Literature Report VII

Palladium-Catalyzed Enantioselective C-H Olefination to Access Planar-Chiral Cyclophanes by Dynamic Kinetic Resolution

Reporter: Yan-Jiang Yu
Checker: Hao-Dong Chen

Dong, Z.; Li, J.; Yao, T.; Zhao, C. *Angew. Chem. Int. Ed.* **2023**, e202315603

2023-12-04

CV of Prof. Zhao Changgui (赵常贵)

Group's goal:

- Medicinal chemistry
- Asymmetric catalysis
- Total synthesis of natural products

Background:

- **2014** Ph.D., Lanzhou University (She, X.-G.)
- **2014-2017** Postdoc., Tsinghua University (Wang, J.)
- **2017-2019** Postdoc., University of Wisconsin-Madison (Tang, W.-P.)
- **2020-Now** Associate Professor, Beijing Normal University

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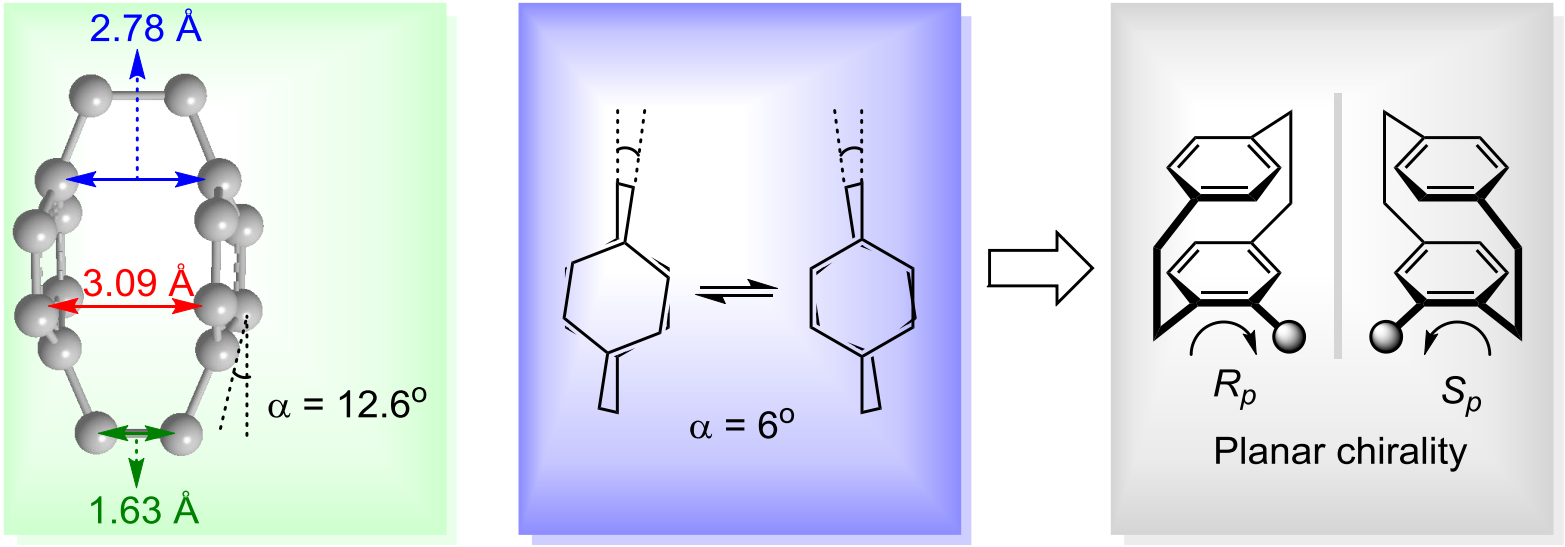
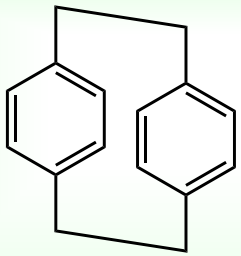
[2.2]paracyclophane



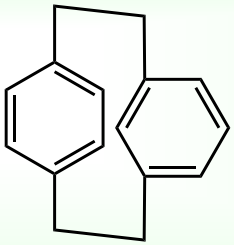
Brown, C. J.; Farthing, A. C. *Nature* **1949**, *164*, 915
Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1955**, *77*, 6289
Hope, H.; Bernstein, J.; Trueblood, K. N. *Acta Cryst. B.* **1972**, *28*, 1733

Introduction

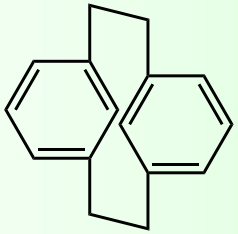
[n]cyclophanes



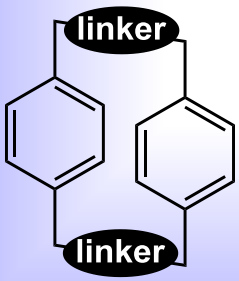
[2.2]para-
cyclophane

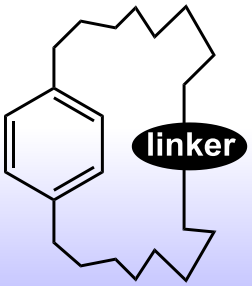


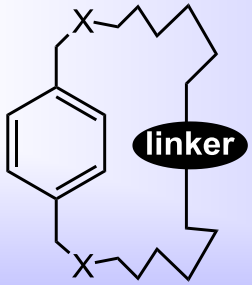
[2.2]meta-
paracyclophane

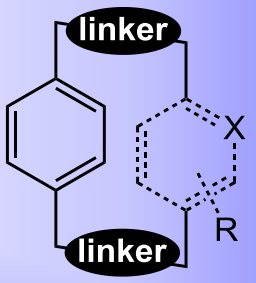


[2.2]meta-
cyclophane









Neumann, P.; Vögtle, F. *Tetrahedron Lett.* **1969**, *60*, 5329
Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, *4*, 204

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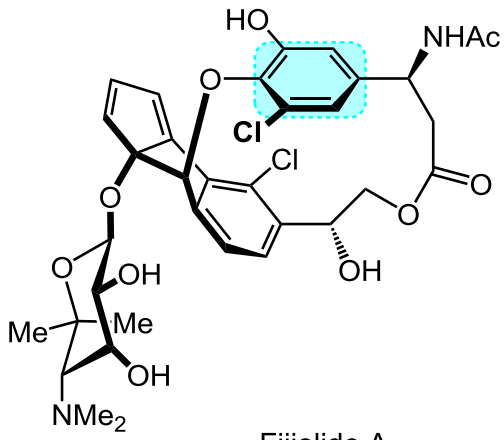
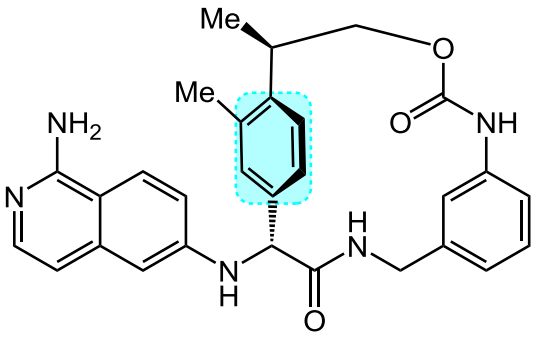
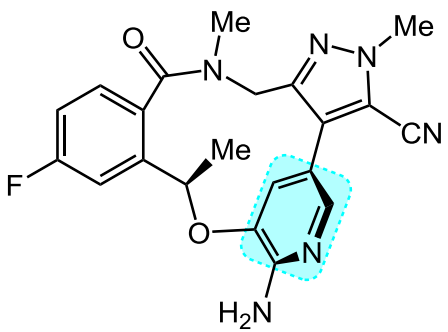


Fijiolide A
(**Natural product**)



FVIIa inhibitior
(**Single atropoisomer**)



Lorlatinib
(**FDA-approved drug**)

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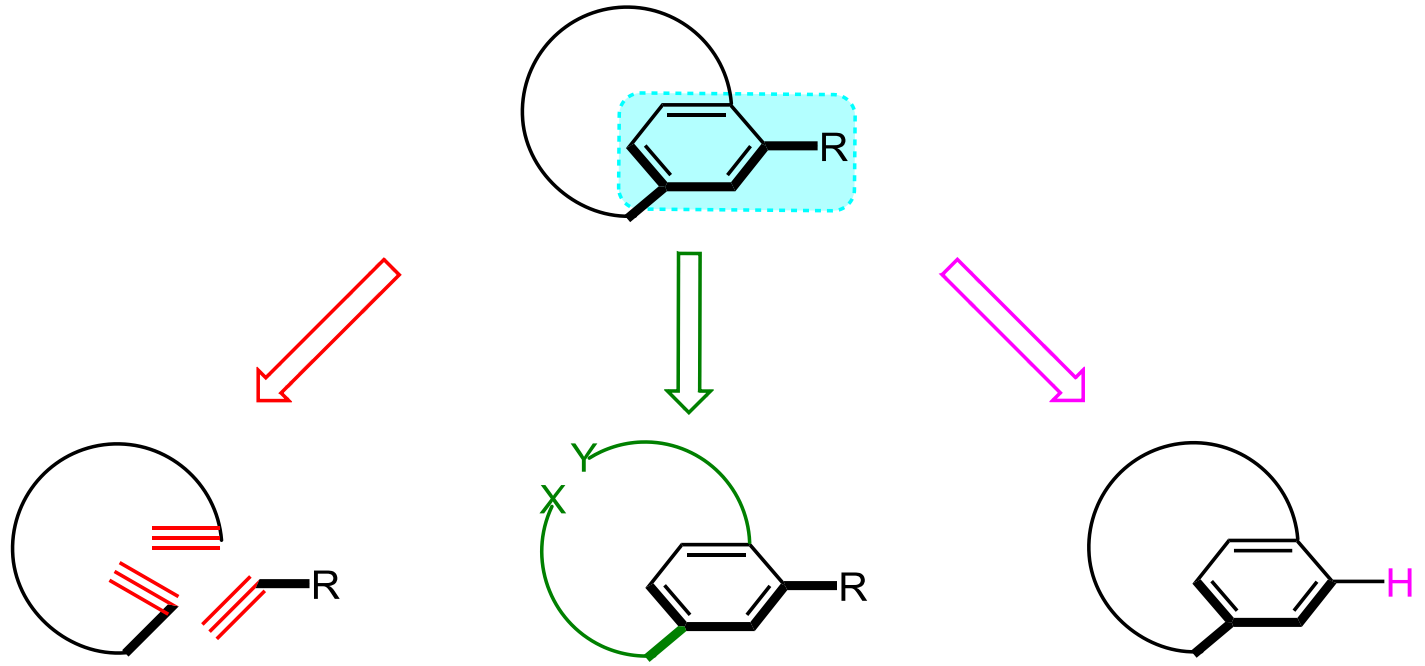
Introduction

Enantioselective synthetic routes to planar chiral [n]paracyclophanes



I) Enantioselective construction of aromatic ring

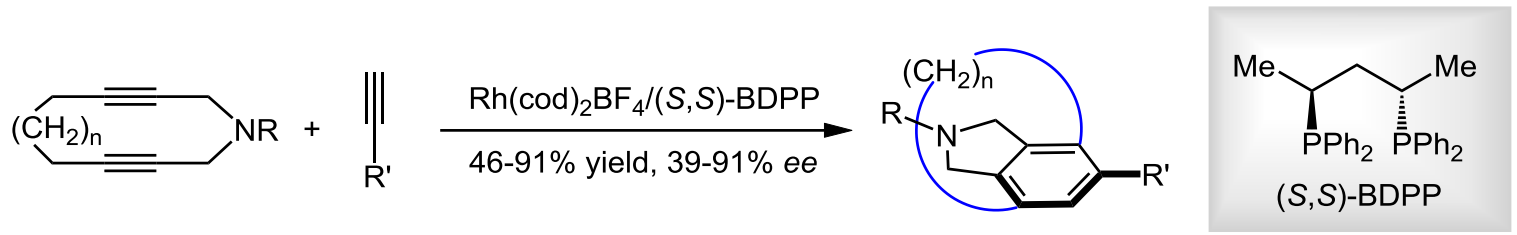
II) Enantioselective construction of *ansa* chain

III) Enantioselective substitution

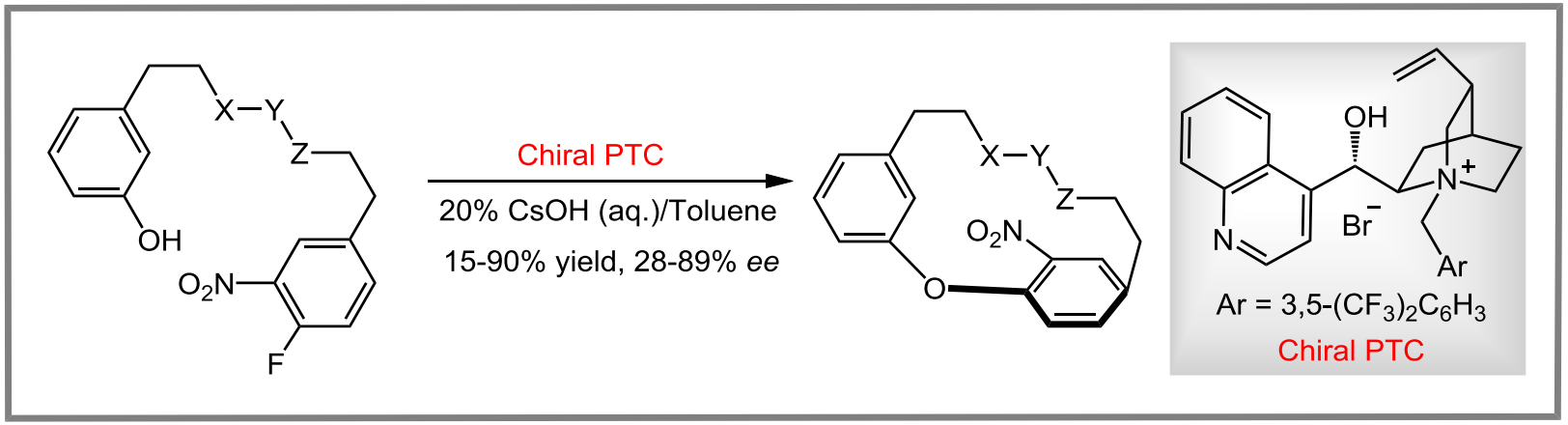
Tanaka, K. *Bull. Chem. Soc. Jpn.* **2018**, *91*, 187

Introduction

I) Enantioselective construction of aromatic ring



II) Enantioselective construction of *ansa* chain



Araki, T.; Noguchi, K.; Tanaka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 5617

Ding, Q.; He, H.; Cai, Q. *Org. Lett.* **2017**, *19*, 1804

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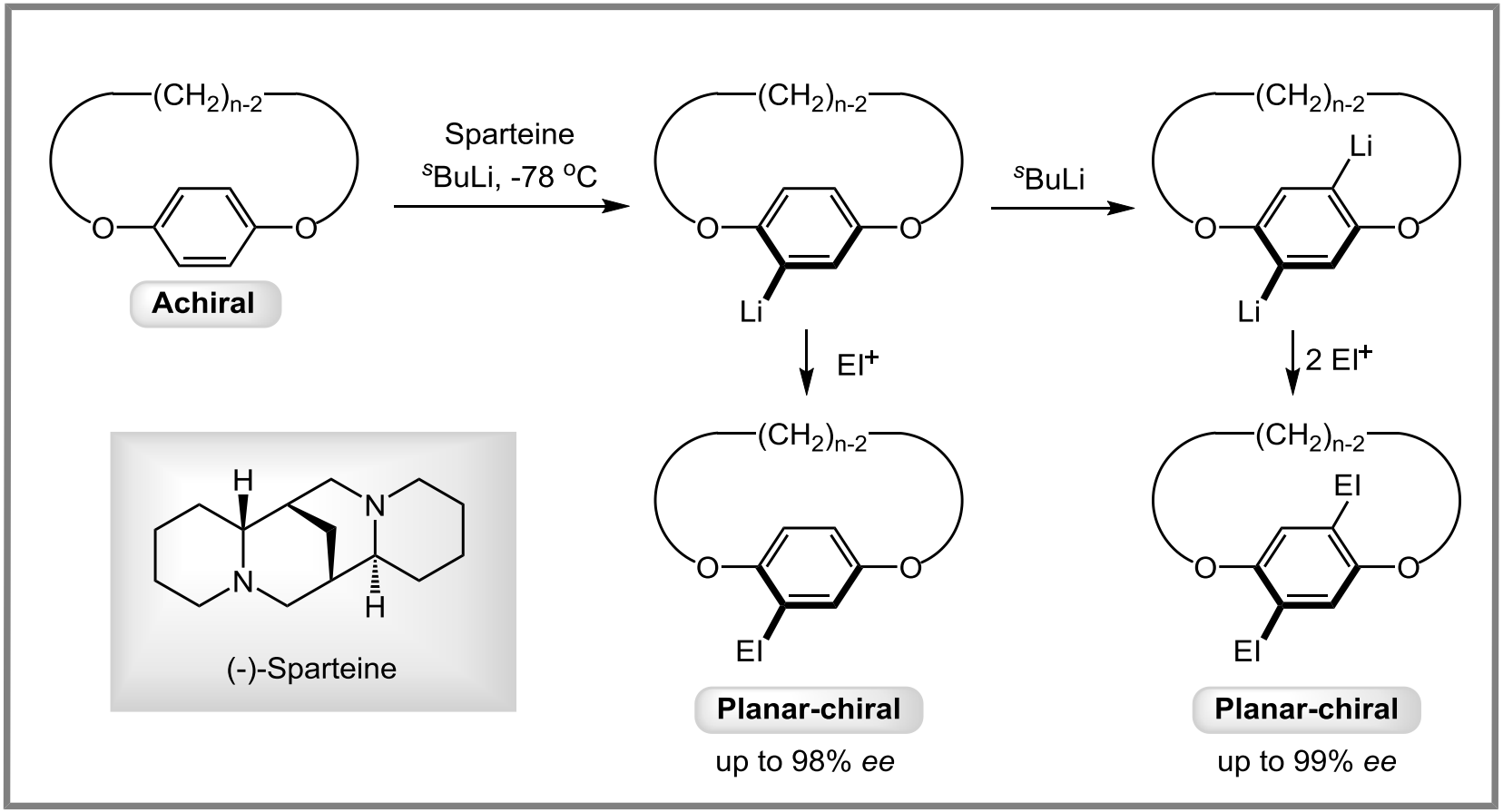
III) Enantioselective substitution

a) Catalytic asymmetric *ortho*-lithiation



Kanda, K.; Endo, K.; Shibata, T. *Org. Lett.* **2010**, *12*, 1980

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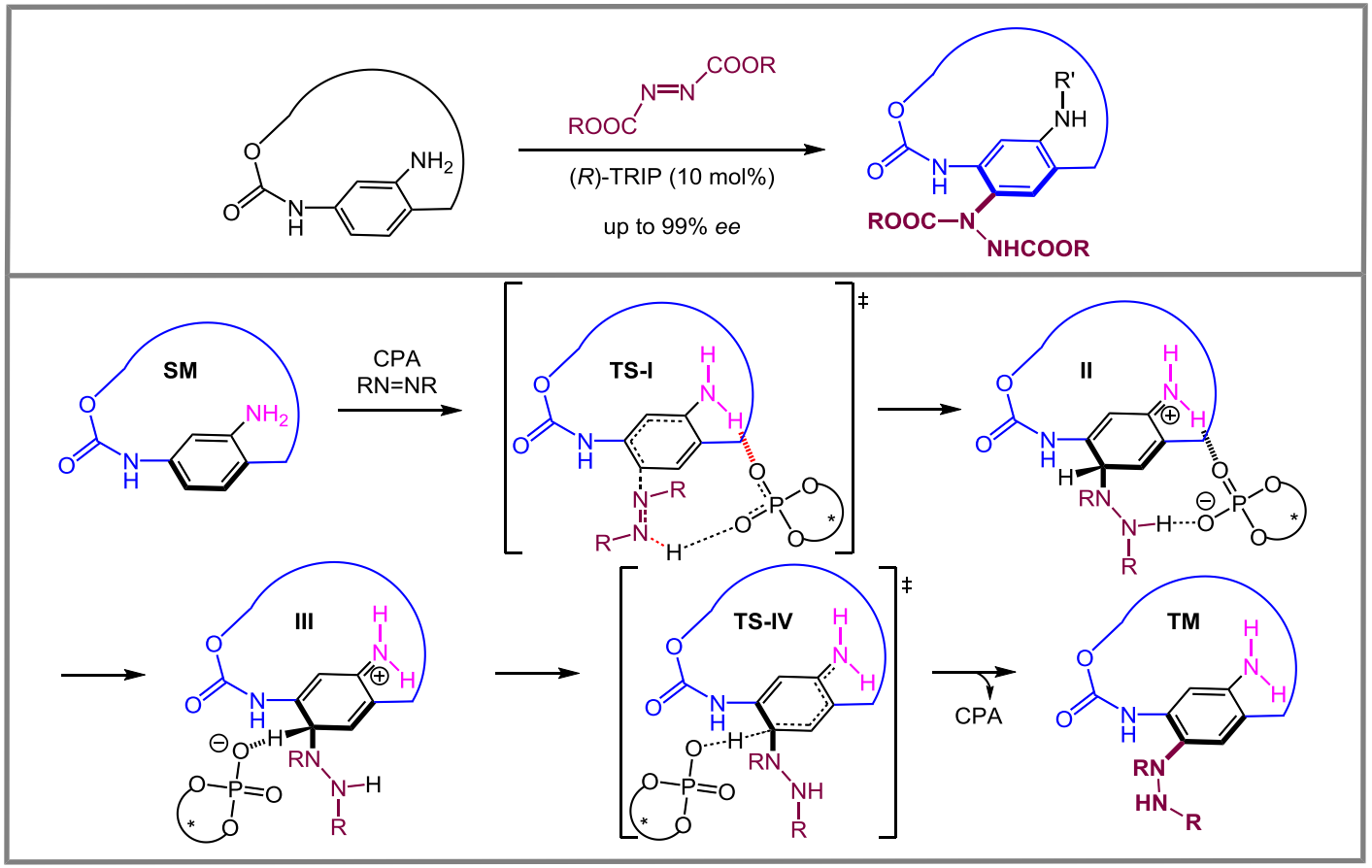
III) Enantioselective substitution

b) Asymmetric electrophilic aromatic amination



Wang, D.; Xue, X.-S.; Yang, X. *Angew. Chem. Int. Ed.* **2022**, *61*, e202201064

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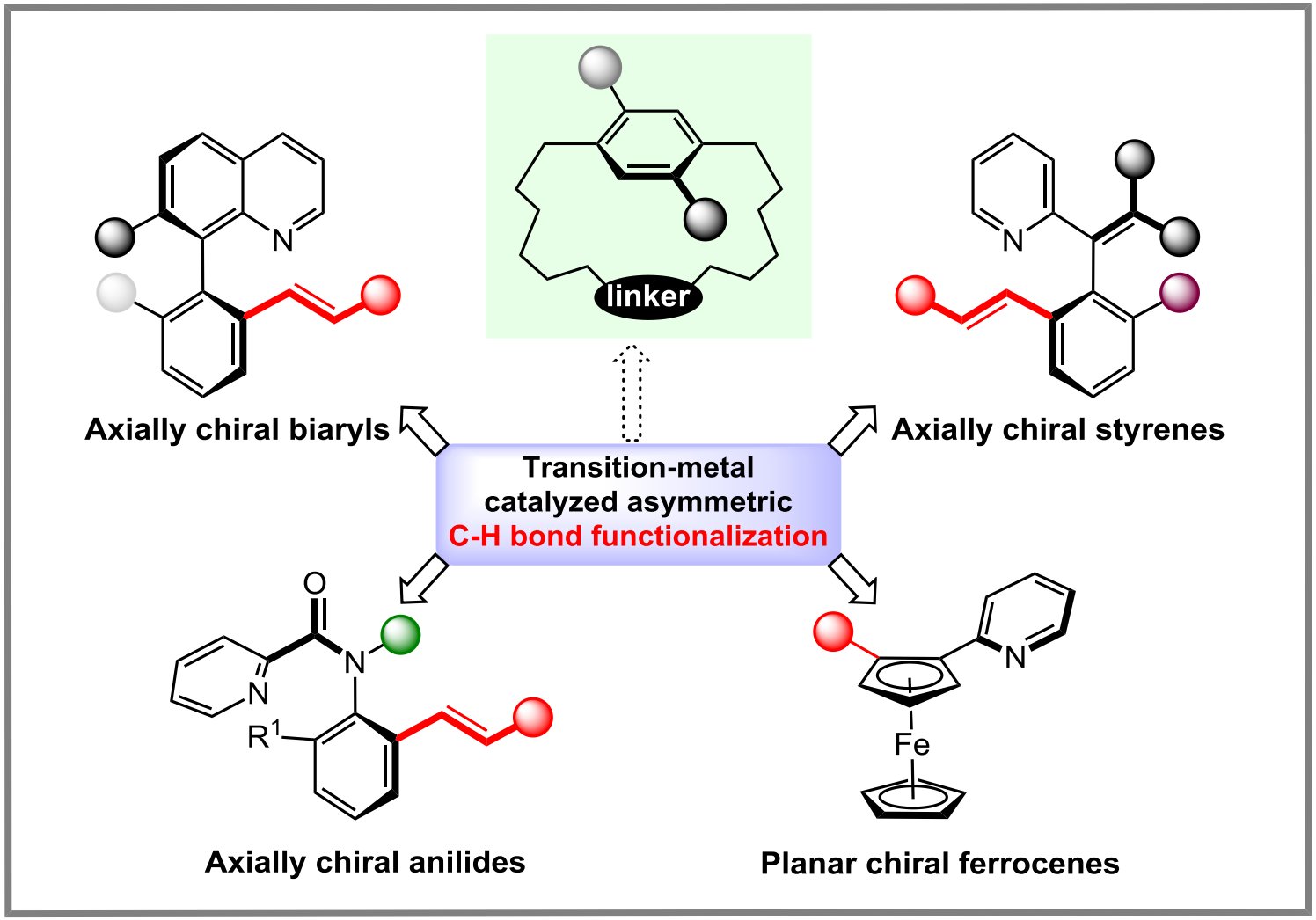

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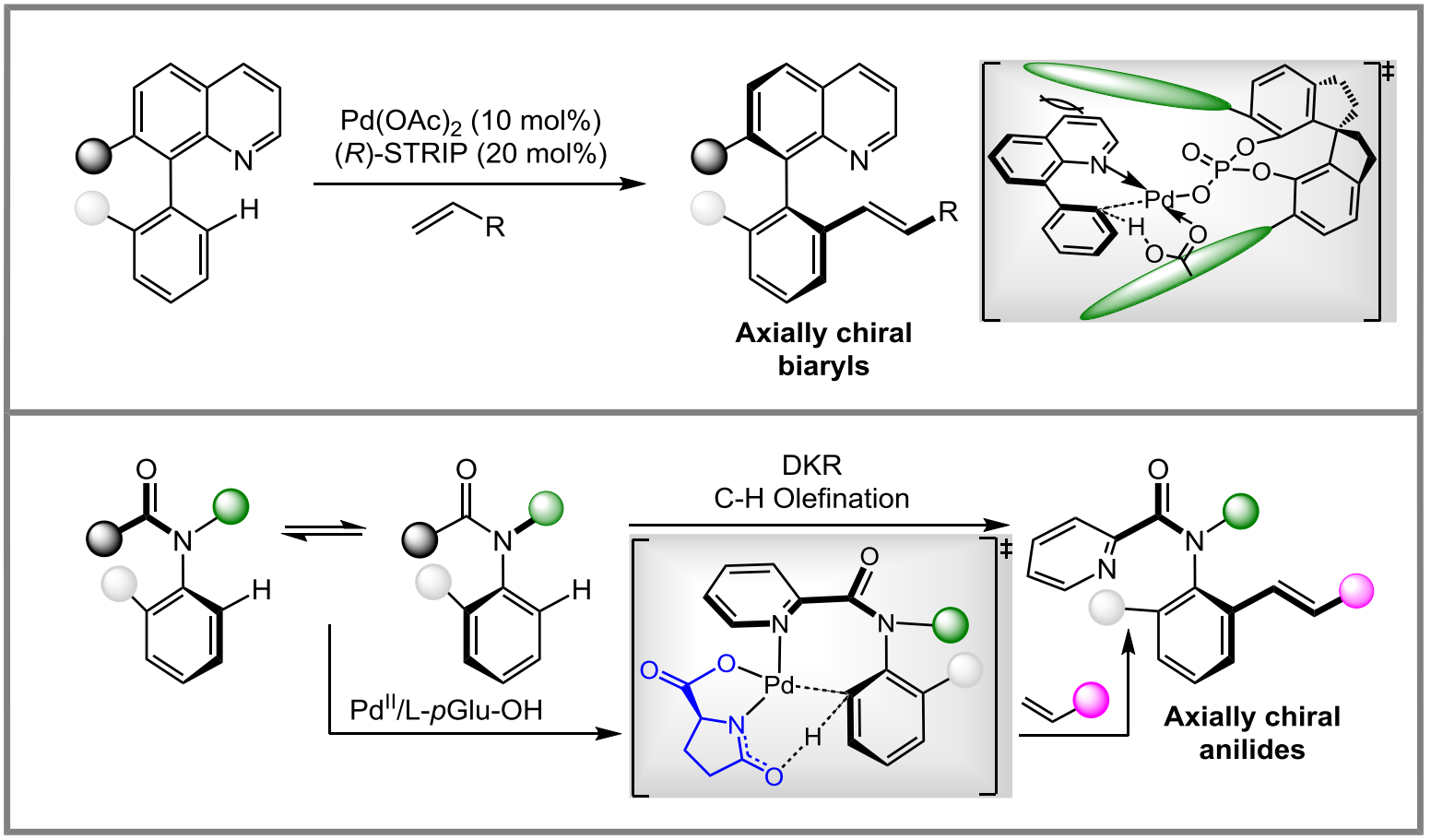

Luo, J.; Lan, Y.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2019**, *58*, 6708
Yao, Q.-J.; Hong, X.; Shi, B.-F. *J. Am. Chem. Soc.* **2020**, *142*, 18266

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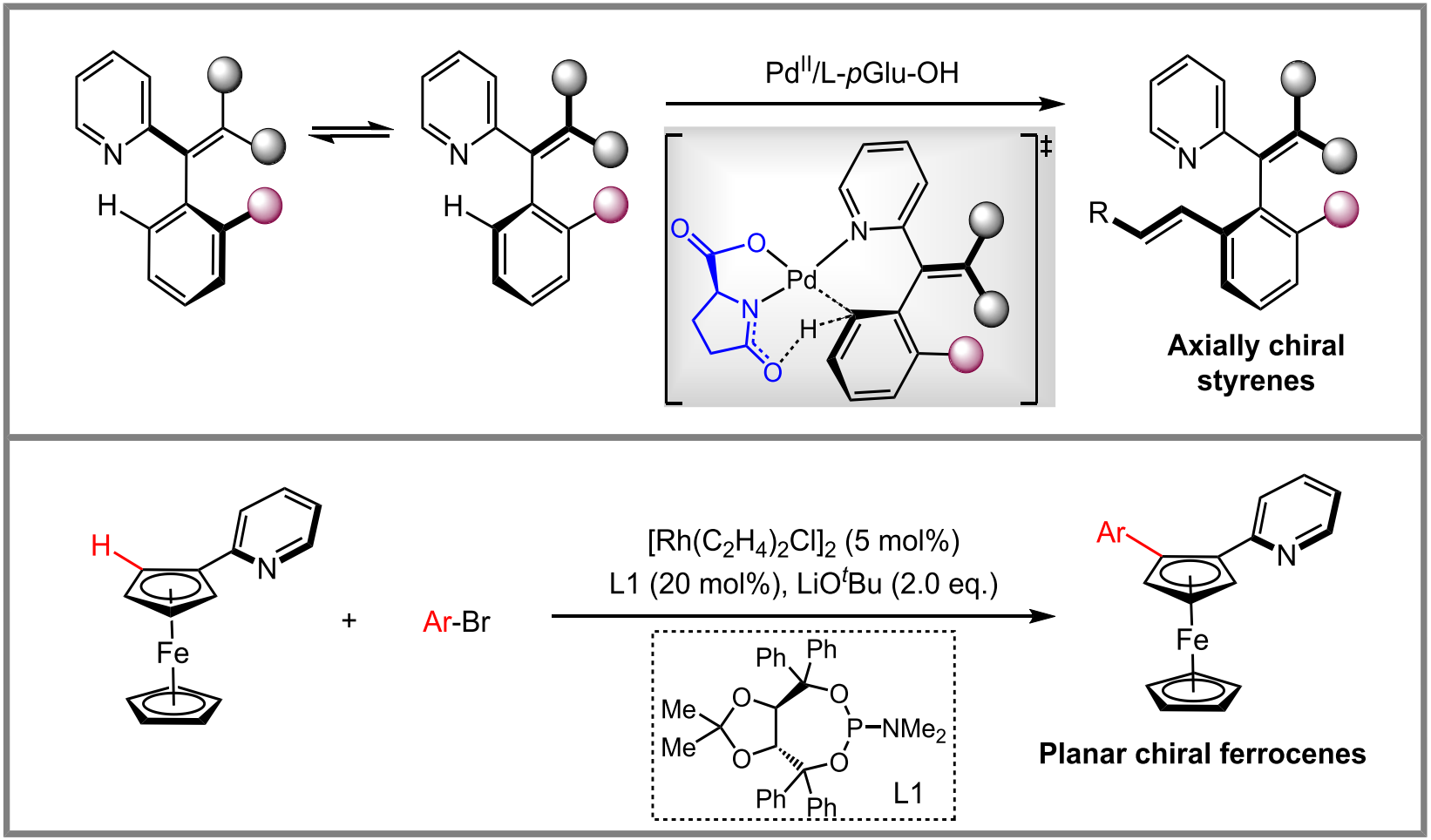

Jin, L.; Hong, X.; Shi, B.-F. *Chem* **2020**, *6*, 479
Liu, C.-X.; Zhang, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765

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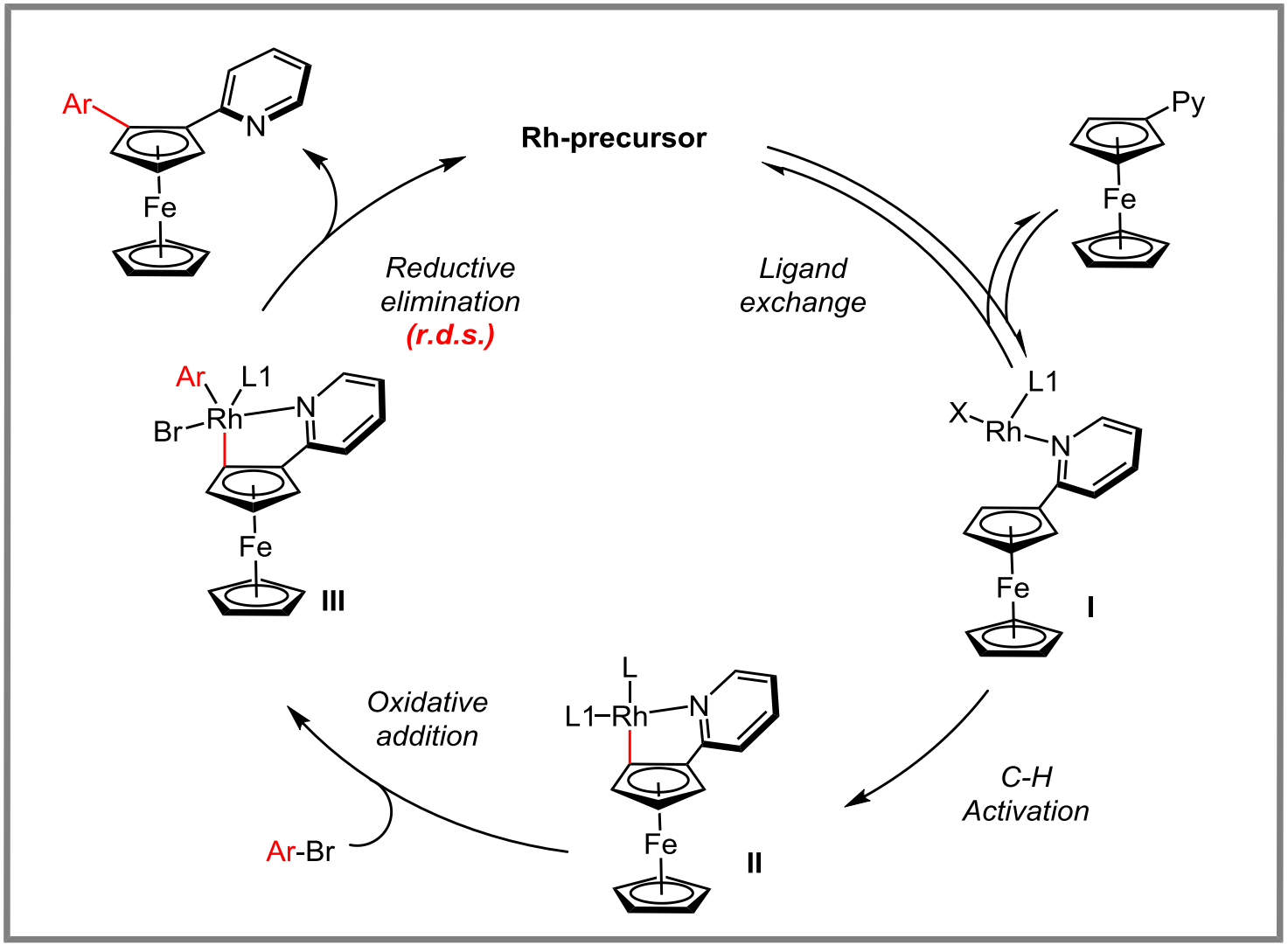
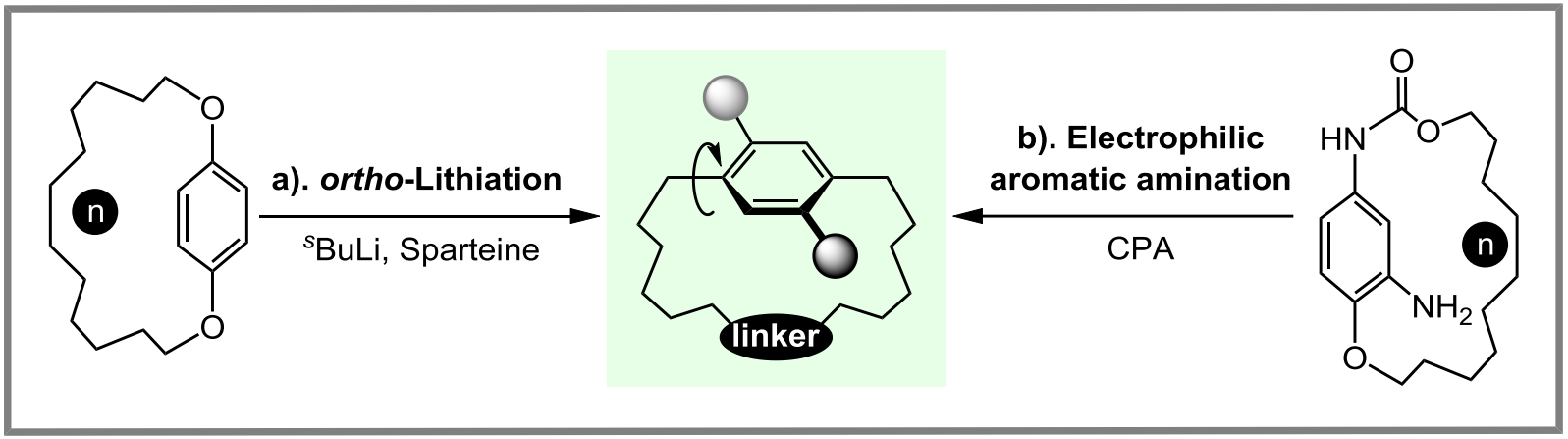
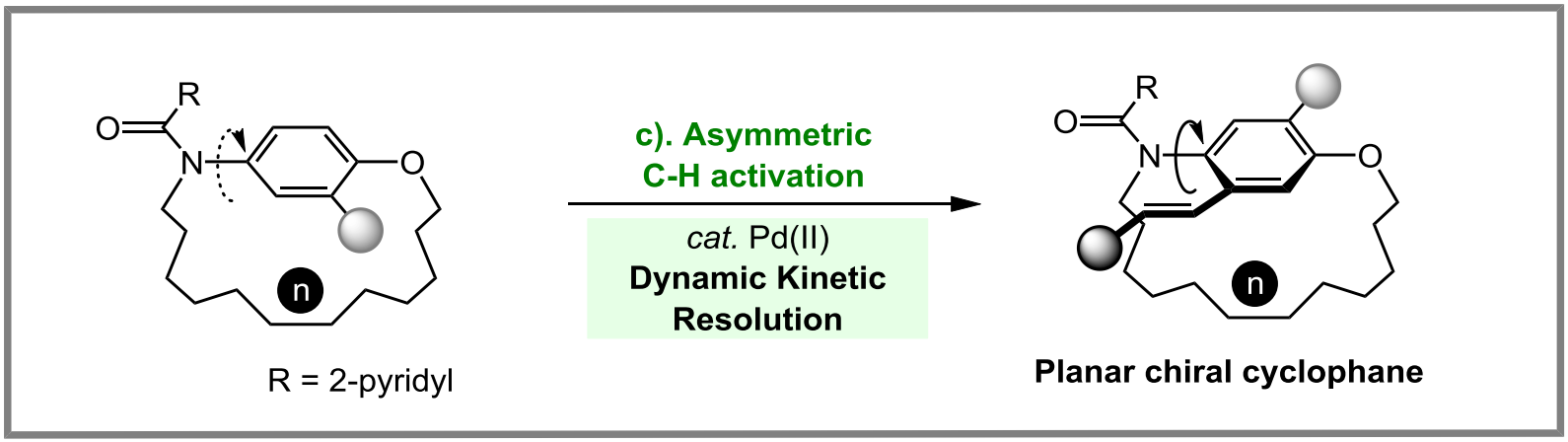


Liu, C.-X.; Zhang, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765

Project synopsis





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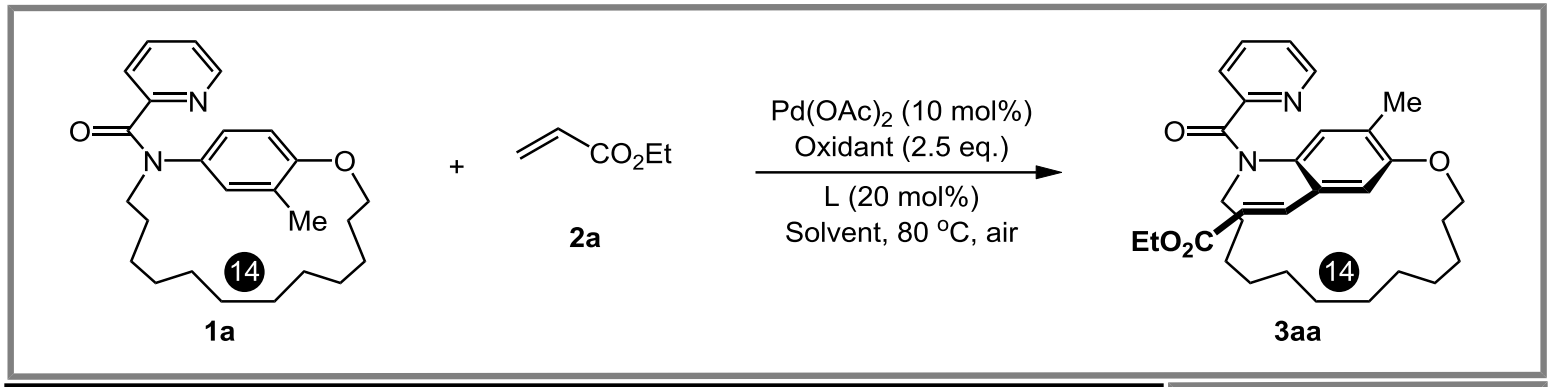
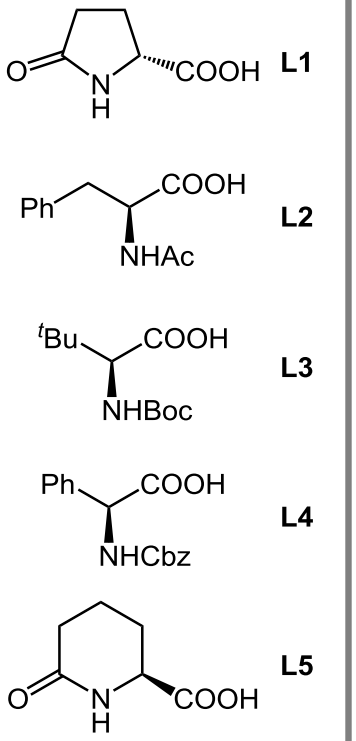
Optimization of reaction conditions

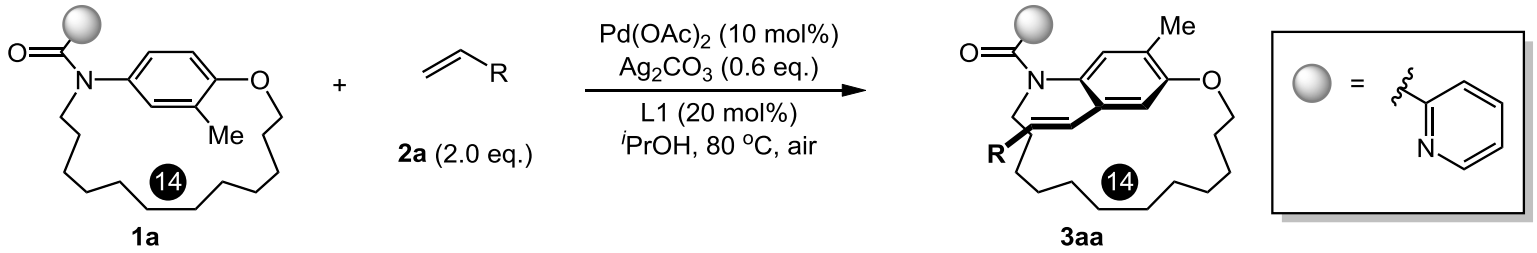


Entry	L	Oxidant	Solvent	Yield (%)	ee (%)
1	**L1**	AgOAc	TFE	61	87
2	**L1**	Ag_2CO_3	TFE	73	96
3	**L1**	$Cu(OAc)_2$	TFE	trace	-
4	**L2**	Ag_2CO_3	TFE	45	-56
5	**L3**	Ag_2CO_3	TFE	54	-22
6	**L4**	Ag_2CO_3	TFE	3	-66
7	**L5**	Ag_2CO_3	TFE	45	0
8	**L1**	Ag_2CO_3	EtOH	93	96
9	**L1**	**Ag_2CO_3**	**^{i}PrOH**	**98 (81)[a]**	**96**

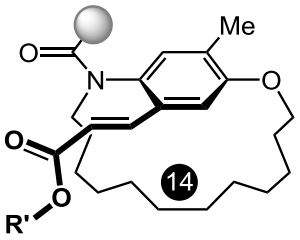
Condition: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), Oxidant (2.5 eq.) and solvent (2.0 mL). [a] Ag_2CO_3 (0.6 eq.) was used.



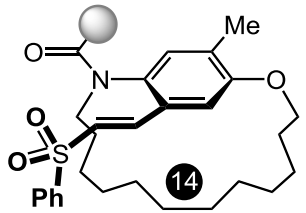
Substrate scope



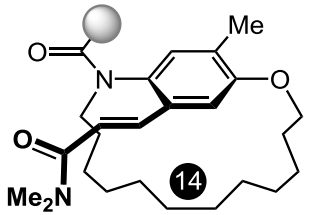
Scope of alkenes



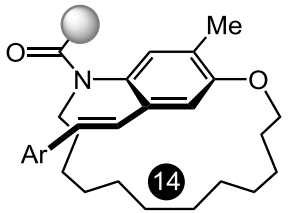
3aa, R' = Et, *cis:trans* = 9:1, 81%, 96% *ee*
3ab, R' = Me, *cis:trans* = 9:1, 89%, 95% *ee*
3ac, R' = ^{n}Bu, *cis:trans* = 8:1, 85%, 96% *ee*
3ad, R' = ^{t}Bu, *cis:trans* = 7:1, 87%, 96% *ee*
3ae, R' = Cy, *cis:trans* = 7:1, 99%, 94% *ee*
3af, R' = Ph, *cis:trans* = 7:1, 83%, 97% *ee*
3ag, R' = Bn, *cis:trans* = 8:1, 90%, 97% *ee*



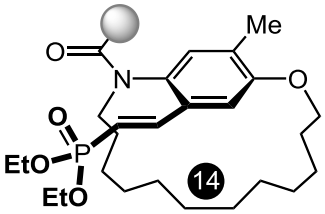
3ao
cis:trans = 6:1, 78%, 94% *ee*



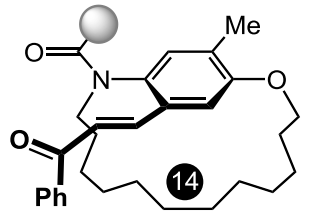
3ap
cis:trans = 7:1, 72%, 99% *ee*



3ah, Ar = 4-$MeOC_6H_4$
cis:trans = 12:1, 65%, 92% *ee*
3ai, Ar = Ph,
cis:trans = 11:1, 50%, 92% *ee*
3aj, Ar = 4-$AcOC_6H_4$
cis:trans = 10:1, 90%, 92% *ee*
3ak, Ar = 3-FC_6H_4,
cis:trans = 11:1, 62%, 88% *ee*
3al, Ar = 4-ClC_6H_4
cis:trans = 7:1, 85%, 85% *ee*
3am, Ar = 4-CNC_6H_4
cis:trans = 9:1, 75%, 90% *ee*

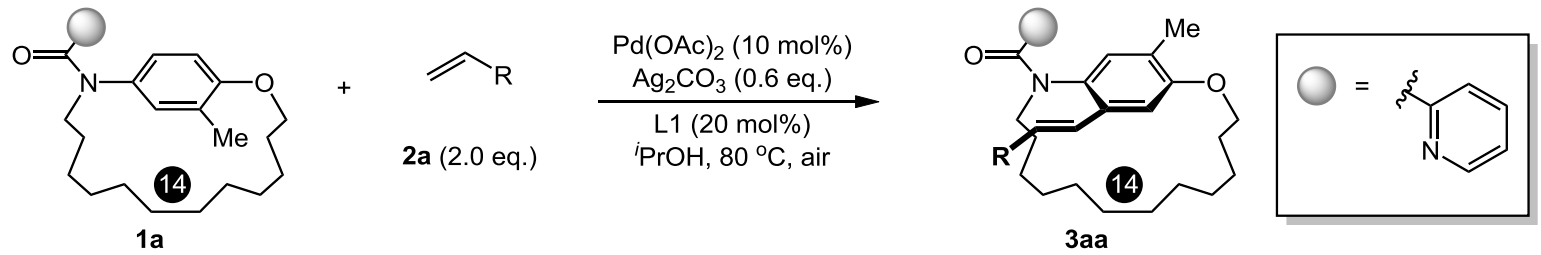


3aq
cis:trans = 7:1, 91%, 76% *ee*

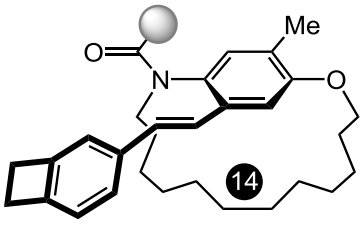


3ar
cis:trans = 5:1, 95%, 85% *ee*

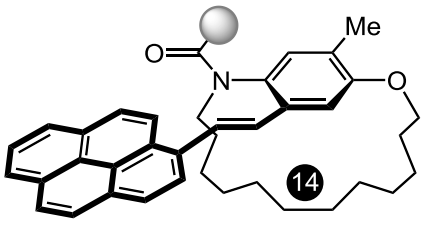
Substrate scope



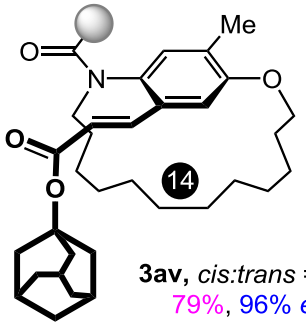
Scope of alkenes



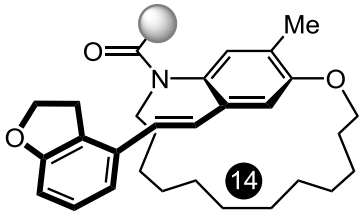
3at
cis:trans = 10:1, 87%, 85% *ee*



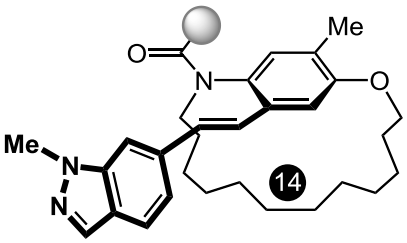
3au
cis:trans = 12:1, 97%, 81% *ee*



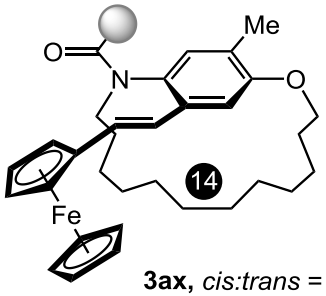
3av, *cis:trans* = 7:1
79%, 96% *ee*



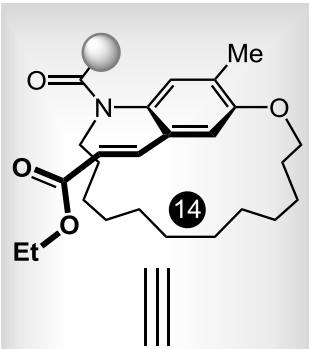
3aw
cis:trans = 4:1, 47%, 48% *ee*

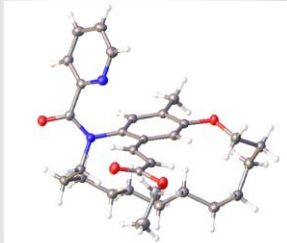


3ay
cis:trans = 9:1, 81%, 91% *ee*



3ax, *cis:trans* = 12:1
86%, 97% *ee*

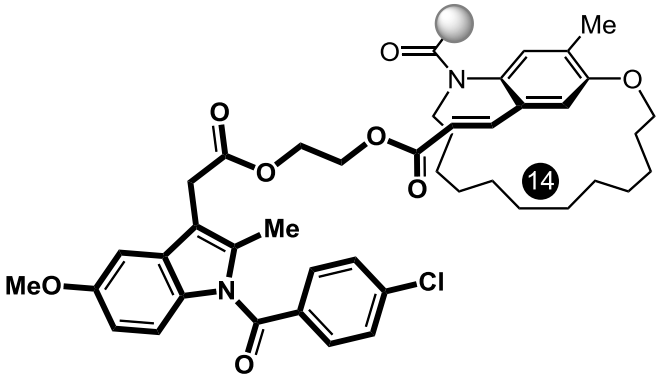




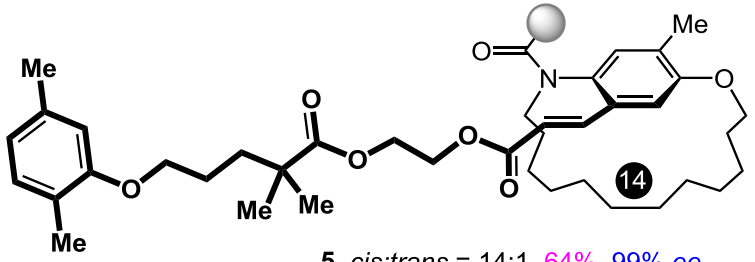
X-ray of **3aa**, CCDC 2281385

Substrate scope

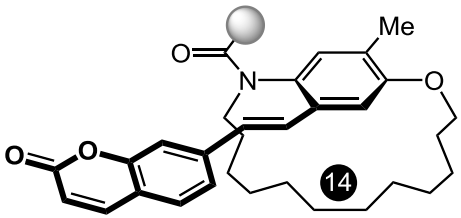
Late-stage modification of bioactive molecules and pharmaceuticals



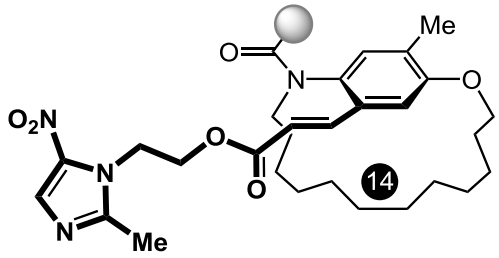
4, *cis:trans* = 7:1, 88%, 90% *ee*
from indomethacin



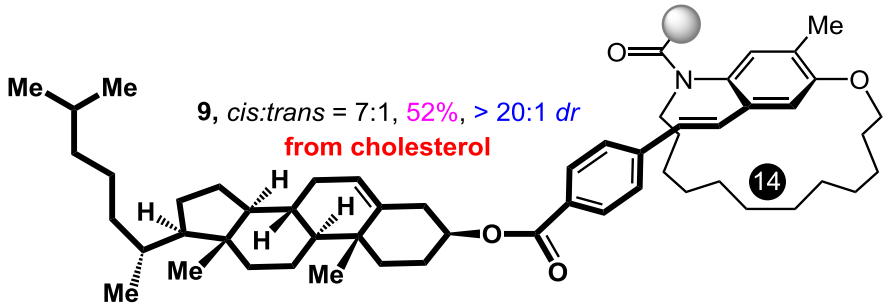
5, *cis:trans* = 14:1, 64%, 99% *ee*
from gemfibrozil



7, *cis:trans* = 5:1, 84%, 82% *ee*
from skimmetin

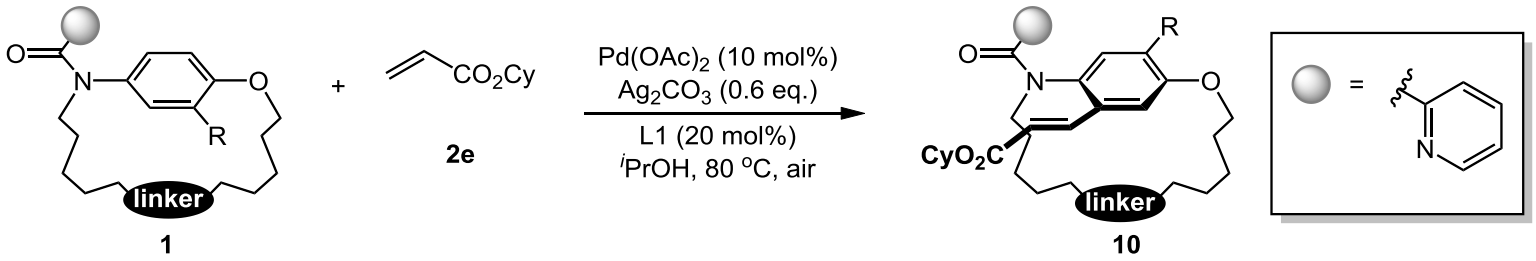


6, *cis:trans* = 7:1, 45%, 94% *ee*
from metronidazole

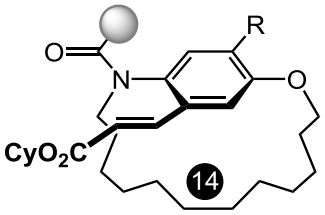


9, *cis:trans* = 7:1, 52%, > 20:1 *dr*
from cholesterol

Substrate scope



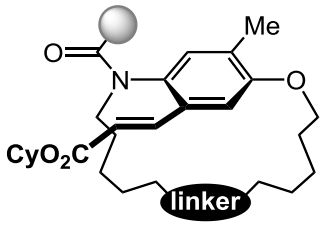
Scope of aromatic ring substituent and ansa chain



10be, R = OMe, *cis:trans* = 9:1
95%, 86% *ee*

10ce, R = Cl, *cis:trans* = 9:1
88%, 98% *ee*

10de, R = 4-CNC_6H_4
cis:trans = 12:1, 86%, 72% ee

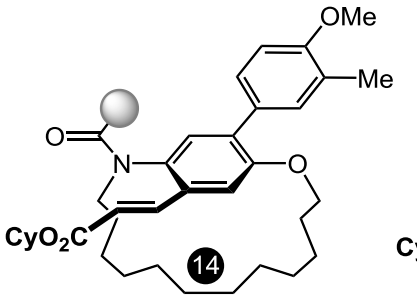


linker: **n = 11**,
10ie, *cis:trans* = 7:1, 74%, 33% *ee*

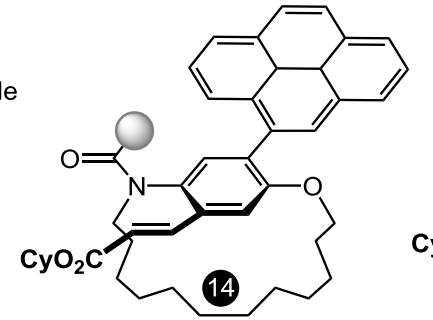
linker: **n = 12**,
10ge, *cis:trans* = 8:1, 98%, 97% *ee*

linker: **n = 13**,
10ke, *cis:trans* = 7:1, 95%, 68% *ee*

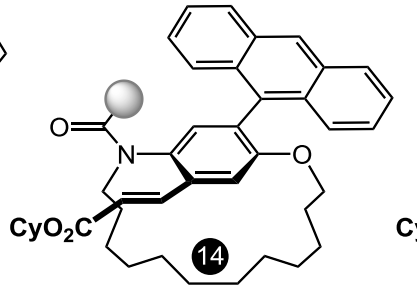
linker: **n = 14**,
3ae, *cis:trans* = 7:1, 99%, 94% *ee*



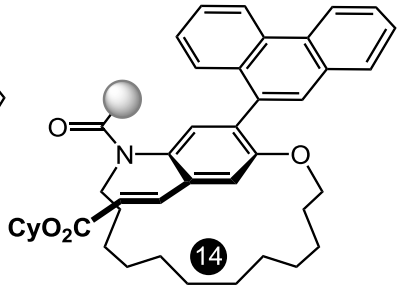
10ee
cis:trans = 7:1, 84%, 94% ee



10fe
cis:trans = 3:1, 84%, 90% *ee*

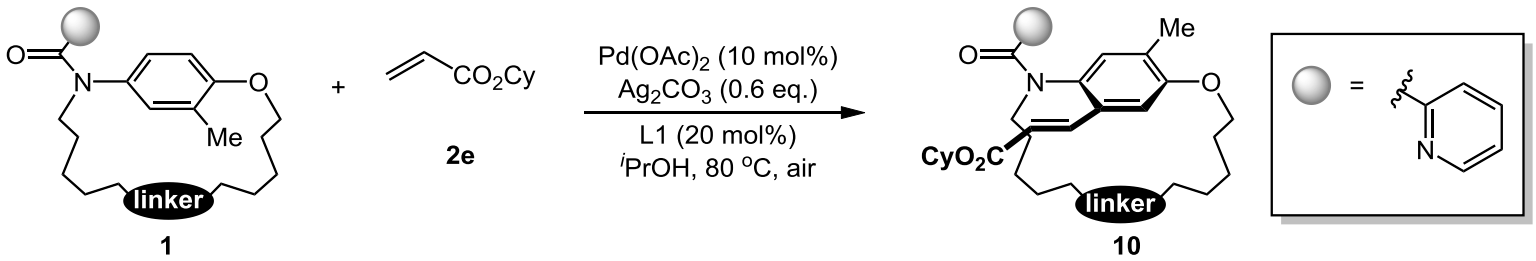


10ge
cis:trans = 16:1, 79%, 66% *ee*

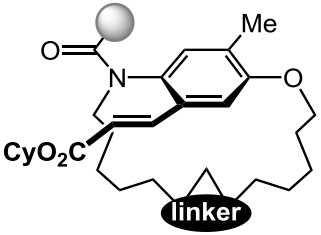


10he
cis:trans = 3:1, 88%, 70% *ee*

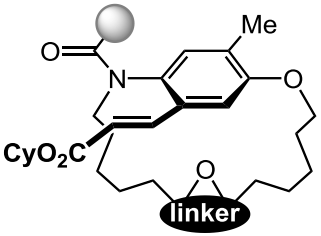
Substrate scope



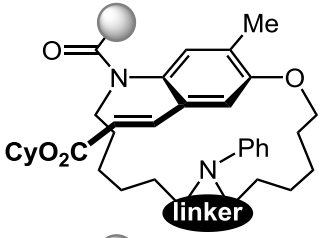
Scope of ansa chain



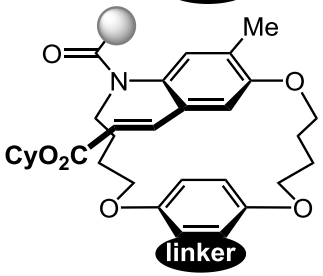
linker: **n = 15, 10le**
cis:trans = 6:1, 83%, 6% *ee*
$\Delta G^{\neq}_{rot}$(80 °C) = 116.2 kJ/mol
$t_{1/2}$(80 °C) = 121 mins



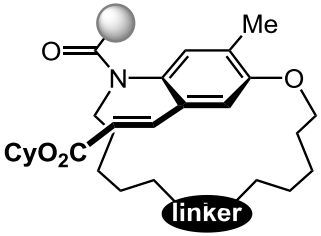
linker: **n = 15, 10me**
cis:trans = 15:1, 70%, 83% *ee*
$\Delta G^{\neq}_{rot}$(80 °C) = 117.2 kJ/mol
$t_{1/2}$(80 °C) = 170 mins



linker: **n = 15, 10ne**
cis:trans = 12:1, 63%, 73% *ee*
$\Delta G^{\neq}_{rot}$(80 °C) = 118.2 kJ/mol
$t_{1/2}$(80 °C) = 243 mins



linker: **n = 12 + 4, 10oe**
cis:trans = 15:1, 76%, 62% *ee*
$\Delta G^{\neq}_{rot}$(65 °C) = 110.3 kJ/mol
$t_{1/2}$(65 °C) = 90 mins



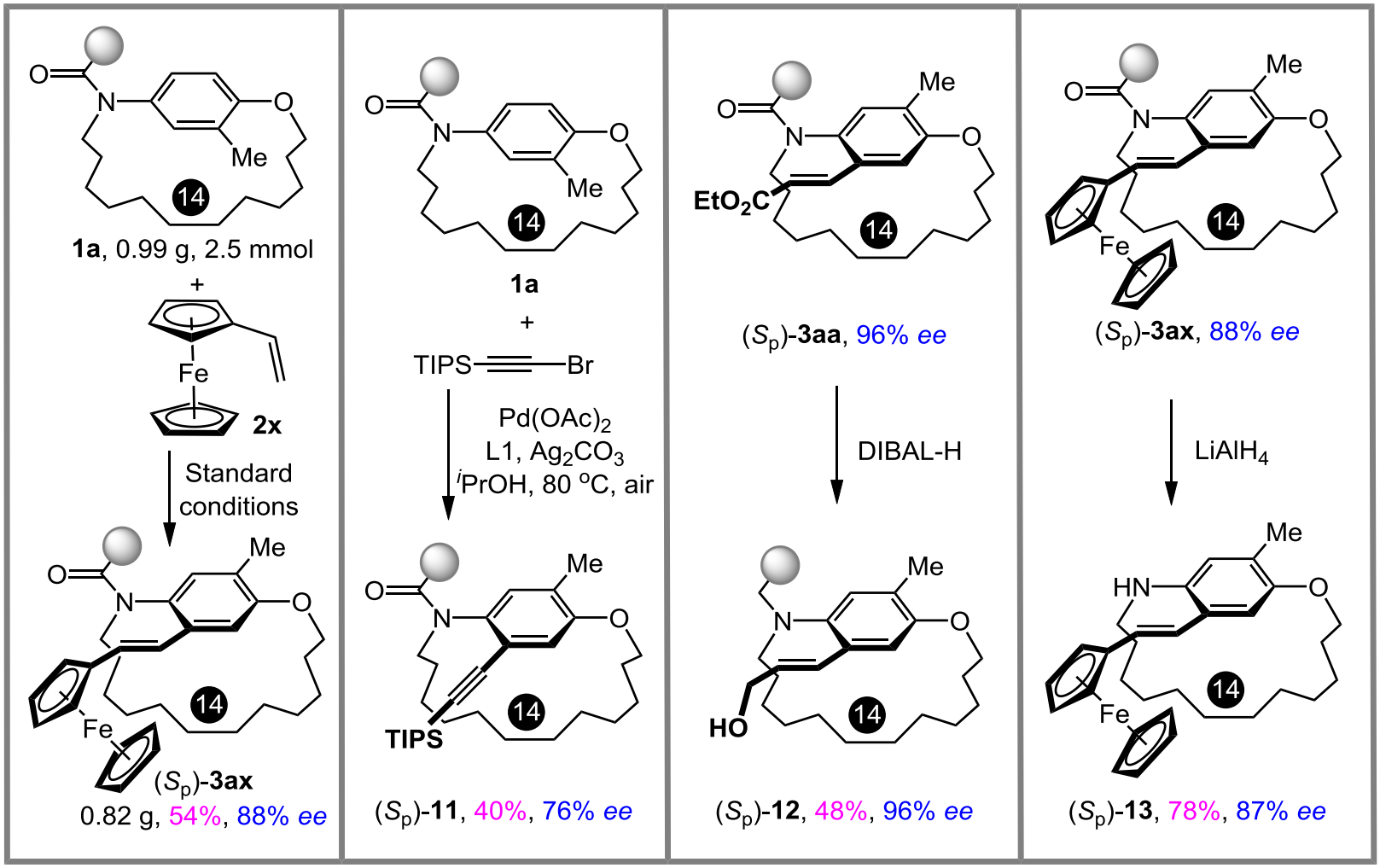
linker: **n = 16, 10pe**, *cis:trans* = 6:1, 78%, **no planar chirality**

linker: **n = 17, 10qe**, *cis:trans* = 6:1, 71%, **no planar chirality**

linker: **n = 18, 10re**, *cis:trans* = 6:1, 67%, **no planar chirality**

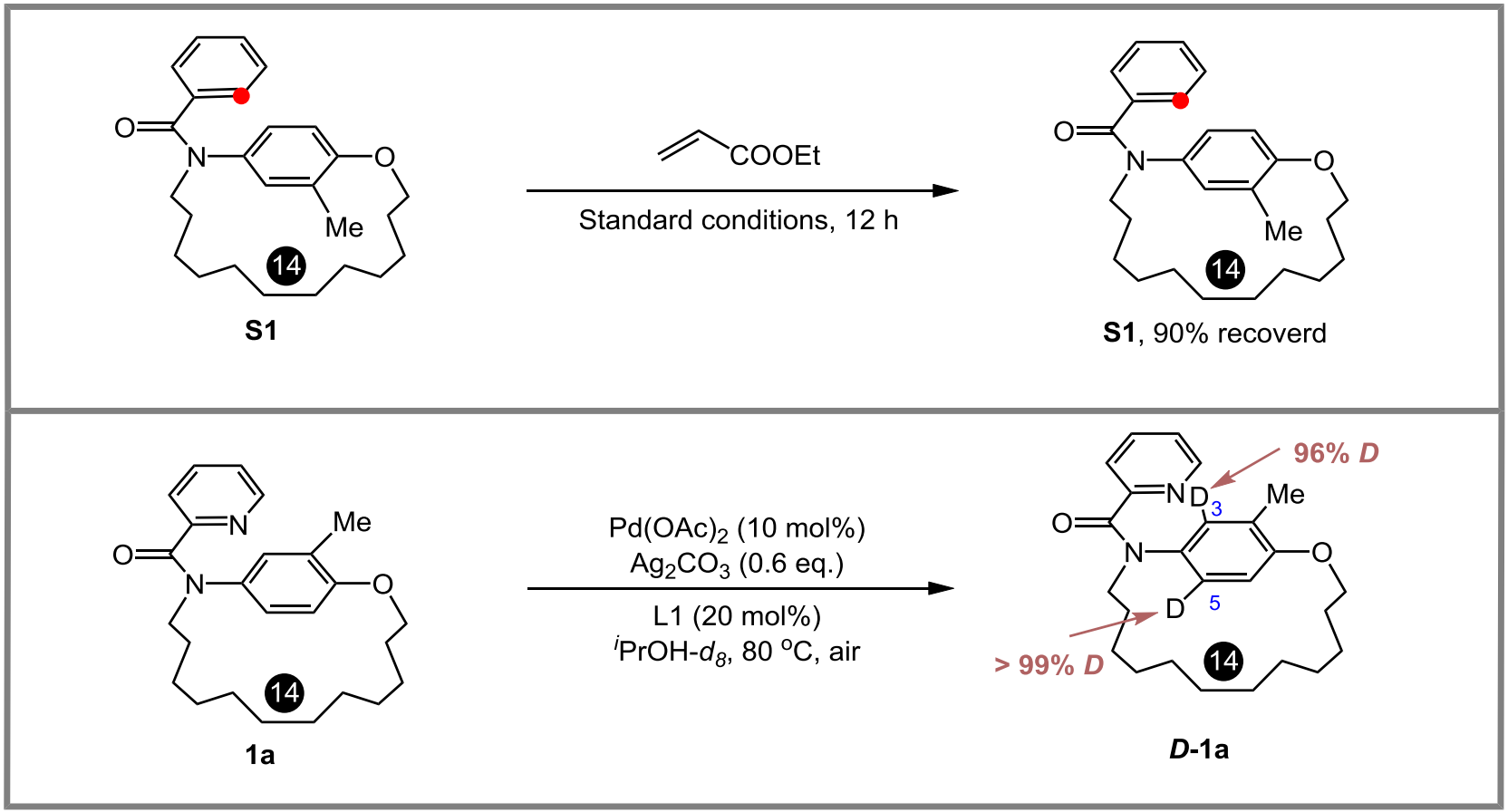
linker: **n = 19, 10se**, *cis:trans* = 6:1, 69%, **no planar chirality**

Scale-up reactions and synthetic application



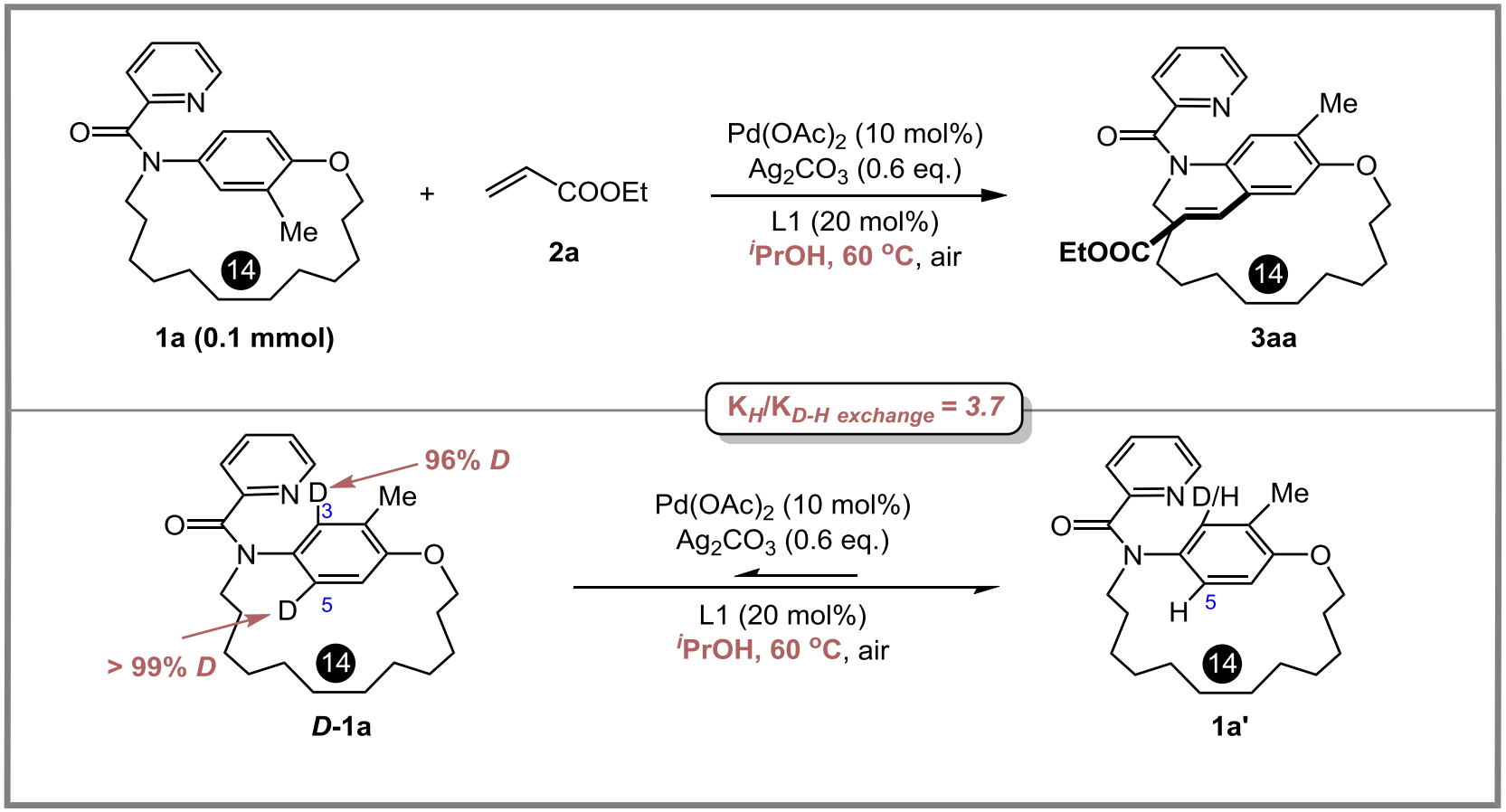
Mechanistic investigation

Deuterium exchange experiments



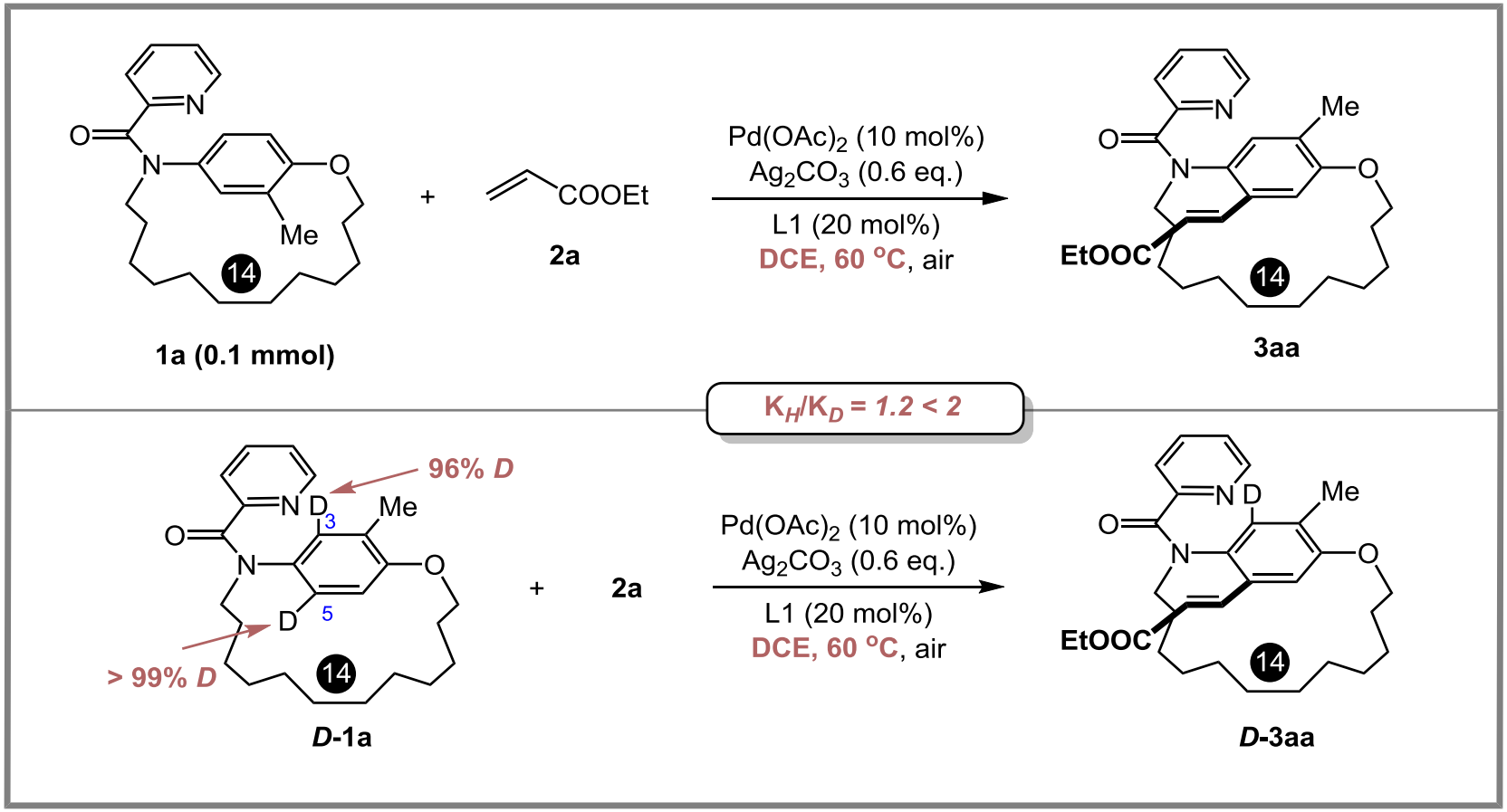
Mechanistic investigation

Kinetic studies

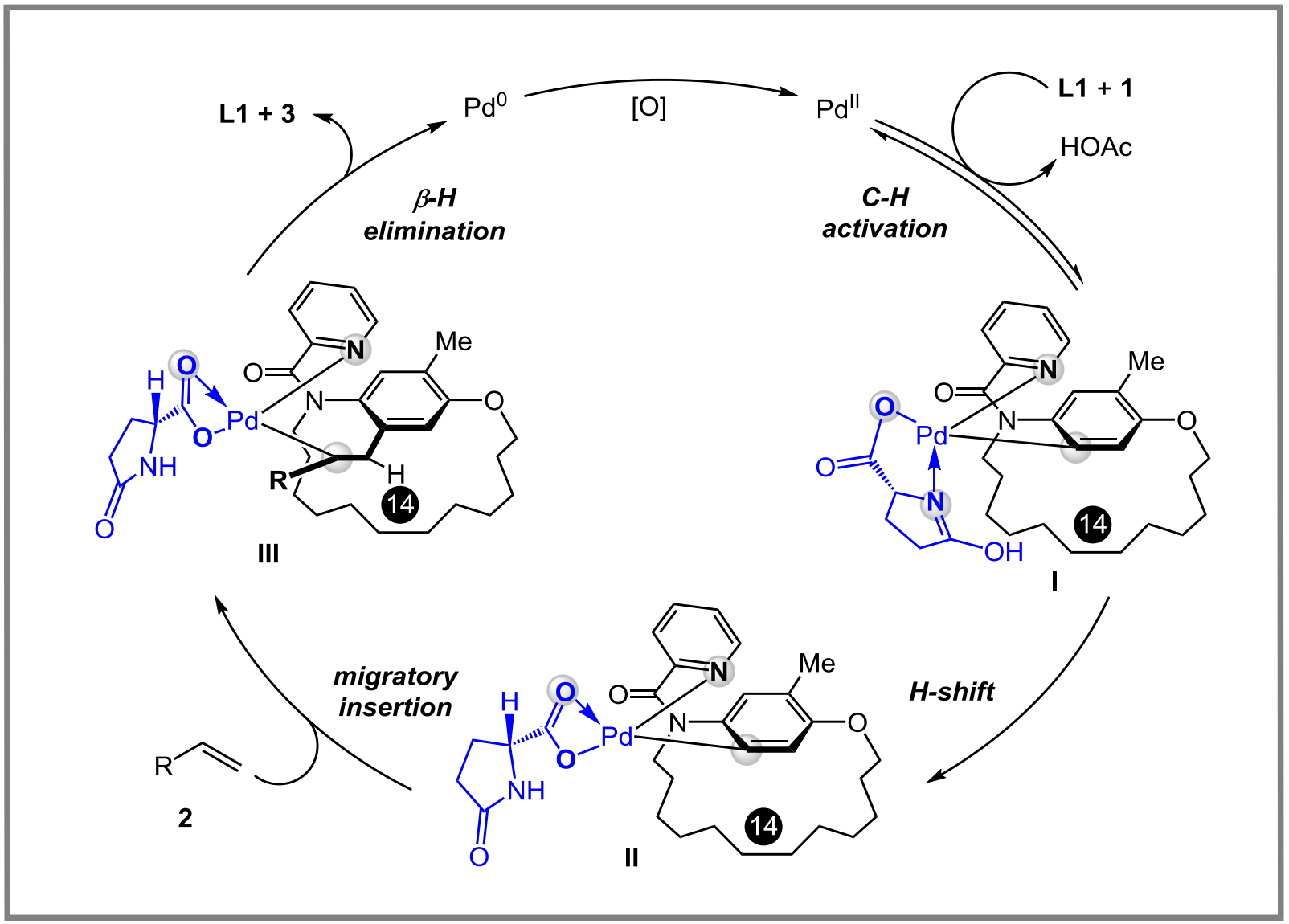


Mechanistic investigation

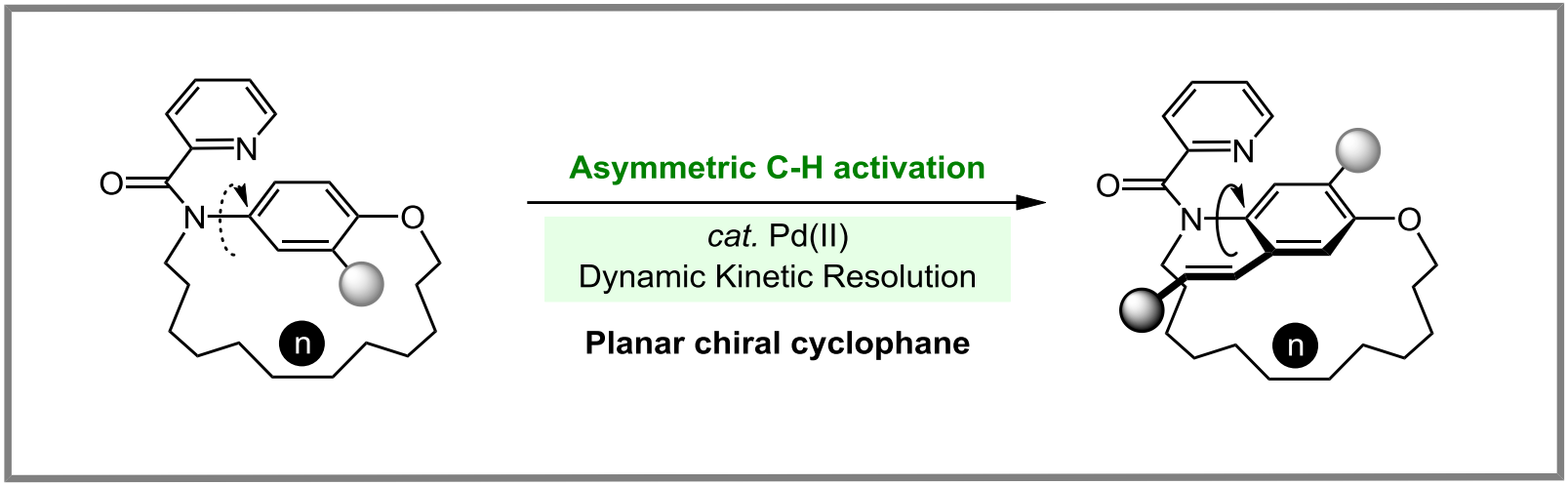
Kinetic studies



Proposed mechanism



Summary



- **Pd^{II}-catalyzed enantioselective C-H olefination by DKR process**
- **Approach to the late-stage modification of bioactive molecules**
- **Investigation of *ansa* chain length scope planar chirality and configurational stability**

The first paragraph

Writing strategy

The characteristic and application of cyclophanes

The synthetic methodology the of cyclophanes

Introduction of this work

- Cyclophanes are molecules containing an aromatic ring bearing a cross-linked alkyl chain, also called *ansa* chain… moieties are present in naturally occurring compounds endowed with distinguished biological activities. For instance, configurationally stable planar-chiral macrocycle Lorlatinib.
- Previous strategy for the synthesis of chiral molecules *via* Pd-catalyzed C-H activation, Enantioselective synthesis of cyclophanes *via* C-H functionalization of benzene ring.
- Herein, we reported the first Pd-catalyzed asymmetric C-H bond activation of prochiral cyclophanes.

The last paragraph

Writing strategy

Summary of this work

- In conclusion, we developed a Pd(II)-catalyzed enantioselective C-H olefination of prochiral cyclophanes by DKR process, providing a wide range of planar-chiral cyclophanes in high yields and with excellent enantioselectivities.

Investigation the origin of planar chirality and configurational stability

- An investigation of *ansa* chain length scope provides details for the origin of planar chirality and configurational stability of cyclophanes.

Outlook of this work

- An application of these planar-chiral scaffolds for library inclusion and asymmetric catalysis is under investigation in our lab.

Representative examples

Cyclophane with a bulky aromatic ring and suitable ansa chain exhibits planar chirality, which arises from locked configurational flip of the aromatic ring around the macrocycle plane. (arise from: 因为, 起因于, 在于, 由于…而形成的, 由…所形成的; stem from, originate from)

Rh-catalyzed de novo benzene ring formation by asymmetric [2+2+2] cycloaddition. (de novo: 从头合成…)

The C-H activation approach is also applicable to the late-stage modification of bioactive molecules and pharmaceuticals. (late-stage modification, 后期修饰；late-stage C-H functionalization，late-Stage diversification)

Thanks
for your attention