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Chemo- and regioselectivity in the reactions between highly electrophilic fluorine containing dicarbonyl compounds and amines. Improved synthesis of the corresponding imines/enamines

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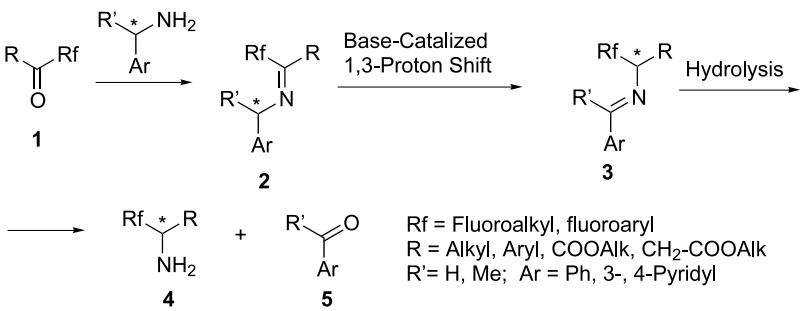
Abstract—Chemo- and regioselectivity in the reactions between highly electrophilic fluorine containing dicarbonyl compounds (ethyl 4,4,4-trifluoroacetoacetate, 3,3,3-trifluoropyruvate and 1,1,1,5,5,5-hexafluoropentane-2,4-dione) and various benzylamines were systematically studied. The results obtained lead to the development of a generalized and practical method for large-scale synthesis of the corresponding imines/enamines, useful starting materials for preparation fluorinated amines and amino acid.

1. Introduction

The 1,3-proton shift reaction (PSR)[1] has emerged as conceptually different to the classical methods,[2] a conventional-reducing-reagent-free approach for a reductive amination of fluorocarbonyl compounds to the corresponding fluorine-containing amines and amino acids.[3–7] This approach, mimicking the biological transamination,[8] i.e. the enzyme-catalyzed interconversion of α-amino and α-keto carboxylic acids,[9] represents the most ideal solution to the reductive amination of carbonyl compounds **1** (Scheme 1). Thus, instead of application of reducing reagents, PSR makes use of the intramolecular reduction–oxidation process via a base-catalyzed 1,3-proton shift in the azaallylic system of azomethines (imines) **2** and **3**. It was shown that the mechanism of this azomethine–azomethine isomerization involves azaallylic anions as intermediates and the equilibrium constants of the isomerization are adequately correlated by the Hammett equation.[10] We were first to demonstrate that the presence of electron-withdrawing perfluoroalkyl or perfluoroaryl groups, in α-position to the imine function in derivatives **2** makes their base-catalyzed isomerization to Schiff bases **3** virtually irreversible and thus synthetically useful.

Previously we reported an efficient application of this base-catalyzed azomethine–azomethine isomerization for preparation of fluorine-containing amines,[4] α- and β-amino acids[5] starting from readily available fluorinated aldehydes and ketones, or α- and β-keto carboxylic acids, respectively. Our most recent achievement in this area is the development of double-PSR methodology for a direct, one-pot conventional-reducing-reagent-free transformation of perfluoroalkyl-carboxylic acids to the corresponding α,α-dihydroperfluoroalkylamines.[11] However, of particular interest are the results reported by other research groups



Scheme 1.

Keywords: chemoselectivity; regioselectivity; nucleophilicity; electrophilicity; enamines; imines; fluorine and compounds.

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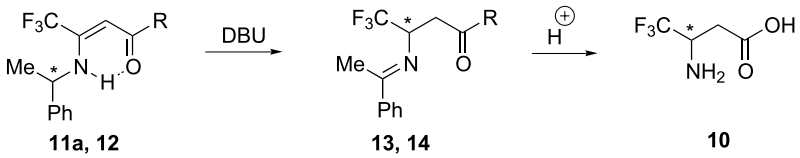


Scheme 2.

on application of the PSR methodology for transamination of fluorine-free carbonyl compounds to the corresponding amino-derivatives[6] as well as the preparation of fluorine-containing phosphorus analogs of α- and β-amino acids.[7]

Despite the apparent generality and synthetic efficiency of the base-catalyzed isomerization of **2** to **3** and their further hydrolysis to target amino compounds **4**, which could be easily separated from the aldehyde or ketone **5**, the PSR methodology,[1,4–7] as a whole process, in some cases is plagued by the relatively low chemical yields on the stage of preparation of the corresponding imines/enamines **2** from the starting carbonyl compounds. In particular, the issue of chemo- and regioselectivity is a major concern in the reactions between benzyl amine and its derivatives with polyfunctional and/or highly electrophilic fluorine containing carbonyl compounds. In this paper we report a full account of a systematic study of the reactions of ethyl 4,4,4-trifluoroacetoacetate (**6**), ethyl 3,3,3-trifluoropyruvate (**7**) and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**8**) with various benzylamines **9a–g**, which lead to the development of a generalized and practical method for large-scale synthesis of the corresponding imines/enamines, and thus to substantial overall improvement of the PSR methodology.

2. Results and discussion

2.1. Control of chemoselectivity in the reactions between ethyl 4,4,4-trifluoroacetoacetate (6) and benzylamines 9a–c

β-Perfluoroalkyl-β-amino acids represent an enormously interesting class of β-amino acids in view of their synthetic and biological applications,[3] and in particular, in the design and synthesis of fluorinated β-peptides.[12,13] Recently we reported a highly enantioselective (>90% ee) method for preparing β-perfluoroalkyl-containing β-amino acids of type **10** (Scheme 2) via DBU-catalyzed PSR of both enamino-ester **11a** and enamino-amid **12** to the corresponding Schiff bases **13** and **14**.[5h] While the isomerization of **11a** and **12** to **13** and **14** as well as sequential hydrolysis of **13** and **14** to the target compound **10** could be conducted with high chemical yields, the method, as a whole, is compromised by the low chemoselectivity and chemical yields on the stage of preparing the starting ester **11a** and amide **12**.

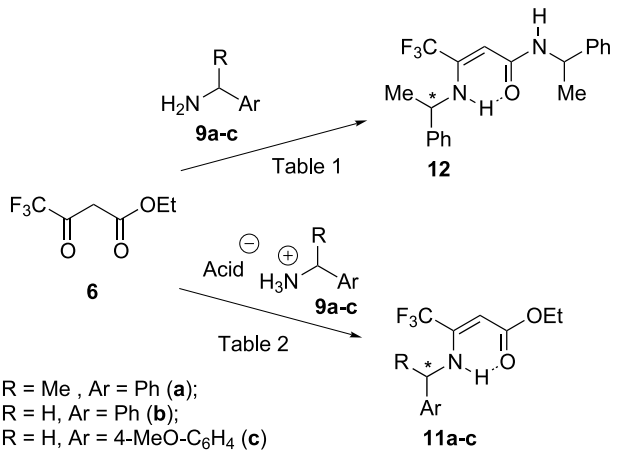
Previously[5f,h] we synthesized compounds **11a** and **12** under conventional reaction conditions, such as acid-catalyzed condensation between ethyl trifluoroacetoacetate (**6**) and optically pure α-phenylethylamine (**9a**) in benzene at reflux using Dean–Stark device to trap the water (Dean–Stark conditions) (Table 1, entry 1). In contrast to the condensations of fluorine-free ethyl acetoacetate with benzylamines which afforded virtually quantitative yield the corresponding enamino-esters,[14] the reaction under study showed poor chemoselectivity giving rise to a mixture of products **11a** and **12** in a ratio of 74.5/25.5 (entry 1). Since both derivatives **11a** and **12** can be used for preparation of amino acid **10**[5h] (Scheme 2), we decided to study this reaction in detail to develop a chemoselective method for practical synthesis of each **11a** and **12**.

2.1.1. Chemoselective preparation of enamino-amide 12 (Scheme 3, Table 1). First we targeted preparation of the enamino-amid **12**, as we thought it could be easily achieved simply by using an excess of amine **9a** in the *p*-toluene sulfonic acid-catalyzed reaction with keto-ester **6** (Dean–Stark conditions). Surprisingly, application of 2.1 equiv. of **9a** did not effect the ratio of products **11a** and **12** (entry 2). However, changing of the solvent (toluene) noticeably accelerated the reaction rate and increased the ratio of the enamino-amid **12** formation (entry 3). Interestingly, further increase in formation of **12** was observed when the reaction was conducted without *p*-toluene sulfonic acid as a catalyst (entry 4). Under these reaction conditions we tried, once again, an application of 3.5 equiv. of amine **9a** to improve

Table 1. Synthesis of enamino-amide **12** as a major product by the reaction of β-keto ester **6** with α-phenylethylamine **9a**

Entry	Solvent	Ratio **6/9a**	*T* (h)	Ratio[a] **11a/12**	Yield[b] (%) **12**
1	Benzene[c]	1/1.1	24	74.5/25.5	17.2[d]
2	Benzene[c]	1/2.1	24	71.3/28.7	23.6
3	Toluene[c]	1/2.5	6	49.1/50.9	43.1
4	Toluene	1/2.5	6	42.7/57.3	43.1
5	Toluene	1/3.5	12	42.5/57.5	45.0
6	Methanol/toluene	1/3.0	3; 3	15.5/84.5	81.1
7	Methanol–water/toluene	1/3.0	3; 3	11.3/88.7	75.4

All reactions were conducted at reflux in the indicated solvent.
[a] Determined by ^{19}F NMR (300 MHz) analysis of the crude reaction mixtures.
[b] Isolated yield of pure product **12**.
[c] Reaction was conducted in the presence of 5 mol% of *p*-toluene sulfonic acid.
[d] Enamino-ester **11a** was isolated in 43% yield.



Scheme 3.

the yield of **12**. Unfortunately, the excess of the amine and even prolonged reaction time did not change the ratio of products **11** and **12** (entry 5). These results clearly suggested that enamino-ester **11a** does not react with amine **9a** to give amid **12**. Indeed, the reaction between pure enamino-ester **11a** with amine **9a**, conducted with and without *p*-toluene sulfonic acid as a catalyst, did not produce any measurable amounts of amid **12**. Based on these results we assumed that preparation of enamino-amid **12** would require special reaction conditions under which amine **9a** would be forced to react first with the ester function of **6** to form the amid moiety and then interact with the keto group of the corresponding intermediate amid to give the enamino functionality. To realize this reaction sequence we designed the following two-step procedure. To block the most reactive keto function of **6** we decided to conduct the first stage using methanol as a reaction medium. We expected that under these conditions the keto of **6** group might react with methanol to form a less reactive semi-ketal derivative while the ester function would still be active to react with amine **9a**. On the second stage, the formation of the enamine moiety, we planned to apply standard conditions, refluxing the reagents in toluene. Thus, keto-ester **6** was treated first with 3.0 equiv. of amine **9a** in methanol at reflux for 3 h. After that, the mixture was evaporated, to remove the excess of methanol. The residue was taken in toluene and refluxed for 3 h. The result of this two-step procedure was rather satisfactory as we obtained a significantly improved yield of the target **12** (entry 6). The best result was obtained when we used methanol–water in a volume ratio 4 to 2, respectively, as a reaction medium for the first stage (entry 7). However, substantial amounts of water in the reaction mixture turned out to be synthetically disadvantageous, complicating the isolation of the target product. Thus, the highest and synthetically useful isolated yield of enamino-amid **12** (81%) on a scale of over 50 g was obtained with the designed two-step procedure using as solvents methanol and toluene on the first and second steps, respectively (entry 6).

2.1.2. Chemoselective preparation of enamino-esters 11a–c (Scheme 3, Table 2). For chemoselective preparation of enamino-ester **11a** we needed to solve just the opposite problem: to increase reactivity of the keto group in **6** and decrease reactivity of the corresponding ester function. We envisioned that the desired result could be also achieved by decreasing the nucleophilicity of the reacting amine. Our reasoning was based on the assumption that decreased nucleophilicity of the amine might prevent, or significantly de-accelerate, the rate of its reaction with the ester group while the condensation with a more electrophilic keto function would still be possible. Therefore, to decrease nucleophilicity of amine **9a** we decided to use its salts with relatively weak acids. First we conducted the reaction between keto-ester **6** and carbonate of **9a**. The result was rather disappointing as we obtained 68:32 ratio of the target enamino-ester **11a** and enamino-amid **12** (entry 1).

Table 2. Synthesis of enamino-esters **11a–c** by the reactions of β-keto ester **6** with benzylamines **a–c**

Entry	**9a–c**	Solvent	Acid[a]	*T* (h)	Ratio[b] **11a–c/12**	Yield[c] (%) **11a–c**
1	**a**	Benzene	H_2CO_3	9	68.1/31.9	57.7
2	**a**	Benzene	None	15	56.1/43.9	–[d]
3	**a**	Benzene	$MeCO_2H$	9	86.9/13.1	84.3
4	**a**	Benzene	$PhCO_2H$	9	79.4/20.6	71.3
5	**a**	Benzene	CF_3CO_2H	9	>99/1	40.5[e]
6	**a**	Benzene	HCO_2H	9	88.7/11.3	87.7
7	**a**	Benzene	HCl	24	44.2/55.8	7.9[f]
8	**a**	*n*-Hexane	$MeCO_2H$	9	93.8/6.2	58.4[g]
9	**a**	$CHCl_3$	HCO_2H	9	>99/1	81.1 (83.3)[h]
10	**a**	$CHCl_3$	$MeCO_2H$	9	95.7/4.3	91.5 (93.7)[h]
11	**b**	$CHCl_3$	$MeCO_2H$	9	>99/1	95.7
12	**c**	$CHCl_3$	$MeCO_2H$	9	>99/1	96.1

All reactions were conducted at reflux in the indicated solvent using 1:1.1 ratio of **6** and **9a–c**.
[a] The indicated acid was used to form in situ the corresponding salt with amine **9a–c**.
[b] Determined by ^{19}F NMR analysis of the crude reaction mixtures.
[c] Isolated yield of pure **11a–c**.
[d] Only **12** was isolated and characterized.
[e] Conversion of **6** and **9a** was about 50%.
[f] Conversion of **6** and **9a** was about 15%.
[g] Conversion **6** and **9a** was about 70%.
[h] Yield obtained on large scale.

However, we reasoned that this result could be attributed to the relative instability of the corresponding carbonate of **9a** in boiling benzene, so the observed ratio of the products **11a** and **12** might be rather an outcome of the direct reaction between keto-ester **6** and free amine **9a**. This assumption was supported by the corresponding reaction that gave a comparable ratio of the products **11a** and **12** (entry 2). In contrast, the reaction of **6** with acetate of **9a** afforded the products with a substantially increased ratio of enamino-ester **11a** (entry 3). Further reactions of keto-ester **6** with benzoic (entry 4), trifluoroacetic (entry 5), formic (entry 6), and hydrochloric (entry 7) acid derived salts of amine **9a** revealed that while the best, virtually complete, regioselectivity could be obtained using the trifluoroacetate of **9a** (entry 5), for preparative purposes the corresponding acetate (entry 3) and formate (entry 6) of **9a** should be reagents of choice. In these cases, in contrast to the conventional method, we did not observe separation of water; therefore, we monitored the reaction completion by ^{19}F NMR. To further improve the regioselectivity, we tried the reactions in different solvents using these non-conventional reaction conditions (no separation of water). For instance, application of acetate of **9a** in the reaction with **6** in hexane, at reflux, showed higher regioselectivity as compared with the result obtained in benzene (entry 8 vs 3). However, the

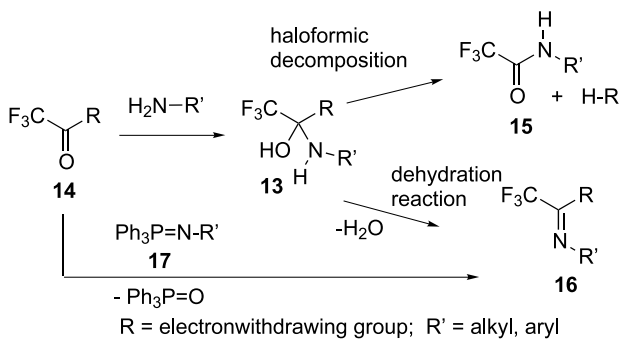
most synthetically useful results were obtained in the reactions conducted in chloroform. Thus, the reaction of keto-ester **6** with formate of amine **9a**, conducted in boiling chloroform, featured virtually complete regioselectivity (entry 9); however, the target product **11a** was isolated in 81% yield. Application of acetate of **9a**, under the same reaction conditions, was also synthetically useful, affording the products **11a** and **12** with a ratio of >95:5 (entry 10). Comparison of these two procedures on a large scale (>100 g) showed that the acetate of **9a** (entry 10) is a reagent of choice for preparing large quantities of enamino-ester **11a**.

Using these findings we conducted the reaction between keto-ester **6** and acetate of benzylamine **9b**. The result was almost perfect from the point of view of regioselectivity and chemical yield of the target enamino ester (entry 11). The same, virtually complete, regioselectivity and high chemical yield were observed in the reaction of the corresponding acetate of *p*-(methoxy)benzylamine **9c** with keto-ester **6** (entry 12).

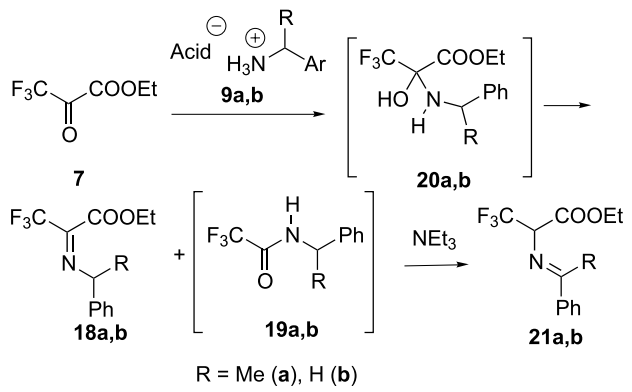
2.2. Control of regioselectivity in the reactions between highly electrophilic fluorine containing carbonyl compounds and benzyl amines

The reactions between fluorinated carbonyl compounds and amines, affording the corresponding intermediate imines, could be considered as the most methodologically straightforward approach for preparing fluorine-containing and biologically relevant amines and amino acids.[3] However, with the increase of fluorine substituents on carbonyl compounds and consequently the electrophilicity of carbonyl compounds, the chemical outcome of their reactions with nucleophilic amines, in general, becomes less and less synthetically useful. Thus, the intermediate *gem*-amino-alcohols **16** (Scheme 4), derived from highly electrophilic carbonyl compounds **14**, tend to undergo a rather haloform type reaction (sometimes referred to as a haloformic decomposition or Lieben haloform reaction[15]), giving rise to trifluoroacetamides **15**, then the dehydration reaction leading to the target imines **16**.[16] Therefore, in general, the regioselectivity in the reactions of highly electrophilic fluorine-containing carbonyl compound with nucleophilic amines represents one of the unsolved synthetic challenges.

Previously we successfully addressed the issue of the regioselectivity by introducing the Staudinger reaction into



Scheme 4.



Scheme 5.

Table 3. Synthesis of imines **18a,b** by the reactions of α-keto ester **7** with benzylamines **9a,b**

Entry	**9a,b**	Solvent	Acid[a]	*T* (h)	Ratio[b] **18a,b/20a,b**	Yield[c] (%) **18a,b**
1	**a**	$CHCl_3$	$MeCO_2H$	9	67.8/32.2	–
2	**a**	$CHCl_3$	$MeCO_2H$	64	>95/5	93.3
3	**b**	$CHCl_3$	$MeCO_2H$	9	<5/95	–
4	**b**	$CHCl_3$	$MeCO_2H$	64	<30/70	–
5	**b**	Toluene	$MeCO_2H$	9	>99/1[d]	65.1[d]
6	**b**	$CHCl_3$	HCO_2H	6	69.7/30.3	63.0

All reactions were conducted at reflux in the indicated solvent using 1:1.1 ratio of **7** and **9a,b**.
[a] The indicated acid was used to form in situ the corresponding salt with amine **9a,b**.
[b] Determined by ^{19}F NMR analysis of the crude reaction mixtures.
[c] Isolated yield of pure products.
[d] The **21b** was isolated as the major reaction product.

the realm of polyfluorinated carbonyl compounds.[17] However, the application of the corresponding *N*-substituted phosphazenes **17** has some synthetic disadvantages such as the preparation of **17** from the corresponding azides and triphenylphosphine and the laborious purification of products **16** from the triphenylphosphine oxide.[17] Taking into account the successful application of salts **9a–d** for chemoselective preparation of enamines **11a–d** (Scheme 3), we decided to study the reactions of these mild nucleophilic reagents with highly electrophilic ethyl 3,3,3-trifluoropyruvate (**7**) and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**8**).

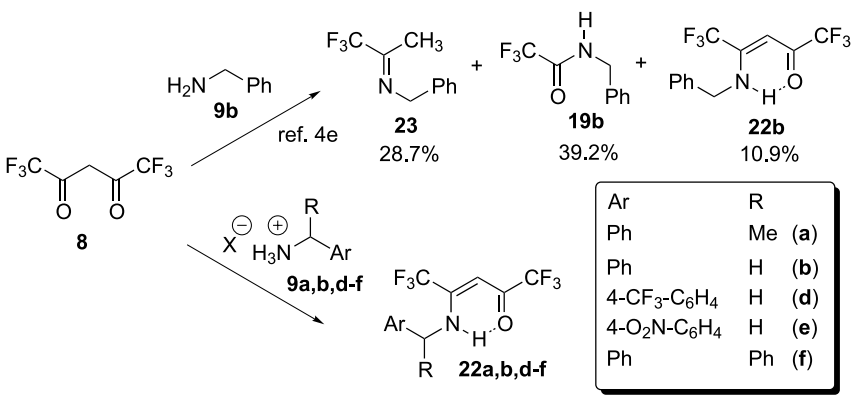
2.2.1. Regioselective synthesis of *N*-(α-phenyl)ethyl- 18a and *N*-benzylimines 18b (Scheme 5, Table 3). Previously we reported that the reaction between α-keto-ester **7** and benzylamine **9b**, conducted at room temperature, afforded *N*-benzylamide **19b** as a major (60% yield) reaction product.[17d] Lowering the reaction temperature to −15°C allowed us to avoid the corresponding haloform type reaction and isolate the *gem*-amino-alcohol **20b** in 90% chemical yield. Similar to benzylamine **9b**, phenylethylamine **9a** reacted with keto-ester **7** at low temperatures to furnish *gem*-amino-alcohol **20a** (95% yield). However, in contrast to **20b**, phenylethylamine-derived **20a** was found to undergo, under the standard Dean–Stark conditions, the corresponding dehydration affording the target imine **18a** in 70% yield.[17d] Further optimization of the reaction conditions allowed us to increase the yield of imine **18a** to 81–83%.[5g] However, the necessity of using toluene as a

solvent for these reactions (no reaction was observed in benzene) caused the formation of noticeable amounts of haloform-type decomposition of intermediate **20a**, thus complicating the purification of target imine **18a** from trifluoroacetamide **19a**.[5g,17d] Therefore application of the salts of amines **9a**,**b** in the condensations with keto-ester **7** under milder conditions looked very promising as an attempt to improve the regioselectivity and thus the synthetic efficiency of these reactions. Since the salts of benzylamines **9a**–**d** with acetic acid gave the best synthetic results in preparation of enamines **11a**–**d** (Schemes 3 and 4), we tested these reagents in the reactions with keto-ester **7**.

Fortunately, our first attempt proved our expectations. Thus monitoring (by ^{19}F NMR) of the reaction conducted in boiling chloroform between acetate of phenylethylamine **9a** and keto-ester **7**, showed that after 9 h of the condensation only two products, the intermediate *gem*-amino alcohol **20a** (s, −80.5 ppm) and target imine **18a** (s, −68.00 ppm); were present in the reaction mixture in a ratio of 2:1 (Table 3, entry 1). These data suggested that under the new reaction conditions the intermediate *gem*-amino-alcohol **20a** slowly but regioselectively undergoes dehydration to afford imine **18a**. The complete transformation of **20a** to **18a** (as detected by ^{19}F NMR) was achieved after about 3 days of refluxing the reaction mixture in chloroform (entry 2). Analysis of the reaction mixture by ^{19}F NMR showed that target imine **18a** could account for at least 95% of the crude product. Among the other compounds in the reaction mixture we could identify *gem*-amino alcohol **20a** (<3%) and product of imine **18a** isomerization, the Schiff base **21a** (d, −72.6) (<2%). Target imine **18a** was isolated in 93% chemical yield, by passing the crude mixture through a short silica-gel column. According to previously published procedures,[5g] imine **18a** was cleanly isomerized to afford **21a** (94% yield). With these promising results in hand, we studied next the reactions of benzyl amine salts **9b** with α-keto-ester **7**.

As discussed previously, all our former attempts to dehydrate the *gem*-amino alcohol **20b**, under the standard Dean–Stark conditions, failed.[17d] Therefore, we were not surprised to observe (controlled by ^{19}F NMR) the stability of compound **20b** (s, −79.8 ppm) under the conditions that caused dehydration of phenylethylamine derivative **20a** (entries 3,4 vs 1,2). Interestingly, the reaction of acetate **9b** with **7** conducted in toluene at reflux, resulted in substantial transformation of the *gem*-amino alcohol **20b** directly to Schiff base **21b** (d, −71.5 ppm), which was isolated in 65% chemical yield by column chromatography (entry 5). These results suggested that application of acetate **9b** in the reaction with **7** is more efficient for dehydration of the intermediate **20b** as compared with the standard Dean–Stark conditions using the solvent (toluene). Another conclusion that could be drawn from these results is that *N*-benzylimine **18b** is highly unstable in boiling toluene and undergoes fast PSR to afford the thermodynamically more stable product **21b**.[18] Nevertheless, after several unsuccessful attempts using various salts of benzylamine **9b**, we finally succeeded in preparing *N*-benzylimine **18b** by the reaction between the trifluoroacetate of benzylamine **9b** and keto-ester **7**. Thus after 6 h of the reaction in chloroform at reflux, we were able to isolate compound **18b** as an individual compound, albeit in moderate 63% yield (entry 6). Our attempts to improve the yield of **18b** by increasing the reaction time unfortunately failed. As could be expected,[4f,g] imine **18b** on treatment with triethylamine underwent the corresponding PSR to afford the Schiff base **21b** at a much faster rate as compared with that of compound **18a**. However, from the point of view of synthetic efficiency and overall chemical yield in preparing the target 3,3,3-trifluoroalanine,[5g] synthesis of phenylethylamine-derived imine **18a**, according to the procedure developed by this study (entry 2) is a recommended method of choice.

2.2.2. Regioselective synthesis of imines 22a,b,d–f derived from 1,1,1,5,5,5-hexafluoropentane-2,4-dione (8) and amines 9a,b,d–f (Scheme 6, Table 4). While the reactions of hexafluoropentane-2,4-dione **8** with low-nucleophilic and polyfunctional arylamines are widely used for preparing various heterocyclic compounds,[19] the condensations of **8** with highly nucleophilic aliphatic amines are of much less synthetic value as they usually lead to haloform reaction products. For instance, previously we failed to prepare the target enamine **22b** by the reaction between diketone **8** and benzylamine **9b** using the conventional Dean–Stark conditions. Instead, we used this reaction to produce in situ highly volatile trifluoroacetone for its further condensation with excess of **9b** to afford the correspondent *N*-benzylimine **23** (Scheme 6).[4e] Interestingly, the yield of the expected enamine **22b** in this reaction was only about 11%. Therefore we were very interested to study the synthetic value of the salts of benzylamines **9** as



Scheme 6.

Table 4. Synthesis of enamines **22a**,**b**,**d**–**f** by the reactions of diketone **8** with benzylamines **9a**,**b**,**d**–**f**

Entry	**9a**,**b**,**d**–**f**	Solvent	Acid[a]	*T* (h)	Ratio[b] **8/22a**,**b**,**d**–**f**	Yield[c] (%) **22a**,**b**,**d**–**f**
1	**a**	$CHCl_3$	$MeCO_2H$	15	64.1/35.9	–
2	**a**	$CHCl_3$	$MeCO_2H$	120	<5/95[d]	55.5
3	**a**[e]	$CHCl_3$	$MeCO_2H$	96	<2/98[f]	–
4	**a**	$CHCl_3$	CF_3CO_2H	15	<51/49	–
5	**a**	$CHCl_3$	CF_3CO_2H	120	>99/1[g]	57.1
6	**a**	Toluene	CF_3CO_2H	9	>93/7	65.4
7	**b**	Toluene	CF_3CO_2H	9	44/56	77.7
8	**d**	Toluene	CF_3CO_2H	9	94/6	65.3
9	**e**	Toluene	CF_3CO_2H	9	>99/1	62.5
10	**f**	Toluene	CF_3CO_2H	9	95/5	62.2

All reactions were conducted at reflux in the indicated solvent using 1:1.1 ratio of **8** and **9a**,**b**,**d**–**f**.
[a] The indicated acid was used to form in situ the corresponding salt with amine **9a**,**b**,**d**–**f**.
[b] Determined by ^{19}F NMR analysis of the crude reaction mixtures.
[c] Isolated yield of pure products.
[d] Content of product **22a** in the reaction mixture was about 85%.
[e] Compounds **8** and acetate **9a** were used in a ratio 1:2.2.
[f] Content of **22a** in the reaction mixture was <70%.
[g] Content of **22a** in the reaction mixture was >83%.

low-nucleophilic reagents for preparing the corresponding enamines **22a**,**b**,**d**–**f**, a virtually unstudied but potentially synthetically useful class of intermediates for preparing polyfunctional fluorinated amino-compounds. Based on the results obtained in this study (Tables 2 and 3), we decided first to react diketone **8** with acetate **9a** in chloroform at reflux. The reaction proceeded quite slowly as after 15 h we observed less than 40% conversion of starting **8** (Table 4, entry 1). Complete transformation of the starting compounds was achieved after 5 days of the reaction and, according to the ^{19}F NMR of the crude reaction mixture, the ratio of the target product **22a** to the rest of byproducts was 85:15. The target enamine **22a** was isolated with 55.5% chemical yield (entry 2).

The increase in the ratio of the acetate of **9a**, relative to diketone **8**, as an attempt to improve the yield of **22a**, resulted in increased formation of the byproducts. According to the ^{19}F NMR of the crude reaction mixture, the content of the target product was <70% (entry 3). Therefore, we decided to use less nucleophilic trifluoroacetate of amine **9a**. The reaction between diketone **8** and trifluoroacetate of **9a** surprisingly proceeded at a comparable with the interaction of **8** with acetate of **9a** reaction rate (entry 4 vs 1). However, the important feature of this reaction was the absence of unwanted byproducts. Continuation of this reaction, in the chloroform at reflux, for 5 days gave a mixture containing, according to the ^{19}F NMR, at least 83% of the target product (entry 5). After numerous attempts, using different salts of **9b** and different solvents, we finally found that toluene, as a reaction medium, and trifluoroacetate of **9a**, as the amino derivative in the reaction with diketone **8**, are the conditions of choice to prepare the target **22a** with a synthetically useful yield (entry 6). According to the ^{19}F NMR of the crude reaction mixture (entry 6), the content of the target product **22a** was at least 93%. Work-up of the reaction mixture (entry 6) allowed us to isolate the product **22a** in 65% yield. To demonstrate a practicality of the developed reaction conditions, using trifluoroacetate of **9a** as a reagent, we performed the reaction on a relatively large scale (20 g) with a successful reproducibility in the chemical yield of the enamine **22a**. With these results in hand, we next studied the generality of the method using various trifluoroacetate salts of benzylamines **9b**,**d**–**f** for preparing the corresponding enamines **22b**,**d**–**f** under the standard conditions (entry 6). The best result, 77.7% yield of enamine **22b**, was obtained in the reaction of diketone **8** with the trifluoroacetate of unsubstituted benzylamine **9b** (entry 7). On the other hand, in the reactions of the corresponding trifluoroacetates of the benzylamines **9d**,**e**, bearing strong electron-withdrawing substituents (entries 8, 9), or sterically bulky moiety **9f** (entry 10), we isolated the target enamines **22d**–**f** in a range of 60–65% chemical yield (entries 8–11). Since the content of the target products **22b**,**d**–**f** in the reaction mixtures, as estimated by ^{19}F NMR of the crude reaction product, is generally above 90%, we believe that the isolated yields could be further improved by proper optimization of the work-up procedure. Nevertheless, comparison of the yield of about 11% of the target enamine **22b**, obtained under the conventional Dean–Stark reaction conditions,[4e] with the generally above 60% yields of enamines **22a**,**b**,**d**–**f**, obtained using trifluoroacetates **9a**,**b**,**d**–**f**, renders the method developed in this study synthetically useful.

In summary, we demonstrated that the problem of chemoselectivity in the reaction between ethyl 4,4,4-trifluoroacetoacetate (**6**) and various benzylamines **9a**–**c** could be successfully solved by designing the appropriate reaction conditions (Tables 1 and 2), allowing for highly chemoselective preparation of enamino-ester **11** and enamino-amid **12**. The acetates and trifluoroacetates of benzylamines **9a**–**f**, used as 'mild nucleophiles' for chemoselective preparation of enamino-ester **11**, were found to be the reagents of choice in the reactions with highly electrophilic fluorinated carbonyl compounds, such as α-keto-ester **7** and diketone **8**, allowing the preparation of the corresponding imines **18a**,**b** and enamines **22a**,**b**,**d**–**f** in synthetically useful chemical yields (Tables 3 and 4). Simplicity of the experimental procedures as well as the relatively high chemical yields, compared to the conventional methods, render the procedures developed in this study synthetically useful for preparing various fluorine-containing and biologically relevant amino-compounds.

3. Experimental

3.1. General

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out under atmosphere without any special caution to exclude air. Unless indicated, ^{1}H, ^{19}F and ^{13}C NMR spectra, were taken in $CDCl_3$ solutions at 299.95, 282.24 and 75.42 MHz, respectively, on an instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS and $CFCl_3$ as the internal standards.

Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H and ^{19}F NMR spectrometry. All new compounds were characterized by ^{1}H, ^{19}F, ^{13}C NMR, by mass spectrometry and/or elemental analysis.

3.1.1. 4,4,4-Trifluoro-3-(1-phenylethylamino)but-2-enoic acid (1-phenylethyl)amide (12) (Scheme 3, Table 1, entry 6). To a solution of keto-ester **6** (50.0 g, 0.27 mol) in methanol (300 mL) at room temperature was added phenylethylamine (98.7 g, 0.81 mol). The resultant mixture was refluxed for 3 h and evaporated in vacuum. To the slurry residue toluene (500 mL) was added and the mixture was refluxed for 3 h using Dean–Stark trap to collect the separating water. The solvent was evaporated in vacuum to dryness and the residue was subjected to chromatography on silica gel using first neat *n*-hexane, to wash out the corresponding enamino-ester **11a**, and then *n*-hexane–AcOEt in a ratio of 10:1 to isolate the target enamino-amid **12** (79.7 g, 81.1%). R_f=0.14 (*n*-hexane/ethyl acetate in a ratio of 4/1); ^{1}H NMR δ 1.49 (d, 1.5H, J=6.6 Hz), 1.4985 (d, 1.5H, J=6.9 Hz), 1.509 (d, 1.5H, J=6.6 Hz), 1.512 (d, 1.5H, J=6.9 Hz), 4.66 (dq, 1H, J=10.8, 6.6 Hz), 4.95 (s, 0.5H), 4.96 (s, 0.5H), 5.16 (dq, 1H, J=7.5, 6.9 Hz), 5.50 (brd, 1H, J=7.5 Hz), 7.25–7.35 (m, 10H), 9.19 (brd, 1H, J=10.8 Hz). ^{19}F NMR δ −66.64 (s). ^{13}C NMR δ 22.12 (s), 22.22 (s), 25.18 (s), 48.50 (s), 53.89 (bq, J_{CF}=2.1 Hz), 88.05 (q, J_{CF}=5.7 Hz), 88.26 (q, J_{CF}=5.5 Hz), 120.51 (q, J_{CF}=277.1 Hz), 125.44 (s), 126.04 (s), 126.07 (s), 127.01 (s), 127.36 (s), 128.57 (s), 128.59 (s), 128.74 (s), 143.31 (s), 143.44 (s), 144.51 (s), 144.63 (s), 145.55 (q, J_{CF}=30.2 Hz), 145.57 (q, J_{CF}=30.2 Hz), 168.16 (s). MS: 362 (M, 5.6), 105 (100). HRMS calcd for $C_{20}H_{21}F_3N_2O$ (M+Na) 385.1504. Found: 385.1678. Anal. calcd for $C_{20}H_{21}F_3N_2O$: C, 66.29; H, 5.84; N, 7.73; F, 15.73. Found: C, 66.34; H, 5.89; N, 7.76; F, 15.67.

3.1.2. 4,4,4-Trifluoro-3-(1-phenylethylamino)but-2-enoic acid ethyl ester (11a) (Scheme 3, Table 2, entry 10). To a solution of acetic acid (166.2 g, 2.77 mol) in the chloroform (700 mL) at room temperature was added phenylethylamine (335.7 g, 27.7 mol), the resultant mixture was stirred for 5 min and a solution of keto-ester **6** (464.4 g, 2.52 mol) in chloroform (800 mL) was added to the mixture. The resultant mixture was refluxed for 3 h followed by evaporation of the solvent in vacuum. The residue was placed on short silica gel column and washed with *n*-hexane to afford the desired product (678.9 g, 93.7%). R_f=0.39 (*n*-hexane/ethyl acetate in a ratio of 4/1); ^{1}H NMR δ 1.29 (t, 3H, J=7.2 Hz), 1.54 (d, 3H, J=6.9 Hz), 4.18 (qm, 2H, J=7.2 Hz), 4.75 (dd, 1H, J=8.7, 6.9 Hz), 5.12 (s, 1H), 7.25–7.34 (m, 5H), 8.63 (brd, 1H, J=6.9 Hz). ^{19}F NMR δ −66.75 (s). ^{13}C NMR δ 14.35 (s), 25.00 (s), 53.99 (q, J_{CF}=2.6 Hz), 59.77 (s), 85.60 (q, J_{CF}=6.0 Hz), 120.33 (q, J_{CF}=277.1 Hz), 125.36 (s), 127.31 (s), 128.73 (s), 143.94 (s), 147.75 (q, J_{CF}=31.1 Hz), 169.97 (s). MS: 287 (M, 5.9), 258 (M−Et, 4.2), 105 (100). HRMS calcd for $C_{14}H_{16}F_3NO_2$ (M+Na) 310.1031. Found: 310.1087. Anal. calcd for $C_{14}H_{16}F_3NO_2$: C, 58.53; H, 5.61; N, 4.88; F, 19.84. Found: C, 58.58; H, 5.63; N, 4.84; F, 19.77.

Enamino-esters **11b**,**c** were prepared according to the procedure described above for the synthesis of **11a**, except that the acetates of benzylamines **9b**,**c** (Table 2, entries 11, 12) were used instead of the acetate of **9a**.

3.1.3. 3-Benzylamino-4,4,4-trifluorobut-2-enoic acid ethyl ester (11b) (Scheme 3, Table 2, entry 11). ^{1}H NMR δ 1.26 (3H, t, J=7.2 Hz), 4.13 (2H, q, J=7.2 Hz), 4.47 (2H, d, J=6.3 Hz), 5.16 (1H, s), 7.5–7.2 (5H, m), 8.43 (1H, brs). ^{19}F NMR δ −67.0 (CF_3, s). ^{13}C NMR δ 169.6, 147.9 (q, J=31.1 Hz), 137.5, 128.7, 127.6, 127.1, 120.2 (q, J=274.7 Hz), 85.2 (q, J=5.9 Hz), 59.7, 48.1 (q, J=2.7 Hz), 14.4. HRMS calcd for $C_{13}H_{14}F_3NO_2$ (M+Na) 296.0874. Found: 296.0755.

3.1.4. 4,4,4-Trifluoro-3-(4-methoxybenzylamino)but-2-enoic acid ethyl ester (11c) (Scheme 3, Table 2, entry 12). ^{1}H NMR δ 8.35 (1H, brs), 7.20 (2H, d, J=8.6 Hz), 6.86 (2H, d, J=8.6 Hz), 5.14 (1H, s), 4.38 (2H, d, J=5.7 Hz), 4.11 (2H, q, J=7.4 Hz), 3.76 (3H, s), 1.23 (3H, t, J=7.4 Hz). ^{19}F NMR δ −66.4 (CF_3, s). ^{13}C NMR δ 169.9, 159.3, 148.2 (q, J=30.8 Hz), 129.8, 128.9, 120.5 (q, J=274.9 Hz), 114.4, 85.2 (q, J=5.9 Hz), 60.0, 55.6, 47.9 (q, J=2.9 Hz), 14.7. HRMS calcd for $C_{14}H_{16}F_3NO_3$ (M+Na) 326.0980. Found: 326.0818.

3.1.5. 3,3,3-Trifluoro-2-(1-phenylethylimino)propionic acid ethyl ester (18a) (Scheme 5, Table 3, entry 2). The procedure described above for the synthesis of enamino-ester **11a** was followed except that the completion of the reaction between keto-ester **7** and acetate of **9a** required 64 h (control by ^{19}F NMR): ^{1}H NMR δ 7.4–7.3 (5H, m), 4.92 (1H, q, J=6.5 Hz), 4.40 (2H, q, J=7.4 Hz), 1.56 (3H, d, J=6.5 Hz), 1.37 (3H, t, J=7.4 Hz). ^{19}F NMR δ −69.5 (CF_3, s). Anal. calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; F, 20.86; N, 5.13. Found: C, 57.24; H, 5.21; F, 20.79; N, 5.09.

3.1.6. 2-Benzylimino-3,3,3-trifluoro-propionic acid ethyl ester (18b) (Scheme 5, Table 3, entry 5). The procedure described above for the synthesis of enamino-ester **11a** was followed except that the reaction was conducted in toluene at reflux (control by ^{19}F NMR); ^{1}H NMR δ 7.4–7.2 (5H, m), 4.91 (2H, d, J=6.5 Hz), 4.42 (2H, q, J=6.9 Hz), 1.39 (3H, t, J=6.9 Hz). ^{19}F NMR δ −69.5 (CF_3, s). Anal. calcd for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; F, 21.99; N, 5.40. Found: C, 55.72; H, 4.73; F, 21.81; N, 5.35.

3.1.7. 1,1,1,5,5,5-Hexafluoro-4-(1-phenylethylamino)-pent-3-en-2-one (22a) (Scheme 6, Table 4, entry 6). To a solution of trifluoroacetic acid (17.3 g, 0.29 mol) in toluene (40 mL) at room temperature was added phenylethylamine **9a** (34.93 g, 0.29 mol) resulting in a formation

of white precipitate. To a resultant mixture a solution of diketone **8** (50.0 g, 0.24 mol) in toluene (100 mL) was added and the reaction vessel was sealed (we used an autoclave with a Teflon tap). The mixture was heated at 95°C (oil bath) for 9 h. After that, the reactor was cooled down, opened and the solvent was evaporated under reduced pressure. The crude reaction mixture was subjected to a silica gel chromatography (*n*-hexane/AcOEt) to afford the target compound **22a** (48.9 g, 65.4%). ^{1}H NMR δ 11.05 (1H, brs), 7.5–7.2 (5H, m), 5.82 (1H, s), 4.94 (1H, dq, J=10.5, 7.1 Hz), 1.65 (3H, d, J=7.1 Hz). ^{19}F NMR δ −66.0 (CF_3, s), −77.0 (CF_3, s). ^{13}C NMR δ 179.6 (q, J=35.0 Hz), 152.6 (q, J=32.6 Hz), 141.2, 128.9, 128.0, 125.2, 119.0 (q, J=276 Hz), 116.6 (q, J=286 Hz), 85.8 (qm, J=5.1 Hz), 55.6 (q, J=7.6 Hz), 24.2. HRMS calcd for $C_{13}H_{11}F_6NO$ (M+Na) 334.0643. Found: 310.1087.

Enamines **22b**,**d**–**f** were prepared using the standard conditions described for synthesis of **22a**. Isolated yields for products **22b**,**d**–**f** are given in Table 4.

3.1.8. 4-Benzylamino-1,1,1,5,5,5-hexafluoropent-3-en-2-one (22b) (Scheme 6, Table 4, entry 7). ^{1}H NMR δ 10.71 (1H, brs), 7.5–7.2 (5H, m), 5.89 (1H, s), 4.66 (2H, d, J=6.0 Hz). ^{19}F NMR δ −66.6 (CF_3, s), −77.1 (CF_3, s). ^{13}C NMR δ 179.6 (q, J=34.9 Hz), 153.4 (q, J=32.2 Hz), 135.1, 129.0, 128.4, 127.3, 119.0 (q, J=276.4 Hz), 116.5 (q, J=285.5 Hz), 86.1 (qm, J=5.0 Hz), 49.1 (q, J=2.9 Hz). HRMS calcd for $C_{12}H_6F_6NO$ (M+Na) 320.0486. Found: 320.0667.

3.1.9. 1,1,1,5,5,5-Hexafluoro-4-(4-trifluoromethylbenzylamino)pent-3-en-2-one (22d) (Scheme 6, Table 4, entry 8). ^{1}H NMR δ 10.72 (1H, brs), 7.67 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.4 Hz), 5.94 (1H, s), 4.72 (2H, d, J=6.3 Hz). ^{19}F NMR δ −62.6 (CF_3, s), −66.5 (CF_3, s), −77.1 (CF_3, s). ^{13}C NMR δ 180.1 (q, J=34.9 Hz), 153.6 (q, J=32.2 Hz), 139.4, 130.7 (q, J=32.6 Hz), 127.4, 126.0 (q, J=3.8 Hz), 123.8 (q, J=269.8 Hz), 119.0 (q, J=276.0 Hz), 116.4 (q, J=285.8 Hz), 86.7 (qm, J=5.0 Hz), 48.4 (q, J=2.9 Hz). HRMS calcd for $C_{13}H_8F_9NO$ (M+Na) 388.03598. Found: 388.056.

3.1.10. 1,1,1,5,5,5-Hexafluoro-4-(4-nitrobenzylamino)-pent-3-en-2-one (22e) (Scheme 6, Table 4, entry 9). Mp 53–54°C. ^{1}H NMR δ 10.66 (1H, brs), 8.20 (2H, d, J=8.9 Hz), 7.40 (2H, d, J=8.9 Hz), 5.89 (1H, s), 4.70 (2H, d, J=6.9 Hz). ^{19}F NMR δ −66.4 (CF_3, s), −77.1 (CF_3, s). ^{13}C NMR δ 180.2 (q, J=35.6 Hz), 153.4 (q, J=32.6 Hz), 147.7, 142.5, 127.8, 124.2, 118.9 (q, J=276.1 Hz), 116.2 (q, J=285.5 Hz), 87.1 (qm, J=5.0 Hz), 48.1 (q, J=2.9 Hz). HRMS calcd for $C_{12}H_8F_6N_2O_3$ (M+Na) 365.03368. Found: 365.0149.

3.1.11. 4-(Benzhydrylamino)-1,1,1,5,5,5-hexafluoropent-3-en-2-one (22f) (Scheme 6, Table 4, entry 10). ^{1}H NMR δ 11.34 (1H, brd, J=7.8 Hz), 7.5–7.2 (10H, m), 6.00 (1H, d, J=10.5 Hz), 5.91 (1H, s). ^{19}F NMR δ −65.7 (CF_3, s), −77.0 (CF_3, s). ^{13}C NMR δ 180.0 (q, J=34.9 Hz), 152 (q, J=32.6 Hz), 139.8, 137.4, 132.2, 129.9, 128.9, 128.1, 128.1, 126.6, 119.0 (q, J=277 Hz), 116.5 (q, J=285.9 Hz), 86.5 (qm, J=5.0 Hz), 63.1 (q, J=2.6 Hz). HRMS calcd for $C_{18}H_{13}F_6NO$ (M+Na) 396.0799. Found: 396.0533.

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