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Review Article

Advances in the Preparation of Fluorinated Isoquinolines: A Decade of Progress

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Heterocyclic molecules incorporating fluorinated isoquinoline components are found in many medicinally and agriculturally important bioactive products as well as industrially impactful materials. Within the past decade, a variety of isoquinolinic ring assembly techniques has enabled the introduction of diverse fluorine-containing functionalities which can enhance potential bioactivity and industrial utility. This review examines recent noncatalyzed and transition metal catalyzed synthetic approaches to the assembly of isoquinoline derivatives that are ring-fluorinated and/or result in the incorporation of fluorine-containing functional groups. Specifically, efficient synthetic methods and regioselectivity in the incorporation of functional groups into isoquinoline ring systems are examined.

1. Introduction

1.1. Discovery of Isoquinoline and Early Synthesis Efforts. Isoquinoline, the bicyclic aromatic heterocycle shown in Figure 1, was first isolated as the sulfate salt from coal tar in 1885 by Hoogewerf and van Dorp [1]. By 1893, several syntheses of isoquinolinoid compounds were published by Pomeranz, Fritsch, Bischler, and Napieralski, reactions which bear their names [2–4]. Early in the 20th century, Pictet, Gams, and Spengler developed slightly different approaches to prepare isoquinoline derivatives [5, 6].

While the synthetic methods shown in Figure 1 enabled construction of different parts of the "A" ring component of the isoquinoline heterocycle, most early preparations required strong acids and refluxing conditions or dehydrating agents and dehydrogenation catalysts which limited functional group survival during the reactions.

1.2. Medicinal and Industrial Uses of Isoquinolines. Since its discovery, isoquinoline has remained an aromatic heterocycle of broad appeal to the synthetic organic, materials science, pharmaceutical, and agrochemical communities. Isoquinoline derivatives have important industrial applications, where they serve as solvents for aromatic molecules, fluorosensors, as components in paints, dyes, and electronic devices [7–9]. Isoquinoline derivatives such as papaverine have been isolated from natural sources and the isoquinolinoid pharmacore can be found in numerous drugs that possess antitumor, anesthetic, and antibiotic properties [10–12]. Figure 2 shows some representative examples of important isoquinoline-based molecules.

1.3. Effects of Fluorine Incorporation on Molecular Properties. When fluorine and fluorine-containing groups are incorporated into molecules, dramatic shifts of molecular properties occur in many instances. The inductive effect brought about by fluorine's high electronegativity and its small van der Waals radius of 1.47 Å changes molecular structural and stereoelectronic properties such as conformation, pK_a, polarity, solubility, and hydrogen-bonding capacity [13–18]. An example of how these alterations bear directly on materials science applications is found in the fluorinated isoquinoline-based electrophosphorescent iridium complexes used in color displays [9]. See Figure 3.

For a number of years, the pharmaceutical industry has leveraged these fluorine-induced molecular property modulations in drug discovery strategies when constructing

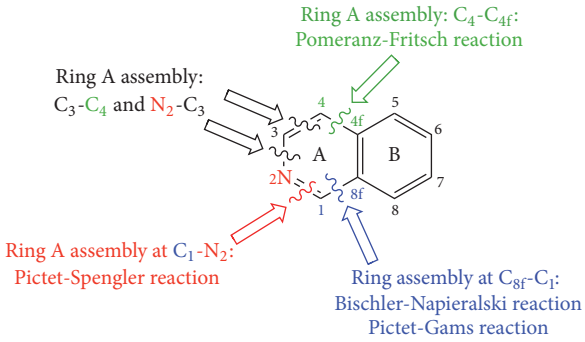


Figure 1: Isoquinoline ring assembly methods.

heteroaromatic pharmacores. Today, nearly 20% of FDA-approved drugs contain fluorine [19]. The very strong σ_{sp3} C-F bond (110 kcal/mol) increases the metabolic stability of drugs, enabling better bioavailability and binding affinity [19–22]. Isoquinolines functionalized with fluorine and fluorine-containing groups, the focus of this review, are key pharmacores with many applications. For example, isoquinoline carboxamides labeled with ^{18}F have found use as radiolabeling ligands for positron emission tomography [22]. Additionally, the preparation of fluorinated, fluoroalkylated, and fluoroarylated isoquinoline variants with antibacterial and antiparasitic properties continues to be an area of significant interest to the medicinal chemistry community. Figure 3 contains several examples of medicinally important isoquinoline derivatives which bear fluorine in their structure.

1.4. Recent Synthesis Efforts in the Preparation of Fluorinated Isoquinolines. This review examines a number of fluorinated isoquinoline preparations which capitalize on noncatalyzed reactions and cyclizations as well as those which employ transition metal catalysis to achieve the isoquinoline architecture. As Figure 4 shows, multiple methods that permit construction of the isoquinoline ring A and ring B components have been advanced and will be examined.

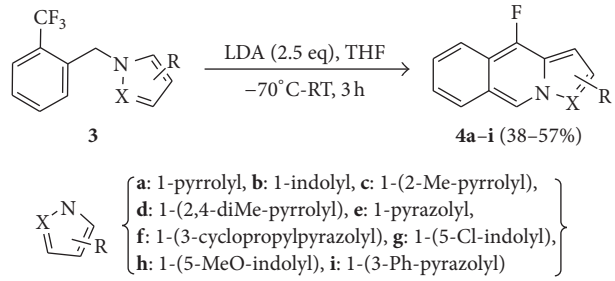
More specifically, we will consider those processes shown in Figure 4 which result in isoquinoline ring fluorinations, di- and trifluoromethylations, fluoroarylations, and trifluoromethylarylations. As Figure 5 indicates, fluorine functionality may be introduced at every carbon center of the isoquinoline core, and more than fifty-five examples will be explored in this review.

We will first examine nontransition metal mediated processes and then discuss the scope of transition metal catalysis in the preparation of fluorine-containing isoquinolines.

2. Ring-Fluorinated, Di- and Trifluoromethylated, Perfluoroalkylated, and Fluoroarylated Isoquinoline Synthesis via Nontransition Metal Mediated Processes

This portion of the review catalogues a broad cross section of isoquinoline preparations reported in the last decade which are not catalyzed by transition metal complexes. Methods

Scheme 1: 1,1-Difluorostyrene aminotosylate cyclization.



Scheme 2: Fused-ring 4-fluoroisoqinoline derivative synthesis.

examined include both intramolecular and intermolecular cycloadditions, tandem reactions, and multicomponent and single-pot processes which produce a wide array of A and B ring-fluorinated, di- and trifluoromethylated, perfluoroalkylated, and fluoroarylated polyfunctional isoquinolines. In addition, several trifluoromethylation and perfluoroalkylation reactions are shown that produce polyfunctional isoquinolines with a high degree of R_f substitution site regioselectivity.

2.1. 3- and 4-Fluoroisoquinolines via Intramolecular Ring A Cyclization at N_2-C_3 and C_3-C_4. Ichikawa and coworkers cyclized the difluoroalkene aminotosylate **1** (Scheme 1) under basic conditions in a 6-endo-trig fashion at N_2-C_3 to obtain the 4-butylated 3-fluoroisoquinoline series **2** in excellent yield [23].

Kiselyov reported a base-promoted intramolecular ring closure of *ortho*-trifluoromethyl benzyl heterocycles **3** en route to nine tricyclic 4-fluoroisoquinoline derivatives **4**. See Scheme 2. The reaction likely proceeds through a C_3-C_4 cyclization of a quinone methide intermediate arising from elimination of fluoride anion [24].

2.2. 6- and 7-Fluoroisoquinolines via Intermolecular Ring A Cyclization at C_{8f}-C_1, N_2-C_3, C_1-N_2, and C_3-C_4. In a recent *Nature* communication, Xie et al. noted that assembly of isoquinoline ring systems at C_{8f}-C_1 and N_2-C_3 by metal-free [4 + 2] cycloadditions was rare [25]. An example of their efforts is shown in Scheme 3, where a microwave-mediated, Brønsted acid-catalyzed [4 + 2] cycloaddition of the *p*-fluorophenyl ynamide **5** and nitriles **6a-b** produces 7-fluoroisoquinolines **7a-b** in good yield. Conversely, Feng and Wu reported in 2016 the base-promoted C_1-N_2 and C_3-C_4

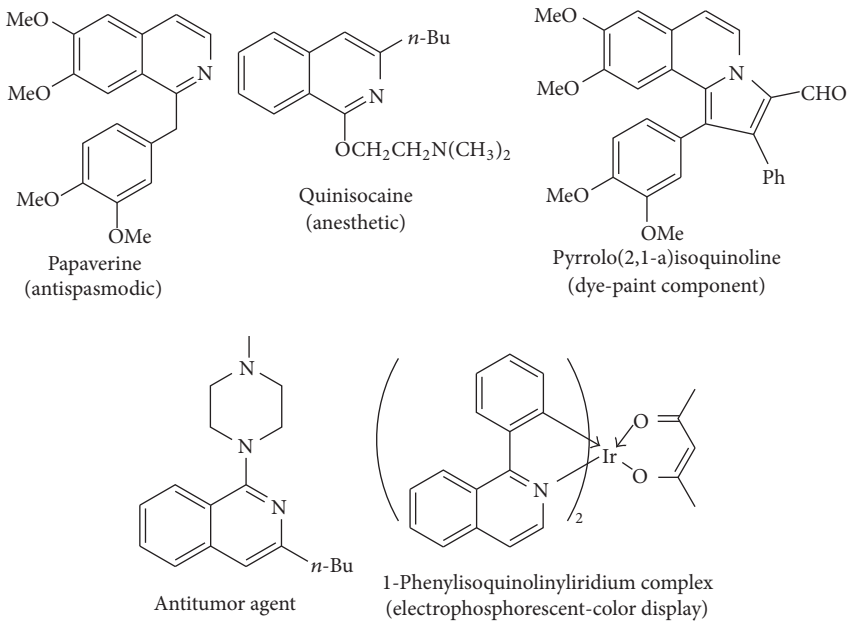


Figure 2: Selected medicinal, agricultural, and industrial isoquinoline derivatives.

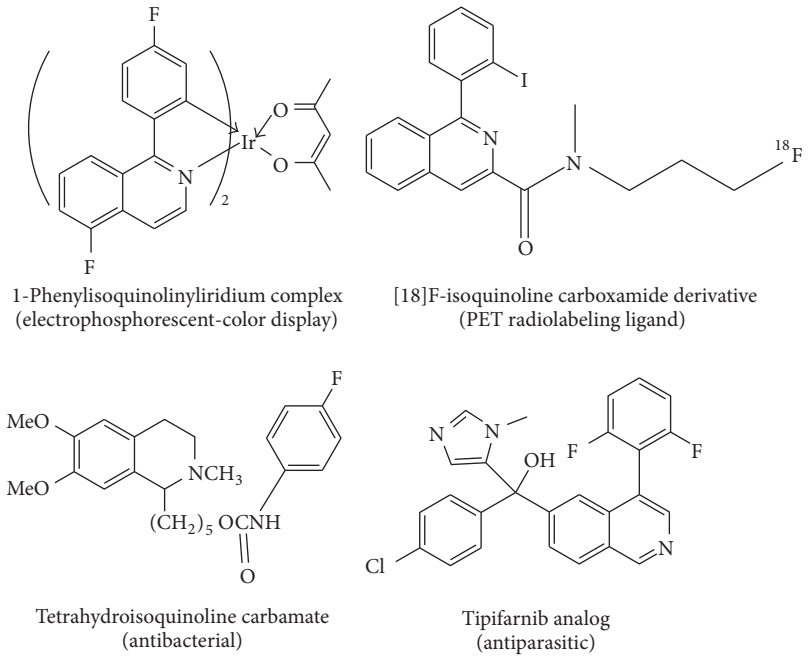


Figure 3: Selected fluorinated isoquinoline derivatives with medicinal and industrial applications.

cycloaddition of benzonitriles **8** and **9** to prepare the 1-amino-isoquinolines **10a**-**b** which are fluorinated at the 6- and 7-positions in moderate yields [26].

Yang et al. employed a tandem C_{8f}-C_1 and C_1-N_2 bond-forming process with azidoacrylate **11** and asymmetric diazo diketone **12** (Scheme 4) to obtain a 1:1 ratio of 7-fluoroisoquinoline isomers **13a** and **13b** in good yield [27]. This interesting reaction cascade begins with the in situ phosphazene formation of **11** via the Staudinger-Meyer reaction with concomitant ketene formation from **12** via a

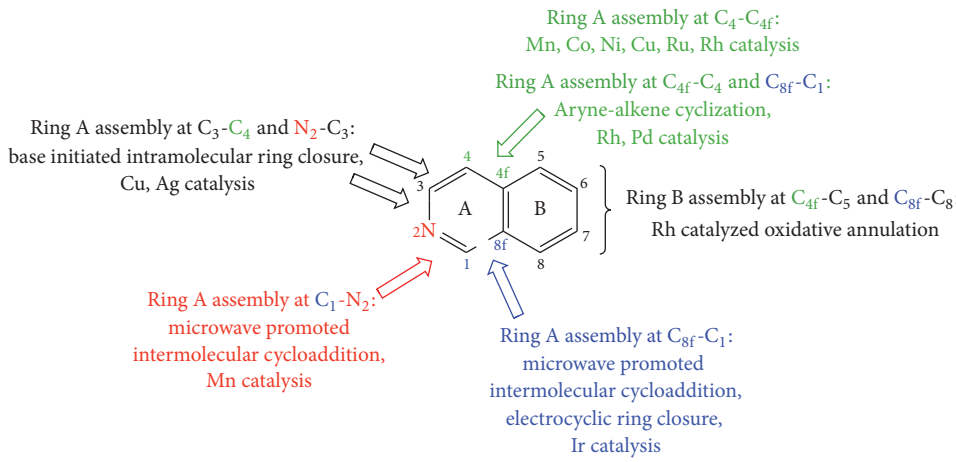


Figure 4: Recent isoquinoline synthesis methods.

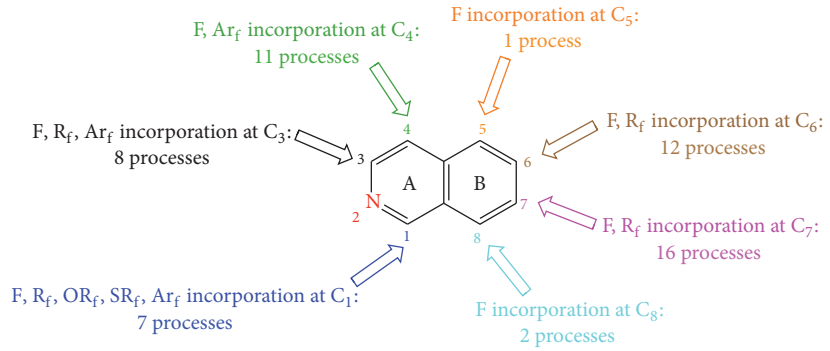
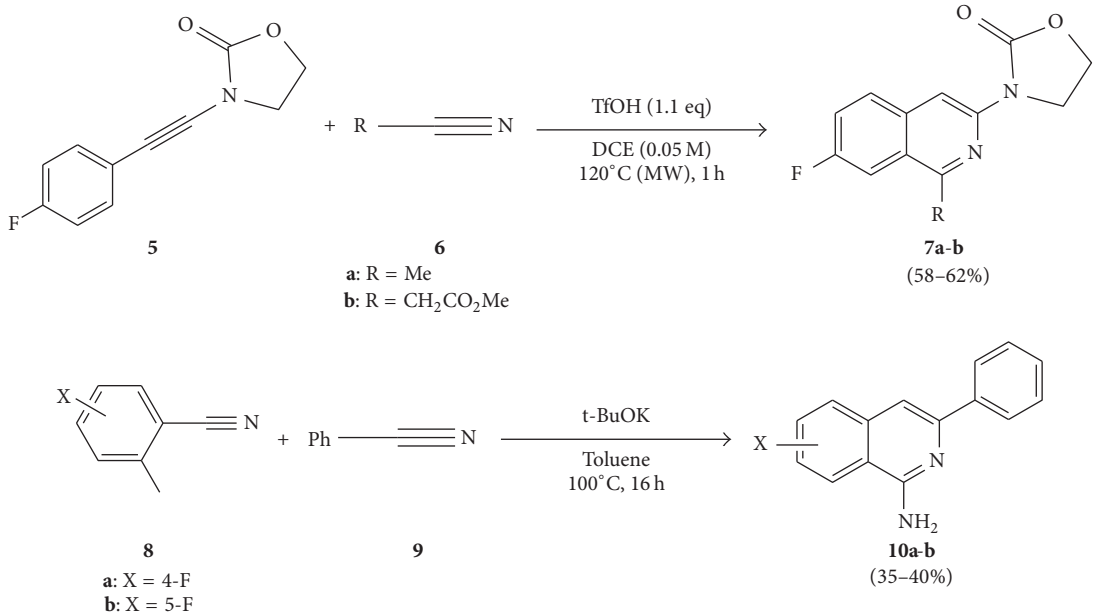
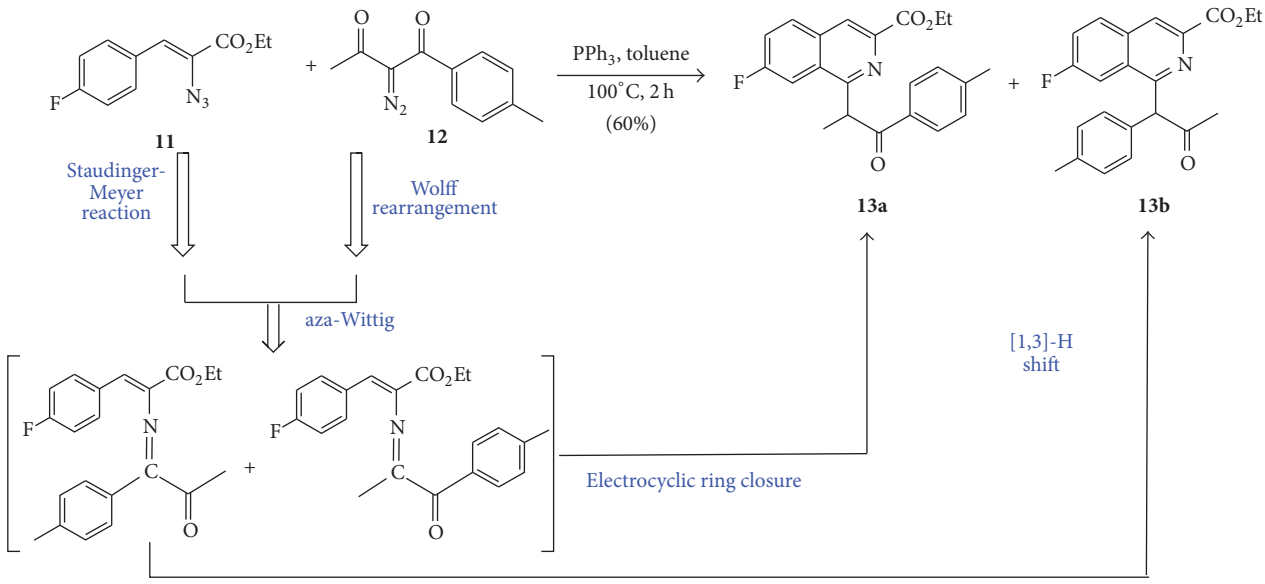


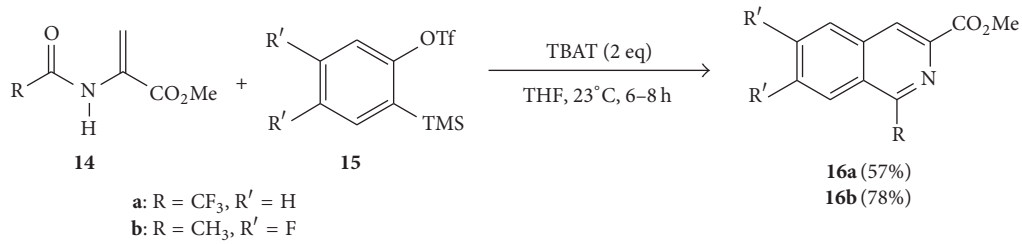
Figure 5: Isoquinoline fluorination, fluoroalkylation, and fluoroarylation sites.



Scheme 3: Preparation of 6- and 7-fluoroisoquinolines via ynamide-nitrile and nitrile-nitrile cycloadditions.



Scheme 4: Triphenylphosphine-mediated 7-fluoroisoquinoline synthesis.



Scheme 5: 6,7-Difluoro- and 1-trifluoromethylisoquinolines via aryne annulation.

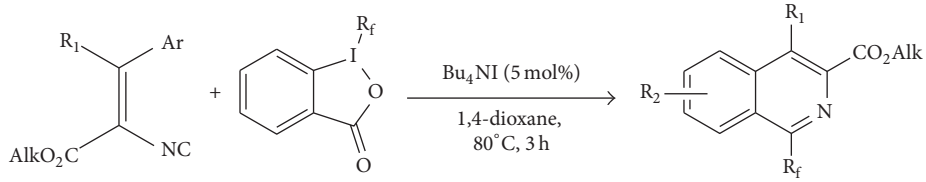
Wolff rearrangement. An aza-Wittig reaction between the phosphazene and ketene yields the isomeric *N*-vinylic ketene imines in brackets. Finally, electrocyclic ring closure and a subsequent [1,3]-H migration leads to the formation of isoquinoline isomers.

2.3. Trifluoromethylated, Ring-Fluorinated, and Perfluorinated Isoquinolines via Inter- and Intramolecular Ring A Cyclizations at C_{8f}-C_1 and C_{4f}-C_4. Stoltz's team leveraged their success in C-C bond insertion reactions to develop a $Bu_4NPh_3SiF_2$ (TBAT) promoted *N*-acyl dehydroamino ester- (**14**) aryne (**15**) C_{8f}-C_1/C_{4f}-C_4 annulation that resulted in the successful synthesis of a series of polysubstituted isoquinolines and indoles [28]. TBAT serves as the fluoride anion source that desilylates **15** to generate the aryne upon loss of the triflate. Scheme 5 depicts the preparation of methyl-3-carboxy-1-trifluoromethylisoquinoline (**16a**) and methyl-3-carboxy-6,7-difluoro-1-methylisoquinoline (**16b**) in good overall yield.

Zhang and Studer [29] recently reported the C_{8f}-C_1 intramolecular cyclization of β-aryl-α-isocyano-acrylates **17** and radical perfluoroalkylation using Togni reagents **18** as the R_f source to produce eighteen examples of highly functionalized 1-trifluoromethyl-, 1-pentafluoroethyl-, and 1-heptafluoropropylisoquinolines **19** in good overall yields. See Scheme 6.

2.4. Preparation of Selectively Trifluoromethylated and Difluoromethylated Isoquinolines at C_1 and C_4. Kuninobu et al. successfully conducted a benzylic trifluoromethylation of the isoquinolinium *N*-oxide **20** using KBF_3CF_3 in BF_3OEt_2 to produce the 1-(2,2,2-trifluoroethyl)isoquinoline **21** in 71% yield [30]. See Scheme 7. As shown in Scheme 8, Ichikawa employed a dehydrogenation treatment of dihydroisoquinoline **22** to achieve the 4-trifluoromethylisoquinoline **23** in high yield. The same substrate was subjected to dehydrofluorination (with subsequent alkene isomerization) to obtain 4-difluoromethylisoquinoline **24** in good yield [31].

2.5. Preparation of 4-Fluoroarylated Isoquinolines. During an examination of tipifarnib analogs for bioactivity, Chennamaneni and coworkers coupled the trityl-protected, tetrahydroisoquinoline **25** with the heterocyclic ketone **26** (Scheme 9) en route to the 4-(2,6-difluorophenyl) isoquinoline **27** in 60% yield [32].



Alk = Me, $R_f = CF_3$

a: R_1 = Ph, R_2 = H
b: R_1 = Ph, R_2 = 6-OMe, 7-OMe
c: R_1 = Ph, R_2 = 7-Cl
d: R_1 = 4-MeC_6H_4, R_2 = 7-Me
e: R_1 = 4-MeOC_6H_4, R_2 = 7-OMe
f: R_1 = 4-ClC_6H_4, R_2 = 7-Cl
g: R_1 = 4-BrC_6H_4, R_2 = 7-Br
h: R_1 = H, R_2 = 7-OMe
i: R_1 = Me, R_2 = H
j: R_1 = Me, R_2 = 7-Me
k: R_1 = *n*-Pr, R_2 = H
l: R_1 = *i*-Pr, R_2 = H
m: R_1 = 4-ClC_6H_4, R_2 = H
n: R_1 = 4-BrC_6H_4, R_2 = H
o: R_1 = cyclohexyl, R_2 = H

Alk = Me, $R_f = CF_2CF_3$

p: R_1 = Ph, R_2 = H

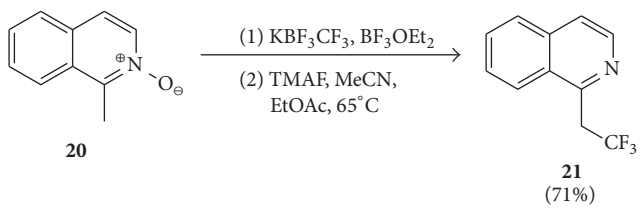
Alk = Me, $R_f = (CF_2)_2CF_3$

q: R_1 = Ph, R_2 = H

Alk = *t*-Bu, $R_f = CF_3$

r: R_1 = Ph, R_2 = H

Scheme 6: 1-Perfluoroalkylisoquinolines via isonitrile cyclization and radical fluoroalkylation.



Scheme 7: Benzylic trifluoromethylation of 1-methylisoquinolinium *N*-oxide.

Using amine **28** and 4-fluorobenzaldehyde shown in Scheme 10, Awuah and Capretta combined microwave conditions and acid-catalysis to condense and cyclize the imine adduct at C_{8f}-C_1 followed by dehydrogenation to produce the 2-(4-fluorophenyl) isoquinoline **29a** in excellent overall yield. In a second reaction, **28** was reacted with 4-fluorophenylacetic acid under microwave conditions in the presence of phosphoryl chloride to prepare the 1-(4-fluorobenzoyl)isoqionoline **29b** in good yield [33].

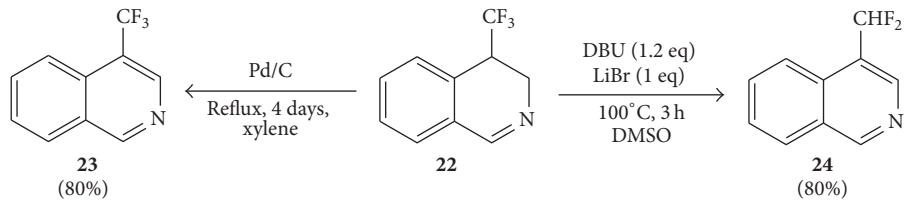
3. Fluorinated, Trifluoromethylated, Fluoroarylated, and Trifluoromethylarylated Isoquinoline Synthesis via Transition Metal Mediated Processes

This section catalogues a representative sample of isoquinoline preparations catalyzed by periods 4, 5, and 6 transition metal complexes. Methods examined include those which produce a wide array of A and B ring-fluorinated, trifluoromethylated, and fluoroarylated polyfunctional isoquinolines. In addition, several selective fluorination and trifluoromethylation reactions, done in concert with transition metal catalysts, are shown that produce polyfunctional isoquinolines with a high degree of fluorination and trifluoromethylation site regiocontrol.

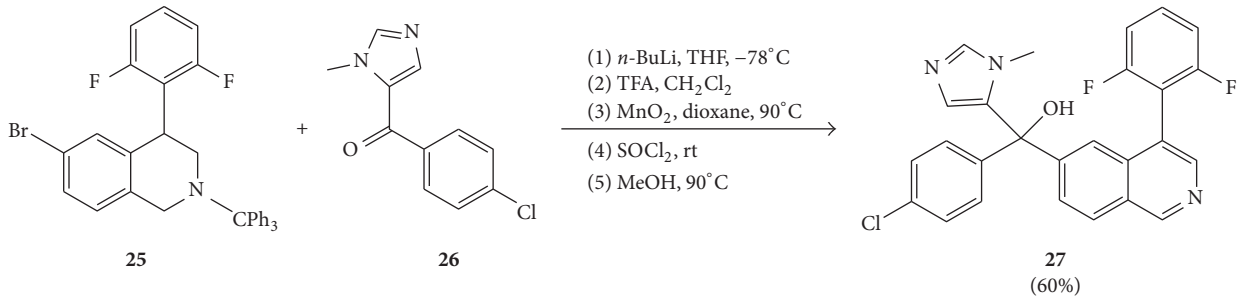
3.1. Period 4 Transition Metal Catalysis: Ring-Fluorinated, Trifluoromethylated, Fluoroarylated, and Trifluoromethylarylated Isoquinolines via Inter- and Intramolecular Ring A Cyclization at N_2-C_3, C_{4f}-C_4, and C_1-C_4

3.1.1. Manganese Catalysis. He et al. researchers utilized the manganese catalyst $MnBn(CO)_5$ in a [4 + 2] annulation at N_2-C_3 and C_{4f}-C_4 of imines **30** and alkynes **31** to prepare six fluorinated isoquinolines **32** in good to excellent yields shown in Scheme 11 [34]. Their strategy affords three ring B fluoroisoquinoline regioisomers (**32a**–**c**) and a trifluoromethylisoquinoline (**32d**) as well as a ring A fluorophenylisoquinoline (**32e**) and a ring A trifluoromethylphenylisoquinoline (**32f**). Mao's group recently reported the manganese catalyzed coupling and cyclization of vinyl isocyanides **33** and assorted arylhydrazines **34** en route to three new examples of 7-fluoroisoqinoline **35a**, the 1-(4-fluorophenyl)-isoquinoline **35b**, and the 1-(4-trifluoromethylphenyl)-isoquinoline **35c** in good overall yields [35].

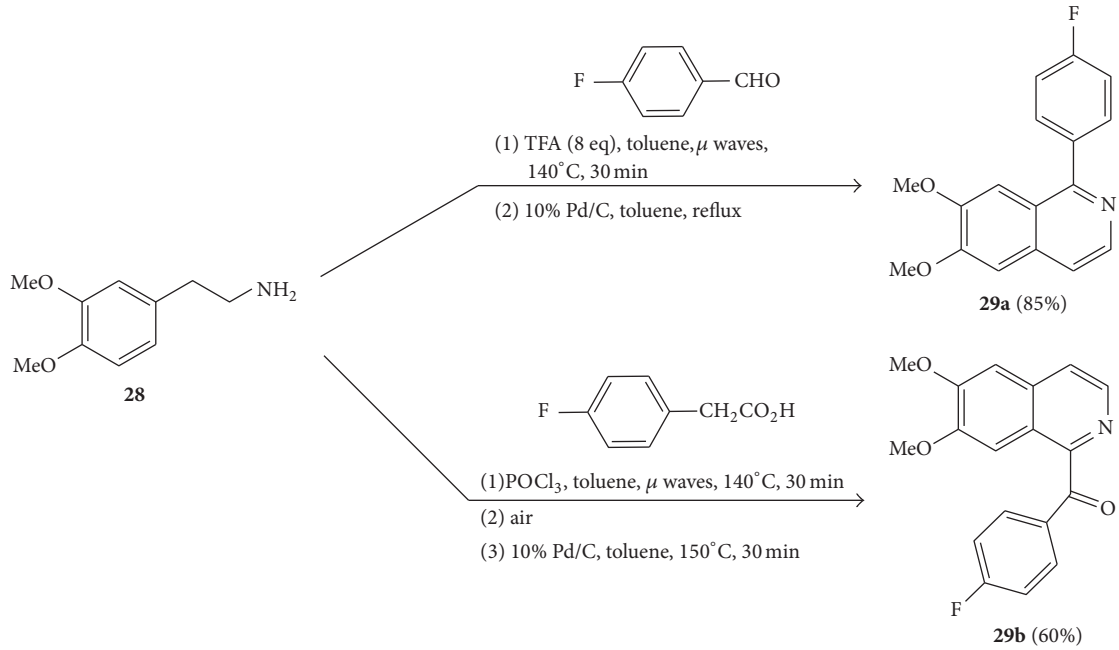
3.1.2. Cobalt Catalysis. Cobalt (III) catalysis has been effectively utilized in N_2-C_3 and C_{4f}-C_4 bond formation/cyclizations of oximes, amidines, and hydrazones to prepare a broad array of isoquinolines bearing fluorine and fluorine-containing groups. Examples are depicted in Scheme 12. Sun and coworkers used $Cp*CoI_2(CO)$ to catalyze the regioselective cyclization of the acyl oxime series **36** with both internal and terminal alkynes **37** en route to a diverse set



Scheme 8: Preparation of 4-trifluoromethyl- and 4-difluoromethylisoquinolines.



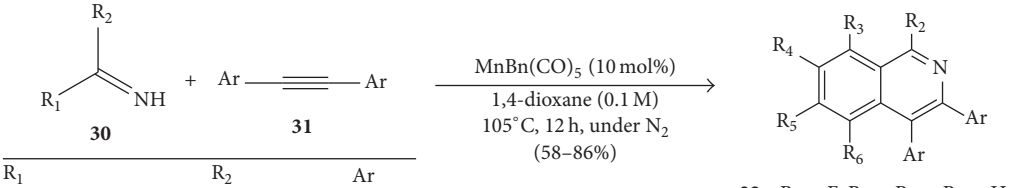
Scheme 9: Preparation of difluoroarylated tipifarnib analog.



Scheme 10: Synthesis of fluorophenyl- and fluorobenzoylisoquinolines.

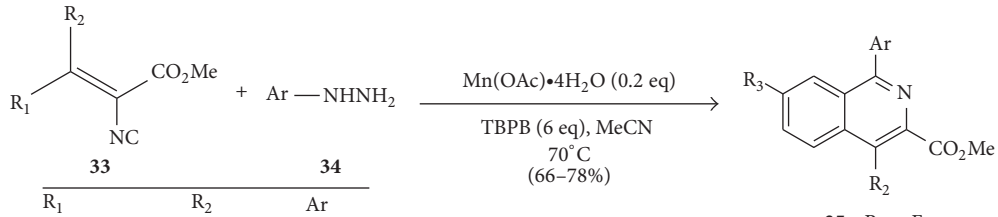
of eleven fluorine-containing isoquinolines **38** [36]. Li's team used the same catalyst system with a slightly different base to couple aryl amidines **39** and diazo compounds **40** to deliver five examples of monofluorinated and trifluoromethylated 1-aminoisoquinolines **41** in fair to excellent yields [37]. Pawar et al. just released a study of Co(III)-catalyzed C–H/N–N bond functionalization of arylhydrazones **42** with internal alkynes **43** for the synthesis of three ring-fluorinated and fluoroarylated isoquinoline derivatives **44** in very good yields [38], while a 2016 report by Yu et al. catalogued the cycloaddition of oxadiazolones **45** with alkynes **46** to prepare eight ring-fluorinated, trifluoromethylated, and fluoroarylated isoquinolines **47** in yields ranging from 45 to 85% [39]. The relatively mild reaction conditions used in these processes permit toleration of a wide scope of substrates.

3.1.3. Nickel Catalysis. Yoshida's group conducted a nickel catalyzed, N_2-C_3/C_{4f}-C_4 bond formation/cycloaddition of



R_1	R_2	Ar
a: 4-FC_6H_4	*n*-Bu	Ph
b: 3-FC_6H_4	*n*-Bu	Ph
c: 2-FC_6H_4	*n*-Bu	Ph
d: 3-$CF_3C_6H_4$	*n*-Bu	Ph
e: 4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-FC_6H_4
f: 4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$CF_3C_6H_4$

32a: R_5 = F, R_3 = R_4 = R_6 = H
32b: R_4 = F, R_3 = R_5 = R_6 = H
32c: R_3 = F, R_4 = R_5 = R_6 = H
32d: R_4 = CF_3, R_3 = R_5 = R_6 = H
32e: R_4 = MeO, R_3 = R_5 = R_6 = H
32f: R_4 = MeO, R_3 = R_5 = R_6 = H



R_1	R_2	Ar
a: 4-FC_6H_4	4-FC_6H_4	Ph
b: Ph	Ph	4-FC_6H_4
c: Ph	Ph	4-$CF_3C_6H_4$

35a: R_3 = F
35b: R_3 = H
35c: R_3 = H

Scheme 11: Manganese catalyzed fluoroisoquinoline synthesis.

aromatic ketoximes **48** with 4-octyne **49** to prepare fluorine-containing isoquinolines **50a** and **50b** in good overall yield [40]. See Scheme 13.

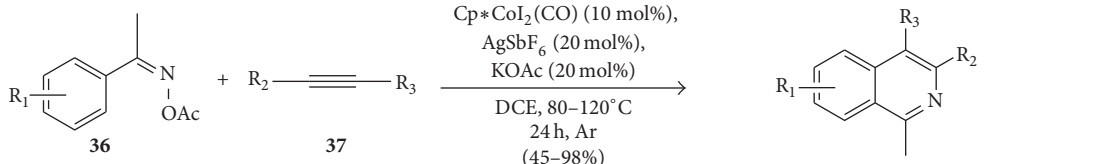
3.1.4. Copper Catalysis. Ohto et al. developed a copper(I)-catalyzed four-component coupling reaction whereby 2-ethynylbenzaldehydes **51**, paraformaldehyde, diisopropylamine, and *t*-$BuNH_2$ were cyclized at N_2-C_3 to give 6-fluoro- and 7-fluoroisoquinolines **52** [41]. See Scheme 14. Fan et al. used isoquinoline-*N*-oxides **53** and the Togni reagent **54** catalyzed by copper(II) triflate, to prepare sixteen 1-(trifluoromethyl)isoquinolines **55** [42]. Mormino et al. subjected 3-bromoisoquinoline **56** to the phenanthroline-ligated copper trifluoromethylating reagent (phen)$CuCF_3$ **57**, preparing the 4-trifluoromethylisoquinoline **58** via a radical substitution [43]. These processes provide the target isoquinolines in good overall yields.

3.2. Period 5 Transition Metal Catalysis: Ring-Fluorinated, Trifluoromethylated, Fluoroarylated, and Trifluoromethylarylated Isoquinolines via Inter- and Intramolecular Ring A Cyclization at N_2-C_3, C_{4f}-C_4, C_{8f}-C_8, and C_1-C_4

3.2.1. Ruthenium Cataliysis. Scheme 15 depicts two ruthenium catalyzed cyclizations to produce fluorine-containing isoquinolines via N_2-C_3 and C_{4f}-C_4 bond formation. He et al. cyclized several diaryl imines **59** with diarylacetylenes **60** with a ruthenium catalyst to prepare six tetrasubstituted, ring-fluorinated, trifluoromethylated, fluoroarylated, and trifluoromethylarylated isoquinolines **61** in yield ranging from 40 to 86% [44]. Chinnagolla and coworkers used a similar methodology and cyclized several diaryl imine chlorides **62** with diarylacetylenes **63** with a ruthenium catalyst to prepare a series of six tetrasubstituted trifluoroethoxyisoquinolines **64** in yield ranging from 61 to 81% [45].

3.2.2. Rhodium Catalysis. Two rhodium-catalyzed preparations of isoquinolines that incorporate fluorine and trifluoromethyl groups are shown in Scheme 16. Qian's group conducted a rhodium-catalyzed C_{8f}-C_8/C_{4f}-C_4 annulation of fluoropicolinamide **65** with diphenylacetylene **66** to produce the tetraphenyl 4-fluoroisoquinoline **67** in excellent yield [46]. Guimond and Fagnou performed a highly efficient rhodium-catalyzed oxidative cross-coupling and C_{4f}-C_4/N_2-C_3 cycloaddition of aldimines **68** and 4-octyne **69** en route to 6-fluoro- and 6-trifluoromethylisoquinolines **70a** and **70b** [47]. These catalyzed processes are believed to occur via a sequence involving Rh (III) insertion followed by reductive elimination/electrocyclization to produce the isoquinolines.

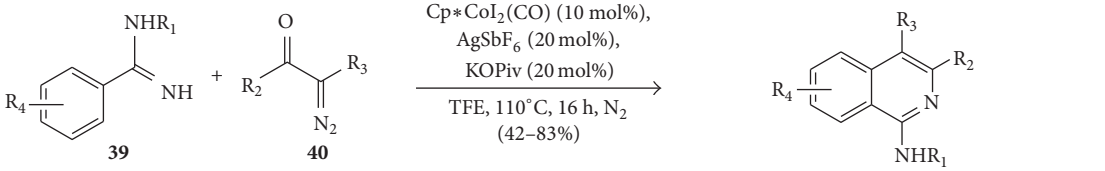
3.2.3. Palladium Catalysis. Scheme 17 depicts work conducted by Pilgrim and coworkers in which the protected aryl bromide series **71**, acetophenone **72**, an electrophile, and ammonium chloride were combined in a palladium catalyzed, three-step, one-pot C_{4f}-C_4/N_2-C_3 cycloaddition process to furnish ring-fluorinated isoquinoline **73a**, a trifluoromethylated isoquinoline **73b,** and trifluoromethylarylated isoquinolines **73c–d** in overall yields ranging from 46 to 73% [48]. This procedure begins with the arylation reaction of an enolate, followed by reaction with Selectfluor II,



36 **37**

a: R_1 = 3-Cl, R_2 = 4-FC_6H_4, R_3 = H
b: R_1 = 3-Br, 4-F, R_2 = 2-MeC_6H_4, R_3 = H
c: R_1 = 3-CF_3, R_2 = 2-MeC_6H_4, R_3 = H
d: R_1 = 3-CF_3, R_2 = $(CH_2)_2Ph$, R_3 = H
e: R_1 = 3-CF_3, R_2 = $(CH_2)_2Me$, R_3 = H
f: R_1 = 3-CF_3, R_2 = $(CH_2)_4Me$, R_3 = H
g: R_1 = 3-CF_3, R_2 = cyclohexyl, R_3 = H
h: R_1 = 3-CF_3, R_2 = R_3 = Ph
i: R_1 = 4-Cl, R_2 = 4-FC_6H_4, R_3 = H
j: R_1 = 4-F, R_2 = Ph, R_3 = H
k: R_1 = 4-CF_3, R_2 = Ph, R_3 = H

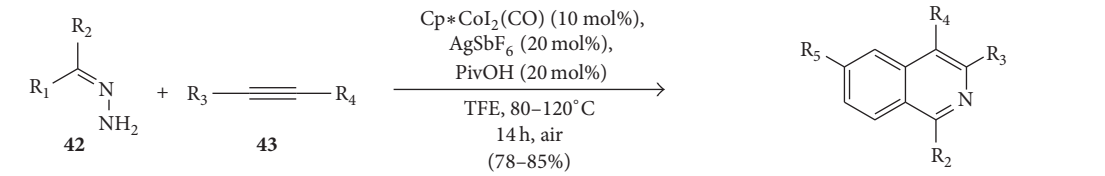
38a: R_1 = 7-Cl, R_2 = 4-FC_6H_4, R_3 = H
38b: R_1 = 7-Br, 4-F, R_2 = 2-MeC_6H_4, R_3 = H
38c: R_1 = 7-CF_3, R_2 = 2-MeC_6H_4, R_3 = H
38d: R_1 = 7-CF_3, R_2 = $(CH_2)_2Ph$, R_3 = H
38e: R_1 = 7-CF_3, R_2 = $(CH_2)_2Me$, R_3 = H
38f: R_1 = 7-CF_3, R_2 = $(CH_2)_4Me$, R_3 = H
38g: R_1 = 7-CF_3, R_2 = cyclohexyl, R_3 = H
38h: R_1 = 7-CF_3, R_2 = R_3 = Ph
38i: R_1 = 6-Cl, R_2 = 4-FC_6H_4, R_3 = H
38j: R_1 = 6-F, R_2 = Ph, R_3 = H
38k: R_1 = 6-CF_3, R_2 = Ph, R_3 = H



39 **40**

a: R_1 = *t*-Bu, R_2 = Me, R_3 = CO_2Et, R_4 = 4-F
b: R_1 = *t*-Bu, R_2 = Me, R_3 = CO_2Et, R_4 = 3-F
c: R_1 = *t*-Bu, R_2 = Me, R_3 = CO_2Et, R_4 = 3-CF_3
d: R_1 = *t*-Bu, R_2 = Me, R_3 = CO_2Et, R_4 = 2-F
e: R_1 = *t*-Bu, R_2 = H, R_3 = Ph, R_4 = 4-F

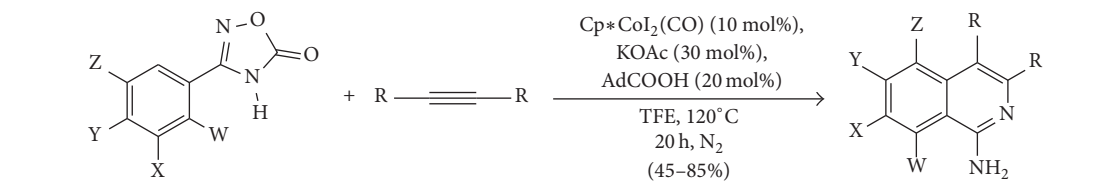
41a: R_1 = *t*-Bu, R_2 = Me, R_3 = CO_2Et, R_4 = 6-F
41b: R_1 = *t*-Bu, R_2 = Me, R_3 = CO_2Et, R_4 = 7-F
41c: R_1 = *t*-Bu, R_2 = Me, R_3 = CO_2Et, R_4 = 7-CF_3
41d: R_1 = *t*-Bu, R_2 = Me, R_3 = CO_2Et, R_4 = 8-F
41e: R_1 = *t*-Bu, R_2 = H, R_3 = Ph, R_4 = 6-F



42 **43**

a: R_1 = R_2 = Ph, R_3 = R_4 = 4-$CF_3C_6H_4$
b: R_1 = R_2 = 4-FC_6H_4, R_3 = R_4 = Ph
c: R_1 = R_2 = Ph, R_3 = R_4 = 4-FC_6H_4

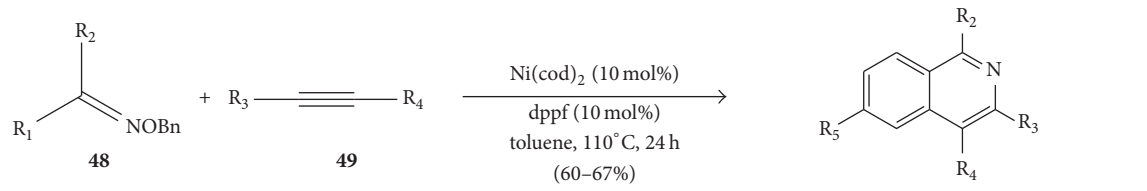
44a: R_2 = Ph, R_3 = R_4 = 4-$CF_3C_6H_4$, R_5 = H
44b: R_2 = 4-FC_6H_4, R_3 = R_4 = Ph, R_5 = F
44c: R_2 = Ph, R_3 = R_4 = 4-FC_6H_4, R_5 = H



45 **46** **47a–h**

a: Y = F, W = X = Z = H	R = Ph
b: Y = 4-CF_3, W = X = Z = H	R = Ph
c: W = F, X = Y = Z = H	R = Ph
d: Y = 4-CF_3,W = X = Z = H	R = Ph
e: W = H, X = Y = Z = F	R = Ph
f: Y = Cl, W = X = Z = H	R = 4-FC_6H_4
g: Y = Cl, W = X = Z = H	R = 2-FC_6H_4
h: Y = Cl, W = X = Z = H	R = 3-FC_6H_4

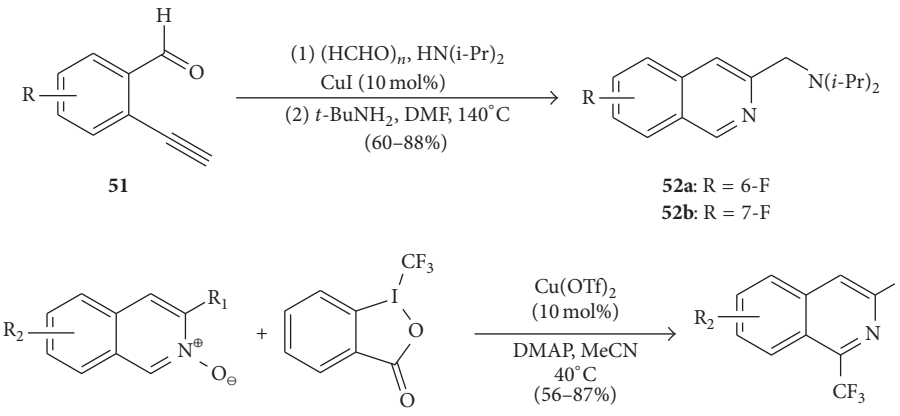
Scheme 12: Cobalt catalyzed fluoroisoquinoline syntheses.



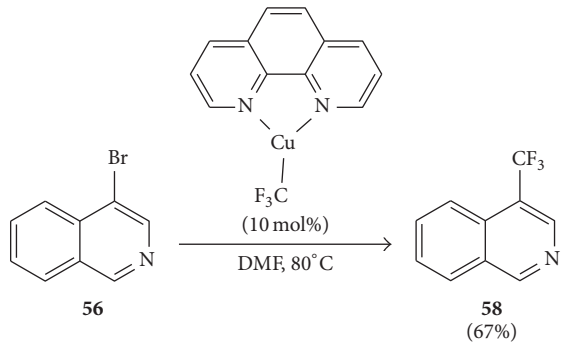
a: $R_1 = R_2 = 4\text{-}FC_6H_4$, $R_3 = R_4 = Pr$
b: $R_1 = 4\text{-}FC_6H_4$, $R_2 = 4\text{-}MeOC_6H_4$, $R_3 = R_4 = Pr$

50a: $R_2 = 4\text{-}FC_6H_4$, $R_3 = R_4 = Pr$, $R_5 = F$
50b: $R_2 = 4\text{-}MeOC_6H_4$, $R_3 = R_4 = Pr$, $R_5 = F$

Scheme 13: Nickel catalyzed 6-fluoro and 1-(4-fluorophenyl)isoquinoline synthesis.



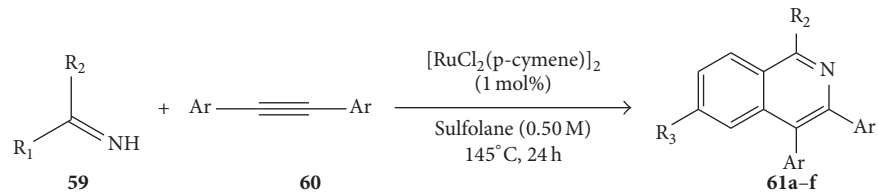
a: R_1 = Ph, R_2 = H
b: R_1 = Ph, R_2 = 6-OMe, 7-OMe
c: R_1 = Ph, R_2 = 7-Cl
d: R_1 = Ph, R_2 = 7-Me
e: R_1 = *t*-Bu, R_2 = H
f: R_1 = *n*-Bu, R_2 = 7-Cl
g: R_1 = Ph, R_2 = 7-F
h: R_1 = Ph, R_2 = 6-F
i: R_1 = Ph, R_2 = 5-OMe
j: R_1 = *t*-Bu, R_2 = H
k: R_1 = *n*-Bu, R_2 = 7-Cl
l: R_1 = *p*-Anisyl, R_2 = H
m: $R_1 = p\text{-}ClC_6H_4$, R_2 = H
n: R_1 = cyclopropyl, R_2 = H
o: R_1 = cyclopropyl, R_2 = 7-F
p: R_1 = cyclopropyl, R_2 = 7-Cl



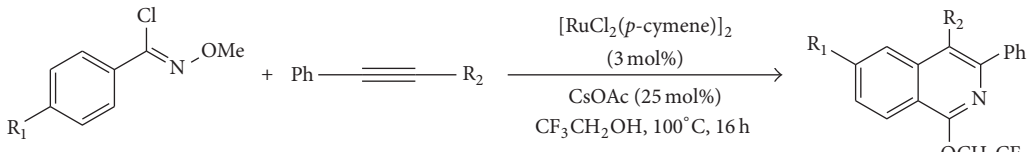
Scheme 14: Copper catalyzed fluoroisoquinoline synthesis.

allyl bromide, or 4-bromobenzotrifluoride, respectively, and aromatization with ammonium chloride.

Scheme 18 shows two $Pd(OAc)_2$ catalyzed isoquinoline producing cyclizations. Tian et al. developed an efficient, Pd-catalyzed Heck reaction in which the 2-triflate substituted aryl ketone series **74** was coupled and intramolecularly cyclized with enamine **75** at C_{4f}-C_4/N_2-C_3 and isomerized to produce four examples of ring-fluorinated and fluoroarylated isoquinolines **76** [49]. Yang's group conducted a palladium catalyzed, microwave-assisted, one-pot reaction via a C_{4f}-C_4/N_2-C_3 cyclization for the synthesis of isoquinolines [50]. The coupling-imination-annulation sequence of reactions using *o*-bromoarylaldehydes **77** and terminal alkynes **78** with ammonium acetate produced three disubstituted

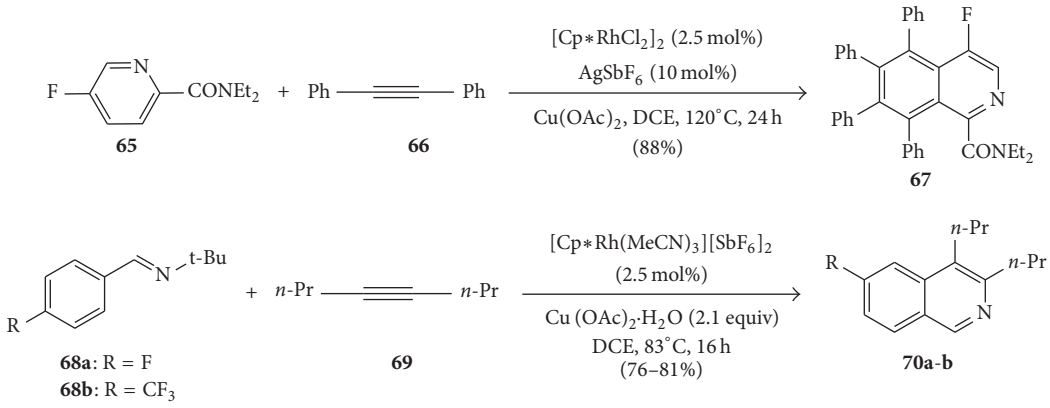


R_1	R_2	Ar	R_3
a: 4-FC_6H_4	4-FC_6H_4	Ph	F
b: 4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	Ph	CF_3
c: 4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-FC_6H_4	MeO
d: 4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$CF_3C_6H_4$	MeO
e: 4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ph, 4-$CF_3C_6H_4$	MeO
f: 4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$CF_3C_6H_4$, 4-$CH_3C_6H_4$	MeO



a: R_1 = F, R_2 = Me
b: R_1 = Cl, R_2 = Et
c: R_1 = Cl, R_2 = *n*-Bu
d: R_1 = Cl, R_2 = allyl
e: R_1 = Cl, R_2 = Ph
f: R_1 = Br, R_2 = Ph

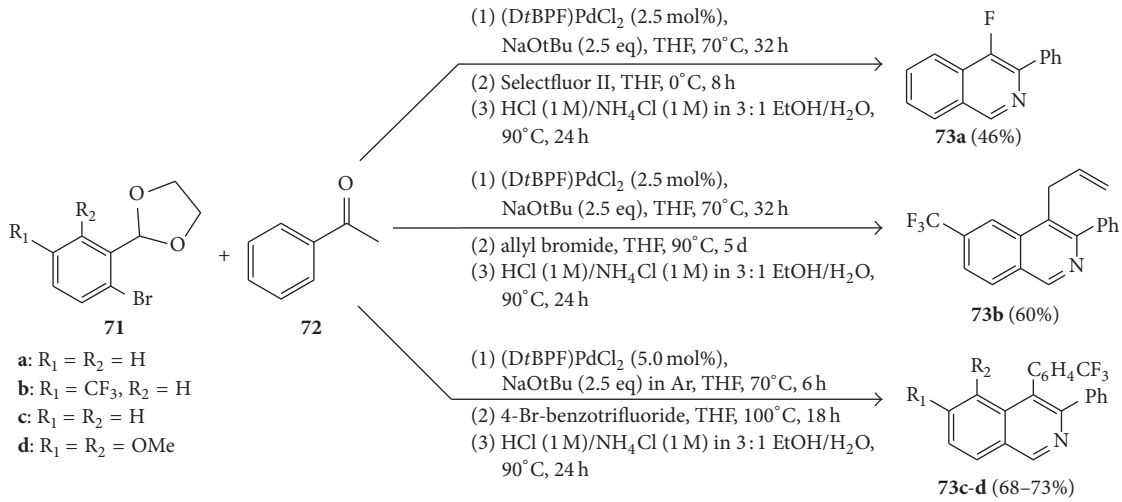
Scheme 15: Ruthenium catalyzed fluoroisoquinoline and trifluoromethylisoquinoline synthesis.



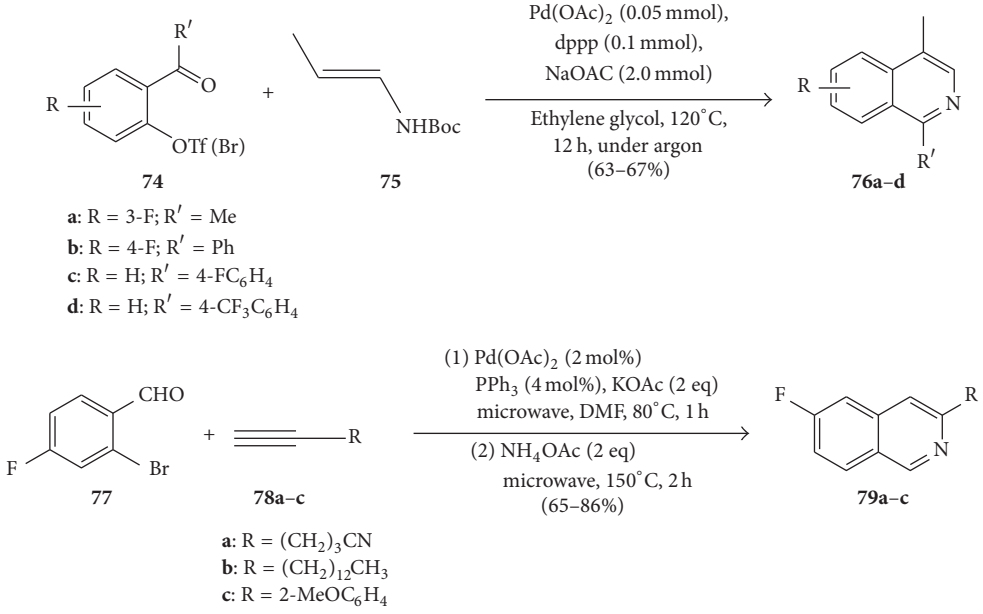
Scheme 16: Rhodium-catalyzed fluoroisoquinoline and trifluoroisoquinoline synthesis.

6-fluoroisoquinolines **79**. These reactions feature a wide range of substrates with various functional groups, and the corresponding products were obtained in good yields.

3.2.4. Silver Catalysis. Several silver (I) catalyzed N_2-C_3 cyclizations of *o*-iminylaryl alkynes have been employed successfully to prepare a broad selection of fluorinated, trifluoromethylthiolated, fluoroarylated, and trifluoromethylarylated isoquinolines. See Scheme 19. Xiao et al. used a silver(I)-catalyzed reaction of 2-alkynylbenzaldoximes **80** with silver (trifluoromethyl)thiolate **81** in the presence of *p*-methoxybenzenesulfonyl chloride to synthesize eleven new 1-[(trifluoromethyl)thio]isoquinolines **82** in yields ranging from 36 to 85% [51]. Xu and Lui utilized an Ag(I)-catalyzed, NFSI aminofluorination of aryliminoalkynes **83** in the development of an efficient synthesis of thirteen examples of 4-fluoroisoquinolines **84** [52]. Jeganathan and Pitchumani used a Ag(I)-exchanged K10-montmorillonite clay catalyzed ring



Scheme 17: Di-t-butylphosphinoferrocene-based palladium catalyzed fluoroisoquinoline and trifluoromethylisoquinoline syntheses.



Scheme 18: $Pd(OAc)_2$ catalyzed fluoroisoquinoline syntheses.

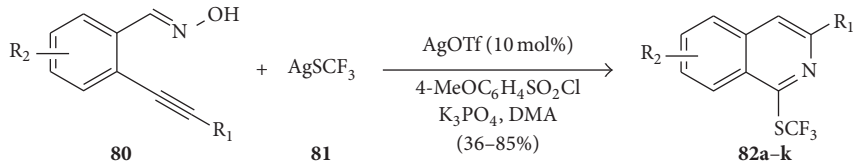
closure of iminoalkynes **85** to prepare three fluoroarylated isoquinolines **86** in good overall yield [53]. This effective cyclization accommodates a variety of iminoalkynes and is noteworthy for its catalyst reusability, simplicity, and environmentally responsible process.

3.3. Period 6 Transition Metal Catalyzed Ring-Fluorinated, Trifluoromethylated, and Fluoroarylated Isoquinolines via Intermolecular Ring A Cyclization at C_{8f}-C_1

3.3.1. Iridium Catalysis. Our final entry highlighted in Scheme 20 is the iridium catalyzed fluoroisoquinoline synthesis via a C_{8f}-C_1 bond-forming/cyclization reaction, conducted by Jiang et al. [54]. This synthesis uses a visible light-promoted insertion of vinyl isocyanides **87** with diphenyliodonium tetrafluoroborate **88** at room temperature to prepare six multisubstituted ring-fluorinated, trifluoromethylated, and fluoroarylated isoquinoline derivatives **89**.

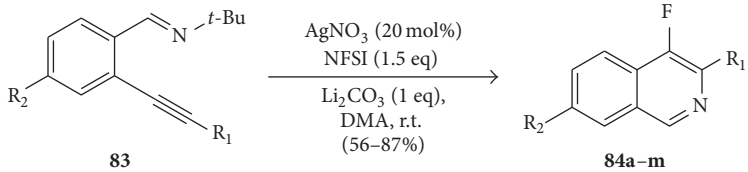
4. Conclusion

The past decade has been a period of intense exploration of new approaches to the preparation of industrially and medicinally important isoquinolines which incorporate fluorine and fluorine-containing functional groups. This review has examined both nonmetal catalyzed and transition metal catalyzed processes that lead to a wide array of isoquinolines that have fluorine and fluorine-containing groups installed at nearly every position on the fused-ring isoquinoline heterocycle. The reactions reviewed span processes which construct the



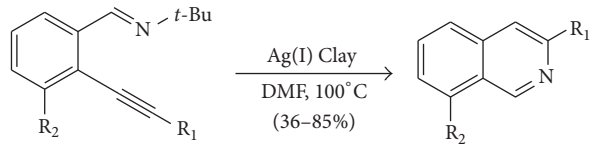
80 **81** **82a–k**

a: R_1 = Ph, R_2 = H
b: R_1 = 4-MeC_6H_4, R_2 = H
c: R_1 = 4-$MeOC_6H_4$, R_2 = H
d: R_1 = 4-FC_6H_4, R_2 = H
e: R_1 = 4-ClC_6H_4, R_2 = H
f: R_1 = cyclopropyl, R_2 = H
g: R_1 = *n*-butyl, R_2 = H
h: R_1 = Ph, R_2 = Me
i: R_1 = Ph, R_2 = OMe
j: R_1 = Ph, R_2 = F
k: R_1 = Ph, R_2 = Cl



83 **84a–m**

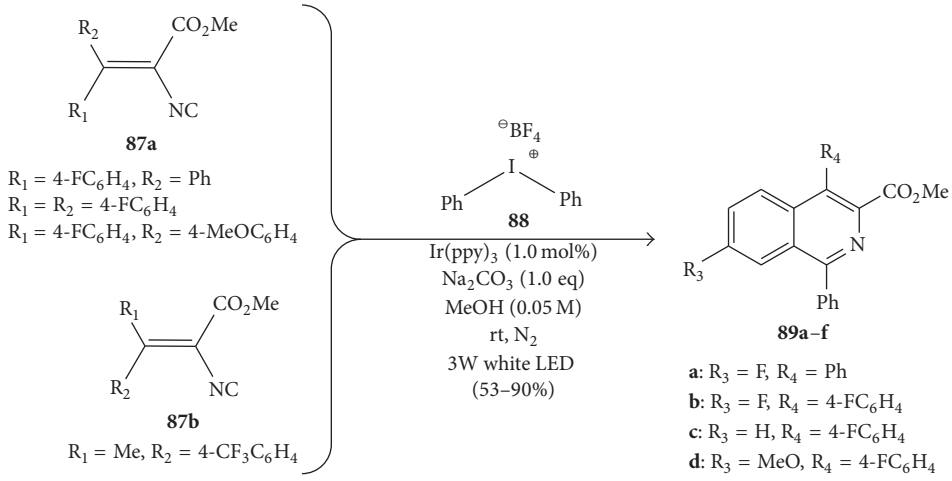
a: R_1 = Bu, R_2 = H
b: R_1 = Bu, R_2 = Cl
c: R_1 = Bu, R_2 = F
d: R_1 = Bu, R_2 = OMe
e: R_1 = *t*-Bu, R_2 = H
f: R_1 = Ph, R_2 = H
g: R_1 = $CH_2NTsBoc$, R_2 = H
h: R_1 = CH_2CH_2OAc, R_2 = H
i: R_1 = $(CH_2)_3CO_2Me$, R_2 = H
j: R_1 = *p*-Anisyl, R_2 = H
k: R_1 = *p*-FC_6H_4, R_2 = H
l: R_1 = cyclohexenyl, R_2 = H
m: R_1 = cyclopropyl, R_2 = H



85 **86a–c**

a: R_1 = 4- $CF_3C_6H_4$, R_2 = H
b: R_1 = 3-$CF_3C_6H_4$, R_2 = H
c: R_1 = 3-FC_6H_4, R_2 = OMe

Scheme 19: Silver catalyzed fluoroisoquinoline syntheses.



Scheme 20: Iridium catalyzed fluoroisoquinoline and trifluoromethylisoquinoline syntheses.

isoquinoline core via both A ring and B ring cyclizations. Additionally, these investigations have led to the discovery of milder reaction conditions, improved yields, enhanced regioselectivity, and site-specific ring monofluorination as well as difluoromethylation, trifluoromethylation, perfluoroalkylation, fluoroarylation, and trifluoromethylarylation examples. In all, more than 30 processes producing over 160 new isoquinoline examples have been highlighted.

Competing Interests

The author declares that there are no competing interests regarding the publication of this paper.

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