Literature Report 3

Enantioselective Synthesis of N-N Biaryl Atropisomers through Iridium(I)-Catalyzed C-H Alkylation with Acrylates

Reporter: Hao-Dong Chen
Checker: Zheng Liu
Date: 2023-09-25

Yin, S.-Y.; Zhou, Q.; You, S.-L. *Angew. Chem. Int. Ed.* **2023**, *62*, e202305067

CV of Prof. Shu-Li You

Background:

- **1992-1996** B.S., Nankai University
- **1996-2001** Ph.D., Shanghai Institution of Organic Chemistry
- **2001-2004** Postdoctoral Fellow, The Scripps Research Institute
- **2004-2006** Principal Investigator, Genomics Institute of the Novartis Research Foundation
- **2006-now** Professor, Shanghai Institute of Organic Chemistry

Research:

- **Catalytic Asymmetric Dearomatization**
- **Catalytic Asymmetric C-H Functionalization**
- **Development of New Chiral Ligands and Catalysts**

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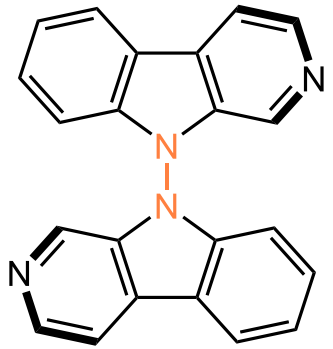
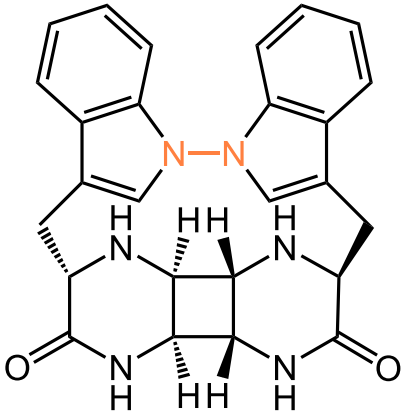
N-N Biaryl Atropisomers



β-Carbonline dimer



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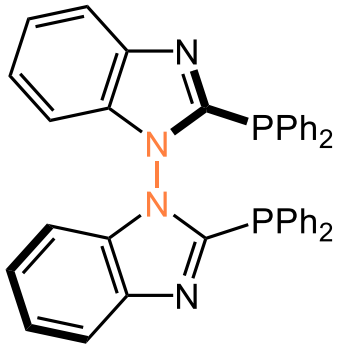


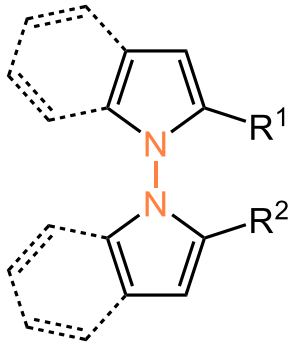
BIMIP

Kearns, P. S.; Coll, J. C.; Rideout, J. A. *et al. J. Nat. Prod.* **1995**, *58*, 1075
Shoeb, M.; Celik, S.; Sarker, S. D. *et al. Tetrahedron* **2005**, *61*, 9001
Benincori, T.; Brenna, E.; Sannicolò, F. *et al. J. Organnmet. Chem.* **1997**, *529*, 445

Introduction

Enantioselective Construction of N-N Biaryl Atropisomers

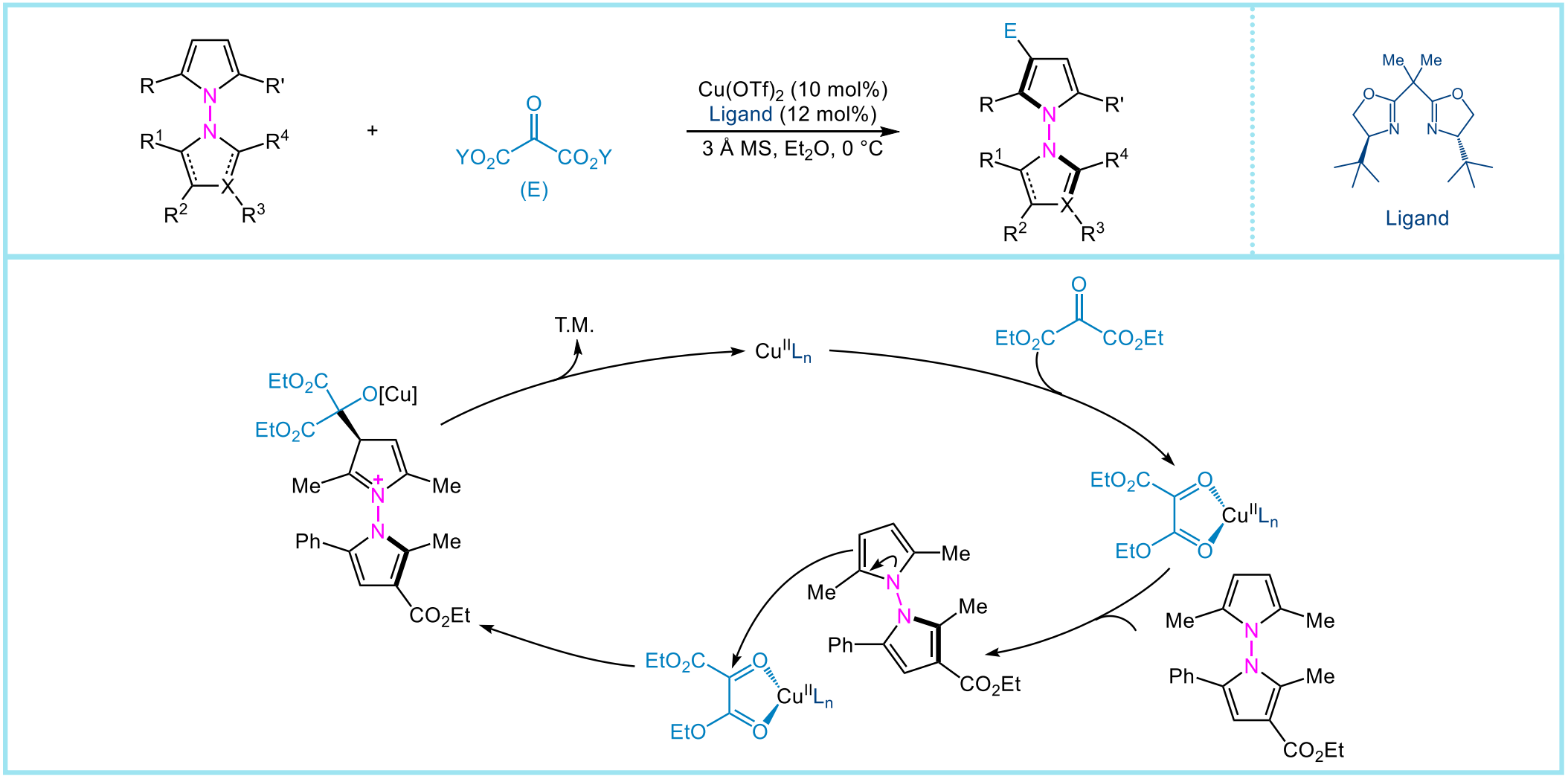
Previous work



- **Liu** Desymmetrization of pyrrole
- **Shi, Zhao** CPA-catalyzed asymmetric pyrrole formation
- **Liu** Pd-catalyzed asymmetric C-N coupling
- **Shi, Yang** CPA-catalyzed asymmetric indole formation
- **Sparr** Pd-catalyzed asymmetric indole formation

Introduction

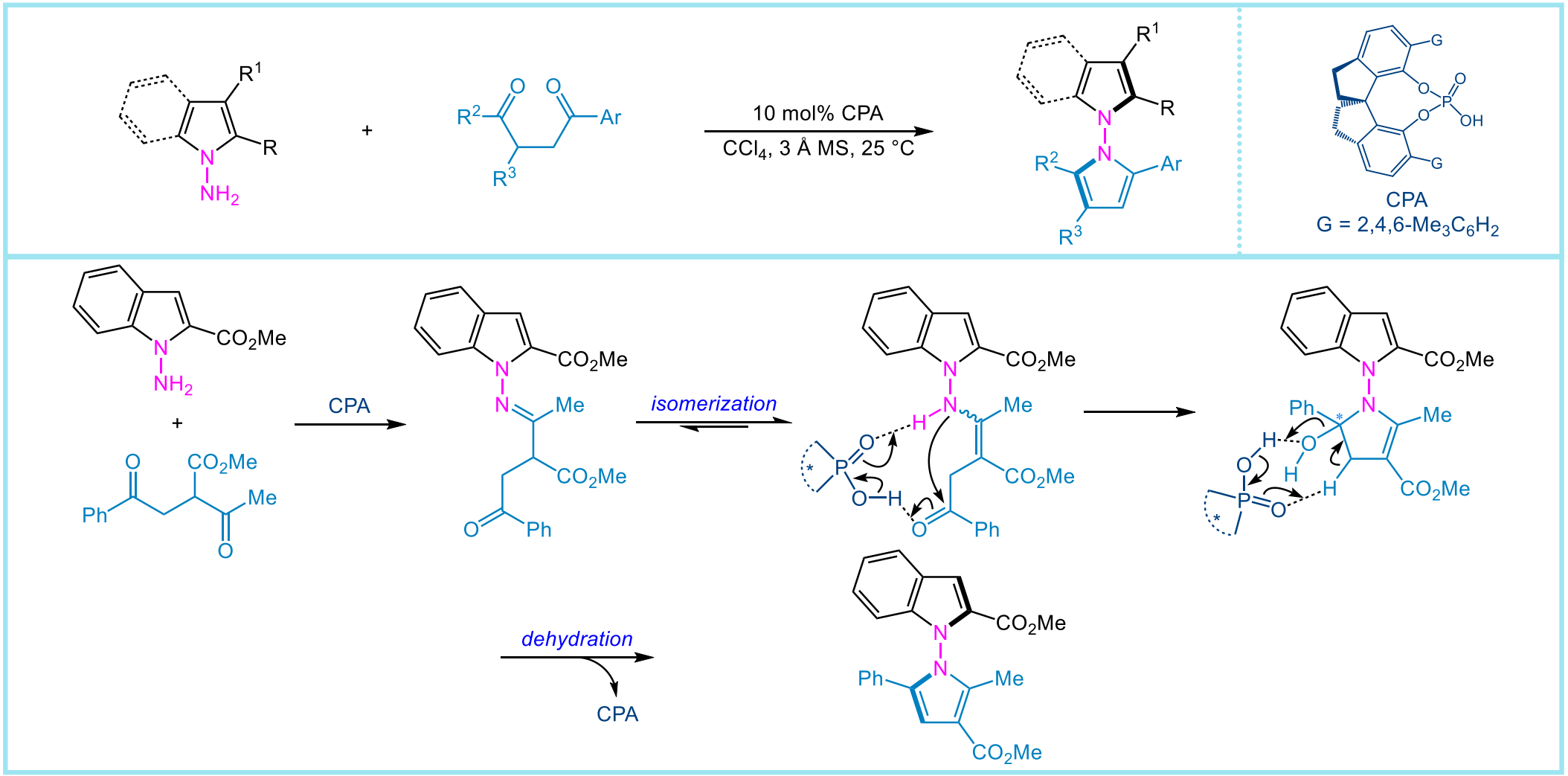
Desymmetrization of Bispyrrole



Wang, X.-M.; Zhang, P.; Liu, R.-R. *et al. J. Am. Chem. Soc.* **2021**, *143*, 15005

Introduction

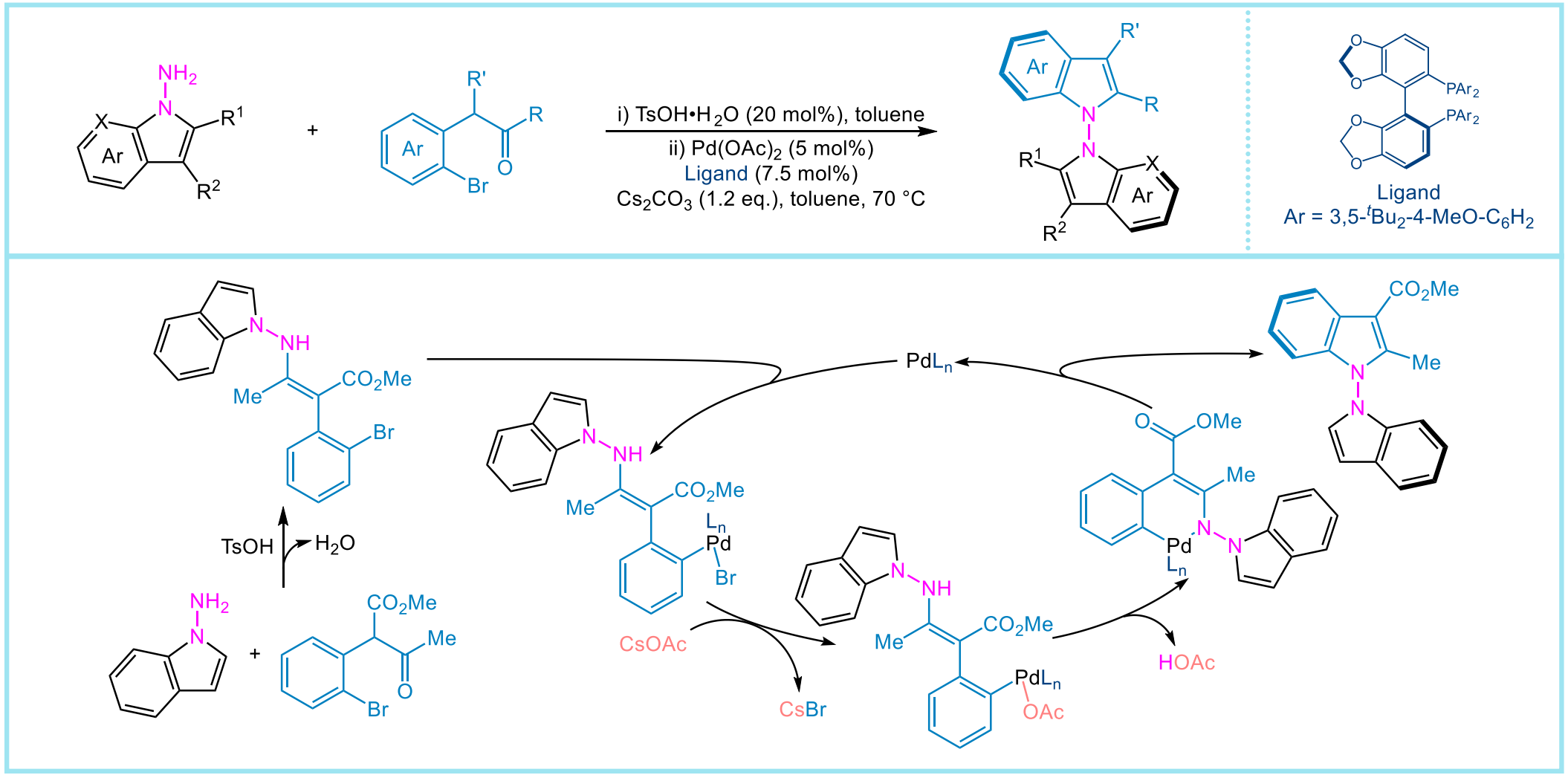
CPA-Catalyzed Asymmetric Pyrrole Formation



Chen, K.-W.; Chen, Z.-H.; Shi, F. *et al. Angew. Chem. Int. Ed.* **2022**, *61*, e202116829

Introduction

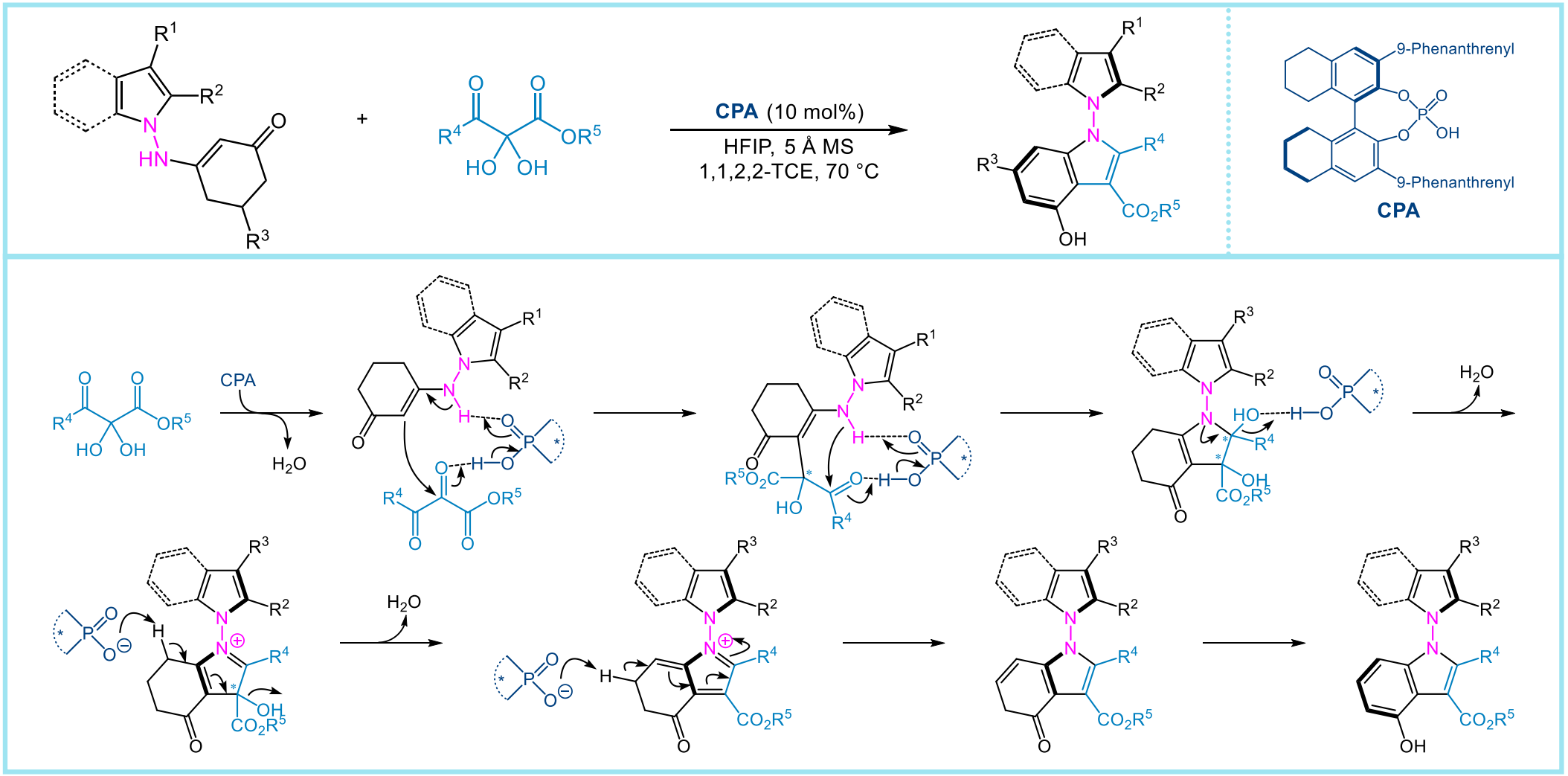
Pd-Catalyzed Asymmetric C-N Coupling



Zhang, P.; Xu, Q.; Liu, R.-R. *et al. Angew. Chem. Int. Ed.* **2022**, *61*, e202212101

Introduction

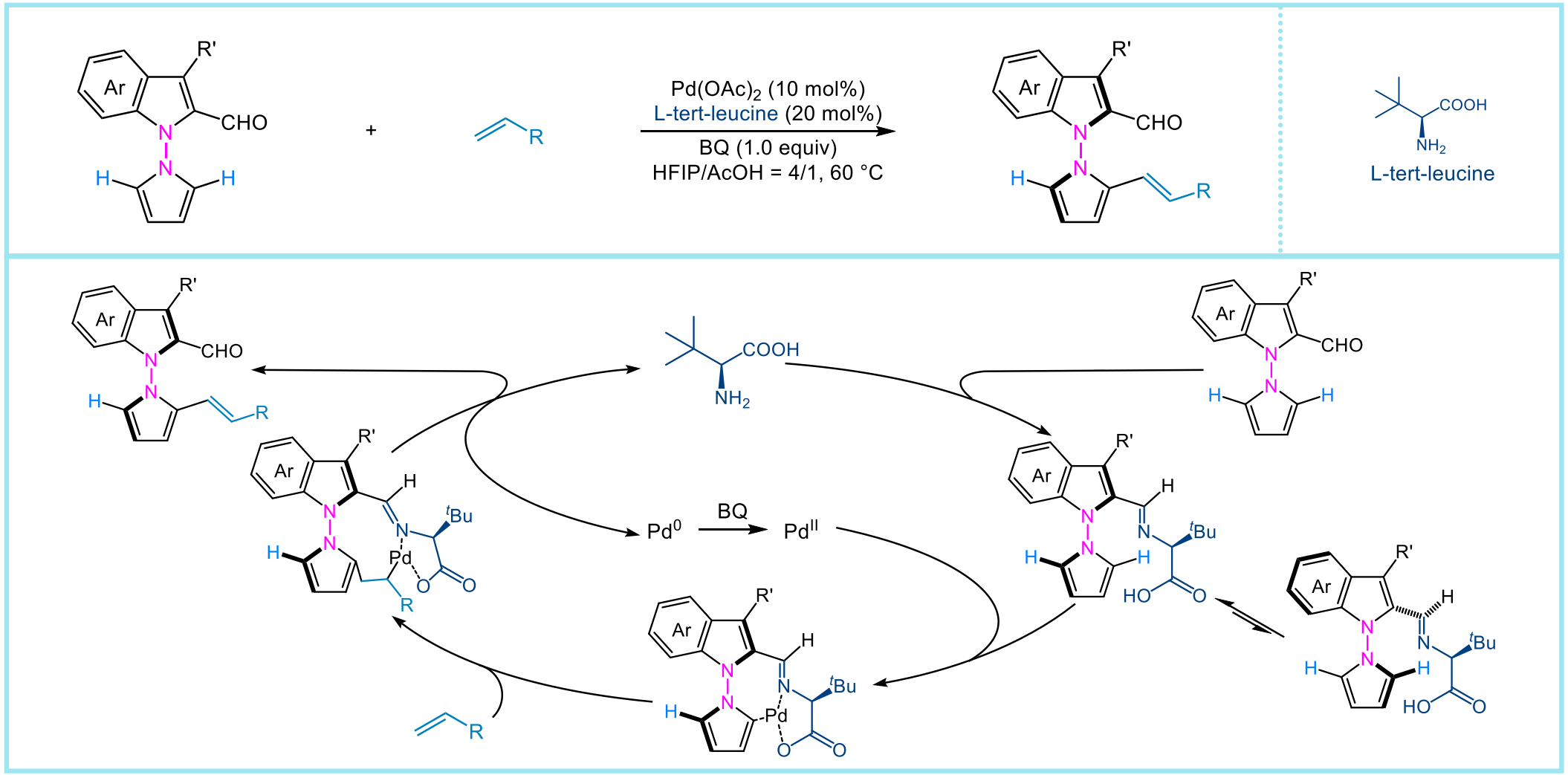
CPA-Catalyzed Asymmetric Indole Formation



Chen, Z.-H.; Li, T.-Z.; Shi, F. *et al. Angew. Chem. Int. Ed.* **2023**, *62*, e202300419

Introduction

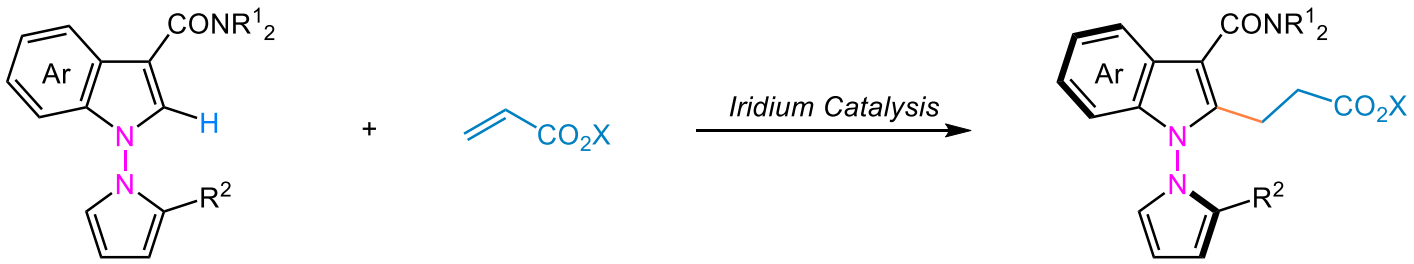
Pd-Catalyzed C-H Functionalization of Pyrroles



Yao, W.; Lu, C.-J.; Liu, R.-R. *et al. Angew. Chem. Int. Ed.* **2023**, *62*, e202218871

Introduction

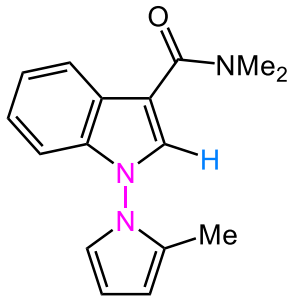
Iridium(I)-Catalyzed Enantioselective Synthesis of N-N Biaryl Atropisomers



- 100% Atom Economy
- Broad Substrate Scope
- Axially Chiral Indole-pyrrole and Bispyrrole Skeletons

Synthesis of N-N Biaryl Atropisomers

Optimization of the Reaction Conditions



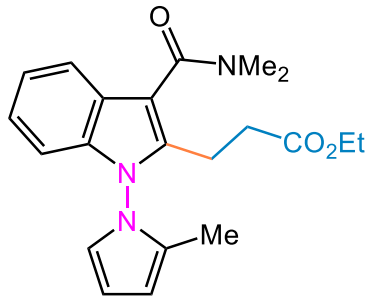
1a (0.10 mmol)

+

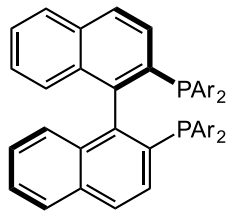
2a (0.50 mmol)

$[Ir(COD)Cl]_2$ (5 mol%)
Ligand (10 mol%)
NaBArF (20 mol%)

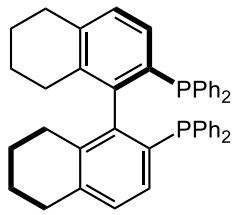
Solvent (0.1 M)
100 °C, 24 h



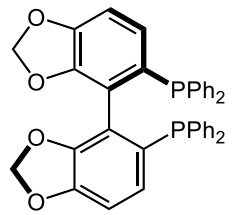
3aa



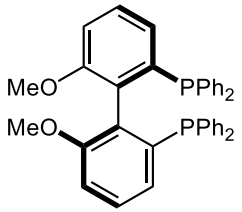
(*R*)-**L1**, Ar = Ph
(*R*)-**L2**, Ar = 4-Me-C_6H_4
(*R*)-**L3**, Ar = 3,5-Me_2-C_6H_3



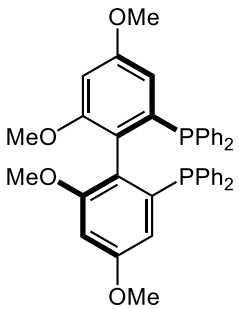
(*R*)-**L4**



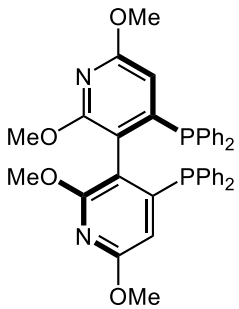
(*R*)-**L5**



(*R*)-**L6**



(*R*)-**L7**

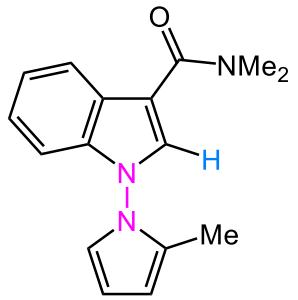


(*R*)-**L8**

Entry	Ligand	Solvent	Yield [%]	Ee [%]
1	**L1**	PhMe	90	93
2	**L2**	PhMe	95	92
3	**L3**	PhMe	>95	97
4	**L4**	PhMe	68	88
5	**L5**	PhMe	27	97
6	**L6**	PhMe	44	97
7	**L7**	PhMe	40	96
8	**L8**	PhMe	35	97
9	**-**	PhMe	0	-

Synthesis of N-N Biaryl Atropisomers

Optimization of the Reaction Conditions

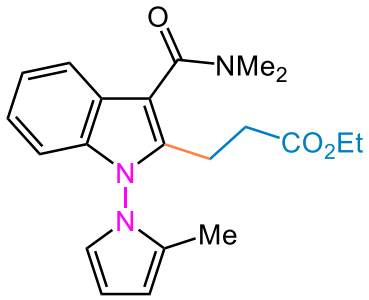


1a (0.10 mmol)

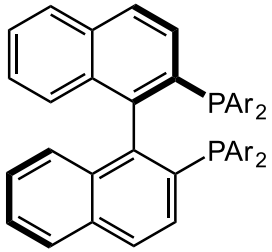
\+

2a (0.50 mmol)

$[Ir(COD)Cl]_2$ (5 mol%)
(*R*)-**L3** (10 mol%)
NaBArF (20 mol%)
Solvent (0.1 M)
100 °C, 24 h



3aa



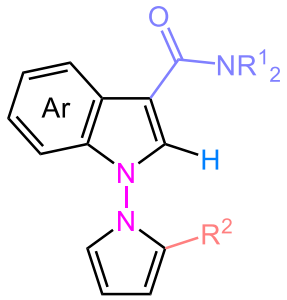
Ar = 3,5-Me_2-C_6H_3
(*R*)-**L3**

Entry	Ligand	Solvent	Yield [%]	Ee [%]
1	**L3**	PhCl	93	97
2	**L3**	DCE	75	98
3	**L3**	THF	44	97
4	**L3**	dioxane	89	97
5[a]	**L3**	PhMe	>95 (93)[b]	98

[a] 2.0 equiv of **2a** were used. [b] Isolated yield of a 0.2 mmol scale reaction in parenthesis.

Synthesis of N-N Biaryl Atropisomers

Substrate Scope



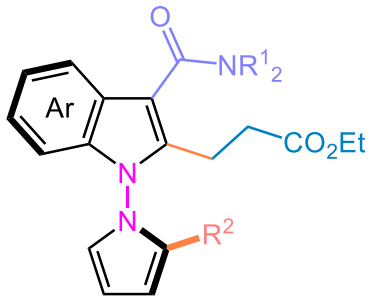
1 (0.2 mmol)

\+

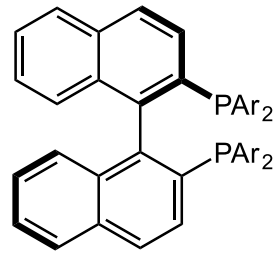
2a (0.4 mmol)

$[Ir(COD)Cl]_2$ (5 mol%)
(*R*)-**L3** (10 mol%)
NaBArF (20 mol%)

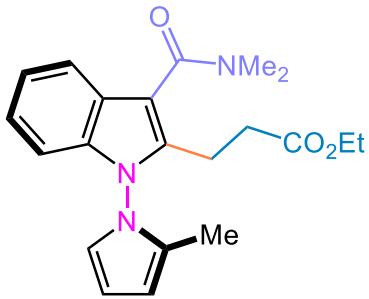
PhMe (0.1 M)
100 °C, 24 h, Ar



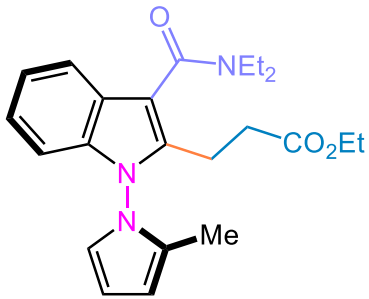
3



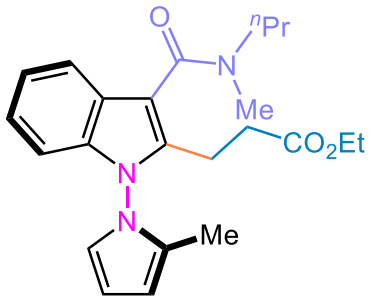
Ar = 3,5-Me$_2$-C$_6$H$_3$
(*R*)-**L3**



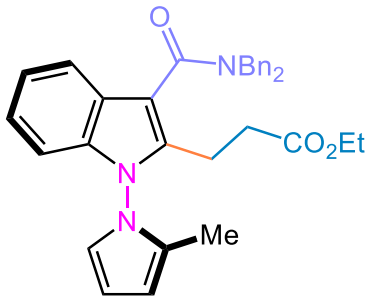
3aa
93% yield
98% ee



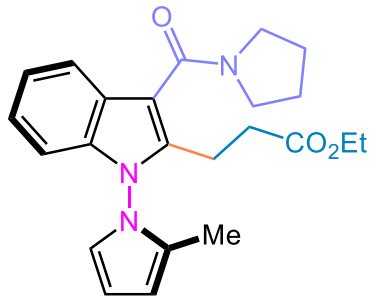
3ba
97% yield
99% ee



3ca
89% yield
96% ee



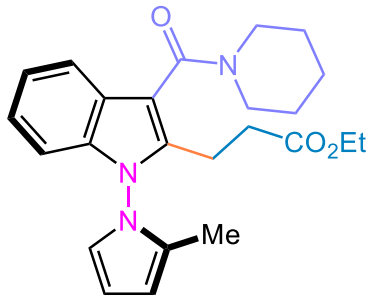
3da (48 h)
70% yield
99% ee



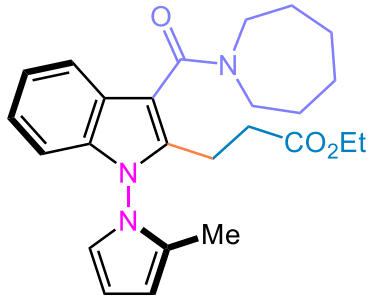
3ea
92% yield
92% ee

Synthesis of N-N Biaryl Atropisomers

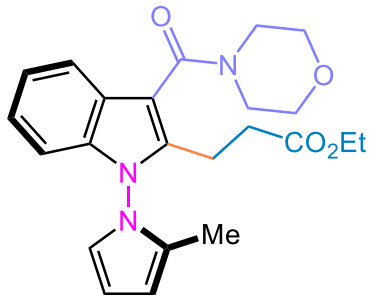
Substrate Scope



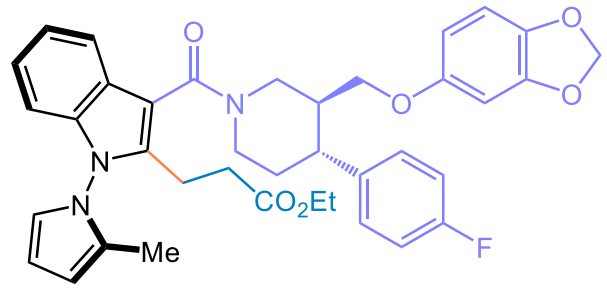
3fa
97% yield
98% ee



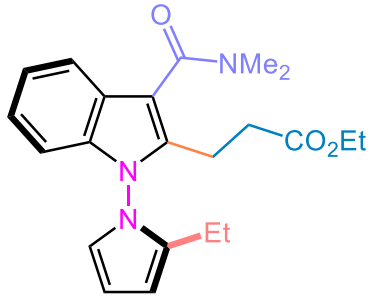
3ga
84% yield
98% ee



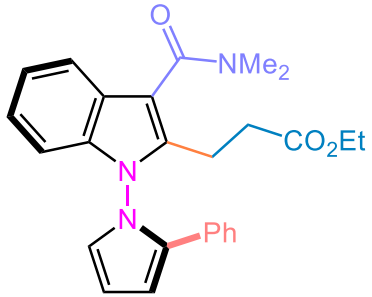
3ha
90% yield
98% ee



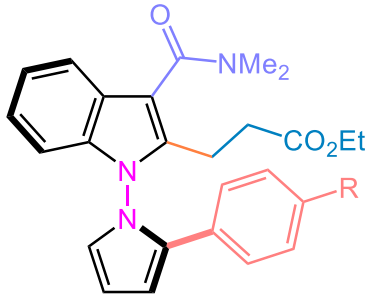
3ia[a]
88% yield, >19:1 dr
from paroxetine



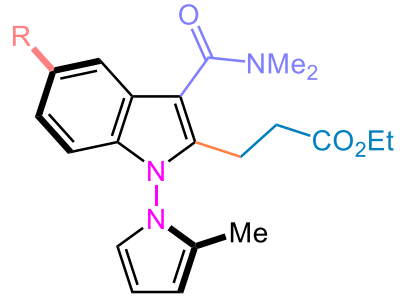
3ja
93% yield
97% ee



3ka
90% yield
99% ee



3la, R = Me, 87% yield, 99% ee
3ma, R = OMe, 95% yield, 99% ee
3na, R = F, 92% yield, 99% ee (36 h)
3oa, R = Cl, 91% yield, 99% ee (36 h)

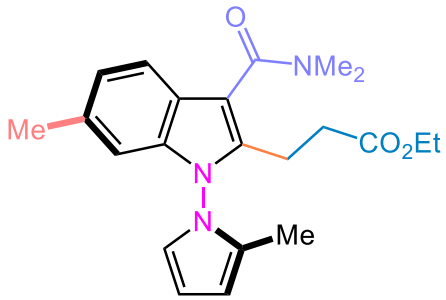


3pa, R = Me, 96% yield, 98% ee
3qa, R = OMe, 95% yield, 97% ee
3ra, R = F, 96% yield, 98% ee
3sa, R = Cl, 96% yield, 98% ee (36 h)
3ta, R = Br, 90% yield, 98% ee (48 h)

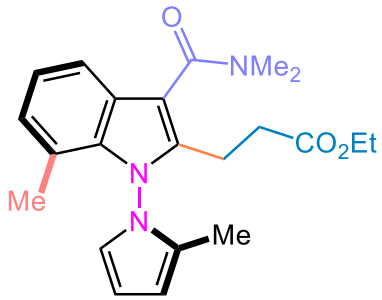
[a] The reaction was carried out in 0.1 mmol scale.

Synthesis of N-N Biaryl Atropisomers

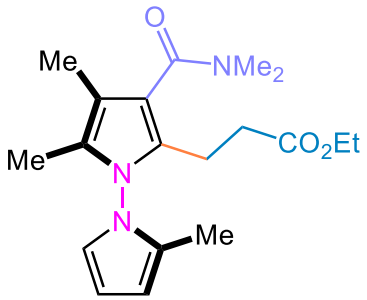
Substrate Scope



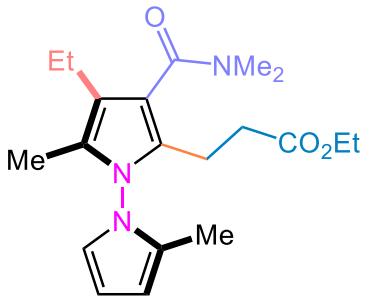
3ua
95% yield
98% ee



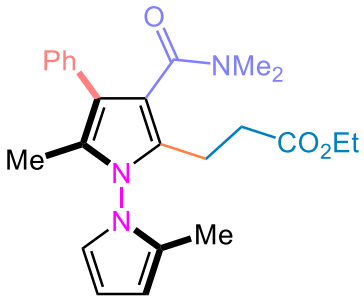
3va
94% yield
97% ee



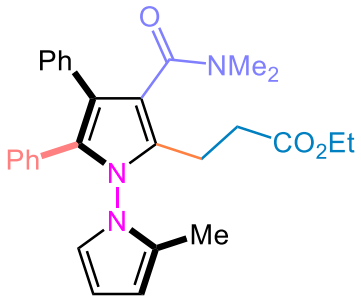
3wa
94% yield
96% ee



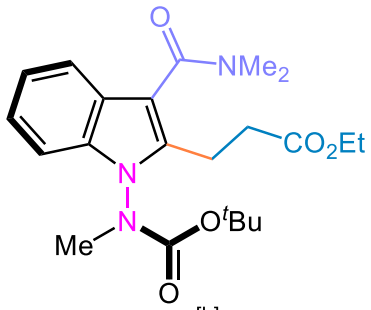
3xa
87% yield
98% ee



3ya
96% yield
93% ee



3za
94% yield
97% ee

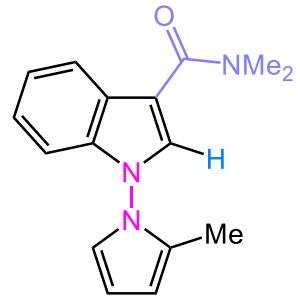


3a'a[b]
37% yield
82% ee

[b] The reaction was carried out at 80 °C in the presence of $[Ir(COD)Cl]_2$ (10 mol%), (*R*)-**L3** (20 mol%) and NaBArF (40 mol%).

Synthesis of N-N Biaryl Atropisomers

Substrate Scope

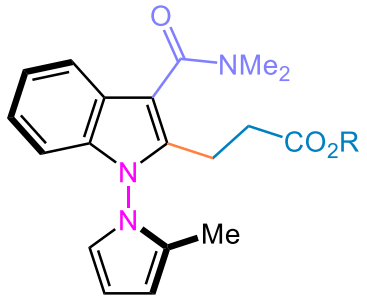


1a (0.2 mmol)

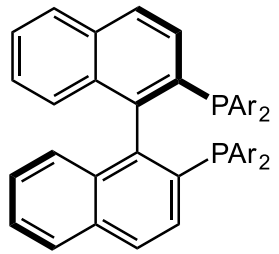
\+

2 (0.4 mmol)

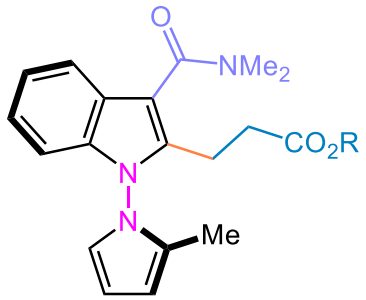
$[Ir(COD)Cl]_2$ (5 mol%)
(*R*)-**L3** (10 mol%)
NaBArF (20 mol%)
PhMe (0.1 M)
100 °C, 24 h, Ar



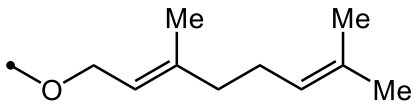
3



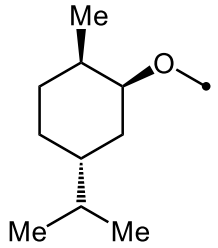
Ar = 3,5-Me_2-C_6H_3
(*R*)-**L3**



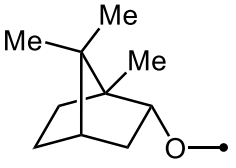
3ab, R = Me, 92% yield, 97% ee
3ac, R = ^{i}Pr, 93% yield, 96% ee
3ad, R = ^{n}Bu, 97% yield, 98% ee
3ae, R = ^{t}Bu, 87% yield, 98% ee (48 h)
3af, R = Cy, 89% yield, 98% ee
3ag, R = Bn, 93% yield, 98% ee
3ah, R = Ph, 93% yield, 98% ee
3ai, R = 2-Nap, 92% yield, 98% ee



3aj[a] (48 h)
57% yield, 98% ee
from geraniol



3ak[a]
96% yield, >19;1 dr
from L-menthol

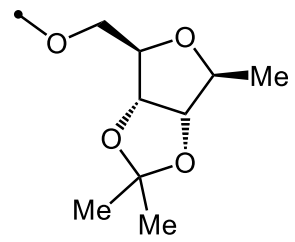


3al[a] (48 h)
95% yield, >19;1 dr
from (-)-borneol

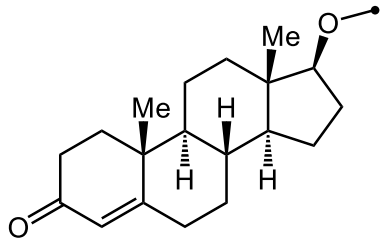
[a] The reaction was carried out in 0.1 mmol scale.

Synthesis of N-N Biaryl Atropisomers

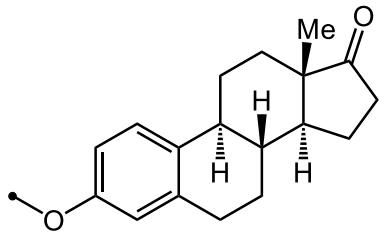
Substrate Scope



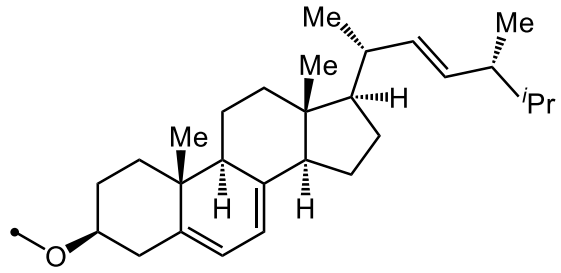
3am[a]
97% yield, >19:1 dr
from D-ribofuranoside



3an[a] (72 h)
86% yield, >19:1 dr
from testosterone



3ao[a] (72 h)
98% yield, >19:1 dr
from estrone

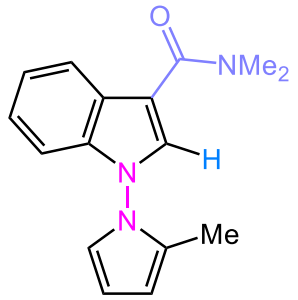


3ap[a] (72 h)
88% yield, >19:1 dr
from ergosterol

[a] The reaction was carried out in 0.1 mmol scale.

Synthesis of N-N Biaryl Atropisomers

Gram-scale Reaction



1a (3 mmol)

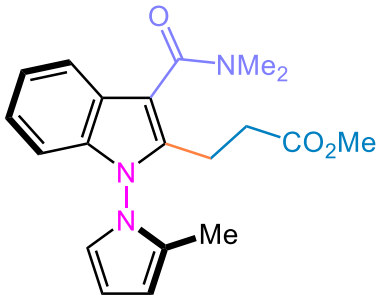
+

2b (6 mmol)

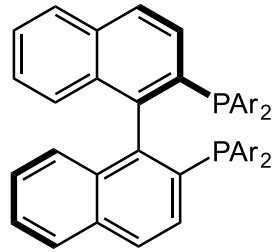
$[Ir(COD)Cl]_2$ (5 mol%)
(*R*)-**L3** (10 mol%)
NaBArF (20 mol%)

PhMe (0.2 M)
100 °C, 48 h, Ar

95% yield, 97% ee

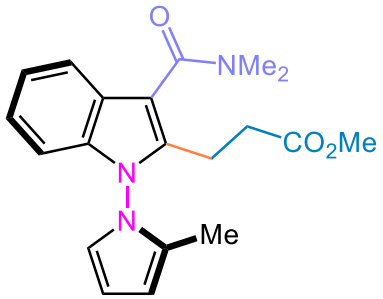


3ab
1.01 g

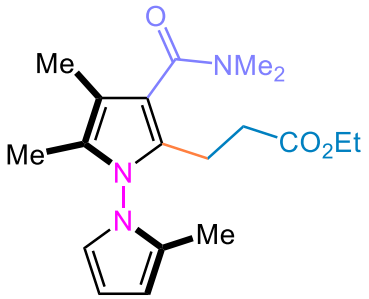


Ar = 3,5-Me_2-C_6H_3
(*R*)-**L3**

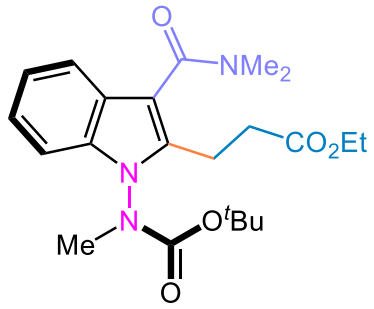
Conformational Stability



3ab, ΔG_{rac} = 36.7 kcal/mol
(160 °C in mesitylene)

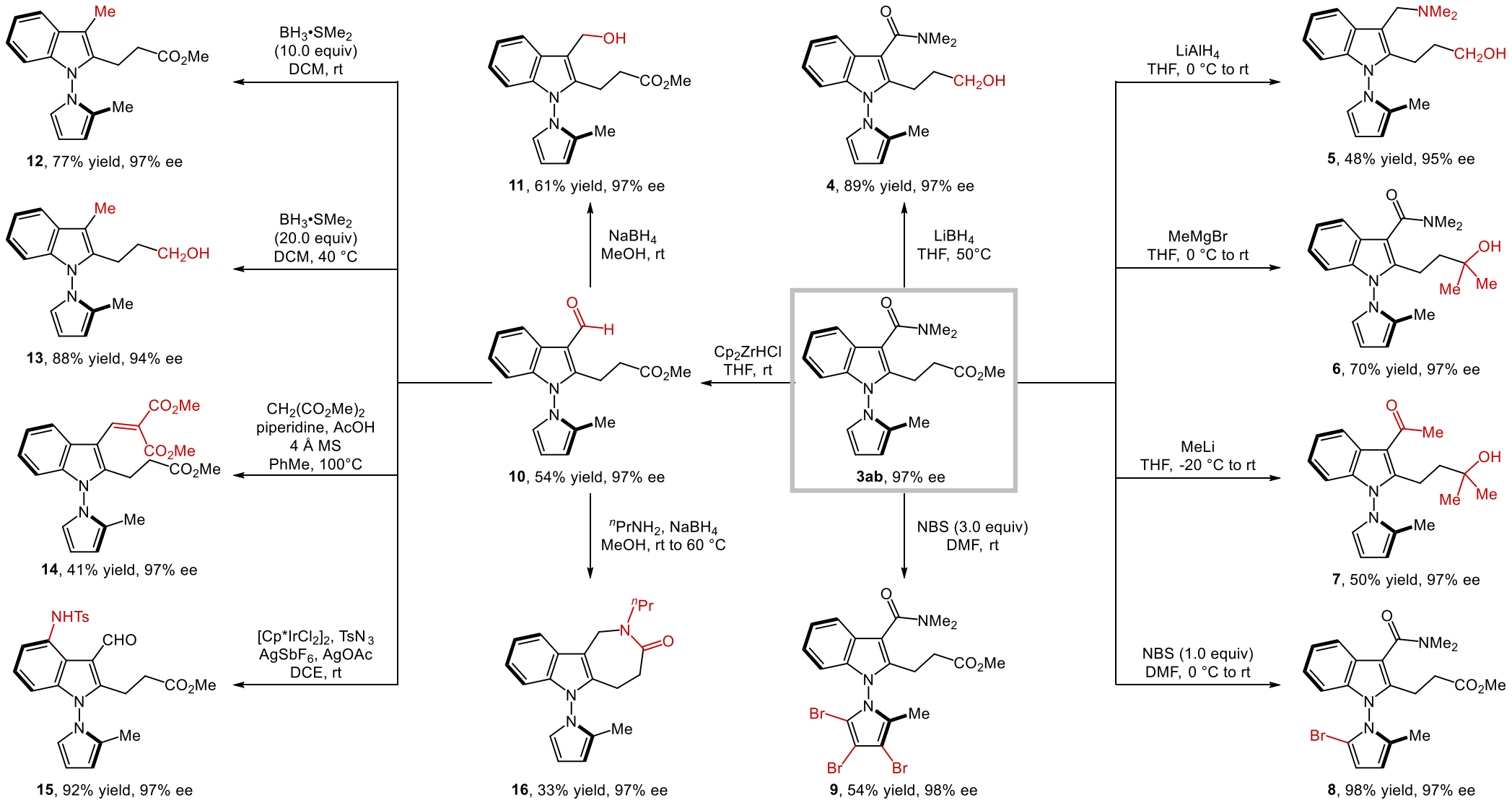


3wa, stable in 160 °C
(160 °C in mesitylene)



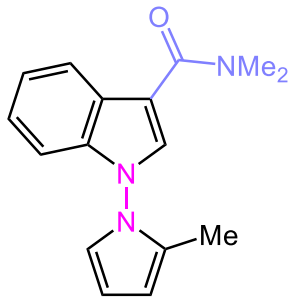
3a'a, ΔG_{rac} = 30.6 kcal/mol
(100 °C in PhMe)

Synthetic Applications



Mechanistic Investigation

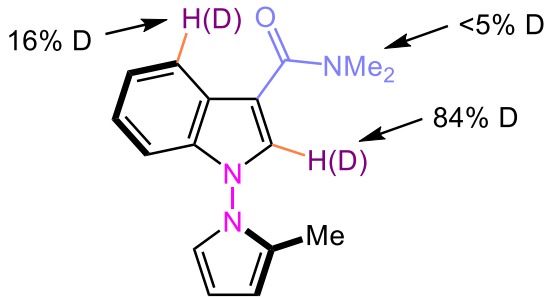
Deuterium Labeling Experiment



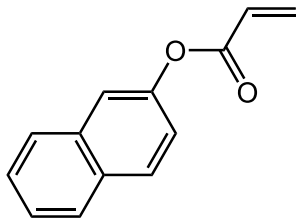
1a (0.1 mmol)

CD_3OD (20.0 equiv)
$[Ir(COD)Cl]_2$ (5 mol%)
(*R*)-**L3** (10 mol%)

NaBArF (20 mol%)
PhMe (0.1 M)
100 °C, 12 h, Ar



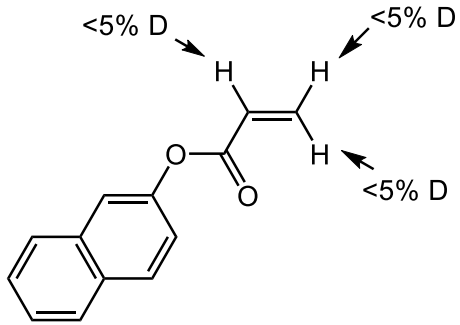
1a-[D], 90% NMR yield



2i (0.1 mmol)

CD_3OD (20.0 equiv)
$[Ir(COD)Cl]_2$ (5 mol%)
(*R*)-**L3** (10 mol%)

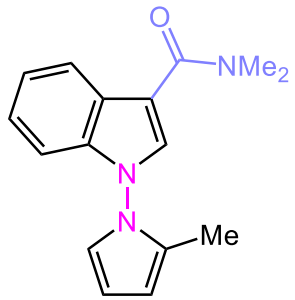
NaBArF (20 mol%)
PhMe (0.1 M)
100 °C, 12 h, Ar



2i, 64% NMR yield

Mechanistic Investigation

Deuterium Labeling Experiment



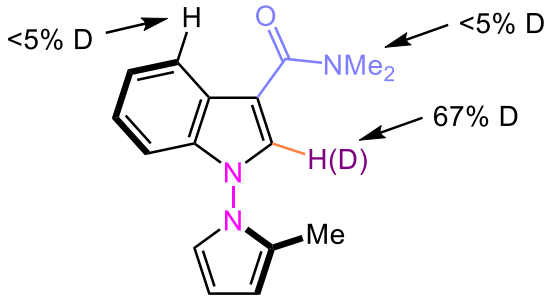
1a (0.1 mmol)

+

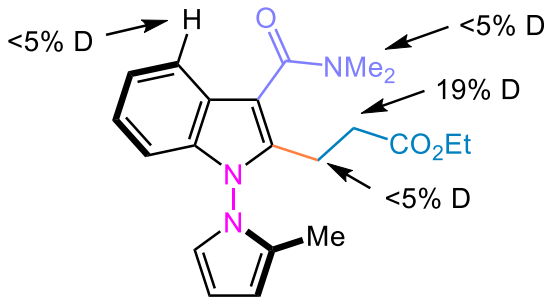
2a (0.2 mmol)

CD_3OD (20.0 equiv)
$[Ir(COD)Cl]_2$ (5 mol%)
(*R*)-**L3** (10 mol%)

NaBArF (20 mol%)
PhMe (0.1 M)
100 °C, 12 h, Ar

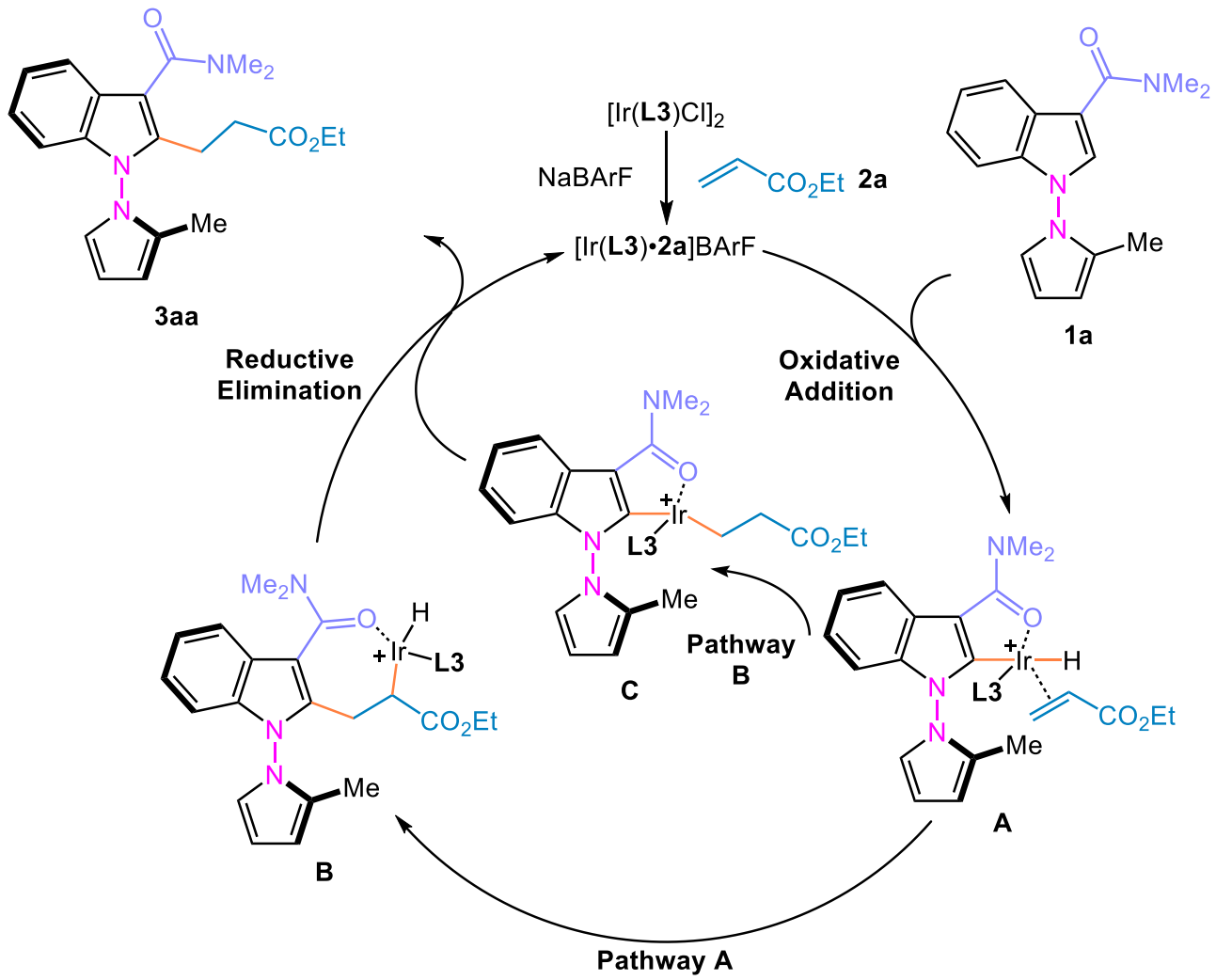


1a-[D], 23% NMR yield

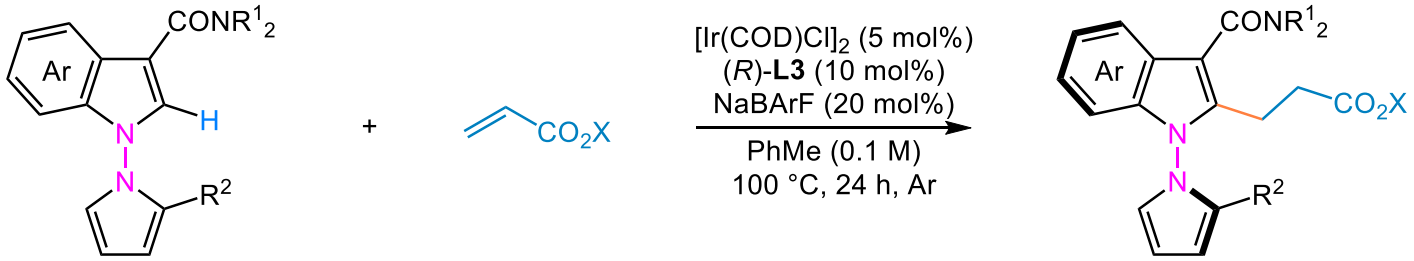


3aa-[D], 65% NMR yield

Proposed Mechanism



Summary



♦100% Atom Economy ♦Excellent Enantioselectivity

♦Axially Chiral Indole-pyrrole and Bispyrrole Skeletons

♦Broad Substrate Scope ♦Diverse Transformations

Strategy for Writing The First Paragraph

The Importance of Biaryl Atropisomers

- ✓ Biaryl atropisomers are common structural motifs in natural products, bioactive molecules, and privileged chiral ligands.

Asymmetric Construction of N-N Atropisomers

- ✓ In sharp contrast to the well-studied biaryl-based C-C atropisomers, catalytic asymmetric construction of N-N atropisomers remained elusive until 2021.

Transition-Metal-Catalyzed Asymmetric C-H Functionalization

- ✓ In recent years, transition-metal-catalyzed asymmetric C-H functionalization has been evolved into a powerful tool for enantioselective synthesis of atropisomers.

Strategy for Writing The Last Paragraph

Summary of This Work

✓ In summary, we have realized an Ir^{I}-catalyzed asymmetric C-H alkylation of N-pyrrole substituted indole derivatives.

Highlights of This Work

✓ This reaction offers a highly efficient construction of a class of indole-pyrrole-type and bispyrrole-type N-N axial atropisomers with excellent enantioselectivity.

Further Expectation

✓ Further studies on the synthesis of N-N biaryl atropisomers via asymmetric C-H functionalization are undergoing in our laboratory.

Representative Examples

- Among axially biaryl atropisomers, N-N biaryl atropisomers were unique and vital skeletons found in a series of chiral molecules including natural products and chiral ligands. (vital，必不可少的；至关重要的)
- Moreover, the substrates bearing a methyl, methoxy, fluoro, chloro, or bromo group at the 5-position of indole were well compatible in this reaction, leaving the chloro and bromo groups intact. (保持…完整)
- The various transformations of the products greatly expanded the diversity of the related N-N atropisomers. (拓宽…的多样性，diversity，多样性)

Acknowledgement

Thanks for your attention