Seminar

固有手性-马鞍形化合物的不对称合成策略

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导　师： 杨俊锋 青年研究员

张俊良 教授

日　期： 2025 年 12 月 5 日

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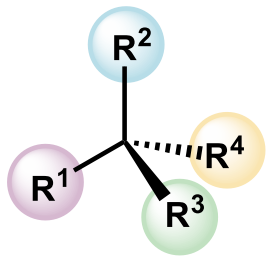
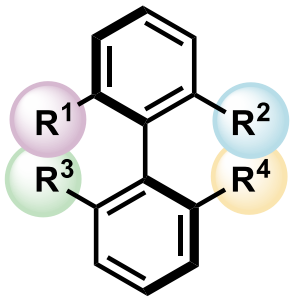
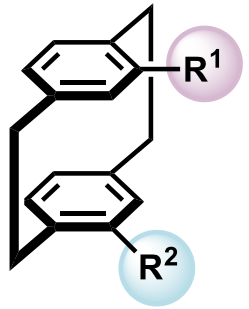
研究背景: 固有手性概念提出



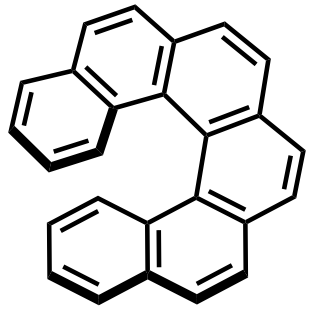
Central chirality



Axial chirality

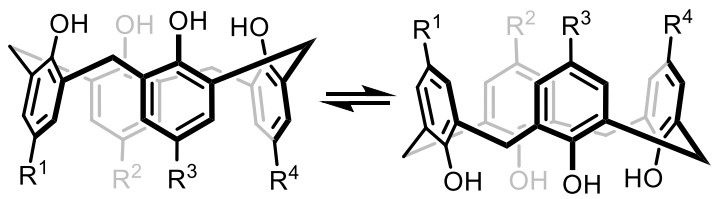


Planar chirality



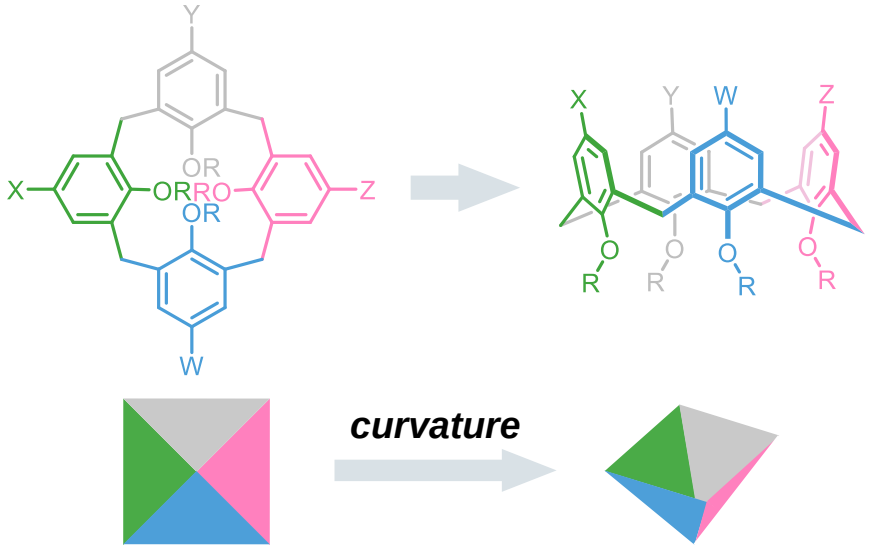
Helical chirality

Böhmer (1994)



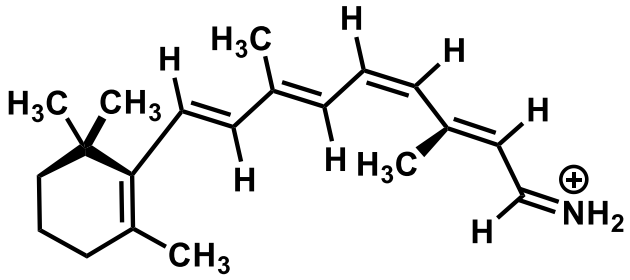
Inherent Chirality

Schiaffino (2004) & Szumna (2010)

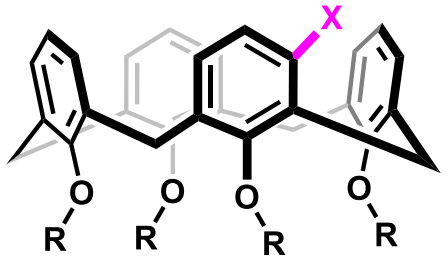


Böhmer, V.; et al. *J. Incl. Phenom. Macrocycl. Chem.* **1994**, *19*, 17-39.
Schiaffino, L.; et al. *New J. Chem.* **2004**, *28*, 1198 -1199.
Szumna, A. *Chem. Soc. Rev.* **2010**, *39*, 4274-4285.

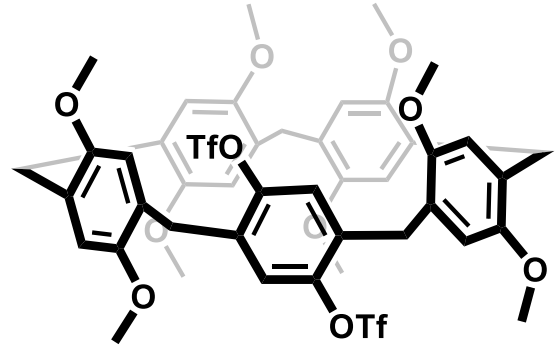
研究背景: 固有手性化合物分类



天然固有手性化合物：视黄醛



杯芳烃



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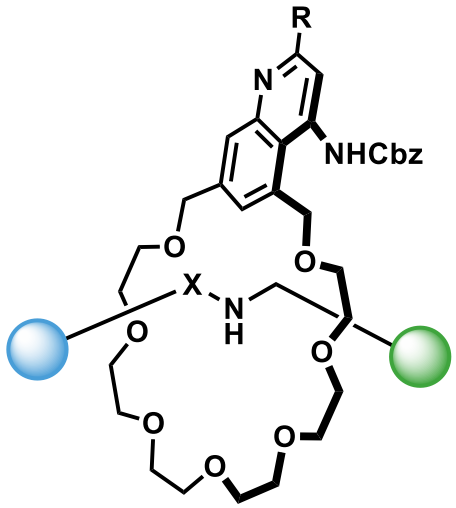
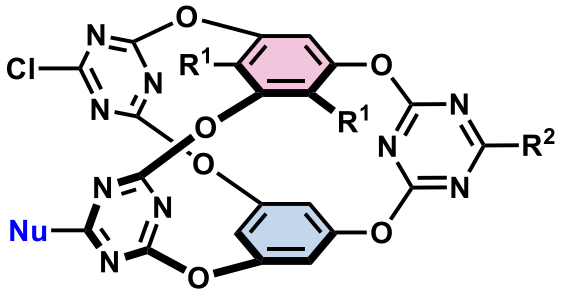
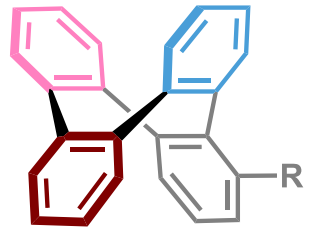


机械互锁分子



棱柱状笼型分子



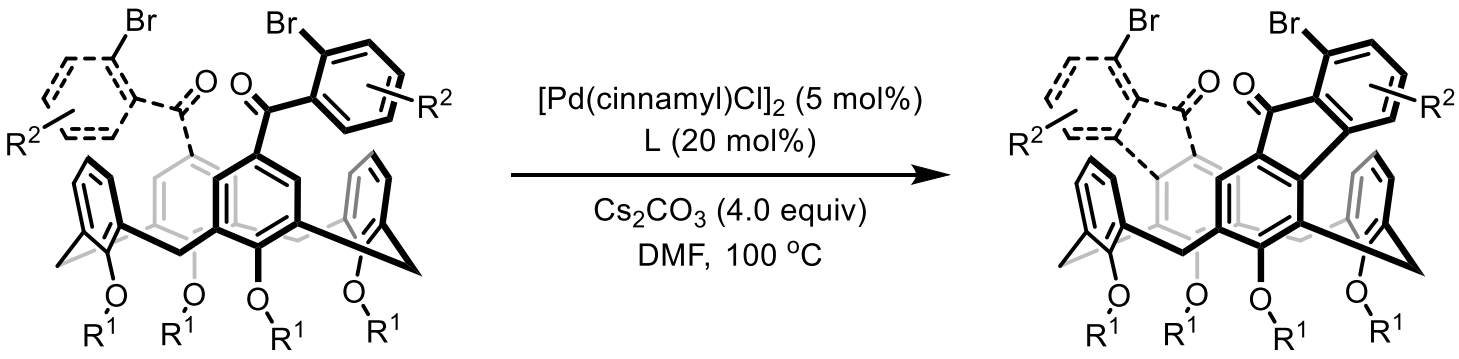
马鞍形骨架

For research on retinal, see: Woody, R. W.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 6170-6181.

研究背景: 固有手性杯芳烃

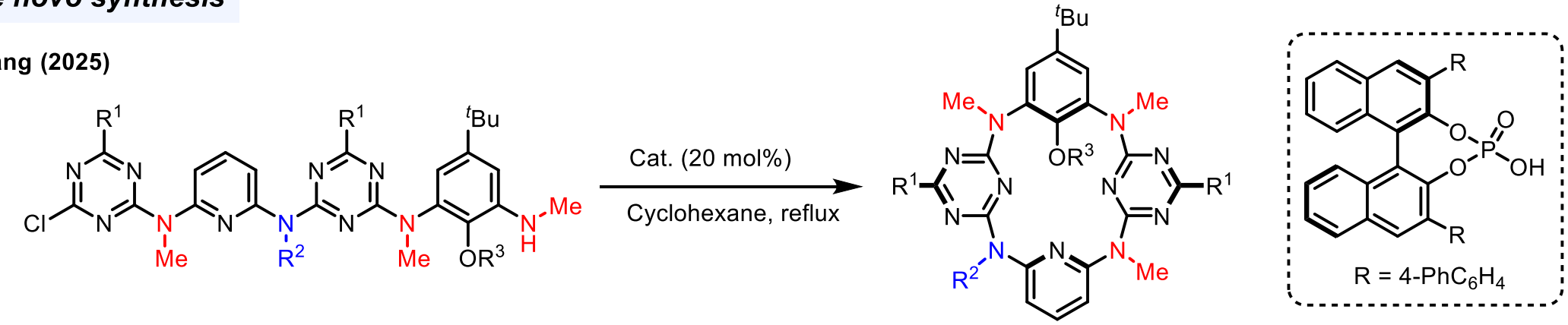
Skeleton modification

Cai (2022)



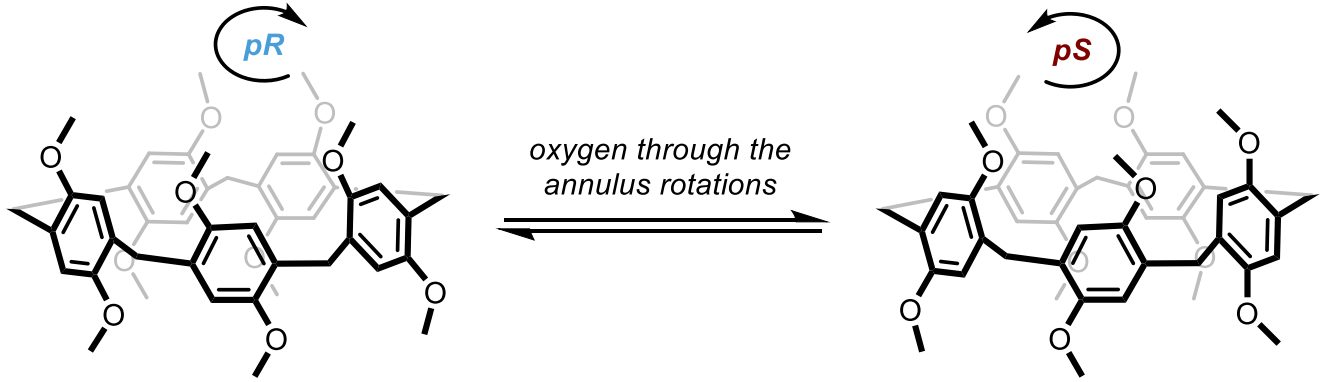
De novo synthesis

Wang (2025)



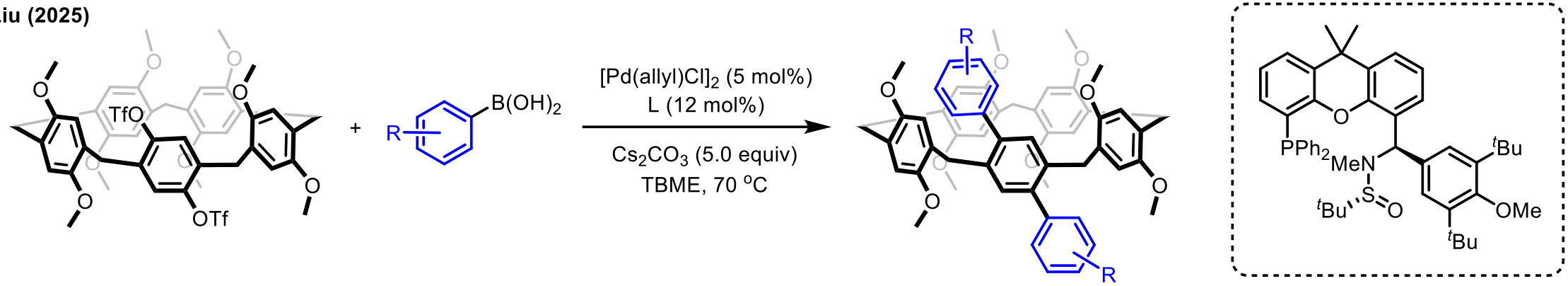
(1) Cai, Q.; et al. *J. Am. Chem. Soc.* **2022**, *144*, 22858−22864. (2) Wang, M.; et al. *Org. Lett.* **2025**, *27*, 4603-4608.
For recent reviews, see: (1) Zhang, F.; et al. *Chem. Soc. Rev.* **2025**, *54*, 10856-10879.
(2) Tong, S. *Acc. Chem. Res.* **2025**, DOI: 10.1021/acs.accounts.5c00609.

研究背景: 固有手性柱芳烃



Extended side-arm

Liu (2025)

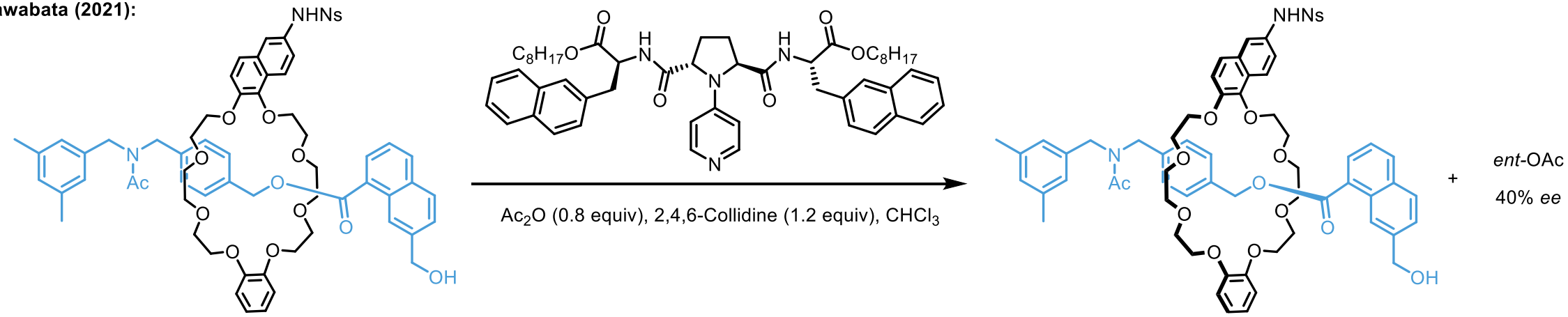


Liu, R.; et al. *Nat. Commun.* **2025**, *16*, 2370.
For review on pillar[*n*]arenes, see: Ogoshi, T.; et al. *Chem. Lett.* **2019**, *48,* 1278-1287.

研究背景: 固有手性轮烷，分子笼

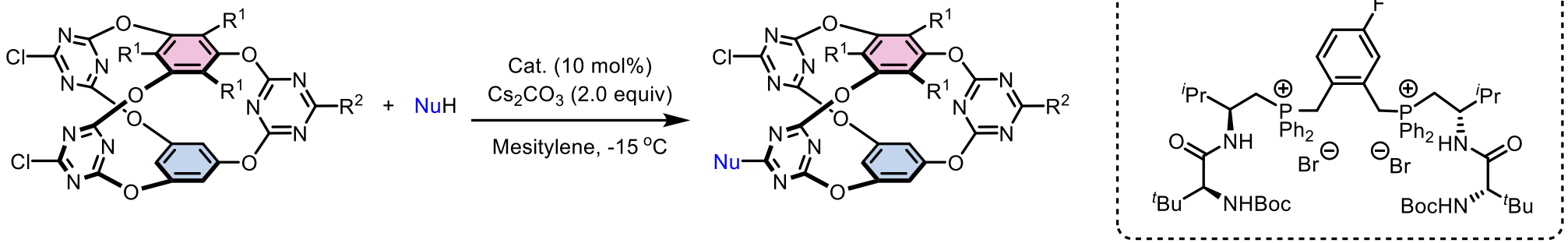
Kinetic resolution

Kawabata (2021):



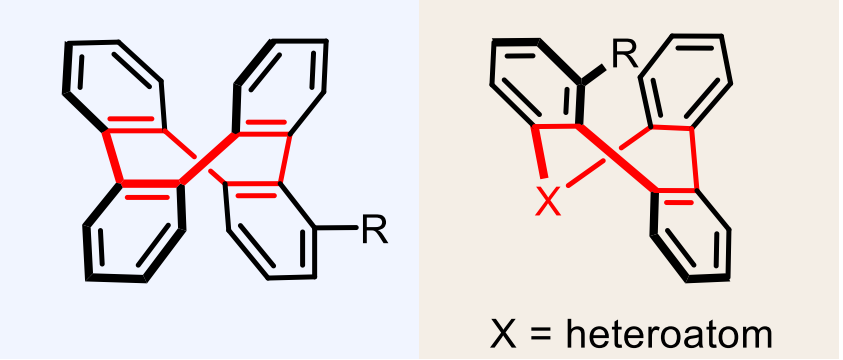
Desymmetrization

Wang (2025)

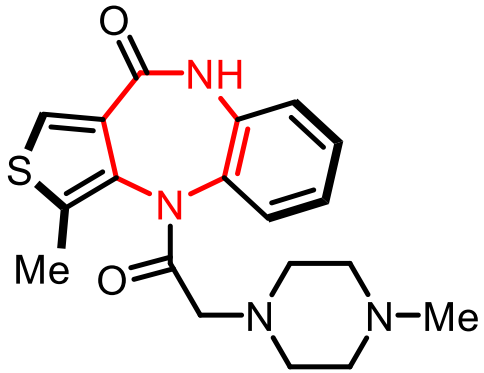


Kawabata, T.; et al. *Nat. Commun.* **2021**, *12*, 404.
Wang, T.; et al. *Angew. Chem. Int. Ed.* **2024**, *63*, e202411889.

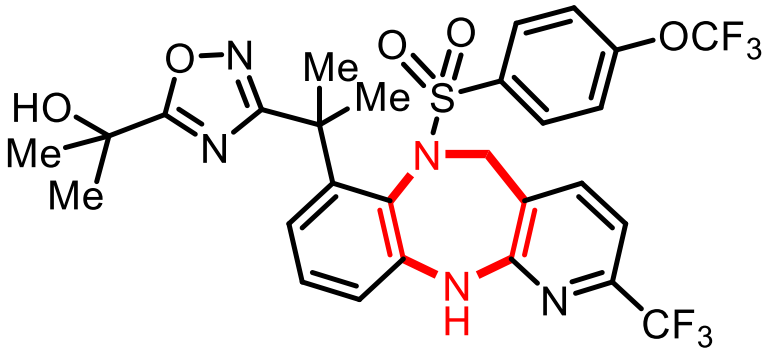
研究背景: 固有手性马鞍形化合物



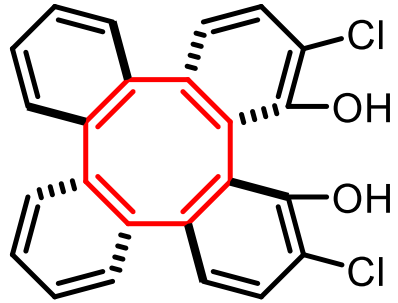
- ***Bioactive molecules***
- ***Material science***
- ***Host–Guest Chemistry***
- ***Ligand for asymmetric catalysis***



Telenzepine



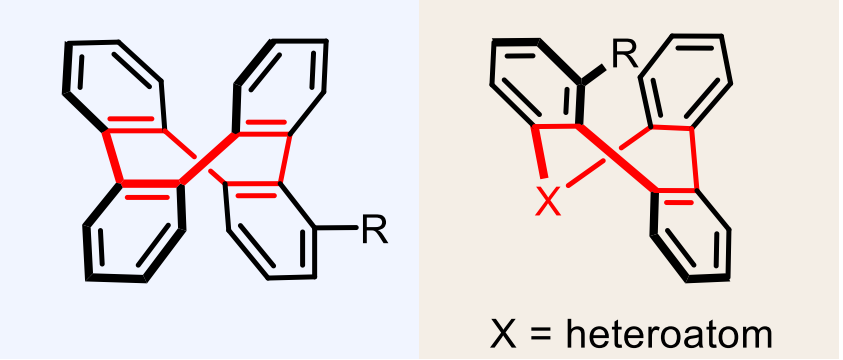
Representative analog of MK-7725



Chiral ligand

For reviews on application, see: (1) Wong, H.; et al. *Synlett*, **2013**, *24*, 2188-2198. (2) Zhu, Q.; et al. *J. Org. Chem.* **2025**, *90*, 5307-5322.

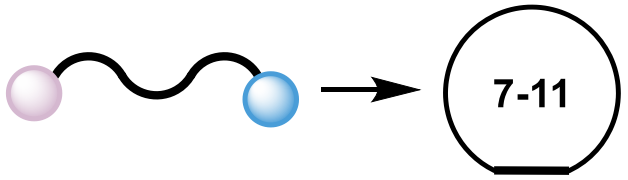
固有手性马鞍形化合物不对称合成策略



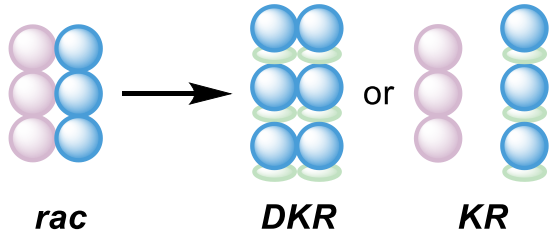
Traditional method

Chiral resolution
or
Chiral auxiliary

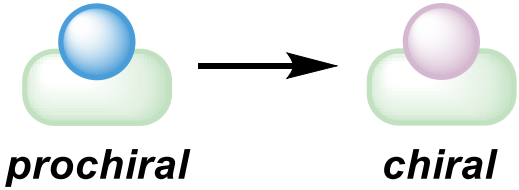
Ring Construction



(Dynamic) Kinetic Resolution



Desymmetrization



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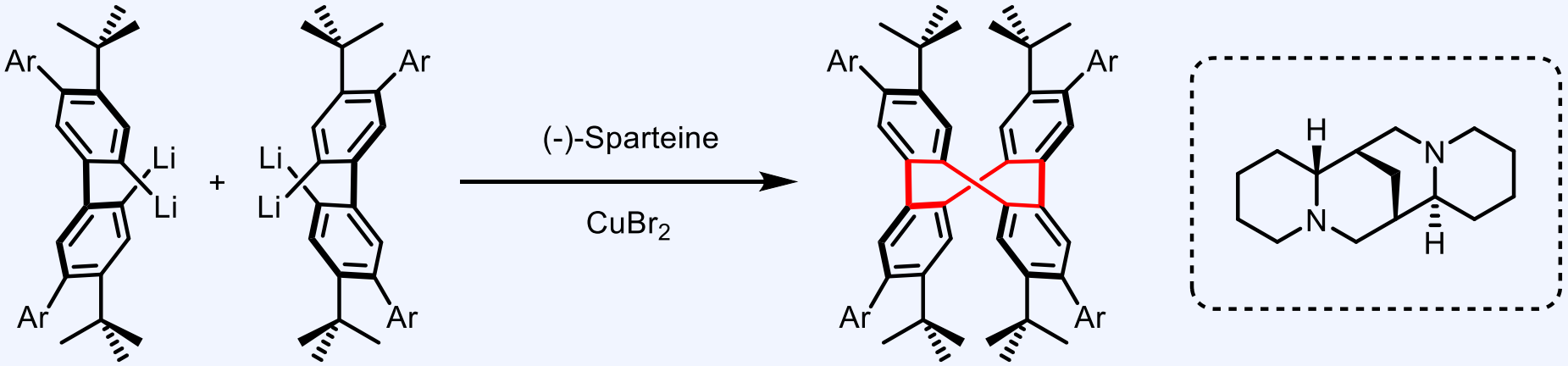
2.1 成环策略

The First Report:

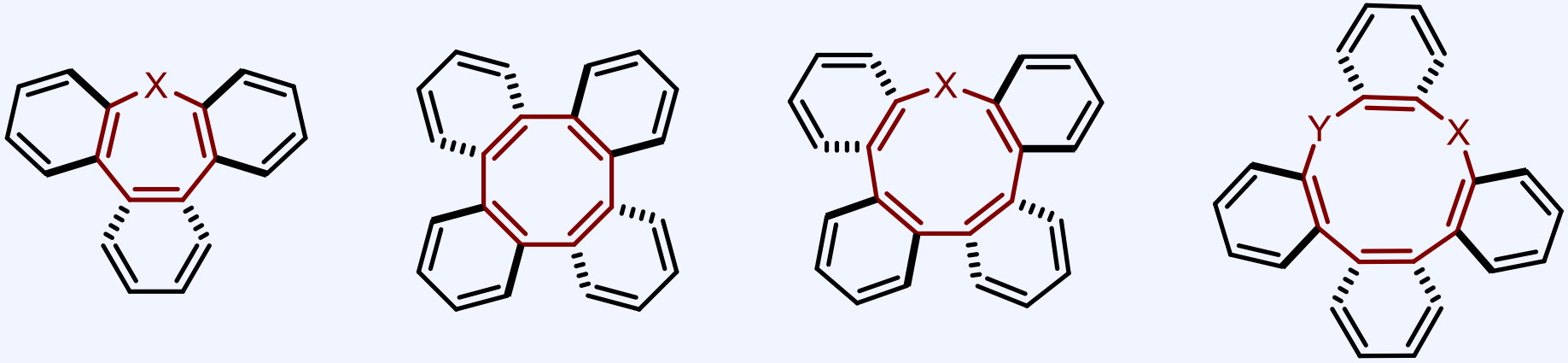
Rajca (2001): *(−)-Sparteine and $CuBr_2$ mediated coupling of 2,2'-dilithiobiaryls*



50-60% *ee*

Rajca, S.; et al. *Tetrahedron*, **2001**, *57*, 3725.

2.1 成环策略



Saddle-shaped scaffolds (X = heteroatom)

Cycloaddition

[2+2+2]

[5+3]

[4+4]

Intramolecular cyclization

S_EAr

S_NAr & S_N2

Esterification

Other strategies

Inner-bond-cleavage

Condensation

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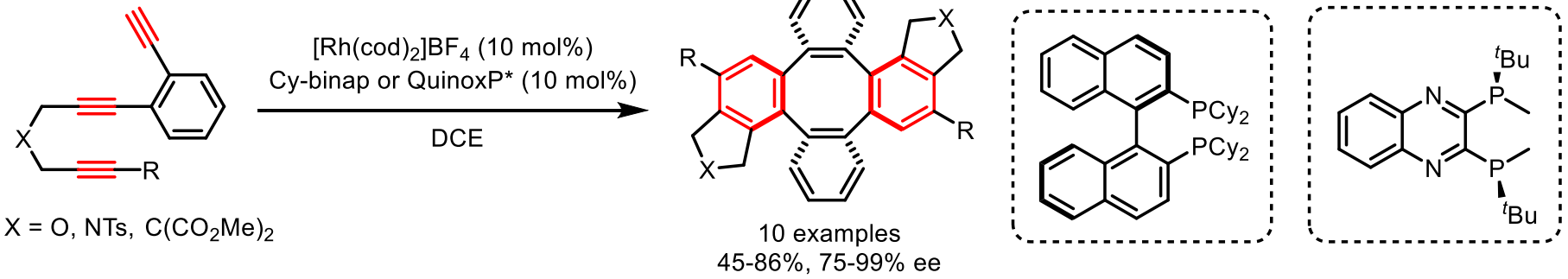
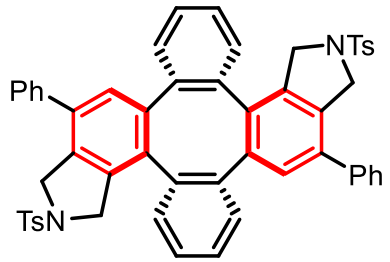
2.1.1 环加成策略：[2+2+2]环加成

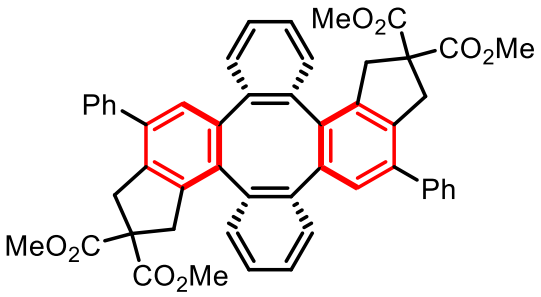
Shibata (2009)



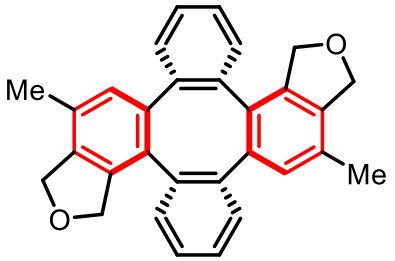
Selected examples



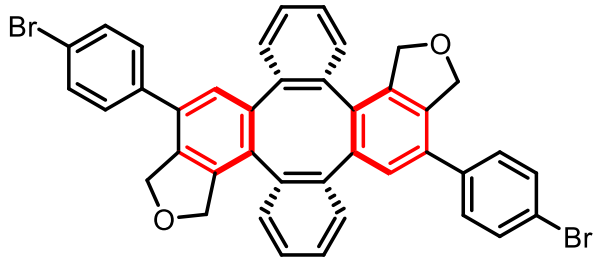
Cy-binap: 62%, 95% *ee*
QuinoxP*: trace



Cy-binap: 45%, 96% *ee*



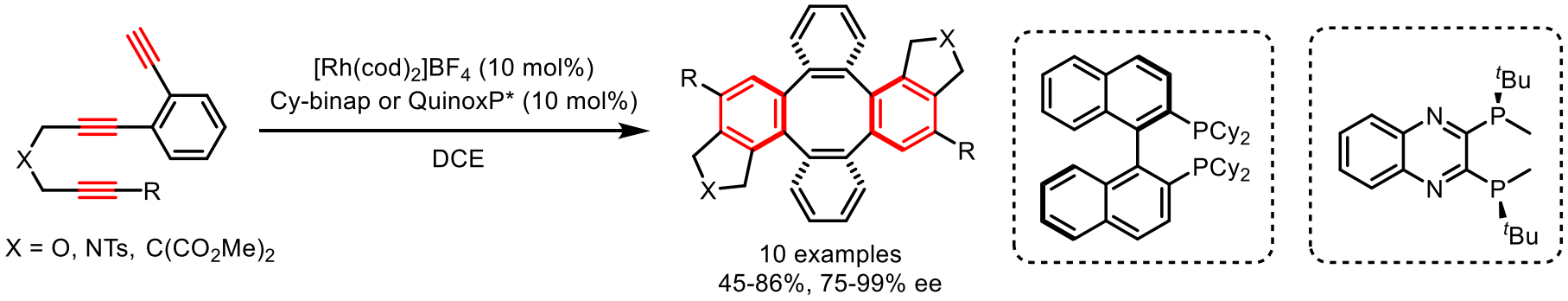
Cy-binap: 80%, 75% *ee*
QuinoxP*: 59%, 83% *ee*



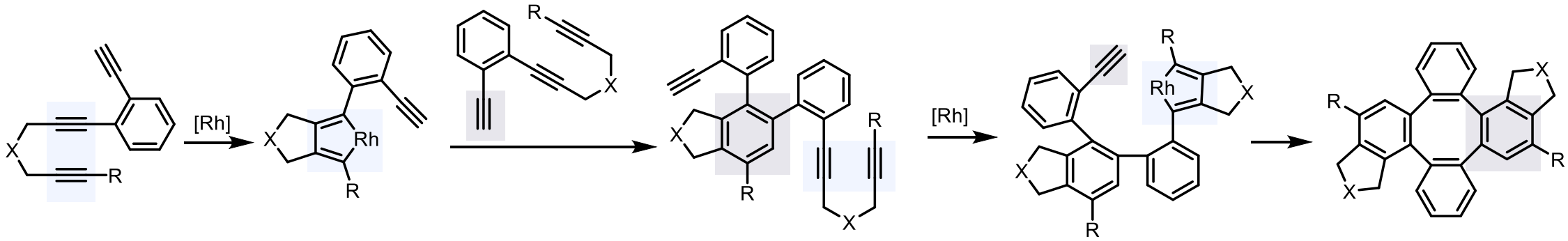
Cy-binap: 56%, >99% *ee*

Shibata, T.; et al. *Angew. Chem. Int. Ed.* **2009**, *48*, 8066.

2.1.1 环加成策略：[2+2+2]环加成



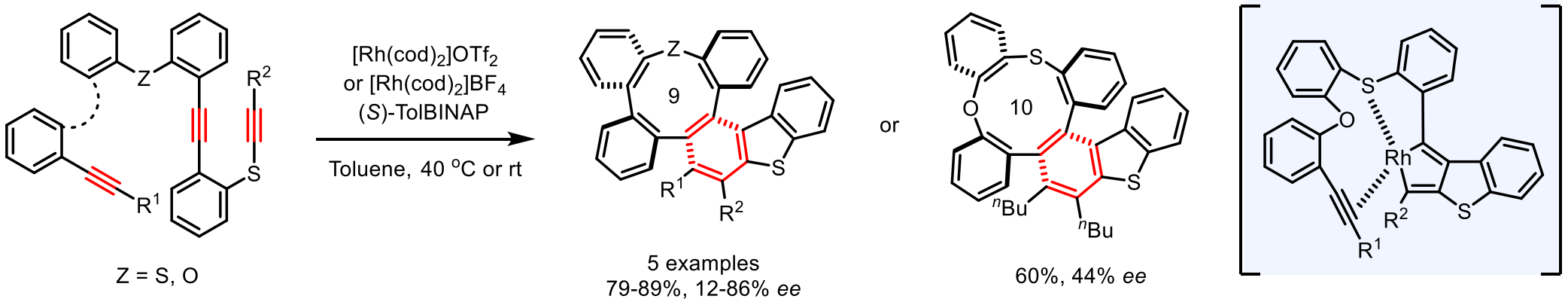
Plausible mechanism

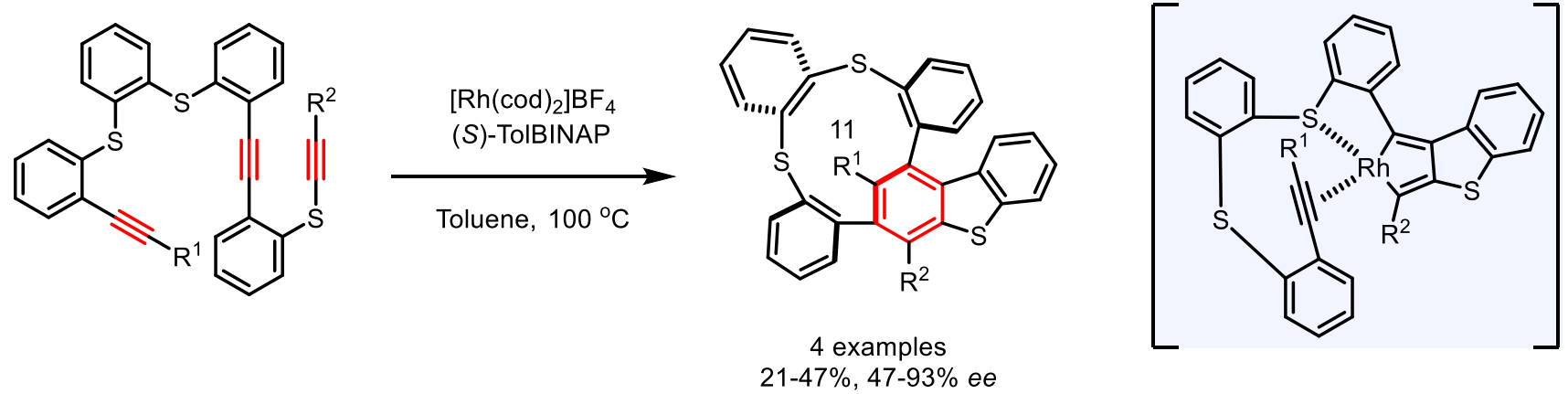


Shibata, T.; et al. *Angew. Chem. Int. Ed.* **2009**, *48*, 8066.

2.1.1 环加成策略：[2+2+2]环加成

Shibata (2019)

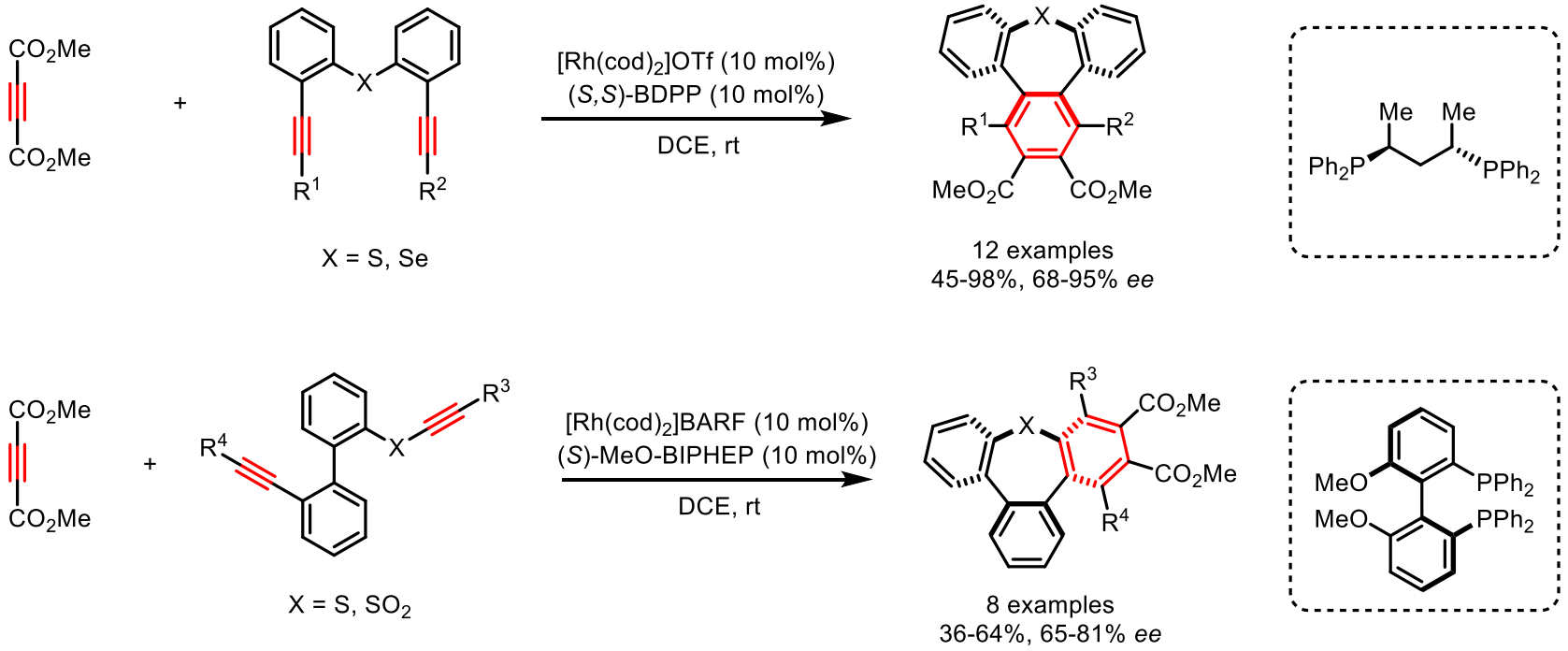




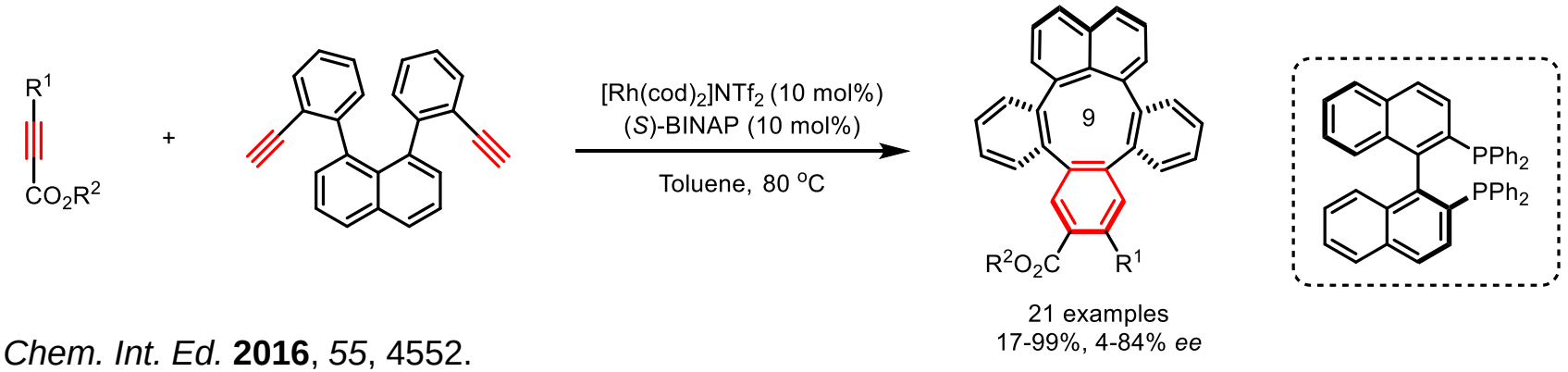
Shibata, T.; et al. *Asian J. Org. Chem.* **2019**, *8*, 970.

2.1.1 环加成策略：[2+2+2]环加成

Shibata (2016)



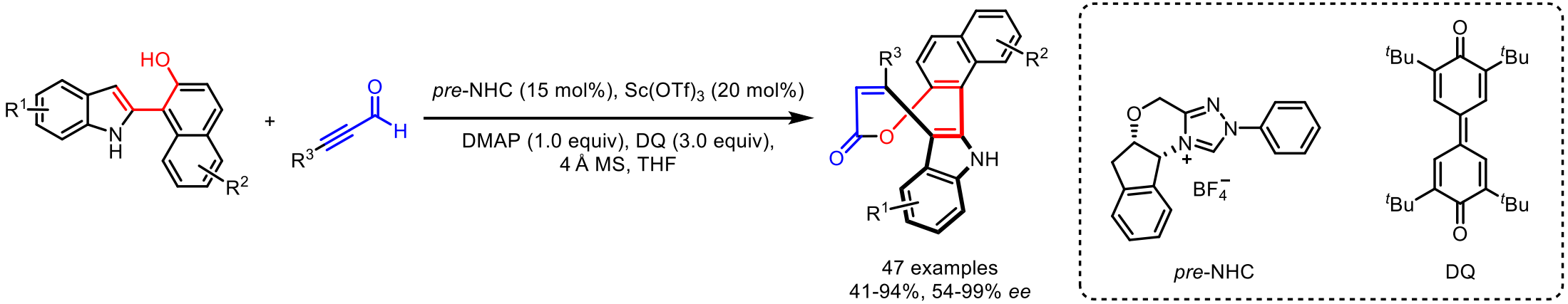
Shibata (2025)



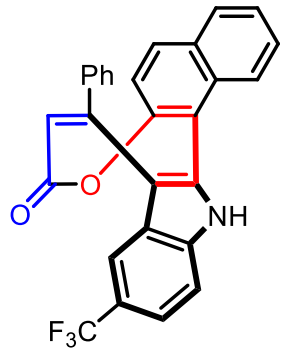
Shibata, T.; et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 4552.
Shibata, T.; et al. *Chem. Eur. J.* **2025**, *31*, e202501193.

2.1.1 环加成策略：[5+3]环加成

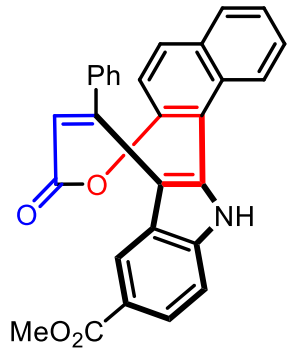
Jiang (2024)



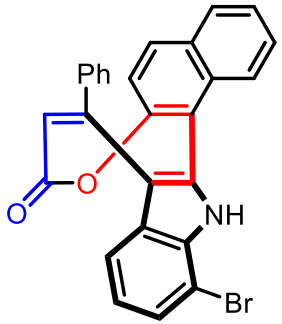
Selected examples



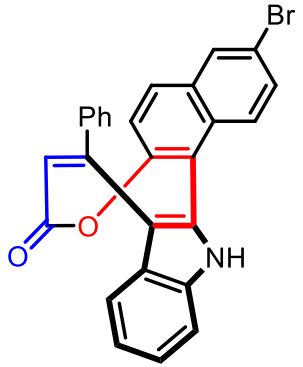
74%, 92% ee



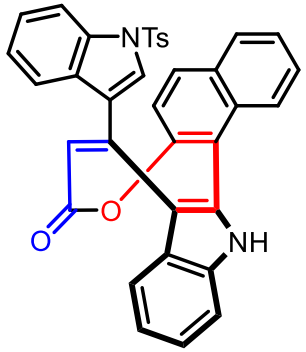
80%, 92% ee



90%, 95% ee



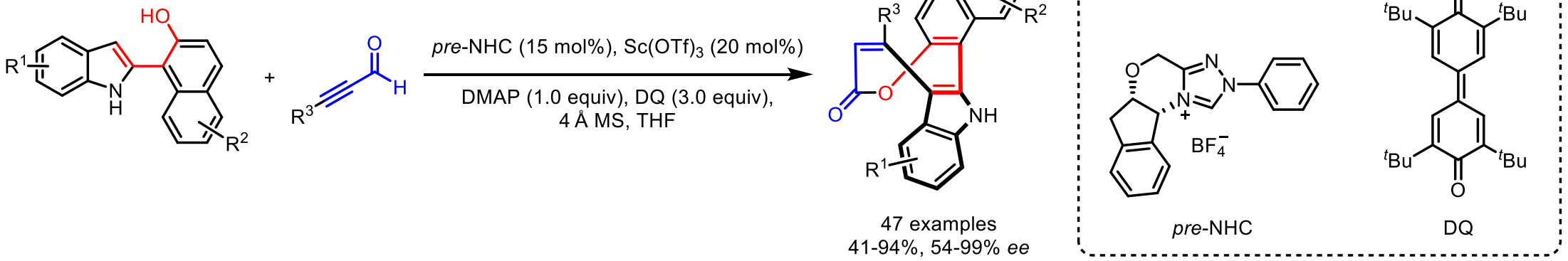
60%, 98% ee



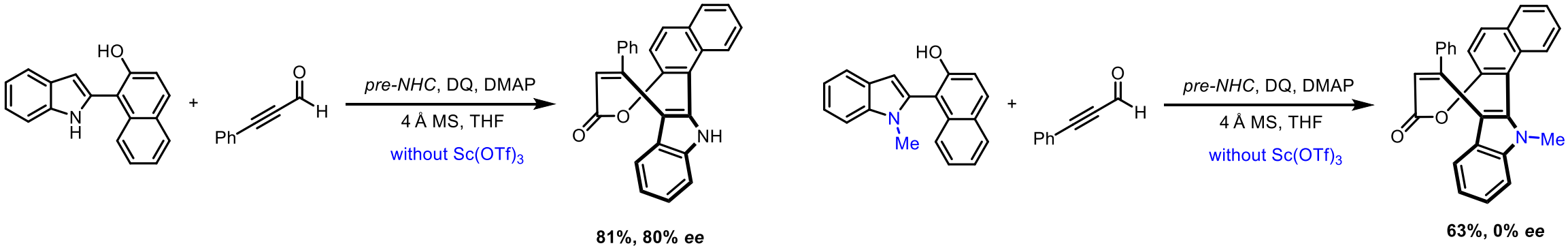
72%, 99% ee

Jiang, B.; et al. *Nat. Commun.* **2024**, *15*, 8474.

2.1.1 环加成策略：[5+3]环加成

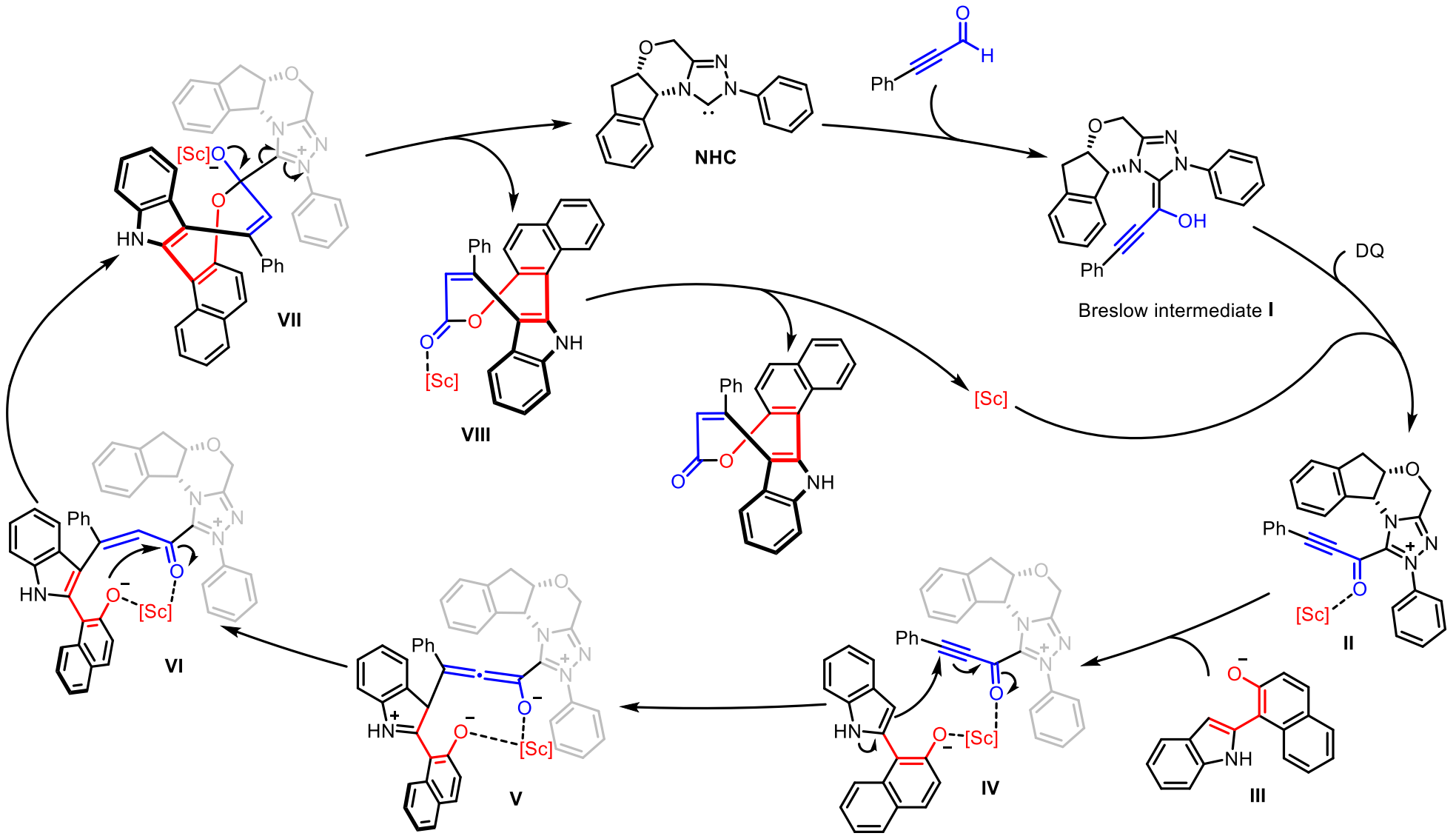


Control experiment



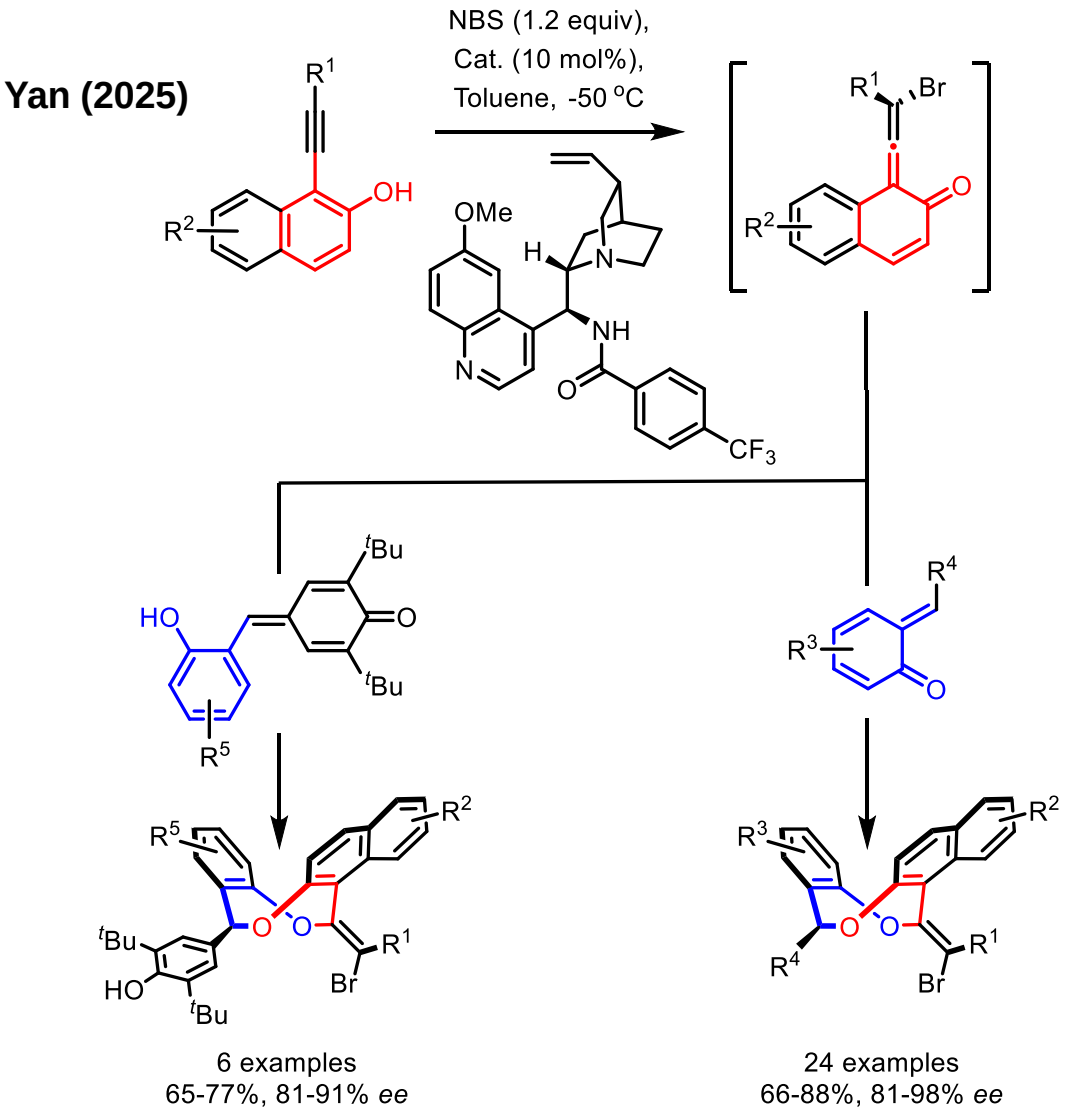
Jiang, B.; et al. *Nat. Commun.* **2024**, *15*, 8474.

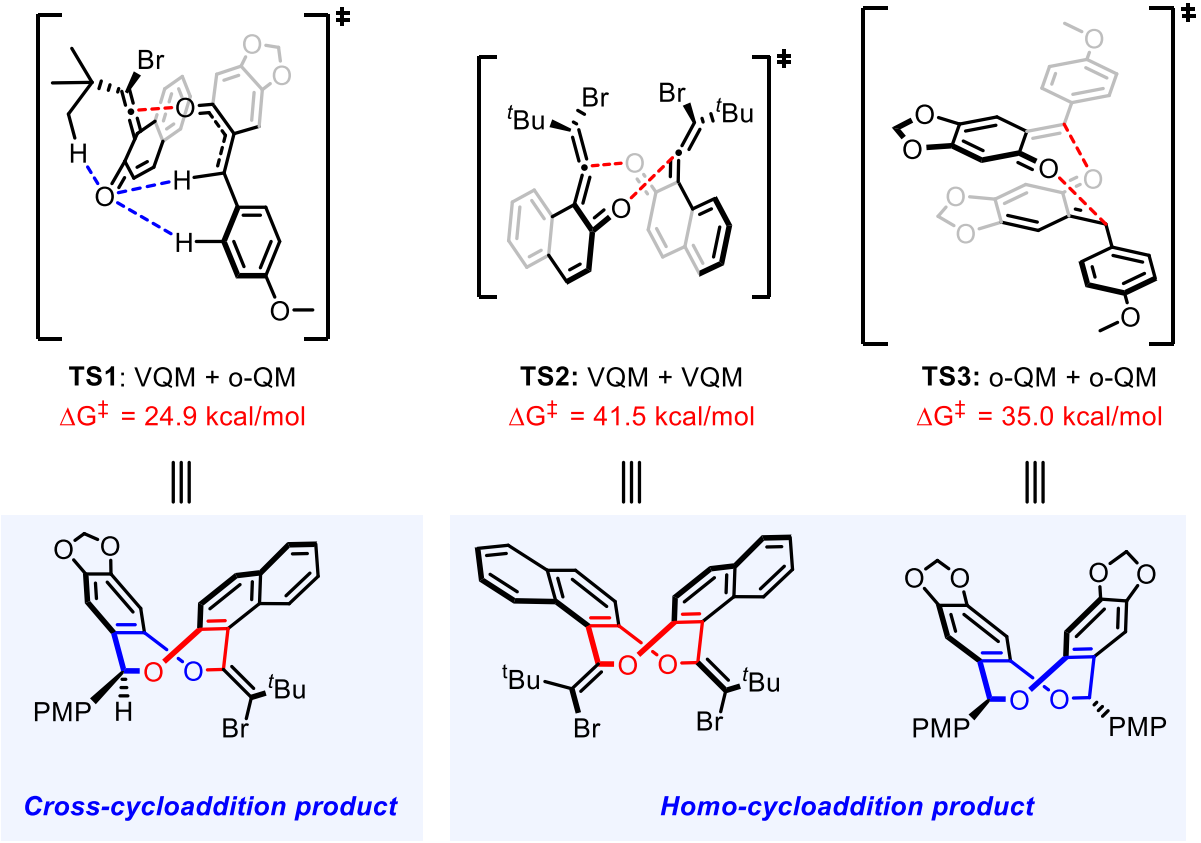
2.1.1 环加成策略：[5+3]环加成



Jiang, B.; et al. *Nat. Commun.* **2024**, *15*, 8474.

2.1.1 环加成策略：[4+4]环加成

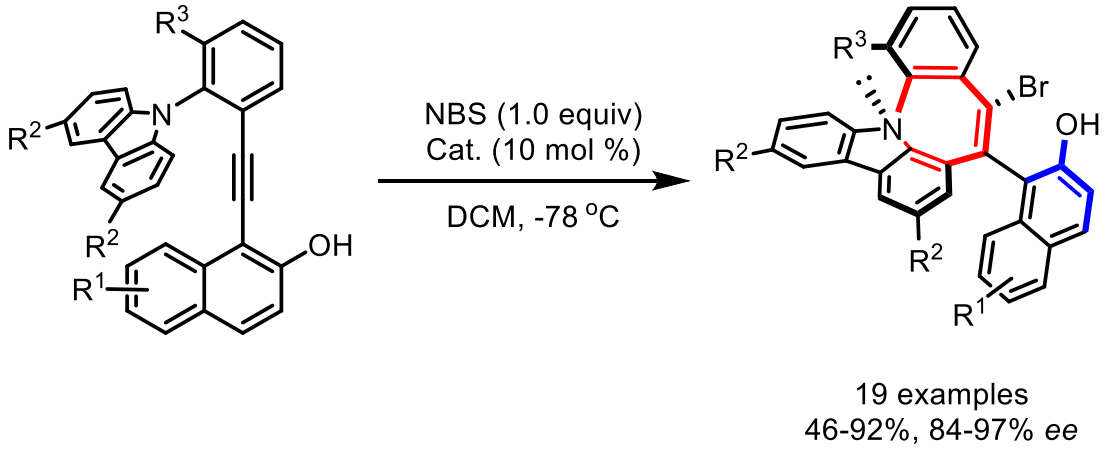




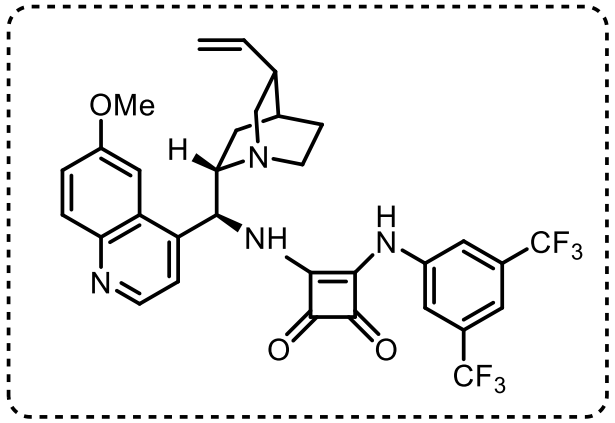
Yan, H.; et al. *Angew. Chem. Int. Ed.* **2025**, *64*, e202416873.

2.1.2 分子内环化策略：芳香亲电取代反应

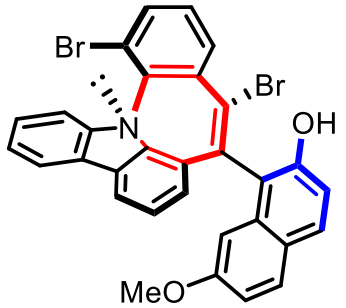
Yan (2021)



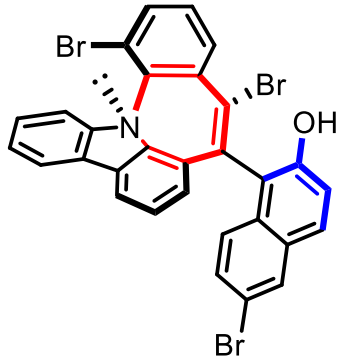
19 examples
46-92%, 84-97% *ee*



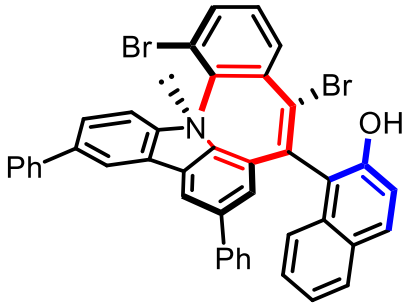
Selected examples



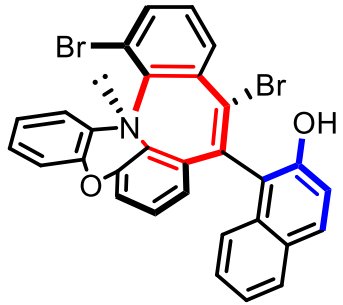
88%, 95% ee



89%, 96% ee



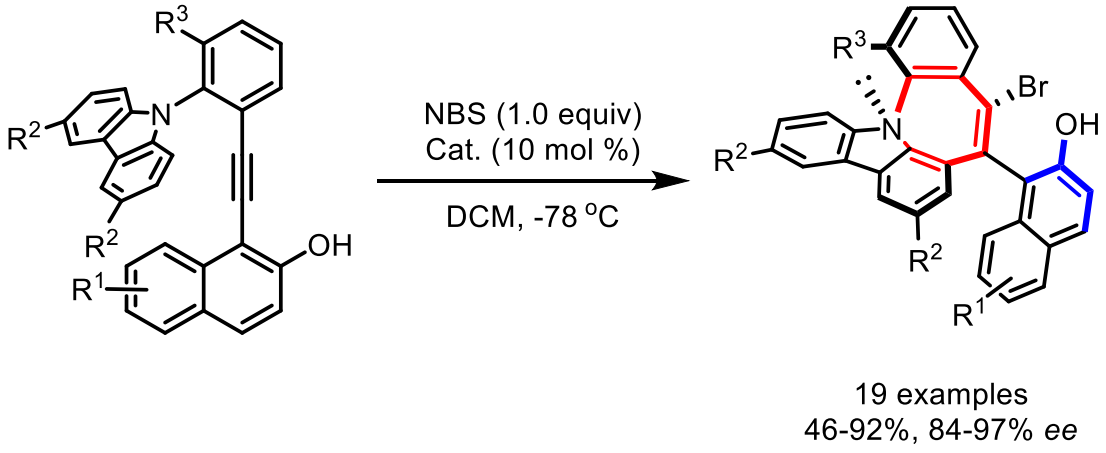
82%, 91% ee



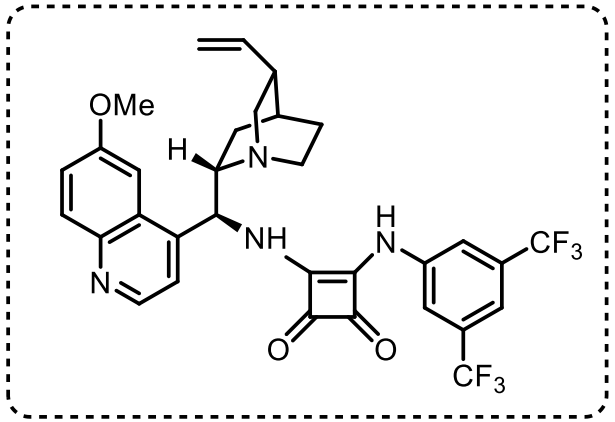
89%, 97% ee

Yan, H.; et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 21486.

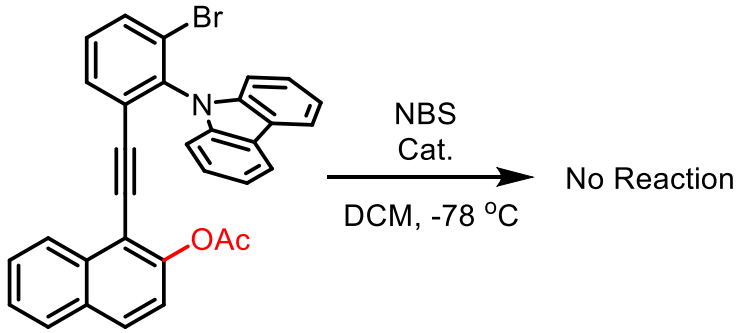
2.1.2 分子内环化策略：芳香亲电取代反应

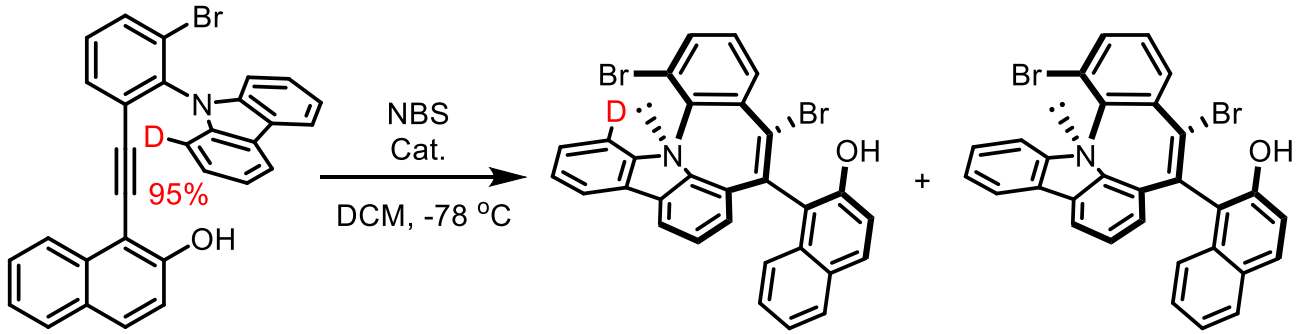


19 examples
46-92%, 84-97% *ee*



Control experiments & Isotopic labeling experiment

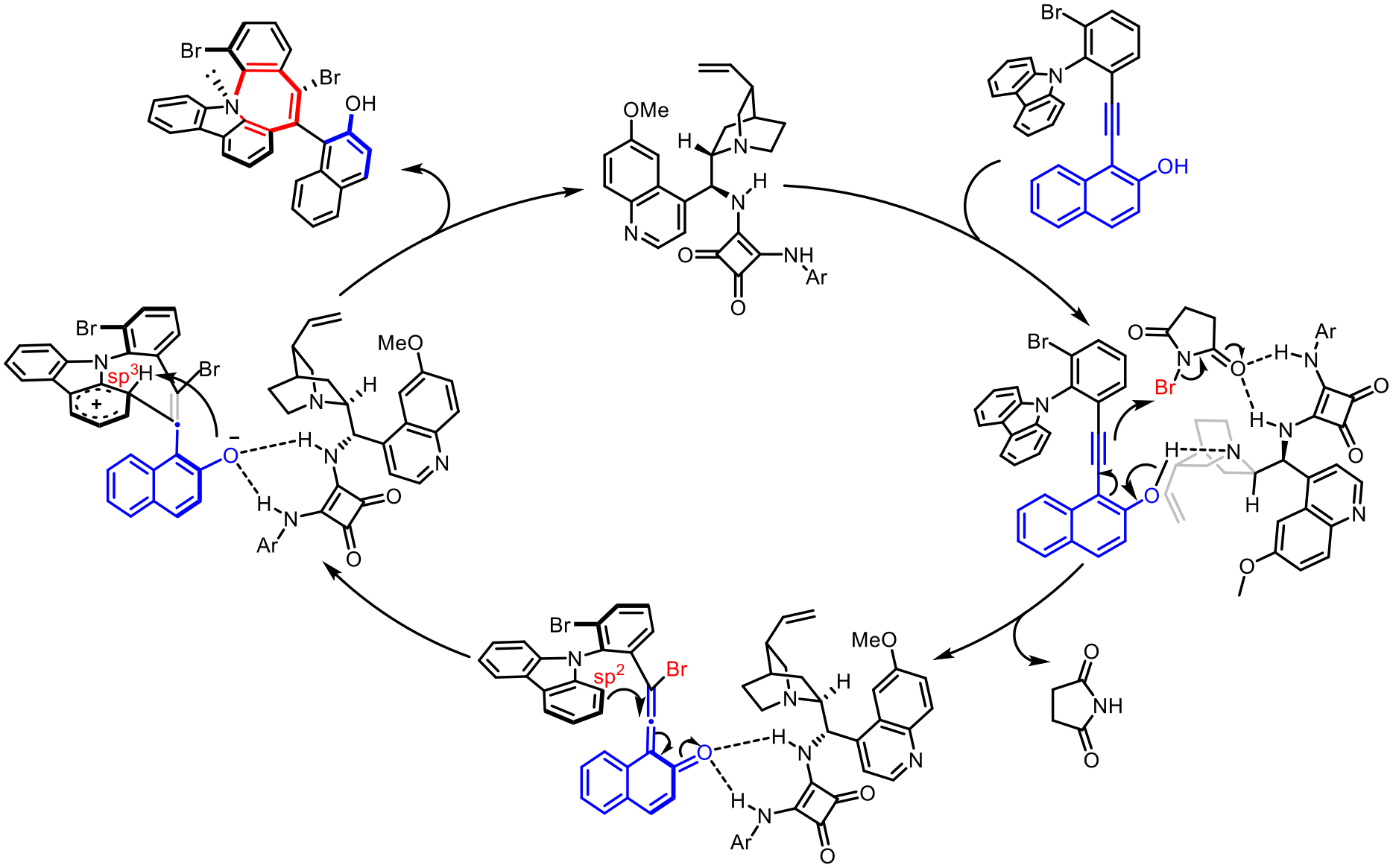




0.44: 0.56
k_H/k_D = 0.87

Yan, H.; et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 21486.

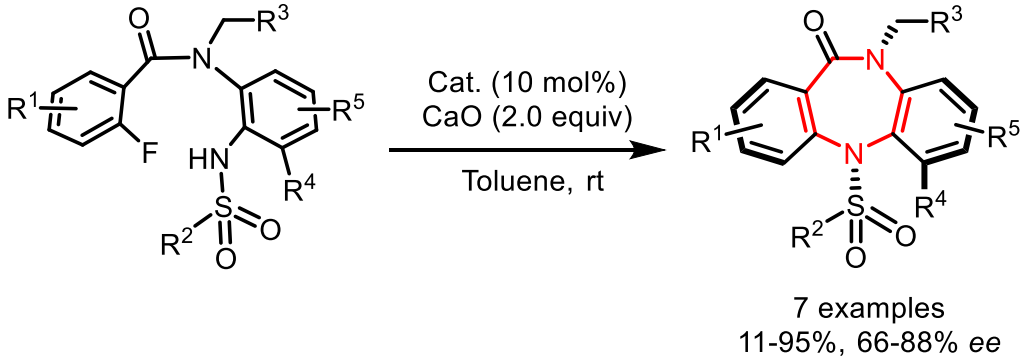
2.1.2 分子内环化策略：芳香亲电取代反应

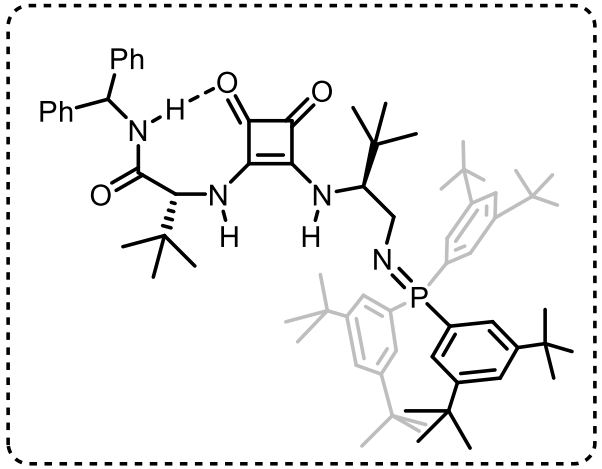


Yan, H.; et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 21486.

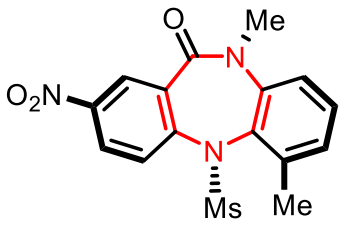
2.1.2 分子内环化策略：亲核取代反应

Miller (2025)

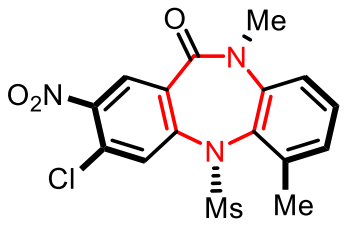




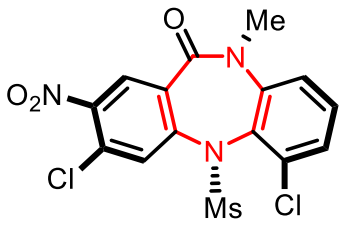
Selected examples



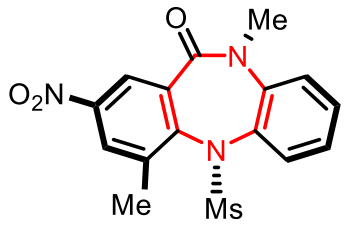
88%, 84% *ee*



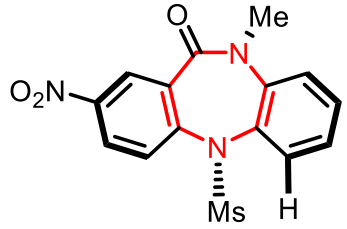
83%, 88% *ee*



11%, 74% *ee*



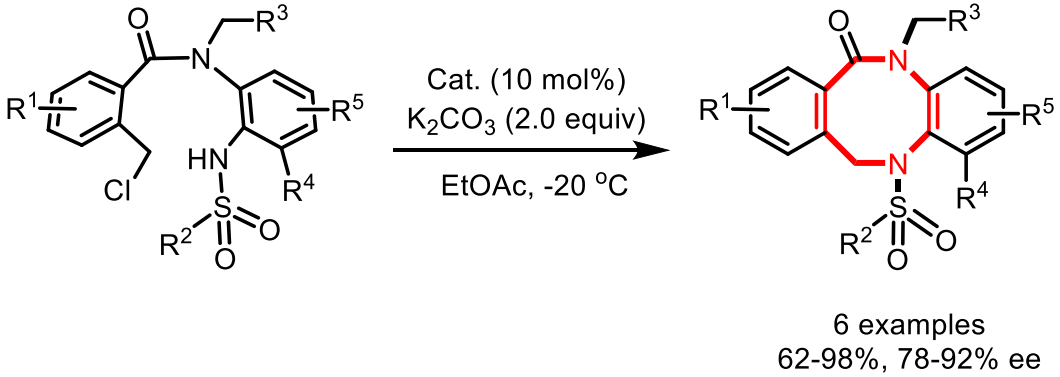
no reaction

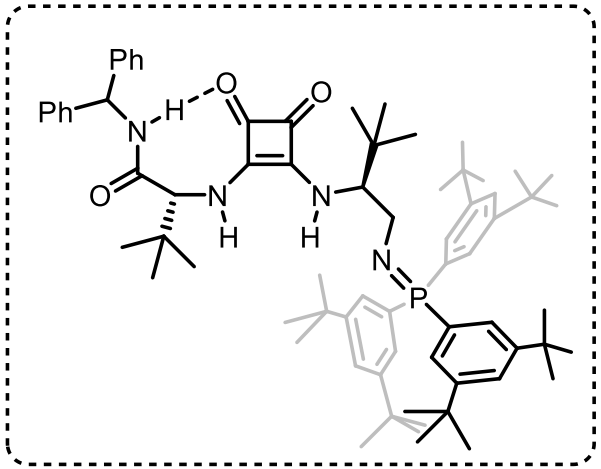


<10%, ~80% *ee*

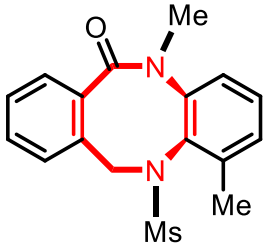
Miller, J.; et al. *J. Am. Chem. Soc.* **2025**, *147*, 4624–4630.

2.1.2 分子内环化策略：亲核取代反应

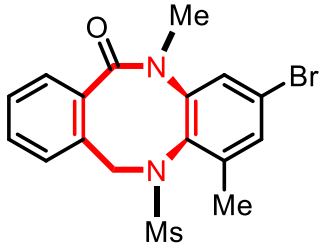




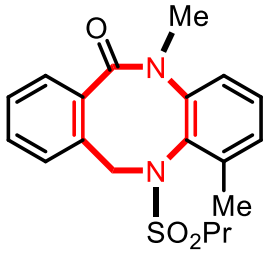
Selected examples



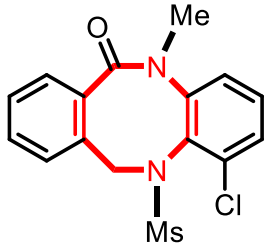
98%, 92% *ee*



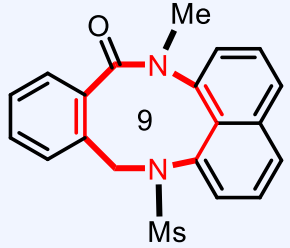
62%, 90% *ee*



92%, 88% *ee*



96%, 84% *ee*

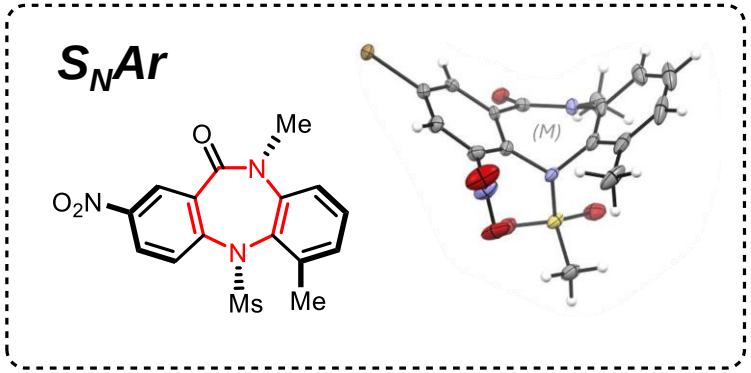


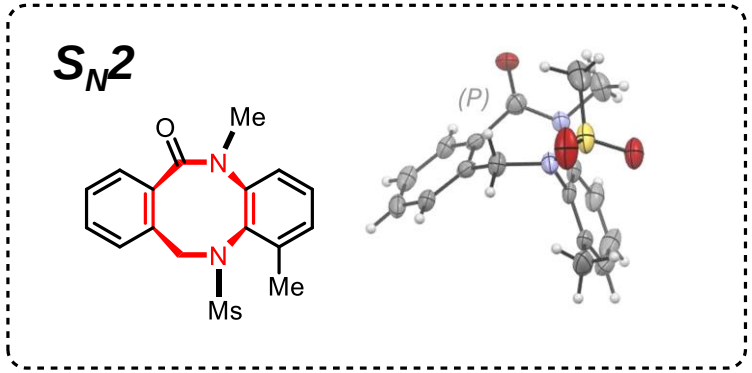
100% conv., 0 *ee*

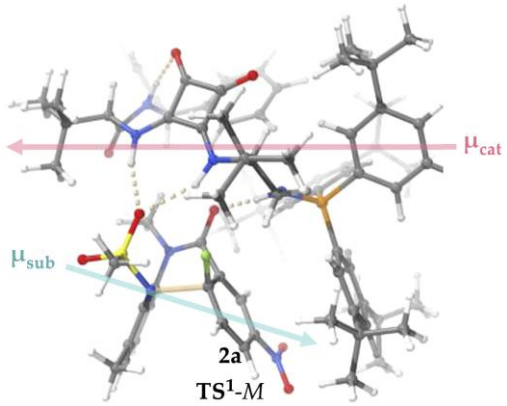
Miller, J.; et al. *J. Am. Chem. Soc.* **2025**, *147*, 4624–4630.

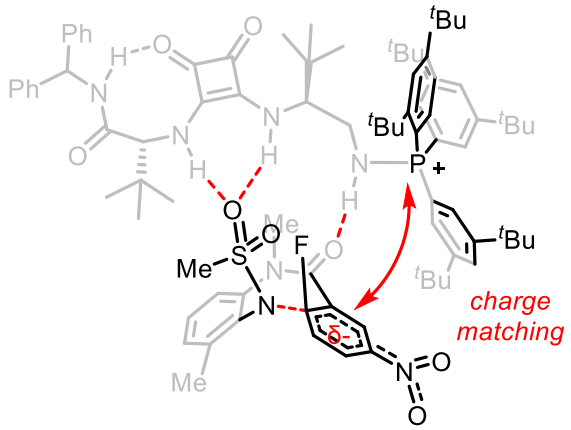
2.1.2 分子内环化策略：亲核取代反应

Transition state

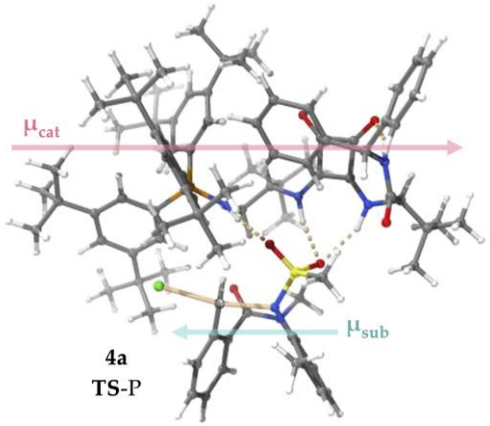


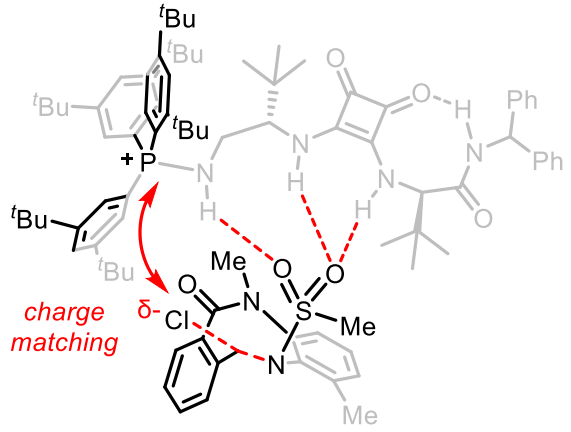






major: $d_{P^+\text{-}Ar^{\delta-}}$ = 4.97 Å
minor: $d_{P^+\text{-}Ar^{\delta-}}$ = 5.62 Å



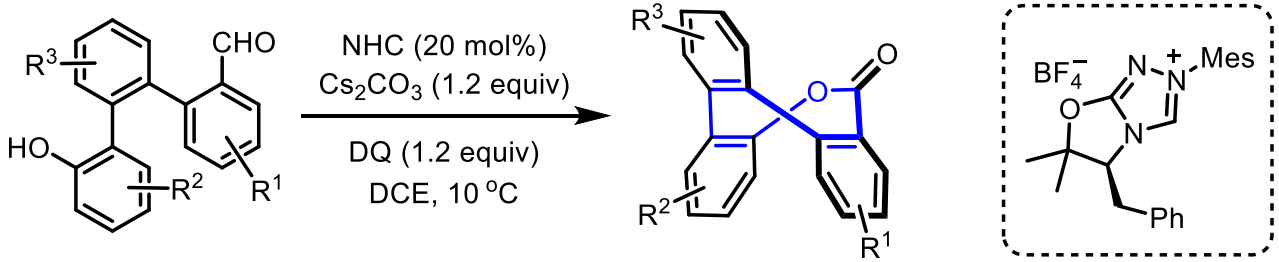


major: $d_{P^+\text{-}Cl^{\delta-}}$ = 4.57 Å
minor: $d_{P^+\text{-}Cl^{\delta-}}$ = 5.51 Å

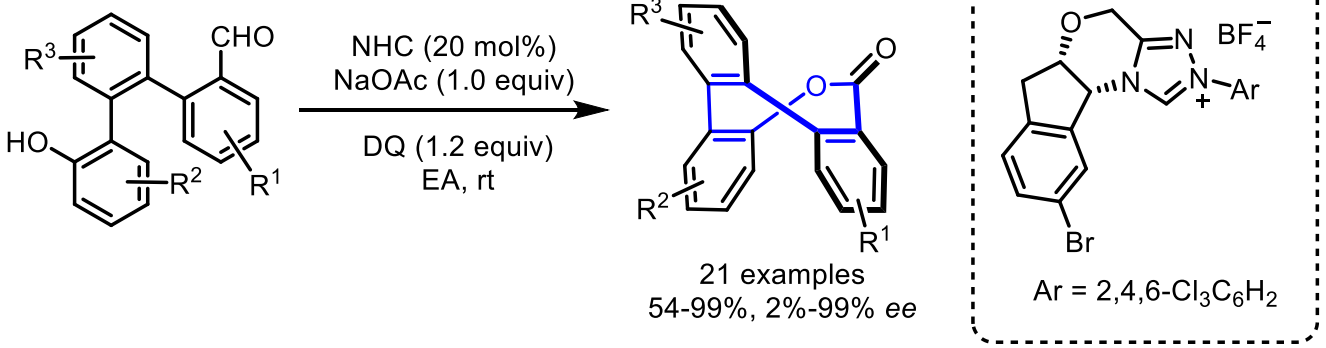
Miller, J.; et al. *J. Am. Chem. Soc.* **2025**, *147*, 4624–4630.

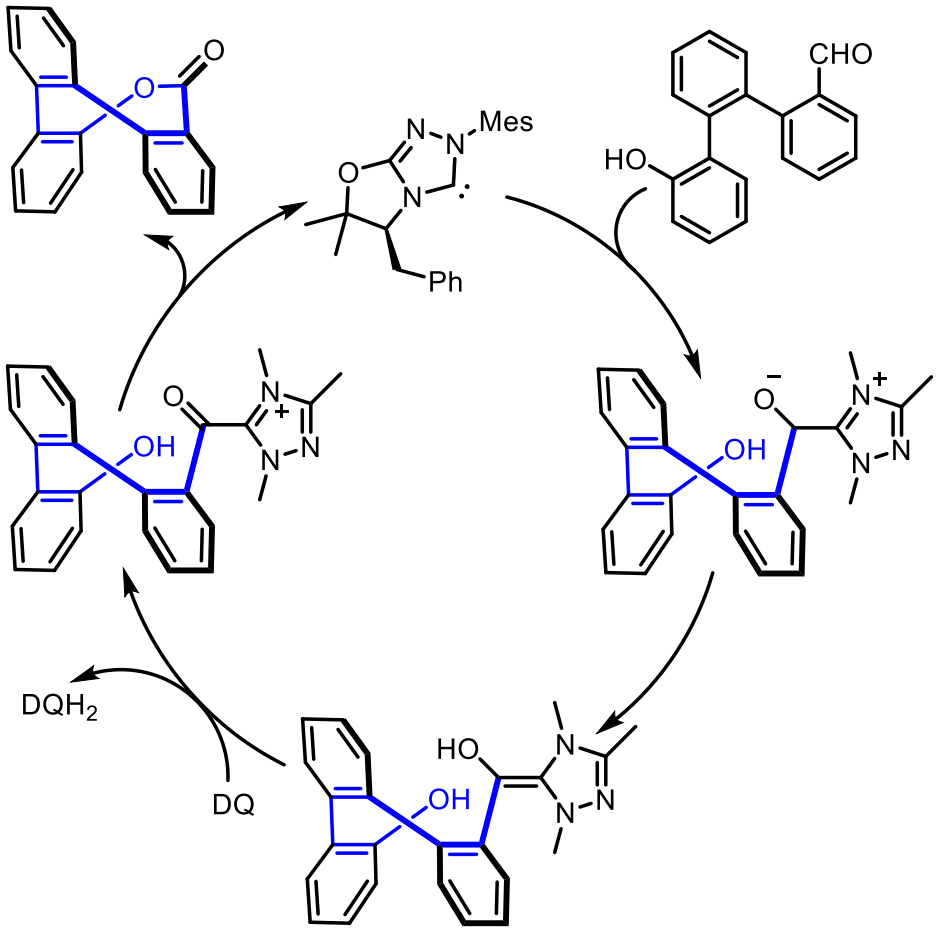
2.1.2 分子内环化策略：卡宾催化酯化反应

Veselý (2025)



Chen (2025)

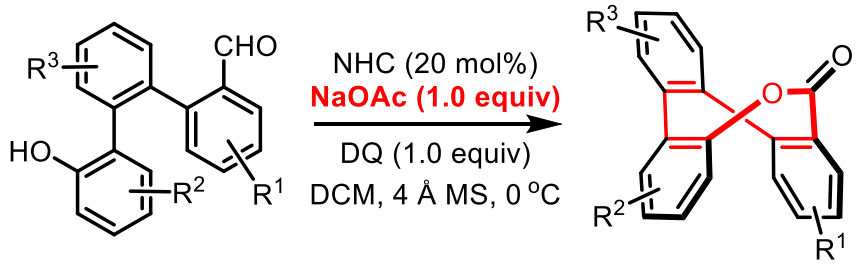




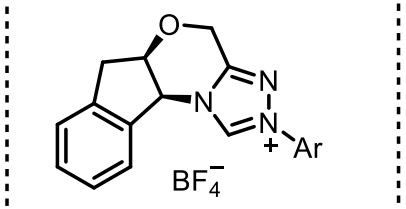
Veselý, J.; et al. *Chem. Sci.* **2025**,*16*, 17369-17373.
Chen, X.; et al. *Org. Lett.* **2025**, *27*, 12343–12349.

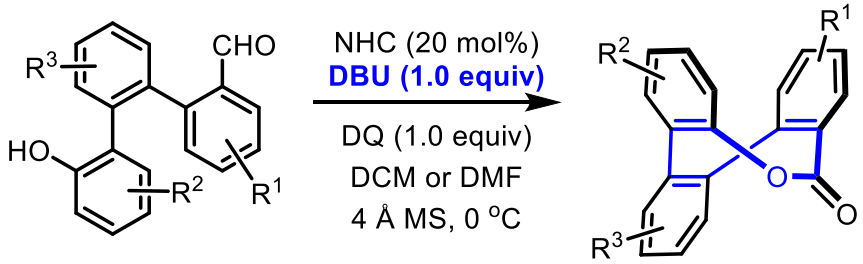
2.1.2 分子内环化策略：卡宾催化酯化反应

Yang (2025)

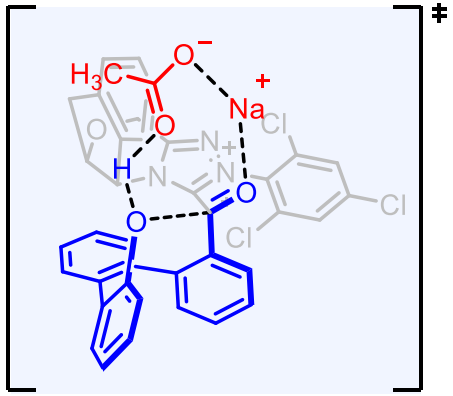


2
34 examples
40-99%, 80-98% *ee*

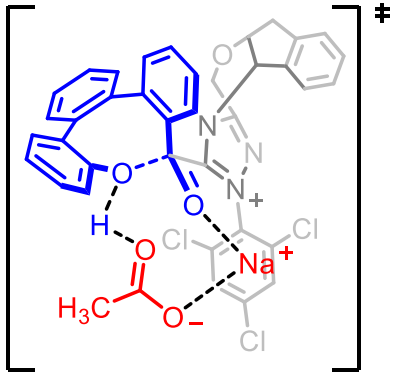




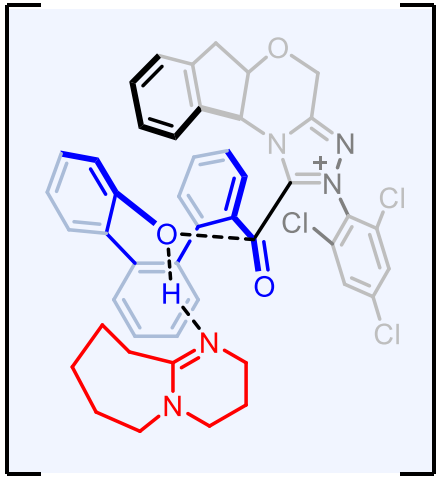
ent-2
34 examples
60-99%, (-80)-(-98)% *ee*



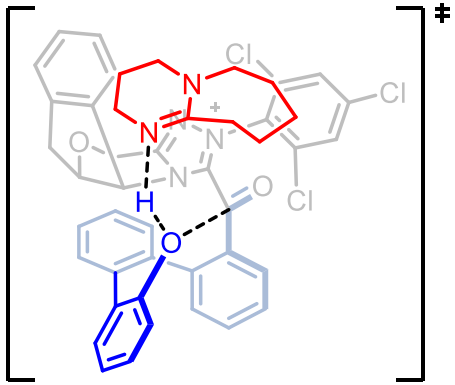
TS_NaOAc_major
$\Delta\Delta G^{\ddagger}$ = 0.0



TS_NaOAc_minor
$\Delta\Delta G^{\ddagger}$ = 1.2



TS_DBU_major
$\Delta\Delta G^{\ddagger}$ = 0.0

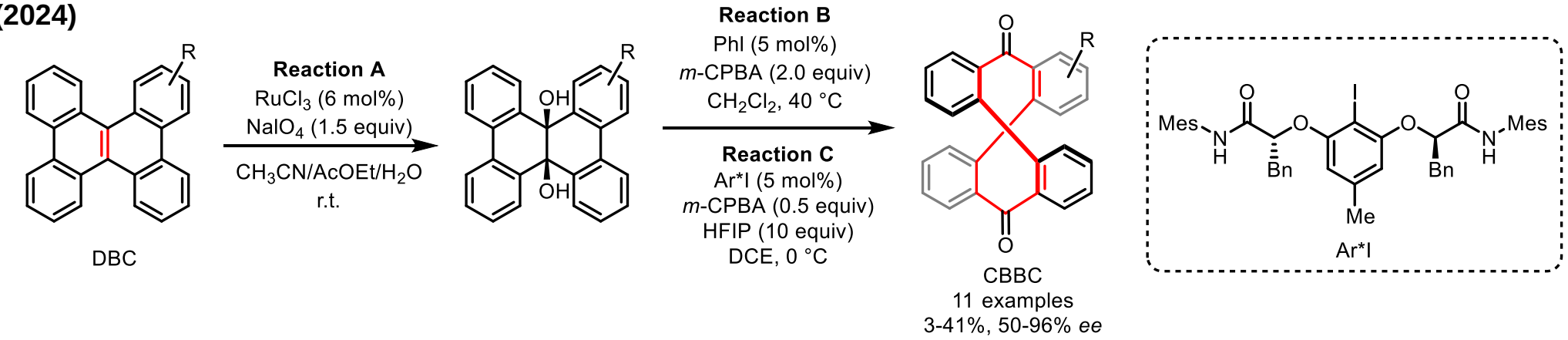


TS_DBU_minor
$\Delta\Delta G^{\ddagger}$ = 0.8

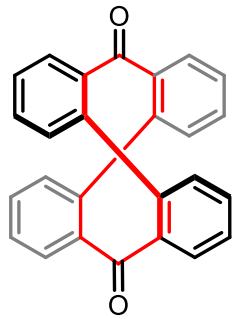
Yang, X.; et al. *J. Am. Chem. Soc.* **2025**, *147*, 30747–30756.

2.1.3 其他策略: 扩环

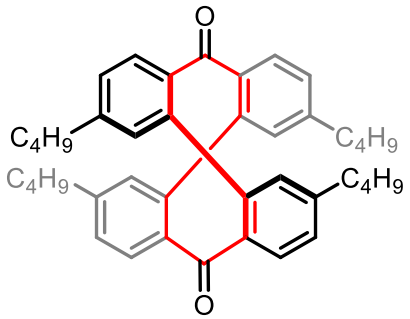
Fukui (2024)



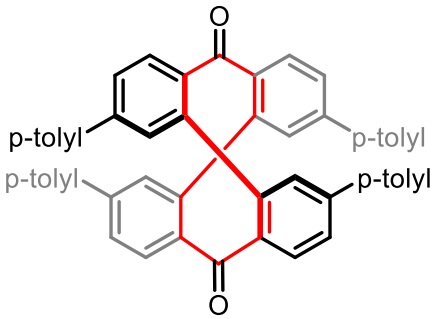
Selected examples



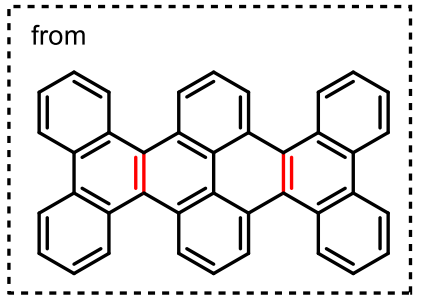
A: 95%; B: 92%;
C: 41% (brsm: 89%), 94% *ee*

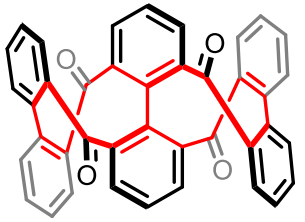


A: 74%; B: 58%;
C: 38% (brsm: 81%), 96% *ee*



A: 83%; B: 86%;
C: 33% (brsm: 80%), 87% *ee*

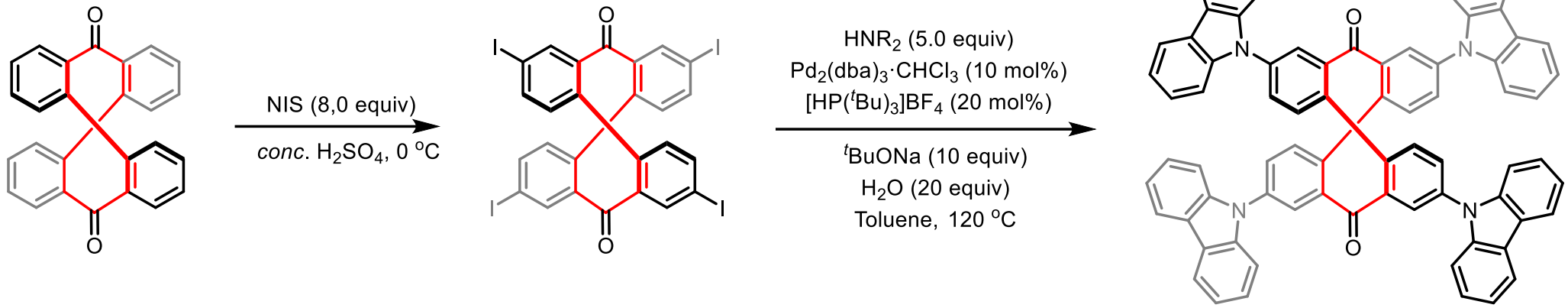




A+B: 59%
A+C: 15%, 71% *ee*

Fukui, N.; et al. *J. Am. Chem. Soc.* **2024**, *146*, 29383–29390.

2.1.3 其他策略: 扩环

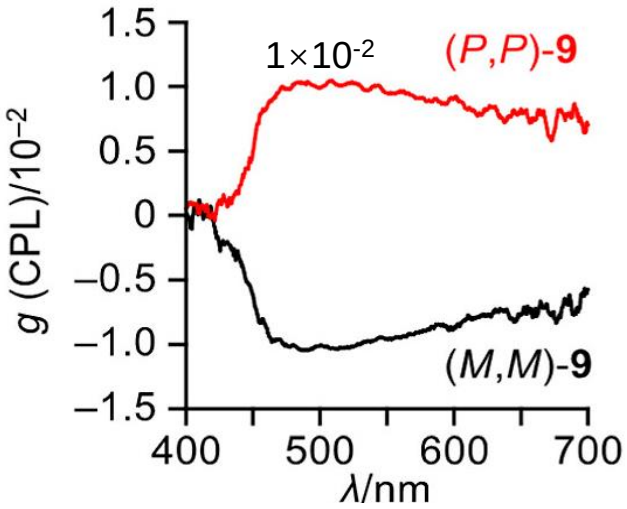


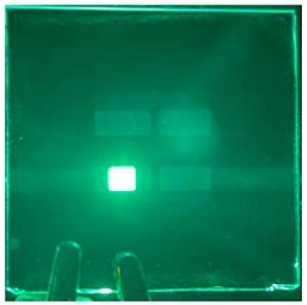
rac-1
(*P,P*)-2a (> 99% *ee*)

rac-2: 58% yield
(*P,P*)-2: 55% yield, > 99% *ee*

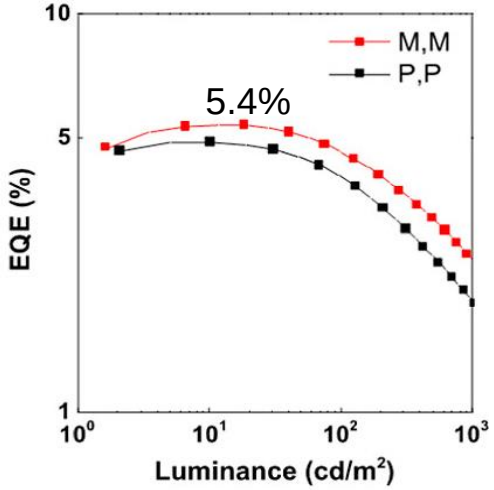
rac-9: 59% yield
(*P,P*)-9: 65% yield, 99% *ee*

圆偏振发光





CIE(x,y)
= (0.23, 0.58)

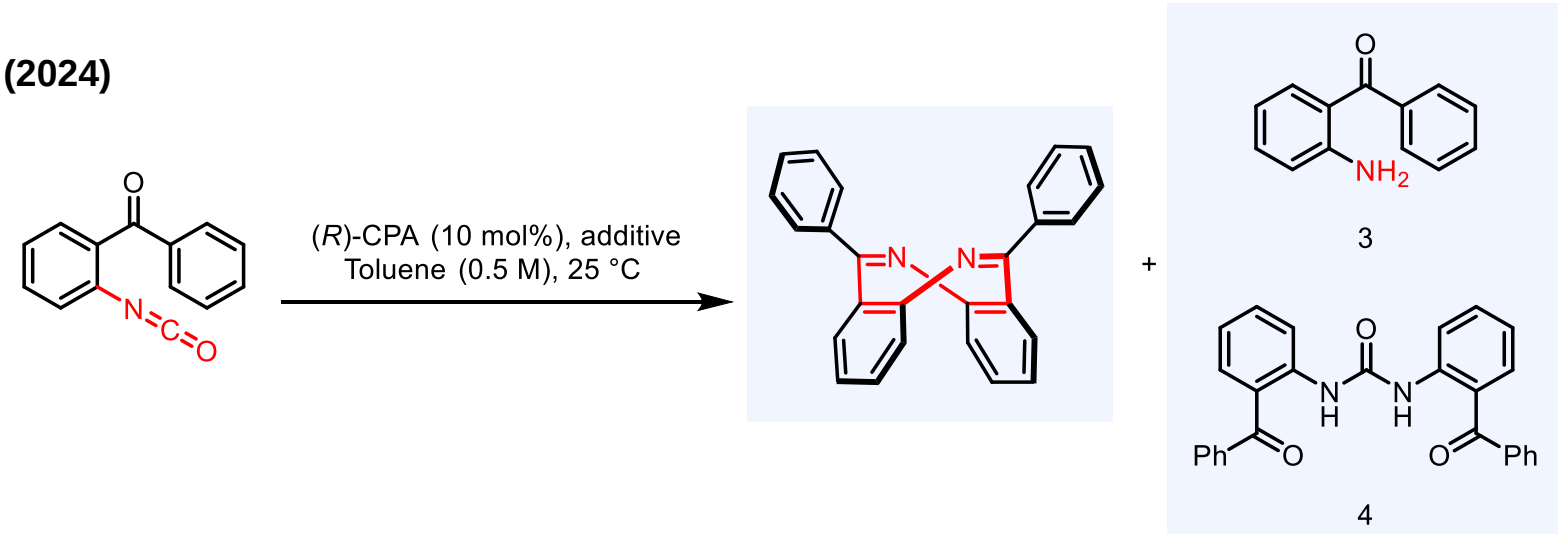


外量子效率

Fukui, N.; et al. *J. Am. Chem. Soc.* **2024**, *146*, 29383–29390.

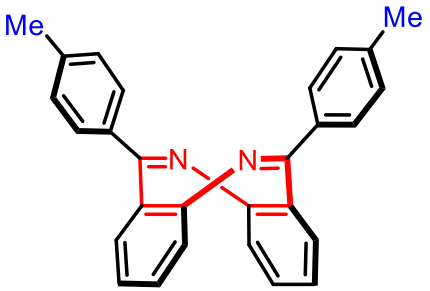
2.1.3 其他策略: 不对称缩合

Yang (2024)

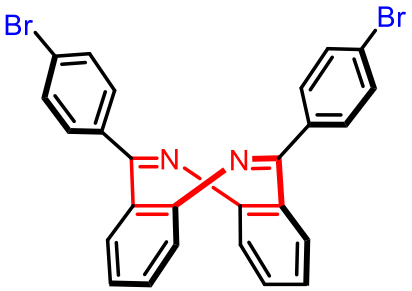


Entry	additive	Yield/%	ee/%
1	4 Å MS (50 mg)	7	42
2	4 (10 mol%)	43	64
3	3 (20 mol%)	84	70
4	3 (20 mol%) & phase separation	60	93

Selected examples ([a]Without phase separation)



38%, 98% *ee*
[a](61%, 66% *ee*)

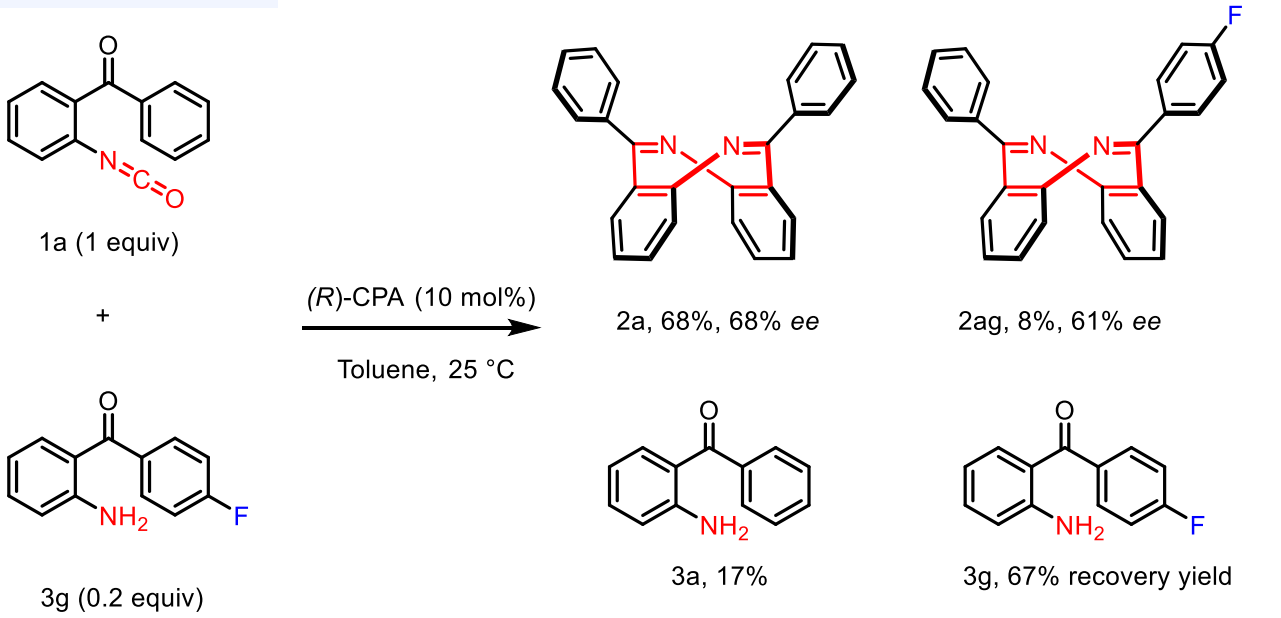


40%, 99% *ee*
[a](60%, 67% *ee*)

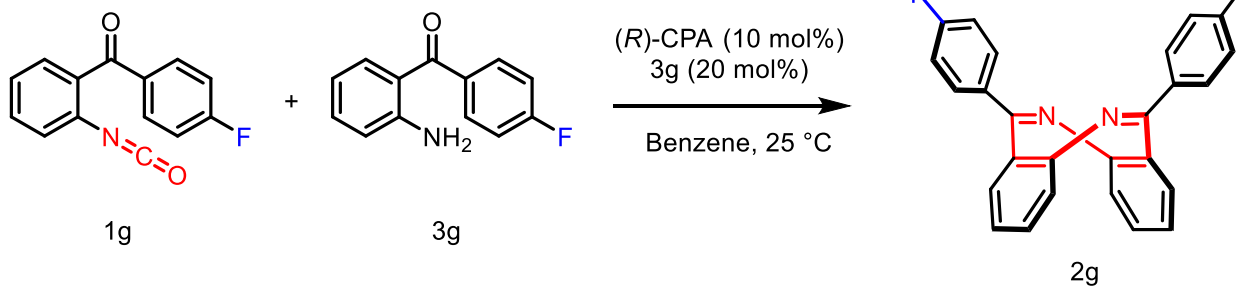
Yang, X.; et al. *Chin. J. Chem.* **2024**, *42*, 1953-1959.

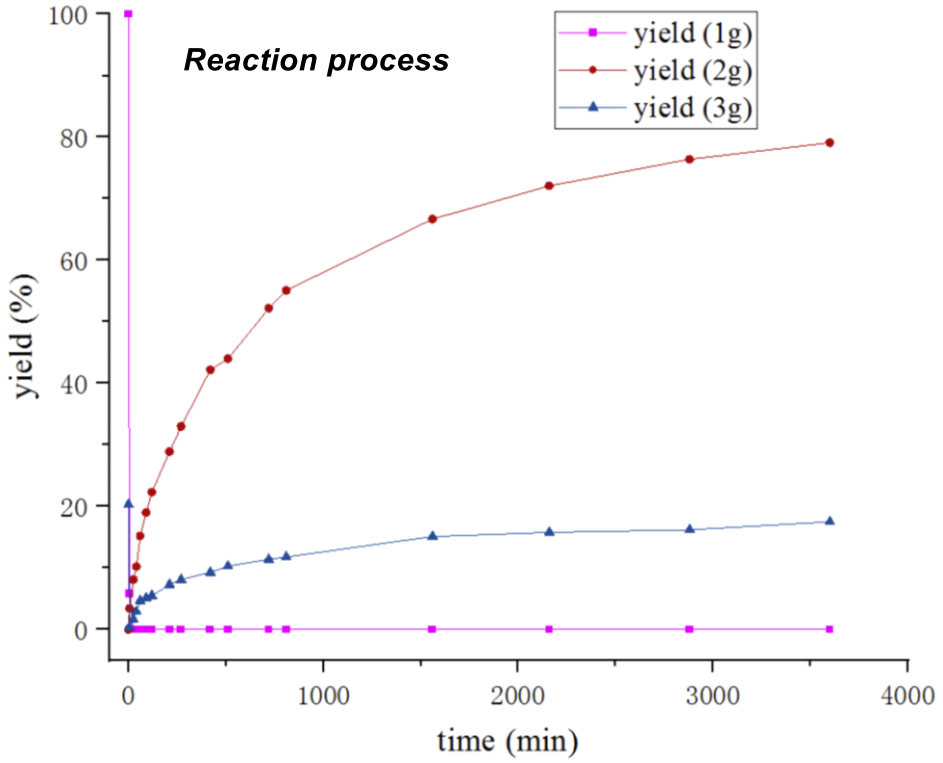
2.1.3 其他策略: 不对称缩合

Cross experiment



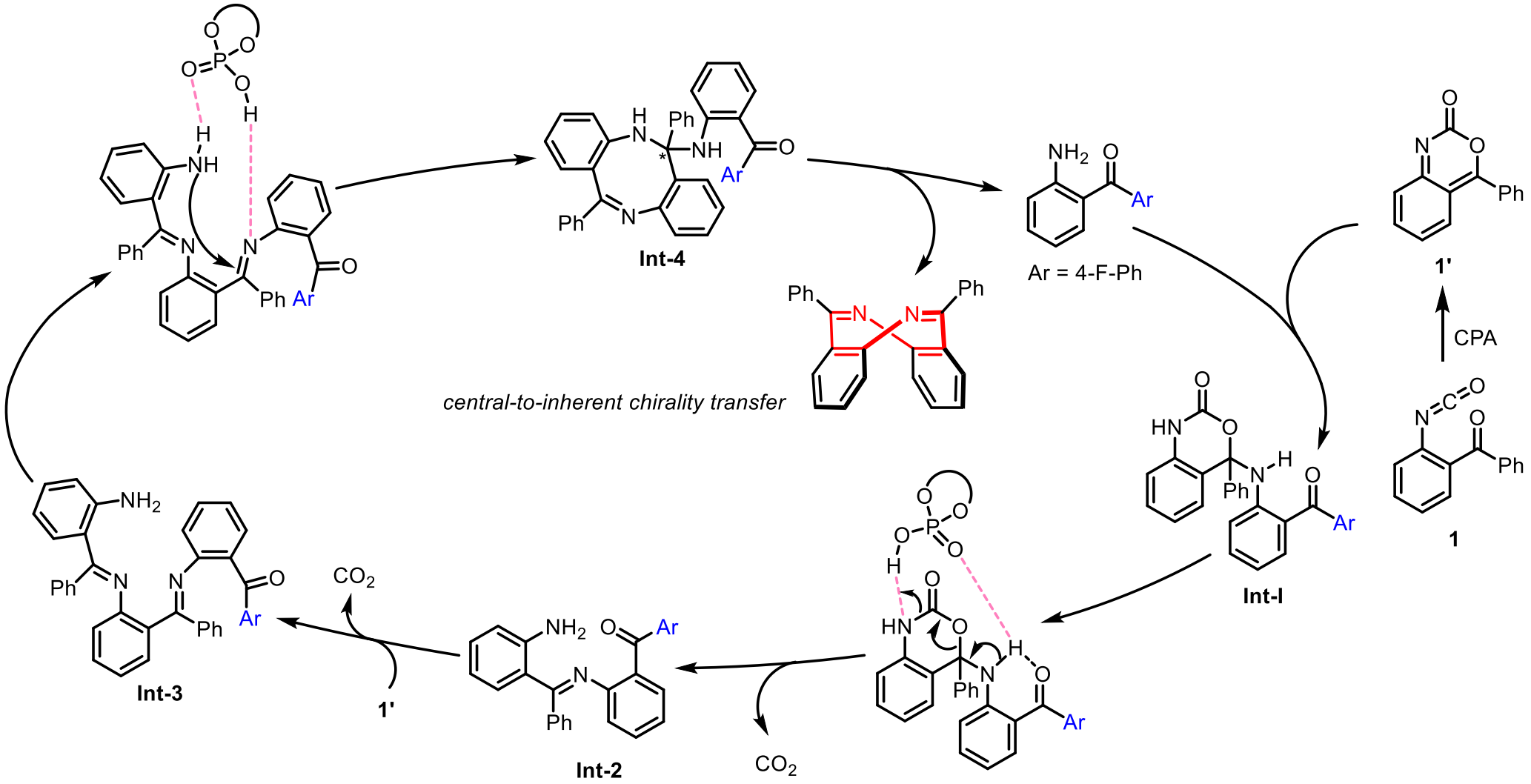
^{19}F-NMR analysis





Yang, X.; et al. *Chin. J. Chem.* **2024**, *42*, 1953-1959.

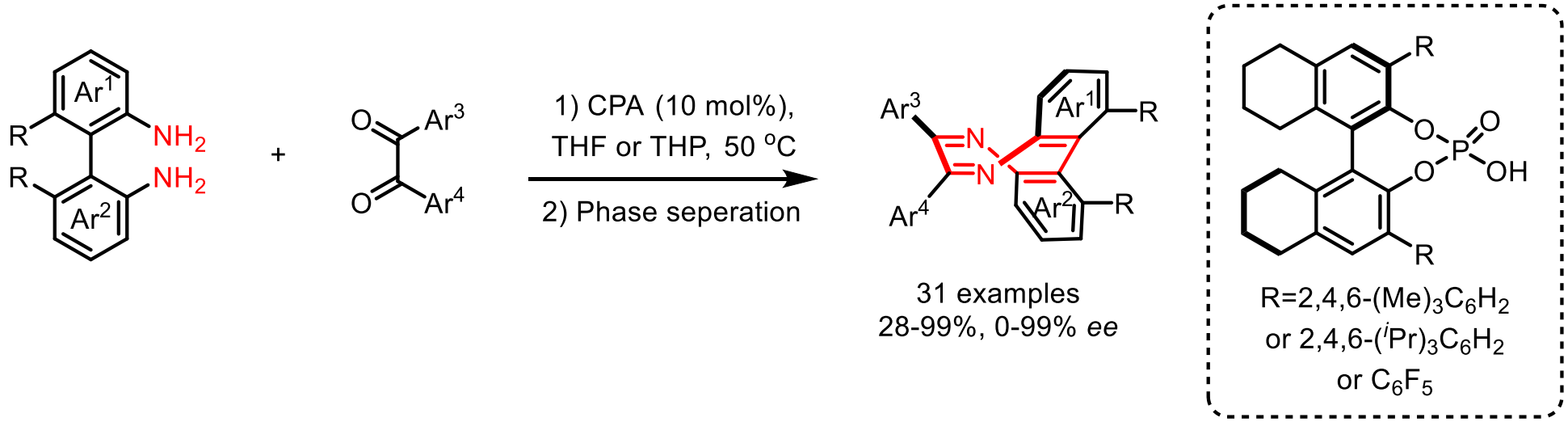
2.1.3 其他策略: 不对称缩合



Yang, X.; et al. *Chin. J. Chem.* **2024**, *42*, 1953-1959.

2.1.3 其他策略: 不对称缩合

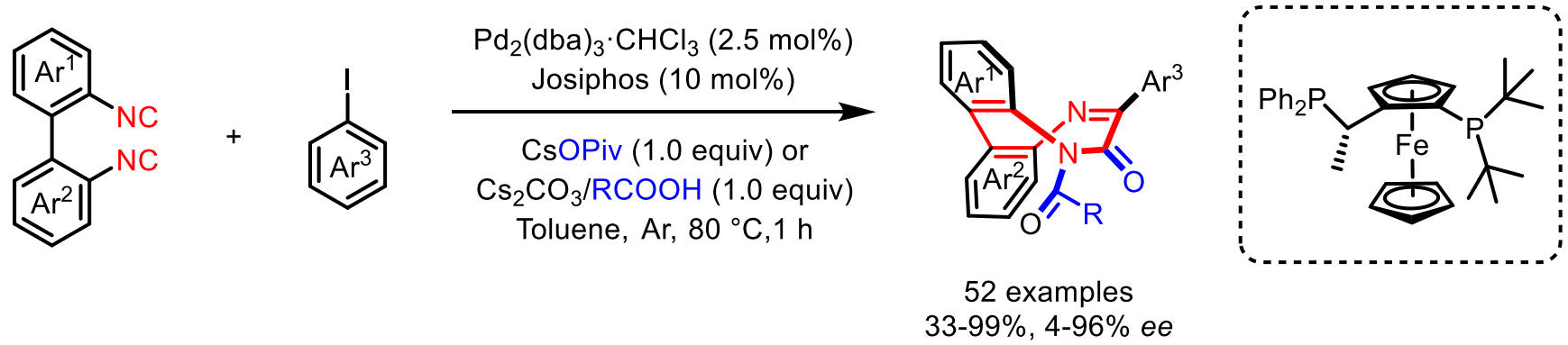
Zhu (2023)



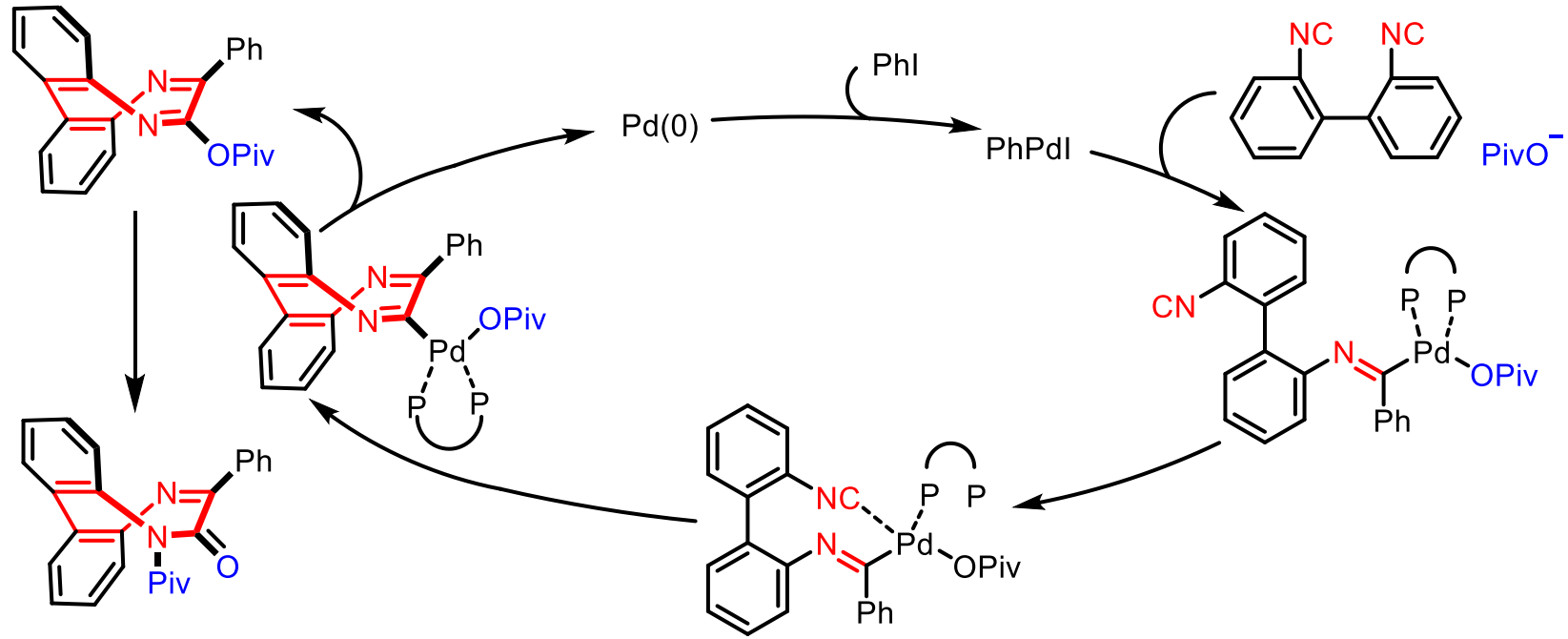
Zhu, Q.; et al. *CCS Chem*. **2023**, *5*, 982–993.

2.1.3 其他策略: 异氰基插入

Zhu (2022)



52 examples
33-99%, 4-96% *ee*

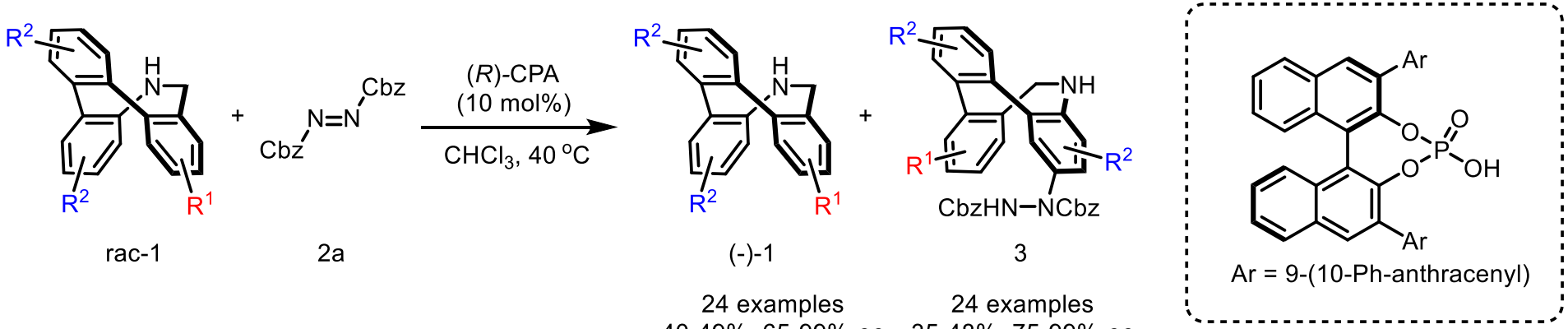


Zhu, Q.; et al. *CCS Chem*. **2022**, *4*, 2897–2905.

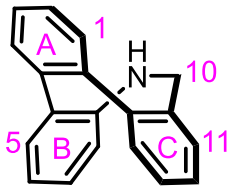
目录

2.2 动力学拆分策略: C-H胺化

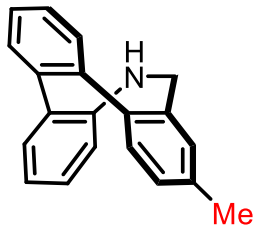
Yang (2024)



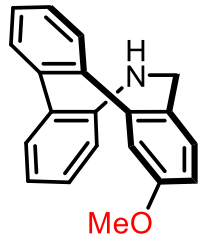
Selected examples



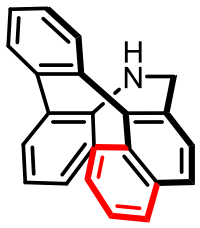
(-)-1a, 47%, 94% *ee*
3a, 46%, 94% *ee*
s=115



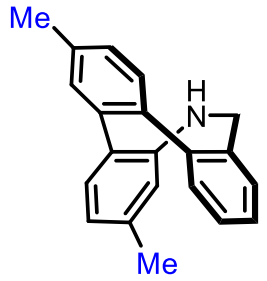
(-)-1b, 47%, 93% *ee*
3b, 46%, 94% *ee*
s=111



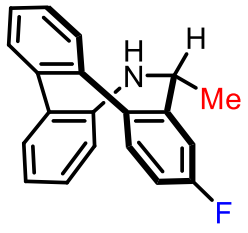
(-)-1j, 43%, 86% *ee*
3j, 40%, 97% *ee*
s=183



(-)-1p, 44%, >99% *ee*
3p, 40%, 97% *ee*
s>348



(-)-1r, 41%, 65% *ee*
3r, 42%, 75% *ee*
s=14



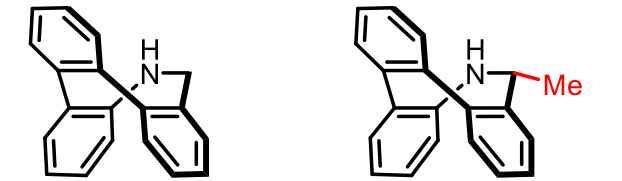
(-)-4b, 48%, 99% *ee*
5b, 47%, 99% *ee*
s=1057

Yang, X.; et al. *Chem Catal.* **2024**, *4*, 100827.

2.2 动力学拆分策略: C-H胺化

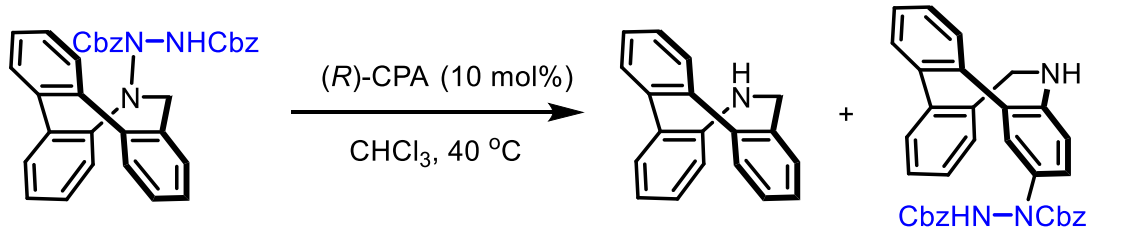
Control experiment

Racemization experiment



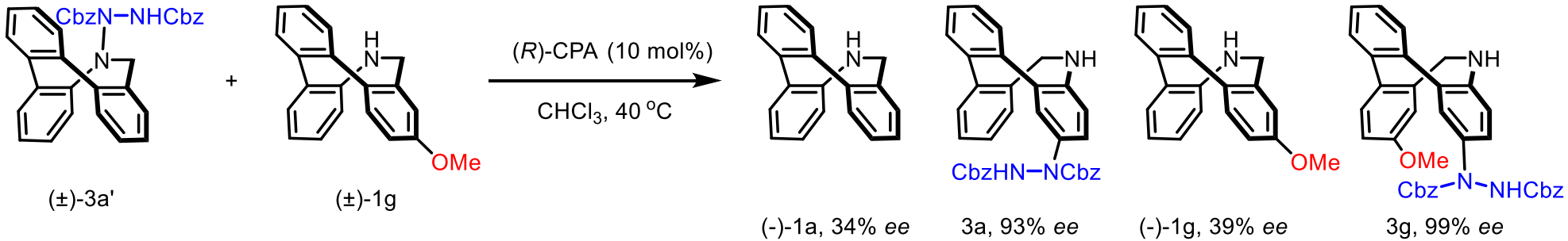
$\Delta G^{\ddagger}$ = 27.3 kcal/mol $\Delta G^{\ddagger}$ = 30.2 kcal/mol

Formal parallel KR process



(±)-3a' (-)-1a, 46%, 97% *ee* 3a, 42%, 94% *ee*

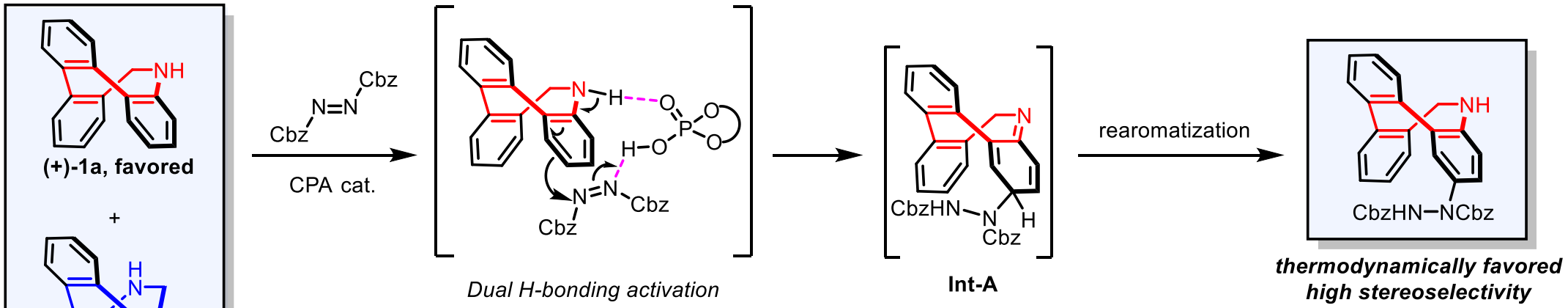
Cross-over experiment

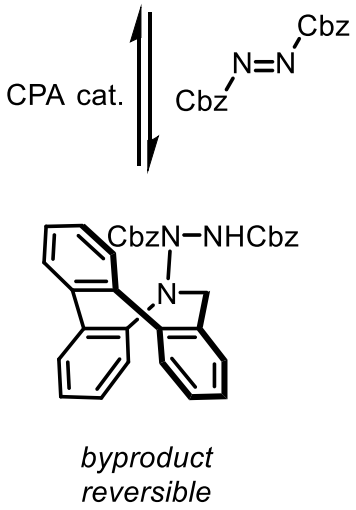


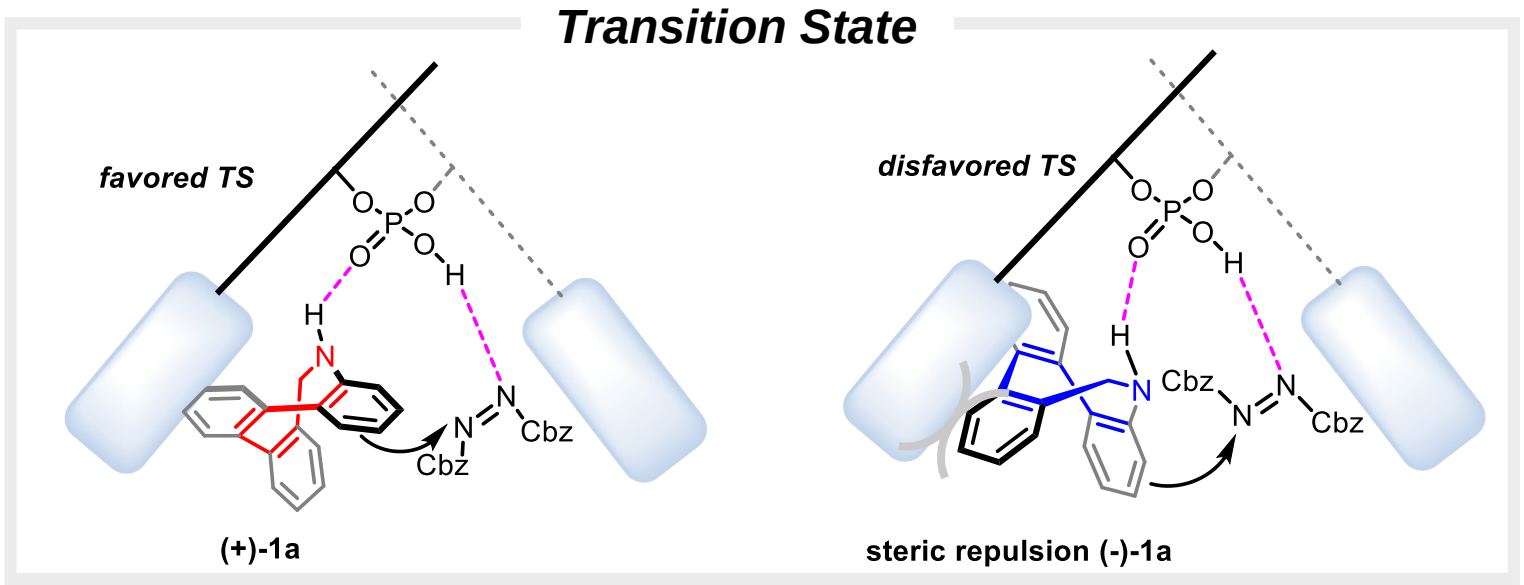
(±)-3a' (±)-1g (-)-1a, 34% *ee* 3a, 93% *ee* (-)-1g, 39% *ee* 3g, 99% *ee*

Yang, X.; et al. *Chem Catal.* **2024**, *4*, 100827.

2.2 动力学拆分策略: C-H胺化

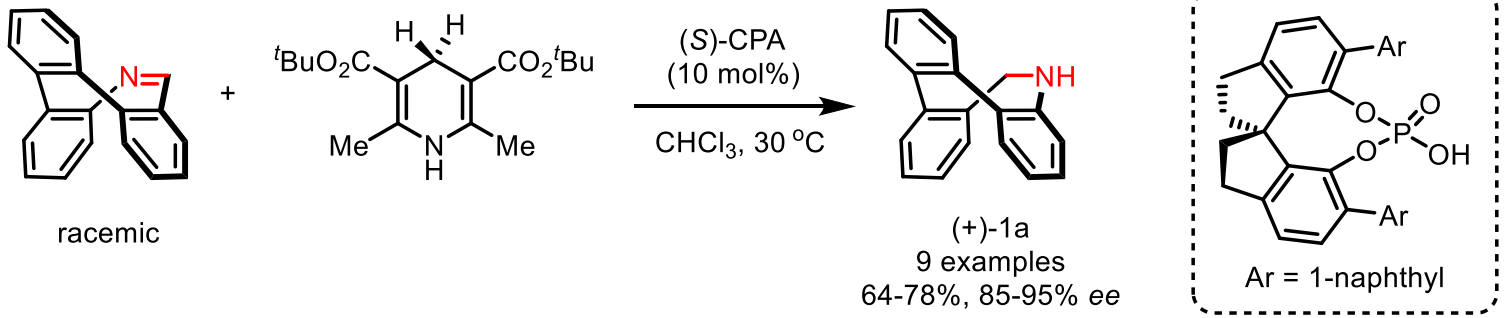




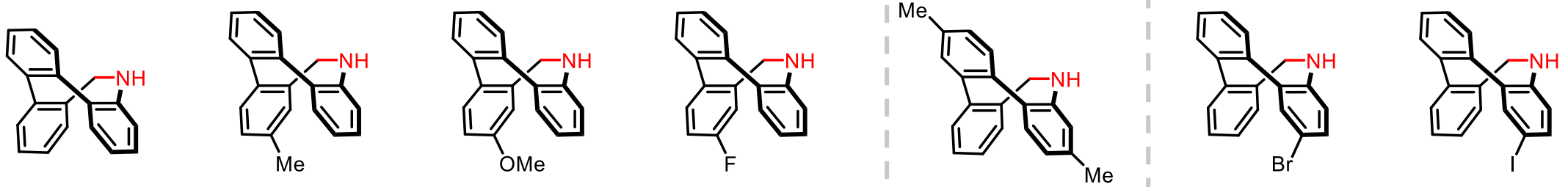


Yang, X.; et al. *Chem Catal.* **2024**, *4*, 100827.

2.2 动态动力学拆分策略: 氢转移反应



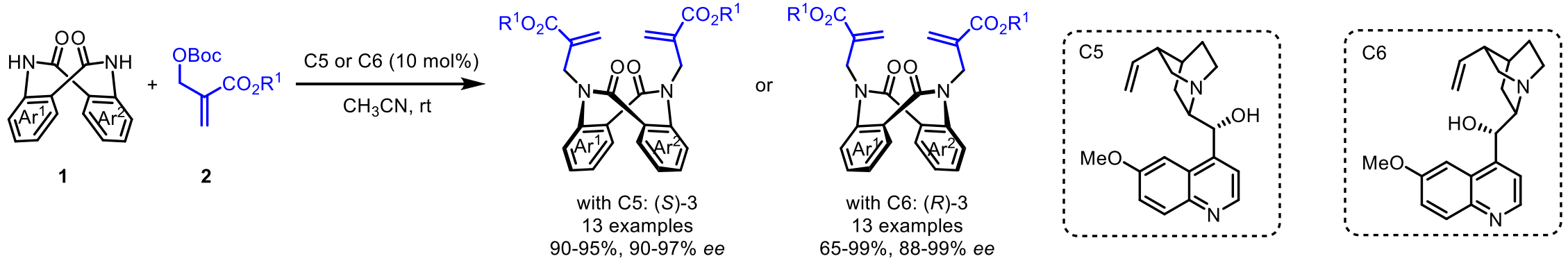
Selected examples



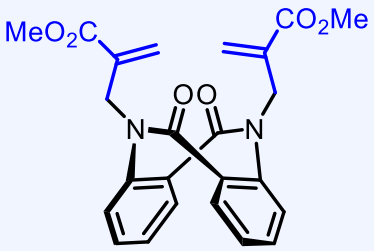
Yang, X.; et al. *Chem Catal.* **2024**, *4*, 100827.

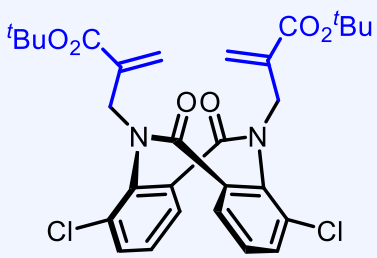
2.2 动态动力学拆分策略: 双烷基化

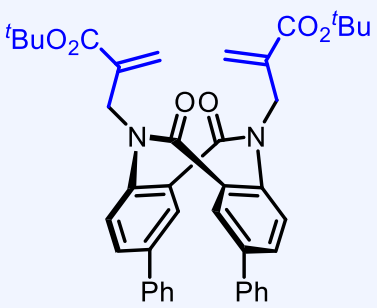
Mei (2024)

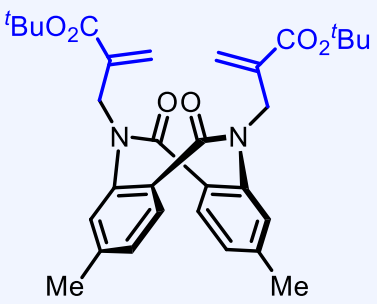


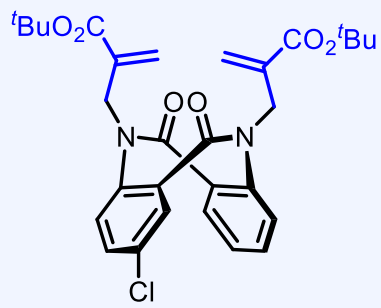
Selected examples


90%, 97% *ee*


92%, 92% *ee*


93%, 95% *ee*

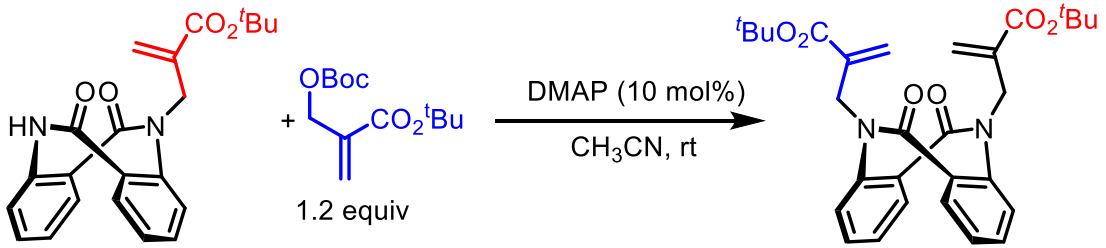

99%, 99% *ee*


89%, 96% *ee*

Mei, G.; et al. *Nat. Commun.* **2024**, *15*, 4580.

2.2 动态动力学拆分策略: 双烷基化

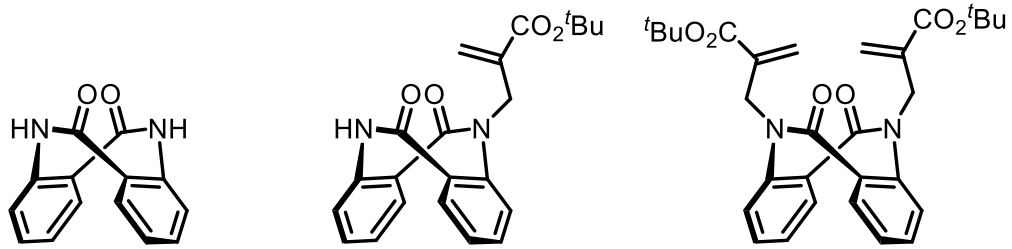
Ee maintenance experiment



(*S*)-1a'
99% *ee*

(*S*)-3a
95%, 99% *ee*

Racemization experiment

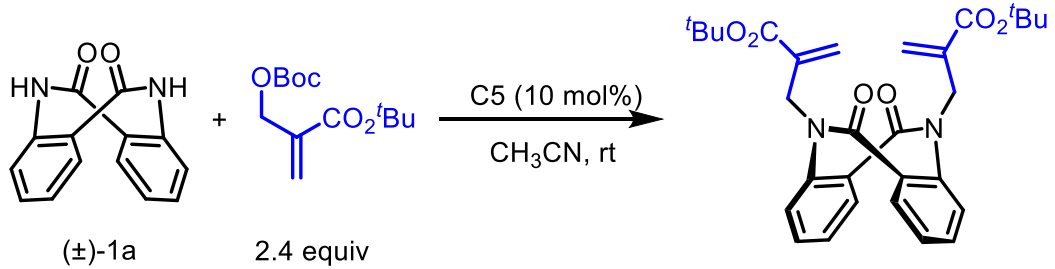


1a
$\Delta G^{\ddagger}$ = 23.3 kcal/mol
at 30 °C in acetonitrile

1a'
$\Delta G^{\ddagger}$ = 28.2 kcal/mol
at 80 °C in acetonitrile

3a
$\Delta G^{\ddagger}$ = 32.6 kcal/mol
at 125 °C in xylene

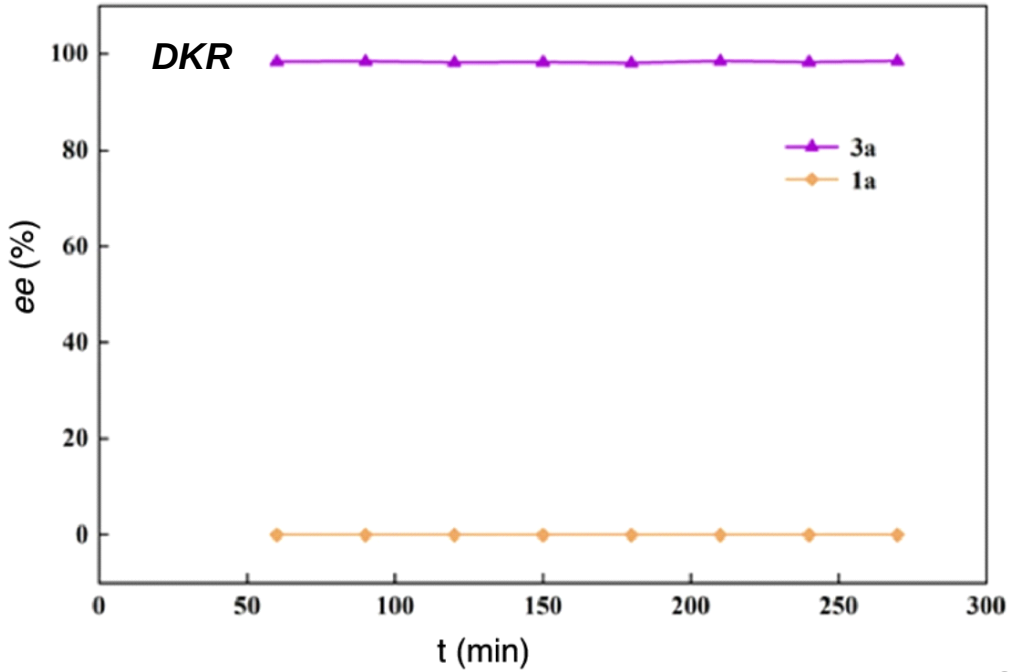
Kinetic experiment



(±)-1a

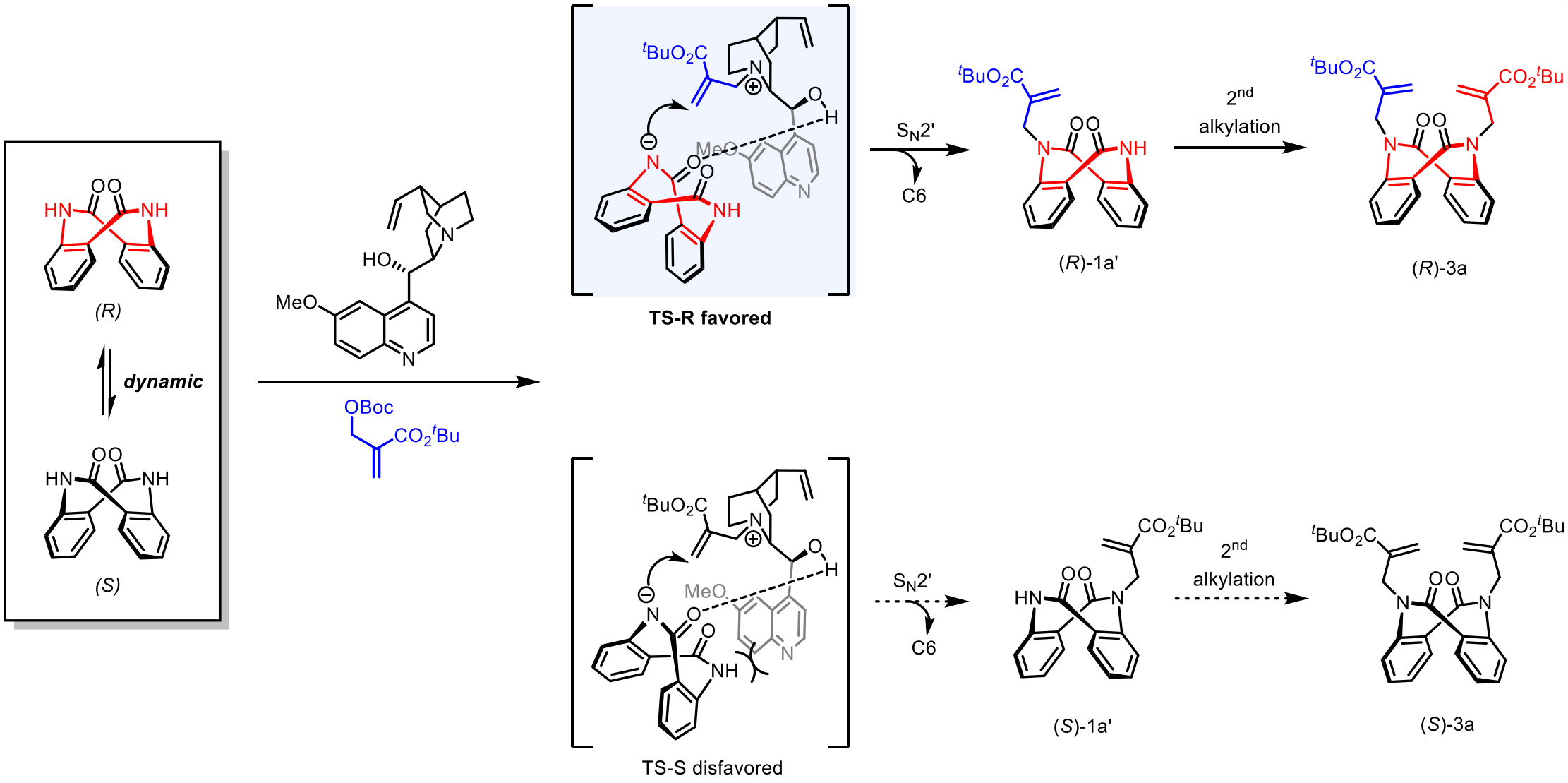
2.4 equiv

(*S*)-3a
95%, 98% *ee*



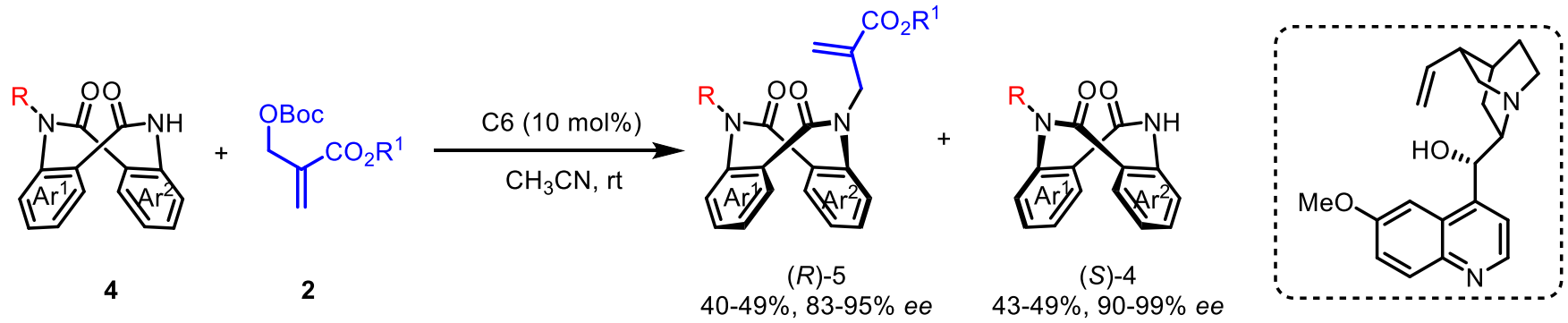
Mei, G.; et al. *Nat. Commun.* **2024**, *15*, 4580.

2.2 动态动力学拆分策略: 双烷基化



Mei, G.; et al. *Nat. Commun.* **2024**, *15*, 4580.

2.2 动力学拆分策略: 单烷基化

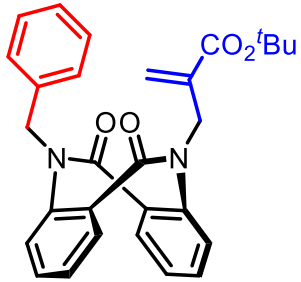


4 **2**

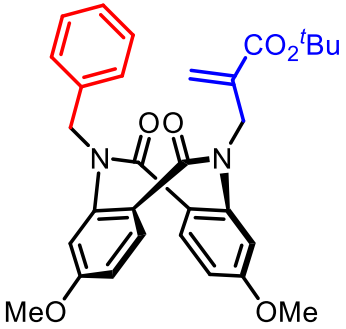
(*R*)-5
40-49%, 83-95% *ee*

(*S*)-4
43-49%, 90-99% *ee*

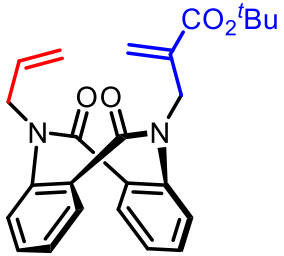
Selected examples



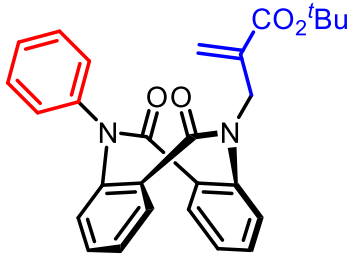
5: 46% yield, 91% *ee*
4: 47% yield, 99% *ee*
s=111



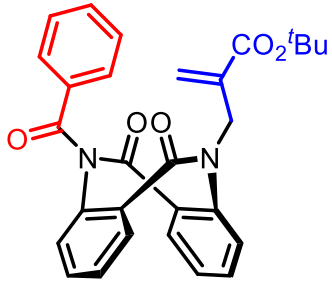
5: 49% yield, 90% *ee*
4: 46% yield, 90% *ee*
s=58



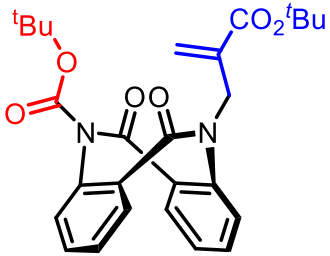
5: 46% yield, 90% *ee*
4: 48% yield, 95% *ee*
s=70



5: 49% yield, 90% *ee*
4: 43% yield, 97% *ee*
s=80



5: 88% yield, 87% *ee*
DKR

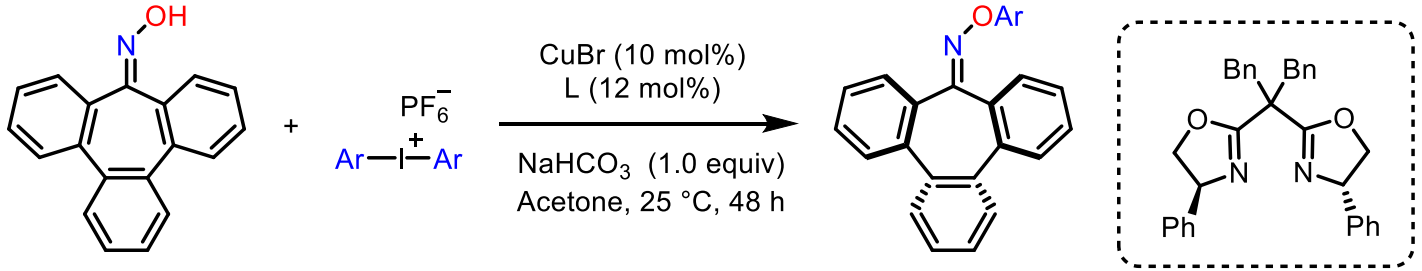


5: 90% yield, 93% *ee*
DKR

Mei, G.; et al. *Nat. Commun.* **2024**, *15*, 4580.

2.2 动态动力学拆分策略: C-O偶联

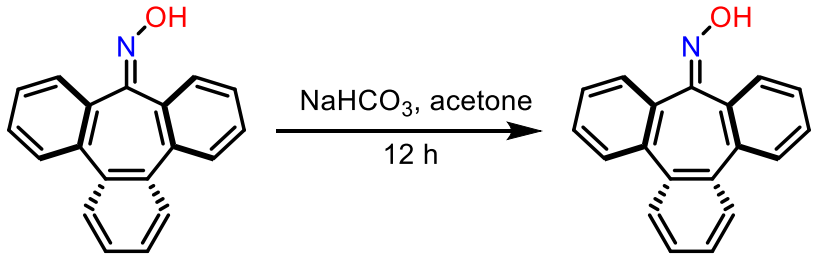
Liu (2025)



$\Delta G^{\ddagger}$ = 27.7 kcal/mol

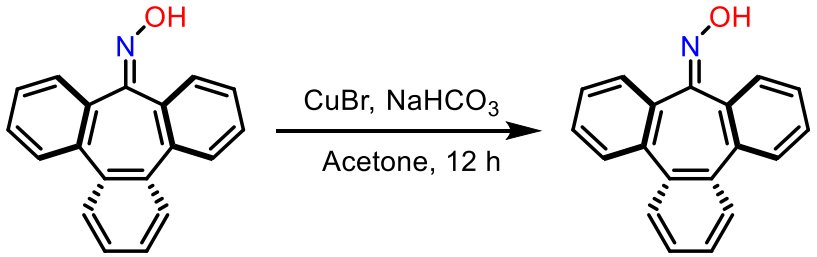
42 examples
35-90%, 40-99% *ee*

Control experiment



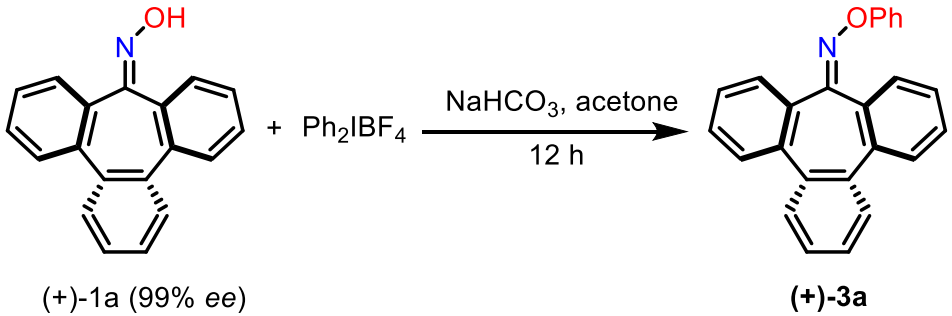
(+)-1a (99% *ee*)

61% ee



(+)-1a (99% *ee*)

5% ee



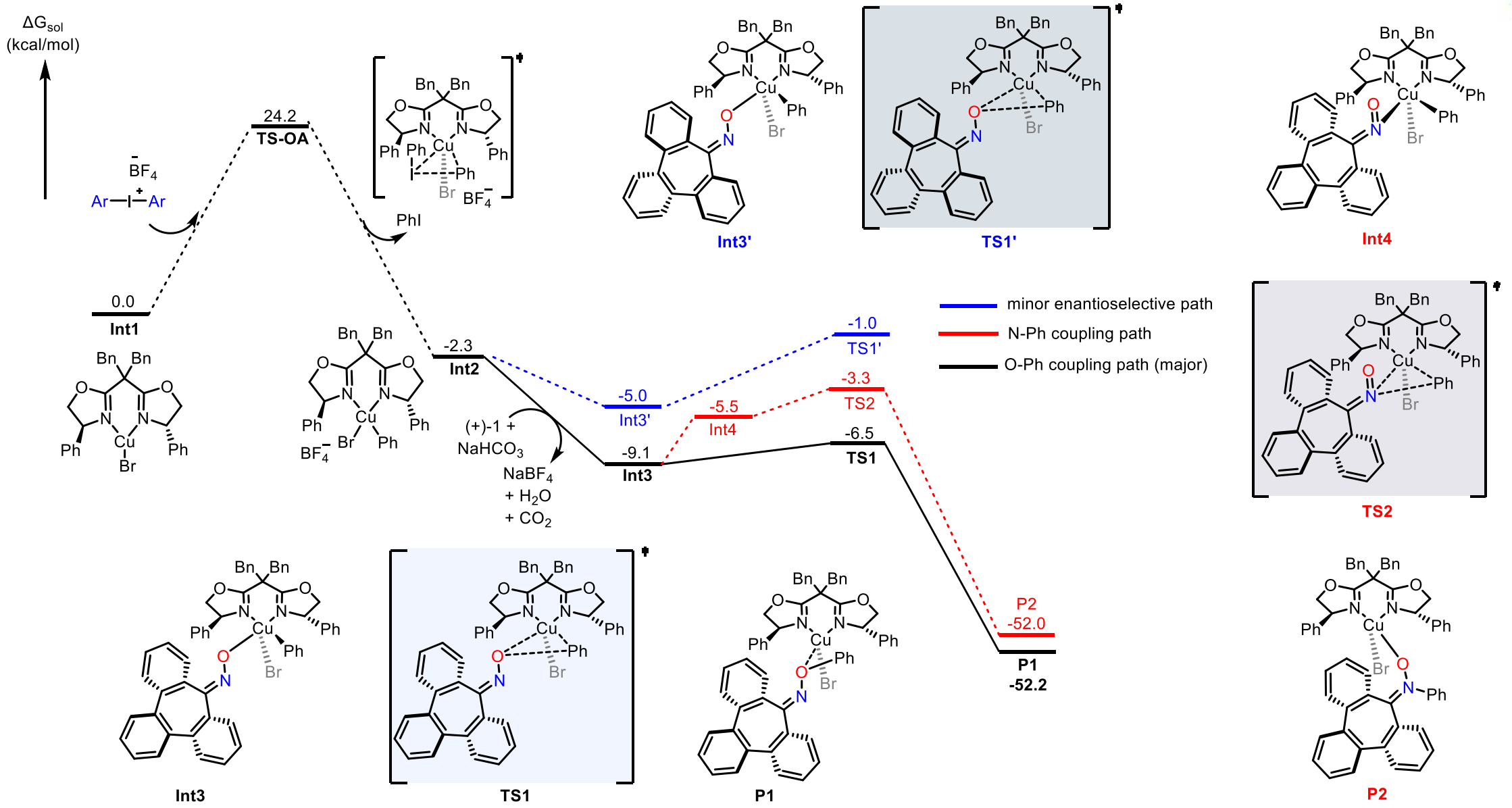
(+)-1a (99% *ee*)

(+)-3a

Entry	L	yield/3a	*ee*/3a
1	without L	60%	66%
2	(*S, S*)-L5	65%	96%
3	(*R, R*)-L5	64%	-80%

Liu, R.; et al. *Nat. Commun.* **2025**, *16*, 2505.

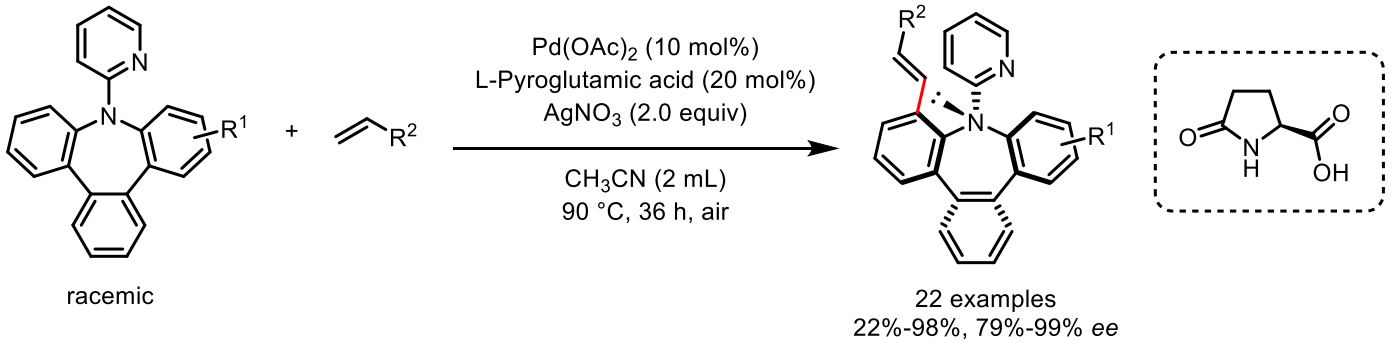
2.2 动态动力学拆分策略: C-O偶联



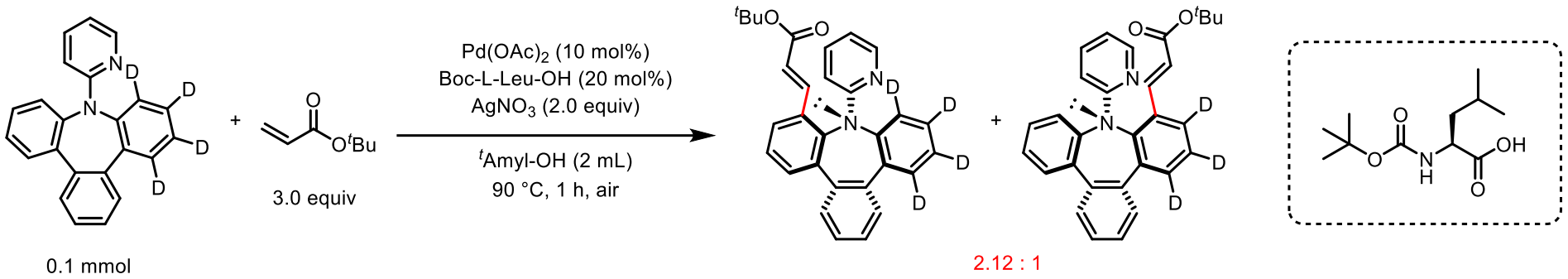
Liu, R.; et al. *Nat. Commun.* **2025**, *16*, 2505.

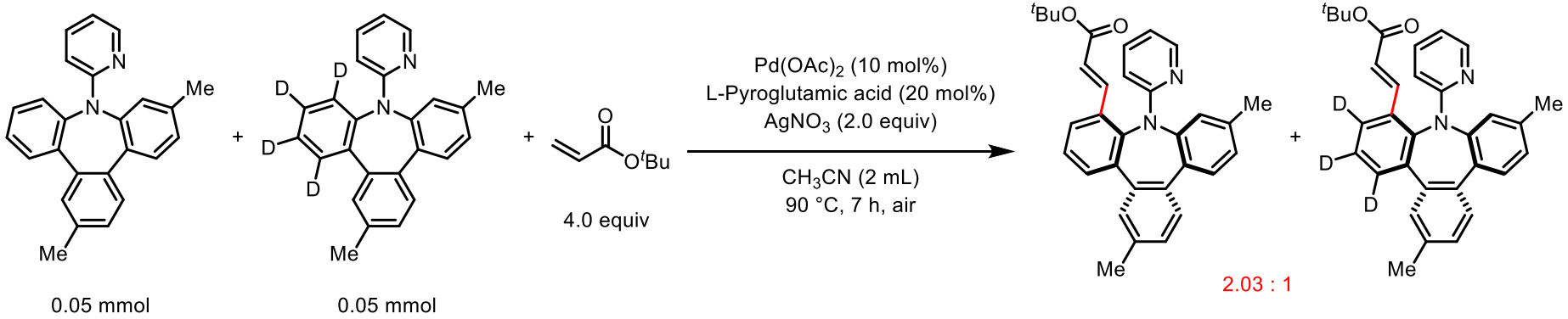
2.2 动态动力学拆分策略: C-H活化

Zhang (2025)



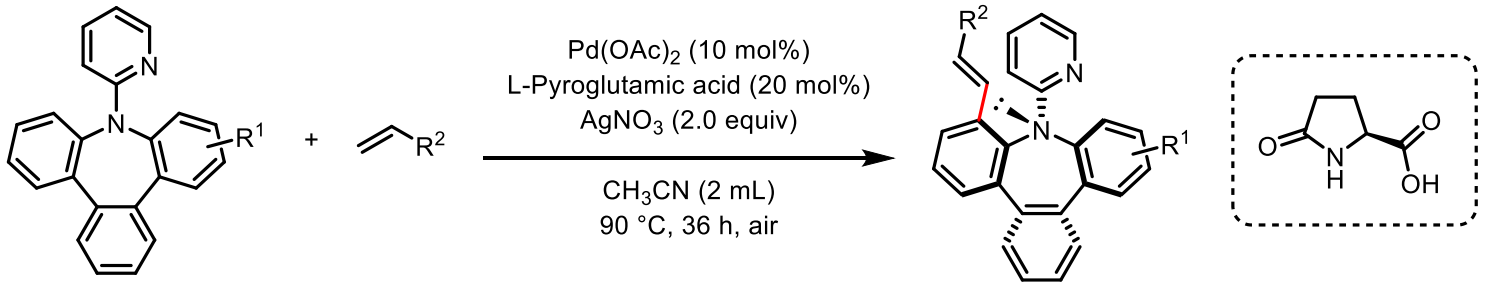
Kinetic isotope effect experiments



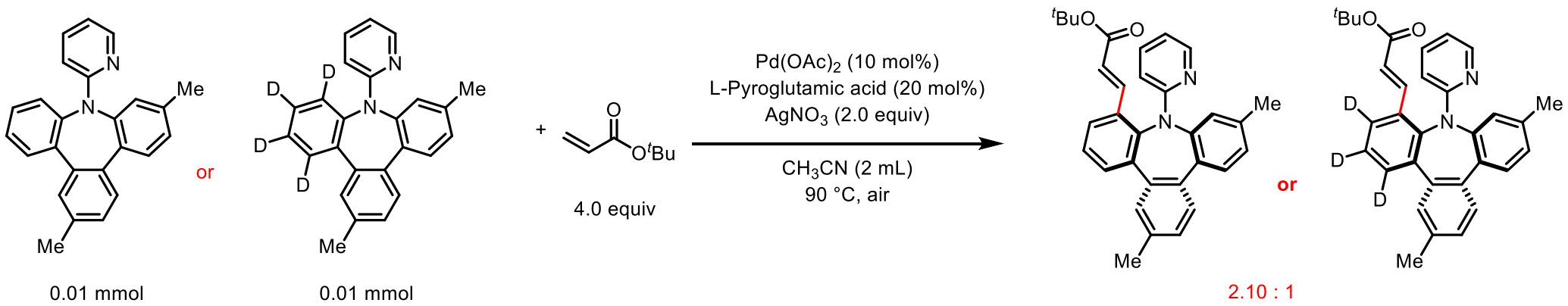


Zhang, Y.; et al. *Chem*, **2025**, 102730.

2.2 动态动力学拆分策略: C-H活化



Kinetic isotope effect experiments



Zhang, Y.; et al. *Chem*, **2025**, 102730.

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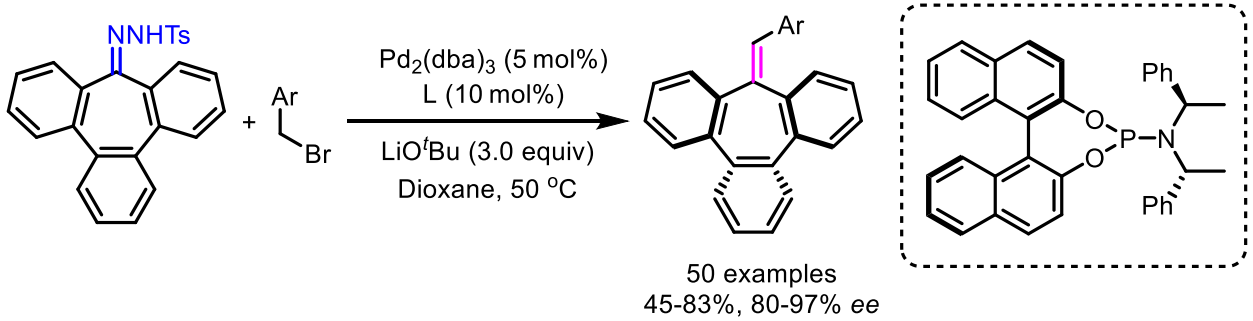
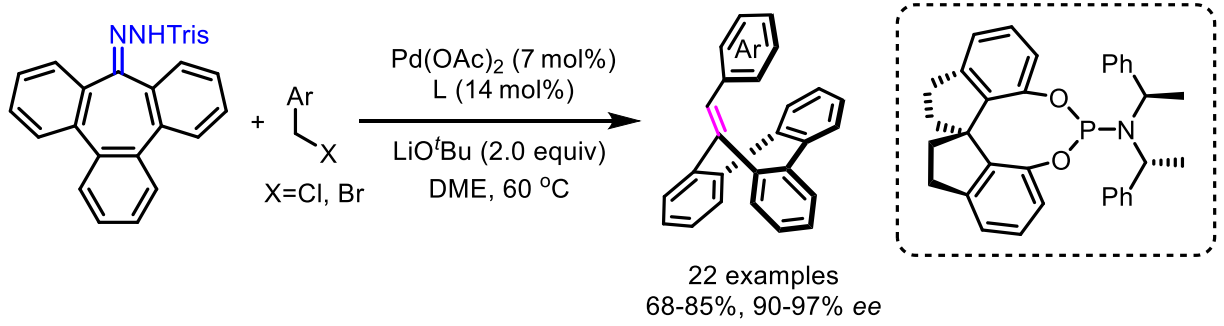
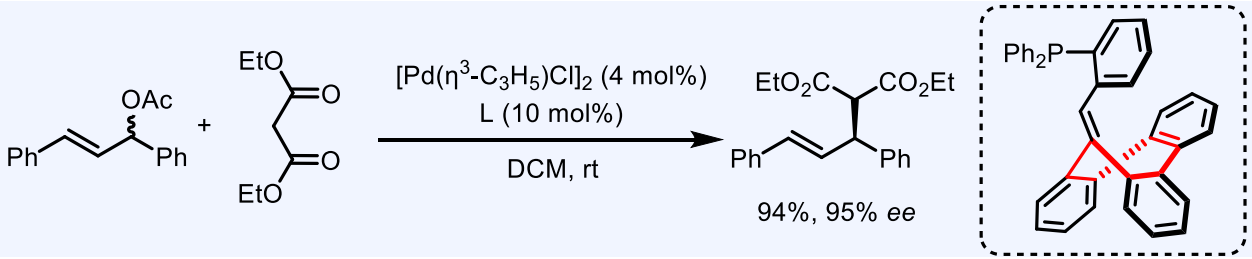
2.3 去对称化策略

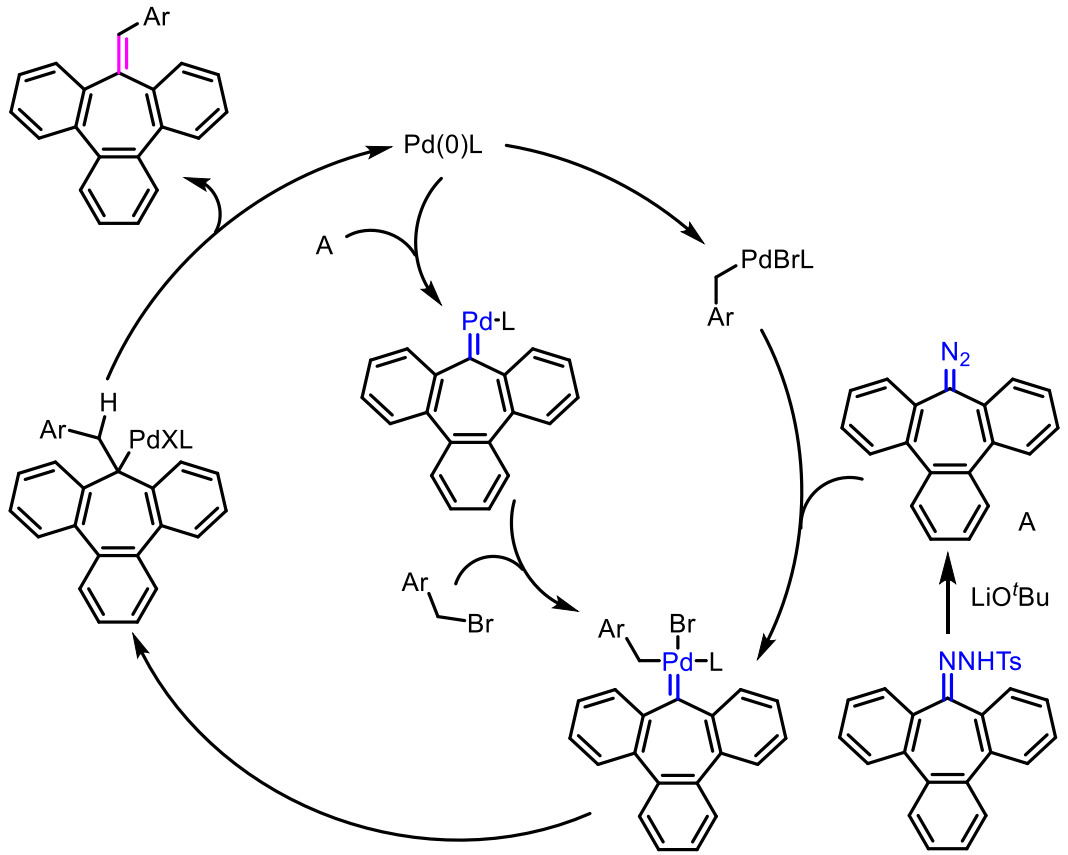
Liu (2024)



Zhu (2024)



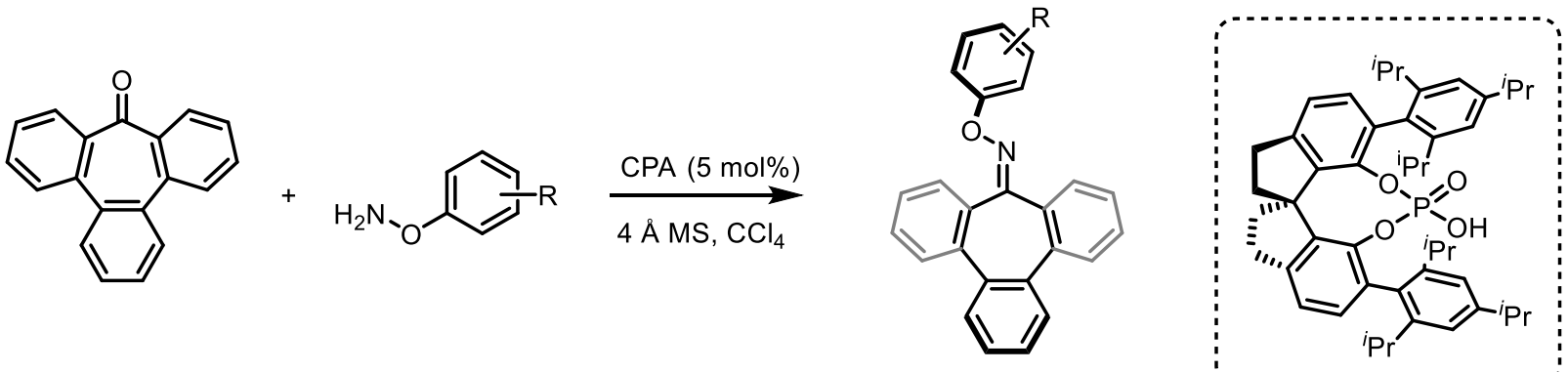




Liu, R.; et al. *Nat. Commun.* **2024**, *15*, 3353.
Zhu, Q.; et al. *Chem Catal.* **2024**, *4*, 100904.

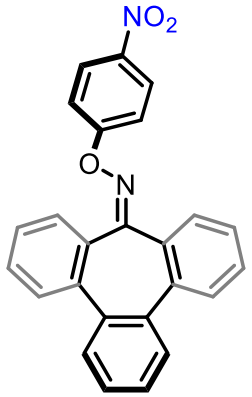
2.3 去对称化策略

Liu (2024)

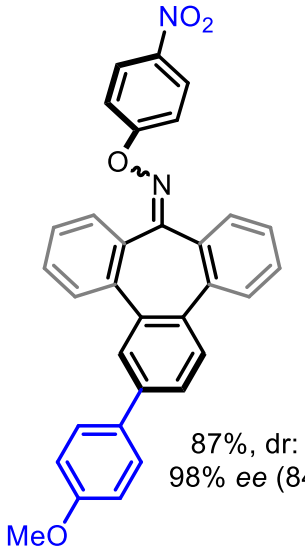


40 examples
33-97%, 64-99% *ee*

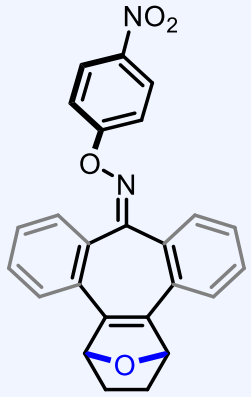
Selected examples



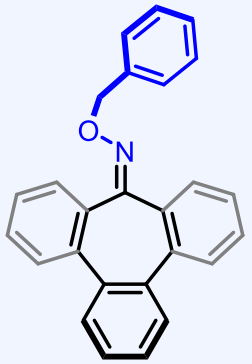
87%, 96% *ee*



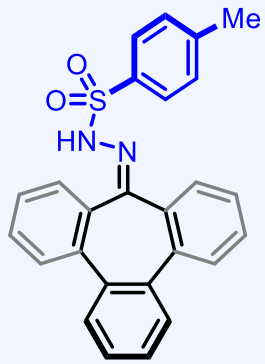
87%, dr: 3.4:1
98% *ee* (84% *ee*)



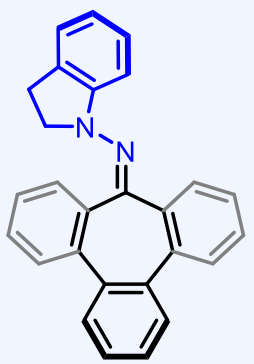
58%, 81% *ee*



80%, 64% *ee*



76%, 75% *ee*



38%, 73% *ee*

Liu, R.; et al. *Angew. Chem., Int. Ed.* **2024**, *63*, e202319289.

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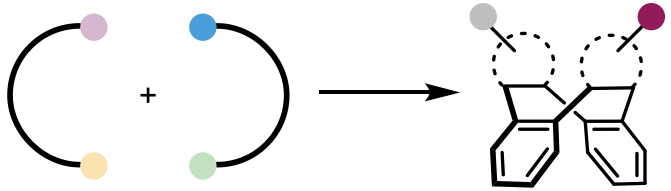
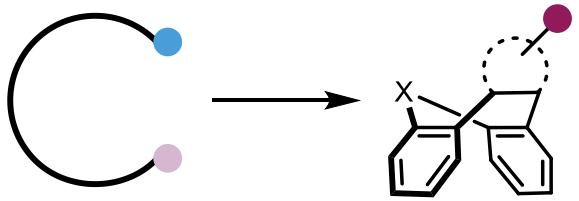
总结

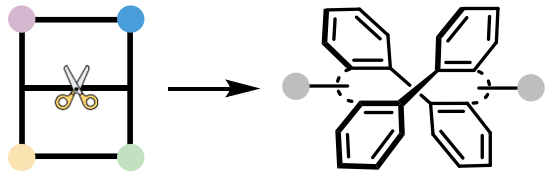
Cycloaddition

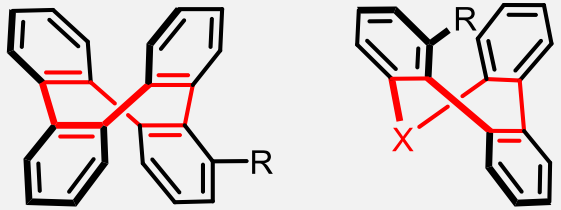


Intramolecular Cyclization



Ring Extension



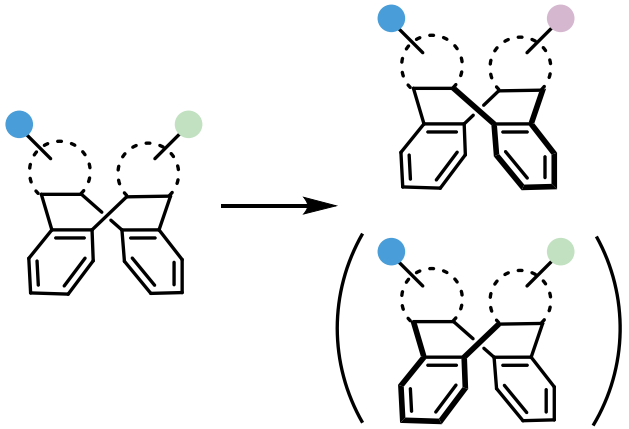


X = heteroatom

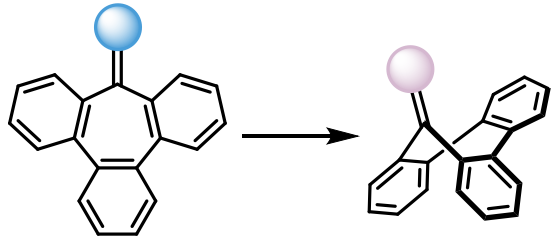
Saddle-shaped scaffolds

Develop new strategies

(Dynamic) Kinetic Resolution



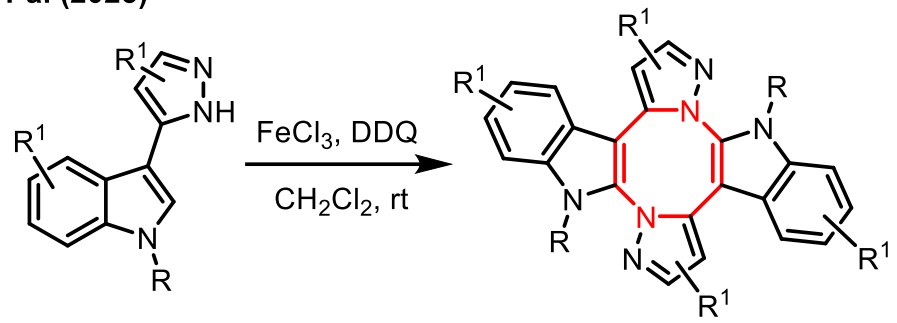
Desymmetrization



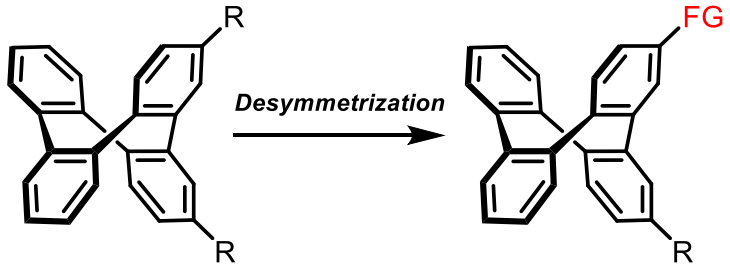
展望

Radical Pathway…

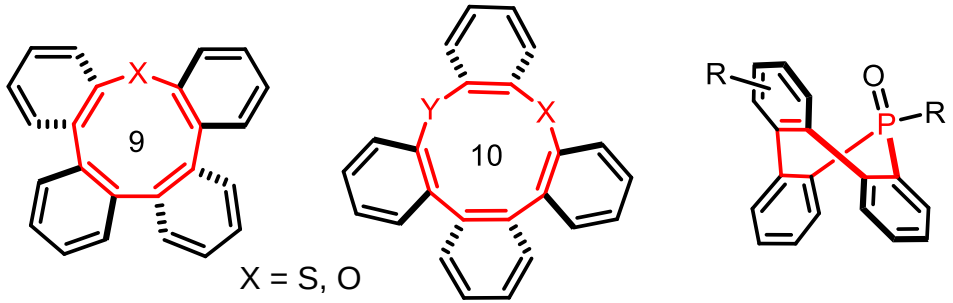
Pal (2025)



More Substrates

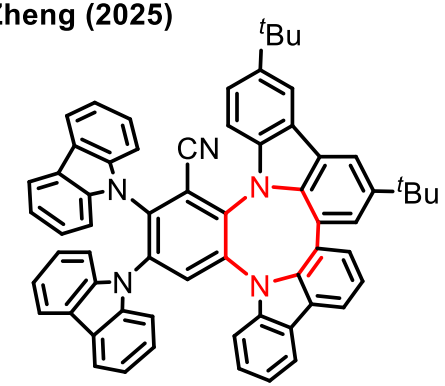


9/10-Membered Ring and Heterocycles



CP-TADF Materials

Zheng (2025)



M8PN

EQE_{max} = 10.5%

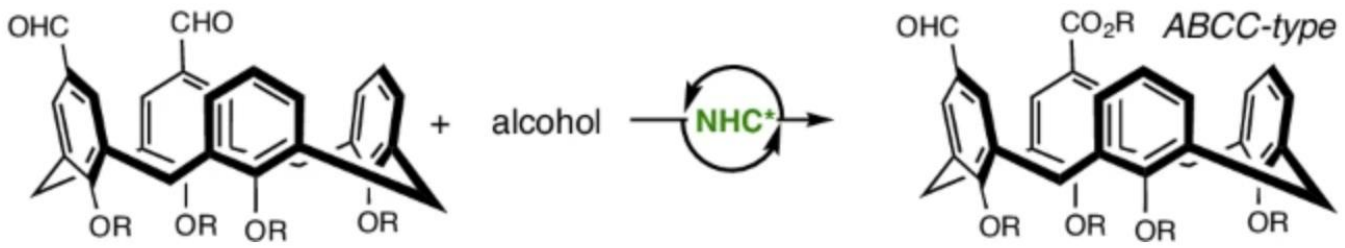
$|g|$ up to 7.0×10^{-3}

谢谢大家！

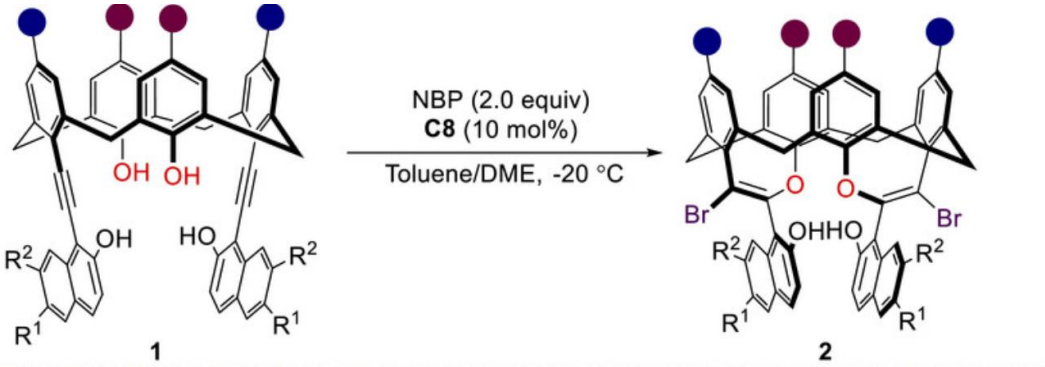
敬请批评指正！

附录: 手性杯芳烃骨架合成

Veselý (2025): NHC catalyzed desymmetric esterification to access inherently chiral calix[4]arenes with an ABCC substitution pattern

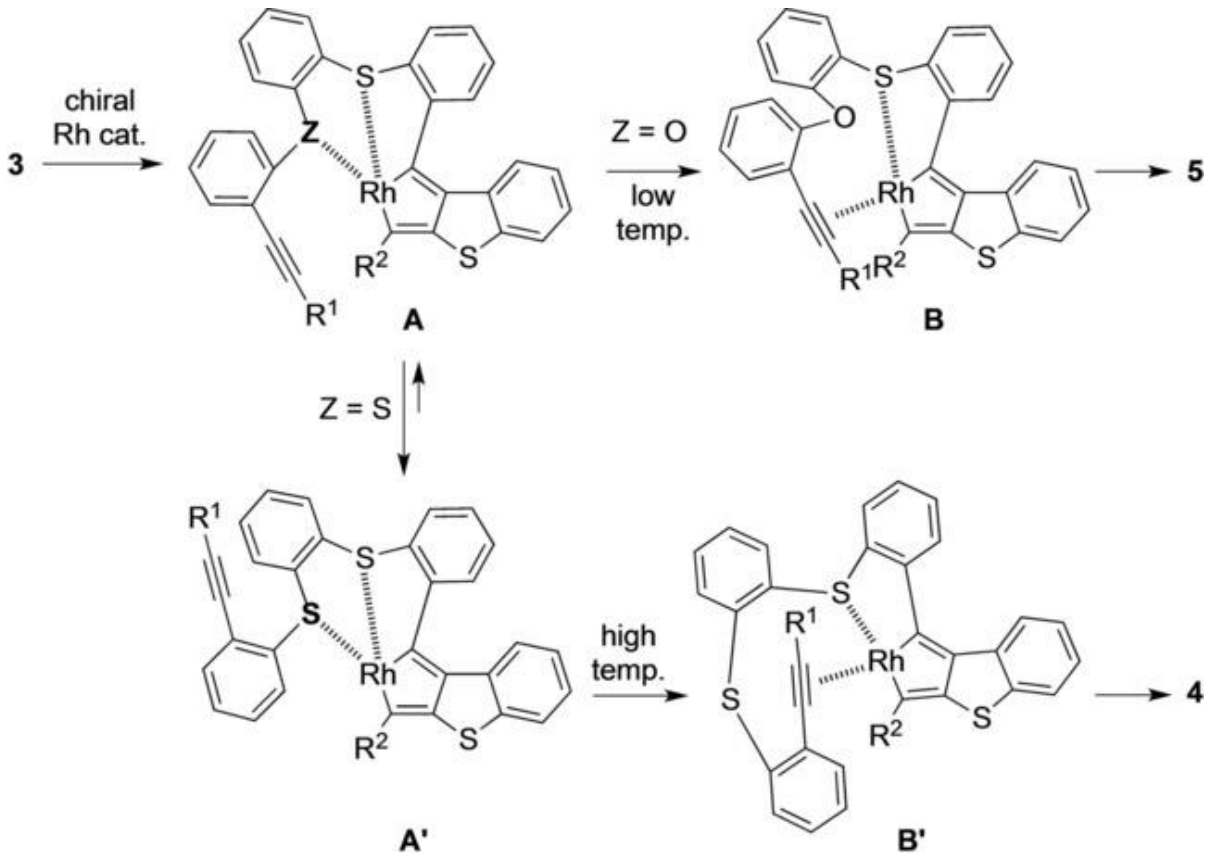


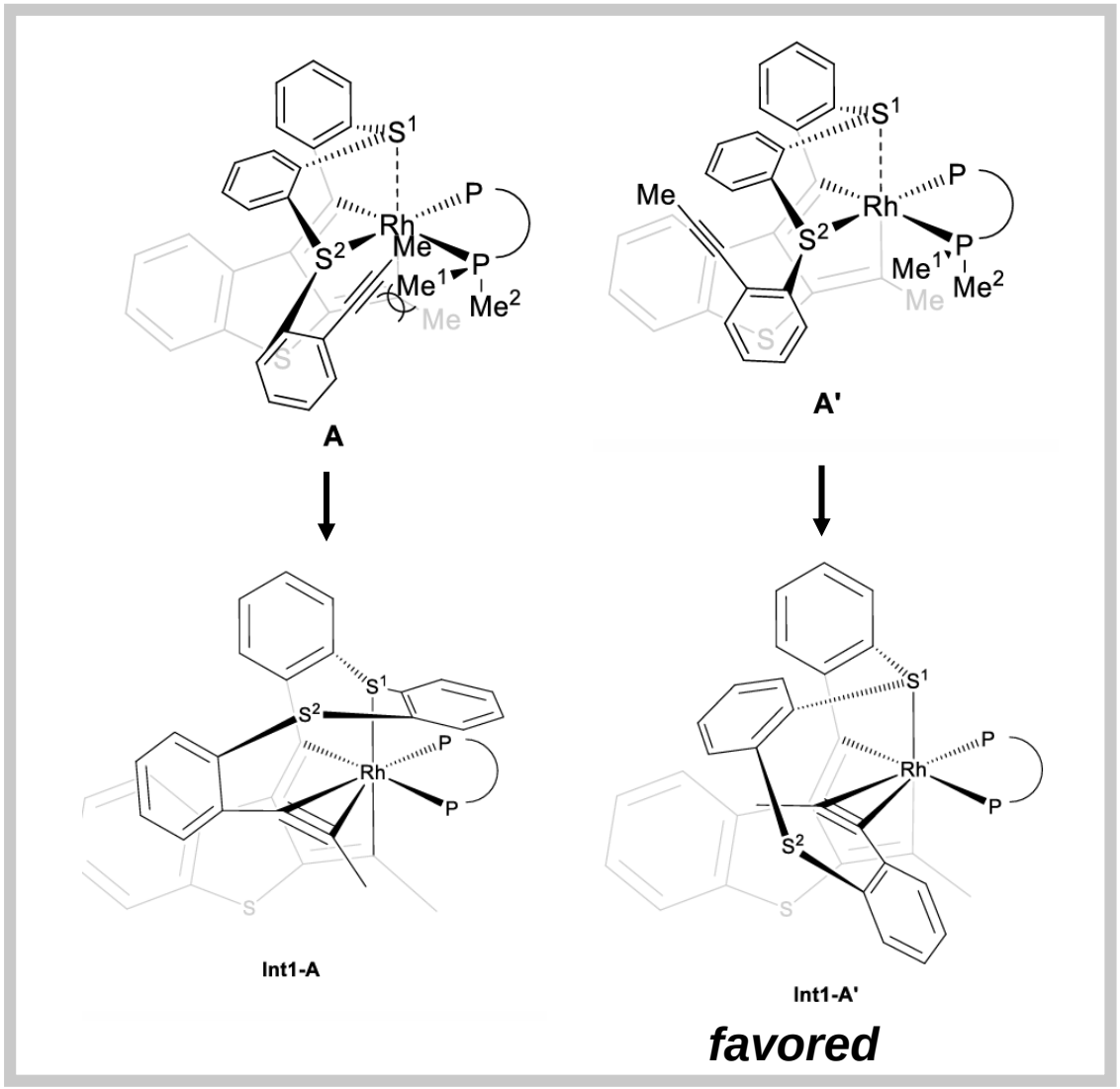
Yan (2025): Asymmetric lower-rim functionalization



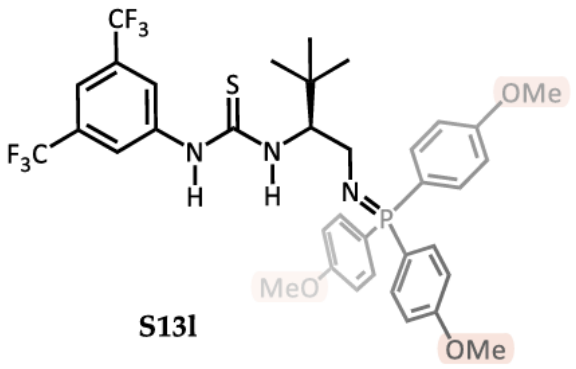
Veselý, J.; et al. *Nat. Commun.* **2025**, *16*, 4443.
Yan, H. et al. *Angew. Chem. Int. Ed.* **2025**, e202518659.

附录: P16

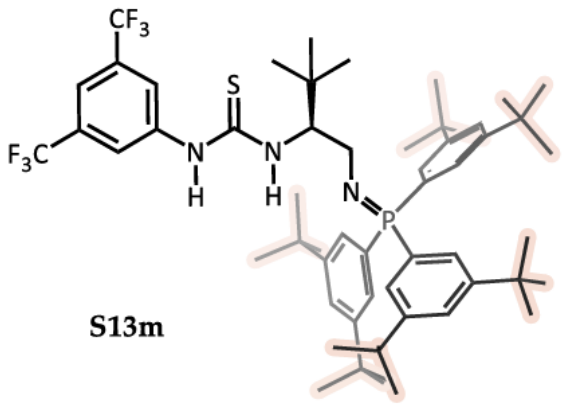

chiral
Rh cat.
3
Z = O
low
temp.
5
A
B
Z = S
high
temp.
4
A'
B'


A
A'
Int1-A
Int1-A'
favored

附录: P27, 29



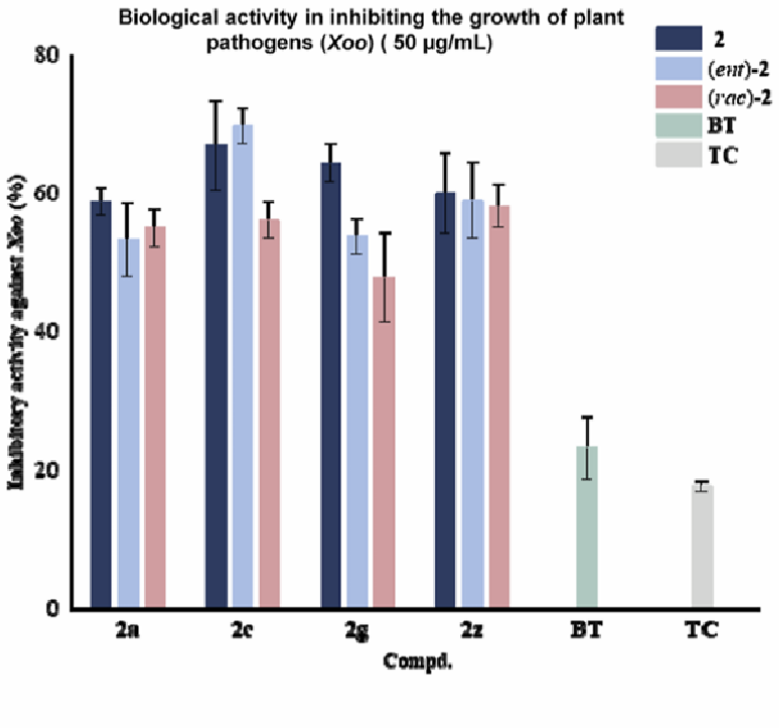
S13l

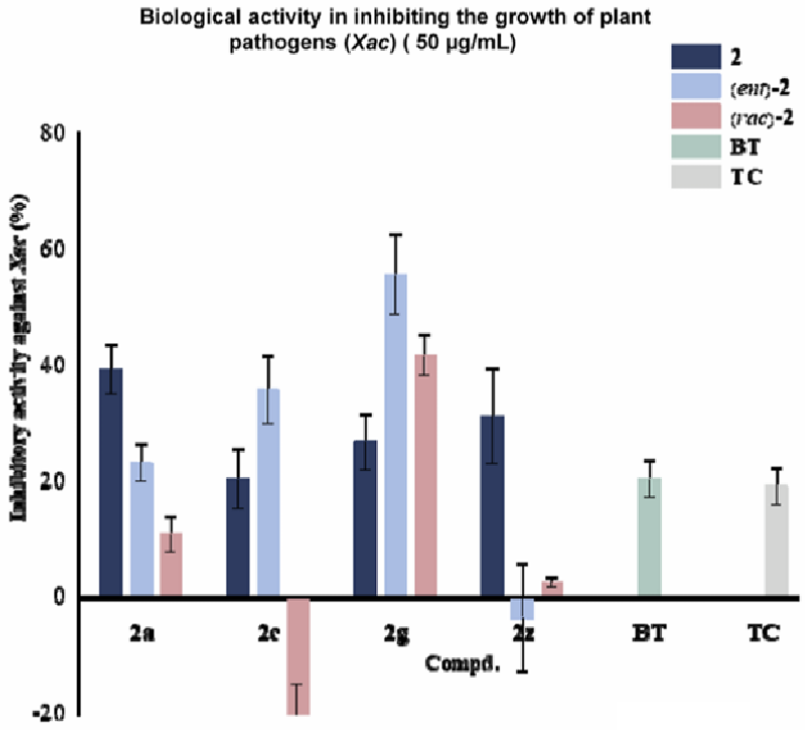


S13m

2a: 96% conv., **80:20** er

2a: 57% conv., **90:10** er





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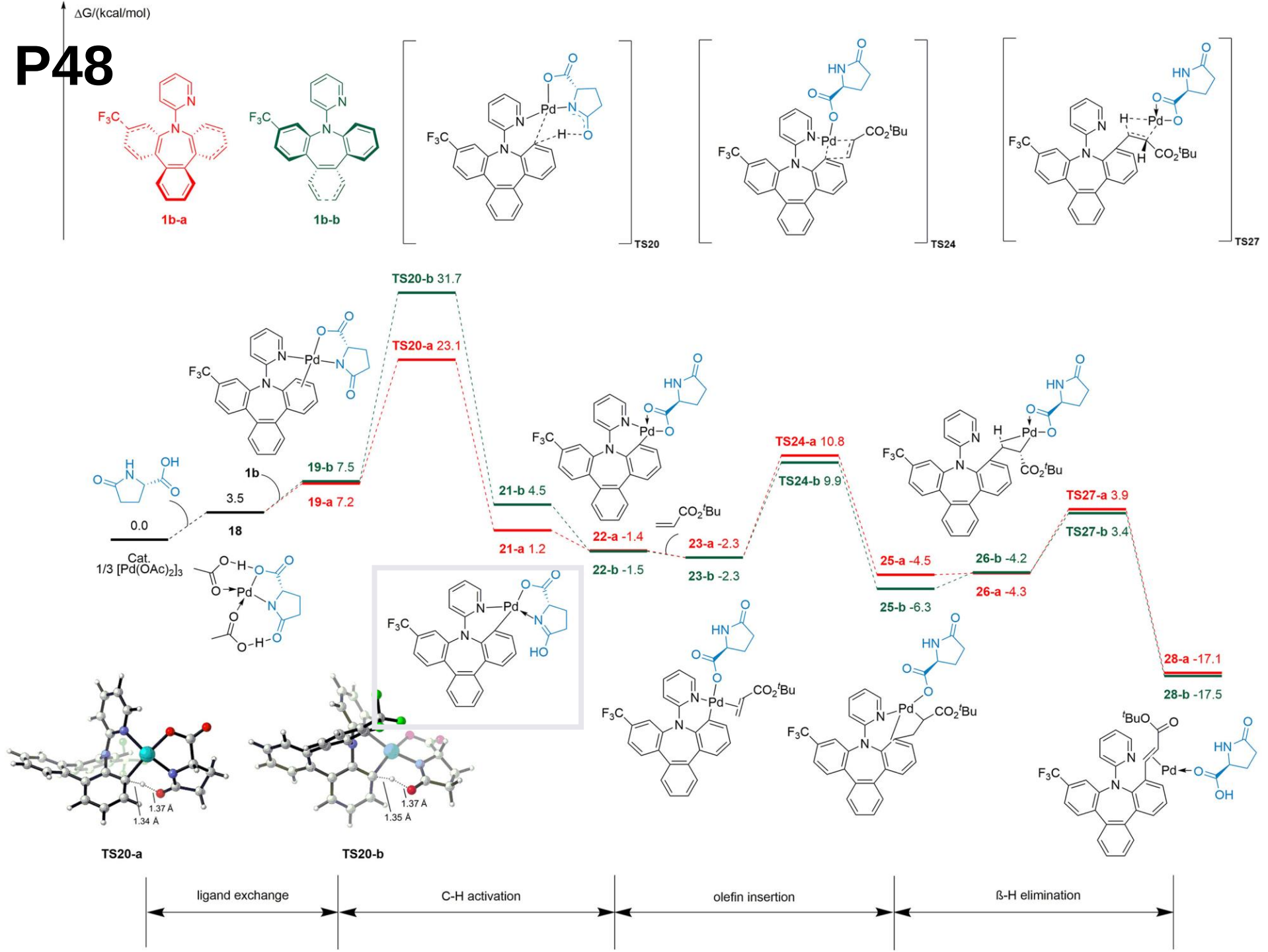
ΔG/(kcal/mol)
1b-a
1b-b
TS20
TS24
TS27
TS20-b 31.7
TS20-a 23.1
19-b 7.5
19-a 7.2
1b
3.5
18
0.0
Cat.
1/3 [Pd(OAc)2]3
21-b 4.5
21-a 1.2
22-a -1.4
22-b -1.5
23-a -2.3
23-b -2.3
TS24-a 10.8
TS24-b 9.9
25-a -4.5
25-b -6.3
26-b -4.2
26-a -4.3
TS27-a 3.9
TS27-b 3.4
28-a -17.1
28-b -17.5
1.37 Å
1.34 Å
1.37 Å
1.35 Å
TS20-a
TS20-b
ligand exchange
C-H activation
olefin insertion
ß-H elimination