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Iridium-Catalyzed Asymmetric Hydrogenation of Fluorinated Olefins Using N,P-Ligands: A Struggle with Hydrogenolysis and Selectivity

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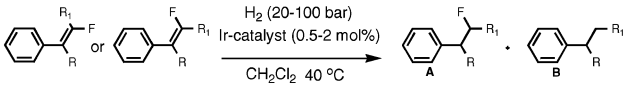
The enantioselective hydrogenation of olefins is one of the most powerful and studied transformations in asymmetric catalysis. The reaction is typically accomplished using complexes of chiral P,P- or N,P-chelating ligands with metals like ruthenium and rhodium.[1] In the past decade, iridium complexes have proven to be efficient catalysts for the enantioselective hydrogenation of olefins.[2] The iridium catalyst developed by Crabtree in 1977[3] was modified by Pfaltz in 1998 to give an iridium-phosphanodihydrooxazole (PHOX) catalyst that could hydrogenate tri- and tetrasubstituted olefins with enantiomeric excesses (ee's) up to 98%.[4] Since then, several other stereoselective iridium-based N,P-ligand catalysts have been reported for the hydrogenation of a limited range of substrates.[5]

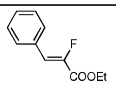
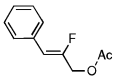
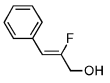
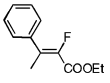
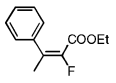
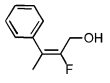
Organofluorine compounds are increasing in popularity within the pharmaceutical industry, and a growing number of active pharmaceutical products now contain fluorine, such as top selling antidepressants like Fluoxetine and Paroxetine.[6] Fluorine can alter the properties of a molecule significantly[7] and "smuggling fluorine into a lead structure enhances the probability of landing a hit almost 10-fold."[8] However, the synthetic methods available for introducing a fluorine-containing stereocenter are still few, and most involve asymmetric fluorination of β-keto esters or β-keto phosphonates.[9] Methods for creating a CHF-bearing stereocenter by asymmetric hydrogenation are even rarer.[10] In a recent patent, Nelson et al. reported on the asymmetric hydrogenation of cyclic vinylfluorides using Rh-Walphos.[11] We therefore wanted to evaluate our newly developed iridium catalysts in the asymmetric hydrogenation of vinylic fluorine compounds to explore the ability of these catalysts to create stereocenters bearing fluorine atoms. Surprisingly, the hydrogenation of fluorine-containing olefins has only been reported a few times. The reason for this might be the ability of vinylic fluorine to be cleaved off.[12] Herein, we report for the first time the successful asymmetric hydrogenation with ee's up to 99% of vinyl fluorides utilizing iridium-based catalysis (Table 1, entries 2 and 3).

To develop this hydrogenation reaction, we first confronted the problem of hydrogenolysis. There are two plausible pathways for the loss of fluorine (Scheme 1). One possibility is that the vinyl fluoride initially undergoes hydrogenation and the fluorine atom is lost from the formed product. A second possibility is that the fluorine atom is first lost from the fluorinated olefin, forming **3**, which is subsequently hydrogenated to compound **4**. The latter route is the most probable, because the vinylic fluorine is more unstable than its saturated counterpart.

Hydrogenation of an *E*/*Z* mixture of ester **1** shows **V**[5i] removes fluorine from the substrate efficiently. This is particularly pronounced in α,α,α-trifluorotoluene solution, with 62% defluorination being observed. When the solvent was changed to CH_2Cl_2, defluorination could be decreased to 40% (Chart 1, complex **V**), but the reaction proceeded slowly. We prepared the racemate of **2**, and subjected it to hydrogenation with complex **V**. Only **2** could be detected, indicating that the loss of fluorine, as expected, follows the latter proposed path shown in Scheme 1.

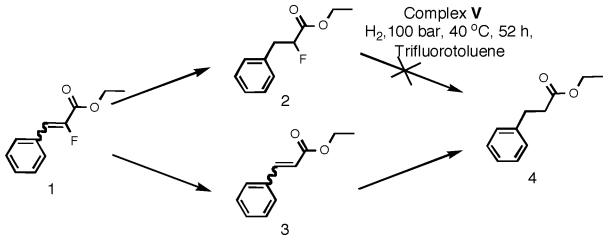
Table 1. Hydrogenation of Fluorine-Containing Olefins[a]



		Complex **I**				Complex **VI**			
Entry	Substrate	Conv.	Ratio A:B	ee[b] (%)	Abs. Conf.[b]	Conv.	Ratio A:B	ee[b] (%)	Abs. Conf.[b]
1		99	98:2	29	(*R*)	0	-	-	-
2		78	88:12	87	(*R*)	82	95:5	**>99**	(*R*)
3		99	94:6	80	(*R*)	97	100:0	**99**	(*R*)
4		21	100:0	57	(-)-(2*R**,3*S**)	30	53:47	rac	-
5		25	100:0	74	(+)-(2*S**,3*S**)	25	70:30	rac	-
6		24	71:29	**90**	(+)-(2*S*,3*S*)	69	91:9	82	(+)-(2*S*,3*S*)

[a] General conditions: 0.5−2.0 mol % catalyst, room temp to 40 °C, dry CH_2Cl_2, 20−100 bar H_2. Ratio and conversion were determined by ^{1}H NMR. [b] Details are given in the Supporting Information.

Scheme 1. The Plausible Defluorination/Hydrogenation and Hydrogenation/Defluorination Routes to **4**.



Similar disappointing results were observed using the analogous thiazole complex **IV**. However, the use of iridium complexes based on the azanorbornyl scaffold (**I**−**III**)[5j,m] resulted in less defluorination. Complex **I** gave the best results, concerning both the level of defluorination and conversion. It was chosen for further evaluation with some trisubstituted substrates (Table 1). The ester (entry 1) required high pressures (100 bar) and elevated temperatures (40 °C) to undergo hydrogenation, whereas the acetate (entry 2) and the alcohol (entry 3) reacted more readily. The highest reaction rates and conversions were observed for the alcohol (entry 3). Full conversion was reached with 20 bar H_2, 0.5 mol % catalyst,

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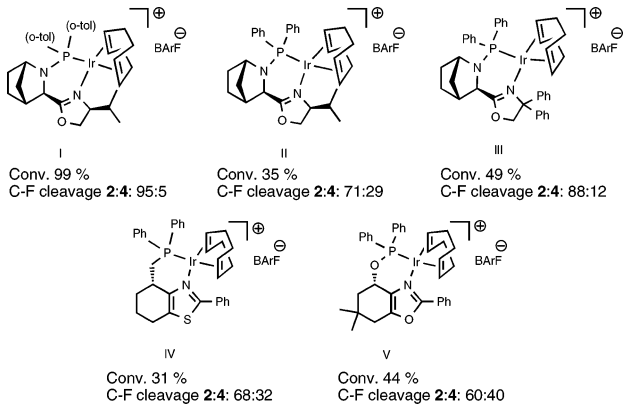
Chart 1. Overview of Conversions and C−F Bond Cleavage in the Hydrogenations of **1**[a]

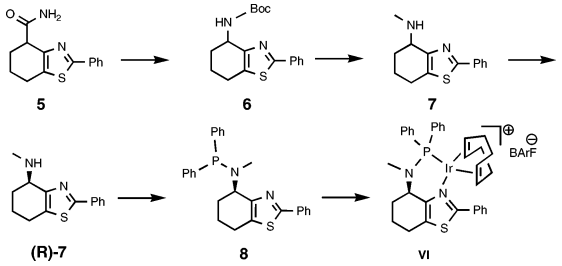


[a] Conditions: 100 Bar H_2, 72 h, 40 °C in CH_2Cl_2.

and 24 h at room temp. The ee's varied from poor (29%, entry 1) to good (87% for entry 2 and 80% for entry 3).

Catalysts **I**−**III** all have a nitrogen atom as the linker between the ligand backbone and the phosphorus-containing group, whereas **IV** and **V** have a methylene group and an oxygen atom, respectively. Given that the azanorbornyl-ligand-based complexes **I**−**III** displayed overall better activity and caused less defluorination than complexes **IV** and **V**, we reasoned that an oxazole or thiazole scaffold containing an amine linker would be an interesting candidate to be evaluated in this type of reactions. Because thiazole-based catalysts have generally performed better than the oxazole-based catalysts for olefin hydrogenation,[5i,k] thiazole was used as the backbone for the new amine-linked ligand. The synthesis of complex **VI** is outlined in Scheme 2.

Scheme 2. Synthesis of Complex VI[a]



[a] Conditions and reagents: See Supporting Information.

Complex **VI** was screened with the trisubstituted substrates and showed excellent selectivity, ee ≥ 99% (entries 2 and 3).

Despite that tetrasubstituted olefins have proven difficult to hydrogenate catalytically, tetrasubstituted fluoroolefins underwent hydrogenation (100 bar, 40 °C, 72 h) with >99% diastereomeric excess (de). Selectivity is increased from 29 to 57% ee (entries 1 and 4) for complex **I** when a methyl group is added to the substrate. For complex **VI**, the selectivities were surprisingly lower with the methylated substrates. Oddly, it did not catalyze the reaction of entry 1, whereas the tetrasubstituted equivalent (entry 4) gave 30% conversion. Hydrogenations of the tetrasubstituted olefins all proceeded via a clean syn-addition of H_2 across the double bond.

We have shown that asymmetric hydrogenation of fluorinated olefins with iridium complexes is possible, often with low catalyst loadings and with low levels of defluorination. Further studies to prepare and evaluate other substrates, and to design complexes that are able to hydrogenate a broader range of fluorinated olefins, are ongoing in our group.

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Supporting Information Available: Experimental details and spectral data for the preparation of the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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