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Modern Approaches for Asymmetric Construction of Carbon −Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs

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Abstract

New methods for preparation of tailormade fluorine-containing compounds are in extremely high demand in nearly every sctor of chemical industry. The asymmetric construction of quaternary C −F stereogenic centers is the most synthetically challenging and, consequently, the least developed area of research. As a reflection of this apparent methodological deficit, pharmaceutical drugs featuring C−F stereogenic centers constitute less than 1% of all fluorine-containing medicines currently on the market or in clinical development. Here we provide a comprehensive review of current research activity in this area, including such general directions as asymmetric electrophilic fluorination via organocatalytic and transition-metal catalyzed reactions, asymmetric elaboration of fluorine-containing substrates via alkylations, Mannich, Michael, and aldol additions, cross-coupling reactions, and biocatalytic approaches.

Graphical Abstract

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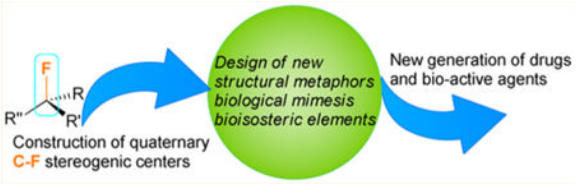

1. INTRODUCTION

Fluorine is the 24th most abundant element in the universe and the 13th most common element in the earthjs crust (0.027% by weight).[1] For example, the life-forming elements, such as carbon (15th), nitrogen (31st) and sulfur (17th), as well as other halogens [Cl (21th), Br (59th), I (63th)] are significantly less common.[2] However, despite its natural abundance, fluorine is virtually completely absent from the biosphere.[3] Three major factors prohibiting chemical and biological evolution of fluorine are (1) the three richest natural sources of fluorine, the minerals fluorospar (CaF_2), fluorapatite ($Ca_5(PO_4)_3F$), and cryolite (Na_3AlF_6) are practically water-insoluble, rendering the corresponding fluoride unavailable for chemical reactions;[4] (2) high oxidation potential of fluorine (−3.06 V, greatly higher than the rest of halogens) makes it impossible to form the corresponding hypohalous intermediates necessary for known enzymatic halogenation;[5] (3) high hydration energy of fluorine (117 kcal/mol) renders fluoride a very poor nucleophile in an aqueous/biological environment and therefore unsuitable to form organic C−F bonds via typical nucleophilic substitutions.[6] Hence, fluorine (fluoride) is virtually xenobiotic except for a handful of monofluoroacetic acid derived compounds.[3]

Nevertheless, virtually man-made fluoro-organic chemistry is currently one of the most hectic areas of current research, exerting a profound effect on the most vital industries such as energy, food, and healthcare. The first spectacular demonstration of fluorine-enabled technological achievements was made during the Manhattan Project (1942–1946), where fluorinated compounds played an absolutely indispensable role in the separation of fissile U-235 from U-238 via centrifugation as well as development of novel chemically inert, stable, and durable materials. Similarly, stabilizing and electronic effects of fluorination on material properties are currently used in the solar cells industry[7–9] and systematic design of functional materials.[10] Medicinal applications of fluorinated molecules can be exemplified by positron emission tomography–computed tomography (PET-CT) using radiotracers labeled with ^{18}F nuclei.[11,12] Other diagnostic tools are based on high NMR sensitivity of fluorine, rendering it as an ideal marker for biological studies.[13] Some particular progress has been made in preparation of various fluorinated amino acids[14–19] and their strategic incorporation into peptides and proteins.[20,21] Another important medicinal diagnostic technique is ^{19}F magnetic resonance imaging (MRI), a superior alternative to the current diagnostic procedures using harmful ionizing radiation.[22,23] This area technology was developed as part of the more general field of fluorous chemistry based on perfluorinated molecules showing omniphobic physicochemical properties.[24–26] Even more decisive impact of fluorinated compounds can be seen in modernization of agrochemical industry.[27] Thus, about half of newly developed pesticides contain some type of fluorination, [8–30] generally leading to increased environmental and metabolic stability as well as enhanced

biological activity. However, the most spectacular impact of fluorine chemistry on modern society is observed in the pharmaceutical industry.[31] Thus, according to the recent survey of the new drug candidates currently in phase II–III clinical trials, fluorine is becoming an increasingly common trait, accounting for about 35% of the designed molecules.[32,33] Most importantly, fluorine is found in more than half of most-prescribed multibillion-dollar pharmaceuticals.[32–34] Furthermore, the beneficial effect of fluorination can be applied in all therapeutic areas for modulation of virtually any type of biological activity. In this regard, it is interesting to note the success of this strategy in the development of small-molecule therapeutics for Ebola virus (EBOV) disease treatment.[35]

One may agree that a full extent of technological innovations enabled by fluorine chemistry is far from being fully explored, rendering research in this area of great practical potential and socioeconomic impact. Indeed, fostered by numerous practical applications, the current research activity in fluorine chemistry is at an all-time high.[36–54] In particular, the development of innovative synthetic methodology, which is providing access to new fluorinated structural motifs with yet unknown physicochemical and biological attributes, is in extremely high demand in nearly every sector of the chemical industry. However, the progress in the development of fluoro-organic methodology was far from balanced. For example, one of the most developed areas is a direct introduction of a trifluoromethyl group and synthetically related processes.[55–67] In sharp contrast, the asymmetric construction of carbon-fluorine quaternary stereogenic centers is the most synthetically challenging and, consequently, the least developed area of research. As a reflection of this apparent methodological deficit, pharmaceutical drugs featuring C–F stereogenic centers constitute less than 1% of all fluorine-containing medicines currently on the market or in the clinical development.[31–33] Some success has been achieved in the development of enantioselective electrophilic fluorination, and this subject has been intensively reviewed.[68–75] On the other hand, the alternative approaches have received much less appreciation in the current literature. Therefore, we trust that a comprehensive review, critically discussing the state-of-the-art of the corresponding methodology, is both strategically timely and scientifically stimulating.

2. MARKETED DRUGS FEATURING QUATERNARY C–F STEREOGENIC CENTERS

Considering the xenobiotic character of fluorine, the idea of modification of bioactive molecules with fluorine atoms, to improve the desired properties, was quite implausible until the early 1950s. Around that time, Fried and Sabo[76] were studying a series of hydrocortisones in which the 9α-hydrogen atom was replaced by halogen. They found that iodo-, bromo-, and chloro-derivatives possessed noticeably higher glucocorticoid activity as compared with that of the parent hormones. Most importantly, they discovered that the bioactivity was inversely proportional to the size of the halogen atom, leading them to a logical curiosity to investigate the corresponding fluoro-derivative. 9α-Fluoro hydrocortisone **2** (Scheme 1) was prepared in about 50% yield by treatment of acetate **1** with anhydrous hydrogen fluoride in alcohol/water-free chloroform at 0 °C for 4.5 h.[77]

Subsequently, it was shown that 9α-fluoro hydrocortisone acetate **2** possessed astonishing ~10.7 times the activity of nonfluorinated cortisone acetate in the rat liver glycogen assay. Deacetylation of **2** with sodium methylate gave rise to 9α-fluoro hydrocortisone **3,** which was patented in 1953 and marketed since August 18, 1955 under the brand names Fludrocortisone, Florinef, and others. Fludrocortisone **3** is still in use for treatment of adrenogenital syndrome, postural hypotension, and adrenal insufficiency and is included in World Health Organization's list of essential medicines.[78] The discovery of fludrocortisone **3** demonstrated that fluorine is a good bioisostere for hydrogen while influencing neighboring functional groups due to its extreme electronegativity. It should also be noted that fludrocortisone **3** was the first fluorine-containing drug approved by the FDA and, at the same time, the first example of pharmaceuticals featuring a quaternary C–F stereogenic center.

Another successful fluorine-containing drug possessing quaternary C–F moiety is synthetic glucocorticoid fluticasone propionate **4** (Figure 1). It is also known in combination with salmeterol **5** under the trade name Advair Diskus, prescribed as an oral inhaler for the treatment of asthma. It is interesting to note that Advair Diskus is in the league of top-performing drugs in terms of prescription and sales rates (>$5.0 billion).[79]

Structurally very similar to fluticasone **4** is difluorinated corticosteroid difluprednate **6** (Scheme 2). This drug possesses a potent clinical efficacy in controlling postoperative inflammation. It was approved by the FDA in June 2008 as the first topical steroid prescribed for inflammation as well as pain associated with ophthalmic procedures.[80,81] It was shown that fluorine substitution for hydrogen in the C6 and C9 positions contributes to the potency of the drug, likely due to the increased lipophilicity and corneal penetration.[82,83]

The first fluorination step in the synthesis of fluticasone **4** and difluprednate **6** involves the selective introduction of the fluorine atom in position 6 of compound **7** using perchloryl fluoride, followed by the removal of secondary acetate moiety to afford intermediate **8.** Successive transformation of **8** to bromohydrin **9** was accomplished with bromo acetamide/ perchloric acid. The latter was converted into epoxide **10** under very mild basic conditions. The second fluorination step is quite similar to the synthesis of fludrocortisone **3** (Scheme 1) and based on the epoxide ring opening with hydrogen fluoride under dry conditions.[84]

Another example of drugs possessing quaternary C–F moiety is solithromycin **13** (Scheme 3), the fluoroketolide antibiotic currently under consideration by the U.S. FDA for treatment of moderate to moderately severe community-acquired bacterial pneumonia.[85] The drug interrupts bacterial protein synthesis, preventing the growth and reproduction by reversibly binding to the bacterial ribosome.[86] It is interesting to note that solithromycin **13** shows noticeably superior inhibition against growth of streptococci carrying a special methyltransferase gene which is thought to be the main cause of the current global macrolide resistance. The effect of the fluorination is difficult to ascertain but can be linked with configurational stability of the fluorinated C2 in solithromycin **13.**[87]

The key, regioselective electrophilic fluorination step of intermediate **11** was performed using 1-chloromehyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborates)

(Selectfluor),[88–90] in the presence of KO*t*-Bu. The final product solithromycin **13** was prepared form **12** in a few steps including copper-catalyzed azide–alkyne cycloaddition with 3-ethynylaniline.[91]

Hepatitis C is a current pandemic liver disease, affecting 130–150 million people worldwide, with high morbidity and mortality rates. Recent progress in the treatment of this disease was made with the development of a new generation of agents acting directly on the viral protein synthesis.[92,93] Among the most effective therapies against HCV infection, is sofosbuvir **14** (Scheme 4), featuring the quaternary stereogenic C–F moiety.[94,95]

In several of the developed protocols[96–99] for preparation of sofosbuvir **14,** the key fluorination step involves the treatment of tertiary alcohol **15** with DAST,[100,101] proceeding with the inversion of the absolute configuration at C2′. It is proposed that the role of the fluorination in this drug is a stabilization of the 3D geometry around the corresponding stereogenic center. Thus, despite the availability of a 3′ hydroxyl group to act as a nucleophile, sofosbuvir **14** acts as a chain terminator because the 2′ methyl group causes a steric clash with an incoming nucleotide triphosphate.[102]

The five above-profiled drugs, fludrocortisone **3,** fluticasone **4,** difluprednate **6,** solithromycin **13,** and sofosbuvir **14,** representing different therapeutic areas, clearly underscore the pharmacophoric importance of the quaternary C–F moiety in the design of modern pharmaceuticals. Quite remarkable is that the C–F quaternary stereogenic centers in these compounds impart rather versatile effects influencing reactivity of the neighboring functional groups, configurational stability of a stereogenic carbon, 3D structure, and overall lipophilicity of the parent biomolecules. Another noticeable trend is that the methodology of fluorine introduction is limited by the reactions discovered 50–70 years ago. One would agree that to realize full pharmaceutical potential of fluorine-containing compounds in general, and these bearing quaternary C–F structural features in particular, there is a critical need for advanced new approaches for chemo- and enantioselective selective construction of quaternary C–F stereogenic centers.

3. MODERN METHODS FOR CONSTRUCTION OF QUATERNARY C–F STEREOGENIC CENTERS

3.1. Introduction of Fluorine

Because of the prevalence of fluorinated pharmaceuticals and pesticides, the asymmetric incorporation of fluorine into organic molecules has attracted considerable attention. Despite significant progress in the development of asymmetric fluorination methodology,[71,74] the asymmetric construction of a fluorine-containing quaternary stereogenic center is still synthetically quite challenging. Herein, we aim to comprehensively cover recent advances in the asymmetric fluorination transformations, especially for catalytic electrophilic enantioselective approaches, resulting in formation of a C–F bond of a quaternary stereogenic center.

In 1988, Differding and Lang reported the first electrophilic enantioselective fluorination of enolates using stoichiometric amounts of chiral *N*-fluoro camphorsultam reagent.[103]

Subsequently, the development of bench-stable and operationally convenient electrophilic fluorinating reagents such as Selectfluor, *N*-fluorobenzenesulfonimide (NFSI), and *N*-fluoro pyridinium salts has marked an important milestone in enantioselective fluorination.[104,105] Since 2000, the practical enantioselective methodology leading to construction of a C–F quaternary stereocenter has been blooming due to the development of chiral N-F reagents derived from in situ generated or isolated *N*-fluoroammonium salts by the combination of equimolar cinchona alkaloids and Selectfluor.[106,107] At the same time, the pioneering research related to a catalytic protocol by using TADDOLato/Ti(II) catalyst for enantioselective fluorination of acyclic *β*-ketone esters with Selectfluor was reported.[108] First, we will provide a brief description of a reagent-controlled process, especially the development of chiral *N*-fluoroammonium salts of cinchona alkaloids, because these studies laid important groundwork for latter methodological advances. Subsequently, comprehensive discussion will be devoted to the catalytic asymmetric scenario including organocatalytic methods (tertiary amine catalysts derived from cinchona alkaloids, primary and secondary amine catalysts via enamine intermediates, cationic and anionic phase-transfer catalyst, etc.) and transition-metal catalyzed transformations. Additionally, F-additions to C=C bonds will be highly emphasized. The fluoro-functionalization of alkenes by electrophilic fluorinating reagent to enantioselective installation of a C–F quaternary stereogenic center is an appealing strategy that converts common alkenes into valuable bioactive fluorinated molecules.

Asymmetric fluorination by using a nucleophilic fluorinating source is much less developed as compared to the electrophilic processes. Here we would like to mention just a handful of known examples. One of them is a stoichiometric, diaster-eoselective fluorination by using a nucleophilic source (Scheme 5). In this case, the anodic fluorination (platinum anode) of the 1,3-oxazolidines **17** derived from l-threonine was performed to afford a-monofluorinated product **18** in 73% yield with 81% de.[109] Recently, an iron(II)-catalyzed diastereoselective olefin aminofluorination, which applied a functionalized hydroxylamine **19** as a nitrogen source and $Et_3N{\cdot}3HF$ as a fluorine source, can afford desired fluorinated product **20** bearing a C–F quaternary carbon in 45% yield with >20:1 dr.[110]

Two special examples related to a catalytic enantioselective approach to construct C–F quaternary carbon by employing nucleophilic fluorinating reagents are presented in Scheme 6. First, the oxidative dearomatization of substituted phenols **21** by $PhI(OAc)_2$ in the presence of HF-pyridine complex was used to generate the fluorinated *meso*-cyclohexadienones intermediate, which then underwent a enantioselective intramolecular Michael addition sequence catalyzed by chiral secondary amine catalyst **C1,** leading to enantioenriched fluorinated product **22** in good yield (83%) and good diastereo- and enantioselectivity (>20:1 dr, 99% ee).[111] Recently, the combination of ArI/HF-pyridine/*m*CPBA system has been applied to perform a nucleophilic fluorination of *β*-dicarbonyl compounds **23** via in situ generation of hypervalent iodine compound $ArIF_2$ by mCPBA, HF, and a catalytic amount of iodoarene (ArI). Subsequently, the catalytic enantioselective scenario was conducted by using substrate with a steric adamantly demanding group and chiral iodoarene, (R)-binaphthyldiiodine, to afford *α*-fluorinated *β*-ketoester **24** in moderate yield and moderate enantioselectivity (56% ee).[112]

3.1.1. Asymmetric Electrophilic Fluorination.—The diastereoselective electrophilic fluorination to construct C–F quaternary stereogenic centers mainly focused on the α-fluorination of carbonyl compounds. The diastereoselectivity in these reactions is controlled by substrate structures bearing chiral auxiliaries to influence the diastereofacial discrimination of the intermediate enolates. The representative examples of bioactive molecules with various functionalities are provided in Scheme 7. For instance, the electrophilic fluorination of dipeptides **25** bearing quaternary chiral amino acid,[113] 2′-ketouridine lithium enolates generated from nucleoside analogues **27,**[114] stabilized sodium enolate generated from azetidinone **30** as antibiotic analogues,[115] or malonate **32** bearing a chiral phenylmenthyl auxiliary,[116] can afford desired α-fluorinated products **33** with moderate to good diastereoselectivity.

To achieve the enantioselective fluorination, a wide variety of chiral sulfonamide-type fluorinating reagents had been developed in earlier examples. For instance, Differding and Liang reported enantioselective fluorination of enolates controlled by chiral sulfonamide-type fluorinating reagents, *N*-fluorocamphorsultam **34,** in 1988.[103] Then Davis's reagents **35**[117,118] and Takeuchi and Shibata's saccharin-type reagents **36–38**[119–121] followed (Scheme 8). However, multistep procedures and using toxic or aggressive reagents for their preparation make these chiral N–F reagents unavailable. Meanwhile, unsatisfactory enantioselectivity and narrow substrate scope further limited their application.

In 2000, the Cahard and the Shibata groups simultaneously reported the introduction new class of N–F electrophilic reagents **39** and **40** derived from naturally occurring cinchona alkaloids.[106,107] In the Cahard's case, the *N*-fluoroammonium salts of cinchona alkaloids were isolated and applied in enantioselective fluorination, and the Shibata's procedure was based on in situ-generated *N*-fluoroammonium salts. Subsequently, a stoichiometric amount of cinchona alkaloids/Selectfluor combinations, or isolated *N*-fluoroammoniun salts of cinchona alkaloids, were proven to enable a wide range of substrates, including silyl enol ethers **43,**[106,122] allylsilanes **46,**[123] 1,3-dicarbonyl compounds **(49,51**),[124] lactones,[125] enolates **60**[107,126] oxindoles **54,**[124] and dipeptides **57,**[113] to covert to corresponding fluorinated products bearing with C–F quaternary stereogenic centers **(44, 47, 50, 52, 55, 58, 61, 63)** in good yields and effective enantioselective control (Scheme 9). In 2013, Cahard, Ma and Shibata developed a new chiral fluorinating reagent **42** as analogues of NFSI based on a chiral 1,1′-binaphthyl moiety with axial chirality[127] In 2013, the Gouverneur group developed a more reactive chiral N–F reagent **41** based on the structural core of Selectfluor with a chiral environment on the dicationic DABCO core,[128] and the application of this reagent in asymmetric fluorocyclization will be discussed in 3.1.1.2. F Additions to C=C Bonds (vide infra).

To further verify the synthetic utility for drug development, the enantioelective fluorination of several bioactive molecules was reported (Scheme 10). For instance, when employing the cinchona alkaloids $(DHQ)_2AQN$ **66**/Selectfluor combinations[129] or isolated F-2-NaphtQN-BF_4 salts,[130] the desired fluorinated oxindole **67,** BSM-204352 (MaxiPost), which serves as an effective opener of maxi-K channels, can be prepared with high yields with good enantioselectivity, and the enantioenriched 20-deoxyl-20-fluorocamptothecin **70,** which can be capable of mimicking the hydrogen bond acceptor during the inhibition of DNA

topoisomerase, can be prepared form asymmetric fluorination of corresponding lactone moiety **68** with good enantioselective control (88% ee).[131]

Additionally, in 2011, the Shibata group reported the preparation of enantiomerically pure 3′-fluorothalidomides **74** by enantiodivergent asymmetric fluorination via the combination of stoichiometric amounts of cinchona alkaloid (dihydroquinine DHQ, **73)** and NFSI with ligands and Lewis acids.[125] By the combination of DHQ/NFSI with $Cu(acac)_2$ and ligand bipy, the fluorinated R-enantiomer **72** can be synthesized in 81% yield with 77% ee, while with the use of tetramethylethylenediamine (TMEDA) as additive, the corresponding *S*-enantiomer **72** can be prepared in 88% yield with 78% ee (Scheme 11).

3.1.1.1. Organocatalytic Methods

3.1.1.1.1. Tertiary Amine Catalysts Derived from Cinchona Alkaloids and Their Analogues.: Although a stoichiometric amount of cinchona alkaloids/Selectfluor combinations or *N*-fluoroammoniun salts of cinchona alkaloids enabled a wide range of substrates as mentioned above (Scheme 9 and Scheme 10) to be converted to the corresponding fluorinated products with effective enantioselective control, the organocatalytic approach of the methodology employing catalytic amounts of cinchona alkaloids and electrophilic fluorinating reagents were still highly desirable and attractive, especially for the enantioselective incorporation of fluorine into organic molecules to construct a chiral quaternary stereogenic center.

In 2006, the Shibata group revealed a protocol for the electrophilic fluorination of cyclic acyl enol ethers with five- or six-membered rings **75** to afford α-fluorinated ketones **76** bearing a C–F quaternary carbon center with moderate enantioselectivity (up to 54% ee) by employing a catalytic amount of DHQB or $(DhQ)_2ANQ$(Scheme 12).[132] To enable the desired catalytic cycle, the initial transfer fluorination from Selectfluor to cinchona alkaloid catalysts, which was considered to form a temporary electrophilic asymmetric fluorinating *N*-fluoroammoniun salts to react with substrates followed by enantioselective transfer fluorination and regenerating the catalysts, should suppress the direct electrophilic fluorination of substrates by achiral Selectofluor. Thus, acetyl enol ethers was chosen as preferable substrates instead of more reactive silyl enol ethers and CH_2Cl_2 was selected as reaction solvent because it can precipitate Selectfluor to further restrain direct fluorination of substrates. Meanwhile, addition of 1.2 equiv inorganic base such as NaOAc was essential to activate the enolates followed by capturing the acetyl cation and counter BF_4^- in the reaction cycle. Although there are several limitations such as substrates, scope, and enantioselectivity in this research, it has proved that the combination of cinchona alkaloids and Selectfluor can be performed in a catalytic scenario.

By 2008, the Shibata group modified their method to further restrain the direct fluorination of more reactive substrates which was supposed to cause inaccessible catalyst regeneration, and they developed the first highly enantioselective catalytic fluorodesilylation reaction of allyl silanes and silyl enol ethers **77** based on the combination of catalytic amount of bis-cinchona alkaloids **(C3, C4)** and *N*-fluorobenzenesulfonimide (NFSI) in the presence of excess inorganic base (Scheme 13).[133] Then biscinchona alkaloids $(DHQ)_2PYR$ or $(DHQ)_2PHAL$ (10 mol %)/NFSI (1.2 equiv)/K_2CO_3 (6.0 equiv) have proven to be an

effective catalytic combination for construction of a chiral quaternary carbon center with a fluoro substituent via the fluorodesilylation of allyl silanes (up to 95% ee) and silyl enol ethers (up to 86% ee) with the requirement for bulky substituents on the substrates (when R in C2 position of allyl silanes changed to Me and H, the ee value decrease obviously to 72% and 51%, respectively), and the opposite *S*-enantiomer of the fluorodesilylation of allyl silanes could be prepared in the presence of the hydroquinidine variant $(DHQD)_2PYR$.

In the plausible catalytic cycle for enantioselective fluorode-silyllation reactions, a stable *N*-fluoroammonium salt **I** derived from the combination of NFSI and bis-cinchona alkaloids can react with K_2CO_3, leading to the formation of corresponding *N*-fluoroammonium KCO_3^- salt **II,** which triggered the fluorodesilylation process followed by enantioselective transfer fluorination from the chiral *N*-fluoroammonium ion to the substrates (Figure 2). Meanwhile, one dihydroquinine moiety with the open conformation in $(DHQ)_2PYR$ confirmed by the X-ray crystal structure analysis was considered to be responsible for the transfer fluorination with high enantioselectivity based on the experimental evidence that *N*-fluorinated quininium and *N*-fluorinated dihydoroquinidium salts exist in the open conformations both in solid and solution states.

Subsequently, they investigated the organocatalyzed enantio-selectivre fluorination of oxindoles **79** in order to probe the further synthetic utility of this catalytic strategy (Scheme 14). After screening the reaction conditions, the modified catalyst $(DHQD)_2AQN$ **(C5,** 5 mol %)/NFSI (1.2 equiv)/CsOH-H_2O (6.0 equiv) system have proven to be effective to construct the enantioenriched fluorine-substituted quaternary carbon centers (up to 85% ee) in CH_3CN/CH_2Cl_2 (3:4) at low temperature –80 °C.

For the enantioselective fluorodesilylation reactions of silyl enol ethers to construct a C–F quaternary stereogenic center, the major limitation of this protocol was the requirement for a bulky substituent on the substrates to improve the enantioselectivity. Then the Shibata group hypothesized that sterically demanding analogues of NFSI could potentially enhance the enantioselective control in this fluorodesilylation process comparing with NFSI. In 2011, the Shibata group reported the method to improve enantioselectivity of the fluorination products **(83, 85)** by modifying the electrophilic fluorinating reagents and designed the steric bulky analogues of NFSI, *N*-fluoro-(3,5-di-*tert*-butyl-4-methoxy)-benzenesulfonimide **82** (NFBSI) (Scheme 15).[134] As mentioned above, the common *N*-fluorinated ammonium of cinchona alkaloid was presumably to be formed in the initial transfer fluorination reaction in catalytic cycle, the steric hindrance originated from an anion of (3,5-*ditert*-butyl-4-methoxy) benzenesulfonimide in this *N*-fluorinated ammonium salt presumably helped to weaken the reactivity of enantioselective fluorination process followed by increasing the enantiomeric excess of the products (the enantioselectivity improved as much as 18% by using NFBSI compared to the use of NFSI).

In 2013, to explore the influence of different kinds of substituents in NFSI on the fluorinating reactivity and selectivity, the He group reported the enantioselective fluorination of oxindoles **86** to construct a carbon-fluorine quaternary stereogenic center by the combination of bis-cinchona alkaloid $(DHQD)_2PHAL$ **(69,** 5 mol %)/structurally modified *N*-fluorobenzenesulfonimides **87** (NFSIs) (1.2 equiv)/K_2CO_3 (6.0 equiv) in CH_2Cl_2/CH_3CN

(3:4) at –80 °C with high enantioselectivity (up to 96% ee) (Scheme 16).[135] They disclosed that modified NFSI reagents bearing an electron-donating and steric bulky *t*-butyl group on the *para* position of the symmetric phenyl ring showed lower electrophilic fluorinating reactivity by cyclic voltammetry and obviously enhanced enantiselectivity compared with using the general NFSI reagent. Furthermore, electron-withdrawing group substituted reagents CF_3-NFSI and CF_3O-NFSI failed to afford target products due to their instability and decomposition in the presence of K_2CO_3.

In 2015, the Wu group reported electrophilic fluorination of oxindoles **89** via the combination of catalytic amounts of cinchona alkaloid $(DHQD)_2ANQ$**(C5,** 5 mol %) and modified Selectfluor **90** bearing two $(PhSO_2)_2N^-$as counterion anions to tune its fluorinating reactivity with low to moderate (up to 55% ee) enantioselectivity (Scheme 17).[136] In the construction of a carbon-fluorine quaternary stereogenic centers in oxindoles **91,** they provide a protocol to make Selectfluor more compatible with cinchona alkaloid by modifying its corresponding anions.

In 2011, an organocatalyzed asymmetric cascade fluorination–heterocyclization to prepare enantiopure fluorinated hetero-cycles, hexahydropyrrolo[2,3-*b*]indole or the tetrahydro-2*H*-furo-[2,3-*b*]indole skeleton bearing a C–F quaternary benzylic carbon center **93,** has been reported by the Gouverneur group. A prochiral indole **92** with a pendant heteronucleophile tethered at the C3 position enables asymmetric fluorocyclization in moderate to good enantioselectivity (52% ee to 84% ee) by the combination of bis-cinchona alkaloid $(DHQ)_2PHAL$ **(C4,** 20 mol %)/NFSI(1.2 equiv)/K_2CO_3(6.0 equiv) in acetone at −78 °C (Scheme 18). The presence of a substituent at C5 position ($R^1 \neq H$) led to a markedly improved enantioselective control in this irreversible fluoroquaternization at C3 followed by the intramolecular capture of the transient iminium intermediate by the pendant oxygen or protected nitrogen nucleophile. Under catalytic reaction conditions, only slight decrease of enantiomeric excess and similar yields were observed by comparing with the use of stoichiometric amount of alkaloid and the level of enantioselectivity was found to be dependent on the nature of the nuecleophile (X = O, 66% ee; X = NTs, 64% ee; X = NOMe 80% ee; X = NBoc 78% ee). Additionally, for probing the reaction mechanism, only less than 2% $(DHQ)_2PHAL^+$-F canbe detected by ^{19}F-NMR at low temperature −78 °C with or without K_2CO_3. Thus, they proposed that the enantioselectivity may not be induced by in situ generated transient chiral N-F cinchona species because fluorine transfer from NFSI to $(DHQ)_2PHAL$ was proved to be ineffective at low temperature and the associative complexation seemed to take place through the effect of hydrogen bonding[138] between the alkaloid catalysts and the indole substrates and/or NFSI.

In 2015, the Wang group reported the asymmetric electrophilic fluorination of 4-substituted isoxazolinones **94** catalyzed by a bis-cinchona alkaloid $(QN)_2PYR$ **(C7,** 10 mol %) in the presence of NFSI (1.1 equiv) and K_3PO_4(1.1 equiv) in $CHCl_3$ (0.1 M) at −60 °C. The enantiopure fluorinated heterocycles bearing a fluorine-containing quaternary stereogenic center **95** were prepared in good yields and good enantioselectivities (up to 91% yield, 85% ee).[139] Meanwhile, to demonstrate the practical utility of the asymmetric fluorination protocol, the 4-fluoroisoxazolinone derivatives **95a** can be provided with high enantioselectivity (>99% ee) after a single recrystallization from gram-scale products which

had been generated in 85% yield and 80% ee under optimized reaction conditions (Scheme 19).

In 2016, the Wang group reported a catalytic asymmetric fluorination process of 4-substituted pyrazolones **96** to provide a series of 4-fluorinated pyrazol-5-ones **97** bearing a C–F quaternary carbon center with good yields and moderate enantioselectivities (from 37% to 81% ee).[140] After screening the reaction conditions, the combination of quinine (10 mol %)/NFSI (1.2 equiv)/Cs_2CO_3 (1.0 equiv)/H_2O (2.0 equiv) in $CHCl_3$ (0.05 M) at −60 °C was chosen as the optimized reaction condition (Scheme 20), and they believed that the acceleration effect caused by the addition of water may be due to the enhanced solubility of the inorganic base in the fluorination process.

3.1.1.1.2. Enamine Catalysis: Chiral Secondary Amine and Primary Amine Catalysis: Chiral aminocatalysis via enamine intermediates has emerged as an appealing strategy for the direct α-fluorination of carbonyl compounds and their analogues, providing access to a fluorinated quaternary stereogenic center in an enantiocontrolled manner.

As for asymmetric electrophilic fluorination of linear aldehydes catalyzed by chiral amino catalysis, the reaction conditions should be screened carefully under the following terms: first, the fluorination process must be faster than directly *N*-fluorination of the aminocatalyst, and second, difluorinated side products and potential racemization caused by second enamine formation from desired monofluorinated aldehydes, which showed the enhancement in acidity of the α proton due to the introduction of high electronegativity of fluorine, was expected to be rigorously avoided.

Then in 2005, the Jørgensen group reported the asymmetric α-fluorination of linear aldehydes **98** catalyzed by a sterically encumbered chiral pyrrolidine derivative **C8** with high enantioselectivity.[141] To restrain catalyst degradation caused by *N*-fluorination of NFSI, lowering the catalysis loading to 1 mol % in specific solvent methyl-*tert*-butyl ether (MTBE) was found to markedly improve the conversion and enantioselectivity. To explain the configurational stability of the optically active products, the hydrogen atom at the newly formed fluorinated chiral center of the preferable imminium ion intermediaters was expected to be located in a sort of hydrophobic pocket which prevented its abstraction to afford the second enamine intermediate. Then they extended the scope of the reaction to the branched aldehyde (only one case) to afford desired product **99** bearing a C–F quaternary stereocenter in 78% yield with 48% ee by employing a modified sterically less-demanding catalyst **C8** (5 mol %) and high temperature (60 °C) (Scheme 21). Although the fluorinated products of branched aldehydes are unable to racemize, as they have no α proton, the enantioselective control for the construction of the C–F quaternary carbon center was still unsatisfactory. Additionally, the α-fluorinated aldehydes were required to derivatize in situ to corresponding optically active β-fluorinated alcohols **100** for subsequent analysis because they could decompose rapidly on silica gel.

In 2005, the Barbas group revealed the direct asymmetric α-fluorination of branched aldehydes **101** catalyzed by chiral secondary amine catalyst derived from pyrrolidine and its analogues with moderate enantioselectivity (up to 66% ee)[142]. As α-fluoro aldehydes have

been proven to be volatile and thermally unstable because they always decompose upon column purification or distillation conditions, the yields for the synthesis of α-fluoro aldehydes **102** were just measured by ^{1}H NMR spectroscopy and GC analysis of crude reaction mixtures. Subjecting branched aldehydes to the combination of chiral amine catalysts (30 mol %) and the electrophilic fluorinating reagent NFSI (1.2 equiv) in THF (0.25 M), the desired optical active α-fluorinated aldehydes bearing a fluorinated tetrasubstituted stereogenic center can be prepared in 99% NMR yield with 45% ee for acyclic substrate in the presence of a sterically demanding triisopropylsilyl (TIPS) group substituted l-prolinol derivative **C9** and in 98% NMR yield with 66% ee for cyclic substrate in the precence of the proline-derived tetrazole catalyst **C10** (Scheme 22). Although high enantoselectivity (up to 96% ee) can be provided in the scenario of linear aldehydes to afford fluorinated trisubstituted stereocenters, a stoichiometric amount of the catalyst was required, and commercially available fluorinating reagents such as Selectfluor, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) (Accufluor), and pyridinium fluorides showed minimal reactivity and afforded the racemic products in very low yield.

In 2008, the Yamamoto group reported the enantioselective installation a fluorinated chiral quaternary carbon centers in *gem*-chlorofluoro carbonyls compounds based on organocatalytic asymmetric α-fluorination.[143] Various optically active α,α-chlorofluoro aldehydes **104** can be prepared in good yields (62–88%) and with high enantioselectivity (82% to 98% ee) from racemic α-chloroaldehydes **103** (3.0 equiv) catalyzed by Jørgensen catalysts **C11** (10 mol %) in the precence of NFSI (1.0 equiv) in MTBE (methyl *tert*-butyl ether; 0.25 M). Subsequently, assessable enantioenriched α, α-cholorofluoro ketones **106** can be prepared from α, α-chlorofluoro aldehydes **104** via nucleophilic addition of a Grignard reagent followed by oxidation using the Dess-Martin reagent without loss of optical purity (Scheme 23).

Furthermore, α-chloro- α-fluoroaldehydes could be prepared in high enantioselectivities via asymmetric α-fluorination of α-alkyl-α-chloroaldehydes **107** mediated by the Jørgensen–Hayashi catalysts **C11** when the starting aldehyde was used in excess over NFSI (Scheme 24). However, when an excess of NFSI with respect to the starting aldehyde was used, the loss in enantiopurity of products were observed. Subsequently, Shibatomi and co-workers insisted on the kinetic resolution process in the asymmetric fluorination mechanism.[144] Thus, the asymmetric induction in this transformation required not only the enantiofacial distinction of enamine intermediates for electrophilic fluorination but also a kinetic resolution for the corresponding (*S*)-α-chloroaldehydes. Moreover, they reported the determination of the absolute configuration of desired α-chloro-α-fluoroaldehydes via X-ray crystallographic analysis of its corresponding α-chloro-α-fluoro-β-keto ester derivatives.

In 2015, the Brenner-Moyer group extended the asymmetric fluorination of α-chloroaldehydes into a one-pot scenario.[145] In other words, they developed a method to install a fluorinated tetrasubstituted stereocenter in *gem*-chlorofluoro compounds from unfunctionalized aldehydes **109.** The starting point for the cascade reactions was to assess the compatibility of the two catalytic reactions, asymmetric chlorination of starting aldehydes, and fluorination of corresponding α-chloroaldehydes. First, *N*-chlorosuccinimide

(NCS) was screened to serve as an electrophilic chlorine source because succinimide, the byproduct of chlorination, had been proven to be harmless for the fluorination step. Subsequently, by employing the l-proline (5 mol %) and NCS (0.95 equiv) in $CHCl_3$ for the chlorination step and the addition of NFSI (0.7 equiv) and Jørgensen-Hayashi catalyst **C11** (33 mol %) in methyl tert-butyl ether (MTBE) as cosolvent followed by reduction the unstable *gem*-chlorofluoro aldehydes in situ, the unfunctionalized aldehydes (1 mmol scale) can be converted to corresponding *gem*-chlorofluoro alcohols in moderate to good yields (54%−87%) with good enantioselective control (81%−98% ee) (Scheme 25).

In 2016, the Juhl group reported a highly diastereoselective access to β-fluoropyrrolidines **111** bearing two adjacent quaternary carbon centers catalyzed by chiral secondary amine catalysts.[146] The starting optically pure pyrrolidines were separated by chiral supercritical fluid chromatography (SFC). For achiral pyrrolidine as an enamine catalyst, the *anti*-products were formed as major products because fluorine approached the least hindered enamine face, and after screening the secondary amine catalysts, they found that imidazolidinone catalysis **C12** could enhance the substrate control to increase the ratio of *anti*-products and jørgensen catalysts **C11** can completely reverse the substrate control to afford the syn-β-fluoropyrrolidines (dr >99:1). The observed diastereodivergence was rationalized by the catalyst-induced diastereofacial discrimination. Meanwhile, classicalj0rgensen catalysts **C11** enable the kinetic resolution of racemic cyclic α-branched aldehyde bearing a pyrrolidine scaffold followed by reduction in situ to afford a fluorinated β-prolinol analogue **112** with vicinal quaternary stereogenic centers in 31% isolated yield with 95% ee (Scheme 26).

Then in 2016, the Juhl group reported a method to enantioselective fluorination of cyclic α-branched aldehydes **113** to afford the desired α-fluorinated aldehydes **114** with a α-fluorinated tetrasubstituted chiral center in high yields and good to high enantioselective control (up to 97% ee).[147] It should be noted that the enantioselectivities in the case of **“d”** (Scheme 27) without branching at the β-positions decreased to 26% ee compared with that of corresponding *gem*-dimethyl substituted analogue **“e”** with high enantioselective control in 97% ee. A lower differentiation of the two α-substituets would afford a mixture of E- and Z-enamine intermediates and, steric hindrance demanded *gem*-dimethyl groups would lead to a better control of the enamine *E/Z* ratio. The high enantioselective control in this transformation needs a high enamine *E/Z* equilibrium constant combined with a fast equilibration rate relative to the rate of fluorination process.[148]

In the consideration of the steric effect, enabling the pyrrolidine ring of the catalyst to stay farthest away from the oxetane scaffold, the Z-enamine, which gives the *Si* face exposed to fluorination, is proposed to be dominant for the 4-spirocyclic substituted substrates. In contrast, for 2-spirocyclic substituted substrates, *E*-enamine intermediates were presumed to be favered and the *Si* face was shielded by chiral amine catalyst (Figure 3).

In 2016, the Quintavalla group reported a protocol for enantioselective construction of a fluorinated quaternary stereogenic center at α position of α,α-dialkyl aldehydes **115** bearing an enantiomerically pure chiral center in the C β-position catalyzed by chiral secondary amine catalysts (Scheme 28).[149] During the catalyst screening, organocatalysts bearing

acidic protons were found to clearly improve the reactivity of the electrophilic fluorination process. Thus, the combination of J0rgensen's diarylprolinols **C11** or ent-**C11** and trifluoroacetic acid as co-catalyst had been shown to enhance the reaction rate and diastereocontrol. Then treatment of chiral γ-nitroaldehydes and 1.2 equiv of NFSI with the combination of **C11** or *ent*-**C11** (15 mol %) and trifluoroacetic acid, in an equimolar amount with respect to the organocatalysts in *tert*-butyl methyl ether (0.24 M) at room temperature for 17–72 h, afforded the desired fluorinated product **116** with moderate to good yields and with high diastereocontrol (dr up to 97:3) and good enantioselectivity (erup to 99:1).

Additionally, for the substrate scope, increasing the steric hindrance at the Cα position was found to decrease the reaction yields and diastereocontrol. On the basis of the computational calculations for reaction mechanism, the enantioselectivity was under catalysis control with a very limited role imposed by the stereocenter on Cβ in substrates. Meanwhile, the fluorination process was found to be faster than the *E/Z*-enamine intermediates equilibration and *E*-enamines are responsible for the formation of the major products.

In 2006, the Jørgensen group reported the asymmetric α-fluorination of α-branched aldehydes **117** catalyzed by a new type of primary amine catalyst, aminated 8-amino-2-naphthol **C13** (Scheme 29), in which the chirality originates from nonbiaryl atropisomerism.[150] The primary amine catalyst **C13** can be prepared by the asymmetric Friedel-Crafts amination of 8-amino-2-naphthol controlled by aminated 6′-hydroxy cincho-na alkaloids with a nonbiaryl atropisomeric functionalization at the 5′-position of the quinoline core. By utilizing the amine catalyst **C13** (5 mol %) and fluorinating reagent NFSI (1.2 equiv) in the solvent mixture of hexane/iPrOH (9:1), the substrates, which have an a-aromatic group without substituent or with electron-withdrawing substituents, can be converted to the corresponding aldehydes **118** bearing a fluorinated quaternary carbon center in moderate yields (up to 60%) and good enantioselective control (up to 90% ee). The chiral induction can be rationally explained by the main E-geometry enamine intermediates, which would only permit the NFSI to attack from the Si-face of the E-enamine. However, for fluorination of aliphatic a-branched aldehydes, the *E/Z*-isomerism of the enamine intermediates, which can cause undistinguishable faces of the enamine, can be responsible for the poor enantioselectivties (less than 31% ee). Additionally, extrapolating from the X-ray analysis of an acylated analogue of the catalysis, the geometry of the enamine intermediate could be stabilized by the intramolecular hydrogen bonding between the carbonyl oxygen of the Boc group in the *N*-1 atom in the aminated 8-amino-2-naphthol **C13** and the enamine NH (Figure 4).

In 2015, the Jacobsen group developed a new primary amine catalyst **C14** for the asymmetric α-fluorination of α-branched aldehydes **120** to afford α-fluorinated quaternary stereogenic centers **121** with high yields (from 74% to 99%) and with moderate to high enantioselective control (48–86% ee) on 1.0 mmol scale (Scheme 30).[151] Although impressive progress had made in the reaction of chiral secondary amine catalyzed α-fluorination of unbranched aldehydes to provide a-trisubstituted products, secondary amines are inappropriate for the reactions of a-branched aldehydes due to the steric demands of the reacting partners.[152] Meanwhile, unfavorable tautomer equilibration and poorer control of

E/Z selectivity of enamine intermediates are the problems inherent to primary amine catalysts, which can induce the formation of less steric hindered enamines.

On the basis of the bifunctional primary aminothioureas designed to activate the hindered carbonyls via formation the nucleophilic enamines and simultaneously activate the electrophiles via hydrogen bonding interaction, the benzamide analogue **C14** was designed and screened as the most effective catalyst (20 mol %), while the dual H-bond donor in aminothioureas and its urea analogue had proved unnecessary. Meanwhile, the combination of achiral acids such as trifluoroacetic acid (TFA, 20 mol %) and inorganic base additives $NaHCO_3$ (1.0 equiv) can enhance both reaction rate and enantioselective control. For probing the scope of substrates, α-aryl-α-methyl substituted aldehydes (12 examples) afforded α-fluorinated products with good enantioselective control (from 69% to 86% ee) and enhanced enantiomeric purity after recrystallization (up to 99% ee), while α-ethyl-substituted and α, α-dialkyl branched aldehydes afforded desired products with significantly lower enantioselectivity.

Additionally, a one gram scale of starting branched aldehydes, 2-phenylpropionaldehyde, can be converted to the corresponding fluorinated products in 99% yield and with 80% ee under optimized reaction conditions. On the basis of the computational analysis (lowest energy calculated structures on B3LYP/6–31G(d)), a plausible stereoinduction model was supported. The intramolecular H-bond between enamine NH and the benzamide carbonyl serves to rigidify the catalyst backbone, and one aryl ring of the terphenyl moiety locating in the one face of the enamine could block accessing to incoming fluorinated electrophile. The E-enamines leading to the formation of *R*-products was calculated to lie 1.28 kcal-mol^{-1} lower than corresponding *Z*-enamine which could induce the minor *S*-enantiomers. Thus, the enantioselective control may be determined and limited by the *E/Z* ratio of the enamine intermediates (Scheme 30).

By 2016, the Shibatomi group reported the enantioselective fluorination of a-branched aldehydes **123** to introduce a fluorine atom onto a tertiary carbon center catalyzed by the chiral primary amine **C15** (Scheme 31).[153] Although similar catalyst structure had already been designed in 1996,[154] there was no research related to its applications. Additionally, the steric hindrance of aryl substituent (Ar = 3,5-*t*BuC_6H_3) in 3,3′-positions on the binaphthyl backbone of the primary amine catalysis exerted impact on the asymmetric induction because employing catalysts without aryl substituents (replacement Ar group by H) in 3,3′-positions provided nearly racemic products. Treatment of *rac*-aldehydes (1.5 equiv) and NFSI (1.0 equiv) in the presence of primary amine catalysis **C15** (10 mol %) and 3,5-dinitrobenzoic acid (10 mol %) as co-catalysis in toluene at 0 °C for 20–48 h, the fluorinated products were isolated after reduction to corresponding primary alcohols **125** with good enantioselectivity (up to 99% ee). The substrate scope was found to be limited to α-alkyl-α-aryl aldehydes as low yields, or disappointingly low enantioselectivity was observed for α,α-dialkyl aldehydes. Subsequently, the resulting α-fluoroaldehydes bearing a quaternary stereogenic center can transform to corresponding α-hydroxyacetals via C–F bond cleavage without obviously loss of enantiomeric purity.

Recently, the Luo group reported a reagent-controlled enantioselectivity switch for organocatalytic asymmetric fluorination of acyclic and cyclic *β*-ketoesters and *β*-ketoamides or 1,3-diketones to construct fluorinated quaternary stereogenic centers by a single chiral primary amine catalysis **C16** (Scheme 32).[155,156] By employing two commercial available electrophilic fluorination reagents NFSI and *N*-fluoro-pyridinium salt (NFPy), the two *R*- and *S*- enantiomers can be prepared with good enantioselectivity, in both cases tuning by one single chiral primary-secondary diamine catalysis **C16.**

For the *R*-selective process, the reaction of *β*-ketoesters **126** were performed under the combination of catalysis **C16** (20 mol %) and dinitrobenzoic acid DNBA-I (20 mol %) with NFSI in chloroform at room temperature for 24–36 h, and R-products **127** (up to 93% ee) can be prepared through an enamine based intermolecular F-attack transition state model **I** tuning by hydrogen bonding interaction between the sulfonyl moiety in NFSI and an the protonated ammonium N–H in amine catalysis to favor the *Re*-facial fluorination. On the other hand, with the combination of catalysis **C16** (20 mol %) and dinitrobenzoic acid DNBA-II (20 mol %) with *N*-fluoro-pyridinium salts as the fluorination reagent in methanol at room temperature, the desired S-configuration products **127** can be obtained in good enantioselectivity (up to 99% ee) via transition state model **II,** which controlled by the electrostatic repulsion between the cationic charged ammonium in amine catalysis and cationic charged pyridinium species (Figure 5).

Additionally, improvement in enantioselectivity can be observed by alternation of the acidic additive from TfOH to dinitrobenzoic acids which can also simplify the reaction manipulation as the resulting salts were bench-stable crystal solids, and primary amine **C16** performed equally as well as its more bulky counterparts such as adamantyl primary amine **C17.** Thus, transition state model **II** would be mainly dominated by electrostatic repulsion of two positively charged species not by steric effect, which also had been demonstrated by DFT calculation at B3LYP/6–31G* level of approximation.

To probe the scope of substrates, for the R-selective process which was controlled by the H-bonding transition state model **I,** under optimized reaction conditions, a variety *β*-keto esters including alkyl, benzyl, allyl, and cinnamyl esters afforded the desired products with high ee value (89%−93% ee) in good yields. Then a variety of *β*-ketoamides including *N*-aliphatic and *N*-aryl amides, 1,3-diketone, and lactone-type substrates provided moderated to good enantioselectivity (from 43% to 83% ee). For S-selective reactions which controlled by electrostatic mode **II,** the yields and enantioselectivity can be comparable to the corresponding R-selective process with the exception of reactions for *β*-ketoamides, wherein the S-selective process afforded high enantioselectivity (84–94% ee). Additionally, a gram-scale reaction also was conducted to probe the utility of the fluorination reaction of benzyl 2-methyl-3-oxobutanoate and the desired R-selective product was prepared in good yield (0.952 g, 85% yield) with 94% ee.

Recently, the Xu group reported the enantioselective fluorination of *β*-ketoesters **128** catalyzed by the combination of cinchona alkaloid-derived chiral primary amines QN-NH_2 **C18** and l-leucine **C19** as dual organocatalysts in good yields and only moderate enantioselectivity (up to 55% ee) (Scheme 33).[157] Furthermore, only racemic *α*-fluorinated

ketones **129** can be obtained in the absence of cocatalyst l-leucine, and the function of each catalyst is still unclear.

3.1.1.1.3. Phase-Transfer Catalysis: The interaction of charged intermediates and reagents in organic transformations with a charged, chiral catalyst has emerged as a powerful strategy for enantioselective synthesis,[158] and the quaternary ammonium cation in a cinchona-derived phase-transfer catalyst could form a nucleophilic ionic complex with an anion of the nucleophile, which will induce the approaching of the electrophiles from the least sterically hindered face of the ionic complex.[159]

In 2002, the Kim group reported the catalytic enantioselective electrophilic fluorination of *β*-keto esters **130** to construct a fluorinated quaternary stereogenic carbon center promoted by quaternary ammonium salts derived from cinchona alkaloids as phase-transfer catalysts (Scheme 34).[160] To enhance the enantioselective control, the introduction of a bulky subunit, the (3,5-di-*tert*-butyl-4-methoxy)benzyl group, into the position of the bridgehead nitrogen of cinchona alkaloids was taken into consideration in catalyst design. Treatment of cyclic *β*-keto esters with NFSI in the presence of a catalytic amount of cationic phase-transfer catalyst **C20** (10 mol %) and inorganic base K_2CO_3 or Cs_2CO_3 in toluene afforded the desired *α*-fluoro *β*-keto esters **131** in good yields and moderate enantiomeric excess (from 48% ee to 69% ee). Then for acyclic substrate **132,** NaH was required in the fluorination process and only 40% ee can be observed.

Then in 2004, they extended the asymmetric fluorination reactions catalyzed by chiral quaternary ammonium salts to other substrates such as acyclic *α*-cyano acetate derivatives (Scheme 35).[161] Treatment aromatic groups substituted *α*-cyano acetates **134** with the cinchona alkaloid derived catalyst **C20** (10 mol %) and fluorinating reagent NFSI in the presence of Cs_2CO_3 in toluene gave the desired *α*-fluorinated products **135** in good yields and good enantioselectivity (from 73% ee to 76% ee).

In 2013, the Lu group revealed the asymmetric fluorination of indane carboxylates **136** bearing a sterically hindered *t*-butyl ester group catalyzed by quaternary ammonium salts derived from cinchona alkaloid to install a fluorine containing quaternary carbon centers (Scheme 36).[162] When employing catalyst **C22** in which the C–9 hydroxy function in cinchonine was protected by sterically bulky adamantoyl group (catalyst **C22** was developed by the Jørgensen group in the year of 2006[163]), the desired *α*-fluorinated products **137** were prepared with satisfactory enantioselectivity (up to 94% ee).

Additionally, they insisted that the negatively charged enolate intermediate, paired with ammonium cation in catalyst **C22** via ionic interaction, was proposed to place into the groove between the quinoline and quinuclidine in transition state (Figure 6). Thus, the sterically hindered adamantoyl group blocked effectively the bottom face of the plane in enolate intermediate, leading the approaching of electrophile from another face with high enantioselectivity.

The C9 position functions in cinchona alkaloids serving as a molecular hinge because four low energy conformers (anti-open, anti-closed, *syn*-open, *syn*-closed) can be generated by

the internal rotations around the C8-C9 and C9-C4′ bonds (Figure 7).[164,165] Thus, governing the internal rotations in cinchonium based catalysts to modulate the conformations and reactivity was highly desirable. In 2012, the Gilmour group reported a class of chiral, fluorinated cinchonium salts for enantio-induction in electrophilic fluorination of *β*-ketoesters **138** (Scheme 37).[166] They provided a strategy by using fluorine stereoelectronic and electrostatic effects (a fluorine-ammoniumion *gauche* effect $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$; $F^{\delta-} \ldots N^+$) for conformational dynamics control (restricting the rotation about C8–C9 bond in catalysis). The antiperiplanar alignment of the C–F bond positioned in C9 of cinchona alkaloid and $C–N^+$ bonds was stereoelectronically disfavored (mismatch between donor and acceptor orbitals), thus ruling out the possible conformers *anti*-closed and *open*-closed. Meanwhile, they found that the installation of the *N*-benzyl group clearly impacted the rotation about C9–C4′ bonds in catalysis, leading to the *anti*-open conformation (X-ray crystal analysis) as majority conformers in the solid state.

For the asymmetric fluorination reaction, as the principle governing catalyst–substrate recognition is electrostatic interaction in nature (ion pairing), the effect of counterion (such as $Cl^–$, $F^–$, $BF_4^–$, $PF_6^–$, $SbF_6^–$) was investigated and no appreciable variation in enantioselectivity was observed, and for the fluorination of *tert* butyl-1-indanone-2-carboxylate, catalysts with H, OH, OMe, and OTMS group located in C9 position, showed lower enantioselective control than fluorinated cinchonium salts **C27** (78% ee). Additionally, the ^1H NMR spectra for the combination of catalysis/Cs_2CO_3/substrate were investigated to probe the structure of the catalyst–substrate complex.

In 2010, the Maruoka group developed a chiral bifunctional phase-transfer catalyst introducing bis(diarylhydroxmethyl) substituents at 3,3′-positions of the chiral binaphthyl core and incorporating the scaffold of thiomorpholine-derived quaternary ammonium salts, which can be applied to asymmetric *α*-fluorination of t-butyl Indane carboxylates and their analogues **140** in high yields and high enantioselective control (8 examples, from 88% ee to 98% ee) (Scheme 38).[167] In the catalysis design, the free hydroxyl group in the moiety of bis(diarylhydroxmethyl) substituent in catalyst **C28** had been proven to be crucial role to obtain high enantioselective control because corresponding methyl-protected catalysts could only afford racemic mixtures.

On the basis of the X-ray analysis of a morpholine-derived bifunctional catalyst, a proposed transition state mode was rationalized by forming an ammonium Z-enolate, which could stabilized by the hydrogen bonding between the enolate oxygen and one hydroxyl group in bis(diarylhydroxmethyl) substituents and ionic interaction between ammonium salt and enolate anion (Figure 8). However, for acyclic *β*-keto esters, only low enantioselectivity (5–20% ee) can be observed.

Although many chiral ammonium salts derived catalysts had been reported in a catalytic electrophilic fluorination, further design and development of new chiral phase-transfer catalysts are still attractive research subjects.[168] In 2013, Ma, Cahard, and co-authors reported the asymmetric electrophilic fluorination of 3-substituted benzofuran-2(3*H*)-ones **142** via phase-transfer catalyst **C29** (2 mol %) based on chiral P-spiro phosphonium scaffold to afford the desired products **143** bearing a fluorinated quaternary stereogenic center in high

yields and only moderate enantioselectivity (up to 56% ee) (Scheme 39).[169] The chiral phosphonium salt **C29** was first developed for asymmetric electrophilic amination of benzofuran-2(3*H*)-ones in the year of 2011.[170] Tailoring of the inorganic base (K_2HPO_4) and initial concentration of the substrate was considered to be crucial for this liquid-liquid phase transfer transformation. Additionally, for the substrates benzofuran-2(3*H*)-ones, the phosphonium salts would serve as preferred catalysts because various quaternary ammonium salts derived from cinchona alkaloids afford poor enantioselectivity (less than 8% ee).

While catalytic electrophilic fluorination via anionic intermediates through ionic interaction (ion pairing) with chiral cationic catalyst, such as quaternary ammonium and phosphonium salt, is well precedented, reports of analogues charge-inverted processes have been rather less explored. The chiral anion phase-transfer catalysis,[158,171] which can bring an insoluble cationic promoter into solution, provides a platform for asymmetric fluorination that proceed via cationic intermediates or that utilize cationic reagents. While the first example of chiral anion PTC was reported by the Toste group,[172] they expanded their methodology to prove the versatility of chiral phosphoric acids for a broad range of substrate classes by using Selectflor, which is normally insoluble in nonpolar media. They envisioned that a lipophilic chiral anionic catalyst, bulky chiral phosphate anions, could extract an insoluble cationic reagent such as Selecfluor from insoluble phase into the organic phase. Ion-pairing of the cationic reagent with the chiral phosphate anions would then provide a chiral environment for the desired enantioselective fluorination. Subsequently, the Toste group developed many attractive catalytic methods to construct a C–F quaternary carbon center with high enantioselectivity by employing the lipophilic, bulky phosphate anions as phase-transfer catalyst. Detailed discussion of asymmetric fluorination of alkenes such as fluoro-cyclization or fluorinative dearomatization process will be presented in 3.1.1.2 F-Additions to C=C Bonds (vide infra).

In 2014, the Toste group developed a dual catalysis method for asymmetric fluorination of α-branched cyclohexanones **144** to generate quaternary fluorine-containing stereocenters involving the merge of two separate catalytic cycles: a chiral lipophilic BINOL derived phosphate anion as phase-transfer catalyst **C30** to active Selectfluor and enamine catalyst employing protected amino acids.[173] First, they hypothesized that the incorporation of amine catalysis would form a transient enamine intermediate as a hydrogen bond donor which can attach to the soluble chiral electrophilic fluorinating reagent generated by the ion exchange between the lipophilic chiral phospahate anion and achiral tetrafluoroborate counteranions of insoluble Selectfluor (Figure 9). Then they also demonstrated the necessity of the chiral controlling elements on both catalysts, anionic phase-transfer catalyst, and chiral primary amine catalyst, in order to obtain high enantioselective control, because in the absence of either, both yield and enantiomeric excess are poor (less than 10% in each case). Additionally, they also found that the small amount of water was critical to achieve high enantioselectivity because the inconsistent levels of moisture in dry inorganic base Na_2CO_3, which had been replaced by $Na_2CO_3H_2O$, can cause some unpredictable outcomes.

Under the optimized reaction condition, by the combinations of chiral phosphoric acid **C31** (5 mol %)/protected amino acids A (20 mol %)/ketone (2.0 equiv)/Selectfluor (1.0 equiv)/ $Na_2CO_3{\cdot}H_2O$ (2.0 equiv) in toluene at room temperature for 40 h, 2-aryl group substituted

cyclohexanones **146** exhibited compatibility to match the two chiral catalysts, leading to high enantioselectivity (from 83% to 94% ee) (Scheme 40). However, no fluorination was observed for 2-alkylcyclohexanones and closely related acyclic ketones.

3.1.1.1.4. Bifunctional Organocatalysts Based on (Thio)urea Backbone.: (Thio)ureas were commonly employed as hydrogen-bonding donors in catalyst design. The combination of (thio)urea scaffolds to activate and control the reactivity of electrophiles with other catalytically active motifs, such as quaternary ammonium salts, to activate nucleophiles, can be expected to form a remarkable bifunctional catalytic system for introduction fluorine into bioactive molecules.

In 2012, the Niu group reported the thiourea–tertiary amine **C32** catalyzed enantioselective fluorination of *β*-keto esters **148** to construct a C–F quaternary carbon center with high enantioselectivity (up to 99% ee) (Scheme 41).[174] After screening the thiourea catalysts, they found that the more steric hindered catalysts produced almost racemic products and they demonstrated the necessity for both thiourea scaffold and tertiary amine motif in order to achieve high enantioselectivity by comparing various catalysts bearing similar core structures. Additionally, the catalyst loading also played a critical role in stereochemical control because the ee value was observed to increase with the increasing catalyst loading (50 mol % catalyst **C32,**99% ee). Then the catalyst loading can be tailored to 10 mol % when employing DMAP (10 mol %) as base in MeOH.

Additionally, The alkoxy group in indanone carboxylate derivatives had shown a great influence on the enantiomeric excess of products because the bulky tertiary butyl group substituted *β*-keto esters can only afford racemic products (Scheme 41), and the acyclic *β*-keto esters and tetralone derivatives generally provided poor enantioselectivity. Subsequently, the authors hypothesized that the thiourea group serving as a hydrogen donor, which can bond to NFSI and the 1,3-dicarbonyl group, could interacted with the tertiary amine group (basic center) in the bifunctional catalyst (Figure 10).

In 2014, the Waser group reported the synthesis of a new class of systematically modified (thio)urea-containing quaternary ammonium salts catalysts based on 1,2-*trans*-cyclohexanedi-amine chiral backbones and evaluation of its catalytic potential in asymmetric *α*-fluorination of *β*-keto esters.[175] Meanwhile, the importance of the bifunctional nature of these catalysts, including the (thio)urea motif, serving as hydrogen bonds donor, and the quaternary ammonium scaffold as phase-transfer catalyst, was demonstrated by control experiments as only racemic mixture can be obtained when employing simplified monofunctional analogues. For the preparation of catalyst **C33,** they provided an alternative synthesis sequence proceeding through an early quaternization, followed by the late-stage introduction of (thio)urea scaffold.

After screening the catalysts, for the electrophilic fluorination reactions, they found that the urea-containing catalysts with an ester-containing aryl group on the urea scaffold performed better than corresponding thioureas. Additionally, increasing the steric hindrance in the moiety of quaternary ammonium was beneficial, leading to some enhancement in enantioselectivity. Thus, by employing catalyst **C33** (2 mol %) and NFSI (1.1 equiv) in the

presence of K_3PO_4 (0.5 M aqueous, 2.0 equiv) in *m*-xylene at −10 °C, the *β*-keto esters especially for adamantly esters can be converted to the corresponding fluorinated products **151** with good enantioselectivity (up to 86% ee) (Scheme 42).

The proposed bifunctional activation transition state model is shown in Figure 11. While the ammonium moiety was considered to activate the enolate anion of keto-esters via ionic interaction, the urea would attach to NFSI proceeding through hydrogen bonding effect, leading to *Re* facial recognition by the fluorinating reagent.

In 2012, the Ma group reported a diastereo- and enantioselective one-pot multistep 1,4-addition and fluorination sequence between pyrazolone derivatives **152** and nitro-olefins **153** catalyzed by the chiral tertiary-amine-thiourea catalyst and achiral benzoic acid as co-catalyst, leading to enantioselective formation of adjacent stereogenic centers, including a C–F quaternary carbon (Scheme 43).[176] To achieve this desired asymmetric sequential transformation, various bifunctional chiral tertiary-amine–thiourea catalysts were initially screened to match the tandem process. Eventually, they found that the saccharide motif derived from l-glucopyranose in catalyst **C34** was critical for controlling the stereochemistry of the two adjacent stereogenic centers in fluorinated products, comparing with the dramatic decrease in diastereo- and enantioselectivity when using similar bifunctional catalysts without a saccharide moiety. In addition, the combination of saccharide-derived catalyst **C34** with external weak acids, such as benzoic acid, was found to improve the enantioselectivity. The access to the keto tautomer of pyrazolin-5-one, which can be activated by protonated tertiary-amine-thiourea catalysts, was proven to be critical for achieving the transformation.

With the aim to explore the scope of substrates, various nitro-styrene derivtives with different substitution patterns on the aromatic ring and alkyl-substituted nitro-alkenes were studied and found to afford the desired products with high level of stereoselectivity (Scheme 43). The 1,4-conjugated addition products can be isolated in quantitative yields with high enantioselectivity by suppressing the fluorination step. However, subjecting Michael addition product to triethylamine and NFSI, the decrease in diastereoselectivity was observed compared with the unchanged stereoselectivity when employing chiral catalyst **C34** for the second dearomatization–fluorination transformation. Thus, the authors insisted that the chiral bifunctional catalyst not only controls the stereochemistry in the first Michael addition step but also plays important role in diastereoselective formation of the C–F bond in the second step.

Proposed mechanism for this one-pot sequential transformation involving two catalytic cycles is presented in Figure 12. In the Michael addition sequence, the nitro-olefin is assumed to attach the thiourea group via hydrogen bonding, while the enol forms of the pyrazolone substrates could coordinate to the multiple hydrogen bonding interaction help the 1,4-addition ammonium center through hydrogen bonding to achieve high products to dissociate from the catalyst and form a highly level of enantioselectivity. In the subsequent fluorination step, organized structure for interaction with NFSI.

In 2013, the Ma group extended their methodology to the synthesis of chiral fluorinated isoxazol-5(4*H*)-ones **156** bearing a C–F quaternary carbon center via similar sequential

conjugate addition/dearomatizative fluorination transformations in high yields with good stereoselectivity (Scheme 44).[177] After optimization of reaction conditions, inorganic base $NaCO_3$ (1.2 equiv) was found to be essential for dearomatizative fluorination process. In addition, the combination of the (*S,S*)-1,2-diphenylethane-1,2-diamine moiety with d-glucopyranose in catalyst design was found to enhance the stereoselectivity because the erosion of the enantiomeric purity was observed when using a thiourea–tertiary amine catalyst without the saccharide motif. Furthermore, catalyst **C35** bearing a cyclic tertiary amine substituents was particularly good for the transformation of various aryl group substituted isoxazol-5(4*H*)-ones **155** and nitroalkenes **153** to the corresponding fluorinated isoxazol-5(4H)-ones **156** in good stereoselectivies (97:3 to 99:1 dr, 62% to 92% ee). On the other hand, alkyl substituted nitro-olefins were found to be unsuitable for this tandem process and no desired products were obtained. Finally, step-by-step control experiments were performed to probe the determining factors in controlling the stereoselectivity of the fluorination step. Similar results had been obtained, as shown above (Figure 12), for the bifunctional catalyst based on thiourea backbone, which was supposed to control the stereochemistry of both Michael addition and subsequent fluorination via hydrogen bonding.

3.1.1.1.5. Miscellaneous Catalysis.: An organocatalytic one-pot and tandem intramolecular oxa-Michael addition/electrophilic fluorination transformations for the preparation of chiral monofluorinated flavanones bearing a C–F quaternary stereo-center has been revealed by the Zhao group in 2009.[178] After the evaluation of different bifunctional catalysts with structural modifications based on quinine and quinidine, the sterically demanding catalysts were proven to be inferior and the trifluoromethyl group containing catalyst **C36** was chosen as the best candidate. Solvent effect was detected in reaction optimization, the decrease of enantioselectivity was observed in chlorine-containing solvents, and a slight increase in the ee values was shown in Et_2O or methyl *tert*-butyl ether at the expense of marked erosion in the yields due to a poor solubility of NFSI in these two solvents. Thus, the desired fluorinated flavanones **158** can be prepared in high yields with good enantioselectivity (up to 96% ee) in the presence of quinidine-derived bifunctional catalyst **C36** (15 mol %), NFSI (1.5 equiv), and Na_2CO_3 (1.2 equiv) in toluene at room temperature (Scheme 45).

Although the organocatalyst seems to play a role in the electrophilic fluorination step, the oxa-Michael addition was assumed as an enantio-discriminating step, which was considered to be induced by the bifunctional catalyst with a free hydroxyl group through hydrogen bonding to activate both nucleophiles and electrophilic acceptors. Subsequently, the oxygen nucleo-phile was supposed to attack the *Re* face of C=C bond in *α,β*-unsatuated ketones, leading to the R-configured intermediate, which would further induce subsequent electrophilic fluorination step to form a C–F quaternary stereocenter in an enantioselective manner.

In 2015, the Wang group reported an organocatalytic asymmetric one-pot and tandem Friedel−Crafts/fluorination process to enable the construction of two vicinal tetrasubstituted stereocenters containing a C−F quaternary carbon in high diastereo- and enantioselectivity (>20:1 dr and up to >99:1 ee).[179] The tandem transformations delivered a class of fluorinated oxindole−pyrazolone adducts via the enantioselective Friedel−Crafts addition of

4-nonsubstituented pyrazolones 160 to isatin-derived ketimines 159 followed by subsequent diastereoselective electrophilic fluorination of the pyrazolone scaffold. In addition, by employing quinine squaramide catalyst C37, which can be used in low loading (0.5 mol %) without obvious impact on the yield and enantioselectivity, the gram scale experiments was efficiently achieved with fully maintained stereoselectivity, demonstrating the practical utility of this tandem transformations (Scheme 46). To probe the stereochemical determining factors in each step of the one-pot sequential process, control experiment via step-by-step procedure had been performed. The stereoselectivity of the electrophilic fluorination of pyrazolone moiety in oxindole−pyrazolone adducts was proven to be a pure substrate-controlled process, which is independent of the chiral catalyst **C37**.

In 2012, the Sun group reported the enantioselective synthesis of β,γ-unsaturated α-fluoro-esters catalyzed by *N*-heterocyclic carbene **C38**.[180] They hypothesized that enals with a leaving group in the γ position could activate byNHC catalyst to form an NHC-bound dienolate, which was expected to react with electrophilic fluorinating reagents to afford α-fluorinated carbonyl compounds. Although the NHC-catalyzed α C−F bonds formation process proceeded in good yield with high enantioselective control (up to 95% ee) in a broad range of enals, a substituent in the α-position significantly slowed down the reaction rate; the desired α-fluoro-ester 163 (only one case) bearing a C−F quaternary carbon center was obtain in poor yield (5%) with moderate enantioselectivity (55% ee) (Scheme 47).

Despite the significant progress in asymmetric electrophilic fluorination catalyzed by organocatalysts based on the skeleton of cinchona alkaloids or (thio)urea, the development of chiral guanidines, which combine the strong basicity of the guanidine moiety and hydrogen-bond donor capacity of its conjugate acid, was still less reported because the lack of a general chiral scaffold that is both easily available and readily tunable in steric and electronic properties.

In 2014, the Wang group developed a series of chiral guanidines based on the tartaric acid skeleton for asymmetric fluorination by using NFSI. Guanidine catalyst **C39** containing 2,6-diisopropylaniline fragment was recognized as a superior promoter for enantioselective fluorination of 1,3-dicarbonyl and α-cyano carbonyl compounds 164 with high yield and moderate to good ee value (up to 84% ee).[181] Notably, β-keto esters bearing a six-membered ring also gave the desired α-fluorinated products with good enantioselectivity (80% ee), and fivemembered cyclic α-cyano carbonyl compounds gave inferior enantioselectivity (39% ee), as compared with the six-membered cyclic substrate (82% ee). Furthermore, cyclic β-diketones afforded the desired products in high yields with poor enantioselectivity. This method also had proven to be unsuitable for acyclic substrate such as acyclic β-keto esters (Scheme 48).

In 2014, the Akiyama group reported the enantioselective fluorination of β-keto esters **166** catalyzed by chiral sodium phosphate **C40**.[182] Two active intermediates, sodium enolate and sodium phosphate, were supposed to form simultaneously in the presence of a slight excess (1.1 equiv) of an inorganic base $NaCO_3$, and the corresponding fluorinated products **167** for indanone and benzofuranone derivatives were obtained in good yield (up to 98%) with good enantioselectivity (up to 92% ee). An investigation of the ester group in substrates showed

that the sterically demanding group such as *tert*-butyl ester (decreasing to 60% ee) was unsuitable for this asymmetric process (Scheme 49). Also, a decreased selectivity was observed in reaction of six-membered ring containing substrate due to the loss of structural rigidity.

For probing the mechanism for the origin of enantiomeric control, the authors argued that the sodium enolate and sodium phosphate species were essential for achieving the selectivity (Figure 13). To rule out the anionic phase-transfer process, under optimized reaction conditions, low yield and very low enantioselectivity (14%) were observed by using Selectfluor instead of NFSI and no reaction can be detected by using *N*-fluoropyridinium triflate salt as a fluorinating reagent. Thus, a 12-membered ring transition state mode combining the Lewis base activation of sodium enolate by oxygen in the phosphate moiety sodium of phosphate moiety was proposed to rationalize the with the Lewis acidic activation between the oxygen in NFSI and origin of enantioselectivity.

In 2014, the Fu group reported the catalytic enantioselective coupling of aryl alkyl ketenes **168** with NFSI and C_6F_5ONa to afford fluorinated products **169** bearing a C–F quaternary carbon center in the α-position to the carbonyl group in high yield with high enantioselectivity (up to 98% ee) (Scheme 50).[183] First, the generation of tertiary alkyl fluorides was observed in very low conversion (<5% yield) by the combination of a planar-chiral nucleophilic catalyst **(C41)** (10 mol %)/NFSI (1.0 equiv)/ketenes (1.0 equiv) without addition of external nucleophiles. Then they hypothesized that the inaccessible catalyst regeneration may be caused by the stability of the proposed *N*-acylpyridinium intermediate toward $(SO_2Ph)_2N^-$ anion. After screening different type of nucleophiles, sodium pentafluorophenoxide was found to be essential for turnover, releasing the catalyst **(C41)** from stable *N*-acylpyridinium intermediate.

The lower ee value was observed with large alkyl groups in aryl alkyl ketenes (for instance, the ee value decreasing from 98% to 80% when changing methyl to cyclo-pentyl), and the gram scale experiment was proven to proceed without the loss of yield and enantioselectivity. Meanwhile, a special case about a dialkyl ketene substrate, methyl, and *i*Pr group substituted ketene gave a promising level of enantioselectivity (73% ee) for the asymmetric fluorination.

For probing the reaction mechanism, two catalytic cycles involving a **C41**-derived chiral enolate as key intermediate (Figure 14) and **C41**-derived chiral N–F reagent were provided to rationalize the enantio-induction. To gain insight into the operative pathway, the ketene was proven to be involved in the rate-determining step via kinetic study to rule out the pathway related to the formation of **C41**-derived chiral N–F reagent, and the enantioselectivity was expected to be determined by the fluorine transfer from NFSI to the enolate intermediate generated by the nucleophilic addition of **C41** to ketene. Additionally, the enantioenriched *N*-acylpyridinium salt intermediate can be isolated in the absence of an added nucleophile and confirmed by X-ray analysis of its derivative.

3.1.1.2. F-Additions to C=C Bonds: The fluoro-functionalization of alkenes by electrophilic fluorinating reagent, as an enantioselective installation of a C–F quaternary

stereogenic center, is an appealing strategy that converts feedstock alkenes into valuable fluorinated molecules for further application. The asymmetric fluoro-cyclizations of active C=C bonds, such as acyl enols,[132] allyl silanes, and silyl enol ethers[133] or prochiral indoles with a pendant heteronucleophile tethered at C3 position,[137] catalyzed by cinchona alkaloids in the presence of Selectfluor or NFSI, has been already discussed in this work *(3.1.1.1.1. Tertiary Amine Catalysts Derived from Cinchona Alkaloids and Their Analogues).* Thus, in this section, we will focus on other asymmetric protocols for fluorination of C=C bonds leading to the construction of fluorine containing quaternary stereocenters. The anionic phase-transfer strategy by using catalysts derived from chiral phosphoric acids highlights the development in asymmetric fluorination of alkenes, including fluoro-cyclization, 1,4-aminofluorination of conjugated dienes, and fluorinative dearomatization of phenols, etc. (vide infra). Additionally, some one-pot and tandem processes involving fluorination postcyclization or nucleophilic addition, the initial nucleophilic sequence followed by fluorination, will also be discussed in this section because it is indirect or formal fluorination of alkenes. Although the preceding review related to asymmetric fluoro-cyclizations of alkenes was provided by the Gouverneur group in 2014,[184] we will further cover advances in the construction of a C–F quaternary carbon center via electrophilic addition to C=C.

3.1.1.2.1. Substrates or Reagents Controlled Asymmetric Fluoro-Functionalization of Alkenes.: In 2013, the Li group reported the silver-catalyzed phosphono-fluorination of unactivated alkenes **170,** the condensation of various alkenes with diethyl phophite and Selectfluor, via a radical process to afford the desired *β*-fluorinated alkylphosphonates **171** in high yield.[185] Then silver-catalyzed oxidative generation of phosphonyl radicals and fluorine atom transfer were proposed to rationalize the reaction mechanism, and two cases were provided to show the diastereoselective control (substrate control) in this transformation (Scheme 51).

In 2013, the Gouverneur group reported the asymmetric electrophilic fluoro-cyclization of indenes **172** bearing a 2-phenylethyl substituent at the C_2 position as nucleophiles. First, the nonenantioselective version of this transformation, under the optimized reaction condition (*N*-fluoro-2,6-dichloropyridinium triflate (1.1 equiv) in the presence of inorganic base $NaHCO_3$ (3.0 equiv) in nitromethane {(0.05 M) at 40 °C for 1 h}, the desired fluoro-cyclization products **173** were predominantly formed as the corresponding *syn*-diastereomers (>20:1 dr) (Scheme 52)

Later, they tried to develop an enantioselective variant of this fluoro-cyclizative transformation. The chiral N-F reagents derived from the combination of cinchona alkaloids and Selectfluor failed to proceed due to the decreased nucleophilic ability of carbon nucleophiles. Subsequently, anionic phase-transfer catalysts were also proven to be inactive because of the requirement for a polar solvent. Thus, a more reactive chiral N–F reagent **175** based on the structural core of Selectfluor with chiral environment on the dicationic DABCO core was prepared. The reagent **175,** bearing the para-electron-withdrawing CF_3 substituents on the aryl rings, was found to be the most reactive. Thus, the tuning of the reactivity and solubility profile of this new N–F reagent can be achieved by tailoring the steric and electronic properties of the aryl group on the DABCO core. Subsequently, by using chiral N–F reagent **175** (1.5 equiv) in 1,4-dioxane, several fluorotetrahydro-5*H*-indeno-[2,1-*c*]-

quinolones **176** can be prepared in good yield (up to 99%) with good enantioselectivity (ee values averaging 71%). Additionally, the structural variation of the substrates can exert a dramatic impact on the enantioselectivity because the corresponding hexahydrobenzo[*k*]phenanthridine was formed with low enantioselectivity (19% ee) (Scheme 53).

3.1.1.2.2. One-Pot and Tandem Process for Fluoro-functionalization of Alkenes.: In 2007, the Ma group reported enantioselective tandem Nazarov cyclization/electrophilic fluorination sequence catalyzed by Lewis acid, $Cu(OTf)_2$/(R)-Ph-bis(oxazoline) **C42,** leading to enantioenriched 1-indanone derivatives **178** with adjacent carbon- and fluorine-substituted quaternary and tertiary stereocenters with moderate to good stereoselective control (up to >49:1 dr, 95.5% ee) (Scheme 54).[186] In their initial exploration, they envisioned that the electrophilic reagents can capture the metal-bound enolate intermediate generated by the first 4n-electrocyclization sequence, and the *trans*-fluorinated indanone derivatives were predominantly formed (dr >49:1) in the presence of achiral Lewis acid catalysts. A similar asymmetric intramolecular oxa-Michael addition/electrophilic fluorination tandem process, catalyzed by an organocatalyst, has already been discussed *(3.1.1.1.5 Miscellaneous Catalysis).*

In 2011, the Ma group reported the copper-catalyzed tandem 1,4-addition/fluorination sequence with a range of acyclic alkylidene β-keto esters **179** and dialkyl-zinc reagents to install a fluorine-substituted quaternary stereocenter adjacent to carbon tertiary stereocenter in good yields and high diastereo- and enantioselective control (up to >99:1 dr, 98% ee) (Scheme 55).[18] To further narrow the space around the P-ligated copper center to improve the stereoselectivity, the sterically bulky substituents were incorporated onto the 3- and 3′-positions of the binaphthol moiety of the axial chirality. Latter, after evaluation of a series of well-defined modular modification on the biphenyl scaffold at 3- and 3′-positions of the binaphthol, chiral monodentate phosphoramidite ligand **L2** was found to perform better in this tandem transformation.

Subsequently, a broad range of alkylidene β-keto esters bearing aryl and heteroaromatic rings can be converted to the corresponding fluorinated products in good yields (72–91%) and satisfactory stereoselectivity (82–97% ee). A gram scale experiment, performed without erosion of the enantiomeric purity of the product, was conducted in order to verify the synthetic utility of this asymmetric tandem transformation (Scheme 55). In addition, the one-pot tandem process was demonstrated to be crucial for controlling the diastereoselectivity in the second electrophilic fluorination because the obvious decrease in diastereoselectivity was observed when the reaction was conducted in a stepwise manner (Scheme 56).

3.1.1.2.3. F-Additions to C=C Bonds Catalyzed by Anionic Phase-Transfer Catalyst: In 2011, the Toste group reported the highly enantioselective fluoro-cyclization of alkenes **181,** including electronically disadvantaged alkenes, with a cationic fluorinating agent and chiral binaphthol-derived phosphates via a phase-transfer process in which chiral anionic catalyst brings an insoluble positively charged reagents or cationic reaction intermediates into the organic phase (Scheme 57).[188] First, they envisioned that the lipophilic, bulky chiral

phosphate anions bearing the hydrophobic alkyl chains attached to the chiral binaphthol backbone such as catalyst **C43** could exchange one or both tetrafluoroborate anions associated with Selectfluor, which normally is insoluble in nonpolar media, to bring the versatile cationic fluorinating agent into organic phase to form a chiral ion pair, bringing the chiral environment for subsequent fluoro-cyclization wherein a pendant nucleophile can attack a π-bond activated by an electrophilic fluorine source. To verify their hypothesis toward the anionic phase-transfer process, enantioenriched spiro-fused oxazolines were prepared from the sequence of fluorination of the enol ether moiety followed by attacking the oxocarbenium ion generated on the initial step by the amide carbonyl moiety in dihydropyran substrates. It should be pointed out that a good yield and only modest decrease in enantioselectivity can be observed for employing less electro-rich alkenes such as an unactivated olefin with only alkyl substituents.

Benzothiophene substrates (two examples) can convert to corresponding spiro-fused oxazolines bearing a C–F quaternary carbon center in moderate yield with good diastereoselectivity (up to >20:1) and enantioselectivity (up to 90% ee). Additionally, the results of control experiments showed that the anionic phase-transfer protocol indeed improved the tolerance toward sensitive functionality, as only a complex mixture can be detected when using Selectfluor under homogeneous conditions, and the slow introduction of the fluorinating agent into solution via forming a chiral ion pair and a reduction in fluorinating reactivity in nonpolar solvent, were considered to be responsible for the improved chemoselectivity.

To explore the mechanism for this phase-transfer protocol, the nonlinear effect between the enantiomeric purity of the catalyst and products was observed by employing a catalyst with six different levels of enantiomeric enrichment, suggesting that both tetrafluoroborate anions in Selectlor are exchanged for chiral phosphate before the reaction with substrates. Then a catalytic cycle was proposed (Figure 15) where two equivalents of phosphate undergo salt metathesis with dicationic Selectfluor to provide chiral soluble ion pairs, which would induce the asymmetric fluoro-cyclization of alkene substrates.

Then in 2012, the Toste group had extended their anionic phase-transfer catalysis strategy by using BINOL-derived phosphate to encompass the enantioselective fluorination of cyclic enamides.[189] After evaluation of the catalysts and optimization of reaction parameters, a combination of **C43** and apolar hexane was chosen as a superior promoter for obtaining high enantioselective control. The inorganic base Na_2CO_3 was proven to be essential to activate phosphoric acids because low conversion with poor stereochemical selectivity was observed in the absence of Na_2CO_3.

The enantioenriched α-fluorinated benzoyl-imines **184** bearing a quaternary fluorinated stereocenters can be prepared from corresponding six-membered ring and five-membered ring enamides **183** with the toleration of various functionality such as methyl, allyl, phenyl, and benzyl groups in good yields (up to 94%) with high enantioselectivity (up to 98% ee). In some cases, the addition of 3-hexanol (5.0 equiv) as an additive was needed to improve the enantioselectivity. Additionally, as for 2-phenyl-cyclohexanone-derived enamide, a slightly reduced enantiose-lectivity (87% ee) and moderate yield (58%) was detected. To further

probe the scope of cyclic enamides, 2-methylcyclohex-anone-derived enamide showed sluggish conversion under the optimized reaction conditions. Meanwhile, enantioenriched geminal chlorofluoro and bromofluoro benzoy-limines can be prepared from chloro- and bromo-substituted enamides in good yields with high enantioselectivity (Scheme 58).

Ahypothesis as to the origin of the observed enantioselectivity was proposed to rationalize the BINOL-derived phosphoric acid catalyzed asymmetric fluorination. Because of the bifunctional nature of chiral sodium phosphate, one oxygen atom in a phosphate anion would attach to Selectfluor via ion pairing interaction while simultaneously activating the enamide via hydrogen bonding between another oxygen atom in a phosphate anion and a NH proton in enamide. Thus, the steric bulk of the tetralone moiety in enamide was supposed to locate in an "open**"** quadrant, with the relatively small amide group positioning as a "closed**"** quadrant (Figure 16). The proposed transition state model was further demonstrated by the experimental results that the high tolerance toward substitutions on enamides. The tetralone moiety in enamide was considered to stay away from the catalyst center in a favored transition state model and thus had no effect on catalyst–substrate binding.

In 2012, the Toste group extended the methodology for asymmetric fluorination of cyclic enamides to tandem oxyfluorination transformations of acyclic aldehyde-derived enamides.[190] The *N*-acyliminium ions, which generated from the fluorination of enamides, could allow the catalyst-controlled addition of an external oxygen nucleophiles via hydrogen bonding interaction, leading to enantioenriched *α*-fluoro *N,O*-aminals. The challenge in this tandem process was enabling the sequential enantioselective transformations via utilizing a single catalyst, which could control the formation of second stereo-center to match or mismatch the inherent diastereo-control derived from the initially installed chiral center. Finally, phenyl-substituted doubly axially chiral phosphate **C44** was proven to produce a clear enhancement in enantioselectivity due to a more rigid and constrained pocket for the acyclic (*Z*)-configured enmides. Both aromatic and aliphatic substituted enamides were compatible in these one-pot tandem oxy-fluorination transformations. Moreover, the enantioenriched C–F quaternary carbon center can be constructed from the hydroxy-fluorination reaction of the *E* and *Z* benzoyl enamide **185** derived from 2-phenylpropionaldehyde (Scheme 59). The (E)-configured substrate reacted with poor diastereoselectivity and very high enantioselectivity (>99% ee), giving rise to *anti*-products **186** due to the results of double stereodifferentiation. For the (*Z*)-configured substrate, the *syn-isomer* was obtained as the major diastereomer (4:1 dr) with reduced enantioselectivity (83% ee) without obvious double stereodifferentiation effect.

In 2013, the Toste group reported the enantioselective 1,4-aminofluorocyclization of conjugated 1,3-dienes **179** catalyzed by lipophilic chiral phosphate as an anionic phase-transfer catalyst, leading to the 6-*endo*-trig cyclization to provide allylic fluorides **188** bearing a C–F quaternary stereocenter (Scheme 60).[191] For evaluation of the BINOL-derived phosphate catalysts, with the aim of enhancing the solubility and selectivity of Selectflor without compromising reactivity, (*R*)**-C45** was chosen as the superior candidate to produce higher enantiomeric excess. Additionally, the inorganic base was found to be critical to control the reactivity and selectivity in this tandem transformation. Thus, the high

conversion and enantioselectivity for the desired fluorinated products generated by 6-*endo*-trig cyclization was observed by using the combination of (*R*)-**C45** (10 mol %)/Na_3PO_4 (1.2 equiv)/Selectfluor (1.5 equiv) in solvent $PhCF_3$ (0.1 M) at room temperature for 36 h.

To account for the origin of the observed stereochemistry of the fluorine containing quaternary carbon center, the authors provided a plausible transition state (Figure 17). Two probable pathways can rationalize the observed diastereoselectivity, selective 1,4-*anti*-addition to the diene via concerted process or through a stepwise process that produces an equilibrating allyl cation intermediate in which one isomer can react preferentially. Subsequently, no reaction was detected for the *Z*-configured substrate, supporting the concerted reaction pathway that would be blocked by increasing a 1,3 strain in the transition state of the *Z*-configured substrate. For probing the substrate scope, under phase-transfer conditions, satisfactory conversion and stereo-selectivity can be observed for electron-rich substrates, which generally decompose in a homogeneous acetonitrile solution of Selectfluor. Although far from the reactive center, substitutions on benzamide arene showed impact on the selectivity and 4-*tert*-butylbenzamide as the nucleophile gave the best results.

When further expanding the substrate scope, the less-reactive diene derived from cyclohexene reacted sluggishly under optimized conditions with Selectfluor as the fluorinating reagent. Thus, to increase the electrophilicity of the fluorine source, structurally modified Selectfluor derivatives were prepared by replaceing the chlorine atom with electron-deficient aryl group. The new Selectfluor type derivatives were proven to be more powerful than Selectfluor in the preparation of octahydro-isoquinoline compounds with a C–F quaternary carbon center (Scheme 61).

Directing groups (DG), which enable the functionalization of nonpolar bonds, to maintain the beneficial polar interactions between the substrate and chiral catalyst, have been proven to be powerful tool for the achievement of selectivity in asymmetric transformations. In 2013, the Toste group revealed a delicate strategy for electrophilic fluorination of alkenes **189** by the combination of directing groups and chiral phosphate anion **C46** as the phase-transfer catalyst, leading to the enantioselective construction of quaternary C–F bonds in *β*-amino and phenolic allylic fluorides **190.**[192] The anionic conjugate bases of chiral phosphoric acids can abstract the positively charged electrophilic intermediate from insoluble phase to the reaction solution via ion pairing interaction. Meanwhile, the hydrogen bonding interaction, which can play a critical role in the enhancement of stereoselectivity, can help substrate to attach to chiral phosphate anion. Thus, they envisioned that an allylic hydrogen-bonding DG would help to direct an ion-paired chiral phosphate species via transition state organization for asym-metric fluorination of alkenes (Scheme 62).

In consideration of previous successful examples with amides as pendant nucleophiles, the allylic amides were chosen as DGs to verify their hypothesis. After evaluation of the phosphoric acids, (*R*)-**C46** can gave improved stereoselectivity due to a tighter binding pocket, and very low enantiomeric excess for fluorination to alkenes was observed in the absence of DG. Additionally, the distance requirement for the directing group was proven to be essential for obtaining high stereoselectivity compared with homoallylic amide analogous with very low enantioselectivity. Subsequently, investigation of the influence of steric and

electronic properties on enantioselectivity was performed to gain better understanding of the requirement for an effective DG. Steric parameters of DG seem to be more important because the increased enantioselectivity was found with the increased steric bulk. Then the substrate scope was explored; substrates with different ring size and benzamide substitution patterns, electron-donating groups substituted fused benzene ring on the bicyclic core, and heterocyclic substrates, proceeded in good yields with high enantioselectivity (up to 97% ee). Additionally, 2-hydroxyphenyl was found to be suitable DG as hydrogen-bond donor in the asymmetric electrophilic fluorination to alkenes, directing the enantioselective construction of *β*-phenolic tertiary and quaternary fluorides with aryl or alkyl substituents. Then they further expended this DG strategy to asymmetric fluorination of allylic alcohols via in situ generation boronic acid monoester as a directing group.[75,193]

In 2013, the Toste group expended the anionic phase-transfer strategy to the direct and highly enantioselective intermolecular fluorinative dearomatization of simple phenols to incorporate a quaternary fluorine stereocenter catalyzed by a BINOL-derived phosphate (*S*)-**C45.**[194] The direct asymmetric dearomatization was considered as a challenging issue because it requires discrimination between enantiotopic faces of the arene during the dearomatization process. They hypothesized that the hydrogen bonding interaction between the donor Phen-OH and the acceptor, phosphoryl oxygen moiety in the soluble chiral phosphate-Selectfluor ion pair, might help the discrimination of the two enantiotopic faces of the phenols, leading to high levels of enantioselectivity. In addition, the reaction of Selectfluor with phenols under homogeneous conditions can afford multiple products depending on substrate structure and reaction conditions. Subjecting 5,6,7,8-tetrahydro-1-naphthol to optimized reaction conditions, the combination of chiral phosphoric acid (*S*)-**C45** (5 mol %) in the presence of Selectfluor and inorganic base Na_2CO_3 in toluene at room temperature, the desired *ortho*-fluorinated product **192** can be prepared in 75% yield with 96% ee. The advantage of employing 2,3-disubstituted phenols **191** as substrates are as follows: First, the *ortho*-selective fluorinative dearomatization would afford the major products. Second, the greater steric differentiation between two sides of the substrates close to the hydrogen-bonding donor position of binding to the catalyst would enhance the enantioselectivity. Then various 2,3-di- and 2,3,4-trisubstituted phenols can be converted to corresponding *ortho*-fluorinated product with high enantioselectivity control (87–96% ee) (Scheme 63).

In the case of o-cresol without substitutions occupying the C–3 position, the [4 + 2] cycloaddition of the chiral 2,4-cyclo-hexadienone intermediates **194** generated from the initial fluorination was observed with good enantioselectivity (Scheme 64), and increasing steric demand of the *ortho* substituent by using *o*-benzylphenol, higher eantioselectivity (97% ee) can be detected. Substrates with benzyl, phenyl, isopropyl, and cyclohexyl group at 2-, 2,4-positions in phenol can afford the [4 + 2] dimer products **195** with good enantioselectivity, and a decreased stereochemical selectivity can be observed by using 2,5-substituted substrates due to the decreasing in the steric differentiation of two sides of phenols (Scheme 64). Subsequently, the [4 + 2] dimer products can undergo retro-[4 + 2]/[4 + 2] sequence with *N*-phenylmaleimide and cyclopentadiene dimer to deliver a single diastereomer without erosion of enantiomeric purity.

Additionally, *para*-fluorinated products can be prepared in low to moderate yields with good enantioselectivity (86% ee) by incorporating a germinal 8,8′ disubstitution moiety without the possibility of *ortho*-selective fluorinative dearomatization (Scheme 65). The para-fluorinated substrate **197** was designed in accordance with the hypothesis that a clear steric distinction between two sides of phenol was essential for improving enantioselectivity. Subsequently, the fluorinated analogue of natural product (–)-grandifloracin was prepared from silylox-ymethylphenol to verify the utility of this method.

In 2017, the You group reported the asymmetric fluorinative dearomatization of tryptamide derivatives via cascade fluorocyclization catalyzed by chiral phosphate anion derived from BINOL backbone as anionic phase-transfer catalyst **C47,** leading to construction of two consecutive quaternary stereogenic centers in fluorinated pyrroloindolines **199** with good enantioselectivity (up to 97% ee).[195] Positive results can be observed when screening polar solvents under homogeneous conditions, the combination of catalyst **C47** (5 or 10 mol %) and proton sponge (1.1 equiv) and Selectfluor (1.1 equiv) in mixed solvents of fluoro-benzene and acetonitrile (1:1) was optimized to be the best conditions. For exploration substrates scope, *N*-Boc protected tryptamines with varied electron-donating (5-Me, 5-MeO, 5-t-Bu) or electron-withdrawing group (5-F, 5-Cl, 5-Br, 5-CF_3, 5-CO_2Et) substituted at the C5 position of the indole moiety were well tolerated (82%−90% ee) (Scheme 66), and 6-Br, 4,6-dihalo-, and 2-alkyl group substituted substrates were also evaluated to provided desired fluorocylization products in moderate yields with good enantioselectivity (85%–97% ee). Additionally, the gram-scale experiment proceeded well without the obvious erosion in enantiomeric purity of the fluorinated products.

The reaction of 3,5-dimethyl substituted substrate gave the hydroxyl group substituted products in 72% yield with 93% ee (Scheme 67). The authors insisted that the fluorinated dearomatized product was thermally unstable due to the steric hindrance on the indole ring, leading to cleavage of the C–F bond to form a stable benzyl carbenium intermediate. To probe the reaction mechanism, the effects of acid and base additives were examined. HBF_4 released from Selectfluor would accelerate the reaction because of the strong background reaction without the addition of chiral phosphoric acids and proton sponge. The hypothesis about the strong background reaction was further supported by the evidence that faster reaction can be detected when external HBF_4 (1.0 equiv) was added and sluggish performance can be observed when proton sponge (1.2 equiv) was employed. Thus, the function of proton sponge in this reaction system is to neutralize HBF_4 in situ and further restrains the racemic transformation.

3.1.1.3. Transition-Metal Catalyzed Reactions: The first example of the catalytic enantioselective α-fluorination of β-keto esters using chiral [$TiCl_2$(TADDOLato)L_2] complex as a catalyst was reported by the Togni group in 2000.[108] Two years later, the Sodeoka group reported Pd(II)-BINAP complex-catalyzed enantioselective α-fluorination of β-keto esters.[196] These papers triggered extensive further work on enantiose-lective electrophilic fluorination of a variety of carbonyl compounds catalyzed by various chiral transition metal complexes, involving not only Ti and Pd but also other late transition metals such as Ni, Cu, Ru, and Zn. This strategy has been shown to have a broad scope. The key chiral intermediates of these reactions are transition metal bidentate enolate complexes

generated under acidic or neutral conditions (Scheme 68). This section deals with these transition-metal-catalyzed fluorination reactions.

3.1.1.3.1. Titanium Catalysis.: In the Togni's first paper,[108] they showed that the isolated and well-defi ned [TiCl2(TADDOLato)L2] complex **C48** acted as an excellent catalyst for enantioselective fluorination reaction with Selectfluor. The α-fluorinated products **201** were obtained in good to excellent yields (up to 90% ee) (Scheme 69a). They examined naphthyl and phenyl complexes **(C48a:** R = 1-naphthyl, L = acetonitrile, and **C48b:** R = phenyl, L_2 = DME) and found that better enantioselectivity was consistently obtained with the naphthyl complex **C48a.** Later, they applied their catalysts to various β-keto esters, β-keto thioesters, β-keto amides, and 1,3-diketones.[197] Although moderate to high asymmetric induction was observed for the acyclic substrates tested (55–90% ee), poor asymmetric induction was observed for some cyclic β-keto esters and 1,3-diketones. They speculated that noncatalyzed background fluorination of the enol form might account for the decrease of ee of the products because poorer enantioselectivity was observed for substrates that exist mainly in enol form rather than keto form (Scheme 69b). When milder NFSI or NFPY-BF_4 was used as the fluorinating reagent instead of highly reactive Selectfluor, increased enantioselectivity was observed for such highly enolized substrates but not for nonenolized substrates, but the reactions using these reagents were very slow.[197–199]

For these reactions, care is necessary to exclude moisture. Addition of a small amount of water deactivated the catalyst, and the reaction slowed down dramatically.[198] To clarify the mechanism of their [$TiCl_2$(TADDOLato)L_2] complex-catalyzed fluorination reaction, they performed computational and experimental studies.[200,201] The absolute stereochemistry of the major enantiomer from the reaction catalyzed by [TiCl$_2$(*R,R*-TADDOLato)L_2] complex was determined to be (*S*). To understand the origin of the enantioselectivity and to elucidate in detail the mechanism of the fluorination step, DFT calculations were performed for the [TiCl(*R,R*-TADDOLato)(enolate)-(NCMe)] complex. The results suggested that in the lowest energy complex, the *Re*-face of the enolate is completely shielded and the fluorine atom can only be delivered from the opposite side (Scheme 70a).[200] This model well explained the absolute stereochemistry. Next, they tried to prepare and isolate the Ti–enolate 1:1 complex. However, only the 1:2 complex was obtained. The solution structure of the [Ti(*R,R*-TADDOLato)-$(enolate)_2$] complex was analyzed in detail by NMR. Six diastereomeric forms are possible for complexes of the type [Ti(*R,R*-TADDOLato) $(enolate)_2$]. In the case of the complex containing the enolate of 2-methyl-3-oxopentanoic acid benzyl ester, several different species were observed, but two major isomers were observed in 7:3 ratio, and the predominant isomer was identified as the C_2 symmetric Face-on-*Re*/Face-on *Re* diastereomer, while the other major isomer was the C_1 symmetric Face-on-Re/Face-on *Si* diastereomer (Scheme 70b). Finally, they determined the crystal structure of the 1:2 complex (for this experiment, they used [Ti(*S,S*-TADDOLato)$(enolate)_2$] having opposite chirality to that used for the catalytic reaction). The C_2-symmetric Face-on-*Si*/Face-on-*Si* structure corresponds to the major isomer observed in the NMR experiment, in which the *Si* face of both enolate planes is completely shielded. Similar NMR experiments for the 1:2 complexes prepared from other keto esters showed that the most abundant diastereomer was always the C_2 symmetric Face-on-*Re*/Face-on *Re* diastereomer, but the abundance of

the other diastereomers varied depending on the structure of the keto esters. The existence of isomeric forms of complexes containing either one or two carbonyl-enolato units, differing by the enantioface being shielded, explains why the enantioselectivity obtained with this system rarely exceeds ca. 90%. The existence of many different configurational and diastereomeric isomers of the octahedral Ti complex with a chiral bidentate ligand makes it difficult to predict the reaction outcome.[201]

The Togni group also applied their Ti catalyst **C48a** to the enantioselective sequential fluoro-chlorination and chloro-fluorination of β-keto esters with active methylene **202** instead of active methine (Scheme 71).[202] The opposite enantiomer was obtained simply by changing the sequence of addition of Selectfluor and NCS, and the α-chloro-α-fluoro-β-ketoesters were obtained with up to 65% ee.

3.1.1.3.2. Palladium Catalysis.: In 2002, the Sodeoka group reported the first example of enantioselective fluorination reactions catalyzed by palladium complex.[196] They found that their original Pd aqua and μ-hydroxo complexes with BINAP-type bisphosphine ligands **C49** and **C50** (Scheme 72a) both worked well as catalysts when NFSI was used as a fluorinating reagent. The fluorination of β-keto esters **206** proceeded smoothly at 20 °C or even lower temperature with excellent enantioselectivity. More than 90% ee was achieved for both acyclic and cyclic substrates (Scheme 72b). In 2007, the Kim group reported asymmetric fluorination reaction of α-chloro-β-keto ester using the Pd monoaqua complex **C51** (Scheme 72b).[203]

This Pd-catalyzed reaction was tolerant ofair and moisture and could be carried out even in an open flask. The reaction proceeded readily in various solvents such as THF, acetone, *i*PrOH, EtOH, and even in pure H_2O without significant loss of enantioselectivity,[204] which is different from the case of the water-sensitive Ti complex (Scheme 73). The reaction catalyzed by **C50b** (X = TfO) also proceeded in ionic liquid [himim][BF_4], affording the fluorinated product with comparable ee to that obtained from the reaction in EtOH, although a longer reaction time was required. After simple extraction of the reaction mixture with ether, the fluorination product, remaining NFSI, and coproduct benzenesulfone-imide were efficiently extracted into the ether phase, whereas the cationic Pd complex remained in the ionic liquid. Therefore, the recovered ionic liquid solution of the catalyst could be directly used for the next reaction. Catalyst immobilized in the ionic liquid was recycled no less than 10 times, maintaining excellent enantioselectivity (91% ee) (Figure 18).[205]

The Sodeoka group observed clean formation of the stable bidentate Pd enolate upon simple mixing of Pd complex **C50** with 1,3-diketone and β-keto ester in NMR experiments.[206–208] Recently, they succeeded in solving the crystal structure of the (R,R)-BINAP-Pd-enolate complex (Figure 18).[208] As expected, the complex has typical square-planar geometry with bidentate coordination of diketone. The bulky *tert*-butyl group of the substrate is oriented toward the *Si* face to avoid steric repulsion with the ligand phenyl group. Therefore, NFSI should approach from the less crowded Re-face to give the (R)-product. Different from the octahedral titanium complex, the Pd (II) complex strongly favors square-planar geometry, and therefore, in the case of the complex with a C_2-symmetric bidentate chiral ligand, only

one enolate complex is generated in the reaction mixture. This is presumably the reason for the robustness and the wide substrate scope of this Pd-catalyzed system.

Interestingly they observed rapid formation of the Pd enolate of the less acidic β-keto amide **208a,** and the fluorination reaction proceeded in a highly enantioselective manner (Scheme 74a). They also solved the crystal structure of the Pd enolate complex of β-keto amide, in which the *tert*-butyl group lies in the plane of the amide backbone, and the square-planar structure is distorted. As a result, the ligand phenyl group on the *Si*-face side is located closer to the α-carbon of the enolate.[208] Diesters **208b** and ester–amides **208c** were also good substrates. In the case of less acidic ester–amide type substrates, addition of a catalytic amount of amine such as 2,6-lutidine was effective to accelerate the reaction without decreasing the enantioselectivity (Scheme 74b).[209,210] Recently, the Kim group reported reactions of several other keto amides **208d** using Pd monoaqua complex **C51b** as a catalyst and 2,6-*di*-*tert*-butyl-4-methylpyridine (DTBMP) as a base (Scheme 74c).[211]

It is noteworthy that this Pd-catalyzed asymmetric fluorination chemistry has been successfully applied to the multikilogram-scale synthesis of a spleen tyrosine kinase (SYL) inhibitor, which has potential applications in a number of therapeutic areas, including rheumatoid arthritis, B-cell lymphoma, and asthma/rhinitis.[212] The GlaxoSmithKline group performed a thorough optimization of the reaction processes to support preclinical and clinical evaluation of this inhibitor. They established a process using menthyl ester as a substrate for the fluorination reaction. Asymmetric fluorination of menthyl ester catalyzed by (*S*)-BINAP-Pd complex worked well on a large scale, and 43.7 kg of the desired fluorinated product was obtained as crystalline solid with perfect selectivity and in 68% yield in two steps from the inexpensive ethyl ester (Scheme 75). This process provided 8 kg of SYK inhibitor in a single batch. This example illustrates the robustness of this Pd-catalyzed chemistry and its potential for industrial application.

The Sodeoka group reported that the Pd catalysts **C49** and **C50** also worked well for not only 1,3-dicarbonyl compounds but also other types of carbonyl compounds. Fluorination reaction of β-keto phosphonate esters **210** afforded fluorophosphonate **211** with excellent enantioselectivity and yield (Scheme 76a).[213,214] The excellent enantioselectivity and absolute stereochemistry of the product suggest that keto phosphonate esters also form a bidentate Pd enolate. Independently, the Kim group reported a similar reaction using the monoaqua Pd complex **C51.**[214–217] The diaqua complex **C49** and the monoaqua complex **C51** showed basically similar reactivity and selectivity. The Sodeoka and the Kim groups also reported asymmetric fluorination of α-aryl-α-cyanophosphate esters, α-aryl-α-cyano-acetate esters, and α-aryl-α-cyanosulfones **212** catalyzed by Pd μ-hydroxo complex **C50** and monoaqua complex **C51** (Scheme 76b).[218–222] The Pd complex with SPANphos ligand **L3** also worked well for the asymmetric fluorination of α-phenyl-α-cyano-acetate.[223]

In 2005, the Sodeoka group reported enantioselective fluorination of oxindole derivatives.[224] The fluorination reaction of unprotected oxindole derivatives was not successful; the reaction was very slow and the enantioselectivity was very low, suggesting that the acidity of the oxindole is not high enough and the monodentate enolate would be conformationally too flexible. Therefore, the effects of electron-withdrawing and coordinating protecting groups

were investigated. Introduction of a carbamate-type protecting group dramatically improved the reactivity, as well as the enantioselectivity, although an acyl group was far less potent.[210] The Boc group was the best, and various oxindole derivatives **215** were obtained with excellent enantioselectivity (Scheme 77a). This result indicated that this Pd enolate chemistry is potentially available not only for carbonyl compounds having an electron-withdrawing/coordinating functional group at the α-position but also for imide-type compounds. This reaction was applied to the enantioselective synthesis of MaxiPost (BMS 204352) **67,** which is a potent potassium channel modulator.[224] Monofluorination of a α-methylene substrate is normally very difficult. When mono-fluorination of tert-butyl 3-oxo-3-phenyl propionate was examined, the difluorinated product (4%) was produced even when only 1 equiv of NFSI was used, and the obtained monofluorinated product (54% yield) was completely racemic, indicating rapid enolization of the monofluoro β-keto ester.[196,204] In the case of the 3-unsubstituted *N*-Boc oxindole, the reaction in THF afforded a 29% yield of monofluorinated oxindole with 21% ee. Interestingly, when the solvent was changed to a 1:1 mixture of 1,2-dichloroethane and methanol, selective ring-opening proceeded in situ, and the phenyl acetic acid derivative was obtained in 53% yield with 93% ee (Scheme 77b). Normally 2.5 mol % catalyst **C49** or **C50** was used for experiments, but in 2014, Yang and Wu published an interesting paper.[225] They prepared a series of substituted NFSI derivatives and examined the potency of these compounds as fluorinating reagents in this Pd-catalyzed fluorination of *N*-Boc-protected oxindole derivatives. They succeeded in reducing the amount of catalyst **C50a** to 0.5 mol % by using (4-F-C6H4SO2)2NF in diethyl ether (Scheme 77c). Recently, asymmetric fluorination of oxindoles using chiral NHC carbene Pd complex was also examined, but the enantioselectivity was only moderate (up to 59%).[226]

The Sodeoka group also reported asymmetric fluorination of α-ketoester **216** catalyzed by the μ-hydroxo complex **C50.**[227] Interestingly, the monofluorinated product **217** was obtained with high optical purity for this substrate (Scheme 78).

Pd complexes also catalyze many other types of reactions, such as allylic substitution and reactions via C–H activation, and recently, several interesting enantioselective fluorination reactions based on such chemistries have been reported.[228–231] These reactions are not discussed here because they do not involve asymmetric construction of a C–F quaternary stereogenic center.

3.1.1.3.3. Nickel Catalysis.: In 2004, the Shibata group reported that Ni- and Cu-bis(oxazoline) complexes also worked well for the enantioselective fluorination reaction of β-keto esters.[232] The reaction of 2-*tert*-butoxycarbonyl-1-indanone **218a** catalyzed by the Ni complex prepared from $Ni(ClO_4)_2$ and (S,S)-Box-Ph ligand **L4** using NFSI as fluorinating reagent gave the (*R*)-fluorinated product **219a** with 93% ee in 87% yield. Interestingly, the opposite enantiomer was obtained when $Cu(OTf)_2$ was used instead of $Ni(ClO_4)_2$ (Scheme 79a). In these reactions, the enantioselectivity seems to be solvent-dependent. Multiple coordination geometries such as square-planar, tetrahedral, square-pyramidal, and octahedral are known for the Ni(II) and Cu (II) complexes, and this may account for the observed variations of the ee and the enantio-switching. This problem was solved by using a C_2-symmetric tridentate ligand, which is expected to form an octahedral bidentate Ni enolate complex. The fluorination reaction of various β-keto esters **218** catalyzed by 10 mol % of

the Ni complex prepared from $Ni(ClO_4)_2$ and (R,R)-DBFOX-Ph ligand **L5** proceeded smoothly to afford the fluorinated product **219** with excellent enantioselectivity (up to 99% ee). The catalyst loading could be reduced to 2 mol % without loss of enantioselectivity. Asymmetric fluorination of oxindole derivatives was also successfully performed and applied to the synthesis of MaxiPost **67.** In the case of oxindole, Ni(OAc) 2–4H2O was used as a catalyst precursor (Scheme 79b).[233]

Similar Ni-catalyzed fluorination reactions of *β*-keto esters using various other chiral ligands **L6-L9** have also been reported by several groups (Scheme 80).[234–239] Among them, Shibatomi and Iwasa reported a unique *N,N,N*-tridentate pyridine ligand **L6** with both chiral binaphthyl and oxazoline groups. Fluorination of *β*-keto esters proceeded in a highly enantioselective manner (up to 99% ee) in the presence of $Ni(ClO_4)_2$ salt. It is noteworthy that their ligand also worked well with $Mg(ClO_4)_2$ to afford highly optically active fluorinated products (up to 99% ee).[234,235]

Ni-Catalyzed asymmetric fluorination of 3-(2-arylacetyl)-2-thiazolidinones **220** was also achieved.[240] In 2007, the Sodeoka group reported the first catalytic asymmetric monofluorination reaction for this type of substrate, catalyzed by (R)-BINAP-$NiCl_2$ complex **C52** in the presence of triethyl silyl triflate and 2,6-lutidine (up to 88% ee) (Scheme 81a). In 2008, the Shibata group also applied their (R,R)-DBFOX-Ni catalyst to this type of substrate (up to 78% ee).[241] In 2009, they found that addition of HFIP accelerated the reaction, and the reaction at −60 °C afforded *α*-aryl-*α*-fluoroacetic acid derivatives **221** with excellent enantioselectivity (up to 99% ee) (Scheme 81b).[242]

3.1.1.3.4. Copper Catalysis.: In 2004, the first Cu-catalyzed enantioselective fluorination of *β*-keto esters was reported by Ma and Cahard.[243] The Cu complex prepared from the bisoxazoline ligand (*R,R*)-Box-Ph **L4** and Cu(OTf)various other chiral ligands were also reported.th various other chiral ligands were also reported. The Bolm group reported asymmetric fluorination catalyzed by the chiral sulfoximine **L10**-Cu complex (Scheme 82b).[244] The Kesavan group reported the reaction using (*S,S*)-Nap-(*R,R*)-Box ligand **L11.** Relatively high enantioselectivity was obtained for less bulky ethyl ester substrates.[245] The Shibatomi and Iwasa group reported a fluorination reaction using a unique chiral spiro oxazoline ligand **L12,** affording products with excellent enantioselectivity (up to 99% ee).[246] The Du group reported a reaction catalyzed by diphenylamine-linked bis(thiazoline) **L13**-$Cu(OTf)_2$ complex; although the substrate scope was very narrow, some products were obtained with up to 99% ee.[247,248] Just recently, a reaction using this ligand under solvent-free conditions in a ball mill was also reported.[249] The Xu group examined Ph-BINMOL-derived salan **L14**-Cu complex and found that fluorination reaction of 1-indanone-2-carboxylate derivatives proceeded with excellent enantioselectivity (up to 99% ee).[250] Queneau examined Cu-catalyzed fluorination reaction using their sugar-modified bipyridine ligands, but only low asymmetric induction was observed (up to 32% ee).[251]

The Shibata group reported a unique approach for asymmetric fluorination. The combination of achiral Cu catalyst **C53** and salmon testis DNA as the chiral source afforded fluorinated indanone derivatives with up to 74% ee (Scheme 82c).[252] By using a chiral Cu catalyst, simultaneous C–C and C–F bond formation was also achieved (See Schemes 54–56).

3.1.1.3.5. Ruthenium Catalysis.: The Togni and Mezzetti group reported asymmetric fluorination of 1,3-dicarbonyl compounds **206** catalyzed by chiral dicationic ruthenium PNNP complex **C54** prepared in situ from [$RuCl_2$]PNNP)] complex and (Et_3O)PF_6 in 2004 (Scheme 83).[253–255] The reactivity and selectivity were solvent-sensitive, and higher reaction rate and ee value were observed in CH_2Cl_2/Et_2O mixed solvent compared with CH_2Cl_2. They also isolated the Ru enolate complex and solved its crystal structure, revealing a tetradentate apical–equatorial coordination of PNNP ligand similar to that of **C54;** they discussed the absolute stereochemistry of the product based on the enolate structure. The same catalyst **C54** was used for oxidative fluorination of aldehyde with $AgHF_2$ as a fluorine source. Although the eantioselectivity was low (up to 27% ee), they proposed an interesting reaction mechanism, in which Ru(lV) species is involved.[256]

3.1.1.3.6. Other Metal Catalysis.: In addition to Ti, Pd, Ni, Cu, and Ru, many other transition metal catalysts have also been examined for asymmetric fluorination. In 2004, the Cahard group reported that (*R,R*)-BOX-Ph complexes of not only Cu$(OTf)_2$ (Scheme 82a) but also various other metal salts such as $Mg(ClO_4)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$, and $La(OTf)_3$ can catalyze the fluorination reaction of β-keto estere.[243,257] Although only low enantioselectivity (up to 17% ee) was observed for the reaction using Mg and lanthanoid complexes, reasonably high asymmetric induction was observed when the (*R,R*)-BOX-Ph-Zn$(OTf)_2$ complex was used as a catalyst (up to 74% ee). They also tested a heterobimetallic complex, Al–Li–BINOL, and obtained moderate asymmetric induction (up to 67% ee) when NFPY-BF_4 was used as fluorinating reagent. In 2005, J0rgesen reported that (*R,R*)-DBFOX-Zn$(ClO4)_2$ catalyzed asymmetric fluorination of β-keto phosphonates **210** (Scheme 84a).[258] Several other groups also tried asymmetric fluorination catalyzed by a zinc salt with chiral ligands, but in most cases, the enantioselectivity was inferior to that obtained with Cu or Ni atalysts having the same ligands.[236,239,244,245,247–249,251] In 2008, the Shibata and Toru group reported enantioselective fluorination of methyl *tert*-butyl malonate esters **222.**[259] They first applied their conditions for the asymmetric fluorination reactions of β-keto esters using Ni catalyst[233] to the malonate esters and obtained high asymmetric induction (up to 89% ee). But much higher enantioselectivities were achieved by using the *(R,R*)-DBFOX-Ph **L5**-Zn(OAc)2 complex, and the desired fluoromalonate esters **223** were obtained with excellent enantioselectivity (up to 99% ee). It is noteworthy that this reaction is applicable for the preparation of α-fluoro-α-heteroatom-substituted malonate esters (Scheme 84b).

In 2006, the Inanaga group reported the first successful examples of rare earth metal complex-catalyzed asymmetric fluorination reaction (Scheme 85a).[260] They found that the scandium complex of F_8-BINOL **C56** worked well as a catalyst for asymmetric fluorination of β-keto esters **218** (up to 88% ee). In 2012, the Feng group achieved highly enantioselective fluorination reaction of oxindole by using their original chiral *N*-oxide ligand **L15** (Scheme 85b).[261] In contrast to other transition metal catalysts, this catalyst can fluorinate unprotected oxindole derivatives to give the fluorooxindoles with excellent enantioselectivity. By using this reaction, they synthesized MaxiPost **67** with 96% ee directly.

In 2010, the Kawatsura and Itoh group reported that cobalt salen complex was an efficient catalyst for the enantioselective fluorination of β-keto esters (Scheme 86a).[262] Furthermore, in 2014, the Xu and Che group reported that iron(III)-salan complex **C57** catalyzed fluorination reaction quite efficiently to give highly optically active β-ketoesters and oxindoles (Scheme 86b).[263]

3.2. Asymmetric Elaboration of F-Containing Substrates

3.2.1. Alkylations.

3.2.1.1. Alkylation Reaction of Fluorinated Carbonyl Compounds.: In 1999, Arai, Shioiri, and co-authors developed an asymmetric catalytic alkylation reaction between α-fluoro cyclic ketone **226** and benzyl bromide with cinchonine based quaternary ammonium bromide as chiral catalyst **C58** (Scheme 87).[264] The chiral catalyst was optimized via variation of substitution on the *N*-benzyl group, and the results showed that the permethyl-substituted phenyl one was the best choice affording the corresponding α-alkyl, α-fluoro cyclic ketone **227** with C–F quaternary stereogenic center in up to 91% ee. Several benzyl bromide and allyl bromide could react smoothly with α-fluoro cyclic ketone with moderate chemical yields. The further transformation of the obtained product **227** has also been carried out to afford corresponding ester compounds **228** via a one-pot Ru-catalyzed oxidation process.

In 2009, Maruoka also developed a phase-transfer catalyzed approach for the synthesis of α-alkyl-β-keto esters **230** with α-fluorinated quaternary center from fluorinated keto-esters **229** and alkyl halides (Scheme 88).[265] The asymmetric organocatalytic reaction used *N*-spiro quaternary ammonium salt **C59** as chiral phase-transfer catalyst and CsOH as base, affording the product in 68–89% chemical yields and 65–88% ee. Several types of alkyl halides, such as Bn, aryl, allyl, propargyl, and methyl halides, were well tolerated.

In 2016, Zhou, Hartwig and co-authors reported a Pd-catalyzed asymmetric arylation of α-fluoroketones **231** with aryl bromides as coupling electrophiles (Scheme 89).[266] The reaction used the combination of palladium complex and BINOL-derived monophosphine as catalyst, resulting in α-fluoro-α-aryl carbonyl compounds **232** in 63–91% yields and 80–94% ee. In this work, aryl triflates also have been developed as aryl precursors to react with α-fluoroketones, and the similar level of yields and enantioselectivities was obtained. Besides α-fluoroketones, the in situ generated fluorinated enolates from *gem*-diols also were used as the coupling partners. Comparing to the results from α-fluoroketones, this detrifluoroacetylative arylation reaction afforded better chemical yield and enantioselectivity.

Shortly after that, the Hartwig group used α-fluorooxindoles **233** as coupling partners for the asymmetric Pd-catalyzed arylation reaction with aryl triflates (Scheme 90).[267] The combination of $Pd(dba)_2$/(R)-Segphos **L18** as a catalyst was employed for this reaction, which catalyzed this transformation to form the α-aryl-α-fluorooxindoles **234** with good yields and high enantioselectivities.

In 2007, Paquin and co-authors reported a Pd-catalyzed asymmetric allylation reaction of silyl protected enolates **235** by using oxazoline derived (S)-t-Bu-PHOX as chiral ligand **L19** and tetrabutylammonium triphenyldifluorosilicate (TBAT) as additive (Scheme 91).[268] This methodology used allyl ethyl carbonate **236** as allyl precursor, allowing preparation of the α-allyl, α-fluoro cyclic ketone **237** with 52–93% yields and 83–95% enantioselectivities. The five-, six- and seven-membered silyl enolates were all tolerated in this reaction.

Asymmetric allylic alkylation represents another efficient strategy for the preparation of chiral α-allyl-α-fluoro carbonyl compounds bearing a quaternary stereogenic C–F center (Scheme 92).[269] Tan, Jiang, and co-authors reported in 2013 an asymmetric allylic alkylation reaction of linear α-fluoro-β-keto-esters **238** by using $(DHQD)_2PHAL$ **69** as organocatalyst. The reaction used Morita-Baylis-Hillman carbonates **239** as electrophilic reagents and afforded the corresponding allylic alkylated product **240** in good chemical yields, good enantilselectivities, and moderate diastereoselectivities.

In 2014, Chen, Guo, and co-authors reported a one-pot Pd-catalyzed asymmetric allylic alkylation reaction for the preparation of α-allyl-α-fluoro ketones **242** with the use of phosphinooxazoline (S)-t-Bu-PHOX **L19** as chiral ligand (Scheme 93).[270] In the presence of strong base (LiHDMS), acyclic α-fluoro ketones **241** were converted into the corresponding tertiary fluorinated enolates, which then reacted with allyl enol carbonates to give the final product in 30–91% chemical yields and 60–90% ee. In the case of allyl enol carbonates substrates, the steric hindrance showed almost no effect on the reaction outcome, and the same level of yield and enantioselectivity was found.

Recently, the Wolf group developed an asymmetric allylic alkylation reaction between tertiary fluorinated enolates generated from C3-fluorinated oxindoles **233** and allylic acetates/carbonates **243** (Scheme 94).[271] The optimization of chiral ligand disclosed that *(S)-t*-Bu-PHOX **L19** was the most efficient one, and the combination with $[\eta^3\text{-}C_3H_5ClPd]_2$ catalyzed the allylic alkylation reaction to give the 3-fluorinated carbon quaternary oxindoles **244** with excellent enantioselectivities (>99% ee) and diastereoselectivities (92:8 → 99:1). The regioselectivity of this asymmetric alkylation reaction has also been examined by using nonsymmetrically substituted allylic acetates, and also excellent regioselectivity was found.

3.2.1.2. Alkylation Reaction of Fluorinated Allyl Enol Carbonates.: In 2005, the Nakamura group reported a Pd-catalyzed enantioselective decarboxylative reaction of α-fluorinated ketoester **245** under room temperature by using chiral phosphines as ligands (Scheme 95).[272] The optimization studies on chiral ligand showed that the substituent on the oxazoline dramatically affects the enantioselectivity, and (*S*)-*t*-Bu-PHOX **L19** gave the best enantioselectivity (up to 99% ee). The reactions of cyclic substrates, including five-, six-, and seven-membered ketoesters, gave good chemical yields and excellent enantioselectivities. However, the obviously lower ee value was obtained from the reactions of linear substrates. This decarboxylative reaction provides an alternative way for chiral α-allyl-α-fluoro ketones **246** containing quaternary C–F center.

The Paquin group developed another decarboxylative method for the preparation of chiral α-allyl-α-fluoro ketones **248** bearing a quaternary stereogenic C–F center by using fluorinated cyclic allyl enol carbonates **247** as starting materials (Scheme 96).[273] This asymmetric Pd-catalyzed allylation reaction also used (*S*)-*t*-Bu-PHOX **L19** as chiral ligand, which converted several fluorinated allyl enol carbonates into corresponding products in 58−97% yields and 30−94% enantioselectivity. The enantioselectivity of this reaction relied on the ratio of ligand to metal catalyst. Lower ratio of ligand to metal catalyst gave the better ee value, and less than 1:1.67 of this ratio is necessary for affording good stereo outcomes. The nonfluorinated cyclic allyl enol carbonates also have been examined, and no such phenomenon was found. The ratios of 1:1.67 and 1.25:1 gave almost the same enantioselectivity.

3.2.1.3. Alkylation Reaction of α-Halo-α-fluoroketones.: In 2014, the Fu group developed a Ni/bis(oxazoline)-catalyzed asymmetric method for the synthesis of α-keto tertiary alkyl fluorides **250** via Negishi reactions (Scheme 97).[274] They used racemic α-halo-α-fluoroketones **249** as starting materials to react with organozinc reagents, resulting in the corresponding fluorinated carbon quaternary keteones with moderate chemical yields and excellent enantioselectivities. The most challenge task of this work is the use of *gem*-dihalides as electrophiles, and only the C–Br bond was selectively broken in this reaction. This reaction provides a new strategy for the construction of fluorine-containing ketones with C–F quaternary stereogenic center.

3.2.2. Mannich Addition Reactions.

3.2.2.1. Mannich Addition Reactions of Chiral Imines.: In 2014, the Han group used detrifluoroacetylatively in situ generated fluorinated enolates as new nucleophiles for the Mannich reaction with CF_3-sulfinylimine without the use of any transition-metal catalysts, affording the corresponding product in excellent chemical yields and high diastereoselectivities.[275] This reaction provides a generalized method for the preparation of α, α-difluoro-β-trifluoromethyl ketones. After that, the Han group designed a cyclic keto-hydrate **251** as the precursor for the tertiary fluorinated enolate, which was used for the construction of quaternary α-fluoro-β-keto-amines **252** (Scheme 98).[276] This cyclic keto-hydrate could work well in the detrifluoroacetylative Mannich reaction and react with chiral *N*-sulfinyl-imines **253** very smoothly via C–C bond cleavage. The reaction was conducted under simple conditions and could complete within 5 min, affording the expected products with excellent chemical yields and >98:2 diastereoselectivities. Besides the usual chiral CF_3-imine, several other chiral imines bearing fluoro-containing groups also were examined in this reaction, which also were well tolerated.

In 2016, the Han group further extended the substrate scope from cyclic keto-hydrates to cyclic amido-hydrates **254** for the asymmetric detrifluoroacetylative[277,278] Mannich reaction with fluorinated imines (Scheme 99).[279] The cyclic amido-hydrates were synthesized from 3-fluoroindolin-2-ones and generated a new type of fluorinated amide enolates in the presence of DIPEA and LiBr. This is the first example of fluorinated amide enolate and could react well with several types of fluorinated imines to give the corresponding α-fluoroalkyl-β-amino-indolin-2-ones **255** bearing C–F quaternary stereogenic centers. The

reaction tolerated a wide range of hydrates, and even the substrates containing free N-H group also worked very well in the reaction. The reactions also showed high diastereoselectivities, and only one diastereomer was found for all the cases (>98:2 dr).

Following this work, the Han group continued their work on the asymmetric detrifluoroacetylative Mannich reaction of 3-fluoroindolin-2-one-derived tertiary enolates with fluorinated imines.[280,281] The trifluoromethyl group of (*S*)-*N*-tert-butane-sulfinylaldimines was further extended to CHF_2, CIF_2, C_4F_9, C_4HF_8, C_5F_{11}, and C_6HF_{12}. Their reactivities were investigated by reaction with detrifluoroacetylatively in situ generated 3-fluoroindolin-2-one-derived enolates. The results showed that also good yields and excellent diastereoselectivities were obtained.

In 2017, the Han group designed and synthesized a *N-tert*-butylsulfinyl-(perfluoro)benzaldimine **256** and used this imine as an electrophile in the asymmetric detrifluoroacetylative Mannich reactions (Scheme 100).[282] Pentafluorophenyl (perfluorophenyl) is an electronic antipode of the common phenyl group,[283–285] which also has been widely used in the chemical and biological area. The Mannich addition reactions of in situ generated enolates proceeded smoothly to give the corresponding quaternary β-perfluorophenyl-amino-indolin-2-ones **257** with moderate yields and diastereoselectivities. Comparing with the results from the reaction of CF_3-imine, the reaction of this imine resulted in obviously lower chemical yields and stereochemical outcomes. It should also be mentioned that free N-H 3-fluoroindolin-2-one-derived hydrates were tolerated in this reaction.

The detrifluoroacetylative Mannich reactions with indolin-2-ones derived *gem*-diols have been reported by the Han group to react with several types of fluorinated aldimines. Then, in 2017, the Han group examined their reactivities in the reactions with nonfluorinated (S_s)-sulfinylimines **258** (Scheme 101).[286] The optimization of reaction conditions disclosed that the reaction could be completed within 10 min at 0 °C. Several types of regular imines with aryl, heteroaryl, alkyl, alkenyl, and alkynyl groups have been examined in the reaction and gave the expected quaternary α-fluoro-β-amino-indolin-2-ones **259** in good yields and excellent diastereoselectivities were obtained.

In 2016, the Li group reported an asymmetric Mannich reaction between α-fluoro esters **260** and *N-tert*-butylsulfinyl imines **258** in the presence of strong base LiHDMS at −70 °C (Scheme 102).[287] Three examples of α-fluoro-α-branched ester substrates, including benzyl, 2-naphthylmethyl, and $BnOCH_2CH_2$-, have been investigated in this reaction, affording the corresponding quaternary α-fluorinated β-amino acids **261** in good chemical yields. The diastereoselectivities were moderate, and three diastereomers were detected in most cases.

In 2016, the Li group reported a similar asymmetric Mannich reaction betweenα-fluoro-α-branched esters **260** and *N-tert*-butylsulfinyl imines **258** with the use of strong base LiHDMS at −70 °C (Scheme 103).[288] In this work, they extended the fluoro esters scope, and the esters bearing α-aryl, alkyl, and allyl were well tolerated, affording good chemical yields. The moderate diastereoselectivities were obtained, and four diastereomers were detected in most cases. The stereoselectivity of this asymmetric Mannich reaction mostly

relied on the steric hindrance of the substitutions on both esters and imines. Substrates with high steric hindrance usually gave excellent results.

Later, the Li group reported α-fluoro ketones **231** as nucleophiles for the asymmetric Mannich reaction with *N*-*tert*-butylsulfinylimines. Comparing with the reactions on α-fluoro esters,[287,288] this reaction used NaHDMS as a strong base and ether as asolvent (Scheme 104).[289] Cyclic α-fluoro ketones could react with a wide range of sulfinylimines bearing varieties of substituents, including aryl, alkyl, and vinyl groups. Also, obviously improved diastereoselectivities were obtained, and usually two diastereomers were detected for most cases.

3.2.2.2. Asymmetric Catalytic Mannich Addition Reactions of Imines.: Besides asymmetric methods based on chiral auxiliary developed for the synthesis of quaternary C–F compounds, asymmetric catalytic Mannich reaction was an alternative way to such structural units. In 2009, Huang, Lu and co-authors reported an organocatalytic Mannich reaction between α-fluorinated ketoesters **263** and Boc-imines **264** with trypto-phan-based bifunctional thiourea **C60** as the chiral catalyst (Scheme 105).[290] The reaction was conducted at −50 °C, resulting in the corresponding α-fluoro- β-ketoesters **265** bearing fluorinated quaternary stereocenters with excellent chemical yields, high diastereoselectivities, and enantioselectivities. Both aliphatic and aromatic ketones reacted with aliphatic/aromatic aldimines very well. The authors also did some derivatization experiments on the products by converting them into α-fluoro-β-amino acids and α-fluoro-β-lactams via cascade reduction, hydrolysis, and cyclization.

Then in 2011, the Kim group reported a related Pd-catalyzed asymmetric Mannich reaction. They used the similar substrates, α-fluoro- β-ketoesters **263** and *N*-Boc-aldimines **264,** by using palladium complexes and BINAP **L21** as the chiral catalyst (Scheme 106).[291] The reaction could be conducted under room temperature, resulting in the expected α-aminated α-fluoro-β-keto esters **265** featuring fluorinated tetrasubstituted carbon centers in excellent enantioselectivities (94−98% ee). The only limitation of this methodology is the diastereoselectivity, and poor diastereoselectivities were obtained for most cases.

In 2016, Wennemers and co-authors reported an asymmetric organocatalyzed Mannich addition reaction of imines **267** with α-fluorinated monothiomalonates **266** as nucleophiles (Scheme 107).[292] The re action used only 1 mol % of bifunctional cinchona alkaloid–thiourea **C60** as a chiral organocatalyst, which catalyzed the reaction very well, affording the corresponding α-fluorinated β-amino thioesters **268** in excellent yields (80−99%), high diastereo (4:1 → 20:1 dr) and enantioselectivities (91−99.9% ee). The protecting group on the amino group showed obvious effect on the chemical yields, and usually the Cbz-protect imines affords obviously higher yields. Furthermore, a wide range scope of imines was tolerated in this system, and even aliphatic aldehyde-derived imines worked very well, resulting in good chemical yields.

In 2010, Jiang, Tan and co-authors reported an asymmetric organocatalytic Mannich reaction of imines **270** by using β-keto acetyloxazolidinone **269** as a new nucleophile, which provided another method for the synthesis of α-fluoro- β-amino acid derivatives **271** bearing

quaternary fluorinated carbon centers (Scheme 108).[293] This asymmetric Mannich reaction used (*S,S*)-bicyclic, guanidine **C62** as organocatalysis, and was carried out at room temperature, converting varieties of β-keto acetyloxazoli-dinone into the corresponding product in excellent yields and high enantio- and diastereoselectivities. The substitutions on the two substrates showed an obvious effect on the stereoselectivity of this reaction. The bulky groups substituted imine and β-keto acetyloxazolidinone gave almost completely controlled stereo-chemical outcome.

In 2011, the Jiang group reported α-fluorinated aromatic cyclic ketones **231** as nucleophiles for the Mannich reaction with imines **272** by using (*S,S*)-bicyclic, guanidine **C62** as chiral organocatalysis (Scheme 109). The reaction was conducted under lower temperature (−20 °C) with 1,2-dichloroethane as solvent, provided the corresponding β-amino ketone **273** in moderate diastereoselectivities and excellent enantioselectivites. Azodicarboxylates **274** were also tried to be reacted with α-fluorinated aromatic cyclic ketones under the similar catalytic asymmetric system. The expected amination products **275** were obtained with high enantioselectivities.

The Trost group also developed an asymmetric catalytic Mannich reaction for the synthesis of β-amino ketone **276** bearing α-fluorinated quaternary stereogenic centers (Scheme 110).[295] α-Fluorinated aromatic ketones **231** were used as nucleophiles to react with Boc-protected aldimines with the combination of ZnEt2/(*R,R*)-prophenol **L22** as chiral catalyst. Optimization ofreaction conditions disclosed that increasing the reaction temperature could give the higher chemical yield, and showed no effect on the diastereo- and enantioselectivity. The highest yield (98%) was found when the reaction was conducted 80 °C. The gram-scale study was also carried out, and excellent chemical yield (98%) and stereochemical outcome (>20:1 dr, 99% ee) were obtained.

The efficient organocatalytic Mannich reaction of α-fluoro cyclic ketones can also be accomplished by using α-amidosulfones as starting materials. Recently, Yan, Song, and co-authors developed an asymmetric Mannich reaction between α-fluoro cyclic ketones **277** and α-amidosulfones **278** with the use of Song's chiral oligoEGs **C63** as a catalyst (Scheme 111).[296] In the presence of catalyst and KF, the in situ generation of imine from α-amidosulfones and generation of enolate from cyclic ketone was performed, which reacted with each other with the aid of a catalyst, affording the corresponding α-fluorinated amino ketones **279** in good chemical yields, good diastereose-lectivities, and high enantioselectivities. It should be mentioned that increasing the temperature to 70 °C gave the best yield and has no effect on the diastereo- and enantioselectivities.

The Wang group revealed a Cu-catalyzed asymmetric detrifluoroacetylative Mannich reaction for synthesis of compounds **281** bearing fluorinated quaternary stereogenic centers (Scheme 112).[297] They employed 2-fluoro-1,3-diketones/hydrates **251** as the precursors of fluorinated enolates to react with isatin derived ketimines **280** in the presence of chiral anthracenyl-substituted cyclohexane-1,2-diamine **L23.** The reaction was conducted under low temperature (−45 or −30 °C), affording the corresponding 3-substituted 3-amino-2-oxindoles **281** with vicinal tetrasubstituted carbon centers in excellent yields (67–99%), good diastereoselectivities (4:1 → 20:1 dr) and enantioselectivities (66–94% ee).

3.2.3. Aldol Addition Reactions.

3.2.3.1. Aldol Addition Reactions of Detrifluoroacetylatively Generated Fluorinated Enolates.: In 2010, Colby[298] and co-authors developed a new 1,1,1,3,3-pentafluoro-2,4-dione system for the preparation of unprotected fluorinated enolates via C–C bond cleavage with the release of trifluoroacetic acid.[91] This detrifluoroacetylative reaction could happen under mild conditions, and the resulted fluorinated enolates are the active intermediates, which have been used as the nucleophiles in the aldol reactions. The Colby group has applied these in situ generated enolates in the aldol reaction with varieties of aldehydes to afford the fluorinated hydroxy ketone within about 3 min.[298] Then, the Wolf group used this new detrifluoroacetylative approach in aldol reaction with trifluoromethyl ketone pentafluorinated β-hydroxy ketone.[299] In 2013, the Wolf group explored the first example on the asymmetric catalytic cascade detrifluoroacetylation and aldol reaction by using copper(II) triflate and chiral bisoxazoline ligand as a catalyst.[300] Such 2,2-difluoro-1,3-diketones also have been used as the precursors of fluorinated enolates for asymmetric aldol reaction with *N*-benzyl isatins.[301]

In 2013, the Wu group reported a new type of linear detrifluoroacetylative precursors, trifluoromethyl α-fluorinated β-keto *gem*-diols **282,** which were used as the substrates for the organocatalytic asymmetric aldol reactions (Scheme 113).[302] The C–C bond cleavage of this monofluorinated *gem*-diols proceeded smoothly to generate the fluorinated enolates, which reacted very well with varieties of *N*-benzyl isatins **283** in the presence of cinchona alkaloid derived thiourea **C64.** The reaction was conducted at room temperature, resulting in the corresponding product **284** with excellent yields and high diastereo- and enantioselectivities. Such *gem*-diols showed lower reactivity to aliphatic aldehydes, dramatically lower chemical yields, and enantioselectivities were observed.

Then, in 2015, the Han group reported a new cyclic α-fluorinated β-keto *gem*-diols **251,** which could be prepared conveniently from cyclic ketones via a two-step process (Scheme 114).[303] These cyclic *gem*-diols were successfully applied as the substrates for asymmetric detrifluoroacetylative aldol reaction. The reaction was carried out under mild conditions by using copper(II)/chiral bisoxazoline **L24** as a catalyst, affording the expected α-fluoro-β-hydroxy ketones **285** in 84–96% yields and up to 99:1 dr and 98% ee. Only the aromatic aldehydes, phenylacetaldehyde, and α,β-unsaturated aldehyde were examined in this system. This asymmetric detrifluoroacetylative aldol reaction provides a new access to the α-fluoro-β-hydroxy ketones bearing C–F quaternary stereogenic centers.

As it should be routinely done in a work on catalytic asymmetric synthesis,[304] the authors conducted SDE (self-disproportionation of enantiomers) tests by achiral chromatography[305] and sublimation[306,307] of some randomly selected aldol products. While the sublimation SDE test was negative, the SDE by achiral chromatography showed noticeable magnitude of about 11% Δee.[308] For example, a routine isolation of a product of 84% ee via achiral chromatography resulted in an enantiomerically enriched (88% ee) first fraction and enantiodepleted (77% ee) last fraction, suggesting that extra care should be taken in the avaluation of the stereochemical outcome. Furthermore, taking into account that fluorine and

fluorine-containing groups are SDE enabling substituents,[309–311] such SDE tests should be a mandatory part of high-quality research in this area.

Using the similar catalytic conditions, Han, Soloshonok, and co-authors tried to use aliphatic aldehydes as substrates for this detrifluoroacetylative aldol reaction (Scheme 115).[312] A wide range of aliphatic aldehydes have been used as substrates, which could be successfully transferred into the corresponding α-fluoro-β-hydroxy ketones **285** with moderate chemical yields. This reaction was conducted at room temperature, affording the aldol adducts as well as the byproduct **286** due to the low reactivity of aldehydes. Especially, almost no desired α-fluoro-β-hydroxy ketone product was obtained at all in the cases of the aldehydes with high steric hindrance.

Recently, Han, Soloshonok, and co-authors developed a Cucatalyzed asymmetric detrifluoroacetylative aldol reaction of aldehydes with in situ generated tertiary enolates derived from fluoro-indolinones (Scheme 116).[313] CuI was optimized as the best catalyst, which catalyzed the transformation efficiently in the presence of bisoxazoline chiral ligand **L25,** resulting in α-fluoro-β-hydroxy-indolin-2-ones **287** containing C–F quaternary stereogenic centers in good yields and enantioselectivities. The solvent showed an obvious effect on the reaction outcome, and *i*PrOH/THF was found to be the best reaction media with the ratio of 1:1. The reaction showed broad substrate generality, and even the aliphatic aldehydes and unprotected *N*-H fluoro-indolinone *gem*-diols could be well tolerated to give good yields and enantioselecitivities. The SDE tests via achiral chromatography,[314] conducted on these aldol addition products, gave moderate magnitude of about 4% Δee.

Recently, Han, Soloshonok, Pan, and co-authors designed a one-pot reaction for the asymmetric synthesis of bicyclic ketoesters containing C–F quaternary stereogenic center, with cyclic α-fluorinated β-keto *gem*-diols and ortho-phthalaldehyde as starting materials.[315] The reaction proceeded smoothly via a complex four-step process, including detrifluoroacetylation, aldol addition, intramolecular cyclization, and oxidation. The combination of trimethylamine and LiBr was used for the detrifluoroacetylative-aldol step and then using PCC to oxidize the intermediate to the final product. This Cu-catalyzed reaction gave bicyclic keto-esters in good chemical yields but poor diastereoselectivity and enantioselectivity.

Shortly after that, the Han group develop a new asymmetric catalytic system for the synthesis of bicyclic keto-esters **290** containing a C–F quaternary stereogenic center (Scheme 117).[316] The ester-aldehyde **288,** instead of *ortho*-phthalalde-hyde, was used as the electrophile, which was found to react very well with detrifluoroacetyl derivatives in situ generated enolates via aldol addition and intramolecular substitution. This Cu-$(OTf)_2$/chiral bisoxazoline-catalyzed asymmetric reaction was conducted at room temperature, affording fluorinated bicyclic keto-esters with moderate yields (49−54%) and good diastereo- (80:20−97:3) and enantioselectivity (59−96%).

3.2.3.2. Aldol Addition Reactions of Fluorinated Silyl Enol Ethers.: In 2014, the Zhou group developed an asymmetric organocatalytic aldol reaction between fluorinated silyl enol ethers **291** and isatins **292,** which used quinine or cinchonine alkaloid urea derivatives as

chiral catalysts **(C65** and **C66)** (Scheme 118).[317] In the cases of 5-halo groups substituted isatins, the reactions used **C66** organocatalyst, affording the expected product **293** in 81−86% ee. The reaction was conducted at −20 °C resulting in up to 98% chemical yields, however, the reaction needed long time for completion (1−5 days). The reaction used fluorinated silyl protected keto-enolates as substrates, generating two adjacent new quaternary stereogenic center, with one of them featuring a C–F quaternary stereogenic center.

3.2.3.3. Aldol Addition Reactions of Decarboxylative Generated Fluorinated Enolates.: In 2016, the Wennemers group used cinchonine alkaloid urea derivatives **C67** as organocatalysts for the asymmetric aldol reactions between in situ generated fluorinated enolates from fluoromalonic acid half-thioesters **294** and aldehydes with THF as solvent under 0 or 10 °C (Scheme 119).[318] They used fluoromalonic acid half-thioesters as masked fluoro enolates, which were transferred to the functionalized fluorinated β-hydroxyl thioesters **295** under mild conditions in moderate to good chemical yields (45−87%). The results showed that aromatic aldehydes and half-thioester bearing electron-donating groups usually worked better, resulting in higher enantioselectivities. They applied this synthetic method for the synthesis of fluorinated atorvastatin, which gave excellent enantioselectivity and diastereoselectivity (>99% ee, > 20:1 dr).

3.2.4. Michael Addition Reactions.—Asymmetric Michael reaction is the other method for the construction of quaternary stereocenter bearing a fluorine atom. A number ofprocedures for the asymmetric addition reaction of fluorinated nucleophiles bearing a carbonyl group to Michael acceptors have been reported.

3.2.4.1. Michael Addition Reactions with Nitro Styrenes as Acceptors.: Asymmetric organocatalytic Michael reactions between nitroolefins and fluorinated β-ketoesters have been well developed for the construction of Michael products with tetrasubstituted C–F centers. In 2009, the Lu group used cinchona alkaloid derived thiourea **C67** as the catalyst for this transformation (Scheme 120).[319] Optimization of reaction conditions showed that the trifluoromethyl substituted quinidine was the best choice and could catalyze the reaction smoothly to give the corresponding α-substituted α-fluoro-β-ketoester **296** in almost quantitative yields and high diastereo-(2.5:1−19:1) and enantioselectivities (95−99% ee). The reaction also showed a wide substrate generality, and varieties of aryl and alkyl nitroolefins worked well with fluorinated nucleophiles. It should be mentioned that the bulky *t*-butyl ester group resulted in a dramatically lower chemical yield and decreased diatereoselectivity.

In 2009, the Wang group also developed an organocatalytic asymmetric Michael addition reaction between α-fluoroketoesters **263** to nitroolefins (Scheme 121).[320] The reaction used cinchona alkaloid-derived compound **C68** bearing a bulky 9-phenanthrenyl substitution as the chiral catalyst and conducted the reaction under room temperature. Only one example of α-fluoroketoester was used to react with several nitroolefins to give the product **296** in excellent chemical yields and high enantioselectivity. The limitation of this method is the

moderate diastereoselectivity (1.7−4:1 dr). One of the products was further converted into the cyclic compound, pyrrolidine, via reduction in the presence of Raney Ni.

In 2009, the Kim group successfully used chiral bifunctional thiourea containing a tertiary amine **C69** as an organocatalyst for the Michael reaction of β-ketoesters bearing an α-fluorine atom to nitroalkenes (Scheme 122).[321] Under the optimized reaction conditions, varieties of α-fluorinated-β-ketoesters **263** could add smoothly with nitroalkenes to give the corresponding chiral Michael adducts **296** bearing a fluorinated quaternary carbon center in moderate diastereoselectivities and excellent enantio-selectivities (83 → 99% ee). A bulky alkyl group on the ester moiety was required for the high diastereoselectivity. Changing the ester group from isopropyl ester to ethyl ester led to a noticeable reduction in diastereoselectivity.

In 2009, Zou, Zhao, and co-authors applied a primary-secondary diamine **C70** as an organocatalyst for the asymmetric Michael reactions of α-fluoro-β-ketoesters **263** with nitroolefins (Scheme 123).[322] The optimization of reaction conditions showed that the diamine bearing steric bulky groups gave the best stereochemical outcome. On the other hand, the addition of acids as additives obviously improved the reaction efficiency, and the combination of TfOH/p-NBA (p-nitrobenzoic acid) could promote the reaction with better yields. In this reaction, both alkyl and aryl ketoesters reacted well with nitro styrenes, affording the corresponding γ-nitro-α-fluoro-β-ketoesters **296** bearing a C–F quaternary carbon center in excellent diastereoselectivities (6:1 → 20:1) and enantioselectivities (89−99% ee). The ^{19}F NMR experiments tracing the process of the reaction showed that the catalytic cycle contains the enamine activation.

α-Fluorinated α-sulfonyl ketones are an efficient type of nucleophile due to their convertibility into varieties of functionalized monofluoromethylated compounds, which are crucial structural unit in many biological compounds. In 2012, Zhao and co-authors applied the α-fluorinated α-sulfonyl ketones **297** in an asymmetric organocatalytic Michael addition reaction to nitro-olefins (Scheme 124).[323] They used tertiary amine based thiourea **C71** as the organocatalyst for this reaction, which afforded the γ-nitro-α-sulfonyl ketones **298** in excellent yields (70−93%) and high diastereo-(5:1−20:1) and enantioselectivities (86−96%). The alkyl group substituted nitroolefins also worked very well in this reaction, and no reduction on the yields and stereochemical outcome was observed.

α-Fluoroalkyl-phosphonates are widely represented in many biologically active compounds, in particular phosphorus analogues of amino acids.[324–327] They also are good candidates for fluorinated nucleophiles and can react with Michael acceptors. In 2015, the Kim group applied α-fluoro ketophosphonates **299** as nucleophiles for the asymmetric Ni-catalyzed Michael addition reaction with nitrostyrenes (Scheme 125).[328] The optimization of reaction conditions showed that chiral 1,2-cyclohexanediamine coordinated dicationic nickel complexes **C72** was the best catalyst, and such catalytic combination promoted the reaction smoothly to give the expected Michael adducts in excellent yields, high stereochemical outcomes (10:1−50:1 dr, 93−99% ee). Increasing heating of the reaction to 50 °C resulted in the best yield (90%) without any reduction of diastereo- and enantioselectivity. The gram-

scale synthesis of this method was also tried, and the same level of yield, dr and ee values was obtained.

In 2015, the Lu group showed that 2-fluoro-1,3-diketones **301** could be successfully used as nucleophiles for the organocatalytic Michael addition reaction to nitroolefins (Scheme 126).[329] After the scanning of organocatalysts, quinine-derived sulfonamide **C72** bearing a 3,5-trifluoromethylphenyl substituent was demonstrated to be the best one for this asymmetric Michael reaction. Several nitro styrenes reacted very well with 2-fluoro-1,3-diketones to afford the corresponding Michael adducts **302** bearing C–F quaternary stereogenic centers in good to excellent yields (89 → 99%) and high diastereo- and enantioselectivities (2:1−8:1 dr, 94 → 99% ee). An isopropyl substituted nitroolefin substrate was examined in this system, but only moderate yield was observed with almost no stereoselectivity.

The asymmetric Michael addition of nitroolefins with fluorinated carbonyl compounds as nucleophiles provided an easy strategy for the synthesis of γ-nitro-α-fluorinated ketone/ester compounds. Although several related examples have been developed, α-fluoro-α-nitroalkanes as nucleophiles for the asymmetric Michael reaction to nitroolefins is rarely reported. In 2014, Lu and co-authors reported asymmetric organocatalytic Michael additions between α-fluoro-α-nitroalkanes **303** and nitroolefins (Scheme 127).[330] The amino acid-incorporating multifunctional quinine-derived compound **C74** was employed as an organocatalyst, which catalyzed the reaction to give the corresponding 1,3-dinitro compounds **304** bearing α-fluoro quaternary centers in good yields (71–95%) and good diastereo- and enantioselectivities (5:1−8:1 dr, 82–96% ee). The most interesting point was that the different diatereomers in most cases could be isolated by the regular flash silica gel chromatographic column. The hydrogenation reduction of the obtained 1,3-dinitro compound was conduct to afford 1,3-diamine compounds.

Recently, the Wennemers group successfully used fluorinated monothiomalonates **305** as nucleophiles for the organocatalytic Michael addition reaction with β-nitrostyrenes to provide a new way for the synthesis of chiral α-fluoro-γ-nitro thioesters **306** with fluorinated tetrasubstituted stereogenic centers (Scheme 128).[331] The epi-cinchonine-urea **C75** was identified as the best catalyst for this reaction after several types of catalyst screening. Under the optimized reaction conditions, fluorinated mono-thiomalonate reacted smoothly with several nitroolefins, resulting in high stereoselectivities (13:1 → 20:1 dr, 95−99% ee).

3.2.4.2. Michael Addition Reactions with Other Reagents as Acceptors.: In 2009, Wong, Tan, and co-authors developed a new type of Michael acceptors, *N*-alkyl maleimides **307,** for the organocatalytic asymmetric Michael reaction of α-fluoro-β-keto esters **263** (Scheme 129).[332] They used (*S*,*S*)-bicyclic, guanidine **C62** as the chiral organocatalysis for this reaction, which showed excellent stereocontrolled ability and only one diastereomer was obtained in almost all the cases. The substitution on the nitrogen atom of maleimides almost has no effect on the reaction efficiency, and ethyl, methyl, cyclohexyl, benzyl, *n*-hexyl, and *t*-butyl were all well tolerated in the current system. On the other hand, varieties of aryl keto-esters worked very well, resulting in excellent yields (80–99%) and high enantioselectivities (83–97% ee).

In 2010, the Lu group developed asymmetric Michael addition reactions with di-*tert*-butyl azodicarboxylate as acceptors to react with α-fluorinated β-keto esters **263,** affording α-fluoro-α-amino-β-keto esters **310** with fluorine containing quaternary stereogenic centers (Scheme 130).[333] Several α-fluorinated β-keto esters were tolerated in the reaction with chiral guanidines derived from cinchona alkaloids **C76** as organocatalysts. The aliphatic keto ester substrates showed lower reactivity and stereoselectivity, and poor enantioselectivities were found (about 50% ee).

Joseph, Delarue-Cochin, and co-workers reported an asymmetric Michael reaction with (*S*)-1-phenylethylamine as a chiral auxiliary (Scheme 131).[334] They used 2-fluoroenaminoesters **311** derived from β-keto esters and (*S*)-1-phenylethylamine as chiral nucleophiles for the Michael addition reaction to α-substituted methyl acrylates under heating or refluxing conditions. The intermediary Michael adducts were obtained, which were directly hydrolysized in the presence of 10% aqueous AcOH at room temperature to give γ-substituted γ-fluoroglutamate **312** bearing a fluorinated quaternary carbon center. Three examples of α-substituted methyl acrylates were examined. The substituents showed much effect on the reaction. In the case of BocNH substituent, no expected adducts were obtained even when the reaction time were prolonged to 15 days. Interestingly, the two diastereomers could be easily separated by the regular silica gel chromatographic column through the thioketalization of the two diastereomers by 1,2-ethanedithiol.

In 2015, the Zhou group used fluorinated enol silyl ethers as nucleophiles for the asymmetric Michael addition to the isatylidene malononitrile **314** (Scheme 132).[335] The chiral secondary amine phosphoramide **C77** derived from 1,2-diaminocyclohexane was used as the organocatalyst for this Michael reaction, which could catalyze this reaction efficiently to give the corresponding adducts **315** in nearly quantitative yields and excellent diastereo- and enantioselectivities (4:1 → 20:1 dr, 84−94% ee). Both bis- and monofluorinated enol silyl ethers derived from α-fluorinated indanone or benzofuranone could be well tolerated in this reaction. Most interestingly, the obtained adducts could be easily reduced into the corresponding alcohols without any loss of enantioselectivity.

In 2014, the Lu group developed 2,3-butadienoates as Michael acceptors for the asymmetric addition reaction with 3-fluorooxindoles **233** for the synthesis of 3-fluoro-3-allyloxindoles containing a C–F quaternary center (Scheme 133).[336] The L-threonine derived phosphine-amide **C78** was demonstrated as the best choice of catalyst, which was able to catalyze the conversion of several 2,3-butadienoates **316** into the corresponding products with excellent yields (88−95%) and high enantioselectivities (83−94% ee). The ester group of 2,3-butadienoates almost have no effect on the reaction efficiency, and the groups including methyl, *t*-butyl, benzyl, and bulky anthryl were all well tolerated in the reaction, affording the same level of yields and enantioselectivities. The control experiments disclosed that the hydrogen bonding interactions between *N*-Boc of 3-fluoro-oxindoles and N-H group of the chiral catalyst led to the observed absolute configuration of the product.

α,β-Unsaturated ketones have also been developed as Michael acceptors for the asymmetric addition reaction with malonates derivatives **319** by Zhao and co-authors for the construction of C–F quaternary stereogenic center (Scheme 134).[337] They established a new catalytic

Michael reaction by using dipeptide-derived multifunctional phosphonium salts **C79** as chiral catalysts. Varieties of α,β-unsaturated ketones were tried in this catalytic system to react with malonates, resulting in excellent yields and high enantioselectivities. In their work, one example of fluorinated nucleophile, dimethyl 2-fluoromalonate, was used as substrate to react with (*E*)-chalcone, resulting in the product **320** with a C–F quaternary stereogenic center in 89% yield and 98% ee.

In 2013, the Lu group developed the first example on the asymmetric organocatalytic Michael reaction with very active vinyl sulfones **321** as Michael acceptors (Scheme 135).[338] The quinine-derived tertiary amine-thiourea **C80** was used as the most efficient organocatalyst, which catalyzed the reaction of 3-fluorinated oxindoles **233** to give the expected products **322** with the best yield and enantioselectivity. Nine different substituted 3-fluorinated oxindoles were examined in the reaction, and the results showed that the substitution on the aromatic ring had almost no effect on the reaction, and >95% chemical yields were obtained for all the cases. The reaction was conducted under room temperature and completed within 1 h, which provides an easy way to sulfone substituted oxindoles containing a fluoro-quaternary stereogenic center.

Very recently, Han, Soloshonok, and co-authors also developed an asymmetric Cu-catalyzed detrifluoroacetylation/Michael reaction by using cyclic fluorinated *gem*-diols **251** as nucleophiles (Scheme 136).[339] They pointed out in this work that several types of Michael acceptors, such as α,β-unsaturated carbonyl derivatives, nitroolefins, and highly reactive *N*-(enoyl)-oxazolidinones,[340–342] have been tried to react with the cyclic fluorinated *gem*-diols, which were not successful. Only the highly reactive 1-(1-(phenylsulfonyl)vinylsulfonyl)benzene **321** could react with cyclic fluorinated *gem*-diols well, resulting in the corresponding products **323** in excellent enantioselectivity and chemical yields. The combination of $Cu(OTf)_2$ and (1S,2S)-1,2-diphenylethane-1,2-diamine **L26** was applied as the chiral catalyst, which promoted the reactions of several types of 2-fluoro-1,3-diketones/hydrates to give the corresponding five-, six, and seven-membered rings and heterocyclic 3-fluoro-2,3-dihydrochromen-4-one derivatives bearing quaternary C–F stereogenic carbon. The authors demonstrated that chromatographic purification of the addition products should be conducted with particular care as a moderate SDE magnitude of 4% Δee[343] was detected under the conditions of routine column chromatography.

3.2.5. Cross-Coupling Reactions.—Macrolides like erythromycin are widely prescribed as antibiotics. The development of new macrolide derivatives with activities against resistant pathogens has been the focus of study of several research groups. As a result, fluorine-substituted analogues of these macrolides have been synthesized. In 2004, the Beebe group reported the palladium-catalyzed Sonogashira coupling reaction of 2-fluoro-9-oxime ketolides **324** with several heteroaryl bromide reagents (Scheme 137).[344] The use of the free alcohol at position 20 resulted in a convergent synthesis of analogues 325 in good yields. The fluorine atom was introduced in an earlier stage by reaction of the NaH-generated enolate with NFSI. Regarding the antibacterial activity, the 2-F analogues showed no improvement when compared to the 2-H compounds.

Later, the Beebe group employed a similar strategy to prepare the diazalides analogues **327** (Scheme 138).[345] The 2-fluoro-6-*O*-propargyl diazalides 326 were used as the partner in the Sonogashira coupling with two different heteroaryl bromide reagents. The 20-*O*-protecting group was further removed by hydrolyses in hot methanol to afford the 6-*O*-heteroarylpropargyl diazalides **327.** The introduction of the 2-fluoro group had no significant effect on the antibacterial activity when compared to the 2-H compounds.

In 2012, the Sugimoto group reported the synthesis of 6-*O*-(heteroaryl-isoxazolyl)propynyl 2-fluoro ketolides **329** in moderate yields via the palladium-catalyzed Sonogashira cross-coupling under copper-free conditions (Scheme 139).[346] The coupling reaction was performed using the free alcohol **328,** which was prepared by fluorination using NFSI, followed by 20-*O*-benzoyl group hydrolysis with methanol. The stereochemistry of fluorinated intermediate **328** was determined by X-ray analysis. The synthesized compounds exhibited promising activity against respiratory pathogens, although a comparison to the parent 2-H analogues was not presented.

Very recently, the Liang group reported the palladium-catalyzed Heck (Scheme 140A) and Sonogashira coupling reactions (Scheme 140B) of allyl-**(330)** and propargyl-**(332)** 9-substituted oxime ketolides, respectively, in low yield.[347] The final desired products **331** and **333** were obtained by subsequent hydrolysis of the 20-acetate (Scheme 140). The combined incorporation of aminopyridyl or carbamoylpyridyl and 2-fluorine atom resulted in high antibacterial activity.

2′-Fluorine containing nucleosides have been synthesized and studied for their antiviral activity. The palladium-catalyzed cyanation, Suzuki, and Stille coupling reactions of **334** with the corresponding nucleophilic partners were reported for the synthesis of 7-heterocyclic substituted 7-deaza-adenine nucleo-sides **336−338,** respectively (Scheme 141A).[348] The coupling reactions were performed under harsh conditions, such as microwave irradiation and high temperatures, to yield the products in low to moderate yields. Furthermore, the phosphoramidate prodrug **341** was prepared from the 3-*O*-THP analogue **339** by using Suzuki coupling reaction conditions (Scheme 141B).

Recently, Zhang, Tu, and co-authors reported the synthesis of several 2′-fluoro-7-deaza purine nucleoside derivatives **343−347** via cross-coupling reactions of iodide **342** with a wide range of nucleophilic parterns using Stille, Suzuki, Sonogashira, or Heck conditions (Scheme 142)[349].

The Ando group studied the modification of α-bromo-α-fluoro-β-lactams. The Kumada coupling reaction of *rac*-**348** with a wide range of aryl and heteroaryl Grignard reagents was achieved using a Ni/chiral bisoxazoline catalytic system. The corresponding *anti*-α-aryl-α-fluoro-β-lactams *rac*-**349** were obtained in high diastereoselectivity and up to 98% yield using (*R*)-PhBOX **L27** as ligand (Scheme 143).[350,351]

Later, The Ando group reported the nickel-catalyzed Suzuki coupling reaction of the same type of substrates with a wide range of aryl-(9-BBN) reagents to yield the anti-isomer in up to 87% yield.[352] The most efficient ligand was bipyridine derivative **L28.** It is worth noting

that the chiral coupling product **351** (Scheme 144) was obtained without erosion of enantiopurity when the reaction was conducted with the enantioenriched α-bromo-α-fluoro-β-lactam **350.**

In both cross-coupling approaches, the respective alkyl reagents partners did not work. However, although not in a cross-coupling approach, the formation of the desired α-alkyl-α-fluoro-β-lactams was possible by alkylation and aldol reaction of these derivatives (Scheme 145).[351,353]

Dominguez prepared and studied the activity of several tetrasubstituted cyclopropane hydroxamic acid derivatives as class Ila histone deacetylase inhibitors.[354] Fluorine substituted derivatives exhibited better biological activity. The final desired products containing different heterocyclic moieties were synthesized through a palladium-catalyzed Suzuki coupling using the fluorinated substrate as the nucleophilic partner and several heteroaryl halides (Scheme 146). The fluorine atom was introduced by reaction of the ketone with LDA followed by NFSI; subsequently, the enantiopure hydroxamic acid products **357** were obtained from chiral HPLC purification.

The Magnus group reported the Suzuki coupling reaction of enantiopure iodo-sulfonamide **358** with 4-carboxylphenylboronic acid using palladium black as the catalyst (Scheme 147).[355] The reaction afforded biphenyl product **359** as a single enantiomer in very good yield (88%). Further elaboration of the product yielded the API LY503430, an AMPA potentiator.

3.3. Biocatalytic Approaches

Despite recent progress in the development of biological catalysts for the enantioselective introduction of fluorine,[356] examples of biocatalytic approaches for the elaboration of quaternary F-containing substrates are mainly based on lipase-catalyzed hydrolysis or transesterification reactions for the kinetic resolution of target molecules. In 1959, the Rigler group reported the dehydrogenation of compound **362** into 21-deoxytriamcinolone **363** by using *Nocardia coralline* (Scheme 148).[357] The desired product **398** was obtained in 53% yield after 11 h of fermentation.

In 1987, Kitazume and Yamamoto reported the hydrolysis of ester derivatives **364** into the corresponding carboxylic acids **365** by using the lipase-MY from *Candida cylindracea.*[358] The target compounds were studied for their activity as inhibitors of angiotensin converting enzyme (Scheme 149).

In 1985, Kamata, Nakamura, Susuki, and co-authors reported the oxidation of **366** into intermediate **367** in 17% yield by using the resting mycelium of *Corynespora cassiicola* (Scheme 150).[359] The steroid derivative **368** exhibited strong binding affinity for the cytoplasmic mineralocorticoid receptor of rat kidney and good aldosterone antagonist activity in an in vivo assay.

In 1997, the Haufe group described the enzymatic kinetic resolution of 1-acetoxy-2-aryl-2-fluoroalkanes by hydrolysis of *rac*-**369** (Scheme 151A) or by acet:ylation of the corresponding alcohol *rac*-**370** (Scheme 151B).[360] Lipase from *Pseudomonas cepacia*

(Amano PS) was found to perform the best for both cases. In general, 61 mg of enzyme per mmol of substrate was used in the hydrolysis reaction. Furthermore, a lower selectivity was observed using the lipase from *Candida cylindracea* (CCL), which afforded the opposite enantiomer in the hydrolysis process. In general, the selectivity of the process increased with the increase in chain length of the substituent of the quaternary center. Introduction of *i*-Bu substituent on the para-position of the phenyl ring (resembling the ibuprofen structure) resulted in low selectivity; however, a lower quantity of enzyme was used.

In 1998, Hirai, Takeuchi and co-authors described the synthesis of chiral 2-fluorinated **372** by desymmetrization of glycol systems **371** and **373** (Scheme 152).[361] The enantioselective hydrolysis of 2-fluorinated diacetates **371** catalyzed by the lipase from porcine pancreas (PPL) afforded the **372** in up to 96% ee (Scheme 152A). On the other hand, the acetylation of 2-fluorinated 1,3-propanediols **373** with vinyl acetate catalyzed by lipase PS afforded the corresponding monoalcohols **372** in up to 95% ee (Scheme 152b).

In 1998, Guanti, Narisano, and co-authors studied the desymmetrization of fluorinated polyfunctionalized C3 synthons by lipase mediated asymmetric monohydrolysis of 2-aryl-2-fluoromalonic acid diesters **373** (Scheme 153A) or monoacetylation of 2-aryl-2-fluoro-1,3-propanediols **376** (Scheme 153B).[362,363] The most efficient lipase was PPL (lipase from porcine pancreas) supported on Celite (S-PPL), which afforded the chiral product in up to 96% ee.

The Haufe group reported the enzymatic kinetic resolution of different racemic 2-fluoro-2-phenylcyclopropyl derivatives by lipase-catalyzed transesterification or hydrolysis (Scheme 154). The best results were achieved using Amano PS in *tert*-butyl methyl ether (MTBE) as solvent.[364,365]

4. CONCLUSIONS

Over the past decade, fluoro-organic methodology has been growing at an extraordinary pace. Now it is commonly recognized that fluorine chemistry is in a league of its own, as fluorine and fluorine-containing groups cannot be considered as merely halogen substituents in terms of both chemical and biological properties. Thus, in most cases, synthesis of tailor-made fluoro-organics requires the discovery of rather unique, novel approaches or significant modifications of some general methods. This aspect of fluorine chemistry is particularly underscored by the invention of chiral electrophilic fluorination reagents, presented as discussed in the first part of this Review. Retrosynthetically attractive, the concept of electrophilic fluorination has received a great deal of attention, resulting in a reasonably good mechanistic validation for the design of new reagents and reaction conditions. Nevertheless, while methodologically very impressive, the electrophilic fluorination approach is still virtually exclusively limited to the fluorination in the α-position to a carbonyl group of structurally rigid aromatic/cyclic substrates. Moreover, with the exception of a handful of examples, the values of stereochemical outcome are still below the synthetically useful level. Most of the progress in this area has been made in catalyst design using more or less standard set of substrates. While this situation is rather logical and allows comparing the catalytic systems, the expansion of the substrate generality is highly

desirable and expected in the near future. Some exciting progress in this direction has already been achieved with the invention of the tandem processes for functionalization of C=C bonds, offering innovative synthetic solution for previously inaccessible structurally complex and biologically relevant molecules. Asymmetric elaboration of C–F containing substrates, constituting the second major part of this Review, is a more matured area of fluorine chemistry, methodologically overlapping with general organic asymmetric synthesis. Thus, approaches based on application of chiral auxiliaries are traditionally reliable, offering synthetically useful solutions for preparation of target molecules featuring quaternary C–F stereogenic centers. Moreover, the possibility of purification of diastereomeric intermediates adds a certain advantage in the preparation of enantiomerically pure samples ready for biological applications. In the asymmetric catalysis area, some particular progress has been achieved in developing Mannich-type additions, allowing synthesis of highly biologically relevant fluorinated amino-compounds. Similar to electrophilic fluorination, this area is also still not very versatile in terms of substrates generality, mostly featuring various transformations around a rather reactive carbonyl group. In the area of biocatalytic transformations, one can notice a particular progress made in enzymatic desymmetrization of substrates containing quaternary C–F pro-chiral carbon. Considering a usually low cost-structure associated with of biocatalytic methods, this approach seems to be of great practical potential. In general, the research critically discussed in this Review represents one of the most intensely competitive areas in the current organic chemistry, oriented to discovery of new fluorinated structural motives and their application in the design of new generations of bioactive compounds.

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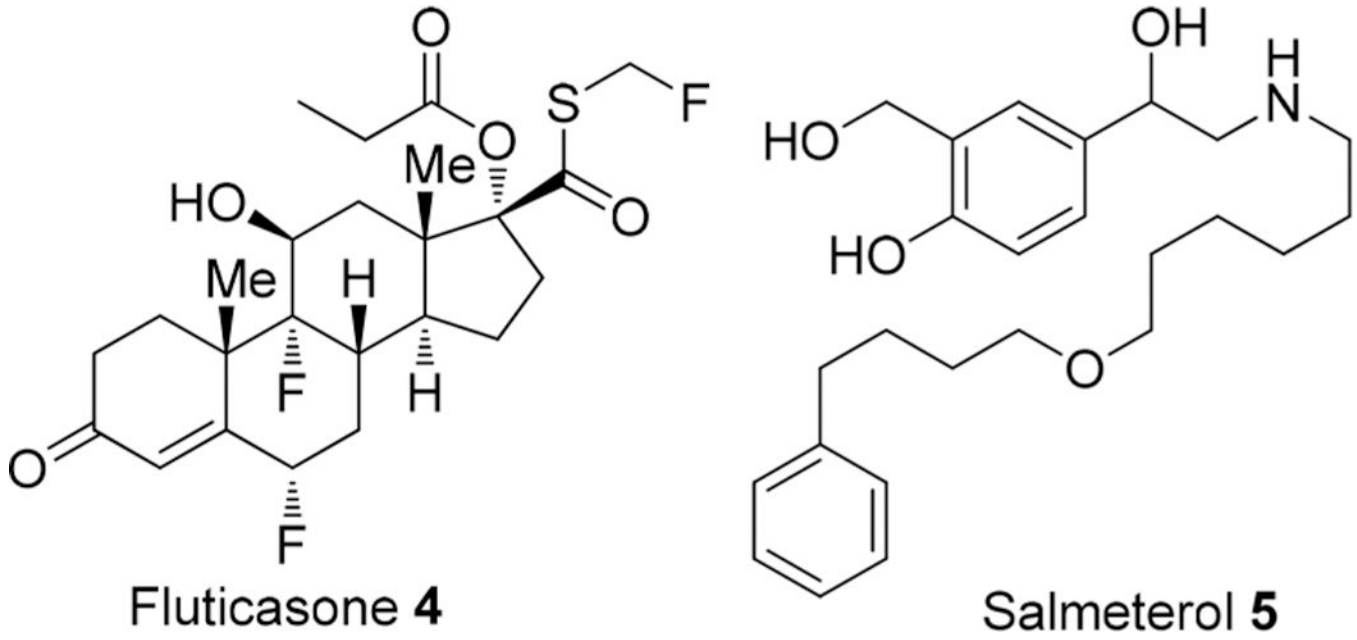


Figure 1.
Structures of fluticasone propionate **4** and salmeterol **5**.

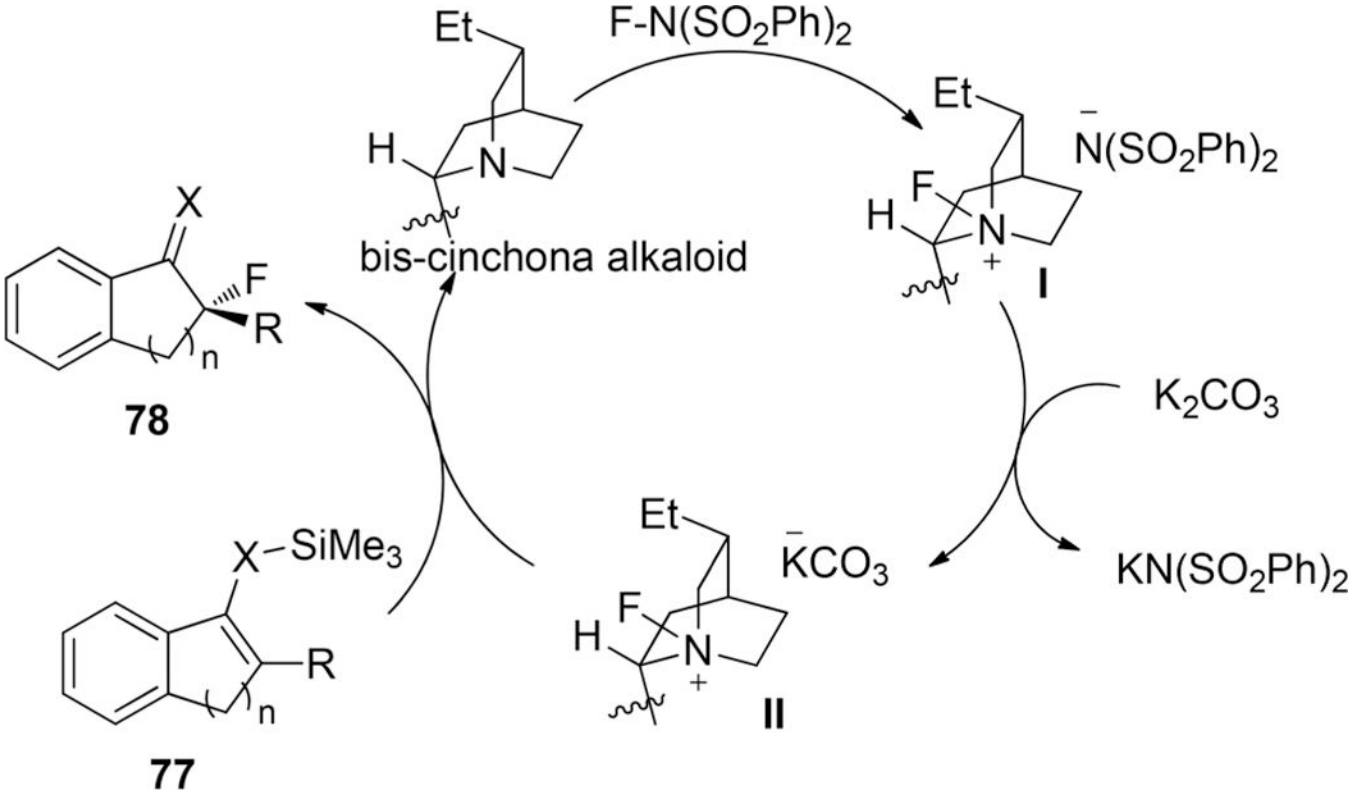


Figure 2.

A plausible catalytic cycle for cinchona alkaloids catalyzed enantioselective fluorodesilylation.

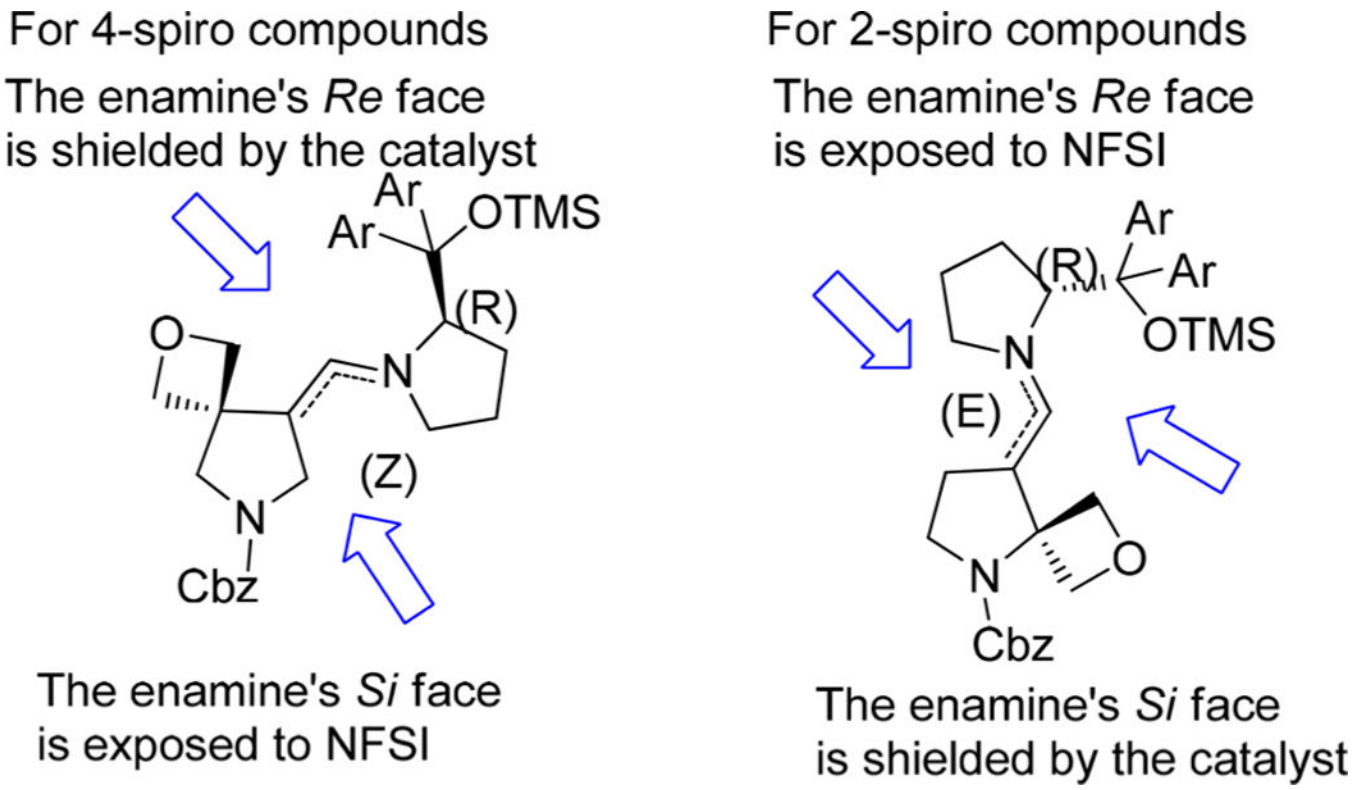


Figure 3.
Enamine transition-state geometries to rationalize the enantioselectivity.

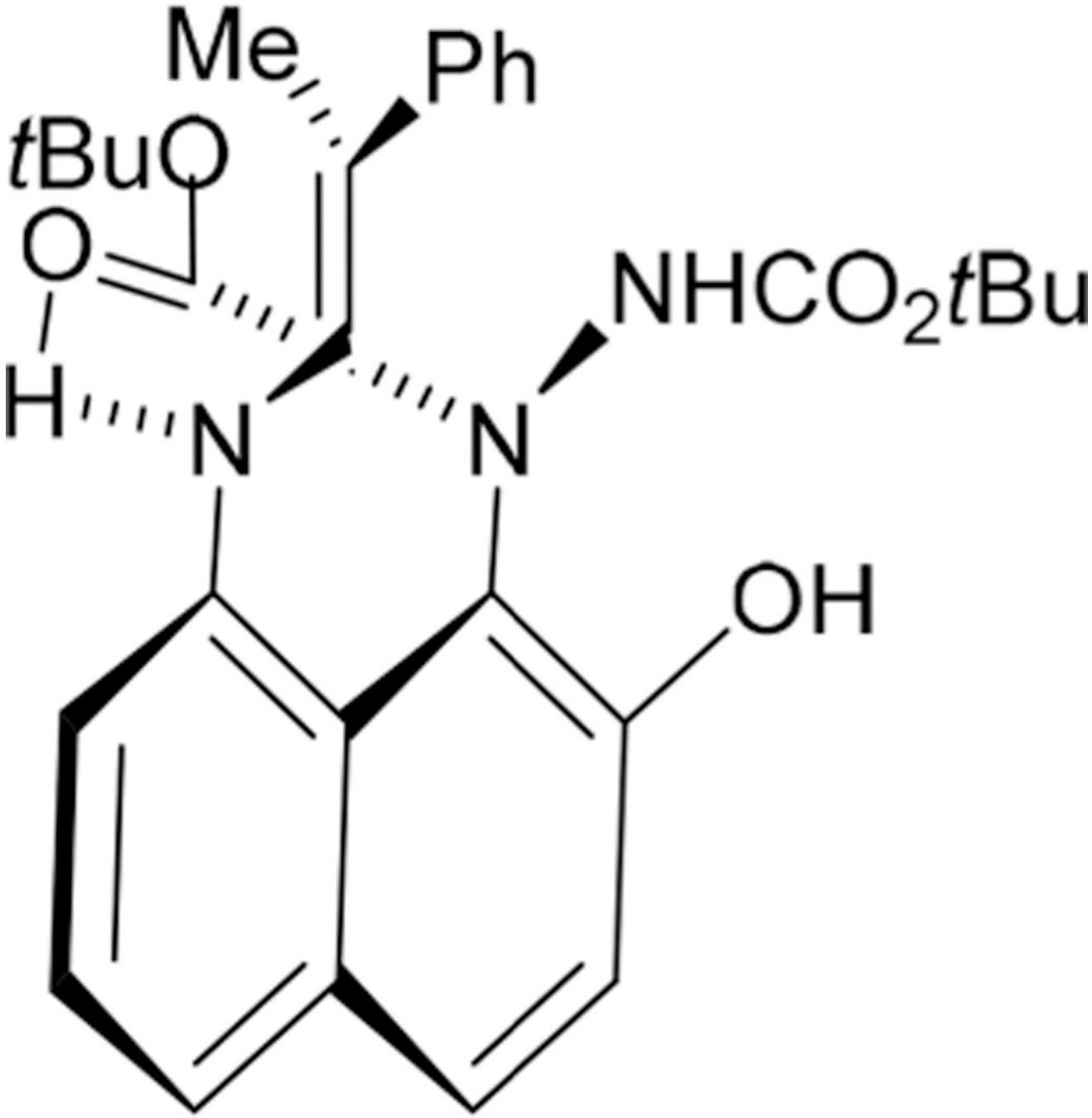


Figure 4.
Possible enamine intermediate showing a proposed intramolecular hydrogen bond.

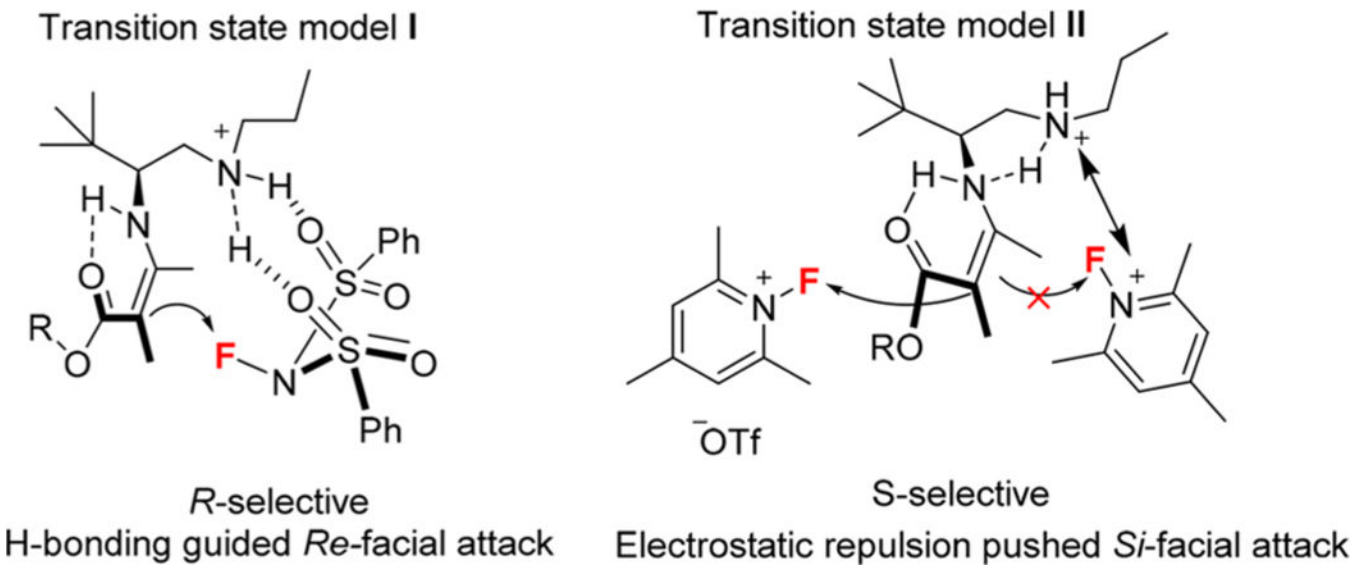


Figure 5.
Proposed transition states (I and II) for the two enantioselectivity switch fluorination reactions.

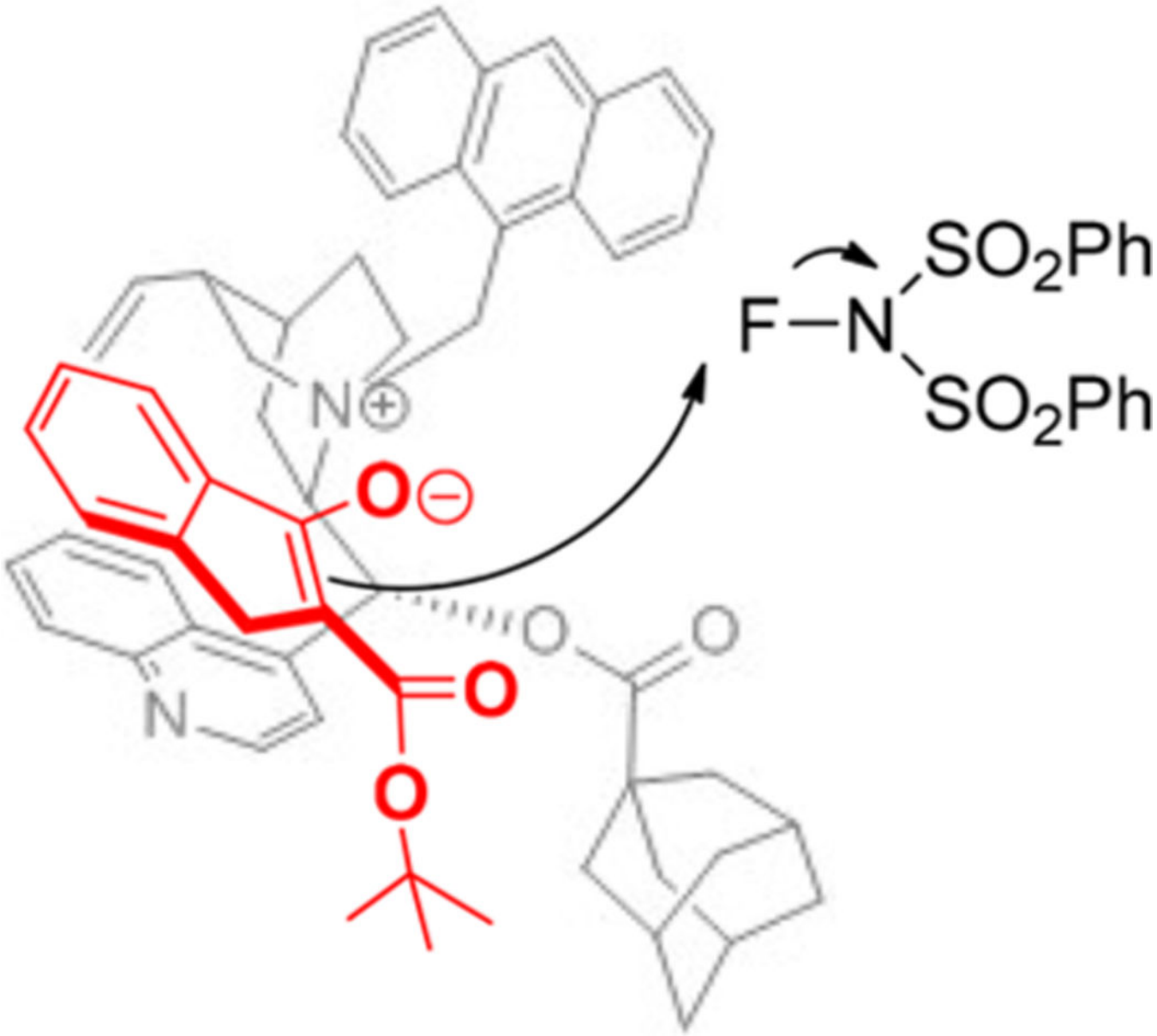


Figure 6.
Proposed transition model for asymmetric fluorination.

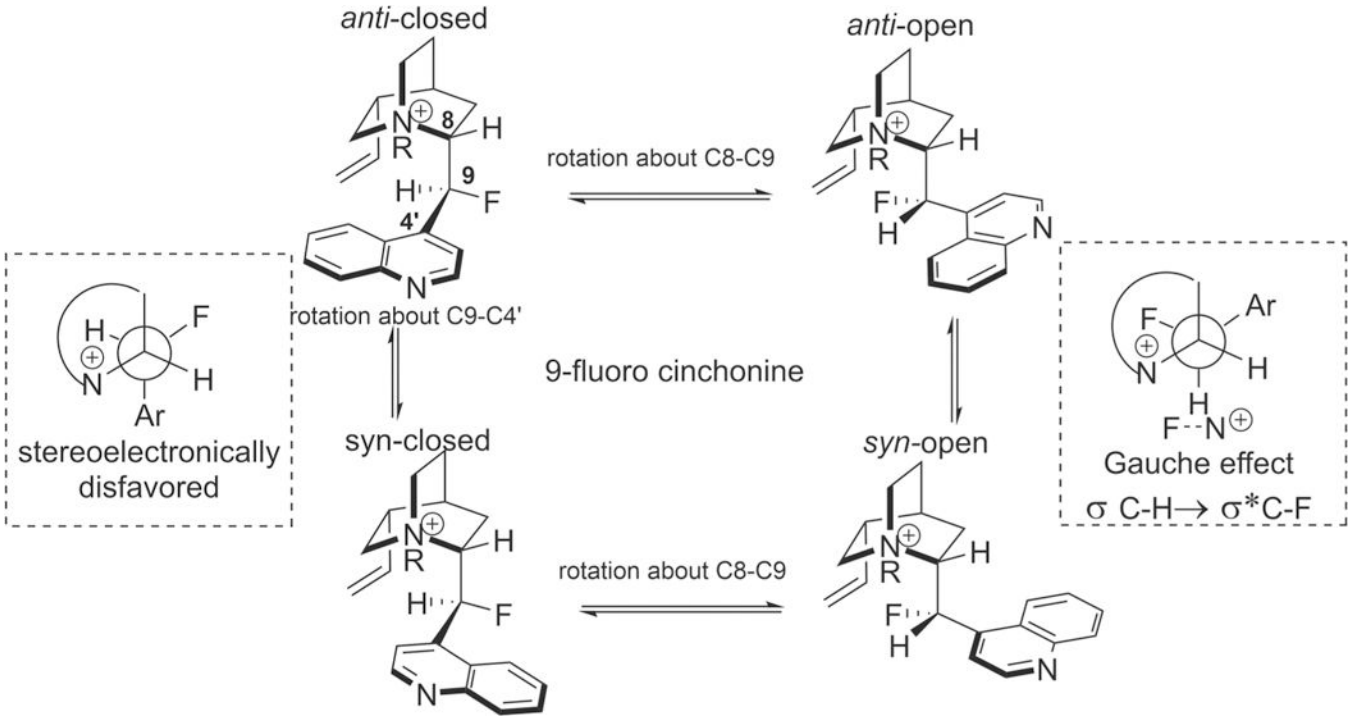


Figure 7.
Fluorine–ammonium ion gauche effect controlling the conformation of 9-fluoro-cinchonine.

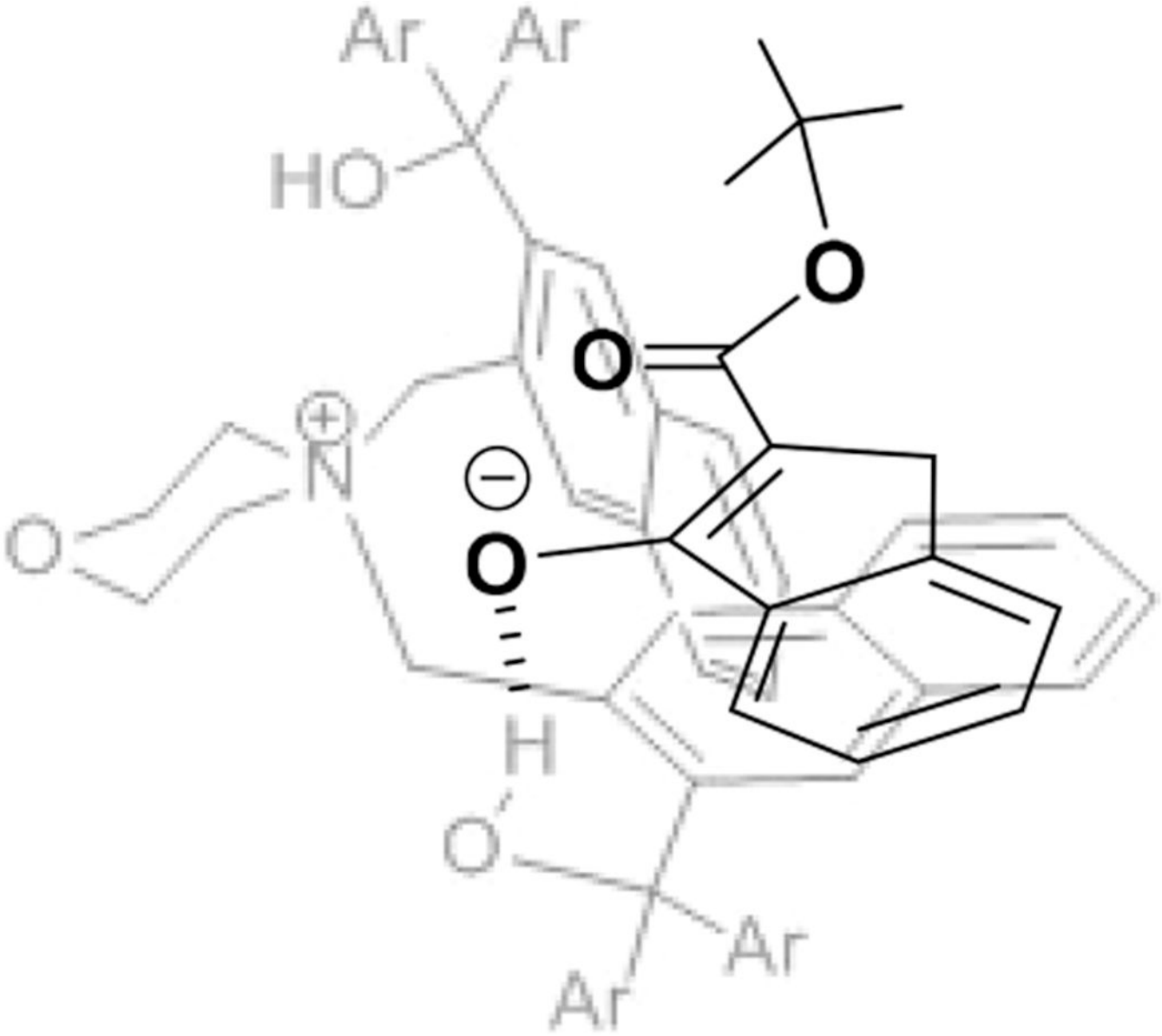


Figure 8.
Proposed transition state structure for asymmetric fluorination of β-keto esters.

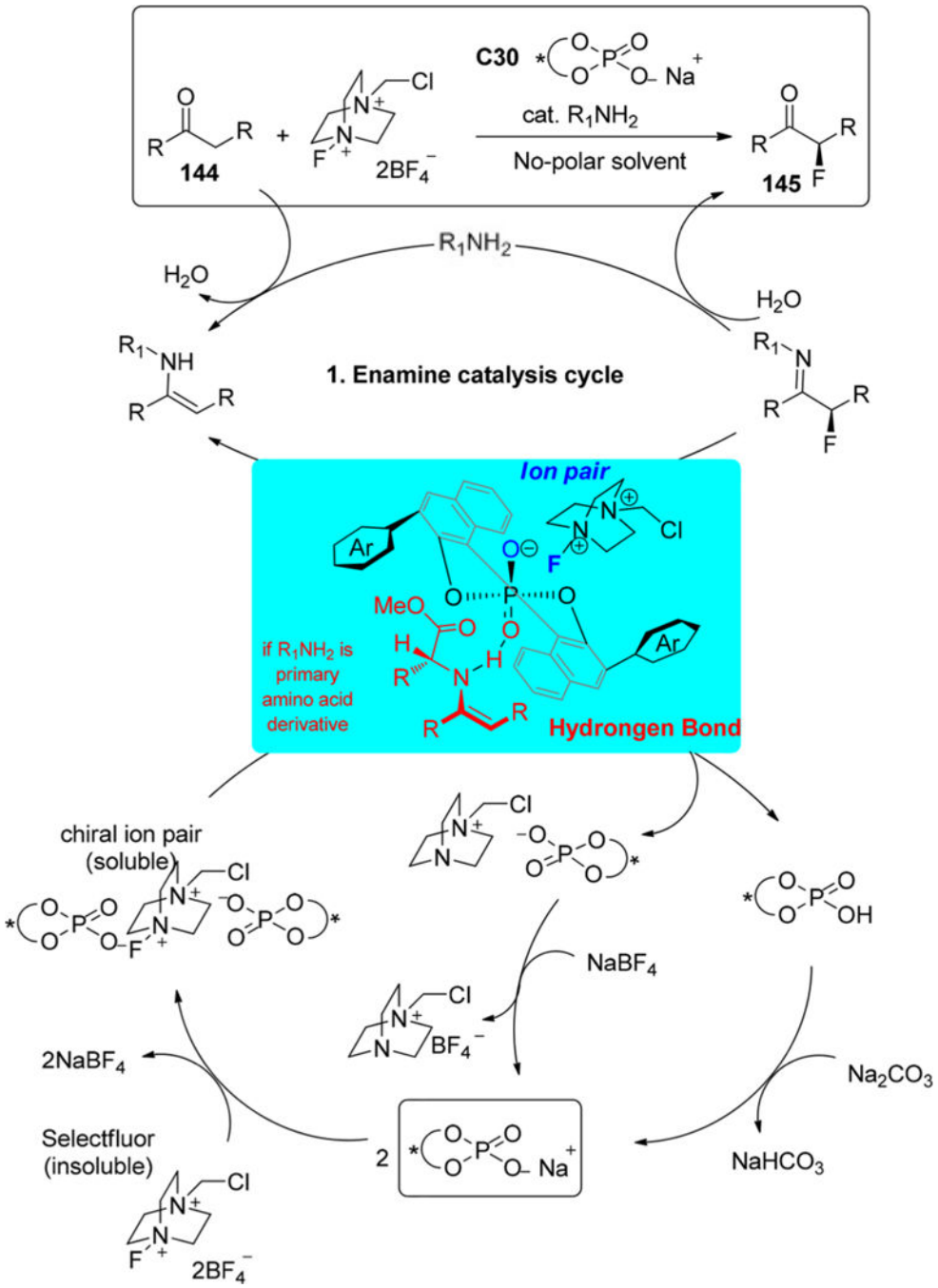


Figure 9.
Proposed dual catalytic cycle for the enantioselective fluorination of ketones.

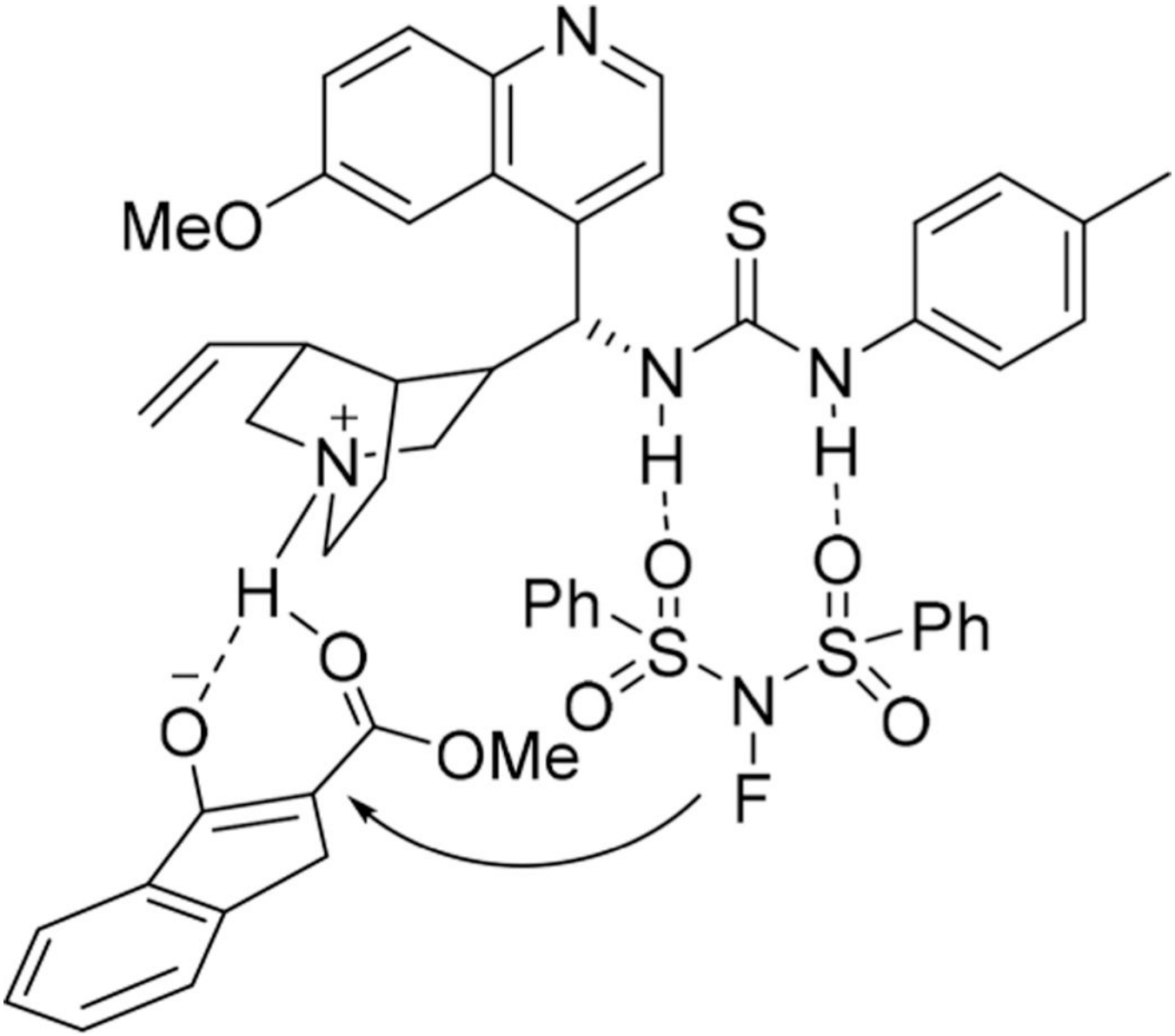


Figure 10.
Proposed transition state for asymmetric fluorination catalyzed by thiourea–tertiary amine.

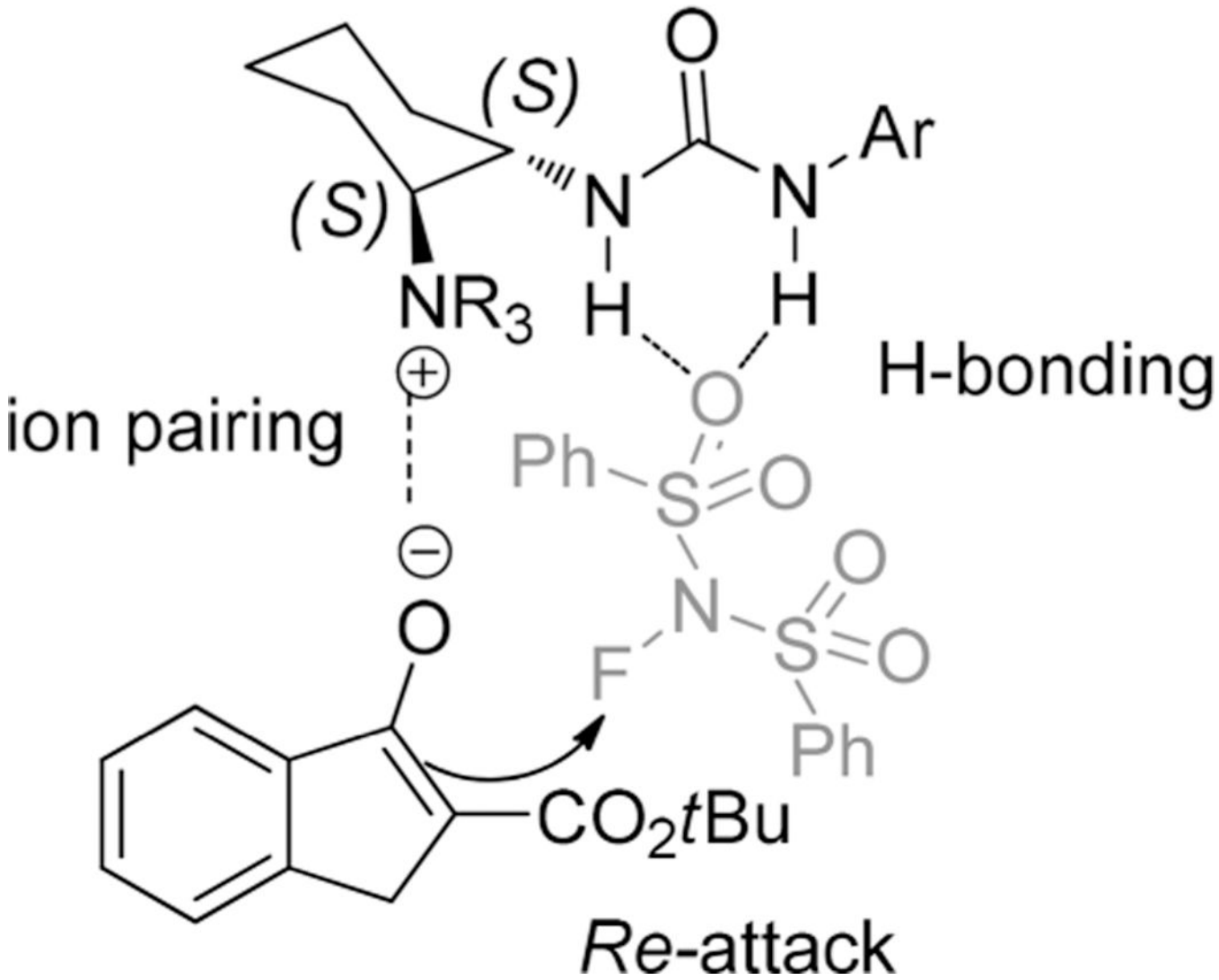


Figure 11.
Proposed activation model of the urea-containing chiral quaternary ammonium salt.

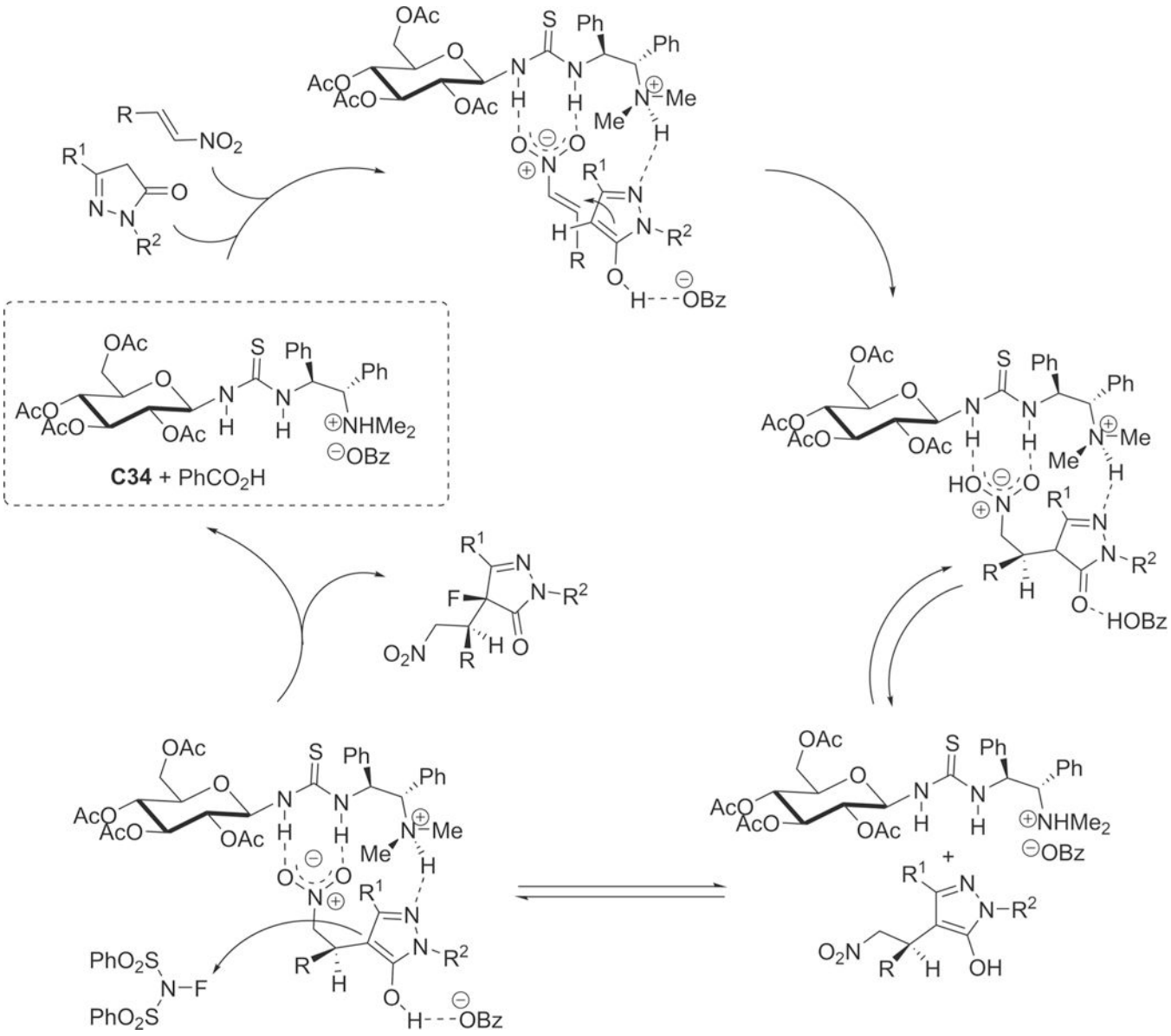


Figure 12.
Proposed mechanism for the 1,4-addition and fluorination sequence.

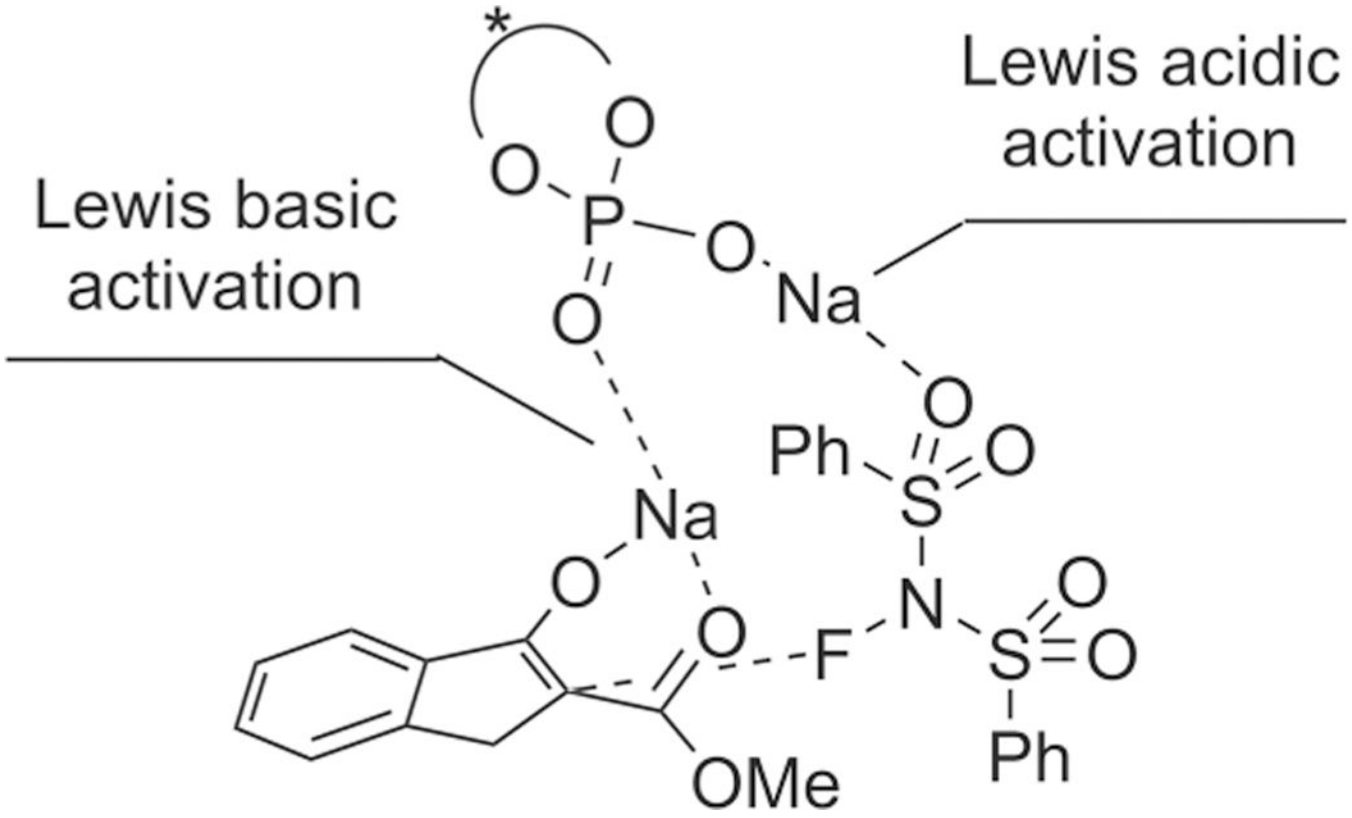


Figure 13.
Proposed transition state mode for fluorination catalyzed by chiral sodium phosphate.

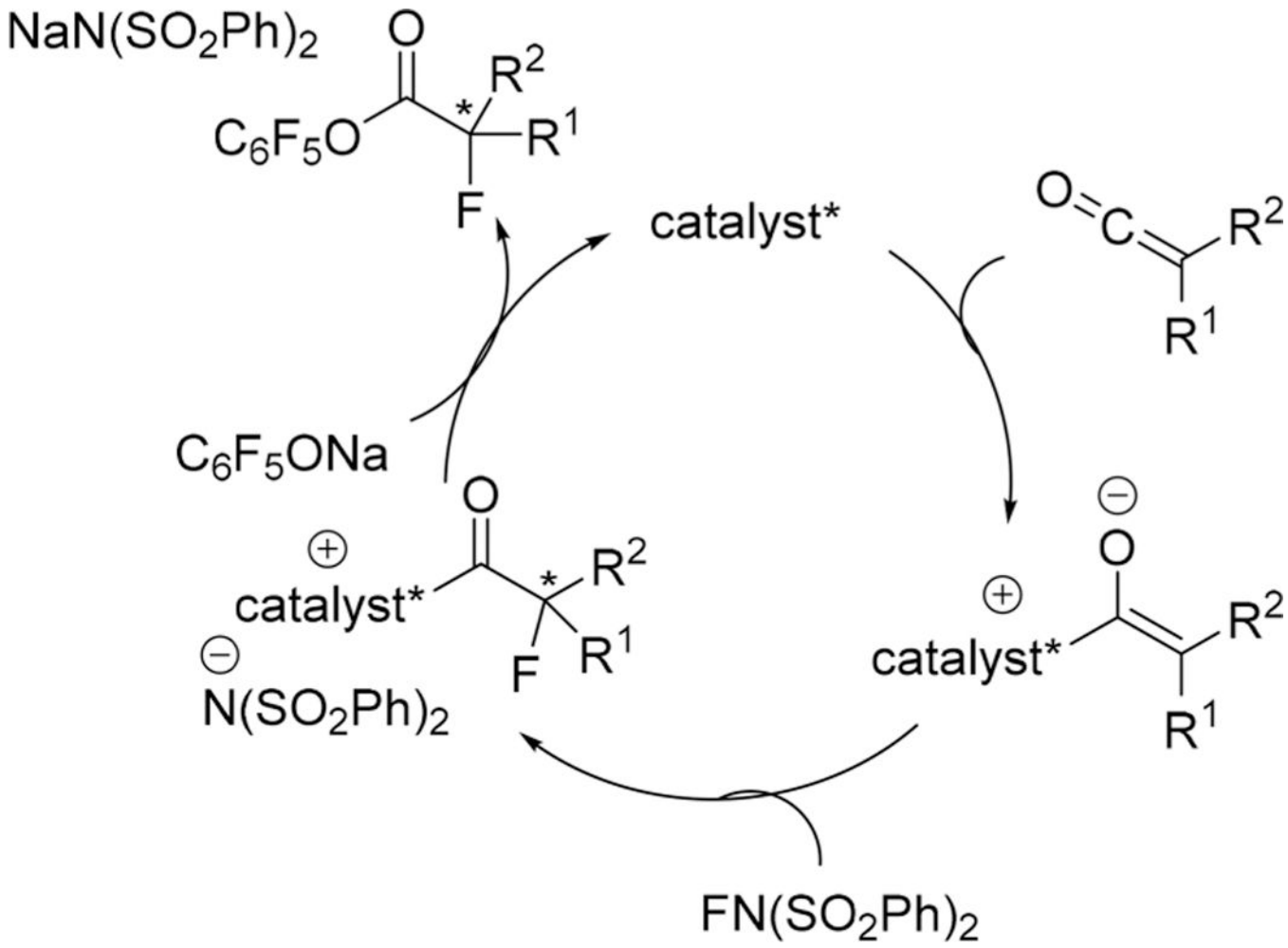


Figure 14.
Possible mechanism for the **C41**-catalyzed enantioselective fluorination of ketenes.

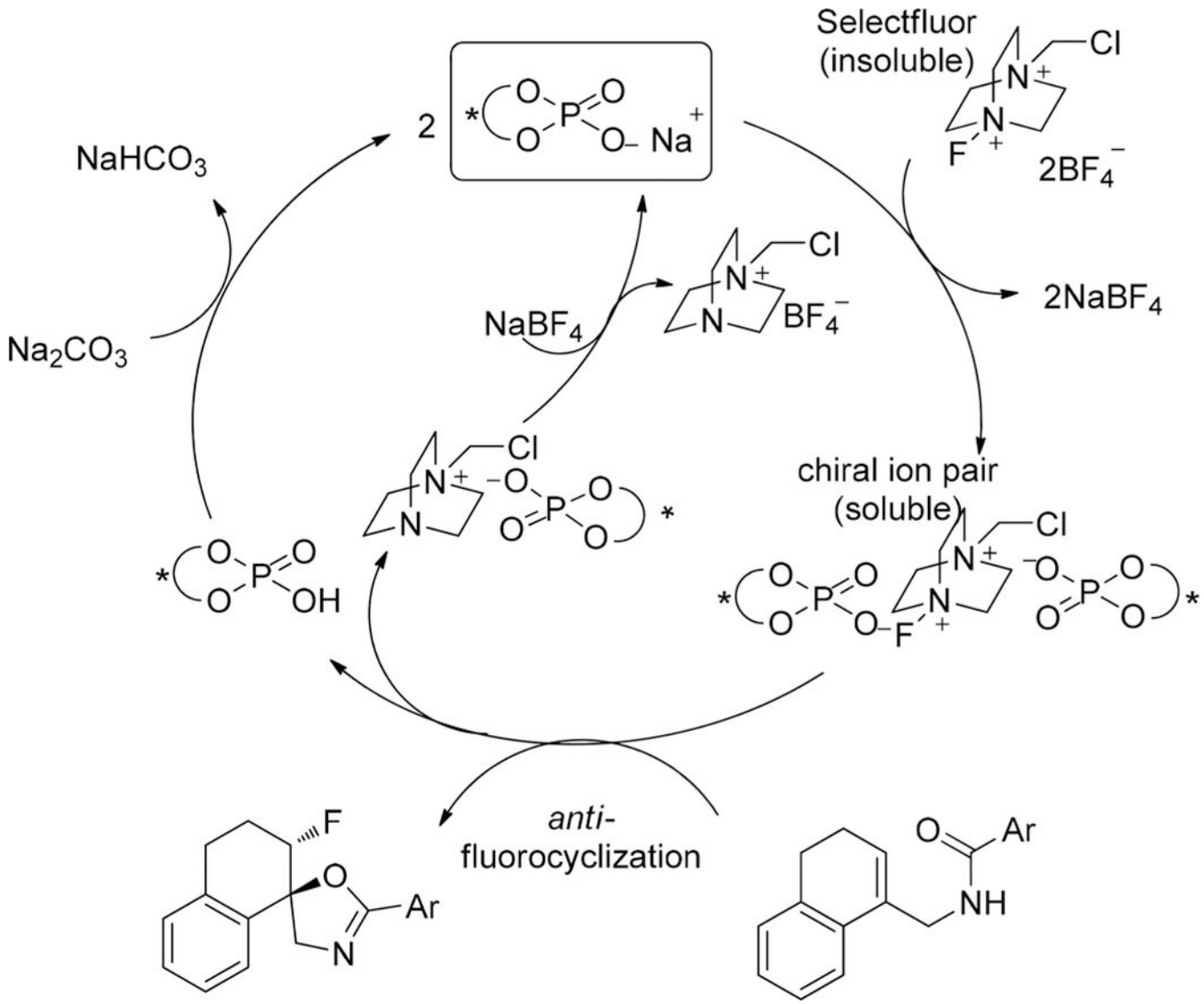


Figure 15.
Proposed catalytic cycle for chiral anion phase-transfer catalyst.

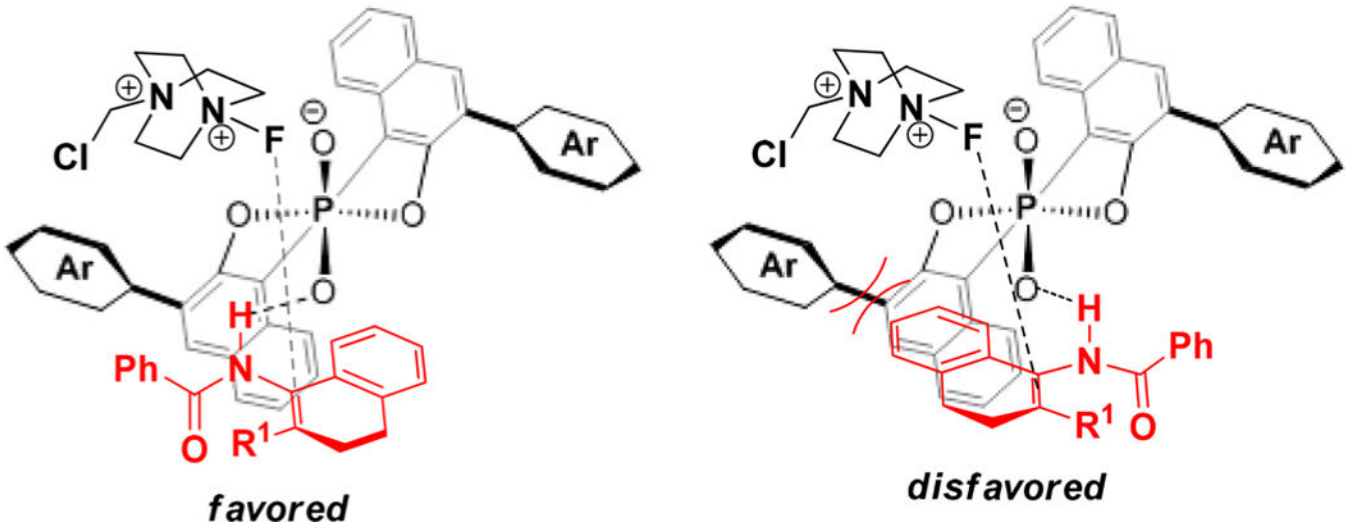


Figure 16.
Proposed transition state model for asymmetric fluorination of cyclic enamides catalyzed by anionic phase-transfer catalyst.

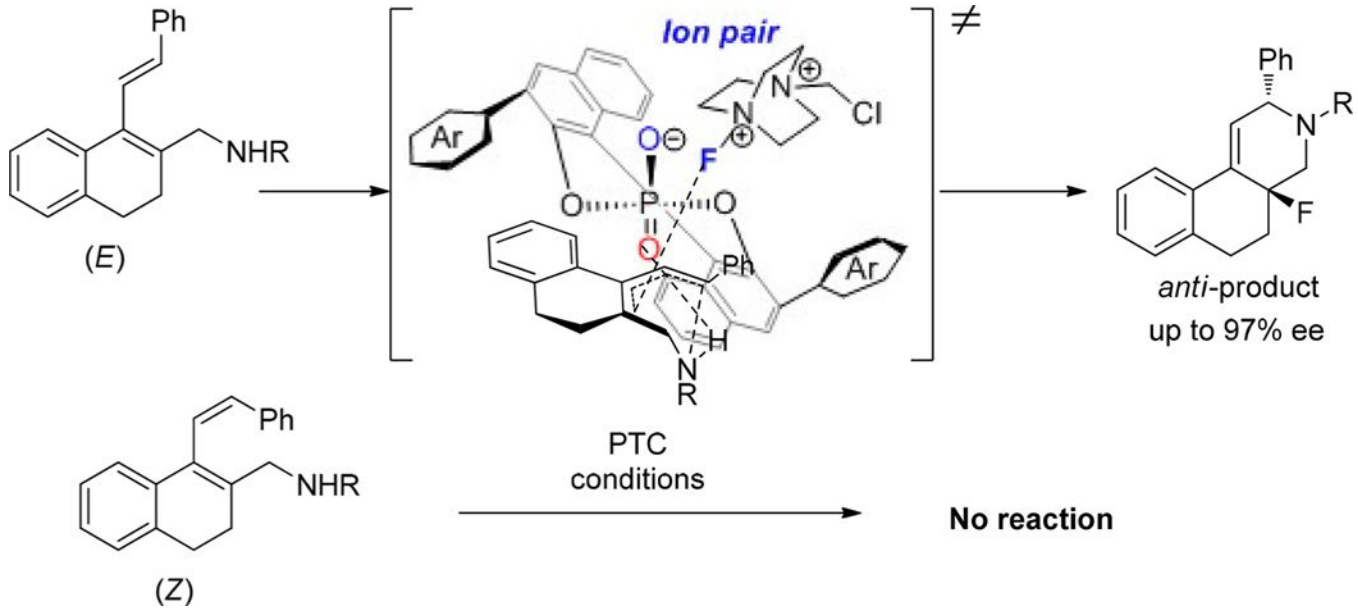


Figure 17.
Suggested origin of diastereo- and regioselectivity for fluoro-amination.

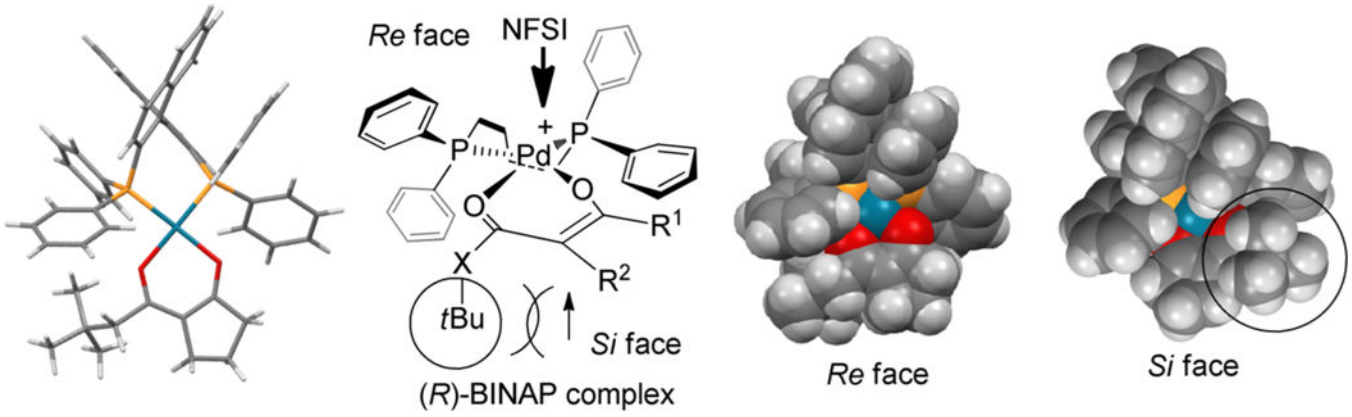
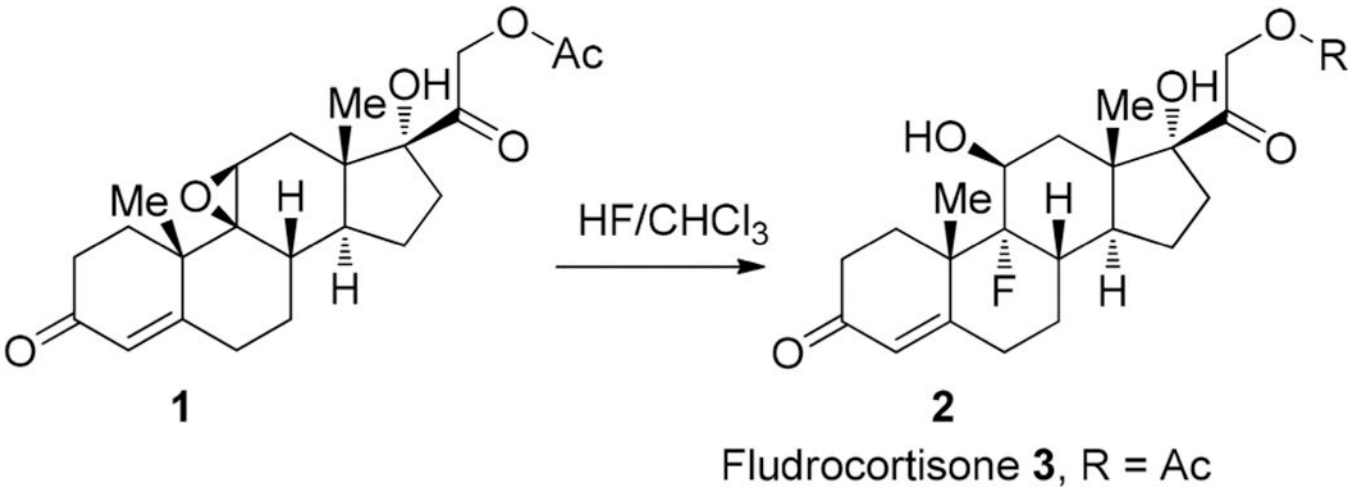
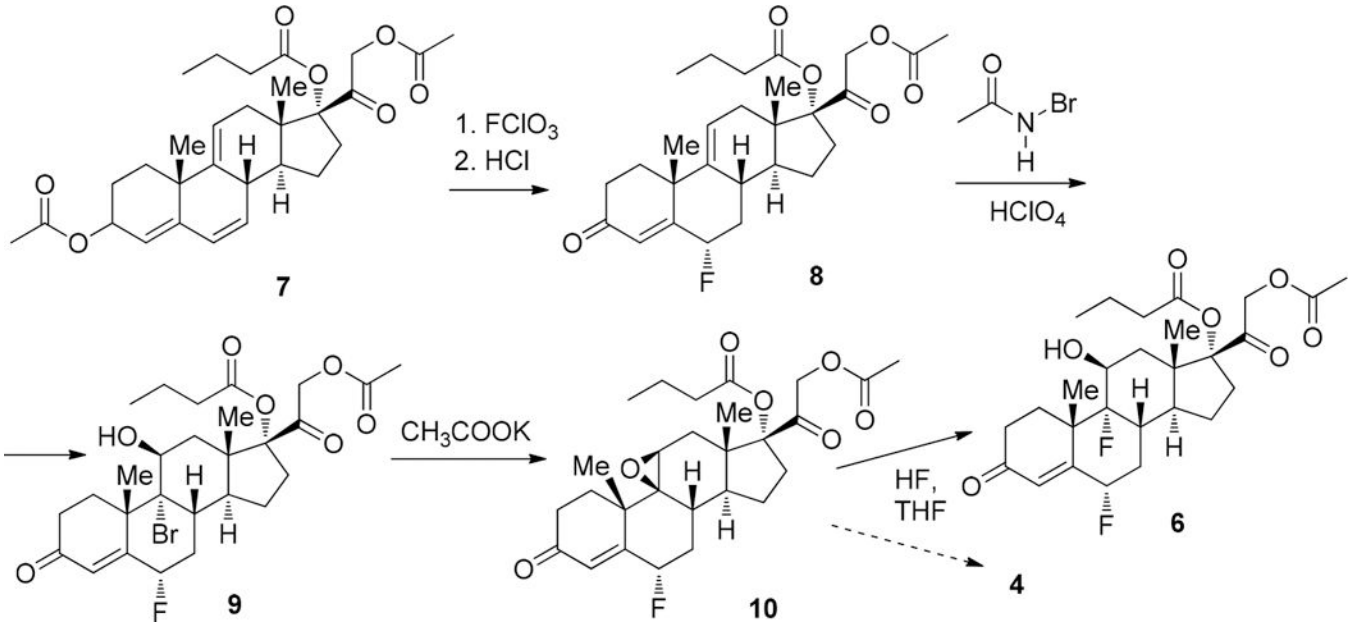


Figure 18.

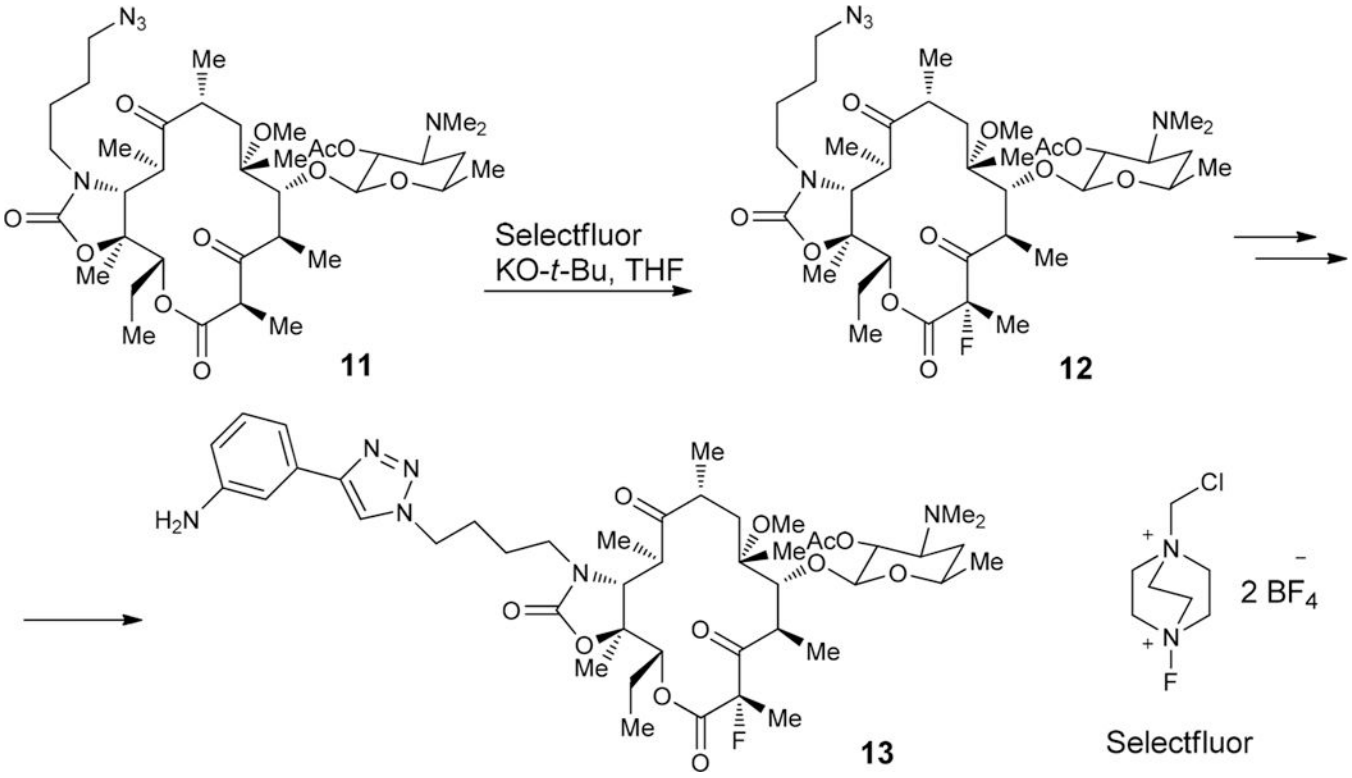


Scheme 1.
Synthesis and Structure of Fludrocortisone 3

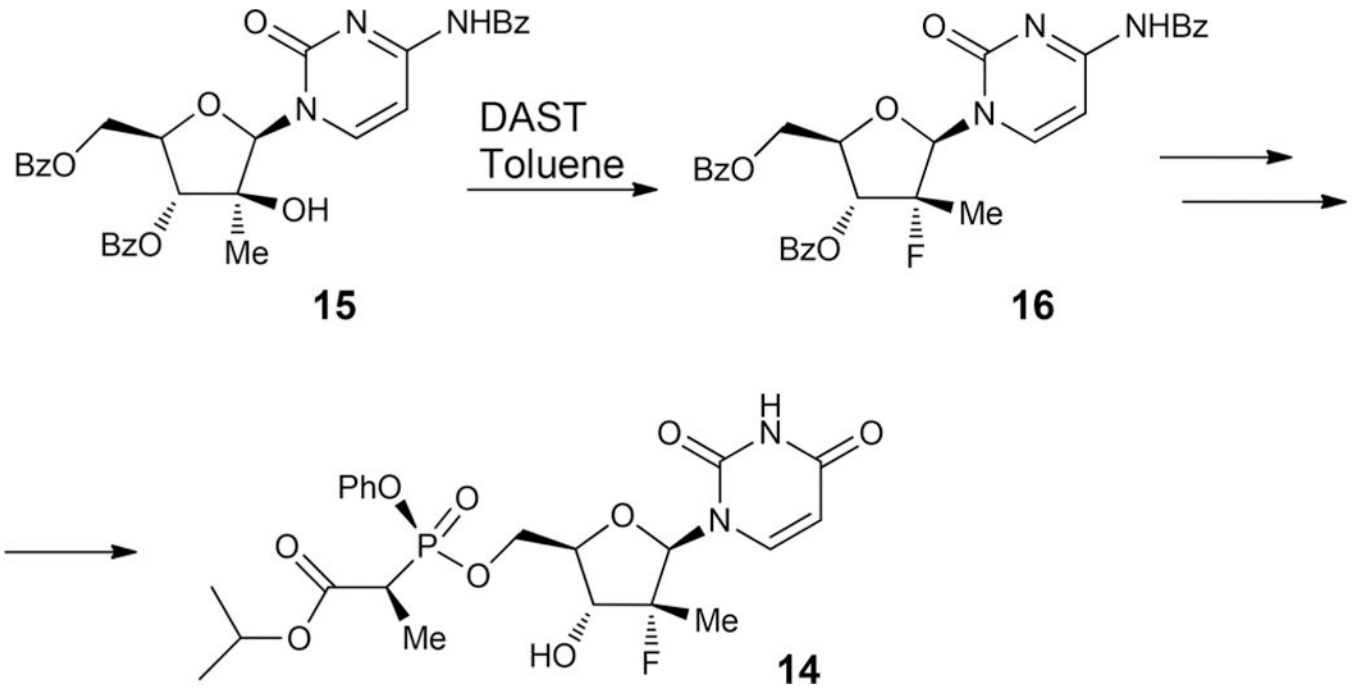


Scheme 2.

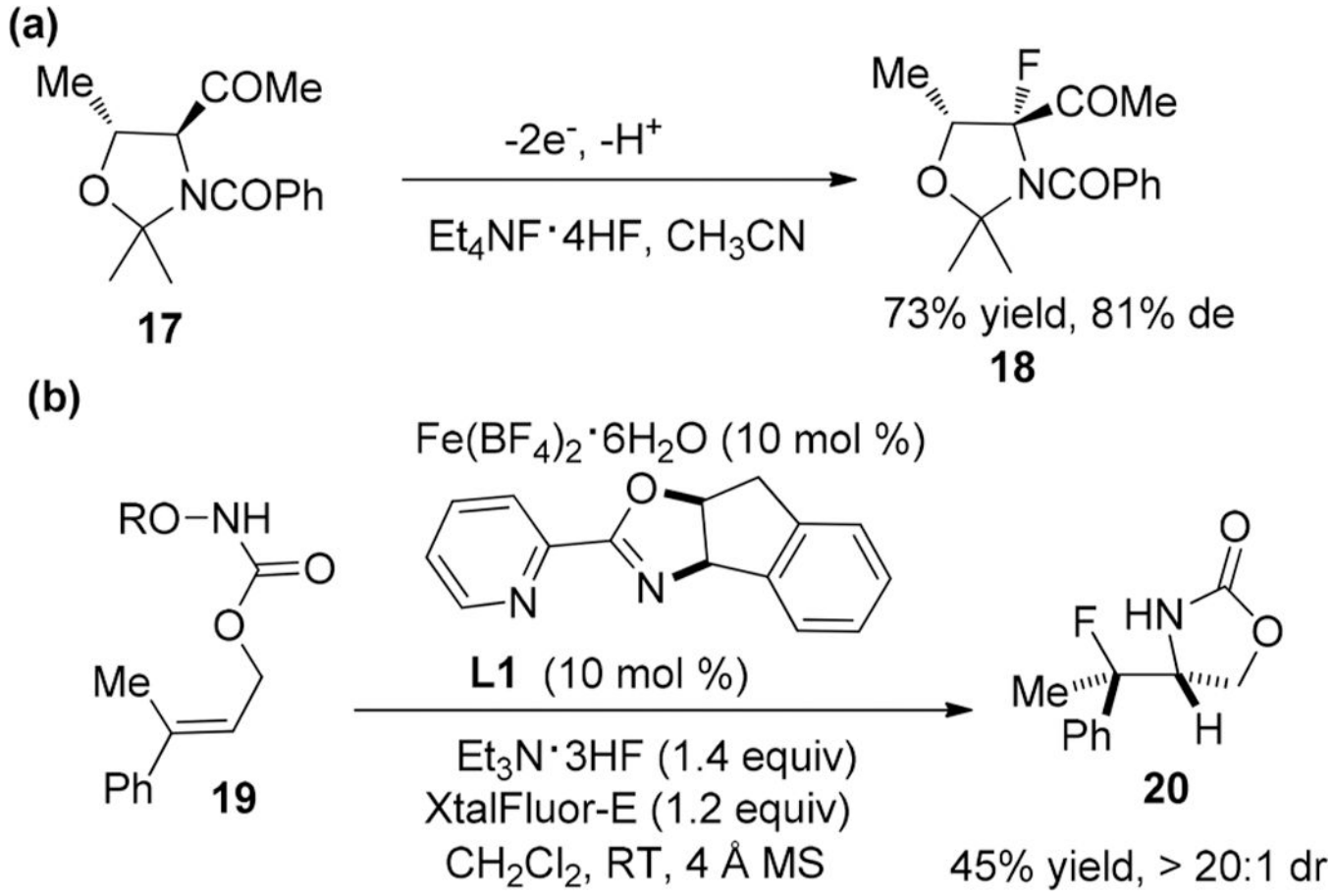
Key Fluorination Steps in the Synthesis of Fluticasone 4 and Difluprednate 6



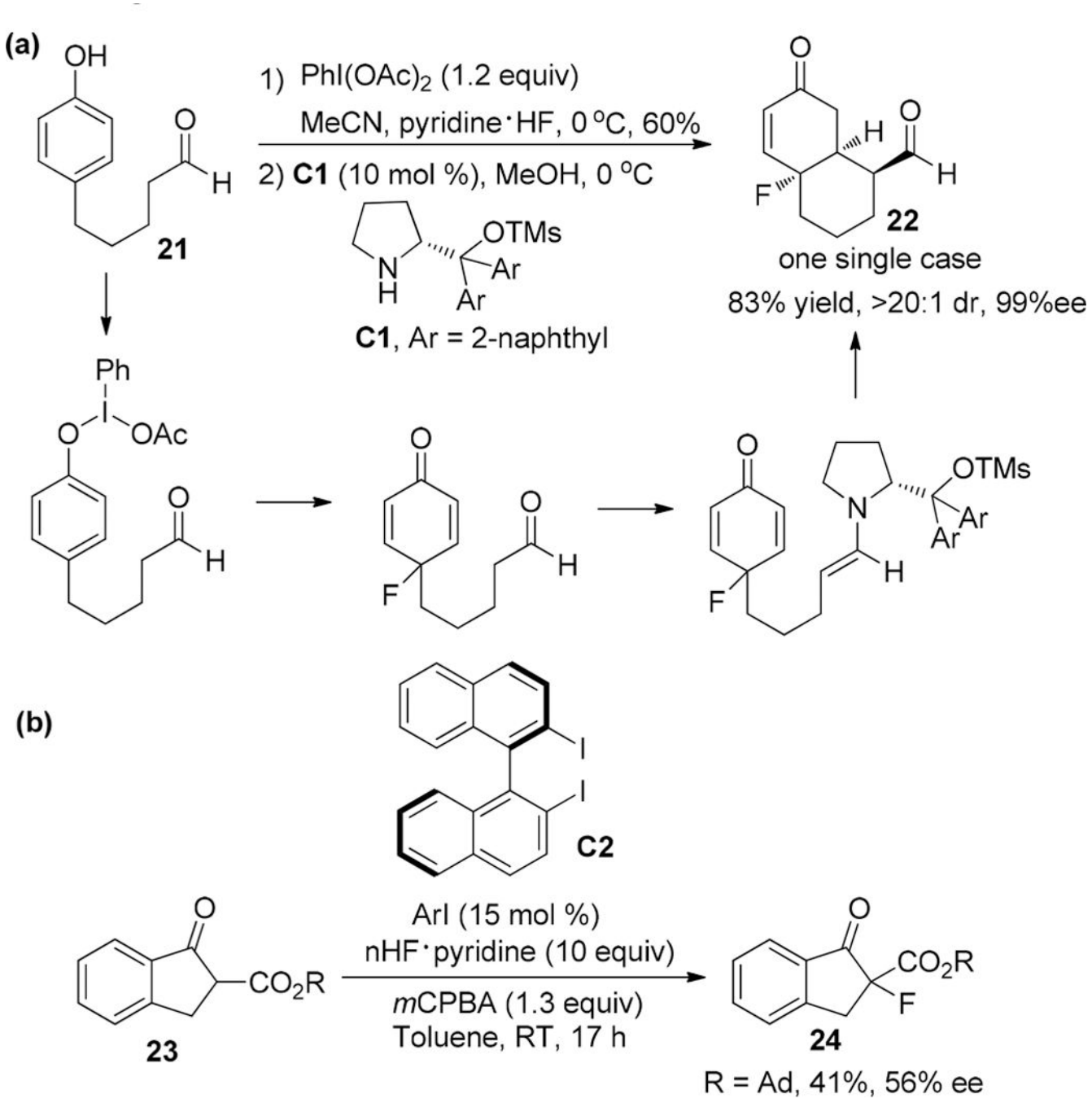
Scheme 3.
Key Fluorination Step in the Synthesis of Solithromycin 13



Scheme 4.
Key Fluorination Step in the Synthesis of Sofosbuvir 14

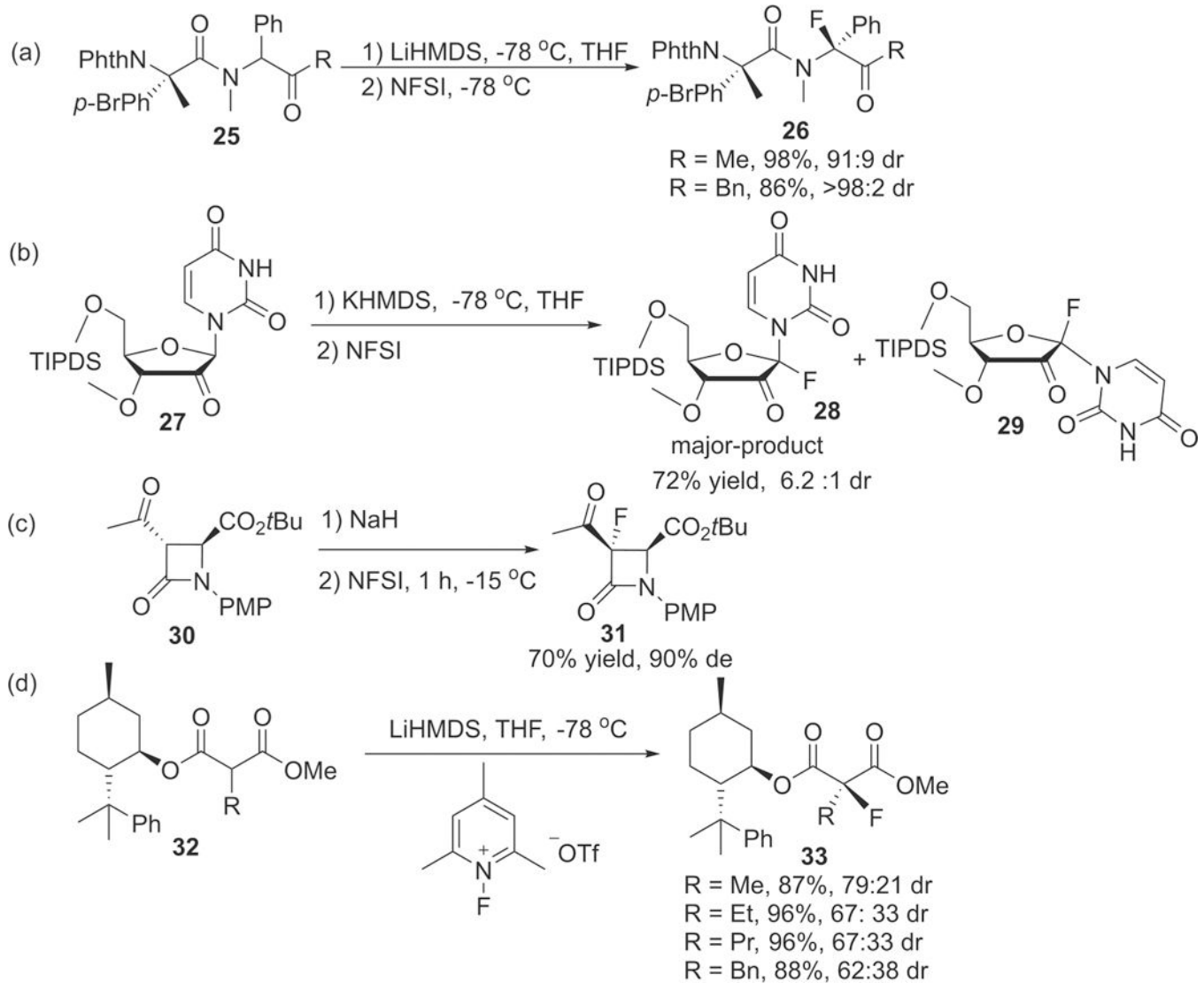


Scheme 5.
Synthesis of α-Monofluorinated Compound 18 (a) and the Target Fluorinated Product 20 (b)



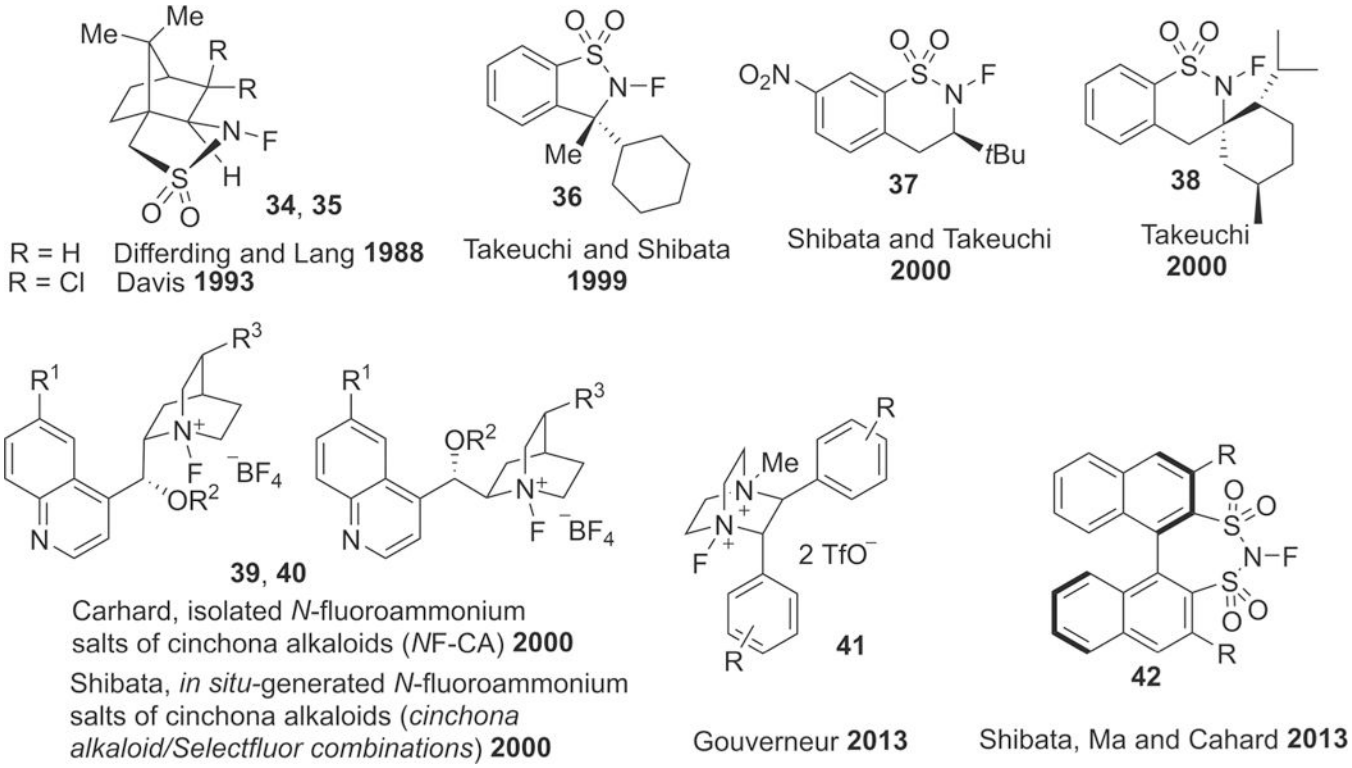
Scheme 6.

Intramolecular Michael Addition Sequence Leading to Fluorinated Product 22 (a) and α-Fluorination Leading to Compound 24 (b)

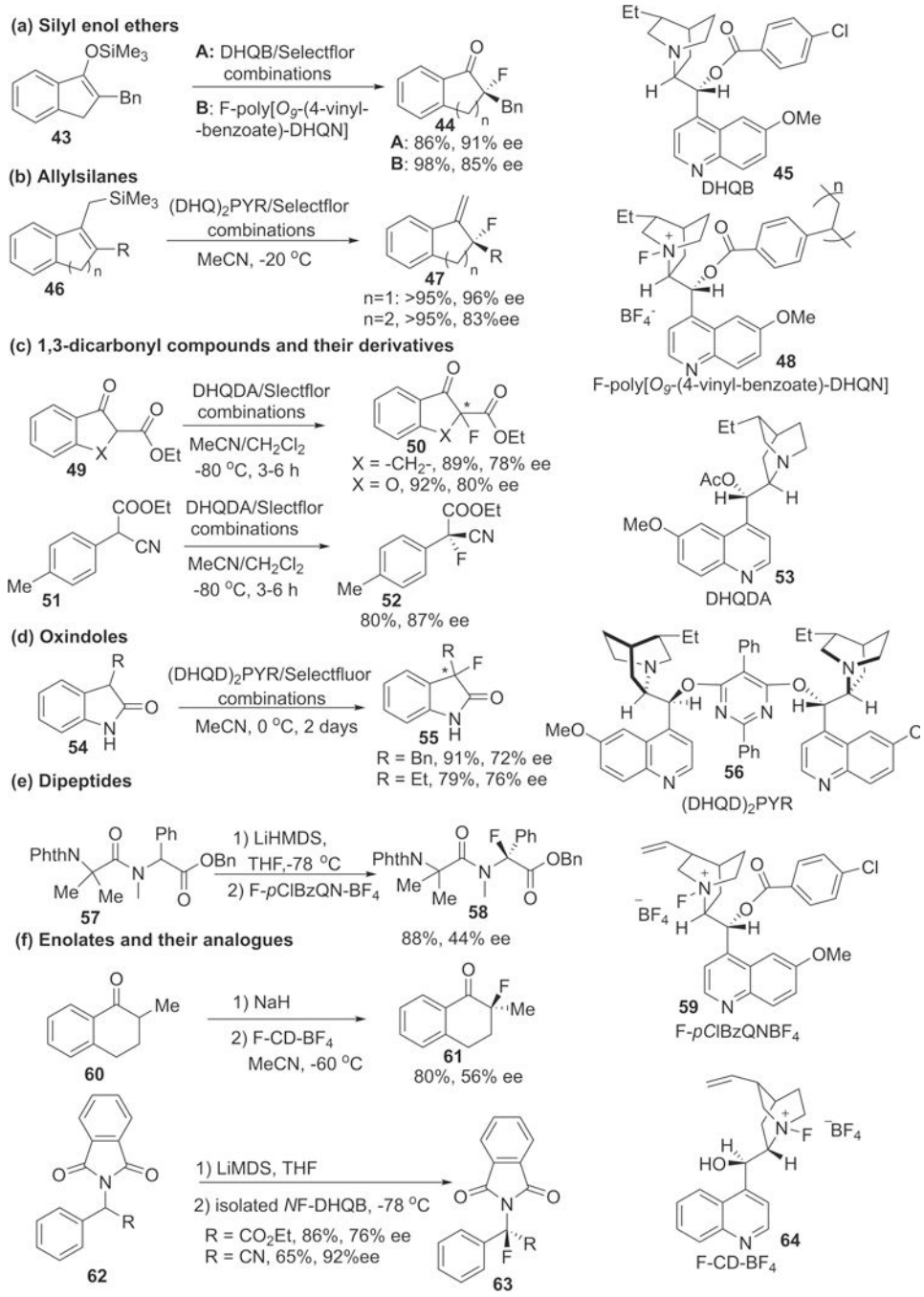


Scheme 7.

Asymmetric Electrophilic Fluorination Affording Compounds 26 (a), 28 (b), 31 (c), and 33 (d)

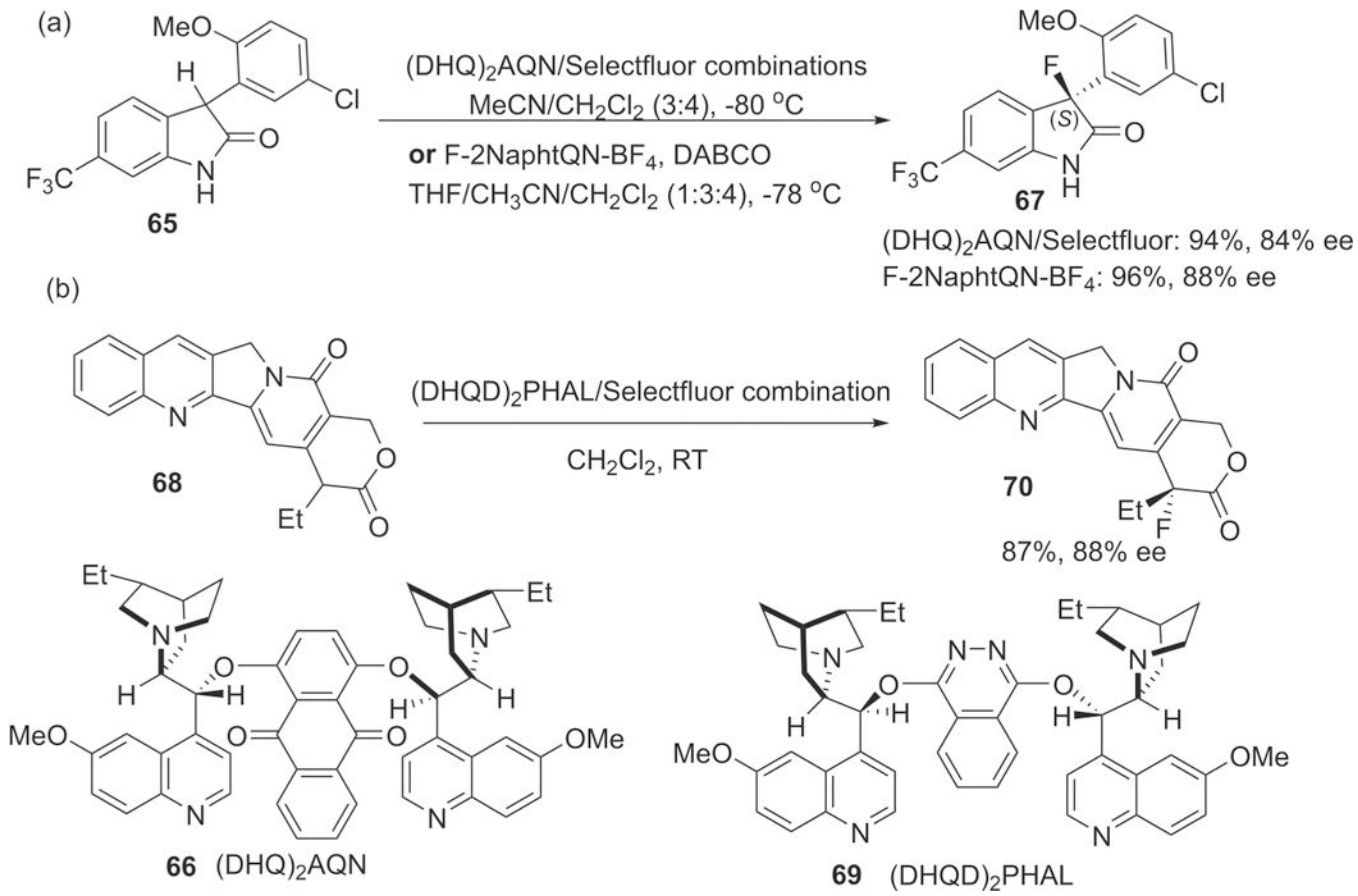


Scheme 8.
Chiral N–F Reagents for Enantioselective Fluorination



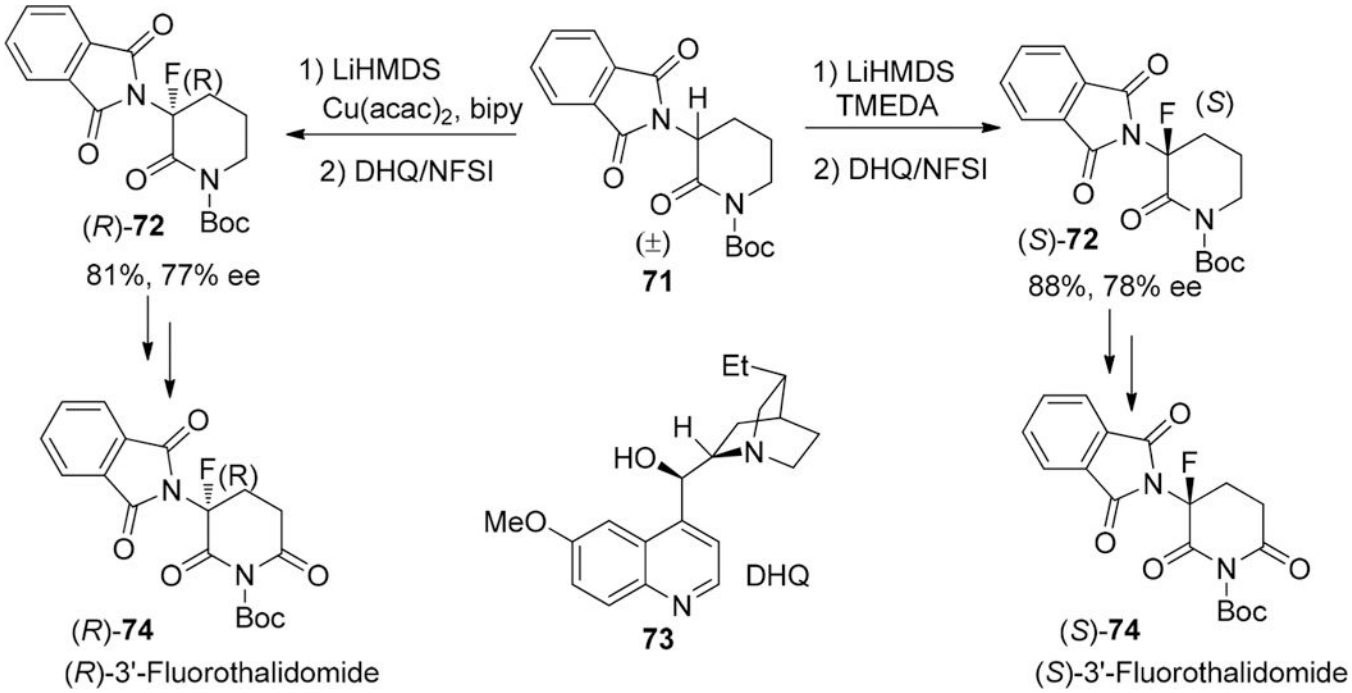
Scheme 9.

Substrate Types for Enantioselective Fluorination Using N–F Reagents: Silyl Enol Ethers (a), Allylsilanes (b), 1,3- Dicarbonyl Compounds (c), Oxindoles (d), Dipeptides (e), and Enolates (f)

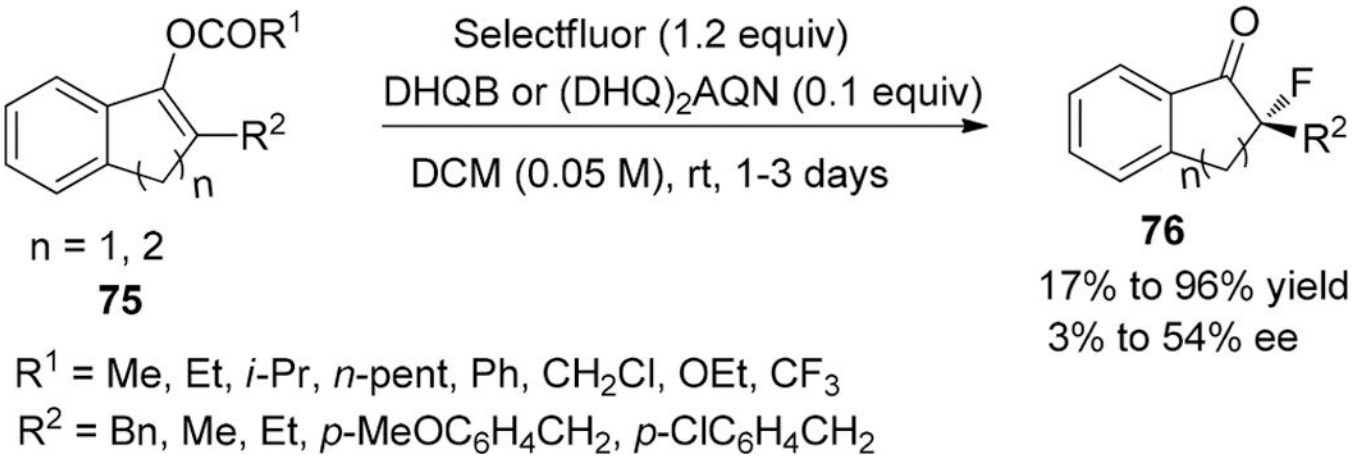


Scheme 10.

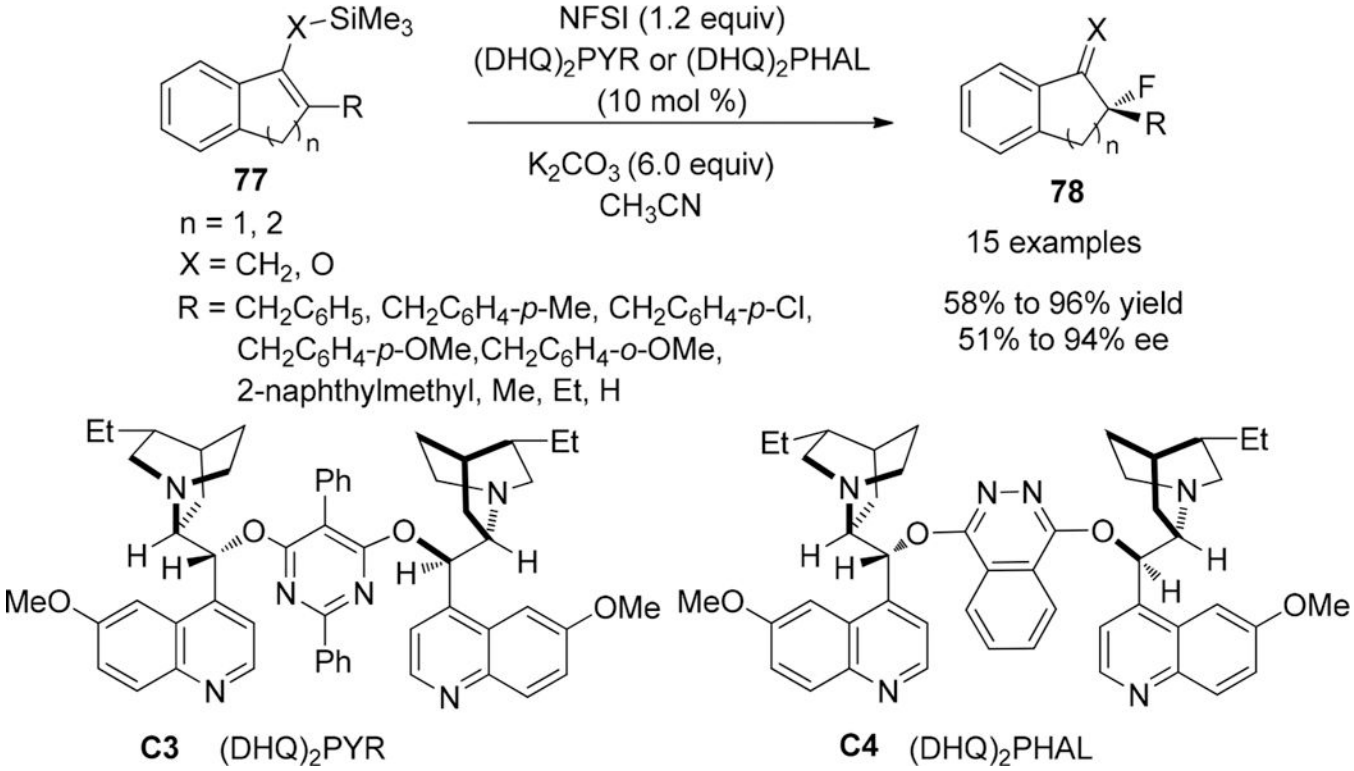
Enantioselective Fluorination Using Cinchona Alkaloid Derived Reagents: Structural Types 65 (a) and 68 (b)



Scheme 11.
Preparation of Enantiomers of 3-Fluorothalidomide 74

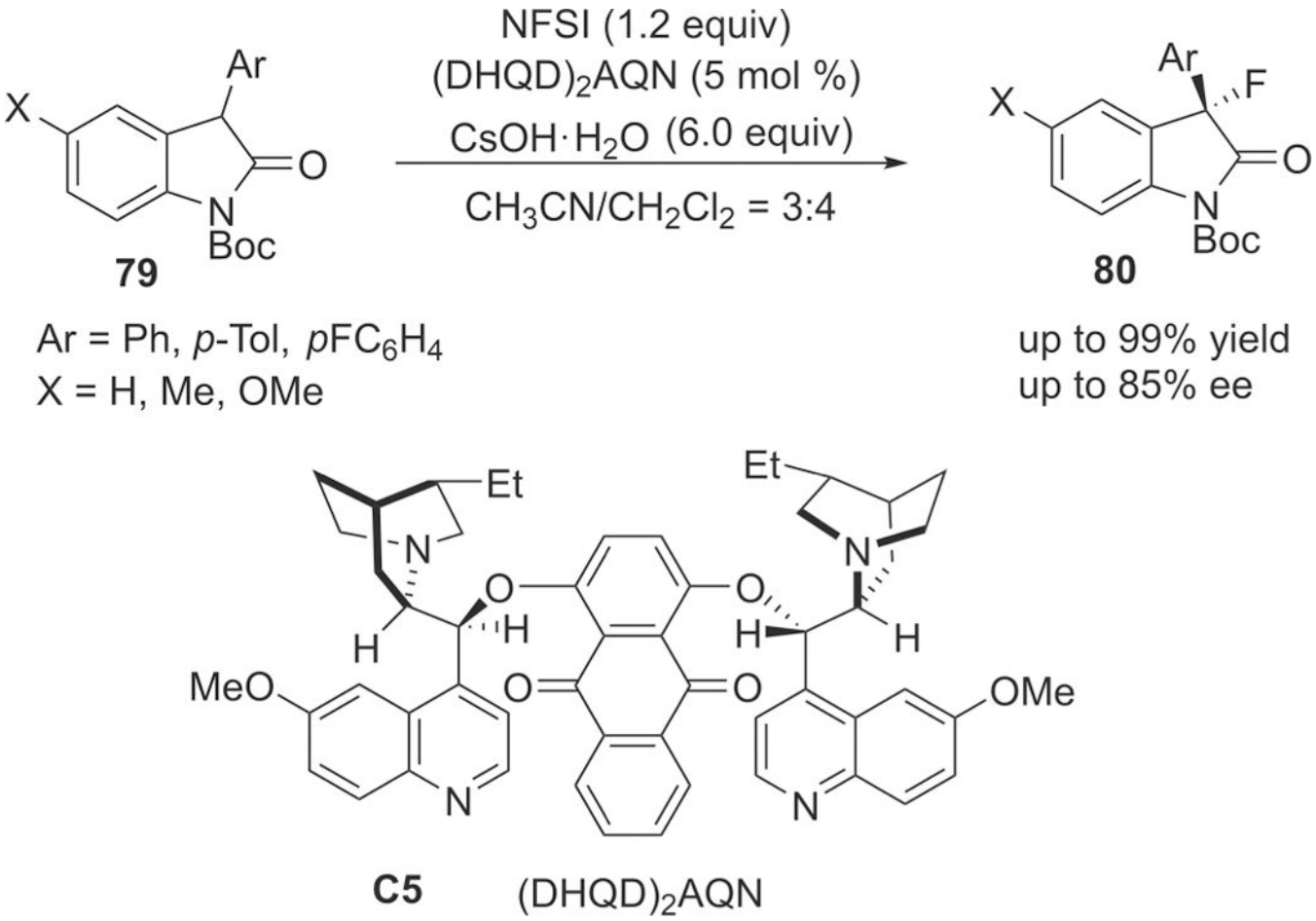


Scheme 12.
Preparation of α-Fluorinated Ketones 76 Bearing a C–F Quaternary Carbon Center

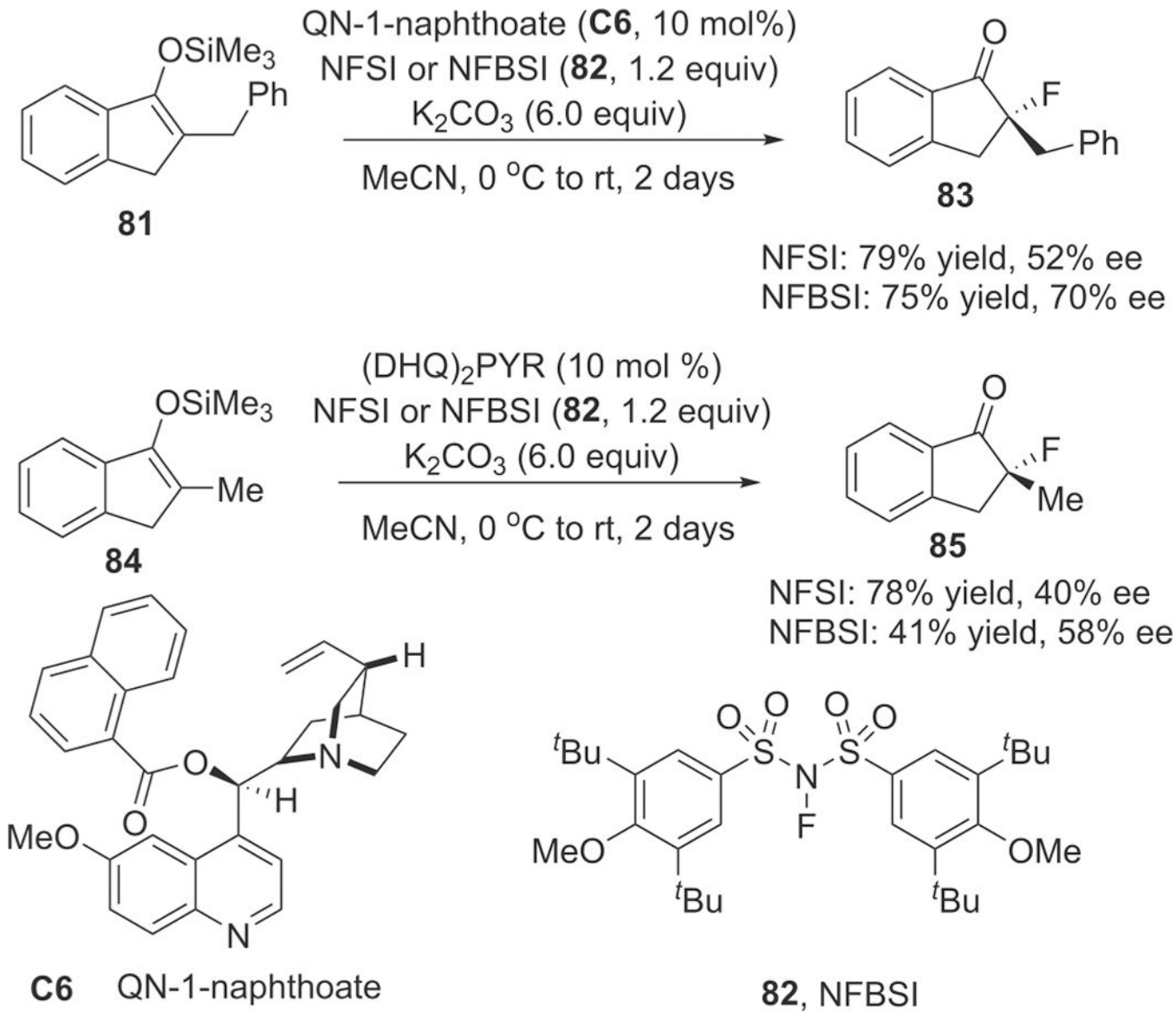


Scheme 13.

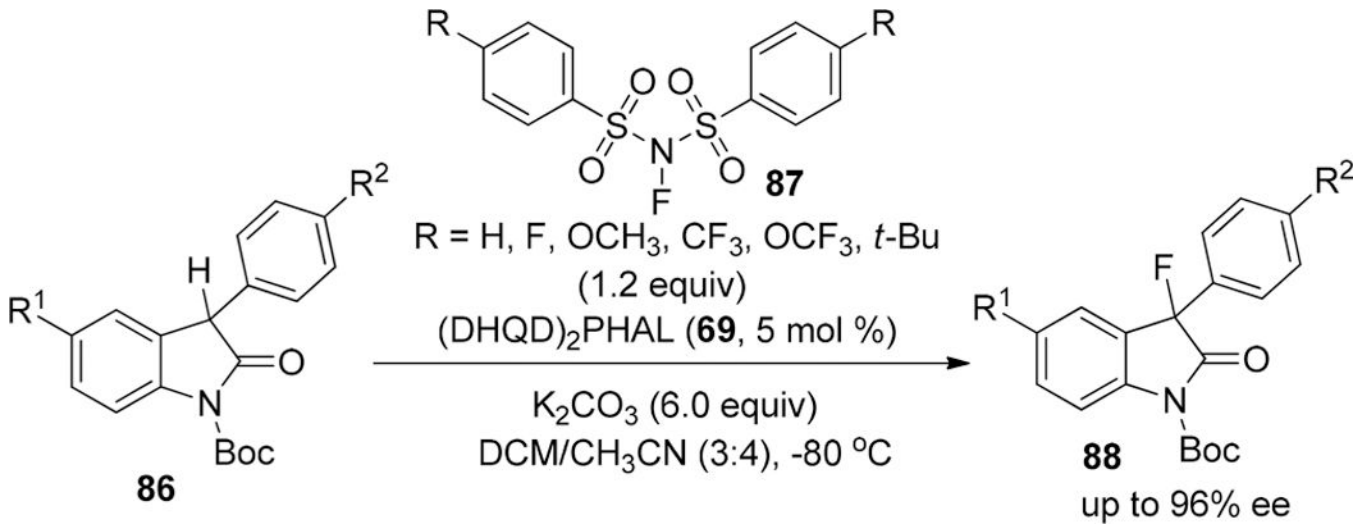
Preparation of α-Fluorinated Ketones 78 Bearing a C–F Quaternary Carbon Center



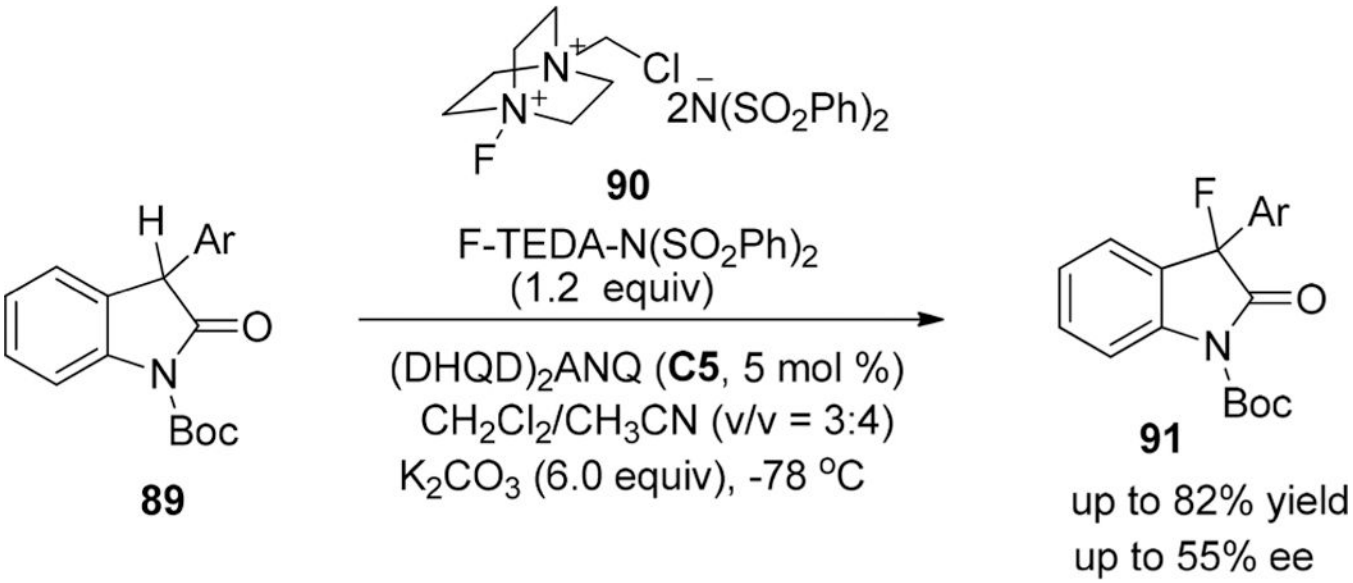
Scheme 14.
Enantioselective Fluorination of Oxindoles



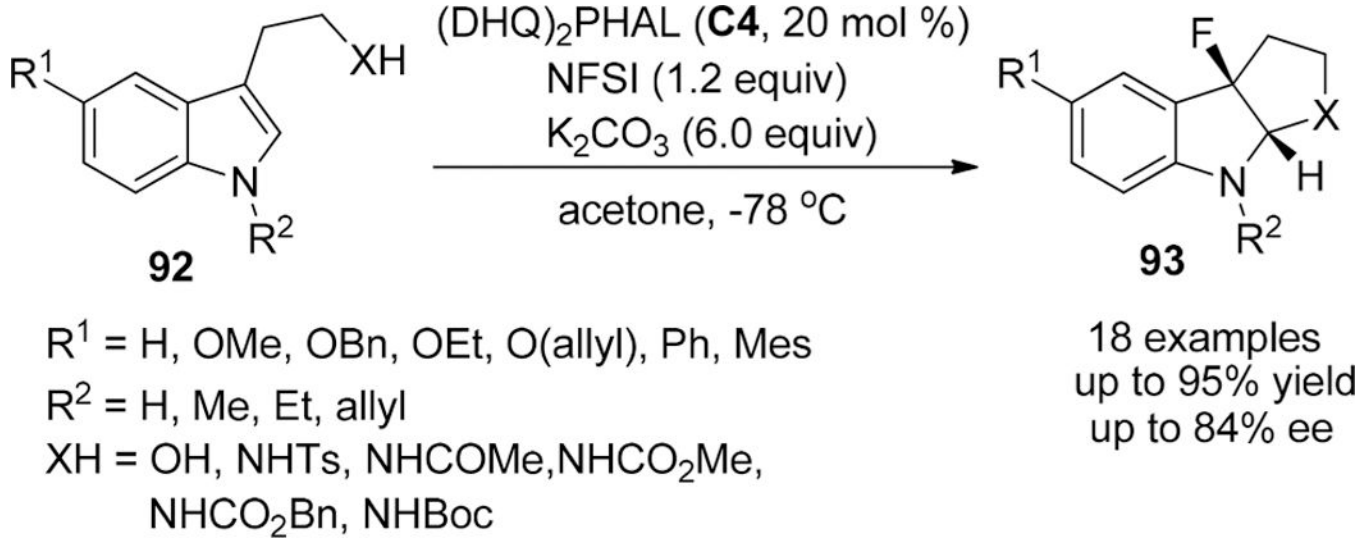
Scheme 15.
Enantioselective Fluorodesilylation Reactions of Silyl Enol Ethers



Scheme 16.
Enantioselective Fluorination of 3-Aryl-oxindoles

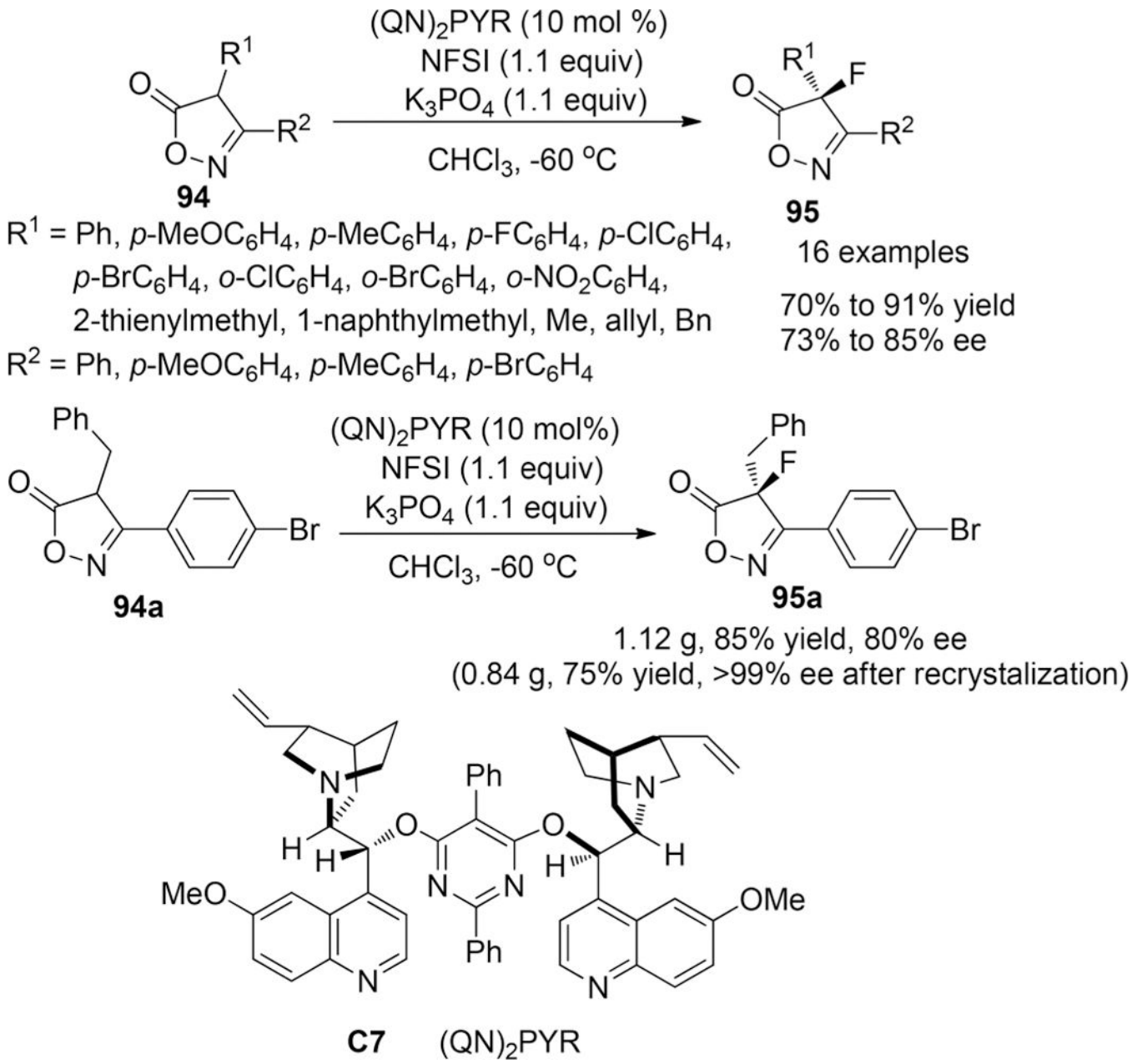


Scheme 17.
Enantioselective Fluorination of 3-Aryl-oxindoles Using Selectfluor

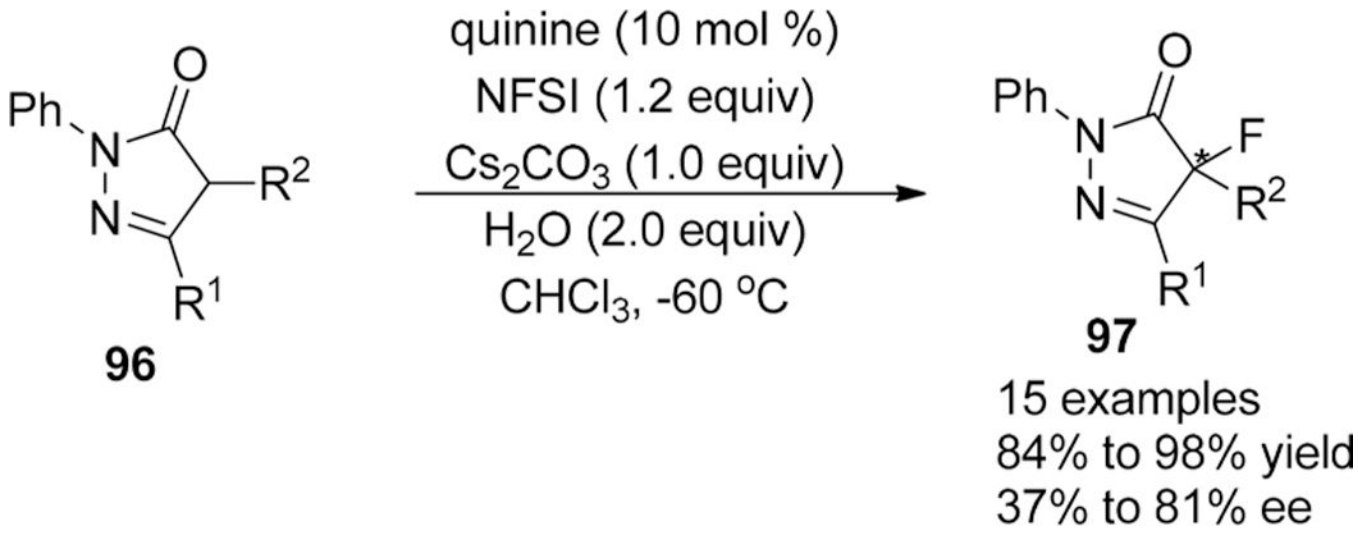


Scheme 18.

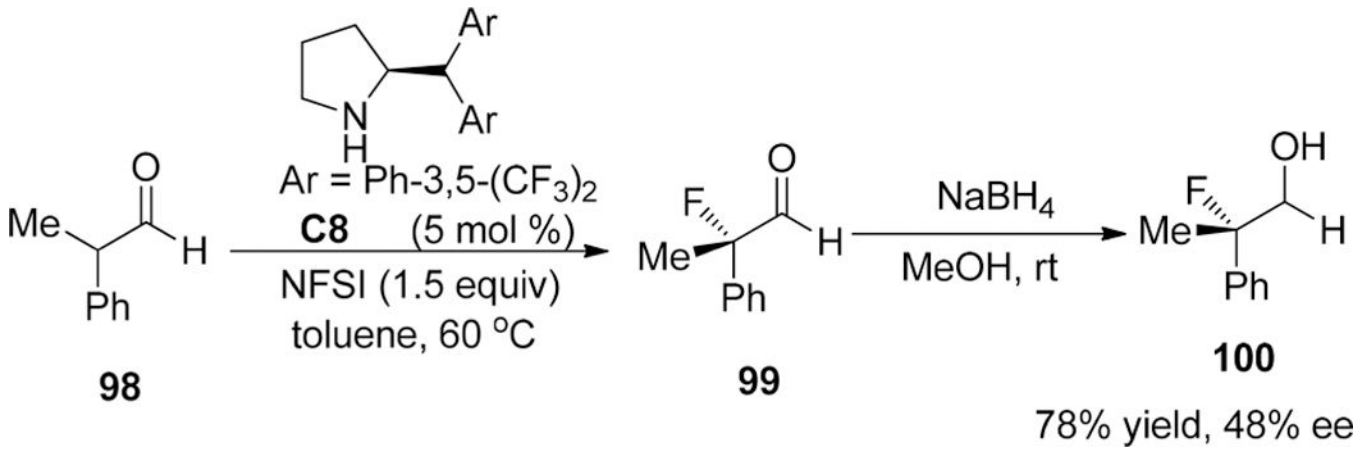
Enantioselective Fluorination–Cyclization of Indoles 92 with a Pendant Heteronucleophile Tethered at C3 Position



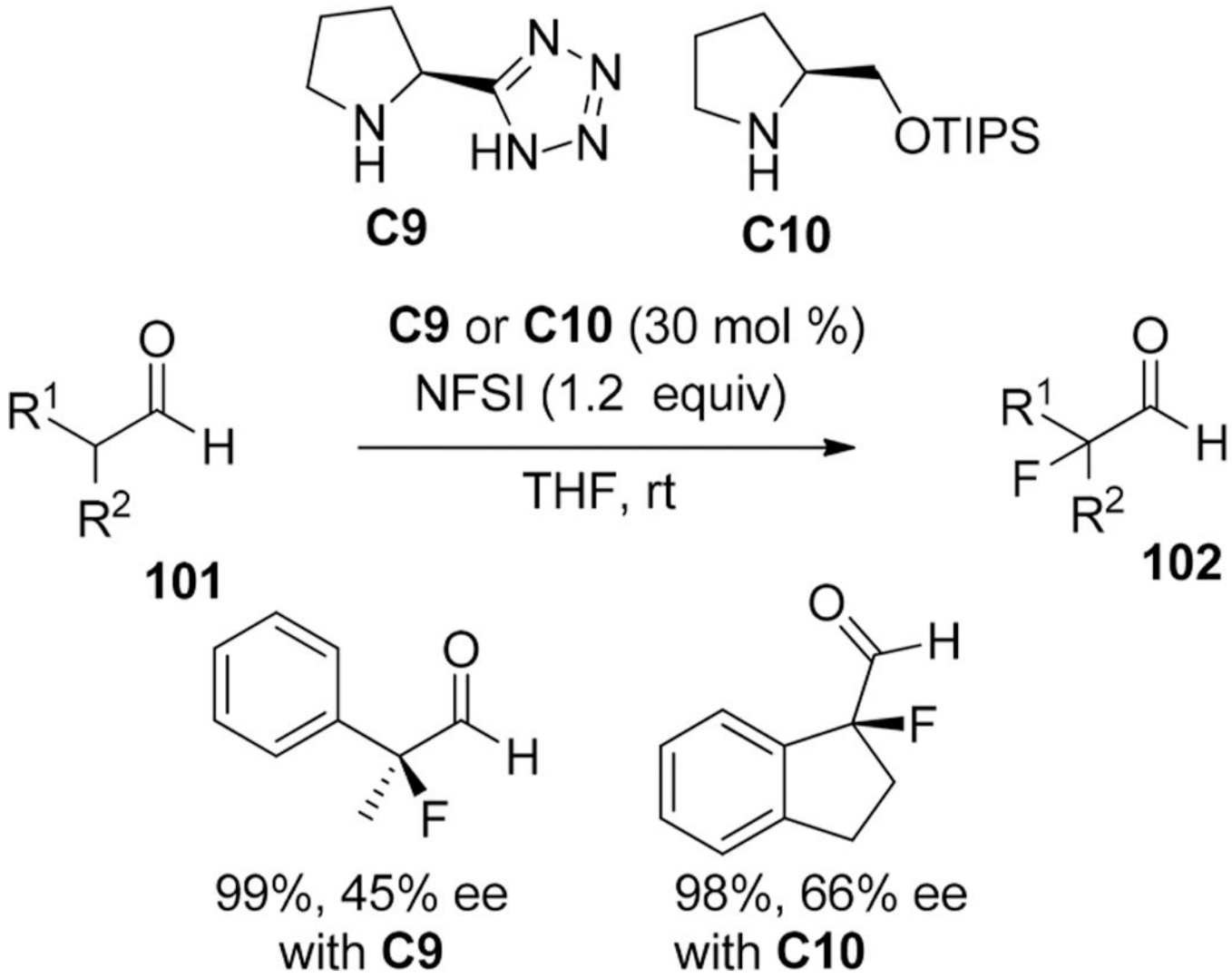
Scheme 19.
Asymmetric Electrophilic Fluorination of 4-Substituted Isoxazolinones 94



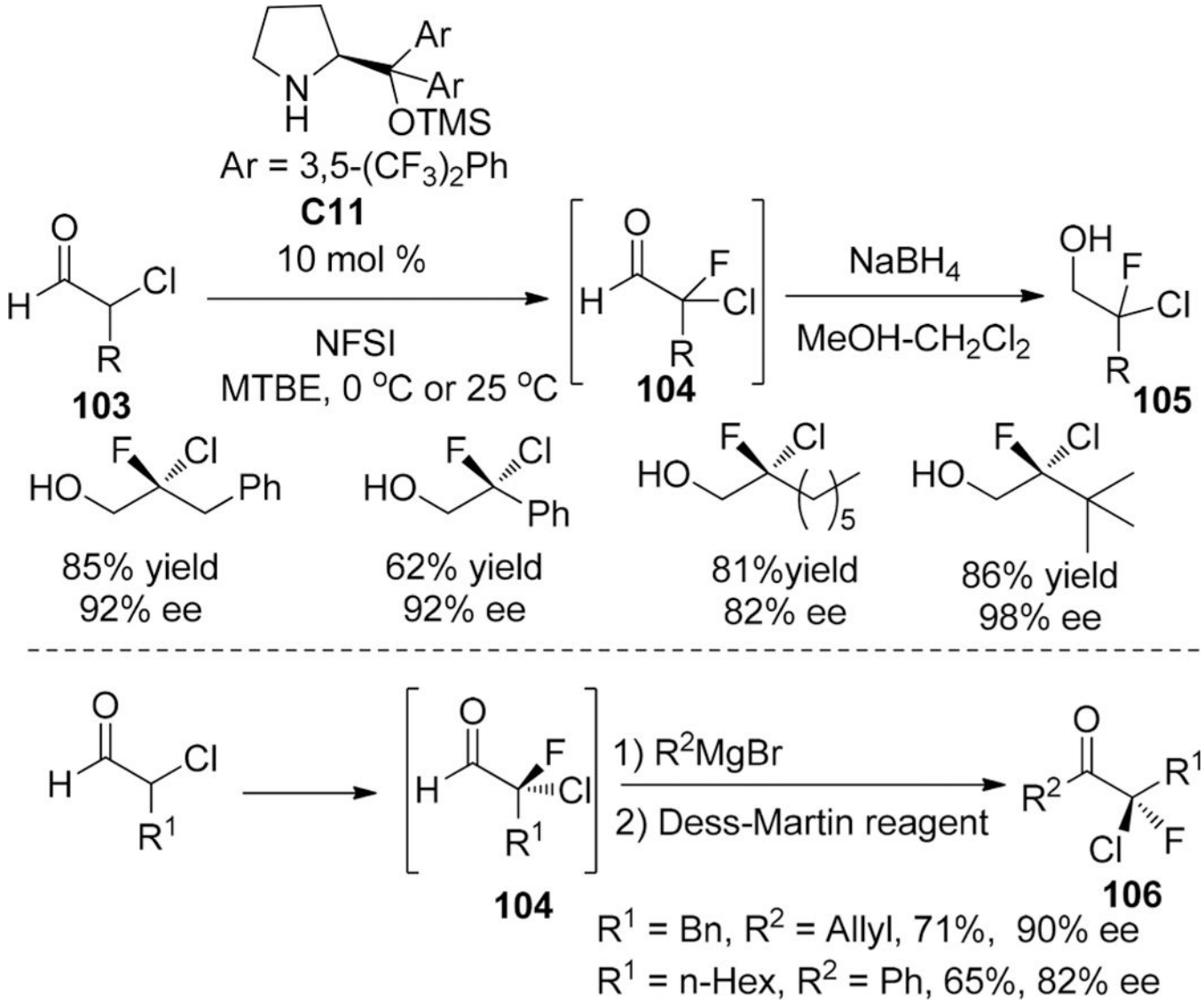
Scheme 20.
Asymmetric Fluorination of 4-Substituted Pyrazolones 96



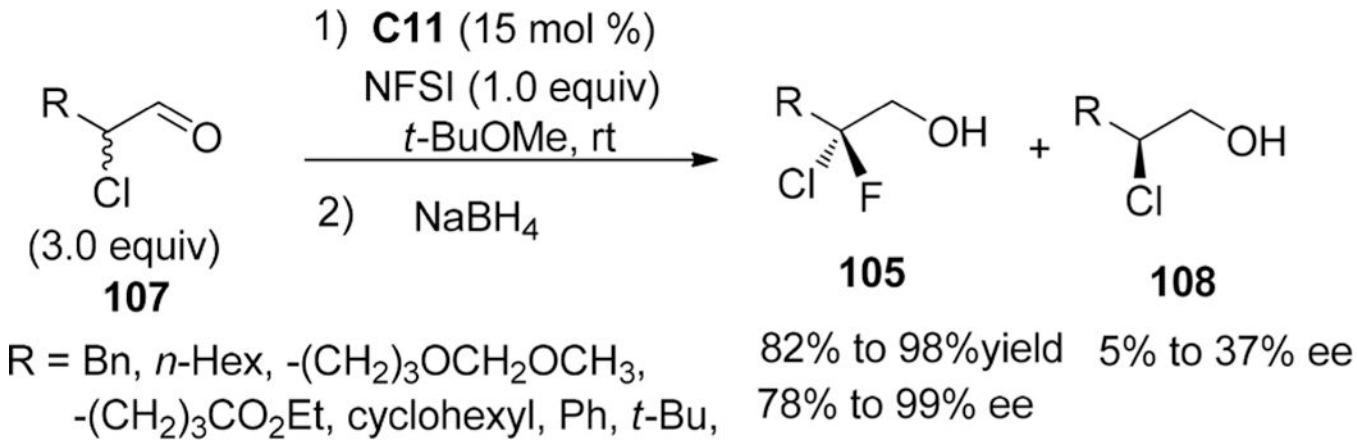
Scheme 21.
Asymmetric α-Fluorination of Linear Aldehydes 98



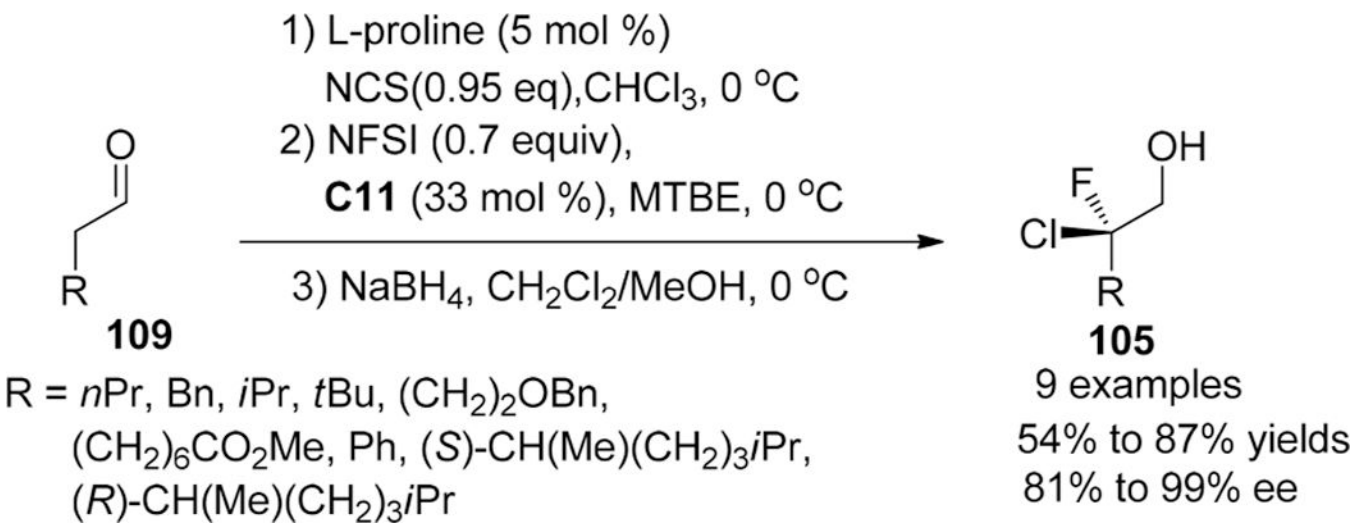
Scheme 22.
Asymmetric α-Fluorination of Branched Aldehydes 101



Scheme 23.
Asymmetric α-Fluorination of α-Chloroaldehydes 103

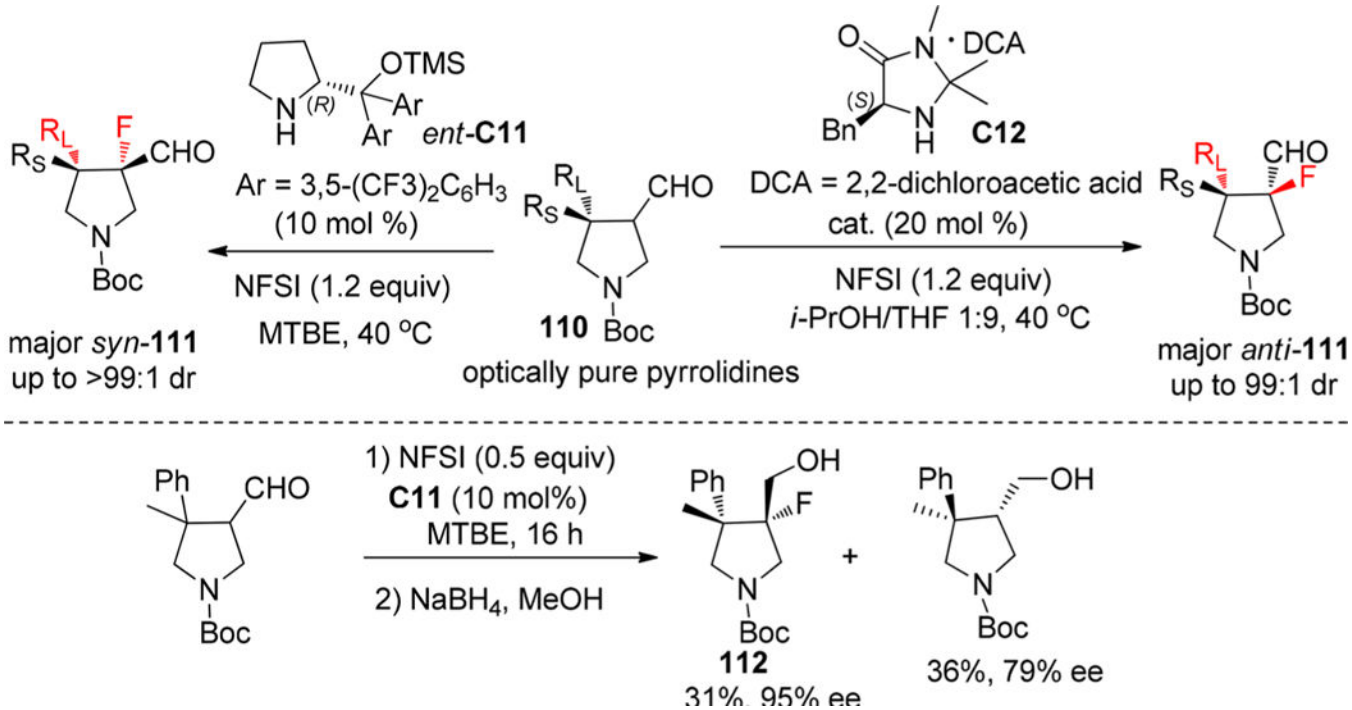


Scheme 24.
Asymmetric α-Fluorination of α-Alkyl-α-chloroaldehydes 107



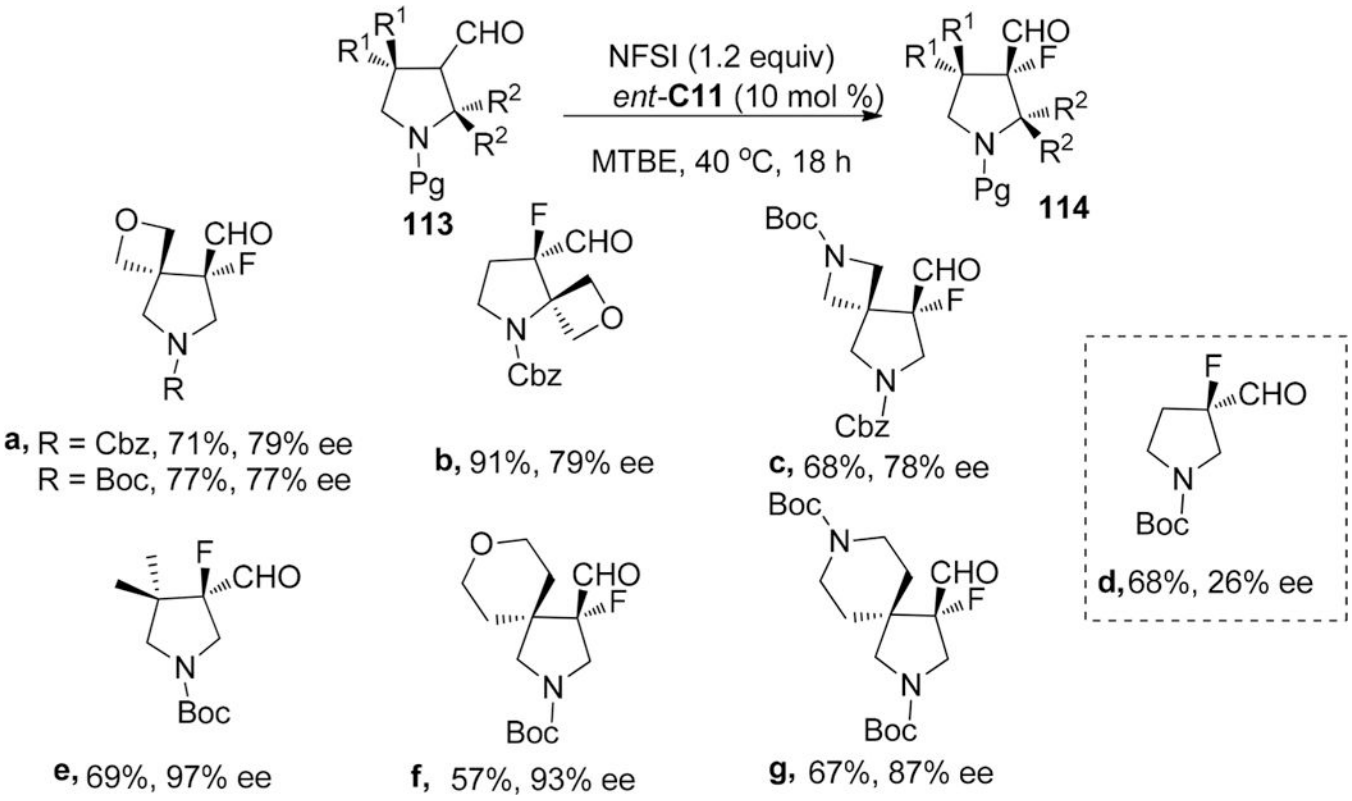
Scheme 25.

Enantioselective Preparation of *gem*-Chlorofluoro Compounds from Unfunctionalized Aldehydes



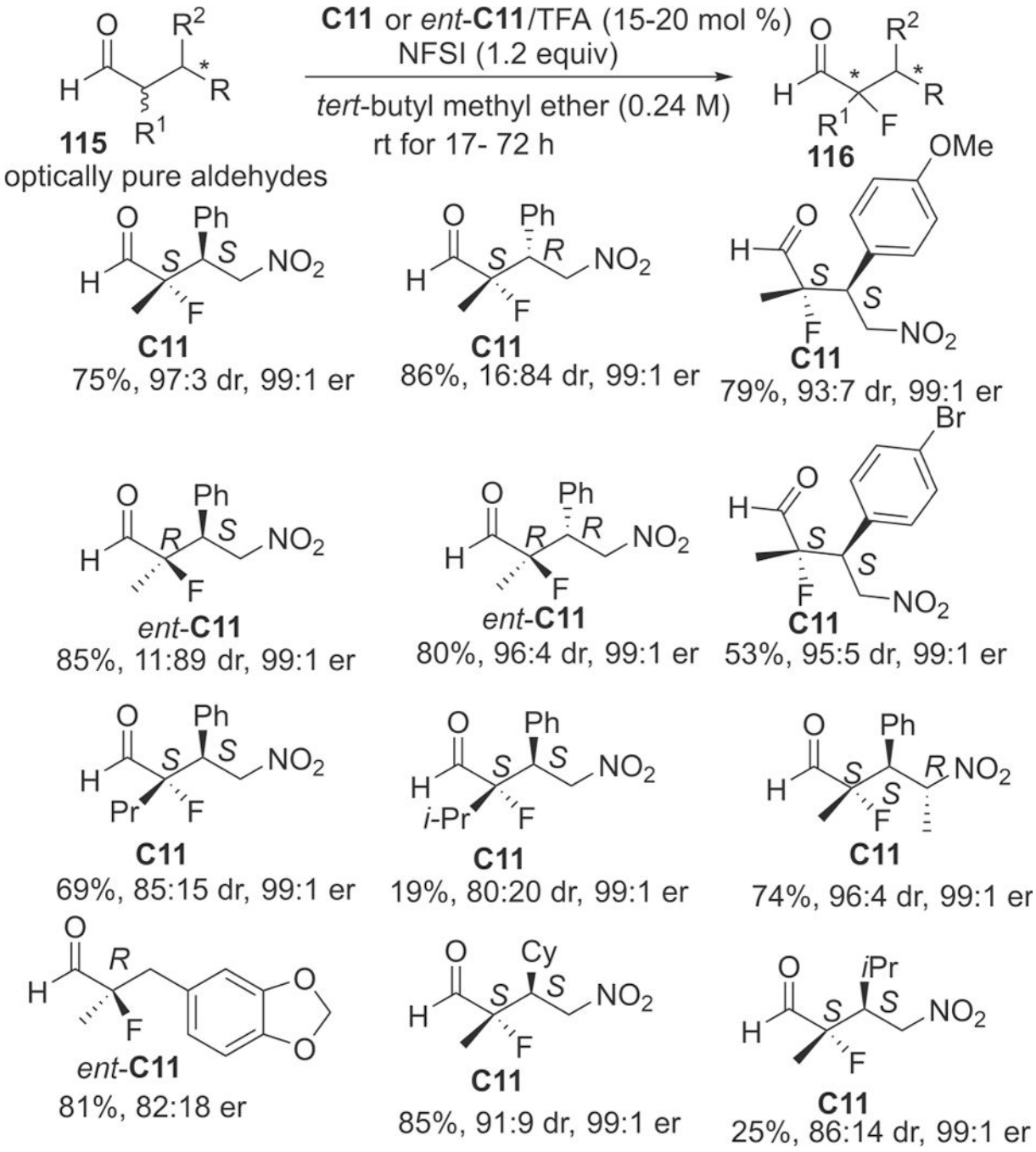
Scheme 26.

Asymmetric Synthesis of Fluorinated β-Prolinol Analogues

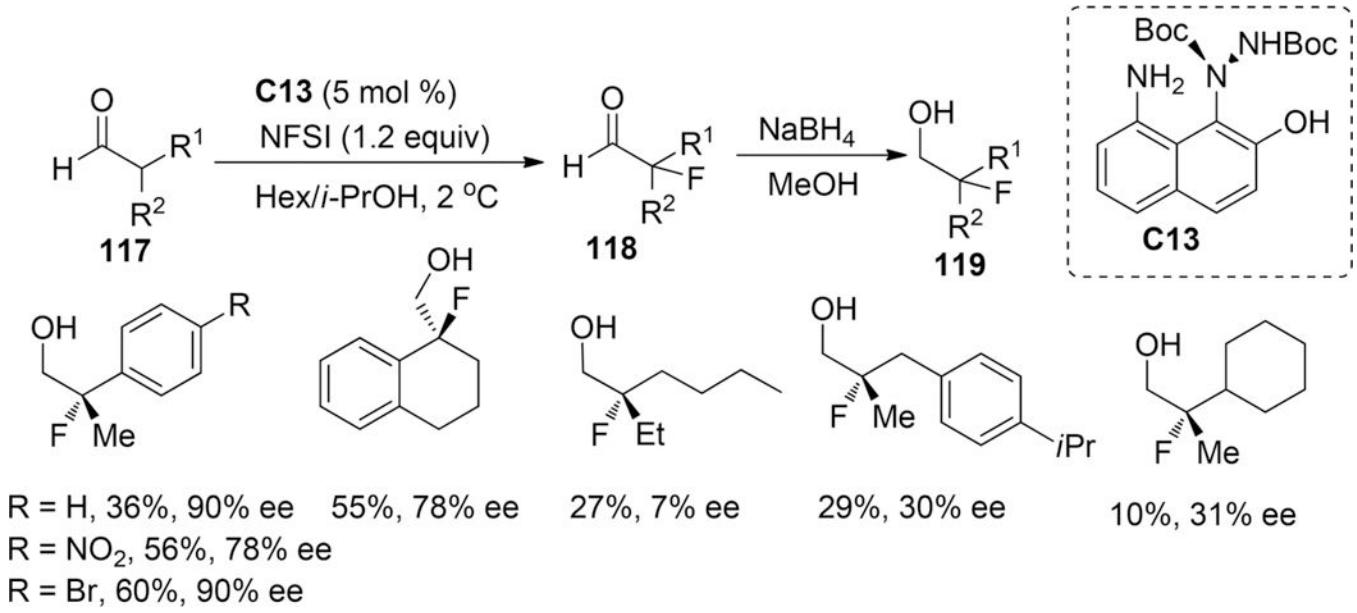


Scheme 27.

Enantioselective Fluorination of Cyclic α-Branched Aldehydes

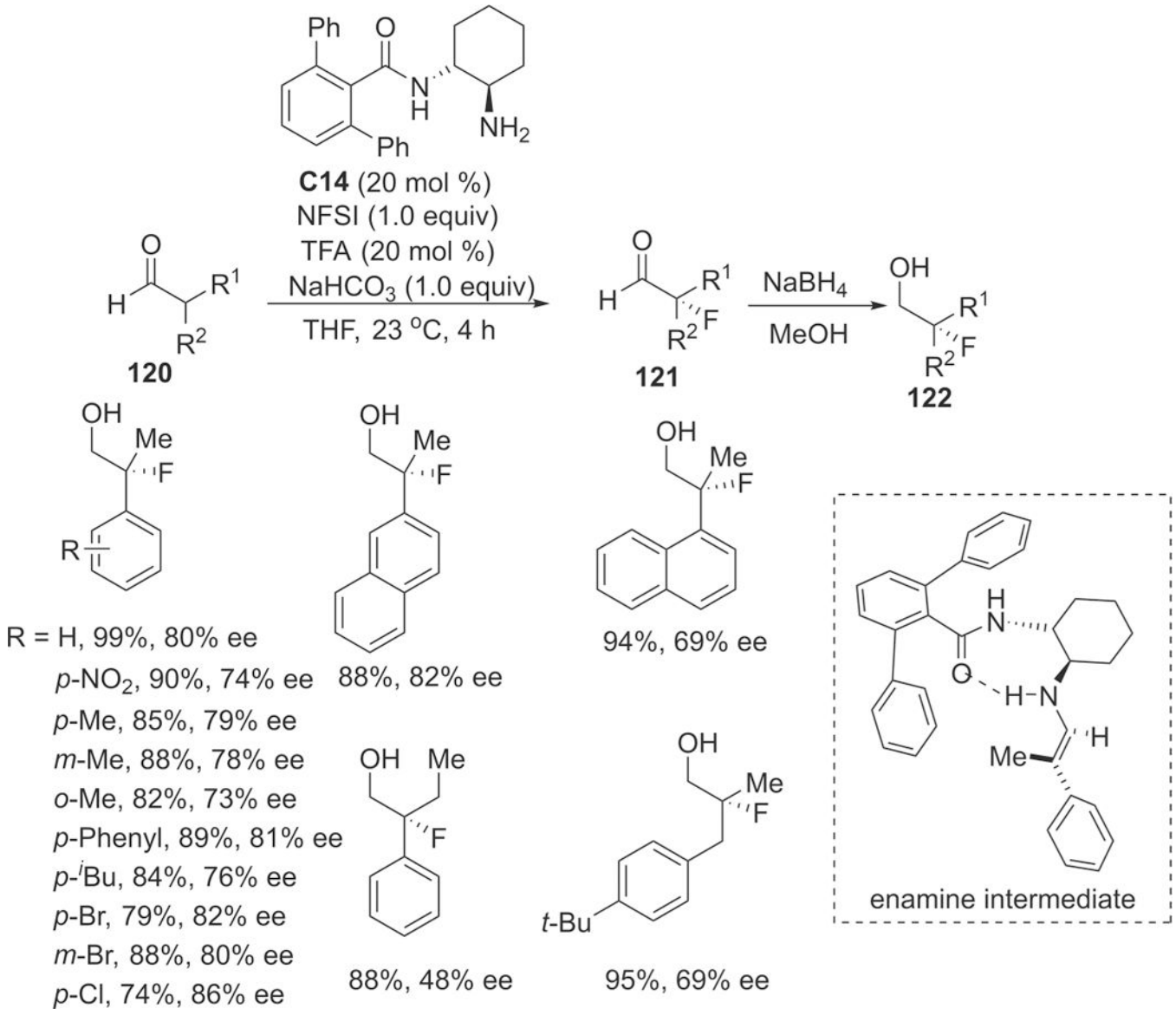


Scheme 28.
Enantioselective Fluorination of α,α-Dialkyl Aldehydes



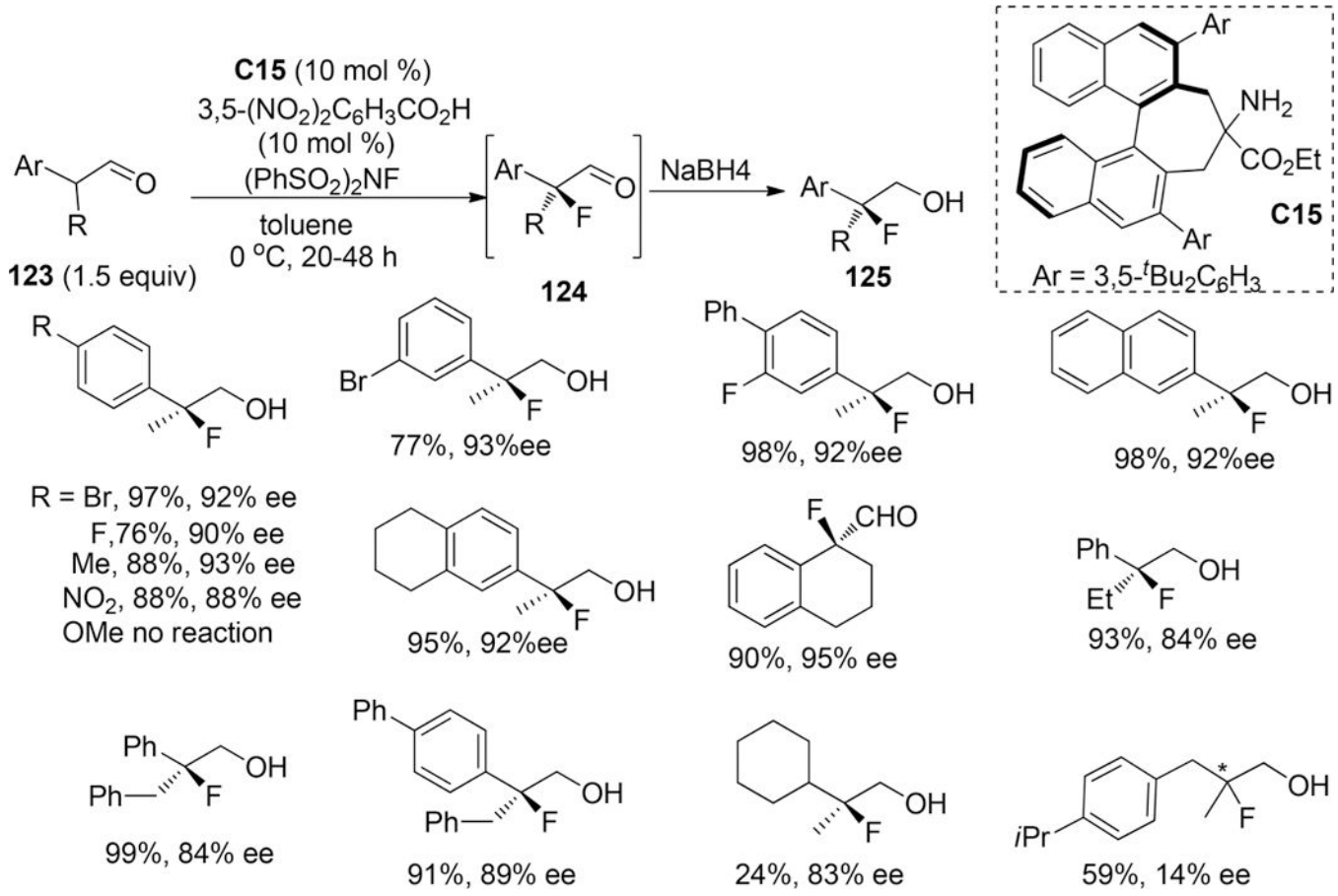
Scheme 29.

Enantioselective Fluorination of α,α-Dialkyl Aldehydes Followed by the Reduction to the Corresponding Alcohols

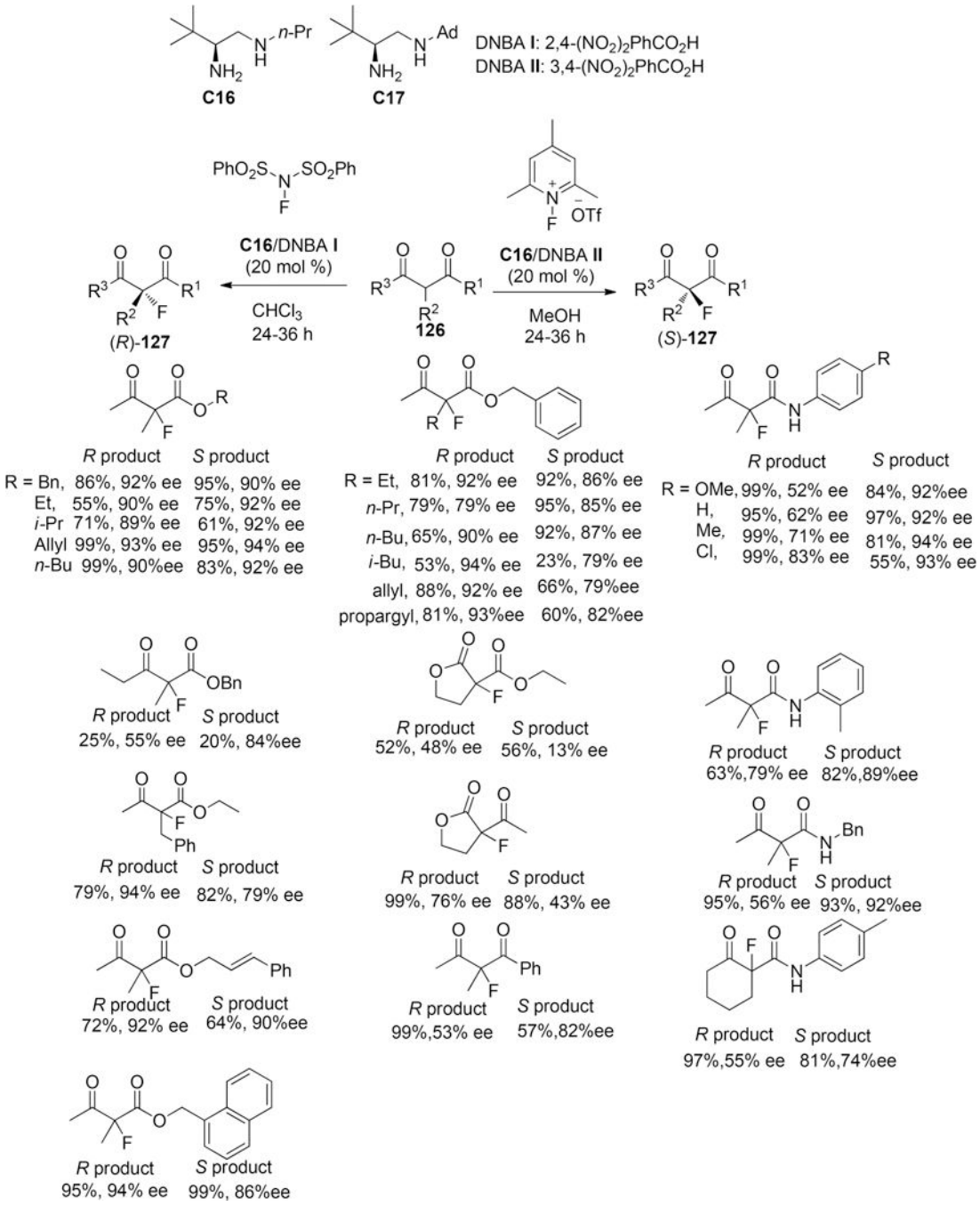


Scheme 30.

Enantioselective Fluorination of α,α-Dialkyl Aldehydes via Enamine Intermediates

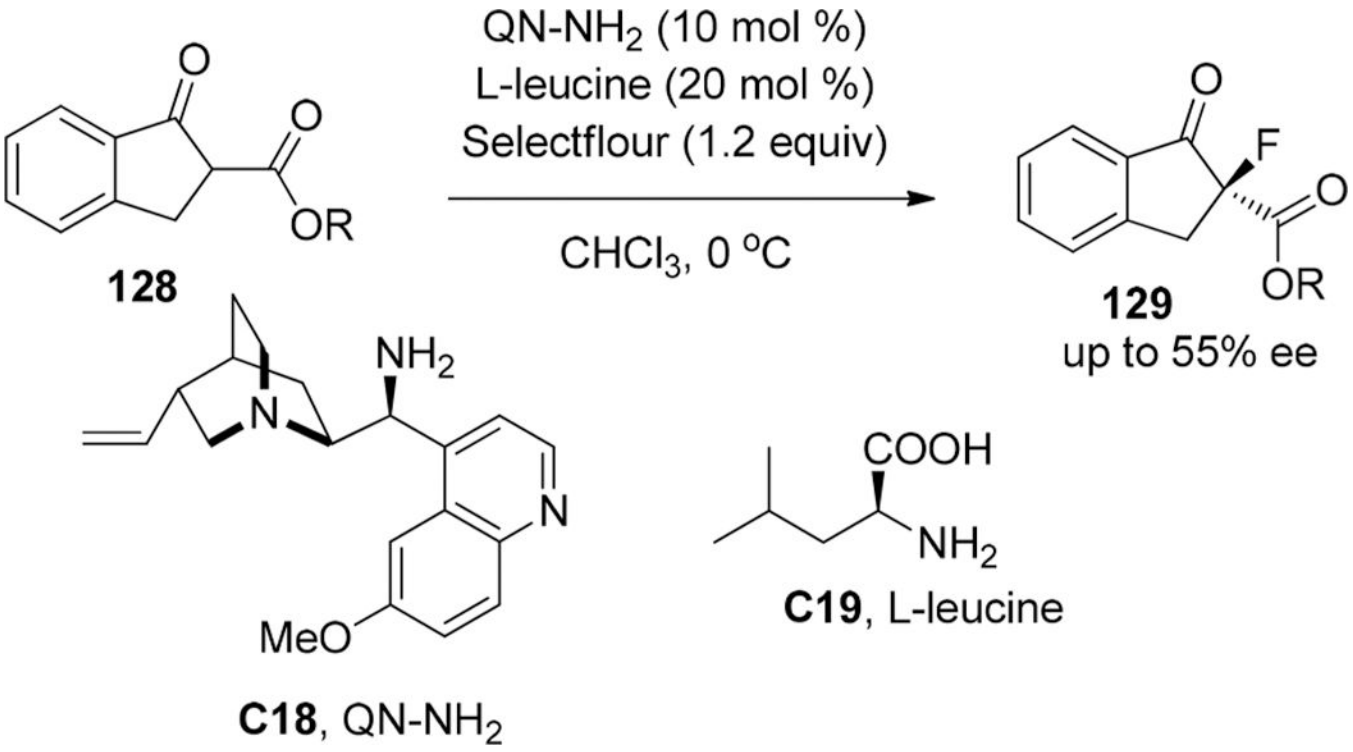


Scheme 31.
Enantioselective Fluorination of α-Aryl-α-alkyl aldehydes

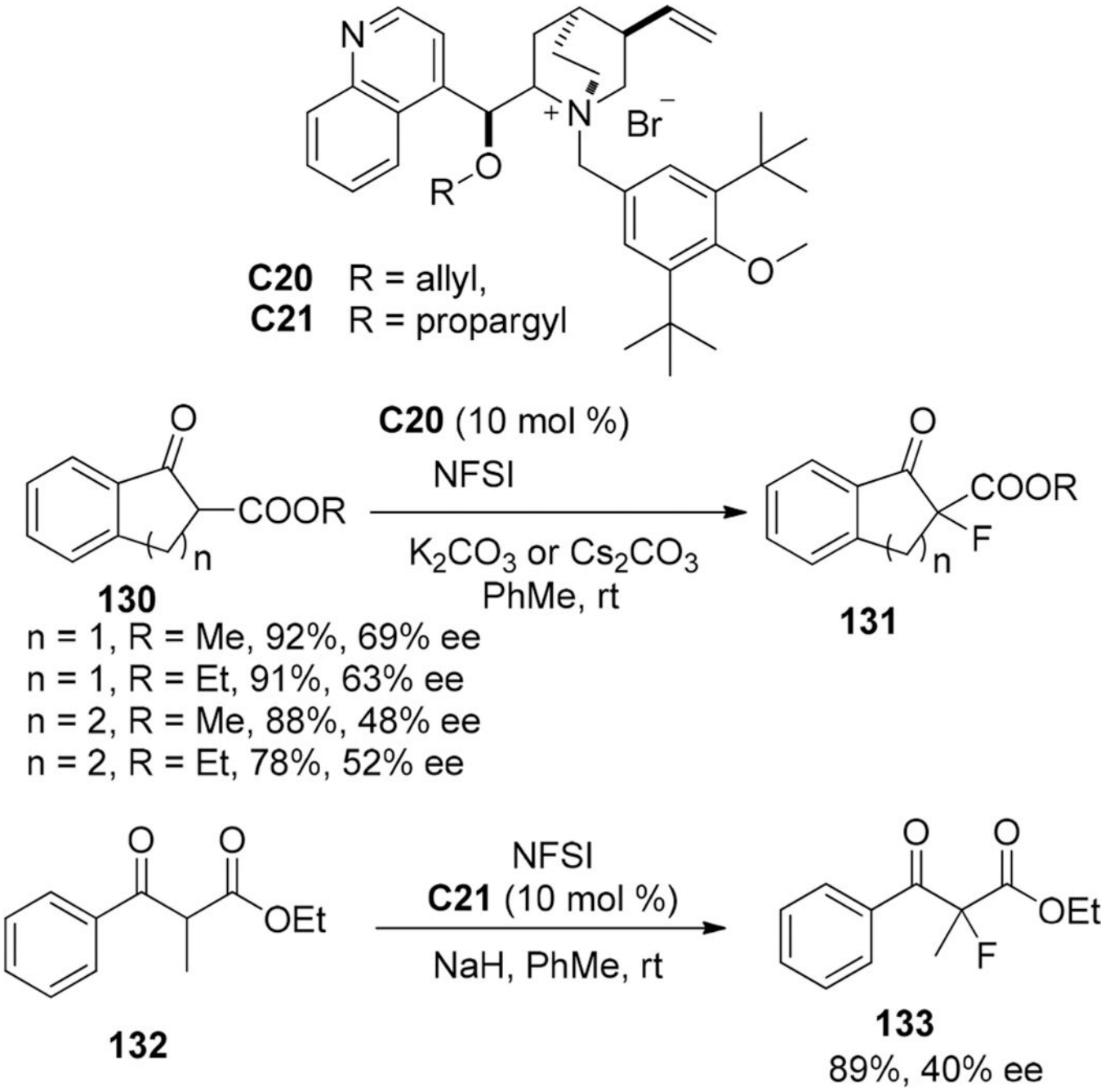


Scheme 32.

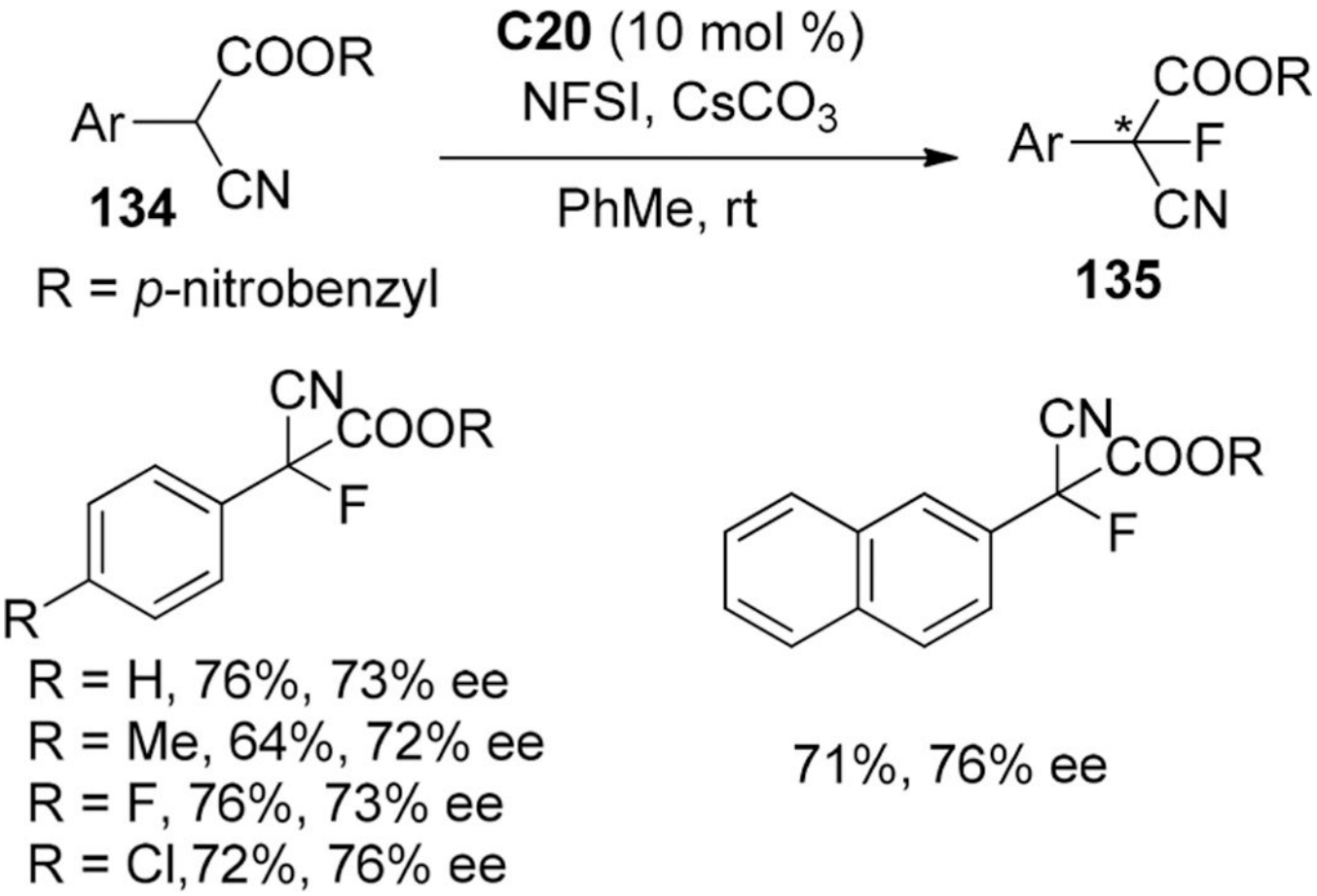
Enantioselective Fluorination of β-Ketoesters 126



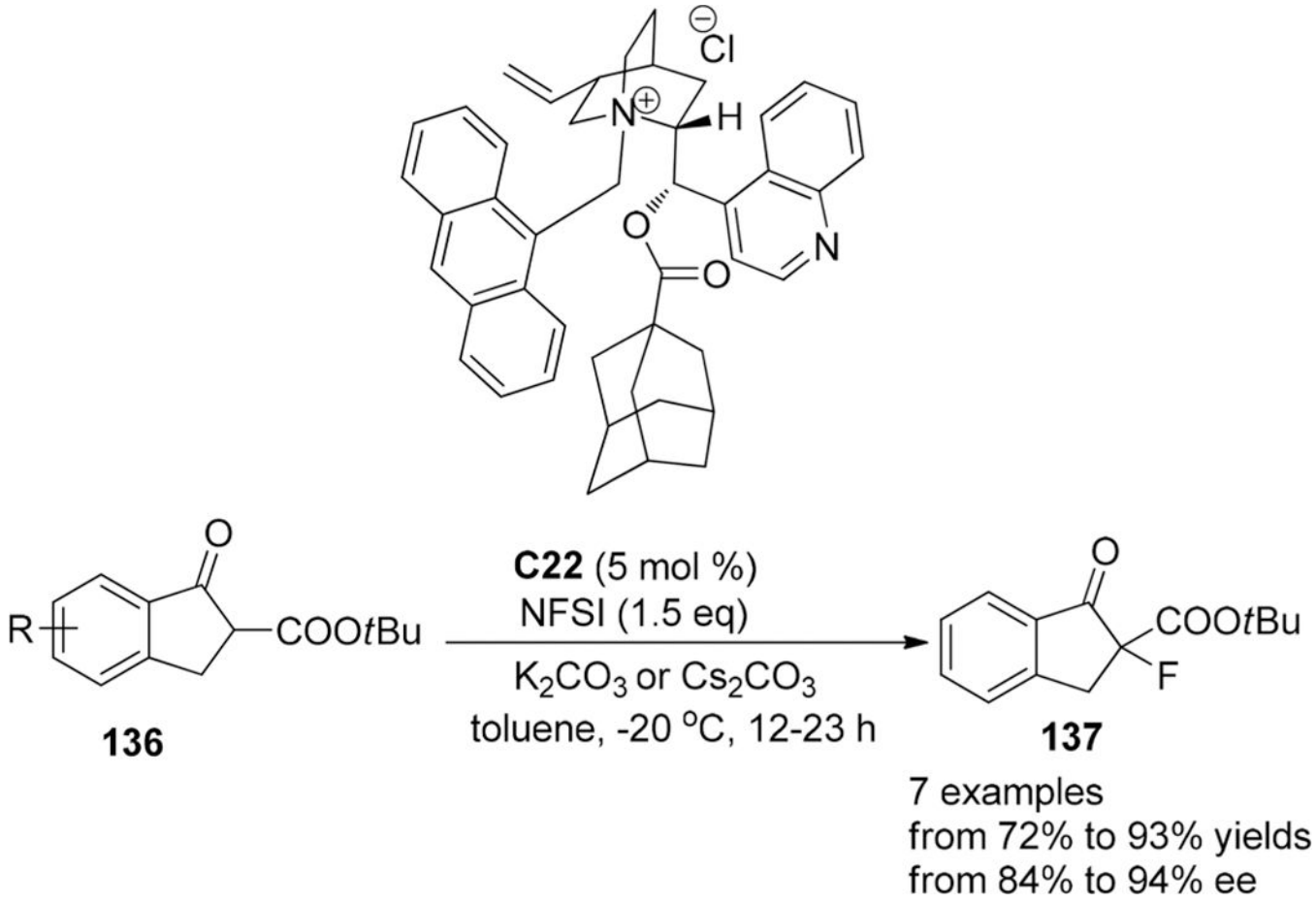
Scheme 33.
Asymmetric Fluorination of β-Ketoesters 128



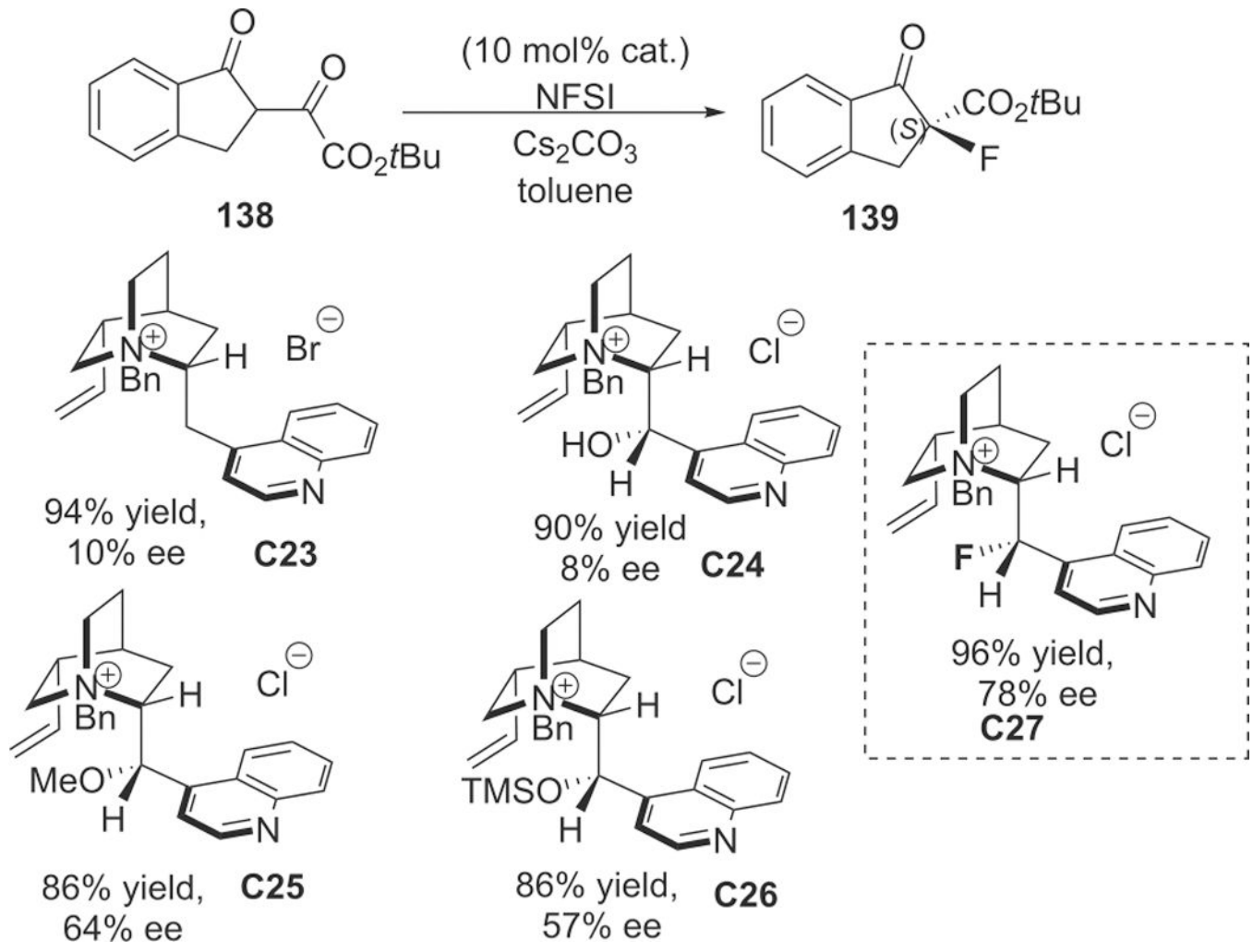
Scheme 34.
Enantioselective Electrophilic Fluorination of β-Keto Esters 130



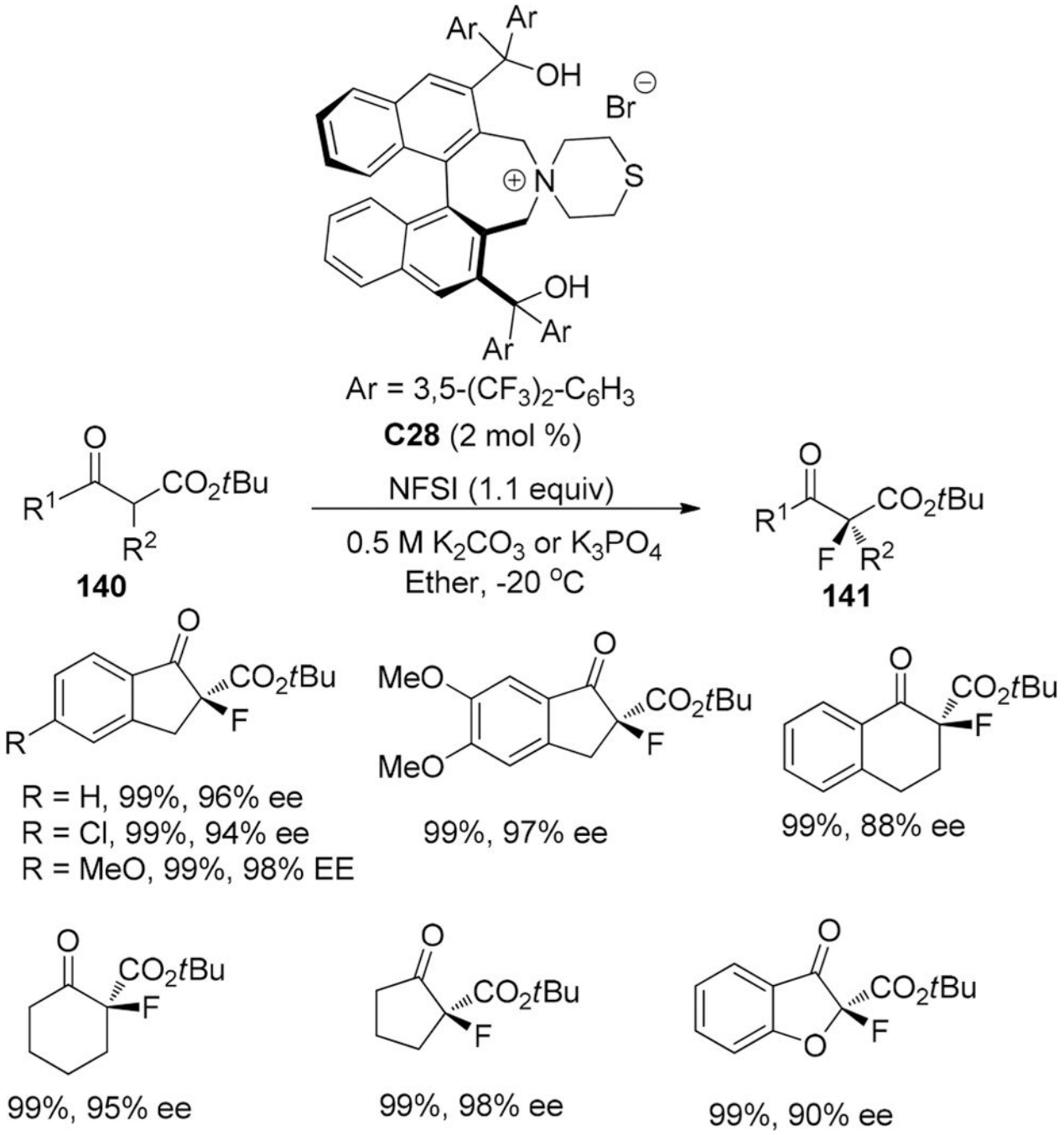
Scheme 35.
Asymmetric Fluorination of α-Cyano Acetates 134



Scheme 36.
Asymmetric Fluorination of Indane Carboxylates 136

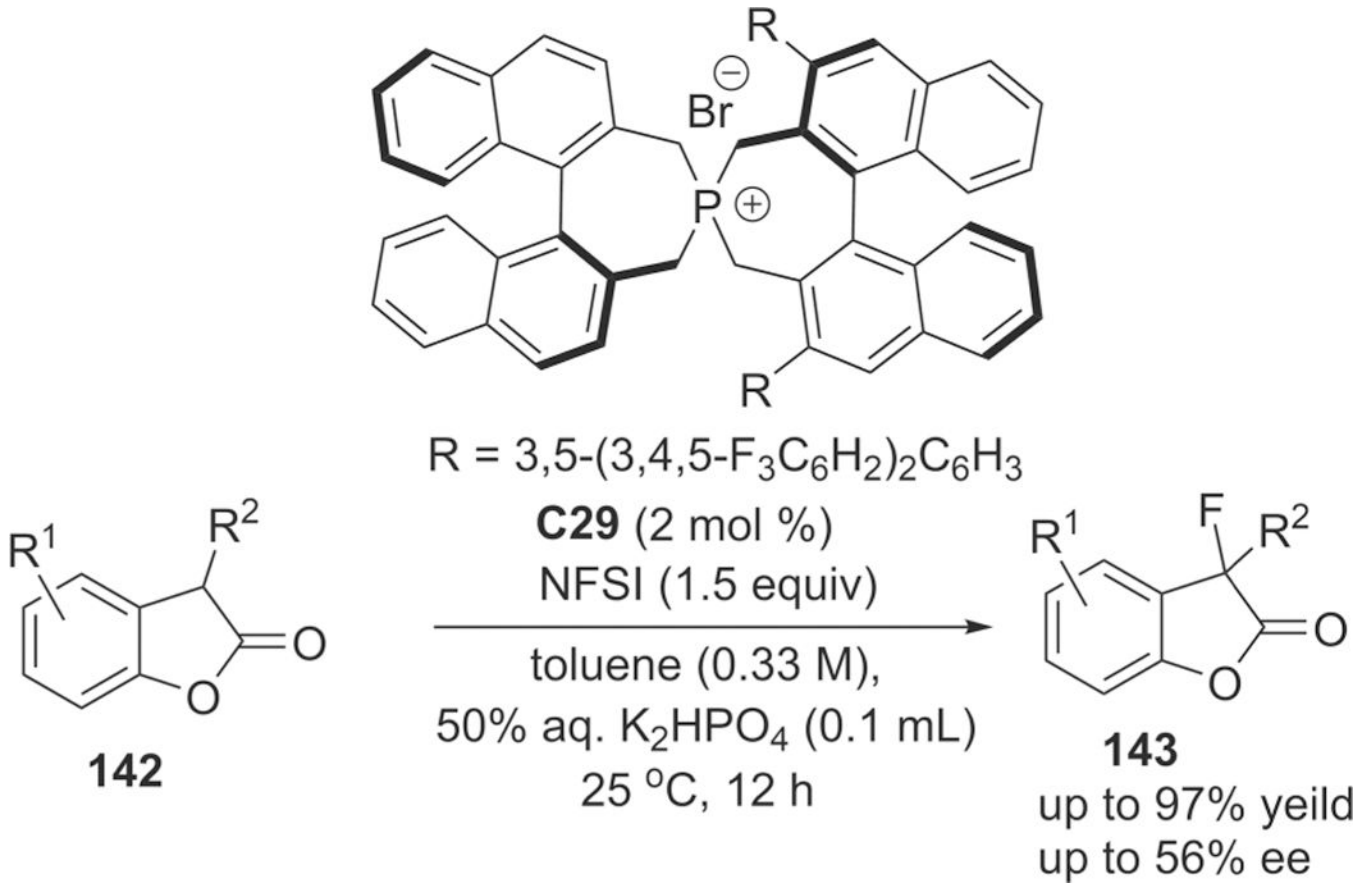


Scheme 37.
Asymmetric Electrophilic Fluorination of β-Ketoesters 138

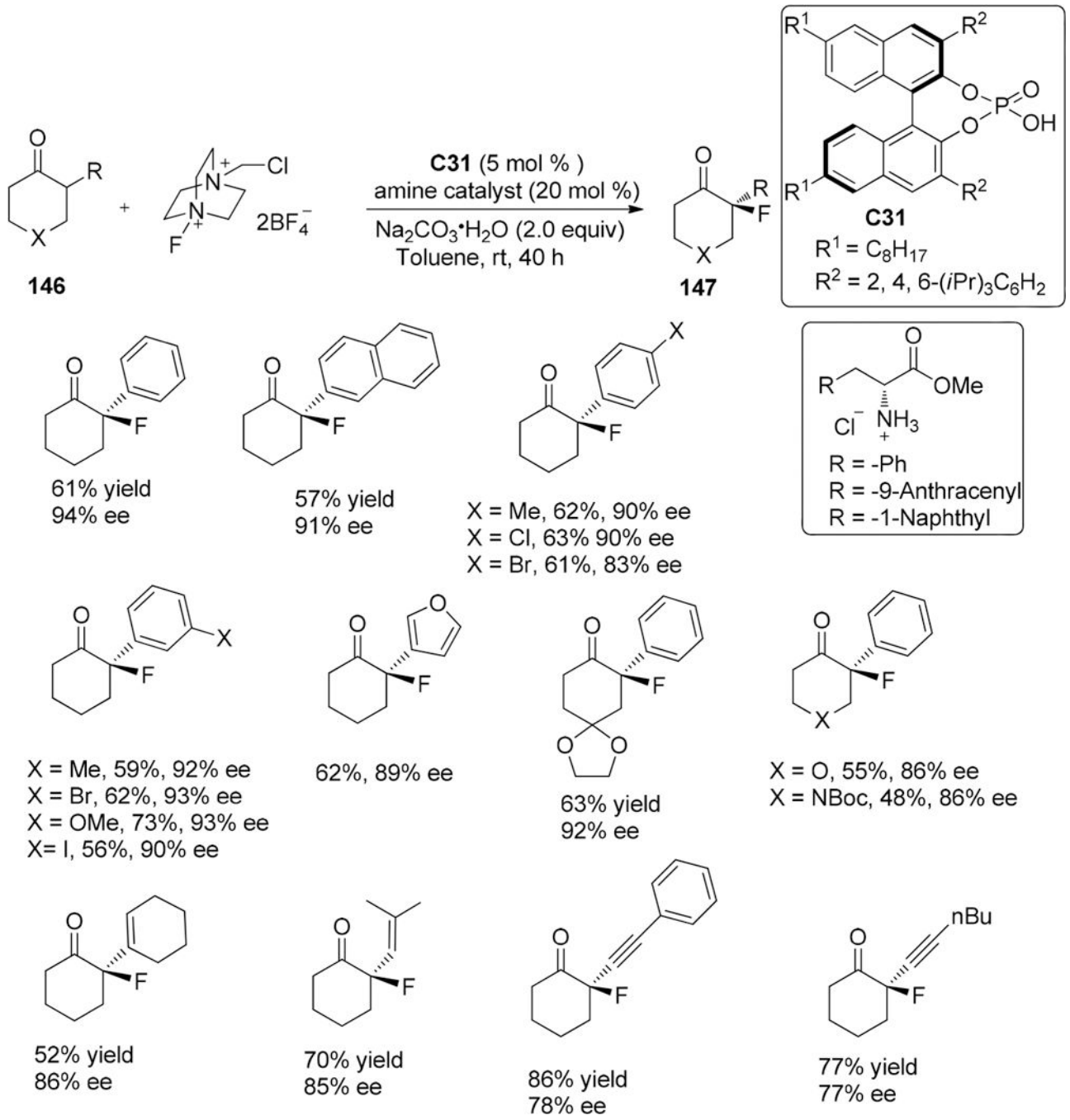


Scheme 38.

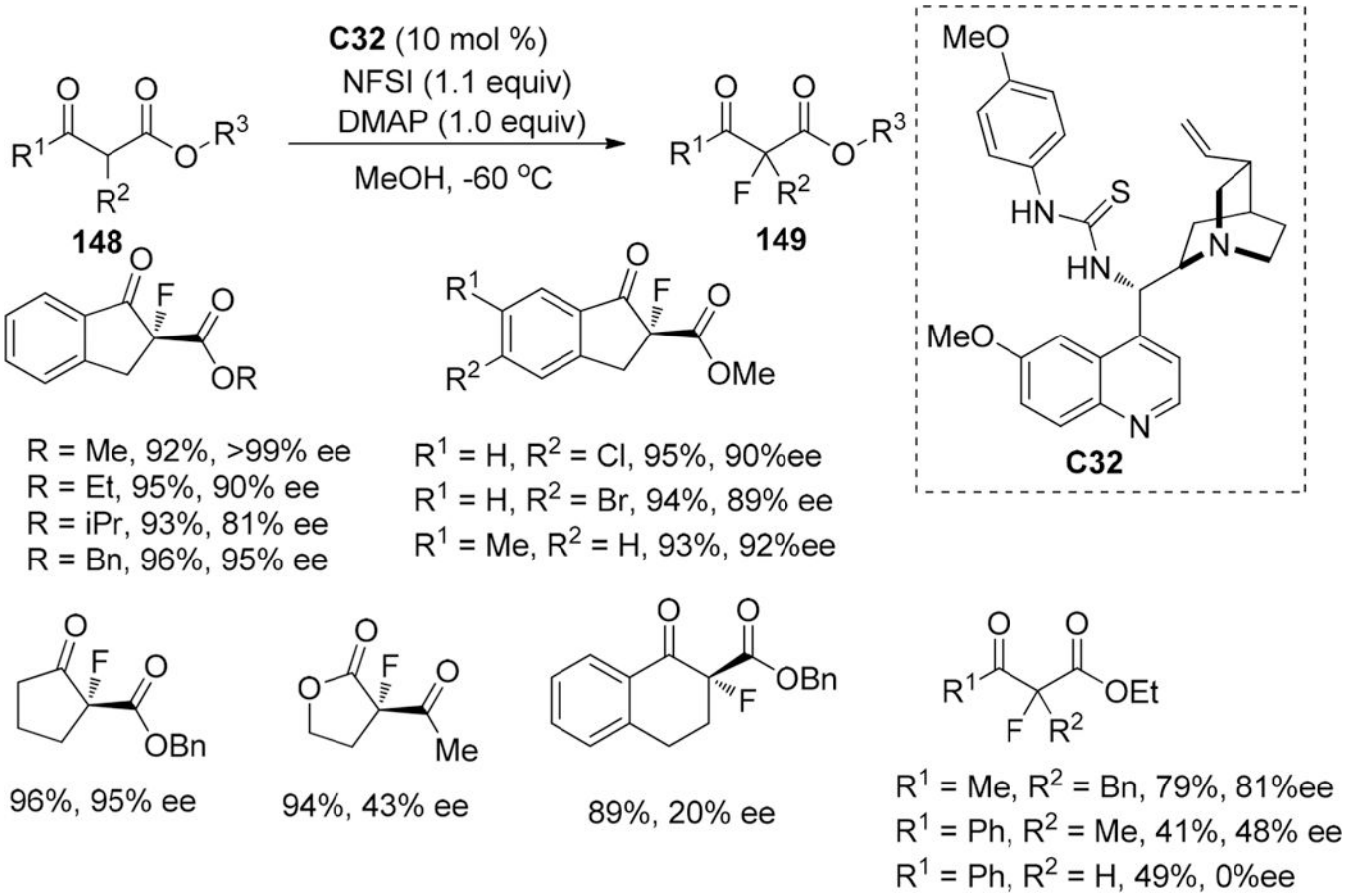
Asymmetric α-Fluorination of t-Butyl Indane Carboxylates and Their Analogues 140



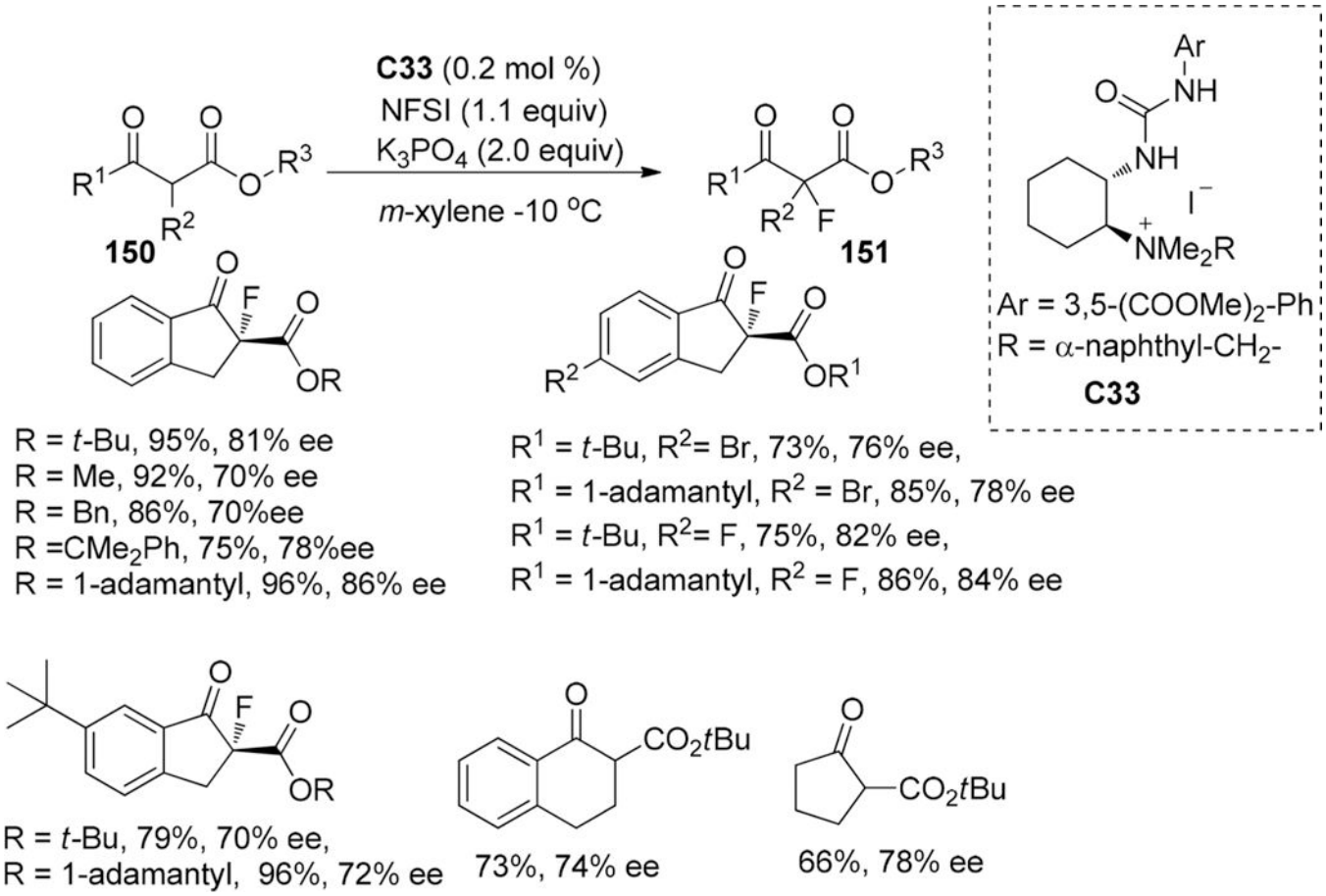
Scheme 39.
Asymmetric Electrophilic Fluorination of 3-Substituted Benzofuran-2(3*H*)-ones 142



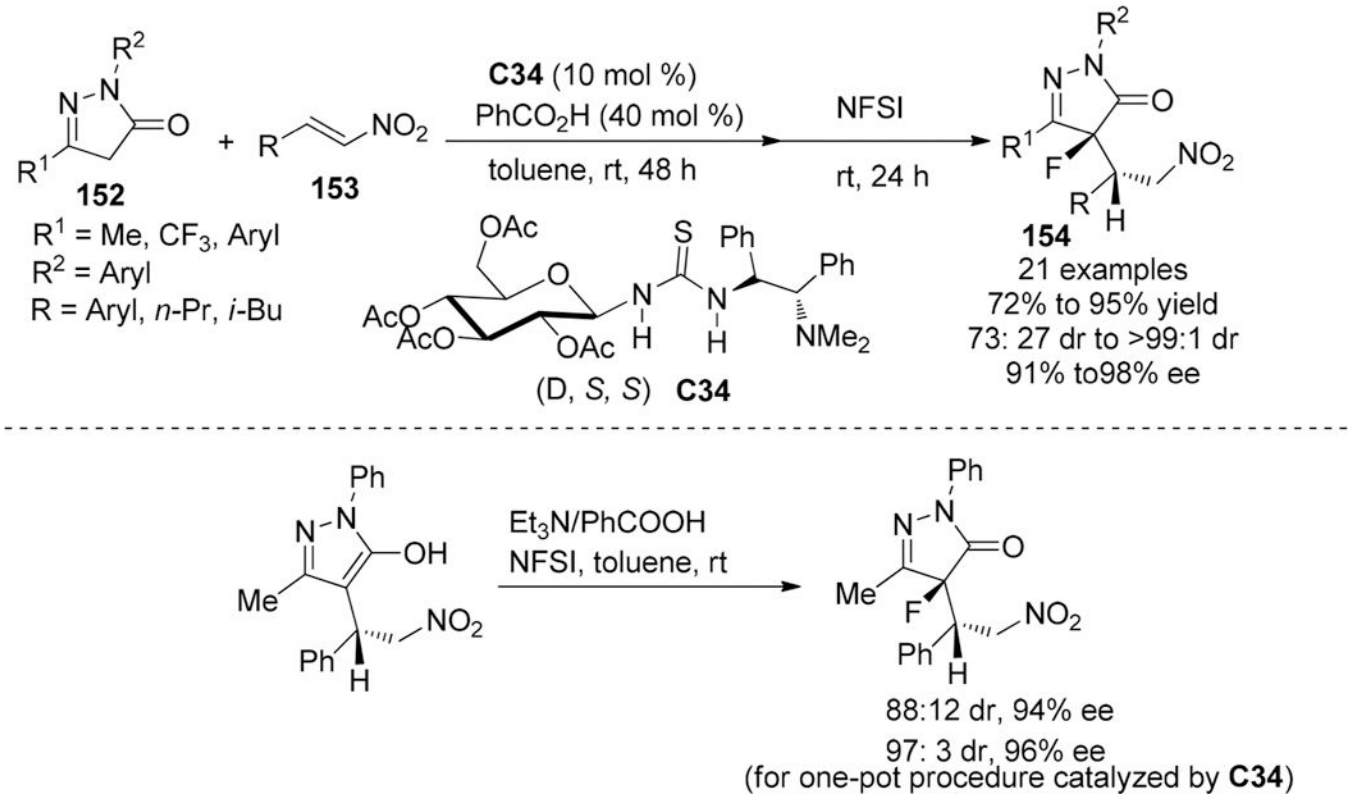
Scheme 40.
Enantioselective Fluorination of Cyclohexanones 146



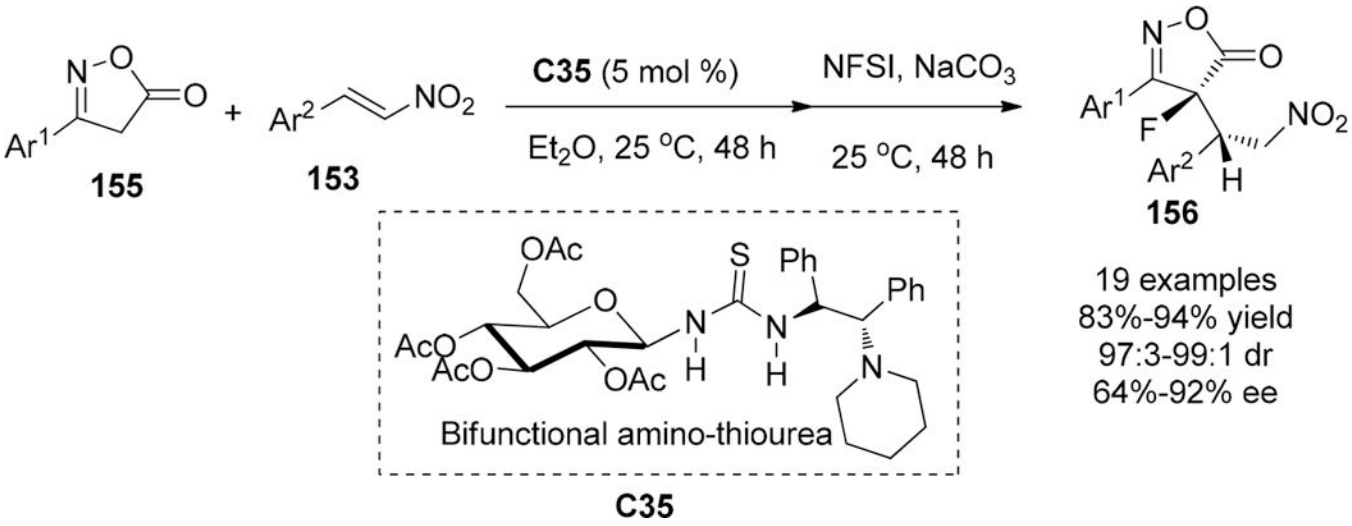
Scheme 41.
Enantioselective Fluorination of β-Keto Esters 148



Scheme 42.
Asymmetric Fluorination of β-Keto Esters 150

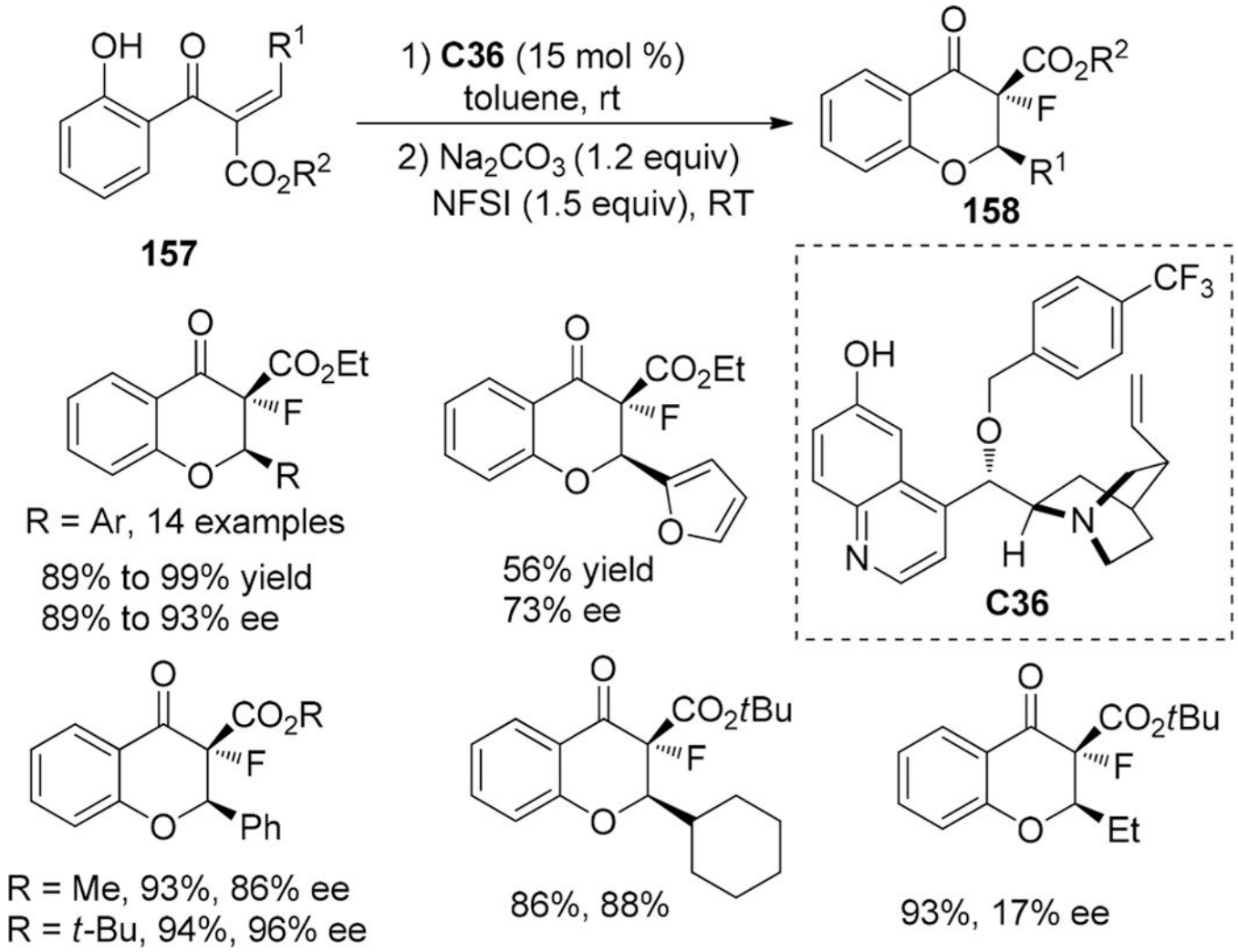


Scheme 43.
Asymmetric Fluorination of Pyrazolone Derivatives 152

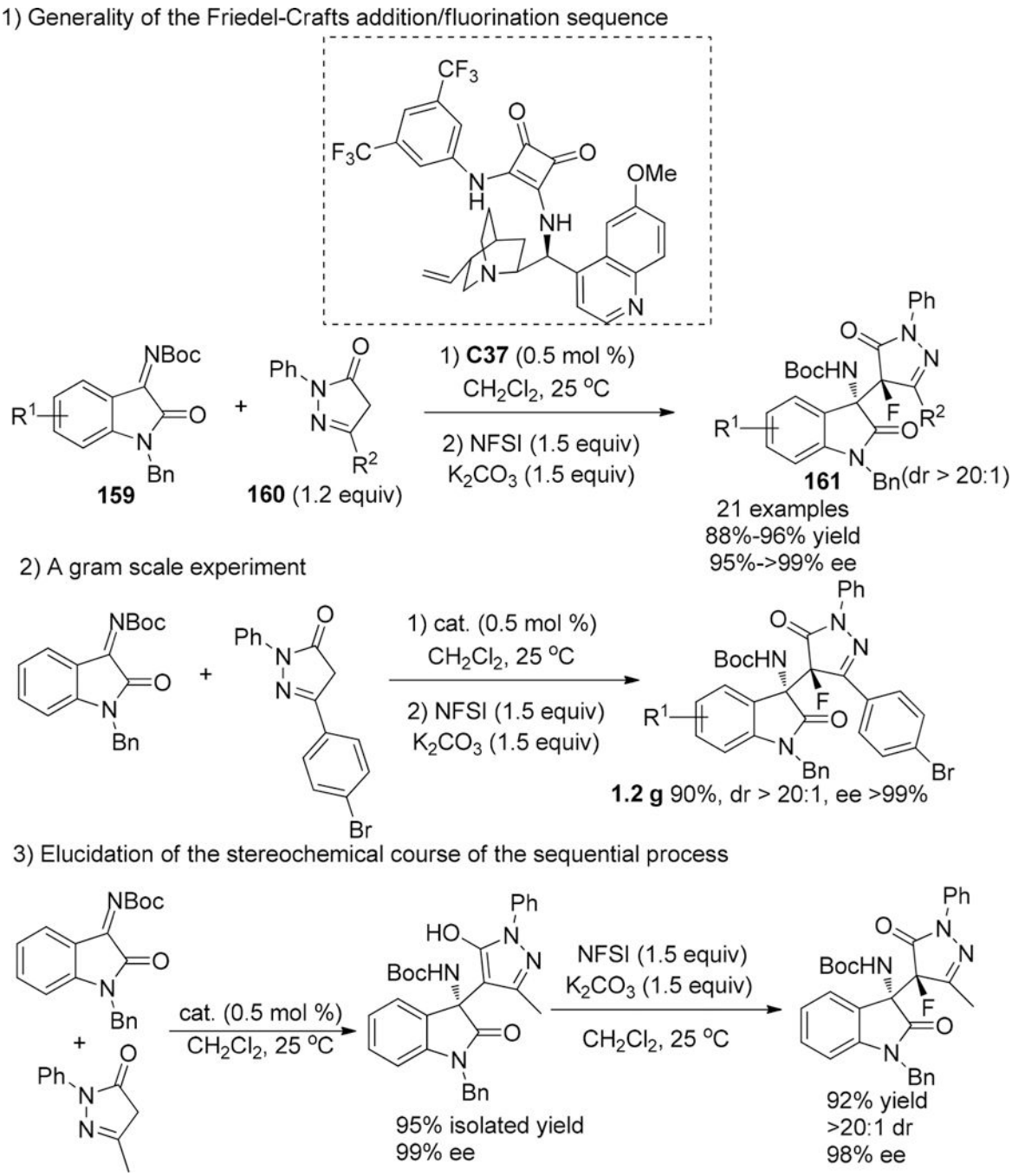


Scheme 44.

Conjugate Addition/Dearomatizative Fluorination of Isoxazol-5(4*H*)-ones 155

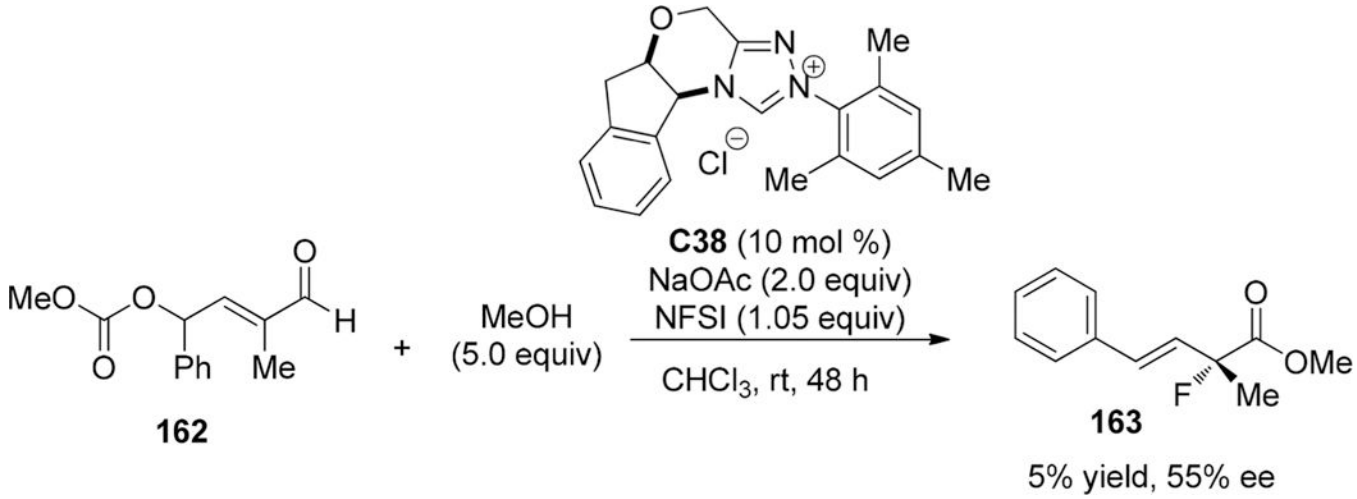


Scheme 45.
oxa-Michael Addition/Electrophilic Fluorination Transformations

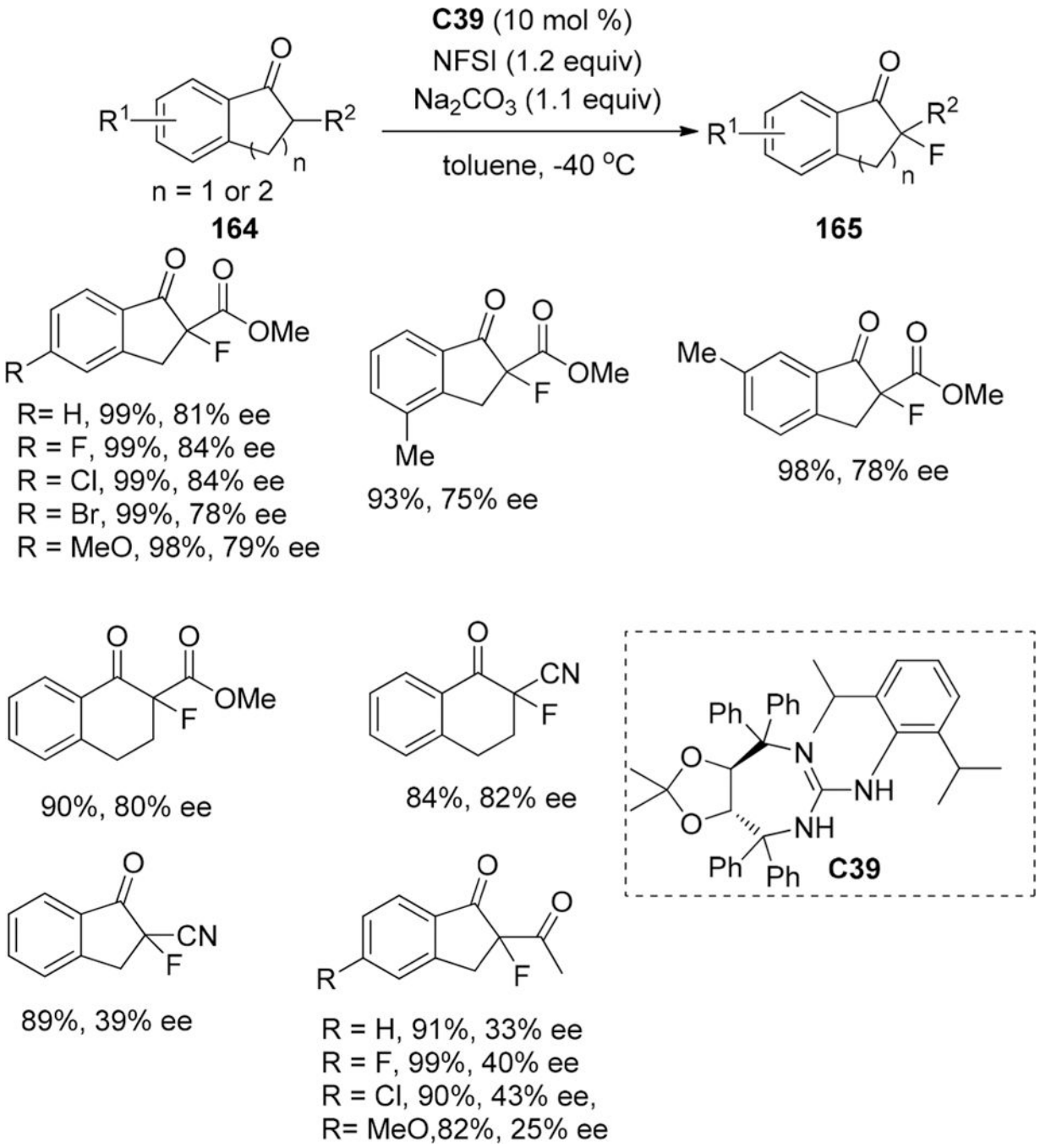


Scheme 46.

Tandem Friedel–Crafts/Fluorination Process: Structural Generality (1), Large-Scale Synthesis (2), and Elucidation of the Stereochemical Outcome (3)

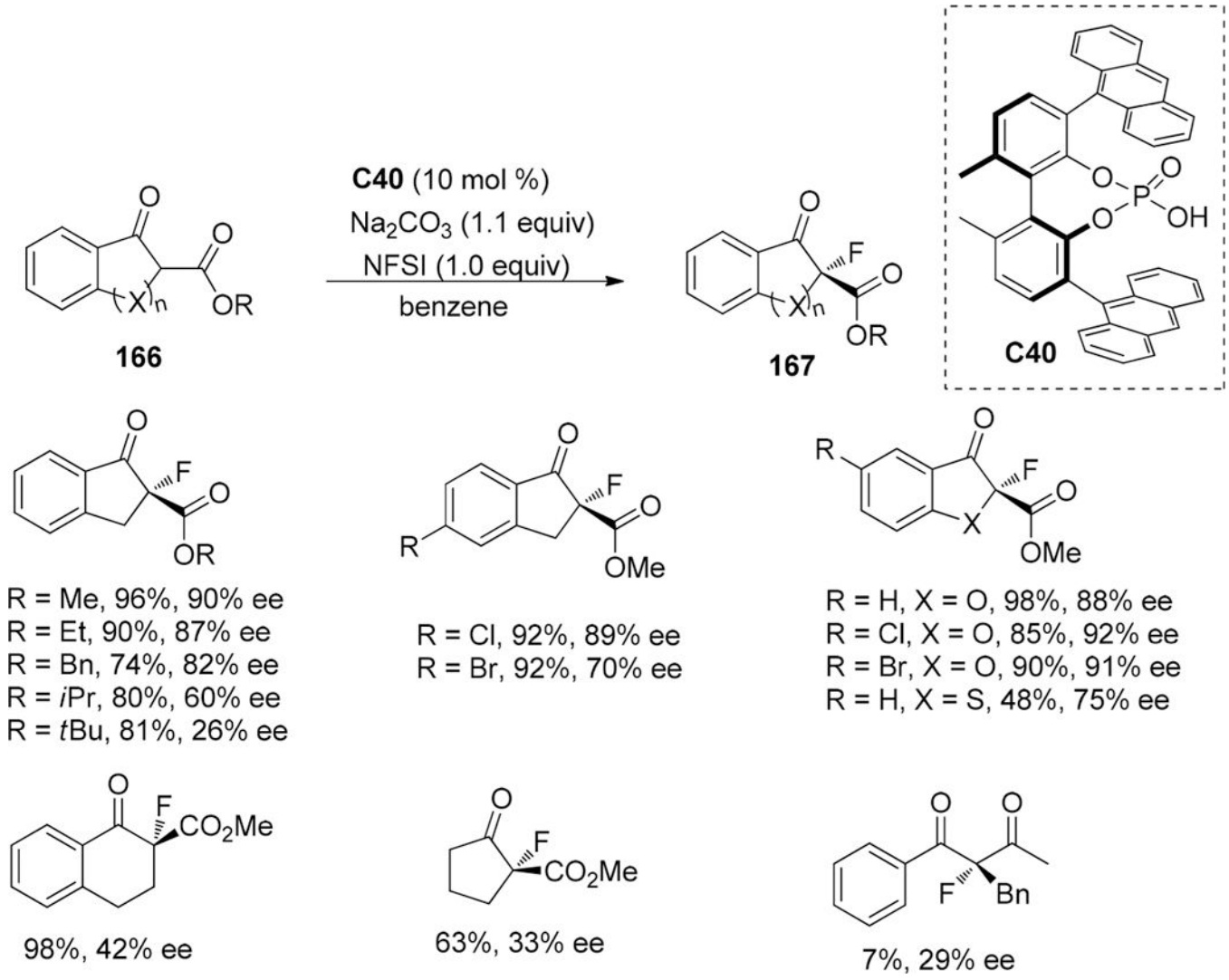


Scheme 47.
Preparation of α-Fluoro-ester 163

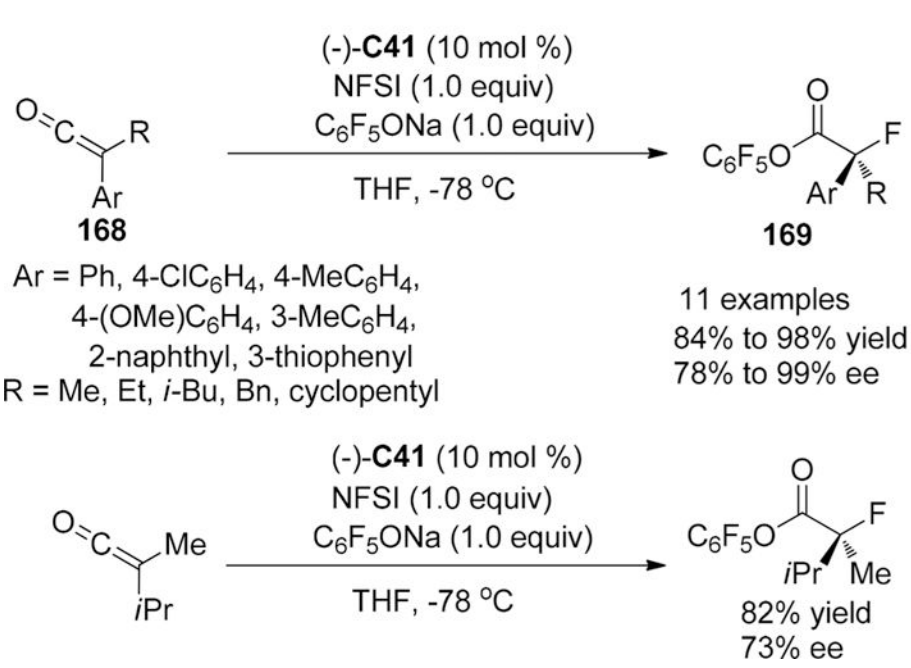


Scheme 48.

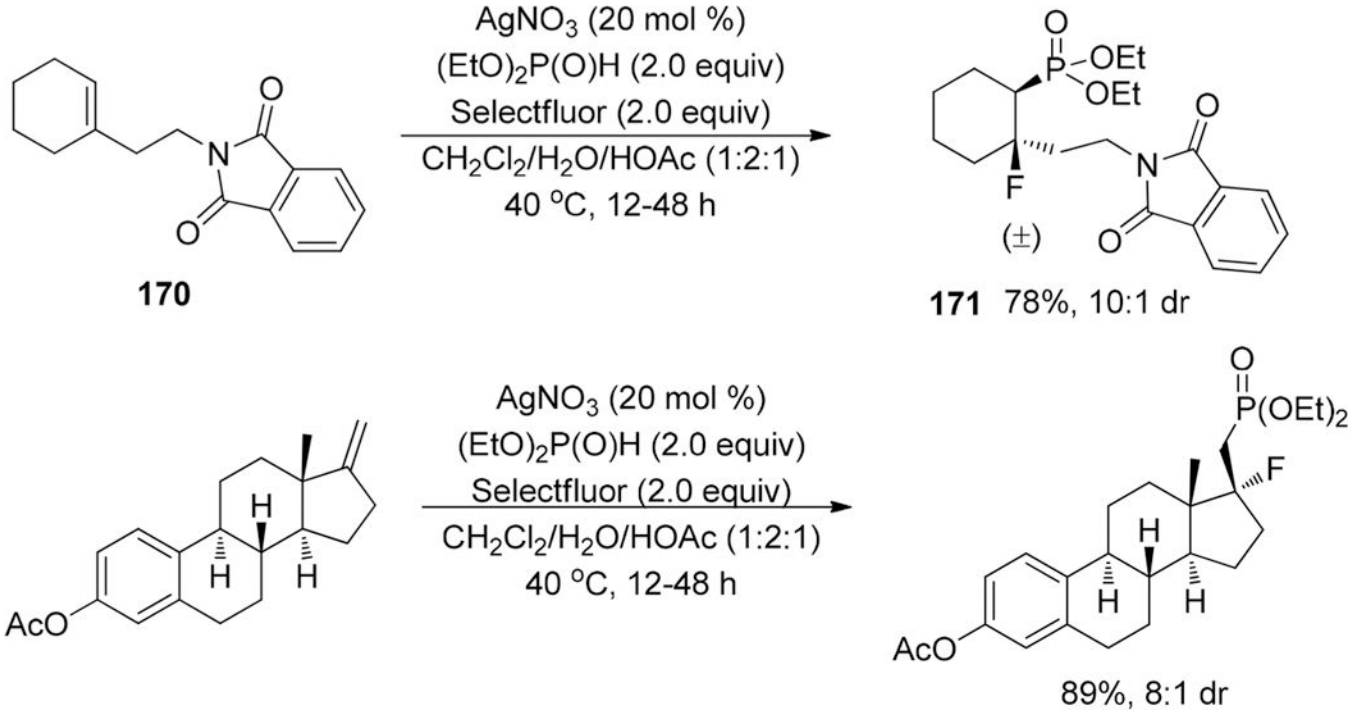
Enantioselective Fluorination of 1,3-Dicarbonyl and α-Cyano Carbonyl Compounds 164



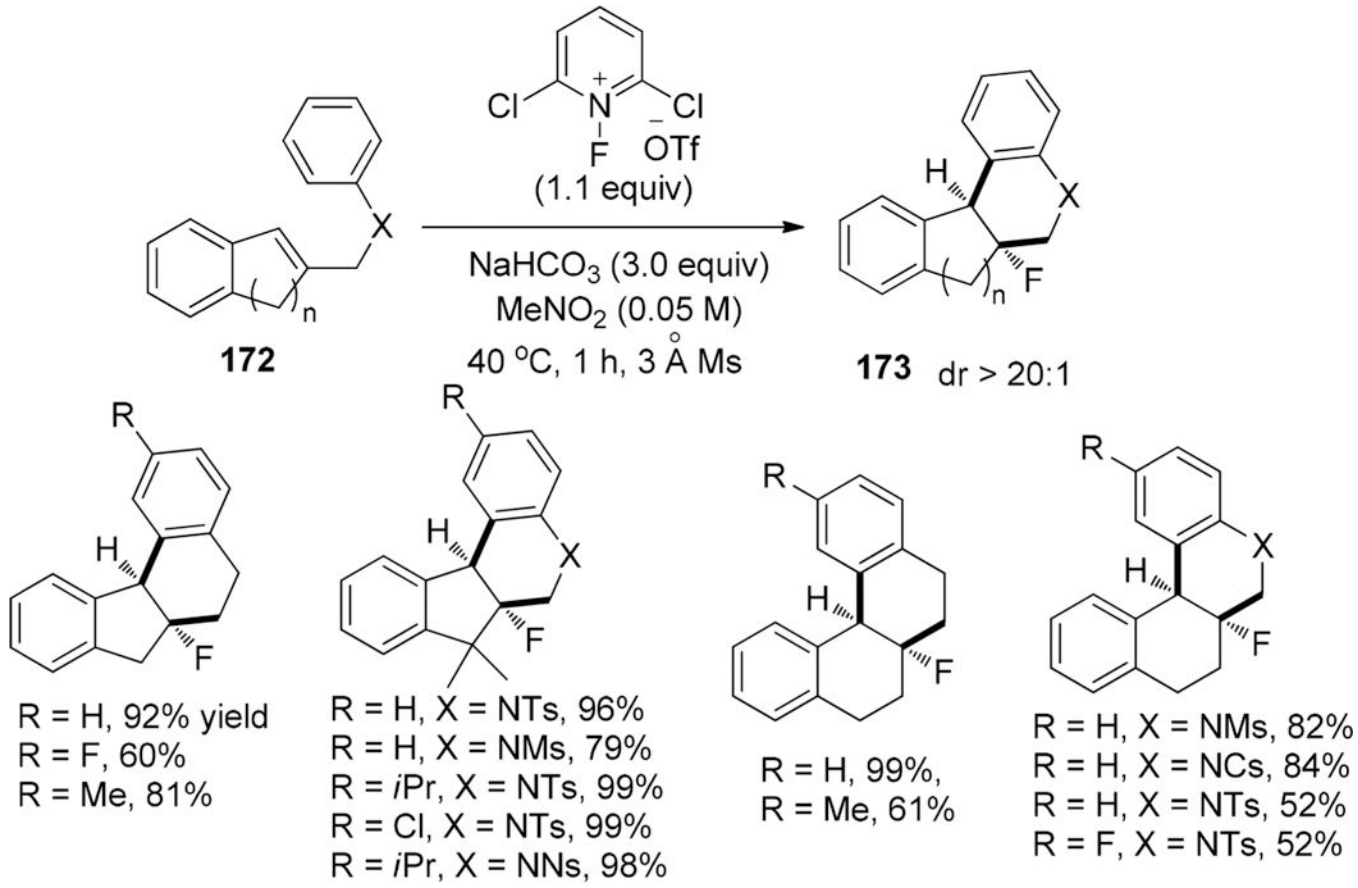
Scheme 49.
Enantioselective Fluorination of β-Keto Esters 166



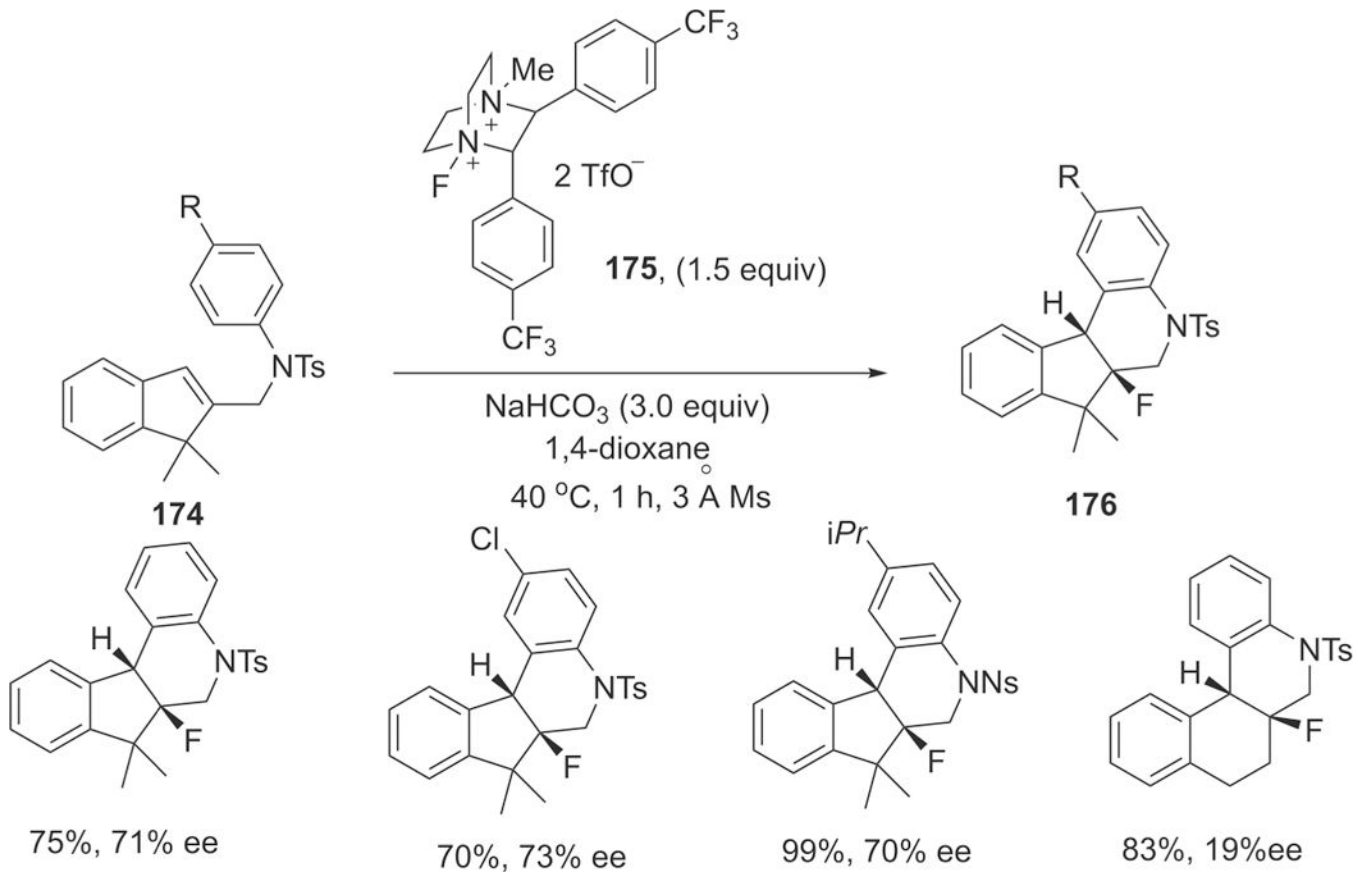
Scheme 50.
Enantioselective Coupling of Aryl Alkyl Ketenes 168



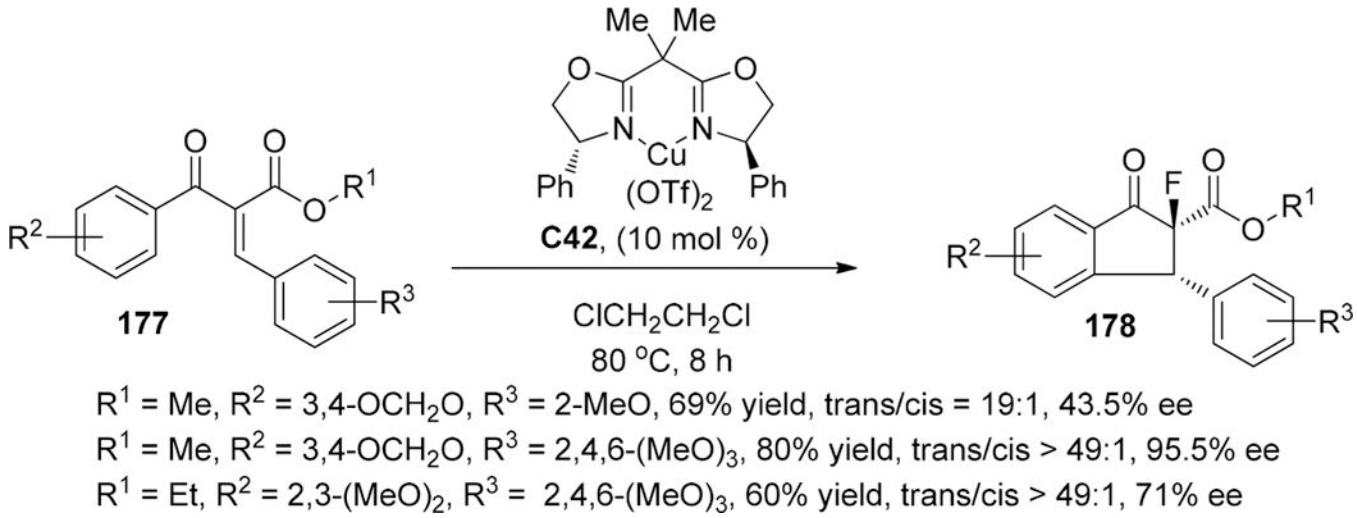
Scheme 51.
Phosphono-fluorination of Unactivated Alkenes 170



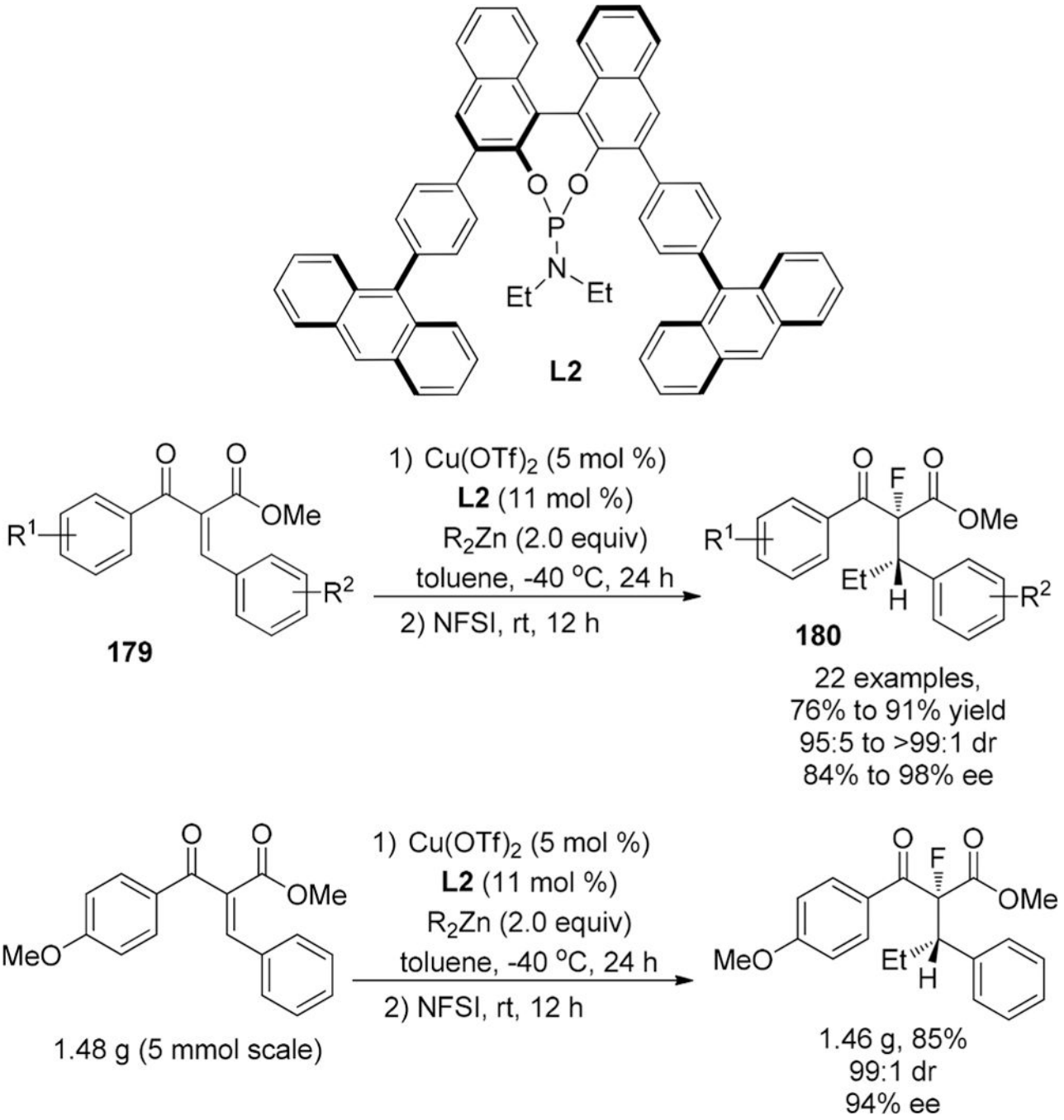
Scheme 52.
Electrophilic Fluoro-cyclization of Indenes 172



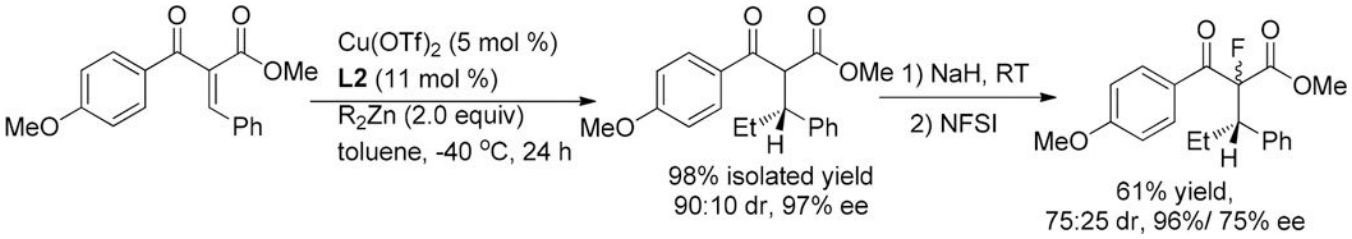
Scheme 53.
Preparation of Fluorotetrahydro-5*H*-indeno-[2,1-*c*]quinolones 176



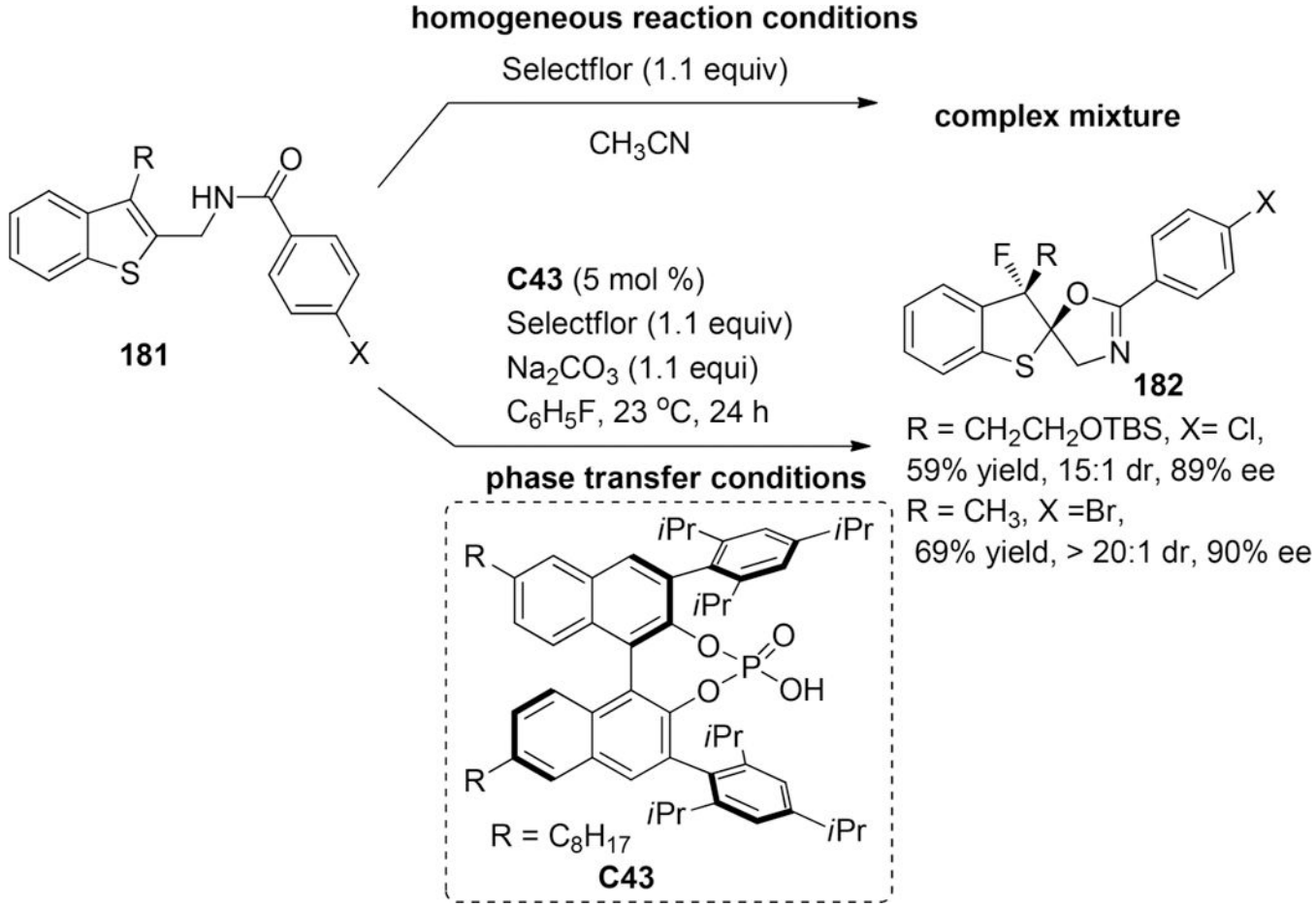
Scheme 54.
Enantioselective Tandem Nazarov Cyclization/Electrophilic Fluorination Sequence



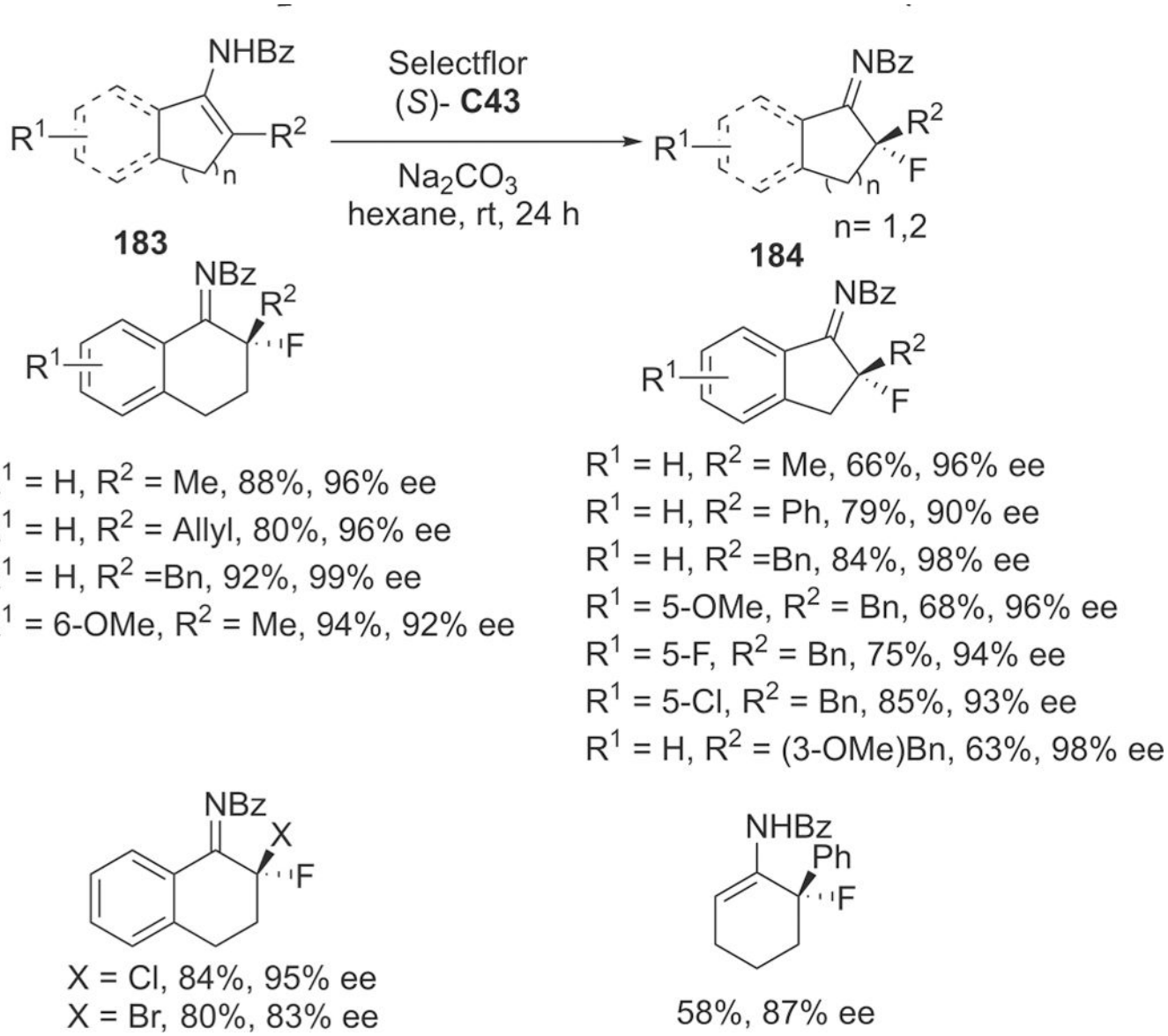
Scheme 55.
Tandem 1,4-Addition/Fluorination Sequence of Acyclic Alkylidene β-Keto Esters 179



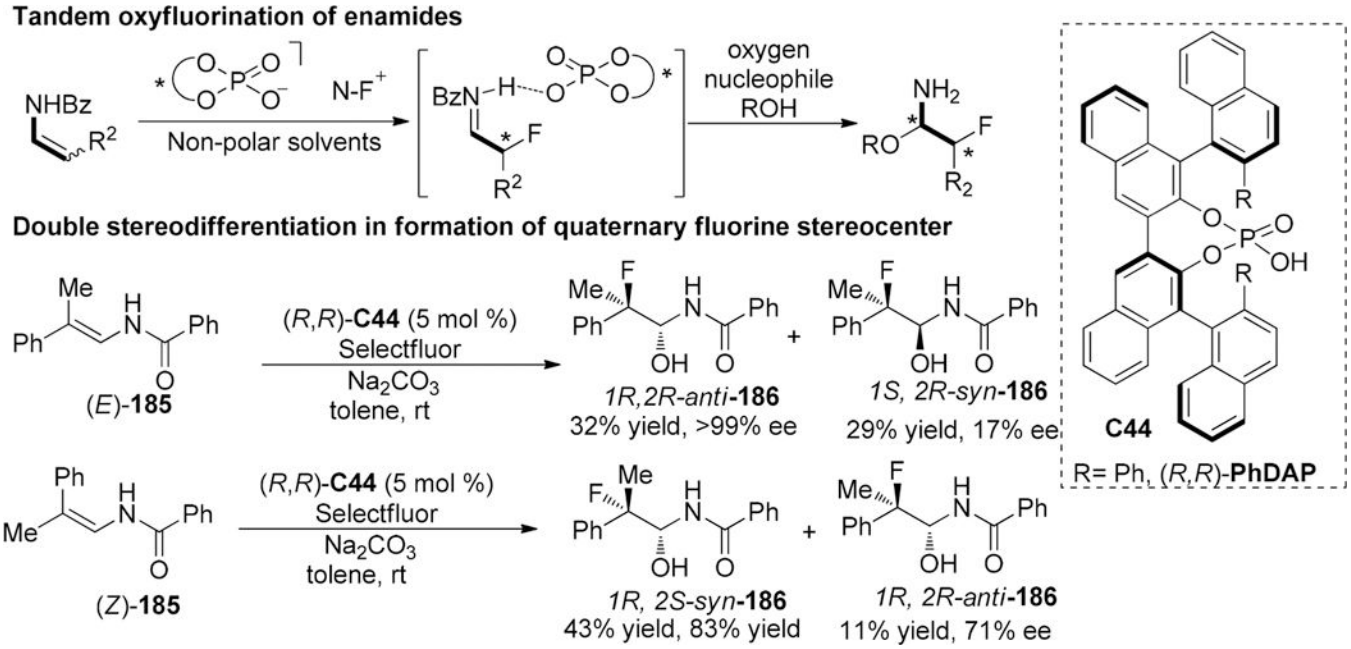
Scheme 56.
Asymmetric Fluorination of Alkylidene β-Keto Esters



Scheme 57.
Enantioselective Fluoro-cyclization of Alkenes 181

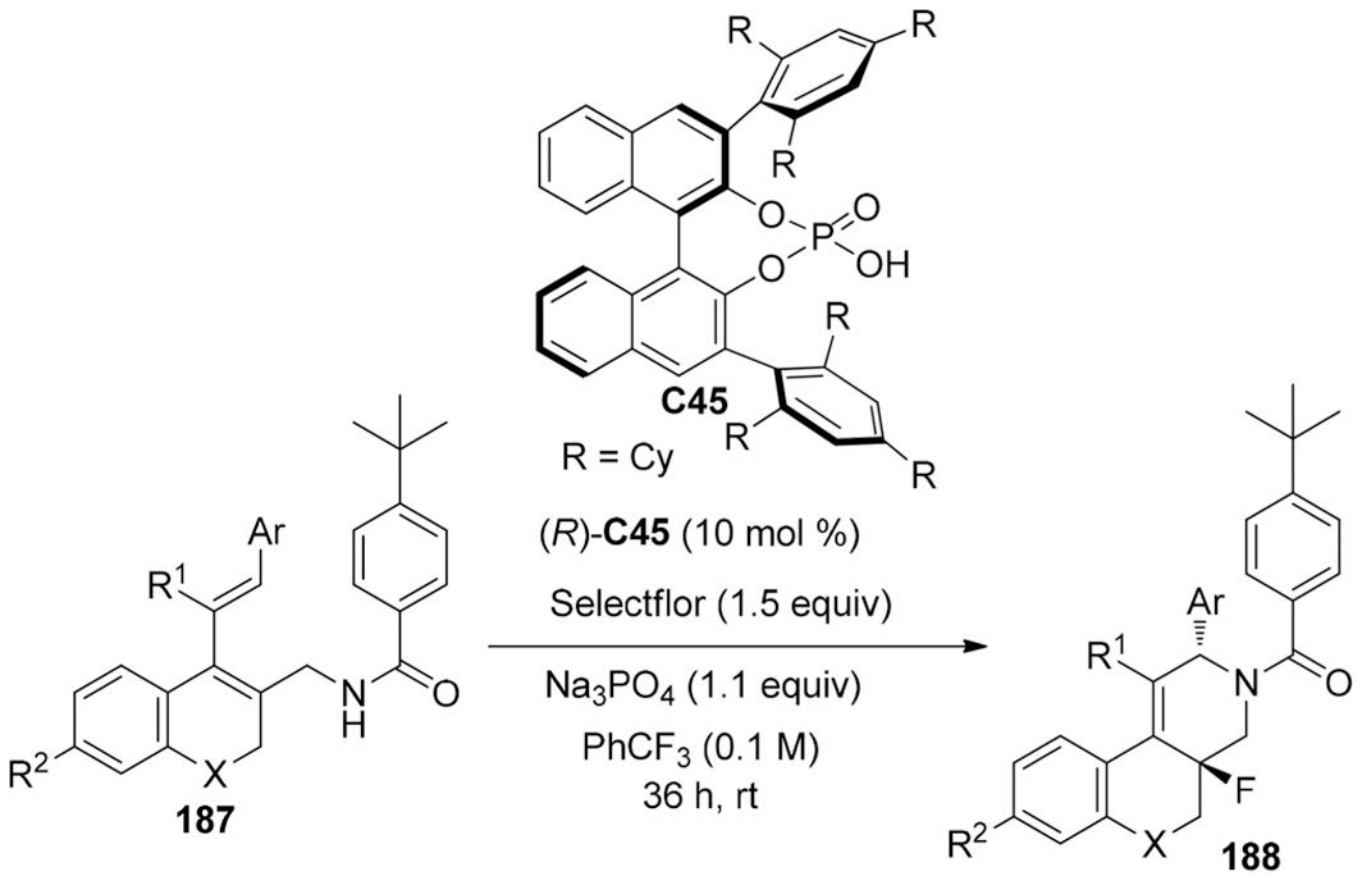


Scheme 58.
Preparation of α-Fluorinated Benzoyl-imines 184



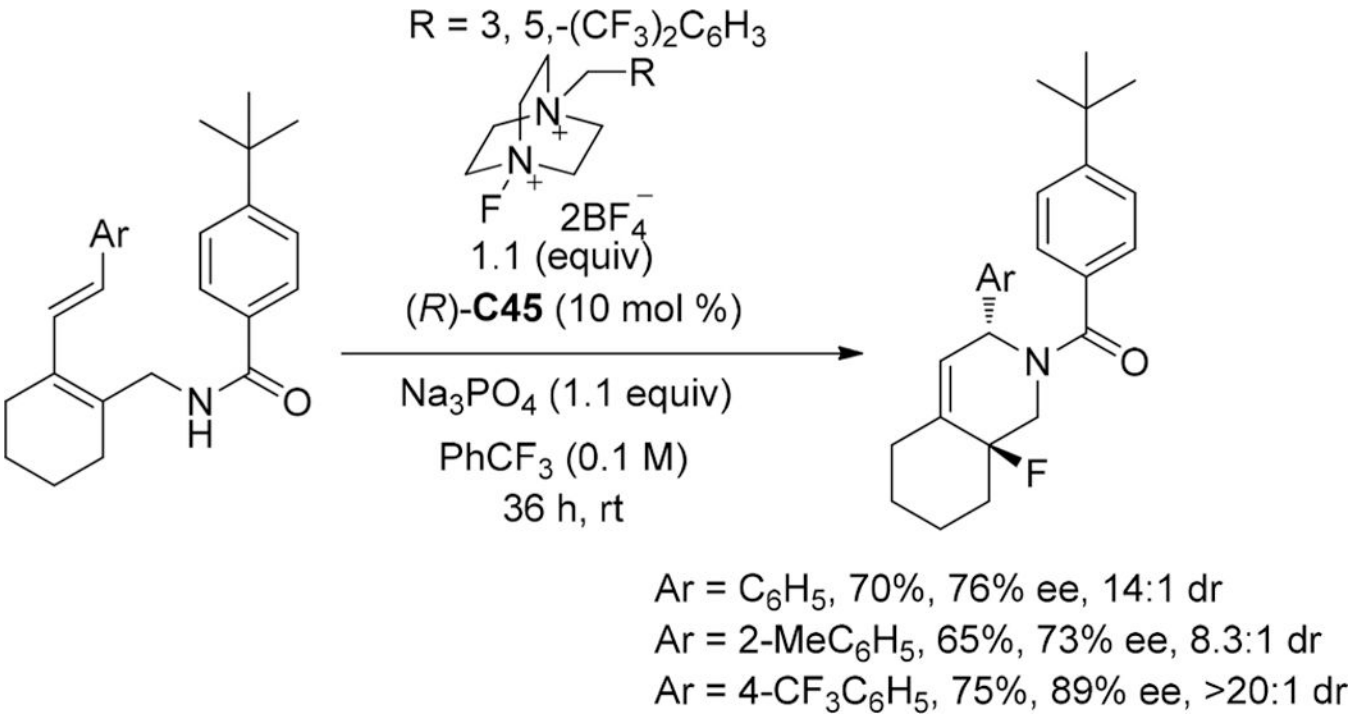
Scheme 59.

Tandem Oxyfluorination Transformations of Acyclic Aldehyde-Derived Enamides

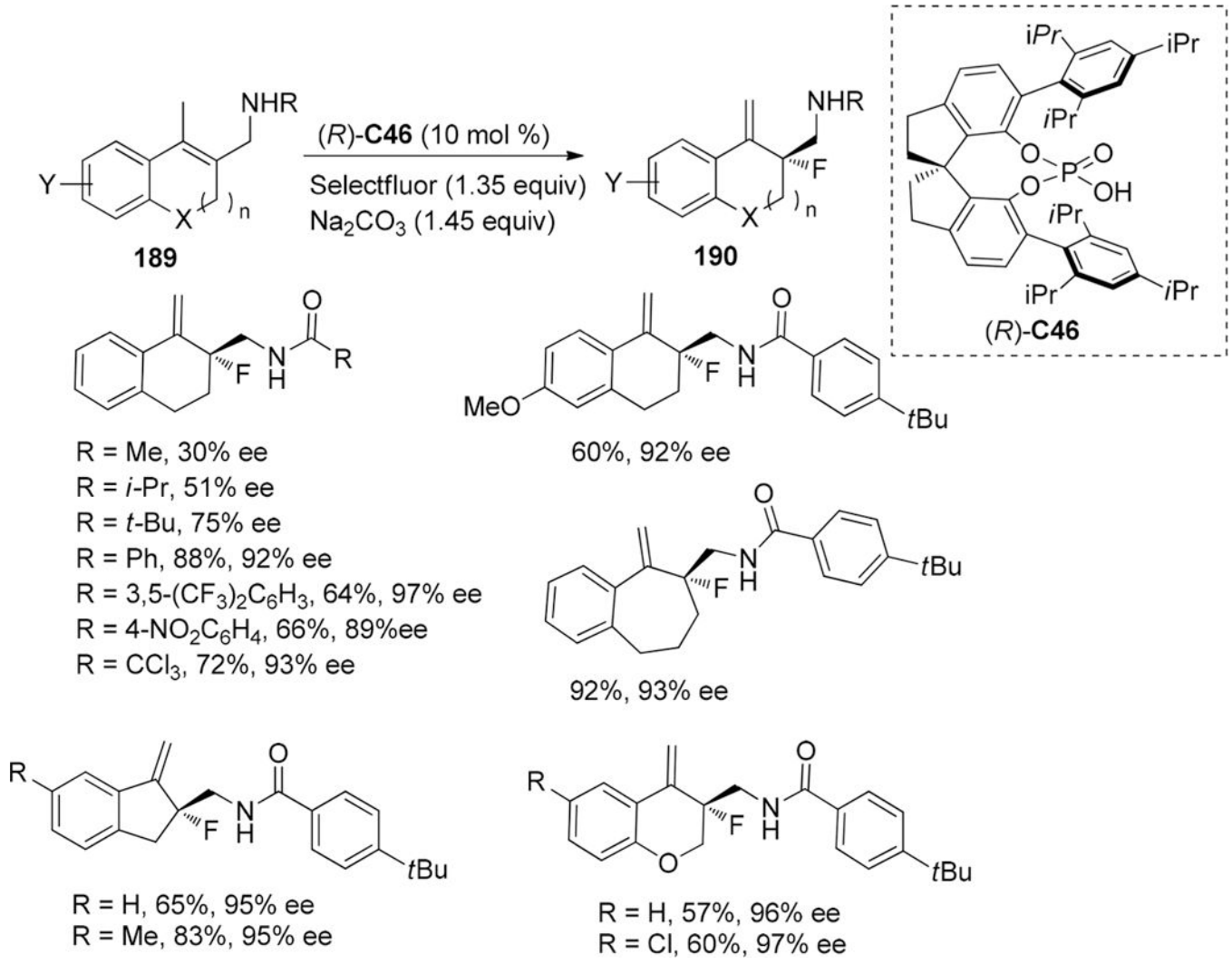


Ar = 2-MeC_6H_4, R^1 = H, R^2 = H, X = -CH_2-, 91%, 96% ee, >20:1 dr
Ar = 3-MeC_6H_4, R^1 = H, R^2 = H, X = -CH_2-, 92%, 92% ee, 5.9:1 dr
Ar = C_6H_5, R^1 = H, R^2 = H, X = -CH_2-, 90%, 92% ee, 6.9:1 dr
Ar = C_6H_5, R^1 = H, R^2 = OMe, X = -CH_2-, 90%, 93% ee, 6.9:1 dr
Ar = C_6H_5, R^1 = H, R^2 = H, X = O, 85%, 91% ee, 5.5:1 dr
Ar = 4-$CF_3C_6H_4$, R^1 = H, R^2 = H, X = -CH_2-, 94%, 95% ee, 10:1 dr
Ar = 4-$MeOC_6H_4$, R^1 = H, R^2 = H, X = -CH_2-, 89%, 93% ee, 7.5:1 dr
Ar = C_6H_5, R^1 = *n*Bu, R^2 = H, X = -CH_2-, 85%, 94% ee, >20:1 dr

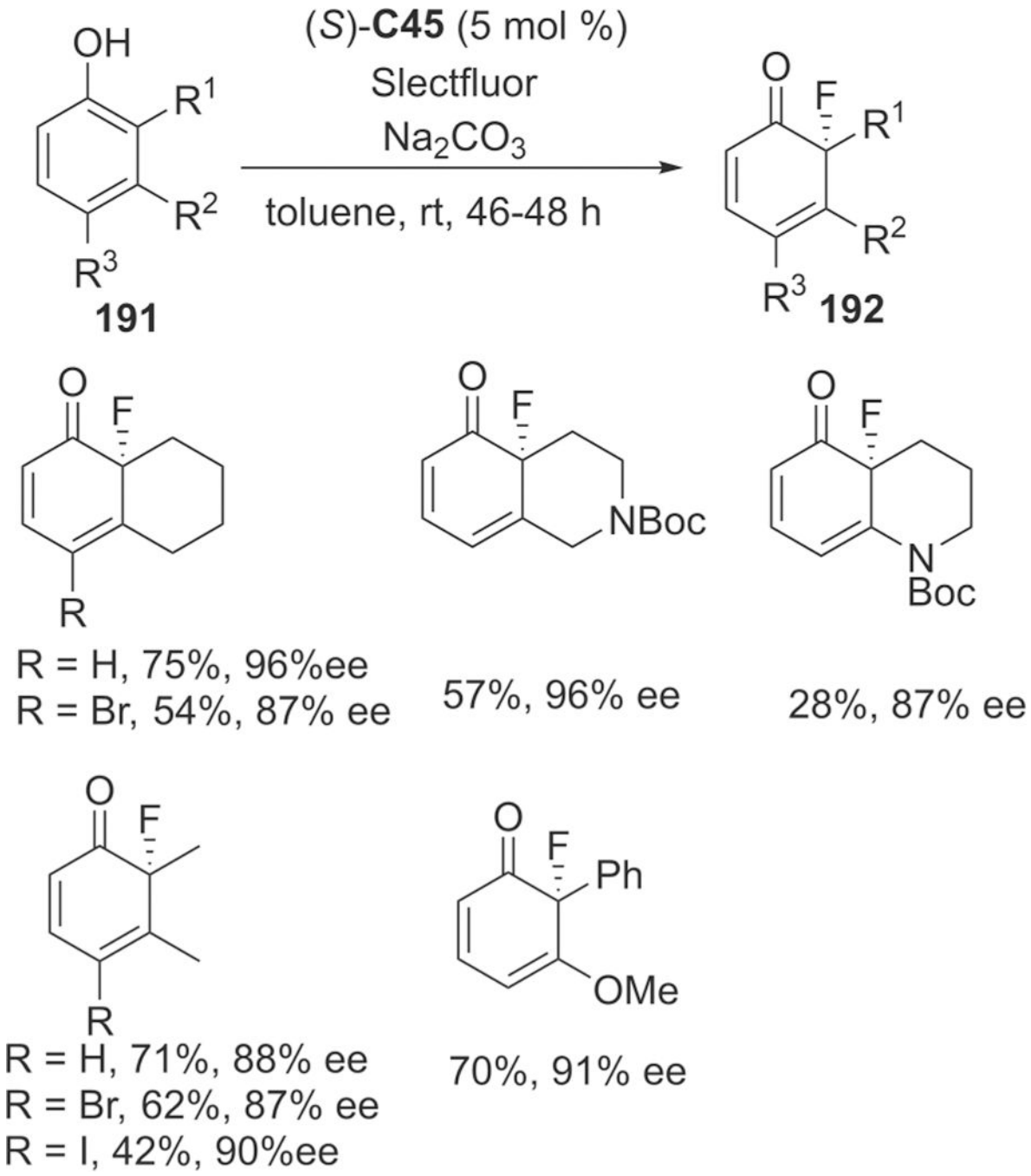
Scheme 60.
Enantioselective 1,4-Aminofluorocyclization of Conjugated 1,3-Dienes



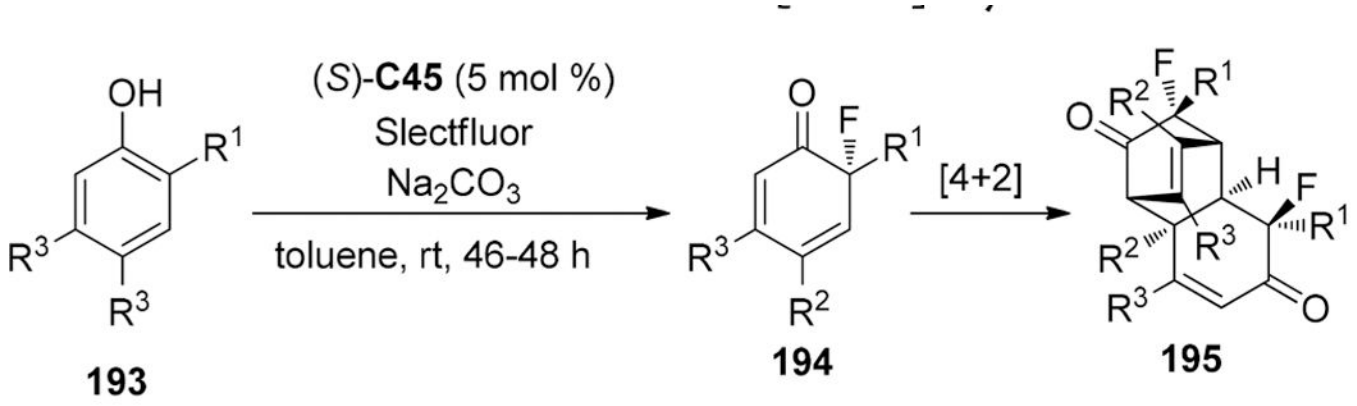
Scheme 61.
Preparation of Octahydro-isoquinoline Compounds with a C–F Quaternary Carbon Center



Scheme 62.
Enantioselective Electrophilic Fluorination of Alkenes 189

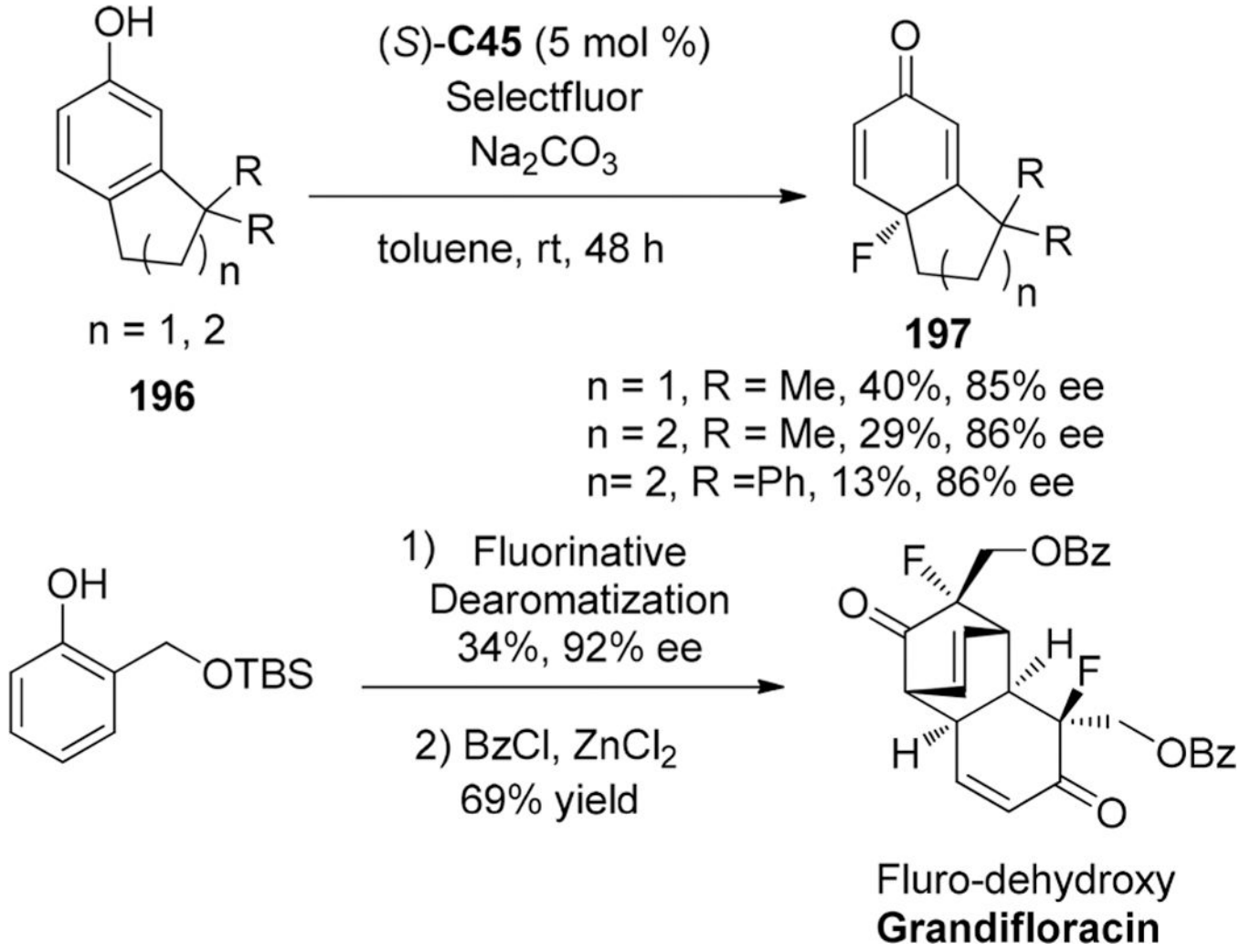


Scheme 63.
Asymmetric Fluorination of 2,3-Disubstituted Phenols 191

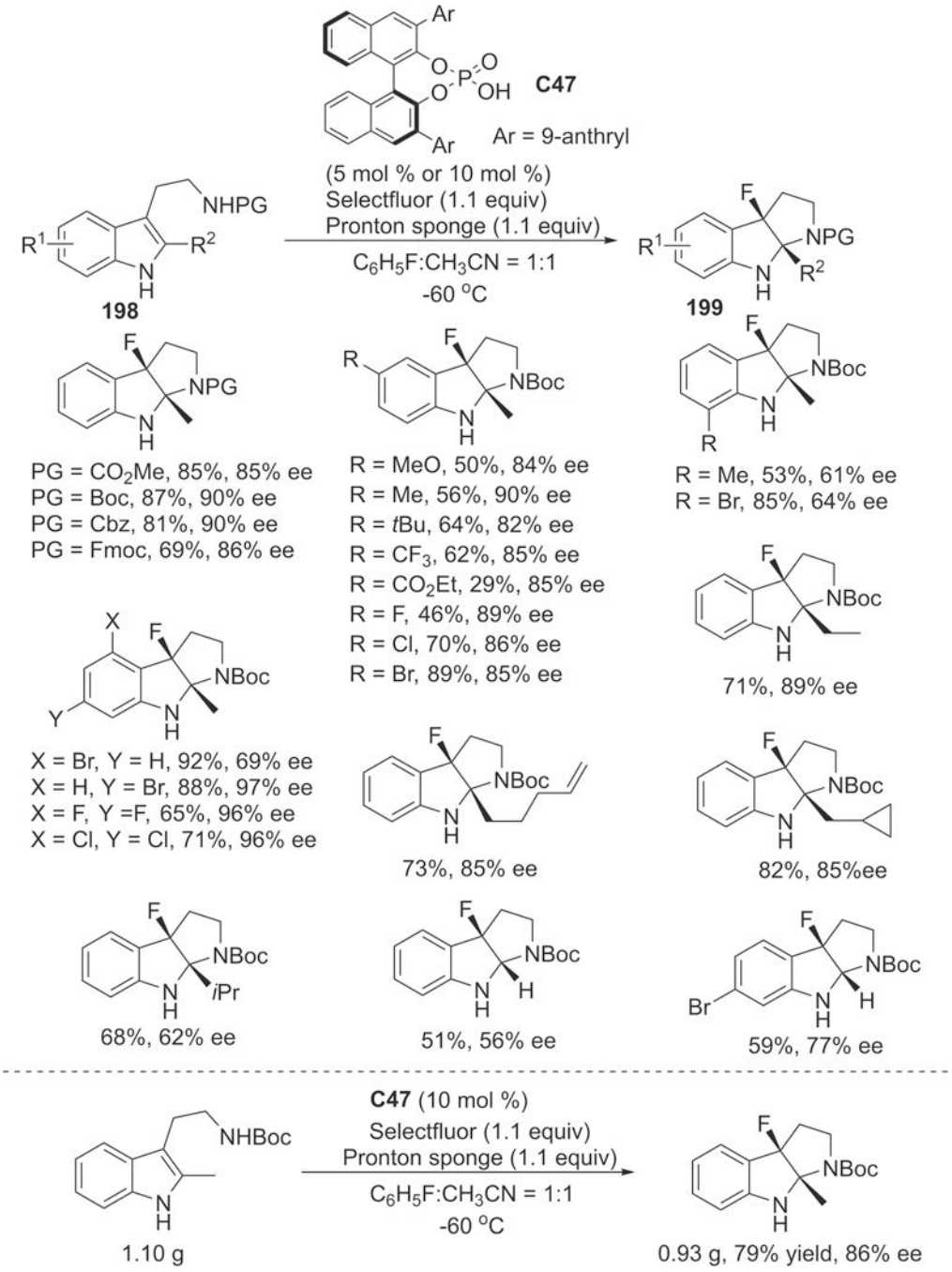


R^1 = Bn, R^2 = H, R^3 =H, 81%, 97% ee
R^1 = Ph, R^2 = H, R^3 =H, 55%, 90% ee
R^1 = Homoallyl, R^2 = H, R^3 =H, 65%, 90% ee
R^1 = allyl, R^2 = H, R^3 =H, 71%, 87% ee
R^1 = *i*-Pr, R^2 = H, R^3 =H, 96%, 91% ee
R^1 = Cy, R^2 = H, R^3 =Me, 75%, 79% ee
R^1 = allyl, R^2 = Me, R^3 =H, 51%, 92% ee
R^1 = Bn, R^2 = Me, R^3 =H, 67%, 90% ee
R^1 = $(CH_2)_3OTBS$, R^2 = H, R^3 =H, 77%, 91% ee

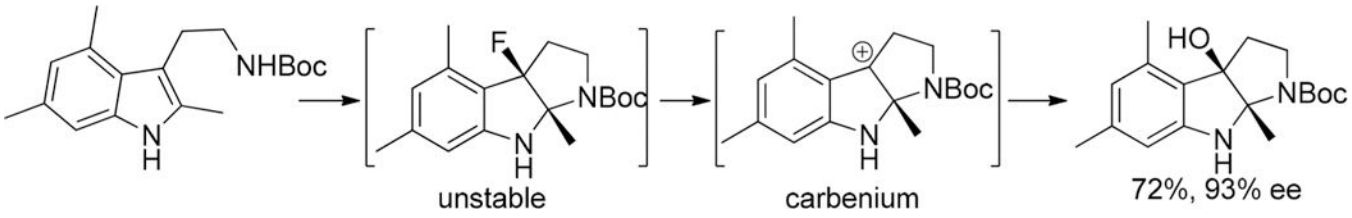
Scheme 64.
Tandem Fluorination-[4 + 2] Cycloaddition



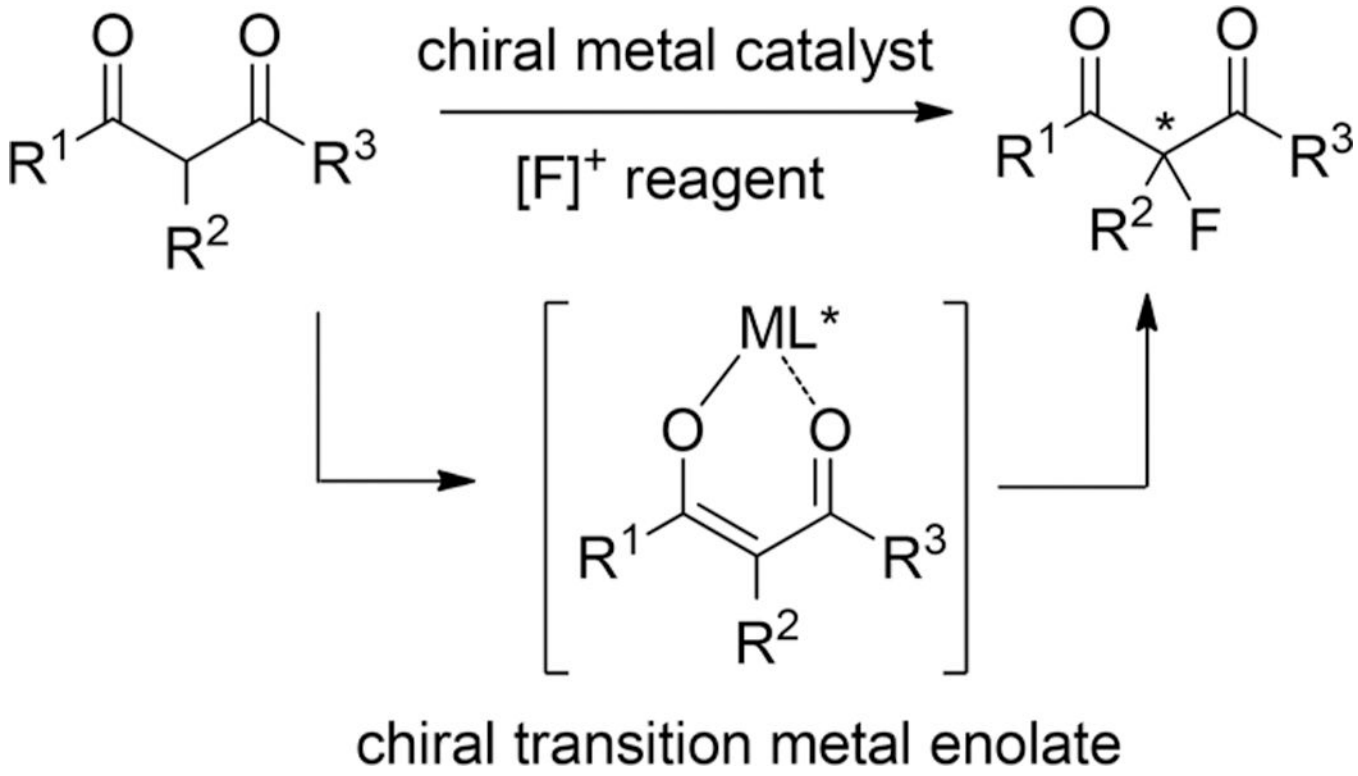
Scheme 65.
Preparation of Fluorinated Analogue of Natural Product (–)-Grandifloracin



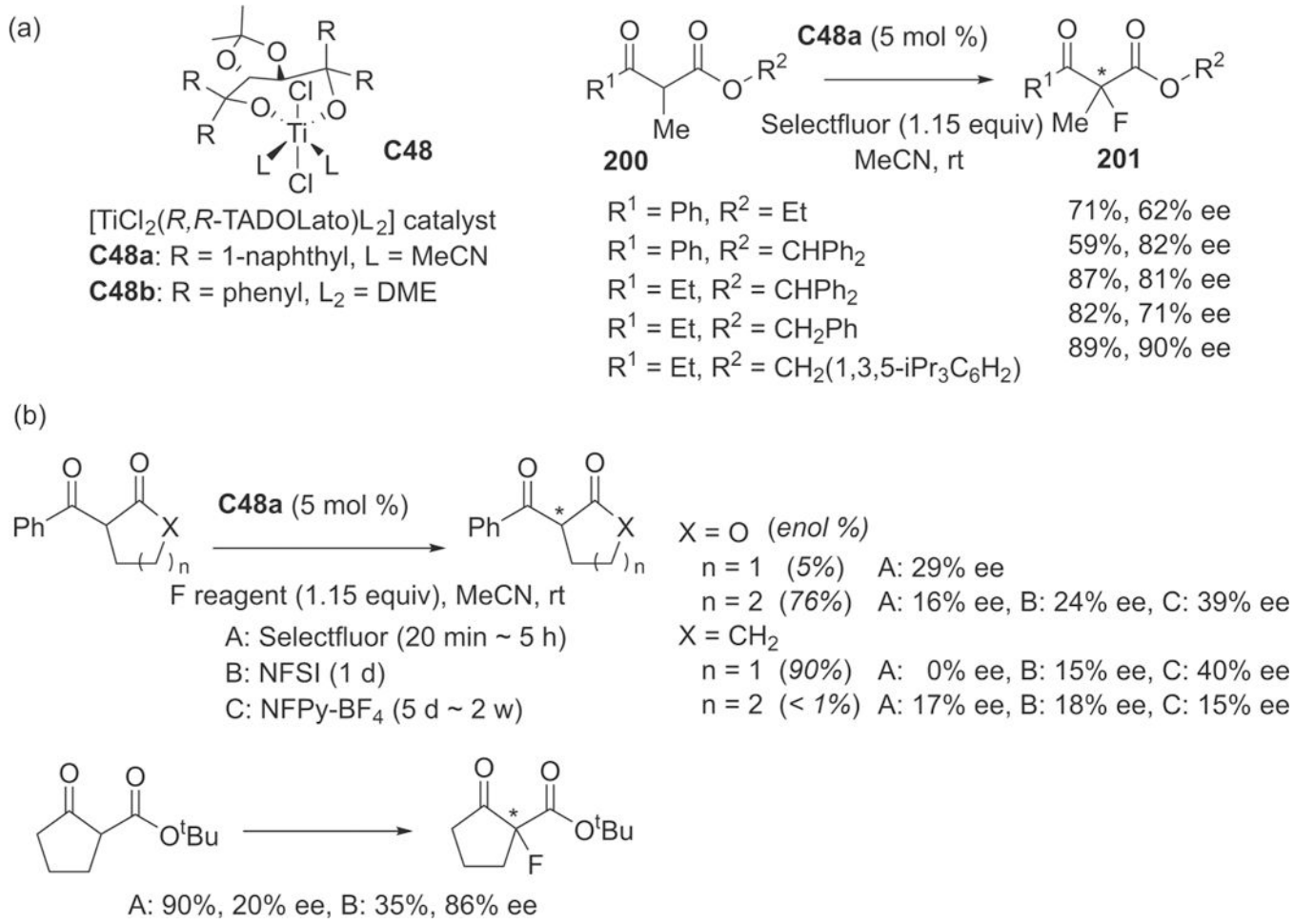
Scheme 66.
Asymmetric Fluorinative Dearomatization of Tryptamide Derivatives



Scheme 67.
Asymmetric Fluorinative Dearomatization of 3,5-Dimethyl Substituted Substrate

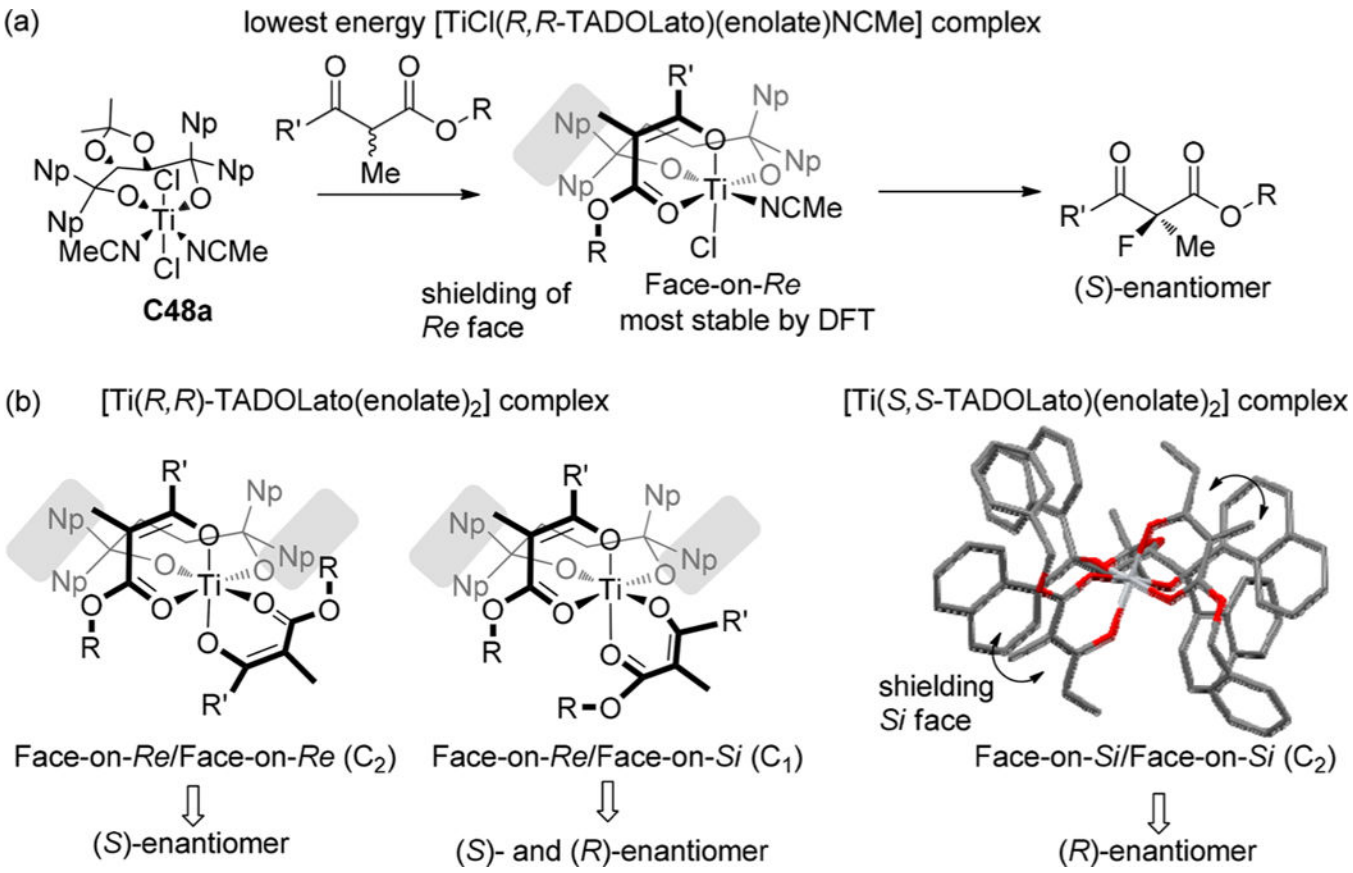


Scheme 68.
Intermediate Transition Metal Bidentate Enolate Complexes

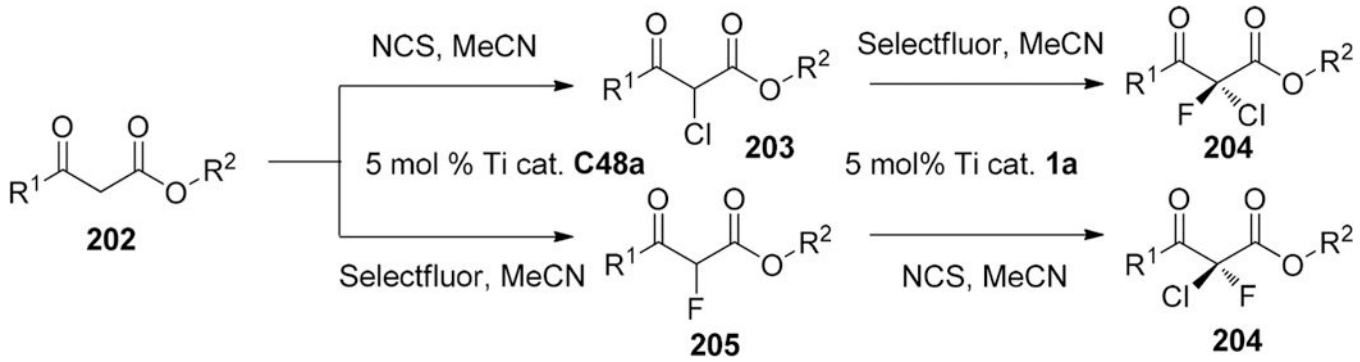


Scheme 69.

Asymmetric Fluorination of Acyclic (a) and Cyclic β-Keto Esters (b)

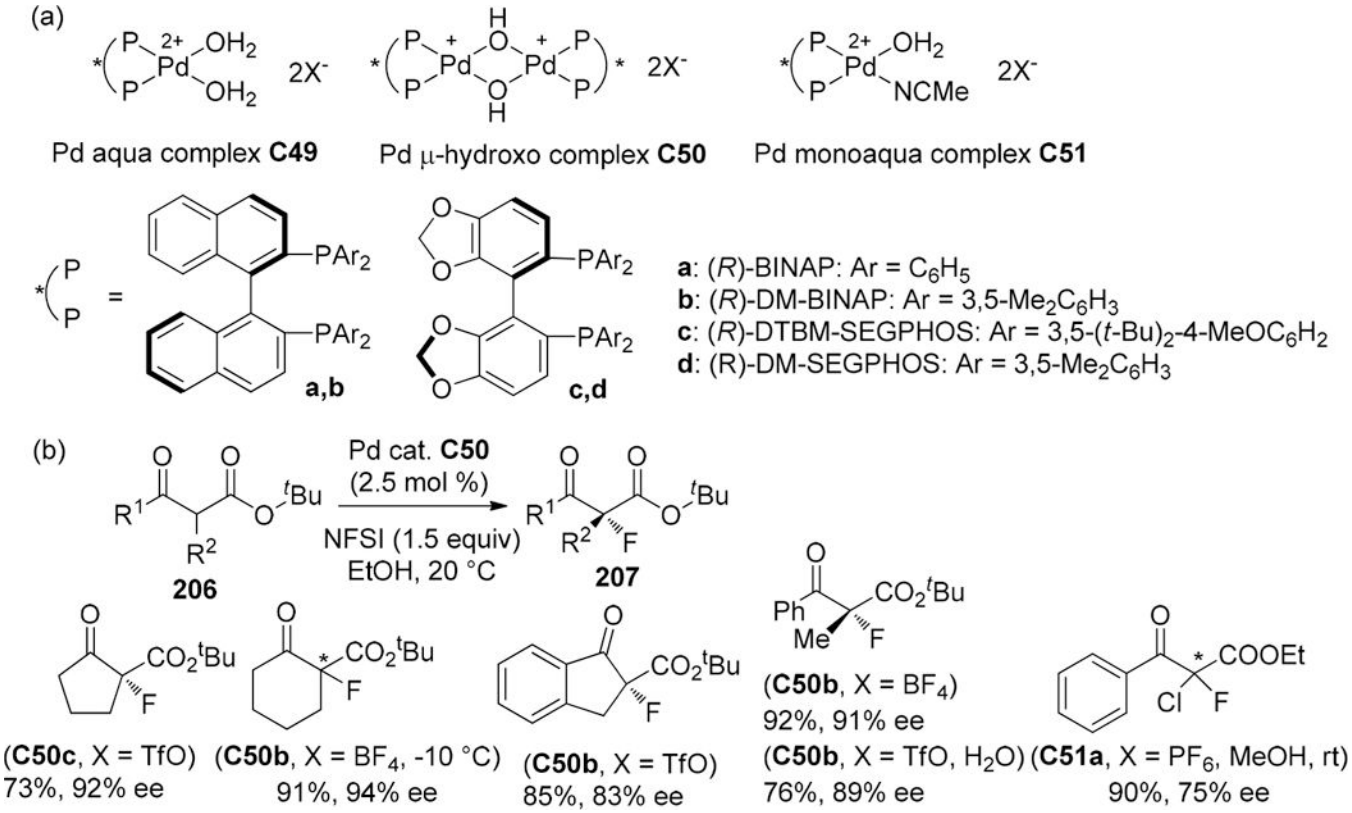


Scheme 70.
Enolate Re-Face (a) and Si-Face (b) Shielding Considerations



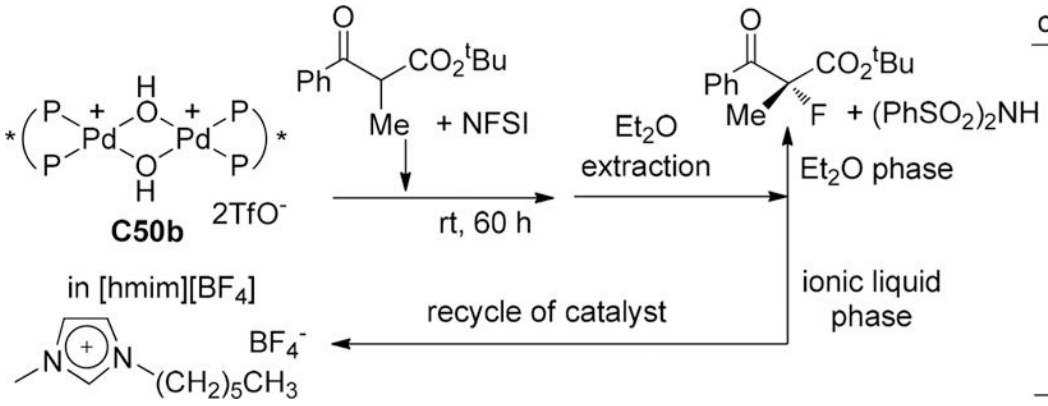
Scheme 71.

Enantioselective Sequential Fluoro-chlorination and Chloro-fluorination of β-Keto Esters



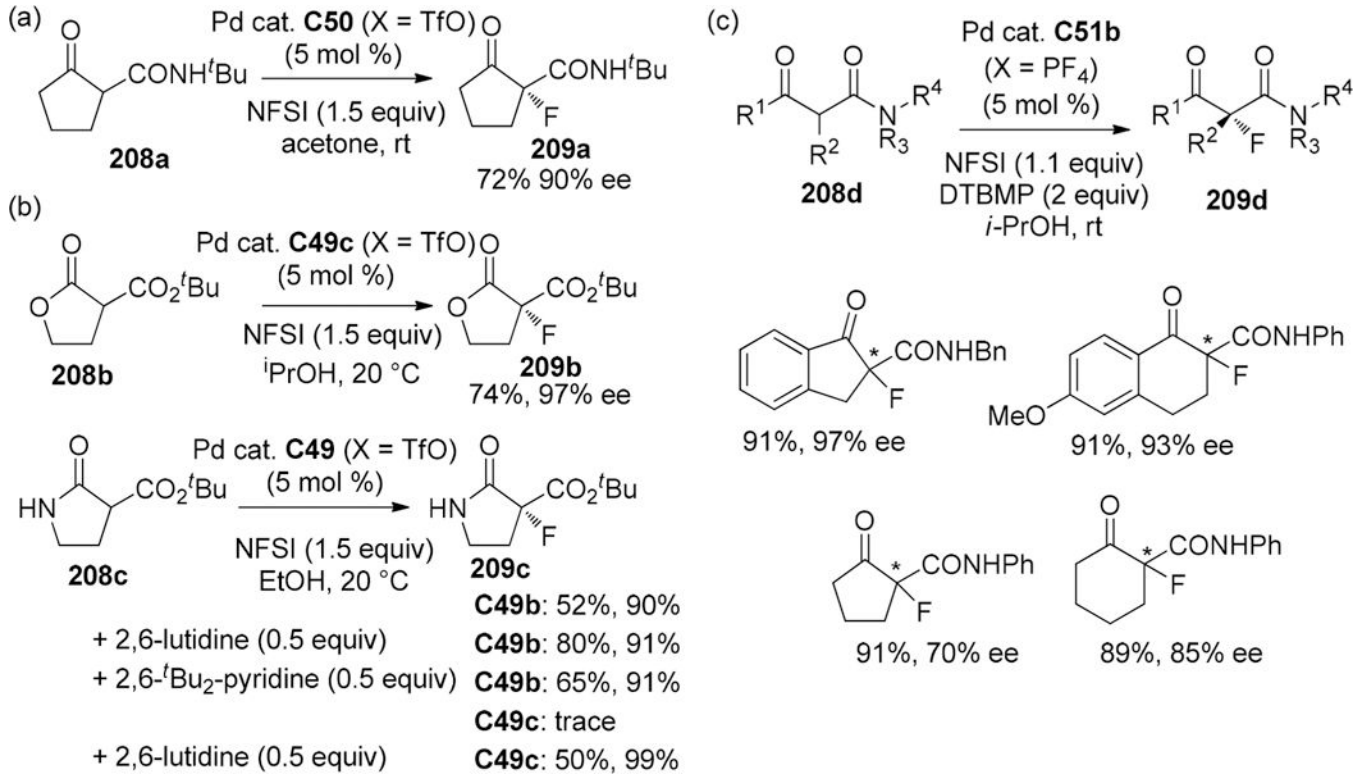
Scheme 72.

Enantioselective Fluorination Reactions Catalyzed by Palladium Complex (a) and Its Application for Acyclic and Cyclic Substrates (b)



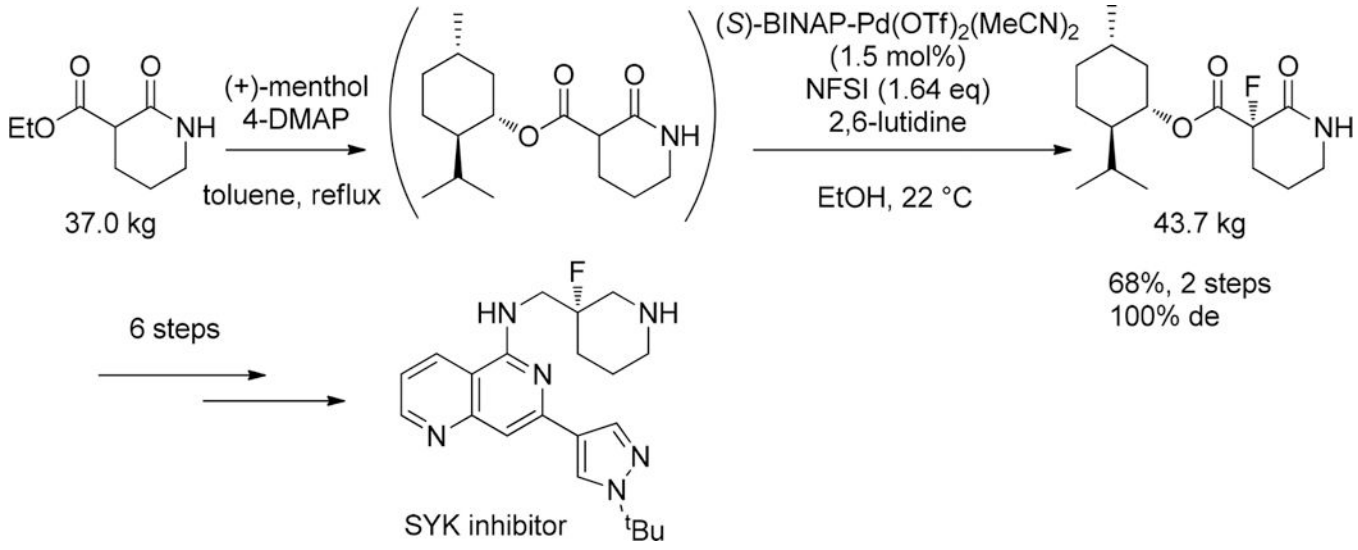
cycle	yield, ee
1	93%, 92% ee
2	80%, 91% ee
3	81%, 91% ee
4	91%, 91% ee
5	81%, 91% ee
6	91%, 91% ee
7	91%, 91% ee
8	86%, 91% ee
9	86%, 91% ee
10	67%, 91% ee

Scheme 73.
Pd-Catalyzed Fluorination of β-Keto Esters

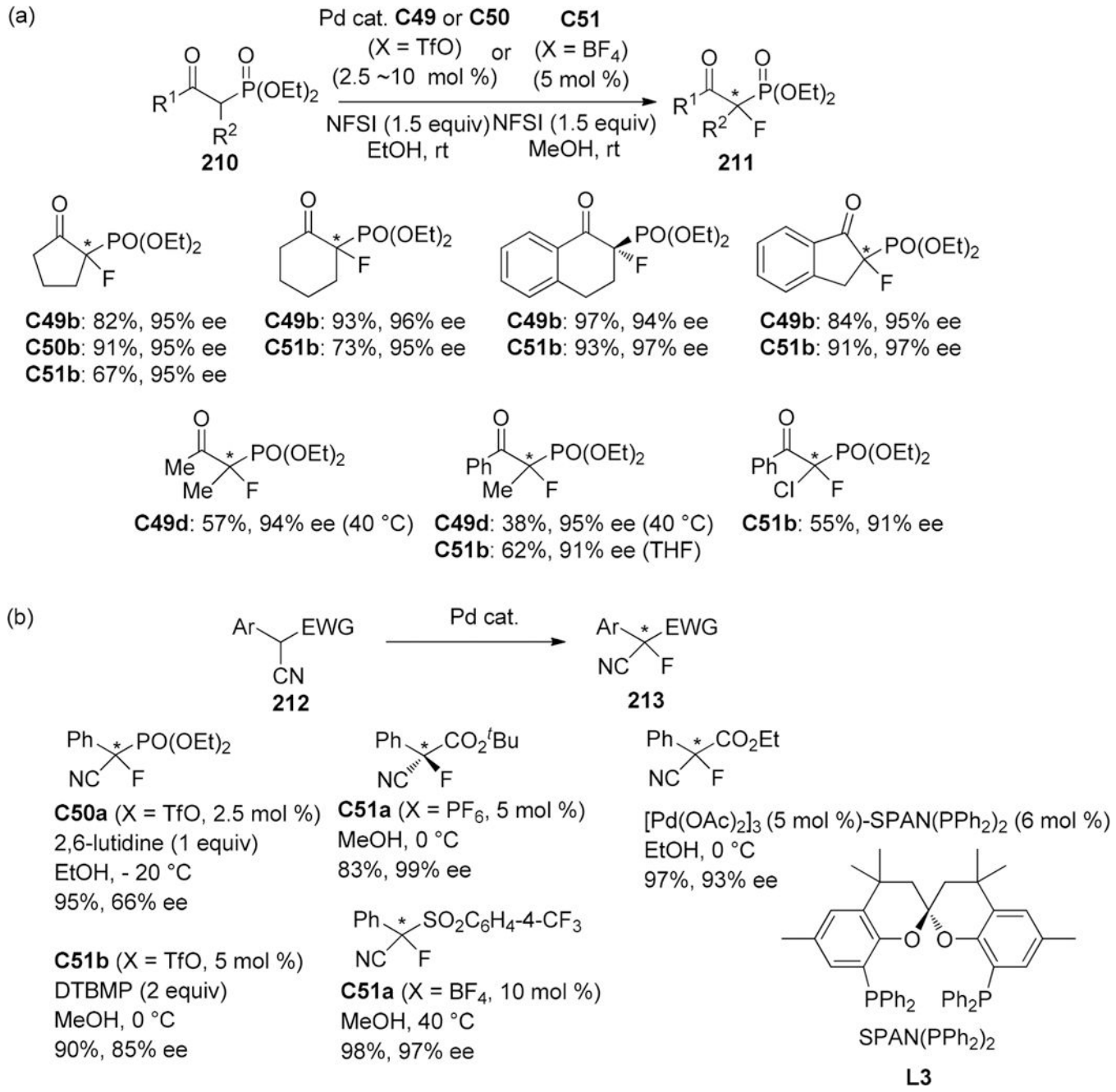


Scheme 74.

Pd-Catalyzed Fluorination of β-Keto Amides (a) and Their Heterocyclic Analogues (b)

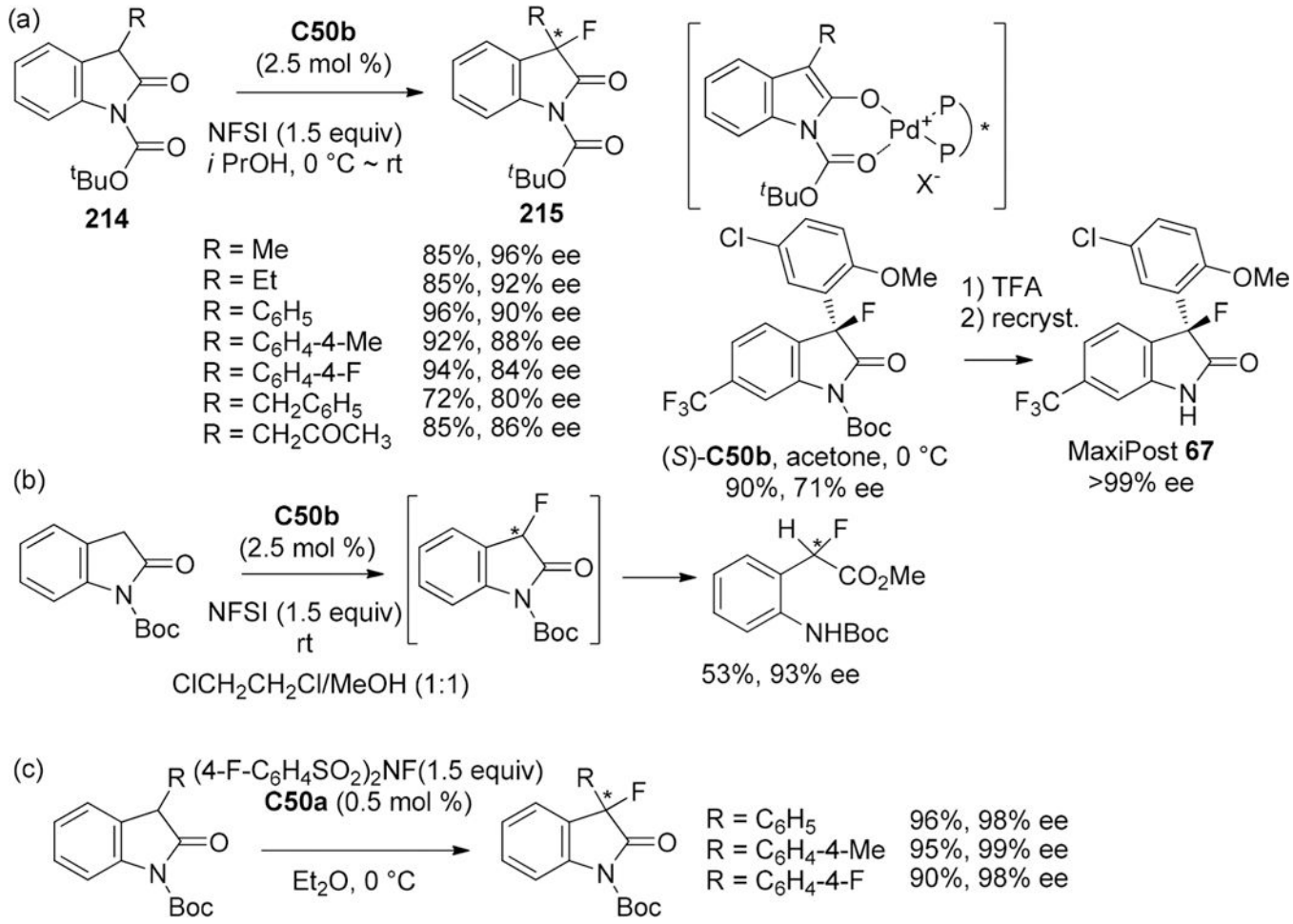


Scheme 75.
Large-Scale Preparation of Commercial SYK Inhibitor



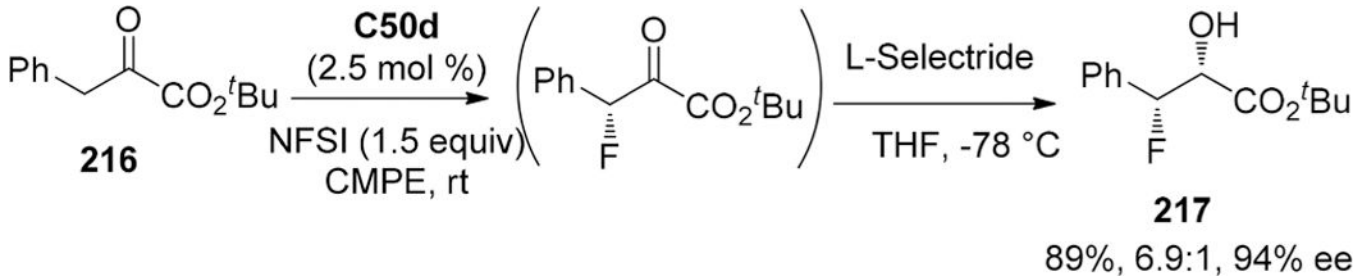
Scheme 76.

Asymmetric Fluorination of β-Keto Phosphonate Esters (a) and α-Aryl-α-cyanophosphate Esters (b)

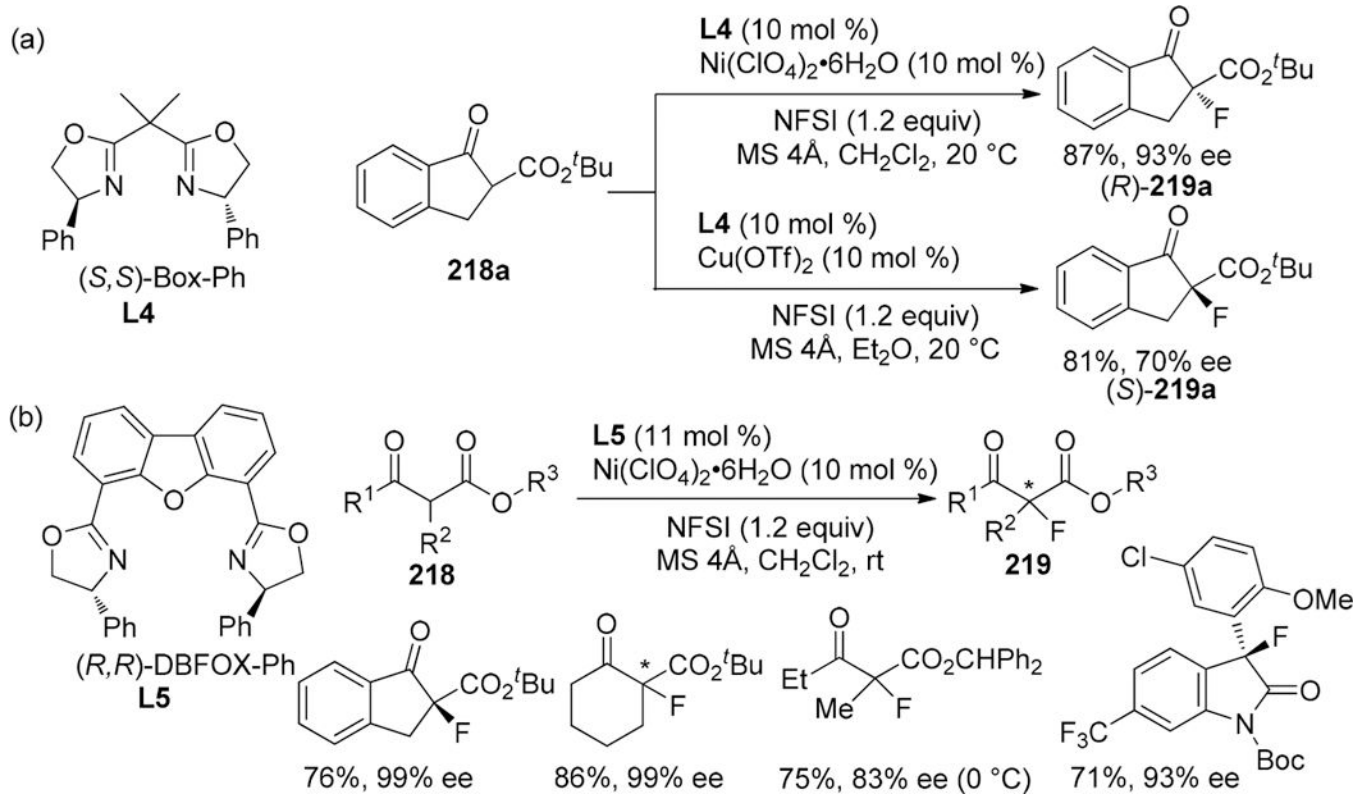


Scheme 77.

Enantioselective Fluorination of Oxindole Derivatives; 3-Substituted *N*-Boc Oxindoles (a), 3-Unsubstituted *N*-Boc Oxindoles (b), and Conditions Using only 0.5 mol % of the Catalysts (c)

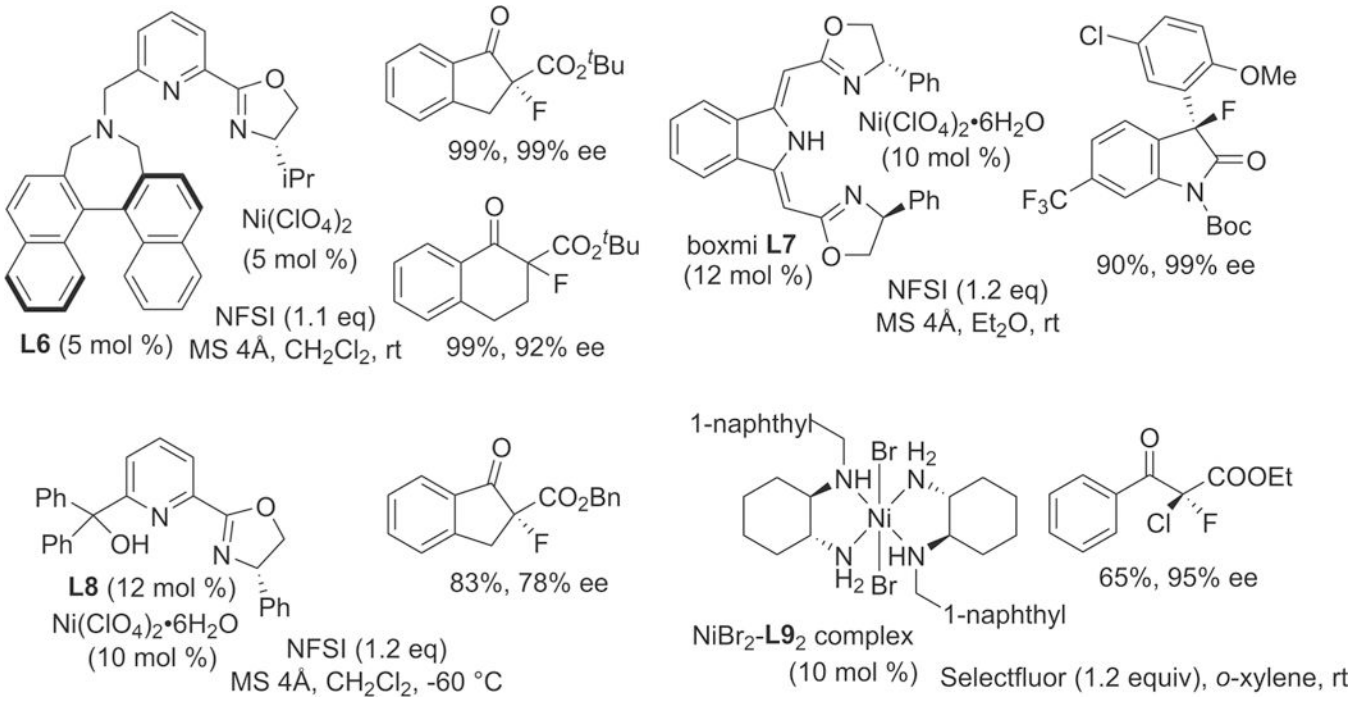


Scheme 78.
Asymmetric Fluorination of α-Ketoester 216



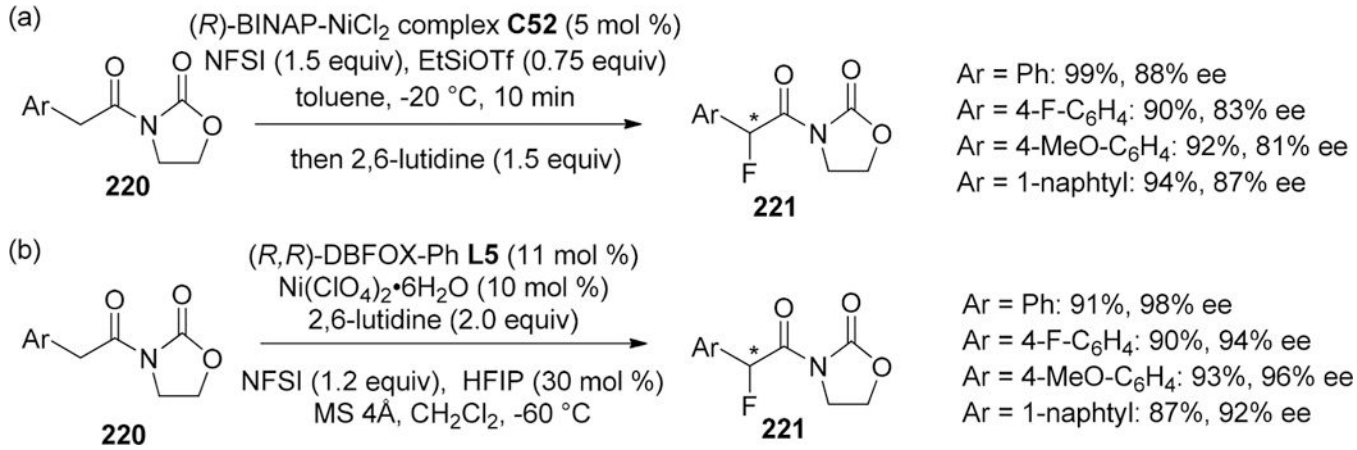
Scheme 79.

Ni- and Cu-Catalyzed Fluorination Using (*S,S*)-Box-Ph Ligand (a) and (*R,R*)-DBFOX-Ph Ligand (b)



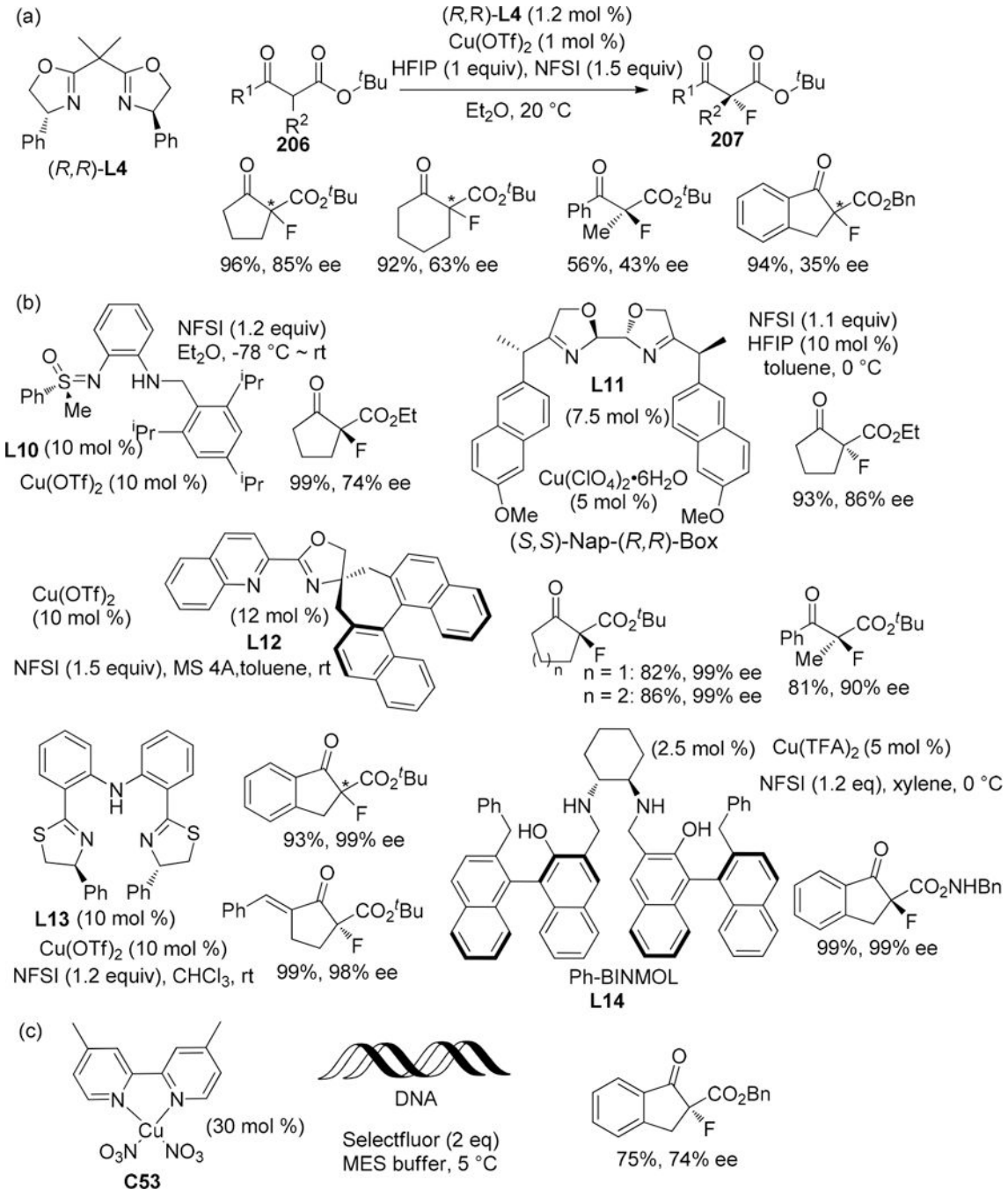
Scheme 80.

Asymmetric Ni-Catalyzed Fluorination of β-Keto Esters



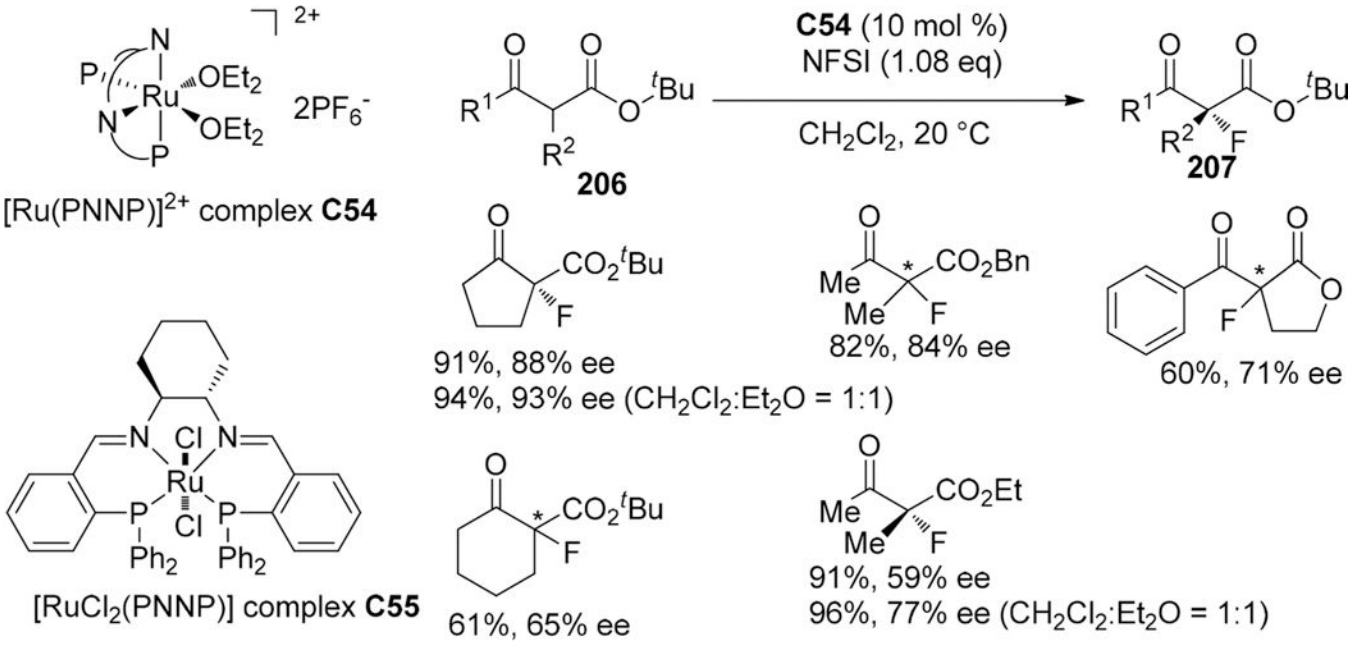
Scheme 81.

Ni-Catalyzed Asymmetric Fluorination Using (*R*)-BINAP (a) and (*R,R*)-DBFOX (b) Ligands



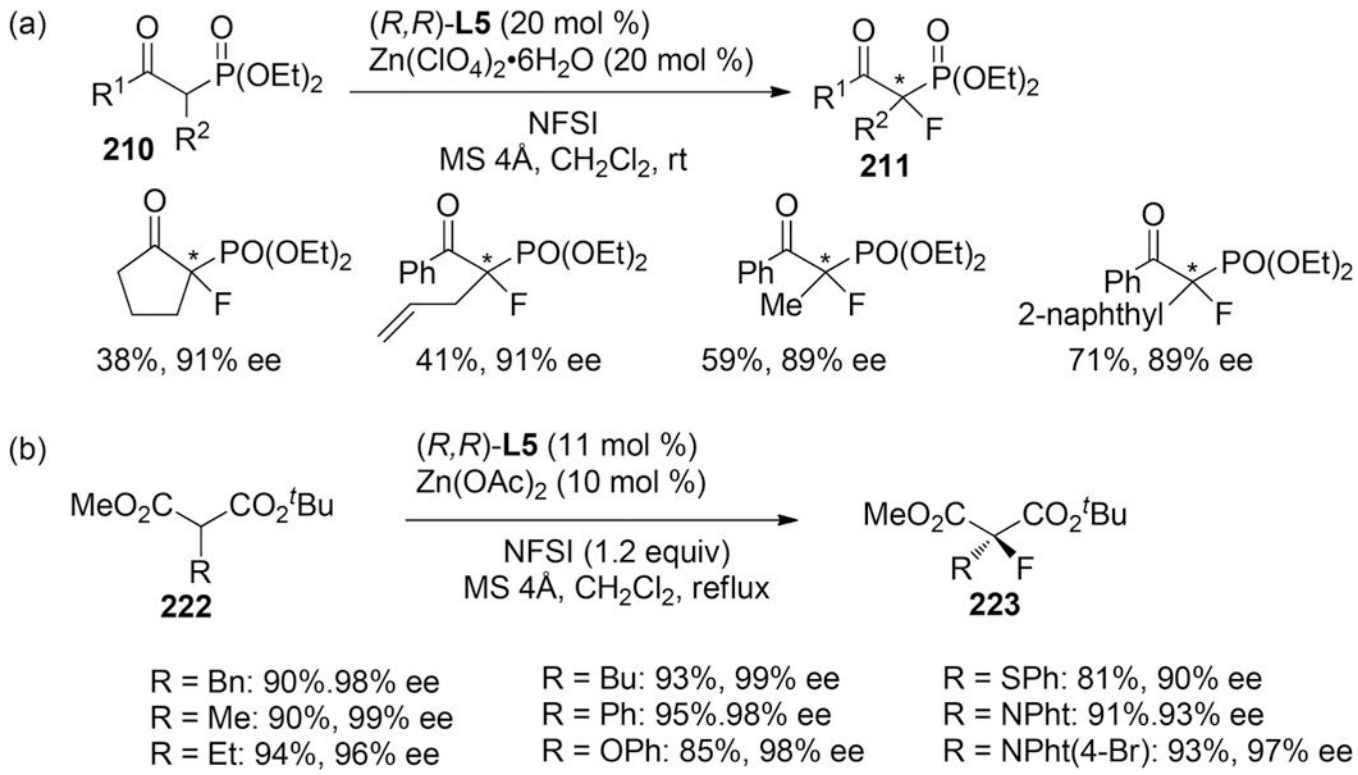
Scheme 82.

Cu-Catalyzed Enantioselective Fluorination of β-Keto Esters Using (*R,R*)-Box-Ph (a), Chiral Sulfoximine, Nap-(*R,R*)-Box, Chiral Spiro Oxazoline, Diphenylamine-Linked Bis(thiazoline), Ph-BINMOL-Derived Salan Ligands (b), and DNA as a Catalyst (c)



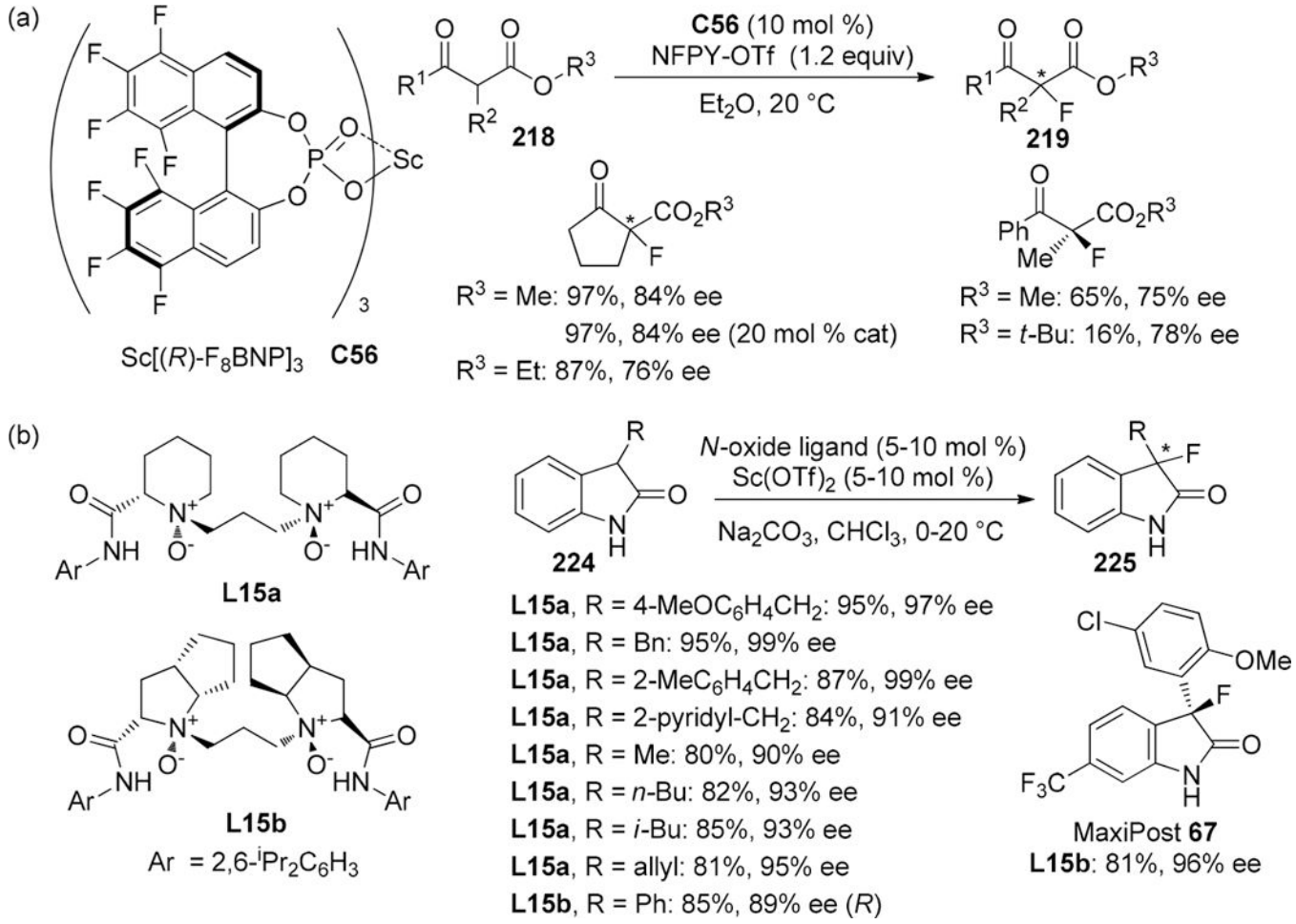
Scheme 83.

Asymmetric Fluorination of 1,3-Dicarbonyl Compounds 206 Catalyzed by Chiral Dicationic Ruthenium PNNP Complex

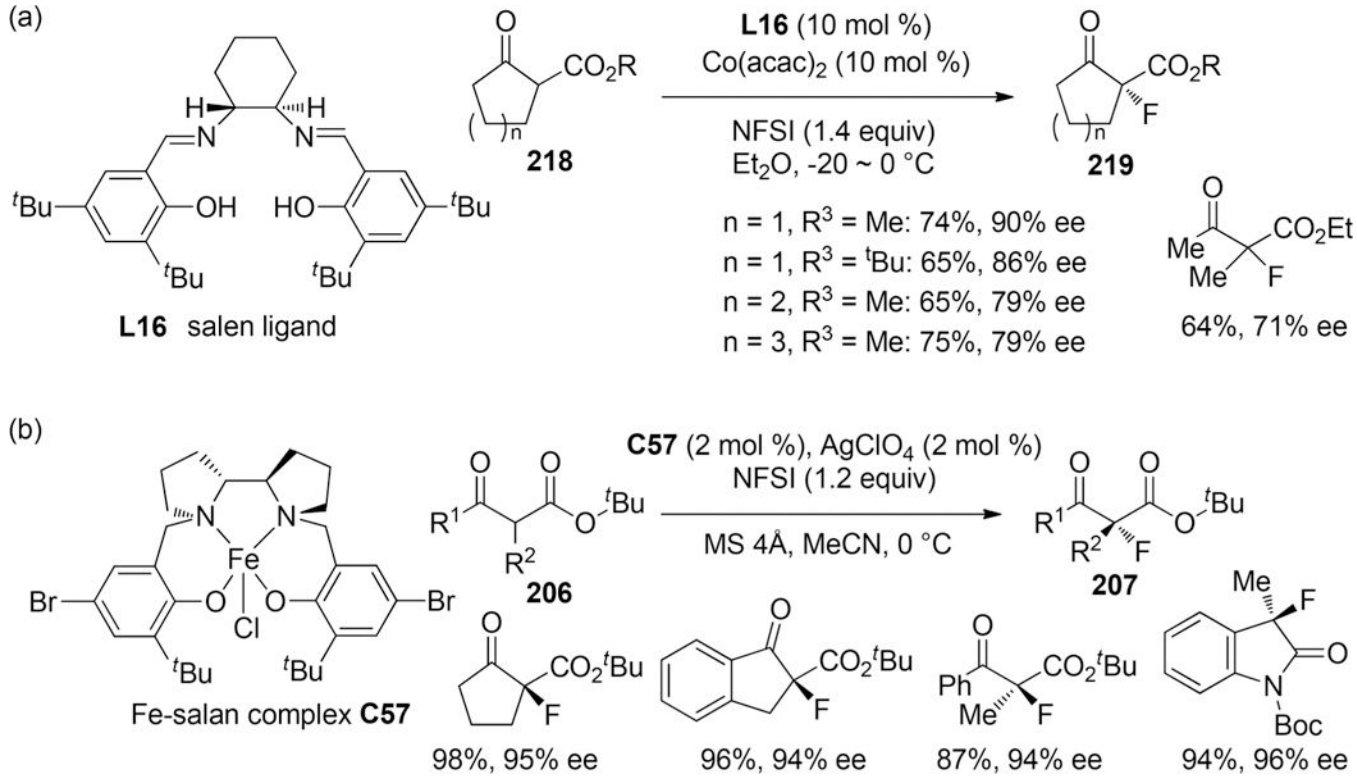


Scheme 84.

Asymmetric Fluorination of β-Keto Phosphonates (a) and Alkyl *tert*-Butyl Malonate Esters (b)

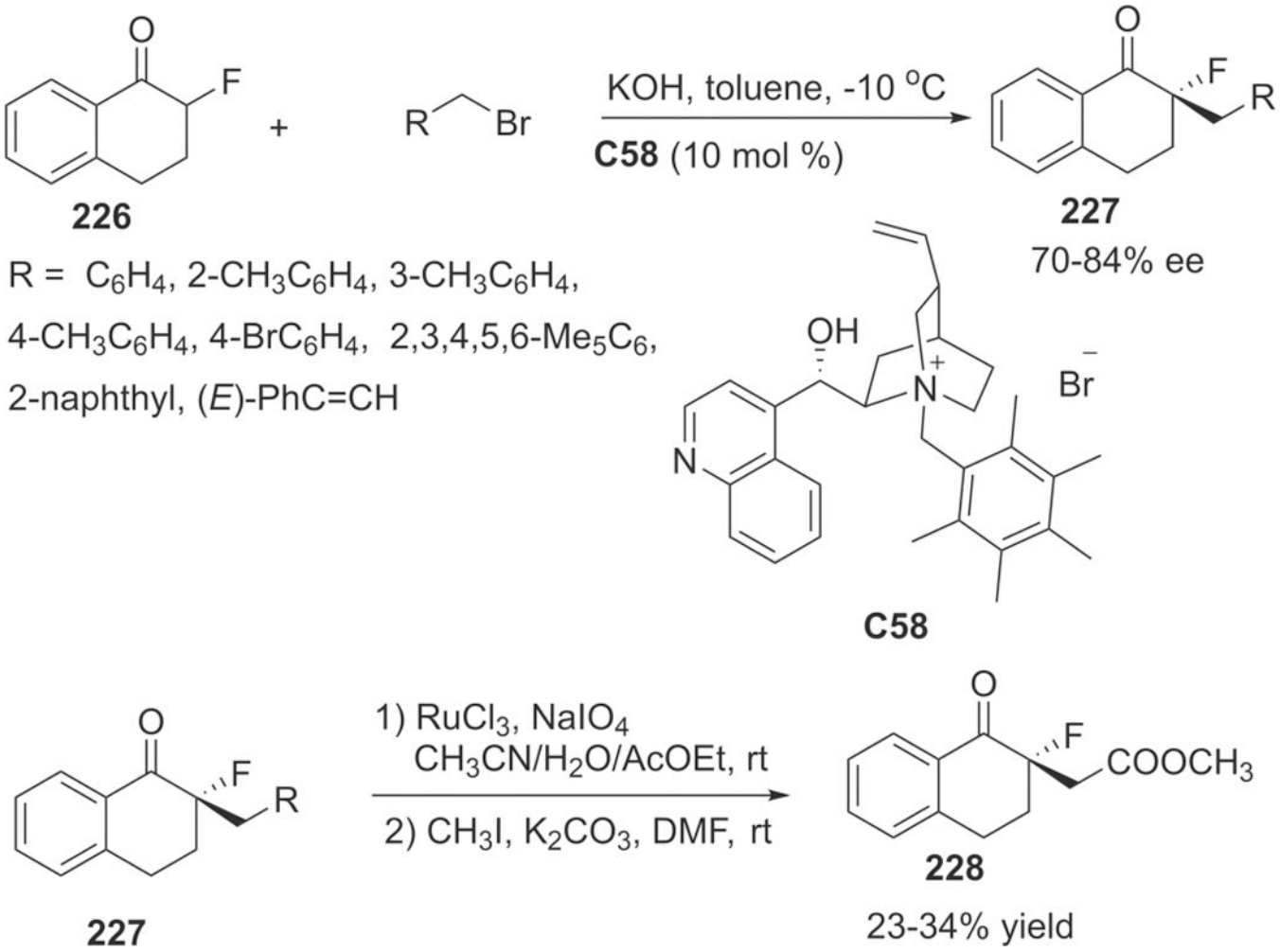


Scheme 85.
Rare Earth Metal Complex-Catalyzed Asymmetric Fluorination

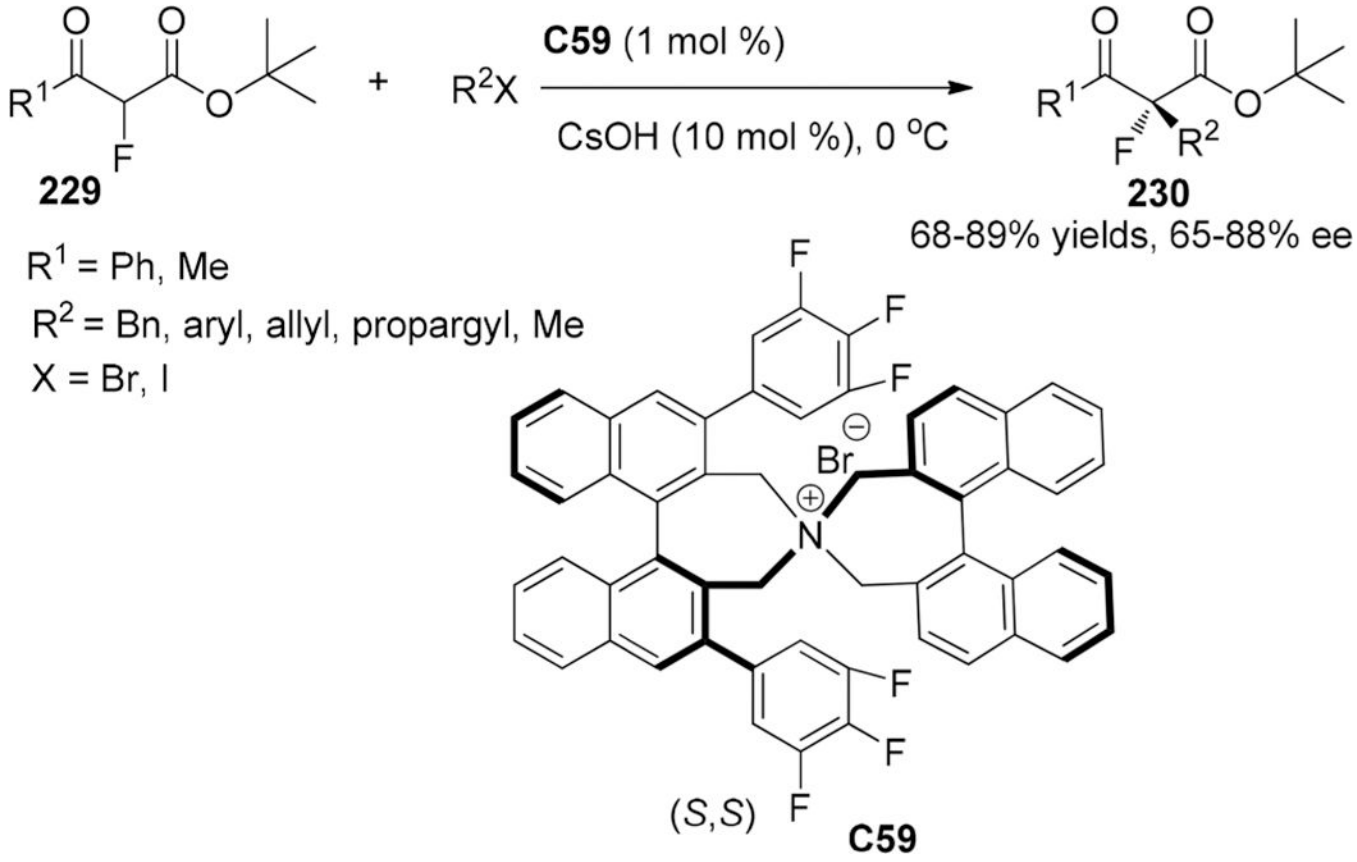


Scheme 86.

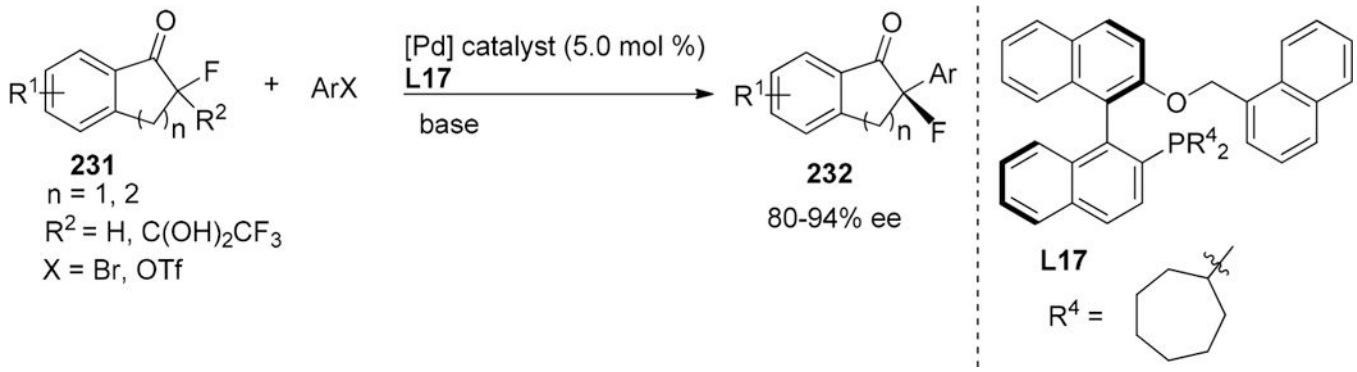
Enantioselective Fluorination of β-Keto Esters Using Chiral Cobalt–Salen Complex (a) and Iron(III)–Salan Complex (b)



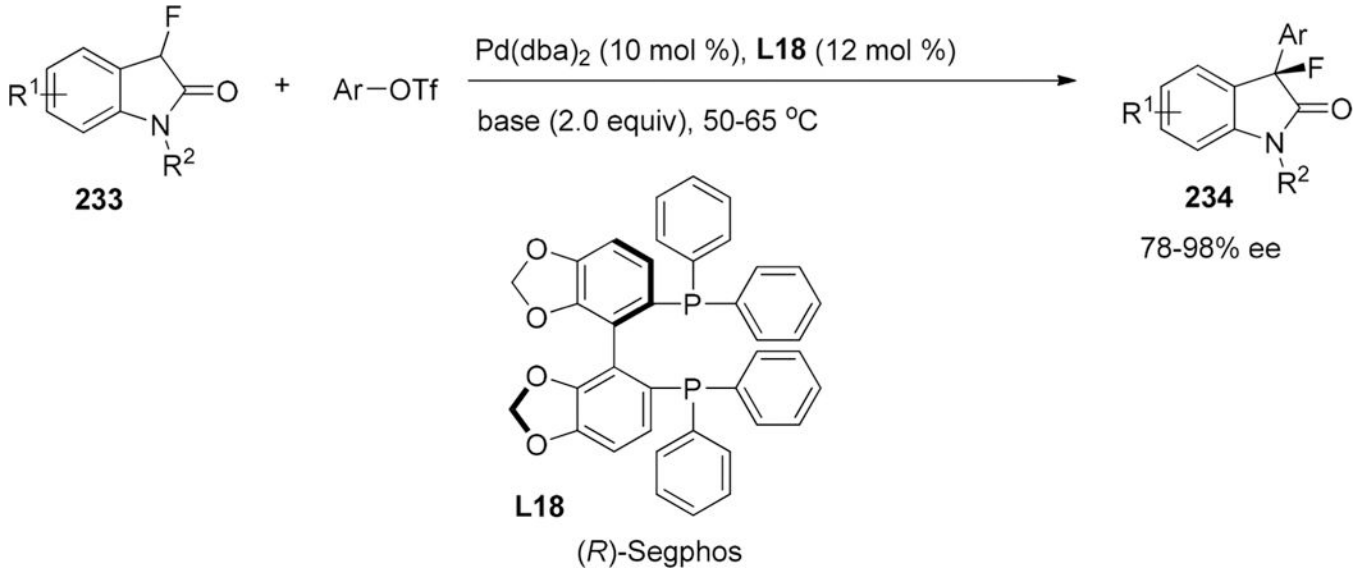
Scheme 87.
Asymmetric Catalytic Alkylation of Cyclic α-Fluoro Ketones



Scheme 88.
Phase-Transfer Catalyzed Asymmetric Alkylations

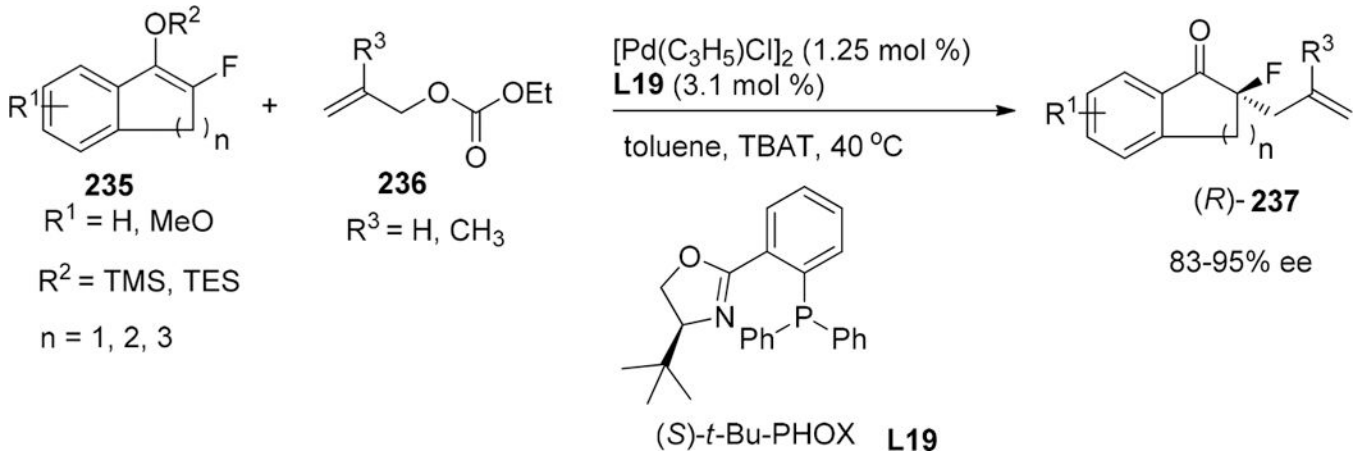


Scheme 89.
Pd-Catalyzed Asymmetric Arylation of α-Fluoroketones



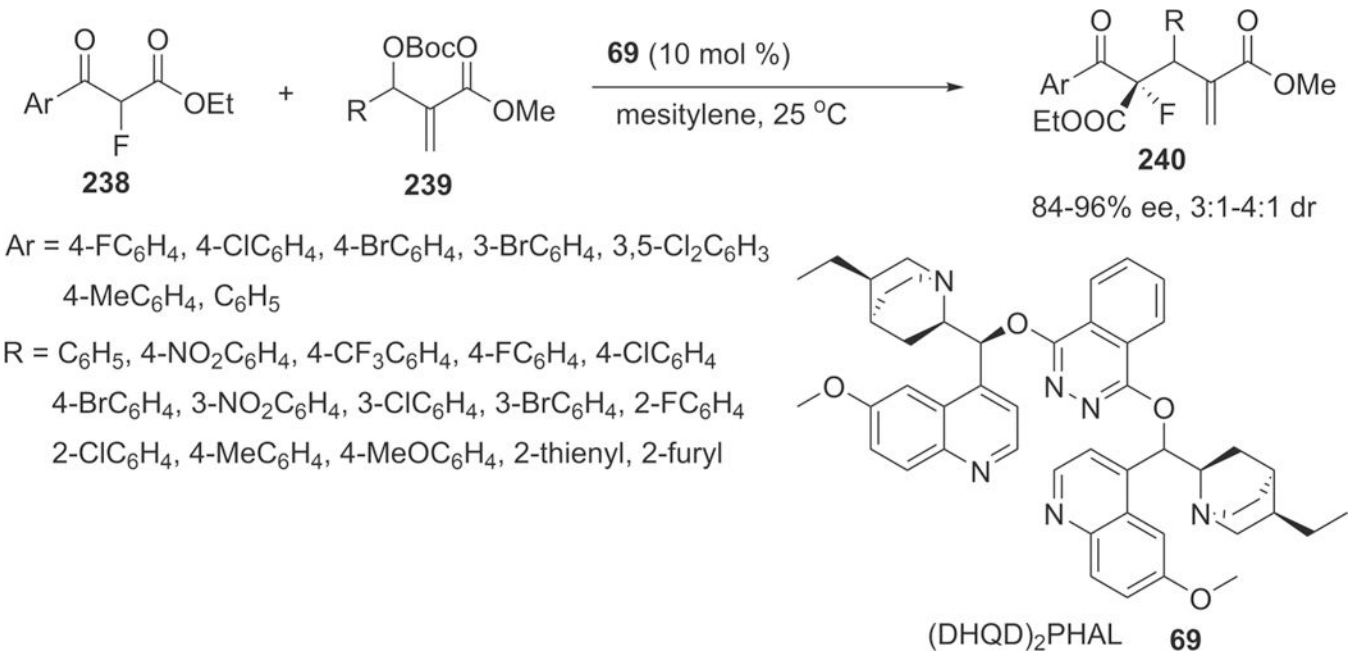
Scheme 90.

Asymmetric Pd-Catalyzed Arylation Reaction with Aryl Triflates

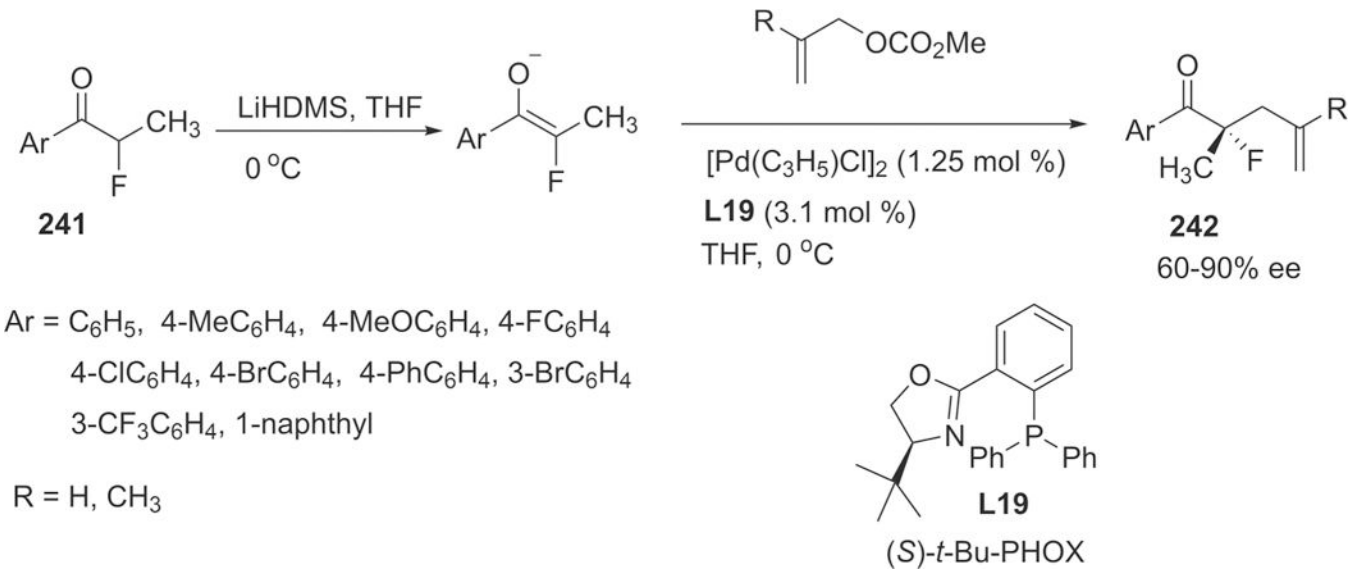


Scheme 91.

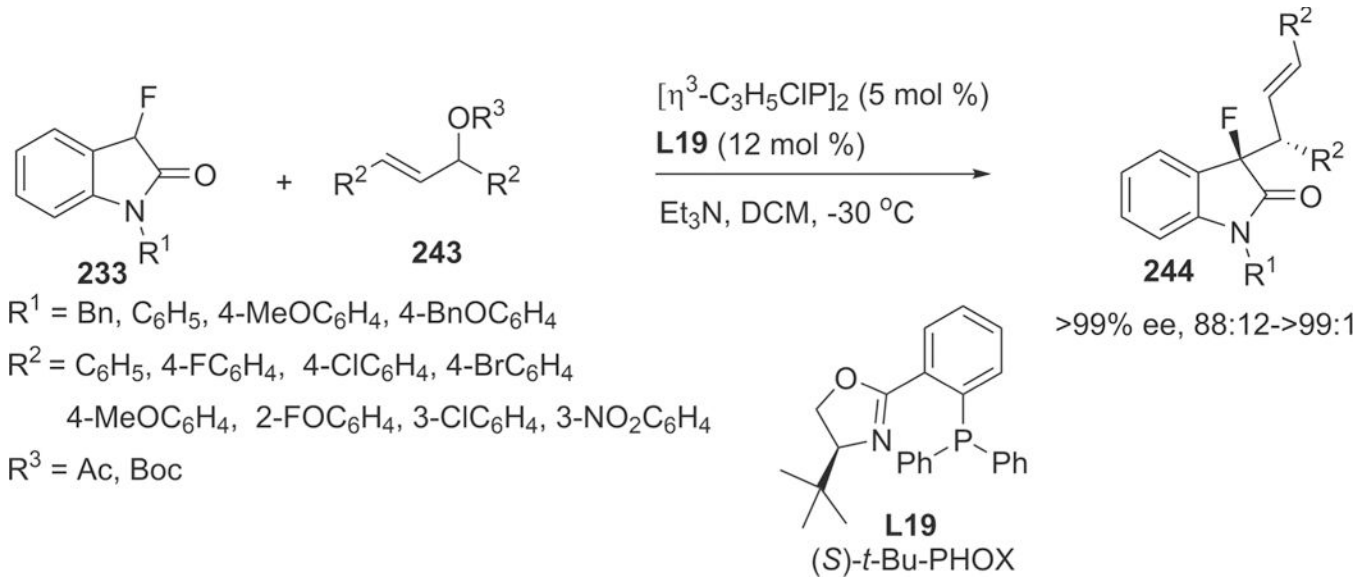
Pd-Catalyzed Asymmetric Allylation Reaction of Silyl Protected Enolates



Scheme 92.
Asymmetric Allylic Alkylation Reaction of Linear α-Fluoro-β-keto Esters

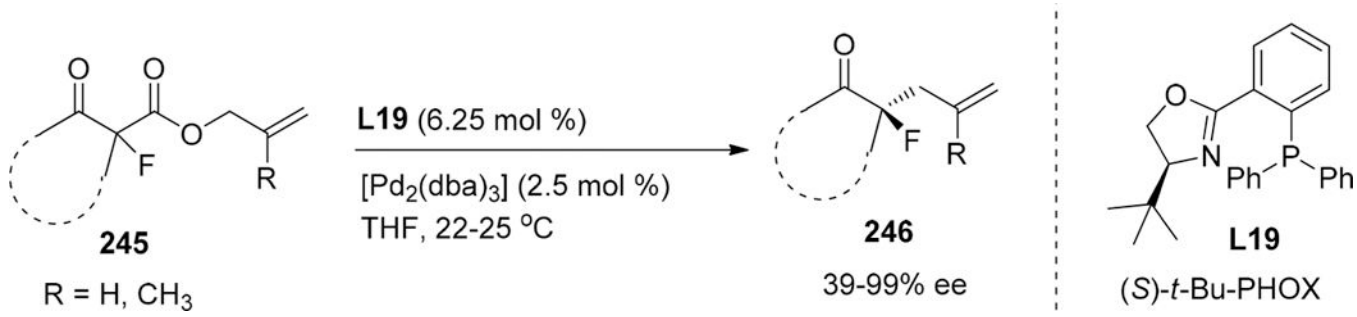


Scheme 93.
Pd-Catalyzed Asymmetric Allylic Alkylation α-Fluoro Ketones



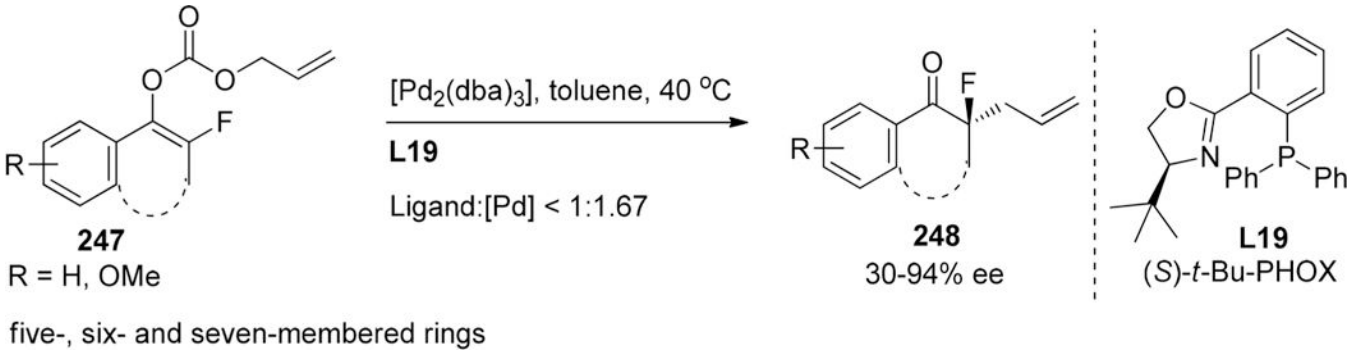
Scheme 94.

Asymmetric Allylic Alkylation of Tertiary Fluorinated Enolates Generated from C3-Fluorinated Oxindoles

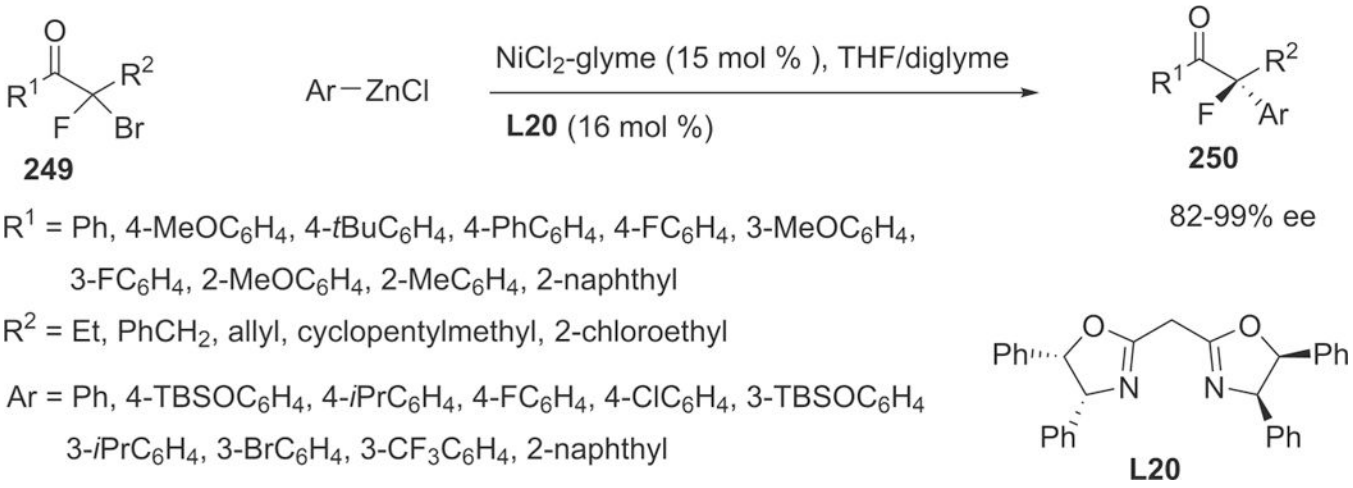


Scheme 95.

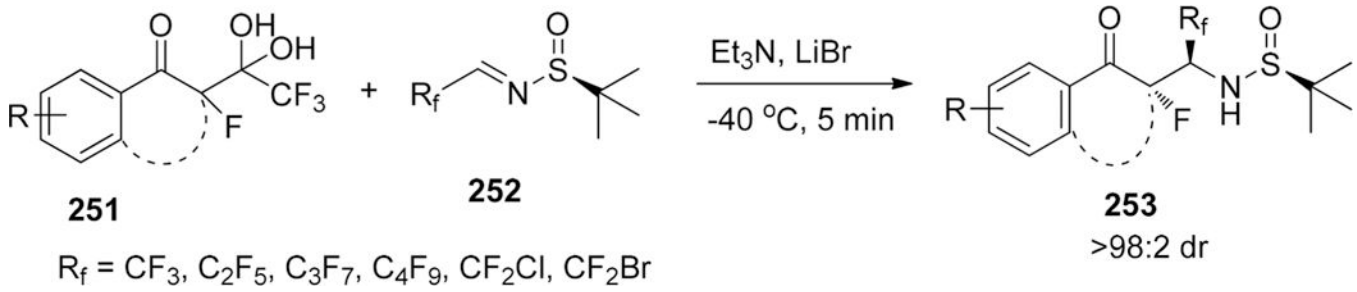
Pd-Catalyzed Enantioselective Decarboxylative Allylation of α-Fluorinated Ketoesters



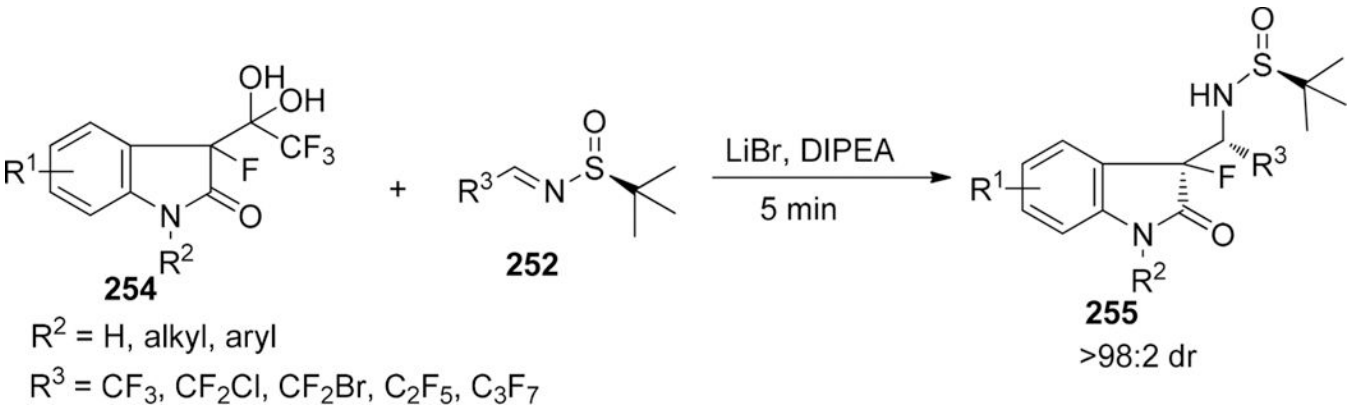
Scheme 96.
Pd-Catalyzed Allylation Reaction Using (*S*)-*t*-Bu-PHOX Ligand



Scheme 97.
Ni/bis(oxazoline)-Catalyzed Asymmetric Alkylation of Racemic α-Halo-α-fluoroketones

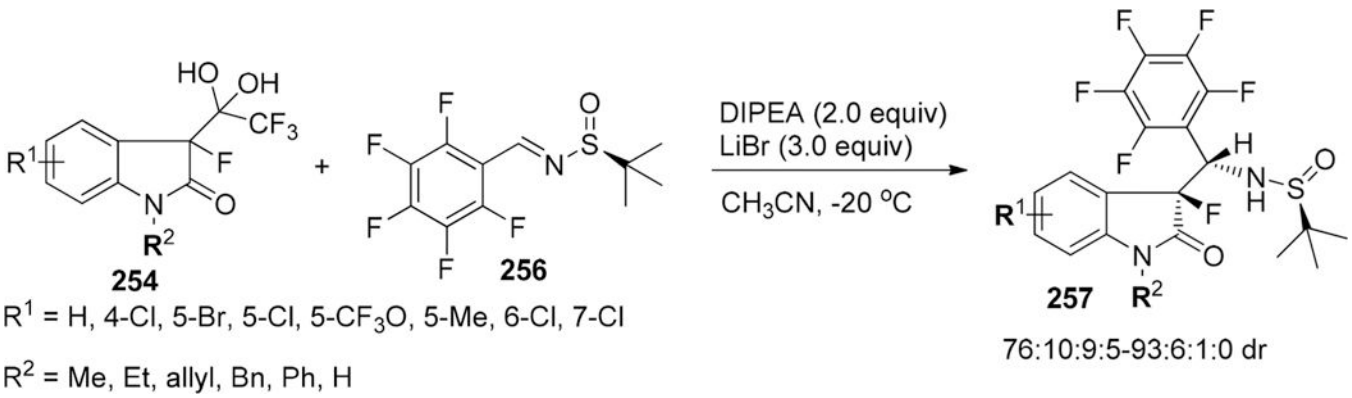


Scheme 98.
Mannich Reactions of Detrifluoroacetylatively in Situ Generated Fluorinated Enolates



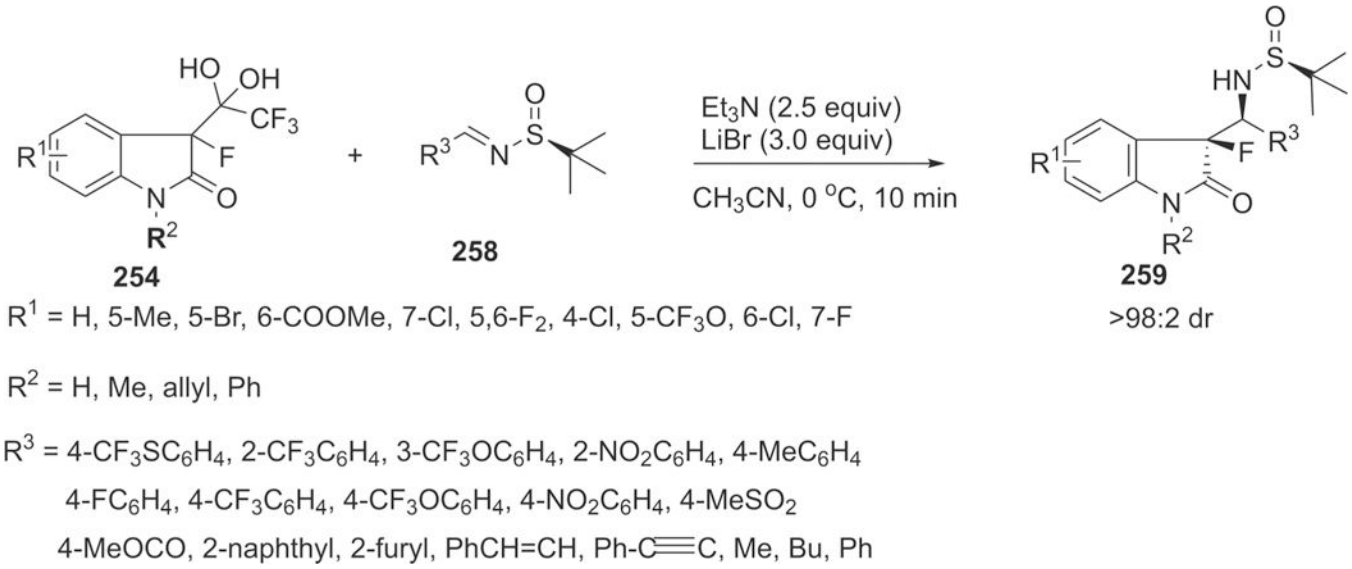
Scheme 99.

Mannich Reactions of Detrifluoroacetylatively in Situ Generated Enolates Derived from 3-Fluoroindolin-2-ones



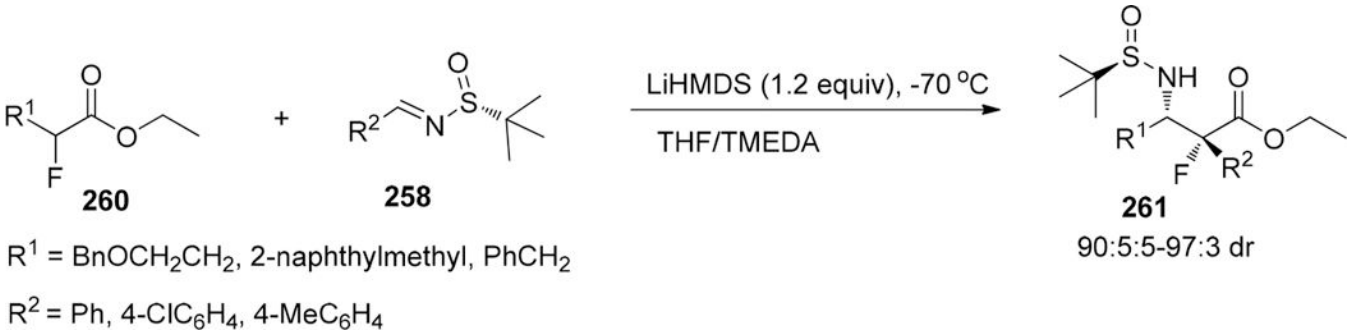
Scheme 100.

Asymmetric Detrifluoroacetylative Mannich Reactions Using *N-tert*-Butylsulfinyl-(perfluoro)benzaldimine



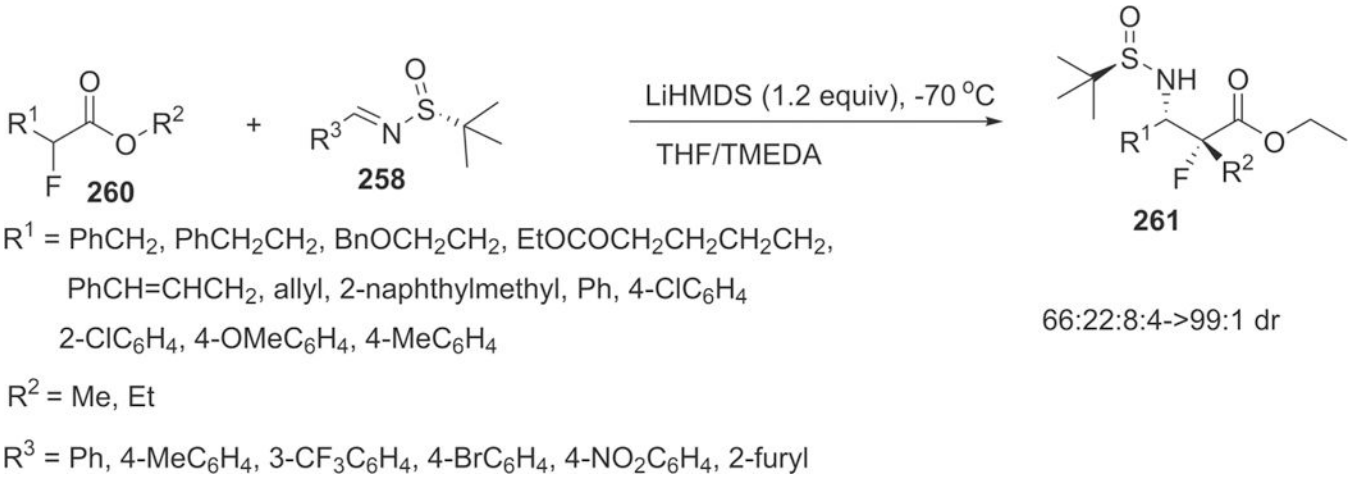
Scheme 101.

Detrifluoroacetylative Mannich Reactions of Indolin-2-ones with Fluorinated Aldimines



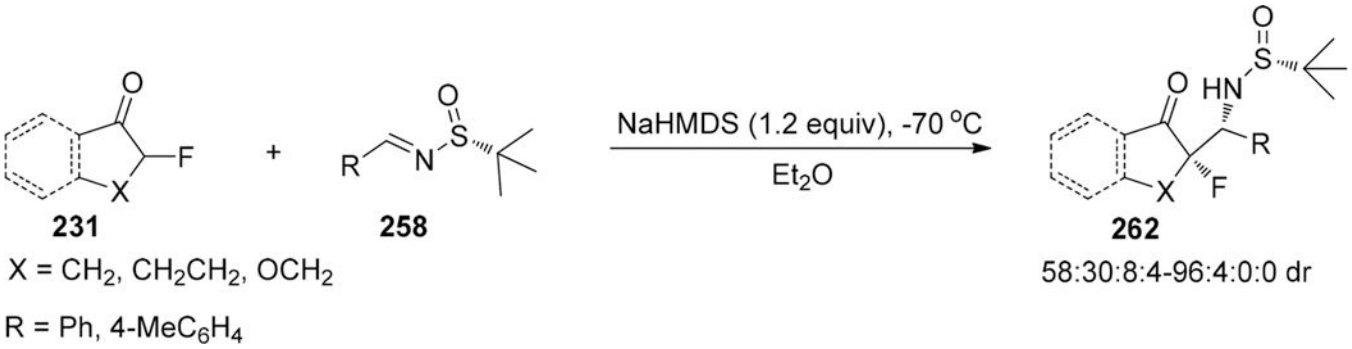
Scheme 102.

Mannich Reactions between *α*-Fluoro Esters and *N-tert*-Butylsulfinyl imines



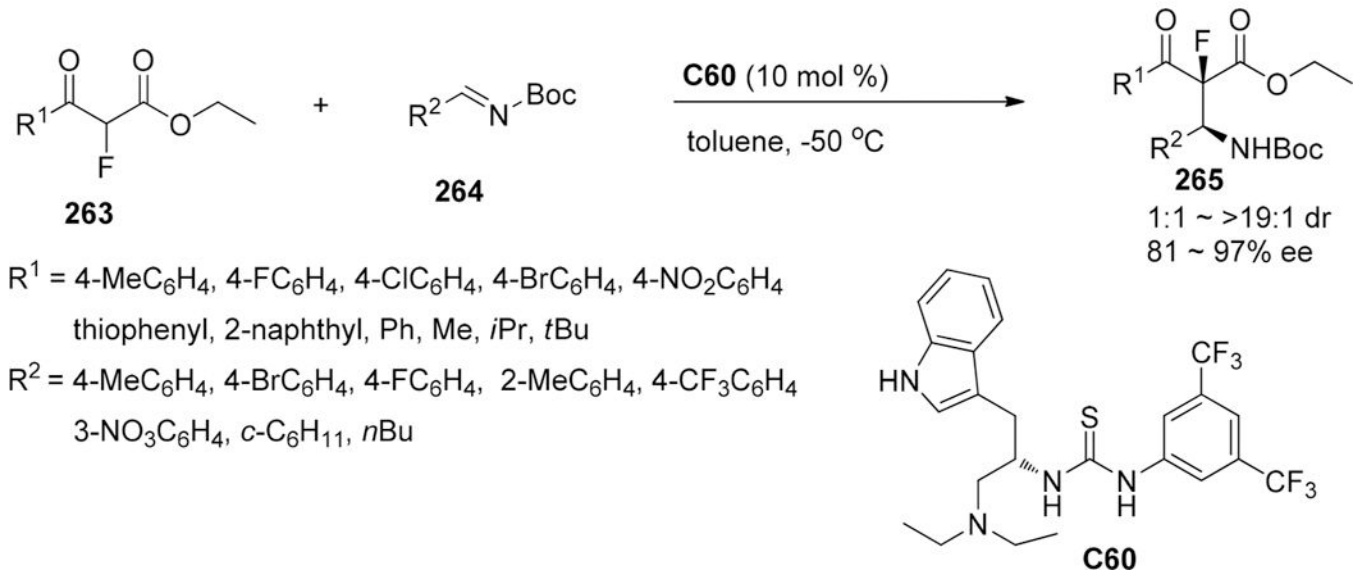
Scheme 103.

Substrate Generality of the Mannich Reactions between *α*-Fluoro Esters and *N-tert*-Butylsulfinyl Imines



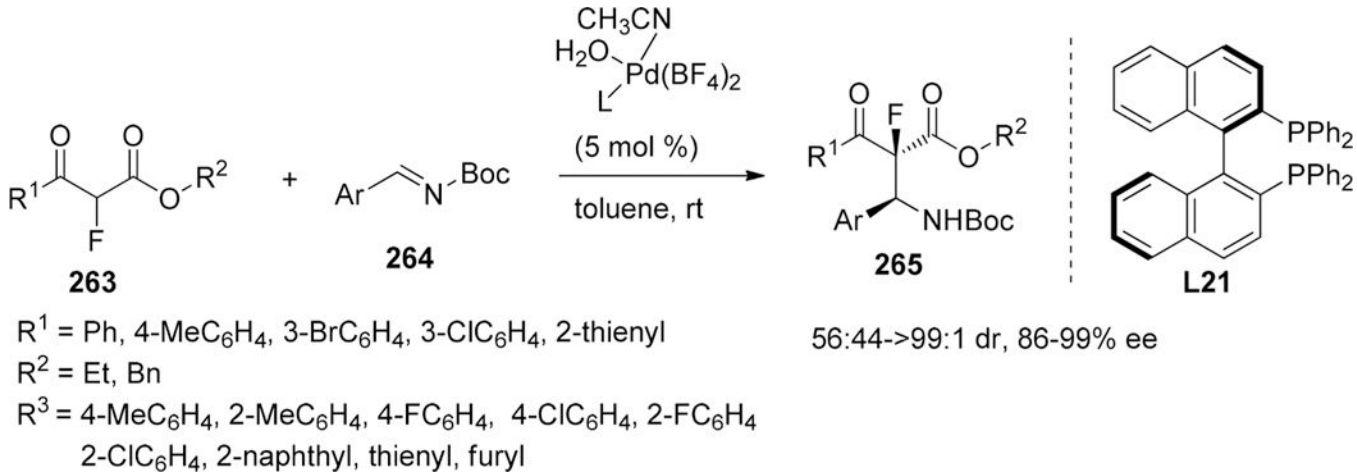
Scheme 104.

Mannich Reactions of α-Fluoro Ketones with *N-tert*-Butylsulfinylimines



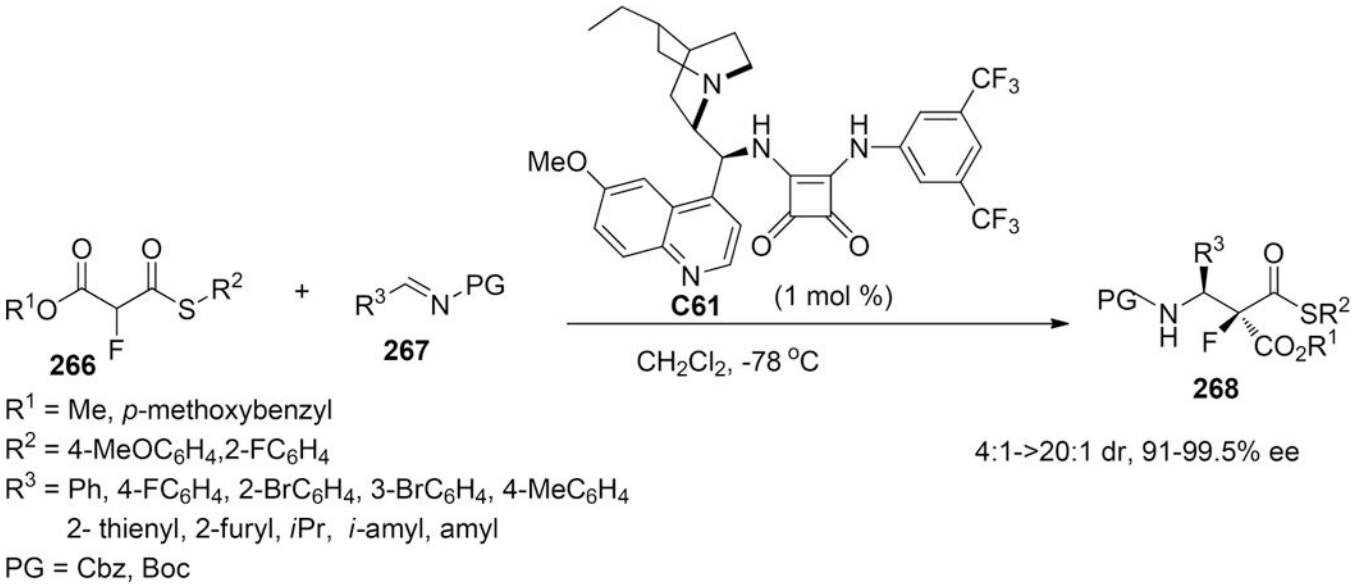
Scheme 105.

Organocatalytic Mannich Reaction between *α*-Fluorinated Ketoesters and *N*-Boc-Protected Imines



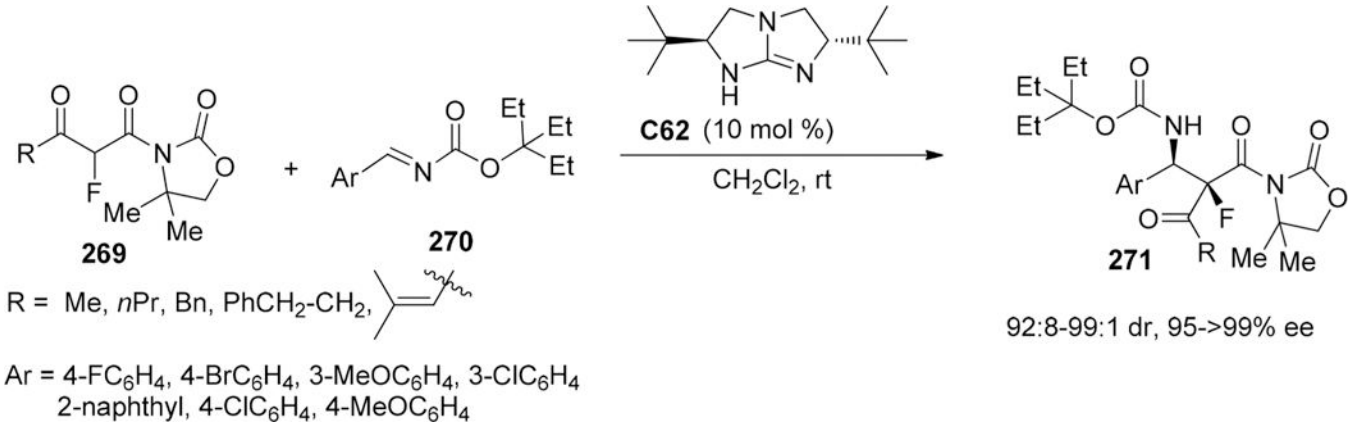
Scheme 106.

Pd-Catalyzed Asymmetric Mannich Reactions of α-Fluoro-β-ketoesters with *N*-Boc-aldimines



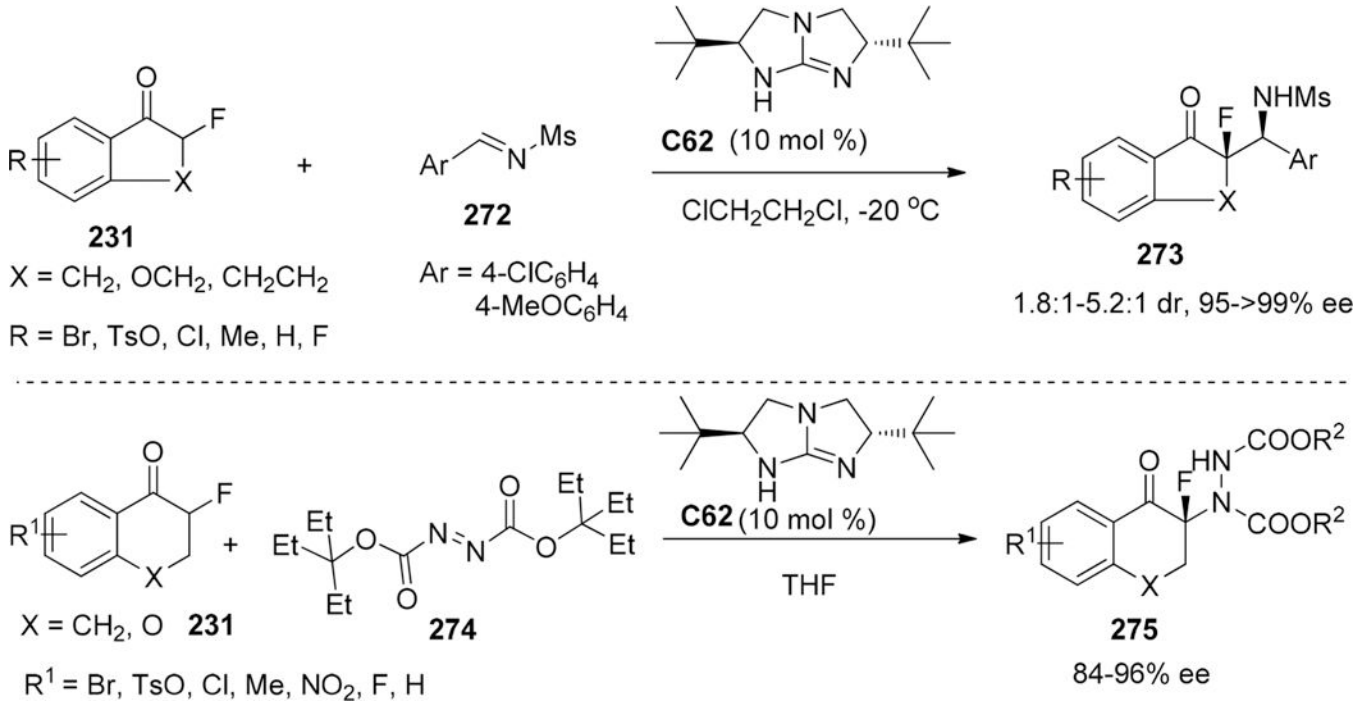
Scheme 107.

Asymmetric Organocatalyzed Mannich Addition Reactions of α-Fluorinated Monothiomalonates with Imines



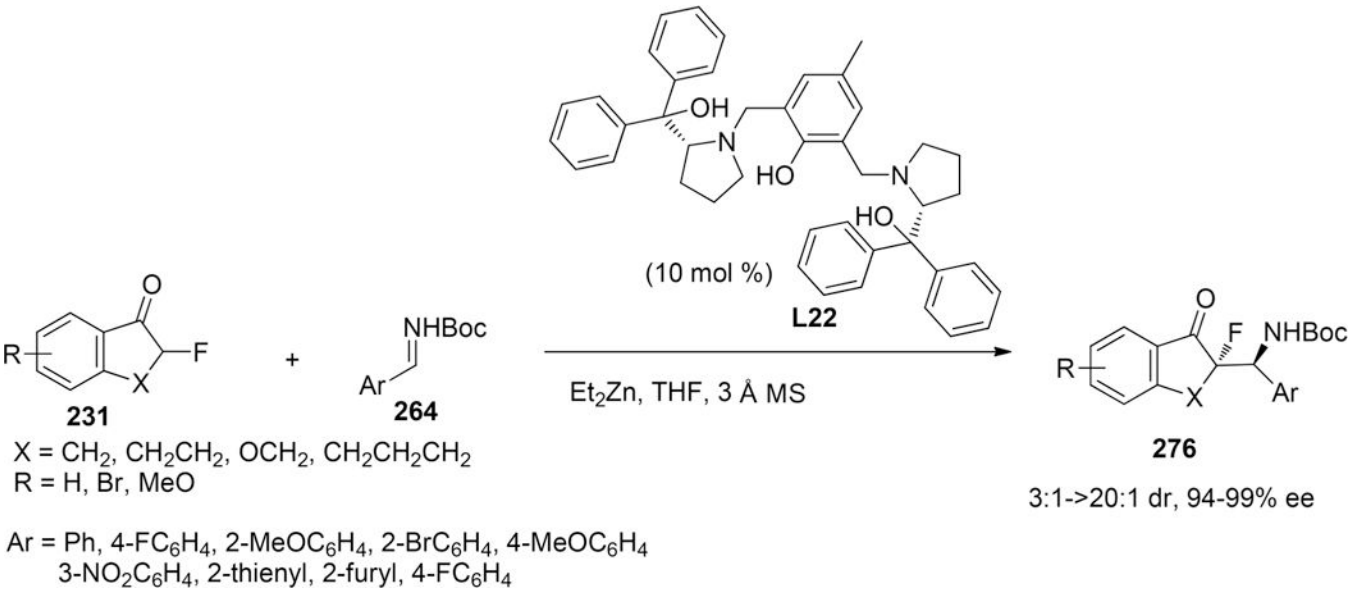
Scheme 108.

Asymmetric Mannich Reactions of Imines with β-Keto Acetyloxazolidinone Protected β-Keto-α-fluoro Esters



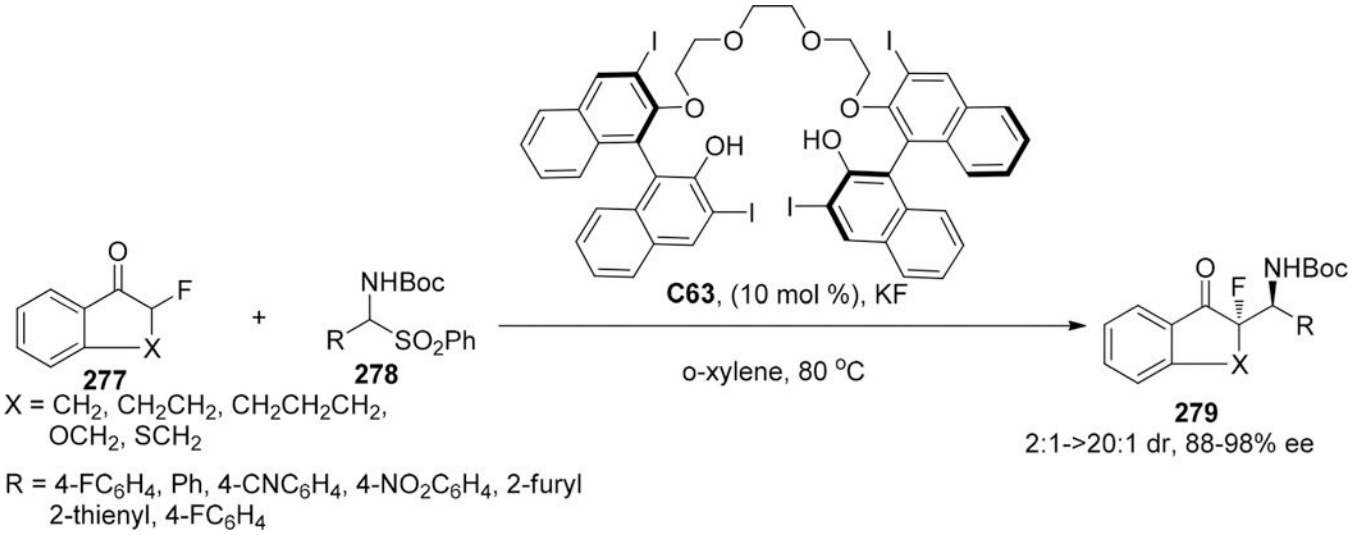
Scheme 109.

Mannich Reactions of α-Fluorinated Aromatic Cyclic Ketones with Imines Catalyzed by (*S,S*)-Bicyclic Guanidine



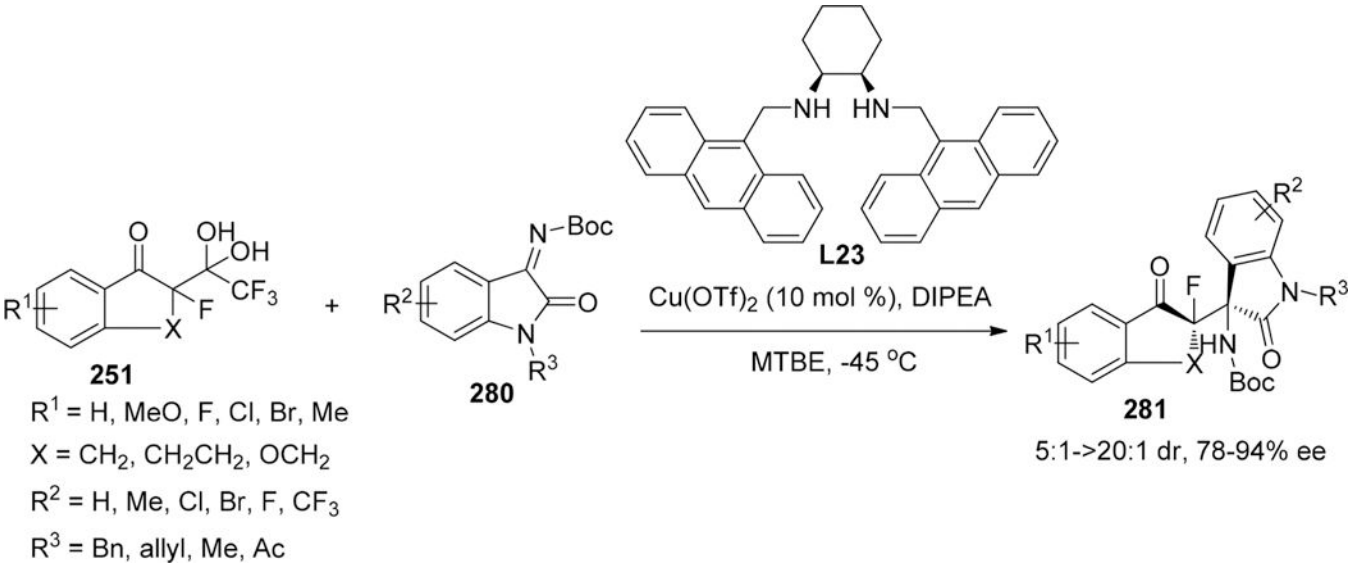
Scheme 110.

Asymmetric Catalytic Mannich Reactions Catalyzed by $ZnEt_2$/(*R,R*)-Prophenol



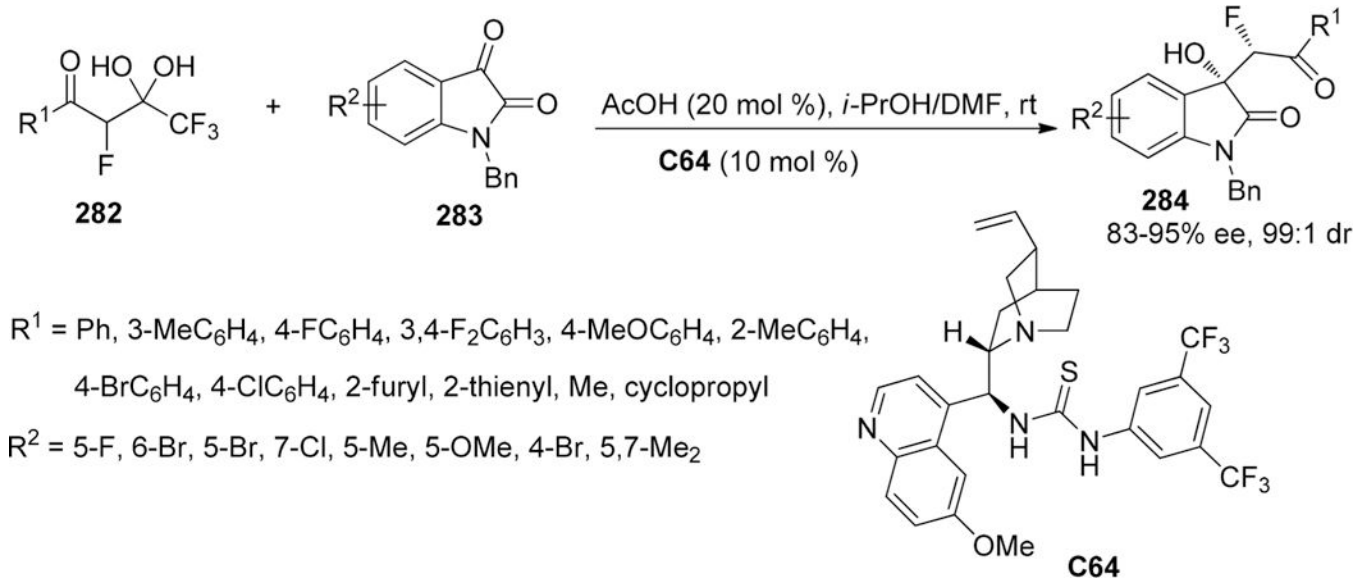
Scheme 111.

Mannich Reactions of α-Fluoro Cyclic Ketones Using Song's Chiral oligoEGs C63 Catalyst

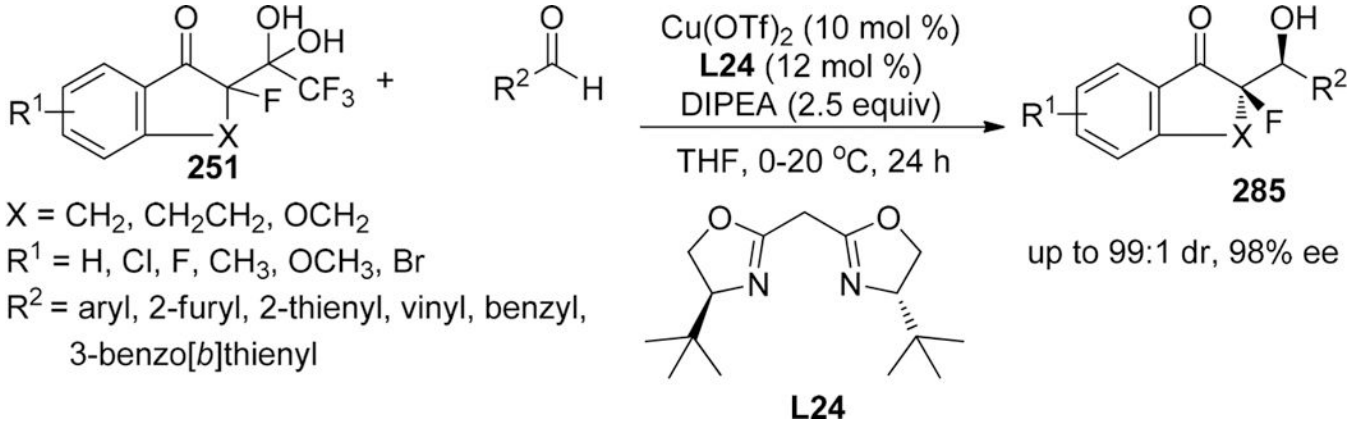


Scheme 112.

Asymmetric Detrifluoroacetylative Mannich Reactions Using Chiral Anthracenyl-Substituted Cyclohexane-1,2-diamine as Organocatalyst

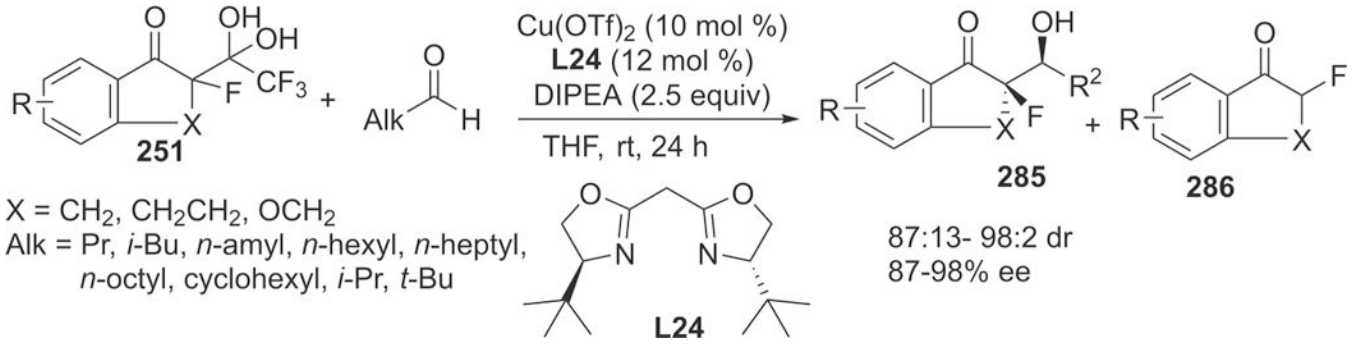


Scheme 113.
Detrifluoroacetylative Aldol Reactions Using Cinchona Alkaloid Derived Thiourea Catalyst



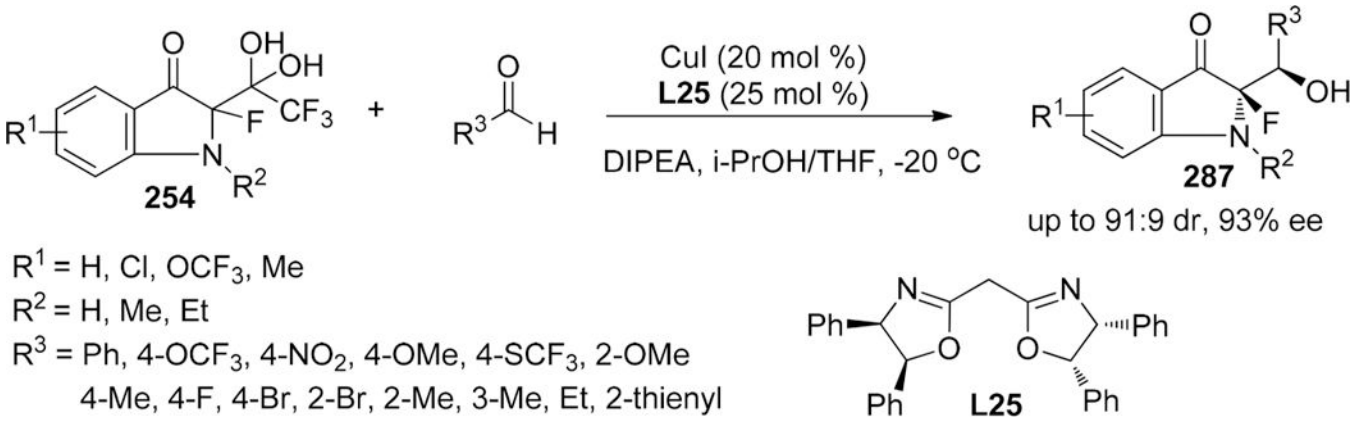
Scheme 114.

Detrifluoroacetylative Aldol Reactions Using Copper(II)/Chiral Bisoxazoline as a Catalyst



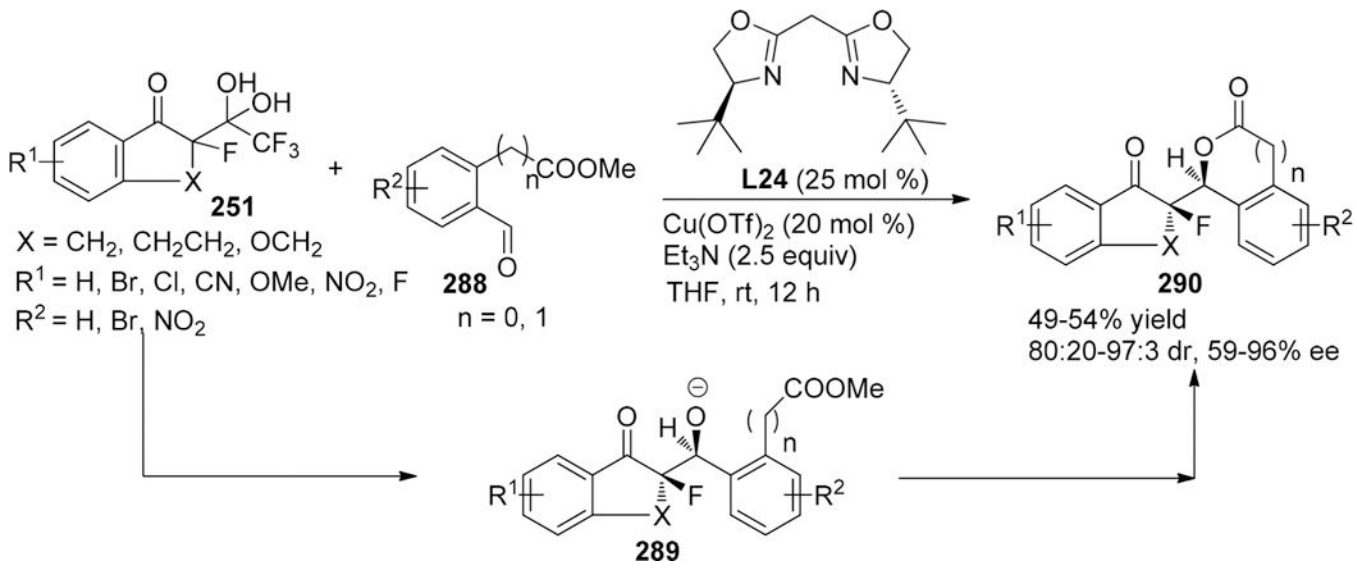
Scheme 115.

Detrifluoroacetylative Aldol Reactions of Alkyl Aldehydes in the Presence of Copper(II)/ Chiral Bisoxazoline as a Catalyst



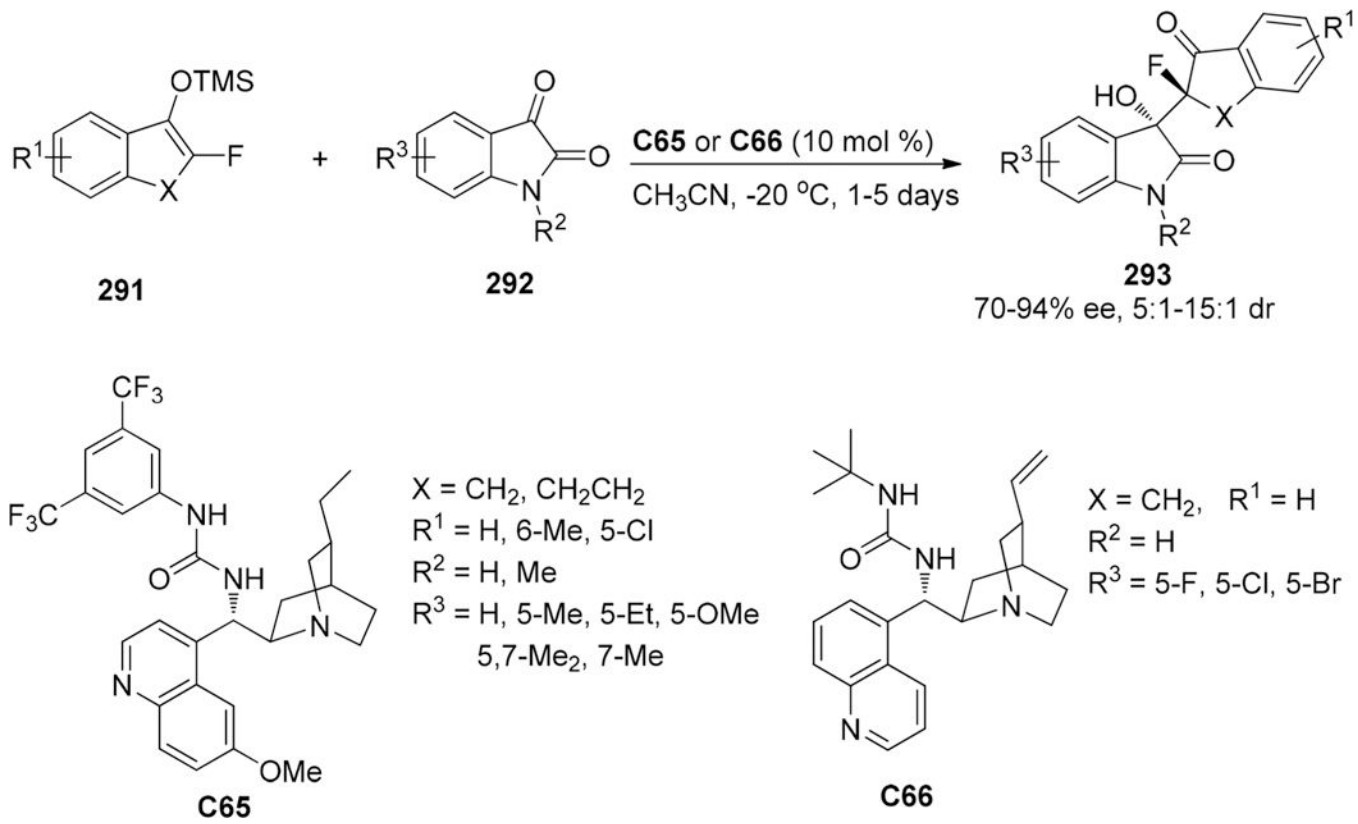
Scheme 116.

Detrifluoroacetylative Aldol Reactions of Aldehydes with Tertiary Enolates Derived from Fluoro-indolinones



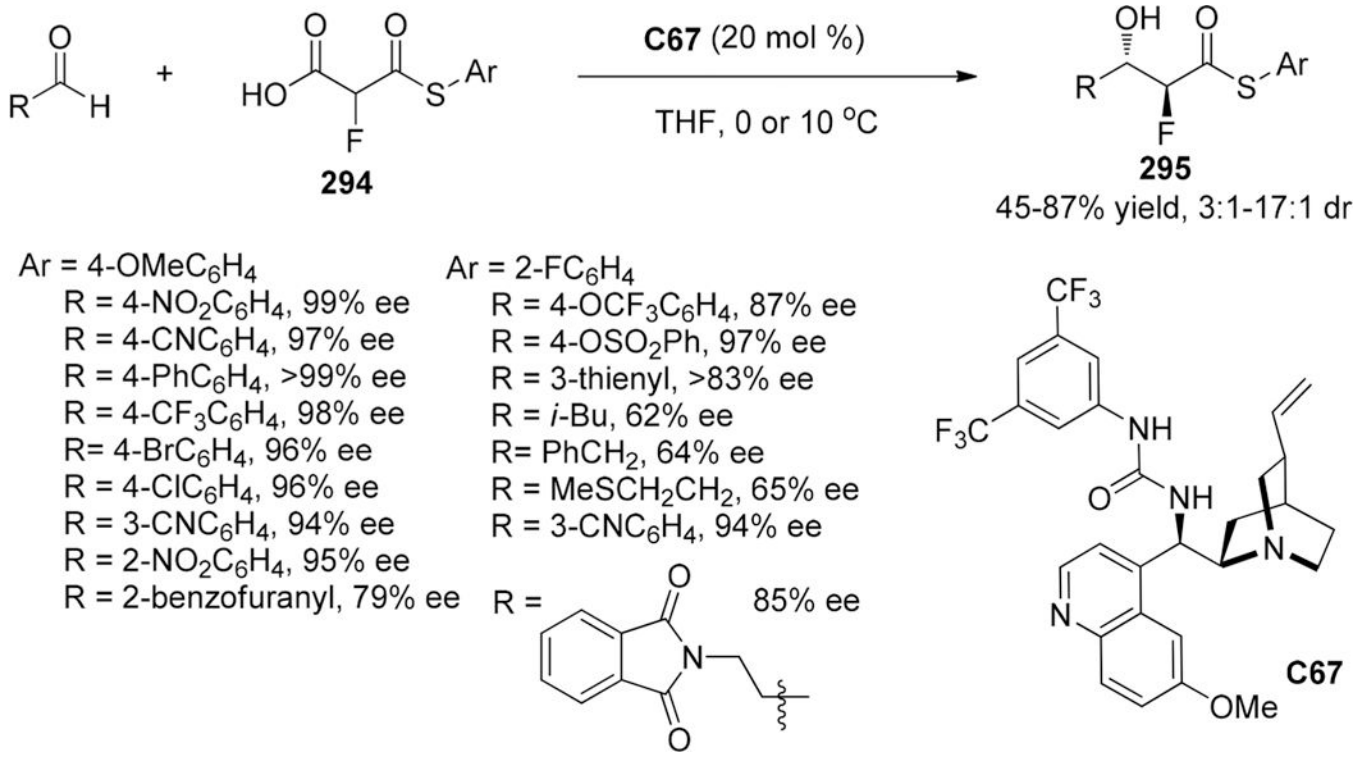
Scheme 117.

Tandem Detrifluoroacetylative Aldol-Cyclization Reactions



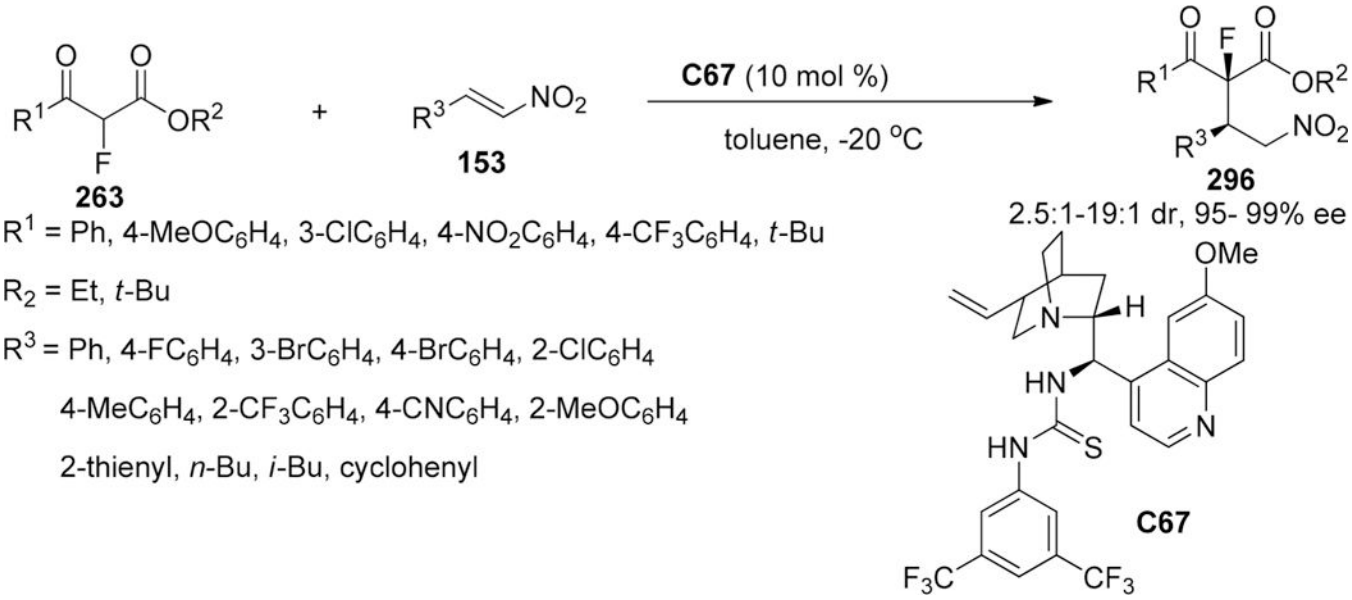
Scheme 118.

Asymmetric Organocatalytic Aldol Reactions between Fluorinated Silyl Enol Ethers and Isatins



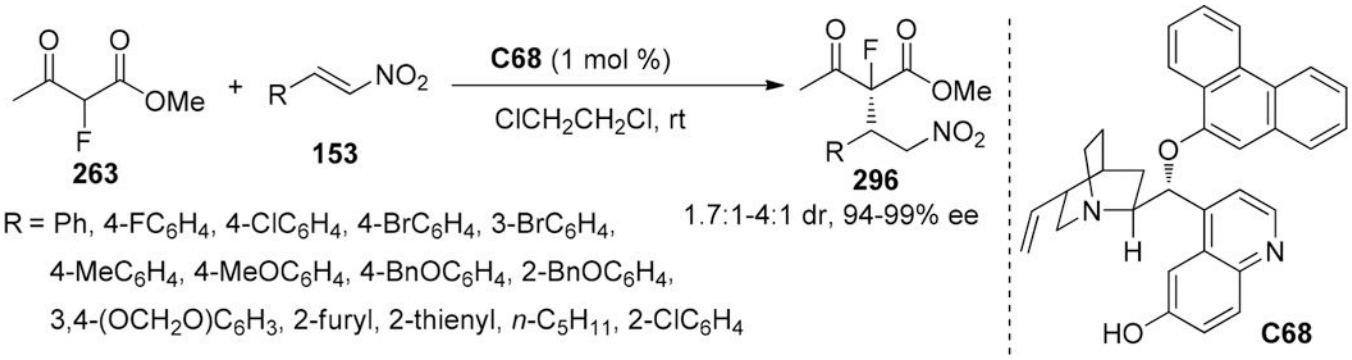
Scheme 119.

Organocatalytic Asymmetric Aldol Reactions between Fluorinated Enolates of Fluoromalonic Acid Half-Thioesters and Aldehydes



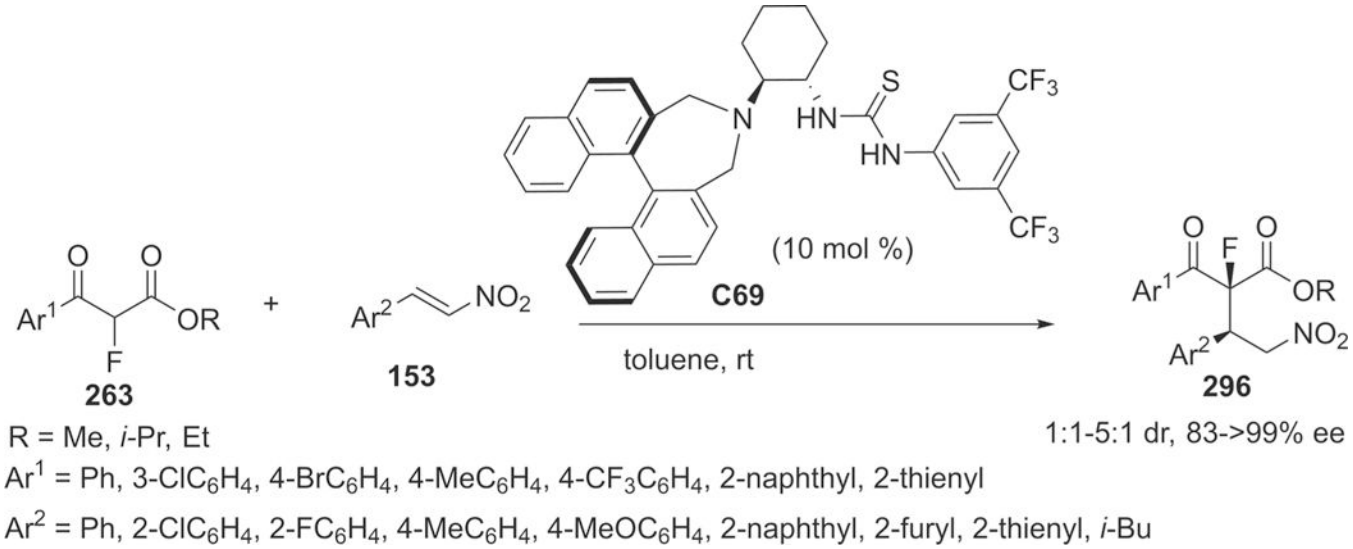
Scheme 120.

Asymmetric Organocatalytic Michael Reactions between Nitroolefins and Fluorinated β-Ketoesters

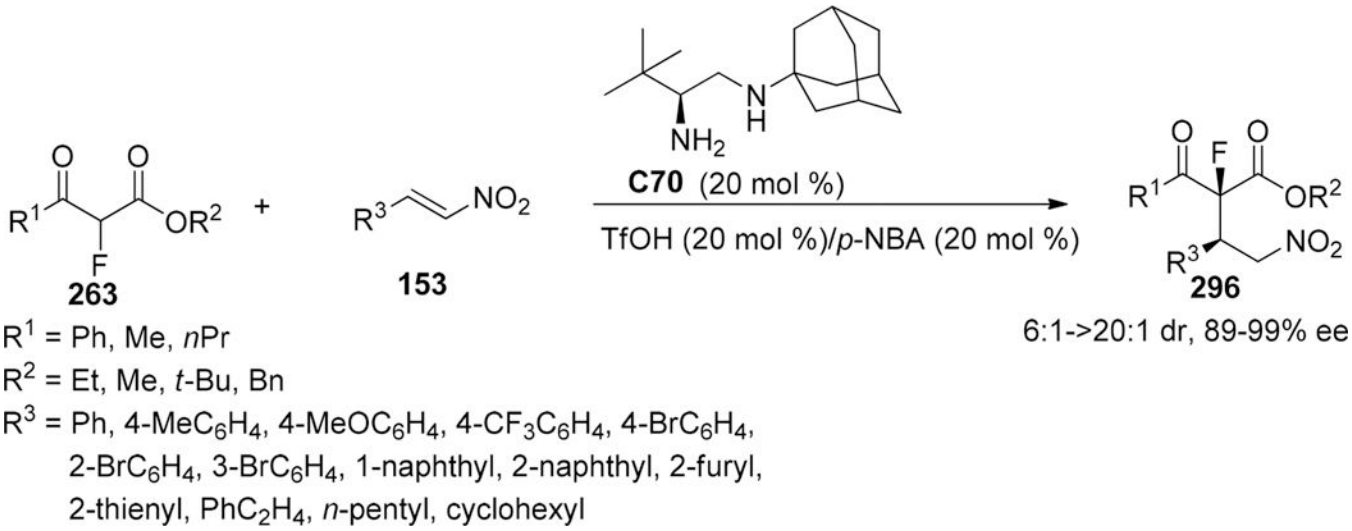


Scheme 121.

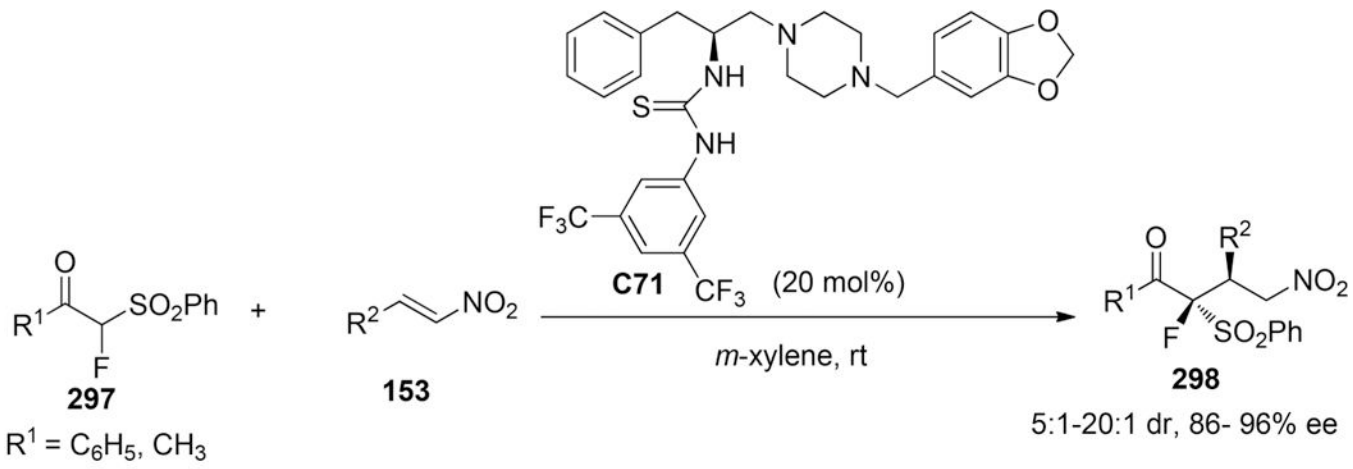
Organocatalytic Asymmetric Michael Addition Reactions between α-Fluoroketoesters to Nitroolefins



Scheme 122.
Bifunctional Thiourea–Tertiary Amine Organocatalytic Michael Reactions of β-Ketoesters



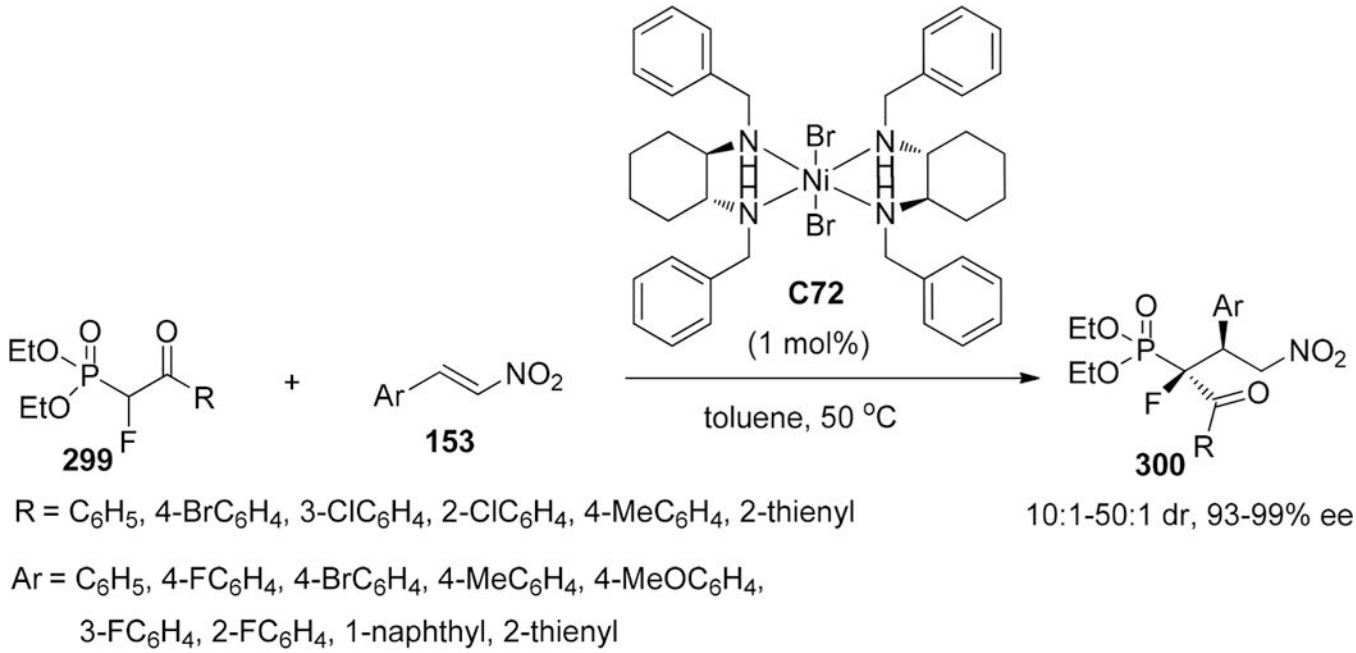
Scheme 123.
Asymmetric Michael Reactions of α-Fluoro-β-ketoesters with Nitroolefins



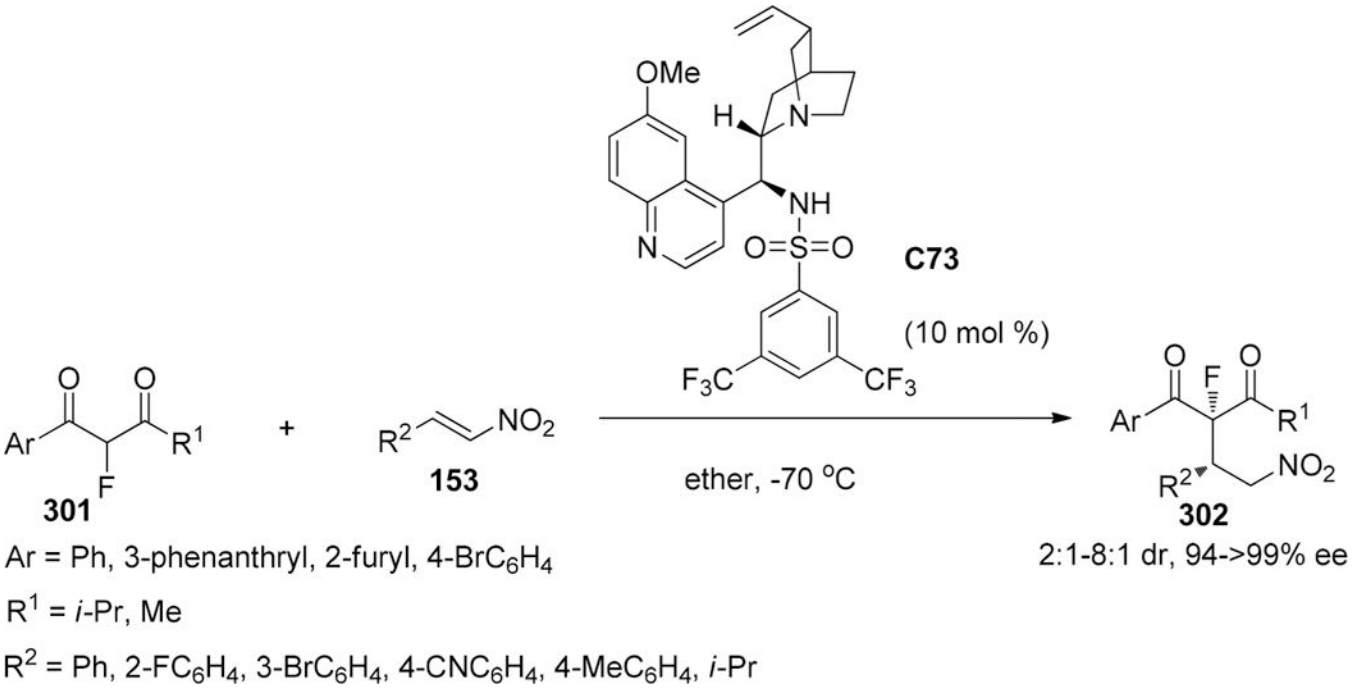
R^1 = C_6H_5, CH_3

R^2 = C_6H_5, 4-FC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-PhC_6H_4, 4-$NO_2C_6H_4$, 2-BrC_6H_4, 3-BrC_6H_4, 1-naphthyl, 2-furyl, 2-thienyl, *n*-Bu, *i*-Pr

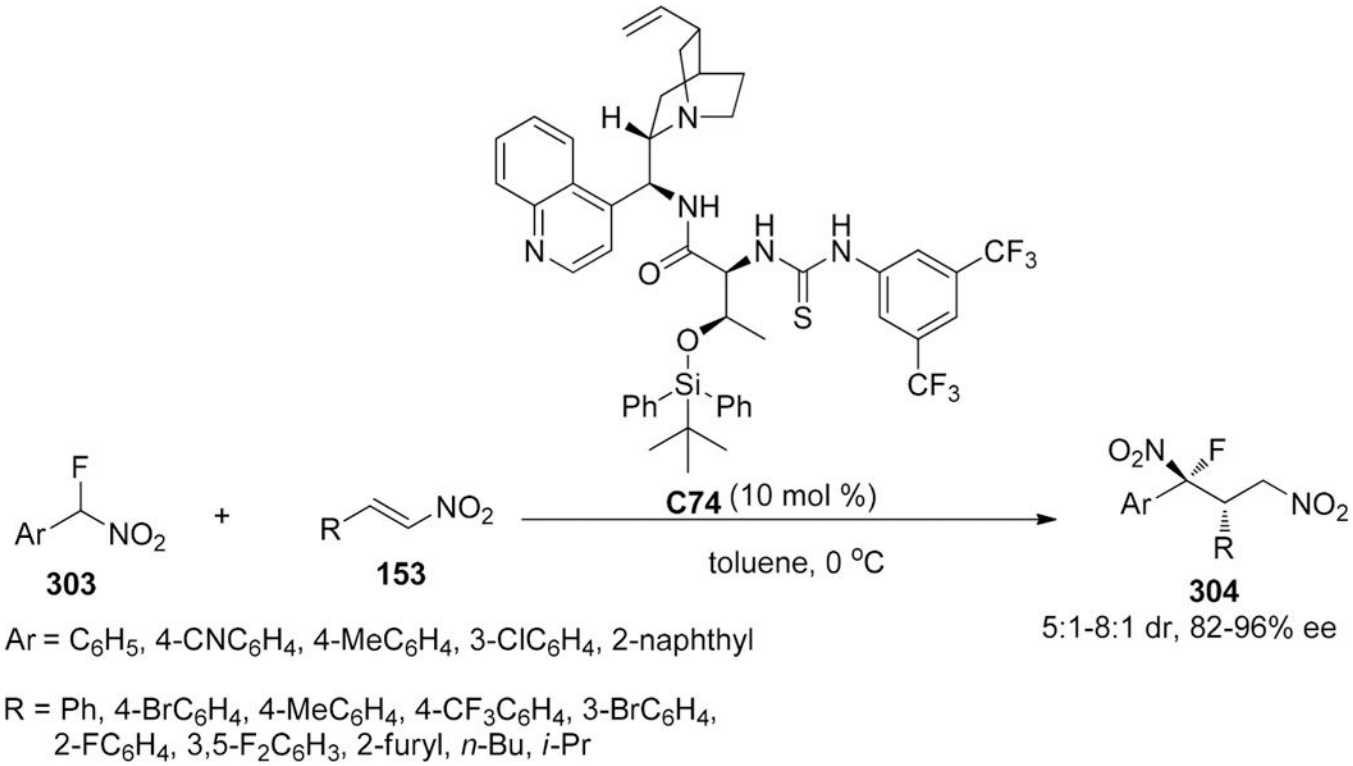
Scheme 124.
Asymmetric Michael Additions of α-Fluorinated-α-sulfonyl Ketones



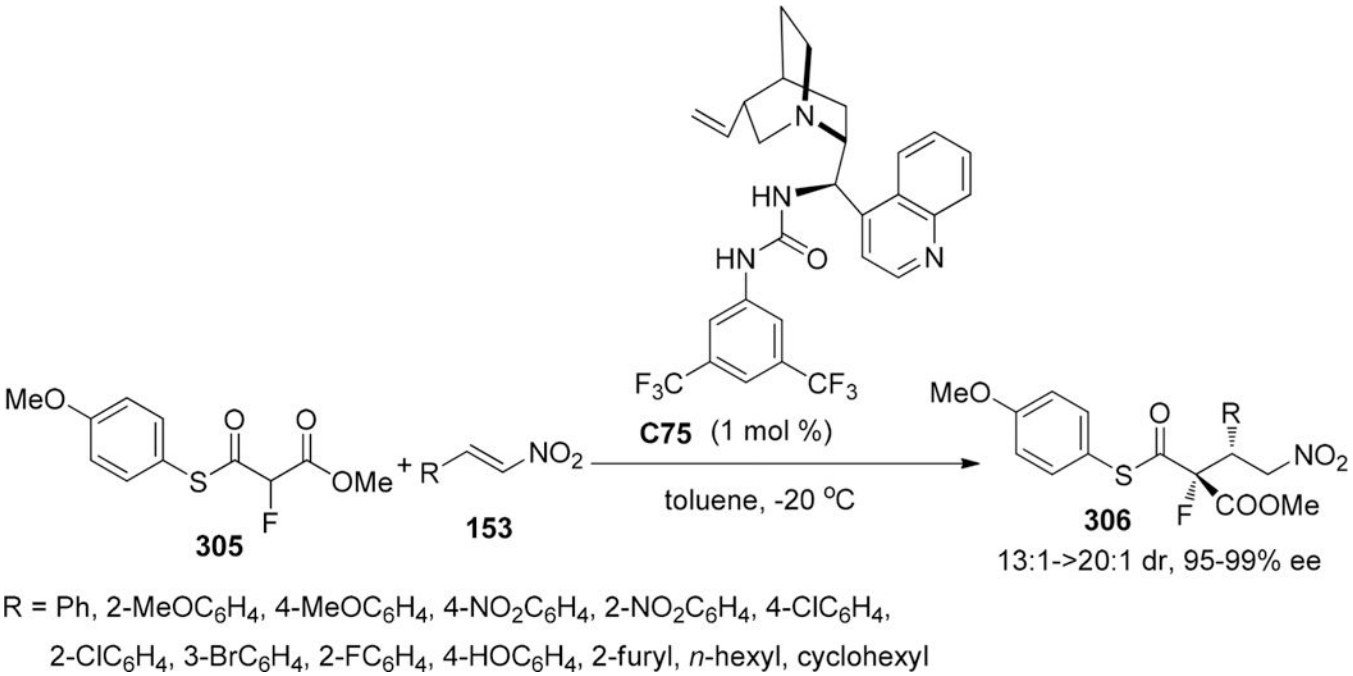
Scheme 125.
Asymmetric Michael Additions of α-Fluoro β-Ketophosphonates



Scheme 126.
Michael Addition Reactions of 2-Fluoro-1,3-diketones with Nitroolefins

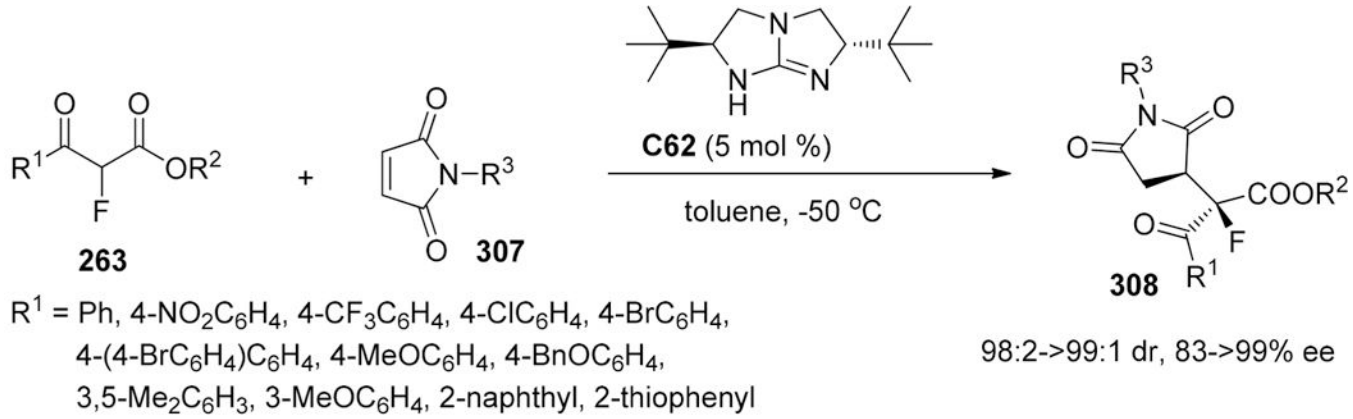


Scheme 127.
Asymmetric Michael Additions of α-Fluorinated Carbonyl Compounds with Nitroolefins



Scheme 128.

Asymmetric Organocatalytic Michael Addition Reactions of Fluorinated Monothiomalonates with β-Nitrostyrenes



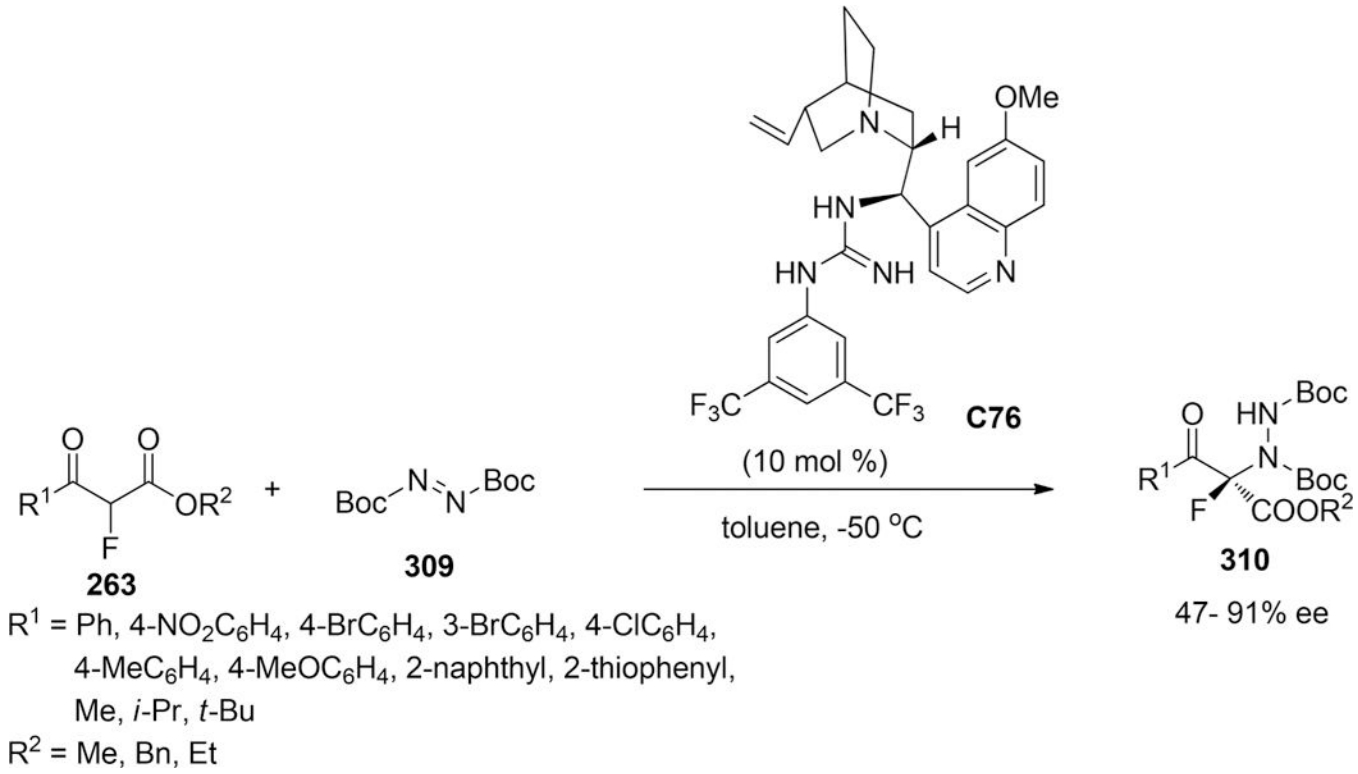
R^1 = Ph, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-(4-BrC_6H_4)C_6H_4, 4-$MeOC_6H_4$, 4-$BnOC_6H_4$, 3,5-$Me_2C_6H_3$, 3-$MeOC_6H_4$, 2-naphthyl, 2-thiophenyl

R^2 = Me, Et

R^3 = Et, Me, cyclohexyl, Bn, *n*-hexyl, *t*-Bu

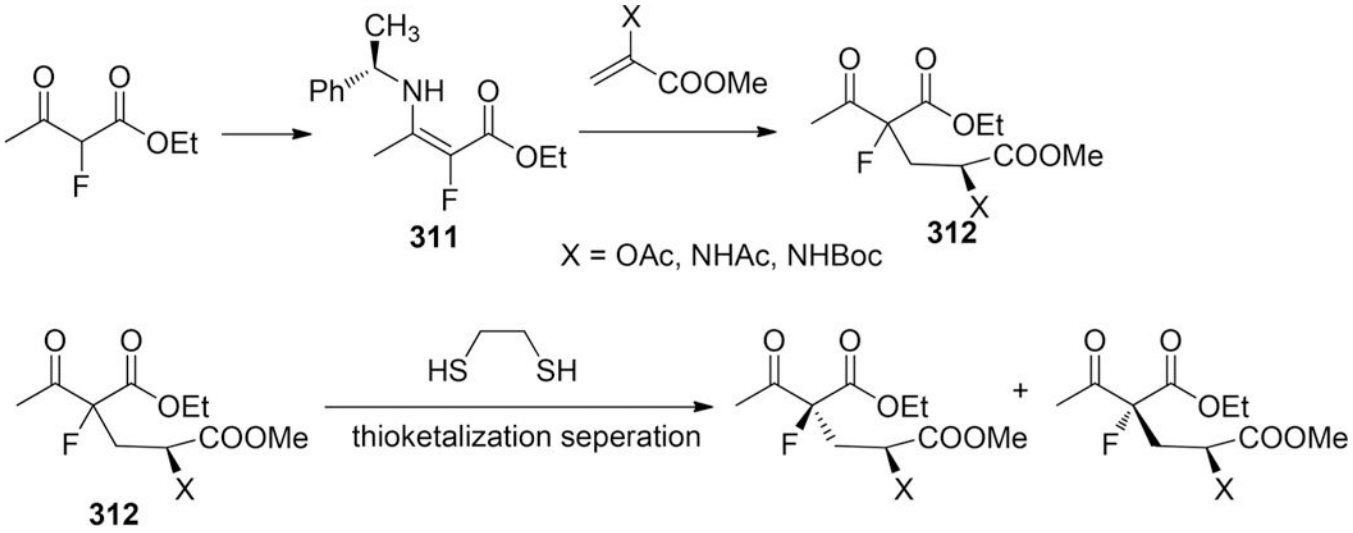
Scheme 129.

Organocatalytic Asymmetric Michael Reactions of α-Fluoro-β-keto Esters with *N*-Alkyl Maleimides



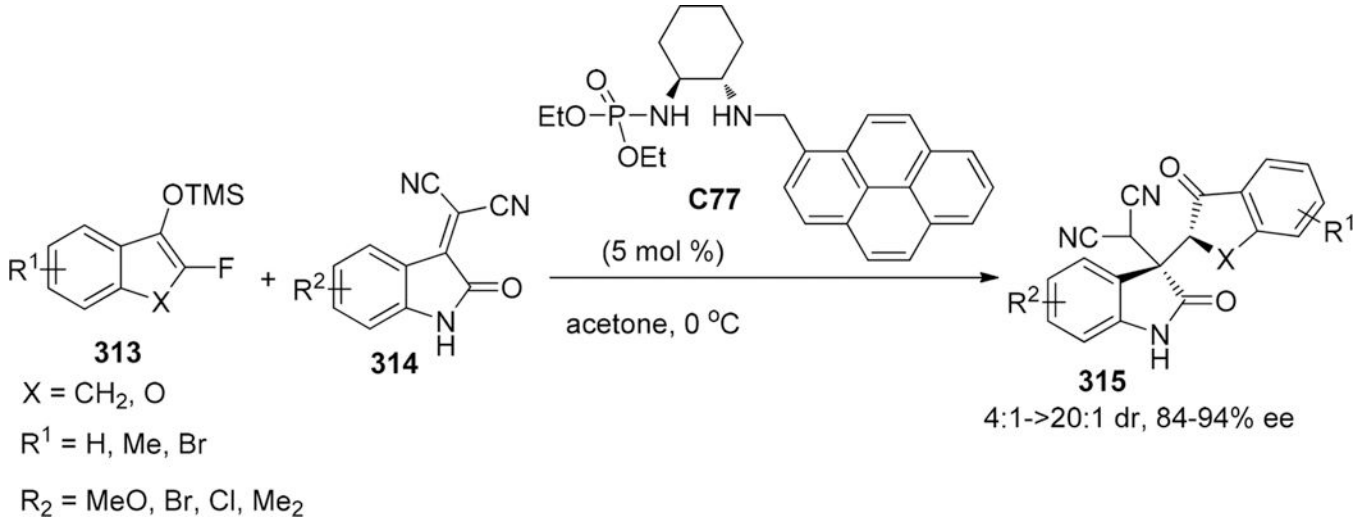
Scheme 130.

Asymmetric Michael Addition Reactions of α-Fluorinated β-Keto Esters with di-*tert*-Butyl Azodicarboxylates



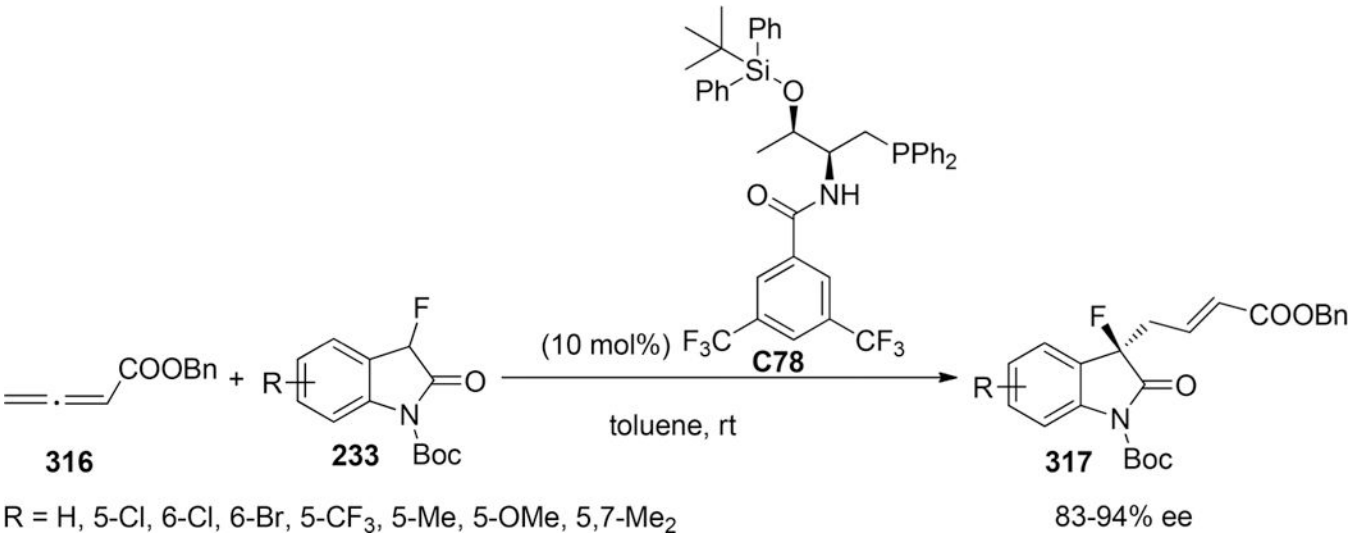
Scheme 131.

Asymmetric Michael Reactions Using (*S*)-1-Phenylethylamine as the Chiral Auxiliary



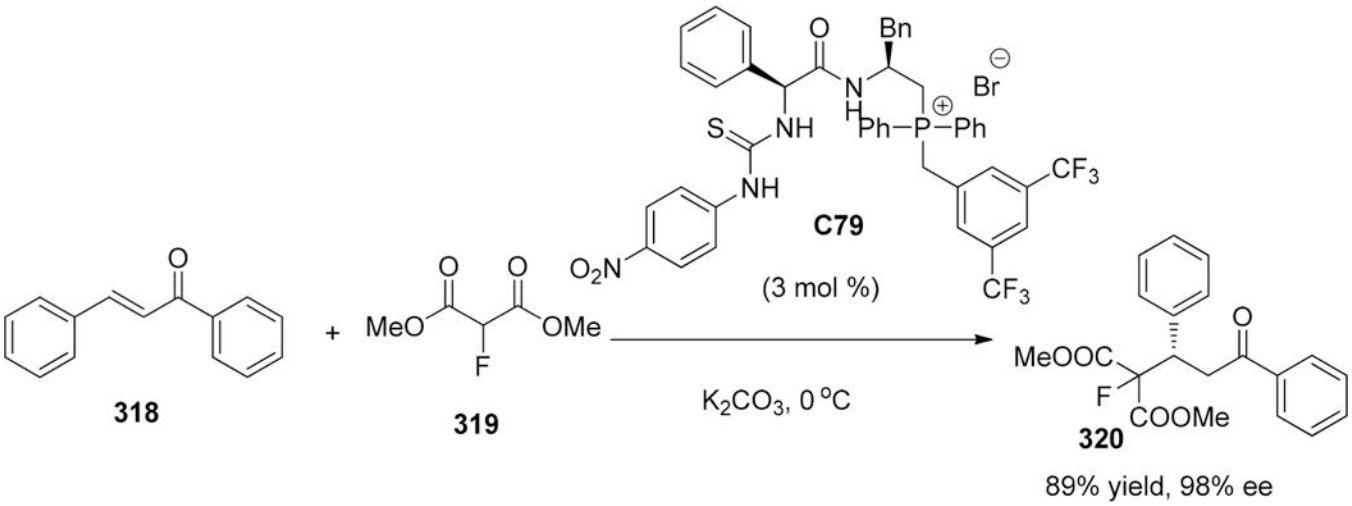
Scheme 132.

Asymmetric Michael Additions of Fluorinated Enol Silyl Ethers with Isatylidene Malononitriles

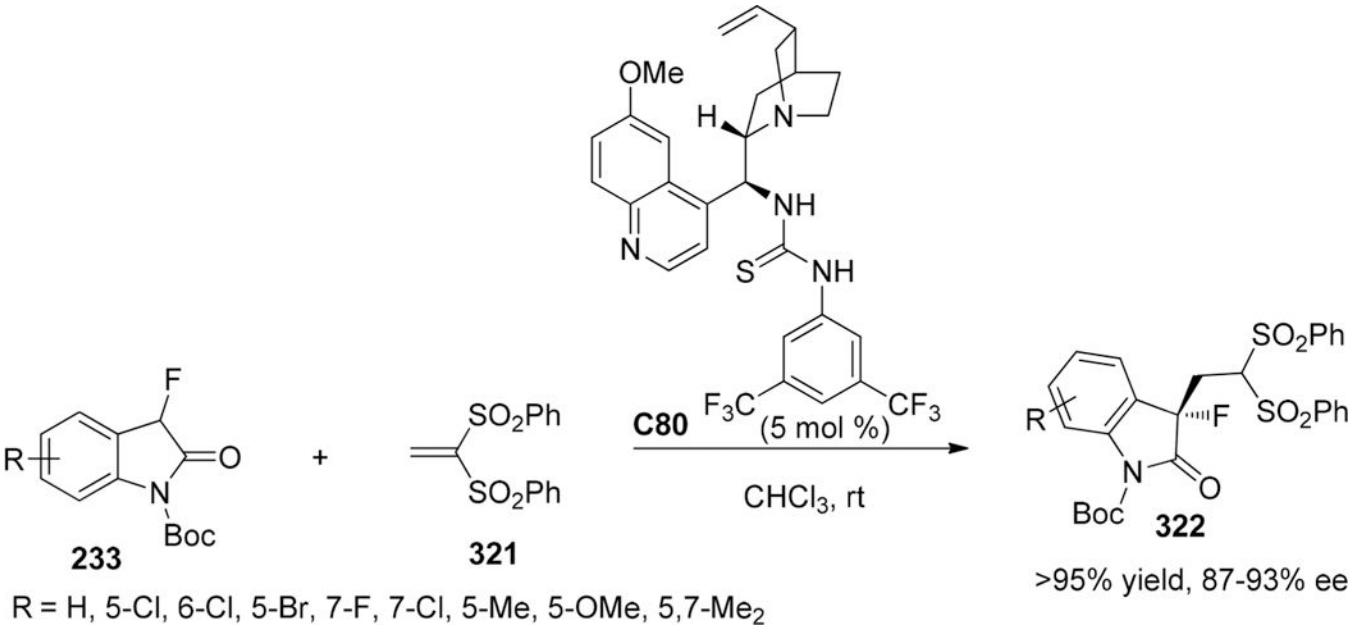


Scheme 133.

Asymmetric Michael Addition Reactions of 2,3-Butadienoates with 3-Fluorooxindoles

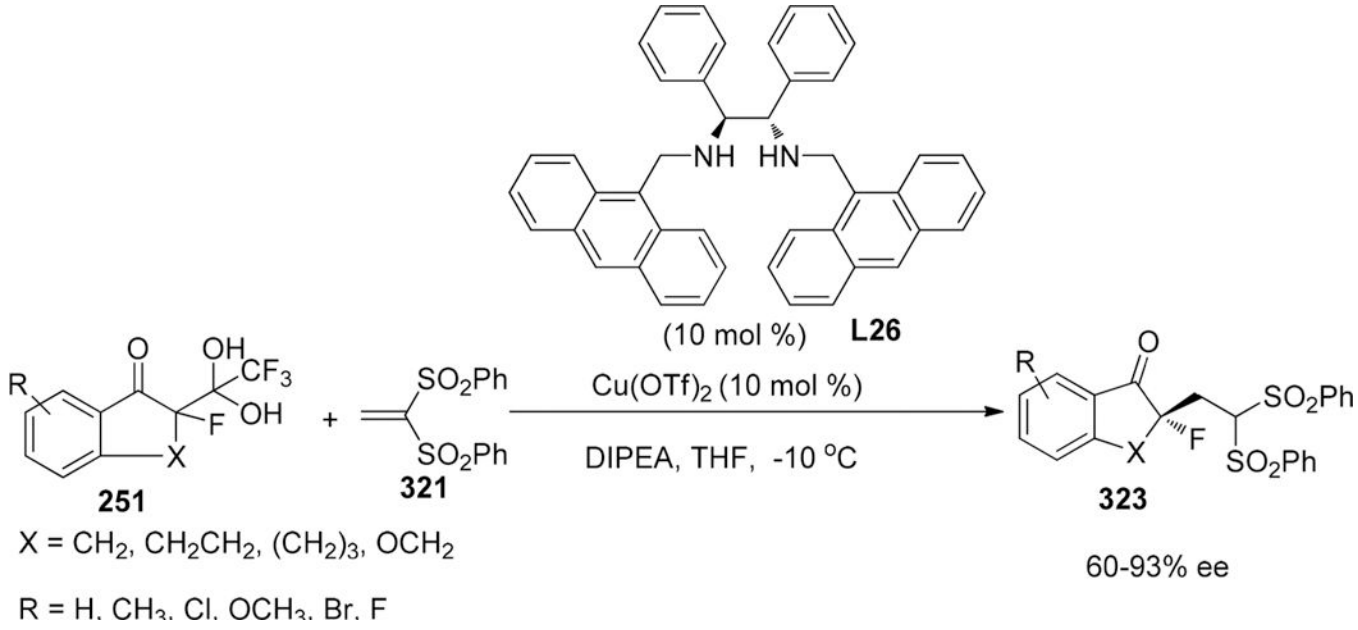


Scheme 134.
Asymmetric Michael Addition Reactions of α,β-Unsaturated Ketones with Malonates

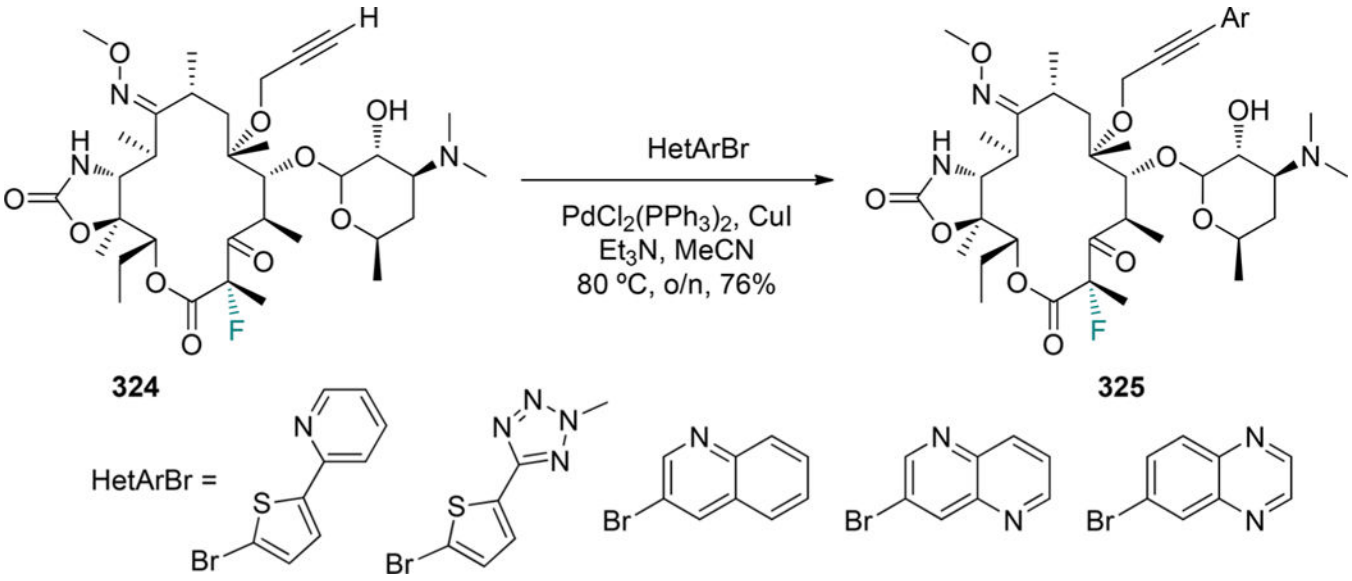


Scheme 135.

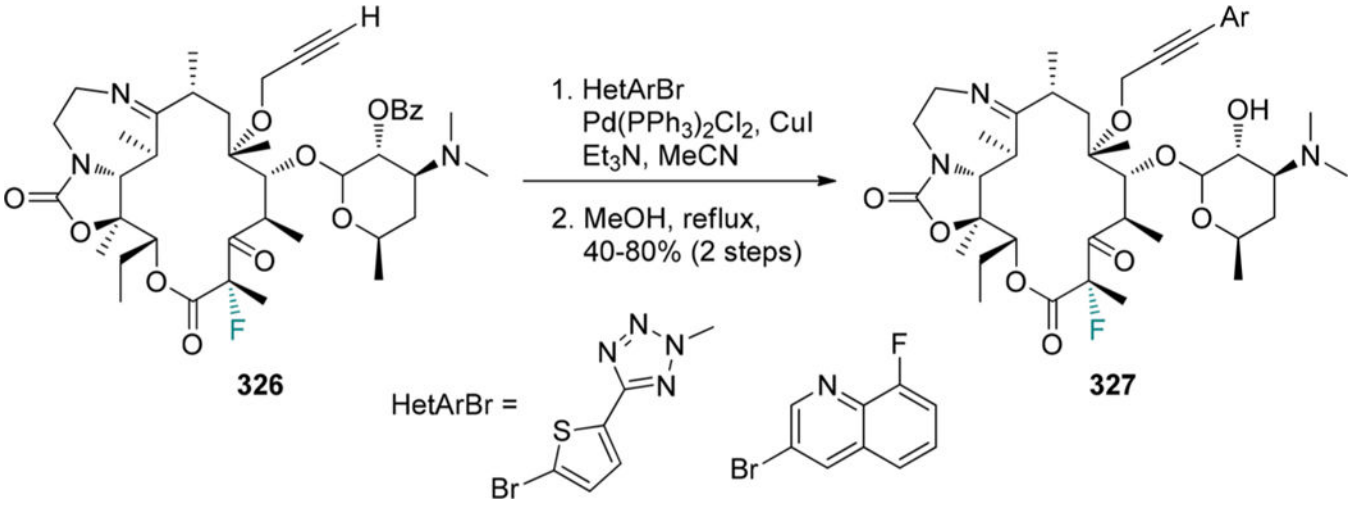
Asymmetric Organocatalytic Michael Reactions Vinyl Sulfones with 3-Fluorinated Oxindoles



Scheme 136.
Cu-Catalyzed Detrifluoroacetylative Michael Addition Reactions

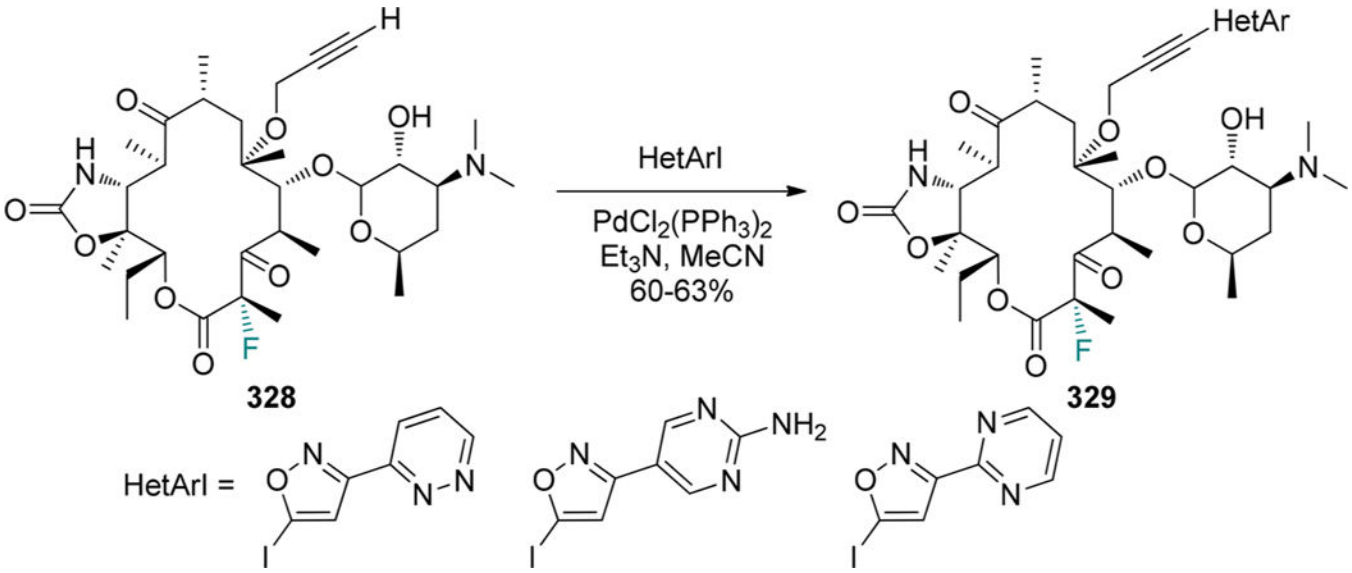


Scheme 137.
Palladium-Catalyzed Sonogashira Coupling Reactions of 2-Fluoro-9-oxime Ketolides

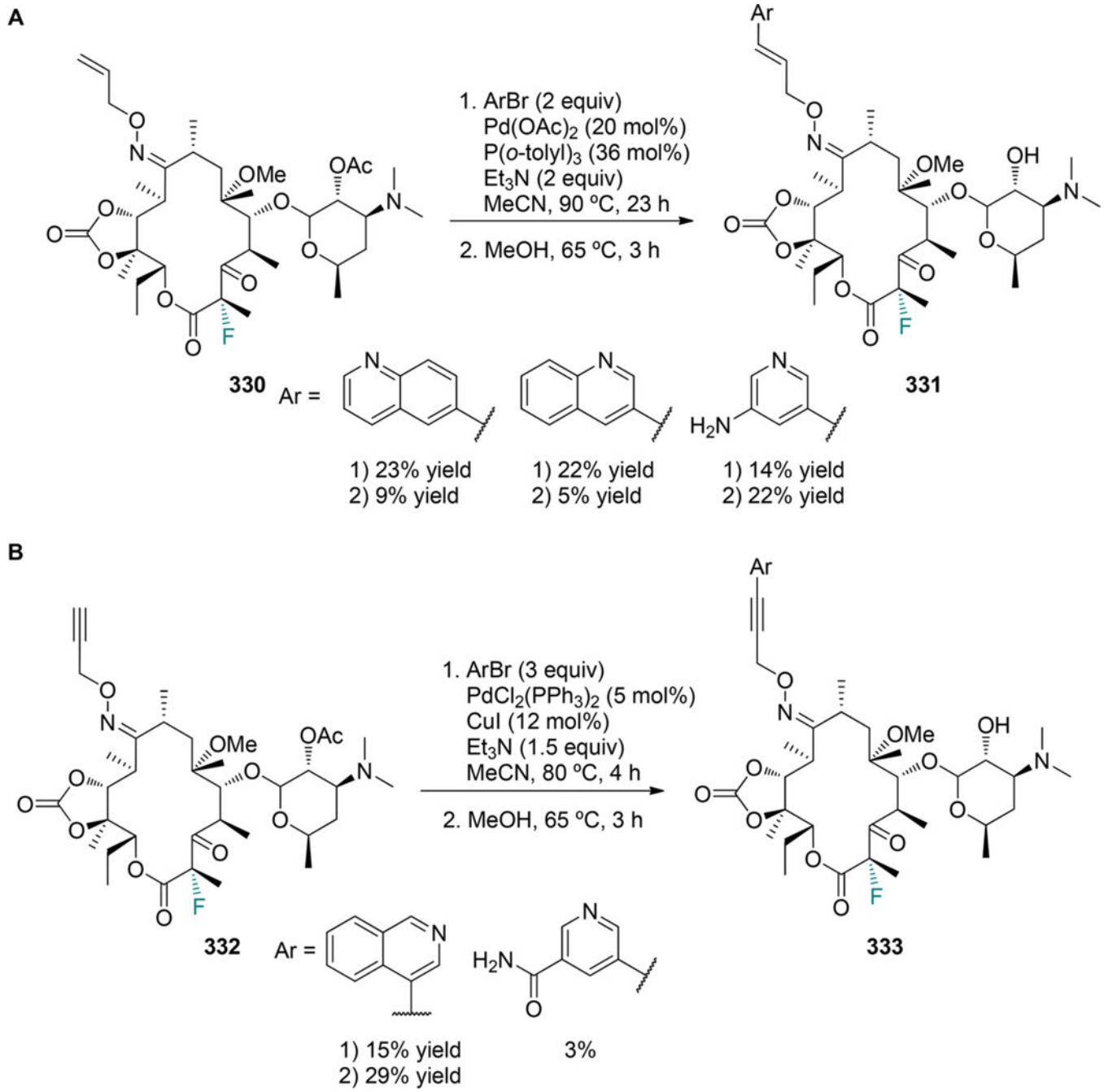


Scheme 138.

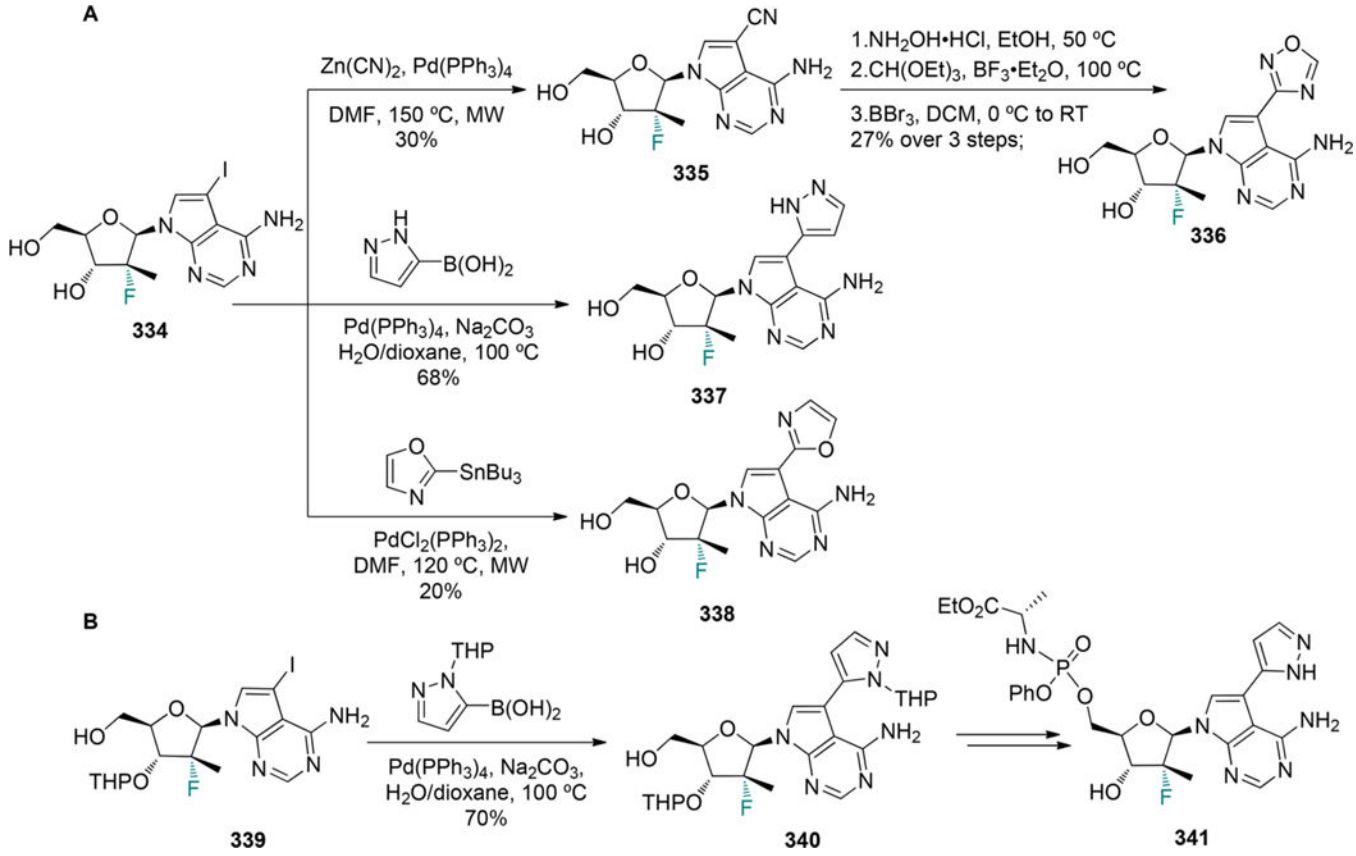
Sonogashira Coupling of 2-Fluoro-6-O-Propargyl Diazalides with Two Different Heteroaryl Bromide Reagents



Scheme 139.
Palladium-Catalyzed Sonogashira Cross-Coupling under Copper-Free Conditions

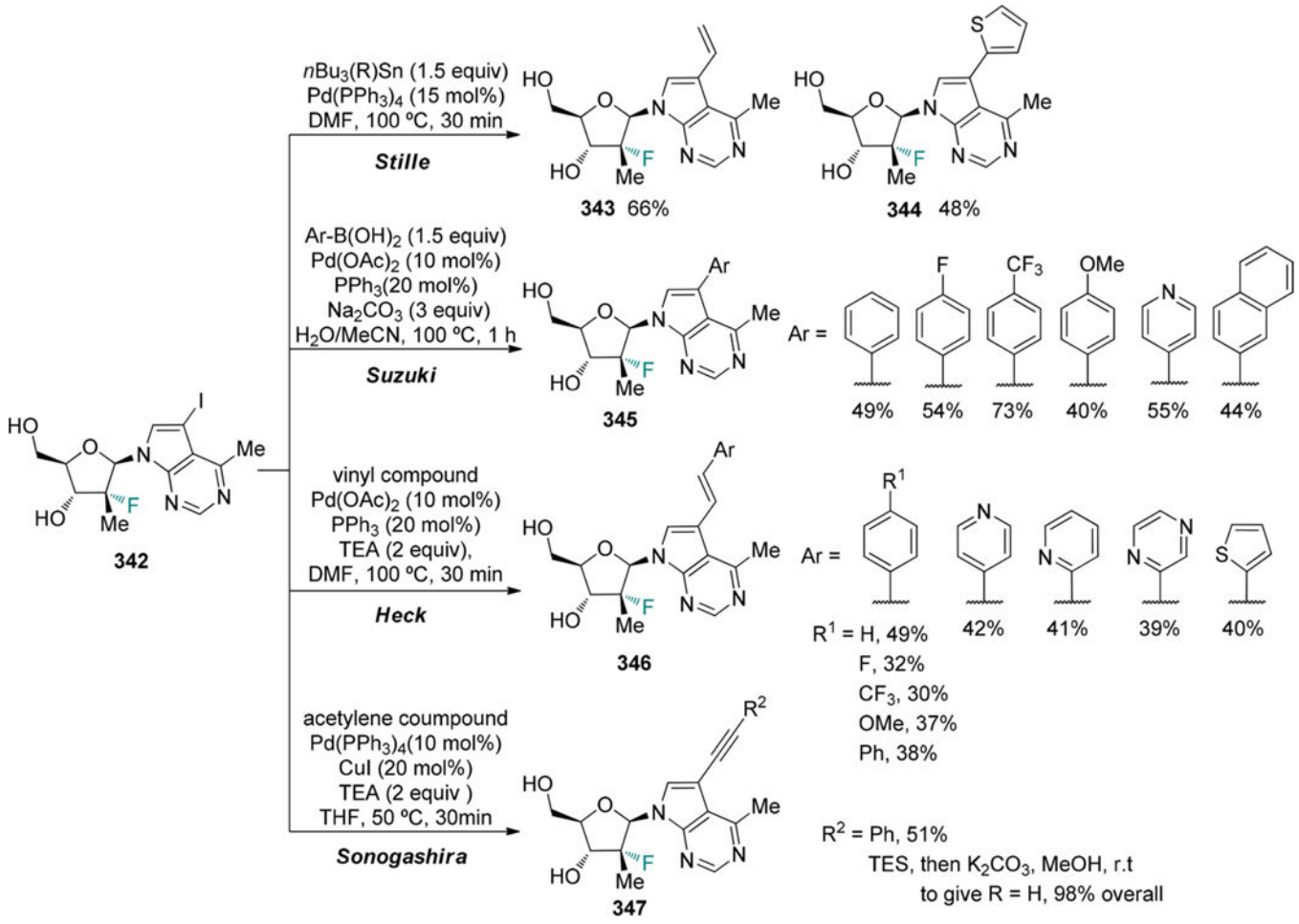


Scheme 140.
Palladium-Catalyzed Heck (A) and Sonogashira (B) Coupling Reactions



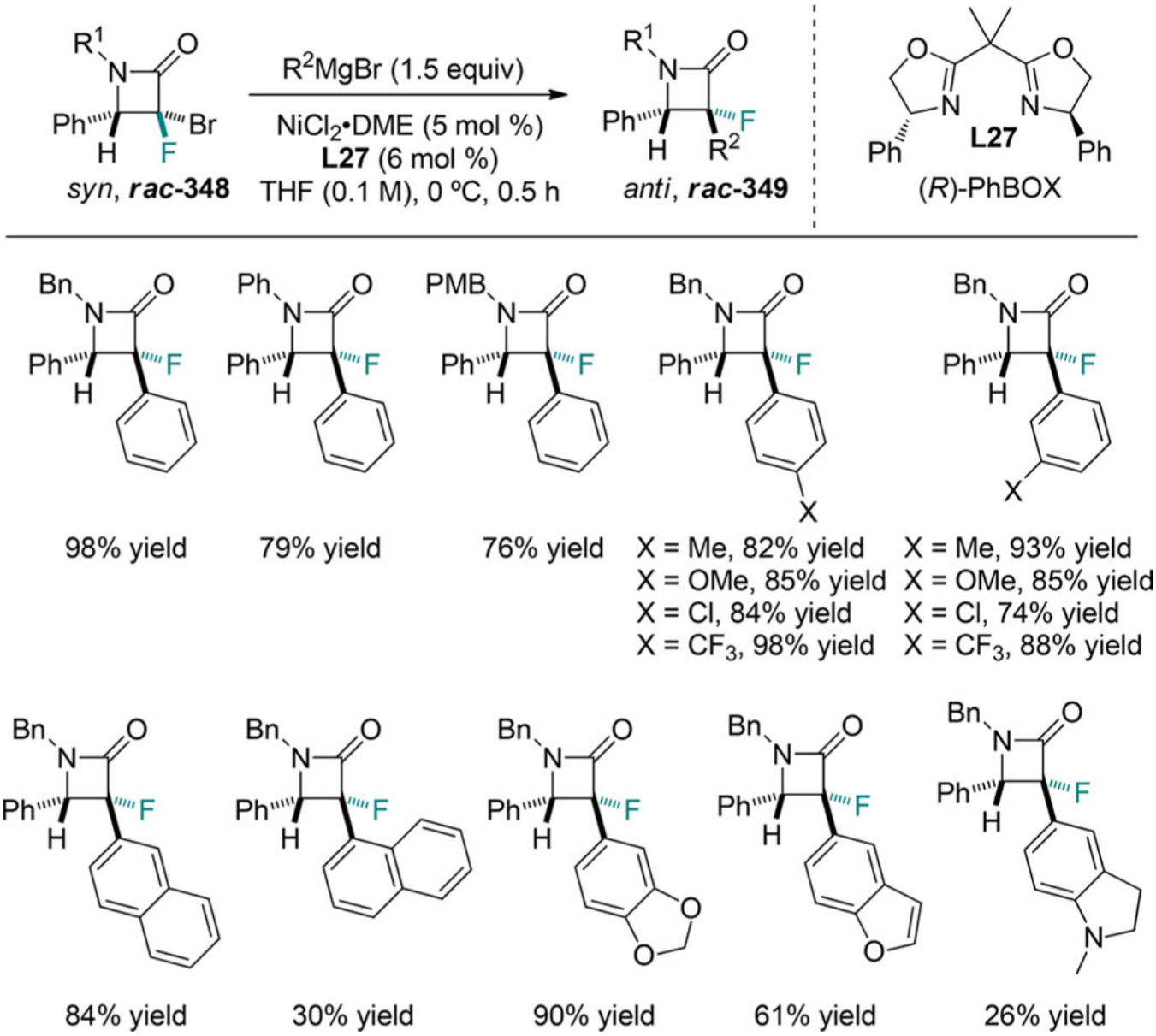
Scheme 141.

Palladium-Catalyzed Cyanation: Suzuki (A) and Stille (B) Coupling Reactions

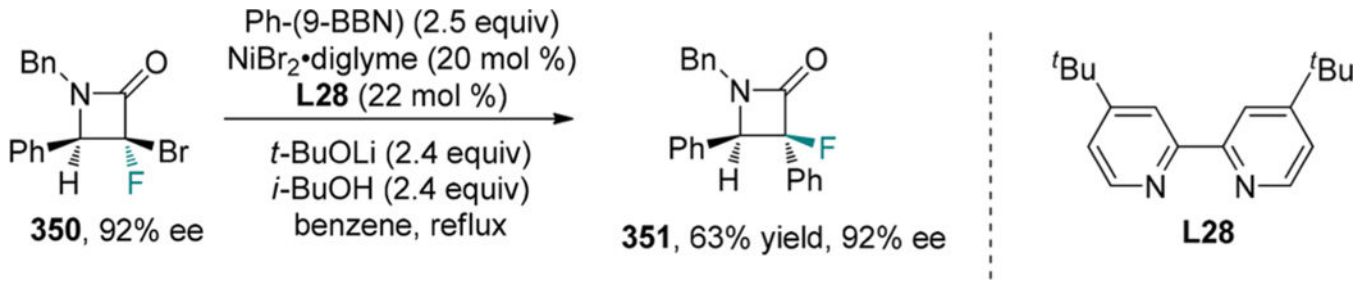


Scheme 142.

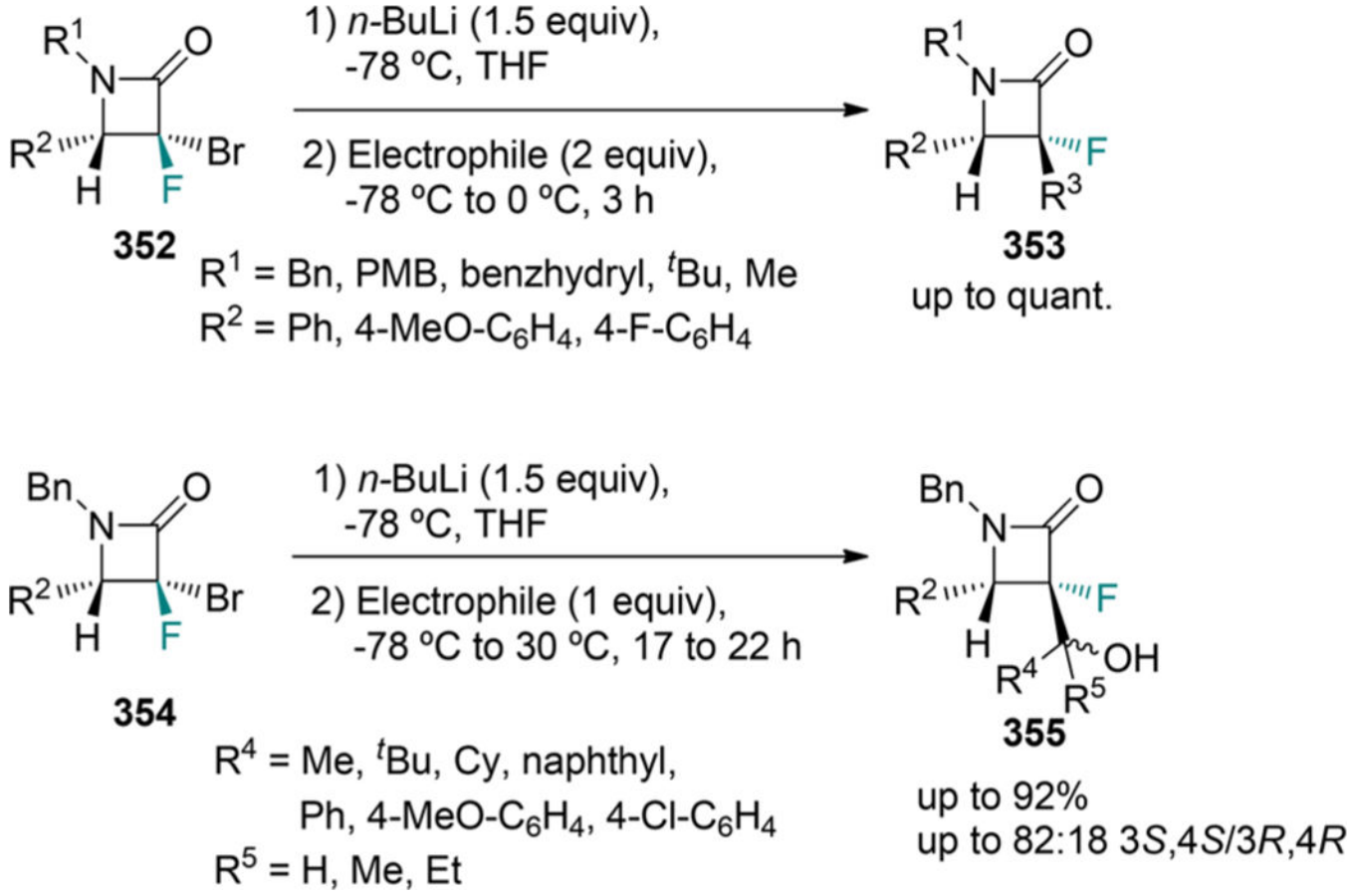
Cross-Coupling Reactions Using Stille, Suzuki, Sonogashira, or Heck Conditions



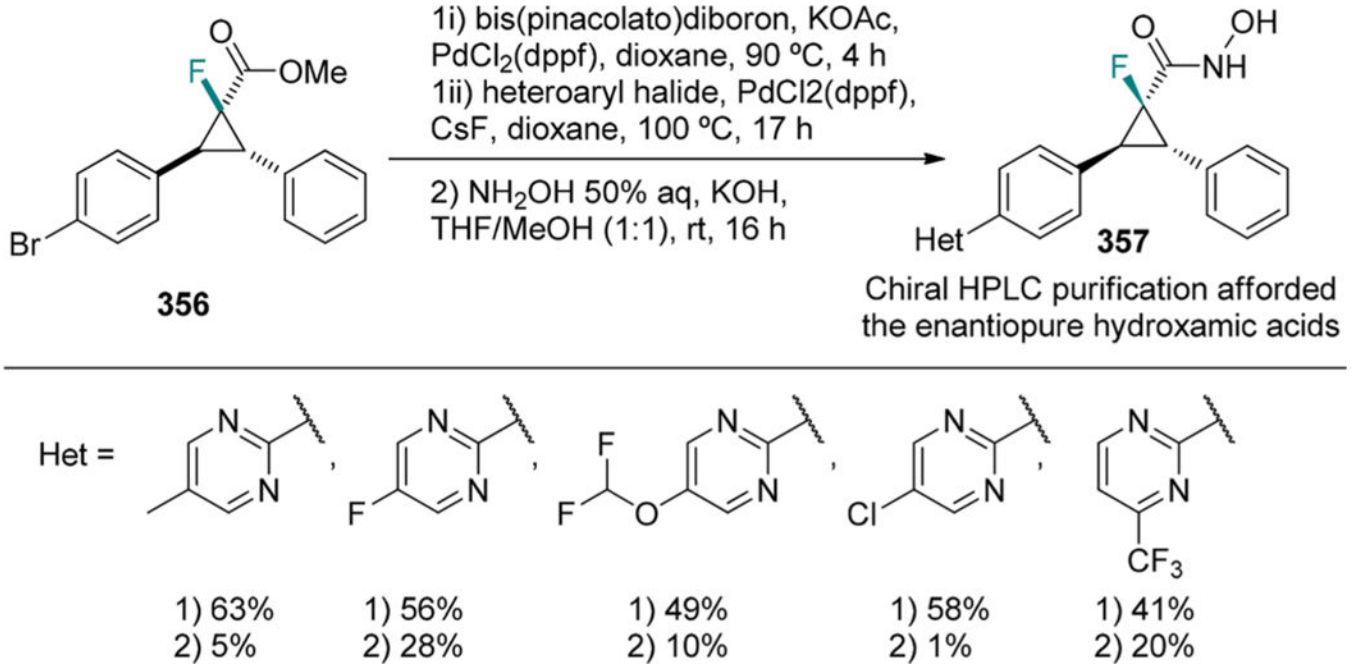
Scheme 143.
Kumada Coupling Reactions



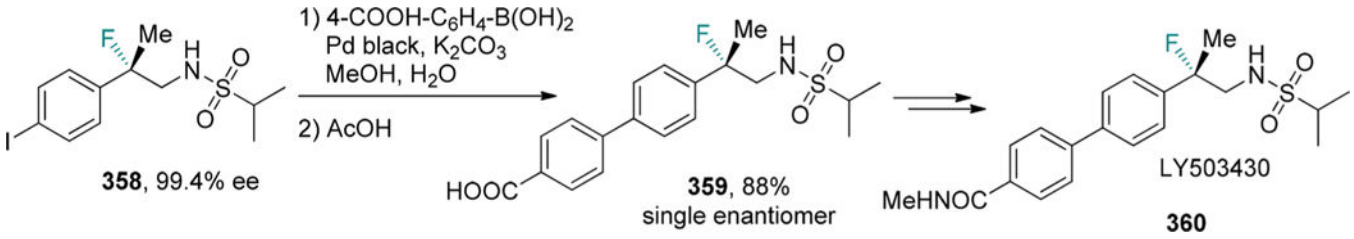
Scheme 144.
Nickel-Catalyzed Suzuki Coupling Reactions



Scheme 145.
Cross-Coupling Approach for the Formation of α-Alkyl-α-fluoro-β-lactams

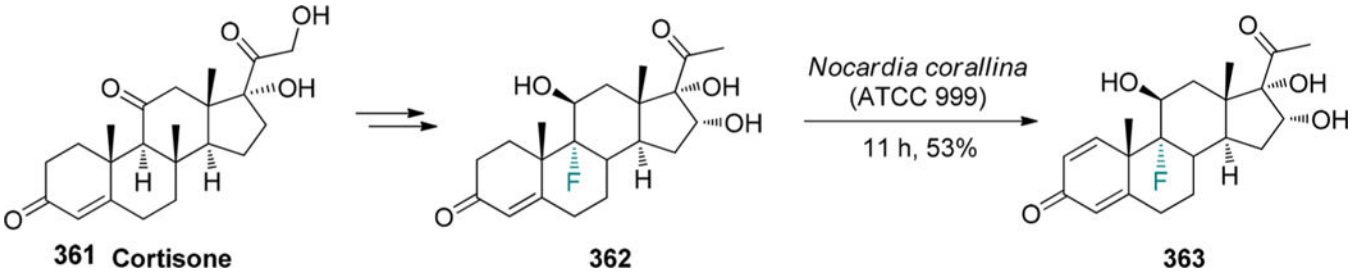


Scheme 146.
Palladium-Catalyzed Suzuki Coupling Reactions

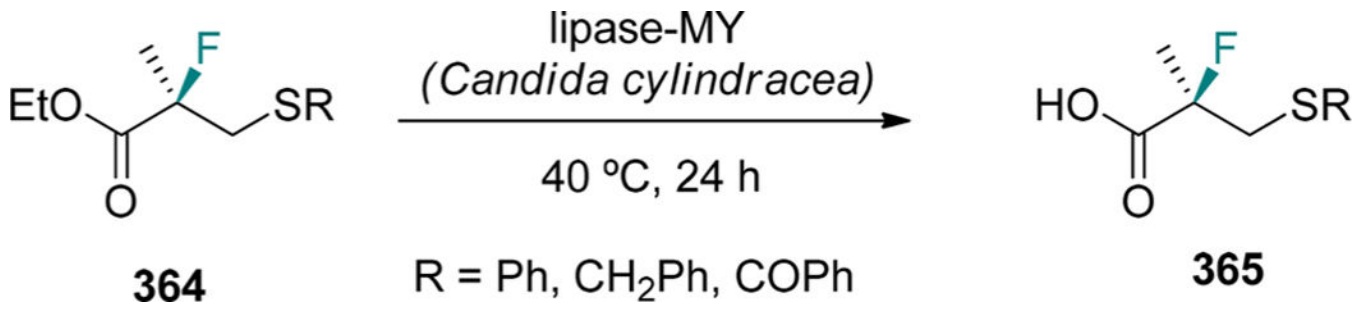


Scheme 147.

Suzuki Coupling Reactions of Iodo-sulfonamide with 4-Carboxylphenylboronic Acid Using Palladium Black as the Catalyst

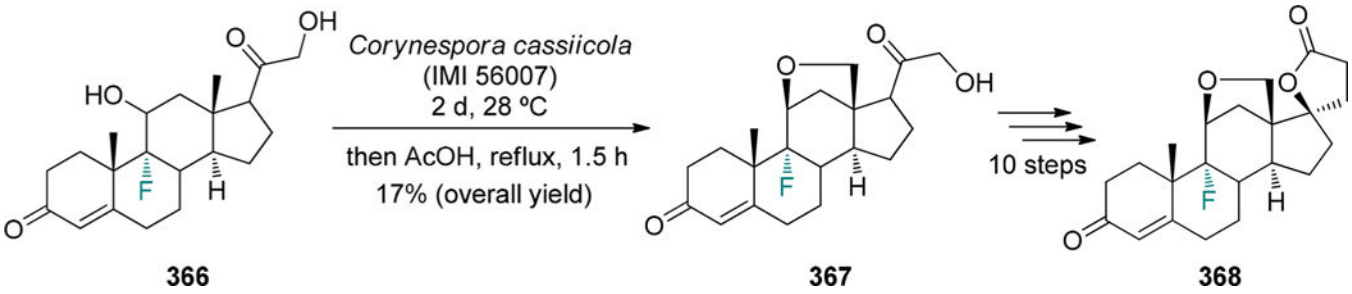


Scheme 148.
Lipase-Catalyzed Transesterification Reactions

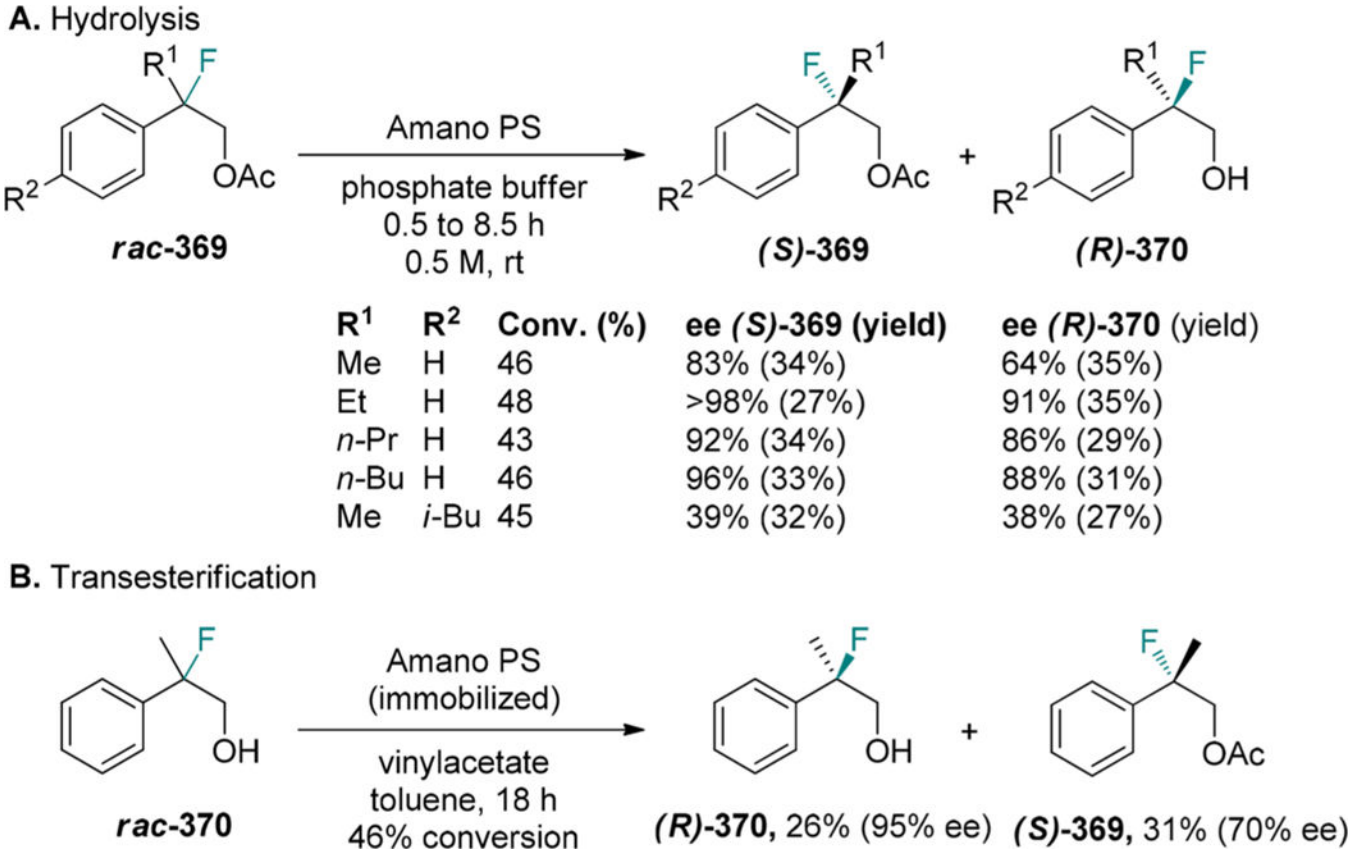


364 **365**

Scheme 149.
Lipase-Catalyzed Hydrolysis Reactions

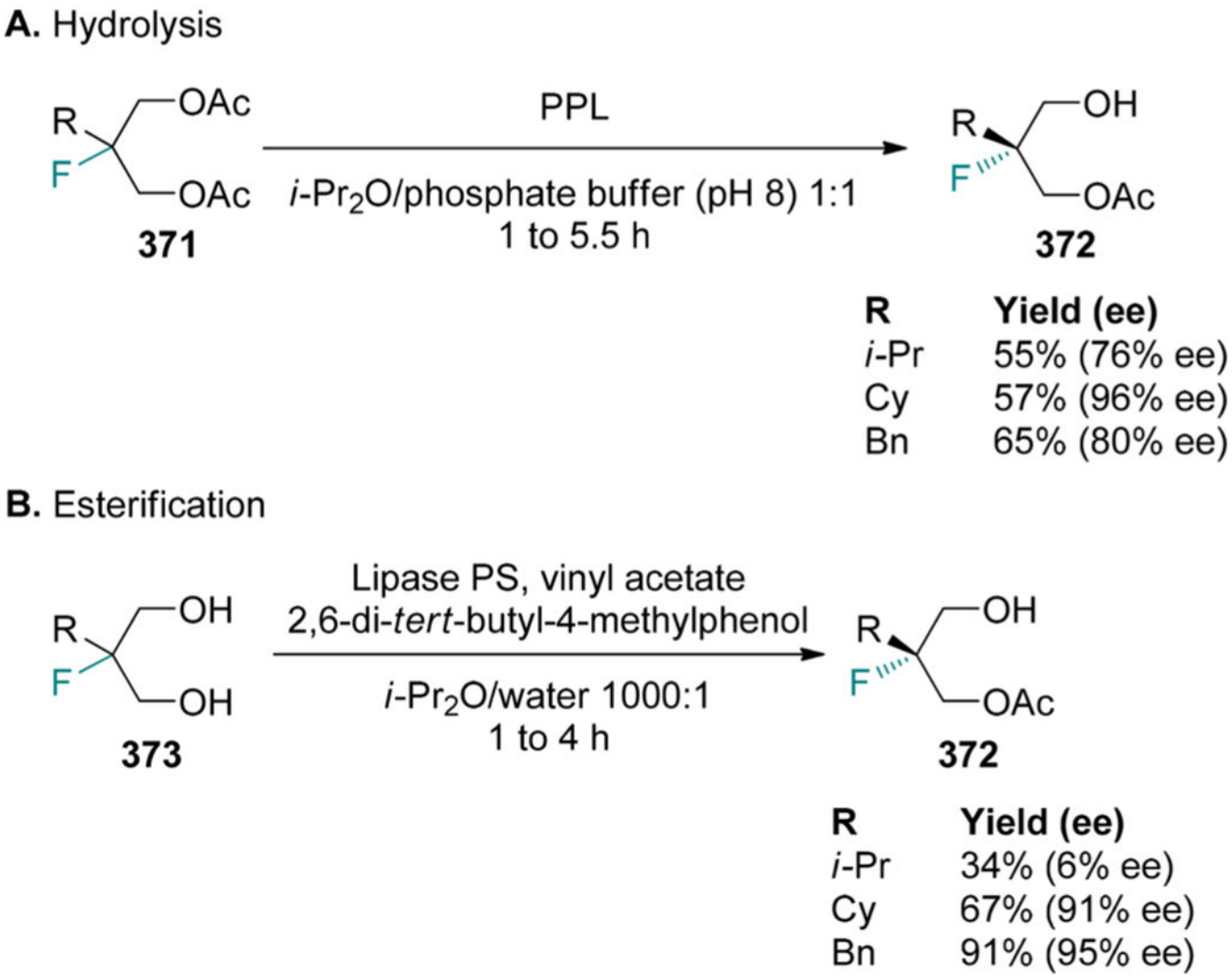


Scheme 150.
Biocatalytic Oxidation Reactions



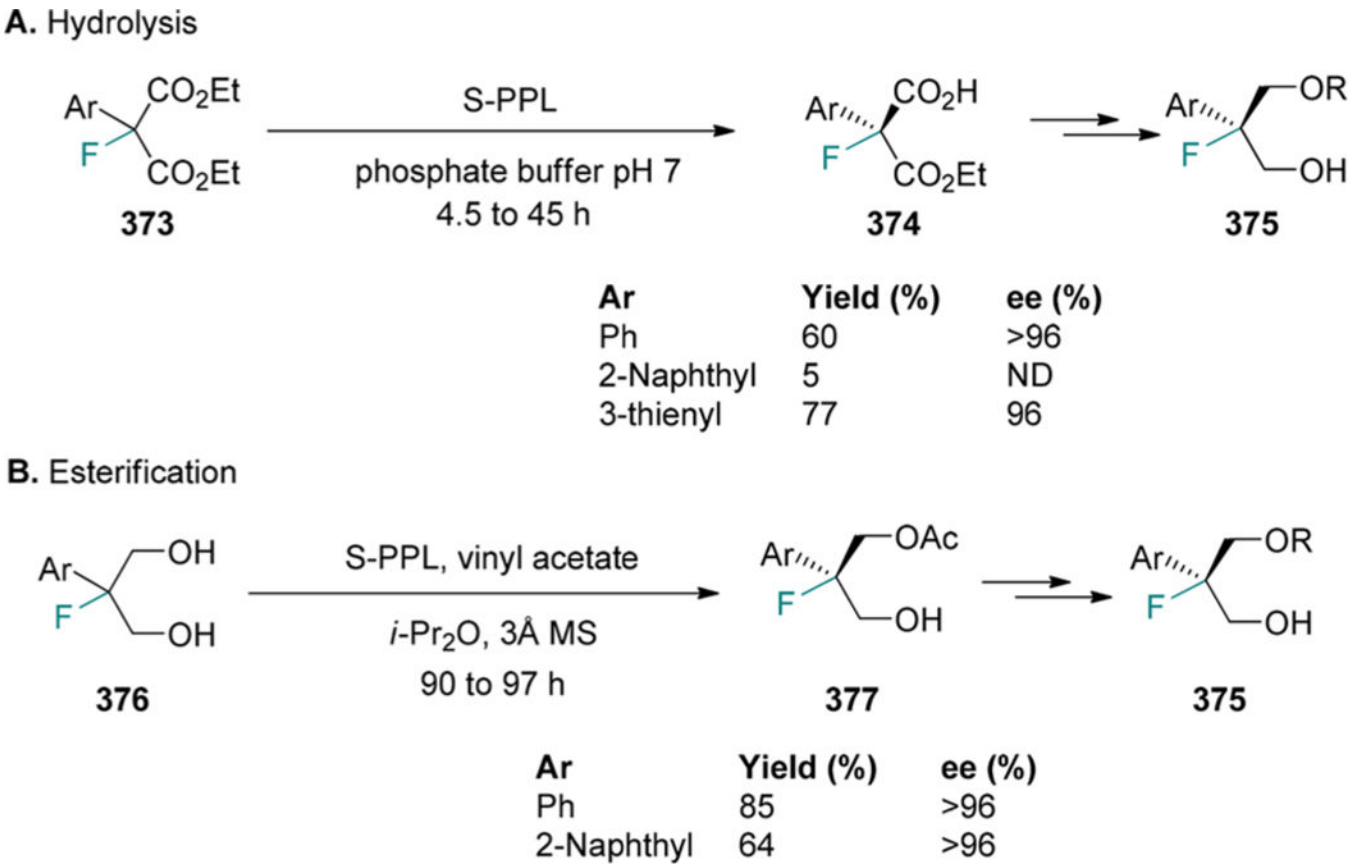
Scheme 151.

Enzymatic Kinetic Resolution of 1-Acetoxy-2-aryl-2-fluoroalkanes by Hydrolysis (A) and Transesterification (B)



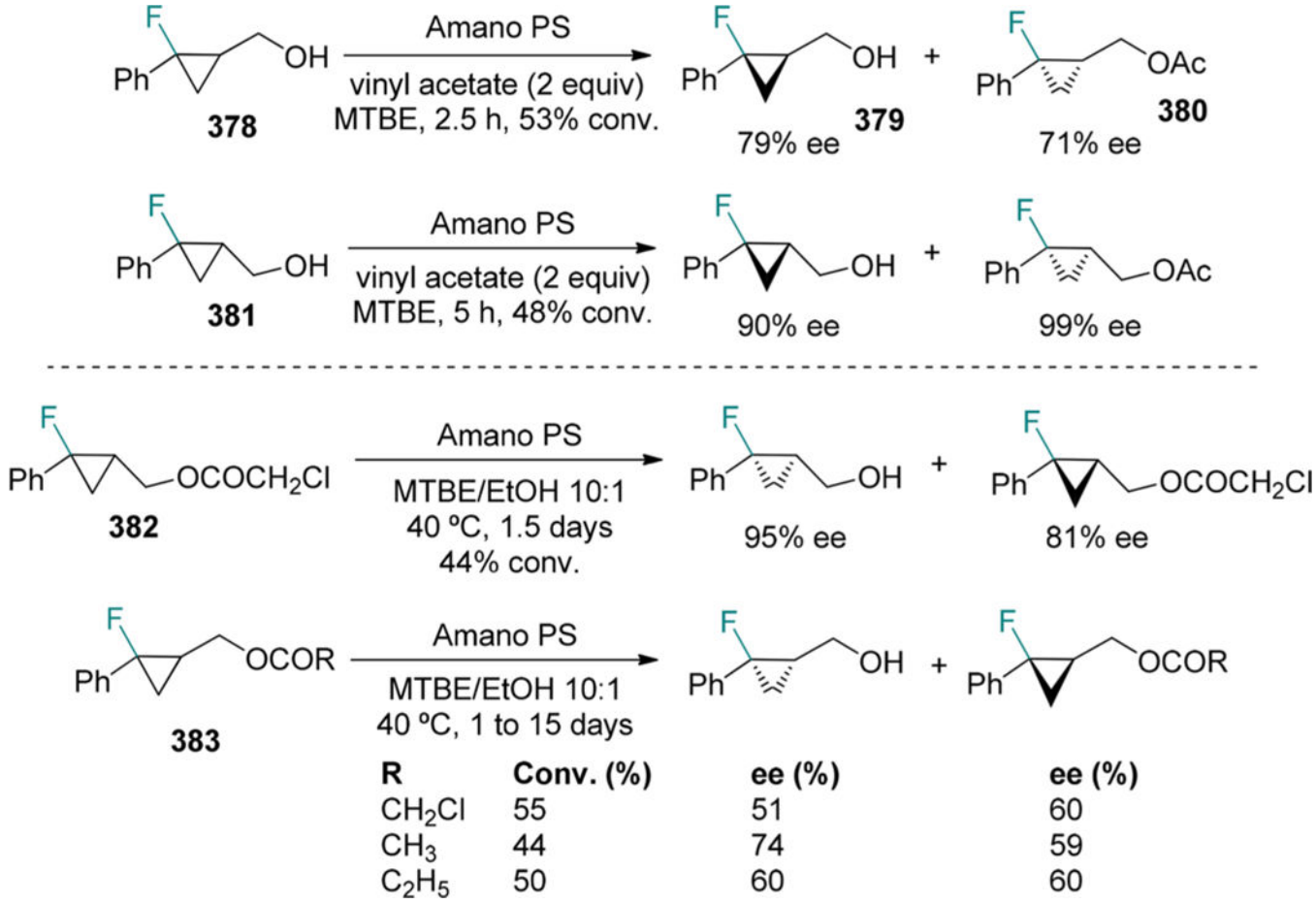
Scheme 152.

Desymmetrization of Glycol Systems by Biocatalytic Hydrolysis (A) and Esterification (B)



Scheme 153.

Desymmetrization of Fluorinated Polyfunctionalized Synthons by Lipase Mediated Asymmetric Hydrolysis (A) and Esterification (B)



Scheme 154.

Kinetic Resolution of Racemic 2-Fluoro-2-phenylcyclopropyl Derivatives by Lipase-Catalyzed Transesterification or Hydrolysis