Syntheses, Properties, and Applications of Fluorinated Isoquinolines

Takeshi Fujita and Junji Ichikawa

Contents

Abstract Fluorinated isoquinolines attract widespread attention as important components of pharmaceuticals and materials, because of their unique characteristics such as biological activities and light-emitting properties. Thus, a number of fluorinated isoquinolines have been synthesized. This chapter covers the syntheses, properties, and applications of ring-fluorinated isoquinolines starting from earlier studies, as well as the syntheses of pyridine-ring-trifluoromethylated isoquinolines. Modern synthetic methodologies for fluorinated isoquinolines have been greatly developed during last decade. These approaches are presented according to the classification based on the standpoint of organic synthesis: (i) the direct introduction of fluorine (or CF_3 group) onto the isoquinoline ring, (ii) the construction of a fused pyridine ring via cyclization of a precursor bearing a pre-fluorinated benzene ring, and (iii) the simultaneous installation of an isoquinoline framework and a fluorine substituent. This chapter also presents a discussion of the application of fluorinated isoquinoline derivatives.

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1 Synergy of Isoquinoline and Fluorine

Isoquinoline, which is a structural isomer of quinoline, possesses a nitrogen-containing heteroaromatics and benzene-ring-fused system. Isoquinolines are widely found in naturally occurring alkaloids [1–3]. Isoquinolines are essential in pharmaceutical, agricultural, and materials sciences because they exhibit various bioactivities and useful physical properties. Among isoquinolines, some tetrahydroisoquinoline derivatives exhibit severe neurotoxicity, which leads to Parkinson's disease [4]. In contrast, a number of isoquinoline-related medicines are flourishing in worldwide pharmaceutical markets. For example, papaverine hydrochloride, morphine, and berberine tannate are prescribed as an antispasmodic drug, a painkiller, and an antidiarrheal, respectively [5].

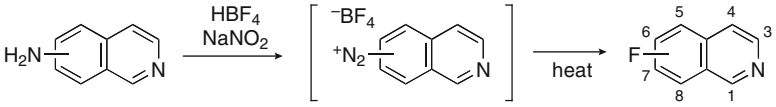
In general, supply of fluorine-containing heterocycles has been mainly expanded for pharmaceutical uses, because electrostatic and steric effects that result from the introduction of fluorine atoms often cause unique bioactivities [6–8]. Fluorinated isoquinolines, i.e., hybrid compounds with an isoquinoline framework and a fluorine substituent, have thus attracted a great deal of attention over the past several decades. A number of fluorinated isoquinolines have been synthesized because of the remarkable progress in synthetic methodologies for fluorinated heterocycles. Substantial enhancements of bioactivities have been observed with respect to some fluorinated isoquinoline derivatives in comparison with the activities of the corresponding fluorine-free compounds. Furthermore, because other isoquinoline-related compounds have exhibited unique light-emitting properties, such compounds are expected to serve as electronic materials.

Some results of previous studies on perfluoroalkylated isoquinolines were recently summarized by Petrov [7]. This chapter focuses on the syntheses, properties, and applications of ring-fluorinated isoquinolines (limited to compounds that retain the aromatic isoquinoline scaffold), starting from the historical background of earlier studies. Additionally, an overview of the syntheses of pyridine-ring-trifluoromethylated derivatives is also given.

2 Earlier Studies on Fluorinated Isoquinolines

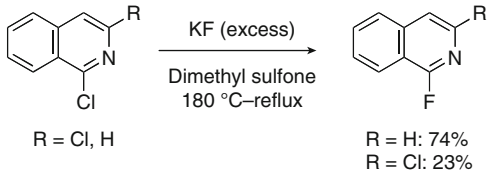
Several typical synthetic methodologies for the preparation of fluorinated isoquinoline derivatives emerged in the 1950s and 1960s. Fundamental reactivities and properties of such compounds were also concomitantly reported. In 1951, Roe and Teague reported the first synthesis of monofluorinated isoquinolines (Scheme 1) [9]. They successfully prepared 1-, 3-, 4-, and 5-fluoroisoquinolines via heating diazonium intermediates

derived from the corresponding aminoisoquinolines on treatment with sodium nitrite and fluoroboric acid, which is the Baltz–Schiemann reaction [10]. In the 1960s, Belsten and Dyke synthesized 8-fluoroisoquinoline, [11] and Bellas and Suschitzky reported the first synthesis of 6- and 7-fluoroisoquinolines (Scheme 1) [12]. Both syntheses involved Baltz–Schiemann reactions similar to those used by Roe and Teague.



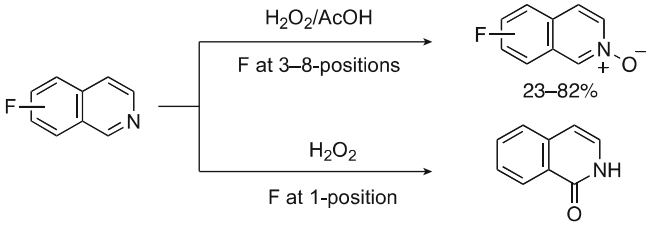
Scheme 1 The Baltz–Shiemann reaction toward ring-fluorinated isoquinolines

An alternative approach to the synthesis of 1-fluoroisoquinolines was accomplished by the nucleophilic aromatic substitution (S_NAr) [12]. The chlorine–fluorine exchange reaction (Halex reaction) [13, 14] was effected in 1-chloroisoquinolines with potassium fluoride to provide 1-fluoroisoquinolines in high yield (Scheme 2). In the case of 1,3-dichloroisoquinoline used as a substrate, 3-chloro-1-fluoroisoquinoline was selectively obtained despite the use of an excess of potassium fluoride. The chemoselectivity was attributed to the lability of the carbon–halogen bond at the 1-position of the isoquinoline ring.



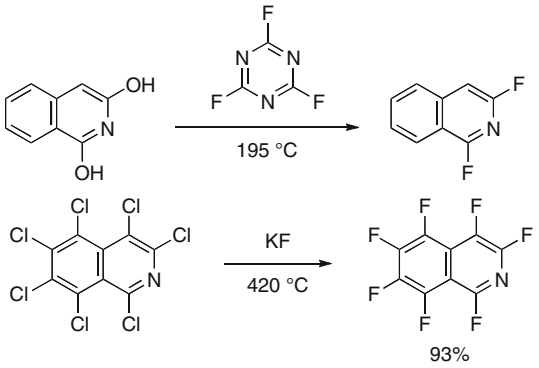
Scheme 2 The Halex reaction toward 1-fluoroisoquinolines

The carbon–fluorine bond at the 1-position of isoquinoline is also reactive. Although isoquinolines bearing a fluorine atom at one of the 3–8-positions were easily converted to the corresponding *N*-oxides by addition of hydroperoxide, 1-fluoroquinoline gave 1-isoquinolone (isocarbostyryl) via nucleophilic replacement of the fluorine substituent under the same reaction conditions (Scheme 3) [12].



Scheme 3 Difference in reactivities of fluorinated isoquinolines

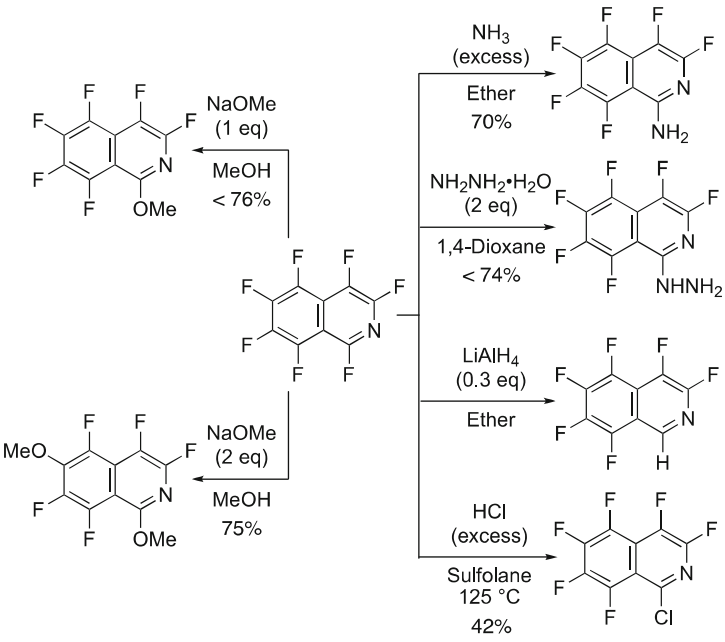
More than one fluorine atoms were introduced onto the isoquinoline framework (Scheme 4). In 1960, Bayer patented the synthesis of 1,3-difluoroisoquinoline, which was derived from 1,3-dihydroxyisoquinoline and cyanuric fluoride [15]. Six years later, Chambers and Musgrave successfully prepared heptafluoroisoquinoline, [16] in which all hydrogen atoms of the parent isoquinoline were replaced by fluorine atoms via a chlorine–fluorine exchange reaction. In this case, heating the mixture of heptachloroisoquinoline and potassium fluoride to 420 °C facilitated global fluorination to provide an excellent yield of heptafluoroisoquinoline.



Scheme 4 Syntheses of di- and perfluorinated isoquinolines

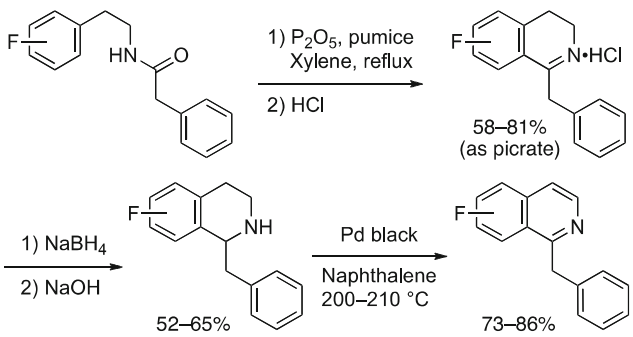
Heptafluoroisoquinoline thus formed easily underwent further S_NAr reactions with various nucleophiles (Scheme 5). Treatment of heptafluoroisoquinoline with an equimolar amount of sodium methoxide selectively afforded hexafluoro-1-methoxyisoquinoline because of the remarkable reactivity of the 1-fluoro substituent (vide supra) [17, 18]. Monosubstitution at the 1-position also selectively occurred in reactions with ammonia, hydrazine, and lithium aluminum hydride to provide 1-aminohexafluoroisoquinoline, 1-hidrazinoisoquinoline, and 1*H*-hexafluoroisoquinoline, respectively. Even anhydrous hydrogen chloride gradually reacted with heptafluoroisoquinoline at a high temperature to give the corresponding 1-chlorinated product [19]. Meanwhile, addition of two equivalents of sodium methoxide selectively gave pentafluoro-1,6-dimethoxyisoquinoline.

For the synthesis of functionalized fluoroisoquinolines, cyclization of *N*-[2-(fluorophenyl)ethyl]amides followed by aromatization was effective, which is called the Bischler–Napieralski reaction and is a typical method for 1-substituted 3,4-dihydroisoquinolines directed toward isoquinoline synthesis [20]. The reaction smoothly proceeded, irrespective of the positions of fluorine, when *N*-[2-(fluorophenyl)ethyl]-2-phenylacetamides were used (Scheme 6) [11]. Notably, 8-fluoro-3,4-dihydroisoquinoline was not obtained by this method because *N*-[2-(3-fluorophenyl)ethyl]-2-phenylacetamides gave 6-fluoro-3,4-dihydroisoquinolines exclusively. The reduction of 3,4-dihydroisoquinolines to



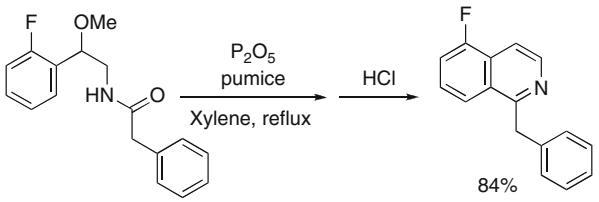
Scheme 5 Nucleophilic aromatic substitutions of heptafluoroisoquinoline

tetrahydroisoquinolines followed by oxidative aromatization provided the corresponding 1-benzyl-fluoroisoquinolines, whereas the direct oxidation of fluorinated 3,4-dihydroisoquinolines failed and led to the loss of fluorine with palladium species [21].



Scheme 6 Synthesis of fluoroisoquinolines via the Bischler–Napieralski reaction

The Pictet–Gams reaction, [22] which is known as a variation of the Bischler–Napieralski reaction, enabled a sequential reaction consisting of cyclization and aromatization to give 1-benzyl-5-fluoroisoquinoline from *N*-[2-(2-fluorophenyl)-2-methoxyethyl]-2-phenylacetamide (Scheme 7) [21].



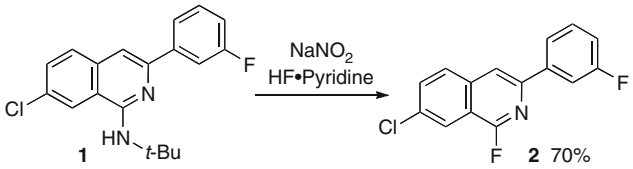
Scheme 7 Synthesis of 5-fluoroisoquinoline via the Pictet–Gams reaction

As it was described previously, fluoroisoquinoline chemistry has begun about half a century ago. Since the predawn of fluoroisoquinoline chemistry, various syntheses of ring-fluorinated isoquinoline derivatives have been accomplished, accompanied by remarkable progress in the aromatic ring fluorination and in the construction of fluorine-containing heterocycles. From the standpoint of organic synthesis, methodologies for fluorinated isoquinolines can be classified into three major groups: (i) the direct fluorination onto the isoquinoline ring, (ii) the construction of a fused pyridine ring via cyclization of a precursor bearing a pre-fluorinated benzene ring, and (iii) the simultaneous installation of an isoquinoline framework and a fluorine substituent. In the following section, modern synthetic methodologies for fluorinated isoquinolines are presented according to this classification. The last section of this chapter presents a discussion of the application of fluorinated isoquinoline derivatives in various scientific fields.

3 Syntheses of Ring-Fluorinated Isoquinolines

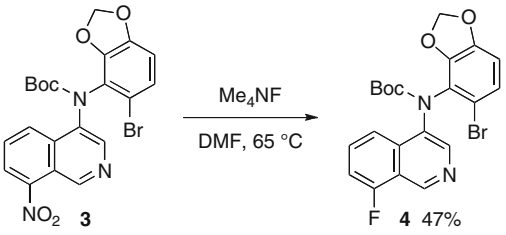
3.1 Direct Ring Fluorination

The Baltz–Schiemann reaction is still one of the most common methods for direct ring fluorination because of the accessibility to aminated isoquinoline derivatives. The original conditions, which involve the use of tetrafluoroboric acid (fluoroboric acid), are still often employed, [23–27] even though several modified procedures have been reported. For example, Myers synthesized 1-fluoroisoquinoline **2** by the dealkylative diazotization of 1-*tert*-butyl-aminoisoquinoline **1** with pyridine hydrofluoride instead of HBF_4 (Scheme 8) [28].



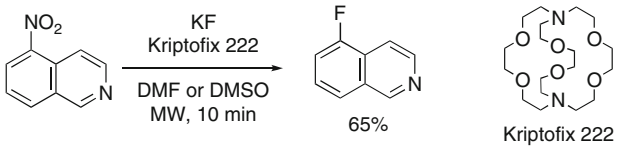
Scheme 8 Synthesis of 1-fluoroisoquinoline via dealkylative diazotization

Among neutral nitrogen substituents, a nitro group on an aromatic ring can be directly converted to a fluorine substituent via the S_NAr mechanism [29–32]. In this fluorodenitration method, tetraalkylammonium fluorides and inorganic fluoride salts have been used as fluorine sources. For example, upon treatment with tetramethylammonium fluoride, 8-nitroisoquinoline **3** afforded 8-fluorinated isoquinoline **4** (Scheme 9) [25].



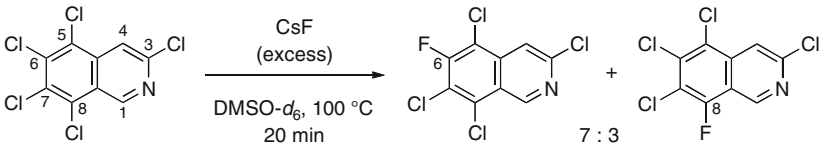
Scheme 9 Synthesis of 8-fluoroisoquinoline via fluorodenitration with Me_4NF

Even potassium fluoride induced fluorodenitration of 5-nitroquinoline with the aid of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]-hexacosane (Kryptofix 222) [33, 34] as a phase transfer agent under microwave irradiation, which led to 5-fluoroquinoline (Scheme 10) [35].

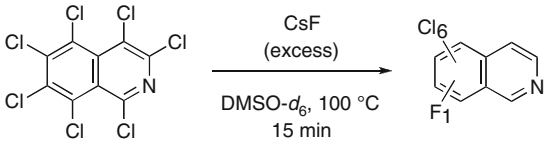


Scheme 10 Synthesis of 5-fluoroisoquinoline via fluorodenitration with KF

The Halex reaction for the synthesis of multi-fluorinated isoquinoline was investigated in detail by Matthews et al., and they attempted chlorine–fluorine exchange reactions of several multi-chlorinated isoquinolines [36]. When 3,5,6,7,8-pentachloroisoquinoline was treated with an excess of cesium fluoride in deuterated dimethyl sulfoxide (DMSO-d_6) at 100 °C, 3,5,7,8-tetrachloro-6-fluoroisoquinoline and 3,5,6,7-tetrachloro-8-fluoroisoquinoline were formed in a 7:3 ratio after 20 min (Scheme 11). The observation of the predominant substitution at the 6-position was consistent with the fact that the 6-position of heptafluoroisoquinoline was the second most reactive to nucleophiles after the 1-position (vide supra, Scheme 5) [17]. Similar reaction conditions were also employed in the reaction of heptachloroisoquinoline, where the 1-position was found to be more reactive than other positions (Scheme 12).



Scheme 11 The Halex reaction of 3,5,6,7,8-pentachloroisoquinoline

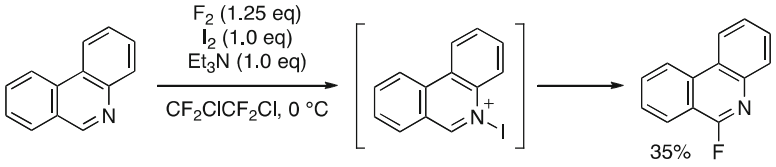


Position	1	3	4	5	6	7	8
Ratio	65	4	0	4	8	6	7

Scheme 12 The Halex reaction of heptachloroisoquinoline

With respect to other positions, Matthews concluded that the reactivity for substitution in heptachloroquinoline was 1>>6=7=8>3=5>4. Notably, the 3-position of haloisoquinolines was less reactive toward nucleophilic substitution even though it was adjacent to the nitrogen atom, whereas the 1-position of haloisoquinolines and the 2-position of haloquinolines were substantially reactive [37].

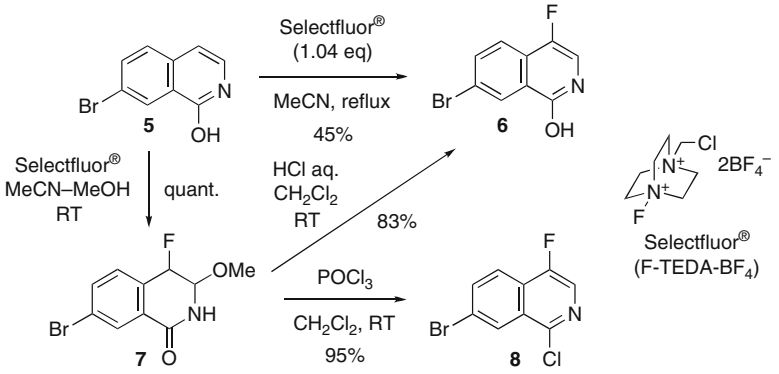
The direct fluorination of a C–H bond of nitrogen-containing heterocycles was achieved with gaseous fluorine and iodine by Chambers and Sandford et al [38]. The mixture of fluorine and iodine served as sources of both I^+ and F^- (Scheme 13). The heterocycles activated by *N*-iodination underwent fluoride attack at the carbon adjacent to the nitrogen atom. Elimination of hydrogen iodide gave the corresponding ring-fluorinated heterocycles. In this report, phenanthridine, a benzo analogue of isoquinoline, was fluorinated to afford 6-fluorophenanthridine.



Scheme 13 Synthesis of 6-fluorophenanthridine via fluorination with F_2 and I_2

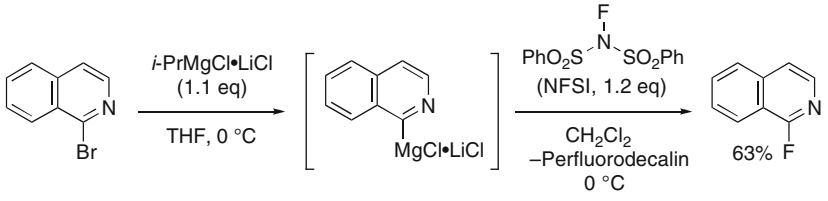
In contrast to nucleophilic fluorination, fluoroisoquinoline syntheses via direct electrophilic fluorination were reported relatively recently. In 2007, Price developed direct electrophilic C–H bond fluorination of an isoquinoline derivative with Selectfluor® (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), F-TEDA), [39] which is known as an efficient electrophilic fluorine source [40–42].

Refluxing the mixture of 6-bromo-1-hydroxyisoquinoline (**5**) and Selectfluor® in acetonitrile afforded 7-bromo-4-fluoro-1-hydroxy-isoquinoline (**6**) as a single isomer in a one-pot reaction (Scheme 14). In contrast, fluorinated methanol adduct **7** was quantitatively produced, when the reaction was conducted at ambient temperature in an acetonitrile–methanol mixed solvent. Subsequent aromatization of **7** with hydrochloric acid gave **6** in high overall yield, whereas the reaction with phosphoryl chloride provided 1-chlorinated 4-fluoroisoquinoline **8** as another variation of 4-fluorinated isoquinoline derivatives.



Scheme 14 Electrophilic fluorination with Selectfluor®

In 2010 Knochel et al. reported the electrophilic fluorination of heteroarylmagnesium reagents by applying their magnesiation methodology, [43, 44] in which heteroaryl bromides underwent a Br–Mg exchange through the addition of an isopropylmagnesium chloride–lithium chloride complex [45–47]. *N*-fluorobenzenesulfonimide (NFSI) was used as an electrophilic fluorinating agent to trap the generated heteroarylmagnesium species in good to excellent yield (Scheme 15). Although electrophilic fluorination of standard aryl Grignard reagents had already been reported, [48] Knochel's method significantly improved the product yields. Thus, 1-fluoroisoquinoline was readily prepared from 1-bromoisoquinoline.

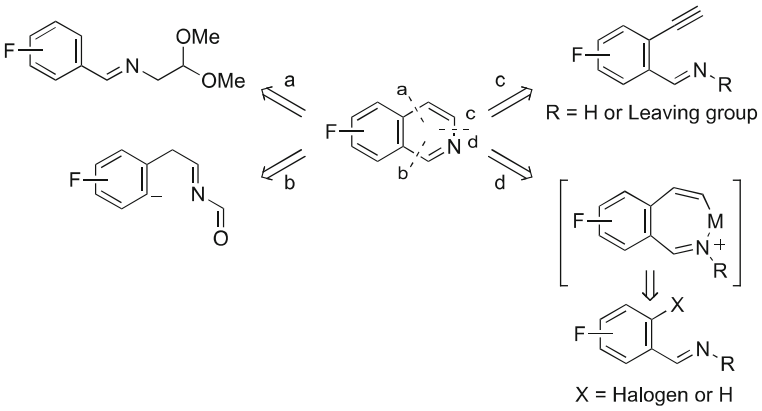


Scheme 15 Electrophilic fluorination of 1-isoquinolylmagnesium reagent

3.2 *Ring Construction of Pre-fluorinated Substrates*

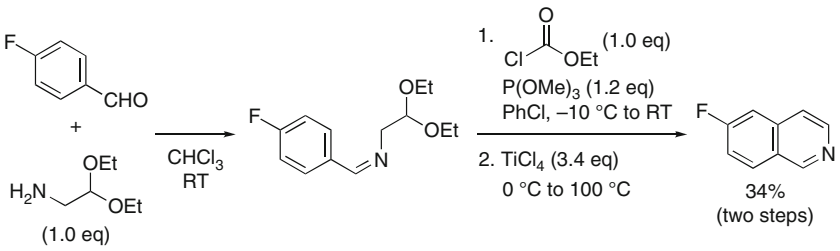
The construction of heterocycles from fluoroarene substrates is an efficient approach to synthesize ring-fluorinated heterocycles with a fused benzene ring because fluoroarenes are relatively easy to access and aromatic C–F bonds are sufficiently robust to survive most of the reaction conditions. Nowadays a wide variety of methodologies for heterocyclic ring construction have been established, this strategy has been predominant in the syntheses of benzene-ring-fluorinated isoquinolines. To employ this strategy, the nitrogen atom must be located at appropriate positions, and cyclization accompanied or followed by aromatization must smoothly proceed.

Aryl or benzyl imines have been commonly used as precursors of isoquinolines. In cases starting with *N*-substituted imines, the substituents on the nitrogen atom should be efficiently incorporated or eventually removed (Scheme 16, routes a–c). The method via simultaneous reductive elimination and removal of *N*-substituents from nitrogen-containing metallacycles is also effective (Scheme 16, route d). The intermediary metallacycles can be mainly obtained from (*ortho*-haloaryl)methanimines.



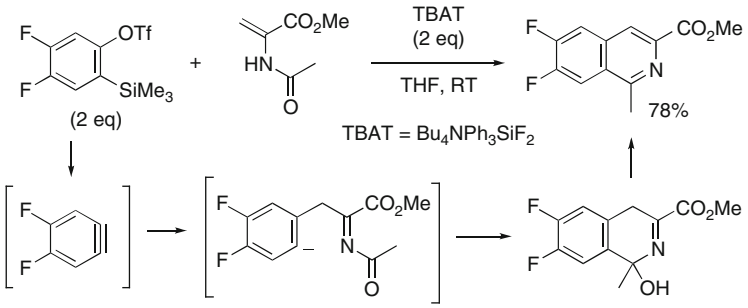
Scheme 16 Approaches to fluoroisoquinolines starting from imines bearing a fluoroaryl group

Benzylideneaminoacetoaldehyde acetals prepared from benzaldehydes have been key intermediates of a well-established method for isoquinoline synthesis known as the Pomeranz–Fritsch reaction (Scheme 16, route a) [49, 50]. Intramolecular cyclization of this type of imines under acidic conditions provided isoquinolines, where the two-carbon substituent on the nitrogen atom was transformed into a part of the isoquinoline ring. For the synthesis of 8-fluoroisoquinoline, the application of the standard procedure gave a low yield of the desired product (3 % in two steps from 2-fluorobenzaldehyde) [51]. However, in the modified procedure using ethyl chloroformate, trimethyl phosphite, and titanium tetrachloride for the cyclization step [52] provided 6-fluoroisoquinoline from 4-fluorobenzaldehyde in 34 % overall yield (Scheme 17) [25].



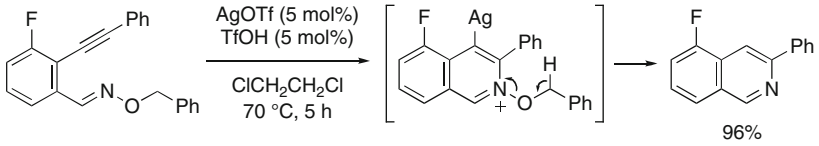
Scheme 17 Synthesis of 6-fluoroisoquinoline via the Pomeranz–Fritsch reaction

Stoltz et al. [53] and Ramtohul et al. [54] independently and almost simultaneously reported an isoquinoline synthesis via the reaction of *N*-acetylenamines with benzynes (Scheme 16, route b; Scheme 18). In this reaction, intermediary *N*-acetylimines underwent nucleophilic attack of the aryl anions to give the corresponding isoquinolines after aromatization. The carbonyl carbon on the nitrogen atom was incorporated into the 1-position of the resulting isoquinolines.



Scheme 18 Synthesis of 6,7-difluoroisoquinoline via the reaction of *N*-acetylenamine with benzyne

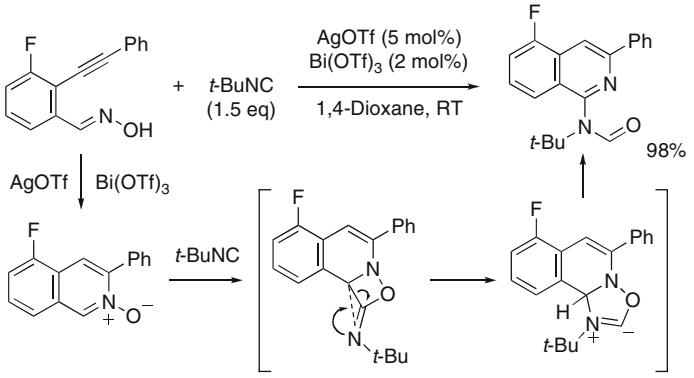
2-Alkynylbenzaldehyde *O*-alkyl oximes were also used as precursors of isoquinolines (Scheme 16, route c). After intramolecular electrophilic cyclization, *N*-alkoxy groups were eliminated to form aldehydes (for example benzaldehyde). Shin et al. synthesized 5-fluoro-3-phenylisoquinoline using a AgOTf/TfOH catalytic system (Scheme 19), [55] while Wu achieved Cu-catalyzed synthesis of several 7-fluoroisoquinoline derivatives [56].



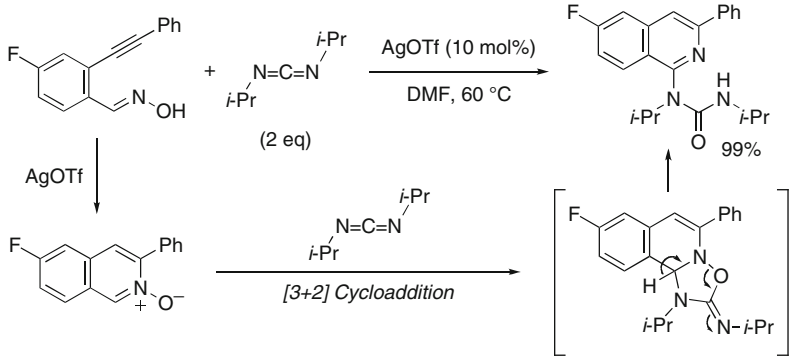
Scheme 19 Ag-catalyzed electrophilic cyclization of 2-alkynylbenzaldehyde *O*-alkyl oxime for 5-fluoroisoquinoline synthesis

The intramolecular electrophilic cyclization of *N*-(2-alkynylbenzylidene)hydrazides or 2-alkynylbenzoaldoximes afforded isoquinolinium-2-ylamides or isoquinoline *N*-oxides, respectively (Scheme 16, route c). The carbon atoms at the 1-position of these compounds were substantially electrophilic because of the polarization of the N–O or N–N bond. Therefore, these isoquinoliniums readily underwent [3+2] cycloaddition and nucleophilic attack to the 1-position, as discussed in the subsequent paragraph.

Wu et al. synthesized a 5-fluoroisoquinoline derivative via the reaction of a 2-alkynylbenzoaldoxime and an isocyanide with a AgOTf/$Bi(OTf)_3$ catalyst (Scheme 20) [57]. Sequential rearrangements were triggered by the addition of the isocyanide to the 1-position of the intermediary isoquinoline *N*-oxide. The [3+2] cycloaddition of the *N*-oxide with a carbodiimide followed by ring-opening also afforded 6- and 7-fluoroisoquinoline derivatives (Scheme 21) [58]. Recently, similar approaches to functionalized fluoroisoquinolines have been frequently adopted [59–65]. In addition to the above-mentioned imine derivatives, *N*-*tert*-butyl imines were used, where the *tert*-butyl group was removed from the nitrogen atom [66]. Furthermore, primary imines have been shown to serve as precursors of fluorinated isoquinolines, albeit under harsh conditions [67, 68].

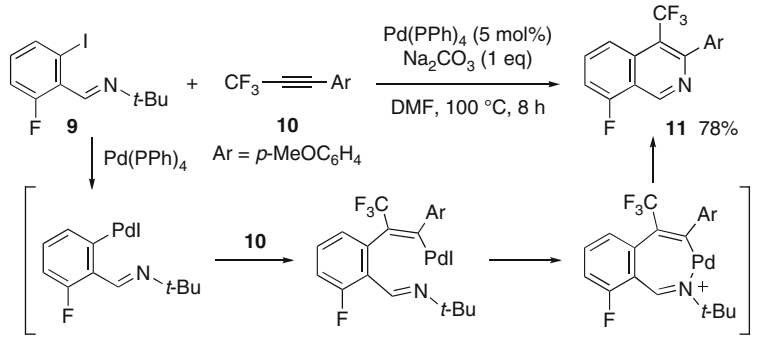


Scheme 20 Ag/Bi-cocatalyzed electrophilic cyclization of 2-alkynylbenzoaldoxime for 5-fluoroisoquinoline synthesis

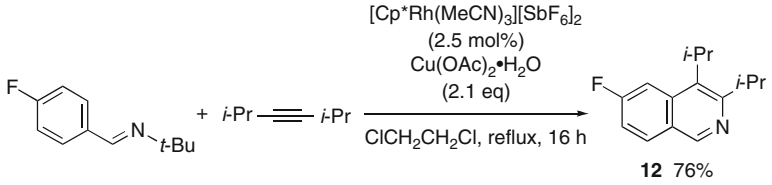


Scheme 21 Ag-catalyzed electrophilic cyclization of 2-alkynylbenzoaldoxime for 6-fluoroisoquinoline synthesis

The reductive elimination from seven-membered nitrogen-containing metallacycles also leads to the construction of the isoquinoline framework (Scheme 16, route d). Such metallacycles result from the insertion of alkynes into metal–aryl bonds mainly formed by oxidative addition of aryl–halogen bonds. Konno et al. achieved the synthesis of 8-fluoroisoquinoline **11** via the reaction of 2-iodobenzylidenamine **9** with trifluoromethylalkyne **10** with the aid of a palladium catalyst (Scheme 22) [69]. Related synthetic methodologies have been established with a nickel catalyst [70] as well as palladium catalysts [71–73]. Fagnou et al. succeeded in a similar isoquinoline synthesis via C–H bond activation with a rhodium catalyst, which provided 6-fluoroisoquinoline **12** (Scheme 23) [74].



Scheme 22 Pd-catalyzed domino insertion/cyclization sequence for 8-fluoroisoquinoline synthesis

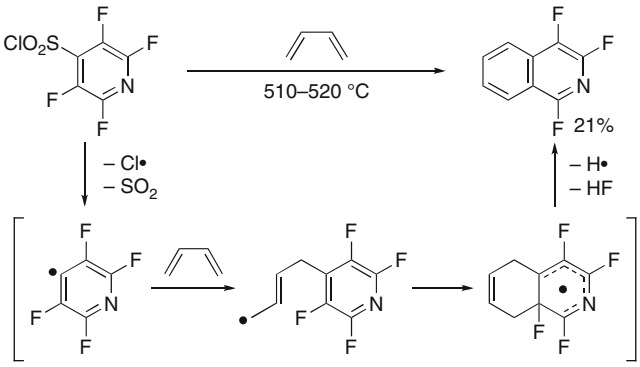


Scheme 23 Route to 6-fluoroisoquinoline via Rh-catalyzed C–H bond activation

Nitrogen-containing functional groups other than imines can also participate in this type of isoquinoline synthesis. For example, nitriles were convenient because they possess no extra groups on the nitrogen atom to be removed. Fluorinated isoquinolines were prepared via the intramolecular and intermolecular reactions of nitriles. The nitrogen atom of nitriles exhibited sufficient nucleophilicity to form C–N bonds that contributed to the construction of isoquinoline scaffolds [75, 76]. Imine-metal species derived from nitriles and organometallic reagents were effective for this purpose [28, 77–79]. Amines, [80–82] amides, [83–86] azides, [87] triazoles, [88] and enamine-type intermediates [89, 90] also served as key precursors for fluorinated isoquinolines.

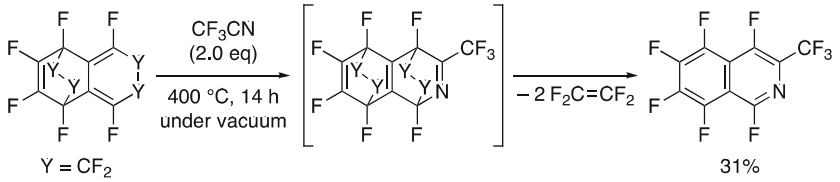
Construction of benzene rings has rarely been conducted in the last stage of fluoroisoquinoline synthesis. The use of fluorinated pyridines as starting materials allows the introduction of fluorine on the heterocyclic ring carbons. Queguiner et al. reported

the multi-step synthesis of an indole-fused 1-fluoroisoquinoline. [91] Platonov et al. synthesized 1,3,4-trifluoroisoquinoline via the copyrolysis of 2,3,5,6-tetrafluoropyridine-4-sulfonyl chloride with butadiene (Scheme 24) [92].



Scheme 24 Synthesis of 1,3,4-trifluoroisoquinoline via copyrolysis of pyridine-4-sulfonyl chloride with butadiene

Exceptionally, there is an example for simultaneous construction of both benzene and pyridine rings toward a perfluorinated isoquinoline. Feast et al. reported the synthesis of perfluoro-3-methylisoquinoline via the hetero Diels–Alder reaction of perfluoro-1,4,6,7-tetrahydro-1,4-ethanonaphthalene with trifluoroacetonitrile followed by pyrolysis, which involved elimination of tetrafluoroethylene (Scheme 25) [93].



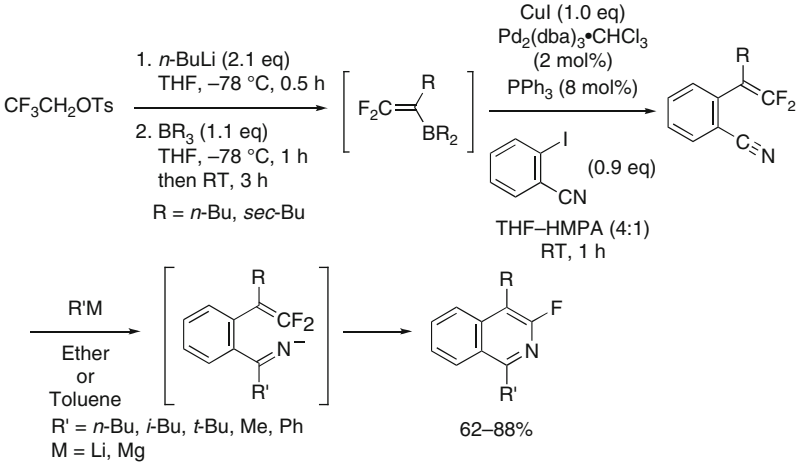
Scheme 25 Synthesis of perfluoro-3-methylisoquinoline via the hetero Diels–Alder reaction

3.3 Simultaneous Installation of an Isoquinoline Framework and a Fluorine Substituent

Intramolecular cyclizations of *ortho*-functionalized *β*,*β*-difluorostyrenes provide a general access to ring-fluorinated heterocycles. In this methodology, both the construction of a heterocyclic nucleus and the introduction of a fluorine substituent are simultaneously effected.

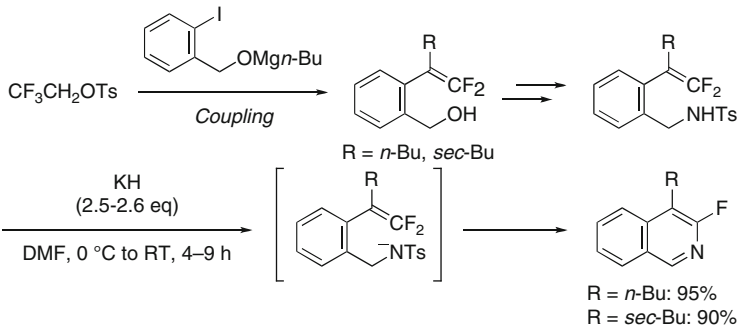
The difluoromethylene carbon of 1,1-difluoro-1-alkenes exhibits strong electrophilicity because of the electron-deficient and highly polarized carbon–carbon

double bond, and thus difluoroalkenes readily react with nucleophiles instead of electrophiles. Furthermore, the nucleophilic attack to difluoroalkenes followed by fluoride elimination (vinylic nucleophilic substitution; S_NV) provides products bearing a fluorovinylic moiety. Ichikawa et al. constructed 5-membered and 6-membered heterocycles via intramolecular S_NV reactions of 1,1-difluoro-1-alkenes [94–96]. This strategy can introduce a fluorine substituent at a prescribed position, whereas the direct fluorination methods generally require regioselective pre-functionalization. This methodology has been successfully applied to the synthesis of 3-fluoroisoquinolines, which has been difficult to prepare with previous methods, including heterocyclic ring construction. *β*,*β*-difluorostyrenes as cyclization precursors have been mainly prepared via palladium-catalyzed coupling of *ortho*-functionalized aryl iodides and difluorovinylborans, which were generated from 2,2,2-trifluoroethyl 4-methylbenzenesulfonate [97, 98]. *o*-Cyano-*β*,*β*-difluorostyrenes thus formed reacted with organometallics to give the corresponding iminyl metal intermediates, which in turn underwent 6-*endo* cyclization to give 3-fluoroisoquinolines (Scheme 26) [99].

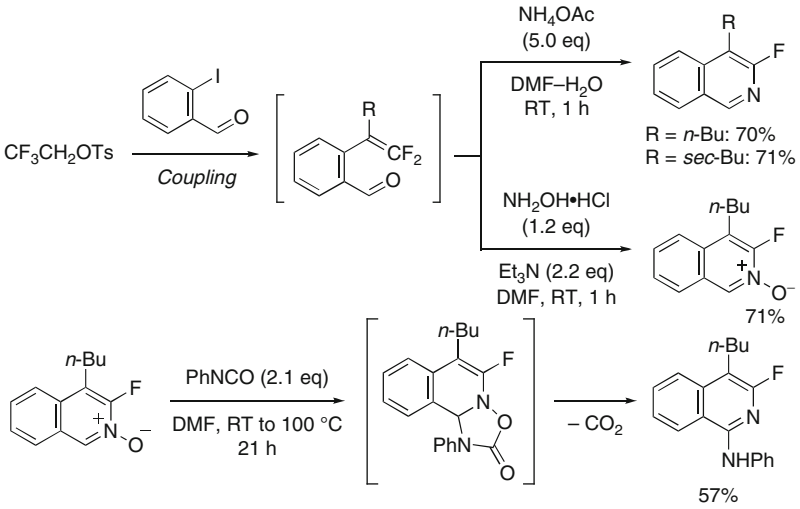


Scheme 26 Synthesis of 3-fluoroisoquinolines via the intramolecular S_NV reaction of iminyl metal intermediates

Sulfonamides are sufficiently reactive to serve as nucleophiles in the reaction with difluorostyrenes under basic conditions (Scheme 27) [100]. Imines and oximes have also been utilized as nucleophiles to provide 3-fluoroisoquinolines and their *N*-oxides, respectively (Scheme 28) [101]. When the isoquinoline *N*-oxide was treated with an isocyanate, the oxygen atom on the nitrogen was consequently eliminated after the 1,3-dipolar addition to afford a 1-amino-3-fluoroisoquinoline (Scheme 28).



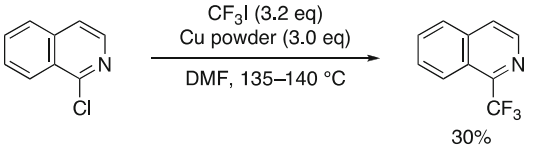
Scheme 27 Synthesis of 3-fluoroisoquinolines via the intramolecular S_NV reaction of difluorostyrenes bearing a sulfonamide moiety



Scheme 28 Synthesis of 3-fluoroisoquinolines via the intramolecular S_NV reaction of difluorostyrenes bearing a formyl group

4 Syntheses of Pyridine-Ring-Trifluoromethylated Isoquinolines

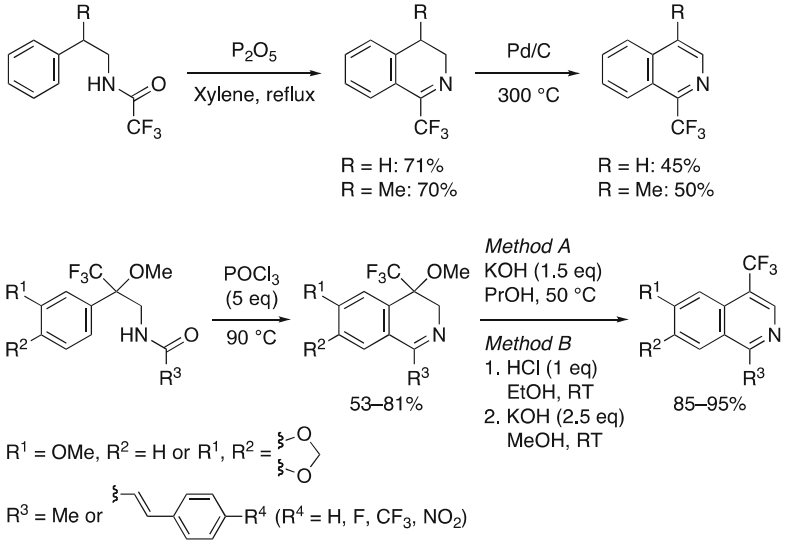
As well as a fluorine substituent, a trifluoromethyl group have recently attracted much attention as the shortest perfluoroalkyl group. A variety of methodologies for the introduction of a trifluoromethyl group into heteroaromatics have been also developed [102]. In 1970, Kobayashi et al. reported the copper-mediated direct trifluoromethylation of aryl and heteroaryl halides using trifluoromethyl iodide as a source of a trifluoromethyl group [103]. Thus, 1-(trifluoromethyl)isoquinoline was synthesized, albeit in low yield (Scheme 29).



Scheme 29 Copper-mediated trifluoromethylation for 1-(trifluoromethyl)isoquinoline synthesis

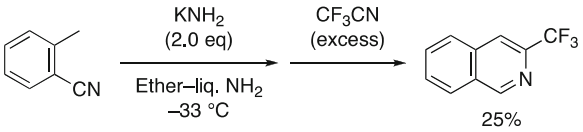
Pyridine-ring-trifluoromethylated isoquinolines are easier to access compared to ring-fluorinated counterparts. Syntheses of pyridine-ring-fluorinated isoquinolines via pyridine-ring construction are mostly difficult except for the 3-fluoroisoquinoline synthesis, which was effected via the intramolecular S_NV reaction of *β*,*β*-difluorostyrenes (see also Sect. 3.3). This is because pyridine-ring closure using fluorine-presubstituted components could be retarded by considerable reactivity changes caused by fluorine substituents. On the other hand, the trifluoromethyl group is rather chemically inert. Thus, pyridine-ring-trifluoromethylated isoquinolines have been successfully synthesized via ring closure of trifluoromethylated precursors. The following is an overview of the syntheses of pyridine-ring-trifluoromethylated isoquinolines.

The Bischler–Napieralski reaction [20] and the Pictet–Gams reaction [22] are both known as typical methods for the construction of the isoquinoline framework as described in Sect. 2. Cambon et al. synthesized 1-(trifluoromethyl)isoquinolines via the Bischler–Napieralski reaction of *N*-(phenethyl)trifluoroacetamides, [104] whereas Simig et al. utilized the Pictet–Gams reaction of *N*-(2-aryl-3,3,3-trifluoro-2-methoxypropyl)amides of acetic or cinnamic acids for the synthesis of 4-(trifluoromethyl)isoquinolines (Scheme 30) [105].

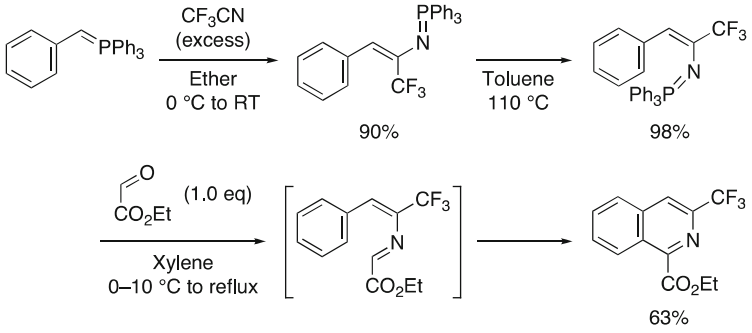


Scheme 30 Syntheses of 1- or 4-(trifluoromethyl)isoquinolines via the Bischler–Napieralski reaction or the Pictet–Gams reaction

Upon pyridine ring construction, small molecules bearing a trifluoromethyl group can be applied to intermolecular reactions as ring components. Trifluoroacetonitrile has been used not only as a component of the pyridine ring but also as a source of a trifluoromethyl group. Nauta et al. reported the synthesis of 3-(trifluoromethyl)isoquinoline via the reaction of 2-methylbenzonitrile with trifluoroacetonitrile under basic conditions (Scheme 31) [106]. Palacios et al. synthesized a 3-trifluoromethylated isoquinoline via electrocyclization of the aza-Wittig reaction product of an *N*-vinylic phosphazene, which was prepared via [2 + 2] cycloaddition of a phosphorus ylide and trifluoroacetonitrile (Scheme 32) [107]. As previously described, Feast et al. also used trifluoroacetonitrile for the synthesis of a 3-(trifluoromethyl)isoquinoline via the hetero Diels–Alder reaction (Scheme 25) [93]. Stoltz et al. used an *N*-trifluoroacetyl dehydroalanine ester for the synthesis of a 1-trifluoromethylated isoquinoline (Scheme 18) [53], whereas Konno et al. used trifluoromethylalkynes for the synthesis of 4-(trifluoromethyl)isoquinolines (Scheme 22) [69].

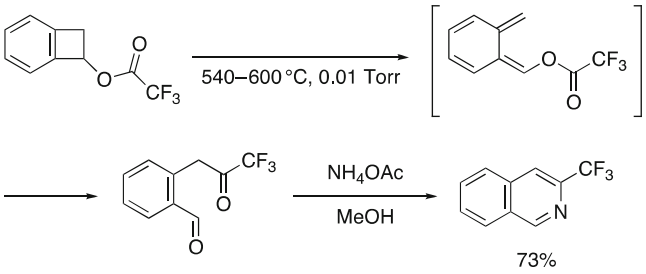


Scheme 31 Synthesis of 3-(trifluoromethyl)isoquinoline using trifluoroacetonitrile



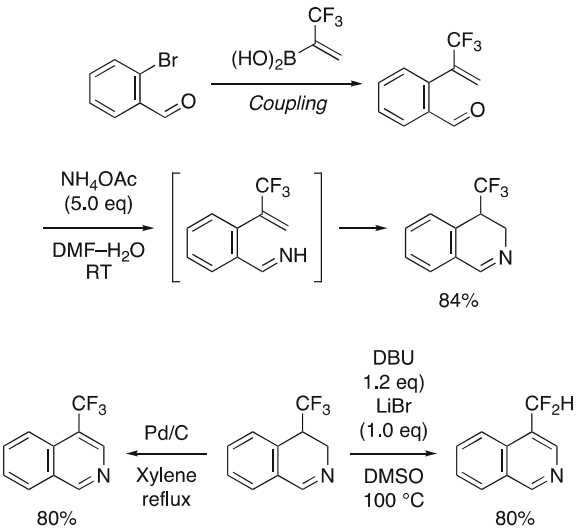
Scheme 32 Synthesis of 3-(trifluoromethyl)isoquinoline using trifluoroacetonitrile via the aza-Wittig reaction

The trifluoromethyl group is inert enough to survive under harsh reaction conditions. Schiess et al. synthesized 3-(trifluoromethyl)isoquinoline via flash vacuum pyrolysis of trifluoroacetyloxybenzocyclobutene (Scheme 33) [108]. Although the skeletal rearrangement required an ultra-high temperature, this reaction proceeded without the loss of the trifluoromethyl group.



Scheme 33 Route to 3-(trifluoromethyl)isoquinoline via flash vacuum pyrolysis

Since the trifluoromethyl group stabilizes the carbanion at its proximal carbon atom due to the strong electron-withdrawing nature, 2-trifluoromethyl-1-alkenes are subject to nucleophilic attack at their 1-positions. Ichikawa et al. have applied such a chemical property of the trifluoromethyl group to intramolecular cyclizations with carbon and heteroatom nucleophiles, which led to various fluorine-containing carbo- and heterocycles [95, 109, 110]. Among the studies, 4-trifluoromethyl-3,4-dihydroisoquinoline was synthesized via 6-*endo-trig* cyclization of the aldimine intermediate derived from an α-trifluoromethylstyrene bearing an *o*-formyl group (Scheme 34) [111]. 4-Trifluoromethyl-3,4-dihydroisoquinoline provided 4-(trifluoromethyl)isoquinoline and 4-(difluoromethyl)isoquinoline under oxidative and basic conditions, respectively. The difluoromethyl group is one of recently-highlighted fluoroalkyl groups, as well as the trifluoromethyl group [112].



Scheme 34 Intramolecular cyclization of *o*-formyl-α-(trifluoromethyl)styrene for 3-(trifluoromethyl)- or 3-(difluoromethyl)isoquinoline synthesis

5 Properties and Applications of Ring-Fluorinated Isoquinoline Derivatives

Ring-fluorinated isoquinoline derivatives thus synthesized exhibit a wide range of bioactivities that rival or surpass those of the original fluorine-free compounds. In addition to such remarkable potentials in the field of pharmaceutical sciences, the formation of supramolecular structures and the use of ligands of light-emitting metal complexes have also attracted considerable attention as possible functions of fluoroisoquinolines. This section describes concrete examples of the properties and applications of fluoroisoquinoline derivatives.

In the 1960s, isoquinoline derivatives were tested in an antitumor assay [113]. French et al. found that 1-formylisoquinoline thiosemicarbazone **13a** was effective for a variety of mouse tumors (Fig. 1a). They subsequently carried out a comprehensive study of antitumor assays using various thiosemicarbazones of 1-formylisoquinolines [24]. Among the compounds tested, 5-fluoro derivative **13b**, along with non-fluorinated compound **13a**, exhibited the strongest activity against L-1210 leukemia and the Lewis lung carcinoma. 7-Fluorinated derivative **13c** was found to be specifically active against the B-16 melanoma. Recently, Zhu et al. developed isoquinoline–pyridine-based protein kinase B/Akt antagonists [114]. 3-Fluorinated isoquinoline derivative **14** served as an effective Akt1 inhibitor (IC_{50}=3.5 nM), and the related compounds worked even in MiaPaCa-2 human pancreatic cancer cells (Fig. 1b).

Isoquinoline derivatives have been expected to serve as drugs for type II diabetes. Protein tyrosine phosphatase 1B (PTB1B) is considered to be one of the targets because it works as a negative regulator of the insulin-signaling pathway. A series of 1-(isoquinolin-1-yl)guanidines was tested as a PTB1B inhibitor by Liu and Wu et al. (Fig. 2a) [65]. They found that 6-fluorinated isoquinoline **15** was highly effective (IC_{50}=6.38 μg/mL). 11β-Hydroxydehydrogenase 1 (11β-HSD1), which catalyzes the transformation of cortisone to cortisol, is another target compound for diabetes therapy. Investigation of various 1-(benzylthio)isoquinolines and 1-(benzylthio)-5,6,7,8-tetrahydroisoquinolines revealed that ring-fluorinated isoquinoline derivatives **16b**, **16c**, and **16e** possess significant activity against 11β-HSD1 as non-fluroinated compound **16a** (Fig. 2b) [115]. Among compounds bearing isoquinoline scaffolds, 7-fluorinated compound **16d** showed the highest activity in the inhibition of both mouse (IC_{50}=7 nM) and human (IC_{50}=2 nM) 11β-HSD1 enzymes.

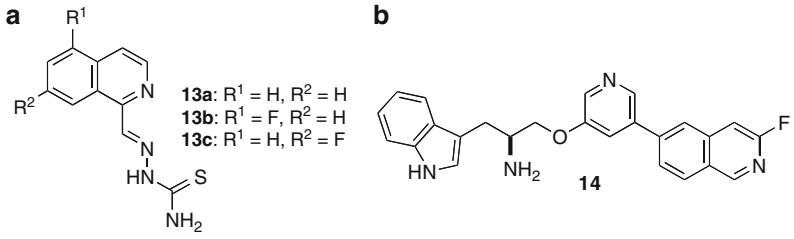
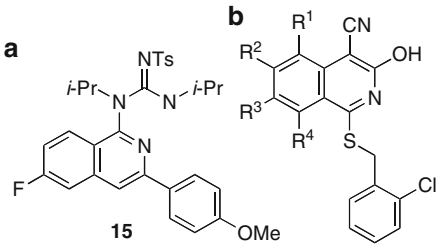


Fig. 1 Antitumor active fluoroisoquinolines



Sample	11β-HSD1 IC_{50} (nM)	
	Human	Mouse
16a: $R^1 = R^2 = R^3 = R^4 = H$	4	19
16b: $R^1 = F$, $R^2 = R^3 = R^4 = H$	8	7
16c: $R^2 = F$, $R^1 = R^3 = R^4 = H$	8	14
16d: $R^3 = F$, $R^1 = R^2 = R^4 = H$	2	7
16e: $R^4 = F$, $R^1 = R^2 = R^3 = H$	6	10

Fig. 2 Drug candidate fluoroisoquinolines for type II diabetes

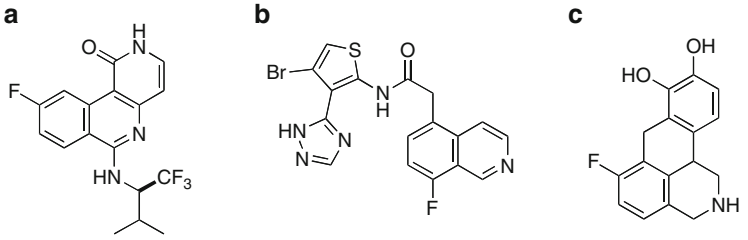


Fig. 3 Fluoroisoquinolines as competitive inhibitors of enzymes and receptors

Napthyridinones inhibit the activity of Janus kinase 2 (JAK2), which plays important roles in hematopoiesis and immune response (Fig. 3a). Among napthyridinones, compounds bearing a 6-fluoroisoquinoline substructure exhibited extraordinary potency as JAK2 inhibitors [85]. Besides above-mentioned fluorinated isoquinolines, aminothiophene-containing fluorinated isoquinolines contributed to the inhibition of the c-Jun N-terminal kinases (JNKs), which are members of the mitogen-activated protein kinase (MAPK) family (Fig. 3b) [27]. Dinapsoline derivatives prepared from fluorinated isoquinolines also showed substantial bioactivities as dopamine receptor agonists (Fig. 3c) [25].

In addition to exhibiting bioactivities, polyfluoroaromatic compounds often display unique properties for accessing supramolecular architectures in crystalline states. Arene and polyfluoroarene molecules are well known to alternately stack through π–π interactions in their 1:1 co-crystals to give columnar structures [116].

Homocrystals of 1,2,3,4-tetrafluoronaphthalene, a partially fluorinated naphthalene, showed an obvious π–π stacking structure with a head-to-tail orientation like co-crystals of arenes and polyfluoroarenes (Fig. 4a) [117]. In contrast, the CF/π interaction [118, 119] was predominant in homocrystals of 1,3,4-trifluoroisoquinoline, in which the C2–F fragment of 1,2,3,4-tetrafluoronaphthalene was replaced by a nitrogen atom (Fig. 4b) [117]. This difference forced 1,3,4-trifluoroisoquinoline to adopt a head-to-head orientation without π–π stacking.

Iridium complexes bearing isoquinoline-based bidentate ligands are phosphorescent (Scheme 35). 1-Phenylisoquinolinyliridium complexes emit red phosphorescence as the result of spin-forbidden triplet metal-to-ligand charge transfer (^{3}MLCT) excitation [26]. Such complexes, including some based on 5-fluoroisoquinoline,

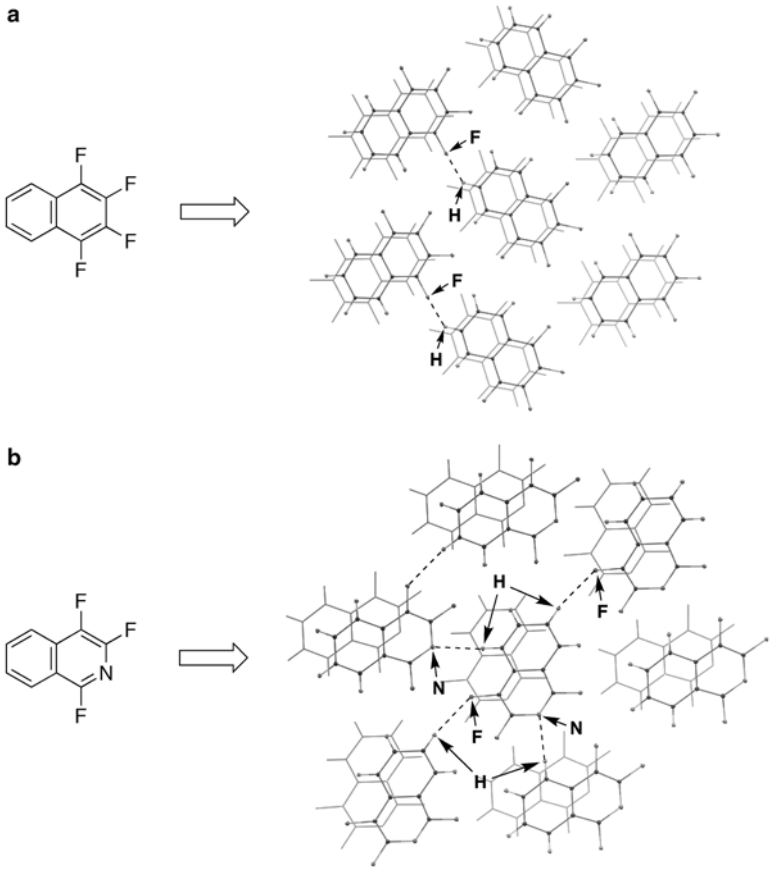
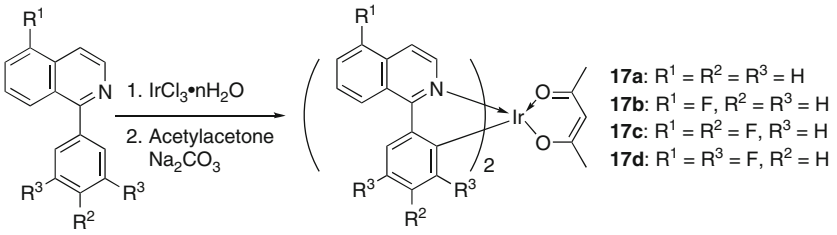


Fig. 4 Supramolecular networks in crystal structures of (**a**) 1,2,3,4-tetrafluoronaphthalene and (**b**) 1,3,4-trifluoroisoquinoline

were utilized for organic light-emitting devices (OLEDs), which were fabricated as follows: 4,4′-*N*,*N*′-dicarbazolebiphenyl (CBP) was used as a host material for iridium complexes, bathocuproine (BCP) was used as a hole blocker, 4,4′-bis(*N*-naphthylphenylamino)biphenyl (NPB) was used as a hole transport layer, and tris(8-hydroxyquinolinyl)aluminum(III) (Alq_3) was used as an electron transport layer. The OLEDs thus fabricated from iridium complexes **17** showed good emission quantum yields and high brightness. For example, [Ir(5-f-1piq)$_2$(acac)] (**17b**; 5-f-1piq = 5-fluoro-1-phenylisoquinoline) showed a turn-on voltage of 35 V, low-working voltages (1,883 cd m^{-2} at 7.1 V and 8,329 cd m^{-2} at 9.0 V), and a maximum brightness of 38,218 cd m^{-2} (14.0 V), which suggests that this complex has strong potential for use in full color displays (Table 1). The emission color coordinates of **17b** on the Commission Internationale de I'Éclairage (CIE) chart were ($x = 0.68$, $y = 0.31$), which is close to the standard red color.



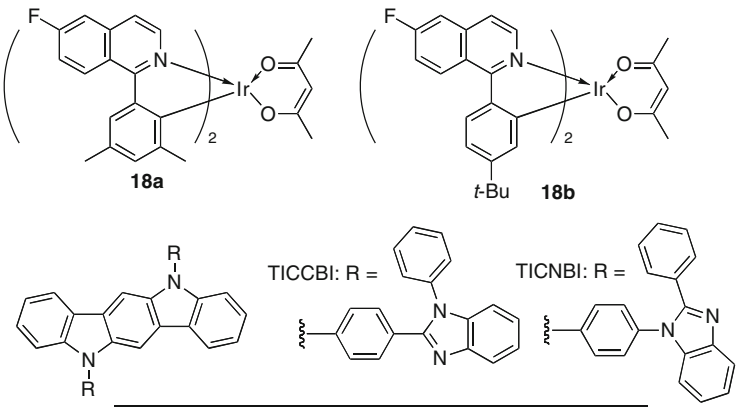
Scheme 35 Preparation of 1-phenylisoquinolinyliridium complexes

Table 1 Electrophosphorescent data of iridium complexes bearing isoquinoline-based bidentate ligands

Complex	Brightness (cd/m^2)	External quantum efficiency (%)	Voltage (V)	CIE coordinates
17a	1,514[a]	8.46	8.53	x = 0.68
	8,224[b]	9.21	11.01	y = 0.32
	24,978[c]	7.00	13.92	
	31,776[d]			
17b	1,883[a]	10.15	7.12	x = 0.68
	8,329[b]	9.00	8.98	y = 0.31
	24, 038[c]	6.50	11.04	
	38,218[d]			
17c	2,603[a]	7.41	7.29	x = 0.60
	9,644[b]	5.28	8.79	y = 0.36
	12,151[c]	4.80	9.16	
	23,606[d]			
17d	1,511[a]	5.48	9.02	x = 0.66
	7,008[b]	5.10	11.35	y = 0.33
	19,661[c]	3.86	14.10	
	31,490[d]			

[a] $J = 20$ mA/cm^2
[b] $J = 20$ mA/cm^2
[c] $J = 20$ mA/cm^2
[d] Maximum brightness at 14 V

Later, iridium complexes with 6-fluoroquinoline-based ligands, (35dmPh-6Fiq)$_2$Ir(acac) (**18a**; 35dmPh-6Fiq = 6-fluoro-1-(3,5-dimethylphenyl)isoquinoline) and (4*t*BuPh-6Fiq)$_2$Ir(acac) (**18b**; 4*t*BuPh-6Fiq = 6-fluoro-1-(4-*tert*-butylphenyl) isoquinoline) were developed as red color emitting phosphorescent materials (Fig. 5) [120]. When these iridium complexes as red emitters were combined with benzimidazole–indolo[3,2-*b*]carbazole-linked molecules (TICCBI and TICNBI) as donor–acceptor bipolar hosts, the OLEDs exhibited high external quantum efficiencies (14.4–15.6 %).



Host: 10% Dopant	η_{ext} (maximum) / %	CIE (x,y)
TICCBI: **18a**	14.4	(0.70, 0.30)
TICCBI: **18b**	15.3	(0.68, 0.32)
TICNBI: **18a**	15.6	(0.69, 0.30)
TICNBI: **18b**	15.5	(0.67, 0.32)

Fig. 5 OLEDs fabricated with iridium complexes bearing 6-fluoroquinoline-based ligands as emitters and TICCBI and TICNBI as donor–acceptor bipolar hosts

6 Conclusions and Perspectives

In this decade, synthetic methodologies for ring-fluorinated isoquinolines have been greatly developed as described above. The Baltz–Shiemann reaction provides a versatile method for the syntheses of isoquinolines bearing a fluorine atom at any position, albeit with difficulties in regioselective prefunctionalization. In the syntheses of benzene-ring-fluorinated isoquinolines, a wide variety of methods can be employed to construct pyridine rings starting from fluorobenzene derivatives. In terms of heterocyclic-ring-fluorinated isoquinolines, 1-fluoroisoquinolines are effectively prepared via either nucleophilic or electrophilic substitution from 1-haloisoquinolines. 3-Fluoroisoquinolines can be selectively synthesized via various intramolecular S_NV reactions of *ortho*-functionalized β,β-difluorostyrenes. 4-Fluoroisoquinolines can be obtained via electrophilic fluorination of 1-hydroxyisoquinolines. As for the syntheses of pyridine-ring-trifluoromethylated isoquinolines, pyridine-ring construction methods are also quite effective.

In addition to the increasing diversity of ring-fluorinated isoquinolines obtained, they have already been utilized not only as drug candidates but also as functional materials. The chemistry of the ring-fluorinated isoquinolines will continue to progress; thus, in the near future, fluoroisoquinolines with predominant properties will emerge in which the characteristics of the fluorine substituent are fully utilized.

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