ORGANIC LETTERS

2001
Vol. 3, No. 3
313−315

Pd-Catalyzed Asymmetric Hydrogenation of α-Fluorinated Iminoesters in Fluorinated Alcohol: A New and Catalytic Enantioselective Synthesis of Fluoro α-Amino Acid Derivatives

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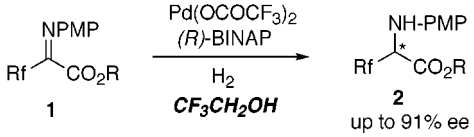
Received August 28, 2000 *(Revised Manuscript Received December 19, 2000)*

ABSTRACT



Under hydrogen pressure, a catalytic amount of palladium(II) trifluoroacetate and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) promoted asymmetric hydrogenation of α-fluorinated iminoesters to afford highly enantioenriched *β*-fluorinated α-amino esters. The yield and ee were much improved by employing fluorinated alcohols such as 2,2,2-trifluoroethanol (up to 91% ee).

Chiral fluorinated amino acids are an important class of nonnatural molecules, and they are receiving increasing attention in the medicinal, agricultural, and material sciences.[1] Therefore, asymmetric synthesis of fluorine-containing amino acids is of particular interest. Asymmetric induction in fluoro amino acid synthesis has been achieved by employing chirally modified substrates (stoichiometric approach) or chiral catalysts (catalytic approach). The former approach, which has been widely investigated, generally provides the target amino acids in an excellent stereoselection[1d] but requires a stoichiometric amount of chiral auxiliaries. However, to date only a few examples of the catalytic approach[2] have been reported despite its synthetic importance. Catalytic asymmetric synthesis of fluoro amino acids is one of the most challenging subjects for further investigation in synthetic organic chemistry. For the construction of a chiral center of α-amino acid, enantioselective reactions of the imino (C═N) moiety in a fluorinated iminoester provide a promising route for catalytic asymmetric fluoro amino acid synthesis. Recently, several excellent examples of catalytic enantioselective reaction of nonfluorinated imines such as reduction, alkylation, cyanation, Mannich-type reactions, and aza Diels−Alder reactions have been reported.[3] Especially, catalytic hydrogenation[4−8] (involving the use of hydrogen gas, the simplest hydrogen source) of ketimines is considered to be important for synthesizing chiral amines

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(1) (a) *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999. (b) *Fluorine-containing Amino Acids: Synthesis and Properties*; Kukhar′, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (d) For asymmteric syntheses of fluorinated amino acids, see: Uneyama, K. in ref 1a, pp 391−418.

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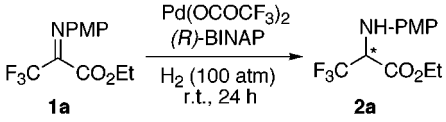
10.1021/ol0002471 CCC: $20.00
Published on Web 01/13/2001

in an industrial process. However, the progress in catalytic enantioselective hydrogenation of imines has been much slower than that of olefins. One serious drawback to the transition-metal-catalyzed hydrogenation of imines is the structural restriction of the substrate imines, namely, *E*/*Z* isomerization of the C=N moiety; each reaction with two geometrical isomers may give a product with different enantioselectivity.[9] Several strategies have overcome such a drawback. The fixation of the C=N bond geometry using cyclic imines, the chelation between metal catalysts and substrate acylhydrazones,[7d,e] and the use of proper additives[5f] have evolved for highly enantioselective hydrogenation of C=N bonds. Despite the easy availability of fluorinated α-iminoesters[10] which serve as a suitable precursor of fluorinated chiral amino acids, to our knowledge, there has been no report of transition-metal-catalyzed asymmetric hydrogenation of fluorinated imines and imino esters with high enantioselectivity. The existence of a fluoroalkyl group would be disadvantageous for selectivity, because it makes the reactivity with nucleophiles much higher and at the same time coordination with catalytic metal weaker. Additionally, it raises the acidity of the α-proton of the product amines, leading to racemization under some reaction conditions. Herein, we describe the first successful, conceptually new (without substrate modification) example of asymmetric hydrogenation of acyclic and weakly coordinate fluorinated iminoesters catalyzed by $Pd(OCOCF_3)_2$−BINAP complex to afford chiral fluoro amino acid derivatives, which involves a dramatic improvement in both product yield and enantioselectivity *by the use of fluorinated alcohol solvents*.

In ordinary (nonfluorinated) solvents, when α-iminoester **1a**[10b] was subjected to hydrogen pressure in the presence of a small amount of chiral palladium complex, α-aminoester **2a** formed in low to moderate ee (Table 1, entries 1−3).

Table 1. Effects of Solvents on Hydrogenation[a]



entry	solvent	2a yield, %[b]	2a ee, %[c]
1	toluene[d,e]	52	39 (*S*)
2	CH_3CO_2H[d]	39	4 (*R*)
3	*i*-PrOH[d]	trace	61 (*S*)
4	CH_3OH	0[g]	0
5	CH_3CH_2OH	29[h]	30 (*R*)
6	CF_3CH_2OH	> 99	88 (*R*)
7[f]	CF_3CH_2OH	84	91 (*R*)
8	$CF_3CF_2CH_2OH$	94	88 (*R*)
9	$(CF_3)_2CHOH$	> 99	69 (*R*)
10	$CF_3(CF_2)_3(CH_2)_2OH$[d]	59	28 (*R*)
11	$CF_3CF_2(CH_2)_3OH$[d]	43	27 (*R*)
12	CF_3CO_2Et[d]	26	5 (*R*)

[a] Reaction conditions: $Pd(OCOCF_3)_2$ 4 mol %, (*R*)-BINAP 6 mol %, H_2 100 atm, TFE, rt, 24 h. PMP = *p*-methoxyphenyl. [b] Isolated yields. [c] Determined by HPLC. [d] $Pd(OCOCH_3)_2$ was used. [e] Reaction temperature was 35 °C. [f] 5 equiv of *n*-Bu_4NHSO_4 was added. [g] $CF_3C(OCH_3)$(NHPMP)-CO_2Et (98%, racemic). [h] $CF_3C(OEt)$(NHPMP)CO_2Et (60%, racemic).

Nucleophilic solvents such as ethanol and methanol attacked the imino carbon of **1** to give α-alkoxylated aminoesters (entries 4 and 5). Surprisingly, in 2,2,2-trifluoroethanol (TFE),[11] both the yield and ee were dramatically improved (entry 6). The ee was further increased by the addition of electrolyte (entry 7). The use of lowered H_2 pressure (10 atm) or amount of catalyst (1 mol % Pd) did not affect the ee of **2a**. Also 2,2,3,3,3-pentafluoro-1-propanol and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) gave comparable results to those of TFE (entries 8 and 9). The decrease of ee in HFIP may be due to slow racemization which was observed on stirring merely **2a** and HFIP. When fluorinated alcohol homologues and ethyl trifluoroacetate were examined as a solvent, both the ee and yields fell off considerably (entries 10−12).

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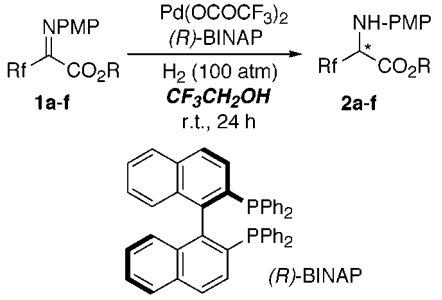
The combination of palladium(II) trifluoroacetate and BINAP[12] gave the best results, while the use of palladium compounds bearing coordinative groups ($PdCl_2$, $Pd_2(dba)_3 \cdot CHCl_3$) or other bidentate chiral ligands (DIOP (8% ee), CHIRAPHOS (5% ee), and BPPFA (<1% ee)) gave poor results. Palladium(II) acetate often works as well as trifluoroacetate, but not in the case of bulky esters such as **1b**,**d**,**e**. Weakly coordinative species are preferred as solvent, counteranion, and additive.

The present protocol is applicable to the enantioenriched synthesis of β-fluorinated amino acids. Thus, other trifluoro- and chlorodifluoromethylated iminoesters **1b**−**d** were also hydrogenated to afford the corresponding alanine derivatives **2b**−**d** stereoselectively (Table 2, entries 2−4). It is noted

Table 2. Asymmetric Hydrogenation of α-Fluorinated Iminoesters **1**[a]



entry	1			2		
		Rf	R		yield, %[b]	ee, %[c]
1	**1a**	CF_3	Et	**2a**	>99	88 (*R*)
2	**1b**	CF_3	*t*-Bu	**2b**	92	85 (*R*)[d]
3	**1c**	CF_3	Bn	**2c**	95	84 (*R*)
4	**1d**	$CClF_2$	*t*-Bu	**2d**	69	81 (*R*)
5	**1e**	C_7F_{15}	Bn	**2e**	98	61 (*R*)[d]
6	**1f**	CHF_2	Bn	**2f**	75	30 (*R*)

[a] Reaction conditions: $Pd(OCOCF_3)_2$ 4 mol %, (*R*)-BINAP 6 mol %, H_2 100 atm, TFE, rt, 24 h. [b] Isolated yields. [c] Determined by HPLC. [d] Determined by ^{19}F NMR at the form of (*S*)-MTPA ester of the corresponding amino alochol.

that no hydrogenolysis was observed for the benzyl ester moiety. The ester **1e** bearing a long perfluoroalkyl chain was also hydrogenated with similar selectivity (entry 5); it is interesting to consider the steric difference between the CF_3 and C_7F_{15} groups. α-Difluoroimine **1f** resulted in moderate ee (entry 6), possibly due to the *E*/*Z* isomerism.[13] *p*-Anisyl, *tert*-butyl, and benzyl protection in **2b** and **2c** can be easily removed to afford free 3,3,3-trifluoroalanine by treatment with ammonium cerium(IV) nitrate, HCl, and H_2/Pd−C, respectively.[2d,10c]

Though the role of TFE in this hydrogenation has not been clarified yet, there have been several reports where fluorinated alcohol was used as a solvent for transition-metal-promoted reactions,[14] including hydrogenation.[11,15] In those works, the role of fluorinated alcohols is rationalized as a stabilizer of active catalyst,[14b] or hydrogen bond donor.[14a,15c] Dihydrogen bonding between fluorinated alcohols and hydride metal complexes has been established in recent inorganic studies.[16] It would suggest that TFE preferably coordinates weakly to palladium and thus can easily be replaced with less coordinative fluorinated imines **1**. TFE also might influence the character of the imino group by protonation or hydrogen bonding.

In summary, we have developed a novel approach for the catalytic asymmetric synthesis of fluoro amino acids which is considered to be an inherently difficult but highly valuable process. The presence of a catalytic amount of $Pd(OCOCF_3)_2$−BINAP in fluorinated alcohols, a simple catalyst system, resulted in highly enantioselective hydrogenation of α-fluorinated imines **1**. Although the origin of the solvent effect is equivocal and the scope and limitations of this homogeneous Pd-catalyst system are still unknown now, the present finding clearly suggests that weakly nucleophilic and thus less coordinative alcohols such as TFE are favorable for asymmetric catalytic hydrogenation of highly reactive fluorinated imines.[17] Further synthetic applications of this catalytic system and precise mechanistic studies on the origin of this remarkable effect are in progress.

Acknowledgment. This work has been supported by the Ministry of Education, Science, Sports and Culture of Japan (Research on Priority Areas, No. 10208212) and the Okayama Foundation for Science and Technology. We also thank SC-NMR Laboratory of Okayama University for ^1H and ^{19}F NMR analyses.

Supporting Information Available: Experimental procedures and details of compound characterization for compounds **1e**,**f** and **2a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) ^{19}F and ^1H NMR spectra of **1f** indicate the existence of *E*- and *Z*-isomers (see Supporting Information). For other iminoesters **1a**−**e**, only one isomer was observed in NMR study.

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(17) We also completed asymmetric hydrogenation of trifluoromethyl imines ($CF_3C{=}N(PMP)Ar$, **1g**) in addition to trifluoromethyl iminoesters **1a**−**f**, which gave enantioenriched trifluoromethylamines ($CF_3CH(NHPMP)$-Ar; 90% ee).