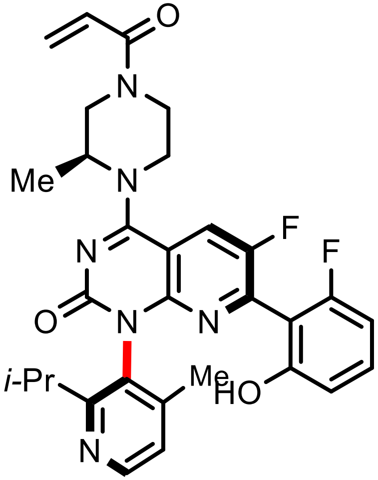
Lecture@Blumberg Institute 2024/08/26

First atroposelective Chan–Lam coupling for the synthesis of axially-chiral C–N linked biaryls and other boron chemistry

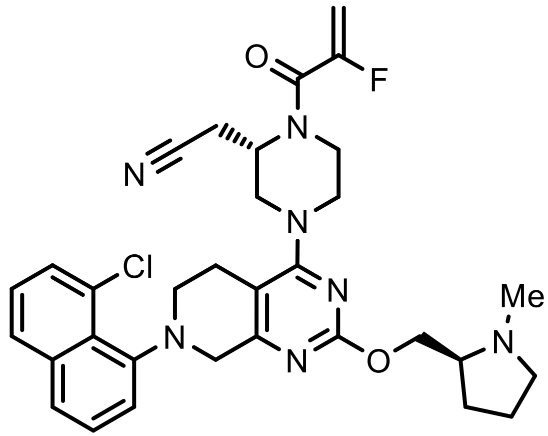
Takashi Ikawa

Gifu Pharmaceutical University, Japan

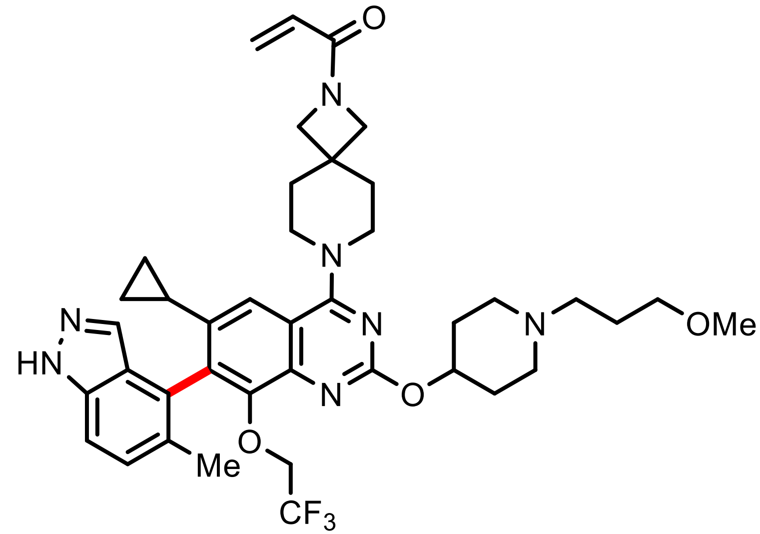
KRAS $G_{12}C$ inhibitor



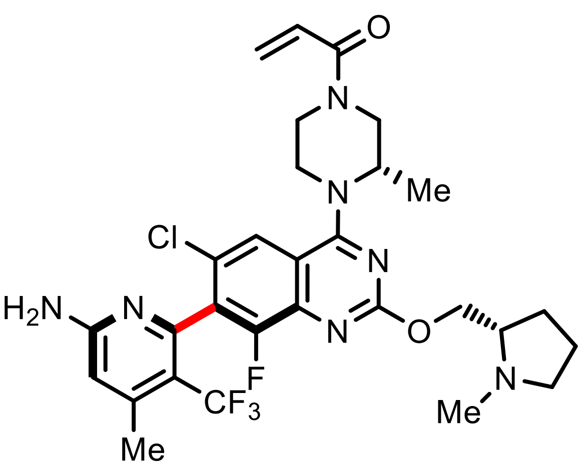
Sotorasib (Amgen)
Lumakras®



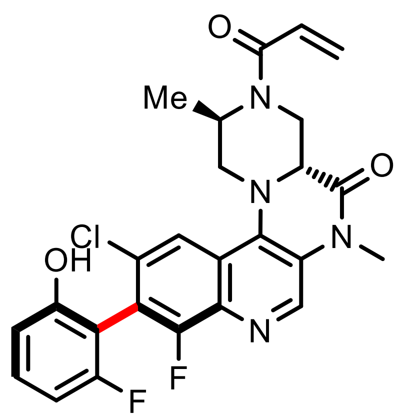
Adagrasib (BMS)
Krazati®



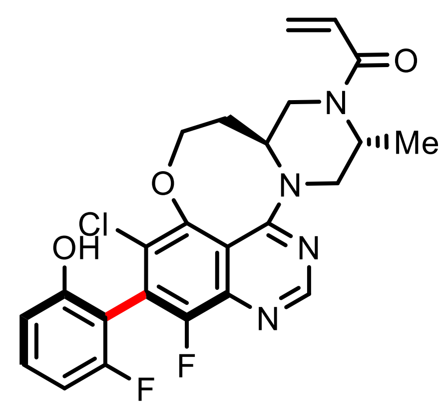
ASP2453 (Asteras)



Divarasib (AstraZeneca)



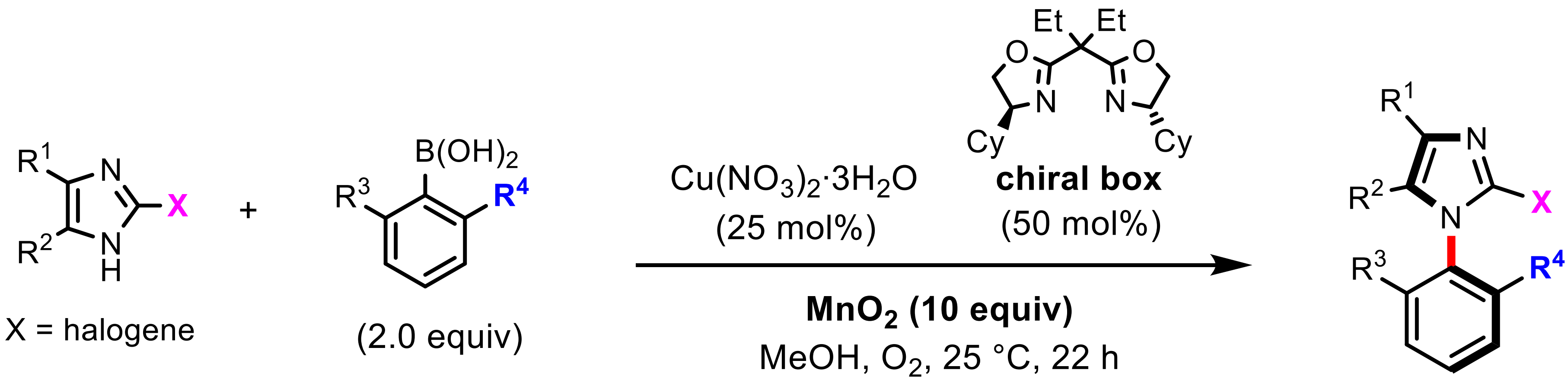
(AstraZeneca)



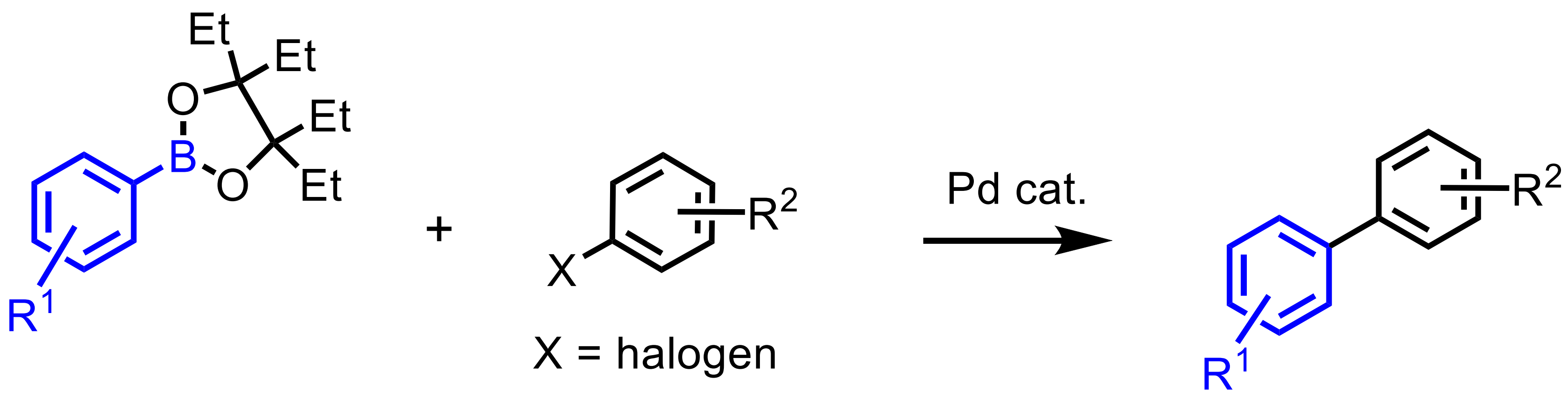
AZD4625 (AstraZeneca)

Today's Topics

1. First atroposelective Chan–Lam coupling

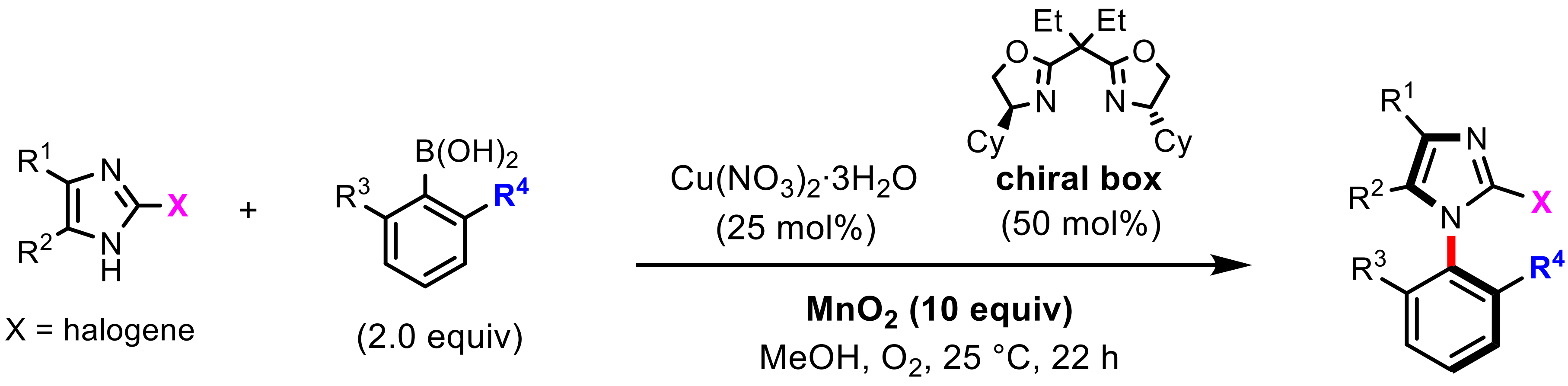


2. New arylboronic acid derivatives, ArB(Epin)

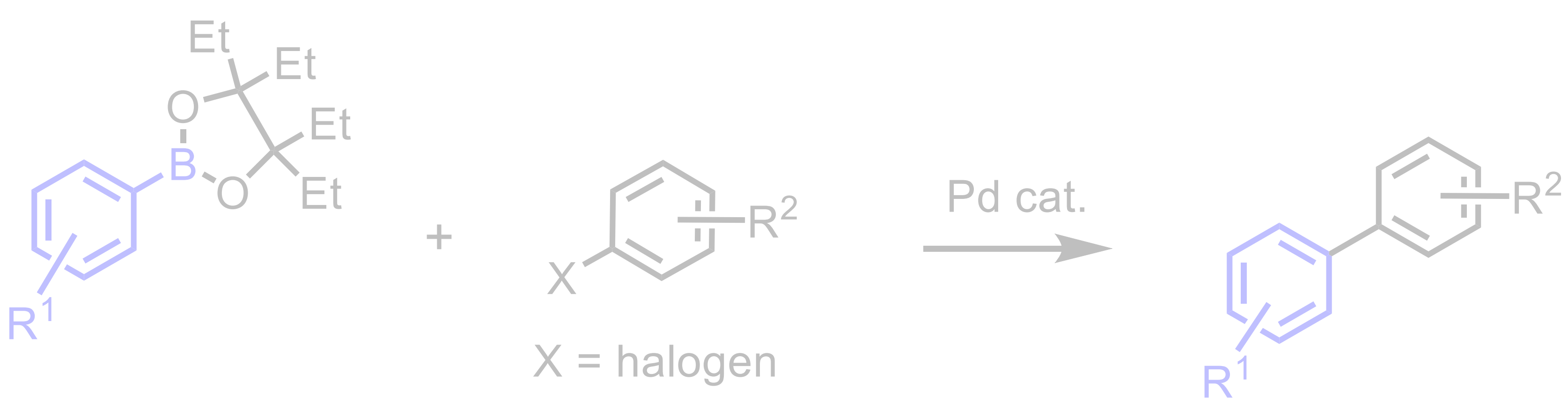


Today's Topics

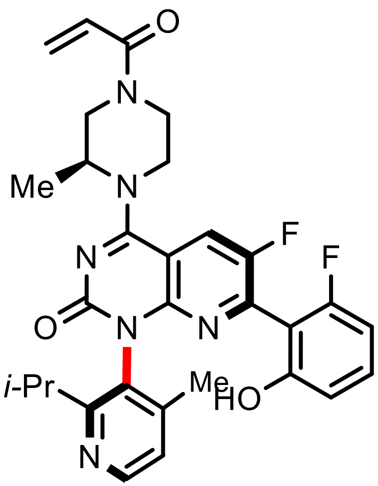
1. First atroposelective Chan–Lam coupling



2. New arylboronic acid derivatives, ArB(Epin)

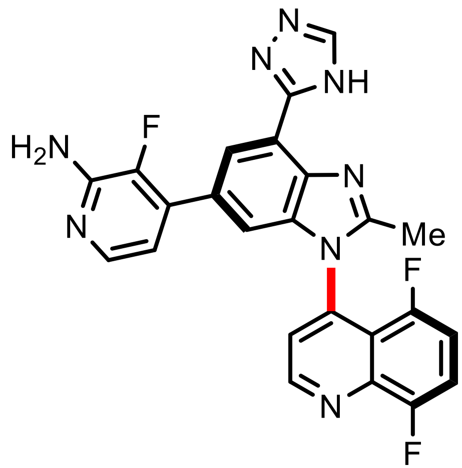


Biologically active C–N axially chiral biaryls



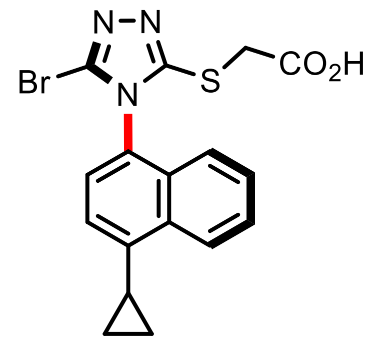
KRAS $G_{12}C$ inhibitor

Sotorasib (Amgen)



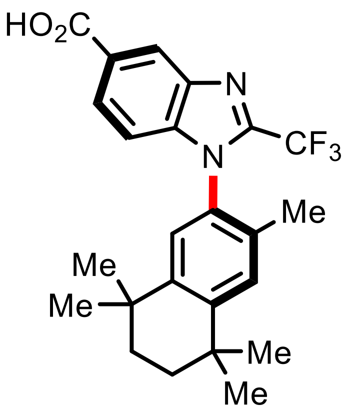
PI3Kβ inhibitor

(Gilead)



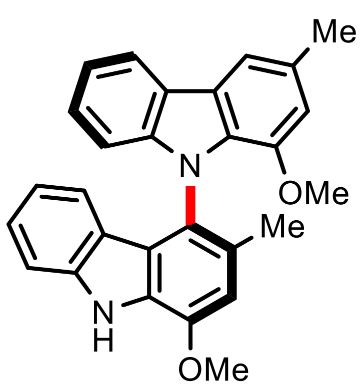
Uric acid
reabsorption inhibitor

Lesinurad (AstraZeneca)

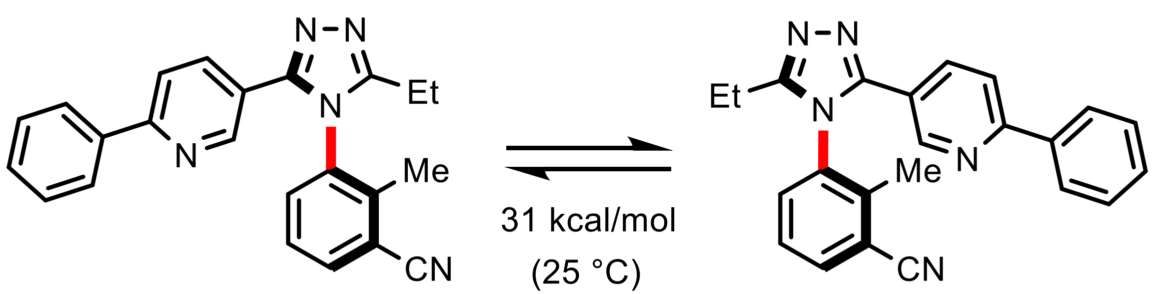


RXR partial agonist

anti-diabetes type 2



Murrastifoline-F



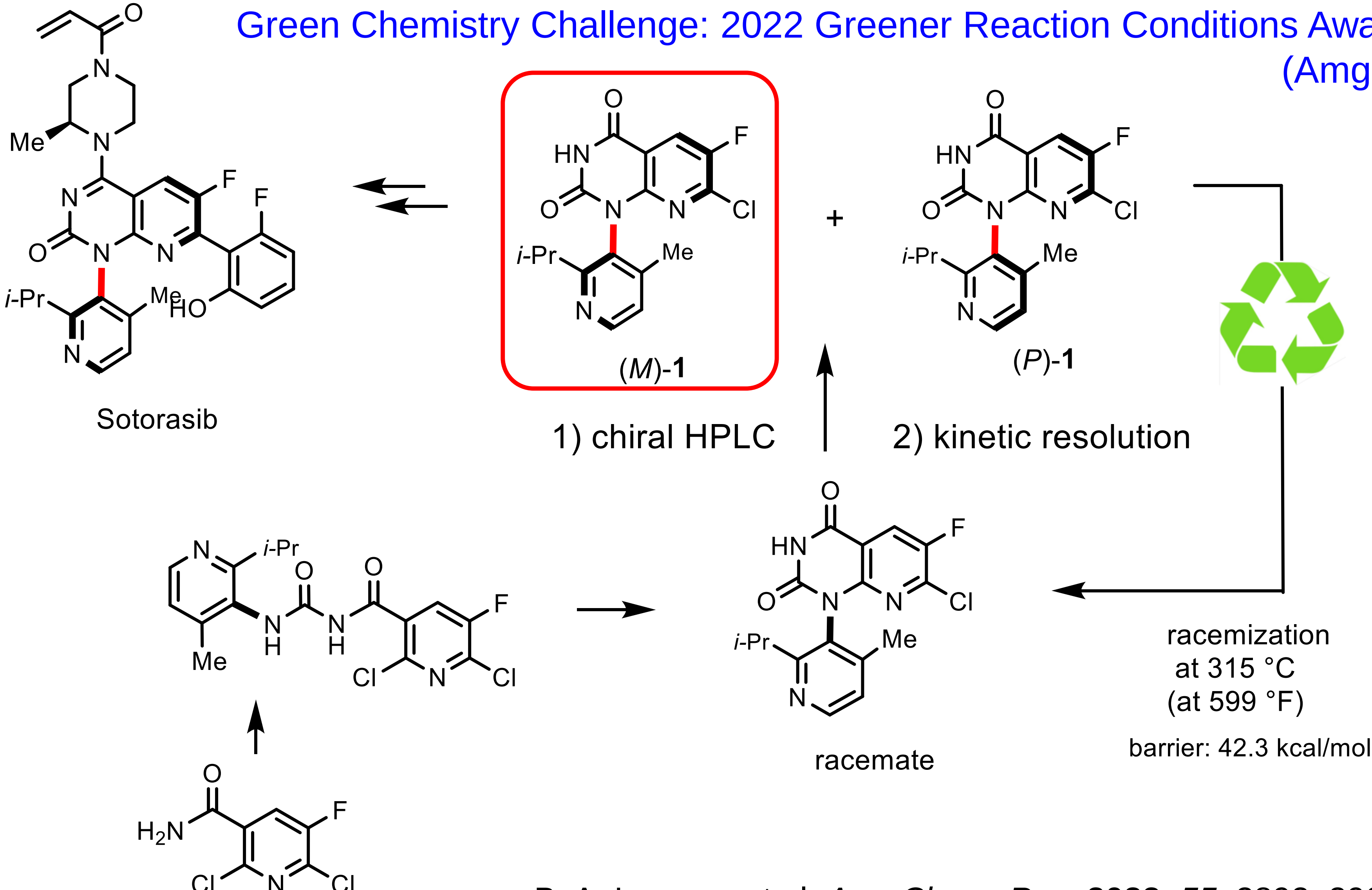
IC_{50} = **0.064 μM**

GlyT1 inhibitor

IC_{50} = **20 μM**

Synthesis of Sotorasib

Green Chemistry Challenge: 2022 Greener Reaction Conditions Award (Amgen)

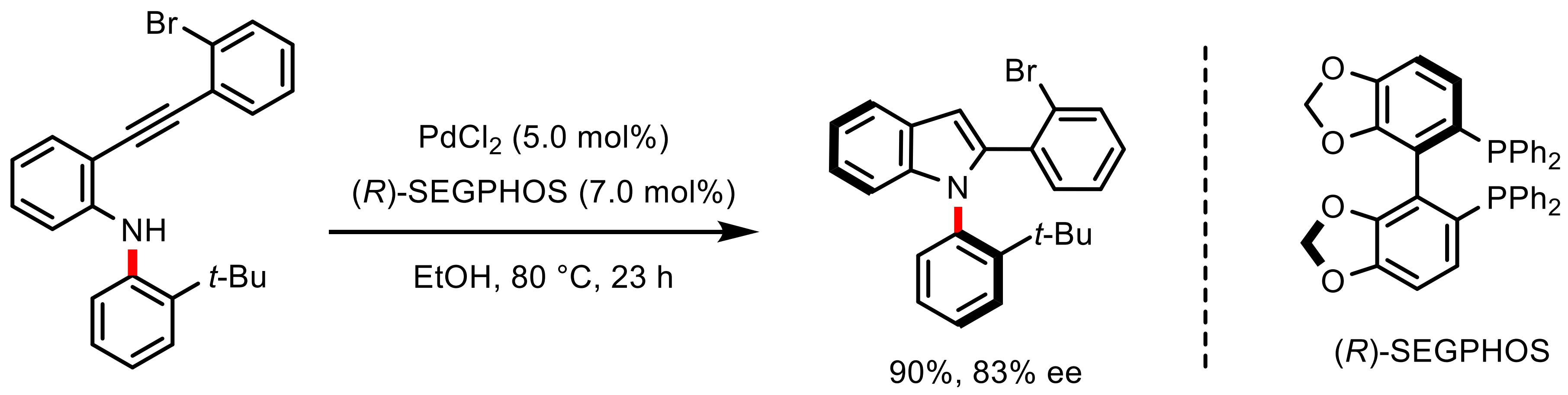


B. A. Lanman et al. *Acc. Chem. Res.* **2022**, *55*, 2892–2903.

https://www.epa.gov/greenchemistry/green-chemistry-challenge-2022-greener-reaction-conditions-award

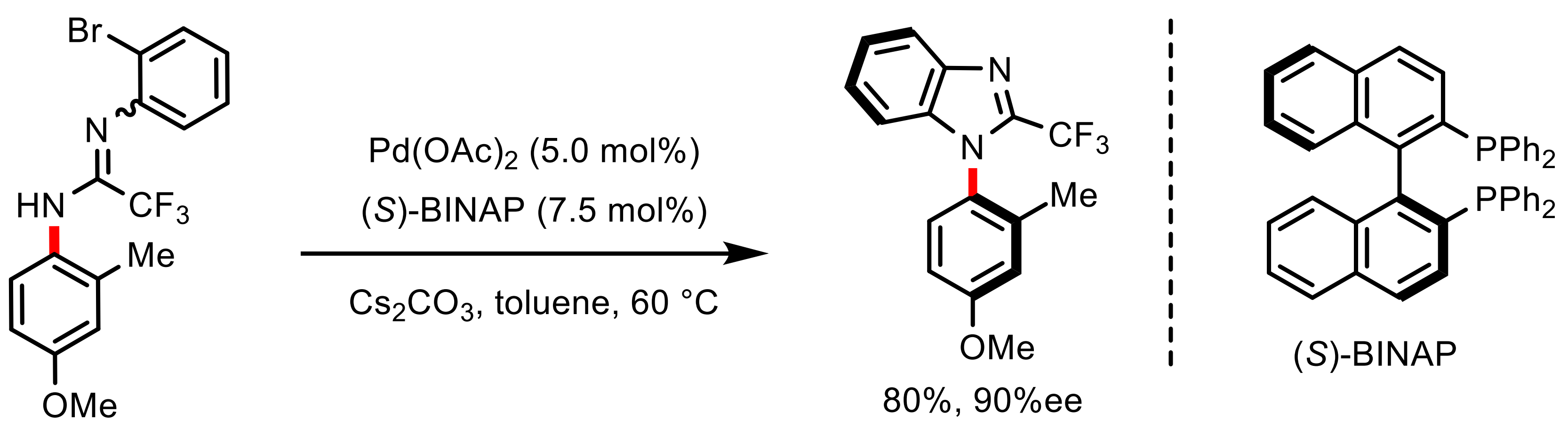
Synthesis of C–N axially chiral biaryls

Enantioselective alkyne cyclization



O. Kitagawa *et al*. *Chem. Eur. J*. **2010**, *16*, 6752–6755.

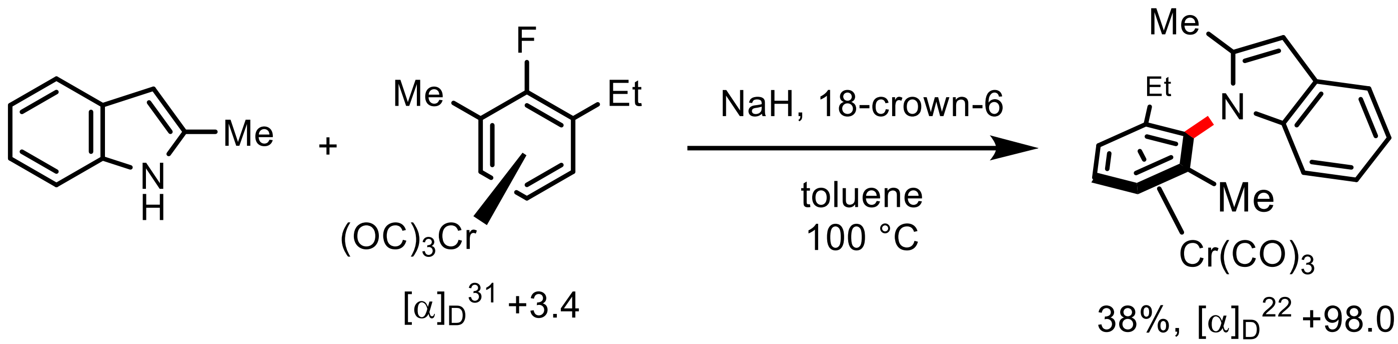
Enantioselective Buchwald-Hartwig reaction



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

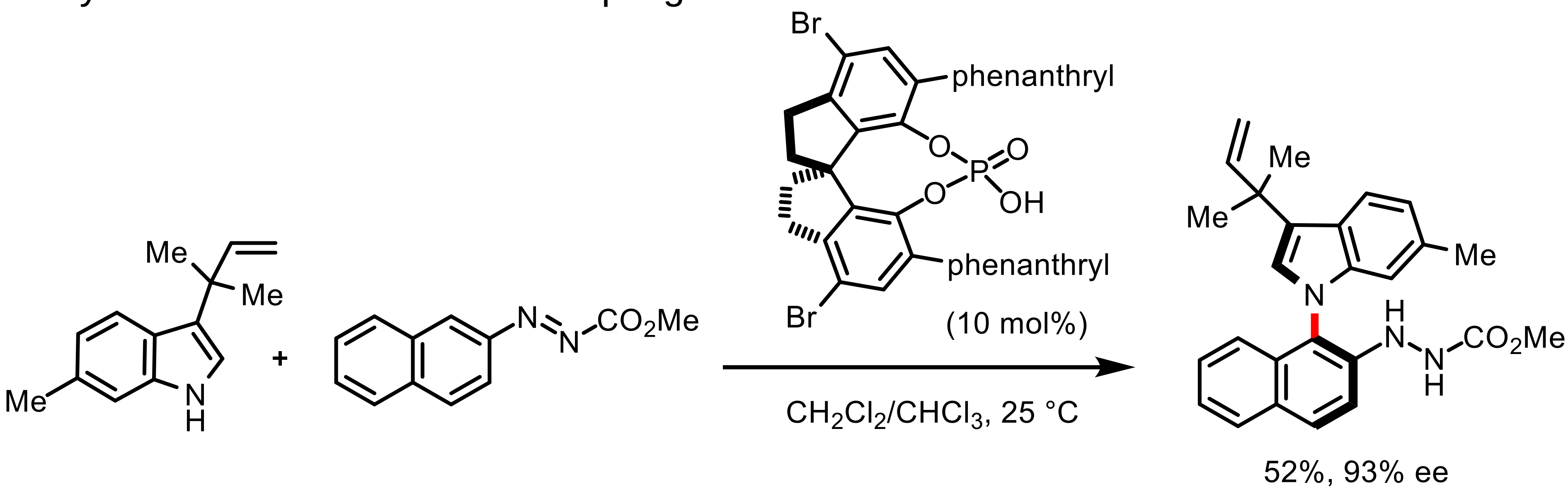
Synthesis of C–N axially chiral biaryls

First stereoselective C–N cross-coupling



K. Kamikawa; M. Uemura et al. *J. Org. Chem.* **2007**, *72*, 3394–3402.

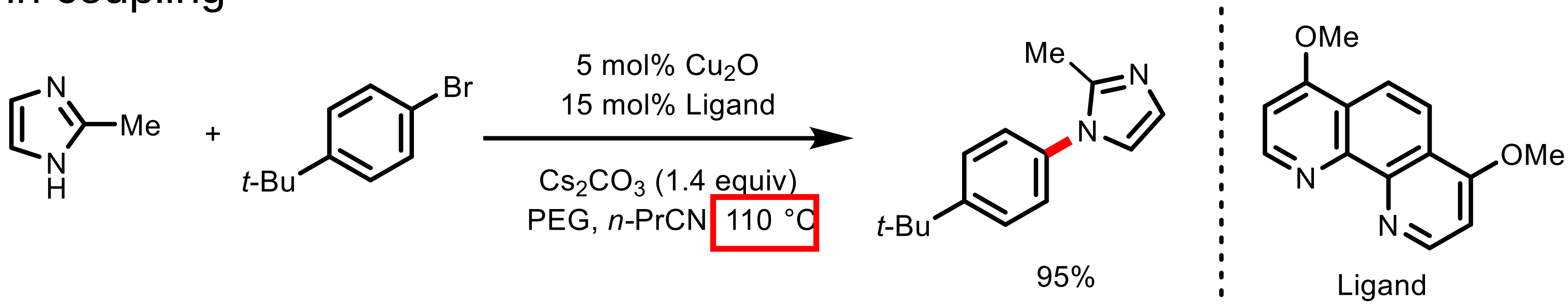
Calytic enantioselective C–N coupling



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

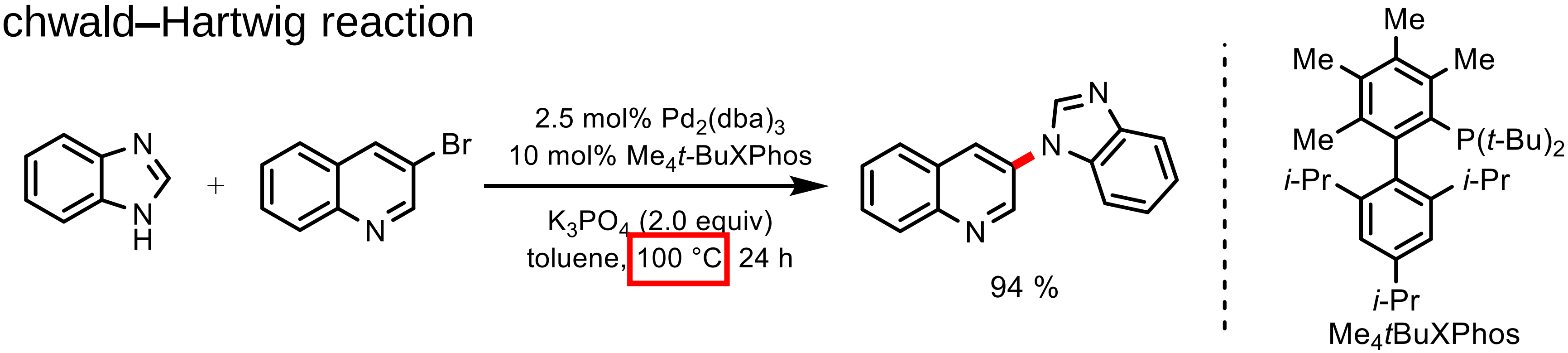
C–N coupling for synthesizing biaryls

Ullmann coupling



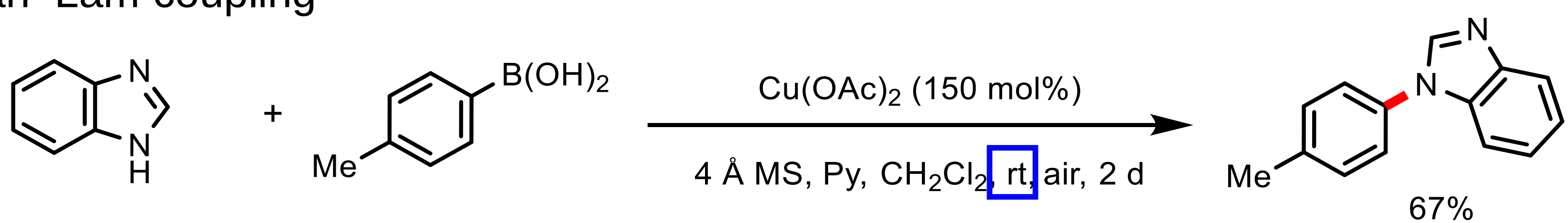
S. L. Buchwald et al. *J. Org. Chem.* **2007**, *16*, 6190–6199.

Buchwald–Hartwig reaction



S. L. Buchwald et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523–6527.

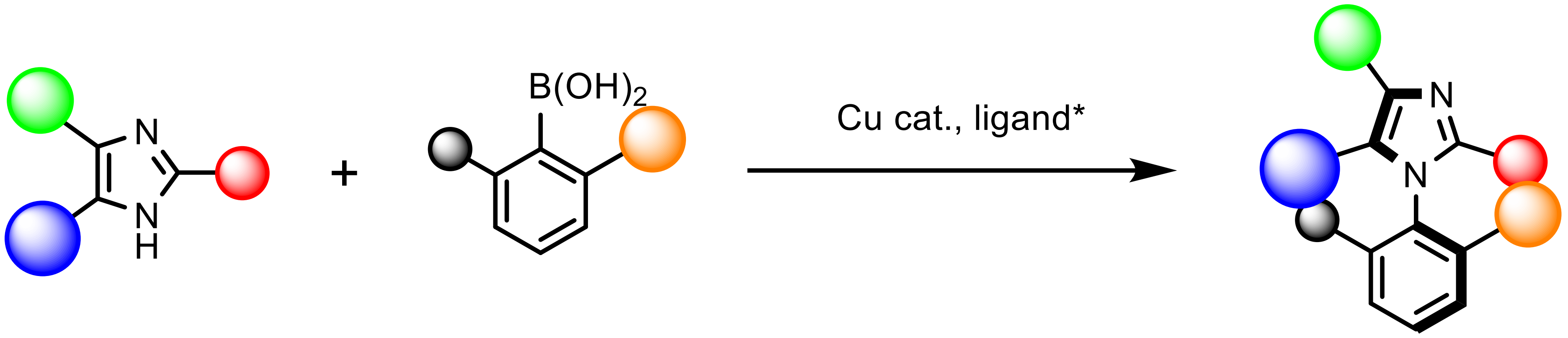
Chan–Lam coupling



P. Y. S. Lam et al. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.

Our strategy

Atroposelective Chan–Lam coupling

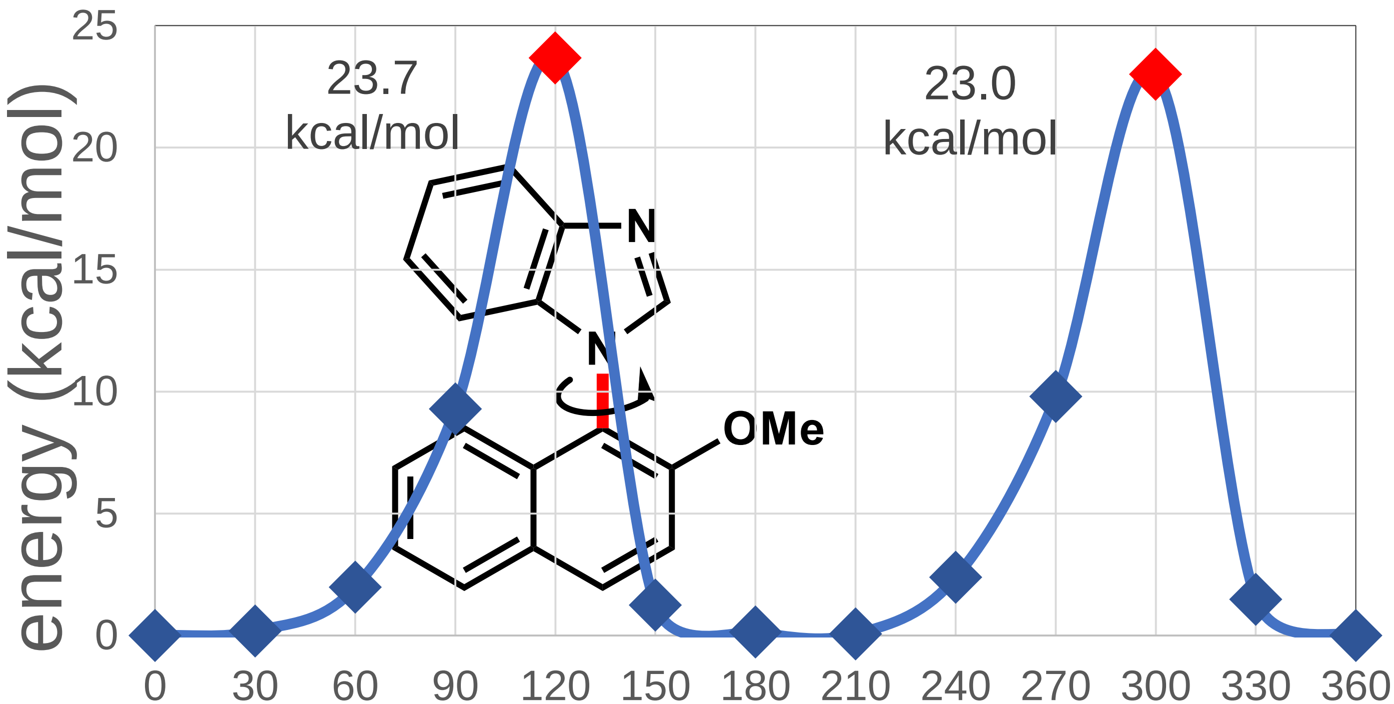


General synthesis of C–N axially chiral biaryls

Issues to be solved

1. Hard to couple between hindered substrates
2. Who knows atroposelective Chan–Lam possible?

Racemization barrier around C–N axis

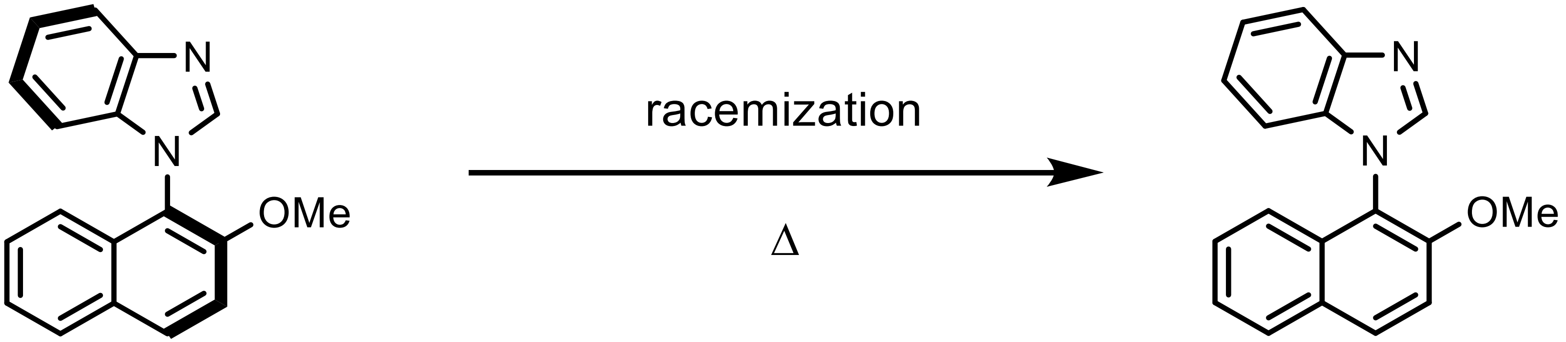


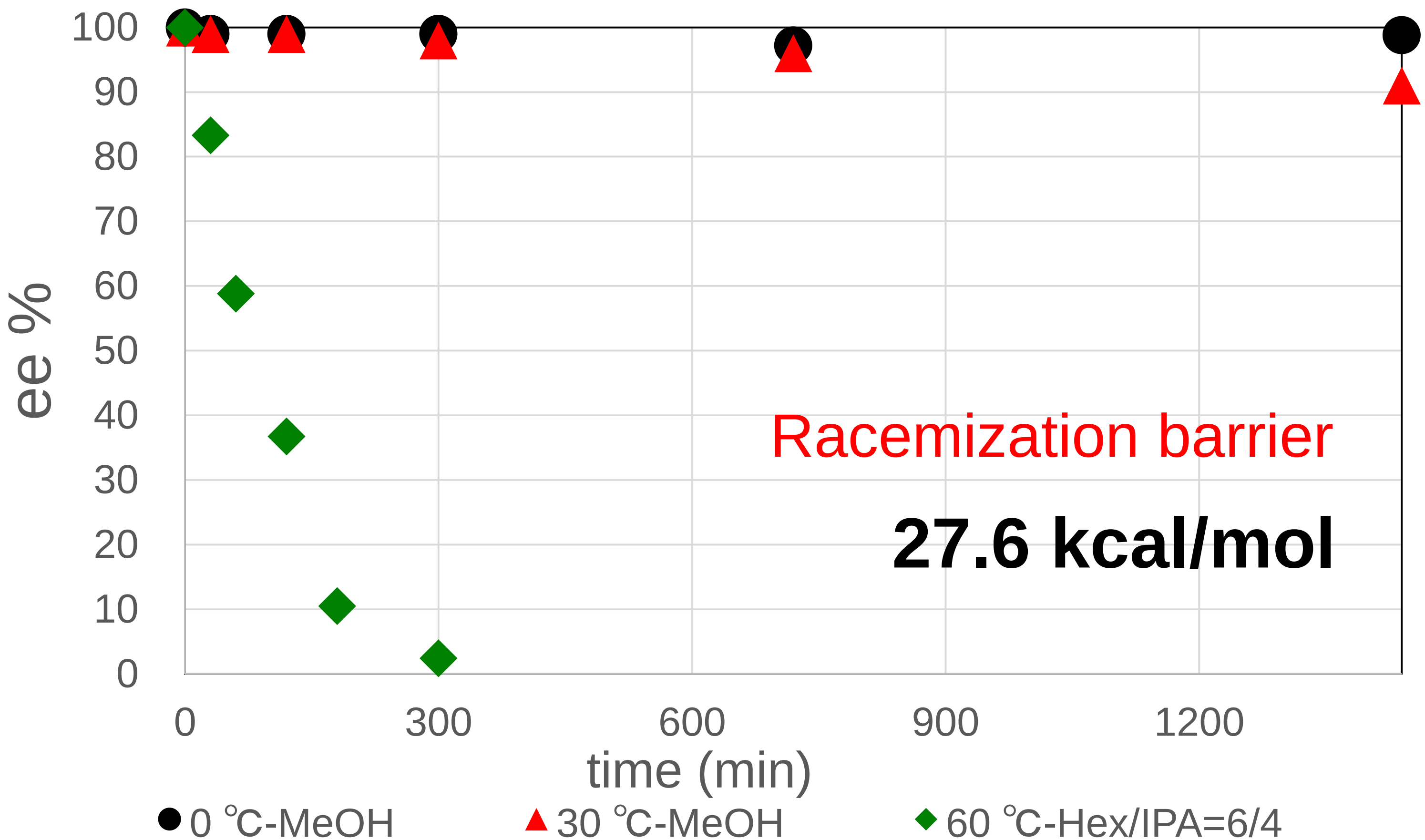
Racemization barrier

23 kcal/mol (Theoretical)

Optimized Geometries at B3LYP/6-31G(d) Level of Theory

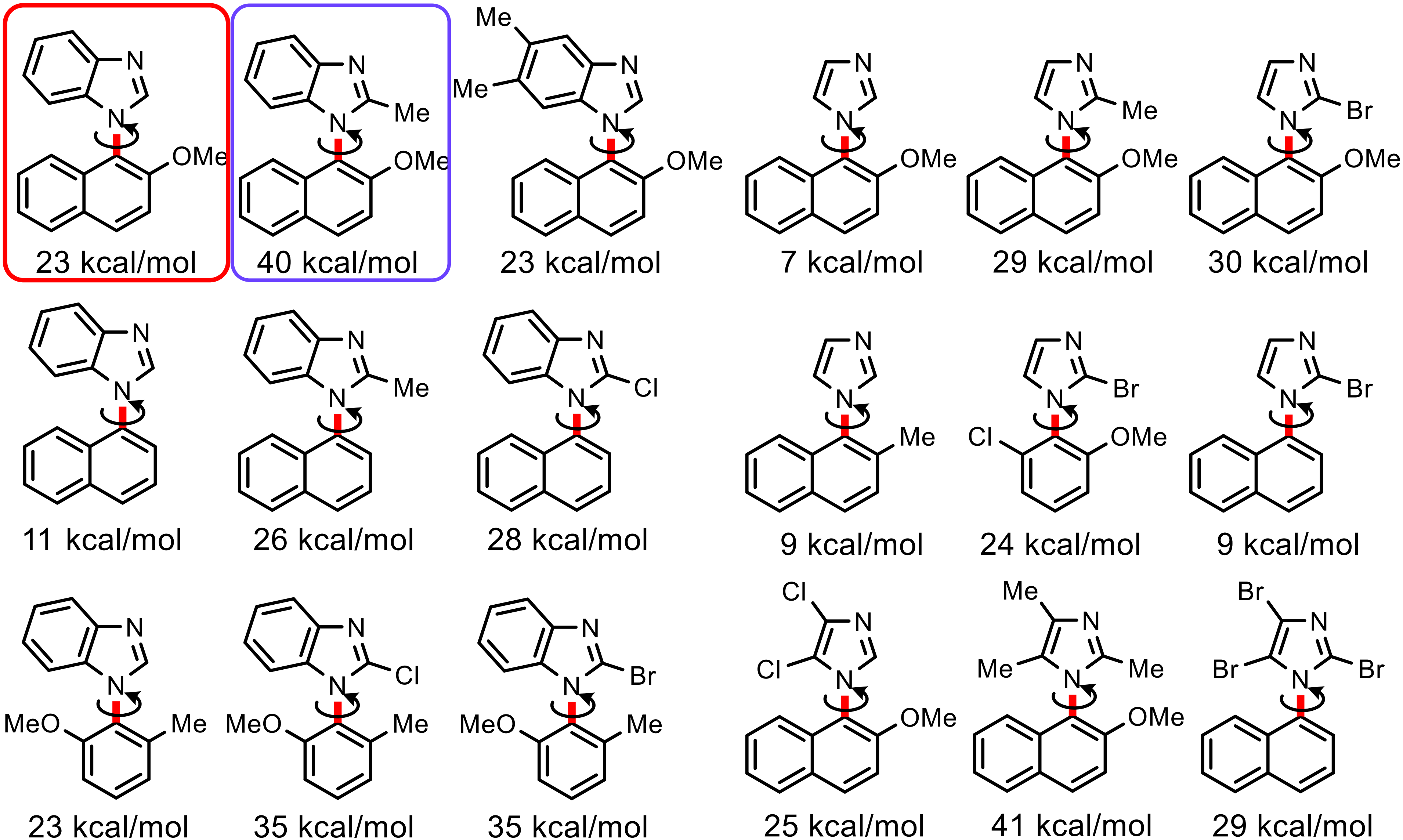
Racemization barrier around C–N axis



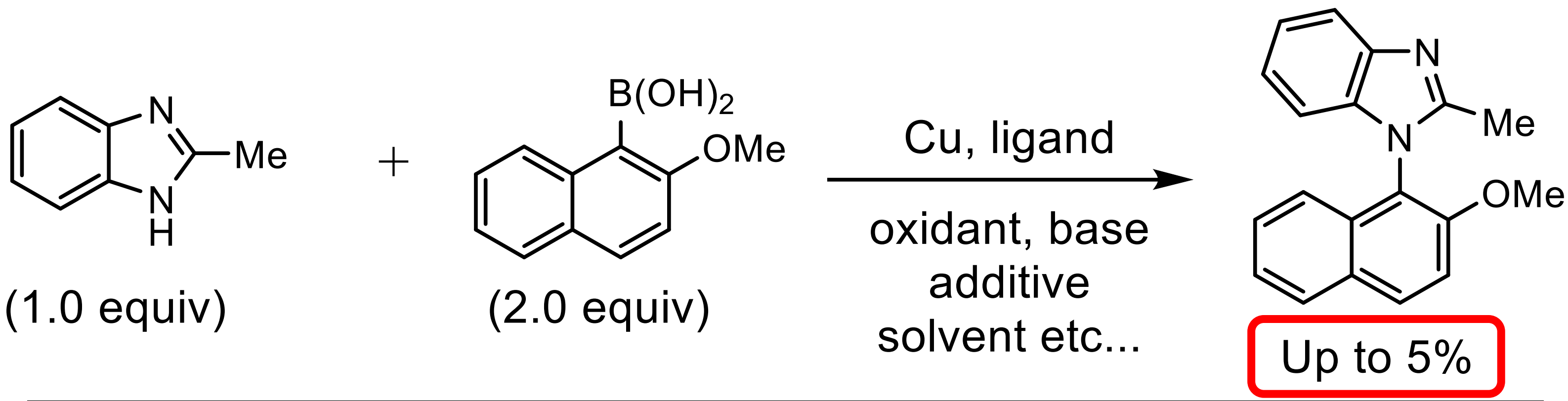


Racemization barriers around C–N axises

N-arylbenzimidazole | *N*-arylimidazole

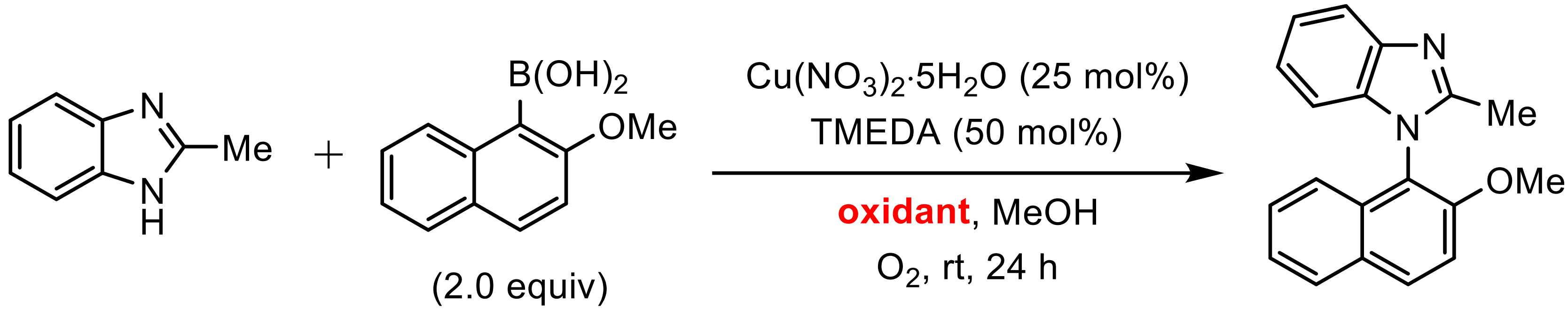


Additive effect of Chan–Lam coupling



variable	
Cu source	$Cu(OAc)_2$, $Cu(OTf)_2$,$Cu(OPiv)_2$, $Cu(acac)_2$, $Cu(TFA)_2$, $CuBr_2$, $CuCl_2$, $CuSO_4$, CuFAP, $[Cu(DMAP)_4I]I$, $[Cu(OH)\cdot TMEDA]_2Cl_2$, $Cu(MeCN)_4PF_6$, CuCl, Cu_2O, Cu_2S, Cu Complex
oxidant	air, O_2, pyridine *N*-oxide, Tempo, $(t\text{-BuO})_2$
base	Et_3N, $(i\text{-Pr})_2NEt$, pyridine, 4-methylpyridine, 2,6-lutidine, K_2CO_3, K_3PO_4, *t*-BuOK, *N*-methylpiperidine, $n\text{-Bu}_4NOH$, $NaOSiMe_3$
solvent	CH_2Cl_2, MeCN, EtOAc, MeOH, EtOH, 1,4-dioxiane, NMP, THF, DMF, PhMe, DMSO, H_2O, *t*-BuOH
ligand	TMEDA, DMAP, NHC derivatives, bipyridines, phosphines, 1,10-phenntholine, iminoarylcarboxylates, iminoarylsulfonates
additive	myristic acid, urea, $B(OH)_3$
temperature	rt–100 °C

Additive effect of Chan–Lam coupling



entry	oxidant (2.0 equiv)	GC yield (%)
1	Ag_2CO_3	0.5
2	Ag_2O	4
3	PIDA	N.D.
4	(*t*-BuO)$_2$	3
5	$Na_2S_2O_4$	N.D.
6	NIS	3
7	V_2O_5	N.D.
8	$Mn(OAc)_2 \cdot 4H_2O$	N.D.
9	MnI_2	N.D.
10	MnO_2	28
11	$MnSO_4 \cdot H_2O$	7
12	CrO_3	N.D.
13	*m*-CPBA	N.D.
14	$NaClO_2$	2
15	$NaClO_4$	8

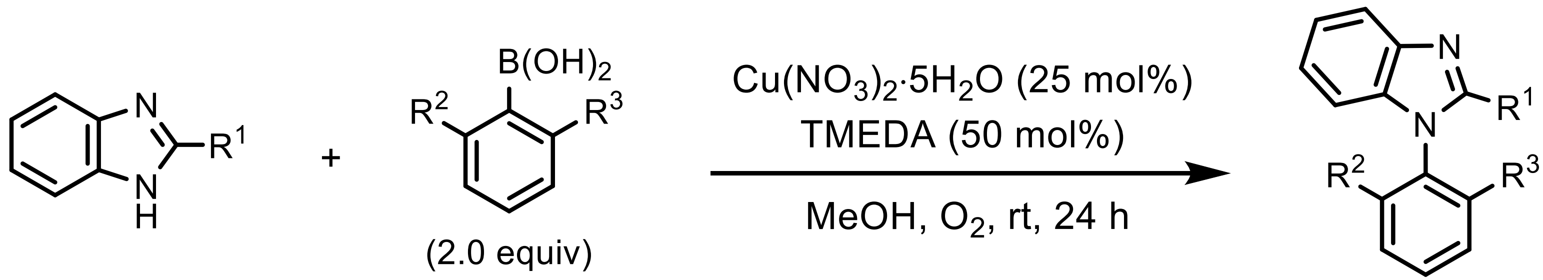
entry	oxidant	GC yield (%)
1	MnO_2 (10 equiv) without O_2	18[a]
2	MnO_2 (2.0 equiv)	28[b]
3	MnO_2 (10 equiv)	37
4	MnO_2 (100 equiv)	62[b]

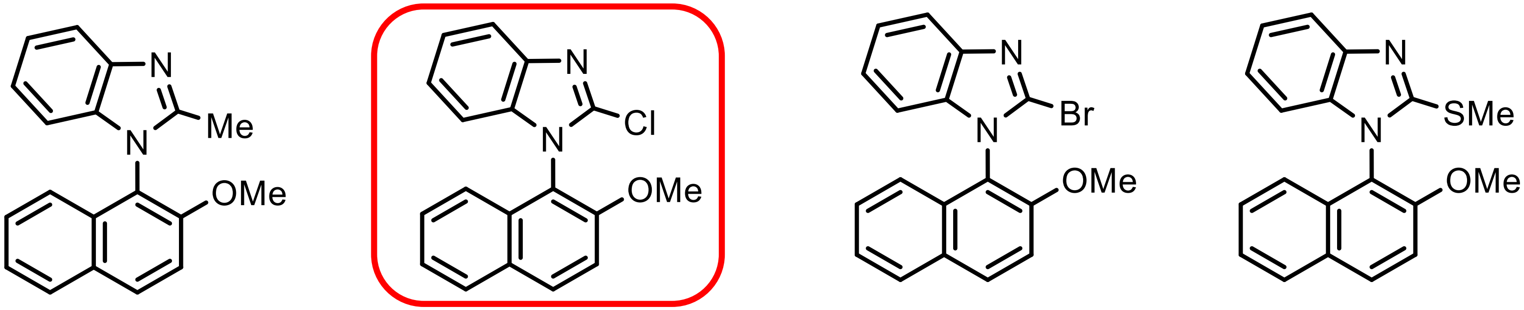
[a]Under Ar atmosphere. [b]Isolated yield.

optimal conditions

Cu : **$Cu(NO_3)_2 \cdot 3H_2O$**
ligand : **TMEDA**
oxidant : **MnO_2 with O_2**
solvent : **MeOH**
temperature : **rt**

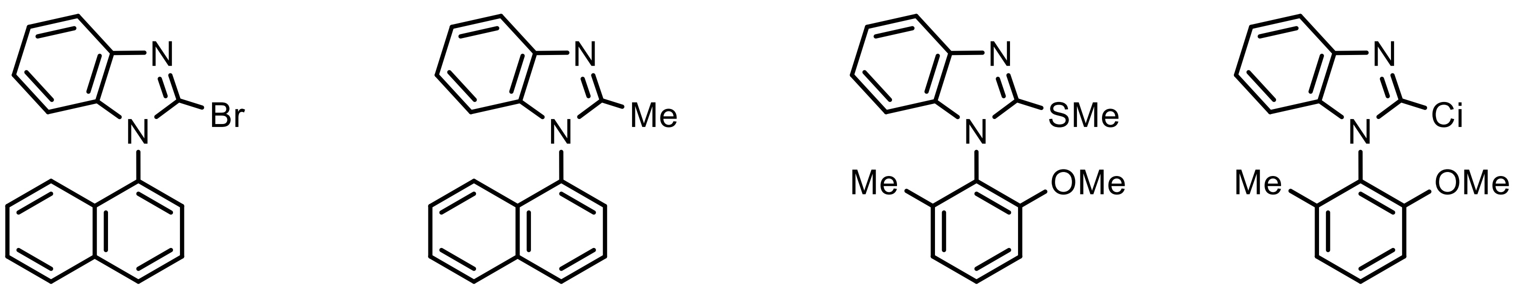
MnO_2 addition effect of Chan–Lam coupling





with MnO_2[a] 62%[b,c] | **99%** | **73%** | **54%**

without MnO_2 5% | 2%[b] | 2%[b]

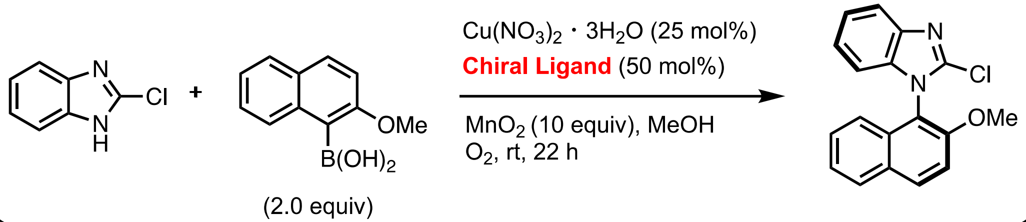


with MnO_2[a] 76% | **58%** | **73%** | **98%**

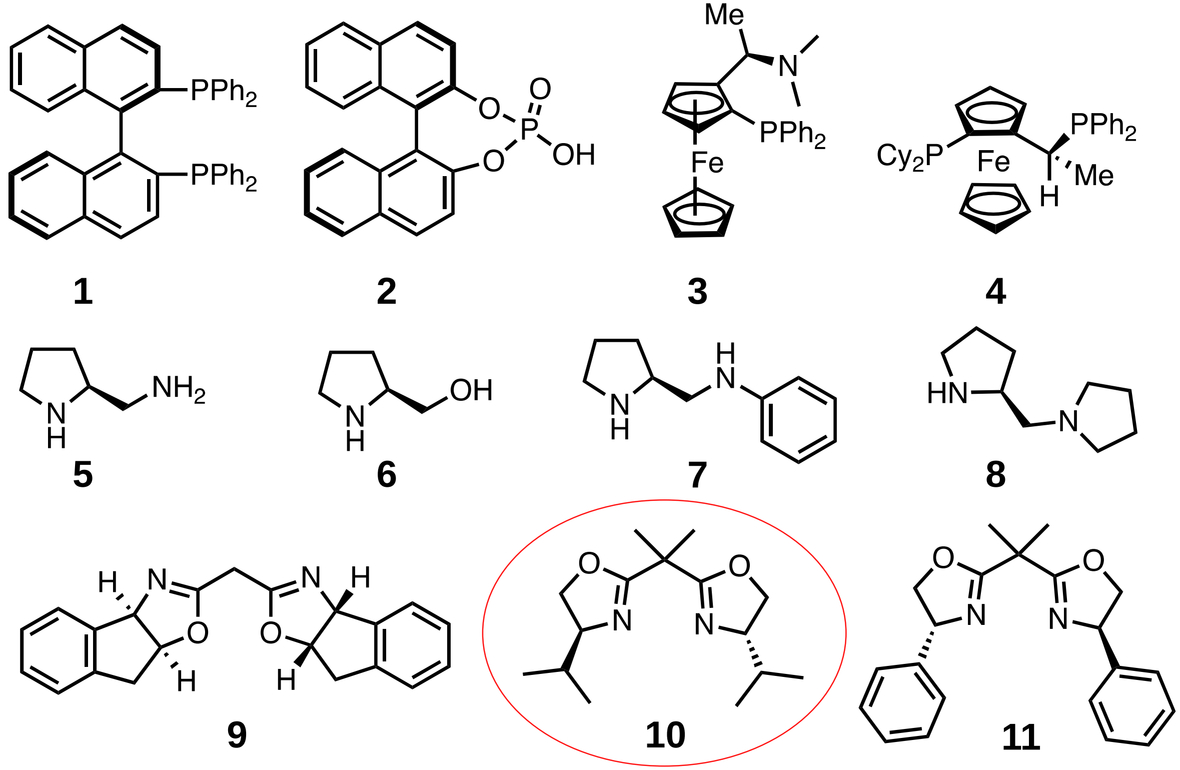
without MnO_2 5% | 12% | 11%[b]

[a]Using 10 equiv of MnO_2. [b]Determined by GC analysis. [c]Using 100 equiv of MnO_2.

Ligand screening (No. 1)

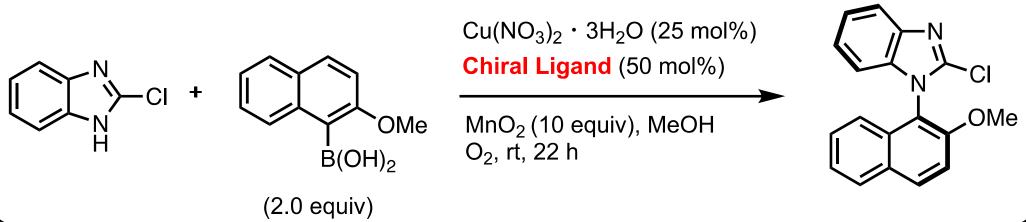


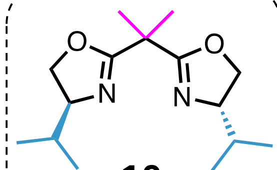
Ligand	GC yield (%)	ee (%)
1	40	1.8
2	21	1.9
3	26	1.8
4	36	1.8
5	1.1	−0.8
6	12	3.2
7	32	−0.3
8	17	29
9	4.2	24
10	81	57
11	90	−25



Screened commercially available 70 chiral ligands

Ligand screening (No. 2)

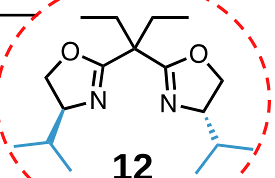




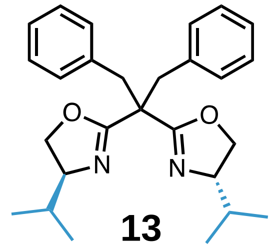
10

Ligand	GC yield (%)	ee (%)
10	81	57
12	93	67
13	48	35
14	37	58
15	86	56
16	87	51
17	94	66
18	>95	44
19	85	69
20	88	74
21	90 (40[a])	75 (76[a])

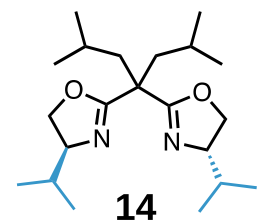
[a]Without MnO_2.



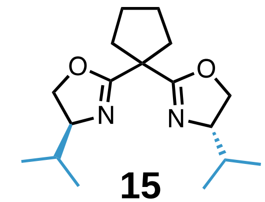
12



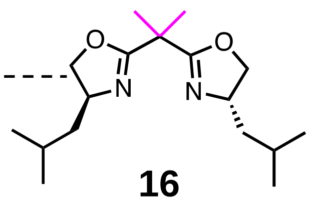
13



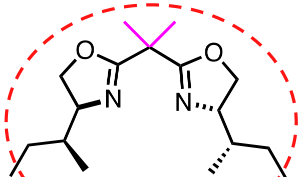
14



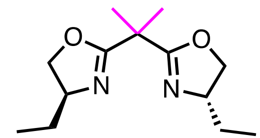
15



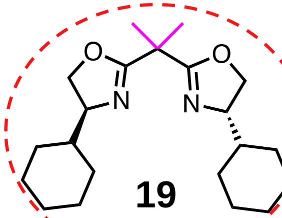
16



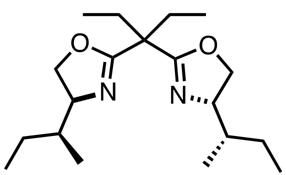
17



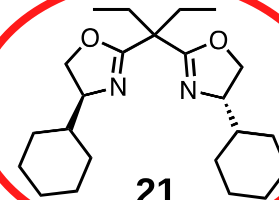
18



19



20

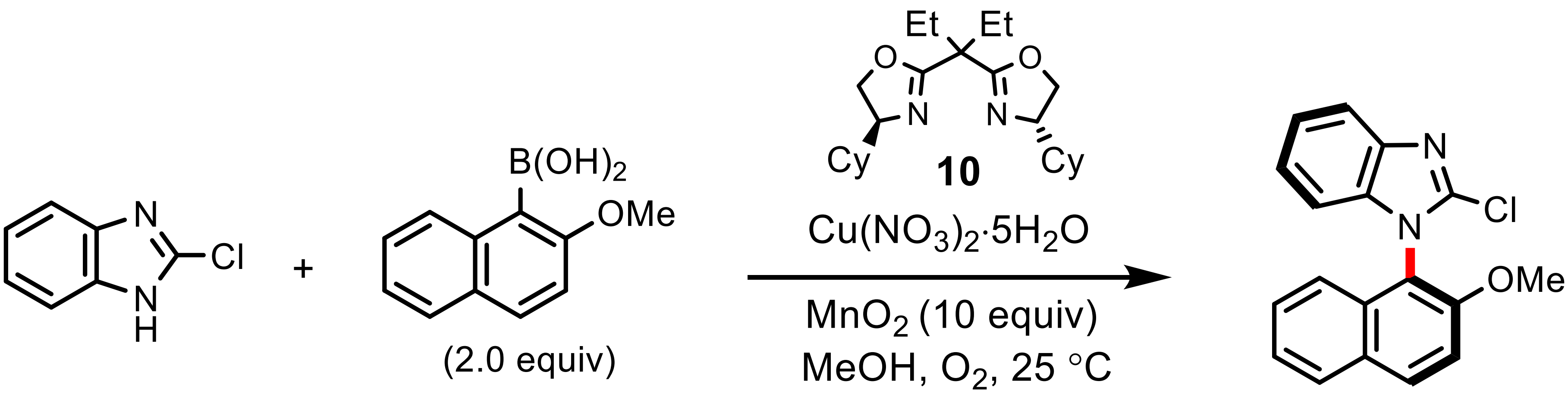


21

optimized ligand

Screened synthesized 22 chiral BOX ligands

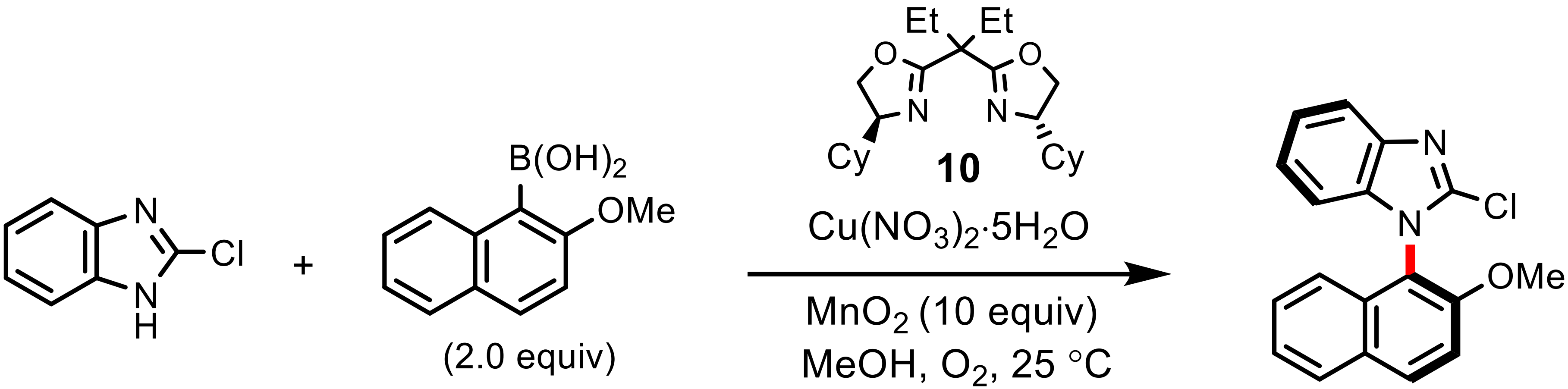
MnO_2 addition effect of Chan–Lam coupling



entry	Cu cat : ligand (mol%)	MnO_2	yield (%)[a)]	ee (%)
1	**25 : 75**	+	**quant**	**72**
2	25 : **75**	–	54	74
3	25 : **50**	+	94	72
4	25 : **50**	–	37	78
5	25 : **25**	+	90	66
6	25 : **25**	–	22	64
7	25 : **12.5**	+	95	48
8	25 : **12.5**	–	16	38
9	25 : **0**	+	33	0
10	25 : **0**	–	9	0

a) Determined by ^{1}H NMR.

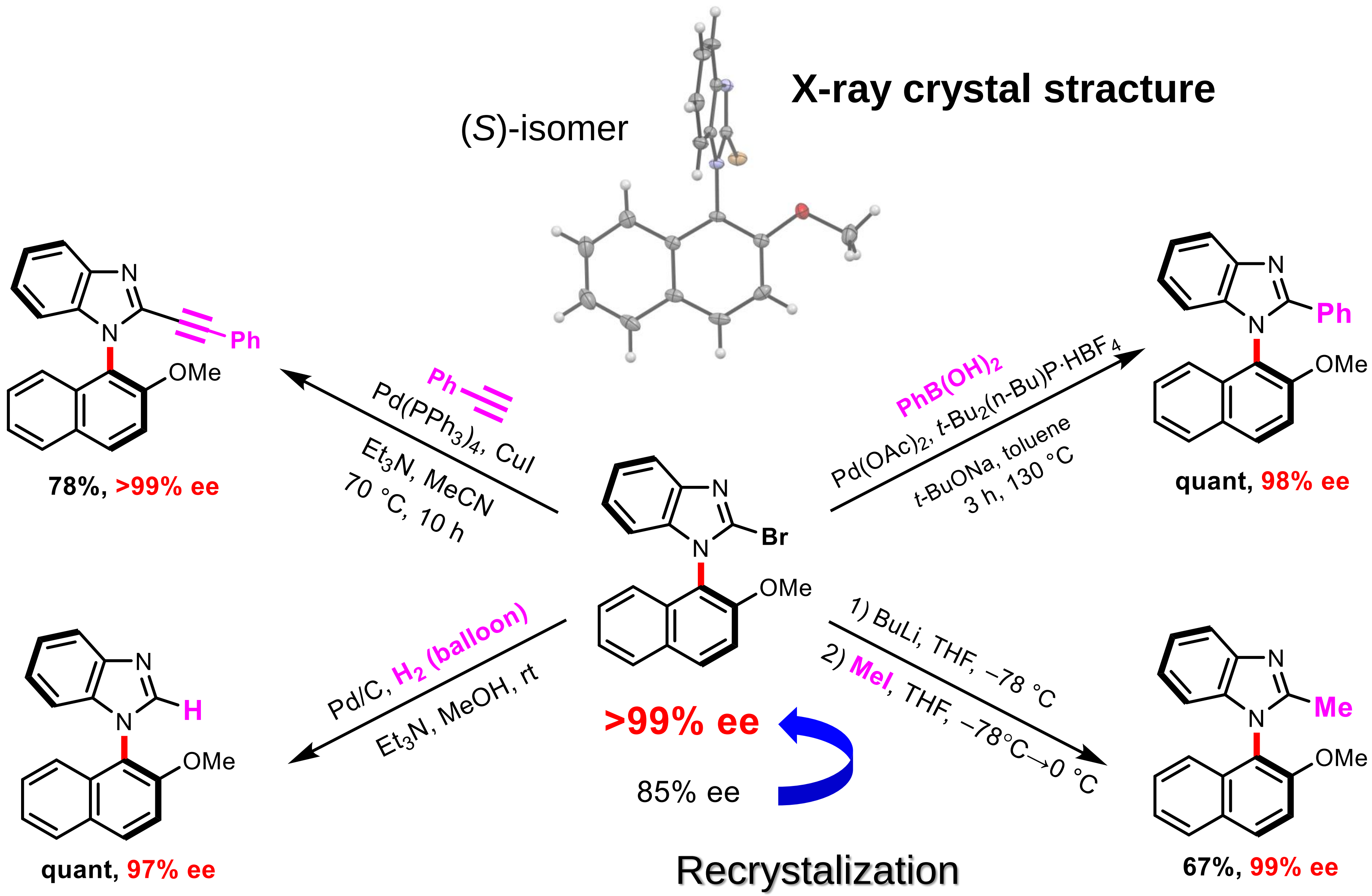
MnO_2 addition effect of Chan–Lam coupling



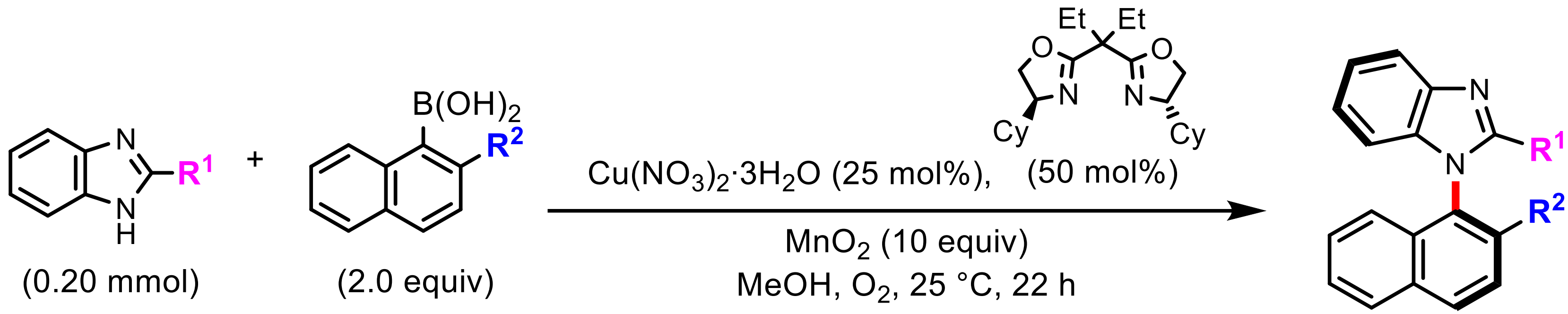
entry	Cu cat : ligand (mol%)	MnO_2	yield (%)[a]	ee (%)
1	25 : **75**	+	quant	72
2	25 : **75**	–	54	74
3	25 : **50**	+	94	72
4	25 : **50**	–	37	78
5	25 : **25**	+	90	66
6	25 : **25**	–	22	64
7	25 : **12.5**	+	95	48
8	25 : **12.5**	–	16	38
9	25 : **0**	+	33	0
10	25 : **0**	–	9	0

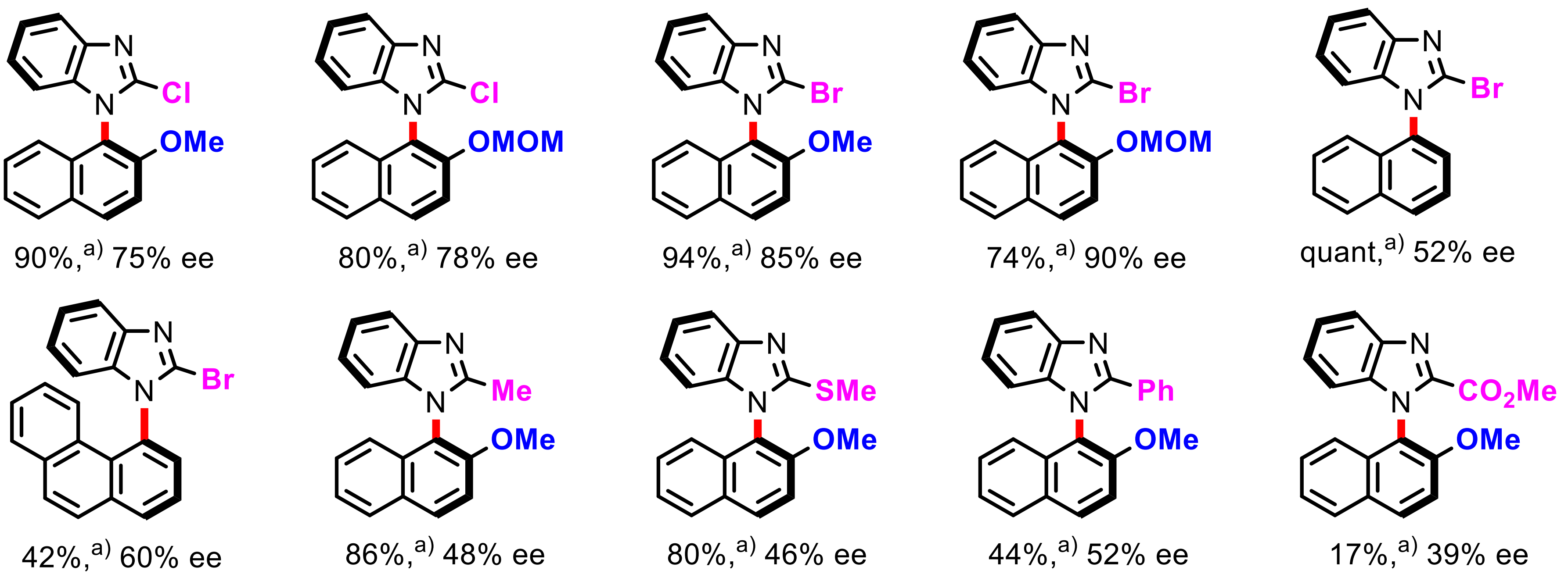
a) Determined by ^{1}H NMR.

Transformation of product bearing bromine



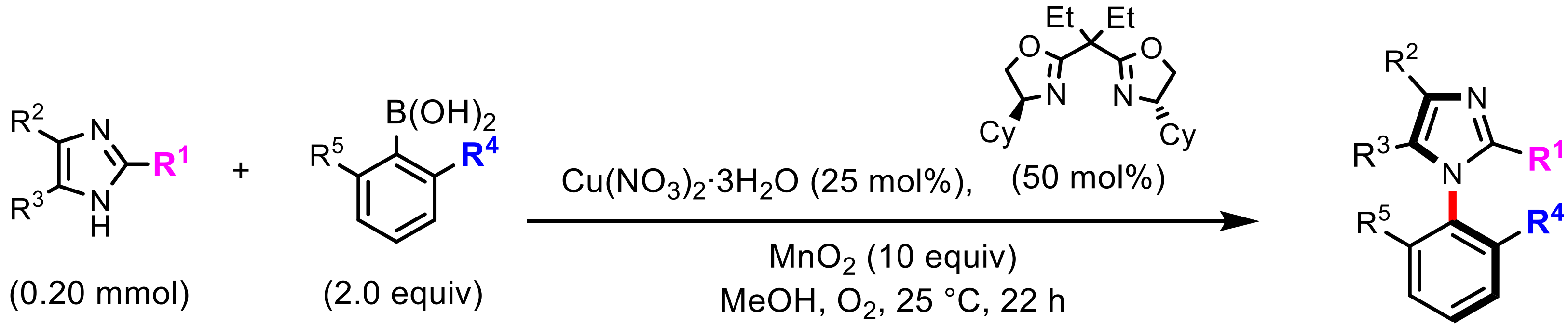
Substrate scope and limitation (No. 1)

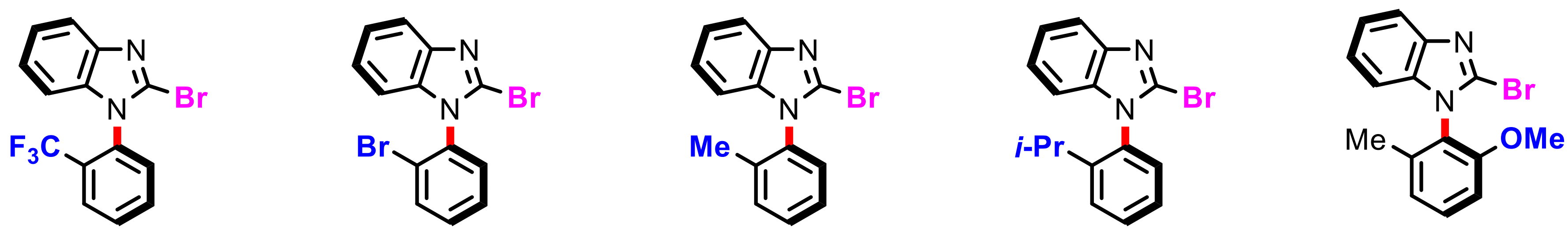




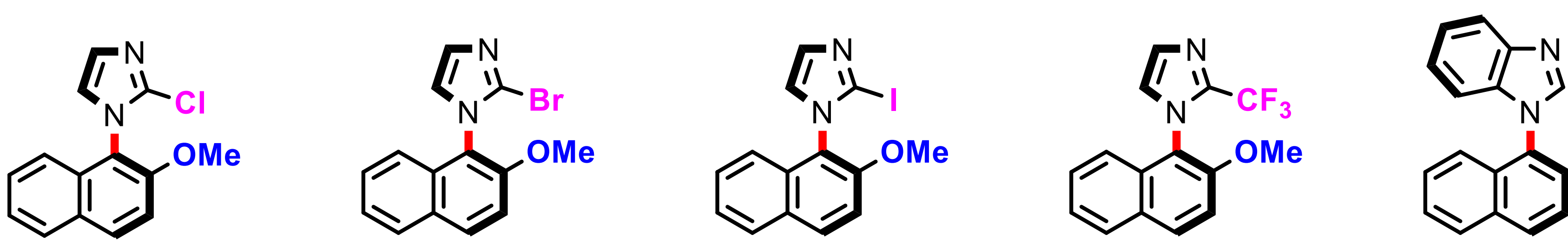
a) Determined by GC analysis.

Substrate scope and limitation (No. 2)





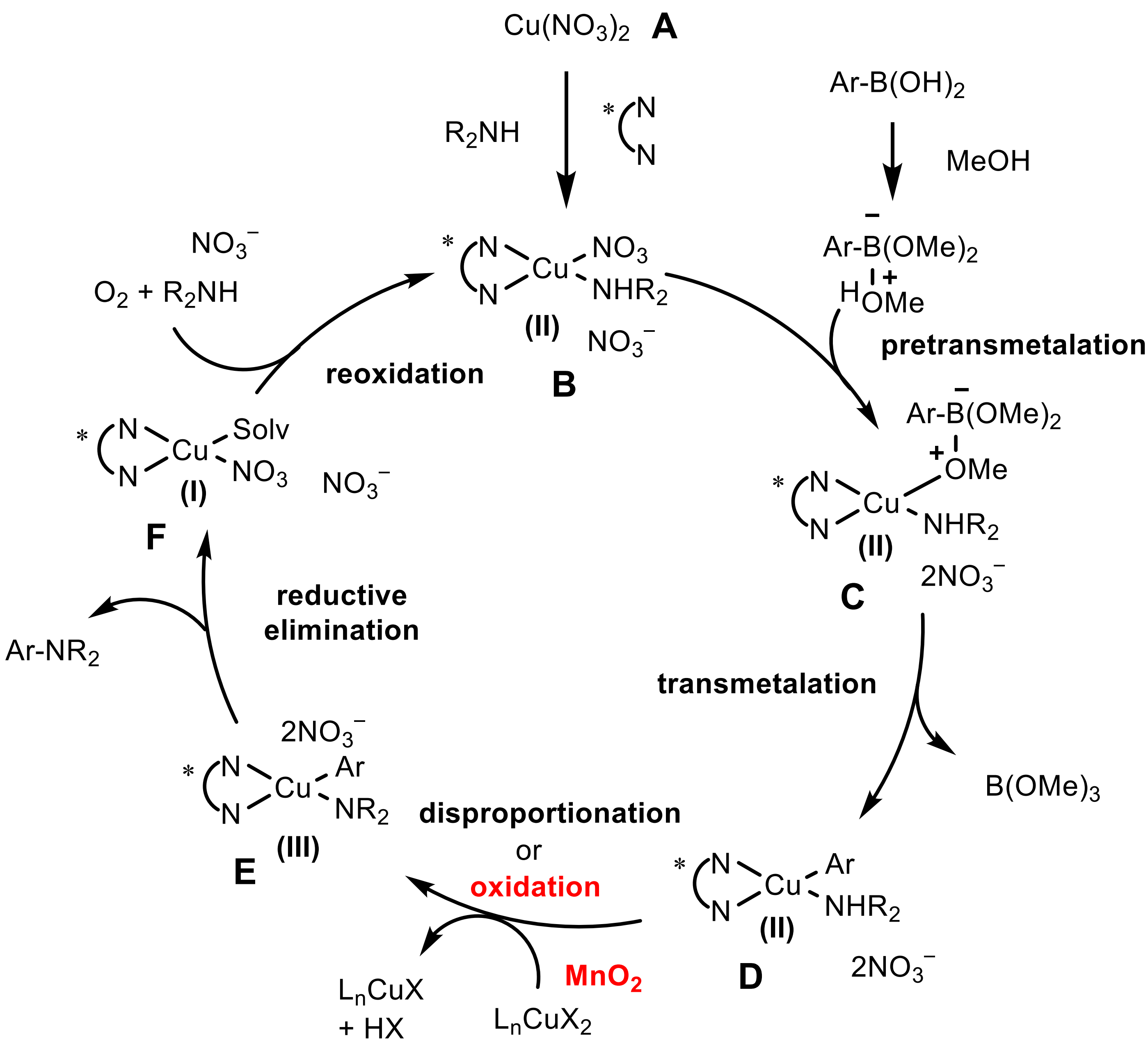
23%,[a] 86% ee | quant,[a] 80% ee | 96%,[a] 56% ee | 44%,[a),b)] 80% ee | quant,[a),b)] 71% ee



quant,[a] 62% ee | 97%,[a] 76% ee | 91%,[a),b)] 62% ee | quant,[a] 64% ee | quant, 4% ee

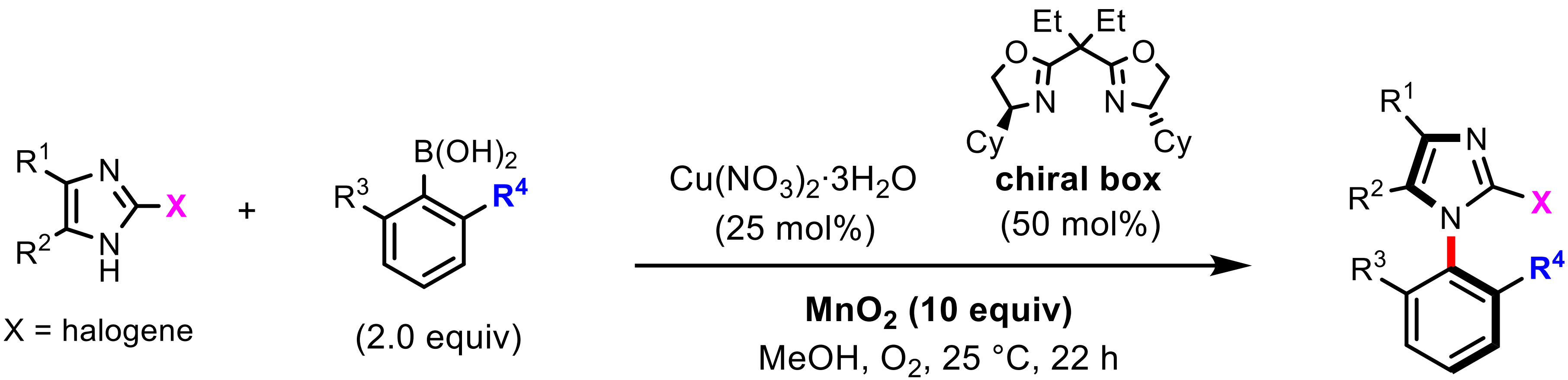
a) Determined by GC analysis. b) Using 100 equiv of MnO_2.

Reaction mechanism of Chan–Lam coupling



Conclusion for Chan–Lam

First atroposelective Chan–Lam coupling



up to >99% yield
up to 90% ee

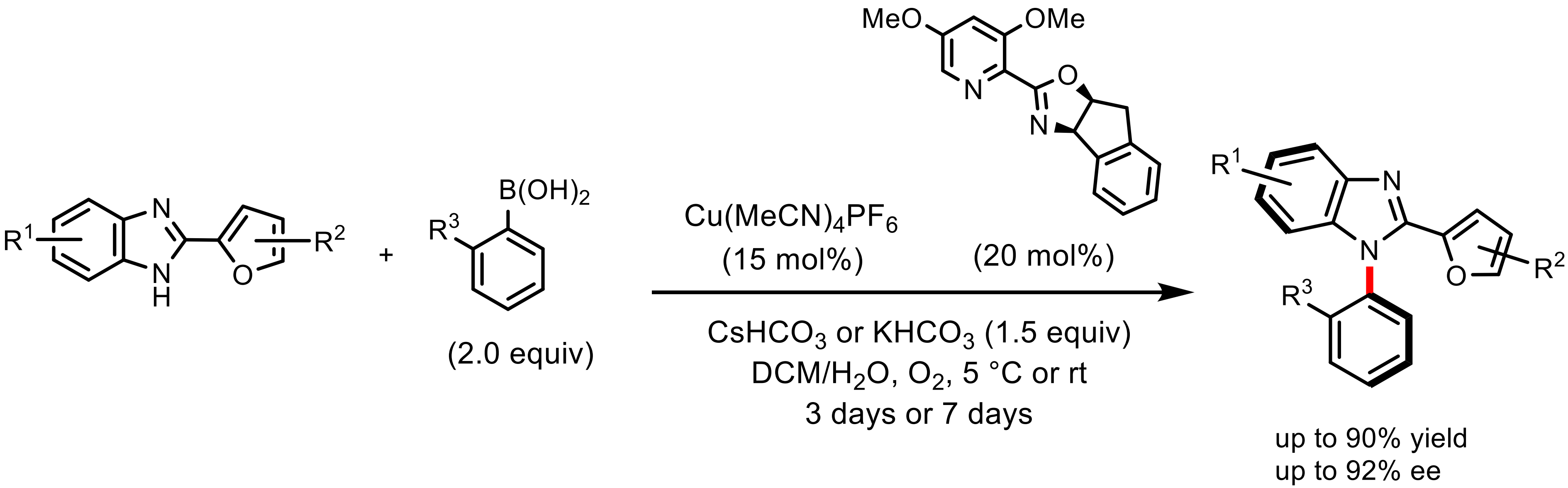
√ First peer-reviewed atropselective Chan–Lam

√ MnO_2 signifincantly accelarete couplings

√ Atroposelectivity controlled by bisoxazoline (BOX)

Chem. Commun. **2024**, *60*, 678–681.

Patureau's report

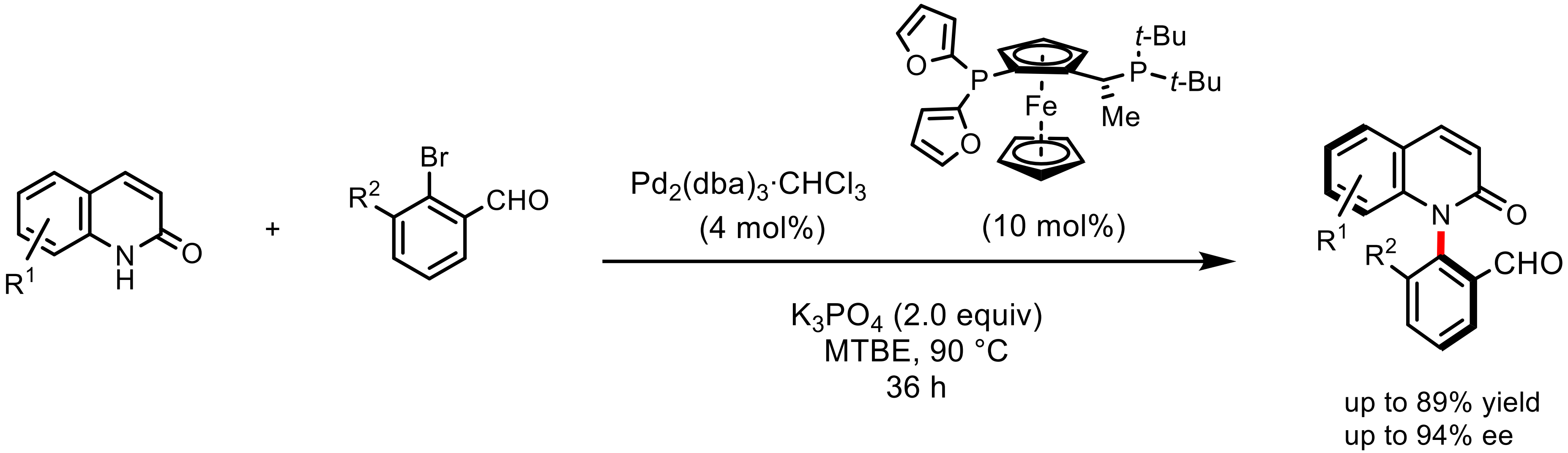


Patureau and his co-workers reported atroposelective Chan–Lam couplings right after accepting our paper.

F. W. Patureau et al. *Chem. Eur. J.* **2024**, *30*, e202304378.

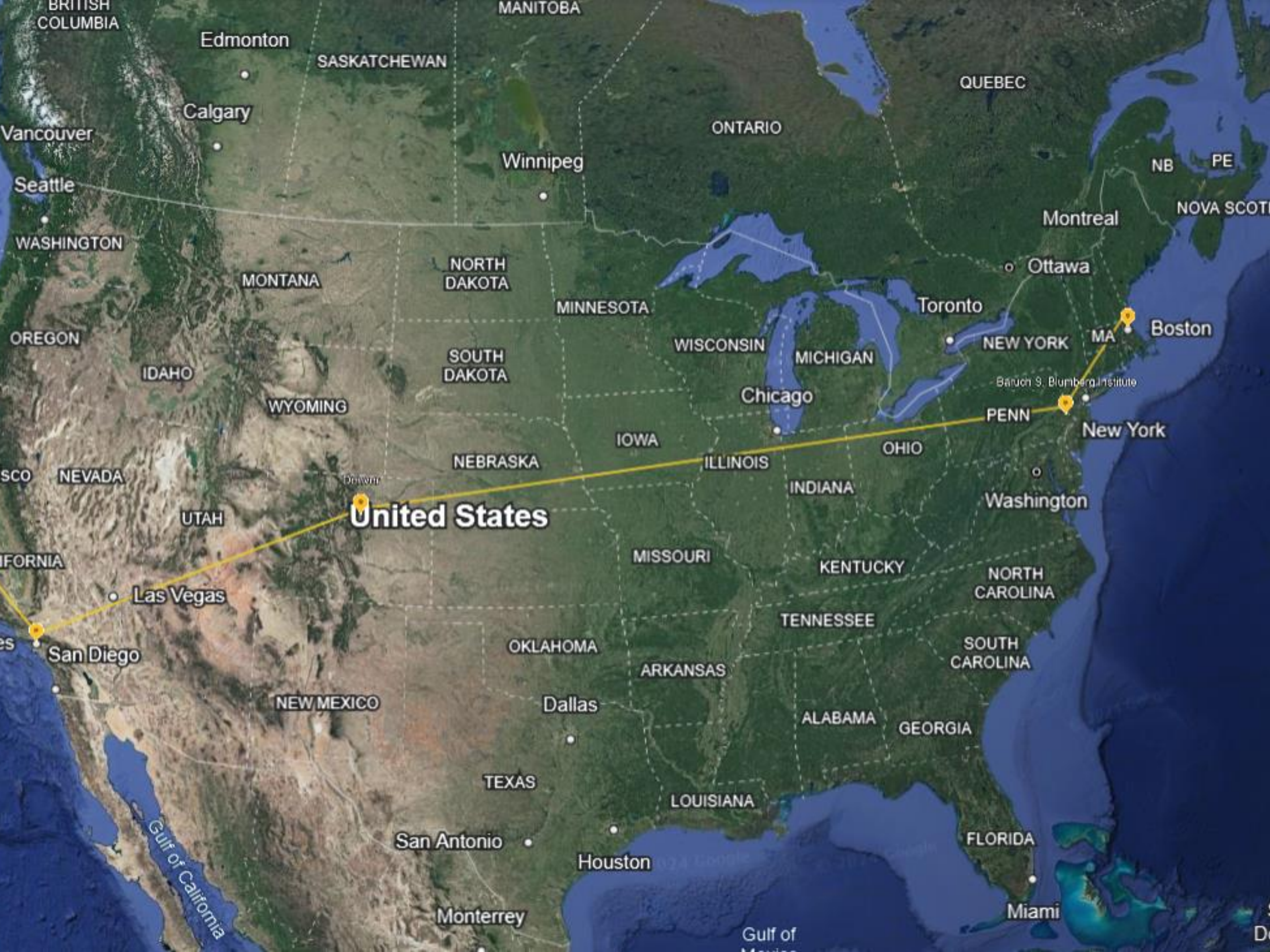
Later on…

Atroposelective Buchwald–Hartwig reaction



Then, Li and his co-workers reported atroposelective Buchwald–Hartwign reaction published in this year.

X. Li et al. *J. Am. Chem. Soc.* **2024**, *146*, 16567–16580.

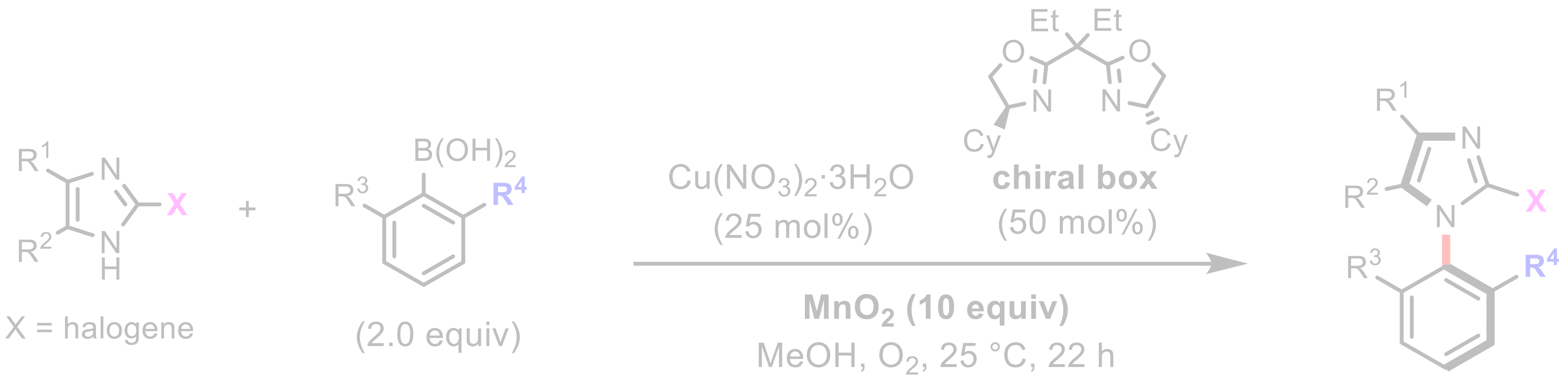


BRITISH COLUMBIA
MANITOBA
Edmonton
SASKATCHEWAN
QUEBEC
Calgary
ONTARIO
Vancouver
Winnipeg
NB
PE
Seattle
NOVA SCOTI
Montreal
WASHINGTON
Ottawa
NORTH DAKOTA
MONTANA
MINNESOTA
Toronto
Boston
OREGON
WISCONSIN
NEW YORK
MA
SOUTH DAKOTA
MICHIGAN
IDAHO
Baruch S. Blumberg Institute
Chicago
WYOMING
PENN
New York
IOWA
OHIO
NEBRASKA
ILLINOIS
NEVADA
INDIANA
Washington
United States
UTAH
MISSOURI
KENTUCKY
NORTH CAROLINA
Las Vegas
TENNESSEE
OKLAHOMA
SOUTH CAROLINA
San Diego
ARKANSAS
NEW MEXICO
Dallas
ALABAMA
GEORGIA
TEXAS
LOUISIANA
Gulf of California
FLORIDA
San Antonio
Houston
Miami
Monterrey
Gulf of

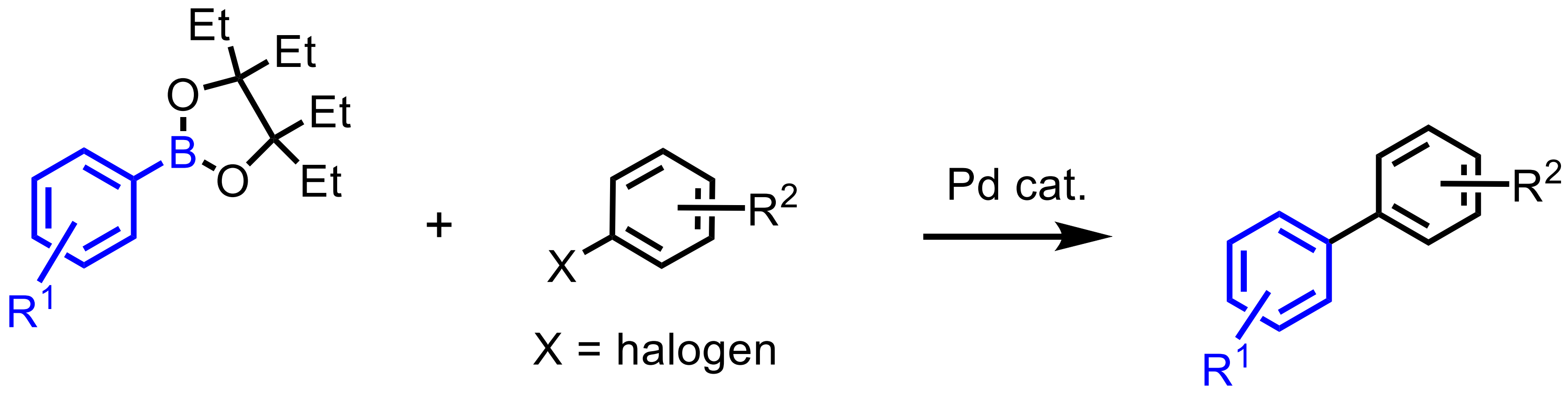
ACS Fall in Denver

Today's Topics

1. First atroposelective Chan–Lam coupling

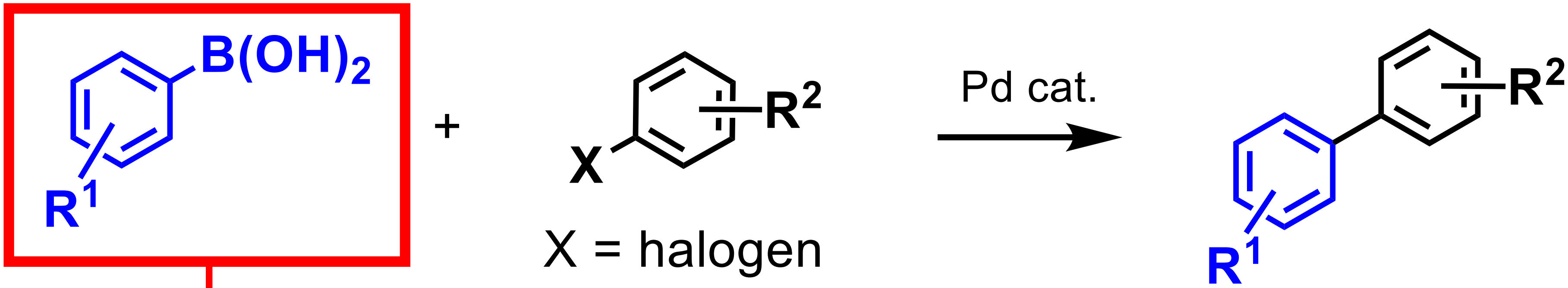


2. New arylboronic acid derivatives, ArB(Epin)



Boronic acid derivatives

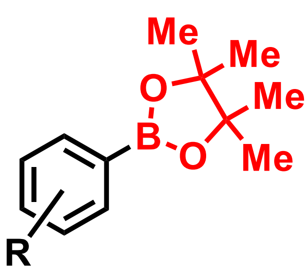
Suzuki-Miyaura coupling



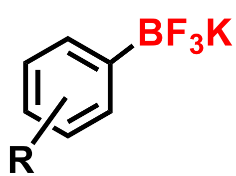
Drawback of aromatic bronic acid

1. Hard to purify and isolate
2. Hard to know exact amount because of dehydration
3. Hard to functionalize aromatic ring

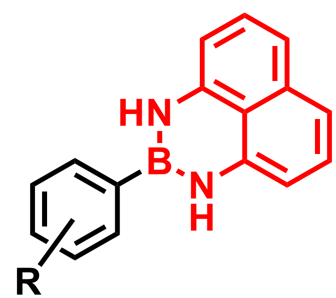
Typical aromatic boronic acid derivatives



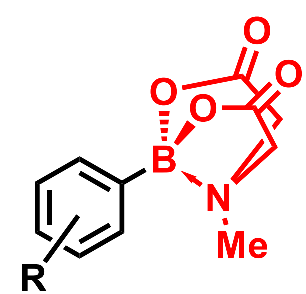
ArB(pin)



trifluoroborate

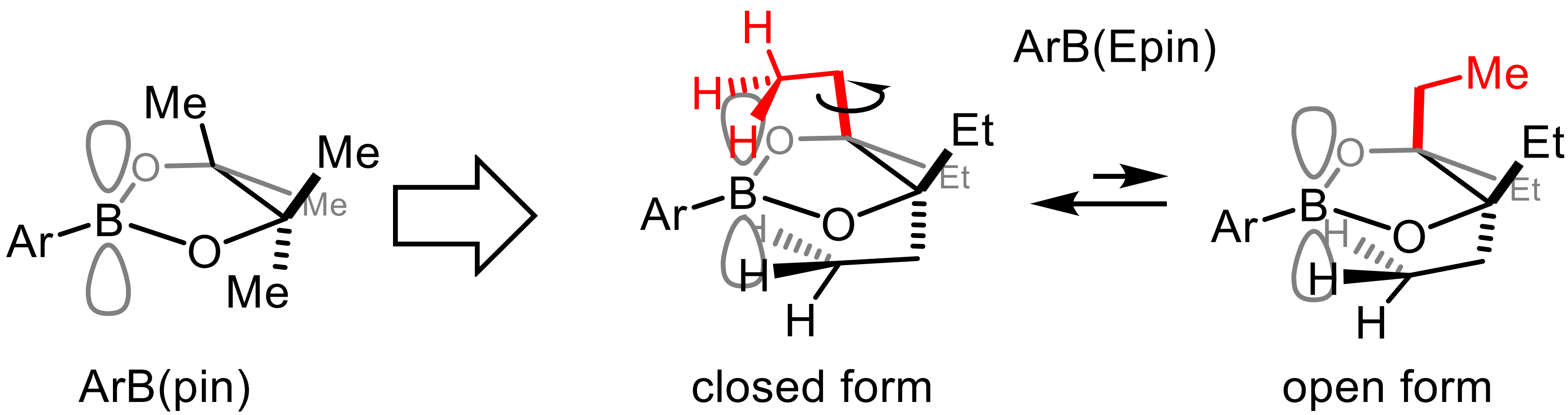


ArB(dan)

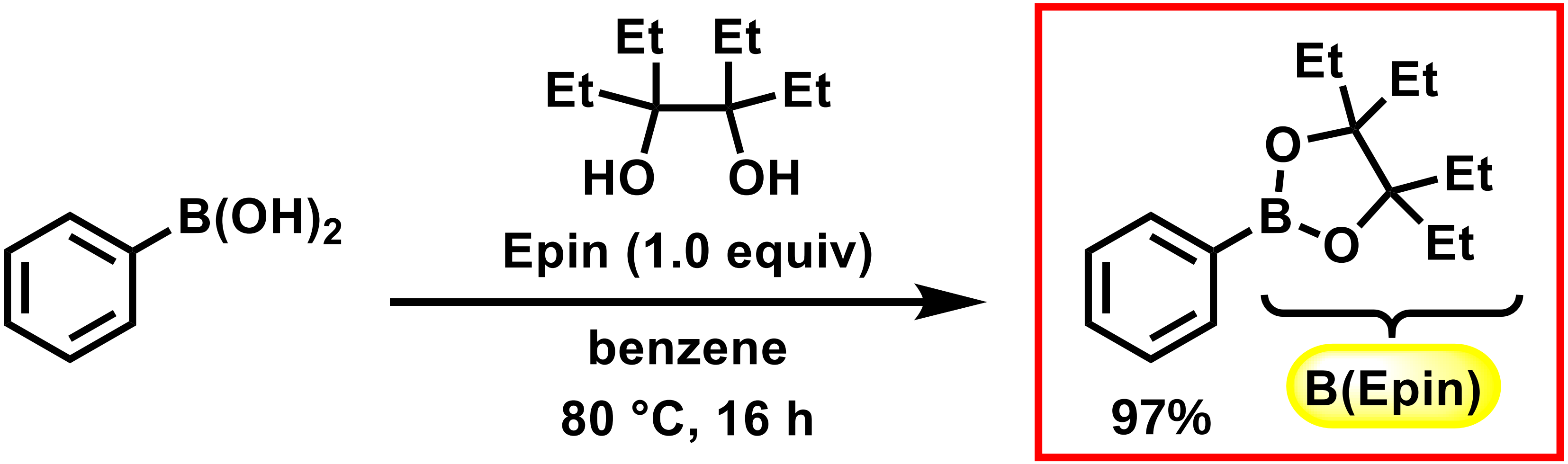


ArB(MIDA)

Concept of this work

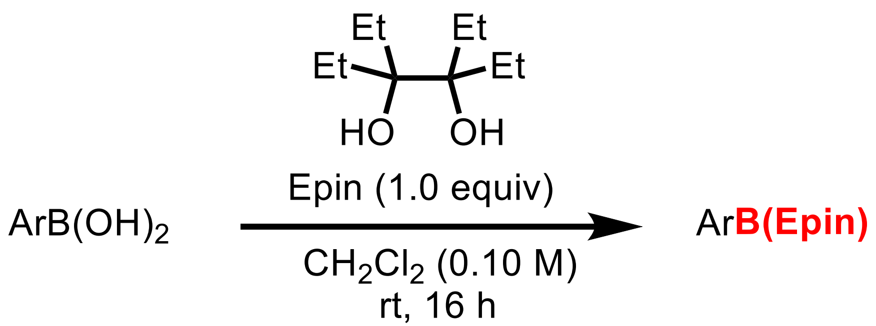


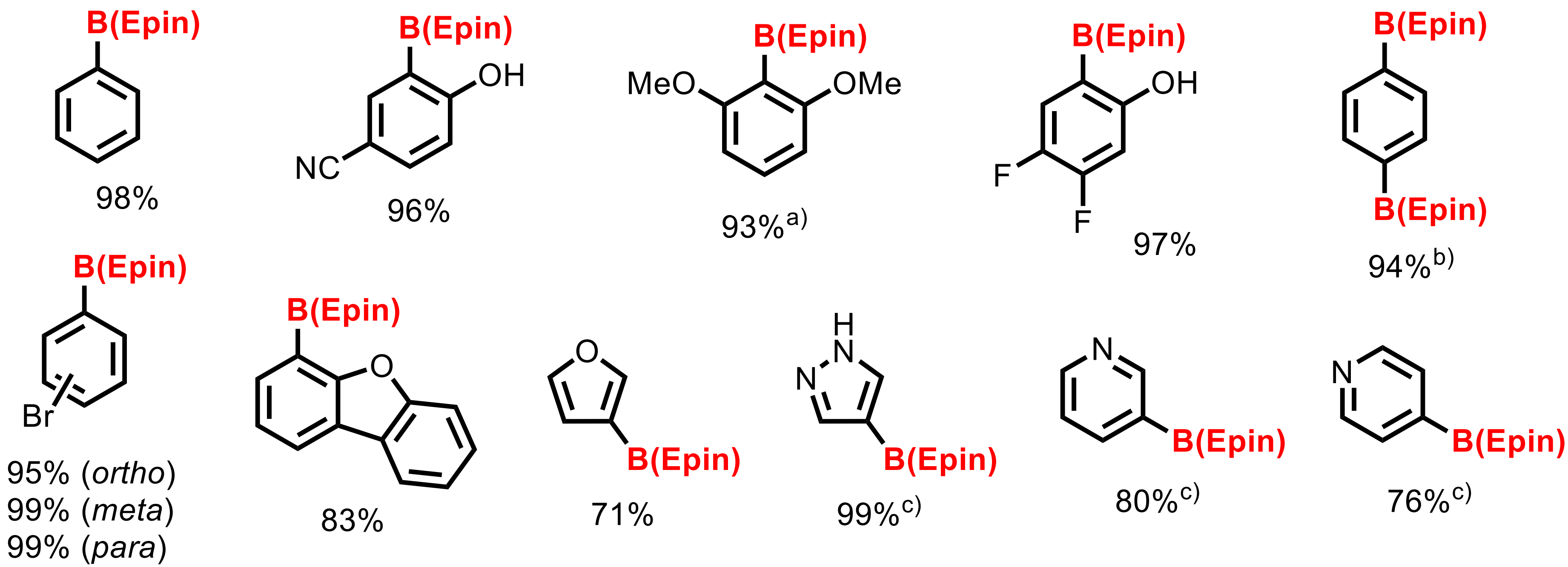
Dynamic protection of empty orbital



Not reported before

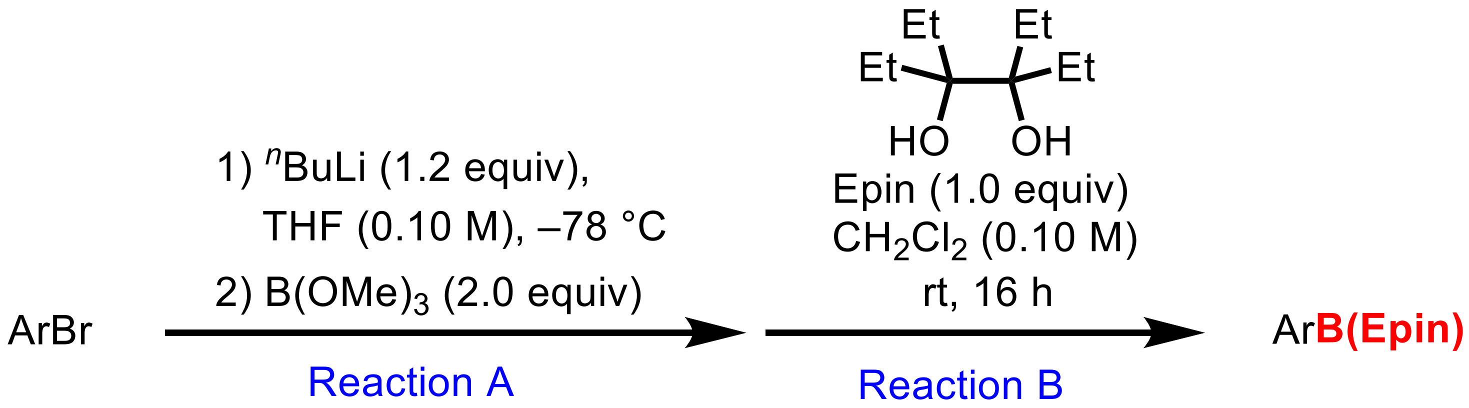
Synthesis of ArB(Epin): Dehydrative esterification

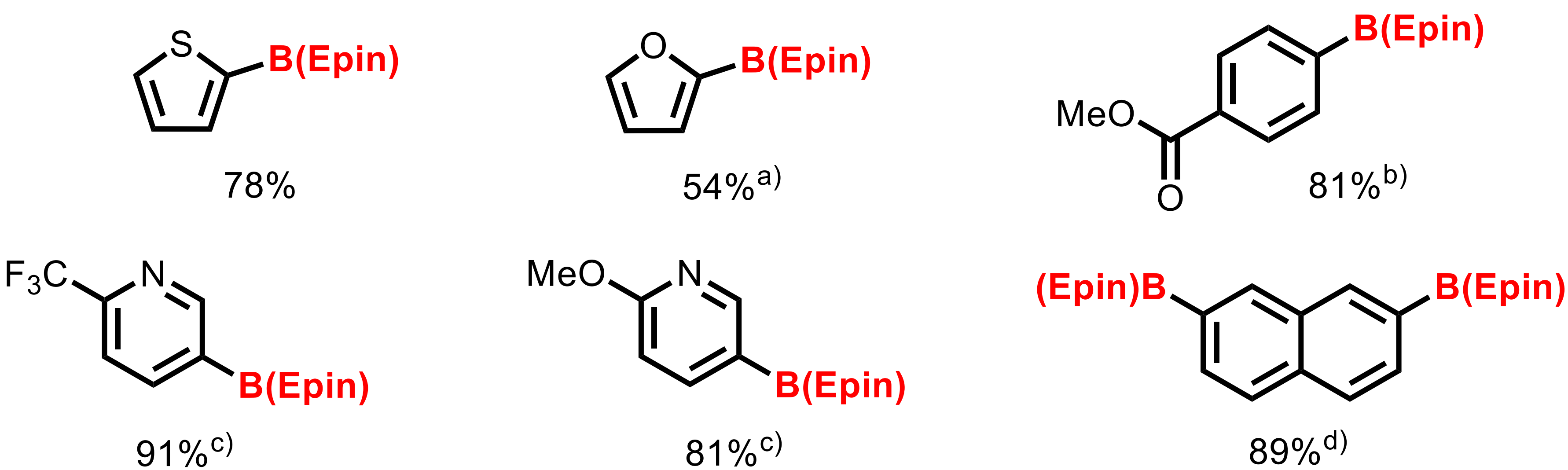




Conditions: $ArB(OH)_2$ (1.0 equiv), Epin (1.0 equiv) in CH_2Cl_2 (0.10 M) at rt for 16 h. a) In benzene (0.10 M) at 80 °C for 16 h. b) Using Epin (2.0 equiv) refluxed in benzene with Dean-Stark for 12 h. c) AcOH (0.10 equiv) was added as an additive and stirred in Et_2O at rt for 16 h.

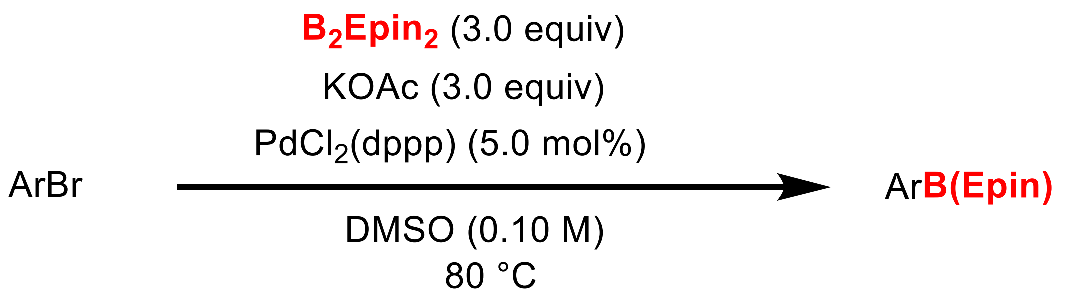
Synthesis of ArB(Epin): Metallation & esterification

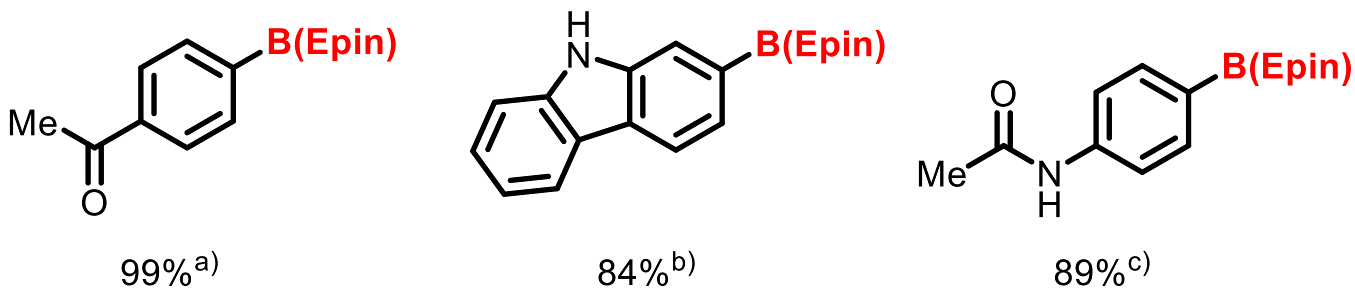


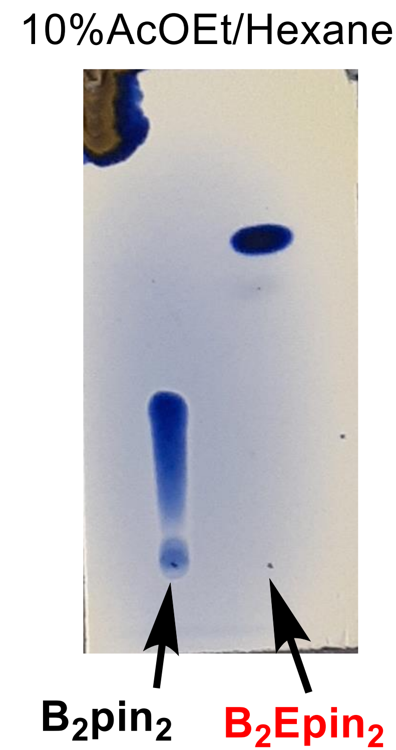


Conditions: ArBr (1.0 equiv), ^{n}BuLi (1.2 equiv), $B(OMe)_3$ (2.0 equiv) in THF (0.10 M) for Reaction A. Epin (1.0 equiv) in CH_2Cl_2 for Reaction B. a) At 40 °C for Reaction B. b) ^{i}PrMgCl･LiCl (1.2 equiv), $B(OMe)_3$ (2.0 equiv) for Reaction A. c) ^{n}BuLi (1.1 equiv), Et_2O (0.10 M) for Reaction A. Epin (1.0 equiv), AcOH (0.10 equiv) for Reaction B. d) ^{t}BuLi (4.2 equiv), $B(OMe)_3$ (2.4 equiv) for Reaction A. Epin (2.0 equiv) in benzene (0.10 M) at 80 °C for 16 h for Reaction B.

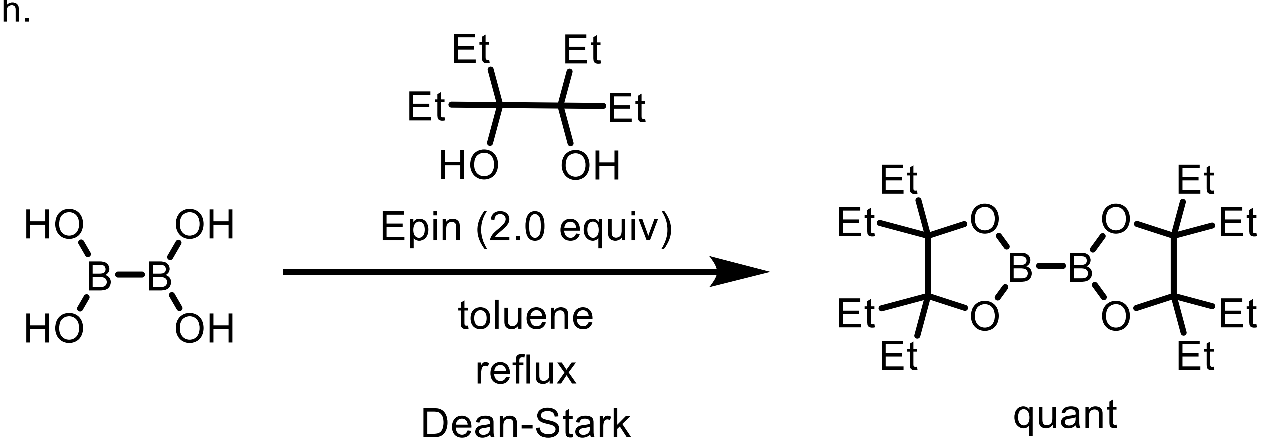
Synthesis of ArB(Epin): Miyaura borylation





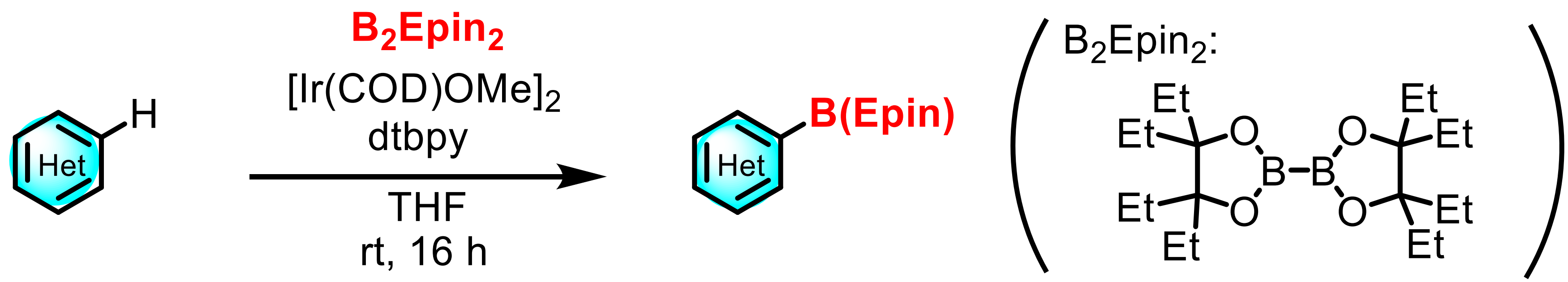


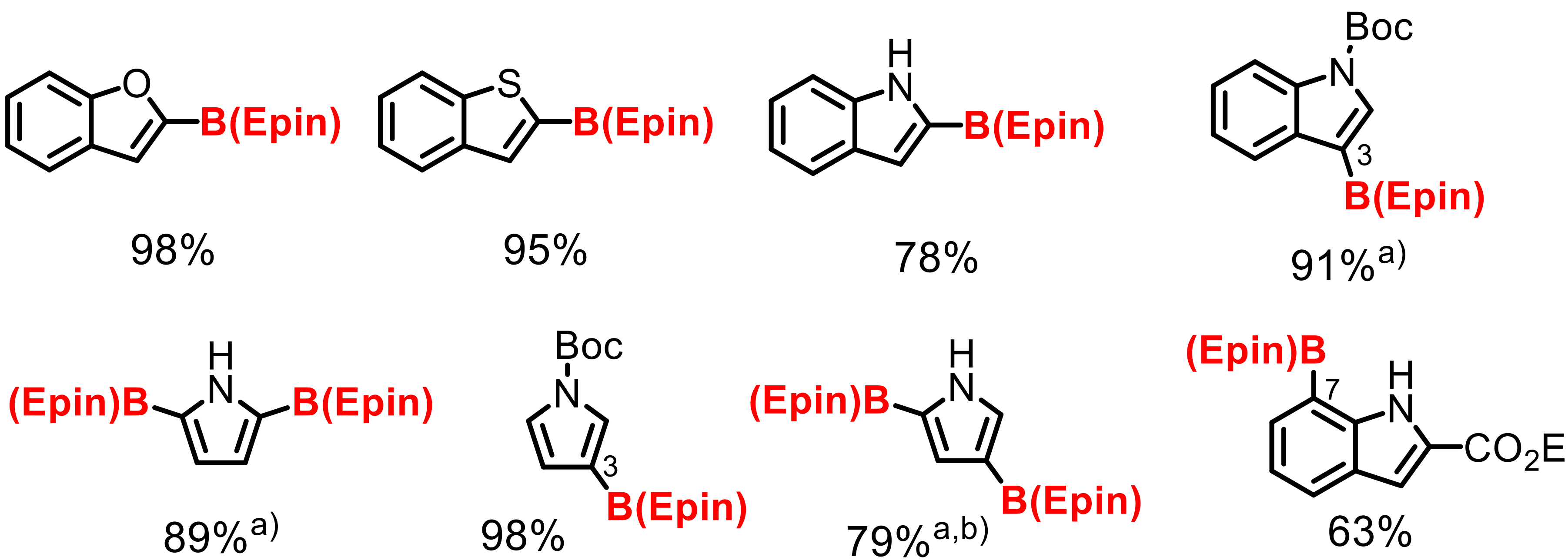
Conditions: ArBr (1.0 equiv), $PdCl_2$(dppp) (5.0 mol%), B_2Epin_2 (3.0 equiv), KOAc (3.0 equiv) in DMSO (0.10 M) at 80 °C. a) B_2Epin_2 (1.5 equiv) for 2 h. b) For 24 h. c) For 2 h.



B_2Epin_2

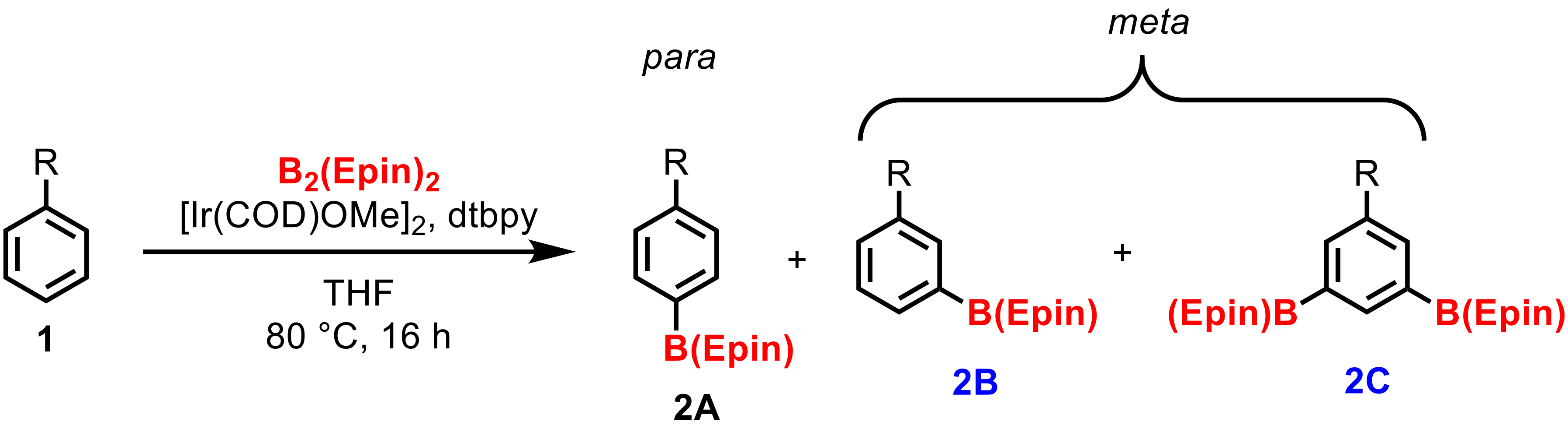
Synthesis of ArB(Epin): C–H borylation (No. 1)





Conditions: Ar–H (0.20 mmol), B_2Epin_2 (1.0 equiv), $[Ir(COD)OMe]_2$ (3.0 mol%), dtbpy (6.0 mol%) in THF (0.10 M) at rt for 16 h. a) At 50 °C. b) Used *N*-Boc pyrrole as a substrate.

Synthesis of ArB(Epin): C–H borylation (No. 2)



Substrate **1**

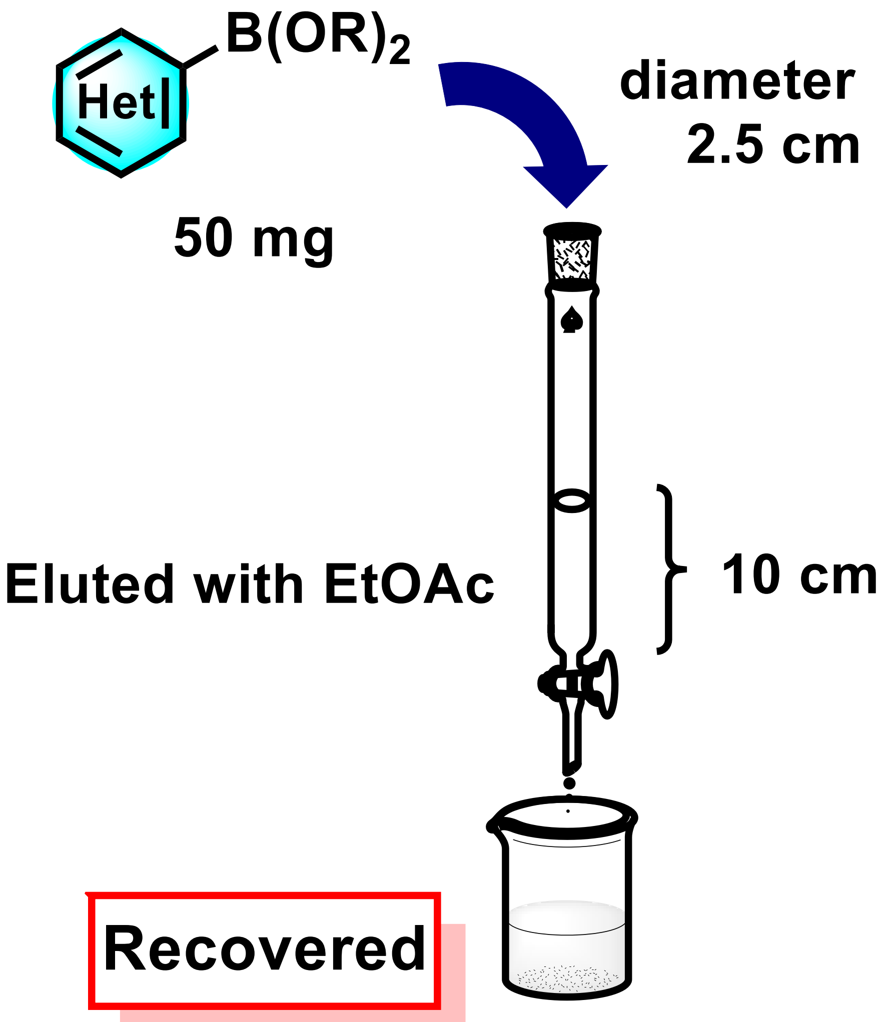
1a **1b** **1c**[b), c)] **1d**[b)]

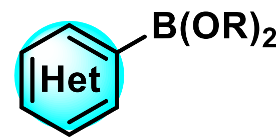
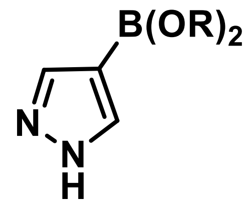
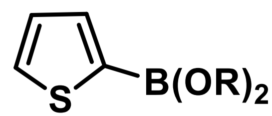
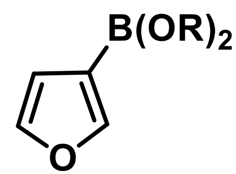
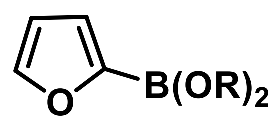
Product **2**

2Aa : **2Ba+2Ca**	**2Ab** : **2Bb+2Cb**	**2Ac** : **2Bc+2Cc**	**2Ad** : **2Bd+2Cd**
(1 : 6.1)	(1 : 6.3)	(1 : 11.1)	(4.4 : 1)
85%	quant	quant	85%

a) Conditions: **3** (0.20 mmol), $B_2(Epin)_2$ (1 eq), $[Ir(COD)OMe]_2$ (3 mol%), dtbpy (6 mol%), THF (0.1 M) at room tempreture for 16 h. b) Hexane as solvent. c) At 50 °C.

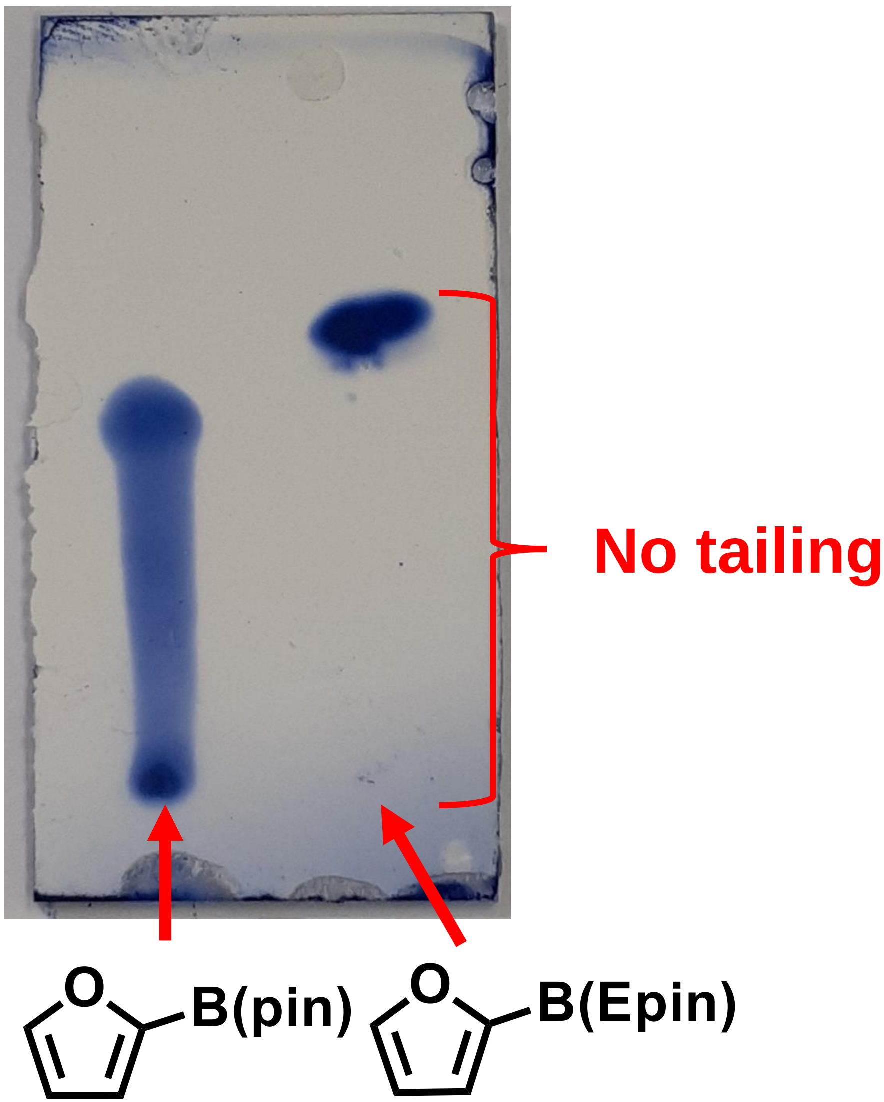
Purfication of ArB(pin) and ArB(Epin)

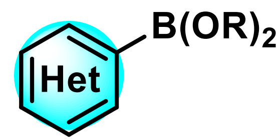
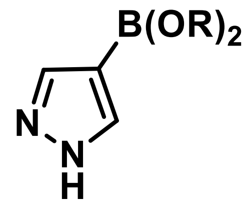
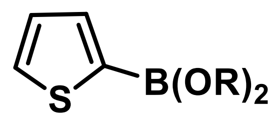
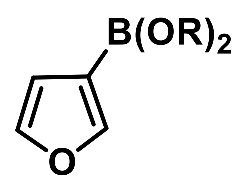
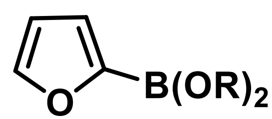


	Recovery (%) B(Epin)	Recovery (%) B(pin)
	98%	81%
	99%	59%
	quant	66%
	99%	22%

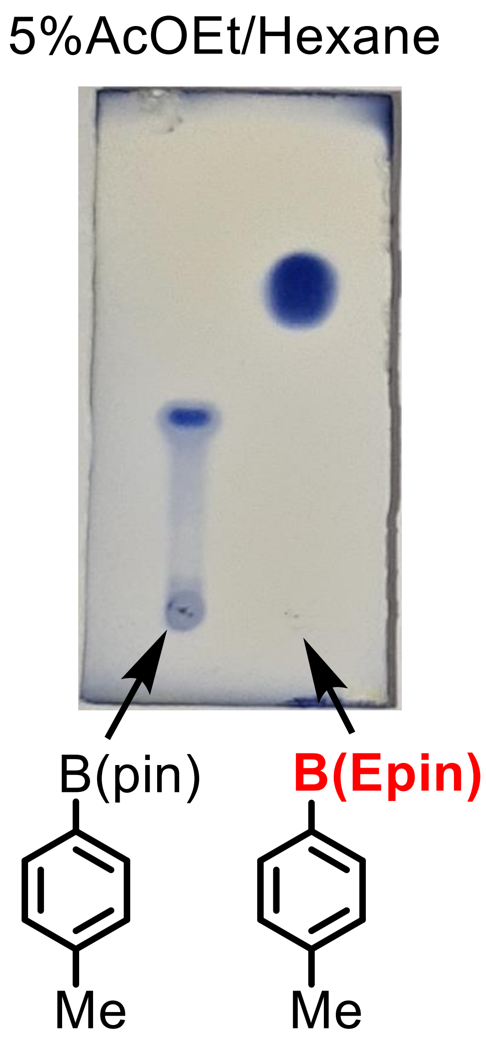
Purfication of ArB(pin) and ArB(Epin)

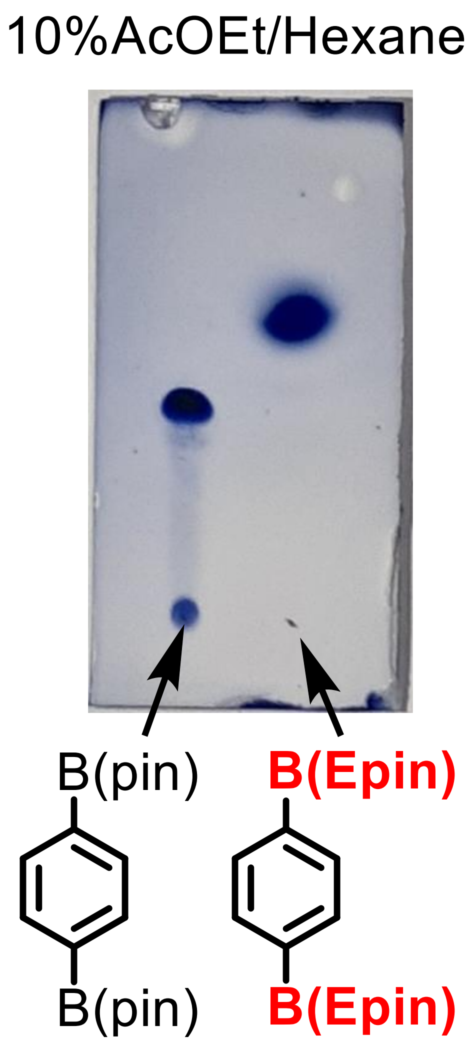
10%AcOEt/Hexane

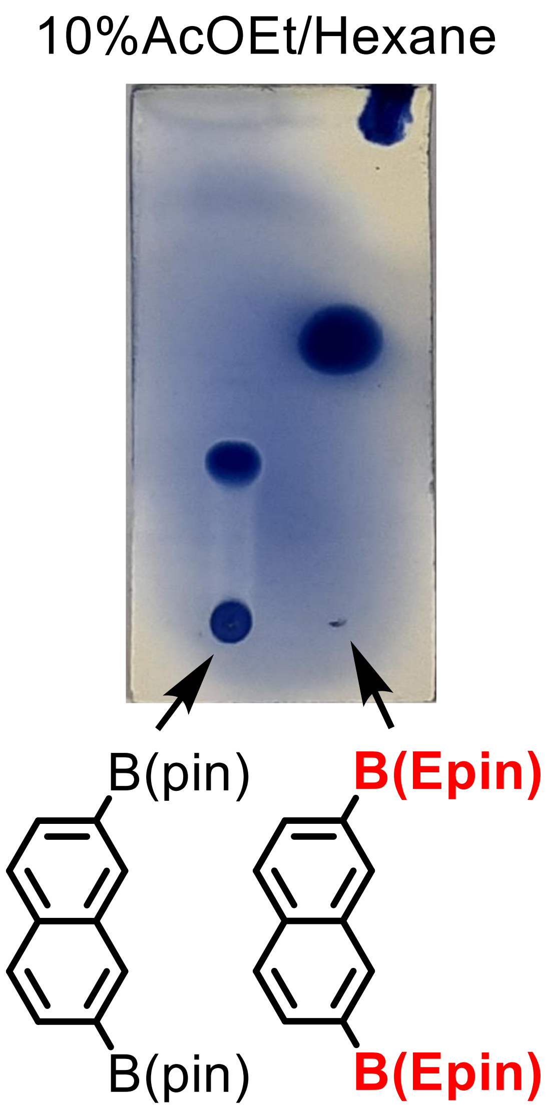


	Recovery (%) B(Epin)	B(pin)
	98%	81%
	99%	59%
	quant	66%
	99%	22%

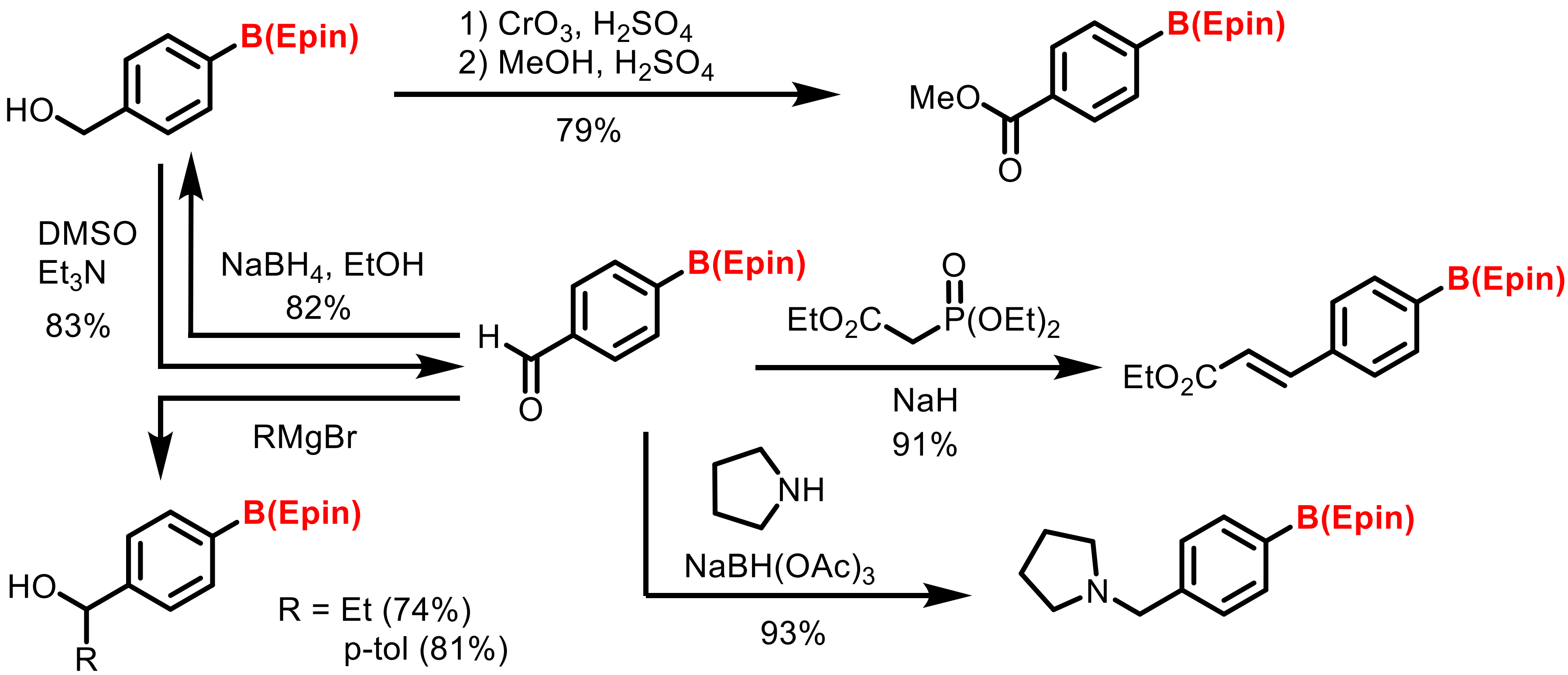
Thin Layer Chromatography (TLC) behavior of ArB(pin) and ArB(Epin)

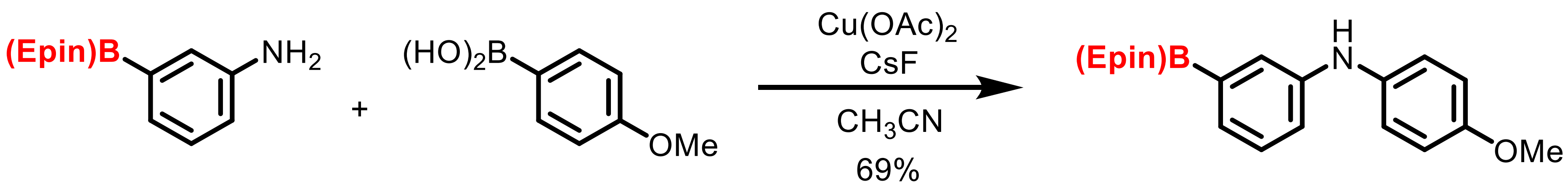




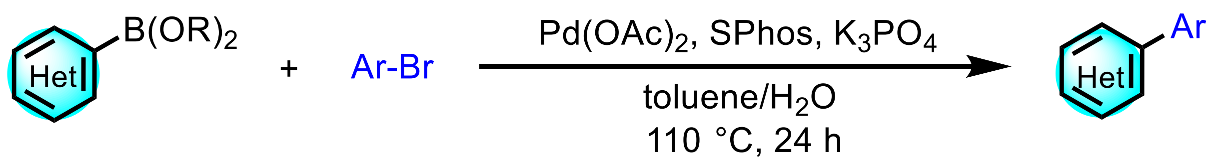


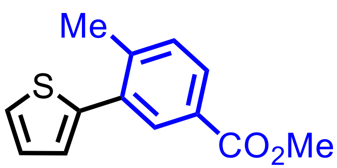
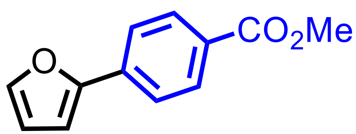
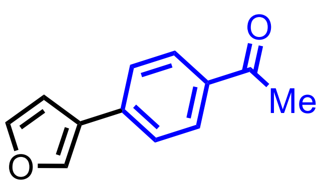
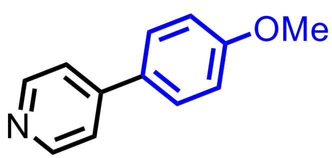
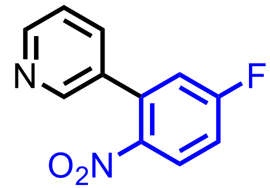
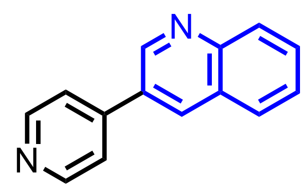
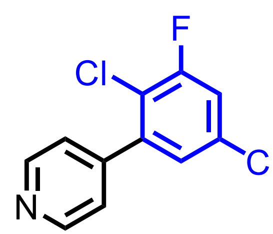
Transformation with ArB(Epin) intact





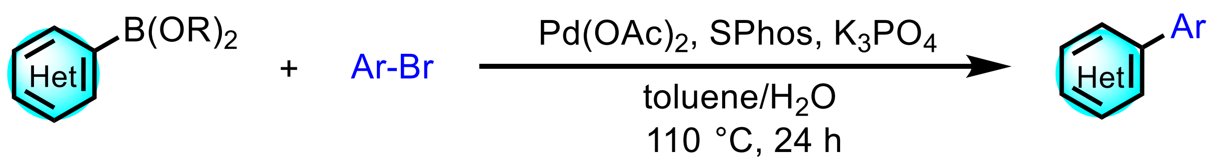
Suzuki coupling of ArB(Epin)

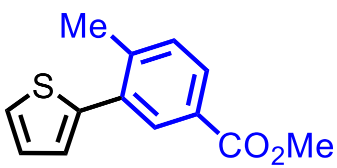
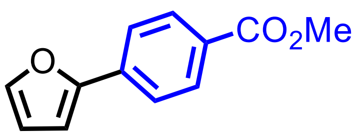
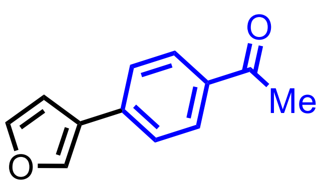
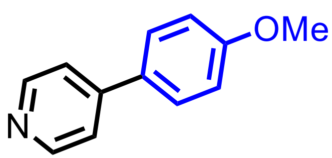
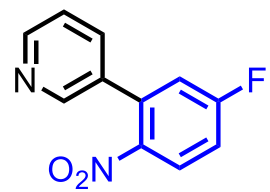
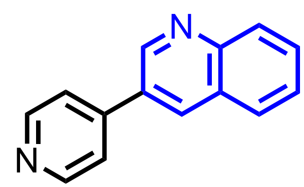
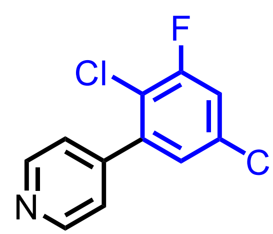


entry	Product	yield (%) B(OH)$_2$	yield (%) B(pin)	yield (%) **B(Epin)**
1		73	95	92
2		5	81	94
3		42	93	95
4		50	69	99
5		0	53	96
6		15	58	99
7		0	0	55

Conditions: ArB(Epin) (1.5 equiv), Pd(OAc)$_2$ (1.0 mol%), SPhos (2.0 mol%), K_3PO_4 (2.0 equiv) in toluene/H_2O (10/1) for 24 h at 110 °C.

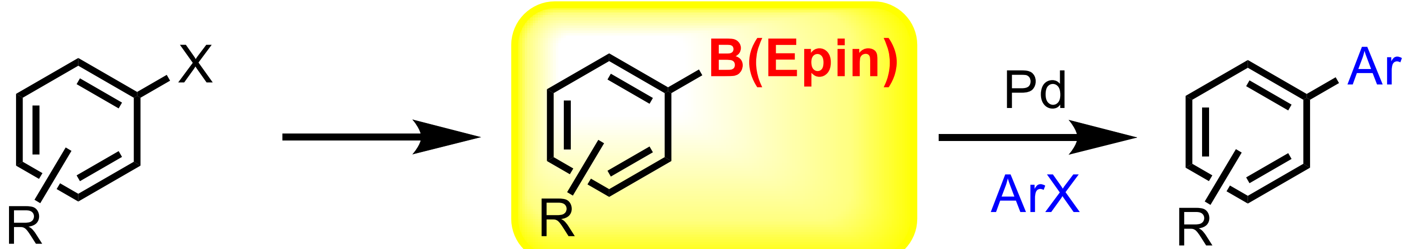
Suzuki coupling of ArB(Epin)



entry	Product	yield (%)		
		$B(OH)_2$	B(pin)	**B(Epin)**
1		73	95	**92**
2		5	81	**94**
3		42	93	**95**
4		50	69	**99**
5		0	53	**96**
6		15	58	**99**
7		0	0	**55**

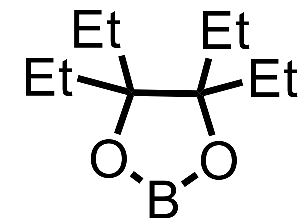
Conditions: ArB(Epin) (1.5 equiv), $Pd(OAc)_2$ (1.0 mol%), SPhos (2.0 mol%), K_3PO_4 (2.0 equiv) in toluene/H_2O (10/1) for 24 h at 110 °C.

Conclusion for boronic acids part

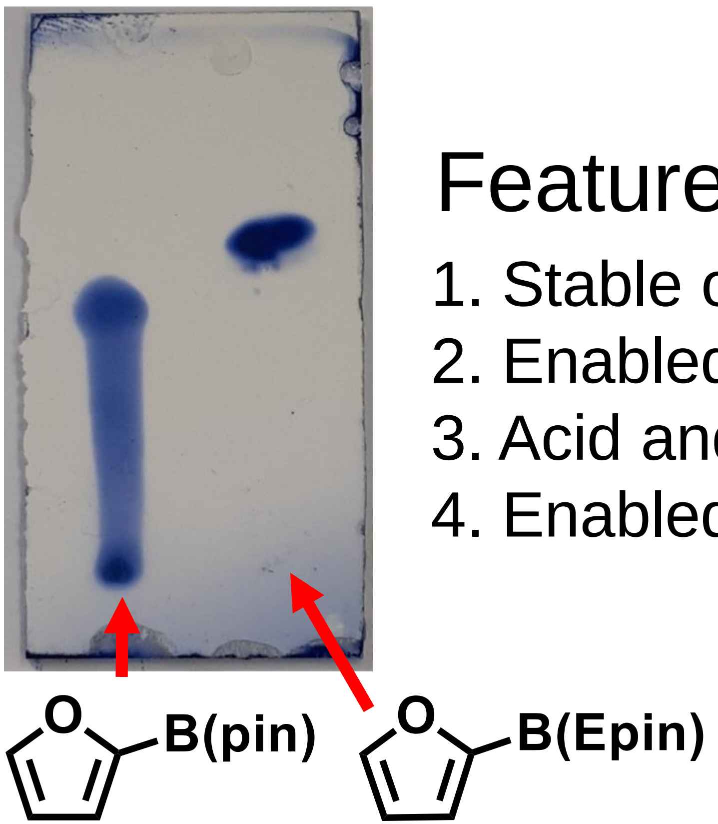


$X = B(OH)_2$
= halogen

WO202218098

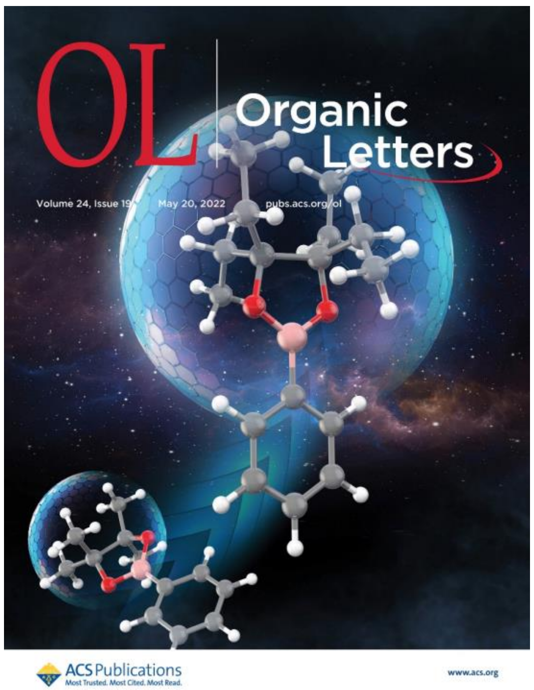


B(Epin)



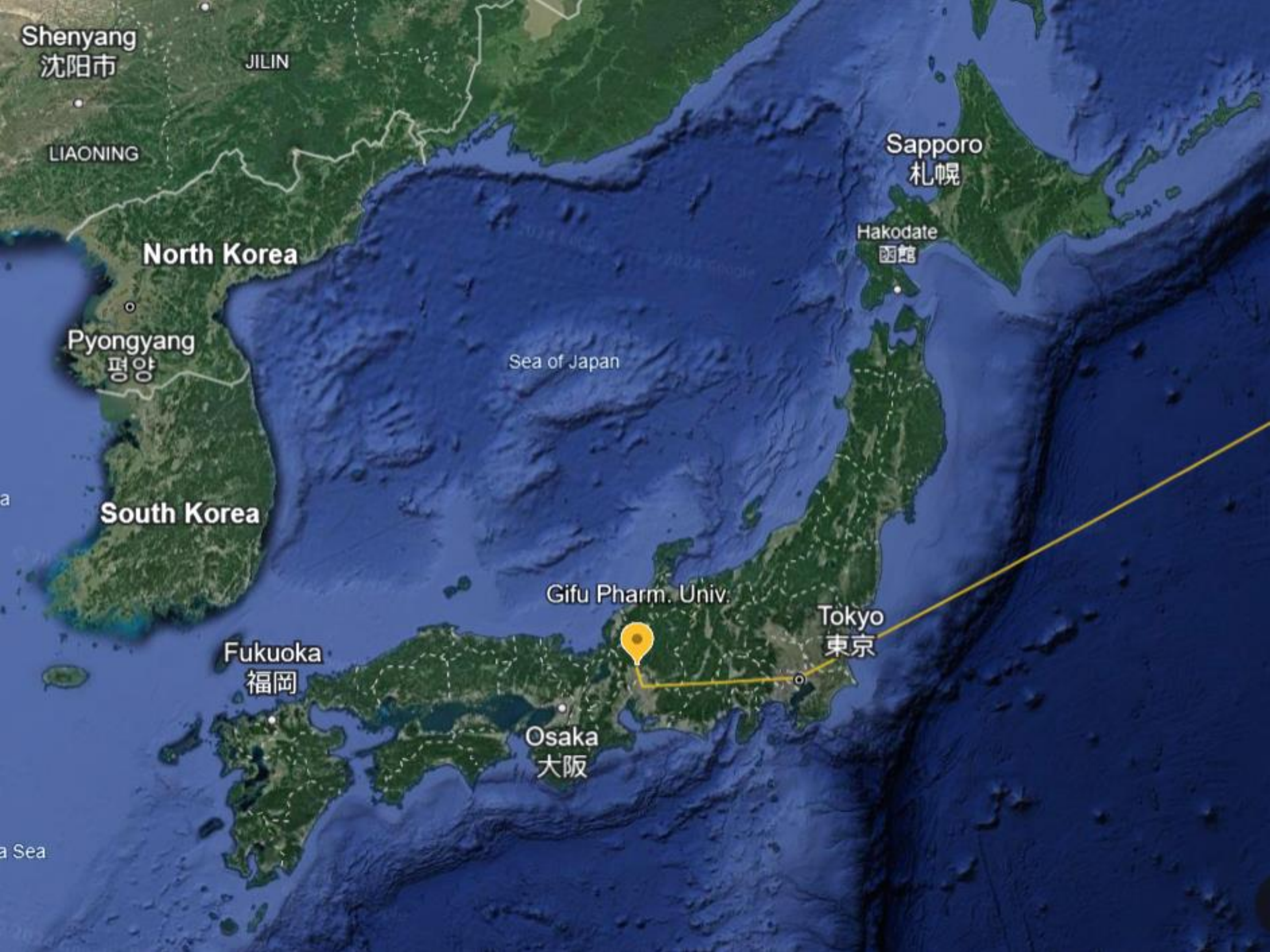
Feature of ArB(Epin)

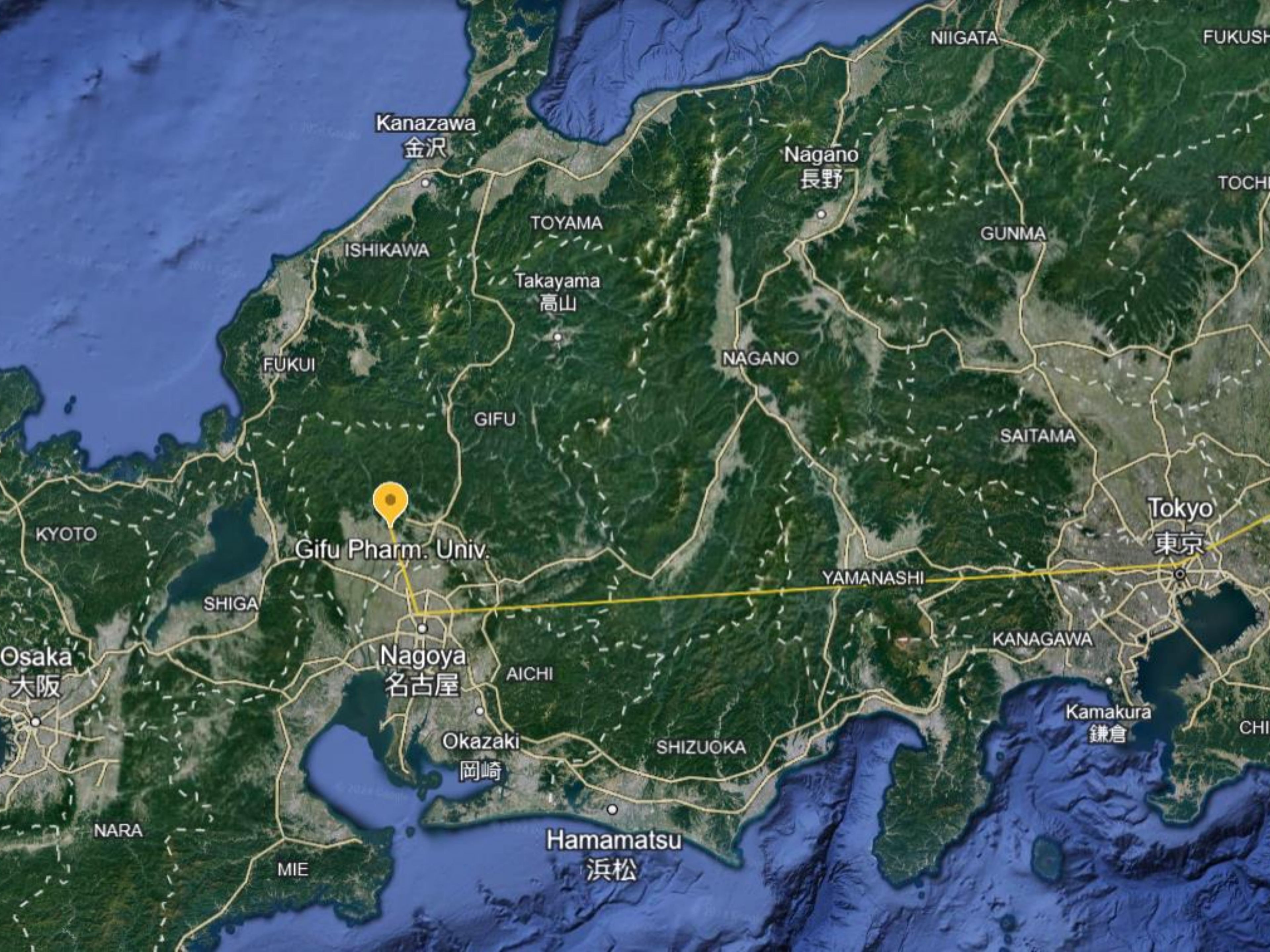
1. Stable on silica gel
2. Enabled functionalization
3. Acid and base stable
4. Enabled Suzuki coupling



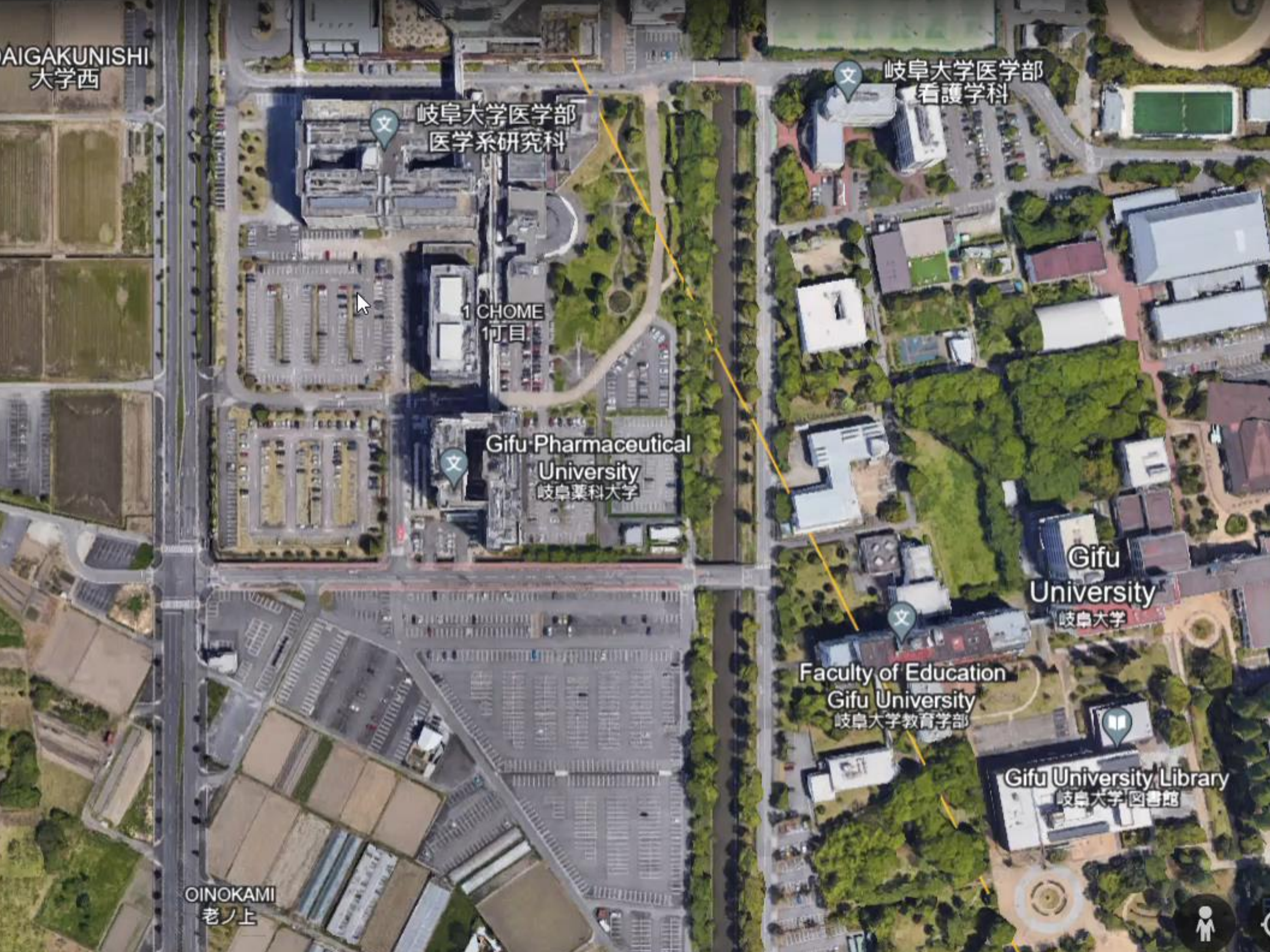
Org. Lett. **2022**, *24*, 3510–3514.

Most viewed *Organic Letters* article in 2022


Shenyang
沈阳市
JILIN
LIAONING
Sapporo
札幌
Hakodate
函館
North Korea
Pyongyang
평양
Sea of Japan
South Korea
Gifu Pharm. Univ.
Tokyo
東京
Fukuoka
福岡
Osaka
大阪
a Sea



NIIGATA
FUKUSH
Kanazawa
金沢
Nagano
長野
TOCHI
TOYAMA
GUNMA
ISHIKAWA
Takayama
高山
NAGANO
FUKUI
GIFU
SAITAMA
Tokyo
東京
KYOTO
Gifu Pharm. Univ.
YAMANASHI
SHIGA
KANAGAWA
Osaka
大阪
Nagoya
名古屋
AICHI
Kamakura
鎌倉
CHI
Okazaki
岡崎
SHIZUOKA
NARA
Hamamatsu
浜松
MIE



DAIGAKUNISHI
大学西
岐阜大学医学部
医学系研究科
岐阜大学医学部
看護学科
1 CHOME
1丁目
Gifu Pharmaceutical
University
岐阜薬科大学
Gifu
University
岐阜大学
Faculty of Education
Gifu University
岐阜大学教育学部
Gifu University Library
岐阜大学 図書館
OINOKAMI
老ノ上

Acknowledgement

Acknowledgement

Prof. Patrick Y. S. Lam

Thank you for your kind attention