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Review

New approaches to enantioselective fluorination: Cinchona alkaloids combinations and chiral ligands/metal complexes

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Abstract

The selective construction of carbon–fluorine bonds is of great interest to medicinal chemists because the replacement of a hydrogen or an oxygen atom with a fluorine atom in biologically active molecules can confer the molecules with improved physicochemical properties and biological activities. Since the first discovery of enantioselective fluorination using *N*-fluorocamphorsultam, our synthetic interest had been focused on the development of chiral *N*-fluorosulfonamide derivatives capable of enantioselective fluorination. However, these initial efforts revealed several limitations in both chemical yields and enantioselectivities of the fluorinated products. We present here the background of our personal story of the enantioselective fluorination reaction and some successful applications of the methods to the design and synthesis of biologically active products. Two novel approaches using cinchona alkaloid/Selectfluor® combinations and chiral ligands/metal complexes have been pursued, respectively. In addition, the recent advances in this area by other groups are also described briefly.

Keywords: Fluorination; Enantioselective; Asymmetric reaction; Cinchona alkaloids; Metal; Organocatalysts; Medicinal chemistry

Contents

1. Introduction

The synthesis of chiral fluoro-organic compounds is an important topic in modern pharmaceutical chemistry [1]. The replacement of a hydrogen or a hydroxyl group with a fluorine atom is an extensively used strategy for enhancement of

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biological activity in the design of analogues of biologically important molecules [2]. The analogues are often regarded as isosteres of the parent molecules because of the following considerations [3]. First, fluorine most closely resembles hydrogen in size among atoms; therefore, the fluorine replacement is often regarded as an isosteric substitution. Second, both from the structural and electronegativity points of view, fluorine and oxygen, not fluorine and hydrogen, are very nearly isosteric. Recent evidence indicated that the advantages of the fluorine substitution include an increase in stability, changes in lipophilicity, introduction of a highly electronegative center, and altered patterns of reactivity of the C–F versus the C–H or C–OH bond. A variety of methodologies of enantioselective synthesis of fluoro-organic compounds have been described [4]. Undoubtedly, an electrophilic introduction of a fluorine atom into a molecule via enantioselective fluorination is a highly versatile synthetic transformation [5]. In this process, fluorine is directly and asymmetrically transferred to an achiral anion. Chiral sulfonamide-type fluorinating reagents were developed for this purpose [6]. Differding and Lang, who first introduced this idea, reported electrophilic enantioselective fluorination of enolates using *N*-fluorocamphorsultam **1a** in 1988 [6a]. Several other reagents of this type including the Davis' reagents [6b,c] **1b,c** and saccharin-type reagents **1d,e** contributed by one of us followed (Fig. 1) [6e–g]. However, these are far from ideal because of low chemical yields and low optical enrichment of the fluorinated products. Furthermore, the reagents themselves are still relatively unavailable because their preparation requires tedious and multi-step procedures, including fluorination with toxic molecular fluorine or explosive gaseous perchloryl fluoride. Due to these drawbacks, there are no reports of the use of these reagents for asymmetric fluorination except for the original papers.

Progress toward truly efficient methodologies for practical use had to await breakthroughs in enantioselective fluorination for a decade. In late 2000, three communications were disclosed along these lines simultaneously. Cinchona alkaloid-mediated enantioselective fluorination by us [7] and Cahard's group [8], and TADDOLato/Ti(II)-catalyzed enantioselective fluorination by Togni's group [9] are two major discoveries. They are so different from the previously reported approach in that they enable access to chiral fluoro-organic compounds with practical levels of enantiomer excess for the first time. Our procedure is based on *in situ-generated N*-fluoroammonium salts of cinchona alkaloids named *cinchona alkaloid/Selectfluor® combinations*. Cahard et al. reported the substantially same approach except for the use of *isolated N*-fluoroammonium salts of cinchona alkaloids (*N*F-CA) instead. Both methodologies have displayed broader substrate generality than so far examined. Silyl enol ethers, metal enolates, α-cyano esters, β-keto esters, oxindoles, lactones, dipeptides, allylsilanes and even more are able to be fluorinated with high enantioselectivities. Togni's approach using TADDOLato/Ti(II) is the first example of a catalytic enantioselective fluorination of β-keto esters and their concept has become an important milestone in this field. As elegantly reviewed articles [10] have now become available concerning recent progress of asymmetric fluorination reaction, this account focuses on the contributions from our laboratory to this dynamic field [7f]. The recent advances in this area by other groups are also summarized briefly.

2. Cinchona alkaloid/Selectfluor® combinations

Our interest in the reagent-controlled enantioselective fluorination prompted us to seek a simple and powerful method, which can be carried out with ease using commercially available reagents without any special requirements. First, we had to shake ourselves free from the conventional idea using *N*-fluorosulfonamides. In recent years, Selectfluor® has been widely used for electrophilic fluorination [11]. It is a quaternary *N*-fluoroammonium salt of 1,4-diazabicyclo[2,2,2]octane (DABCO) with an interesting implication for designing asymmetric reagents based on the use of chiral, non-racemic *N*-fluoroammonium salts. On examining the structural features of Selectfluor®, we noticed that it is analogous to cinchona alkaloids that have a praiseworthy history in asymmetric synthesis [12] (Fig. 2). A chiral version of Selectfluor® surprisingly was unknown in the literature at that time, to the best of our knowledge. It would be produced via a transfer-fluorination from Selectfluor® to a cinchona alkaloid, which is likely to be associated with the special features of their structures. Relief from the dication state of Selectfluor® to generate two monocations of ammonium salts provides the thermodynamic driving force for the transfer (Scheme 1). Indeed, Banks et al. demonstrated in their early report, albeit with simple compounds, transfer fluorination reactions [13].

We tested this idea using a quinine/Selectfluor® combination prepared in situ from both commercially available quinine and Selectfluor® to enable the enantioselective fluorination of

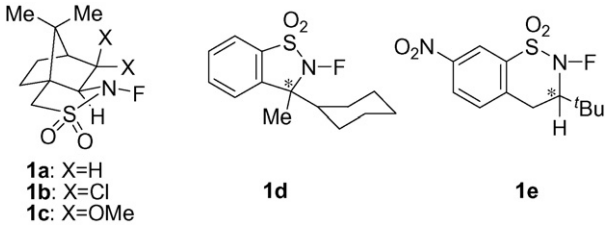


Fig. 1. 1st Generation for enantioselective fluorination: *N*-fluorocamphorsultam and related reagents.

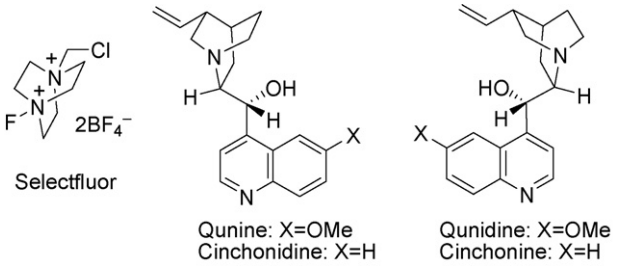
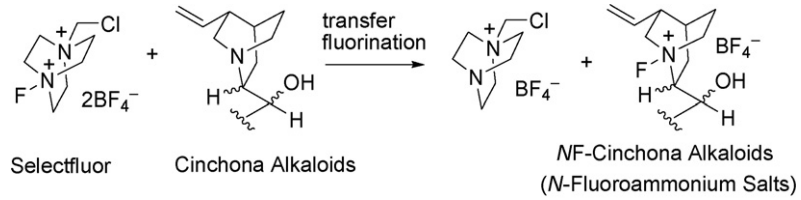
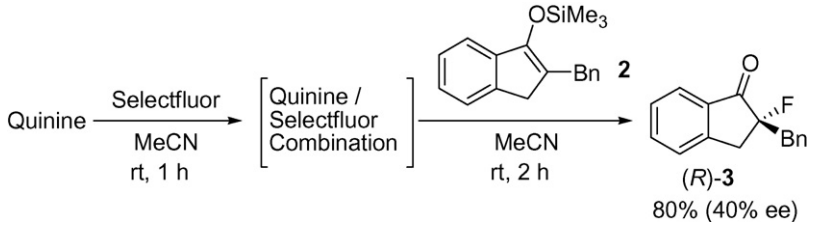


Fig. 2. Selectfluor® and cinchona alkaloids, quinine, quinidine, cinchonidine and cinchonine.



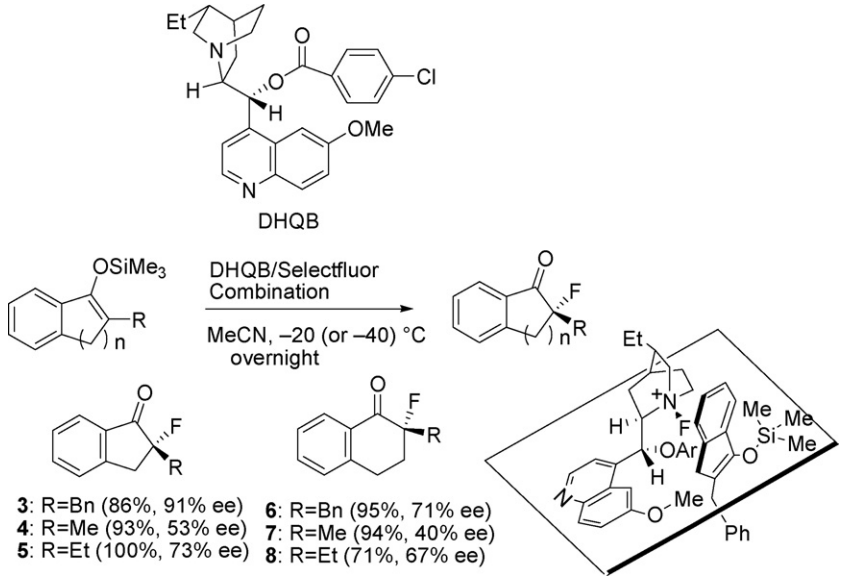
Scheme 1. Transfer-fluorination from Selectfluor® to cinchona alkaloids.



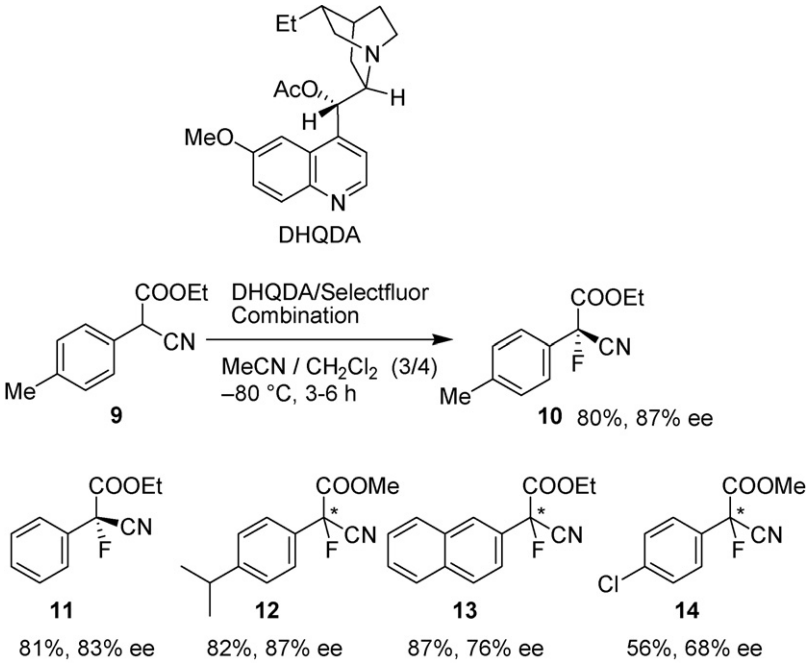
Scheme 2. Preliminary results of enantioselective fluorination with quinine/Selectfluor® combination.

trimethylsilyl enol ether of 2-benzyl-1-indanone (**2**). The results, both from the view of conversion and enantioselectivity, deserved attention. Silyl enol ether **2** was fluorinated nicely to furnish (*R*)-2-benzyl-2-fluoroindanone (**3**) in 80% yield with 40% ee (Scheme 2). The preliminary result encouraged us to investigate other systems in an attempt to improve enantioselectivity. After screening several commercially available cinchona alkaloids as chiral sources for further optimization, we found that a DHQB/Selectfluor® combination (DHQB: dihydroquinine *p*-chlorobenzoate) in MeCN effected the enantioselective fluorination of **2** to furnish **3** with more than 90% ee, favoring the *R* stereochemistry. The generality of the DHQB/Selectfluor® combination for enantioselective fluorination with a series of indanones and tetralones is summarized (Scheme 3). The corresponding 2-fluoroindanones **3–5** and 2-fluorotetralones **6–8** were obtained in excellent yields of 71–100%, and enantioselectivities of up to 91% ee. The stereochemical outcome of the fluorination with the combination was consistent with a projection described in Scheme 3, which was derived through an X-ray crystallographic study revealed in the following section.

We next investigated the effectiveness of our system for the enantioselective fluorination of acyclic esters. Chiral, nonracemic acyclic monofluoro compounds have many applications, for example as chiral derivatizing agents [14], as chiral building blocks, and as synthetic intermediates for fluorine-containing chiral liquid crystals [15]. Ethyl α-cyano-α-fluoro-α-tolylacetate (**10**), an efficient chiral derivatizing reagent, was selected as a target molecule. While the fluorination of ethyl α-cyano-α-tolylacetate (**9**) by the use of the DHQB/Selectfluor® combination gave **10** with moderate ee, a DHQDA/Selectfluor® combination (DHQDA: dihydroquinidine acetate) in MeCN/CH_2Cl_2 was an excellent system for fluorination of **9**, giving a dramatic improvement in ee to 87% with (*S*)-enantioselection.



Scheme 3. Enantioselective fluorination of silyl enol ethers with DHQB/Selectfluor® combination.



Scheme 4. Enantioselective fuorination of α-cyano esters with DHQDA/Selectfluor® combination.

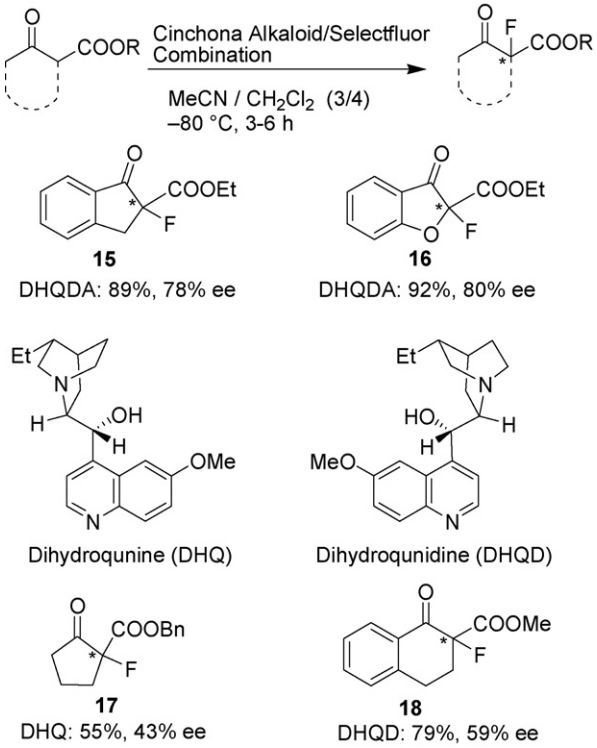
Fluorination of other acyclic α-cyano esters using the DHQDA/Selectfluor® combination provided products **11–14** with similar high ees (Scheme 4). Previously, α-cyano-α-fluoro-α-arylacetates had been prepared either by separation of diastereomeric derivatives or by enzymatic resolution, and this work represents the first example of their direct asymmetric synthesis.

Cyclic β-keto esters can also be efficiently fluorinated with high enantioselection by the DHQDA/Selectfluor® combination (78–80% ee). As with the fluorination of α-cyano esters, because of the high acidity of the reactive centers, β-keto esters were fluorinated very smoothly without pre-conversion to the corresponding silyl enol ethers. However, the DHQDA system was not effective for the preparation of fluorinated β-keto esters **17** and **18**. These enantioselections were improved to 43% ee and 59% ee, respectively, when the reaction was mediated by either dihydroquinine (DHQ)/Selectfluor® or dihydroquinidine (DHQD)/Selectfluor® combination (Scheme 5).

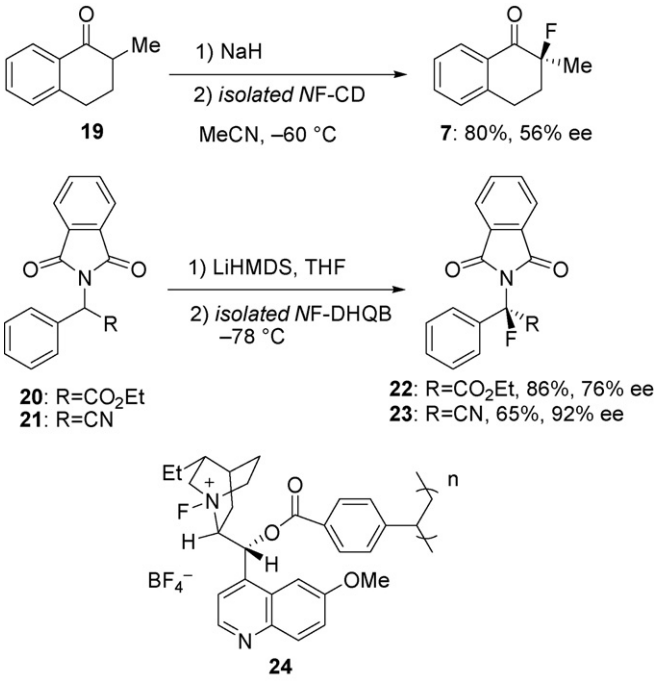
The cinchona alkaloid-mediated enantioselctive fluorination was discovered not only by us but also Cahard et al. [8] independently and simultaneously. Selected examples are shown in Scheme 6. Sodium enolate of 2-methyltetralone (**19**) was fluorinated by *isolated N*-fluoroammonium salt of cinchonidine (*N*F-CD) to give **7** in 80% yield with 56% ee [8a]. Fluorination of *N*-phthaloylphenylglycinate **20** and *N*-phthaloylphenylglycinonitrile **21** by *isolated N*-fluoroammonium salt of DHQB (*N*F-DHQB) gave α-fluorinated analogues **22** and **23** with high ees [8c]. Cahard et al. demonstrated that the enantioselective fluorination using *N*-fluoroammonium salts can also be performed in ionic liquid [hmim][PF_6] without significant alteration in the enantioselectivity [8d]. In addition, *N*-fluoroammonium salt of polystyrene-bound cinchona alkaloid **24** was developed as a recyclable reagent (Scheme 6) [8g].

It should be mentioned that, for a similar purpose, we also developed a fluorous-DHQB as a fluorous-phase soluble cinchona alkaloid for a fluorous-organic biphasic system (Fig. 3) [18].

We were next interested in 3-fluorooxindoles **26**. Because of the steric relationship between the C–F functionality and



Scheme 5. Enantioselective fluorination of β-keto esters with cinchona alkaloid/Selectfluor® combinations.



Scheme 6. Enantioselective fluorination based on cinchona alkaloids by Cahard's group.

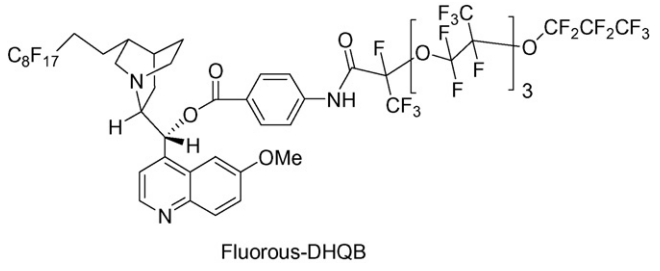
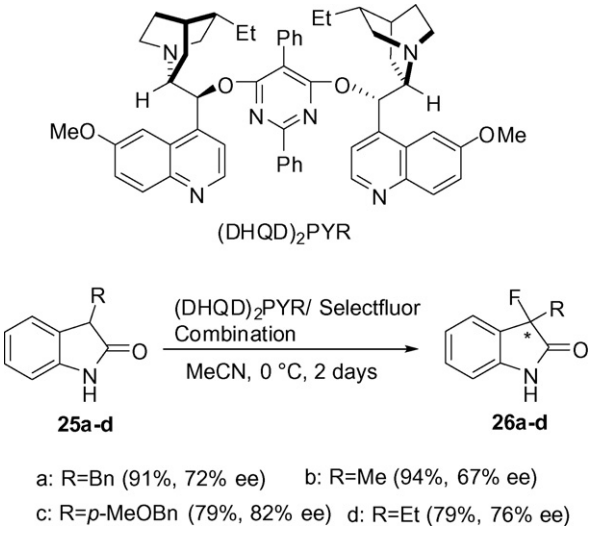


Fig. 3. DHQB with two fluorous ponytails.

both the C–H and C–OH moieties, 3-fluorooxindoles are potential mimics of both the corresponding oxindoles and 3-hydroxyoxindoles that are often found as metabolites of indoles. Although several methods are available for the preparation of racemic **26**, as yet no enantioselective synthesis has been reported. Therefore, we examined oxindoles **25** as substrates for enantioselective fluorination using the cinchona alkaloid/Selectfluor® combinations. Fluorination of **25** using the best combinations described in the previous section (DHQDA and DHQB) gave unsatisfactory enantioselectivities. However, good levels of enantioselection in the fluorination of **25** were achieved using *bis*-cinchona alkaloid/Selectfluor® combinations. Thus, the $(DHQD)_2PYR$/Selectfluor® combination in MeCN afforded excellent yields of **26** with good to high enantioselectivities up to 82% ee (Scheme 7). After our work, several groups have contributed to the development of successful methods for the asymmetric synthesis of 3-fluorooxindoles [8d,25e].



Scheme 7. $(DHQD)_2PYR$/Selectfluor® combination is effective for enantioselective fluorination of oxindoles.

3. Structure of *N*-fluoroammnoiun salts of cinchona alkalioids

The structure of the species, *N*-fluoroammoniun salt of cinchona alkaloid produced by the combination, is easily ascertained with both ^{19}F NMR spectroscopy and X-ray crystallography. The 254 MHz ^{19}F NMR spectrum of Selectfluor® in CD_3CN at room temperature showed a peak at 49 ppm (singlet, Selectfluor® *N*-F), whereas the spectrum of DHQB/Selectfluor® (0.5/1) combination in CD_3CN displayed two singlets of equal intensity at 49 ppm and at 44 ppm. As we expected, the signal at 49 ppm disappeared completely with the addition of DHQB (1.0 equiv) while the peak at 44 ppm remained. These NMR spectroscopic studies suggested the proposed presence and involvement of *N*-fluoroammonium salt of DHQB (*N*F-DHQB) in the reaction solution (Fig. 4). The putative *N*F-cinchona alkaloid was fully realized in the X-ray structure of *N*-fluoroammonium salt of quinine (*N*F-QN) isolated from the quinine/Selectfluor® combination. The crystal structure of *N*F-QN is shown in Fig. 5. It is well-known that cinchona alkaloids in principle can adopt four different conformations (two closed-type conformations and two open-type conformations) [16]. This X-ray analysis showed that our *N*F-QN molecule exists in a so-called open conformation III. In parallel with our studies with the *N*F-QN, Cahard et al. also reported an X-ray crystallographic analysis of *N*-fluoroammonium salt of cinchonidine (*N*F-CD) [8b].

4. Drug development: synthesis of BMS-204352 (MaxiPost®)

As have been presented, our innovative solutions to enantioselective fluorination reactions using *N*-fluoroammonium salts of cinchona alkaloids are now in hand. We next demonstrated the utility of this method for drug development. The novel fluorooxindole, BMS-204352 (MaxiPost®), is being developed by Bristol-Myers Squibb Pharmaceutical Research

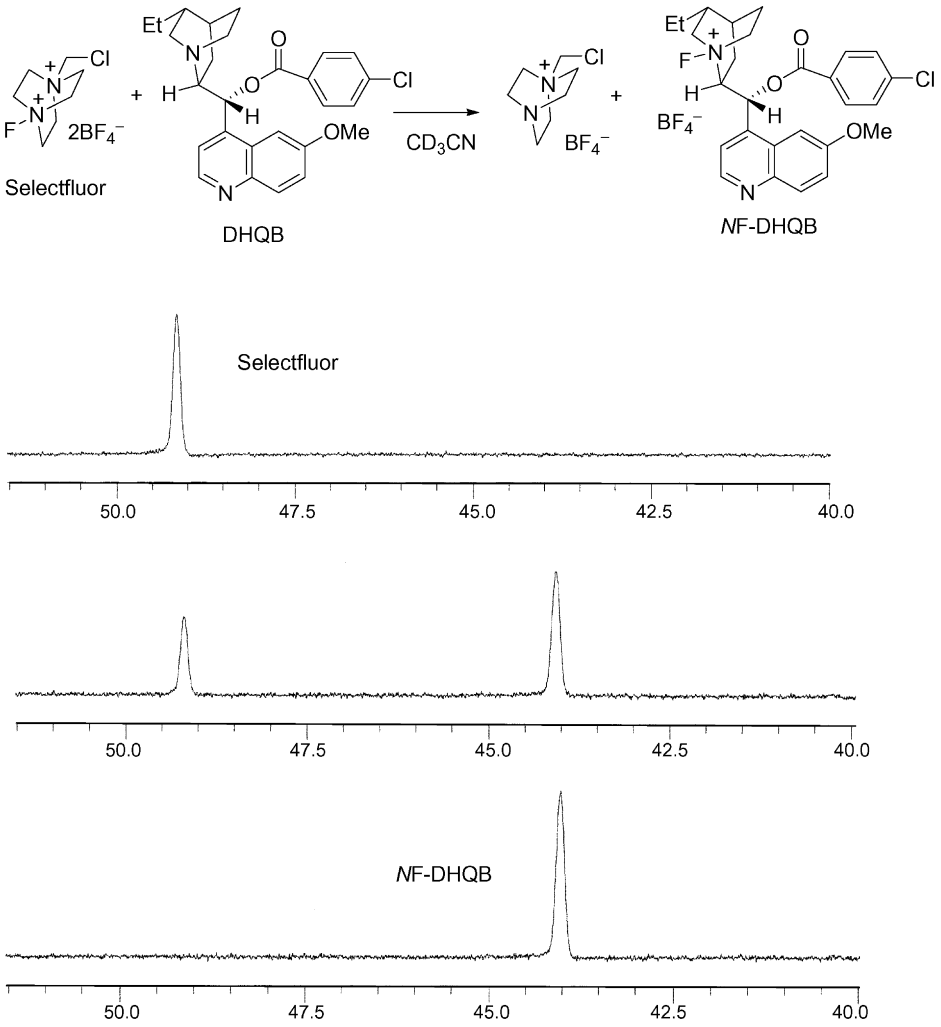


Fig. 4. The 254 MHz ^{19}F NMR spectrum of Selectfluor® and the combination in CD_3CN. Top: Downfield region of the ^{19}F NMR spectrum of Selectfluor® in CD_3CN. Middle: The same region after the addition 0.5 equiv of DHQB. Bottom: The same region after the addition 1.0 equiv of DHQB, leading to the quantitative formation of *N*F-DHQB.

Institute as a potent, effective opener of maxi-K potassium channels [17]. MaxiPost® is a chiral, non-racemic compound, a key structural feature of which is the fluorine atom bonded to the asymmetric quaternary carbon center at C-3 in the oxindole ring. Although both enantiomers of MaxiPost® are active, the *S* isomer consistently gives a more robust response and has been developed as MaxiPost®. The *S*-enantiomer, MaxiPost®, was isolated using direct chiral HPLC resolution or through the formation and separation of the diastereomeric salts. No enantioselective synthesis had been reported at that time. We thus examined the enantioselective fluorination of the parent oxindole **27**. While previously optimized cinchona alkaloid/Selectfluor® combinations based on DHQB, DHQDA $(DHQD)_2PYR$ gave unacceptable enantioselectivities in the formation of MaxiPost®, the enantioselective fluorination of the parent oxindole **27** was employed using $(DHQ)_2AQN$/Selectfluor® combination to give MaxiPost® in excellent yield and in 84% ee [7c]. The reaction was also carried out in environmentally attractive solvents such as ionic liquid and/or water for industrial processes to furnish the MaxiPost® in high yields, although enantioselectivities are moderate, up to 60% ee (Table 1) [18]. A bit later, a similar result for the synthesis of MaxiPost® utilizing *isolated N*-fluoroammonium salt of 2-NapthtQN was also reported by Cahard et al. [8e] (Scheme 8).

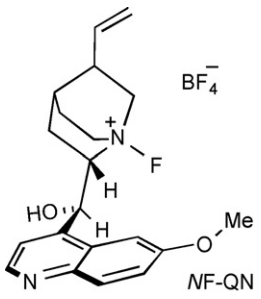


Fig. 5. X-ray crystallographic structure of *N*F-QN.

5. Drug development: design and synthesis of 20-deoxy-20-fluorocamptothecin (20-FluoroCPT)

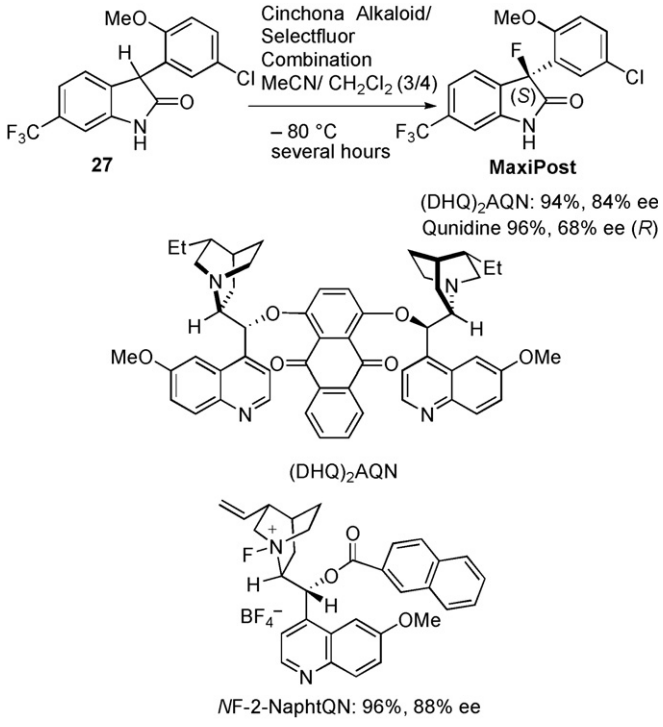
We were next interested in the design and synthesis of camptothecin isostere. Camptothecin (CPT), a natural product

Table 1
Enantioselective synthesis of MaxiPost® in ionic liquid [emim][OTf]

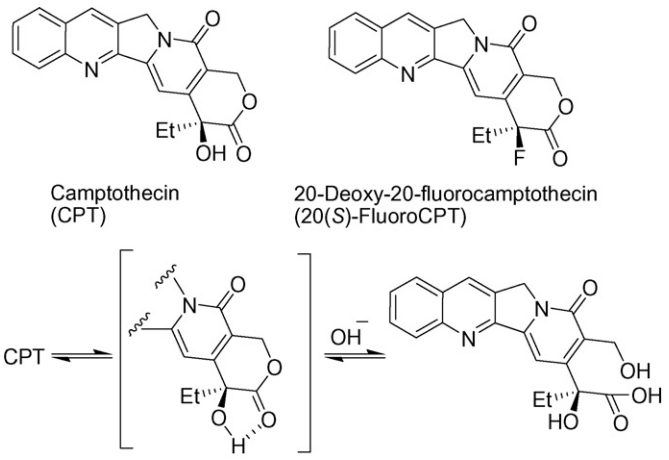
Alkaloid	Solvents	Yield (%)	ee (%)	Configuration
QD	[emim][OTf]	84	23	*R*
QD	MeCN/[emim][OTf] = 9/1	74	39	*R*
QD	MeCN/[emim][OTf] = 7/3	82	46	*R*
QD	MeCN/[emim][OTf] = 5/5	89	46	*R*
QD	MeCN/[emim][OTf] = 3/7	81	32	*R*
QN	MeCN/[emim][OTf] = 5/5	55	35	*S*
CN	MeCN/[emim][OTf] = 5/5	83	39	*R*
CD	MeCN/[emim][OTf] = 5/5	99	11	*S*
$(DHQ)_2AQN$	MeCN/[emim][OTf] = 5/5	95	60	*S*
QD	$MeCN/H_2O$	95	28	*R*
QN	$MeCN/H_2O$	90	25	*S*
CN	$MeCN/H_2O$	98	13	*R*
CD	$MeCN/H_2O$	96	9	*S*
$(DHQ)_2AQN$	$MeCN/H_2O$	99	17	*S*
$(DHQD)_2PHAL$	$MeCN/H_2O$	91	41	*S*
$(DHQ)_2AQN$	$[emim][OTf]/H_2O$	88	2	*S*
$(DHQD)_2PHAL$	$[emim][OTf]/H_2O$	86	42	*S*
QD	$[emim][OTf]/H_2O$	85	38	*R*
QN	$[emim][OTf]/H_2O$	84	21	*S*
CN	$[emim][OTf]/H_2O$	95	30	*S*
CD	$[emim][OTf]/H_2O$	83	21	*R*

The reaction was performed at 0 °C for several hours.

isolated from extracts of the Chinese tree *Camptotheca acuminata* in 1958, possesses impressive activity against leukemias and a variety of solid tumors [19]. However, severe toxicities such as myelosuppression, vomiting, and diarrhea necessitated cessation of clinical trials of CPT. Inhibition of DNA topoisomerase I has been shown to be the mechanism of the action of CPT. The 20(*S*)-hydroxyl group in CPT is crucial

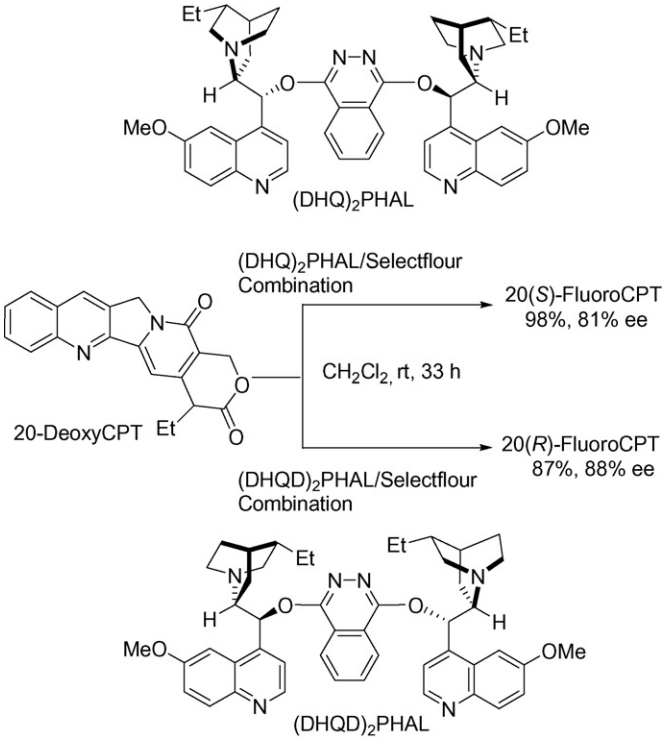


Scheme 8. Enantioselective synthesis of MaxiPost®.



Scheme 9. Design of 20-deoxy-20-fluorocamptothecin.

for potent anti-tumor activity. On the other hand, the hydroxyl group is also believed to contribute to the E-ring lactone opening by intramolecular hydrogen bonding (Scheme 9). The ring-opening form has lower efficacy. We therefore come up with the idea to synthesize 20-deoxy-20-fluorocamptothecin (20-FluoroCPT). It may be capable of mimicking the hydrogen bond acceptor during the inhibition of DNA topoisomerase I. In addition, the absence of an intramolecular hydrogen bond may decrease the reactivity of the E lactone ring. Direct enantioselective fluorination of the lactone moiety of 20-deoxyCPT by cinchona alkaloid/Selectfluor® combinations was examined. Good levels of enantioselection were achieved using *bis*-cinchona alkaloid/Selectfluor® combinations (Scheme 10). Thus, $(DHQ)_2PHAL$/Selectfluor® combination



Scheme 10. Synthesis of 20-deoxy-20-fluorocamptothecin.

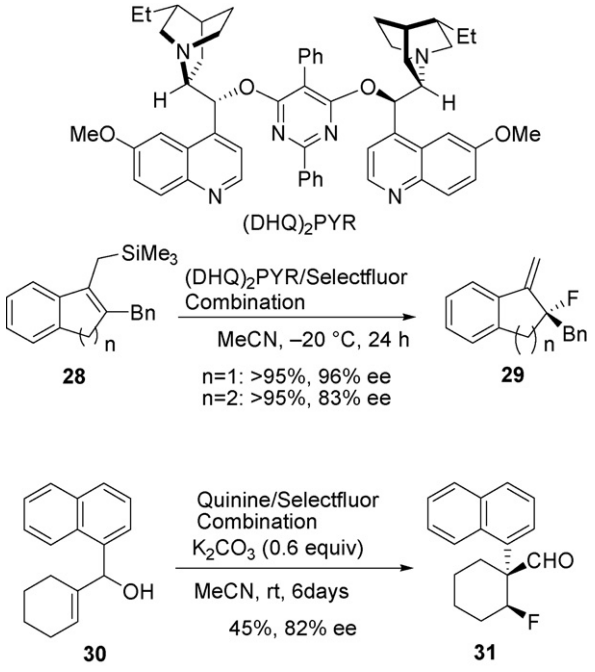
in CH_2Cl_2 at room temperature afforded 20(*S*)-FluoroCPT in 98% with 81% ee. Reverse stereoselectivity was observed in the reaction using $(DHQD)_2PHAL$/Selectfluor® combination to give 20(*R*)-FluoroCPT in 87% yield with 88% ee [7d]. A year later, Curran et al. also reported the synthesis and biological activity of the 20-FluoroCPT [20].

6. Enantioselective fluorination beyond the substrates scope

Whereas the methods so far described had apparently been limited to the α-fluorination of carbonyl compounds, significant extensions of this strategy were disclosed by Gouverneur and co-workers [21] and, more recently, by Tu and co-workers [22] (Scheme 11). Using our $(DHQ)_2PYR$/Selectfluor® combination, allyl silanes **28** were elegantly fluorinated in MeCN via the fluoro-desilylation pathway, leading to allylic fluorides **29** with very high enantioselectivities. Asymmetric semipinacol rearrangement of allylic alcohols **30** was effectively induced by a quinine/Selectfluor® combination to give β-fluoroaldehydes **31** with an α-quaternary carbon center in moderate yield with good enantioselectivity. These successful applications exhibit signs of exceptional scope that enable many types of chiral fluoro-organocompounds to be accessed by the cinchona alkaloid/Selectfluor® combinations.

7. Catalytic approaches based on cinchona alkaloid/Selectfluor® combinations

The procedure based on the cinchona alkaloid/Selectfluor® combinations, although efficient as mentioned, requires stoichiometric amounts of cinchona alkaloids and, therefore,



Scheme 11. Enantioselective allylic fluoro-desilylation and asymmetric semipinacol rearrangement induced by cinchona alkaloid/Selectfluor® combinations.

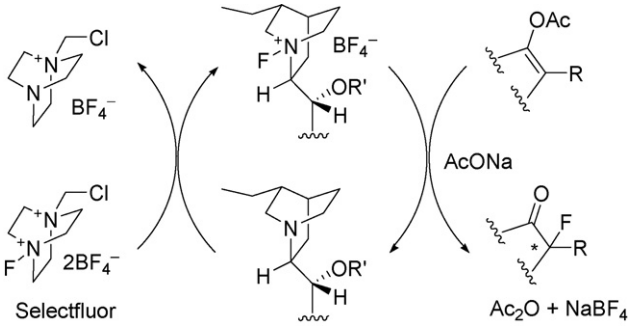
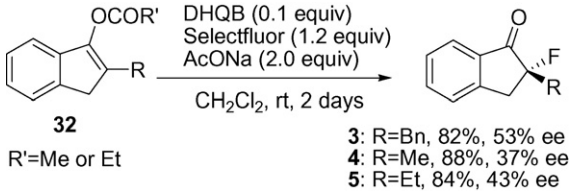


Fig. 6. Ideal catalytic process of enantioselective fluorination catalyzed by cinchona alkaloids.

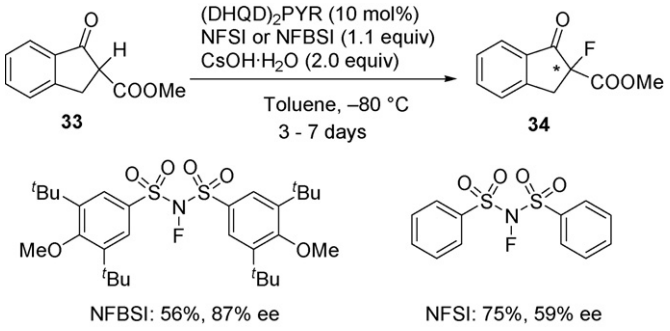
a catalytic version of the reaction is highly desirable. As expected, however, the enantioselectivity of the product was markedly decreased when the reaction was performed using a catalytic amount of cinchona alkaloids. Even though several groups have been enthusiastically working in the enantioselective fluorination via the cinchona alkaloid strategy [7,8,10,21,22] there was not a single report on a catalytic version of the reaction.

For this long-awaited issue, we have recently provided a solution with partial success [23]. First, we turned our attention to the reaction mechanism to find an ideal solution to the problem. The high reactivity of the silyl enol ether (see Scheme 3) to the requisite Selectfluor® may in part be responsible for the poor enantioselectivity observed. The background reaction should be as rapid as the transfer fluorination from Selectfluor® to cinchona alkaloids. The desired catalytic cycle would involve the generation of cinchona alkaloid/Selectfluor® combination, fluorination of an enolate by the combination and the release of the cinchona alkaloids to regenerate the catalyst. In order to decrease the reactivity of the substrate, we selected acetyl enol ethers, which are not reactive enough toward Selectfluor®. Addition of a base can help the desired activation of the enolate followed by trapping of the acetyl cation (Ac^+) and BF_4^- in the reaction cycle, which is an important feature of our plan to achieve a catalytic turnover (Fig. 6). Along those lines, the first protocol has been accomplished by employing acyl enol ethers as substrates with Selectfluor® in the presence of a catalytic amount of DHQB and 1.2 equivalents of sodium acetate in CH_2Cl_2 to furnish α-fluoroketones in good yields and with moderate enantioselectivities of up to 53% ee (Scheme 12).

Not surprisingly, experiments with β-keto esters under the above catalytic conditions were less successful. The competing



Scheme 12. Catalytic enantioselective fluorination induced by DHQB/Selectfluor® combination.



Scheme 13. Cinchona alkaloid-catalyzed enantioselective fluorination of β-keto ester with NFBSI.

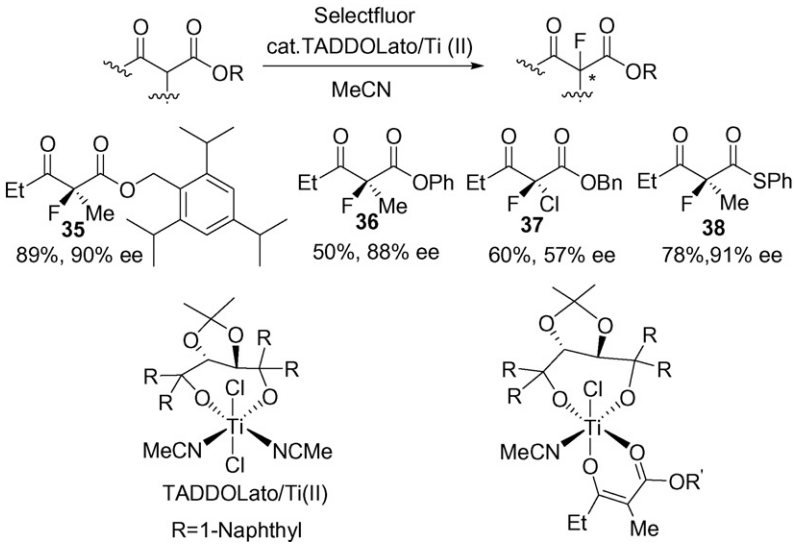
non-enantioselective background fluorination of β-keto esters by Selectfluor® is much faster than the transfer fluorination from Selectfluor® to cinchona alkaloids. The use of less reactive reagents for fluorination would have an advantage, which enables transfer fluorination to cinchona alkaloids, before the fluorinating reagents take part in the background fluorination process. We therefore screened fluorinating reagents and found that previously unknown, sterically demanding *N*-fluoro-(3,5-di-*tert*-butyl-4-methoxy)benzenesulfonimide (NFBSI) is quite effective in the cinchona alkaloid-catalyzed enantioselective fluorination of indanon-2-carboxylate (**33**) to furnish **34** in 56% yield with 87% ee [24]. Commercially available *N*-fluorobenzenesulfonimide (NFSI) can also be used in the reaction, although the enantioselectivity is moderate (59% ee, Scheme 13).

8. Catalytic enantioselective fluorination of 1,3-dicarbonyl compounds featuring two-point binding

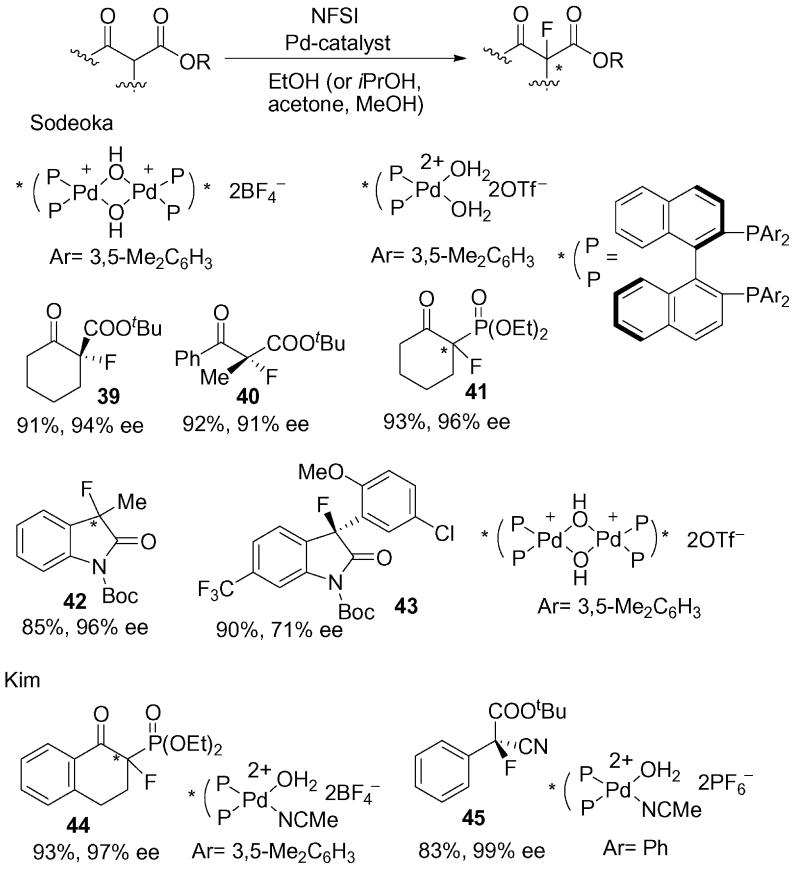
The first example of a catalytic enantioselective fluorination came from Togni's group in late 2000 that β-keto esters were enantioselectively fluorinated with Selectfluor® in the presence of a catalytic amount of TADDOLato/Ti(II) to furnish the corresponding α-fluorinated β-keto esters with up to 91% ee [9]. The notable feature in this process involves the ability of the TADDOLato/Ti(II) to allow the β-keto esters to participate in the catalytic cycle via coordination at their two carbonyl oxygens that stabilizes the transition state, and hence effects enantioselective electrophilic fluorination by Selectfluor® (Scheme 14) [9c]. This observation eventually led to the successful development of a two-point binding protocol for the catalytic enantioselective fluorination. Several groups have now reported interesting variations in this area. The earliest was a report by Sodeoka et al. that the palladium BINAP complexes enable catalysis of the enantioselective fluorination of β-keto esters with very high enantioselectivites [25a]. An electrophilic fluorinating reagent, NFSI, was used instead of Selectfluor®. While the substrate generality had not been fully explored in the initial paper [9a], the Sodeoka method utilizing palladium complexes allows access to a very broad range of fluorinated 1,3-dicarbonyl compounds including acyclic and cyclic β-keto esters with very high control of enantioselectivity in many instances. The scope of the methodology utilizing chiral palladium complexes has now been extended successfully by two groups, Sodeoka and co-workers [25] and Kim et al. [26], to the enantioselective fluorination of β-keto phosphonates, α-cyano esters and even oxindoles (Scheme 15). The palladium complexes enabled to be immobilized in ionic liquids to reuse for enantioselective fluorination no less than 10 times with levels of efficiency comparable to those obtained in usual organic solvents [25b].

9. Catalytic enantio-flexible fluorination reaction of β-keto esters

While much of the chemistry surrounding the catalytic enantioselective fluorination of 1,3-dicarbonyl compounds using chiral ligands/metal has been very well documented as mentioned above, it should be noted that the methodology using these chiral catalysts is restricted to the production of only one



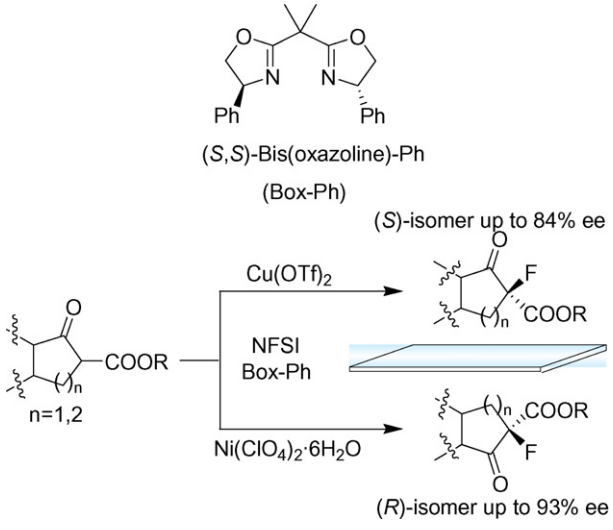
Scheme 14. First catalytic enantioselective fluorination by Togni's group.



Scheme 15. Catalytic enantioselective fluorination using Pd-BINAP catalysts.

enantiomer. Therefore, the preparation of both antipodes of catalysts is inevitable for getting target compounds with the desired stereochemistry. Inspired by the successes for the catalytic enantioselective fluorination by Togni and co-workers [9] and Sodeoka and co-workers [25], we were actively working to develop an enantioselective fluorination reaction that produces either product enantiomer selectively, depending on the reaction conditions, from only one chiral ligand. This obviates the requirement to produce both catalyst antipodes. We came across one solution demonstrating that one catalyst enantiomer could be used to produce both enantiomers of the target fluorinated compounds. Specifically, in the presence of *bis*(oxazoline)-Ph (Box-Ph), fluorination with NFSI produced selectively either antipode of the fluorinated products, depending on the metal salt employed, with moderate to high enantioselectivities (Scheme 16) [27]. For instance, when the fluorination of β-keto esters was carried out with NFSI in the presence of a catalytic amount of Box-Ph/Cu(II), the reaction predominately gave the fluorides with (*S*) configuration at the newly generated chiral center in up to 84% ee. Conversely, when the fluorination was carried out using a catalytic amount of Box-Ph/Ni(II) instead, the reaction outcome changed dramatically to afford the opposite (*R*) isomers with up to 93% ee. Some representative examples are shown in Fig. 7. An interesting phenomenon, as ‘‘elective’’ enantioselectivity, has been observed in the fluorination of a series of β-keto esters. Using the same chiral ligand, but switching the metal catalyst from Cu(II) to Ni(II) gave a complete reversal of enantioselectivity, although the enantioselectivities are varied with the substrates structure.

A working hypothesis for the selectivity observed with Cu(II) or Ni(II) is presented. The *S*-selectivity can be explained using a distorted square planar geometry model relative to Cu(II). The ligand phenyl group in the down-side shields the back face of the enolate. Thus, NFSI approaches the reactive



Scheme 16. Catalytic enantio-flexible fluorination of β-keto esters.

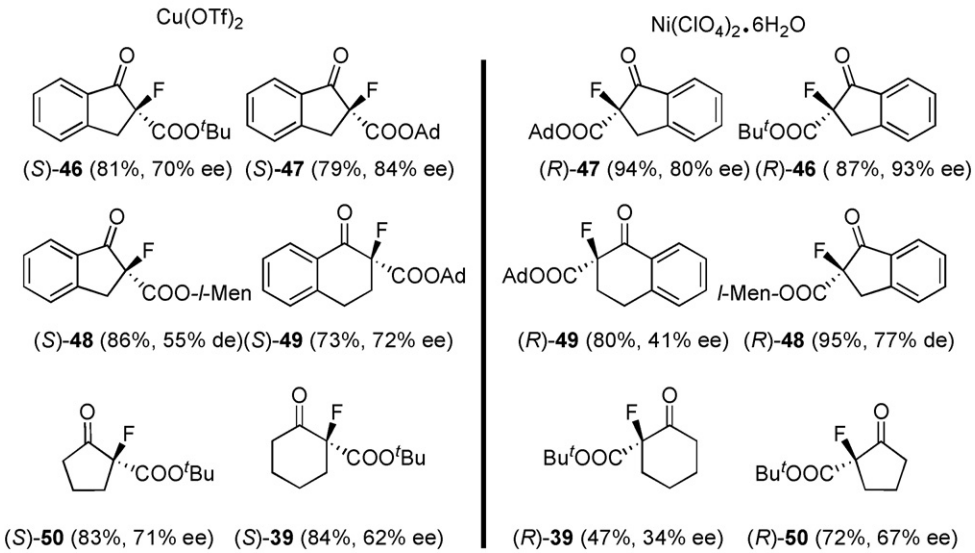


Fig. 7. Products obtained via enantio-flexible fluorination reaction using Box-Ph/ Cu(II) or Box-Ph/Ni(II).

center in the substrate from the *Si* face. On the other hand, in the reaction with the Ni(II) complex, the origin of the reversed sense of stereo-induction could be a consequence of a change in the metal center geometry from distorted square planar to square pyramidal in the transition state (Fig. 8).

It should be mentioned that just before the publication of this work, Box-Ph/Cu(II)-catalyzed enantioselective fluorination of β-keto esters in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was independently reported by Ma and Cahard [28]. The heterobimetallic BINOL/Al/Li combination with NFPY/BF_4 (*N*-fluoropyridinium tetrafluoroborate) was also demonstrated for the catalytic enantioselective fluorination of β-keto esters by the same group (Fig. 9) [29].

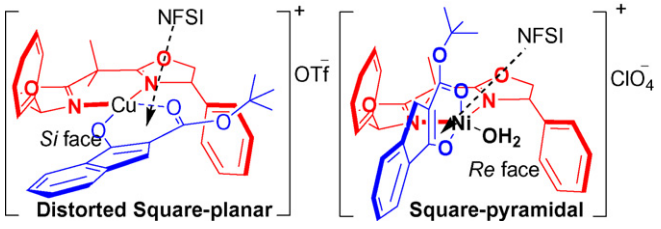


Fig. 8. Transition state structures.

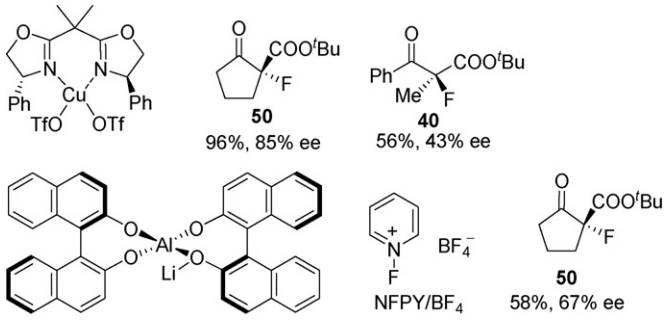


Fig. 9. Catalytic enantioselective fluorination by Cahard's group.

10. DBFOX/Ni(II)-catalyzed enantioselective fluorination of 1,3-dicarbonyl compounds

These improved methodologies by others and us have made great contributions; however, the levels of enantioselectivity were not high enough. We therefore surveyed a range of catalysts to achieve the ideal enantioselective fluorination and found that the DBFOX ligand, which is well-known as Kanemasa's catalyst for asymmetric Diels–Alder and Michael addition reactions [30], was highly effective in our fluorination process. Enantioselective fluorination of a wide range of substrates capable of two-point binding including both cyclic and acyclic β-keto esters using 10 mol% of DBFOX/Ni(II) in CH_2Cl_2 indicated the extraordinarily reliable and high enantioselectivity up to 99% ee (Scheme 17) [31]. It is notable that catalyst loading can be reduced to 2 mol% without any loss of enantioselectivity. We assumed that an octahedral complex coordinated with a water molecule for substrate/DBFOX/Ni(II) is a transition state structure. In the complex, one of the faces is covered so efficiently that the NFSI approaches from the *Si* face of the substrate (Fig. 10).

The DBFOX/Ni(II) catalyst also demonstrates the power of enantioselective fluorination reaction in medicinal chemistry.

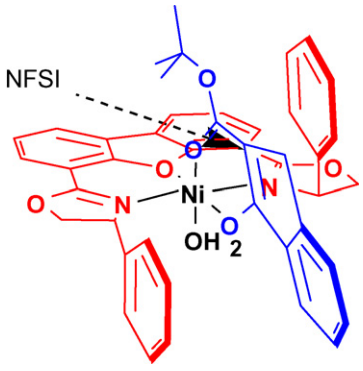
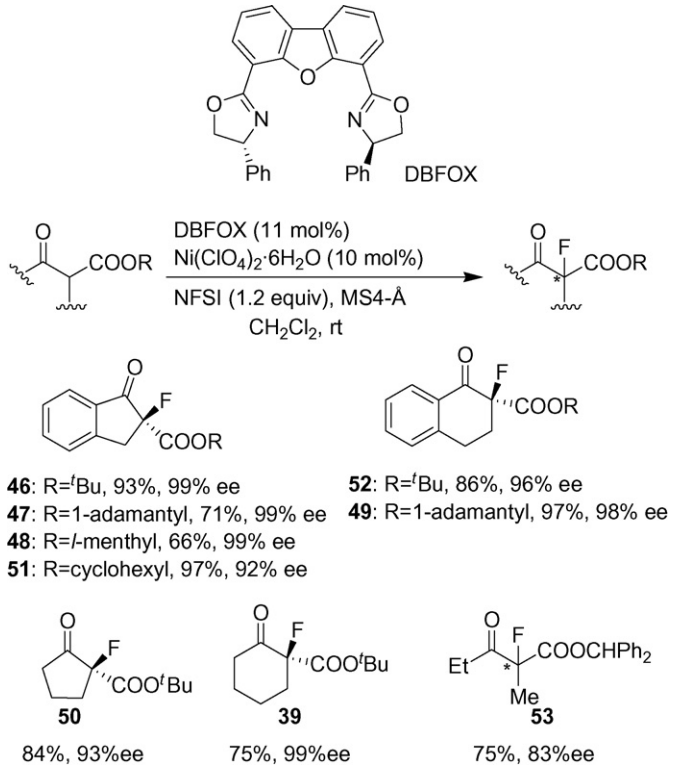


Fig. 10. Transition state structure.



Scheme 17. DBFOX/Ni(II)-catalyzed enantioselective fluorination gave products with extremely high ee values.

Fluorooxindoles are pharmaceutically important and these types of molecules were first enantioselectively synthesized by us utilizing a stoichiometric amount of a cinchona alkaloid/Selectfluor® combination [7c]. To reveal the further synthetic utility of the DBFOX/Ni(II) fluorination system, we examined the fluorination of the oxindoles **54** capable of two-point binding under slightly different reaction conditions, DBFOX/$Ni(OAc)_2$ in CH_2Cl_2. This fluorination system allowed for a significant degree of enantioselectivity irrespective of the substrates used up to 96% ee (Scheme 18). It is noted that MaxiPost® can be derived from **43**. We should mention that Sodeoka's group demonstrated very similar enantioselectivity

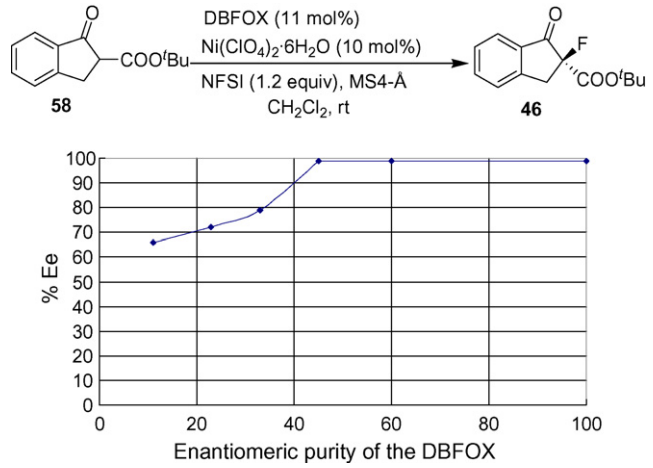


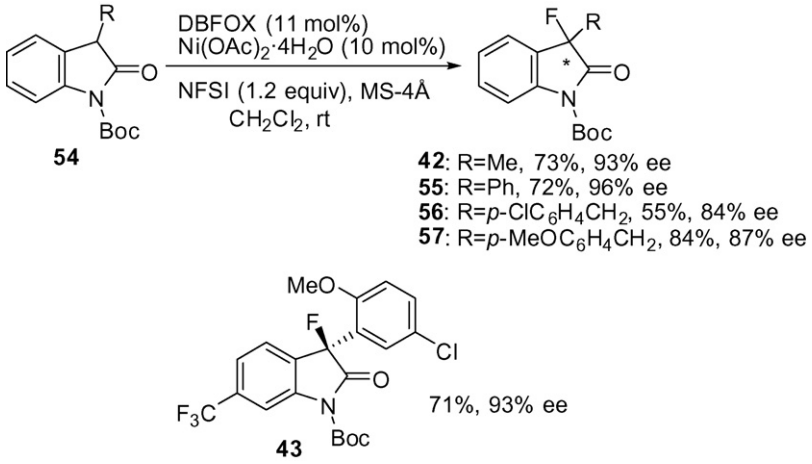
Fig. 11. Chiral amplification in the enantioselective fluorination catalyzed by DBFOX/Ni(II).

profiles for the fluorination of oxindoles based on their original bidentate strategy [25e].

It is important to point out that the chiral amplification in the fluorination was observed in our systems. Fluorination of *tert*-butyl indanon-2-carboxylate (**58**) with NFSI was carried out in the presence of DBFOX/Ni(II), enantiopurity of which was varied from 11% to 60%. Fig. 11 shows the relationship between the enantiomeric purity of the DBFOX ligand used and the enantioselectivity observed. When the DBFOX ligand had ee values of 45% and 11%, fluorinated product **46** was obtained with 99% and 66% ee, respectively.

11. Enantioselective fluorination based on the two-point binding approach by other groups

Other approaches under a similar concept but using different ligands/metal complexes have since found widespread use. The cationic Ru(II) complex was briefly communicated to be a feasible catalyst for enantioselective fluorination of β-keto esters by Togni's group in 2004 [9f,10b]. Bernardi and Jørgensen demonstrated the enantioselective fluorination of β-keto phosphonates using a DBFOX/Zn(II) complex [32] in



Scheme 18. Chiral fluorooxindoles prepared by DBFOX/Ni(II) catalyst.

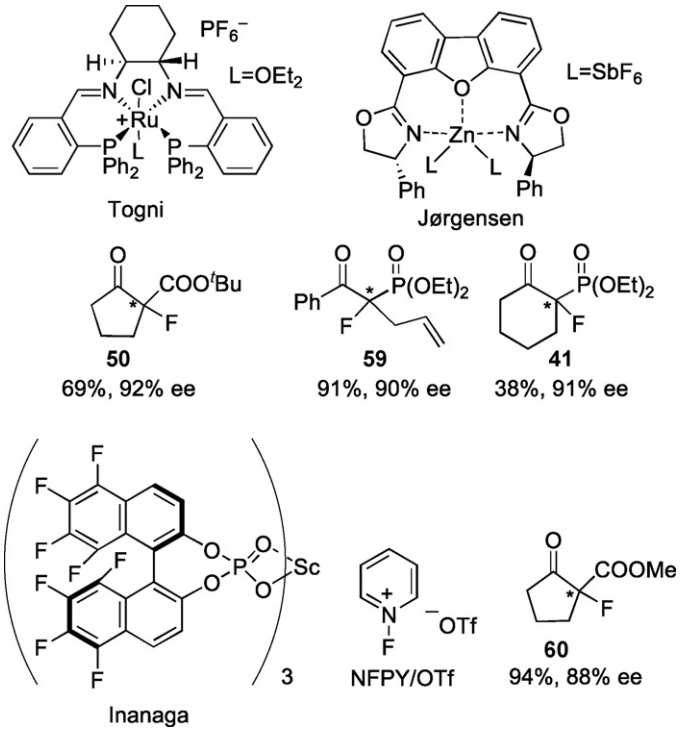


Fig. 12. Variation of catalysts for enantioselective fluorination.

early 2005 (Fig. 12). Enantioselective fluorination of β-keto esters was also carried out using a Sc[(*R*)-F_8BNP]$_3$ catalyst by Inanaga and co-workers [33]. They showed *N*-fluoropyridinium triflate (NFPY/OTf) was suitable as a fluorinating reagent in this method. The similar observation was reported by Cahard et al. (previous section, Fig. 9) [29].

12. Recent innovations: enantioselective fluorination by organocatalysts

The use of organocatalaysts for asymmetric synthesis has emerged as a powerful tool in the past few years [34]. In particular, recent progress of proline-catalyzed direct aldol reaction has sparked a revolution in this area. A phase transfer-catalyzed protocol by Kim and Park in 2002 (Fig. 13) [35], and our recent example of cinchona alkaloid-catalyzed enantioselective fluorination [23] (Schemes 12 and 13, in the previous section) are available; however, they require a stoichiometric amount of an *inorganic base* as well, and, therefore, are not truly organocatalytic reactions. Enders' group developed the first organocatalytic enantioselective fluorination using proline and its derivatives in early 2005 [36]. Cyclohexanone was fluorinated with Selectfluor® in the presence of 3-hydroxylproline (**63**), although the enantioselectivity was rather low (34% ee). Shortly after the Enders report, three groups, Jørgensen and co-workers [37], Barbas and co-workers [38] and MacMillan and co-workers [39], simultaneously disclosed an organocatalyzed, highly enantioselective electrophilic fluorination of aldehydes using NFSI. All the methods are based on the proline derivatives-catalyzed fluorination and they are equally efficient in terms of both enantioselectivity and substrate generality, albeit the reaction conditions are quite different. Selected examples are shown in Fig. 14. In 2006, Jørgensen et al. have found the very unique example that optically active 8-amino-2-naphtol **67** is highly catalytically active as well as enantioselective for the direct fluorination of α-branched aldehydes using NFSI. The catalyst **67** is the first organocatalyst based on non-biaryl atropoisomerism [40]. While the enantioselective fluorination

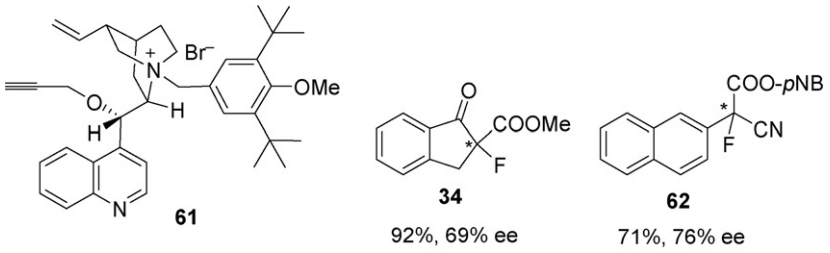


Fig. 13. Phase transfer-catalyzed enantioselective fluorination by Kim's group.

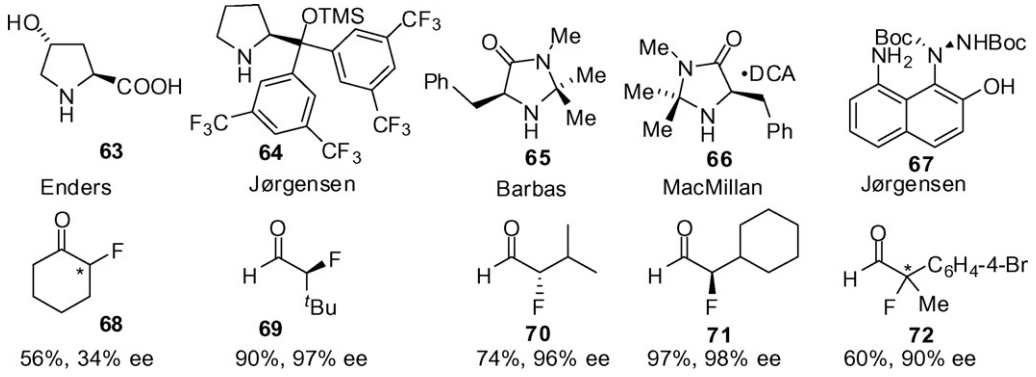


Fig. 14. Selected examples of organocatalytic fluorination from Enders, Jørgensen, Barbas and MacMillan groups.

based on the two-point binding approach using metal salts and chiral ligands is strictly limited to 1,3-dicarbonyl compounds and related substrates, these oraganocatalyst protocols can be effectively utilized for the enantioselective fluorination of a wide range of aldehydes.

13. Conclusion

We have herein mainly discussed our participation in this emerging field. Through their generality and enantioselectivity, the three communications in 2000 by others [8,9] and us [7] were the first major departure from the initial idea postulated by Defferding and Lang in 1988 [6]. More recent innovations in this area are set to the use of organocatalysts for enantioselective fluorination reaction. Procedures that provide a variety of chiral fluoro-organic compounds in high yields and with excellent enantioselectivities are now becoming available, and most of the issues concerning enantioselective fluorination seem to have been accomplished. However, it is hoped more unique methodology in this field will be appearing in the near future [41].

Acknowledgments

We are indebted to all of our co-workers and collaborators, whose names are cited in the references, for their intellectual and experimental contributions. Financial support by TOSOH F-TECH INC., Japan Science & Technology (JST) Agency, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (17350047, 17590087).

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