Catalytic asymmetric fluorinations

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The appearance of structurally diverse fluorinating reagents displaying a large spectrum of reactivity has been critical to the development of the catalytic asymmetric fluorination processes known to date. In this article, we discuss how this area of research emerged and which strategies have allowed for the successful development of both nucleophilic and electrophilic catalytic enantioselective fluorinations. We also present the fundamental understanding of catalytic activity and enantioselectivity for the most efficient processes and highlight the first synthetic application with the preparation of a complex fluorinated target.

Introduction

Chemists have developed numerous catalytic asymmetric processes that transform prochiral substrates into chiral products with impressive levels of enantioselectivity. Enzymes,[1] transition metal complexes[2] or small organic compounds[3] are commonly used as catalytic species to mediate a wide variety of fundamental reactions such as hydrogenation, isomerisation, epoxidation, dihydroxylation, cyclopropanations and aziridination of alkenes, carbonyl reductions or additions, aldol condensations or pericyclic processes.[4] Catalytic asymmetric halogenations have also attracted considerable attention, as the resulting products have long been valued as useful synthetic intermediates.[5] These reactions allow for the preparation of various halogenated intermediates or products not readily available from natural sources. In this respect, synthetic routes to enantiopure fluorinated compounds are highly valuable as naturally occurring fluorinated compounds are extremely rare, especially metabolites featuring the F-group on a stereogenic centre.[6] Owing to their unique properties, fluoro-organic compounds are eminently important in the agrochemical and pharmaceutical industry.[7] Chiral non-racemic compounds containing a stereogenic C–F centre have also appeared in liquid crystals.[8] Therefore it is not surprising that research in the field of synthetic fluorine chemistry is flourishing more than ever. To date, both transition metal complexes and organocatalysts have led to numerous successful enantioselective fluorinations. This article provides an overview of this exciting and rapidly growing field since

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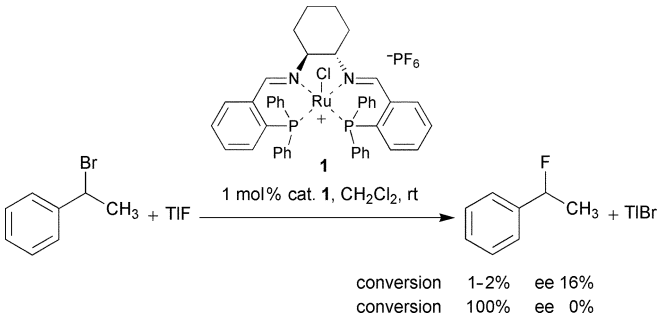
its outset in 2000 and highlights future challenges for the years to come.[9] The known catalytic asymmetric fluorinations reported in the literature fall broadly into two categories: processes based on the use of transition metal complexes, or on organocatalysts.

Asymmetric catalytic metal-mediated fluorinations

Two general strategies can be considered for the development of a catalytic asymmetric fluorination based on the use of metal complexes: the use of enantiopure metal–fluoro complexes as catalysts for nucleophilic fluorination reactions or, alternatively, the nucleophilic or electrophilic fluorination of substrates activated by non-racemic chiral Lewis acids. The first approach is probably the most challenging. Preliminary work in this direction has been carried out by Togni *et al.* who have reported the synthesis and reactivity of Ru(II) fluoro complexes (Scheme 1).[10,11] These complexes were found to be nucleophilic fluorinating reagents, efficiently undergoing halide metathesis allowing for the conversion of various allylic and benzylic bromides into the corresponding fluorides with concomitant formation of the Ru–bromo complex.[10] This metathesis process could be catalytic using a sub-stoichiometric amount of the ruthenium species **1** in combination with thallium fluoride, which acts as both the stoichiometric fluoride source and the halide scavenger.[11] However, only a very modest asymmetric induction (ee ≈ 16%) was measured at low conversion, for the fluorination of racemic 1-phenyl ethyl bromide with various non-racemic chiral Ru–F complexes. The observation that the enantioselectivity decayed toward 0% ee when the substrate was completely consumed, indicated that the enantiomeric excess measured at low conversion was likely the result of a kinetic resolution process. Although no catalytic enantioselective fluorination process emerged from this study, this preliminary work is encouraging as it suggests that metal–fluoride complexes are suitable fluorinating reagents and could therefore potentially lead to successful enantioselective catalytic fluorinations.

The second approach featuring the fluorination of substrates activated by chiral Lewis acids proved to be highly successful for the development of both *nucleophilic and electrophilic* catalytic enantioselective fluorinations, although most efforts focused on the use of electrophilic fluorinating reagents.

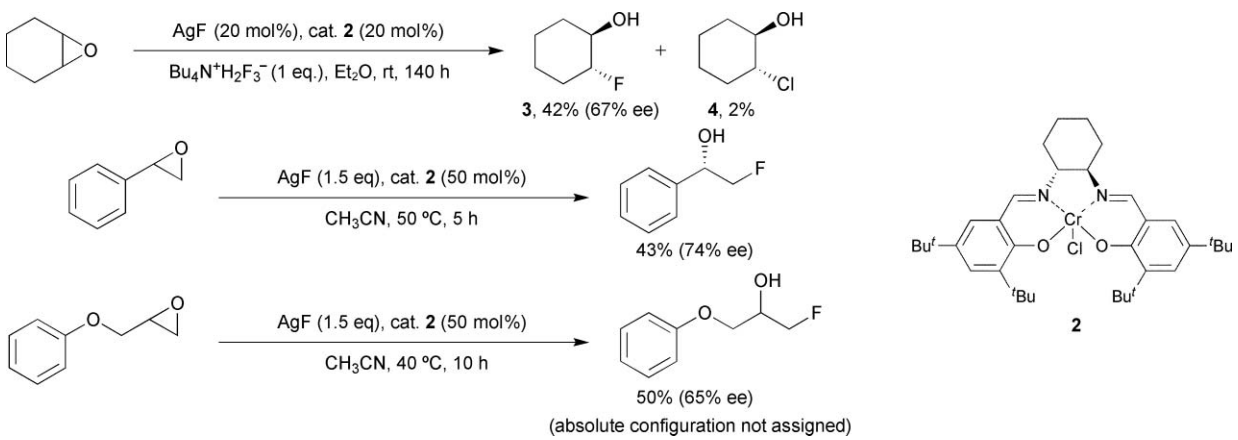


Scheme 1 Halide metathesis with Ru complex **1**.

Nucleophilic fluorination

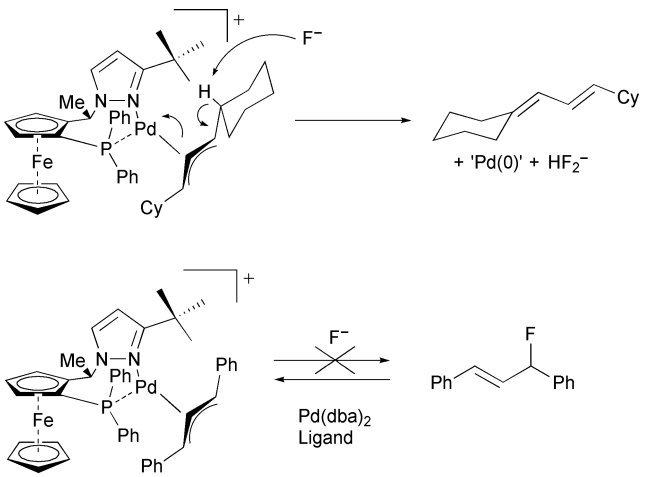
Catalytic enantioselective nucleophilic fluorinations are rare, with only few examples reported in the literature. Haufe and co-workers have examined the enantioselective desymmetrisation of *meso*-epoxides upon ring-opening with nucleophilic fluorinating reagents. Initial attempts with chiral Eu^{III} complexes led to very low asymmetric induction.[12] Cyclohexene oxide was, however, desymmetrised successfully with a variety of fluoride sources in presence of Jacobsen's Cr-Salen complex **2** as the catalytic chiral Lewis acid. A stoichiometric amount of $Bu_4N^+H_2F_3^-$ combined with 20 mol% of catalyst **2** and 20 mol% of silver fluoride afforded *anti*-fluorocyclohexanol (**3**) in 67% ee and 42% yield, together with traces of the undesired chlorohydrin **4**. Moderate enantioselectivities (44–74% ee) were obtained when AgF was the main fluorinating agent, but these desymmetrisations required stoichiometric or 50 mol% of the chromium complex **2**. The reaction was successfully applied to cyclopentene and cycloheptene oxides but failed with some other *meso* substrates. Racemic unsymmetrical epoxides, such as styrene oxide and phenyl glycidyl ether, reacted under similar conditions delivering enantioenriched fluorohydrins with 74 and 65% ee, respectively. The high level of enantiocontrol as well as diastereocontrol for these reactions suggested that an S_N2 process is likely to operate in the ring-opening process (Scheme 2).

In an unrelated study, the beneficial effect of fluoride additives on the enantioselective intermolecular hydroamination reaction



Scheme 2 Enantioselective nucleophilic fluorinations of epoxides catalysed by Cr(III) complex **2**.

catalyzed by Ir(I) complexes led to the question of whether or not fluoride could attack cationic Pd(II) π-allyl complexes.[13] If this reaction is possible, it can lead to the development of an enantioselective allylic fluorination process. Several experiments and theoretical studies revealed that no such reaction could be realized and that this process is highly endothermic.[11a,13,14] The addition of fluoride to cationic 1,3-dicyclohexyl Pd(II) π-allyl complexes led to products of elimination with the fluoride acting as a base and not as a nucleophile. It is noteworthy that 1,3-diphenyl allyl fluoride reacted in the presence of Pd(0) catalysts and underwent oxidative addition leading to the corresponding cationic Pd(II) π-allyl complex. These results suggest that the nucleophilic fluorination of η^3 Pd π-allyl complexes is not a viable transformation for the development of a catalytic enantioselective route to allylic fluorides (Scheme 3).

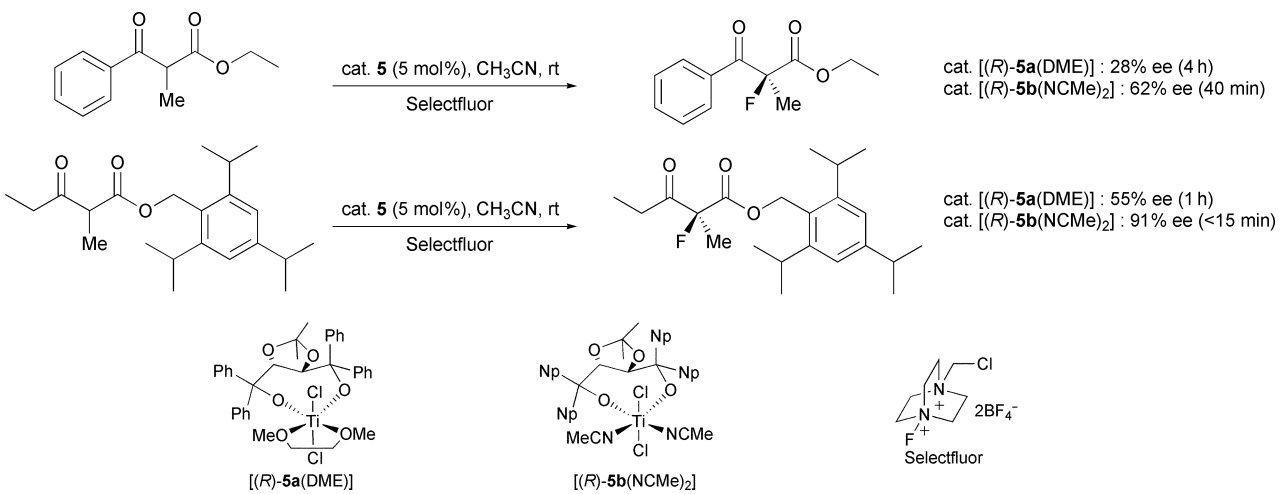


Scheme 3 Attempts towards Pd-mediated allylic fluorinations.

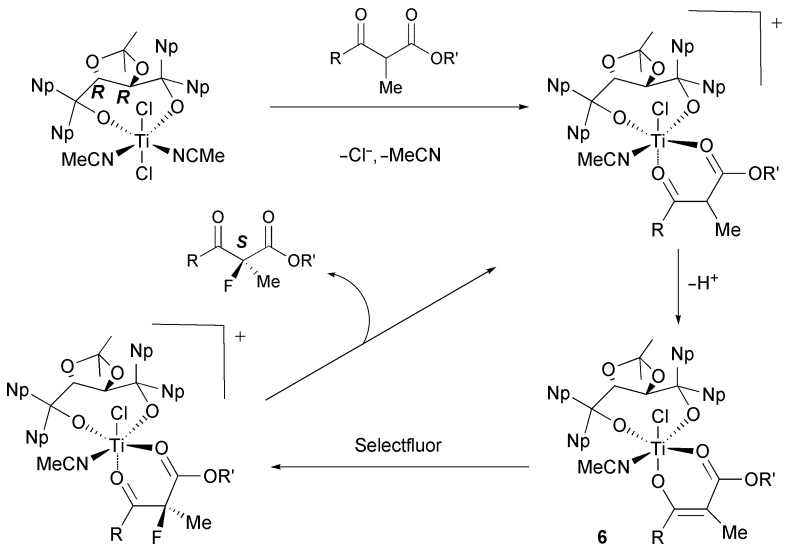
Electrophilic fluorination

With the emergence of electrophilic fluorinating agents of tuned reactivity, the fluorination of unactivated or activated carbonyl groups on the α-position became possible, and these advances prompted many groups to develop a catalytic asymmetric variant for this transformation. Studies in racemic series on the reactivity of 1,3-dicarbonyls in the presence of $[N–F]^+$ reagents demonstrated that the addition of sub-stoichoimetric amounts of a Lewis acid, such as zinc dichloride, facilitates enolisation and subsequent electrophilic fluorination.[15] With the aim of developing a catalytic enantioselective electrophilic fluorination of activated β-ketoesters, Togni and Hintermann screened a series of transition metal complexes and discovered that TADDOL-modified titanium complexes gave the best results with Selectfluor as the fluorinating agent.[16] A catalyst loading of 5 mol% of complex **5a** or **5b** was sufficient to fluorinate, at room temperature, branched β-ketoesters in high yields (80–95%) with enantiomeric excesses ranging from 62 to 91% (Scheme 4). The steric bulk of the catalytic species played a major role in the level of enantiocontrol. For all reactions, the presence of naphthyl (Np) groups instead of phenyl (Ph) groups on the catalyst increased the enantiomeric excess of the resulting fluorinated product. Similarly, the use of substrates with the ester group derived from a bulky alcohol was beneficial, as reflected by the higher ee of the corresponding fluorinated ketoesters. The approach is restricted to branched β-ketoesters, since the Ti-catalyst can induce enolisation of tertiary fluorinated α-carbon, leading to racemisation and formation of achiral α,α-difluorinated ketones.

Based on the experimental results, a mechanism has been proposed for the fluorination and verified by theoretical studies.[17] The bidentate β-ketoester, which in the absence of catalyst would react slowly with Selectfluor,[15b] coordinates to the metal complex and subsequently undergoes fast enolisation, with concomitant elimination of a chloride ligand from the complex, leading to a neutral intermediate **6** (Scheme 5). Computational studies on the structure of intermediate **6** show that, for the most stable diastereomer, the naphthyl group of the TADDOL ligand shields the *Re*-face of the enolate, directing the attack of the fluorinated reagent to the more available *Si*-face. This is in accordance with the sense of enantiocontrol observed experimentally (*S*-configuration). Although Selectfluor is more often referred to as an electrophilic source of fluorine,[18] the authors propose a single electron transfer (SET) process as the most likely mechanism for the fluorination step. Computational studies on the fluorine transfer in acetonitrile indicate that, at short distances, SET



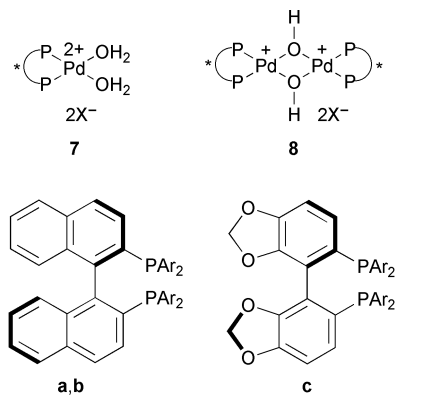
Scheme 4 Catalytic enantioselective fluorinations of β-ketoesters catalysed by Ti(TADDOL) complexes **5a** and **5b**.



Scheme 5 Intermediates involved in the stereocontrolled attack of the enolate to the fluorine source.

occurs from the enolate to the $[N–F]^+$ reagent. Small amounts of chlorinated product (4%) were detected for less reactive substrates, possibly with the chloride source originating from the catalyst. Since Selectfluor is inert towards chloride,[19] a single electron transfer from a free chloride ion to a [N–F] radical delivering a Cl radical would account for the by-product observed. Indeed, a radical scavenger prevented the chlorination without affecting the fluorination, a result supporting this mechanistic hypothesis. This landmark paper sets the stage for further developments.

Sodeoka and co-workers further exploited the concept of two-point binding of 1,3-dicarbonyl compounds and performed successful catalytic asymmetric fluorinations of β-ketoesters in the presence of Pd-based complexes derived from homochiral bis(phosphanes) (**7** and **8**, Scheme 6).[20] For these catalytic systems, *N*-fluorobenzenesulfonimide (NFSI) was the preferred and most effective fluorinating agent. In the reactions, the β-ketoesters were activated to form a chiral palladium enolate, which reacted with NFSI. The fluorination of *tert*-butyl 2-oxocyclopentanecarboxylate (**9**) with NFSI in the presence of



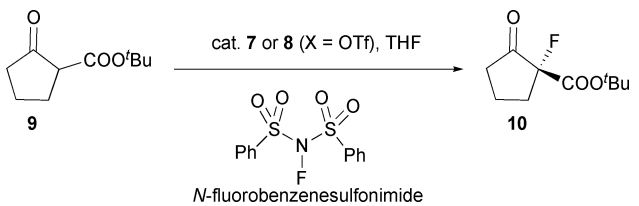
Scheme 6 Pd complexes used in enantioselective fluorinations of enolisable carbonyls.

5 mol% of catalyst **7a** in THF afforded the 2-fluorocyclopentanone derivative **10** in 72% yield and 79% ee (Table 1, entry 1). The use of more congested catalysts such as **7b** or **8c** was found to be beneficial, improving both the chemical yield and the level of enantiocontrol for the fluorination (Table 1, entries 2 and 3). The catalyst loading could be reduced to 2.5 mol% although longer reaction times were then required to reach completion. Interestingly, the use of a polar solvent such as ethanol allows for the reaction to be completed within 18 h at room temperature without loss of enantiomeric excess for the product (Table 1, entry 4).

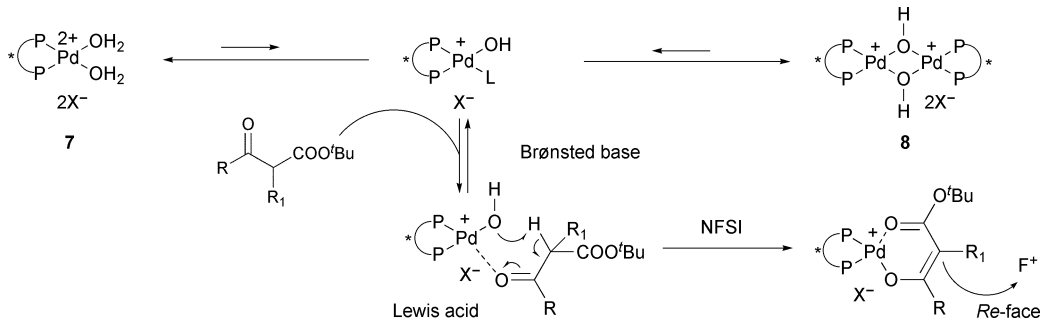
The scope and limitation of this catalytic process was subsequently established and a variety of cyclic and acyclic β-ketoesters were fluorinated under the optimised conditions (NFSI in the presence of 2.5 mol% of catalyst **8c** in ethanol) in high yields (82–96%) and ee (83–94%). As the use of polar solvents complicates the recovery and recycling of the catalysts, a procedure upon which the catalysts are immobilized in an ionic liquid was developed, allowing for the fluorination to be run for ten cycles without loss of enantioselectivity.[21]

The authors proposed that the reactive form of the catalyst is possibly a bifunctional 'PdOH' complex, which exhibits both

Table 1 Catalytic enantioselective fluorination of *tert*-butyl 2-oxocyclopentanecarboxylate (**9**) with Pd–aquo complexes



Entry	Catalyst (mol%)	Solvent	T/°C	t/h	Yield (%)	Ee (%)
1	**7a** (5)	THF	−20	12	72	79
2	**7b** (5)	THF	−20	39	99	88
3	**8c** (2.5)	THF	10	48	93	92
4	**8c** (2.5)	EtOH	20	18	73	92

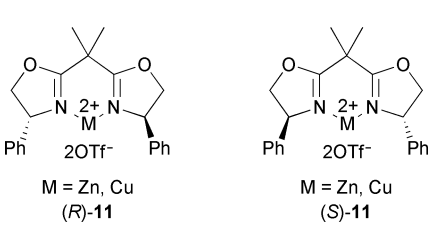


Scheme 7 Pd(OH) complex-mediated activation of β-ketoesters in electrophilic fluorinations.

Brønsted base and Lewis acid properties, with the metal activating the carbonyl in a Lewis acid fashion and the hydroxy group acting as a base for the deprotonation of the α-carbon.[22] The high level of enantiocontrol observed would arise from congestion of one face of the enolate by a steric interaction between the ester group of the substrate and one of the aryl groups of the phosphine ligand, a hypothesis supported by the superior efficiency of catalyst **8c** featuring 3,5-di-(*tert*-butyl)phenyl groups (Scheme 7).

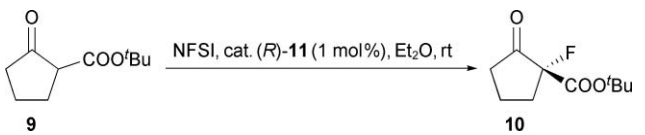
The fluorination of the unsubstituted β-ketoester *tert*-butyl 3-oxo-3-phenylpropanoate afforded 54% of racemic monofluorinated product along with a trace amount (4%) of the difluoro derivative.[20] These results suggest that in the presence of the catalyst, enolisation of the monofluoro-β-ketoester occurred under the reaction conditions leading to racemisation. The reaction is therefore limited to the preparation of quaternary fluorinated centres, similar to the Ti–TADDOL-mediated process developed by Togni and Hintermann.[16]

Following these studies, Cahard[23,24] and Shibata *et al.*[25] selected structurally similar β-ketoester substrates for the identification of additional metal-based catalysts allowing for enantiocontrolled electrophilic fluorination. They found that Cu(II) and Zn(II) in combination with C_2-symmetric chiral bis(oxazoline) ligands (**11**, Scheme 8) were highly efficient catalytic entities for the enantioselective fluorination of these substrates. For the fluorination of *tert*-butyl 2-oxocyclopentanecarboxylate (**9**), Cahard and Ma demonstrated that the copper complex $Cu(OTf)_2$/(*R*)-PhBOX [Cu–(*R*)-**11**] was superior as shorter reaction times were required for the fluorination to reach completion (Table 2, entries 1 and 2).[23] In the presence of 1 mol% of Cu–(*R*)-**11** and one equivalent of NFSI at 20 °C in diethyl ether, *tert*-butyl (+)-1-fluoro-oxocyclopentanecarboxylate (**10**) was isolated in 96% yield and 73% ee (entry 2). The addition of one equivalent of hexafluoroisopropyl alcohol (HFIP) improved the asymmetric induction (85% ee) without affecting the yield (96%, entry 3). HFIP has already been found to be beneficial in other copper-catalysed reactions such as Mukaiyama–Michael and amination reactions, presumably facilitating the release of the product from the catalyst.[26] Other cyclic and acyclic α-fluoro-β-ketoesters could be prepared in good yields but with lower enantioselectivities. The authors also reported that the heterobimetallic complex Li–Al-bis(naphthoxide) catalysed the fluorination of **9** with similar levels of enantiocontrol leading to the formation of fluorinated compound **10** in 58% yield and with a respectable enantiomeric excess of 67%. For this reaction, *N*-fluoropyridinium tetrafluoroborate (NFPY) was the fluorinating reagent and HFIP was used as the additive.[24] This catalytic system was not further explored.



Scheme 8 Bis(oxazoline)–metal complexes as catalyst for the fluorination of β-ketoesters.

Table 2 Catalytic enantioselective fluorination of *tert*-butyl 2-oxocyclopentanecarboxylate (**9**) with Cu(II) and Zn(II) complexes

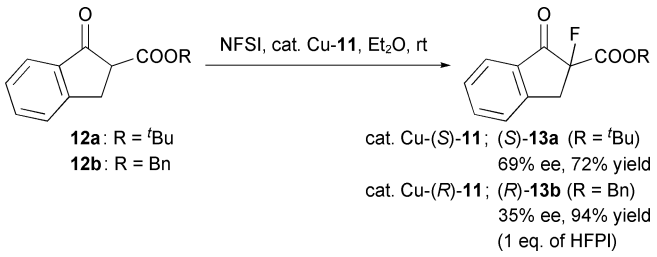


Entry	Catalyst (*R*, mol%)	*t*/h	Yield (%)	Ee (%)
1	Zn-**11** (10)	12	84	74
2	Cu-**11** (1)	0.5	96	73
3[a]	Cu-**11** (1)	0.5	96	85

[a] Reaction carried out in the presence of 1 equiv. of HFIP.

The results of Cahard[23,24] are consistent with data obtained independently by Shibata *et al.* on the fluorination of ketoesters derived from *tert*-butyl 1-indanone-2-carboxylate (**12a**).[25] The $Cu(OTf)_2$/(*S*)-PhBOX [Cu–(*S*)-**11**, Scheme 8] catalyst proved again its efficiency, affording 69% ee and 72% yield of *tert*-butyl (*S*)-2-fluoro-1-indanone-2-carboxylate (**13a**) when the fluorination was performed in diethyl ether at room temperature using NFSI as the fluorinating reagent. It is noteworthy that the benzyl ester (*R*)-**13b** was obtained with a lower level of enantiocontrol (35% ee) under similar reaction conditions, demonstrating once again the importance of the choice of the ester group (Scheme 9).[24]

Moreover, Shibata *et al.* showed that the fluorination of *tert*-butyl 1-indanone-2-carboxylate (**12a**) in dichloromethane in the presence of 10 mol% of Ni–(*S*)-(PhBOX) delivered the fluorinated product of opposite absolute configuration (*R*-enantiomer) but with a similar level of enantiocontrol (76% ee).[25] This reversal of stereoinduction originates from the difference in geometry around the metal centre upon complexation with the substrate. The structures of Cu(BOX) complexes, known to catalyse a broad

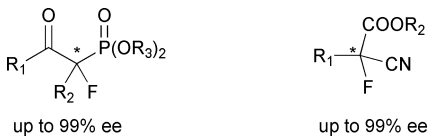


Scheme 9 Fluorination of indanones **12** with Cu–(PhBOX). The effect of the ester group on the ee.

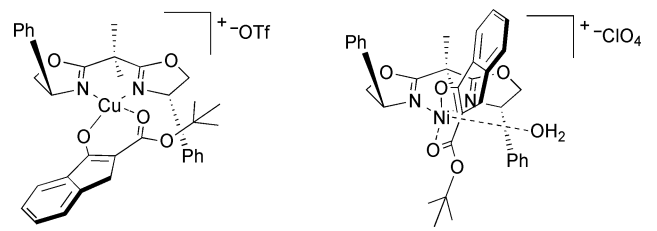
range of asymmetric reactions, have been thoroughly investigated and the geometry of the reactive intermediates involved in the key reaction steps has been clearly elucidated.[27] Theoretical calculations as well as crystal structures indicate that the metal coordinates ketoesters in a two-point binding fashion adopting a distorted square pyramidal geometry. For substrate **12a**, the asymmetric induction for the fluorination is consequently the result of steric interactions between the substituents (aryl or *tert*-butyl) of the ligand and the *tert*-butyl ester group of the substrate. Therefore, one face of the enolate reacts preferentially with the fluorine source. On the other hand, substrates coordinated to nickel complexes adopt a tetrahedral geometry around the metal. In this case, π–π interactions between the ligand and the aromatic ring of the substrate would be responsible for the preferential attack to the *Re*-face.[25] Additional studies revealed that the dielectric constant of the solvent and the presence (or absence) of achiral ancillary ligand, such as water, could also affect the geometry of the metal–substrate complex, therefore reversing the sense of stereoinduction (Scheme 10).[28]

A significant increase in enantiocontrol was achieved with the more rigid, tridentate ligand 4,6-bis((*R*)-4-phenyl-4,5-dihydro-oxazol-2-yl)dibenzo[b,d]furan (dbfox-Ph).[29] The fluorination in the presence of Ni(II) complexes derived from dbfox-Ph, such as **14**, was found to be a highly enantioselective process for a variety of two-point binding substrates, such as cyclic β-ketoesters, acyclic β-ketoesters and oxindoles (83–99% ee). This work led to a catalytic enantioselective preparation of the BOC-protected precursor of BMS-204352 (MaxiPost), an effective opener of maxi-K channels (Scheme 11). Sodeoka and co-workers achieved the synthesis of the same target molecule by asymmetric fluorination in presence of Pd(bisphosphane) complex **8b**.[30]

The catalytic enantioselective synthesis of oxindoles and Maxi-Post illustrates that fluorination mediated by transition metal complexes is not limited to β-ketoesters substrates. Enantioenriched fluorinated targets successfully prepared by catalytic fluorination also include α-fluoro-β-ketophosphonates[31] and α-fluorocyanoacetates,[32] now accessible in the presence of non-racemic chiral Pd–aquo complexes or Ni(II), Zn(II) and Cu(II) bis(oxazoline) catalysts (Scheme 12).



Scheme 12 Enantioenriched fluorinated β-ketophosphonates and α-cyanoesters are accessible *via* metal-mediated catalysis.



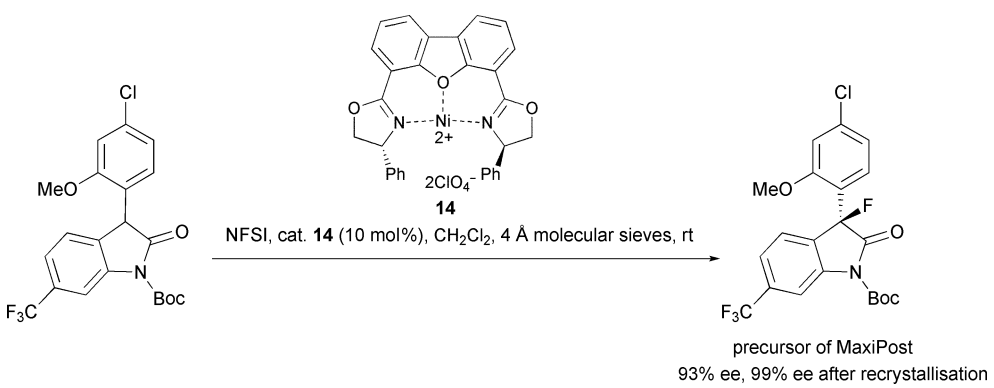
Scheme 10 Geometries for the complexes of **12a** with Cu–(*S*)-BOX (left) or Ni–(*S*)-BOX (right).

These results showed that metal-mediated fluorination is a viable approach for the preparation of enantioenriched fluorinated products. Although numerous substrates were successfully fluorinated, this approach remains ineffective for the formation of enolisable α-fluorinated carbonyl products and is more often restricted to substrates which feature two binding points. These limitations prompted other research groups to investigate conceptually novel approaches towards catalytic enantioselective fluorination.

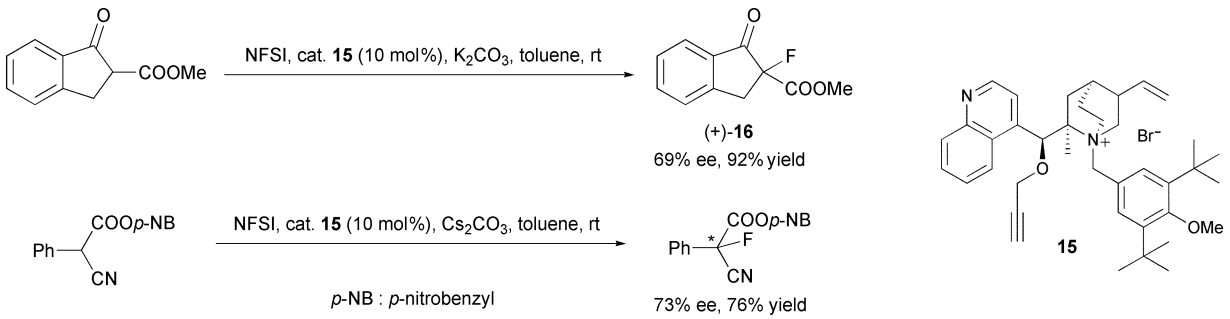
Asymmetric organocatalytic fluorinations

Phase-transfer catalysis with cinchona alkaloid derivatives

Studies carried out by Shibata *et al.*[33] and Cahard *et al.*[34] demonstrated that *N*-fluoroammonium salts smoothly exchange fluorine with cinchona alkaloids, generating a new fluorinated chiral reagent. This strategy was successfully used for the preparation



Scheme 11 Catalytic asymmetric synthesis of MaxiPost with Ni–(*R*)-(dbfox) catalyst **14**.

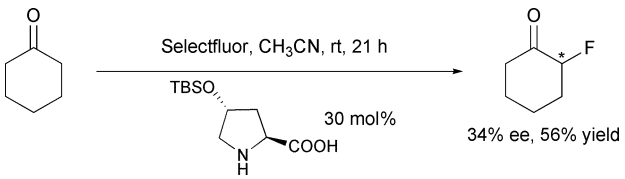


Scheme 13 Catalytic fluorination with cinchona alkaloid **15** under phase-transfer conditions.

of enantioenriched α-fluoro-β-ketoesters,[33,34] α-fluoro-β-cyanoesters,[33] 2-fluoro-1-oxindoles,[33] allylic fluorides[35] and precursors of fluorinated amino acids.[36] The development of a catalytic variant of this process was compromised by the higher reactivity of Selectfluor in comparison with the *in situ*-generated, non-racemic, chiral fluorinating reagent.[9b] Kim and Park subsequently developed a conceptually different catalytic method based on the use of quaternised cinchona alkaloids and NFSI.[37] They performed the fluorination of β-ketoesters using chiral quaternary salts in combination with a stoichiometric amount of NFSI under phase-transfer conditions. The electrophilic fluorination of activated indanones was performed with NFSI in the presence of phase-transfer catalysts **15** derived from cinchona alkaloids (10 mol%) and an inorganic base, such as K_2CO_3 or Cs_2CO_3. Optimal reaction conditions provided the α-fluoroindanone **16** in 92% yield and in moderate enantioselectivity (69% ee). This approach was extended to the fluorination of α-cyanoacetates allowing for the preparation of the corresponding fluorinated products with moderate ee values (73–76%) and yields ranging from 64 to 76% (Scheme 13).[38]

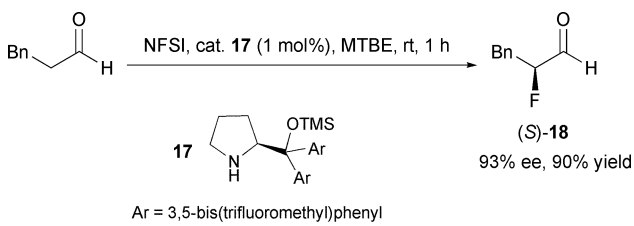
Homogeneous catalysis using proline and imidazolidinone derivatives

Enamine and iminium intermediates derived from carbonyls and chiral secondary amines have been exploited for numerous asymmetric reactions with electrophiles, nucleophiles and for cycloaddition reactions.[39] Recently, three research groups have reported simultaneously their findings on the use of various cyclic secondary amines as catalysts for the direct α-fluorination of aldehydes with excellent asymmetric induction.[40–42] These results were a significant improvement in comparison with a study carried out by Enders and Hüttl on the very first direct organocatalytic α-fluorination of aldehydes and ketones.[43] This preliminary work focused on the fluorination of a series of enolisable and non-enolisable aldehydes using *S*-proline as the catalytic entity, and on the fluorination of cyclohexanone in the presence of eight different organocatalysts. All these reactions used Selectfluor as the fluorinating reagent. *S*-Proline proved to be a poor catalyst for the fluorination of aldehydes as the fluorinated products were formed in moderate yields. No enantiomeric excesses were reported for these reactions. Out of the eight catalysts used for the fluorination of cyclohexanone, the highest reaction rate was obtained with *S*-proline. After 2.5 h, 43% of the substrate was converted into the desired fluorinated ketone with an enantiomeric excess of 29%. Slightly better conversions (up to 60%) and ee values (up to 34%) were obtained with unprotected or silyl-protected hydroxyproline derivatives, when the reaction was left for up to 21 h (Scheme 14).



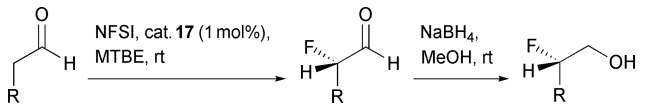
Scheme 14 Fluorination of cyclohexanone with Selectfluor promoted by a proline derivative.

Further studies carried out by Barbas and co-workers,[40] Jørgensen's group[41] and MacMillan and Beeson[42] revealed that the choice of the fluorinating reagent was crucial for these organocatalysed reactions. One major issue to be addressed upon enantioselective fluorination of aldehydes is the need to suppress further enolisation of the newly formed enantioenriched, fluorinated compound that could lead to racemisation and/or the formation of achiral, difluorinated side-products. The reaction conditions reported by Jørgensen and co-workers allow for the introduction of the fluorine α to the carbonyl group of unbranched aldehydes with high enantiomeric excesses and chemical conversions.[41] A total consumption of NSFI was observed for the fluorination of 3-phenylpropanal in methyl-*tert*-butyl ether at room temperature after 1 h with 10 mol% of TMS-protected (*S*)-2-(diphenylmethyl)pyrrolidine (**17**), which was found to be the best chirality promoter (Scheme 15). A lower catalyst loading of 1 mol% provided better conversion (from 53 to >90%), suppressing further fluorination of the primary α-fluoroaldehyde product (*S*-**18**) whilst maintaining the enantioselectivity (93%). Owing to their instability, the products were isolated more often as the corresponding α-fluoroalcohols after their reduction with hydrides sources.



Scheme 15 Organocatalytic fluorination of 3-phenylpropanal with proline derivative **17**.

Table 3 α-Fluorination of aldehydes catalysed by amine **17**



Entry	R	*t*/h	Yield (%)	Ee (%)
1	Pr	6	>95[a]	96
2	^{t}Bu	2	>90[a]	97
3	1-Ad	2	75[b]	96

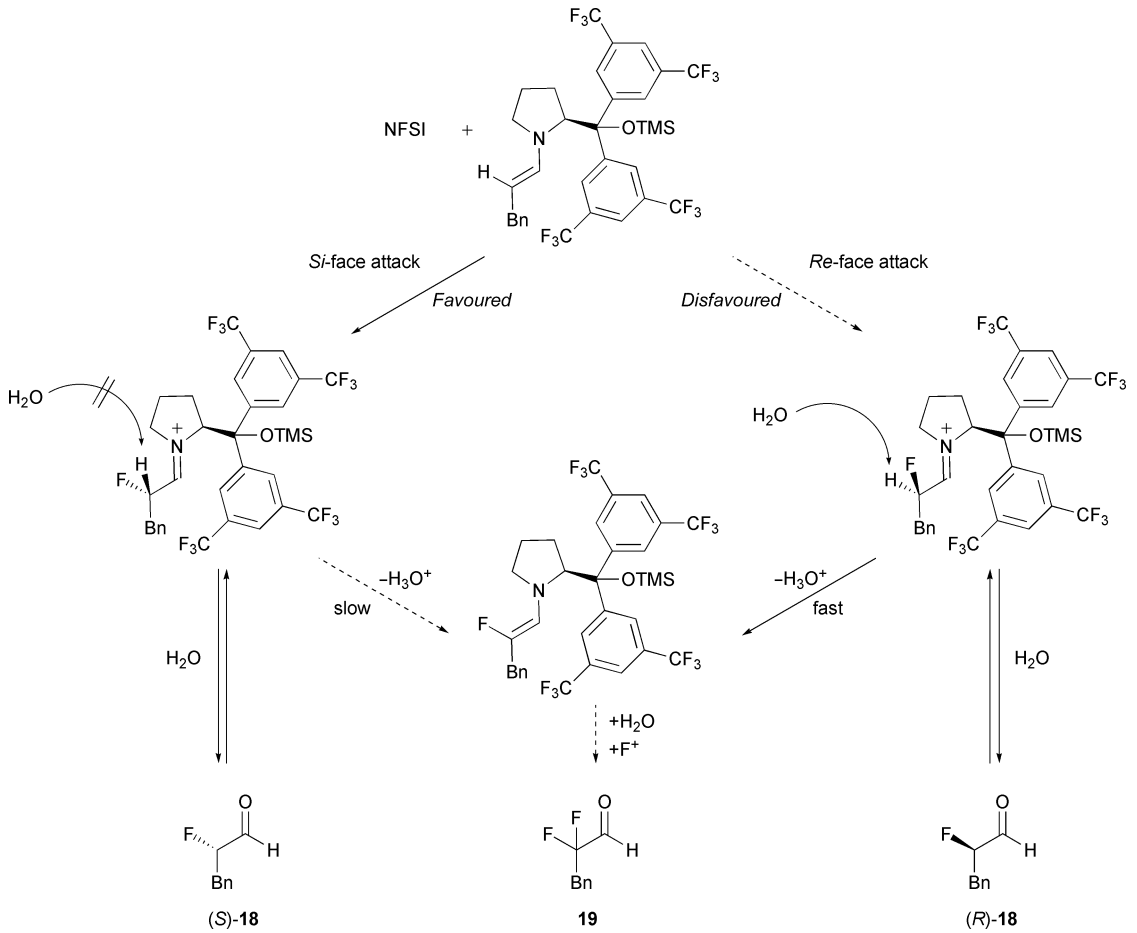
[a] Yield based on GC analysis of the crude mixture. [b] Yield of the isolated alcohol after reduction with sodium borohydride.

The groups of both Jørgensen[41] and Barbas[40] observed that the rate of fluorination for aldehydes bearing an additional α-substituent was decreased due to steric hindrance. On the other hand, additional substitution on the β-carbon of the aldehyde did not affect the chemical conversion and the level of enantiocontrol. Fluoroaldehydes were obtained with excellent enantioselectivity, even in presence of sterically demanding β-substituents such as the adamantyl group (Table 3).[41]

The observed stereochemical integrity of the newly formed fluorinated stereogenic centre under the reaction conditions could not easily be rationalised on steric grounds by a higher energy transition state for the formation of the fluorinated enamine **19**, due the relatively small Van der Waals *radius* of the fluorine in comparison with hydrogen.[44] A close examination of the preferential fluorinated (*S*,*S*)-iminium intermediate resulting from an attack of NFSI on the *Si*-face of the enamine revealed that the remaining α-hydrogen atom is protected toward deprotonation by the shielding substituents present on the catalyst, preventing racemisation through enamine formation. The traces of unwanted difluorinated aldehyde are likely to be the result of further fluorination of the minor disfavoured (*R*,*S*)-iminium intermediate featuring a more exposed α-hydrogen (Scheme 16).

A control experiment was undertaken to confirm this hypothesis. Upon treatment of a racemic mixture of the α-fluoroaldehyde **18** with 0.5 equivalents of NFSI and 1 mol% of catalyst **17**, 20% of difluorinated product was formed. The monofluoroaldehyde **18** was recovered from this kinetic resolution experiment in 20% enantiomeric excess in favour of the *S*-enantiomer. This control experiment confirmed the hypothesis that the *R*-enantiomer is indeed much more prone to enolise in the presence of the organocatalyst **17** (Scheme 17).

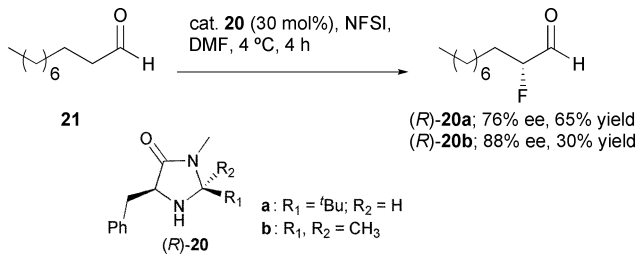
Organocatalysts containing an imidazolidinone core unit promote high asymmetric inductions in a wide range of reactions based on enamine and iminium intermediates.[39] Their recent use for the enantioselective fluorination of aldehydes confirms their



Scheme 16 Proposed explanation for the configurational stability of (*S*)-**18** under the reaction conditions.

Scheme 17 Kinetic resolution experiment with (±)-**18**.

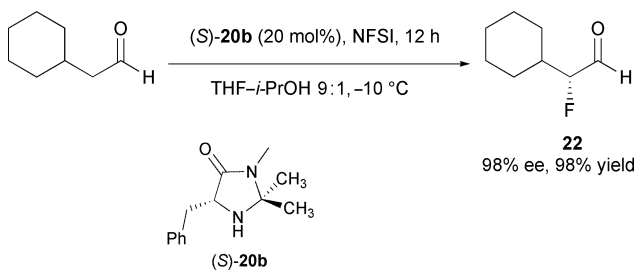
broad reaction scope. In the catalyst screening carried out by Barbas's group, imidazolidinones **20a** and **20b** afforded higher enantiomeric excesses than proline-based catalysts. Using 30 mol% of catalyst **20a** and **20b** in DMF at 4°C, the linear aldehyde **21** was fluorinated in 76% and 88% ee, respectively.[40] A better conversion was obtained with catalyst **20a** (Scheme 18).



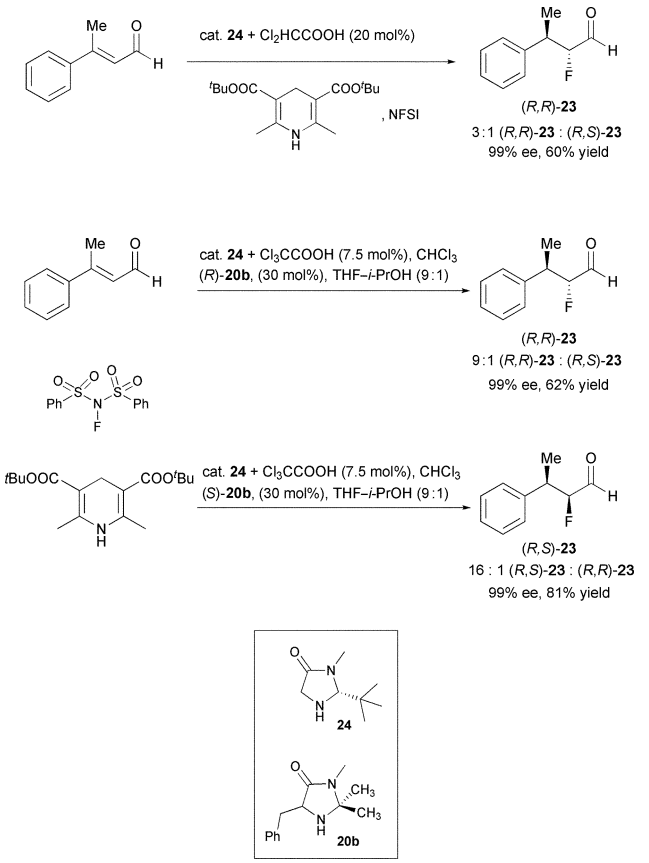
Scheme 18 Enantioselective fluorination of **21** in the presence of NFSI and catalyst (*R*)-**20a** or **b**.

Much higher enantioselectivities (up to 96%) were obtained with a series of linear aldehydes when the chiral imidazolidinones were used in stoichiometric amounts. For branched aldehydes, high yields of moderately enantioenriched fluorinated products were obtained with proline-based catalysts (28 to 66% ee).

Simultaneously, independent work was carried out by MacMillan and Beeson.[42] They also used *N*-fluorobenzenesulfonimide as a fluorine source, a reagent that could "presumably participate in the requisite closed transition state *via* sulfone-proton bonding and concomitant fluorine/enamine activation". They showed that, compared to Barbas's reaction conditions, a much higher level of enantiocontrol can be achieved using a slightly different catalyst and changing the reaction solvent. Fluoroaldehyde **22** was obtained with excellent ee (98%) and yield (98%) using 20 mol% of the dichloroacetic salt of catalyst (*S*)-**20b** when the reaction was performed at −10 °C in a 9 : 1 mixture of THF and isopropanol (Scheme 19). Interestingly, high levels of enantiocontrol could be obtained in a wide range of solvents, including acetone, providing that 10% of isopropanol was present as the co-solvent. Similarly to proline **17**, catalyst **20b** tolerates the presence of bulky substituents on the α-carbon of the aldehyde. A range of functional groups (protected amines, esters and olefins)



Scheme 19 Highly enantioselective synthesis of fluoroaldehyde **22** using (*S*)-**20b**.



Scheme 20 Diastereo- and enantioselective 'formal addition of HF' by organo-cascade catalysis.

was found to be compatible with this catalytic fluorination process. The reaction conditions are remarkably mild as they allowed for the preparation of highly enolisable fluorinated targets such as (*R*)-2-fluorophenylacetaldehyde. Full mechanistic details remain to be elucidated to understand the origin of enantiocontrol and to validate their initial working hypothesis (Scheme 19).

The possibility of applying organocatalysis to the preparation of complex molecular structures through specific catalytic pathways is superbly demonstrated by MacMillan and co-workers in their first report on enantioselective organo-cascade catalysis.[45] In this study, imidazolidinones are involved in a cascade of catalytic processes that allows for the asymmetric addition of both a nucleophile and an electrophile to α,β-unsaturated aldehydes. This concept was applied to a series of nucleophiles and electrophiles, including the use of a hydride reagent combined with an electrophilic source of fluorine. These reactions effectively allowed the asymmetric addition of HF across trisubstituted olefin systems, an overall transformation with no precedent in asymmetric synthesis. In a first catalytic cycle, the catalyst activates the conjugated double bond towards Michael addition with a hydride *via* an iminium intermediate. After consumption of the hydride, the catalyst triggers the formation of the nucleophilic enamine, which then reacts with NFSI. Based on this strategy, (2*R*,3*R*)-2-fluoro-3-phenylbutanal, (*R*,*R*)-**23**, was formed in 60% yield with excellent enantioselectivity (99% ee) and moderate level of diastereocontrol (*anti*/*syn* 3 : 1) when (*E*)-3-phenylbut-2-enal was treated with

20 mol% of catalyst **24** in the presence of a stoichiometric amount of the Hantzsch ester as the hydride source and NFSI as the electrophilic fluorinating agent. The sense and level of enantio- and diastereocontrol of each catalytic step could also be programmed employing a one-pot combination of two discrete amine catalysts. Both diastereomers of **23** were accessible in high enantiomeric excesses (99% ee) and diastereomeric ratios by using the same pair of catalysts, keeping identical the absolute configuration of the 'iminium catalyst' but inverting the absolute configuration of the 'enamine catalyst'. The judicious choice of simple amine catalysts could therefore control both the diastereo- and enantioselective outcome of these cascade reactions (Scheme 20).

Conclusions and perspectives

Within a period of *ca.* five years, spectacular advances have been made with the emergence of truly efficient catalytic and enantioselective fluorination processes. Conceptually, in the enantioselective catalytic fluorinations reported to date, the chiral environment is defined on the substrate, which is subsequently fluorinated by an achiral fluorine source (substrate control). Therefore the methodologies are severely restricted by matching substrate/catalyst interaction. Very preliminary studies suggest that *in situ*-generated chiral N–F reagents may be produced and could offer a solution towards catalytic enantioselective fluorinations, but so far the enantiomeric excesses remain modest.[46] Chiral catalytic entities able to deliver a fluorine atom from the metal to the substrate have yet to be developed. Most of these reactions allowed for the preparation of an α-fluorinated carbonyl motif. To date, processes relying on the use of transition metals are limited to substrates prone to enolise, more often ketoesters, leading to products with fluorinated quaternary centres. This limitation has been lifted with the appearance of the first organocatalytic fluorinations, which allow the preparation of enantioenriched structurally diverse enolisable fluorinated aldehydes. Although Enders obtained encouraging results, none of the catalytic processes reported in the literature are synthetically suitable for the enantioselective fluorination of unactivated ketones and this constitutes a challenge for the future. Also, the enantioselective fluorination of less activated positions remains unexplored although attempts were made towards the development of a catalytic enantioselective route to allylic fluorides. This may be the reason why this chemistry has been applied to only one more complex target synthesis, the preparation of MaxiPost. With continuing progress in catalyst design, practical routes to complex fluorinated targets with multiple stereocentres may be realized in the future to introduce all stereochemical elements independently and efficiently. Of particular interest, would be the development of catalytic routes to targets featuring more than one fluorinated stereogenic centre or the development of innovative strategies towards catalytic enantioselective nucleophilic or electrophilic trifluoromethylation.

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