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Enantioselective halogenation reactions

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Stereoselective halogenation reactions, in particular fluorinations, are not everyday's chemistry despite the fundamental and still increasing significance of fluorinated molecules, *e.g.*, for the life science industry. The selective fluorination of a bioactive compound can be generally beneficial in terms of a possible increased intrinsic activity, enhanced chemical and metabolic stability, and improved pharmacokinetics. It is clear that more efficient and selective methodologies for the introduction of fluorine into organic molecules are still needed. We review in this article latest progresses in the area of enantioselective fluorinations, with particular emphasis on new catalytic reactions and extend our discussion to similar reactions involving the other halogens.

Introduction

Transformations involving the formation of a C–X bond (X = halogen atom) concomitantly to the selective generation of a new stereogenic center have received far less attention than enantioselective C–C, C–O and C–N bond forming reactions and hydrogenations. This is the case in spite of the fact that the resulting products constitute valuable intermediates with potentially broad applications in synthesis. Among stereoselective halogenation reactions, enantioselective fluorinations are a special case. The physical and chemical properties of fluorine, the most electronegative element in the periodic system, enables it to be used as a substitute for hydrogen and the hydroxy group with wide reaching implications for reactivity and stability of many compounds, in particular, biologically active ones.[1] Applications of chiral non-racemic compounds containing a stereogenic C–F centre are wide spread and range from pharmaceuticals[2] to liquid crystals.[3,4] As a consequence, there has been a wealth of methodologies developed for the stereocontrolled introduction of fluorine into organic molecules, largely relying on diastereoselective fluorination and nucleophilic substitution strategies.[3,4] Efficient enantioselective entries remain, however, relatively rare and only in the past five years progress towards potentially attractive solutions was made.[5]

Stereocontrolled synthesis of non-fluoro halogenated compounds are also gaining momentum. Nevertheless, enantioselective entries to halogenated compounds having a halogen atom attached to a stereogenic centre, and especially catalytic processes remain still a vastly unexplored area of research.

The intention of this account is to give an overview on recent developments of enantioselective halogenation reactions with the emphasis on catalytic strategies because of our direct involvement in this latter area. We shall note that our contribution in developing the first enantioselective catalytic fluorination reaction started from scratch. No specific experience in fluoro-organic chemistry was available in our group when the work was started, and our efforts were primarily guided by the desire to "put-in-asymmetric-catalysis" where there was no asymmetric catalysis before. It is therefore important that we summarise in this article previous work dealing with the use of stoichiometric amounts of chiral fluorinating agents before discussing catalytic reactions since this also reflects the chronological development of this field. Moreover, the related chemistry involving the other three halogens is objectively less important than fluorination, but conceptually interesting approaches have been reported recently that will be treated separately here.

Enantioselective fluorination reactions

There is a great number of reports on the asymmetric synthesis of fluoro-organic compounds with a stereogenic C–F centre. Synthetically useful enantioselective approaches to this important class of compounds are still rare, and have found only recently applications in the construction of pharmacologically useful building blocks. An exciting development in this field has been the discovery of the catalytic electrophilic enantioselective fluorination mediated by chiral non-racemic transition metal Lewis acids. The following sections will give an overview on stoichiometric approaches concentrating on recent developments, followed by a comprehensive account on catalytic strategies.

Chiral auxiliary based stoichiometric approaches to enantioselective fluorination

An important route to the enantioselective introduction of fluorine into organic molecules is the reaction of enolisable substrates with chiral non-racemic electrophilic fluorinating agents under reagent-control.[6] Differding and Lang were the first to apply this methodology to the fluorination of enolates derived from ketones and β-ketoesters using optically active fluorinating agents.[7] In this pioneering study, camphor-derived *N*-fluoro sultam **2** was used to fluorinate the sodium enolate of β-ketoester **1** thereby generating

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Antonio Togni studied chemistry at the Swiss Federal Institute of Technology (ETH) Zurich, where he completed his Ph.D. in 1983, working with the late Luigi M. Venanzi. After a postdoctoral stay at the California Institute of Technology in John E. Bercaw's group he joined in 1985 the Central Research Laboratories of Ciba-Geigy Ltd., Basel, where he spent seven years as a research scientist in the field of asymmetric catalysis. In 1992 he was appointed Assistant Professor at the Laboratory of Inorganic Chemistry at ETH and became a Full Professor of Organometallic Chemistry in 1999. His main research interest is in the field of asymmetric catalysis.

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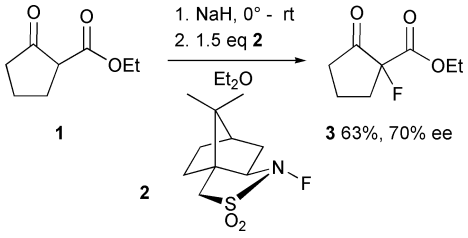


Scheme 1

2-carboethoxy-2-fluorocyclopentanone **3** in 63% yield and in 70% ee which represented the highest ee obtained in this study (Scheme 1).

The same strategy was adopted later by other researchers and efforts in particular from the groups of Davis and Takeuchi brought forward N–F reagents derived from the chiral pool, such as **4–6**,[8,9] as well as designed enantiopure sultams **7–9** (Chart 1).[10,11,12] Typical test substrates were *in situ* generated enolates of 2-substituted-1-tetralones and 1-indanones, as well as β-ketoesters. Table 1 summarises some of the best results obtained with enolates derived from 2-substituted-tetralones **10a** and **10b**.

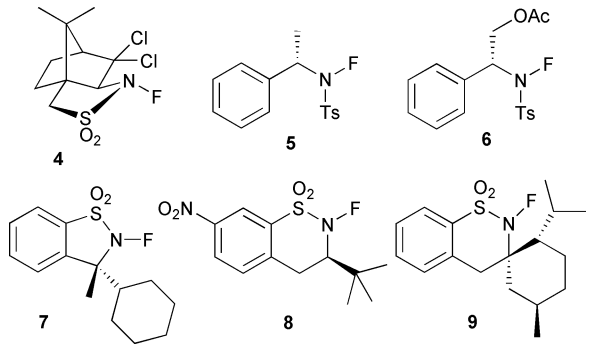
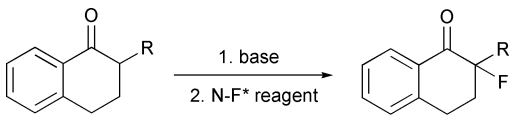


Chart 1

Other substrates tested in these studies gave generally moderate yields and low to moderate enantioselectivites. It should be mentioned that a comparison of the results obtained is difficult due to differences in reaction conditions. However, reagent **7** gave tetralones **11a** and **11b** in reasonable selectivities with an (*S*)-configuration and represents the best performing non-chiral pool derived optically active electrophilic fluorinating agent reported to date. The stereochemical outcome of the fluorination with **7** was suggested by the authors to derive from a chelation of the sultam to the lithium-enolate prior to "F$^+$" transfer in the transition state (Fig. 1).[10]

Although reagents **4–9** seem to be promising, their syntheses require several steps so that, except from the original work, no further applications of these reagents have been reported.

Table 1 Enantioselective fluorination of ketones **10a** and **10b** with N–F reagents **4–9**



Entry	N–F* reagent	Base	Product	Yield (%)	ee (%)	Config.
1	**4**	NaHMDS	**11a**	53	76	(*S*)
2	**7**	LDA	**11a**	67	74	(*S*)
3	**9**	LHMDS	**11a**	65	70	(*S*)
4	**8**	LHMDS	**11a**	79	62	(*R*)
5	**7**	LDA	**11b**	79	88	(*S*)
6	**5**	KHMDS	**11b**	53	48	—

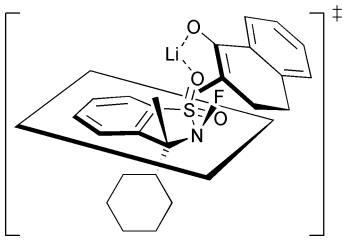
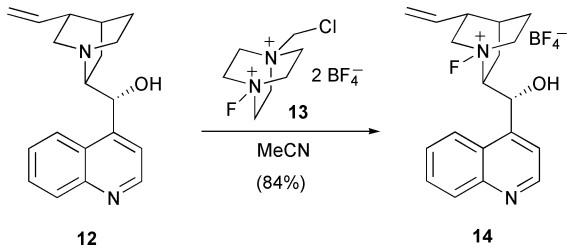


Fig. 1 Proposed rationale for the stereochemical outcome in the fluorination of **Li-11a** and **Li-11b**.

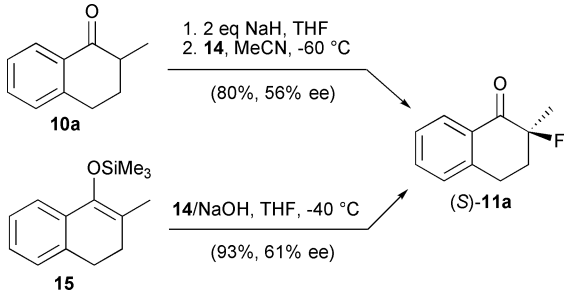
A major development in the area of asymmetric fluorination was the introduction of quaternary *N*-fluoro ammonium salts based on cinchona alkaloids (CA) as electrophilic fluorinating agents which was independently reported by the groups of Cahard and Takeuchi. These charged [N–F]$^+$ reagents have several advantages over N–F reagents **4–9**. Firstly, cinchona alkaloids are commercially available in both pseudo-enantiomeric forms and have a record as efficient chiral auxiliaries. Secondly, based on studies by Banks and Syvret,[13] the quinuclidine moiety can be fluorinated under mild conditions *via* fluorine-transfer from commercially available fluorinating agents (see below). Finally, charged [N–F]$^+$ reagents are more reactive so that more substrate classes and weak nucleophiles such as silyl enol ethers can be fluorinated. The latter was demonstrated by Cahard with *N*-fluorocinchonidinium tetrafluoroborate **14** which was isolated upon reaction of cinchonidine **12** with F-TEDA[14] (**13**, also referred to as Selectfluor) in acetonitrile in 84% yield (Scheme 2).[15]



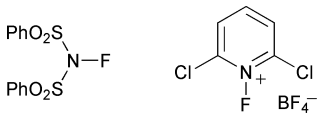
Scheme 2

N–F salt **14** was shown to fluorinate both the sodium enolate of **10a**, as well as silyl enol ether **15** to afford 2-fluoro-tetralone, (*S*)-**11a**, in high yield and in comparable enantioselectivity (Scheme 3). In the latter case, it was found that the addition of sodium hydroxide had a beneficial effect on both reactivity and selectivity. In a related study, Cahard demonstrated that not only F-TEDA was capable of fluorine-transfer to cinchona alkaloids but also the less expensive reagent NFSI, **16** (*N*-fluorobenzenesulfonimide) and the fluoropyridinium salt **17** which possesses a higher active-fluorine contents (3.94 mmol g^{-1}).[16] Moreover, it was shown that the selectivities obtained were comparable to those obtained using [N–F]$^+$ CA's generated from F-TEDA.

Takeuchi, Shibata and co-workers disclosed a detailed study on the use of *in situ* generated cinchona alkaloid N–F reagents.[17,18] These could be reacted directly, among others, with various β-ketoesters, α-cyanoesters and silyl enol ethers to furnish the

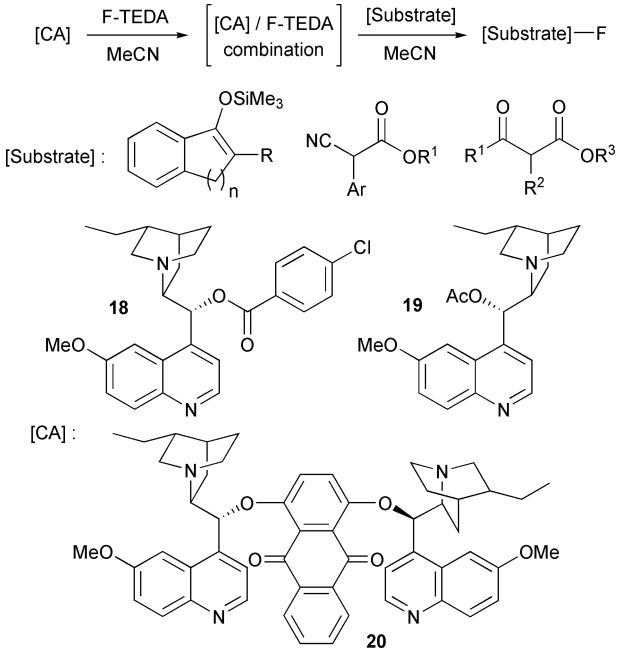


Scheme 3



16 **17**

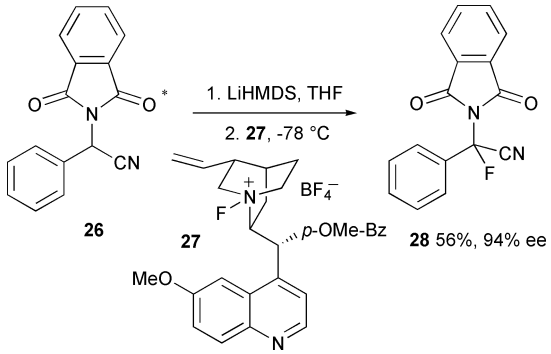
corresponding α-fluorinated products in excellent yields, making this procedure practical and easy to use for electrophilic enantioselective fluorinations (Scheme 4).



Scheme 4

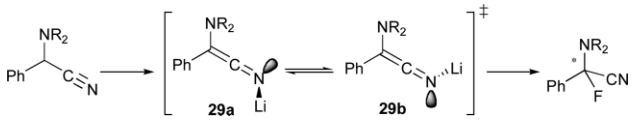
$[N–F]^+$ reagents were generally prepared by the reaction of CA's with F-TEDA in MeCN solution prior to the addition of a substrate. This allowed rapid screening of many CA derivatives, enabling an efficient and fast optimisation of reaction conditions for a given substrate. Illustrated below is a selection of fluorinated compounds that gave the highest enantioselectivities obtained in these studies utilising $[N–F]^+$ reagents generated *in situ* from dihydroquinine 4-chlorobenzoate (DHQB) **18**, dihydroquinidine acetate (DHQDA) **19**, and bis-CA [$(DHQ)_2AQN$] **20** (Chart 2). Of special interest are fluoro-compounds **22** and **25** which were synthesised for the first time *via* an enantioselective approach. α-Cyano-α-fluoro-aryl acetates such as (*S*)-**22** are efficient derivatising agents for the determination of the absolute configuration of chiral non-racemic secondary alcohols.[19] 3-Fluorooxindoles such as **25** are potential mimics of both the corresponding oxindoles and 3-hydroxyoxindoles that are often found as metabolites of indoles.[20]

Fluorinated amino acids and peptides have been the focus of many studies in recent years.[21] However, the enantioselective synthesis of α-fluoro-α-amino acid derivatives remains an unsolved challenge.[22] Cahard and co-workers recently described the first enantioselective α-fluorination of α-amino acid precursors. This was achieved *via* a deprotonation/fluorination sequence of amino-protected phenylglycine esters and phenylglycinonitriles using CA based $[N–F]^+$ reagents.[23] Indeed, a variety of such reagents, readily accessible upon the esterification of the alkaloid hydroxy group, were screened. Generally, amino-protected phenylglycine esters gave lower ee's than the corresponding phenylglycinonitriles. Utilising quinine **27**, *N*-phthaloylphenylglycinonitrile **26** could be fluorinated to give product **28** in 56% yield and in very high 94% ee (Scheme 5).



Scheme 5

The proposed rational for the high enantioselectivity is the formation of an axially chiral enantiomeric pair of metalated ketenimines **29a** and **29b** which rapidly interconvert even at low temperature (Scheme 6). The enantiomerically enriched fluorinated product is then obtained from a kinetic dynamic resolution of the two enantiomers.



Scheme 6

Limitations encountered with the use of *N*-fluoroalkaloid salts are usually the low temperature required for high enantioselectivites, as well as a limited choice of solvents, most commonly MeCN. Moreover, possible recovery of the cinchona alkaloid would enhance the versatility of reagent-controlled enantioselective electrophilic fluorination even further. An approach to this end was described by Cahard and co-workers in which fluorinations where performed in ionic liquids (IL).[24] It was demonstrated in this study that, for example, the reaction of silyl enol ether **30** with quinine derivative 1-Napht-**32** (*N*-fluoro-2-naphthoyl-quininium tetrafluoroborate) in IL **31** at 0 °C produced the corresponding 2-fluoro-1-indanone **21** in 93% yield and in an ee of 86%. In comparison, the fluorination in MeCN at −40 °C proceeded to give the product in 75% ee. It was further demonstrated that the CA based $[N–F]^+$ reagents could be prepared *in situ* in IL and that, after the reaction, the immobilised CA could be "reloaded" by F-TEDA or NFSI and reused without any loss in selectivity.

The utility of the enantioselective fluorination with CA based $[N–F]^+$ reagents in the synthesis of medicinally important targets

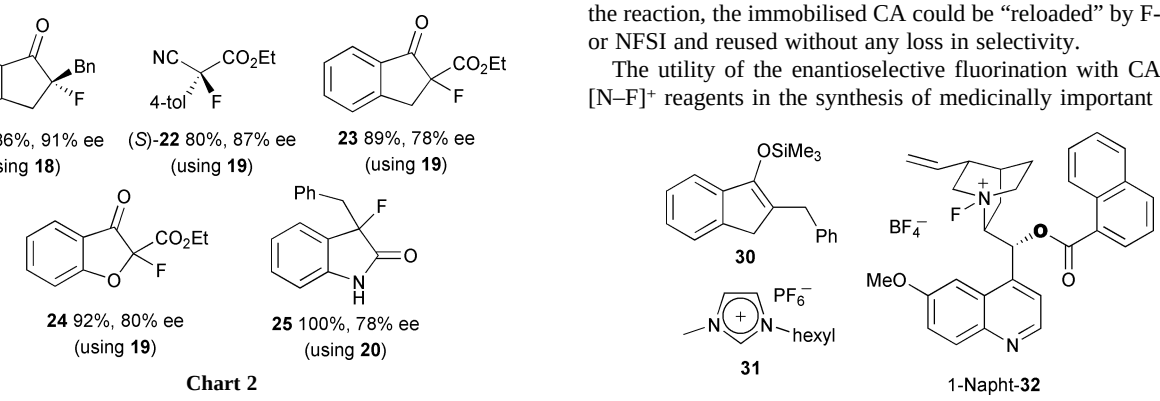
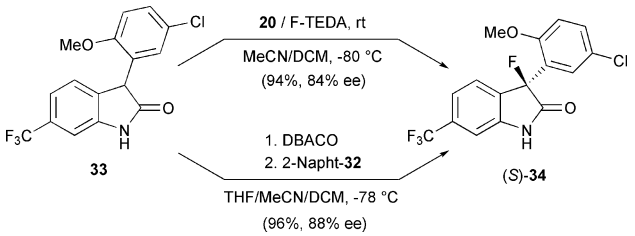


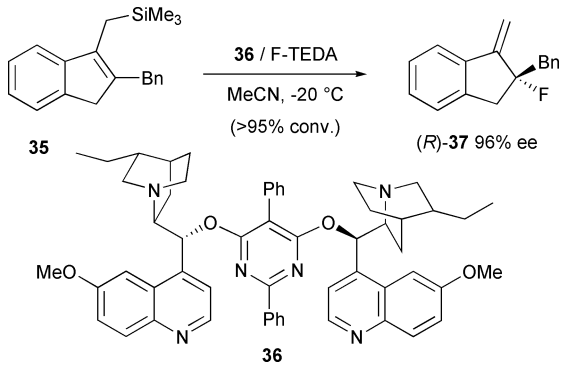
Chart 2

was demonstrated very recently by Shibata and Cahard who disclosed independently the first enantioselective synthesis of BMS-204352 (MaxiPost) (*S*)-**34**.[25,26] This fluoroxindole is currently being assessed worldwide in phase III clinical trials for the treatment of acute ischemic stroke. Both groups described a direct enantioselective electrophilic fluorination to (*S*)-**34**, starting from the parent oxindole **33** (Scheme 7). Shibata employed an *in situ* prepared [N–F]$^+$ reagent from bis-alkaloid **20** and F-TEDA and obtained (*S*)-**34** in excellent yield and in 84% ee, whereas Cahard utilised the isolated [N–F]$^+$ salt 2-Napht-**32** and DABCO (1,4-diaza-bicyclo[2,2,2]octane) as the base to afford (*S*)-**34** in very high 96% yield and in a slightly improved ee of 88%. In both cases a single recrystallisation resulted in an increased enantiopurity of > 99%.



Scheme 7

Most of the strategies described above are aimed at a general and efficient enantioselective synthesis of α-fluorocarbonyl compounds. Gouverneur and co-workers reported recently on an approach for the regio- and enantioselective synthesis of allylic fluorides by electrophilic fluorodesilylation of allyl silanes.[27] Using the protocol developed by Shibata *et al*.,[17] allyl silane **35** was reacted at −20 °C with an *in situ* prepared [N–F]$^+$ reagent derived from the bis-alkaloid **36** [$(DHQ)_2PYR$)] to produce the allylic fluoride (*R*)-**37** with complete conversion and with an excellent enantioselectivity of 96% (Scheme 8).[28] Additionally, the influence of an increased steric bulk of the silyl group was investigated and it was found that it had a beneficial effect on the enantioselectivity.



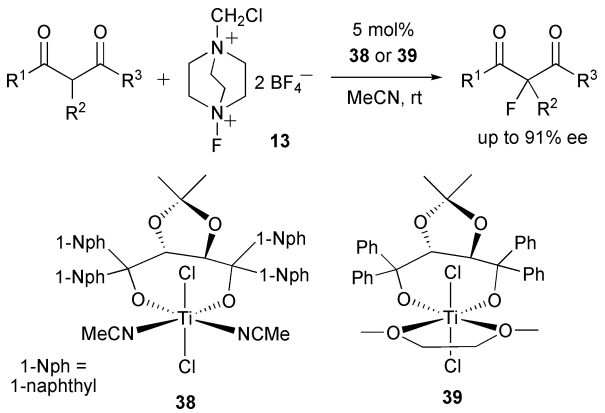
Scheme 8

Catalytic enantioselective electrophilic fluorination

As illustrated in the previous section, many innovative solutions to stoichiometric enantioselective fluorination reactions are now at hand. However, efficient catalytic processes remain a very desirable objective, and it is somewhat surprising that it has attracted the attention of only a few research groups in most recent years.

Electrophilic fluorination of 1,3-dicarbonyl compounds and in particular β-ketoesters has been the focus of numerous studies.[29] These reactions proceed usually *via* the corresponding enol (or enolate) form. Furthermore, it has been shown that the addition of substoichiometric amounts of a Lewis acid (LA) such as zinc chloride significantly accelerates product formation which can be attributed to the triggering of the enolisation process by the LA.[29a] This observation, already reported in 1990, constituted the very key of our working hypothesis, in view of developing a catalytic process. Thus, we envisaged that the use of a chiral non-racemic transition-metal Lewis acid to promote the enolisation process would enable to produce optically active α-fluorinated 1,3-dicarbonyl compounds, as long as the fluorination step occurs on the coordinated enol (or enolate). This concept was first realised four years ago in our laboratory.[30]

A screening of commonly used LA's quickly indicated that titanium LA's are the catalysts of choice for the fluorination of β-ketoesters using F-TEDA. Among the successful LA's tested, Ti(diolato) complexes proved to be efficient in catalysing this reaction. Optimisation studies and screening of chiral non-racemic Ti(diolato) complexes revealed that Ti(TADDOLato)[31] complexes such as **38** and **39** are the best performing catalysts in terms of yields and enantioselectivity (Scheme 9).[32] These complexes could be isolated as air stable crystalline solids and gave more reliable results than those obtained using catalysts generated *in situ*.[33] Thus, a variety of 1,3-dicarbonyl compounds and derivatives thereof could be fluorinated in moderate to high yields and with enantiomeric excesses up to 91%.



Scheme 9

Typical and convenient reaction conditions are as follows: 5 mol% of **38** or **39** as catalysts in MeCN, room temperature, F-TEDA as the fluorinating agent, and reaction times ranging from a few minutes to a few hours. A selection of representative examples is illustrated in Chart 3.[34]

Using $TiCl_2$[(*R*,*R*)-TADDOLato] complex **38**, α-fluoro-β-ketoesters **40–44** were obtained in a confirmed (*S*)-configuration. Our mechanistic working hypothesis for the observed selectivity is depicted in Scheme 10 and Fig. 2. Coordination of the starting

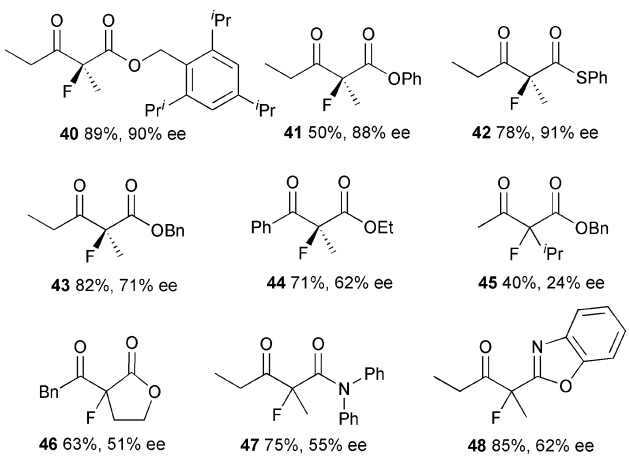
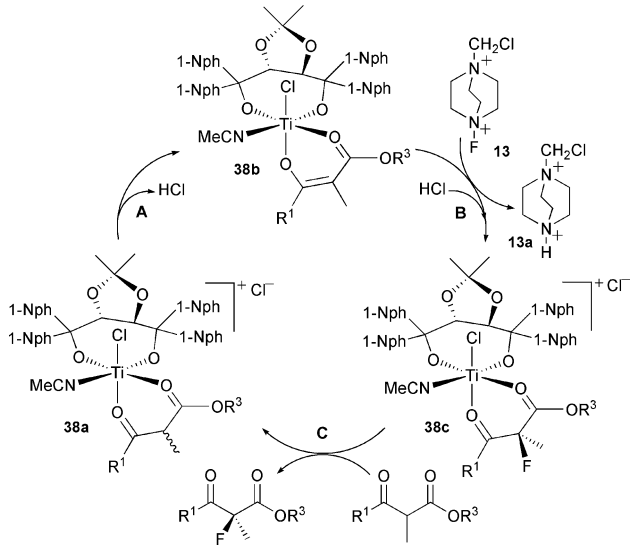


Chart 3



Scheme 10

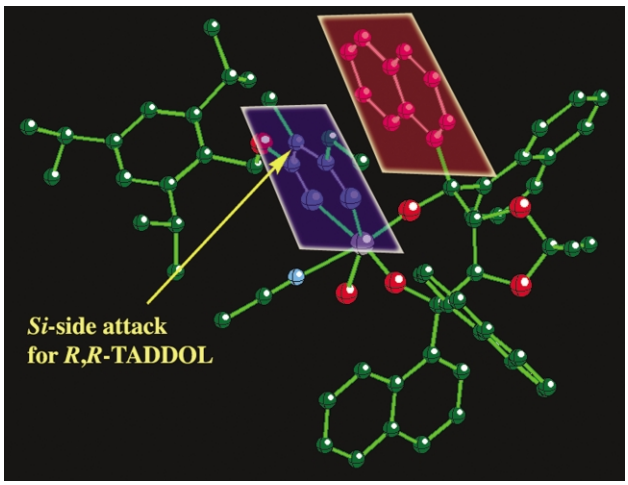


Fig. 2 QM/MM structure of the intermediate involved in the fluorination leading to compound **40** (Chart 3). The almost perfectly parallel arrangement of one of the two face-on 1-naphthyl groups of the ligand to the coordinated β-ketoesterenolate is highlighted by the red and blue planes.

material to **38** requires the concomitant dissociation of a MeCN molecule and a chloro ligand leading to the cationic Ti-intermediate **38a** that undergoes deprotonation to the neutral Ti-enolato complex **38b** which is the key intermediate in the catalytic cycle (step **A**).

There are eight possible diastereoisomeric forms of this complex and the one with the Ti configuration as shown in Fig. 2 is the most stable, according to an extensive QM/MM first-principle molecular dynamics study.[35] This diastereoisomer reacts with F-TEDA exclusively at the *si*-face of the coordinated enolate due to the shielding of the *re*-face by one of the two face-on oriented 1-naphthyl groups, thus explaining the origin of enantioselection in absolute terms (step **B**, Fig. 2). Our computational studies (molecular dynamics at finite temperature and including simulation of a solvent cage of *ca*. 500 MeCN molecules) indicate that the very fluorine transfer step occurs *via* a single-electron-transfer (SET). Fundamental frontier-orbital requirements for SET to promote N–F bond cleavage and C–F bond formation are met. The HOMO of the Ti(β-ketoesterenolato) intermediate corresponds to the HOMO of the enolate, implying that one electron is removed from the coordinated deprotonated substrate, thus functioning as a reducing agent. The $[N–F]^+$ is the electron-acceptor whose LUMO has the character of σ* orbital for the N–F bond (Fig. 3). SET generates a singlet diradical — correspondingly the reaction mixture is EPR-

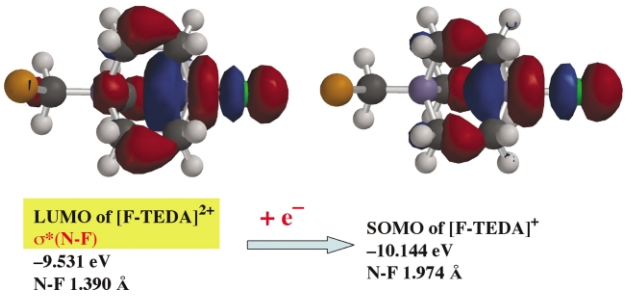
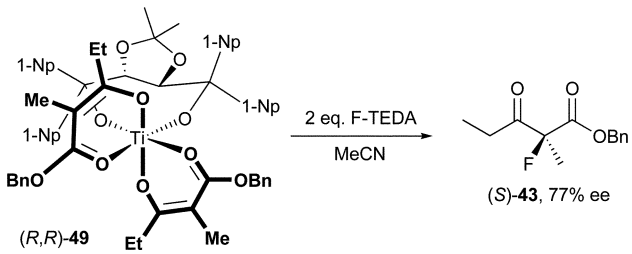


Fig. 3 LUMO of F-TEDA and SOMO of its reduced form at the B3LYP/6-31G* level.

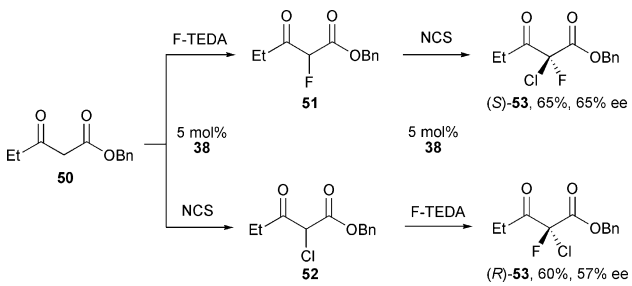
silent — in which the N–F bond is significantly lengthened. C–F bond formation is the consequence of a radical recombination during which the neutral F atom is transferred from nitrogen to the central carbon atom of the β-ketoesterenolate.

Attempts to prepare mono-enolato complex **38b** by the reaction of **38** with sodium enolates resulted only in the formation of a diastereomeric mixture of bis-enolato complexes such as **49**, although mono-1,3-diketonato adducts of Ti(TADDOLato) complexes of the same type are known.[36] Reaction of isolated (*R*,*R*)-**49** with F-TEDA gave the fluorinated product (*S*)-**43** in slightly higher enantioselectivity than the corresponding reaction carried out *in situ* (Scheme 11).



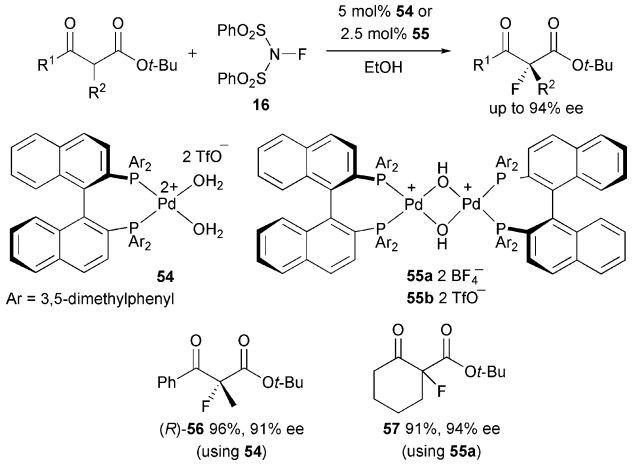
Scheme 11

The methodology described above was extended to the enantioselective synthesis of α-chloro-α-fluoro-β-ketoesters employing a one pot heterodihalogenation procedure catalysed by titanium complex (*R*,*R*)-**38** (Scheme 12, for electrophilic chlorination reactions, see below).[37] The stereochemical outcome is determined in the second halogenation step and, depending on the desired product absolute stereochemistry, the sequence of halogenation can be altered to afford either enantiomers of **53** with comparable yields and enantioselectivities, while utilizing the same enantiomeric form of the catalyst.



Scheme 12

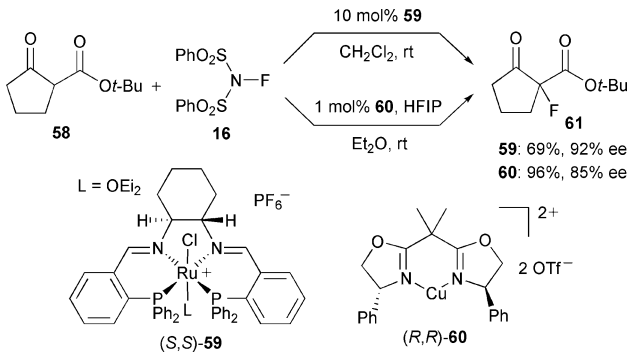
Inspired by our work with Ti, Sodeoka and co-workers recently reported on an efficient catalytic system for the enantioselective electrophilic fluorination based on late transition metal LA's. Dicationic bis-aqua palladium complex **54** or related dinuclear cationic bis-hydroxy palladium complex **55** were shown to be capable of catalysing the fluorination of several cyclic and acyclic β-ketoesters in high yields (up to 96%) and enantioselectivities in excess of 90% (Scheme 13).[38]



Scheme 13

Reactions were carried out in polar solvents such as EtOH with 5 mol% of **54** or with 2.5 mol% of **55** using NFSI as the fluorinating agent. Employing complex **54**, α-fluoro-β-ketoester (*R*)-**56** was obtained in 96% yield and in 91% ee on a one-gram scale. Lowering the reaction temperature to −10 °C had a beneficial effect on the enantioselecivity so that the fluorinated 2-oxo-cyclohexanecarboxylate derivative **57** was obtained in 94% ee using catalyst **55a**. As for the titanium case discussed above, the fluorination in this system is proposed to proceed *via* an enolato-palladium complex.[39] The same group reported on the immobilisation and reuse of catalyst **55b** in IL which represents an attractive alternative to the system working in more common solvents. Here, excellent results could be obtained in terms of the reproducibility of the ee's even after 10 catalytic cycles. For instance, the fluorination of **56** could be carried out with immobilised **55b** in [hmim][BF_4] (**31**) in 93% yield and in 92% ee. The recycled catalyst still gave a yield of 67% and an ee of 91% after 10 catalytic cycles.[40]

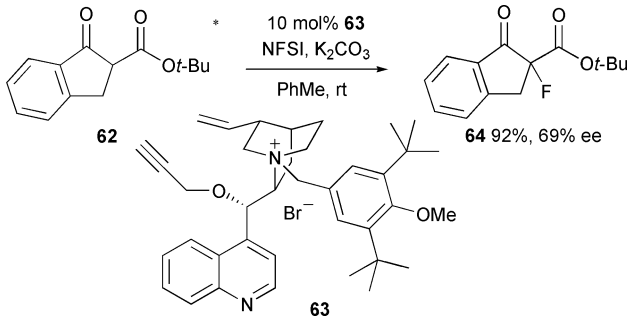
Sodeoka's findings with Pd demonstrate that "soft" late transition metal LA's are suitable catalysts for electrophilic fluorination. Preliminary results from our laboratory show that the cationic Ru(II) complex (*S,S*)-**59** — previously applied by Mezzetti and co-workers in the catalytic enantioselective cyclopropanation of alkenes[41] — is a viable catalyst for the enantioselective fluorination of β-ketoesters.[42] Thus, using 10 mol% of (*S,S*)-**59** and NFSI, **16**, as the fluorinating agent, β-ketoester **58** was converted to the corresponding *tert*-butyl 2-fluoro-2-oxo-cyclopentanecarboxylate **61** in 69% yield and with an excellent ee of 92%, matching the best result obtained by Sodeoka for this substrate (Scheme 14).



Scheme 14

Very recently, Ma and Cahard successfully exploited enantiopure bisoxazoline-copper (II) complexes as catalysts in the enantioselective electrophilic fluorination of β-ketoesters.[43] Using NFSI as the fluorinating agent and diethyl ether or toluene as the solvent, several metal triflate salts and BOX ligands were screened in this study and it was found that all catalysed the fluorination of β-ketoester **59**. Copper(II) and zinc(II) triflate in combination with (*R,R*)-Ph-BOX proved to be most efficient and gave the fluorinated product **61** in an enantioselectivity of 74%. In the case of copper complex (*R,R*)-**60**, catalyst loading could be decreased to 0.1 mol% without a significant drop in enantioselectivity. The highest enantioselectivity of 85% in this study along with an excellent yield of 96% was obtained employing 1 mol% of complex (*R,R*)-**60** with HFIP (hexafluoro-*iso*-propanol) as an additive (Scheme 14).

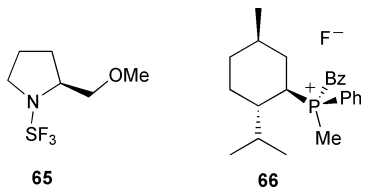
An organo-catalytic approach to electrophilic enantioselective fluorination has been reported by Kim and Park which is based on enantioselective phase-transfer catalysis promoted by quaternary ammonium cinchona alkaloid salts.[44] In this study, indanone carboxylate **62** was treated with NFSI in the presence of 10 mol% of ammonium salt **63** and potassium carbonate at room temperature in toluene to afford fluoro-carboxylate **64** in 92% yield and 69 % ee (Scheme 15).



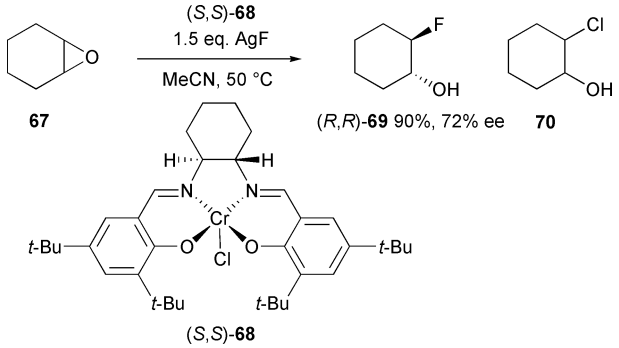
Scheme 15

Stoichiometric and catalytic enantioselective nucleophilic fluorination

A first attempt to achieve an enantioselective nucleophilic fluorination is dating back to 1989.[45] In this study, fluorodehydroxylation of racemic ethyl (2-trimethylsiloxy)propanoate using the chiral, enantiopure DAST (diethylaminosulfur trifluoride) analogue **65** under kinetic resolution conditions resulted in an enantiomeric excess of 16% for the produced ethyl 2-fluoropropanoate. More recently, a paper appeared describing a similar approach using enantiopure phosphonium salt **66** for the fluorination of 2-bromopropiophenone which gave enantiomerically enriched 2-fluoropropiophenone.[46]



There are two reports on attempts to develop a catalytic enantioselective fluorination reaction using a nucleophilic fluorine source. In these studies, chiral LA-catalysed F^--attack on *meso*-epoxides facilitate the asymmetric ring-opening reaction (ARO) thereby forming non-racemic fluorohydrins.[47,48] Several enantiopure LA's, together with various F^- sources, were screened using cyclohexane oxide **67** as the test substrate. Jacobsen's (salen)chromium chloride complex **68** promoted the ring opening of **67** with silver fluoride. However, attempts to reach satisfactory yields and enantioselectivities failed when **68** was used in catalytic amounts. In addition, chlorohydrin **70** was often formed as a side product when complex **68** was used in catalytic or substoichiometric amounts. Employing a stoichiometric amount of (*S,S*)-**68** and 1.5 eq. of silver fluoride in MeCN gave fluorohydrin (*R,R*)-**69** in 90% isolated yield and respectable 72% ee (Scheme 16).

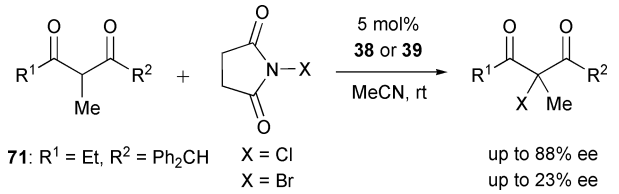


Scheme 16

Enantioselective chlorination, bromination and iodination reactions

Catalytic enantioselective electrophilic halogenation reactions

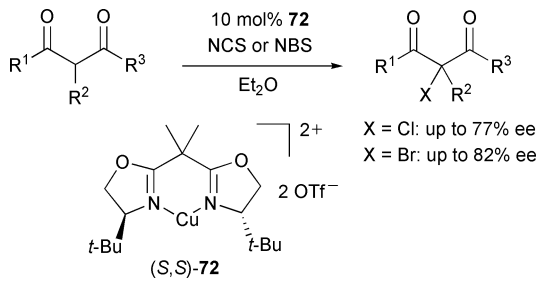
Initial enantioselective electrophilic chlorination and bromination reactions of β-ketoesters catalysed by Ti(TADDOLato) complexes, in analogy to fluorinations, were reported from this laboratory.[49] Halogenations are carried out at room temperature with 5 mol% of (*R*,*R*)-**38** or (*R*,*R*)-**39** using NCS (*N*-chlorosuccinimide) and NBS (*N*-bromosuccinimide) as halogenating agents (Scheme 17).



Scheme 17

In the case of chlorination, the enantioselectivities obtained are comparable to those afforded by the analogous fluorination, with the best example being β-ketoester **71**. Employing (*R*,*R*)-**38** as the catalyst, the α-chlorinated product is isolated with a (*S*)-configuration in 94% yield and 88% ee. Enantioselectivities for brominations, however, were substantially lower so that using (*R*,*R*)-**39** bromination of **71** produced the corresponding α-brominated β-ketoester in 90% yield and in only 23% ee. These significant differences in selectivity may be due to the larger extent of the uncatalysed reaction in the case of the more reactive NBS. However, for the catalytic reaction we put forward similar mechanistic considerations as for the corresponding fluorination, in particular in view of SET processes involving NCS and NBS.

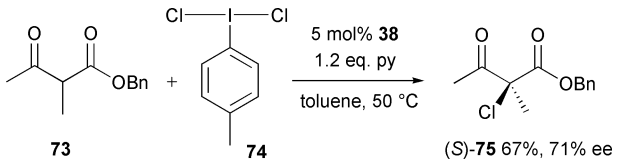
In a similar approach and in analogy to the fluorinations described above, Jørgensen and co-workers disclosed very recently the chlorination and bromination of cyclic and acyclic β-ketoesters exploiting bisoxazoline-copper(II) complexes as catalysts, as shown in Scheme 18.[50] In this study, α-bromo- and α-chloro-β-ketoesters were obtained with excellent yields and with good enantioselectivities of up to 77% (R^1 = Me, R^2 = Me, R^1 = Et) for the chlorination and up to 82% (R^1 = R^2 = $(CH_2)_4$, R^1 = Et) for the bromination using 10 mol% of complex **72** with NCS and NBS



Scheme 18

as the halogenating agents. The corresponding chlorination of a β-diketone with the same catalytic system gave low enantioselectivity. The absolute configuration of the products was assigned as (*S*) which could be accounted for by an X-ray crystal structure determination of a Cu(II)(enolato) complex where the face-selectivity of the halogenation was apparent.

Hypervalent iodine compounds are very useful reagents in synthesis. Application of these reagents in asymmetric catalysis has, however, been largely neglected in spite of the fact that many transformations, otherwise difficult to accomplish, proceed with these highly reactive compounds under mild and selective reaction conditions. We have recently been successful in utilising readily available dichloroiodotoluene (**74**) in the enantioselective electrophilic chlorination of β-ketoesters using our Ti(TADDOLato) complex (*R*,*R*)-**38**.[51] The illustrated β-ketoester **73**, for instance, could be chlorinated in toluene at 50 °C to give (*S*)-**75** in 67% yield and in 71% ee (Scheme 19). This reaction showed a significant temperature dependence so that carrying out the reaction at room temperature resulted in a lower enantioselecivity of 45%. Furthermore, fast addition of **74** gave the product in substantially lower ee's. In a related study, we have succeeded, to the best of our knowledge for the first time, in employing chlorine in an enantioselective α-chlorination of enolisable substrates. Under identical conditions to those illustrated in Scheme 19, (*S*)-**75** was obtained in unoptimised 62% yield and in low but promising 30% ee.[50] We regard this as being an important result, showing that enantioselective reactions are possible even when utilising the halogens in their elemental form. Will this be possible also with fluorine? The near future shall tell.



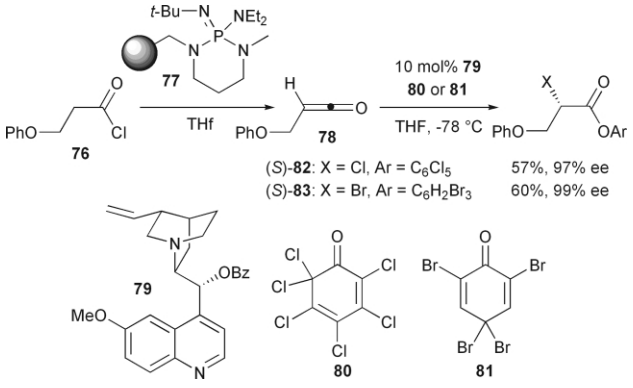
Scheme 19

A highly attractive approach to the catalytic enantioselective electrophilic halogenation is the tandem halogenation/esterification process of acyl halides catalysed by catalytic amounts of cinchona alkaloid leading to highly enantiomerically enriched versatile α-haloesters, as reported by Lectka and co-workers.[52] These reactions proceed *via* an *in situ* generated ketene which is attacked by the cinchona alkaloid thereby generating a chiral zwitterionic enolate. This enolate reacts with the electrophilic halogenating agent, with concomitant release of the corresponding phenolate anions, to the products. For example, treatment of acyl chloride **76** with the basic resin BEMP **77**, a triaminophosphonamide imine bound to a polymeric support, results in the formation of ketene **78** (Scheme 20). Treatment of this ketene with 10 mol% of benzoylquinine **79** and the perhaloquinone-derived halogenating agents **80** and **81**, α-chloroester (*S*)-**82** and α-bromoester (*S*)-**83** are obtained in moderate yields, but in very high enantioselectivties. In a subsequent study, Lectka presented a modified procedure in which the basic resin BEMP **77** is replaced by inexpensive potassium carbonate.[53]

Catalytic enantioselective nucleophilic halogenation reactions

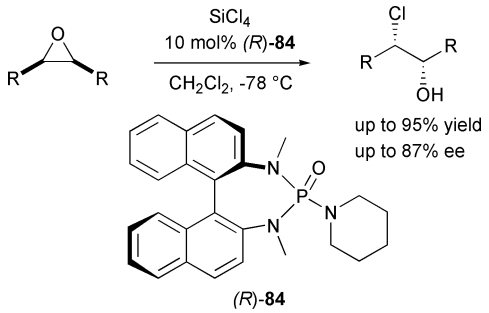
The enantioselective desymmetrisation of *meso*-epoxides by ring opening with halide anions, affording the corresponding vicinal halohydrins, is a particularly attractive strategy for enantioselective halogenations. Early successful work in this area, which will not be reviewed here, has relied upon the stoichiometric use of chiral non-racemic LA halides such as *B*-halodiisopinocampheylboranes.[54]

The catalytic ARO of epoxides with halides was pioneered by Denmark utilising the concept of chiral Lewis base catalysis.[55,56] In these studies, various *meso*-epoxides were converted in high yields



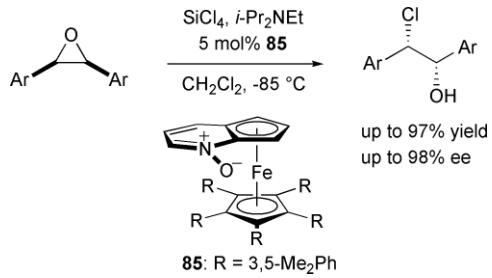
Scheme 20

into vicinal chlorohydrins with silicon tetrachloride as the chloride source and 10 mol% of enantiopure phosphoramide (*S*)-**84** as the catalyst (Scheme 21). The best enantioselectivity was obtained with *cis*-stilbene oxide affording (*S*,*S*)-2-chloro-1,2-diphenyl-ethanol with 87% ee, whereas cyclopentane oxide gave almost racemic chlorohydrin, and cyclohexane oxide the (*S*,*S*)-product in 52% ee.



Scheme 21

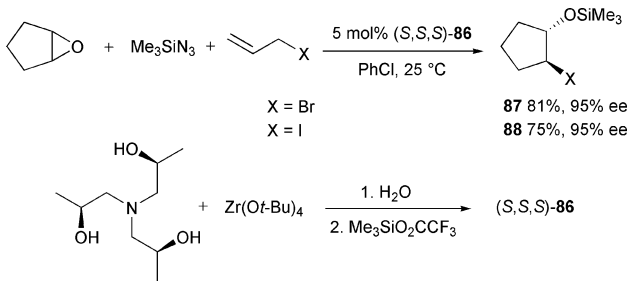
In a related approach Fu and co-workers made use of the planar chiral pyridine *N*-oxide **85** to catalyse the opening of *meso*-epoxides with $SiCl_4$.[57] Here again, *cis*-stilbene oxide analogues performed best, giving in the case of Ar = 4-(trifluoromethyl)phenyl a yield of 93% with a very high enantioselectivity of 98% using 5 mol% of **85** (Scheme 22). The addition of Hünig's base was necessary in order to minimise HCl formation from the hydrolysis of $SiCl_4$, which is proposed to promote non-stereoselective ring opening as a background reaction.



Scheme 22

Strategies based on enantioselective desymmetrisation of *meso*-epoxides with halide sources promoted by chiral transition metal catalyst have also been developed. Jacobsen reported that ARO of cyclohexane oxide with a chloride source using Cr(salen) complex **67**, a very efficient catalyst for the desymmetrisation of *meso*-epoxides using $TMSN_3$, resulted in moderate ee of < 50% for the opened product.[58]

A rather interesting approach to enantiomerically enriched bromo- and iodohydrins through the desymmetrisation of *meso*-epoxides catalysed by pre-catalyst (*S*,*S*,*S*)-**86** was described by Nugent.[59] Complex (*S*,*S*,*S*)-**86** generates an effective catalyst for the enantioselective addition of azide to cyclohexane oxide which is believed to operate *via* a discrete zirconium azide intermediate.[60] This system exploits the fact that the azide transfer is relatively slow in comparison to nucleophilic displacement by halide sources which are in this case allyl iodide and allyl bromide. Using 5 mol% of (*S*,*S*,*S*)-**86** under the reaction conditions illustrated in Scheme 23, trimethylsilylbromohydrin and the corresponding iodohydrin could be obtained in 81% and 75% yield, respectively, and in an excellent enantioselectivity of 95%. This procedure allows the preparation of bromohydrins which are very versatile chiral building blocks.



Scheme 23

Conclusion and outlook

The development of useful enantioselective halogenation reactions has for long time been in great demand due to the potentially rich branching chemistry of the enantiomerically enriched products they deliver. Many innovative solutions have been developed over the past five years, most notably, catalytic approaches such as enantioselective electrophilic halogenation reactions of enolisable substrates and the desymmetrisation of *meso*-epoxides by halide sources. It is only a matter of time until the versatile multifunctional halogenated building blocks accessible with these methods will find application in the synthesis of complex chiral molecules difficult to access otherwise.

This short article illustrates how progresses in the area of enantioselective organohalogen chemistry are the result of the concerted effort of many researchers in the various fields connected to synthetic chemistry. Best example for this is the advance in electrophilic fluorination which would have not been possible without the invention of mild and selective fluorinating agents such as F-TEDA. We are very confident that homogeneous catalysis shall provide new solutions in the future.

Organometallic chemists have been busy demonstrating how transition metal complexes are able to selectively *split* the C–F bond, thus generating fluoro complexes. However, that the latter species might be involved in stereoselective C–F bond *forming* processes, such as fluoro complexes in nucleophilic fluorinations, has been the topic of only very rare reports so far.[61]

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