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Biomimetic Base-Catalyzed [1,3]-Proton Shift Reaction. A Practical Synthesis of β-Fluoroalkyl-β-Amino Acids[1]

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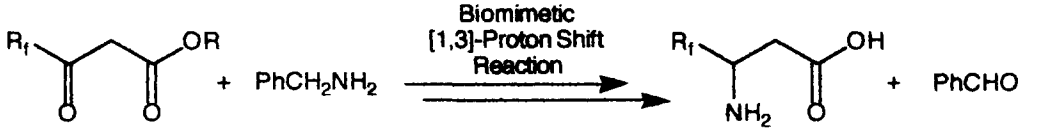
Abstract: An efficient approach to practical synthesis of β-fluoroalkyl-β-amino acids is described. The method consists in the reducing reagent-free base-catalyzed biomimetic transamination reaction between fluorinated β-keto carboxylic esters and benzylamine. This transformation involves two sequential base-catalyzed [1,3]-proton transfers giving rise to corresponding *N*-benzylidene derivatives as the products of final thermodynamic equilibration, directed by the electron-withdrawing character of fluoroalkyl groups. Opportunity for catalytic enantiocontrolled synthesis of targeted β-amino acids with application of monochiral base, as a catalyst for these isomerizations, is demonstrated. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

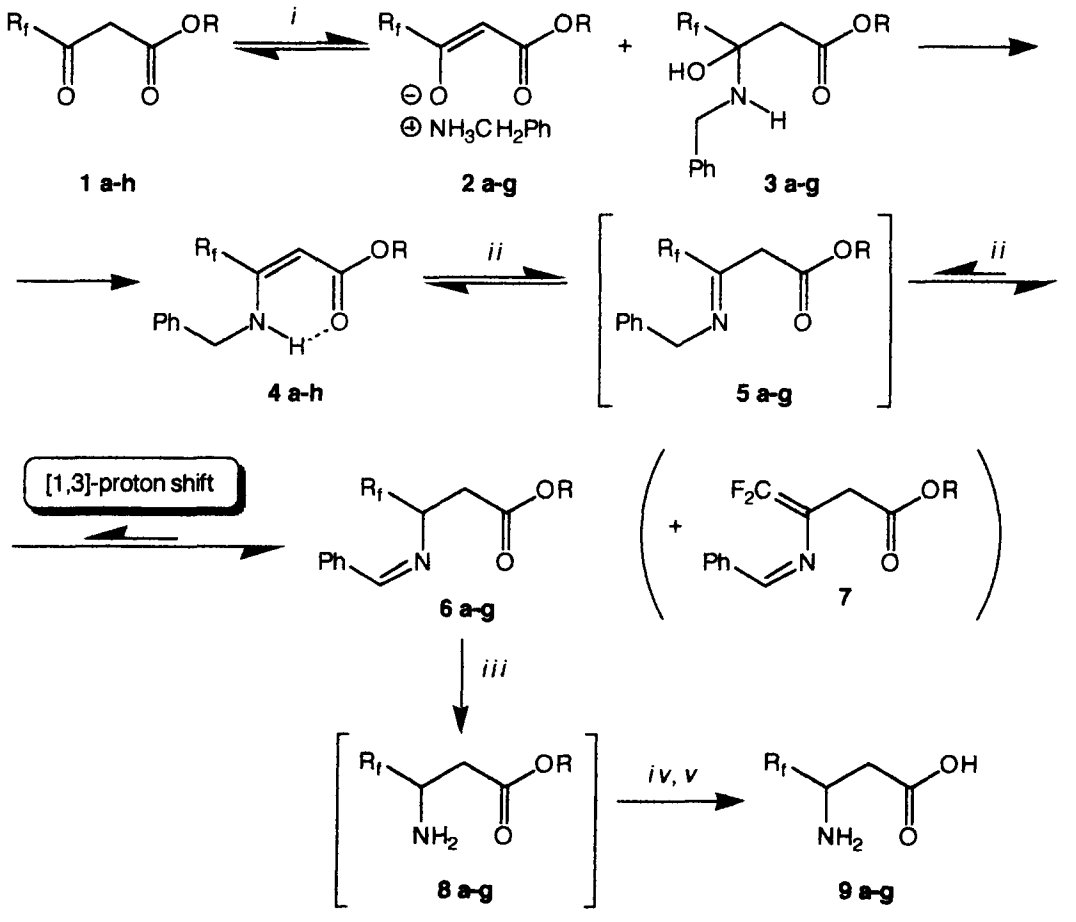
The development of new synthetic approaches to amino acids and their derivatives has been a topic of long-standing interest in organic chemistry. Currently, synthesis of non-proteinogenic, unusual amino acids, and in particular, β-amino acids, as highly promising biologically active compounds of high pharmaceutical and medicinal interest, has received considerable attention.[3] Although a vast variety of β-amino acids has been synthesized[4] little is known about the chemistry and biological activity of fluorine-containing β-amino acids. However, in the light of apparent biomedicinal benefits of fluorine substitution for hydrogen achieved in the area of α-amino acids,[5] interest towards fluoro-substituted β-amino acids becomes obvious. Here we would like to present general approach to the series of β-fluoroalkyl-β-amino acids *via* base-catalyzed [1,3]-proton shift reaction, that is a reducing agent-free biomimetic reductive amination of fluorinated β-keto carboxylic esters (Scheme 1). Ready availability of all reagents employed, reliability and simplicity of experimental procedure would make this method synthetically useful for preparing of fluoroalkyl β-amino acids of biological interest.



Scheme 1

RESULTS

***Synthesis of Starting β-Keto Carboxylic Esters* 1a-h.** β-Keto carboxylic esters **1a-g** were readily prepared by the reaction of corresponding fluorine-containing ethyl or methyl acetates with ethyl or methyl acetate, respectively, in the presence of sodium hydride according to the literature procedure.[6] Methyl 4,4,4-trifluoroacetoacetate **1a**, methyl chlorodifluoroacetoacetate **1g**, ethyl 3-keto-4,4,5,5,5-pentafluoropentanoate **1b**, and ethyl acetoacetate **1h** are also commercially available.



	a	b	c	d	e	f	g	h
R_f	CF_3	C_2F_5	C_3F_7	CHF_2	$H(CF_2)_2$	$H(CF_2)_4$	$CClF_2$	CH_3
R	CH_3	C_2H_5	C_2H_5	C_2H_5	CH_3	CH_3	CH_3	C_2H_5

Scheme 2. *Reagents and Conditions*: *i*, benzene, Ph-CH_2-NH_2, Dowex-50 (H^+ -form) or *p*-$TolSO_3H$, reflux; *ii*, base, see Table 1; *iii*, 2*N* HCl, room temperature, 2h; *iv*, 6*N* HCl, 90 °C, 6h; *v*, Dowex-50, 0.2*N* NH_4OH

***Condensation of β-Keto Carboxylic Esters* 1a-h *with Benzylamine. Synthesis of N-Benzyl Enamines* 4a-h.** Methyl trifluoroacetylacetate **1a** readily reacts in benzene or toluene solution with benzylamine forming a mixture of salt **2a** and *gem*-aminoalcohol **3a** in nearly quantitative yield (Scheme 2). Due to high stability of **2a**, it was isolated in pure state and fully characterized by elemental analysis and NMR spectra. Thus, ^{1}H-NMR spectrum of salt **2a** supports its structure by showing the methyl and benzyl resonances as well as a singlet at δ 4.62 (1H) assigned to the vinyl proton. A relatively sharp peak at δ 8.60 (3H) was assigned to the benzyl ammonium ion. Its narrow half-width (2.9 Hz) indicated rapid exchange and equivalence of the three protons on the NMR time scale. Furthermore, a pattern of ^{13}C-NMR spectrum of **2a** is very similar to that of enamine **4a** and shows the presence of C,C double bond in the salt **2a**. Refluxing of a mixture of **2a** and **3a** in benzene solution in the presence of *p*-toluene sulfonic acid or cation-exchange resin Dowex-50 gives desired enamine **4a** in fairly good (80%) isolated yield along with the corresponding amide (10-15%). Assuming that enamine **4a** can not be produced directly from salt **2a**, we can suggest that under the reaction conditions employed there is an equilibrium between methyl trifluoroacetylacetate **1a** and compounds **2a**, **3a**, and correspondingly, enamine **4a** is formed by dehydration of *gem*-aminoalkohol **3a**. A similar pattern of reactivity was also observed in the reaction of other fluorinated β-keto carboxylic esters **1b-g** with benzylamine, which provided corresponding enamines **4b-g** in moderate-to-good isolated yield. Hydrocarbon enamine **4h** was prepared according to the same procedure, however formation of any intermediate products was not observed. According to ^{1}H-NMR and IR spectra of compounds **4a-h** they exist almost entirely as enamines, stabilized by intramolecular hydrogen bond.

***[1,3]-Proton Shift Reaction. Isomerization of Enamines* 4a-g *into N-benzylidene Derivatives* 6a-g.** Triethylamine (TEA) was found to be ineffective, as a base, of catalyzing isomerization of trifluoromethyl-containing enamine **4a** to aldimine **6a** at room temperature (Table 1, entry 1). However, in boiling TEA this transformation occurs smoothly within reasonable reaction time span giving rise to the targeted Schiff base **6a** in synthetically valuable isolated yield (entry 2). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), much more strong base than triethylamine, is very effective for this isomerization allowing complete transformation of **4a** to **6a** within 2 h at 50 °C, being taken even in a catalytic amount (entry 3).

In contrast to **4a**, enamines **4b,c**, bearing perfluoroethyl and propyl groups, which are more electron-withdrawing than CF_3,[7] can be effectively isomerized in TEA solution at room temperature (25 °C) (entries 4,6). Carrying out of these isomerizations at elevated temperature greatly accelerates reaction rates, however heating of **4b,c** in neat TEA causes sizable formation of byproducts. Optimal, from preparative point of view, is a heating of enamines **4b,c** in a mixture (1/1) of TEA with hexane at 70 °C. Under these reaction conditions desired aldimines **6b,c** can be prepared with over 70% yield (entries 5,7).

In sharp contrast to enamines **4a-c**, compound **4d**, bearing a less electron-withdrawing difluoromethyl group can not be isomerized to corresponding aldimine **6d** under the action of TEA (entry 8). Low reactivity of enamine **4d** can be overcome with application of DBU as a base at elevated temperature. Thus, an exposure of **4d** with 5 mol% of DBU at 100 °C for 21 h gives desired aldimine **6d** with 61% yield (entry 9). Application of TEA as a solvent for this reaction and 10 mol% of DBU as a catalyst substantially improves chemical yield of imine **6d** up to 73% (entry 10).

Homologies of enamine **4d**, compounds **4e,f** with ω-hydroperfluoroethyl and butyl groups, electron-withdrawing effect of which is comparable to that of perfluoroalkyl analogs, show similar reactivities to

enamines **4b,c**. Thus, their complete isomerization to aldimines **6e,f** can be achieved in TEA solution at room temperature for 48-56 h or for 6 h at reflux temperature (entries 11-14).

Substitution of a fluorine atom with a chlorine one in the trifluoromethyl group of enamine **4a** has dramatic consequences on the outcome of enamine-aldimine isomerization. Thus, chlorodifluoromethyl-containing enamine **4g**, similarly to trifluoromethylated analog **4a**, can be easily isomerized in refluxing TEA to corresponding aldimine **6g**, which, in contrast to **6a**, undergoes further dehydrochlorination to give unsaturated compound **7** as the main reaction product. Lowering of the reaction temperature to reduce the rate of undesirable elimination reaction allowed only minute improvement of aldimine **6g** yield (entries 15,16).

And finally, all attempts to isomerize fluorine-free aldimine **6h** even under drastic reaction conditions (entry 17) were unsuccessful.

Hydrolysis of Aldimines 6a-g to β-Fluoroalkyl-β-Amino Acids 9a-g. Deprotection of *N*-benzylidene β-amino acid esters **6a-g** to free amino acids **9a-g** can be easily performed as one-pot two-stage acidic hydrolysis. First, under the action of 2*N* hydrochloric acid on a solution of Schiff bases **6a-g** in ether at room temperature for 2 h (Scheme 2) *N*-benzylidene group of **6a-g** was cleaved to give corresponding ester hydrochlorides **8a-g**. Compounds **8a-g** without purification were next hydrolyzed with 6*N* HCl at 90 °C for 6

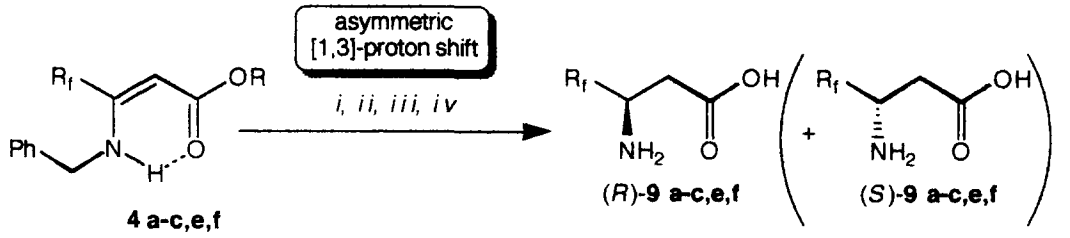
Table 1. Base-catalyzed isomerization of enamines 4a-g to aldimines 6a-g

Entry	Enamine **4**		Conditions[a]			Yield[b], %	
	R_f	R	base[c]	temp.	time (h)	**6**	**9**
1	(**a**) CF_3	CH_3	NEt_3	room	24	trace	
2	(**a**) CF_3	CH_3	NEt_3	reflux	12	84	77
3	(**a**) CF_3	CH_3	DBU[d]	50 °C	2	76	-
4	(**b**) C_2F_5	C_2H_5	NEt_3	room	42	67	-
5	(**b**) C_2F_5	C_2H_5	NEt_3[e]	70 °C	6	74	70
6	(**c**) C_3F_7	C_2H_5	NEt_3	room	35	72	83
7	(**c**) C_3F_7	C_2H_5	NEt_3[e]	70 °C	6	70	-
8	(**d**) HCF_2	C_2H_5	NEt_3	reflux	24	no reaction	
9	(**d**) HCF_2	C_2H_5	DBU[d]	100 °C	10	61	-
10	(**d**) HCF_2	C_2H_5	DBU[d,f]	reflux	24	73	77
11	(**e**) $H(CF_2)_2$	CH_3	NEt_3	room	48	85	80
12	(**e**) $H(CF_2)_2$	CH_3	NEt_3	reflux	6	79	-
13	(**f**) $H(CF_2)_4$	CH_3	NEt_3	room	56	87	81
14	(**f**) $H(CF_2)_4$	CH_3	NEt_3	reflux	6	80	-
15	(**g**) $CClF_2$	CH_3	NEt_3	reflux	5	20[g]	
16	(**g**) $CClF_2$	CH_3	NEt_3[e]	50 °C	21	23[g]	73
17	(**h**) CH_3	C_2H_5	DBU[h]	150 °C	24	no reaction	

[a] Conversion of starting enamine **4a-g** more than 95%, as controlled by GLC. [b] Isolated yield. [c] Except where noted, reactions were run in triethylamine solution. [d] Imine/DBU ratio 1/0.05-0.1. [e] In solution (1/1) of triethylamine and hexane. [f] Triethylamine was used as a solvent. [g] In a mixture with compound **7**. [h] Enamine **4h**/DBU ratio 1/1.

h and resultant amino acids **9a-g** were isolated in pure state by using cation-exchange resin Dowex-50. Without optimization of hydrolysis procedure, amino acids **9a-g** were obtained with over 70% yield (Table 1).

***Asymmetric version of [1,3]-Proton Shift Reaction. Monochiral base-catalyzed Isomerization of Enamines* 4a-c,e,f.** Taking into account that β-fluoroalkyl-β-amino acids **9** have been designed as potentially biologically active compounds, their availability in an enantiomerically pure state is highly necessary. Recently we have reported on preparation of both (*R*)- and (*S*)-enantiomers of β-amino acids **9** *via* biocatalytic resolution of **9**, as *N*-phenylacetyl derivatives, in the presence of penicillin acylase (EC 3.5.1.11) from *Escherichia coli*.[8] Since asymmetric synthesis, particularly in its catalytic version, represents the most desirable solutions for preparing monochiral compounds,[9] we have investigated the possibility for asymmetric isomerization of enamines **4** to aldimines **6** by using a chiral base. In the present study, we have checked the catalytic abilities of commercially available (*R*)-(+)-*N*,*N*-dimethyl-1-phenylethylamine (**10**), (1*R*,2*S*)-(-)-*N*-methyl ephedrine (**11**) and (-)-cinchonidine (**12**). All experiments were run under the similar reaction conditions in the presence of 9-13 mol % of chiral base at 100 °C for 26-65 h (Scheme 3, Table 2). After completion of the isomerization (monitored by GLC) resultant *N*-benzylidene derivatives were hydrolyzed to give free amino acids **9**, enantiomeric composition of which was determined by means of chiral HPLC analysis[10] using biocatalytically prepared[8b] (*R*)- and (*S*)-**9** as corresponding standards. As it follows from the results obtained, all three chiral bases **10-12** are effective in catalyzing the isomerization of **4a-c,e,f** to **6a-c,e,f**, but only cinchonidine **12** is able to effect the transformation in a stereoselective sense (Table 2) favoring formation of (*R*)-configurated products (Table 2, entries 3-8). The highest values of enantioselectivity (29-36% ee) (entries 5-7) were recorded for isomerization of enamines **4b,c,e** bearing per(poly)fluoroethyl (**b,e**) or *n*-perfluoropropyl (**c**) side chains, while trifluoromethyl **4a** and ω-hydroperfluorobutyl **4f** derivatives gave corresponding products with sizably lower enantioselectivity (entries 3, 8). Due to a very low (up to 9-13 mol %) solubility of (-)-cinchonidine (**12**) in the starting enamines **4b,c,e** even at 100 °C, there was no possibility to explore the influence of increasing concentrations of catalyst **12** on both the rate and enantioselectivity of isomerizations under study. However, application of 5 mol % of **12** significantly decreased the rate of **4a** enamine isomerization, but did not influence its enantioselectivity (entry 4).



	a	b	c	e	f
R_f	CF_3	C_2F_5	C_3F_7	$H(CF_2)_2$	$H(CF_2)_4$
R	CH_3	C_2H_5	C_2H_5	CH_3	CH_3

Scheme 3. *Reagents and Conditions*: *i*, chiral base, see Table 2; *ii*, 2*N* HCl, room temperature, 2h; *iii*, 6*N* HCl, 90 °C, 6h; *iv*, Dowex-50, 0.2*N* NH_4OH

Table 2. Monochiral base-catalyzed asymmetric [1,3]-proton shift reaction

Entry	Enamine **4**		Conditions[a]			Yield[b], %		% ee[c]
	R_f	R	base, (mol%)	temp., °C	time, h	**3a-e**	**4a-e**	(config)
1	(**a**) CF_3	CH_3	**10** (10)	80	30	89	87	0
2	(**a**) CF_3	CH_3	**11** (10)	80	40	81	91	0
3	(**a**) CF_3	CH_3	**12** (9)	100	50	74	93	16 (*R*)
4	(**a**) CF_3	CH_3	**12** (5)	100	50	21[d]	-	15 (*R*)
5	(**b**) C_2F_5	C_2H_5	**12** (10)	100	40	69	89	29 (*R*)
6	(**c**) C_3F_7	C_2H_5	**12** (12)	100	65	68	91	30 (*R*)
7	(**e**) $H(CF_2)_2$	CH_3	**12** (10)	100	26	71	88	36 (*R*)
8	(**f**) $H(CF_2)_4$	CH_3	**12** (13)	100	65	67	88	20 (*R*)

[a] All reactions were run without solvent. [b] Isolated yield. [c] Determined by HPLC analysis of **9a-c,e,f** with a chiral stationary phase column, ref. 9. See also text. [d] Less than 50% conversion of starting enamine.

DISCUSSION

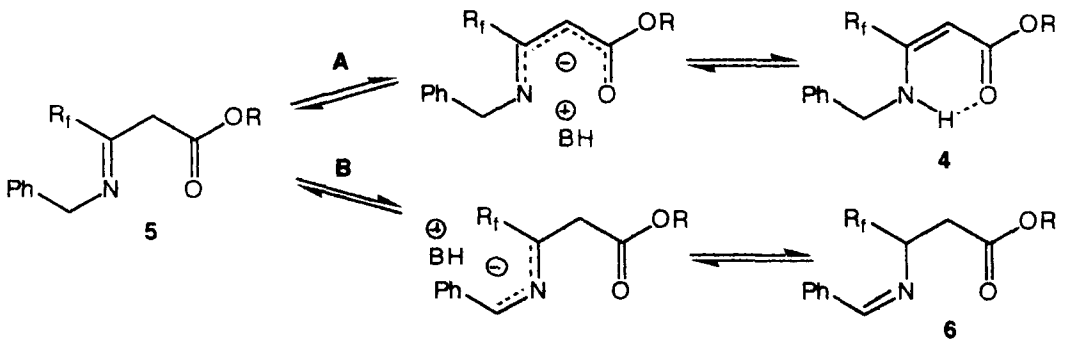
Azomethine—azomethine isomerization is critically involved in the biological enzyme-catalyzed interconversion of α-amino and α-keto carboxylic acids through corresponding imines derived from pyridoxal and pyridoxamine respectively.[11] A systematic study of this biochemical transamination primarily by Cram *et all.*,[12] have revealed the following key features of the process: a) a mechanism of the reaction involves azaallylic anions as intermediates; b) the isomerization occurs intramolecularly, in a cis or suprafacial manner across the face of delocalized azaallylic anion; c) equilibrium constants of the isomerization are adequately correlated by the Hammett equation.[12,13] Thus, biochemical azomethine—azomethine isomerization provides a convenient intramolecural oxidation—reduction process and the lure of its synthetic application for preparative reducing reagent-free transamination of carbonyl compounds has attracted a great deal of interest in the past. Some progress in this line has been achieved with application of synthetic pyridoxamine analogs for transamination of α-keto carboxylic acids to corresponding α-amino acids under the reaction conditions which closely approximate those of biological transamination, *i. e.* aqueous medium and the presence of zinc ions.[14] By contrast, azomethine—azomethine isomerizations in organic solvents, with application of α-(aryl)alkylamines as analogs of pyridoxamine, occur under only the drastic reaction conditions, with equilibrium usually not lying well on the side of desired products.[12,15] Accordingly, no generalized synthetic applications of azomethine—azomethine isomerization have been reported so far.

Taking into account that intermediacy of azaallylic carbanions in the base-catalyzed imine isomerization has been unambiguously demonstrated,[12] the involvement of fluorinated carbonyl compounds in this reaction could be hardly anticipated, since β-fluorine-containing anions are known to be susceptible of fluorine β-elimination.[16] However, we have found that *N*-(benzyl)imines of perfluoroalkyl carbonyl compounds surprisingly easily, in the presence of organic bases at room temperature, undergo isomerization to corresponding *N*-benzylidene derivatives which, upon mild acidic hydrolysis, release desired fluoro-amino compounds. The beneficial effect of α-perfluoroalkyl group on reactivity and position of *N*-benzyl—*N*-

benzylidene derivatives equilibrium, nearly entirely shifted towards the latter, has been recognized as a basis for practical synthesis of biologically important fluoro-amino compounds. Our previous investigations in this line have demonstrated a synthetic value of this biomimetic approach, referred as [1,3]-proton shift reaction, for transamination of perfluoroalkyl aldehydes, ketones and α-keto carboxylic esters.[17]

Transamination of fluorinated β-keto carboxylic esters, *via* [1,3]-proton shift reaction, seemed to be the most difficult target, since in this case there are two competing [1,3]-proton transfers, azomethine **5** — enamine **4** and azomethine **5** — azomethine **6** isomerizations (Scheme 4), and, as it was established for hydrocarbon analogs, the former process is much more favorable than the later.[15] Moreover, enamines **4** are additionally stabilized by the intramolecular hydrogen bond and no equilibrium between **4** and ketimine **5** was detected in the absence of a base. Accordingly, fluorine-free enamine **4h** showed an expected pattern of reactivity, being isolated unchanged after the treatment under the forced reaction conditions (Table 1, entry 17). In sharp contrast to this, fluorine-containing enamines **4a-g** isomerized, under the mild reaction conditions, to aldimines **6a-g**, albeit with different rate and outcome (Table 1). The base-catalyzed transformation of fluorinated enamines **4** to aldimines **6** might proceed *via* two sequential base-catalyzed [1,3]-proton transfers through ketimine **5** (Scheme 4) including two proton abstractions, from **4** and **5**, followed by collapses to covalent states **5** and **6**, respectively. The reason behind the dramatic difference in the reactivity between hydrocarbon enamine **4h** and fluorinated derivatives **4a-g**, could be reasonably ascribed to the electron-withdrawing feature of fluoroalkyl groups which effectively stabilizing corresponding carbanion, cause thermodynamic preference of aldimine structure **6** over **4** and **5** (Scheme 4). This mechanistic assumption is strongly supported by the dependence of isomerization rates of fluorinated enamines **4a-g** to aldimines **6a-g** upon the nature of fluoroalkyl group. In the series of enamines **4a-g**, the observed relative reactivities are in the order per(poly)fluoroalkyl substituted **4b,c,e,f** > trifluoromethyl and chlorodifluoromethyl derivatives **4a,g** >> difluoromethyl-containing enamine **4d**, that is in good agreement with corresponding order of σ_m values[18] of fluoroalkyl groups: C_2F_5, C_3F_7, $H(CF_2)_2$, $H(CF_2)_4$ ($\sigma_m \approx 0{,}47$), CF_3 ($\sigma_m = 0{,}44$), CHF_2 ($\sigma_m = 0{,}29$).[19]

Intermediacy of azaallylic carbanion in the base-catalyzed isomerizations under study is also strongly suggested by the outcome of chlorodifluoromethyl derivative **4g** [1,3]-proton shift reaction. In this case (Scheme 2, Table 1, entries 15,16), isomerization of **4g** to aldimine **6g** was accompanied by dehydrochlorination process, yielding compound **7** as the major product. Our attempts to reduce elimination reaction have shown that enamine **4g** isomerization and formation of **7** proceed with equal rates, and thus compound **7** is rather the result of direct



Scheme 4. **A** = Azomethine—enamine isomerization;
B = Azomethine—azomethine isomerization

carbanion stabilization through β-halogen elimination than a product of further transformation of resultant aldimine **6g**. Preferential formation of dehydrochlorinated product **7** in the base-catalyzed isomerization of enamine **4g** was rather surprising, since in the rest of successful isomerizations of **4a-f** to **6a-f** no detectable amount of dehydrofluorination reaction was observed. A possible explanation may be that carbon-chlorine bond is weaker than carbon-fluorine one, but this is highly speculative.

As a final goal of this study, we have checked possibility of carrying out isomerization of enamines **4** to chiral aldimines **6** in an asymmetric sense. As it follows from the results summarized in Table 2, enantioselectivity of aldimines **6** stereogenic center formation could be controlled by an external monochiral base, used even in a catalytic amount. Despite that the highest value of the asymmetric induction achieved with application of (-)-cinchonidine (**12**) as a chiral base (Table 2, entries 5-7) is far from a synthetically useful level, this result, coupled with the observation that reaction proceeds only through the catalyzed pathway (entry 3 vs 4), gives a ground to believe that enhancement of enantioselectivity would be possible with a proper design of monochiral base as a catalyst for [1,3]-proton shift reaction.

CONCLUSIONS

This work has demonstrated that fluorinated enamines **4a-g**, derived from appropriate β-keto esters and benzylamine, in strike contrast to fluorine-free analog **4h**, easily undergo two sequential base-catalyzed [1,3]-proton transfers, giving rise to aldimines **6a-g** as the final products of thermodynamic equilibration. Qualitative correlation between the electron-withdrawing effects (σ_m) of fluorine-containing substituents and enamines **4** ability of isomerizing to **6**, has been demonstrated. The presence of chlorine atom in β-position of rearranging azaallylic system dramatically changes outcome of the reaction, favoring formation of dehydrochlorinated product **7**. Application of monochiral base [(-)-cinchonidine] as a catalyst for these isomerizations allows enantiocontrolled formation of stereogenic center of aldimines **6**. Targeted β-fluoroalkyl substituted β-amino acids of biological interest can be easily released under the conditions of mild acidic hydrolysis.

Application of commercially available and inexpensive reagents, a simple set of reaction conditions and generally high chemical yields makes this biomimetic method synthetically attractive as an alternative to orthodox methodology employing reducing agents.

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EXPERIMENTAL SECTION

General. All melting points and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Specord-IR spectrometer. ^{1}H-NMR spectra were measured on a Varian VXR-300 (299.94 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard in organic solvents and sealed in a glass capillary for D_2O solutions. ^{13}C-NMR spectra were recorded with $CDCl_3$ as an internal standard on a Gemini-200 (199.98 MHz) spectrometer. ^{19}F-NMR spectra were recorded on a Bruker WP-200 (188.98 MHz) instrument; σ_F values are p.p.m upfield from $CFCl_3$ which was used as an internal standard in organic solvents

and sealed in a glass capillary for D_2O solutions. All solvents and reagents were obtained commercially in high purity and were used without further purification unless indicated.

Chiral HPLC analyses were carried out according to the procedure described previously.[8b]

***Synthesis of Salt* 2a.** To the cooled (5 °C) solution of 0.85 g of keto ester **1a** (5 mmol) in dry benzene (5 ml) 0.59 g of benzylamine (5.5 mmol) were added dropwise for 30 min. under stirring. When addition was over, the reaction mixture was stirred for 1 h more at room temperature. The precipitated salt **2a** was filtered off and washed with benzene, the yield was 1.1 g (79%). The salt **2a** was recrystallized from hexane for elemental analysis. Mp 120 - 121 °C. ^{1}H-NMR (CD_3SOCD_3): δ = 3.41 (s, 3H, OCH_3), 4.02 (s, 2H, NCH_2), 4.62 (s, 1H, CH), 7.28 - 7.45 (m, 5H, C_6H_5), 8.60 (br s, 3H, $^+NH_3$). ^{13}C-NMR (CD_3SOCD_3): δ = 168.8 (s, CO), 166.5 (q, $^2J_{C\text{-}F}$ = 27.8 Hz, CF_3-*C*=), 134.6 (s, C_{arom}), 129.1 (s, C_{arom}), 128.7 (s, C_{arom}), 128.5 (s, C_{arom}), 120.0 (q, $^1J_{C\text{-}F}$ = 292.0, CF_3), 77.7 (s, =CH-), 48.8 (s, CH_3), 42.5 (s, NCH_2). Anal. Calcd for $C_{12}H_{14}F_3NO_3$: C, 51.99; H, 5.09; F, 20.56. Found: C, 52.03; H, 5.08; F, 20.65.

Synthesis of Enamines* 4a-h. *General Method. Benzylamine (0.55 mol) was added dropwise to the solution of keto ester **1a-h** (0.5 mol) in benzene (400 ml) at room temperature. When addition was over, 1 g of cation exchange resin Dowex-50 (H^+-form) was added to the solution and the mixture was boiled using the Dean-Starkh device until the theoretical amount of water was removed. Filtration, evaporation in vacuum (40 - 50 °C, 20 - 30 mm Hg), and distillation of the reaction mixture yielded corresponding enamines **4a-h.**

(*Z*)-Enamine 4a: colorless oil. 80%, bp 139 - 141 °C at 11 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 3.62 s, (3H, CH_3), 4.50 (d, *J* = 6.6 Hz, 2H, CH_2), 5.14 (s, 1H, CH), 7.30 - 7.42 (m, 5H, C_6H_5), 8.63 (br t, *J* = 6.6 Hz, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ = 169.9 (s, CO), 148.9 (q, $^2J_{C\text{-}F}$ = 30.8, CF_3-*C*=), 137.6 (s, C_{arom}), 128.9 (s, C_{arom}), 127.9 (s, C_{arom}), 127.4 (s, C_{arom}), 120.0 (q, $^1J_{C\text{-}F}$ = 292.0, CF_3), 84.8 (q, $^3J_{C\text{-}F}$ = 5.8, CH), 51.3 (s, CH_3), 47.9 (s, NCH_2). ^{19}F-NMR ($CDCl_3$): δ = -65.9 (s, CF_3). IR: (CH_2Cl_2) ν = 1670 (C=O), 1630 (C=C), 3200 (NH). Anal. Calcd for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; F, 21.99. Found: C, 55.74; H, 4.53; F, 22.00. ***N*-Benzyl Amide of 4a:** isolated by column chromatography on SiO_2; eluting system *n*-hexane/ethyl acetate (4:1), *Rf* 0.21; mp 59-61 °C. ^{1}H-NMR ($CDCl_3$): δ = 4.44 [d, *J* = 6.3 Hz, 4H, $(CH_2)_2$], 5.00 (s, 1H, CH), 5.56 (m, 1H, NH), 7.24 - 7.37 [m, 10H, $(C_6H_5)_2$], 9.05 (m, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ = 168.94 (s, CO), 146.2 (q, $^2J_{C\text{-}F}$ = 30.2, CF_3-*C*=), 138.4 (s, C_{arom}), 138.3 (s, C_{arom}), 128.9 (s, $2C_{arom}$), 127.8 (s, C_{arom}), 127.7 (s, C_{arom}), 127.6 (s, C_{arom}), 127.4 (s, C_{arom}), 120.3 (q, $^1J_{C\text{-}F}$ = 276.8, CF_3), 87.4 (q, $^3J_{C\text{-}F}$ = 5.7, CH), 48.05 (q, $^3J_{C\text{-}F}$ = 2.9, NCH_2), 43.3 (s, NCH_2). ^{19}F-NMR ($CDCl_3$): δ = -66.91 (s, CF_3).

(*Z*)-Enamine 4b: colorless oil. 65%, bp 95 - 100 °C at 0.05 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3H, CH_3), 4.12 (q, *J* = 7.2 Hz, 2H, CH_2), 4.45 (d, *J* = 6.9 Hz, 2H, NCH_2), 5.15 (s, 1H, CH), 7.30 - 7.39 (m, 5H, C_6H_5), 8.70 (m, 1H, NH). ^{19}F-NMR ($CDCl_3$): δ = -115.3 (m, 2F, CF_2), -84.3 (s, 3F, CF_3). IR: (CH_2Cl_2) ν = 1675 (C=O), 1630 (C=C), 3200 (NH). Anal. Calcd for $C_{14}H_{14}F_5NO_2$: C, 52.02; H, 4.36; F, 29.39. Found: C, 51.93; H, 4.31; F, 29.59.

(*Z*)-Enamine 4c: colorless oil. 63%, bp 130 - 136 °C at 0.15 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3H, CH_3), 4.06 (q, *J* = 7.2 Hz, 2H, CH_2), 4.44 (m, 2H, NCH_2), 5.04 (s, 1H, CH), 7.20 - 7.27 (m, 5H, C_6H_5), 8.53 (m, 1H, NH). IR: (CH_2Cl_2) ν = 1675 (C=O), 1633 (C=C), 3220 (NH). Anal. Calcd for $C_{15}H_{14}F_7NO_2$: C, 48.26; H, 3.78; F, 35.63. Found: C, 48.39; H, 3.73; F, 35.81.

(*Z*)-Enamine 4d: colorless oil. 85%, bp 110 - 115 °C at 0.1 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3H, CH_3), 4.13 (q, *J* = 7.1 Hz, 2H, CH_2), 4.52 (d, *J* = 6.6 Hz, 2H, NCH_2), 4.89 (s, 1H, CH), 6.02 (t, J_{HF} = 53.7 Hz, 1H, CHF_2), 7.25 - 7.34 (m, 5H, C_6H_5), 8.40 (d, *J* = 6.6 Hz, 1H, NH). Anal. Calcd for $C_{13}H_{15}F_2NO_2$: C, 61.17; H, 5.92; F, 14.89. Found: C, 61.03; H, 5.84; F, 15.01.

(*Z*)-Enamine 4e: colorless oil. 72%, bp 114 - 117 °C at 0.05 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 3.64 (s, 3H, CH_3), 4.57 (m, 2H, NCH_2), 5.01 (br s, 1H, CH), 6.54 (t t, $^2J_{HF}$ = 52.0 Hz, $^3J_{HF}$ = 5.1 Hz, 1H,

CHF_2), 7.25 - 7.49 (m, 5H, C_6H_5), 8.63 (m, 1H, NH). Anal. Calcd for $C_{13}H_{13}F_4NO_2$: C, 53.61; H, 4.50; F, 26.10. Found: C, 53.44; H, 4.47; F, 26.29.

(Z)-Enamine 4f: colorless oil. 69%, bp 124 - 128 °C at 0.05 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 3.63 (s, 3H, CH_3), 4.46 (d, J = 6.0 Hz, 2H, NCH_2), 5.01 (s, 1H, CH), 6.06 (t t, $^2J_{HF}$ = 51.9 Hz, $^3J_{HF}$ = 5.4 Hz, 1H, CHF_2), 7.20 - 7.40 (m, 5H, C_6H_5), 8.61 (br t, J = 6.0 Hz, 1H, NH). Anal. Calcd for $C_{15}H_{13}F_8NO_2$: C, 46.04; H, 3.35; F, 38.85. Found: C, 45.87; H, 3.19; F, 39.09.

(Z)-Enamine 4g: colorless oil. 50%, bp 110 - 115 °C at 0.15 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 3.67 (s, 3H, CH_3), 4.57 (d, J = 6.3 Hz, 2H, NCH_2), 5.13 (s, 1H, CH), 7.25 - 7.33 (m, 5H, C_6H_5), 8.62 (d, J = 6.3 Hz, 1H, NH). IR: (CH_2Cl_2) ν = 1660 (C=O), 1625 (C=C), 3250 (NH). Anal. Calcd for $C_{12}H_{12}ClF_2NO_2$: C, 52.28; H, 4.39; F, 13.78. Found: C, 52.31; H, 4.39; F, 13.75.

(Z)-Enamine 4h: colorless oil. 89%, bp 150 - 154 °C at 11 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 1.21 (t, J = 7.2 Hz, 3H, CH_3), 4.05 (q, J = 7.2 Hz, 2H, CH_2), 4.41 (d, J = 6.6 Hz, 2H, NCH_2), 4.73 (s, 1H, CH), 7.25 - 7.35 (m, 5H, C_6H_5), 8.41 (m, 1H, NH).

Isomerization of Enamines 4a-g into Aldimines* 6a-g. *General Method. The isomerization reactions were run under the conditions recorded in the Table 1. After completion of the isomerization (control by GLC or NMR analysis) triethylamine was evaporated in vacuum (40- 50 °C, 20 - 30 mm Hg) and the residue was distilled to give aldimines **6a-g**.

Aldimine 6a: colorless oil. 84%, bp 136 - 139 °C at 11 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 2.78, 2.92 (ABX, J_{AB} = 16.5 Hz, J_{AX} = 9.6 Hz, J_{BX} = 3.3 Hz, 2H, CH_2), 3.52 (s, 3H, CH_3), 4.29 (q d d, J_{HH} = 9.6 Hz, J_{HH} = 3.3 Hz, J_{HF} = 7.5 Hz, 1H, CH), 7.35 - 7.45 (m, 5H, C_6H_5), 8.47 (s, 1H, CH=N). ^{19}F-NMR ($CDCl_3$): δ = -76.31 (d, J_{HF} = 7.5 Hz, CF_3). IR: (CH_2Cl_2) ν = 1730 (C=O), 1610 (C=N). Anal. Calcd for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; F, 21.99. Found: C, 55.81; H, 4.66; F, 22.12.

Aldimine 6b: colorless oil. 74%, bp 95 - 100 °C at 0.05 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 1.19 (t, J = 7.2 Hz, 3H, CH_3), 2.80 - 2.95 (m, 2H, CH_2), 4.10 (m, 2H, OCH_2), 4.35 (m, 1H, CH), 7.35 - 7.60 (m, 5H, C_6H_5), 8.41 (s, 1H, CH=N). ^{19}F-NMR ($CDCl_3$): δ = -124.11 (AB, J_{AB} = 426,0 Hz, 2F, CF_2), -82.18 (s, 3F, CF_3). Anal. Calcd for $C_{14}H_{14}F_5NO_2$: C, 52.02; H, 4.36; F, 29.39. Found: C, 52.13; H, 4.27; F, 29.22.

Aldimine 6c: colorless oil. 72%, bp 82 - 83 °C at 0.02 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 1.18 (t, J = 7.2 Hz, 3H, CH_3), 2.91, 2.98 (ABX, J_{AB} = 16.5 Hz, J_{AX} = 8.4 Hz, J_{BX} = 3.0 Hz, 2H, CH_2), 4.10 (q, J = 7.2 Hz, 2H, OCH_2), 4.40 (m, 1H, CH), 7.40 - 7.78 (m, 5H, C_6H_5), 8.40 (s, 1H, CH=N). ^{19}F-NMR ($CDCl_3$): δ = from -117.19 to -128.02 (m, 4F, CF_2CF_2), -81.92 (s, 3F, CF_3). Anal. Calcd for $C_{15}H_{14}F_7NO_2$: C, 48.26; H, 3.78; F, 35.63. Found: C, 48.21; H, 3.84; F, 35.49.

Aldimine 6d: colorless oil. 73%, bp 90 - 95 °C at 0.05 mm Hg; ^{19}F-NMR ($CDCl_3$): δ = -128.7, -125.0 (ABX, J_{AB} = 282.0 Hz, J_{AX} = J_{BX} = 55.0 Hz, CF_2). Anal. Calcd for $C_{13}H_{15}F_2NO_2$: C, 61.17; H, 5.92; F, 14.89. Found: C, 61.07; H, 5.87; F, 14.73.

Aldimine 6e: colorless oil. 85%, bp 100 - 105 °C at 0.05 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 3.69 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 4.35 (m, 1H, CH), 6.38 (t t, $^2J_{HF}$ = 52.0 Hz, $^3J_{HF}$ = 5.6 Hz, 1H, CHF_2), 7.20 - 7.78 (m, 5H, C_6H_5), 8.52 (s, 1H, CH=N). Anal. Calcd for $C_{13}H_{13}F_4NO_2$: C, 53.61; H, 4.50; F, 26.10. Found: C, 53.74; H, 4.75; F, 26.01.

Aldimine 6f: colorless oil. 80%, bp 100 - 105 °C at 0.01 mm Hg; ^{1}H-NMR ($CDCl_3$): δ = 3.67 (s, 3H, CH_3), 2.96 (m, 2H, CH_2), 4.46 (m, 1H, CH), 6.34 (t t, $^2J_{HF}$ = 51.0 Hz, $^3J_{HF}$ = 6.0 Hz, 1H, CHF_2), 7.30 - 7.60 (m, 5H, C_6H_5), 8.41 (s, 1H, CH=N). Anal. Calcd for $C_{15}H_{13}F_8NO_2$: C, 46.04; H, 3.35; F, 38.85. Found: C, 45.91; H, 3.21; F, 38.69.

Aldimine 6g in mixture with compound 7; ratio 6g/7 = 1/4: colorless oil. bp 90 - 95 °C at 0.05 mm Hg; **Aldimine 6g:** ^{1}H-NMR ($CDCl_3$): δ = 2.94, 2.98 (ABX, J_{AB} = 16.1 Hz, J_{AX} = 8.2 Hz, J_{BX} = 3.1 Hz, 2H, CH_2), 3.63 (s, 3H, CH_3), 4.32 (m, 1H, CH), 6.83 - 7.41 (m, 5H, C_6H_5), 8.42 (s, 1H, CH=N). ^{19}F-NMR ($CDCl_3$): δ = -60.51, -62.70 (ABX, J_{AB} = 174 Hz, J_{AX} = J_{BX} = 9.0 Hz, $CClF_2$). **Compound**

7: ^{1}H-NMR ($CDCl_3$): δ = 3.43 (m, 2H, CH_2), 3.70 (s, 3H, CH_3), 6.83 - 7.41 (m, 5H, C_6H_5), 8.21 (s, 1H, CH=N). ^{19}F-NMR ($CDCl_3$): δ = -90.18 (m, 1F, CF), -96.33 (m, 1F, CF).

Hydrolysis of Aldimines* 6a-g *and Isolation of β-Fluoroalkyl-β-Alanynes* 9a-g. *General Method. The solution of Schiff base **5a-g** (0.27 mol) in diethyl ether (150 ml) was poured under stirring in 2*N* HCl (200 ml). The mixture was stirred for 1h more, the ether phase removed and the aqueous phase washed with ester (3 x 50 ml) and evaporated to dryness. The dry residue was mixed with 6*N* HCl (70 ml) and heated at 90 °C for 6 h. Evaporation and Dowex-50 (H^+-form) column chromatography of the residue yielded corresponding amino acids **9a-g**. In order to prepare analytically pure samples amino acids **9c,f** were converted into the corresponding hydrochlorides.

4,4,4-Trifluoro-3-aminobutanoic acid 9a: 77 %, mp 190 °C (decomp.) from CH_3OH. ^{1}H-NMR (CD_3SOCD_3): δ = 2.77, 3.00 (ABX, J_{AB} = 17.8 Hz, J_{AX} = 8.8 Hz, J_{BX} = 4.2 Hz, 2H, CH_2), 4.39 (q d d, *J* = 8.8 Hz, *J* = 4.2 Hz, *J* = 10.8 Hz, 1H, CH). Anal. Calcd for $C_4H_6F_3NO_2$: C, 30.58; H, 3.85; F, 36.28; N, 8.92. Found: C, 30.63; H, 3.89; F 36.18; N, 8.86.

5,5,5,4,4-Pentafluoro-3-aminopentanoic acid 9b: 70 %, mp 168 °C (decomp.) from H_2O. ^{1}H-NMR (0.1 N DCl in D_2O): δ = 2.77, 2.98 (ABX, J_{AB} = 18.2 Hz, J_{AX} = 9.1 Hz, J_{BX} = 4.0 Hz, 2H, CH_2), 4.46 (q d d, *J* = 9.1 Hz, *J* = 4.2 Hz, *J* = 12.8 Hz, 1H, CH). ^{19}F-NMR (D_2O): δ = -83.5 (s, 3F, CF_3), -121.8, -125.5 (AB, J_{AB} = 256 Hz, 2F, CF_2). Anal. Calcd for $C_5H_6F_5NO_2$: C, 28.99; H, 2.92; F, 45.87; N, 6.76. Found: C, 29.10; H, 2.96; F, 45.77; N, 6.84.

6,6,6,5,5,4,4-Hexafluoro-3-aminohexanoic acid hydrochloride 9c: 83 % (for free amino acid), mp 193 °C (decomp.) from 6*N* HCl. ^{1}H-NMR (0.1 N DCl in D_2O): δ = 2.75, 2.98 (ABX, J_{AB} = 18.0 Hz, J_{AX} = 9.3 Hz, J_{BX} = 3.3 Hz, 2H, CH_2), 4.52 (m, 1H, CH). Anal. Calcd for $C_6H_6F_7NO_2$ HCl: C, 24.55; H, 2.40; Cl, 12.08. Found: C, 24.21; H, 1.84; Cl, 12.14.

4,4-Difluoro-3-aminobutanoic acid 9d: 77 %, mp 192 - 194 °C (decomp.) from H_2O. ^{1}H-NMR (D_2O): δ = 2.21, 2.41 (ABX, J_{AB} = 16.3 Hz, J_{AX} = 9.0 Hz, J_{BX} = 4.8 Hz, 2H, CH_2), 3.26 (m, 1H, CH), 5.87 (t d, J_{HF} = 56.5 Hz, J_{HH} = 3.3 Hz, 1H, CHF_2). ^{19}F-NMR (D_2O): δ = -127.7 (d, *J* = 56.5 Hz, CHF_2). Anal. Calcd for $C_4H_7F_2NO_2$: C, 34.54; H, 5.07; F, 27.32; N, 10.07. Found: C, 34.61; H, 5.14; F, 27.31; N, 10.13.

5,5,4,4-Tetrafluoro-3-aminopentanoic acid 9e: 80 %, mp 162 - 163 °C (decomp.) from H_2O. ^{1}H-NMR (CD_3OD): δ = 2.42 - 3.03 (m, 2H, CH_2), 4.55 (m, 1H, CH), 6.14 (t t, J_{HF} = 53.3 Hz, J_{HF} = 4.2 Hz, 1H, CHF_2). Anal. Calcd for $C_5H_7F_4NO_2$: C, 31.75; H, 3.73; F, 40.19; N, 7.41. Found: C, 31.68; H, 3.70; F, 40.34; N, 7.43.

7,7,6,6,5,5,4,4-Octafluoro-3-aminoheptanoic acid hydrochloride 9f: 81 % (for free amino acid), mp 196 - 198 °C (decomp.) from 6*N* HCl. ^{1}H-NMR (CD_3OD): δ = 2.79, 3.13 (ABX, J_{AB} = 18.2 Hz, J_{AX} = 8.4 Hz, J_{BX} = 4.2 Hz, 2H, CH_2), 4.64 (m, 1H, CH), 6.71 (t t, $^2J_{HF}$ = 51.2 Hz, $^3J_{HF}$ = 5.5 Hz, 1H, CHF_2). Anal. Calcd for $C_7H_7F_8NO_2$ HCl: C, 25.82; H, 2.47; Cl, 10.89. Found: C, 24.61; H, 2.27; Cl, 10.76.

4-Chloro-4,4-difluoro-3-aminobutanoic acid 9g: 73 %, mp 231 °C (decomp.) from H_2O. ^{1}H-NMR (H_2O): δ = 2.74, 2.96 (ABX, J_{AB} = 18.1 Hz, J_{AX} = 9.0 Hz, J_{BX} = 3.5 Hz, 2H, CH_2), 4.43 (m, 1H, CH). ^{19}F-NMR (D_2O): δ = -52.8, -47.8 (ABX, J_{AB} = 293.0 Hz, J_{AX} = J_{BX} = 4.9 Hz, $CClF_2$). Anal. Calcd for $C_4H_6ClF_2NO_2$: C, 27.68; H, 3.48; Cl, 20.43; F, 21.90. Found: C, 27.74; H, 3.45; Cl, 20.31; F, 22.06.

Isomerization of Enamines* 4a-c,e,f *in the presence of chiral bases. Isomerizations of enamines **4a-c,e,f** in the presence of (*R*)-(+)-*N*,*N*-dimethyl-1-phenylethylamine (**10**), (1*R*,2*S*)-(-)-*N*-methyl ephedrine (**11**) and (-)-cinchonidine (**12**) were performed on 3 mmol scale under the reaction conditions listed in Table 2. Reactions were monitored by GLC and upon completion resultant aldimines were distilled and hydrolyzed to free amino acids, similarly to the procedure described for TEA-catalyzed isomerizations. Yields and values of enantiomeric purity for products obtained are recorded in Table 2.

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