Enantioselective Biomimetic Transamination of β-Keto Carboxylic Acid Derivatives. An Efficient Asymmetric Synthesis of β-(Fluoroalkyl) β-Amino Acids

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In recent years, β-amino acids have received a great deal of attention due to a wide range of their potential biomedicinal and synthetic applications.[1] In this context, considering the exciting benefits of fluorine substitution for hydrogen disclosed for the family of α-amino acids,[2] the development of new synthetic methodology for preparing fluorine-containing and enantiomerically pure β-amino acids is of particular interest. In this paper, we report the first practical asymmetric synthesis of β-(fluoroalkyl) β-amino acids of high optical purity via enantioselective biomimetic transamination of the corresponding β-keto carboxylic acids derivatives.

A reducing agent-free biomimetic reductive amination, referred to as [1,3]-proton shift reaction (PSR),[3] is emerging as an efficient, preparatively useful, generalized method for the synthesis of various fluorine-containing amino compounds of biomedicinal and synthetic importance.[2,4] To achieve a reductive transformation of a carbonyl to an amino group, PSR makes use of a biomimetic[5] transposition of an imine functionality via base-catalyzed azomethine−azomethine isomerization, an intramolecular reductive-oxidative process, and thus is conceptually different from the well-tried purely chemical methodology relying heavily on the use of external reducing agents.[6] In particular, racemic β-(fluoroalkyl) β-amino acids **1** can be easily prepared by the base-assisted isomerization of the corresponding enamines, derived from β-keto carboxylic esters and benzylamine or picolylamines.[3a,c] For preparing β-amino acids **1** in enantiomerically pure form, we have developed a biocatalytic approach involving resolution of the corresponding *N*-phenylacetyl derivatives of **1** with penicillin acylase.[7] Nevertheless, the lure of a direct asymmetric synthesis of fluoro amino acids via enantioselective PSR, providing the most efficient access to these biomedicinally important compounds, has been attracting our attention for many years.[8] The challenge associated with the asymmetric PSR, in general, is provided by the nature of the reaction. As it follows from the mechanism of azomethine−azomethine isomerization, the targeted base-assisted proton transfer occurs from a less to a more configurationally unstable stereogenic center and accordingly, under the thermodynamically controlled conditions, cannot be realized in an asymmetric sense.[9] In the series of fundamental works designed to reveal the mechanism and stereochemical course of the biological transamination, Cram et al. have demonstrated that in the certain model azomethine−azomethine isomerizations of hydrocarbon imines [1,3]-proton transfer occurs intramolecularly in a suprafacial, stereoselective manner.[10] However, the reversibility of the isomerizations and substantial racemization of the both starting and resultant compounds were shown to be the problems that would plague the asymmetric biomimetic transamination methodology.

Recently, we have discovered that, in striking contrast to the hydrocarbon imines, the Schiff bases derived from fluoroalkyl ketones and (*S*)-α-phenylethylamine under certain reaction conditions could be isomerized to the corresponding *N*-(α-phenylethylidene) derivatives with the enantioselectivity ranging from 88 to 97% ee.[3d] However, the first attempt to expand these findings on the asymmetric synthesis of fluorinated amino acids via transamination of α-keto perfluorocarboxylic esters gave totally discouraging results. We have found that the isomerization of *N*-(α-phenyl)ethylimine of ethyl trifluoropyruvate, while easily occurring, afforded the virtually racemic *N*-(α-phenylethylidene)trifluoroalanine ethyl ester, presumably, through the nonasymmetric reaction route.[3e] Thus, with these intriguing successes and failures we set about the development of enantioselective transamination of β-keto carboxylic acids, which are structurally similar to both fluoroalkyl ketones and α-keto carboxylic acids.

The starting compounds **4a**−**c** and **5** were readily synthesized by the direct condensation between an appropriate β-keto ester **2a**−**c** and (*S*)-α-phenylethylamine **3** (Scheme 1). An important characteristic of these substrates is that they exist as (*Z*)-enamines, stabilized by the intramolecular hydrogen bond. First, we have tried to isomerize enamine **4a** under the conditions previously established for the analogous transformation of the corresponding *N*-benzyl derivative.[3a] However, after *N*-(α-phenylethyl)enamine **4a** was heated in a triethylamine (TEA) solution at 100−150 °C for more than 300 h, starting compound **4a** was recovered chemi-

(1) For the most recent reviews on β-amino acids see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; VCH−Wiley: New York, 1997.

(2) For general reviews on fluorine-containing amino acids see: *Fluorine-Containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1995.

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Scheme 1

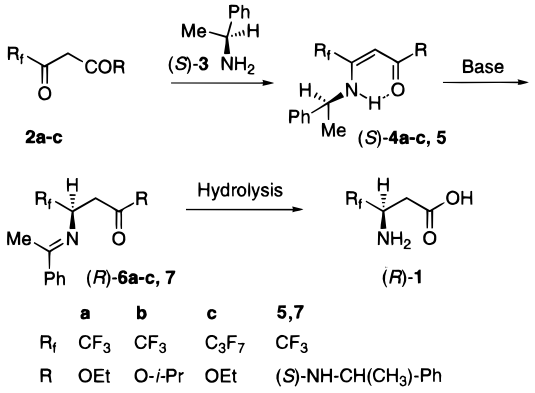


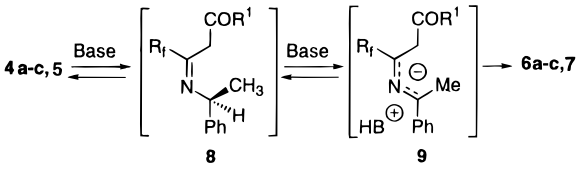
Table 1. Isomerizations of (*S*)-4a−c and 5 to (*R*)-6a−c and (*R*)-7[a]

entry		base (equiv)	*T*, °C	time, h	yield,[c] %	ee, %
1	**4a**	NEt_3 (100)	100−150	>300	no reaction	
2	**4a**	DABCO (1)[b]	150	120	60	61
3	**4a**	DABCO (2)	120	2	40	75
4	**4a**	DBU (0.1)	125	2	57	50
5	**4a**	DBU (1)	75	40	78	87
6	**4a**	DBU (2)	75	24	85	88
7	**4b**	DBU (2.1)	75	24	83	89
8	**5**	DABCO (1)[b]	150	168	73	77
9	**5**	DBU (2.2)	75	24	88	92
10	**4c**	DBU (2)	75	34	57	96

[a] All reactions were run under oxygen-free argon atmosphere. The absolute configuration of the products (*R*)-**5a**−**c** and (*R*)-**6** was determined by optical rotation; see the text. Ee values were determined by chiral HPLC analysis of the corresponding *N*-(3,5-dinitrobenzoyl) derivatives. [b] TEA was used as a solvent.

cally and optically intact (Table 1, entry 1). Addition of a molar amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) to a solution of enamine **4a** in TEA allowed for the isomerization to occur, albeit at the high temperature and with a slow reaction rate. The targeted Schiff base of β-alanine **6a**, isolated in 60% yield, was found to be of moderate (61% ee) enantiomeric purity (entry 2). The application of 2 mol excess of DABCO substantially accelerated the isomerization, providing a complete transformation of enamine **4a** to Schiff base **6a** at 120 °C for 2 h. However, the isomerization was accompanied by a sizable formation of byproducts affording the target product **6a** in low yield but with an enhanced enantiomeric purity (entry 3). The use of more strong bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in place of TEA or DABCO, was expected to facilitate the isomerization.[3c] Thus, at 125 °C, the DBU, taken in a catalytic amount, was effective in catalyzing the isomerization. These reaction conditions also lead to a substantial formation of byproducts allowing us to isolate the targeted product **6a** in moderate chemical yield and in 50% ee (entry 4). In a sharp contrast to these results, the application of DBU in a molar amount allowed for the reaction to proceed with a reasonable rate at a relatively low temperature that had the dramatic consequences on the chemical and stereochemical outcomes of the isomerization. Thus, enamine **4a** was cleanly isomerized at 75 °C in the presence of a molar amount of DBU to afford Schiff base **6a** of high enantiomeric purity (87% ee) in 78% chemical yield (entry 5). A further increase of the DBU ratio allowed us to achieve the isomerization of **4a** to **6a** with the enhanced reaction rate and better stereochemical outcome (85% yield, 88% ee) (entry 6). Under the same reaction conditions, the

Scheme 2



isomerization of enamine **4b**, bearing a bulkier isopropyl ester group, gave target product **6b** with similar stereochemical results (83% yield, 89% ee) (entry 7). The isomerizations of enamine−amide derivatives, such as **5**, have not been previously studied. We have found that, despite the presence of the potentially reactive amide functionality in compound **5**, its base-assisted isomerizations to the targeted Schiff base **7** follow the pattern of reactivity and stereochemical outcome disclosed for the isomerizations of enamine−esters **4a**,**b**. Thus, the isomerization of **5** conducted in the presence of DABCO proceeded with a low reaction rate, even at high temperature, giving rise to the targeted product **7** with moderate both chemical yield and enantiomeric purity (entry 8). By contrast, in the DBU solution enamine−amide **5** was efficiently isomerized at 75 °C to afford **7** with synthetically useful chemical yield and enantioselectivity (entry 9). Finally, to demonstrate the generality of this method for preparing β-(perfluoroalkyl)-β-alanines, the isomerization of perfluoropropyl-containing enamine−ester **4c** was studied. We have found that in the DBU solution at 75 °C the transformation of **4c** to **6c** occurs with a bit lower reaction rate, as compared with the isomerizations of trifluoromethyl derivatives **4a**,**b** and **5**; however, it affords the product in excellent (96% ee) enantiopurity (entry 10).

Schiff bases of β-amino acids **6a**−**c** and **7** were readily hydrolyzed under the standard reaction conditions[3a] to give free β-alanines **1** in high chemical yield (Scheme 1). Comparison of the $[\alpha]_D$ values of thus obtained amino acids **1** with those reported in the literature[7] have revealed their (*R*) absolute configuration.

The results obtained suggest that, despite the fact that final products **6a**−**c** and **7** are obviously prone to racemization in the presence of strong bases, they can be prepared in high enantiomeric purity via biomimetic DBU-assisted isomerization of the corresponding enamines **4a**−**c** and **5**. Considering the stereochemical outcome of the reactions studied, we could suggest the isomerization to proceed through the asymmetric 2-azaallyl anion **9** (Scheme 2). To account for the (*R*) absolute configuration of the product, one might assume that the proton transfer within **9** occurs in the stereoselective suprafacial manner. Realization of the asymmetric state **9** would imply that the perfluoroalkyl group (CF_3, C_3F_7) might provide the (*E*) geometrical homogeneity of the intermediate ketimine **8** and play the enantiodirecting role of a sterically larger substituent.

In summary, this study has disclosed a practical asymmetric entry to the family of biomedically important β-(fluoroalkyl) β-amino acids **1**. Considering the possibilities of further elaboration of the functional groups in **1**, a wide range of synthetic applications of this enantioselective transamination for preparing biologically interesting compounds are readily envisaged.

Supporting Information Available: Experimental procedures and characterization of all numbered compounds (5 pages).

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