



Asymmetric oxidative α -fluorination of 2-alkylphenylacetaldehydes with AgHF_2 and ruthenium/PNNP catalysts

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ABSTRACT

During attempts directed at epoxide ring opening with different HF sources, we discovered that the Lewis acidic $[\text{RuCl}(\text{PNNP})]^+$ (**1**) or $[\text{Ru}(\text{OEt}_2)_2(\text{PNNP})]^{2+}$ (**2**) catalysts promote the [1,2]-phenyl shift (Meinwald rearrangement) in phenyl-substituted epoxides to give the corresponding 2-alkylphenylacetaldehydes, which are fluorinated at the α -position in the presence of silver bifluoride (AgHF_2) (PNNP is (1*S*,2*S*)-*N,N'*-bis[*o*-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine). The optimization of aldehyde fluorination with PhCH(R)CHO ($\text{R} = \text{Me, Et, 'Pr, 'Bu}$) as substrates showed that catalyst **[1]** SbF_6 gives a moderate degree of enantioselectivity (up to 27% ee) and 35% yield. The substrate scope is limited to benzylic aldehydes. The reaction is unprecedented for transition metal catalysts. Circumstantial evidence suggests that the mechanism involves chemical oxidation followed by enantioselective fluorination with F^- .

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1. Introduction

In the wake of the recent interest in the catalytic generation of C–F stereocenters, a number of efficient methods for the asymmetric catalytic fluorination of dicarbonyl compounds have been developed by our [1,2] and other groups [3]. In contrast, catalytic methods for the fluorination of monocarbonyl compounds, and in particular of aldehydes, have been developing at a slower pace. In 2005, Enders and Hüttl [4], Jørgensen and co-workers [5], Barbas and co-workers [6], and MacMillan and co-workers [7] independently published efficient methods for the organocatalytic asymmetric α -fluorination of aliphatic aldehydes and ketones with electrophilic N–F reagents. With the standard proline- and imidazolidinone-based catalysts, α -aryl substituted, and in particular α,α -disubstituted aldehydes, gave low enantioselectivity, though, and different structural motifs had to be introduced as catalysts [8]. The perusal of the literature shows that chiral catalysts based on transition metals have never been used for the α -fluorination of aldehydes. At most, achiral complexes have been used as co-catalysts in asymmetric organocatalysis [9].

An alternative method for the α -fluorination of monocarbonyl compounds involves the electrochemical [10–13] or chemical [14] oxidation of the substrate, followed by trapping

the generated cation with a source of nucleophilic fluoride. Using this strategy, a variety of α -(aryltio)carbonyl compounds were successfully fluorinated under oxidative electrolytic conditions [10], including chiral substrates in a diastereoselective fashion [11]. Also non-sulfur containing α -aryl ketones, esters, and nitriles [12] can be fluorinated electrolytically (and display diastereoselectivity when chiral) [13]. The reaction is initiated by the anodic one-electron oxidation of the aryl group. Deprotonation in the α -position generates a benzylic radical that is further oxidized to the benzylic cation. The reaction with F^- from $\text{Et}_3\text{N} \cdot 3\text{HF}$ then leads to the desired α -fluoroester [12b]. However, the oxidation of the carbonyl compounds was invariably carried out by electrolysis and not by chemical oxidation.

Despite the fact that intensive research in the field of catalytic enantioselective fluorination has been conducted for several years now, a strategy that includes oxidation followed by reaction with fluoride has never been employed. Herein, we describe the asymmetric, oxidative α -fluorination of 2-alkylphenylacetaldehydes with AgHF_2 catalyzed by Ru/PNNP complexes, which is apparently related to oxidative fluorination. We serendipitously discovered this reaction during attempts of developing a truly catalytic version of the enantioselective hydrofluorinations of epoxides achieved by Haufe, who used stoichiometric or sub-stoichiometric amounts of chromium(III) complexes [15]. This study is part of our interest in the application of ruthenium/PNNP complexes in a number of atom-transfer reactions (epoxidation, cyclopropanation, hydroxylation, and Michael addition) [16], as

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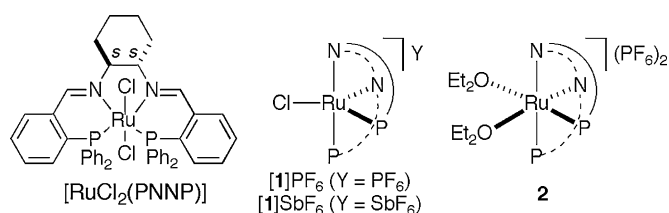


Chart 1.

well as asymmetric nucleophilic [17] and electrophilic fluorination [2].

2. Results

2.1. Hydrofluorination of epoxides

In a preliminary study, we tested the five-coordinate, monocationic catalyst $[\text{RuCl}_2(\text{PNNP})](\text{PF}_6)$ (**1**), prepared from $[\text{RuCl}_2(\text{PNNP})]$ and TiPF_6 (1 equiv) for the hydrofluorination of the model substrate *meso*-cyclopentene oxide with different HF sources (Chart 1, Table 1). The reactions with $\text{Et}_3\text{N}\cdot 3\text{HF}$, $(\text{Bu}_4\text{N})\text{H}_2\text{F}_3$, KHF_2 , and PhCOF led to epoxide polymerization or gave no conversion at all. However, with the insoluble HF source silver(I) bifluoride (AgHF_2), cyclopentene oxide (**3a**) was hydrofluorinated to the corresponding racemic fluorohydrin *trans*-2-fluorocyclopentan-1-ol (**4a**) (run 5). Polymers with incorporated fluorine (abbreviated as F-polymers) were observed as by-products in varying quantities, depending on the amount of AgHF_2 used (runs 6, 7).

As no enantioselectivity was obtained with $[\text{RuCl}_2(\text{PNNP})]^+$ (**1**) as catalyst, we turned our attention to the dicationic complex $[\text{Ru}(\text{OEt}_2)_2(\text{PNNP})]^{2+}$ (**2**), prepared by double chloride abstraction from $[\text{RuCl}_2(\text{PNNP})]$ with $(\text{Et}_3\text{O})\text{PF}_6$ (2 equiv) [16c]. Complex **2** is strong enough as Lewis acid to effect rapid epoxide polymerization when added to an excess of **3a** (10 equiv). The optimization of the reaction conditions showed that the polymerization of the epoxide can be disfavored by adding the epoxide (dissolved in CH_2Cl_2) slowly by syringe pump to the heterogeneous mixture of catalyst **2** (20 mol%) and AgHF_2 in CH_2Cl_2 (Table 2). PTFE tubes, protected from light with aluminium foil, were used as reaction vessels. The best results were obtained by adding the epoxide over 2 h to a

Table 1
Screening of HF sources for the hydrofluorination of *meso*-epoxide **3a**.

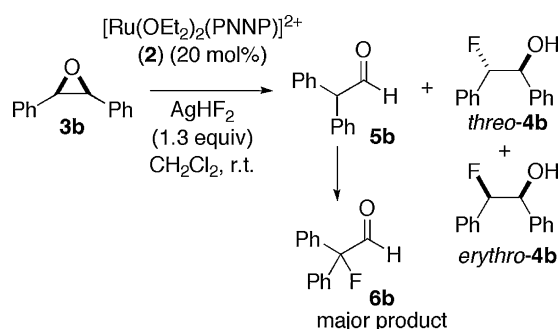
run	HF source (equiv)	Time (h)	Conversion (%)	(rac)- 4a :F-polymers ^a
1	$\text{Et}_3\text{N}\cdot 3\text{HF}$ (1.5)	96	Quantitative	^b
2	$(\text{Bu}_4\text{N})\text{H}_2\text{F}_3$ (1.0)	96	0	–
3 ^c	KHF_2 (1.5)	24	94	^b
4 ^d	PhCOF (1.1)	96	0	–
5	AgHF_2 (1.0)	96	92	1.5:1
6	AgHF_2 (2.0)	24	Quantitative	2.7:1
7	AgHF_2 (4.0)	24	Quantitative	2.3:1

^a Ratios were determined by integration of the ^{19}F NMR signals of the crude reaction mixture.

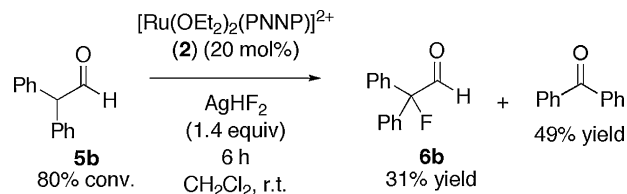
^b Only unfluorinated polymers were formed.

^c $[\text{Ru}(\text{OEt}_2)_2(\text{PNNP})](\text{PF}_6)_2$ (**2**) (20 mol%) was used as catalyst.

^d The expected product was *O*-benzoyl-protected **4a**.



Scheme 1.



Scheme 2.

CH_2Cl_2 solution of **2** (20 mol%) and AgHF_2 (2.0 equiv). Under these conditions, cyclopentene oxide **3a** underwent ring opening (95% conversion within 24 h) to **4a**, which was obtained in 11% yield and with an enantioselectivity of 25% ee (run 1). The low yield suggests that polymerization is the main reaction pathway under these conditions, though.

Surprisingly, with *cis*-stilbene oxide (**3b**) as substrate, fluorodiphenylacetaldehyde (**6b**) was the major product in the reaction mixture after 24 h, together with the side-products *threo*-**4b**, *erythro*-**4b**, and diphenylacetaldehyde (**5b**) (Scheme 1). The ratio of fluorodiphenylacetaldehyde **6b** to the fluorohydrins **4b** is 5:1:1 by integration of the ^{19}F NMR signals. The occurrence of both diastereoisomers in the above experiment suggests the hydrofluorination of **3b** might imply Lewis acid-catalyzed ring-opening of **3b** to give a benzylic carbocation, whose lifetime is long enough to undergo isomerization before being trapped by fluoride. It has been previously shown that diphenylacetaldehyde is the product of a Lewis acid-catalyzed Meinwald rearrangement involving a [1,2]-phenyl shift [18]. As the most intriguing feature of the above reaction was the formation of the fluorinated aldehyde, we devised an independent reaction starting from diphenylacetaldehyde.

Table 2
Asymmetric hydrofluorination of *meso*-epoxide **3a** by $[\text{Ru}(\text{OEt}_2)_2(\text{PNNP})](\text{PF}_6)_2$ (**2**).

Run	Addition time (h)	AgHF_2 (equiv)	Reaction time (h) ^a	Conversion ^b (%)	Yield ^b (%)	ee (%)
1	2	2.0	24	95	11	25
2	2.5	1.0	21	93	9	25
3 ^c	2.5	1.2	96	54	4	15
4	24	1.0	10	70	2	12

^a After completion of epoxide addition.

^b Determined by quantitative GC analysis of the reaction mixtures after precipitation of the catalyst with hexane.

^c A catalyst loading of 5 mol% was used.

2.2. α -Fluorination of diphenylacetaldehyde

Diphenylacetaldehyde (**5b**) was treated with AgHF_2 (1.4 equiv) in the presence of **2** (20 mol%) as catalyst in CH_2Cl_2 (Scheme 2). Within 6 h, 80% of **5b** was converted to a mixture of fluorodiphenylacetaldehyde (**6b**) and benzophenone [19] in 31% and 49% yields, respectively (as determined by integration of the ^1H NMR spectra). Neither stilbene oxide nor fluorohydrins were observed in the reaction mixture. That excludes the possibility of a retro Meinwald rearrangement (aldehyde \rightarrow epoxide), and proves that diphenylacetaldehyde is directly fluorinated in α -position by AgHF_2 with complex **2** as catalyst. We were fascinated by this finding, because oxidative fluorination with a nucleophilic fluoride source might be used as a complementary approach for the α -fluorination of carbonyl compounds, reactions that are usually accomplished by expensive and non-atom-economic electrophilic N–F fluorinating agents [20]. Aldehydes with two different α -substituents, from which chiral α -fluoroaldehydes might be obtained, were the substrates of choice.

2.3. Asymmetric α -fluorination of aldehydes

As a prostereogenic substrate for the asymmetric α -fluorination of aldehydes with AgHF_2 , we chose the commercially available 2-phenylpropionaldehyde (**5a**). The phenyl and methyl substituents in α -position to the aldehyde carbonyl group allow for the formation of a fluorinated quaternary stereogenic center. The absence of a further α -proton prevents racemization after the fluorination step. We initiated our investigations by exposing **5a** to reaction conditions similar to those that effected the Meinwald rearrangement and α -fluorination of *cis*-stilbene oxide or the direct α -fluorination of diphenylacetaldehyde. The reactions were carried out by adding a solution containing the catalyst and **5a** to AgHF_2 in a PTFE tube that was protected from light. As α -fluorinated aldehydes are generally not stable, and tend to decompose upon chromatography [5,6,21], the reaction mixtures were worked up either by rapid filtration through a short plug of Al_2O_3 or by precipitation of the catalyst with hexane. Yields were determined by integration of ^{19}F NMR signals with internal standards hexafluorobenzene or octafluoronaphthalene, and the enantioselectivity by GC analysis on chiral column (Table 3).

First fluorination attempts of **5a** were carried out in the presence of AgHF_2 (2.4 equiv) and of $[\text{Ru}(\text{OEt}_2)_2(\text{PNNP})]^{2+}$ (**2**) (20 mol%) as catalyst, which was freshly prepared from $[\text{RuCl}_2(\text{PNNP})]$ and $(\text{Et}_3\text{O})\text{PF}_6$ (2 equiv) in dichloromethane at room temperature. Under these conditions, no conversion was observed (run 1). Upon raising the temperature, racemic 2-fluoro-2-phenylpropionaldehyde (**6a**) was obtained (run 2). In 1,2-

Table 3
Catalyst $[\text{Ru}(\text{OEt}_2)_2(\text{PNNP})](\text{PF}_6)_2$ (**2**) for the α -fluorination of **5a**.

Run	Catalyst 2 (mol%)	Solvent	Time (h)	Yield ^a (%)	ee (%)
1 ^b	20	CH_2Cl_2	24	0	–
2 ^c	5	CH_2Cl_2	24	20	0
3	5	1,2- $\text{C}_2\text{H}_4\text{Cl}_2$	20	12	18

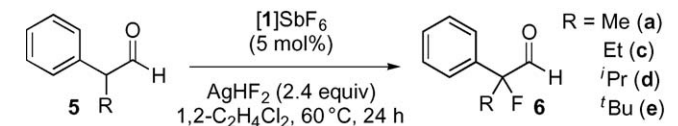
^a Determined by integration of the ^{19}F NMR signals with internal standard hexafluorobenzene or octafluoronaphthalene.

^b 1.3 equiv of AgHF_2 were used at room temperature.

^c The mixture was heated to 60 °C in a sealed PTFE tube.

Table 4

α -Fluorination of differently substituted 2-alkylphenylacetaldehydes with $[\text{1}]\text{SbF}_6$ as catalyst.



Run	Substrate	R	Yield (%) ^a	ee (%)
1	5a	Me	24	27
2	5c	Et	35	23
3	5d	ⁱ Pr	31	18
4	5e	^t Bu	13	n.d. ^b

^a Determined by integration of the ^{19}F NMR signals with internal standard octafluoronaphthalene.

^b No separation of the enantiomers was achieved by chiral GC analysis.

dichloroethane at 60 °C, **5a** is fluorinated to **6a** in 12% yield and 18% ee (run 3). In all these reactions, acetophenone, the product of oxidative decarbonylation of **5a** is observed as by-product in variable amounts [19]. Using the non-silver fluoride sources KHF_2 or $\text{Et}_3\text{N} \cdot 3\text{HF}$ did not effect α -fluorination. With AgF , the reaction was found to be even slower, whereas the strong oxidants AgF_2 or XeF_2 lead to extensive decomposition.

As a further optimization step, we tested the five-coordinate complex $[\text{RuCl}(\text{PNNP})]\text{SbF}_6$ ($[\text{1}]\text{SbF}_6$) in the fluorination of 2-phenylpropionaldehyde (**5a**), which gave 24% yield and 27% ee after a reaction time of 24 h (Table 4, run 1) [22]. Experiments in toluene, THF, and 1,4-dioxane gave lower conversion of **5a** and did not improve the enantioselectivity. To assess the effect of increased steric bulk of the α -alkyl groups, we tested aldehydes PhCH(R)CHO ($\text{R} = \text{Et}$, **5c**; ⁱPr, **5d**; ^tBu, **5e**) (runs 2–4). The higher homologues **5c** and **5d** give better yields, with 35% and 31%, respectively (runs 2 and 3) and only trace amounts of the corresponding phenyl alkyl ketones (products of oxidative decarbonylation). The enantiomeric excesses are lower though, reaching 23% ee for **6c**, and 18% ee for **6d**. The *tert*-butyl-substituted aldehyde **5e** is poorly reactive, and was fluorinated in 13% yield only (entry 4). The enantioselectivity was not determined, as the enantiomers were not separable by chiral GC analysis. The results in Table 4 show that an increase of steric bulk of the alkyl group influences enantioselectivity to a hardly significant extent.

To assess whether aldehydes other than 2-alkylphenylacetaldehydes would undergo Ru/PNNP -catalyzed α -fluorination, we tested some primary aldehydes (**5f–h**) and a 2,2-dialkylacetaldehyde (**5i**), as well as the methyl ketone **5j** and the ethyl ester **5k** as analogues of aldehyde **5a** possessing different carbonyl functional groups (Chart 2). However, all of them were unreactive under the catalysis conditions of Table 4. This observation is in line with the lower reactivity of 2-phenylpropionaldehyde (**5a**) as compared to diphenylacetaldehyde **5b**, which reacts in CH_2Cl_2 at room

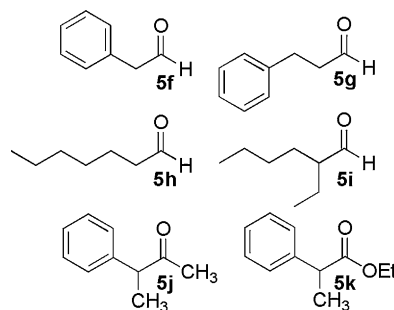
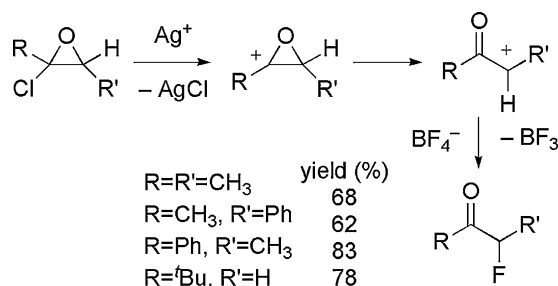
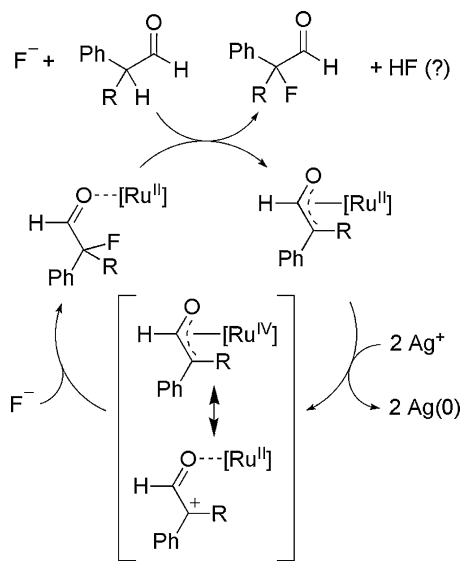


Chart 2.



Scheme 3.



Scheme 4.

temperature (Scheme 2). The fact that **5a** requires higher temperatures for the α -fluorination indicates that the lack of the aromatic group decreases the reactivity of the substrate considerably. Thus, the presence of at least one aromatic substituent in α -position of an aldehyde seems to be mandatory to achieve a useful reactivity. In sum, the substrate scope for the α -fluorination with AgHF_2 is narrow at the moment, as reactive substrates are restricted to secondary aldehydes bearing both an aryl and an alkyl group in α -position.

3. Discussion

As only silver(I) salts are active in the fluorination of aldehydes, we conclude that the reaction requires the presence of an oxidant. As an enolizable aldehyde is nucleophilic in the α -position, and AgHF_2 is a source of nucleophilic F^- ions, we speculate that, during the course of the reaction, the aldehyde is oxidized, which results in the observed umpolung. The overall process is therefore similar to the known electrochemical α -fluorination of thiols or carbonyl compounds mentioned above [10–13]. The oxidation of the aldehyde seems to be the only viable pathway because the oxidation of F^- is obviously impossible owing to its high standard potential ($1/2 \text{F}_2 + \text{e}^- \rightarrow \text{F}^-$; $E^0 = +2.87 \text{ V}$) [23]. The reduction of silver(I) is supported by the observation of grey solids after completion of the reactions, which we interpret as elemental silver ($\text{Ag}^+ + \text{e}^- \rightarrow \text{Ag}^0$; $E^0 = +0.80 \text{ V}$) [24]. The requirement for two equivalents of Ag^+ suggests that the aldehyde undergoes a two-electron oxidation to an α -carbonyl cation, or to a synthetic equivalent thereof. At a first glance, this seems rather unlikely because carbocations are destabilized by electron-withdrawing

groups in α -position. On the other hand, it would explain why the reactivity decreases according to **5b** > **5a** > 2,2-dialkylacetaldehyde \sim primary aldehydes, which corresponds to the number of cation-stabilizing α -aromatic groups.

Also, despite the destabilization of carbocations by electron-withdrawing groups, there are many examples in the literature showing that such cations can indeed be generated, studied, and used as intermediates in synthetic methods [25,26]. Examples thereof are the solvolysis of carbonyl compounds with a good leaving group in α -position (e.g., OMs or OTf), loss of N_2 from α -diazo carbonyl compounds after reaction with an electrophile, or reactions of silver(I) salts with α -bromo carbonyl compounds [25]. Alternatively, the enolates of α,α -diaryl substituted ketones or aldehydes can be transformed to α -carbonyl radicals and α -carbonyl cations [27] via subsequent one-electron oxidation steps with the one-electron oxidant tris(1,10-phenanthroline)iron(III) hexafluorophosphate $[\text{Fe}(\text{phen})_3](\text{PF}_6)_3$ (2 equiv), which is strong enough to effect both one-electron transfers ($[\text{Fe}(\text{phen})_3]^{3+} + \text{e}^- \rightarrow [\text{Fe}(\text{phen})_3]^{2+}$; $E^0 = +1.15 \text{ V}$) [24].

Interestingly, an example of α -fluorination of ketones has been reported, which was found to proceed via α -carbonyl cations (Scheme 3). Rearrangement of *in situ* generated oxirenium cations to the corresponding α -keto cations and reaction with BF_4^- as fluoride source gave α -fluoroketones in good yields [28]. In view of the widespread reports about the occurrence of α -carbonyl cations and the order of reactivity that we observe for differently substituted aldehydes, we consider the oxidation of the aldehyde to an α -carbonyl cation as a possible mechanism for the α -fluorination of aldehydes with AgHF_2 , as sketched in Scheme 4. Deprotonation of the enolizable aldehyde by fluoride may form an oxalyl complex of ruthenium(II), which is oxidized by two equivalents of $\text{Ag}(\text{I})$ to give a species that can be regarded either as an oxalyl complex of ruthenium(IV) or, equivalently, as a ruthenium(II) complex of an α -carbonyl cation. Finally, nucleophilic attack by fluoride gives the fluorinated aldehyde and regenerates the catalyst [29]. We stress that the mechanism in Scheme 4 is meant to be a mere working hypothesis. In particular, as we did not attempt to detect the HF or other by-products, the very stoichiometry of the reaction is yet uncertain.

4. Conclusion and outlook

This is the first transition metal catalyzed enantioselective α -fluorination of aldehydes. Although we were not able to assess the role of the ruthenium catalyst yet, the asymmetric induction clearly shows that the chiral Ru/PNNP complex is involved in the enantiodiscriminating step. Circumstantial evidence suggests that the mechanism involves chemical oxidation followed by enantioselective fluorination with F^- . In fact, the presence of AgHF_2 , which combines a F^- source with an oxidant (Ag^+), is pivotal. The underlying concept might be developed into a cheap and atom-economic alternative to the α -fluorination of carbonyl compounds with electrophilic N–F reagents. Further goals encompass a better reproducibility of the enantioselectivity and a broader substrate scope, that is, not limited to aldehydes with both a phenyl and an alkyl group in α -position.

5. Experimental

5.1. General experimental procedures

Reactions with air- or moisture-sensitive materials were carried out under an argon atmosphere using Schlenk techniques. Complexes **1**[PF_6] [16a], **1**[SbF_6] [16d], and **2** [16c] were prepared by published procedures. ^1H , ^{13}C , ^{19}F , and ^{31}P NMR spectra were recorded on Bruker AVANCE spectrometers AC 200, DPX 250, and

DPX 300. ^1H and ^{13}C positive chemical shifts in ppm are downfield from tetramethylsilane. ^{19}F NMR spectra were referenced to external CFCl_3 and ^{31}P NMR spectra were referenced to external 85% H_3PO_4 . GC–MS was performed on a Thermo Finnigan Trace instrument. Substrate **5c** was prepared by a reduction–oxidation sequence from (rac)-2-phenylbutyric acid, whereas **5d** and **5e** were synthesized by epoxidation of the corresponding phenyl alkyl ketones with dimethylsulfonium methylide and subsequent Meinwald rearrangement catalyzed by $\text{BF}_3\cdot\text{OEt}_2$ [30].

5.2. General procedure for ruthenium catalyzed α -fluorination of aldehydes

AgSbF_6 (8.2 mg, 24.0 μmol , 0.05 equiv) was added to a solution of $[\text{RuCl}_2(\text{PNNP})]$ (20.0 mg, 24.0 μmol , 0.05 equiv) in dry 1,2-dichloroethane (2 mL). The mixture was stirred for 15 h in the dark, giving a brown suspension. The appropriate aldehyde **5** (0.48 mmol, 1 equiv) was added, then the suspension was filtered into a PTFE tube containing AgHF_2 (168 mg, 1.14 mmol, 2.4 equiv), diluted with 1,2-dichloroethane (1 mL), and stirred at 60 °C in the dark for 24 h. After cooling to r.t., the reaction mixture was filtered through a short plug of Al_2O_3 with CH_2Cl_2 as eluent, and concentrated under reduced pressure. A CH_2Cl_2 solution of the residue was used for GC–MS and chiral GC analysis. Yields were determined by integration of the ^{19}F NMR signals, using a known amount of octafluoronaphthalene as an internal standard (^{19}F NMR signals at δ –145.1 and –153.6). A delay time of $d_1 > 30$ s was applied between pulses to ensure the complete relaxation of the fluorine nuclei in different chemical environments. Enantiomeric excesses were determined by chiral GC on a Supelco α -DEX 120 column (30 m \times 0.25 mm, film 0.25 μm), split injector (42 mL/min, 200 °C), He carrier (1.4 mL/min).

5.3. 2-Fluoro-2-phenylpropionaldehyde (6a)

Prepared according to the general procedure from aldehyde **5a** (64 mg, 0.48 mmol). Yield: 17.8 mg (0.117 mmol, 24%). Acetophenone was identified as side-product by ^1H NMR spectroscopy and GC–MS. The NMR spectral data of the product are consistent with reported values [21a,31]. ^1H NMR (CDCl_3 , 200.1 MHz): δ 9.74 (d, 1H, $J_{\text{F,H}} = 4.9$ Hz, CHO), 7.62–7.15 (m, 5 H, arom. H), 1.82 (d, 3H, $J_{\text{F,H}} = 22.7$ Hz, CH_3). ^{19}F NMR (CDCl_3 , 188.3 MHz): δ –160.9 (dq, 1 F, $J_{\text{F,H}} = 22.7$, 4.9 Hz). GC–MS: **6a**: $t_{\text{R}} = 8.8$ min; m/z 152 (M^+ , 9), 123 ($[\text{M}-\text{CHO}]^+$, 100), 103 ($[\text{M}-\text{CHO}-\text{HF}]^+$, 81). Acetophenone: $t_{\text{R}} = 9.6$ min; m/z 120 (M^+ , 27), 105 ($[\text{M}-\text{CH}_3]^+$, 100), 77 (C_6H_5^+ , 73). Chiral GC: oven 56 °C isotherm; $t_{\text{R}} = 48.9$ (major) and 50.3 min; 27% ee.

5.4. 2-Fluoro-2-phenylbutyraldehyde (6c)

Prepared according to the general procedure from aldehyde **5c** (71 mg, 0.48 mmol). Yield: 28.0 mg (0.168 mmol, 35%). Propiophenone was identified as a side-product by ^1H NMR spectroscopy and GC–MS. ^1H NMR (CDCl_3 , 200.1 MHz): δ 9.77 (d, 1H, $J_{\text{F,H}} = 5.6$ Hz, CHO), 7.65–7.20 (m, 5 H, arom. H), 2.40–2.00 (m, 2H, CH_2), 0.99 (dd, 3 H, $J = 7.4$, 7.4 Hz, CH_3). ^{19}F NMR (CDCl_3 , 188.3 MHz): δ –175.6 (ddd, 1 F, $J_{\text{F,H}} = 26.1$, 23.2, 5.6 Hz). GC–MS: **6c**: $t_{\text{R}} = 10.7$ min; m/z 166 (M^+ , 3), 137 ($[\text{M}-\text{CHO}]^+$, 100), 117 ($[\text{M}-\text{CHO}-\text{HF}]^+$, 78). Propiophenone: $t_{\text{R}} = 11.7$ min; m/z 134 (M^+ , 14), 105 ($[\text{M}-\text{C}_2\text{H}_5]^+$, 100), 77 (C_6H_5^+ , 57). Chiral GC: oven 66 °C isotherm; $t_{\text{R}} = 54.3$ (major) and 55.9 min; 23% ee.

5.5. 2-Fluoro-3-methyl-2-phenylbutyraldehyde (6d)

Prepared according to the general procedure from aldehyde **5d** (79 mg, 0.49 mmol). Yield: 27.6 mg (0.153 mmol, 31%). ^1H NMR

(CDCl_3 , 200.1 MHz): δ 9.77 (d, 1H, $J_{\text{F,H}} = 6.7$ Hz, CHO), 7.60–7.15 (m, 5 H, arom. H), 2.63–2.40 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.12 (d, 3 H, $J = 6.8$ Hz, $\text{CH}(\text{CH}_3)(\text{CH}'_3)$), 0.82 (d, 3 H, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)(\text{CH}'_3)$). ^{19}F NMR (CDCl_3 , 188.3 MHz): δ –189.8 (dd, 1 F, $J_{\text{F,H}} = 31.9$, 6.7 Hz). GC–MS: **6d**: $t_{\text{R}} = 12.0$ min; m/z 180 (M^+ , 5), 151 ($[\text{M}-\text{CHO}]^+$, 100), 131 ($[\text{M}-\text{CHO}-\text{HF}]^+$, 74). Chiral GC: oven 75 °C isotherm; $t_{\text{R}} = 49.9$ (major) and 51.1 min; 18% ee.

5.6. 2-Fluoro-3,3-dimethyl-2-phenylbutyraldehyde (6e)

Prepared according to the general procedure from aldehyde **5e** (85 mg, 0.48 mmol). Yield: 12.1 mg (0.063 mmol, 13%). 2,2-dimethylpropiophenone was identified as a side-product by ^1H NMR spectroscopy and GC–MS. ^1H NMR (CDCl_3 , 200.1 MHz): δ 9.96 (d, 1H, $J_{\text{F,H}} = 8.2$ Hz, CHO), 7.55–7.23 (m, 5 H, arom. H), 1.08 (s, 9 H, $\text{C}(\text{CH}_3)_3$). ^{19}F NMR (CDCl_3 , 188.3 MHz): δ –170.6 (d, 1 F, $J_{\text{F,H}} = 8.2$ Hz). GC–MS: **6e**: $t_{\text{R}} = 13.2$ min; m/z 194 (M^+ , 1), 165 ($[\text{M}-\text{CHO}]^+$, 36), 138 ($[\text{M}-\text{C}_4\text{H}_8]^+$, 100). 2,2-Dimethylpropiophenone: $t_{\text{R}} = 12.9$ min; m/z 162 (M^+ , 4), 105 ($[\text{M}-\text{C}_4\text{H}_9]^+$, 100), 77 (C_6H_5^+ , 23).

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