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N-Fluoro Ammonium salts of *Cinchona* Alkaloids in Enantioselective Electrophilic Fluorination

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Abstract: From 2000, our two research groups independently and simultaneously designed and developed a novel family of electrophilic fluorinating reagents based on the use of *Cinchona* alkaloids. The chiral *N*-fluoro ammonium salts demonstrated the highest efficiency compared to prior art in enantioselective electrophilic fluorination for a wide range of substrates. In this account, we tell our respective stories, how the same idea germinated in our laboratories, the characterization of the chiral reagents, the use in stoichiometric quantity then the development of a catalytic version, the application to the synthesis of chiral fluorinated molecules of pharmaceutical interest, and finally the exploitation of our reagents by other teams and for other applications.

Keywords: fluorine, *Cinchona* alkaloid, chiral ammonium salts, fluorinating agents, asymmetric synthesis.

Biographical sketches:



Norio Shibata is a Professor at the Nagoya Institute of Technology. He received a Ph.D. from Osaka University (Pr. Yasuyuki Kita, 1993). He worked at Dyson Perrins Laboratory, Oxford University (Sir Pr. Jack E. Baldwin, 1994–1996), Sagami Chemical Research Institute (Dr. Shiro Terashima, 1996), Toyama Medical & Pharmaceutical University (1997–2003), and Nagoya Institute of Technology (2003–). He received the RSC Fluorine Prize (2005), Fluorine Chemistry Research Incentive Award in Research Foundation ITSUU Laboratory (2009), Prizes for Science and Technology, The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology (2014), CSJ Award for Creative Work (2015), CCS W.-Y. Huang Fluorine Prize (2015), ACS Award for Creative Work in Fluorine Chemistry (2019) and Green and Sustainable Chemistry Awards by the Minister of Education, Culture, Sports, Science and Technology (2019), SIS Award (2019), the Fellow of Royal Society of Chemistry (2021). His research interests are synthetic and medicinal fluorine chemistry.



Dominique Cahard is a CNRS Director of Research. His career started in 1994 with a PhD from the University of Rouen under the supervision of Pr. Jean-Marie Poirier and Pr. Pierre Duhamel. He enjoyed two postdoctoral positions with Pr. Chris McGuigan in Southampton (UK) and then in Cardiff (Wales), and with Pr. Tadashi Nakata at RIKEN, Tokyo (Japan). In 1996, he joined the CNRS as an associate researcher, completed his Habilitation in 2001, and was promoted to Director of Research in 2007. He has published more than 150 papers, patents, books and book chapters and gave 100 invited lectures worldwide. His current research interests concern innovative methodologies for asymmetric synthesis of fluorinated molecules.

1. Introduction

The research and development of new reagents for the direct introduction of fluorine and fluorine motifs have long been a priority to contribute a bright future in organofluorine chemistry. Such reagents together with innovative methodologies have flourished in recent decades to the great satisfaction of well-established researchers in the field but also to newcomers of the next generation of fluorine chemists. Creation of a carbon-fluorine bond concomitantly with the formation of a stereogenic carbon center has long been and is still nowadays a formidable achievement.^[1] Back to the year 2000, the field of asymmetric electrophilic fluorination was restricted to diastereoselective approaches exploiting chiral auxiliaries and to the use of a few chiral N–F reagents, which all required laborious multistep processes including

either the use of FCIO_3 or F_2 to ultimately create the N–F bond.^[2] At the turn of the 2000s, a major breakthrough and a significant step towards a wide development of enantioselective electrophilic fluorination was the independent and simultaneous discovery of *N*-fluoro *Cinchona* alkaloids by both of us, which constitute a new generation of enantioselective fluorinating agents, unprecedented charged $[\text{N-F}]^+$ chiral reagents, demonstrating both higher electrophilicity^[3] and enantioselectivity than the preceding neutral reagents. Advantageously, these novel reagents were easily prepared in a one-step transfer–fluorination on the naturally occurring *Cinchona* alkaloids free of handling elemental fluorine. If our work has been so well recognized, it is also thanks to the outstanding research involvements in the very vibrant field of asymmetric electrophilic fluorination by the groups of Togni, Gouverneur, Sodeoka, MacMillan, Barbas, Jørgensen, to cite the main protagonists. By means of transition-metal catalysis or organocatalysis, which include phase-transfer conditions, a variety of approaches nicely complemented our contribution with the use of chiral, non-racemic fluorinating agents. Equally decisive was the emergence of reagents such as Selectfluor and NFSI (*N*-Fluorobenzenesulfonimide) without which nothing would have been possible.^[4]

2. The birth of an idea

When from your mind emerges an idea for a new chemistry project, the first thing to do is to check the novelty and possible precedence in the literature. Having made sure of these points, the experimental work begins, the results accumulate and the time comes to publish. In a relatively virgin field, it is unlikely that the same idea will be developed at the same time in another laboratory in the world. However, this is what happened with *N*-fluoro ammonium salts of *Cinchona* alkaloids.

2.1. Within the French laboratory

During my PhD in the laboratory of Pr. Pierre Duhamel and Dr. Lucette Duhamel, I was exposed to the chemistry of enantioselective protonation by means of chiral protonating agents.^[5] For instance, the concept of chiral water was investigated in enolate chemistry by means of H_2O molecules in the presence of *Cinchona* alkaloids. As an extension, I imagined that replacing the proton by an atom that is sterically the closest to it, namely the fluorine atom, could allow to achieve asymmetric fluorination. I was familiar with the use of *Cinchona* alkaloids as phase-transfer catalysts but I was a total novice in fluorine chemistry. My idea was to synthesize *N*-fluoro ammonium salts of *Cinchona* alkaloids, $[\text{N-F}]^+$ reagents, by analogy with the ammonium salts $[\text{N-H}]^+$ used in protonation. Considering that preceded neutral N-F reagents were obtained with the aid of elemental fluorine for the N–F bond formation, I worked to have a safe working environment for handling fluorine. However, it was not possible to obtain approval in order to comply with the safety regulations in force in my institute. This was a blessing in disguise. As a result of a bibliographic search, the transfer-fluorination reported by Banks, Syvret *et al*.^[6] in 1995 prompted me to apply this safer approach taking advantage of the recently developed Selectfluor reagent (Figure 1). Naturally occurring *Cinchona* alkaloids mixed with a stoichiometric amount of Selectfluor in acetonitrile resulted in the quantitative formation of the corresponding *N*-fluoro ammonium salts. With such reagent in hand, we rapidly demonstrated their ability to transfer an electrophilic fluorine atom on an enolate in an asymmetric manner. Armed with this result, the Rhodia company, which had a long partnership history with my laboratory, was consulted to establish a new work force to develop the project. Rhodia has shown a strong interest in investigating new ideas in fluorine chemistry and has provided financial and intellectual support.^[7] Indeed, one PhD and one postdoc were recruited in my lab under the guidance of my colleague Dr Jean-Christophe Plaquevent and myself. At the same time, an international working group was set up that included groups of Bernard Langlois in Lyon (France) and of Véronique Gouverneur in Oxford (UK) working on different aspects of fluorine chemistry and reporting at regular meetings.

2.2. Within the Japanese laboratory

I decided to make fluorine chemistry my life's work when I got a position as a lecturer at Toyama Medical and Pharmaceutical University (now Toyama University) in 1997.^[8] My decision was motivated by the research style of Sir Pr. Jack E. Baldwin (JEB, Dyson Perrins laboratory, Oxford, UK), who dedicated his life to penicillin biosynthesis.^[9] JEB is my hero, and I wanted to be like him, so I chose fluorine for my research life. On my return to Japan after my stay in Oxford in 1996,^[10] I worked at the Sagami Chemical Research Institute, where many researchers have traditionally worked with fluorine chemistry, represented by chemists such as Pr. I. Ojima, Dr. T. Umemoto, and others. Then, I moved to Toyama from Sagami in 1997, where Pr. Takeuchi was also in the community of fluorine chemistry. Spontaneously, I joined the project on the development of asymmetric fluorination. At that time, *N*-fluoro camphor-type asymmetric reagents (Figure 1) were reported by Differding and Lang (1988)^[11] and Davis (1993 & 1998),^[12] but both the reactivity and the enantioselectivity of these reagents were not so attractive. Therefore, we designed a series of new chiral N-F reagents for electrophilic fluorination: CMIT-F (1999),^[13] BNBT-F (1999),^[14] and l-menthone-variant (2000) (Figure 1).^[15] While this series of reagents showed relatively high reactivity and enantioselectivity for the fluorination reaction of lithium enolates with up to 80% ee, the reagents have the main drawback of their multi-step synthesis that

includes fluorination with gaseous toxic fluorine or FCIO_4 and chiral separation. Thus, I decided to develop a new reaction system that can be performed using only commercially available reagents. In the summer of 1997, I enjoyed the 15th International Symposium on Fluorine Chemistry (Vancouver), where I met Dr. R. G. Syvret. He introduced me with Selectfluor as a new electrophilic fluorinating reagent.^[6, 16] While preparing CMIT-F with one of my students, Miss E. Suzuki, we found that molecular structure of Selectfluor has similarities with *Cinchona* alkaloids, which have a laudable history in asymmetric synthesis. We envisaged that *N*-fluoro ammonium salts of *Cinchona* alkaloids could be prepared by transfer-fluorination from Selectfluor to *Cinchona* alkaloids, probably due to the difference in stability between the di- and mono-cations. Although Selectfluor was commercially available in the early 2000, it was expensive at that time, so I had to prepare Selectfluor from 1,4-diazabicyclo[2.2.2]octane (DABCO) using gaseous fluorine, which I was familiar with in my laboratory.

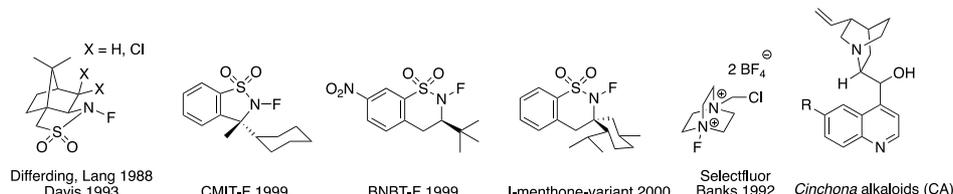
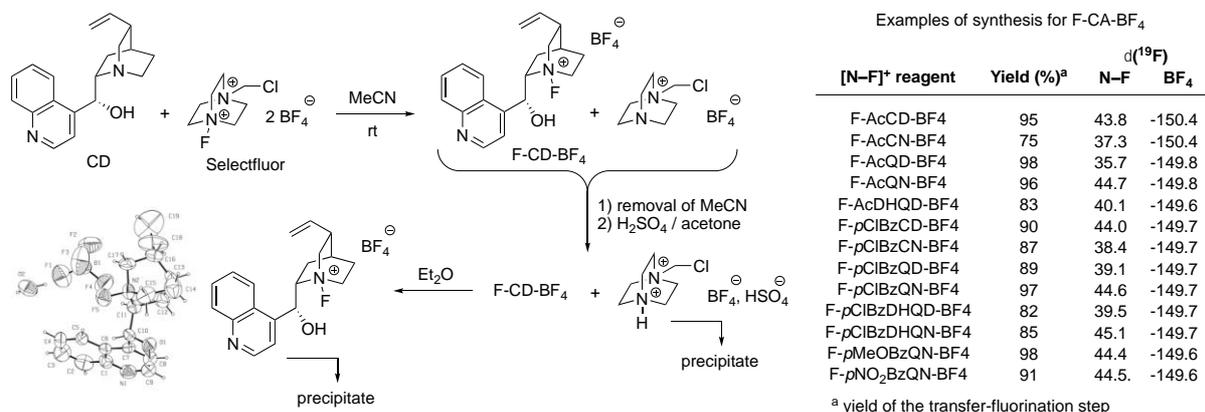


Figure 1. First generation of chiral fluorinating reagents, Selectfluor and *Cinchona* alkaloids.

3. Isolated purified reagents versus in situ generation of the same

Although the same idea was in the back of our minds, two different approaches were carried out to reach the designed *N*-fluoro ammonium salts. In the French laboratory, we carried out the transfer-fluorination by means of Selectfluor on the *Cinchona* alkaloids using equimolar amounts of the reagents.^[17] The fluorine atom was selectively transferred to the quinuclidinic nitrogen atom and not to the quinoleinic one at room temperature in acetonitrile. In order to fully ascertain the structure of the new $[\text{N}-\text{F}]^+$ reagents and to explore their potential in enantioselective fluorination, we developed a double precipitation procedure to first remove the Selectfluor residue as its protonated ammonium salt and second to further purify the desired salt by precipitation in diethyl ether. A slow crystallization afforded suitable crystals for X-Ray analysis that gave clear evidence of the N-F bond on the cinchonidine (Scheme 1).^[18] The generic name given to these new molecules was F-CA- BF_4 : F for the N-F bond, CA for *Cinchona* alkaloid (CD for cinchonidine, CN for cinchonine, QD for quinidine, QN for quinine) and BF_4 for the counter-anion. Subsequently, acetyl and benzoyl esters of *Cinchona* alkaloids were synthesized (Scheme 1). The pure isolated *N*-fluoro ammonium salts of *Cinchona* alkaloids were then engaged in various reactions to delineate their potential to transfer an electrophilic fluorine atom in an asymmetric way.



Scheme 1. Synthesis, purification and X-Ray structure of F-CD- BF_4 .

In Japan, we succeeded in preparing *N*-fluoro ammonium salts of *Cinchona* alkaloids in situ by the transfer-fluorination of Selectfluor to *Cinchona* alkaloids.^[19] The procedure involves merely mixing dicationic Selectfluor and corresponding *Cinchona* alkaloids in MeCN at room temperature. In addition to the basic *Cinchona* alkaloids such as QD and dihydroquinine (DHQ), we also selected dihydroquinine-4-chlorobenzoate (DHQB), dihydroquinidine acetate (DHQDA), bis-*Cinchona* alkaloids, $(\text{DHQ})_2\text{PHAL}$, $(\text{DHQD})_2\text{PHAL}$, $(\text{DHQD})_2\text{PYR}$, and $(\text{DHQ})_2\text{AQN}$ (Figure 2), as they are powerful catalysts in many asymmetric reactions that include the Sharpless asymmetric dihydroxylation. The formation of *N*-fluoro ammonium salts of the *Cinchona* alkaloids was easily confirmed by ¹⁹F NMR since the fluorine signal of the *N*-fluoro ammonium salt of Selectfluor promptly disappears while a new signal of the *N*-fluoro ammonium salts of *Cinchona*

alkaloids appears. The structures of in situ-generated *N*-fluoro ammonium salts of *Cinchona* alkaloids (NF-CA) are shown in Figure 2.

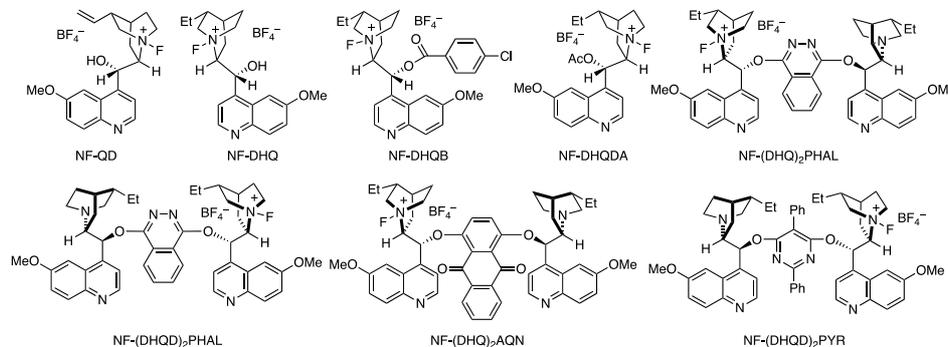
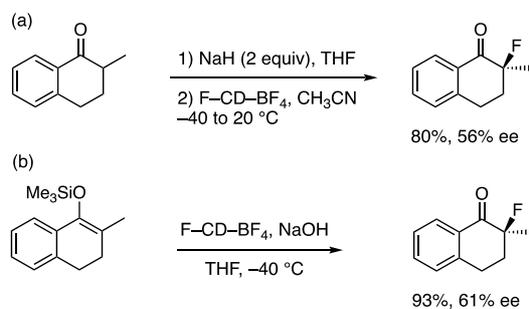


Figure 2. Second generation of chiral fluorinating reagents in situ generated from *Cinchona* alkaloids / Selectfluor combination (NF-CA).

4. Applications in enantioselective fluorination

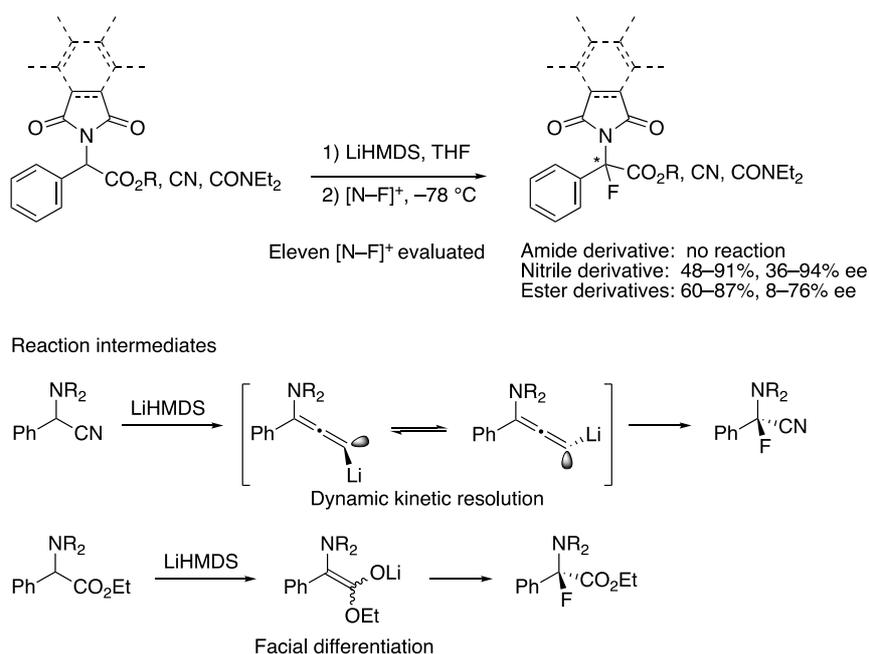
In the French laboratory, we first examined this novel class of electrophilic fluorinating agents in the fluorination of enolates and silyl enol ethers. Because previous fluorinating agents were tested on enolates of carbonyl compounds, we had the opportunity to make a direct comparison between reported uncharged N–F reagents and our novel ammonium $[N-F]^+$ agents. As model substrate, 2-methyl-1-tetralone was chosen, again to afford a comparison with literature data. Sodium or potassium enolates were generated with sodium hydride or potassium *t*-butoxide, respectively.^[20] We noticed that two equivalents of base allowed to reach full conversion and high yields of the desired 2-fluoro-2-methyl-1-tetralone, probably because the enolate was reprotonated by the OH group of cinchonidine. When the OH group of the alkaloid was masked as a benzoate, only one equivalent of base was required. Of the four main *Cinchona* alkaloids, cinchonidine delivered the best enantioselectivity with a modest 56% ee (Scheme 3a).^[17] Other tetralone derivatives as well as β -ketoesters were evaluated with different F-CA- BF_4 but the enantioselectivity was not improved.



Scheme 3. Preliminary experiments for the fluorination of enolates and enol derivatives.

Next, we considered the direct fluorination of silyl enol ethers anticipating that this new class of chiral $[N-F]^+$ reagents would possess stronger fluorinating power compared with neutral N–F reagents. Indeed, we carried out the first enantioselective electrophilic fluorination on a silyl enol ether of 2-methyl-1-tetralone in high yield with a slightly improved enantioselectivity by comparison of the fluorination of the sodium enolate (Scheme 3b).^[17] The addition of sodium hydroxide was crucial to achieve this level of enantioselectivity probably by deprotonation of the OH group of the alkaloid offering a different transition-state in the enantiodiscriminating step. It is worth noting that we sometimes obtained up to 92% ee value in this reaction but this excellent result was not reproducible. We rapidly understood the reason of this discrepancy. In the process of purification on column chromatography, fractions were eluted in test tubes and a tube containing the desired fluoroketone, as traced by TLC, was analyzed on chiral GC to determine the ee value. Not being aware of the self-disproportionation of enantiomers (SDE) at that time, we observed different ee values between single tube analysis and collect of all tubes containing the fluoroketone.^[21] We then changed the way to do things and results presented in our papers have correct ee values. This clearly indicates that 2-fluoro-2-methyl-1-tetralone expresses the SDE phenomenon.

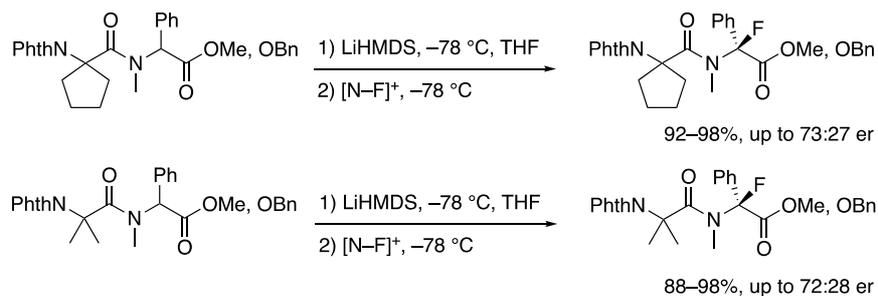
After these preliminary experiments, we focused our attention on fluorinated amino acids, which were and still are of great interest for incorporation into peptides and study of their properties. A large number of unnatural fluorinated amino acids are nowadays available in the literature and methods for their incorporation into proteins have significantly advanced. Back in 2001, there was no report on the enantioselective synthesis of α -fluoro- α -amino acids. It is generally accepted that *N*-unprotected α -fluoro- α -amino acids featuring the NH–CF motif are unstable species because of easy dehydrofluorination. Consequently, we conducted a screening of substrates that included imido-protected phenylglycine esters, phenylglycinonitrile as well as phenylglycine *N,N*-diethylamide. The imido groups investigated were: phthaloyl, tetrachlorophthaloyl, succinoyl, and dimethylmaleoyl. The α -deprotonation was realized with LiHMDS and the fluorination was conducted by screening of a wide range of [N–F]⁺ reagents. *N,N*-diethyl-*N*-phthaloyl-2-phenylglycinoamide failed to react with our [N–F]⁺ reagents while phenylglycine esters (Me, Et, Bn) and phenylglycinonitrile afforded the desired α -fluorinated- α -amino acids in satisfactory yields with up to 94% enantioselectivity, a level never reached before in any enantioselective fluorination (Scheme 4).^[22] Of the F-CA-BF₄ evaluated with phenylglycine esters, we demonstrated that *O*-acetyl performed better than *O*-benzoyl and much better than free OH alkaloids. Starting with phenylglycinonitrile, we noticed that the enantioselectivity was higher with *O*-benzoyl alkaloids than with *O*-acetyl ones. The highest enantiomeric excess of 94% was obtained in the fluorination of *N*-phthaloylphenylglycinonitrile with the *O*-(*p*-methoxybenzoyl)-*N*-fluoroquininium tetrafluoroborate.



Scheme 4. Enantioselective electrophilic fluorination of *N*-protected phenylglycine derivatives using various [N–F]⁺ *Cinchona* alkaloids.

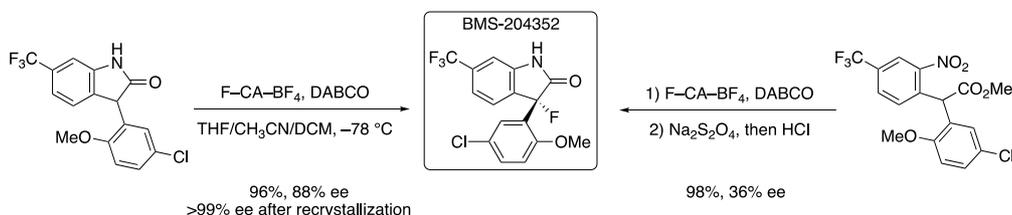
Fluorination of nitrile derivatives gave significantly higher ee values compared to the fluorination of ester derivatives. The origin of this could be found in considering the corresponding metalated intermediates. Deprotonation of the nitrile gave the nitrile anion that presumably exists as enantiomeric metalated ketenimines featuring an axial chirality prone to rapidly racemize even at –78 °C. An efficient dynamic kinetic resolution of the two metalated ketenimines could explain the high enantioselectivity of the electrophilic fluorination. In the case of esters, deprotonation generates a prochiral sp² enolate as a mixture of *E* and *Z* stereoisomers and the stereoselectivity is the result of a facial differentiation (Scheme 4).

To circumvent the intrinsic instability of the NH–CF motif that prevent incorporation into peptides, we decided to investigate the direct asymmetric electrophilic fluorination of *N*-methylated dipeptides (Scheme 5).^[23] *N*-Methylamino acids are worth studying as they are found in both natural and therapeutic products. Dipeptides used in our study were obtained from either *N*-phthalimide-1-aminocyclopentanecarboxylic acid or *N*-phthalimide-2-aminoisobutyric acid by coupling with *N*-methyl-phenylglycine ester. A single racemic stereogenic center at the *N*-methyl-phenylglycine residue was deprotonated by means of LiHMDS and reacted with various *N*-fluoro *Cinchona* alkaloid derivatives in a structure enantioselectivity relationship study. By using pseudo enantiomeric [N–F]⁺ *Cinchona* alkaloids we were able to obtain the fluorinated dipeptides with opposite configurations. However, the enantiomeric ratios were only moderate. In the same piece of work, we got better stereoselectivity of up to 98:2 dr in a diastereoselective approach by intramolecular control of the fluorination starting from dipeptides featuring a quaternary chiral amino acid and racemic *N*-methyl-phenylglycine.^[23]



Scheme 5. Enantioselective electrophilic fluorination of dipeptides.

To further illustrate the potential of *N*-fluoro ammonium salts of *Cinchona* alkaloids, we undertook the synthesis of BMS-204352, which was found to be a potent opener of Maxi-K channels in the treatment or prevention of ischemic stroke at Bristol-Myers Squibb laboratories^[24] and, more recently, for the treatment of Fragile X Syndrome.^[25] Before our work, the optically pure (*R*)- and (*S*)-BMS-204352 were obtained by resolution of a synthetic intermediate or by preparative HPLC. Our approach was based on an enantioselective electrophilic fluorination with the aid of our *N*-fluoro ammonium salts via two synthetic pathways. Enantioselectivity as high as 88% was achieved and >99% after a single recrystallization.^[26] The fluorination of oxindole precursor (Scheme 6, left) was performed in 96% yield with 88% ee by means of F-2NaphtQN-BF₄. Alternatively, acyclic α -fluorester was first synthesized and subsequently cyclized upon reduction of the nitro group (Scheme 6, right); however, this route did not lead to good enantioselectivity.

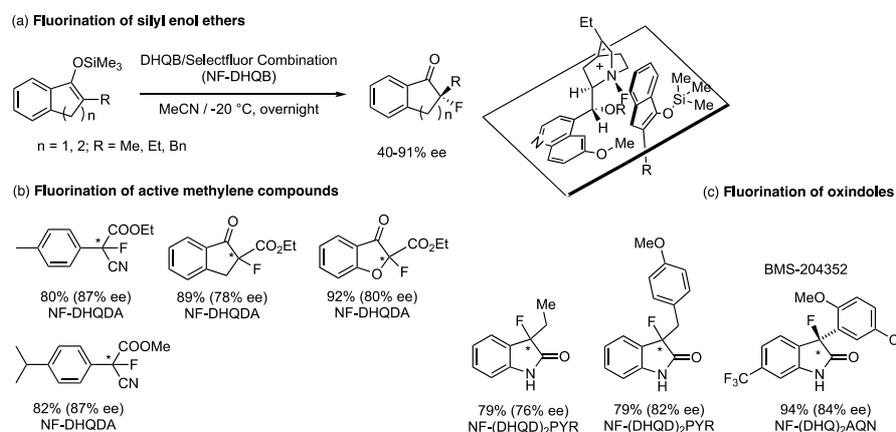


Scheme 6. Enantioselective electrophilic fluorination of dipeptides.

Although *Cinchona* alkaloids are abundant natural products, it is of interest to recycle them for reuse in particular for modified alkaloids that require additional synthetic steps and are often more efficient in terms of enantioselection. This point convinced us to look for recycling methods of the chiral vector after its use in fluorination reactions. Several strategies were adopted that include the use of ionic liquids and polymer-supported reagents. Selectfluor used in the transfer fluorination step is soluble in ionic liquids allowing, for example, the fluorination of indoles in high yields.^[27] Taking advantage of the selective solubility of *Cinchona* alkaloids in ionic liquids in preference to classic organic solvents, we demonstrated that ionic liquids were superior not only in terms of experimental conditions to recover and recycle the alkaloids but also in terms of enantioselectivity in the fluorination of silyl enol ethers.^[28] In the same vein, we designed several polystyrene-bound *Cinchona* alkaloids for application in enantioselective electrophilic fluorination of silyl enol ethers. This polystyrene-bound *N*-fluoro ammonium salts exhibited similar efficiency and easy purification of the fluorinated reaction products even after three recycles without erosion of stereochemical performance.^[29] Overall, the *N*-fluoro ammonium salts of *Cinchona* alkaloids contributed to the arsenal of asymmetric approaches we have developed for the electrophilic fluorination that include enantioselective phase-transfer catalysis,^[30] and metal-catalyzed reactions.^[31]

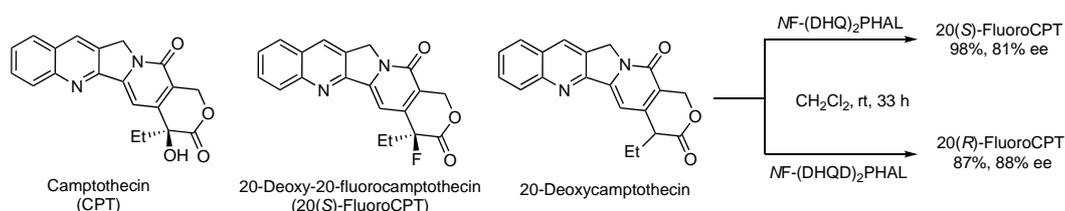
In the Japanese laboratory, the asymmetric fluorination of silyl enol ethers was first investigated (Scheme 7a).^[19] In situ generated NF-DHQB by mixing DHQB and Selectfluor in MeCN gave good results in the asymmetric fluorination of silyl enol ethers of variously decorated indanones or tetralones. The corresponding fluorinated cyclic ketones were obtained in high yields and with high enantioselectivities, without being significantly affected by the substituents. A mechanism for the asymmetric fluorination reaction of silyl enol ethers was proposed based on the results of the X-ray crystallographic analysis of NF-CA. In addition to silyl enol ethers, acyclic and cyclic substrates with active CH moieties can be fluorinated asymmetrically with in situ generated NF-*Cinchona* alkaloids with high enantioselectivity (Scheme 7b). These active CH substrates do not require prior activation by silylation or the addition of a base; simply mixing the reaction substrates with the *Cinchona* alkaloid / Selectfluor combination successfully yielded the desired fluorinated products. NF-DHQDA generally shown good results for asymmetric fluorination of cyclic β -ketoesters, while NF-DHQB was unsatisfactory. NF-DHQDA was also an excellent reagent for asymmetric fluorination of acyclic aryl cyanoacetates. In all cases, the corresponding fluorinated products were successfully obtained in much higher yields than those reported previously for this type of asymmetric reaction. Oxindoles have been actively studied in the pharmaceutical field owing to their bioactive properties. In particular, 3-hydroxy-oxindole is a vital enzyme inhibitor, in which a hydroxyl group replaces the hydrogen at position 3 in oxindoles. Therefore, we decided to synthesize 3-fluoro-oxindoles as isosteres of either

oxindoles or 3-hydroxyoxindoles via an asymmetric fluorination reaction. In this case, we found that the bis-structured NF-*Cinchona* alkaloids, such as NF-(DHQD)₂PYR and NF-(DHQ)₂AQN gave the corresponding fluorinated oxindoles with high enantioselectivity, while the previously successful NF-DHQB and NF-DHQDA did not yield good results (Scheme 7c).^[32] BMS-204352 was enantioselectively synthesized by NF-(DHQ)₂AQN in 84% ee and 94% yield.^[33]



Scheme 7. Fluorination of silyl enol ethers, active methylene compounds, and oxindoles with NF-CA.

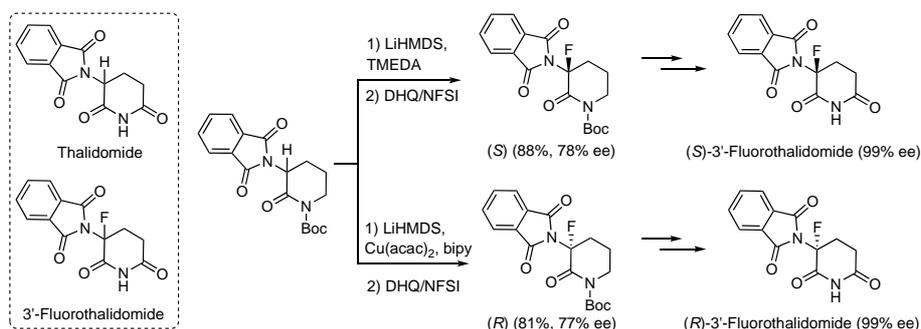
Camptothecin (CPT) is a naturally occurring alkaloid with anti-cancer properties that targets topoisomerase I, an enzyme involved in DNA replication and repair. The design of CPT derivatives with improved pharmacological properties has been an active area of research. Therefore, we designed 20-deoxy-20-fluorocamptothecin (20-FluoroCPT) as a potential isostere for CPT. The introduction of a fluorine atom at the 20-position of CPT, instead of the natural OH group, might enhance its antitumor activity and improve its pharmacokinetic properties, such as solubility and bioavailability. This is because the 20-position affects the stability of the lactone ring, which is essential for CPT activity, and the substitution of a fluorine atom can stabilize this lactone ring and improve the overall stability of the molecule. The direct enantioselective fluorination of the lactone moiety of 20-deoxyCPT by the *Cinchona* alkaloid / Selectfluor combination was investigated. Good levels of enantioselectivity were achieved using the *bis-Cinchona* alkaloid / Selectfluor combination (NF-CA). For example, the (DHQ)₂PHAL / Selectfluor combination in CH₂Cl₂ at room temperature gave 20(*S*)-fluoroCPT in 98% yield with 81% ee. Reverse stereoselectivity was observed in the reaction using the (DHQD)₂PHAL / Selectfluor combination to give 20(*R*)-fluoroCPT in 87% yield with 88% ee (Scheme 8).^[34]



Scheme 8. Fluorination of 20-deoxyCPT to both antipodes of 20-FluoroCPT with NF-CA.

Thalidomide was originally marketed in the late 1950s to the early 1960s as a sedative and a treatment for morning sickness in pregnant women. However, it was later discovered that the drug caused severe congenital disabilities in the children of women who took it during pregnancy. The teratogenic effect of thalidomide is thought to be caused by the interaction of an enantiomer of thalidomide with a specific protein associated with teratogenicity. However, this drug has been approved for use in specific conditions, including multiple myeloma, leprosy, and certain inflammatory diseases. Despite its resurgence, thalidomide remains a controversial drug. Researchers continue to study the mechanisms underlying the teratogenic effects of thalidomide to develop safer drugs and to better understand the causes of birth defects. As a result, fluorinated thalidomide was developed as an isostere of thalidomide.^[35] An essential advantage of fluorinated thalidomide is that it prevents the racemization (conversion between enantiomers) that occurs with thalidomide in vivo. Both enantiomerically pure (*S*)- and (*R*)-3'-fluorothalidomides were successfully synthesized via enantiodivergent electrophilic fluorination using NF-DHQ prepared from hydroquinine (DHQ) and NFSI. Interestingly, either mirror image of 3'-fluorothalidomide can be selectively accessed via the choice of additives (Scheme 9). The use of tetramethylethylenediamine (TMEDA) afforded fluorinated (*S*)-isomer with 78% ee, and Cu(acac)₂/bipy (acac: acetylacetonate, bipy: 2,2'-bipyridine) afforded the antipode (*R*)-isomer with 77% ee.^[36] The fluorinated thalidomide is

effective for treating multiple myeloma, and the (S)-enantiomer of 3'-fluorothalidomide is much more potent.^[37] Excitingly, enantiomers of 3'-fluorothalidomide do not show the teratogenicity.^[38]



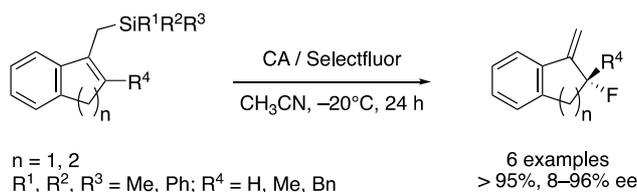
Scheme 9. Enantiodivergent fluorination via NF-DHQ (derived from DHQ and NFSI). Synthesis of both antipodes of 3'-fluorothalidomide

Despite the efficiency of enantioselective fluorination and the ready availability of *N*-fluoro ammonium salts derived from *Cinchona* alkaloid / Selectfluor (or NFSI) combinations, this system required stoichiometric amounts of *Cinchona* alkaloids. Therefore, a catalytic version of the reaction was highly desirable; this problem was partially solved in 2006^[39] and full success was achieved in 2008^[32] and 2011.^[40]

5. Applications of our approach by other groups

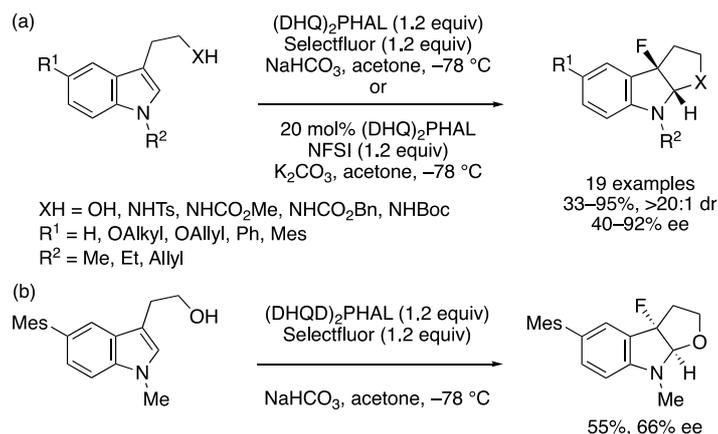
After our initial reports, a good number of applications of this methodology were reported in the literature. Except in rare examples, the reaction mechanisms, in particular the possible formation of *N*-fluoro ammonium salts were not commented.

As early as 2003, our enantiopure *N*-fluoro *Cinchona* alkaloids were exploited in the fluorodesilylation of allylsilanes by V. Gouverneur and co-workers taking advantage of the electrophilicity of these reagents and the β effect of the silicon atom (Scheme 10).^[41] A high level of enantioselectivity was reached (up to 96%) in the synthesis of allylic fluorides using a combination of Selectfluor and an alkaloid, preferably (DHQ)₂PYR.



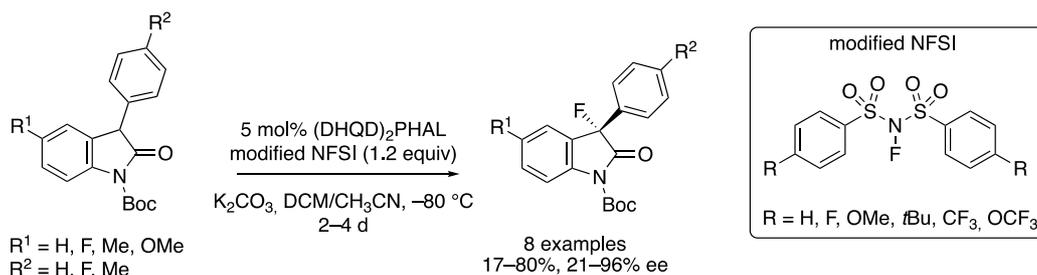
Scheme 10. Fluorodesilylation of allylsilanes.

The group of V. Gouverneur and co-workers further employed *N*-fluoro *Cinchona* alkaloids in a first example of organocatalyzed enantioselective fluorocyclization of indoles to end up with new pyrrolo- and furo-fused indoles featuring a fluorinated quaternary carbon center (Scheme 11a).^[42] Two procedures were equally successful either using stoichiometric amounts of (DHQ)₂PHAL and Selectfluor or 20 mol% of the same alkaloid with 1.2 equiv of NFSI. Using the pseudo-enantiomeric alkaloid (DHQD)₂PHAL as reported by X. Jiang, Y.Y. Yeung and co-workers in 2019 afforded the antipode product in a lower 66% ee value (Scheme 11b).^[43] These authors designed mimics of *Cinchona* alkaloids, i.e. amino-acid-derived phthalazines, readily available in both enantiomeric forms to achieve high level of enantioselectivities in the fluorocyclization of indoles (up to 99% ee) together with the guarantee to access both antipode products in equal level of enantioselectivity.



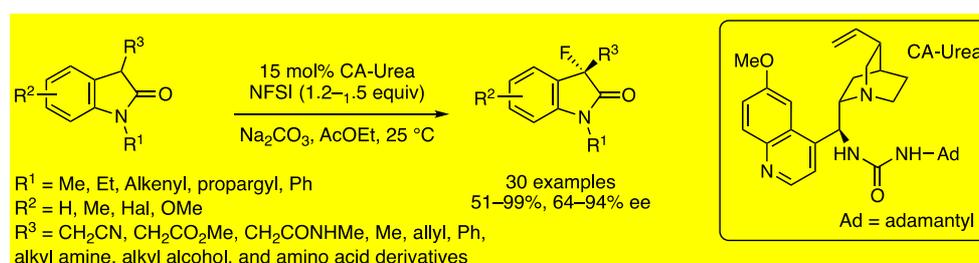
Scheme 11. Fluorocyclization of indoles.

As demonstrated by our groups, not only Selectfluor but also NFSI is suitable for the transfer-fluorination. In this context, X.J. Yang, H.M. He and co-workers in 2013 designed NFSI analogs bearing a substituent at the *p*-aryl positions. These structurally modified NFSI were evaluated in the enantioselective fluorination of *N*-Boc oxindoles in the presence of a catalytic amount, as low as 5 mol%, of (DHQD)₂PHAL (Scheme 12).^[44] High enantioselectivity could be reached but at the expense of the conversion even after a long reaction time at low temperature. For example, a *p*-*t*Bu substituent on the phenyl rings of the NFSI analog enhanced the enantioselectivity but is detrimental to the reactivity. A catalytic cycle was suggested; it involves the formation of F-CA-N(SO₂Ar)₂ and the anion metathesis to give F-CA-KCO₃ salt in the reaction with the potassium enolate derived from the oxindole.



Scheme 12. Fluorination of 3-aryl oxindoles.

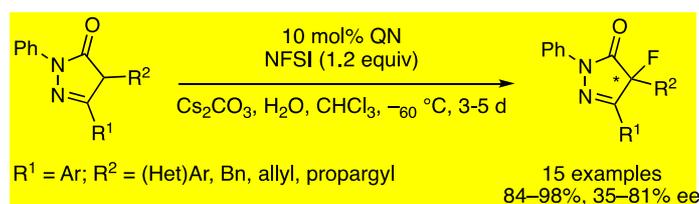
For another example of design of alternative achiral fluorine sources, the preparation of F-TEDA-N(SO₂Ph)₂ was described by X. Yang, X. Wu and co-workers in 2015. With this new fluorinating agent in hand, they reported the asymmetric fluorination of oxindoles using a combination of this reagent with 5 mol% of (DHQD)₂AQN (we guess this bis-alkaloid was used as discrepancy exists in name and structure in the paper). The results described as “bad” by the authors showed up to 77% ee.^[45] More recently, better results in the fluorination of 3-functionalized oxindoles were demonstrated by Jiang, Y.Y. Yeung and co-workers in 2018. A large range of enantioenriched 3-methylene nitrile 3-fluoro-2-oxindoles and derivatives, *N*-protected or not, featuring various decorations were obtained in high yields and enantioselectivities in the presence of 15 mol% of a *Cinchona*-based urea catalyst and slight excess of NFSI (Scheme 13).^[46]



Scheme 13. Fluorination of 3-functionalized oxindoles.

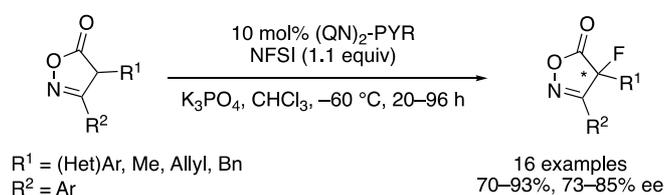
Other nitrogen containing heterocycles were subjected to the enantioselective electrophilic fluorination. B. Wang and co-workers reported in 2016 a catalytic asymmetric fluorination of 4-substituted pyrazolones with NFSI by means of 10

mol% of quinine (Scheme 14).^[47] The mechanism was not elucidated; however, it is reasonable to assume that F-QN-N(SO₂Ph)₂ was generated in situ to induce a good level of enantioselectivity.



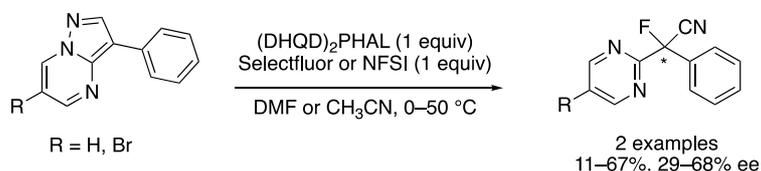
Scheme 14. Fluorination of 4-substituted pyrazolones.

In the same vein, 4-substituted isoxazolinones were enantioselectively fluorinated with NFSI and 10 mol % of (QN)₂PYR. This piece of work done by Y. Song in 2015 was clearly inspired by our pioneering reports on the use of *N*-fluoro ammonium salt of *Cinchona* alkaloids (Scheme 15).^[48] High yields and good enantioselectivities were obtained for a series of 4-fluoroisoxazolinone derivatives featuring a fluorinated stereogenic quaternary carbon center.



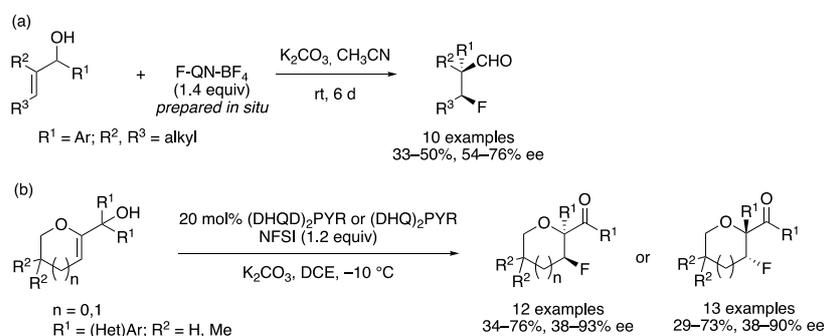
Scheme 15. Fluorination of 4-substituted isoxazolinones.

The group of J. Yamaguchi in 2022 discovered that the treatment of bicyclic azaarenes with an electrophilic fluorinating agent caused the ring-opening fluorination through N-N bond cleavage to deliver pyrimidine phenyl cyano fluoro methylene compounds. With the aid of stoichiometric amounts of (DHQD)₂PHAL and Selectfluor or NFSI, this unprecedented reaction proceeded in moderate yields and ee values (Scheme 16).^[49]



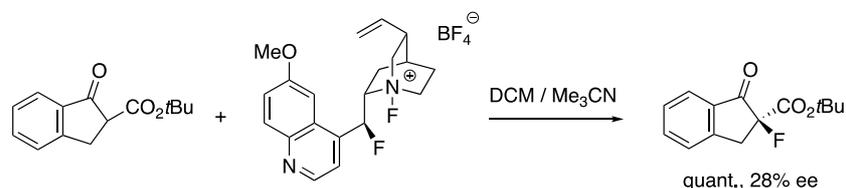
Scheme 16. Ring-opening fluorination of bicyclic azaarenes.

Between 2005 and 2012, the group of Y.Q. Tu and co-workers developed a sequence fluorination / semipinacol rearrangement of allylic alcohols. First, a stoichiometric combination QN / Selectfluor was employed to generate a series of α -quaternary β -fluoro aldehydes (Scheme 17a).^[50] Next, the catalytic approach was applied and demonstrated high efficiency to access a wide range of β -fluoro ketones variously decorated. Two series of experiments were conducted with (DHQD)₂PYR and (DHQ)₂PYR to afford both enantiomers of the products (Scheme 17b).^[51]



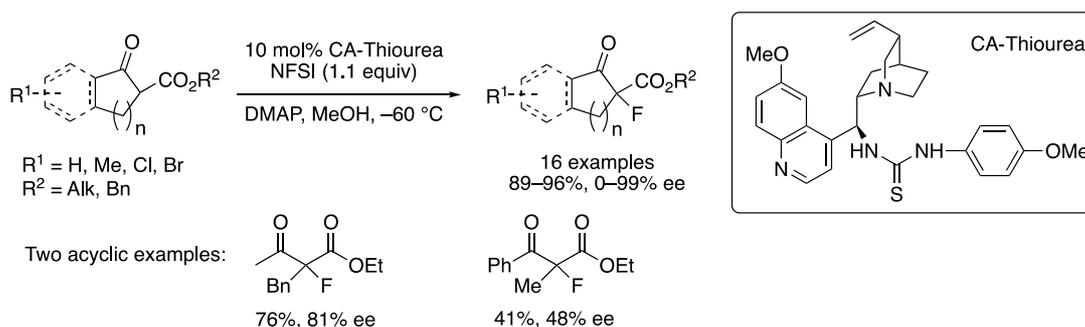
Scheme 17. Fluorination / semipinacol rearrangement toward β -fluoro aldehydes and ketones.

In an in-depth study of fluorinated *Cinchona* alkaloids in enantioselective catalysis, R. Gilmour and co-workers reported in 2012 the preparation of an *N*-fluoro ammonium salt of 9-fluoro quinidine obtained by reaction with Selectfluor and isolated it to be engaged in the fluorination of a β -ketoester. Although the corresponding α -fluoro- β -ketoester was obtained quantitatively, a modest 28% ee was measured (Scheme 18).^[52] Replacing the 9-OH group of the alkaloid by a 9-F has detrimental impact on the enantioselectivity.



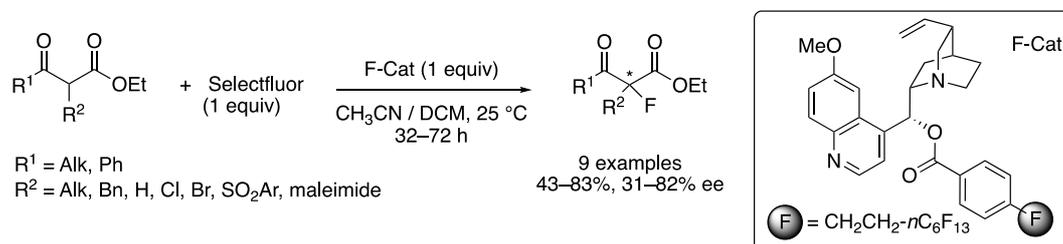
Scheme 18. Fluorination of a β -ketoester with F-(9-deoxy-9-fluoro QD)-BF₄.

The enantioselective fluorination of cyclic and acyclic β -ketoesters was achieved more efficiently in the presence of thiourea-based *Cinchona* alkaloid catalysts and NFSI in slight excess as demonstrated by Y. Hu and co-workers in 2012. A wide range of catalysts were examined as well as different types of substrates (Scheme 19).^[53] With indanone derivatives, ee values were high except for the *t*Butyl ester (0% ee). Tetralone derived substrates gave only low ee values in the range 11-20%. In addition, two acyclic β -ketoesters were fluorinated with enantioselectivities ranging 48-81% ee. A mechanism was proposed involving an ion pair formed between the enolate and the quinuclidinium ion and concomitant H-bonding interactions between the thiourea and NFSI. The formation of a *N*-fluoro ammonium salt was not precluded.



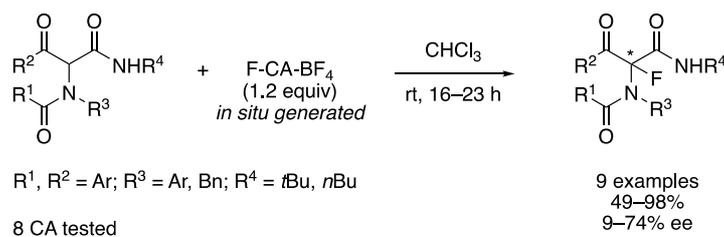
Scheme 19. Fluorination of β -ketoesters with NFSI / CA-Thiourea.

A specific study of the fluorination of acyclic β -ketoesters with Selectfluor and a stoichiometric amount of recyclable fluorous *Cinchona* alkaloid was described by W.B. Yi, W. Zhang and co-workers in 2012 (Scheme 20).^[54] Lower amounts of fluorous *Cinchona* alkaloid resulted in lower ee values together with decreased reactivity albeit the possibility to recover and reuse the fluorous species after separation on a fluorous silica gel cartridge.



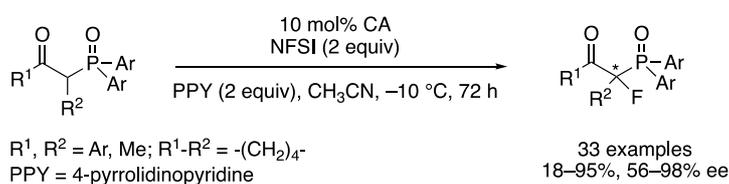
Scheme 20. Fluorination of β -ketoesters with Selectfluor / Fluorous CA.

Other 1,3 dicarbonyl compounds are Ugi adducts that were subjected to electrophilic fluorination at the peptidyl position by means of in situ preformed F-CA-BF₄ as reported by V.A. Peshkov and co-workers in 2020 (Scheme 21).^[55] Notably, the use of a catalytic quantity of quinine led to much lower yield and ee value compared to the same reaction under stoichiometric conditions. Although an extensive investigation was carried out, the highest enantioselectivity observed did not exceed 74% ee value.



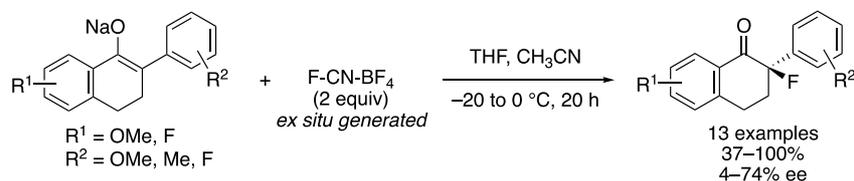
Scheme 21. Fluorination of Ugi adducts.

Subsequently, in 2021, F.M. Zhang and co-workers carried out the enantioselective electrophilic fluorination of β -ketodiarylphosphine oxides to yield the corresponding α -fluoro derivatives (Scheme 22).^[56] Two equivalents of NFSI were combined with 10 mol % of CA to secure efficient fluorination reaction. Here again, starting from the same material and switching the pseudo-enantiomeric catalysts allowed to access both enantioenriched isomers with similar, high levels of enantioselectivity. The base of choice in this reaction was 4-pyrrolidinopyridine in acetonitrile even though Cs_2CO_3 in acetone performed equally well.



Scheme 22. Fluorination of β -ketodiarylphosphine oxides.

The enantioselective fluorination of monocarbonyl compounds was also investigated. For instance, α -aryl-tetralones reacted via their sodium enolate as reported by C. Najera, P.R.R. Costa and co-workers in 2019 using an *ex situ* prepared acetonitrile solution of cinchonine and Selectfluor (Scheme 23).^[57] This way, a good number of fluorotetralones were obtained in up to 74% ee. Other *Cinchona* alkaloids were evaluated but were less efficient; surprisingly (DHQD)₂PHAL gave no reaction.



Scheme 23. Fluorination of α -aryl-tetralones.

Finally, I. Marek and co-workers in 2018 described one example of enantioselective fluorination of a stereodefined fully substituted silyl ketene hemiaminal. Having developed a stereoselective preparation of silyl enol derivatives from yncarbamates, a diastereoselective version of the fluorination was first realized with up to 86% dr as well as an enantioselective version using 20 mol% of (DHQ)₂PHAL albeit in a modest 60% ee (Scheme 24).^[58]

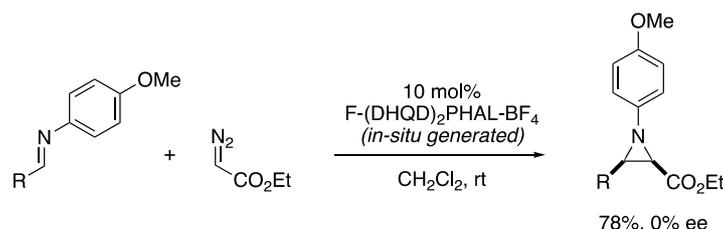


Scheme 24. Fluorination of disubstituted silyl ketene hemiaminals.

6. Other uses of *N*-fluoro ammonium salts of *Cinchona* alkaloids

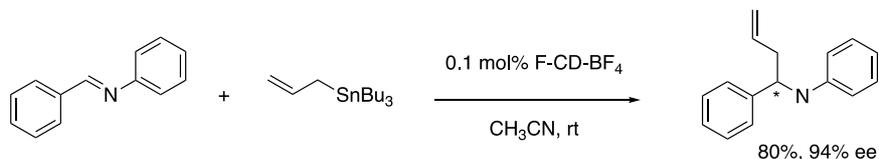
Apart from the development of chiral *N*-fluoro ammonium salts in enantioselective electrophilic fluorination, two papers, to our knowledge, documented other roles in asymmetric synthesis.

Activation of imines with metal Lewis acids or with Brønsted acids is a common strategy in the synthesis of aziridines. An interesting alternative was proposed in 2009 by S. Bew and coworkers who reported on the *N*-fluoropyridinium triflate catalyzed synthesis of *N*-aryl aziridines by activation of *N*-aryl imines by means of highly electrophilic fluoronium source and subsequent reaction with ethyl diazoacetate. This way, several aziridines were obtained in moderate to high yields with complete *cis* stereochemistry or total absence of selectivity depending on the imine substrates. It was next envisioned that this activation mode could be effective in the presence of a chiral electrophilic fluorinating agent derived from *Cinchona* alkaloids, F-(DHQD)₂PHAL-BF₄, which was generated in situ (Scheme 25). Unfortunately, only the racemic aziridine was obtained.^[59] The conditions of in situ generation of the chiral [N-F]⁺ reagent are not provided but we can reasonably think that the achiral F⁺ donor employed (not specified) for the transfer fluorination was responsible of the catalysis in a more efficient way than the chiral one. The possibility of catalysis by pyridinium triflate generated in situ by trace water was ruled out by experiments under vigorous exclusion of water as well as by mass spectroscopy analysis.



Scheme 25. Chiral F⁺ donor-catalyzed aziridine synthesis.

In the same vein but more successfully, the allylation of (*E*)-*N*-benzylideneaniline using allyltributyltin in the presence of F-CD-BF₄ afforded the corresponding enantioenriched amine with 94% ee (Scheme 26).^[60] A single example was provided with HPLC trace but the mechanism was not investigated. It was proposed that the chiral [N-F]⁺ reagent behaves as a Lewis acid to activate the imine moiety in the nucleophilic allylation. One can also suggest that fluoride from BF₄ anion activate the nucleophile forming an ionic pair with the [N-F]⁺ cation to induce enantioselectivity.



Scheme 26. F-CD-BF₄ catalyzed allylation of imine.

Acknowledgements

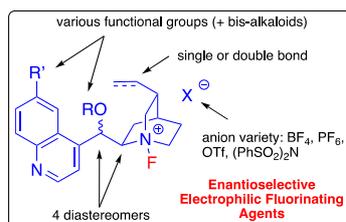
D.C. thanks the CNRS, Rhodia company, and Normandy university for their support all along the development of this research. N.S. thanks the JSPS KAKENHI (JP 21H01933), Tosoh-finechem Corporation, UBE Corporation, and Nagoya Institute of Technology.

Keywords: fluorine chemistry • *Cinchona* alkaloids • enantioselective synthesis • fluorination • electrophilic reagent

Entry for the Table of Contents

Layout 1:
PERSONAL ACCOUNT

The parallel development by our two research groups of chiral *N*-fluoro ammonium salts of *Cinchona* alkaloids in enantioselective electrophilic fluorination is told. We further present applications of our approach by other groups for the same as well as other purposes.



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