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Copper(II) triflate-bis(oxazoline)-catalysed enantioselective electrophilic fluorination of β-ketoesters

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Abstract—A new efficient catalytic enantioselective electrophilic fluorination of cyclic and acyclic β-ketoesters is developed. As low as 1 mol% of chiral bis(oxazoline)-copper triflate complexes catalyses the fluorination by means of *N*-fluorobenzenesulfonimide. The use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) is crucial for achieving high enantioselectivity.

1. Introduction

The asymmetric synthesis of stereogenic fluorinated carbon centres is highly challenging. Currently enantioselective electrophilic fluorination relies on chiral *N*-fluoroammonium salts and transition metal catalysts.[1] Reagent-controlled enantioselective fluorination has previously been described by us[2] and others.[3] Our approach involves enantiopure *N*-fluoroammonium salts derived from the naturally occurring *cinchona* alkaloids. These fluorinating agents have successfully been applied to the asymmetric fluorination of various substrates including ketone and ester enolates, β-ketoesters, silyl enol ethers and nitrile anions, with enantiomeric excesses up to 94%. Achiral *N*-F reagents such as Selectfluor or *N*-fluorobenzenesulfonimide (NFSI) were also used in the enantioselective fluorination of β-ketoesters mediated by chiral phase-transfer catalysts leading to a good ee (69%).[4] Simultaneously to our work, the first transition metal catalysed fluorination has been achieved by Togni et al.[5] The fluorination of β-ketoesters with Selectfluor in the presence of 5 mol% of [$TiCl_2$(TADDOLato)] catalyst was reported to give up to 90% ee for a substituted benzyl acyclic ester. In this approach, computational and experimental studies support a single-electron transfer mechanism for the fluorination.[5b] Following this pioneering work, Sodeoka et al. reported an efficient enantioselective fluorination of various acyclic and cyclic β-ketoesters catalysed by chiral BINAP–palladium complexes.[6] The fluorination was carried out with NFSI in ethanol in the presence of 2.5 mol% of catalyst to give a record ee of 94%. α-Substituted α-fluorinated β-ketoesters are valuable units, which can easily be transformed into highly functionalised compounds. Despite the advances in enantioselective fluorination, the development of new catalytic systems for this important reaction is still required. In particular, we have been interested in the evaluation of nitrogen-containing ligands, which are complementary to the oxygen- and phosphorus-containing ligands investigated, respectively by Togni and Sodeoka.

Herein we report a new efficient catalytic enantioselective electrophilic fluorination of both cyclic and acyclic β-ketoesters by means of chiral bis(oxazoline)-copper complexes leading to enantioenriched fluorinated compounds in high yields and good enantioselectivities. The positive impact on the enantiomeric excess of achiral additives such as HFIP is also reported.

2. Results and discussion

In order to determine suitable reaction conditions for the catalytic enantioselective fluorination of β-ketoesters, 1-fluoro-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester **1a** was employed as a model compound for screening of different fluorine donors, Lewis acids and chiral ligands (Scheme 1).

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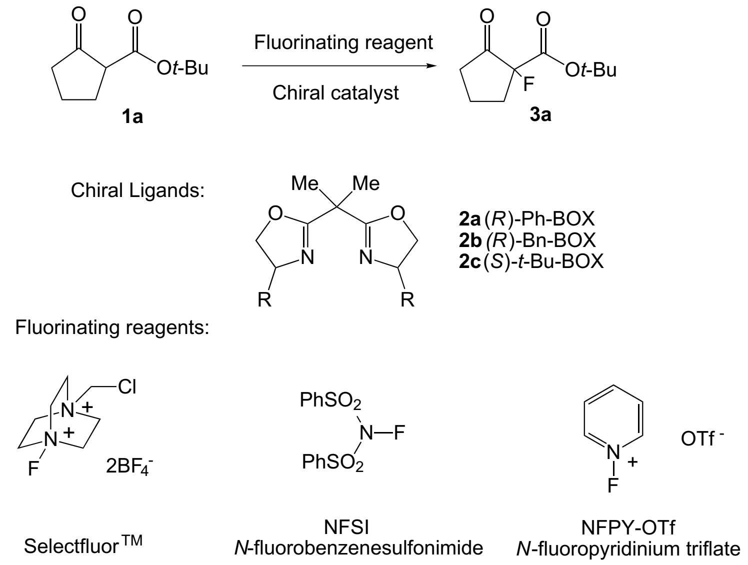


Scheme 1. Enantioselective fluorination of 1-fluoro-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester **1a**.

Some representative results are listed in Table 1. NFSI proved to be the best fluorine donor, the catalytic enantioselective fluorination of **1a** proceeded in excellent yield in dichloromethane and **3a** was obtained in 47% ee (Table 1, entries 1–3). Interestingly, the enantioselectivity of the fluorinated products was highly dependent on the solvent. We found that the use of toluene and ether resulted in higher enantioselectivities (73% ee and 74% ee, respectively; Table 1, entries 5 and 6). Additionally, the metal ion was crucial for the success of this reaction. It was found that copper(II) and zinc(II) possessed the properties necessary for both the in situ generation of the enolate species from **1a** and, in combination with chiral C_2-symmetric ligands, the stereoselectivity of the reaction (Table 1, entries 6 and 8). It is notable that the catalyst loading can be reduced to 0.1 mol%, while still maintaining catalytic activity and good enantioselectivity (Table 1, entry 13). In addition, the stereoselectivity was also independent of the reaction temperature (Table 1, entries 14 and 15). The use of the $Cu(OTf)_2$/Bn-BOX **2b** and *t*-Bu-BOX **2c** catalysts resulted in a significant drop in enantioselectivities of

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_2Cl_2	None	rt	16	97	36 (+)
2	**2a**-$Cu(OTf)_2$ (10)	NFPY-OTf	CH_2Cl_2	None	rt	3	98	35 (+)
3	**2a**-$Cu(OTf)_2$ (10)	NFSI	CH_2Cl_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	*i*-Pr_2NEt	rt	12	90	70 (+)
19	**2a**-$Cu(OTf)_2$ (1)	NFSI	Et_2O	2,6-lutidine	rt	12	89	70 (+)
20	**2a**-$Cu(OTf)_2$ (1)	NFSI	Et_2O	*t*-BuOK	rt	4	94	4 (+)
21	**2a**-$Cu(OTf)_2$ (1)	NFSI	Et_2O	3 Å MS	rt	36	72	70 (+)
22	**2a**-$Cu(OTf)_2$ (1)	NFSI	Et_2O	HFIP	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.

product **3a** to 5% and 20% ee, respectively (Table 1, entries 16 and 17).

To improve the enantioselectivity, we screened a series of achiral additives.[7] The addition of base additives did not improve the enantiomeric excess of **3a**, while **2a**-Cu(OTf)$_2$ retained the catalytic activity and good enantioselectivity, although a sulfonimide [(PhSO$_2$)$_2$NH] with high acidity was increasingly formed during the reaction (Table 1, entries 18 and 19). However, the addition of a strong base such as *t*-BuOK resulted in the loss of enantioselectivity (Table 1, entry 20). The use of molecular sieves led to a longer reaction time, a lower yield, and similar enantioselectivity (Table 1, entry 21). Inspired by Evans' and Jørgensen's works on the use of electron-poor alcohols as additives in copper(II)-catalysed aldol, Mannich and amination reactions,[8] one equivalent of HFIP, as an additive, was added to the reaction leading to a dramatic increase in enantioselectivity to 85% ee (Table 1, entry 22). The role of HFIP is to promote the release of the fluorinated product from the catalyst, thus assisting catalyst turnover.[9]

Under the optimised reaction conditions, the enantioselective electrophilic fluorination of a variety of cyclic and acyclic β-ketoesters **1a–g** was undertaken to afford the optically active fluorinated adducts **3a–g** in good to excellent yields (Table 2). With cyclic β-ketoesters **1a–d** the enantioselectivities were in the range of 35–85% ee, while for the acyclic β-ketoesters **1e–g**, up to 52% ee was obtained.

The absolute configuration of the fluorined product **3e** was determined to be *S* by comparison of the optical rotation with the one reported in the literature.[6a] The stereochemistry of fluorination reactions in the presence of the chiral copper complex can be explained using the transition-state model proposed in Figure 1. The copper centre adopts a distorted square-planar geometry[10] with the phenyl groups and *t*-butyl group of substrate **1e**, avoiding the severe steric interaction with phenyl group of bis(oxazoline) ligand. As a result, NFSI could react preferably from less hindered *Si*-face of the enolate to give good enantioselectivity.

3. Conclusion

In conclusion, we have developed a simple and efficient catalytic asymmetric fluorination of both acyclic and cyclic β-ketoesters using electrophilic fluorinating agents such as NFSI, and Cu(OTf)$_2$/(*R*)-Ph-bis(oxazoline) as catalyst. The reaction proceeds in high yields with the corresponding optically active fluorinated products being obtained in moderate to good enantioselectivities.

4. Experimental

4.1. General

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a BRUKER DPX 300 spectrometer in CDCl$_3$, and δ (ppm) is quoted relative to the residual signal of CDCl$_3$ ($\delta_H = 7.26$ ppm) for ^{1}H NMR and relative to the central CDCl$_3$ resonance ($\delta_c = 77.0$ ppm) for ^{13}C NMR. Trichlorofluoromethane served as the internal standard ($\delta_F = 0$ ppm) for ^{19}F NMR. Flash chromatography was performed on silica gel Merck Kieselgel 60 (230–400 Mesh). Solvents were distilled according to standard procedures. Optical rotations were measured on a Perkin–Elmer 341 polarimeter, CHCl$_3$ and MeOH were used as solvent. The enantiomeric excesses (ees) of the products were determined by HPLC (Waters 600 apparatus equipped with Chiralcel OD-H, OJ or Chiralpak AD-H[11] columns) and by GC (Packard 5890 instrument equipped with Supelco BETADEX-120 column). Ligands **2b** and **2c**, Cu(OTf)$_2$, Mg(ClO$_4$)$_2$, Zn(OTf)$_2$, Sc(OTf)$_3$, La(OTf)$_3$ and fluorinating agents (NFSI, Selectfluor and *N*-fluoropyridinium triflate) were purchased and used as received. Ligand **2a** was prepared following literature procedure.[12]

4.2. General procedure for catalytic asymmetric fluorination of β-ketoesters

In an oven-dried Schlenk tube equipped with a magnetic stirrer bar, Cu(OTf)$_2$ (7.5 mg, 0.02 mmol) and (*R*)-(+)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) (8.1 mg, 0.024 mmol) were stirred under vacuum for 2 h and filled with argon. Distilled ether (10 mL) was added and the solution stirred for 1 h. For reactions run with 1 mol% of catalyst, an aliquot of the solution (1 mL) was transferred to another oven-dried Schlenk tube and dry ether (1 mL) was added. The β-ketoester (0.2 mmol) was then added, followed by the addition of HFIP (21 μL, 0.2 mmol) and fluorinating reagent (0.3 mmol). After the time stated in Table 2, the product was isolated by flash chromatography (cyclohexane/ethyl acetate as eluent).

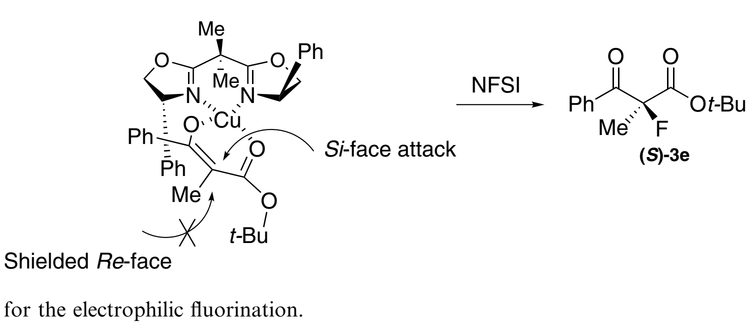
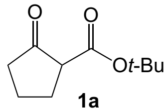
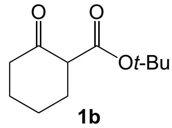
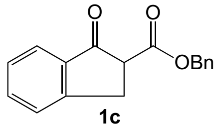
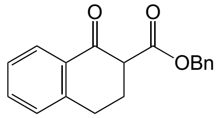
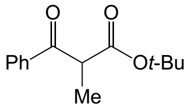
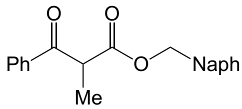
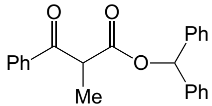


Figure 1. Stereochemical model for the electrophilic fluorination.

Table 2. Enantioselective fluorination of cyclic and acyclic β-ketoesters **1a–g** with NFSI catalysed by 1 mol% Cu(OTf)$_2$-(*R*)-Ph-BOX at 20 °C in ether in the presence of 1 equivalent of HFIP[a]

β-ketoester	Time (h)	Product	Yield (%)[b]	Ee (%)[c]
 **1a**	0.5	**3a**	96	85 (+)
 **1b**	3	**3b**	92	63 (+)
 **1c**	0.5	**3c**	94	35 (+)
 **1d**	0.5	**3d**	92	38 (+)
 **1e**	96	**3e**	56	43 (−) (*S*)[d]
 **1f**	2	**3f**	88	40 (−)
 **1g**	48	**3g**	72	52 (−)

[a] Reactions were run at 20 °C on 0.2 mmol scale.

[b] Yields of isolated products.

[c] GC and HPLC with chiral columns were used to determine the ee values.

[d] See Ref. 6a.

4.2.1. 1-Fluoro-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester 3a.[6a]

^{1}H NMR (300 MHz, CDCl$_3$) 1.48 (s, 9H), 2.04–2.11 (m, 2H), 2.14–2.35 (m, 1H), 2.42–2.57 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 18.4 (d, $J = 3.5$ Hz), 28.3, 34.2 (d, $J = 21.2$ Hz), 36.1, 84.4, 94.8 (d, $J = 199.9$ Hz), 166.8 (d, $J = 27.6$ Hz), 208.5 (d, $J = 17.0$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$/CFCl$_3$) δ −163.2; $[\alpha]_D^{20} = +68.0$ (*c* 1.23, CHCl$_3$) (80% ee); GC (Betadex-120, 15 m × 0.25 mm × 0.25 μm, initial temperature 70 °C, final temperature 120 °C, rate 1 °C/min, inj. temperature 220 °C, det. temperature 220 °C) t_r (minor) = 35.4 min, t_r (major) = 35.9 min.

4.2.2. 1-Fluoro-2-oxo-cyclohexanecarboxylic acid *tert*-butyl ester 3b.[6a]

^{1}H NMR (300 MHz, CDCl$_3$) δ 1.45 (s, 9H), 1.72–2.04 (m, 5H), 2.32–2.58 (m, 3H), 2.42–2.57 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.6 (d, $J = 6.4$ Hz), 26.9, 28.3, 36.4 (d, $J = 21.2$ Hz), 40.3, 84.3, 96.8 (d, $J = 196.4$ Hz), 166.1 (d, $J = 24.8$ Hz), 202.7 (d, $J = 20.0$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$/CFCl$_3$) δ −159.7; $[\alpha]_D^{20} = +65.2$ (*c* 1.2, CHCl$_3$) (52% ee); HPLC (Chiralpak AD-H, *n*-heptane/*i*-propanol = 99.5/0.5, 1 mL/min, 215 nm) t_r (minor) = 11.3 min, t_r (major) = 14.2 min.

4.2.3. 2-Fluoro-1-oxo-indan-2-carboxylic acid benzyl ester 3c.

^{1}H NMR (300 MHz, CDCl$_3$) δ 3.36 (dd, 1H, $J = 17.7$ Hz, 23.0 Hz), 3.70 (dd, 1H, $J = 17.7$ Hz, 11.7 Hz), 5.14 (d, 1H, $J = 12.3$ Hz), 5.22 (d, 1H, $J = 12.3$ Hz), 7.16–7.38 (m, 5H), 7.40–7.68 (m, 3H), 7.70–7.95 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 38.6 (d, $J = 24$ Hz), 68.2, 95.0 (d, $J = 202.1$ Hz), 126.1, 127.0, 128.4, 128.9, 129.1, 129.9,130.2, 133.7 135.0, 136.2, 137.2, 151.2 (d, $J = 3.5$ Hz), 167.4 (d, $J = 28.3$ Hz), 195.4 (d, $J = 18.4$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$/CFCl$_3$) δ −165.0; $[\alpha]_D^{20} = -6.0$ (*c* 1.99, MeOH) (35% ee); HPLC (Chiralcel OD-H, *n*-hexane/*i*-propanol = 94/6, 1 mL/min, 254 nm) t_r (major) = 13.5 min, t_r (minor) = 15.1 min.

4.2.4. 2-Fluoro-1-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid benzyl ester 3d.[13] ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.40–2.73 (m, 2H), 2.87–3.13 (m, 2H), 5.14 (d, 1H, $J = 12.1$ Hz), 5.23 (d, 1H, $J = 12.1$ Hz), 7.15–7.32 (m, 7H), 7.48 (td, 1H, $J = 7.5$ Hz, 1.2 Hz), 8.00 (dd, 1H, $J = 7.9$ Hz, 1.1 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 25.2 (d, $J = 7.0$ Hz), 32.2 (d, $J = 22.6$ Hz), 68.1, 93.7 (d, $J = 193.6$ Hz), 127.7, 128.4, 128.8(d, $J = 1.4$ Hz), 128.9, 129.0, 129.2, 131.0, 135.0, 135.1, 143.5, 167.6 (d, $J = 26.9$ Hz), 189.0 (d, $J = 19.1$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$/CFCl$_3$) δ −165.0; $[\alpha]_D^{20} = +24.0$ (*c* 1.2, MeOH) (38% ee); HPLC (Chiralcel OD-H, *n*-hexane/*i*-propanol = 97/3, 1 mL/min, 254 nm) t_r (major) = 14.9 min, t_r (minor) = 17.7 min.

4.2.5. (*S*)-2-Fluoro-2-methyl-3-oxo-3-phenyl-propionic acid *tert*-butyl ester 3e.[6a] ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.37 (s, 9H), 1.81 (d, 3H, $J = 22.3$ Hz), 7.43–7.48 (m, 2H), 7.55–7.60 (m, 1H), 8.01–8.05 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 20.9 (d, $J = 23.3$ Hz), 28.0, 84.4, 97.0 (d, $J = 193.5$ Hz), 128.9, 129.9, 130.0, 133.9, 134.0, 134.1, 167.9 (d, $J = 25.5$ Hz), 192.1 (d, $J = 25.4$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$/CFCl$_3$) δ −151.3; $[\alpha]_D^{20} = -10.9$ (*c* 0.55, CHCl$_3$) (43% ee); HPLC (Chiralpak AD-H, *n*-heptane/*i*-propanol = 99.5/0.5, 1 mL/min, 246 nm) t_r (minor) = 6.9 min, t_r (major) = 7.5 min.

4.2.6. 2-Fluoro-2-methyl-3-oxo-butyric acid naphthalen-1-ylmethyl ester 3f.[5a] ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.67 (d, 3H, $J = 22.2$ Hz), 2.22 (d, 3H, $J = 4.9$ Hz), 5.69 (d, 2H, $J = 3.4$ Hz), 7.45–7.58 (m, 4H), 7.86–7.96 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 18.8 (d, $J = 22.5$ Hz), 23.9, 65.5, 96.6 (d, $J = 194.3$ Hz), 122.1, 124.2, 125.1, 125.8, 126.8, 127.8, 128.8, 129.0, 130.0, 132.4, 165.7 (d, $J = 26.2$ Hz), 201.1 (d, $J = 29.0$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$/CFCl$_3$) δ −157.4; $[\alpha]_D^{20} = -10.4$ (*c* 1.2, MeOH) (40% ee); HPLC (Chiralcel OJ, *n*-hexane/*i*-propanol = 96/4, 1 mL/min, 254 nm) t_r (major) = 21.5 min, t_r (minor) = 26.5 min.

4.2.7. 2-Fluoro-2-methyl-3-oxo-3-phenyl-propionic acid benzhydryl ester 3g.[5a] ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.81 (d, 3H, $J = 22.6$ Hz), 6.83 (s, 1H), 6.95–7.28 (m, 12H), 7.42–7.43 (m, 1H), 7.85–7.90 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) 21.2 (d, $J = 23.2$ Hz), 79.3, 97.1 (d, $J = 193.8$ Hz), 127.1, 127.5, 128.4, 128.8 (d, $J = 2.8$ Hz), 128.8, 129.0, 130.0, 130.1, 133.6 (d, $J = 3.5$ Hz), 134.3, 138.9, 139.1, 168.0 (d, $J = 26.0$ Hz), 191.5 (d, $J = 24.6$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$/CFCl$_3$) δ −152.2; $[\alpha]_D^{20} = -20.5$ (*c* 1.92, MeOH) (52% ee); HPLC (Chiralcel OJ, *n*-hexane/*i*-propanol = 95/5, 1 mL/min, 254 nm) t_r (minor) = 15.2 min, t_r (major) = 20.9 min.

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