Literature Report

Oxidative enantioselective α-fluorination of aliphatic aldehydes enabled by *N*-hetero-cyclic carbene catalysis

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Checker: Yue Ji
Date: 2015-11-03

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Tsinghua University
Angew. Chem. Int. Ed. **2015**, *54*, 656-659.

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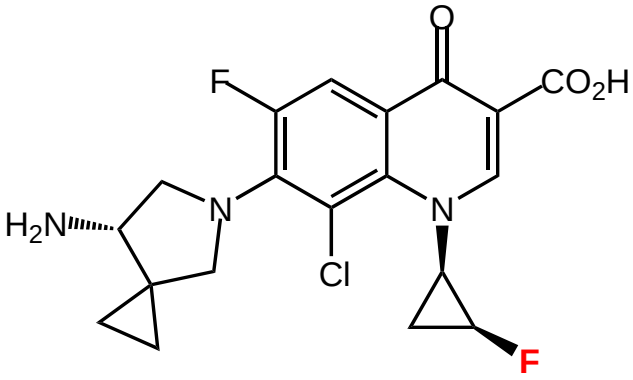
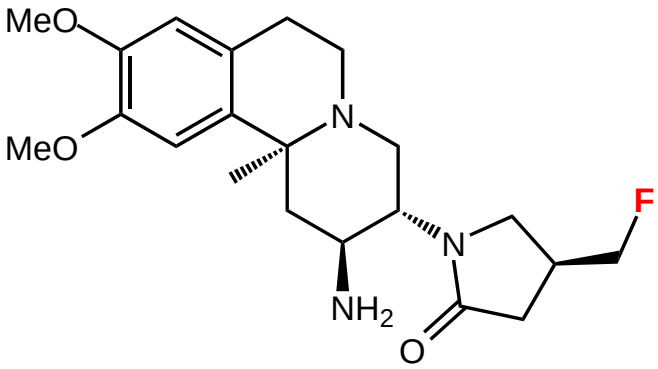
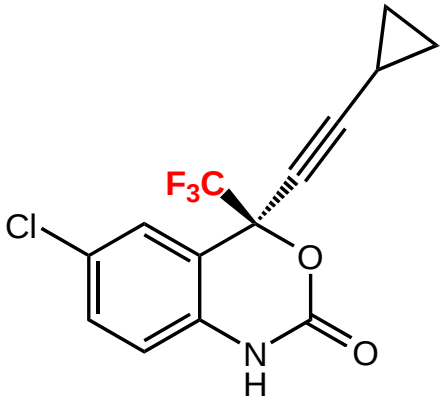


治疗严重难治的细菌感染



II-型糖尿病用药

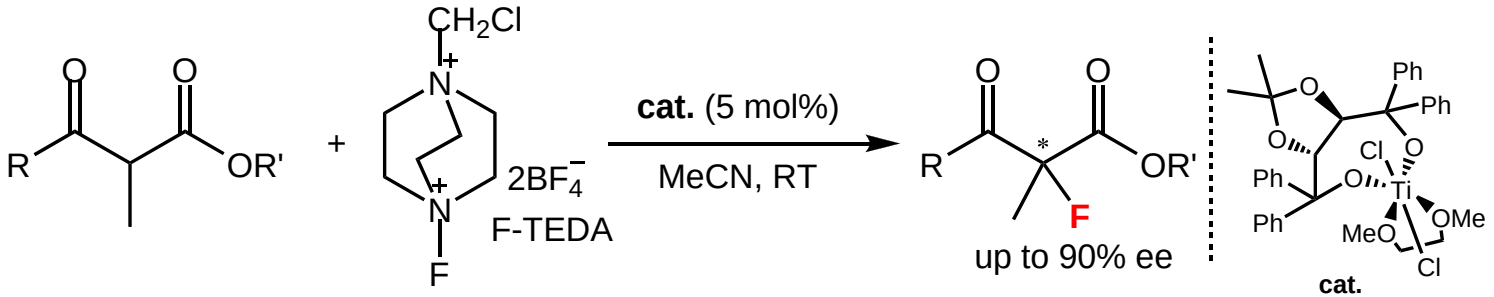


治疗人类免疫缺陷病毒HIV-I型

20% of drugs contain "**F**"

Purser, S. *et al. Chem. Soc. Rev.* **2008**, *37*, 320–330.

Introduction



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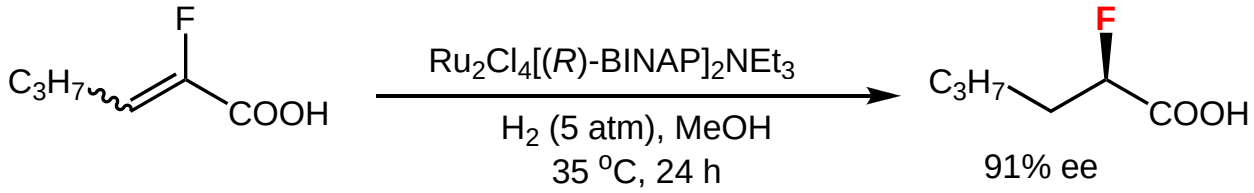

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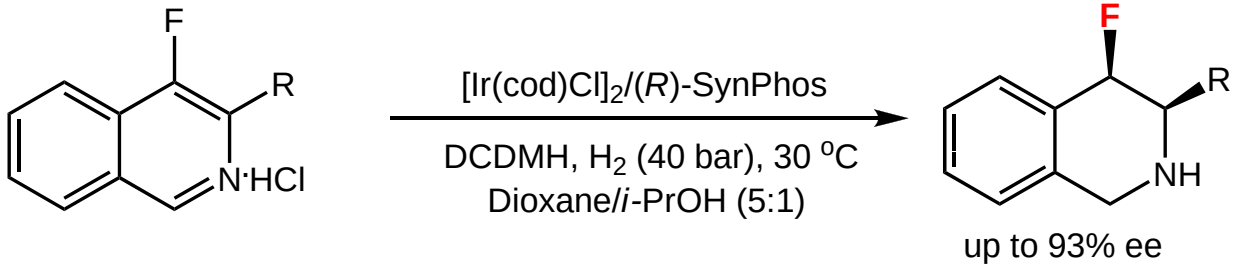
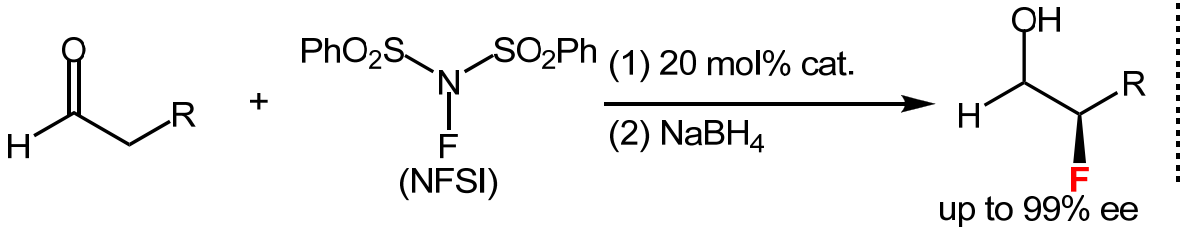
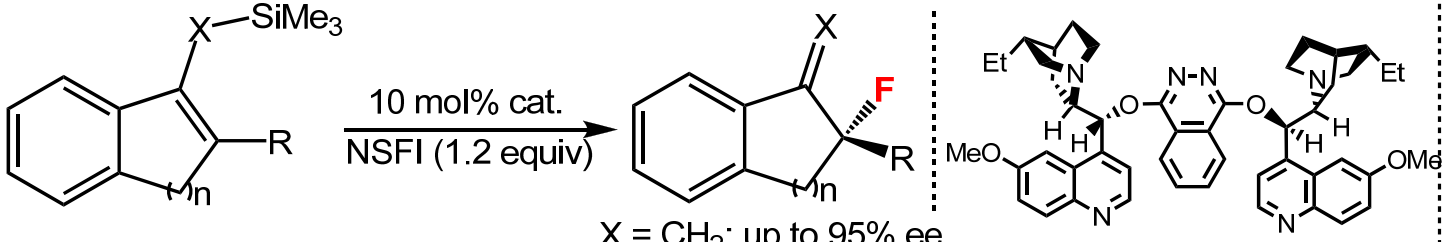


Zhou, Y.-G. *et al. Chem. Commun*. **2013**, *49*, 8537-8539.

Introduction

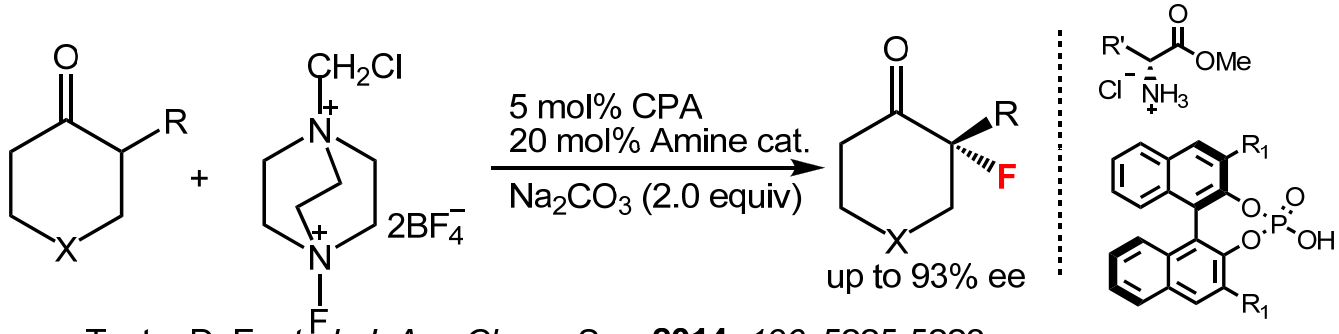


MacMillan, D. W. C. *et al. J. Am. Chem. Soc.* **2005**, *132*, 8826-8828;
Jφrgensen, K. A. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 3703-3706;
Barbas, C. F. III *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 3706-3710.



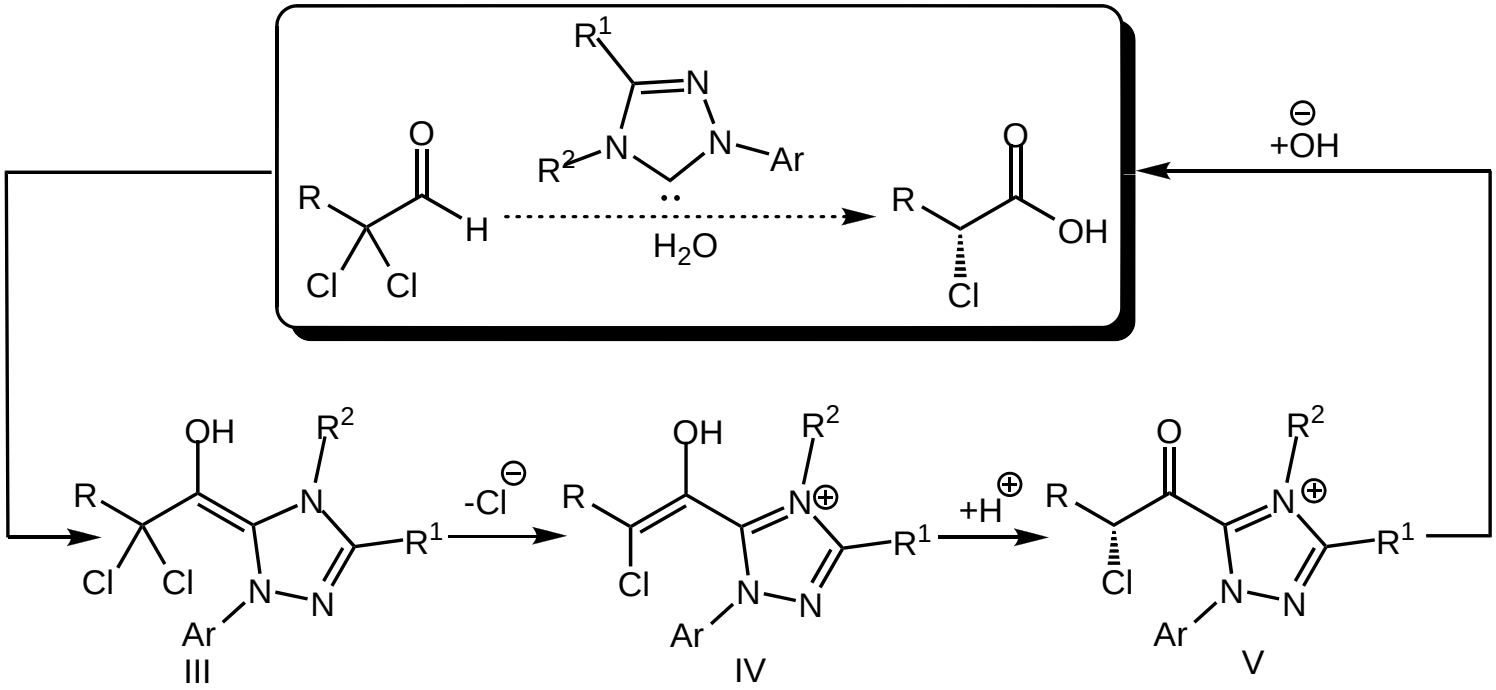
X = CH_2; up to 95% ee
X = O; up to 86% ee

Shibata, N. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 4157-4161.



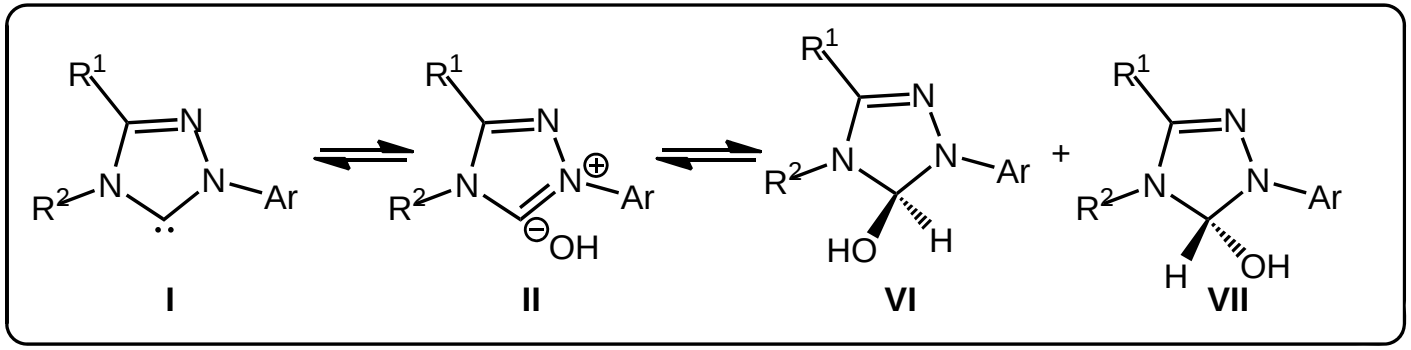
Toste, D. F. *et al. J. Am. Chem. Soc.* **2014**, *136*, 5225-5228.

N-heterocyclic carbene catalyzed asymmetric hydration: direct synthesis of α-protio and α-deuterio α-chloro and α-fluoro carboxylic acids

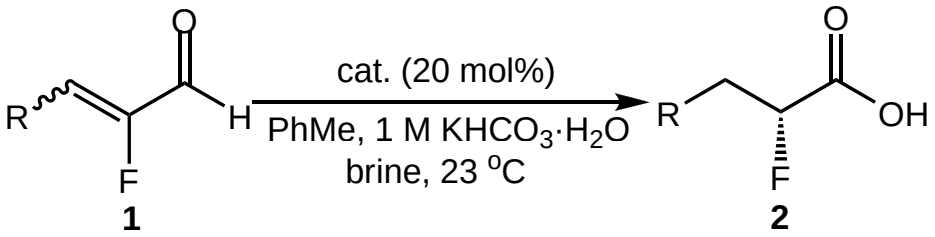


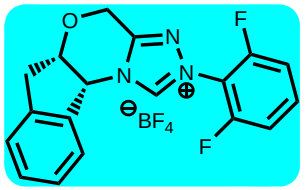
Rovis, T. *et al. J. Am. Chem. Soc.* **2010**, *132*, 2860–2861.

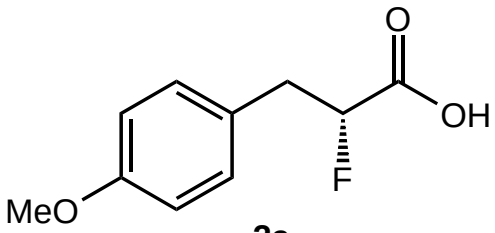
Hemiaminal Formation



Scope of α-fluoro carboxylic acids

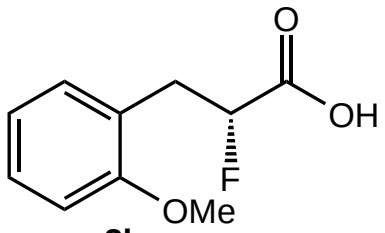






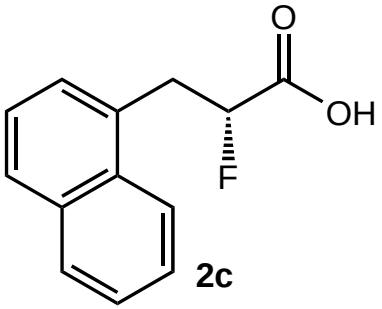
2a

(*Z*): 93% ee, 84% yield
(*E*): 93% ee, 42% yield
mixture: 93% ee, 74% yield



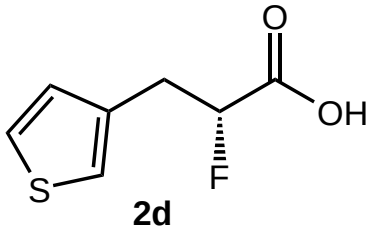
2b

96% ee, 80% yield



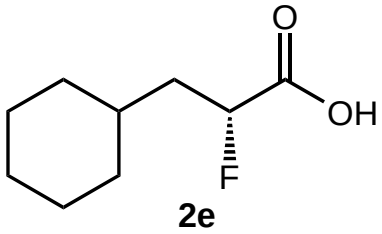
2c

94% ee, 77% yield



2d

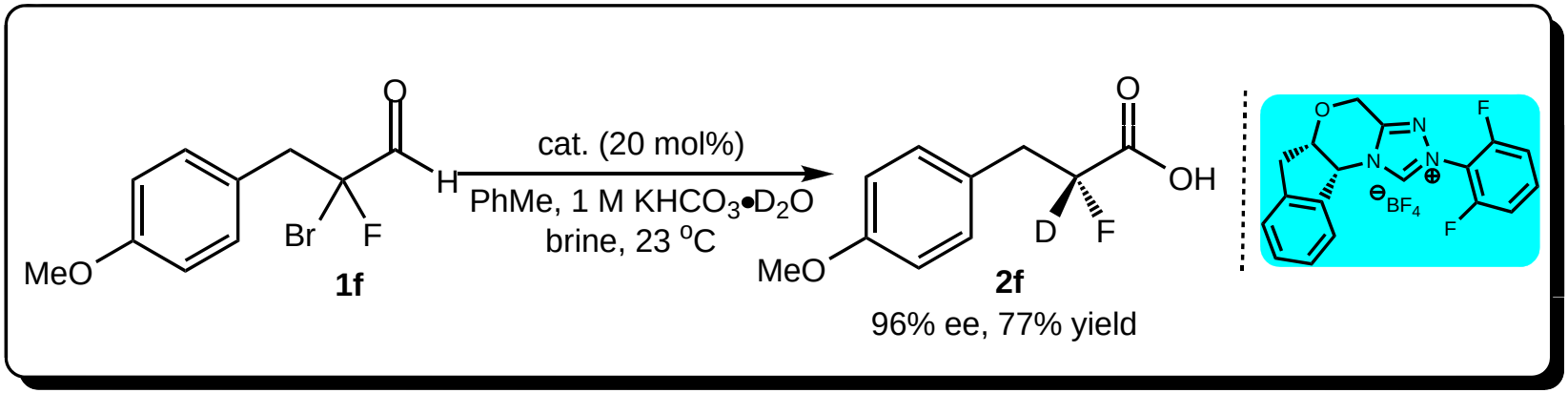
90% ee, 70% yield



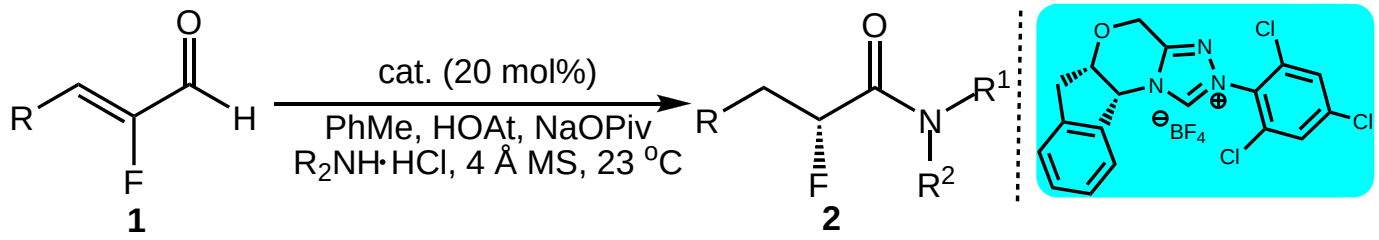
2e

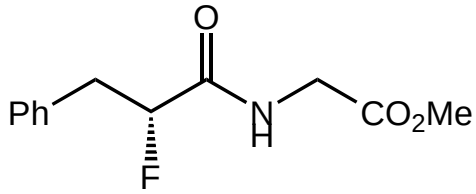
96% ee, 65% yield

α-Deuteron in an asymmetric fashion using D_2O

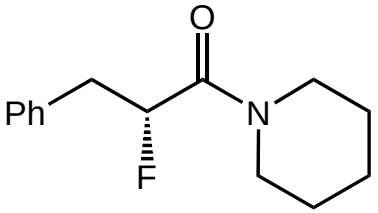


Asymmetric NHC-catalyzed synthesis of α-fluoroamides from readily accessible α-fluoroenals

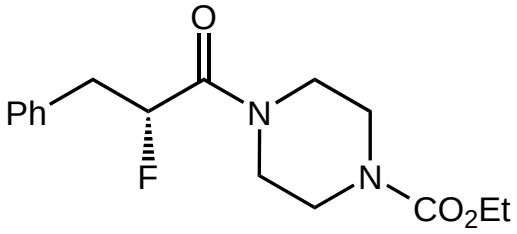




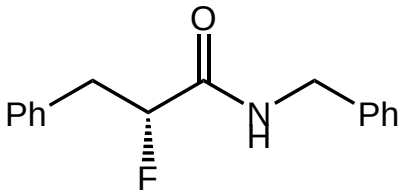
2a: 92% ee, 75% yield



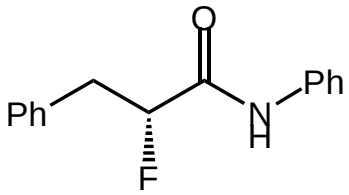
2b: 90% ee, 81% yield



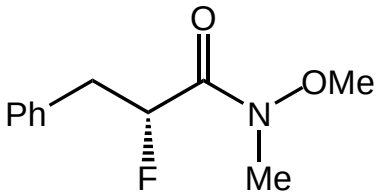
2c: 92% ee, 60% yield



2d: 92% ee, 63% yield



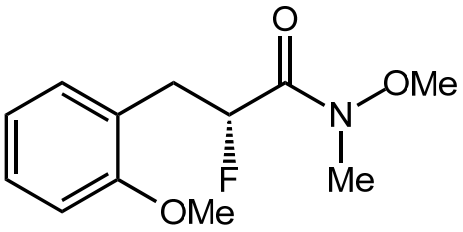
2e: 90% ee, 71% yield



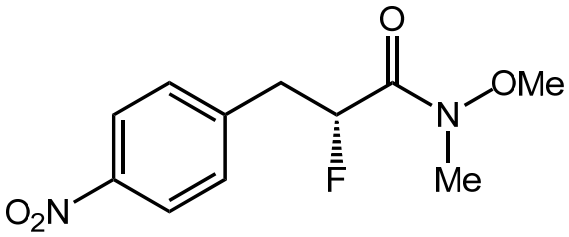
2f: 96% ee, 96% yield

Rovis, T. *et al. Chem. Sci.* **2013**, *4*, 1674-1679.

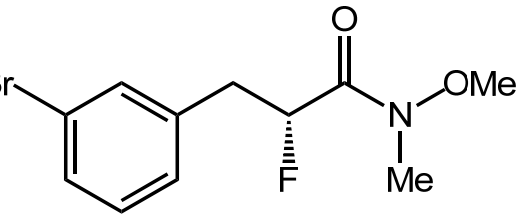
Scope of α-fluoroamides



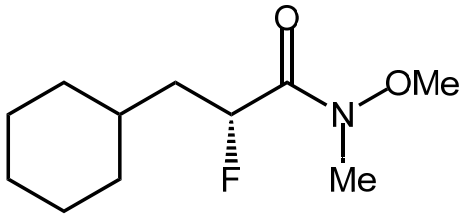
2g: 92% ee, 79% yield



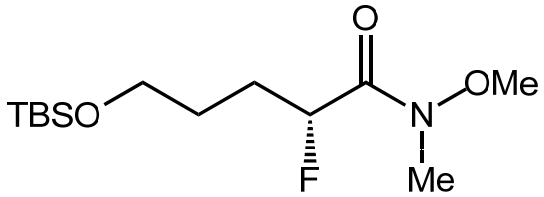
2h: 92% ee, 78% yield



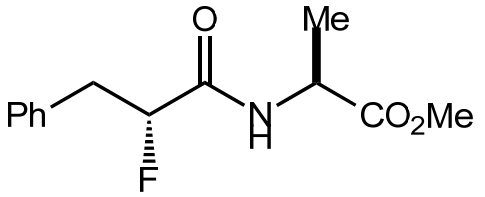
2i: 88% ee, 86% yield



2j: 98% ee, 99% yield

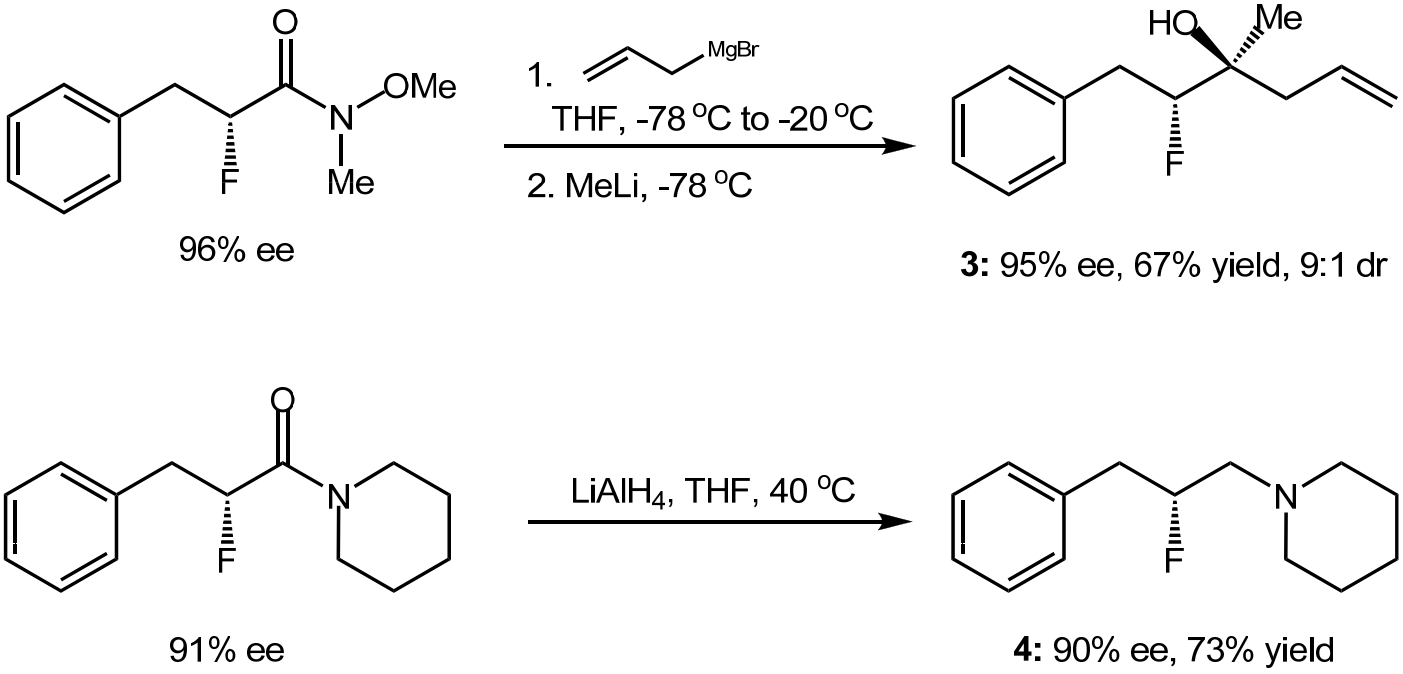


2j: 92% ee, 98% yield

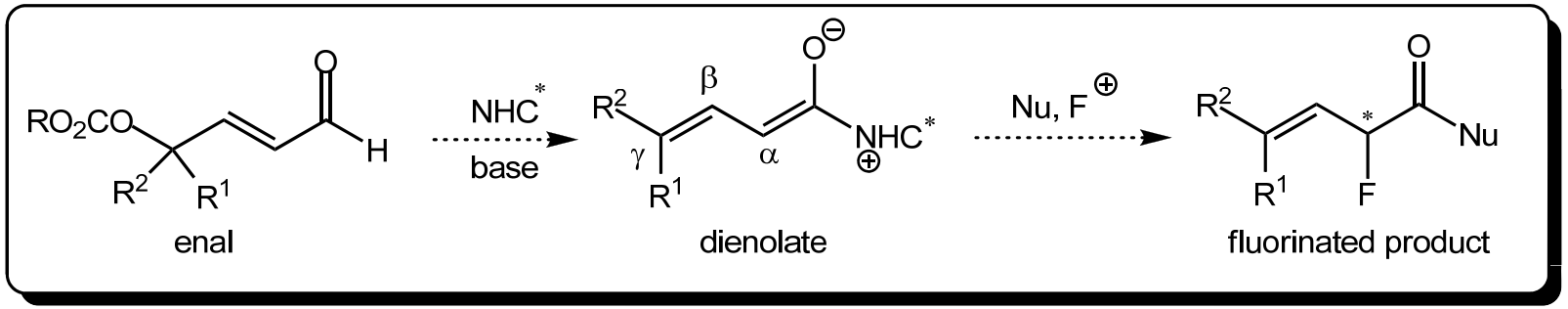


2k: 70% yield, 97:3 dr

Transformations of α-fluoroamides



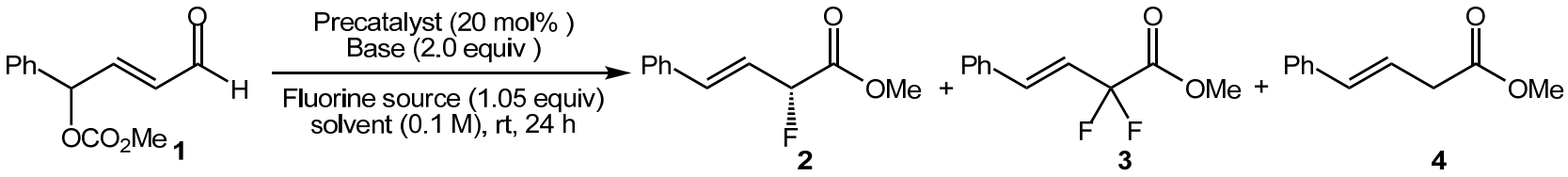
Enantioselective synthesis of β,γ-unsaturated α-fluoro-esters catalyzed by *N*-heterocyclic carbenes

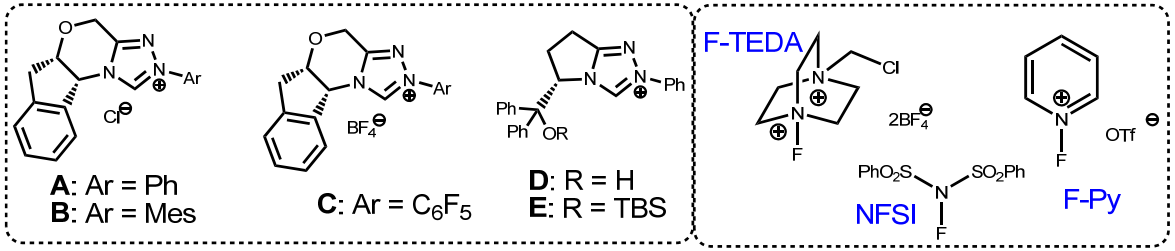


Challenges:
- Regioselectivity (α versus γ)
- Mono-versus difluorination (enolizable product)
- Fluorination versus protonation
- Stereocontrol (small F atom)
- Product racemization (basic conditions)

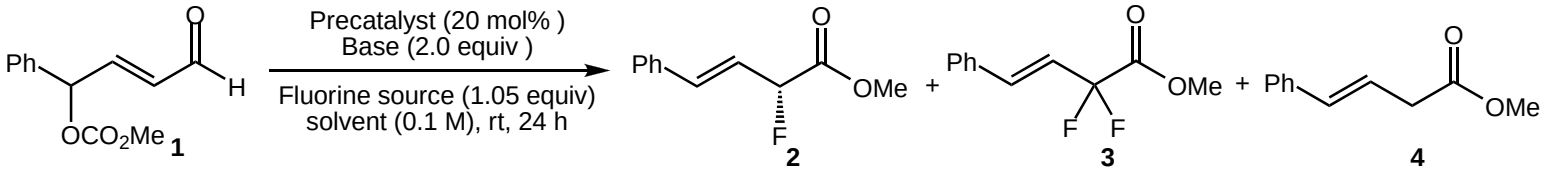
Sun, J. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 10359-10363.

Effect of reaction parameters





Effect of reaction parameters



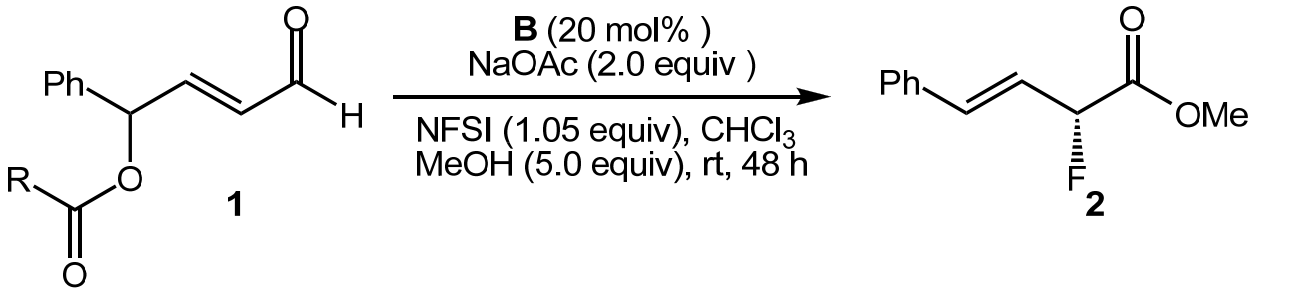
Entry	Precat.	Base	Fluorine source	Solvent	Yield of **2** (%)	Ee of **2** (%)	**2**:**3**:**4**
1	**A**	NaOAc	F-TEDA	DCM	22	5	53:36:11
2	**B**	NaOAc	F-TEDA	DCM	32	75	66:27:7
3	**C**	NaOAc	F-TEDA	DCM	48	12	87:10:3
4	**D**	NaOAc	F-TEDA	DCM	n.r.	-	-
5	**E**	NaOAc	F-TEDA	DCM	n.r.	-	-
6	**B**	NaOAc	F-Py	DCM	0	-	-
7	**B**	NaOAc	NFSI	DCM	20	94	67:33:0

Effect of reaction parameters

8	**B**	NaOAc	NFSI	THF	<10	-	21:76:3
9	**B**	NaOAc	NFSI	CH_3CN	0	-	0:100:0
10	**B**	NaOAc	NFSI	$CHCl_3$	55	92	82:18:0
11	**B**	NaOAc	NFSI	Benzene	26	91	61:39:0
12	**B**	DBU	NFSI	$CHCl_3$	0	-	0:100:0
13	**B**	HCO_2Na	NFSI	$CHCl_3$	n.r.	-	-
14	**B**	K_3PO_4	NFSI	$CHCl_3$	0	-	0:100:0
15	**B**	-	NFSI	$CHCl_3$	n.r.	-	-
16 [a]	**B**	NaOAc	NFSI	$CHCl_3$	82	92	>98:1:1
17 [a,b]	**B**	**NaOAc**	**NFSI**	**$CHCl_3$**	**91**	**92**	**>98:1:1**

[a] Additive MeOH; [b] The concentration was 0.05 M, **B =** 10 mol%.

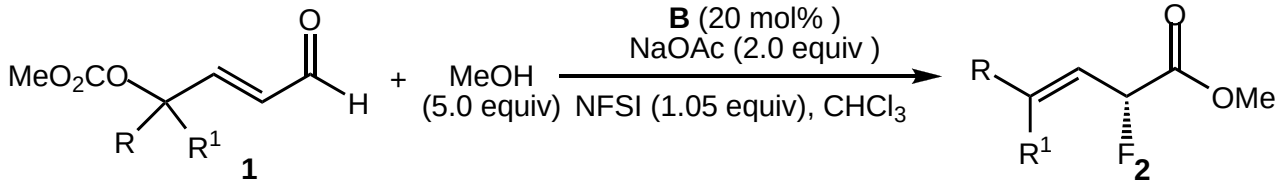
Effect of reaction parameters

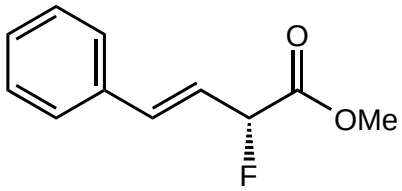


1: R = OMe
5: R = OEt
6: R = O^{t}Bu
7: R = Me

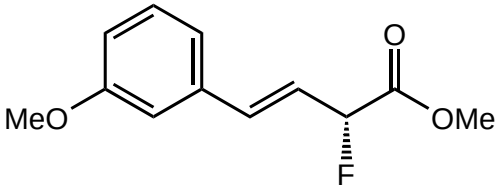
74% yield, 92% ee
72% yield, 92% ee
61% yield, 92% ee
73% yield, 92% ee

Scope of α-fluoroesters

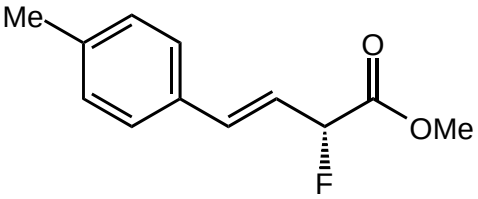




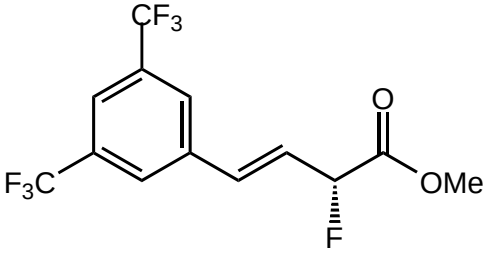
2: 92% ee, 74% yield



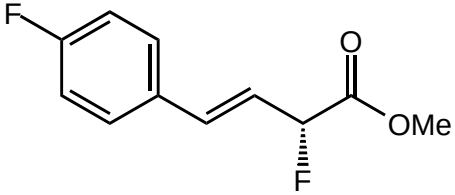
8: 93% ee, 75% yield



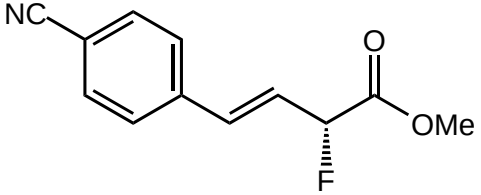
9: 93% ee, 62% yield



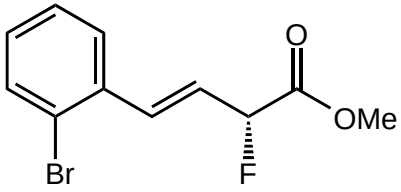
10: 85% ee, 71% yield



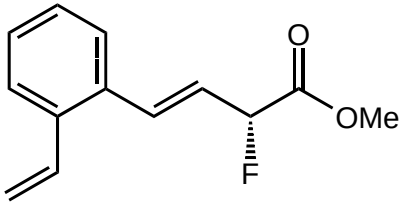
11: 92% ee, 71% yield



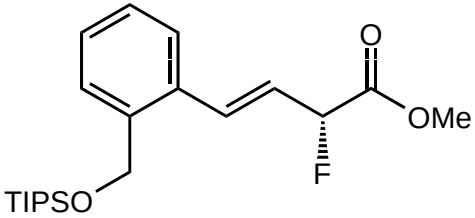
12: 86% ee, 86% yield



13: 92% ee, 82% yield

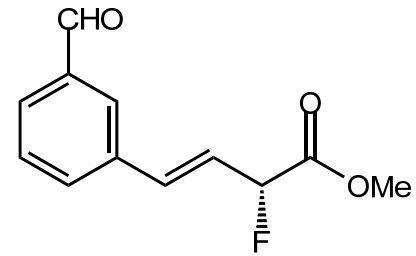


14: 91% ee, 68% yield

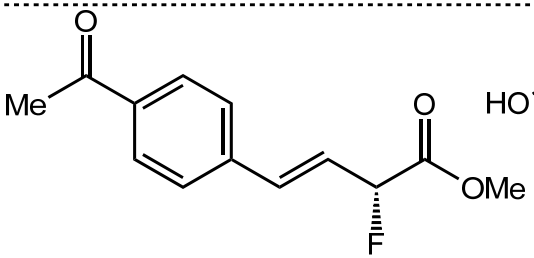


15: 91% ee, 79% yield

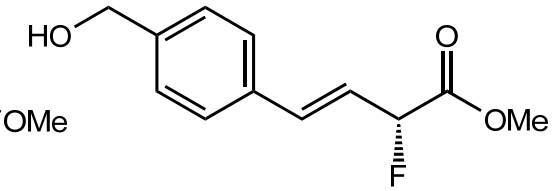
Scope of α-fluoroesters



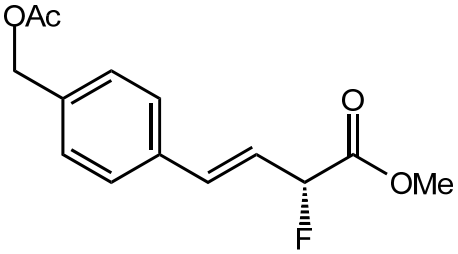
16: 92% ee, 74% yield



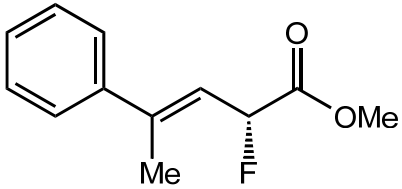
17: 91% ee, 81% yield



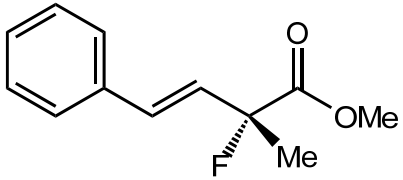
18: 92% ee, 73% yield



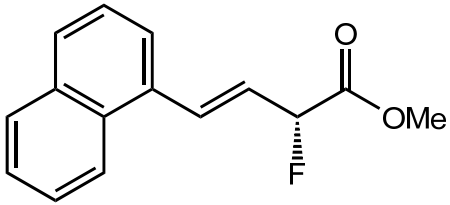
19: 92% ee, 81% yield



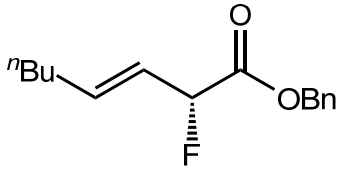
20: 77% ee, 67% yield



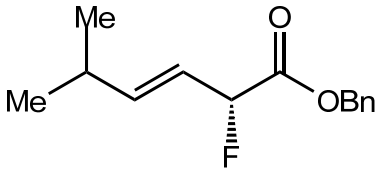
21: 55% ee, 5% yield



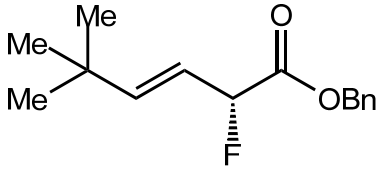
22: 64% yield
(*Z*/*E* = *6.3:1*)
90% ee (*E*);
96% ee (*Z*)



23: 86% yield
(*Z*/*E* = *3:2*)
95% ee (*E*);
97% ee (*Z*)

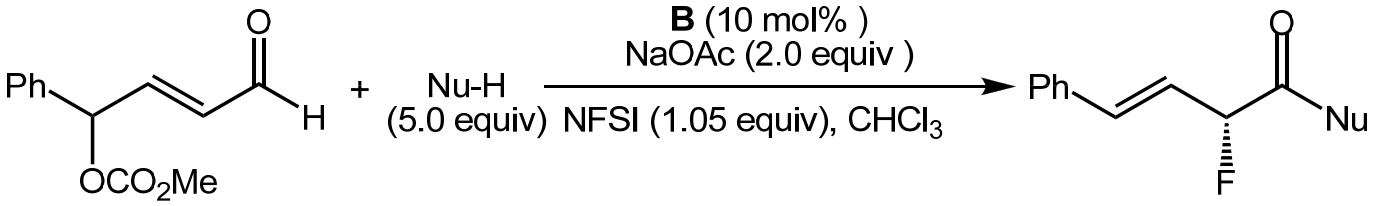


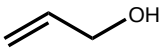
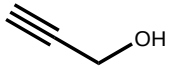
24: 74% yield
(*Z*/*E* = *5.3:2*)
94% ee (*E*);
93% ee (*Z*)



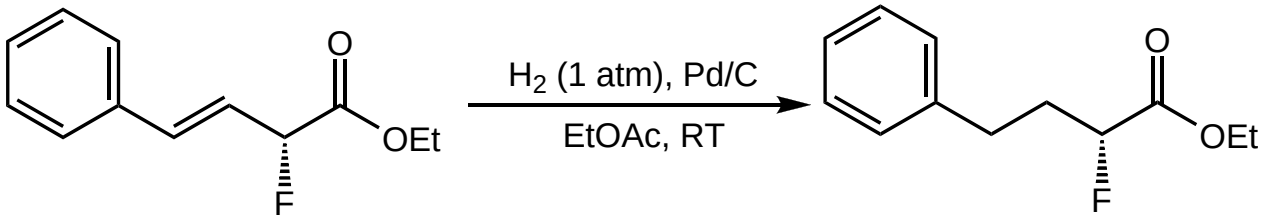
25: 61% yield
(*E*/*Z* > *99:1*)
95% ee

Scope of α-fluoroesters



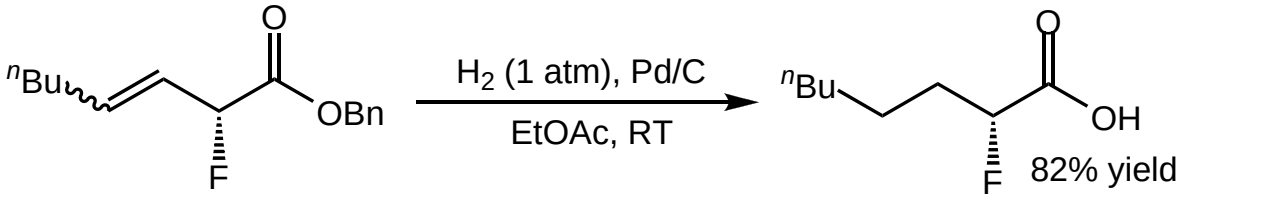
Entry	Nu-H	Product	Yield (%)	Ee (%)
1	EtOH	26	72	90
2	^{i}PrOH	27	51	96
3	BuOH	28	64	94
4		29	73	91
5		30	72	92
6	CD_3OD	31	69	93

Transformations of α-fluorinated esters



26: 90% ee

32: 91% ee, 90% yield

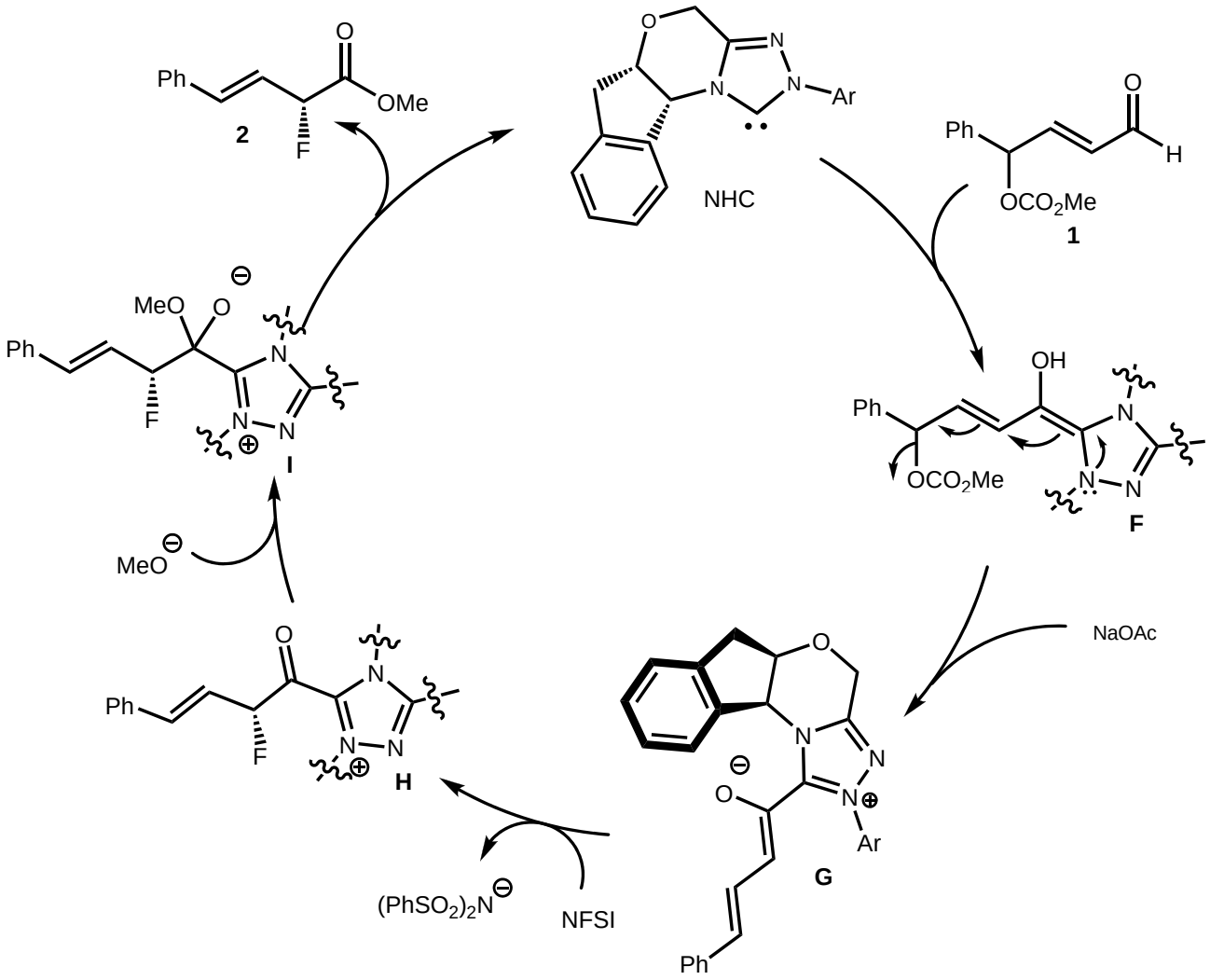


82% yield

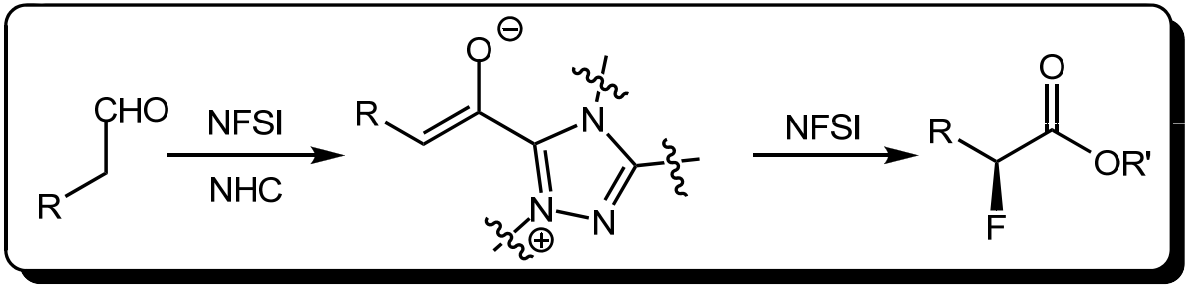
23: (*E*/*Z* = 3:2, 90% ee)

33: $[\alpha]_D^{28}$ = + 9.7 (c = 1.25, $CHCl_3$)

Postulated mechanism



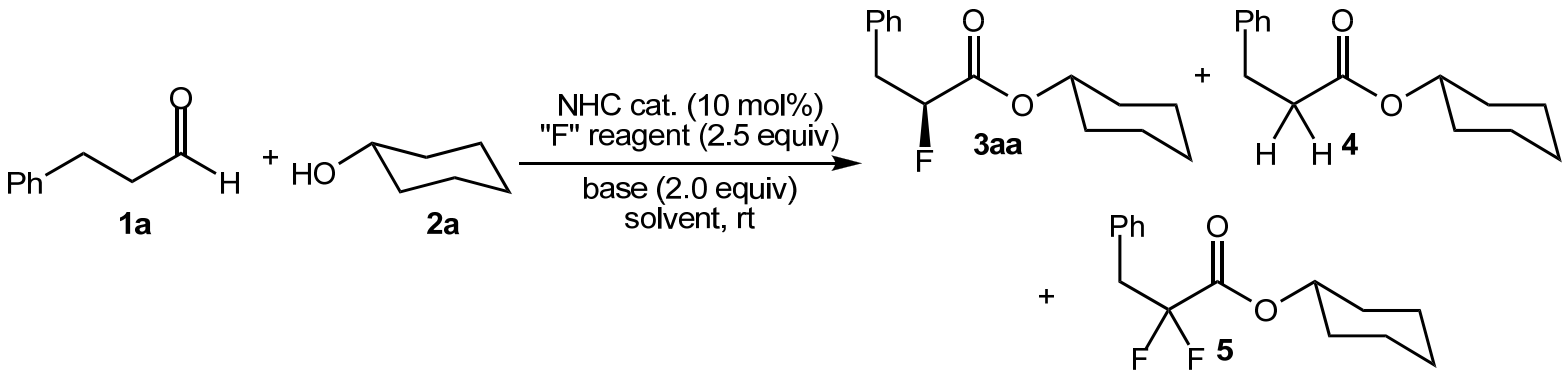
Oxidative enantioselective α-fluorination of aliphatic aldehydes enabled by *N*-heterocyclic carbene catalysis

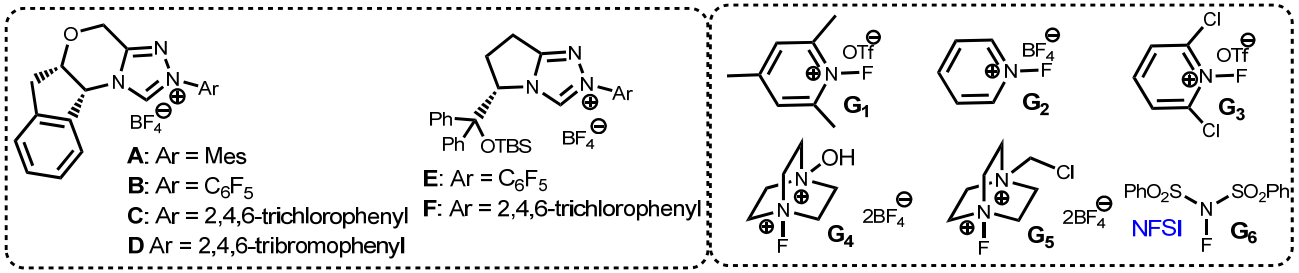


- NFSI as oxidant
- NFSI as "F" resource
- C-F bond formation
- Monofluorination
- Readily available aldehyde

Wang, J. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 656-659.

Optimization of the conditions





Optimization of the conditions

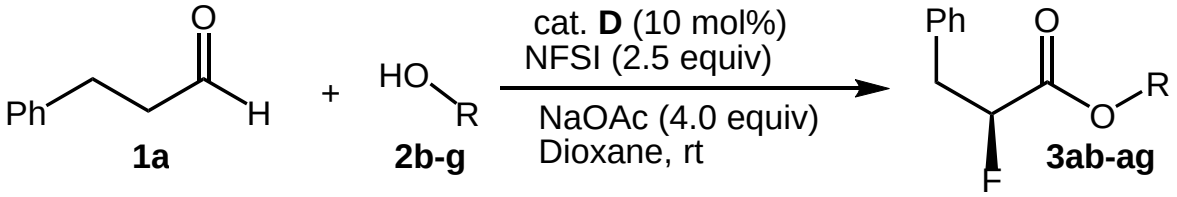
Entry	NHC	Base	Solvent	"F" reagent	**3aa** Yield (%)	**3aa** Ee (%)	**4** Yield (%)	**5**
1	**A**	K_2CO_3	toluene	**G6**	n.r.	-	-	trace
2	**B**	K_2CO_3	toluene	**G6**	66	74	10	trace
3	**C**	K_2CO_3	toluene	**G6**	84	92	<5	trace
4	**D**	K_2CO_3	toluene	**G6**	86	92	<5	trace
5	**E**	K_2CO_3	toluene	**G6**	<5	-	12	trace
6	**F**	K_2CO_3	toluene	**G6**	-	-	20	trace
7	**D**	K_2CO_3	DCM	**G6**	56	93	<10	trace
8	**D**	K_2CO_3	THF	**G6**	46	86	<10	trace
9	**D**	K_2CO_3	dioxane	**G6**	72	94	<5	trace

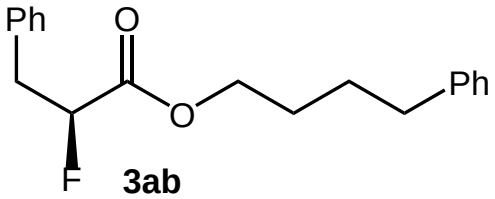
Optimization of the conditions

Entry	Base	"F" reagent	**3aa** Yield (%)	**3aa** Ee (%)	**4** Yield (%)	**5**
10	$PhCO_2Na$	**G6**	50	92	<5	trace
11	K_3PO_4	**G6**	77	94	<5	trace
12	NaOAc	**G6**	78	96	<5	trace
13 [a]	**NaOAc**	**G6**	**84**	**96**	**<5**	**trace**
14	NaOAc	**G1**	n.r.	-	-	-
15	NaOAc	**G2**	n.r.	-	-	-
16	NaOAc	**G3**	n.r.	-	-	-
17	NaOAc	**G4**	<5	-	-	-
18	NaOAc	**G5**	31	83	-	-

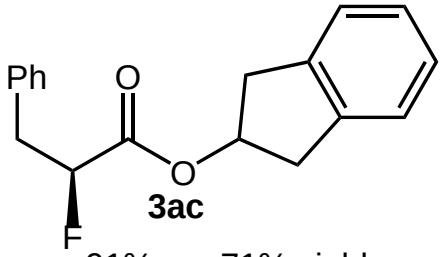
[a] NaOAc (4.0 equiv)

Scope with respect to the alcohol

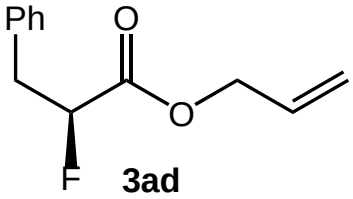




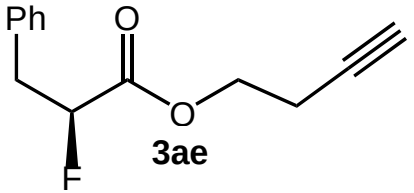
90% ee, 78% yield



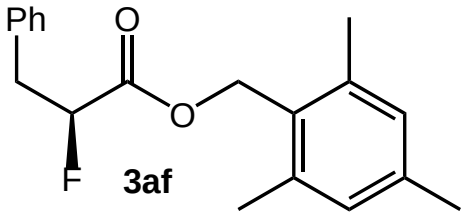
91% ee, 71% yield



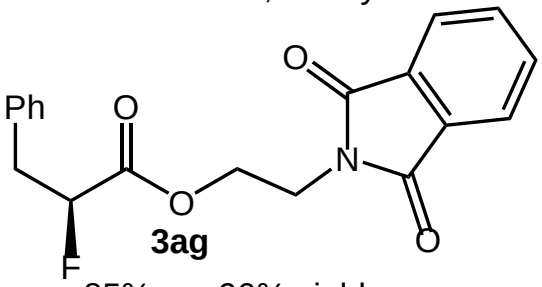
73% ee, 89% yield



79% ee, 92% yield

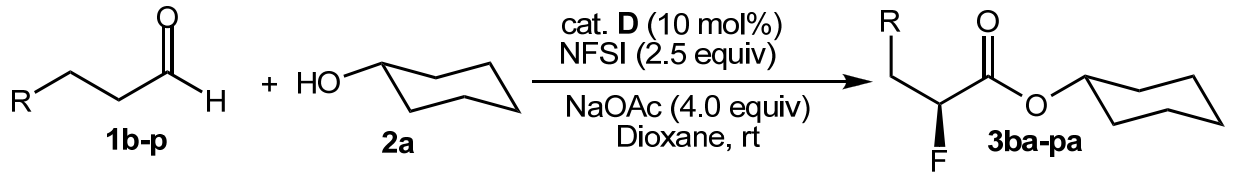


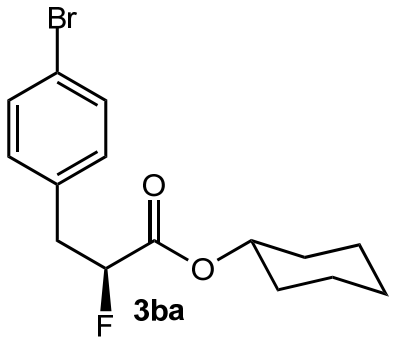
91% ee, 86% yield



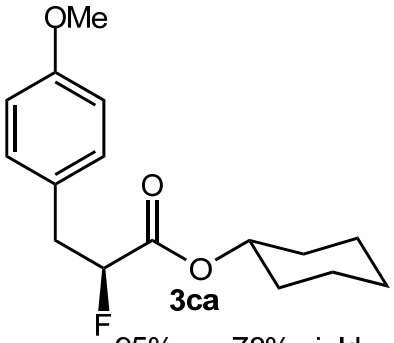
85% ee, 90% yield

Scope with respect to the aldehyde

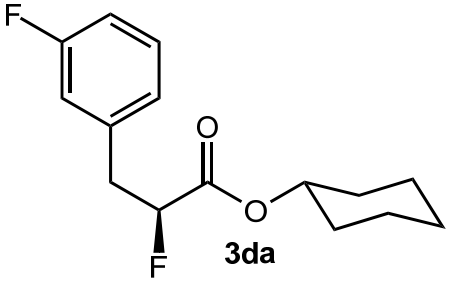




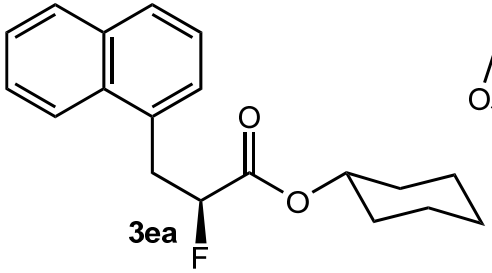
96% ee, 88% yield



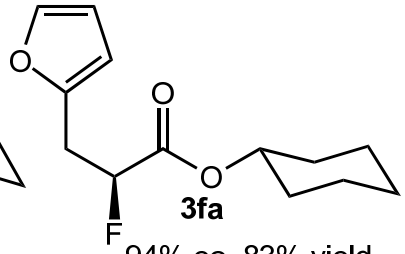
95% ee, 78% yield



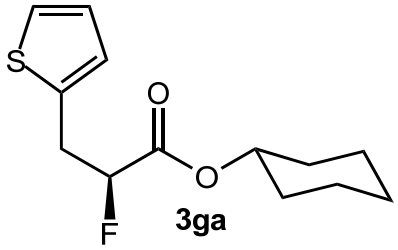
95% ee, 84% yield



94% ee, 84% yield

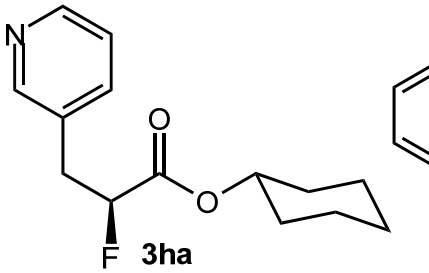


94% ee, 83% yield



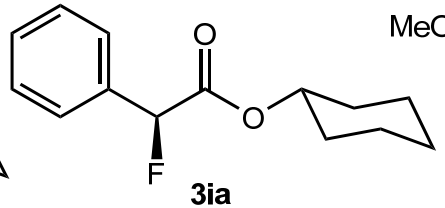
95% ee, 83% yield

Scope with respect to the aldehyde



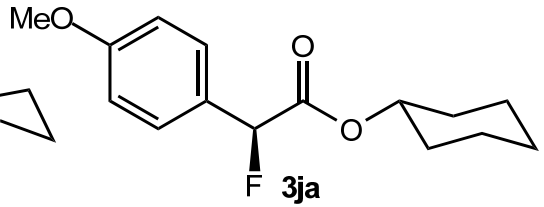
3ha

96% ee, 79% yield



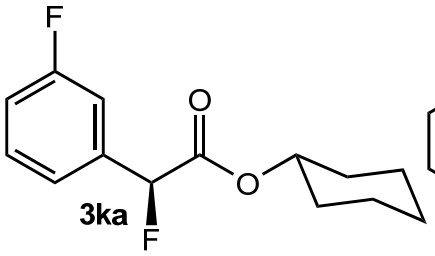
3ia

98% ee, 73% yield



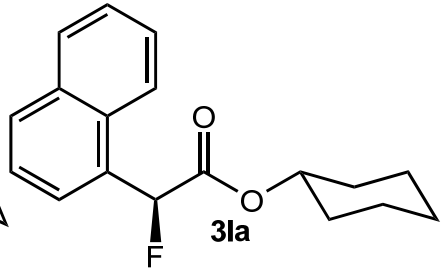
3ja

92% ee, 74% yield



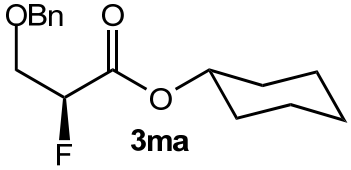
3ka

95% ee, 76% yield



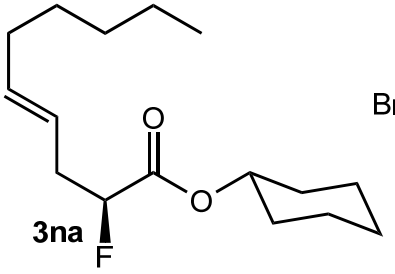
3la

96% ee, 71% yield



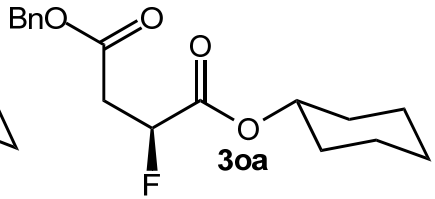
3ma

88% ee, 80% yield



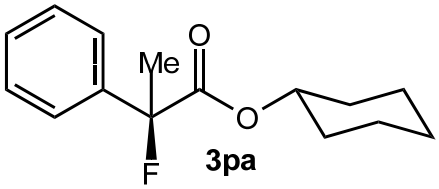
3na

98% ee, 81% yield



3oa

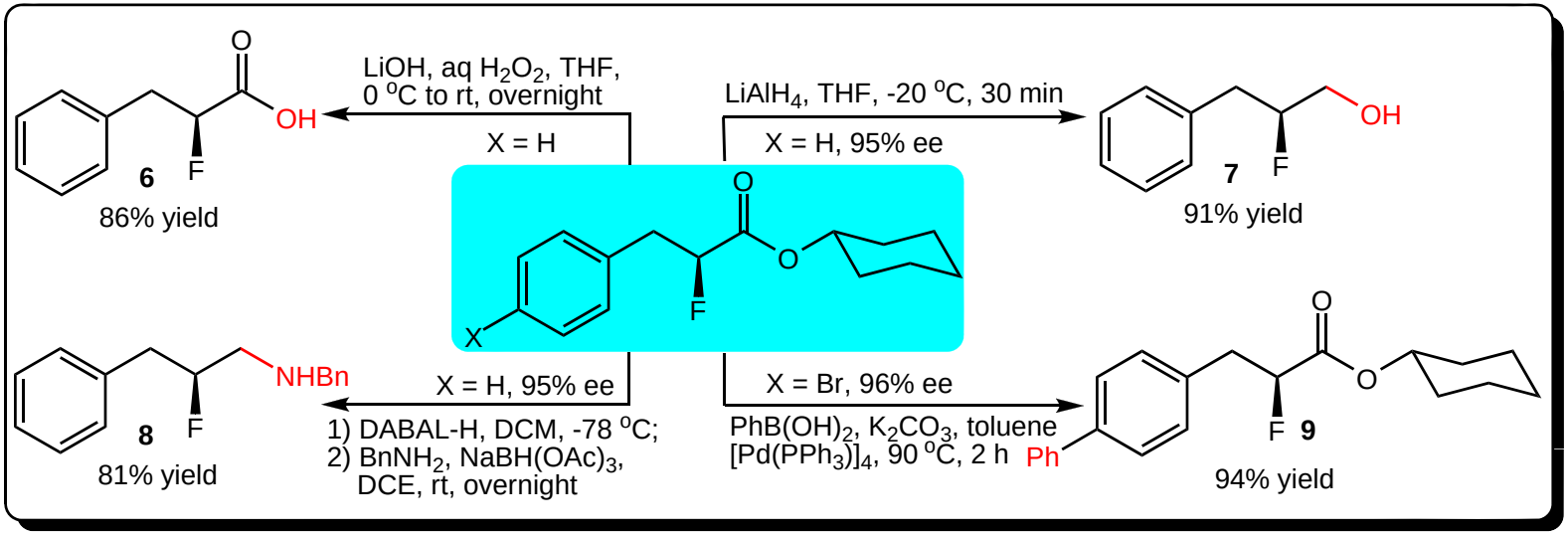
80% ee, 82% yield



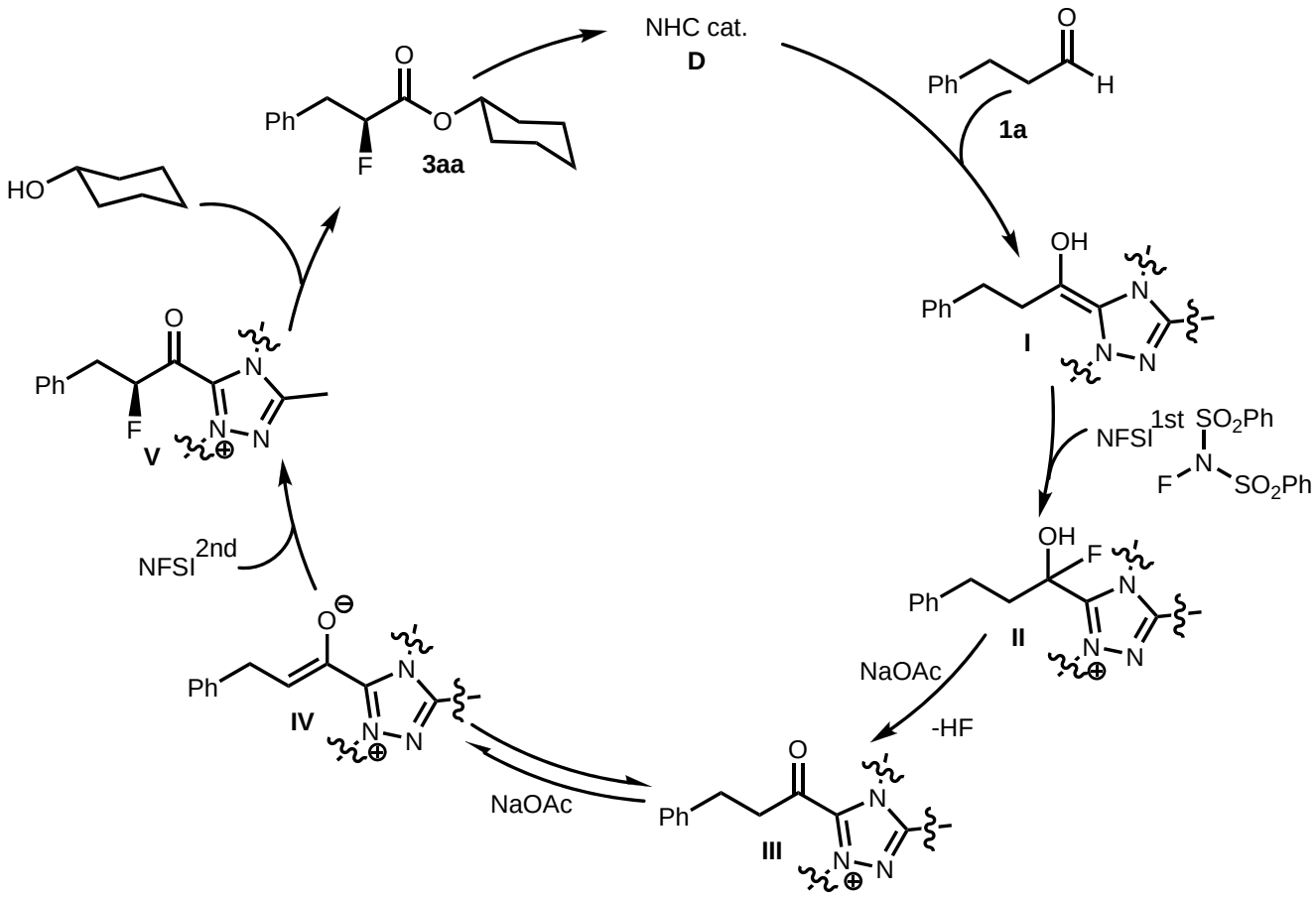
3pa

77% ee, 78% yield

Transformations of α-fluorinated esters

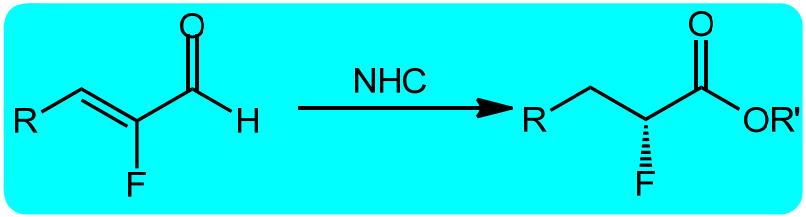


Postulated mechanism

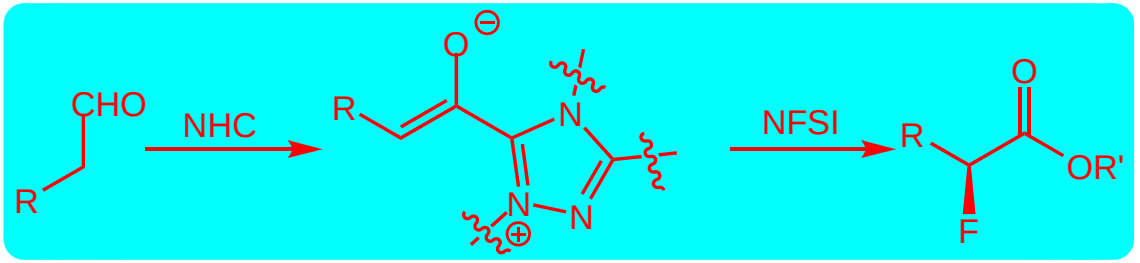


Summary

Rovis's work



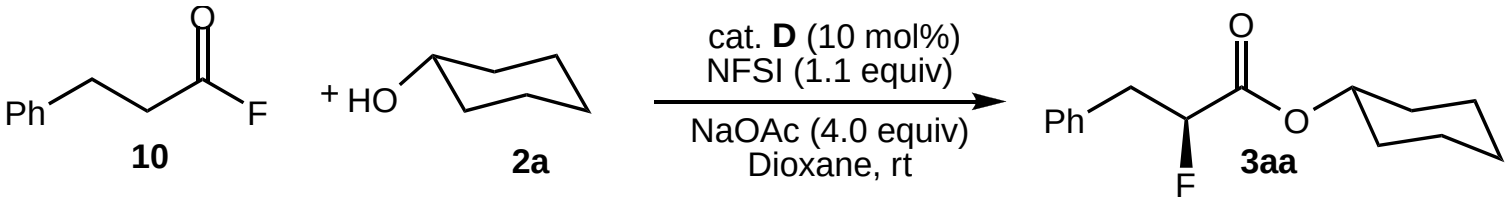
Sun and Wang's work



Organofluorine compounds display a wide range of distinct physical properties which often render them valuable to the pharmaceutical companies and agrochemical industries. In particular, fluorine atom incorporation has become an effective tool for medicinal chemists to alter the bioactivity of drug candidates. Despite the broad-spectrum utility of such C-F bond containing compounds, it is remarkable to consider that only a few catalytic methods exist for the asymmetric installation of fluorine onto carbogenic frameworks and that most of these methods have focused on the generation of non-enolizable products such as α-alkyl-β-ketoesters. Given that chiral α-fluoro carbonyl compounds have been identified as high-value synthons for chemical synthesis, great progress has been made by employing chiral metal complexes for electrophilic fluorination of activated Ketones, nucleophilic fluorination of ketenes, and using nucleophilic fluorine sources for enantioselective allylic fluorination. Enamine catalysis has furnished a number of protocols for highly enantioselective α-fluorination of aldehydes and ketones. Cinchona alkaloids have been effective for fluorination of carbon nucleophiles and in a dual catalysis mechanism to enable the fluorination of acyl chlorides. Recently, a combination of chiral-anion phase-transfer catalysis and enamine catalysis has been reported to

generate α-branched α-fluoroketones. Surprisingly, despite the availability of a variety of N-heterocyclic carbene (NHC) catalysts. In contrast to the NHC-catalyzed α-C-C bond formation reaction the disclosures of enantioselective α-fluorination of simple aliphatic aldehydes catalyzed by chiral NHC catalysts has not yet been reported. Herein, we report the first example of oxidative enantioselective α-fluorination of simple aliphatic aldehydes catalyzed by an NHC catalyst. It is noteworthy that NFSI is disclosed not only as an electrophilic fluorinating resource but also as an oxidant in asymmetric organocatalysis.

In summary, the first study of an NHC-catalyzed oxidative enantioselective α-fluorination of simple aliphatic aldehydes using NFSI, which plays two roles, is presented. In the presence of an appropriate combination of a NHC precatalyst, a base, an oxidant (NFSI), and a “F” resource (NFSI), the C-F bond formation occurs directly at the a position of simple aliphatic aldehydes and proceeds with high to excellent enantioselectivities.



96% ee, 90% yield