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Short communication

Continuous-flow asymmetric biomimetic transamination

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Dedicated to Academician of National Academy of Sciences of Ukraine, Professor Valerii Pavlovich Kukhar (Institute of Bioorganic Chemistry and Petrochemistry of National Academy of Sciences of Ukraine) on the occasion of his 67th birthday.

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ABSTRACT

This study has demonstrated that conceptually new continuous-flow reaction procedure for biomimetic transamination of perfluoroalkyl-containing ketones is substantially more efficient as compared with conventional in-flask approach, allowing preparation of the target fluorinated amines with generally improved chemical yields and enantioselectivity.

In recent decade the development of synthetic methodology mimicking biological processes has been at the forefront of organic chemistry [1]. The major advantage of the biomimetic approach over traditional, purely chemical methods is that it is based on transition metal-free organocatalytic reactions, offering a "greener" and operationally convenient [2] methodological option for preparation of various organic compounds. In particular, the biological cofactor pyridoxal 5′-phosphate-catalyzed transamination [3] inspired many organic chemists to discover its mechanism [4] and develop its chemical models [5] for possible synthetic applications (Scheme 1).

The major issue in using the principle of biological transamination is the control of equilibrium between imines **3** and **4**, which serves as an intramolecular reduction–oxidation step. Usually, this type of azomethine–azomethine isomerization occurs quite sluggishly and requires application of relatively strong base-catalyst [5b]. In general, the control of equilibrium between **3** and **4** could be provided in combination of highly electrophilic carbonyl compound **2** and nucleophilic amine **1** or, vice versa, electrophilic amine **1** and nucleophilic carbonyl compound **2**. Since the latter option is virtually impossible, the realistic synthetic application of biological transamination should focus on the maximum possible differences between the electrophilicity of a carbonyl compound **2** and nucleophilicity of an amine **1**. However, there is still a great degree of synthetic flexibility as one may target preparation of carbonyl compound **6** (oxidative deamination) or amine **1** (reductive amination). Both processes were successfully realized with the development of particularly electrophilic carbonyl compounds **2** [6] and amines **5**, structurally mimicking the enzymatic pyridoxal [7,8].

Of particular importance is application of this biomimetic methodology for reductive amination of fluorinated carbonyl compounds (Scheme 2). Due to the strong electron-withdrawing nature of fluorine the equilibrium between the corresponding imines **3** and **4** is virtually completely shifted towards **4** rendering this reaction extraordinary general and truly practical for preparation of fluorine-containing amines and amino acids. Thus, as shown in Scheme 2, fluoroalkyl/fluoroaryl aldehydes and ketones **7** (R = H, alkyl, aryl) can be efficiently transaminated to the corresponding amines **8** using benzylamine, as a reducing

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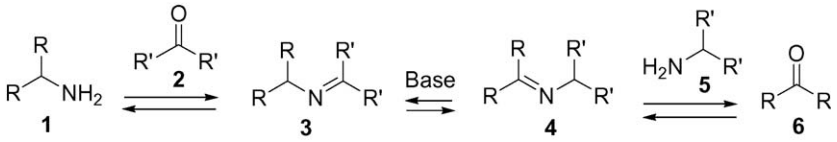
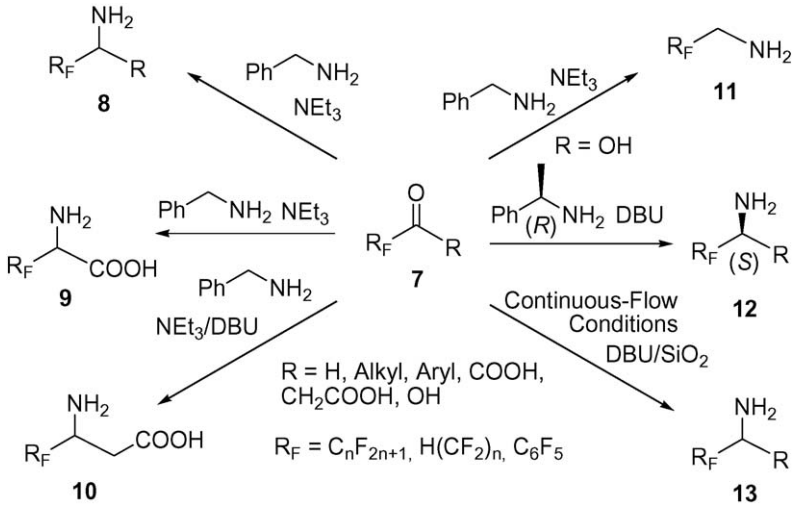


Scheme 1. General scheme for biomimetic oxidative deamination/reductive amination.



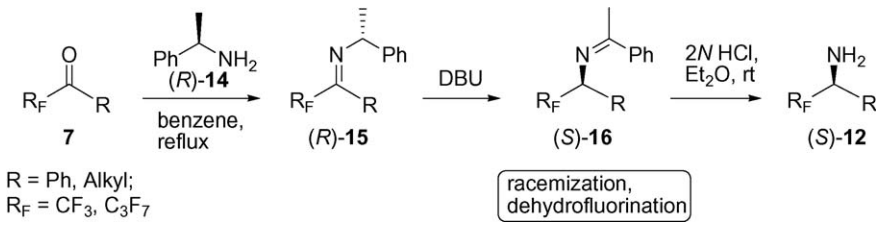
Scheme 2. Biomimetic reductive amination of fluorinated carbonyl compounds.

reagent, and triethylamine as a catalyst [9]. Under the similar conditions α-keto carboxylic acids **7** (R = COOH) give rise to α-amino acids **9** [10,11]. Preparation of β-amino acids **10** from β-keto acids **7** (R = CH_2COOH), requires a stronger base but can be performed in excellent chemical yields [12,13]. Of particular interest is a unique example of double biomimetic transamination of fluorinated acids **7** (R = OH) to amines **11**. In this case, the seven-step process involves two triethylamine-catalyzed 1,3-proton shift transfers as well as triphenylphosphine-catalyzed chlorotropic shift, thus allowing both α-protons of starting benzylamine be used as "reducing reagents" [14]. Asymmetric version of this process with application of α-(phenyl)ethylamine allows preparation of the corresponding fluorinated amines and amino acids **12** in relatively high enantiomeric purity [15].

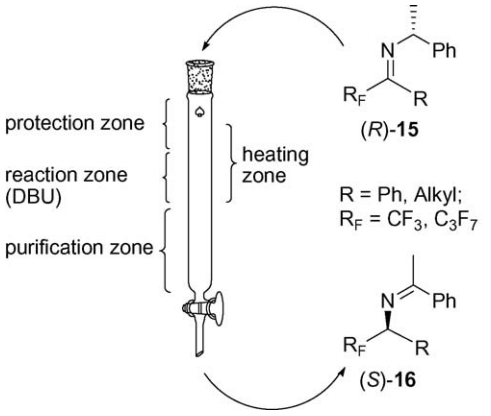
Recently, our group has explored a new dimension in this area with the development of continuous-flow reaction conditions for biomimetic reductive amination of fluorinated carbonyl compounds **7** to amines **13** (R = Ph, Alkyl), using silica-adsorbed DBU as catalyst for on-column process [16]. Taking into account that the corresponding continuous-flow process cannot be realized using the conventional reductive amination methods, this new direction takes truly full advantage of the intramolecular reduction/oxidation nature of biomimetic transamination. As a next logical step, we report here the first example of asymmetric biomimetic reductive amination under continuous-flow reaction conditions.

As shown in Scheme 2, the literature procedure [15f] includes condensation of ketones **7** with chiral amine **14** to form imines **15** followed by their DBU-catalyzed isomerization to Schiff bases **16**, which can be easily hydrolyzed to furnish the target amines **12**. The key step of the process, the transformation of **15** to **16**, is virtually irreversible and notably enantioselective (up to 97% ee) making this reaction practically useful. However, there are two general complications in this isomerization stemming from high C–H acidity (driving force of reaction) of compounds **16**. Thus, derivatives **16** are substantially less configurationally stable, as compared with **15**, and therefore prone to racemization, especially in the presence of strong base, like DBU. For instance, in the transformation of **15** (R = Ph, $C_F = CF_3$) to corresponding 16, the stereochemical out come can range from 50 to 87% ee, depending on the reaction conditions used (temperature, nature and amount of base). Furthermore, the high C–H acidity of **16** is also the cause for some dehydrofluorination leading to decreased chemical yields (ranging from 64 to 98%) [15f] (Scheme 3).

In principle, these problems cannot be solved under the conventional "in-flask" conditions as the issues of chemical yield-enantioselectivity vs. conditions (base-temperature–time) are naturally inter-convened and one factor cannot be improved without sacrifice of the other. Ideally, to solve these complications compounds **16** should be isolated from the reaction medium immediately upon their formation. In this regard, the continuous-



Scheme 3. Asymmetric biomimetic reductive amination of fluorinated carbonyl compounds.



15	R	R_F	16 yield(%) (%ee)/ (lit. 15f)
a	Ph	CF_3	95 (93)/98 (77)
b	Bn	CF_3	93 (91)/86 (88)
c	Me	CF_3	95 (93)/94 (93)
d	Et	CF_3	92 (91)/87 (87)
e	Me	C_3F_7	87 (95)/74 (97)

Scheme 4. Continuous-flow asymmetric biomimetic transamination.

flow reaction conditions can offer a reasonable promise as the exposure products **16** to the base can be controlled by the elution rate.

To realize this possibility we built the continuous-flow reaction column shown in Scheme 4. The difference from the previously reported [16] design is that the DBU-catalyzed isomerization of compounds **16** take place at substantially slower rates as compared with the corresponding *N*-benzyl derivatives. Therefore, we need to add the "heating zone" unit, which can be easily implemented using a usual heating spiral or a mantle, covering completely the "reaction zone" and about half of the "protection zone".

After some experimentation the optimal column construction for the continuous-flow reactions was found as follows: the usual Pyrex-glass column was charged about 3/4 of the volume with a silica gel (200–300 mesh) (hexanes). Next, a calculated amount of DBU [17] (0.30 wt.% of the whole amount of silica gel) in a solution of dichloromethane was charged carefully onto the top and allowed to percolate down to the surface. Then an additional amount (1/4 of the whole amount) of silica gel was charged carefully onto the column. A heating mantle was attached to the column and the temperature was set at 50 °C. Imines **15a–e** were charged onto top of the column as a solution (10 mol%) in hexanes/acetonitrile (4/1). The rate of elution vs. completion of the isomerization (^{19}F NMR) was a key issue to limit to the very minimum essential the time of the products **16** exposure to the DBU in the "reaction zone". After painstaking experimentations we found that, for the indicated above amount of DBU and the imine **15** concentration, the elution rate about 1 drop per three seconds provided for >95% conversion of starting compounds **15a–e** to the imines **16a–e**. The structure and purity of the products **16a–e** were confirmed by NMR and their enantiomeric composition was determined using SUMICHIRAL OA-4500; eluent: *n*-hexane/dichloromethane/ethanol = 60/30/10.

As it follows from the data presented in Scheme 4, the chemical and stereochemical outcome of these continuous-flow reactions, to our delight, was noticeably positive as in most of cases the chemical yield and/or enantioselectivity was improved. For instance, in the most difficult case of preparation of derivative **16a**, in which the C–H acidity is the highest in the series, we obtained the product **16a** with similar yield but with substantially increased enantioselectivity, from 77 [15f] to 93% ee. In the case of **16b**, containing benzyl and trifluoromethyl groups we were able to improve both chemical yield (from 86 to 93%) and stereoselectivity (from 88 to 91% ee). Interestingly, no visible advance was observed in preparation of methyl/trifluoromethyl derivative **16c**, while its ethyl analog **16d** was obtained with both, albeit slightly, improved yield and enantioselectivity. Finally, in the case of the most unstable (dehydrofluorination) in the series compound **16e** noticeable increase in chemical yield was observed (from 74 to 87%).

These preliminary data strongly suggest that the continuous-flow reaction conditions are obviously advantageous over traditional in-flack approach for preparation of biologically important fluorinated amino compounds via asymmetric biomimetic transamination. Optimization, generalization and advancement of this novel continuous-flow reaction procedure are currently under investigation and will be reported in due course.

In summary, we demonstrated that conceptually new continuous-flow reaction procedure for biomimetic transamination of perfluoroalkyl-containing ketones is substantially more efficient as compared with conventional in flask approach, allowing preparation of the target fluorinated amines with generally improved chemical yields and enantioselectivity. We are confident that this new dimension in the practice of biomimetic transamination is an important step-up in the development of truly practical and environmentally benign metal-free synthetic methodology.

Acknowledgments

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[17] Typical set up of the column and experiment: a glass column (3.9 cm × 104 cm) was charged with 260 g of silica gel (hexanes). While leaving about 1 cm of the solvent on top of silica gel, a suspension of 130 g of silica gel in dichloromethane containing 1.3 g of DBU was charged onto the top and allowed to percolate down to the surface of silica gel. Finally, additional 150 g of silica gel (hexanes) was added on the top of the column allowing the solvent to percolate down to the surface of silica gel completely. A heating mantle was attached to the column covering fully the corresponding "reaction zone" and about half of the "protection zone"; the temperature was set at 50 °C. Using thus prepared column, a solution [10 mol% in hexanes/acetonitrile (4/1)] of fluorinated imines **16a–e** was eluted through the column at the rate of 1 drop per second. UV-active fractions (detection by TLC) were collected and evaporated to afford products **16a–e** (for yields and enantioselectivity, see Scheme 4).