Fluorine in metal-catalyzed asymmetric transformations: the lightest halogen causing a massive effect

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This review aims at providing an overview of the most significant applications of fluorine-containing ligands reported in the literature starting from 2001 until mid-2021. The ligands are classified according to the nature of the donor atoms involved. This review highlights both metal–ligand interactions and the structure–reactivity relationships resulting from the presence of the fluorine atom or fluorine-containing substituents on chiral catalysts.

1. Introduction

Fluoroorganic molecules have received widespread interest in recent research in view of the fact that their synthesis is virtually missing from any biological processes. Being the 13th most abundant element in the lithosphere, fluorine is mostly present in water-insoluble minerals, i.e., fluorspar (CaF₂), cryolite (Na₃AlF₆), and fluoroapatite (Ca₅(PO₄)₃F), which limits its uptake into living organisms. Also, the nucleophilicity of fluoride is diminished by its high hydration energy, and therefore, this anion is inadequate for any nucleophilic substitution reactions in aqueous media. As a result, only a dozen of naturally occurring fluorometabolites, i.e., fluoroacetic acid, ω-fluorinated fatty acids, (2R,3R)-2-fluorocitric acid, (2S,3S,4R,5R)-nucleocidin, and (2S,3S)-4-fluorothreonine, have been identified so far. Since then, such scarcity has been compensated for by man-made fluorine-containing pharmaceuticals, of which many have been welcomed as blockbuster drugs on the market. Molecular conformation, membrane permeability, and metabolic stability are all properties affected by fluorine substitution, but the impact on the pharmacodynamics and pharmacokinetics of a lead remains quite unpredictable. The

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Table 1  Electronegativities of selected atoms and functional groups

| Atom or group | $x_p$ | $x_e$ | $x_H$ | $x_J$ |
|---------------|-------|-------|-------|-------|
| H             | 2.20  | 2.28  | —     | —     |
| F             | 3.98  | 3.95  | —     | —     |
| Cl            | 3.16  | 3.03  | —     | —     |
| Br            | 2.96  | 2.80  | —     | —     |
| I             | 2.66  | 2.47  | —     | —     |
| NO$_2$        | —     | 3.40  | —     | —     |
| CN            | —     | 3.30  | —     | —     |
| CF$_3$        | —     | 3.35  | 3.46  | 3.29  |
| CHF$_2$       | —     | —     | 3.00  | 2.94  |
| CH$_2$F       | —     | —     | 2.61  | 2.61  |
| CH$_3$        | —     | 2.30  | 2.27  | 2.30  |

specific behaviour of fluorinated compounds arises from the short, strong, and highly polarized C–F bond that electrostatically pairs with the neighbouring atoms, bonds, and lone pairs.$^5$ Instead of being targeted only for biological activity purposes, various chiral organofluorine compounds were employed as catalysts in asymmetric transformations.$^6$ Among the known strategies for designing enhanced stereodiscriminating catalysts,$^7$ the conversion of known catalytic systems into F-containing ones unlocked new interesting features ensuing from the fluorine effect. Chiral fluorinated catalysts benefit from (i) electronically and (ii) sterically customized properties and (iii) being used in fluorous biphasic systems (FBS). Since an increased reactivity in acid catalysts is often a synonym of electronic deficiency, Pauling ($x_p$), empirical ($x_e$), Huheey ($x_H$), and Jaffé ($x_J$) electronegativities values are provided for a selection of atoms and groups (Table 1).$^8$ Fluorine is the most electronegative element on the Pauling scale ($x_p = 3.98$) and is most frequently used as an electronically impoverishing substituent in ligands. The CF$_3$ group is also electronically deficient, much more than other C-based substituents, and its $x$ value is similar to the ones of the CN and NO$_2$ groups, known as strongly electron withdrawing groups (EWG). A set of steric parameters, e.g., $A$ values ($-\Delta G$),$^9$ Taft ($-E_c$),$^{10}$ Charton ($\nu$),$^{11}$ and biphenyl rotational interference values ($J^P$),$^{12}$ and Boltzmann-weighted Sterimol parameters ($wB_1$, $wL$, and $wB_3$),$^{13}$ eases the comparison of bulkiness between selected atoms and functional groups (Table 2). Fluorine is a small element (van der Waals radius = 1.47 Å vs. 1.20 Å for H vs. 1.52 Å for O)$^{14}$ and generally causes minimal steric perturbation upon H to F exchange, whereas the substitution of C–H by C–F in a methyl group successively leads to an increase in size (Me < CH$_2$F < CHF$_2$ < CF$_3$). Thus, fluorine is a powerful tool to increase the steric hindrance – even more in polyfluoralkyl groups – rendering the CF$_3$ group as a bulky substituent in the general order Me < iPr < CF$_3$ < Ph < Bu. The CF$_3$ group is a key component for fine-tuning simultaneously the steric and electronic properties, which is undeniably of great interest for ligand design. Following the “like dissolves like” principle, a chiral ligand bearing sufficiently long perfluoralkyl chains, i.e., ponytails (RF), acquires a strong affinity for the fluorous phase, also called “fluorophilicity”.$^{15}$ This engineered technology involves the temperature-dependent miscibility of fluorous-organic solvents leading to partition of two phases at lower temperature. The fluorous ligand (or catalyst) can be selectively separated from the reactant/product mixture and recovered using various experimental methods.

The synergistic participation of the steric, electronic, and physical properties brought up by the chiral fluorinated ligand may modulate the stereoselective event of a reaction positively vs. “fluorine-free transition states (TS)”. This review highlights both metal–ligand interactions and structure–reactivity relationship related to the presence of the fluorine atom or fluorine-containing substituents on chiral catalysts. The article focuses on the molecular architecture of the ligands rather than on the type of reaction they were employed in. The selection of chiral fluoroorganic ligands is classified according to $O$, $N$, $N$, $P$, $P$, and $C$-binding modes with metals. The advantages of using catalytic systems involving fluorine for both the reactivity and the stereochemical outcomes are highlighted, compared,
and discussed. Furthermore, the effects on the stereochemical outcome arising from using fluorinated ligands vs. non-fluorinated ones are often provided when both results were available in the literature. The set of examples for promoting the massive effect of fluorine in metal-catalyzed asymmetric catalysis is not exhaustive; hence fluorinated reactants, solvents, additives, and Brønsted acids-based catalysts are not reviewed herein.

2. Chiral fluoroorganometallic complexes

2.1 O-Based binding modes

2.1.1 Phosphoric acids. Chiral phosphoric acid (CPA) ligands ($R_a$)-1–3 and ($S_a$)-4 were obtained by the phosphorylation of fluorinated 1,1’-bi-2-naphthol (BINOL)-type ligands and were described as promising candidates for enantioselective applications [Fig. 1]. As an example, the fluorination of $\beta$-ketoesters 5–8 using the 3:1 ($R_a$)-1/ScCl$_3$ complex afforded the corresponding $\alpha$-fluorinated products 9–12 with 78–84% ee (Scheme 1). The importance of the eight fluorine atoms was demonstrated based on the low 11% ee obtained for (+)-9 using the Sc$^{III}$ salt of the non-fluorinated CPA. On the other hand, ($R_a$)-2 17 and ($R_a$)-3 18 were respectively employed with CuI salts in the synthesis of chiral polyfluoro N-containing compounds, albeit with modest ees.

In another application, cycloadducts ($S,R,R$)-15 and endo-($R,S,S,S$)-16, respectively obtained from the hetero-Diels–Alder (HDA) and the Diels–Alder (DA) reactions between dienophile 13 and cyclopentadiene 14, were synthesized with excellent yields and stereoselectivities using the binary ($S_a$)-4/In$^{III}$ catalytic system (Scheme 2). In most cases, a higher chemo-/stereoselectivity was noted for the HDA cycloadduct vs. the DA one. The stereoselective induction was explained by the important $\pi$, $\pi$ interaction, arising from an electrostatic pairing between one electronically deficient perfluorophenyl ring and diene 14, together with highly sensitive ortho positions occupied by F atoms.

2.1.2 Carboxylates and alkoxides. Known as valuable catalysts in the chemistry of diazo compounds, chiral Rh$^{III}$ tetraakis(carboxylates) are rather expensive to be easily used in industrial applications. The recyclable chiral fluorous Rh$^{III}$ complex ($S$)-18 was then targeted in the cyclopropanation reaction of diazoester 19 and styrene 20 (Scheme 3). Whereas it was less selective in terms of ee than ($S$)-17, the perfluoroalkyl chain allowed an efficient recovery of the catalyst using both liquid and solid fluorous phase extraction strategies. Slight improvements of the chiral induction were obtained in the insertion reaction of 19 into the C–H bond of cyclohexane using ($S$)-18 under either homogeneous or heterogeneous conditions.

Various enantioselective organic transformations were performed using more sophisticated CF$_3$-containing BINOL-based chiral catalysts (Fig. 2). Indeed, the synergetic activation using self-assembled bifunctional chiral catalysis was shown as an efficient strategy in the hydrophosphonylation reaction of aldehydes. The multiple reactive sites of catalyst ($R_a$)-22, generated in situ in the presence of Ti(OiPr)$_4$, CF$_3$-aryl-substituted BINOL, and (–)-cinchonidine, allowed cooperative interactions between steric and electronic properties, as postulated in the transition state model of the reaction. Also,
trifluoromethylated BINOLates showed excellent chiral induction in the desymmetrization of C$_2$-symmetric phosphaferrocar- cenes via ring-closing metathesis using MoVII-catalysts ($R$)–23 and ($R$)–24.$^{22}$

2.1.3 Diols. Since hydrobenzoin 25 is cheap and readily available in its $R,R$ and $S,S$ enantiomeric forms, chiral TiIV complexes have employed the 1,2-diphenylethane-1,2-diol scaffold in the enantioselective oxidation reaction of 4-methylthioanisole 30 using cumyl hydrogen peroxide (CHP) as the oxidant (Scheme 4, conditions A).$^{24}$ The incorporation of OMe and CF$_3$ groups onto the chiral backbone of ($R,R$)–26 and ($R,R$)–27 led to electronically modified TiIV catalysts of lower capacity for chiral induction. As observed experimentally, a reversal of the asymmetric induction was observed using the 4-CF$_3$-C$_6$H$_4$ group (26% ee for ($R$)–36) vs. the unsubstituted one (80% ee for ($S$)–36), resulting in optically active sulfoxides of opposite signs. As postulated, competing mechanisms, arising from divergent binding modes with the TiIV centre, led to a decreased purity of 31 as the $S$ enantiomer and to a complete reversal of the sense of chiral induction in favour of ($R$)–31. The TiIV-catalyzed asymmetric oxidation of aromatic sulfides was also demonstrated using a BINOL ligand comprising fluorine atoms at the 5, 5’, 6, 6’, 7, 7’, 8, and 8’ positions (Scheme 4, conditions B).$^{24}$ The oxidation of 30 by the ($R$)–28/TiIV system afforded ($R$)–31 with virtually no enantioselectivity. Again, a reversal of the chiral induction was observed when ($R$)–29 was employed and sulf- oxide 31 was obtained as the $S$ enantiomer in 80% ee. In the case of F$_3$BINOL ($R$)–29, the tenfold increase in acidity of the hydroxyl groups ($pK_a = 9.28$ vs. 10.28 for ($R$)–28) and the more positive oxidation potential ($E_2 = 2.07$ V vs. 1.47 V for ($R$)–28) are believed to result in a more configurationally stable chiral environment of the TiIV-based catalyst.

Being recognized along with BINOL as “privileged ligands”,$^{25}$ $\alpha,\alpha',\alpha''$-tetraethyl-1,3-dioxolane-4,5-dimethanol (TADDOL) ligands have inspired the design of ligands 32–35, bearing $\alpha,\alpha',\alpha''$-trifluorooalkyl and $\alpha,\alpha',\alpha''$-tetrafluoroalkyl chains (Fig. 3).$^{26}$ Being successfully employed in the Ti($^4$PrO)$_4$-catalyzed methylation of various aldehydes, ligands ($R,S,S$)–32–34 afforded similar levels of chiral induction (ca. 95% ee) in the benchmark reaction using benzaldehyde. Notably, shortening the fluorinated pendants had no effect on the efficiency of the catalyst ($C_6F_5$ vs. $C_8F_{17}$), but the recyclability of the ligand was reduced; hence the use of an expensive fluorous solvent was therefore needed for extraction. Interestingly, only the tetra- kis(perfluoroalkyl) analogue ($R,R$)–35 was obtained from ($R,S,S$)–34, whereas the incorporation of a fourth perfluoroalkyl chain failed for diol ($R,S,S$)–32 and ($R,S,S$)–33 due to higher steric congestion. However, the ($R,R$)–35/TiIV catalyst was noticed to be inactive in the tested catalytic application.

TADDOL-like fluorous ligands.

![Fig. 3] TADDOL-like fluorous ligands.

Scheme 4  TiIV-Catalyzed sulfoxidation reaction – ($R,R$)-hydrobenzoin and ($R$)-BINOL derivatives.

Scheme 5  Alkylation addition reaction of Ph$_2$Zn to cinnamaldehyde – ($R$)–36 vs. ($S$)–37.
which favours the ligand-controlled pathway vs. the uncatalyzed background reaction.

Enantioselective applications in fluorous biphasic systems (FBS) were described for perfluorobutyl, -hexyl, and -octyl BINOL derivatives, i.e., \((R)_{40-42}, \(S)_{43-46}, 32c,29\) and \((R,S,S)_{47}\) (Fig. 4).\(^{30}\) As an example, the addition of diethylzinc to benzaldehyde was tackled to evaluate the increase of enantioselectivity. The protonation of the SmIII-enolate, observed from X-ray diﬀraction (XRD) analysis, the hexafluoroalkyl chains have provided chiral ligands the ability to be recycled through various fluorous phase extraction strategies.

Overall, the increase in acidity of hydroxyl groups is a direct effect from the incorporation of ﬂuorine atoms onto chiral ligands. Similarly, electronically deﬁcient O-binding sites allow better interactions with the metal involved giving a more compact TS, resulting in an increased asymmetric induction and even in a complete reversal of it. Perfluoroalkyl chains have provided chiral ligands the ability to be recycled through various fluorous phase extraction strategies.

### 2.2 \(N_{O}\)-Based binding modes

#### 2.2.1 Diols

A sterically hindered catalytic site was built from 2,2\(^{\prime}\)-bipyridinediol \((S,S)_{61}\) to take advantage of the steroelectric properties of CF\(_3\) groups at the \(\alpha,\alpha\)\(^{\prime}\)-positions of the OH moieties. A selection of aromatic, heteroaromatic, and aliphatic alcohols \((R)_{53}, (R)_{55},\) and \(70-77\) were obtained in good to excellent yields (up to 99%) and enantioselectivities (up to 95% ee) using a Zn\(^{II}\)-mediated reaction (Scheme 8).\(^{34}\) As observed from X-ray diﬀraction (XRD) analysis, the hexa- and octa-bridged \((R,R)_{61}/\text{Zn(OTf)}_{2}\) complex led to the hypothesis of coherent transition state models of distinct conﬁgurations – either as exo-trans or endo-trans – giving the major and minor enantiomers, respectively. Interestingly, \((S)\)-ibuprofen was employed for the resolution of the \(\alpha\)-CF\(_3\) alcohol, and 2,2\(^{\prime}\)-bipyridinediol \(61\) was synthesized in both enantiomeric forms with excellent stereoselectivities (97% de and >99% ee for \(R,R\); >99.5% de and >99.5% ee for \(S,S\)).

Chiral Schiff’s base ligands \((S)_{78-83}\), containing an \(\alpha\)-CF\(_3\)-alcohol at a \(C\)-stereocentre, were used in the addition of inducing maximum steric hindrance. Moreover, the \((R,S,R,R)_{60}/\text{Ti}^{IV}\) catalytic system was proﬁtably applied in fluorous catalysis, and the chiral ligand was recovered quantitatively over seven cycles using an optimized binary solvent system of FC-72/CH\(_2\)Cl\(_2\) (2 : 1).\(^{36}\)

![Scheme 7 Ti\(^{IV}\)-Catalyzed ethylation reaction using \(\alpha,\alpha\)\(^{\prime}\)-\(\mathrm{CF}_{3}\)\(-\mathrm{C}_{n}\)\(-\mathrm{diol}\) ligands.](image)
diethylzinc to benzaldehyde 48 (Scheme 9). Ligands (S)-79–81, substituted at the ortho position with a Me or a tBu group, failed to increase the chiral induction. Only para-substituted (S)-82 afforded (R)-53 with similar ee to (S)-78. A non-linear relationship with a minimum enantiomeric amplification, together with high resolution mass spectrometry (HRMS) analysis, suggested that the dimeric [(S)-78]2/ZnII complex is the active catalyst. The C-stereocentre of Schiff’s base ligands (S)-78–83 was constructed by the enantioselective reduction of the o-nitrophenyl-α-CF3-ketone using the (R)-CBS oxazaborolidine reagent. Surprisingly, the non-fluorinated analogues of these Schiff’s base ligands have not been described in the literature so far.

2.2.2 β-Amino alcohols. Fluorinated β-amino alcohol ligands 84–95 have been used in various asymmetric transformations involving the alkylation of aldehydes (Scheme 10). In the Et2Zn alkylation reaction of benzaldehyde, only the organozinc catalyst prepared from (S)-88 led to a maximum enantioselectivity, notwithstanding the presence of the Me or iPr substituents on the ligand at the a-position of the hydroxyl group giving (S)-89 and (S)-90 with bulkier quaternary carbon stereocentres (Scheme 10, left). Correlation studies on the catalyst loading (2–50 mol%) have demonstrated a strong dependence between the increased amount of (S)-88–90 and the ee observed on (R)-53, whereas no dependency was determined for the non-fluorinated analogues (S)-94 and (S)-95; the superior degree of aggregation of CF3-containing β-amino alcohol ligands, particularly for the (S)-88/ZnII catalyst, strongly participated in the mechanism to reach higher chiral induction of alcohol (R)-53. A wider library of β-amino α-CF3-alcohol ligands were screened in the Reformatsky reaction of PhCHO (Scheme 10, right). The ees obtained with ligands (S)-84 and (S)-85, containing a primary or a secondary amine, were much lower than the ones provided using tertiary amine-based ligands. Furthermore, (S)-86 possessing a N,N-dimethyl-amino group led to the highest 81% ee of (R)-96 in comparison with the other ligands having diisopropylamine ((S)-87), piperidine ((S)-88), and carbazole ((S)-91) motifs at the β-position. As shown on (S,S)-92 and (S,S)-93, the benzene ring bearing β-amino α-CF3-alcohols tethered at the 1,2 and 1,3 positions were considerably less efficient than (S)-86. The aggregation effect of

![Scheme 8](image1)

2,2'-Bipyridine-α,α'-CF3-diol/ZnII-mediated ethylation reaction of aldehydes.

![Scheme 9](image2)

ZnII-Mediated ethylation reaction of 48 using Schiff’s bases bearing an α-CF3-alcohol.

![Scheme 10](image3)

Et2Zn alkylation (left) and Reformatsky (right) reactions of benzaldehyde using amino-alcohol derivatives.
such trifluoromethylated ligands with ZnII species was also found beneficial for the enantioselectivity (\((S)-88\) vs. \((S)-94\)).

ZnII-Catalyzed alkylation of aldehydes was also performed using substituted \(\text{N}-\text{methyl-L-prolinol}\) bearing \(\alpha,\alpha\)-aryl groups substituted by a F atom or a C\(_8\)F\(_{17}\) chain at the para position. Through Ag\(^+\) catalysis, the 1,3-dipolar cycloaddition reaction was disclosed using 2,3-dihydroimidazo[1,2-\(a\)]pyridine-based DHIPOH ligands, substituted by a CF\(_3\) group at the C6 position of the quinoline backbone, but they only showed modest chiral inductions among the tested ligands.\(^{40}\)

The CuII-catalyzed aldol reaction of \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters with coumarin-3-ones was investigated using various prolinol derivatives (\((S)-97-102\)) (Scheme 11).\(^{41}\) Supported by density-functional theory (DFT) calculations, the nucleophilic attack of coumarin-3-one was hypothesized to occur from the Si-face of the \(\alpha\)-ketoester in order to prepare predominantly the \(S,R\) diastereoisomer of 103 with good yields (67–93\%) and low to excellent enantioselectivities (56–94\% ee). According to the experimental results, the values of the observed ees were decreased when electron withdrawing groups were present on the aromatic rings.

The Brønsted base/Lewis acid cooperative catalysis was highlighted by the formation of dinuclear ZnII catalysts in the presence of bis(prolinol)phenols (\((S,S)-104-106\)) (Fig. 5).\(^{42}\) Unfortunately, lower stereoselectivities were obtained using (\(S,S\))-104-106 vs. the non-fluorinated ligands in both the cycladdition reactions.\(^{44}\)

2.2.3 \(\beta\)-Amido chalcogens. \(N\)-Polyfluoroacyl \(\beta\)-chalceno amide ligands (\(S\))-107–113 were employed conjointly with a PdII salt in the asymmetric allylic alkylation reaction of rac-114 using dimethyl malonate 115 (Scheme 12).\(^{43}\) Ligand \((S\))-107 containing a sulfur atom provided \((R\))-116 with the best enantioselectivity among the chalcogen series (\(S > Se > Te\)). Additionally, modifications of the electronic nature of the thioether group ((\(S\))-110, (\(S\))-111) and the side chain attached to the stereo centre (\((S\))-112) failed to improve the level of chiral induction. Surprisingly, an excellent 99\% ee was observed on \((R\))-116 when a perfluorinated amide group was introduced on the optimal skeleton of ligand (\(S\))-113, which was recovered by a liquid-liquid extraction and was further employed in a subsequent allylic alkylation reaction with no loss of chiral induction.

2.2.4 Salens. Condensation of numerous fluoruous salicylaldehydes (A–E) with (\(R\),\(R\))-1,2-diaminocyclohexane (DACH) and (\(R\),\(R\))-1,2-diphenylethylenediamine (DPEN) generated salen ligands (\(R\),\(R\))-117–121 and (\(R\),\(R\))-122–124 (Fig. 6). Both types of

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**Scheme 11** Postulated TS for the CuII-catalyzed aldol reaction.

**Scheme 12** \(\beta\)-Amido chalcogen/PdII-catalyzed asymmetric allylic alkylation reaction.

**Scheme 13** PhIO-assisted epoxidation reaction using chiral FeIII complexes.

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Fig. 5 Fluorinated bis(prolinol)phenol-type of ligands.

Fig. 6 Salen ligands bearing fluorinated motifs.
ligands were mixed with MnIII, CoII, or IrII salts, and these salen/metal catalysts showed high levels of stereoinduction in various catalytic applications using FBS.

The efficiency of FeIII(salen) catalysts was compared in the asymmetric epoxidation reaction of 127, from which a higher level of chiral induction was mainly attributed to the fluorophilic effect (Scheme 13).49 According to crystallographic experiments, two distinct structures of the catalyst (R,R)-125 and (R,R)-126, bearing respectively C4H9 and C4F9 chains, were presented. Catalyst (R,R)-126, because of intramolecular stacking of the C4F9 chains arising in it, was described to adopt a unique umbrella conformation, which was more efficient to afford enantiomerically enriched (S)-128 than the usual C2-symmetrical stepped conformation of metal(salen) complexes.

Structural insights into the C2-symmetric complexes prepared from the combination of fluoruous diamino-dialkoxy ligands and TiIV and ZrIV cations were obtained from various spectroscopic and crystallographic analyses.50

2.2.5 Carboxamidates. Tetrakis(carboxamidates) derivatives of chiral dirhodium catalysts 129–131, bearing α,α-fluorine atoms, were developed by Doyle to increase the catalytic activity, while maintaining high levels of asymmetric induction for selected transformations: (i) insertion reaction into the Si–H bond (left), (ii) intramolecular cyclopropanation (up), and (iii) ylide formation/[2,3]-sigmatropic rearrangement (right) reactions (Scheme 14).51 All tested catalysts, (S)-129, (R)-130, and (R)-131, showed increased reactivity towards diazo compounds 19, 133, and 135, although the stereoselectivities of products 132, (S,R)-134, 136, and 137 were lower than the ones obtained with their corresponding non-fluorinated analogues.

Chiral dirhodium catalyst P-cis-anti-139 was employed in the [2 + 1]-cycladdition reaction of ethyl α-diazoacetate 135 and hept-1-yn 140 (Scheme 15).52 Other mono- and tris(amidate)-bridged RhII complexes were prepared from the N-triflylimidazolidinone precursor (R,R)-138, but all led to (S)-141 with lower enantioselectivities (~95% ee). The trans-vicinal CF3 groups on the imidazolidinone backbone brought up interesting features to (R,R)-138, i.e., high sterically hindered and electron deficient chelating N atoms.

To sum up, ligands bearing a trifluoromethyl substituent for inducing chirality are scarce, but the potential of using the CF3 group to provide an important steric hindrance at the α position of alcohols and amines has been disclosed in various studies. Furthermore, the beneficial synergy of both the steric and the electronic properties for optimal enantioselectivity was demonstrated in the comparison study performed using CF3-containing ligand 88 and its Me- and Pr-analogs in the ethylation reaction of benzaldehyde. The fluorophilic effect is also responsible for significant conformational changes to classical salen complexes leading to a new conformation adopted by the F-tagged ligand–metal complex.

2.3 N-Based binding modes

2.3.1 Diamines and diimines. Chiral 1,2-diaminocyclohexane (DACH)-derived diimine ligands (R,R)-142–147 have been promoted in asymmetric catalysis in the pioneering work by Jacobsen in both the olefin aziridination and the carbene insertion into the Si–H bond (Fig. 7).53 In CuI catalysis, Evans described the Diels–Alder reaction of 3-acyrloyl-2-oxazolidinone 148 with cyclopentadiene 14 as being highly enantioselective when (R,R)-142, bearing two 2,6-

![Scheme 14 Various applications of chiral RhII catalysts in diazo chemistry.](image1)

![Scheme 15 [2 + 1]-Cycloaddition reaction catalyzed by the [(R,R)-138]/RhII complex.](image2)

![Fig. 7 Fluorinated motifs incorporated into DACH-type diimine ligands.](image3)

![Scheme 16 CuI-Catalyzed Diels–Alder reaction – diimine ligand screening.](image4)
dichlorophenyl arms, was used (Scheme 16). Interestingly, fluorine substitution at the 2,6- and 2,3,4,5,6-positions of the aryl group led to lower enantioselectivities of (1R,2R,4R)-149, but higher enantiomers 150-152/CuI complexes (Scheme 17).

The insertion reaction of 1-(1,1′-binaphthyl)-2,2,2-trifluoro-1-diazo-ethane 153 into PhMe₂Si-H was performed using chiral diimine CuI catalysts (Scheme 17). In comparison with the best 84% ee obtained with (R,R)-142, the fluorinated diimine analogues (R,R)-145 and (R,R)-146 led to unsatisfactory 40% ee and 16% ee, respectively. Being very interested towards a ligand design approach, 2,6-dichlorobenzaldehyde and other chiral diimine scaffolds, i.e., (S,S)-1,1′-binaphthyl-2,2′-diamine, (S,S)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene, and (S,S)-DPEN, were condensed together to generate new diimine-type ligands with distinct bite angles. However, the 150–152/CuI catalysts failed to give the insertion product with higher enantioselectivities than (R,R)-142. As shown in this study, any mix-and-match combinations involving a chiral diimine precursor and a desired aldehyde could lead to potential candidates being used for chiral induction.

Chiral diimine ligands are prepared from the simple reductive amination of diimine precursors, e.g., using sodium borohydride. Numerous aldehydes containing different F-patterns were first treated with (R,R)-DACH and then reduced with NaBH₄ or NaBH(OAc)₃, to give chiral 1,2-diamine ligands (R,R)-155–161. The ability for chiral induction of these electronically deficient ligands was studied in the Ni²-catalyzed C-alkylation reaction of 1-nitropropane 163 by z-bromoamide rac-162 (Scheme 18). Independent of the nature of the substituent (F, CF₃, or OCF₃), fluorine substitution at the 3-, 4-, 2,6-, and 3,4,5-positions of the aromatic ring afforded syn-(R,S)-164 with up to 82% ee, whereas a good 86% ee, together with a low 16% yield, was observed when using the C₆F₅ analogue. Optimal results were obtained with the (R,R)-160/Ni⁰ system, and this catalyst was proven highly efficient to prepare 26 β-nitroamides with excellent stereoselectivities (up to 90% de_syn and 99% ee_syn).

Chiral DACH- and DPEN-based Ni⁰ complexes (R,R)-165 and (R,R)-166 with N,N′-4-fluorobenzylamine arms were employed as moisture- and air-stable pre-catalysts in enantioselective transformations (Scheme 19). The z-hydrazination reaction of z-fluoro-β-ketoester 167 with di-tert-butyl azodicarboxylate (DBAD) 168 was successfully performed using (R,R)-165, where z-amino-β-ketoester 169 was obtained in 86% yield and 73% ee (Scheme 19, eqn (a)). Similarly, the (R,R)-166-catalyzed conjugate addition reaction of diethyl malonate 171 to β-nitrostyrene 170 was reported to give an excellent enantioselectivity on Michael adduct (S)-172 (Scheme 19, eqn (b)). When using 1-nitropent-1-ene as the substrate, (R,R)-166 afforded promising 89% ee of (R)-diethyl 2-(1-nitropentan-2-yl)malonate, which is a key

Scheme 17 Cu¹-Catalyzed carbene insertion reaction into the Si–H bond – chiral diimine possessing various bite angles.

Scheme 18 Ni²-Catalyzed C-alkylation reaction – optimization of the chiral diimine ligand.

Scheme 19 Ni⁰ complexes employed in addition-type reactions.
intermediate in the synthesis of brivaracetam having antiepileptic properties.

Polyfluorinated diamine and diimine types of ligands were obtained by the incorporation of perfluoroalkyl chains to be used in various synthetic applications involving fluorous biphasic systems (Fig. 8). Chiral perfluorinated DACH-type diamine ligand (R,R)-175 was more tolerant towards decomposition vs. diimine (R,R)-173 over the recycling of both Ir\(^{1}\) and Cu\(^{1}\) catalysts.\(^{6,61}\) In terms of chiral induction, the (R,R)-175/Cu\(^{1}\) catalyst afforded the trans-(1R,2R)-cyclopropane, obtained from styrene 20 and ethyl diazoacetate 135, in 62% ee, whereas a low 6% ee of the opposite 1S,2S enantiomer was observed when using the diimine analogue. Furthermore, non-cyclic C\(_2\)-symmetric tertiary diamines also led to poor levels of enantioselectivity (ca. 15% ee) probably due to a too flexible environment around the Cu\(^{1}\) centre. Starting from (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol, the incorporation of C\(_9\)F\(_7\) ponsyls tethered to the sterogenic carbons of the 1,2-diamine core allowed the preparation of unique fluorous diimine and diamine ligands. Unfortunately, poor levels of stereoinduction were obtained in the ATH reaction of acetophenone in a fluorous solvent using either Ir\(^{1}\) or Ru\(^{1}\) catalysts made from (R,R)-174 or (R,R)-176.\(^{62}\) Alternatively, the introduction of perfluoro-heptyl and -octyl chains directly on both N atoms led to aliphatic diamino-cyclohexane (R,R)-177-180, which were found promising only in the Cu\(^{1}\)-catalyzed cyclopropanation of styrene 20 among the tested reagents.\(^{63}\)

Overall, the 1,2-diphenylethylenediamine scaffold is scarcely described in the literature for the synthesis of fluorinated diimine and diamine ligands. To overcome this situation, an efficient method was described for the synthesis of DPEN-type ligands with diaryl-substituted backbones via a diaza-Cope rearrangement of (S,S)-1,2-bis-(2-hydroxyphenyl)-ethylenediamine 181 (or (R,R)-181) in the presence of the desired aldehyde.\(^{64}\) Following the described protocol, fluorinated DPEN (R,R)-185-187 were synthesized in high yields (77–87%) via the condensation of (S,S)-181 with aldehyde 182-184, i.e., 4-F-C\(_6\)H\(_4\)-CHO, C\(_6\)F\(_5\)-CHO, and 4-CF\(_3\)-C\(_6\)H\(_4\)-CHO (Scheme 20). The diaza-Cope rearrangement was postulated to proceed through a six-membered chair transition state giving the desired diimines with chiral inversion of the C-stereocentres. This method is highly useful for the preparation of F-containing DPENs, which could be used as enantiopure building blocks – either as the R,R, or the S,S – to give diimine- and diamine-based designer ligands.

**2.3.2 Sulfonamides.** The sulfonylation of simple DPEN ligands with various aromatic sulfonyl precursors where fluorine substitution appears on all carbons of the aryl paved the way to a wide library of N-(tosyl)-1,2-phenylethylenediamine (TsDPEN) ligands (S,S)-191-197 (Fig. 9). Their complexation with Ru\(^{1}\) salts was proven valuable for both the tandem hydration/asymmetric transfer hydrogenation (ATH) of alkenes\(^{66}\) and the asymmetric hydrogenation (AH) of bisquinoline,\(^{67}\) where (S,S)-191-196 and (R,R)-193 were respectively used. Fluorous dendritic (S,S)-197 showed an enhanced activity and recyclability of the Ru\(^{1}\) catalyst towards the ATH reaction of aromatic ketones into secondary alcohols, which were obtained with excellent ees.\(^{68}\) During the optimization of the reaction conditions, (R,R)-193 and (R,R)-194 were screened, but the latter

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**Scheme 20** Stereospecific preparation of C\(_2\)-symmetric fluorinated DPEN ligands.

**Scheme 21** Ti\(^{IV}\)-Catalyzed epoxidation reaction of geraniol.

**Scheme 22** Rh\(^{III}\)-Catalyzed ATH reaction of 201 into (R)-202.

**Fig. 9** F-containing tosylated (S,S)-DPEN ligands in Ru\(^{II}\) complexes.
was chosen as the optimal chiral ligand in the Ir\textsuperscript{III}-catalyzed ATH reaction of 2,9-dimethyl-1,10-phenanthroline.\textsuperscript{29}

The ATH of \(N\)-protected 4-quinolone \textbf{201} using the formic acid/triethylamine mixture as the hydrogen source was performed using chiral Rh\textsuperscript{III} complexes \((R,R)\)-\textbf{199}–\textbf{200} (Scheme 22).\textsuperscript{79} All three catalysts afforded excellent chiral inductions, but the partial cleavage of the tert-butyloxy-carbonyl (Boc) group occurred when using a stronger Lewis acidic catalyst; hence lower yields of \((R)-\textbf{202}\) were obtained using \((R,R)-\textbf{199}\) and \((R,R)-\textbf{200}\).

A 3,5-difluoromethylated phenyl ring was incorporated into a Cinchona-alkaloid-based sulphonamide ligand, which was employed as the chiral source in the Cu\textsuperscript{II}-catalyzed radical oxytrifluoromethylation of alkenyl oximes.\textsuperscript{71} The Simmons-Smith cyclopropanation of allylic alcohols was performed using \textit{in situ} generated Zn\textsuperscript{II} complexes from fluorous sulphonamide ligands, where both ligands were easily recovered by fluorous solid phase extraction.\textsuperscript{72}

### 2.3.3 Imidazolines

The \((S,S)\)-DPEN scaffold was further employed as the chiral synthon for the synthesis of imidazolinedi-aryl substituted ligands in the highly enantioselective Friedel–Crafts alkylation reaction of indoles with ethyl 3,3,3-trifluoropropionate \textbf{208} (Scheme 23).\textsuperscript{73} Among them, fluorophenylene bisimidazole (PheBIM) \((S,S)\)-\textbf{203}–\textbf{206} – particularly ligands \((S,S)\)-\textbf{203} and \((S,S)\)-\textbf{206} possessing a CF\(_3\) group at the \(p\)-position of the phenyl ring – afforded \textbf{209} with good enantioselectivities when indole \textbf{207} was used as the nucleophile.

The alkylation of terminal alkynes and diazo compounds, generated \textit{in situ} by MnO\(_2\)-assisted oxidation of their corresponding hydrazones in a continuous flow system, was disclosed as being highly enantioselective (89–97% ee) under Cu\textsuperscript{I} catalysis (Scheme 24).\textsuperscript{74} A library of pyridine bisimidazole (PyBIM) ligands bearing \(N\)-aryl substituents, \(i.e.,\) 4-CF\(_3\)-C\(_6\)H\(_4\), 3,5-(CF\(_3\))\(_2\)-C\(_6\)H\(_4\), and 4-CF\(_3\)-3,5-F\(_2\)-C\(_6\)H\(_2\), was screened, but only \((S,S)\)-\textbf{210}, comprising 4-SF\(_3\)-C\(_6\)H\(_4\) groups, showed an optimal chiral induction. Noteworthily, these chiral ligands were synthesized from the treatment of a pyridine-2,6-dimido chloride precursor, derived from \((S)\)-\textit{tert-leucinol}, with the corresponding fluorinated aniline, such as 4-(pentafluoro)aniline in the case of \((S,S)\)-\textbf{210}. As postulated, enantioenriched allene \((R)\)-\textbf{213} was synthesized via the concerted Cu–C bond insertion of the \((S,S)\)-\textbf{210}/Cu\textsuperscript{I} acetylide intermediate into the diazo compound \textbf{211}, which approaches with the H near the \(^{13}\)Bu group of the ligand to induce minimal steric strains. The scope was further extended to propargylamides derived from \((S)\)-ibuprofen, penicillin \(G\), \((R,R)\)-atorvastatin, and others, and excellent stereoselectivities were highlighted in the disclosed method.

### 2.3.4 Oxazolines

Tetrahydrofuran derivatives were synthesized with excellent stereoselectivities via the \([3 + 2]\) cycloaddition of racemic cyclopropanes with various aldehydes using a \(\text{Bu}–\text{pyridine bis(oxazoline)}\ (\text{PyBOX})\) ligand.\textsuperscript{75} The selection of electronically modified \(para\)-substituted \(\text{Bu}–\text{PyBOX}\) ligands \((S,S)-\textbf{214}–\textbf{216}\) has induced significant alteration of the yields rather than the ees, even though \((S,S)-\textbf{215}\) afforded 2,5-dihydro-2H-THF \((R,R)-\textbf{218}\) with the best enantiomercial control (Scheme 25). However, the \(p\)-Cl-\(\text{Bu}–\text{PyBOX}\) showed a slightly better efficiency (74% yield, \(>98\%\) de, \(92\%\) ee) and, therefore, was chosen to

![Scheme 23](image)

**Scheme 23** Friedel–Crafts alkylation reaction using chiral PHEBIM ligands.

![Scheme 24](image)

**Scheme 24** Cu\textsuperscript{I}-Catalyzed allenylation reaction and the postulated TS.

![Scheme 25](image)

**Scheme 25** Mg\textsuperscript{II}-Catalyzed dynamic kinetic asymmetric \([3 + 2]\) cycloaddition reaction.
Fluorous chiral bis(oxazoline)-derived ligands.

Fig. 10 Fluorous chiral bis(oxazoline)-derived ligands.

evaluate the scope of the reaction. An opposite trend was observed in the CuII-catalyzed allenylation reaction presented above, where the optimization studies performed on model substrates, using p-R3Pr-PyBOX ligands instead of tBu-PyBOX, led to the corresponding allene with 47% ee (R = CF3), 68% ee (R = H), and 70% ee (R = OMe).24

Chiral pyridine(oxazoline) (PyOX) ligands bearing a CF3-substituted C5 position were tested, but virtually no conversion was noted in the PdII-catalyzed dihydroxylation reaction of catechol and trans-1-phenyl-1,3-butadiene.78 Other examples of mono-oxazoline tethered CF3-based ligands were presented as amido-oxazolinate/ZnII and sulfoxide-oxazoline/PdII complexes.77

Similarly, fluorous bis(oxazoline) (BOX) ligands were synthesized and used with various metals to attain solubilization of the obtained chiral catalysts in fluorous solvents (Fig. 10). Starting from BOX derivatives, the incorporation of perfluoroalkyl substituents, comprising C8F17 and C10F21 chains, on the methylene bridge afforded (S,S)-219–221 and (R,R)-222 and (R,R)-223. High ees were obtained using these chiral ligands in the PdII-catalyzed dihydroxylation reaction of catechol and trans-1-phenyl-1,3-butadiene.79 Other examples of mono-oxazoline tethered CF3-based ligands were presented as amido-oxazolinate/ZnII and sulfoxide-oxazoline/PdII complexes.77

Using CuII or ScIII catalysis.83–85 Importantly, the great ability of the triazole ring for coordination with copper salts was offset by the perfluoroalkyl group effect on azabis(oxazoline) ligand (S,S)-232 or its F51N9-tripodal analogue. As a result, high enantioenrichments were afforded in the benzoylation, Friedel-Crafts alkylation, and Henry reactions.84

The strategy of preventing the immobilization of BOX chiral ligands onto poly(ethylene glycol) (PEG) materials was further explored using (S,S)-233–236 (Fig. 11). Two substitution motifs comprising perfluoroalkyl chains, A85 or B86 were included in the structure of the BOX ligands. The fluorinated moieties, which were separated from the coordination sites by an appropriate spacer to reduce any undesired interactions, allowed excellent recovery and recycling of the ligands via practical procedures.

All things considered, the availability of many fluorinated aldehydes gives the access to a larger diversity of C2-symmetric chiral diamine and diimine ligands. The variety of functionalization patterns brought by introducing fluorine at every carbon of the aromatic ring has facilitated the fine-tuning of the Lewis acidity of a catalyst through electronically modified properties. Chiral ligands bearing the SF5 group have been limited due to the scarcity of the availability of the building blocks, and therefore, the pyridine bis(imidazoline) ligand is considered as a major breakthrough. Importantly, not only the recycling of chiral fluorous catalysts remains a key objective using various strategies, but the incorporation of diverse fluorous chains also led to ligand design in fluorous biphasic systems.

Fig. 11 Perfluoroalkyl motifs for chiral BOX ligands.
2.4 N,P-Based binding modes

2.4.1 Monophosphines. A wide variety of F-containing phosphino(oxazoline) (PHOX) chiral ligands were synthesized via the Ullmann-like coupling reaction of 2-bromo aryl derivatives (Scheme 26). The simple reaction conditions, involving copper iodide and 1,2-dimethylethylenediamine (DMEDA), afforded good yields, notwithstanding the steric and the electronic properties of the substrate. Noteworthily, a considerably increased catalytic activity of the Pd

protonation reaction. According to the postulated TS, both t-Bu and MeO groups pointing upwards – from the ligand and the substrate, respectively – induce a high sterically hindered environment and lead the protonation to occur preferentially via the Si-face (Scheme 27). As a result, isoflavanone (R)-246 was obtained with excellent yield and enantioselectivity.

A highly enantioselective Pd

catalyzed asymmetric alkylation reaction was described as an important key step in the synthetic route of (+)-elatol, a spirobicyclic natural product belonging to the family of chamigrene. Favourable complexation with palladium salts was achieved using strong \(\pi\)-acceptor bis(perfluoroalkyl)phosphino oxazoline (FOX) ligands for the alkylation of monosubstituted allyl esters.

The synthesis of naturally occurring and non-natural isoflavones, members of the flavonoid class, was also targeted using (S)-245 through a Pd

Scheme 26 Ullman-like coupling reaction for the synthesis of PHOX ligands.

Scheme 27 Postulated TS for the synthesis of isoflavone (R)-246.

anti-selectivity mainly depends on the nature of the substituent rather than its position on the ligand. In the presence of CuClO

chemical product with lower enantioselectivity than its non-fluorinated analogue (66% ee vs. 82% ee).

The Pd

catalyzed allylic alkylation reaction was performed using (S)-prolinol-based fluorous aminophosphine (S)-256 and (S)-257 (Scheme 29). High enantioselectivities were obtained from the addition of dimethyl malonate 115, a first deproto-
catalysts ([(S)-116]: 86% ee using (S)-256; 92% ee using (S)-257). The temperature-dependent solubility of the (S)-257/PdII catalyst was investigated, and these studies revealed the possibility to recover the fluorous catalyst via its precipitation in cold hexane.

2.4.2 Diphosphines. Fluorinated (S,S)-DACH-derived P2N2-tetradentate ligand (S,S)-258 was employed in the RuII-catalyzed cyclopropanation reaction of α-methyl styrene 259 with ethyl α-diazoacetate 135 (Scheme 30).

95 The presence of 4-CF3-C6H4 groups was beneficial for the synthesis of cyclopropane 260 with good 70% de cis, 86% ee cis, and 34% ee trans, whereas the non-fluorinated analogue afforded 260 with low 52% de cis, 23% ee cis, and 18% ee trans. When using styrene 20 and 1-octene as substrates, the [RuCl(OEt2)(S,S)-258]PF6 catalyst was also highly diastereoselective for the corresponding cis cyclopropanes. Again, CF3-substituted aryl groups were incorporated into a (S,S)-DPEN-based PNNP ligand, of which chiral FeII complexes were found to be highly electronically deficient, but inactive in the asymmetric transfer hydrogenation of acetophenone.

2.4.3 Axially chiral monophosphines. The important F-containing atropisomeric 1,1'-biphenyl architecture, i.e., 4,4',6,6'-tetrakis-trifluoromethyl-biphenyl-2,2'-diamine (TF-BIPHAM) (Sa)(Ra)-261, was obtained as an enantiopure material via the resolution of (Sa,S)- and (Ra,S)-10-camphoroyl-based disulfonamide diastereoisomers and was employed in the synthesis of chiral amine–phosphine ligands (Fig. 12). The first generation of C2-symmetric N,N'-PR2-TF-BIPHAM ligands (Sa)-262–265, comprising diaryl- and dialklyphosphinyl groups, exhibited excellent asymmetric induction in the RhI-catalyzed hydrogenation of enamides.47 Catalytic applications towards the synthesis of enantioenriched saturated heterocycles via a highly efficient 1,3-dipolar cycloaddition reaction, using CuI (ref. 98) or AgI (ref. 99) catalysis, were developed using the second generation of ligands. Indeed, the scope of these ligands was extended to include mono-N-phospanyl (TF-BIPHAMPhos) derivatives (Sa)-266–269. When using the (Sa)-268/AgI catalytic system, pyrrolidine endo-(R,R,R)-272 was afforded in excellent yields and stereoselectivities via the 1,3-dipolar cycloaddition of in situ generated azomethine ylides, as shown using imine 271, to vinyl sulfone 270 through the more accessible Si face of the imine (Scheme 31).46b

The CuI-catalyzed three-component alkylation reaction from 276, 277, and rac-278, followed by the AuI-catalyzed dehydrative cyclization reaction of alkenediyol 279 into 280, was
described as highly enantioselective using phosphino(imidazoline) (StackPHIM) \((R_u,R,R)-274\) (Scheme 32).

Since the imidazole analogue \((S_u)-273\) (StackPhos ligands)\(^{186}\) and \((R,R)-275\) (having no axial chirality) both led to 2-aminoalkyl furan \(280\) \((R\ or\ S)\) with lower enantiomeric enrichments, the complementary between the stereocentres and the chiral axis to reach higher ee was demonstrated. Further fine-tuning of the \(274/\text{Cu}^1\) catalyst was highlighted by the combination of the \((R,R)-\text{DPEN}\) scaffold with the \(R_u\) or the \(S_u\) atropisomer, resulting in an increased chiral induction of \(280\) from 82% ee \((R)\) to 94% ee \((S)\). Noteworthy, atropisomerism of configurationally stable \(P,N\)-ligands 273 and 274 arises from \(\pi,\pi\)-stacking interactions between the naphthyl and \(\text{C}_6\text{F}_5\) moieties. Being determined experimentally at 50 °C, rotational energy barriers \((\Delta G^\ddagger)\) of 26.8 kcal mol\(^{-1}\) \((R_u\ into\ S_u)\) and 27.5 kcal mol\(^{-1}\) \((S_u\ into\ R_u)\) have proven that both atropisomers of 274 could be synthesized, separated and successfully employed as chiral ligands in metal catalysis. However, the absence of fluorine atoms considerably lowered the \(\Delta G^\ddagger\) values of \(R_u\sim S_u\) \((or\ S_u\sim R_u)\) interconversion, and epimerization of \(281\) occurred easily even at room temperature.

### 2.4.4 Ferrocenes

The popular 3,5-bis(trifluoromethyl) phenyl scaffold was incorporated into chiral ferrocenyl-derived \(P,N\)-containing ligands (Fig. 13). Indeed, imine-, amine-, and oxazoline-based phosphine ligands \(282–284\) were successfully used in the \(\text{Pd}^{11}\)-catalyzed allylic alkylation,\(^{181}\) the \(\text{Rh}^{11}\)-catalyzed hydrogenation,\(^{182}\) and the \(\text{Cu}^{1}\)-catalyzed 1,3-dipolar cycloaddition reactions.\(^{183}\) In the last case, the divergent \(\text{exo}/\text{endo}\) selectivities observed from the experimental results were rationalized through computational studies. Interestingly, the postulated TS models suggested that two different chelation modes of the substrate were arising from the electron-deficient \(\text{Ar}_p\) substituents of \((S_p,S)\)-284 vs. the electron-rich phenyl rings of its non-fluorinated analogue. Moreover, closely related ferrocenyl-based bis(perfluoroalkyl)phosphino(oxazoline) ligands were designed in a series of bulky \(\text{Bu},\ \text{Ph}\) and \(\text{Bn}\) substituents at the \(C\)-stereocentre.\(^{189,183}\)

In brief, the widespread use of 4-CF\(_3\) and 3,5-(CF\(_3\))\(_2\) motifs on the aromatic scaffold of the ligands was highlighted in this section. Importantly, the \(\text{C}_6\text{F}_5\) group has been demonstrated as highly efficient when used in axially chiral phosphines, whereas its electrostatic pairing with the \(\pi\) system of the naphthyl moity has induced a rotational energy barrier allowing atropisomerism. Also, the use of \(o,o'\)-CF\(_3\) within the TF-BIPHAM architecture was proved valuable in this strategy.

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### 2.5 P-Based binding modes

#### 2.5.1 Planar chiral diphosphines

Electron-poor diphosphine ligands were described for JosiPhos- and WalPhos-type ferrocenes \(283–289\) and \((R_p,R)-290–292\), respectively (Fig. 14). Chiral ligands \((S_p,R)-285,106\) \((R_p,S)-286,106a,107\) and \((S_p,R)-287106a\) were tested in the \(\text{Ir}^{1}\) or \(\text{Rh}^{11}\)-catalyzed hydrogenation and the \(\text{Pd}^{11}/\text{Cu}^{1}\)-co-catalyzed Heck/Sonogashira asymmetric reactions, but only high chiral inductions were obtained by using the \((R_p,S)-286/\text{Pd}^{1}\) catalyst. An application of fluorinated JosiPhos ligands in ionic liquids was demonstrated using \((S_p,R)-288, i.e.,\) the imidazolium-based analogue of \((S_p,R)-286\), in combination with \([\text{Rh}(\text{norbornadiene})_2]\)BF\(_4\).\(^{107a}\) The asymmetric hydrogenation reaction of methyl acetamidoacrylate, run under biphasic tert-butyl methyl ether/\([\text{bmim}]\)BF\(_4\) conditions, afforded the corresponding product with 99% ee using either \((S_p,R)-286\) or \((S_p,R)-288\). More importantly, the ionic tag on \((S_p,R)-288\) allows better recyclability of the fluorinated catalyst in the chosen co-solvent system. Chiral thiourea-derived diphosphine ligand \((R_p,S)-289\) was used in the \(\text{Rh}^{11}\)-catalyzed hydrogenation

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Fig. 13 Chiral ferrocenyl-derived ligands containing the 3,5-(CF\(_3\))\(_2\)-\(\text{C}_6\text{H}_5\) group.

Fig. 14 Fluorinated JosiPhos- and WalPhos-type of ligands.

Scheme 33 Hydrogenation reaction using electronically modified WalPhos ligands.
classes of axially chiral bisphosphine ligands comprising the 1,1'-biphenyl system. 

Fig. 15  F-Containing MeO-BIPHEP derivatives.

Fig. 16 Classes of axially chiral biphosphine ligands comprising the 1,1'-biphenyl system.
selected classes of ligands, the narrowest dihedral angle was attributed to DifluorPhos-type ligands ($\theta \sim 67^\circ$), whereas BINAP derivatives ($\theta \sim 86^\circ$) were located at the other end of the steric scale. Overall, all electronically impoverished ligands, with specific steric profiles, showed excellent chiral inductions when complexed with the appropriate Lewis acid in various asymmetric reactions.

Strategies towards the recycling of the chiral ligand have encouraged the derivatization of BINAPs to incorporate perfluoroalkyl chains within their skeleton (Fig. 17). Fluorine substitution upon the naphthyl-backbone was then chosen for the synthesis of $(R_a)_{-325}$. The asymmetric Heck reaction of 2,3-dihydrofuran was successfully performed in the benzene/FC-72 system using $(R_a)_{-325}/Pd^{II}$. \footnote{28b} The Ru$^{II}$-catalyzed hydrogenation reaction of dimethyl itaconate was described using heavier fluoronated BINAP $(S_a)_{-326}$, which was immobilized on fluorous silica gel. \footnote{125} Excellent retention of the fluorous ligand within the silica pores, via noncovalent interactions with the $C_8F_{17}$ chains, permitted its recycling without the use of conventional biphasic extraction methods. Similar to $(R_a)_{-325}$, F-containing BINAPs $(R_a)_{-327}$ and $(R_a)_{-328}$ were developed for their great ability as “light” fluorous ligands to be extracted from the other organic compounds via simple FRP column chromatography. \footnote{126} Introducing the perfluoroalkyl chain at the P atom, as highlighted by $(R_a)_{-329}$, afforded poor ees in three metal-catalyzed reactions potentially due to the proximity of the fluorous tails to the activating site. \footnote{127} The relatively low fluorine content of $(R_a)_{-329}$ (51.5%) failed to give satisfactory chiral inductions in FBS. However, $(R_a)_{-329}$ was separated from the reaction mixture quickly using liquid–liquid extraction by perfluorocarbons.

Research towards the development of greener synthetic methods focused on the replacement of commonly used organic solvents by less hazardous and more environmentally benign alternatives, e.g., supercritical carbon dioxide (scCO$_2$). The Rh$^{I}$-catalyzed hydroformylation reaction of mono-substituted alkenes \footnote{20–331–333} was performed in supercritical fluids using phosphine–phosphite BINAPHOS $(R_a,S_a)_{-330}$ (Scheme 35). \footnote{128} The aldehydes 334–337 were obtained with good regioselectivities and enantioselectivities using the $(R_a,S_a)_{-330}/Rh^{I}$ catalytic system. Considered as CO$_2$-philic, the perfluoroalkyl chains permitted sufficient solubility of the ligand to be used under homogeneous reaction conditions. Moreover, $C_4F_9$, $C_6F_{13}$, and $C_8F_{17}$ ponytails were incorporated into the 1,10-binaphthyl core to generate $[R_F(CH_2)_3]^{–}$-BINAPHOS analogues. \footnote{129}

2.5.3 Phosphoramidites. A wide library of monodentate phosphoramidite ligands was designed for numerous metal-catalyzed asymmetric reactions (Fig. 18). \footnote{130} Following the long-arm approach, substituted phenyl rings were incorporated at the 3,3$'$-positions of the binaphthol skeleton in order to enhance chiral inductions. Indeed, the space surrounding the ligated metal centre was considerably restricted by bulky 3,5-$(CF_3)_2$ and 4-NO$_2$ aromatic rings, as observed in $(S_a)_{-342}/(R_a)_{-343}$ and $(S_a)_{-344}/(R_a)_{-345}$, respectively. An additional fine-tuning of the chiral ligands was possible at the amine moiety,
where electron-deficient benzyl substituents ([S₆]-344 ([R₆]-345) or hindered piperidine ([R₆]-343) were generally more beneficial as observed from the obtained ees. A set of ([R,R]-TADDOL-derived phosphoramidite ligands were screened in the PdII/CuI-catalyzed alkylation reaction, but only the aryl substituents bearing bulky TMS groups and one electron withdrawing F atom afforded the optimal chiral induction.\(^{131}\)

([R]-BINOL-based phosphate ligands, generated from 3,5-bis(trifluoromethyl)phenol and 2,2,2-trifluoroethanol, were considered as promising ligands in the synthesis of RhI complexes and their use in enantioselective catalysis in ionic liquids.\(^{132}\)

### 2.5.4 Other P ligands.

Fluorinated monophosphine, stereogenic phosphine, and sugar-derived phosphinite ligands have been complexed with various noble metals (Fig. 19). The [10–1–10] copolymer poly(quinoline-2,3-diyl)phosphine (PQXphos) (S,S)-(R)-346, having P helicity, was employed as a screened ligand in the asymmetric PdII-catalyzed Suzuki–Miyaura coupling reaction, giving only a moderate chiral induction.\(^{133}\)

Interestingly, the sense of the chirality ([R], or [S]) at the active site of 346 would be induced, according to the structure models,\(^{134}\) by the helicity adopted by the polymer either in the right-handed (P) or the left-handed (M) helix geometry, respectively. Another monodentate (1R,3R,4S)-menthyl-based phosphine ligand, bearing two C₆F₁₃ and C₈F₁₇ ponytails, was reported to give fluorous chiral catalysts when mixed with IrI and RhI salts.\(^{135}\)

Chiral at P atoms, diphenylphosphine ligand (S,S)-347, belonging to the class of 1,1-bis(diphenylphosphino)ferrocenes (dppf), was designed to modulate the stereoselective event in the PdII-catalyzed nucleophilic substitution of allylic acetates.\(^{136}\)

When rac-114 and 115 were used as substrates, the combination of the bulky 1-naphthyl substituent with the electronically deficient 4-F-C₆H₄ unit afforded a slightly lower enantioselectivity (61% ee of ([S]-116) than the unfluorinated one (68% ee of ([R]-116) and its electron donating analogue (4-OME-C₆H₄; 69% ee of ([S]-116). A PtII-catalyzed alkylation of linked secondary phosphines (HRP–PRH) in the presence of various benzyl bromides, comprising F- and CF₃-containing ones, led to P-stereogenic diphosphines with low stereoselectivities.\(^{137}\)

The hydrogenation of a variety dehydroamino acids was reported using chiral phosphinite/RhI catalysts made from various carbohydrate scaffolds.\(^{138}\)

Being highly dependent on the P-aryl substituent, the level of chiral induction was demonstrated to be considerably higher when using electron-rich bis(3,5-dimethylphenyl) groups vs. electron-poor ones, such as C₂,C₃-bis-(di-4-fluorophenyl)phosphine ligand (2R,3S)-348, derived from phenyl β-D-glucopyranoside. Furthermore, a ([R,R]-DIOP-like 4-(trifluoromethyl)phenyboronate diphosphine ligand was synthesized and mixed with RhI, PdII, and PtII salts to generate heterobimetallic complexes.\(^{139}\)

In general, the 3,5-(CF₃)₂-C₆H₄ substituent has been widely used in P-based chiral ligands. Various fluorous ponytails were incorporated into BINAP ligands to give “heavy” and “light” fluorous analogues to be used in distinct synthetic applications. Major advancements were demonstrated using CO₂-philic BINAPHOS ligands bearing perfluoroalkyl chains, in the enantioselective hydroformylation reaction performed in supercritical carbon dioxide. Noteworthily, this section has detailed numerous mono- and diphosphines incorporating a large range of structurally diverse fluorine containing groups.

### 2.6 P,O-Based binding modes

Being O-alkylated with perfluoroalkyl chains at the very last step of the synthesis, 2-(diphenylphosphino)-2′-alkoxy-1,1′-binaphthyl ([MOP] ([R])-349) was used together with [Pd(η⁴-C₆H₄Cl)], in the asymmetric alkylation reaction of β-dicarbonyl derivatives with 1,3-diphenyl-2-propenyl rac-114 (Scheme 36).\(^{137,139}\)

The corresponding alkylated products ([R]-116 and 353–355) were obtained in moderate to excellent yields, and good ees were obtained. Noteworthily, ([R]-349) was completely extracted from the reaction mixture using n-perfluoroctane, whereas the catalytic activity of the recycled PdII complex was lost when used in subsequent reactions.

### 2.7 C-Based binding modes

#### 2.7.1 Diaminocarbenes

Chiral AuI complexes ([R]-356–358 involving acyclic dianocarbene ligands were described as efficient catalysts in the cyclization reaction of...
alkynylbenzaldehyde 359 and tPrOH (Scheme 37). Cyclo-
aduct (R)-360 was obtained in various levels of enantiose-
lectivity depending on the presence of the 3,5-(CF₃)₂-C₆H₄ group on
the adjacent naphthyl ring ((R)₃-357 and (R)₃-358 vs. (R)₃-
356). As revealed by XRD and DFT studies, strong Auᴵ⁺–π inter-
actions with the electron-deficient F-arene give an increased
stability to the catalyst, by limiting the number of possible
rotamers, therefore locating the chiral environment in the
optimal orientation. Bulkier substituents at the amine moiety
((S)-PhMeCH vs. tPr) further enhanced steric interactions
around the Auᴵ centre and thus the obtained enantioselectivity.

N-heterocyclic carbene (NHC)–Cuᴵ catalysts (S,S)-361–363
were employed in the asymmetric allylic arylation (AAr) of
aliphatic allylic bromides 364–366 with PhMgBr (Scheme 38).³¹
Overall, the substitution by sterically hindered and electron-
deficient aryl groups onto chiral NHC–Cuᴵ complexes, e.g.,
(S,S)-362 and (S,S)-363, was found beneficial to obtain a higher
regioselectivity towards the γ-regioisomers 367–369 than (S,S)-
361. When using the allylic bromide 364, the best enantiose-
lectivity was afforded by using (S,S)-361, but sterically and
electronically fine-tuned catalysts considerably improved the γ-
selectivity (367:370 up to 92:8). Excellent regioselectivity for
(R)-368 was obtained particularly with (S,S)-362, whereas excel-
ent enantioselectivities were rather observed when using (S,S)-
361 and (S,S)-363. The NHC–Cuᴵ-catalyzed AAr of 366 led to α-
product 372 preferentially, and only the F-containing catalyst
(S,S)-363 afforded (R)-369 with the best regio- and enantiose-
lectivity when using a sterically hindered Bu-substrate.

2.7.2 Dienes. The fluorination reaction of allylic tri-
chloroacetimidates rac-374 was performed via a dynamic
kinetic asymmetric transformation (DKAT) mechanism using
the Irᴵ pre-catalyst [(S,S)-373] (Scheme 39).¹² Chelated by the
fluorinated (S,S)-bicyclo[3.3.0]octadiene ligand, the Irᴵ centre
generated, via ionization of the substrate, the lowest energeti-
cally π-allyl intermediate of the computed diastereomeric TsSs.
Accordingly, the most substituted carbon undergoes nucleo-
philic attack of the fluoride from the outer-sphere, and (R)-375
was obtained with excellent regio- and enantioselectivities.

Rhᴵ– or Irᴵ-catalyzed highly enantioselective organic trans-
fornations, i.e., arylation,¹³ conjugate addition,¹⁴ and cycliza-
tion reactions,¹⁵ were demonstrated using C₂-symmetric
tetrafluorobenzobarrelene (tfb) ligands 376–384 (Fig. 20). The
bicyclic [2.2.2]octatetraene skeleton was obtained in both R,R and
S,S enantiomeric forms via the resolution of the racemic
mixture by high pressure chiral liquid chromatography. Once
the desired arms attached, the electronically deficient diene
ligands 376–384 strongly chelate metal cations, and high steri-
cally hindered environments are then created in the upper right
and lower left quadrants.¹⁶

3. Conclusions

The introduction of the fluorine atom has revealed a positive
modulation of stereoselective events using metal catalysis. An
optimal balance between an ideal substrate activation and an
inherent stability of the catalyst can be established by using
these electron-deficient ligands. The examples presented herein
demonstrate that the fluorine atom fine-tunes both electronic
and steric properties of the chiral catalyst. The high availability
of F-containing aromatic compounds, particularly bearing the
3,5-(CF₃)₂-C₆H₄ and the 4-CF₃-C₆H₄ motifs, favours their

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incorporation into desired specific positions. Generally, their high electron withdrawing ability was exploited for reaching increased acidity of the chelated Lewis acid. Also, the chiral environments were often better defined by the participation of the fluorinated aromatic ring through electrostatic pairing, both with the metal centre in the inner sphere and the substrate orientation in the outer sphere. The use of the fluorine atom and polyfluorinated groups as a steric bulk remains underdeveloped in asymmetric catalysis. Unexpected high chiral inductions, which are scarcely reported in the literature, are likely to arise from the intrinsic steric properties of bulky polyfluorinated substituents. Besides stereoelectronic reasons, the presence of fluorine in chiral ligands is also valuable from a green chemistry perspective. The fluorophilic effect, which is observed in the presence of perfluoroalkyl chains, has indeed opened the field of asymmetric catalysis into fluoruous biphasic systems. Due to easy extraction procedures, many advantages were highlighted by the recycling of the chiral catalyst over multiple runs without the loss of chiral induction over time. Not only is the fluorine atom considered as a highly multifunctional tool for ligand design, but also its judicious employment is of paramount importance for metal-catalyzed asymmetric transformations.

Author contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest
There are no conflicts to declare.

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