



HAL
open science

Oxidation: C–X Bond Formation (X=Halogen, S, Se)

Samir Bouzbouz, Dominique Cahard

► **To cite this version:**

Samir Bouzbouz, Dominique Cahard. Oxidation: C–X Bond Formation (X=Halogen, S, Se). Hisashi Yamamoto; Erick Carreira. *Comprehensive Chirality*, inPress, 10.1016/B978-0-32-390644-9.00027-5 . hal-03858965

HAL Id: hal-03858965

<https://hal.science/hal-03858965>

Submitted on 24 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

7.9 Oxidation: C–X Bond Formation (X=Halogen, S, Se)

Samir Bouzbouz and **Dominique Cahard**, CNRS, Mont Saint Aignan, France

Abstract: The field of enantioselective C–X bond formation (X = halogen, S, Se) has grown steadily over the past decade. It is particularly true of electrophilic enantioselective fluorination owing to the beneficial effects of fluorination for tuning the biological activity of drug candidates. Other halogenations (X = Cl, Br) remain less developed. Other oxidations of C–H bonds include the sulfenylation, especially the trifluoromethylthiolation, and the selenenylation. Outstanding results are presented on the direct enantioselective C–X bond formation via C–H functionalization by means of electrophilic reagents and powerful asymmetric synthesis methodologies.

Key points:

- The enantioselective electrophilic fluorination with the aid of chiral fluorinating agents, by means of organocatalysis including phase-transfer catalysis, and by means of transition-metal catalysis is presented.
- Analogous chlorination and bromination exploiting asymmetric synthesis methodologies complement the C–Hal bond formations.
- The enantioselective electrophilic sulfenylation and selenenylation are also presented.

Keywords: Fluorination – Chlorination – Bromination – Sulfenylation – Selenylation – Thiocyanation – Trifluoromethylthiolation – Electrophilic reagents – Enantioselectivity – Organocatalysis – Metal-catalysis – Phase-transfer catalysis

7.9.1 Introduction

7.9.2 Enantioselective Electrophilic Fluorination

7.9.2.1 Chiral Fluorinating Agents

7.9.2.2 Organocatalytic Fluorination

7.9.2.3 Chiral Phase-Transfer Catalysis

7.9.2.3.1 with Chiral Cations

7.9.2.3.2 with Chiral Anions

7.9.2.4 Transition-metal Catalysis

7.9.3 Enantioselective Electrophilic Chlorination

7.9.3.1 Organocatalytic Chlorination

7.9.3.2 Transition-metal Catalysis

7.9.4 Enantioselective Electrophilic Bromination

7.9.5 Enantioselective Electrophilic Sulfenylation

7.9.5.1 Sulfenylation (SAr, SAlk)

7.9.5.1.1 Organocatalytic Sulfenylation

7.9.5.1.2 Transition-metal Catalyzed Sulfenylation

7.9.5.2 Thiocyanation (SCN)

7.9.5.3 Trifluoromethylthiolation (SCF₃)

7.9.5.3.1 Chiral Trifluoromethylthiolating Agents

7.9.5.3.2 Organocatalytic Trifluoromethylthiolation

7.9.5.3.3	Transition-metal Catalyzed Trifluoromethylthiolation
7.9.5.4	Disulfur transfer (SSCF ₃)
7.9.5.5	Difluoromethylthiolation (SCF ₂ H) and Monofluoromethylthiolation (SCFH ₂)
7.9.6	Enantioselective Electrophilic Selenenylation
7.9.6.1	Organocatalytic Selenenylation
7.9.6.2	Transition-metal Catalysis
7.9.7	Conclusion and Outlook
References	

7.9.1 Introduction

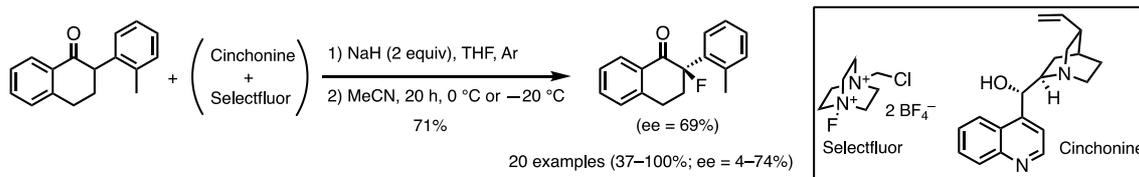
This chapter covers the literature from 2012 to end of 2021 that appears after the first edition of *Comprehensive Chirality*. During this last decade, the field of enantioselective C–X bond formation (X = halogen, S, Se) has grown steadily. It is particularly true of electrophilic enantioselective fluorination owing to the beneficial effects of fluorination for tuning the biological activity of new drug candidates. Other halogenations (X = Cl, Br) remain less developed as a consequence of a lower interest for the corresponding halogenated products. The second most investigated oxidation of C–H bonds is the sulfenylation, specifically the trifluoromethylthiolation for direct introduction of the biologically relevant emerging SCF₃ motif, which, once again, illustrates the high interest for fluorine. Outstanding results were reported on the direct enantioselective C–X bond formation via C–H functionalization by means of electrophilic reagents and powerful asymmetric synthesis methodologies. This chapter is organized by C–X type bond formation and sub-categorized by type of approach: use of stoichiometric chiral agents, organocatalytic reactions with a special focus on phase-transfer catalysis, and transition-metal catalysis. Not covered in this chapter are the diastereoselective reactions that are mentioned in Volumes 1 and 2 nor the olefin difunctionalization that is described in Volume 5.

7.9.2 Enantioselective Electrophilic Fluorination

The C–F bond formation, a fortiori with concomitant creation of a stereogenic center, is of the utmost interest to optimize the performances of pharmaceutical, agrochemical and material products. With that aim in mind, numerous applications of the two most popular electrophilic fluorinating agents, NFSI and Selectfluor, in organocatalytic and metal-catalyzed processes have been intensively investigated. Chiral analogues of NFSI and Selectfluor were also developed.

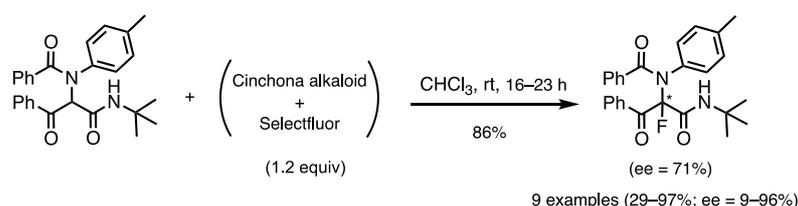
7.9.2.1 Chiral Fluorinating Agents

Following the pioneering works conducted independently by Shibata and Cahard groups, a few asymmetric fluorinations have been performed using chiral fluorinating agents obtained by combination of a chiral alkaloid and an electrophilic fluorine source. This strategy was used in the enantioselective fluorination of α -aryl-tetralones via a combination of a cinchona alkaloid and Selectfluor (Scheme 1).¹ The results are very sensitive to the structure of the alkaloid, the decoration of the substrate and to the reaction temperature. In particular, the enantioselectivity showed a strong dependence of the α -aryl substituent (α -alkyl ketones were not studied).



Scheme 1 Enantioselective electrophilic fluorination of α -aryl-tetralones

Using the same strategy, the enantioselective fluorination of α -amino keto amides was accomplished in a post-Ugi functionalization. The reactivity and the enantioselectivity strongly depend on the nature of the alkaloid used (13 alkaloids tested) as well as on the nature of the substrate substituents (Scheme 2).²



Scheme 2 Enantioselective electrophilic fluorination of Ugi adducts, α -amino keto amides

In 2013, two new chiral fluorinating agents were developed. The Gouverneur group prepared a reagent by adding aryl groups to Selectfluor's framework (Figure 1) for use in asymmetric tandem electrophilic fluorination-cyclization reactions (see volume 5).³ In a joint work, Shibata, Ma and Cahard designed chiral *N*-fluorodibenzenesulfonimides as chiral analogues of NFSI. The enantioselective fluorination was demonstrated in cyclic β -keto esters and in the synthesis of BMS-204352 with up to 86 % ee (Figure 1).⁴

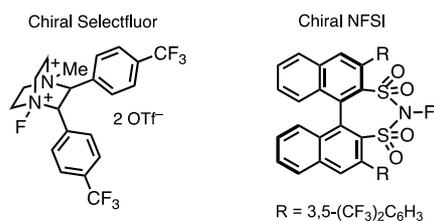


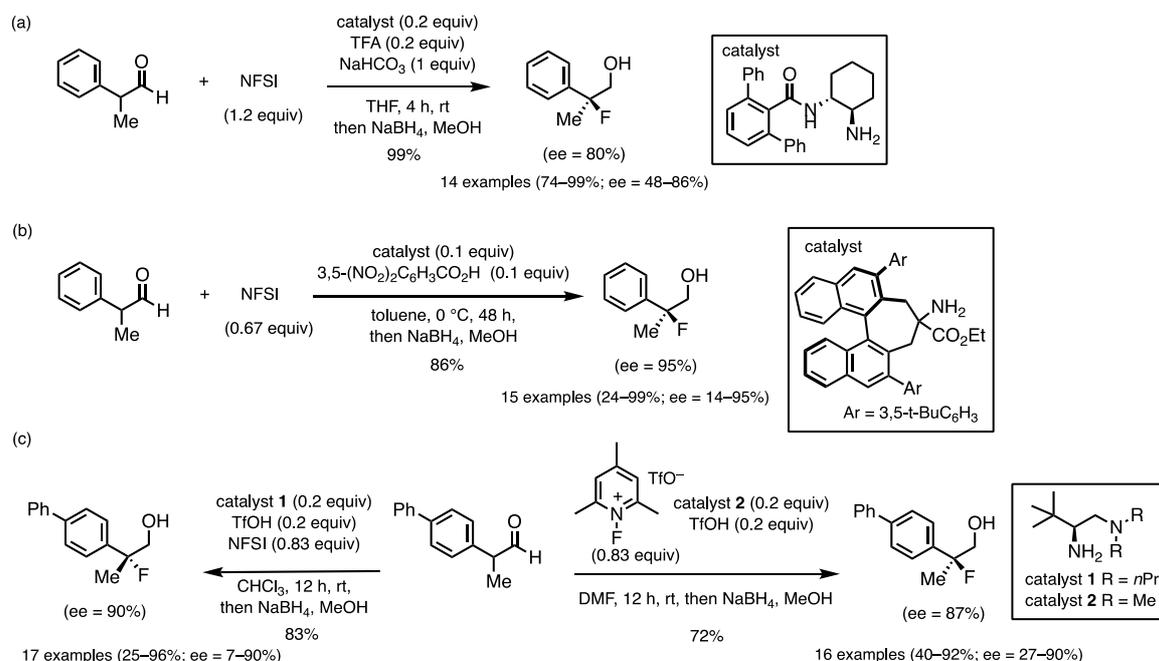
Figure 1 Chiral Selectfluor and NFSI analogues

7.9.2.2 Organocatalytic Fluorination

A well-developed approach in reactions of aldehydes to create α -stereogenic centers involve aminocatalysis via enamine intermediates. Although the stereodiscriminating step involves a diastereoselective addition on an intermediate to which the catalyst is covalently attached, we think of interest to mention some examples in this chapter in complement to other diastereoselective approaches presented in Volumes 1 and 2.

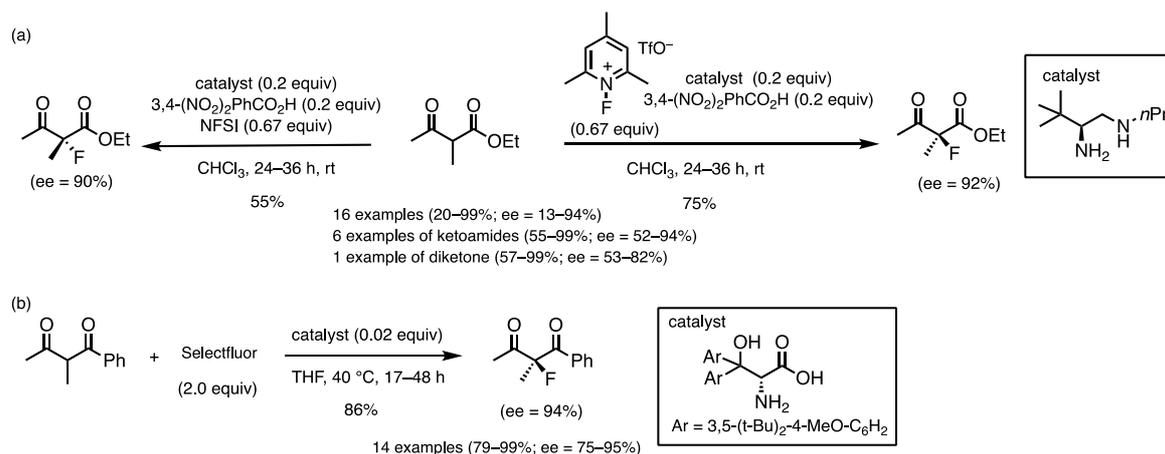
Chiral primary amines have been shown to be very efficient catalysts for reactions with branched aldehydes. For instance, aminobenzamide catalysts derived from chiral 1,2-diaminocyclohexane promoted efficient α -fluorination of α,α -disubstituted aldehydes with

high enantioselectivities (Scheme 3a).⁵ In the same vein, new chiral primary amine catalysts featuring an ester function and aryl substituents at the 3,3'-positions of the binaphthyl backbone were successfully applied in the enantioselective fluorination of branched aldehydes affording high enantioselectivities (Scheme 3b).⁶ Interestingly, when simple diamine (primary/tertiary) were employed, it was noted that switching the fluorination reagent from NFSI to *N*-fluoro pyridiniums gave access to both enantiomers in good yields and high enantioselectivities (Scheme 3c).⁷



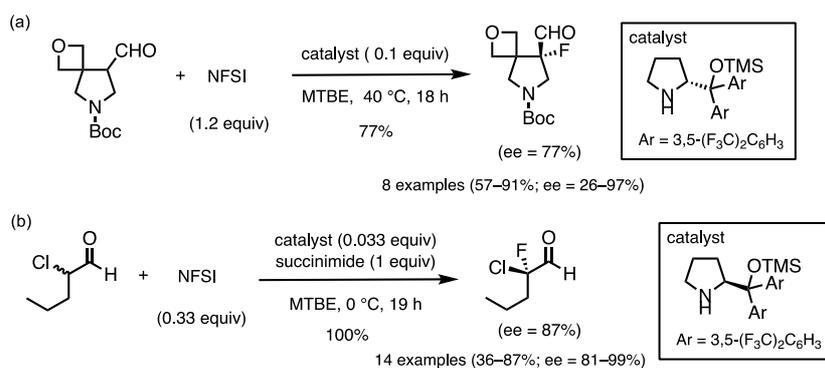
Scheme 3 Aminocatalysis for asymmetric α - fluorination of branched aldehydes

The same observation was done in the organocatalytic asymmetric fluorination of cyclic and acyclic β -keto carbonyls. Here again, a simple exchange of the fluorination reagent while keeping the same primary amine as catalyst made it possible to reverse the enantioselectivity. Mechanistic studies revealed H-bonding (with NFSI) and electrostatic repulsions (with *N*-fluoro pyridiniums) as key interactions in transition-state models for the same chiral primary amine catalyst (Scheme 4a).⁸ Primary amines derived from β,β -diaryl serine served in the fluorination of α - substituted β - diketones. The carboxylic group of β,β -diaryl serine plays an important role in enhancing the electrophilicity of the fluorine donor and in positioning the reaction partners in the transition state (Scheme 4b).⁹



Scheme 4 Aminocatalysis for asymmetric α -fluorination of β -keto carbonyls

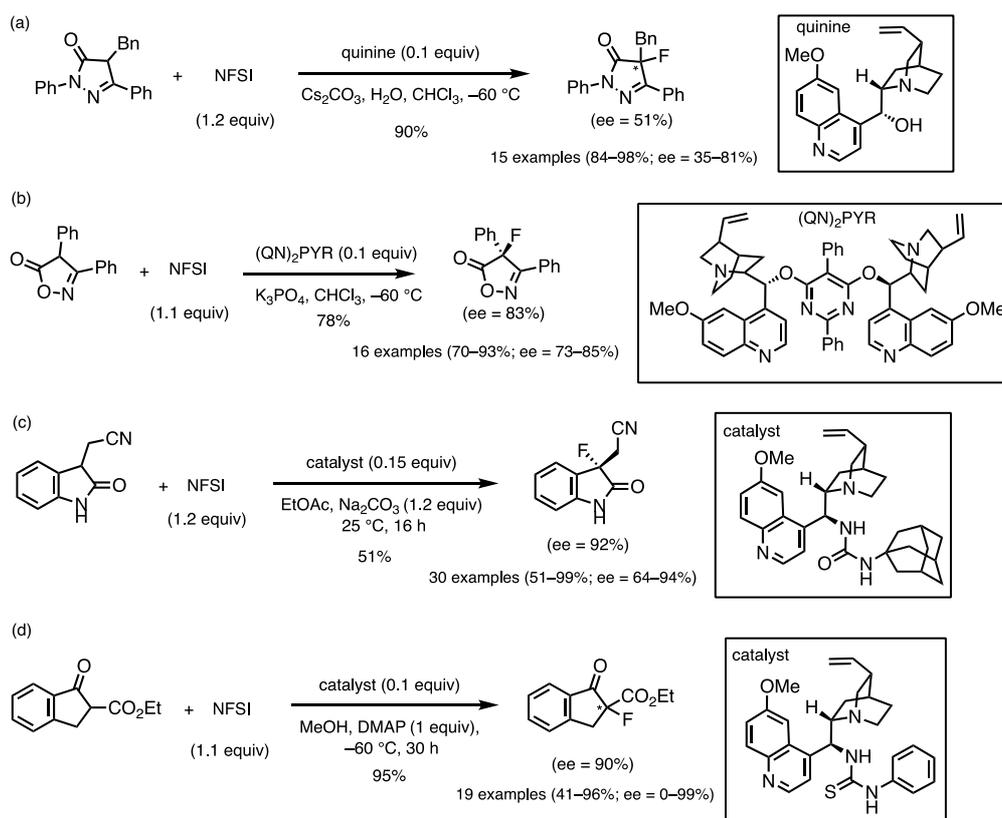
Well-established silylated α,α -diaryl prolinol derivatives were found to be efficient enamine organocatalysts in the fluorination of *N*-Boc-pyrrolidine-3-carboxaldehyde disubstituted at C4 including spirocyclic substituents. A series of eight fluorinated spirocyclic pyrrolidine carbaldehydes were synthesized in high yields and enantioselectivities (Scheme 5a).¹⁰ With the aid of same or antipode of silylated α,α -diaryl prolinol derivative, an enantioselective catalytic approach for the synthesis of *gem*-chlorofluoro compounds was developed from chlorinated aldehydes using NFSI as the source of fluorine. Noteworthy, a cascade one-pot procedure starting from non-halogenated aldehydes allowed to introduce a chlorine and a fluorine atom successively in good yields with high enantioselectivities. In this approach the first created stereogenic center featuring the chlorine is destroyed during the fluorination step and the geometry of the sp² intermediate species impacts the enantiomeric excess of the final dihalogeno product (Scheme 5b).¹¹



Scheme 5 Enantioselective fluorination of aldehydes by prolinol-derived enamine catalysis

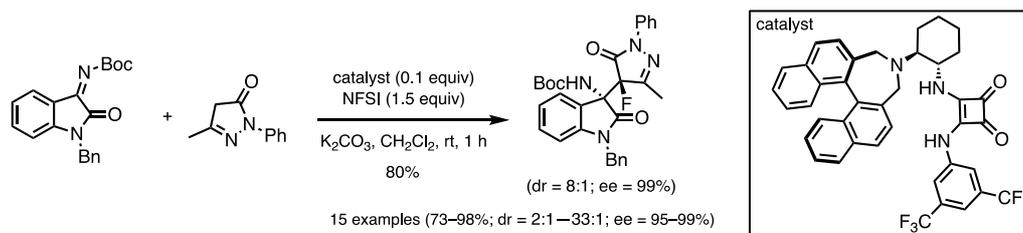
Cinchona alkaloids are privileged catalysts in a wide range of transformations that include electrophilic fluorinations. Native alkaloids, bis-alkaloids, urea- and thiourea-modified alkaloids have been evaluated in the fluorination of various substrate types. A simple process was developed for the asymmetric construction of 4-fluoro-4-substituted pyrazolones using natural quinine as catalyst in good to high yields with moderate to good enantioselectivities (Scheme 6a).¹² Note that in this reaction the bis-cinchona alkaloid catalyst (QN)₂PYR gave poor enantioselectivity (ee = 8%). In contrast, (QN)₂PYR revealed to

be the most powerful catalyst in the asymmetric fluorination of 4-substituted isoxazolinones (Scheme 6b).¹³ Electron-rich urea attached to cinchona catalysts were able to achieve the asymmetric fluorination of 3-functionalized oxindoles with NFSI as the fluorination reagent. Various 3-fluoro-3-substituted-2-oxindoles have been obtained with good yields and good enantioselectivities (Scheme 6c).¹⁴ A mechanism was speculated involving the generation of a $[N-F]^+$ chiral reagent (see 7.9.2.1), but no clear evidence was provided. As an alternative, bifunctional chiral thiourea organocatalysts were successfully engaged in the enantioselective fluorination of mainly cyclic β -keto esters using NFSI as fluorine source. The fluorinated products were obtained in high yields with moderate to good enantioselectivities. The few tested acyclic β -keto esters gave a same level of results. (Scheme 6d).¹⁵



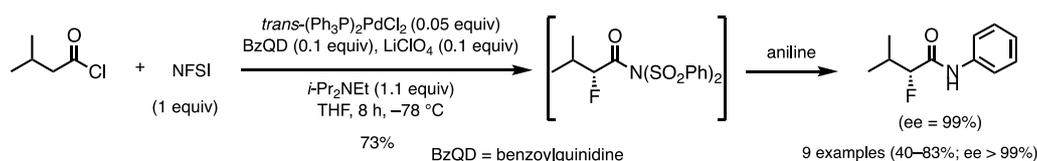
Scheme 6 Catalytic asymmetric fluorinations by means of cinchona alkaloids and derivatives

A different approach toward 4-fluoro-4-substituted pyrazolones that are highly functionalized was carried out through an enantioselective organocatalytic Mannich reaction / electrophilic fluorination sequence. In this sequence, 1-phenyl-1*H*-pyrazol-5(4*H*)-ones reacted with ketimine derivatives derived from isatins and NFSI under catalysis by squaramide catalysts featuring a binaphthyl tertiary amine and a diaminocyclohexane subunit. This reaction provides convenient access to chiral 3-amino-3-(4-fluoropyrazol-4-yl)-substituted oxindole derivatives in high yields with moderate to excellent dia- and enantioselectivities (Scheme 7).¹⁶



Scheme 7 Organocatalytic Mannich / fluorination sequence on pyrazolones

To complete this subsection on organocatalytic fluorinations, the approach developed by Lectka's group is described. The source of chirality is indeed a cinchona alkaloid organocatalyst but the fluorination requires an additional transition-metal catalyst in a dual activation of the intermediate enolate. The asymmetric fluorination of sensitive carbonyl substrates such as acid chlorides has been achieved in a three-component catalysis in which the three catalysts work cooperatively: a chiral nucleophile (benzoylquinidine) and a transition-metal catalyst (a Pd complex) to generate and to dually activate the enolate, plus an alkali metal Lewis acid (Li salt) to activate the fluorinating agent NFSI. This original strategy gives moderate to good yields and almost perfect enantioselectivity (Scheme 8).¹⁷



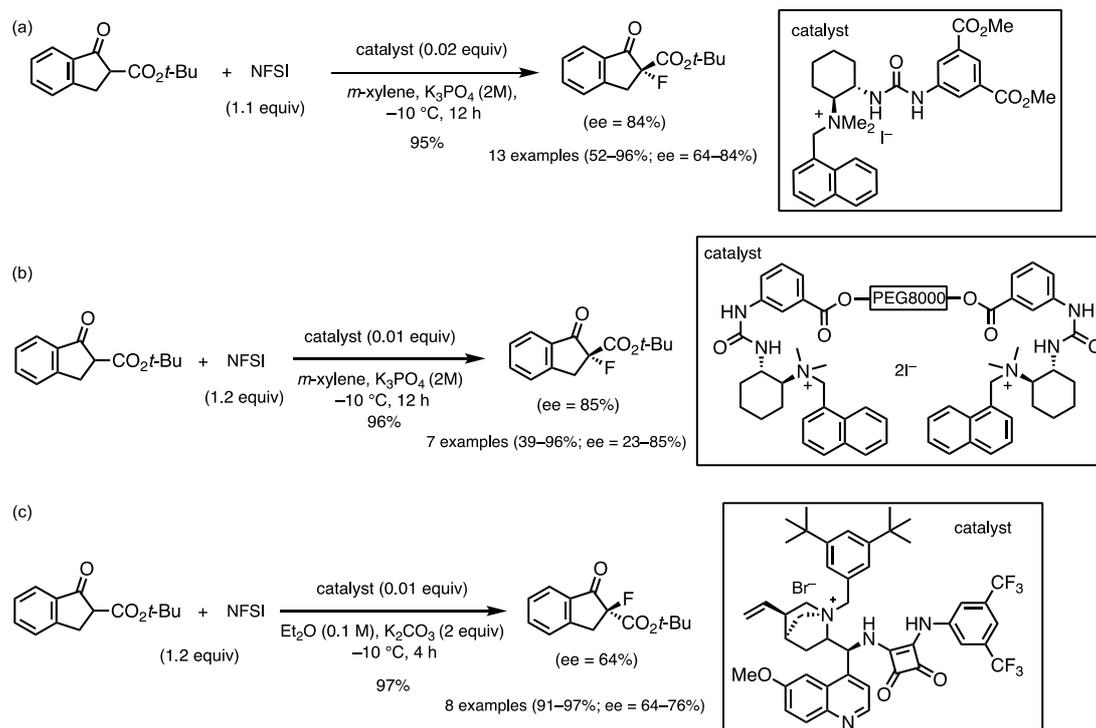
Scheme 8 Catalytic enantioselective α -fluorination of acid chlorides

7.9.2.3 Chiral Phase-Transfer Catalysis

7.9.2.3.1 with Chiral Cations

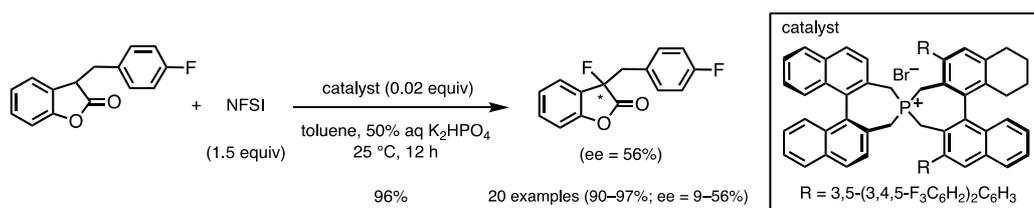
In asymmetric phase-transfer catalysis, chiral ammonium and chiral phosphonium cations dominate the field. This strategy has emerged for the electrophilic fluorination of nucleophilic substrates. Several bifunctional (thio)urea-containing quaternary ammonium salts having a chiral diaminocyclohexane backbone were engaged in the enantioselective fluorination of β -keto esters. In particular, the urea derivatives afforded α -fluoro- β -keto esters in high yield and enantioselectivities (Scheme 9a).¹⁸ The ammonium motif was proposed to activate and position the enolate while the urea moiety is supposed to coordinate and activate the NFSI within a highly ordered transition state. The reaction was exemplified only with cyclic β -keto esters. A PEG-bound urea-containing ammonium salt was designed to ease recovery and for multiple reuses. It shown similar level of efficiency compared to the free catalyst (Scheme 9b).¹⁹ One acyclic β -keto ester reacted but in a 39% yield and with 23% ee. In the aim to find even more efficient catalysts, a new class of chiral phase-transfer catalysts containing a squaramide motif attached to a cinchona alkaloid being quaternarized at the quinuclidine nitrogen was applied to the asymmetric fluorination of β -keto esters with NFSI. High yields and moderate to good enantioselectivities were obtained albeit only cyclic β -keto esters were used as substrates. In this transformation, it was

demonstrated that both the quaternary ammonium center and the squaramide moiety were of crucial importance (Scheme 9c).²⁰



Scheme 9 Phase-transfer catalyzed fluorination of β -keto esters with chiral ammonium salts

The exploitation of chiral phosphonium salts as catalyst has been reported once in asymmetric electrophilic fluorination of 3-substituted benzofuran-2(3*H*)-ones under phase-transfer catalysis to give the fluorinated products in excellent yields yet with low to moderate enantioselectivities up to 56% ee (Scheme 10).²¹

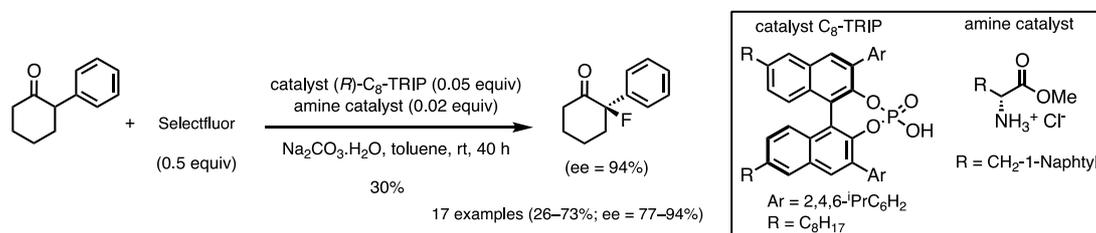


Scheme 10 Asymmetric electrophilic fluorination of 3-substituted benzofuran-2(3*H*)-ones

7.9.2.3.2 with Chiral Anions

Chiral anion phase-transfer catalysis, introduced by the Toste group, exploited chiral lipophilic BINOL-derived phosphates to transport dicationic electrophilic Selectfluor from the solid phase to the organic phase. The phase-transfer protocol was coupled with an enamine activation cycle for the α -fluorination of α -branched cyclohexanones. The two catalytic cycles operate in concert to deliver α -fluoro ketones successfully. The enantioselectivity of the reaction was strongly influenced by the nature of the amine; matched and mismatched effects based on the chirality of amine–phosphoric acid pair were observed (Scheme 11).²²

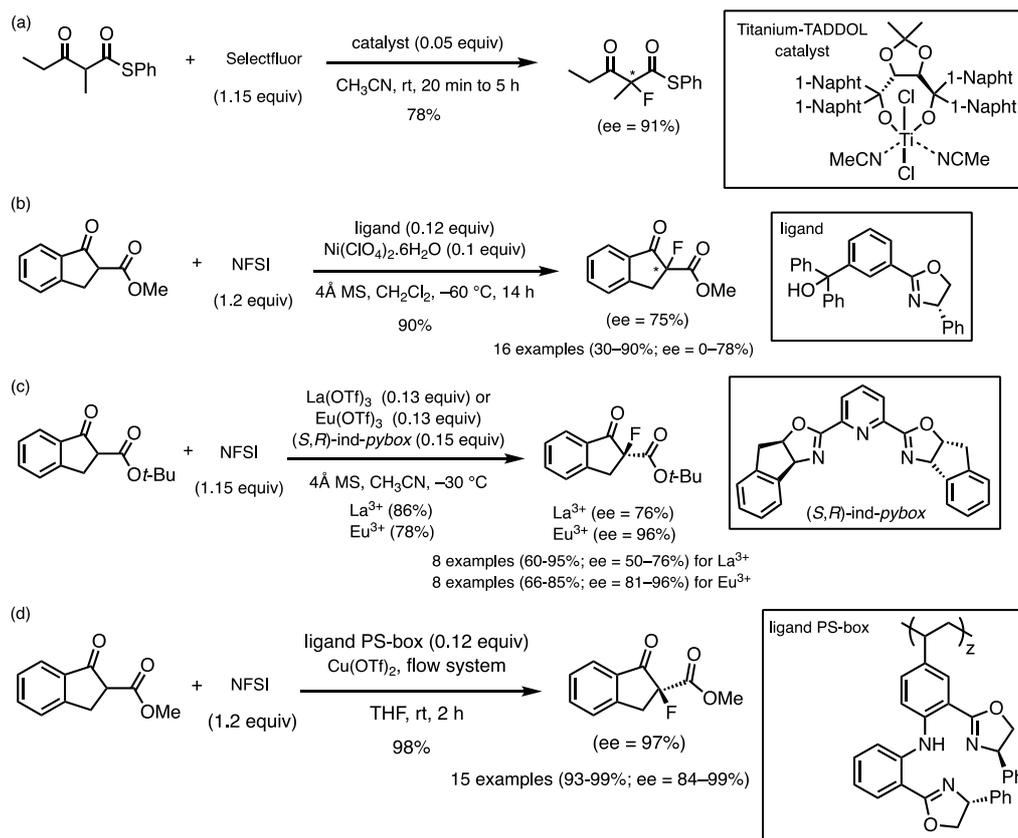
The scope was initially limited to 2-aryl cyclohexanones; however, fluorination was extended to 2-alkenyl and 2-alkynyl cyclohexanones with similar efficiency but 2-alkylcyclohexanones failed to react. The concept of chiral anion phase-transfer catalysis was expanded to the fluorination of enamides, allylic alcohols and to the fluorocyclization of olefins (see Volume 5).



Scheme 11 Asymmetric fluorination of α -branched cyclohexanones

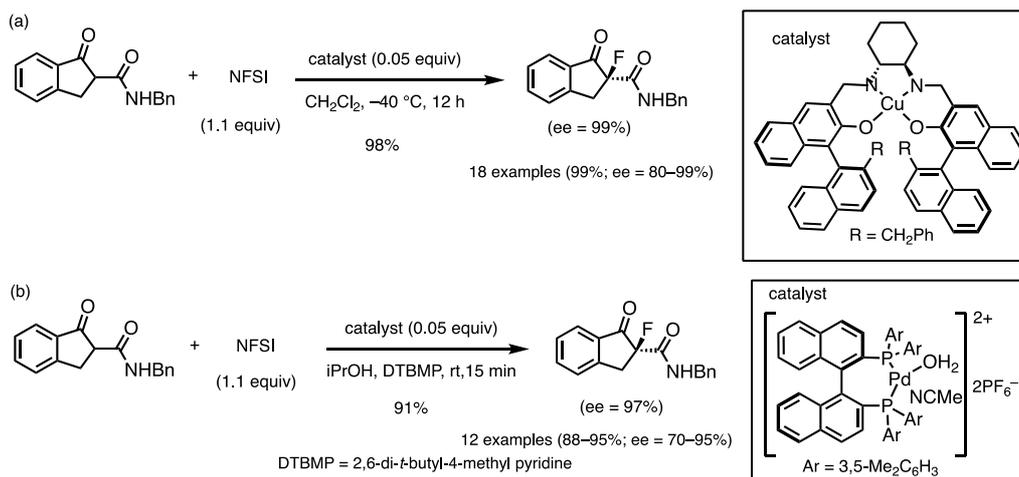
7.9.2.4 Transition-metal Catalysis

The asymmetric fluorination has been widely studied via transition-metal mediated catalytic enantioselective processes. Several works on C–F bond formation with concomitant generation of a stereogenic carbon center have been focused on activated β -carbonyl compounds. In continuation of the pioneering work by Togni and co-workers, the titanium-TADDOLate catalyzed fluorination was performed on a wide scope of cyclic and acyclic β -carbonyl compounds in order to delineate the potential of the method. In a complete study, over 60 substrates were tested that include β -keto esters, β -keto thioesters, β -keto amides, α -acyl lactones, and 1,3-diketones in the Selectfluor mediated fluorination in the presence of 5 mol% of TiCl₂(naphthalen-1-yl)-TADDOLate as catalyst. See one example in Scheme 12a.²³ Others studies were conducted essentially on 1-indanone- and 1-tetralone-2-carboxylates as substrates. Mono-oxazoline ligands combined with Ni(ClO₄)₂·H₂O gave good results only for a narrow substrate scope; indeed, tetralone derivatives, acyclic β -keto esters as well as *t*-Bu ester derivatives gave very low enantioselectivities (Scheme 12b).²⁴ Chiral pybox-type C₂-symmetric ligands with lanthanide triflates (La, Eu) and using NFSI gave moderate to good results albeit only indanone carboxylates were presented (Scheme 12c).²⁵ The Box ligands could also be supported on polystyrene in batch and in flow systems but again the scope was limited to indanone carboxylates (Scheme 12d).²⁶

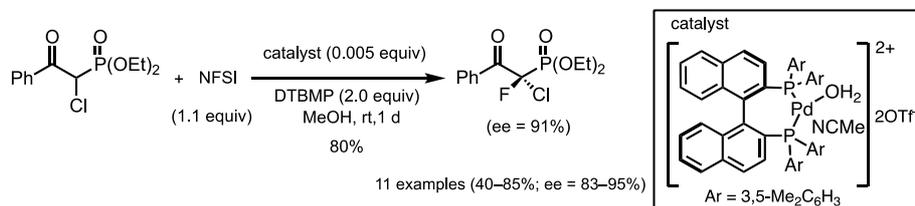


Scheme 12 Metal-catalyzed enantioselective fluorination of β -keto (thio)esters

The case of β -keto amides has received particular attention in electrophilic fluorination. These substrates were specifically studied in the presence of Ar-BINMOL-derived salan–Copper (II) system and NFSI (scheme 13a).²⁷ This catalytic system exhibited high enantioselectivities for indanone-derived β -keto amides. A non-benzo-fused cyclopentanone derivative as well as a single tetralone-derived β -keto amide were tested leading to 80% and 89% ee values, respectively, and in quantitative yields. Good reactivity and excellent enantioselectivities were also obtained in fluorinations mediated by a chiral palladium-based dicationic complex derived from BINAP (Scheme 13b).²⁸ The same type of catalyst was further employed in the enantioselective electrophilic fluorination of α -chloro- β -keto phosphonates at a lower catalytic loading (0.5 mol%) with excellent enantioselectivities (Scheme 14).²⁹

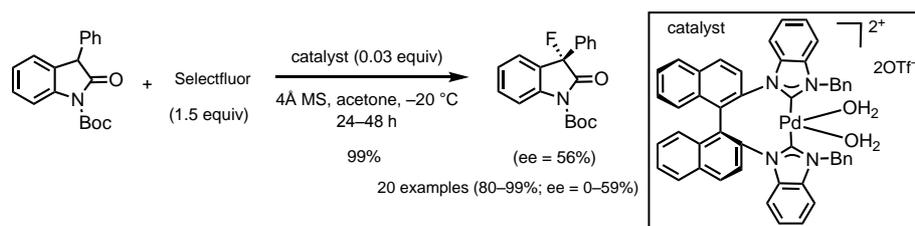


Scheme 13 Metal-catalyzed enantioselective fluorination of β -keto amides



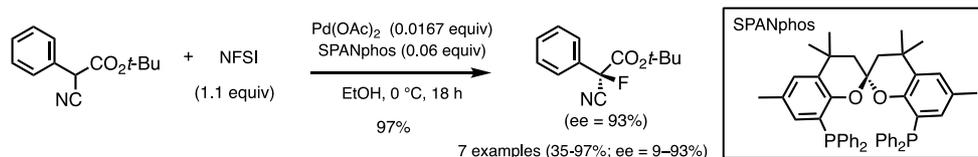
Scheme 14 Palladium-catalyzed enantioselective fluorination of α -chloro- β -keto phosphonates

When the amide function is inserted in the substrate as in oxindoles, chiral C_2 symmetrical *N*-heterocyclic carbene (NHC) palladium diaquo complexes and Selectfluor were found to allow the enantioselective fluorination of oxindoles in high yields and with moderate enantioselectivities (Scheme 15).³⁰



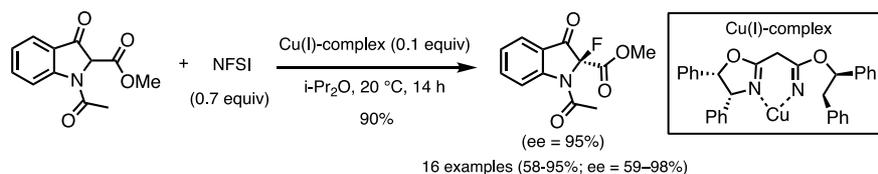
Scheme 15 Fluorination of oxindoles by Selectfluor and a bis-NHC ligated Pd(II) complex

Using α -cyano esters as activated substrates in the asymmetric fluorination was quite successful when palladium acetate / SPANphos was employed as catalyst and NFSI as F^+ donor. Depending on the nature of the substituent on the aryl moiety of the cyano ester, very different levels of enantioselectivities were measured from 9 to 93% ee (Scheme 16).³¹ Only α -aryl- α -cyano esters were considered in this study.



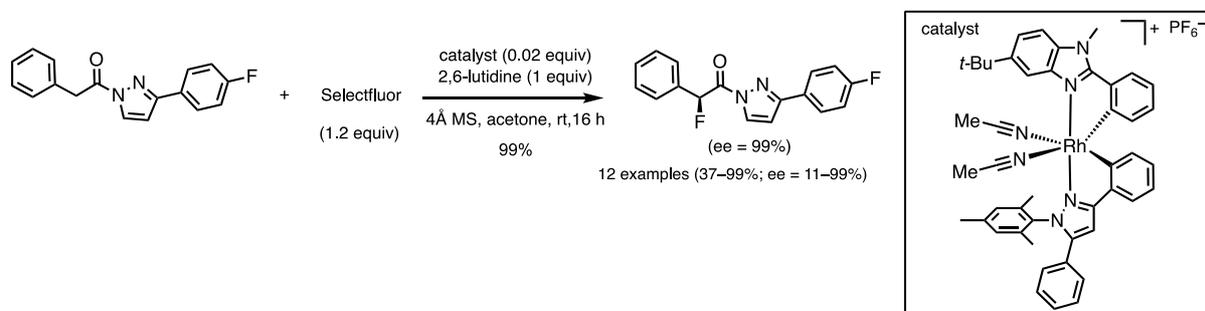
Scheme 16 SPANphos ligands in palladium-catalyzed asymmetric fluorination of α -cyano esters

Among the less encountered substrate types in electrophilic fluorination, one can note 3-indolinone-2-carboxylates for which high degree of enantioselectivity was observed using a catalytic amount of a chiral copper (I) bis-oxazoline complex and NFSI (Scheme 17).³²



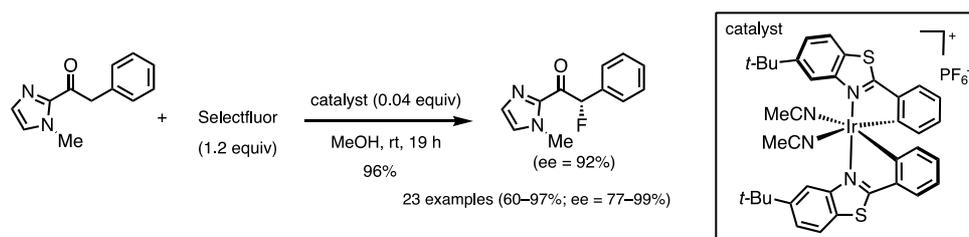
Scheme 17 Enantioselective fluorination of 3-indolinone-2-carboxylates

N-Acyl pyrazoles featuring a α -aryl residue are less acidic carboxylic acid derivatives compared to the previously mentioned substrates but still could be engaged in enantioselective fluorinations. Selectfluor in the presence of a non- C_2 -symmetrical chiral-rhodium catalyst provided the fluorinated product in high ee values (Scheme 18).³³ The catalytic performance of the non- C_2 -symmetrical rhodium catalysts revealed to be superior to the related C_2 -symmetrical rhodium catalysts.



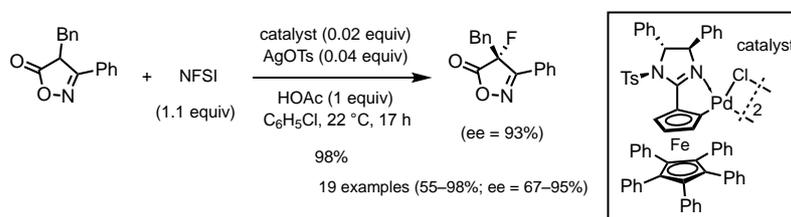
Scheme 18 Enantioselective fluorination of *N*-acyl pyrazoles

In the same vein, 2-acyl imidazoles were fluorinated enantioselectively with the aid of a chiral iridium catalyst and Selectfluor enabling smooth access to fluorinated 2-acyl imidazoles (Scheme 19).³⁴



Scheme 19 Iridium complex-catalyzed α -fluorination of 2-acyl imidazoles

In order to synthesize chiral fluorinated amino acid derivatives possessing a tetrasubstituted fluorinated stereocenter, an asymmetric fluorination of isoxazolinones was developed for the enantioselective creation of the C–F bond. This transformation was achieved via a catalytic process involving a planar chiral ferrocene bis-palladacycle that provided high enantioselectivities (Scheme 20).³⁵ The fluorinated isoxazolinones are useful precursors of enantiopure β -amino acid derivatives and 3-fluorinated azetidines.



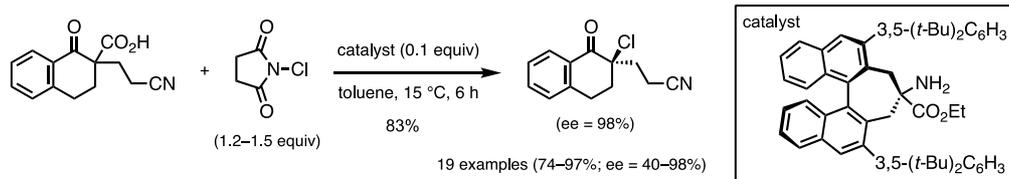
Scheme 20 Asymmetric fluorination of isoxazolinones

7.9.3 Enantioselective Electrophilic Chlorination

Less developed than the fluorination, the electrophilic enantioselective chlorination is nevertheless an important topic because of the potential applications of the chiral chlorinated molecules as intermediates for the synthesis of natural products and new pharmaceuticals. The field has benefited from catalysts and methods that are successfully used in fluorination reactions. No new chiral non racemic chlorinating agent was developed since 2007.

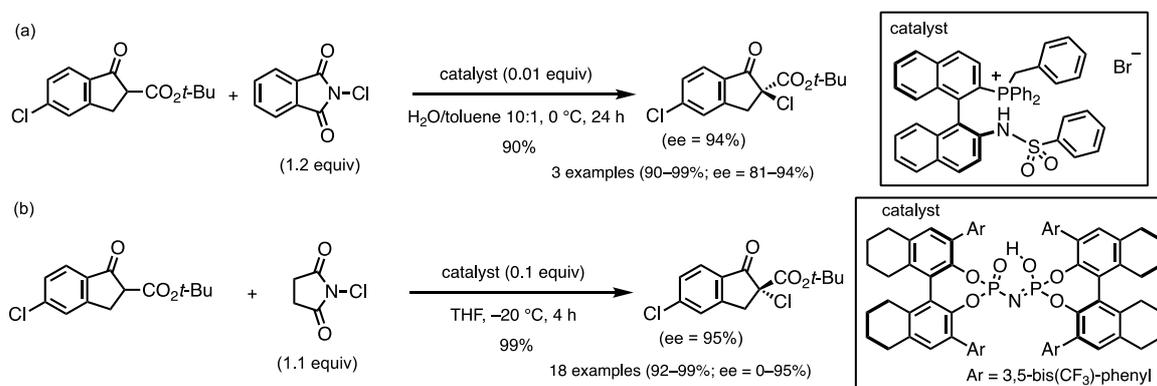
7.9.3.1 Organocatalytic Chlorination

Halogenation of monocarbonyl compounds requires activation at the α -position, which was realized through the decarboxylation of β -keto carboxylic acids. In this approach, the enantioselective decarboxylative chlorination is mediated by a chiral ion-pair organocatalyst made with a 1,1'-binaphthyl-based chiral amino ester and the generated enolate to afford tertiary and secondary chlorides with excellent ee values (Scheme 21).³⁶



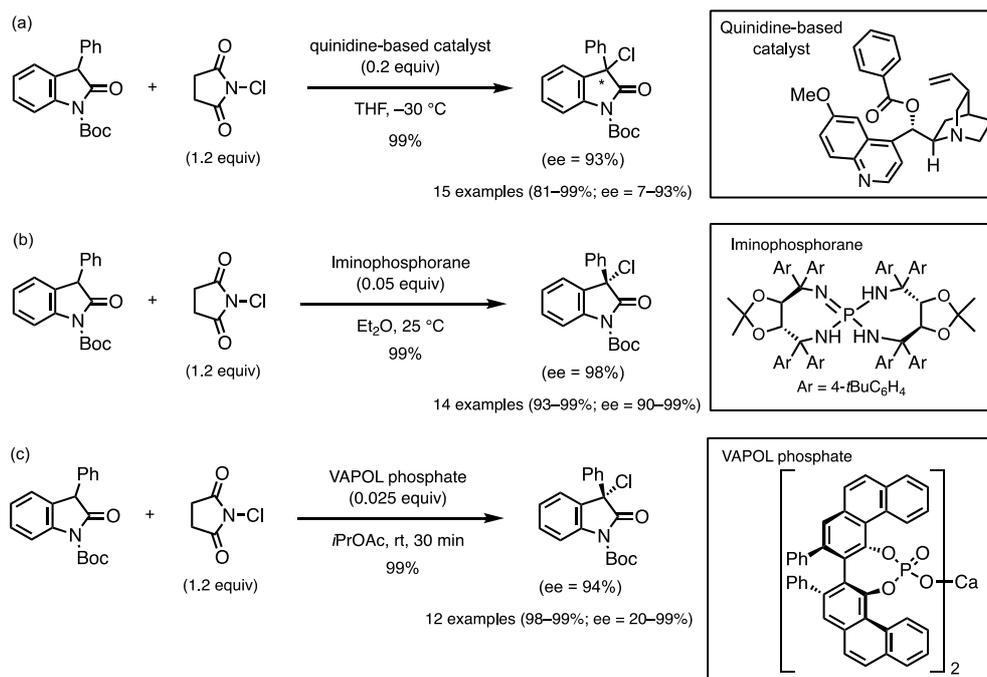
Scheme 21 Decarboxylative enantioselective chlorination of β -keto carboxylic acids

More frequently encountered are the β -keto esters and the oxindoles as substrates for the chlorination. For example, the chlorination of β -keto esters derived from indanone under base-free phase-transfer catalysis by means of quaternary phosphonium bromides featuring a benzenesulfonamide moiety was highly efficient (for use of similar catalysts in sulfenylation see section 7.9.6.1.1) (Scheme 22a).³⁷ Chiral imidophosphoric acids could also be employed as efficient catalysts for the chlorination of cyclic β -keto esters and β -keto amides derived from indanones (Scheme 22b).³⁸ Note that a single case of tetralone derivative gave 0% ee.



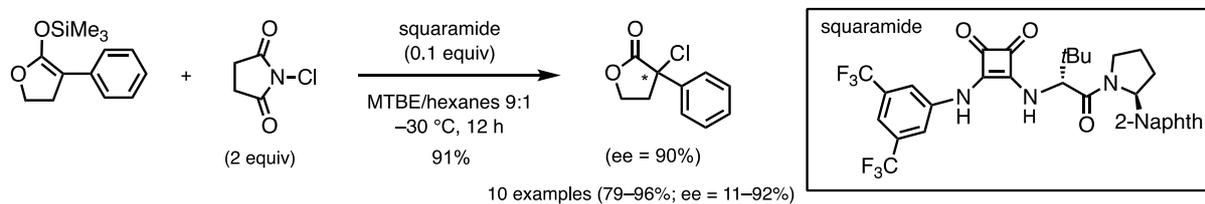
Scheme 22 Organocatalyzed enantioselective chlorination of β -keto esters

A variety of effective organocatalysts were employed for the enantioselective chlorination of 3-substituted oxindoles, mainly 3-aryl- but also a few cases of 3-alkyl oxindoles. After a systematic screening of the chlorine source, it appeared that *N*-chlorosuccinimide (NCS) was the most appropriate donor. With regard to the catalysts, *O*-benzoylquinidine (Scheme 23a),³⁹ chiral iminophosphoranes (Scheme 23b)⁴⁰ and chiral calcium VAPOL phosphates (Scheme 23c)⁴¹ all delivered high levels of enantioselectivity. The chiral iminophosphoranes performed well on 3-Me- and 3-Bn-oxindoles (90% ees) and were easily recycled. Other *N*-protecting group than Boc led to lower ee values.



Scheme 23 Organocatalyzed enantioselective chlorination of oxindoles

In addition, one example of chlorination of silyl ketene acetals with the aid of chiral arylpyrrolidino squaramide catalysts and NCS was reported to afford tertiary α -chloro esters with decent ee values (Scheme 24).⁴²

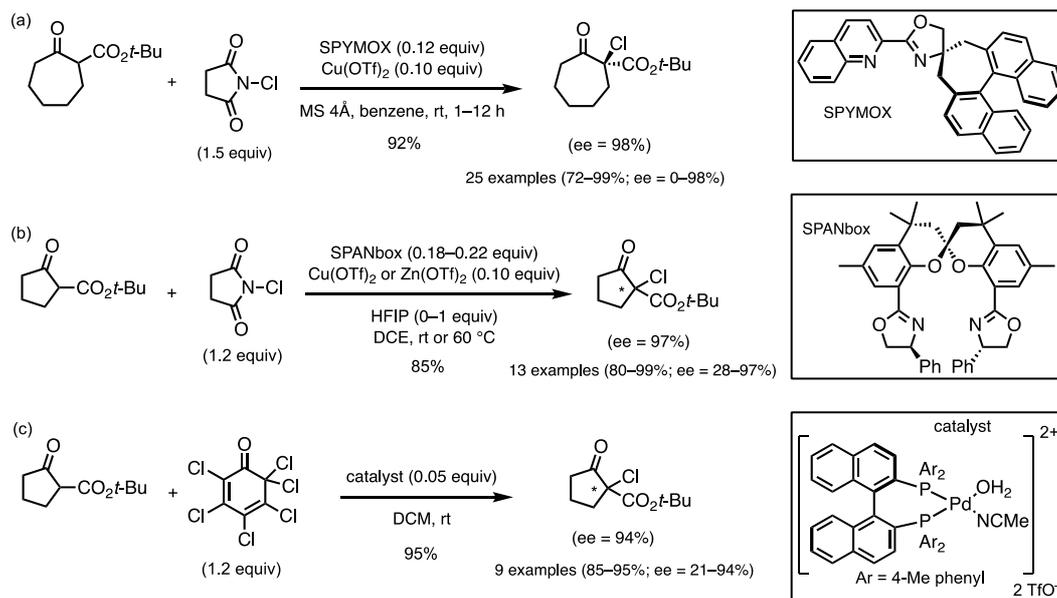


Scheme 24 Organocatalyzed enantioselective chlorination of silyl ketene acetals

7.9.3.2 Transition-metal Catalysis

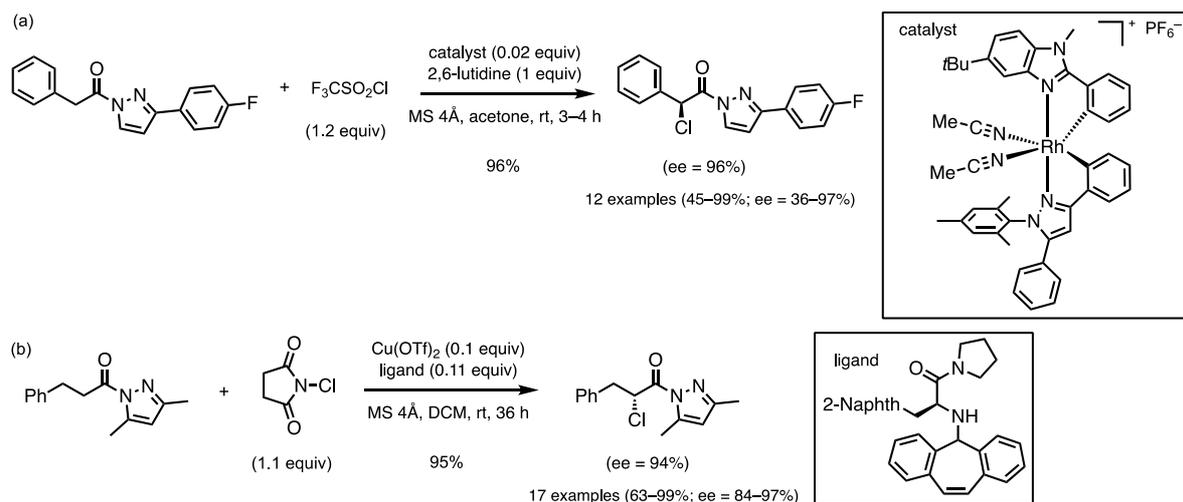
The concomitant formation of a C–Cl bond and stereoselective generation of a new stereogenic carbon center have also received attention through the use of chiral organometallic catalysts in the presence of diverse sources of electrophilic chlorine. Acyclic and cyclic β -keto esters were chlorinated highly enantioselectively with NCS using chiral Lewis acid catalysts composed of Cu(OTf)₂ and spirooxazoline ligands (SPYMOX) (Scheme 25a).⁴³ Some limitations appeared for the chlorination of α -cyano acetates (0% ee) while β -keto phosphonates gave 18–37% ee values. For cyclic β -keto esters only, the spiro-2,2'-bichroman-based chiral bisoxazoline ligands (SPANbox) combined with either Cu(OTf)₂ or Zn(OTf)₂ gave moderate to high enantioselectivities (Scheme 25b).⁴⁴ Alternatively, the electrophilic chlorination was conducted in the presence of a dicationic palladium BINAP-based complex in up to 94% ee (Scheme 25c).⁴⁵ In this latter case, the hexachlorocyclohex-

2,4-dienone was employed as chlorine source and a single example of acyclic β -keto ester led to a poor 21% ee.



Scheme 25 Metal-catalyzed enantioselective chlorination of β -keto esters

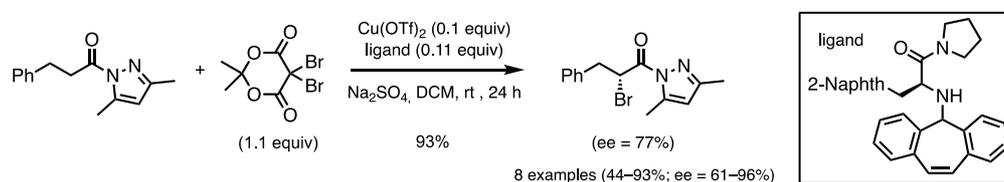
Apart from β -keto esters, two reports were dedicated to the metal-catalyzed chlorination of *N*-acyl pyrazoles. These less acidic carboxylic acid derivatives, compared to the above mentioned substrates, were engaged in the enantioselective chlorination using trifluoromethanesulfonyl chloride as chlorine source and a non- C_2 -symmetrical chiral-at-rhodium catalyst (Scheme 26a).³³ This piece of work followed the α -fluorination reported in section 7.9.2.4. *N*-acyl pyrazoles featuring a α -(het)aryl residue provided the chlorinated products in high ee values while the α -propyl substrates could not be converted. A *N*-acyl pyrazole with a α -ester function was also evaluated but both the yield and the enantioselectivity were moderate. For the purpose of expanding the substrate scope, a novel π -Cu(II)- π complex made of Cu(OTf)₂ and 3-(2-naphthyl)-L-alanine-derived amide was designed to catalyze the enantioselective α -chlorination of *N*-acyl-3,5-dimethylpyrazoles (Scheme 26b).⁴⁶ With such a complex, the enolate was generated without an external base and reacted with NCS, which was preferred to the corrosive trifluoromethanesulfonyl chloride. High enantioselectivities were recorded for both aryl and alkyl *N*-acyl pyrazoles. Extension to α -bromination was also reported (see section 7.9.4).



Scheme 26 Metal-catalyzed enantioselective chlorination of *N*-acyl pyrazoles

7.9.4 Enantioselective Electrophilic Bromination

α -Bromination of aldehydes under covalent organocatalysis (see Volumes 1 and 2) and the bromoaminocyclization of alkenes (see Volume 5) are rare cases of asymmetric electrophilic bromination. Related to this section, a single case of copper-catalyzed α -bromination of *N*-acyl-3,5-dimethylpyrazoles was reported (Scheme 27).⁴⁶ The bromination by means of Meldrum's 5,5-dibromo acid was as efficient as the chlorination (see Scheme 26b).



Scheme 27 Metal-catalyzed enantioselective bromination of *N*-acyl pyrazoles

7.9.5 Enantioselective Electrophilic Sulfonylation

Chiral sulfur-containing compounds obtained by direct C–S bond formation with concomitant creation of a stereogenic carbon center have grown significantly over the past decade in particular with the blossoming of enantioselective electrophilic trifluoromethylthiolation. Indeed, the direct introduction of the SCF₃ motif is widely represented compared to the sulfonylation by non-fluorinated sulfonyl groups and also to the thiocyanation. Optically pure electrophilic SCF₃ and SCF₂H donors have been designed and demonstrated high levels of enantioinduction. Otherwise, no new chiral sulfonylating agent (SR with R \neq Rf) appears since the first edition of *Comprehensive Chirality*. Various approaches using organocatalysts were developed while a single transition-metal catalyzed sulfonylation was reported. Note that several asymmetric sulfonylations of alkenes have

been reported as first step in cascade reactions involving a subsequent intramolecular cyclization through C–O or C–N bond formation; these reactions are detailed in Volume 5.

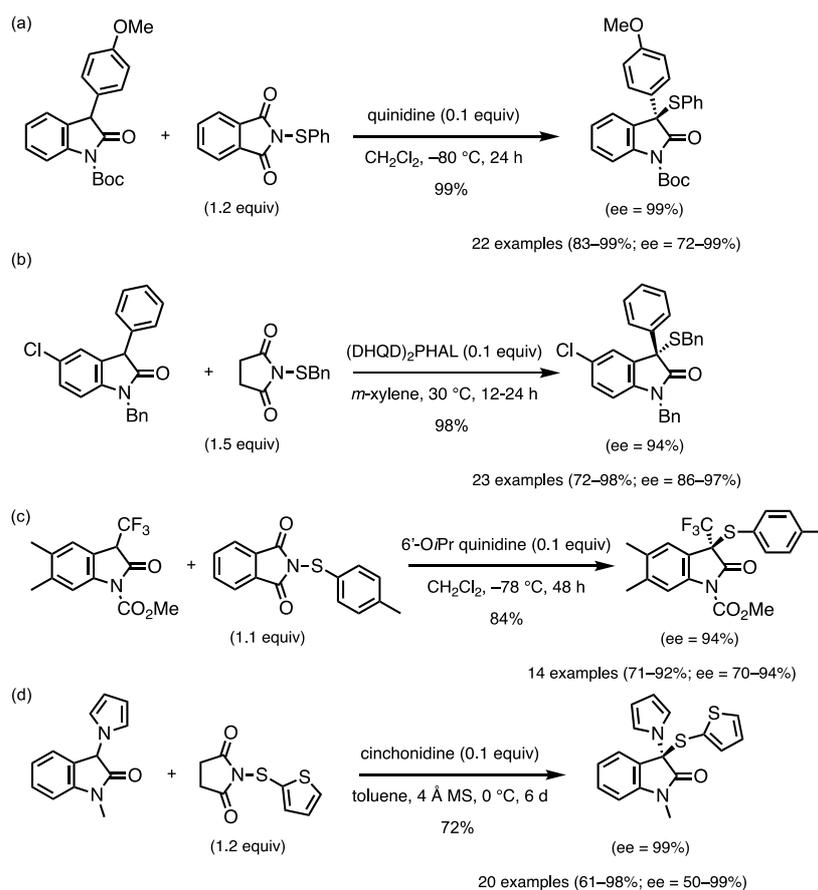
7.9.5.1 Sulfenylation (SAr, SAlk)

In the past decade, the transition-metal-free sulfenylation was preferentially investigated to the detriment of the organometallic approach. One reason for this is that sulfur-containing reagents could combine with the metal in undesired interactions. Consequently, organocatalytic enantioselective sulfenylation reactions largely dominate.

7.9.5.1.1 Organocatalytic Sulfenylation

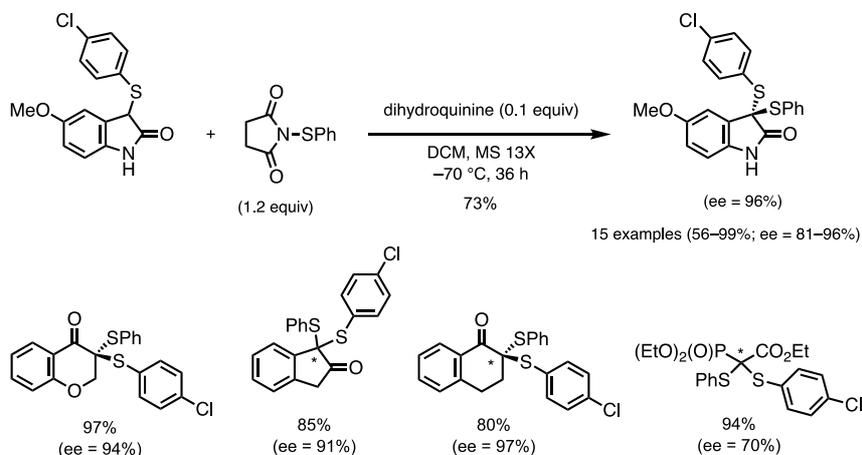
In this section, we describe the noncovalent organocatalysis with a wide variety of organocatalysts including phase-transfer catalysts. The covalent organocatalysis with chiral amines is mentioned in Volumes 1 and 2.^{47, 48} Substrate types are multiple as are the sulfur sources. The enantioselective sulfenylations presented hereafter are classified by type of organocatalysts: cinchona alkaloid derivatives, guanidines, iminophosphoranes, and phase-transfer catalysts.

A variety of cinchona alkaloid-based catalysts were investigated in the sulfenylation of 3-substituted oxindoles as the most frequently encountered substrate type. Indeed, oxindoles featuring a quaternary carbon center at C3 are important pharmaceutically active molecules that justify the enantioselective synthesis of sulfur-containing derivatives. The sulfenylation of *N*-Boc 3-substituted oxindoles with *N*-(phenylthio)phthalimide catalyzed by quinidine offered excellent yields and enantioselectivities for 3-aryl substrates and to a lesser extent for 3-alkyl substrates (Scheme 28a).⁴⁹ Other *N*-substituents (Me, Ph, Bn, H) led to ee values below 39%. Other examined cinchona alkaloids that included bis-cinchona derivatives demonstrated high catalytic activities but significantly lower enantioselectivities. Concurrently, it was found that combining bis-cinchona alkaloid (DHQD)₂PHAL with *N*-(sulfanyl)succinimides (SBn, SAr, SAlk) allowed the high enantioselective sulfenylation of *N*-benzyl 3-aryl oxindoles in 86–95% ee at 30 °C (Scheme 28b).⁵⁰ Switching from (DHQD)₂PHAL to its pseudo-enantiomeric (DHQ)₂PHAL allowed to access the two antipodes of the sulfenylated products. Variations at C3 were undertaken using 3-CF₃ oxindoles (Scheme 28c)⁵¹ and 3-pyrrolyl oxindoles (Scheme 28d)⁵², which in the presence of 6'-*O*iPr quinidine or cinchonidine, respectively, were successfully sulfenylated. However, some limitations appeared with 3-CF₃ oxindoles bearing electron-withdrawing groups on the benzo-fused ring that reacted poorly under the otherwise optimized conditions.



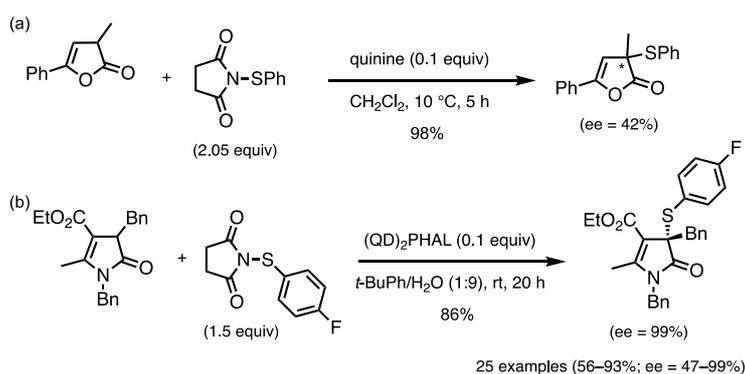
Scheme 28 Organocatalyzed enantioselective sulfenylation of 3-substituted oxindoles

Dithioketals chiral at the quaternary carbon featuring two different sulfur motifs were prepared with high enantioselectivity starting from α -thio oxindoles. The combination of dihydroquinine and N -SCF₃ succinimide required a long reaction time at -70 °C to provide good results (Scheme 29).⁵³ Other dithioketals derived from 2- and 3-benzofuranones, 1- and 2-indanones, tetralone, cyclopentanone and even from a phosphonoacetate were prepared using the same reaction conditions in high yields with good to high enantioselectivities (Scheme 29).



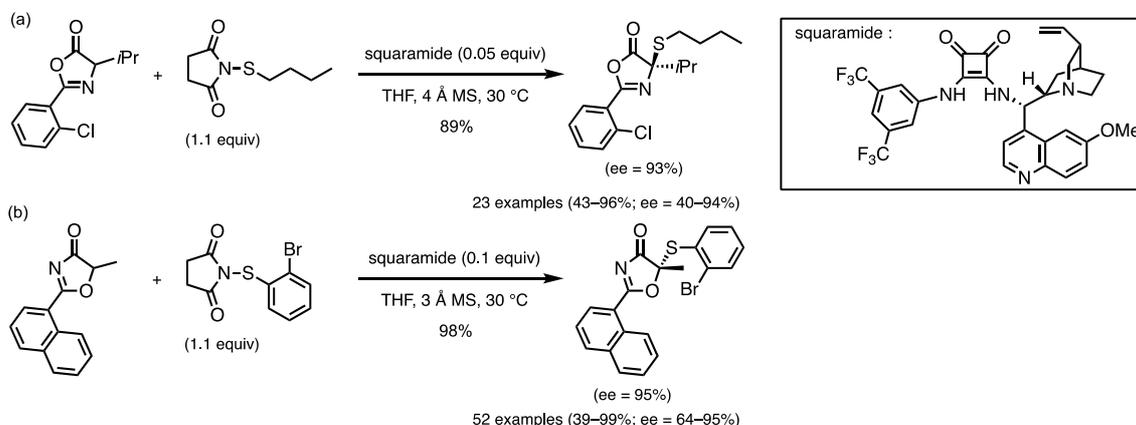
Scheme 29 Organocatalyzed enantioselective construction of dithioketals

Apart from oxindole substrates, one can note a single example of sulfenylation of a butenolide albeit with a low enantioselectivity in absence of optimization (Scheme 30a).⁵⁴ Conversely, a thorough investigation of the sulfenylation of deconjugated butyrolactams afforded a wide range of highly decorated γ -lactams (Scheme 30b).⁵⁵ Various *N*-(sulfanyl)succinimides (SBn, SAr, SHetAr, SAlk) were engaged with the bis cinchona alkaloid (QD)₂PHAL as the most enantioselective catalyst in a solvent mixture consisting of *t*-butylbenzene and water. Water permitted a significant rate acceleration caused by a hydrophobic hydration effect. Under these conditions, moderate to high yields and enantioselectivities were recorded. Extension to α -selenylation was also reported (see section 7.9.6.1).



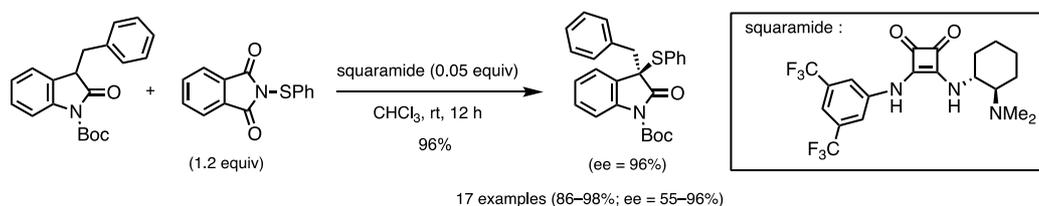
Scheme 30 Organocatalyzed enantioselective sulfenylation of a butenolide (a) and deconjugated butyrolactams (b)

In most of these works, catalyst structure-activity relationship studies were performed in order to identify the most efficient catalyst in a peculiar reaction. Off them are the cinchona-alkaloid-derived squaramides, capable of hydrogen-bonding activation mode, as demonstrated in the sulfenylation of azlactones by means of various *N*-(sulfanyl)succinimides (SBn, SAr, SAlk). The optically enriched sulfenylated products were obtained at 30 °C with 5 mol% of squaramide in up to 94% ee (Scheme 31a).⁵⁶ Further ring-opening allowed to access interesting α -sulfenyl α -amino acid derivatives. The same research group extended this sulfenylation method to 5*H*-oxazol-4-ones with equally high yields and enantioselectivities. Here again, several aryl-, benzyl- and alkylthio groups were transferred in the presence of cinchona-alkaloid-derived squaramides (Scheme 31b).⁵⁷



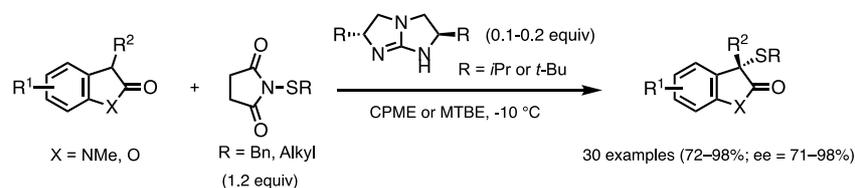
Scheme 31 Squaramide-catalyzed enantioselective sulfenylation of azlactones (a) and 5H-oxazol-4-ones (b)

To be complete with the squaramide family, one example was reported showcasing the superiority of a squaramide bearing a diaminocyclohexane subunit instead of a cinchona alkaloid. The sulfenylation of *N*-Boc oxindoles with *N*-thioaryl phthalimides was performed at rt in chloroform in the presence of 5 mol% of the bifunctional squaramide (Scheme 32).⁵⁸



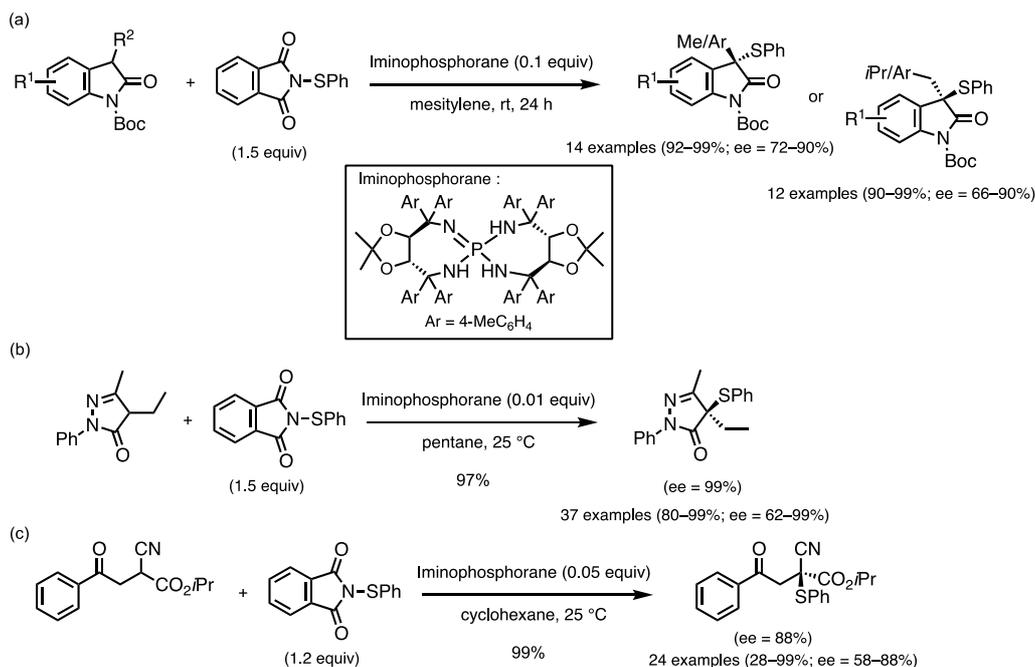
Scheme 32 Squaramide-catalyzed enantioselective sulfenylation of *N*-Boc oxindoles

Chiral C_2 -symmetric bicyclic guanidines exhibit high level of enantioselectivity in a wide range of reactions including the sulfenylation of oxindoles and benzofuran-2(3*H*)-ones (Scheme 33).⁵⁹ A large series of 3-sulfenylated (SR = SBn, Salkyl) products were synthesized in high yields with enantioselectivities up to 98%. Five guanidines featuring different side chains were tested and the quantity of catalyst was adjusted depending on the type of substrate. In that respect, 20 mol% of *i*Pr guanidine was optimal for the sulfenylation of *N*-Me oxindoles whereas 10 mol% of *t*-Bu guanidine performed best with benzofuran-2(3*H*)-ones.



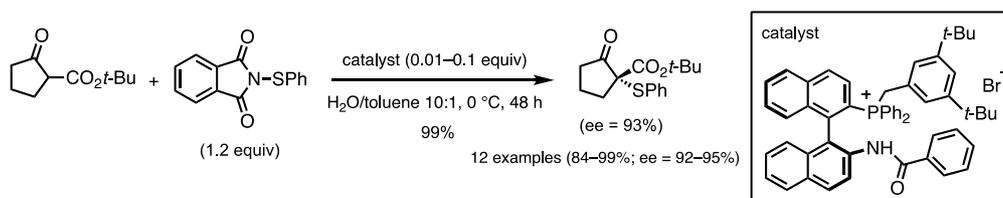
Scheme 33 Guanidine-catalyzed enantioselective sulfenylation of *N*-Me oxindoles and benzofuran-2(3*H*)-ones

Iminophosphoranes derived from tartaric acid, previously used in the asymmetric chlorination of oxindoles (see section 7.9.3.1), also catalyzed efficiently the sulfenylation of 3-substituted *N*-Boc oxindoles (Scheme 34a).⁶⁰ The most remarkable fact was to observe a reversal of the main enantiomer as the function of the nature of the 3-substituent. Indeed, 3-Ar and 3-Me substituted oxindoles delivered *S*-configured products while 3-Bn and 3-*i*Pr substituted oxindoles ended up with *R*-configured products. The same group also exploited these chiral iminophosphoranes for the sulfenylation of 4-substituted pyrazolones (4-alkyl and 4-benzyl) bearing C5-Me or C5-Ar substituents with excellent enantioselectivities (Scheme 34b).⁶¹ Finally, 2-substituted alkylcyanoacetates were also engaged in the sulfenylation reaction under similar reaction conditions to afford quaternary stereogenic centers in up to 88% ee (Scheme 34c).⁶²



Scheme 34 Iminophosphorane-catalyzed enantioselective sulfenylation of *N*-Boc oxindoles (a), 4-substituted pyrazolones (b) and 2-substituted alkylcyanoacetates (c)

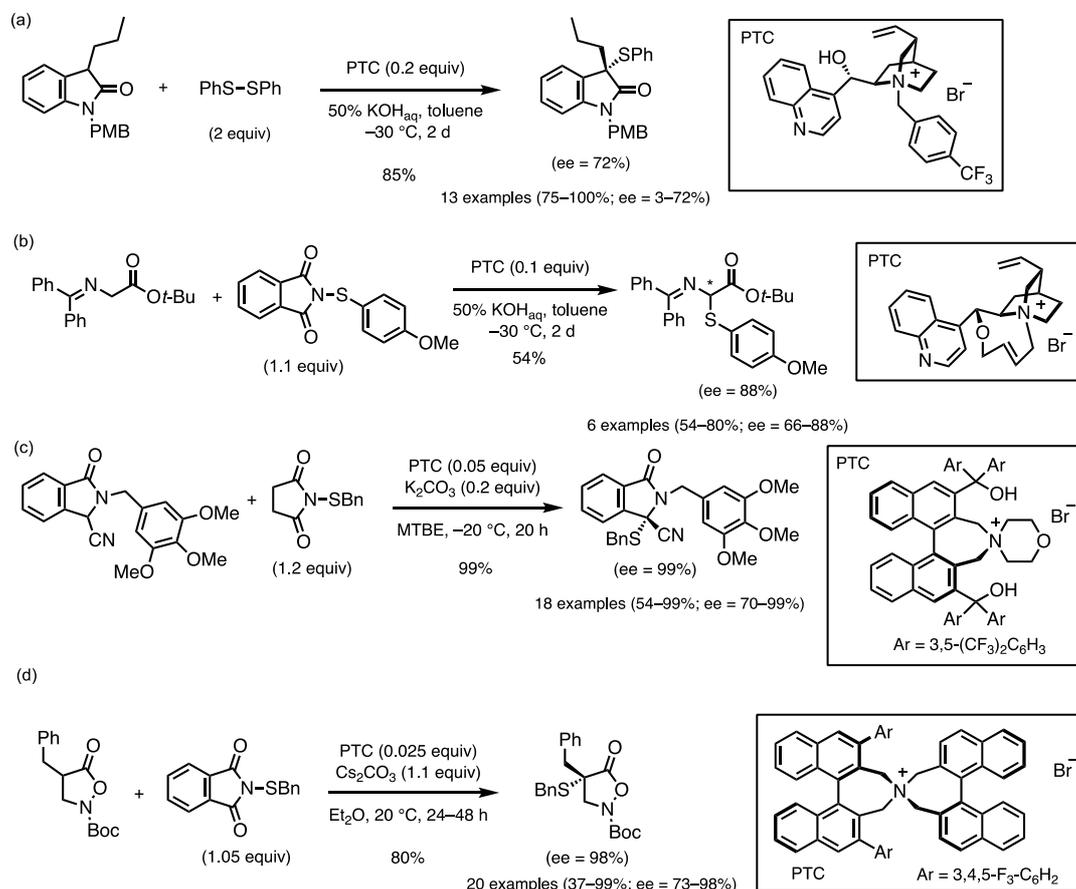
To conclude this section, we now turn to organocatalysis under phase-transfer conditions by means of quaternary phosphonium and ammonium salts. For the sulfenylation of β -keto esters derived from indanone and cyclopentanone, a series of axially chiral bifunctional quaternary phosphonium bromides were designed (for use of the same catalysts in chlorination see section 7.9.3.1). Tuning the amide moiety on the catalyst allowed to achieve high yields and enantioselectivities in the sulfenylation by means of *N*-(phenylthio)phthalimide under base-free conditions (Scheme 35).³⁷



Scheme 35 Phosphonium-catalyzed asymmetric sulfenylation of β -keto esters

Chiral ammonium salt ion pairing catalysts were more frequently used probably due to their easier access, in particular those derived from cinchona alkaloids. In the sulfenylation of 3-substituted-2-oxindoles, a cinchoninium bromide performed better than spirobinaphthyl ammonium or tartrate derived bis-ammonium salts. This example is a rare case employing diphenyl disulfide as sulfur source and the reaction was suggested to proceed through a radical mechanism (Scheme 36a).⁶³ A quirky cinchona ammonium with an eight-membered cycle was designed for the sulfenylation of a glycine Schiff base. The enantioselectivity was moderate but this is the unique example of a sulfenylated product featuring a tertiary carbon center (Scheme 36b).⁶⁴ In the sulfenylation of isoindolinones, a morpholine-connected Maruoka's bifunctional ammonium salt proved to be superior to other

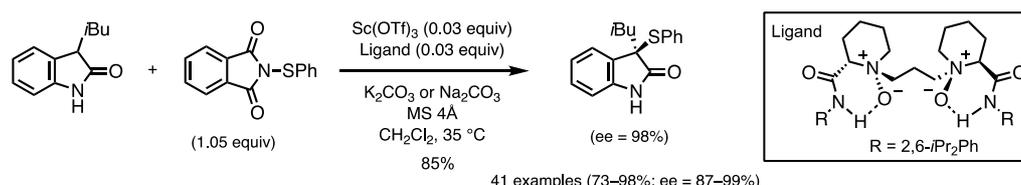
ammonium salts. Excellent yields and enantioselectivities were recorded for a wide range of substrates and sulfur group transferred (Scheme 36c) (see section 7.9.5.3.2 for application in trifluoromethylthiolation).⁶⁵ Finally, the α -sulfenylation of isoxazolidin-5-ones was conducted with Maruoka's *N*-spiro quaternary ammonium catalysts to furnish an entry to $\beta^{2,2}$ -amino acid derivatives with high enantioselectivities (Scheme 36d).⁶⁶



Scheme 36 Phase-transfer catalyzed asymmetric sulfenylation of various substrates

7.9.5.1.2 Transition-metal Catalyzed Sulfenylation

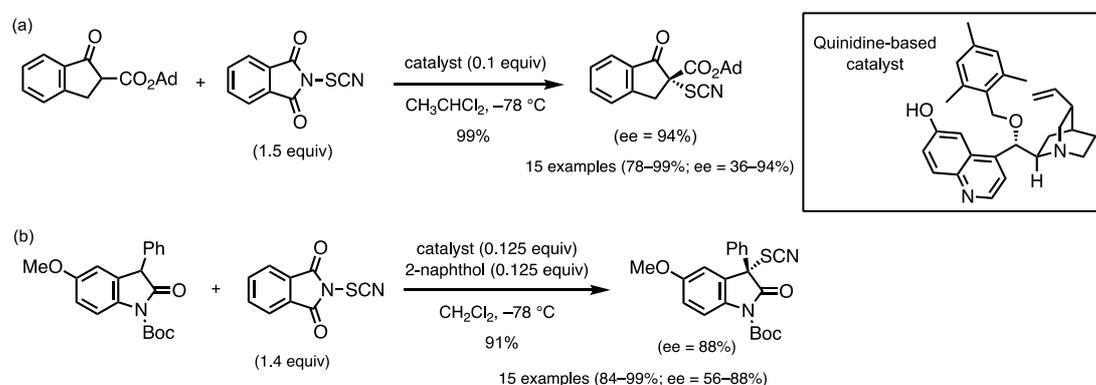
In a rare example of sulfenylation mediated by an organometallic species, the cooperative catalysis of a chiral *N,N'*-dioxide-Sc(OTf)₃ complex and a brønsted base was effective for the highly enantioselective α -sulfenylation of unprotected 3-substituted oxindoles with *N*-(phenylthio)phthalimide. High yields and gram-scale experiments further demonstrated the synthetic utility of the catalyst system (Scheme 37).⁶⁷



Scheme 37 Metal-catalyzed asymmetric sulfenylation of 3-substituted oxindoles

7.9.5.2 Thiocyanation (SCN)

The organocatalytic enantioselective α -thiocyanation of cyclic β -keto esters was reported only once by using cinchona alkaloid-modified catalysts and *N*-thiocyanatophthalimide as the electrophilic thiocyanating agent (Scheme 38a).⁶⁸ Of the most effective catalysts, C9-benzylic ether and C6'-OH quinidine derivatives provided excellent yields and high enantioselectivities for various cyclic α -thiocyanato β -keto esters. One acyclic β -keto ester failed to react under the same protocol. Rather logically, the antipode was obtained with a very similar ee value by switching from a quinidine- to a quinine-based catalyst. The same authors further extended the enantioselective α -thiocyanation to 3-aryl oxindoles (Scheme 38b).⁶⁹ The reactions were performed in the presence of 2-naphthol as a proton relay additive forming hydrogen-bond interactions. Excellent yields and moderate to high enantioselectivities were reported. Apart from 3-benzyl oxindole that gave only 20% ee value and *N*-Boc 3-*i*Pr oxindole for which only trace amount of product was detected.



Scheme 38 Organocatalyzed enantioselective α -thiocyanation of cyclic β -keto esters (a) and oxindoles (b)

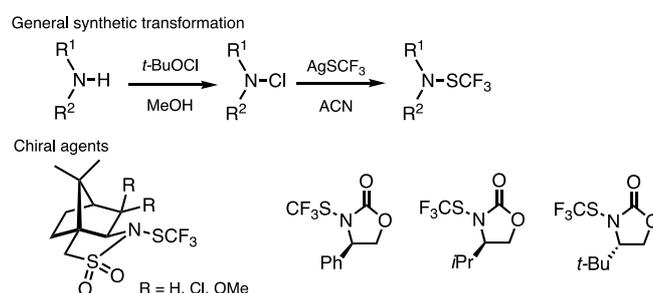
7.9.5.3 Trifluoromethylthiolation (SCF_3)

Direct introduction of the SCF_3 motif at $\text{C}(\text{sp}^3)$ centers with emphasis for chirality control has developed rapidly from 2013. This is due to the fact that the trifluoromethylthio group is one of the most lipophilic substituents and a privileged metabolically stable motif to provide excellent physicochemical and pharmacokinetic properties to drug candidate molecules. Several electrophilic reagents featuring a $\text{N}-\text{SCF}_3$ or a $\text{O}-\text{SCF}_3$ bond were designed, which in combination with chiral organic or transition-metal catalysts produce chiral $\text{C}-\text{SCF}_3$ products. Furthermore, a few chiral $\text{N}-\text{SCF}_3$ agents were designed and used under stoichiometric conditions.

7.9.5.3.1 Chiral Trifluoromethylthiolating Agents

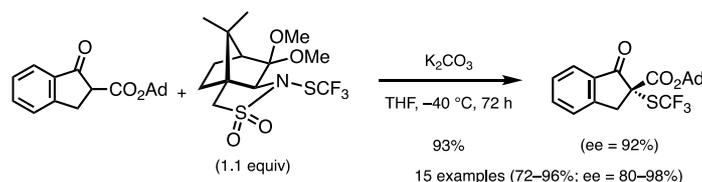
The enantioselective trifluoromethylthiolation with the aid of preformed optically pure trifluoromethylthiolating agents was based on nitrogen containing camphorsultam and oxazolidinone derivatives. These agents are obtained in a two-step sequence that involve the reaction of the starting chiral $\text{N}-\text{H}$ compound with *tert*-butyl hypochlorite in methanol

followed by treatment with AgSCF_3 in acetonitrile (Scheme 39).⁷⁰ The camphorsultam derivatives demonstrated much higher enantioselectivities than oxazolidinone derivatives in the reaction with prochiral β -keto esters, oxindoles and benzofuranones.



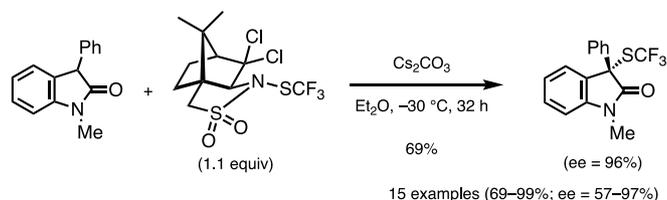
Scheme 39 Chiral trifluoromethylthiolating agents

The optimized conditions were found for the *gem*-dimethoxycamphorsultam derivative in the asymmetric α -trifluoromethylthiolation of cyclic β -keto esters. A panel of indanone and tetralone β -keto esters produced the corresponding α -trifluoromethylthiolated derivatives in excellent yields and enantioselectivities up to 98% ee (Scheme 40).⁷⁰ Electron-donating substituents on the aromatic ring could be tolerated and the enantioselectivity was not dependent on the size of the ester moiety. Nevertheless, increased temperature was necessary to achieve high conversion of substrates featuring electron-withdrawing substituents.



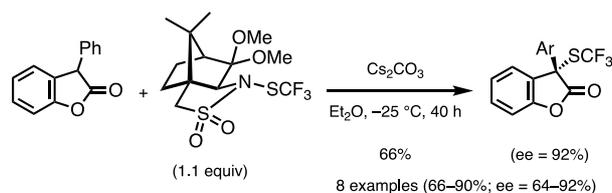
Scheme 40 Trifluoromethylthiolation of β -keto esters

Similar conditions could be employed to trifluoromethylate 3-aryloxindoles in high yields and enantioselectivities (Scheme 41).⁷⁰ Whatever the electronic properties of the aryl substituents at C3, the reaction was efficient using either the *gem*-dimethoxy- or the *gem*-dichlorocamphorsultam N-SCF_3 agents. The latter agent allowed to get slightly improved ee values and gave a moderate enantioselective reaction with 3-methyl oxindoles (76%; ee = 79%).



Scheme 41 Trifluoromethylthiolation of 3-aryloxindoles

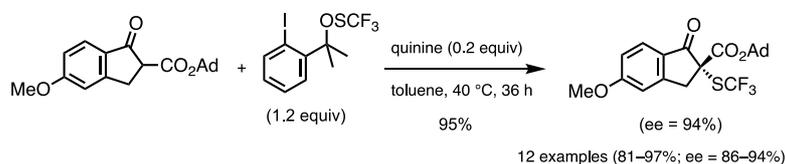
Finally, optically enriched 2-trifluoromethylthio-2-aryl benzofuran-2(3*H*)-ones could also be prepared with the camphorsultam trifluoromethylthiolating agent in good yields and moderate enantioselectivities (Scheme 42).⁷⁰



Scheme 42 Trifluoromethylthiolation of 2-benzofuran-2(3*H*)-ones

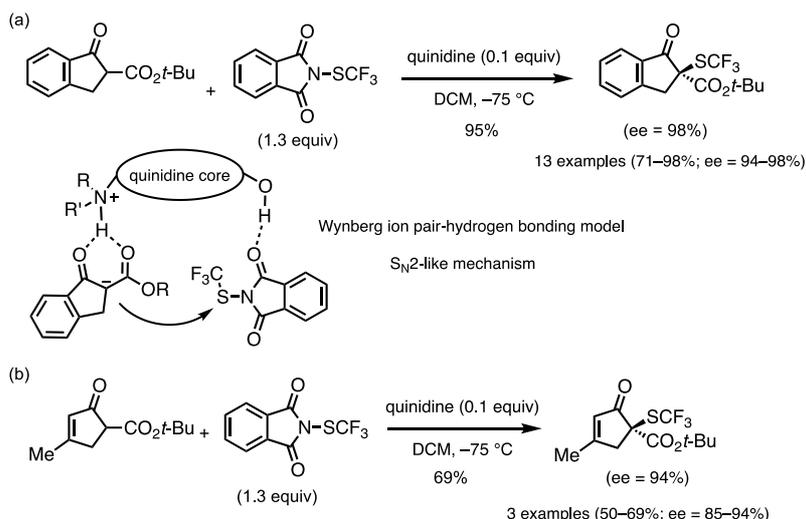
7.9.5.3.2 Organocatalytic Trifluoromethylthiolation

The catalytic asymmetric α -trifluoromethylthiolation of cyclic β -keto esters was reported for the first time by using cinchona alkaloid catalysts and either Shen's trifluoromethylsulfenate reagent (Shen's approach)⁷¹ or *N*-(trifluoromethylthio)phthalimide (Rueping's approach)⁷² as the electrophilic trifluoromethylthiolating agents. By means of Shen's trifluoromethylsulfenate reagent, quinine demonstrated high efficiency to catalyze the trifluoromethylthiolation of indanone-type adamantyl β -keto esters (Scheme 43). Various decorated aromatic rings on the substrates were tolerated but the reaction was quite sensitive to the steric hindrance of the ester moiety. Adamantyl esters gave high yields and enantiomeric excesses while methyl and ethyl esters gave 42 and 49% ee, respectively. When applied to the cyclopentanone β -keto ester, the reaction conditions gave 95% yield and 94% ee value; however, a very low conversion was observed in the case of tetralone and 1-benzosuberone derivatives pointing out the compatibility issue with regard to ring size (see later in the text for the solving of this problem under phase-transfer conditions).⁷¹



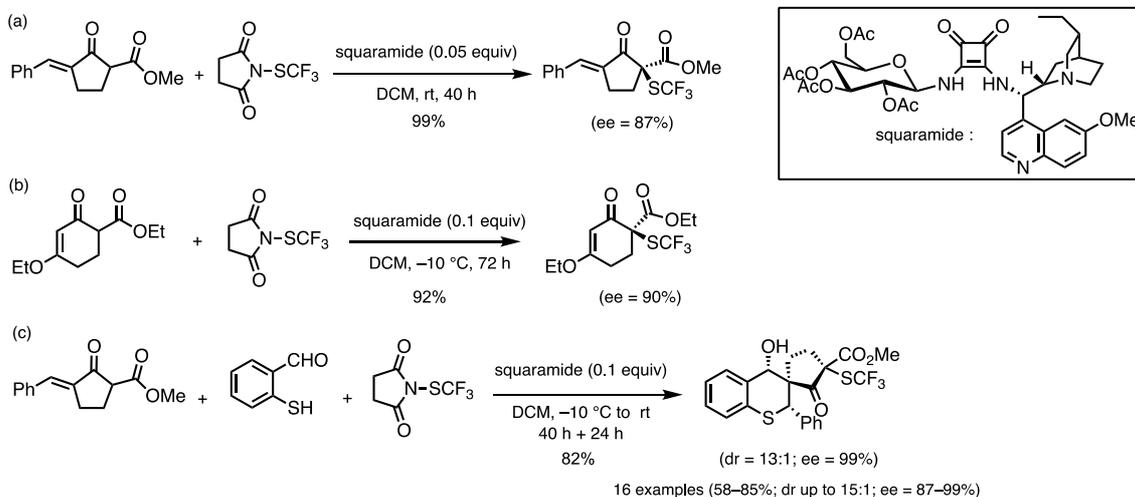
Scheme 43 Organocatalyzed trifluoromethylthiolation of β -keto esters

Simultaneously and independently, Rueping's group described a similar methodology based on the chirality of the cinchona alkaloids among which quinidine was shown to be the most efficient catalyst in combination with *N*-(trifluoromethylthio)phthalimide as the electrophilic SCF_3 donor (Scheme 44).⁷² In contrast to Shen's results, the size of the ester group had very little influence on the enantioselectivity of the reaction since Me, Et, Bn esters were well tolerated (Scheme 44a). Moreover, a tetralone β -keto ester was trifluoromethylated with this catalytic system in 46% yield and 99% ee. Elucidation of the reaction mechanism was performed computationally and the Wynberg ion pair-hydrogen bonding model was assigned.⁷³ Additionally, cyclopentanone-based β -keto esters were trifluoromethylated in moderate yields and good enantioselectivities (Scheme 44b).



Scheme 44 Organocatalyzed trifluoromethylthiolation of β -keto esters (a) and cyclopentenone-based β -keto esters (b).

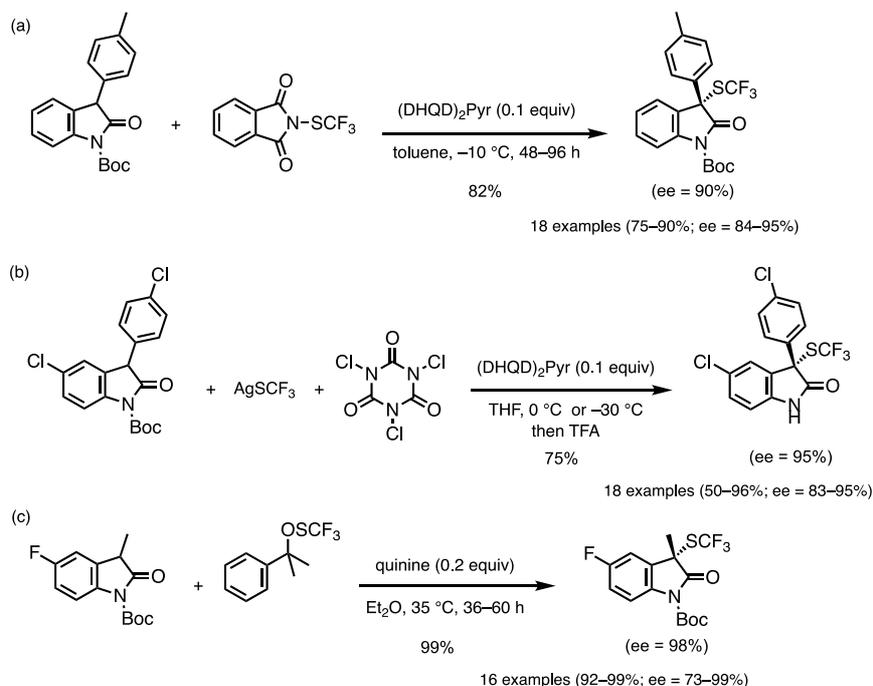
Squaramides derived from hydroquinine and D-glucopyranose were reported as another organocatalytic variant of the trifluoromethylthiolation of cycloalkenone β -keto esters with the aid of *N*-trifluoromethylthiosuccinimide (Scheme 45a,b).⁷⁴ When a 2-mercaptobenzaldehyde derivative was added as a third reactant, these one-pot conditions allowed a cascade conjugate addition / aldolization to produce interesting SCF_3 -bearing spiro-cyclopentanone thiochromanes (Scheme 45c).⁷⁴



Scheme 45 Organocatalyzed trifluoromethylthiolation of cycloalkenones by means of a squaramide catalyst.

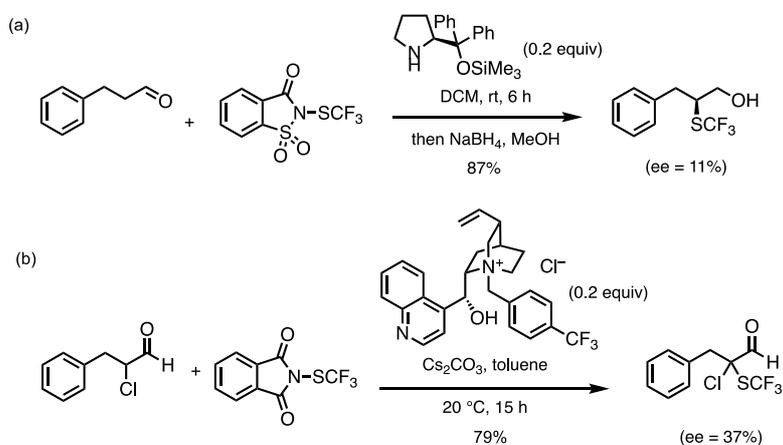
Capitalizing on the results obtained with β -keto esters (see earlier in the text), Rueping *et al.* applied the trifluoromethylthiolation to oxindoles. Analogous reaction conditions, but exploiting the bis-cinchona alkaloid $(\text{DHQD})_2\text{Pyr}$ to achieve high enantioselectivity, afforded the desired 3- SCF_3 -3-aryl *N*-Boc-oxindoles (Scheme 46a).⁷⁵ Alternatively, an oxidative trifluoromethylthiolation was developed from AgSCF_3 and trichloroisocyanuric acid (TCCA), a system that generates an electrophilic SCF_3 donor species (not fully elucidated, one

possibility could be F_3CSCF_3). Here again, 3-aryl *N*-Boc-oxindoles were trifluoromethylthiolated successfully (Scheme 46b).⁷⁶ Finally, conditions were found for the trifluoromethylthiolation of 3-alkyl oxindoles with the aid of Shen's trifluoromethylthio peroxide and a catalytic amount of quinine (Scheme 46c).⁷⁷ This specific SCF_3 donor was crucial to reach high enantioselectivities for 3- SCF_3 -3-alkyl oxindoles whereas *N*-(trifluoromethylthio)phthalimide gave significantly lower ee values. A complementarity in scope was thus demonstrated.



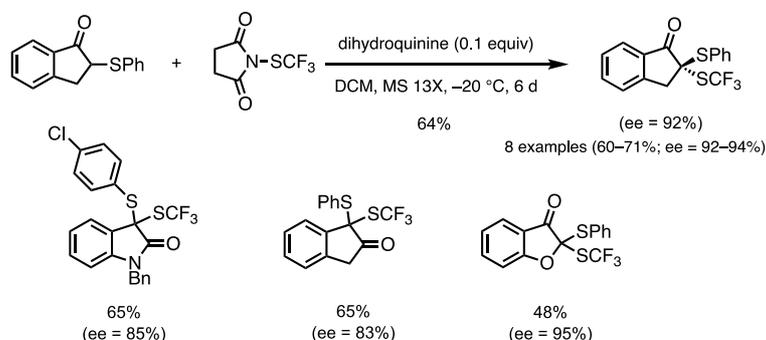
Scheme 46 Organocatalyzed enantioselective α -trifluoromethylthiolation of oxindoles

The α -trifluoromethylthiolation of aldehydes was also attempted but only very modest results and a narrow scope were reported. Either using the Hayashi-Jørgensen catalyst (Scheme 47a)⁷⁸ or a phase-transfer catalyst (Scheme 47b),⁷⁹ no efficient enantioselective version was reported.



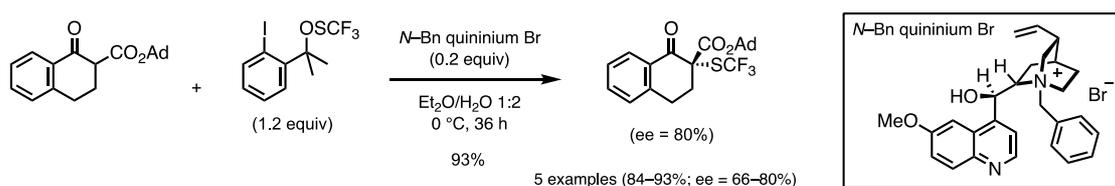
Scheme 47 Organocatalyzed enantioselective α -trifluoromethylthiolation of aldehydes

Dithioketals chiral at the quaternary carbon featuring a SCF₃ motif were prepared with high enantioselectivity starting from α -thio ketones as in indanone thioesters. The combination of dihydroquinine and *N*-SCF₃ succinimide required a long reaction time at -20 °C to reach satisfactory results (Scheme 48).⁵³ Three other dithioketals derived from an oxindole, a 2-indanone, and a 3-benzofuranone were prepared using the same reaction conditions in moderate yields with good to high enantioselectivities (Scheme 48).



Scheme 48 Organocatalyzed enantioselective construction of dithioketals

Asymmetric phase-transfer catalysis (PTC) by means of chiral quaternary ammonium salt ion pairing catalysts is a strategy widely applied for selective α -functionalization reactions. Such organocatalytic PTC approach is complementary to the above-mentioned strategies in the field of organocatalysis. Using neutral cinchona alkaloid-based catalysts, Shen observed a large reactivity difference when switching from cyclopentanone β -keto ester to larger size cycles as in tetralone and 1-benzosuberone derivatives. By replacing quinine with the *N*-benzyl quininium bromide, tetralone β -keto esters could react with the trifluoromethylsulfenate reagent in high yields and moderate enantioselectivities (Scheme 49).⁷¹ Seven-membered ring in 1-benzofuranone derivatives and cyclohexanone derivatives free of the fused aromatic ring also gave satisfactory results. However, no improvement was noted in the case of acyclic substrates.



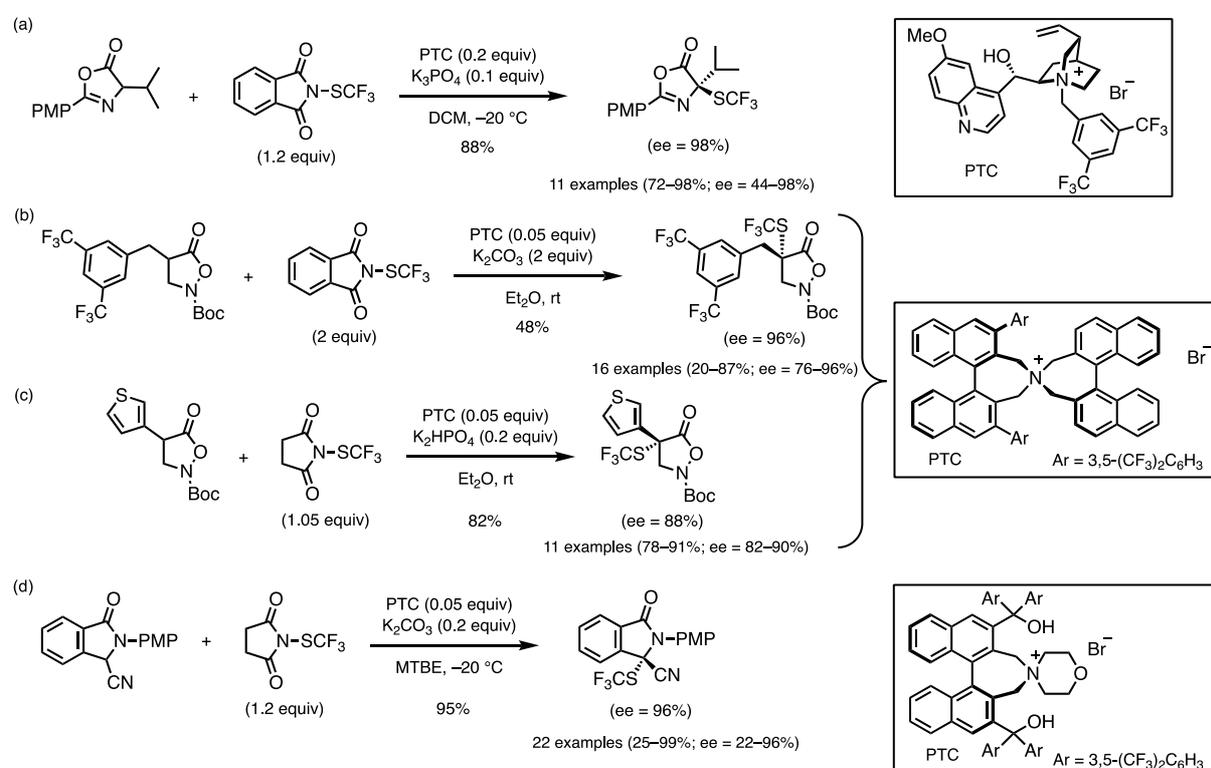
Scheme 49 Organocatalyzed trifluoromethylthiolation of tetralone-based adamantly β -keto esters under PTC

More recently, PTC conditions were reinvestigated on a wider substrate scope that include azlactones, 4-substituted isoxazolidin-5-ones, and 3-substituted isoindolinones for their high interest as biologically relevant frameworks. The enantioselective trifluoromethylthiolation at the C4 position of azlactones was performed in the presence of a quinine-base ammonium catalyst. Better results were obtained with electron-rich 2-aryl groups such as 4-MeOPh (PMP) as 4-CNPh and 4-CF₃Ph gave no reaction. A variety of aryl and alkyl substituents at C4 are compatible with the reaction conditions; nonetheless, limitations

appeared with Me, Ph, and *t*-Bu groups that led to the decomposition of the starting material (Scheme 50a).⁸⁰

Maruoka's *N*-spiro ammonium phase-transfer catalysts were employed in the synthesis of α -SCF₃- β ^{2,2}-amino acids by electrophilic trifluoromethylthiolation of 4-substituted isoxazolidin-5-ones and subsequent N–O bond cleavage (Scheme 50b).⁸¹ Substrates featuring an α -benzyl pendant afforded good to moderate yields and high enantioselectivities while α -aryl analogues performed less selectively (ee = 68–76%). For these latter substrates, similar but more selective reaction conditions were developed with the *N*-SCF₃ succinimide reagent and the same Maruoka's catalyst (Scheme 50c).⁸²

For the trifluoromethylthiolation of 3-substituted isoindolinones, the search for an optimal catalyst revealed the morpholine-connected Maruoka's bifunctional ammonium salt as catalyst of choice to reach high levels of enantioinduction. Both cyano and ester groups at C3 together with variously decorated aromatics and *N*-substituents afforded a wide range of enantioenriched 3-SCF₃ isoindolinones (Scheme 50d).⁶⁵

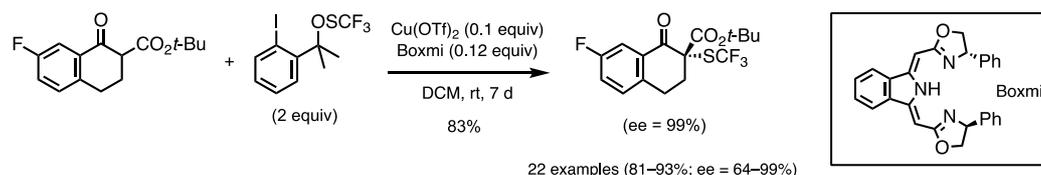


Scheme 50 Phase-transfer catalyzed trifluoromethylthiolation of azlactones (a), 4-substituted isoxazolidin-5-ones (b and c), and 3-substituted isoindolinones (d)

7.9.5.3.3 Transition-metal Catalyzed Trifluoromethylthiolation

Building on the efficiency of the Boxmi chiral pincer ligands in electrophilic asymmetric fluorination (see section 7.9.2.4), Gade *et al.* extended the application scope to the trifluoromethylthiolation of β -keto esters with the aid of Shen's trifluoromethylsulfonate (Scheme 51).⁸³ High yields and enantioselectivities were reported irrespective of ring size and the nature of the ester group. This generality contrasts with some methods using organocatalysis. Indeed, indanone, tetralone, cyclopentenone, and cyclohexanone scaffolds

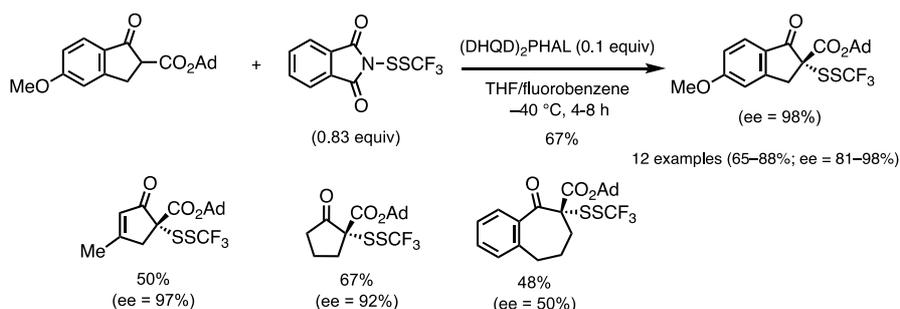
as well as various substitution patterns were tolerated and did not significantly affect the enantioselectivity.



Scheme 51 Copper-catalyzed trifluoromethylthiolation of β -keto esters

7.9.5.4 Disulfur transfer (SSCF₃)

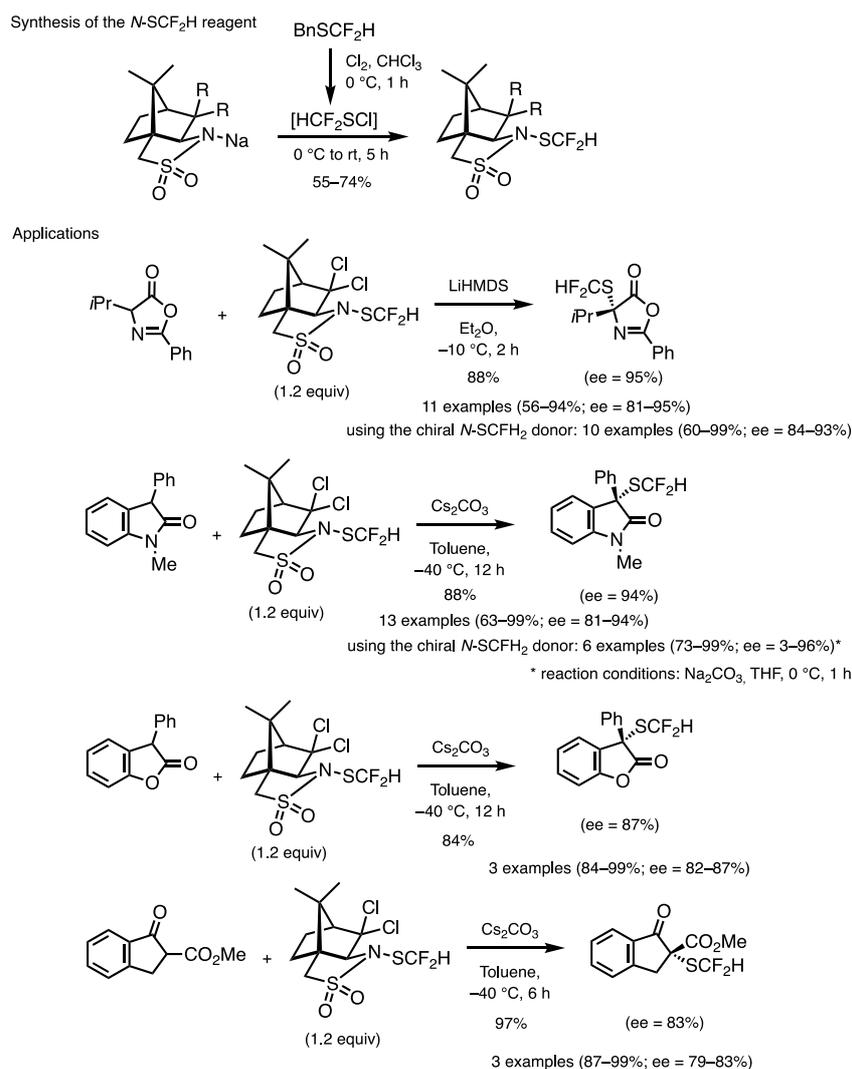
In connection with the synthesis of polythiomethyl ethers as relevant structural motifs in biologically active natural products, dithiotrifluoromethylated β -keto esters were prepared by means of the electrophilic *N*-dithiotrifluoromethyl phthalimide. Good to excellent enantioselectivities were obtained for various β -keto esters (essentially indanone derivatives) in reactions catalyzed by the bis-cinchona alkaloid (DHQD)₂PHAL (Scheme 52).⁸⁴



Scheme 52 Organocatalyzed asymmetric dithiotrifluoromethylation of β -keto esters

7.9.5.5 Difluoromethylthiolation (SCF₂H) and monofluoromethylthiolation (SCFH₂)

A logical extension of the *N*-SCF₃ camphorsultam trifluoromethylthiolating agents (section 7.9.5.3.1) was the preparation of electrophilic difluoromethylthiolating agents featuring this privileged camphorsultam scaffold and a *N*-SCF₂H motif.⁸⁵ Their preparation required the in situ conversion of difluoromethylbenzylthioether into difluoromethanesulfonyl chloride with a solution of chlorine in chloroform followed by the addition of the camphorsultam sodium salt. Of particular investigation was the *gem*-dichlorocamphorsultam *N*-SCF₂H reagent in reaction with a variety of soft carbon nucleophiles such as oxazolones, oxindoles, benzofuranones and β -keto esters. Good to excellent yields and enantioselectivities were obtained in all cases (Scheme 53). Of particular interest, the SCF₂H oxazolones could be ring-opened to produce difluoromethylthiolated amino acid derivatives potentially eligible for peptide synthesis. Similarly, a monofluoromethylthiolating agent was designed.⁸⁶



Scheme 53 Chiral di- and monofluoromethylthiolating agents and applications

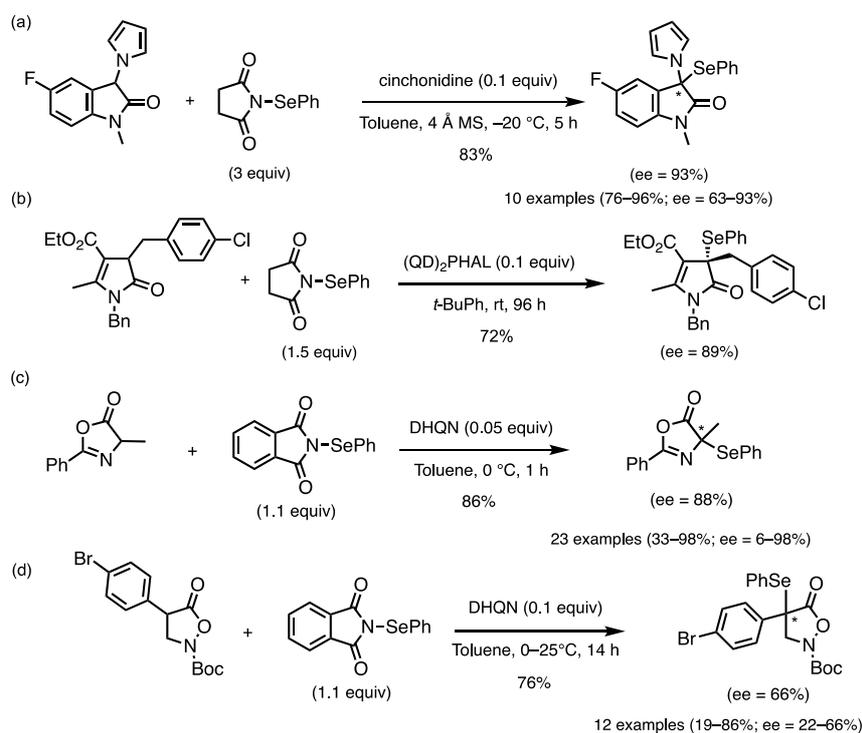
7.9.6 Enantioselective Electrophilic Selenenylation

To the best of our knowledge, no new chiral selenenylating reagents was reported since the pioneering works in the eighties. Asymmetric selenenylations under covalent organocatalysis for which the stereodiscriminating step is diastereoselective are described in Volumes 1 and 2. The selenofunctionalization of C=C bonds is reported in Volume 5.

7.9.6.1 Organocatalytic Selenenylation

The selenenylation reactions described in this section are extensions of the sulfenylation reactions presented in section 7.9.5.1.1. The selenenylation of 3-pyrrolyl oxindoles by *N*-(phenylseleno) succinimide in the presence of 10 mol% of cinchonidine gave the C3-N,Se-containing oxindoles in good enantioselectivities provided that N1 is protected (Scheme 54a).⁵² Similarly, the selenenylation of one deconjugated butyrolactam was reported with the aid of the bis cinchona alkaloid (QD)₂PHAL with 89% ee (Scheme 54b).⁵⁵ Towards selenium-containing amino acids, the enantioselective electrophilic α-selenenylation of azlactones and isoazolidin-5-ones mediated by cinchona alkaloids as simple organocatalysts

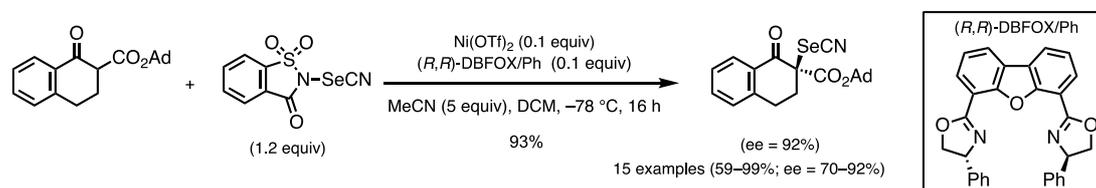
gave the α -Se- α -amino acid and α -Se- β -amino acid derivatives, respectively (Scheme 54c,d).⁸⁷



Scheme 54 Organocatalyzed asymmetric selenenylation of 3-pyrrolyl oxindoles (a), one deconjugated butyrolactam (b), azlactones (c), and isoazolidin-5-ones (d)

7.9.6.2 Transition-metal Catalysis

The Lewis acid-catalyzed asymmetric selenocyanation of β -keto ester derived from tetralones was conducted in the presence of Ni(OTf)₂ and (*R,R*)-DBFOX/Ph employing the novel *N*-(selenocyanato) saccharin as SeCN source (Scheme 55).⁸⁸ Some limitations appeared with indanone-based substrates (0% ee) and with deviation of the adamantyl ester (ee = 13 and 45% for Me and *i*-Bu esters, respectively).



Scheme 55 Ni-Catalyzed asymmetric selenocyanation of β -keto esters

7.9.7 Conclusion and Outlook

The enantioselective C–X bond formation reactions (halogenation, sulfenylation, and selenylation) have steadily risen over the reference period from 2012. The number of references has doubled in the last ten years! A great number of electrophilic reagents appeared particularly for the sulfenylation with emphasis for the electrophilic

fluoromethylthiolation. Several new and efficient protocols for catalytic enantioselective reactions mediated by *de novo* designed chiral organocatalysts and ligands for metal-catalyzed reactions illustrate the high interest for this research field. Future advances are expected toward the broadening of the substrate scope as well as applications of protocols to more complex molecules, for instance in the late-stage C–X bond formation on pharmaceutical molecules for new drug discovery.

References

1. Souza, L. G.; de O. Domingos, J. L.; de A. Fernandes, T.; Renno, M. N.; Sansano, J. M.; Najera, C.; Costa, P. R. R. *J. Fluorine Chem.* **2019**, *217*, 72-79.
2. Wang, Y.; Wang, G.; Peshkov, A. A.; Yao, R.; Hasan, M.; Zaman, M.; Liu, C.; Kashtanov, S.; Pereshivko, O. P.; Peshkov, V. A. *Beilstein J. Org. Chem.* **2020**, *16*, 1963-1973.
3. Wolstenhulme, J. R.; Rosenqvist, J.; Lozano, O.; Ilupeju, J.; Wurz, N.; Engle, K. M.; Pidgeon, G. W.; Moore, P. R.; Sandford, G.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 9796-9800.
4. Zhu, C.-L.; Maeno, M.; Zhang, F.-G.; Shigehiro, T.; Kagawa, T.; Kawada, K.; Shibata, N.; Ma, J.-A.; Cahard, D. *Eur. J. Org. Chem.* **2013**, *2013*, 6501-6505.
5. Witten, M. R.; Jacobsen, E. N. *Org. Lett.* **2015**, *17*, 2772-2775.
6. Shibatomi, K.; Kitahara, K.; Okimi, T.; Abe, Y.; Iwasa, S. *Chem. Sci.* **2016**, *7*, 1388-1392.
7. Cui, L.; You, Y. e.; Mi, X.; Luo, S. *J. Org. Chem.* **2018**, *83*, 4250-4256.
8. You, Y. e.; Zhang, L.; Luo, S. *Chem. Sci.* **2017**, *8*, 621-626.
9. Poorsadeghi, S.; Endo, K.; Arimitsu, S. *Org. Lett.* **2022**, *24*, 420-424.
10. Fjelbye, K.; Marigo, M.; Clausen, R. P.; Juhl, K. *Synlett* **2017**, *28*, 425-428.
11. Hayes, M. D.; Rodríguez-Alvarado, M.; Brenner-Moyer, S. E. *Tetrahedron Lett.* **2015**, *56*, 4718-4720.
12. Bao, X.; Wei, S.; Zou, L.; Song, Y.; Qu, J.; Wang, B. *Tetrahedron: Asymmetry* **2016**, *27*, 436-441.
13. Zhang, H.; Wang, B.; Cui, L.; Bao, X.; Qu, J.; Song, Y. *Eur. J. Org. Chem.* **2015**, *2015*, 2143-2147.
14. Jiang, X.; Wang, H.; He, H.; Wang, W.; Wang, Y.; Ke, Z.; Yeung, Y.-Y. *Adv. Synth. Catal.* **2018**, *360*, 4710-4714.
15. Xu, J.; Hu, Y.; Huang, D.; Wang, K.-H.; Xu, C.; Niu, T. *Adv. Synth. Catal.* **2012**, *354*, 515-526.
16. Jung, H. I.; Park, J. H.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2018**, *39*, 1442-1448.
17. Erb, J.; Paull, D. H.; Dudding, T.; Belding, L.; Lectka, T. *J. Am. Chem. Soc.* **2011**, *133*, 7536-7546.
18. Novacek, J.; Waser, M. *Eur. J. Org. Chem.* **2014**, *2014*, 802-809.
19. Zhang, B.; Shi, L.; Guo, R.; Liu, S. *ARKIVOC* **2016**, *2016*, 363-370.
20. Wang, B.; He, Y.; Fu, X.; Wei, Z.; Lin, Y.; Duan, H. *Synlett* **2015**, *26*, 2588-2592.
21. Zhu, C.-L.; Fu, X.-Y.; Wei, A.-J.; Cahard, D.; Ma, J.-A. *J. Fluorine Chem.* **2013**, *150*, 60-66.
22. Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225-5228.
23. Bertogg, A.; Hintermann, L.; Huber, D. P.; Perseghini, M.; Sanna, M.; Togni, A. *Helv. Chim. Acta* **2012**, *95*, 353-403.

24. Niu, T.; Han, X.; Huang, D.; Wang, K.-H.; Su, Y.; Hu, Y.; Fu, Y. *J. Fluorine Chem.* **2015**, *175*, 6-11.
25. Granados, A.; Sarró, P.; Vallribera, A. *Molecules* **2019**, *24*, 1141.
26. Wang, B.; Wang, Y.; Jiang, Y.; Chu, M.; Qi, S.; Ju, W.; Xu, D. *Org. Biomol. Chem.* **2018**, *16*, 7702-7710.
27. Zheng, L.-S.; Wei, Y.-L.; Jiang, K.-Z.; Deng, Y.; Zheng, Z.-J.; Xu, L.-W. *Adv. Synth. Catal.* **2014**, *356*, 3769-3776.
28. Kwon, S. J.; Kim, D. Y. *J. Fluorine Chem.* **2015**, *180*, 201-207.
29. Woo, S. B.; Suh, C. W.; Koh, K. O.; Kim, D. Y. *Tetrahedron Lett.* **2013**, *54*, 3359-3362.
30. Zhang, R.; Wang, D.; Xu, Q.; Jiang, J.; Shi, M. *Chin. J. Chem.* **2012**, *30*, 1295-1304.
31. Jacquet, O.; Clément, N. D.; Blanco, C.; Belmonte, M. M.; Benet-Buchholz, J.; van Leeuwen, P. W. N. M. *Eur. J. Org. Chem.* **2012**, *2012*, 4844-4852.
32. Banik, S.; Sahoo, T.; Sridhar, B.; Subba Reddy, B. V. *Org. Biomol. Chem.* **2021**, *19*, 6085-6091.
33. Grell, Y.; Xie, X.; Ivlev, S. I.; Meggers, E. *ACS Catal.* **2021**, *11*, 11396-11406.
34. Xu, G.-Q.; Liang, H.; Fang, J.; Jia, Z.-L.; Chen, J.-Q.; Xu, P.-F. *Chem. Asian J.* **2016**, *11*, 3355-3358.
35. Wannemacher, N.; Pfeffer, C.; Frey, W.; Peters, R. *J. Org. Chem.* **2021**, *87*, 670-682.
36. Shibatomi, K.; Kitahara, K.; Sasaki, N.; Kawasaki, Y.; Fujisawa, I.; Iwasa, S. *Nat. Commun.* **2017**, *8*, 15600.
37. Shirakawa, S.; Tokuda, T.; Kasai, A.; Maruoka, K. *Org. Lett.* **2013**, *15*, 3350-3353.
38. Guan, X.; An, D.; Liu, G.; Zhang, H.; Gao, J.; Zhou, T.; Zhang, G.; Zhang, S. *Tetrahedron Lett.* **2018**, *59*, 2418-2421.
39. Zhao, M.-X.; Zhang, Z.-W.; Chen, M.-X.; Tang, W.-H.; Shi, M. *Eur. J. Org. Chem.* **2011**, *2011*, 3001-3008.
40. Gao, X.; Han, J.; Wang, L. *Org. Lett.* **2015**, *17*, 4596-4599.
41. Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339-3341.
42. Liu, R. Y.; Wasa, M.; Jacobsen, E. N. *Tetrahedron Lett.* **2015**, *56*, 3428-3430.
43. Shibatomi, K.; Soga, Y.; Narayama, A.; Fujisawa, I.; Iwasa, S. *J. Am. Chem. Soc.* **2012**, *134*, 9836-9839.
44. Li, J.; Pan, W.; Wang, Z.; Zhang, X.; Ding, K. *Adv. Synth. Catal.* **2012**, *354*, 1980-1986.
45. Kang, Y. K.; Kim, H. H.; Koh, K. O.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 3811-3814.
46. Nishimura, K.; Wang, Y.; Ogura, Y.; Kumagai, J.; Ishihara, K. *ACS Catal.* **2022**, *1012*-1017.
47. Cui, L.; You, Y. e.; Mi, X.; Luo, S. *Org. Chem. Front.* **2018**, *5*, 2313-2316.
48. Rota, F.; Benhamou, L.; Sheppard, T. D. *Synlett* **2016**, *27*, 33-36.
49. Li, X.; Liu, C.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2012**, *14*, 4374-4377.
50. Han, Z.; Chen, W.; Dong, S.; Yang, C.; Liu, H.; Pan, Y.; Yan, L.; Jiang, Z. *Org. Lett.* **2012**, *14*, 4670-4673.
51. E, Y.; Yuan, T.; Yin, L.; Xu, Y. *Tetrahedron Lett.* **2017**, *58*, 2521-2524.
52. You, Y.; Wu, Z.-J.; Wang, Z.-H.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 8470-8477.
53. Liao, K.; Zhou, F.; Yu, J. S.; Gao, W. M.; Zhou, J. *Chem. Commun.* **2015**, *51*, 16255-16258.
54. Zhao, J.-Q.; Luo, S.-W.; Zhang, X.-M.; Xu, X.-Y.; Zhou, M.-Q.; Yuan, W.-C. *Tetrahedron* **2017**, *73*, 5444-5450.

55. Singha Roy, S. J.; Mukherjee, S. *Org. Biomol. Chem.* **2017**, *15*, 6921-6925.
56. Qiao, B.; Liu, X.; Duan, S.; Yan, L.; Jiang, Z. *Org. Lett.* **2014**, *16*, 672-675.
57. Xu, M.; Qiao, B.; Duan, S.; Liu, H.; Jiang, Z. *Tetrahedron* **2014**, *70*, 8696-8702.
58. Wang, C.; Yang, X.; Loh, C. C. J.; Raabe, G.; Enders, D. *Chem. Eur. J.* **2012**, *18*, 11531-11535.
59. Huang, L.; Li, J.; Zhao, Y.; Ye, X.; Liu, Y.; Yan, L.; Tan, C.-H.; Liu, H.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 8933-8941.
60. Gao, X.; Han, J.; Wang, L. *Synthesis* **2016**, *48*, 2603-2611.
61. Han, J.; Zhang, Y.; Wu, X.-Y.; Wong, H. N. C. *Chem. Commun.* **2019**, *55*, 397-400.
62. Zhang, Y.; Wong, H. N. C.; Wu, X.-Y.; Han, J. *Tetrahedron Lett.* **2020**, *61*, 151755-151758.
63. Nagata, K.; Sano, D.; Aoyama, O.; Kanemitsu, T.; Miyazaki, M.; Odanaka, Y.; Machida, A.; Itoh, T. *Heterocycles* **2016**, *92*, 631-635.
64. Yunde, Z.; Shengxin, C.; Qiuhan, Y.; Ziyu, W.; Zhenya, D. *Austin J Anal Pharm Chem* **2016**, *3*, 1075-1076.
65. Eitzinger, A.; Otevreil, J.; Haider, V.; Macchia, A.; Massa, A.; Faust, K.; Spingler, B.; Berkessel, A.; Waser, M. *Adv. Synth. Catal.* **2021**, *363*, 1955-1962.
66. Cadart, T.; Berthonneau, C.; Levacher, V.; Perrio, S.; Brière, J.-F. *Chem. Eur. J.* **2016**, *22*, 15261-15264.
67. Cai, Y.; Li, J.; Chen, W.; Xie, M.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2012**, *14*, 2726-2729.
68. Qiu, J.; Wu, D.; Karmaker, P. G.; Yin, H.; Chen, F.-X. *Org. Lett.* **2018**, *20*, 1600-1603.
69. Qiu, J.; Wu, D.; Yuan, L.; Long, P.; Yin, H.; Chen, F.-X. *J. Org. Chem.* **2019**, *84*, 7917-7926.
70. Zhang, H.; Leng, X.; Wan, X.; Shen, Q. *Org. Chem. Front.* **2017**, *4*, 1051-1057.
71. Wang, X.; Yang, T.; Cheng, X.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 12860-12864.
72. Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresi, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12856-12859.
73. Li, M.; Xue, X.-S.; Cheng, J.-P. *ACS Catal.* **2017**, 7977-7986.
74. Zhao, B.-L.; Du, D.-M. *Org. Lett.* **2017**, *19*, 1036-1039.
75. Rueping, M.; Liu, X.; Bootwicha, T.; Pluta, R.; Merkens, C. *Chem. Commun.* **2014**, *50*, 2508-2511.
76. Zhu, X. L.; Xu, J. H.; Cheng, D. J.; Zhao, L. J.; Liu, X. Y.; Tan, B. *Org. Lett.* **2014**, *16*, 2192-2195.
77. Yang, T.; Shen, Q.; Lu, L. *Chinese J. Chem.* **2014**, *32*, 678-680.
78. Hu, L.; Wu, M.; Wan, H.; Wang, J.; Wang, G.; Guo, H.; Sun, S. *New J. Chem.* **2016**, *40*, 6550-6553.
79. Gelat, F.; Poisson, T.; Biju, A. T.; Pannecoucke, X.; Besset, T. *Eur. J. Org. Chem.* **2018**, *2018*, 3693-3696.
80. Sicignano, M.; Rodriguez, R. I.; Capaccio, V.; Borello, F.; Cano, R.; De Riccardis, F.; Bernardi, L.; Diaz-Tendero, S.; Della Sala, G.; Aleman, J. *Org. Biomol. Chem.* **2020**, *18*, 2914-2920.
81. Capaccio, V.; Sicignano, M.; Rodriguez, R. I.; Della Sala, G.; Aleman, J. *Org. Lett.* **2020**, *22*, 219-223.
82. Eitzinger, A.; Briere, J. F.; Cahard, D.; Waser, M. *Org. Biomol. Chem.* **2020**, *18*, 405-408.
83. Deng, Q.-H.; Rettenmeier, C.; Wadepohl, H.; Gade, L. H. *Chem. Eur. J.* **2014**, *20*, 93-97.
84. Gao, W.-C.; Liu, J.; Jiang, X. *Org. Chem. Front.* **2021**, *8*, 1275-1279.

85. Zhang, H.; Wan, X.; Shen, Q. *Chin. J. Chem.* **2019**, *37*, 1041-1050.
86. Zhang, H.; Shen, Q. *Tetrahedron* **2021**, *101*, 132508.
87. Haider, V.; Zebrowski, P.; Michalke, J.; Monkowius, U.; Waser, M. *Org. Biomol. Chem.* **2022**, *20*, 824-830.
88. Wu, D.; Qiu, J.; Li, C.; Yuan, L.; Yin, H.; Chen, F.-X. *J. Org. Chem.* **2020**, *85*, 934-941.