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Catalytic Enantioselective Fluorination of α-Chloro-β-keto Esters in the Presence of Chiral Nickel Complexes

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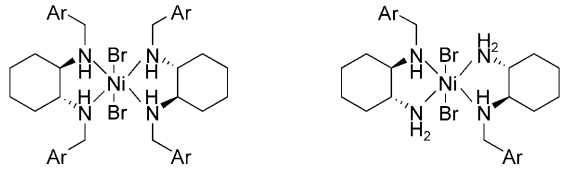
Abstract: The catalytic enantioselective electrophilic fluorination promoted by chiral nickel complexes is described. The treatment of α-chloro-β-keto esters with Selectfluor under mild reaction conditions afforded the corresponding fluorinated α-chloro-β-keto esters with excellent enantioselectivities (up to 99% *ee*).

Keywords: asymmetric catalysis; chiral nickel complexes; α-chloro-β-keto esters; electrophilic fluorination

The chemistry of organofluorine compounds is a rapidly developing area of research because of their importance in biochemical and medicinal applications and material science.[1] Introduction of a fluorine atom into biologically active compounds often leads to a significant and frequently beneficial modification of their biological characteristics due to the unique properties of the fluorine atom.[2] Chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center have been utilized in studies of enzyme mechanisms and as intermediates in asymmetric syntheses.[3] However, the use of optically active compounds containing a fluorine atom at a stereogenic carbon center is restricted by the limited availability of effective methods for the enantioselective construction of fluorinated quaternary carbon centers. Thus, the development of effective methodologies for the preparation of chiral organic fluorine compounds through C–F bond formation is still a highly desirable goal in synthetic organic chemistry.[4] Until now, a number of enantioselective fluorinations have been achieved by regent-controlled and catalytic enantioselective fluorination.[5] Since the first catalytic enantioseletive fluorination by Togni,[6] these reactions have been attracting much attention.[7–11] Recently, several groups have reported on catalytic enantioselective fluorinations of active methine derivatives using chiral Lewis acids such as BINAP-Pd(II) and transition metal-bis(oxazoline) complexes and organocatalysts such as cinchonine-derived quaternary ammonium salts, imidazolidinone, and proline derivatives.[7–11] A few synthetic methods for the preparation of α-chloro-α-fluoro-β-keto esters are reported. In general, α-chloro-α-fluoro-β-keto esters are prepared by the electrophilic fluorination of α-chloro-β-keto esters using NFSI or F_2 in the presence of formic acid.[12] Togni has recently reported the first catalytic enantioselective synthesis of α-chloro-α-fluoro-β-keto esters using chiral titanium complexes with up to 65% enantiomeric excess.[13] Recently, we have developed Pd(II)-catalyzed enantioselective fluorination of α-chloro-β-keto esters with up to 77% enantioselectivity.[14]

As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[15] we recently reported the catalytic enantioselective amination and Michael-type reaction of active methines in the presence of chiral nickel(II) complexes developed by the Evans group.[16–17] In this communication, we wish to report the catalytic enantioseletive electrophilic α-fluorination of α-chloro-β-keto esters using chiral nickel complexes **4** (Figure 1) which are air- and moisture-stable.

To determine suitable reaction conditions for the catalytic enantioselective fluorination of α-chloro-β-keto esters,[18] we initially investigated the reaction system with ethyl 2-chloro-oxo-3-*p*-tolylpropanoate (**1a**) and F-TEDA {**2a**, Selectfluor, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)} in the presence of 10 mol% of chiral nickel(II) catalyst in toluene at room temperature. We first examined the impact of the structure of electrophilic fluorinating reagents **2a–2d** on enantioselectivities



4a: Ar = phenyl
4b: Ar = 4-fluorophenyl
4c: Ar = 1-naphthyl
4d: Ar = thiophen-2-yl

4e: Ar = phenyl
4f: Ar = 1-naphthyl
4g: Ar = 9-anthracenyl

Figure 1. Structures of chiral nickel complexes **4**.

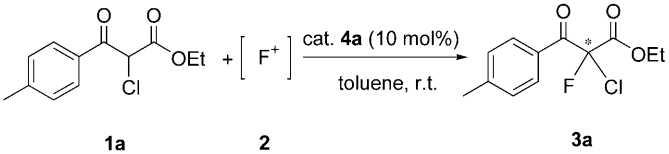
(Table 1, 37–75% *ee*, entries 1–4). The best results have been obtained with Selectfluor (**2a**).

To improve the enantioselectivity, we examined a series of chiral diamine ligands in catalysts **4** (Table 2). By screening chiral nickel(II) complexes **4a–f**, we found that catalyst **4f** was the best catalyst for this enantioselective electrophilic fluorination, affording the corresponding product **3a** in 95% *ee* and 68% yield at room temperature (Table 2, entry 6). Decreasing the catalyst loading showed a significant decrease in yields and slightly decreased the enantioselectivities.

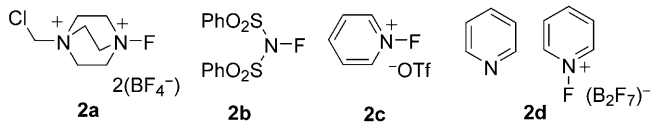
Concerning the solvent, the use of non-polar solvents such as toluene and *o*-xylene gave the best results (Table 3, entries 7 and 8), whereas the fluorination in alcohol, H_2O, DCM, THF, and acetone led to slightly lower enantioselectivities (entries 1–6). Lowering the temperature in toluene decreased the yields but with similar enantioselectivity (entries 9–11).

To examine the generality of the catalytic enantioselective fluorination of α-chloro-β-keto esters **1** by

Table 1. Effect of fluorinating reagents **2**.



1a **2** **3a**

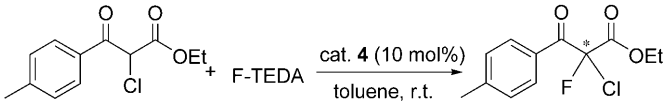


2a **2b** **2c** **2d**

Entry	**2**	Time [d]	Yield[a] [%]	*ee*[b] [%]
1	**2a**	2	71	75
2	**2b**	2	40	37
3	**2c**	2	42	67
4	**2d**	4	13	40

[a] Isolated yields.
[b] Enantiopurity was determined by HPLC analysis using a Chiralcel OB-H column.

Table 2. Effect of the catalysts **4**.

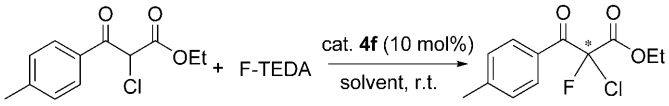


1a **2a** **3a**

Entry	Cat. **4**	Time [d]	Yield[a] [%]	*ee*[b] [%]
1	**4a**	2	71	75
2	**4b**	2	56	85
3	**4c**	2	61	82
4	**4d**	2	65	85
5	**4e**	2	62	90
6	**4f**	1	63	95
7	**4g**	1	69	91

[a] Isolated yields.
[b] Enantiopurity was determined by HPLC analysis using a Chiralcel OB-H column.

Table 3. Effects of the solvents and temperature.



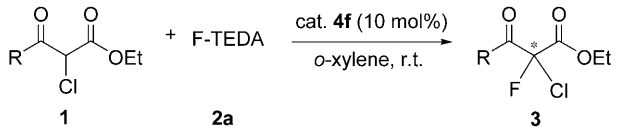
1a **2a** **3a**

Entry	Solvent	Temp. [°C]	Cat. **4**	Time [d]	Yield[a] [%]	*ee*[b] [%]
1	MeOH	r.t.	**4f**	2	81	21
2	EtOH	r.t.	**4f**	1	63	71
3	H_2O	r.t.	**4f**	1	79	33
4	DCM	r.t.	**4f**	1	45	93
5	THF	r.t.	**4f**	1	65	85
6	acetone	r.t.	**4f**	1	68	73
7	toluene	r.t.	**4f**	1	63	95
8	*o*-xylene	r.t.	**4f**	1	67	95
9	toluene	r.t.	**4e**	2	62	90
10	toluene	−20	**4e**	2	31	90
11	toluene	−40	**4e**	4	25	91

[a] Isolated yields.
[b] Enantiopurity was determined by HPLC analysis using a Chiralcel OB-H column.

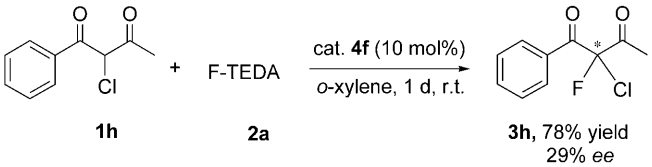
using chiral nickel complex **4f**, we studied the fluorination of α-chloro-β-keto ester derivatives **1** under optimum reaction conditions.[19] As can be seen by the results summarized in Table 4, the corresponding α-chloro-α-fluoro-β-keto esters **3** were obtained in moderate to high yields and excellent enantioselctivities (89-99% *ee*). The absolute configuration of **3b** was determined to be *S* by comparing chiral HPLC data to the published values of ref.[13] On the other hand, ethyl 2-chloro-3-oxobutanoate (**1g**) could not be fluorinated under identical conditions (Table 4, entry 7).

Table 4. Catalytic enantioselective fluorination of α-chloro-β-keto esters **1**.



Entry	1	R	Time [d]	Product, Yield[a] [%]	*ee*[b] [%]
1	**1a**	*p*-MeC_6H_4	1	**3a**, 67	95
2	**1b**	Ph	1	**3b**, 65	95 [*S*]
3	**1c**	*p*-$CF_3C_6H_4$	1	**3c**, 71	90
4[c]	**1d**	*p*-BrC_6H_4	1	**3d**, 83	92
5[c]	**1e**	3-ClC_6H_4	2	**3e**, 85	89
6	**1f**	2-naphthyl	1	**3f**, 65	99
7	**1g**	Me	2	**3g**, –	–

[a] Isolated yields.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Reaction performed with 30 mol% catalyst loading.



Scheme 1.

Furthermore, 2-chloro-1-phenylbutane-1,3-dione (**1h)** was also used as a substrate in this enantioselective fluorination under the standard conditions. It was found that the corresponding product **3h** was obtained in 78% yield and 29% *ee* (Scheme 1).

In summary, we have accomplished the efficient catalytic enantioselective electrophilic α-fluorination of various α-chloro-β-keto esters **1** with good enantioselectivity (up to 99% *ee*) with nickel complex **4f** as chiral catalyst. It should be noted that this fluorination reaction proceeded well using air- and moisture-stable chiral nickel complexes. Current efforts are directed towards developing synthetic applications of this α-fluorination reaction.

Experimental Section

Typical Procedure for the Fluorination of Ethyl 2-Chloro-3-oxo-3-*p*-tolylpropanoate (1a) and Selectfluor (2a) in the Presence of Chiral Nickel(II) Catalyst 4f

A mixture of ethyl 2-chloro-3-oxo-3-*p*-tolyllpropanoate **1a** (24.1 mg, 0.1 mmol) and catalyst **4f** (7.8 mg, 0.01 mmol) in *o*-xylene (0.4 mL) was stirred at room temperature for 5 min and then Selectfluor **2a** (42.5 mg, 0.12 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The resulting solution was concentrated under vacuum and the obtained residue was purified by flash chromatography (EtOAc-hexane, 1:10) to afford ethyl 2-chloro-2-fluoro-3-oxo-3-*p*-tolylpropanoate **3a**; yield: 17.3 mg (67%); $[\alpha]_D^{24}$: −18.4 (*c* 1.0, $CHCl_3$, 95% *ee*); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 2.44 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.97 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.7$, 21.8, 64.1, 103.11 (d, $J = 263.1$ Hz), 129.5, 130.3, 146.1, 163.1 (d, $J = 27.0$ Hz), 184.2 (d, $J = 24.5$ Hz); HR-MS (ESI): $m/z = 259.0543$, calcd. for $C_{12}H_{13}ClFO_3$ $[M+H]^+$: 259.0537; HPLC (*n*-hexane: *i*-PrOH = 97:3, 254 nm, 1.0 mL min^{-1}, Chiralcel OB-H column): $t_R = 6.6$ min (minor), $t_R = 7.5$ (major).

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[19] We have checked the possibility of self-disproportionation of chiral fluorinated products **3** in line with the suggestion made by one of the reviewer. Chiral fluorinated product (**3a**) was not subjected to the self-disproportionation of enantiomers *via* chromatographic purification and evaporation steps. See the Supporting Information for details.

