Literature Report

Copper-Catalyzed Regioselective Borylfluoromethylation of Alkenes

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Checker: Xiang Li
Date: 2020-01-06

Wu, N.-Y.; Xu, X.-H.; Qing, F.-L.
ACS Catal. **2019**, *9*, 5726-5731.

CV of Prof. Qing, F.-L.

Research:

- Oxidative fluoroalkylation;
- Radical fluoroalkylation;
- Methodologies for synthesis of fluoro-organic compounds

Background:

- **xxxx-1990** Ph.D., Shanghai Institute of Organic Chemistry
- **1992-1995** Post Doctorate, Wyeth Research
- **1995-now** Professor, Shanghai Institute of Organic Chemistry

Contents

Bioisosterism

生物电子等排体(Bioisosterism)是由化学电子等排体衍化而来的。化学电子等排体概念是由Langmuir于1919年首先提出的，他认为: 原子、官能团和分子由于类似的电子结构，其物理化学性质也相似。这些类似性往往发生在元素周期表中同族原子中，即外层电子相同或近似，其大小和质量相差不大的那些原子。而横排相近的那些原子则很少有相同趋向。例如，Cl和Br的化学性质比C和Cl更相似。虽然Cl和I在同一主族，最外电子层也相同，但其大小如范德华半径和原子量则有较大差异。

近代Burger等人按照其发展衍生化过程，将生物电子等排体分成了如下两种类型：

经典的生物电子等排体：a. 一价原子和基团；b. 二价原子和基团；c. 三价原子和基团；d. 四价原子和基团；e.环系等价体。

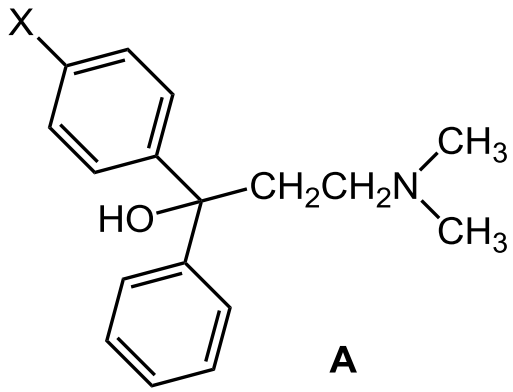
非经典的生物电子等排体：a.可交换的基团；b. 环与非环结构。

Bioisosterism

一价等排体	二价等排体	三价等排体	四价等排体	环内相当体
F, OH, NH_2, CH_3	-O-	-N=	=C=	-CH=CH-
Cl, SH, PH_2	-S-	-P=	$=N^+=$	-S-
Br	-Se-	-As=	$=P^+=$	-O-
I	-Te-	-Sb=	$=As^+=$	-NH-
		-CH=	$=Sb^+=$	

Bioisosterism

一价电子等排体在药物设计中的应用



A

X	pA_2
H	8.00
F	8.51
Cl	8.65

例如从抗组胺药盐酸苯海拉明衍生成的氯苯海拉明（是一种抗过敏药物），其苯环上氢原子用同族的一价电子等排体卤素互换时，抗组胺作用随卤原子的原子量增加而增加。

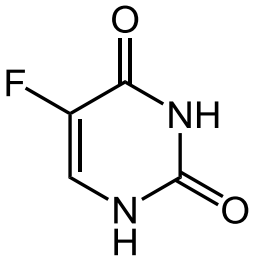
Bioisosterism

一价电子等排体在药物设计中的应用

卤素原子中，F是比较特殊的，它是卤素中电负性最大的元素，其形成的有机C-F键相当稳定，且由于F原子的体积小，因而常认为F是H的非经典电子等排体。在药物设计中，常用F代替H，由此得到的生物电子等排体的生物活性往往增强。

如果替代H的F原子在生物反应中最终要除去的话，则可能产生拮抗作用。这是因为，C-F键相当稳定，在代谢过程不易分解，不干干扰含氟药物与相应细胞受体间的相互作用，能在分子水平代替正常代谢物，欺骗性地掺入生物大分子，导致致死合成（lethal synthesis）。

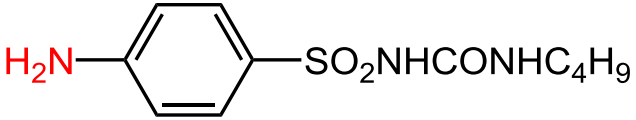
5-氟尿嘧啶就是按此原理设计的一个抗肿瘤药物的实例



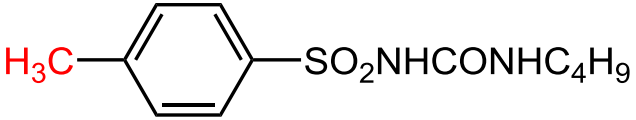
B

Bioisosterism

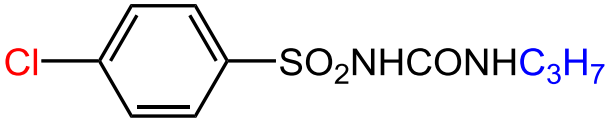
一价电子等排体在药物设计中的应用



C



D

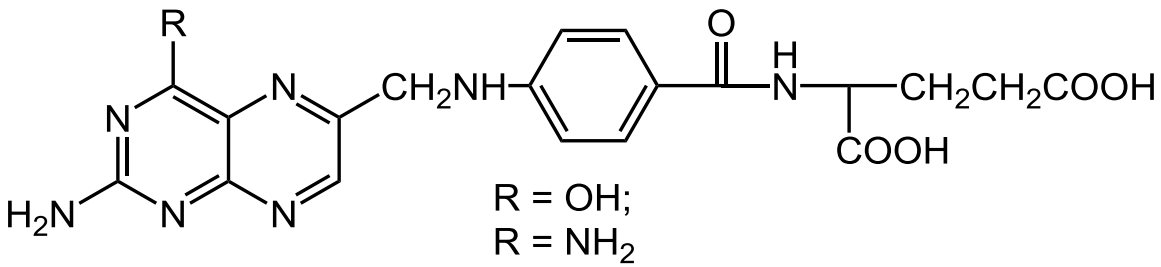


E

-F(Cl)、OH、-NH_2和CH_3，都是经典的一价电子等排体，它们之间可以互相置换。例如，在口服降血糖药物的研发过程中，最早从磺胺类药物中发现胺磺丁脲C，分子中的芳胺基用甲基替代得到的甲磺丁脲 D，其将血糖活性明显增强，后再用电子等排体Cl替代其中的CH_3，并将丁基改为丙基，由此制得的氯磺丙脲E，生物半衰期延长，毒性亦减少。

Bioisosterism

一价电子等排体在药物设计中的应用

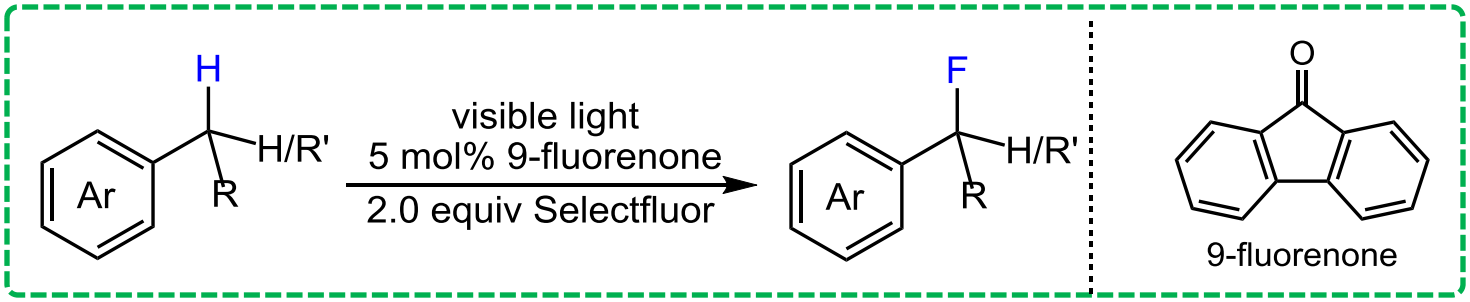


F

叶酸的-OH被其电子等排体-NH_2取代，生成其代谢拮抗剂氨基碟啶。失去原来叶酸的生理功能，发现其与二氢叶酸还原酶的结合力增强一万至五万倍，从而成为叶酸的拮抗剂。用于治疗白血病。

Introduction

C-H fluorination of CH_3



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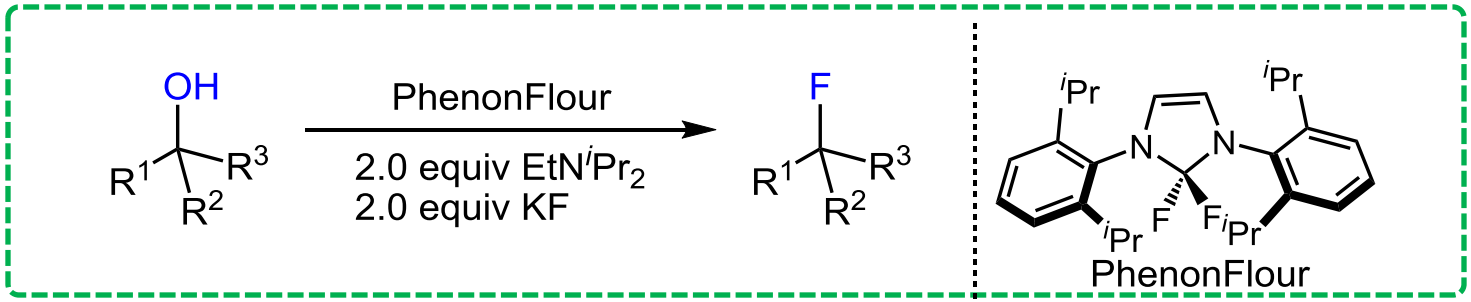
Fluorination of functionalized substrates



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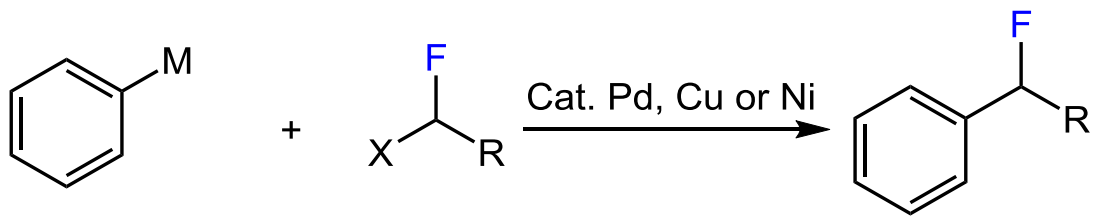
Introduction

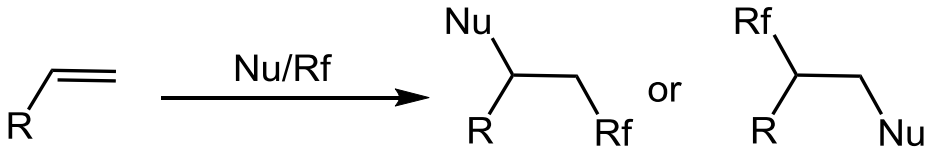
Direct fluoromethylation



M = B, Mg, Zn, Si, X, etc.

Baran, P. S. *et al*. Science **2018**, *360*, 75; *et al.*

Difunctionalization of alkenes



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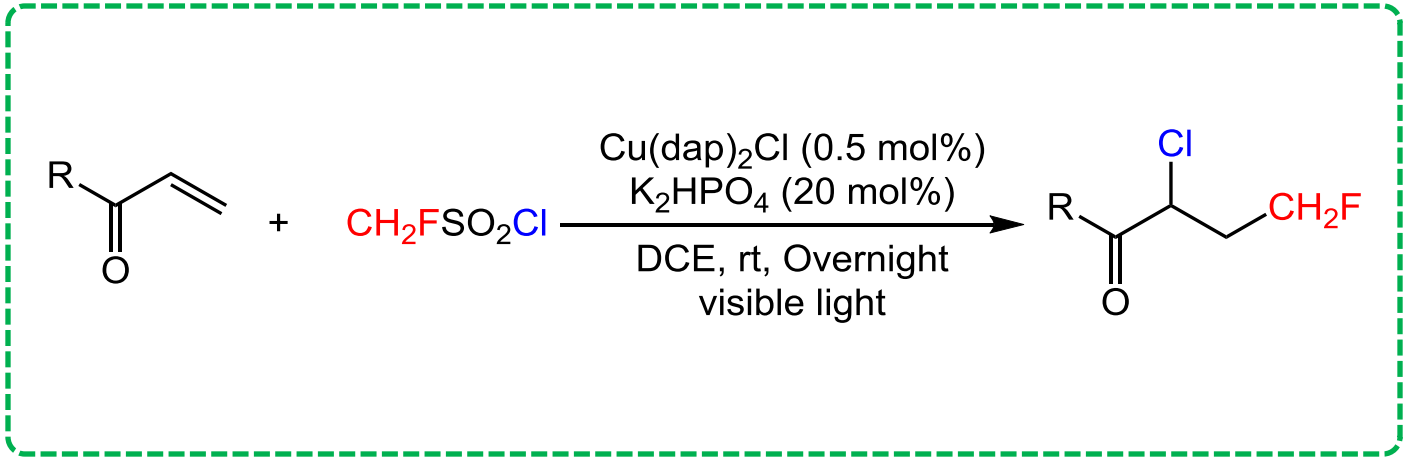

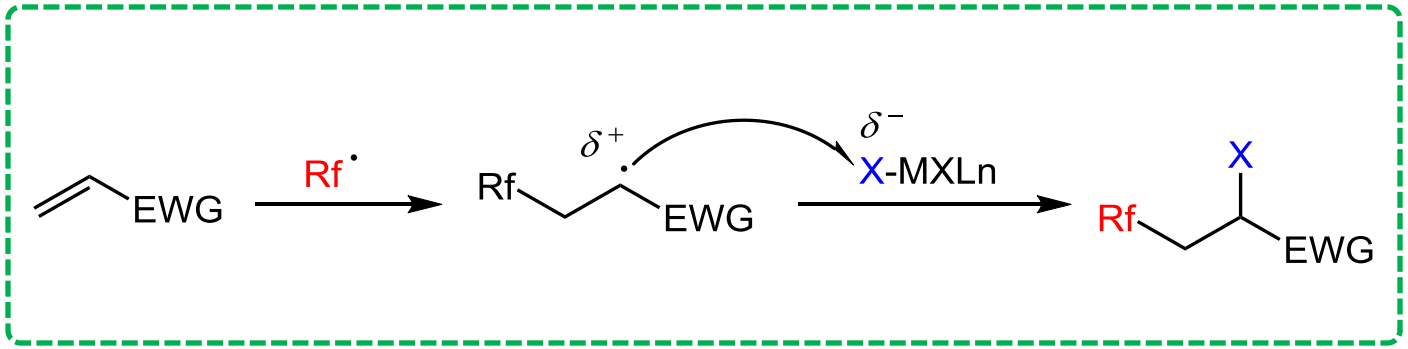

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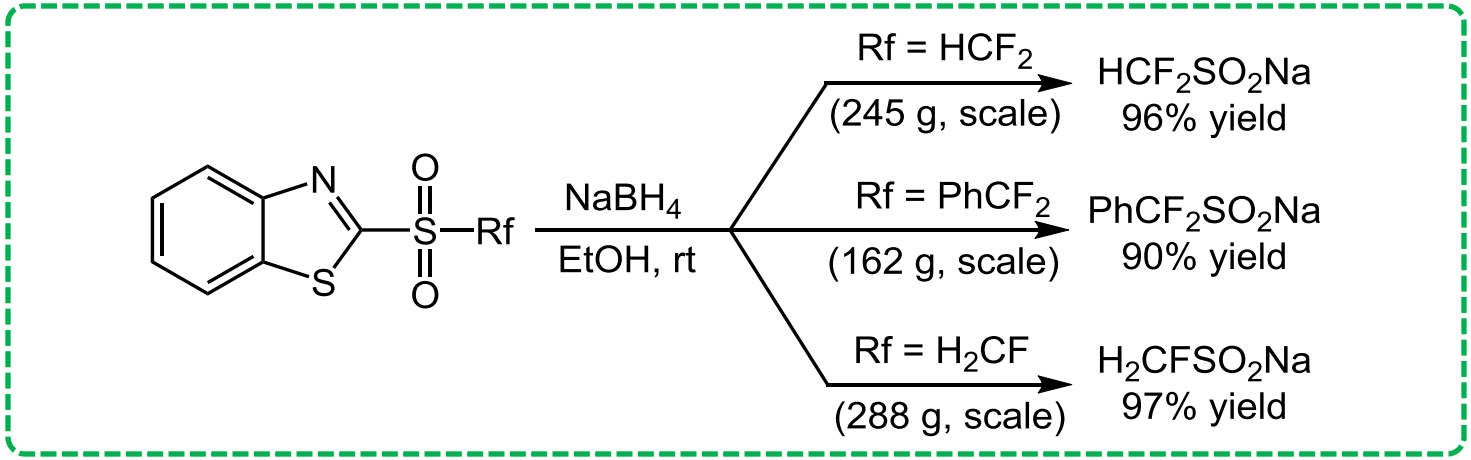

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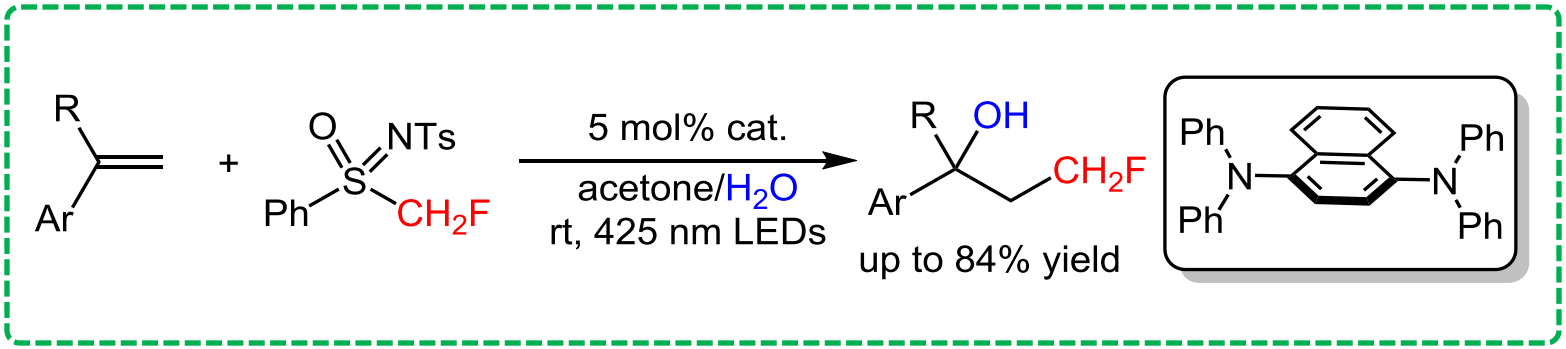

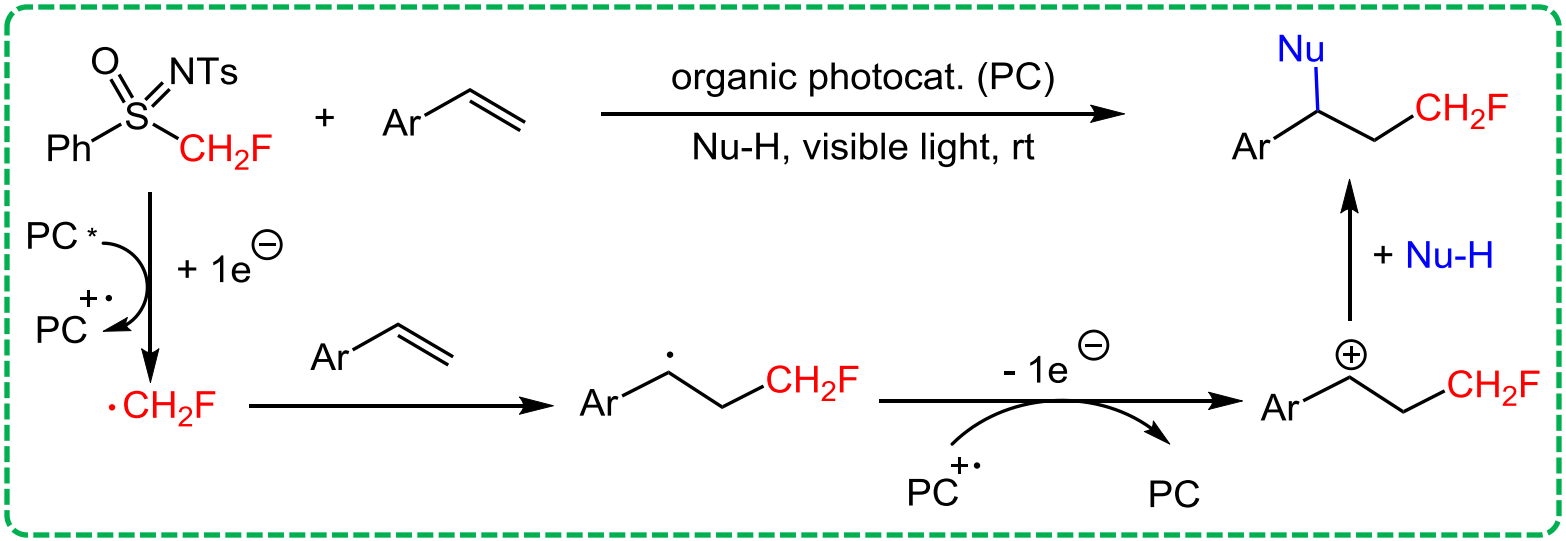

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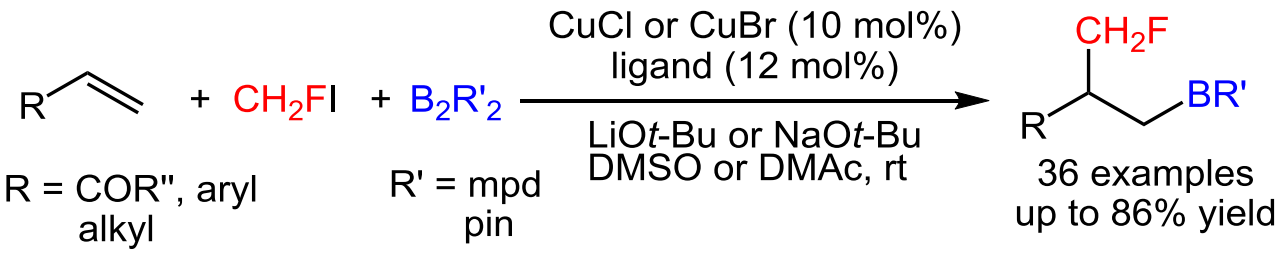
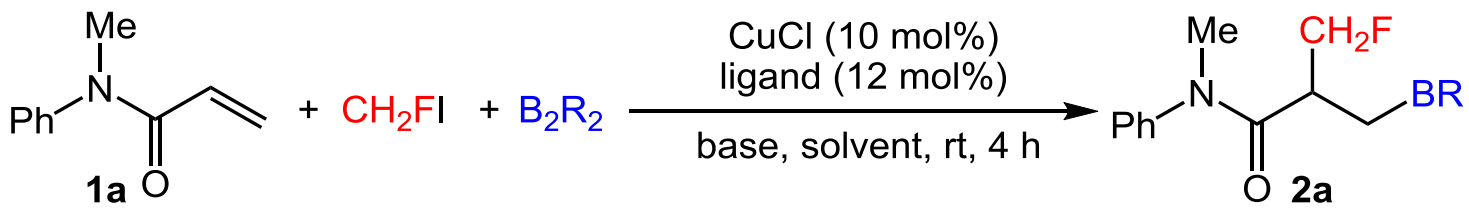


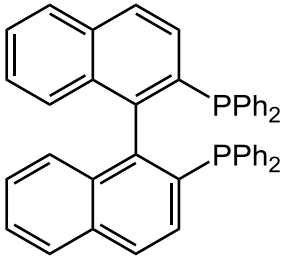
Wu, N.-Y.; Xu, X.-H.; Qing, F.-L. *ACS Catal.* **2019**, *9*, 5726.

Optimization of Reaction Conditions

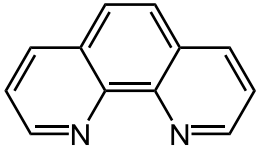


entry [a]	ligand	base	solvent	B_2R_2	yield [b]
1	Binap	NaO*t*-Bu	THF	B_2pin_2	trace
2	Binap	NaO*t*-Bu	toluene	B_2pin_2	0
3	Binap	NaO*t*-Bu	DMAc	B_2pin_2	41
4	Binap	NaO*t*-Bu	DMF	B_2pin_2	61
5	Binap	NaO*t*-Bu	**DMSO**	B_2pin_2	65
6	phen	NaO*t*-Bu	DMSO	B_2pin_2	48
7	IMes	NaO*t*-Bu	DMSO	B_2pin_2	52
8	dppbz	NaO*t*-Bu	DMSO	B_2pin_2	63
9	XantPhos	NaO*t*-Bu	DMSO	B_2pin_2	35

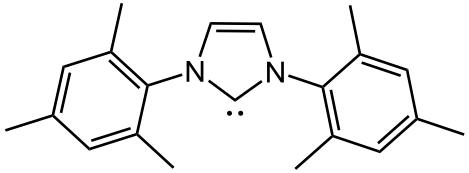
Ligands and B_2R_2



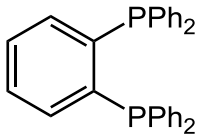
Binap



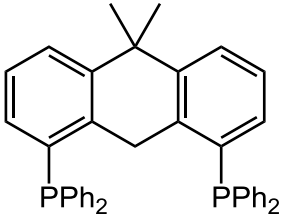
phen



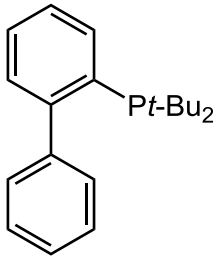
IMes



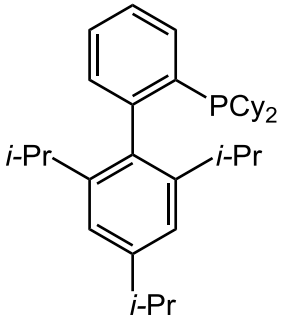
dppbz



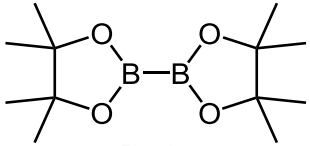
XantPhos



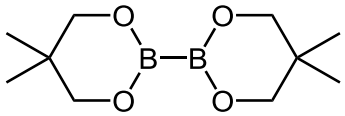
JohnPhos



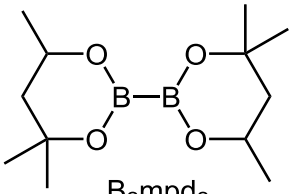
XPhos



B_2pin_2



B_2neo_2



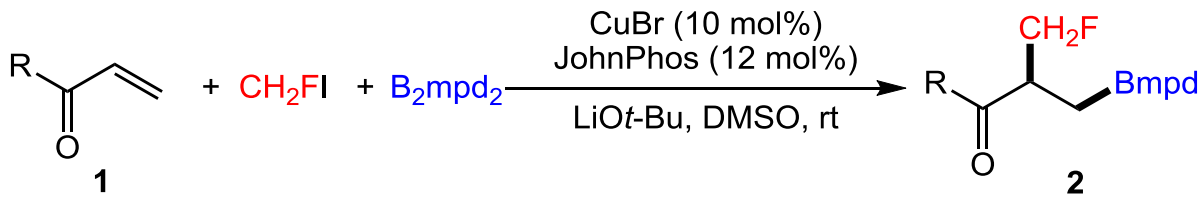
B_2mpd_2

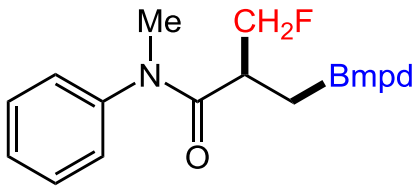
Optimization of Reaction Conditions

entry [a]	ligand	base	solvent	B_2R_2	yield [b]
10	**JohnPhos**	NaO*t*-Bu	DMSO	B_2pin_2	70
11	XPhos	NaO*t*-Bu	DMSO	B_2pin_2	61
12	PPh_3	NaO*t*-Bu	DMSO	B_2pin_2	60
13	PCy_3	NaO*t*-Bu	DMSO	B_2pin_2	57
14	JohnPhos	KO*t*-Bu	DMSO	B_2pin_2	7
15	JohnPhos	**LiO*t*-Bu**	DMSO	B_2pin_2	78
16	JohnPhos	LiOMe	DMSO	B_2pin_2	0
17	JohnPhos	LiO*t*-Bu	DMSO	B_2neo_2	72
18	JohnPhos	LiO*t*-Bu	DMSO	**B_2mpd_2**	88
19 [c]	**JohnPhos**	**LiO*t*-Bu**	**DMSO**	**B_2mpd_2**	**93**
20 [d]	JohnPhos	LiO*t*-Bu	DMSO	B_2mpd_2	76

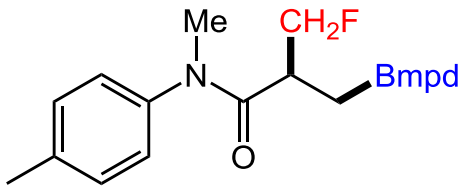
[a] Reaction conditions: **1a** (0.2 mmol), B_2R_2 (0.3 mmol), ICH_2F (0.3 mmol), CuCl (0.02 mmol), ligand (0.024 mmol), base (0.36 mmol), solvent (2.0 mL), rt, under N_2, 4 h. [b] Yields determined by ^{19}F NMR using fluorobenzene as an internal standard. [c] CuBr. [d] CuI.

Borylfluoromethylation of Acrylamides

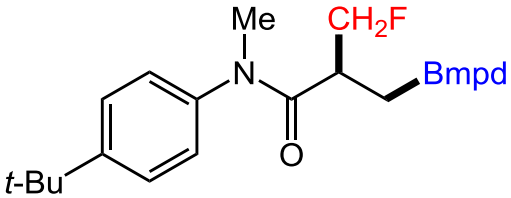




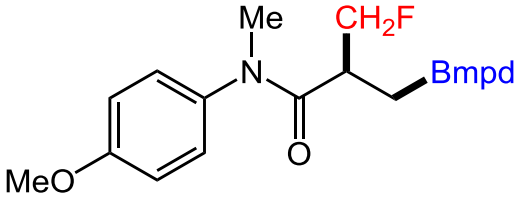
2a 84% (45:55)



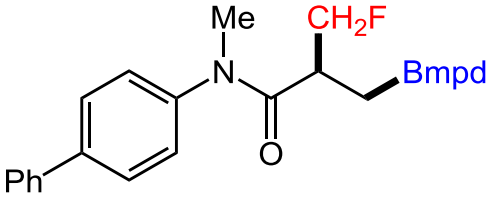
2b 85% (47:53)



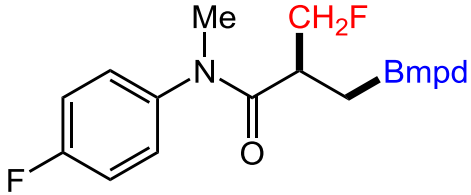
2c 80% (47:53)



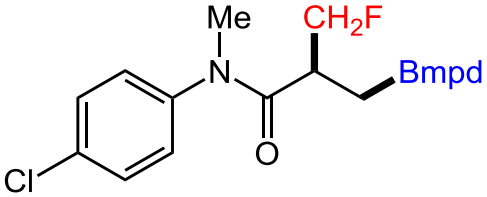
2d 86% (49:51)



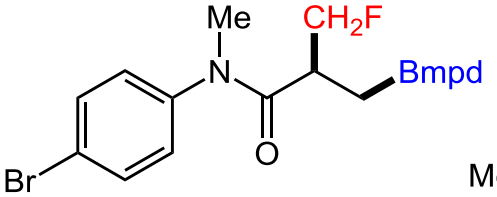
2e 76% (49:51)



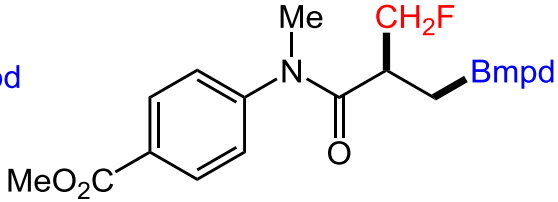
2f 63% (45:55)



2g 61% (45:55)

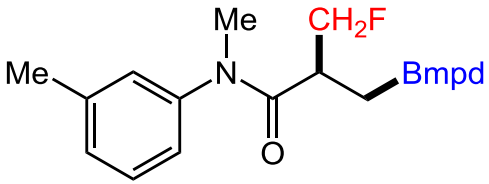


2h 63% (45:55)

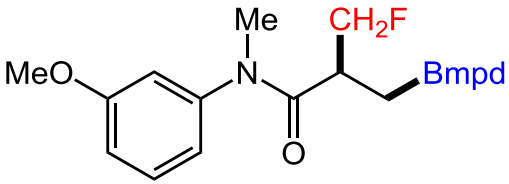


2i 52% (43:57)

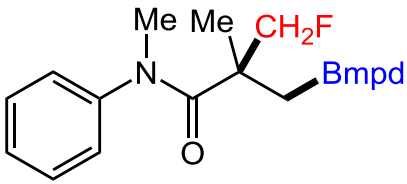
Borylfluoromethylation of Acrylamides



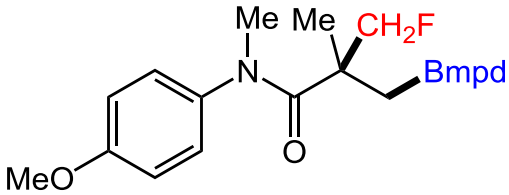
2j 75% (45:55)



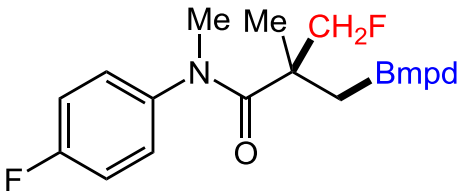
2k 74% (45:55)



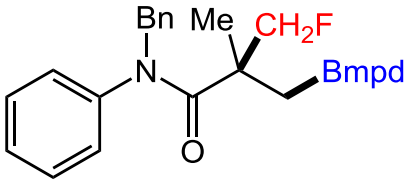
2l 73% (43:57)



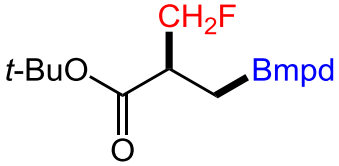
2m 71% (43:57)



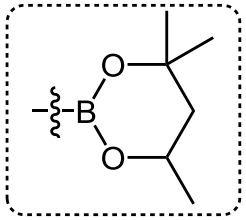
2n 75% (43:57)



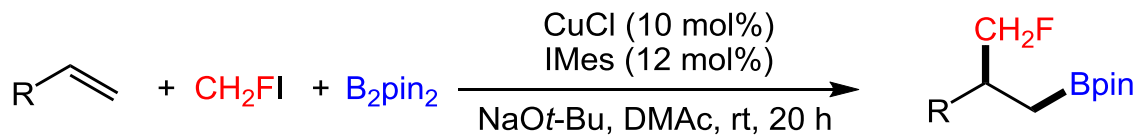
2o 65% (43:57)



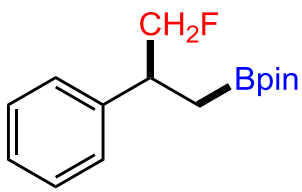
2p 47% (42:58)



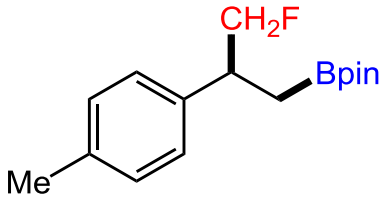
Borylfluoromethylation of Alkenes



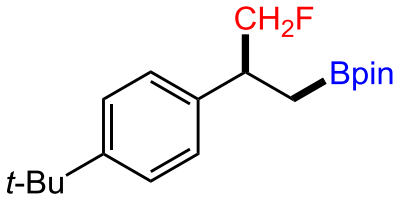
3 **4**



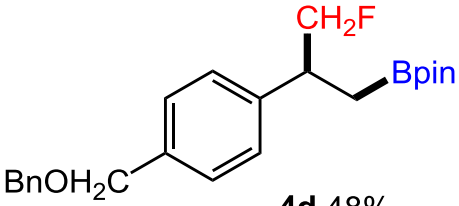
4a 81%



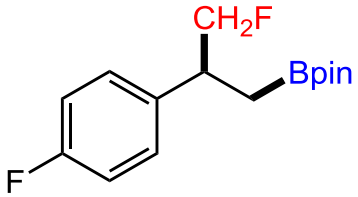
4b 61%



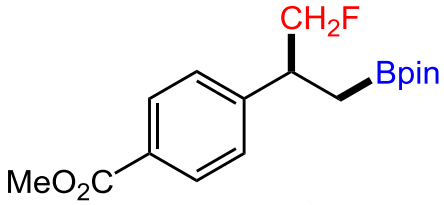
4c 56%



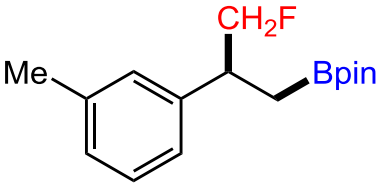
4d 48%



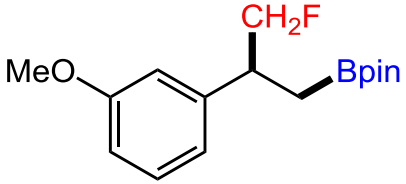
4e 55%



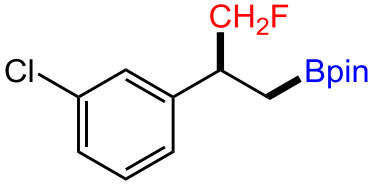
4f 44%



4g 61%

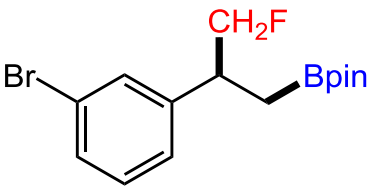


4h 47%

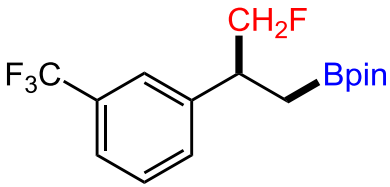


4i 65%

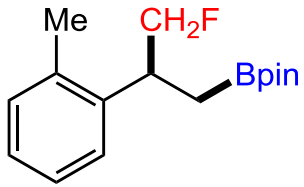
Borylfluoromethylation of Alkenes



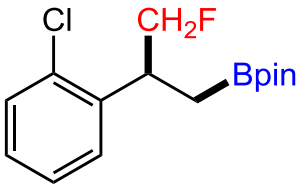
4j 51%



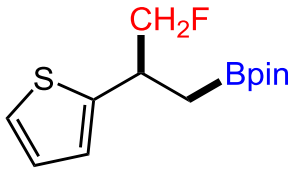
4k 68%



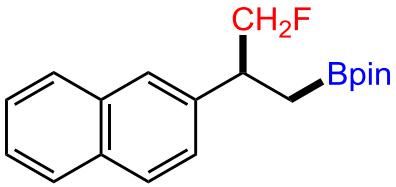
4l 66%



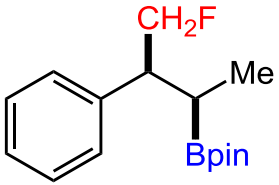
4m 72%



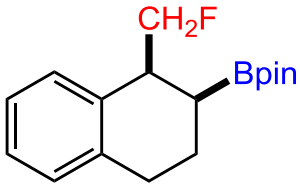
4n 36%



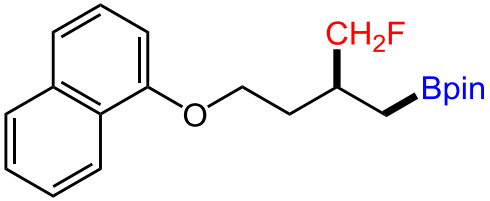
4o 51%



4p 43% (>99:1)

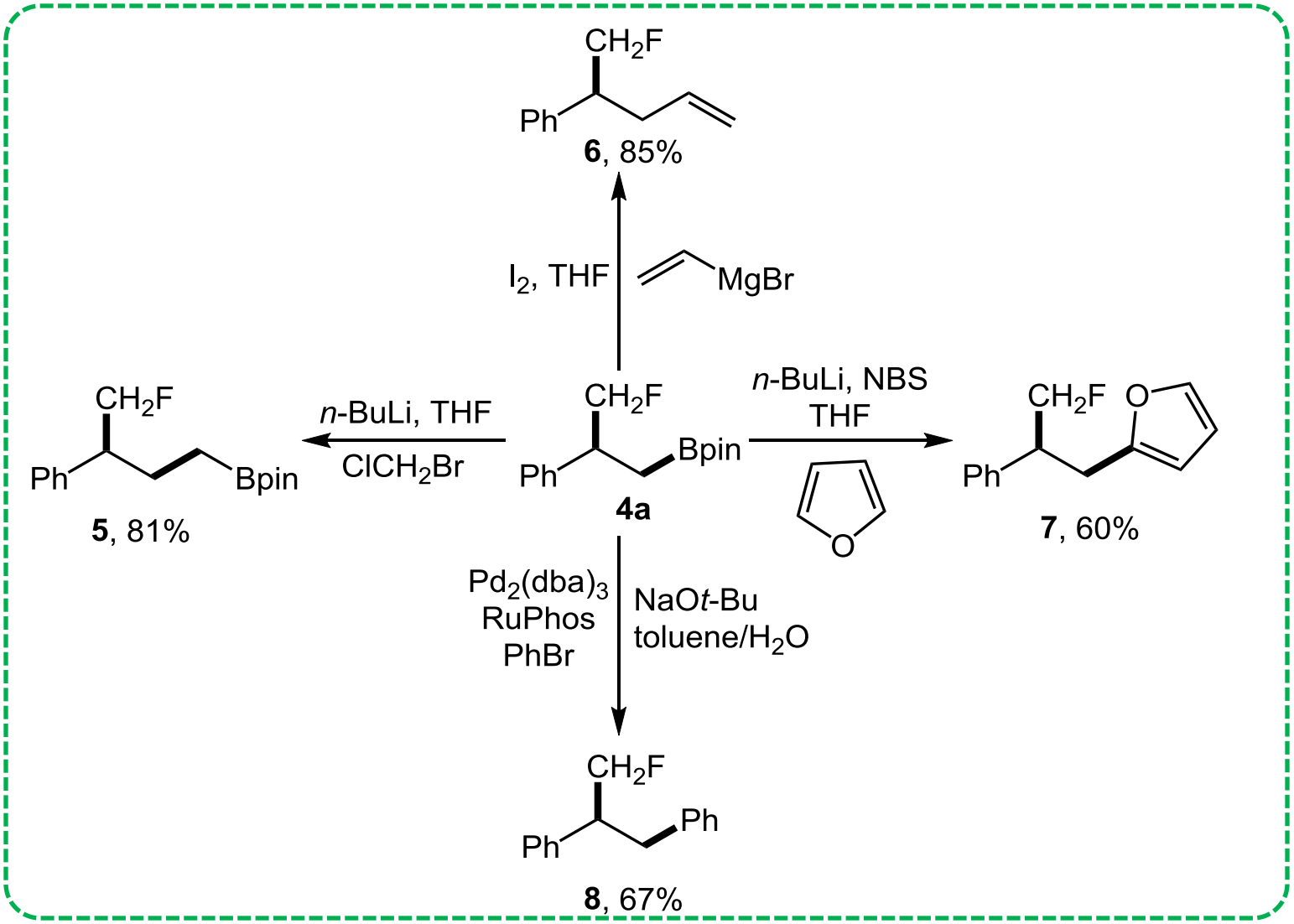


4q 44% (>99:1)

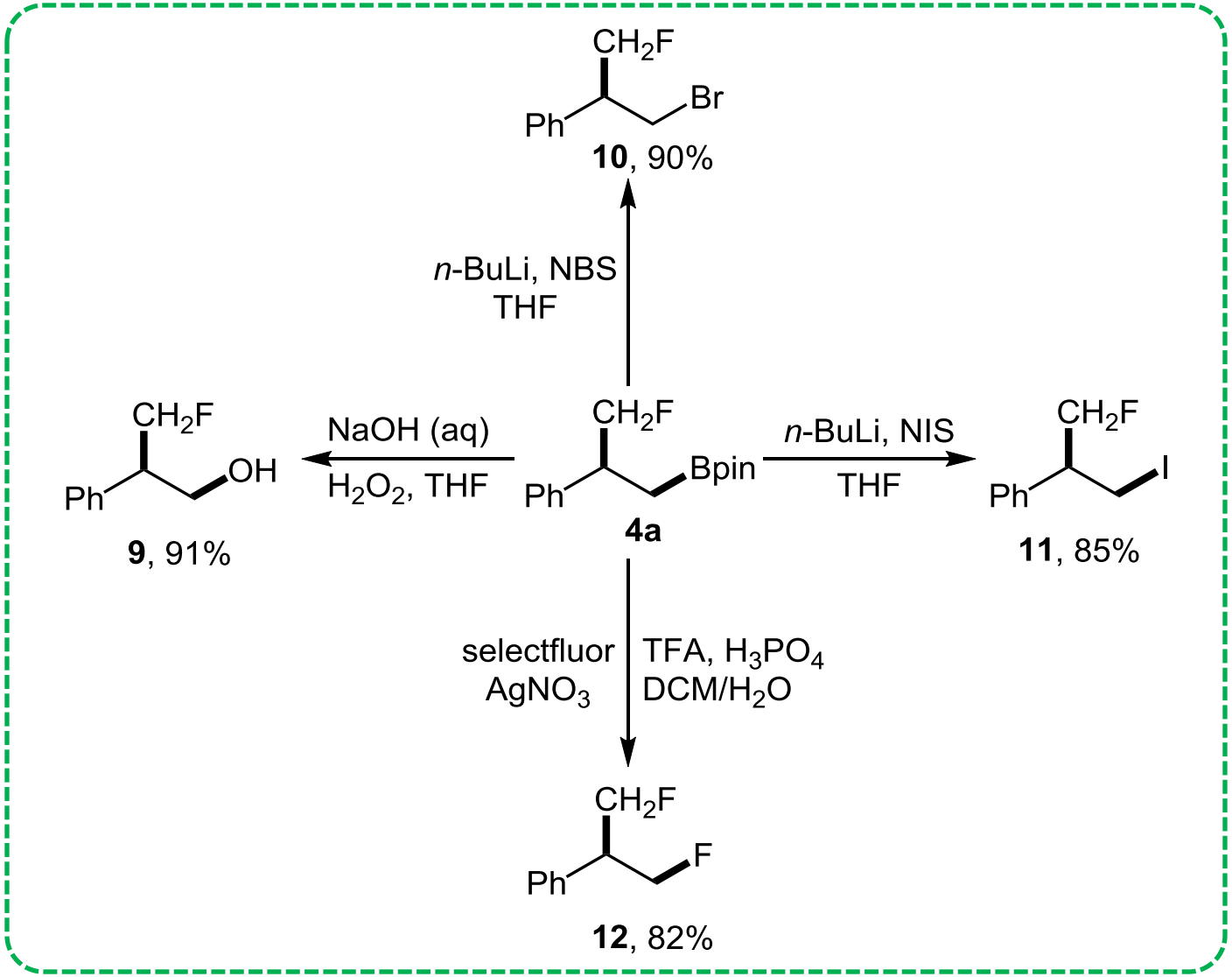


4r 23%

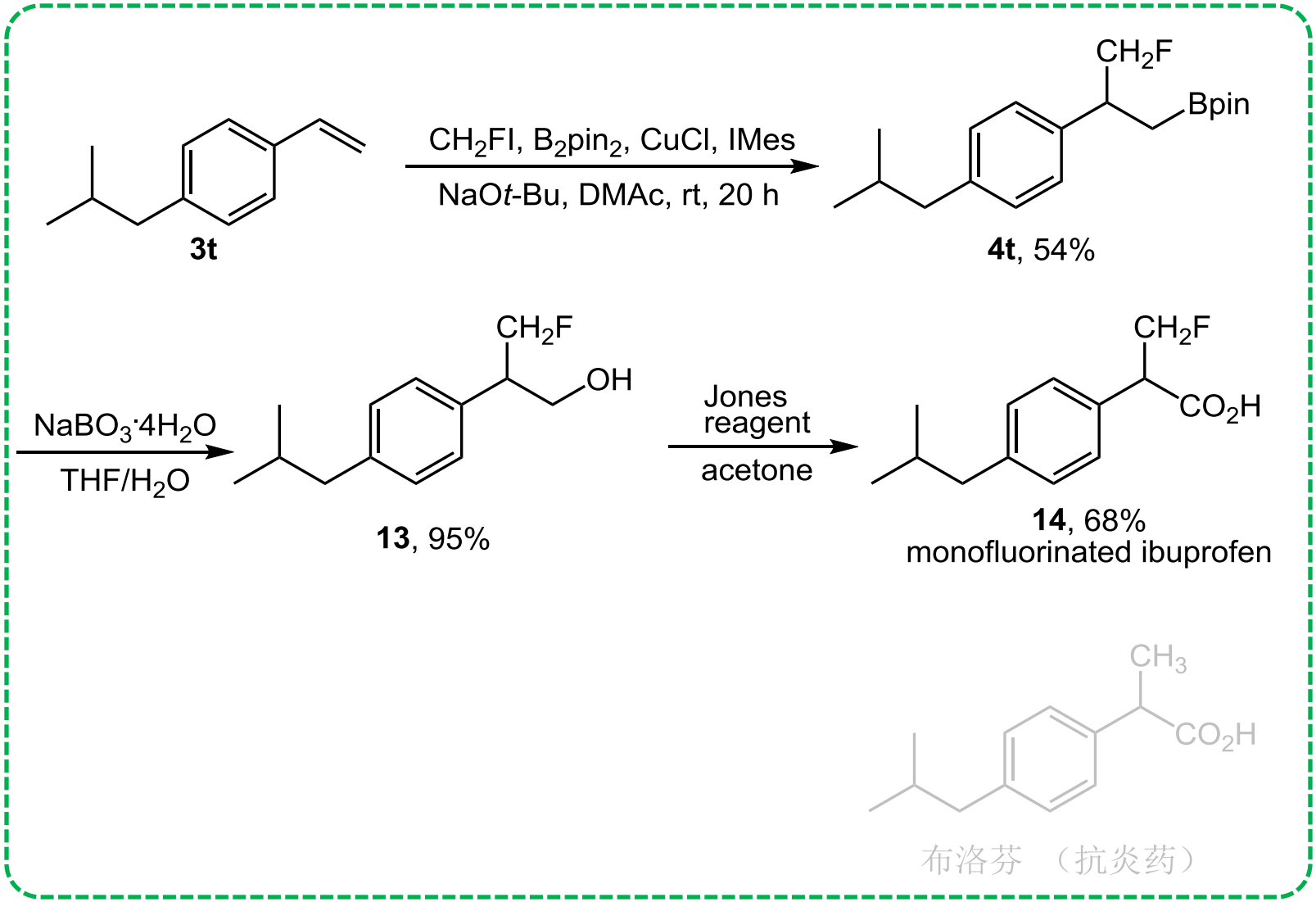
Transformations of Compound 4a



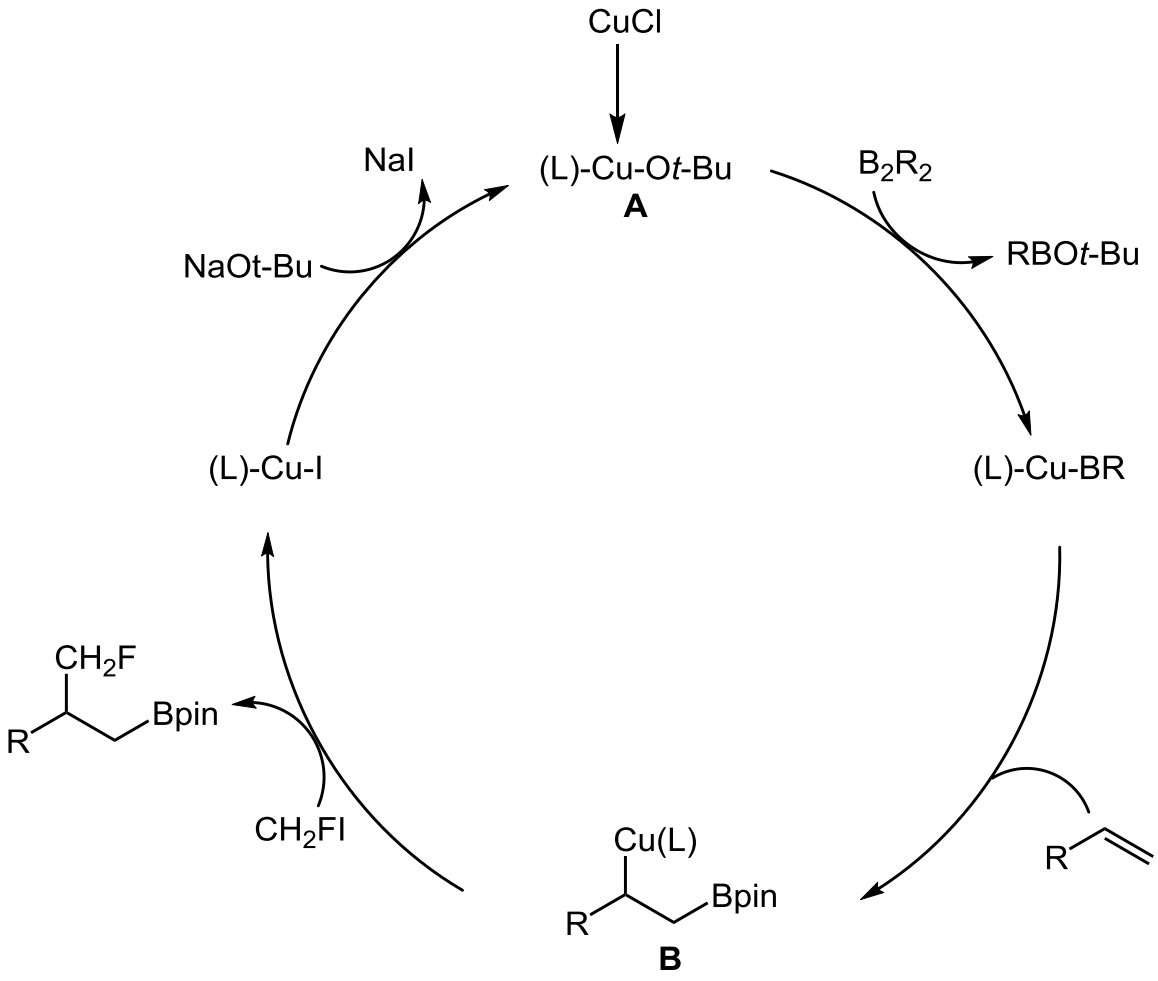
Transformations of Compound 4a



Preparation of Monofluorinated Ibuprofen



Proposed Catalytic Cycle



The First Paragraph

Writing Strategy

The importance of incorporation of fluorine atom into molecules

↓

Methods for synthesis of fluoromethylated compounds

The First Paragraph

The presence of fluorine atom(s) in a group could affect its electronic and physicochemical properties. For instance, fluoromethyl group (CH_2F) normally acts as a metabolically stable bioisostere for methyl group (CH_3). Furthermore, the CH_2F group is also considered as a CH_2OH group mimic. As a consequence, the fluoro-methylated compounds have widespread applications in agrochemicals, pharmaceuticals, and materials. Conventionally, the fluoromethylated compounds are prepared via C-H fluorination of CH_3-containing compounds or fluorination of functionalized substrates. However, these methods have some limitations, such as narrow substrate scope, low regioselectivity, or prior installation of a functional group.

The First Paragraph

Alternatively, the method of choice for the preparation of fluoromethylated compounds involves indirect fluoromethylation using fluoromethylating agents bearing a suitable auxiliary, followed by the removal of the auxiliary. Compared with the indirect methods, the direct fluoromethylation through electrophilic, nucleophilic, and radial pathways are more attractive because of the atom and step economy. Recently, the groups of Zhang, Hu, Wang, and Baran have also reported transition metal catalyzed direct fluoromethylation of aryl boronic acids(esters), halides, and zinc reagents.

The Last Paragraph

Writing Strategy

The summary of their work

↓

The significance of this work

↓

The next plan of the group

The Last Paragraph

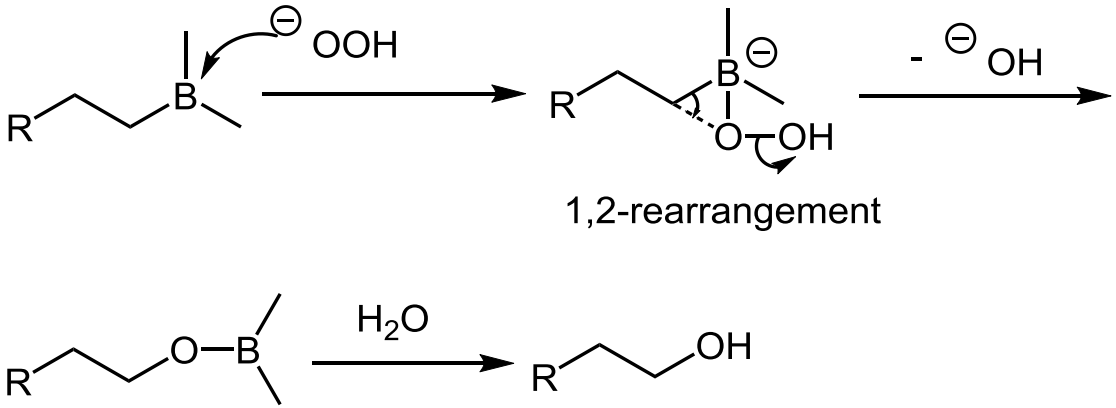
In summary, we have developed a copper-catalyzed regioselective borylfluoromethylation of acrylamides, styrenes, and unactivated alkenes with fluoromethyl iodide and diboron reagents. This reaction proceeded smoothly to deliver *β*-fluoromethyl alkylboronates in good yields. The resulting products are useful synthetic intermediates for various potentially valuable fluoromethylated compounds. Efforts to explore Cu-catalyzed difunctionalization reactions for the preparation of other fluoroalkylated compounds are ongoing in our laboratory.

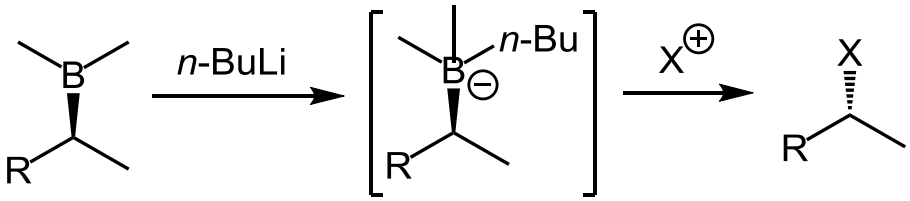
Representative Examples

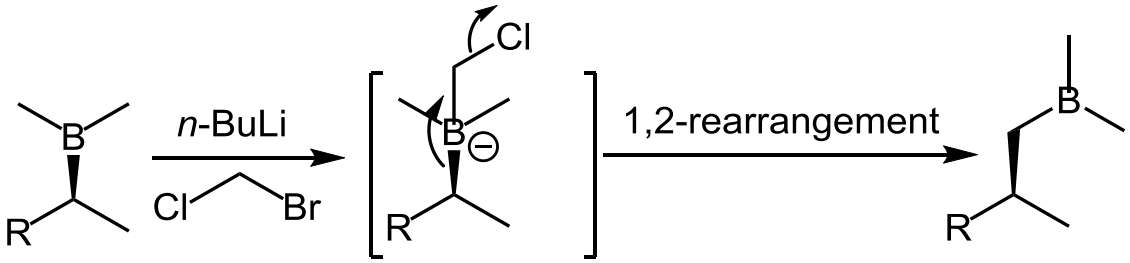
However, these methods **have some limitations**, such as narrow substrate scope, low regioselectivity, or prior installation of a functional group. (对先前发展的一些方法存在不足的描写)

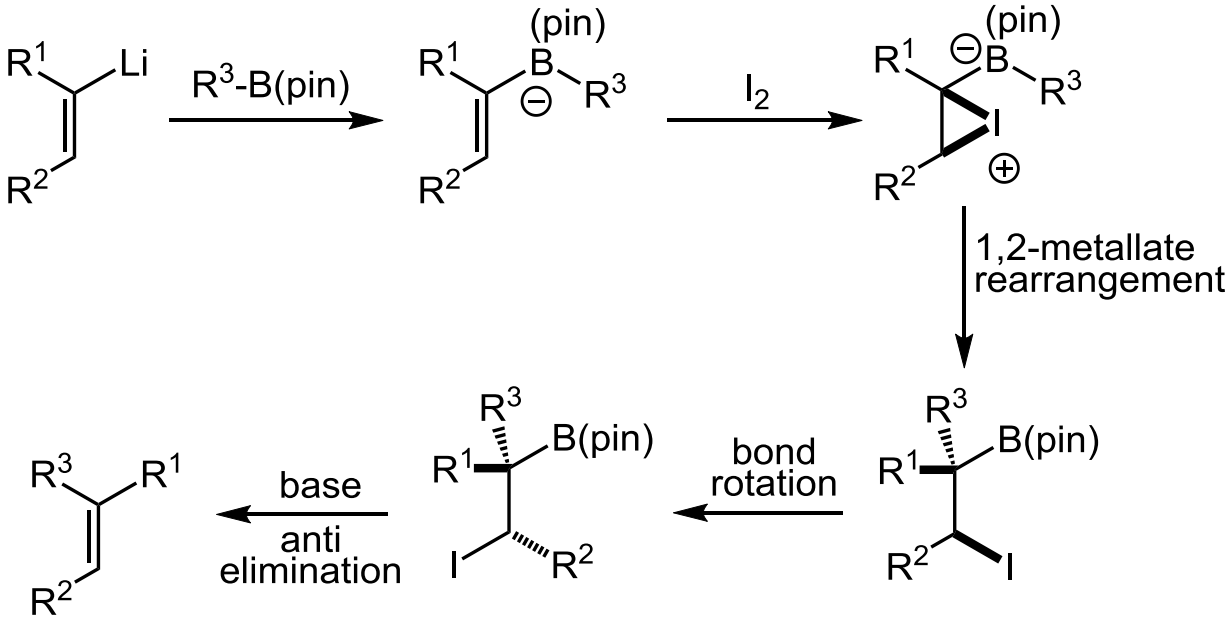
Inspired by these works, **we envisioned that** the boryl-cupration of alkenes, followed by electrophilic fluoro-methylation, might serve as a novel method for fluoromethylation of alkenes. (提出课题设想的描写）

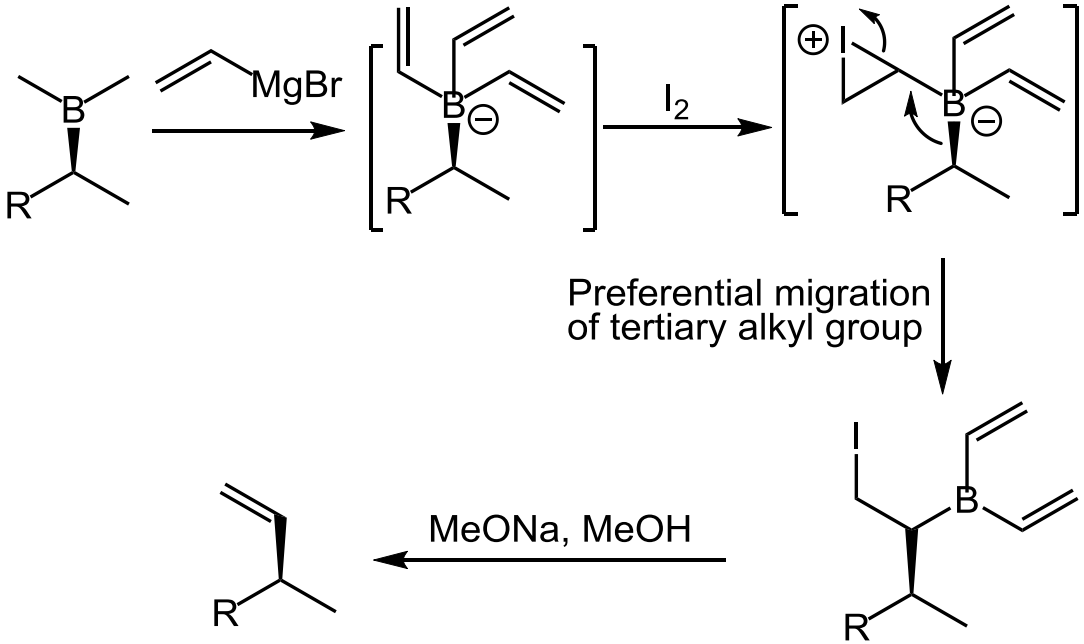
To illustrate the application of this protocol, the further transformations of the borylfluoromethylated product **4a** were surveyed. (产物衍生的描写）

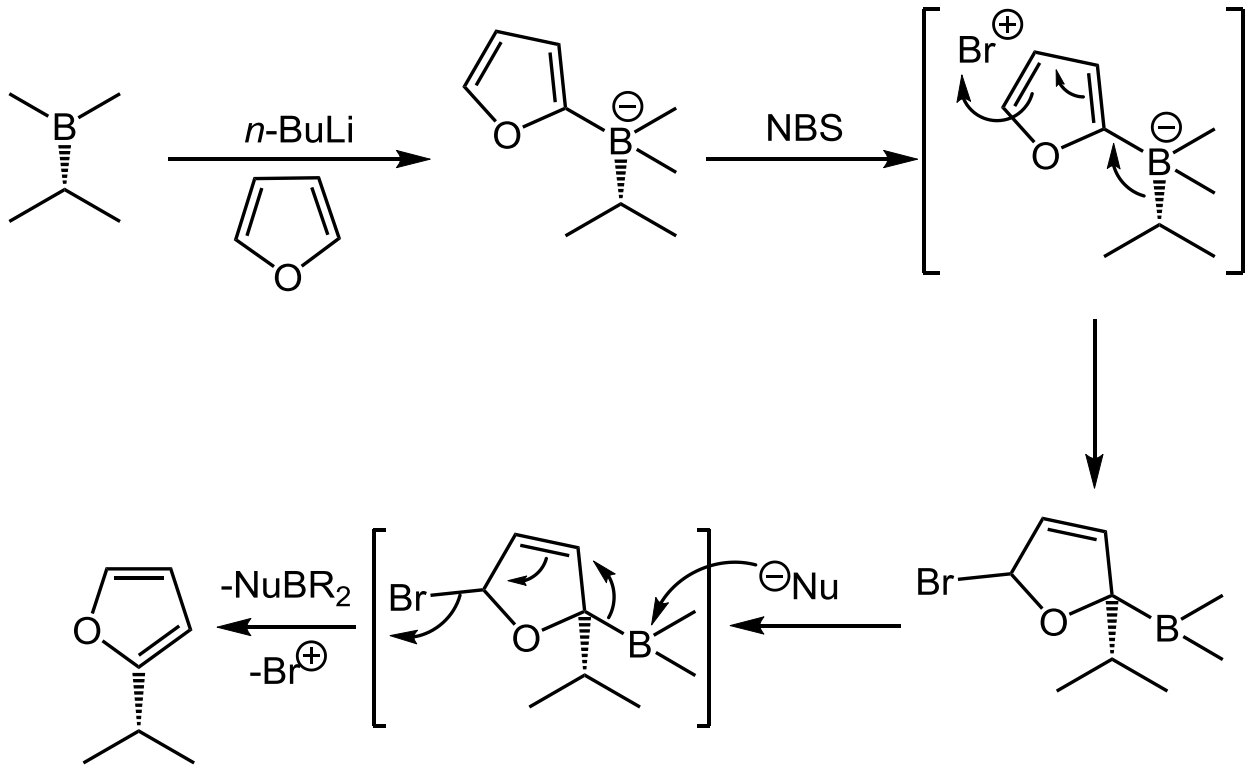

OOH
R
B
R
B
O
OH
- OH
1,2-rearrangement
R
O
B
H2O
R
OH


B
R
n-BuLi
B
n-Bu
R
X⊕
X
R


B
R
n-BuLi
Cl
Br
Cl
B
R
1,2-rearrangement
B
R


R1
Li
R2
R3-B(pin)
(pin)
B
R3
I2
I
1,2-metallate
rearrangement
bond
rotation
B(pin)
base
anti
elimination


MgBr
B
R
I2
I
Preferential migration
of tertiary alkyl group
MeONa, MeOH


B
n-BuLi
O
O
B
NBS
Br
O
B
Br
O
B
⊖Nu
Br
O
B
-NuBR2
-Br⊕
O