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Elemental fluorine, Part 23: Direct fluorination of β-ketoesters as an approach to enantioselective fluorination☆

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ABSTRACT

Attempts to develop a direct enantioselective fluorination protocol using elemental fluorine and an appropriate Lewis acid and chiral ligand system are described.

1. Introduction

Chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic centre are becoming increasingly important with applications in biological chemistry, medicinal chemistry, materials, enzyme mechanism studies and asymmetric syntheses [2,3] continuing to develop. Consequently, the availability of effective methodologies for the preparation of chiral fluorinated systems is a very important research goal and perhaps the most direct method for the preparation of fluorinated stereogenic centres is enantioselective fluorination. Since Differding introduced chiral *N*-fluorocamphorsultam, which was the first example of a chiral, electrophilic N-F reagent in 1988 [4] a number of reagent-controlled enantioselective electrophilic fluorination reactions have been reported and various *N*-fluorocamphorsultam- [5,6], *N*-fluoro-*N*-tosyl- [7] and *N*-fluorocinchona alkaloid derivatives [8–14] have been utilised for the regio- and stereoselective introduction of carbon–fluorine bonds into a range of organic substrates, principally at sites that are adjacent to carbonyl functionality.

The first example of catalytic enantioselective fluorination was reported by Hintermann and Togni in 2000 [15] for which catalytic amounts of a Lewis acid, predominantly a titanium or aluminium species, was found to accelerate electrophilic fluorination reactions of 1,3-ketoesters by Selectfluor™ by catalyzing the enolisation process [16–18]. Subsequently, Sodeoka developed an efficient catalytic fluorination of 1,3-ketoesters using chiral palladium complexes [19] and *N*-fluorosuccinimide.

While the majority of enantioselective fluorination reactions that have been reported utilise electrophilic N-F reagents as the fluorinating agent, Kaneko reported enantioselective preparation of 2-fluoro-1,3-ketoesters from β-ketoesters bearing a (−)-menthone chiral auxiliary using elemental fluorine [20].

In earlier studies, we established that hydrated copper nitrate effectively catalysed direct fluorination of 2-substituted carbonyl compounds [21] and we reasoned that direct use of elemental fluorine for catalytic enantioselective fluorination may be possible if a suitable 'fluorine-tolerant' homochiral catalyst system could be identified. In this paper, we describe our preliminary attempts to develop a direct enantioselective fluorination protocol using elemental fluorine and an appropriate catalytic Lewis acid and chiral ligand system.

2. Results and discussion

Previously, we established that efficient fluorination of β-ketoesters occurs if either the equilibrium enol concentration is high or the rate of enolisation of the β-ketoester substrate is rapid [22]. Consequently, for investigations concerning catalytic fluorination processes, substrates that bear substituents at the 2-position for which the enol concentration at equilibrium is low and

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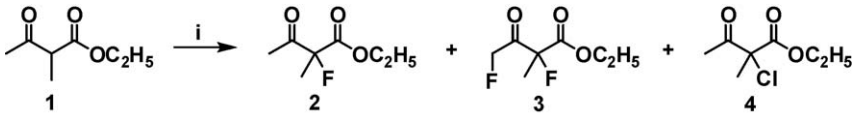
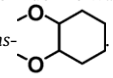
Table 1
Catalysts f or direct fluorination of ethyl 2-methyl-3-oxo-butanoate **1**.



(i) 10% F_2/N_2 (1.2 equiv.), catalyst (0.1 equiv.), CH_3CN, 0 °C.

Entry	Catalyst	Conv. (GC, %)	Yield (GC, %)		
			2	3	4
1	None[a]	6	–	–	–
2	$TiCl_4$[a]	49	13	7	77
3	$TiCl_4$[b,c]	63	4	–	96
4	$TiCl_2(OR)_2$[d]	32	5	–	78
5	$HfCl_4$	25	Trace	Trace	~100
6	$Sc(OTf)_3$	53	58	32	–
7	$La(OTf)_3$	44	58	32	–
8	$Cu(NO_3)_2{\cdot}2.5H_2O$	51	53	–	–
9	$Cu(acac)_2$[c,e]	4	–	–	–
10	$Cu(OTf)_2$	59	16	9	–
11	$Ni(NO_3)_2{\cdot}6H_2O$	32	68	–	–
12	$Pd(NO_3)_2{\cdot}xH_2O$	3	~100	Trace	–
13	AgOTf	<1	Trace	–	–
14	$In(NO_3)_3{\cdot}5H_2O$	3	~100	–	–
15	$Bi(NO_3)_3{\cdot}5H_2O$	4	27	–	–

Yield based upon conversion of starting materials.
[a] 2.0 equiv. of fluorine was used.
[b] 0.2 equiv. of catalyst was used.
[c] 1.0 equiv. of fluorine was used.
[d] $(OR)_2$=*trans*- 
[e] 0.05 equiv. of catalyst was used.

the rate of enolisation is slow are required. Since, ethyl 2-methyl-3-oxobutanoate **1** has an equilibrium keto concentration of 92% and a slow rate of enolisation (half life *ca.* 3 h in formic acid [22]), we utilised **1** for our initial fluorination studies. As expected, fluorination of **1** with no catalyst present in acetonitrile gave very low conversion (6%, Entry 1, Table 1) and so this substrate was an ideal model compound to investigate the catalytic effect of various metal salt systems upon direct fluorination processes. Direct fluorination of **1** using elemental fluorine in the presence of a range of Lewis acids catalysts are collated in Table 1. All reactions were carried out in acetonitrile solution at 0 °C and monitored by GC and ^{19}F NMR analysis.

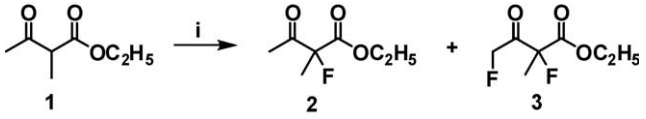
Reactions for which titanium tetrachloride (Entry 2, 3), titanium (*trans*-cyclohexanediolato) dichloride (Entry 4) and hafnium tetrachloride (Entry 5) were the catalysts proceeded to give the chlorinated derivative **4** as the major product and a possible mechanism for this chlorination reaction is shown in Scheme 1.

Chlorination of, for example, the titanium enolate species **5** by chlorine monofluoride (Cl-F), generated by reaction between the chloro-titanium species and elemental fluorine, is postulated. Titanium (IV) chloride is eventually transformed into titanium (IV) fluoride, which has been established to be inactive in enolisation processes [15].

Lanthanide triflates accelerate the fluorination process to some extent and both scandium triflate (Entry 6) and lanthanum triflate (Entry 7) gave about 40–50% conversion. The main products were the 2-fluorinated adduct **2**, but considerable amounts of the 2,4-difluorinated system 3 were also obtained. Hydrated copper nitrate and nickel nitrate are known to be effective catalysts for the fluorination of diethyl malonate [21] and, indeed, were found to be suitable catalysts in this case (Entry 8, 11). In contrast, palladium (II) complexes such as palladium (II) nitrate, which were found to be excellent catalysts for enantioselective fluorination of β-ketoesters using NFSI, showed almost no catalytic activity in direct fluorination reactions (Entry 12).

Our initial screening studies (Table 1) indicated that the most effective catalytic activity for fluorination processes were shown by scandium, copper and nickel salts. Consequently, we used these findings to investigate possible catalyst/ligand combinations for enantioselective fluorination but, first, however, we assessed the use of appropriate catalysts for fluorination reactions of **1** in the presence of racemic mixtures of various auxiliaries or ligands (Table 2).

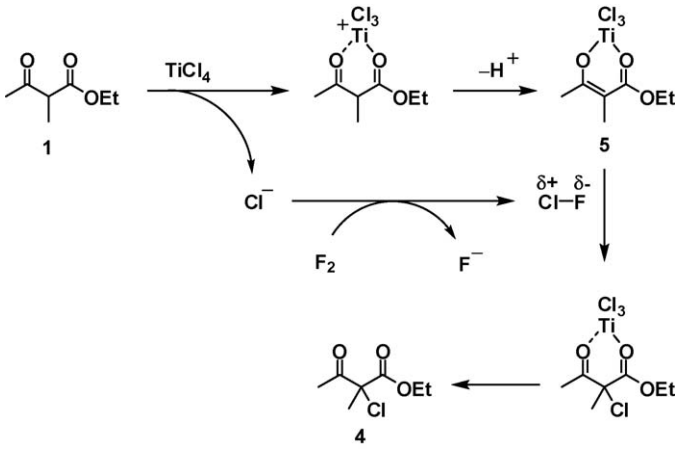
Table 2
Fluorination of **1** using metal salt/racemic ligand combinations.



(i) 10% F_2/N_2 (1.2 equiv.), catalyst (0.1 equiv.), CH_3CN, 0 °C.

Entry	Catalyst		Conv. (GC, %)	Yield[a] (GC, %)	
				2	3
1[b]	$Sc(OTf)_3$	BINOL, PMP[c]	<1	Trace	Trace
2	$Cu(NO_3)_2{\cdot}2.5H_2O$	$2Ph_3P$	34	29	Trace
3	$Cu(NO_3)_2{\cdot}2.5H_2O$	rac-BINAP	45	8	Trace
4	CuF_2	rac-BINAP	<1	Trace	Trace
5	$Ni(NO_3)_2{\cdot}6H_2O$	$2Ph_3P$	15	~100	Trace
6	$Ni(NO_3)_2$ $6H_2O$	rac-BINAP	36	~100	Trace
7	$Ni(NO_3)_2{\cdot}6H_2O$	DIPHOS[d]	20	~100	Trace
8[e]	$Ni(NO_3)_2{\cdot}6H_2O$	rac-BINAP	73	97	3

[a] Yield based upon conversion of starting material.
[b] CH_3CN/CH_2Cl_2, 9:1 was used as a solvent.
[c] PMP, 1,2,2,6,6-pentamethyl-piperidine.
[d] DIPHOS, 1,2-bis(diphenylphosphino)ethane.
[e] Fluorine, 5.0 equiv.



Scheme 1. Chlorination of ethyl 2-methyl-3-oxobutanoate.

A copper nitrate and phosphine ligand system mixture (Entry 2) gave much less desired fluorinated compound **1** than using only copper nitrate as a catalyst (Table 1: Entry 2, 3) and this is thought to be caused by reduction of copper (II) species accompanied by oxidation of the phosphine ligands [23]. Also, copper (II) fluoride and *racemic*-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) (Entry 4) did not show any catalytic activity. In contrast, a nickel nitrate and phosphine ligand system was quite effective for selective fluorination of **1**. The nickel nitrate/triphenylphosphine (1:2) system gave almost 100% selectivity, although the conversion was 15% (Entry 5). In the case of using *racemic*-BINAP and nickel nitrate, the conversion was improved to 36% (Entry 6) and, subsequently, when 5 equiv. of fluorine were used for the reaction, 73% conversion and 97% selectivity was achieved (Entry 8). Consequently, we were hopeful of applying this catalytic system to enantioselective fluorination reactions by using a single enantiomer of BINAP as the ligand in fluorination reactions of appropriate β-ketoesters.

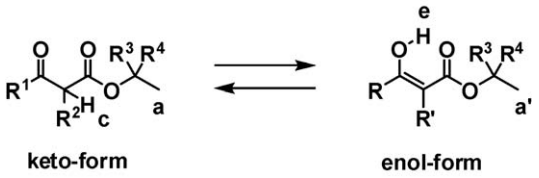
Cyclic β-ketoesters, which gave quite high enantioselectivities in previously reported palladium catalysed fluorination reactions [16], were selected for investigation of catalytic enantioselective direct fluorination using the nickel nitrate–BINAP system, because ee measurements of the fluorinated products by NMR methods has already been established [19]. *t*-Butyl 2-oxocyclopentane carboxylate **7** and *t*-butyl 2-oxocyclohexane carboxylate **9** were prepared following literature processes [24,25].

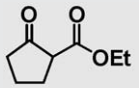
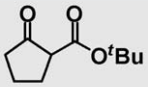
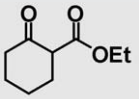
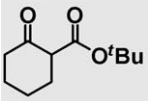
Before enantioselective fluorination reactions were attempted, the initial enol contents of 1,3-ketoesters in acetonitrile-d_3 solution were measured by ^{1}H NMR (Table 3) to determine whether these substrates would, for example, have suitably low equilibrium enol content for use as substrates in fluorination reactions.

Ethyl 2-oxocyclopentanecarboxylate **6** and *t*-butyl 2-oxocyclopentane-carboxylate **7** have very low enol contents at equilibrium whereas ethyl 2-oxo-cyclohexane carboxylate **8** and *t*-butyl 2-oxocyclohexanecarboxylate **9** showed higher equilibrium enol contents. From these results, fluorination of **6** and **7** should occur very slowly without catalyst and be suitable substrates for catalytic fluorination studies and this is confirmed by experiment, for example, **6** gave only 17% conversion upon fluorination in acetonitrile solution (Table 4, Entry 1). In contrast, **8** and **9** would react very efficiently with fluorine alone and are not suitable substrates for catalysis studies.

The catalyst system consisting of nickel nitrate and *racemic*-BINAP was applied to the fluorination of suitable cyclic 1,3-ketoester substrates **6** and **7** to determine the fluorination conditions before using the corresponding expensive chiral ligands and also to obtain racemic samples of the fluorinated products for analysis (Table 4).

Table 3
Enol contents of β-ketoesters in acetonitrile-*d*3.



β-ketoester	Time[a]	keto-form, %[b], (ppm)	enol-form, %[c], (ppm)
 **6**	<30 min	91 (2.95)	–
	1 month	88	–
 **7**	<30 min	92 (2.81)	–
	1 month	93	–
 **8**	<30 min	20 (3.22)	71 (12.04)
	1 month	39	50
 **9**	<30 min	28 (3.08)	64 (12.13)
	1 month	31[d] (1.24) 67 72[d]	69[d] (1.28) 25 28[d]

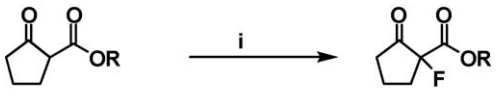
[a] The sample solution were allowed to equilibrate for the time at room temperature before the measurement.
[b] Based on integrated values of resonance of c vs (a + a′).
[c] Based on integrated values of resonance of e vs (a + a′).
[d] Based on integrated values of resonance of a vs (a + a′).

Fluorination of both ethyl 2-oxo-cyclopentane carboxylate **6** (Entry 2) and *t*-butyl 2-oxo-cyclopentane carboxylate **7** (Entry 3) proceeded smoothly and 100% conversions were achieved using the BINAP/Ni catalyst system. Racemic products **10** and **11** were both isolated by silica gel column chromatography.

Finally, fluorination of **6** and **7** using nickel nitrate and enantiomerically pure *R*-BINAP were carried out (Table 5).

Nickel nitrate and BINAP were mixed together to give a reaction mixture that contained a precipitate which slowly dissolved during the course of the reaction and the enantiomeric excess of the products were determined by chiral shift reagent ^{1}H NMR experiments using increasing amounts of europium *tris*[3-hepta-fluoropropylhydroxy-methylene]-(+)-camphorate] [Eu(hfc)$_3$]. In all cases the reactions gave 99–100% conversion and 69–82% isolated yield but, unfortunately, no obvious enantioselectivity

Table 4
Fluorination of cyclic β-ketoesters.



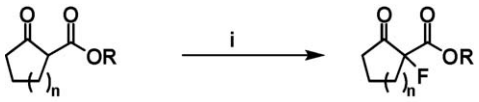
6, R = Et 10, R = Et
7, R = *t*-Bu 11, R = *t*-Bu

(i) 10% F_2/N_2 (3.0 equiv.), $Ni(NO_3)_2{\cdot}6H_2O$ (0.1 equiv.), rac-BINAP (0.1 equiv.), CH_3CN, 0 °C.

Entry	β-ketoester	Conv. (GC, %)	GC yield (%)	Isolated yield (%)
1[a]	6	17		
2	6	100	100	81
3	7	100	100	88

[a] Reaction without catalyst.

Table 5
Attempted enantioselective fluorination.



6, R = Et 10, R = Et
7, R = *t*-Bu 11, R = *t*-Bu

(i) 10% F_2/N_2 (3.0 equiv.), $Ni(NO_3)_2{\cdot}6H_2O$ (0.1 equiv.) *rac*-BINAP (0.1 equiv.), CH_3CN, 0 °C.

Entry	R-ketoester	GC analysis		Isolated yield (%)	%ee[a]
		%Conv.	%Yield		
1	6	100	100	82	<1
2	7	100	100	73	(<1)[a]

[a] Enantiomeric excess determined by ^{1}H NMR shift experiments using $Eu(hfc)_3$.

(ee < 1%) was observed indicating that fluorination of the systems occurs very rapidly.

3. Conclusions

The feasibility of catalytic enantioselective fluorination of 1,3-ketoesters with elemental fluorine has been assessed. A series of metal salts were examined in the fluorination of model compound **1** and several salts showed an acceleration of the enolisation process leading to higher conversions and yields of fluorinated products. For chlorinated titanium–catalyst systems, chlorination proceeded efficiently while nickel nitrate and BINAP allowed efficient fluorination at the 2-position. However, attempts at enantioselective fluorination of 1,3-ketoesters using elemental fluorine and a combination of nickel nitrate and homochiral BINAP ligands were unsuccessful and we conclude that elemental fluorine is possibly too reactive to lead to enantioselective reactions for these systems. Therefore, it is unlikely that homochiral systems bearing fluorine at the sterogenic centre at positions adjacent to carbonyl functionality can be synthesised efficiently by direct fluorination processes under the conditions utilised.

4. Experimental

4.1. General

All starting materials were obtained commercially and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a spectrometer operating at 500 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. Mass spectra were recorded on a VG 7070E spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. The progress of reactions was monitored by ^{19}F NMR and column chromatography was carried out on silica gel.

4.2. Direct fluorination reactions

4.2.1. General procedure—catalyst screening

A mixture containing ethyl 2-methyl-3-oxobutanoate **1** (300 mg, 2.10 mmol), catalyst (indicated below, Table 6), and freshly distilled anhydrous acetonitrile (20 mL) was placed in the small PTFE reactor. The mixture was purged with N_2 and immersed in a cooling bath of 0 °C. Elemental fluorine (4.2 mmol) as a 10% (*v*/*v*) mixture with nitrogen was introduced at a flow rate of 10 mL/min into the rapidly stirred mixture *via* PTFE tubing, following experimental details discussed earlier [1,21–22]. The reaction mixture was purged with N_2 for 30 min. The reaction mixture was poured into water (20 mL), neutralised by $NaHCO_3$, and extracted with chloroform (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to give a crude product which was analysed by ^{19}F NMR and GC–MS and compared to an authentic sample. Pure samples of **2** and **4** were isolated from crude product obtained in Entries 8 and 3, respectively as indicated below.

Entry 8: Purification of the crude product by flash chromatography [silica gel: 20 g, eluent: hexane/ethyl acetate (8:1)] provided ethyl 2-fluoro-2-methyl-3-oxobutanoate **2** (72 mg, 22%) as a colourless oil; δ_H 1.29 (3H, t, *J* 7.0, CH_2CH_3), 1.66 (3H, d, $^3J_{HF}$ 22.0, $CFCH_3$), 2.31 (3H, d, $^4J_{HF}$ 4.5, $CH_3C{=}O$), 4.26 (2H, q, *J* 7.0, CH_2); δ_C 13.9 (s, CH_2CH_3), 19.7 (d, $^2J_{CF}$ 23.0, $CFCH_3$), 24.9 (s, $CH_3C{=}O$), 62.6 (s, CH_2), 97.6 (d, $^1J_{CF}$ 193.0, CF), 166.8 (d, $^2J_{CF}$ 25.0, CFCOO), 202.3 (d, $^2J_{CF}$ 28.5, CH_3COCF); IR (neat) 2987, 1756, 1736, 1374, 1361, 1280, 1141, 1108, 1019 cm^{-1}; *m*/*z* (EI$^+$) 163 ([M+H]$^+$, 1%), 120 ([M−C_2H_2O]$^+$, 98), 92 (100); (Found: [M]$^+$, 162.0686. $C_7H_{11}FO_3$ requires 162.0687); spectral data as compared to the literature data [22].

Entry 3: Purification of the crude product by flash chromatography [silica gel: 20 g, eluent: hexane/ethyl acetate (20:1)] provided ethyl 2-chloro-2-methyl-3-oxobutanoate **4** (174 mg, 49%) as a colourless oil; δ_H 1.28 (3H, t, *J* 7.0, CH_2CH_3), 1.80 (3H, s, $CClCH_3$), 2.35 (3H, s, $CH_3C{=}O$), 4.26 (2H, q, *J* 7.0, CH_2); δ_C 13.8 (s, CH_2CH_3), 24.2 (s, $CClCH_3$), 25.2 (s, $CH_3C{=}O$), 63.0 (s, OCH_2), 70.7 (s,

Table 6
Initial catalyst screening reactions.

Entry	Catalyst	mg, mmol
1	–	–
2	Titanium (IV) chloride	36, 0.19
3	Titanium (IV) chloride	76, 0.40
4	Titanium (*trans*-cyclohexane-1,2-diolato) dichloride	0.2 M, 1 mL, 0.2 mmol
5	Hafnium (IV) chloride	65, 0.20
6	Scandium (III) triflate	99, 0.20
7	Lanthanum (III) triflate	117, 0.205
8	Copper (II) nitrate hemipentahydrate	47, 0.20
9	Copper (II) acetylacetonate	28, 0.11
10	Copper (II) triflate	72, 0.20
11	Nickel (II) nitrate hexahydrate	58, 0.20
12	Palladium (II) nitrate hydrate	53, 0.20
13	Silver (I) triflate	52, 0.20
14	Indium (III) nitrate pentahydrate	78, 0.20
15	Bismuth (III) nitrate pentahydrate	97, 0.20

Table 7
Fluorination of **1** using catalyst and racemic ligand combinations.

Entry	Catalyst	mg, mmol	Ligand	mg, mmol
1	Scandium (III) triflate	98, 0.20	BINOL	69, 0.24
			1,2,2,6,6-pentamethylpiperidine	75, 0.48
2	Copper (II) nitrate hemipentahydrate	48, 0.21	Triphenylphosphine	107, 0.41
3	Copper (II) nitrate hemipentahydrate	47, 0.20	*racemic*-BINAP	124, 0.20
4	Copper (II) fluoride	21, 0.21	*racemic*-BINAP	127, 0.20
5	Nickel (II) nitrate hexahydrate	57, 0.20	Triphenylphosphine	106, 0.40
6	Nickel (II) nitrate hexahydrate	58, 0.20	*racemic*-BINAP	126, 0.20
7	Nickel (II) nitrate hexahydrate	58, 0.20	1,2-diphenylphosphinoethane	80, 0.20
8	Nickel (II) nitrate hexahydrate	58, 0.20	*racemic*-BINAP	126, 0.20

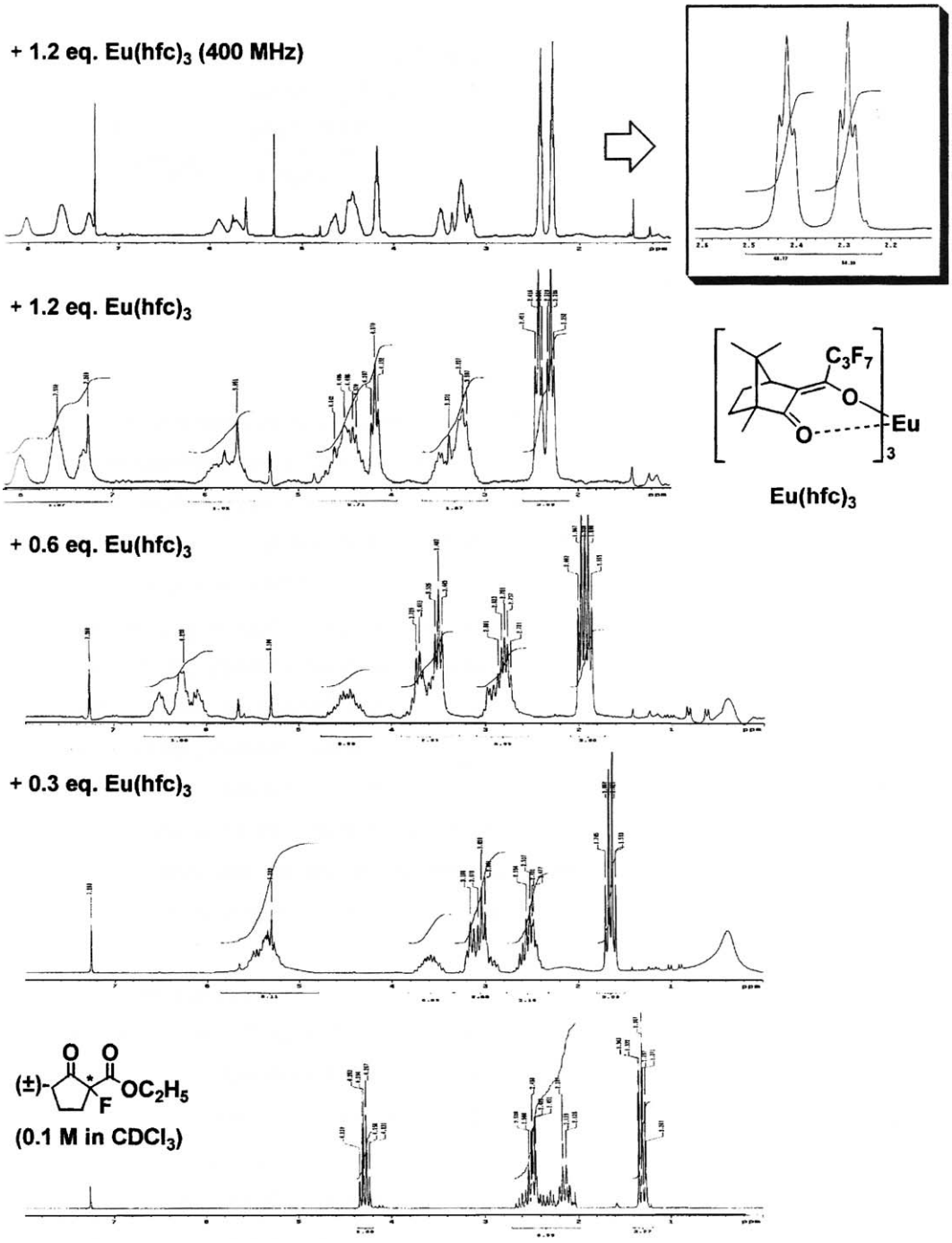


Fig. 1. ^{1}H NMR chemical shift experiments using Eu(hfc)$_3$.

*C*Cl), 168.0 (s, CCl*C*OO), 198.7 (s, CH_3*C*OCCl); IR (neat) 2986, 1733, 1255, 1124 cm^{-1}; *m/z* (EI^+) 179 ([M+H]$^+$ ($C_7H_{12}{}^{35}ClO_3$), 1%), 138 ([M−C_2H_2O]$^+$ ($C_5H_9{}^{37}ClO_2$), 53), 136 ([M−C_2H_2O]$^+$ ($C_5H_9{}^{35}ClO_2$), 89), 110 (63), 108 (86).

Entry 4: Titanium (*trans*-cyclohexanediolato) dichloride was prepared by the following procedure. *trans*-1,2-Cyclohxanediol (116 mg, 1.00 mmol) was added to a mixture of titanium (IV) chloride (190 mg, 1.00 mmol) and anhydrous acetonitrile (5 mL). The solvent was evaporated and the residue redissolved in anhydrous acetonitrile (5 mL) and used directly.

4.2.2. Fluorination reactions in the presence of catalysts and racemic mixtures of various auxiliaries or ligands

A mixture containing ethyl 2-methyl-3-oxobutanoate **1** (300 mg, 2.10 mmol), catalyst (Table 7), ligand (Table 7) and freshly distilled anhydrous acetonitrile (20 mL) was reacted with fluorine following the procedure outlined above to give a crude product which was analysed by ^{19}F NMR and GC–MS and spectral data were compared to an authentic sample as described above.

4.2.3. Estimation of enol contents of β-ketoesters

Each compound was dissolved in acetonitrile-d_3 in 0.1 M and ^1H NMR spectra (400 MHz) were recorded within 30 min and 1 month. Ratios of keto:enol forms are given in Table 3.

Ethyl 2-methyl-3-oxobutanoate **1**: keto form: δ_H 1.02 (3H, t, *J* 7.0, OCH_2CH_3), 1.04 (3H, d, *J* 7.0, $CHCH_3$), 1.98 (s, CH_3CO), 3.37 (1H, q, *J* 7.0, $CHCH_3$), 3.94 (2H, q, *J* 7.0, OCH_2CH_3); enol form: δ_H 1.02 (3H, t, *J* 7.0, OCH_2CH_3), 1.04 (3H, d, *J* 7.0, $CHCH_3$), 1.98 (s, CH_3CO), 3.81–4.01 (2H, m, OCH_2CH_3), 12.50 (1H, s, O*H*).

Ethyl 2-oxocyclopentanecarboxylate **6**: keto form: δ_H 1.02 (3H, t, *J* 7.0, OCH_2CH_3), 1.59–2.32 (6H, m, CH_2), 2.95 (1H, t, *J* 9.0, keto-C*H*), 3.92 (1H, q, *J* 7.0, keto-OCH_2CH_3); enol form: δ_H 1.02 (3H, t, *J* 7.0, OCH_2CH_3), 1.59–2.32 (6H, m, CH_2), 3.85–4.00 (2H, m, OCH_2CH_3).

t-Butyl 2-oxocyclopentanecarboxylate **7**: keto form: δ_H 1.22 (9H, s, $C(CH_3)_3$), 1.57–2.31 (6H, m, CH_2), 2.81 (1H, t, *J* 9.0, C*H*).

Ethyl 2-oxocyclohexanecarboxylate **8**: keto form: δ_H 1.02 (3H, t, *J* 7.0, OCH_2CH_3), 1.37–2.25 (8H, m, CH_2), 3.22 (1H, ddd, *J* 11.0, 5.5, 1.0, C*H*), 3.94 (2H, dq, *J* 7.0, 2.5, OCH_2CH_3); enol form: δ_H 1.04 (3H, t, *J* 7.0, OCH_2CH_3), 1.37–2.25 (8H, m, CH_2), 3.99 (2H, q, *J* 7.0, OCH_2CH_3), 12.04 (1H, s, O*H*).

t-Butyl 2-oxocyclohexanecarboxylate **9**: keto form: δ_H 1.24 (9H, s, $C(CH_3)_3$), 1.33–2.16 (8H, m, CH_2), 3.08 (1H, dd, *J* 9.5, 6.5, C*H*); enol form: δ_H 1.28 (9H, s, $C(CH_3)_3$), 1.33–2.16 (8H, m, CH_2), 12.13 (1H, s, O*H*).

4.2.4. Catalytic direct fluorination of cyclic 1,3-ketoesters

4.2.4.1. General procedure. A mixture containing nickel (II) nitrate hexahydrate, *racemic*-BINAP derivative and anhydrous acetonitrile (15 mL) was placed in the PTFE reactor. The mixture was sonicated for 5 min, and stirred for 30 min. The substrate in anhydrous acetonitrile (5 mL) was added to the mixture, reacted with fluorine and worked up as described above to give a crude product which was analysed by ^{19}F NMR and GC–MS.

4.2.4.2. Catalytic direct fluorination of cyclic 1,3-ketoesters using a racemic catalyst.

4.2.4.2.1. Fluorination of ethyl 2-oxocyclopentanecarboxylate 6. Table 4, Entry 2: Ethyl 2-oxocyclopentanecarboxylate **6** (312 mg, 2.00 mmol), nickel (II) nitrate hexahydrate (58 mg, 0.20 mmol), *racemic*-BINAP (126 mg, 0.20 mmol) and elemental fluorine (6.00 mmol) gave a yellowish oil (549 mg, 100% conv.). Purification by flash chromatography [silica gel: 20 g, eluent: hexane/ethyl acetate (8:1)] gave ethyl 1-fluoro-2-oxocyclopentanecarboxylate **10** (280 mg, 81%) as a colourless oil; δ_H 1.28 (3H, t, *J* 7.0, CH_3), 2.2–2.6 (4H, m, CH_2), 2.55 (2H, m, $CH_2C{=}O$), 4.26 (2H, q, *J* 7.0, OCH_2); δ_C 13.9 (s, CH_3), 17.9 (d, $^3J_{CF}$ 3.5, $CFCH_2CH_2$), 33.8 (d, $^2J_{CF}$ 21.0, CH_2CF), 35.6 (s, $CH_2C{=}O$), 63.4 (s, OCH_2), 94.5 (d, $^1J_{CF}$ 200.0, *C*F), 167.3 (d, $^2J_{CF}$ 27.0, CFCOO), 207.5 (d, $^2J_{CF}$ 17.0, CH_2*C*OCF); δ_F −164.5 (m); IR (neat) 2984, 1771, 1752, 1729, 1294, 1165, 1022 cm^{-1}; *m/z* (EI^+) 174 ([M]$^+$, 21%), 146 ([M−C_2H_4]$^+$, 27), 117 (71), 91 (100); (ES^+) (Found: [M+NH_4]$^+$, 192.1032. $C_8H_{15}FNO_3$ requires 192.1030); spectral data compared to the literature data [26].

^1H NMR chemical shift experiments using various quantities of Eu(hfc)$_3$ were performed (Fig. 1) and the integrations of the $CH_2C{=}O$ resonances located at 2.15 ppm allowed the ratios of enantiomers to be established.

4.2.4.2.2. Fluorination of t-butyl 2-oxocyclopentanecarboxylate 7. Table 4, Entry 3: *t*-Butyl 2-oxocyclopentanecarboxylate **7** (368 mg, 2.00 mmol), nickel (II) nitrate hexahydrate (58 mg, 0.20 mmol), *racemic*-BINAP (126 mg, 0.20 mmol), and elemental fluorine (6.00 mmol) gave a yellowish oil (360 mg, 100% conv.). Purification by flash chromatography [silica gel: 20 g, eluent: hexane/ethyl acetate (8:1)] provided *t*-butyl 1-fluoro-2-oxocyclopentanecarboxylate **11** (357 mg, 88%) as a colourless oil; δ_H 1.47 (9H, s, $C(CH_3)_3$), 2.09 (2H, quin, *J* 7.5, CH_2CH_2CF), 2.2–2.5 (4H, m, CH_2); δ_C 18.0 (d, $^3J_{CF}$ 3.5, CH_2CH_2CF), 27.8 (s, $C(CH_3)_3$), 33.8 (d, $^2J_{CF}$ 21.0, CH_2CF), 35.7 (s, CH_2CO), 83.9 (s, $C(CH_3)_3$), 94.3 (d, $^1J_{CF}$ 200.0, *C*F), 166.3 (d, $^2J_{CF}$ 28.0, CFCOO), 208.1 (d, $^2J_{CF}$ 18.0, CH_2COCF); δ_F −163.3 (m); IR (neat) 2979, 1768, 1751, 1719, 1371, 1151, 1127, 842 cm^{-1}; *m/z* (EI^+) 202 ([M]$^+$, 5%), 187 ([M−CH_3]$^+$, 25), 146 ([M−C_4H_8]$^+$, 82); (Found: [M]$^+$, 202.1010. $C_{10}H_{15}FO_3$ requires 202.1005); as compared to the literature data [19].

4.2.4.2.3. Attempted catalytic enantioselective direct fluorination of 1,3-ketoesters. Ethyl 2-oxocyclopentanecarboxylate **6** (312 mg, 2.00 mmol), nickel (II) nitrate hexahydrate (58 mg, 0.20 mmol), (*R*)-BINAP (126 mg, 0.20 mmol), and elemental fluorine (10.0 mmol) gave a yellowish oil (580 mg, 100% conv.). Purification by flash chromatography [silica gel: 20 g, eluent: hexane/ethyl acetate (8:1)] provided ethyl 1-fluoro-2-oxocyclopentanecarboxylate **10** (286 mg, 82%) as a colourless oil (<1% ee); spectral data as above.

t-Butyl 2-oxocyclopentanecarboxylate **7** (368 mg, 2.00 mmol), nickel (II) nitrate hexahydrate (58 mg, 0.20 mmol), (*R*)-BINAP (126 mg, 0.20 mmol), and elemental fluorine (10.0 mmol) gave a yellowish oil (683 mg, 100% conv.). Purification by flash chromatography [silica gel: 20 g, eluent: hexane/ethyl acetate (8:1)] provided *t*-butyl 1-fluoro-2-oxocyclopentanecarboxylate **11** (293 mg, 73%) as a colourless oil (<1% ee); spectral data as above.

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