

Literature Report

Atroposelective Synthesis of Axially Chiral Arylpyrroles and Styrenes

Reporter : Zhong Yan

Checker : Ji Zhou

Date : 2017-06-05

Tan, B. *et al.* *J. Am. Chem. Soc.* **2017**, *139*, 1714.

Tan, B. *et al.* *Nat. Commun.* **2017**, *8*, 15238.

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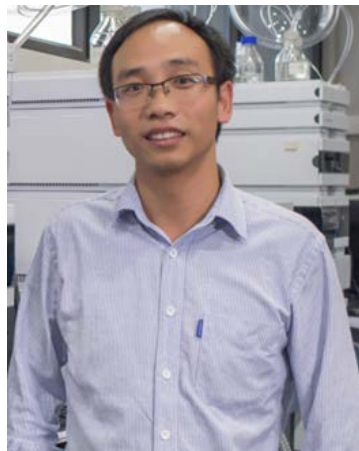
1 Introduction

2 Atroposelective Synthesis of Axially Chiral Arylpyrroles

3 Atroposelective Synthesis of Axially Chiral Styrenes

4 Summary

CV of Bin Tan



Bin Tan

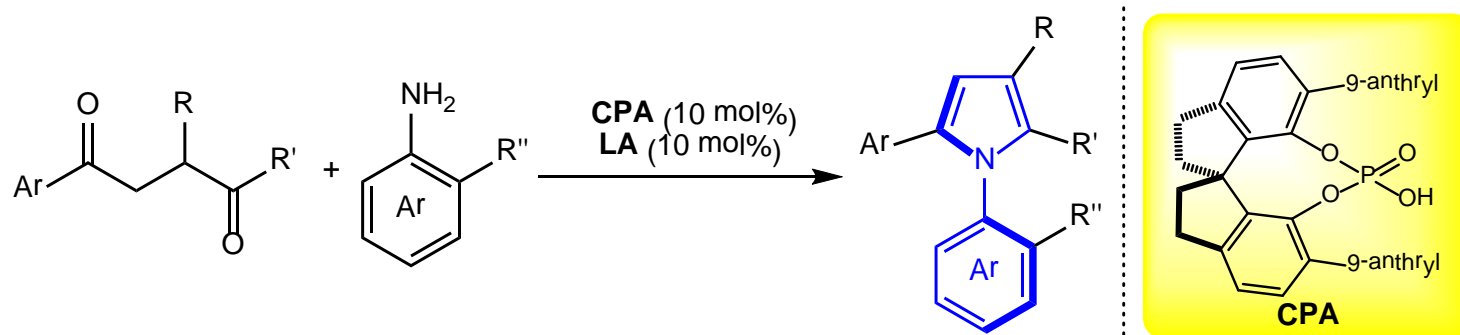
Education:

- 2002–2005 M.S., Xiamen University
- 2006–2010 Ph.D., Nanyang Technological University, Singapore
- 2010–2012 Postdoc., The Scripps Research Institute
- 2012–2017 Associate Professor., South University of Science and Technology

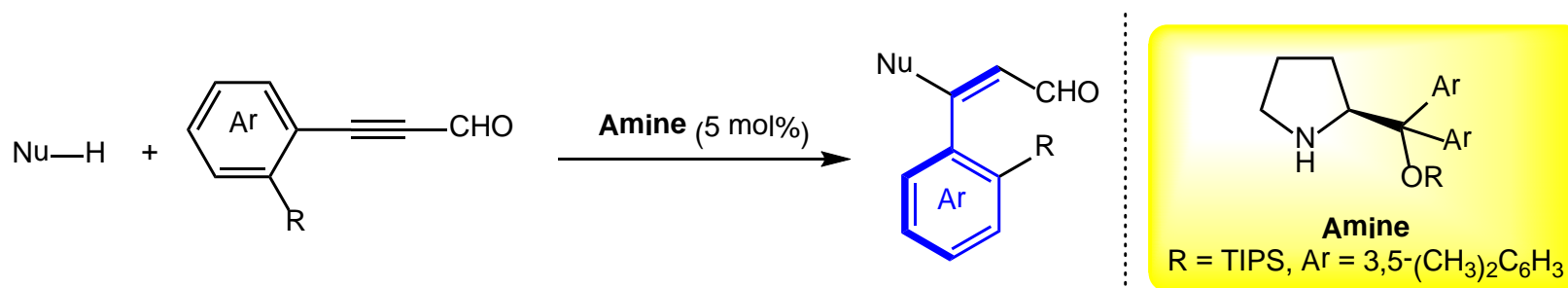
Research:

- ◆ 核心骨架结构导向的催化不对称合成
- ◆ 现代催化体系和绿色合成新方法的开发
- ◆ 金属与有机催化协同的催化体系应用
- ◆ 手性药物的开发和天然产物策略全合成

Introduction

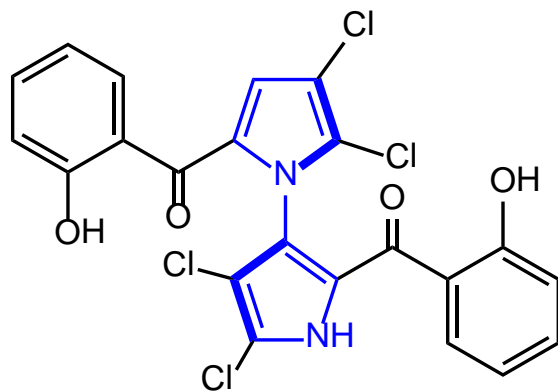


Tan, B. *et al.* *J. Am. Chem. Soc.* **2017**, 139, 1714.

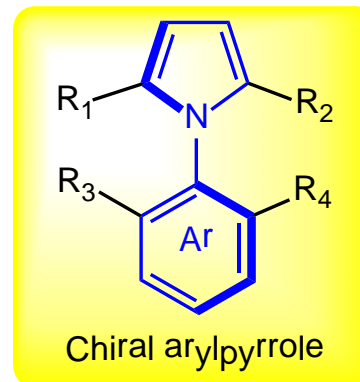


Tan, B. *et al.* *Nat. Commun.* **2017**, 8, 15238.

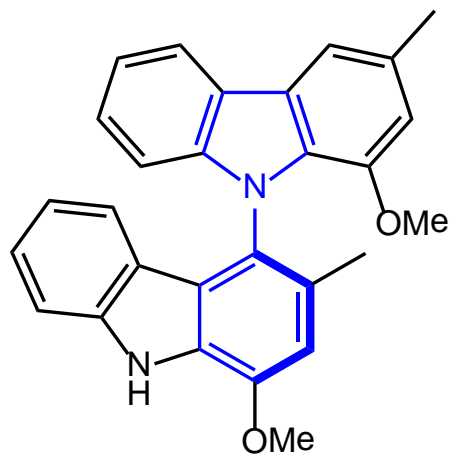
Axially Chiral Arylpyrroles



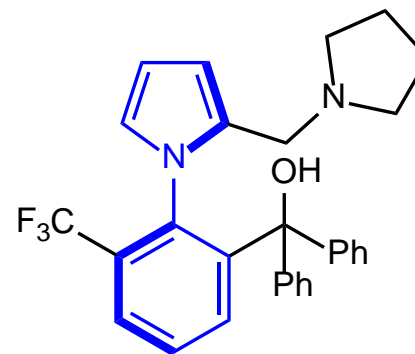
A
Marinopyrrole



Chiral arylpyrrole

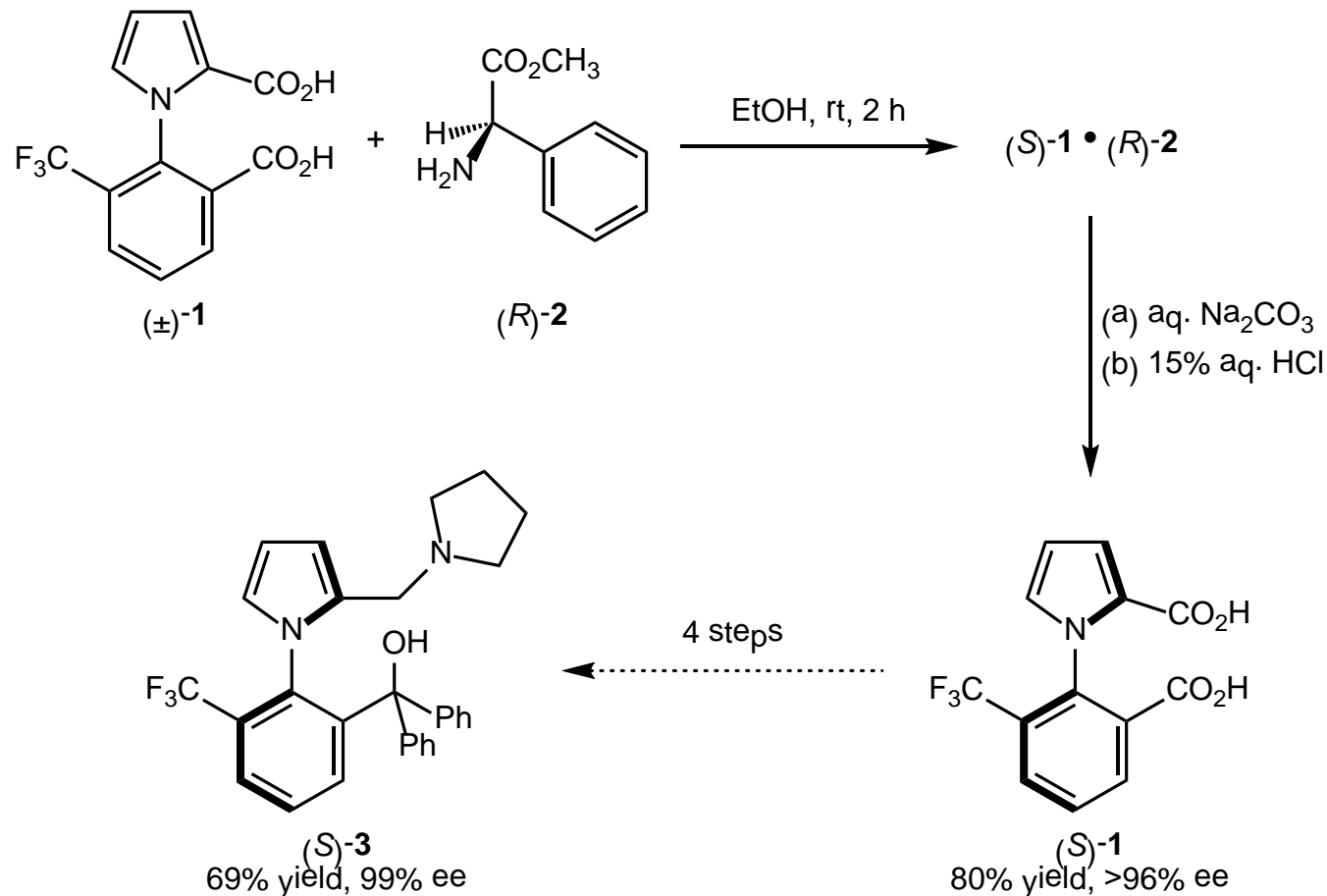


B
Murrastifoline-F



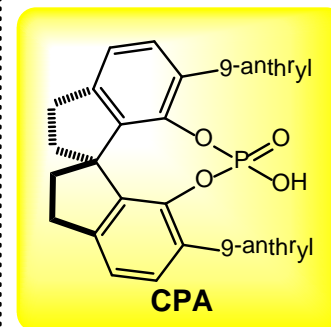
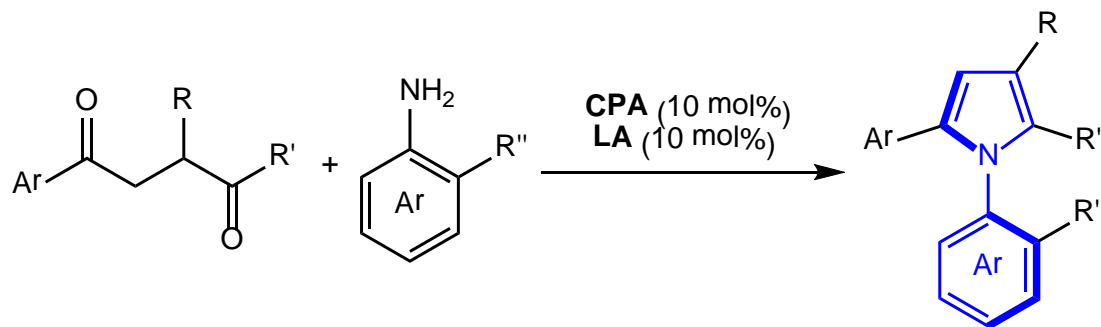
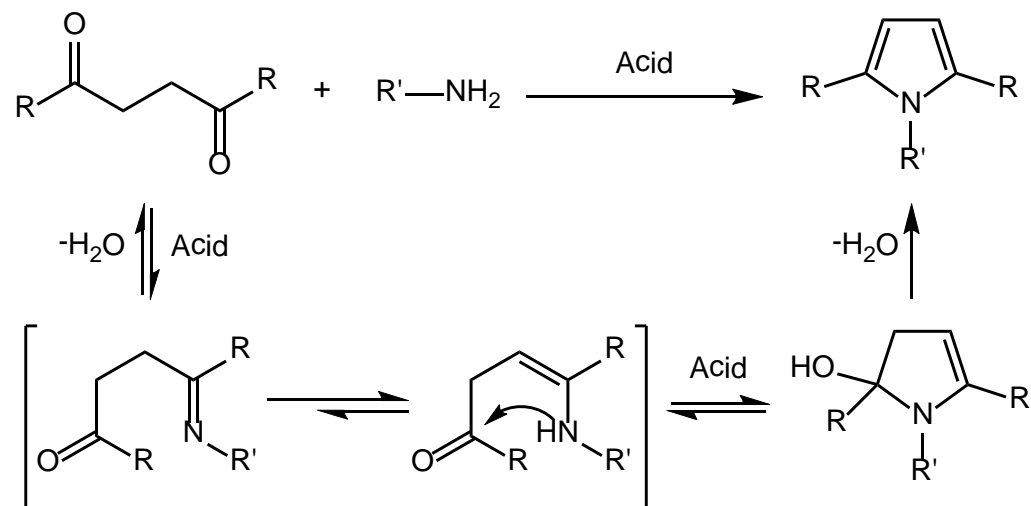
C
Amino alcohol
chiral ligand

Resolution of Racemic Arylpyrroles



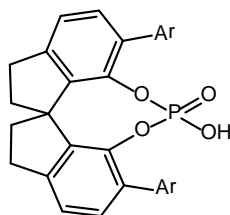
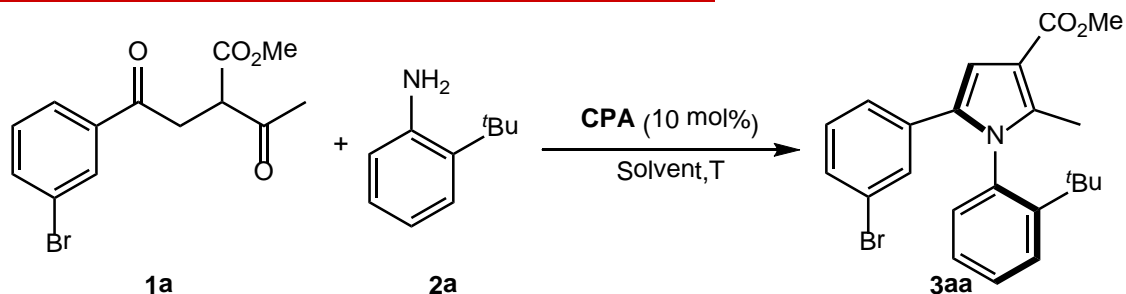
Asymmetric Paal-Knorr Reaction

Paal-Knorr reaction

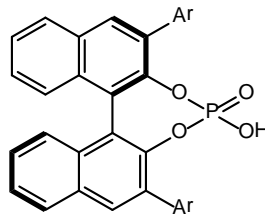


30 examples
up to 95% yield
up to 97% ee

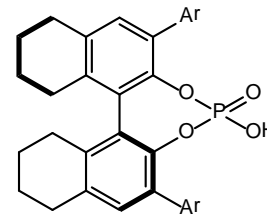
Asymmetric Paal-Knorr Reaction



(*R*)-**C1**: Ar = 9-phenanthryl
 (*R*)-**C2**: Ar = 3,5-(CF₃)₂C₆H₃
 (*S*)-**C3**: Ar = 9-anthryl
 (*S*)-**C4**: Ar = 2,4,6-*i*Pr₃C₆H₂
 (*S*)-**C5**: Ar = 1-pyrenyl
 (*S*)-**C6**: Ar = 1-naphthyl
 (*S*)-**C7**: Ar = 4-ClC₆H₄



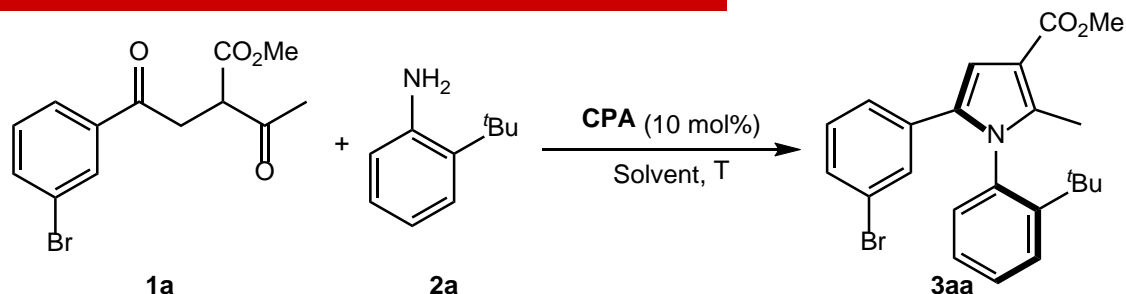
(*R*)-**C8**: Ar = 9-phenanthryl
 (*R*)-**C9**: Ar = 9-anthryl



(*S*)-**C10**: Ar = 9-phenanthryl

Entry	CPA	T	Solvent	Yield (%)	Ee (%)
1	(<i>R</i>)- C1	rt	CCl ₄	94	-68
2	(<i>R</i>)- C2	rt	CCl ₄	90	-13
3	(<i>S</i>)- C3	rt	CCl ₄	94	72
4	(<i>S</i>)- C4	rt	CCl ₄	91	70
5	(<i>S</i>)- C5	rt	CCl ₄	93	66
6	(<i>S</i>)- C6	rt	CCl ₄	92	53
7	(<i>S</i>)- C7	rt	CCl ₄	90	14

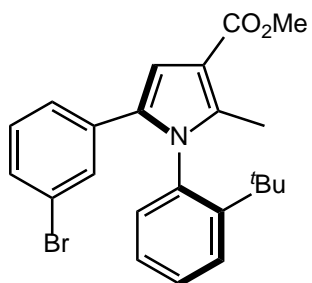
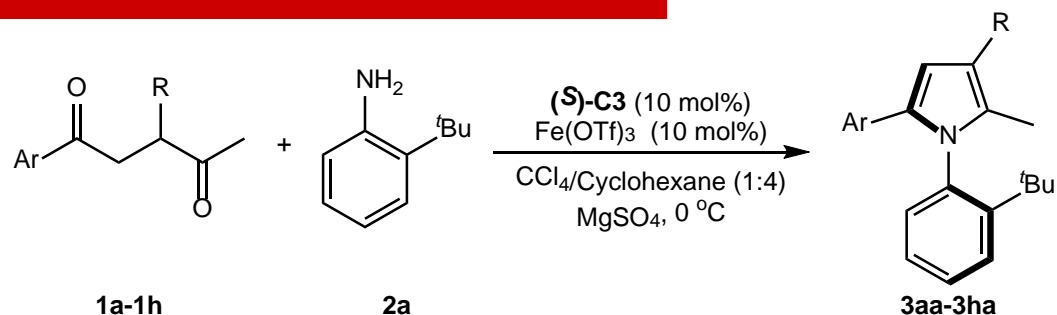
Asymmetric Paal-Knorr Reaction



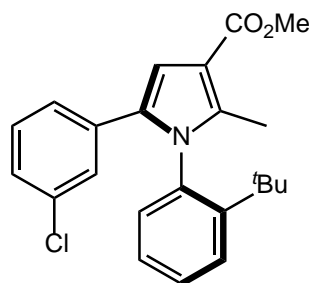
Entry	CPA	T	Solvent	Yield (%)	Ee (%)
8	(R)-C8	rt	CCl ₄	92	<5
9	(R)-C9	rt	CCl ₄	91	6
10	(S)-C10	rt	CCl ₄	92	-9
11	(S)-C3	rt	DCM	71	43
12	(S)-C3	rt	Toluene	89	61
13	(S)-C3	rt	Cyclohexane	92	61
14	(S)-C3	rt	MeOH	57	-52
15	(S)-C3	0	CCl ₄	82	75
16 ^a	(S)-C3	0	CCl ₄	84	78
17 ^b	(S)-C3	0	CCl ₄	85	88
18 ^b	(S)-C3	0	CCl ₄ /Cyclohexane (1:4)	95	96

^a MgSO₄ (100 mg) was added, ^b MgSO₄ (100 mg) and Fe(OTf)₃ (10 mol%) was added.

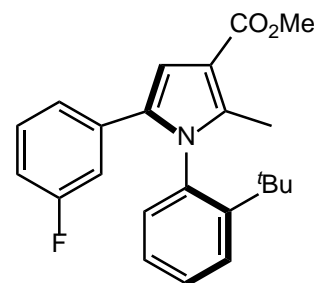
Substrate Scope



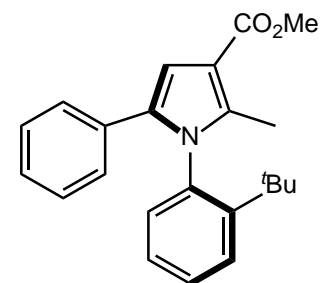
3aa
4.0 d, 96% ee (95%)



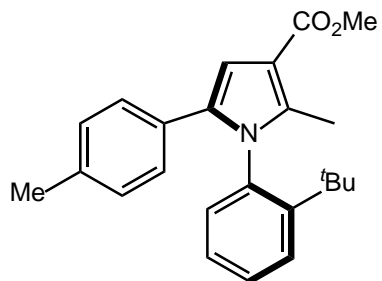
3ba
4.0 d, 95% ee (93%)



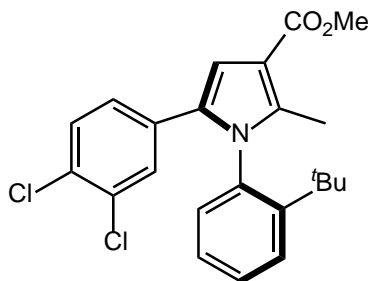
3ca
3.5 d, 95% ee (91%)



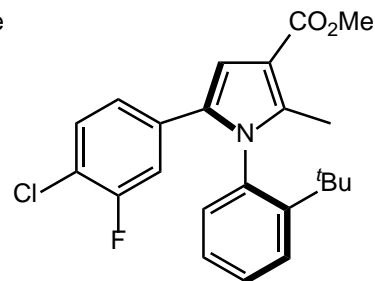
3da
4.0 d, 90% ee (93%)



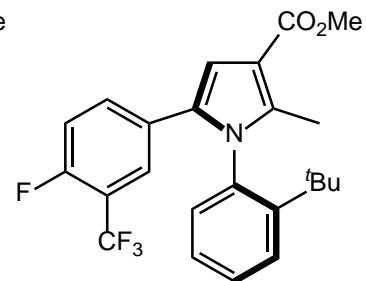
3ea
4.0 d, 86% ee (91%)



3fa
4.0 d, 94% ee (94%)

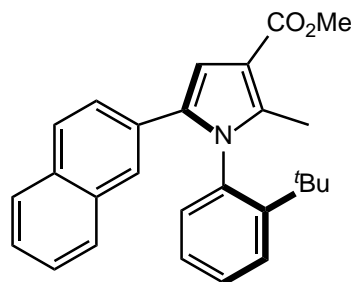
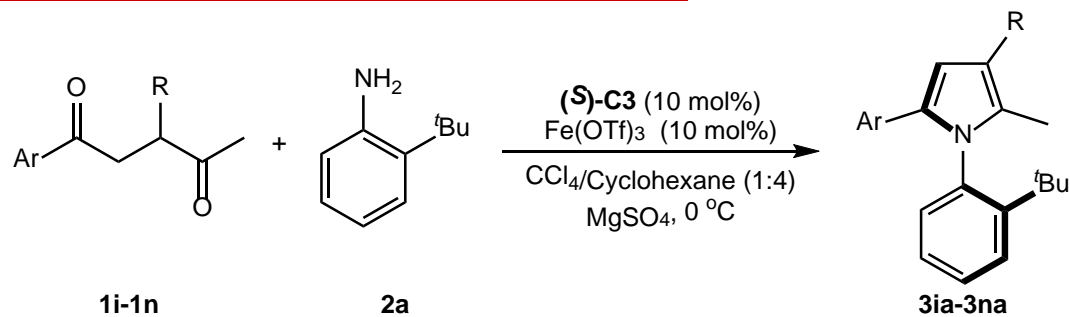


3ga
4.0 d, 95% ee (92%)

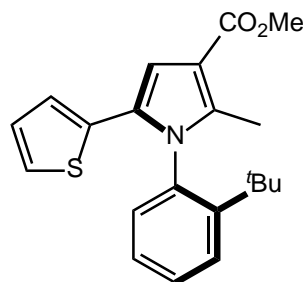


3ha
3.5 d, 97% ee (93%)

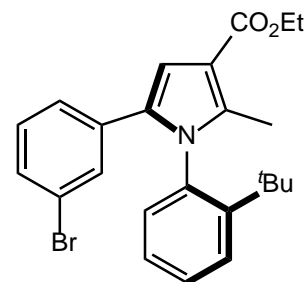
Substrate Scope



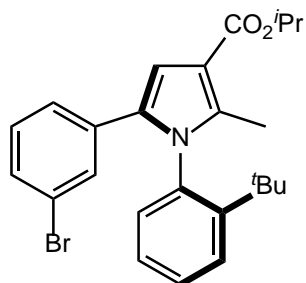
3ia
4.5 d, 86% ee (86%)



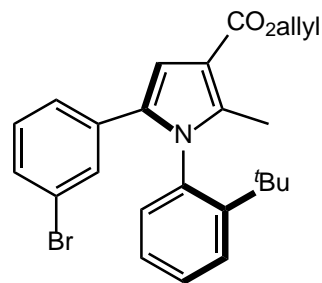
3ja
4.5 d, 86% ee (93%)



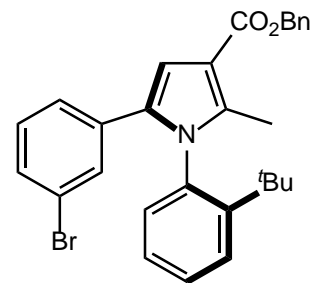
3ka
4.0 d, 96% ee (94%)



3la
4.0 d, 96% ee (92%)

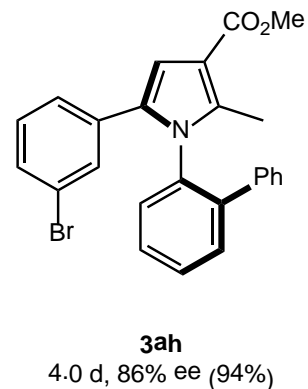
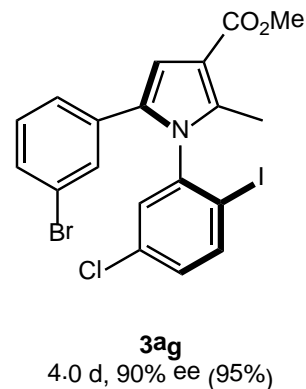
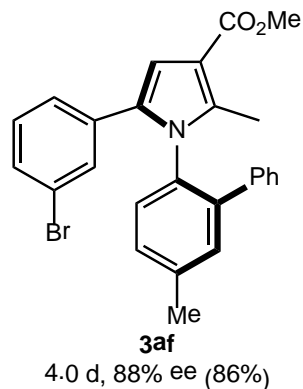
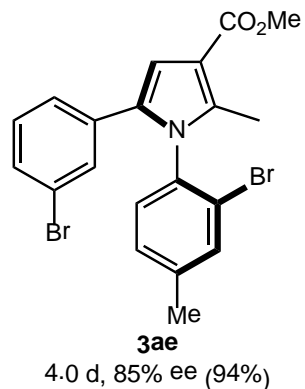
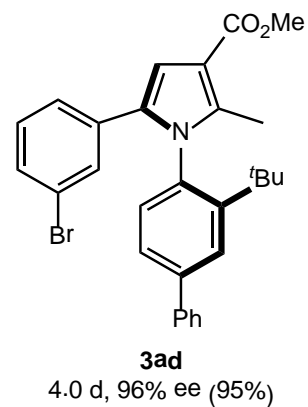
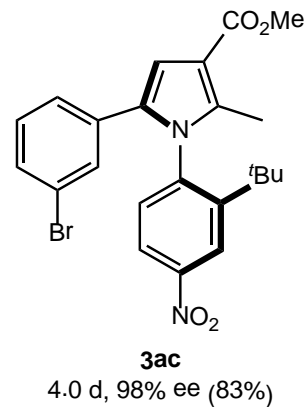
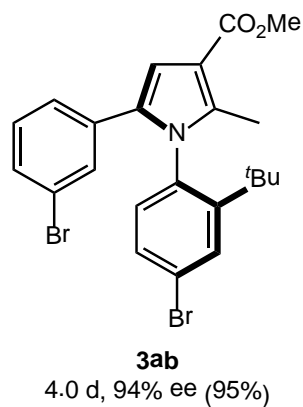
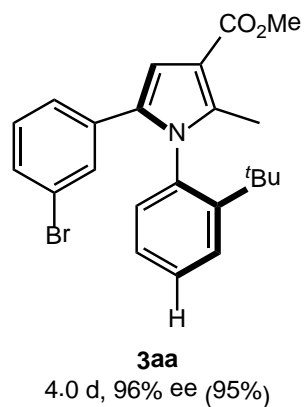
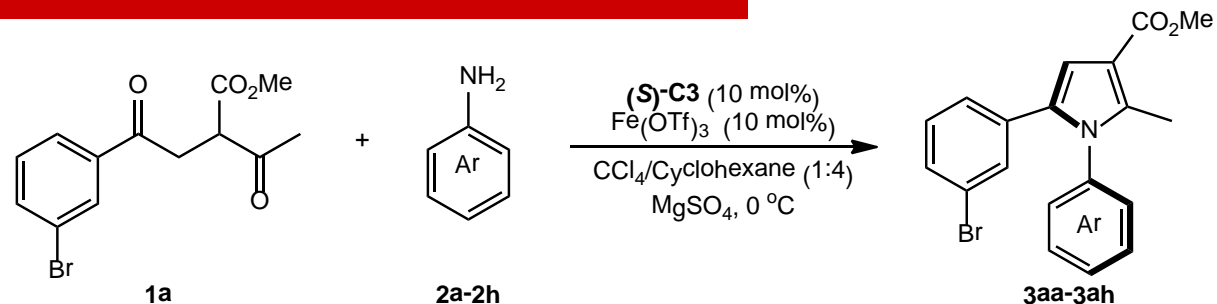


3ma
4.0 d, 95% ee (90%)

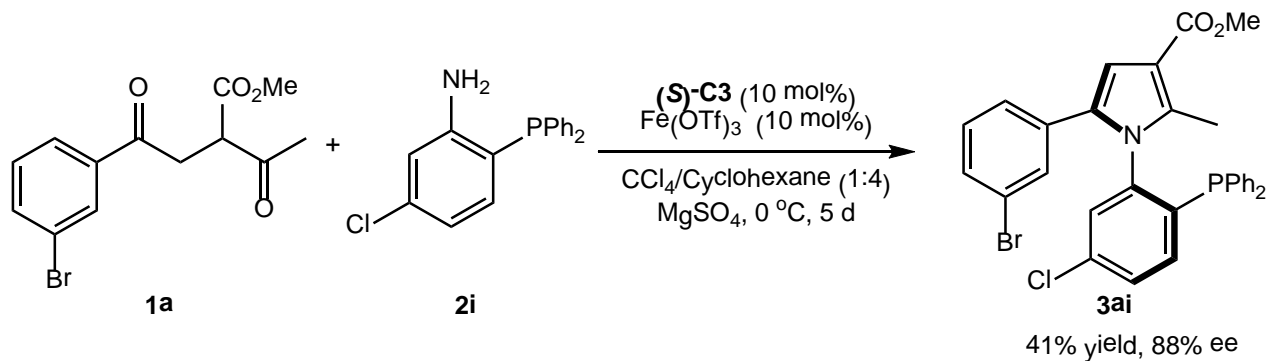
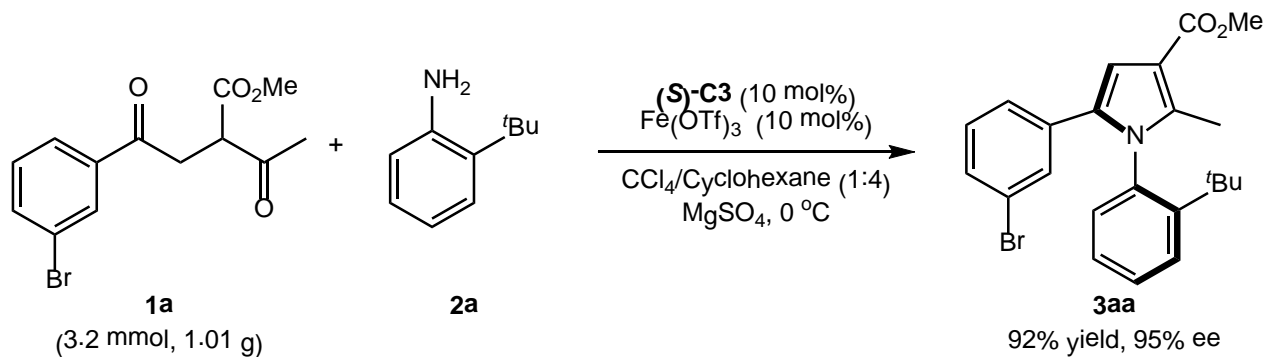


3na
4.0 d, 94% ee (91%)

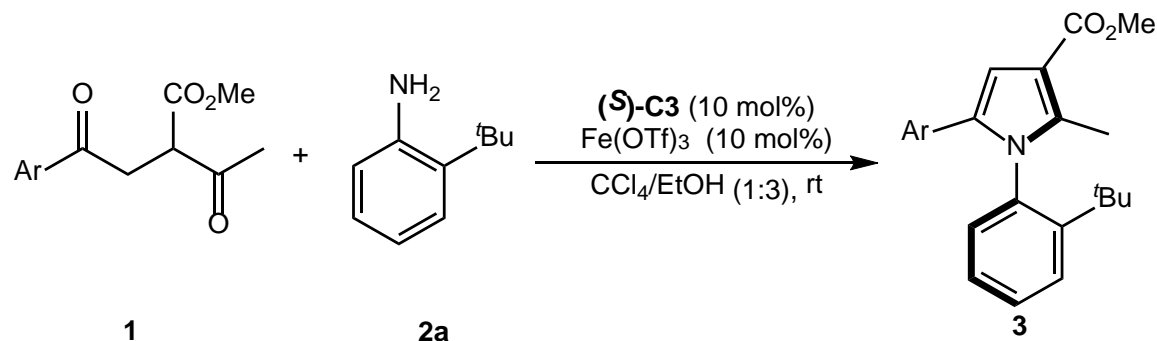
Substrate Scope



Synthetic Application



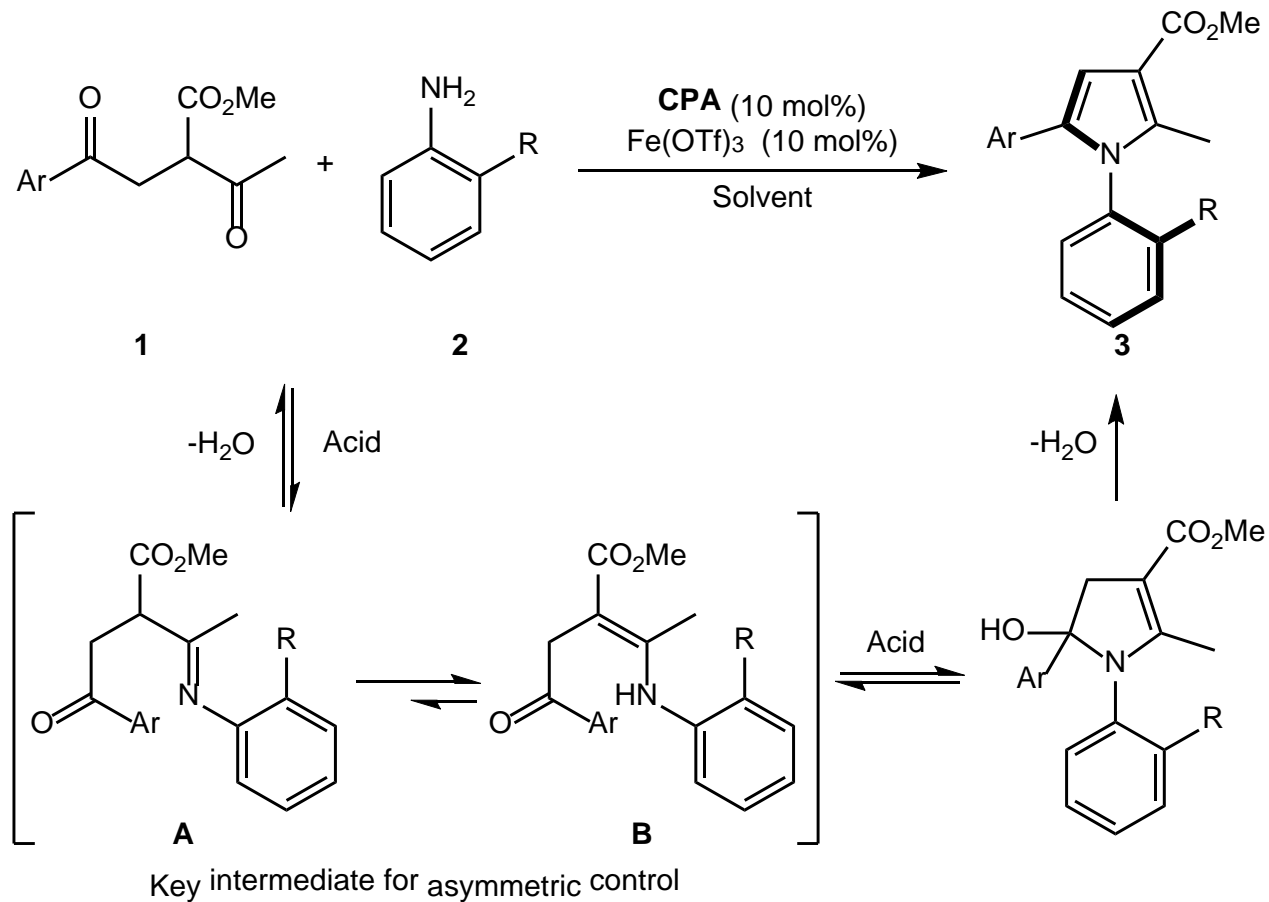
Generality of the Solvent-Dependence



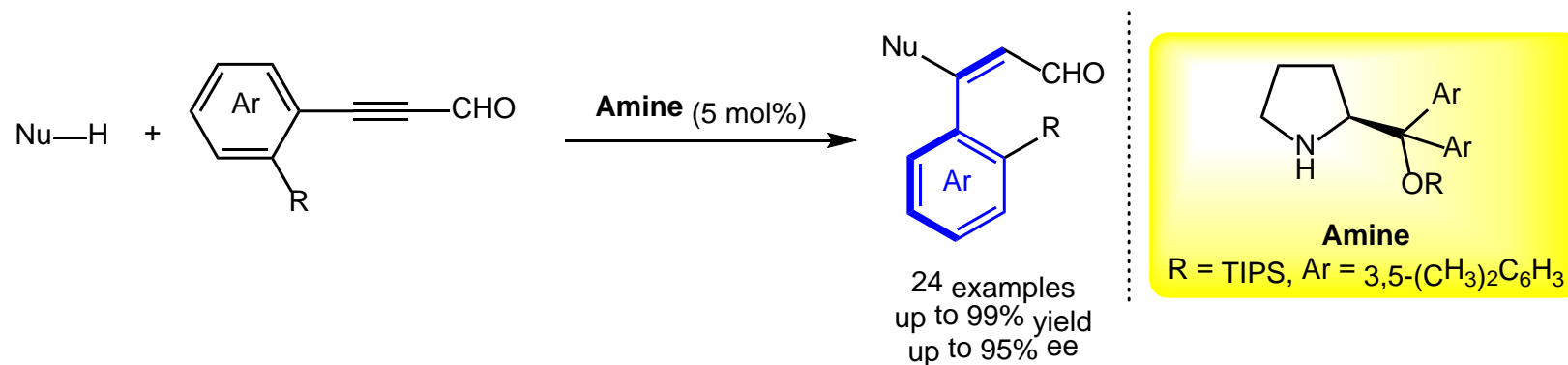
Entry ^a	Ar	(S)-3	Yield (%) ^b	Ee (%) ^c
1	3-Br-C ₆ H ₄	3aa	83	-75
2	3-Cl-C ₆ H ₄	3ba	83	-76
3	3-F-C ₆ H ₄	3ca	82	-76
4	2-naphthyl	3ia	77	-73
5	2-thienyl	3ja	83	-74

^a **1** (0.15 mmol), **2a** (0.1 mmol), **(S)-C3** (0.01 mmol) and $\text{Fe}(\text{OTf})_3$ (0.01 mmol) in CCl_4/EtOH (0.5 mL/1.5 mL). ^b Isolated yield. ^c Determined by HPLC.

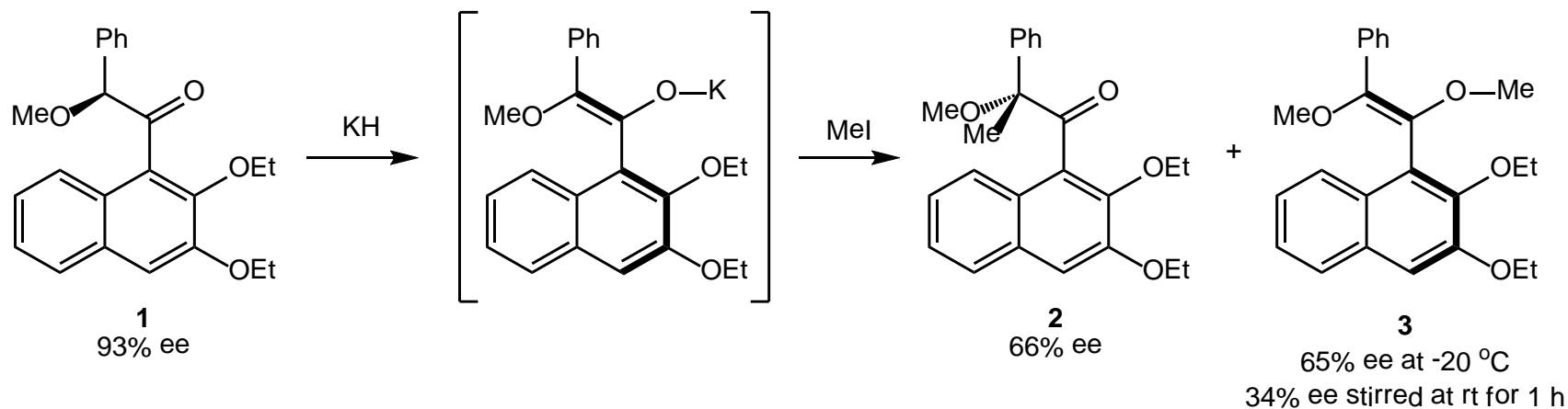
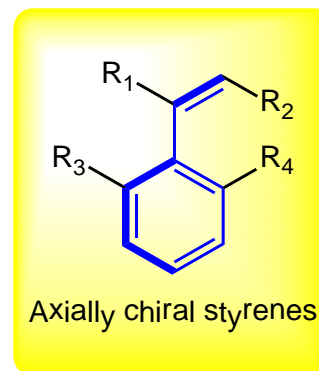
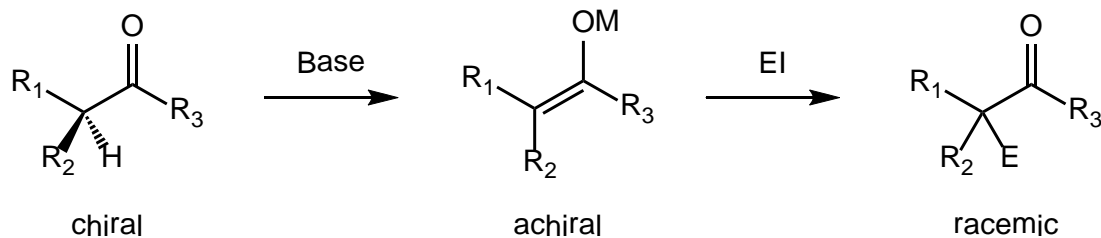
Proposed Reaction Process



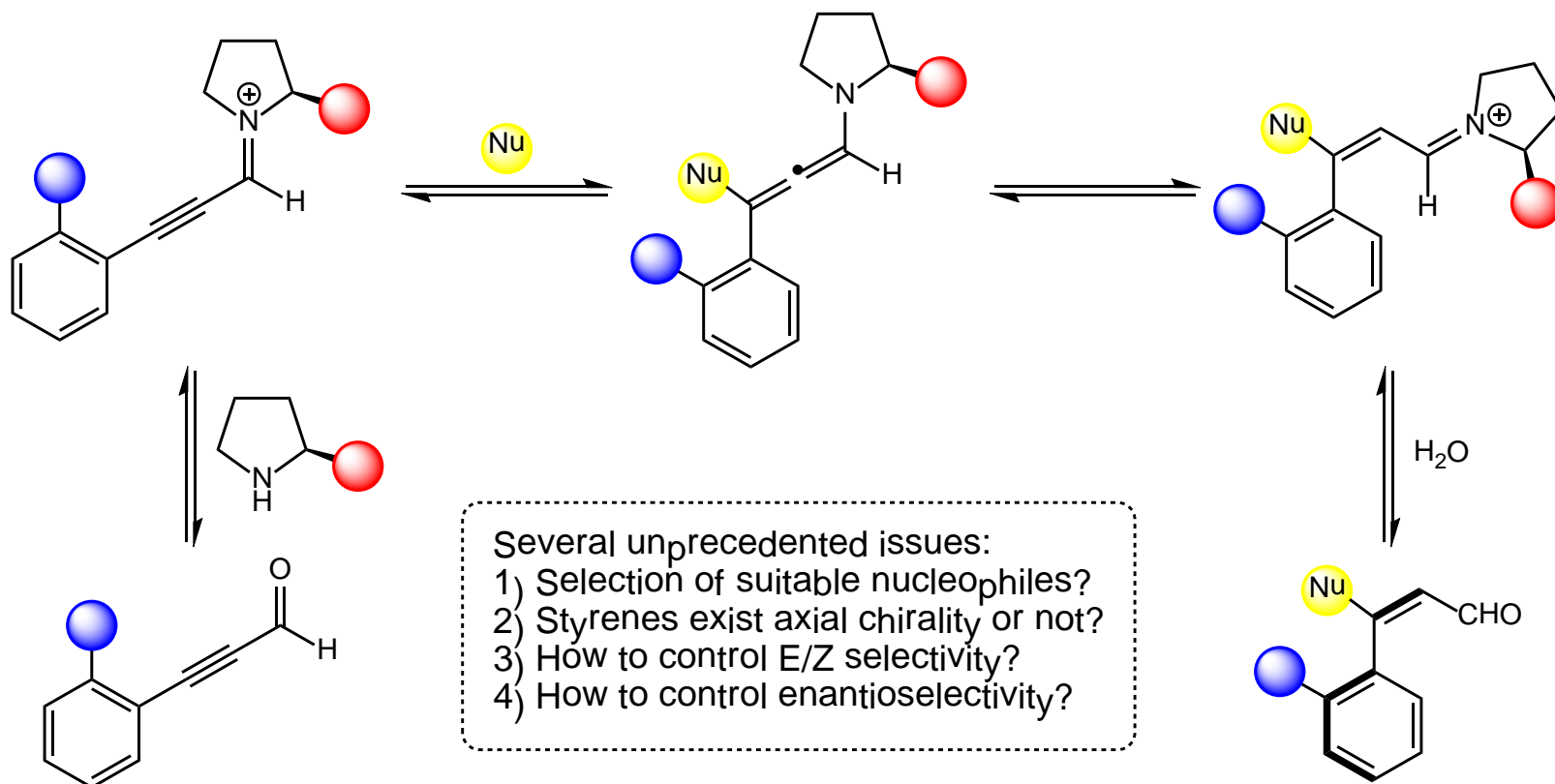
Synthesis of Axially Chiral Styrenes



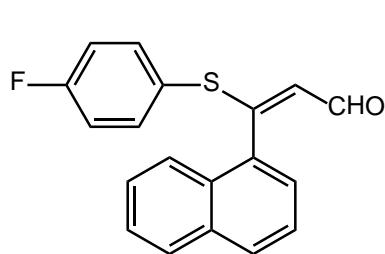
Axially Chiral Styrenes



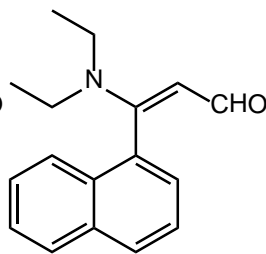
Synthesis of Axially Chiral Styrenes



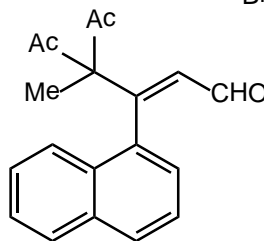
Computed Rotation Barriers



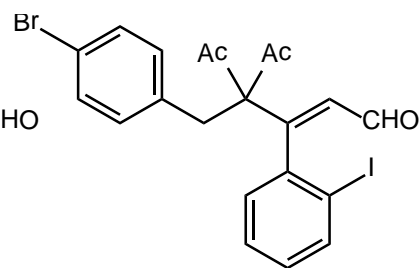
A



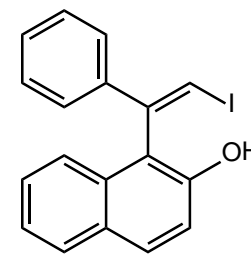
B



C



D



E

Barrier	67.8 KJ/mol
$t_{1/2}$ (25 °C)	0.081 s

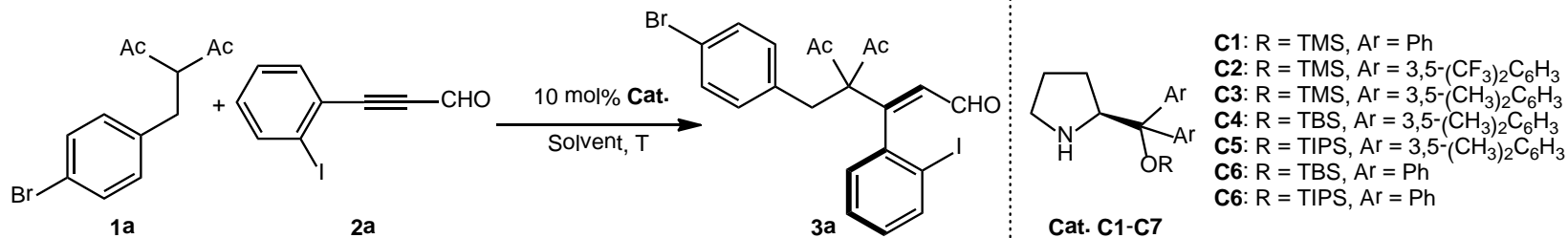
Barrier	123.1 KJ/mol
$t_{1/2}$	4476 days

Barrier	106.3 KJ/mol
$t_{1/2}$	5 days

Barrier	127.2 KJ/mol
$t_{1/2}$	24590 days

Barrier	122.2 KJ/mol
$t_{1/2}$	3272 days

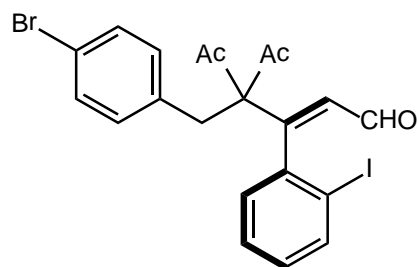
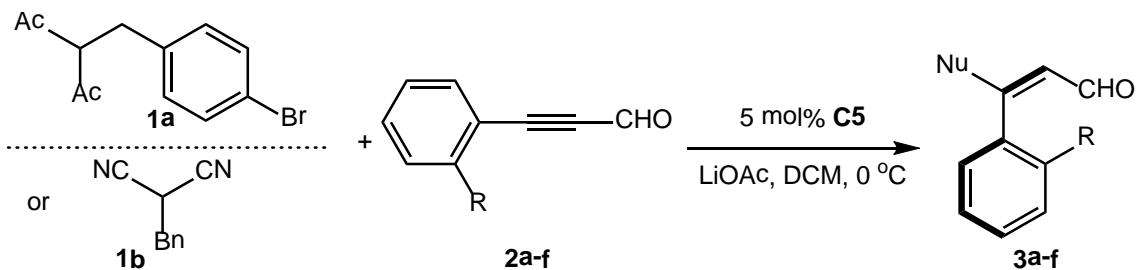
Optimization of the Reactions



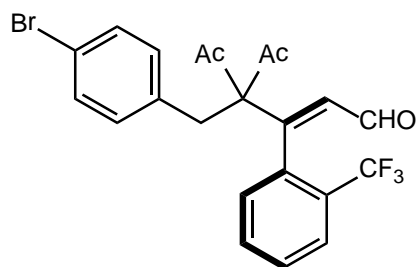
Entry ^a	Cat.	T	Solvent	Yield (%) ^b	Ee (%) ^c
1	C1	rt	CHCl ₃	74	65
2	C2	rt	CHCl ₃	trace	ND
3	C3	rt	CHCl ₃	93	65
4	C4	rt	CHCl ₃	97	83
5	C5	rt	CHCl ₃	54	90
6	C6	rt	CHCl ₃	90	85
7	C7	rt	CHCl ₃	54	86
8	C5	rt	DCM	95	90
9	C5	rt	toluene	78	88
10	C5 (5 mol%)	rt	DCM	94	90
11	C5 (5 mol%)	0	DCM	55	94
12	C5 (5 mol%)	-20	DCM	trace	ND
13^d	C5 (5 mol%)	0	DCM	96	94

^a 1a (0.05 mmol), 2a (1.1 eq.), cat. (10 mol%), solvent (0.5 mL), rt, 24 h. ^b Isolated yield. ^c Determined by HPLC. ^d LiOAc (0.025 mmol) was added.

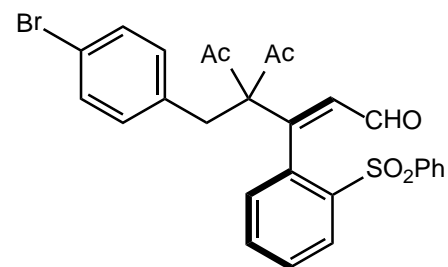
Substrate Scope



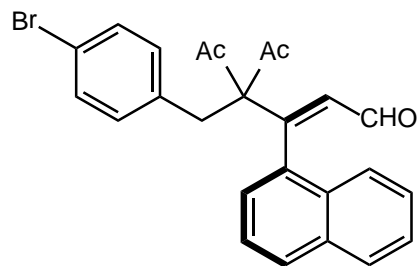
96% yield, 94% ee



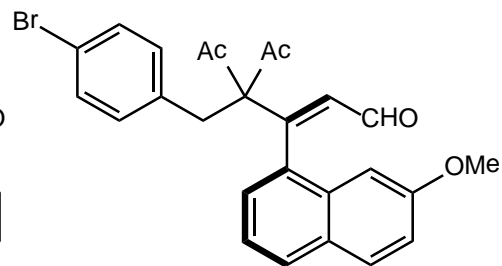
95% yield, 90% ee



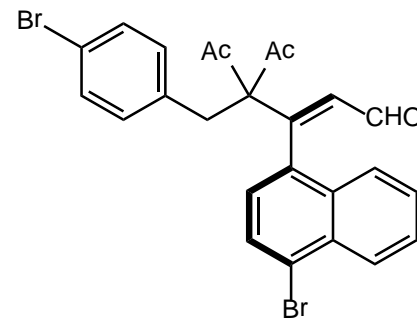
40% yield
82% ee (*Z/E* = 96/4)



99% yield, 92% ee

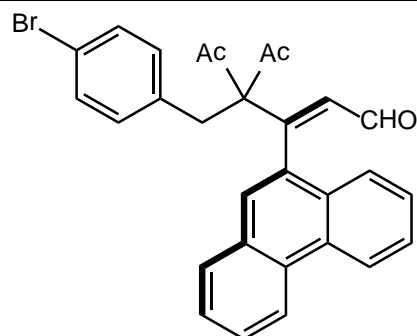
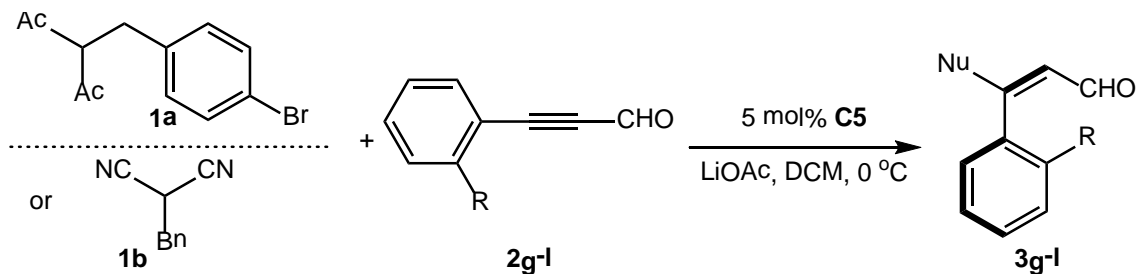


75% yield, 87% ee

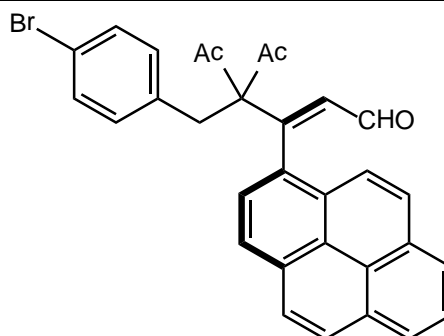


99% yield, 88% ee

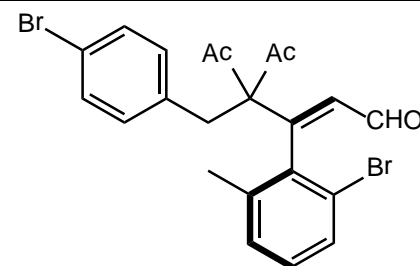
Substrate Scope



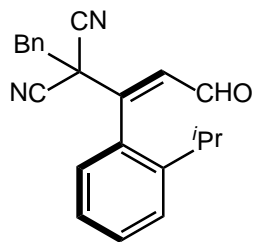
3g
99% yield, 88% ee



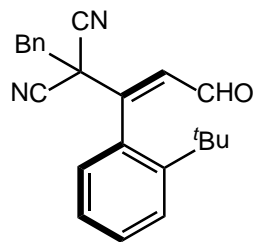
3h
99% yield, 87% ee



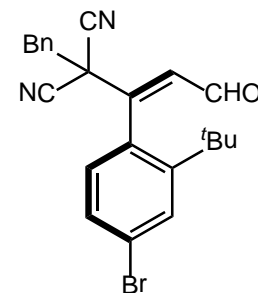
3i
89% yield, 54% ee



3j
99% yield, 95% ee

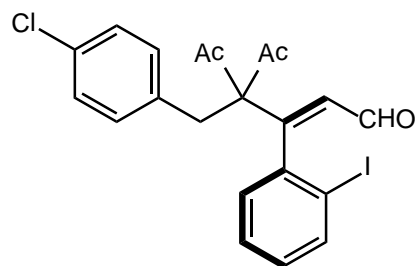
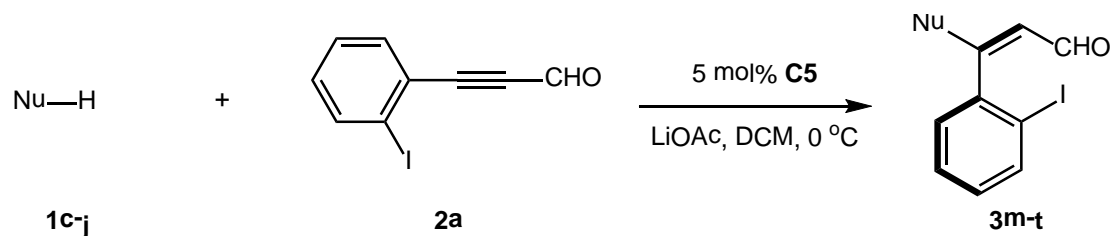


3k
93% yield, 94% ee

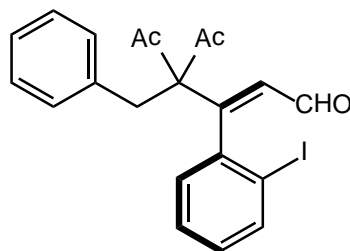


3l
98% yield, 86% ee

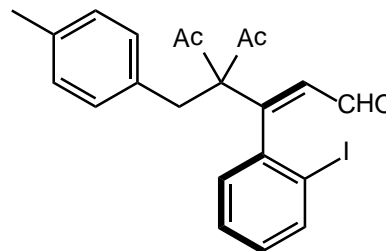
Substrate Scope



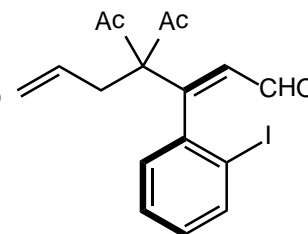
3m
92% yield, 94% ee



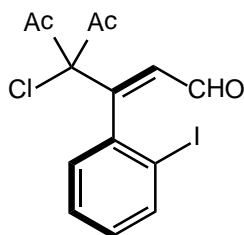
3n
89% yield, 94% ee



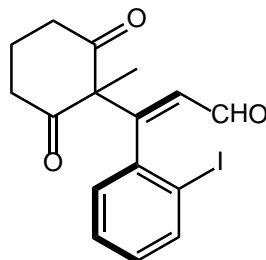
3o
99% yield, 94% ee



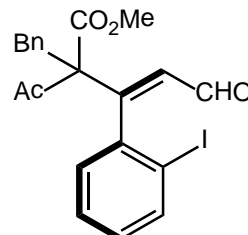
3p
87% yield, 94% ee



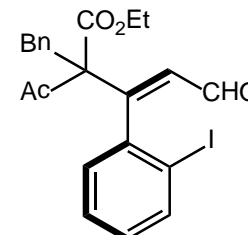
3q
49% yield, 90% ee



3r
57% yield
90% ee (*Z/E* = 90/10)

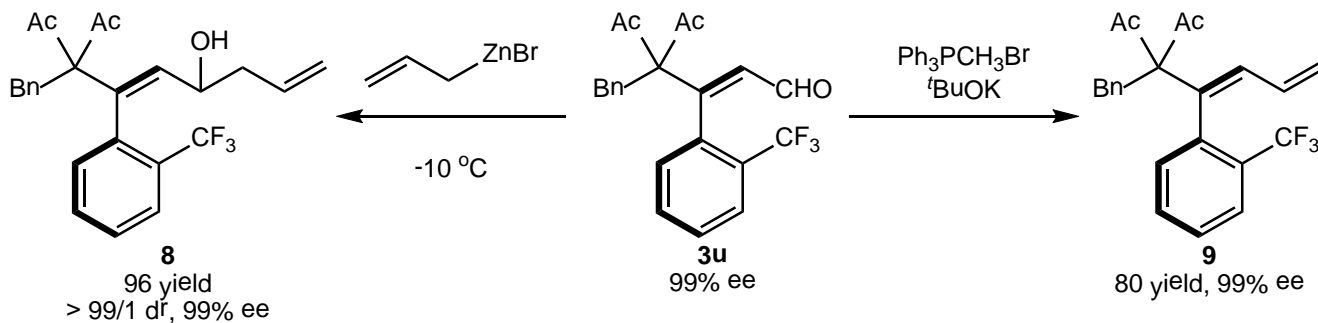
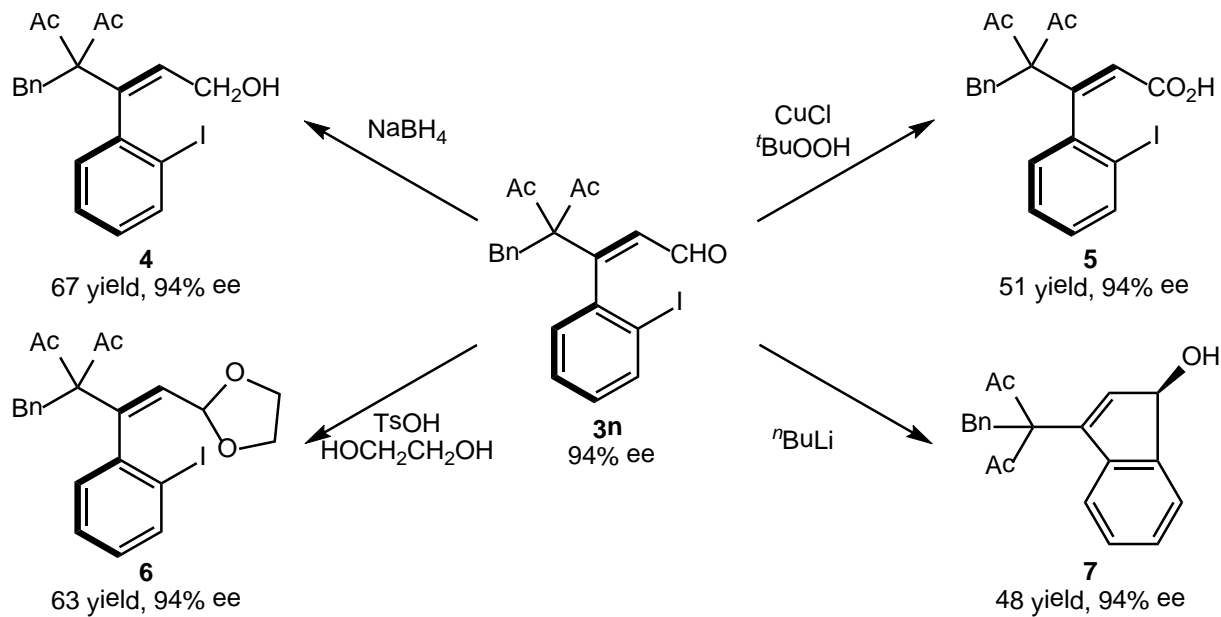


3s
93% yield, 2.1:1 dr
85% ee (major)
96% ee (minor)

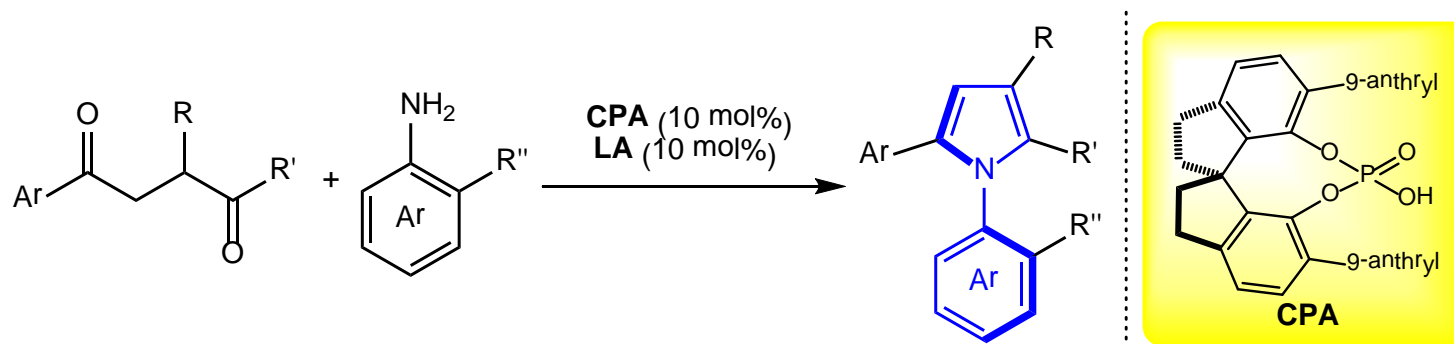


3t
97% yield, 2.3:1 dr
86% ee (major)
94% ee (minor)

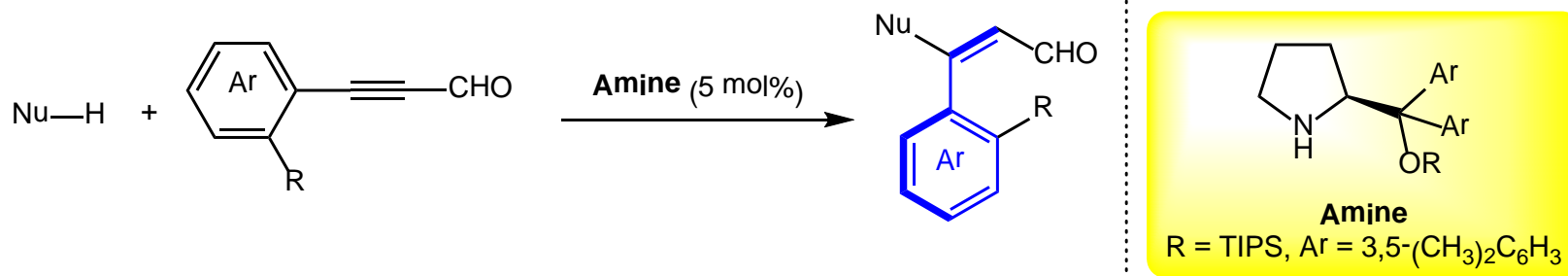
Synthetic Application



Summary



Tan, B. *et al.* *J. Am. Chem. Soc.* **2017**, *139*, 1714.



Tan, B. *et al.* *Nat. Commun.* **2017**, *8*, 15238.

The First Paragraph

As one of the most prominent classes of heterocyclic compounds, pyrroles are key structural motifs in biologically active compounds and useful building blocks in the synthesis of natural products, as well as in material sciences. Accordingly, their synthesis has always been among the most important research areas in synthetic chemistry and numerous methods have been widely developed. One of the most common approaches for the construction of pyrroles is the Paal–Knorr reaction in which 1,4-diketones are converted into pyrroles from the reaction with primary amine or ammonia by acid-mediated dehydrative cyclization. Remarkably, this reaction was first reported in 1884; however, catalytic asymmetric Paal–Knorr pyrrole synthesis still remained elusive to date.

The First Paragraph

One of the easily missing reasons is the absence of intrinsic chirality at the pyrrole, revealing no obvious handle for asymmetric induction. We questioned whether the formation of chiral pyrroles in the course of the reaction would be feasible. Here we report an acid-catalyzed asymmetric Paal–Knorr reaction for atroposelective synthesis of axially chiral arylpyrroles

The Last Paragraph

In summary, we have developed a general and efficient method for accessing enantiomerically pure arylpyrroles by utilizing the first catalytic asymmetric Paal–Knorr reaction. A wide range of axially chiral arylpyrroles were obtained in high yields with good to excellent enantioselectivities. The combined-acid catalytic system involving a Lewis acid and a chiral phosphoric acid was the key point to improve the enantioselectivity. Interestingly, an unexpected solvent-dependent inversion of the enantioselectivity was observed. We anticipate that this strategy will be applied to natural product synthesis and the axially chiral arylpyrroles will have potential application in asymmetric catalysis.
