Literature Report VI

Palladium-Catalyzed Atroposelective Kinetic C-H Olefination and Allylation for the Synthesis of C-B Axial Chirality

Reporter: Gao-Wei Wang
Checker: Li-Xia Liu
Date: 2023-11-27

Xu, J.; Qiu, W.; Zhang, X.; Wu, Z.; Zhang, Z.; Yang, K.; Song, Q.

Angew. Chem. Int. Ed. **2023**, e202313388

CV of Prof. Qiuling Song (宋秋玲)

Background:

- **1994-1998** B.S., Zhengzhou University
- **1998-2001** M.S., Peking University (Prof. Zhenfeng Xi)
- **2002-2006** Ph.D., Princeton University (Prof. Robert A Pascal)
- **2007-2011** Researcher/Project Director, U.S. Pharmaceutical Company
- **2012-2023** Associate Professor/Professor, Huaqiao University
- **2023-Now** Professor, Fuzhou University

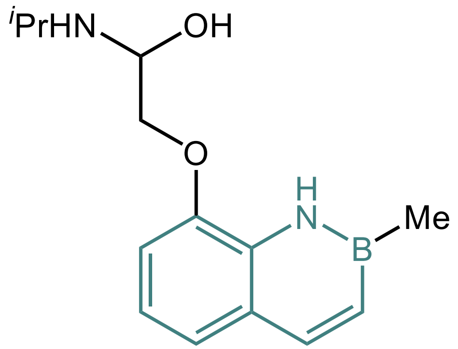
Research:

- Organoboron chemistry
- Organic fluorine chemistry
- Radical chemistry and bioactive molecular synthetic chemistry

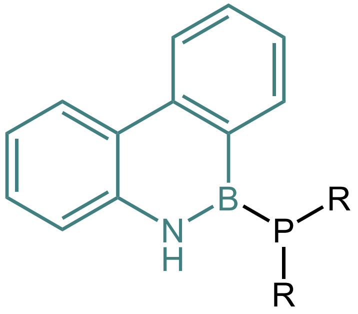
Contents

Introduction

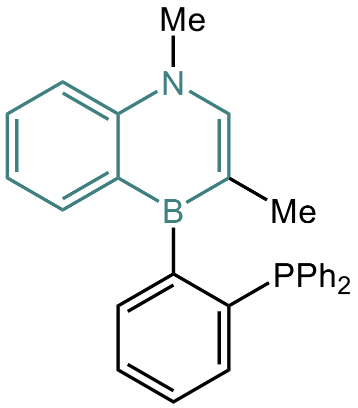
Applications of 1,2-azaborines



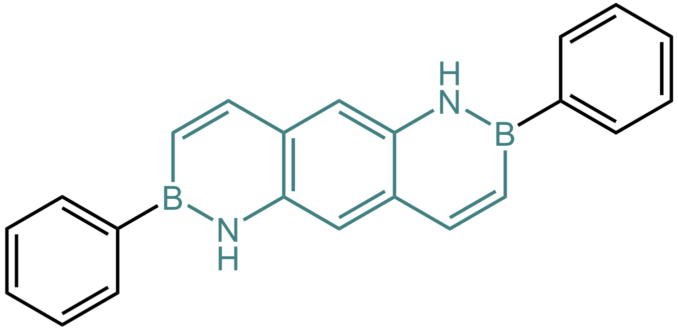
BN-Propanolol



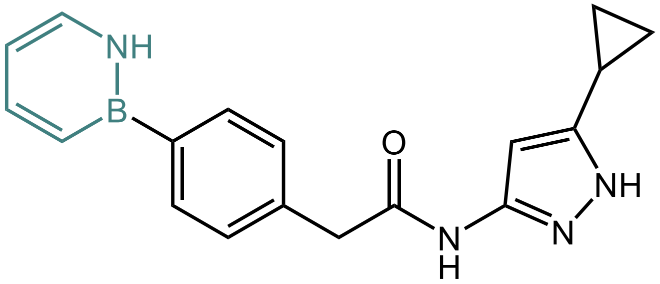
B-P ligand



Senphos

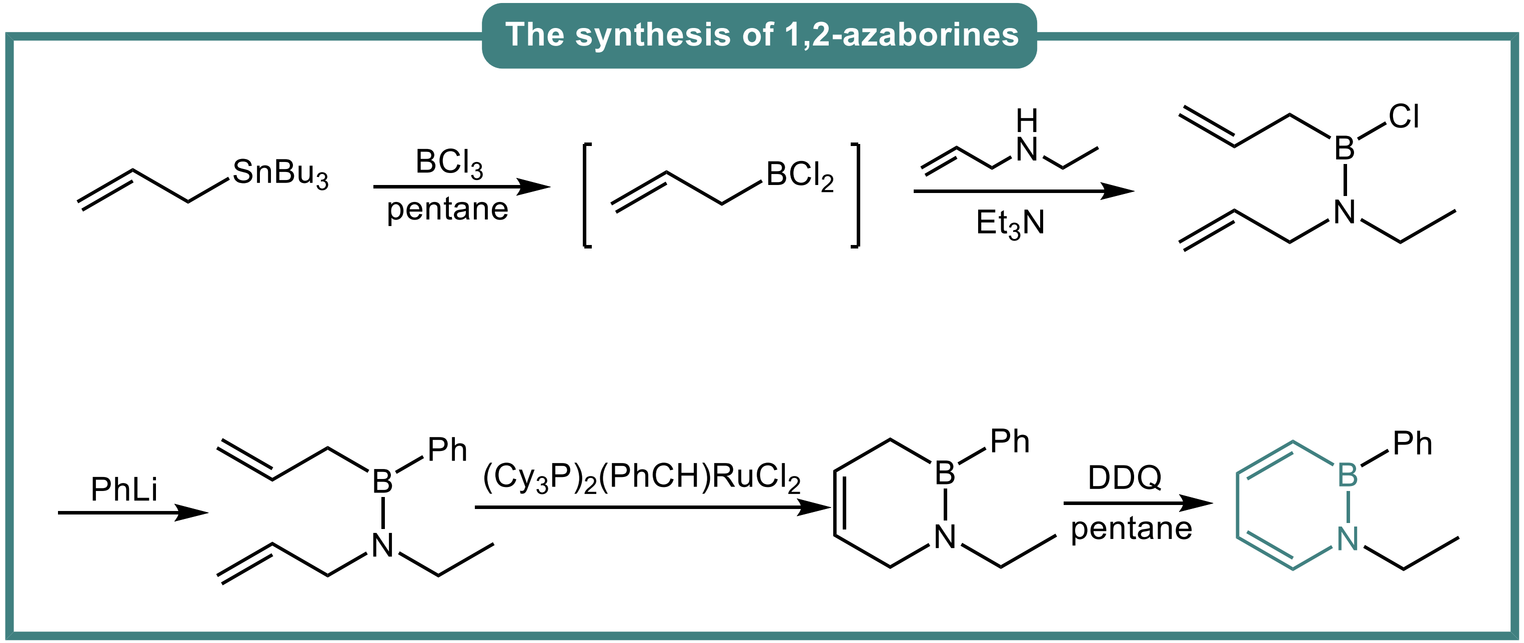


DPBNA



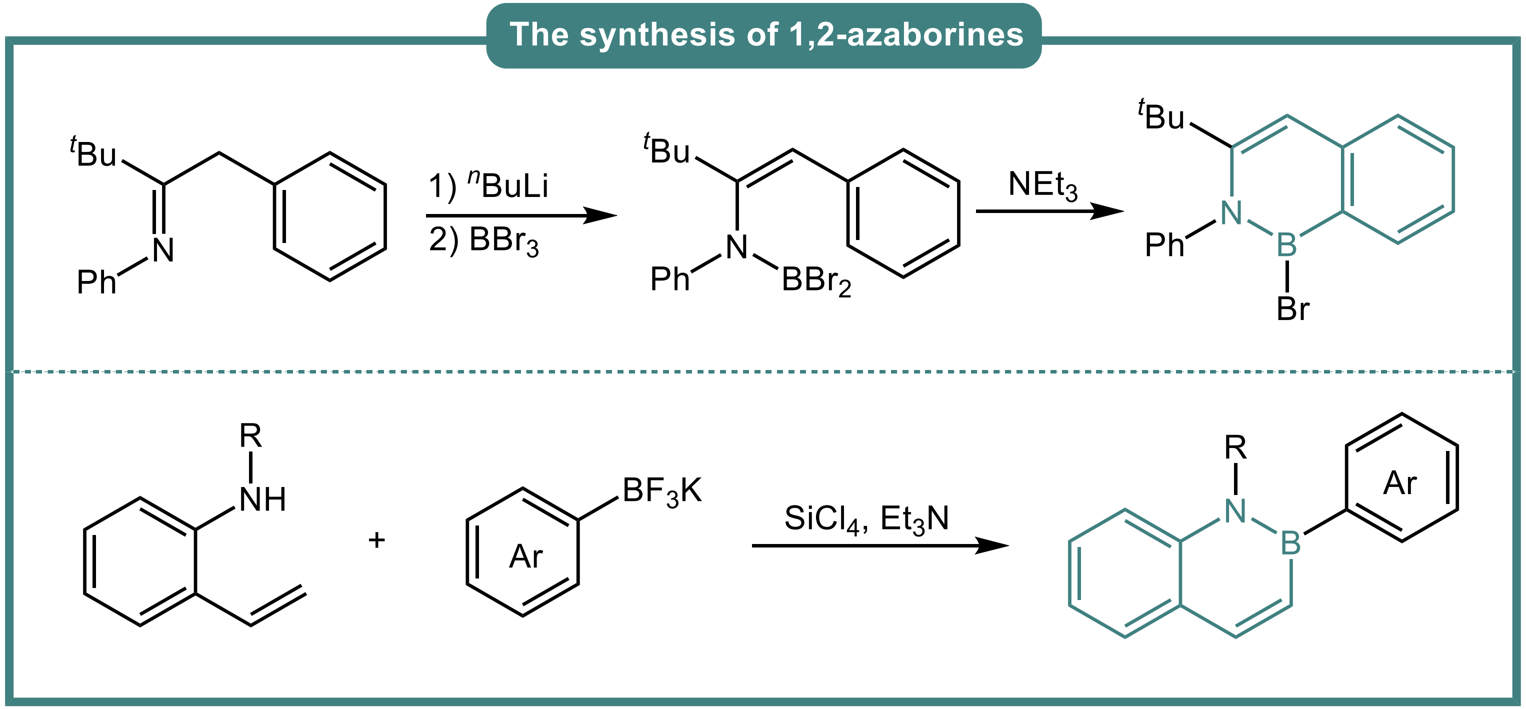
CDK2 inhibitor

The synthesis of 1,2-azaborines



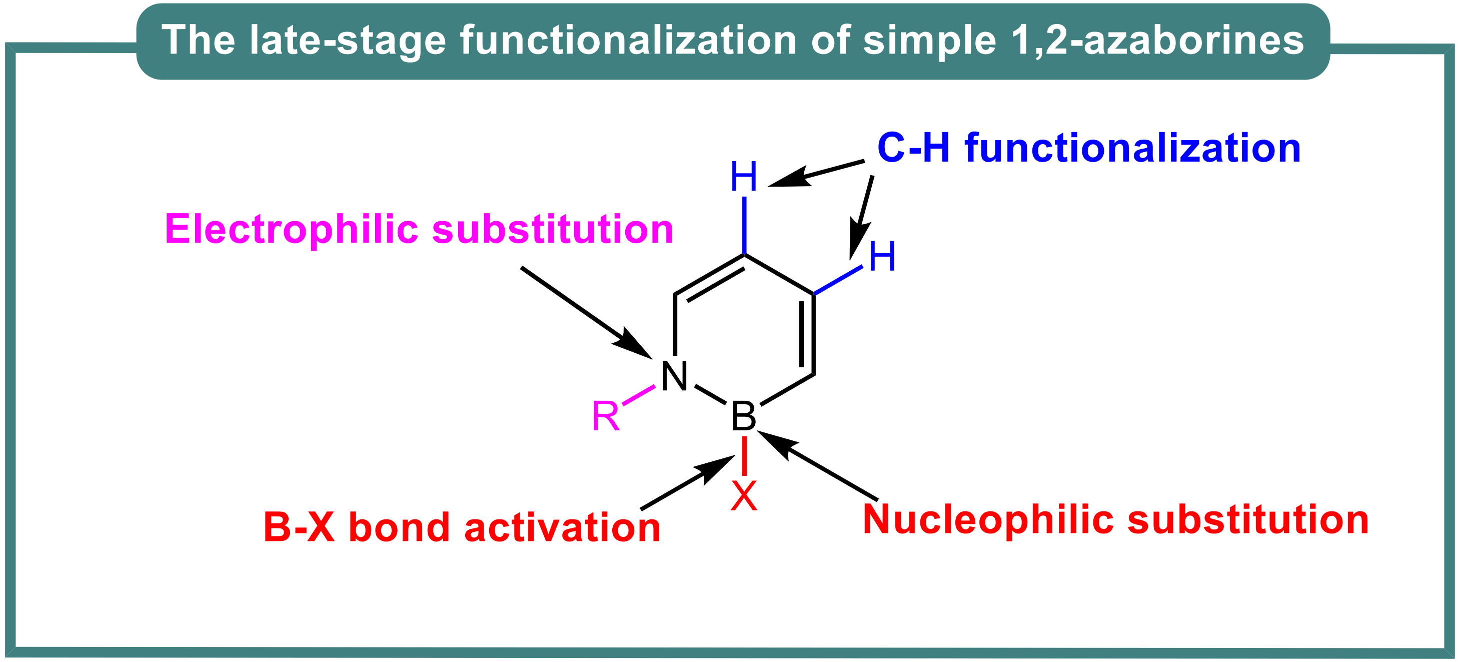
Ashe, A. J.; Fang, X. *Org. Lett.* **2000**, *2*, 2089-2091

The synthesis of 1,2-azaborines

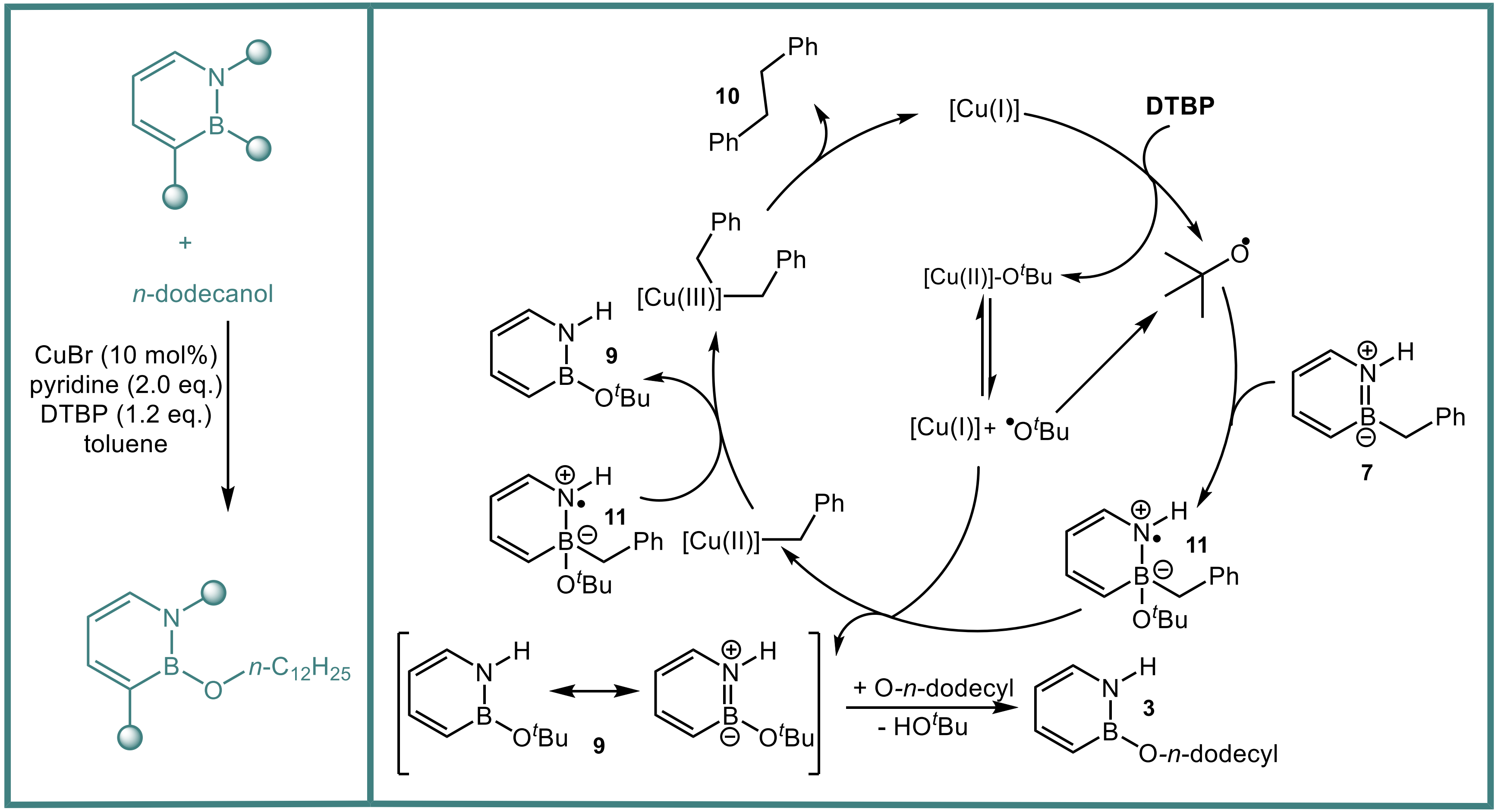


Liu, X.; Cui, C. *J. Org. Chem.* **2015**, *80*, 3737-3744
Davies, G. H. M.; Molander, G. A. *J. Org. Chem.* **2017**, *82*, 549-555

The late-stage functionalization of 1,2-azaborines

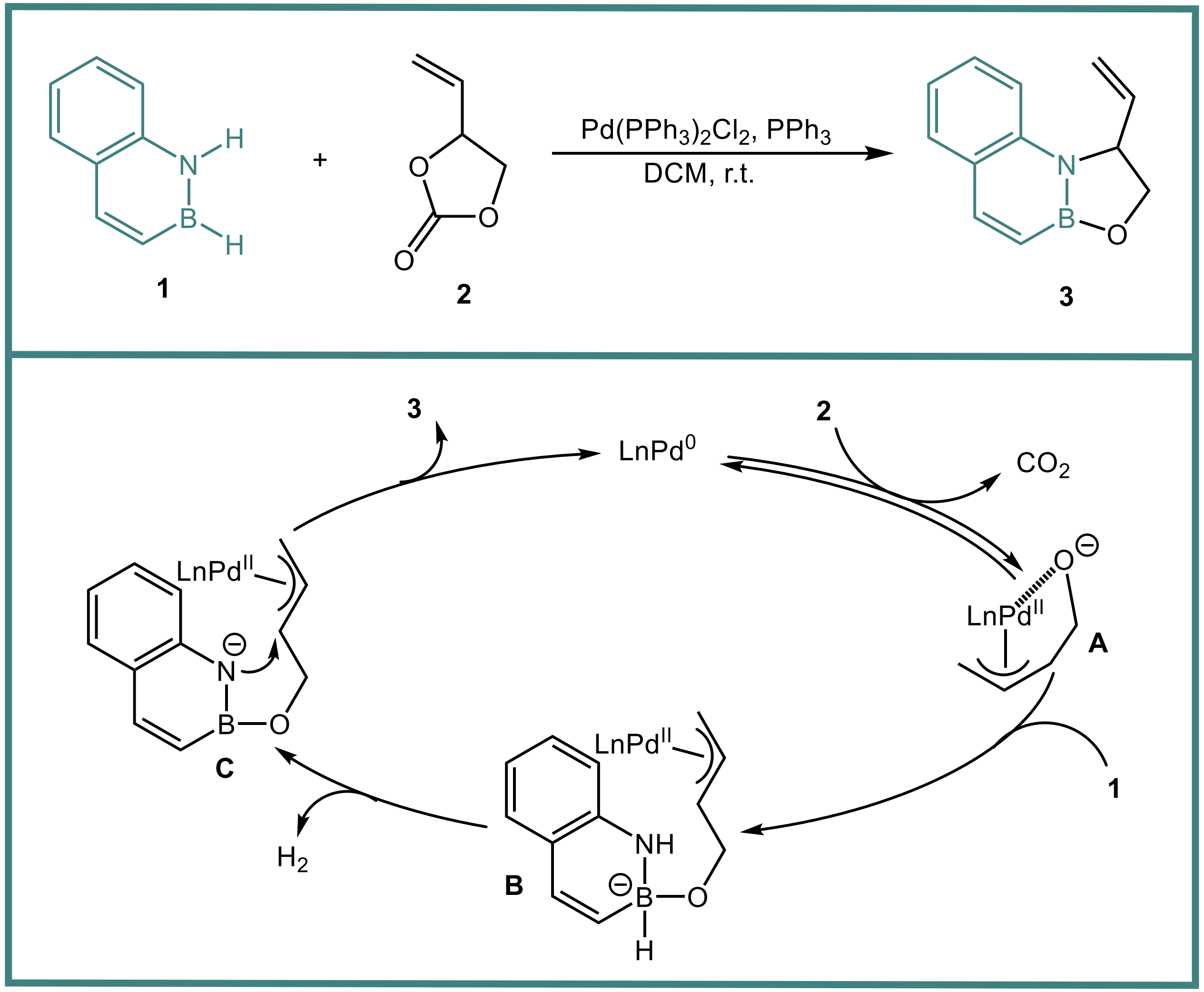


Nucleophilic substitution at boron atom



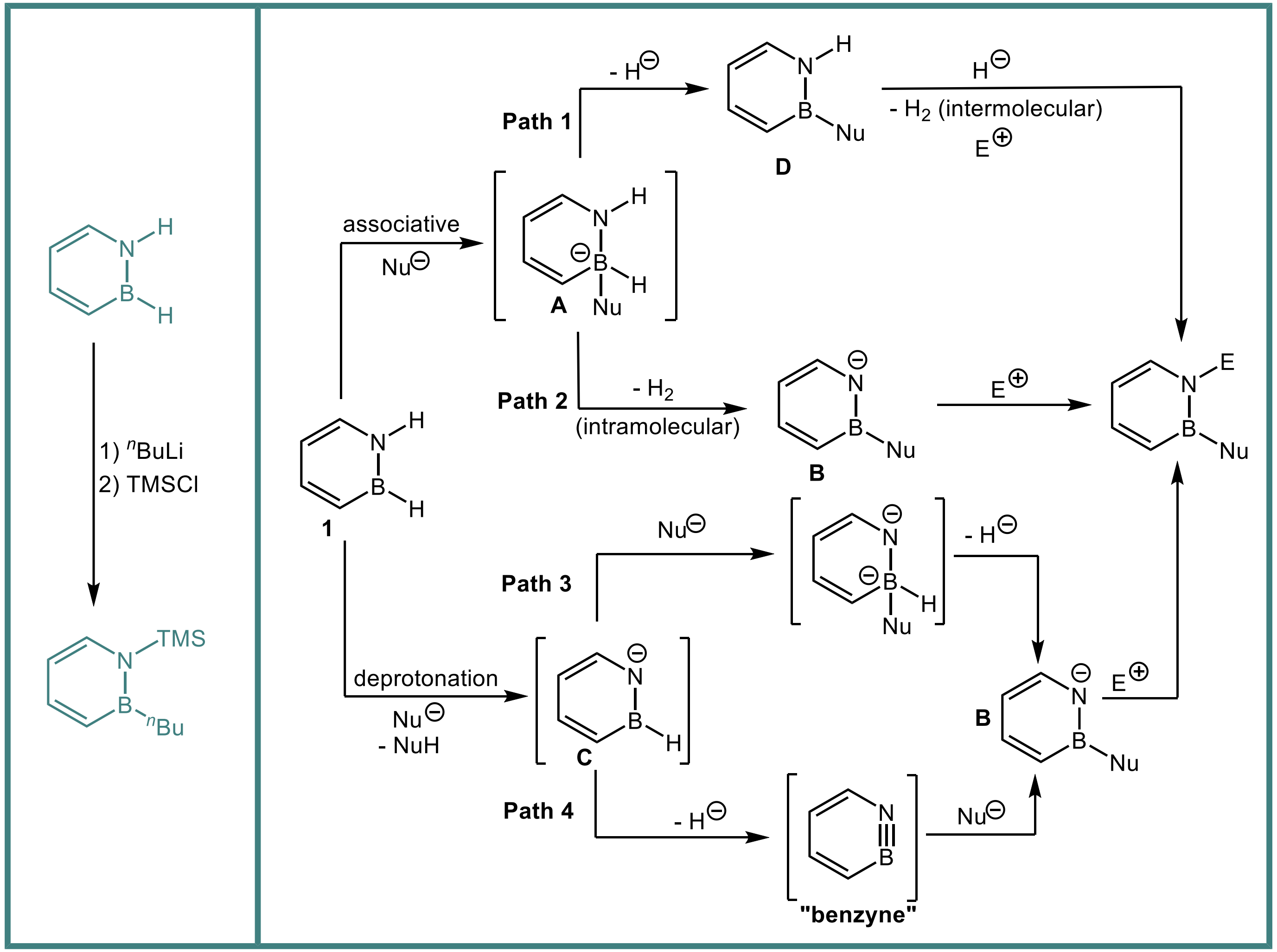
Baggett, A. W.; Liu, S.-Y. *J. Am. Chem. Soc.* **2017**, *139*, 15259-15264

B-X bond activation



Morita, T.; Nakamura, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202113558

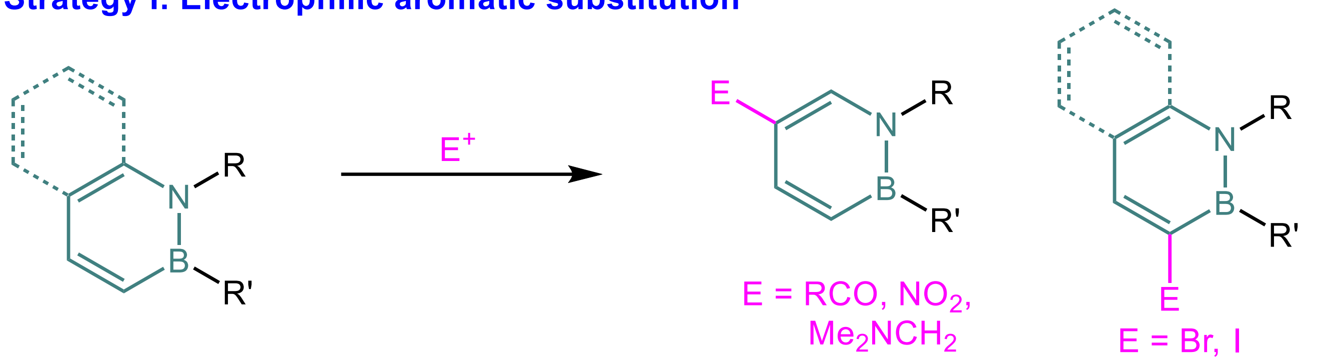
Electrophilic substitution at nitrogen atom



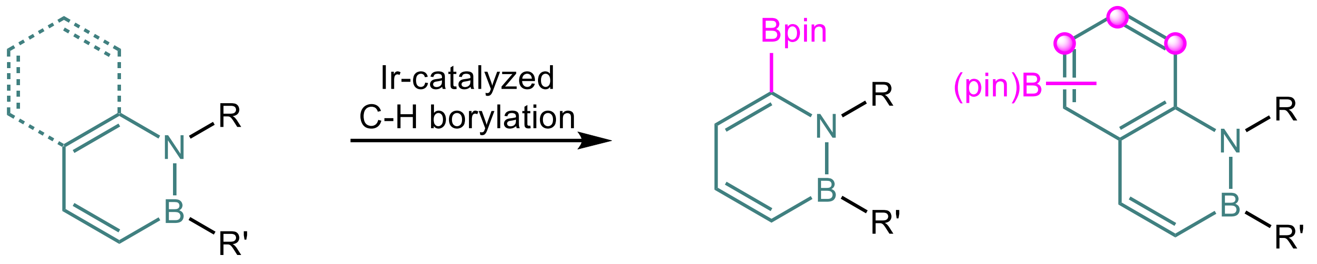
Lamm, A. N.; Liu, S.-Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 8157-8160

C-H functionalizations

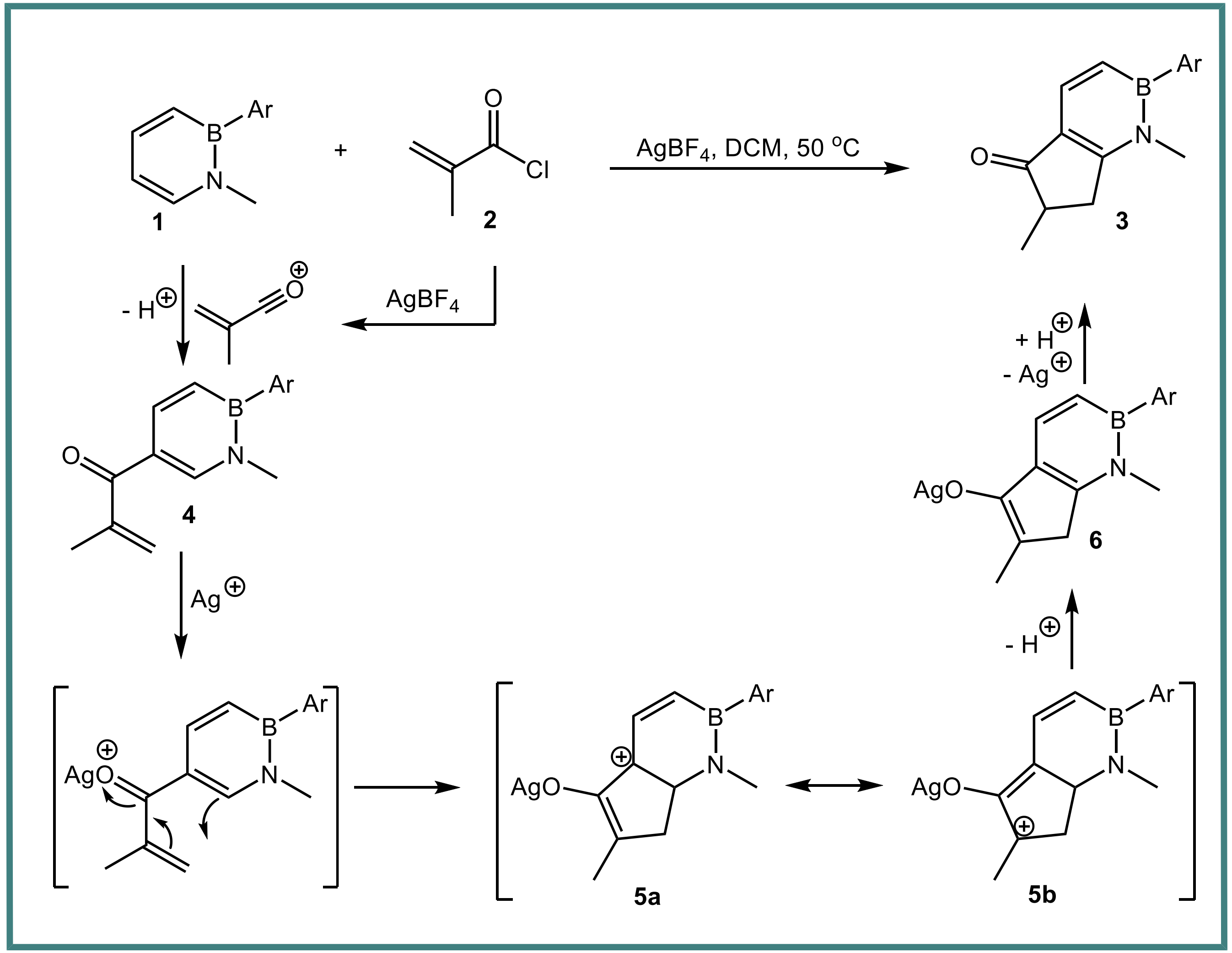
Strategy I: Electrophilic aromatic substitution



Strategy II: Transition metal-catalyzed C-H functionalization

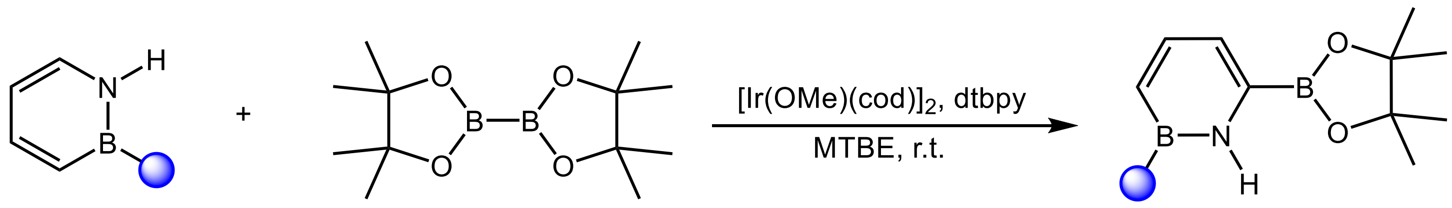


Electrophilic aromatic substitution

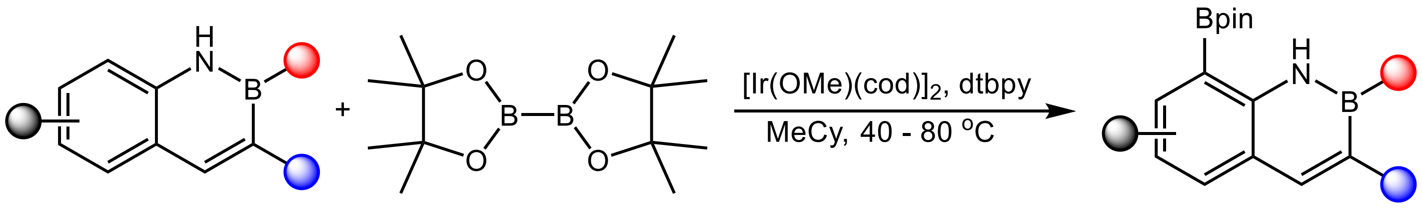


Zhang, Y.; Fang, X. *J. Org. Chem.* **2017**, *82*, 12877-12887

Transition metal-catalyzed C-H functionalization

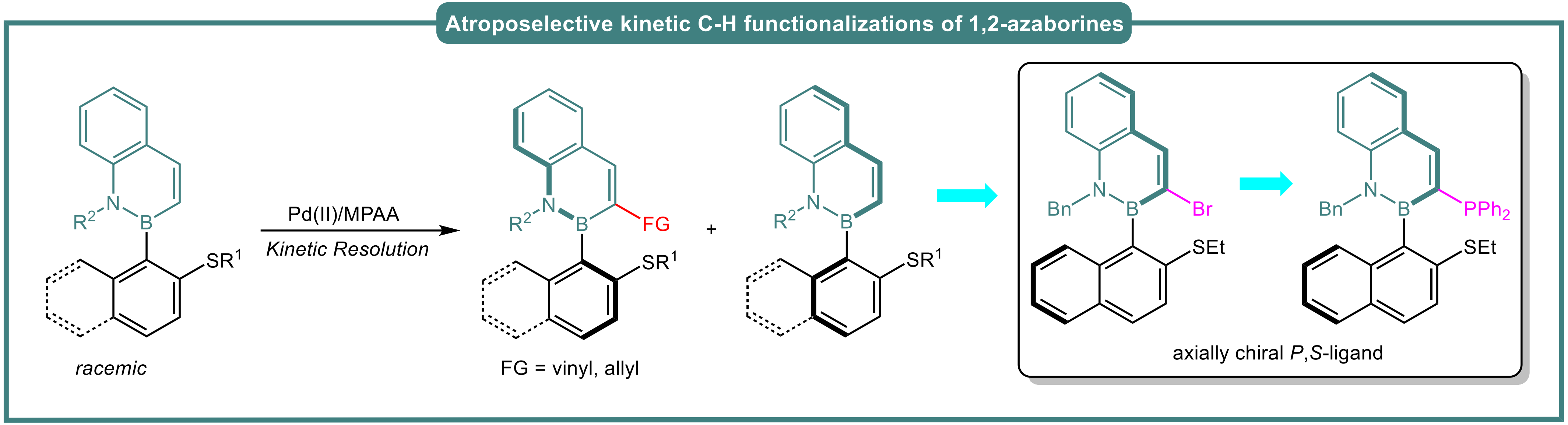


Baggett, A. W.; Liu, S.-Y. *J. Am. Chem. Soc.* **2015**, *137*, 5536-5541



Davies, G. H. M.; Molander, G. A. *J. Org. Chem.* **2017**, *82*, 8072-8084

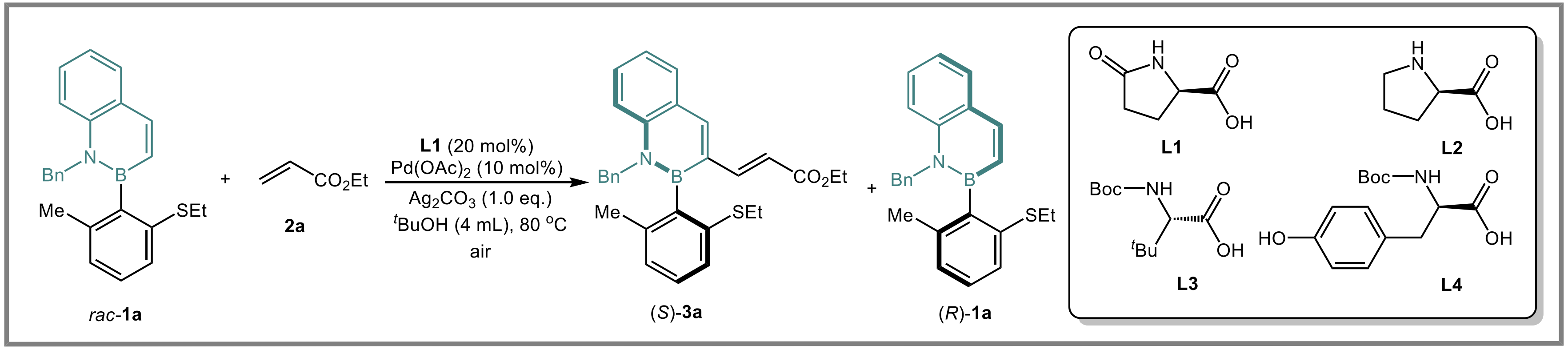
Project synopsis



Challenges:

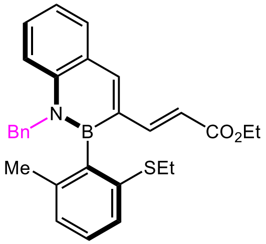
- Most C-H functionalization reactions involve oxidants, and fragile C-B bond may not be compatible
- The catalytic asymmetric synthesis of C-B axial chirality is more challenge due to the innate lower rotational barrier

Optimization of reaction conditions

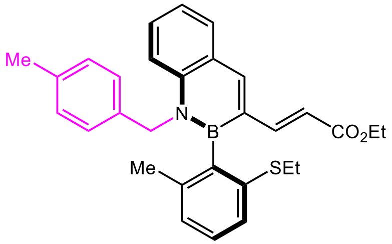


Entry	variation from the "standard conditions"	(S)-3a Yield (%)	(S)-3a Ee (%)	(R)-1a Yield (%)	(R)-1a Ee (%)	S
1	none	47	94	45	97	136
2	**L2** instead of **L1**	0	-	95	-	1
3	**L3** instead of **L1**	55	24	42	74	3.2
4	**L4** instead of **L1**	44	0	55	0	-
5	AgCl instead of Ag_2CO_3	10	87	86	10	16
6	AgOAc instead of Ag_2CO_3	31	82	58	30	14
7	Et_2O instead of ^{t}BuOH	10	70	73	7	6
8	^{t}BuOH 2 mL instead of ^{t}BuOH 4 mL	38	90	45	97	79

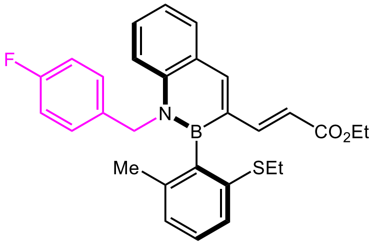
Scope of 1,2-benzazaborines



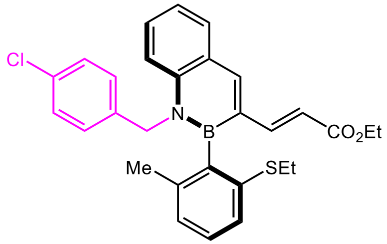
3a, 47%, 94% ee
1a, 45%, 97% ee
C = 51%, S = 136, 18 h



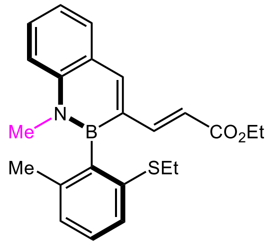
3b, 43%, 93% ee
1b, 45%, 96% ee
C = 51%, S = 108, 120 h



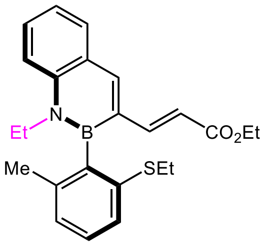
3c, 42%, 94% ee
1c, 45%, 94% ee
C = 50%, S = 115, 60 h



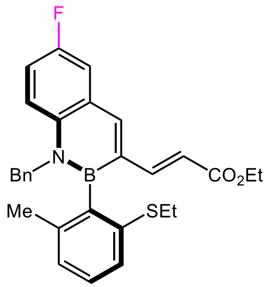
3d, 40%, 94% ee
1d, 43%, 90% ee
C = 49%, S = 100, 40 h



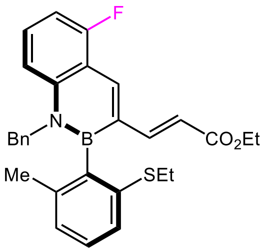
3e, 47%, 91% ee
1e, 45%, 94% ee
C = 51%, S = 75, 18 h



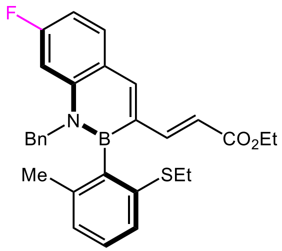
3f, 40%, 91% ee
1f, 45%, 95% ee
C = 51%, S = 79, 72 h



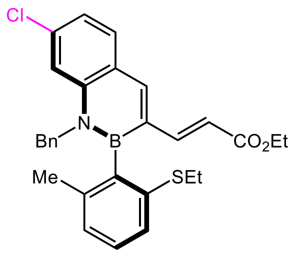
3g, 47%, 94% ee
1g, 40%, 95% ee
C = 55%, S = 121, 120 h



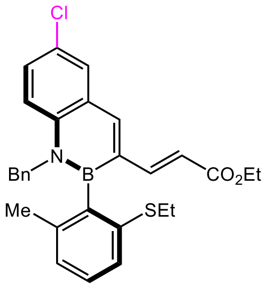
3h, 43%, 94% ee
1h, 44%, 91% ee
C = 49%, S = 103, 72 h



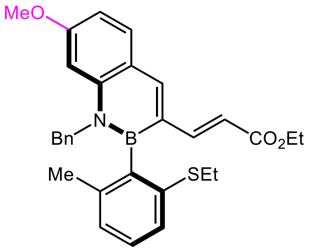
3i, 44%, 94% ee
1i, 42%, 91% ee
C = 49%, S = 103, 48 h



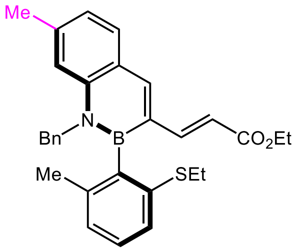
3j, 41%, 94% ee
1j, 45%, 93% ee
C = 50%, S = 110, 32 h



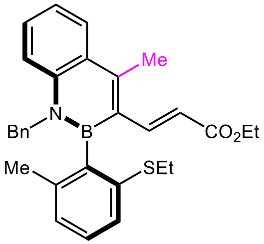
3k, 41%, 92% ee
1k, 39%, 93% ee
C = 50%, S = 82, 122 h



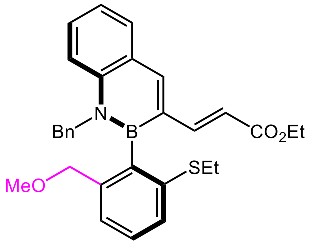
3l, 47%, 93% ee
1l, 45%, 93% ee
C = 50%, S = 94, 12 h



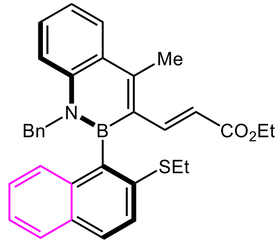
3m, 41%, 90% ee
1m, 45%, 98% ee
C = 52%, S = 87, 18 h



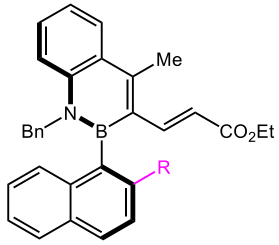
3n, trace
1n, 95%, rac



3o, 42%, 96% ee
1o, 41%, 96% ee
C = 50%, S = 194, 52 h

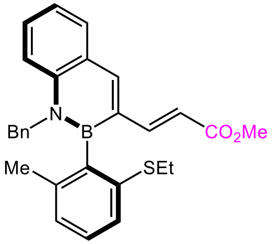


3p, 42%, 96% ee
1p, 41%, 94% ee
C = 49%, S = 175, 52 h

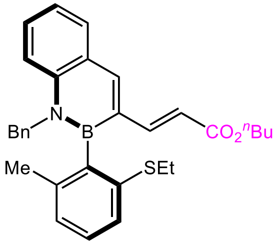


R = OMe, **3q**, n.r.
R = $Ph_2(O)P$, **3r**, trace

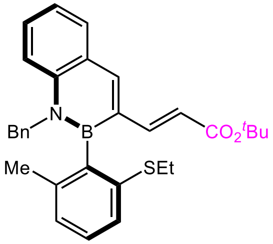
Scope of olefins



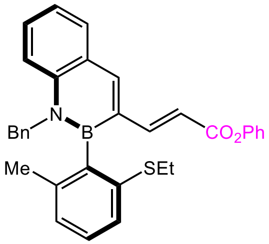
3s, 47%, 93% ee
1a, 45%, 93% ee
C = 50%, S = 94, 18 h



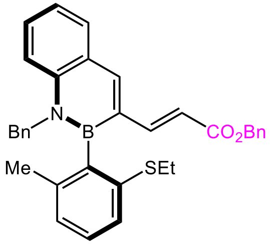
3t, 37%, 94% ee
1a, 45%, 92% ee
C = 49%, S = 106, 60 h



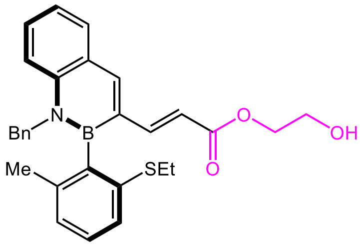
3u, 37%, 93% ee
1a, 42%, 91% ee
C = 49%, S = 88, 18 h



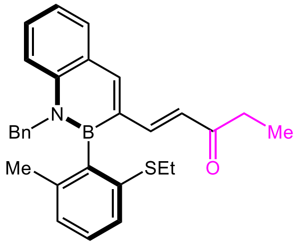
3v, 47%, 93% ee
1a, 45%, 91% ee
C = 49%, S = 88, 93 h



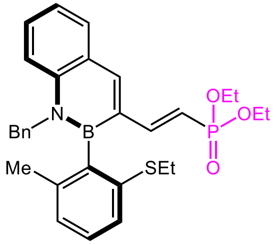
3w, 47%, 94% ee
1a, 45%, 93% ee
C = 50%, S = 110, 18 h



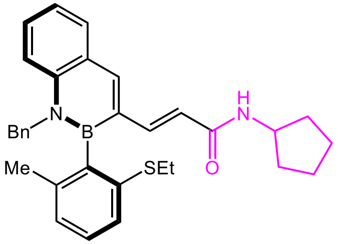
3x, 37%, 94% ee
1a, 40%, 94% ee
C = 50%, S = 115, 48 h



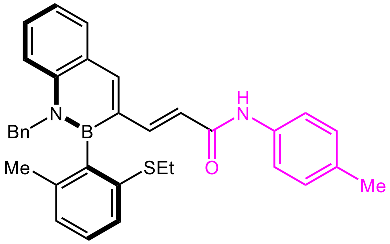
3y, 38%, 96% ee
1a, 43%, 92% ee
C = 51%, S = 94, 38 h



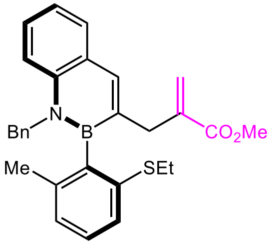
3z, 41%, 94% ee
1a, 45%, 96% ee
C = 50%, S = 127, 36 h



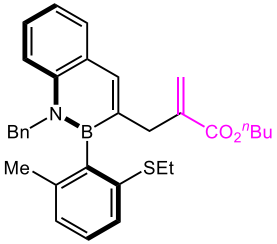
3aa, 37%, 92% ee
1a, 41%, 94% ee
C = 51%, S = 85, 20 h



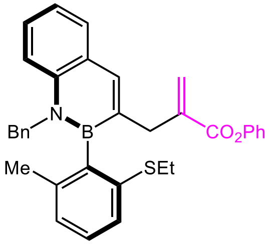
3ab, 47%, 92% ee
1a, 45%, 95% ee
C = 51%, S = 89, 17 h



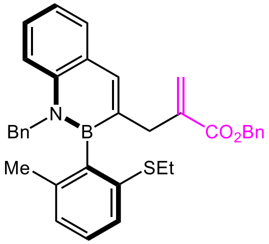
3ac, 37%, 91% ee
1a, 43%, 94% ee
C = 51%, S = 75, 18 h



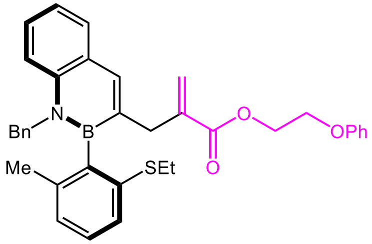
3ad, 39%, 87% ee
1a, 41%, 91% ee
C = 51%, S = 45, 96 h



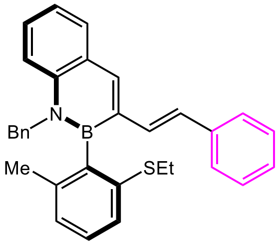
3ae, 38%, 91% ee
1a, 40%, 93% ee
C = 51%, S = 72, 18 h



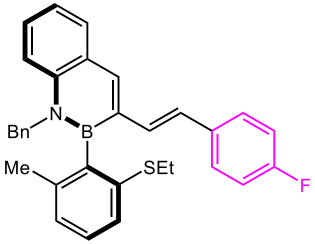
3af, 40%, 87% ee
1a, 40%, 98% ee
C = 53%, S = 65, 48 h



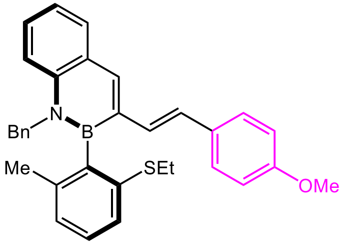
3ag, 42%, 94% ee
1a, 45%, 93% ee
C = 50%, S = 110, 118 h



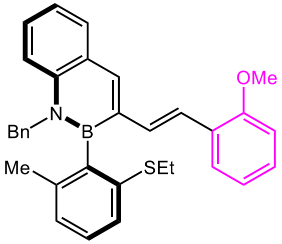
3ah, 32%, 93% ee
1a, 41%, 93% ee
C = 50%, S = 94, 62 h



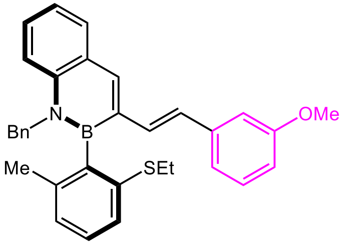
3ai, 28%, 90% ee
1a, 40%, 90% ee
C = 50%, S = 58, 97 h



3aj, 37%, 98% ee
1a, 42%, 94% ee
C = 49%, S = 354, 48 h

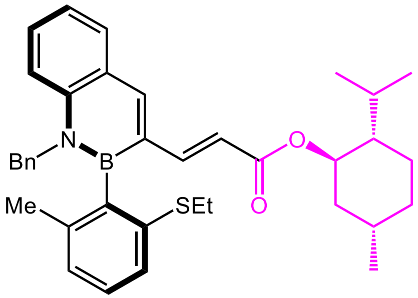


3ak, 35%, 95% ee
1a, 43%, 91% ee
C = 49%, S = 124, 48 h

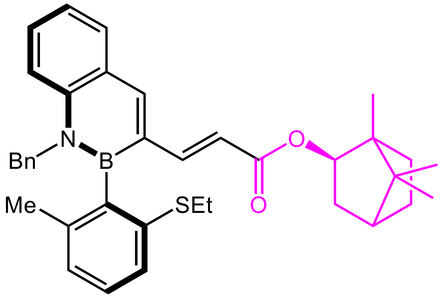


3al, 33%, 87% ee
1a, 45%, 90% ee
C = 51%, S = 44, 36 h

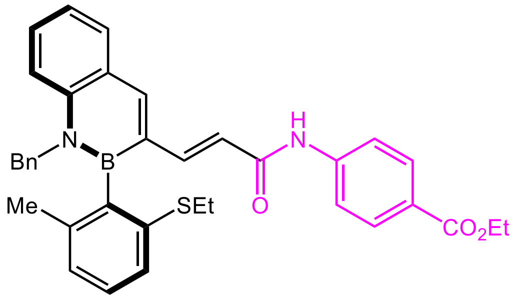
Late-stage modification of complex molecules



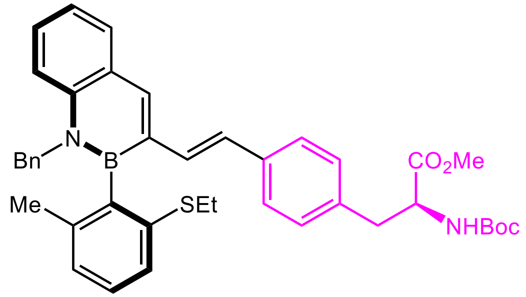
3am, 44%, dr > 20 : 1
1a, 42%, 90% ee
36 h



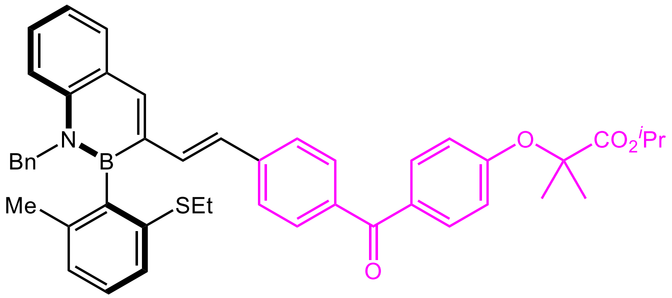
3an, 45%, dr > 20 : 1
1a, 38%, 91% ee
36 h



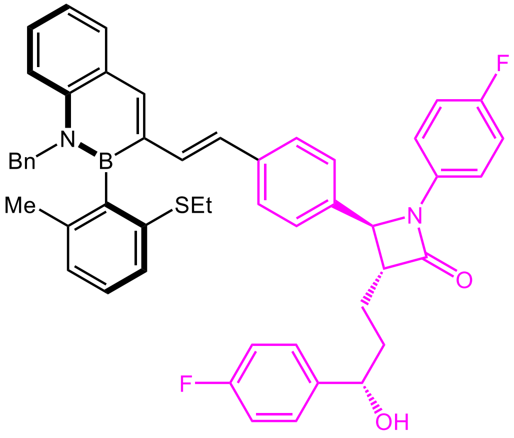
3ao, 47%, 89% ee
1a, 45%, 95% ee
C = 51%, S = 64, 18 h



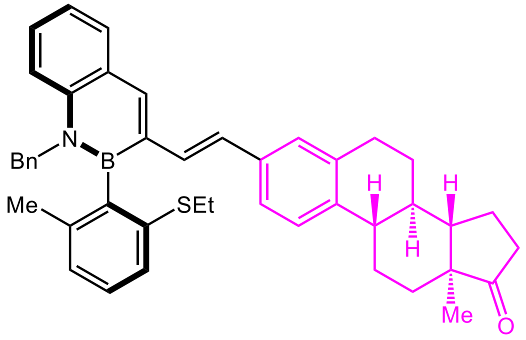
3ap, 42%, dr > 20 : 1
1a, 45%, 97% ee
72 h



3aq, 45%, 84% ee
1a, 45%, 96% ee
C = 53%, S = 45, 48 h

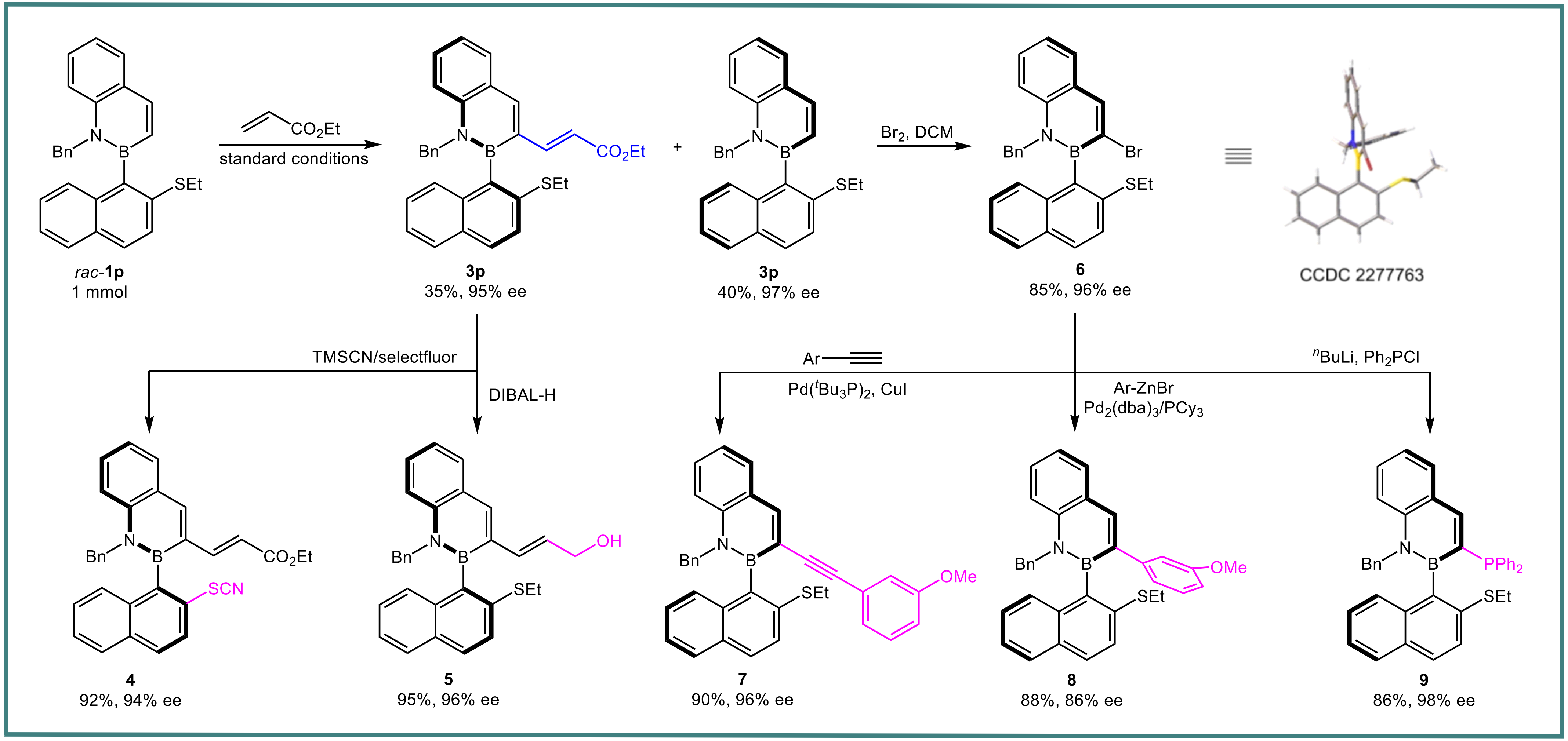


3ar, 35%, dr = 3 : 1
1a, 45%, 95% ee
96 h

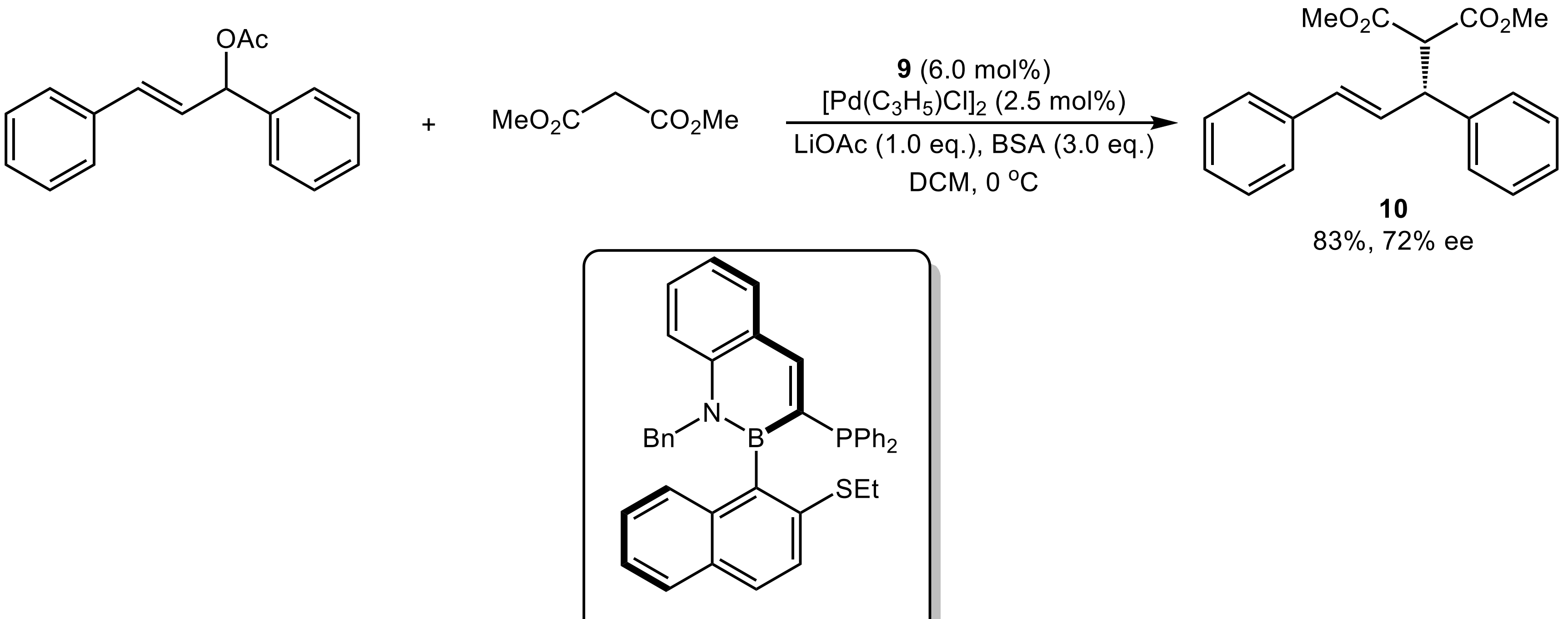


3as, 39%, dr > 20 : 1
1a, 45%, 90% ee
48 h

Scale-up preparation and transformations



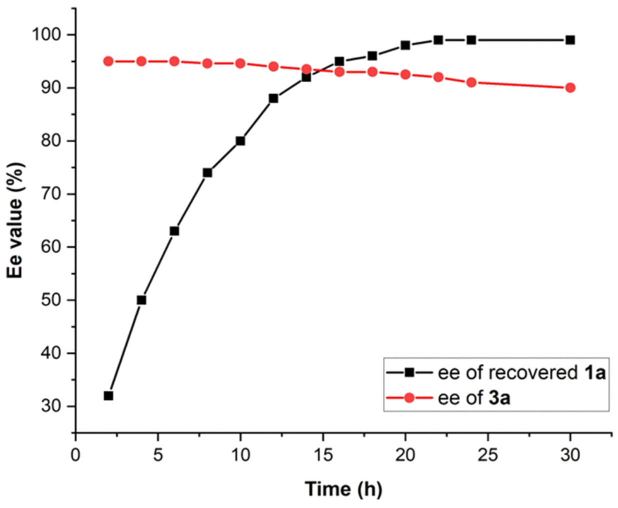
Evaluation of the axially chiral P, S-ligand



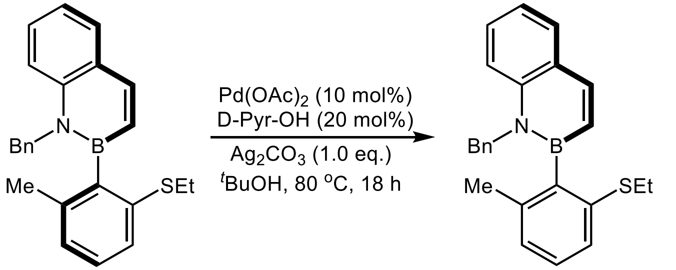
9 chiral *P*, *S*-ligand

Mechanistic studies

A, Plot of ee value with respect to time

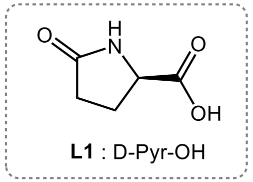


B, Racemization experiment

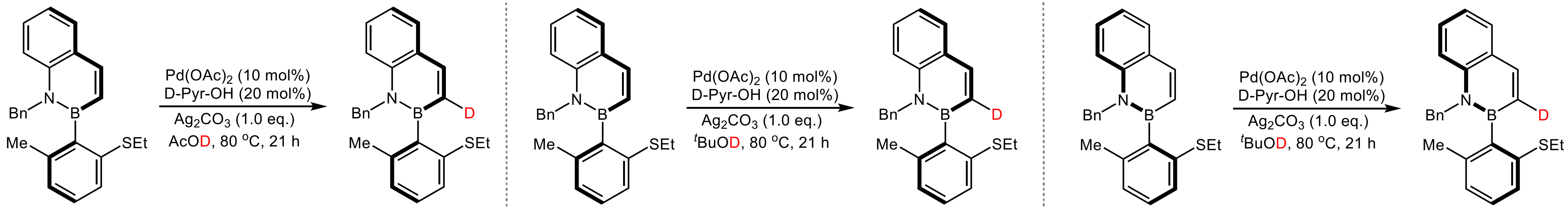


(*R*)-**1a**
> 99% ee

> 96% ee



C, Probing of reversible C-H activation



(*R*)-**1a**
> 99% ee

> 99% D

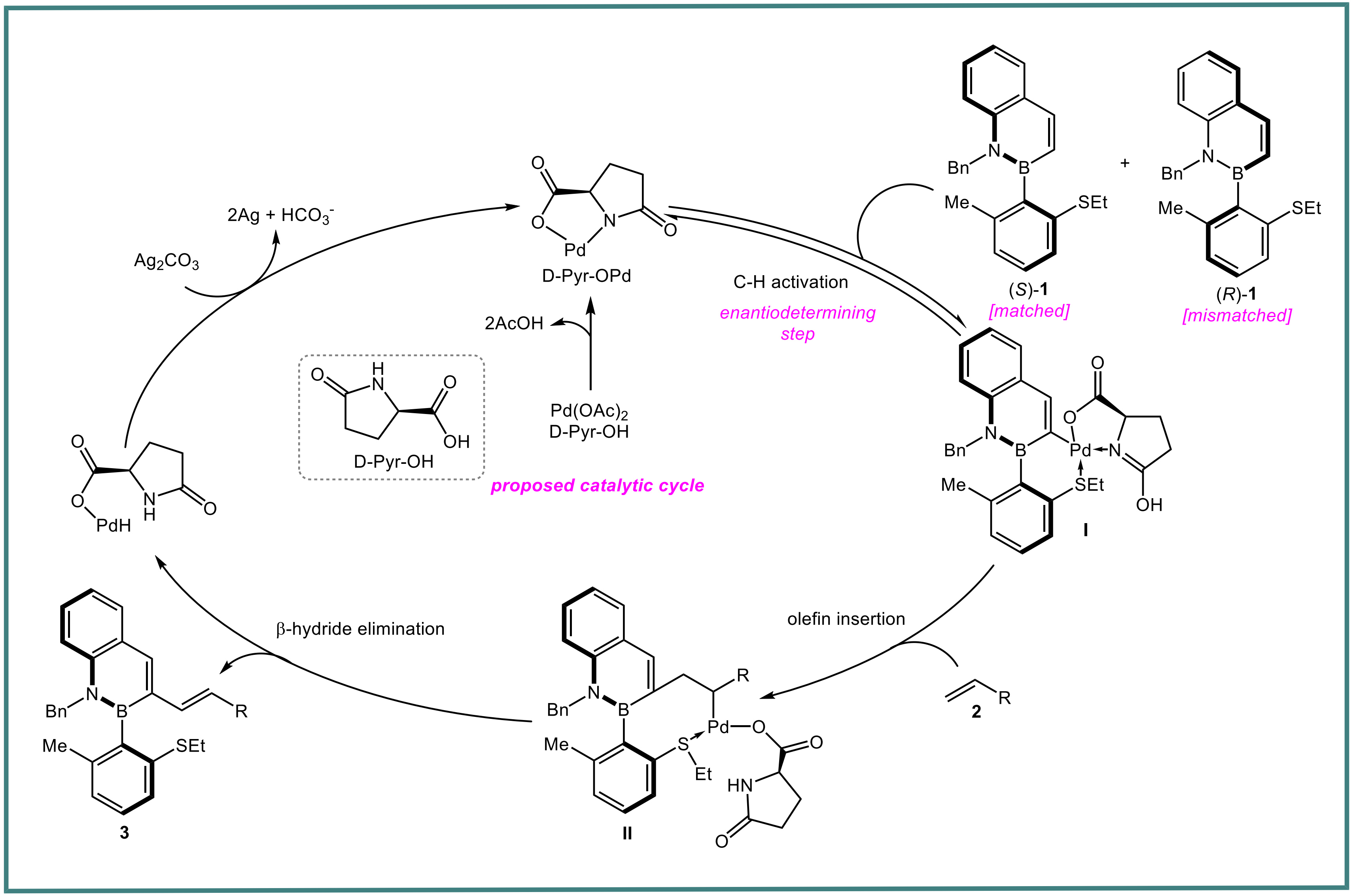
(*R*)-**1a**
> 99% ee

No D
w/o Ag_2CO_3, No D

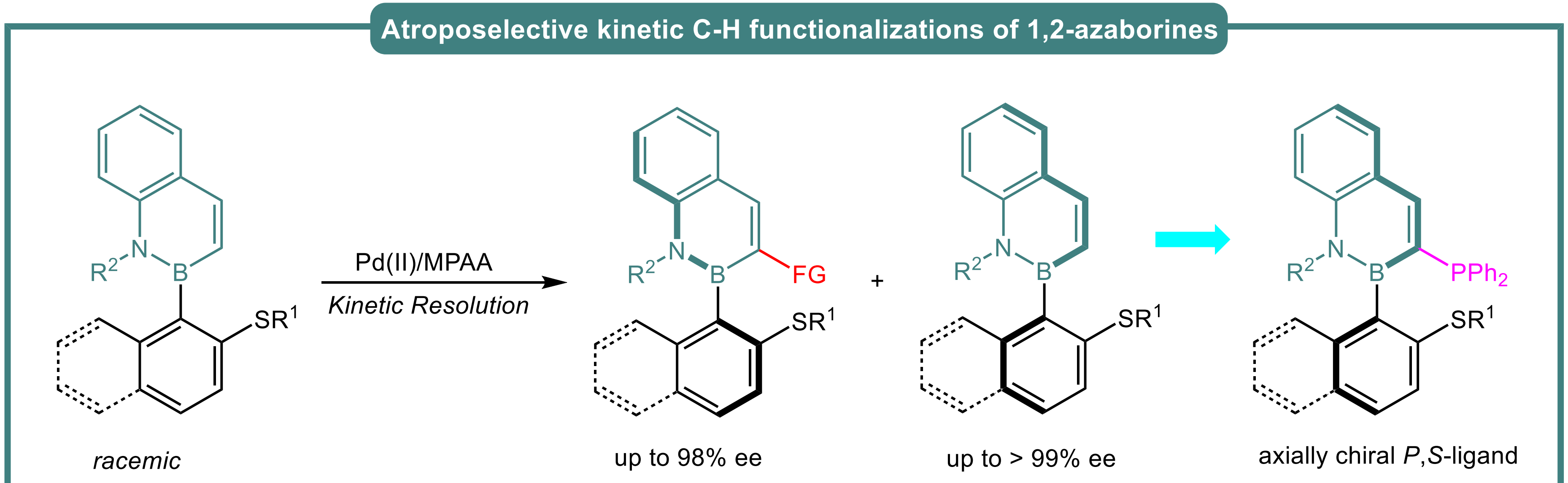
(*S*)-**1a**
> 99% ee

37% D
w/o Ag_2CO_3, > 99% D

Proposed mechanism



Summary



♥ Broad substrate scope (42 examples) ♥ High atroposelectivity (*S* up to 354) ♥ Excellent stereoselectivity (complete *Z*-selectivity)

Writing strategy

◻ The First Paragraph

1,2-氮杂硼烷的
性质及其应用

↓

1,2-氮杂硼烷的
合成及后期修饰

↓

引出本文工作

- ✓ BN-heterocycles, derived from the replacement of a C=C bond with a B-N bond, can maintain aromatic character as electronic isosteres of arenes that expand the aromatic chemical space. 1,2-Azaborines, one of BN-heterocycles, have attracted considerable interest due to its unique properties and relatively high stability, which are prominent in functional materials and ligands.
- ✓ To Due to their wide applications, many efforts have focused on the synthesis of 1,2-azaborines. To meet continually growing demand on complex 1,2-azaborine motifs, considerable efforts have been devoted to the late stage functionalization of simple 1,2-azaborines
- ✓ Herein, we report the Pd(II)/MPAA-catalyzed atroposelective C-H olefination and allylation of 1,2-benzazaborines. This transformation achieves a kinetic resolution of 2-aryl-1,2-benzazaborines, thus representing a novel and straight-forward route to construct C-B axial chirality.

Writing Strategy

☐ The Last Paragraph

总结工作

↓

本文亮点

↓

展望

- ✓ In conclusion, the atroposelective C-H olefination and al-allylation reactions of 1,2-benzazaborines have been developed as novel and straightforward routes to prepare challenging C-B axial chirality.
- ✓ For This transformation features kinetic resolution, broad substrate scope, high atroposelectivity (S factor up to 354), and excellent stereoselectivity (complete *Z* selectivity).
- ✓ The potential value of this reaction was further demonstrated by the diversified transformations of two kinds of C-B axially chiral 2-aryl- 1,2-benzazaborines. We believe that this research will not only enrich the late-stage functionalization of 1,2-azaborines, but also provide an avenue to prepare significant chiral 1,2-azaborines.

Representative examples

- ✓ Their 1,2-Azaborines, one of BN-heterocycles, have attracted considerable interest due to its unique properties and relatively high stability, which are prominent in functional materials and ligands. (*adj*, 杰出的)
- ✓ From the very beginning, we realized that a suitable DG is the key to the success of this atroposelective C H functionalization reactions of 1,2-benzazaborines. (从一开始…)
- ✓ The potential value of this reaction was further demonstrated by the diversified transformations of two kinds of C B axially chiral 2-aryl-1,2-benzazaborines. (用于文章最后的展望)

Acknowledgment

Thanks
for your attention !