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Enantioselective Pd-Catalyzed Hydrogenation of Fluorinated Imines: Facile Access to Chiral Fluorinated Amines

Mu-Wang Chen, Ying Duan, Qing-An Chen, Duo-Sheng Wang, Chang-Bin Yu, and Yong-Gui Zhou*

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China

ygzhou@dicp.ac.cn

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ABSTRACT

An enantioselective hydrogenation of simple fluorinated imines has been developed using $Pd(OCOCF_3)_2$/(*R*)-Cl-MeO-BIPHEP as a catalyst, and up to 94% ee was achieved. This method provides an efficient route to enantioenriched fluorinated amines.

Because of the unusual and often profound effects on physical and biological properties imparted by introduction of the fluorine atom into organic molecules,[1] perfluoroalkylamines have become important building blocks in various fluorinated biologically active compounds, and asymmetric synthesis of chiral perfluoroalkylamines is a significant task of organic synthesis.[2] In the past decades, some progress on asymmetric synthesis of perfluoroalkylamines has been achieved by employing substrate transformation,[3] catalytic asymmetric reduction,[4] and enantioselective addition.[5] We envision that asymmetric hydrogenation of the corresponding fluorinated ketimines is one of the most convenient routes

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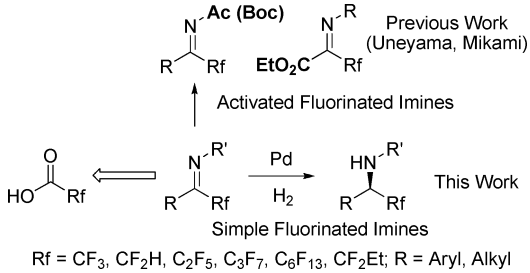
to obtain chiral amines in terms of simplicity and atom efficiency. However, because of difficulties in the stereoselective synthesis and asymmetric hydrogenation of fluorinated imines, to date only a few examples of the metal-catalyzed asymmetric hydrogenation of perfluoroalkylimines have been reported.[6] Uneyama[6a,b] and Mikami[6c] described the asymmetric hydrogenation of activated α-fluorinated iminoesters and *N*-Boc or *N*-Ac imines with moderate to high enantioselectivity, respectively. For the asymmetric hydrogenation of simple acyclic fluorinated imines, only low conversion and enantioselectivity were obtained using the chiral Ir- or Rh-complexes.[6d,e] Therefore, developing an efficient and general method to simple fluorinated ketimines and their asymmetric hydrogenation is highly desirable. Herein, we describe the enantioselective hydrogenation of simple fluorinated imines (Scheme 1).

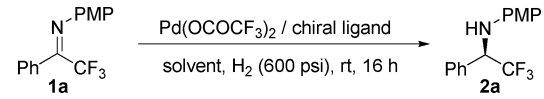
Scheme 1. Asymmetric Hydrogenation of Simple Fluorinated Imines



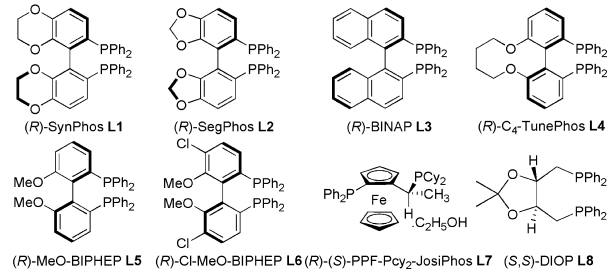
Perfluoroalkyl ketimines **1** were synthesized according to slightly modified literature procedures.[7,8] It is noteworthy that the ketimines **1** are single (*Z*)-isomers except **1l** with a difluoromethyl group. The formation of the single (*Z*)-isomer may be attributed to hyperconjugative interaction of a lone electron pair of nitrogen into the σ^* orbital of the carbon−carbon bond between the imine and Rf group.[9,6c]

Ketimine (**1a**) was chosen as a model substrate, and $Pd(OCOCF_3)_2$/(*R*)-SynPhos was used as a catalyst[10,11] for optimization of reaction conditions. Initial investigations were concentrated on finding optimal solvents, and we found that solvent effect played a crucial role in obtaining both good activity and enantioselectivity (Table 1, entries 1−4), trifluoroethanol (TFE) being the most effective solvent. Some chiral bisphosphine ligands were tested, high enantioselectivities were obtained (entries 5−11), and the best result was achieved with (*R*)-Cl-MeO-BIPHEP **L6** (entry 9, 93% ee). The use a lower catalyst loading (2 mol % Pd) did not affect the ee of **2a**, but the yield was slightly lower (entry 12), the main reason for which may be the hydrolysis of fluorinated imines. Gratifyingly, when 4 Å MS was added,[10b] full conversion with the identical enantioselectivity was obtained (entry 13, 93% ee). The Ir/f-Binaphane/I_2 system was also tested for the asymmetric hydrogenation of **1a** with poor results.[12,13]

Table 1. Optimization of the Asymmetric Hydrogenation of Imine **1a**[a]



entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	TFE	96	83 (*R*)
2[d]	**L1**	THF	<5	N/A
3[d]	**L1**	CH_2Cl_2	<5	N/A
4[d]	**L1**	EtOH	<5	N/A
5	**L2**	TFE	97	90 (*R*)
6	**L3**	TFE	95	90 (*R*)
7	**L4**	TFE	92	89 (*R*)
8	**L5**	TFE	99	88 (*R*)
9	**L6**	TFE	93	93 (*R*)
10	**L7**	TFE	92	43 (*R*)
11[d]	**L8**	TFE	<5	N/A
12[e]	**L6**	TFE	68	92 (*R*)
13[e,f]	**L6**	TFE	99	93 (*R*)



[a] Conditions: 0.125 mmol imine **1a**, $Pd(OCOCF_3)_2$ (4 mol %), chiral ligand (4.8 mol %), 3 mL of solvent, 16 h, rt. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by ^{1}H NMR. [e] With 2 mol % catalyst. [f] With 40 mg 4 Å MS. [g] Conditions: 0.125 mmol imine **1a**, $[Ir(COD)Cl]_2$ (1 mol %), (*S*,*S*)-f-Binaphane (2.2 mol %), I_2 (10 mol %), 24 h.

Under the optimized reaction conditions [$Pd(OCOCF_3)_2$/(*R*)-Cl-MeO-BIPHEP, TFE, 600 psi H_2, 4 Å MS and rt], a

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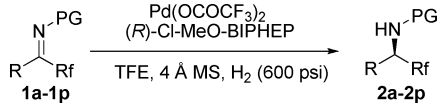
(12) 24% yield and 5% ee were obtained.

wide variety of imines **1** were tested to examine the reaction scope, as shown in Table 2. Different aryl groups on the

Table 2. Pd-Catalyzed Hydrogenation of Fluorinated Imines **1**[a]



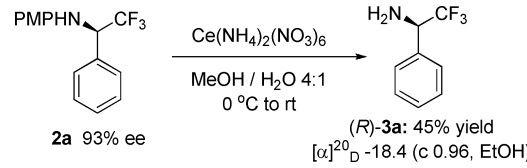
entry	PG	R	Rf	yield (%)[b]	ee (%)[c]
1	4-MeO-C_6H_4	Ph	CF_3	99 (**2a**)	93 (*R*)
2	Ph	Ph	CF_3	91 (**2b**)	93 (*R*)
3	4-Me-C_6H_4	Ph	CF_3	88 (**2c**)	93 (*R*)
4	4-MeO-C_6H_4	4-Me-C_6H_4	CF_3	92 (**2d**)	92 (*R*)
5	4-MeO-C_6H_4	3-Me-C_6H_4	CF_3	95 (**2e**)	93 (*R*)
6	4-MeO-C_6H_4	2-Me-C_6H_4	CF_3	90 (**2f**)	84 (*R*)
7	4-MeO-C_6H_4	4-MeO-C_6H_4	CF_3	97 (**2g**)	92 (*R*)
8	4-MeO-C_6H_4	4-CF_3-C_6H_4	CF_3	95 (**2h**)	93 (*R*)
9	4-MeO-C_6H_4	3,5-F_2-C_6H_3	CF_3	87 (**2i**)	94 (*R*)
10[d]	4-MeO-C_6H_4	*n*-Bu	CF_3	99 (**2j**)	89 (*R*)
11[d]	4-MeO-C_6H_4	$PhCH_2CH_2$	CF_3	97 (**2k**)	92 (*R*)
12	4-MeO-C_6H_4	Ph	CF_2H	88 (**2l**)	69 (*R*)
13	4-MeO-C_6H_4	Ph	CF_2Et	94 (**2m**)	86 (*R*)
14	4-MeO-C_6H_4	Ph	C_2F_5	95 (**2n**)	84 (*R*)
15	4-MeO-C_6H_4	Ph	C_3F_7	85 (**2o**)	84 (*R*)
16[d]	4-MeO-C_6H_4	Ph	C_6F_{13}	97 (**2p**)	86 (*R*)

[a] Conditions: 0.125 mmol imine **1**, $Pd(OCOCF_3)_2$ (2 mol %), (*R*)-Cl-MeO-BIPHEP (2.4 mol %), 40 mg of 4 Å MS, 3 mL of TFE, 16 h, rt. [b] Isolated yield. [c] Determined by HPLC. [d] (*R*)-SynPhos as ligand.

nitrogen atom of imines can be tolerated with excellent enantioselectivities and full conversions (entries 1−3). Considering the ease with which the *p*-methoxylphenyl (PMP) group can be removed, PMP was selected for the additional studies. Substrates with electron-donating (entries 4−7) or electron-withdrawing (entries 8 and 9) groups on aryl substituents can be successfully hydrogenated to give the corresponding fluorinated amines with high ee's. It is noteworthy that the enantioselectivities achieved with Pd catalyst for the hydrogenation of simple fluorinated imine **1** are the highest reported to date. Subsequently, alkyl-substituted fluorinated imines **1j** and **1k** were also tested, and 89% and 92% ee's were obtained, respectively (entries 10 and 11). The imines **1n**−**1p** bearing longer perfluoroalkyl chains were also hydrogenated smoothly with 84−86% ee's (entries 14−16). Difluoroalkyl-substituted substrates were also subjected to asymmetric hydrogenation under the standard condition, giving 69% and 86% ee's (entries 12 and 13).

The *p*-methoxyphenyl (PMP) group of hydrogenated products can be readily removed under the known conditions.[14] Oxidative cleavage of the hydrogenation product **2a** with $Ce(NH_4)_2(NO_3)_6$ (CAN) gave 2,2,2-trifluoro-1-phenethyl-amine (*R*)-**3a** (Scheme 2). The (*R*)-stereochemistry was assigned by comparison of optical rotation with that in the literature ($[\alpha]^{20}_D$ −21.6 for 100% ee (*c* 3.1, EtOH)[3b] and $[\alpha]^{20}_D$ −17.7 for 81% ee (*c* 3.4, EtOH)[3d]).

Scheme 2. Removal of the *p*-Methoxyphenyl (PMP) Group of Fluorinated Amine **2a**



In summary, a direct approach to chiral perfluoroalkylamine has been successfully developed via Pd-catalyzed asymmetric hydrogenation of the simple fluorinated imines under mild conditions with up to 94% ee; simple fluorinated ketimines can be conveniently synthesized from the commercially available fluorinated carboxylic acids. Our ongoing experiments are focused on exploring other palladium-catalyzed asymmetric hydrogenation reactions.

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Supporting Information Available: Experimental, spectroscopic, computational, and crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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