Literature Report

Phosphine-Catalyzed Asymmetric Umpolung Addition of Trifluoromethyl Ketimines to Morita–Baylis–Hillman Carbonates

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Checker: Yue Ji
Date: 2016-10-24

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Author introduction

East China Normal University

Developing new synthetic reactions of conjugated enynes and small rings such as cyclopropane, oxiranes and aziridines; Designing novel chiral ligand for gold, palladium, rhodium *etc* catalyzed reactions.

Education:

- **B.S.** Applied Chemistry, Tianjin University, Tianjin, China (Sept.1993-July 1997) Supervisors: Prof. Wenqin Zhang and Prof. Chunbao Li
- **Ph.D.** Organic Chemistry/Organometallic Chemistry (Sept.1997-July 2002) Shanghai Institute of Organic Chemistry (SIOC), CAS, Shanghai, China Supervisor: Prof. Shengming Ma

Research experience:

Humboldt Fellow (Oct. 2003- Dec. 2004)
Institute of Organic Chemistry, University of Cologne, Germany.
Supervisor: Prof. Hans-Günther Schmalz
Research associate (Feb.2005-Oct. 2006)
Department of Chemistry, University of Chicago, USA.
Supervisors: Prof. Chuan He and Stephen Kent

Contents

Introduction

Umpolung or **polarity inversion** in organic chemistry is the chemical modification of a functional group with the aim of the reversal of polarity of that group. This modification allows secondary reactions of this functional group that would otherwise not be possible. The concept was introduced by D. Seebach (hence the German word umpolung for reversed polarity) and E. J. Corey.

Cyanide-type umpolung

Carbonyl umpolung

Amine umpolung

3-Membered rings

Oxidative bond formation

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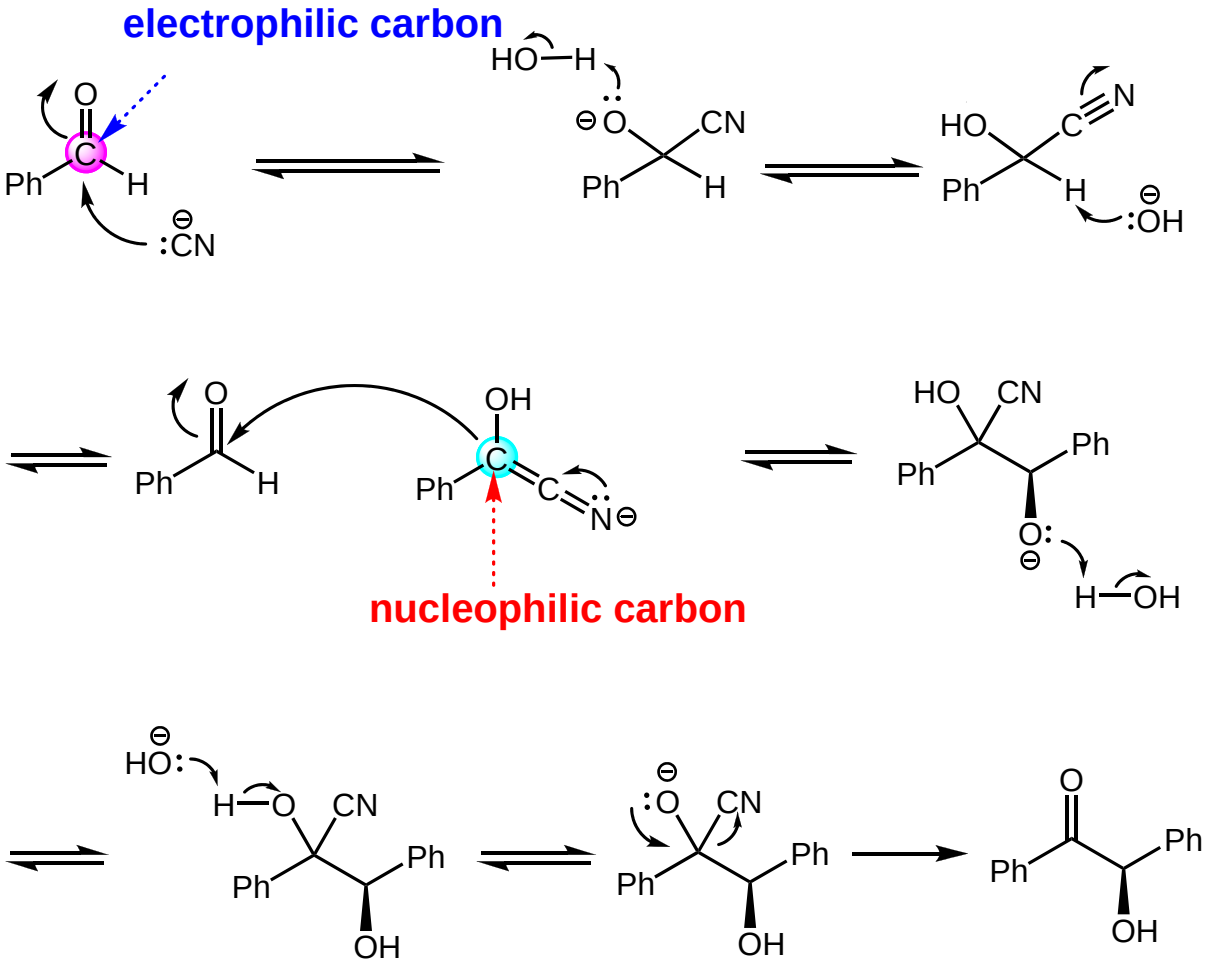
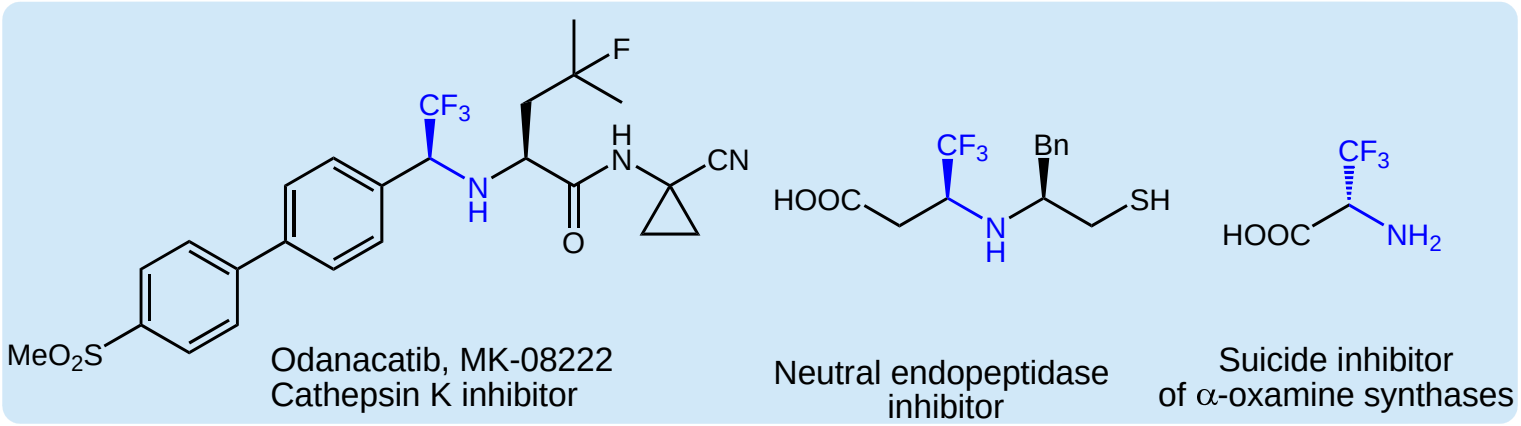
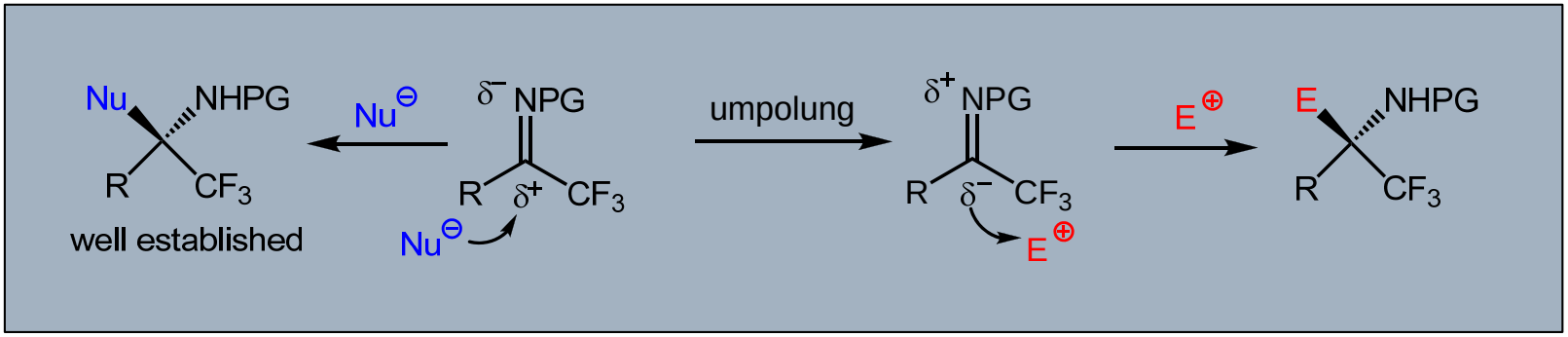
https://en.wikipedia.org/wiki/Umpolung

Benzoin condensation

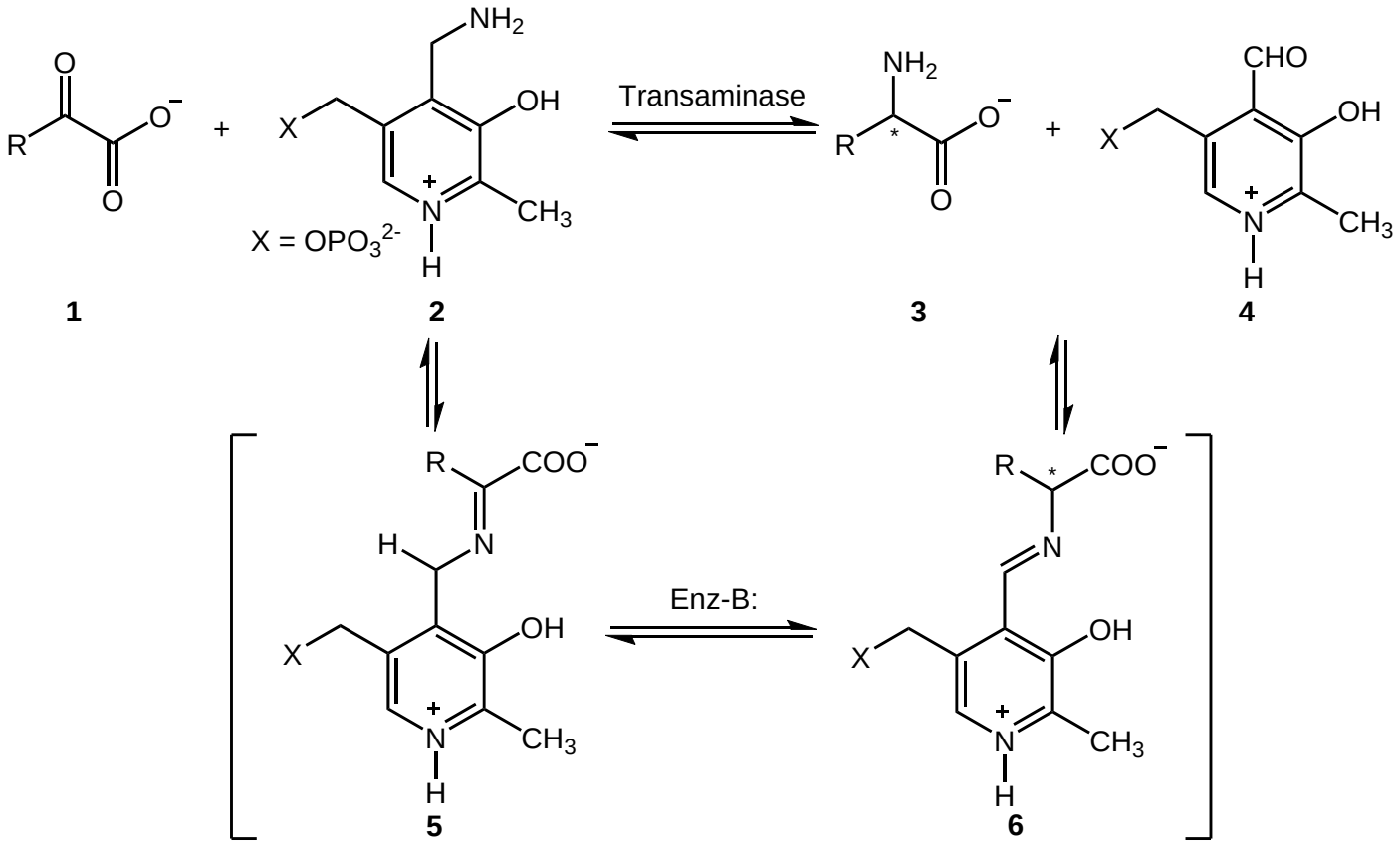


Introduction

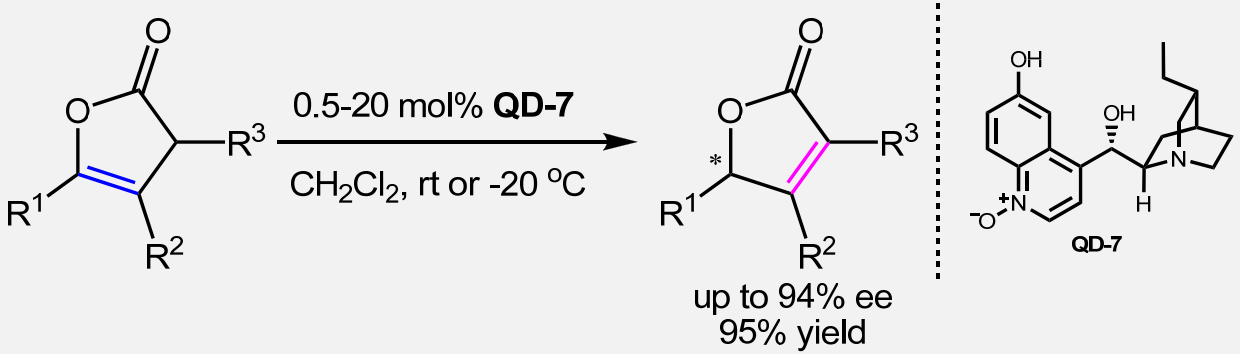




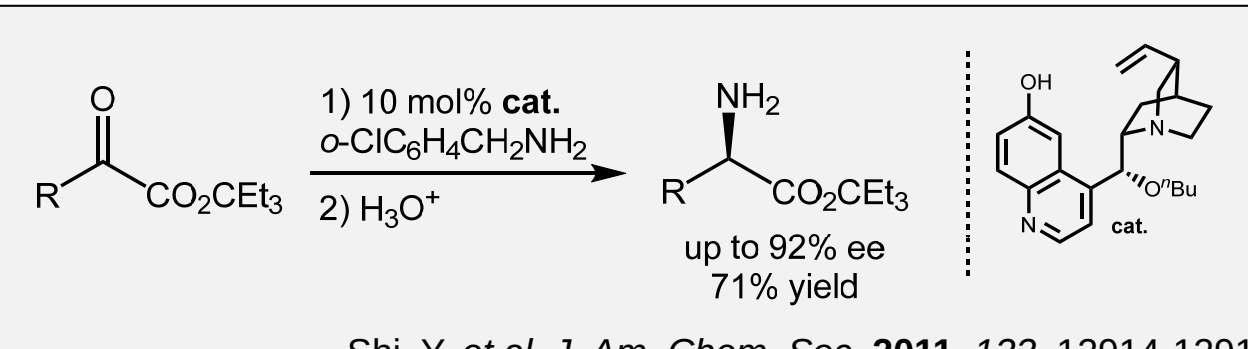
Biological transamination



Isomerization of olefins/imines

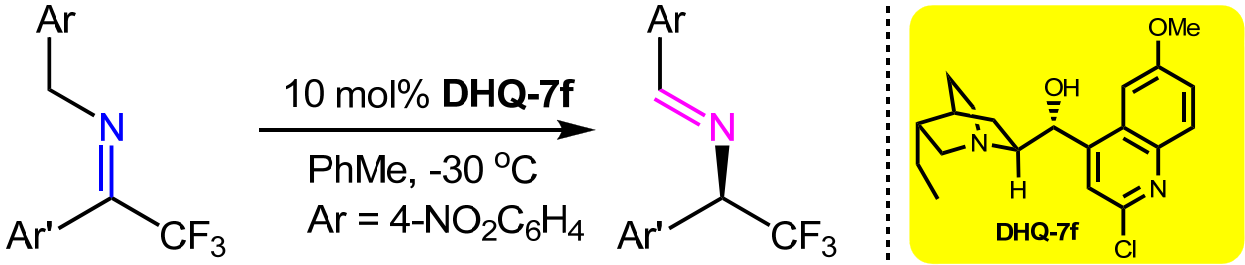


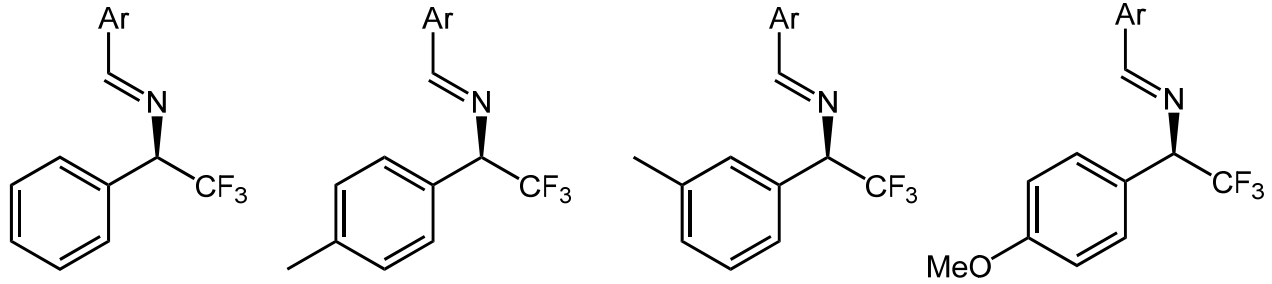
Deng, L. *et al*. *J. Am. Chem. Soc.* **2011**, *133*, 12458-12461.



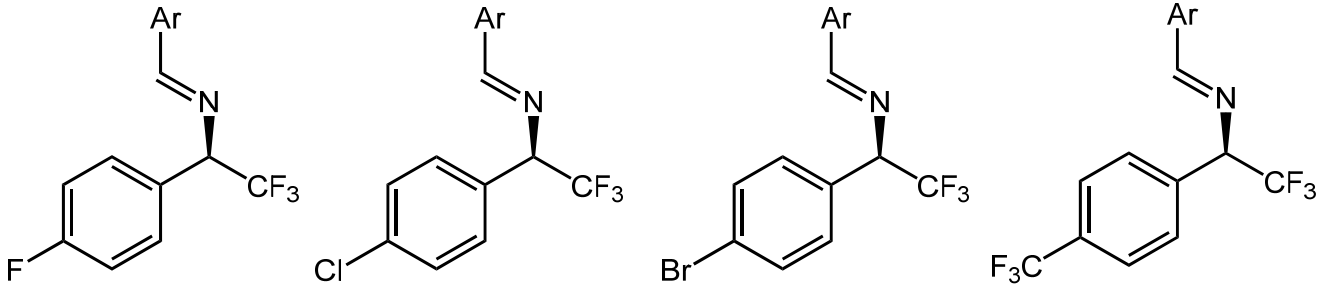
Shi, Y. *et al*. *J. Am. Chem. Soc.* **2011**, *133*, 12914-12917.

Catalytic enantioselective isomerization of imines





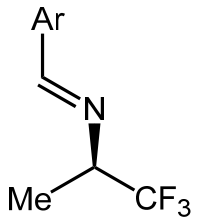
90% ee, 75% yield | 90% ee, 76% yield | 90% ee, 70% yield | 90% ee, 71% yield



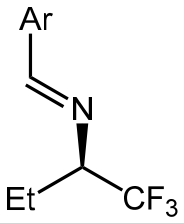
91% ee, 79% yield | 88% ee, 69% yield | 86% ee, 79% yield | 80% ee, 81% yield

Deng, L. *et al*. *J. Am. Chem. Soc.* **2012**, *134,* 14334-14337.

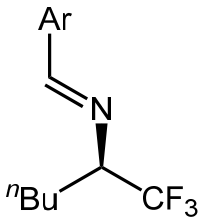
Asymmetric isomerization of alkyl trifluoromethyl imines



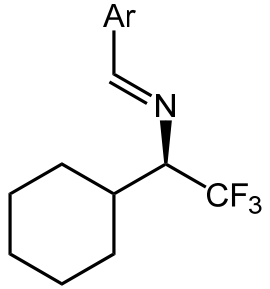
90% ee, 61% yield



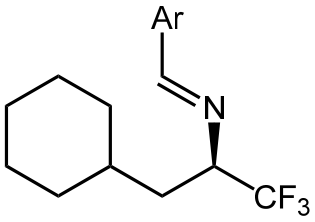
93% ee, 66% yield



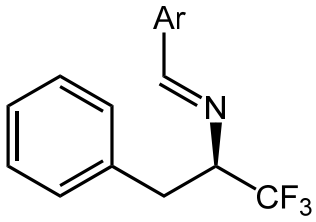
92% ee, 69% yield



91% ee, 58% yield

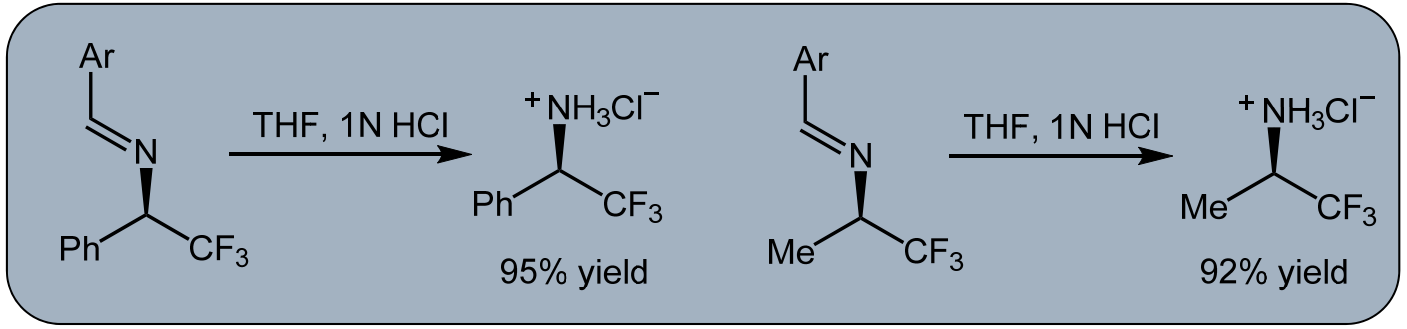


94% ee, 60% yield

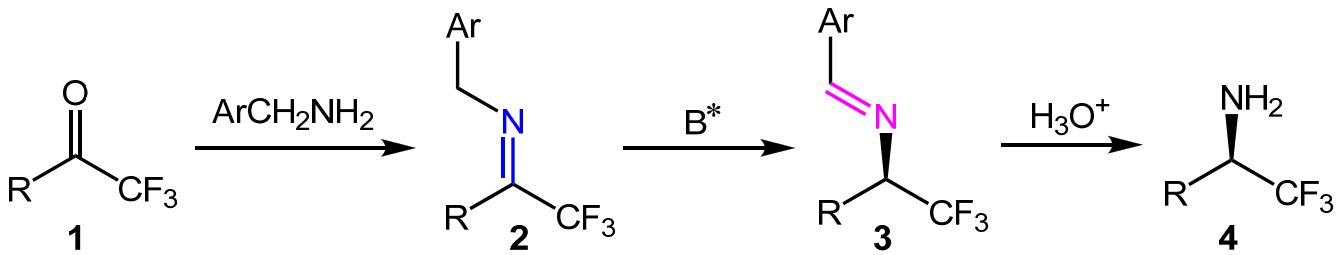


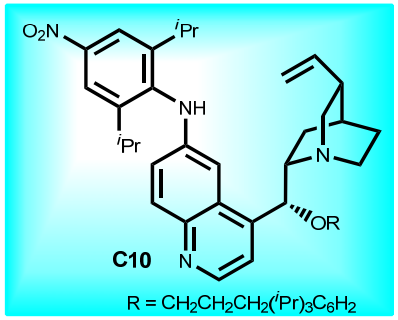
87% ee, 65% yield

Hydrolysis of the *N*-protecting group



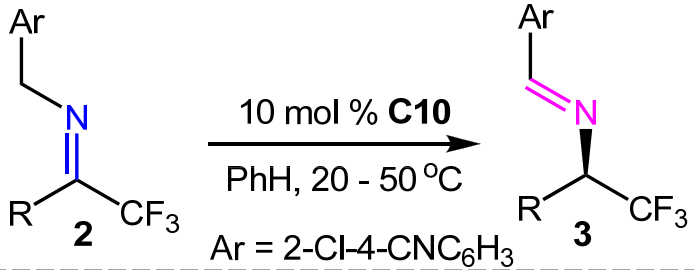
Asymmetric biomimetic transamination

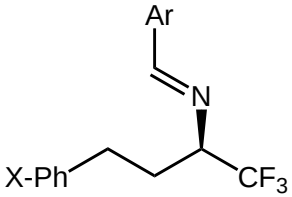




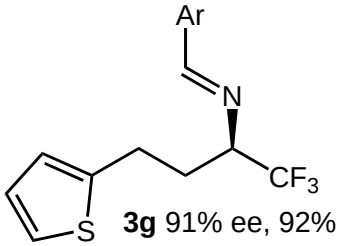
Shi, Y. *et al*. *Chem. Commun.* **2013**, *49,* 1404-1406.

Catalytic asymmetric H shift of trifluoromethylimines

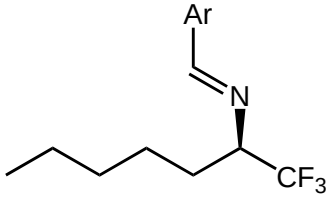




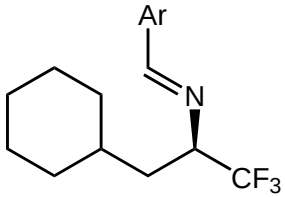
3a: X = H, 94% ee, 99% yield
3b: X = *o*-Cl, 94% ee, 99% yield
3c: X = *o*-Br, 94% ee, 98% yield
3d: X = *p*-Me, 94% ee, 99% yield
3e: X = *p*-Cl, 93% ee, 99% yield
3f: X = *p*-OMe, 94% ee, 98% yield



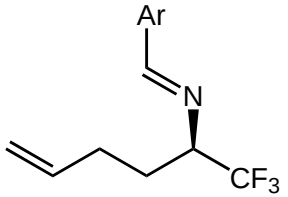
3g 91% ee, 92% yield



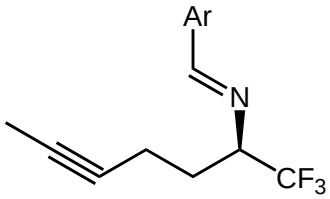
3h 94% ee, 95% yield



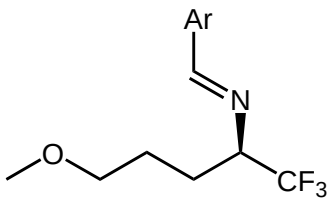
3i 94% ee, 96% yield



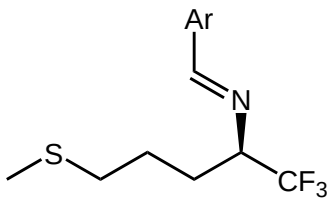
3j 90% ee, 95% yield



3k 90% ee, 95% yield

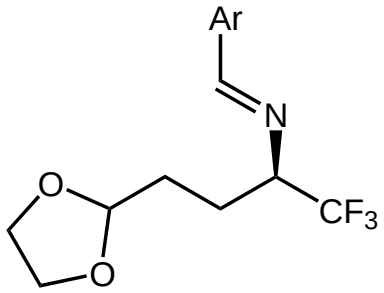


3l 86% ee, 93% yield

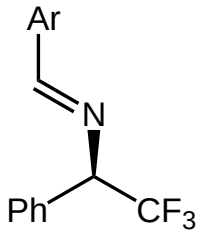


3m 90% ee, 99% yield

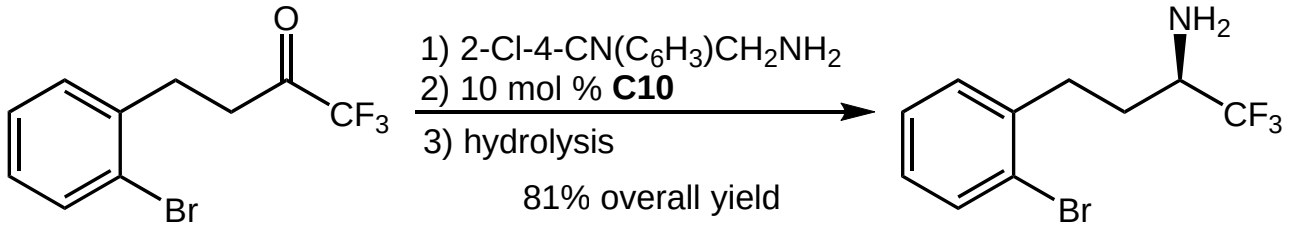
Further transformation of the product

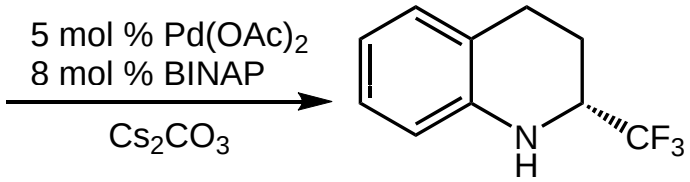


3n 86% ee, 94% yield



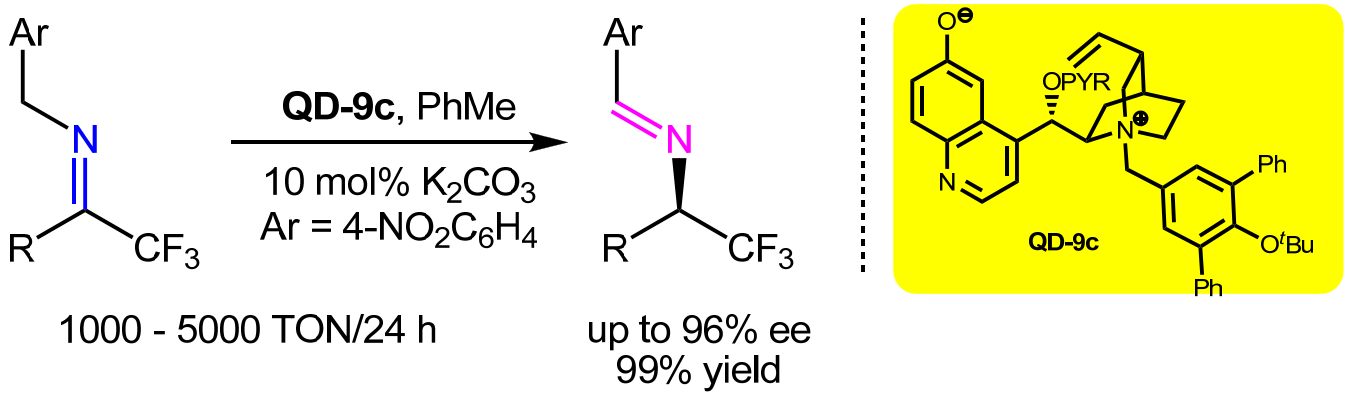
3o 67% ee, 99% yield

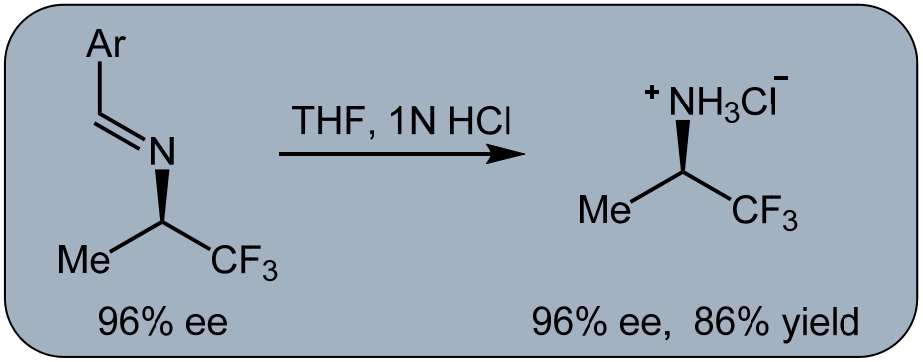




94% ee, 91% yield

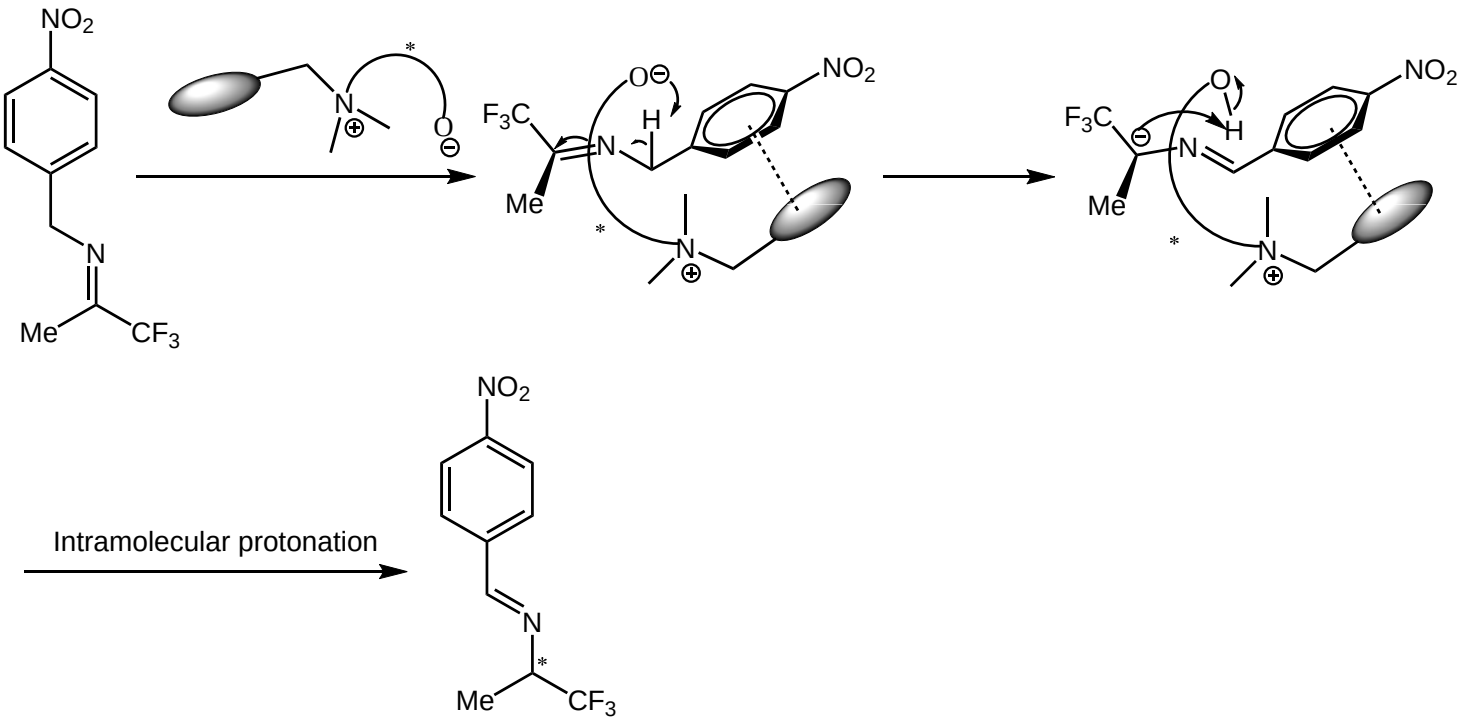
Enantioselective isomerization of trifluoromethyl imines



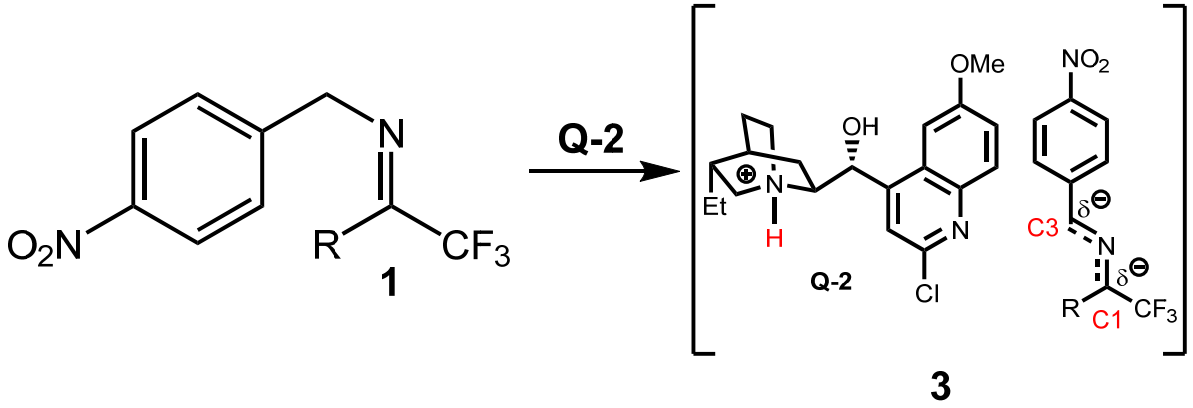


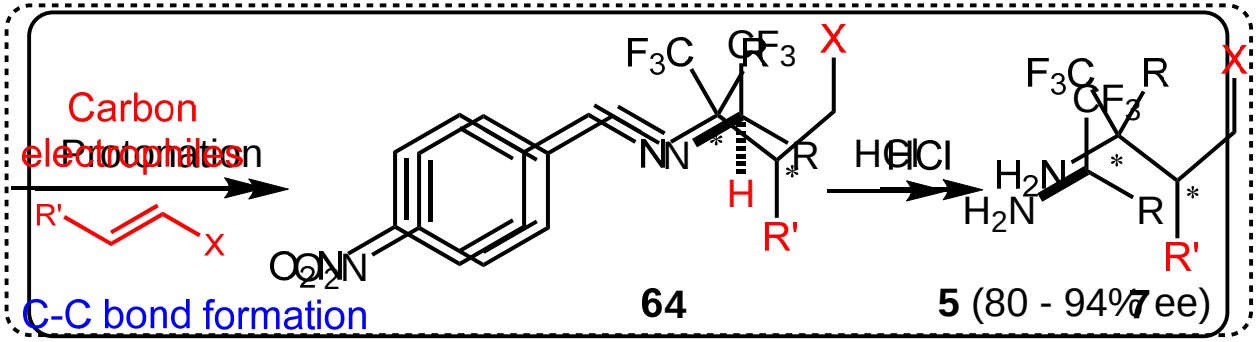
Deng, L. *et al*. *J. Am. Chem. Soc.* **2016**, *138,* 12297-12302.

Working hypotheses



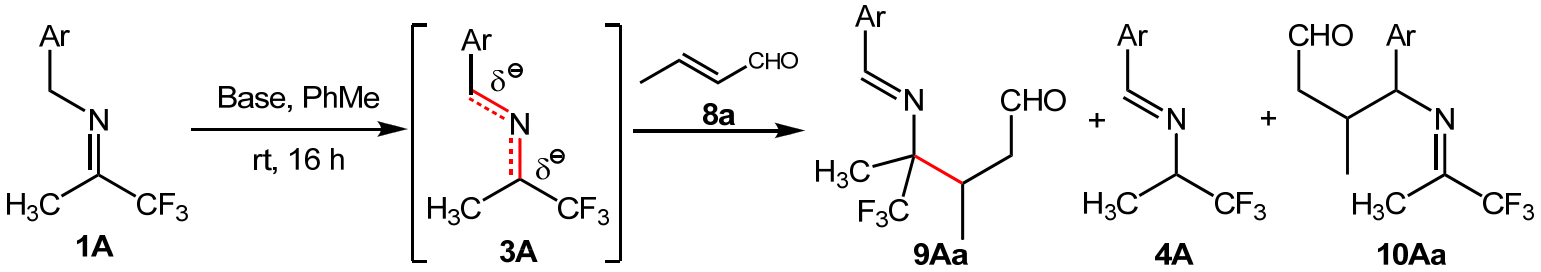
Catalytic asymmetric umpolung reactions of imines

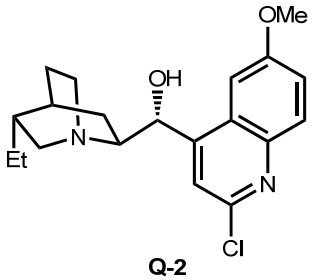




Deng, L. *et al*. *Nature* **2015**, *523*, 445-450.

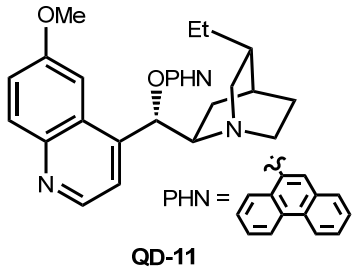
Experiments with chiral base catalysts





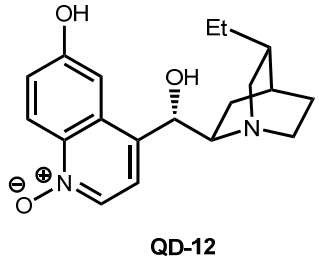
Q-2

Conv. (%)	**9/4**
84	0/100



QD-11

Conv. (%)	**9/4**
32	0/100

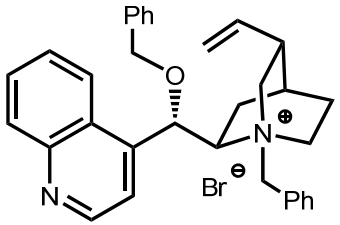


QD-12

Conv. (%)	**9/4**
9	0/100

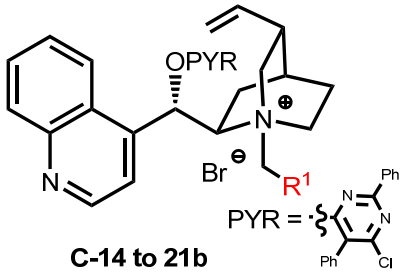
Conditions: rt, 10 mol% catalyst, 16 h.

Experiments with chiral base catalysts



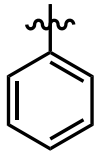
C-13

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)
41	2/98; ND	ND	ND



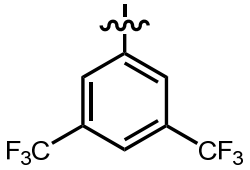
C-14 to 21b

R^1 =



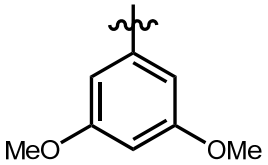
C-14

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)	
18	11/89; ND	ND	ND	rt
58	37/63; >95/5	82/18	39	-20 °C



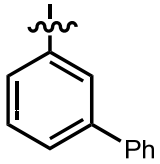
C-15

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)
54	36/64; >95/5	67/33	18



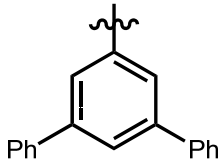
C-16

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)	
84	34/66; >95/5	76/24	40	
41	32/68; >95/5	74/26	39	(1.0 mol% Cat.)



C-17

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)
14	67/33; >95/5	87/13	68

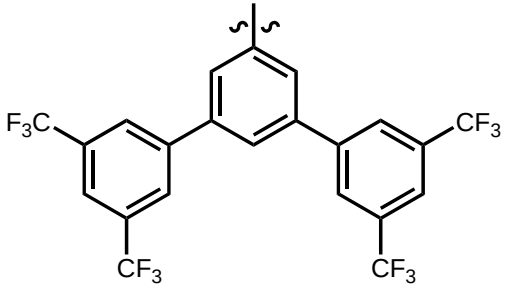


C-18

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)
40	74/26; >95/5	86/14	77

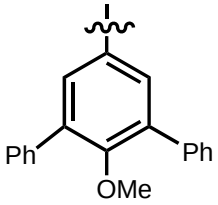
Conditions: 10 mol% catalyst, 10 mol% $KOH_{(aq.)}$, 16 h.

Experiments with chiral base catalysts



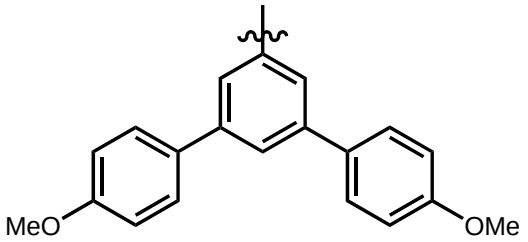
C-19

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)
39	45/55; >95/5	96/4	55



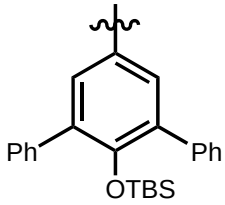
C-21a

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)
88	94/6; >95/5	91/9	91



C-20

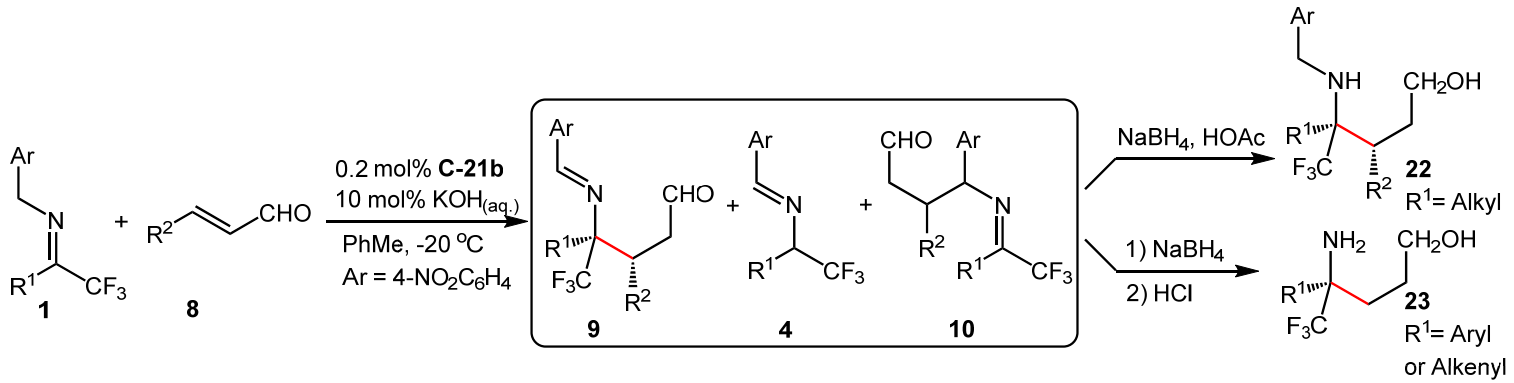
Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)
66	68/32; >95/5	91/9	85



C-21b

Conv. (%)	**9/4; 9/10**	d.r. of **9**	ee of **9** (%)
99	99/1; >95/5	93/7	96
97	99/1; >95/5	93/7	95 (0.2 mol% Cat.)

Substrate scope



Entry	R^1	Conv. (%)	Dr of **9**	Yield (%)	Ee (%)
1	CH_3	99	93/7	81 (**22Aa**)	95
2	C_2H_5	97	91/9	84 (**22Ba**)	94
3	C_4H_9	98	91/9	83 (**22Ca**)	96
4	BrC_4H_8	99	91/9	75 (**22Da**)	96
5	$BnOC_3H_6$	94	91/9	72 (**22Ea**)	96
6	$CyCH_2$	98	93/7	54 (**22Fa**)	95

R^2 = Me; **9**/**4**, **9**/**10** : >95/5

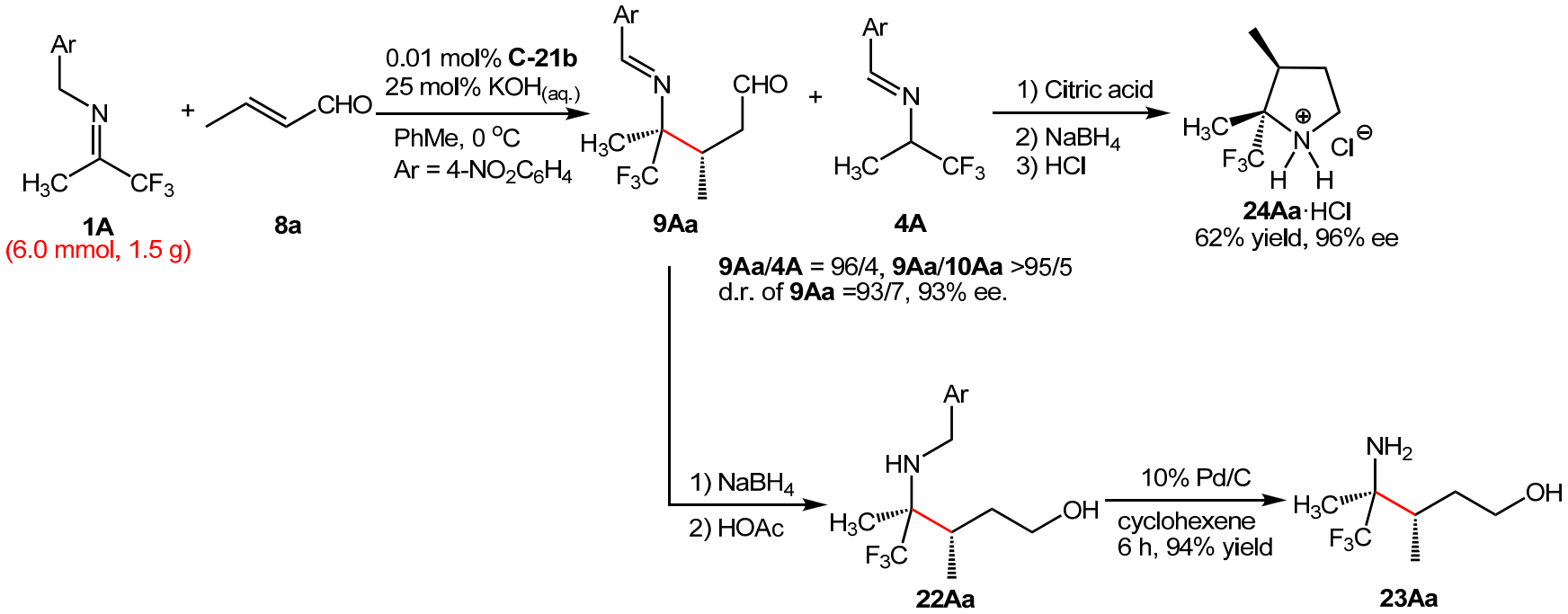
Substrate scope

Entry	R^2 (R^1 = Me)	Conv. (%)	**9/4**; **9/10**	Yield (%)	Ee (%)
7	C_2H_5	99	89/11; >95/5	64 (**22Ab**)	95
8	C_6H_{13}	93	86/14; >95/5	51 (**22Ac**)	96
9	Ph	93	>95/5; 68/32;	51 (**22Ad**)	91

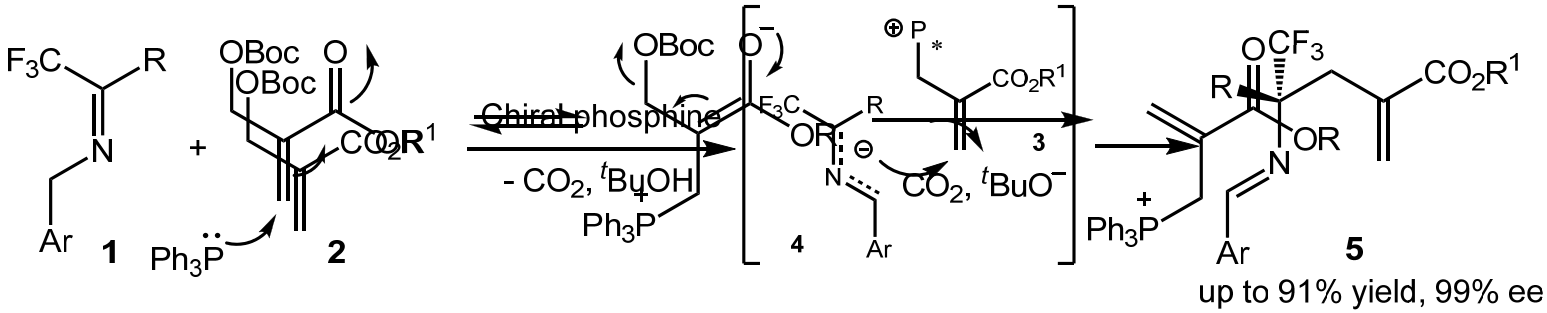
Dr of **9** > 95/5

Entry	R^1 (R^2 = H)	Conv. (%)	**9/4**; **9/10**	Yield (%)	Ee (%)
10	CH_3	95	>95/5; >95/5	89 (**22Ae**)	92
11	C_2H_5	99	>95/5; >95/5	82 (**22Be**)	91
12	BrC_4H_8	97	>95/5; >95/5	84 (**22De**)	91
13	$CyCH_2$	99	>95/5; >95/5	90 (**22Fe**)	92
14	Ph	99	94/6; >95/5	71 (**23Ga**)	94
15	*p*-$MeOC_6H_4$	94	92/8; >95/5	67 (**23He**)	94
16	*p*-$CF_3C_6H_4$	99	88/12; >95/5	78 (**23Ie**)	92
17	C_6H_4CHCH	99	>95/5; >95/5	90 (**23Je**)	93

Gram-scale reaction and synthetic applications

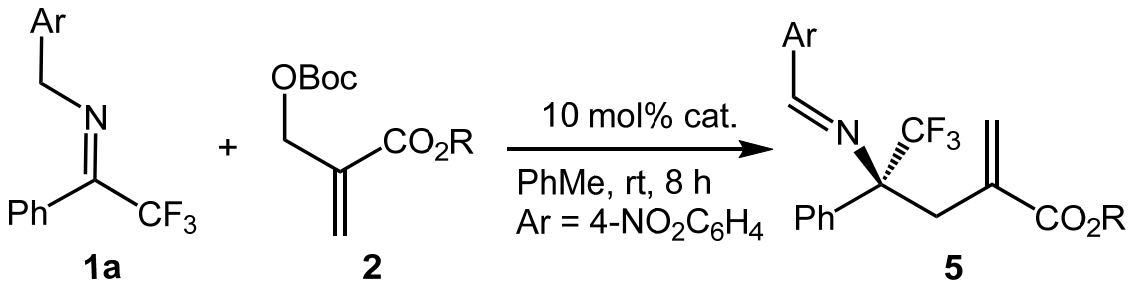


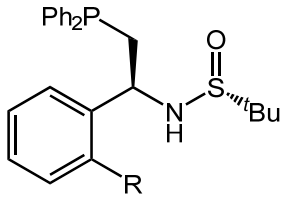
Asymmetric umpolung reaction of imines with MBH carbonates



Zhang, J. *et al*. *Angew. Chem. Int. Ed.* **2016**, *55,* 13316-13320.

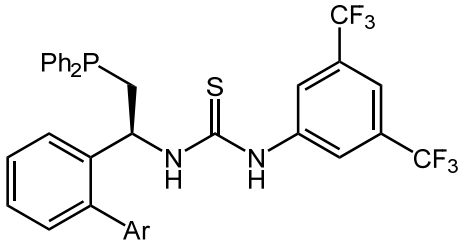
Reaction optimization--chiral phosphine catalysts



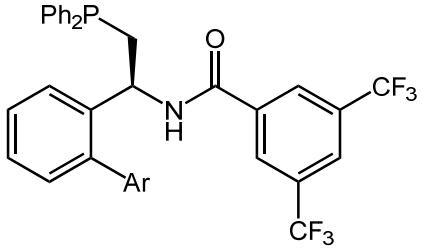


(S, R_S)

R	yield (%)	ee (%)
H	61	62
Ph	67	60
p-$MeOC_6H_4$	62	57
p-PhC_6H_4	65	62
2-naphthalenyl	68	58
9-anthracenyl	72	75
3,5-$(^tBu)_2C_6H_3$	67	55
3,5-$(Ph)_2C_6H_3$	71	60



(S)-**P9**, Ar = anthracenyl
(70% yield, 42% ee)



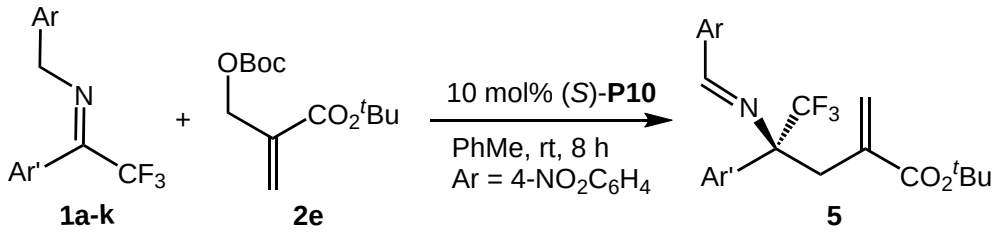
(S)-**P10**, Ar = anthracenyl
(78% yield, 81% ee)

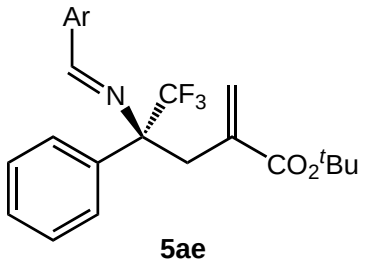
Reaction optimization

Entry [a]	R	Solvent	Yield (%) [b]	Ee (%) [c]
1	Me (**2a**)	PhMe	78	81
2	Et (**2b**)	PhMe	74	92
3	Bn (**2c**)	PhMe	77	80
4	^{i}Pr (**2d**)	PhMe	75	96
5	**^{t}Bu (2e)**	**PhMe**	**85**	**98**
6	^{t}Bu (**2e**)	THF	78	95
7	^{t}Bu (**2e**)	DCM	84	95
8	^{t}Bu (**2e**)	Et_2O	79	94
9 [d]	^{t}Bu (**2e**)	PhMe	82	99
10 [e]	^{t}Bu (B)	PhMe	73	97

[a] Unless otherwise specified, **1a** (0.2 mmol), **2** (0.3 mmol), catalyst (0.02 mmol), solvent (2 mL), RT. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 0 ^{o}C. [e] 5.0 mol% catalyst, 24 h.

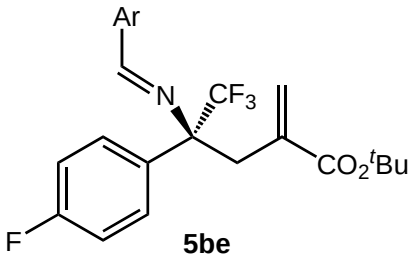
Substrate scope--aryl trifluoromethyl imines





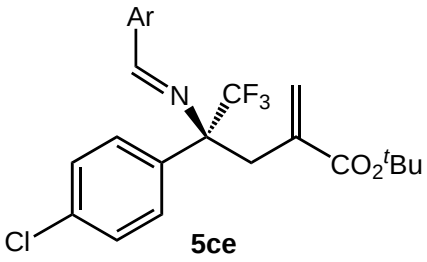
5ae

85% yield, 98% ee
78% yield, 97% ee (5 mmol)



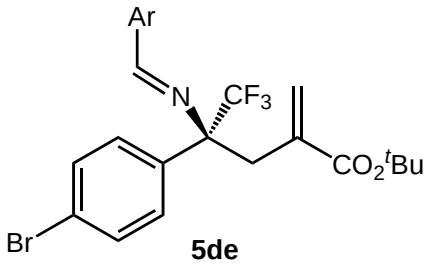
5be

91% yield, 95% ee



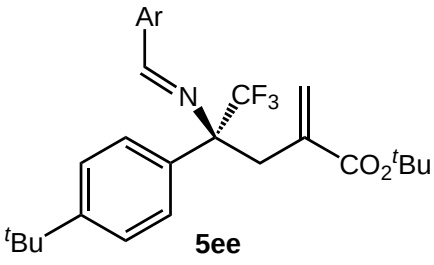
5ce

90% yield, 93% ee



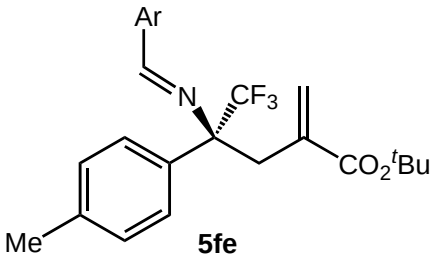
5de

82% yield, 96% ee



5ee

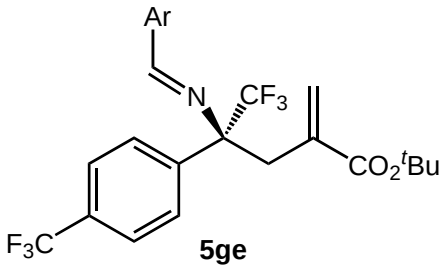
88% yield, 99% ee



5fe

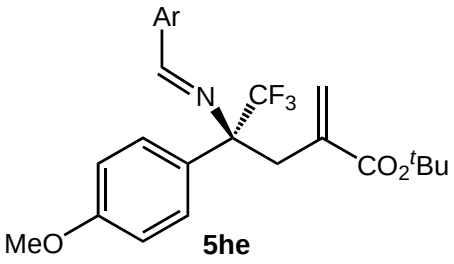
90% yield, 95% ee

Substrate scope--aryl trifluoromethyl imines



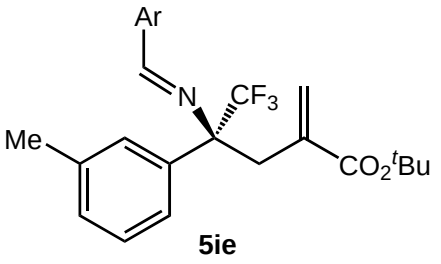
5ge

80% yield, 93% ee



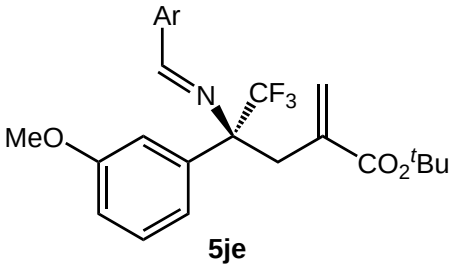
5he

78% yield, 95% ee



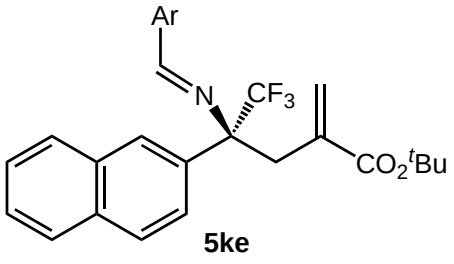
5ie

85% yield, 94% ee



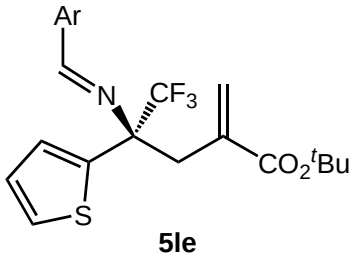
5je

80% yield, 95% ee



5ke

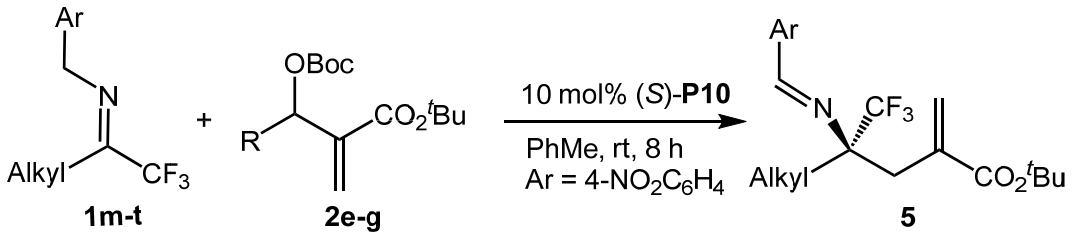
82% yield, 94% ee

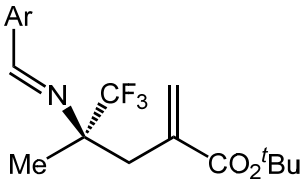


5le

70% yield, 96% ee

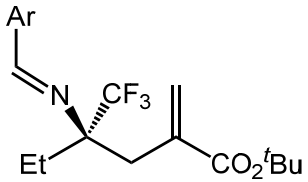
Substrate scope--alkyl trifluoromethyl imines





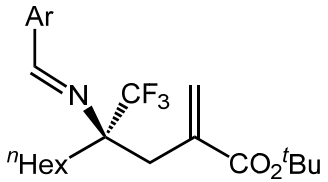
5me

90% yield, 98% ee
85% yield, 98% ee (5.0 mmol)



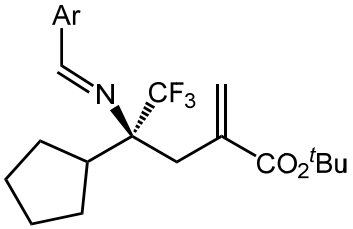
5ne

86% yield, 97% ee



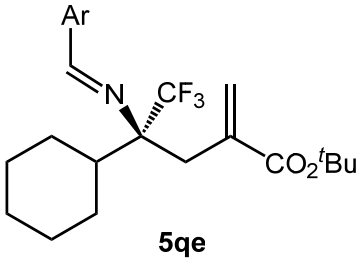
5oe

89% yield, 96% ee



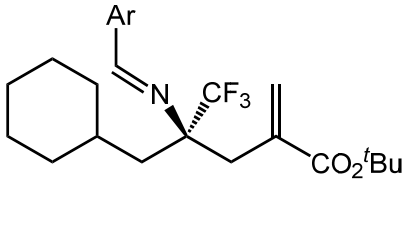
5pe

83% yield, 91% ee



5qe

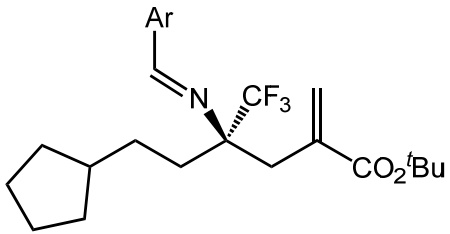
81% yield, 90% ee



5re

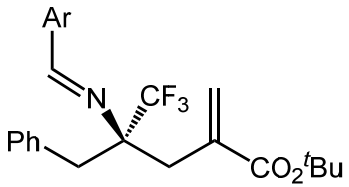
85% yield, 96% ee

Substrate scope--alkyl trifluoromethyl imines



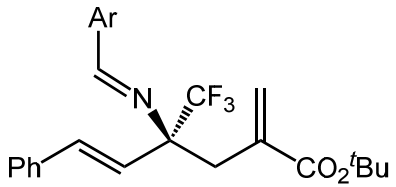
5se

90% yield, 99% ee



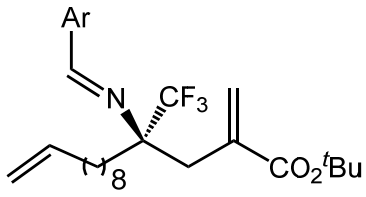
5te

82% yield, 98% ee



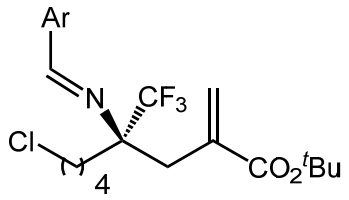
5ue

73% yield, 91% ee



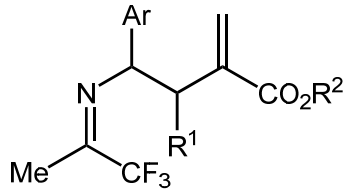
5ve

79% yield, 96% ee



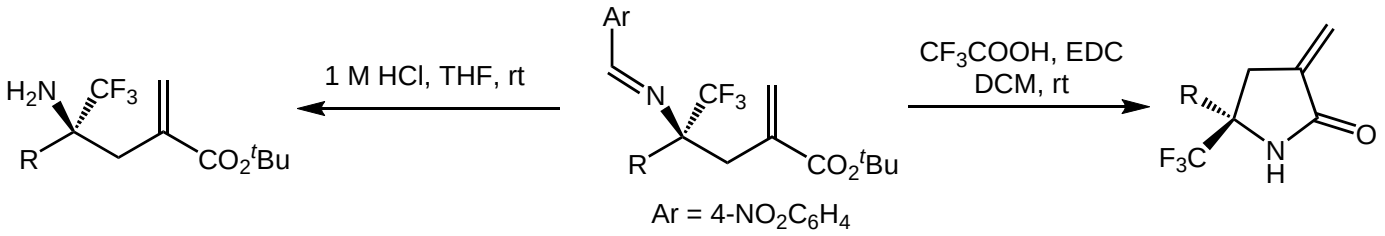
5we

81% yield, 96% ee



5mf: R^1 = Me, R^2 = ^{t}Bu, 51% yield
5:1 d.r., 73% ee, 94% ee
5mg: R^1 = Ph, R^2 = Et, 47% yield
2:1 d.r., 97% ee, 60% ee

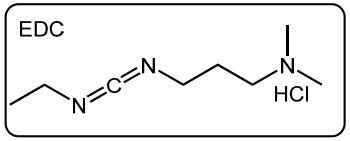
Further transformations of the products



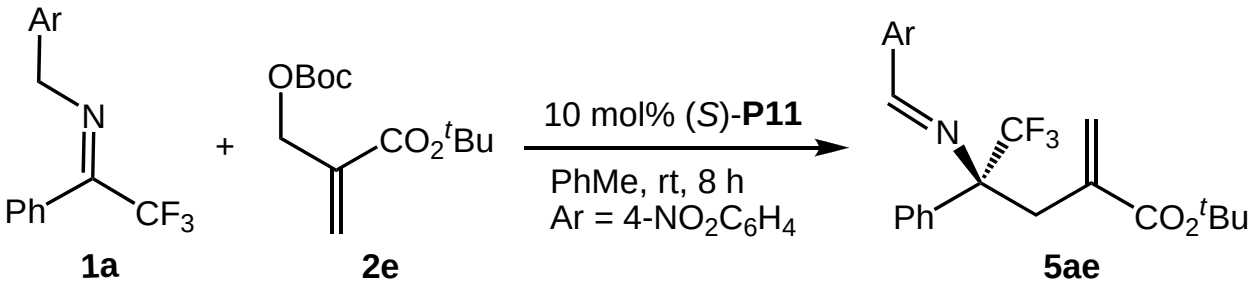
6ae, 92% yield, 97% ee
6me,90% yield, 98% ee

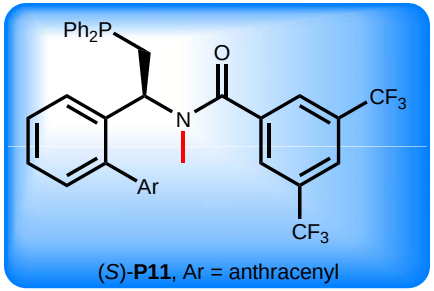
5ae, R = Ph, 97% ee
5me, R = Me, 98% ee

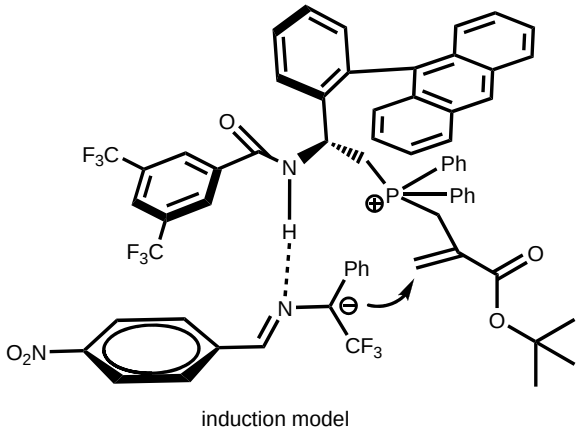
7ae, 78% yield, 95% ee
7me, 74% yield, 98% ee



The NH-effect study and the chirality induction model



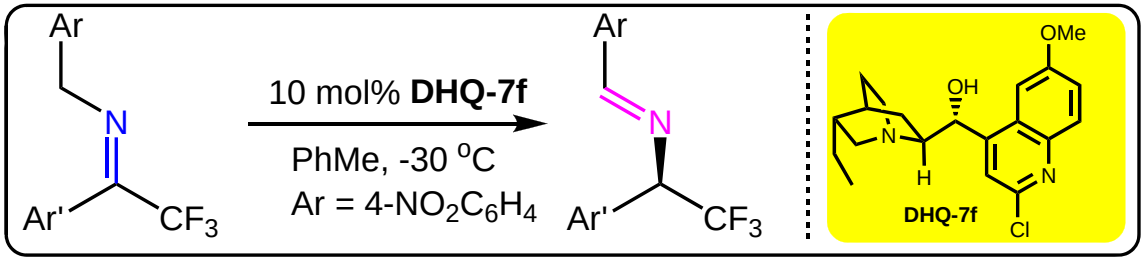




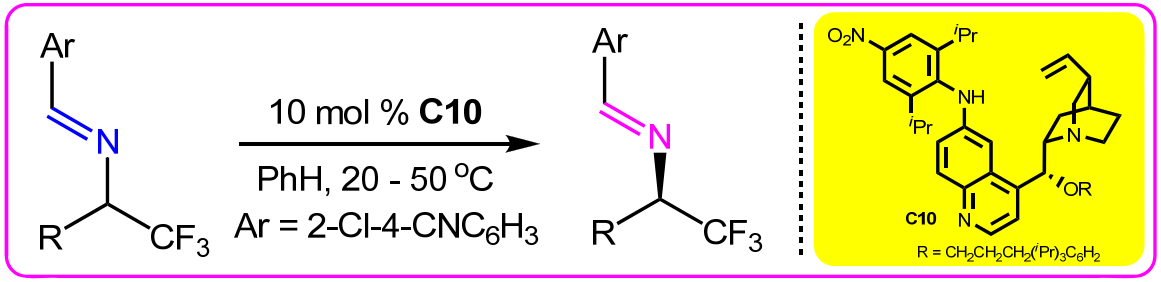
induction model

Summary

Deng's work

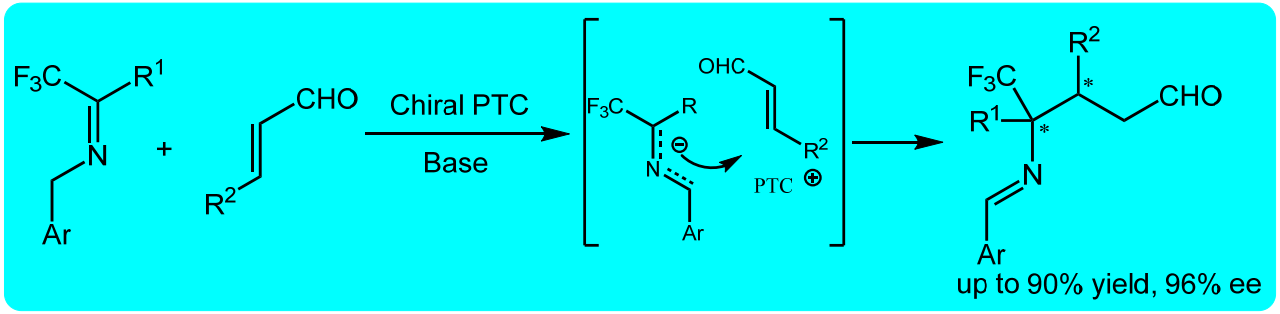


Shi's work

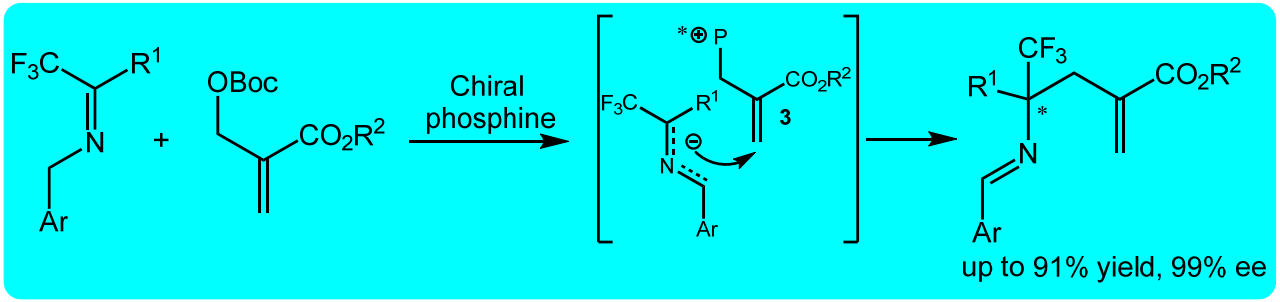


Summary

Deng's work first example of C-C bond formation



Zhang's work second example of C-C bond formation



Introduction

The presence of fluorine in organic molecules of pharmaceutical and agrochemical importance has had a beneficial yet unique impact on the bioactivities of the molecules, and led to a rapidly increasing demand for developing novel methodology to efficiently synthesize organofluorine compounds. Among fluorinated compounds, chiral trifluoromethyl amines were widely found as the key structural subunits in many biologically interesting compounds, and were recognized to improve lipophilicity and metabolic stability over that of the corresponding methyl amines.（对含氟化合物重要性进行介绍）

In light of their importance, various powerful strategies for the synthesis of chiral trifluoromethyl amines have been developed in the past years. The strategy which takes advantage of the inherent electrophilicity of prochiral trifluoromethyl imines and their reaction with various nucleophiles has received much attention and several elegant reactions have been reported. For example, the groups of Hoveyda, Ye, and Huang disclosed highly enantioselective nucleophilic additions to trifluoromethyl ketimines catalyzed by chiral metal or organic catalysts.（过去发展了一系列有效的方法来构建手性含三氟甲基胺化合物）

Introduction

Although these methods are effective, they are often hampered by the multistep preparation of the reactants as well as the narrow range of products, that is, only aromatic trifluoromethyl amines could be obtained.（目前这些方法存在的一些缺陷）Consequently, the development of novel and general method for enantioenriched trifluoromethyl amines bearing a chiral tertiary stereocenter is still highly desirable.（发展一些新方法的必要性）

Summary

In summary, we have developed a new method for asymmetric synthesis of enantioenriched trifluoromethyl amines with a chiral tertiary stereocenter by a highly effective and enantioselective phosphine-catalyzed umpolung addition of trifluoromethyl imines to MBH carbonates under mild reaction conditions. The salient features for this transformation include general substrate scope, mild reaction conditions, good yields, high enantioselectivity, ease of scale-up to gram scale, and easy conversion into valuable chiral γ-trifluoromethyl amines, α-methylene esters, and α-methylene γ-lactams.（该方法的优点）Further studies, including the application of this new type of chiral phosphine to other related reactions, and the metal-catalyzed asymmetric umpolung coupling reaction of trifluoromethyl ketimines are underway, and will be reported in due course.