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Diastereo- and Enantioselective Synthesis of Fluorine Motifs with Two Contiguous Stereogenic Centers

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Supporting Information

ABSTRACT: The synthesis of chiral fluorine containing motifs, in particular, chiral fluorine molecules with two contiguous stereogenic centers, has attracted much interest in research due to the limited number of methods available for their preparation. Herein, we report an atom-economical and highly stereoselective synthesis of chiral fluorine molecules with two contiguous stereogenic centers via azabicyclo iridium–oxazoline–phosphine-catalyzed hydrogenation of readily available vinyl fluorides. Various aromatic, aliphatic, and heterocyclic systems with a variety of functional groups were found to be compatible with the reaction and provide the highly desirable product as single diastereomers with excellent enantioselectivities.

INTRODUCTION

Fluorine, on the basis of its unique special properties, holds an esteemed position in modern research¹ and plays an important role in agrochemical,² pharmaceutical,^{1b,c} material sciences,³ biochemistry,^{1b–d,4} and medicinal chemistry.^{1b–d,5} Approximately 30% of all agrochemicals and almost 20% of all pharmaceuticals contain a fluorine atom. Despite being an exceptional pharmacological modulator, selective introduction of fluorine into organic molecules presents difficulties. Indeed, the few numbers in nature of biosynthesized natural molecules containing fluorine^{6,7} arguably prove the difficulty concerning the installation of the fluorine atom. The asymmetric introduction of fluorine thus relies on synthetic organic chemistry and has become one of the most desired and sought-after enhancements in the toolbox of fluorination chemistry.⁸ However, general stereoselective fluorination methods for the access of versatile fluorinated building blocks is still narrow and restricts the availability of structurally diverse fluorinated molecules. Drugs such as dexamethasone, fluticasone propionate, or a fluorothalimolide analogue containing a chiral fluorine carbon atom with another adjacent chiral center represents another major challenge as they require enantioselective generation of an asymmetric fluorinated molecule with two contiguous asymmetric centers. Recent progress in this area has expanded the availability of fluorinated molecule with two contiguous chiral centers.^{8a,b,h,k,m,t,u,9} the repertoire of asymmetric methodologies is still limited and requires either high catalyst loadings,^{8f,9a,10} a mixture of catalysts,^{10b,11} sophisticated reaction conditions,¹² or multiple steps^{10e,13} or offers borderline diastereoselectivity^{10g,14} and enantioselectivity^{10b,c,15} resulting in a mixture of products.¹⁶

In asymmetric catalysis, enantioselective hydrogenation is one of the most fundamental and atom-economical processes in organic chemistry.¹⁷ Steric hindrance by substituents and difficulties in the differentiation of the prochiral faces of the fully substituted olefin by the catalyst make tetra-substituted olefins very challenging substrates for hydrogenation.¹⁸ In addition, defluorination and the unpredictable behavior of the fluorine molecule make tetra-substituted vinyl fluorides even more challenging substrates for hydrogenation.¹⁹ However, the asymmetric hydrogenation of tetra-substituted vinyl fluorides would enable enantioselective generation of two contiguous stereogenic centers containing the fluorine atom at one of the stereocenters, in one simple step.²⁰ Cognizant of the aforementioned limitations, we set out to develop a general, simple, and efficient atom-economical protocol for the highly diastereoselective and enantioselective synthesis of chiral fluorine compounds containing two stereogenic centers (Scheme 1).

RESULTS AND DISCUSSION

The initial investigation focused on the hydrogenation of the inactivated tetra-substituted vinyl fluoride (*E*)-diethyl-2-fluoro-

Scheme 1. Atom-Economical Stereoselective Preparation of Asymmetric Fluorine Motifs

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65 3-phenylmaleate **1a** using various N,P-iridium complexes with
 66 the aim to achieve high reactivity and high enantioselectivity
 67 but avoiding defluorination, which is a common side product
 68 in this reaction. Based on previous experience of N,P-iridium-
 69 catalyzed asymmetric hydrogenation of tetra-substituted
 70 olefins,^{20a,b} we first chose the bicyclic iridium-N,P complex
 71 containing either the thiazole or oxazoline ring for our current
 72 study (Table 1). When N,P-iridium complex **A** bearing the

Table 1. Evaluation of N,P-Iridium Catalysts in the Asymmetric Hydrogenation of **1a**^a

<p>A Conv. 3%</p>		<p>B Conv. 11% >99% dr; 54% ee</p>	
<p>C Conv. 0%</p>		<p>D Conv. 46% 2a:3a = 88:12 >99% dr; >99% ee</p>	
<p>E Conv. 47% 2a:3a = 90:10 >99% dr; >99% ee</p>		<p>F Conv. 96% 2a:3a = 92:08 >99% dr; >99% ee</p>	

^aReaction conditions: 0.05 mmol of substrate, 1 mol % of catalyst, 0.5 mL of toluene. The conversion was determined by ¹H NMR, and the enantiomeric excess was determined by GC/MS using chiral stationary phases.

Table 2. Optimization of Hydrogenation of Tetra-Substituted Vinyl Fluoride **4**^a

entry	substrate	H ₂ (bar)	catalyst (mol %)	conversion (%)	yield (% of 5)	de-F (6)	ee (%) ^b
1	4a	100	1.0	94	91	0	97
2	4b	100	1.0	99	98	0	97
3	4a	50	1.0	92	88	0	98
4	4b	50	1.0	99	98	0	97
5	4a	20	1.0	90	86	0	98
6	4b	20	1.0	99	97	0	98
7	4a	20	0.5	71	68	0	96
8	4b	20	0.5	99	76	0	97
9	4a	10	1.0	65	60	0	96
10	4b	10	1.0	99	65	0	97

^aReaction conditions: 0.05 mmol of **4**, catalyst **F**, 0.5 mL of CH₂Cl₂, 24 h, rt. The conversion was determined by ¹H NMR. Yields are isolated yield. ^bEnantiomeric excess was determined by SFC or chiral GC/MS using chiral stationary phases.

tolylbut-2-enoate (**4a**) and (*E*)-2-fluoro-3-*p*-tolylbut-2-en-1-ol (**4b**), were selected (see Supporting Information for details). A promising result of 94% conversion and full conversion for **4b** was obtained without generating any de-F, with excellent diastereoselectivity (>99%) and enantioselectivity (97% ee) using 1.0 mol % of catalyst **F** (entries 1 and 2). For both substrates **4a** and **4b**, a gradual decrease in the H₂ pressure from 100 bar (entries 1 and 2) to 50 bar (entries 3 and 4) to 20 bar (entries 5 and 6) using 1 mol % of catalyst **F** was effective in terms of conversion and de-F. Decreasing the H₂ pressure did not have any negative effect on either the enantioselectivity (98% ee) or the diastereoselectivity. However, a decrease in the catalyst loading for substrate **4a** from 1.0 mol % (entry 5) to 0.5 mol % (entry 7) at 20 bar of H₂ pressure significantly decreased the conversion (71%). Further decreasing the H₂ pressure to 10 bar using 1 mol % of catalyst **F** (entry 9) lowered the conversion (65%). Similarly, for substrate **4b**, a significantly lower quantity of desired product **5b** (76% yield) was observed when decreasing catalyst loading from 1 to 0.5 mol % at 20 bar H₂ pressure, probably due to the formation of undesired side products (entry 8), which could be either the indene derivative formed by Friedel–Crafts alkylation²¹ or the ether derivative formed by the dimerization of the alcohol.²² A H₂ pressure of 10 bar using 1 mol % of catalyst **F** afforded **5b** in 65% yield along with 30% side products, without any de-F (entry 10). Hence, an optimization study for both substrates **4a** and **4b** confirmed that 20 bar H₂ pressure with 1 mol % of catalyst **F** is the most suitable in terms of stereoselectivity, conversion, and de-F (entries 5 and 6).

With the optimized reaction conditions established, we evaluated various (*E*)-2-fluoromaleate substrates **1** (Table 3) having different substituents. A large number of diesters were successfully hydrogenated to generate the desired products **2a** to **2p** in mostly excellent conversion (0–16% de-F) with perfect diastereoselectivities and enantioselectivities. The (*E*)-2-fluoromaleate substrates having different ester groups (Me, Et, Bn) resulted in full conversions and very high stereoselectivities. Replacing phenyl with the 2-naphthyl or 2-thienyl

thiazole moiety was used, only 3% of the starting material was consumed to provide the anticipated product **2a**. A comparable result of 11% conversion of the starting material **1a** was obtained by changing the basic heterocycle of the N,P-iridium complex from thiazole to oxazoline (**B**). A decrease in the steric hindrance around the phosphorus center of the oxazoline moiety (**C**) failed to give any conversion to the desired product. Unexpectedly and gratifyingly, replacing the bulkier diphenyl with the less sterically demanding isopropyl group on the oxazoline ring (**D**) resulted in the successful hydrogenation of **1a** in 46% conversion with complete diastereoselectivity (>99%) and excellent enantiomeric excess (>99%). Interestingly, negligible defluorinated product **3a** (12%) was observed, which is a common and hitherto unsolved problem in hydrogenations of vinyl fluorides.^{19b} Further optimization of the ligand led to oxazoline N,P-iridium complex **E** containing the 2,4-di-MePh substituent on phosphorus, which gave a result slightly better than that with complex **D**. To further increase the steric hindrance around phosphorus, the *ortho*-methyl group was changed to an *ortho*-ethyl group and afforded new oxazoline N,P-iridium complex **F**. This complex provided a superior result (96% conversion) under the same reaction conditions with only 8% de-F and perfect diastereoselectivity (>99% dr) and enantioselectivity (>99% ee).

After successfully optimizing the new and effective catalyst **F** for the hydrogenation of vinyl fluoride **1a**, we turned to optimizing the other reaction parameters (Table 2). For this purpose, two different substrates, (*E*)-ethyl 2-fluoro-3-*p*-

Table 3. Hydrogenation of Various Fluoromaleate^a

$\begin{array}{c} \text{R}^1\text{O}_2\text{C} \\ \\ \text{R} \end{array} \text{C}=\text{C} \begin{array}{c} \text{CO}_2\text{R}^2 \\ \\ \text{F} \end{array} \quad \xrightarrow[\text{toluene, r.t., 24h}]{\text{Ir-N,P catalyst, H}_2 \text{ (100 bar)}} \begin{array}{c} \text{R}^1\text{O}_2\text{C} \\ \\ \text{R} \end{array} \text{CH}(\text{F})\text{CH}_2\text{CO}_2\text{R}^2 + \begin{array}{c} \text{R}^1\text{O}_2\text{C} \\ \\ \text{R} \end{array} \text{CH}(\text{F})\text{CH}_2\text{CO}_2\text{R}^2 \quad \text{3 (de-F)}$
2a^b 96% conv. 92% yield 8% de-F >99% dr, >99% ee	2b^c 91% conv. 86% yield 9% de-F >99% dr, >99% ee
2c^c 99% conv. 97% yield 13% de-F >99% dr, >99% ee	2d 99% conv. 98% yield 7% de-F >99% dr, >99% ee
2e 99% conv. 97% yield 9% de-F >99% dr, >99% ee	2f^d 99% conv. 97% yield 10% de-F >99% dr, >99% ee
2g^d 99% conv. 97% yield 6% de-F >99% dr, >99% ee	2h 99% conv. 97% yield 7% de-F >99% dr, >99% ee
2i^d 99% conv. 98% yield 9% de-F >99% dr, >99% ee	2j^e 99% conv. 96% yield 15% de-F >99% dr, >99% ee
2k^d 99% conv. 98% yield 7% de-F >99% dr, >99% ee	2l^f 20% conv. 19% yield 0% de-F >99% dr, 96% ee
2m^g 31% conv. 30% yield 0% de-F >99% dr, 97% ee	2n^g 22% conv. 20% yield 0% de-F >99% dr, >99% ee
2o^h 51% conv. 48% yield 2% de-F >99% dr, >99% ee	2p 40% conv. 38% yield 16% de-F >99% dr, 91% ee

^aReaction conditions: 0.05 mmol of substrate, 1 mol % of catalyst F, 0.5 mL of toluene. The conversion was determined by ¹H NMR. Yields are isolated hydrogenated product, in some cases containing small amounts of de-F product. Enantiomeric excess was determined by SFC or GC/MS using chiral stationary phases. ^bWith 1.0 mol % of catalyst F, 8% de-F byproduct. ^cWith 1.5 mol % of catalyst F. ^dWith 2 mol % of catalyst F. ^eWith 4 mol % of catalyst F. ^fWith 2 mol % of catalyst A. ^gWith 3 mol % of catalyst A. ^hWith 4 mol % of catalyst D.

Interestingly, substrates having aliphatic substituents can be hydrogenated in high levels of stereoselectivity, albeit in lower yield (27% conversion with 15% de-F) and inferior enantioselectivity (87% ee), as was observed for diethyl 2-fluoro-3-methylmaleate substrate using catalyst F. Catalyst A was used to hydrogenate diethyl 2-fluoro-3-methylmaleate to give **2l** in 96% ee without any generation of de-F product (0%). Similarly, various aliphatic substituted 3-fluoromaleates reacted sluggishly under the optimal reaction conditions but with excellent enantioselectivity. For ethyl-3-fluoromaleate or isopropyl-3-fluoromaleate, using catalyst A, product diethyl 2-ethyl-3-fluorosuccinate **2m** (97% ee) or 2-fluoro-3-isopropylsuccinate **2n** was obtained in excellent ee (>99%) without de-F. Catalyst D (4 mol %) proved to be more beneficial for hydrogenation of *tert*-butyl-3-fluoromaleate, affording diethyl 2-(*tert*-butyl)-3-fluorosuccinate **2o** in 51% conversion with excellent >99% ee and almost no defluorination (2% de-F). The aliphatic substrate dimethyl 2-fluoro-3-propylmaleate was hydrogenated using catalyst F to give dimethyl 2-fluoro-3-propylsuccinate **2p** in 40% conversion and in good enantioselectivity (91% ee). Using the reaction conditions reported here, various types of fluoromaleate were hydrogenated to the corresponding fluorosuccinate in mostly good to excellent yield, with exceptional diastereoselectivities and enantioselectivities (>99%). Most significantly, with no or very small amounts of de-F being observed, this method emphasizes that this catalytic system is very general for fluoromaleate olefins.

To further explore the efficacy of this oxazoline N,P-iridium-catalyzed hydrogenation of vinyl fluorides, different types of substrates **4** containing various functional groups as well as substituents (Table 4) were evaluated under the hydrogenation

Table 4. Hydrogenation of Various Vinyl Fluoride Containing Different Functional Groups^a

$\begin{array}{c} \text{R}^1 \\ \\ \text{R} \end{array} \text{C}=\text{C} \begin{array}{c} \text{F} \\ \\ \text{R}^2 \end{array} \quad \xrightarrow[\text{CH}_2\text{Cl}_2, \text{ r.t., 24h}]{\text{Ir-N,P catalyst (F), H}_2 \text{ (20 bar)}} \begin{array}{c} \text{R}^1 \\ \\ \text{R} \end{array} \text{CH}(\text{F})\text{CH}_2\text{R}^2 + \begin{array}{c} \text{R}^1 \\ \\ \text{R} \end{array} \text{CH}(\text{F})\text{CH}_2\text{R}^2 \quad \text{6}$
5a 90% yield (>99%) >99% dr, 98% ee	5b 99% yield (>99%) >99% dr, 97% ee
5c 71% yield (>99%) >99% dr, 98% ee	5d 42% yield (>99%) >99% dr, 98% ee
5e 94% yield (>99%) >99% dr, 98% ee	5f 99% yield (>99%) >99% dr, 97% ee
5g 99% yield (>99%) >99% dr, 91% ee	5h^b 99% yield (>99%) >99% dr, 90% ee
5i 99% yield (>99%) >99% dr, 97% ee	5j 99% yield (>99%) >99% dr, >99% ee
5k 99% yield (>99%) >99% dr, 91% ee	5l 99% yield (>99%) >99% dr, 93% ee

^aReaction conditions: 0.05 mmol of substrate, 1 mol % of catalyst F, 0.5 mL of CH₂Cl₂. Enantiomeric excess was determined by SFC or GC/MS using chiral stationary phases. ^bWith 2 mol % of catalyst F.

Table 5. Hydrogenation of Various Aliphatic Vinyl Fluorides^a **Scheme 2. (a) Atom-Economical Preparation of 3-Fluorobutan-2-yl)benzene and (b) Synthesis of Ethyl 2,4,4,4-Tetrafluoro-3-phenylbutanoate**

with two contiguous stereogenic centers, one chiral center containing F and another CF₃, was synthesized.

Finally, we wanted to demonstrate the usefulness of the hydrogenated fluorosuccinates as precursors for the synthesis of various types of enantiomerically enriched fluorine containing compounds. The two esters in the hydrogenated product 2c can easily be differentiated by an orthogonal deprotection using Pd–C in toluene under 1 bar hydrogen pressure to give the desired 4-ethoxy-3-fluoro-4-oxo-2-phenylbutanoic acid 14 in 90% isolated yields as well as excellent ee (>99%) (Scheme 3).

We also performed a gram-scale control experiment. Applying 0.5 mol % of catalyst F and scaling up the reaction to 1 g of starting material (4j), 5j was obtained with a similar result (99% yield, no defluorination, >99% dr, and 97% ee) (Scheme 4). Accordingly, this Ir-catalyzed hydrogenation reaction was confirmed to be particularly robust solution for the large-scale production of chiral fluorine molecules with two

Scheme 3. Conversion of Fluorosuccinates to Ethoxy-3-fluoro-4-oxo-2-phenylbutanoic Acid

Scheme 4. Gram-Scale Production of Chiral Fluorine Molecules with Two Contiguous Stereogenic Centers

CONCLUSION

In conclusion, we have developed a new azabicyclo iridium oxazoline phosphine complex, which is very selective and efficient in the hydrogenation of tetra-substituted vinyl fluorides. The reaction enables a simple yet highly stereoselective preparation of chiral fluorine molecules with two contiguous stereogenic centers. The developed protocol has an exceptionally wide substrate scope and is equally effective for various aromatic and aliphatic tetra-substituted vinyl fluorides, providing chiral fluoroalkanes in excellent yield, diastereoselectivity, and enantioselectivity. In addition, another major improvement of this simple but unique catalytic hydrogenation process is that it significantly overcomes the problems of defluorination.

ASSOCIATED CONTENT

Supporting Information

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Additional experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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Scheme 5. Determination of Absolute Configuration of Olefin 4d

on the oxazoline ring occupies quadrant i, which becomes the sterically hindered quadrant. The *o*-EtPh groups on the phosphorus partially occupy quadrant iv, which therefore becomes the semihindered quadrant. The other quadrants (ii and iii) do not have any significant parts of the ligand pointing toward the incoming alkene and are considered to be open quadrants. For the tetra-substituted vinyl fluorides, the olefin (**4d**) is placed *trans* to phosphorus in such a way that the smallest substituents (F) occupy the hindered quadrant i to give the most sterically favored arrangement (Scheme 5d). The other arrangements are sterically unfavored. So according to this model, the predicted absolute configuration of the hydrogenated product **5d** would be 2R,3R. This absolute configuration was confirmed by transformation into the known allylic alcohol.²⁵

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