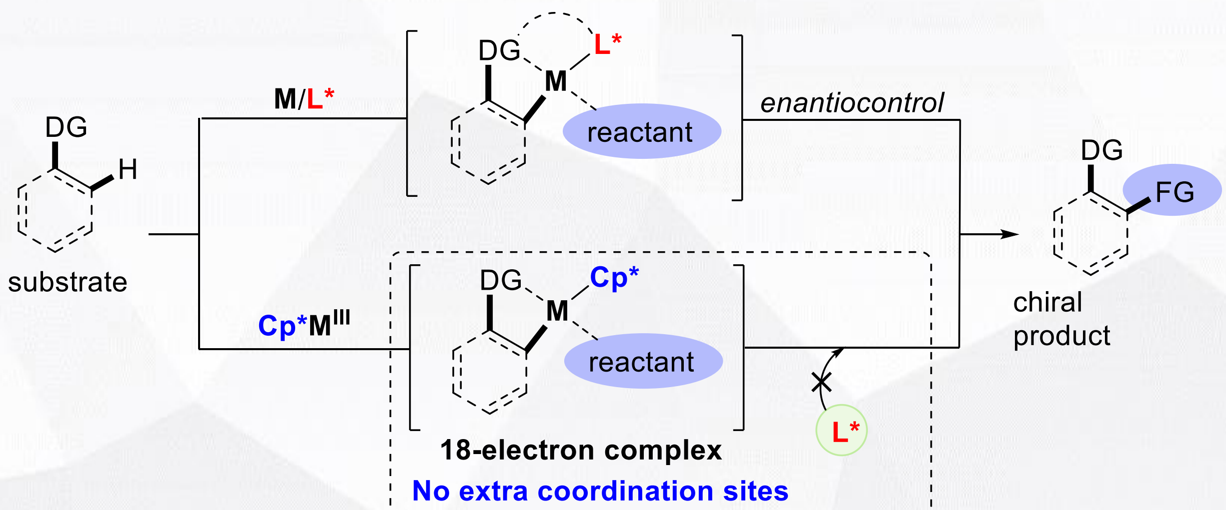
Cp*M^{III} catalyst and its problem in enantiocontrol

1) Cp*M^{III} catalyst for C-H functionalization



- ♦ High reactivity
- ♦ Good functional-group tolerance
- ♦ Robustness

2) Problem for enantiocontrol after C-H activition



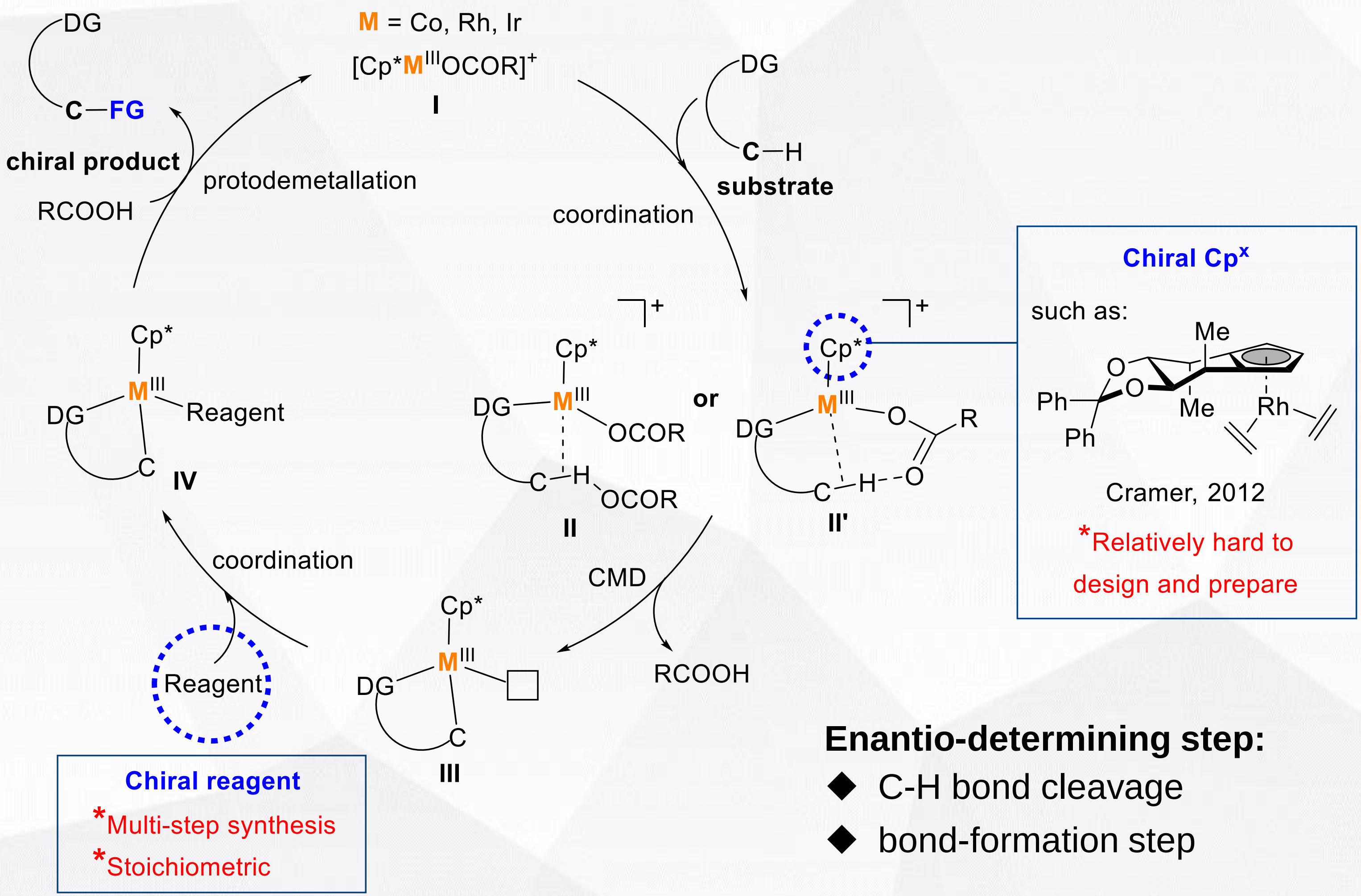
How to control enantioselectivity?

- Chang, S. et al. *Chem. - Asian J.* **2018**, *13*, 1089-1102.
- Matsunaga, S. et al. *ACS Catal.* **2021**, *11*, 6455-6466.

Background

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C−H Functionalization

General mechanism of enantioselective C−H functionalization



Enantio-determining step:

- C-H bond cleavage
- bond-formation step

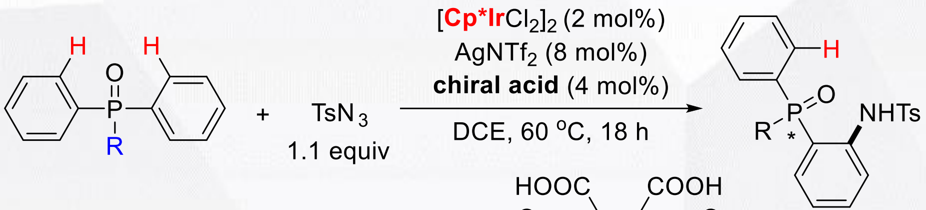
□ Ellman, J. A. et al. *J. Org. Chem.* **2016**, *81*, 1547-1557.
□ Cramer, N. et al. *Science* **2012**, *338*, 504-506.
□ Cramer, N. et al. *Angew. Chem., Int. Ed.* **2021**, *60*, 13198-13224.
□ Matsunaga, S. et al. *Synlett* **2019**, *30*, 1384-1400.
□ Matsunaga, S. et al. *ACS Catal.* **2021**, *11*, 6455-6466.

Background

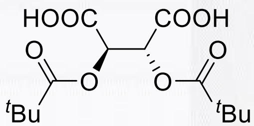
Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

01

Seminal study of this topic

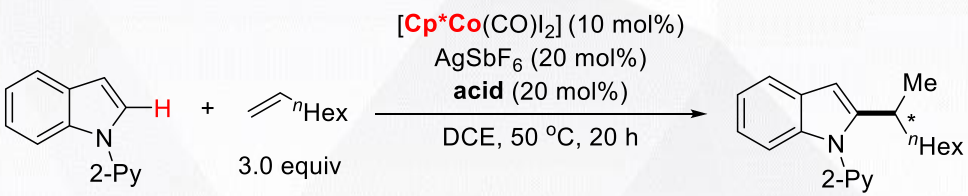


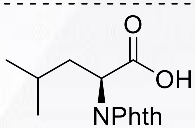
chiral acid:



R =	-Me	-Bn	-^{t}Bu	-Cy	-N^{i}Pr$_2$
yield	80%	91%	88%	84%	44%
ee	11%	19%	27%	32%	31%

>> Chang, S. 2015



acid:		
	1-AdCOOH	**yield**: 80% (b/l = 95:5)
	 L-Phth-Leu-OH	**yield**: 37% (b/l = 93:7) **ee: 27%**

>> Ackermann, L. 2017

☐ Chang, S. et al. *Tetrahedron* **2015**, *71*, 4504-4511.
☐ Ackermann, L. et al. *Angew. Chem., Int. Ed.* **2017**, *56*, 10378-10382.

02

Achiral $Cp^xM(III)$-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

2.1 Chiral Induction via **Chiral Anion**

2.2 Chiral Induction via **Noncovalent Interaction**

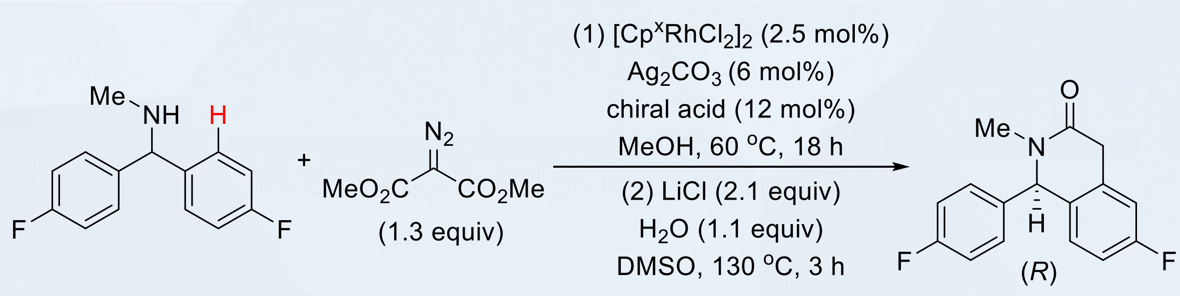
2.3 Chiral Induction via **Covalent Interaction**

Chiral Induction via Chiral Anion

2.1

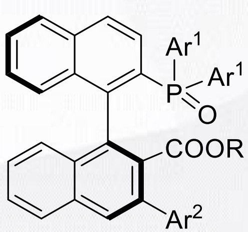
Achiral $Cp^xM(III)$-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> Matsunaga, S. 2018



➤ **Screening**

entry	[Rh]	chiral acid	yield / %	e.r.
1	$[Cp^*RhCl_2]_2$	**a**	67	75.5:24.5
2	$[Cp^*RhCl_2]_2$	**b**	56	70.5:29.5
3	$[Cp^*RhCl_2]_2$	**c**	82	71:29
4	$[Cp^*RhCl_2]_2$	**d**	54	94.5:5.5
5	$[Cp^*RhCl_2]_2$	**e**	84	96:4
6	$[Cp^*RhCl_2]_2$	**f**	0	/
7	$[Cp^{Me4}RhCl_2]_2$	**e**	80	96:4
8	$[Cp^{*tBu}RhCl_2]_2$	**e**	34	91:9
9	$[Cp^{Et}RhCl_2]_2$	**e**	51	93.5:6.5



R = H

a: Ar^1 = Ph, Ar^2 = H

b: Ar^1 = 4-MeOC_6H_4, Ar^2 = H

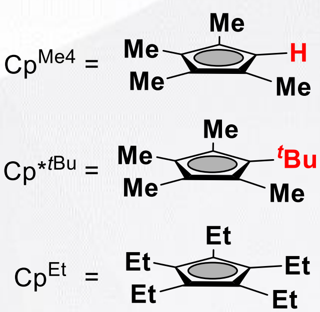
c: Ar^1 = 3,5-$(CF_3)_2$-C_6H_4, Ar_2 = H

d: Ar^1 = 3,5-$(CF_3)_2$-C_6H_4, Ar^2 = 3,5-${}^tBu_2$-4-MeO-C_6H_4

e: Ar^1 = 3,4,5-F_3-C_6H_4, Ar^2 = 3,5-${}^tBu_2$-4-MeO-C_6H_4

R = Me

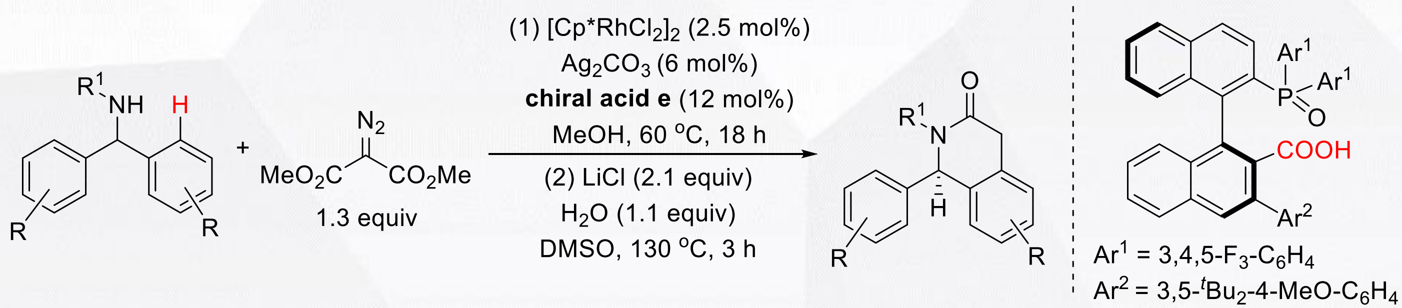
f: Ar^1 = 3,4,5-F_3-C_6H_4, Ar^2 = 3,5-${}^tBu_2$-4-MeO-C_6H_4



☐ Matsunaga, S. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 12048-12052.

Chiral Induction via Chiral Anion

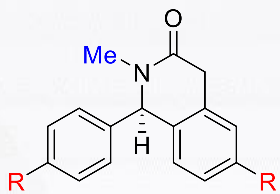
Achiral Cp^xM(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization



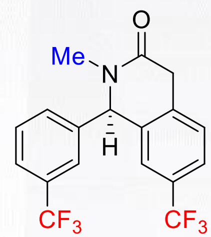
➢ Scope

selected examples

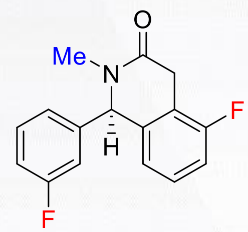
R^1 = Me



R = F, 84%, 96:4 e.r.
R = Cl, 71%, 95:5 e.r.
R = Br, 50%, 94:6 e.r.
R = CF_3, 87%, 94:6 e.r.
R = OMe, 77%, 92:8 e.r.[a,b]
R = OTs, 75%, 91.5:8.5 e.r.[a]

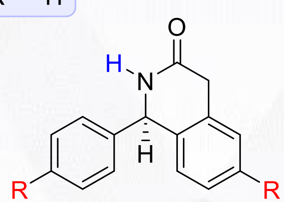


62%, 98.5:1.5 e.r.

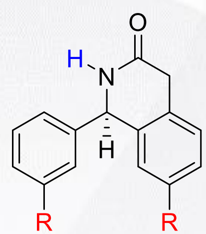


66%, 90.5:9.5 e.r.

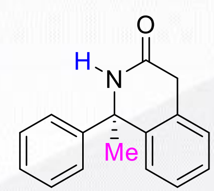
R^1 = H



R = H, 62%, 92:8 e.r.[a]
R = Cl, 68%, 93.5:6.5 e.r.
R = Br, 55%, 91:9 e.r.
R = OMe, 70%, 90:10 e.r.[a,b]



R = Br, 79%, 93.5:6.5 e.r.
R = CF_3, 70%, 97:3 e.r.
R = CO_2Et, 54%, 95.5:4.5 e.r.



84%, 90:10 e.r.[a].

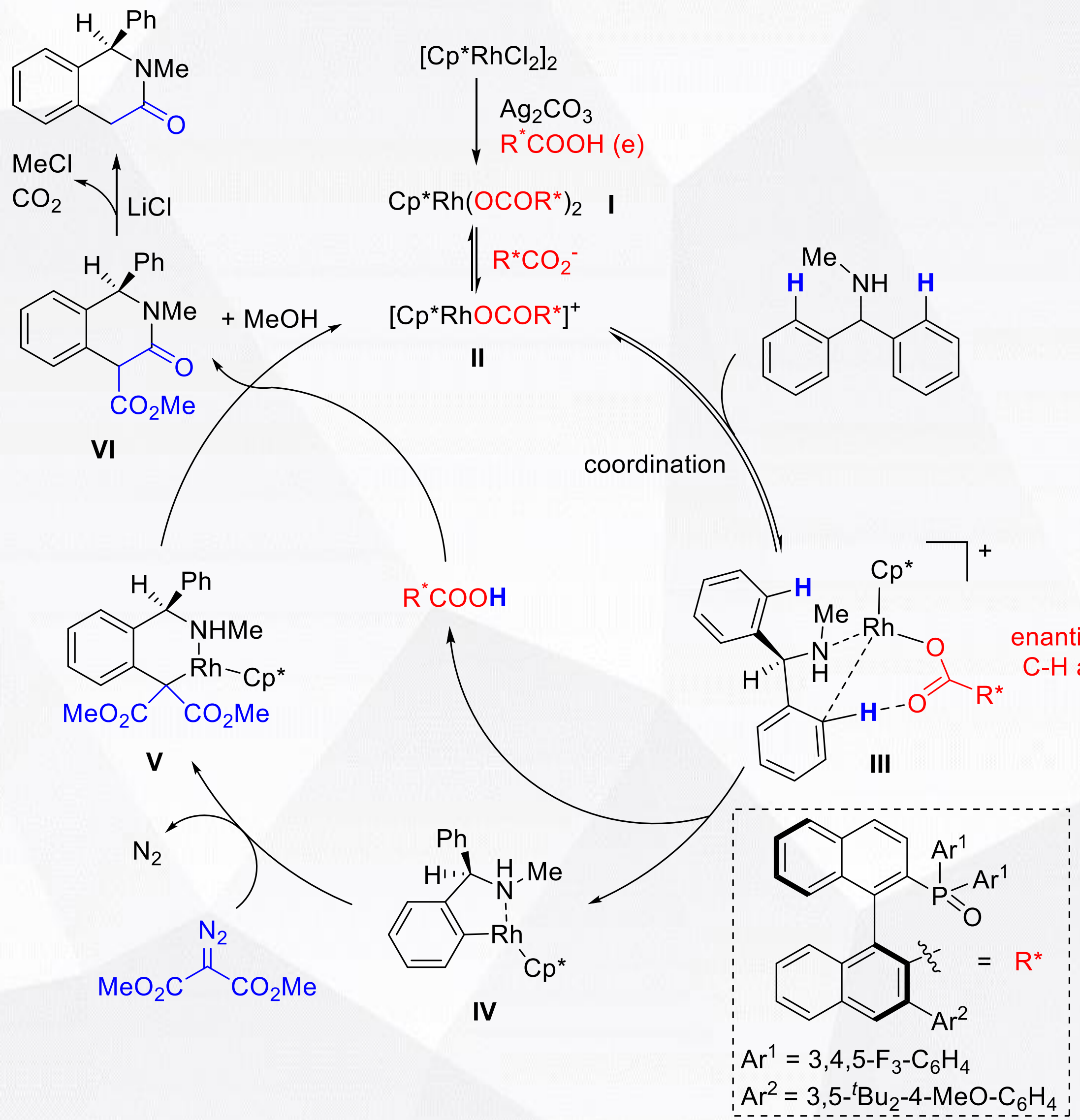
[a] $[Cp^{Me4}RhCl_2]_2$ was used instead of $[Cp^*RhCl_2]_2$; [b] AgOTf (12 mol%) was used instead of Ag_2CO_3.

☐ Matsunaga, S. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 12048-12052.

Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➢ **Mechanism**



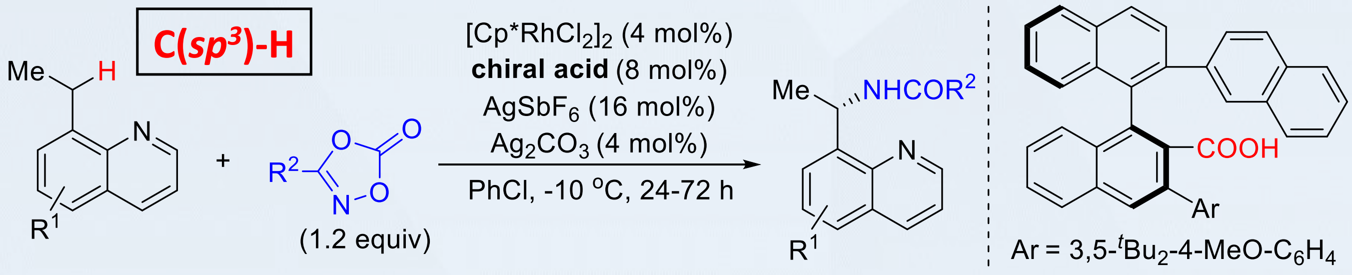
□ Matsunaga, S. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 12048-12052.

Chiral Induction via Chiral Anion

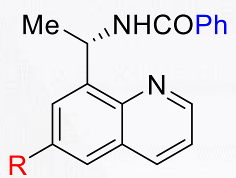
Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> Matsunaga, S. 2019

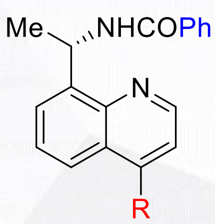
➢ Scope



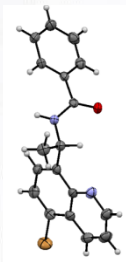
selected examples

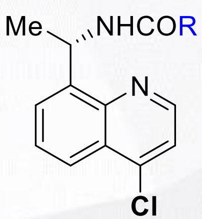


R = H, 87%, 92:8 e.r.[a]
R = OMe, 62%, 91:9 e.r.[a]

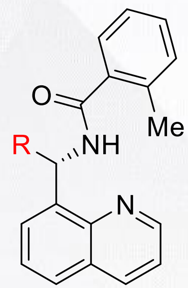


R = OMe, 87%, 91:9 e.r.[a]
R = Cl, 74%, 94:6 e.r.
R = Br, 61%, 94:6 e.r.
R = Ph, 76%, 94:6 e.r.
R = COMe, 85%, 94:6 e.r.





R = 2-MeC$_6$H$_4$, 98%, 93:7 e.r.
R = 3-MeC$_6$H$_4$, 90%, 92:8 e.r.
R = 4-MeOC$_6$H$_4$, 64%, 93:7 e.r.[b]
R = 2-furyl, 79%, 94:6 e.r.
R = **^{n}Pr**, 90%, 93:7 e.r.



R = Et, 72%, 93:7 e.r.[a,c]
R = ^{n}Bu, 70%, 93:7 e.r.[a,c]

[a] 4 °C; [b] -20 °C; [c] 30 mol% Ag$_2$CO$_3$

□ Matsunaga, S. et al. *Angew. Chem., Int. Ed.* **2019**, *58*, 18154-18158.

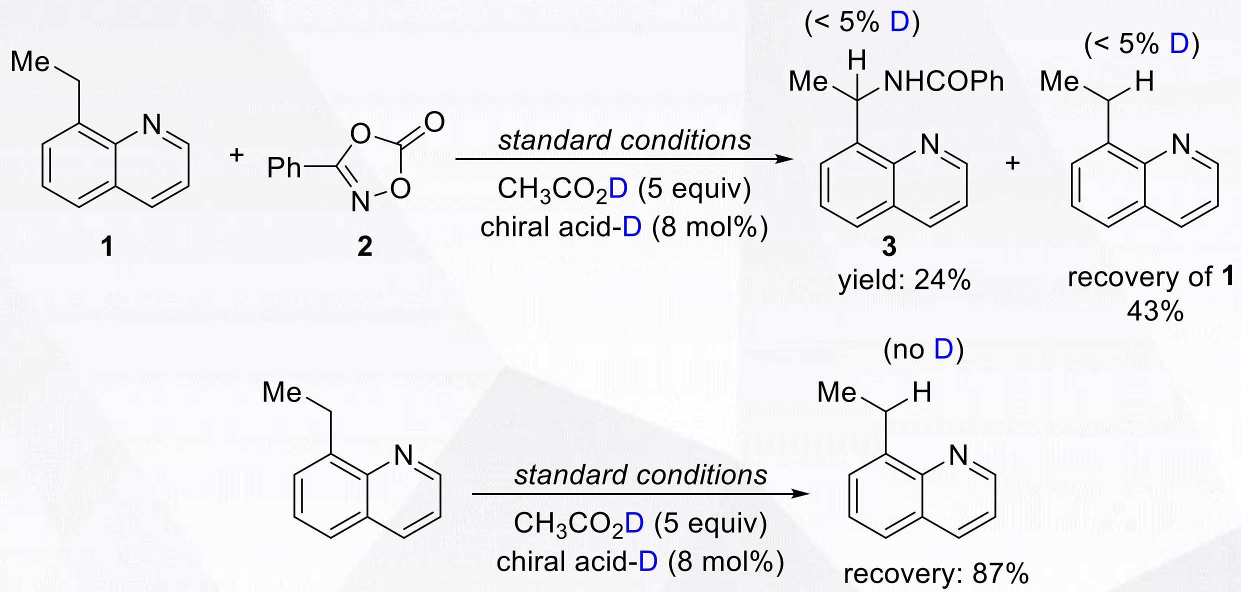
Chiral Induction via Chiral Anion

2.1

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C−H Functionalization

H/D exchange experiments to check the reversibility of the C−H activation step

➢ **Mechanism**



almost irreversible enantiocontrol step

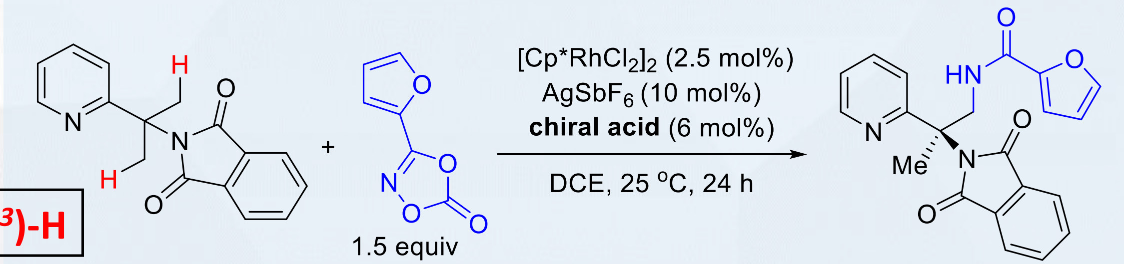
☐ Matsunaga, S. et al. *Angew. Chem., Int. Ed.* **2019**, *58*, 18154-18158.

Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> **Matsunaga, S. 2021**

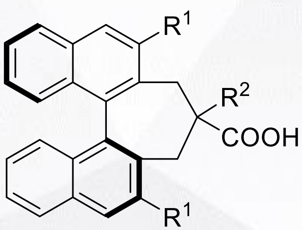
C(sp^3)-H



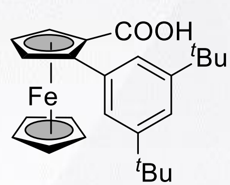
➢ **Screening**

entry	chiral acid	yield / %	e.r.
1	**A1**	84	86:14
2	**A2**	>90	82:18
3	**A3**	>90	83:17
4	**A4**	87	87:13
5[a]	**A4**	77	92:8
6[a,b]	**A4**	88	94:6
7	**B**	>90	66:34
8	**C**	>90	38:62

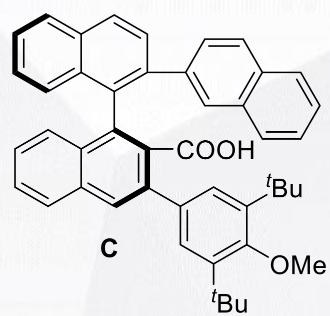
[a] $[Cp^{*tBu}RhCl_2]_2$; [b] 4 °C, 0.5 M, 48 h



A1: R^1 = H, R^2 = C_6H_5
A2: R^1 = O^{t}Bu, R^2 = C_6H_5
A3: R^1 = H, R^2 = 4-MeOC_6H_4
A4: R^1 = H, R^2 = 4-FC_6H_4



B

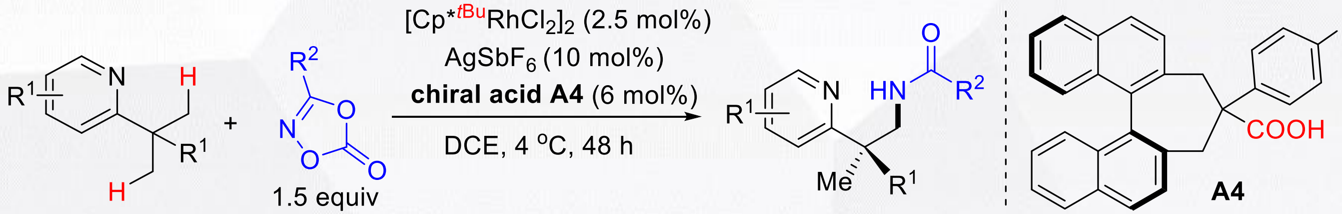


C

☐ Matsunaga, S. et al. *ACS Catal*. **2021**, *11*, 4271-4277.

Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

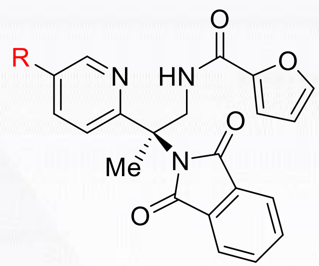


A4

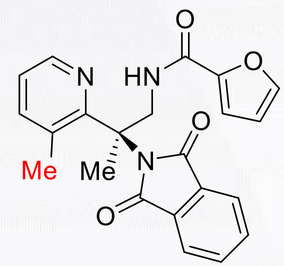
selected examples

➢ **Scope**

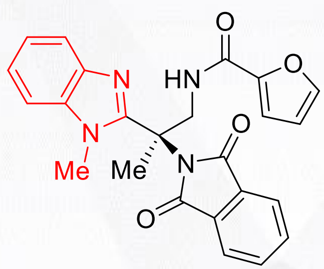
88%, 94:6 e.r.



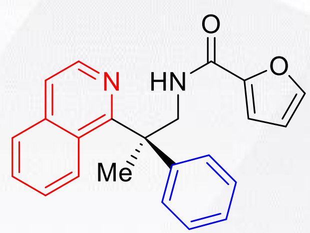
R = Me, 88%, 94:6 e.r.
R = F, 43%, 89:11 e.r.[a,b]



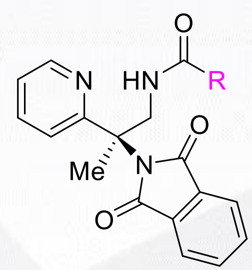
95%, 96:4 e.r.



88%, 94:6 e.r.[c,d]



98%, 86:14 e.r.



R = 4-MeOC$_6$H$_4$, 62%, 94:6 e.r.[c,d]
R = 2-thienyl, 63%, 94:6 e.r.
R = ^{n}Pr, 86%, 94:6 e.r.[c,d]

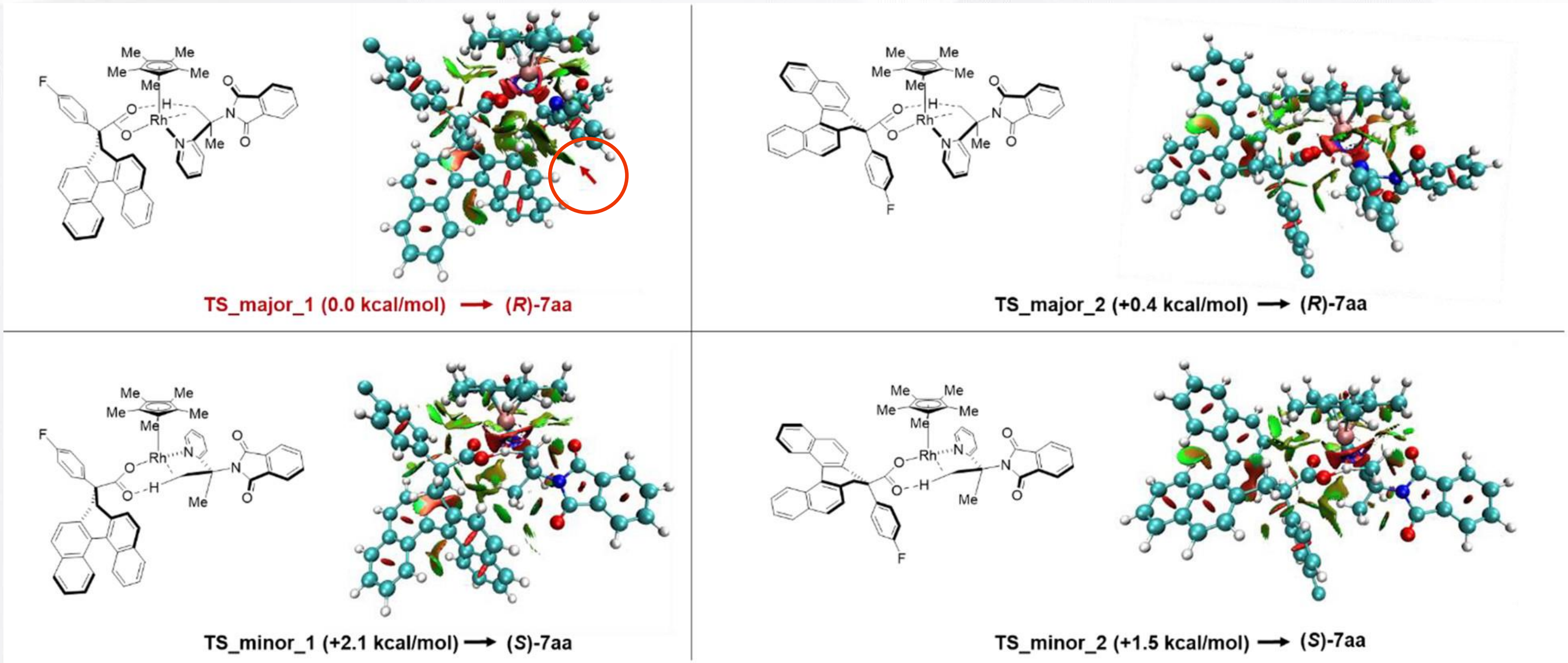
[a] [Cp*^{tBu}RhCl$_2$]$_2$ (4 mol%), AgSbF$_6$ (16 mol%); [b] 72 h; [c] 25 ^{o}C; [d] [Cp*RhCl$_2$]$_2$ (2.5 mol%)

☐ Matsunaga, S. et al. *ACS Catal*. **2021**, *11*, 4271-4277.

Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➢ **DFT**



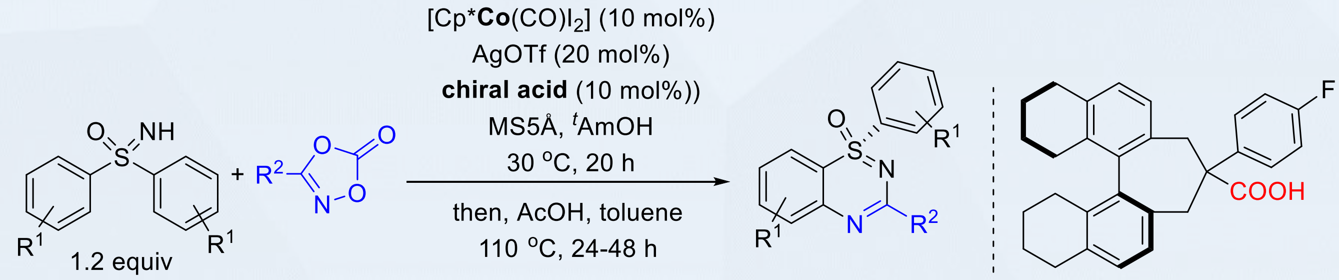
Plausible Transition-State Structures
(relative Gibbs energies and noncovalent interaction plots)
Method: M06/def2TZVPP+SMD(DCE)//M06L/def2SVP

□ Matsunaga, S. et al. *ACS Catal*. **2021**, *11*, 4271-4277.

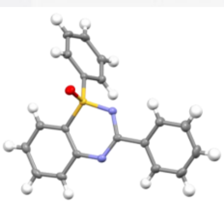
Chiral Induction via Chiral Anion

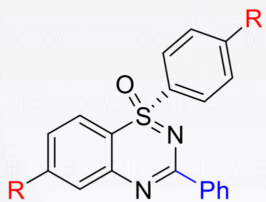
Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> Matsunaga, S. 2022

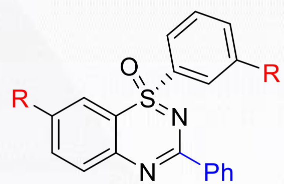


Scope

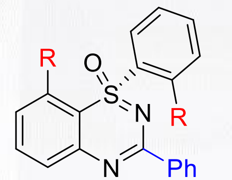




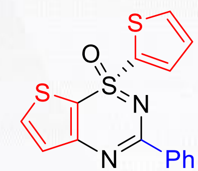
R = H, 75%, 96:4 e.r.
R = Br, 79%, 96:4 e.r.
R = Me, 52%, 97:3 e.r.
R = OMe, 61%, 97:3 e.r.



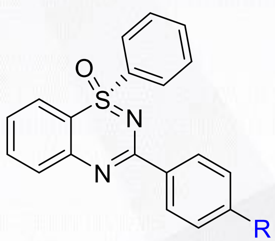
R = Cl, 70%, 91:9 e.r.
R = Me, 83%, 96:4 e.r.



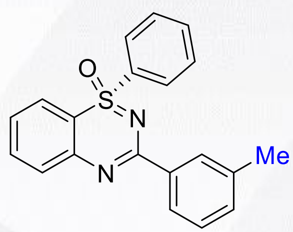
R = F, 96%, 96:4 e.r.
R = Me, 87%, 97:3 e.r.



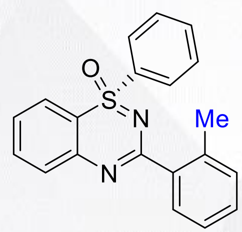
43%, 93:7 e.r.



R = CF_3, 53%, 94:6 e.r..
R = Me, 66%, 93:7 e.r.
R = OMe, 68%, 96:4 e.r.



66%, 93:7 e.r.



74%, 98:2 e.r.

R = 2-thienyl, 75%, 97:3 e.r.
R = Me, 51%, 97:3 e.r.
R = (*E*)-CH=CPh, 63%, 97:3 e.r.

Matsunaga, S. et al. *Angew. Chem., Int. Ed.* **2022**, e202205341.

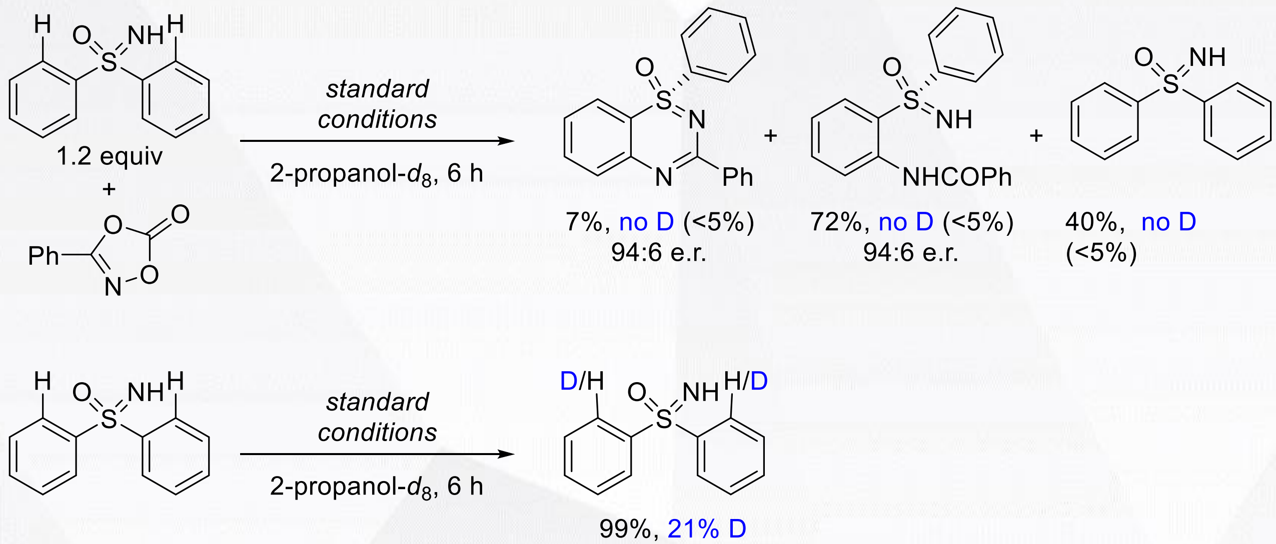
2.1

Chiral Induction via Chiral Anion

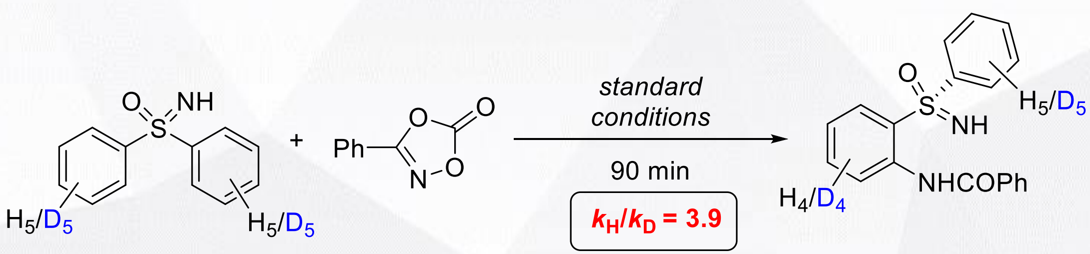
Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➢ **Mechanism**

1) H/D exchange experiments



2) Parallel KIE experiments



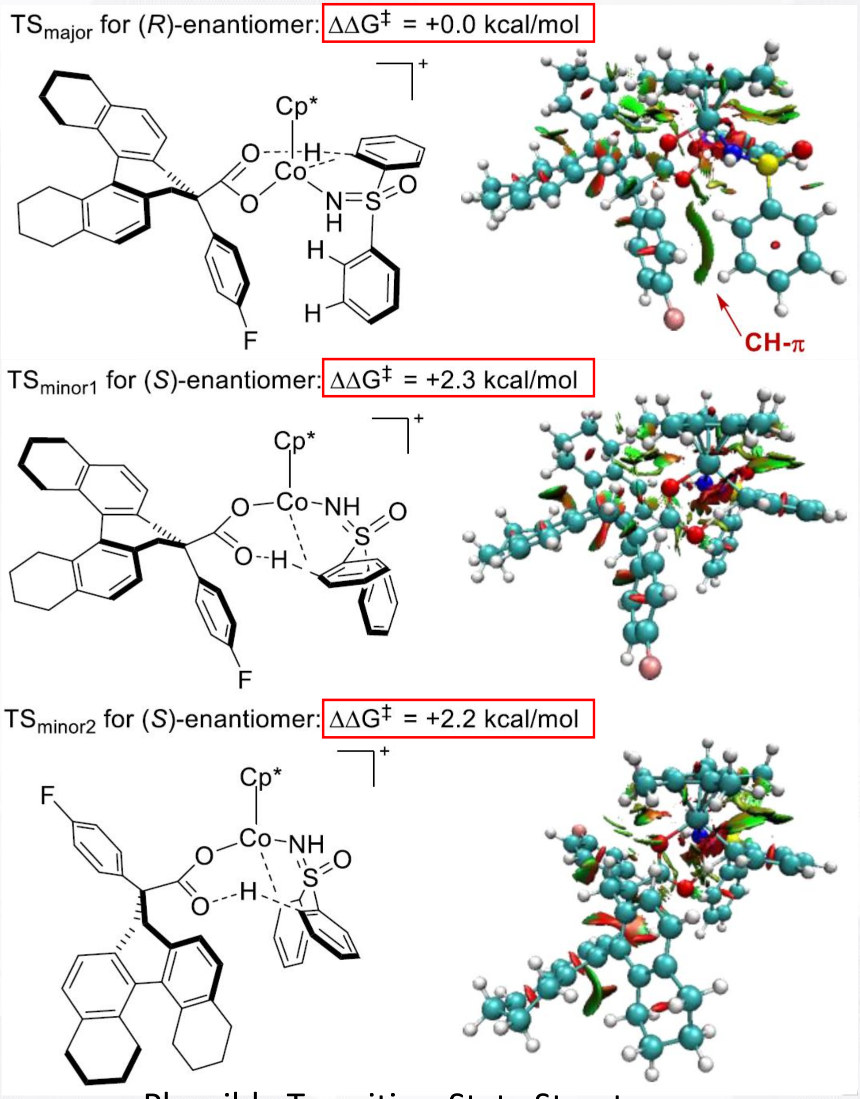
☐ Matsunaga, S. et al. *Angew. Chem., Int. Ed.* **2022**, e202205341.

2.1

Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C−H Functionalization

➢ **Mechanism**



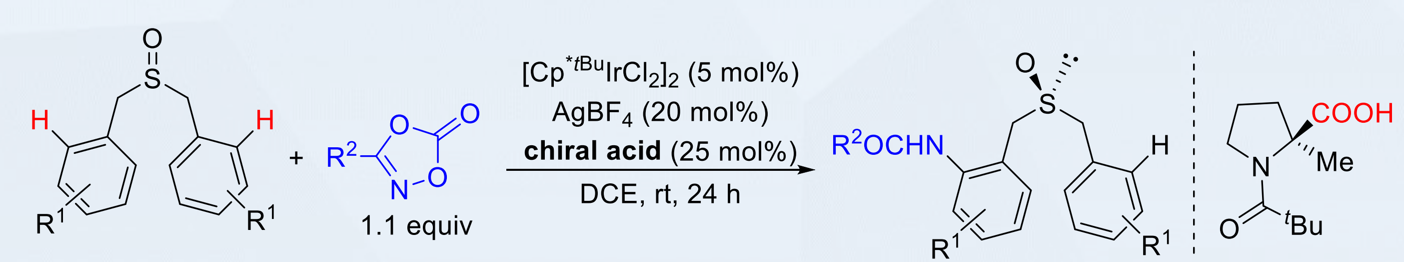
Plausible Transition-State Structures
(relative Gibbs energies and noncovalent interaction plots)
Method: M06/def2TZVPP+SMD(^{t}BuOH)//M06L/def2SVP

☐ Matsunaga, S. et al. *Angew. Chem., Int. Ed.* **2022**, e202205341.

Chiral Induction via Chiral Anion

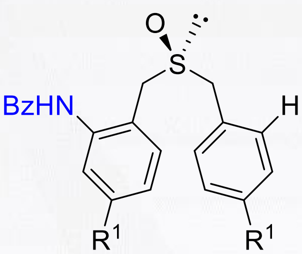
Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> He, C. 2020

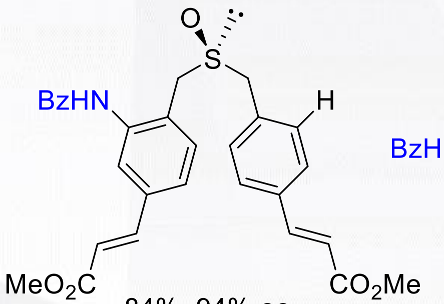


selected examples

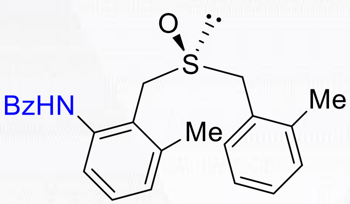
➢ **Scope**



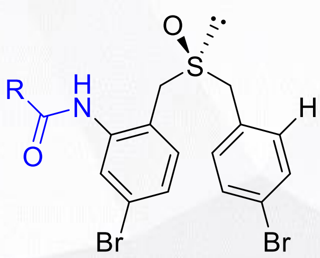
R^1 = OMe, 80%, 95% ee
R^1 = CO_2Me, 72%, 96% ee
R^1 = CF_3, 75%, 96% ee
R^1 = F, 76%, 96% ee
R^1 = Br, 79%, 97% ee
R^1 = I, 77%, 93% ee



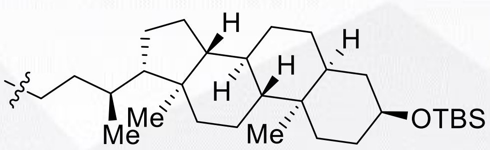
84%, 94% ee



58%, 85% ee



R = 2-MeC_6H_4, 44%, 94% ee
R = 4-$MeOC_6H_4$, 42%, 94% ee
R = 4-$NO_2C_6H_4$, 80%, 93% ee
R = 2-thienly, 86%, 96% ee
R = 2-naphthyl, 51%, 84% ee
R = Me, 65%, 95% ee

R = 

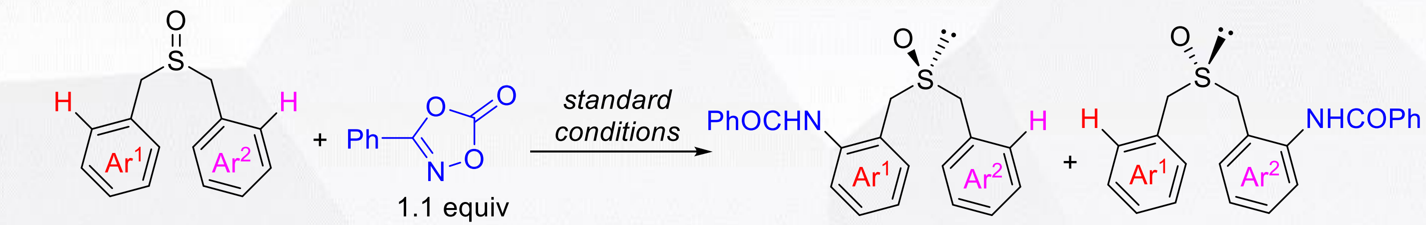
from lithocholic acid
58%, 97% de

Desymmetrization

☐ He, C. et al. *ACS Catal*. **2020**, *10*, 7207-7215.

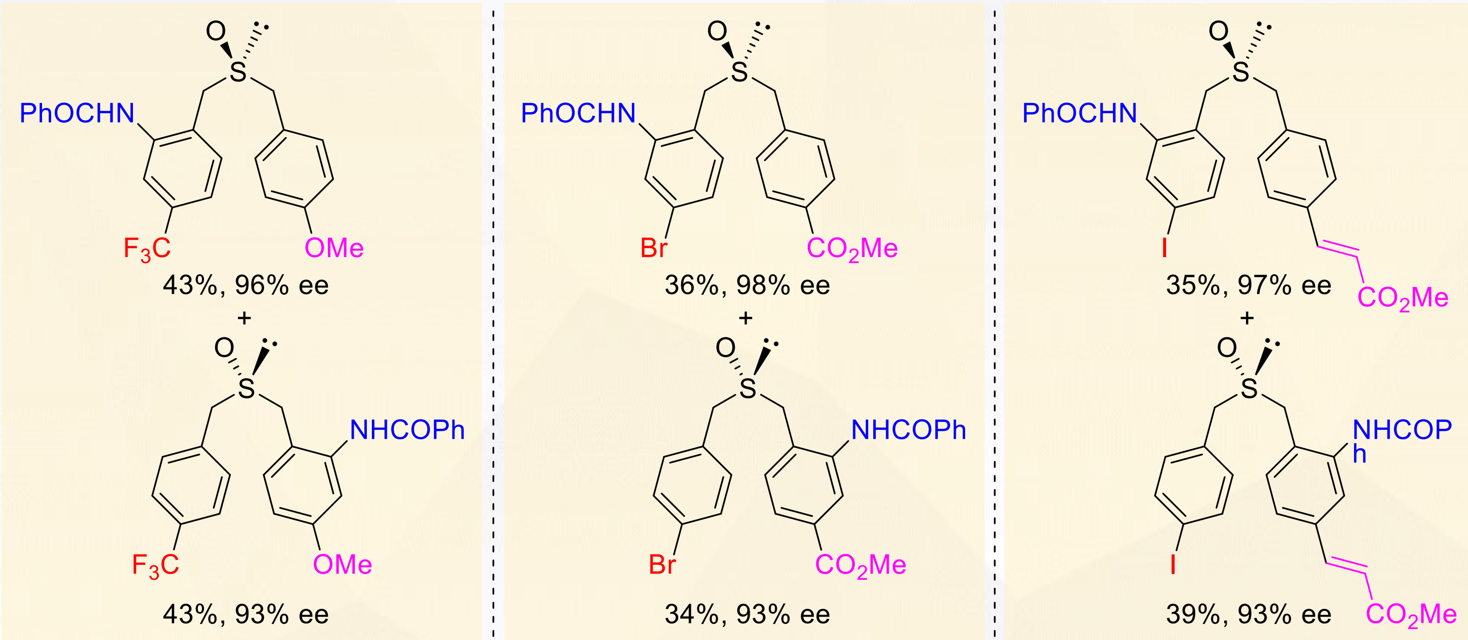
Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization



selected examples

- **Scope**



Parallel Kinetic Resolution (**PKR**)

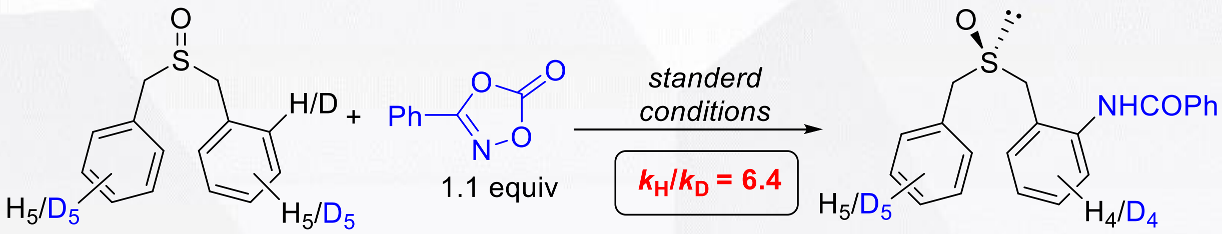
☐ He, C. et al. *ACS Catal*. **2020**, *10*, 7207-7215.

Chiral Induction via Chiral Anion

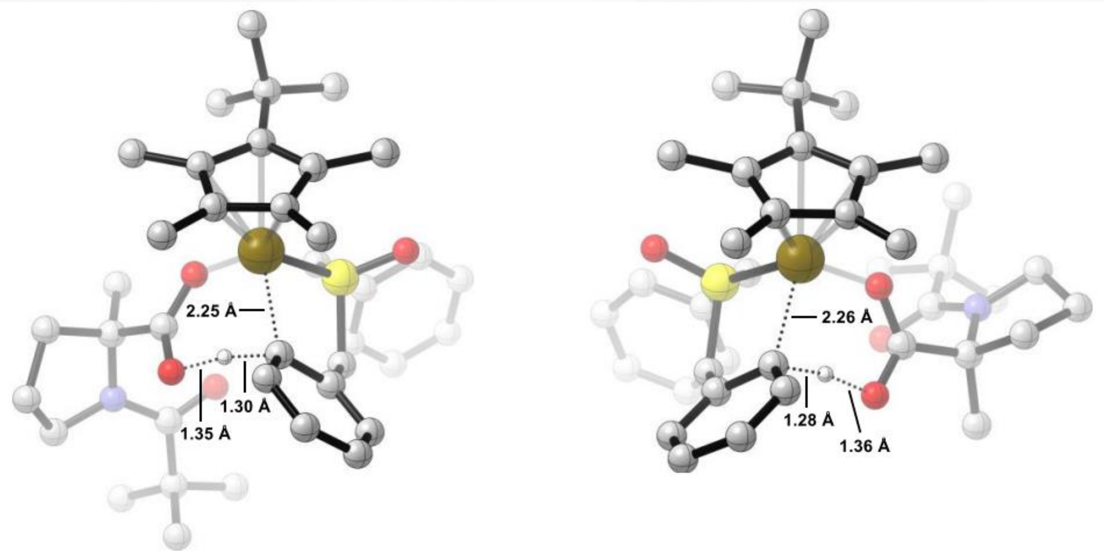
Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C−H Functionalization

- **Mechanism**

(1) KIE determined from two parallel reactions



(2) Stereocontrol model rationalizing the origin of the enantioselectivity



TS_*S* (favored) **TS_*R* (disfavored)**

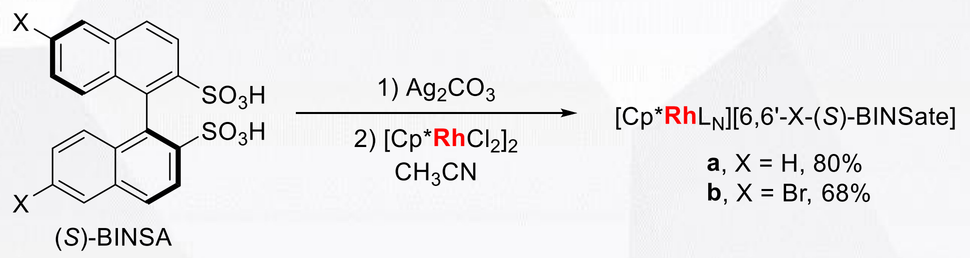
$\Delta\Delta G_{R\text{-}S}^{\neq}$ = 2.6 kcal/mol

- He, C. et al. *ACS Catal*. **2020**, *10*, 7207-7215.

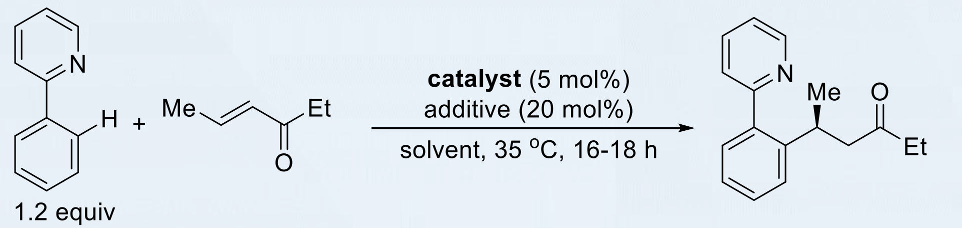
Chiral Induction via Chiral Anion

Achiral Cp^xM(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> **Matsunaga, S. 2018**



➤ **Screening**



entry	**catalyst**	additive	solvent	yield / %	e.r.
1	**a**	/	toluene	21	66:34
2	**a**	/	THF	79	80:20
3	**a**	/	DCE	>95	81:19
4	**a**	/	MeOH	12	63:37
5	**a**	2-Methylquinoline	DCE	86	86:14
6	**a**	2-Methylquinoline MS3Å	DCE	59	90:10
7	**b**	2-Methylquinoline MS3Å	DCE	60	92:8
8[a]	**b**	2-Methylquinoline MS3Å	DCE	84	91:9

[a] 1.1 equiv of enone, 48 h; MS3Å (4 mg/ 0.1 mmol)

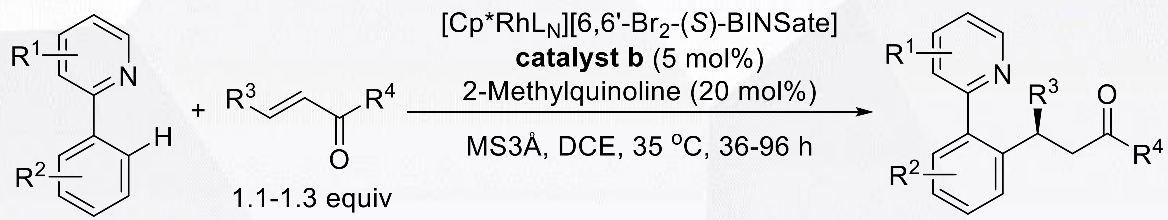
☐ Matsunaga, S. et al. *Nat. Catal.* **2018**, *1*, 585-591.

2.1

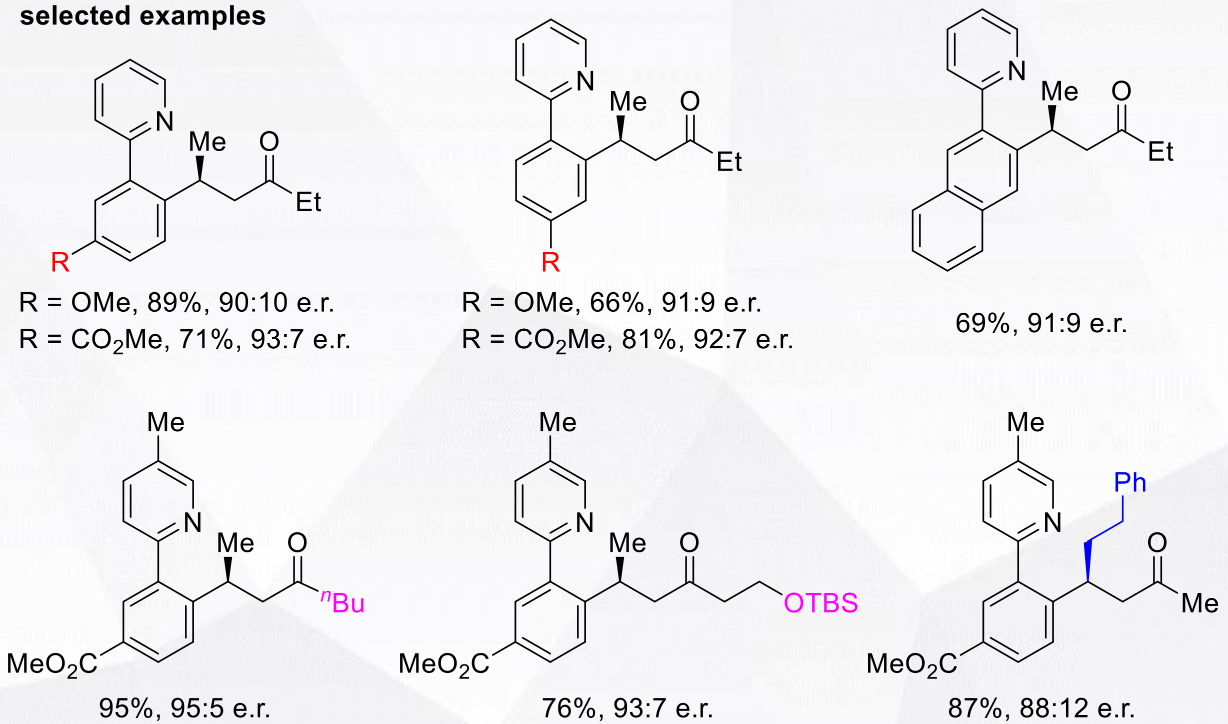
Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➢ **Scope**



selected examples



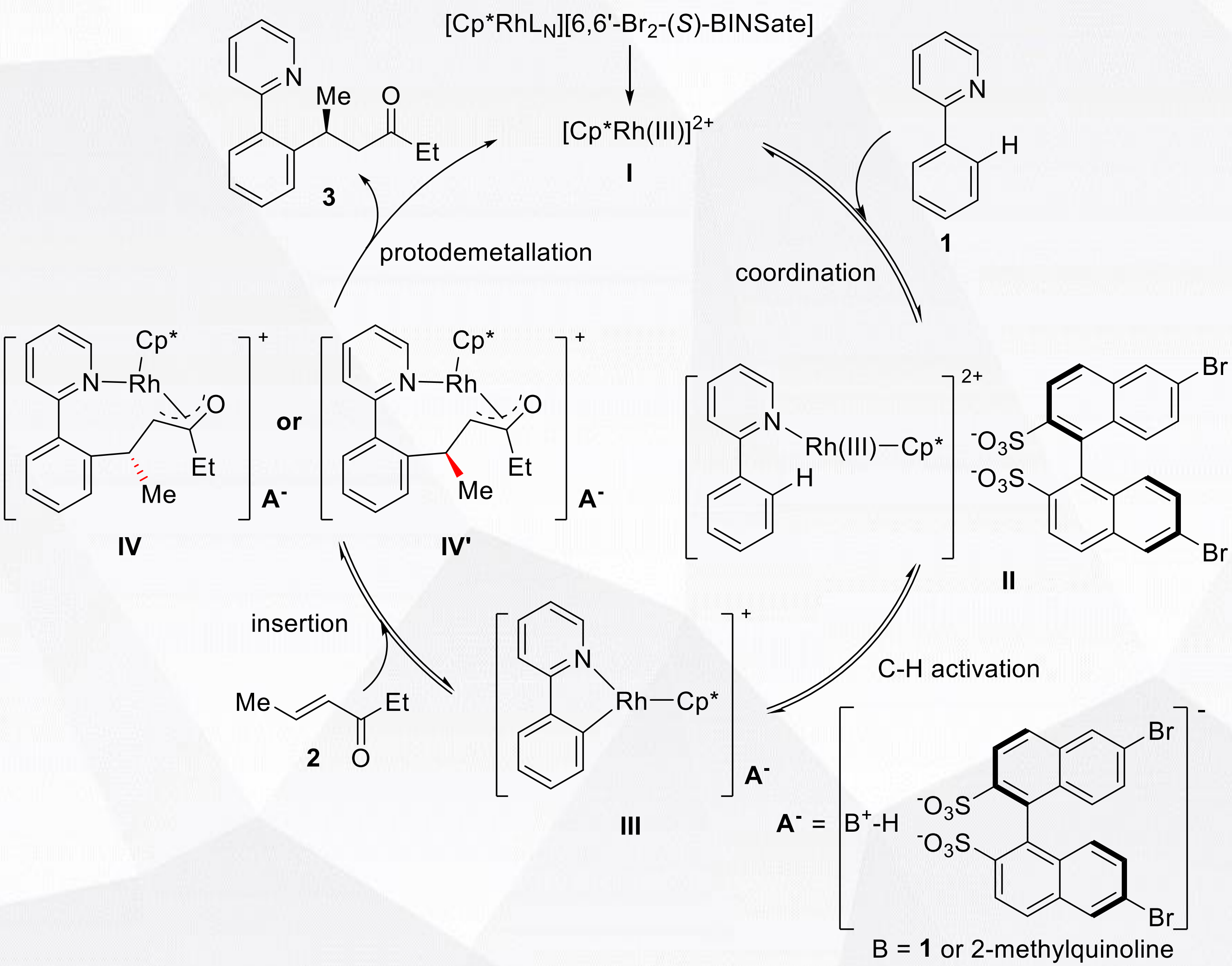
◻ Matsunaga, S. et al. *Nat. Catal.* **2018**, *1*, 585-591.

2.1

Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➢ **Mechanism**

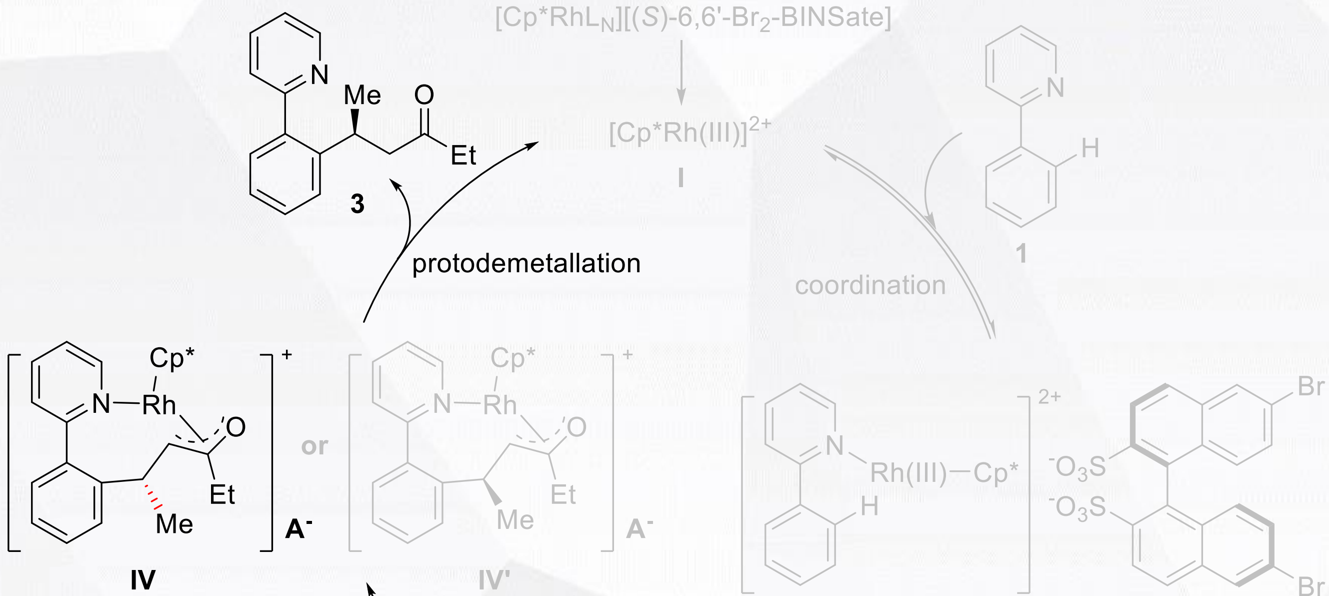


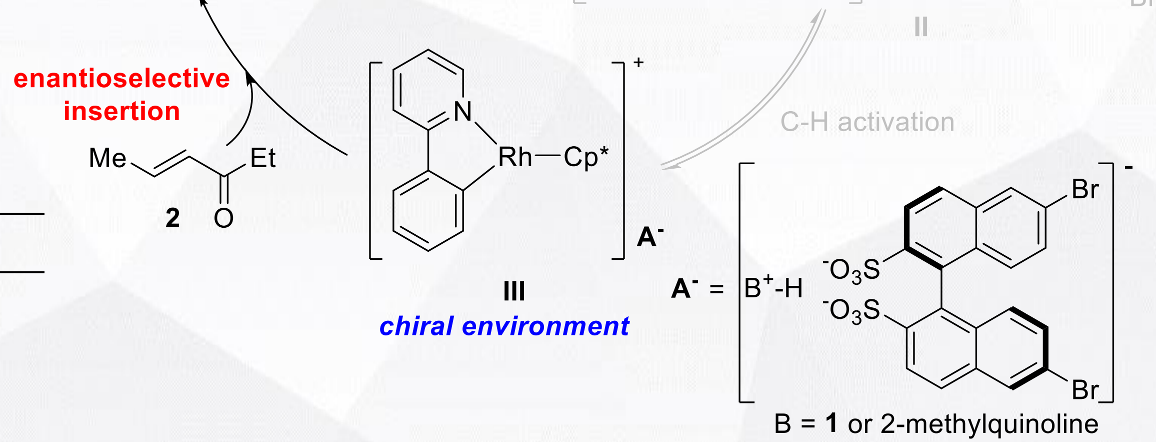
☐ Matsunaga, S. et al. *Nat. Catal.* **2018**, *1*, 585-591.

Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➢ **Mechanism**





this work

	solvent	e.r.
polarity ↓	toluene	66:34
	DCE	81:19
	THF	80:20
	MeOH	63:37

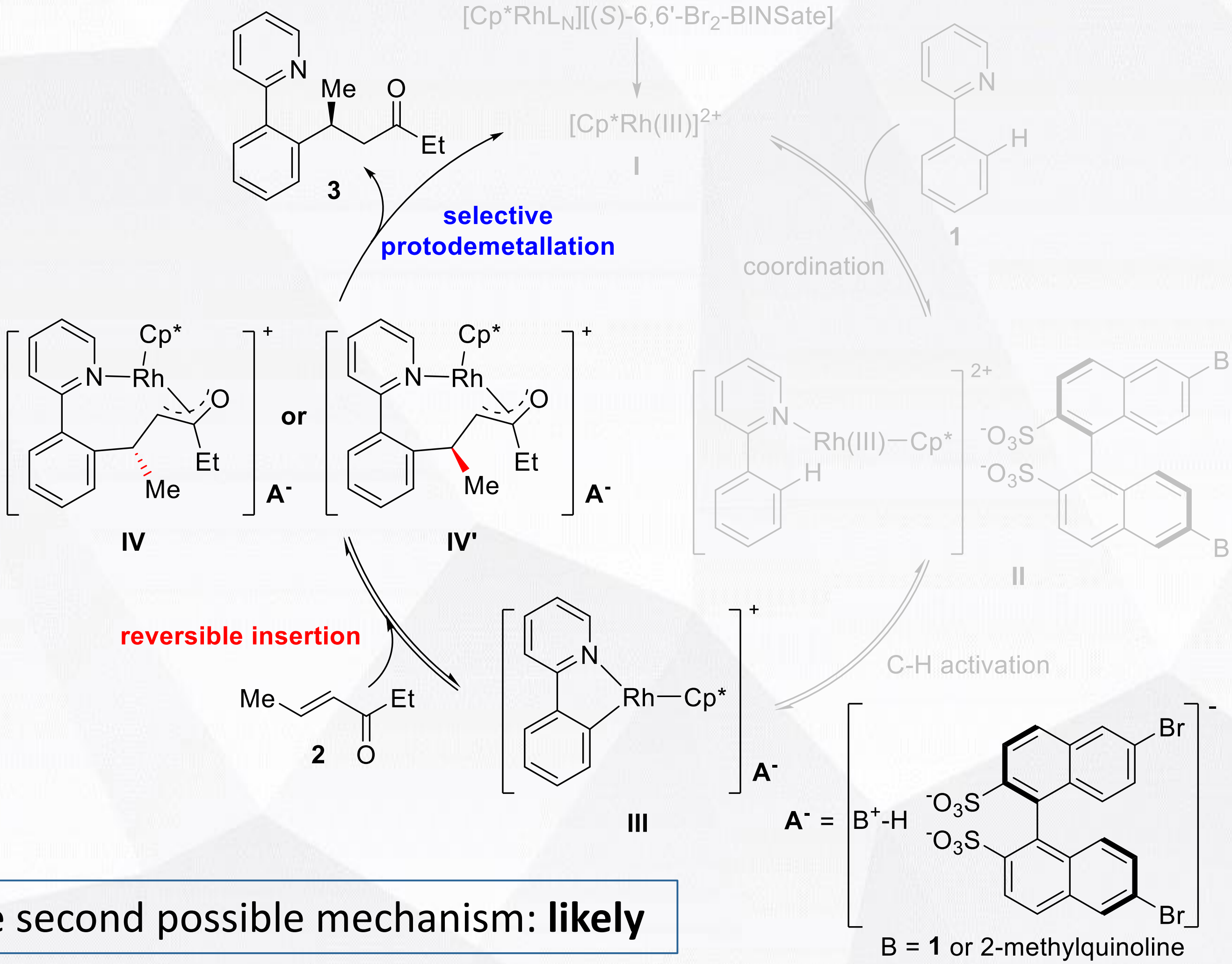
The first possible mechanism: **unlikely**

☐ Matsunaga, S. et al. *Nat. Catal.* **2018**, *1*, 585-591.

Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➤ **Mechanism**



The second possible mechanism: **likely**

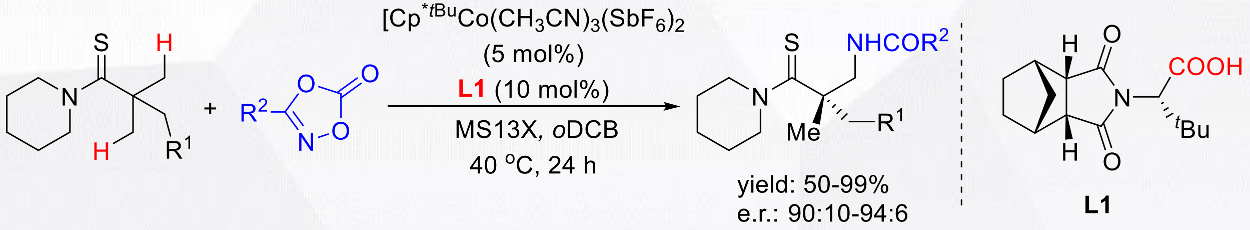
☐ Matsunaga, S. et al. *Nat. Catal.* **2018**, *1*, 585-591.

2.1

Chiral Induction via Chiral Anion

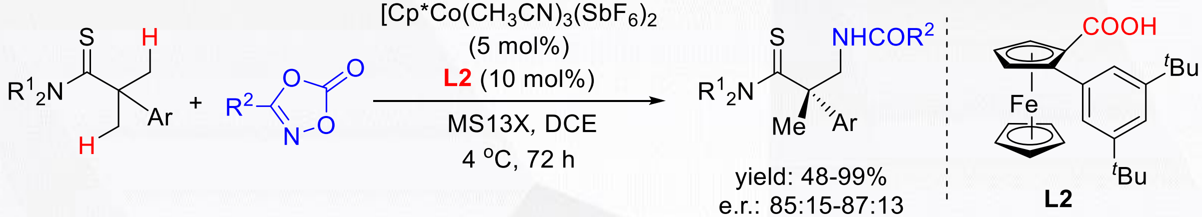
Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

2019:



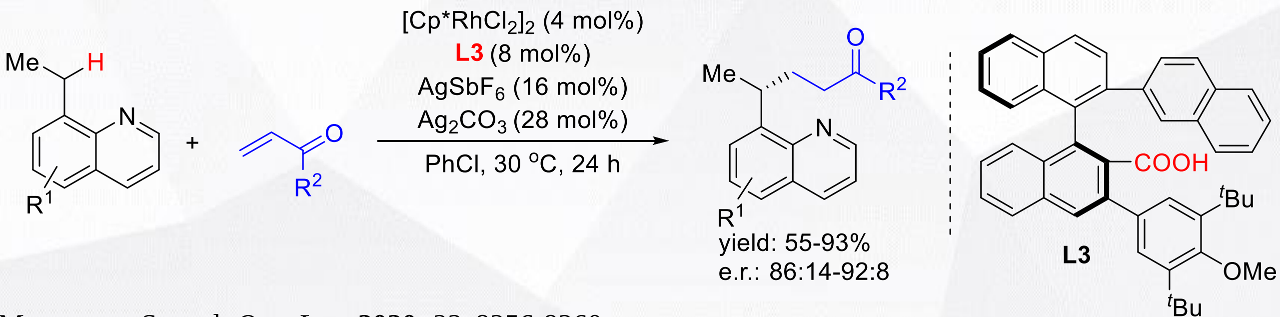
☐ Matsunaga, S. et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 1153-1157.

2019:



☐ Matsunaga, S. et al. *Organometallics* **2019**, *38*, 3921-3926.

2020:

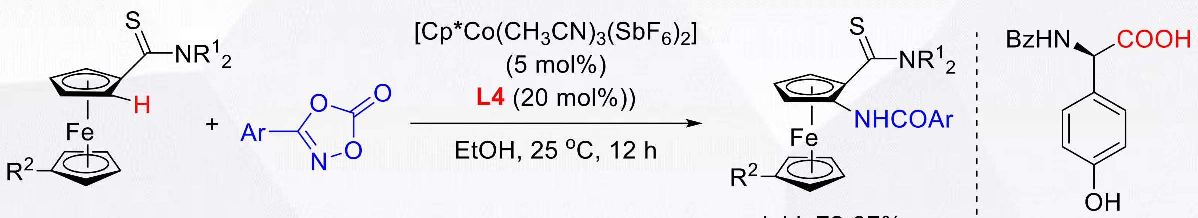


☐ Matsunaga, S. et al. *Org. Lett.* **2020**, *22*, 8256-8260.

2.1 Chiral Induction via Chiral Anion

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

2019:

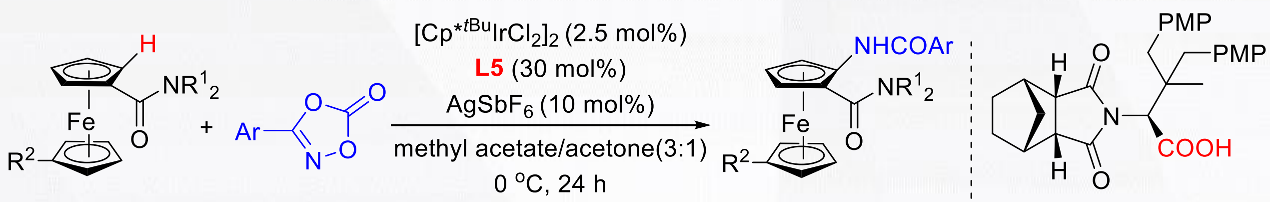


yield: 72-97%
e.r.: 67:33-76:24

L4

☐ Shi, B.-F. et al. *Org. Lett.* **2019**, *21*, 1895-1899.

2020:

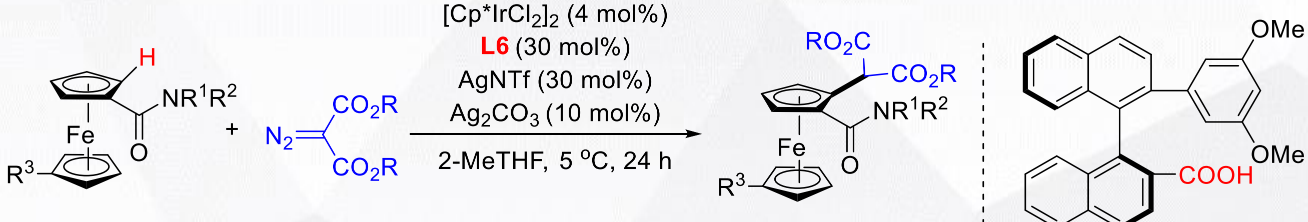


yield: 60-98%
e.r.: 91:9-98:2

L5

☐ Shi, B.-F. et al. *ACS Catal.* **2020**, *10*, 7117-7122.

2021:



yield: 60-87%
e.r.: 82:18-94:6

L6

☐ Sun, B. et al. *Org. Chem. Front.* **2021**, *8*, 6923-6930.

More examples:

☐ Duan, W.-L. *ACS Catal.* **2022**, *12*, 193-199.
☐ Matsunaga, S. et al. *Asian J. Org. Chem.* **2020**, *9*, 368-371.
☐ Ackermann, L. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 15425-15429.

02

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

2.1 Chiral Induction via **Chiral Anion**

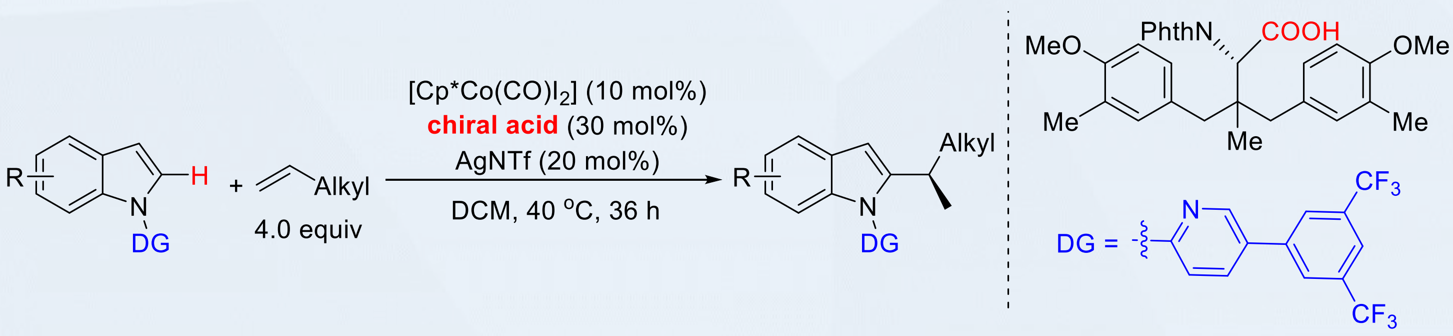
2.2 Chiral Induction via **Noncovalent Interaction**

2.3 Chiral Induction via **Covalent Interaction**

2.2 Chiral Induction via Noncovalent Interaction

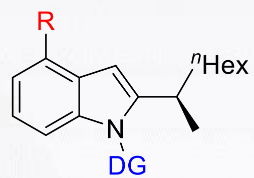
Achiral Cp^xM(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> Shi, B.-F. 2021

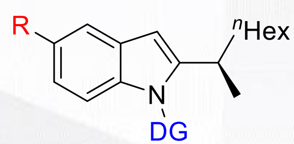


➢ Scope

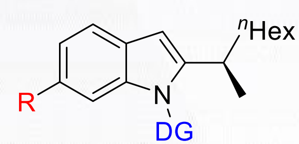
selected examples



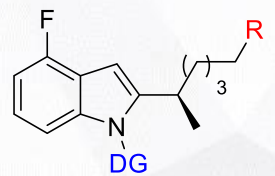
R = H, 75%, 90% ee (b/l = 97:3)
R = F, 93%, 91% ee (b/l = 98:2)



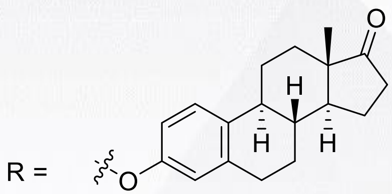
R = OMe, 71%, 92% ee (93:7)
R = NO_2, 78%, 92% ee



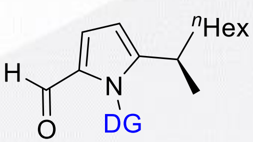
R = OMe, 42%, 90% ee (98:2)
R = F, 93%, 90% ee (99:1)



R = Br, 80%, 90% ee (95.5:4.5)
R = OH, 65%, 88% ee (96:4)[a]



from estrone
72%, 95:5 dr, (94:6)[b]



78%, 86% ee[c]

[a] 3.0 equiv alkene, [b] 2.0 equiv alkene, [c] room temperature

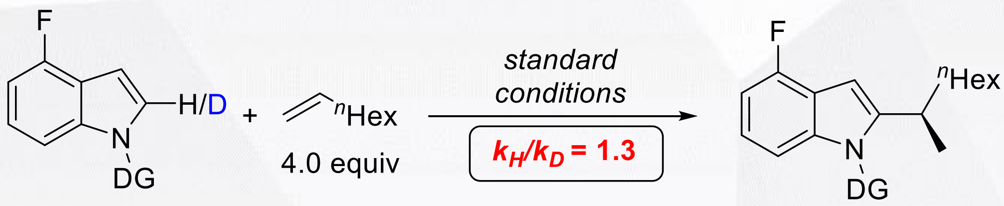
☐ Shi, B.-F. et al. *J. Am. Chem. Soc.* **2021**, *143*, 19112-19120.

Chiral Induction via Noncovalent Interaction

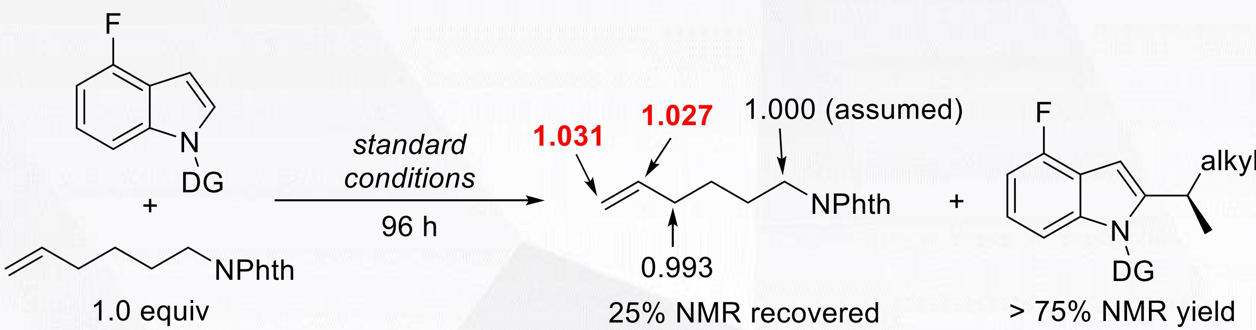
Achiral Cp^xM(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

Mechanism

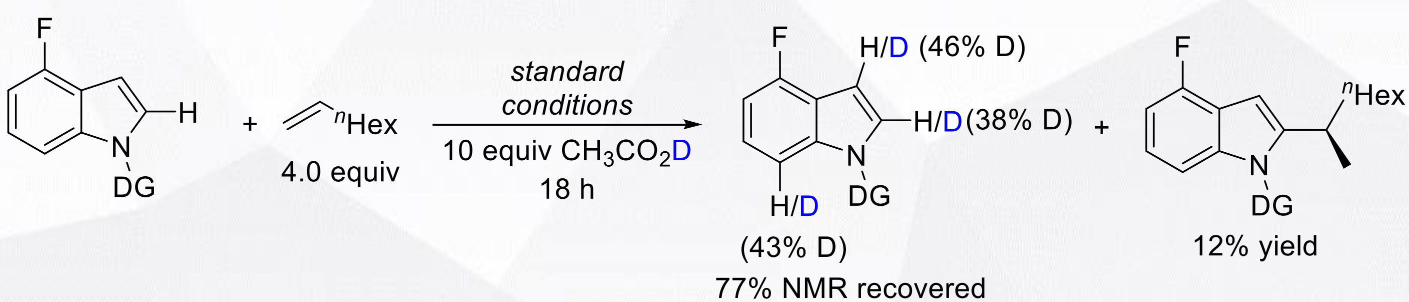
1) Determination of H/D KIE



2) Determination of natural abundance ^{13}C KIE



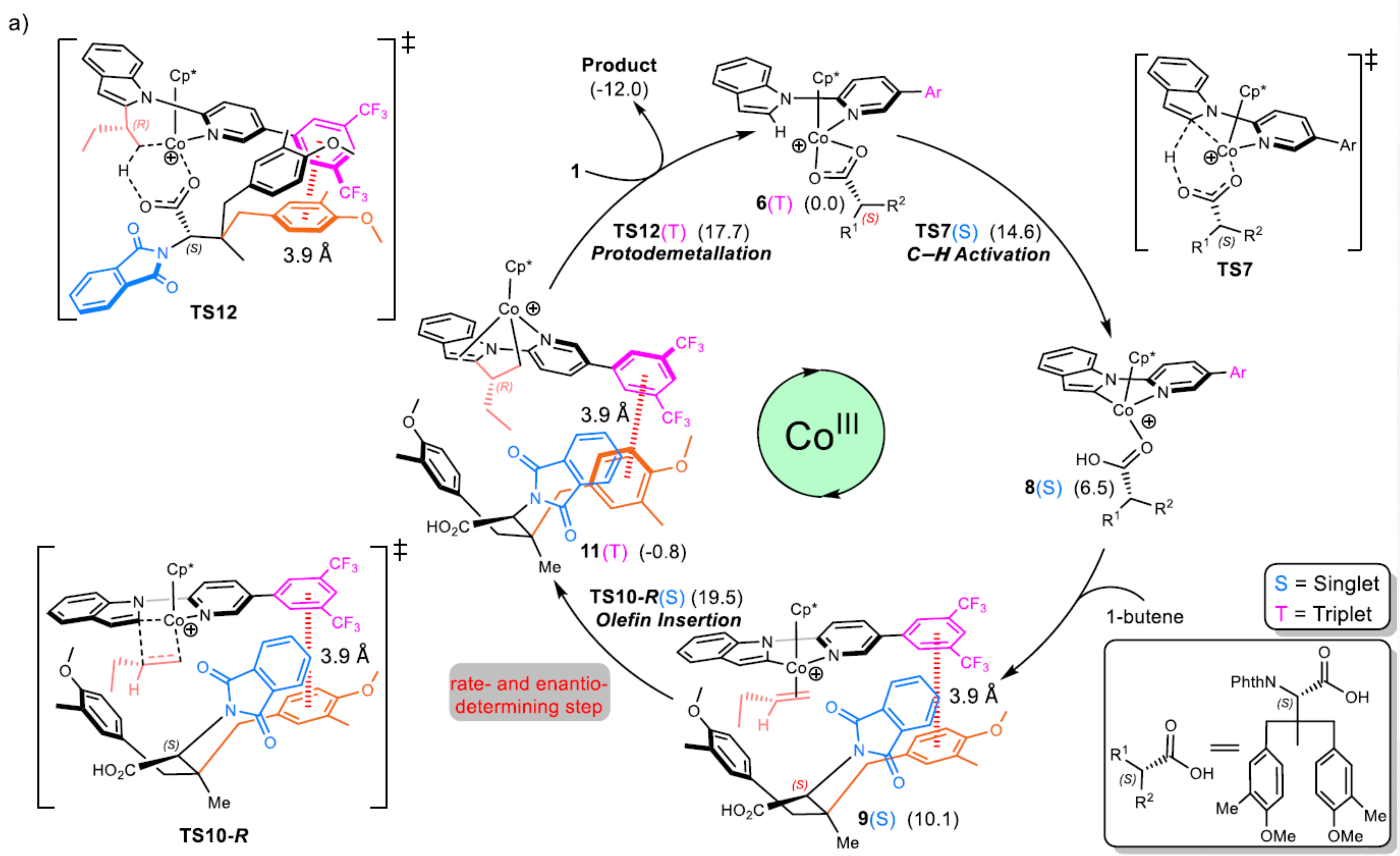
3) H/D exchange



Shi, B.-F. et al. *J. Am. Chem. Soc.* **2021**, *143*, 19112-19120.

2.2 Chiral Induction via Noncovalent Interaction

Achiral Cp^xM(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization



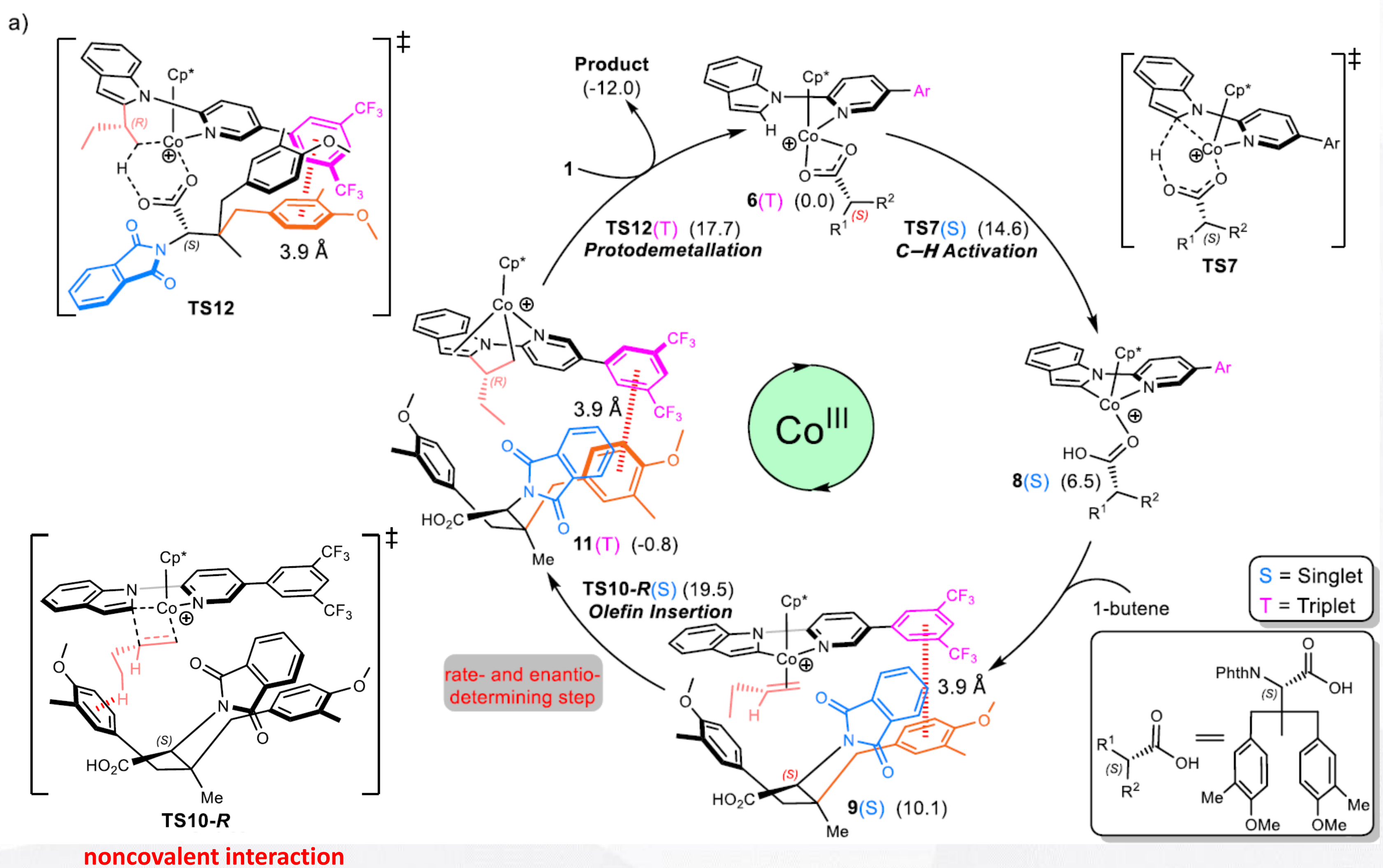
noncovalent interaction

Method: PBE0-D3/def2-TZVPP-SMD(DCM)//PBE0/def2-svp

□ Shi, B.-F. et al. *J. Am. Chem. Soc.* **2021**, *143*, 19112-19120.

Chiral Induction via Noncovalent Interaction

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization



Method: PBE0-D3/def2-TZVPP-SMD(DCM)//PBE0/def2-svp

☐ Shi, B.-F. et al. *J. Am. Chem. Soc.* **2021**, *143*, 19112-19120.

02

Achiral $Cp^xM(III)$-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

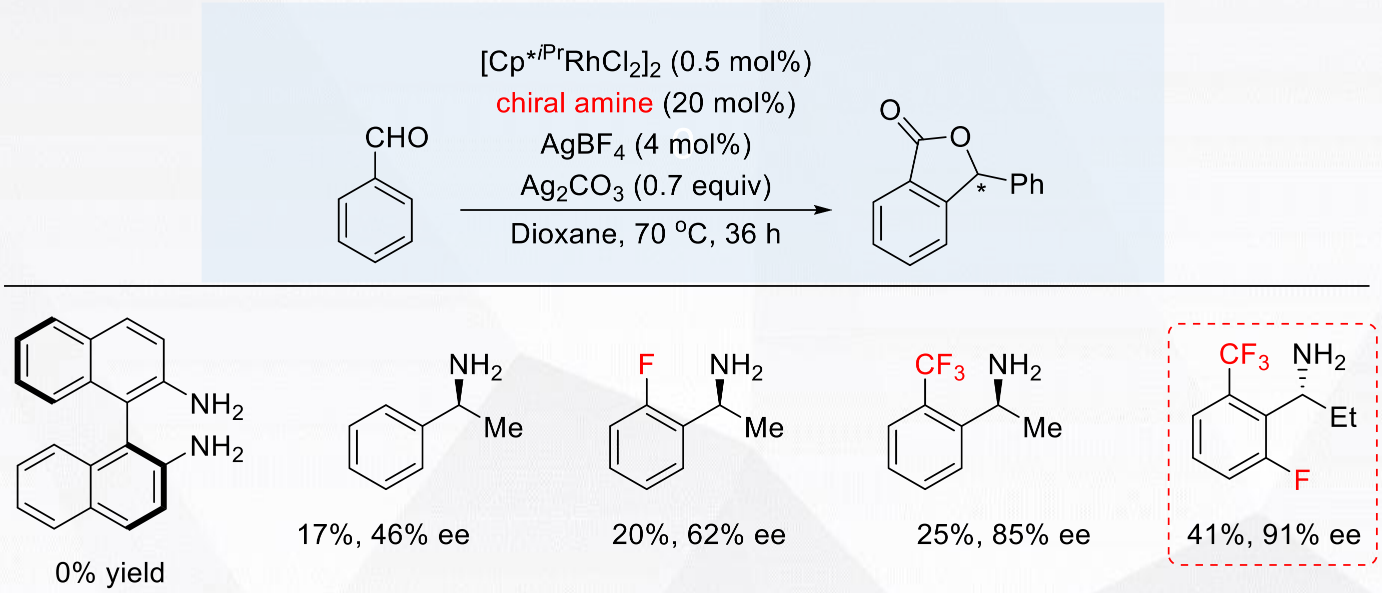
Chiral Induction via Covalent Interaction

Achiral $Cp^xM(III)$-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> **Wang, J. 2019**

Chiral **Transient Directing Group** (TDG) Strategy

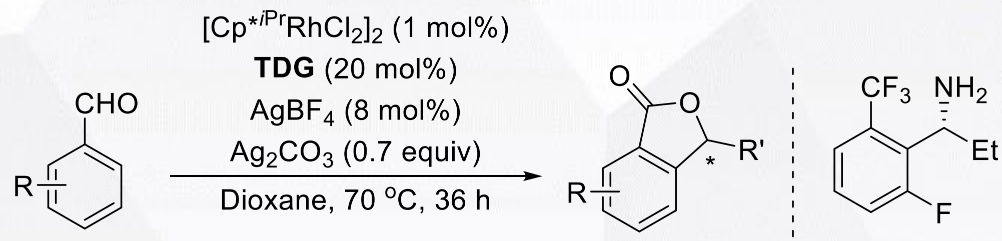
➢ **Screening**



□ Wang, J. et al. *Chem. Eur. J.* **2019**, *25*, 4688-4694.

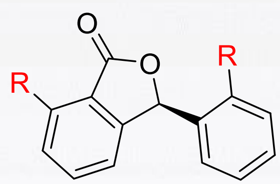
Chiral Induction via Covalent Interaction

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

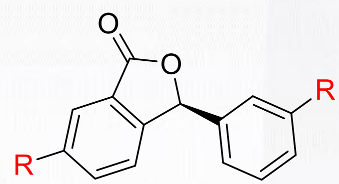


➢ **Scope**

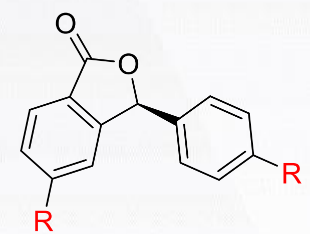
selected examples: same aldehyde



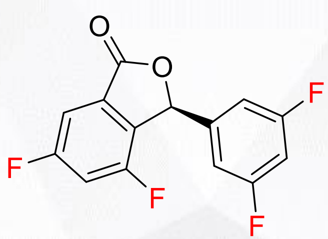
R = H, 64%, 92% ee
R = F, 15%, 97% ee



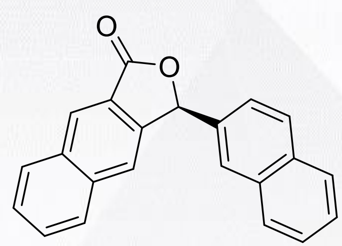
R = Me, 57%, 95% ee
R = Br, 32%, 98% ee



R = Me, 50%, 93% ee
R = Ph, 42%, 91% ee
R = Br, 43%, 93% ee
R = CF_3, 34%, 92% ee



61%, 87% ee



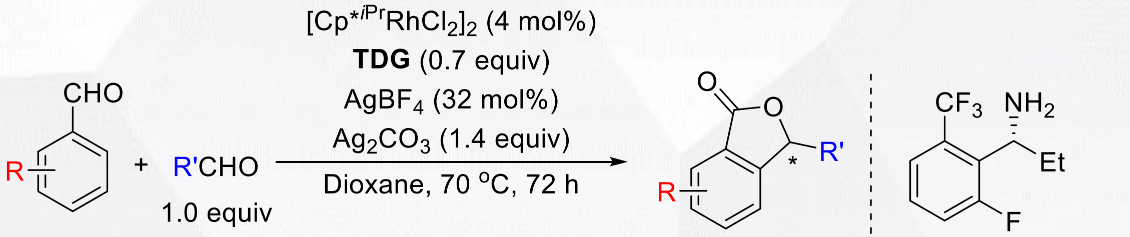
30%, 61% ee

☐ Wang, J. et al. *Chem. Eur. J.* **2019**, *25*, 4688-4694.

2.3

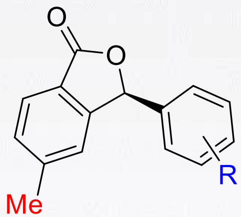
Chiral Induction via Covalent Interaction

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

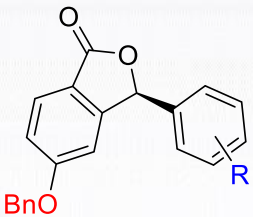


selected examples: different aldehyde

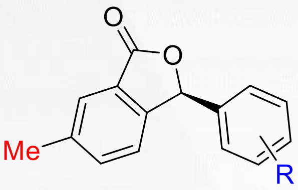
➤ **Scope**



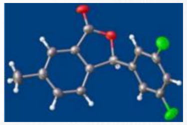
R = 3,5-F_2, 44% (major), 96% ee
R = 4-NO_2, 42%, 74% ee
R = 4-CF_3, 38%, >99% ee

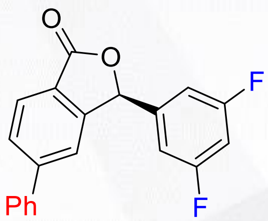


R = 4-CO_2Me, 37%, >99% ee
R = 3,5-F_2, 47%, 97% ee
R = 4-CF_3, 31%, 95% ee



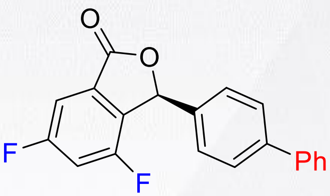
R = 4-CO_2Me, 42%, 92% ee
R = 4-CF_3, 33%, 96% ee
R = 3,5-F_2, 40%, 93% ee



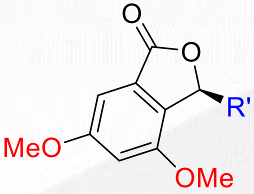


30%, 94% ee

2.3 : 1



13%, 86% ee



R' = CO_2Et, 64%, 76% ee
R' = ^{n}Bu, 13%, 93% ee
R' = Cy, 22%, 93% ee

☐ Wang, J. et al. *Chem. Eur. J.* **2019**, *25*, 4688-4694.

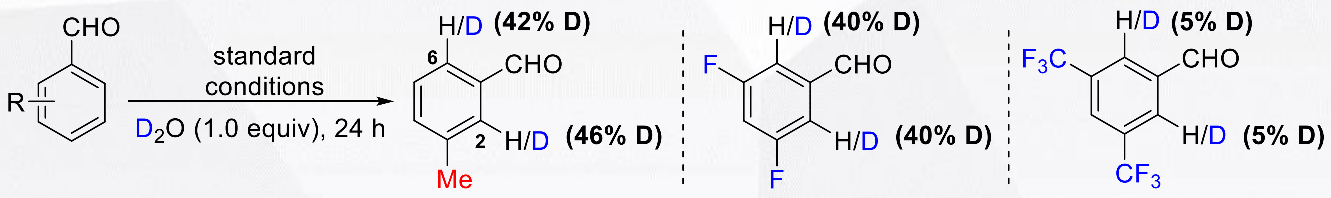
2.3

Chiral Induction via Covalent Interaction

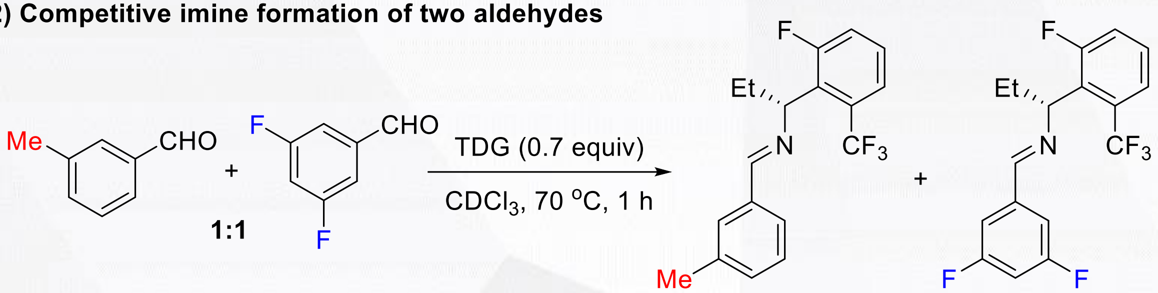
Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➢ **Mechanism**

1) H/D exchange for C-H activtion step

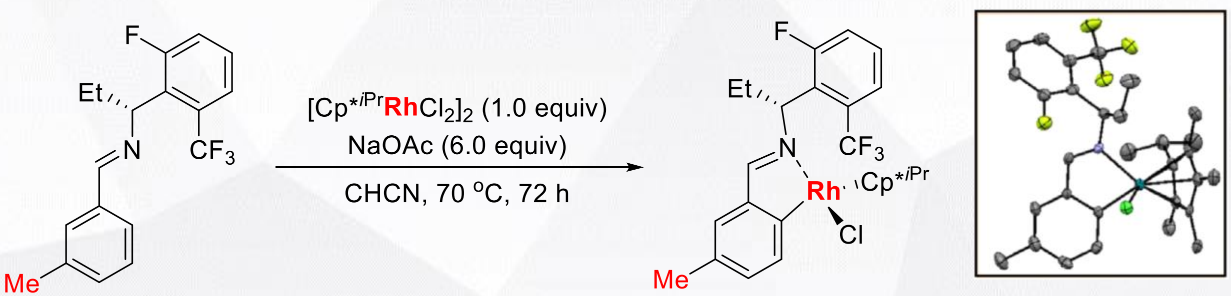


2) Competitive imine formation of two aldehydes



1 : 2.2

3) Synthesis of rhodacycle intermediate and investigation of activity



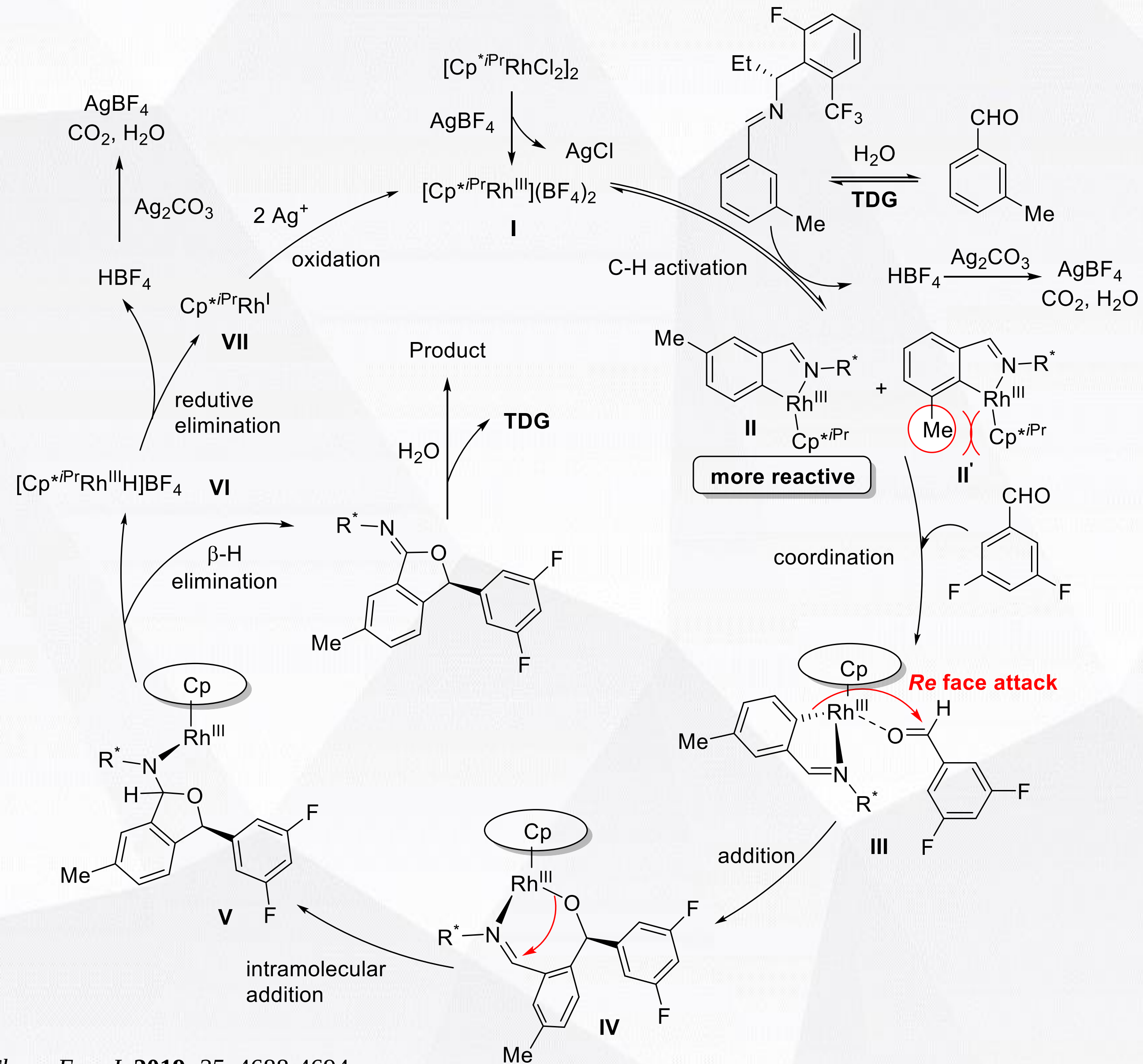
Rhodium center: *R*-configuration
32% yield

☐ Wang, J. et al. *Chem. Eur. J.* **2019**, *25*, 4688-4694.

2.3 Chiral Induction via Covalent Interaction

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C−H Functionalization

➢ **Mechanism**



□ Wang, J. et al. *Chem. Eur. J.* **2019**, *25*, 4688-4694.

2.3

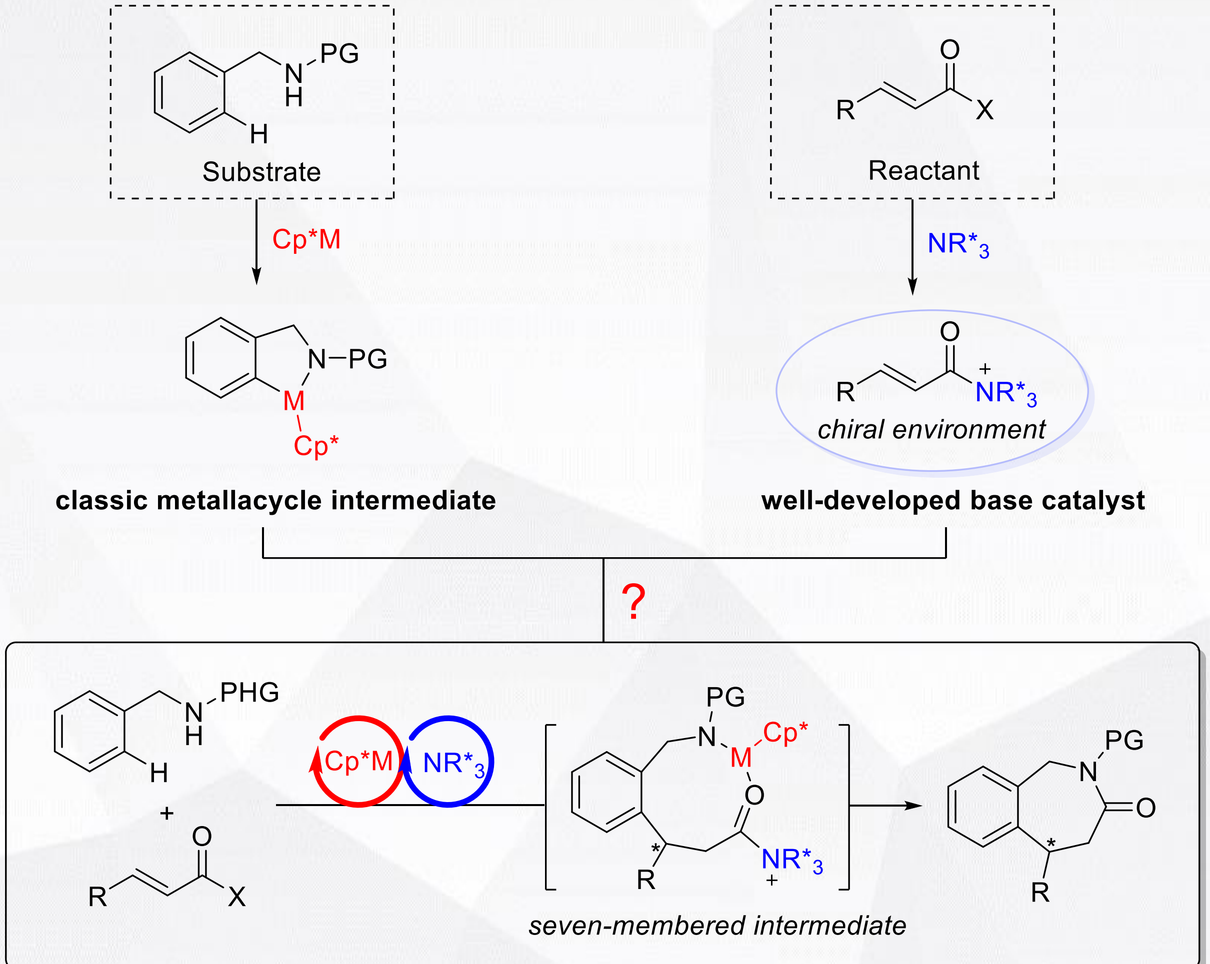
Chiral Induction via Covalent Interaction

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

>> Matsunaga, S. 2022

Chiral **Lewis Base** Cooperative Catalysis

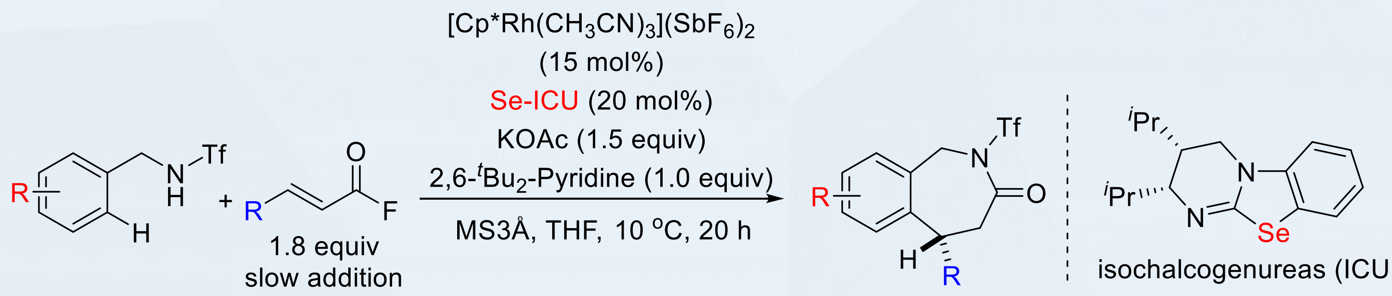
➤ **Design**



☐ Matsunaga, S. et al. *J. Am. Chem. Soc.* **2022**, *144*, 7058-7065.

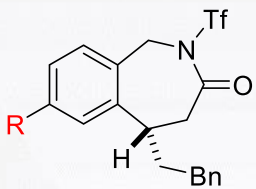
2.3 Chiral Induction via Covalent Interaction

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C−H Functionalization

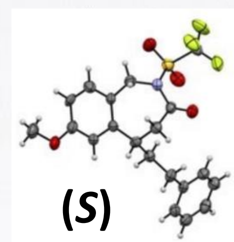


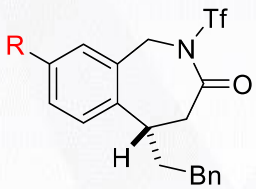
Scope

selected examples

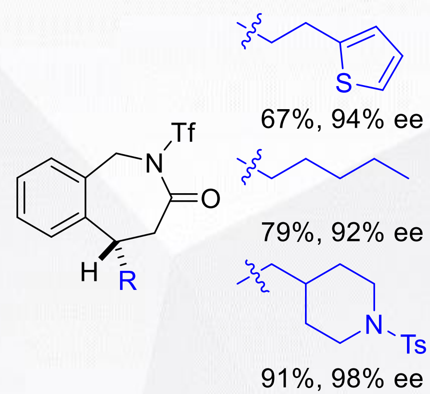


R = Me, 80%, 90% ee
R = OMe, 62%, 94% ee
R = CO_2Me, 78%, 94% ee
R = Cl, 77%, 96% ee





R = Me, 54%, 88% ee
R = Cl, 48%, 96% ee
R = Br, 51%, 96% ee
R = I, 58%, 96% ee



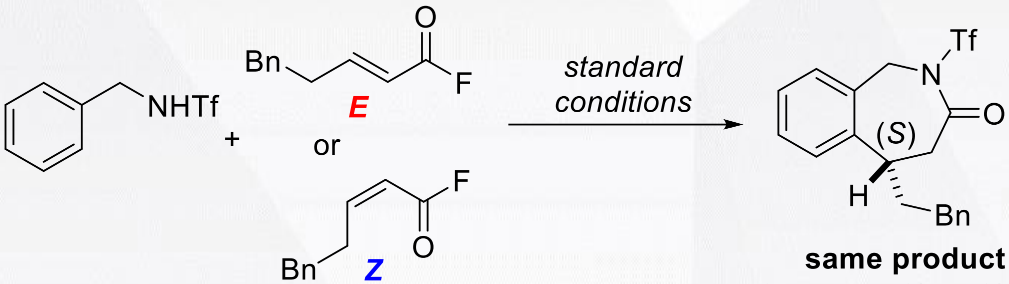
☐ Matsunaga, S. et al. *J. Am. Chem. Soc.* **2022**, *144*, 7058-7065.

Chiral Induction via Covalent Interaction

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

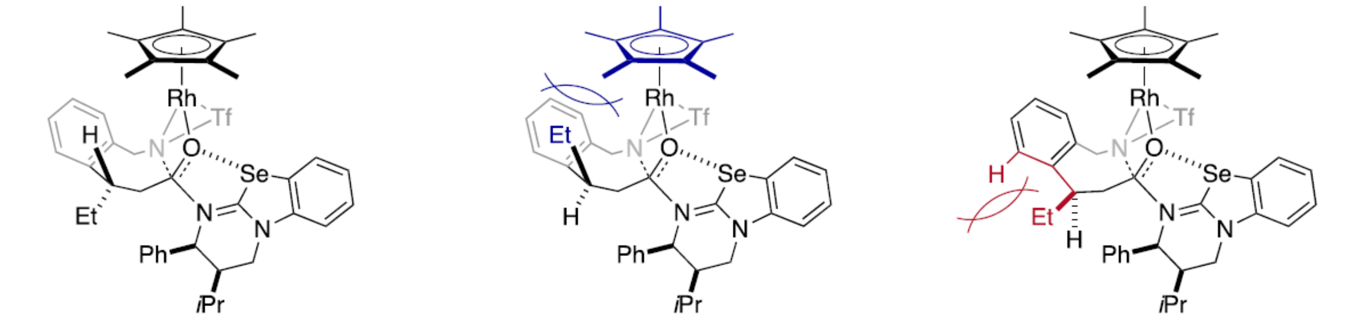
➢ **Mechanism**

1) Enantioselectivity of the reaction with *Z*- or *E*-reactant



same product
from *E*: 83%, 94% ee
from *Z*: 85%, 96% ee

2) Plausible transition-state structures for the cyclization step



TS1_major (0.0 kcal/mol) → (*S*)-**5** TS2_minor_1 (+10.7 kcal/mol) → (*R*)-**5** TS2_minor_2 (+2.8 kcal/mol) → (*R*)-**5**

Method: M06/def2-TZVPP+SMD(THF)//M06-L/def2-SVP+SMD(THF)

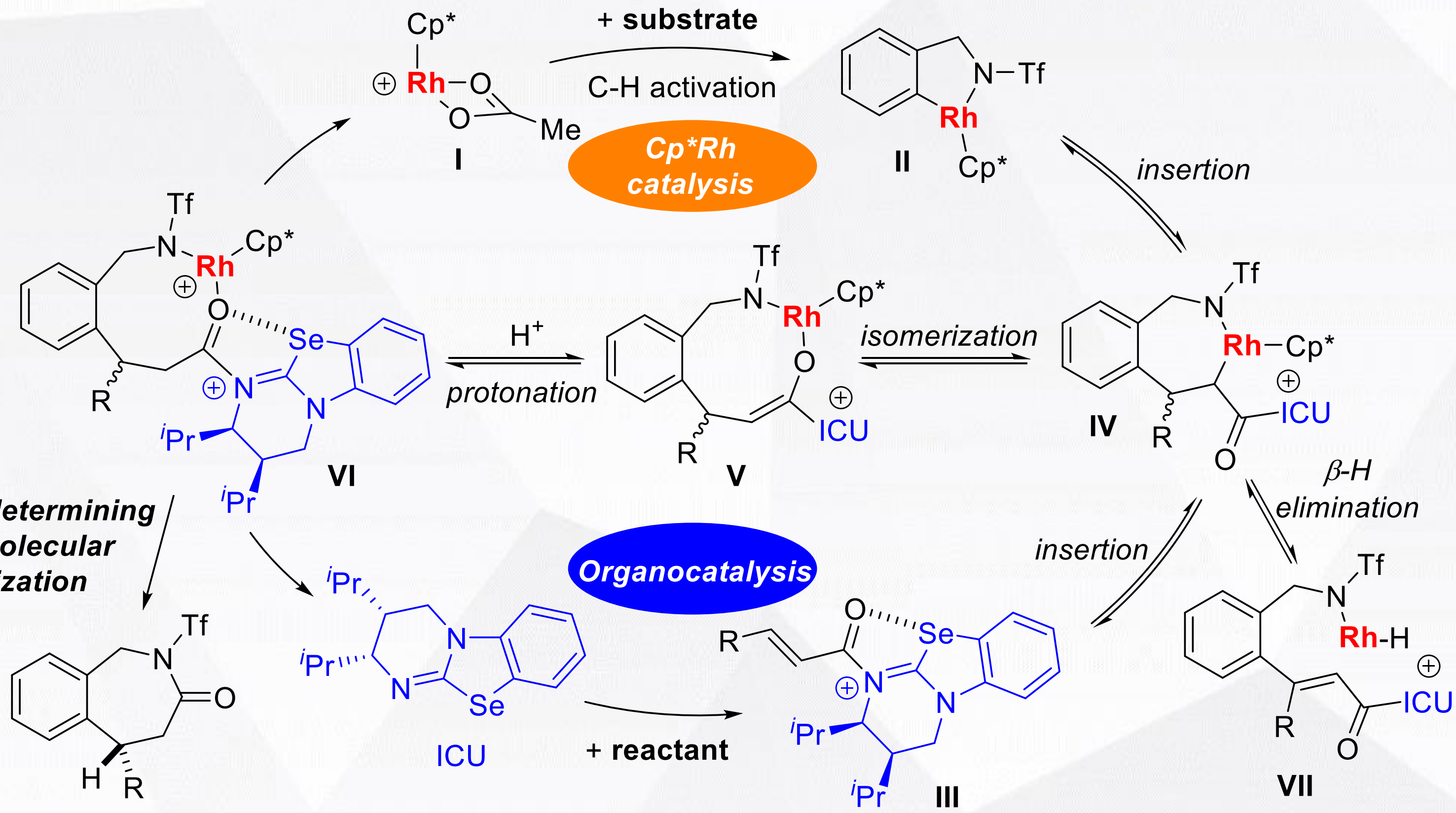
◻ Matsunaga, S. et al. *J. Am. Chem. Soc.* **2022**, *144*, 7058-7065.

Chiral Induction via Covalent Interaction

2.3

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

➢ **Mechanism**



□ Matsunaga, S. et al. *J. Am. Chem. Soc.* **2022**, *144*, 7058-7065.

03

Summary & Outlook

Achiral $Cp^xM(III)$-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

Summary

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

Chiral Anion

Chang, S.; Matsunaga, S.; He, C.; Shi, B.-F.; et al.

- Binaphthyl Carboxylic Acids/Sulfonates
- Amino Acid Derivatives

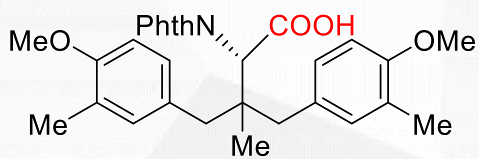
***Asymmetric CMD*:** Desymmetrization
Parallel Kinetic Resolution

***Asymmetric Protodemetallation*:** Addition Reaction

- Diverse Structures
- General Applicability
- Ambiguous Mechanism

Noncovalent Interaction

Shi, B.-F.

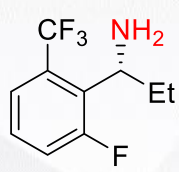


through:
π–π stacking

- Accurate Recognition
- Hard to Design

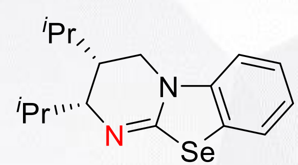
Covalent Interaction

Wang, J.



Chiral Amine TDG

Matsunaga, S.



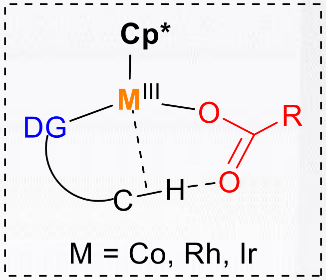
Chiral Lewis base (ICU)

- Strong Interaction
- Robust Enantiocontrol
- Restricted Scope

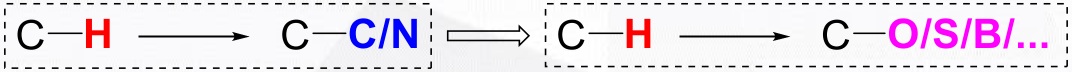
Outlook

Achiral Cp^{x}M(III)-Catalyzed (M = Co, Rh, Ir) Asymmetric C–H Functionalization

- Further developments to understand **the adaptabilities** among metal catalyst, ligand, and directing group



- **Bond-forming types** can be further extended beyond C-C/C-N bonds



- Further **mechanistic studies** to further understand the process of **chiral induction via chiral anion**

- **DFT calculations** can be used to improve the effect of ligand design for **chiral induction via noncovalent interaction**

THANKS FOR YOUR ATTENTION