Electrophilic Fluorination with 1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate and NFSI (N-Fluorobenzenesulfonimide) reagents directed towards the synthesis of heterocycles ; Current Trends

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Abstract

The phytochemical screening and the antidiarrhoeal activities of the crude extracts from the leaves *Landolphiaowariensis* were carried out using standard methods. The results of the phytochemical screening showed that the plant contained alkaloids, saponins, tannins, flavonoids and glycosides. The results of the antidiarrhoeal screening of the crude extracts showed that *Landolphiaowariensis* exhibited zone of inhibition ranging from 15 mm to 35 mm against test microbes. Ethyl-acetate extract of the *Landolphiawariensis* being the most active fraction was subjected to column chromatography, leading to the isolation of single compound that showed a high activities (zone of inhibition from 8mm to 32mm) against these causative agents of diarrhoea (*Salmonella Typhi, Shigelladysentriaeand Escherichaia Colirespectively*). Spectroscopic analysis of the isolated compound using $^1H_{NMR}$, $^{13}C_{NMR}$, IR and GCMS showed that the compound was Cis-9-Octadecenoic acid. The result of this works therefore showed that the extract from the leaves of *Landolphiaowariensis* could be used for the treatment of diarrhoea and other diseases caused by targeted microorganisms.

Keywords: Antidiarrheal; *Landolphiaowariensis*; Isolation; Cis-9-Octadecenoic Acid

Introduction

The development of fluorination chemistry began more than 100 years ago with the first examples of nucleophilic and electrophilic fluorination reactions being reported in the second half of the 19th century [1,2]. Fluorinated molecules plays a significant role in pharmaceutical/medicinal [3,4] agrochemical [5,6] and material sciences [7] due to the unique properties of fluorine atom [8]. The introduction of fluorine atom can modulate the properties of biologically active compounds, since this may lead to changes in lipophilicity, chemical reactivity, solubility, conformation, ability of hydrogen-bonding [9]. As a result, 30-40% of agrochemicals and 20-25% of pharmaceuticals on the market are estimated to contain fluorine [10].

The efficacy of agrochemicals and pharmaceuticals oftenly enhanced or it is due to the presence of fluorine atom in the structure [11]. Frequently, these type of compounds can be synthesized from small moieties in which fluorine is located at a specific site, or often it is desirable to introduce the element directly in order to obtain the desired chemical composition [12,13]. Electrophilic fluorination is one of the most direct methods for selective introduction of fluorine into organic compounds [14]. In this respect, various reagents for electrophilic fluorination have been developed till now as shown in (Figure 1). Elemental fluorine itself is one of the most powerful reagents [15].

However, fluoroxcompounds [16], such as CF_3OF, $CF_3C(O)OF$, $CsSO_4F$, and $CH_3C(O)OF_{13}$ some of which are generated in situ, are exciting reagents for the introduction of fluorine electrophilically into a wide variety of organic compounds [17,18]. Most electrophilic fluorinating reagents are ultimately derived from fluorine gas, the strongest elemental oxidant known, which is synthesized by electrolysis of potassium difluoride in hydrogen fluoride [19]. Electrophilic fluorination reactions with highly oxidizing fluorinating reagents [20] such

as fluorine gas, hypofluorites, fluoroxysulfates, and perchloryl fluoride are challenging to perform due to the high reactivity of the reagents. Xenon difluoride was developed as a more stable electrophilic fluorination source, but its high oxidation potential still limits the tolerance of this reagent to functional groups [21].

The development of crystalline, benchtop-stable fluorinating reagents such as N-fluorobis (phenyl) sulfonimide (NFSI) [19] and related analogues [22,23], N-fluoropyridinium salts [24], and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2] octane bis(tetrafluoroborate) (Selectfluor, F-TEDABF4) [25]

was crucial for the development of selective, functional-group-tolerant fluorination methods. Another class of electrophilic fluorinating reagents with the general structure R_2N-F or R_3N^+-F began to gain popularity. In comparison to the previous reagents, these compounds were stable, safer, milder and less expensive to produce. Furthermore, some of these compounds proved to be as reactive as established reagents in some cases, which were also capable of a degree of selectivity that was previously unattainable [26]. Efforts by Umemoto et al. led to the first isolatable N-fluoropyridinium salts, which had good activity and were amenable to commercial production [27] (Figure 1).

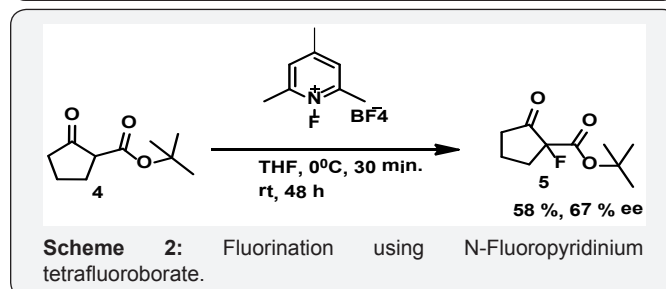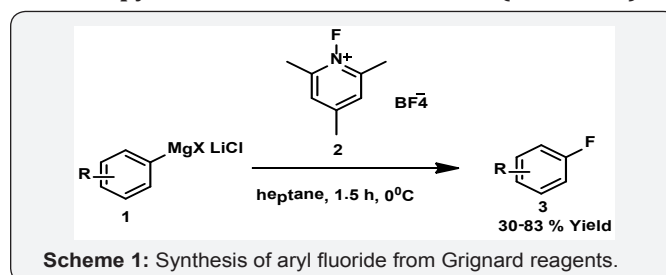**Figure 1:** Electrophilic fluorinating reagents.
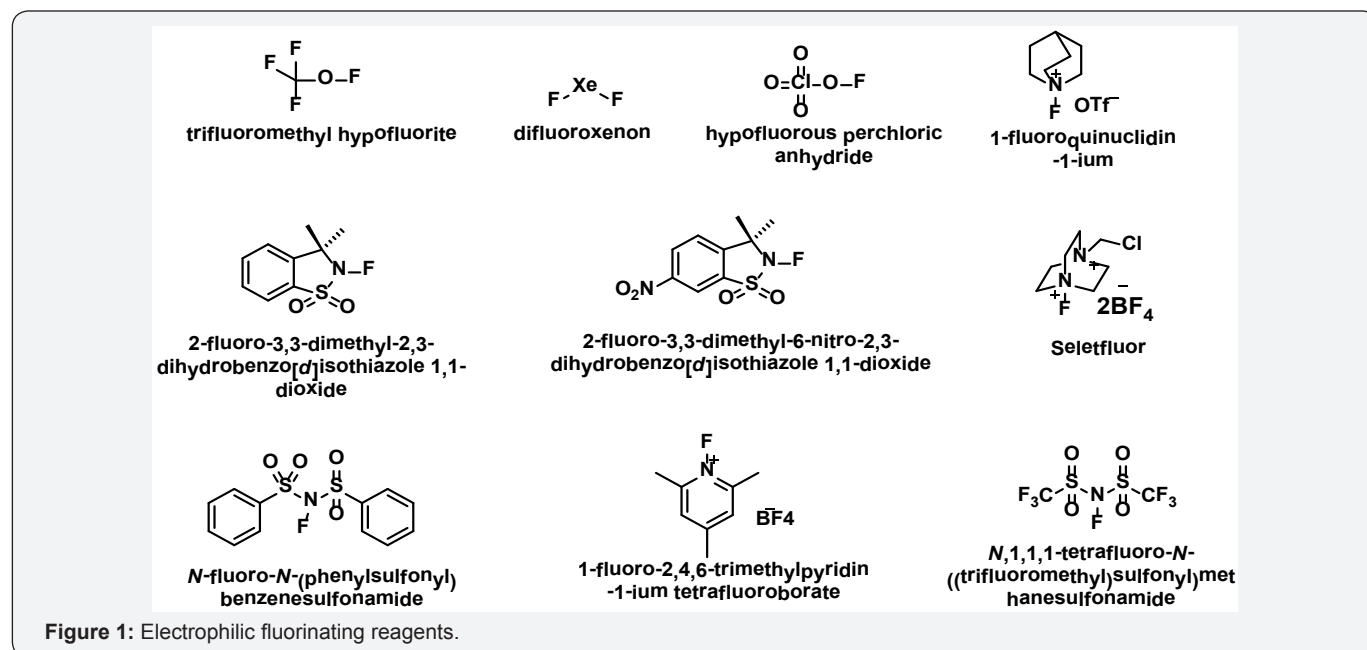
The important role of the counter anion, which influences the reactivity, selectivity, and stability of the reagent, was also demonstrated [28]. Des Marteau and co-workers later reported the discovery of N-fluorobis [(trifluoromethyl) sulfonyl] imide, accessed by the reaction of bis [(trifluoromethyl) ulfonyl]-imide with fluorine gas [29,30]. The synthesis of this compound, which is still one of the most powerful sources of electrophilic fluorine, was a step forward in the identification of a stable source of electrophilic fluorine with desirable physical properties. One major drawback is that it is not commercially available, so that the use of fluorine gas for its preparation in the laboratory is ultimately required.

More recently, the development of the reagent NFSI presented a major advance for electrophilic fluorination, as it is a reliable, mild, stable, and effective source of electrophilic fluorine that lends itself to large-scale synthesis and is commercially available. A number of reagents, each with its advantages and disadvantages, currently exist for the electrophilic incorporation of fluorine and have been the subject of several reviews [31-34]. In the present review, we give a comprehensive overview of the literature reports emphasizing on two potential electrophilic fluorinating reagents 1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate and NFSI (N-Fluorobenzenesulfonimide).

Electrophilic Fluorinating Reagents

N-Fluoropyridinium tetrafluoroborate: (Scheme 1)

Scheme 1: Synthesis of aryl fluoride from Grignard reagents.

Scheme 2: Fluorination using N-Fluoropyridinium tetrafluoroborate.

In (Scheme 1), Lagow and co. workers used N-Fluoropyridinium tetrafluoroborate as fluorinating reagent among the N-fluoropyridinium salt series and can react as

an electrophilic fluorine source. Exhibiting almost the same reactivity as other related N-fluoropyridinium salts, albeit with a somewhat lower solubility, it has a high fluorine content (103 g kg^{-1}) [35] (Scheme 2).

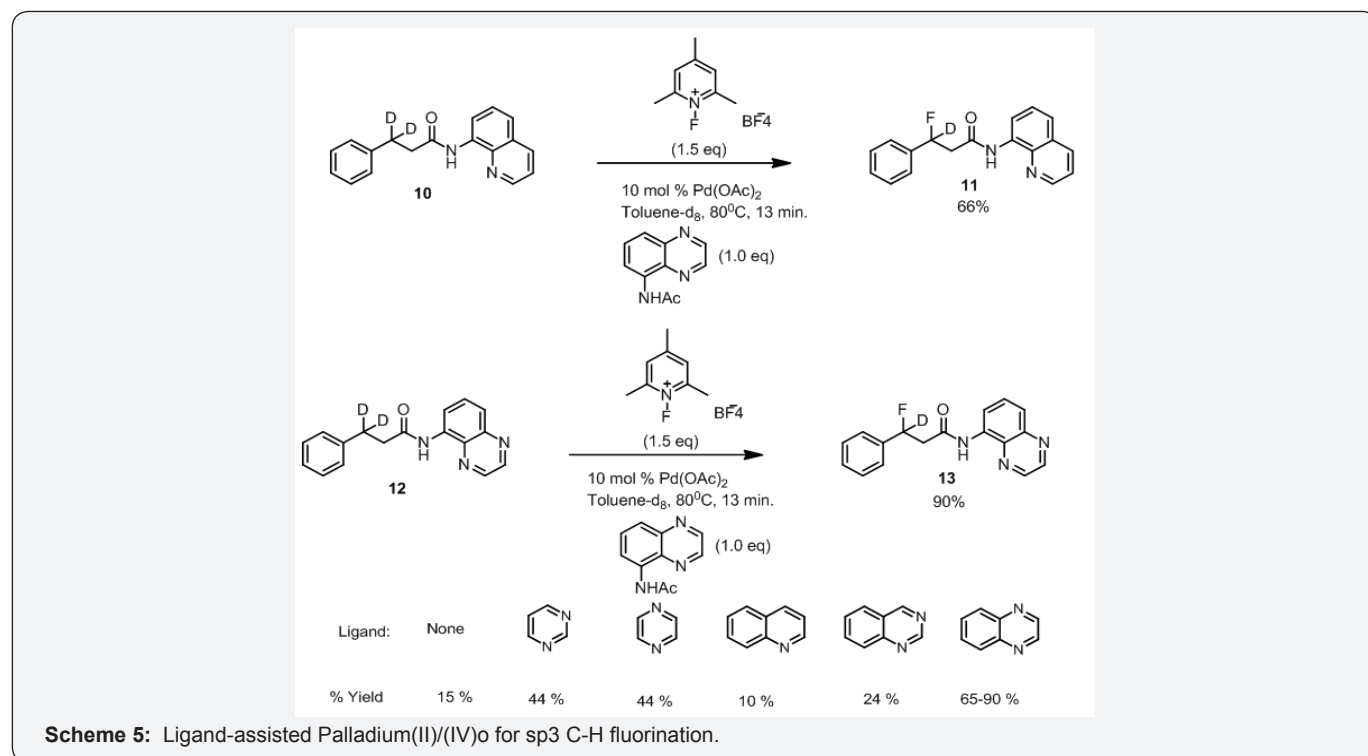**Scheme 3:** Palladium catalyzed fluorination of carbon-hydrogen bonds.
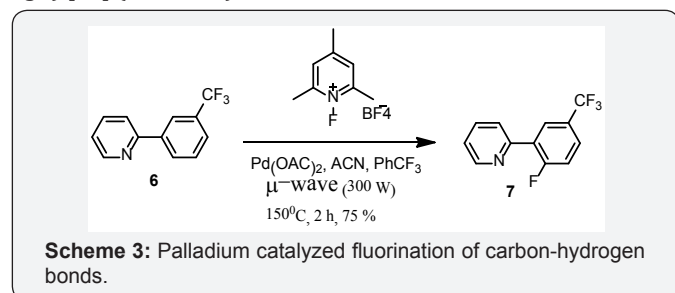
Tomita, K. and Co workers used *N*-Fluoropyridinium tetrafluoroborate as fluorinating reagent as shown in (Scheme 2). In this case of fluorination of 1-(trimethylsilyloxy) cyclohexene, the yields and/or rates of reaction are not satisfactory, compared to those of the triflateanalog, because of the reduced solubility of fluorinating reagents in CH_2Cl_2. The same reactions performed in acetonitrile, however, give similar results [36] and efficient enantioselective electrophilic fluorination of β-ketoesters can be achieved. It can be seen that use of NFPY (N-fluoropyridinium tetrafluoroborate) resulted in moderate enantioselectivities. Interestingly, the addition of the electron-poor alcohol HFIP (1,1,1,3,3,3-hexafluoroisopropanol) as additive led to an increase in enantioselectivity to 67% ee [37](Scheme 3).
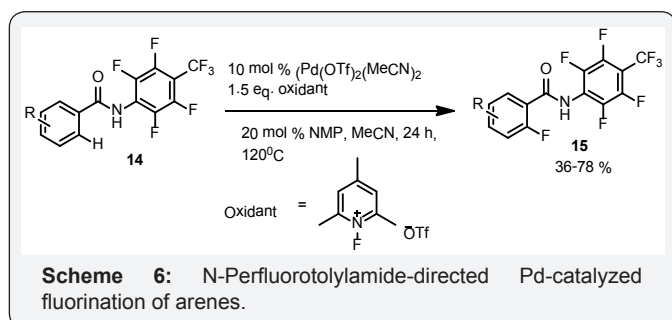
1-fluoro-2,4,6-trimethylpyridin-1-iumtetrafluoroborate was selected as the best electrophilic fluorine donor for palladium-catalyzed fluorination on 2-arylpyridines. In Scheme 3, Takeru Furuya and Co-workers used Palladium catalysed fluorination

of organic molecules. The C-H activation/oxidative fluorination process allows *ortho*-fluorination of the aryl ring under microwave irradiation [38] (Scheme 4).

Scheme 4: Palladium-catalyzed fluorination of 8-methylquinoline.
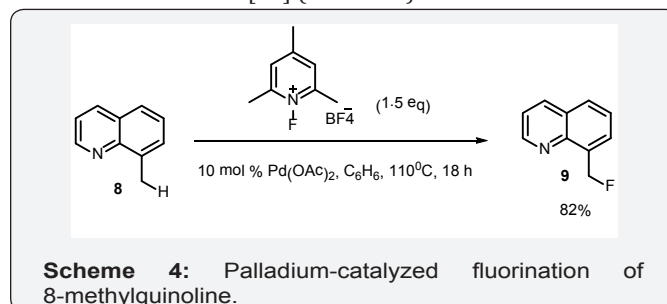
In Scheme 4, Sanford and co workers used Palladium-catalyzed fluorination of 8-methylquinoline. Initial investigations focused on the Pd (OAc)$_2$-catalyzed benzylic fluorination of 8-methylquinoline. This substrate was selected because it undergoes facile quinoline-directed C-H activation at Pd(II) to generate a 6-benzyl-Pd species and, as such, has been shown to serve as an excellent substrate for related Pd-catalyzed C-H activation/oxidative functionalization reactions [39,40]. An initial screen of F$^+$ reagents under thermal reaction conditions (10 mol % of Pd (OAc)$_2$, 110 °C, 13 h, benzene) revealed that several conditions affected the desired benzylic C-H bond fluorination reaction, providing desired compound in modest 9-36% yields while using different fluorinating reagents [41]. However, *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate served as a highly effective F$^+$ source affording products in a dramatically improved 82% isolated yield. Importantly, control reactions in the absence of Pd catalyst showed none of the fluorinated product [42].

Scheme 5: Ligand-assisted Palladium(II)/(IV)o for sp3 C-H fluorination.

Scheme 6: N-Perfluorotolylamide-directed Pd-catalyzed fluorination of arenes.
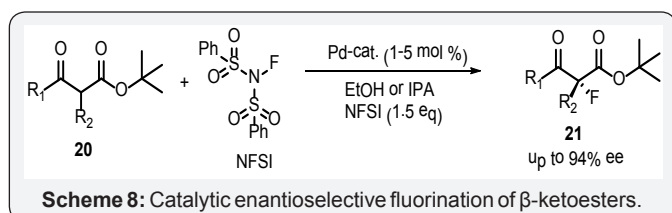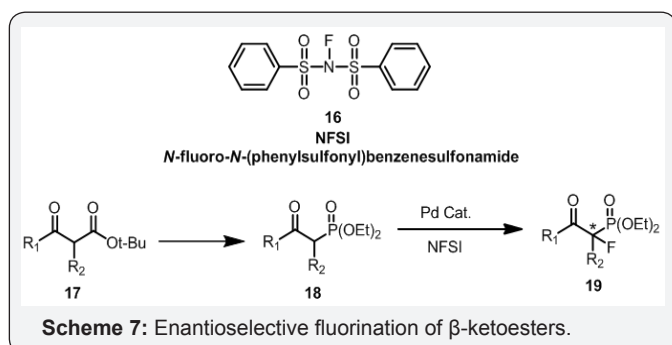
In Scheme 5, experimental investigation concludes a change of rate limiting step using 8-aminoquinoline vs. 8-aminoquinoxaline as directing group by affecting the key Pd (II) to Pd(IV) oxidation step. This finding led to the discovery of a simple ligand capable of lowering the activation energy for the oxidation of Pd. This intriguing mechanistic journey provides new clues into oxidative C-H functionalization reactions. We expect these results will stimulate the development of new C-H functionalization reactions. It is being observed that if 8-aminoquinoline vs. 8-aminoquinoxaline are removed from the reaction mixture the rate of reaction is affected and the overall yield of the reaction affected by 42 %. If the reaction performed without ligand the yield is only 15% and the yields vary with different ligands [43] (Scheme 5) and (Scheme 6).
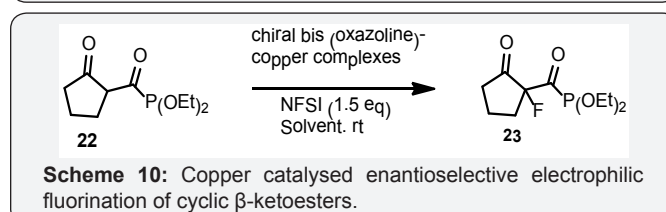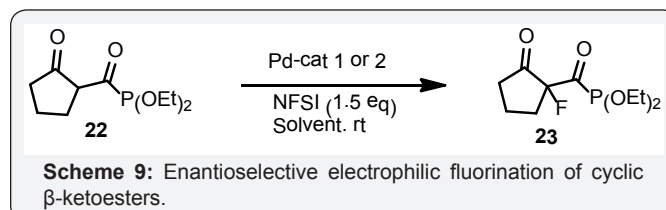
Double fluorination through two subsequent ortho fluorination events was addressed with a weakly coordinating anionic *ortho*-directing group N-perfluorotolylamide derived from benzoic acid that allows for rapid displacement of the monofluorinated product by the substrate, thus affording high selectivity for monofluorination (Scheme 6).

Electrophilic fluorination using N-fluoro-N-(phenylsulfonyl) benzene sulphonamide (NFSI):
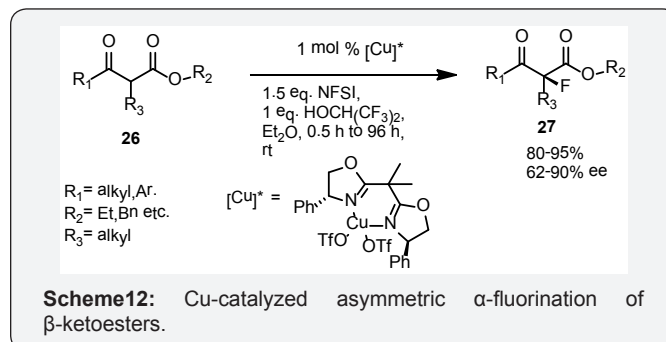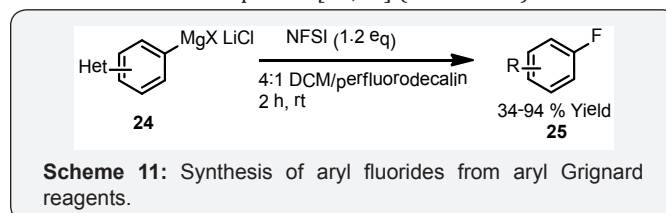

Scheme 7: Enantioselective fluorination of β-ketoesters.

Scheme 8: Catalytic enantioselective fluorination of β-ketoesters.

Mikiko Sodeoka co-workers reported a highly efficient catalytic enantioselective fluorination of β-ketoesters (Scheme 7) [44]. In the presence of a catalytic amount of

chiral Pd complexes, a variety of β-ketoesters reacted with N-fluorobenzenesulfonimide (NFSI) in an alcoholic solvent such as EtOH to afford the corresponding fluorinated products with excellent enantioselectivity (up to 94% ee). Various substrates including cyclic and acyclic β-ketophosphonates underwent the reaction with N-fluorobenzenesulfonimide (NFSI) in EtOH to give the corresponding fluorinated products in a highly enantioselective manner (94-98% ee). (Schemes 8 & 9) and (Scheme 10)

Scheme 9: Enantioselective electrophilic fluorination of cyclic β-ketoesters.

Scheme 10: Copper catalysed enantioselective electrophilic fluorination of cyclic β-ketoesters.

Dominique Cahard and Co workers developed a new efficient catalytic enantioselective electrophilic fluorination of acyclic (Scheme 8) and (Scheme 9) cyclic β-ketoesters is developed [45]. As low as 1 mol% of chiral bis (oxazoline)-copper triflate complexes catalyses the fluorination by means of N-fluorobenzenesulfonimide (NFSI). The use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) is crucial for achieving high enantioselectivity [46]. Herein a new efficient catalytic enantioselective electrophilic fluorination of both cyclic and acyclic β-ketoesters by means of chiral bis (oxazoline)-copper complexes leading to enantio enriched fluorinated compounds in high yields and good enantioselectivities (scheme 10). The positive impact on the enantiomeric excess of achiral additives such as HFIP is also reported [47,48] (Scheme 11).

Scheme 11: Synthesis of aryl fluorides from aryl Grignard reagents.

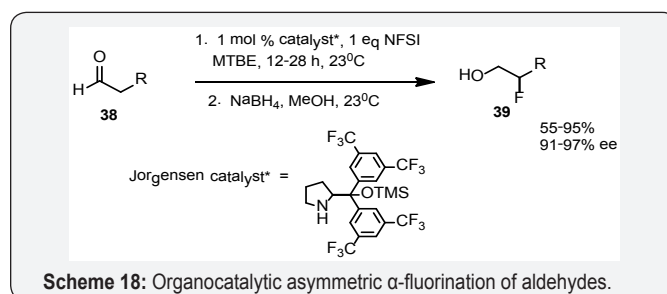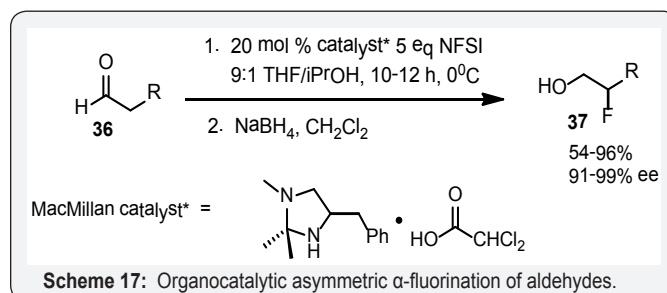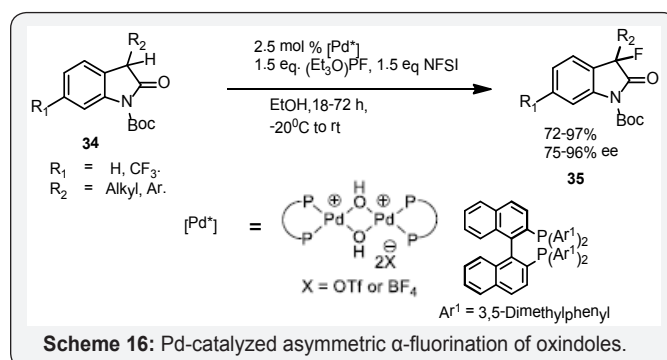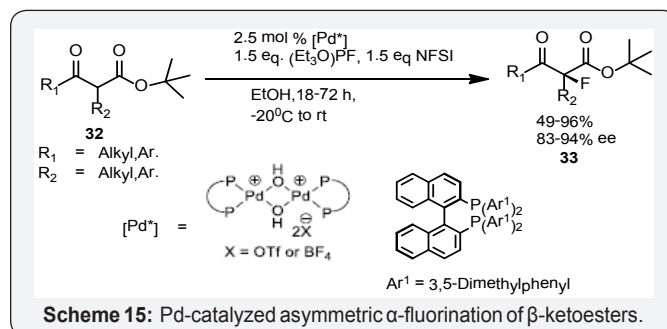**Scheme12:** Cu-catalyzed asymmetric α-fluorination of β-ketoesters.

In (Scheme 11), fluorination of Grignard reagents with electrophilic N-fluorinated reagents NFSI is the most reliable method with simple aryl nucleophiles but is narrow in scope due to the basicity and nucleophilicity of the arylmagnesium reagents [49,50]. Through appropriate choice of solvent and reagents, undesired protodemetallation products can be minimized [51]. More recent work by Meng and Li demonstrated the regioselective para fluorination of anilides with PhI(OPiv)2 and hydrogen fluoride/pyridine [52](Scheme 12).

Scheme13: Ni-catalyzed asymmetric α-fluorination of β-ketoesters and N-Boc oxindoles.
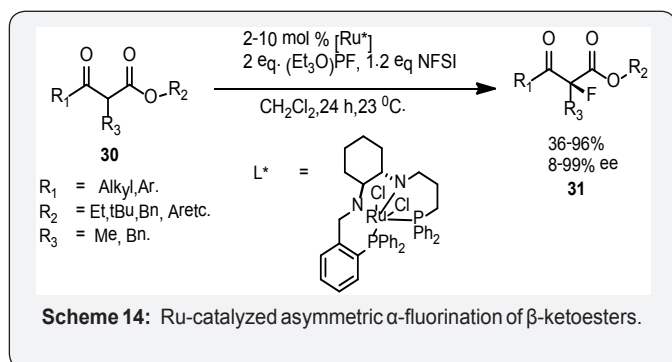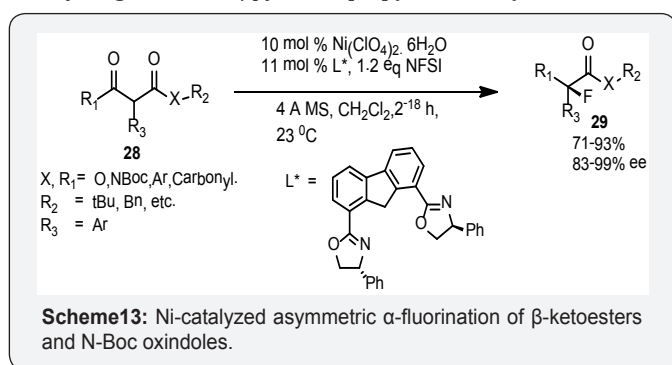
Scheme 14: Ru-catalyzed asymmetric α-fluorination of β-ketoesters.

Several methods have exploited the two-point binding of dicarbonyl compounds to chiral lewis acid complexes to control enantioselective fluorination. Asymmetric fluorination of β-ketoesters was 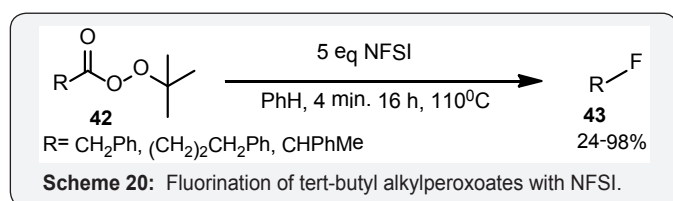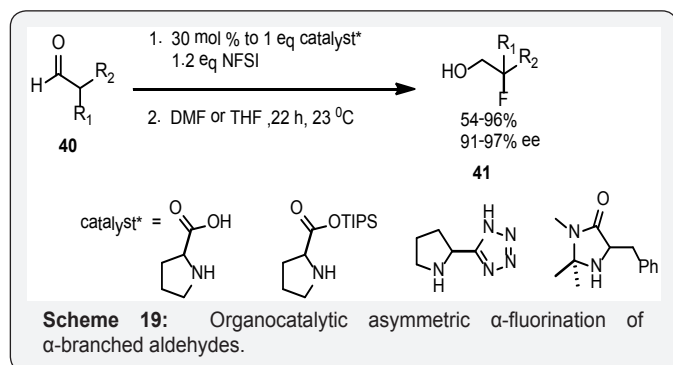achieved with Cu (II)- (Scheme-12) and (Scheme 13) [53]. Several methods have exploited the two-point binding of dicarbonyl compounds to chiral lewis acid complexes to control enantioselective fluorination. Asymmetric fluorination of β-ketoesters was achieved with Ni (II)-BOX complexes (Scheme 13) [54] by Cahard and Shibata/Toru, respectively (Scheme 14).

Chiral bis (imino) bis (phosphine) ruthenium (II) complex by Togni (Scheme 14) [55] and scandium binapthyl phosphate complexes by Inanaga [56]. The Ni-catalyzed reaction, using a 10 mol% catalyst loading, has demonstrated the broadest substrate scope so far, and allows for α-fluorination of a variety of β-ketoesters and N-Boc-protected amides [52] in 71-93% yield and 83-99% ee, respectively. The catalytic enantioselective α-fluorination of α-substituted methyl, tert-butyl malonate was accomplished via chiral lewis acid catalysis with Zn (II) acetate, (R,R)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) ligand, and NFSI. This approach was specifically optimized for the malonate substrate en route to the enantioselective synthesis of fluorinated β-lactams [57,58].

Scheme 15: Pd-catalyzed asymmetric α-fluorination of β-ketoesters.

Scheme 16: Pd-catalyzed asymmetric α-fluorination of oxindoles.

Scheme 17: Organocatalytic asymmetric α-fluorination of aldehydes.

Scheme 18: Organocatalytic asymmetric α-fluorination of aldehydes.

Chiral Pd-BINAP complexes developed by Sodeoka shown in (Scheme 15) and (Scheme 16) catalyzes the enantioselective fluorination of α-ketoesters [59], β-ketoesters (Scheme 11), [60] β-ketophosphonates, [61] oxindoles, [62] and α-ester lactones/lactams [63]. The use of chiral palladium complexes was particularly successful for the α-fluorination of acyclic α-ketoesters, cyclic and acyclic tert-butyl β-ketoester as well as oxindoles α-substituted with an electronically diverse range of aryl and alkylgroups [59-62] (Scheme 17). The aldehyde α-fluorination method described by MacMillan demonstrates a broader substrate scope, (Scheme 17) [64]. These fluorinated compounds are useful for the synthesis of different biological active heterocycles [65]. Jørgensen and co workers used NFSI and organocatalytic α-fluorination of aldehydes. (Scheme 18)

[66] While the method described the utilization of lower loadings of catalyst and electrophilic fluorinating reagent. Branched aldehydes constitute difficult substrates for enantioselective α-fluorination; nonetheless.

**Scheme 19:** Organocatalytic asymmetric α-fluorination of α-branched aldehydes.

Scheme 20: Fluorination of tert-butyl alkylperoxoates with NFSI.

Barbas (Scheme 19) [67] accomplished the enantioselective organocatalytic α-fluorination of aldehydes. Similarly, enantioselective α-fluorination of ketones is possible using enaminecatalysis [68]. Barbas reported a promising 98-99% yield and 45-66% *ee* for this class of substrates. The fluorinated aldehyde products are especially useful for the synthesis of enantiopure β-fluoroamines, which can be obtained by a chiral sulfinyl imine condensation, directed reduction sequence of the enantioenriched fluorinated aldehyde [69] (Scheme 20). The N-F bonds in electrophilic fluorinating reagents have relatively low bond dissociation energies (2.84 eV for N-fluorosultam) [70]. Under photolysis or thermolysis conditions, a variety of *tert*-butyl alkyl peroxoates afforded the corresponding alkyl fluorides upon treatment with NFSI (Scheme 20) [71]. Primary alkyl fluoride formation was not efficient, which supports the mechanism hypothesis of radical intermediates.

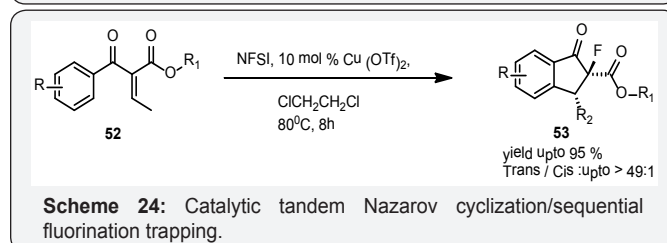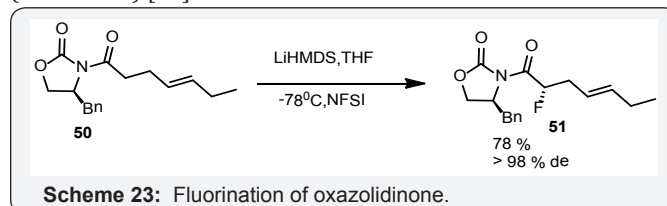**Scheme 21:** Intermolecular aminofluorination of styrenes with NFSI.
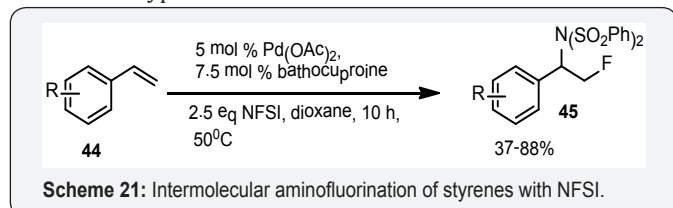
The intermolecular amino fluorination of styrene's (Scheme 21) [72] can be facilitated by the use of palladium catalysts as described by Liu. Although reactions accomplish amino fluorination of alkenes, different approaches were employed and different reaction mechanisms proposed for each case. Intermolecular amino fluorination is thought to occur via fluoro-palladation involving substrate, NFSI and the active palladium complex, followed by oxidation to a putative Pd (IV) species, and subsequent reductive elimination to form a carbon–nitrogen bond. The formation C-F bonds at sp³ carbon centers by reductive elimination from high-valent transition-metal complexes has also been investigated with Pt (IV) complexes [73,74].

Enantiopure (R)-silyl ketones were prepared by diastereoselective silylation of the (S)-or (R)-1-amino-2-methoxy methylpyrrolidine (SAMP/RAMP) hydrazone and used as substrates in diastereoselective electrophilic fluorinations in which the silyl group acts as a traceless directing group. Lithium enolates of chiral compound generated by LDA were fluorinated with enantiopure (R)-silyl ketones were prepared by diastereoselective silylation of the (S)-or(R)-1-amino-2-methoxymethylpyrrolidine (SAMP/RAMP) hydrazone and used as substrates in diastereoselective electrophilic fluorinations in which the silyl group acts as a traceless directing group [75].

Scheme 22: Electrophilic fluorination of (R)-silyl ketones.
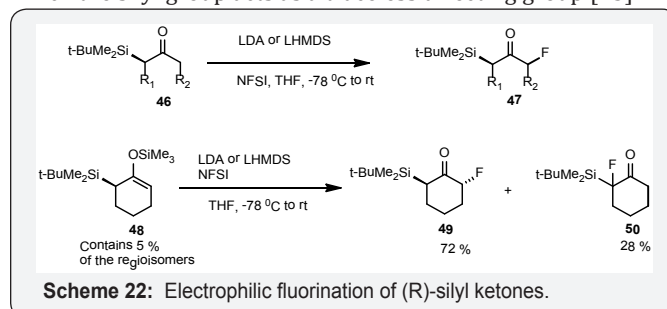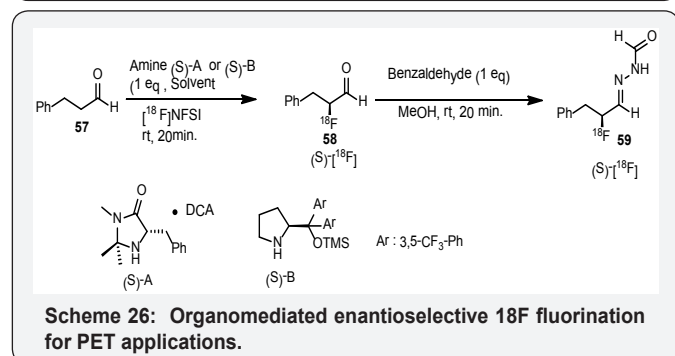
Lithium enolates of compound generated by LDA were fluorinated with NFSI in good yields and with high diastereomeric excesses. Interestingly, LiHMDS allowed reverse diastereoselectivity to be obtained. The diastereoselectivity was found to reflect the ratio of enolate stereomers, with NFSI reacting only from the less sterically hindered enolate face. This concept was also applied to silyl enol ether; however, the fluorination gave rise to a significant amount of regioisomers (Scheme 22) [76].

Scheme 23: Fluorination of oxazolidinone.

Scheme 24: Catalytic tandem Nazarov cyclization/sequential fluorination trapping.

A chiral oxazolidinone auxiliary was also used by Stauton and co-workers to direct the addition of a fluorine atom in the preparation of fluoro analogue as a biosynthetic precursor of the ionophore antibiotic tetronasin (Scheme 23) [77]. A new catalytic stereo selective tandem transformation via Nazarov cyclization/ electrophilic fluorination has been accomplished (Scheme 24). This sequence is efficiently catalyzed by a Cu (II) complex to

afford fluorine-containing 1-indanone derivatives with two new stereocenters with high diastereoselectivity (trans/cis up to 49/1). Three examples of catalytic enantioselective tandem transformation are presented [78] (Scheme 25).

Scheme 25: Synthesis of aryl fluorides from aryl Grignard reagents.

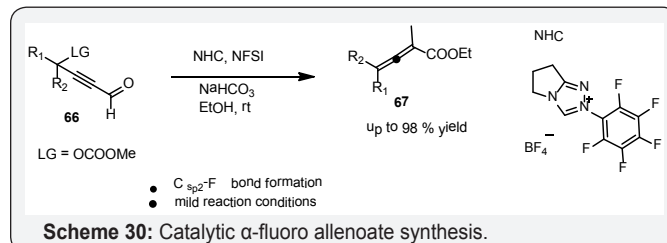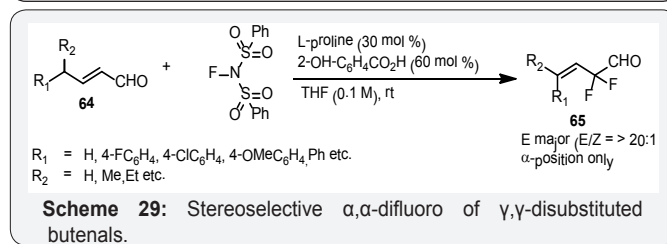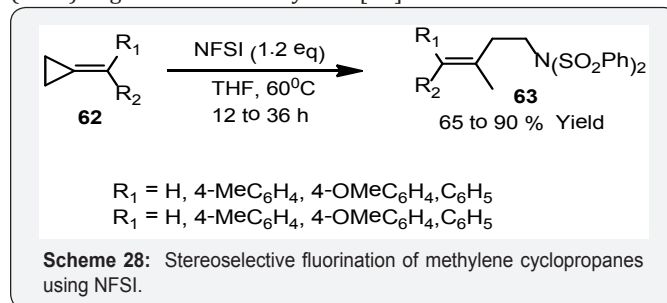**Scheme 26: Organomediated enantioselective 18F fluorination for PET applications.**
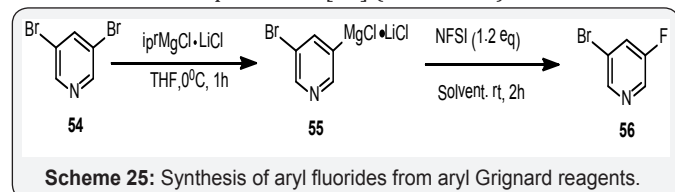
In (Scheme 25), Paul Knochel and co-workers developed a simple, convenient and highly versatile one-pot method for converting aromatic and heteroaromatic bromides or iodides into the corresponding fluorides by choosing an optimized different solvent mixture. This procedure allows a direct access to fluorinated pyridines, thiophenes, pyrroles and isoquinolines as well as to sterically congested fluorine-substituted benzenes, which are otherwise difficult to prepare. Further investigations of this potentially practical synthetic method are currently underway [79] (Scheme 26).

Scheme 27: Diastereoselective fluorination of α, β-unsaturated chiral oxazolidinone.
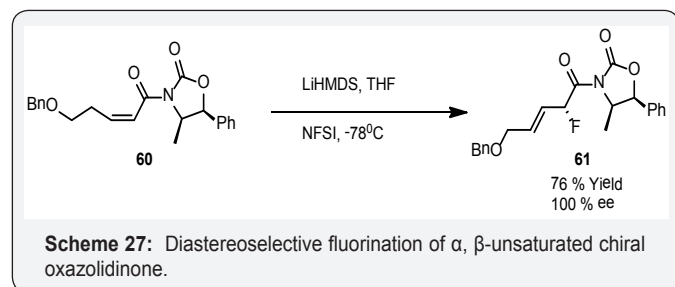
The first organomediated asymmetric ^{18}F fluorination has been accomplished using a chiral imidazolidinone and [^{18}F] *N*-fluorobenzenesulfonimide in (Scheme 26). This method provides access to enantioenriched18F-labeled α-fluoroaldehydes (>90% ee), which are versatile chiral ^{18}F synthons for the synthesis of radiotracers. The utility of this process is demonstrated with the synthesis of the PET (positron emission tomography) tracer (2S,4S)-4-[18F] fluoroglutamic acid [80](Scheme 27).
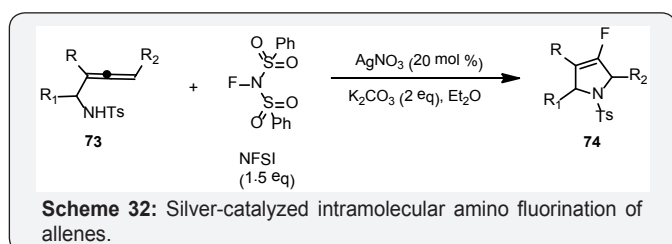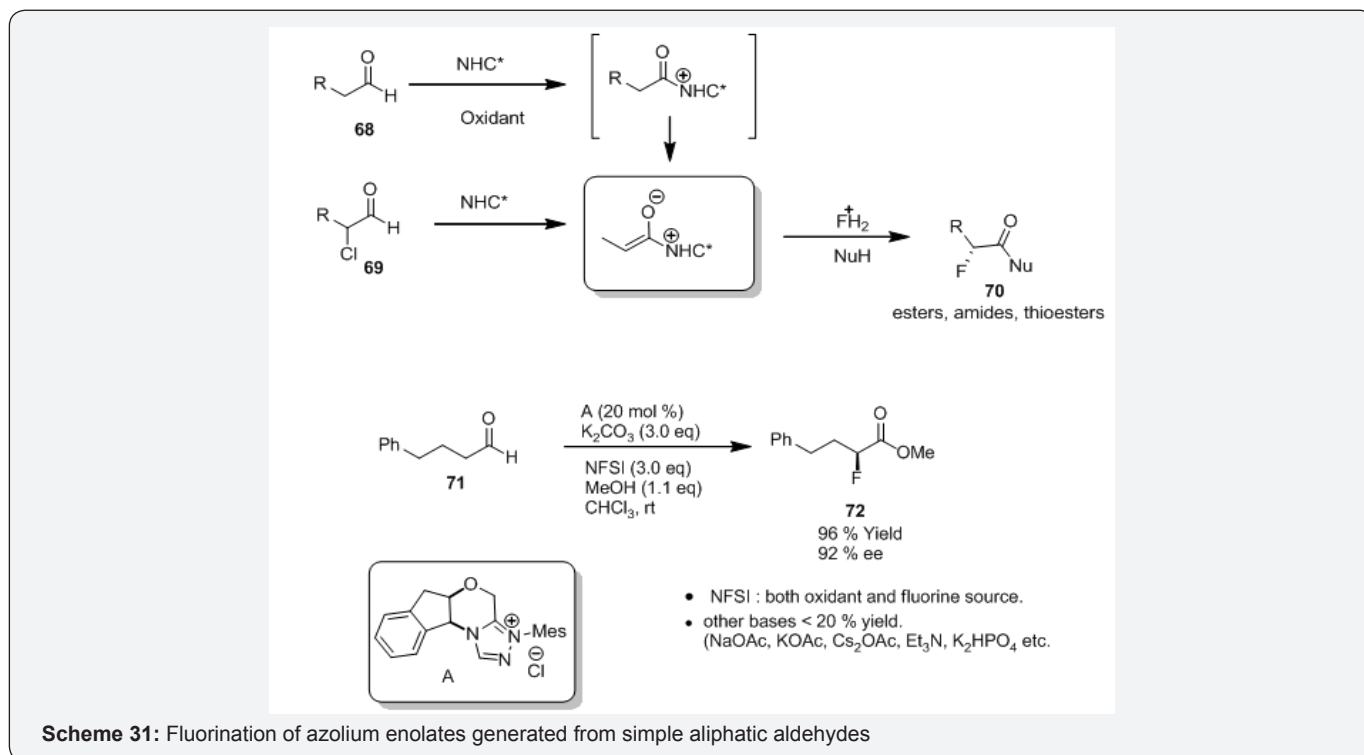
Diastereoselective fluorination of α,β-unsaturated chiral oxazolidinone was conducted by reaction of LiHMDS followed by addition of NFSI to produce a single diastereomer in 76% yield (Scheme 27).The complete diastereoselectivity reached

with NFSI, compared to 82% de with NFOBS, was attributed to the greater steric bulk of NFSI. The reaction provided a nice example of deconjugative electrophilic fluorination. The acyclic fluoro compound was employed in the synthesis of fluoro carbohydrates [81,82] (Scheme 28). Baoming and co workers reports in (Scheme 28) that a convenient and efficient method for fluorination of methylene cyclopropanes is reported. This is exemplified in the stereo selective preparation of N-[(E)-3-fluorobut-3-en-1-yl]-benzene sulfonimides by the reaction of methylene cyclopropanes with N-fluorobenzene sulfonimide (NFSI) in good to excellent yields [83].

Scheme 28: Stereoselective fluorination of methylene cyclopropanes using NFSI.

Scheme 29: Stereoselective α,α-difluoro of γ,γ-disubstituted butenals.

Scheme 30: Catalytic α-fluoro allenoate synthesis.

The allylic moieties has been found in many bioactive compounds and medicines, and compounds with a fluorine atom at the α-position of an allylic moiety, allylic fluorides, have exhibited excellent enhancement of the bioactivity of their parent compounds [84,85]. Furthermore, allyl fluorides have served as versatile intermediates in the synthesis of a large number of fluorinated compounds [86,87] motivating the development of numerous synthetic methods with controlled -regio and stereoselectivity for allylic fluorides in (scheme 29) and (Scheme 30) [88,89].

The first catalytic α-fluoro allenoate synthesis is described by complete the structure with a suitable combination of N-heterocyclic carbine precatalyst, base, and fluorine reagent, the reaction proceeded smoothly to yield a wide range of α-fluoro allenoates with excellent chemoselectivity (Scheme 30). These substituted α-fluorinated allenoates have been synthesized for the first time, and they are versatile synthetic intermediates toward other useful fluorine-containing building blocks [90].

Scheme 31: Fluorination of azolium enolates generated from simple aliphatic aldehydes

Scheme 32: Silver-catalyzed intramolecular amino fluorination of allenes.

The asymmetric fluorination of azolium enolates that are generated from readily available simple aliphatic aldehydes or α-chloro aldehydes and N-heterocyclic carbenes (NHCs) is described in (Scheme 31). The process significantly expands the synthetic utility of NHC-catalyzed fluorination and provides facile access to a wide range of α-fluoro esters, amides, and thioesters with excellent enantioselectivity [91]. Catalytic systems that are based on N-heterocyclic carbenes (NHCs) have proven to be versatile in particular for establishing the α-stereogenic center of esters via key azolium enolate intermediates [92](Scheme 32).

Scheme 33: Enantioselective fluorocyclization of prochiral indoles.
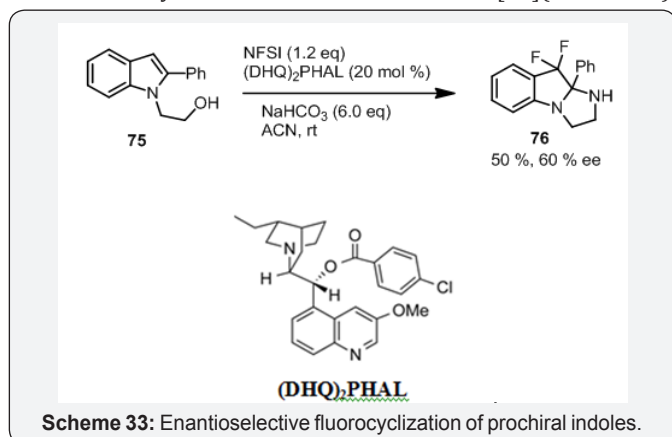
Guosheng Liu and co workers reported a novel silver-catalyzed intramolecular amino fluorination of allenes for the synthesis of 4-fluoro-2,5-dihydropyrroles, in which the vinyl C-Ag bond is cleaved using NFSI to afford vinyl C-F bonds [93]. In addition, further convenient aromatization of fluorinated dihydropyrroles readily afforded the corresponding 4-fluoropyrrole derivatives (Scheme 33). In Scheme 33, Prochiral indole 75 was also subjected to the optimized fluorocyclization conditions, which afforded the difluorinated tricyclic tetrahydro oxazolo [3,2-a] indole 76 in 50% yield, 60% ee [94] (Scheme 34).

R =	yield
Bn,	56 %
$(CH_2)_7CH_3$	67 %
$p(OMe)-C_6H_4CH_2$	65 %
$p(Br)-C_6H_4CH_2$	69 %

Scheme 34: One-pot synthesis of optically active propargylic fluorides.
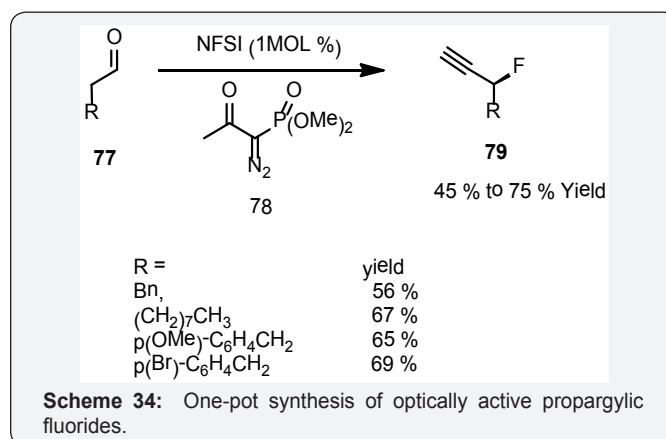
In (Scheme 34), Jørgensen and co-workers reported a simple, direct one-pot organocatalytic approach to the formation of optically active propargylic fluorides 79. This consists of organocatalytic α-fluorination of aldehydes followed by homologation with the Ohira-Bestman reagent 78, providing optically active propargylic fluorides [95,96].

Conclusion

The most significant, conceptual advances over the past decade in the area of fluorination, broadly defined, were made in the reactions that led to the formation of C-F, most prominently by organo and transition-metal catalysis. The most challenging transformation remains the formation of the parent C-F bond, primarily due to the high hydration energy of fluoride, strong metal-fluorine bonds and the highly polarized nature of bonds to fluorine. Reagents of the NF class, several of which are now commercially available, provide the organic chemist with a relatively safe and practical means of selectively positioning fluorine at chosen carbanionic-type sites in molecules. However, the reagents stability in storage and ease of use are achieved at the cost of employing an R2N or R3N+-organic carrier. For many large-scale uses elemental fluorine, somehow "tamed" to act as a predictably selective electrophile, would ultimately be the most economical and environmentally "greener" alternative.

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