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SYNTHETIC METHODS FOR RING-FLUORINATED PYRROLE DERIVATIVES

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Abstract – The synthesis of pyrrole ring-fluorinated heterocyclic compounds has been increasingly studied in response to the rising demand for these compounds as potential drugs, agrochemicals, and advanced materials. The approaches to their synthesis are grouped into two categories in terms of how the fluorine substituents are introduced: (i) direct fluorination of the existing pyrrole and related rings and (ii) the construction of pyrrole rings via fluorine-containing precursors. This review overviews recent synthetic methods for ring-fluorinated pyrrole derivatives according to the types of reactions.

CONTENTS

1. INTRODUCTION

Ring-fluorinated pyrroles and indoles have recently attracted much attention in pharmaceutical and agrochemical sciences. This interest has presumably originated because these compounds are hybrids of 5-membered nitrogen heterocycles and fluorine-containing compounds, both of which are considered to

be important components of bioactive compounds. A number of 3-fluorinated pyrrole derivatives, including 3-fluoroindoles, have been expected to serve as drugs for various cancers (Figure 1a),[1] mosquito-borne diseases (Figure 1b),[2] thrombosis (Figure 1c),[3] and botulism (Figure 1d).[4] Among 2-fluorinated pyrrole derivatives, a small number of 2-fluoroindoles have been studied as promising candidates for immune-response activators (Figure 1e).[5]

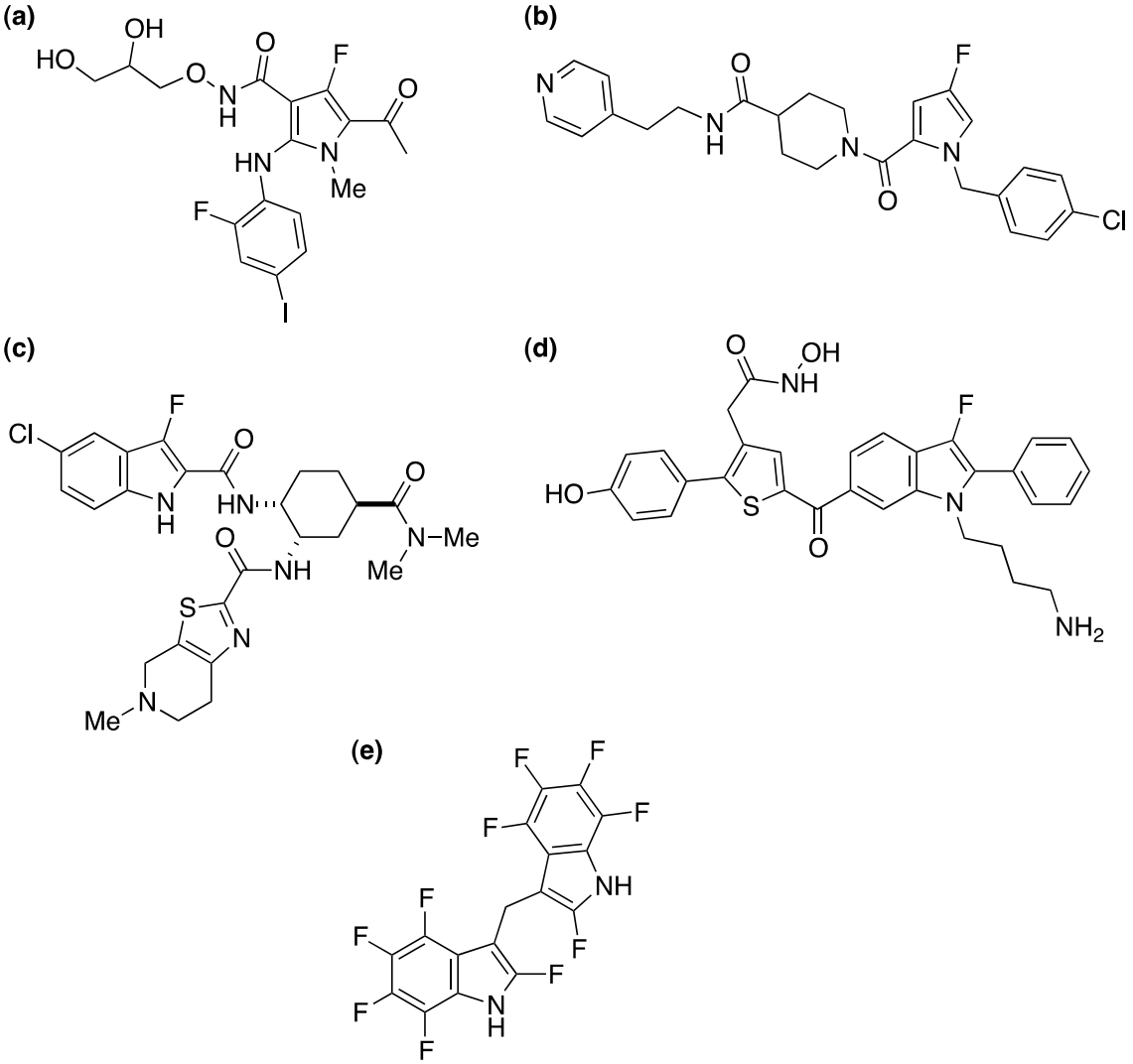


Figure 1. Bioactive ring-fluorinated pyrroles and indoles

Moreover, some 3-fluoropyrroles and their metal complexes show significant potential for use in materials science applications. While 3-fluoropyrroles, such as a tetrafluorodipyrrolylquinoxaline (Figure 2a),[6] an octafluorocalix[4]pyrrole (Figure 2b),[6,7] and a (tetrafluorodipyrrolyl-1,3-propanedionato)boron complex (Figure 2c),[8–11] have played roles as anion receptors, a cobalt(III) octafluorocorrole complex was used as a catalyst for the hydrogen evolution reaction from water (Figure 2d).[12] These findings on the potential utilities of ring-fluorinated pyrroles and indoles are attributed to steady accumulation of synthetic methodology for fluorine-containing heterocyclic compounds.

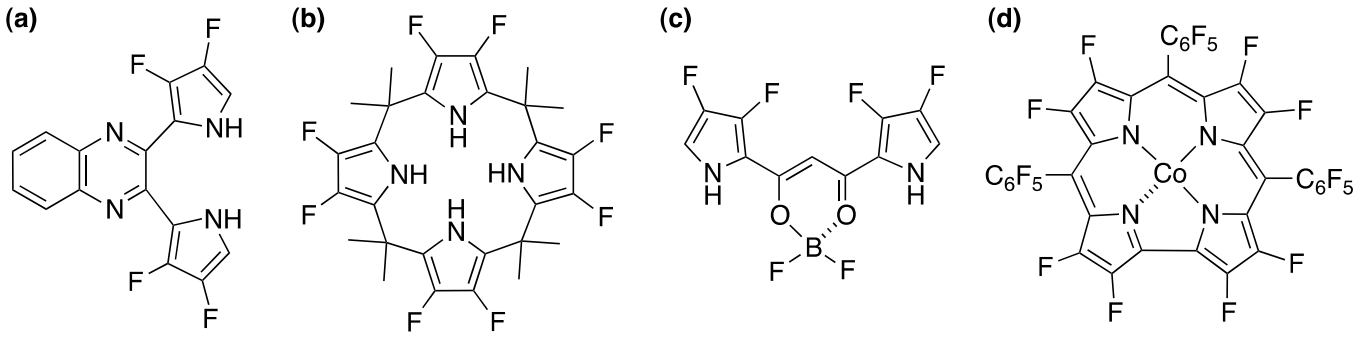


Figure 2. 3-Fluoropyrroles used as materials

The synthetic methods for heterocyclic ring-fluorinated pyrroles and indoles are grouped into two major categories: (i) direct fluorination of the existing pyrrole and related rings and (ii) the construction of pyrrole rings via cyclization of fluorine-containing precursors. The former methods (i) that involve the direct fluorination of rings have long been commonly used for the syntheses of ring-fluorinated pyrroles and indoles. In these methods, both electrophilic fluorination by fluorine cation equivalents and nucleophilic fluorination by fluorides are possible. In contrast, we and other groups have recently developed methods for the construction of ring-fluorinated pyrrole frameworks via cyclization of fluorine-containing precursors. These latter methods (ii) enable the simultaneous construction of pyrrole rings and regioselective installation of fluorine substituents. This review describes synthetic methodologies for pyrrole ring-fluorinated heterocycles, divided into the aforementioned two categories. Since we focus on heteroaromatic ring-fluorinated compounds, benzene ring-fluorinated compounds, non-aromatic compounds,[13,14] and fluorinated porphyrins (and their analogues)[15] are not covered in this review.

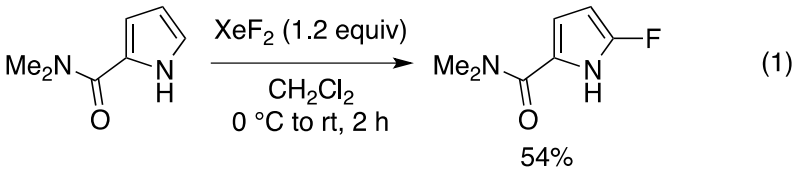
2. DIRECT FLUORINATION OF PYRROLE AND RELATED RINGS

Direct fluorination is a straightforward synthetic method for fluorinated heterocycles. Although this method has potential problems related to regioselectivity and the use of expensive and/or toxic fluorinating agents, it enables late-stage fluorination, which is one of the major aspects of the synthesis of fluorine-containing target molecules. Electrophilic fluorination and nucleophilic fluorination are sequentially described in this chapter.

2.1. Electrophilic Fluorination

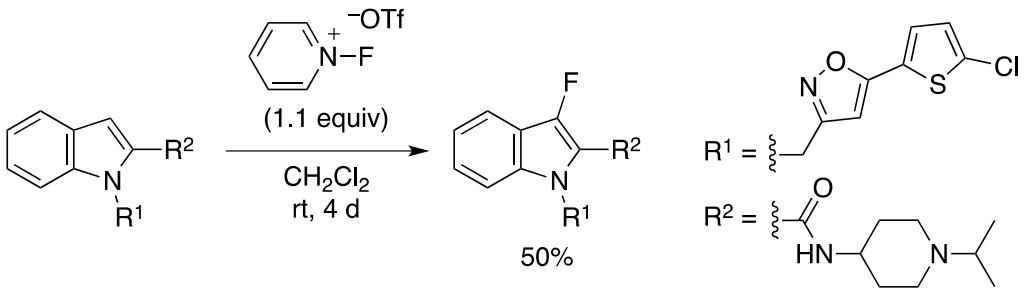
Direct fluorination of pyrrole and indole rings has typically been achieved using electrophilic fluorine sources. When molecular fluorine was employed as a fluorinating agent for a pyrrole derivative, the 3-fluorinated product was preferentially obtained, albeit in a low yield.[16,17] However, the use of milder electrophilic fluorine sources enabled effective and regioselective fluorination of pyrrole and indole rings

via aromatic substitution at their 2- and 3- positions, respectively. This positional selectivity tendency is consistent with other electrophilic substitution reactions of pyrrole and indole frameworks. For example, Scott et al. reported the synthesis of 2-fluoropyrroles by using xenon difluoride (eq. 1).[18,19] Upon treatment with 1.2 equiv. of xenon difluoride, pyrrole derivatives underwent regioselective fluorination to afford the corresponding 2-fluoropyrroles exclusively.



(1)

Further development of various electrophilic fluorine sources has expanded the substrate scope.[20–23] Fluoropyridinium (eq. 2),[24] *N*-fluorobenzenesulfonimide (NFSI, eq. 3),[25] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA, Selectfluor®, eq. 4)[26–30] have thus been used for electrophilic fluorination at the 2-positions of pyrroles and the 3-positions of indoles.



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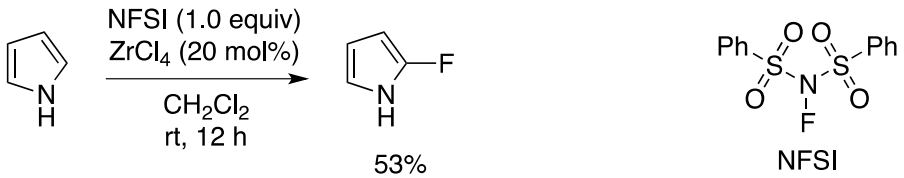

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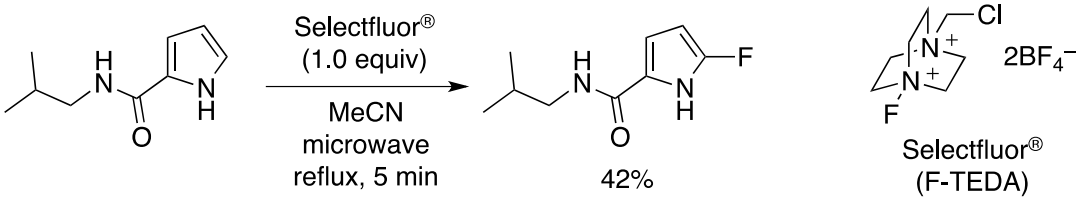
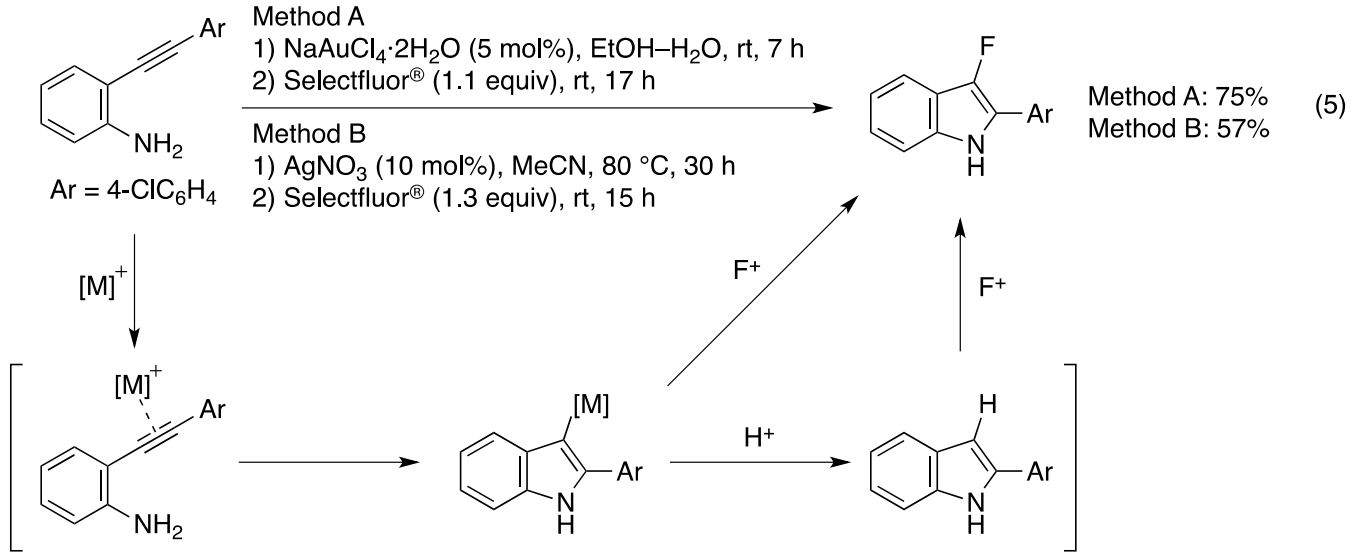
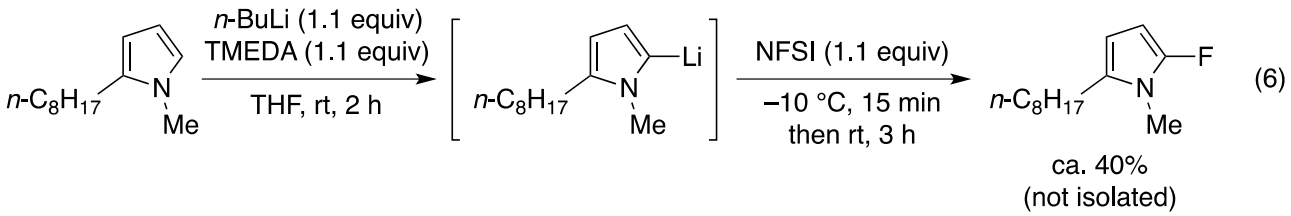


(4)

The synthesis of 3-fluoroindoles can also be achieved using a one-pot sequence of transition-metal-catalyzed pyrrole ring construction and electrophilic fluorination. In the presence of a gold[31] or silver catalyst,[32] the treatment of 2-alkynylaniline substrates with Selectfluor® afforded the corresponding 3-fluoroindoles (eq. 5). In this reaction, an intramolecular cyclization first proceeds via electrophilic activation of the alkyne moieties of the substrates. The resulting 3-metalated indoles undergo fluorodemetalation or protonation followed by fluorination via electrophilic substitution to provide the final 3-fluoroindoles.

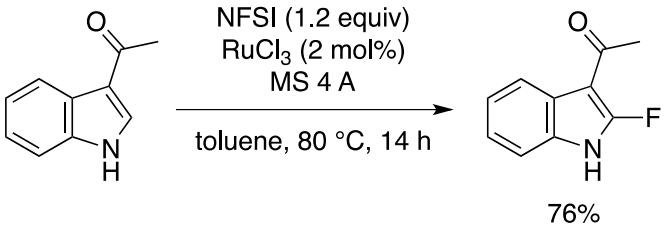


Electrophilic fluorination of 2-metalated pyrroles, generated via direct lithiation of pyrroles, is a reliable method of regioselectively forming 2-fluoropyrroles. Upon treatment with butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, an *N*-methylpyrrole derivative underwent selective lithiation at its 2-position (eq. 6).[33] The reaction of the intermediary lithiopyrrole thus formed with NFSI afforded the corresponding 2-fluoropyrrole.



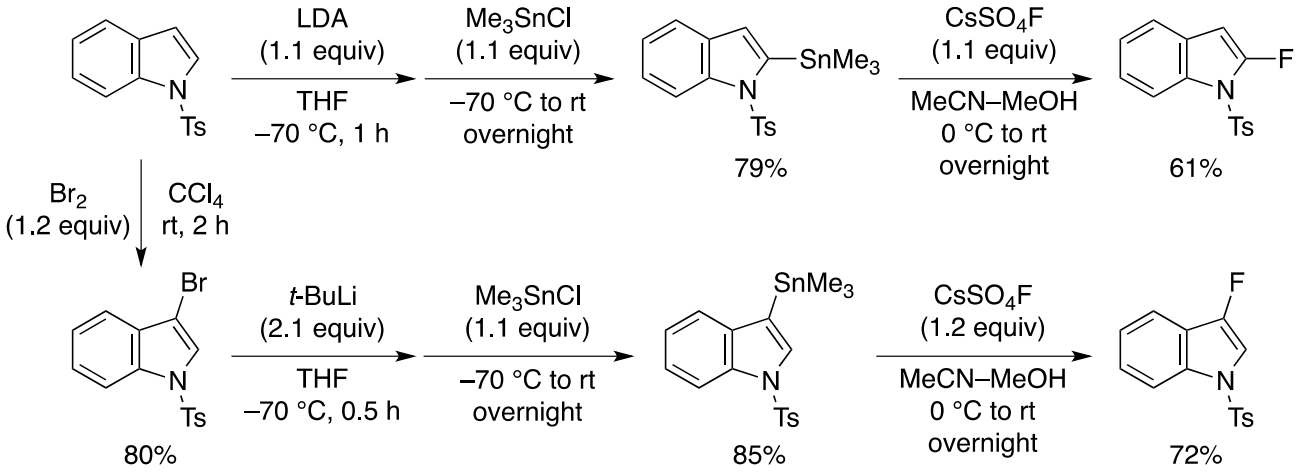
Unlike the normal positional tendency, electrophilic fluorination of the 3-positions of pyrroles and the 2-positions of indoles has been achieved in the following ways: by using substrates with substituents at more reactive sites and/or via fluorodemetalation of metalated intermediates generated by direct metalation or metal–halogen exchange. In the presence of a ruthenium catalyst, the 2-position of

3-acetylindole was successfully fluorinated using NFSI (eq. 7).[34] Furthermore, a 3-fluoropyrrole derivative was obtained by fluorination of a 2,5-disubstituted pyrrole by Selectfluor®, albeit in a low yield.[30]



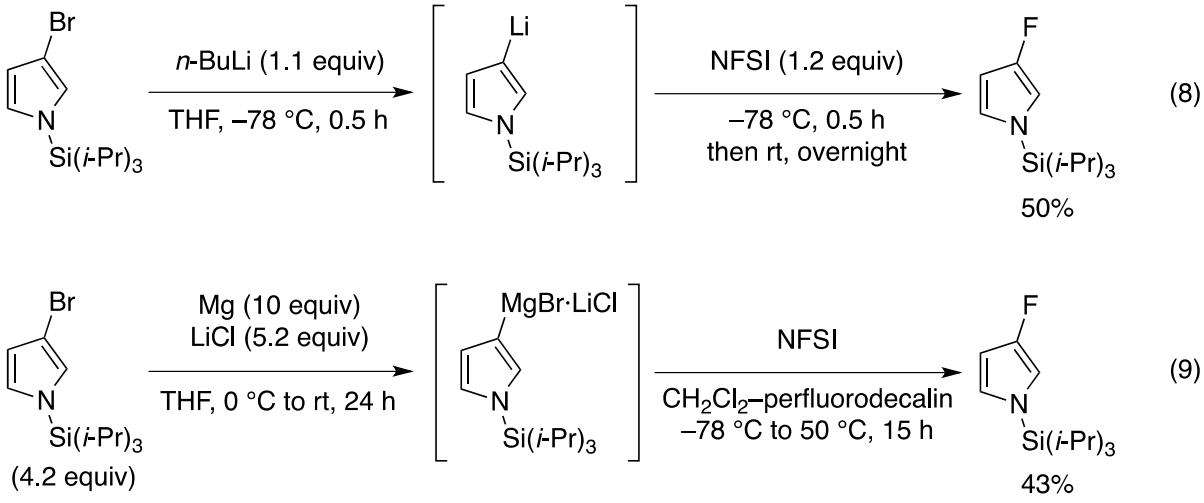
(7)

Since direct lithiation of indoles proceeds at their 2-positions, Widdowson et al. reported the synthesis of 2-fluoroindoles via stannylation and fluorination (Scheme 1).[35,36] The synthesis of 2-stannylindoles was achieved starting from *N*-substituted indoles using a sequence of lithiation by lithium diisopropylamide (LDA) and stannylation by trimethylstannyl chloride. Fluorination of the resulting stannylindoles using cesium fluoroxysulfate afforded 2-fluoroindoles. In addition, 3-fluoroindoles were synthesized in a similar manner via 3-stannylindoles, generated using a sequence of lithium–halogen exchange and stannylation (or palladium-catalyzed stannylation with a distannane), starting from 3-bromoindoles (Scheme 1).



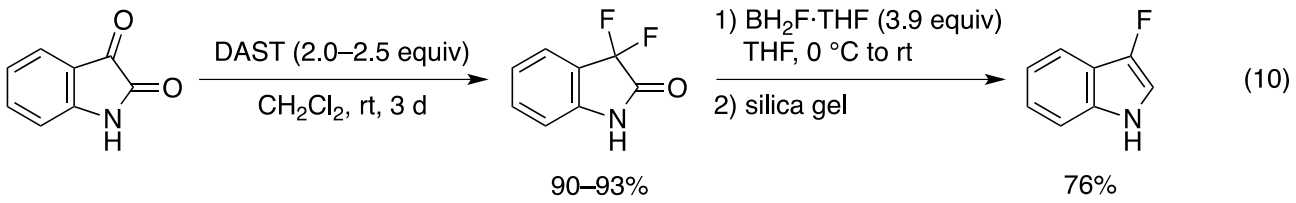
Scheme 1. Synthesis of 2- and 3-fluoroindoles via stannyl intermediates

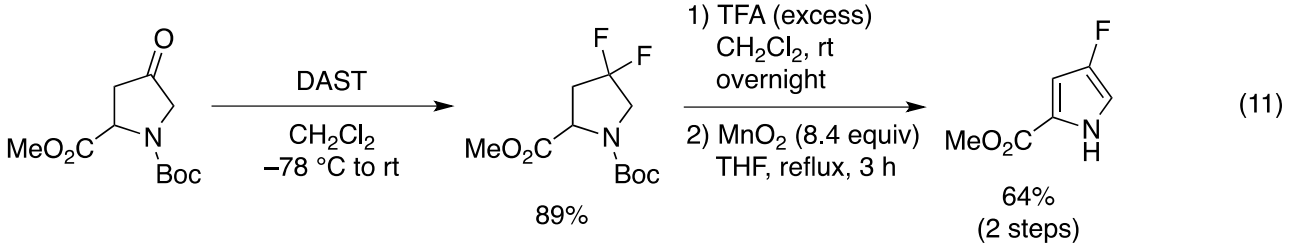
Since metal–halogen exchange readily proceeds at the 3-positions of pyrroles, 3-fluoropyrroles have been synthesized from 3-bromopyrroles via fluorination of the metalated intermediates. Whereas Barnes et al. reported the synthesis of 3-fluoropyrroles via lithiation of 3-bromopyrroles and fluorination by NFSI (eq. 8),[37] Knochel et al. synthesized a 3-fluoropyrrole via a 3-magnesioindole, generated using magnesium turnings and lithium chloride, in a similar manner (eq. 9).[38,39]



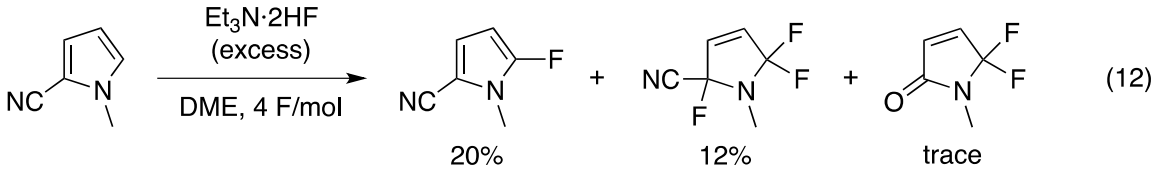
2.2. Nucleophilic Fluorination

Although nucleophilic fluorination of pyrrole and related frameworks is less common for the syntheses of fluoropyrroles and fluoroindoles than electrophilic fluorination, several types of their synthetic methods use fluorides. Stepwise synthesis of fluoropyrroles and fluoroindoles has been accomplished via deoxygenative nucleophilic difluorination with diethylaminosulfur trifluoride (DAST) as a key step. Garden et al. reported the synthesis of 3-fluoroindoles from isatin substrates via nucleophilic difluorination, followed by reduction and elimination (eq. 10).[40] In this protocol, site-selective deoxygenative difluorination of isatins proceeded with DAST to afford 3,3-difluoro-2-oxindoles. Subsequent reaction of the difluorooxindoles thus formed with BH_2F·THF gave 3-fluoroindoles. On the other hand, Leroy reported the synthesis of a 3-fluoropyrrole starting from a 3-pyrrolidinone derivative (eq. 11).[41] Deoxygenative difluorination of a 3-pyrrolidinone substrate was effected with DAST to afford the corresponding 3,3-difluoropyrrolidine.[42] A 3-fluoropyrrole derivative was obtained via HF elimination and dehydrogenation of the 3,3-difluoropyrrolidine.





Alternatively, direct C–H bond fluorination of pyrroles and indoles by fluoride species has been achieved involving oxidation processes. Fuchigami et al. reported the synthesis of 2-fluoropyrroles by using an electrochemical method (eq. 12).[43,44] Electrochemical oxidation of *N*-methylpyrroles in 1,2-dimethoxyethane (DME), using triethylamine hydrofluoride species as supporting electrolytes, afforded a mixture of 2-fluoropyrroles and fluorodihydropyrrole derivatives. The choice of conditions induced preferential formation of 2-fluoropyrroles. On the other hand, Daugulis et al. reported copper-catalyzed fluorination via C–H bond activation (eq. 13).[45] In the presence of a copper catalyst, an indole bearing a directing group at the 3-position was treated with silver(I) fluoride and *N*-methylmorpholine *N*-oxide (NMO) to afford the corresponding 2-fluoroindole, in which NMO served as an oxidant.



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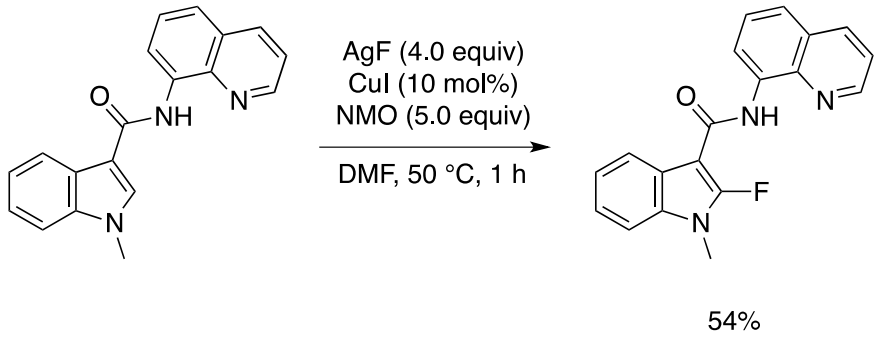


(13)

3. PYRROLE RING CONSTRUCTION VIA FLUORINATED PRECURSORS

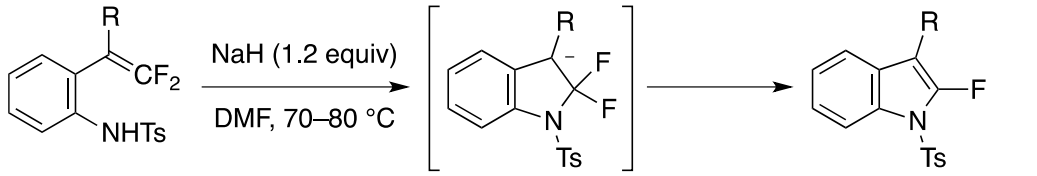
Simultaneous installation of pyrrole rings and fluorine substituents is conducted via intramolecular cyclization of fluorine-containing precursors, which is an alternative synthetic method for ring-fluorinated pyrroles. This strategy typically involves a building-block approach using inexpensive, small, fluorine-containing molecules. Furthermore, regioselective installation of fluorine substituents can definitely be realized by rationally designed ring constructions.

3.1. Nucleophilic 5-*endo-trig* Cyclization

gem-Difluoroalkenes (1,1-difluoro-1-alkenes) are subjected to nucleophilic attacks on the carbon atom α to the fluorine substituents because of their electron-deficient and polarized natures. Thus, nucleophilic vinylic substitution (S_NV)[46] readily proceeds via nucleophilic addition and fluoride elimination. We have

discovered that such a powerful reactivity of 1,1-difluoro-1-alkenes induced intramolecular cyclizations even in a 5-*endo-trig* fashion, which are considered to be disfavored according to Baldwin's rules,[47,48] as well as favored 6-*endo-trig* cyclizations.[49–56] This protocol has been successfully applied to the syntheses of 2-fluoroindole and 2-fluoropyrrole derivatives.

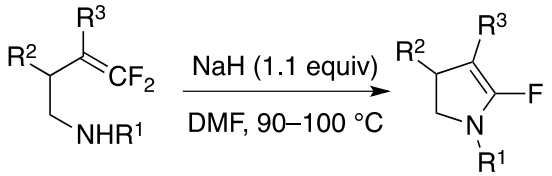
First, we achieved the synthesis of 2-fluoroindoles via the 5-*endo-trig* cyclization of β,β-difluoro-*o*-tosylamidostyrenes (eq. 14).[56–60] Treatment of β,β-difluoro-*o*-tosylamidostyrenes with 1.2 equiv. of sodium hydride effectively afforded 2-fluoroindoles. In this process, the 5-*endo-trig* cyclization proceeded via intramolecular addition of the nucleophilic amido group to the difluoroalkene moieties, followed by β-fluorine elimination from the anionic intermediate. The β,β-difluorostyrenes bearing oxygen and sulfur nucleophiles as substituents also underwent 5-*endo-trig* cyclization under appropriate conditions, leading to the synthesis of 2-fluorobenzofurans and 2-fluorobenzothiophenes, respectively.



R = *n*-Bu: 84% (7 h)
R = *sec*-Bu: 81% (5 h)
R = H: 73% (23 h)

(14)

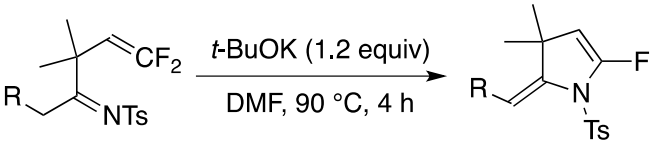
Similarly, 5-fluoro-2,3-dihydro-1*H*-pyrroles were synthesized via the 5-*endo-trig* cyclization of 4,4-difluorohomoallylic amines and amides (eq. 15).[61] Even when a β,β-difluoro-α,β-unsaturated ester bearing a 2-tosylamidoethyl group was employed as the substrate, the 5-*endo-trig* cyclization proceeded to the difluoromethylene carbon, and the 5-*exo-trig* cyclization product was not obtained at all (eq. 15).



R^1 = Ph, R^2 = Me, R^3 = $(CH_2)_3Ph$: 62% (24 h)
R^1 = Ts, R^2 = Me, R^3 = $CH_2CH(Me)Ph$: 80% (4 d)
R^1 = Ts, R^2 = H, R^3 = CO_2Me: 62% (0.3 h)

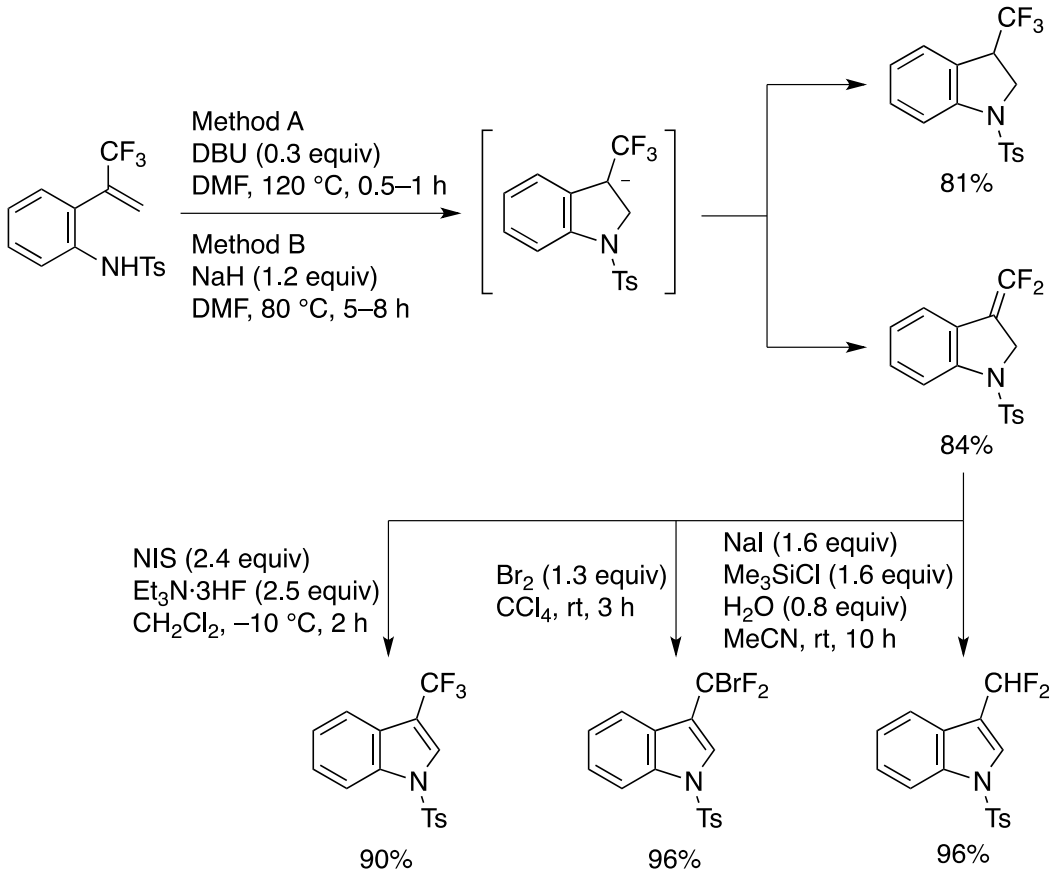
(15)

More recently, we achieved 5-*endo-trig* cyclization of 3,3-difluoroallyl imines under basic conditions (eq. 16).[62] Upon treatment with 1.2 equiv. of potassium *tert*-butoxide, 3,3-difluoroallylic imines effectively underwent 5-*endo-trig* cyclization via their metalloenamide forms to afford 5-fluorinated 2-alkylidene-2,3-dihydropyrroles via exclusive *N*-cyclization. Similarly, 3,3-difluoroallylic ketones were readily cyclized by addition of potassium hydride via their metalloenolate forms to give the corresponding 5-fluorinated 2-alkylidene-2,3-dihydrofurans.[62,63]



(16)

In association with the aforementioned processes of difluoroalkenes, we also adopted trifluoromethylalkenes, specifically, *o*-tosylamido-α-trifluoromethylstyrenes, in the 5-*endo-trig* cyclization, by taking advantage of their high reactivities toward nucleophiles.[64–66] When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as the base, *o*-tosylamido-α-trifluoromethylstyrenes underwent a sequence of addition and protonation to afford 3-trifluoromethylated indolines (Scheme 2, Method A). In contrast, the use of sodium hydride as the base induced addition followed by β-fluorine elimination (S_N2'-type reaction), leading to the formation of 3-difluoromethyleneindolines (Scheme 2, Method B). The difluoromethyleneindolines thus obtained were successfully transformed into 3-trifluoromethyl-, 3-bromodifluoromethyl-, and 3-difluoromethyl-indoles upon treatment with *N*-iodosuccinimide (NIS)/triethylamine trihydrofluoride, molecular bromine (Br_2), and sodium iodide/trimethylsilyl chloride/water, respectively. Furthermore, the above-mentioned two types of 5-*endo-trig* cyclizations also work with 3-trifluoromethylhomoallylic amides, yielding 3-trifluoromethyl- and 3-difluoromethylenepyrrolidines.[64–66]

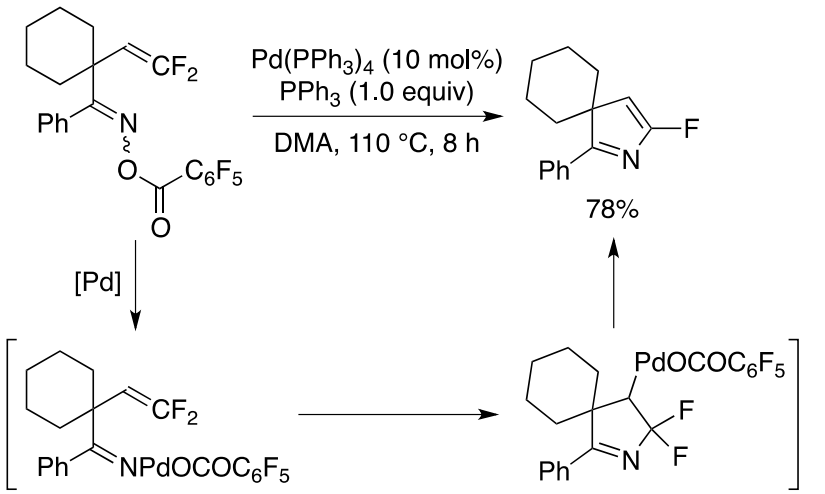


Scheme 2. Synthesis of fluorine-containing indole derivatives via 5-*endo-trig* cyclization

3.2. Transition-Metal-Catalyzed Cyclization

Transition-metal-mediated cyclization of fluorine-containing precursors is another effective method of synthesizing ring-fluorinated pyrrole and indole derivatives. We and other groups achieved their syntheses via ring construction catalyzed by transition metals.

We have accomplished transition-metal-catalyzed amino-Heck-type cyclization[67] and electrophilic cyclization of 1,1-difluoro-1-alkene substrates. First, we achieved the amino-Heck-type 5-*endo* cyclization of 3,3-difluoroallylic ketone oximes (eq. 17).[68,69] In the presence of a palladium(0) catalyst, 3,3-difluoroallylic ketone *O*-pentafluorobenzoyloximes underwent cyclization involving the following three steps: (1) oxidative addition of the N–O bond, (2) 5-*endo* insertion, and (3) β-fluorine elimination, which afforded 5-fluoro-3*H*-pyrroles. The palladium(II) fluoride species formed in this reaction was reduced with triphenylphosphine to regenerate the catalytically active palladium(0) species. Moreover, the amino-Heck-type 5-*endo* cyclization of 2-(trifluoromethyl)allylic ketone oximes also proceeded in a similar manner to give 4-difluoromethylene-1-pyrrolines (eq. 18).[69,70]



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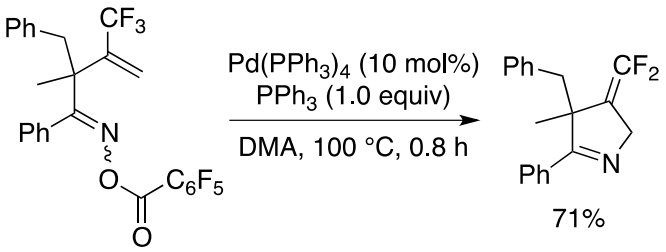
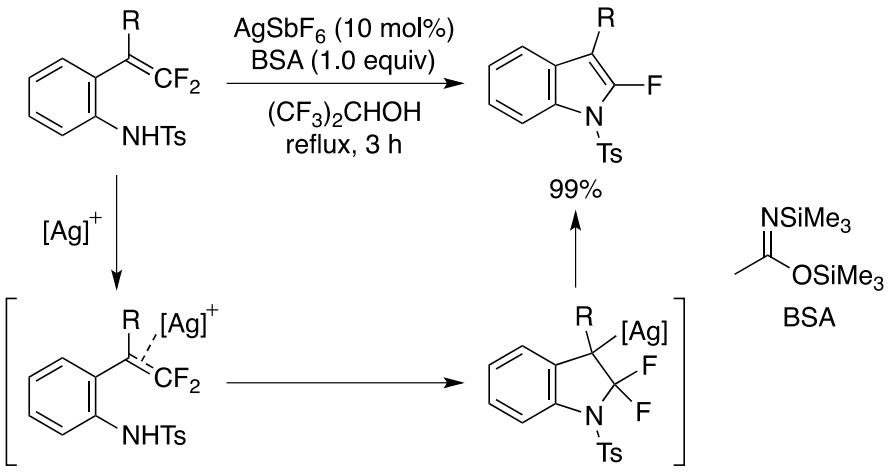


(18)

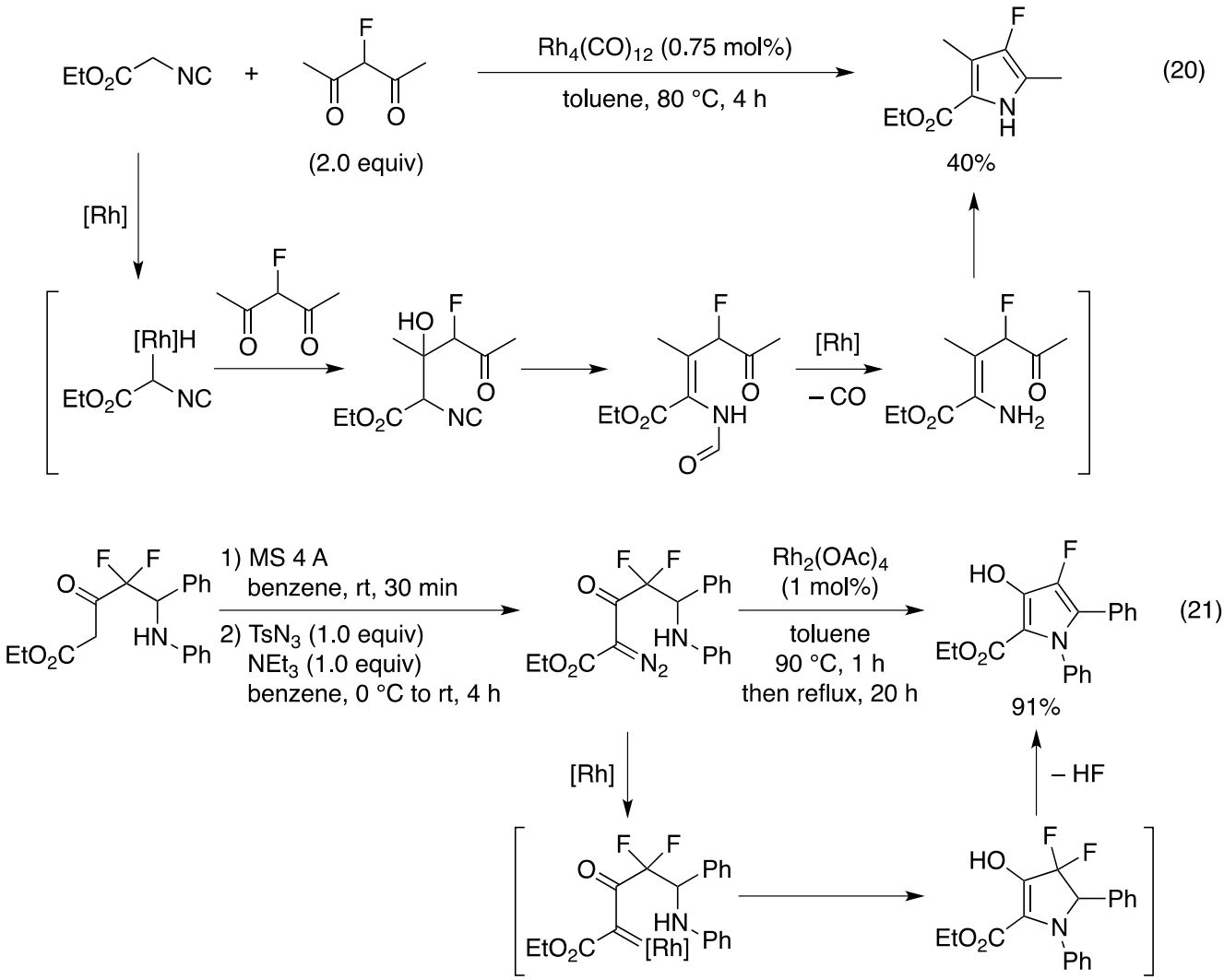
Since 1,1-difluoro-1-alkenes are electron-deficient alkenes, their electrophilic activation has been troublesome.[71–74] Nevertheless, we have developed a methodology for electrophilic activation of 1,1-difluoro-1-alkenes by using cationic palladium(II) catalysts to construct carbocycles[75–77] and heterocycles.[78] Most recently, we achieved silver(I)-catalyzed electrophilic activation of

β,β-difluorostyrenes for fluoroindole synthesis (eq. 19).[79] Complexation with a silver(I) catalyst promoted the electrophilic 5-*endo*-*trig* cyclization of β,β-difluoro-*o*-sulfonamidostyrenes in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) to afford 2-fluoroindoles. This cyclization successfully proceeds via 5-*endo* aminometalation and subsequent β-fluorine elimination. Addition of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) was the key to regenerating the active silver(I) species.

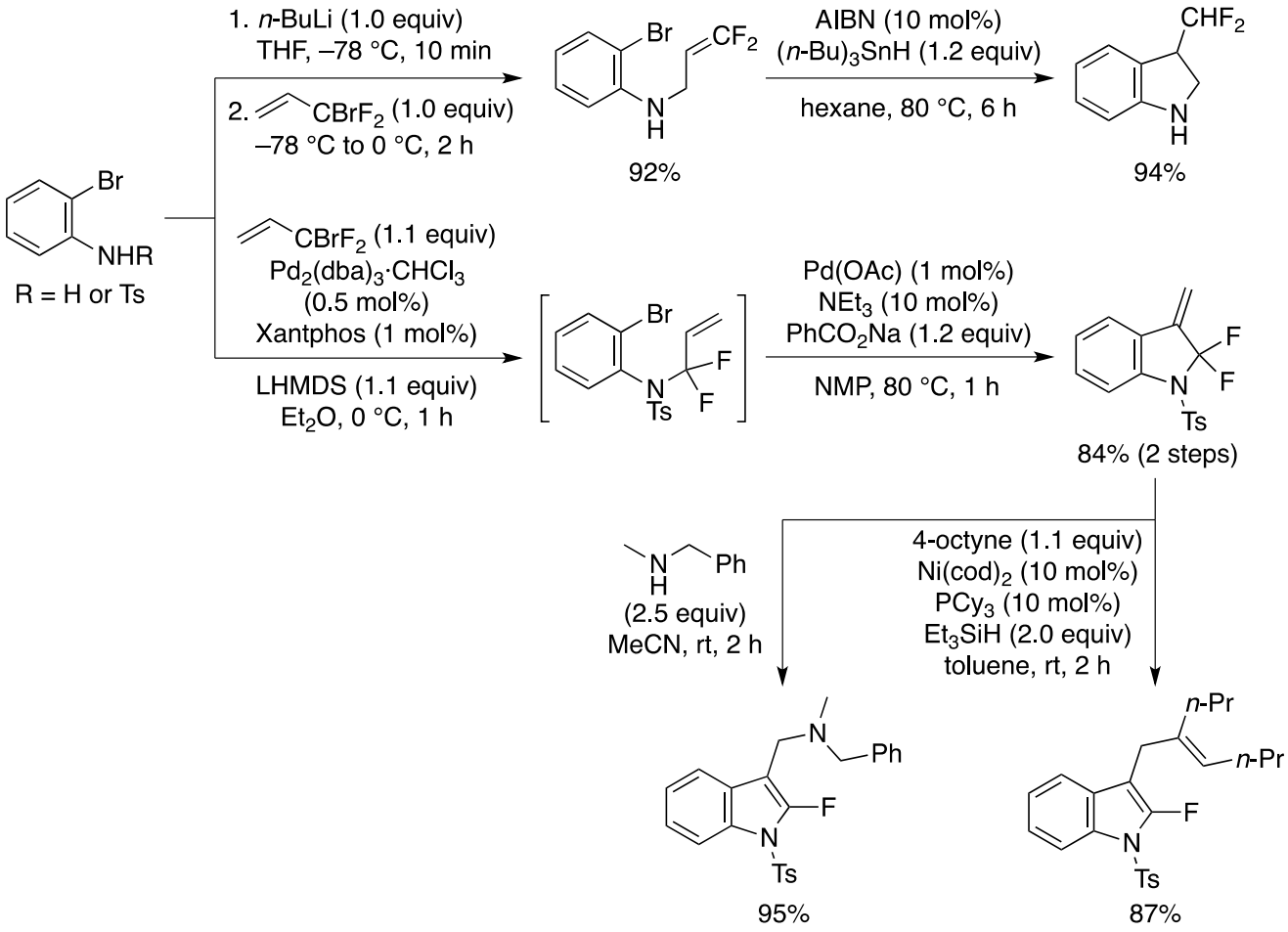


(19)

Rhodium-catalyzed reactions have been applied to the synthesis of 3-fluoropyrrole derivatives. Murahashi et al. reported a 3-fluoropyrrole synthesis by rhodium-catalyzed annulation between a fluorinated 1,3-dione and an isonitrile (eq. 20).[80] In the presence of tetrarhodium dodecacarbonyl, treatment of 3-fluoro-2,4-pentanedione with ethyl isocyanoacetate afforded the corresponding 3-fluoropyrrole. In this reaction, the rhodium catalyst probably promotes α-C–H bond activation of the starting isonitrile and decarbonylation from the amide intermediate. Zhu et al. synthesized 3-fluoropyrroles via intramolecular N–H insertion of intermediary rhodium carbenoids (eq. 21).[81] In the presence of a catalytic amount of rhodium(II) acetate dimer, δ-amino-α-diazo-γ,γ-difluoro-β-ketoesters, prepared by the diazo transfer reaction of δ-amino-γ,γ-difluoro-β-ketoesters, underwent cyclization along with elimination of hydrogen fluoride to afford 3-fluoropyrroles.



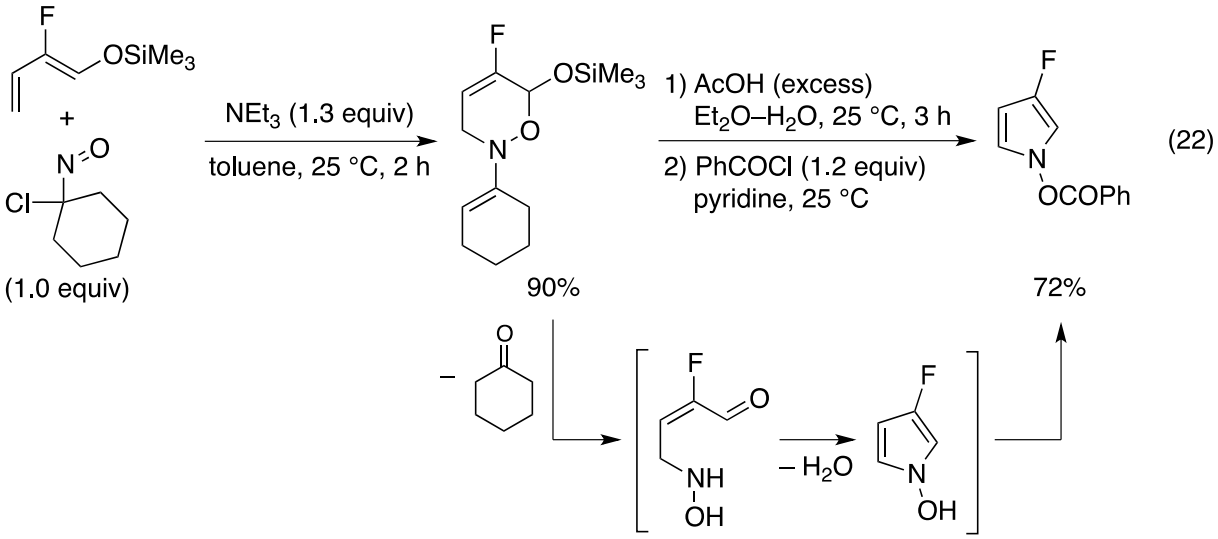
Quite recently, we synthesized various types of fluorine-containing indole derivatives via regioswitchable difluoroallylation of aniline derivatives (Scheme 3). Upon treatment with 3-bromo-3,3-difluoroprop-1-ene, 3,3-difluoroallylation of 2-bromoanilines proceeded exclusively via the S_N2' reaction under basic conditions without a transition metal species.[82] In contrast, a palladium catalyst selectively promoted 1,1-difluoroallylation via the Tsuji–Trost reaction.[83] In the former case, subsequent radical 5-*exo* cyclization gave 3-(difluoromethyl)indolines.[82] The 1,1-difluoroallylated compounds obtained in the latter reaction underwent an intramolecular Heck cyclization to afford 2,2-difluoro-3-methyleneindoline derivatives.[83] Further transformations via both the S_N2'-type reaction with a secondary amine[64–66] and the nickel-catalyzed defluorinative coupling with an alkyne[84] effectively produced 2-fluoroindoles.

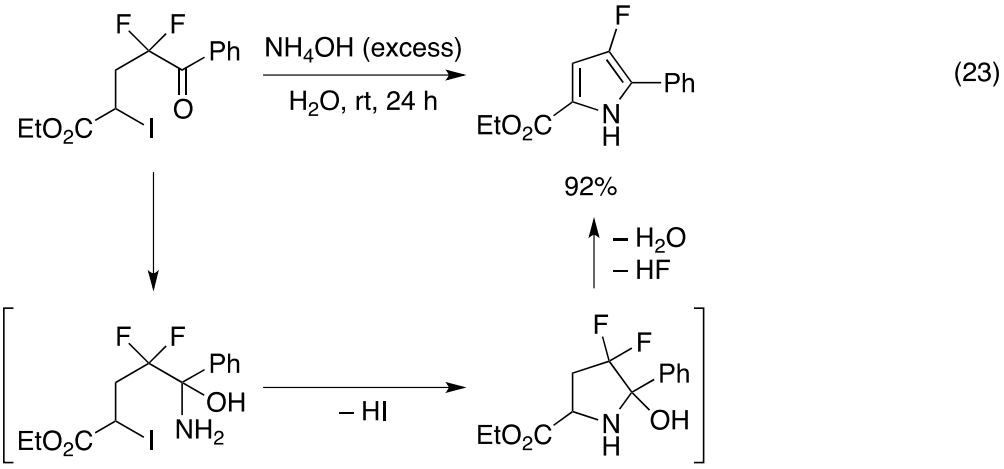


Scheme 3. Synthesis of fluorinated indole derivatives via regioswitchable difluoroallylation

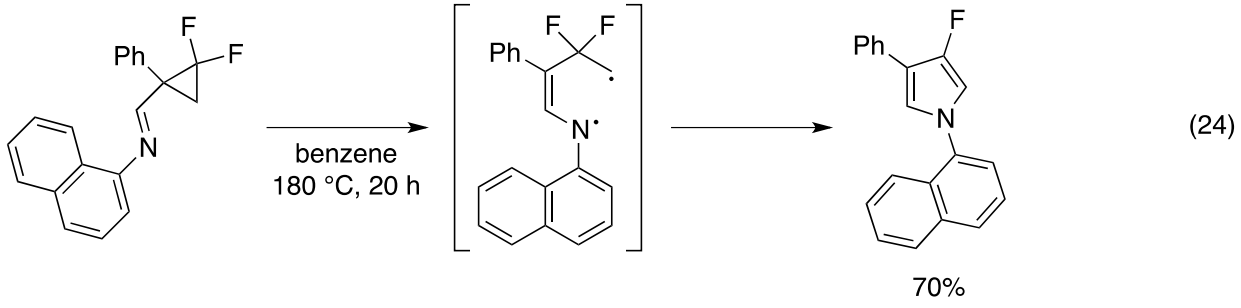
3.3. Other Types of Cyclization

Several other methods for simultaneous installation of pyrrole rings and fluorines have been developed. Schlosser et al. reported the synthesis of 3-fluoropyrroles via the hetero Diels–Alder reaction between 2-fluoro-1,3-dienes and nitroso compounds as the key step (eq. 22).[85] The reaction of 2-fluoro-1-trimethylsiloxy-1,3-dienes and 1-chloro-1-nitrosocyclohexane afforded 5-fluoro-3,6-dihydro-1,2-oxazines as the sole products. Subsequent acid treatment promoted ring-opening and *N*-cyclization, leading to the construction of 3-fluorinated pyrrole rings. Burton et al. also synthesized 3-fluoropyrroles via the intramolecular S_N2 reaction of α,α-difluoro-γ-iodoketones (eq. 23).[86] Cyclization of the intermediary hemiaminals, formed from the difluoroketone substrates and excess ammonium hydroxide, effectively proceeded to afford the corresponding 3-fluoropyrroles.

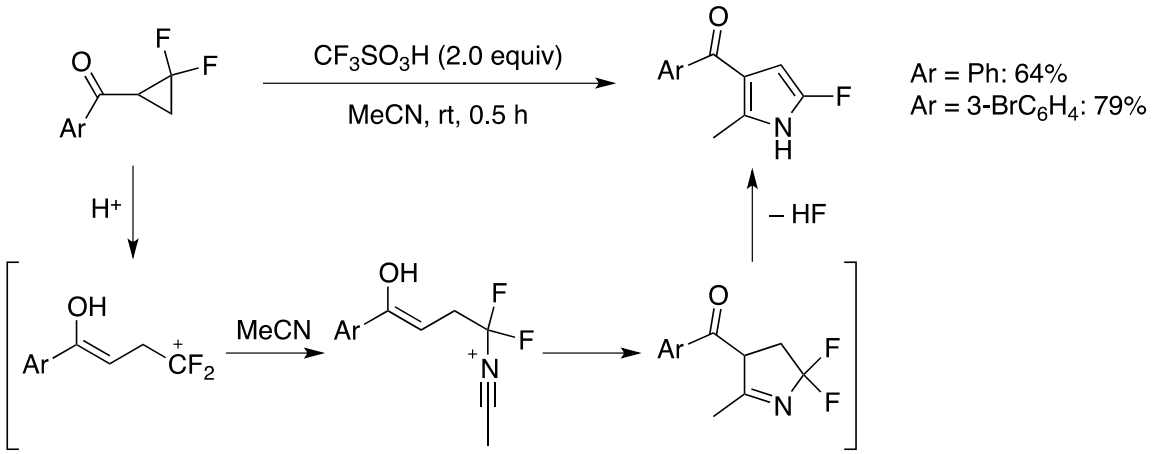




Both 2-fluoropyrroles and 3-fluoropyrroles have been synthesized from *gem*-difluorocyclopropanes via a ring-opening/C–N bond formation sequence. Kagabu et al. reported 3-fluoropyrrole synthesis via radical cleavage of *gem*-difluorocyclopropanes (eq. 24).[87] When (2,2-difluorocyclopropyl)imines were heated at 180 °C, thermal homolytic cleavage of the C–C bond of the *gem*-difluorocyclopropane moieties occurred, followed by recombination of the generated carbon and nitrogen radicals to selectively construct 3,3-difluoro-2,3-dihydropyrrrole rings. Subsequent aromatization via elimination of hydrogen fluoride afforded 3-fluoropyrroles. In contrast, Xiao et al. achieved the synthesis of 2-fluoroindoles via acid-mediated difluorocyclopropane ring-opening and annulation with nitriles (eq. 25).[88] Upon treatment with trifluoromethanesulfonic acid in acetonitrile, *gem*-difluorocyclopropyl ketones underwent ring-opening to generate the intermediary cationic species. The reaction of the cations with acetonitrile, followed by ring closure and elimination of hydrogen fluoride, gave 2-fluoroindoles successfully.

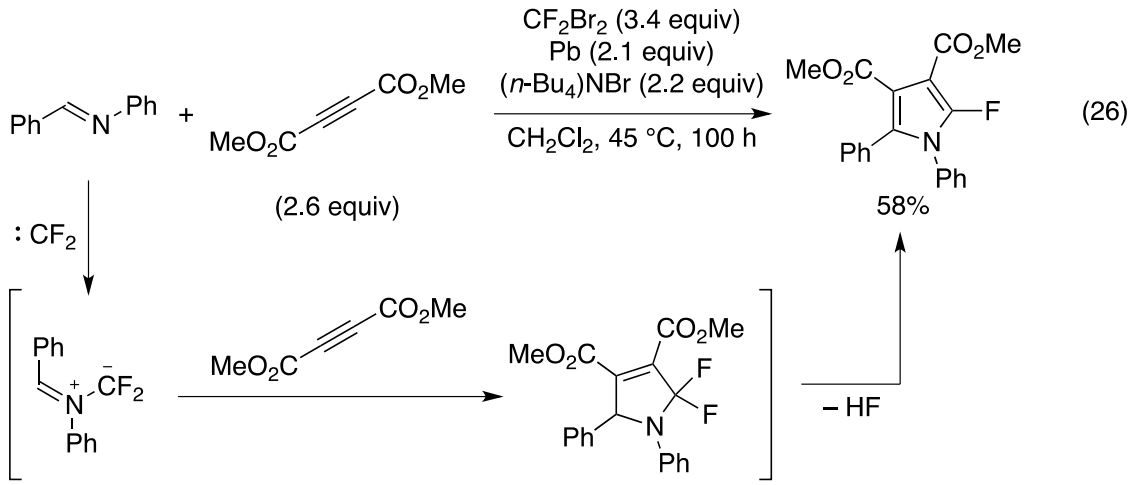


(24)

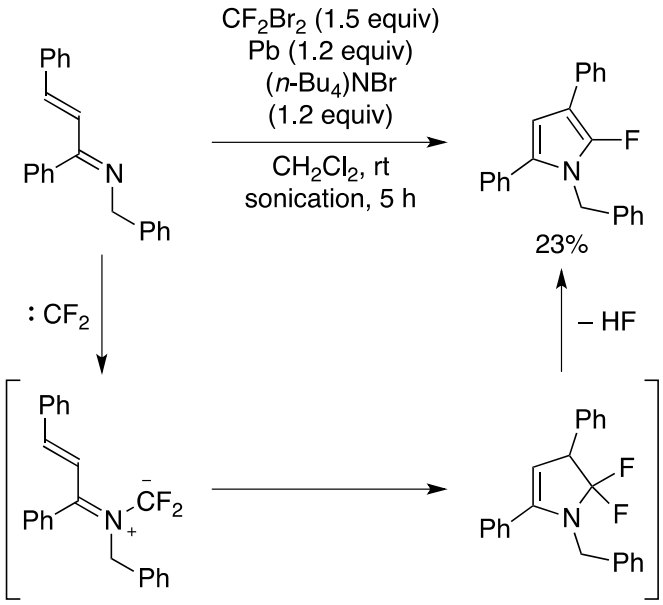


(25)

Annulation of fluorine-containing azomethine ylides generated from imines and difluorocarbene provides 2-fluoropyrroles. Novikov and Khlebnikov et al. prepared difluorocarbene by treatment of dibromodifluoromethane with lead powder in the presence of tetrabutylammonium bromide, and then applied the formed difluorocarbene to the generation of azomethine ylides. They first conducted [3+2] cycloaddition between the azomethine ylides and alkynes (eq. 26).[89–91] They also achieved cyclization by intramolecular conjugate addition of the difluoroazomethine ylides generated from 1,3-azadienes and difluorocarbene (eq. 27).[92] Thus, 2-fluoropyrrole derivatives were obtained after elimination of hydrogen fluoride in both cases.



(26)



(27)

4. CONCLUSION

As stated above, the numbers of synthetic methods for ring-fluorinated pyrroles and indoles have significantly increased with the emergence of new fluorinating agents and cyclization protocols. These developments will enable the mass production of various types of fluoropyrroles and -indoles for applied research. Since these compounds are characterized by important structural elements with medicinal and agrochemical activities, namely, fluorine substituents and nitrogen-containing five-membered rings, they may save mankind from terrible diseases and food shortages in the future.

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