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Preparation of Fluoroalkyl Imines, Amines, Enamines, Ketones, α-Amino Carbonyls, and α-Amino Acids from Primary Enamine Phosphonates†

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A simple method for preparation of fluoroalkyl β-enaminophosphonates **1** from alkylphosphonates **2** and perfluoroalkyl nitriles **3** is reported. Olefination reaction of functionalized phosphates **1** with aldehydes gives α,β-unsaturated imines **5**. Acid hydrolysis of these fluoroalkyl derivatives **5** affords α,β-unsaturated ketones **6,** while their selective reduction with hydrides leads to the formation of allylamines **7**, enamines **8,** and saturated ketones **9** or amines **10**. Selective oxidative cleavage of the carbon−carbon double bond of allylamines **7** gives fluorinated α-amino aldehydes **12**, α-amino ketones **13**, or α-amino acid derivatives **14**.

Introduction

The development of efficient and mild methods for organofluorine compound synthesis represents a broad area of organic chemistry since the incorporation of a fluorine-containing group into an organic molecule dramatically alters its physical, chemical, and biological properties.[1] These changes in properties make them suitable for diverse applications in synthetic, agricultural, and medicinal chemistry as well as in materials science.[2] Among them, special interest has been focused in developing synthetic methods for the preparation of fluorinated building blocks since they can be used for the efficient and/or selective preparation of fluorine-containing molecules with biological activity and commercial applications.[3]

Moreover, enamines have attracted a great deal of attention in recent years because of their range of applications,[4,5] and especially metaloenamines,[6] carbanions derived from enamines or enolizable imines, are useful substrates for the regio- and stereoselective carbon−carbon bonds formation reaction with electrophilic reagents.[7,8] However, primary enamines, despite their potential interest as synthons in organic synthesis for the preparation of acyclic and cyclic derivatives, have been less studied, given that they are not stable unless conjugated with an electron-withdrawing group on the β-carbon atom.[9] In this context, we have used functionalized aminophosphorus derivatives for the preparation of three-,[10] five-,[11] and six-membered[12] phosphorus-substituted nitrogen heterocycles, as well as the synthesis of stable primary enamines[13] derived from phosphonates and phosphazenes in the β position and their synthetic

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use for the preparation of functionalized acyclic compounds[14] and phosphorus-containing heterocycles.[15] With this in mind, we are interested in the design of stable primary β-enaminophosphonates containing fluoroalkyl substitents for the following reasons: (a) these primary enamines contain a stabilizing group, the phosphonate in the β position, that could favor the isolation and stabilization of the primary enamine;[9] (b) these reagents could be very interesting synthons for the preparation of heterocycles in a way similar to that described for enamines;[5,6] (c) the presence of the phosphonyl group opens up the possibility of the use of these substrates for olefination reactions (Wadsworth−Emmons reaction), and therefore, they might be used as building blocks for the stereoselective carbon−carbon double bond construction;[16] (d) phosphorus substituents could regulate important biological functions and increase biological activity, in a way similar to that reported for pharmaceuticals;[17] (e) the α-fluoroalkyl group could affect to the stability of the primary enamine group. Moreover, as far as we know, only β-fluoro-substituted primary enamines,[18a,b] α,β-fluorodisubstituted primary enamines,[18c] and three types of α-fluoro substituted primary enamines containing a sulfinyl,[19a] an alkoxycarbonyl,[19b−e] and a carbonyl group[19f,g] have been reported, and one example of preparation of a fluorinated primary enamine containing a phosphonate group by reaction of 1,2,3,3,3-pentafluoropropenyl phosphonates with ammonia has been described.[19h]

Continuing with our interest in the design of new phosphorus-substituted building blocks and in this case containing also fluoroalkyl substituents, we report here an easy and selective synthesis of primary β-enaminophosphonates containing fluoroalkyl substituents in the α position **I** (Figure 1), as well as their use as versatile tools for the formation of fluoro-containing derivatives such as imines **V**, nitrogen derivatives, and α-aminocarbonyl compounds (see Figure 1). Retrosynthetically, we

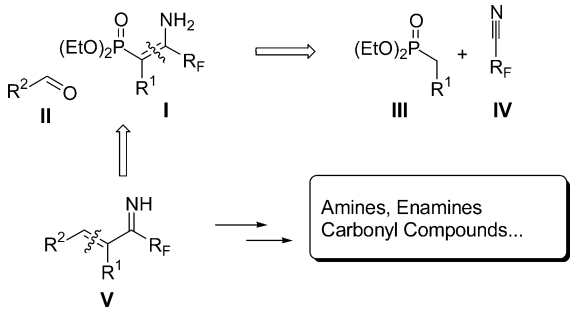
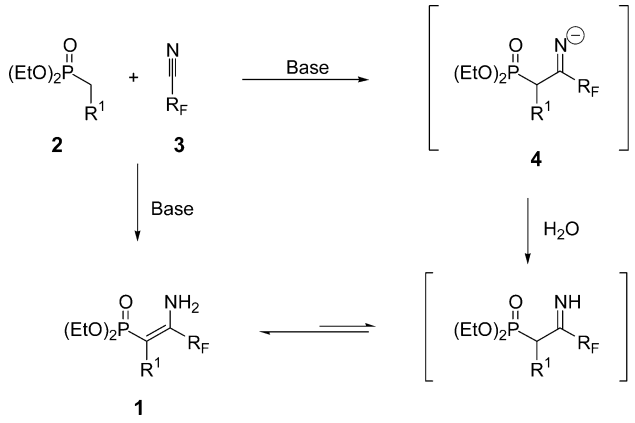


FIGURE 1. Design and synthetic strategy.

SCHEME 1. Synthesis of β-Enaminophosphonates 1



envisaged obtaining primary enamines **I** through simple addition of fluoroalkyl nitriles **IV** to metalated alkyl phosphonates in a way similar to that reported for simple primary enamines derived from phosphazenes and phosphonates.[13] Olefination reaction of enamines **I** with aldehydes **II** and the use of α,β-unsaturated imines **V** as intermediates for the preparation of fluoroalkyl substituted saturated and allylamines, enamines, saturated and unsaturated ketones, α-amino-aldehydes, α-aminoketones, and α-amino acids is also explored.[20]

Results and Discussion

Synthesis of (*Z*)-Primary β-Enaminophosphonates 1 from Phoshonates 2 and Fluoroalkylnitriles 3. We first explored the preparation of the (*Z*)-primary β-enaminophosphonates **1**. Reaction of fluoroalkylnitriles **3**[21] (R^1 = CF_3, C_2F_5, C_7F_{15}, CH_2F) with diethyl alkylphosphonates **2** (R^1 = H, CH_3) in the presence of base (MeLi or LDA)[22] in an inert atmosphere gave after workup trifluoromethyl-substituted β-enaminephosphonates **1** (Scheme 1) in good yields (see Table 1, entries 1−6), in a way similar to that previously reported for other phosphorus derivatives.[13] Spectroscopic data are consistent

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(21) $C_7F_{15}CN$ was purchased from Lancaster, and FCH_2CN was purchased from Aldrich. However, CF_3CN and C_2F_5CN were freshly prepared by dehydration of the corresponding amides (CF_3CONH_2, $C_2F_5CONH_2$): Reisner, D. B.; Horning, E. C. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 144−145.

(22) CF_3CN and C_2F_5CN are gases and were bubbled though the solution of phosphonates **2** in the presence of MeLi. However, C_7F_{15}-CN and FCH_2CN are liquid and were added to the solution of phosphonates **2** in the presence of LDA.

TABLE 1. Synthesis of Fluorinated Primary Enaminophosphonates 1

entry	compd	R^1	R_F	base	yield[a] (%)
1	**1a**	H	CF_3	MeLi	81
2	**1b**	H	C_2F_5	MeLi	85
3	**1c**	H	C_7F_{15}	LDA	87
4	**1d**	H	CH_2F	LDA	79
5	**1e**	CH_3	CF_3	MeLi	42
6	**1f**	CH_3	C_7F_{15}	LDA	82

[a] Yields refer to isolated compounds.

with the proposed structure and indicate that they were isolated as the *Z*-isomers. Thus, for compound **1a**, only one signal was observed in ^{31}P (δ_P = 21.9 ppm) and ^{19}F NMR (δ_P = −104.8 ppm). Likewise, in the ^1H NMR spectrum a well-resolved doublet at δ_H = 4.34 ppm ($^2J_{PH}$ = 8.7 Hz) for the vinylic proton was observed, while the ^{13}C NMR spectrum showed absorptions at δ_C = 77.0 ppm ($^1J_{PC}$ = 192.9 Hz, $^3J_{FC}$ = 3.6 Hz, $^2J_{PC}$ = 5.6 Hz) and at δ_C = 149.5 ppm ($^2J_{PC}$ = 33.2 Hz, $^2J_{FC}$ = 7.6 Hz) for vinylic carbon atoms, and at δ_C = 120.0 ppm ($^1J_{FC}$ = 276.4 Hz, $^3J_{PC}$ = 28.7 Hz) for the fluoromethyl group. $^{13}C-^{31}P$ coupling constant ($^3J_{PC}$) in the range of 25−30 Hz showed that the fluoro-substituted alkyl group (R_F) and the phosphorus atom in enamines **1** are related trans.[23]

Formation of primary enamines **1** can be assumed to proceed via protonation of ketimino intermediates **4**, followed by prototropic tautomerization of β-iminophosphonates (Scheme 1). The scope of the reaction was not limited to α-trifluoromethylenamines **1a**,**e** ($R_F = CF_3$) (see Table 1, entries 1, 5), since perfluoroalkyl- **1b** ($R_F = C_2F_5$), **1c**,**f** ($R_F = C_7F_{15}$) (see Table 1, entries 2, 3, and 6), and α-monofluoromethylenamines ($R_F = CH_2F$) **1d** (see Table 1, entry 4) were also prepared.

Synthesis of N-Nonsubstituted Fluoroalkyl α,β-Unsaturated Imines 5 and α,β-Unsaturated Ketones 6. α,β-Unsaturated fluroalkyl ketones are key intermediates in organic synthesis for the preparation of acyclic and heterocyclic derivatives[24] and in medicinal chemistry[25] and have been prepared from boronic acids,[26a] esters,[26b,c] enamines,[26d−f] tellurides,[26g] or from trifluoromethyl ketones.[26h−j] However, while *N*-methyl-[27a,b] and *N*-phenyl-unsaturated[27c,d] imines has been prepared, the N-nonsubstituted fluoroalkyl α,β-unsaturated imines have not been described.[20] With this in mind, we thought that fluorinated unsaturated imines could be prepared from fluoroalkyl substituted primary enamino phosphonates **1** by olefination reaction with aldehydes in a way similar to that reported for other enamines,[8a,c] while fluorinated unsaturated ketones could be prepared by olefination reaction of the same enamines **1** and subsequent acid hydrolysis.

SCHEME 2. Preparation of α,β-Unsaturated Imines 5 and Ketones 6

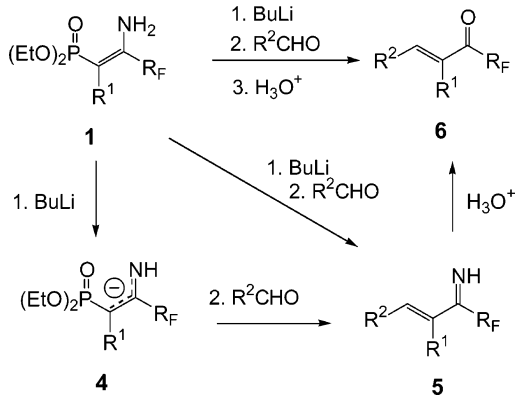

TABLE 2. Preparation of Fluorinated α,β-Unsaturated Imines 5

entry	compd	R^1	R^2	R_F	*E*/*Z* ratio[a]	yield[b] (%)
1	**5a**	H	*p*-CH_3Ph	CF_3	1/2	91 (57)[c]
2	**5b**	H	PhCH=CH	CF_3	1/2	85
3	**5c**	H	2-thienyl	C_2F_5	1/2	83 (51)[c]
4	**5d**	CH_3	*p*-CH_3Ph	CF_3	1/5	87

[a] *E*/*Z* isomer ratio from ^1H NMR. [b] Yields of crude isolated compounds. [c] Yields of pure compounds isolated at reduced pressure (10^{-5} Torr).

Reaction of primary enamines **1a**,**b** (R^1 = H) with butyllithium, followed by the addition of aromatic and heteroaromatic aldehydes, gave N-nonsubstituted fluoroalkyl α,β-unsaturated imines **5** (Scheme 2, Table 2, entries 1−3) in a stereoselective fashion and in good yields. 1-Azabutadienes **5** are unstable, but they can be isolated (see experimental part) and kept in the refrigerator 2−3 days. However, for our subsequent synthetic purposes they can be used without isolation. These imines **5** are obtained as a mixture of *E* and *Z* isomers toward the C=N bouble bond (see Table 2). Vicinal $^3J_{HH}$ coupling constants in the range of 16−17 Hz between the vinylic protons of **5** are consistent with the *E* configuration of the carbon−carbon double bond.[8c,d] The reaction can also be extended to 3-methyl-substituted primary enamine **1e** (R^1= CH_3) to obtain C-3-substituted 1-aza-1,3-butadiene **5d** (see Table 2, entry 4). Formation of compounds **5** can be explained by olefination reaction of enamines **1**.

These results prompted us to extend this reaction and to explore whether fluorinated primary β-enaminophos-

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TABLE 3. Preparation of Fluorinated α,β-Unsaturated Ketones 6

entry	compd	R^1	R^2	R_F	yield[a] (%)
1	**6a**	H	*p*-CH_3Ph	CF_3	76
2	**6b**	H	PhCH=CH	CF_3	84
3	**6c**	H	2-Fur	CF_3	63
4	**6d**	H	*p*-FPh	CF_3	65
5	**6e**	H	c-C_6H_{11}	CF_3	83
6	**6f**	H	*p*-FPh	CH_2F	56[b]
7	**6g**	H	*p*-CH_3Ph	C_2F_5	82
8	**6h**	H	2-thienyl	C_2F_5	64
9	**6i**	CH_3	*p*-CH_3Ph	CF_3	71
10	**6j**	CH_3	2-Fur	CF_3	62
11	**6k**	CH_3	PhCH=CH	CF_3	71

[a] Yields refer to isolated compounds. [b] Yields from phosphonate **2**.

phonates **1** could also be useful intermediates for the preparation of α,β-unsaturated ketones **6**. Treatment of primary enamines **1** with butyllithium, followed by the addition of aldehydes and acid hydrolysis (H_2SO_4 5 M), afforded a stereoselective synthesis of α,β-unsaturated ketones **6a**−**k** (Scheme 2), obtained only as the *E* isomers (see Table 3). Formation of compounds **6** can be explained by olefination reaction of enamines **1**, followed by hydrolysis of the *N*-unsubstituted 1-azadienes **5**. Ketones **6** can also be obtained in "one-pot" reaction from phosphonates **2**, by subsequent addition of base, fluoronitriles, aldehydes, and acid hydrolysis (Table 3, entry 6).

Synthesis of Allylamines 7, Enamines 8, Ketones 9, and Saturated Amines 10. Imines are starting materials for the preparation of amines,[4] and in our case the presence of a conjugate C−C double bond opens the possibility not only of selective 1,2-reduction but also of 1,4-reduction,[28] as well as C−N and C−C double-bond reduction to obtain saturated amines. For this reason, we explored the regioselective reduction of α,β-unsaturated imines **5** because we thought these substrates could be used for the preparation of allylamines, enamines, and saturated amines containing fluoroalkyl-substituted substituents. Fluorinated allylamine derivatives represent an important class of compounds for their pharmacological interest given their activities as irreversible inhibitors of serine proteases[29a] and monoamine oxidases.[29b,c] In this context, secondary trifluoromethyl allylamines have been prepared by Lewis acid-catalyzed addition of acetylenes to trifluoroacetaldehyde *N*,*N*-aminals,[30a] by vinylmagnesium bromide addition to *N*-acylimines derived from trifluoroacetaldehyde generated "in situ"[30b] or by nucleophilic trifluoromethylation of *N*-tosylaldimines[30c] and optically active sulfinyl-aldimine.[30d]

We explored initially the selective 1,2 reduction (C=N) of imines **5**. Sodium borohydride, sodium cyanoborohydride, and DIBAL were studied, and the best results were observed when α,β-unsaturated imines were generated "in situ" from enaminephosphonates **1** and sodium borohydride in methanol at very low temperature (−78 °C) was used. Reaction of primary enamines **1a**−**d** (R^1 = H) with butyllithium, followed by the addition of aromatic and heteroaromatic aldehydes and subsequent treatment of the reaction mixture with $NaBH_4$ in methanol at −78 °C, gave primary fluoroalkyl allylamines **7a**−**f** (Scheme 3) in a stereoselective fashion (1,2-addition) and in good yields (Table 4, entries 1−6). Vicinal $^3J_{HH}$ coupling constants in the range of 16−17 Hz between the vinylic protons of amines **7** are consistent with the *E* configuration of the carbon−carbon double bond. The reaction can also be extended to 3-methyl-substituted primary enamine **1e** ($R^1 = CH_3$) to obtain C-β-substituted allylamine **7g**,**h** (see Table 4, entries 7, 8). From a preparative point of view, it is noteworthy that the synthesis of allylamines **7** does not require the isolation and purification of enamines **1** and that they can be obtained in a "one-pot" reaction from phosphonates **3**, when after the addition of base and fluronitriles **2**, a subsequent addition of aldehydes and hydride is carried out (Table 4, entry 6). Therefore, this procedure is quite general and highly selective affording exclusively the *E* stereoisomer not only of α-trifluoromethyl allylamines **7a**,**b**,**g**,**h** ($R_F = CF_3$), but also of perfluoroalkyl **7c**,**d**,**e** ($R_F = C_nF_{2n+1}$, n = 2, 7) and of α-monofluoromethyl allylamines **7f** ($R_F = CH_2F$).

Subsequently, we studied the selective 1,4 reduction of conjugated imines **5**, because by means of this process we might obtain the until now unknown fluoroalkyl-substituted enamines **8** without stabilizing groups in β position. Lithium aluminum hydride and borane were explored, and the best results were observed when α,β-unsaturated imines **5** were reduced with borane at low temperature. Addittion of BH_3·Me_2S on α,β-unsaturated imines **5** generated "in situ" from primary enamines **1a**,**b**

SCHEME 3. Reactivity of α,β-Unsaturated Imines 5

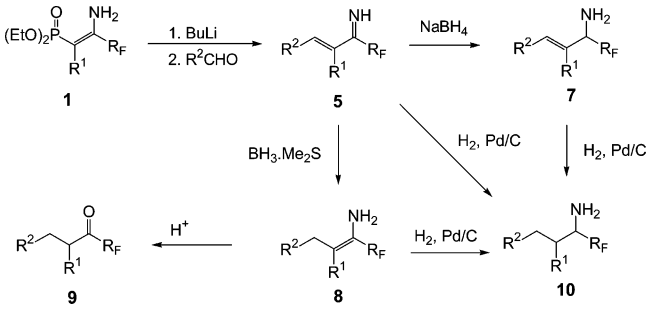

TABLE 4. Preparation of Fluorinated Allyl Amines 7

entry	compd	R^1	R^2	R_F	yield[a,b] (%)
1	**7a**	H	*p*-CH_3Ph	CF_3	65
2	**7b**	H	PhCH=CH	CF_3	54
3	**7c**	H	*p*-CH_3Ph	C_2F_5	73
4	**7d**	H	*p*-FPh	C_2F_5	52
5	**7e**	H	PhCH=CH	C_7F_{15}	54
6	**7f**	H	*p*-FPh	CH_2F	57[c]
7	**7g**	CH_3	*p*-CH_3Ph	CF_3	71
8	**7h**	CH_3	2-Fur	CF_3	53

[a] Yields refer to isolated compounds. [b] Yields from enamines **1**. [c] Yields from phosphonates **3** ("one-pot" procedure).

(28) For an example of selective 1,2- and 1,4-addition of organolithium reagents to unsaturated aldimines, see: Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K. *J. Org. Chem.* **2001**, *66*, 7051 and references cited therein.

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TABLE 5. Preparation of Fluorinated Enamines 8

entry	compd	R^1	R^2	R_F	**7/8** ratio[a]	yield[b] (%)
1	**8a**	H	*p*-CH_3Ph	CF_3	10/90	53[c,d] (58)[d,e]
2	**8b**	H	PhCH=CH	CF_3	34/66	30[c,f]
3	**8c**	H	2-thienyl	C_2F_5	5/95	41[c,f]
4	**8d**	CH_3	*p*-CH_3Ph	CF_3	10/90	31[c,f]
5	**8e**	CH_3	2-Fur	CF_3	17/83	23[c,f]

[a] Calculated from ^{1}H and ^{19}F NMR spectra of crude reaction mixture. [b] Yields refer to isolated compounds. [c] Yields of compound **8** from enamines **1**. [d] Purified by column chromatography. [e] Yield of compounds **8** from imines **5**. [f] Purified by vacuum distillation (10^{-5} Torr).

TABLE 6. Preparation of Fluorinated Saturated Ketones 9 and Amines 10

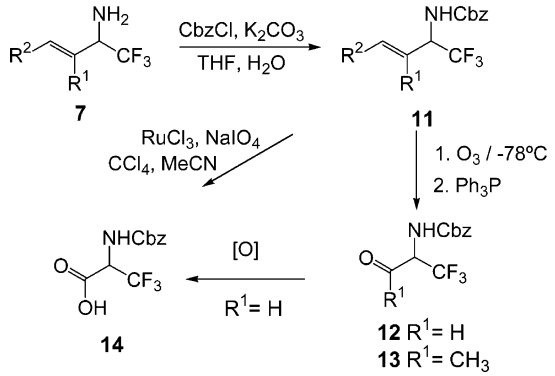
entry	compd	R^1	R^2	R_F	yield[a] (%)
1	**9a**	H	*p*-CH_3Ph	CF_3	65
2	**9b**	H	PhCH=CH	CF_3	60
3	**9c**	H	2-thienyl	C_2F_5	53
4	**10a**	H	*p*-CH_3Ph	CF_3	82[b] (65)[c] (75)[d] (69)[e]
5	**10b**	H	*p*-FPh	C_2F_5	77[b]
6	**10c**	CH_3	*p*-CH_3Ph	CF_3	82[b] (75)[d] (69)[e]

[a] Yields refer to isolated compounds. [b] Yields of compound **10** from allylamine **7**. [c] Yields of compound **10** from enamine **8**. [d] Yields of compound **10** from unsaturated imines **5**. [e] Yields of compound **7** from enamines **1**.

(R^1 = H) led to the formation (1,4-addition) of primary fluoroalkyl enamines **8a**−**e** (Scheme 3) as major products (Table 5, entries 1−5), with a small proportion of allylamines **7** (1,2-addition). Both products can be separated and isolated through column chomatography or distillation at reduced pressure (10^{-5} Torr). A similar yield was obtained when the process was performed with α,*β*-unsaturated imine **5a** (see Table 5, entry 1). Spectroscopic data are consistent with the proposed structure and indicate that enamines **8** were isolated as the *Z*-isomers on the basis of NOE experiments. Thus, in mass spectrometry compound **8a** showed the molecular ion (*m/e* 215, 54%) and only one signal was observed in ^{19}F NMR (δ_P = −71.2 ppm) for this compound **8a**. Likewise, the ^{1}H NMR spectrum showed a triplet at δ_H = 5.16 ppm ($^3J_{HH}$ = 7.3 Hz) for the vinylic proton, while in the ^{13}C NMR spectrum absorptions at δ_C = 104.7 ppm and at δ_C = 131.3 ppm ($^2J_{FC}$ = 31.7 Hz) for vinylic carbon atoms were observed. As far as we know, this process represent the first synthesis of fluoroalkyl enamines **8** without an electron withdrawing group in *β* position. In this case, fluoroalkyl group in α seems to stabilize the primary enamino group of these substrates.

These compounds **8** can be used as starting material for the preparation of saturated ketones. Acid hydrolysis of enamines **8** (Scheme 3) with 5 M H_2SO_4 in ether and at room temperature gave fluoroalkyl-substituted ketones **9** (see Table 6, entries 1−3). Moreover, not only allylamines **7** but also enamines **8** can be used for the preparation of saturated fluoroalkylamines **10** (Scheme 3). Selective reduction of the C−C double bond of allylamines **7** can be achieved at room temperature by its catalytic reduction in the presence of palladium on carbon and acetic acid as solvent, and saturated fluoroalkylamines **10** are obtained (see Table 6, entries 4−6). Likewise, saturated amines can also be prepared by catalytic reduction (Pd/C) either of enamines **8** in ethanol (see Table 6, entry 4) or of α,*β*-unsaturated imines **5** (see Table 6, entries 4, 6). Amines **10** can also be obtained in a "one-pot" reaction from phosphonates **1**, by subsequent addition of base, aldehydes, and catalytic reduction of the C−C double bond (see Table 6, entries 4, 6). Therefore, not only *β*-enamino phosphonates **1**, but also unsaturated imines **5** can be synthetic intermediates (Scheme 3) for the preparation of allylamines **7**, enamines **8,** saturated fluoroalkyl ketones **9**, and amines **10**.

SCHEME 4. Preparation of α-Aminocarbonyl Derivatives 12−14



Synthesis of Fluoroalkyl Substituted α-Aminoaldehydes 12, -ketones 13, and -acids 14. Fluorinated allylamines **7** can be used as building blocks for the preparation of fluorine-containing α-amino-carbonyl compounds and α-amino acids by oxidative cleavage reaction of the carbon−carbon double bond. Allylamines **7a** (R^1 = H) and **7g** (R^1 = CH_3) were converted into the benzyl carbamates **11** by reaction with benzyl chloroformiate, and then the double bond of C-*β*-unsubstituted allylamine **11a** (R^1 = H) was selectively cleaved by ozonolysis (O_3) in the presence of triphenylphosphine at low temperature (−78 °C) to give the *N*-Cbz α-amino aldehyde containing a trifluoromethyl group in the α position **12** (R^1 = H)[31] in good yields (73%). Similarly, the oxidation of *N*-protected (Cbz) allylamine containing a methyl group in the *β* position **7g** (R^1 = CH_3) with ozone and triphenylphosphine led to the formation of fluorinated α-amino ketone **13** (R^1 = CH_3) (82%). However, when the double bond was cleaved using the Sharpless ($RuCl_3$-sodium periodate) method[32] the corresponding *N*-Cbz α-amino acid **14** was obtained (65%) (Scheme 4). Fluorine-containing amino acids and aldehydes are important compounds in organic synthesis and in medicinal chemistry[3a,b] and several methods of preparation of these compounds have been described in recent years.[3a,b,33,34] However, as far as we know, only one example of synthesis of an alkyl α-fluoroalkyl α-amino ketone[35] have been described.

(31) The oxidation of the α-amino aldehyde to the corresponding α-amino acid takes place very easily in the presence of air.

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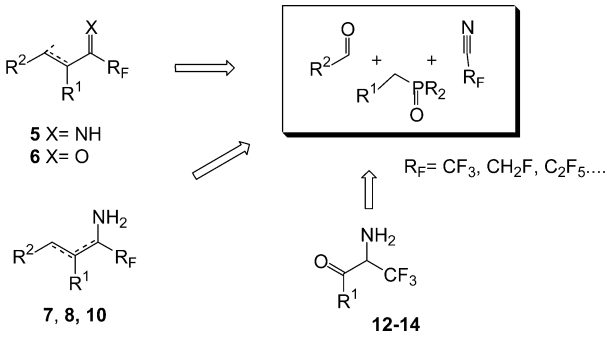
SCHEME 5. Synthetic Applications of β-Enaminephosphonates or of Their Precursors (Fluoronitriles and Phosphonates)



Conclusions

In conclusion, the first synthesis of fluoroalkyl N-nonsubstituted α,β-unsaturated imines **5** (X = NH) is described. The process involves the olefination reaction of easily available β-enaminephosphonates with aldehydes and under mild reaction conditions or the reaction of fluoronitriles and alkyl phosphonates in the presence of base and subsequent addition of aldehydes (Scheme 5). These imines **5** (X = NH) are versatile intermediates for the preparation of fluorinated α,β-unsaturated ketones **6** (X = O), as well as for the synthesis of nitrogen derivatives such as allylamines **7**, primary enamines **8**, saturated amines **10**, and α-amino carbonyl derivatives **12**−**14**. Simple fluorinated building blocks are useful compounds not only for their application in organic synthesis[2,3] but also for their biological activities.[1−3] These results may expand the scope and potential of fluorine preparative organic synthesis.

Experimental Section

General Procedure for Preparation of Fluorinated β-Enaminophosphonates (1). A solution of diethylphosphonate **2** (5 mmol) in THF (10 mL) was added to a solution of base (MeLi or LDA) (5 mmol) in THF (15 mL) at −78 °C and under N_2 atmosphere. The mixture was stirred for 1 h at −78 °C. Then the corresponding fluorinated nitrile **3** was added into the solution. The reaction was allowed to warm to room temperature. The resulting mixture was washed three times with water (20 mL), extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

Diethyl 2-amino-2-trifluoromethylethenylphosphonate (1a) (1.00 g, 81%) obtained as a white solid: mp 63−65 °C; IR (KBr) 3348, 3206, 1217, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (bs, 2H, NH_2), 4.34 (d, J = 8.7 Hz, 1H, CH), 3.96 (m, 4H, OCH_2), 1.25 (m, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5 (dq, J = 33.2, 7.6 Hz, C−N), 120.0 (dq, J = 276.4, 28.7 Hz, CF_3), 77.0 (d, J = 192.6 Hz, CH), 61.6 (OCH_2), 16.1 (CH_3); ^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3. Anal. Calcd for $C_7H_{13}F_3NO_3P$: C, 34.02; H, 5.30; N, 5.67. Found: C, 34.14; H, 5.25; N, 5.73.

General Procedure for the Preparation of Fluorinated α,β-Unsaturated Imines (5). Butyllithium (1.6 M in hexanes) (2 mmol) was added to a solution of fluorinated enaminophosphonate **1** (5 mmol) in THF at 0 °C and under N_2 atmosphere. The mixture was stirred for 1 h at the same temperature. Then, a solution of the corresponding aldehyde (2 mmol) in THF (15 mL) was added, and the reaction was stirred at room temperature until TLC showed the disappearance of the enaminophosphonate **1**. The resulting mixture was extracted with CH_2Cl_2 and filtered through Celite and concentrated under vacuum. 1-Azabutadienes **5** are unstable, but they can be isolated and kept in the refrigerator for 2−3 days.

4-*p*-Tolyl-2-trifluoromethyl-1-aza-1,3-butadiene (5a) (388 mg, 91%) obtained as a pale yellow oil: bp 40−41(10^{-5} Torr); IR (neat) 3293, 2981, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.45 (bs, 1H, NH), 10.31 (bs, 1H, NH), 7.59 (d, J = 16.5 Hz, 1H, =CH), 7.43−7.36 (m, 5H, =CH, H_{ar}), 7.17 (d, J = 7.8 Hz, 4H, H_{ar}), 6.82 (d, J = 16.5 Hz, 1H, =CH), 6.58 (d, J = 16.6 Hz, 1H, =CH), 2.35 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (q, J = 31.7 Hz, C=N), 162.2 (q, J = 31.7 Hz, C=N), 141.1 (CH), 140.9 (Car-C), 140.5, 139.9 (=CH), 132.0 (Car-C), 131.4, 129.6 (Car-C), 129.5, 127.8, 127.7, 120.1 (q, J = 279.5 Hz, CF_3), 118.2 (q, J = 281.5 Hz, CF_3), 118.1 (=CH), 117.6, 21.2 (2 × CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.9, −72.2; MS(EI) m/z 214 (M^+ + 1, 100).

General Procedure for the Preparation of Fluorinated α,β-Unsaturated Ketones (6). Butyllithium (1.6 M in hexanes) (5 mmol) was added to a solution of fluorinated enaminophosphonate **1** (5 mmol) in THF at 0 °C and under N_2 atmosphere. The mixture was stirred for 1 h at the same temperature. Then, a solution of the corresponding aldehyde (5 mmol) in THF (15 mL) was added, and the reaction was stirred at room temperature until TLC showed the disappearance of the enamino phosphonate **1**. A solution of H_2SO_4 5 M (3 mL) was added, and the reaction was stirred for 1 h. The organic layer was extracted with Et_2O, washed with water, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

(*E*)-1,1,1-Trifluoro-4-*p*-tolyl-3-buten-2-one (6a) (325 mg, 76%) obtained as a pale yellow oil: R_f 0.87 (ethyl acetate); IR (neat) 2936, 1598, 1194 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 15.9 Hz, 1H, CH), 7.48−7.17 (m, 4H, H_{arom}), 6.91 (d, J = 15.9 Hz, 1H, =CH), 2.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9 (q, J = 34.7 Hz, C=O), 150.2 (=CH), 143.5 (C_{arom}), 130.3−129.3 (C_{arom}), 116.4 (q, J = 290.5 Hz, CF_3), 115.5 (CH), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.3. Anal. Calcd for $C_{11}H_9F_3O$: C, 61.68; H, 4.20. Found: C, 61.65; H, 4.14.

General Procedure for the Preparation of Fluorinated Allylic Amines (7). Butyllithium (1.6 M in hexanes) (5 mmol) was added to a solution of fluorinated enaminophosphonate **1** (5 mmol) in THF at 0 °C and under N_2 atmosphere. The mixture was stirred for 1 h at the same temperature. Then, a solution of the corresponding aldehyde (5 mmol) in THF (15 mL) was added, and the reaction was stirred at room temperature until TLC showed the disappearance of the enaminophosphonate **1**. The reaction was cooled to −78 °C, and $NaBH_4$ (10 mmol) and MeOH (25 mL) were added. After 1 h at −78 °C, the mixture was warmed to rt, 3% HCl (15 mL) was added, and stirring was continued for 1 h. The mixture was made alkaline (pH 12) with NaOH pellets and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

1,1,1-Trifluoro-4-*p*-tolyl-3-buten-2-amine (7a) (322 mg, 75%) obtained as a pale yellow oil: R_f 0.85 (ethyl acetate); IR (neat) 3371, 3294, 2927, 1121 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 15.9 Hz, 1H, CH), 7.11−7.24 (m, 4H, H_{arom}), 6.67 (d, J = 16.1 Hz, 1H, CH), 6.03 (dd, J = 16.1, 6.5 Hz, 1H, CH), 3.87 (m, 1H, CH), 2.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.1−138.3 (C_{arom}), 55.9 (q, J = 30.2 Hz, CH), 21.1 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.1. Anal. Calcd for $C_{11}H_{12}F_3N$: C, 61.39; H, 5.62; N, 6.51. Found: C, 61.47; H, 5.67; N, 6.59.

General Procedure for the Preparation of Fluorinated Enamines (8). Butyllithium (1.6 M in hexanes) (2 mmol) was added to a solution of fluorinated enaminophosphonate **1** (2 mmol) in THF at 0 °C and under N_2 atmosphere. The mixture was stirred for 1 h at the same temperature.

Then, a solution of the corresponding aldehyde (2 mmol) in THF (6 mL) was added, and the reaction was stirred at room temperature until TLC showed the disappearance of the enamino phosphonate **1**. The reaction was cooled to −78 °C, BH_3·SMe_2 1.0 M in CH_2Cl_2 (2.22 mL, 2.22 mmmol) was added, and the reaction was stirred at −78 °C until TLC showed the disappearance of the α,β-unsaturated imine **5**. A solution of $NaHCO_3$ (10 mL) was added, and the reaction was warmed to rt. The organic layer was extracted with Et_2O, washed with water, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. The crude product was purified by vacuum distillation or by chromatography using silica gel (hexane/ethyl acetate).

1,1,1-Trifluoro-4-*p*-tolyl-2-buten-2-amine (8a) (228 mg, 53%) obtained as a pale yellow oil: R_f 0.62 (hexane/ethyl acetate,7/3); IR (neat) 3463, 3378, 2923, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.00−7.06 (m, 4H, H_{arom}), 5.16 (t, J = 7.3 Hz, 1H, =CH), 3.22 (d, J = 7.3 Hz, 2H, CH_2), 3.13 (bs, 2H, NH_2), 2.25 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 135.9 (C_{arom}), 131.3 (q, J = 31.7 Hz, =C), 129.3 (C_{arom}), 128.0, 122.0 (q, J = 272.4 Hz, CF_3), 104.7 (=CH), 30.6 (CH_2), 20.9 (CH_3); ^{19}F NMR (282 MHz, CD_3OD) δ −71.2. Anal. Calcd for $C_{11}H_{12}F_3N$: C, 61.39; H, 5.62; N, 6.51. Found: C, 61.58; H, 5.55; N, 6.39.

General Procedure for the Preparation of Fluorinated Saturated Ketones (9). A solution of H_2SO_4 5M (0.5 mL) was added to a solution of fluorinated enamine **8** (1 mmol) in Et_2O The mixture was stirred for 2 h at room temperature. The organic layer was extracted with Et_2O (3 × 10 mL), washed with water, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

1,1,1-Trifluoro-4-*p*-tolyl-2-butanone (9a) (140 mg, 65%) obtained as a pale yellow oil: R_f 0.52 (hexane/ethyl acetate,7/3); IR (neat) 3013, 1750, 1120 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.01−7.11 (m, 4H, H_{arom}), 2.87−2.96 (m, 4H, 2 × CH_2), 2.24 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 190.7 (q, J = 35.2 Hz, C=O), 135.2 (C_{arom}), 129.3 (C_{arom}), 128.1, 115.5 (q, J = 292.1 Hz, CF_3), 38.1(CH_2), 27.8 (CH_2), 20.8 (CH_3); ^{19}F NMR (282 MHz, CD_3OD) δ −79.6. Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 61.42; H, 5.06.

General Procedure A for the Preparation of Fluorinated Saturated Amines (10). To a solution of corresponding fluorinated allylic amine **7** (1 mmol) and Pd/C (0.1 mmol) in acetic acid (6 mL) was applied 80 psi of hydrogen, and the reaction mixture was stirred until TLC showed the disappearance of the allylic amine **7**. A saturated solution of Na_2CO_3 (15 mL) was added, and the reaction was filtrated through Celite. The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. The crude product was purified by by chromatography using silica gel (ethyl acetate).

General Procedure B for Preparation of Fluorinated Saturated Amines (10) from α,β-Unsaturated Imine (5). To a solution of corrresponding α,β-unsaturated imine **5** (1 mmol) and Pd/C (0.1 mmoles) in ethanol (6 mL) was applied 80 psi of hydrogen, and the reaction was stirred until TLC showed the disappearance of the imine **5**. Then the reaction was filtrated through Celite, and the solvent was evaporated under vacuum. The crude product was purified by vacuum distillation or by chromatography using silica gel (ethyl acetate) to afford compounds **10**.

1,1,1-Trifluoro-4-*p*-tolyl-2-butanamine (10a). The general procedure A was followed using 1,1,1-trifluoro-4-*p*-tolyl-3-buten-2-amine **7a**. Chromatographic purification gave 178 mg (82%) of compound **10a** as a pale yellow oil: R_f 0.41 (hexane/ethyl acetate,7/3); IR (neat) 3406, 3330, 2925, 1121 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.02 (s, 4H, H_{arom}), 2.97−3.04 (m, 1H, CH), 2.74−2.83 (m, 1H, CH_2), 2.56−2.66 (m, 1H, CH_2), 2.24 (s, 3H, CH_3), 1.88−2.00 (m, 1H, CH_2), 1.51−1.64 (m, 1H, CH_2), 1.18 (bs, 2H, NH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 137.7 (C_{arom}), 135.6, 129.2 (C_{arom}), 128.3, 126.8 (q, J = 281.5 Hz, CF_3), 52.9 (q, J = 28.7 Hz, C-CF_3), 31.4(CH_2), 31.1 (CH_2), 20.9 (CH_3); ^{19}F NMR (282 MHz, CD_3OD) δ −79.2. Anal. Calcd for $C_{11}H_{14}F_3N$: C, 60.82; H, 6.50; N, 6.45. Found: C, 60.55; H, 6.44; N, 6.56.

General Procedure for the Preparation of Benzyloxycarbonyl Allylamines (11). $NaHCO_3$ (92 mg, 1.1 mmol) was added to a solution of corresponding allylamines **7** (1 mmol) in THF (4 mL) at 0 °C. Then a solution of benzyl chloroformiate (0.20 mL, 1.35 mmol) in THF (4 mL) was added by dripping. The reaction was stirred at room temperature until TLC showed the disappearance of the allylamines **7**. The organic layer was extracted with ethyl acetate (2 × 50 mL), washed with saturated solution of NaCl, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

***N*-Benzyloxycarbonyl-1,1,1-trifluoro-4-*p*-tolyl-3-buten-2-amine (11a).** The general procedure was followed using 1,1,1-trifluoro-4-*p*-tolyl-3-buten-2-amine **7a**. Chromatographic purification gave 283 mg (81%) of compound **11a** as a white solid: R_f 0.58 (hexane/ethyl acetate,7/3); mp 142−144 °C; IR (neat) 3296, 3036, 2964, 1695, 1541, 1244 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.36 (s, 5H, H_{arom}), 7.27 (d, J = 8.1 Hz, H_{arom}), 7.14 (d, J = 8.1 Hz, H_{arom}), 6.71 (d, J = 15.9 Hz, 1H, =CH), 6.04 (dd, J = 15.9, 6.1 Hz, 1H, =CH), 5.04−5.11 (m, 2H, NH, CHCF), 2.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 155.5 (C=O), 138.6 (C_{arom}), 135.7(=C), 132.5, 129.3 (C_{arom}), 128.5, 128.3, 128.1, 126.6, 124.4 (q, J = 282.0 Hz, CF_3), 117.8 (=C), 67.6 (CH_2O), 54.7 (q, J = 31.7 Hz, CH−NH_2), 21.1 (CH_3); ^{19}F NMR (282 MHz, CD_3OD) δ -76.4. Anal. Calcd for $C_{19}H_{18}F_3NO_2$: C, 65.32; H, 5.19; N, 4.01. Found: C, 65.45; H, 5.14; N, 4.06.

General Procedure for the Preparation of Fluoroalkyl-Substituted α-Aminoaldehyde (12) and Ketone (13). O_3 was bubbled through a solution of corresponding benzyloxycarbonyl allylamines **11** (1 mmol) in CH_2Cl_2 (16 mL) and methanol (4 mL) at −78 °C until TLC showed the disappearance of the allylamines **11**. Then PPh_3 (1 mmol) in THF (4 mL) was added. The reaction was stirred for 2 h at room temperature. The solvent was evaporated under vacuum, and the crude product was purified by chromatography using silica gel (hexane/ethyl acetate). α-Aminoaldehyde **12** and ketone **13** are unstable and can be oxidized to compound **14** very easily in the presence of air.

2-(*N*-Benzyloxycarbonylamino)-3,3,3-trifluoropropanal (12). The general procedure was followed using *N*-benzyloxycarbonyl-1,1,1-trifluoro-4-*p*-tolyl-3-buten-2-amine **11a**. Chromatographic purification gave 190 mg (73%) of compound **12** as a pale yellow oil: R_f 0.11 (hexane/ethyl acetate,7/3); IR (neat) 3310, 2964, 1723, 1692, 1537, 1184 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 9.69 (s, 1H, CHO), 7.25−7.35 (m, 5H, H_{arom}), 5.15 (s, 2H, CH_2), 4.16−4.45 (m, 1H, CH−CF_3); ^{13}C NMR (75 MHz, CD_3OD) δ 190.1 (C=O), 155.5 (COO), 135.3 (C_{arom}), 128.6 (C_{arom}), 128.5, 128.2, 120.7 (q, J = 283.0 Hz, CF_3), 68.1 (CH_2O), 61.5 (q, J = 29.7 Hz, CH−NH); ^{19}F NMR (282 MHz, CD_3OD) δ −71.3.

3-(*N*-Benzyloxycarbonylamino)-4,4,4-trifluoro-2-butanone (13). The general procedure was followed using *N*-benzyloxycarbonyl-1,1,1-trifluoro-3-methyl-4-*p*-tolyl-3-buten-2-amine **11b**. Chromatographic purification gave 225 mg (82%) of compound **13** as a white solid: R_f 0.48 (hexane/ethyl acetate,7/3); mp 105−106 °C; IR (neat) 3314, 2966, 1732, 1695, 1541 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.36 (s, 5H, H_{arom}), 5.78 (bs, 1H, NH), 5.15 (s, 2H, CH_2), 5.06 (q, J = 7.3 Hz, 1H, CH), 2.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 197.2 (C=O), 155.6 (COO), 135.3 (C_{arom}), 128.5 (C_{arom}), 128.3, 128.1, 122.7 (q, J = 283.0 Hz, CF_3), 67.7 (CH_2O), 60.9 (q, J = 30.7 Hz, CH), 28.7 (CH_3); ^{19}F NMR (282 MHz, CD_3OD) δ −71.6. Anal. Calcd for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39; N, 5.09. Found: C, 52.51; H, 4.28; N, 5.17.

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Supporting Information Available: Experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, IR, and ^{19}F NMR) for compounds **1b**−**f**, **5b**−**d**, **6b**−**k**, **7b**−**h**, **8b**−**e**, **9b**,**c**, **10a**−**c**, **11b**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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