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Catalytic Asymmetric Synthesis of β-Fluoroalkyl-β-Amino Acids *via* Biomimetic [1,3]-Proton Shift Reaction

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Abstract: [1,3]-Proton shift reaction of *N*-benzylenamines **1a-e**, derived from β-polyfluoroalkyl-β-ketocarboxylic esters and benzylamine, was catalyzed by (-)-cinchonidine (5-13 mol %) to give good yields (67-89%) of enantiomerically enriched (up to 36% ee) *N*-benzylidene derivatives **3a-e**. The resulting products **3a-e** were readily hydrolyzed into the corresponding optically active (*R*)-β-polyfluoroalkyl-β-amino acids **4a-e** (87-93% yield).

Recently we have developed a new general approach to fluorine-containing amines and β-amino acids *via* biomimetic transamination of corresponding carbonyl compounds with benzylamine.[2] Taking into account that fluorinated amino compounds available by this method are of great pharmaceutical interest,[3] the asymmetric version of the [1,3]-proton shift reaction is highly desirable. We report herein the new kind of catalytic asymmetric transformation,[4] namely, enantioselective [1,3]-proton transfer catalyzed by a chiral base in azaallylic system of *N*-benzylimines **2a-e** resulting in the formation of thermodynamically favored *N*-benzylidene derivatives **3a-e**. In a preliminary study, we have checked the catalytic abilities of (*R*)-(+)-*N*,*N*-dimethyl-1-phenylethylamine (**5**), (1*R*,2*S*)-(-)-*N*-methyl ephedrine (**6**) and (-)-cinchonidine (**7**). All reactions were performed in similar conditions: the starting enamines **1a-e** were heated in the presence of 9-13 mol % of catalyst **5-7** at 100 °C for 26-65 hr and after completion of the isomerization (monitored by GLC or ^{19}F-NMR analysis) corresponding *N*-benzylidene derivatives **3a-e** were isolated by distillation and hydrolyzed to free amino acids **4a-e**. The enantiomeric composition of free amino acids **4a-e** was studied by means of chiral HPLC analysis.[5] As experiments revealed, all three bases **5-7** were effective in catalyzing the transformation of **1a-e** to **3a-e**, but only (-)-cinchonidine (**6**) was able to effect such a transformation in a stereoselective sense (Table 1). In all cases of cinchonidine-catalyzed isomerization the enantiomeric induction was in the same sense ((*R*)-enantiomer is dominant[6]), but dependent on the length of fluorocarbon side chain in the enamines **1a-e**.

Scheme 1

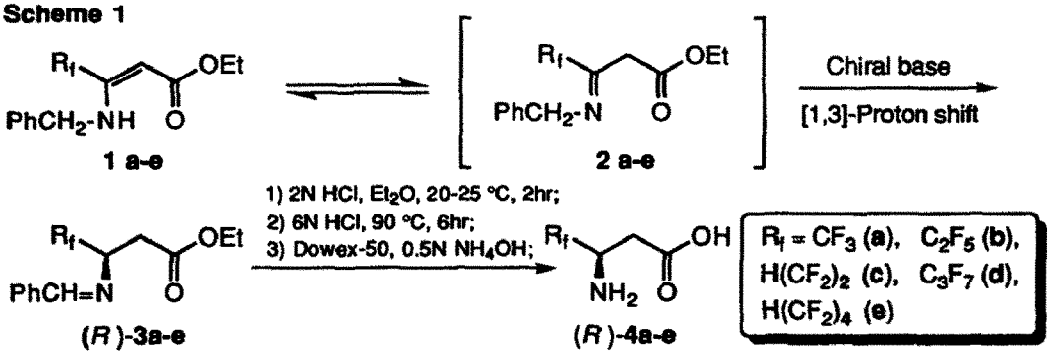

Table 1. Chiral base-catalyzed asymmetric [1,3]-proton shift

entry	R_f	conditions[a]			yield[b], %		% ee[c]
		base, (mol%)	temp., °C	time, h	**3a-e**	**4a-e**	(config)[c]
1	(**a**) CF_3	**5** (10)	80	30	89	87	0
2	(**a**) CF_3	**6** (10)	80	40	81	91	0
3	(**a**) CF_3	**7** (9)	100	50	74	93	16 (*R*)
4	(**a**) CF_3	**7** (5)	100	50	21[d]	-	15 (*R*)
5	(**b**) C_2F_5	**7** (10)	100	40	69	89	29 (*R*)
6	(**c**) $H(C_2F_4)$	**7** (10)	100	26	71	88	36 (*R*)
7	(**d**) C_3F_7	**7** (12)	100	65	68	91	30 (*R*)
8	(**e**) $H(C_4F_8)$	**7** (13)	100	65	67	88	20 (*R*)

[a] All reactions were run in the presence of corresponding catalyst **5-7** without any solvent. [b] Isolated yield. [c] Determined by HPLC analysis of **4a-e** with a chiral stationary phase column (Chiral Pro/Cu Si 100 (Serva)). See ref 5, 6. [d] Less than 50% conversion of starting enamine.

The highest values of ee 29-36% (entries 5-7) were observed for isomerization of enamines **1b-d** which possess two or three carbon atoms in side chains (C_2F_5, $H(CF_2)_2$, C_3F_7). The 9-13 mol % level of (-)-cinchonidine (**7**) is limited with its solubility in starting enamines **1a-e** at 100 °C. The 5 mol % level of catalyst **7** significantly decreases the rate of isomerization, but does not influence enantioselectivity (entry 4). This observation suggests that the reaction proceeds only through the catalyzed pathway.

In conclusion, the first example of catalytic asymmetric synthesis of fluorine-containing amino compounds *via* biomimetic [1,3]-proton shift reaction was achieved. Even modest enantiomeric excesses observed with (-)-cinchonidine (**7**) suggest that this approach is promising in the perspective of an asymmetric synthesis of β-fluoroalkyl-β-amino acids.

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References and Notes

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