Seminar

碳氮键轴手性化合物的催化不对称合成

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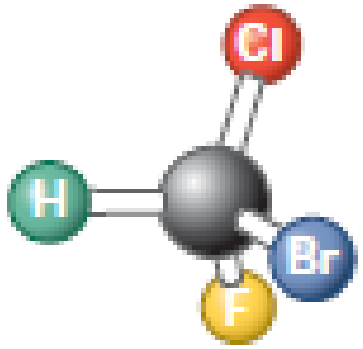
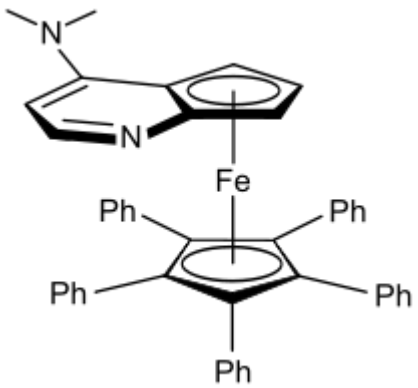
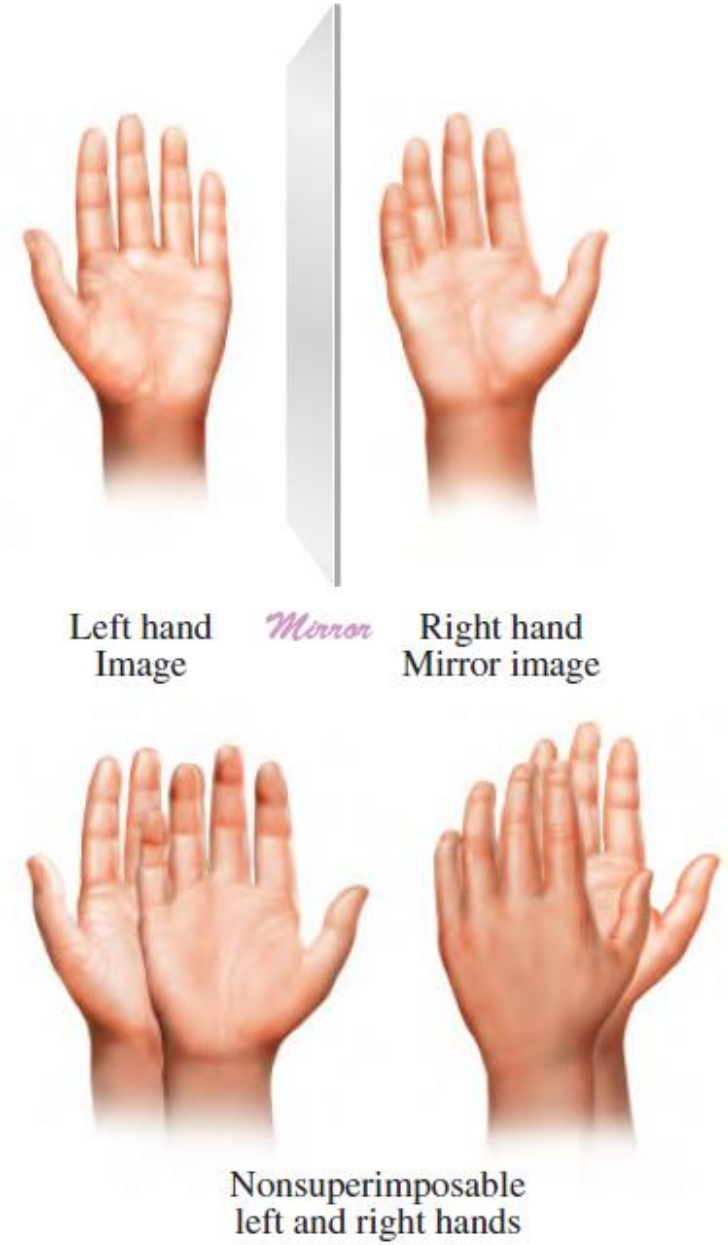
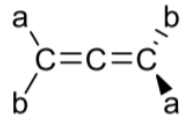


中心手性

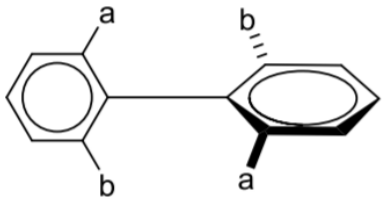


平面手性



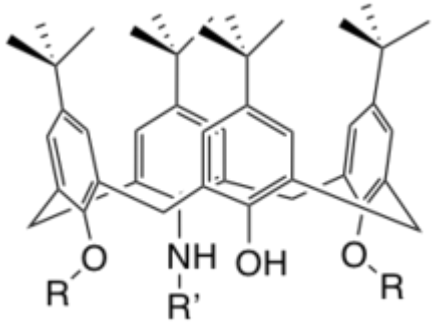


Allenes



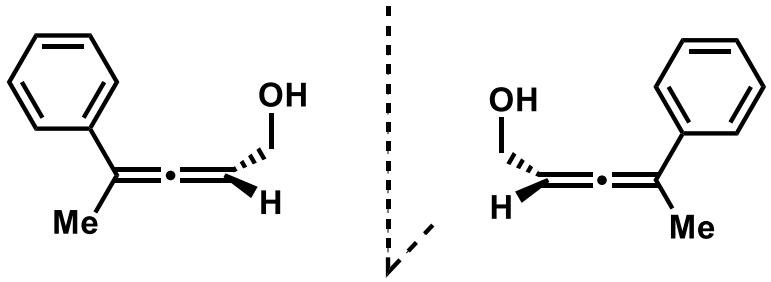
Substituted biphenyls

轴手性

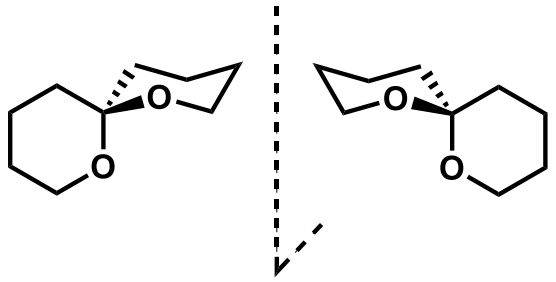


固有手性

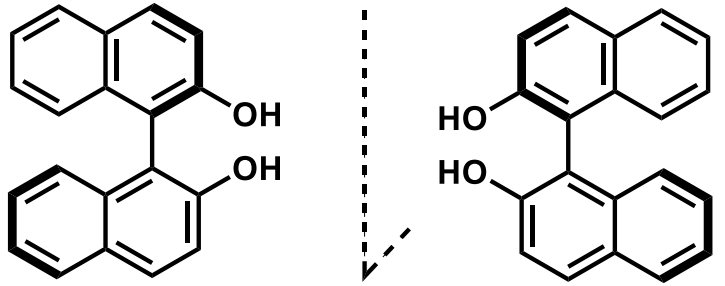
轴手性关注度日益提升



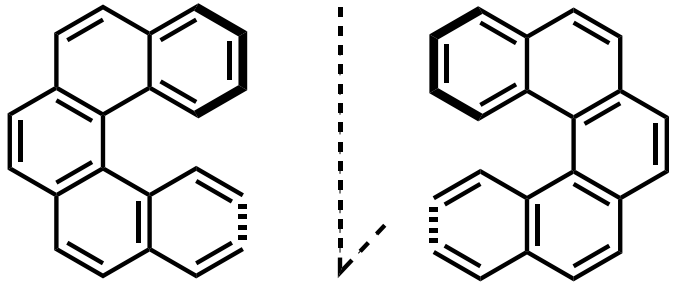
allene chirality



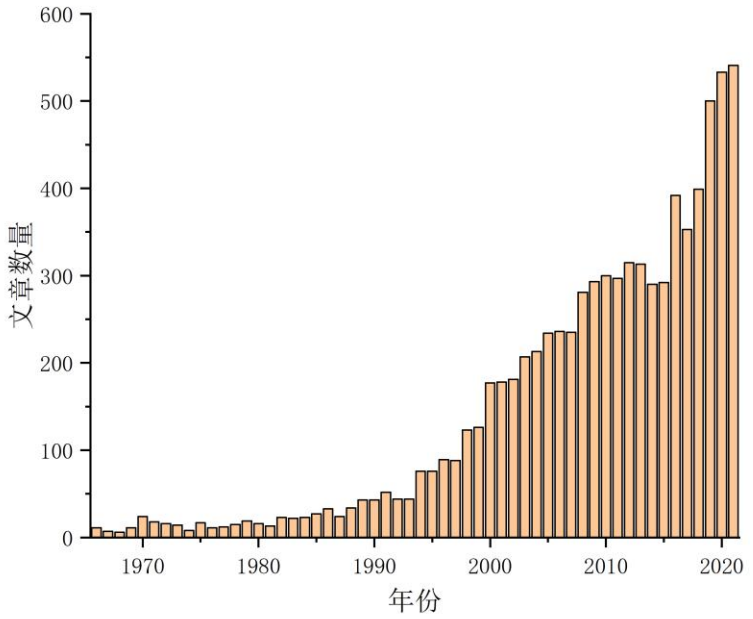
spirocyclic chirality



biaryl chirality

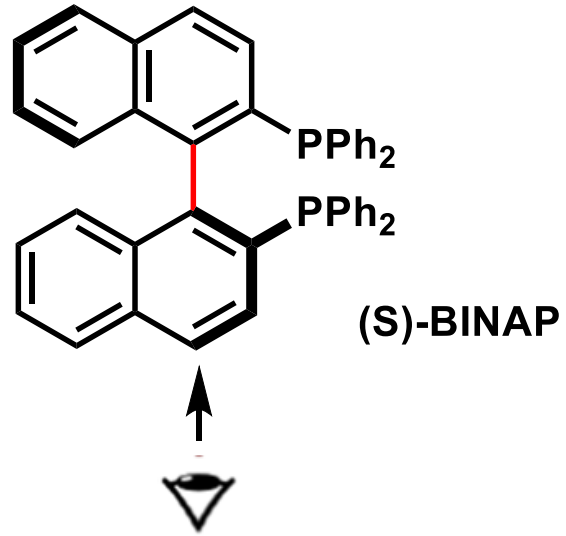


helical chirality

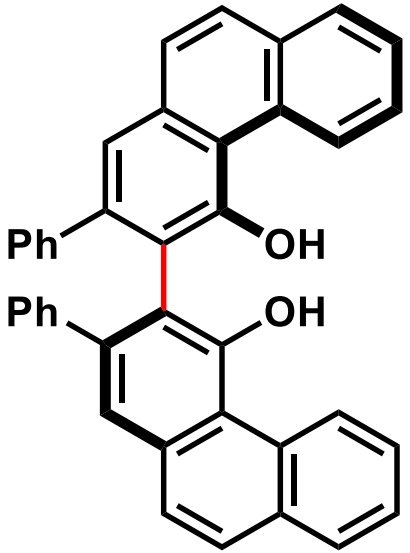


Cahn–Ingold–Prelog priority rules

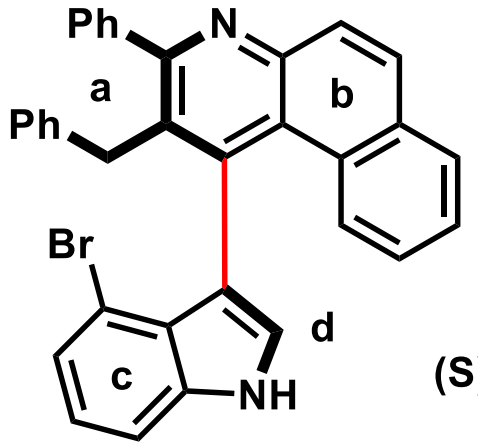
CIP rules apply, considering that the substituents in front have priority over the ones in the back.



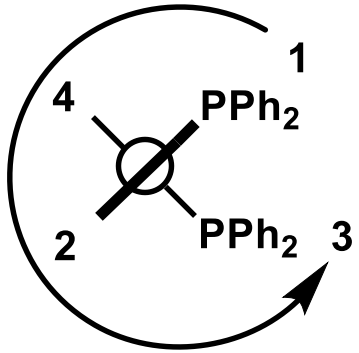
(S)-BINAP

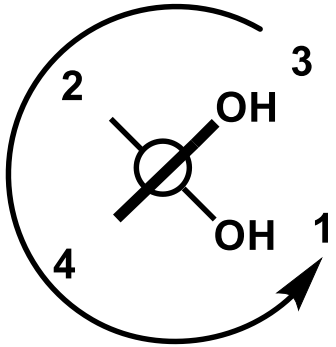


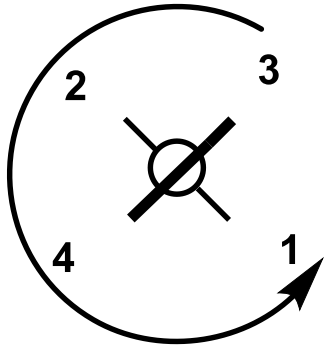
(R)-VAPOL



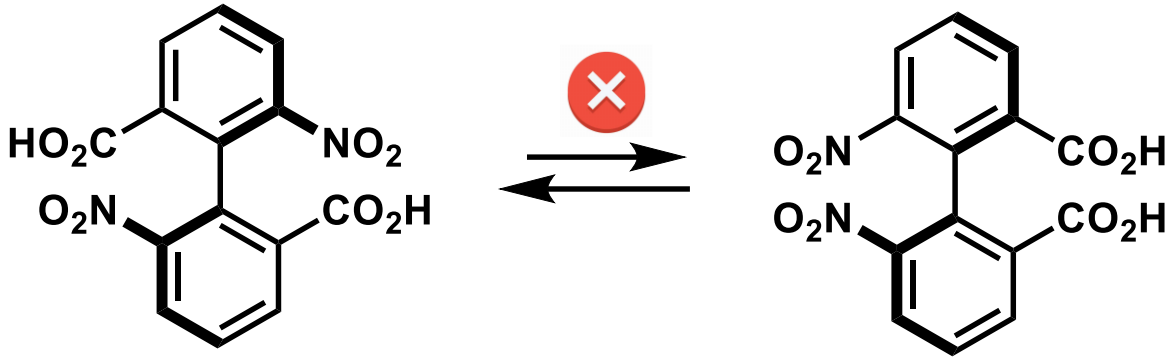
(S)



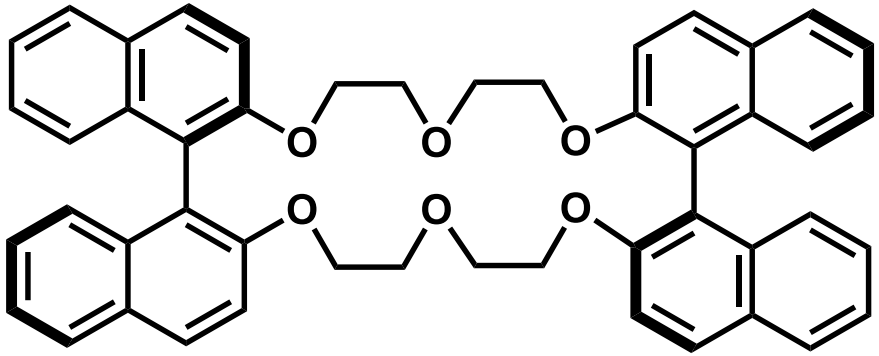




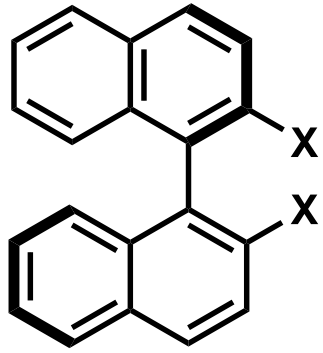
阻转异构体



Christie and Kenner, 1922, first report



DonaldJames Cram, 1987, Nobel prize



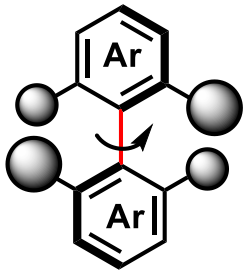
X = PPh_2 (BINAP)
X = OH (BINOL)

Noyori, 2001, Nobel prize

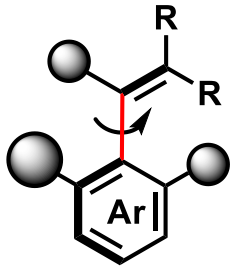
a) G. H. Christie, J. Kenner, *J. Am. Chem. Soc.* **1922**, *121*, 614-620.
b) Donald J. Cram, *J. Am. Chem. Soc.* **1973**, *95*, 2692-2693.
c) R. Noyori, *Angew. Chem., Int. Ed.* **2001**, *41*, 6398-6401.

C-X键的阻转异构体

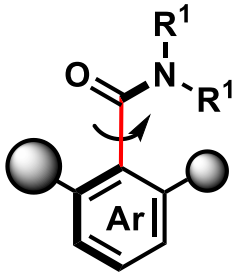
Atropisomers around C-X bond



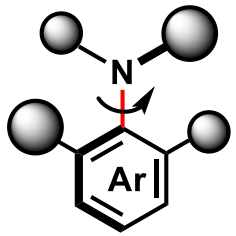
biaryls



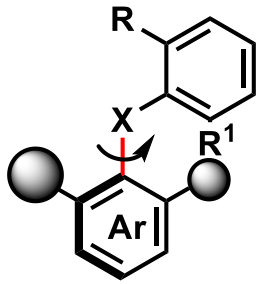
styrenes



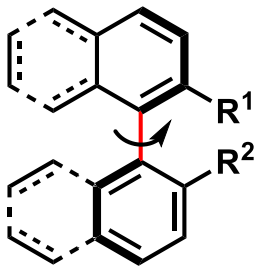
amides



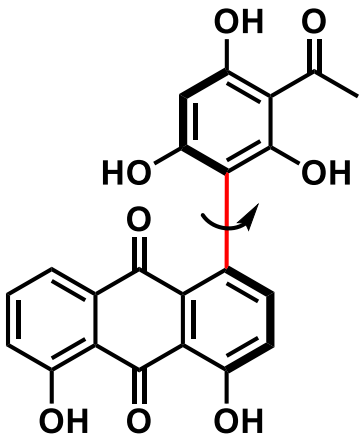
anilides
C-N bond



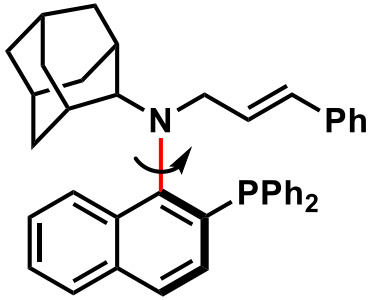
X = O/S
C-O/C-S bond



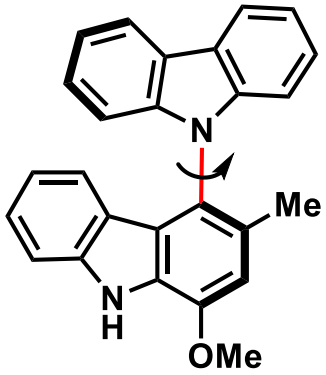
BINOL
NOBIN, BINAM



Knipholone

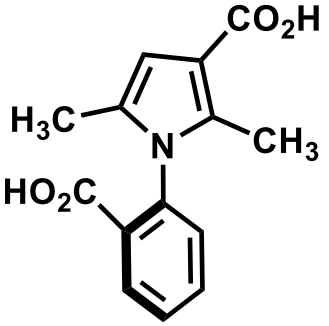


chiral ligand

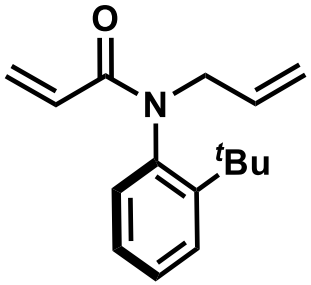


Murrastifoline-F

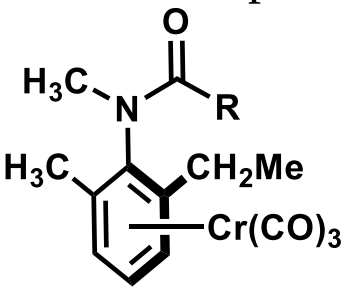
a) X. Li, et al., *J. Am. Chem. Soc.* **2018**, *140*, 12836-12843.
b) R. Adams, et al., *J. Am. Chem. Soc.* **1931**, *53*, 374-376.
c) T. Taguchii, et al., *J. Org. Chem.* **1998**, *63*, 2634-2640.
d) M. Uemura, et al., *Org. Lett.* **2000**, *2*, 1907-1910.



Roger Adams, 1931, first report



Osamu Kitagawa, 1997, first optically active example



Uemura， 2000, first enantioselective synthesis

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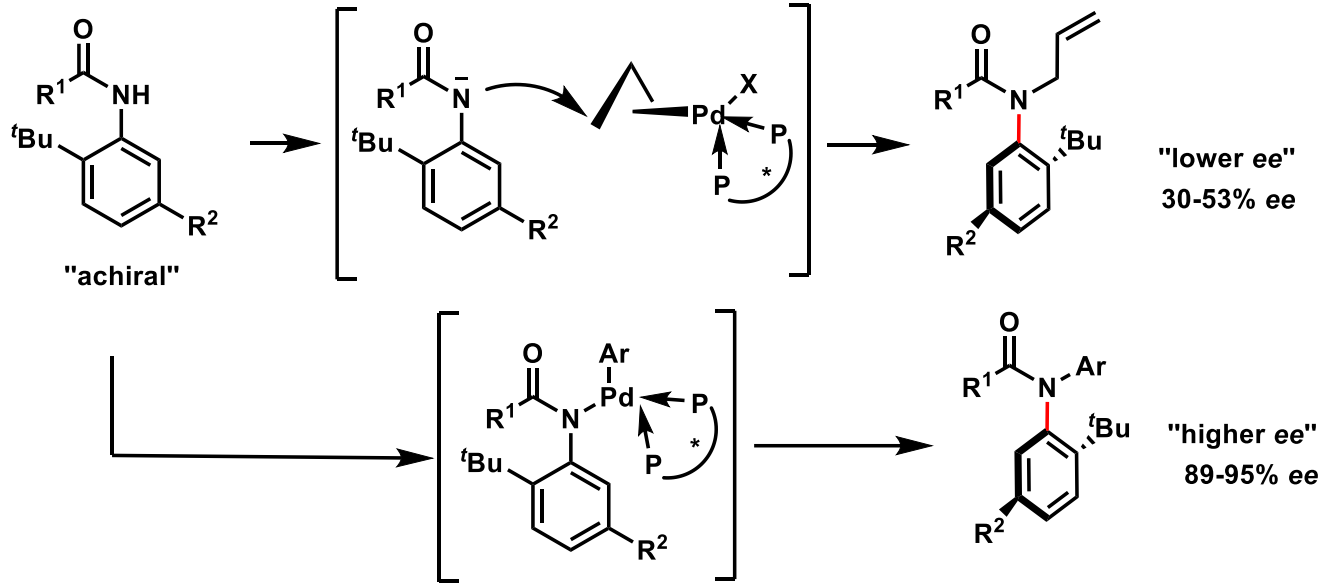
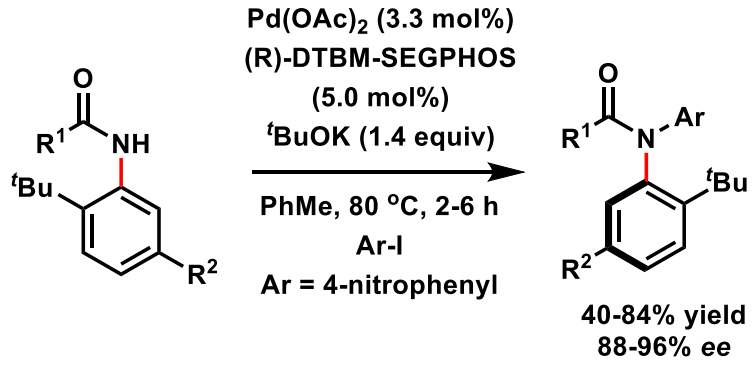
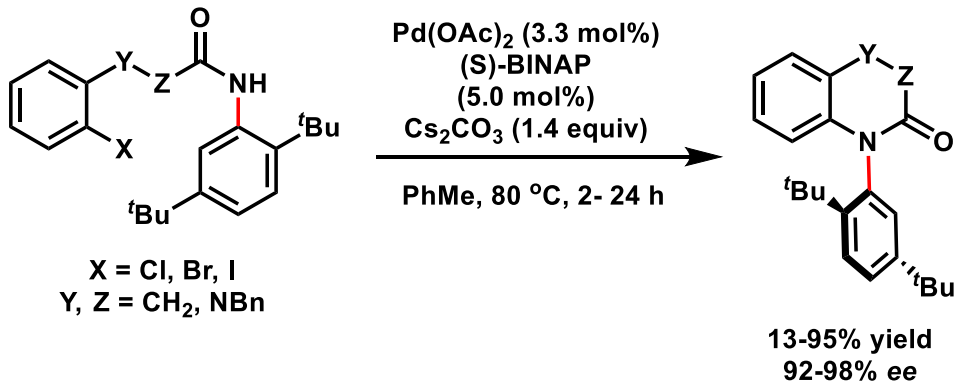


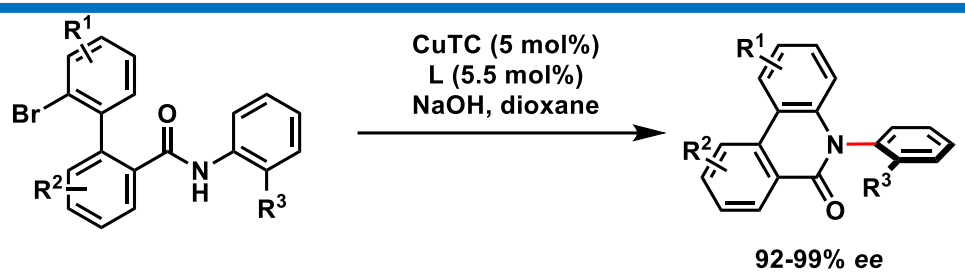


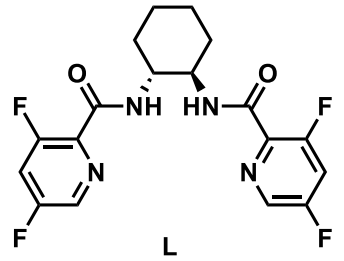


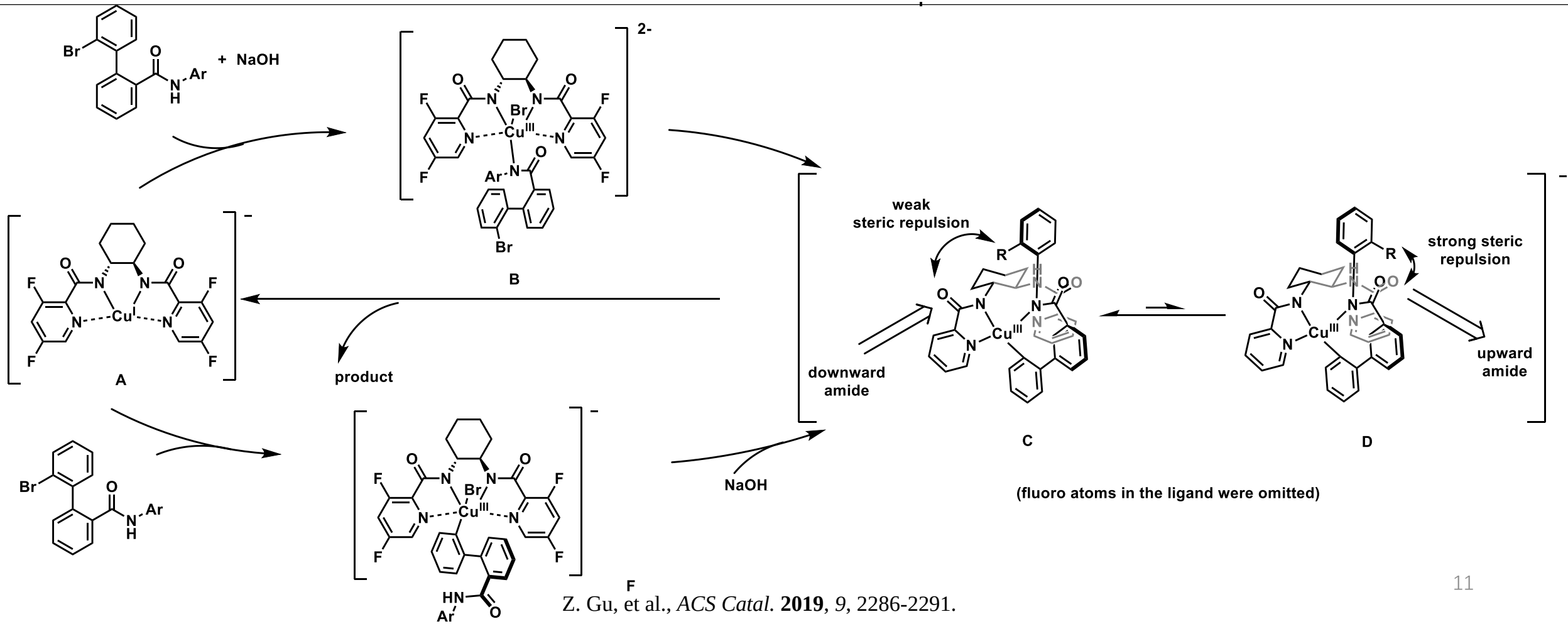
T. Taguchi, et al., *J. Am. Chem. Soc.* **2005**, *127*, 3676-3677.

T. Taguchi, et al., *J. Am. Chem. Soc.* **2006**, *128*, 12923-12931.

N-H官能团化

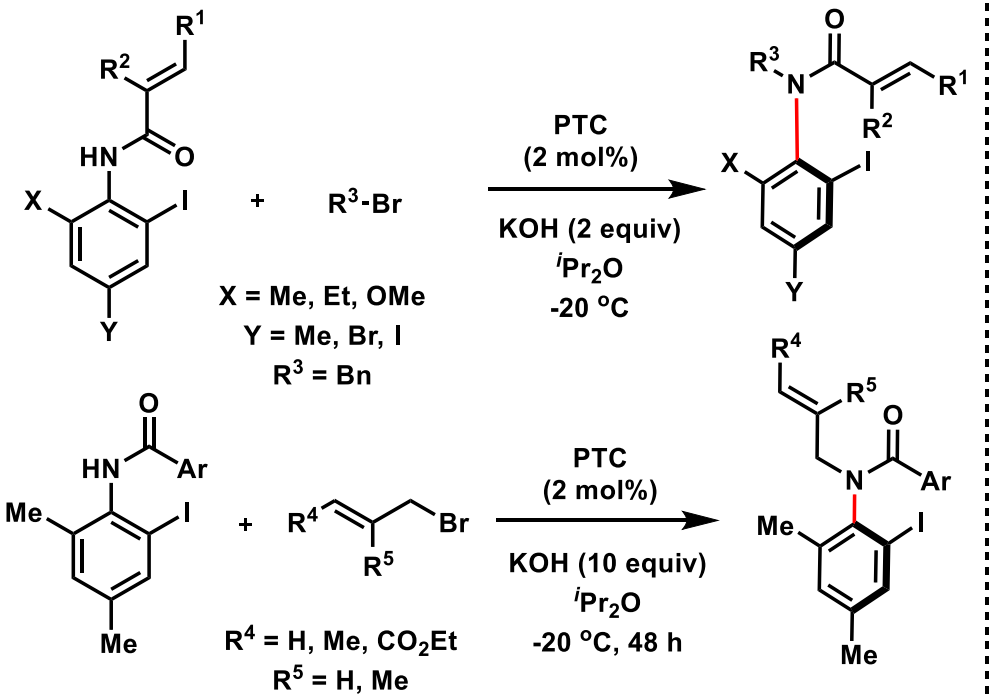


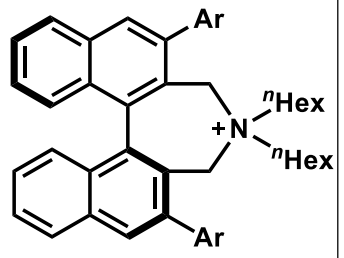




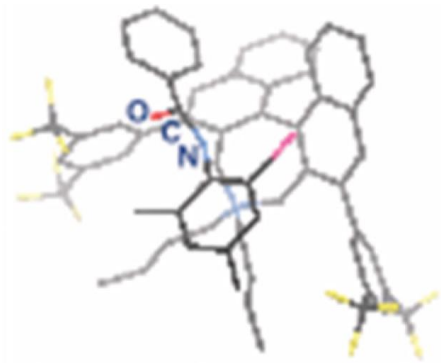
Z. Gu, et al., *ACS Catal.* **2019**, *9*, 2286-2291.

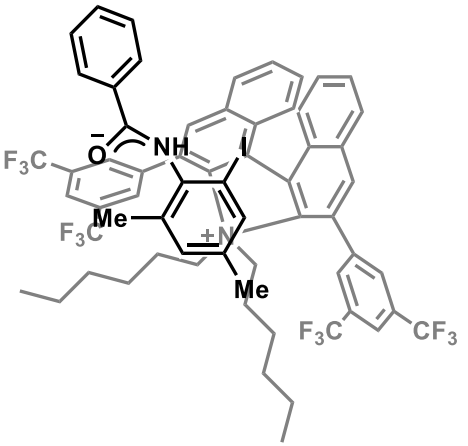
N-H官能团化

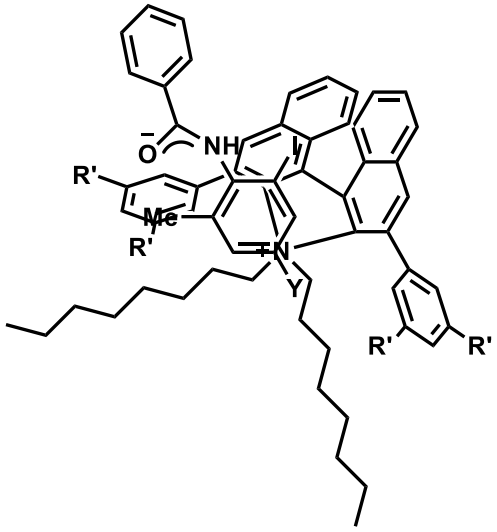


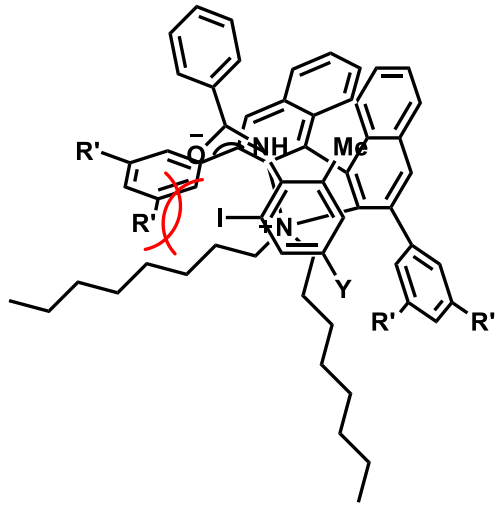


Ar = 3,5-[3,5-^{t}Bu$_2$-C$_6$H$_3$]$_2$-C$_6$H$_3$
PTC



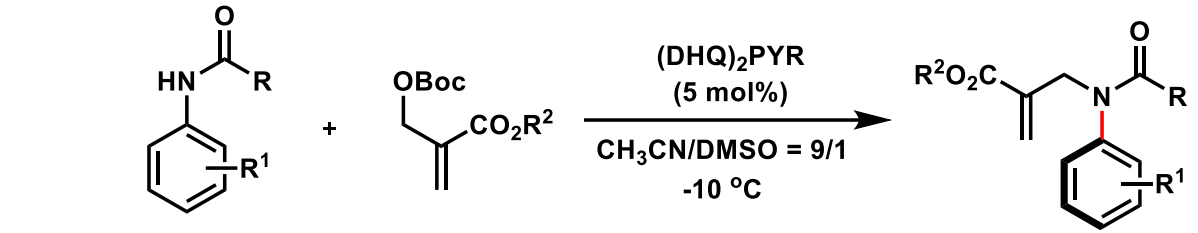


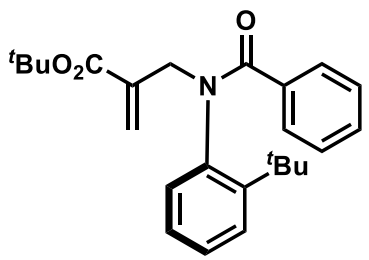




K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 916-919.

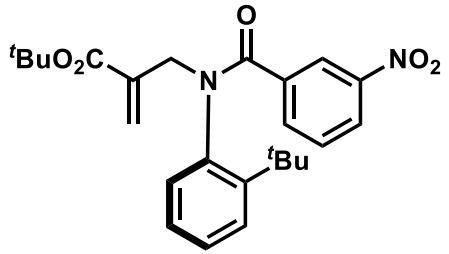
N-H官能团化





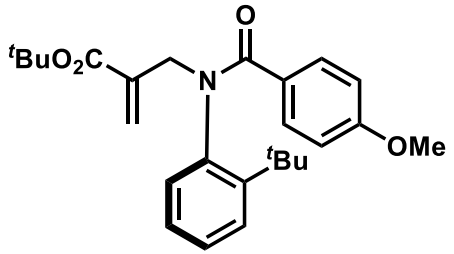
$\Delta G^{\neq}$ = 27.3 kcal/mol

$t_{1/2}$ = 1.12 h



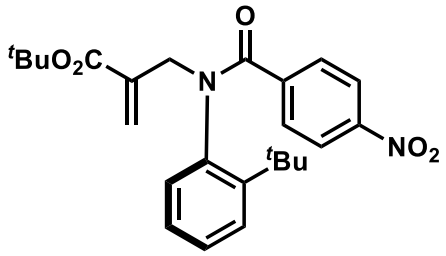
$\Delta G^{\neq}$ = 28.5 kcal/mol

$t_{1/2}$ = 6.61 h



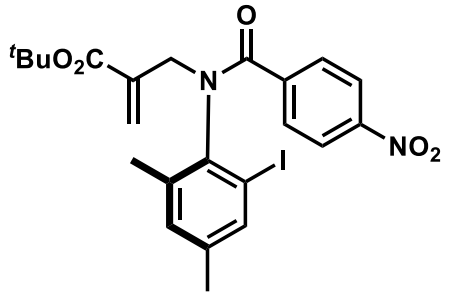
$\Delta G^{\neq}$ = 27.0 kcal/mol

$t_{1/2}$ = 0.66 h



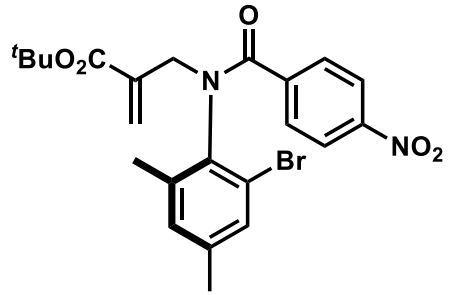
$\Delta G^{\neq}$ = 27.5 kcal/mol

$t_{1/2}$ = 1.53 h



$\Delta G^{\neq}$ = 29.1 kcal/mol

$t_{1/2}$ = 13.24 h



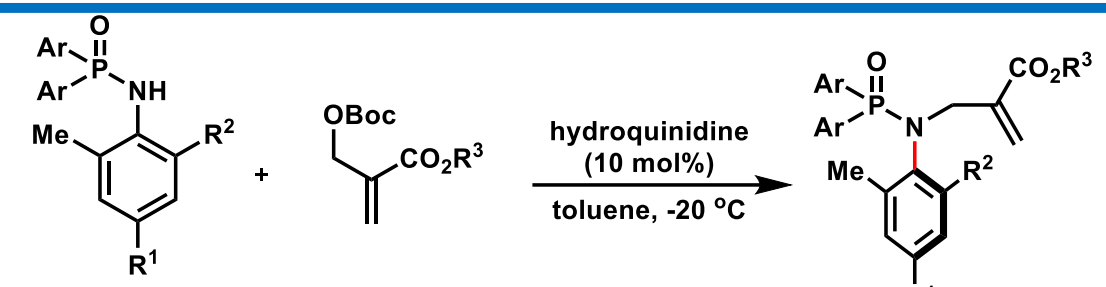
$\Delta G^{\neq}$ = 28.4 kcal/mol

$t_{1/2}$ = 5.14 h

Measured at 80 °C in isopropanol.

X. Li, et al., *J. Am. Chem. Soc.* **2018**, *140*, 12836-12843.

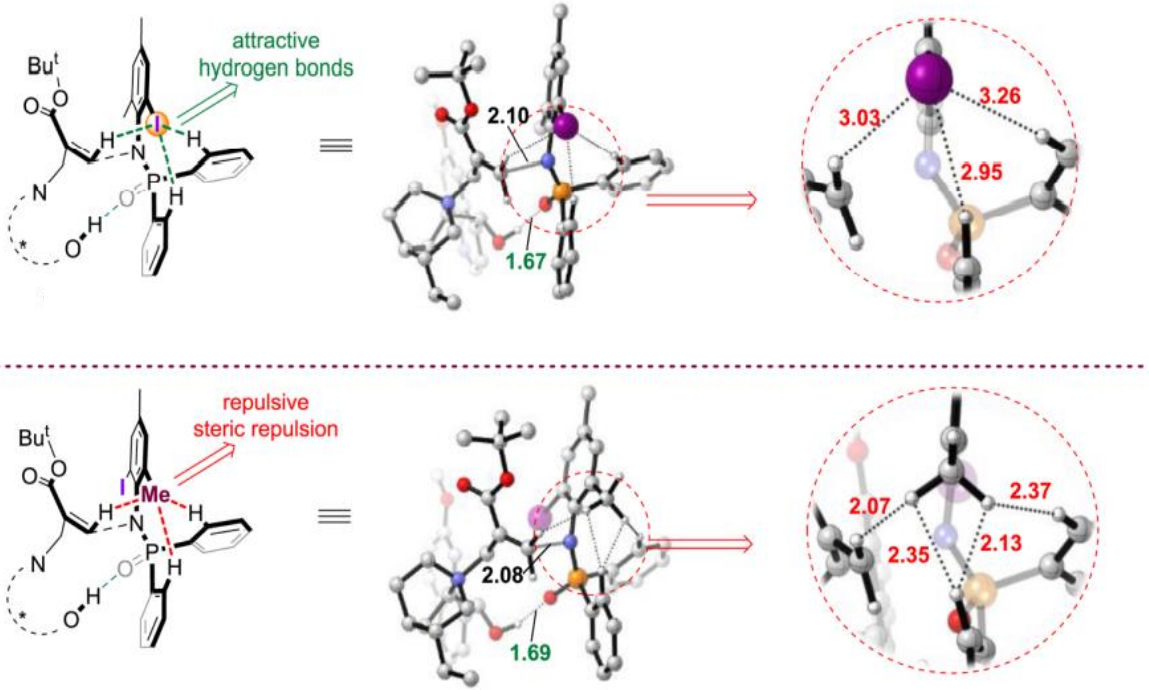
N-H官能团化

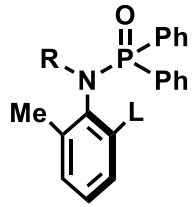


R^1 = Me, Et, Cl, Br, I

R^2 = H, I, Br, Cl, ^{i}Pr

Ortho-substituted halogen groups of aniline can form weak hydrogen bonds, which are helpful for the stereocontrol of the reaction.

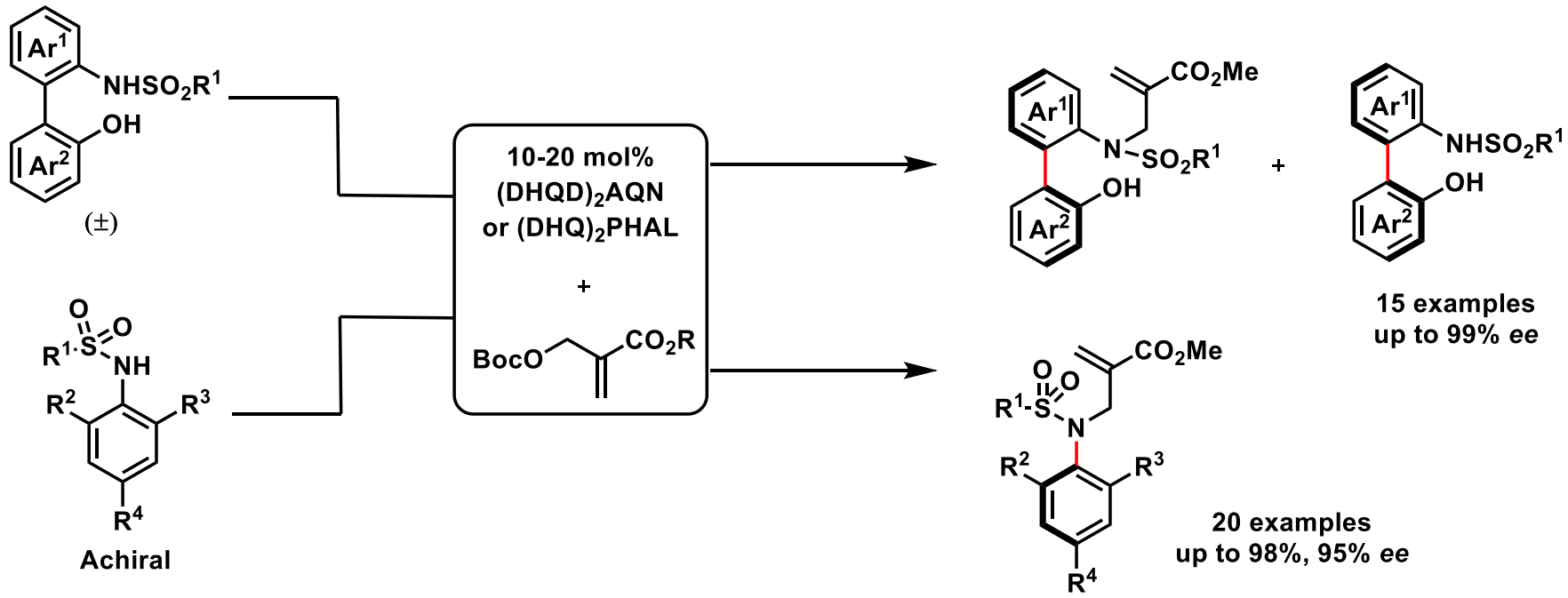




	L = I, Br, High e.r.		L = ^{i}Pr, ^{t}Bu Low e.r.	
Substituent L:	I	Br	^{i}Pr	^{t}Bu
e.r. value:	96:4	94:6	56:44	rac

X. Li, et al., *ACS Catal.* **2020**, *10*, 2324-2333.

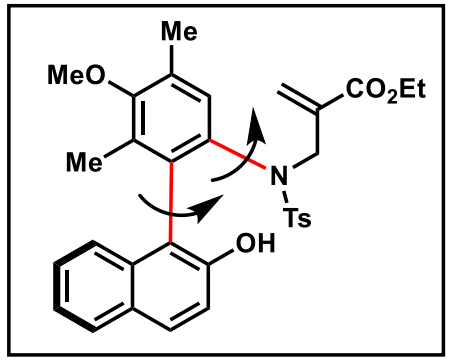
N-H官能团化



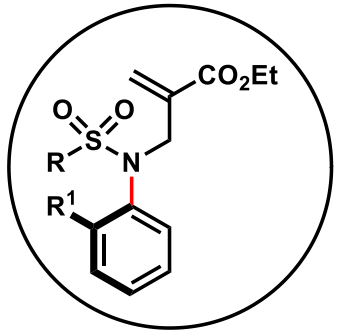
Y. Zhao, et al., *Nat. Commun.* **2019**, *10*, 3061-3069.

N-H官能团化

Observation of axially chiral sulfonamide

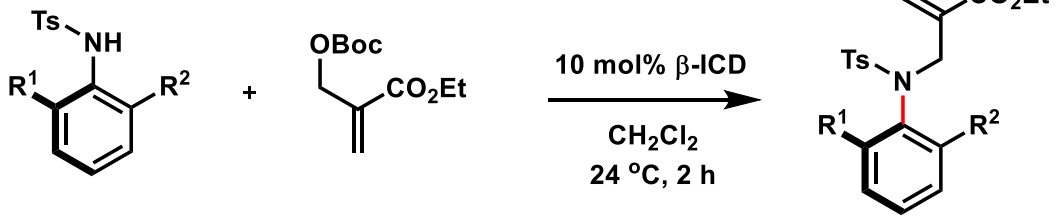


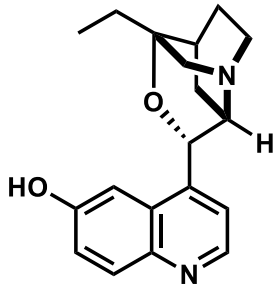
1 : 2 dr(increased to 1:1 in 12 h)



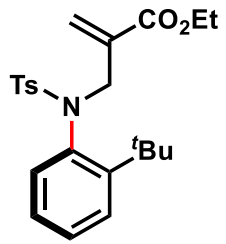
New axially chiral entity?

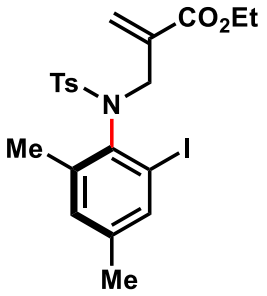
Exploration of the configurational stability of sulfonamides

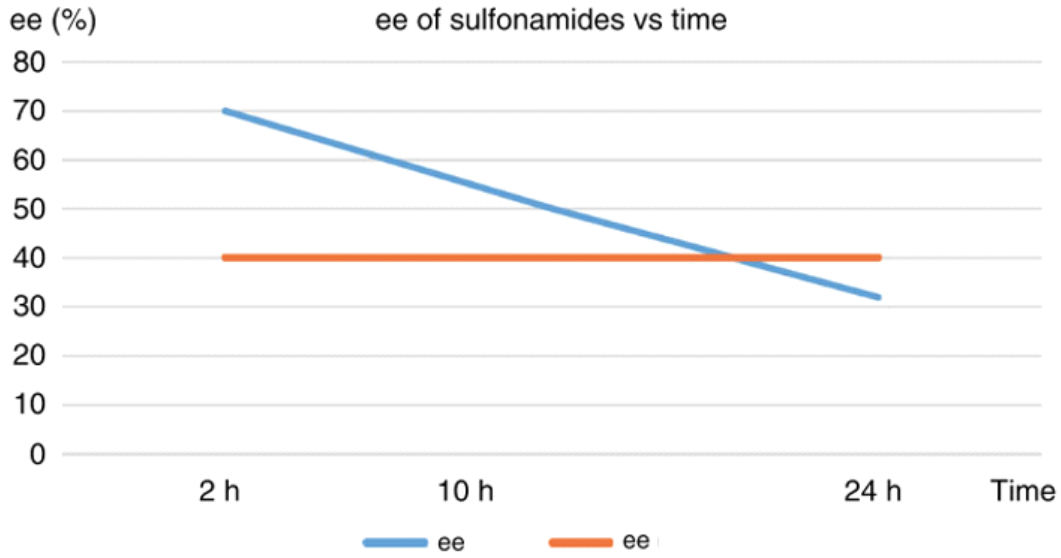




β-ICD

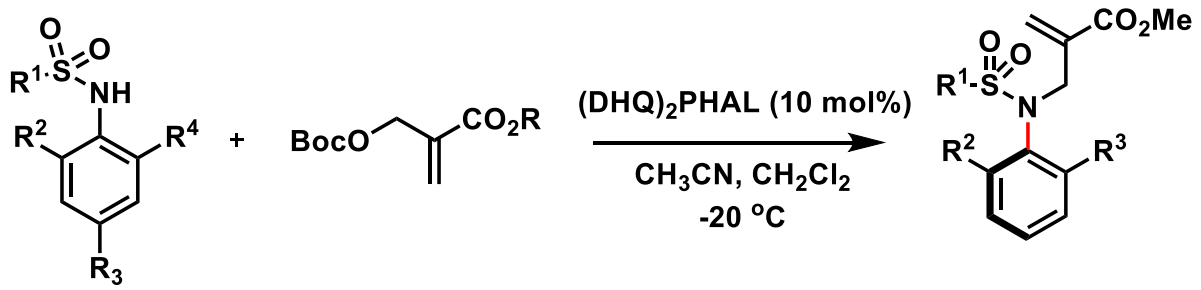


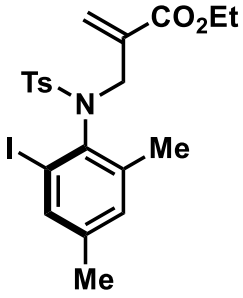




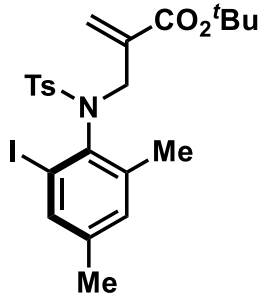
Y. Zhao, et al., *Nat. Commun.* **2019**, *10*, 3061-3069.

N-H官能团化

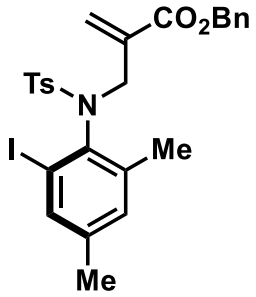




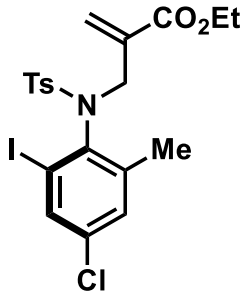
85%, 92% *ee*



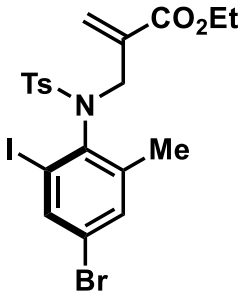
80%, 92% *ee*



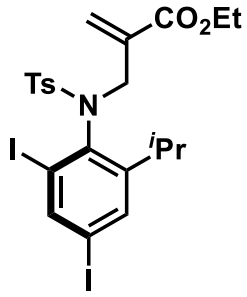
98%, 92% *ee*



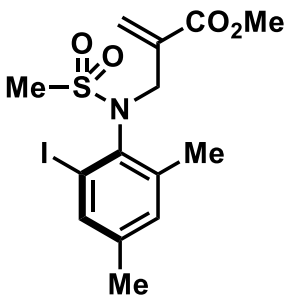
81%, 91% *ee*



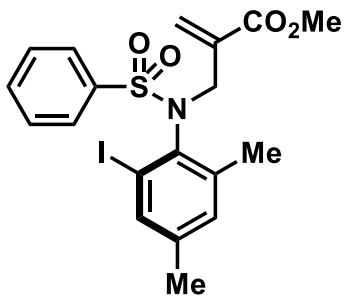
78%, 91% *ee*



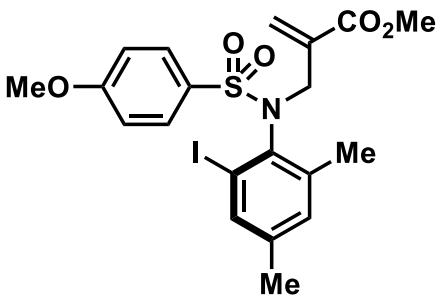
80%, 92% *ee*



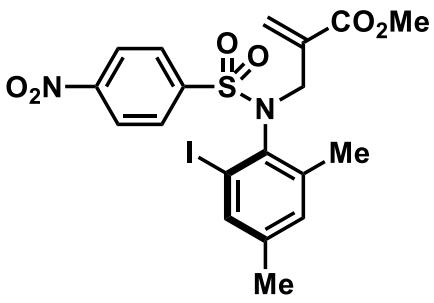
85%, 87% *ee*



76%, 90% *ee*



83%, 93% *ee*



80%, 91% *ee*

Y. Zhao, et al., *Nat. Commun.* **2019**, *10*, 3061-3069.

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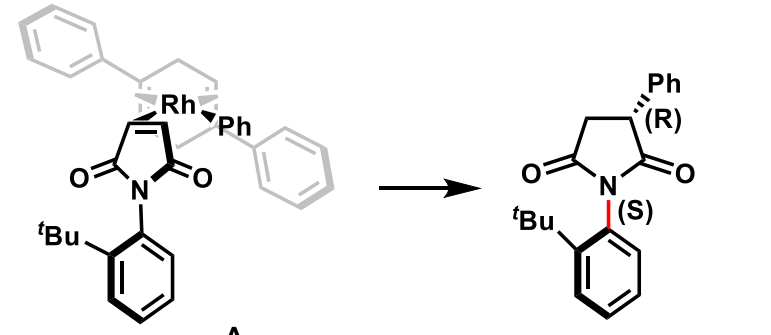
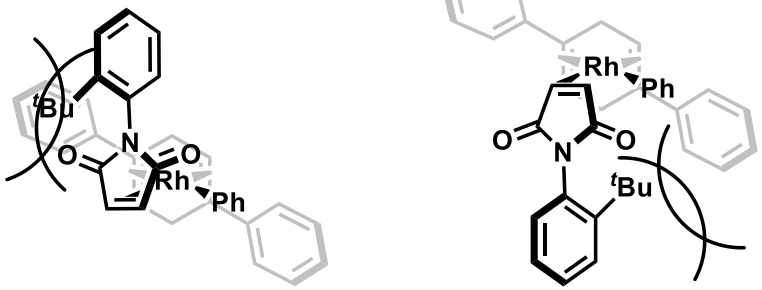
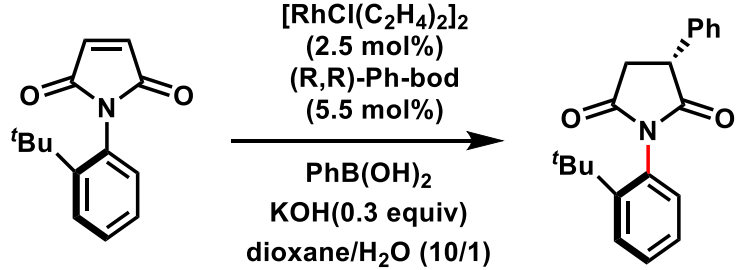


A

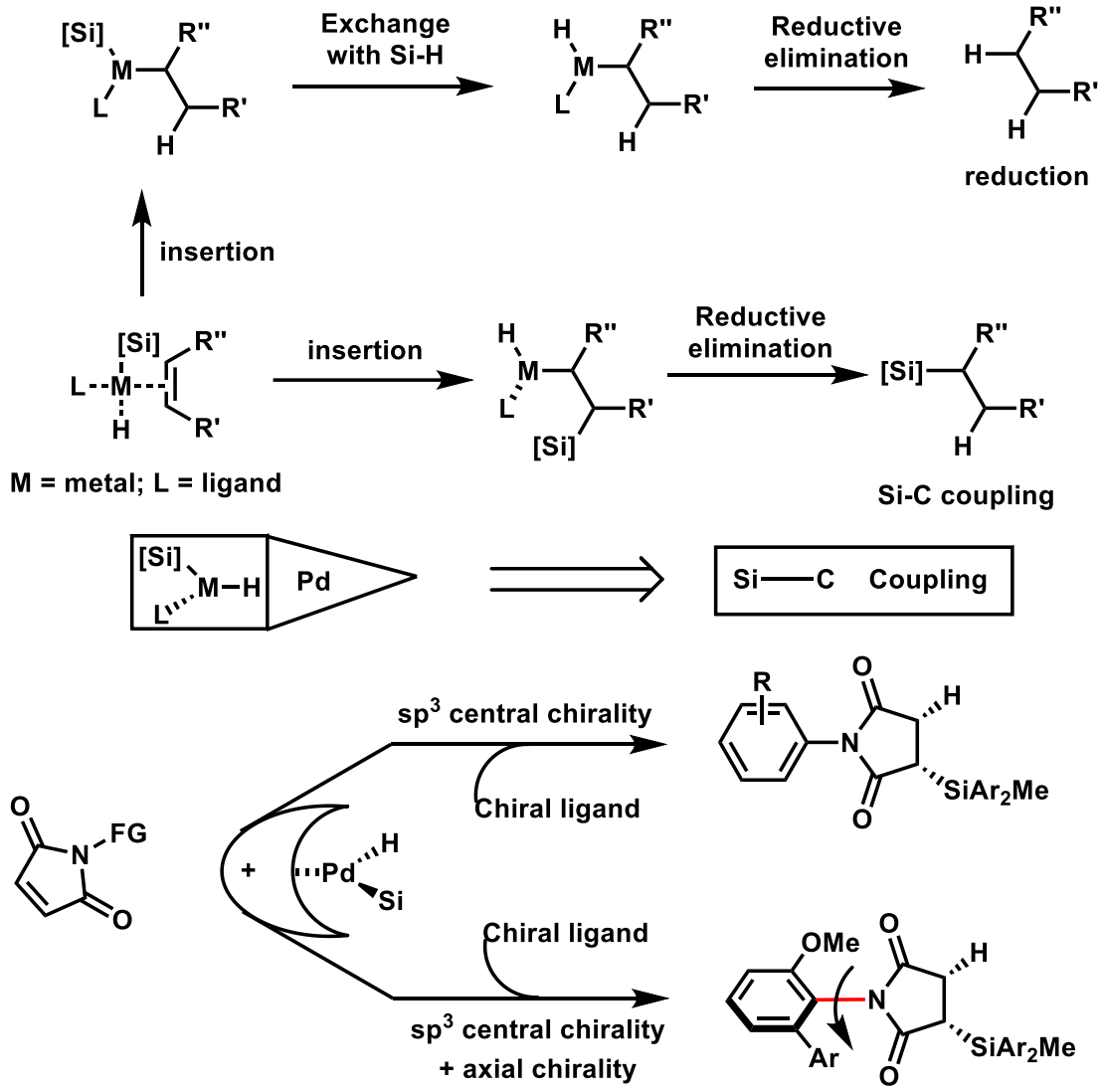


B C



96% yield
96:4 dr, 99% *ee*

R. Shintani, et al., *Tetrahedron.* **2007**, *63*, 8529-8536.



L. Xu, et al., *Nat. Commun.* **2020**, *11*, 2904-2913.

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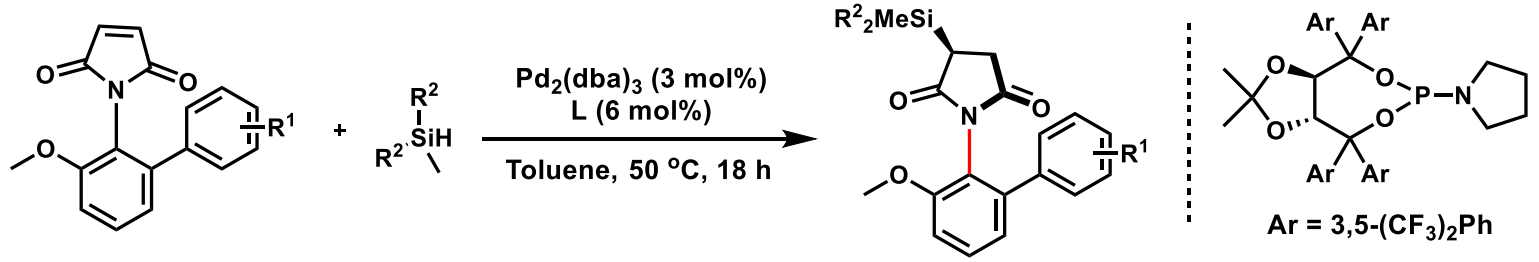
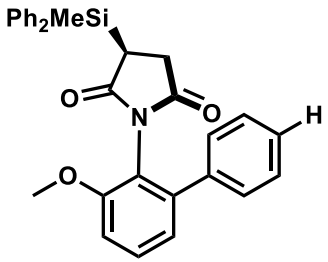
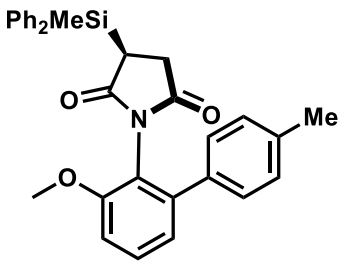
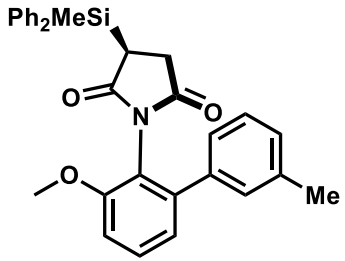




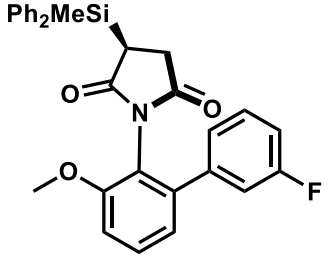
82%, 94% *ee*, d.r. = 95:5



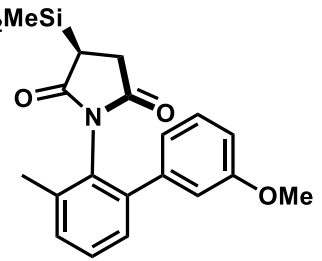
85%, 92% *ee*, d.r. = 95:5



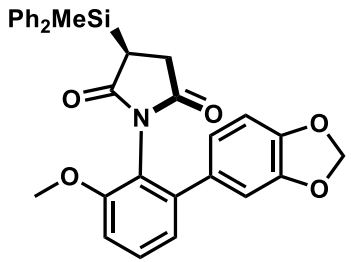
95%, 94% *ee*, d.r. = 99:1



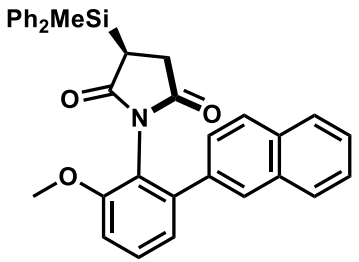
92%, 94% *ee*, d.r. = 96:4



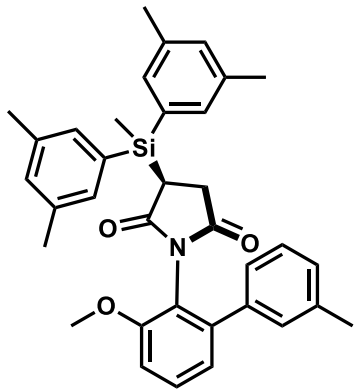
90%, 93% *ee*, d.r. => 99:1



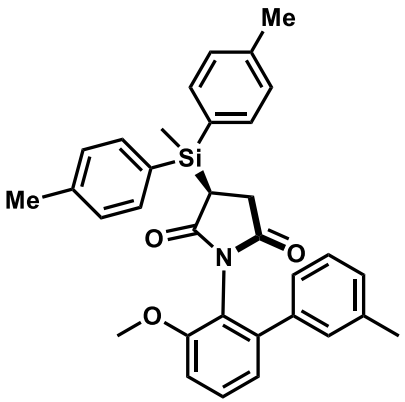
97%, 94% *ee*, d.r. = 99:1



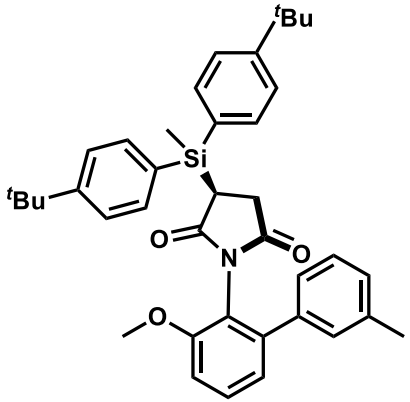
60%, 89% *ee*, d.r. = 92:8



94%, 95% *ee*, d.r. = > 99:1



95%, 95% *ee*, d.r. = > 99:1



37%, 92% *ee*, d.r. = > 99:1

L. Xu, et al., *Nat. Commun.* **2020**, *11*, 2904-2913.

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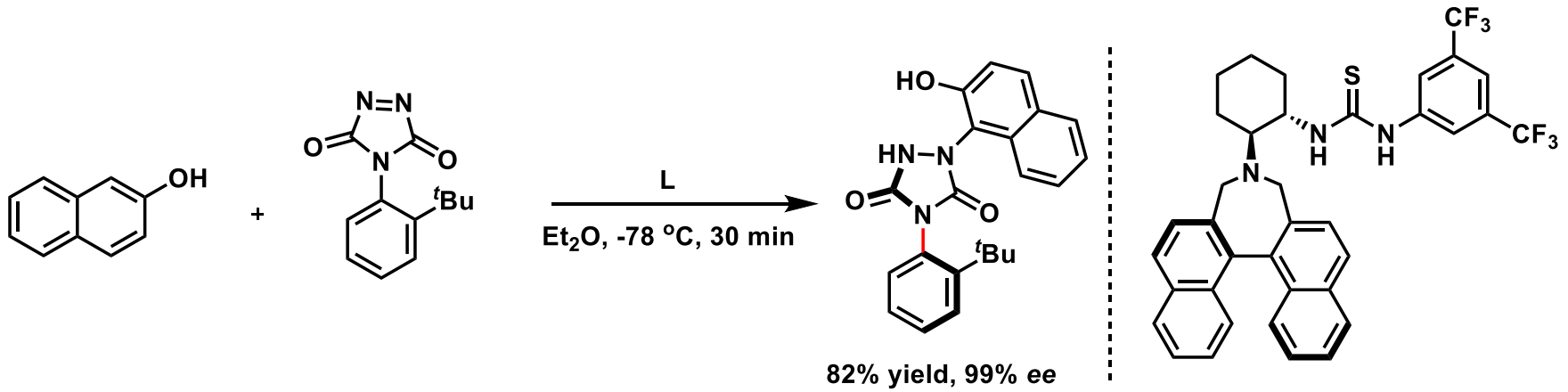

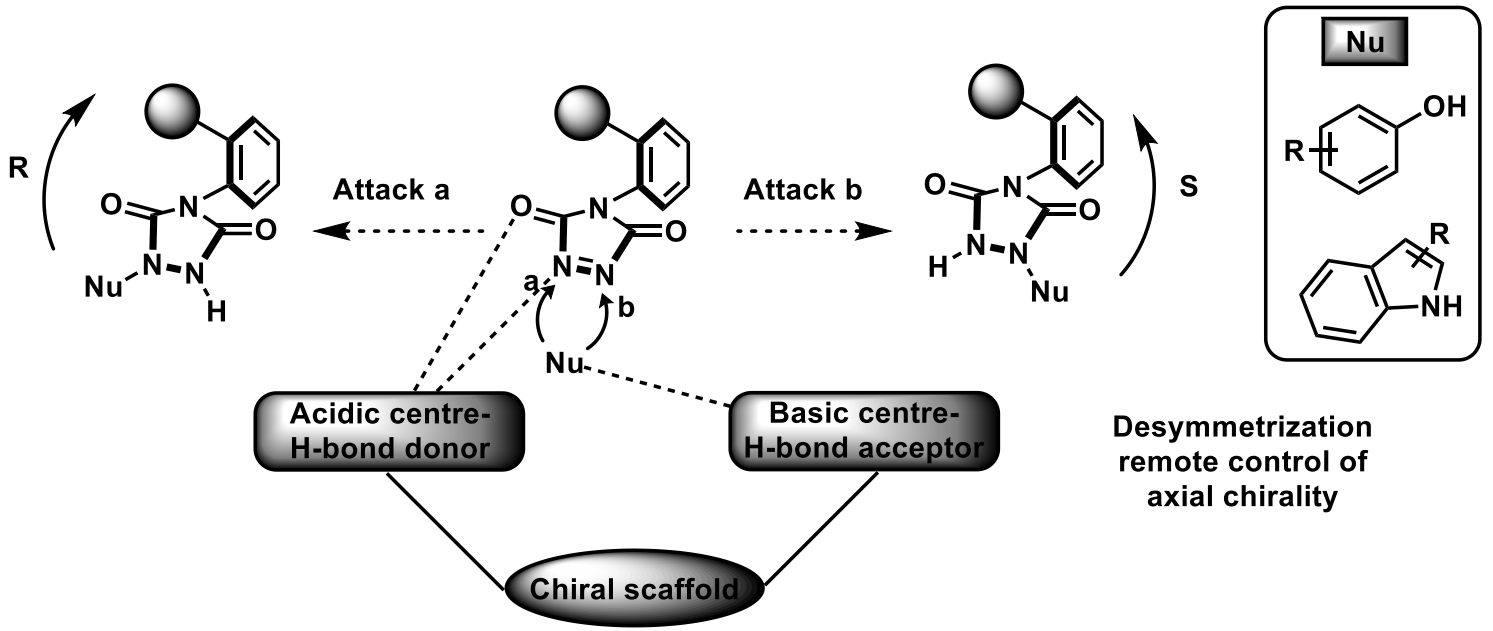

B. Tan, et al., *Nat. Commun.* **2016**, *7*, 10677-10687.

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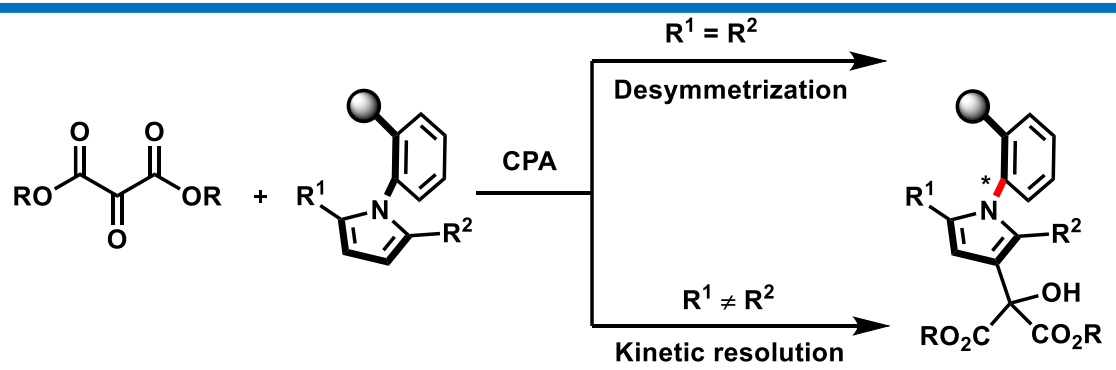
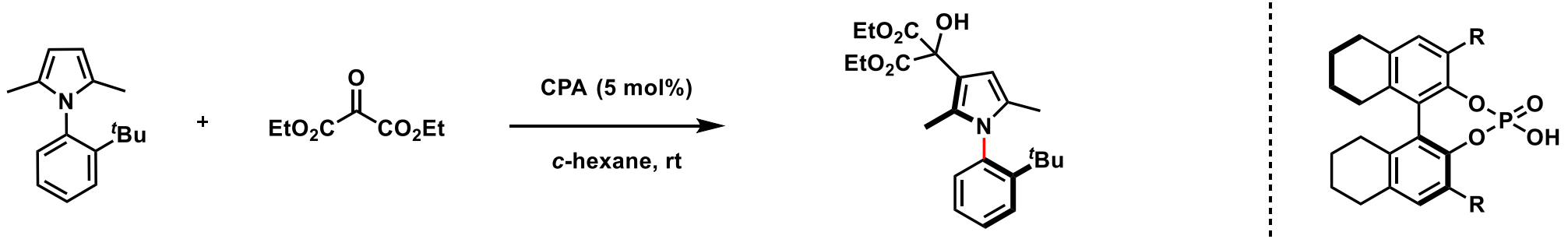
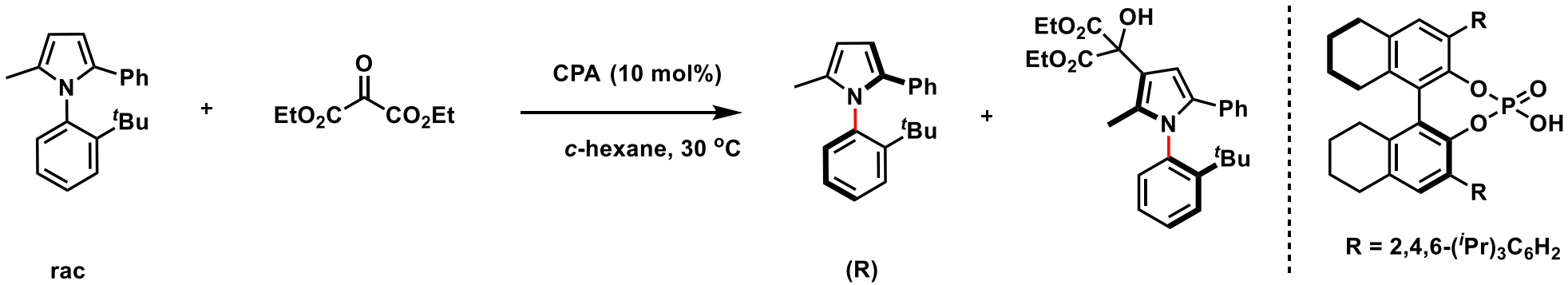




R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$



rac

(R)

R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$

B. Tan, et al., *Nat. Commun.* **2019**, *10*, 566-575.

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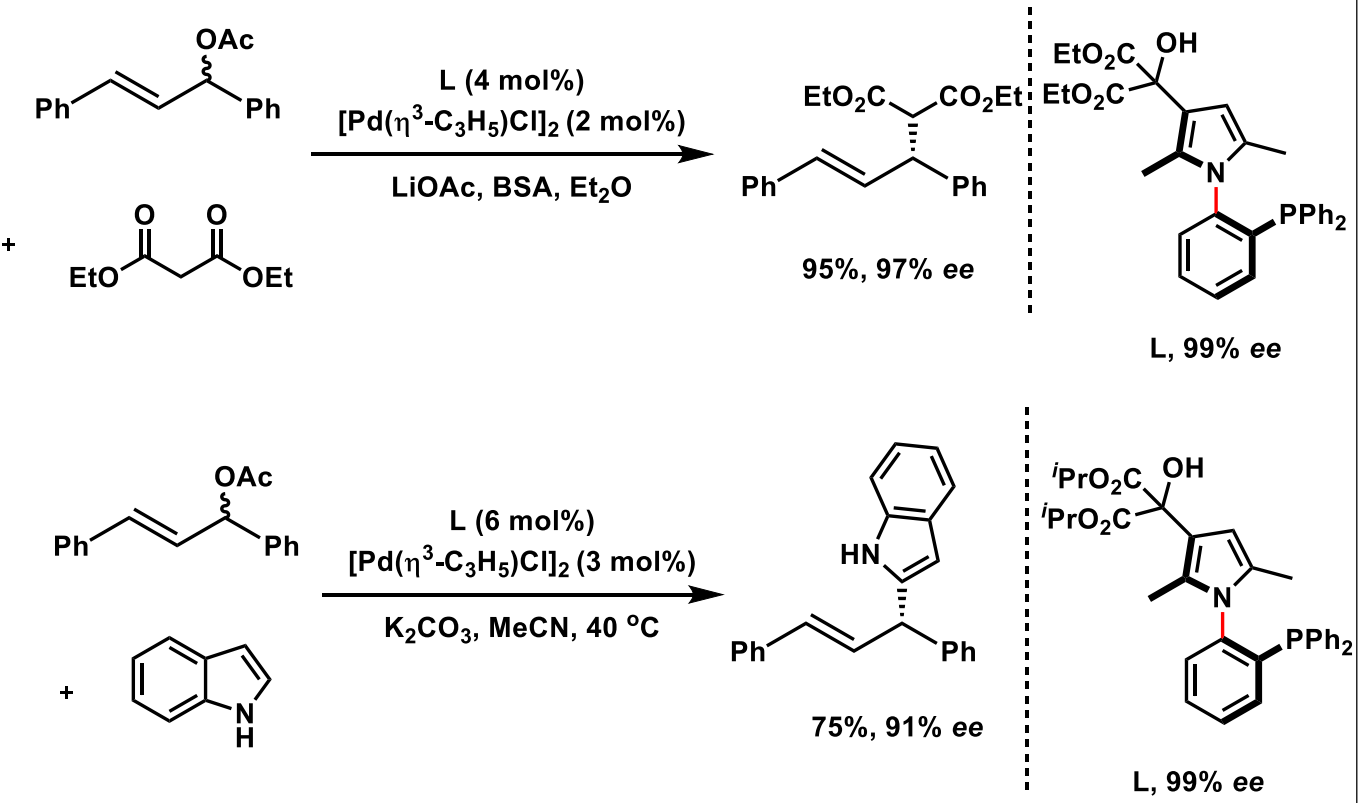
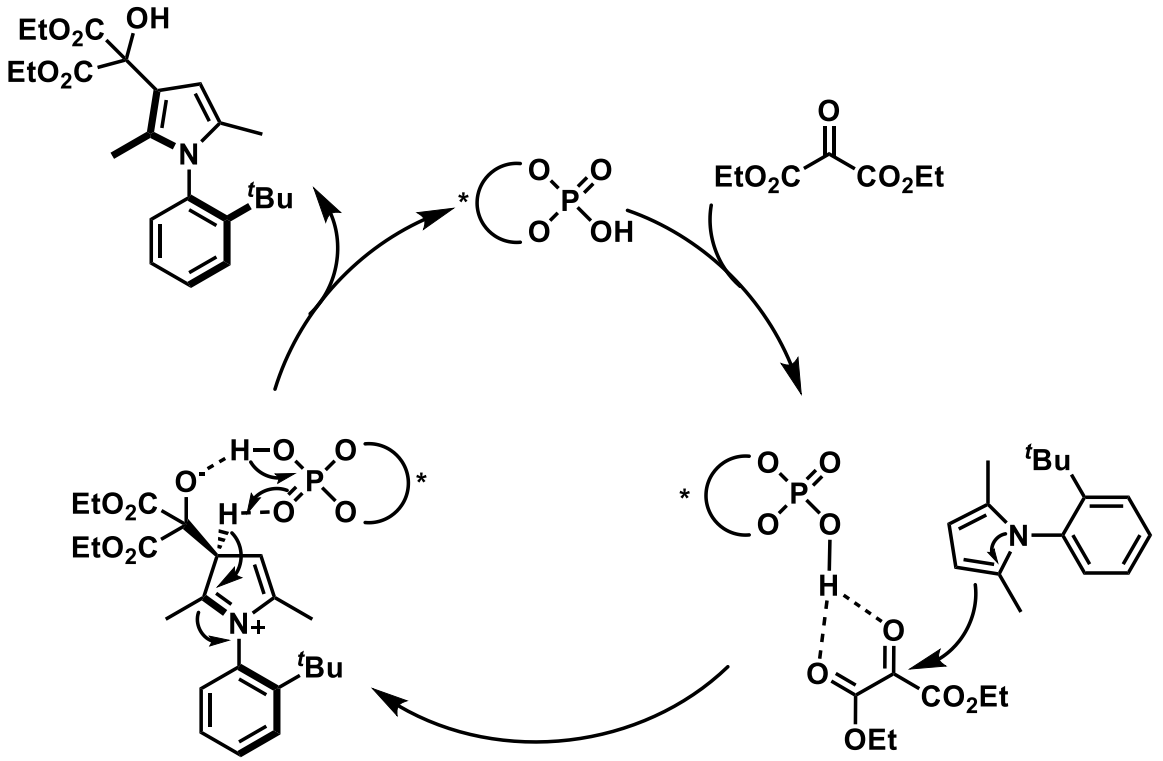
Application



Mechanism



B. Tan, et al., *Nat. Commun.* **2019**, *10*, 566-575.

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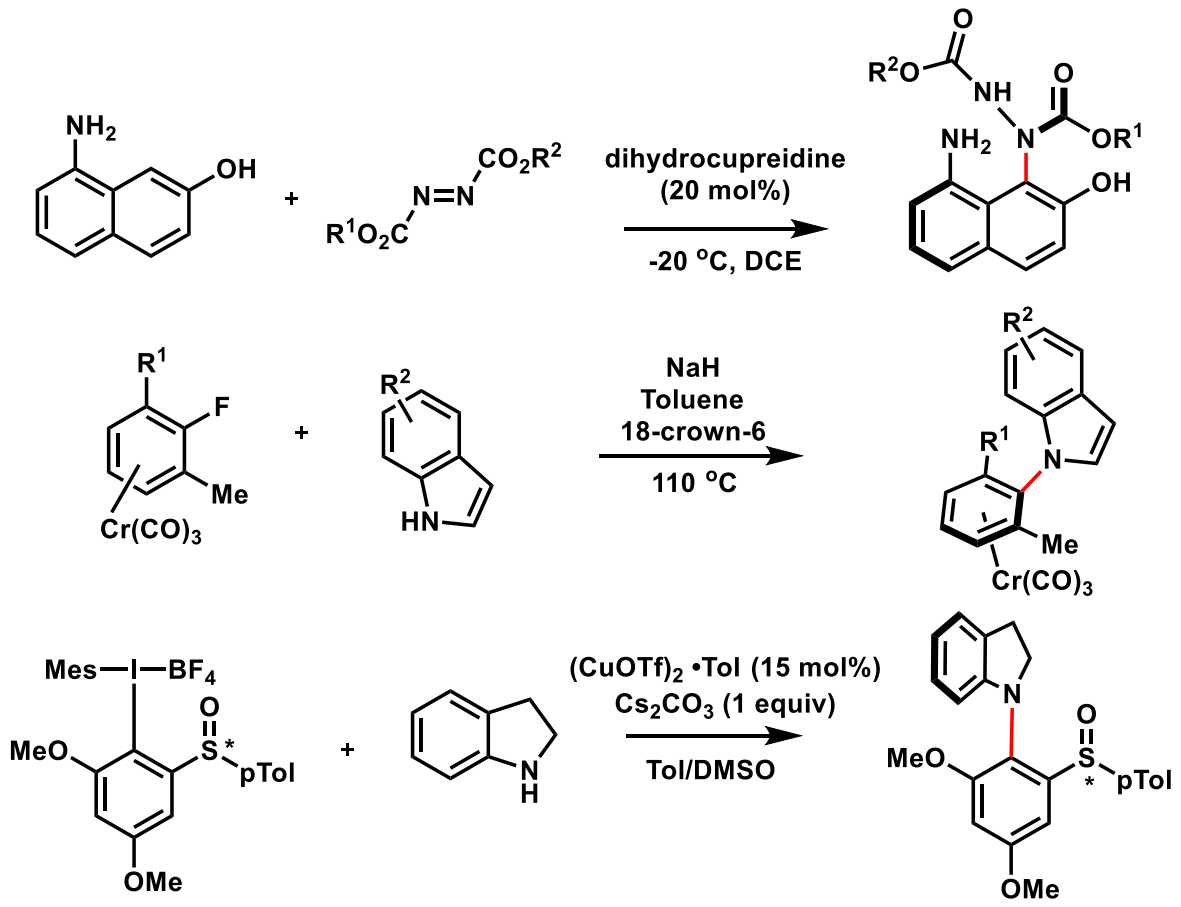
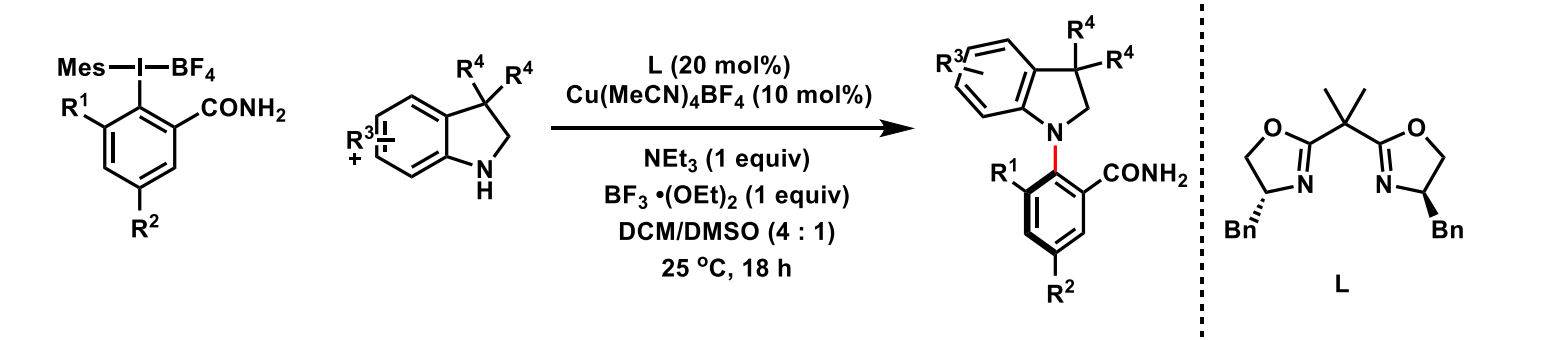
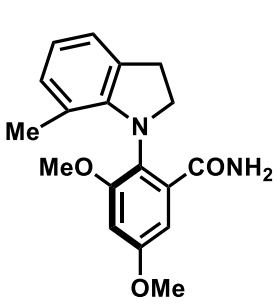


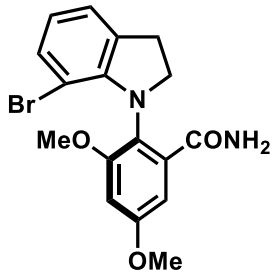
a) K. A. Jørgensen, et al., *Angew. Chem. Int. Ed.* **2006**, *45*, 1147-1151.
b) M. Uemura, et al., *J. Org. Chem.* **2007**, *72*, 3394-3402.
c) F. Colobert, et al., *ACS Catal.* **2018**, *8*, 2805−2809.

直接构建C-N键

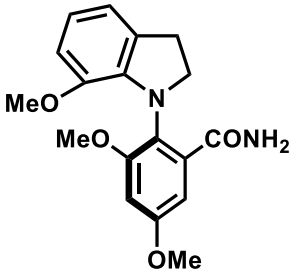




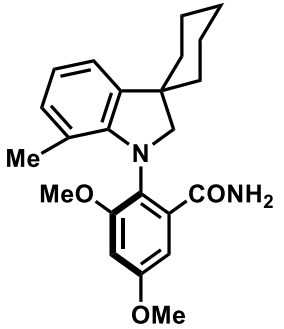
76%, 98% *ee*



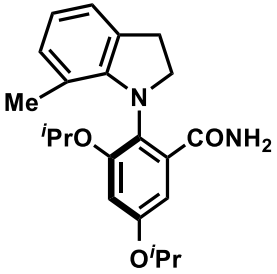
64%, 98% *ee*



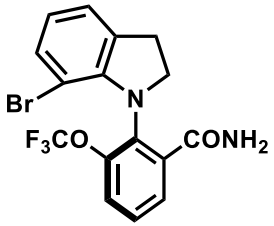
34%, 78% *ee*



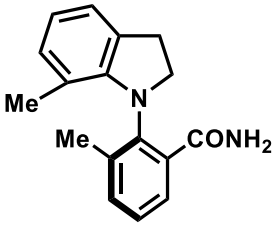
74%, 96% *ee*



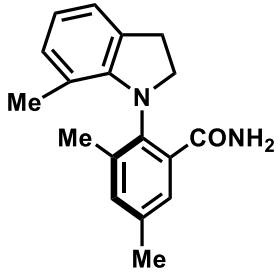
74%, 88% *ee*



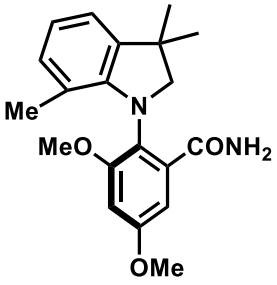
54%, 92% *ee*



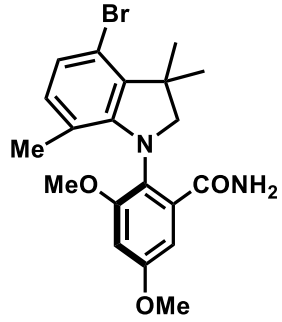
32%, 80% *ee*



54%, 80% *ee*



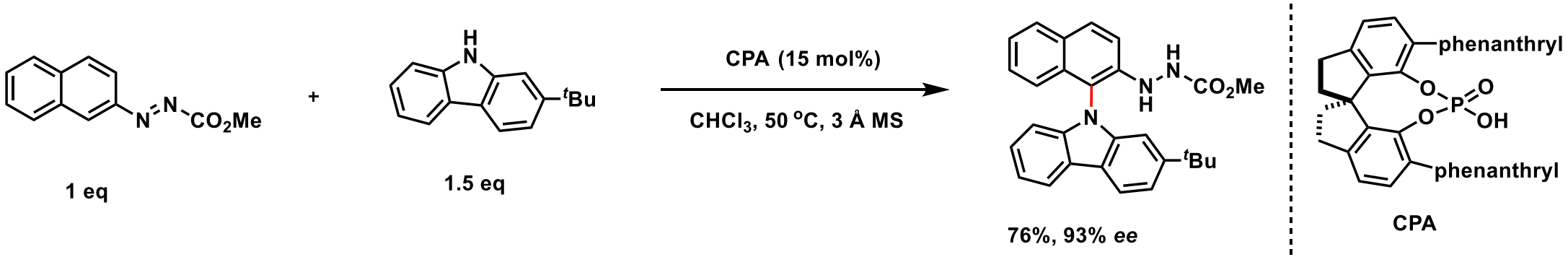
68%, 90% *ee*

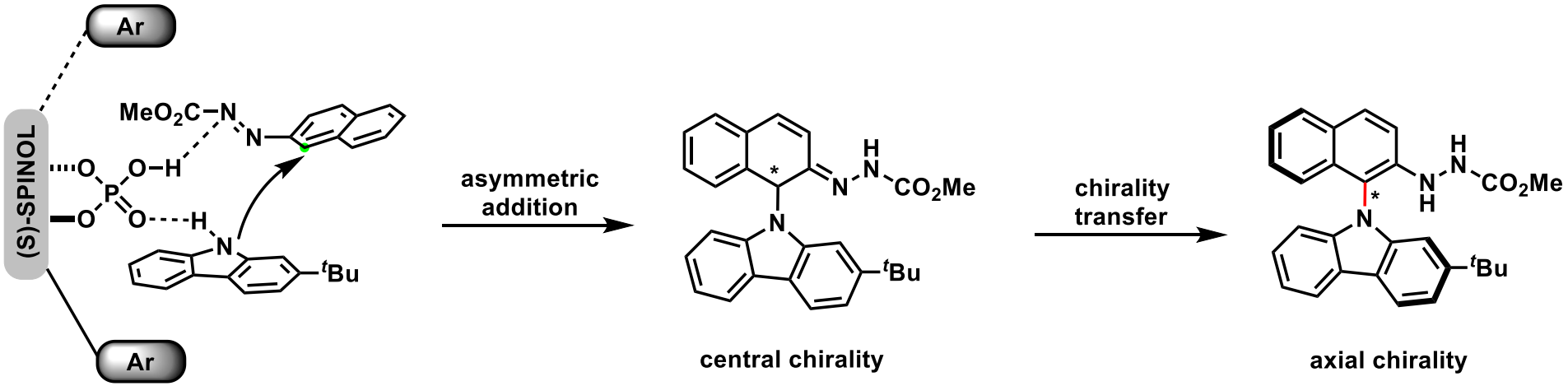


52%, 96% *ee*

F. Colobert, et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 8844-8848.

直接构建C-N键





B. Tan, et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 6775-6779.

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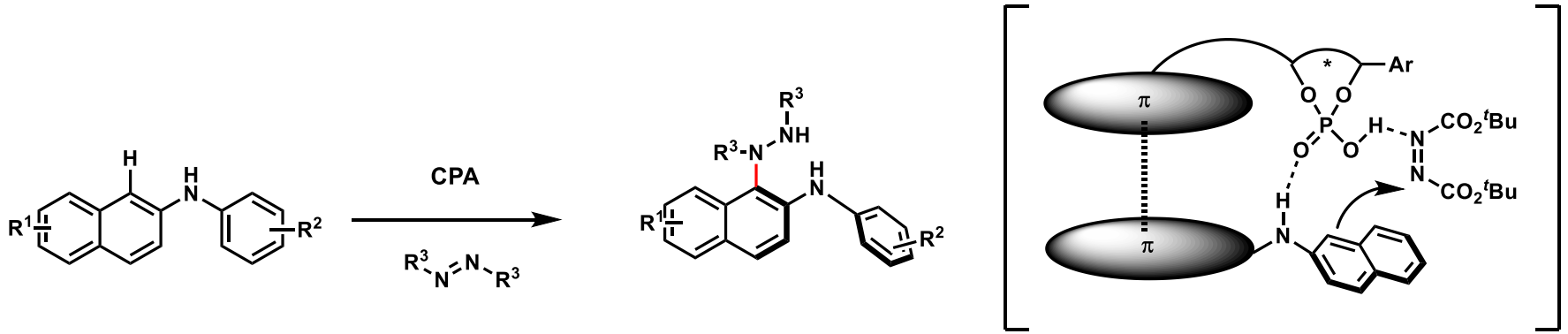
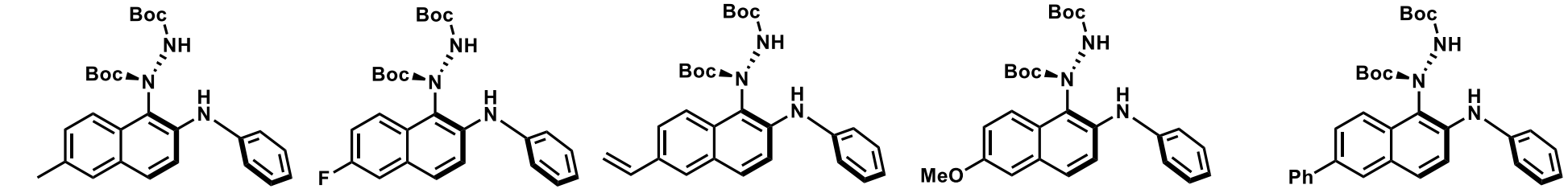
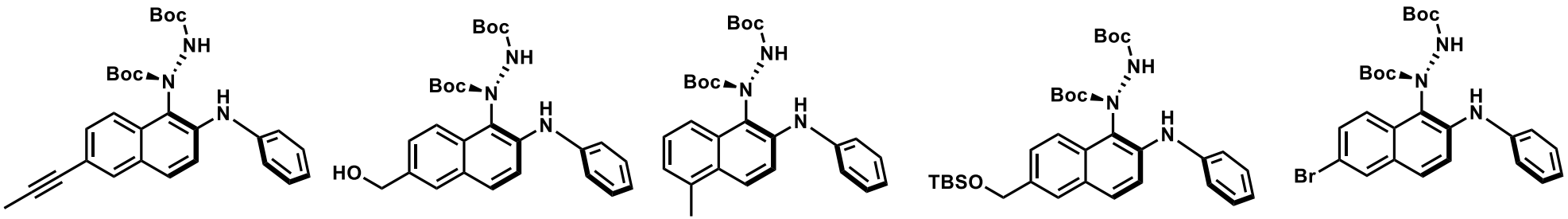




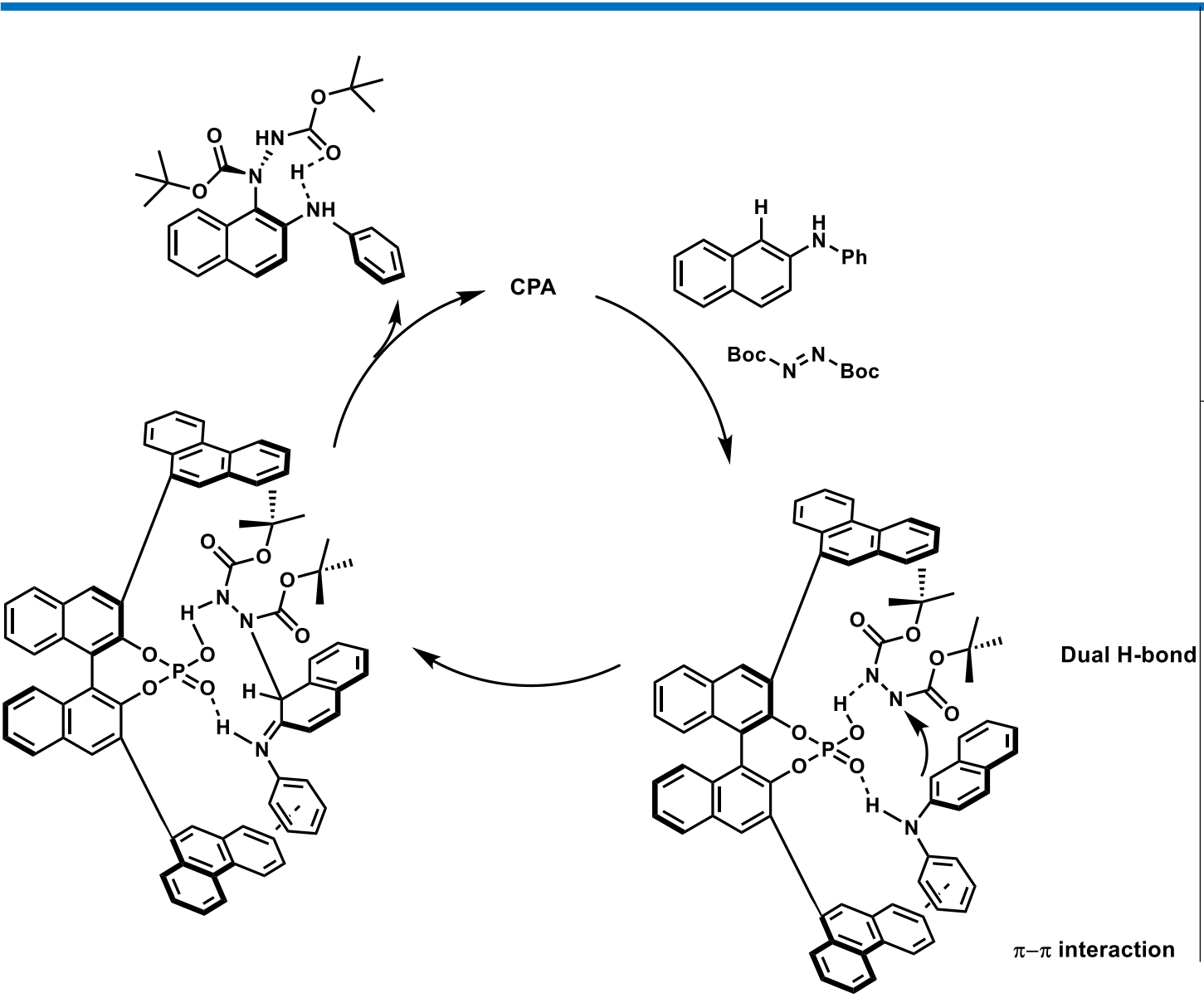
92%, 93% *ee* | 81%, 93% *ee* | 82%, 94% *ee* | 93%, 92% *ee* | 71%, 92% *ee*



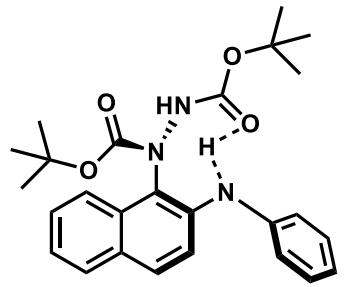
77%, 92% *ee* | 47%, 92% *ee* | 90%, 93% *ee* | 91%, 92% *ee* | 51%, 92% *ee*

S. Zhang, et al., *Nat. Commun.* **2019**, *10*, 3063-3012.

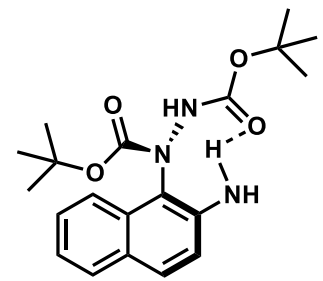
直接构建C-N键



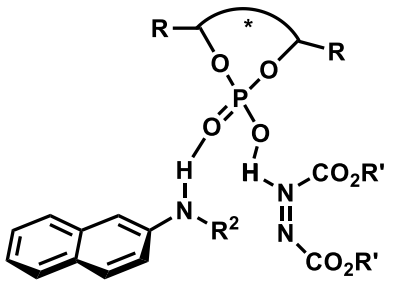
$t_{1/2\ rac}$ = 26 min



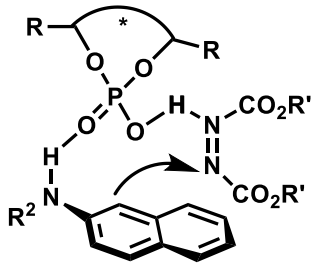
$t_{1/2\ rac}$ = 4257 min

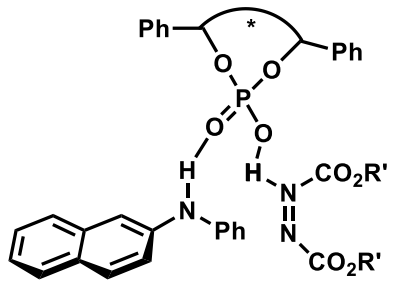


$t_{1/2\ rac}$ = 30886 min

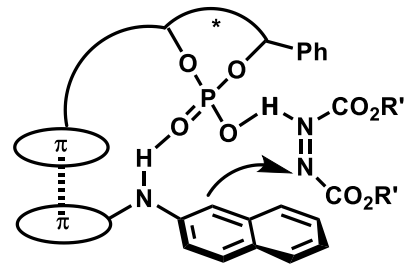


Dual H-bond control





π-π interaction
& dual H-bond
concerted control



S. Zhang, et al., *Nat. Commun.* **2019**, *10*, 3063.

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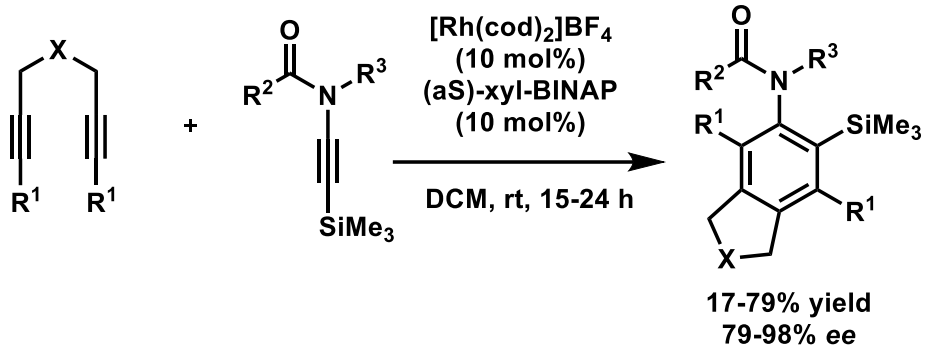

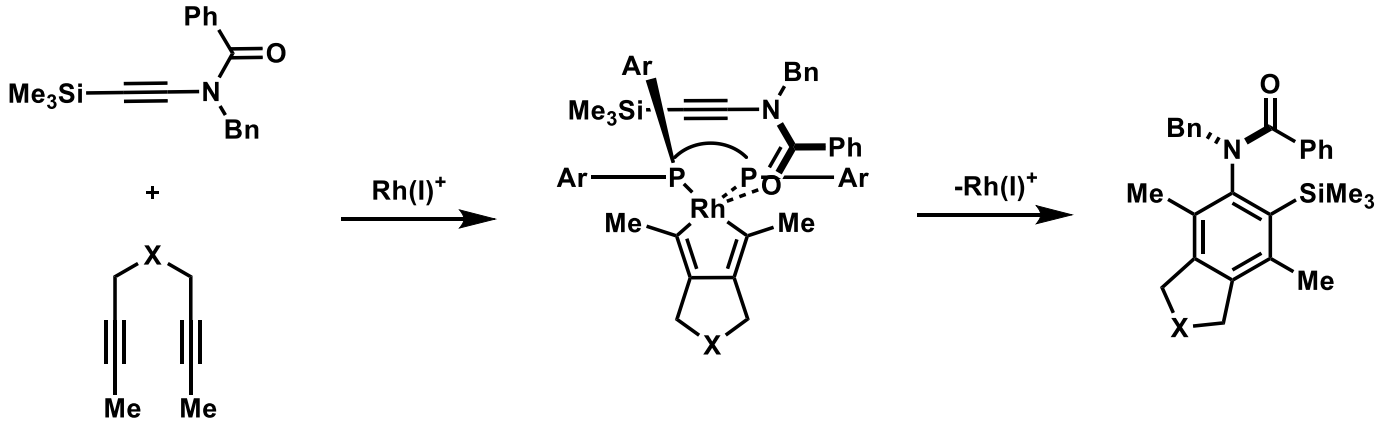

K. Tanaka, et al., *J. Am. Chem. Soc*. **2006**, *128*, 4586-4587.

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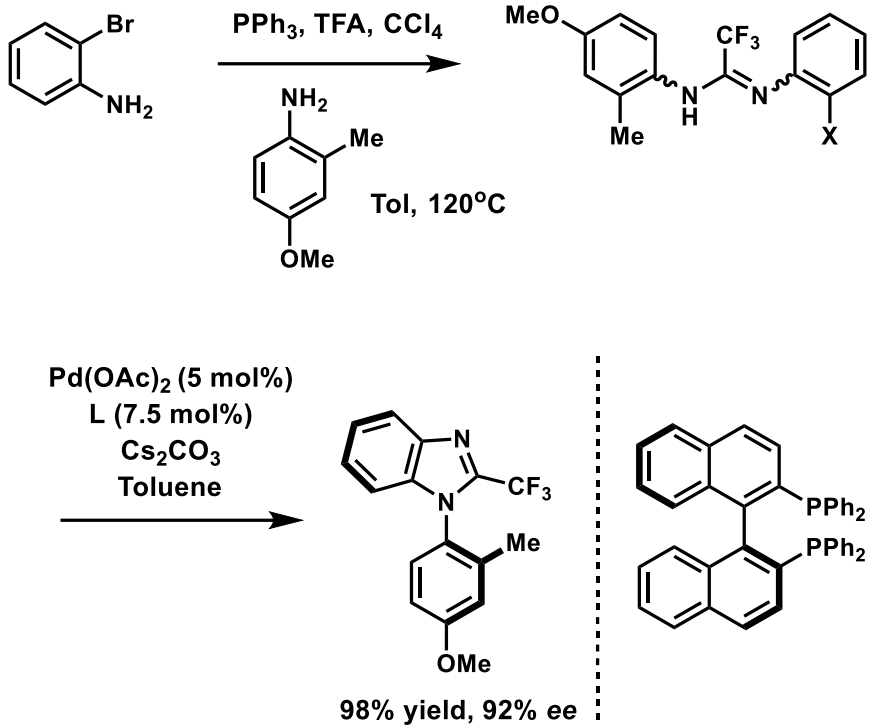

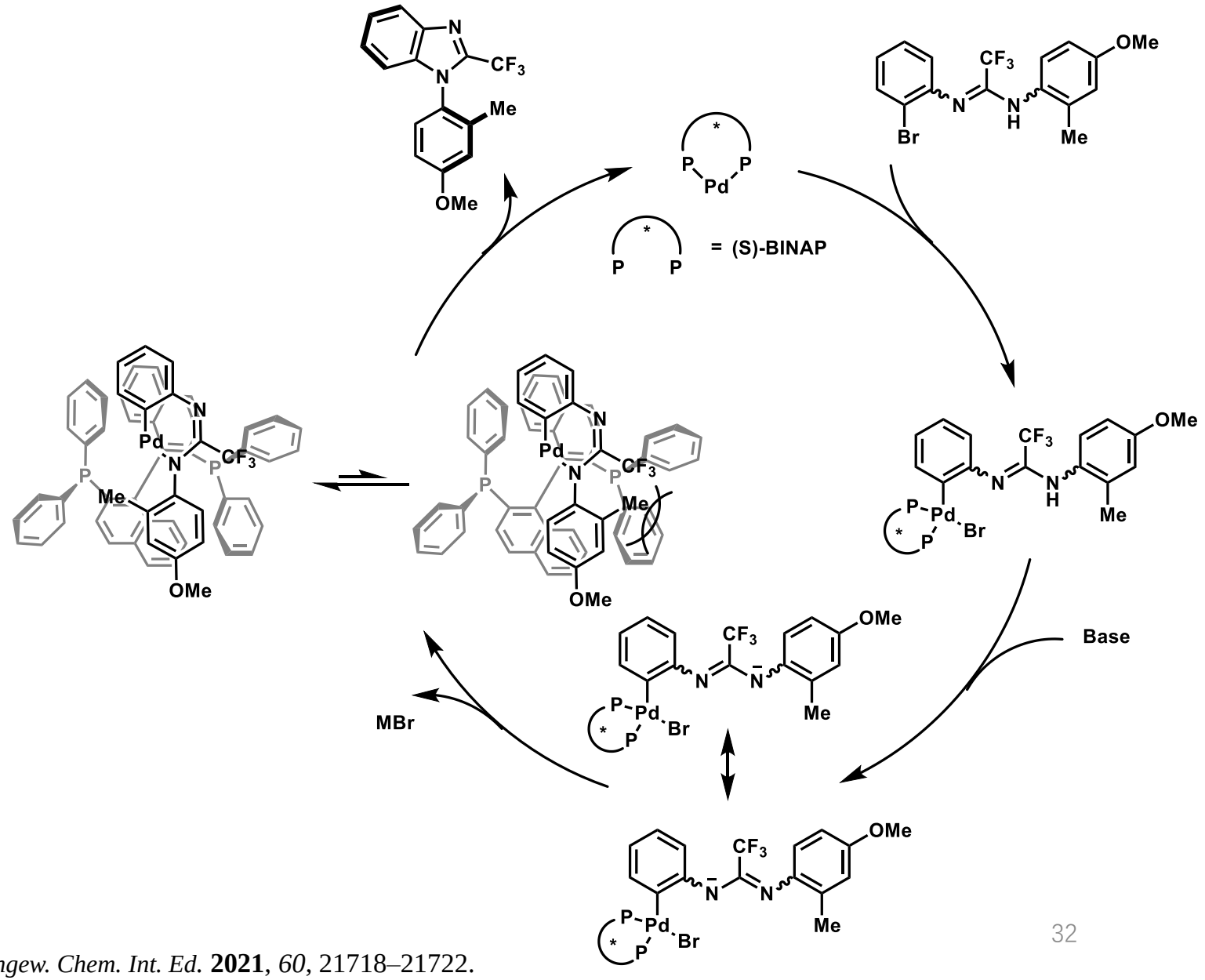

R. Liu, et al., *Angew. Chem. Int. Ed.* **2021**, *60*, 21718–21722.

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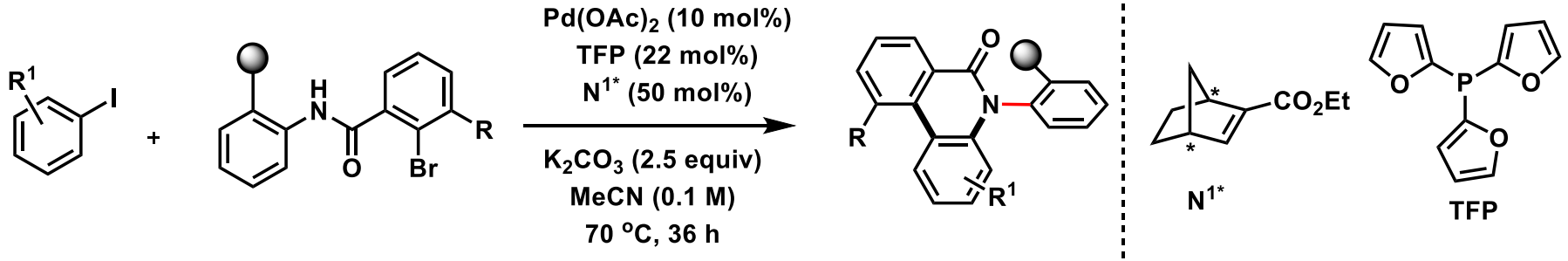
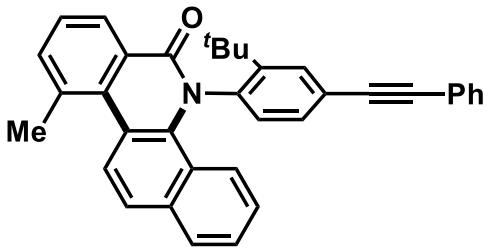
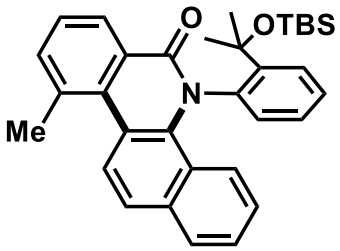
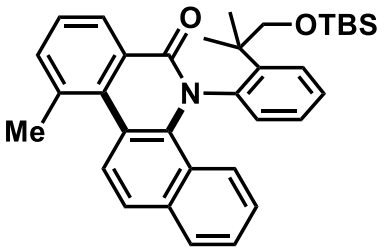




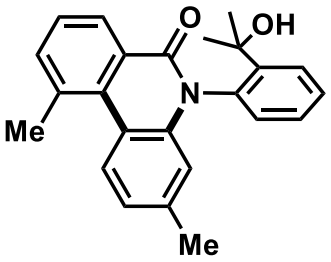
78%, 97% *ee*



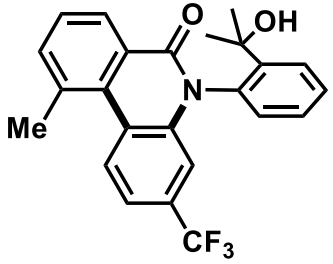
62%, 92% *ee*



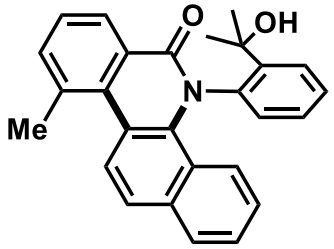
82%, 98% *ee*



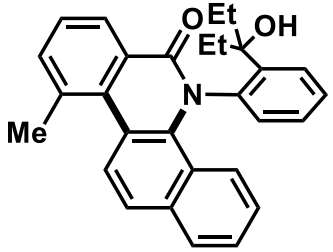
43%, 92% *ee*



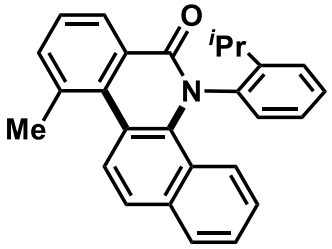
66%, 95% *ee*



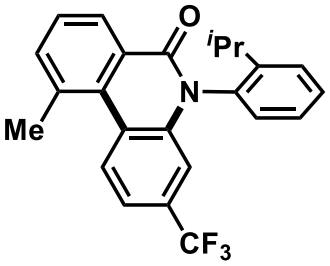
85%, 0% *ee*



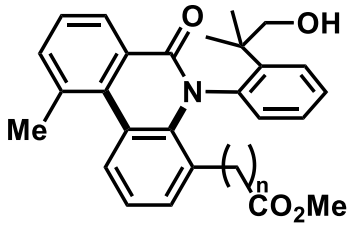
67%, 5% *ee*



98%, 0% *ee*



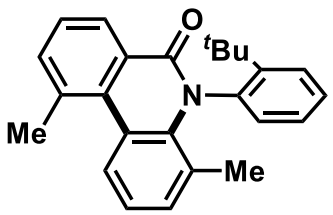
52%, 91% *ee*



n = 1 61%, 92% *ee*
n = 2 52%, 88% *ee*

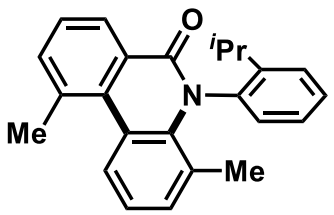
Q. Zhou, *et al.*, *Chem.* **2021**, *7*,1–16.

从头建含氮杂环/芳环



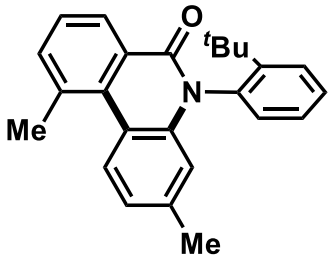
92% *ee*

$\Delta G^{\neq}_{rot}$ = 30.5 kcal/mol



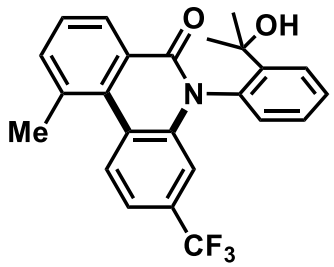
0% *ee*

$\Delta G^{\neq}_{rot}$ = 21.7 kcal/mol



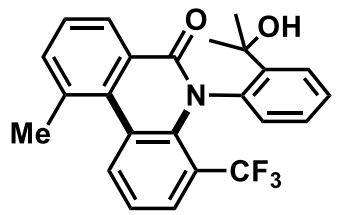
93% *ee*

$\Delta G^{\neq}_{rot}$ = 38.5 kcal/mol



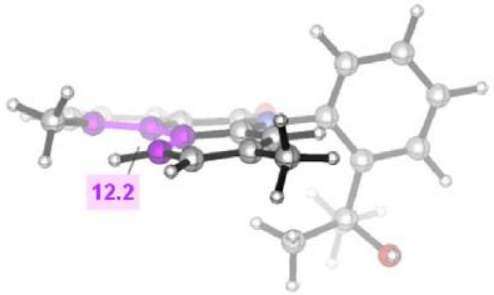
95% *ee*

$\Delta G^{\neq}_{rot}$ = 33.8 kcal/mol



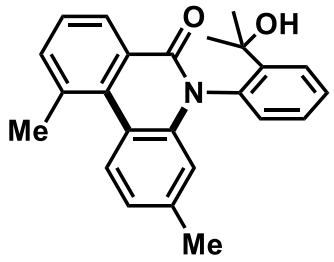
0% *ee*

$\Delta G^{\neq}_{rot}$ = 26.0 kcal/mol



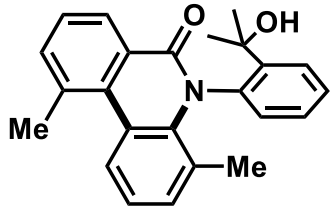
DFT optimized geometry

≡



92% *ee*

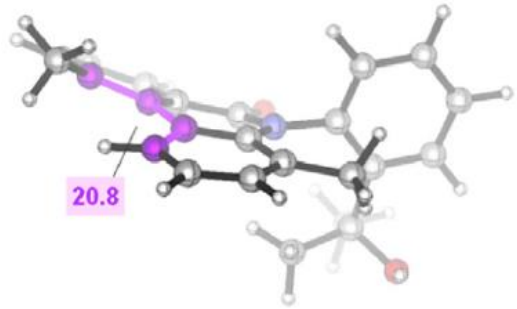
$\Delta G^{\neq}_{rot}$ = 33.0 kcal/mol



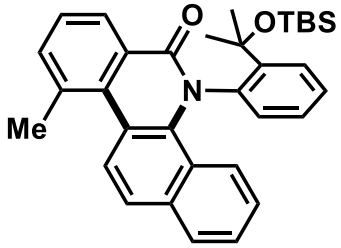
0% *ee*

$\Delta G^{\neq}_{rot}$ = 25.9 kcal/mol

≡



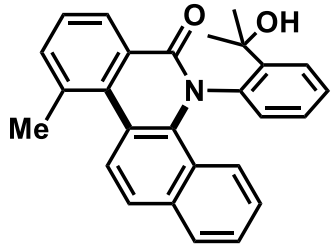
DFT optimized geometry



92% *ee*

TBAF

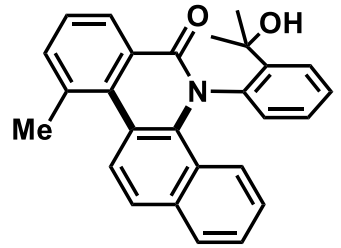
THF, rt, 24 h



70% *ee*

*i*PrOH, 70 °C, 3 h

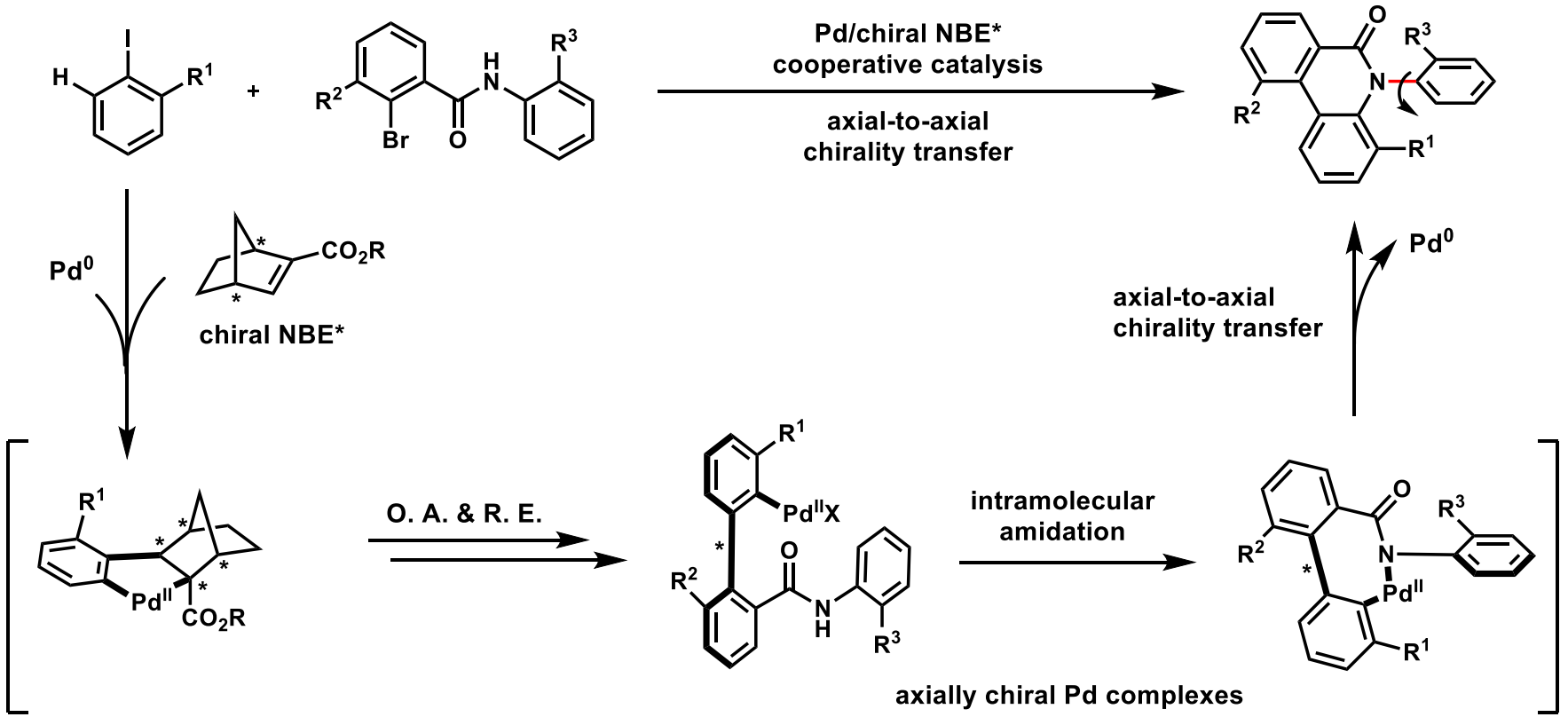
$\Delta G^{\neq}_{rot}$ = 26.7 kcal/mol



0% *ee*

Q. Zhou, *et al.*, *Chem.* **2021**, *7*,1–16.

从头建含氮杂环/芳环



Q. Zhou, *et al*., *Chem.* **2021**, *7*,1–16.

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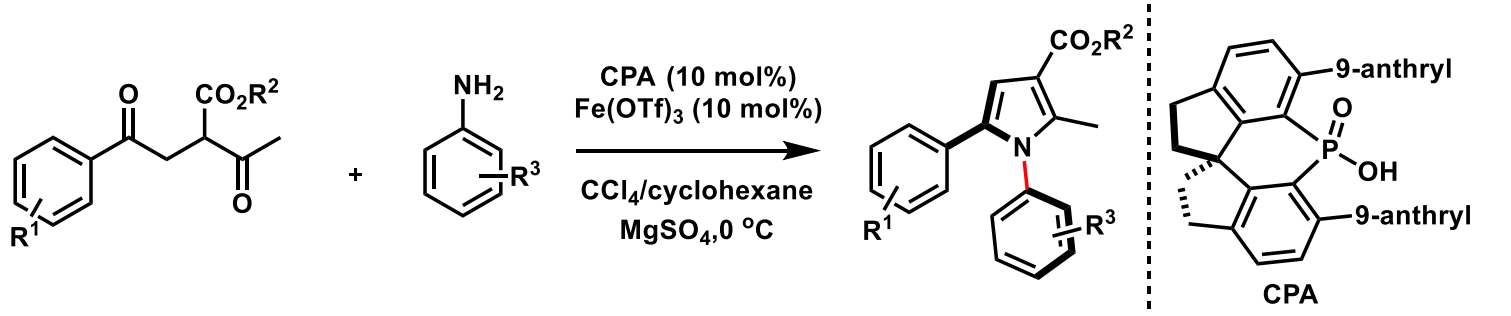
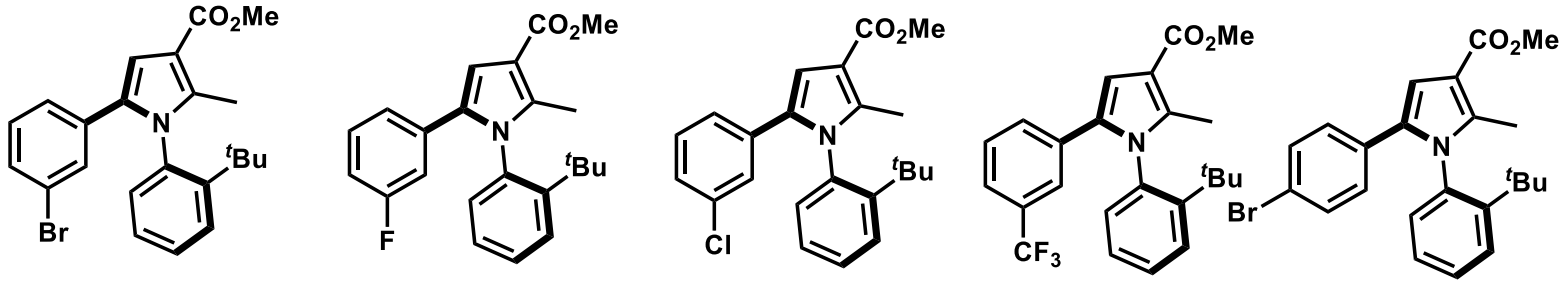
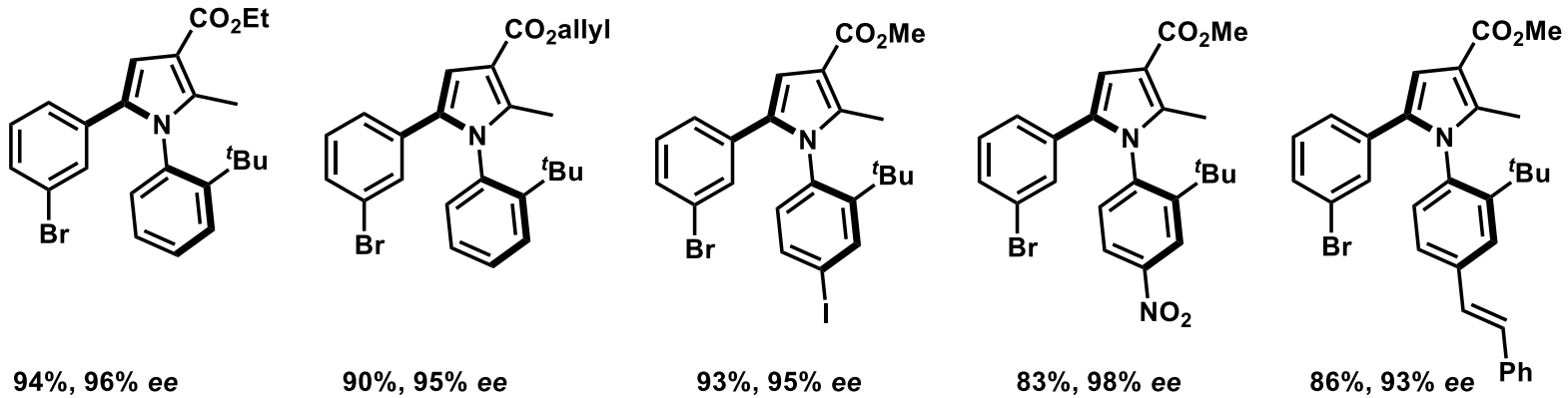




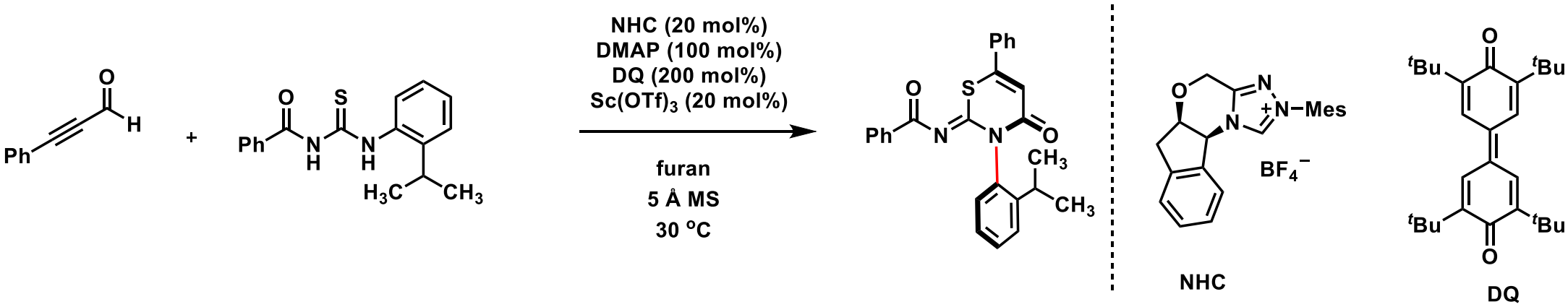
95%, 96% *ee*　91%, 95% *ee*　93%, 95% *ee*　94%, 96% *ee*　90%, 92% *ee*

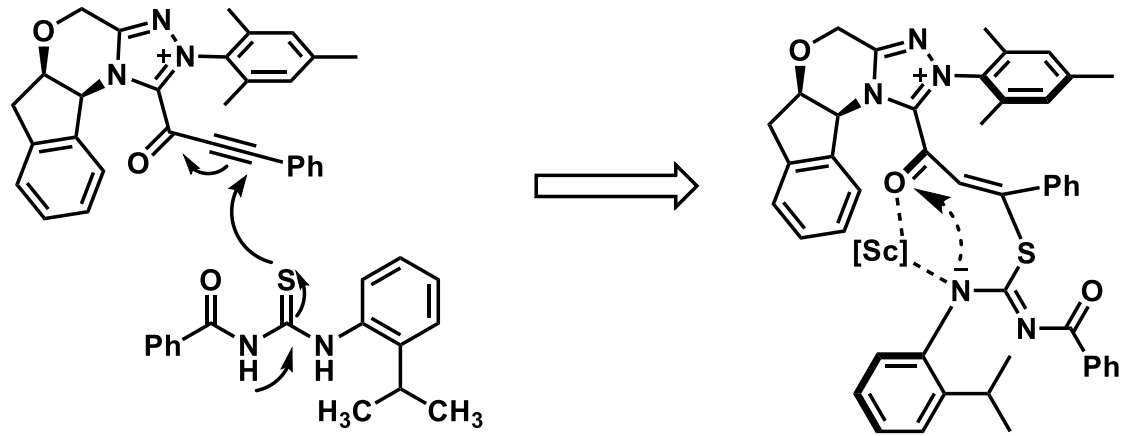


94%, 96% *ee*　90%, 95% *ee*　93%, 95% *ee*　83%, 98% *ee*　86%, 93% *ee*

B. Tan, et al., *J. Am. Chem. Soc.* **2017**, *139*, 1714-1717.

从头建含氮杂环/芳环





Z. Jin, et al., *Angew. Chem. Int. Ed.* **2021**, *60*, 9362–9367.

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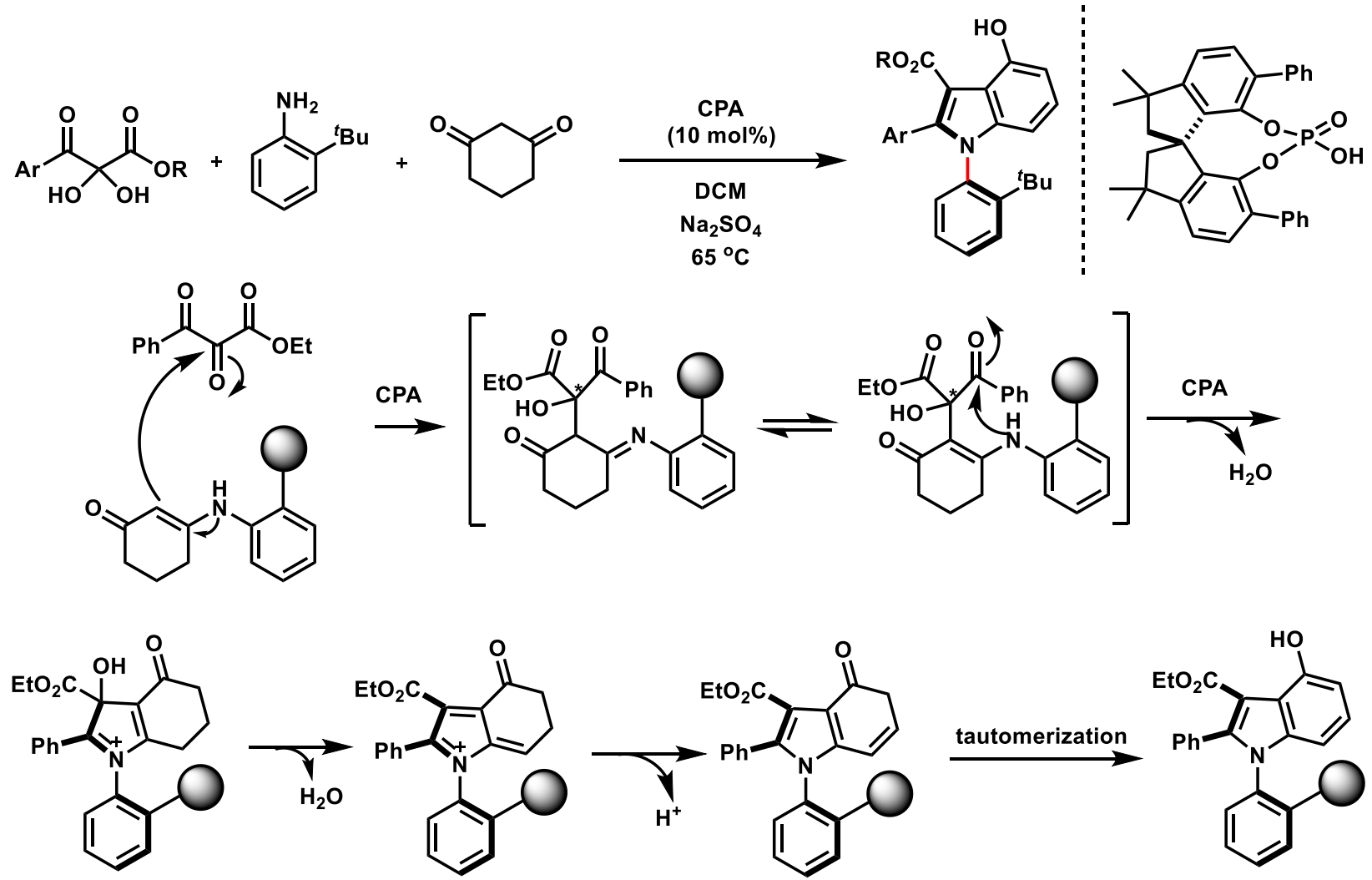

X. Lin, et al., *Angew. Chem. Int. Ed.* **2019**, *58*, 15824-15828.

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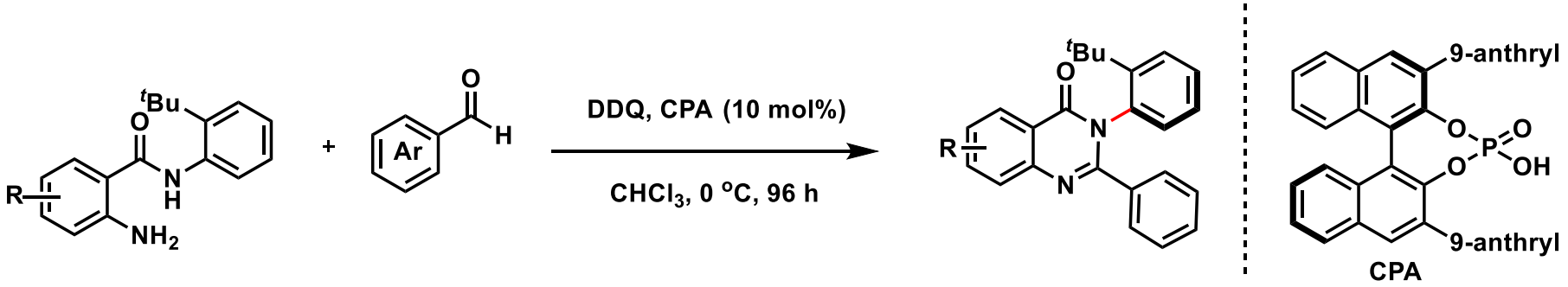


95%, 97% *ee*

95%, 94% *ee*

99%, 94% *ee*

90%, 91% *ee*

96%, 95% *ee*

96%, 92% *ee*

94%, 93% *ee*

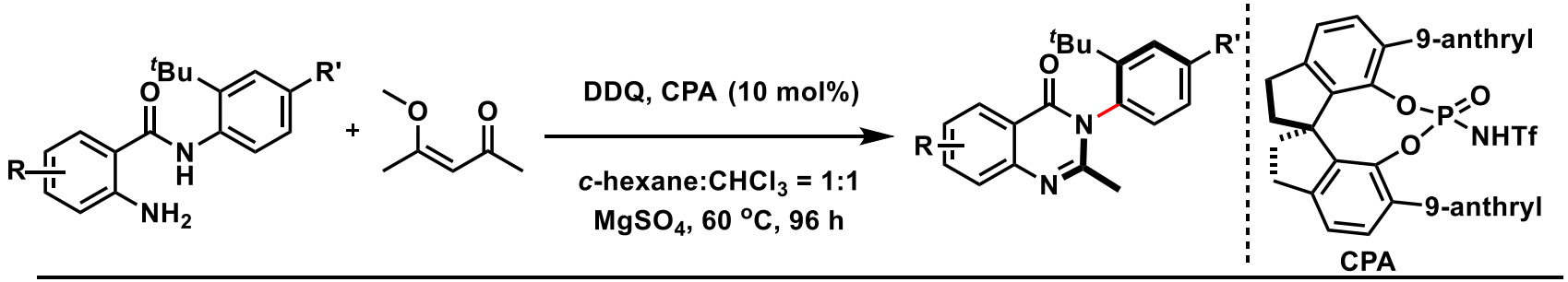
97%, 95% *ee*

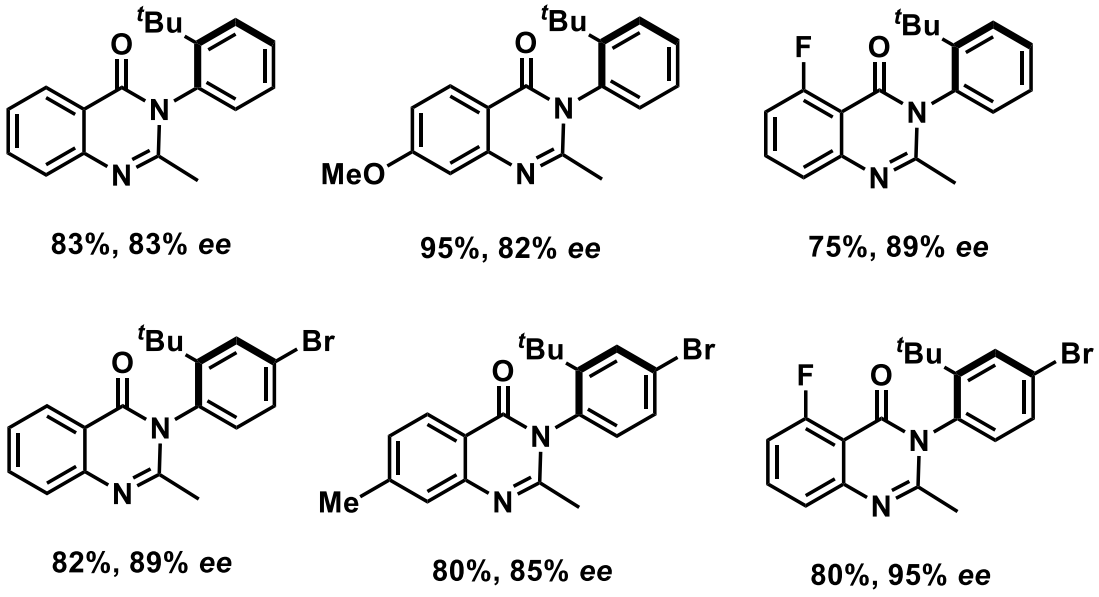
98%, 93% *ee*

95%, 94% *ee*

B. Tan, et al., *Nat. Commun.* **2017**, *8*, 15489-15498.

从头建含氮杂环/芳环





B. Tan, et al., *Nat. Commun.* **2017**, *8*, 15489-15498.

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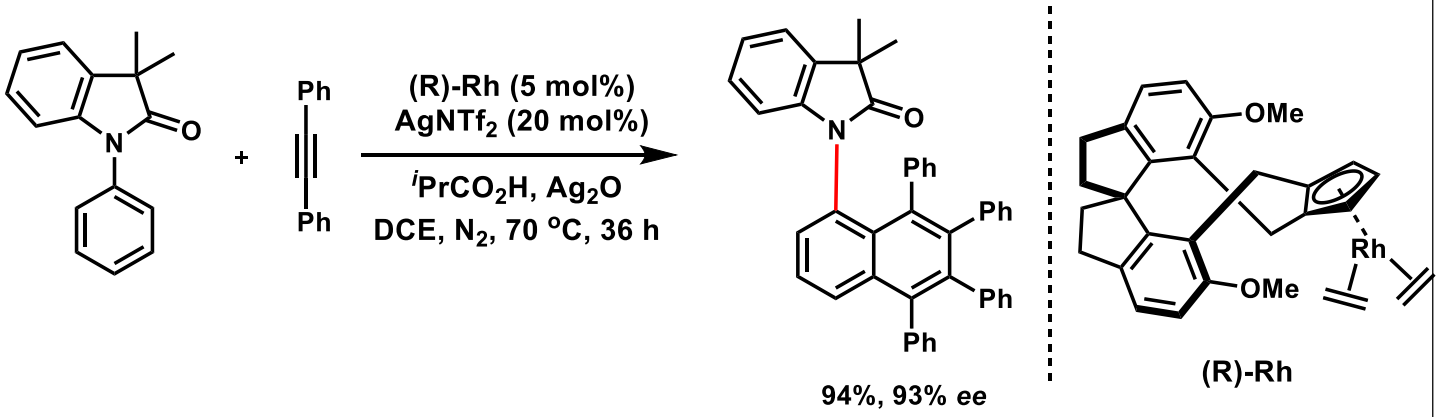
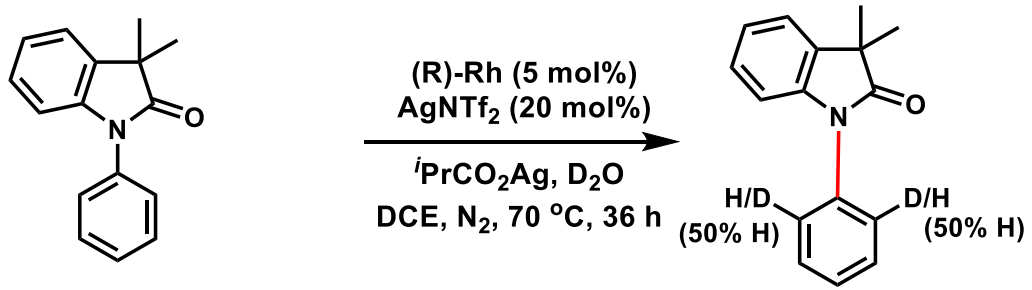
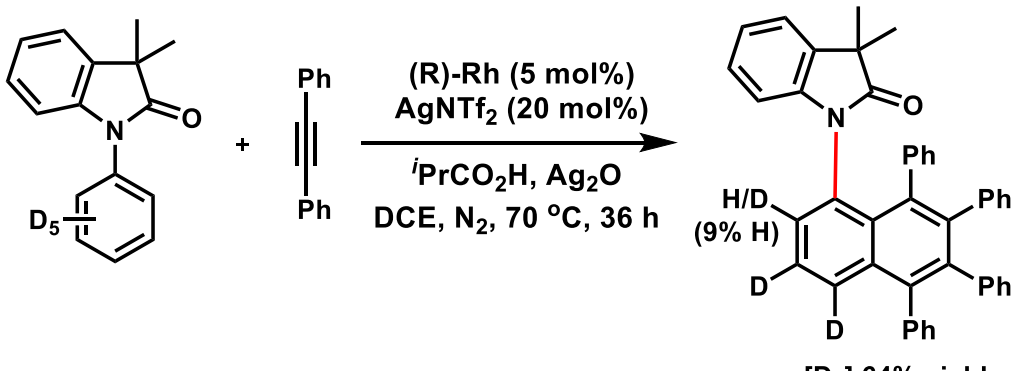
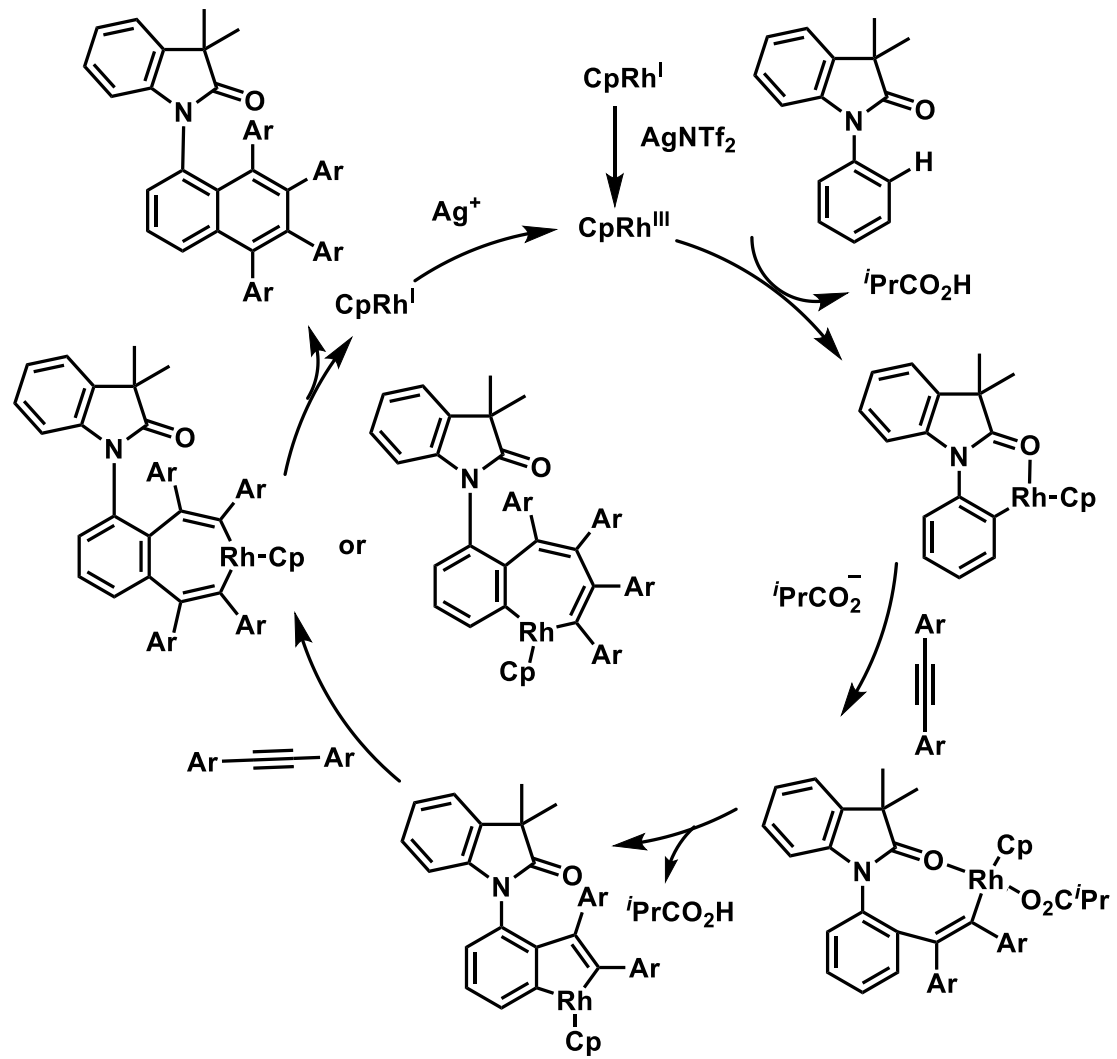
C-H官能团化



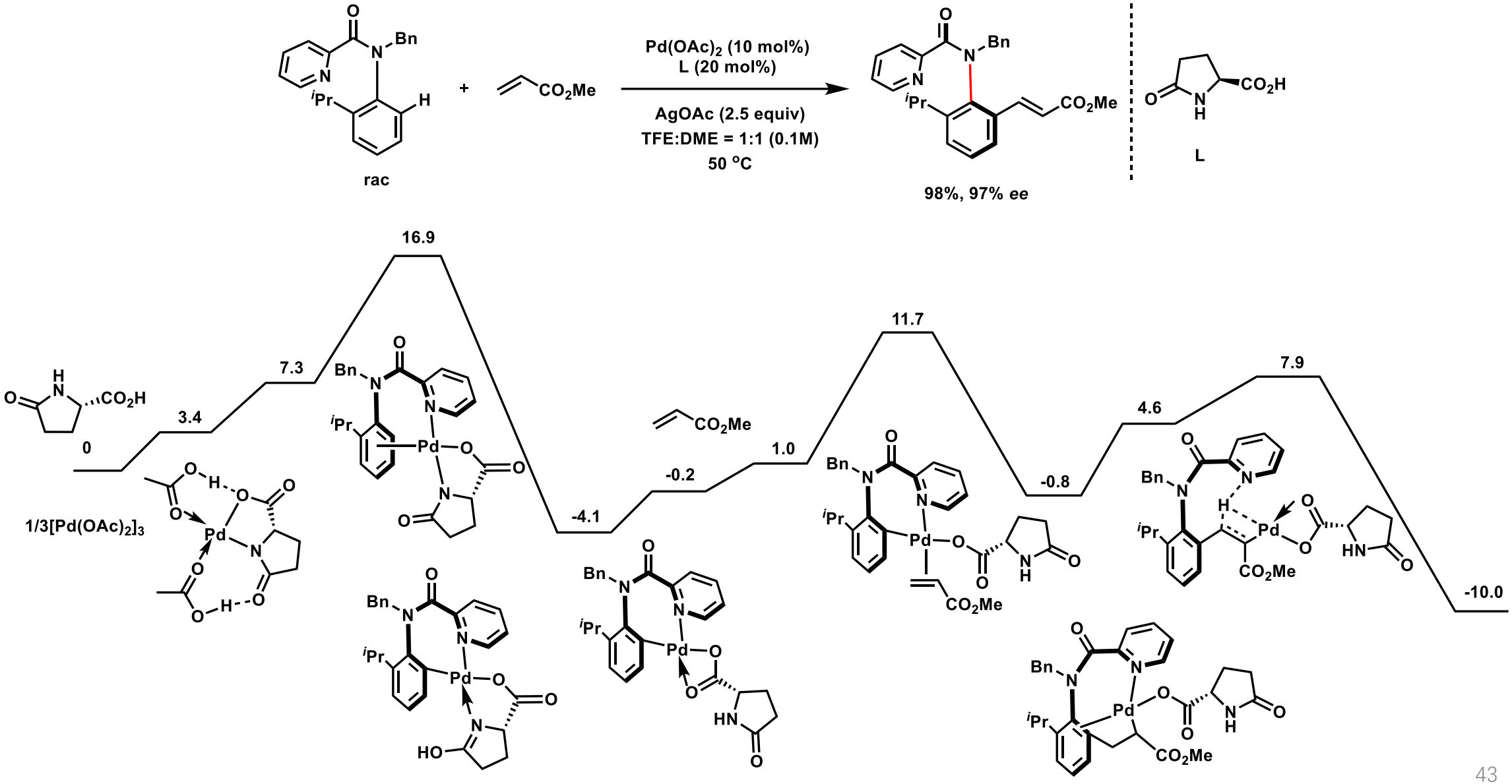






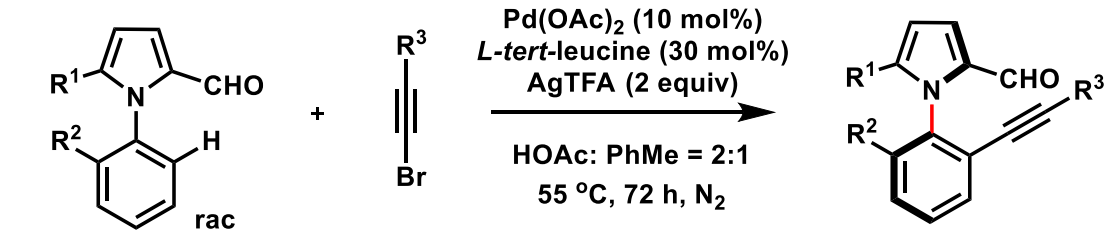
J. Wang, et al., *Angew. Chem. Int. Ed.* **2019**, *58*, 6732-6736.

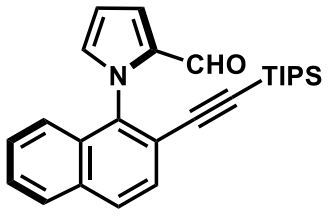
C-H官能团化



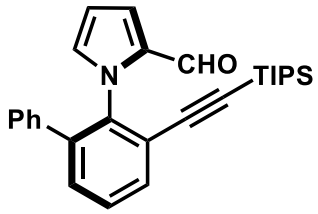
B. Shi, et al., *J. Am. Chem. Soc.* **2020**, *142*, 18266-18276.

C-H官能团化

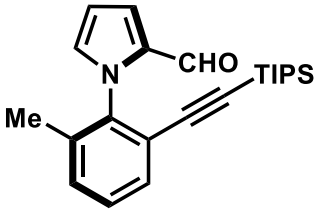




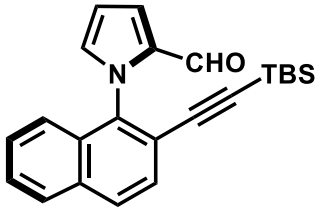
37%, 98% *ee*



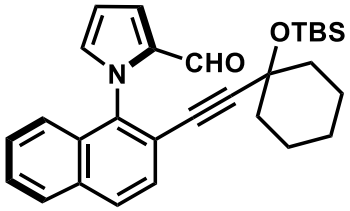
67%, 64% *ee*



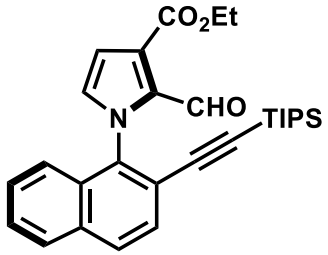
66%, 98% *ee*



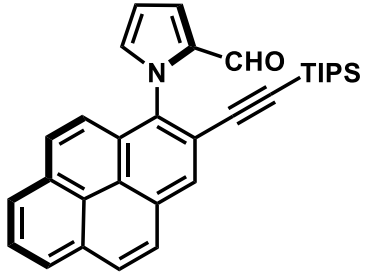
50%, 97% *ee*



61%, 98% *ee*



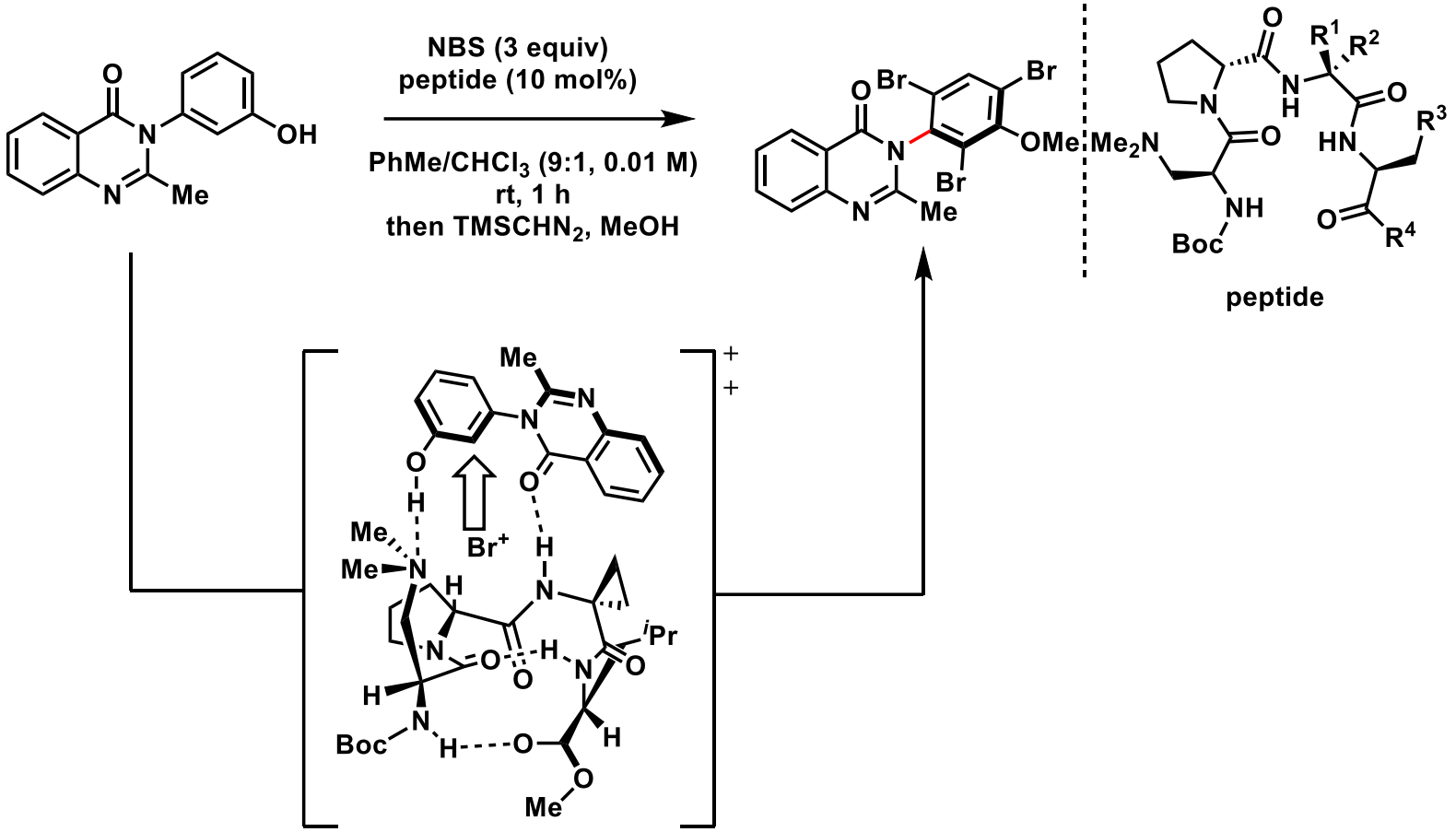
87%, 98% *ee*



63%, >99% *ee*

B. Shi, et al., *ACS Catalysis.* **2019**, *9*, 1956-1961.

C-H官能团化



a) S. J. Miller, et al., *J. Am. Chem. Soc*. **2018**, *140*, 868-871.
b) S. J. Miller, et al., *J. Am. Chem. Soc*. **2015**, *137*, 12369−12377.

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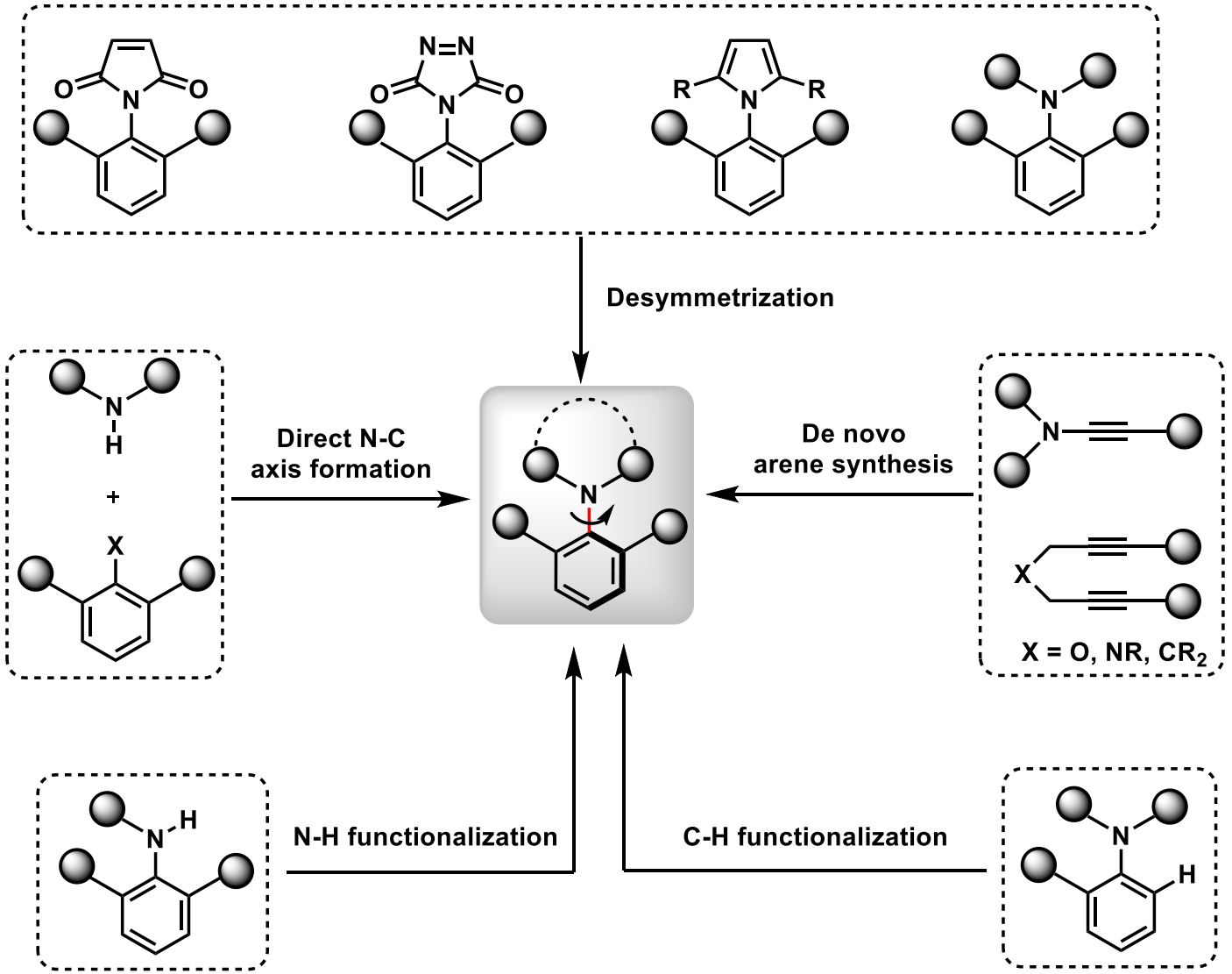
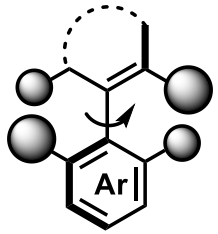
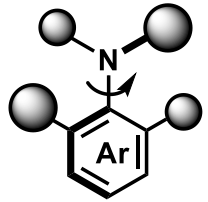
C-N键轴手性的构建策略



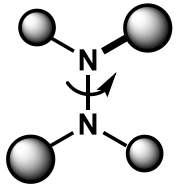
总结与展望



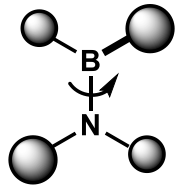
C-C bond
developed



C-X bond
underdeveloped

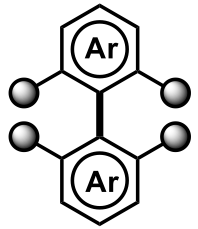


N-N bond
rarely developed

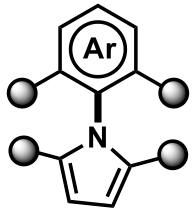


B-N bond

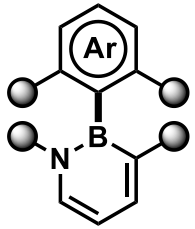
Bond length of stereogenic axis in various (hetero)biaryl atropisomers



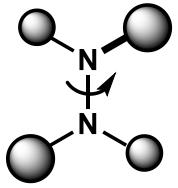
C-C atropisomers
C-C bond: 1.48 A



C-N atropisomers
C-N bond: 1.44 A



C-B atropisomers
C-B bond: 1.58 A

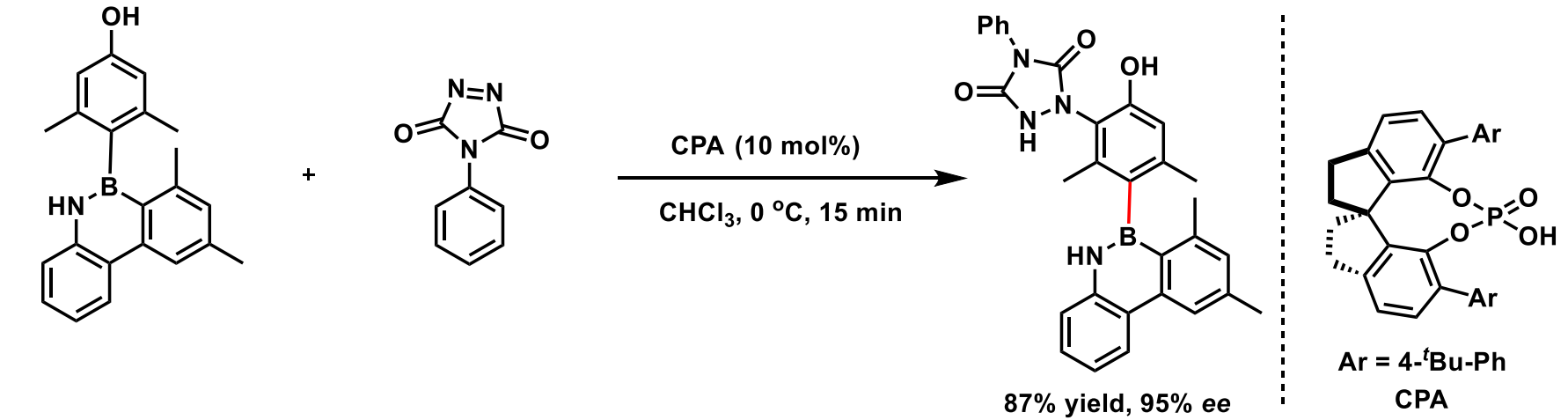


N-N atropisomers

Challenges(C-B)
Longer C-B bond length
Limited structural diversity
Lower axis rotation barrier
No enantiocontrol mode

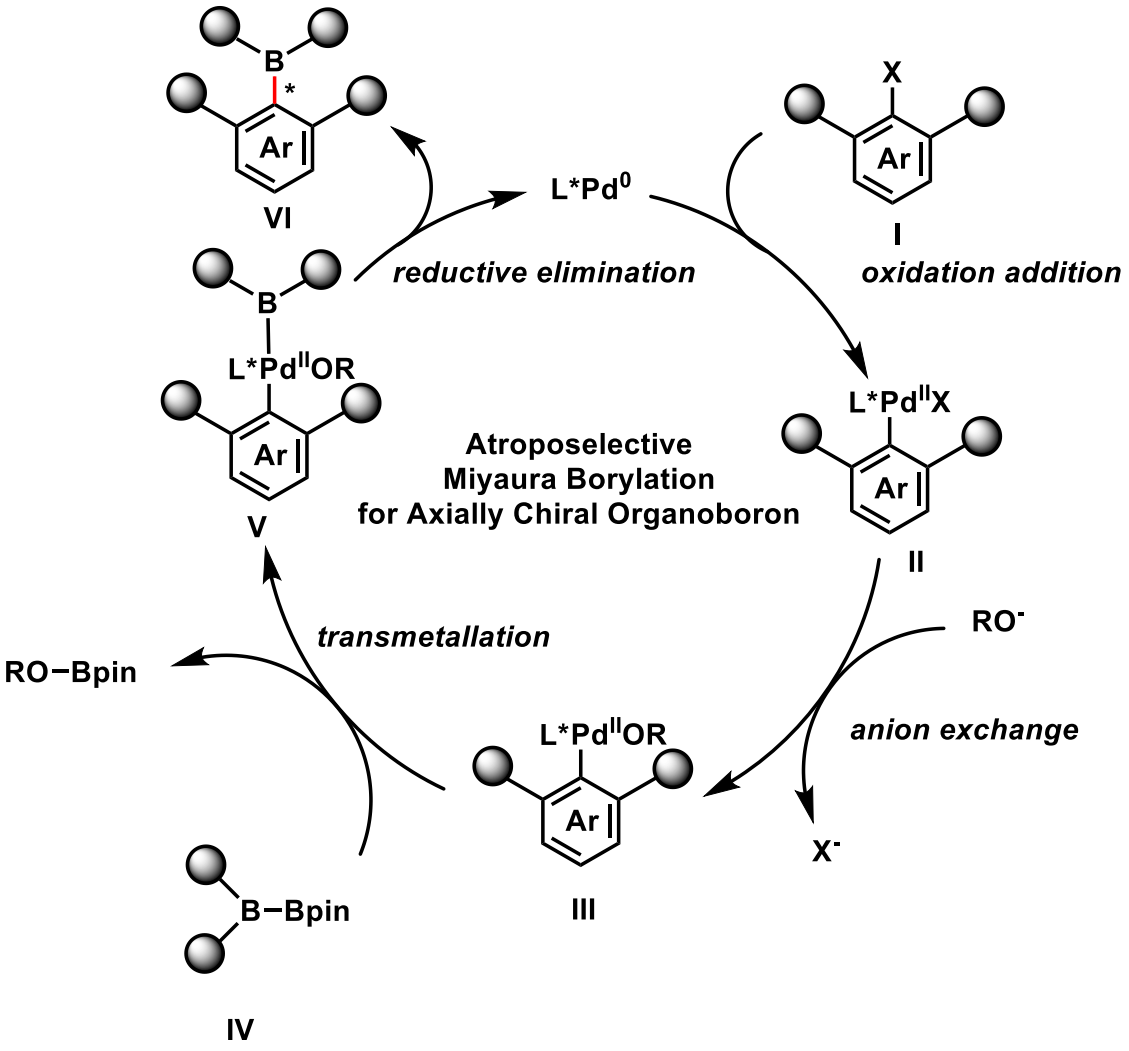
Challenges(N-N)
Weeker single bond
Deplanarization
Lower rotational barriers
Less stable conformation

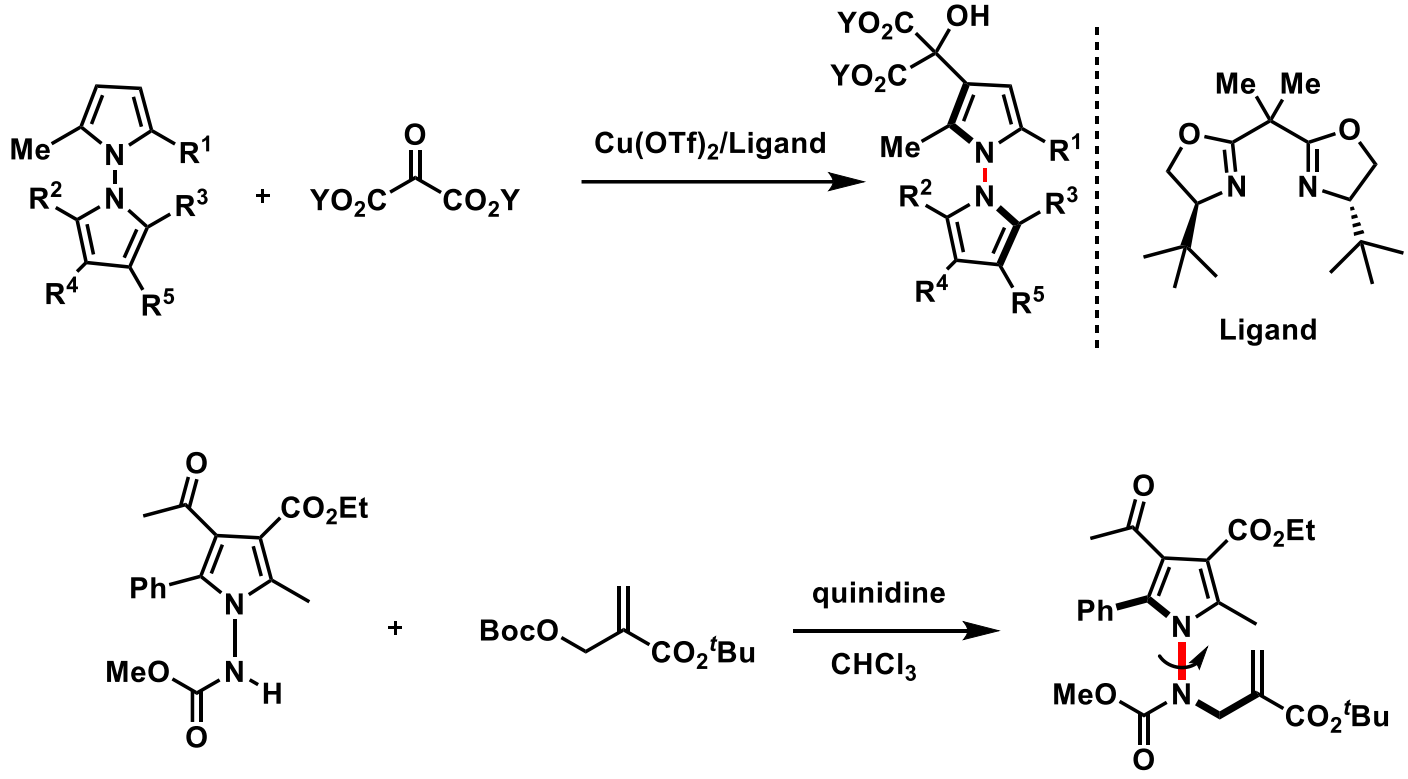
总结与展望



B. Tan, et al., *J. Am. Chem. Soc.* **2021**, *143*, 12924−12929.

总结与展望





a) Q. Song, et al., *J. Am. Chem. Soc.* **2021**, *143*, 10048−10053.
b) R. Liu, et al., *J Am Chem Soc.* **2021**, *143*, 15005-15010.
c) Y. Lu, et al., *Chem.* **2021**, *7*, 1-15.

THANKS FOR YOUR KIND ATTENTION