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Asymmetric Fluorocyclizations of Alkenes

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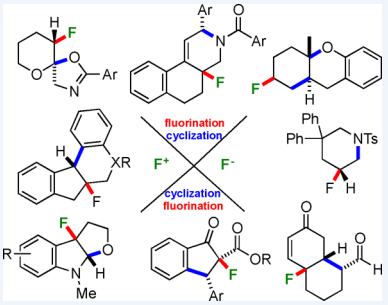
CONSPECTUS: The vicinal fluorofunctionalization of alkenes is an attractive transformation that converts feedstock olefins into valuable cyclic fluorinated molecules for application in the pharmaceutical, agrochemical, medical, and material sectors. The challenges associated with asymmetric fluorocyclizations induced by F^+ reagents are distinct from other types of halocyclizations. Processes initiated by the addition of an F^+ reagent onto an alkene do not involve the reversible formation of bridged fluoronium ions but generate acyclic β-fluorocationic intermediates. This mechanistic feature implies that fluorocyclizations are not stereospecific. A discontinuity exists between the importance of this class of fluorocyclization and the activation modes currently available to implement successful catalysis. Progress toward fluorocyclization has been achieved by investing in neutral and cationic [NF] reagent development. The body of work on asymmetric fluorination using chiral cationic $[NF]^+$ reagents prepared by fluorine transfer from the dicationic $[NF]^{2+}$ reagent Selectfluor to quinuclidines, inspired the development of asymmetric F^+-induced fluorocyclizations catalyzed by cinchona alkaloids; for catalysis, the use of *N*-fluorobenzenesulfonimide, which is less reactive than Selectfluor, ensures that the achiral F^+ source remains unreactive toward the alkene. These organocatalyzed enantioselective fluorocyclizations can be applied to indoles to install the fluorine on a quaternary benzylic stereogenic carbon center and to afford fluorinated analogues of natural products featuring the hexahydropyrrolo[2,3-*b*]indole or the tetrahydro-2*H*-furo[2,3-*b*]indole skeleton. In an alternative approach, the poor solubility of dicationic Selectfluor bis(tetrafluoroborate) in nonpolar solvent was exploited with anionic phase transfer catalysis as the operating activation mode. Exchange of the tetrafluoroborate ions of Selectfluor with bulky lipophilic chiral anions (e.g., TRIP and derivatives) brings into solution the resulting chiral Selectfluor reagent, now capable of asymmetric fluorocyclization. This strategy is best applied to a subset of substrates bearing a nucleophilic pendent group (benzamide is best) capable of hydrogen bonding for association with the chiral phosphate catalyst. These contributions focused on fluoroheterocyclization involving either O- or N-nucleophiles. As for other halocyclizations, alkenes armed with π C-nucleophiles represent the most demanding class of substrates for asymmetric F^+-induced electrophilic fluorination−cyclization. Successful implementation required the design of new chiral Selectfluor reagents featuring stereogenicity on the DABCO core. These reagents, accessible from chiral vicinal diamines, allowed the synthesis of unusual chiral fluorine-containing tetracyclic compounds, some composed of carbon, hydrogen, and fluorine exclusively. The challenges associated with F^+-induced fluorocarbocyclizations prompted methodologists to consider chemistry where the $C_{sp}{}^3$−F bond formation event follows a catalyst-controlled cyclization. An exciting development built on in the area of transition metal π-cyclization of polyenes leading to cationic metal−alkyl intermediates. When intercepted by oxidative fluorodemetalation with a F^+ source, the resulting products are complex polycyclic structures emerging from an overall catalytic cascade fluorocarbocyclization. Complementing F^+-based reactions, examples of fluorocyclizations with fluoride in the presence of an oxidant were reported. Despite some exciting developments, the field of asymmetric fluorocyclizations is in its infancy and undoubtedly requires new activation modes, catalysts, as well as F^+ and F^- reagents to progress into general retrosynthetic approach toward enantioenriched fluorocycles. Numerous opportunities emerge, not least the use of a latent fluorine source as a means to minimize background fluorination.



1. INTRODUCTION

In recent years, fluorine chemistry has undergone intensive development with the appearance of some very effective reactions for applications in the agrochemical, pharmaceutical, and material industries.[1] Priority has been given toward effective catalytic methods to access fluoro(hetero)arenes because of the prevalence of these motifs in, for example, drug discovery. This body of work has significantly improved both our ability to construct $C_{sp}{}^2$−F bonds and our mechanistic understanding of cross-coupling chemistry for the attachment of fluorine substituents onto complex targets.[2] With the aim to expand the chemical space available for drug discovery and for other applications, substrates other than arenes must be investigated. Alkenes present challenges distinct from the ones encountered with (hetero)arenes, both in terms of reactivity and selectivity. The intermolecular vicinal fluorofunctionalization of alkenes is a highly attractive but demanding process, since the three components of this reaction must be assembled in a regio- and stereocontrolled manner. One can simplify the problem by studying the reactivity of alkenes tethered with a functional group that could take part in a fluorocyclization process and interact reversibly with a suitable catalytic entity for rate acceleration and control over selectivity.

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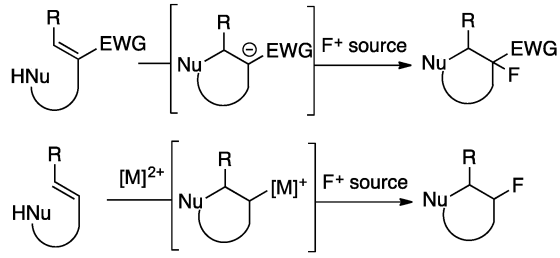
In this Account, we present a discussion of electrophilic and nucleophilic fluorination approaches toward enantioselective fluorocyclizations of prochiral alkenes with commentaries on the importance of the fluorine source on reactivity and selectivity. The term fluorocyclization refers to processes that involve C−F bond formation prior to or post cyclization. In this piece, we are not intending to present a comprehensive review on asymmetric fluorocyclization, but the focus is on discussing transformations selected for their mechanistic insight and/or appealing synthetic value.

Halocyclizations induced by an electrophilic halogenating reagent have been studied extensively, but asymmetric catalytic variants have only recently been reported. In an authoritative review, Denmark and co-workers critically discussed the challenges associated with this chemistry.[3] To achieve catalysis, the nature of the halogenating reagent is important as it should remain unreactive toward the alkene unless activated in the presence of the catalyst, either a Brønsted acid, Lewis acid, or Lewis base; alternatively, the halogenating reagent can be rendered soluble and therefore reactive under phase transfer catalysis. A key factor toward successful enantioselective halofunctionalization is the recognition that enantioenriched haliranium ions could racemize through olefin-to-olefin transfer,[4] a process that must be suppressed if occurring faster than nucleophilic capture; racemization of the haliranium ion generates diastereomeric ion pairs that may react with different rates. With these considerations in mind, catalytic enantioselective halocyclizations were successfully demonstrated relying on control elements designed to maintain close association between the chiral catalyst and the haliranium ion intermediate. This was achieved through dative or Coulombic interactions between a Lewis base and the haliranium ion itself, or between the catalyst and the alkene presenting with functional groups capable of hydrogen bonding association. Alternatively, the interaction of a Lewis basic site on the substrate with a chiral Lewis acid can provide the necessary chiral environment for activated capture of the haliranium ion. To date, chiral ion pairing catalysis is possibly one of the most successful strategies for enantioselective halofunctionalization reactions.

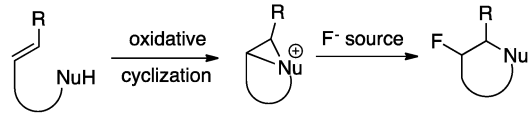
Electrophilic fluorocyclizations have progressed slowly until the recent surge of interest for fluorine chemistry. Since the halogen source was found critically important in iodo-, bromo-, and chlorocyclizations,[5] it is perhaps the difficulties associated with the preparation of new electrophilic sources of fluorine that caused such delays. Most commercially available "F^+" sources are prepared from F_2, and few institutions have the expertise to handle this gaseous reagent, should new F^+ reagents be required. More fundamentally, the electrophilic fluorination-functionalization of alkenes is mechanistically distinct from other halogenation as this reaction does not involve a bridged fluoronium ion but generates an acyclic cationic intermediate instead. Halonium ions, in which positively charged chlorine, bromine, and iodine are equivalently attached to two carbon atoms through three-center bonds, are well documented and the formation of these ions have given important insights into the origins of stereoselectivity in iodo-, bromo-, and chlorocyclizations. Chemical and theoretical evidence for the transient generation of a symmetrical fluoronium ion from a carefully designed precursor was recently reported, but the ability of fluorine to form a fluoronium ion is the exception rather than the rule.[6] This implies that the fluorofunctionalization of olefins is not a stereospecific process. Further complications emerge with the realization that so-called electrophilic fluorination can involve single electron transfer processes.[7] Various asymmetric fluorocyclizations were reported in recent years to access enantioenriched mono- and polycyclic products. Not all asymmetric fluorocyclizations are catalytic processes, illustrating the challenges associated with this field of research. Existing efforts may be broadly divided into distinct categories since C−F bond formation may occur post or prior to cyclization, two mechanistic scenarios leading to products resulting from net asymmetric fluorocyclization. Most approaches make use of electrophilic fluorination reagents, but selected fluorocyclizations where C−F bond formation results from fluoride attack are known; these reactions are performed with an oxidant. These approaches are discussed commenting on the origin of stereocontrol and on the mode of activation for catalytic processes (Scheme 1).

Scheme 1. Classification of Strategies for Fluorocyclization[a]

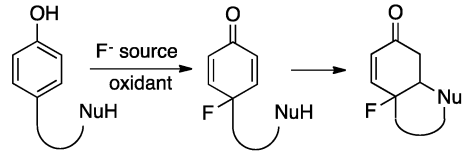
Type I. *Electrophilic fluorination post cyclization*



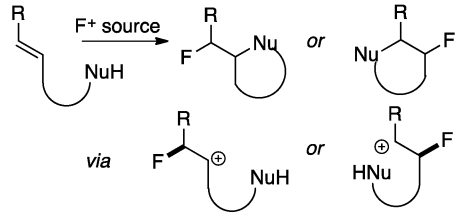
Type II. *Nucleophilic fluorination post oxidative cyclization*



Type III. *Cyclization post oxidative nucleophilic fluorination*



Type IV. *Cyclization post electrophilic fluorination*



[a]EWG = Electron withdrawing group. [M] = Metal.

2. FLUORINATION POST CYCLIZATION

Early work on enantioselective fluorocyclization focused on cyclization−fluorination sequences employing *electrophilic fluorine sources* (type I). This chemistry employs a metal catalyst that activates the alkene toward cyclization either through an ancillary activating carbonyl-containing functional group or via C=C bond activation (π-acidic metals). The intermediate resulting from cyclization is then captured by an electrophilic fluorine source.

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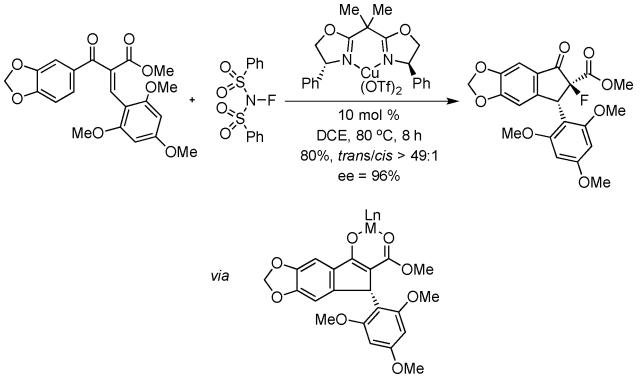
A study from Ma and co-workers in 2007 showed that alkylidene β-ketoesters capable of two-point binding association with the $Cu(OTf)_2$ catalyst underwent Nazarov 4π-electrocyclization with capture of the resulting metal bound enolate with *N*-fluorobenzenesulfonimide (NFSI) (Scheme 2).[8] The

Scheme 2. Cu-Catalyzed Asymmetric Nazarov 4π-Electrocyclization Preceding Fluorination

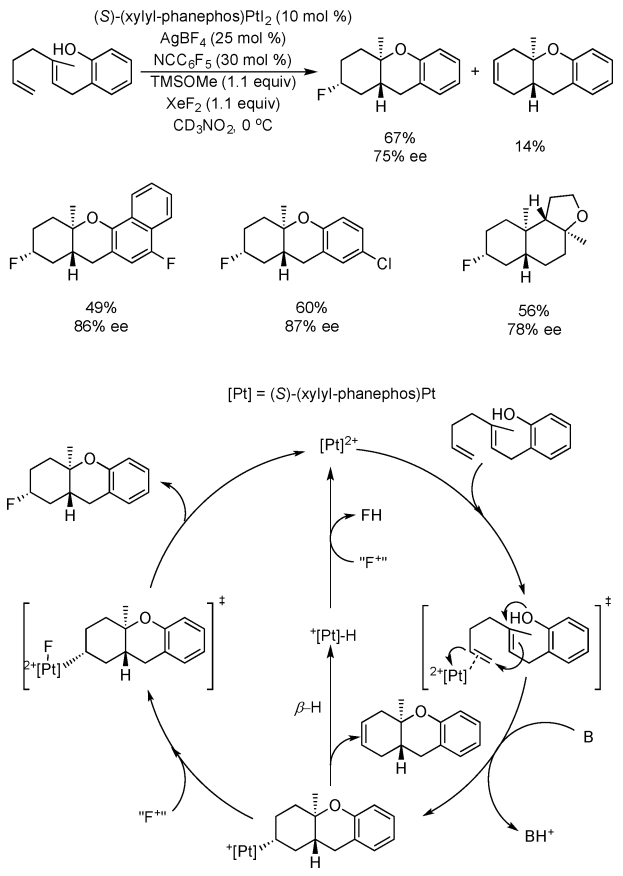


fluorinated indanones were formed as a single stereoisomer (diastereomeric ratios (dr) were typically superior to 20:1), a result prompting the development of an asymmetric catalytic variant of this process. The combined use of $Cu(OTf)_2$ and (*R*)-Ph-bis(oxazoline) provided enantiometric excess (ee) ranging from 34% to 96% with a narrow substrate scope. Attempts by the group of Kawatsura and Itoh to expand the synthetic value of this process with the preparation of 5-fluorocyclopentenones from acyclic divinylketones met with little success.[9]

Gagné and co-workers exploited the rich chemistry of transition metal catalyzed π-cyclization and metal−carbon fluorination reactions to achieve the catalytic enantioselective cyclization-fluorination of polyenes.[10] The process employs a soft Lewis acidic Pt(II) complex to induce C−C bond forming cationic olefin cascade cyclization (Scheme 3). The resulting cationic Pt-alkyl intermediate is then intercepted by oxidative Pt−C fluorination with an F^+ source. Phenol-containing dienes and trienes underwent cyclization−fluorination in the presence of the active (*S*)-(xylyl-phanephos)$Pt(NCC_6H_5)_2[(BF_4)_2]$ catalyst and XeF_2 to afford various C3-fluorinated carbocycles with ee reaching 88%. The products arising from competitive β-hydride elimination could not be entirely suppressed (<25%), a side reaction leading to HF contamination. Since HF enhances the reactivity of XeF_2, a scavenger (TMSOMe) was required to prevent direct fluorination of phenol. Less reactive F^+ sources led predominantly to elimination. This process requires the chiral ligated Pt(II) catalyst to induce enantioselective cascade cyclization, followed by F^+ oxidation of the resulting enantioenriched $C_{sp}{}^3$−Pt(II) intermediate to generate a putative [Pt(IV)]F dication, undergoing stereoretentive reductive elimination. This study is significant as the underlying principles to achieve catalysis and stereocontrol may be applied to synthesize various fluorine containing carbo- and heterocycles with control over absolute and relative stereochemistry. The identification of a suitable F^+ reagent is likely to play a critical role for such developments to materialize.

Numerous fluorocyclizations featuring a cyclization followed by nucleophilic fluorination are known for the preparation of racemic fluorine containing products (type II) (Scheme 1).

Scheme 3. Pt(II)-Catalyzed Cascade Cyclization−Fluorination[a]



[a](*S*)-Xylyl-phanephos = (*S*)-4,12-bis[di(3,5-xylyl)phosphino]-[2.2]-paracyclophane.

Oxa- and aza-Prins fluorination cyclizations afforded 4-fluoropyran and 4-fluoro-piperidine heterocycles using $BF_3{\cdot}OEt_2$.[11] The moderate diastereoselectivity of these reactions has discouraged further studies to achieve enantiocontrol. Liu and co-workers disclosed a series of fluoroamination of unactivated alkenes, and advanced a Pd(II)/Pd(IV) catalytic process for these reactions performed with $PhI(OPiv)_2$ and AgF.[12,13] A metal free variant employing $PhI(OPiv)_2$ and HF·pyridine in the presence of $BF_3{\cdot}OEt_2$ was applied to convert tosyl-protected pent-4-en-1-amines to 3-fluoropiperidines.[14] This transformation is reminiscent of the various fluorocyclizations of alcohols and carboxylic acids conducted with iodoarene difluorides in the presence of amine−HF complexes. All these reactions lead to racemic products.

Inspired by these precedents, Nevado and co-workers enhanced the synthetic value of this chemistry by employing chiral difluoroiodonium reagents to induce enantiocontrol (Scheme 4A).[15] This work is an example of asymmetric fluorocyclization of type II, employing an $ArI(III)F_2$ reagent to induce oxidative cyclization with release of fluoride for C−F bond construction. Fluoropiperidines and fluoroazepanes possessing a single stereogenic carbon were generated from terminal sulfonamide-containing alkenes with ee reaching 81%. Mechanistic experiments examining the reactivity of [*D*]*E*- and [*D*]*Z*-alkene informed that these *endo* fluorocyclizations are stereospecific. A reaction mechanism involving oxidation of the sulfonamide rather than the alkene was proposed. The chiral

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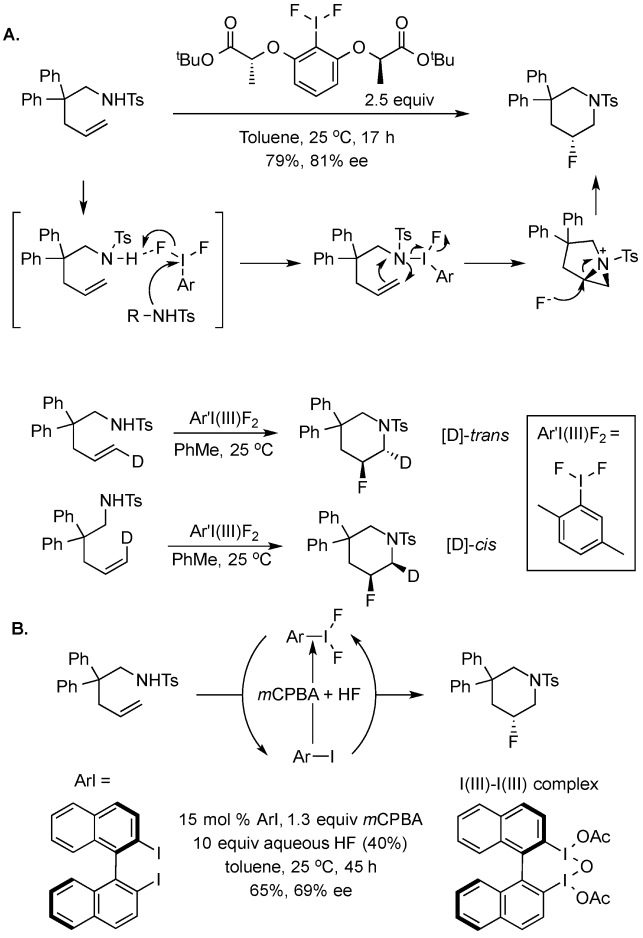
Scheme 4. Asymmetric Oxidative Fluoroamination of Prochiral Alkenes



iodoarene difluoride acts both as oxidant and fluoride source by inducing asymmetric oxidative aziridination followed by regio- and diastereoselective fluoride opening of the highly strained cationic bicycle at the most substituted carbon.

In an elegant study, Kita, Shibata, and their co-workers demonstrated that asymmetric fluoroamination of alkenes can be performed catalytically in toluene using 10 mol % of (*R*)-binaphthyl diiodide and *m*-CPBA as the stoichiometric oxidant in the presence of an excess of aqueous HF (Scheme 4B).[16] Under these conditions, (*R*)-5-fluoro-3,3-diphenyl-1-tosylpiperidine was isolated in 65% yield and 69% ee. Preliminary mechanistic studies using stoichiometric amount of independently prepared I(III)−I(III) complex indicate that oxygen-bridged hypervalent I(III)−I(III) species would be reactive for this transformation. The origin of the stereochemical outcome is not known, but the $\pi-\pi$ interaction between the phenyl-substituted alkene and the catalyst could play a key role since the enantioselectivity dropped significantly to 3% ee when the two phenyl of the substrate are replaced with methyl groups.

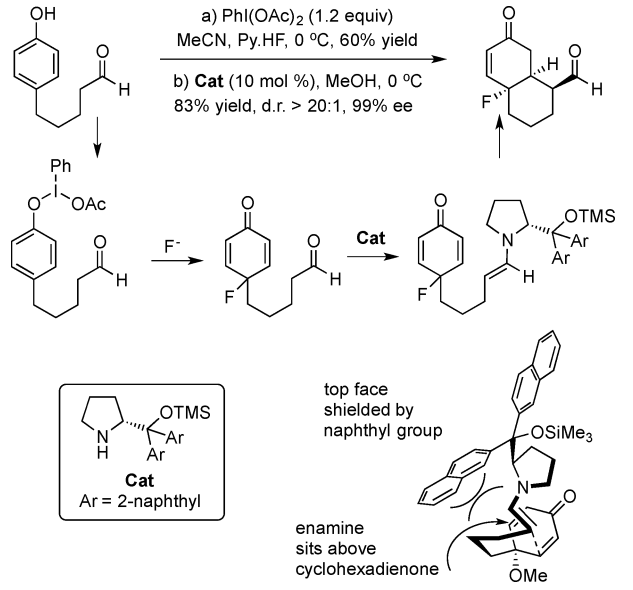
Nonterminal alkenes that could lead to the formation of diastereomeric cyclized products were not considered for these asymmetric fluoroaminations.

3. CYCLIZATION POST FLUORINATION

The literature on asymmetric fluorination−cyclization is more extensive, with all employing electrophilic $[NF]^+$ reagents, except for one reaction. For transformations using an $[F]^+$ reagent, the lack of evidence for the formation of a fluoronium intermediate sharply contrasts with the haliranium intermediates formed for other X^+-induced halocyclizations. The enantiodetermining step of type IV asymmetric electrophilic fluorocyclizations consists of net "F^+ addition" onto the alkene leading to $C_{sp}{}^3$−F stereogenicity, a process affording a cationic intermediate captured intramolecularly with a nucleophile. Regio- and enantiocontrol upon F^+ addition must be achieved prior to cyclization, a challenge particularly acute for structurally unbiased nonterminal alkenes. In this section, we comment on the unique transformation employing a fluoride source and illustrating a type III fluorocyclization; we then survey the work of the Gouverneur and Toste research groups that contribute to the development of type IV fluorocyclizations setting these advances in the broader context.

In 2007, Gaunt and co-workers reported an asymmetric fluorination-cyclization of type III (Scheme 5).[17] Exploiting the

Scheme 5. Oxidative Fluorination Followed of Phenols Followed by Enantioselective Organocatalytic Michael Addition



inherent reactivity of phenols toward oxidation with the hypervalent iodine reagent $PhI(OAc)_2$, a para-substituted phenol was dearomatized in the presence of Olah's reagent (HF.pyridine). The subsequent cyclization of the resulting 4-fluorocyclohexa-2,5-dien-1-one was accomplished via asymmetric enamine catalysis on the pendent aldehyde using 10 mol % of Jørgensen's pyrrolidine catalyst. Under these conditions, Michael addition took place to furnish a fluorinated decalin with excellent enantio- and diastereocontrol. The sense of enantiocontrol was rationalized by evoking an *endo*-like attack onto the *Si* face of the fluoro-cyclohexadienone. For this fluorocarbocyclization, the enantiodetermining desymmetrization event elegantly bypasses the challenges associated with asymmetric catalytic fluorination. This unique example of asymmetric oxidative fluorocyclization reaction that utilizes a nucleophilic fluorine source illustrates how readily accessible substituted phenols may be converted into complex molecular architectures with $C_{sp}{}^3$−F stereogenicity.

All the fluorocyclizations discussed so far are distinct from archetypical halocyclizations that are induced by an electro-

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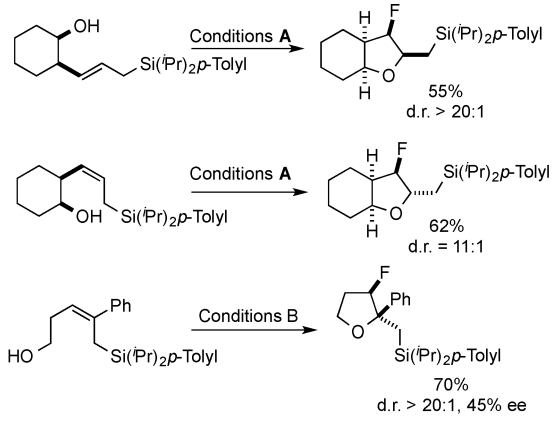
philic halogen reagent. Hereafter, we discuss efforts from the Gouverneur and Toste groups to realize control over this most fundamental reaction allowing access to enantioenriched fluorine containing hetero- and carbocycles.

Our strategy seeks inspiration from the body of work on reagent-controlled asymmetric fluorination that served as a starting point toward the development of the first asymmetric electrophilic fluorocyclization type IV. Various groups reported the synthesis of chiral neutral and cationic [NF] reagents and their use for stereogenic C_{sp}^3–F bond construction. Chiral $[NF]^+$ reagents derived from cinchona alkaloids have been used extensively because they are readily prepared by quantitative fluorine transfer from the dicationic $[NF]^{2+}$ reagent Selectfluor.[18,19] $[NF]^+$ Reagents are typically significantly less reactive than the $[NF]^{2+}$ reagents, a reactivity profile presenting significant challenges for methodologists interested in fluorination–cyclization of unactivated feedstock alkenes. In our hands, the lack of reactivity of homoallylic alcohols toward *N*-fluoroquiniclidinium salts encouraged the use of temporarily activated alkenes. Our early work on asymmetric fluorination of allylsilanes (allyl anion equivalents)[20] as a route to allyl fluorides led us to consider allylsilanes as 1,2-dipoles for intramolecular electrophilic fluoroetherification (Scheme 6).[21]

Scheme 6. Stereospecific Asymmetric Fluorocyclization of Silyl-Activated Alkenes[a]



[a](DHQ)$_2$PYR = Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether.

This strategy required homoallylic alcohols activated with silyl groups bulkier than trimethylsilyl to prevent desilylation in favor of intramolecular nucleophilic capture of the silyl-stabilized *β*-fluorocation generated upon F^+ addition onto the alkene. After fluorocyclization, the silyl group could be oxidatively deleted releasing a hydroxyl functionality in place of the silyl group. The *endo* cyclizations of allylsilanes were successfully performed using NFSI or Selectfluor. These reactions are stereospecific leading to *syn* and *anti* 3-fluorotetrahydrofurans from the *E*- and *Z*-alkenes respectively, with dr > 20:1 for *E*-alkenes and dr in the range of 10:1 for *Z*-alkenes. The reaction of the chiral $[NF]^+$ reagent derived from (DHQ)$_2$PYR with silyl-activated (*Z*)- 4-phenyl-pent-3-en-1-ol led to the desired enantioenriched *trans*-3-fluoro-2-phenyl-tetrahydrofuran with a dr > 20:1, but ee not exceeding 50%. Based on X-ray crystallography and NMR studies, Shibata and co-workers reported that chiral *N*-fluoro(dihydro)quininium salts exist in the open conformation in both the solid and solution states.[22] The authors proposed that the sense of enantiocontrol for asymmetric fluorination other than fluorocyclizations is the result of steric interaction guiding selective substrate orientation within the cleft cavity of the alkaloid. These $[NF]^+$ reagents work efficiently for a narrow range of substrates. This efficacy scope corroborates our observation since we found that asymmetric fluorocyclizations are not suitable for a range of other allylsilanes that were reactive but afforded low enantiomeric excesses. Further development in fluorocyclization using this reagent-controlled approach would therefore require more reactive chiral F^+ reagents capable of more precise association with the substrate to augment enantiometric ratio (er) and broaden the substrate scope of this approach. In our laboratory, the development of an asymmetric catalytic fluorocyclization took priority.

The convenience of generating chiral N–F reagents in situ from Selectfluor, prior to substrate addition, is attractive but the higher reactivity of Selectfluor versus *N*-fluorocinchonium salts implies that enantioselective catalysis with substoichiometric amount of cinchona alkaloid is difficult to achieve with such systems. Fluorine transfer from less reactive F^+ sources offers a possible solution to this problem. Shibata and co-workers demonstrated the feasibility of this approach with various cinchona alkaloid catalyzed enantioselective fluorinations of silyl enol ethers, allylsilanes and oxindoles.[23] The key to success was the replacement of Selectfluor with less reactive NFSI and the addition of excess K_2CO_3 using acetonitrile as the reaction solvent. The authors proposed a catalytic cycle featuring the chiral *N*-fluoroammonium sulfonimide salt formed in situ and engaging in anion exchange with K_2CO_3 to afford the putative reactive chiral F^+ species (Scheme 7A). Catalysis was achieved with er mirroring the results obtained using stoichiometric amount of cinchona alkaloids. These precedents laid a solid foundation toward the development of type IV catalytic enantioselective fluorocyclizations. Our initial investigations toward this goal focused on the reactivity of prochiral tryptamine derivatives since the core indole motif is known to undergo electrophilic fluorocyclization with moderately reactive achiral F^+ reagent, for example *N*-fluorotrimethylpyridinium triflate.[24] The asymmetric fluorocyclization of variously substituted indoles was successful upon treatment with chiral $[NF]^+$ reagents derived from Selectfluor and various cinchona alkaloids.[25] To achieve catalysis, NFSI was used as the parent achiral F^+ source. Enantioenriched tetrahydrofuroindoles were formed with er reaching 96:04 when the reaction was performed in acetone at −78 °C with (DHQ)$_2$PHAL (20 mol %), *N*-fluorobenzenesulfonimide, and K_2CO_3 in excess. These reactions represent the first examples of type IV catalytic enantioselective electrophilic fluorocyclizations. Indoles substituted with various *N*-protected amines such as NH-tosyl, $NHCO_2Me$, and NHBoc groups participated efficiently in these reactions (Scheme 7B). The cyclization products were formed as single *cis* diastereomers, a stereochemical outcome imposed by the formation of the bicyclic [3.3.0] system. The absolute configuration unambiguously assigned by X-ray diffraction studies on a single crystal indicates that the sense of enantiocontrol is consistent with the asymmetric fluorination of structurally related cyclic substrates such as allylsilanes or

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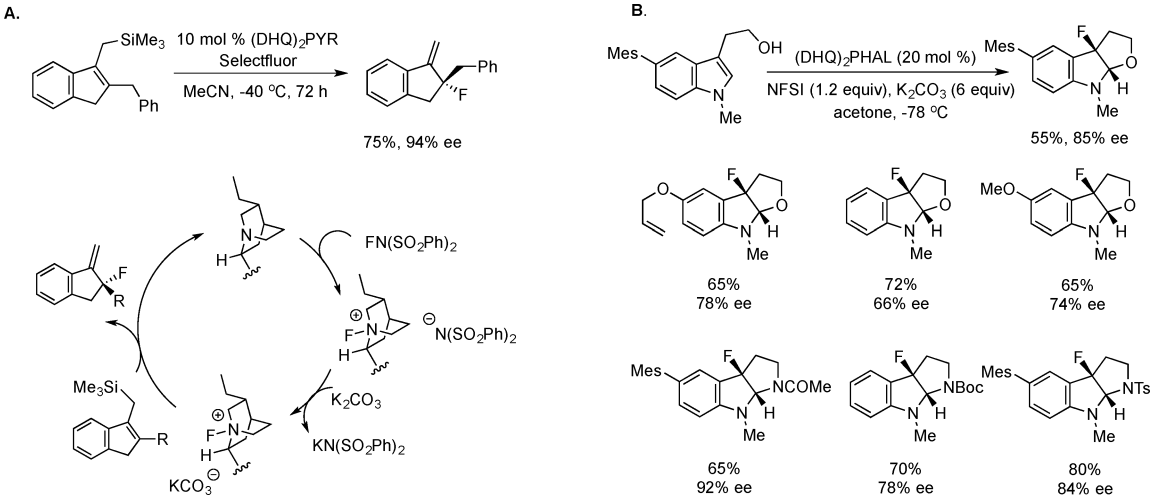
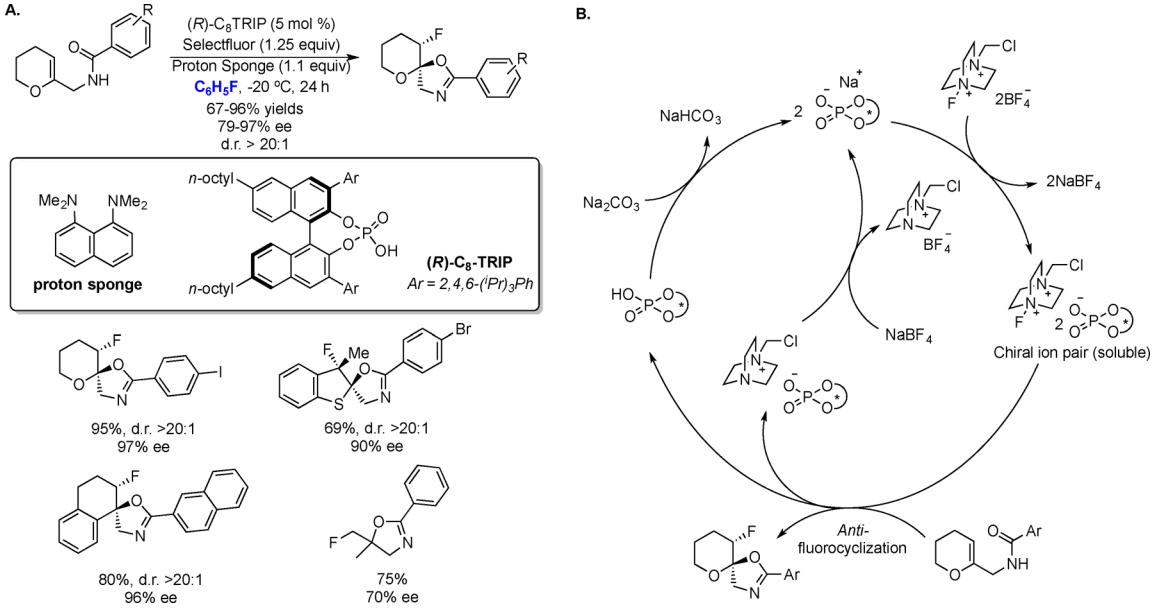
Scheme 7. (A) Catalytic Asymmetric Fluorination of Allylsilanes and Proposed Catalytic Cycle and (B) Catalytic Asymmetric Fluorocyclization of Indoles[a]



[a](DHQ)$_2$PHAL = hydroquinine 1,4-phthalazinediyl diether.

Scheme 8. (A) Fluorocyclization of Dihydropyrans under Chiral Ion Pairing Catalysis and (B) Suggested Catalytic Cycle



oxindoles. Preliminary ^{19}F NMR studies demonstrate that fluorine transfer from NFSI to (DHQ)$_2$PHAL does not take place at −78 °C, a result advocating against a mechanism involving in situ formation of F(DHQ)$_2$PHAL$^+$. This led us to propose that associative complexation takes place possibly through hydrogen bonding of the cinchona alkaloid catalyst with the indole substrate and/or NFSI. This hypothesis would be consistent with the level of enantioselectivity found to be dependent on ability of the pending nucleophile (OH, NHCOMe, NHBoc, NHTos) to engage in hydrogen bonding.[26]

This chemistry inspired the development of an asymmetric catalytic fluorolactonization performed with Selectfluor, Na_2CO_3, and a catalytic amount of (DHQ)$_2$PHAL (hydroquinine 1,4-phthalazinediyldiether) in hexane. The resulting fluoromethyl-substituted isobenzofuran was formed but er did not exceed 65:35.[27]

Catalytic processes based on chiral anions[28] served as a conceptual platform toward phase transfer catalysis as an activation mode for catalytic enantioselective fluorocyclizations. Toste and co-workers recognized that the insolubility of dicationic Selectfluor bis(tetrafluoroborate) in nonpolar solvents may be exploited for the development of an elegant "charge-inverted" phase transfer catalytic process (Scheme 8).[29] Bulky lipophilic chiral anions could exchange with the tetrafluoroborate ions of Selectfluor to bring the resulting reagent in solution in the form of a now reactive chiral ion pair capable of asymmetric fluorination. This hypothesis was validated with the enantioselective electrophilic fluorocyclization of dihydropyrans, dihydronaphtalenes, benzothiophenes, and acyclic *gem*-disubstituted alkenes all possessing a benzamide group as the nucleophile. Commercially available 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (TRIP) and selected derivatives (e.g., (*R*)-C8-TRIP) proved to be highly efficient catalysts for reactions

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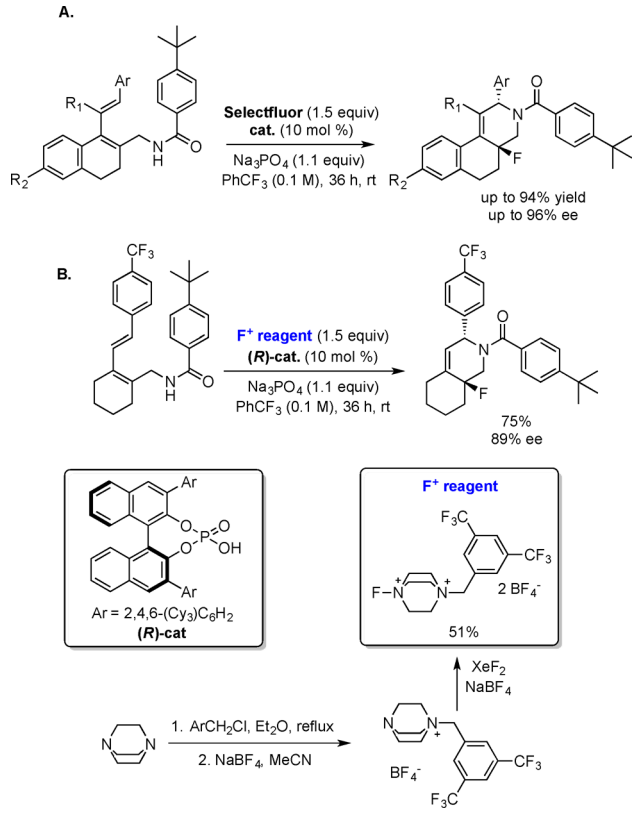
performed in fluorobenzene. *anti*-Fluorocyclizations with the amide nucleophile reacting at oxygen led to dihydrooxazole-containing products formed in high yields and high er of up to 99:01; the reactions were less effective in terms of enantiocontrol (er 85:15) for acyclic alkenes. The nonlinear relationship between the enantiopurity of the anionic catalyst and product led the authors to propose that both tetrafluoroborates are exchanged with chiral phosphates, and this is prior to reaction with the prochiral substrate. Further studies expand the scope of this mode of catalysis to cyclic enamides. For these reactions, it was proposed that one of the two oxygens of the chiral phosphate anion forms an ion pair with Selectfluor, while the other activates the enamide-substrate through hydrogen bonding. This synergic association accounts both for catalysis and the sense of enantiocontrol.[30,31]

This strategy is applicable to substrates aligned with the reactivity profile of Selectfluor with control over enantioselectivity being dependent on the ability of the prochiral alkene to expose preferentially one enantiotopic face toward the in situ generated dicationic chiral $[NF]^{2+}$ reagent. To date, only alkenes with amide nucleophiles engaged in fluorocyclizations, likely due to the ability of this particular nucleophile to associate adequately with the $[NF]^{2+}$ reagent through hydrogen bonding. Structural diversity is however permitted around the alkene. Conjugated 1,3-dienes substituted with benzamides participated effectively in asymmetric fluorocyclization under anionic reverse phase transfer catalysis.[32] These reactions led to cyclized products resulting from net 1,4-fluorofunctionalization with er reaching 98:2 when using chiral anion TCYP. For these systems, Toste and co-workers suggest that the pendent amido nucleophile engages in *N*-cyclization through concerted *anti*-1,4-addition across the diene, not through a pathway involving an equilibrating allyl cation; this mechanistic hypothesis is supported by a control experiment conducted with a substrate that was unable to react in a concerted fashion due to increased $A^{1,3}$ strain in the proposed transition state. A range of 6-*endo*-trig 1,4-fluoroamination of 1,3-dienes led to functionalized benz[*f*]isoquinolines with variable levels of distereoselectivity but consistently high ee. Control over selectivity was found to be dependent on the substrate; for 1,3-dienes embedded within the dihydronaphtalene structural core, substitution of the diene with a terminal unsubstituted phenyl group (Ar = Ph; Scheme 9A) led to products with reduced dr but er remained consistently superior to 95:05. Less reactive dienic systems required a more reactive electrophilic fluorinating reagent since no reaction occurred using Selectfluor. This was achieved by replacing the chloromethyl group of Selectfluor with a more powerful electron-withdrawing group. These new reagents are easy to access as fluorination of the dabconium core resulting from *N*-monoquaternization was possible with XeF_2, which has the distinct advantage of yielding Xe and fluoride as the reaction byproducts to facilitate purification. The requirement for structural fine-tuning of halogenating reagents is common in halocyclization methodology, but this study demonstrates that Selectfluor can be structurally modified to enhance both reactivity and selectivity; these new reagents afforded the products of fluorocyclization in good yields, dr > 20:1 and ee reaching 89% (Scheme 9B).

The Toste group applied the concept of reverse chiral anion phase transfer catalysis to various asymmetric reactions inclusive of allylic fluorinations.[33] A fluoro-oxycyclization byproduct was detected (<15% yield) when subjecting α-methyl substituted dihydronaphthalenes with amide directing

Scheme 9. (A) Asymmetric Catalytic Fluoroamidation of 1,3-dienes and (B) Fluorocyclization of Less Activated Systems Using Modified Selectfluor



groups to fluorination. The cyclization product predominates when the reaction was performed under homogeneous conditions regardless of the presence of catalyst. Mechanistic investigations suggest the involvement of a concerted fluorination−deprotonation, a process possibly assisted by either the phosphate anion or the amide group located on the substrate. This mechanistic path is distinct from electrophilic fluorination leading to a carbocationic intermediate and may offer opportunities to impose diastereospecificity in addition to enantiocontrol (Scheme 10).

To this point, all type IV fluorocyclizations employed alkenes substituted with heteronucleophiles. Electrophilic halocarbocyclizations requiring capture of the reactive intermediates with a π C-nucleophile represent a class of notoriously challenging processes that have required the development of new X^+ sources for successful implementation. Asymmetric variations are limited to the work of Ishihara and co-workers who reported an enantioselective iodocarbocyclization of phenyl-substituted trienes requiring stoichiometric amount of chiral Lewis base (phosphoramidite) and *N*-iodosuccinimide.[34] Only racemic products were formed using substoichiometric amount of the chiral Lewis base. Considering the importance of fluorinated carbocycles (e.g., steroids) in medicinal chemistry, it is remarkable that asymmetric fluorocarbocyclization of alkenes was not investigated until the Pt-mediated type I fluorocyclization process of Gagné.

Alkenes or arenes could serve as C-nucleophiles, and both motifs present with distinct challenges. The initial F^+−olefin reaction generates a β-fluoro carbocation that would react with an alkene to form a new carbocationic species, with all reactive intermediates amenable to nonproductive termination path-

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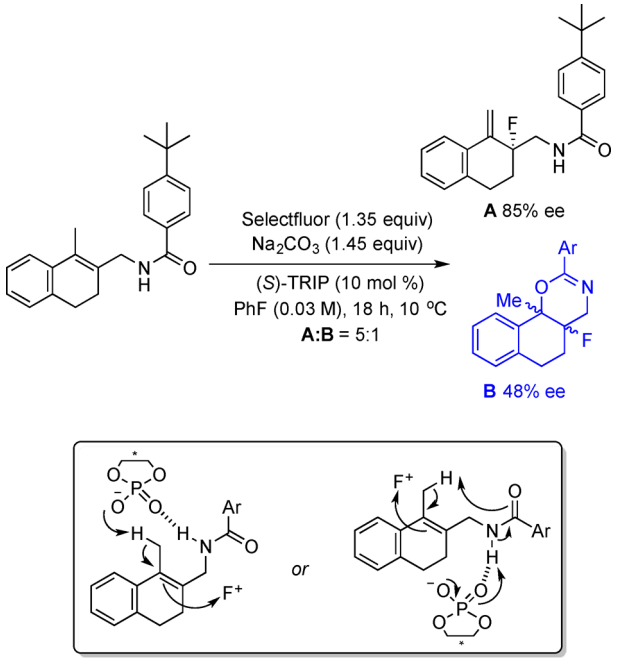
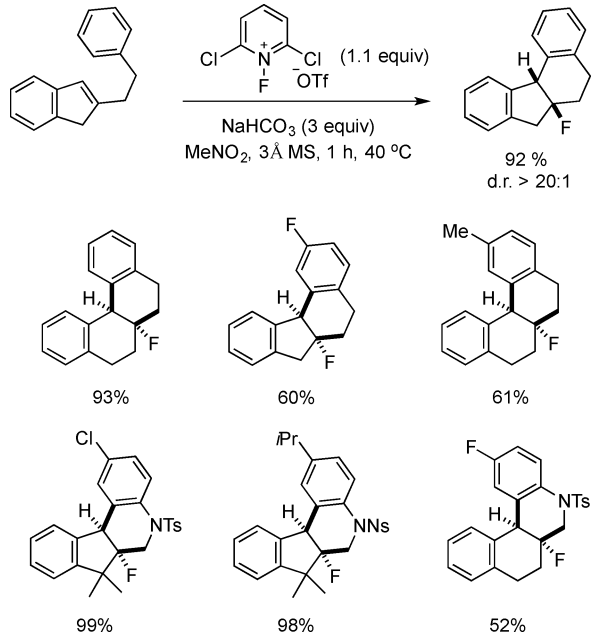
Scheme 10. Fluoro-Oxycyclization from Amide Directed Asymmetric Fluorination of α-Methyl Dihydronaphthalenes



Scheme 11. Fluorocarbocyclization of Indenes and 1,2-Dihydronaphtalenes[a]



[a]For all products, dr > 20:1.

ways. Such a cascade process requires careful orchestration of all elementary steps, not least control over alkene chemoselectivity for the initial F^+ addition event. Arenes do not present the problem of alkene selectivity, but the nucleophilicity of arenes toward carbocations may influence fluorocarbocyclization efficacy; the parametrization of these factors was presented by Mayr et al. who discussed the effects of π-nucleophilicity in the context of C−C bond-forming reactions.[35] To simplify matters, we focused on the fluorocarbocyclization of aryl-substituted alkenes and studied this system in racemic series prior to envisaging the production of enantioenriched fluorocarbocyclic products.

Preliminary investigation probed the reactivity of indene C-2 substituted with 2-phenylethyl with various F^+ sources.[36] NFSI led to competitive net addition across the double bond, and Selectfluor was ineffective in acetonitrile as this solvent led to fluoro-Ritter products. Selectfluor and *N*-fluoro-2,6 dichloropyridinium triflate were effective in nitromethane affording the desired product in 59% and 92% yield, respectively. Under optimized conditions consisting of treatment of the substrate with 1.1 equiv of the *N*-fluoro-2,6 dichloropyridinium triflate in nitromethane for 1 h at 40 °C, numerous C-2 substituted indenes and 1,2-dihydronaphtalenes participated in the fluorocarbocyclization affording novel helical-shaped tetracyclic products formed exclusively as *cis* diastereomers, with the fluorine substituent on a quaternary carbon at the ring junction (Scheme 11).

Our success in the validation of a metal free electrophilic fluorocarbocyclization led us to consider the feasibility of an asymmetric variant using preformed $[NF]^+$ reagents derived from cinchona alkaloids. No reaction took place with these reagents, an outcome defining the limitation of these chiral $[NF]^+$ reagents and highlighting the difference of reactivity between $[NF]^+$ and $[NF]^{2+}$ reagents derived from quinuclidine and 1,4-diazabicyclo[2.2.2]octane (DABCO), respectively. We considered reverse anionic phase transfer catalysis next. No reaction occurred when 2-phenethyl-1*H*-indene was reacted with Selectfluor, $NaHCO_3$, and 10 mol % of the chiral phosphonic acid (*R*)-TRIP (3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogen phosphate) in apolar solvents. The use of nitromethane instead of hexanes induced fluorocarbocyclization, but this polar solvent afforded the carbocyclized product as a racemate. The absence of amide functionality amenable to engage in hydrogen bonding with the chiral phosphonic acid may be responsible for this outcome. Since catalytic manifolds successfully applied to type IV fluoroheterocyclization failed to deliver, we sought to focus on the development of an asymmetric fluorocarbocyclization with the design of novel chiral $[NF]^{2+}$ dicationic reagents featuring stereogenicity on the DABCO core. This new class of chiral reagents should display a reactivity profile similar to Selectfluor, may benefit from tunable reactivity as well as solubility, and could induce superior enantioefficiency varying the substituents located onto the DABCO core. Conventional chemistry was applied to prepare chiral DABCOs that were subjected to *N*-quaternization with MeOTf followed by *N*-fluorination with F_2. As an alternative to F_2, the commercially available *N*-fluoro-pentachloropyridinium triflate enabled complete and clean fluorine transfer to *N*-methylated DABCO precursor; this protocol allows for in situ formation of chiral Selectfluor reagents as an alternative to the use of preformed reagents (Scheme 12).

Asymmetric fluorocarbocyclization took place with these novel chiral $[NF]^{2+}$ reagents, with conversion and ee varying as a function of the structural features of these reagents as well as the solvent. Optimization of the reaction conditions revealed that dioxane was best but DCM and DCE were also effective. This observation had significance in itself since homogeneous electrophilic fluorination reactions are typically restricted to highly polar solvents such as acetonitrile, acetic acid, or even water. Therefore, adding chirality to Selectfluor-type reagents offers a platform not only to control enantioselectivity but also as a handle to tailor solubility. Optimized conditions consisted

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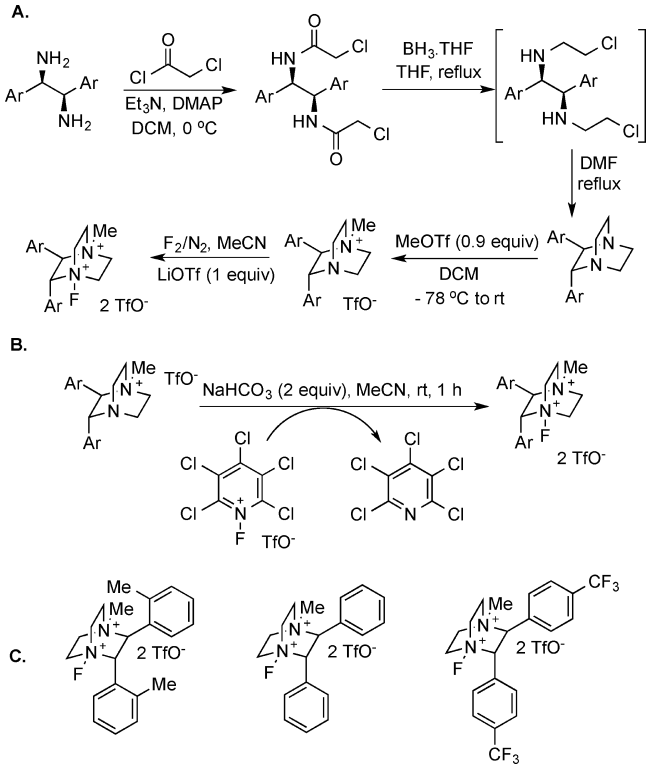
Scheme 12. Chiral Selectfluor[a]



[a](A) Synthesis from chiral non racemic vicinal diamines. (B) Fluorine transfer from *N*-fluoro-pentachloropyridinium triflate. (C) Chiral $[NF]^{2+}$ reagents of increased reactivity (left to right).

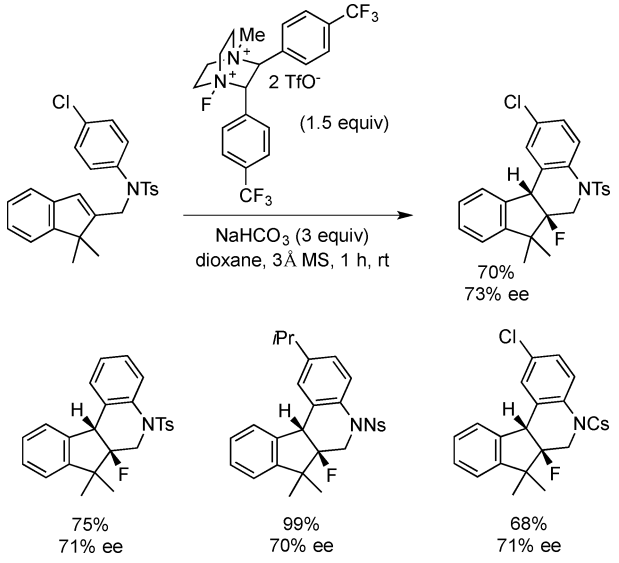
of treating the substrate (e.g., *N*-(4-chlorophenyl)-*N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-4-methylbenzenesulfonamide) with 3 equiv of $NaHCO_3$ and 1.5 equiv of chiral Selectfluor in 1,4-dioxane for 1 h. Fluorocarbocyclization led to the desired product that was afforded in 62% yield and 76% ee. Application of the optimized conditions to a range of substrates delivered products in excellent yields and ee averaging 70%. The method allows access to tetracyclic molecules possessing a carbon–fluorine quaternary stereocenter. The novel $[NF]^{2+}$ reagents used for this chemistry may find applications for the asymmetric fluorination of other substrates which are problematic using currently available strategies. Since their solubility profile can be tuned through variation of the substituents located on the DABCO core, it may become possible to adapt these chiral dicationic salts for use in phase-transfer catalysis (Scheme 13).

Alexakis and co-workers recently reported a catalytic asymmetric fluorocarbocyclization for allylic cyclopropanols and cyclobutanols.[37] This elegant phase-transfer catalyzed process consisting of a fluorination followed by Wagner–Meerwein rearrangement was performed with a catalytic amount of axially chiral phosphoric acid derived from (R_a)-binol (Scheme 14). The reaction tolerates a wide range of substitution on the aryl motif, but could not be extended to allylic alcohols lacking the aromatic ring.

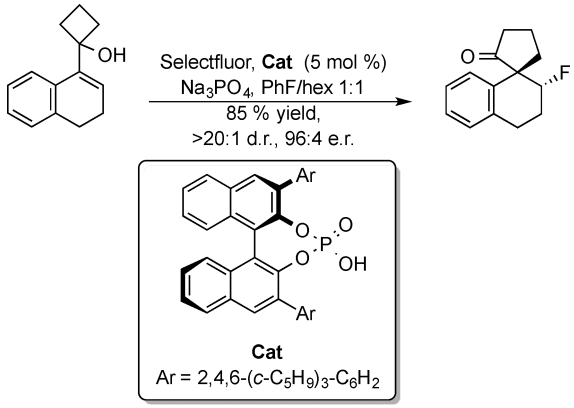
4. SUMMARY AND OUTLOOK

The number of methods available to produce fluorine-containing hetero- or carbocycles remains limited, in part due to the challenges associated with the design of effective modes of activation to achieve catalysis. Many options were considered

Scheme 13. Asymmetric Fluorocarbocyclization



Scheme 14. Asymmetric Fluorocarbocyclization via Wagner–Meerwein Rearrangement



other than F^+-induced fluorination-cyclization of type IV. An exciting development emerged from the conceptualization of catalyst controlled cation–olefin reaction. Using electrophilic Pt(II) complexes as precision tools to direct cascade cyclization, fluorinated carbocycles were produced by stereoretentive fluorodemetalation post cyclization, thereby offering an elegant solution for type I catalytic fluorocarbocyclization. For fluorination–cyclization processes induced by F^+ source (type IV), asymmetric catalysis with cinchona alkaloids delivered complex enantioenriched fluorine-containing heterocycles but a clearer understanding of the exact nature of the mode of activation operating will be required to expand the scope of this approach. Chiral ion pairing catalysis has also emerged as an attractive strategy with the solubility properties of $[NF]^{2+}$ reagents cleverly exploited to minimize uncatalyzed fluorination. For control over enantioselectivity, this approach seems limited to substrates armed with neighboring functional group (amides as protic heteronucleophiles) able to interact through hydrogen bonding with the lipophilic anionic catalyst. F^+-Induced fluorocarbocyclizations proved to be most challenging and required the development of a new class of $[NF]^{2+}$ reagent derived from chiral DABCO. To date, no catalytic variant of this transformation is available but progress was made on sequential fluorination–Wagner–Meerwein rearrangement of

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allylic cyclopropanols and alike. One striking observation for the systems in place is the lack of flexibility over substrate scope. Each method imposed restriction over the structural feature of the substrates for reactivity and/or control over enantioselectivity. Future developments will require new modes of activation, new catalysts, and new nucleophilic or electrophilic fluorine sources presenting with a range of reactivity and solubility profiles; we note that latent sources of fluorine have not been considered in this context. These directions represent an important growth opportunity, but only if one invests in understanding further the fundamental mechanistic features of individual catalytic transformation. An exciting goal is the development of a catalytic asymmetric F^+-induced cascade cyclization of a prochiral polyene with control over product, diastereo-, and enantioselectivity. It is likely that future advances in asymmetric fluorocyclization methodology that address the problem of substrate tolerance will require further advancement in general catalytic enantioselective fluorination processes.

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Notes

The authors declare no competing financial interest.

Biographies

Jamie Wolstenhulme completed his MChem in 2009 at the University of Oxford before joining the group of Prof. V. Gouverneur (University of Oxford, U.K.). He obtained his DPhil in 2013 and has since taken up a Postdoctoral research position under the supervision of Dr. Martin Smith (University of Oxford, U.K.).

Véronique Gouverneur received her PhD in chemistry at the UCL (Belgium) with Prof. L. Ghosez. She moved to a postdoctoral position at the Scripps Research Institute (La Jolla, CA) with Prof. R. A. Lerner. She then returned to Europe with a position at the University Louis Pasteur (France). She started her research career at the University of Oxford in 1998 and became Professor in 2008. Her research aims at expanding the scope of fluorine chemistry, with a focus on new approaches toward fluorinated molecules for medicinal applications.

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