Catalytic enantioselective synthesis of fluoromethylated stereocenters by asymmetric hydrogenation

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Fluoromethyl groups possess specific sterically and electronically properties that serve as bioisosteres of alcohol, thiol, nitro, and other functional groups, which are important in an assortment of molecular recognition processes. Herein we report a catalytic method for the asymmetric synthesis of a variety of enantioenriched products bearing fluoromethylated stereocenters with excellent yields and enantioselectivities. Various N,P-ligands were designed and applied in the hydrogenation of fluoromethylated olefins and vinyl fluorides.

Introduction

Organofluorine compounds, on the basis of their special chemical and biological properties, are widely used in pharmaceuticals, agrochemistry, and materials science. In pharmaceuticals, the incorporation of a fluorine atom or fluorinated group into a biologically active compound usually modifies the biological and physicochemical properties by improving potency, lipophilicity, metabolic stability, binding affinity, and bioavailability. As a result, fluoromethylated analogues have become a potential class of drug candidates to be useful in structure-based drug design. In terms of biososterism, monofluoromethyl (CHF₂) and difluoromethyl (CHF₂) groups are inert, isosteric and isopolar to an OH or SH group in biologically active molecules and enzyme active sites. As a result, a variety of structurally diverse CH₂F, CHF₂ and CF₃ containing drugs have been developed (Fig. 1).[1,2]

Hence, in modern organic chemistry and in drug discovery, the development of versatile fluoromethylated molecules in an efficient fashion (especially in enantioenriched version) are very active research areas. Although distinct approaches[3] are available for the asymmetric construction of the C(sp³)–CF₃ function, little attention has been devoted towards asymmetric construction of the C(sp³)–CHF₂ and C(sp³)–CH₂F functions. The most common used strategies for the construction of the C(sp³)–CHF₂ stereocenter are monofluoromethylation using 1-fluorobis(phenylsulfonyl)methane (FBSM), fluoro(phenylsulfonyl)methane (FSM), 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide (FBDT), or α-fluoro-α-nitro(phenylsulfonyl)methane as the fluoromethide equivalent (Scheme 1A).[4] Other strategies consist of diastereoselective monofluoromethylation of chiral N-(tert-butylsulfinyl)aldimines/ketimines using fluoromethyl phenyl sulphone. Enantioenriched difluoromethylated compounds are synthesized by reacting nucleophiles or electrophiles with difluoromethylation reagents, for example, PhSO₂CF₂H, TMSCF₂Ph, Me₂SiCF₂H, Me₂SiCF₂SO₂Ph, HCF₂SO₂Cl, etc., or asymmetric addition of CF₂H containing prochiral compounds such as imines, olefins, and carbonyl groups (Scheme 1B).[5] However, the existing methods often require complex reaction conditions. Reduction of fluoromethylalkenes, on the other hand, remains unexplored but could be a broadly effective strategy for the construction of enantioenriched stereogenic centers bearing either CH₂F, CHF₂ or CF₃ group by using a single general strategy.[6,7,8,9,10]

**Fig. 1** Fluoromethylated drugs.
In asymmetric catalysis, enantioselective hydrogenation of alkenes using an appropriate transition metal catalyst and chiral ligand is one of the most fundamental and atom-economic processes. Rh and Ru catalysts are widely used for asymmetric hydrogenation of olefins having strong coordinating functional group such as amides or carboxylic acids in close proximity to the double bond. For olefins having weak coordinating groups or non-coordinating groups, Ir complexes are the most effective catalyst. Several Ru<sup>III</sup>,<sup>11</sup> Rh<sup>I</sup>,<sup>12</sup> and Pd<sup>II</sup> (ref. 15) complexes were found effective for hydrogenation of some specific CF<sub>3</sub> substituted olefins with a coordinating group near the substrate double bond (Scheme 1C, left). Fortunately, Ir complexes complement the substrate limitations of Rh/Ru catalyzed enantioselective hydrogenation and are efficient catalysts for enantioselective hydrogenation of CF<sub>3</sub> substituted olefins with the weak chelating group. In our previous knowledge of iridium-N,P<sub>13</sub> complex (catalyst <b>F</b>) we investigated the effect of varying the substituents on phosphine. Replacing the aliphatic iPr group with aromatic group (Ph) resulted in a slight change of enantioselectivity to 92% ee with 72% conversion (entry 3). However, replacing the phenyl group with ortho-tolyl group on the bicyclic thiazole iridium-N,P catalyst (catalyst <b>D</b>) resulted in complete conversion (99%) to the desired product <b>2a</b> with the same level of enantioselectivity (92% ee, entry 4).

Further optimization of the reaction conditions with catalyst <b>D</b> was carried out by lowering the catalyst loading from 1.0 mol% to 0.5 mol% as well as the H<sub>2</sub> pressure from 10 bar to 5 bar, respectively (Table 1, entry 5, for details, see ESI†). Using PhCF<sub>3</sub> as solvent (entry 7) provided slightly better enantioselectivity (94% ee). To further increase enantioselectivity, we prepared a few new catalysts by varying the electronic density and steric hindrance on phosphorus. Catalyst with 2,4-di-MePh substituent (catalyst <b>E</b>, entry 8) gave the same result as complex <b>F</b>. Changing the ortho-tolyl group to an o-ethylphenyl group afforded new thiazole N,P-iridium complex <b>G</b> with slightly improved enantioselectivity (95% ee, entry 9). Gratifyingly, adding a small electron-withdrawing (F) substituent on the aromatic ring of thiazole moiety (catalyst <b>H</b>) led to the best result in terms of enantioselectivity (96% ee) and conversion (99%, entry 10).

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**Scheme 1** Strategies for the construction of fluoromethylated stereocenters. (A) Construction of the C(sp<sup>3</sup>)–CH<sub>2</sub>F stereogenic center; (B) construction of the C(sp<sup>3</sup>)–CH<sub>2</sub>F stereogenic center; (C) construction of the fluoromethylated stereogenic center via hydrogenation; (D) This work.

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**Results and discussion**

Difluoromethylated olefins were first chosen as the fluoromethylated olefin substrate for our study. We used (E)-ethyl 4,4-difluoro-3-phenylbut-2-enoate <b>1a</b> as the model substrate and an iridium complex with a bicyclic backbone ligand as the catalyst for this asymmetric hydrogenation (Table 1). Hydrogenation of <b>1a</b> using azabicyclo iridium oxazoline phosphine complex <b>A</b> (1 mol% catalyst, CH<sub>2</sub>Cl<sub>2</sub>, 10 bar H<sub>2</sub>) gave excellent conversion in 4 h but poor enantioselectivity (95% conversion, 21% ee) of the desired product <b>2a</b> (entry 1). However, the thiazole N,P-iridium complex <b>B</b> dramatically increased the enantioselectivity (91% ee) with very good conversion (91%, entry 2). Based on our previous knowledge of iridium-N,P catalyzed asymmetric hydrogenation,<sup>e,f</sup> we investigated the effect of varying the substituents on phosphine. Replacing the aliphatic iPr group with aromatic group (Ph) resulted in a slight change of enantioselectivity to 92% ee with 72% conversion (entry 3). However, replacing the phenyl group with ortho-tolyl group on the bicyclic thiazole iridium-N,P catalyst (catalyst <b>D</b>) resulted in complete conversion (99%) to the desired product <b>2a</b> with the same level of enantioselectivity (92% ee, entry 4).

Further optimization of the reaction conditions with catalyst <b>D</b> was carried out by lowering the catalyst loading from 1.0 mol% to 0.5 mol% as well as the H<sub>2</sub> pressure from 10 bar to 5 bar, respectively (Table 1, entry 5, for details, see ESI†). Using PhCF<sub>3</sub> as solvent (entry 7) provided slightly better enantioselectivity (94% ee). To further increase enantioselectivity, we prepared a few new catalysts by varying the electronic density and steric hindrance on phosphorus. Catalyst with 2,4-di-MePh substituent (catalyst <b>E</b>, entry 8) gave the same result as complex <b>D</b>. Changing the ortho-tolyl group to an o-ethylphenyl group afforded new thiazole N,P-iridium complex <b>F</b> with slightly improved enantioselectivity (95% ee, entry 9). Gratifyingly, adding a small electron-withdrawing (F) substituent on the aromatic ring of thiazole moiety (catalyst <b>H</b>) led to the best result in terms of enantioselectivity (96% ee) and conversion (99%, entry 10). On the other hand, the electron-donating (OMe) substituent on aromatic ring of thiazole moiety (catalyst <b>H</b>) led to a dramatic decrease in enantioselectivity (94% ee, entry 10).

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**Table 1** Optimization study<sup>a</sup>

| Entry | Catalyst (mol%) | H<sub>2</sub> (bar) | Solvent | Time (h) | Conversion (%) | ee (%) |
|-------|-----------------|-------------------|---------|----------|----------------|-------|
| 1     | A (1.0)         | 10                | CH<sub>2</sub>Cl<sub>2</sub> | 4        | 95             | 21    |
| 2     | B (1.0)         | 10                | CH<sub>2</sub>Cl<sub>2</sub> | 4        | 91             | 91    |
| 3     | C (1.0)         | 10                | CH<sub>2</sub>Cl<sub>2</sub> | 4        | 72             | 92    |
| 4     | D (1.0)         | 10                | CH<sub>2</sub>Cl<sub>2</sub> | 4        | 99             | 92    |
| 5     | D (0.5)         | 5                 | CH<sub>2</sub>Cl<sub>2</sub> | 4        | 99             | 92    |
| 6     | D (0.5)         | 5                 | Toluene | 4        | 99             | 93    |
| 7     | D (0.5)         | 5                 | PhCF<sub>3</sub> | 4        | 99             | 94    |
| 8     | E (0.5)         | 5                 | PhCF<sub>3</sub> | 4        | 99             | 94    |
| 9     | F (0.5)         | 5                 | PhCF<sub>3</sub> | 4        | 99             | 95    |
| 10    | G (0.5)         | 5                 | PhCF<sub>3</sub> | 4        | 99             | 96    |
| 11    | H(0.5)          | 5                 | PhCF<sub>3</sub> | 4        | 17             | 90    |

<sup>a</sup> Reaction conditions: 0.05 mmol of <b>1a</b>, 0.5 mL solvent. The conversion was determined by 1H-NMR. Enantiomeric excess was determined by GCMS using a chiral stationary phase.
to much lower conversion (17%) and slightly lower enantioselectivity of 90% ee (entry 11). Thus, among these effectively designed new catalyst, a phenyl ring with F atom at para position on thiazole moiety and ortho-tolyl group on phosphorus (catalyst G, 0.5 mol%) in PhCF₃ under 5 bar H₂ pressure for 4 h provided the superior result in enantioselectivity (96% ee) with excellent 99% conversion (entry 10).

With the optimized reaction conditions established, we evaluated the hydrogenation of various (E)-fluorinated olefins 1 having different substituents (Table 2). A variety of difluoromethylated olefins (E)-1a–1l having different ester groups and with either electron-donating or electron-withdrawing substituents on the phenyl rings were successfully hydrogenated to deliver the desired products 2a–2l in excellent yield (94–99%) and enantioselectivities (90–98% ee). When evaluating the Z-isomer (Z-1f, Z-1g and Z-1m), lower enantioselectivities but the same major enantiomers were observed (83% ee, 75% ee and 72% ee, respectively). Interestingly, substrates with electron-withdrawing substituents seem advantageous for higher enantioselectivity. Carbocyclic CHF₂ olefins (1n–1o) were hydrogenated in excellent yield but with significant variations in enantioselectivities. Benzo-fused cyclohexyl ring substrate 1n gave 77% ee while substrate with five-member ring (1o) provided 99% ee. Aliphatic CHF₂ olefins were also tested and they generally resulted in lower reactivity. Nevertheless, we managed to hydrogenate compound 1p with a moderate conversion and good ee (90%). When the H on CHF₂ group was replaced by strong electron- withdrawing CF₃ group, the olefin was also hydrogenated much sluggishly and provided 2q in only 43% yield with 81% ee. After successfully hydrogenating various trisubstituted (E)-CHF₂ olefins, tetrasubstituted CHF₂ olefin (1r) was efficiently hydrogenated [2r] in 99% yield, excellent diastereoselectivity (>99% d.r.) and enantioselectivity (91% ee). The effectiveness of this stereoselective hydrogenation process was further investigated by evaluating various CF₃ containing olefins to produce chiral CF₃ alkanes. Various CF₃ containing trisubstituted β,β-unsaturated esters or ketone were successfully hydrogenated under the standard conditions with good yields [80–99%] and enantioselectivities [87–96% ee, 2s–2u]. Similarly, the developed protocol was equally efficient for tetrasubstituted CF₃ containing aliphatic olefins (1v and 1w) which were efficiently hydrogenated in excellent yields (99%) and diastereoselectivities (>99% d.r.) with high enantioselectivity (88%)

Table 2 Substrate scope²

| Entry | Substrate Structure | Product Structure | Yield (%) | ee (%) |
|-------|---------------------|------------------|----------|-------|
| a     | R=H, Cat. D         | R=Me            | 95       | 92    |
| b     | R=F, Cat. G         | R=Me            | 99       | 93    |
| c     | R=Me                | R=Me            | 99       | 92    |
| d     | R=Me                | R=Me            | 99       | 91    |
| e     | R=Me                | R=Me            | 99       | 90    |
| f     | R=Me                | R=Me            | 99       | 89    |
| g     | R=Me                | R=Me            | 99       | 87    |
| h     | R=Me                | R=Me            | 99       | 86    |
| i     | R=Me                | R=Me            | 99       | 84    |
| j     | R=Me                | R=Me            | 99       | 82    |

² Reaction conditions: 0.15 mmol of E-substrate, 0.5 mol% catalyst G, 5 bar H₂, 1.5 mL PhCF₃, 4 h. ³ 1.0 mol% catalyst ent-D, 100 bar H₂. ⁴ 0.5 mol% catalyst D, 10 bar H₂, 1.5 mL CH₂Cl₂. ⁵ 2.0 mol% catalyst D, 10 bar H₂, 1.5 mL CH₂Cl₂. Yields are isolated hydrogenated product. Enantiomeric excess was determined by SFC or GCMS using chiral stationary phases.
and 82% ee respectively). In addition, CH$_2$F containing olefin was also hydrogenated in an exceptionally good yield (99%) with good enantioselectivity (84% ee) and slight defluorination (9%). The successful examples in Table 2 emphasizes that this azabicyclo iridium thiazole phosphine catalyst is very general for various fluoromethylated olefins.

To further study the effectiveness of this developed method for the catalytic asymmetric synthesis of fluoromethylated stereogenic centers, a different class of olefins (vinyl fluoride), which affords the chiral monofluorinated molecule, was also evaluated. For these vinyl fluorides, catalyst B (1 mol%) was the most suitable catalyst using 20 bar H$_2$ pressure for 24 h (see ESI for optimization details). Employing the newly optimized reaction conditions, a variety of unfunctionalized naphthalene fused vinyl-fluoride substrates were efficiently hydrogenated in excellent enantioselectivity (90–98% ee, Table 3, 4a–h) although in some cases the conversions are low (3c, 73%; 3d, 40%; 3e, 40%; 3h, 70%). Notably, substrates having the bulky secondary (Pr, Cy) substituent were hydrogenated in high levels of stereoselectivity (4d–e). Both substrates with electron-donating (Me, OMe) or electron-withdrawing (F) substituents were tolerated (3f–h), however; substrates bearing electron-donating substituents were slightly more favorable in terms of reactivity (3f–g). A small amount of de-F byproduct (3–11%) were detected in the hydrogenation, however considering the challenges generally associated with hydrogenation of vinyl-fluoride, this efficient hydrogenation still highlights this catalytic protocol as general for fluorne-containing olefins to synthesize enantioenriched fluoromethylated compounds.

Interestingly, in this work, an enantioconvergent outcome was observed, where the E and Z isomers of fluoromethylated olefins were successfully hydrogenated using catalyst ent-D. Both isomers produced the same enantiomer in favor. The three different types of fluoromethylated olefins, including CH$_2$F, CHF$_2$ and CF$_3$ groups, underwent enantioconvergent hydrogenation (Table 4, entries 1–3). However, removal of fluorine from the substrate (Table 4, entry 4) provided an enantiodivergent hydrogenation outcome (Table 4, entry 4), which suggested fluorine played an important role in the enantio-discrimination step. Our recent work on an efficient convergent hydrogenation using Ir–N,P complexes with a weak chelating group on the double bond suggested that z-prochiral olefins underwent an enantioconvergent hydrogenation while b-prochiral olefins reacted in an enantidivergent manner. In this case, conversely, b-prochiral fluoromethylated olefin react in an enantioconvergent manner. We speculate that this could be due to the chelation effect or the electronic effect of the fluorine atom. Further investigations are still in progress.

The efficacy of the asymmetric synthesis of fluoromethylated compounds were investigated in gram-scale under standard reaction conditions. Product 2a was obtained in 97% yield with 96% ee (Scheme 2). This synthesized enantioenriched fluoromethylated compound was transformed into a variety of many useful chiral fluorinated derivatives, such as alcohol, aldehyde, acid, Weinreb amide, ketone and nitrile (Scheme 2A) with almost perfect retention of enantiopurity. Interestingly, acid 11 provided (S)-3-(dichloromethyl)-2,3-dihydro-1H-inden-1-one 13 under Friedel–Crafts reaction condition. In the presence of AlCl$_3$, difluoromethyl group underwent halogen exchange while preserving enantioenriched purity. Based on these successful transformations, some difluoromethylated natural products were accessed (Scheme 2B). Weinreb amide 14 was further transformed into difluorinated analogue of natural products 15. Synthetically versatile intermediate alcohol was transferred into bromide 17 which could be further transformed into the difluorinated analogue of alpha-curcumene 18.

| Table 3 | Hydrogenation of various vinyl-fluorides |

| Entry | Olefin | Isomer Product Conversion (%) ee (%) |
|-------|--------|-------------------------------------|
| 1     | E-1a   | 99                                  | 92 (S) |
| 2     | Z-1a   | 99                                  | 55 (S) |
| 3     | E/Z (1:1) | 99                        | 71 (S) |
| 4     | 99 (9% de-F) | 84 (S)                         |

| Table 4 | Hydrogenation of both E and Z isomers of fluoromethylated and non-fluoromethylated olefins |

| Entry | Olefin | Isomer Product Conversion (%) ee (%) |
|-------|--------|-------------------------------------|
| 1     | E-1a   | 99                                  | 92 (S) |
| 2     | Z-1a   | 99                                  | 55 (S) |
| 3     | E/Z (1:1) | 99                        | 71 (S) |
| 4     | 99 (9% de-F) | 84 (S)                         |

a Reaction conditions: 0.05 mmol of substrate, 1.0 mol% catalyst ent-D, 0.5 mL PhCF$_3$, 10 bar H$_2$. Enantiomeric excess was determined by SFC or GCMS using chiral stationary phases.

|$^a$ Reaction conditions: 0.15 mmol of substrate, 1.0 mol% catalyst B, 3 mL PhCF$_3$, 20 bar H$_2$. Yields are isolated hydrogenated product.

$^b$ The conversion was determined by $^1$H-NMR. Enantiomeric excess was determined by HPLC or GCMS using chiral stationary phases.
Conclusions

In summary, we have developed a catalytic, asymmetric methodology to synthesize various products bearing fluoromethylated stereocenters, which are important bioisosteres in drug discovery. Different types of fluoromethylated olefins and vinyl fluorides were hydrogenated successfully by effective new catalyst design. In addition, an interesting enantioconvergency was observed, which indicated that fluorine has the potential to control the enantioselectivity due to its special properties.

Data availability

All experimental data associated with this work are available in the ESI.

Author contributions

P. G. Andersson and T. Zhou supervised the project and conceived experiments. J. Yang and S. Ponra designed the project, optimized the reaction, performed the major of experiments, and prepared the Supporting Information. X. Li, B. B. C. Peters, and L. Massaro prepared some of the starting materials and evaluated some hydrogenation reactions. P. G. Andersson, J. Yang, and S. Ponra wrote the paper. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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