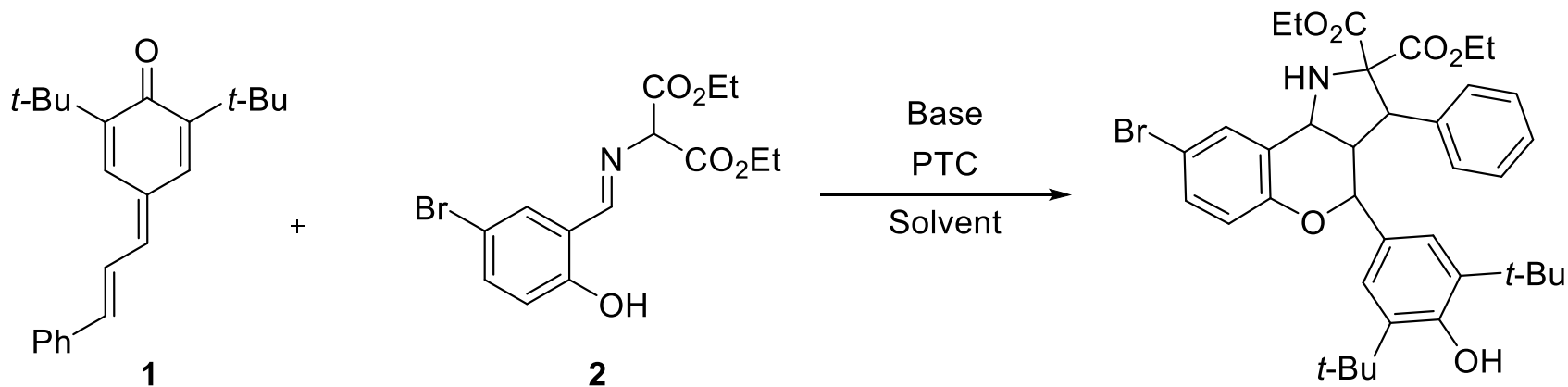


Synthesis of  
Chromeno[4,3-*b*]pyrrolidine  
Derivatives using  
**Phase Transfer Catalysts**

Category : Chemistry

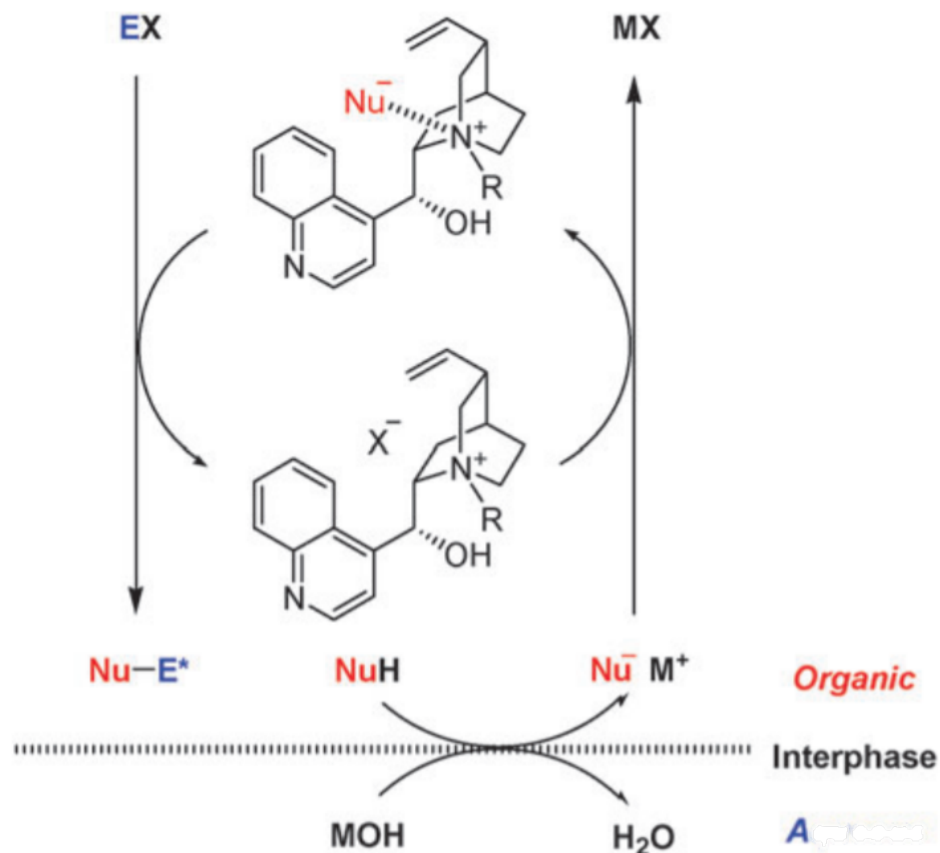
# Introduction



Target reaction equation

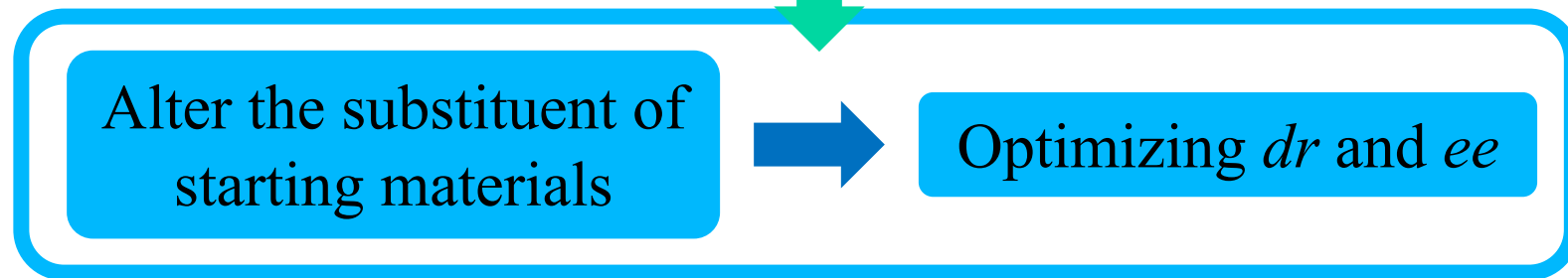
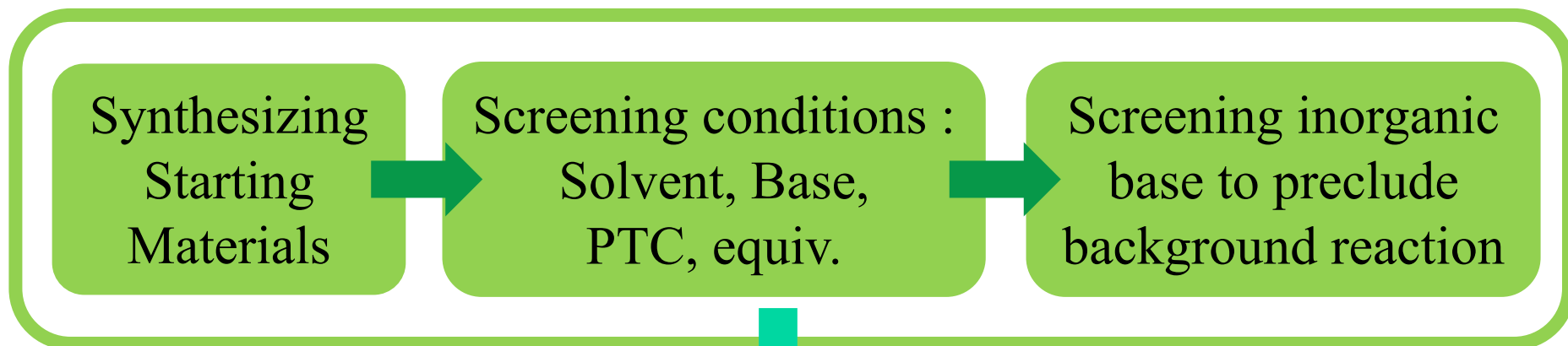
# Introduction

- PTC is soluble in organic phase
- PTC is also soluble in aqueous phase because it's a Quaternary Ammonium Salt
- PTC can assist inorganic base to catalyze the reaction



# Methodology

## Preliminary works



## Research emphasis

# Results

	solvent	PTC	Base	eq. (1a:2a:PTC:Base)	time (hr)	yield [%]
1	dichloromethane	TBAI	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	5	45
2	dichloromethane	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	2	70
3	dichloromethane	TBAB	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	6	58
4	dichloromethane	TBAF	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	2	34
5	dichloromethane	TMAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	2	26
6	dichloromethane	TOAB	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	2	70
7	dichloroethane	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	2	25
8	chloroform	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	2	63
9	ethyl acetate	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	1	62
10	toluene	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	3	60
11	tetrahydrofuran	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	1	54
12	dimethyl sulfoxide	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	1	16
13	acetonitrile	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	1	68
14	methanol	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	24	-
15	dichloromethane	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.1:0.1:3.0	1	70
16	dichloromethane	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.0:1.3:0.1:3.0	2	75
17	dichloromethane	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.1:1.0:0.1:3.0	1	61
18	dichloromethane	TBAC	K <sub>2</sub> CO <sub>3</sub>	1.3:1.0:0.1:3.0	1	48

# Results

Entry	Quinine	R <sup>1</sup>	X	Time ( hr )	Yield ( % )	ee ( % )
1	QN	Ph	Cl	3	66	10
2	QN	3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	Br	18	56	11
3	QN	Naphthalene	Cl	1	54	15
4	QN	Anthracene	Cl	24	79	26
5	CD	3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	Br	24	68	11
6	CD	Anthracene	Cl	24	48	18
7	QD	3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	Br	48	75	6
8	CN	3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	Br	48	66	6

# Results

Entry	R <sup>1</sup>	R <sup>2</sup>	Time (hr)	Yield (%)	Yield of Intermediate (%)	<i>ee</i> (%)
1	3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	Bn	3	26	52	6
2	3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	Allyl	24	74	0	6
3	3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	Thiourea derivative	3	41	0	0
4	3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	Amide-Ph	18	28	52	0
5	Amide-Ph	H	18	46	14	0
6	Amide-3,5-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	H	18	46	12	29

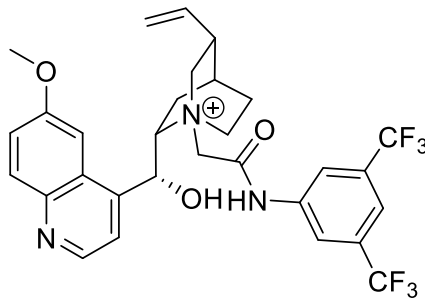
# Results

Entry	Base	1 hour	2 hours	3 hours	24 hours
1	KOH	18	28	30	84
2	NaOH	48	18	19	22
3	K <sub>3</sub> PO <sub>4</sub>	0	0	7	50
4	Na <sub>2</sub> CO <sub>3</sub>	0	0	0	0
5	K <sub>2</sub> CO <sub>3</sub>	27	49	57	80
6	Cs <sub>2</sub> CO <sub>3</sub>	71	82	ND	84
7	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	0	0	0	0

# Conclusions

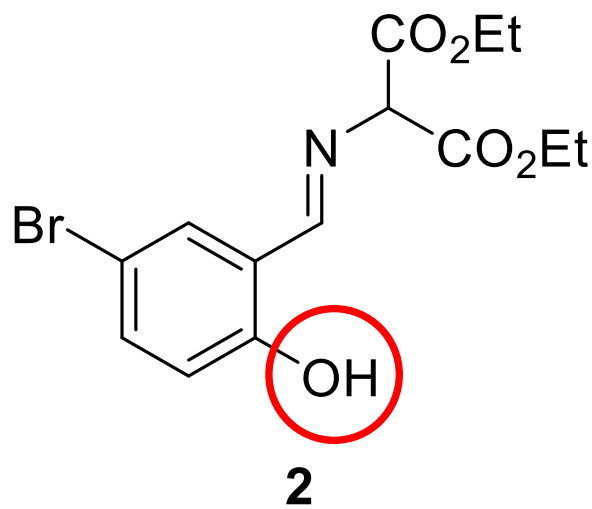
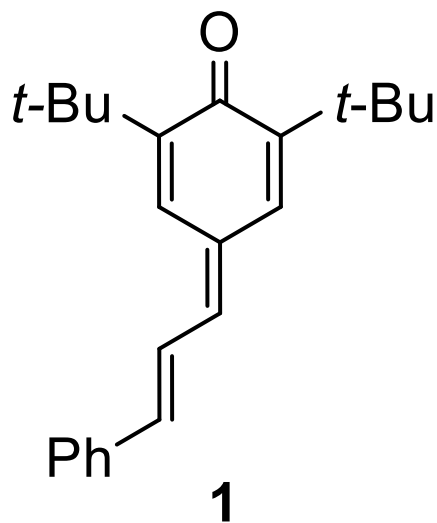
	Type	equiv.	Dosage
Starting material 1	X	1.0	0.2 mmol
Starting material 2	X	1.3	0.26 mmol
PTC (achiral)	TBAC	0.4	0.08 mmol
Base	K <sub>2</sub> CO <sub>3</sub>	3.0	0.6 mmol
Solvent	DCM	X	0.5 mL

The best chiral PTC : Main structure : QN, R<sup>1</sup> = Amide-3,5-CF<sub>3</sub>C<sub>6</sub>H<sub>3</sub> , R<sup>2</sup> = H



# Interpretation of these results

The reason of low *ee* of our experiment is that the structure of starting material **1** is flat, and the hydroxyl of starting material **2** has a great activity of reacting.



# Future works

- Place protecting group on the hydroxyl of starting material 2
- Change the  $R^1$  on chiral PTCs to different electron-withdrawing groups
- Alter the substituent of starting materials

# References

- Organic Chemistry Portal. Michael Addition. From <https://www.organic-chemistry.org/namedreactions/michael-addition.shtm>
- Xin Liu, Dongming Lu, Jia-Hong Wu, Jian-Ping Tan, Chunhui Jiang, Guowei Gao, Tianli Wang (2020). Stereoselective Synthesis of CF<sub>3</sub>-Containing Spirooxindoles via 1,3-Dipolar Cycloaddition by Dipeptide-Based Phosphonium Salt Catalysis. From <https://onlinelibrary.wiley.com/doi/full/10.1002/adsc.202000001>