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

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o-Formyl-substituted *β*,*β*-difluorostyrenes readily react with $NH_2OH{\cdot}HCl$ 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 (HON=CH– or HN=CH–). *β*,*β*-Difluorostyrenes bearing an *o*-diazenyl group (HN=N–), generated by reduction of the corresponding diazonium ions, undergo a similar substitution to afford 3-fluorinated cinnolines.

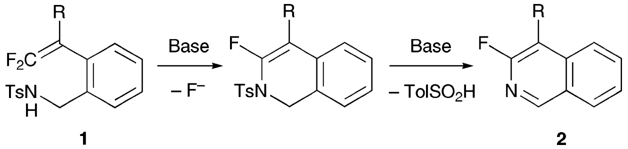
Introduction

Isoquinolines and related derivatives including cinnolines are found in many bioactive natural products. They constitute key structural components in pharmaceuticals and 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**.

On the other hand, nitrogen nucleophiles with an N=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*-oxides[8] or cinnolines[9] starting from *o*-formyl- or *o*-amino-substituted *β*,*β*-difluorostyrenes, respectively.

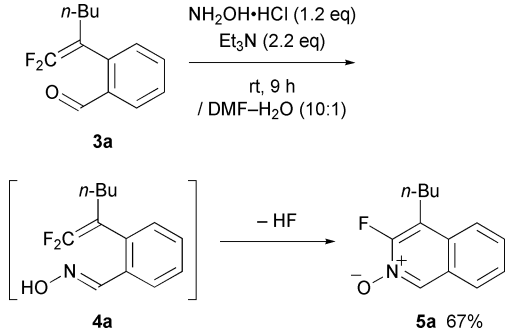


Scheme 1 Construction of isoquinoline frameworks *via* substitution and elimination.

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 hydroxyamine hydrochloride ($NH_2OH{\cdot}HCl$) in the presence of Et_3N. Unexpectedly, the reaction directly produced 3-fluoroquinoline *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



Scheme 2 Construction of isoquinoline frameworks *via* substitution from **4**.

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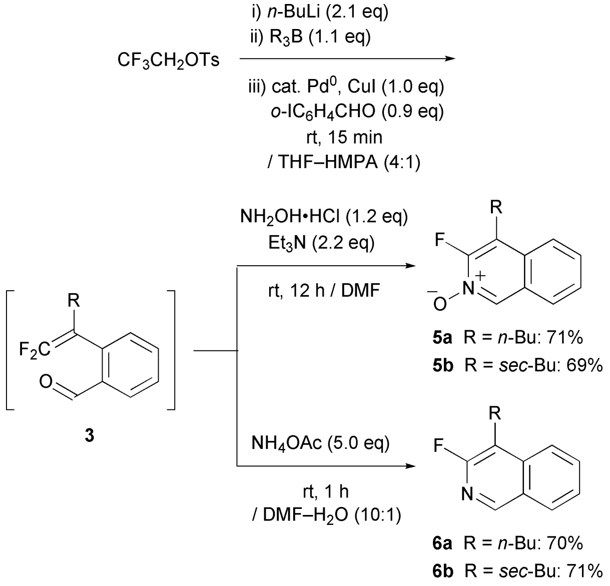
† Classical Balz–Schiemann (fluorodediazotization) and Halex (halogen exchange) approaches are still extensively used. See ref. 7.

vinylic substitution, followed by deprotonation on the oxygen, leading to the final product, isoquinoline *N*-oxide **5a**.‡

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*-iodobenzaldehyde[10] afforded **3a** in 84% yield, as determined by ^{19}F 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**, the process of which could improve the synthesis of **5**. After the generation of difluorovinylboranes from 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (CF_3CH_2OTs) and their coupling reaction with *o*-iodobenzaldehyde, the crude products were treated with $NH_2OH{\cdot}HCl$, 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, respectively (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 NH_4OAc 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).‡



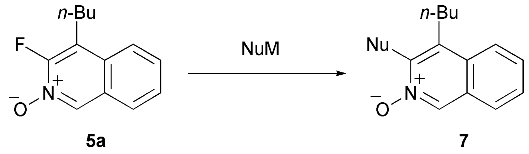
Scheme 3 Synthesis of 3-fluoroisoquinoline *N*-oxides **5** and 3-fluoroisoquinolines **6**.

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 allow the introduction of another substituent into the isoquinoline frameworks. 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*-oxides **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]

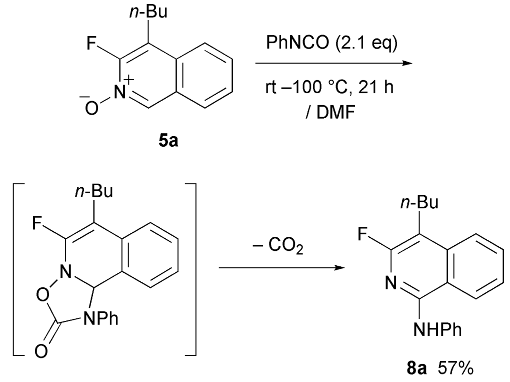
Table 1 Introduction of substituents at the 3-position of **5a**

Entry	NuM/eq.	Solvent	Conditions	Yield (%) (**7**)
1	*t*-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**)



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

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 CF_3CH_2OTs and *o*-iodobenzaldehyde.



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

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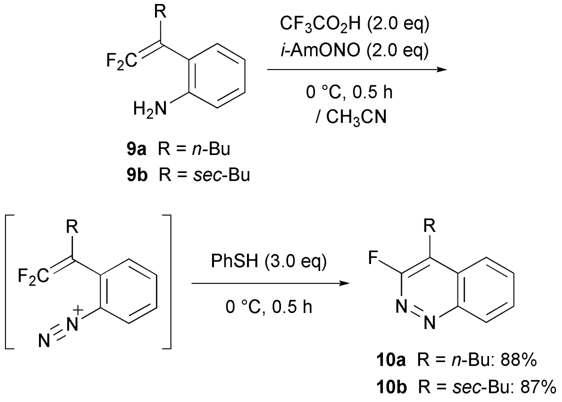
‡ The possibility of 6π-electrocyclization in the formation of **5**, **6**, and **10** cannot be ruled out.

§ Recently, a site-selective (C-1) direct arylation of isoquinoline *N*-oxides has been reported, see ref. 11.

Synthesis of 3-fluorocinnolines

As shown in Scheme 3, the direct construction of isoquinoline frameworks has been successfully achieved by the intramolecular substitution of the oxime and imine sp^2 nitrogen (HON=CH– and HN=CH–). Using these tactics, we next investigated the intramolecular substitution of a diimide sp^2 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 CF_3CH_2OTs and *o*-iodoaniline,[12] were treated with isoamyl nitrite (*i*-AmONO) for diazotization, and then subsequently reduced with *n*-Bu_3SnH. 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-fluoroccinnolines **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 CF_3CH_2OTs, 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

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a JEOL JNM-A-500 or a Bruker DRX 500 spectrometer. ^{1}H NMR chemical shifts (δ_H) are given in ppm downfield from Me_4Si. ^{13}C NMR chemical shifts (δ_C) are given in ppm downfield from Me_4Si, relative to chloroform-*d* (δ = 77.0). ^{19}F NMR chemical shifts (δ_F) are given in ppm downfield from C_6F_6. 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 CaH_2 and stored over 4Å molecular sieves. Acetonitrile (CH_3CN) was distilled under reduced pressure from CaH_2 and stored over 3Å molecular sieves. Hexamethylphosphoric triamide (HMPA) was distilled under reduced pressure from CaH_2 and stored over 4Å molecular sieves. 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 CF_3CH_2OTs (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 Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (Et_2O–hexane, 1 : 20) to give **3a** (441 mg, 62%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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. ^{19}F NMR (470 MHz, $CDCl_3$) 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) ν_{max} 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 $C_{13}H_{14}F_2O$ 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 CF_3CH_2OTs (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 Et_2O 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, crude aldehyde **3a**, was dissolved in DMF (3.0 mL). The resulting mixture was treated with $NH_2OH{\cdot}HCl$ (160 mg, 0.96 mmol) and Et_3N (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 $CHCl_3$ 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F 46.7 (d, J_{FH} = 6 Hz). IR (KBr disk) ν_{max} 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 $C_{13}H_{14}FNO$: C, 71.21; H, 6.44; N, 6.39%.

4-(Butan-2-yl)-3-fluoroisoqunoline *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), CF_3CH_2OTs (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 $NH_2OH{\cdot}HCl$ (160 mg, 0.96 mmol) and Et_3N (0.22 mL, 1.8 mmol) in DMF (3.0 mL). Purification by thin layer chromatography on silica gel (MeOH–AcOEt, 1 : 20) gave **5b** (109 mg, 69%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.90 (3H, t, J = 7.2 Hz), 1.48 (3H, dd, J = 7.2Hz, 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F 50.9 (br s). IR (KBr disk) ν_{max} 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 $C_{13}H_{14}FNO$ 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 CF_3CH_2OTs (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 Et_2O three times. The combined extracts were washed with water and brine, and then dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was dissolved in DMF (4.5 mL). The resulting mixture was treated with H_2O (0.45 mL) and NH_4OAc (173 mg, 2.2 mmol) and then stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O, and organic materials were extracted with AcOEt three times. The combined extracts were washed with water and brine, and then 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 : 10, and then benzene–hexane, 2 : 1) to give **6a** (64 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F 79.3 (br s). IR (neat) ν_{max} 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 $C_{13}H_{14}FN$: 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), CF_3CH_2OTs (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 NH_4OAc (173 mg, 2.2 mmol) and H_2O (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%). ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F 86.1 (br s). IR (neat) ν_{max} 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 $C_{13}H_{14}FN$: 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 H_2O–THF. 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 (MeOH–AcOEt, 1 : 20) to give **7a** (74 mg, 72%) as colorless crystals. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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) ν_{max} 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 $C_{17}H_{23}NO_2$ 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 Na_2SO_4. 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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) ν_{max} 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 $C_{19}H_{19}NOS$ 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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) ν_{max} 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 $C_{17}H_{22}N_2O$ 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 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 : 3) to give **8a** (55 mg, 57%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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, $J_{CF} = 230$ Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F 79.4 (br s). IR (neat) ν_{max} 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 $C_{19}H_{19}FN_2$: 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 CF_3CH_2OTs (308 mg, 1.21 mmol) in THF (10 mL) at −78 °C over 10 min. The reaction mixture was stirred for 20 min at −78 °C, and then tributylborane (1.33 mL, 1.0 M in THF, 1.33 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 (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 °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. ^{1}H 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, $J_{HF} = 2.3, 2.3$ 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, $J_{CF} = 3, 3$ Hz), 89.1 (dd, $J_{CF} = 22, 17$ Hz), 115.6, 118.4, 119.0 (d, $J_{CF} = 3$ Hz), 128.9, 130.6, (d, $J_{CF} = 2$ Hz), 144.3, 152.8 (dd, $J_{CF} = 290, 288$ Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F 68.7 (1F, d, $J_{FF} = 43$ Hz), 72.7 (1F, d, $J_{FF} = 43$ Hz). IR (neat) ν_{max} 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 $C_{12}H_{15}F_2N$: 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), CF_3CH_2OTs (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. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 °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, $(CD_3)_2SO$, 100 °C) δ_C 10.1, 17.2, 26.9, 34.5, 92.4 (dd, $J_{CF} = 16, 16$ Hz), 114.5, 115.4, 116.1, 127.8, 129.6, 145.8, 151.7 (dd, $J_{CF} = 290, 288$ Hz). ^{19}F NMR (470 MHz, $(CD_3)_2SO$, 100 °C) δ_F 71.2 (1F, br d, $J_{FF} = 49$ Hz), 74.1 (1F, br d, $J_{FF} = 49$ Hz). IR (neat) ν_{max} 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 $C_{12}H_{15}F_2N$ 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 CF_3CO_2H (0.045 mL, 0.61 mmol) and *i*-AmONO (0.081 mL, 0.61 mmol) at 0 °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 °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. ^{1}H 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, $J_{CF} = 25$ Hz), 122.8 (d, $J_{CF} = 7$ Hz), 129.2 (d, $J_{CF} = 2$ Hz), 129.4 (d, $J_{CF} = 5$ Hz), 130.5, 131.5, 150.5 (d, $J_{CF} = 2$ Hz), 162.4 (d, $J_{CF} = 236$ Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F 67.6 (br s). IR (neat) ν_{max} 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 $C_{12}H_{13}FN_2$: 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), CF_3CO_2H (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. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.87 (3H, t, $J = 7.2$ Hz), 1.49 (3H, dd, $J = 7.2$ Hz, $J_{HF} = 1.5$ 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, $J_{CF} = 3$ Hz), 28.2 (d, $J_{CF} = 4$ Hz), 33.0 (d, $J_{CF} = 3$ Hz), 122.9 (d, $J_{CF} = 6$ Hz), 125.8 (d, $J_{CF} = 22$ Hz), 129.1 (d, $J_{CF} = 2$ Hz), 129.4 (d, $J_{CF} = 7$ Hz), 130.7, 131.5, 150.6, 162.4 (d, $J_{CF} = 238$ Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F 74.1 (br s). IR (neat) ν_{max} 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 $C_{12}H_{13}FN_2$: C, 70.57; H, 6.42; N, 13.72%.

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