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Enantioselective fluorination of β-ketoesters using tartrate derived

bidentate bioxazoline-Cu(II) complexes

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ABSTRACT

Enantioselective fluorination of aliphatic cyclic and acyclic β -ketoesters was achieved in excellent yield (up to 98%) with moderate to good enantioselectivities (up to 86% ee) using tartrate derived bidentate bioxazoline-Cu(II) complexes. This is the first report of a bioxazoline which forms a 5-membered chelate inducing enantioselectivity in the asymmetric fluorination of β -ketoesters.

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1. Introduction

Access to stereogenic fluorinated carbon centers can be achieved by enantioselective electrophilic fluorination. Fluorinated molecules can often interact with biological targets more effectively than their non-fluorinated analogues, thus playing a key role in pharmacokinetics.¹ As a result, the development of chiral ligands for electrophilic fluorination to construct a stereogenic fluorinated carbon center is a prominent area of research in the field of asymmetric catalysis.²

The first enantioselective fluorination of β -ketoesters was developed by Togni using [TiCl₂(TADDOLato)]-complex and achieved up to 90% enantioselectivity using Selectfluor.³ The Pd/BINAP complexes in combination with *N*-fluorobenzene sulfonimide (NFSI) were used by Sodeoka for an efficient enantioselective synthesis of various α -fluoro- β -ketoesters.⁴ These two successful investigations paved the way for the development of several catalytic enantioselective fluorinations. For example Togni⁵ and Sodeoka⁶ independently continued their efforts in synthesizing enantioselective fluorinated β-ketoesters and oxindoles. In addition to these findings, enantioselective fluorination using chiral organophosphate-Sc complexes by Inanaga,^{7a} 2,2'-bipyridine-3,3'-dicarboxylic esters and amides with copper by Queneau et al.,^{7b} sulphoximines-copper complexes by Bolm,^{7c} chiral diamine-nickel complexes by Kim,^{7d} Co-salen by Itoh et al.,^{7e} and most recently Pd/SPANphos by Leeuwen^{7f} was reported to synthesize fluorinated β-ketoesters. Chiral organocatalysts such as cinchona alkaloids, chiral quarternary ammonium salts, and chiral thioureas were also utilized in order to make optically active fluorinated molecules.⁸

Shibata initiated the use of bis(oxazoline) ligand **1** (Fig. 1) with Ni(II) or Cu(II) for the enantioselective fluorination of various 1-indanone-2-carboxylates and achieved up to 93% enantioselectivity.⁹ Independently Cahard also utilized the same catalytic system for the asymmetric fluorination of various β -ketoesters using



Figure 1. Oxazoline ligands.





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Figure 2. Bidentate bioxazoline ligands from tartaric acid.

several electrophilic fluorinating agents.¹⁰ Despite the good enantioselectivity, the efficiency of the method was not demonstrated using various substrates. Moreover good selectivity was only possible with β -ketoesters, which possessed bulky ester constituents such as t-butyl/adamantyl or menthyl. Since the well known bisoxazolines failed to mediate enantioselective fluorinations with a broad substrate scope, DBFOX-Ph 2 (Fig. 1) was applied for the same reactions with good substrate scope.¹¹ N,N,N-Tridentate ligand **3** was exploited with various Lewis acids for asymmetric fluorination of β -ketoesters.¹² DBFOX-Ph **2** was the most effective catalyst for the construction of fluorinated stereogenic centers. Although ligands 2 and 3 showed excellent enantioselectivity in the asymmetric fluorination reaction, the synthesis of DBFOX-Ph 2 precursor demands tedious reaction conditions such as s-BuLi, while the synthesis of ligand **3** involves a resolution. Any catalytic system which could overcome some of these difficulties discussed would be desirable.

Due to poor chiral induction, ligand **4** (Fig. 1) has been less explored.¹³ The poor chirality transfer of tartrate derived bioxazoline **4** was overcome by the introduction of an additional chiral appendage near the coordination sphere. This new class of chiral ligand **5** (Fig. 2) was used efficiently in various asymmetric transformations such as asymmetric Henry reactions,^{14a} enantioselective propargylamine synthesis,^{14b} and asymmetric allylic alkylations.^{14c} The paucity of synthetic methods to synthesize a stereogenic center with fluorine prompted us to explore the efficiency of ligand **5** (Fig. 2) in asymmetric fluorinations, since it can be obtained from commercially available and inexpensive chiral sources through simple organic transformations.

2. Results and discussion

It was reported that (*S*,*S*)-Nap-(*S*,*S*)-Box **5a** (Fig. 2) efficiently mediated enantioselective Henry reactions and the addition of alkynes to imines. Hence, our initial attempt at enantioselective fluorination was carried out using **5a** in combination with various metal salts in order to find the most suitable metal partner. Fluorination of ethyl 2-oxocyclopentanecarboxylate **6a** using NFSI as an electrophilic fluorinating agent was chosen as a model reaction. It is reported in the literature that the nature of the metal ion may influence the stereochemical outcome of the products.¹⁵ Shibata et al. also made a similar observation in the case of the asymmetric fluorination of β -ketoesters.⁹ On similar lines, the asymmetric fluorination of β -ketoesters using ligand **5a** with Cu salts furnished the (*S*)-isomer (Table 1, entries 1–3), while the use of a Zn salt resulted in the (*R*)-isomer (Table 1, entry 4). Among the various metal salts screened Cu(ClO₄)₂·6H₂O was observed to be the best in terms of enantioselectivity (Table 1, entry 3).

Table 1

Optimization of the conditions for (*S*,*S*)-Nap-(*S*,*S*)-Box **5a**-catalyzed enantioselective fluorination of ethyl 2-oxocyclopentanecarboxylate **6a**^a



^a Reaction conditions: **5a** (7.5 mol %), metal salt (5 mol %), **6a** (1 equiv), and NFSI (1.1 equiv) in 1 mL of dichloromethane.

^b Isolated yield.

^c Determined by a chiralpak AS-H column; the absolute configuration of **7a** was assigned by comparison of the specific rotation.^{7c}

Since Cu(ClO₄)₂·6H₂O gave the best enantioselectivity, it was chosen for further optimization of the reaction conditions. There is no literature precedence of utilizing ligand **4** in the asymmetric fluorination of β -ketoesters. As a result, the substituent effect of bioxazoline ligands **4** was investigated. Tartrate derived bioxazoline ligands **4a–4d**, which do not possess an additional chiral appendage, failed to induce good enantioselectivity. Although the reaction was efficient, poor enantioselectivity was obtained when using these ligands (Table 2, entries 1–4). It is unambiguous from these observations that an attachment of a chiral appendage is essential for asymmetric induction. Since ligand **5** contains two stereogenic centers, there is a possibility of four diastereomeric ligands 5a-5d. It is important to identify which diastereomeric ligand might catalyze the enantioselective fluorination the best. Evaluation of **5a–5d** in the presence of Cu(ClO₄)₂·6H₂O using NFSI afforded the corresponding fluorinated product 7a in very good yield. From the results (Table 2, entries 4-8) one can deduce that the combination of (R) and (S) is required for better enantioselectivity. From Table 2 it can be seen that bioxazoline ligands 5b and 5c, which are enantiomers, afforded the product with identical enantioselectivity (Table 2, entries 6-7).

Table 2

Identification of bioxazoline ligands in the enantioselective fluorination of ethyl 2-oxocyclopentanecarboxylate 6aª



Reaction conditions: ligand (7.5 mol %), Cu(ClO₄)₂·6H₂O (5 mol %), **6a** (1 equiv), and NFSI (1.1 equiv) in 1 mL of dichloromethane at 25 °C.

Isolated vield

Determined by a chiralpak AS-H column.

It should be noted that while ligands **5a** and **5d** provided very good enantioselectivities in asymmetric Henry reactions, alkyne additions to imines and asymmetric allylic alkylations, in the case of asymmetric fluorinations the diastereomeric pair of **5a** and **5d**, that is bioxazoline ligands 5b and 5c, was better in inducing enantioselectivity. The observed difference in the ability of these ligands 5a and 5c to induce asymmetric induction is explained by the proposed transition-state model in Figure 3. In order to obtain the (S)-isomer of the fluorinated molecule, β -ketoester **6a** might approach the metal coordination site of ligand 5a, as depicted in Figure 3a, although it is sterically not favored. The Si-face attack of the electrophile is responsible for the formation



(R)-isomer with 70% ee

Figure 3. Proposed transition state models for enantioselective fluorinations.

of the (S)-isomer. In the case of ligand **5c**, Re-face attack and the lack of a steric interaction are proposed for the observed enhancement in enantioselectivity as well as the stereochemical outcome. It was shown in the previous results that the absolute configuration of the product was effectively dictated by the chirality of the oxazoline backbone,^{14a} while similar observations were made in the enantioselective fluorination. Chimeric ligands 5e and 5f derived from tartaric acid and ibuprofen failed to induce good enantioselectivity (Table 2, entries 9-10). Since the asymmetric induction by ligand **5c** was better than the other ligands, further optimization studies were performed using this ligand.

Under the standard reaction conditions, the fluorination of ethyl 2-oxocyclopentanecarboxylate **6a** in chlorinated solvents such as chloroform (CHCl₃) and dichloroethane proceeded very efficiently to afford **7a** in excellent yield but with moderate enantioselectivity (60% and 77% ee) (Table 3, entries 1–2). Use of ether solvents such as diethylether, dioxane, and tetrahydrofuran (THF) did not increase the enantioselectivity (Table 3, entries 3-5). Although excellent yields (87-95%) were obtained in the case of polar solvents such as acetonitrile (CH₃CN), hexafluoro-2-propanol (HFIP), and acetone, only moderate enantioselectivity was observed (Table 3, entries 6-8). The use of a non-polar solvent, such as toluene, afforded the product with good enantioselectivity (82% ee, Table 3, entry 9). Toluene was thus identified as a suitable reaction medium.

Table 3

Effect of solvents on enantioselectivity in the formation of 7a^a

	Ga COOEt 5c	/ Cu(ClO₄)•2H₂O NFSI, 25 °C	O F COOEt 7a	
Entry	Solvent	Time (h)	Yield ^b (%)	ee ^c (%)
1	CHCl₃	3	97	77
2	Dichloroethane	3	96	60
3	Diethylether	5	77	74
4	Dioxane	4	82	61
5	THF	3	93	71
6	CH ₃ CN	4	88	52
7	HFIP	6	87	57
8	Acetone	3	91	54
0	Toluene	3	95	82

^a Reaction conditions: 5c (7.5 mol %), Cu(ClO₄)₂·6H₂O (5 mol %), 6a (1 equiv), and NFSI (1.1 equiv) in 1 mL of solvent at 25 °C.

^b Isolated yield.

^c Determined by a chiralpak AS-H column.

Table 4 Additive effects on the enantioselective formation of 7a^a

	COOEt	5c / Cu(C NFSI,	IO ₄)·2H ₂ O	O F COOEt	
Entry	Additive ^b	Time (h)	Temp (^O C)	Yield ^c (%)	ee ^d (%)
1	MS (4 Å)	3	25	93	82
2	NaBAr _F	3	25	78	31
3	HFIP	4	25	94	80
4	HFIP	8	0	93	86
5	HFIP	12	-20	88	86

^a Reaction conditions: **5c** (7.5 mol %), Cu(ClO₄)₂·6H₂O (5 mol %), **6a** (1 equiv), and NFSI (1.1 equiv) in 1 mL of toluene.

^b 10 mol % of additives was added.

^c Isolated yield.

^d Determined by chiralpak AS-H column.

In order to improve the enantioselectivity of the fluorination reaction further, we evaluated the effect of additives due to earlier reports on enhanced enantioselectivity with additives.¹⁶The use of molecular sieves did not improve the enantioselectivity (Table 4, entry 1). The use of a borate salt as an additive dramatically reduced the enantiomeric excess of **7a** (Table 4, entry 2). Cahard reported an increase in enantioselectivity in the asymmetric fluorination with the addition of a trace amount of HFIP.^{10a} Katsuki and Shibasaki independently found that HFIP promoted the release of the fluorinated product from the catalyst, thus assisting catalyst turnover.¹⁷

These observations encouraged us to use 10 mol % of HFIP as an additive in the formation of **7a**. Carrying out the reaction at room temperature did not enhance the enantioselectivity (Table 4, entry 3). Lowering the temperature to 0 °C with HFIP as the additives increases the enantioselectivity marginally to 86% (Table 4, entry 4). Lowering the temperature further did not lead to an increase in the enantioselectivity (Table 4, entry 5). From these optimization studies, we concluded that (*S*,*S*)-Nap-(*R*,*R*)-Box **5c** was the most suitable ligand in combination with Cu(ClO₄)₂·6H₂O in toluene and 10 mol % of HFIP at 0 °C for the effective asymmetric fluorination reactions of β -ketoesters.

Table 5

Enantioselective fluorination of β-ketoesters using bioxazoline 5c^a



^a Reaction conditions: **5c** (7.5 mol %), Cu(ClO₄)₂·6H₂O (5 mol %), **6** (1 equiv), and NFSI (1.1 equiv) in 1 mL of toluene and 10 mol % of HFIP at 0 °C.

^b Isolated yield.

^c Determined by chiral HPLC.

The optimized reaction conditions were then applied to the enantioselective fluorination reactions of various β-ketoesters and the results are shown in Table 5. As shown in Table 5, various aliphatic Bketoesters were successfully converted into their corresponding αfluoro-β-ketoesters 7a-7e in excellent yields and with good enantioselectivities. However, in the case of aromatic β-ketoesters, low enantioselectivities were observed. These observations are in agreement with similar results reported by Itoh et al.^{7e} The enantioselective fluorination using (S,S)-ip-pybox and (R,R)-Jacobson's salen ligands showed high enantioselectivity for aliphatic substrates compared to aromatic substrates. It is noteworthy that the most readily available and inexpensive substrate 6a was identified as the most suitable substrate, giving the expected fluorinated product 7a in 93% yield with 86% ee (Table 5, entry 1). The methyl ester of cyclopentanone-2-carboxylate also showed 72% enantioselectivity with 96% vield (Table 5, entry 2). The notable advantage of our catalytic system over existing methods is that most of the reported catalysts need bulky tert-butyl ester substrates in order to achieve high enantioselectivity. We also utilized *t*-butyl-2-cyclopentanonecarboxylate 6c and found that the bulkiness did not enhance the enantioselectivity (83% ee) further (Table 5, entry 3). Enlarging the ring size to a 6-membered size decreased the enantioselectivity to 52% although the yield was excellent (Table 5, entry 4). This protocol works very well for acyclic β-ketoester 6e. Ethyl 2-methyl-3-oxobutanoate 6e underwent fluorination in 84% yield and with 70% enantioselectivity (Table 5, entry 5). Only ketoesters containing aromatic rings afforded the corresponding fluorinated product in low to poor enantioselectivity (Table 5, entries 6-7). In summary this is the first report of a bioxazoline which forms a 5-membered chelate catalyzing the asymmetric fluorination of β -ketoesters with fair to very good enantioselectivity.

3. Conclusion

In conclusion, tartrate derived bioxazolines containing a chiral appendage were successfully applied for the asymmetric fluorinations of β -ketoesters. (*S*,*S*)-Nap-(*R*,*R*)-Box **5c** was identified as the most suitable diastereomeric ligand to construct a stereogenic C–F bond. The use of these ligands in other asymmetric transformations is currently being developed in our laboratory.

4. Experimental

4.1. General

Tartrate derived bioxazoline ligands **4a–4d** and **4e** and bioxazolines with an additional stereogenic center **5a–5f** were synthesized according to the literature.^{13,14a} ¹H and ¹³C NMR spectra were recorded in CDCl₃ solution on a Bruker AVANCE III 500 MHz spectrometer operating at 500 and 125 MHz. Chemical shifts are expressed in ppm values using TMS as an internal standard. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer. The enantiomeric excess (ee) was determined by HPLC using a chiral column on a SHIMADZU liquid chromatography equipped with PDA detector. The chiral columns used were Chiralpak AS-H, Chiralcel OD-H, Chiralpak AD-H, and RESTEK Rt-bDEXsm chiral columns. Optical rotations were determined on Rudolph, Autopol IV digital polarimeter. TLC was carried out using Kieselgel 60 F254 aluminum sheets (Merck 1.05554).

4.2. General experimental procedure for the catalytic enantioselective fluorination reaction

Reactions were performed on a 0.5 mmol scale: $Cu(ClO_4)_2 \cdot 6H_2O$ (7 mg, 5 mol %) and ligand **5c** (14 mg, 7.5 mol %) were stirred in

toluene (1 mL) and HFIP (0.1 mL) under Ar at 25 °C. After stirring for 2 h, ketoester **6** (1 equiv) and NFSI (1 equiv) were added at 0 °C and the reaction mixture was stirred for 6–10 h at the same temperature. Completion of the reaction was monitored by TLC and then it was directly loaded onto a column. Elution with 10% EtOAc in hexanes afforded the fluorinated ketoester **7** in 84–98% of yield.

4.3. (R)-Ethyl 1-fluoro-2-oxocyclopentanecarboxylate 7a

¹H NMR (500 MHz, CDCl₃): *δ* = 4.28 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.26 (dq, *J* = 10.9, 7.2 Hz, 1H), 2.60–2.44 (m, 3H), 2.38–2.22 (m, 1H), 2.20–2.04 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm; ¹³C NMR (125.7 MHz, CDCl₃): *δ* = 207.39 (d, *J* = 17.1 Hz), 167.3 (d, *J* = 27.0 Hz), 94.7 (d, *J* = 199.9 Hz), 62.4, 35.8, 34.0 (d, *J* = 20.9), 18.2 (d, *J* = 3.3 Hz), 14.2 ppm; enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (98:2 hexanes:isopropanol, 0.5 mL/min, 190 nm); major enantiomer *t*_r = 23.3 min, minor enantiomer *t*_r = 26.3 min; 86%; $[\alpha]_D^{25} = +73.2$ (*c* 1.50, CHCl₃). The absolute stereochemistry was assigned as (*R*) based on comparison of the measured rotation with the literature value.^{7c}

4.4. (R)-Methyl 1-fluoro-2-oxocyclopentanecarboxylate 7b

¹H NMR (500 MHz, CDCl₃): *δ* = 3.81 (s, 3H), 2.62–2.40 (m, 3H), 2.39–2.23 (m, 1H), 2.20–2.04 (m, 2H) ppm; ¹³C NMR (125.7 MHz, CDCl₃): *δ* = 207.2 (d, *J* = 16.9 Hz), 167.8 (d, *J* = 27.1 Hz), 94.8 (d, *J* = 199.9 Hz), 53.1, 35.8, 34.0 (d, *J* = 20.9 Hz), 18.2 (d, *J* = 3.2 Hz) ppm; enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (98:2 hexanes:isopropanol, 0.5 mL/min, 220 nm); major enantiomer t_r = 33.1 min, minor enantiomer t_r = 36.4 min; 72%; $[\alpha]_D^{25}$ = +69.7 (*c* 1.20, CHCl₃). The absolute stereochemistry was assigned as (*R*) based on comparison of the measured rotation with the literature value.^{7c}

4.5. (R)-tert-Butyl 1-fluoro-2-oxocyclopentanecarboxylate 7c

¹H NMR (500 MHz, CDCl₃): *δ* = 2.57–2.42 (m, 3H), 2.35–2.14 (m, 1H), 2.11–2.04 (m, 2H), 1.48 (s, 9H) ppm; ¹³C NMR (125.7 MHz, CDCl₃): *δ* = 208.5 (d, *J* = 17.0 Hz), 166.8 (d, *J* = 27.6 Hz), 94.8 (d, *J* = 199.9 Hz), 84.4, 36.1, 34.2 (d, *J* = 21.2 Hz), 28.3, 18.4 (d, *J* = 3.5 Hz) ppm; enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 hexanes:isopropanol, 0.4 mL/min, 290 nm); major enantiomer *t*_r = 21.5 min, minor enantiomer *t*_r = 17.8 min; 83%; $[\alpha]_D^{25} = +61.4$ (*c* 0.25, CHCl₃). The absolute stereochemistry was assigned as (*R*) based on the retention times in HPLC reported in the literature.¹¹

4.6. (R)-Ethyl 1-fluoro-2-oxocyclohexanecarboxylate 7d

¹H NMR (500 MHz, CDCl₃): δ = 4.29 (q, *J* = 7.1 Hz, 2H), 2.71 (m, 1H), 2.64–2.55 (m, 1H), 2.53–2.37 (m, 1H), 2.20–2.06 (m, 1H), 1.99–1.77 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm; ¹³C NMR (125.7 MHz, CDCl₃): δ = 201.7 (d, *J* = 19.8 Hz), 166.8 (d, *J* = 24.8 Hz), 96.3 (d, *J* = 196.5 Hz), 39.7, 62.4, 36.1 (d, *J* = 21.6 Hz), 26.6, 21.0 (d, *J* = 5.9 Hz), 14.1 ppm; enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 heptane:isopropanol, 0.4 mL/min, 210 nm); major enantiomer t_r = 22.7 min, minor enantiomer t_r = 23.9 min; 52% ee; $[\alpha]_D^{25}$ = +39.6 (*c* 1.0, CHCl₃). The absolute stereochemistry was assigned as (*R*) based on the retention times in HPLC reported in the literature.^{7c}

4.7. (R)-Ethyl 2-fluoro-2-methyl-3-oxobutanoate 7e

¹H NMR (500 MHz, CDCl₃): δ = 4.27 (q, *J* = 7.1 Hz, 2H), 2.32 (d, *J* = 4.5 Hz, 3H), 1.68 (d, *J* = 22.2 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm;

¹³C NMR (125.7 MHz, CDCl₃): *δ* = 202.2 (d, *J* = 28.5 Hz), 166.7 (d, *J* = 25.1 Hz), 97.6 (d, *J* = 193.3 Hz), 25.1, 62.7, 19.9 (d, *J* = 22.8 Hz), 14.1 ppm; enantiomeric excess was determined by GC with (RESTEK Rt-bDEXsm, isotherm 120 °C, H₂) major enantiomer t_r = 13.2 min, minor enantiomer t_r = 12.5 min; 70%; [α]_D²⁵ = -62.1 (*c* 0.70, CHCl₃). The absolute stereochemistry was assigned as (*R*) based on the analogous optical rotation values.^{7c}

4.8. (*R*)-Ethyl 2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 7f

¹H NMR (500 MHz, CDCl₃): *δ* = 7.83 (d, *J* = 7.5 Hz, 1H), 7.69 (td, *J* = 7.2, 1.0 Hz, 1H), 7.50–7.46 (m, 2H), 4.27 (q, *J* = 7.0 Hz, 2H), 3.78 (dd, *J* = 17.5, 17.5 Hz, 1H), 3.42 (dd, *J* = 17.5, 17.5 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C NMR (125.7 MHz, CDCl₃): *δ* = 195.2 (d, *J* = 18.8 Hz), 167.2 (d, *J* = 27.6 Hz), 150.8 (d, *J* = 3.7 Hz), 136.6, 133.2, 128.5, 126.5, 125.6, 94.4 (d, *J* = 201.1 Hz), 62.5, 38.2 (d, *J* = 23.8 Hz), 13.9 ppm; enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexanes:isopropanol, 1.0 mL/min, 254 nm); major enantiomer $t_r = 8.6$ min, minor enantiomer $t_r = 9.5$ min; 34% ee; $[\alpha]_{25}^{25} = -4.0$ (*c* 1.0, CHCl₃). The absolute stereochemistry was assigned as (*R*) based on the retention times in HPLC and specific rotation value reported in the literature.^{8c}

4.9. (*R*)-Ethyl 2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2carboxylate 7g

¹H NMR (500 MHz, CDCl₃): *δ* = 8.09–7.05 (m, 1H), 7.59–7.52 (m, 1H), 7.40–7.27 (m, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.24–3.02 (m, 2H), 2.86–2.47 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C NMR (125.7 MHz, CDCl₃): *δ* = 188.6 (d, *J* = 18.4 Hz), 167.3 (d, *J* = 25.8 Hz), 143.1, 134.0, 130.5, 129.2, 128.7, 127.2, 93.1 (d, *J* = 117.4 Hz), 62.3, 31.7 (d, *J* = 22.0 Hz), 24.9, 13.9 ppm; enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexanes: isopropanol, 0.7 mL/min, 254 nm); major enantiomer t_r = 10.6 min, minor enantiomer t_r = 11.1 min; 16% ee; $[\alpha]_D^{25} = -2.0 (c 1.0, CHCl_3)$. The absolute stereochemistry was assigned as (*R*) based on the retention times in HPLC and specific rotation value reported in the literature.^{8c}

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