Intramolecular Cyclization of β,β -Difluorostyrenes Bearing an Iminomethyl or a Diazenyl Group at the *Ortho* Position: Synthesis of 3-Fluorinated Isoquinoline and Cinnoline Derivatives

Junji Ichikawa,^{*a} Yukinori Wada,^b Hiroyuki Kuroki,^c Jun Mihara^b and Ryo Nadano^b

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o-Formyl-substituted β,β -difluorostyrenes readily react with $\text{NH}_2\text{OH}\cdot\text{HCl}$ or NH_4OAc to afford 3-fluoroisoquinoline derivatives in good yield via (i) the formation of the corresponding oximes or imines and (ii) subsequent intramolecular replacement of a vinylic fluorine by the sp^2 nitrogen of the iminomethyl group ($\text{HON}=\text{CH}-$ or $\text{HN}=\text{CH}-$). β,β -Difluorostyrenes bearing an *o*-diazenyl group ($\text{HN}=\text{N}-$), generated by reduction of the corresponding diazonium ions, undergo a similar substitution to afford 3-fluorinated cinnolines.

Introduction

Isoquinolines and related derivatives including cinnolines are found in many bioactive natural products. They constitute key structural components in pharmaceuticals, agrochemicals, as well as materials such as dyestuffs and liquid crystals.^{1,2} As a consequence, their synthesis has been a topic of much research over the past years.^{3,4}

The introduction of fluorine into the original molecules has come into wide use as one of the most efficient methods for modification of their biological activities as well as their physical and chemical properties. Thus, fluorine-containing isoquinoline derivatives have attracted considerable attention.⁵ Despite the great utility and immense potential of ring-fluorinated isoquinoline frameworks, both as components and intermediates,⁶ there still remain problems in their synthesis.⁷⁻⁹

In our recent publications, we have reported the construction of isoquinoline frameworks via the intramolecular substitution of tosylamidate anions, nitrogen nucleophiles bearing an N–C single bond (sp^3 -type nucleophiles), for vinylic fluorines in *ortho*-functionalized β,β -difluorostyrenes **1** (Scheme 1).^{8a} This ring formation is promoted by the unique reactivity of 1,1-difluoro-1-alkenes toward nucleophilic substitution of their vinylic fluorines via addition–elimination processes,^{5c} followed by aromatization via elimination of a sulfinic acid to provide the heteroaromatic system **2**.

Scheme 1 Construction of isoquinoline nuclei via substitution and elimination

On the other hand, nitrogen nucleophiles with an $\text{N}=\text{Y}$

double bond (sp^2 nucleophiles) would give rise to the direct construction of heteroaromatic rings.^{8b} Thus, we investigated a replacement of the vinylic fluorines by nitrogen nucleophiles such as oxime, imine, and diimide nitrogens to synthesize isoquinoline derivatives. Herein, we wish to report a facile synthesis of 3-fluorinated isoquinolines and their *N*-oxides⁸ or cinnolines⁹ starting from *o*-formyl- or *o*-amino-substituted β,β -difluorostyrenes, respectively.

Results and discussion

Synthesis of 3-fluoroisoquinoline *N*-oxides and 3-fluoroisoquinolines

For the purpose of preparing the starting β,β -difluorostyrenes **4** with an oxime moiety at the *ortho* position, β,β -difluoro-*o*-formylstyrenes **3** were treated with hydroxylamine hydrochloride ($\text{NH}_2\text{OH}\cdot\text{HCl}$) in the presence of Et_3N . Unexpectedly, the reaction directly produced 3-fluoroisoquinoline *N*-oxide **5a** in 67% yield, instead of the expected oxime **4a** (Scheme 2). This result suggests that β,β -difluoro-*o*-formylstyrene **3a** was initially converted into oxime **4a**, which in turn readily underwent the intramolecular vinylic substitution, followed by deprotonation on the oxygen, leading to the final product, isoquinoline *N*-oxide **5a**.[‡]

Scheme 2 Construction of isoquinoline nuclei via substitution from **4**

Although this cyclization successfully proceeded, there was

a drawback in the thermal instability of the starting material, β,β -difluoro-*o*-formylstyrenes **3**. The coupling reaction of an in-situ generated 2,2-difluorovinylborane with *o*-iodobenzaldehyde¹⁰ afforded **3a** in 84% yield, as determined by ¹⁹F NMR, while the isolated yield was reduced to 62% after silica gel column chromatography. Then, we tried to combine the coupling reaction and the cyclization without purification of unstable **3**, which process could improve the synthesis of **5**. After the generation of difluorovinylboranes from 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (CF₃CH₂OTs) and their coupling reaction with *o*-iodobenzaldehyde, the crude products were treated with NH₂OH·HCl, leading to the isoquinoline *N*-oxides **5a** and **5b** (R = *n*-Bu and *sec*-Bu) in 71% and 69% yields from the starting *o*-iodobenzaldehyde (Scheme 3).

As further examples of this type of cyclization, we examined a similar in-situ preparation of imine nitrogen nucleophiles (HN=CH-). When the crude formylstyrenes **3** were treated with NH₄OAc as an ammonia source, dehydration and subsequent cyclization were smoothly induced to give isoquinolines **6a** and **6b** (R = *n*-Bu and *sec*-Bu) in 70% and 71% yields based on *o*-iodobenzaldehyde, respectively (Scheme 3).‡

Scheme 3 Synthesis of 3-fluoroisoquinoline *N*-oxides **5** and 3-fluoroisoquinolines **6**

Reactions of 3-fluoroisoquinoline *N*-oxides

The remaining fluorines in isoquinoline *N*-oxides **5** were expected to be quite reactive toward replacement by nucleophiles via similar addition–elimination processes, which allows the introduction of another substituent into the isoquinoline nuclei. Initially, we attempted the reaction of **5a** with oxygen and sulfur nucleophiles. On treatment of **5a** with KO^{*t*}-Bu or LiSPh as a nucleophile in THF, the expected substitution of the fluorine proceeded to give the corresponding isoquinoline *N*-oxide **7a** or **7b** bearing an oxygen or a sulfur functional group at the 3-position (Scheme 4; Table 1, entries 1 and 2). A nitrogen nucleophile,

pyrrolidine, also brought about a similar substitution under less basic conditions to yield **7c** (Table 1, entry 3). Thus, the reaction of **5a** with nucleophiles occurred regioselectively at the 3-position via *ipso*-attack, whereas it is known that isoquinolines are highly reactive toward nucleophiles at their 1-position.^{8e}

Scheme 4 Introduction of substituent at the 3-position of **5a** via substitution

Table 1 Introduction of Substituent at the 3-Position of **5a**

Entry	NuM (eq)	Solvent	Conditions	Yield/% (7)
1	<i>t</i> -BuOK (1.5)	THF	−78 °C, 0.5 h	72 (7a)
2	PhSLi (1.5)	THF	−78 °C to 0 °C, 5 h	85 (7b)
3	pyrrolidine (4.1)	Toluene	reflux, 23 h	74 (7c)

In addition, the cycloaddition of **5a** was attempted by employing phenylisocyanate (PhNCO) as a dipolarophile, because isoquinoline *N*-oxides are well known to act as 1,3-dipoles. On treatment of **5a** with PhNCO in DMF, the expected reaction proceeded with accompanying decarboxylation to give 1-anilino-3-fluoroisoquinoline **8a**. In contrast to the above-mentioned introduction of a substituent at the 3-position, the amino group was exclusively introduced at the 1-position (Scheme 5).^{¶11} Thus, these sequences of processes provide a versatile method for the synthesis of 3,4-disubstituted and 1,3,4-trisubstituted isoquinoline derivatives starting from CF₃CH₂OTs and *o*-iodobenzaldehyde.

Scheme 5 Introduction of substituent at the 1-position of **5a** via 1,3-dipolar addition

Synthesis of 3-fluorocinnolines

As shown in Scheme 3, the direct construction of isoquinoline nuclei has been successfully achieved by the intramolecular substitution of the oxime and imine sp² nitrogen (HON=CH- and HN=CH-). Using this tactics, we next investigated the intramolecular substitution of a diimide sp² nitrogen (HN=N-), where the imino carbon was replaced by a nitrogen atom. This reaction would result in the construction of the cinnoline ring structure.

o-Amino- β,β -difluorostyrenes **9**, prepared from CF₃CH₂OTs and *o*-iodoaniline,¹² were treated with isoamyl nitrite (*i*-AmONO) for diazotization, and then subsequently reduced with *n*-Bu₃SnH. The expected intramolecular substitution of the terminal diazenyl nitrogen (HN=N-) proceeded smoothly, to give 3-fluorocinnoline **10a** in 58% yield.† Then we tried several other reducing reagents, and found that benzenethiol raised the yield of **10a** and **10b** (R = *n*-Bu and *sec*-Bu) to 88% and 87%, respectively (Scheme 6). In the reaction of **9a**, diphenyl disulfide (PhSSPh) was obtained in 90% yield based on PhSH, which implies that PhSH definitely acted as a reducing agent.

Scheme 6 Synthesis of 3-fluorocinnolines **10**

Conclusion

We have accomplished the construction of isoquinoline and cinnoline frameworks via intramolecular cyclization of β,β -difluorostyrenes bearing a hydroxyiminomethyl (HON=CH-), an iminomethyl (HN=CH-) or a diazenyl (HN=N-) group at the *ortho* position. The β,β -difluorostyrenes, prepared from CF₃CH₂OTs, trialkylboranes and *o*-formyl- or *o*-amino-substituted aryl iodides, readily undergo six-membered ring closure via dehydration or diazotization under mild conditions compatible with a variety of functional groups. Thus, this sequence provides a facile method for the synthesis of selectively ring-fluorinated nitrogen heterocycles.

Experimental

¹H NMR, ¹³C NMR, and ¹⁹F NMR spectra were recorded on a JEOL JNM-A-500 or a Bruker DRX 500 spectrometer. ¹H NMR chemical shifts (δ_{H}) are given in ppm downfield from Me₄Si. ¹³C NMR chemical shifts (δ_{C}) are given in ppm downfield from Me₄Si, relative to chloroform-*d* ($\delta = 77.0$). ¹⁹F NMR chemical shifts (δ_{F}) are given in ppm downfield from C₆F₆. IR spectra were recorded on a Shimadzu IR-408 spectrometer or a JEOL JIR-WINSPEC50 spectrometer. Elemental analyses were performed with a YANAKO MT-6 CHN Corder apparatus. Mass spectra were taken with a JEOL MS-700M spectrometer. All reactions were carried out under nitrogen. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. *N,N*-Dimethylformamide (DMF) was distilled under

reduced pressure from CaH₂ and stored over molecular sieves 4Å. Acetonitrile (CH₃CN) was distilled under reduced pressure from CaH₂ and stored over molecular sieves 3Å. Hexamethylphosphoric triamide (HMPA) was distilled under reduced pressure from CaH₂ and stored over molecular sieves 4Å. Toluene was distilled and stored over sodium. Column chromatography and preparative thin-layer chromatography were performed on silica gel (Kanto Chemical Co. Inc., Silica Gel 60 and Wako Pure Chemical Industries, Ltd., B5-F), respectively.

Synthesis of 3-fluoroisoquinoline *N*-oxides and 3-fluoroisoquinolines

o-(1,1-Difluorohex-1-en-2-yl)benzaldehyde (**3a**)

Butyllithium (5.0 mL, 1.7 M in hexane, 8.4 mmol) was added to a solution of CF₃CH₂OTs (1.0 g, 4.0 mmol) in THF (20 mL) at -78 °C over 10 min. The reaction mixture was stirred for 20 min at -78 °C, and then tributylborane (4.4 mL, 1.0 M in THF, 4.4 mmol) was added at -78 °C. After being stirred for 1 h, the reaction mixture was allowed to warm up to room temperature and stirred for an additional 3 h. The solution was treated with HMPA (5.0 mL), triphenylphosphine (30 mg, 0.11 mmol), and tris(dibenzylideneacetone)dipalladium-chloroform (1/1) (29 mg, 0.028 mmol) and stirred for 15 min. To the resulting solution were added *o*-iodobenzaldehyde (738 mg, 3.2 mmol) and copper(I) iodide (757 mg, 4.0 mmol). After the mixture was stirred for 20 min at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through a Celite pad, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (Et₂O-hexane 1:20) to give **3a** (441 mg, 62%) as a pale yellow liquid. ¹H NMR (500 MHz, CDCl₃) δ_{H} 0.86 (3H, t, *J* = 7.2 Hz), 1.29–1.35 (4H, m), 2.37–2.43 (2H, m), 7.31 (1H, dd, *J* = 7.6, 0.6 Hz), 7.47 (1H, dd, *J* = 7.6, 7.6 Hz), 7.61 (1H, ddd, *J* = 7.6, 7.6, 1.5 Hz), 7.96 (1H, dd, *J* = 7.6, 1.5 Hz), 10.16 (1H, d, *J* = 1.5 Hz). ¹³C NMR (126 MHz, CDCl₃) δ_{C} 13.6, 22.2, 29.5 (d, *J*_{CF} = 3 Hz), 29.5, 89.1 (dd, *J*_{CF} = 24, 17 Hz), 128.3, 128.6, 130.6 (d, *J*_{CF} = 2 Hz), 133.9, 134.1, 137.3 (d, *J*_{CF} = 4 Hz), 152.7 (dd, *J*_{CF} = 290, 287 Hz), 191.1. ¹⁹F NMR (470 MHz, CDCl₃) δ_{F} 70.0 (1F, dt, *J*_{FF} = 43 Hz, *J*_{FH} = 3 Hz), 72.8 (1F, dd, *J*_{FF} = 43 Hz, *J*_{FH} = 2 Hz). IR (neat) 2970, 2950, 2890, 1840, 1745, 1705, 1600, 1470, 1465, 1245 cm⁻¹. MS (EI, 70 eV) *m/z* 224 (M⁺, 20%), 205 (44), 131 (100), 91 (44). HRMS *m/z* calcd for C₁₃H₁₄F₂O 224.1013 (M⁺); found 224.1000.

4-Butyl-3-fluoroisoquinoline *N*-oxide (**5a**)

Butyllithium (1.1 mL, 1.49 M in hexane, 1.7 mmol) was added to a THF (4.5 mL) solution of CF₃CH₂OTs (203 mg, 0.80 mmol) at -78 °C over 10 min. The reaction mixture was stirred for 20 min at -78 °C, and then tributylborane (0.88 mL, 1.0 M in THF, 0.88 mmol) was added at -78 °C. After being stirred for 1 h, the reaction mixture was allowed to warm up to room temperature and stirred for an additional 3 h. The solution was treated with HMPA (1.5 mL), triphenylphosphine (17 mg, 0.065 mmol) and

tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (25 mg, 0.024 mmol) and stirred for 15 min. To the resulting solution was added *o*-iodobenzaldehyde (167 mg, 0.72 mmol) and copper(I) iodide (153 mg, 0.80 mmol). After the mixture was stirred for 15 min at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through a Celite pad, and then organic materials were extracted with Et₂O three times. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue, crude aldehyde **3a**, was dissolved in DMF (3.0 mL). The resulting mixture was treated with NH₂OH·HCl (160 mg, 0.96 mmol) and Et₃N (0.22 mL, 1.8 mmol) and stirred for 12 h. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with CHCl₃ three times. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (MeOH–AcOEt 1:20) to give **5a** (112 mg, 71%) as a pale yellow liquid. ¹H NMR (500 MHz, CDCl₃) δ_H 0.98 (3H, t, *J* = 7.5 Hz), 1.47 (2H, tq, *J* = 7.5, 7.5 Hz), 1.69 (2H, tt, *J* = 7.5, 7.5 Hz), 3.06 (2H, dt, *J* = 7.5 Hz, *J*_{HF} = 2.0 Hz), 7.59 (1H, t, *J* = 7.8 Hz), 7.66 (1H, t, *J* = 7.8 Hz), 7.74 (1H, d, *J* = 7.8 Hz), 7.90 (1H, d, *J* = 7.8 Hz), 8.75 (1H, d, *J*_{HF} = 6.4 Hz). ¹³C NMR (126 MHz, CDCl₃) δ_C 13.8, 22.6, 24.3, 31.5, 119.0 (d, *J*_{CF} = 17 Hz), 123.2 (d, *J*_{CF} = 6 Hz), 125.6 (d, *J*_{CF} = 2 Hz), 126.1 (d, *J*_{CF} = 3 Hz), 128.2, 128.2, 129.5, 135.6 (d, *J*_{CF} = 7 Hz), 153.5 (d, *J*_{CF} = 252 Hz). ¹⁹F NMR (470 MHz, CDCl₃) δ_F 46.7 (d, *J*_{FH} = 6 Hz). IR (KBr disk) 1630, 1605, 1500, 1485, 1440, 1390, 1325, 1240, 1190, 1120 cm⁻¹. MS (EI, 70 eV) *m/z* 219 (*M*⁺, 100%), 160 (72), 149 (47), 101 (17). Anal. Found: C, 71.15; H, 6.43; N, 6.24. Calcd for C₁₃H₁₄FNO: C, 71.21; H, 6.44; N, 6.39%.

4-(Butan-2-yl)-3-fluoroisoquinoline *N*-oxide (**5b**)

Compound **5b** was prepared by the method described for **5a** using butyllithium (1.1 mL, 1.49 M in hexane, 1.7 mmol), CF₃CH₂OTs (203 mg, 0.80 mmol), tri(butan-2-yl)borane (0.88 mL, 1.0 M in THF, 0.88 mmol), HMPA (1.5 mL), triphenylphosphine (17 mg, 0.065 mmol), tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (25 mg, 0.024 mmol), *o*-iodobenzaldehyde (167 mg, 0.72 mmol) and copper(I) iodide (153 mg, 0.80 mmol) in THF (4.5 mL). Then, crude aldehyde **3b** was treated with NH₂OH·HCl (160 mg, 0.96 mmol) and Et₃N (0.22 mL, 1.8 mmol) in DMF (3.0 mL). Purification by thin layer chromatography on silica gel (MeOH–AcOEt 1:20) to give **5b** (109 mg, 69%) as a pale yellow liquid. ¹H NMR (500 MHz, CDCl₃) δ_H 0.90 (3H, t, *J* = 7.2 Hz), 1.48 (3H, dd, *J* = 7.2 Hz, *J*_{HF} = 1.4 Hz), 1.84–2.04 (2H, m), 3.50 (1H, tq, *J* = 7.2, 7.2 Hz), 7.58 (1H, dd, *J* = 7.8, 7.8 Hz), 7.65 (1H, dd, *J* = 7.8, 7.8 Hz), 7.74 (1H, d, *J* = 7.8 Hz), 8.05 (1H, d, *J* = 7.8 Hz), 8.77 (1H, d, *J*_{HF} = 6.4 Hz). ¹³C NMR (126 MHz, CDCl₃) δ_C 12.7, 18.9 (d, *J*_{CF} = 4 Hz), 28.2 (d, *J*_{CF} = 3 Hz), 33.6, 123.2 (d, *J*_{CF} = 15 Hz), 123.3 (d, *J*_{CF} = 4 Hz), 125.8 (d, *J*_{CF} = 2 Hz), 126.2 (d, *J*_{CF} = 3 Hz), 128.0 (d, *J*_{CF} = 3 Hz), 129.5, 129.6 (d, *J*_{CF} = 8 Hz), 135.7 (d, *J*_{CF} = 8 Hz), 153.9 (d, *J*_{CF} = 256 Hz). ¹⁹F NMR (470 MHz, CDCl₃) δ_F 50.9 (br s). IR (KBr disk) 2960, 2940, 2870, 1480, 1435, 1315, 1230, 1215, 1190, 1120, 920 cm⁻¹. MS (EI, 70 eV) *m/z* 219

(*M*⁺, 100%), 174 (50), 115 (47). HRMS *m/z* calcd for C₁₃H₁₄FNO 219.1059 (*M*⁺); found 219.1082.

4-Butyl-3-fluoroisoquinoline (**6a**)

Butyllithium (0.65 mL, 1.62 M in hexane, 1.05 mmol) was added to a THF (2.5 mL) solution of CF₃CH₂OTs (127 mg, 0.50 mmol) at –78 °C over 10 min. The reaction mixture was stirred for 20 min at –78 °C, and then tributylborane (0.55 mL, 1.0 M in THF, 0.55 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was allowed to warm up to room temperature and stirred for an additional 3 h. The solution was treated with HMPA (0.63 mL), triphenylphosphine (11 mg, 0.040 mmol), and tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (10 mg, 0.010 mmol) and stirred for 15 min. To the resulting solution were added *o*-iodobenzaldehyde (104 mg, 0.45 mmol) and copper(I) iodide (95 mg, 0.50 mmol). After the mixture had been stirred for 20 min at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through a Celite pad, and then organic materials were extracted with Et₂O three times. The combined extracts were washed with water and brine, and then dried over MgSO₄. After removal of the solvent under reduced pressure, the residue was dissolved in DMF (4.5 mL). The resulting mixture was treated with H₂O (0.45 mL) and NH₄OAc (173 mg, 2.2 mmol) and then stirred for 1 h at room temperature. The reaction mixture was diluted with H₂O, and organic materials were extracted with AcOEt three times. The combined extracts were washed with water and brine, and then dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:10, and then benzene–hexane 2:1) to give **6a** (64 mg, 70%). ¹H NMR (500 MHz, CDCl₃) δ_H 0.97 (3H, t, *J* = 7.5 Hz), 1.46 (2H, tq, *J* = 7.5, 7.5 Hz), 1.63–1.71 (2H, m), 3.03 (2H, dt, *J* = 7.5 Hz, *J*_{HF} = 0.9 Hz), 7.52 (1H, ddd, *J* = 8.0, 8.0 Hz, *J*_{HF} = 0.8 Hz), 7.71 (1H, dd, *J* = 8.0, 8.0 Hz), 7.97 (1H, d, *J* = 8.0 Hz), 7.99 (1H, d, *J* = 8.0 Hz), 8.80 (1H, s). ¹³C NMR (126 MHz, CDCl₃) δ_C 13.9, 22.8, 24.1, 32.1, 115.0 (d, *J*_{CF} = 30 Hz), 122.9 (d, *J*_{CF} = 7 Hz), 125.6 (d, *J*_{CF} = 2 Hz), 127.6 (d, *J*_{CF} = 2 Hz), 128.4, 130.7, 138.4 (d, *J*_{CF} = 6 Hz), 148.6 (d, *J*_{CF} = 16 Hz), 159.1 (d, *J*_{CF} = 232 Hz). ¹⁹F NMR (470 MHz, CDCl₃) δ_F 79.3 (br s). IR (neat) 2960, 2930, 2870, 1620, 1590, 1440, 1425, 1250, 1220, 750 cm⁻¹. MS (EI, 20 eV) *m/z* 203 (*M*⁺, 67%), 160 (100). Anal. Found: C, 76.54; H, 6.95; N, 6.76. Calcd for C₁₃H₁₄FN: C, 76.82; H, 6.94; N, 6.89%.

4-(Butan-2-yl)-3-fluoroisoquinoline (**6b**)

Compound **6b** was prepared by the method described for **6a** using butyllithium (0.65 mL, 1.62 M in hexane, 1.05 mmol), CF₃CH₂OTs (127 mg, 0.50 mmol), tri(butan-2-yl)butylborane (0.55 mL, 1.0 M in THF, 0.55 mmol), HMPA (0.63 mL), triphenylphosphine (11 mg, 0.040 mmol), tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (10 mg, 0.010 mmol), *o*-iodobenzaldehyde (104 mg, 0.45 mmol) and copper(I) iodide (95 mg, 0.50 mmol) in THF (2.5 mL). Then, crude aldehyde **3b** was treated with NH₄OAc (173 mg, 2.2 mmol) and H₂O (0.22 mL, 1.8 mmol) in DMF (4.5 mL).

Purification by thin layer chromatography on silica gel (AcOEt–hexane 1:10, and then benzene–AcOEt–hexane 1:10:10) to give **6b** (65 mg, 71%). ¹H NMR (500 MHz, CDCl₃) δ_H 0.86 (3H, t, *J* = 7.3 Hz), 1.46 (3H, dd, *J* = 7.3 Hz, *J*_{HF} = 1.5 Hz), 1.82–2.14 (2H, m), 3.49 (1H, tq, *J* = 7.3, 7.3 Hz), 7.52 (1H, dd, *J* = 7.9, 7.9 Hz), 7.70 (1H, dd, *J* = 7.9, 7.9 Hz), 7.98 (1H, d, *J* = 7.9 Hz), 8.14 (1H, d, *J* = 7.9 Hz), 8.81 (1H, s). ¹³C NMR (126 MHz, CDCl₃) δ_C 12.8, 19.3 (d, *J*_{CF} = 3 Hz), 28.5 (d, *J*_{CF} = 3 Hz), 33.0 (d, *J*_{CF} = 4 Hz), 119.1 (d, *J*_{CF} = 26 Hz), 123.1 (d, *J*_{CF} = 6 Hz), 125.5 (d, *J*_{CF} = 2 Hz), 127.6 (d, *J*_{CF} = 2 Hz), 128.5, 130.6, 138.5 (d, *J*_{CF} = 7 Hz), 148.8 (d, *J*_{CF} = 17 Hz), 159.3 (d, *J*_{CF} = 235 Hz). ¹⁹F NMR (470 MHz, CDCl₃) δ_F 86.1 (br s). IR (neat) 2964, 2873, 1623, 1585, 1567, 1500, 1442, 1423, 1380, 1268, 1247, 1153, 933, 752 cm^{−1}. MS (EI, 70 eV) *m/z* 203 (M⁺, 37%), 174 (100), 154 (17), 149 (14). Anal. Found: C, 76.58; H, 7.00; N, 6.80. Calcd for C₁₃H₁₄FN: C, 76.82; H, 6.94; N, 6.89%.

Reactions of 3-fluoroisoquinoline N-oxides

3-*tert*-Butoxy-4-butylisoquinoline N-oxide (**7a**)

To a solution of potassium *tert*-butoxide (63 mg, 0.56 mmol) in THF (2.5 mL) was added a solution of **5a** (82 mg, 0.37 mmol) in THF (2.0 mL) at −78 °C. After the mixture was stirred for 30 min at −78 °C, the reaction was quenched with H₂O–THF. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (MeOH–AcOEt 1:20) to give **7a** (74 mg, 72%) as colorless crystals. ¹H NMR (500 MHz, CDCl₃) δ_H 0.99 (3H, t, *J* = 7.5 Hz), 1.49 (2H, tq, *J* = 7.5, 7.5 Hz), 1.62 (9H, s), 1.61–1.68 (2H, m), 3.07 (2H, t, *J* = 7.5 Hz), 7.47 (1H, dd, *J* = 7.8, 7.8 Hz), 7.54 (1H, ddd, *J* = 7.8, 7.8, 1.2 Hz), 7.64 (1H, d, *J* = 7.8 Hz), 7.82 (1H, d, *J* = 7.8 Hz), 8.67 (1H, s). ¹³C NMR (126 MHz, CDCl₃) δ_C 13.9, 23.0, 26.6, 29.1, 31.9, 87.2, 123.5, 125.1, 126.1, 127.2, 127.4, 128.2, 129.6, 135.0, 152.1. IR (KBr disk) 2960, 2920, 1590, 1465, 1360, 1320, 1230, 1180, 1150, 750 cm^{−1}. MS (EI, 20 eV) *m/z* 273 (M⁺, 2%), 217 (100), 201 (15), 158 (12). HRMS *m/z* calcd for C₁₇H₂₃NO₂ 273.1729 (M⁺); found 273.1752.

4-Butyl-3-phenylthioisoquinoline N-oxide (**7b**)

To a solution of thiophenol (54 mL, 0.53 mmol) in THF (1.0 mL) was added butyllithium (0.35 mL, 1.51 M in hexane, 0.53 mmol) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, and then a solution of **5a** (96 mg, 0.44 mmol) in THF (2.0 mL) was added at −78 °C. After being stirred for 3 h, the mixture was allowed to warm up to 0 °C and stirred for an additional 2 h. The reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with MeOH–AcOEt (1:20) three times. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (MeOH–AcOEt 1:20) to give **7b** (115 mg, 85%) as colorless crystals. ¹H NMR (500 MHz, CDCl₃) δ_H 0.97 (3H, t, *J* = 7.6 Hz), 1.51 (2H, tq, *J* = 7.6, 7.6 Hz), 1.63 (2H, tt, *J* = 7.6, 7.6 Hz), 3.43 (2H, t, *J* = 7.6 Hz), 7.14–7.19 (1H, m), 7.21–7.24 (4H, m), 7.58–7.63

(2H, m), 7.67–7.70 (1H, m), 7.93–7.96 (1H, m), 8.81 (1H, s). ¹³C NMR (126 MHz, CDCl₃) δ_C 13.8, 23.0, 31.4, 32.8, 124.5, 125.3, 126.5, 127.8, 127.9, 128.8, 129.1, 129.4, 129.6, 134.5, 135.0, 141.8, 144.1. IR (KBr disk) 3050, 2950, 2920, 1580, 1565, 1480, 1320, 1185, 1135, 740 cm^{−1}. MS (EI, 70 eV) *m/z* 309 (M⁺, 9%), 292 (100), 250 (75), 174 (75), 115 (22), 77 (12). HRMS *m/z* calcd for C₁₉H₁₉NOS 309.1187 (M⁺); found 309.1216.

4-Butyl-3-(pyrrolidin-1-yl)isoquinoline N-oxide (**7c**)

To a solution of **5a** (77 mg, 0.35 mmol) in toluene (2.0 mL) was added pyrrolidine (0.12 mL, 1.4 mmol) at room temperature. After the reaction mixture was heated at reflux for 23 h, volatile components were removed by evaporation under reduced pressure. The residue was purified by thin layer chromatography on silica gel (MeOH–AcOEt 1:20) to give **7c** (69 mg, 74%) as a pale brown solid. ¹H NMR (500 MHz, CDCl₃) δ_H 1.00 (3H, t, *J* = 7.4 Hz), 1.50 (2H, tq, *J* = 7.4, 7.4 Hz), 1.59–1.67 (2H, m), 2.06–2.10 (4H, m), 3.11–3.15 (2H, m), 3.35 (4H, br s), 7.48–7.53 (2H, m), 7.64 (1H, dd, *J* = 7.3, 1.2 Hz), 7.86 (1H, d, *J* = 8.5 Hz), 8.67 (1H, s). ¹³C NMR (126 MHz, CDCl₃) δ_C 13.9, 23.2, 26.7, 27.9, 33.0, 49.5, 124.2, 125.1, 127.7, 127.8, 128.0, 129.5, 135.3, 135.9, 148.6. IR (KBr disk) 3286, 2954, 2925, 1473, 1430, 1321, 1226, 1168, 1122, 759 cm^{−1}. MS (EI, 20 eV) *m/z* 270 (M⁺, 12%), 254 (100). HRMS *m/z* calcd for C₁₇H₂₂N₂O 270.1732 (M⁺); found 270.1764.

4-Butyl-3-fluoro-1-anilinoisoquinoline (**8a**)

To a solution of **5a** (73 mg, 0.32 mmol) in DMF (4.0 mL) was added phenyl isocyanate (0.074 mL, 0.68 mmol). After the reaction mixture was stirred at 100 °C for 21 h, phosphate buffer (pH 7) was added. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:3) to give **8a** (55 mg, 57%) as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃) δ_H 0.95 (3H, t, *J* = 7.5 Hz), 1.43 (2H, tq, *J* = 7.5, 7.5 Hz), 1.61 (2H, tt, *J* = 7.5, 7.5 Hz), 2.89 (2H, t, *J* = 7.5 Hz), 7.05 (1H, tt, *J* = 7.5, 1.1 Hz), 7.15 (1H, br s), 7.34 (2H, dd, *J* = 8.6, 7.5 Hz), 7.42 (1H, dd, *J* = 7.8, 7.8 Hz), 7.64 (1H, dd, *J* = 7.8, 7.8 Hz), 7.68 (2H, dd, *J* = 8.6, 1.1 Hz), 7.88 (1H, d, *J* = 7.8 Hz), 7.89 (1H, d, *J* = 7.8 Hz). ¹³C NMR (126 MHz, CDCl₃) δ_C 14.0, 22.6, 23.6, 32.2, 104.4 (d, *J*_{CF} = 31 Hz), 117.0 (d, *J*_{CF} = 2 Hz), 120.0, 122.0, 122.9, 123.9 (d, *J*_{CF} = 7 Hz), 124.5 (d, *J*_{CF} = 2 Hz), 129.0, 130.3, 139.7 (d, *J*_{CF} = 7 Hz), 139.7, 149.8 (d, *J*_{CF} = 20 Hz), 157.2 (d, *J*_{CF} = 20 Hz). ¹⁹F NMR (470 MHz, CDCl₃) δ_F 79.4 (br s). IR (neat) 3450, 2950, 2870, 1620, 1540, 1440, 1415, 1340, 1120, 755 cm^{−1}. MS (EI, 70 eV) *m/z* 294 (M⁺, 45%), 251 (100), 204 (7), 128 (7), 77 (19). Anal. Found: C, 77.22; H, 6.64; N, 9.31. Calcd for C₁₉H₁₉FN₂: C, 77.52; H, 6.51; N, 9.52%.

Synthesis of 3-fluorocinnolines

o-(1,1-Difluorohex-1-en-2-yl)aniline (**9a**)

Butyllithium (1.56 mL, 1.63 M in hexane, 2.5 mmol) was added to a solution of CF₃CH₂OTs (308 mg, 1.21 mmol) in

THF (10 mL) at $-78\text{ }^{\circ}\text{C}$ over 10 min. The reaction mixture was stirred for 20 min at $-78\text{ }^{\circ}\text{C}$, and then tributylborane (1.33 mL, 1.0 M in THF, 1.33 mmol) was added at $-78\text{ }^{\circ}\text{C}$. After being stirred for 1 h, the reaction mixture was allowed to warm up to room temperature and stirred for an additional 3 h. The solution was treated with HMPA (3.0 mL), triphenylphosphine (25 mg, 0.10 mmol) and tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (25 mg, 0.024 mmol) and stirred for 15 min. To the solution was added the magnesium salt [generated from *o*-iodoaniline (238 mg, 1.09 mmol) and dibutylmagnesium (2.47 mL, 0.44 M in Et_2O , 1.09 mmol) in THF (3.0 mL) at $0\text{ }^{\circ}\text{C}$] and copper(I) iodide (230 mg, 1.21 mmol). After the mixture had been stirred for 1 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through a Celite pad, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (AcOEt–hexane 1:10) to give **9a** (176 mg, 77%) as a yellow liquid. ^1H NMR (500 MHz, CDCl_3) δ_{H} 0.87 (3H, t, $J = 7.1$ Hz), 1.30–1.35 (4H, m), 2.29 (2H, tdd, $J = 7.0$ Hz, $J_{\text{HF}} = 2.3$, 2.3 Hz), 3.66 (2H, br s), 6.70–6.77 (2H, m), 7.00 (1H, dd, $J = 7.6$, 1.5 Hz), 7.12 (1H, ddd, $J = 7.6$, 7.6, 1.5 Hz). ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 13.8, 22.4, 27.7, 29.8 (dd, $J_{\text{CF}} = 3$, 3 Hz), 89.1 (dd, $J_{\text{CF}} = 22$, 17 Hz), 115.6, 118.4, 119.0 (d, $J_{\text{CF}} = 3$ Hz), 128.9, 130.6, (d, $J_{\text{CF}} = 2$ Hz), 144.3, 152.8 (dd, $J_{\text{CF}} = 290$, 288 Hz). ^{19}F NMR (470 MHz, CDCl_3) δ_{F} 68.7 (1F, d, $J_{\text{FF}} = 43$ Hz), 72.7 (1F, d, $J_{\text{FF}} = 43$ Hz). IR (neat) 3475, 3375, 2960, 2930, 2860, 1740, 1620, 1495, 1230 cm^{-1} . MS (EI, 70 eV) m/z 211 (M^+ , 100%), 168 (59), 148 (43). Anal. Found: C, 68.14; H, 7.07; N, 6.52. Calcd for $\text{C}_{12}\text{H}_{15}\text{F}_2\text{N}$: C, 68.23; H, 7.16; N, 6.63%.

***o*-(1,1-Difluoro-3-methylpent-1-en-2-yl)aniline (9b)**

Compound **9b** was prepared by the method described for **9a** using butyllithium (1.56 mL, 1.63 M in hexane, 2.5 mmol), $\text{CF}_3\text{CH}_2\text{OTs}$ (308 mg, 1.21 mmol), THF (10 mL), tri(butan-2-yl)borane (1.33 mL, 1.0 M in THF, 1.33 mmol), HMPA (3.0 mL), triphenylphosphine (25 mg, 0.10 mmol), tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (25 mg, 0.024 mmol), *o*-iodoaniline (238 mg, 1.09 mmol), dibutylmagnesium (2.47 mL, 0.44 M in Et_2O , 1.09 mmol), THF (3.0 mL) and copper(I) iodide (230 mg, 1.21 mmol). Purification by thin layer chromatography on silica gel (AcOEt–hexane 1:5) gave **9b** (157 mg, 68%) as a pale yellow liquid. ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, $100\text{ }^{\circ}\text{C}$) δ_{H} 0.99 (3H, t, $J = 7.3$ Hz), 1.03–1.15 (3H, m), 1.31–1.45 (1H, m), 1.54–1.66 (1H, m), 2.44–2.58 (1H, m), 4.58 (2H, br s), 6.62 (1H, ddd, $J = 7.4$, 7.4, 1.4 Hz), 6.79 (1H, d, $J = 7.4$ Hz), 6.92 (1H, d, $J = 7.4$ Hz), 7.07 (1H, ddd, $J = 7.4$, 7.4, 1.4 Hz). ^{13}C NMR (126 MHz, $(\text{CD}_3)_2\text{SO}$, $100\text{ }^{\circ}\text{C}$) δ_{C} 10.1, 17.2, 26.9, 34.5, 92.4 (dd, $J_{\text{CF}} = 16$, 16 Hz), 114.5, 115.4, 116.1, 127.8, 129.6, 145.8, 151.7 (dd, $J_{\text{CF}} = 290$, 288 Hz). ^{19}F NMR (470 MHz, $(\text{CD}_3)_2\text{SO}$, $100\text{ }^{\circ}\text{C}$) δ_{F} 71.2 (1F, br d, $J_{\text{FF}} = 49$ Hz), 74.1 (1F, br d, $J_{\text{FF}} = 49$ Hz). IR (neat) 3390, 2960, 1730, 1615, 1495, 1455, 1300, 1215, 935, 750 cm^{-1} . MS (EI, 70 eV) m/z 211 (M^+ , 100%),

182 (57), 162 (82). HRMS m/z calcd for $\text{C}_{12}\text{H}_{15}\text{F}_2\text{N}$ 211.1173 (M^+); found 211.1184.

4-Butyl-3-fluorocinnoline (10a)

To a solution of **9a** (65 mg, 0.31 mmol) in CH_3CN (3.0 mL) were added $\text{CF}_3\text{CO}_2\text{H}$ (0.045 mL, 0.61 mmol) and *i*-AmONO (0.081 mL, 0.61 mmol) at $0\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred for 30 min. The mixture was treated with thiophenol (0.10 mL, 0.92 mmol) and then stirred for 30 min at $0\text{ }^{\circ}\text{C}$. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:5) to give **10a** (55 mg, 88%) as a yellow liquid. ^1H NMR (500 MHz, CDCl_3) δ_{H} 0.98 (3H, t, $J = 7.6$ Hz), 1.47 (2H, tq, $J = 7.6$, 7.6 Hz), 1.71 (2H, tt, $J = 7.6$, 7.6 Hz), 3.09 (2H, t, $J = 7.6$ Hz), 7.76–7.80 (2H, m), 8.00–8.05 (1H, m), 8.48–8.52 (1H, m). ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 13.8, 22.8, 23.7, 31.7, 122.0 (d, $J_{\text{CF}} = 25$ Hz), 122.8 (d, $J_{\text{CF}} = 7$ Hz), 129.2 (d, $J_{\text{CF}} = 2$ Hz), 129.4 (d, $J_{\text{CF}} = 5$ Hz), 130.5, 131.5, 150.5 (d, $J_{\text{CF}} = 2$ Hz), 162.4 (d, $J_{\text{CF}} = 236$ Hz). ^{19}F NMR (470 MHz CDCl_3) δ_{F} 67.6 (br s). IR (neat) 2960, 2870, 1620, 1580, 1535, 1440, 1320, 1235, 1135, 1080, 965, 760 cm^{-1} . MS (EI, 70 eV) m/z 204 (M^+ , 100%), 162 (43), 133 (47). Anal. Found: C, 70.32; H, 6.28; N, 13.34. Calcd for $\text{C}_{12}\text{H}_{13}\text{FN}_2$: C, 70.57; H, 6.42; N, 13.72%.

4-(Butan-2-yl)-3-fluorocinnoline (10b)

Compound **10b** was prepared by the method described for **10a** using CH_3CN (3.0 mL), $\text{CF}_3\text{CO}_2\text{H}$ (0.053 mL, 0.72 mmol), *i*-AmONO (0.10 mL, 0.72 mmol), **9b** (76 mg, 0.36 mmol) and thiophenol (0.11 mL, 1.1 mmol). Purification by thin layer chromatography on silica gel (AcOEt–hexane 1:5) gave **10b** (64 mg, 87%) as a yellow liquid. ^1H NMR (500 MHz, CDCl_3) δ_{H} 0.87 (3H, t, $J = 7.2$ Hz), 1.49 (3H, dd, $J = 7.2$ Hz, $J_{\text{HF}} = 1.5$ Hz), 1.87–2.03 (2H, m), 3.57 (1H, tq, $J = 7.2$, 7.2 Hz), 7.75–7.80 (2H, m), 8.14–8.20 (1H, m), 8.48–8.54 (1H, m). ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 12.7, 18.9 (d, $J_{\text{CF}} = 3$ Hz), 28.2 (d, $J_{\text{CF}} = 4$ Hz), 33.0 (d, $J_{\text{CF}} = 3$ Hz), 122.9 (d, $J_{\text{CF}} = 6$ Hz), 125.8 (d, $J_{\text{CF}} = 22$ Hz), 129.1 (d, $J_{\text{CF}} = 2$ Hz), 129.4 (d, $J_{\text{CF}} = 7$ Hz), 130.7, 131.5, 150.6, 162.4 (d, $J_{\text{CF}} = 238$ Hz). ^{19}F NMR (470 MHz CDCl_3) δ_{F} 74.1 (br s). IR (neat) 2960, 2940, 2860, 1565, 1525, 1435, 1315, 1235, 1130, 760 cm^{-1} . MS (EI, 20 eV) m/z 204 (M^+ , 100%), 146 (34). Anal. Found: C, 70.32; H, 6.54; N, 13.50. Calcd for $\text{C}_{12}\text{H}_{13}\text{FN}_2$: C, 70.57; H, 6.42; N, 13.72%.

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Notes and references

^a Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan.
Fax: +81 29 853 4237; Tel: +81 29 853 4237;

^s E-mail: junji@chem.tsukuba.ac.jp

^b Department of Chemistry, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

^c Department of Applied Chemistry, Kyushu Institute of Technology, Sensui-cho, Tobata, Kitakyushu 804-8550, Japan.

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† Classical Baltz–Schiemann (fluorodediazotization) and Halex (halogen exchange) approaches are still extensively used. See, ref. 7.

‡ The possibility of 6 π -electrocyclization in the formation of **5**, **6**, and **10** cannot be ruled out.

¶ Recently, a site-selective (C-1), direct arylation of isoquinoline *N*-oxides has been reported.

- 1 For a review on isoquinolines, see: (a) K. W. Bentley, *The Isoquinoline Alkaloids*, Harwood Academic, Amsterdam, 1998. For a review on isoquinoline *N*-oxides, see: (b) A. Albin and S. Pietra, ed., *Heterocyclic N-oxides*, CRC Press, Boca Raton, 1991.
- 2 For a review on cinnolines, see: W. Lewgond and A. Stanczak, *Arch. Pharm. (Weinheim, Ger.)*, 2007, **340**, 65–80.
- 3 For isoquinoline synthesis, see: (a) M. Ivarez and J. A. Joule, *Science of Synthesis*, 2004, **15**, 661–838; (b) K. Kobayashi, K. Hayashi, K. Miyamoto, O. Morikawa and H. Konishi, *Synthesis*, **2006**, 2934–2938 and references therein. For isoquinoline *N*-oxide synthesis, see: (c) T. Sakamoto, Y. Kondo, N. Miura, K. Hayashi and H. Yamanaka, *Heterocycles*, 1986, **24**, 2311–2314.
- 4 For cinnoline synthesis, see: (a) N. Haider and W. Holzer, *Science of Synthesis*, 2004, **16**, 251–313; (b) A. Slevin, T. Koolmeister and M. Scobie, *Chem. Commun.*, **2007**, 2506–2508; (c) N. A. Zolnikova, L. G. Fedenok and N. E. Polyakov, *Org. Prep. Proced. Int.*, 2006, **38**, 476–480; (d) D. B. Kimball, T. J. R. Weakley and M. M. Haley, *J. Org. Chem.*, 2002, **67**, 6395–6405 and references therein. (e) C. Rüchardt and V. Hassmann, *Liebigs Ann. Chem.*, **1980**, 908–927.
- 5 For reviews, see: (a) M. J. Silvester, *Adv. Heterocycl. Chem.*, 1994, **59**, 1–38; (b) M. J. Silvester, *Aldrichimica Acta*, 1991, **24**, 31–38; (c) R. E. Banks, B. E. Smart and J. C. Tatlow, ed., *Organofluorine Chemistry, Principles and Commercial Applications*, Plenum, New York, 1994; (d) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2004.
- 6 For cross-coupling of aryl fluorides, see: (a) T. J. Korn, M. A. Schade, S. Wirth and P. Knochel, *Org. Lett.*, 2006, **8**, 725–728. (b) T. Saeki, Y. Takashima and K. Tamao, *Synlett*, **2005**, 1771–1774 and references therein. (c) L. Ackermann, R. Born, J. H. Spatz and D. Meyer, *Angew. Chem. Int. Ed.*, 2005, **44**, 7216–7219. (d) F. Mongin, L. Mojovic, B. Guillet, F. Trécourt and G. Quéguiner, *J. Org. Chem.* 2002, **67**, 8991–8994. (e) T. Braun and R. N. Perutz, *Chem. Commun.* **2002**, 2749–2757. For nucleophilic replacement of heteroaryl fluorides, see: (f) E. Arzel, P. Rocca, P. Grellier, M. Labaëid, F. Frappier, F. Guéritte, C. Gaspard, F. Marsais, A. Godard and G. Quéguiner, *J. Med. Chem.*, 2001, **44**, 949–960.
- 7 M. Hudlicky, A. E. Pavlath, ed., *Chemistry of Organic Fluorine Compounds II*, American Chemical Society, Washington, DC, 1995.
- 8 For reports on the synthesis of 3-fluoroisoquinolines, see: (a) J. Ichikawa, K. Sakoda, H. Moriyama and Y. Wada, *Synthesis*, **2006**, 1590–1598; (b) J. Ichikawa, Y. Wada, H. Miyazaki, T. Mori and H. Kuroki, *Org. Lett.*, 2003, **5**, 1455–1458; (c) V. G. Kolehkhina, A. M. Maksimov, V. E. Platonov and O. I. Osina, *Russ. Chem. Bull.*, 2001, **50**, 322–323; (d) J. L. Neumeyer and K. K. Weinhardt, *J. Med. Chem.*, 1970, **13**, 613–616. For a report on the synthesis and reaction of 3-fluoroisoquinoline *N*-oxides, see: (e) M. Bellas and H. Suschitzky, *J. Chem. Soc.*, **1964**, 4561–4564.
- 9 For reports on the synthesis of fluorocinnolines, see: (a) T. Miyamoto, and J. Matsumoto, *Chem. Pharm. Bull.*, 1988, **36**, 1321–1327; (b) R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *J. Chem. Soc. Chem. Commun.*, **1970**, 739–740; (c) R. N. Castle, K. Adachi and W. D. Guither, *J. Heterocycl. Chem.*, 1965, **2**, 459–462.
- 10 J. Ichikawa, *J. Fluorine Chem.*, 2000, **105**, 257–263.

- 11 (a) L.-C. Champeau, D. R. Stuart and K. Fagnou, *Aldrichimica Acta*, 2007, **40**, 35–41; (b) J.-P. Leclerc and K. Fagnou, *Angew. Chem. Int. Ed.*, 2006, **45**, 7781–7786.
- 12 J. Ichikawa, Y. Wada, M. Fujiwara and K. Sakoda, *Synthesis*, **2002**, 1917–1936.

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