Literature Report 8

Chiral Bidentate Boryl Ligand Enabled Iridium Catalyzed Asymmetric C(sp^2)-H Borylation of Diarylmethylamines

Reporter : Huan-Ping Xie

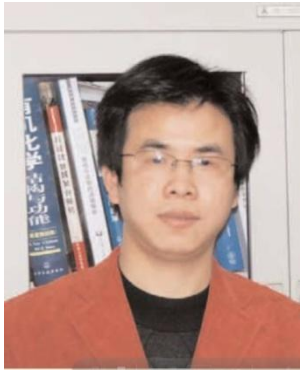
Checker : Yang Zhao

Date : 2019-05-13

Su, B.; Shi, Z.-J.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2017**, *56*, 7205.
Zou, X.; Ke, Z.; Xu, S. *J. Am. Chem. Soc.* **2019**, *141*, 5334.

Contents

CV of Senmiao Xu



Senmiao Xu

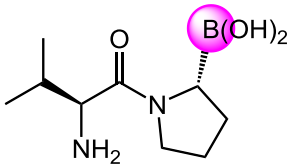
Education:

- **2000-2004** B.S., Zhejiang University;
- **2004-2009** Ph.D., SIOC (K. Ding);
- **2009-2010** Postdoc., Kyoto University (K. Maruoka);
- **2010-2013** Postdoc., Oregon University (S.-Y. Liu);
- **2013-2015** Postdoc., Boston College (S.-Y. Liu);
- **2015-now** Prof., Lanzhou Institute of Chemical Physics.

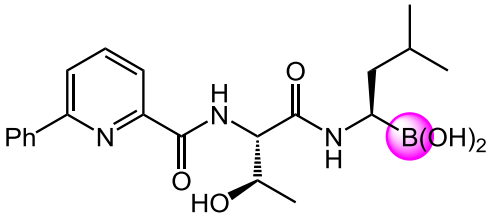
Research:

- Catalytic oxidation and novel atomic economy reaction;
- Design, synthesis and application of new ligands and catalysts.

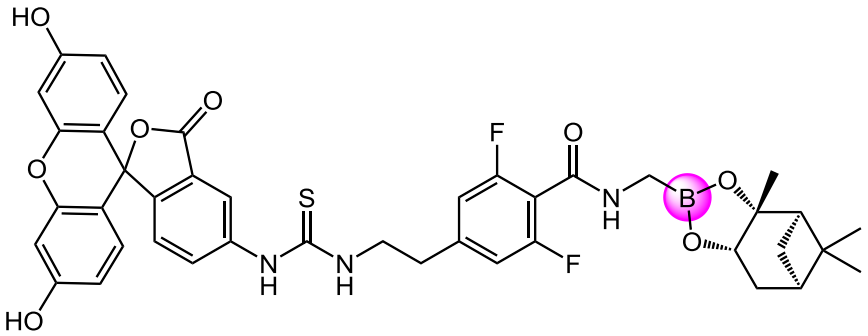
Introduction



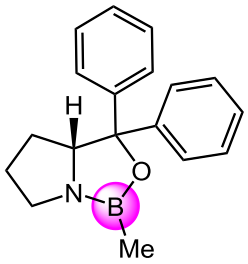
Talabostat
DPP4 Inhibitor
Phase II lung cancer, melanoma, leukemia



Delanzomib
Phase I clinical trials
(solid tumours)



PBPs and β-lactamases tracer



CBS reduction

Cativiela, C. *et al. Chem. Soc. Rev*. **2016**, *45*, 2291.

Introduction

Synthetic routes:

(I) Brown hydroboration

(II) Matteson homologation

(II) Lithiation-borylation

(IV) Transition-metal-catalyzed coupling reaction

(V) Carbene insertion into B-H bonds

(VI) C-C coupling of *gem*-diboron compounds

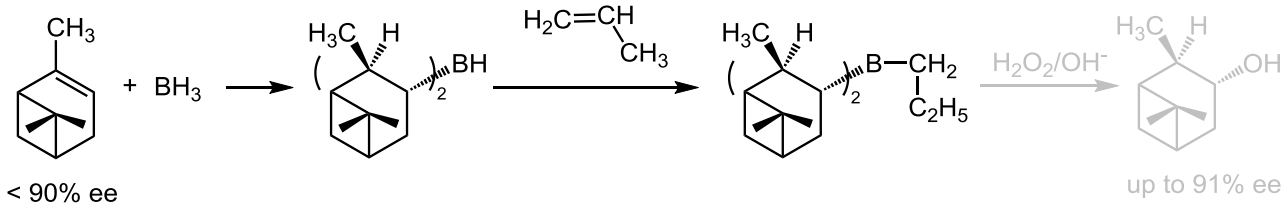
(VII) Addition of "Bpin-M" to unsaturated bonds

(VIII) Addition of "BpinCHR-M" to unsaturated bonds

(IX) Borylation of C-H bonds

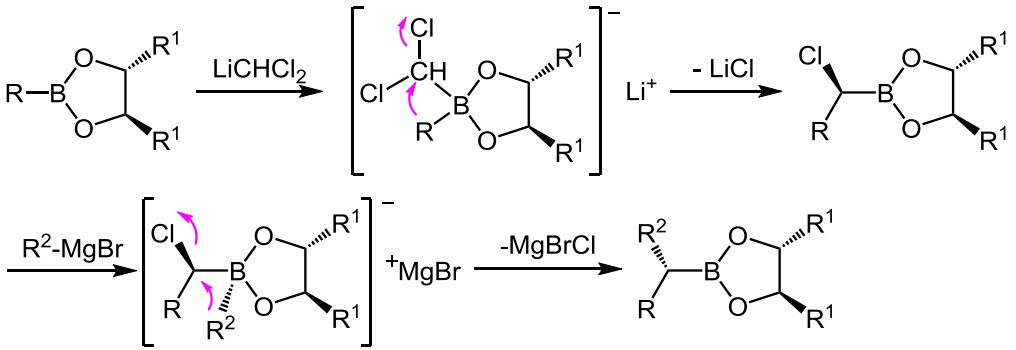
Introduction

Brown hydroboration



Brown, H. C. *et al. J. Am. Chem. Soc.* **1961**, *83*, 486.

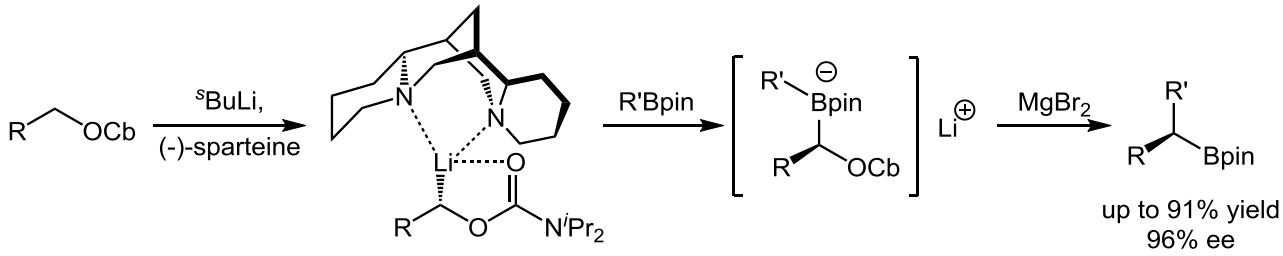
Matteson reaction



Matteson, D. S. *et al. Chem. Rev*. **1989**, *89*, 1535.

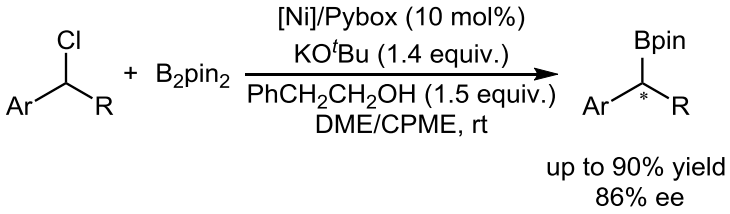
Introduction

Lithiation-borylation



Aggarwal, V. K. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 7491.

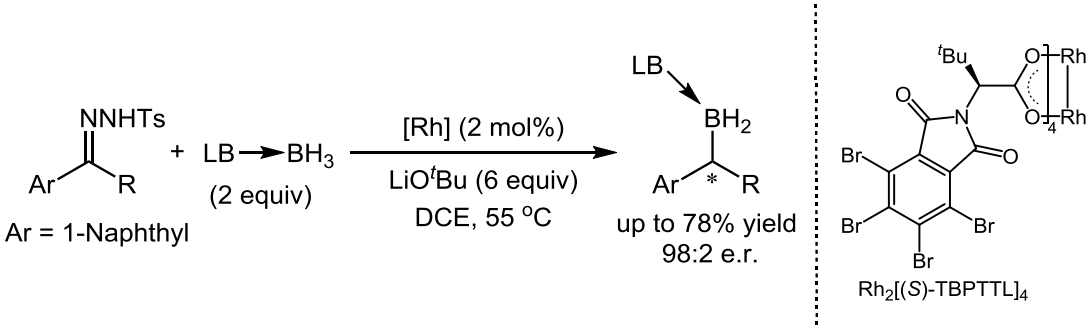
Transition-metal-catalyzed coupling reaction



Fu, G. C. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 14529.

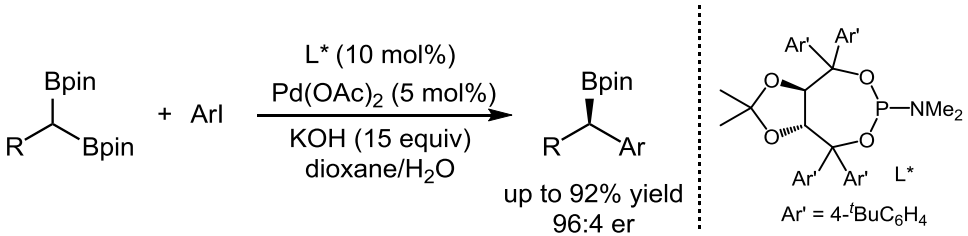
Introduction

Carbene insertion into B-H bonds



Zhou, Q.-L. *et al. J. Am. Chem. Soc.* **2018**, *140*, 10663.

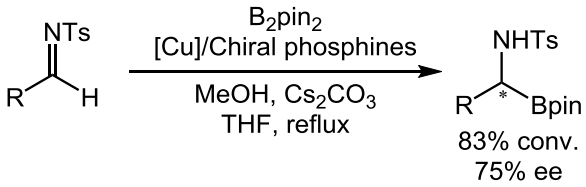
C-C coupling of *gem*-diboron compounds



Morken, J. P. *et al. J. Am. Chem. Soc.* **2014**, *136*, 6534.

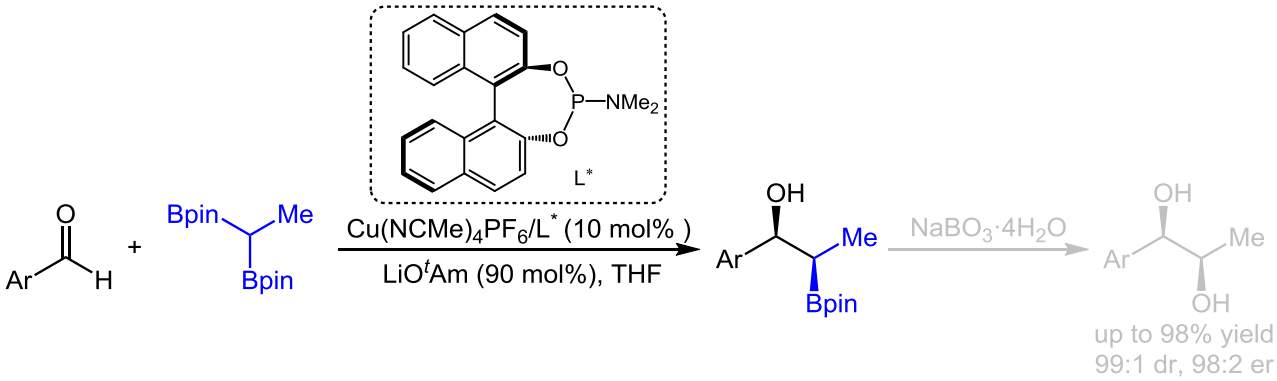
Introduction

Addition of “Bpin-M” to unsaturated bonds



Fernandez, E. *et al. Chem. Commun*. 2012, 48, 3769.

Addition of “BpinCHR-M” to unsaturated bonds

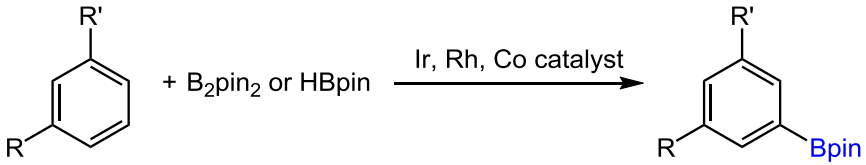


Meek, S. J. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6176.

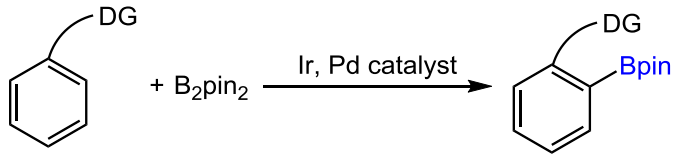
Introduction

C-H Bonds Borylation Catalyzed by Transition Metals

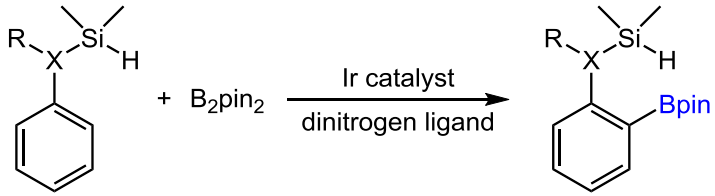
Previous work: a) undirected C-H borylation:



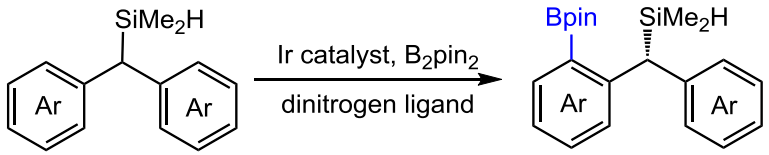
b) directed C-H borylation:



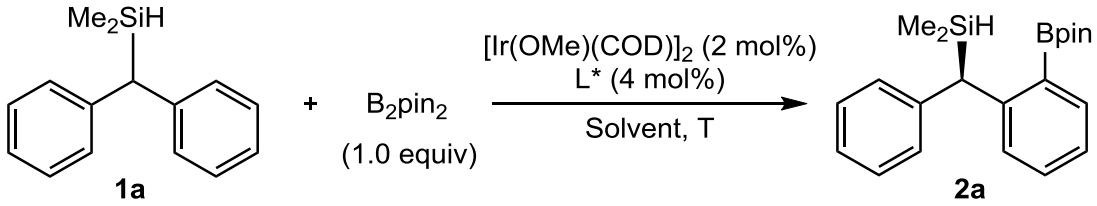
c) silyl directed C-H borylation:



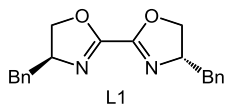
This work: d) the first enantioselective Ir-catalyzed C-H borylation

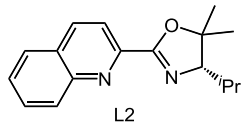


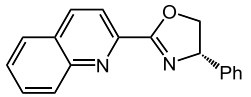
Condition Optimization

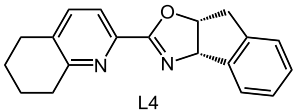


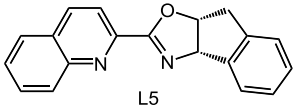
entry[a]	solvent	T (°C)	L*	yield (%)[b]	er[c]
1	THF	25	L1	<5	--
2	THF	25	L2	26	53:47
3	THF	25	L3	70	62:38
4	THF	25	L4	54	76:24
5	THF	25	L5	62	85:15
6	THF	0	L5	66	87:13
7	Hexane	0	L5	58	95:5
8	Octane	0	L5	62	95:5
9	MTBE	0	L5	60	96:4
10[d]	MTBE	0	L5	89	96:4





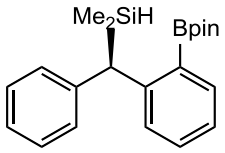




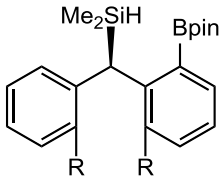


[a] Conditions: **1a** (0.1 mmol), $[Ir(OMe)(COD)]_2$ (2 mol%), L* (4 mol%), B_2pin_2 (0.1 mmol) in solvent (1.0 mL). [b] The yields obtained by ^1H NMR with CH_2Br_2 as internal standard. [c] er values were determined by chiral HPLC. [d] 1.2 equiv of B_2pin_2 was used, $[Ir(OMe)(COD)]_2$ (3 mol%) and L5 (6 mol%) was used.

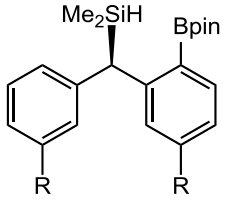
Substrate Scope



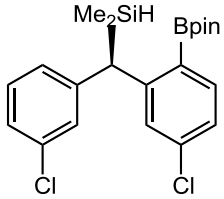
2a: 81%, 96:4 er



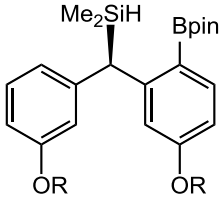
2b: R = F, 61%, 88:12 er
2c: R = Me, 60%, 73:27 er



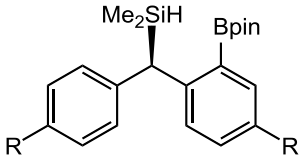
2d: R = Me, 62%, 96:4 er
2e: R = Ph, 74%, 95:5 er



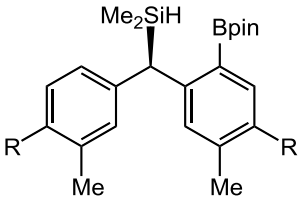
2f: 60%, 85:15 er



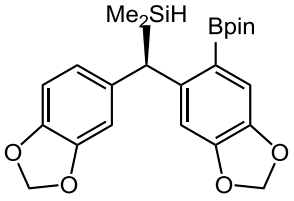
2g: R = Me, 78%, 96:4 er
2h: R = Bn, 72%, 98:2 er
2i: R = Ph, 72%, 96:4 er



2j: R = F, 70%, 61:39 er
2k: R = Me, 73%, 94:6 er
2l: R = ^{t}Bu, 75%, 92:8 er
2m: R = Ph, 83%, 90:10 er
2n: R = TMS, 63%, 76:24 er

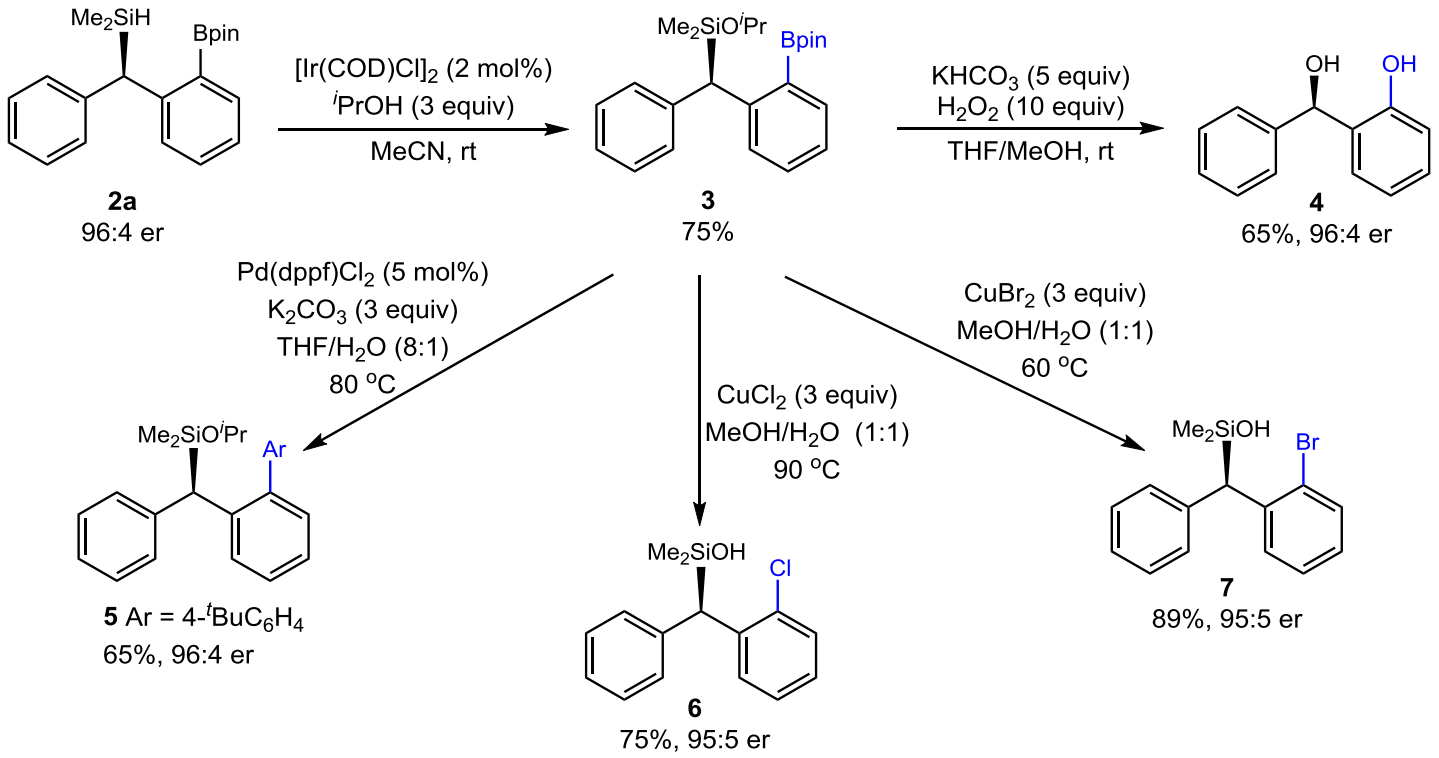


2o: R = Me, 55%, 95:5 er
2p: R = OMe, 69%, 92:8 er



2q: 65%, 96:4 er

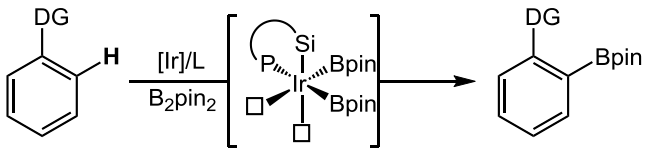
Transformations of Products

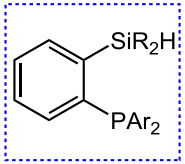


Stoltz, B. M. *et al. J. Am. Chem. Soc.* **2018**, *140*, 10109.

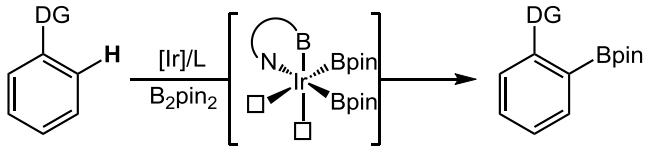
Introduction

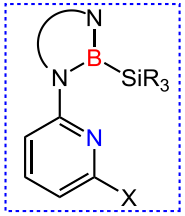
Smith's work: Silyl Phosphorus ligand for *ortho* borylation



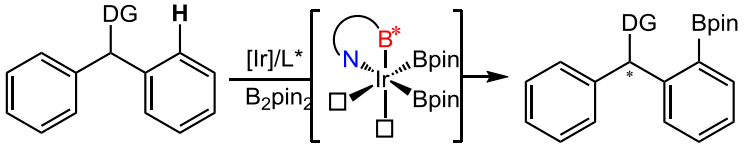


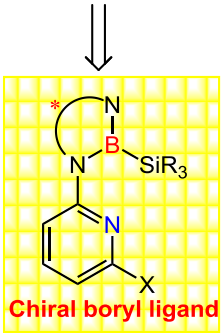
Li Pengfei: Single N,B-ligand for *ortho* borylation





This work: Chiral boryl ligand for *ortho* borylation

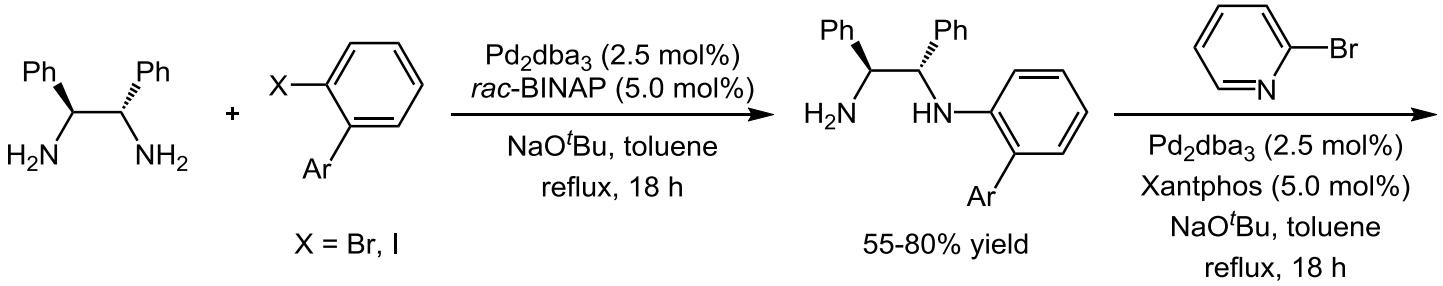


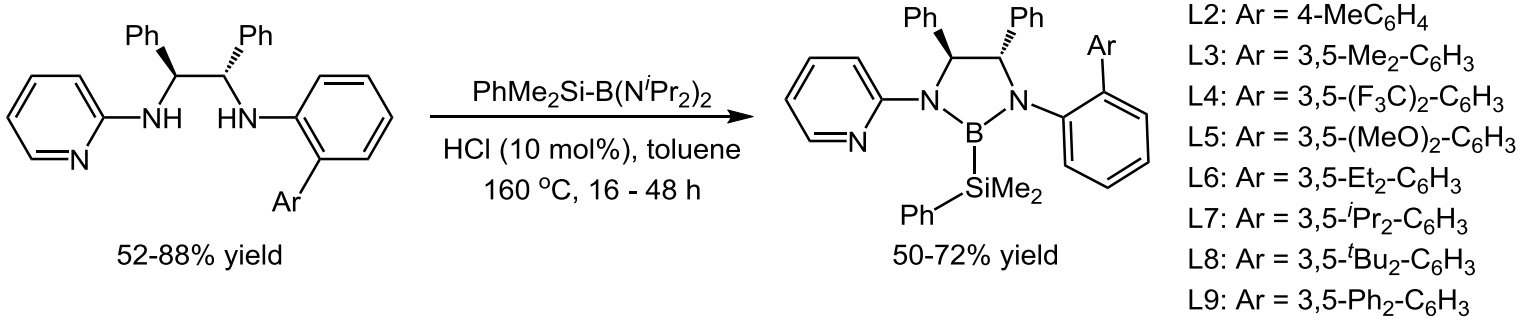


Smith, M. R., III. *et al. J. Am. Chem. Soc*. **2014**, *136*, 14345.

Li, P. *et al. J. Am. Chem. Soc.* **2017**, *139*, 91.

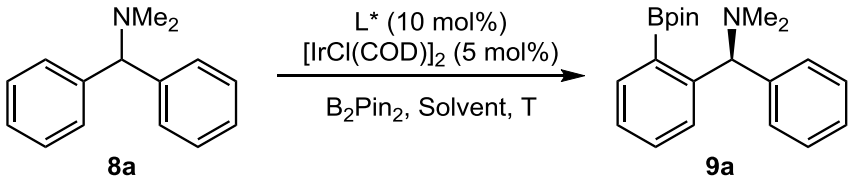
Synthesis of Organoboron Compounds





L1: Ar = Ph
L2: Ar = 4-MeC_6H_4
L3: Ar = 3,5-Me_2-C_6H_3
L4: Ar = 3,5-$(F_3C)_2$-C_6H_3
L5: Ar = 3,5-$(MeO)_2$-C_6H_3
L6: Ar = 3,5-Et_2-C_6H_3
L7: Ar = 3,5-$^{i}Pr_2$-C_6H_3
L8: Ar = 3,5-$^{t}Bu_2$-C_6H_3
L9: Ar = 3,5-Ph_2-C_6H_3

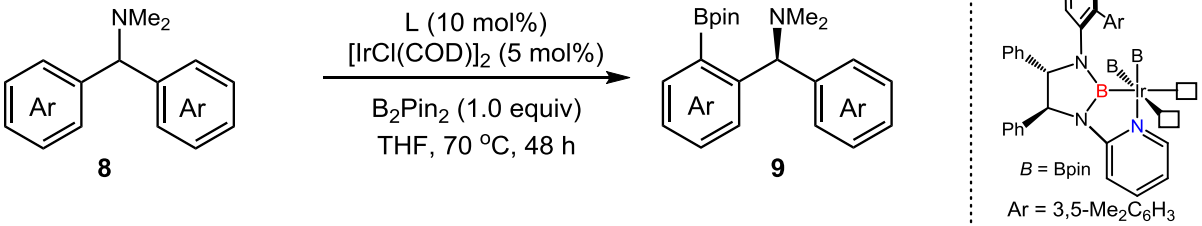
Condition Optimization

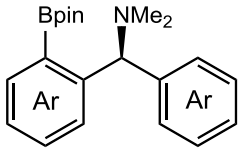


entry[a]	L*	solvent	yield (%)[b]	ee (%)[c]
1	none	THF	trace	n.d.
2	L1	THF	58	19
3	L2	THF	67	13
4	L3	THF	95	90
5	L4	THF	90	85
6	L3	1,4-dioxane	90	74
7	L3	^{n}hexane	87	74
8[d]	L3	THF	98(88)	94

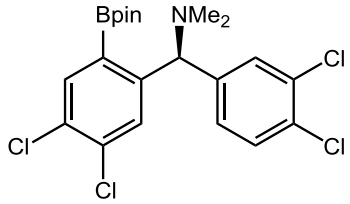
[a] Conditions: **8a** (0.1 mmol), $[IrCl(COD)]_2$ (5 mol%), L* (10 mol%), B_2pin_2 (1.0 mmol) in THF (1.0 mL) at 80 °C for 12 h. [b] Yield of **9a** was determined by ^1H NMR using CH_2Br_2 as internal standard. [c] The enantiomeric excess was determined by chiral HPLC. [d] The reaction temperature was 70 °C.

Substrate Scope

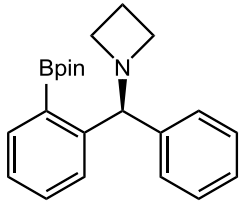




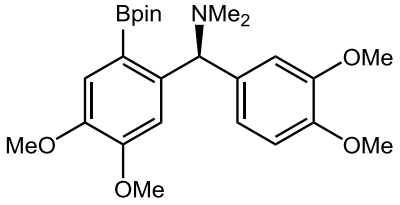
9a: Ar = Ph, 88%, 94% ee
9b: Ar = 4-MeC_6H_4, 70%, 88% ee
9c: Ar = 4-$MeOC_6H_4$, 76%, 85% ee
9d: Ar = 4-FC_6H_4, 82%, 90% ee
9e: Ar = 4-ClC_6H_4, 95%, 88% ee
9f: Ar = 4-BrC_6H_4, 66%, 82% ee
9g: Ar = 4-$F_3CC_6H_4$, 65%, 95% ee
9h: Ar = 4-$F_3COC_6H_4$, 86%, 82% ee
9i: Ar = 4-PhC_6H_4, 79%, 90% ee
9j: Ar = 3-$F_3CC_6H_4$, 90%, 96% ee
9k: Ar =3-MeC_6H_4, 70%, 81% ee
9l: Ar = 3-ClC_6H_4, 74%, 95% ee



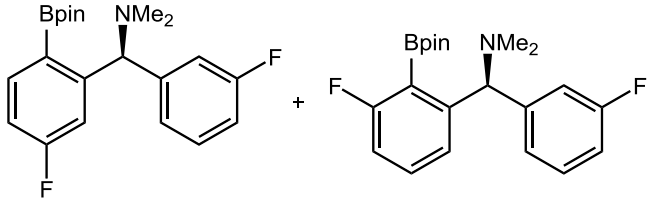
9m: 83%, 88% ee



9n: 60%, 86% ee

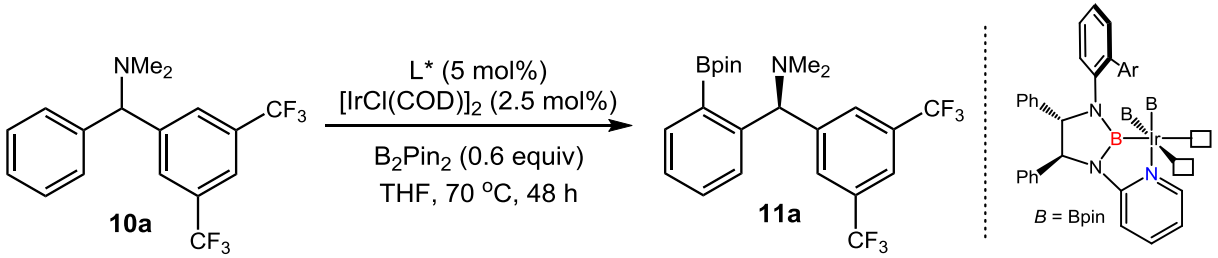


9o: 70%, 87% ee



9p+9p': (ratio of regioisomers: 4:1)
77% yield, 94% ee/89% ee

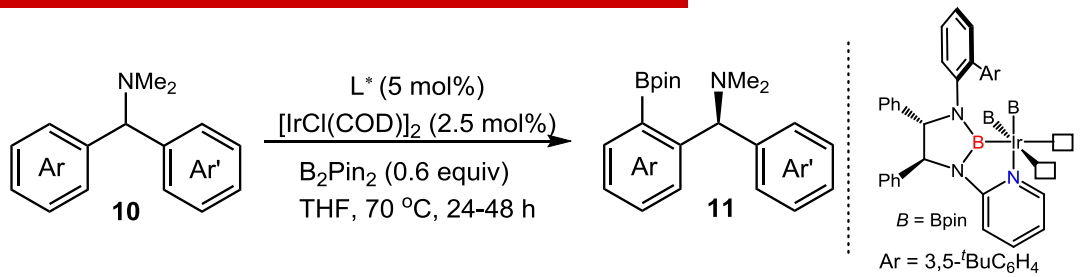
Condition Optimization



entry[a]	L*	*conv.* (%)[b]	ee_{11a} (%)[d]	ee_{10a} (%)[c]	*s*[e]
1	L3	35	89	48	28
2	L4	26	85	30	17
3	L6	19	96	22	39
4	L7	26	93	33	44
5	L8	30	94	41	68

[a] Conditions: **10a** (0.1 mmol), $[IrCl(COD)]_2$ (2.5 mol%), L* (5 mol%), B_2pin_2 (0.06 mmol) in THF (1.0 mL) at 70 °C for 24-48 h. [b] Conversion was calculated by $[ee_{10a}/(ee_{11a} + ee_{10a})]$. [c] ee_{10a} was determined using GC on a chiral B-DA column; [d] ee_{11a} was determined by chiral HPLC after oxidation with $NaBO_3$. [e] $s = K_{fast}/K_{slow} = \ln[(1 - conv./100)(1 - ee_{10a}/100)/\ln[(1 - conv./100)(1 + ee_{10a}/100)]$.

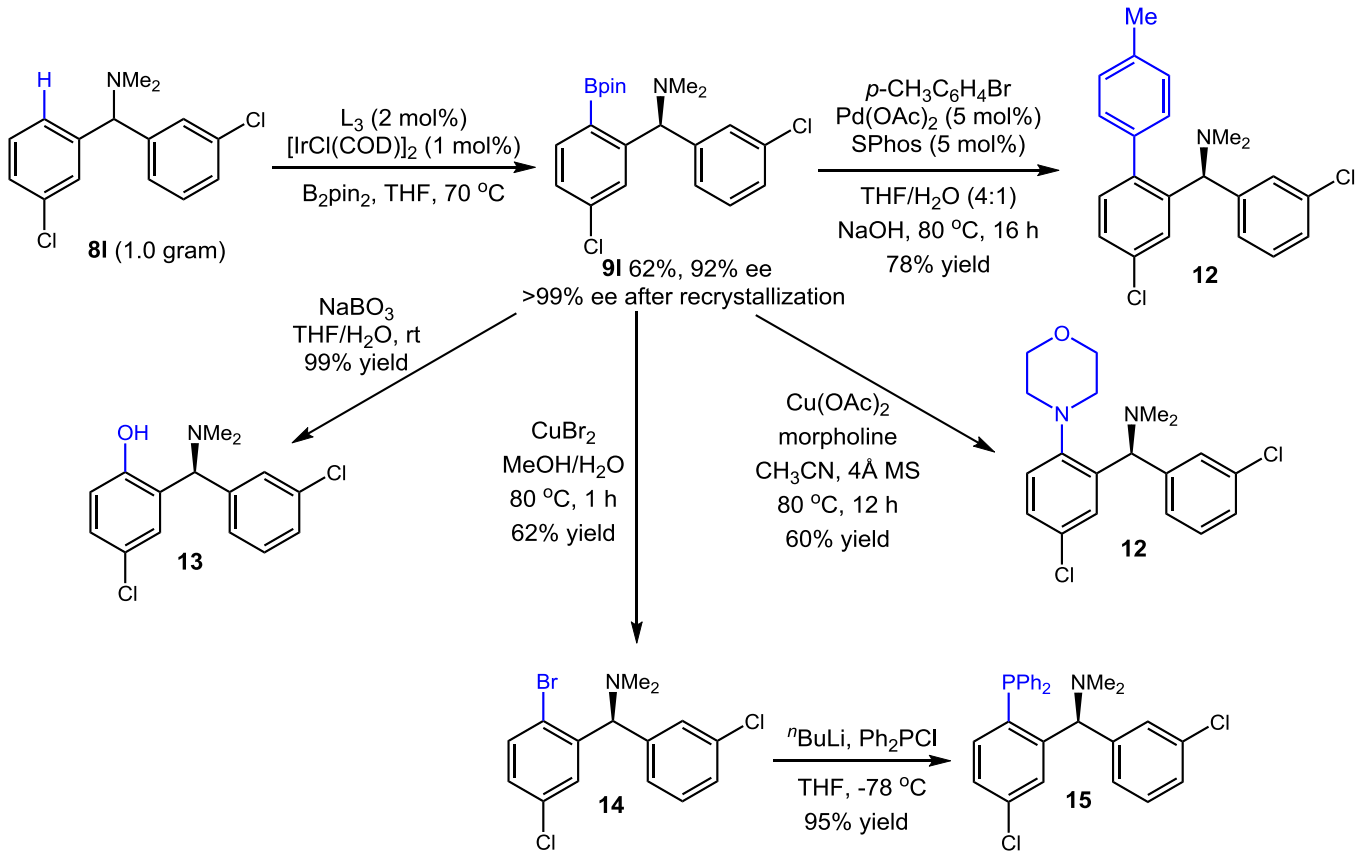
Substrate Scope



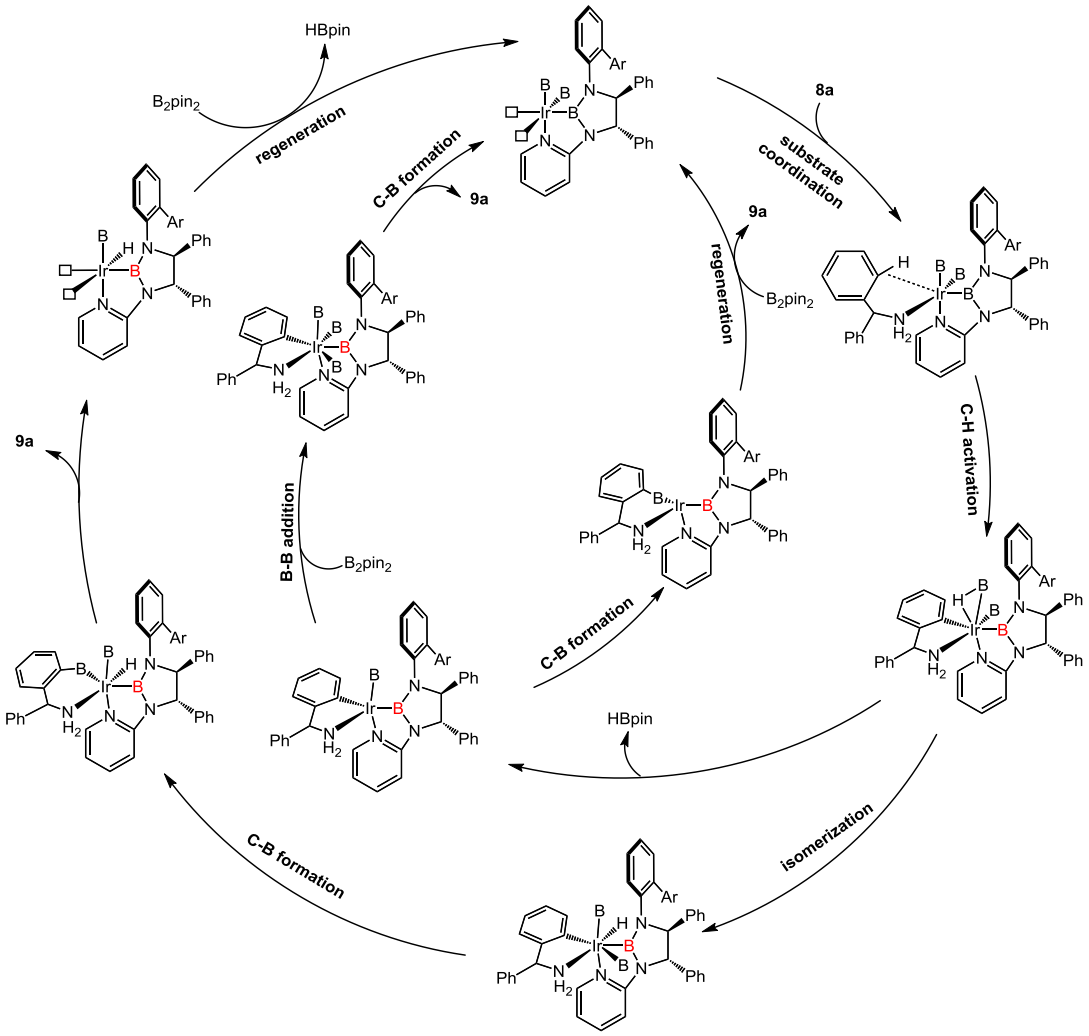
entry[a]	Ar; Ar'	*conv.* (%)[b]	ee_{11} (%)[c]	ee_{10} (%)[c]	*s*[d]
1	Ph; 3,5-$(CF_3)_2C_6H_3$	30	94	41	68
2	3-MeC_6H_4; 3,5-$(CF_3)_2C_6H_3$	30	90	40	25
3	3-ClC_6H_4; 3-MeO-5-MeC_6H_3	28	90	35	27
4	Ph; 3,5-$(MeO)_2C_6H_3$	33	85	42	19
5[e]	3-PhC_6H_4; 3-Me-5-ClC_6H_3	39	87	55	23
6[e]	3-PhC_6H_4; 3-MeO-5-ClC_6H_3	37	87	51	24
7[e]	3-PhC_6H_4; 3,5-$(CF_3)_2C_6H_3$	27	93	34	33
8[f]	Ph; 3,5-$Br_2C_6H_3$	24	90	28	22
9[g]	3-ClC_6H_4; 3-MeO-5-$CF_3C_6H_3$	50	88	88	45

[a] Conditions: **10** (0.1 mmol), $[IrCl(COD)]_2$ (2.5 mol%), L* (5 mol%), B_2pin_2 (0.06 mmol) in THF (1.0 mL) at 70 °C for 24-48 h. [b] Conversion was calculated by $[ee_{10}/(ee_{11} + ee_{10})]$. [c] ee_{10} was determined using GC or HPLC on chiral stationary phase; [c] ee_{11} was determined by chiral HPLC after oxidation with $NaBO_3$. [d] $s = K_{fast}/K_{slow} = \ln[(1 - conv./100)(1 - ee_{10}/100)/\ln[(1 - conv./100)(1 + ee_{10}/100)]$. [e] 0.80 equiv of B_2pin_2 was used. [f] 1.2 equiv of B_2pin_2 was used. [g] 1.2 equiv of B_2pin_2 was used.

Synthetic Application

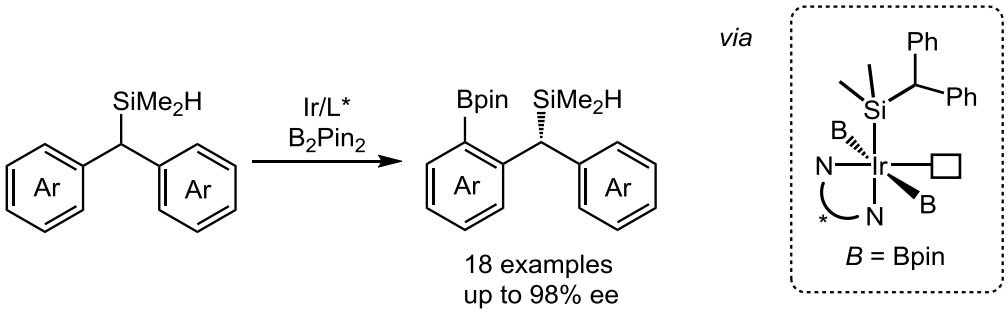


Proposed Mechanism



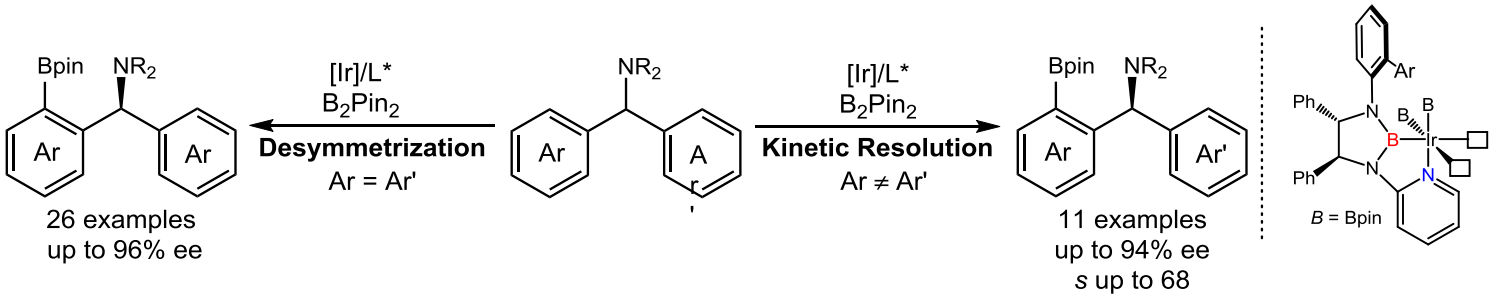
Summary

Asymmetric C(sp^2)-H Borylation (Relay-directed)



Hartwig, J. F. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 7205.

Asymmetric C(sp^2)-H Borylation (Chelate-directed)



Xu, S. *et al. J. Am. Chem. Soc.* **2019**, *141*, 5334.

The First Paragraph

Optically active organoboron compounds are of great importance in synthetic chemistry, drug discovery, and catalysis. Accordingly, a number of synthetic methods for these compounds have been developed during the past decades. Early methods usually rely on chiral reagents and auxiliaries, including lithiation-borylation and Matteson homologation.

The First Paragraph

Some of these suffered from harsh reaction conditions. Transition-metal-catalyzed asymmetric carbon-boron coupling of carbon-halogen bonds, asymmetric hydroboration of π unsaturated substrates, carbene insertion into B-H bonds, and C-C coupling of gem-diboron compounds have been developed under mild conditions. These methods are also compatible with a wide range of functional groups. However, substrates for these reactions need to be prefunctionalized, which will cost extra reaction steps, purifications, and other reagents.

The Last Paragraph

We have developed a new class of bidentate chiral boryl ligands, which enable chelate-directed iridium-catalyzed asymmetric C(sp^2)-H borylation using free amines as directing groups. With this protocol, we realized Ir-catalyzed desymmetrization of prochiral diarylmethylamines and kinetic resolution racemic diarylmethylamines for the first time. This protocol provides a vast range of optically active diarylmethylamines with excellent enantio-selectivities.

The Last Paragraph

We also demonstrated that the borylated products can be used as versatile precursors in the preparation of a variety of functionalized chiral diarylmethylamines, including potent ligands. Further applications of chiral boryl ligands in other catalytic asymmetric transformations are currently underway in our laboratory.

Acknowledgement

Thanks for your kind attention!