Synthesis of 4-Halogenated 3-Fluoro-6-methoxyquinolines: Key Building Blocks for the Synthesis of Antibiotics

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Abstract: A practical and scalable 4-step route is presented for the synthesis of 4-bromo-3-fluoro-6-methoxyoquinoline and 3-fluoro-4-iodo-6-methoxyoquinoline from readily available 2,4-dichloro-3-fluoroquinoline with an overall yield of 81–85%. Halogenated quinoline building blocks have found much use in antimicrobial drug discovery, and the method reported here would be useful for the synthesis of these compounds.

Key words: antibiotic, quinolone, fluorine, heterocycle, regioselectivity

Fluoroquinolines and fluoroquinolones are important heterocyclic motifs of antibacterial compounds[1,2] with improved pharmacological properties compared to their nonfluorinated counterparts.[3] In recent years, there has been a growing interest in 4-substituted 3-fluoro-6-methoxyquinolines and heterocyclic analogues thereof for the synthesis of novel topoisomerase inhibitors, such as **1** (viquidacin/NXL-101)[4] and the antibiotic **2**[5] (Figure 1).

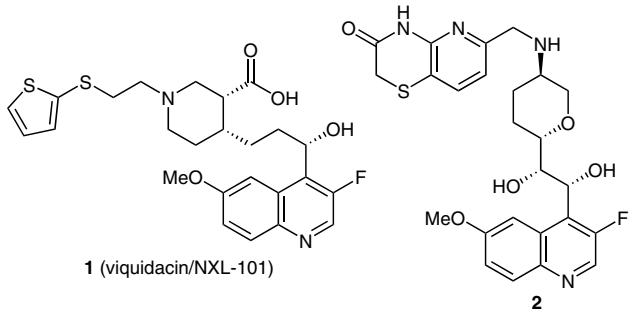
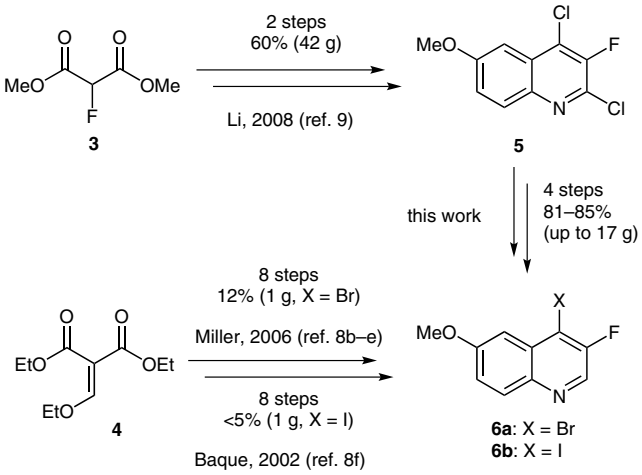


Figure 1 Viquidacin (**1**) and a recent investigational MRSA antibiotic **2**

These compounds have displayed potent antibiotic effects against Gram-positive bacteria, including methicillin-resistant strains of *Staphylococcus aureus* (MRSA), in preclinical and clinical studies. Viquidacin entered phase I clinical trials, but was later withdrawn upon the observation of QT interval prolongation in healthy subjects.[6] Several research teams in academia and industry have investigated viquidacin-related compounds to increase the safety margin against relevant antitargets.[7] However, a particularly important substructure of these next generation topoisomerase inhibitors remains a 4-substituted 3-fluoro-6-methoxyquinoline. To facilitate carbon–carbon bond formation at the 4-position of a 3-fluoro-6-methoxyquinoline, the corresponding 4-halogenated derivatives have been investigated.[8] To the best of our knowledge, the only available routes to these building blocks are an 8-step synthesis of 4-bromo-3-fluoro-6-methoxyquinoline (**6a**), which proceeds with an overall yield of 12%[8b–e] and an 8-step synthesis 3-fluoro-4-iodo-6-methoxyquinoline (**6b**) with an overall yield below 5%.[8f] For both of these routes, only 1 g of final product was reported. However, a scalable route to 2,4-dichloro-3-fluoro-6-methoxyquinoline (**5**) was reported by Li and co-workers (Scheme 1),[9] and we envisioned that this compound would be a suitable starting material for the synthesis of 4-halogenated derivatives **6a** and **6b**. To facilitate downstream functionalization, we proposed that iodine could be introduced through regioselective hydrodechlorination at the 2-position of quinoline **5**,[10,11] followed by substitution of chlorine with iodine at the 4-position.



Scheme 1 Synthetic routes to 3-fluoro-4-halo-6-methoxyquinolines **6a** and **6b**

Attempts were made to optimize reaction conditions with respect to hydrogen source, catalyst, solvent, and tem-

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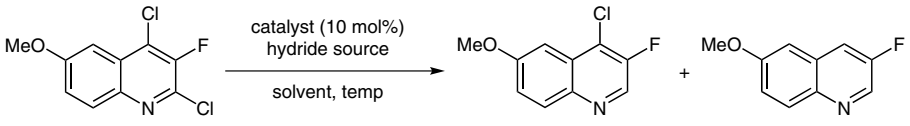
perature (Table 1). Hydrodechlorination with 1 equivalent of the hydride source (ammonium formate, Table 1, entry 1) revealed incomplete regioselectivity, providing a 3:1 mixture of mono- and bis-hydrodechlorinated products **7** and **8**, along with unconverted starting material **5**. When $Pd(PPh_3)_4$ was used as a catalyst, no hydrodechlorination was observed, neither in methanol nor in THF (entries 2–4) and further experiments with Pd/C in THF were also unsuccessful (entries 5 and 6). Changing the solvent to a water–1,4-dioxane mixture did not improve the regioselectivity (entries 7 and 8), and neither did the use of formic acid as hydride source (entry 9).

Addition of base was then attempted, and DIPEA was found to give mixtures of products (entries 10 and 11), whereas formation of the undesired bis-hydrodechlorinated product **8** could be minimized when Et_3N was employed, even at elevated temperatures (entry 12–16). Since **7** and **8** were difficult to separate via column chromatography, formation of the latter had to be completely suppressed. After careful optimization of temperature and reagent stoichiometries, the best result was obtained with HCO_2H (4 equiv) and Et_3N (18 equiv) in 1,4-dioxane–water at 70 °C, which provided an 80:2 mixture of **7** and **8**, leaving 18% of the starting material unconverted (entry 16). Using these conditions, the desired product **7** was obtained in an isolated yield of 71% on a 0.5 gram scale. However, to our disappointment, this yield was not reproducible with gram-scale reactions and we therefore set out to investigate a more practical strategy to regiodifferentiate the 2- and 4-positions of **5**.

Regioselective transformations of 2,4-dichloroquinolines are known in the literature. For example, nucleophiles react preferentially at the 4-position, under basic conditions,[12] whereas chlorine at the 2-position may be exchanged preferentially under acidic conditions.[13] Preliminary studies on **5** using basic reaction conditions revealed formation of side-products through competitive substitution of fluorine at the 3-position, and it was therefore decided to pursue acidic reaction conditions to selectively direct reactions to the 2-position. Rewardingly, the use of refluxing acetic acid gave a clean conversion of **5** into **9**, perfectly differentiating the 2- and 4-positions, and

Table 1 Regioselective Hydrodechlorination of 2,4-Dichloro-3-fluoro-6-methoxyquinoline **5**



5 **7** **8**

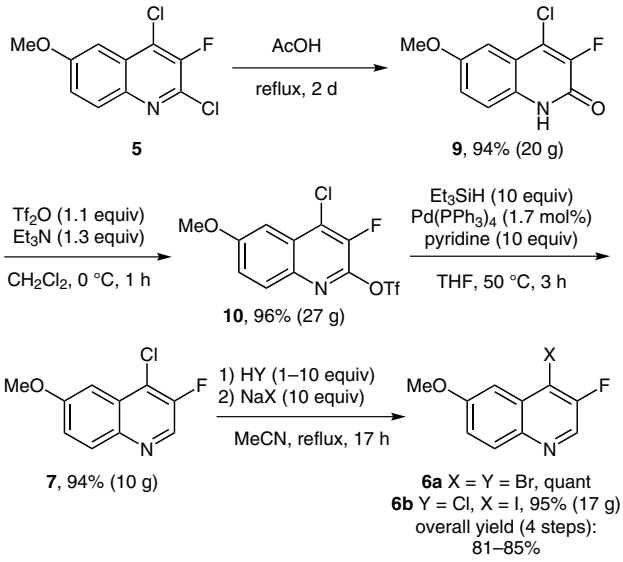
Entry	Catalyst	Hydride source	Base	Solvent	Temp (°C)	Ratio of **5**/**7**/**8**[a,b]
1	Pd/C	$HCOONH_4$ (1 equiv)	–	MeOH	25	80:15:5
2	$Pd(PPh_3)_4$	HCO_2NH_4 (1 equiv)	–	MeOH	25	100:0:0
3	$Pd(PPh_3)_4$	HCO_2NH_4 (1 equiv)	–	THF	25	100:0:0
4	$Pd(PPh_3)_4$	HCO_2NH_4 (1 equiv)	–	THF	65	100:0:0
5	Pd/C	HCO_2NH_4 (1 equiv)	–	THF	25	100:0:0
6	Pd/C	HCO_2NH_4 (1 equiv)	–	THF	65	100:0:0
7	Pd/C	HCO_2NH_4 (1 equiv)	–	1,4-dioxane–H_2O (4:1)	25	85:13:2
8	Pd/C	HCO_2NH_4 (2 equiv)	–	1,4-dioxane–H_2O (4:1)	10	49:25:26[c]
9	Pd/C	HCO_2H (1 equiv)	–	1,4-dioxane–H_2O (4:1)	25	53:29:18[c]
10	Pd/C	HCO_2H (1 equiv)	DIPEA (5 equiv)	1,4-dioxane–H_2O (4:1)	25	100:0:0
11	Pd/C	HCO_2H (1 equiv)	DIPEA (5 equiv)	1,4-dioxane–H_2O (4:1)	80	65:21:14
12	Pd/C	HCO_2H (1 equiv)	Et_3N (6 equiv)	1,4-dioxane–H_2O (9:3)	25	100:0:0
13	Pd/C	HCO_2H (1 equiv)	Et_3N (18 equiv)	1,4-dioxane–H_2O (2:1)	60	100:0:0
14	Pd/C	HCO_2H (1 equiv)	Et_3N (18 equiv)	1,4-dioxane–H_2O (2:1)	70	50:50:0
15	Pd/C	HCO_2H (2 equiv)	Et_3N (18 equiv)	1,4-dioxane–H_2O (2:1)	80	5:77:18
16	Pd/C	HCO_2H (4 equiv)	Et_3N (18 equiv)	1,4-dioxane–H_2O (2:1)	70	18:80:2[d]

[a] As determined by UPLC-MS after 30 min (PDA detector).
[b] Reactions were run on a 15–40 mg scale unless otherwise noted.
[c] Hydrodechlorination at the 4-position observed.
[d] Isolated yield of **7**: 71% (0.5 g).

allowed for easy and simple purification by filtration to isolate the product in near-quantitative yield (Scheme 2). The quinolone oxygen in **9** was then triflated to establish an even more reactive moiety at the 2-position for the reductive removal. Initial attempts to carry out a chemoselective hydrodetriflation of **10** with $Pd(PPh_3)_4$ and formic acid resulted in significant amounts of the quinolone **9**, thus the hydride source was changed to Et_3SiH. This eliminated the quinolone formation, but instead a mixture of **7** and **8** was obtained (Table 2, entries 1 and 2). Interestingly, the use of only 1 equivalent Et_3SiH gave a 1:1:1 mixture of **10**, **7**, and **8**, with complete consumption of the hydride source. We hypothesized that undesired activation of the 4-position could be caused by reaction of the quinoline nitrogen (N1) in **7** with the Et_3SiOTf generated in the event of hydrodetriflation.

To suppress any undesired activation, an excess of pyridine was added, which satisfyingly favored the formation of **7** (entry 3). Following optimization of temperature and stoichiometries, conditions for chemoselective removal of the triflate group were finally provided (entry 7), noting that a reaction time exceeding 30 minutes lead to amounts of **8** detectable by HPLC analysis. By changing the solvent from DMF to THF it was possible to slow down the reaction rate significantly, still maintaining the high chemoselectivity (entry 8). Additionally, the use of THF as solvent allowed for a lower catalyst loading (1.7 mol%) and these conditions were applied for the gram-scale synthesis of **7** in near-quantitative yields (entry 9).

To introduce a versatile handle with high reactivity in a variety of chemical transformations, the chlorine of **7** was



Scheme 2 Synthesis of 3-fluoro-4-halo-6-methoxyquinolines

replaced with either bromine or iodine to obtain the desired key building blocks **6a** and **6b**. The halogen exchange was efficiently mediated by the corresponding sodium salts upon activation of the 4-position through protonation of the quinoline nitrogen (N1).[14] This procedure works quantitatively and the iodide **6b** was prepared on a gram scale, relying on simple filtration to purify the final crystalline product.

In summary, a practical, scalable and high-yielding 4-step route (81–85% overall yield) to 3-fluoro-4-halo-6-meth-

Table 2 Optimization of Reductive Hydrodetriflation of **10**

10 **7** **8**

Entry	$Pd(PPh_3)_4$ (mol%)	Et_3SiH (equiv)	Pyridine (equiv)	Solvent	Temp (°C)	Time[a]	Ratio of **10**:**7**:**8**[b]
1	1.7	10	–	DMF	60	10 min	0:25:75
2	1.7	1	–	DMF	50	30 min	33:33:33
3	1.7	2	10	DMF	60	10 min	0:78:22
4	1.7	1.5	10	DMF	50	30 min	0:89:11
5	1.7	1.5	10	DMF	40	1.5 h	45:50:5
6	1.7	10	10	DMF	50	1.5 h	0:85:15
7	5	10	10	DMF	50	30 min	0:100:0
8	5	10	10	THF	50	3 h	0:100:0
9	1.7	10	10	THF	50	3 h	0:100:0[c]

[a] After full conversion or no further reaction of **10**.
[b] As determined by UPLC-MS (PDA-detector).
[c] Isolated yield of **7**: 94% (10 g).

oxyquinolines from readily available 2,4-dichloro-3-fluoroquinoline has been developed. 3-Fluoro-4-halo-6-methoxyquinolines are convenient building blocks for the synthesis of the viquidacin family of antibiotics and we believe that this report will facilitate the synthesis of many more analogues for biological studies in the future.

Commercially available reagents were used without further purification. All solvents were of HPLC quality. Flash column chromatography was performed using pore size 60Å, 35–70 μ silica gel. For the recording of ^{1}H NMR and ^{13}C NMR spectra, a Bruker 400 MHz Ascend with a Prodigy cryoprobe (100 MHz for ^{13}C) was used. IR analysis was performed on a Bruker Alpha FT-IR spectrometer. Analytical RP-UPLC-MS (ESI) analysis was performed on a Waters AQUITY RP-UPLC system equipped with a diode array detector using an AQUITY UPLC BEH C18 column (*d* 1.7 μm, 2.1 × 50 mm; column temp: 65 °C; flow: 0.6 mL/min). The LC system was coupled to a SQD mass spectrometer. Analytical LC-HRMS (ESI) analysis was performed on an Agilent 1100 RP-LC system equipped with a diode array detector using a Phenomenex Luna C18 column (*d* 3 μm, 2.1 × 50 mm; column temp: 40 °C; flow: 0.4 mL/min.). The LC system was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a Lock Mass probe operating in positive electrospray mode. Melting points were measured using a Thomas Hoover capillary melting point apparatus.

4-Chloro-3-fluoro-6-methoxyquinolin-2(1*H*)-one (9)

2,4-Dichloro-3-fluoro-6-methoxyquinoline (**5**; 22.7 g, 92.3 mmol) was suspended in AcOH (300 mL) and stirred at reflux for 48 h. Then, H_2O (200 mL) was added and the reaction mixture was allowed to cool to r.t. The title compound was isolated as a white solid by filtration; yield: 19.7 g (94%); mp 258–260 °C.

IR (ATR, neat): 2813, 1649, 1609, 1497, 1210, 1031, 830 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.48 (s, 1 H), 7.36 (d, *J* = 8.9 Hz, 1 H), 7.27 (dd, *J* = 8.9, 2.6 Hz, 1 H), 7.23 (d, *J* = 2.6 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.2, 153.6 (d, $J_{C,F}$ = 26.0 Hz), 148.3 (d, $J_{C,F}$ = 251.0 Hz), 129.1 (d, $J_{C,F}$ = 2.4 Hz), 124.9 (d, $J_{C,F}$ = 15.6 Hz), 119.9 (d, $J_{C,F}$ = 3.0 Hz), 117.5, 117.2, 105.6 (d, $J_{C,F}$ = 6.3 Hz), 55.60.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8ClFNO_2$: 228.0222; found: 228.0232.

4-Chloro-3-fluoro-6-methoxyquinolin-2-yl Trifluoromethanesulfonate (10)

4-Chloro-3-fluoro-6-methoxyquinolin-2(1*H*)-one (**9**; 17.9 g, 78.6 mmol) and Et_3N (10.3 g, 14.2 mL, 102 mmol) were suspended in CH_2Cl_2 (225 mL) and cooled to 0 °C under an argon atmosphere. Tf_2O (26.8 g, 16.0 mL, 94.9 mmol) was added dropwise over 30–45 min. After the addition, the reaction mixture was stirred at 0 °C for 1 hour whereupon H_2O (100 mL) was added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The remaining crude was purified by flash column chromatography [gradient from 1:4 to 1:1 EtOAc–heptane, R_f = 0.31 (1:4 EtOAc–heptane)] to give the title compound as an off-white solid; yield: 27.2 g (96%); mp 64–66 °C.

IR (ATR, neat): 3092, 2979, 2948, 1620, 1504, 1207, 1021, 808 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 9.2 Hz, 1 H), 7.43 (ddd, *J* = 9.2, 2.7, 0.5 Hz, 1 H), 7.36 (d, *J* = 2.7 Hz, 1 H), 4.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 145.2, 142.5, 140.7 (d, $J_{C–F}$ = 17.2 Hz), 137.1 (d, $J_{C–F}$ = 4.4 Hz), 131.1 (d, $J_{C–F}$ = 1.6 Hz), 129.0 (d, $J_{C–F}$ = 1.4 Hz), 128.1 (d, $J_{C–F}$ = 14.1 Hz), 124.0 (d, $J_{C–F}$ = 2.9 Hz), 118.7 (q, $J_{C–F}$ = 320.8 Hz), 101.9 (d, $J_{C–F}$ = 5.3 Hz), 56.1.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{11}H_7ClF_4NO_4S$: 359.9715; found: 359.9716.

4-Chloro-3-fluoro-6-methoxyquinoline (7)

4-Chloro-3-fluoro-6-methoxyquinolin-2-yl triflate (**10**; 18.7 g, 52.0 mmol), $Pd(PPh_3)_4$ (0.991 g, 0.86 mmol), and THF (260 mL) was heated to 50 °C, whereupon pyridine (41.1g, 41.9 mL, 520 mmol) and Et_3SiH (60.3 g, 82.8 mL, 520 mmol) were added. After 3.5 h, the solvent was removed in vacuo and the remaining liquid was diluted with EtOAc to a volume of 100 mL and washed with sat. aq $NaHCO_3$ (150 mL) followed by sat. aq NH_4Cl (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The remaining crude was purified by flash column chromatography (EtOAc–heptane, gradient from 1:9 to 1:4, R_f = 0.29 in 1:4 EtOAc–heptane) to give the title compound as a white solid; yield: 10.3 g (94%); mp 94–96 °C.

IR (ATR, neat): 3016, 2951, 2831, 1620, 1494, 1215, 1017, 824 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 0.7 Hz, 1 H), 8.04 (d, *J* = 10.0 Hz, 1 H), 7.44–7.34 (m, 2 H), 3.99 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 152.9 (d, $J_{C,F}$ = 257.2 Hz), 141.9 (d, $J_{C,F}$ = 2.9 Hz), 138.0 (d, $J_{C,F}$ = 26.6 Hz), 131.6 (d, $J_{C,F}$ = 0.7 Hz), 128.4, 124.2 (d, $J_{C,F}$ = 15.0 Hz), 122.2 (d, $J_{C,F}$ = 3.0 Hz), 101.4 (d, $J_{C,F}$ = 5.5 Hz), 55.9.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{10}H_8ClFNO$: 212.0273; found: 212.0272.

4-Bromo-3-fluoro-6-methoxyquinoline (6a)

[CAS Reg. No.: 872714-63-1]

4-Chloro-3-fluoro-6-methoxyquinoline (**7**; 0.10 g, 0.473 mmol) was dissolved in MeCN (2.36 mL) followed by the addition of 33% HBr in AcOH (0.828 mL, 4.73 mmol) and NaBr (0.486 g, 4.73 mmol). After stirring at reflux for 24 h, the reaction mixture was concentrated in vacuo and the residue was taken up in a mixture of CH_2Cl_2 (50 mL) and H_2O (25 mL). The mixture was then basified to pH >10 with aq 2 M NaOH and the layers were separated. The organic layer was washed with aq 0.002 M NaOH (25 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated in vacuo to give the title compound as a white solid; yield: 121 mg (quant); mp 127–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 8.00 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.37–7.33 (m, 2 H), 3.99 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 154.3 (d, $J_{C–F}$ = 255.8 Hz), 141.9, 137.8 (d, $J_{C–F}$ = 28.2 Hz), 131.6, 129.7, 122.2 (d, $J_{C–F}$ = 3.1 Hz), 115.6 (d, $J_{C–F}$ = 18.2 Hz), 104.1 (d, $J_{C–F}$ = 5.4 Hz), 55.90.

3-Fluoro-4-iodo-6-methoxyquinoline (6b)

4-Chloro-3-fluoro-6-methoxyquinoline (**7**; 12.7 g, 60.0 mmol) was dissolved in CH_2Cl_2 (100 mL) followed by the addition of 2 M HCl in Et_2O (33 mL). The mixture was concentrated in vacuo to give the 4-chloro-3-fluoro-6-methoxyquinoline hydrochloride salt as a yellow solid. The salt was suspended in MeCN (300 mL) together with NaI (89.9 g, 600 mmol).[15] After stirring at reflux for 17 h, the reaction was quenched by the addition of an aqueous solution containing 5% $Na_2S_2O_3$ and 10% K_2CO_3 (220 mL). The organic solvent was evaporated in vacuo and the title product was isolated as a white solid by filtration; yield: 17.3 g (95%); mp 171–172 °C.

IR (ATR, neat): 3012, 2959, 2826, 1616, 1495, 1222, 1016, 821 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 7.98 (d, $J_{C–F}$ = 9.1 Hz, 1 H), 7.33 (dd, $J_{C–F}$ = 9.1, 2.5 Hz, 1 H), 7.27 (d, $J_{C–F}$ = 2.5 Hz, 1 H), 4.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 157.7 (d, *J* = 253.8 Hz), 141.4, 137.1 (d, *J* = 30.3 Hz), 132.4, 131.6, 122.0 (d, *J* = 3.1 Hz), 109.2 (d, *J* = 5.1 Hz), 94.0 (d, *J* = 22.4 Hz), 55.9.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{10}H_8FINO$: 303.9629; found: 303.9631.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

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