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Synthesis of fluorine-containing compounds under operationally convenient conditions

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Abstract

This paper describes a concept of 'operationally convenient conditions', gives a short overview of synthetic applications of bio-mimetic reductive amination under such conditions and discusses new kinetic data on the mechanism of 1,3-proton shift transfer.

Keywords: Operationally convenient conditions; 1,3-Proton-shift-reaction; Imines; Fluorine and compounds

1. Introduction

In the past decade we have witnessed a fundamental re-evaluation of a paradigm of organic synthesis, in particular, its purpose, efficiency, practicality and convenience. The concepts defined in Noyori's [1] and List's [2] perfect reactions, Trost's atom economy [3], green chemistry and environmentally benign processes, which should be of major concern to all people living on this planet [4], and Sharpless' click chemistry [5] have changed our perception of organic synthesis. The common theme in these four concepts is a shift of focus from a synthetic target to a synthesis itself. It could be safely assumed that, in principle, any natural product of challenging complexity is within the reach of current synthetic organic chemistry, provided the appropriate budget and dozens of talented, hard-working students are also available. It also could be assumed that the overall yield of that challenging natural product synthesis will be in the range of 1–5%, as a result of imperfect reactions. So, what is a perfect reaction? Each of the aforementioned concepts has its own, slightly different definition of synthetic perfection. However, there is one straightforward definition of a perfect reaction which sets, in our opinion, an ultimate challenge; it states: 'the ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting the product from the drain hole' [6]. Despite its joke-like style, we found this definition very instructive. It focuses on the true values of organic synthesis, which could be generally defined as operationally convenient conditions [7]. Drawn almost directly from the above definition, the operationally convenient conditions may include: (a) an absence of solvent or application of a commercial-grade solvent (no need for vigorous drying or degassing), (b) no moisture-, oxygen-sensitive reagents, (c) easily maintainable temperatures (ideally ambient temperature), (d) simple work-up procedures (filtration and extraction), and (e) quantitative chemical yield and stereochemical outcome (no separations/purifications). Clearly, the cost of such processes would be attractive in chemical manufacturing. However, the identification of such processes is a truly challenging goal that will require the discovery and development of new reactions and methodology.

1.1. Short overview of synthetic applications of 1,3-proton shift reaction (1,3-PSR)

1.1.1. Bio-mimetic reductive amination via 1,3-proton shift reaction — general description

For quite some time, we have been interested in the unconventional reductive amination of fluoro-carbonyl compounds to the corresponding fluorinated amines and amino acids [8]. This reaction does not require an external

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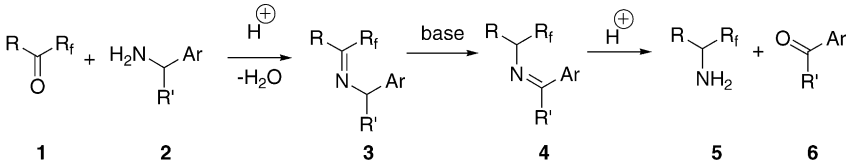


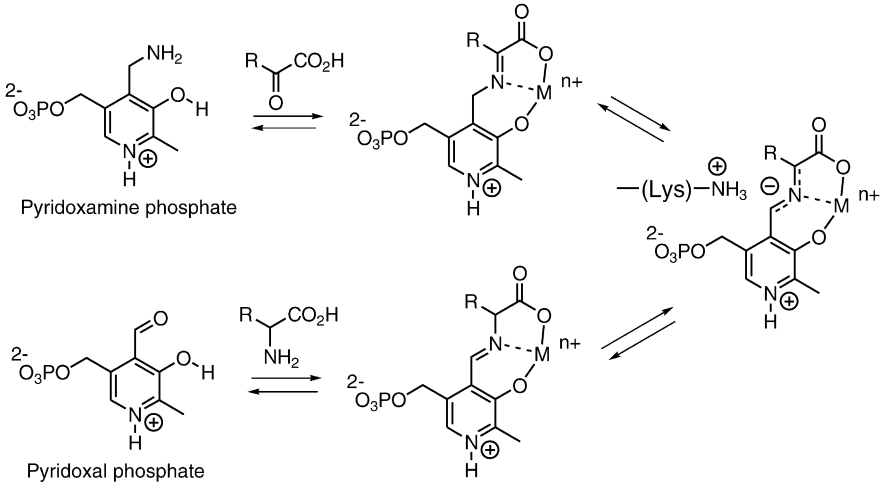
Scheme 1. Bio-mimetic reductive amination: 1,3-proton shift reaction.

reducing reagent, but instead makes use of an intramolecular oxidation–reduction process via a 1,3-proton shift transfer (Scheme 1). In biology this transformation is known as enzymatic transamination, which is catalyzed by the co-factors pyridoxal, to perform a transformation of α-amino acid to α-keto acid, and pyridoxamine, to convert α-keto acid to α-amino acid (Scheme 2) [9].

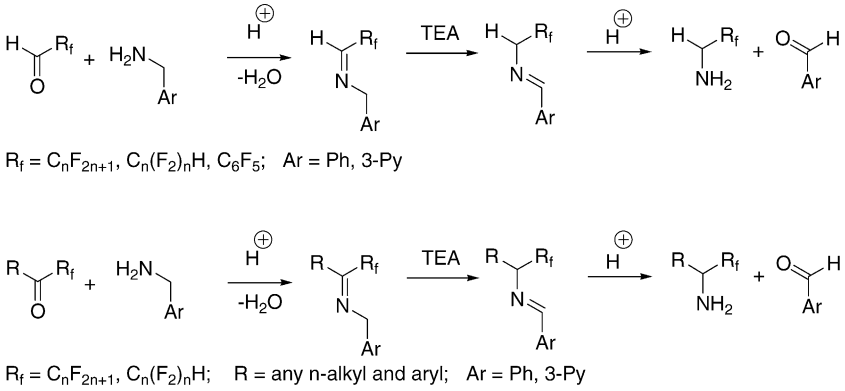
From a synthetic standpoint, the bio-mimetic reductive amination, or as we refer to it, 1,3-proton shift reaction, has numerous advantages over conventional chemical methods currently available for the reductive amination of fluoro-carbonyl compounds [10,11]. The process consists of three steps, as simple as ABC: (A) preparation of imine **3** by condensation of fluoro-carbonyl compound **1** with benzylamine derivative **2**; (B) organic base-catalyzed isomerization of **3** to **4**; (C) acidic hydrolysis of **4** to furnish the target amine **5**. The first step, synthesis of imine **3**, is usually conducted under Dean–Stark conditions. While this method is relatively general, simple and economical, the reported chemical yields (<95%) prompted us to develop a more practical protocol [12]. We found that application of benzylamine salts or derivatives of benzylamine **2** with carboxylic acid derivatives allowed us to conduct the condensations under milder conditions and resulted in complete consumption of the starting fluoro-carbonyl compound **1**. The additional advantage of this method is the potential to control the regio- and chemo-selectivity of the reactions of highly electrophilic and/or polyfunctional fluoro-carbonyl compounds, in addition to the easily amenable reaction conditions, which may be tailored by the choice of the corresponding carboxylic acid. The reactions are usually conducted in dichlomethane, chloroform or benzene and the product, imine **3,** can be isolated by simple extraction without further purification. Prepared imine **3** can be isomerized to the Schiff base **4** by treatment with an organic base, usually triethylamine (TEA) or DBU at temperatures ranging from ambient to 75 °C. The isomerization of imine **3** to Schiff base **4** is usually complete and in most cases can be conducted without solvent. After removal and recovery of TEA under high vacuum, product **4** can be hydrolyzed under biphasic conditions using various acids, usually aqueous HCl and ether. This hydrolysis reaction can literally be conducted in a 'bath tub' and the final product **5** can be 'collected from the drain hole' as an aqueous solution of its hydrochloric salt. The only other product of the process is the corresponding oxidation product **6** of the starting amine. This co-product is usually benzaldehyde or acetophenone, which can easily be recovered from the organic phase and purified to a commercial grade.

1.1.2. 1,3-Proton shift reaction — reductive amination of fluorine-containing aldehydes, ketones, α- and β-keto carboxylic acids

In a series of publications from our laboratories, we have demonstrated the application of the 1,3-PSR for the efficient reductive amination of aliphatic and aromatic aldehydes, alkyl fluoroalkyl and aryl fluoroalkyl ketones



Scheme 2. Biological transamination.

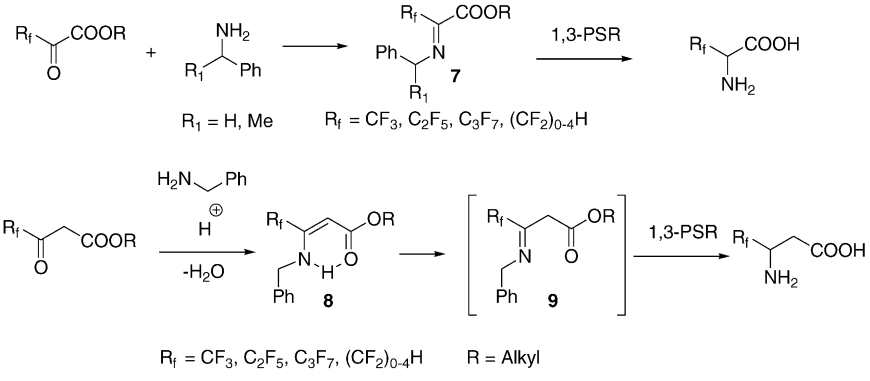


Scheme 3. Bio-mimetic reductive amination of aliphatic and aromatic aldehydes and ketones.

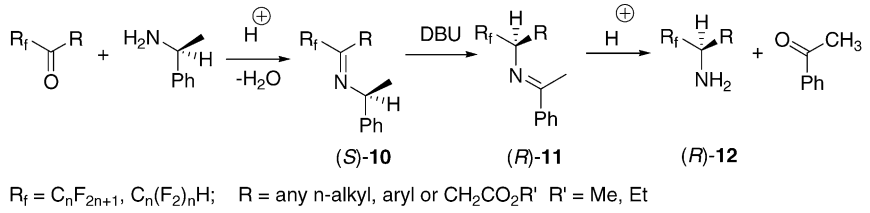
[13], and α- and β-keto carboxylic acids [14]. The reductive amination of fluoro-aldehydes (Scheme 3) is usually conducted at ambient temperature, without solvent in the presence of 1–2 equivalents of TEA. The reaction rates of the reductive amination of ketones (Scheme 3) are noticeably slower, though the transformation takes place at ambient temperature. At elevated temperatures (40–50 °C), or in the presence of a stronger base, like DBU, reaction rates are greatly accelerated leading to a clean and complete isomerization. The reductive amination of fluorinated alkyl α-keto carboxylates (Scheme 4) occurs at very high reaction rates, as the resultant products **7** are very CH-acidic. The corresponding carbanion is stabilized by three electron-withdrawing substituents: perfluoroalkyl, alkoxycarbonyl and Schiff base groups. Relatively weak bases, such as aniline and pyridine, are capable of catalyzing these isomerizations. By contrast, the reductive amination of alkyl β-keto carboxylates represents the most difficult case. Thus, these reactions, if catalyzed by TEA, require prolonged heating at 75 °C, or application of DBU as a base. The reason behind the low reactivity is that the starting compounds exist as enamines **8** stabilized by intramolecular hydrogen bonding (Scheme 4). The enamine–azometine isomerization, leading to the formation of corresponding imine **9**, is the rate-determining step, which usually requires high temperature or a strong base to proceed at a reasonable reaction rate.

1.1.3. 1,3-Proton shift reaction — asymmetric reductive amination of fluorine-containing ketones and β-keto carboxylic acids

As a logical next step in the development of the 1,3-PSR methodology, we explored its application to the asymmetric synthesis of fluorinated amines and amino acids. α-Phenylethylamine, a chiral analog of benzylamine, is readily available in both enantiomeric forms and is quite inexpensive. The corresponding *N*-(α-phenylethyl)imine **10** (Scheme 5) can be easily prepared under Dean–Stark conditions in reasonably good chemical yields (>90%). The presence of the electron-donating α-methyl group in imine **10** renders the methyne proton much less CH-acidic, and as a result, with a few exceptions [15], TEA is unable to catalyze the isomerization. However, application of a stronger base, such as DBU, in sub-molar amounts (slow reaction rates) or excess amounts (fast reaction rates) allows for clean and complete isomerization of imine **10** to Schiff base **11**. The enantioselectivity of the proton transfer in the series of trifluoromethyl-containing substrates is usually greater than 85% e.e. A few examples of the asymmetric transformations of the perfluoroethyl- and perfluoropropyl-containing imines



Scheme 4. Bio-mimetic reduction of aliphatic α- and β-keto carboxylic acid.



Scheme 5. Asymmetric bio-mimetic reductive of aliphatic and aromatic ketones and β-keto esters.

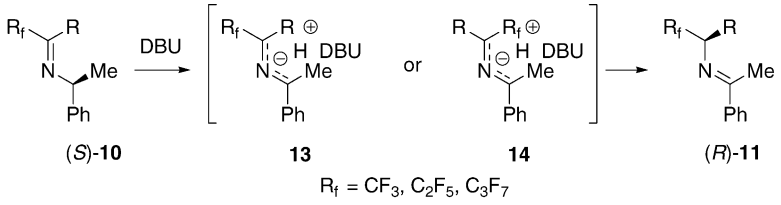


Fig. 1. Transition states 13 and 14 in the asymmetric 1,3-PSR.

suggest that the stereochemical outcome is a function of the steric bulk of the fluoroalkyl group, as in these cases the enantioselectivity can be as high as 97–99% e.e. Usual hydrolysis of product **11** furnishes the hydrochloric salts of amines and amino acids **12** which can be further obtained in enantiomerically pure form by a single crystallization. To account for the observed stereochemical outcome, we constructed transition state (TS) **13** (Fig. 1). The trifluoromethyl group and the phenyl group in TS **13** occupy the position of the larger groups thus minimizing repulsive steric interactions. The stereochemical outcome predicted by TS **13** is in full accordance with the observed result: (*S*)-configured imine **10** gave rise to product **11** of (*S*) absolute configuration. To explain the increased enantioselectivity observed in the reactions of perfluoroethyl- and perfluoropropyl-containing imines **10**, we can suggest that a second possible TS leading to the (*S*)-configured fluoro-imine **11** is TS **14** in which the trifluoromethyl group is in unfavorably close proximity to the methyl group. With increasing size of the perfluoroalkyl group, TS **14** becomes more and more disfavored leading to higher enantioselectivity.

1.1.4. Double 1,3-proton shift reaction — direct reductive amination of perfluoro carboxylic acids to α,α-dihydroperfluoroamines

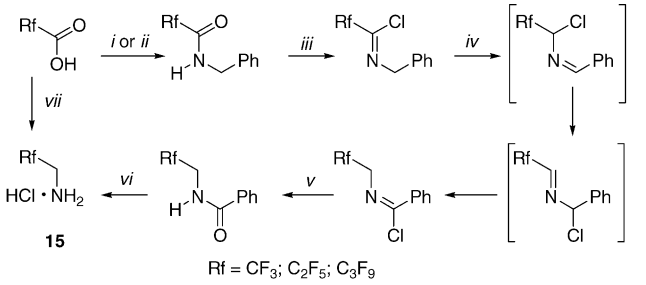
Our most recent advance in the development of the 1,3-PSR methodology is a direct reductive amination of perfluoroalkyl carboxylic acids to α,α-dihydroperfluoroalkylamines [16]. The process involves a unique reaction sequence consisting of a TEA-catalyzed 1,3-proton shift followed by triphenylphosphine-catalyzed 1,3-chlorotropic shift leading to a second TEA-catalyzed 1,3-proton shift, which completes the reductive amination of the carboxylic group to a primary amine group (Scheme 6). The discovered 'double' 1,3-PSR procedure is, to the best of our knowledge, unique in that there are no disclosed or similar reactions reported in the literature.

Taking into account that the whole procedure involves seven reactions, the obtained yield of product **15** (Rf = CF_3) was truly remarkable. This procedure was successfully applied on a 10-g scale to demonstrate its preparative value and reliability.

2. Results and discussion

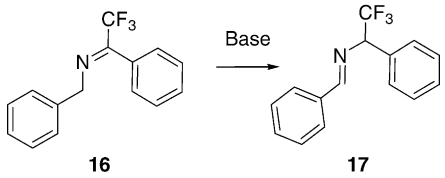
In order to realize the exciting synthetic potential of this bio-mimetic reductive amination we initiated a systematic study to develop a detailed understanding of its mechanism, to find and creatively use the means to control its rate and regio- and stereo-selectivity, and to realize the full practical applications of this method.

As discussed above, the majority of the 1,3-proton shift reactions were conducted without solvent using only TEA and DBU as bases. Therefore, we decided to investigate the kinetics of the 1,3-proton shift reaction in different solvents using a series of bases differing in relative basicity, steric bulkiness, and overall structure in an attempt to find the most



Key: (*i*) $(CF_3CO)_2$, $BnNH_2$, $CHCl_3$ 0 °C; (*ii*) Ph_3P (1.6 eq)/CCl_4 (1.07 eq), $BnNH_2$ (2 eq), $CHCl_3$ reflux, 40 min; (*iii*) Ph_3P (1.6 eq)/CCl_4 (1.07 eq), $CHCl_3$ reflux, 40 min; (*iv*) Ph_3P/TEA (cat),$CHCl_3$ reflux, 40 min; (*v*) TEA (3 eq)/H_2O (2 eq), $CHCl_3$ reflux, overnight ; (*vi*) MeOH/HCl (conc) 2/1 v, reflux, 24 hr; (*vii*) $BnNH_2$ (1 eq), Ph_3P (4 eq)/CCl_4 (4 eq), TEA (1.5 eq), $CHCl_3$ reflux, 40 min, then (*v*) and (*vi*)

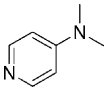
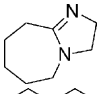
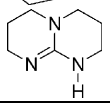
Scheme 6. Double 1,3-proton shift reaction.



Scheme 7. Base catalyzed isomerization of imine **16** to **17**.

efficient reaction conditions. As a model reaction we chose the isomerization of *N*-benzyl imine **16** derived from trifluoroacetophenone (Scheme 7). Our choice was based on the observation that imines containing hydrogen atom(s) in the α-position to the CN double bond can undergo base-catalyzed enaminolization and thus interfere with the accuracy of the kinetic data. The starting imine **16** was prepared by our new 'low basicity' method without contamination of the product imine **17**. The isomerizations of **16** to **17** were conducted in two solvents, in aprotic nonpolar benzene and in protic polar methanol. The results are summarized in Table 1. This data revealed several interesting details. (1) Exceptionally high catalytic activity of guanidine which cannot be accounted for merely by the relative basicity of the base. For instance, DBU, being as strong a base as guanidine, showed much lower catalytic activity. (2) For a majority of the bases the reaction rates in methanol were found to be noticeably higher compared to the reactions performed in benzene. DBU and guanidine, however, showed the opposite trend being much more effective in benzene and less catalytically active in methanol. (3) The reactions conducted in benzene showed a clear dependence of the reaction rates on the relative basicity of the base used. The reactions performed in methanol proceeded with quite similar reaction rates almost regardless of the nature of the base used. To account for these rather unexpected results, we suggest that in the reactions studied, not one, but several modes of 1,3-proton shift transfer take place depending on the nature of the base and solvent used. Fig. 2 shows four different transition states that we were able to construct based on these preliminary results. TS **18** is a usual TS one that is available in the

Table 1
Kinetics of the isomerization of imine **16** to **17**

pK_a	Base	Solvent			
		Benzene[a]	MeOH[a]	Benzene[b]	MeOH[b]
11.09	$NHEt_2$	5.25	9.5	11.2	19.8
11.01	NEt_3	7.4	5.4	14.9	9.4
~12	NEt (*i*-Pr)$_2$	0.3	5.2	0.7	9.2
9.2		8.3	3.3	21.7	8.1
13.6			44.7 (0.1/1)	467 (0.2/1)	99.7 (0.2/1)
~13		723 (0.1/1)	148 (0.1/1)	866 (0.2/1)	339.4 (0.2/1)

Temperature = 23.5 °C.
[a] Ratio base/substrate: 1/1.
[b] Ratio base/substrate: 2/1.

literature [17]. In this case the base abstracts the proton, forms a tight ion-pair and proton, along with ammonium cation, and moves to a more CH-acidic carbon to form a new covalent bond. In our opinion, this TS may cleanly operate in aprotic medium with a tertiary amine as a base. This TS can also take place in protic medium or with a secondary amine as a base. However, in an OH-containing solvent, for example methanol, formation of a network of hydrogen bonds may take place allowing for a TA of type **19**. In this case the role of the base is narrowed to the formation of an ion-pair while the proton can be delivered from an OH moiety via simultaneous breakage of two bonds (N–H and OH) and formation of two new bonds (C–H and OH). A different mode of 1,3-proton shift transfer, TS **20**, can be realized in the DBU-catalyzed reactions. In this case the proton can move alone within the ion-pair transferring the positive charge from one nitrogen of a DBU molecule to another. Finally, one more transition state, TS **21**, can be envisioned for guanidine-catalyzed reactions. Due to the nature of guanidine, it can work as a bifunctional catalyst abstracting a proton from one nitrogen and delivering a

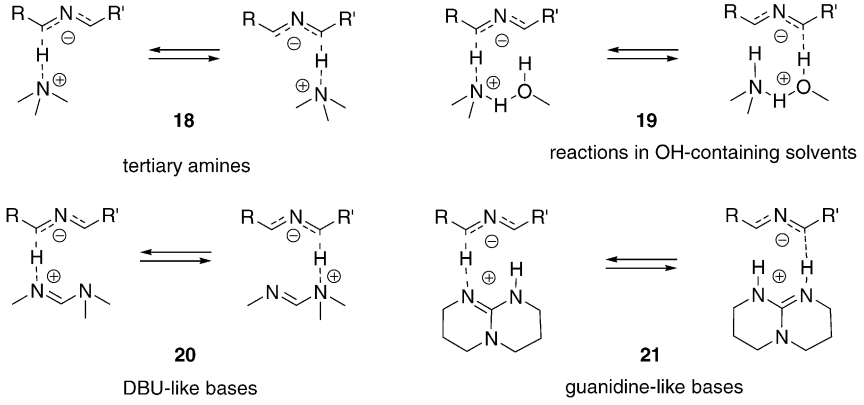


Fig. 2. Four possible transition states of 1,3-proton shift transfer.

proton from a N–H group. Realization of TS **21** would require ideal alignment of the molecules of imine **16** and guanidine; however, once it is formed the proton transfer might occur at a very fast reaction rate as no movement of charged species are required.

Currently we are continuing to collect kinetic data using a wider range of solvents and bases. In particular, we are planning to study the 1,3-proton shift in ionic liquids using chiral organic bases. These results will be reported in full in due course.

3. Experimental section

All kinetic experiments were conducted under the same conditions with the initial concentration of imine **16** $C_0 = 0.379$ M and base $C_b = 0.379$ M and another double concentration of base $C_b = 0.758$ M in either benzene or methanol at 23.5 °C. Corresponding concentrations of DBU and TBD bases are $C_b = 0.0379$ M and another double concentration of base $C_b = 0.0758$ M in either benzene or methanol at 23.5 °C. The ratio of imines **16** and **17** was monitored by ^{19}F-NMR by measuring the disappearance of the peak (singlet) corresponding to imine **16** (−70 ppm) and appearance of the peak (doublet) corresponding to imine **17** at −74.0 ppm. The rate constant was calculated according to the formula for a first-order process (for spectroscopic characterization of imines **16** and **17** see Ref. [13b]).

Acknowledgments

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