Highly Enantioselective Transfer of Chirality from a Less to a More Configurationally Unstable Stereogenic Center. A Practical Asymmetric Synthesis of (Fluoroalkyl)amines *via* Biomimetic Transamination

Vadim A. Soloshonok* and Taizo Ono

National Industrial Research Institute of Nagoya, Hirate-cho 1-1, Kita-ku, Nagoya City, Aichi Prefecture 462, Japan

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[1,3]-Proton shift reaction (PSR), a reducing agent-free biomimetic reductive amination,[1] is emerging as a convenient, preparatively useful generalized method for the synthesis of various fluorine-containing amino compounds of a wide range of potential biomedicinal and synthetic applications.[2] To achieve the desired transformation of a carbonyl to an amino group, PSR makes use of biomimetic transposition[3] of an imine functionality *via* base-catalyzed azomethine−azomethine isomerization and thus is conceptually different from the well-tried purely chemical methodology relying heavily on the use of external reducing agents.[4] However, for that exciting synthetic potential of PSR to be realized in full, the asymmetric PSR, allowing for preparing enantiomerically pure targets, must be developed. On the other hand, the mechanism of hydrocarbon base-catalyzed azomethine−azomethine isomerization was shown to involve the formation of a delocalized 2-azaallyl anion, the evolution of which to the new covalent state is a function of thermodynamic preference of the tautomeric Schiff bases and could be adequately correlated by the Hammett equation.[5] In other words, the equilibrium of the isomerization is shifted toward a more C−H acidic tautomer. In terms of stereochemistry, it means that the proton transfer occurs *from a less to a more configurationally unstable stereogenic center*. The methodology for such a kind of asymmetric transformation is virtually undeveloped and thermodynamically not allowed.[6,7] In this paper, we report a successful solution to these problems that allows for an efficient, generalized synthesis of (α-fluoroalkyl)amines of high enantiomeric purity *via* asymmetric PSR.

The starting chiral Schiff bases **3a**−**e** were readily synthesized by the direct condensation between an appropriate ketone **1a**−**e** and (*S*)-α-phenylethylamine (**2**) (Scheme 1). An important characteristic of these substrates is that they exist as individual *anti* isomers (by NMR). For the initial studies of the isomerization of **3a** to **4a**, we tried to apply as mild as possible reaction conditions, since the targeted product **4a** is obviously prone to racemization under the forcing conditions or when strong base is used.[8] Unfortunately, ketimine **3a**, as well as the rest of the *N*-(α-phenylethyl) derivatives **3b**−**e**, were found to be totally inert under the conditions previously established for isomerizations of the *N*-benzyl analogs.[1b] Thus, no isomerization of **3a** to **4a** was observed in triethylamine (TEA) solution for more than 1 week. However, at 150 °C the isomerization was achieved, albeit with a slow reaction rate, to afford targeted **4a** in moderate isolated yield (Table 1, entry 1). Enantiomeric purity of the product **4a**, determined directly for **4a** or for its *N*-(3,5-dinitrobenzoyl) derivative, was shown to be 50% ee. Further, we have found that the addition of DABCO (0.5 equiv) or DBU (0.1 equiv) to the TEA solution allows the isomerization to be completed under milder conditions (Table 1, entries 2 and 3) to give the product **4a** with both substantially enhanced chemical yield and enantiomeric purity. Drawing inspiration from these findings, we performed the isomerization in neat DBU. The result was rather impressive: the isomerization was completed at 50 °C after only 1 h, furnishing the product **4a** in excellent chemical yield and with markedly enhanced enantiomeric purity (Table 1, entry 4). Lowering of the reaction temperature (Table 1, entry 5) decreased the isomerization rate but afforded the product in higher enantiomeric purity (Table 1, entry 5 *vs* 4). While working with the isomerization of **3a** to **4a**, we noticed that the DBU/substrate ratio has a dramatic influence on the isomerization rate. This observation was quite unexpected as it is not consistent with a purely catalytic role of the base in these isomerizations. However, the results in entries 6 and 7 of Table 1 clearly demonstrate that the isomerization rate is a function of the ratio DBU/**3a**. At this stage, we can suggest that DBU, apart from the role of the catalyst, works as a unique reaction medium facilitating the isomerization. Whatever the effect of DBU, the synthetic result was quite valuable: the isomerization of ketimine **3a** in neat DBU solution afforded Schiff base **4a** in 95% yield and in 87% ee (Table 1, entry 7). These results (Table 1) indicate that, as we expected, Schiff base **4a** is configurationally unstable toward the basic conditions, but, surprisingly, under certain conditions (DBU, 1−2 equiv) isomerization of **3a** to **4a** occurs with a much higher rate than the racemization of **4a**, allowing its preparation in both high chemical yield and enantiomeric purity.

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(2) For a general discussion of the biological activity and importance of fluorinated amino compounds see the following monographs: (a) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993. (b) *Fluorine-Containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994. (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, D.C., 1996. For the most recent publications see: (d) *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Resnati, G., Soloshonok, V. A., Eds.; Tetrahedron Symposium-in-Print No. 58; *Tetrahedron* **1996**, *52*, 1−330.

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(4) For the most recent and comprehensive publication on conventional reductive amination of carbonyl compounds see: Abdel-Magid, A.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849 and references cited therein.

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(6) (a) Jaeger, D. A.; Broadhurst, M. D.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 717. (b) Guthrie, R. D.; Jaeger, D. A.; Meister, W.; Cram, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 5137. (c) Jaeger, D. A.; Cram, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 5153 and other references of this group cited therein.

(7) Kukhar, V. P.; Soloshonok, V. A.; Galushko, S. V.; Rozhenko, A. B. *Dokl. Akad. Nauk SSSR* **1990**, *310*, 886 (Engl. transl. p 26).

(8) We have shown that forced reaction conditions and strong bases cause dehydrofluorination of Schiff bases of type **4**; see refs 1b and 7.

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Scheme 1

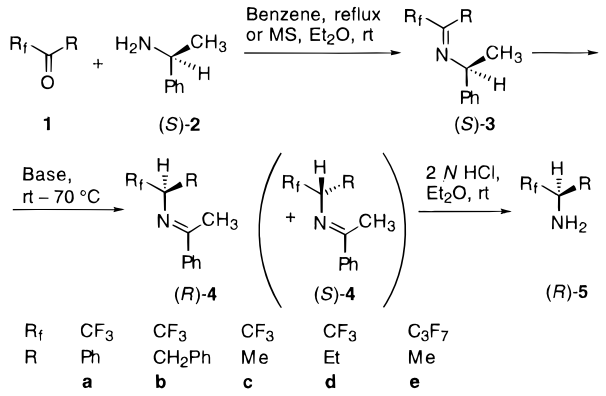

Table 1. Optimization of Reaction Conditions: Isomerizations of (*S*)-3a to (*R*)-4a[a]

entry	base (equiv)	*T*, °C	time, h	yield,[b] %	ee,[c] %
1	TEA[d]	150	120	64	50
2	TEA[d]/DABCO (0.5)	100	30	76	55
3	TEA[d]/DBU (0.1)	50	130	80	60
4	DBU (1)	50	1	98	77
5	DBU (1)	18	7	95	84
6	DBU (0.5)	19	15	73[e]	81
7	DBU (2)	19	4	95	87

[a] All reactions were run under dry argon atmosphere; 10−1 mmol scale. [b] Isolated yield of analytically pure material. [c] (*R*)-Absolute configuration of **4a** was determined by optical rotation; ee values determined by chiral HPLC analysis of *N*-(3,5-dinitrobenzoyl) derivative. [d] TEA was used as solvent. [e] Conversion of **3a** to **4a** 90%.

Table 2. Asymmetric Isomerizations of (*S*)-3b−d to (*R*)-4b−d[a]

		imine		base	*T*,	time,	yield,[b]	ee,[c]
entry		R	R_f	(equiv)	°C	h	%	%
1	**b**	Bn	CF_3	DBU (1)	50	9	86	88
2	**b**	Bn	CF_3	DBU (1)	80	2	82	85
3	**b**	Bn	CF_3	DBU (2)	21	42.5	93	88
4	**c**	Me	CF_3	DBU (1)	60	18	90	93
5	**c**	Me	CF_3	DBU (1.5)	60	15	94	93
6	**d**	Et	CF_3	DBU (1)	60	18	87	87
7	**d**	Et	CF_3	DBU (1.5)	60	15	90	87
8	**e**	Me	C_3F_7	DBU (1.5)	60	15	74	97

[a] All reactions were run under dry argon atmosphere. [b] Isolated yield of analytically pure material. [c] Determined by chiral HPLC analysis of *N*-(3,5-dinitrobenzoyl) derivatives.

Assuming that the asymmetric outcome of the isomerization might be a function of the stereochemical discrimination between substituents at the imine carbon, we selected four types of substrates bearing the trifluoromethyl group *vs* benzyl **3b**, methyl **3c**, ethyl **3d**, and perfluoropropyl *vs* methyl group **3e**, which would allow us to evaluate the generality of the method. The results are collected in Table 2. Isomerization of highly enaminolizable (trifluoromethyl)benzylimine **3b** was of particular interest as it is known that for hydrocarbon imines base-catalyzed azomethine−enamine isomerization is a much more favorable process than relative azomethine−azomethine prototropy.[5c] In contrast to this worrisome expectation, imine **3b** was completely isomerized in neat DBU (1 equiv) at 50 °C for 9 h to give Schiff base **4b** in both high chemical yield and enantiomeric purity (Table 2, entry 1). At an elevated temperature (80 °C), the isomerization proceeded with a higher reaction rate furnishing, however, the product **4b** in lower yield and enantiomeric purity (Table 2, entry 2). The application of 2 equiv of DBU accelerated the isomerization, allowing us to achieve complete transformation of **3b** to **4b** at room temperature (21 °C) to give the targeted **4b** in highest chemical yield and in 88% ee (Table 2, entry 3).

Stereochemical discrimination between methyl and trifluoromethyl groups is always very intriguing. We have found that isomerization of imine **3c** in neat DBU (1 equiv) occurs smoothly at 60 °C in 18 h to provide **4c** in high chemical yield and in 93% ee (Table 2, entry 4). Also, in this case, the increase in the ratio DBU/**3c** accelerated the isomerization to afford product **4c** in the same ee (Table 2, entry 5). Under the same reaction conditions, the isomerization of (trifluoromethyl)ethylimine **3d** gave the desired product **4d** with lower stereoselectivity (87% ee), suggesting that the enantioselectivity of the proton transfer is dependent on the size of the substituent at the imine carbon (Table 2, entries 6 and 7).

In contrast to isomerizations of (trifluoromethyl)imines **3a**−**d**, transformation of perfluoropropyl derivative **3e** in a solution of DBU (1.5 equiv) at 60 °C was accompanied by a sizable formation of byproducts. However, the targeted product **4e** was isolated in synthetically useful 74% yield and with excellent enantioselectivity (97% ee) (Table 2, entry 8).

From the data obtained the following important conclusions can be drawn at this stage. First, *despite the apparently lower configurational stability of Schiff bases **4a**−**e** than that of starting imines **3a**−**e**,*[9] *the isomerization of **3a**−**e** to **4a**−**e** can be conducted with very high enantioselectivity*. Second, the application of the DBU in a submolar ratio to the starting imine, as the base and as the solvent, is critical for both the rate and the stereochemical outcome of the reactions. Finally, the results obtained highlight the exciting stereodirecting features of the perfluoroalkyl group (CF_3, C_3F_7). Thus, this group provides geometrical homogeneity of the initial imines **3a**−**e** and plays the role of an enantiocontrolling group in the isomerizations of **3a**−**e** to **4a**−**e**.

In summary, this study has disclosed a unique example of a highly enantioselective [1,3]-proton transfer from a less to a more configurationally unstable stereogenic center. A wide range of synthetic applications of this asymmetric, reducing reagent-free transamination for preparing biologically interesting fluoro amino compounds are readily envisaged. The extreme simplicity of the experimental procedure and the ready availability of all starting materials, combined with substrate generality, high chemical, and optical yields of the targeted products, render this biomimetic approach an immediately useful alternative to existing methods.[10] Worthy of further investigation are the very intriguing stereodirecting features of the perfluoroalkyl group. These, along with the expansion of this methodology to other classes of carbonyl compounds, are under active study.

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Supporting Information Available: Experimental procedures and characterization of all numbered compounds as well as *N*-(3,5-dinitrobenzoyl) derivatives of the corresponding fluoro amines (7 pages).

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(9) It clearly follows from the fact that, for instance, in boiling TEA product **4a** easily undergoes racemization while the starting **3a** remains stereochemically intact; see Table 1.

(10) (a) Asymmetric reduction: Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2436. (b) Classical resolution: Wang, Y.; Mosher, H. S. *Tetrahedron Lett.* **1991**,*32*, 987.