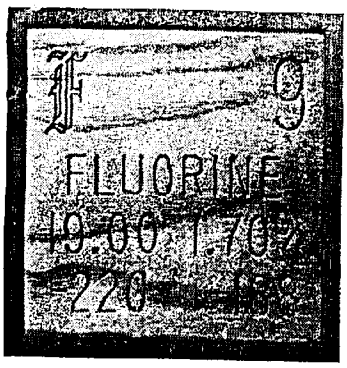


Literature Seminar (2004/05/15)
D3 M. Suzuki

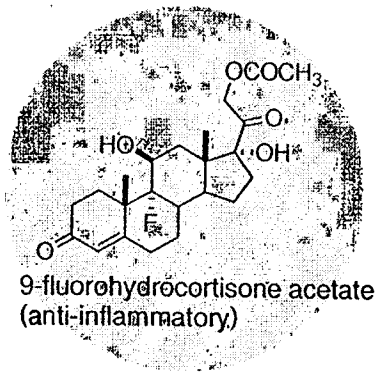
Fluorine Chemistry

~Construction of Fluorinated Organic Compounds ~

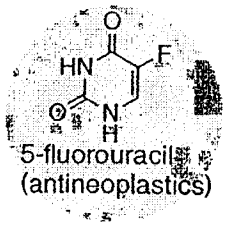
The synthesis of fluoro-organic compounds is an important topic in modern chemistry. The replacement of hydrogen or hydroxy with fluorine is an extensively used strategy for enhancement of activity in the design of important molecules. The several advantages of fluorine substitution include an increase in stability, changes in lipophilicity, introduction of a center of high electronegativity, and altered patterns of reactivity of the C-F vs the C-H bond.

Bio-, Organic chemistry

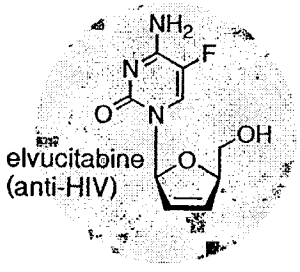
(pharmaceuticals and other materials)



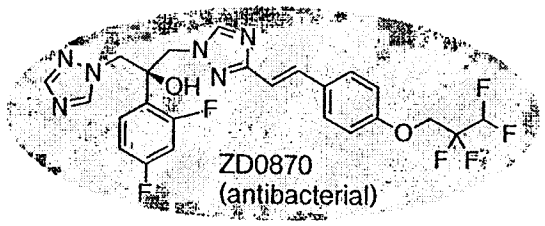
9-fluorohydrocortisone acetate
(anti-inflammatory)



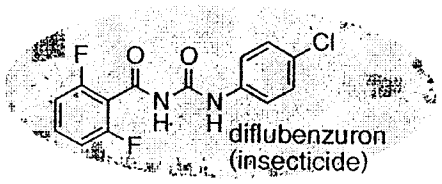
5-fluorouracil
(antineoplastics)



elvucitabine
(anti-HIV)



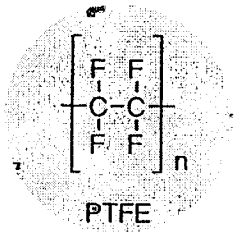
ZD0870
(antibacterial)



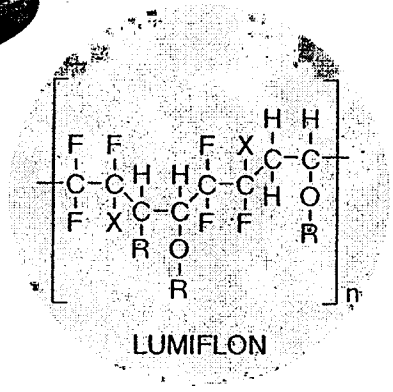
diflubenzuron
(insecticide)

Functional materials chemistry

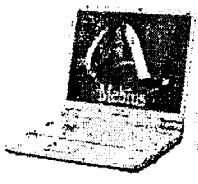
(liquid crystals and other compounds)

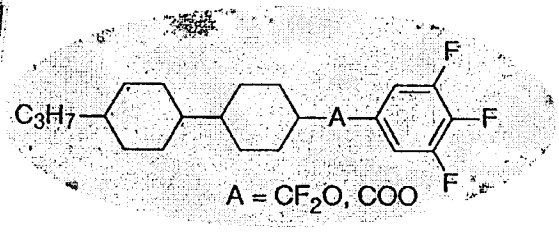


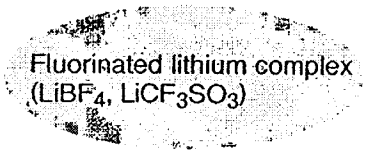
PTFE



LUMIFLON







Fluorinated lithium complex
($LiBF_4$, $LiCF_3SO_3$)

Contents

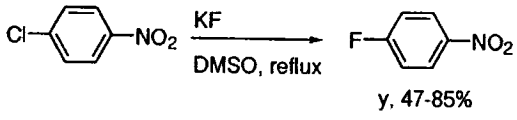
1. Classification of construction of fluorinated compounds
2. What's the fluorine ? (properties and effects of the fluorine atom ...)
3. Fluorination of organic compounds (asymmetric reaction)

1.

Construction of fluorinated compounds (Organic or Inorganic)

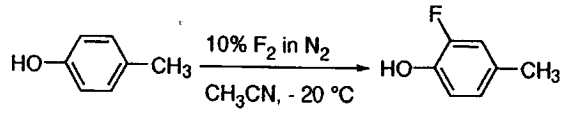
- Conversion of fluorinated compound (introduce R_f, RCH_2F ...)
- Introduction of elemental fluorine
  - 1. Nnucleophilic fluorination
  - 2. Electrophilic
  - 3. Rradicalic

Nucleophilic rxn.



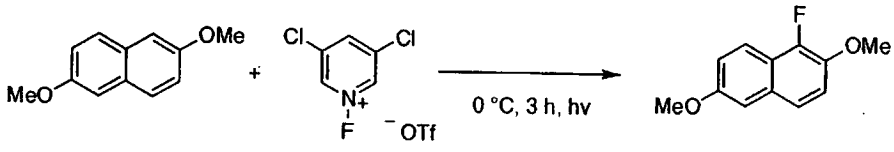
y, 47-85%

Electrophilic rxn.



y, 39%

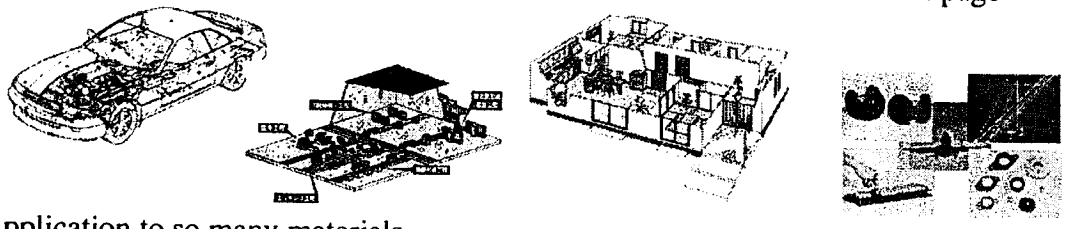
Radicalic rxn.



- 1. Nucleophilic fluorination
- 2. Electrophilic
  - A) Racemic reaction
  - B) Diastereoselective reaction
  - C) Direct asymmetric reaction --- Lang, Davis, Togni, Cahard, Sodeoka ... (from *stoichiometric* to *catalytic* reaction)

pioneering work

Next page



Application to so many materials

Crystal structure and mechanism of a bacterial fluorinating enzyme

Changkang Dong[1], Fanglu Huang[1], Hai Deng[1], Christoph Schaffrath[1], Jonathan B. Spencer[2], David O'Hagan[1] & James H. Naismith[1]

Nature 427, 561-565, (2004)

Sea water contains 1.3 ppm fluoride and 19000 ppm chloride

Crystallographic phase

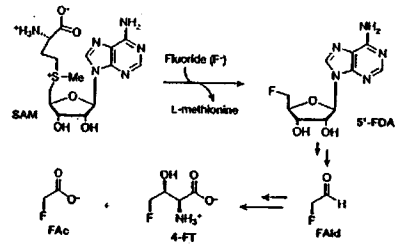
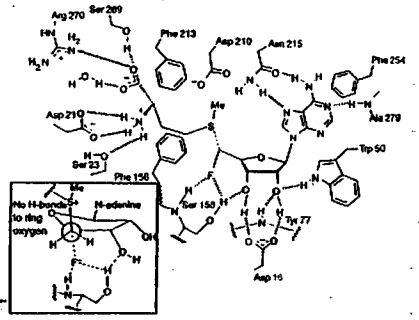


Figure 1 5'-FDAS from *S. cattleya* catalyses the formation of 5'-FDA from SAM and an F^- ion. 5'-FDA is the first-formed organofluorine metabolite, which is ultimately converted to fluoroacetate (FAc) and 4-fluorothreonine (4-FT) through fluoroacetaldehyde (FAld) by *S. cattleya*[26]. FAc is a toxin and 4-FT has antibiotic activity.

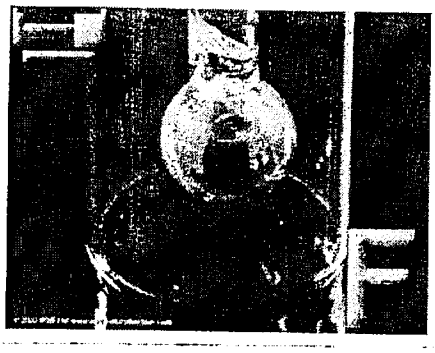


only one enzyme that can convert fluoride to organic fluorine has been described. JACS. 123, 7350-7351

Streptomyces cattleya can form carbon-fluorine bond.

only 13 naturally occurring organofluorine compounds have so far been found. The rarity of natural fluorinated products contrasts with the identification of about 3500 naturally occurring halogenated compounds.

2.



Isolation: (1886) H. Moissan

by electrolysis of anhydrous hydrogen fluoride (HF)

Fluorine occurs combined in the widely distributed mineral fluorite (Calcium fluoride, fluorspar), its chief source, in the minerals cryolite and fluoroapatite, and in small amounts in seawater, bones and teeth.

Chem. Rev. 2004, 104, 1-16.

Properties of the Fluorine Atom.

1) Steric effect: Me < ^iPr < CF_3 < ^tBu. (Es values)

2) Electronic effect: Table 1

3) Bond energy: Table 1

4) Lipophilicity: large lipophilicity assists.

5) Hydrogen bonding: Fig. 4

6) Position emission tomography (PET):

a short-lived isotope ^{18}F ($t_{1/2}$ = 110 min)

Figure 3. Energy barriers of the single bond rotation.

Table 1. Several Properties of H, F, Cl, and O (OH)

	IP[a] (kcal/mol)	EA[b] (kcal/mol)	vdW radius (Pauling) (Å)	EN[c] (Pauling)	BE[d] CH_3–X (kcal/mol)	CH_3–X (Å)
H	313.6	17.7	1.20	2.1	99	1.09
F	401.8	79.5	1.35	4.0	116	1.39
Cl	299.0	83.3	1.80	3.0	81	1.77
O (OH)	310.4	33.7	1.40	3.5	86	1.43

[a] IP = ionization potential. [b] EA = electron affinity. [c] EN = electronegativity. [d] BE = bond energy.

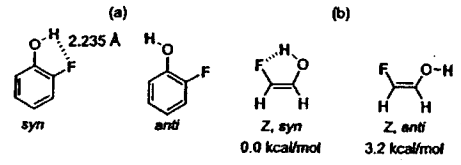


Figure 4. Hydrogen-bonding effect of fluorine-containing compounds.

Fluorine Effects

1) Mimic effect: Fig. 5

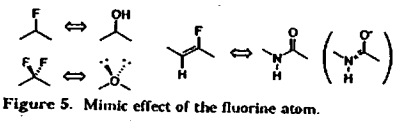


Figure 5. Mimic effect of the fluorine atom.

another effect: Fig. 6

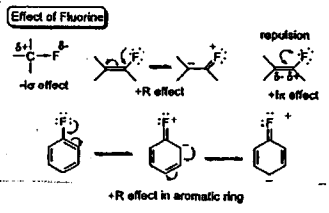


Figure 6. Various effects of the fluorine atom and the trifluoromethyl group

3. Fluorination of Organic Compounds (Asymmetric Reaction)

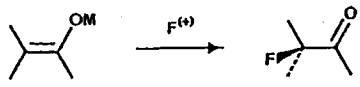
NEW FLUORINATING REAGENTS - I. THE FIRST ENANTIOSELECTIVE FLUORINATION REACTION

Edmond Differding and Robert W. Lang*
Central Research Laboratories, Ciba-Geigy AG,
CH-4002 Basel, Switzerland

Tetrahedron Lett. 1988, 29, 6087-6090.
Lang's work

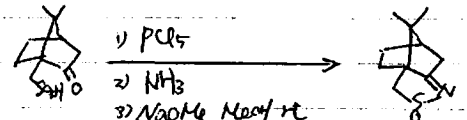
An important breakthrough occurred when Differding and Lang reported the first example of enantioselective fluorination of a β-ketoester enolate in up to 70% ee by using an N-fluorosultam derived from camphor.

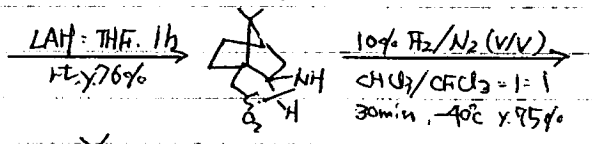
Scheme 1



M = Metal

Synthesis of (-)-3





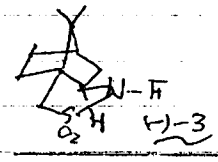
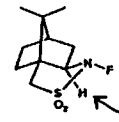
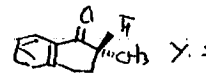


Table. Enantioselective Fluorination Reactions Using N-Fluoro Sultams (-)-3 and (+)-5

Entry	N-Fluoro Sultam	Product[a]	Reaction Conditions	ee[b]	Yield[c]
1	 (-)-3		NaH; Et_2O; 0° - r.t. 1.5 equiv. (-)-3	70%	63% (63%) ↑SM

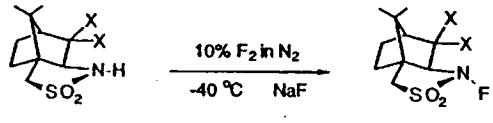
HF elimination occured? by the meso enolate.

In one example the ee reached 70% for the fluorination of a β-ketoester enolate, but with other enolates the ees and yield were much poorer.

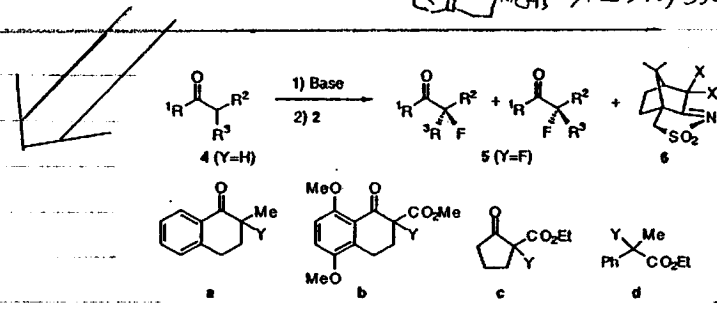


y. ≤ 5%, 35% ee

Tetrahedron Lett., 1993, 34, 3971-3974.
Davis's work



(-)-1a, (+)-1b — a: X=H, b: X=Cl — (-)-2a, (+)-2b



- 2b generally gave higher yield of 5 than did 2a
- 2b occured at -78°C whereas 2a requires higher temperatures.
- Higher yields with 2b may also reflect less H-F elimination giving 6b at the low temperatures. (entry 5 and 6.)

Table: Asymmetric Fluorination of Enolates using N-Fluoro Camphorsultams 2.

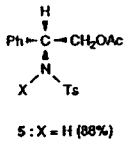
entry	Ketone/ Ester 4	Sultam[a] 2	Reaction Conditions Base/Solvent/Temp.%	Products ee[b] (config.) [% Yield][c] $[\alpha]_D^{20}$ (c, $CHCl_3$)
1	4a	(-)-2a (X=H)[d]	LDA/THF/-78°-r.t.	5a, 35 [<5]
2		(+)-2b (X=Cl)	LDA/THF/-78°	5a, 10 (S) [49], 6b [25], -2.9° (1.4)
3		e	NaHMDS/THF/-78-0°,[f]	5a, 67 (S) [41], 6b [17], 5a (Y=Cl) [11]
4		e	NaHMDS/THF/-78°	5a, 65 (S) [40] 6b [30] -20.4 (1.8)
5		(-)-2b (X=Cl)[g]	NaHMDS/THF/-78-0°	5a, 75 (R) [40], 6b [32], +21.8° (1.5)
6			NaHMDS/THF/-78°	5a, 65 (R) [50], 6b [20] +20.1° (2.0)
7	4b	(-)-2a (X=H)	NaH/Et_2O/0°-r.t.[h]	5b, 25 [28], 6b [28], -2.68° (1.6)
8		(-)-2b (X=Cl)	NaH/Et_2O/0°-r.t.	5b, 46 [>95], +4.93° (1.4)
9			NaHMDS/THF/-78-0°,[d]	5b, 26 [57], 6b [28], +2.83° (2.1)
10	4c	(-)-2a (X=H)[d]	NaH/Et_2O/0°-r.t.	5c, 70 [63], -18.5° (4.8)[h]
11		(+)-2b (X=Cl)[e]	NaH/Et_2O/-78-0°	5c, 34 [59], 6b [27], -9.5° (5.24)
12	4d	(+)-2a (X=H)[d]	LDA/THF/-78°-r.t.	5d, 35 [<10],
13		(+)-2b (X=Cl)	LDA/THF/-78°	5d, 29 [62], 6b, [21]
14			NaHMDS/THF/-78°	5d, 33 [54], 6b, [24], +0.92° (1.1)

a) 1.5 Equivalents of 2 used unless otherwise noted. b) Ee's determined using Eu(hfc)3. c) Isolated yields. d) Reference 8. e) 0.8 Equivalents of (+)-2b used. f) Monochloro imine of 6 isolated.[11] g) Addition of the enolate to 2. h) This work.

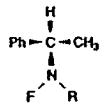
4/12

Takeuchi, Shibata's work.

Chem. Pharm. Bull. 45(6)1085-1088(1997) They first synthesized new enantioselective fluorinating agents based on the use of readily available chiral amine as starting materials.



5 : X = H (88%)
6 : X = F (27%)



10 : R = Ts (52%)
11 : R = Ms (13%)

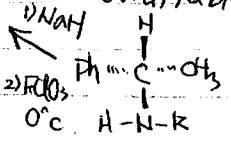
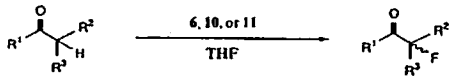
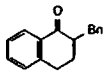
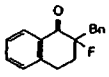


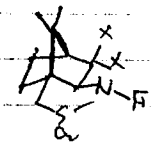
Table 2. Enantioselective Fluorination of Some Active Methine Compounds with the N–F Derivative 6, 10, or 11



14—16 17—19

Entry	Starting material	Fluorinating reagent	Conditions (base, temp.)	Product	ee (yield), %
1		6 (1.1 eq)	LDA, −40— −20 °C		9 (6)
2		10 (1.1 eq)	LDA, −40— −20 °C		54 (26)
3		10 (1.1 eq)	KHMDS, −40— −20 °C		48 (53)
4		11 (1.1 eq)	LDA, −40— −20 °C		6 (8)
	14			17	

Their initial experiments have not produced practical fluorinating agents. The low chemical yields in the fluorinations presumably reflect low reactivities of these N-fluoro compounds.



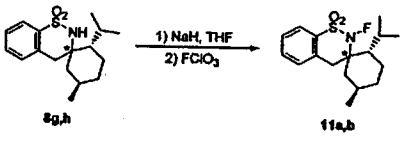
modification is difficult!!

~~Acyclic N-fluoro-agents~~ Cyclic N-fluorosulfonamides agents should be more effective?

Next work

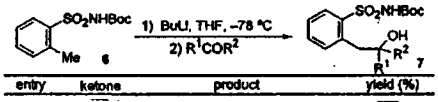
JOC 2000, 65, 7583-7587

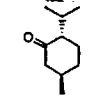
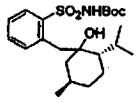
Scheme 2

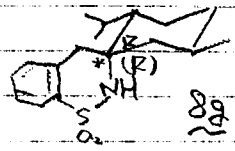


8g,h 11a,b

Table 1. Formation of the Carbinol Sulfonamides 7a–g via *o*-Methyl Lithiation of 6 Followed by Reaction with Ketones

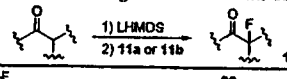


entry	ketone	product	yield (%)
7		 7g	95

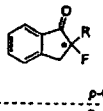
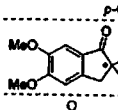
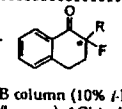


8g

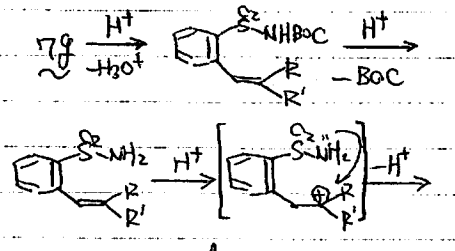
Table 3. Asymmetric Fluorination of Aryl Ketone Enolates Using *N*-Fluorosultams 11



12

entry	N-F Sultam	Products	R		ee (%)	config	isolated yield(%)
1	11a		Me	12a	40[a]	S[d]	76
2	11b		Me	12b	13[a]	R	69
3	11a		Bn	12c	54[a]	S	59
4	11b		Bn	12d	24[a]	R	42
5	11a		p-OMe-Bn	12e	51[b]	ND[e]	52
6	11a			12f	33[c]	ND[e]	61
7	11a		Me	12g	70[a]	S	65
8	11a		Bn	12h	56[b]	S	61

[a] Chiral OB column (10% *i*-PrOH/hexane). [b] Chiral OJ column (10% *i*-PrOH/hexane). [c] Chiral OJ column (EtOH). [d] References 4 and 6. [e] ND: not determined.

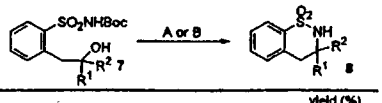


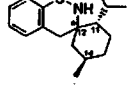
8g partial racemization might occur in this acid-mediated cyclization.

↑ Method A

method B : S_N2 process.

Table 2. Formation of the Sultams 8a–g by Cyclization of the Sulfonamides 7



entry	sulfonamide 7	sultam 8	yield (%) A[a]	yield (%) B[b]
7	7g	 8g[c] 8h[c]	35[d]	91[e]

[a] Method A: $MeSO_3H$, CH_2Cl_2, rt, 24 h. [b] Method B: TMSCl, NaI, MeCN, reflux, 1 h. [c] 8g: (11*S*,12*R*,14*R*)-isomer. 8h: (11*S*,12*S*,14*R*)-isomer. [d] 8g:8h = 1:2.5. [e] 8g:8h = 5.5:1.

reversed ratio

Method B : S_N2 process.

This agent exhibited modest asymmetric inducing abilities with the highest ee obtained being 7a/e. This is comparable to Differding and Davis' agents.

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J. Am. Chem. Soc. 2000, 122, 10728−10729

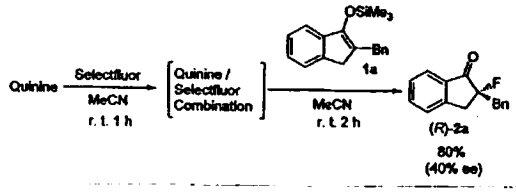
A Fundamentally New Approach to Enantioselective Fluorination Based on Cinchona Alkaloid Derivatives/Selectfluor Combination

Norio Shibata, Emiko Suzuki, and Yoshio Takeuchi*

~2000

Chiral sulfonamide-type fluorinating agents have been developed for enantioselective fluorination. However these are far from ideal because of low chemical yield and low optical purity of the fluorinated products. These agents = • requires tedious and multistep procedures.
• using toxic molecular fluorine or perchloryl fluoride.

Scheme 1. Fluorination of 1a by Quinine/Selectfluor Combination



First enantioselective fluorination was examined with quinine/Selectfluor combination.
* This two reagents are commercially available.

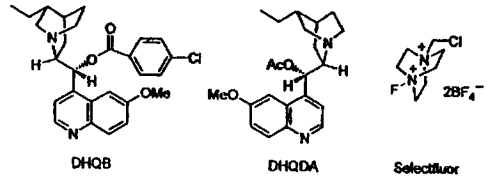
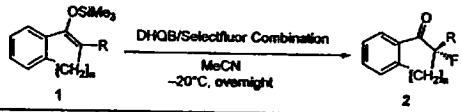


Figure 1.

Table 1. Fluorination of Silyl Enol Ether 1 by DHQB/Selectfluor Combination



entry	1	n	R	2	yield (%)	ee (%)[a]	configuration[b]
1	1a	1	Bn	2a	99	89	*R*
2[c]	1a	1	Bn	2a	86	91	*R*
3	1b	1	Me	2b	93	54	*R*
4	1c	1	Et	2c	99	73	*R*
5	1d	2	Me	2d	94	42	*R*
6[d]	1e	2	Et	2e	71	67	*R*
7	1f	2	Bn	2f	95	71	*S*

[a] Determined by HPLC analysis using a Chiralcel OB or OD. [b] The absolute configuration of 2 was assigned on the basis of the HPLC analysis using a Chiralcel compared with the authentic samples prepared according to ref 6. [c] Fluorination was carried out at −80 °C in MeCN/CH_2Cl_2 (3/4) for 48 h. [d] Fluorination was carried out at −50 °C in MeCN/CH_2Cl_2 (3/4) for 12 h.

Substrates generality were obtained in high yield with moderate to high enantiomeric excess (Table1)

This system toward to acyclic esters was examined. (Table2)

acyclic α-monofluoro compounds have many applications chiral derivatizing agents, chiral building blocks...

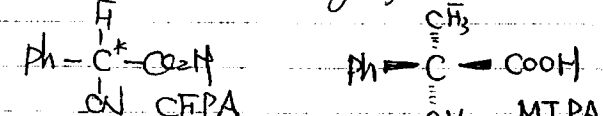
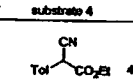
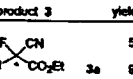
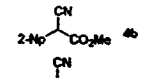
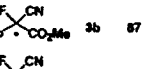
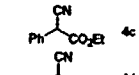
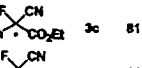
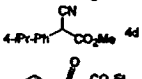
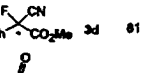
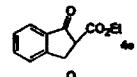
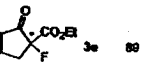
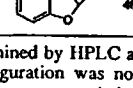
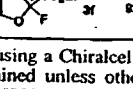


Table 2. Enantioselective Fluorination of 4 with DHQDA/Selectfluor Combination in MeCN/CH_2Cl_2 at −80 °C

entry	substrate 4		product 3		yield (%)	ee (%)[a]
1[b]		4a		3a	56	29(*R*)
2[d]					99	51(*R*)
3					80	87(*S*)
4		4b		3b	87	76
5		4c		3c	81	83
6		4d		3d	81	83
7		4e		3e	89	78
8		4f		3f	92	80

[a] Determined by HPLC analysis using a Chiralcel OB, OD, AS, or AD. Configuration was not determined unless otherwise indicated. [b] Fluorination was carried out by DHQB/Selectfluor combination in MeCN at −20 °C. [c] The absolute configuration of 4a was assigned on the basis of the HPLC analysis using a Chiralcel compared with the authentic samples prepared according to ref 14. [d] Fluorination was carried out by DHQB/Selectfluor combination in MeCN/CH_2Cl_2(3/4) at −80 °C. Tol = *p*-tolyl, Np = 2-naphthyl, 4-*i*Pr-Ph = 4-isopropylphenyl.

⑥ ~ quinine (Q) / Selectfluor (S) combination was prepared ~
a) (Q) + (S) in dry MeCN, MS3Å, rt. 1h then SM was added
b) SM + Q in MeCN/CH_2Cl_2, rt, 1h then −80°C, (S) was added

(Result) a) high yield and ee b) racemic. 76% yield ⇒ Why??
they proposed that NF-DHQB-BF_4 and NF-DHQDA-BF_4 Fig 2 generated in situ by "fluorine transfer" of the cinchona alkaloid by Selectfluor

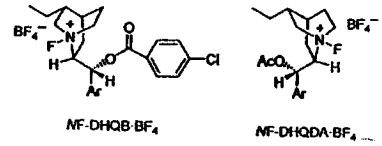


Figure 2.

from ^{19}F-NMR spectroscopy. 6/12

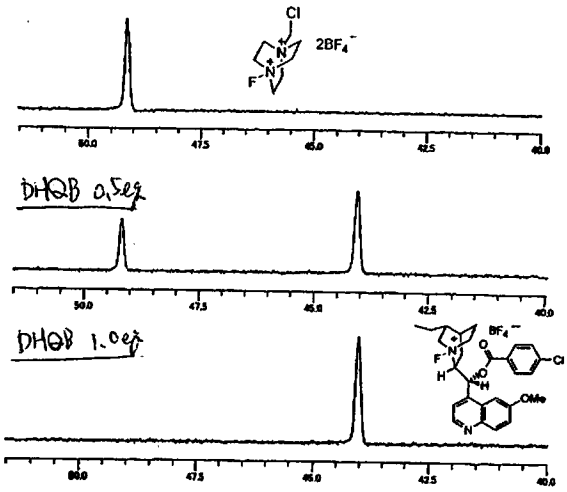
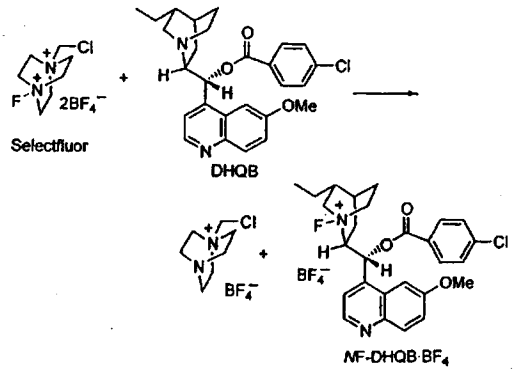


Figure 3. The 254 MHz ^{19}F NMR spectrum of Selectfluor and the combination in CD_3CN. Top: Downfield region of the ^{19}F NMR spectrum of Selectfluor in CD_3CN. Middle: The same region after the addition of 0.5 equiv of DHQB. Bottom: The same region after the addition of 1.0 equiv of DHQB, leading to the quantitative formation of *N*F-DHQB·BF_4.

Scheme 2. Transfer-Fluorination of DHQB with Selectfluor



JACS 2001 123, 7001-7009

Cinchona alkaloid must produced as asymmetric environment around the fluorine atom.

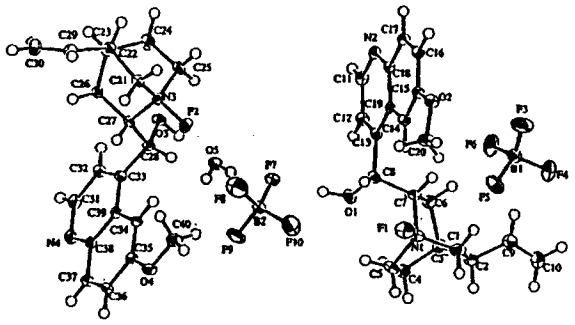


Figure 4. X-ray crystallographic structure of *N*F-Q·BF_4.

The length of N(1)-F(1) is 1.4912(2) Å, longer than that of the N-F bond of selectfluor (1.37(2) Å)

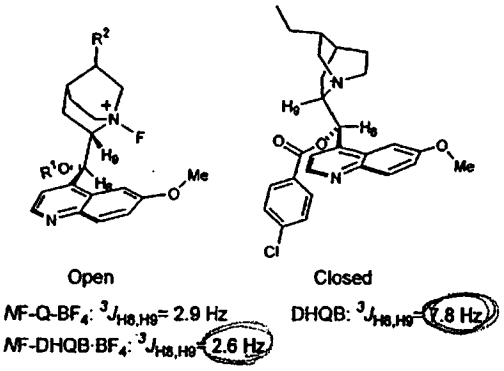
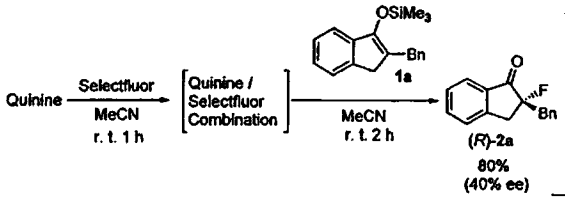


Figure 5. Schematic drawing showing (a) the open and (b) the closed conformation of the quinine derivatives.

conformational change
closed → open
(N → N⊕-F)

Scheme 1. Fluorination of 1a by Quinine/Selectfluor Combination



calculations for quinidine predict the open conformation to be 2.0 kcal/mol more stable than the close conformation. (AM1)

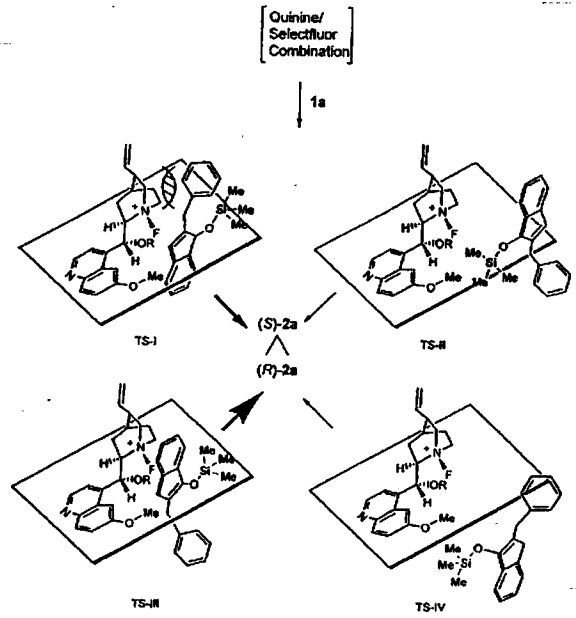


Figure 6. Proposed transition-state assemblies.

Ts-II and Ts-IV : disfavored — Steric consideration (trimethylsilyl group)

Ts-I : benzyl group position near the methylene protons of quinuclidinium moiety. ⇒ less likely

Ts-III : favored ⇒ (R)-selective

Acatalytic version of this fluorination reaction is under investigation

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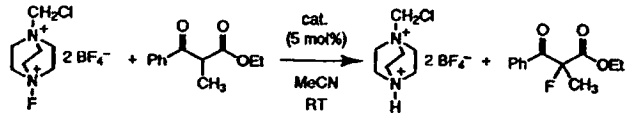
Togni's work

Catalytic Enantioselective Fluorination of β-Ketoesters**

Lukas Hintermann and Antonio Togni*

Angew. Chem. Int. Ed. 2000, 39, 4359–4362

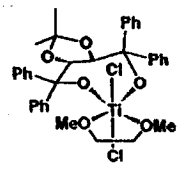


Scheme 1. The catalytic fluorination of **1a** with F-TEDA.

1) 1a + satd. F-TEDA sol. in MeCN, rt
No Reaction. (low enol content < 5%)

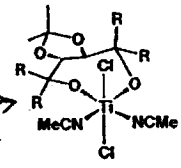
2) + Lewis acid (5 mol% level)
effectively catalyzed the rxn.

3) Using 3a as a catalyst
racemic 1a took place (less than 5h)
yield: good, ee: 28% (2a)



[(*R*)-3a(DME)]

air stable →

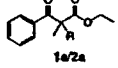
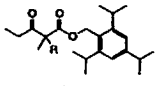


[(*R*)-3b(NCMe)2]
R=1-naphthyl

Catalyst screening
the steric bulk of the catalyst is important with stereoselectivity
Using 3b as a catalyst is best result (Table 2)

This is the first catalytic, enantioselective fluorination of β-ketoesters.

Table 2. Selected results of catalytic enantioselective fluorination reactions using isolated [TiCl2(TADDOLato)] complexes.

1 (R = H) (racemic) 2 (R = F)	Selectivity (Reaction time) cat. = (*R*)-3a	 cat. = (*R*)-3b	$[\alpha]_D^{20}$(2)[a] [ee [%]]	δ(19F)(2)[b]	HPLC analysis[c]	
 1a/2a	28% ee (*S*) (4 h)	62% ee (40 min)	+53.8 (c = 0.545) [61.7]	−152.3	OB 0.5	96/4 *13.5/16.0*
 1b/2b	55% ee (1 h)	90% ee (< 15 min)	+24.1 (c = 1.11) [85.6]	−159.2	OD-H 0.3	99.8/0.2 *27.8/29.8*

[a] Measured in MeOH at room temperature on a sample of given *ee* [value in square brackets]. [b] Measured in $CDCl_3$, relative to $CFCl_3$. [c] Daicel Chiralcel 25 cm column type; solvent mixture: hexane/*i*PrOH (v/v); flow rate in mL min^{-1}. Retention times (HPLC) in min of *minor*/*major* enantiomer (UV detection at λ = 210 nm and 254 nm). [d] (*S*)-3b: d.r. = 16:84. [e] Not determined. [f] The difference of the shifts between the two diastereomers is Δδ = 0.01.

Haufe's work

Journal of Fluorine Chemistry 104 (2000) 247–254

JOURNAL OF FLUORINE CHEMISTRY
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Enantioselective introduction of fluoride into organic compounds
First asymmetric ring opening of epoxides by hydrofluorinating reagents

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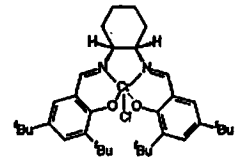
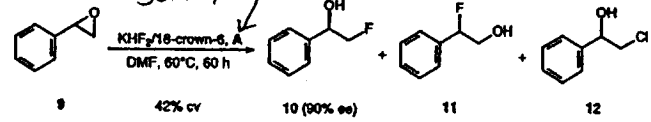
Received 5 January 2000; accepted 7 February 2000

This type of reaction has been successfully accomplished with many different nucleophiles mediated or catalyzed by different Lewis acid.
No results on the application of fluoride have been published as yet.



A

Scheme 4.



9 — 42% cv — 10 (90% ee) — 11 — 12

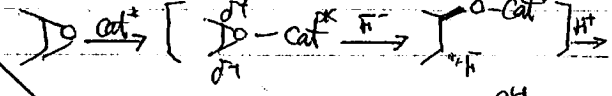
Scheme 7.

10 : 11 = 92 : 8
86%

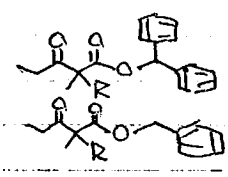
12
14%

Cat A (10 mol%), 55% of 9 conversion
110 h at 90°C 10 : 50% ee

There is only one example.

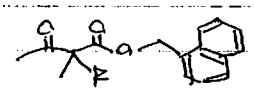


SN 2-like mechanism

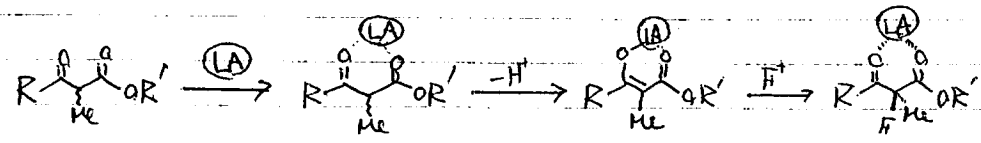


81% ee

71% ee



68% ee

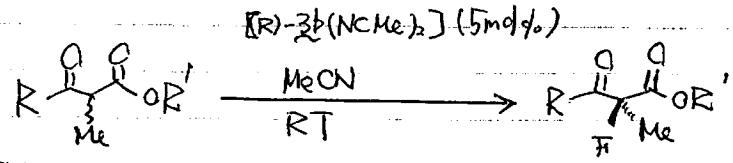


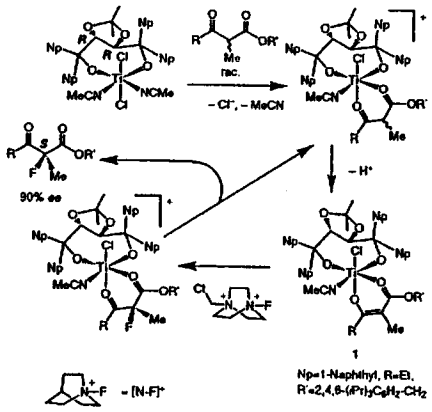
⟹ Mechanistic Study

The Mechanism of Catalytic Enantioselective Fluorination: Computational and Experimental Studies

Stefano Piana, Ingrid Devillers, Antonio Togni,* and Ursula Rothlisberger*

Angew. Chem. Int. Ed. 2002, 41, 979 - 982.

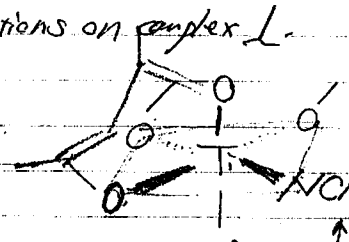




Scheme 1. Simplified mechanistic hypothesis for the Ti-catalyzed asymmetric fluorination reaction. The $[N-F]^+$ ion reagent used in the computational studies is also shown.

1) β-ketoester coordinates to the catalyst
2) the octahedral mono-chloro Ti(enolate) complex 1 is formed. (reactive species)
3) complex 1 is fluorinated by F-TEDA.

They performed density functional theory (DFT) based mixed quantum mechanical/molecular mechanical (QM/MM) calculations on complex 1.



4-6 kcal mol⁻¹ less stable

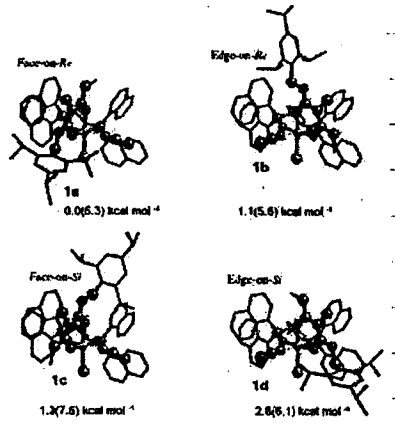


Figure 1. Structure and relative energies of the four most stable Ti(enolato) complexes with the chloro ligand (green) in axial position with respect to the plane of the Ti(TADDOLato) chelate. Hydrogen atoms are omitted for clarity. The energies of the corresponding stereoisomers with an equatorial chloride ligand are given in parenthesis. All the groups directly bound to the titanium were treated at the DFT level and are represented as balls and sticks. All other atoms are shown as sticks and were accounted for by a classical force field.[19]

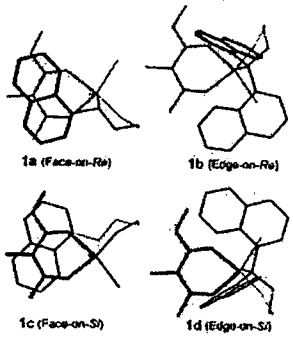


Figure 2. Schematic projections on enolate plane (red) for the calculated structures 1a–d showing the shielding of one of the enolate enantiofaces by either a face-on or an edge-on naphthyl group (for a definition of face-on and edge-on orientations of aryl groups in TADDOLs, see ref. [3]).

1a and 1c the enolate fragment and one of the two face-on oriented naphthyl groups are almost perfectly parallel. (Fig 2)

Re-face of the enolate in 1a is completely shielded and a fluorine atom can only be delivered from apposite side. (1a is the most stable isomer)

⇒ correctly absolute configuration was observed.

This is the first example of a catalytic asymmetric fluorination of β-ketoesters. But only for one substrate have higher enantioselectivity (90%).

Cahard's work

Design, Synthesis, and Evaluation of a Novel Class of Enantioselective Electrophilic Fluorinating Agents: *N*-Fluoro Ammonium Salts of *cinchona* Alkaloids (F-CA-BF$_4$)

Dominique Cahard,*[,†] Christophe Audouard,[†] Jean-Christophe Plaquevent,[†] and Nicolas Roques[‡]

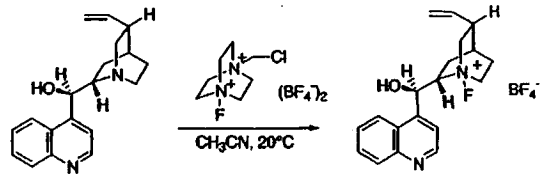
UPRES-A 6014 de l'IRCOF (Institut de Recherche en Chimie Organique Fine), Université de Rouen, Rue Tesnière, F-76821 Mont Saint Aignan Cedex, France, and Rhodia Recherches, 85, Avenue des Frères Perret, F-69192 Saint Fons, France

dominique.cahard@univ-rouen.fr

Received September 18, 2000

ORGANIC LETTERS
2000
Vol. 2, No. 23
3699–3701

Scheme 1. Synthesis of F-CD-BF$_4$



< Background >

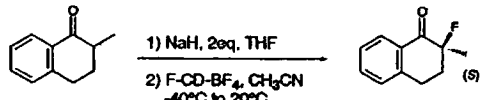
The synthesis of fluorinating agents requires several steps by means of either elemental F$_2$ or FClO$_3$.

Convenient and cheap fluorinating agents were needed.

~ First transfer-fluorination approach by Bank ~

J. Fluorine Chem. 1995, 73, 255-257.

Scheme 2. Fluorination of the Enolate of 2-Methyl-1-tetralone

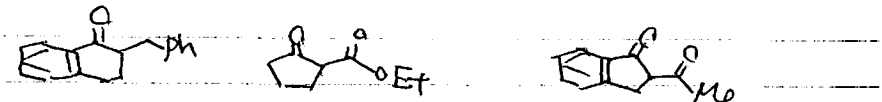


ee up to 56%
yd 80 -98 %

yd was max 50% until 2000.

Addition of Sodium hydroxide improved both the reactivity and the stereoselectivity.

another substrates were examined.



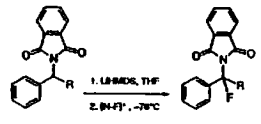
y. 96%, 82% ee y. 98%, 49% ee y. 95% , 36% ee

Electrophilic Fluorination Mediated by Cinchona Alkaloids: Highly Enantioselective Synthesis of α-Fluoro-α-phenylglycine Derivatives**

Barbara Mohar, Jérôme Baudoux, Jean-Christophe Plaquevent, and Dominique Cahard*

Angew. Chem. Int. Ed. 2001, 40, 4214-4216

Table 2. Selected results of the enantioselective electrophilic fluorination of *N*-phthaloylphenylglycine derivatives using various [N–F]$^+$ cinchona alkaloids.



94% ee

[N–F]$^+$	R = CO_2Et		R = CN	
	ee [%][a]	Yield [%][b]	ee [%][a]	Yield [%][b]
F-CD-BF$_4$	8	65	36	48
F-AcCD-BF$_4$	42	87	52	91
F-AcQN-BF$_4$	76	79	80	88
F-*p*ClBzQN-BF$_4$	68	73	91	70
F-*p*ClBzDHQN-BF$_4$	76	86	92	65
F-*p*MeOBzQN-BF$_4$	66	64	94	56
F-*p*NO$_2$BzQN-BF$_4$	60	60	90	58
F-CN-BF$_4$	26	62	48	68
F-*p*ClBzCN-BF$_4$	28	67	66	70
F-AcDHQD-BF$_4$	50	60	75	72
F-*p*ClBzDHQD-BF$_4$	38	65	82	64

[a] Determined by HPLC analysis using a column Chiralcel OD. [b] Isolated, chromatographically pure material.

The enantioselective synthesis of α-fluoro-α-amino acids were no reported.

This is the first reaction.

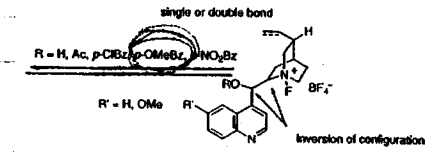
OH free of cinchona alkaloids is very effectable.

unprotected hydroxy function (7-98% ee)

ee was higher [QN-F]$^+$ > [CD-F]$^+$

[QD-F]$^+$ > [CN-F]$^+$

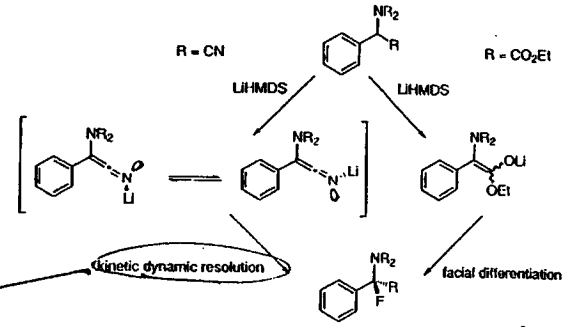
cinchona alkaloids, with a view to improving the enantioselectivity and to pinpointing the factors governing the enantioselection (Scheme 1).



Scheme 1. Structure–enantioselectivity relationship (SER) studies on [N–F]$^+$ cinchona alkaloids.

effect on oMe group??

Higher ee observed for the nitrile derivative compared to the ethyl ester derivative. Why?



Angew. Chem. Int. Ed. 28 (1989) 277-297.

Scheme 2. Postulated intermediates in enantioselective fluorination.

10/12

the best fluorine donor.

Table 1. Catalytic asymmetric fluorination of 1-fluoro-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester 1a[a]

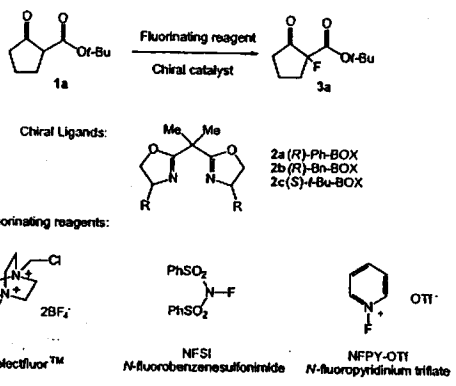
Entry	Catalyst (mol%)	F-donor	Solvent	Achiral additive[b]	Temperature (°C)	Time (h)	Yield (%)[c]	Ee (%)[d]
1	2a-Cu(OTf)$_2$ (10)	Selectfluor	CH_3Cl_2	None	rt	16	97	36 (+)
2	2a-Cu(OTf)$_2$ (10)	NFPY-OTf	CH_3Cl_2	None	rt	3	98	35 (+)
3	2a-Cu(OTf)$_2$ (10)	NFSI	CH_3Cl_2	None	rt	3	84	47 (+)
4	2a-Cu(OTf)$_2$ (10)	NFSI	THF	None	rt	0.5	96	57 (+)
5	2a-Cu(OTf)$_2$ (10)	NFSI	Toluene	None	rt	2	90	73 (+)
6	2a-Cu(OTf)$_2$ (10)	NFSI	Et_2O	None	rt	0.5	95	74 (+)
7	2a-Mg(ClO$_4$)$_2$ (10)	NFSI	Et_2O	None	rt	48	80	7 (−)
8	2a-Zn(OTf)$_2$ (10)	NFSI	Et_2O	None	rt	12	84	74 (+)
9	2a-Zn(OTf)$_2$ (10)	NFSI	Toluene	None	rt	48	74	47 (+)
10	2a-Sc(OTf)$_3$ (10)	NFSI	Et_2O	None	rt	2.5	86	17 (+)
11	2a-La(OTf)$_3$ (10)	NFSI	Et_2O	None	rt	48	84	14 (+)
12	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	None	rt	0.5	96	73 (+)
13	2a-Cu(OTf)$_2$ (0.1)	NFSI	Et_2O	None	rt	0.5	89	72 (+)
14	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	None	0	4	86	69 (+)
15	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	None	−20	48	82	72 (+)
16	2b-Cu(OTf)$_2$ (1)	NFSI	Et_2O	None	rt	2	87	5 (−)
17	2c-Cu(OTf)$_2$ (1)	NFSI	Et_2O	None	rt	2	91	20 (+)
18	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	base	rt	12	90	70 (+)
19	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	*i*-Pr$_2$NEt	rt	12	89	70 (+)
20	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	2,6-lutidine	rt	4	94	4 (+)
21	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	*t*-BuOK	rt	36	72	70 (+)
22	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	3Å MS	rt	0.5	96	85 (+)
23	2a-Cu(OTf)$_2$ (1)	NFSI	Et_2O	HFIP	0	0.5	94	82 (+)

[a] Reactions were run at 20 °C on 0.2 mmol scale.
[b] One equivalent of additive was used.
[c] Yields of isolated products.
[d] GC with chiral column was used to determine the ee values.

HFIP: to promote the release of the fluorinated product from the catalyst.

higher enantioselectivity.

J.-A. Ma, D. Cahard / Tetrahedron: Asymmetry 15 (2004) 1007–1011



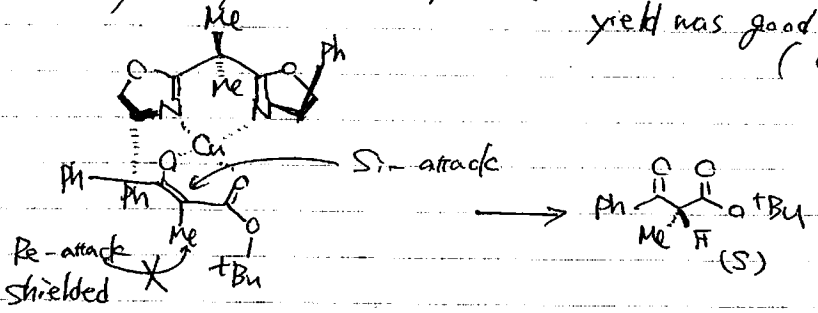
Scheme 1. Enantioselective fluorination of 1-fluoro-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester 1a.

Only two examples which catalytic enantio-selective fluorination were reported by Togni and Sodeoka.

a variety of cyclic and acyclic β-keto esters was undertaken

yield was good to excellent but ee was moderate
(up to 98%) (up to 85%)

cyclic 92% ee acyclic case.



Kim's work

Michael reaction promote

Catalytic Enantioselective Fluorination of β-Keto Esters by Phase-Transfer Catalysis Using Chiral Quaternary Ammonium Salts

Dae Young Kim* and Eun Joo Park

ORGANIC LETTERS 2002 Vol. 4, No. 4 545–547

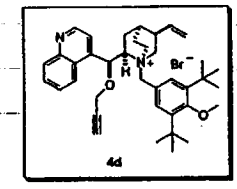
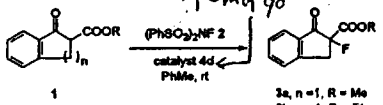


Table 2. Catalytic Enantioselective Fluorination of 1 with Phase-Transfer Catalyst 4d

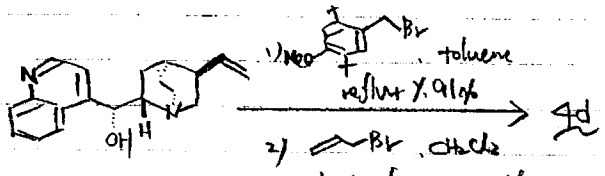


entry	*n*	R	base	yields (%)	ee[a](%)
1	1, 1a	Me	K_2CO_3	3a, 92	69
2	1, 1a	Me	Cs_2CO_3	3a, 94	60
3	1, 1b	Et	K_2CO_3	3b, 92	50
4	1, 1b	Et	Cs_2CO_3	3b, 91	63
5	2, 1c	Me	RbOH	3c, 87	40
6	2, 1c	Me	Cs_2CO_3	3c, 88	48
7	2, 1d	Et	K_2CO_3	3d, 74	41
8	2, 1d	Et	CsOH	3d, 78	52

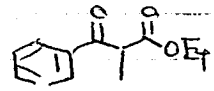
[a] Enantiopurity of 3 were determined by HPLC analysis with a Chiralcel OD-H column, 2-propanol–hexane (1:9), 1.0 mL/min, λ_{max} = 254 nm. It was established by analysis of racemic 3 that the enantiomers were fully resolved. The excessive enantiomer was (+)-3.

Phase-transfer catalyst is a clean and efficient processes involving high yield, operational simplicity, mild conditions, low cost, safety, and environmental profit.

yield was excellent but ee was moderate.



β-keto ester:



Y. 89% 40% ee

11/12

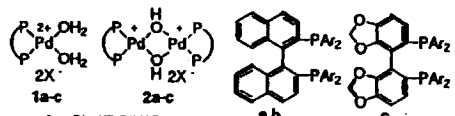
Sodeoka's work

J|A|C|S
COMMUNICATIONS
Published on Web 11/14/2002

An Efficient Enantioselective Fluorination of Various β-Ketoesters Catalyzed by Chiral Palladium Complexes

Yoshitaka Hamashima, Kenji Yagi,[1] Hisashi Takano, László Tamás, and Mikiko Sodeoka*
Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, Katahira, Sendai, Miyagi 980-8577, Japan, and PRESTO, Japan Science and Technology Corporation (JST)

Received September 9, 2002



a: Ar = Ph: (*R*)-BINAP
b: Ar = 3,5-dimethylphenyl: (*R*)-DM-BINAP
c: Ar = 3,5-di(tert-butyl)-4-methoxyphenyl: (*R*)-DTBM-SEGPHOS

Substrate selection : 3a

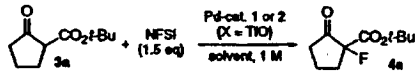
3a (fluorination product) is nonenolizable optically active α-substituted α-fluoro β-ketoester.

α-Substituted - α-fluorinated β-ketoester
⇓
increase antibiotic activity, versatile synthetic precursors

They found that a chiral palladium enolate was formed directly from β-ketoesters using palladium complex 1c-2.
⇓
The rxn of 3a with NFSI (1.5eq) proceeded smoothly with 5 mol% 1a (Table 1)

A series of chiral phosphine ligands were examined (R)-DM-BINAP and (R)-DTBM-SEGPHOS were useful.

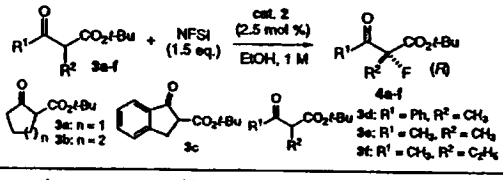
Table 1. Optimization of the Reaction Conditions



entry	catalyst (mol %)[a]	solvent	temp (°C)	time (h)	yield (%)	ee[b] (%)
1	1a (5)	THF	−20	12	72	79
2	1b (5)	THF	−20	39	99	88
3	1c (5)	THF	0	72	89	90
4	2c (2.5)	THF	10	48	83	92
5	2c (2.5)	acetone	10	48	93	92
6	2c (2.5)	EtOH	20	18	73	92

[a] Catalyst amount. [b] Determined by HPLC analysis.

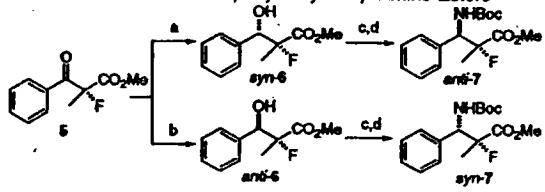
Table 2. Catalytic Enantioselective Fluorination of β-Ketoesters



entry	ketoester	catalyst (X)	temp (°C)	time (h)	yield (%)	ee (%)
1[a]	3a	2c (TfO)	20	18	90	92
2	3b	2b (BF_4)	−10	20	91	94
3	3c	2b (TfO)	−20	36	85	83[b]
4	3d	2b (BF_4)	20	40	92	91[b]
5	3e	2c (TfO)	20	72	49[c]	91
6	3f	2b (TfO)	20	42	88	87
7[d]	3b	2b (BF_4)	0	20	82	91
8[e]	3d	1b (TfO)	20	48	96	91

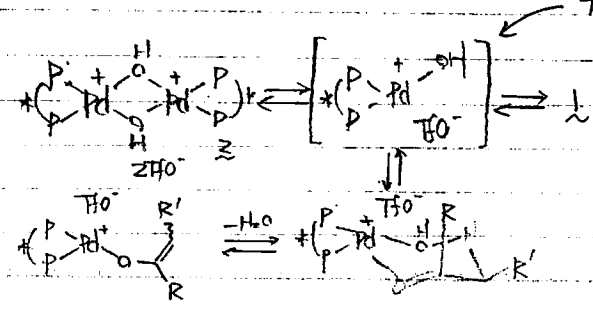
[a] *i*-PrOH was used instead of EtOH. [b] The absolute configuration was determined to be *R* after the conversion. [c] Lower yield due to the volatility of 4e. [d] 2b (1 mol %) was used. 2.5 M 3b. [e] 1-g scale.

Scheme 1. Conversion into β-Hydroxy and β-Amino Esters[a]

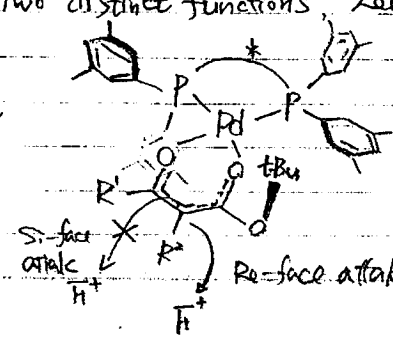


[a] Conditions: a. $PhMe_2SiH$ (3.0), TBAF (2.0), DMF, 0 °C, 10 min, 83% (dr = >95/5); b. Ph_3SiH (3.0), TFA, rt, 3 h, 75% (dr = >95/5); c. Ph_3P (1.5), DEAD (1.5), DPPA (1.2), THF, rt, 2 h, 79% from *syn*-6, 73% from *anti*-6; d. Pd/C, H_2, $(Boc)_2O$, MeOH, 1 h, 80% for *anti*-7, 57% for *syn*-7.

β-hydroxy or β-amino acid are one of the functional units.
3c was easily converted β-hydroxy acid or β-amino acid.



two distinct functions, Lewis acidity and Brønsted basicity



square-planar palladium complex

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