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RESEARCH ARTICLE

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Asymmetric Synthesis of Alkyl Fluorides: Hydrogenation of Fluorinated Olefins

Sudipta Ponra,[!a] Jianping Yang,[!a] Sutthichat Kerdphon[a] and Pher G. Andersson*[a,b]

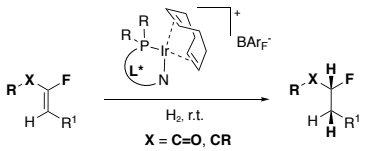
Abstract: The development of new general methods for the synthesis of chiral fluorine-containing molecules is important for several scientific disciplines. By the Ir-catalyzed asymmetric hydrogenation of *tri*-substituted vinyl-fluorides, a straightforward preparation of chiral organofluorine molecules is disclosed. The developed method represents a catalytic asymmetric process that enables the synthesis of chiral fluorine molecules with or without carbonyl framework. Owing to the tunable steric and electronic properties of azabicyclo iridium-thiazole-phosphine catalyst, this stereoselective reaction could be optimized and found compatible with various aromatic, aliphatic and heterocyclic systems with a variety of functional groups providing the highly desirable product in excellent yield and enantioselectivities.

Introduction

Stereo-defined organofluorine compounds possess unique physical properties and are highly important in agrochemicals, pharmaceuticals, material sciences[1] and medicinal chemistry.[2] Despite its widespread use as a pharmacological modulator; the asymmetric installation of fluorine onto organic molecules presents challenges. The limited number of asymmetric fluorine molecules[3] in nature makes its availability dependent on organic synthesis. Hence, the development of new, simple and efficient methods to access a diverse array of novel chiral fluorinated derivatives, has become a highly prioritized research area.[1b,4] Among the distinct approaches available for the asymmetric construction of the C(sp^3)-F stereogenic center,[4c,e] is the commonly exploited technique of α-fluorination of enolate or enolate-equivalents,[5] fluorination of olefins,[6] and asymmetric addition of nucleophilic fluorides to carbon electrophiles.[7] α-Fluorination of carbonyl derivatives is undeniably a viable strategy[5] however it is limited to either aldehyde,[5b,c,8] β-keto esters[9] or cyclic ketones[10] while simple acyclic ketonic substrates are met with difficulties. Although a number of fluorination methods for acyclic ketonic substrates have been reported,[11] the asymmetric version is still very limited.[11c-f] Most of the asymmetric methods require multi steps and have a limited substrate scope.[11c-e] Negishi cross coupling of racemic α,α-dihaloketones has been shown to be an effective strategy but is restricted to only aromatic tertiary alkyl fluorides.[11f] The tractability of such reported methods however, are restricted to substrates containing carbonyl groups. For substrates without a carbonyl group, other techniques are required for asymmetric generation of the C-F bond. Despite the availability of a variety of methods, a simple and general asymmetric protocol, irrespective of the presence of a carbonyl group, has remained comprehensively elusive for a long time. These limitations of asymmetric fluorination have prompted us to devise a new atom economical, highly enantioselective synthetic method for versatile fluorinated molecules.

Asymmetric hydrogenation of alkenes using transition metal catalysts is one of the most fundamental and atom economical processes for synthetic organic chemistry.[12] Moreover, excellent chemo-, regio-, and enantioselectivity can be obtained by the appropriate choice of metal and chiral chelating ligand. The presence of strongly coordinating functional groups such as amides and carboxylic acids in close proximity to the double bond facilitates hydrogenation with the use of Rh, Ru or Ir catalysts.[13] For olefins having no coordinating or only weakly coordinating groups, Ir complexes are the catalysts of choice.[14] Usually, for iridium-catalyzed hydrogenations, the smallest substituent (hydrogen for a trisubstituted olefin) determines which enantioface of the olefin preferentially coordinates to Ir in the enantioselectivity-determining transition state. Having two small substituents (H and F) in tri-substituted vinyl-F presents a challenge since more than one orientation of the olefin is possible, resulting in enantiomeric mixtures of the product. The electron withdrawing behavior of the fluorine together with frequent de-fluorination (de-F) that occurs during hydrogenation, makes *tri*-substituted vinyl-fluorides even more difficult substrates to hydrogenate.[15]

Vinyl fluorides are however relatively easy to prepare and the development of a suitable catalyst for the asymmetric hydrogenation of *tri*-substituted vinyl fluorides would enable the generation of various chiral fluorine molecules with and without the carbonyl framework, in one simple step.[16] With the above-mentioned limitations in mind, we set out to develop an atom economical protocol for asymmetric hydrogenation of *tri*-substituted vinyl fluorides (Scheme 1).



Scheme 1. Atom economical synthesis of asymmetric fluorine motifs.

Results and Discussion

Recently, we successfully developed a diastereo- and enantioselective synthesis of fluorine motifs with two contiguous stereogenic centers by highly selective and efficient hydrogenation of *tetra*-substituted vinyl fluorides.[16d] Motivated by this accomplishment, we selected (*Z*)-2-fluoro-1,3-diphenylpropenone **1a** as an the model substrate and azabicyclo iridium oxazoline phosphine complex **A** as the catalyst for this asymmetric hydrogenation. However, applying our previously

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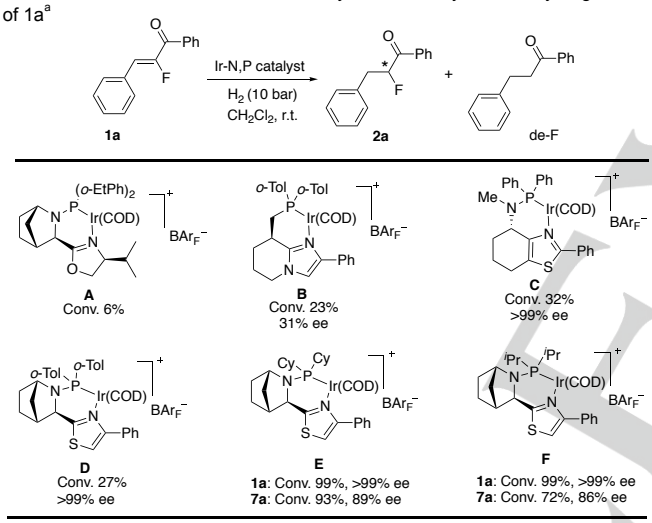
optimized catalytic method (1 mol% catalyst, CH_2Cl_2, 10 bar H_2) to substrate **1a** gave only trace amounts (6% conversion) of the desired product **2a** (Table 1). Based on our previous knowledge of N,P-iridium-catalyzed asymmetric hydrogenation,[16a,b] we started to optimize the basic skeleton of the heterocycle of the N,P-iridium complex. Imidazole **B** provided a comparable result of 23% conversion of starting material **1a** to **2a** but with poor enantioselectivity (31% ee). Encouragingly, the thiazole N,P-iridium complex dramatically increased the enantioselectivity (>99% ee). However, despite their high enantioselectivity, both catalysts **C** and **D** provided moderate conversion (32% and 27% respectively) of the desired product (entries 3 and 4). Next, the effect of the substituents on phosphine was studied. Gratifyingly, replacing the two *ortho*-tolyl groups with suitable aliphatic substituents on the bicyclic thiazole N,P-iridium catalyst resulted in much higher conversion to the desired product **2**. Iridium complexes with cyclohexyl **E** or isopropyl **F** on the phosphorus resulted in the successful hydrogenation of **1a** in 99% conversion with excellent enantiomeric excess (>99%).

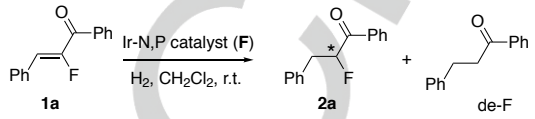
Table 1. Evaluation of N,P-iridium catalysts in the asymmetric hydrogenation of 1a[a]



[a] Reaction conditions: 0.05 mmol of **1a**, 1 mol% catalyst, 0.5 mL CH_2Cl_2. The conversion was determined by ^{1}H-NMR. Enantiomeric excess was determined by SFC.

After successfully designing the new effective catalyst **E** and **F**, we carried out further optimization of the catalyst loading and hydrogen pressure (Table 2). A decrease in the catalyst loading for substrate **1a** from 1.0 mol% (entry 1) to 0.5 mol% (entry 2) at 10 bar of H_2 pressure did not affect the conversion and enantioselectivity (99% conversion, >99% ee). However, a further decrease in the catalyst loading to 0.3 mol% (entry 3) significantly decreased the conversion (71%). By maintaining the catalyst loading at 0.5 mol% and decreasing the reaction time to 2 hours, the product was obtained with 99% conversion and >99% ee (entry 4). Reducing the reaction time to 1 hour gave 95% conversion (entry 5) with 0.5 mol% of catalyst **F**. A gradual decrease of the H_2 pressure from 10 bar (entry 4) to 5 bar (entry 6) using 0.5 mol% of catalyst **F** in 2 hours did not change the conversion. A further decrease in the pressure to 2 bar resulted in a lower conversion (entry 7). Remarkably, in all cases the enantioselectivity (>99% ee) was maintained. Hence, the optimal conditions with regards to conversion and enantioselectivity for substrate **1a** are 0.5 mol% catalyst loading of catalyst **F**, 5 bar H_2 pressure for 2 hours (entry 6). It should be mentioned that no defluorinated (de-F) product was detected which is a frequent problem in hydrogenations of vinyl fluorides.[15b]

Table 2. Optimization of hydrogenation of vinyl fluoride 1a[a]

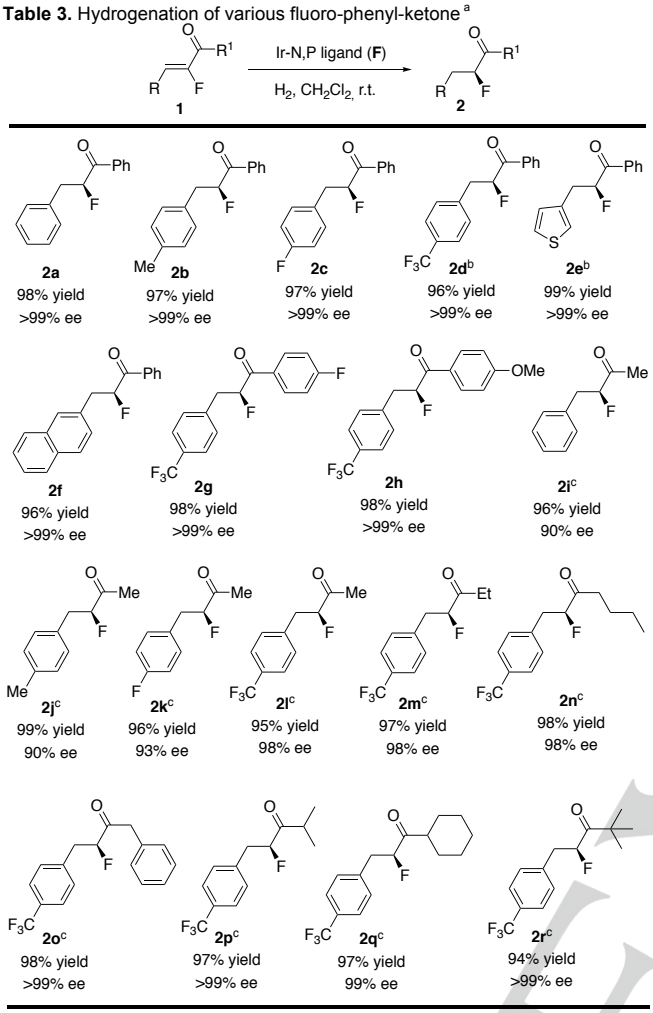


Entry	H_2 (bar)	Time (h)	Catalyst (mol%)	Conversion (%)	de-F	ee (%)[b]
1.	10	24	**F** (1.0)	99	0	>99
2.	10	24	**F** (0.5)	99	0	>99
3.	10	24	**F** (0.3)	76	0	>99
4.	10	2	**F** (0.5)	99	0	>99
5.	10	1	**F** (0.5)	95	0	>99
6.	5	2	**F** (0.5)	99	0	>99
7.	2	2	**F** (0.5)	77	0	>99

[a] Reaction conditions: 0.05 mmol of **1a**, 0.5 mL CH_2Cl_2. The conversion was determined by ^{1}H-NMR. Enantiomeric excess was determined by SFC.

With the optimized reaction conditions established, we evaluated the hydrogenation of various (*Z*)-3-fluoropent-3-en-2-one substrates **1** (Table 3) having different substituents. A variety of phenyl ketones were successfully hydrogenated to generate the desired products **2a**-**2h** in excellent yield and enantioselectivity. The (*Z*)-2-fluoro-1,3-diphenylprop-2-en-1-one substrates with either electron-donating or electron-withdrawing substituents on the phenyl rings were well tolerated and provided high isolated yields and excellent enantioselectivities of the desired products. Replacing the phenyl with the heterocyclic (3-thienyl) or 2-naphthyl substituent yielded **2e** (99% yield) or **2f** (96% yield) in excellent ee (>99%). Next we examined the effect of replacing the carbonyl phenyl substituent into various aliphatic side chains. For these substrates the optimal reaction conditions were 1.0 mol% of catalyst **G**, 10 bar H_2 pressure for 24 hours. Methyl substituted substrates performed very well irrespective of the electron-donating and electron-withdrawing substituents in the aromatic ring with excellent yields and enantioselectivities. Interestingly, substrates with electron-withdrawing substituents seem advantageous for higher enantioselectivity. Various substituted (*Z*)-3-fluoro-4-(4-(trifluoromethyl)phenyl)but-3-en-2-ones where Me was replaced with other aliphatic substituent such as Et, ^{n}Bu or Bn also reacted smoothly and resulted in excellent yields (97-98%) and enantiomeric excess (98->99% ee). Secondary (^{i}Pr, Cy) and tertiary aliphatic groups (^{t}Bu), all afforded the desired products **2p**, **2q** and **2r** in exceptional yields (94-97%) and ee (99->99%). Another significant aspect is that no de-F was observed in any of these examples, which underlines the usefulness of this catalytic method.

Table 3. Hydrogenation of various fluoro-phenyl-ketone [a]

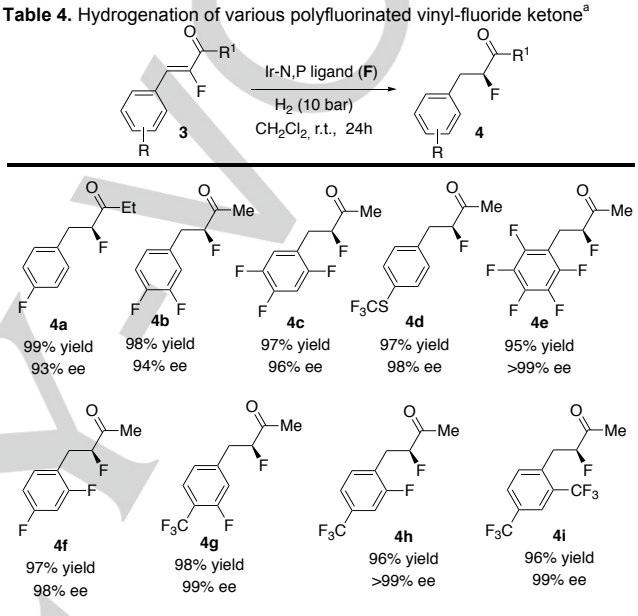


[a] Reaction conditions: 0.05 mmol of substrate, 0.5 mol% catalyst **F**, 5 bar H_2, 0.5 mL CH_2Cl_2, 2h. [b] Reaction time 6h. [c] 1.0 mol% catalyst **F**, 10 bar H_2, 24h. Yields are isolated hydrogenated product. Enantiomeric excess was determined by SFC or GC/MS using chiral stationary phases.

Considering that polyfluorinated compounds are very useful molecules in various scientific disciplines[17] as well as the fact that de-F during hydrogenation of vinyl-fluorides presents potential challenges,[15] a further study of polyfluorinated vinyl fluoride ketones was carried out (Table 4). A number of polyfluorinated substrates were evaluated under standard conditions and irrespective of the position of the fluorine or trifluoromethyl in the aromatic ring, no trace of de-F products was observed. In all cases, high yields (95-99%) and enantioselectivities (93->99% ee) were obtained for the polyfluorinated products.

The efficacy of this stereoselective hydrogenation process was further investigated by evaluating various substrates that would produce completely aliphatic chiral fluorine molecules (Table 5). It was observed that the developed protocol was not dependent on the aliphatic or aromatic nature of the substituents and gratifyingly a number of aliphatic vinyl fluorides were also efficiently hydrogenated in good to excellent yield with very high enantioselectivitiy. Interestingly, various acyclic or cyclic primary (**6a**-**6g**), secondary (**6h**-**6n**), and tertiary (**6o**) aliphatic substituents afforded excellent results. However, the conversion of the aliphatic substrates occasionally depends on the sterics around the C=C double bond of the vinyl-F. These steric effects were easily overcome by using a higher pressure (50 bar), which led to good yields for bulky aliphatic substituent products such as **6i**, **6l**, and **6n** as well as the tertiary aliphatic substituted product **6o**. Thus, the challenging aliphatic fluorine molecules with different substituents were effectively synthesized with good to excellent yield and ee, which shows the extended scope of this hydrogenation process.

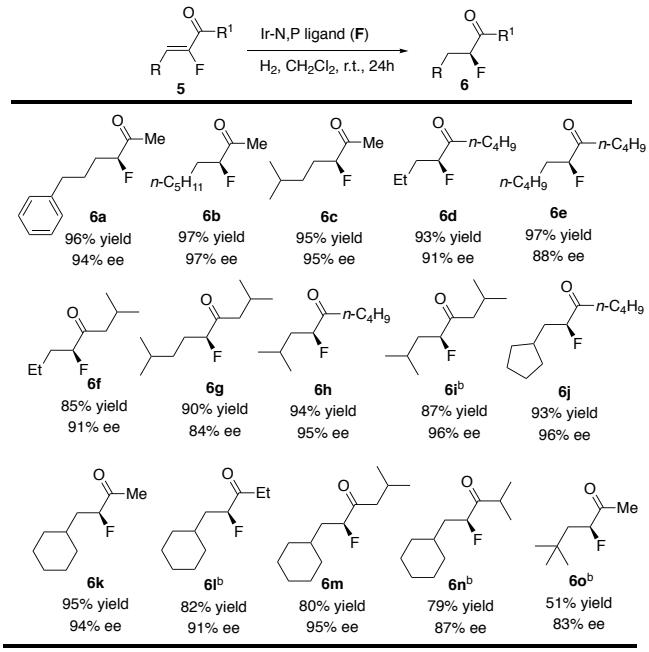
Table 4. Hydrogenation of various polyfluorinated vinyl-fluoride ketone[a]



[a] Reaction conditions: 0.05 mmol of substrate, 1 mol% catalyst **F**, 0.5 mL CH_2Cl_2. Yields are isolated hydrogenated product. Enantiomeric excess was determined by GC/MS using chiral stationary phases.

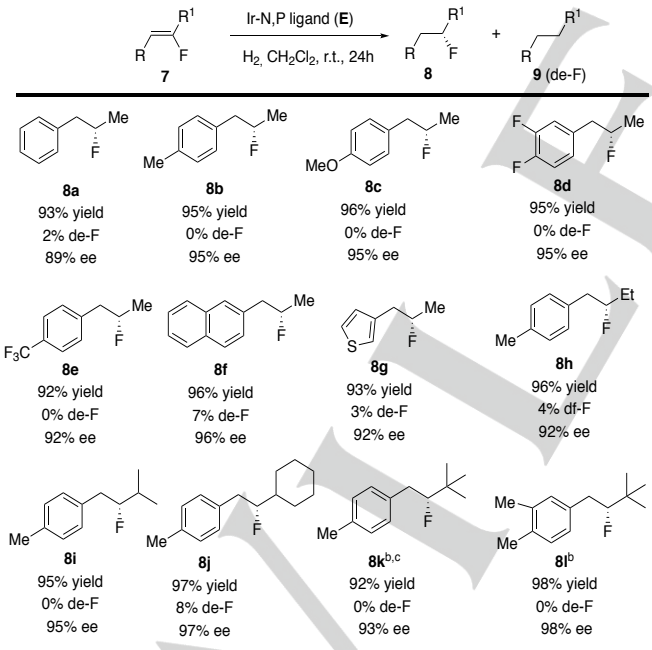
To further study the effectiveness of this developed method for the catalytic asymmetric synthesis of alkyl fluorides, various vinyl fluorides without a carbonyl functional group were also evaluated. For this class of substrates it was found that catalyst **E** is most suitable (see Supporting Information for optimization details). Employing the same conditions as used previously, catalyst **E** was found effective for a variety of un-functionalized vinyl-fluoride substrates and produced no or very small amounts of de-F product (Table 6). Electron-donating (-Me and -OMe) or electron-withdrawing (-F, -CF_3) substituents on the aromatic ring were both tolerated however; the electron-donating substituent on the benzene ring was slightly favorable both in terms of yield and enantioselectivity. Naphthyl or heterocyclic substituted vinyl-F also works very effectively. Notably, substrates having bulky secondary (^{i}Pr or Cy) or tertiary (^{t}Bu) substituents were hydrogenated in high levels of stereoselectivity. However, for substrates containing the *tert*-butyl substituent the reaction was slow under standard reaction conditions. This was easily overcome by either increasing the catalyst loading (**8k**) and/or by increasing the H_2 pressure (**8l**). The fruitful examples presented here emphasizes that this catalytic system is very general for fluoro-olefins.

Table 5. Hydrogenation of various aliphatic vinyl-fluorides [a]



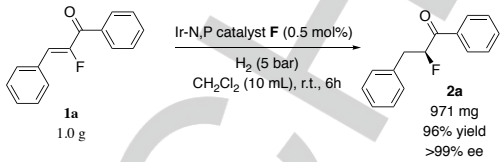
[a] Reaction conditions: 0.05 mmol of substrate, 1 mol% catalyst **F**, 0.5 mL CH_2Cl_2, 10 bar H_2. [b] 50 bar H_2. Yields are isolated hydrogenated product. Enantiomeric excess was determined by GC/MS using chiral stationary phases.

Table 6. Hydrogenation of various substituted 2-fluoropropenyl benzene [a]



[a] Reaction conditions: 0.05 mmol of substrate, 1 mol% catalyst **E**, 20 bar H_2, 0.5 mL CH_2Cl_2. [b] 100 bar H_2, [c] 2 mol% catalyst **E**. Yields are isolated hydrogenated product, in some cases containing small amount of de-F product. Enantiomeric excess was determined by SFC or GC/MS using chiral stationary phases.

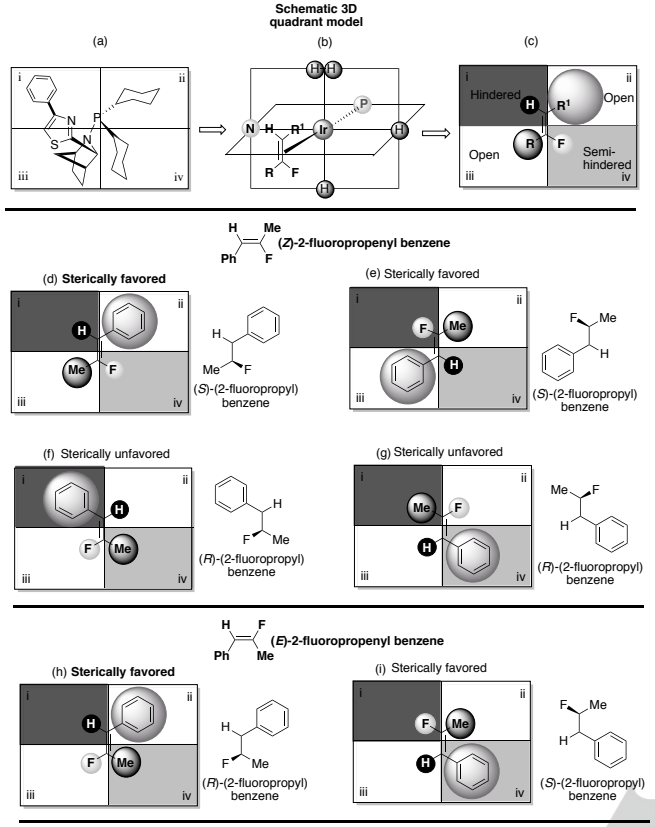
This Ir-catalyzed hydrogenation reaction was also found to be particularly robust for the preparative scale production of chiral fluorine molecules under mild reaction conditions. A gram-scale set-up using for 1.0 g of starting material **1a**, 0.5 mol% of catalyst **F**, 5 bar H_2 produced the desired compound **2a** in excellent 96% yield and >99% ee without any de-F products (Scheme 2).



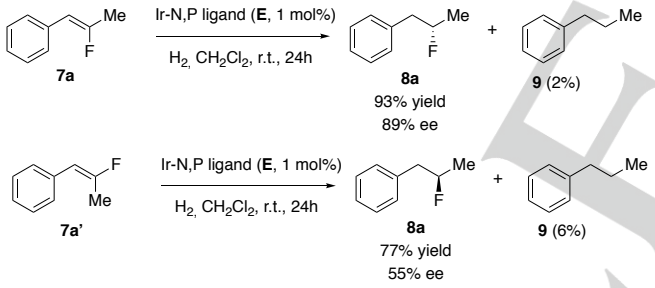
Scheme 2. Gram-scale production of chiral fluorine molecule.

Computional[12e, 18] and experimental studies[19] suggests that the enantioselectivity of Ir-catalyzed asymmetric hydrogenations depend mainly on the steric interactions between the substrate olefin and co-ordination environment around the N,P-iridium catalyst. A quadrant model has been developed[12e, 18] to explain the enantioselectivity. The ligand is positioned as shown in Scheme 3a, having the iridium atom in the center of the four quadrants (Scheme 3b). The olefin then coordinates vertically *trans* to phosphorous as shown in Scheme 3c. The phenyl on the thiazole points outward making quadrant **i** sterically hindered. One of the cyclohexyl group on the phosphorus also points slightly outwards, making quadrant **iv** a semi-hindered quadrant. Quadrant **ii** and **iii** are considered as open quadrants since there are no obstructions from the ligand here. When the tri-substituted (*Z*)-vinylflouride olefin **7a** is placed *trans* to phosphorus, such that the smallest substituent (H) occupies the hindered quadrant **i** and the other small substituent (F) occupies the semi-hindered quadrant **iv**, this should result in a favored arrangement (Scheme 3d). Considering the similar size of H and F another sterically favorable arrangement is also possible placing fluorine in the sterically hindered quadrant **i** (Scheme 3e). The other two possible arrangements (Scheme 3f, 3g) are sterically unfavoured. Thus, based on the quadrant model, both of the sterically favored orientations of the vinylflouride olefin **7a** results in hydrogenation from the same face of the olefin and the predicted absolute configuration of hydrogenated product **8a** is *S* which is in agreement with the experimental results (see Supporting Information for absolute configuration determination).[20]

However, in case of the (*E*)-vinylflouride olefin **7a′** the two sterically favored orientations (Scheme 3h and 3i) will take place from opposite faces which would result in the formation of mixtures of *R* and *S* products. These predictions are in well agreement with experimental results (Scheme 4) as the (*Z*)-vinylflouride olefin (**7a**) provides product **8a** with high enantioselectvity (89% ee) while the (*E*)-isomer gives the corresponding products in enantiomeric mixture of 55% ee.



Scheme 3. Determination of absolute configuration of olefin **7a**



Scheme 4. Hydrogenation of both *Z* and *E* isomer of vinylfluoride **7a**.

Conclusion

In summary, we have developed a new azabicyclo iridium-thiazole-phosphine-complex, which is very general and efficient for the stereoselective synthesis of various alkyl fluorides, thereby complementing previous catalytic asymmetric synthesis for organofluorine compounds, which usually work either with or without the carbonyl framework. The developed protocol is simple as well unique and significantly overcomes the problem of defluorination. It has been effectively used on various aromatic and aliphatic *tri*-substituted vinyl-fluorides, providing chiral fluoro-alkanes in excellent yield and enantioselectivity.

Experimental Section

Experimental Details are available in Supporting Information section.

Acknowledgements

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Keywords: Asymmetric hydrogenation • vinyl-fluoride • N,P-iridium catalyst • organofluorine • carbonyl framework

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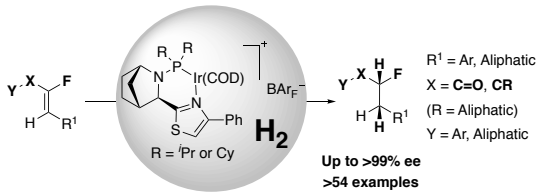

A new general method for the synthesis of asymmetric alkyl fluorides is developed. The method relies on Ir-catalyzed asymmetric hydrogenation of different *tri*-substituted vinyl-fluorides. It provides the first catalytic asymmetric process that enables the synthesis of different array of chiral organofluorine molecules with and without carbonyl framework with different electronic nature in excellent yield and enantioselectivities.

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