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The Reactivity of α-Fluoroketones with PLP Dependent Enzymes: Transaminases as Hydrodefluorinases

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A chemical method for the treatment of harmful halogenated compounds that has recently become of interest is the reductive dehalogenation of carbon-halogen bonds. In the case of a fluorine atom, this process is called hydrodefluorination. While many transition metal-based approaches now exist to reductively defluorinate aromatic fluoroarenes, the cleavage of C–F bonds in aliphatic compounds is not so well-developed. Here we propose a biocatalytic approach exploiting a promiscuous activity exhibited by transaminases (TAs). Hence, a series of α-fluoroketones have been defluorinated with excellent conversions using *Chromobacterium violaceum* and *Arthrobacter* sp. TAs under mild conditions and in aqueous medium, using a stoichiometric amount of an amine (*e.g.* 2-propylamine) as reagent and formally releasing its oxidized form (*e.g.* acetone), with ammonia and hydrogen fluoride as by-products. It is also demonstrated that this process can be performed in a regio- or stereoselective fashion.

Introduction

Organic halides are very important compounds due to their high synthetic versatility as reagents, solvents, and intermediates in organic synthesis. On one hand, their occurrence as drug candidates and other biologically active compounds is prominent,[1] but on the other they can present adverse properties from an environmental point of view, as they are slowly degraded. This is especially true for the fluorinated compounds, as fluorine is currently recognized as one of the most relevant heteroatoms when included in drug molecules. This is due to its capacity to modify molecular properties such as lipophilicity, metabolic stability or acidity, among others,[2] but also because of its role as a fundamental constituent of pollutants such chlorofluorocarbons (CFCs).[3] The special properties that fluorine confers to organic molecules is to a large extent due to the small size of this atom and the strength of the C–F bonds. Thus, the increasing interest around this halogen has gone in hand with the development of very efficient and selective synthetic pathways to obtain fluorinated compounds.[4]

Due to the inert nature of fluorinated compounds, many efforts have focused on their degradation, but since oxidative methods or incineration can produce toxic wastes, reductive alternatives are envisaged as safer methodologies. Among them, the cleavage of a C–X into a C–H bond, *i.e.* hydrodehalogenation[3,5] (hydrodefluorination, when X=F),[6,7] is one of the most promising chemical approaches to degrade these compounds. When dealing with fluorinated derivatives, most of these transformations rely on the application of transition metal complexes under harsh conditions on fluoroarene substrates.[6] Hence, the design of novel methods that proceed under more environmentally friendly conditions[8] and that can also reductively defluorinate aliphatic compounds,[9] is nowadays extremely desirable.

One appealing solution would be the development of suitable transformations using biocatalysts, since they require in general mild reaction conditions. In fact, the formation and cleavage of C–X bonds, when X=Cl or Br, mediated by (de)halogenases, is a valuable synthetic tool that has acquired significant relevance in recent years.[10] For instance, focusing on enzymatic dehalogenation reactions,[11] haloalkane dehalogenases[12] and halohydrin dehalogenases[13] have already found interesting applications. Also, defluorination processes have been known to be mediated by enzymes for some

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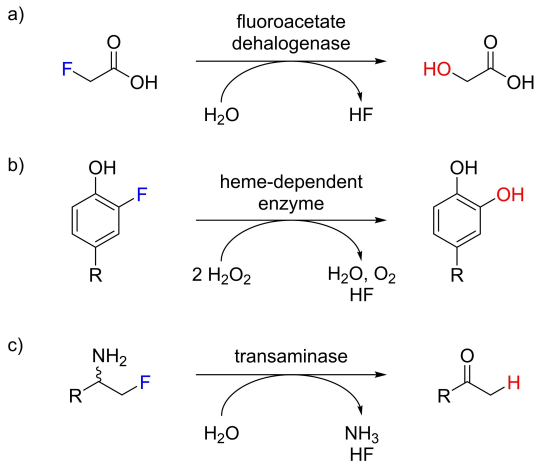
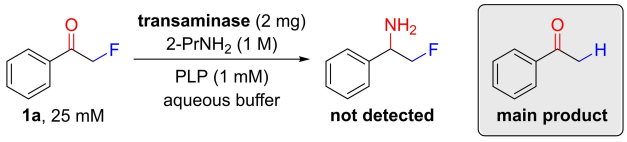
decades.[14] Fluoroacetate dehalogenases belong to a family of biocatalysts present in different bacteria which defluorinate fluoroacetic acid, a natural compound, into glycolic acid (Scheme 1a),[14] and heme-dependent enzymes such as cytochromes P450 can oxyfunctionalize fluoroarene derivatives into the corresponding phenolic compounds (Scheme 1b).[15] However, very few reports have described biocatalytic hydrodefluorination reactions.

We recently demonstrated that transaminases (TAs) possess a promiscuous hydrodefluorinase activity transforming β-fluoroamines to the corresponding defluorinated ketones *via* a tandem hydrodefluorination–deamination pathway in the absence of an amine acceptor (Scheme 1c).[16] Due to the increasing interest in the application of TAs with perfluorinated substrates to synthesize the corresponding enantioenriched amines,[17] and the potential activities that β-fluoroamines[18] present as inhibitors of pyridoxal 5'-phosphate (PLP)-dependent enzymes,[19] we decided to study the enzymatic synthesis of these derivatives. The amination of α-fluoroketones using NADPH-dependent reductive aminases (RedAms) yielded mixtures of amine and alcohol products, the latter through direct reduction of the carbonyl group.[20] In this study, we therefore considered an alternative approach, in which the TA-catalyzed transformation of α-fluoroketones would yield exclusively the β-fluoroamines as products with high conversion and enantiomeric excess. However, the study has instead revealed that the TA-dependent transformation of α-fluoroketones leads to hydrodefluorination to give the ketone products.



Scheme 1. Enzymatic (hydro)defluorination examples.



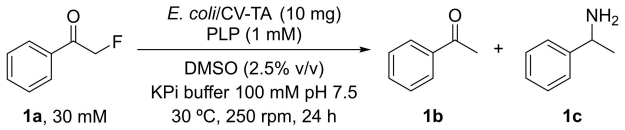
Scheme 2. Amination *vs* hydrodefluorination reaction of **1 a** using transaminases.

Results and Discussion

The initial aim of the study was the TA-catalyzed amination of α-fluoroacetophenone (**1 a**, 30 mM), which was tested with a set of 23 transaminases (2 mg) purchased from Codexis Inc. under typical reaction conditions using 1 M 2-propylamine (2-PrNH$_2$) as the amine donor to obtain the enantioenriched β-fluoroamine (Scheme 2 and Figure S1, Supporting Information). However, these reactions did not afford the corresponding aminated compound but rather acetophenone (**1 b**) as the only product. Just in two cases, 1-phenylethylamine (**1 c**) was also evolved as a minor co-product. The absence or low production of amine **1 c** in these reactions was interesting as **1 b** is known to be a good substrate for TAs,[21] suggesting that the hydrodefluorination process progressed with simultaneous deactivation of the TAs.[16,19,22] Due to the fact that examples of hydrodefluorination of α-fluorinated carbonyl compounds are scarce,[23] and also given the interest in developing a catalytic alternative under mild conditions in aqueous medium, we decided to optimize this biotransformation.

In the case of the defluorination of β-fluoroamines, the addition of an amine acceptor (*i.e.*, acetone) was not necessary,[16] so we first studied the minimum amount of the amine donor (2-PrNH$_2$) to achieve high conversions of **1 b** starting from **1 a**. To set up these experiments, lyophilized whole cells of *Escherichia coli* containing recombinant TAs from *Chromobacterium violaceum* (CV-TA)[24] or *Arthrobacter* sp. (ArR-TA)[25] were selected as biocatalysts (10 mg) because they showed good hydrodefluorinase activity.[16] As can be seen from the data obtained with CV-TA (Table 1), it was necessary to add at least a stoichiometric amount of 2-PrNH$_2$ (entry 5) to obtain a quantitative conversion of **1 b**. Lower amounts of 2-PrNH$_2$ led to incomplete formation of the hydrodefluorinated ketone (entries 1–4), and the use of pyridoxamine-5-phosphate (PMP) as cofactor instead of PLP did not improve the transformation (entry 2 and Figure S2 in the Supporting Information). It was

Table 1. Effect of the concentration of the amine donor in the hydrodefluorination process of ketone **1 a** catalyzed by CV-TA.[a]



Entry	[2-PrNH$_2$] [mM]	Conversion [%][b] 1 a	1 b	1 c
1	–	77	23	<1
2[c]	–	87	13	<1
3[d]	10	61	39	<1
4	25	21	79	<1
5	30	<1	>99	<1
6	50	<1	>99	<1
7[d]	50	<1	>99	<1
8	100	<1	>99	<1

[a] For reaction conditions, see the Experimental Section. [b] Measured by GC analysis. [c] Pyridoxamine (PMP, 1 mM) instead of PLP. [d] L-Alanine as the amine donor.

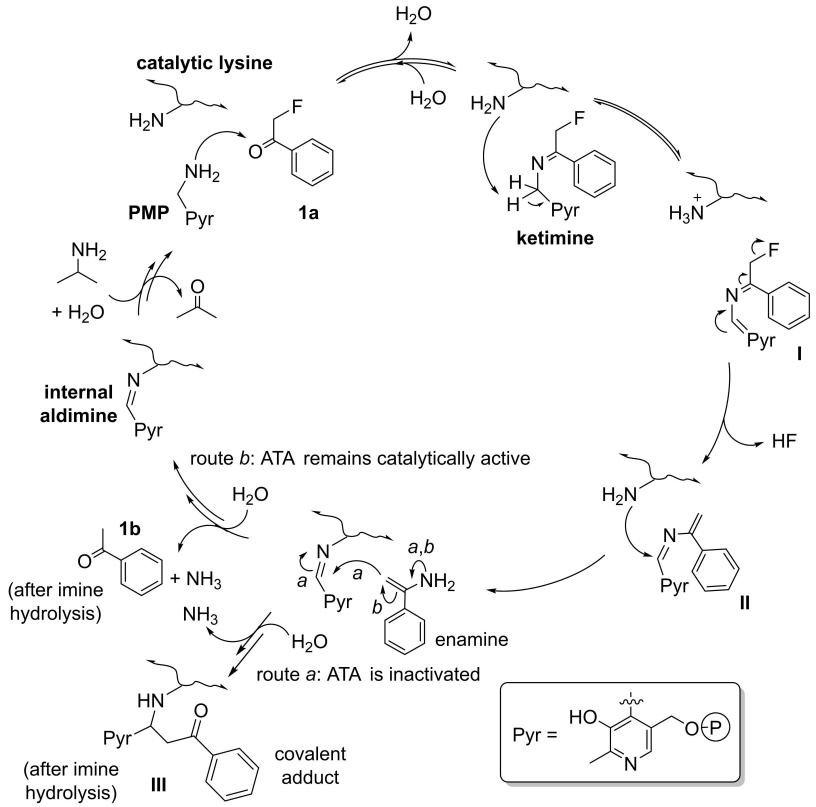
demonstrated that L-alanine also worked as an activation reagent (entry 7 and Figure S3 in the Supporting Information). Similar trends were observed for ArR-TA (Figures S2 and S4). Moreover, these conditions, in which the concentration of the amine donor was kept low, together with the concomitant enzymatic inhibition, abolished the formation of the amine **1c**.[26]

The necessity of the amine donor for the hydrodefluorination of an α-fluorinated ketone, but not of an amine acceptor for the dehalogenation of a β-fluoroamine, can be explained with reference to the proposed mechanism (Scheme 3),[16,19] The main difference between both processes is that whereas the β-fluoroamine interacts directly with PLP to form the external aldimine adduct, releasing after a few steps the defluorinated ketone and PLP,[16] with the hydrodefluorination reaction of an α-fluoroketone such as **1a**, this must react with PMP to produce the ketimine adduct, which after isomerization into intermediate **I** and loss of the fluorine atom, gives intermediate **II**. The catalytic lysine of the TA can then attack the imine bond to generate the internal aldimine together with an enamine derivative, which can further react by one of two different pathways: it can attack the internal aldimine providing, after imine hydrolysis, a covalent adduct (**III**) that will inactivate the transaminase irreversibly (route *a*),[27] or it can be simply hydrolyzed in the reaction medium affording the defluorinated ketone **1b** (route *b*), with the TA remaining active. Afterwards, a molecule of the amine reagent (2-$PrNH_2$ in this case) will be necessary to close the cycle in re-forming the PMP. Overall, the hydrodefluorination process involves a molecule of an amine reagent and a water molecule, affording as by-products the oxidized amine, NH_3 and HF.

In order to study the scope of this transformation, various α-fluoroketones (**2**–**9a**) were synthesized following a previously described methodology.[16,20,28] Based on the results obtained for the model substrate **1a**, we performed the hydrodefluorination experiments using two different amine concentrations (30 mM and 100 mM) and CV-TA (10 mg) as catalyst (Figure 1 and Figure S5).

While enzymatic inactivation proceeds concurrently with the defluorination reaction, it did not greatly affect the outcome of the reaction. Although conversions at 30 mM of the amine donor were usually high (>97% for 6 out of 10 substrates), we finally selected 100 mM as the optimum concentration, since in some cases better results were observed (especially for ketones **5a**, **6a**, and **8a**, Figure 1). Different derivatives, including those bearing electron-donating or electron-withdrawing groups at the phenyl moiety were obtained with high conversions (>90% after 24 h) and excellent selectivities, not detecting in any case the formation of the 1-arylethylamines as co-products. 2-$PrNH_2$ and L-alanine could be used as amine reagents, although slightly better results were usually attained with 2-propylamine, especially at 30 mM (Figure S5). It was very interesting to note that the alkyl C–F bond was selectively cleaved even in the presence of aromatic C–Br (**4a**) or C–I (**5a**) bonds.

In addition, the hydrodefluorination process was demonstrated to be regioselective for difluorinated ketone **2a**, thus



Scheme 3. Proposed inhibition (route *a*) and dehalogenation (route *b*) mechanisms as catalyzed by TAs employing the α-fluoroketone **1a**.

providing fluoroarene **2b** as the only product. This selective defluorination is particularly challenging by other chemical means. When we followed a protocol described by Sajiki and co-workers, previously employed for the hydrodefluorination of ketone **2b**[29] using platinum on carbon in a hydroalcoholic mixture, but in this case with **2a** as substrate, a mixture of defluorinated ketones **2b** and **1b** was attained after 4 h (Figure 2).

We then performed the biotransformation of **2a** on a semi-preparative scale. Thus, 30 mg each of the fluorinated ketones **2a** and **6a** were defluorinated using *E. coli*/CV-TA (180–210 mg) into the corresponding ketones **2b** (90% yield) and **6b** (40% yield) after a simple extraction protocol (Experimental Section).

Due to the excellent reactivity and selectivity shown by TAs with α-fluoroketones in these processes, as the next step we turned our attention to α-bromo- and α-chloroacetophenone (**10a**) as substrates. While the brominated carbonyl compound was too reactive and formed different by-products even in the absence of the enzyme, due to its reactivity with the amine (data not shown), chlorinated ketone **10a** was selectively dehalogenated, forming acetophenone as the only product (Scheme 4a and Figure S6). Although the reaction proceeded more slowly in comparison with fluorinated ketone **1a**, CV-TA and ArR-TA (10 mg) were able to quantitatively convert the α-chloroketone with a slight molar excess of 2-PrNH$_2$ (1.7 to 3.3-fold). These results demonstrate that TAs can also catalyze a promiscuous hydrodechlorinase reaction.

One of the properties of enzyme-catalyzed reactions most valued by organic chemists is their excellent stereoselectivity. We hence envisaged the possibility of employing TAs as catalysts for stereoselective hydrodefluorination processes. To the best of our knowledge, there is no report regarding an enantioselective hydrodefluorination reaction on fluorinated alkyl compounds,[30] apart from the tandem hydrodefluorination-deamination process on β-fluoroamines described by our groups.[16] An exhaustive enzymatic screening was done with **11a** under different reaction conditions (Tables S1 and S2), and while in most cases modest enantioselectivities were observed, a variant of *Arthrobacter* sp. transaminase, ArRmut11-TA (10 mg),[17e] defluorinated this substrate to give propiophenone (**11b**), and residual **11a** with an enantiomeric excess of up to 80% (Scheme 4b). This is a very interesting result because the transaminase must discriminate between the groups at the α position of the reacting center (a methyl and a fluorine atom), which are not very different in size. In addition, this chiral ketone can slowly racemize over time in the reaction medium (Figure S7), so this result likely underestimates the enzyme selectivity. It should also be noted that in some cases 1-phenylpropan-1-amine and an unknown by-product were also detected, but usually with low conversions (< 20%).

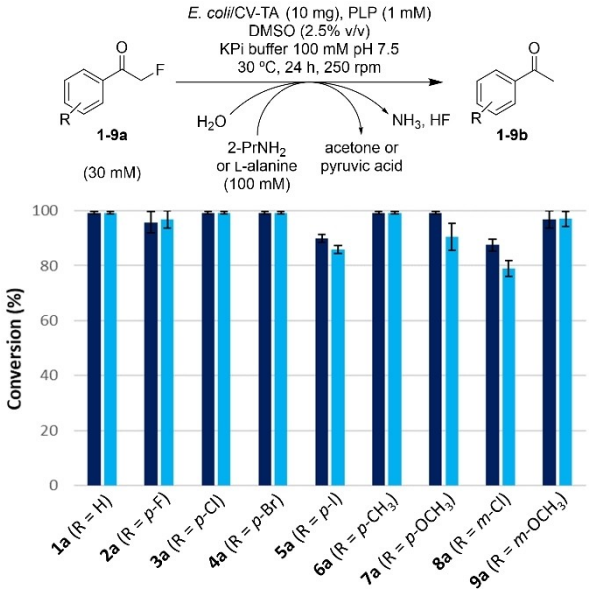


Figure 1. Conversions measured by GC in the hydrodefluorination reaction of α-fluoroketones **1**–**9a** to give dehalogenated ketones **1**–**9b** catalyzed by CV-TA using 2-propylamine (dark blue) or L-alanine (light blue) at 100 mM concentration.

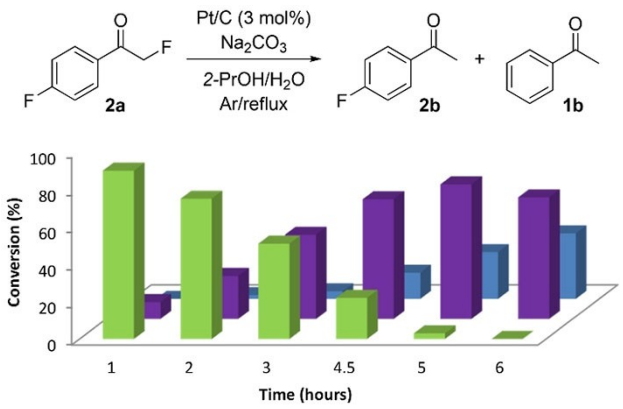
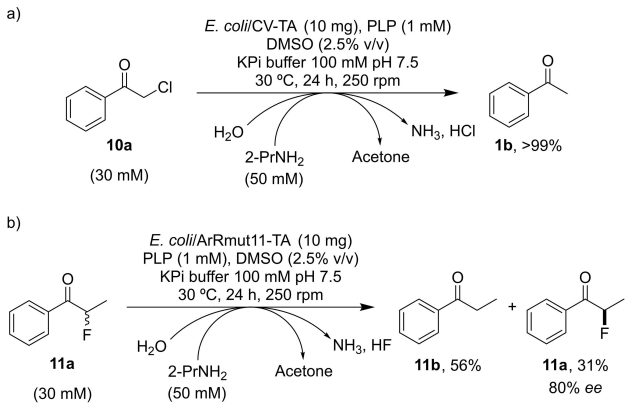


Figure 2. Hydrodefluorination of **2a** employing Pt/C. Color code: green **2a**, purple **2b**, blue **1b**.



Scheme 4. a) Hydrodehalogenation of α-chloroacetophenone (**10a**) catalyzed by CV-TA. b) Enantioselective hydrodefluorination of ketone **11a** using ArRmut11-TA.

Conclusions

The selective hydrodefluorination of α-fluoroketones or aldehydes is a difficult transformation as these carbonyl compounds are highly reactive, and apart from the C–F bond reduction, the C=O bond can also be reduced. In fact, most of the reported catalytic hydrodefluorination protocols rely on the use of transition metal complexes over fluoroarene or alkenyl substrates under harsh reaction conditions. Recently, we described a tandem hydrodefluorination–deamination reaction on β-fluoroamines due to the promiscuous catalytic hydrodefluorinase activity shown by TAs. Following this study, we have now applied these enzymes to cleave the C–F bond in various α-fluoroketones to give the corresponding defluorinated ketones with high conversions under very mild conditions and in aqueous medium. To achieve this goal, a stoichiometric amount of an amine reagent (*e.g.*, 2-$PrNH_2$) was necessary, affording the oxidized amine (*e.g.*, acetone), ammonia and hydrogen fluoride as co-products. This transformation has proven to be *chemo*-selective (reducing a C–F *vs* C=O bond) as well as *regio*selective (breaking an aliphatic C–F *vs* an aromatic C–F bond) and *stereo*selective (preferentially defluorinating an enantiomer of a chiral fluorinated alkyl compound). To improve these processes, enzyme engineering could be envisaged as a method for gaining access to more stereoselective hydrodefluorinases for the synthesis of enantiopure α-fluoro carbonyl derivatives.

Experimental Section

General enzymatic hydrodehalogenation protocol: In an Eppendorf tube, the corresponding transaminase [commercial TA (2 mg), or lyophilized cells overexpressing the TA (10 mg)] was placed, and then a mixture of phosphate buffer (100 mM, pH 7.5, 1 mM PLP) with the desired concentration of the amine donor (2-propylamine or D- or L-alanine, 30–100 mM) and DMSO (12.5 μL, final volume: 0.5 mL) were added. Finally, the corresponding substrate **1–11 a** (30 mM) was added into the reaction mixture, and it was shaken at 30 °C and 250 rpm for 24 h in an orbital shaker. The reaction was stopped by addition of a saturated aqueous solution of Na_2CO_3 (350 μL) and extracted with ethyl acetate (3×350 μL). The organic layers were separated by centrifugation (14,400 rpm), combined and dried over Na_2SO_4. The conversion was measured by GC-FID (see the Supporting Information for analytical conditions).

Hydrodefluorination of 2 a and 6 a at semi-preparative scale: In an Erlenmeyer flask, lyophilized cells of *E. coli*/CV-TA (for **2 a**: 210 mg and for **6 a**: 180 mg) were placed and then a mixture of phosphate buffer (100 mM, pH 7.5, 30 mM 2-$PrNH_2$, 1 mM PLP) and MeCN (for **2 a**: 160 μL, final volume: 6.4 mL and for **6 a**: 165 μL, final volume: 6.6 mL). Finally, the corresponding substrates **2 a** and **6 a** (30 mg, 30 mM) were added into the reaction mixture, and it was shaken at 30 °C and 250 rpm for 45 h in an orbital shaker. Conversion was measured by GC-FID (see the Supporting Information for analytical conditions). The reaction was extracted with EtOAc (6×6 mL) until there was no organic product in the aqueous phase (confirmed by TLC). Organic phases were combined, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure affording dehalogenated products **2 b** (24 mg, 90% yield) and **6 b** (11 mg, 40% yield). ^{1}H-NMR spectra of the obtained products were compared with samples of the commercially available ketones.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: transaminases · fluorine chemistry · catalytic promiscuity · hydrodefluorination · biocatalysis

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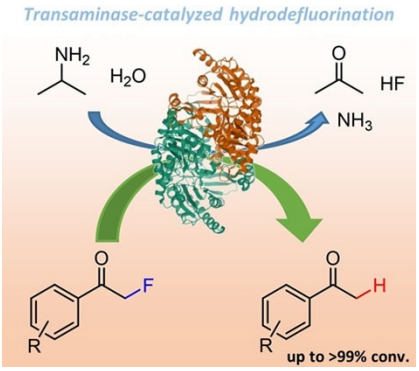
The hydrodefluorination of various α-fluoroketones has been performed under mild reaction conditions and in aqueous medium taking advantage of the promiscuous activity shown by transaminases using a stoichiometric amount of, *e.g.* 2-propylamine, releasing in this case acetone, ammonia and hydrogen fluoride as by-products. The process could be done in a regio- or even in a stereoselective manner.



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