Available online at www.sciencedirect.com
ScienceDirect
Journal of Fluorine Chemistry 128 (2007) 500–506
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Enantioselective organocatalytic route to trifluoromethyl-β-amino acids using chiral bases

Valérie Michaut [a], François Metz [b], Jean-Marc Paris [b,1], Jean-Christophe Plaquevent [a,*]

[a] UMR-CNRS 6014, IRCOF, Université de Rouen, rue Tesnière, F-76821 Mont-Saint-Aignan Cedex, France
[b] Rhodia Recherches, Centre de Recherches de Lyon, 85 avenue des Frères Perret F-69192 Saint-Fons, France

Received 3 November 2006; received in revised form 22 December 2006; accepted 28 December 2006
Available online 4 January 2007

Abstract

Herein are studied new aspects of enantioselective (1,3) proton transfer of ethyl-4,4,4-trifluoroacetoacetate (ETFAA) amino derivatives. When catalyzed by an appropriate chiral base, ee's as high as 71% are observed. Special emphasis is given to mechanistic insights of the reaction by use of deuterated derivative. All results converge on a deprotonation as both rate and asymmetric determining step. This study opens a new route to trifluoromethylated chiral building blocks.

Keywords: Trifluoromethyl compounds; β-Amino acids and derivatives; Chiral bases; Proton shift transfer reaction; Asymmetric synthesis

1. Introduction

Special features of the fluorine atom make it attractive for the design of analogs of biologically important compounds. It is well known that the introduction of fluorine atom strongly modifies the biological and pharmacological activity in a molecule [1]. The isosteric and isoelectronic nature of the fluorine to the hydroxyl group renders fluorinated analogs as useful pharmacological lead compounds. Today, it is estimated that about 20–25% of drugs contain at least one fluorine atom [2].

To obtain fluorinated compounds, two main strategies can be followed: the first one consists in the synthesis of an unfluorinated precursor of the target molecule, followed by introduction of fluorine at a late stage of the synthesis using fluorinating methodologies. The other strategy is to use fluorine containing starting materials. In this respect, ethyl-4,4,4-trifluoroacetoacetate (ETFAA) is a good candidate since it is easy to handle and readily available.

β-Amino acids are of great importance because of their biological properties, their occurrence in natural products and as convenient precursors for β-lactams [3].

Taking into account the potential of both fluorinated compounds and β-amino acids, it is of great interest to synthesize β-fluorinated β-amino acids in an asymmetric way [4]. The base-catalyzed 1,3-proton shift reaction ((1,3)PSR) allows the isomerization of imines **1** to imines **2** to take place (Fig. 1).

As stated by Soloshonok et al. [5], the overall process leading to **B** from **A** consists in a biomimetic transamination, in which there is no need for any added reducing agent (Fig. 1). By conducting this reaction with β-keto esters as starting materials, β-amino acids are synthesized. This reaction was intensively studied by Soloshonok et al. firstly in its non-asymmetric version for which high yields were obtained [5,6]. Then, the diastereoselective version of the (1,3)PSR gave good results when chiral amine was used (Fig. 2) [7]. However, the enantioselective (1,3) proton transfer catalyzed by a chiral base was almost unexplored with only three chiral bases tested [8]. In the case of ETFAA derivative, the best enantiomeric excess was then obtained with (−)-cinchonidine but was only 16% (Fig. 2). As our group is interested in enantioselective methods for the access to fluorinated building blocks [9], we decided to re-examine the enantioselective version of the (1,3)PSR, a problem that remains unsolved. If successful, this approach

* Corresponding author. Tel.: +33 235522464; fax: +33 235522971.
E-mail address: jean-christophe.plaquevent@univ-rouen.fr (J.-C. Plaquevent).
[1] Present address: CNRS-UMR 7573, Ecole Nationale Supérieure de Chimie de Paris, 11 Rue Pierre et Marie Curie, F-75231 Paris Cedex 05, France.

0022-1139/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2006.12.013

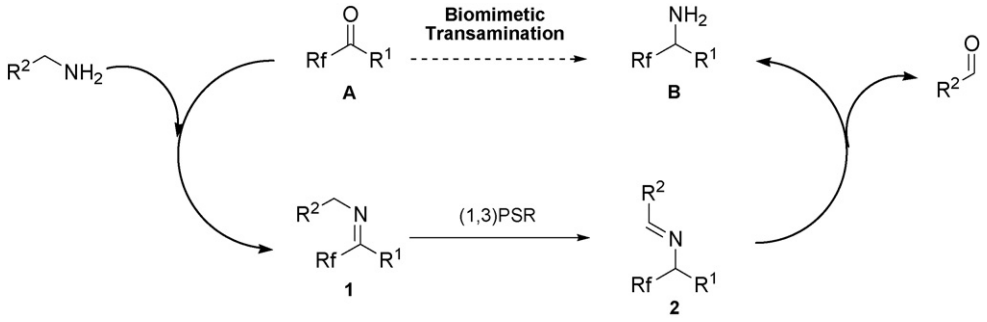


Fig. 1. Biomimetic transamination via (1,3) proton shift reaction.

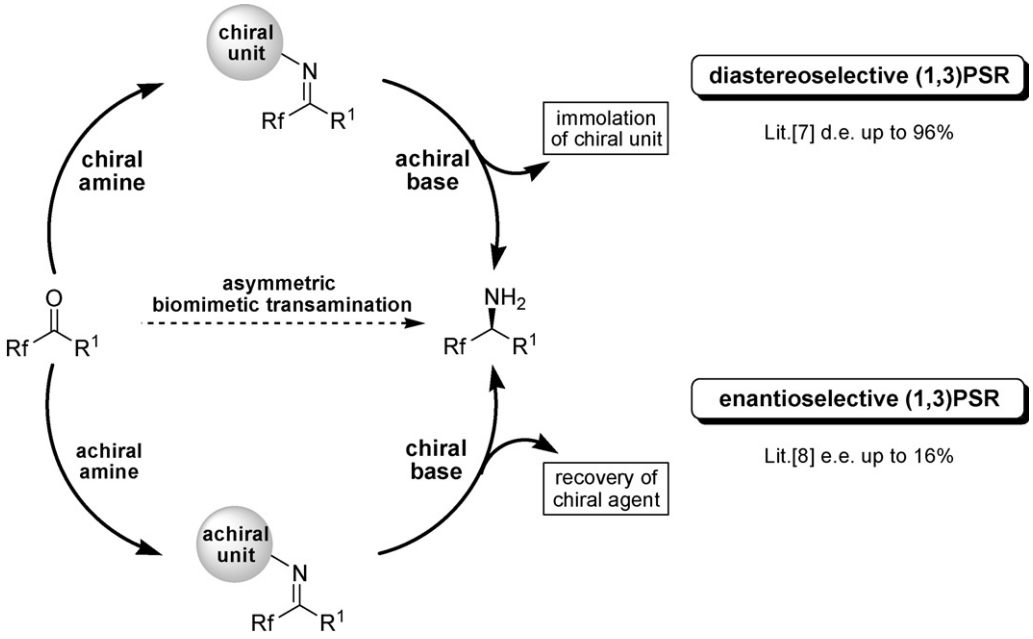


Fig. 2. General strategies for asymmetric biomimetic transamination.

would be more ''chirally economic'' than the diastereoselective version, in which the inherent drawback is the self-immolation of the chiral auxiliary (Fig. 2).

2. Results and discussion

A first set of experiments was conducted with enamine **3a**, product of the condensation of ETFAA with benzylamine.

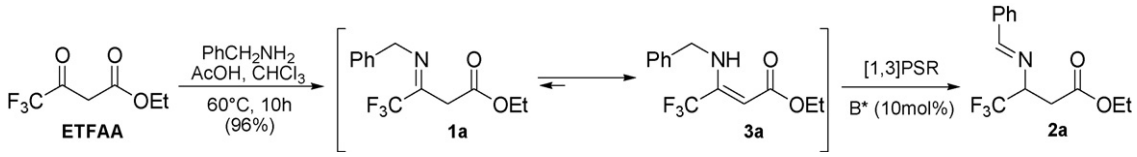
Synthesis of **3a** from ETFAA was performed according to Soloshonok's conditions [10], and yielded directly the enamine instead of imine **1a**, because of internal stabilization by hydrogen bond formation, but (1,3)PSR proceeds via the tautomeric imine form **1a** (Scheme 1).

Reaction conditions were optimized and several chiral bases derived from cinchona alkaloids tested (Fig. 3). The reaction rate is very dependent on both the temperature and the nature of the solvent. The higher the temperature, the faster the isomerization rate. In the same way, the reaction time is greatly shortened in a polar solvent. However, we observed that the enantiomeric excess evolved in the opposite way and is lowered in those conditions (high temperature, polar solvent). The screening of chiral bases was therefore performed in toluene at 110 °C (Table 1).

Worthy of note is that with **3a** as starting material, reaction times are quite long. Among the four cinchona alkaloids, the best enantiomeric excess (20%) is obtained with cinchonine as chiral base (Table 1, entry 4). The bis-alkaloid $(DHQ)_2PYR$ leads to higher enantiomeric excess (entry 5) and finally the best result is obtained with an ether derivative, the hydroquinine 4-methyl-2-quinolylether (MQE-DHQN) and reaches 43% (entry 8).

The best enantiomeric excess obtained here is much better than the best one in the literature for the enantioselective (1,3)PSR (43% versus 16%) [8]. However, in order to improve this promising result, a better understanding of the mechanism of the reaction was needed. Therefore, we decided to conduct the reaction with deuterated enamine **d-3a**, prepared by reducing benzonitrile with $LiAlD_4$ and condensing the resulting deuterated benzylamine with ETFAA following the usual procedure.

With **d-3a** as starting material, the (1,3)PSR is performed in three different kinds of solvents: toluene, acetonitrile and



Scheme 1. First set of experiments.

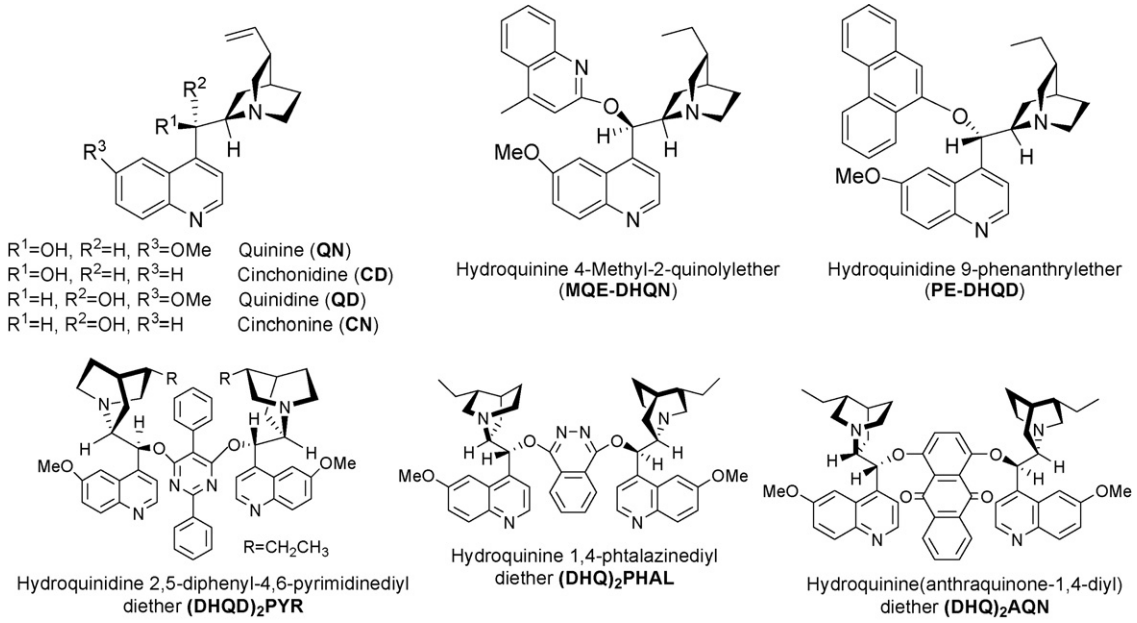


Fig. 3. Chiral bases tested.

butan-1-ol. In all cases, imine **d-2a** is the only product (Scheme 2); this observation supports a suprafacial deprotonation-reprotonation mechanism. On the other hand, each time, the reaction rate is about two times slower with **d-3a** than with the hydrogenated starting material **3a**: an isotopic effect is observed and the deprotonation step of the imine **d-1a** is considered to be the rate determining step. Thus the observation that the reaction proceeds faster in a polar solvent is rather obvious since polarity is expected to favour the deprotonation step. The fact that a similar result is obtained in protic and in aprotic solvents suggests that the asymmetric step is based on an enantioselective discrimination of prochiral benzylic protons.

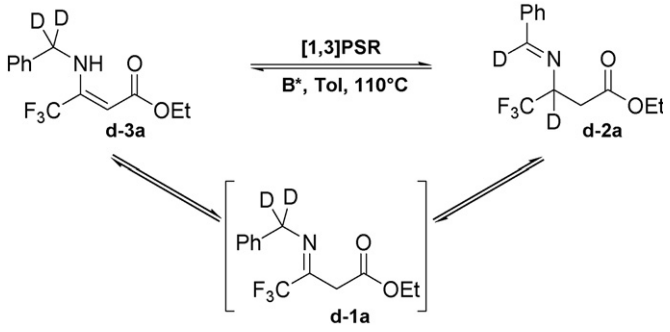
As we assumed that the reaction rate depends on the acidity of the benzylic proton, we decided to study the influence of the nature of the amine moiety. Increasing the acidity of the benzylic proton would allow the reaction to be performed in less drastic conditions in hope of increasing the enantiomeric excess.

Soloshonok et al. studied this effect for the transamination of fluorinated β-keto carboxylic ester but only in a non

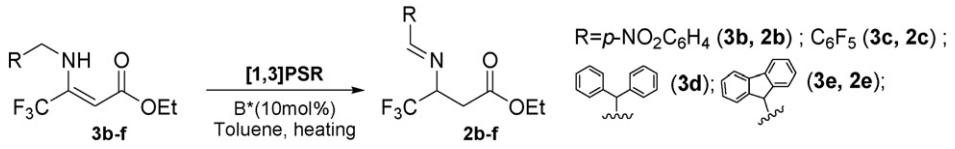
Table 1
Screening of chiral bases

Entry	Chiral base	Reaction time	Conv. (%)[a]	ee (%)[b]	Conf.[c]
1	QN	46 h	92	10	*S*
2	QD	46 h	89	3	*R*
3	CD	46 h	100	12	*R*
4	CN	46 h	49	20	*S*
5	$(DHQD)_2PYR$)	5 d	14	36	*R*
6	$(DHQ)_2AQN$)	2.5 d	67	20	*S*
7	$(DHQ)_2PHAL$)	5 d	0	–	–
8	**(MQE-DHQN)**	**5 d**	**20**	**43**	***S***

[a] Conversion was determined by ^{19}F NMR.
[b] Enantiomeric excess measured by HPLC on chiracel OD-H column with hexane/*i*PrOH (99.9/0.1) as eluent.
[c] Absolute configuration determined by hydrolysis into the corresponding amino acid hydrochloride and comparison of optical rotation with literature data (see Section 4) [11].



Scheme 2. (1,3)PSR with deuterated enamine.



Scheme 3. Role of the amine moiety.

Table 2
Screening of enamines **3** and chiral bases; best results obtained

Entry	Enamine	Chiral base	Reaction conditions	Conv. (%)[a]	ee (%)[b]	Conf.[c]
1	3b	MQE-DHQN	110 °C, 16 h	100	53	*S*
2	3b	MQE-DHQN	80 °C, 16 h	100	56	*S*
3	3b	MQE-DHQN	50 °C, 5d	100	56	*S*
4	3b	$(DHQD)_2PYR$	80 °C, 16 h	100	33	*R*
5	3b	$(DHQ)_2AQN$	80 °C, 16 h	87	26	*S*
6	**3b**	**$(DHQ)_2PHAL$**	**80 °C, 24 h**	**100**	**71**	***S***
7	3c	MQE-DHQN	50 °C, 48 h	40	54	–
8	3d	CN or MQE-DHQN	50 to 110 °C, up to 4 days	–	–	–
9	3e	MQE-DHQN	80 °C, 20 h	44	21	*R*
10	3e	$(DHQD)_2PYR$	80 °C, 48 h	15	24	*S*
11	3e	$(DHQ)_2AQN$	80 °C, 20 h	61	33	*R*

[a] Conversion was determined by ^{19}F NMR.
[b] Enantiomeric excess measured by HPLC on chiracel OD-H column with hexane/*i*PrOH (98/2) as eluent.
[c] Absolute configuration determined by hydrolysis into the corresponding amino acid hydrochloride and comparison of optical rotation with literature data (see Section 4) [11].

asymmetric way [12]. We decided to perform the (1,3)PSR with enamines obtained by condensation of ETFAA and *p*-NO_2-benzylamine (enamine **3b**), pentafluorobenzylamine (enamine **3c**), benzhydrylamine (enamine **3d**), and 9-aminofluorene (enamine **3e**) (Scheme 3).

We first conducted the reaction with the enamine **3b** at different temperatures. The reaction rate, as it was predicted, is accelerated in comparison with the enamine **3a** derived from benzylamine. The screening of chiral bases revealed quite good results concerning enantiomeric excess. With the ether derivative of quinine (MQE-DHQN) a 56% enantiomeric excess is obtained (Table 2, entry 2) and moreover, the bis-alkaloid $(DHQ)_2PHAL$ leads to a 71% enantiomeric excess (Table 2, entry 6).

With **3b** as starting material, we also studied the effect of the concentration in chiral base on reaction rate. (1,3)PSR is therefore conducted with 5, 10 and 20 mol% of MQE-DHQN at 80 °C in toluene (Fig. 4).

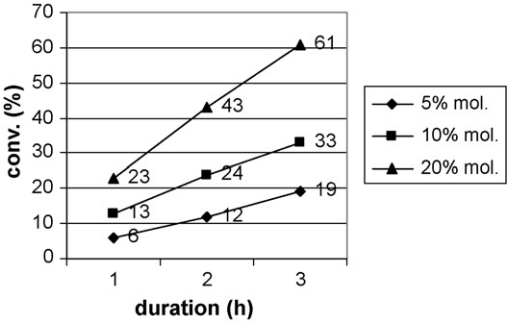


Fig. 4. Effect of the base concentration on reaction rate.

It seems that the reaction rate depends linearly on the concentration of base and this result is also in accordance with the deprotonation being the rate determining step.

Having those promising results, we continued our study with the other enamines at different temperatures and with different chiral bases. Best results are summarized in Table 2.

For **3c**, after 48 h, the conversion was only 40% and a 54% enantiomeric excess was observed (Table 2, entry 7). With **3d**, the reaction did not occur (Table 2, entry 8). In comparison, with **3e**, the isomerization took place. These data can be rationalized by the fact that in the benzhydrylamine moiety, the two phenyl rings are allowed to rotate whereas in the aminofluorene moiety they are blocked. Enamine **3d** is therefore more hindered than **3e** and that could explain its lack of reactivity. With **3e**, best enantiomeric excesses were obtained with $(DHQ)_2AQN$ but reached only 33% (Table 2, entry 11). Moreover, for **2b** and **2e**, configuration of major isomer, obtained with a same chiral base, is opposite (Table 2: entry 1 versus entry 9; entry 4 versus entry 10; entry 5 versus entry 11), whereas the same configuration is obtained for **2b** with **2a** when a same chiral base is used (Table 1, entry 8 versus Table 2, entry 1; Table 1, entry 5 versus Table 2, entry 4). To explain this observation, we assume that two different kinds of enantiotopic discrimination can arise. In the case of imine **1a** or **1b**, bearing a benzyl moiety, there are two prochiral benzylic protons and therefore, enantiotopic atoms discrimination takes place (Fig. 5). In the case of imine **1e** there is only one acidic proton and the chiral base leads to enantiotopic face discrimination (Fig. 5). It should be noted that this observation is in accordance with the deprotonation being the asymmetric determining step as stated above.

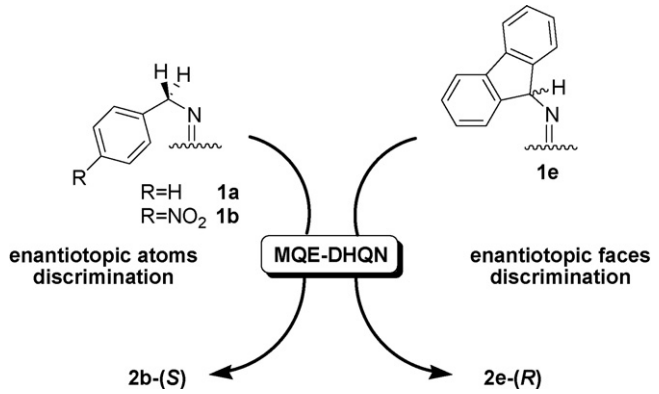


Fig. 5. Enantiodivergent discrimination.

3. Conclusion

We studied enantioselective (1,3) proton transfer of ETFAA derivatives catalyzed by a chiral base. Special emphasis was placed on the mechanistic aspect of the reaction by use of a deuterated enamine and all results support a deprotonation step as both rate and asymmetric determining step.

Both reaction conditions and influence of the nature of the starting material were considered; the best enantiomeric excess was obtained with $(DHQ)_2PHAL$ as chiral base and reaches 71% which is far better than previous results reported in the literature up to now for organocatalytic enantioselective (1,3)PSR. This study opens a new route to trifluoromethylated chiral building blocks. We are currently exploring transformations of the obtained β-trifluoromethylated β-amino acids for the construction of various fluorinated targets [13].

4. Experimental

4.1. General

Toluene was distilled from sodium and benzophenone under argon atmosphere. Acetonitrile and butan-1-ol were distilled on calcium hydride. Thin layer chromatography was performed using silica TLC plates (silica gel 60 F254, Merck). Products were visualized under UV light (254 nm) and then revealed by potassium permanganate aqueous solution. Flash chromatographies were performed on silica gel column (silica gel Si60 0.040–0.063 mm, Merck).

Infra Red spectra were recorded on a Perkin-Elmer 16PCFT-IR and wave numbers are given in cm^{-1}. NMR Spectra were performed on a Bruker Avance 300. Chemical shifts of ^1H NMR (300 MHz) were expressed in parts per million downfield from tetramethylsilane external standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR (75.5 MHz) were expressed in parts per million downfield from $CDCl_3$ as internal standard ($\delta = 77.16$). Chemical shifts of ^{19}F NMR (282 MHz) were expressed in parts per million downfield from $CFCl_3$ as internal standard ($\delta = 0$). Coupling constants are reported in hertz (Hz). Abbreviations used for signals observed are: **s** for singlet, **d** for doublet, **t** for triplet, **q** for quartet, **dd** for double doublet, **dt** for double triplet, **m** for multiplet and **b** for broad. HPLC analyses were carried out on either a HP series 1100 using a HP 3395 integrator or a Waters 600 with a Waters 486 UV detector and a Waters 746 integrator. Chiral columns used are Chiralcel OD-H and Chiralpak AD-H. Gas chromatography (GC) was performed on a Hewlett Packard HP 5890A series II using a Hewlett Packard HP 3396 series II integrator. Mass spectrometry was performed on a Shimadzu GCMS-QP2010 in EI or CI mode. Elementary Analyses were realised on a CE instruments EA 1110.

4.2. General procedure for the synthesis of enamines, typical example with enamine *3b*: (Z)-ethyl 3-(4-nitrobenzylamino)-4,4,4-trifluorobut-2-enoate (*3b*)

A solution of 4-nitrobenzylamine hydrochloride in aqueous Na_2CO_3 was extracted with dichloromethane. Organic layers were combined, dried over $MgSO_4$, filtrated and evaporated under vacuum. 4-Nitrobenzylamine thus obtained (1.06 g, 7 mmol) was added at room temperature to a solution of glacial acetic acid (0.42 g, 7 mmol) in chloroform (2 mL). After stirring for 5 min at room temperature, ETFAA (1.16 g, 6.3 mmol) diluted in chloroform (1 mL), was added. The resultant mixture was refluxed for 2 h followed by evaporation of the solvent in vacuum. The residue was placed on a silica gel column and eluted with a mixture of cyclohexane/ethyl acetate (5/1) to afford the desired product (1.80 g, 90%) as pale yellow solid.

$C_{13}H_{13}F_3N_2O_4$, MW = 318.25, pale yellow solid, Mp = 68 °C; IR (cm^{-1}): 3275 (NH); 3109, 3083 (CH_{Aro}); 2997, 2962, 2856 (CH_3, CH_2); 1676 (db_{CIS}); 1630 (CO); 1605 (db_{Aro}); 1516, 1351 (NO_2); RMN ^{19}F ($CDCl_3$): −66.9 (3F, s); RMN ^1H ($CDCl_3$): 1.28 (3H, t, $J = 7.2$), 4.17 (2H, q, $J = 7.2$), 4.58 (2H, d, $J = 6.7$), 5.24 (1H, s), 7.45 (2H, d, $J = 8.7$), 8.22 (2H, d, $J = 8.7$), 8.59 (1H, bb); RMN ^{13}C ($CDCl_3$): 14.3, 47.3, 60.2, 87.0 (q, $J = 5.6$), 120.3 (q, $J = 277.0$), 124.2, 127.7, 145.6, 147.6, 147.9 (q, $J = 31.0$), 169.9; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 98/2, 1 mL min^{-1}, 254 nm): 9.03 min; GC–MS (EI): 271(100), 245(49), 289(61), 318($M^{+\bullet}$); Anal. Calcd. for $C_{13}H_{13}F_3N_2O_4$: C, 49.06; H, 4.12; N, 8.80; Found: C, 49.05; H, 4.02; N, 8.74.

4.3. (Z)-Ethyl 3-(benzylamino)-4,4,4-trifluorobut-2-enoate (*3a*)

$C_{13}H_{14}F_3NO_2$, MW = 273.25, yellow oil; IR (cm^{-1}): 3283 (NH); 3031 (CH_{Aro}); 2982 (CH_3); 2936 (CH_2); 1672 (db_{CIS}); 1632 (CO); RMN ^{19}F ($CDCl_3$): −67.0 (3F, s); RMN ^1H ($CDCl_3$): 1.18 (3H, t, $J = 7.1$), 4.05 (2H, q, $J = 7.1$), 4.39 (2H, d, $J = 6.4$), 5.08 (1H, s), 7.21 (5H, m), 8.37 (1H, bb); RMN ^{13}C ($CDCl_3$): 14.3, 48.1, 59.8, 85.3 (q, $J = 5.9$), 120.4 (q, $J = 277.0$), 127.3, 127.9, 128.9, 137.8, 148.2 (q, $J_{C\text{-}F} = 31.0$), 169.9; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 99.9/0.1, 1 mL min^{-1}, 254 nm): 14.4 min; GC (BPX5, 23 m, 40 °C (5 min), 8 °C/min, 280 °C): 16.6 min; GC–MS (EI): 91(100), 200(52), 273($M^{+\bullet}$); Anal. Calcd. for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13; Found: C, 57.06; H, 4.98; N, 5.39.

*4.4. (Z)-Ethyl 4,4,4-trifluoro-3-(perfluorobenzylamino)but-2-enoate (**3c**)*

$C_{13}H_9F_8NO_2$, MW = 363.20, yellow oil; IR (cm^{-1}): 3288, 3232 (NH); 2985 (CH_3); 2941, 2901 (CH_2); 1675 (db_{CIS}); 1636 (CO); RMN ^{19}F ($CDCl_3$): −66.9 (3F, s), −143.6 (2F, m), −153.9 (1F, t, J = 20.6), −161.5 (2F, m); RMN ^1H ($CDCl_3$): 1.26 (3H, t, J = 7.2), 4.14 (2H, q, J = 7.2), 4.54 (2H, d, J = 6.4), 5.19 (1H, s), 8.45 (1H, bs); RMN ^{13}C ($CDCl_3$): 14.3, 35.9, 60.3, 87.5, 110.0, 120.2 (q, J = 276.5), 136.1, 139.6, 143.8, 147.1 (q, J = 31.6), 169.8; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 99.5/0.5, 1 mL min^{-1}, 254 nm): 7.01 min.

*4.5. (Z)-Ethyl 3-[(1-$^2H_2$) benzylamino]-4,4,4-trifluorobut-2-enoate (**d-3a**)*

$C_{13}H_{12}D_2F_3NO_2$, MW = 275.26, colourless oil; IR (cm^{-1}): 3277, 3232 (NH); 3064, 3030 (CH_{Aro}); 2980 (CH_3); 2929 (CH_2); 1672 (db_{CIS}); 1630 (CO); RMN ^{19}F ($CDCl_3$): −67.1 (3F, s); RMN ^1H ($CDCl_3$): 1.16 (3H, t, J = 7.2), 4.04 (2H, q, J = 7.2), 5.08 (1H, s), 7.17–7.29 (5H), 8.35 (1H, bs); RMN ^{13}C ($CDCl_3$): 14.4, 47.6 (m), 59.8, 85.3, 120.4 (q, J = 277.0), 129.0, 128.0, 127.4, 137.7, 148.3 (q, J = 31.1), 170.0; GC–MS (EI): 93(100); 227(26); 246(41); 275($M^{+\bullet}$); Anal. Calcd. for $C_{13}H_{12}D_2F_3NO_2$: C, 56.72; H, 5.86; N, 5.09; Found: C, 56.71; H, 5.91; N, 5.19.

*4.6. (Z)-Ethyl 3-(benzhydrylamino)-4,4,4-trifluorobut-2-enoate (**3d**)*

$C_{19}H_{18}F_3NO_2$, MW = 349.35, white solid, Mp = 76–78 °C; IR (cm^{-1}): 3198 (NH); 2985 (CH_{Aro}); 1667 (CO); 1625 (cdb); 1493–1446 (CH_2-CH_3); RMN ^{19}F ($CDCl_3$): −66.3 (3F, s); RMN ^1H ($CDCl_3$): 1.19 (3H, t, J = 7.1), 4.09 (2H, q, J = 7.1), 5.23 (1H, s), 5.84 (1H, d, J = 10.9), 7.35–7.37 (10H, m), 9.0 (1H, bd, J = 10.9); RMN ^{13}C ($CDCl_3$): 14.4, 60.0, 62.0, 86.6 (q, J = 5.6), 120.4 (q, J = 277.7), 127.1, 127.7, 128.9, 142.0, 147.6 (q, $J_{C\text{-}F}$ = 31.8), 169.9; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 99.9/0.1, 1 mL min^{-1}, 254 nm): 6.6 min; Anal. Calcd. for $C_{19}H_{18}F_3NO_2$: C, 65.32; H, 5.19; N, 4.01; Found: C, 65.54; H, 5.13; N, 4.04.

*4.7. (Z)-Ethyl 3-(9H-fluoren-9-ylamino)-4,4,4-trifluorobut-2-enoate (**3e**)*

$C_{19}H_{16}F_3NO_2$, MW = 347.33, white solid, Mp = 100–102 °C; IR (cm^{-1}): 3226 (NH); 3064 (CH_{Aro}); 2981 (CH_2-CH_3); 1673 (CO); 1628 (cdb); RMN ^{19}F ($CDCl_3$): −65.2 (3F, s); RMN ^1H ($CDCl_3$): 1.23 (3H, t, J = 7.1), 4.06 (2H, q, J = 7.1), 5.27 (1H, s), 5.64 (1H, d, J = 11.3), 7.32 (2H, t, J = 7.5), 7.41 (2H, t, J = 7.5), 7.53 (2H, t, J = 7.5), 7.7 (2H, t, J = 7.5), 8.26 (1H, bd); RMN ^{13}C ($CDCl_3$): 14.3, 59.8, 59.9, 86.0 (q, J = 5.6), 120.8 (q, J = 277.0), 120.2, 125.1, 128.0, 129.1, 140.3, 144.0, 148.4 (q, J = 30.4), 169.6; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 99.5/0.5, 1 mL min^{-1}, 254 nm): 15.6 min; Anal. Calcd. for $C_{19}H_{16}F_3NO_2$: C, 65.70; H, 4.64; N, 4.03; Found: C, 65.54; H, 4.61; N, 3.96.

*4.8. General procedure for the (1,3) enantioselective proton shift reaction using cinchona alkaloids as chiral base: typical example with enamine **3b***

In a flask were introduced, $(DHQ)_2PHAL$ (20 mg, 0.025 mmol), enamine **3b** (79.6 mg, 0.25 mmol) and distilled toluene (1 mL). The resultant mixture was stirred and heated. Reaction was followed by ^{19}F NMR. After 24 h at 80 °C, solvent was evaporated in vacuum, the residue was put on a short silica gel column and eluted with cyclohexane/ethyl acetate (10/1) to afford desired product, imine **2b** (18 mg, 90%) as yellow oil. The chiral base could be recovered by eluting it with a mixture of dichloromethane/methanol (97/3).

*4.9. (E)-Ethyl 3-(4-nitrobenzylideneamino)-4,4,4-trifluorobutanoate (**2b**)*

$C_{13}H_{13}F_3N_2O_4$, MW = 318.25, yellow oil; IR (cm^{-1}): 3083 (CH_{Aro}); 2986 (CH_3); 2937 (CH_2); 1637 (CO); 1650 (CN); 1526, 1348 (NO_{2Aro}); RMN ^{19}F ($CDCl_3$): −75.4 (3F, d, J = 6.8); RMN ^1H ($CDCl_3$,): 1.20 (3H, t, J = 7.2), 2.93 (2H, d, J = 7.2), 4.11 (2H, m), 4.30 (1H, m), 7.96 (2H, d, J = 8.7), 8.28 (2H, d, J = 8.7), 8.52 (1H, s); RMN ^{13}C ($CDCl_3$): 14.2, 34.2, 61.4, 67.9 (q, J = 28.3), 124.0, 124.8 (q, J = 279.9), 129.7, 140.4, 149.8, 165.3, 169.8; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 98/2, 1 mL min^{-1}, 254 nm): (*S*): 10.3 min, (*R*): 12.7 min; Anal. Calcd. for $C_{13}H_{13}F_3N_2O_4$: C, 49.06; H, 4.12; N, 8.80; Found: C, 49.13; H, 4.17; N, 8.80.

*4.10. (E)-Ethyl 3-(benzylideneamino)-4,4,4-trifluorobutanoate (**2a**)*

$C_{13}H_{14}F_3NO_2$, MW = 273.25, colourless oil; IR (cm^{-1}): 3064 (CH_{Aro}); 2985 (CH_3); 2890 (CH_2); 1739 (CO); 1647 (CN); RMN ^{19}F ($CDCl_3$): −75.5 (3F, d, J = 6.8); RMN ^1H ($CDCl_3$): 1.09 (3H, t, J = 7.1), 2.81 (2H, d, J = 6.4), 3.99 (2H, 2q, J = 7.1), 4.15 (1H, m), 7.34 (3H, m), 7.68 (2H, m), 8.32 (1H, s); RMN ^{13}C ($CDCl_3$): 14.1, 34.6, 61.1, 68.1 (q, J = 29.0), 124.6 (q, J = 280.6), 131.8, 130.6, 128.7, 135.2, 167.4, 169.8; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 99.9/0.1, 1 mL min^{-1}, 254 nm): (*S*): 12.6 min, (*R*): 23.3 min; Anal. Calcd. for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13; Found: C, 57.06; H, 5.23; N, 5.27.

*4.11. (E)-Ethyl 3-(3-^2H)-[(1-^2H) benzylideneamino]-4,4,4-trifluorobutanoate (**d-2a**)*

$C_{13}H_{12}D_2F_3NO_2$, MW = 275.26, colourless oil; IR (cm^{-1}): 3064 (CH_{Aro}); 2980 (CH_3); 2907 (CH_2); 1737 (CO); 1630 (CN); RMN ^{19}F ($CDCl_3$): −75.7 (3F, s); RMN ^1H ($CDCl_3$): 1.2 (3H, t, J = 7.1), 2.90 (2H, s), 4.10 (2H, q, J = 7.1), 7.39–7.49 (3H, m), 7.77–7.80 (2H, m); RMN ^{13}C ($CDCl_3$): 14.2, 34.6, 61.2, 125.1 (q, J = 279.9), 128.5, 128.8, 131.9, 135.1, 167.2 (t, J = 24.8), 170.0; GC–MS (CI, CH_4): 276 (M + 1); 304 (M + 2CH_4); GC–MS (EI): 105 (100); 202 (26); 246 (36); 275 ($M^{+\bullet}$).

4.12. (E)-Ethyl 4,4,4-trifluoro-3-(perfluorobenzylideneamino)butanoate (**2c**)

$C_{13}H_9F_8NO_2$, MW = 363.20, yellow oil; IR (cm^{-1}): 2985 (CH_3); 2935, 2907 (CH_2); 1637 (CO), 1653 (CN); RMN ^{19}F ($CDCl_3$, 282 MHz, δ): −75.5 (3F, d, J = 6.8), −141.6 (2F, m), −149.3 (1F, J = 21.8, J = 3.4), −161.8 (2F, m); RMN ^1H ($CDCl_3$, 300 MHz, δ): 1.26 (3H, t, J = 7.2), 4.14 (2H, q, J = 7.2), 4.15 (2H, m), 4.25 (1H, m), 5.19 (1H, s), 8.55 (1H, s); RMN ^{13}C ($CDCl_3$, 75.5 MHz, δ): 14.2, 34.2, 61.4, 69.1 (q, J = 29.0), 108.8, 109.1, 124.5, 124.8 (q, J = 279.9), 136.2, 139.5, 144.7, 156.3, 157.8, 169.6; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 99.5/0.5, 1 mL min^{-1}, 254 nm): 5.4, 14.2 min.

4.13. Ethyl 3-(9H-fluoren-9-ylideneamino)-4,4,4-trifluorobutanoate (**2e**)

$C_{19}H_{16}F_3NO_2$, MW = 347.33, white solid, Mp = 88–90 °C; IR (cm^{-1}): 3053 (CH_{Aro}); 2985 (CH_2-CH_3); 1734 (CO); RMN ^{19}F ($CDCl_3$): −75.7 (3F, d, J = 6.8); RMN ^1H ($CDCl_3$): 1.12 (3H, t, J = 7.1), 2.76 (1H, dd, J = 16.2, J = 6.03), 3.02 (1H, dd, J = 16.2, J = 7.2), 4.06 (2H, q, J = 7.1), 5.49 (1H, m), 7.22 (2H, m), 7.36 (2H, m), 7.46, 7.56 (2H, d, J = 7.5), 7.74, 7.98 (2H, d, J = 7.5); RMN ^{13}C ($CDCl_3$): 14.1, 35.8, 59.4 (q, J = 28.9), 61.4, 119.5, 120.7, 123.6, 127.4, 128.6, 131.9, 132.4, 131.2 (q, J = 296.1), 138.1, 141.3, 144.5, 166.7; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 99.5/0.5, 1 mL min^{-1}, 254 nm): (*R*): 12.5, (*S*): 18.1 min; Anal. Calcd. for $C_{19}H_{16}F_3NO_2$: C, 65.70; H, 4.64; N, 4.03; Found: C, 65.46; H, 4.53; N, 3.97.

4.14. General procedure for hydrolysis of imines: 3-amino-4,4,4-trifluorobutanoic acid hydrochloride

Mixture of imine diluted in a solution of HCl 6 M was refluxed during 3 h. Organic layer was extracted with dichloromethane. Aqueous layer was recovered and water was evaporated in vacuum. Hydrochloride of desired amino acid was obtained.

$C_4H_7ClF_3NO_2$, MW = 193.55, white solid, Mp = 168–170 °C; IR (cm^{-1}): 3400 (OH); 2907 (NH); 1731 (CO); 1418 (C-O); RMN ^{19}F (CD_3OD): −74.3 (3F, d, J = 6.8); RMN ^1H (CD_3OD, 300 MHz, δ): 2.88 (1H, dd, J = 8.7, J = 17.7), 3.05 (1H, dd, J = 4.1, J = 17.7), 4.52 (1H, m), 5.25 (4H, bb); RMN ^{13}C (CD_3OD, 75.5 MHz, δ): 31.9, 50.7 (q, J = 32.5), 125.1 (q, J = 279.9), 171.2; Anal. Calcd. for $C_4H_7ClF_3NO_2$: C, 24.82; H, 3.65; N, 7.24; Found: C, 24.84; H, 3.73; N, 7.18.

Acknowledgement

Rhodia Recherches and CNRS are gratefully acknowledged for a research grant to VM.

References

[1] (a) J.P. Bégué, D. Bonnet-Delpon, Chimie bioorganique et médicinale du fluor EDP Sciences/CNRS Eds. (2005).
(b) B.E. Smart, J. Fluorine Chem. 109 (2001) 3–11;
(c) D. O'Hagan, H.S. Rzepa, Chem. Commun. (1997) 645–652;
(d) M. Schlosser, Angew. Chem. Int. Ed. 110 (1998) 1496–1513.
[2] (a) J.P. Bégué, D. Bonnet-Delpon, J. Fluorine Chem. 127 (2006) 992–1012;
(b) C. Isanbor, D. O'Hagan, J. Fluorine Chem. 127 (2006) 303–319;
(c) K. Kirk, J. Fluorine Chem. 127 (2006) 1013–1029.
[3] (a) M. Liu, M.P. Sibi, Tetrahedron 58 (2002) 7991–8035;
(b) R.P. Cheng, S.H. Gellman, W.F. DeGrado, Chem. Rev. 101 (2001) 3219–3232;
(c) D. Seebach, T. Kimmerlin, R. Sebesta, M.A. Campo, A.K. Beck, Tetrahedron 60 (2004) 7455–7506.
[4] (a) F. Huguenot, T. Brigaud, J. Org. Chem. 71 (2006) 2159–2162;
(b) X.L. Qiu, W.D. Meng, F.L. Qing, Tetrahedron 60 (2004) 6711–6745, and references cited therein;
(c) N. Lebouvier, C. Laroche, F. Huguenot, T. Brigaud, Tetrahedron 43 (2002) 2827–2830.
[5] (a) T. Ono, P. Kukhar, V.A. Soloshonok, J. Org. Chem. 61 (1996) 6563–6569;
(b) V.A. Soloshonok, A.G. Kirilenko, V.P. Kukhar, Tetrahedron Lett. 34 (1993) 3621–3624.
[6] V.A. Soloshonok, D.O. Berbasov, J. Fluorine Chem. 125 (2004) 1757–1763.
[7] (a) V.A. Soloshonok, H. Ohkura, M. Yasumoto, J. Fluorine Chem. 127 (2006) 889–893;
(b) V.A. Soloshonok, H. Ohkura, M. Yasumoto, J. Fluorine Chem. 127 (2006) 924–929;
(c) V.A. Soloshonok, H. Ohkura, M. Yasumoto, J. Fluorine Chem. 127 (2006) 930–935;
(d) V.A. Soloshonok, I.V. Soloshonok, V.P. Kukhar, V.K. Svedas, J. Org. Chem. 63 (1998) 1878–1884;
(e) V.A. Soloshonok, T. Ono, I.V. Soloshonok, J. Org. Chem. 62 (1997) 7538–7539;
(f) V.A. Soloshonok, T. Ono, J. Org. Chem. 62 (1997) 3030–3031.
[8] (a) V.A. Soloshonok, V.P. Kukhar, Tetrahedron 52 (1996) 6953–6964;
(b) V.A. Soloshonok, A.G. Kirilenko, S.V. Galushko, V.P. Kukhar, Tetrahedron Lett. 35 (1994) 5063–5064.
[9] (a) B. Mohar, J. Baudoux, J.C. Plaquevent, D. Cahard, Angew. Chem. Int. Ed. 40 (2001) 4214–4216;
(b) D. Cahard, C. Audouard, J.C. Plaquevent, N. Roques, Org. Lett. 2 (2000) 3699–3701.
[10] H. Ohkura, D.O. Berbasov, V.A. Soloshonok, Tetrahedron 59 (2003) 1647–1656.
[11] V.A. Soloshonok, A.G. Kirilenko, N.A. Fokina, I.P. Shishkina, S.V. Galushko, V.P. Kukhar, V.K. Svedas, V. Kozlova, Tetrahedron Asymm. 5 (1994) 1119–1126.
[12] V.A. Soloshonok, T. Ono, Tetrahedron 52 (1996) 14701–14712.
[13] V. Michaut, Dissertation, Rouen University (France), 2006, and results to be published.