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Solution-, Solid-Phase, and Fluorous Synthesis of β,β-Difluorinated Cyclic Quaternary α-Amino Acid Derivatives: A Comparative Study

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Abstract: The diastereoselective synthesis of cyclic β,β-difluorinated α-amino acid derivatives bearing a quaternary stereocenter is described. The process relies on the chemo- and diastereoselective addition of allylic organometallic reagents to fluorinated α-imino esters and a subsequent ring-closing metathesis reaction (RCM). Complete selectivity in the nucleophilic addition was achieved with (*R*)-phenylglycinol methyl ether as a chiral auxiliary. The resulting amino acids were introduced into peptide chains, which could facilitate the preparation of potentially bioactive dipeptide derivatives. In addition, the solution synthesis of these cyclic fluorinated α-amino acids was successfully adapted to solid-phase and fluorous-phase techniques. The reaction times and final deprotection were clearly more favorable in the latter, in which a fluorous trimethylsilylethanol (TMSE) tag was used. The tag was then easily removed upon treatment with TBAF in a high-yield transesterification process.

Keywords: amino acids · fluorous synthesis · metathesis · quaternary stereocenters · solid-phase synthesis

Introduction

Fluorine is an outstanding element in organic chemistry. Despite its natural abundance on earth, it occurs extremely rarely in biological compounds, a fact which implies that the vast majority of fluoro-organic compounds are man-made. The usual strategies for introducing fluorine into a molecule involve either direct fluorination (in electrophilic or nucleophilic fashion) or, more commonly, the use of fluorinated building blocks.[1]

Currently, fluorinated compounds are popular targets in the field of medicinal chemistry because they have led to a large number of highly effective drugs.[2] In many cases, the incorporation of fluorine into biologically active compounds can alter both drug metabolism and enzyme substrate recognition.[3] Among such compounds, fluorinated amino acids have recently emerged as valuable building blocks for designing hyperstable protein folds as well as for directing highly specific protein–protein interactions.[4] Due to their unique electronic properties, fluorinated amino acids have dramatic effects on protein stability, protein–protein and ligand–receptor interactions, and the physical properties of protein-based materials. Furthermore, the incorporation of fluorine into peptides and proteins provides an opportunity to study the conformational properties and metabolic processes of these substances with the aid of ^{19}F NMR techniques. Still, despite the promising features of organic fluorine derivatives in peptide chemistry, they have attracted relatively little interest in the field of peptide design and protein engineering.[5] The main reason is the limited synthetic access to fluorinated amino acids and the elaborate methods that are often required for their incorporation into peptide chains. Even rarer are examples of the preparation of quaternary cyclic fluorinated α-amino acids, and of the few there are, most deal with fluorinated 1-aminocyclopropane carboxylic acids.

The substitution patterns of the cyclic quaternary α-amino acids are depicted in Figure 1, and show a nitrogen atom either outside the ring (**I** and **II**) or included in the cyclic backbone (**III** and **IV**).

Although very little is known about the chemistry and applications of these derivatives, several synthetic approaches

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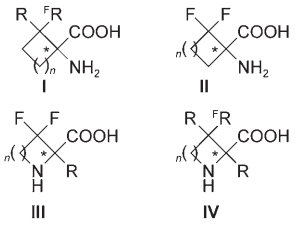
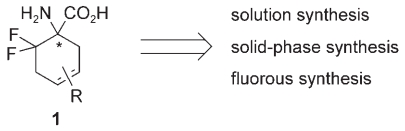


Figure 1. Fluorinated cyclic quaternary α-amino acids.

have been reported. For example, Uneyama et al. have described the preparation of enantiomerically pure trifluoro-1-aminocyclopropane carboxylic acids (type **I**) by means of a highly selective chiral epoxide ring opening.[6] To date, three different strategies have been used to access derivatives of type **III**: while Chen et al. used a Claisen rearrangement/iodolactonization sequence followed by a classic chemical resolution to provide (*S*)-4,4-difluoro-3,3-dimethyl proline,[7] Uneyama et al. employed an enantioselective hydrogenation catalyzed by Pd-BINAP with subsequent cyclization to prepare optically pure β,β-difluoroproline derivatives.[8] The third strategy was developed by our group and entailed an enantioselective preparation of these systems with chiral sulfoxides and with an RCM as the key step.[9]

With regard to type **IV** fluorinated amino acids, Osipov, Dixneuf et al. used RCM methods to obtain fluorinated pipecolic and pyrroline ester derivatives.[10] More recently, the same authors prepared fluorinated bicyclic α-amino acids in a tandem alkenylation/cyclopropanation protocol mediated by a ruthenium catalyst.[11] Rutjes has also very recently prepared fluorinated pipecolic esters starting from allyl glycine and using an RCM to effect the cyclization.[12] Finally, Brigaud et al. reported the synthesis of enantiomerically pure α-trifluoromethyl proline through diastereoselective allylation reaction of (*R*)-phenylglycinol-based oxazolidines.[13]

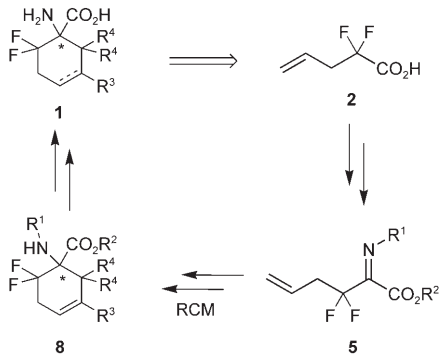
To the best of our knowledge, only one example of fluorinated cyclic α-amino acids **II** has been reported, namely (*R*)-1-amino-2,2-difluorocyclopropanecarboxylic acid, which has been synthesized with an asymmetric acetylation of a prochiral cyclopropanediol catalyzed by a lipase as a key step.[14] In the present paper we describe the study and development of a new strategy for the enantioselective preparation of a new family of type **II** derivatives, 2,2-difluoro-1-aminocyclohexane carboxylic acids, starting with α,α-difluoroalkenylic acids and using an RCM for the cyclization step.[15] The preparation of these derivatives with both solid-phase and fluorous-phase techniques will also be described (Scheme 1).



Scheme 1. Methods for the synthesis of 2,2-difluoro-1-aminocyclohexane carboxylic acids **1**.

Results and Discussion

Solution synthesis of fluorinated α-amino acids 1: The synthetic route by which we obtained fluorinated derivatives **1** is depicted in Scheme 2. The synthesis involved the use of 2,2-difluoro-4-pentenoic acid (**2**)[16] as a starting material, which was then converted into α-imino esters **5** in three steps. The precursor for the ring-closing metathesis reaction was obtained through stereoselective nucleophilic allylation of the imine moiety of **5**, which created a quaternary stereocenter. After cyclization by means of an RCM,[17] subsequent removal of the *N*- and *O*-protecting groups afforded the desired α-amino acids **1**.



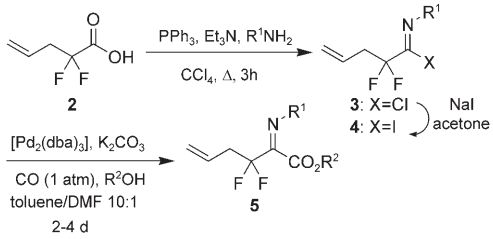
Scheme 2. Synthetic approach for the preparation of β,β-difluorinated cyclic α-amino acids **1**.

Following the methodology described by Uneyama and co-workers,[18] we first transformed **2** into imidoyl chlorides **3**,[19] which led to the corresponding imidoyl iodides **4** in quantitative yield. The alkoxycarbonylation reaction of compounds **4** with several alcohols in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ as a catalyst afforded α-imino esters **5** in

Abstract in Spanish: *Se describe la síntesis diastereoselectiva de derivados de α-aminoácidos cíclicos β,β-difluorados. El proceso se basa en la adición quimio- y diastereoselectiva de reactivos organometálicos alílicos a α-iminoésteres fluorados y posterior reacción de metátesis con cierre de anillo (RCM). Se consiguió una completa selectividad en la adición nucleofílica con el éter metílico de (*R*)-fenilglicinol como auxiliar quiral. Los aminoácidos resultantes se pudieron introducir en cadenas peptídicas, permitiendo la preparación de derivados dipeptídicos potencialmente bioactivos. Además, la síntesis en disolución de estos α-aminoácidos cíclicos fluorados se adaptó con éxito a las técnicas de fase sólida y fluorosa. Los tiempos de reacción y desprotección final fueron claramente más favorables en la síntesis fluorosa, empleando el tag fluoroso trimetilsilil etanol (TMSE), el cual se eliminó fácilmente mediante tratamiento con TBAF, en un proceso de transesterificación con elevado rendimiento.*

moderate isolated yields (Table 1).[20,21] Because this reaction was sensitive to the steric hindrance of the alcohol nucleophiles, ethanol, benzyl alcohol, and 2-(trimethylsilyl)ethanol

Table 1. Preparation of fluorinated α-imino esters **5**.



Entry	R^1	**3** ([%])[a]	R^2	**5** ([%])[a]
1	PMP[b]	**3a** (80)	Et	**5a** (55)
2	PMP[b]	**3a**	Bn	**5b** (60)
3	PMP[b]	**3a**	TMSE[c]	**5c** (52)
4	PMP[b]	**3a**	*i*Pr	**5d** (20)
5	PMP[b]	**3a**	*t*Bu	**5e** (20)
6	(*S*)-PhCH(Me)	**3b** (60)	Bn	**5f** (70)
7	(*R*)-phegly-OMe[d]	**3c** (70)	Bn	**5g** (50)
8	(*R*)-phegly-OMe[d]	**3c**	TMSE[c]	**5h** (51)

[a] Isolated yields. [b] PMP = *p*-$MeOC_6H_4$. [c] TMSE = 2-trimethylsilylethyl. [d] (*R*)-phegly-OMe = (*R*)-$PhCH(CH_2OMe)$.

reacted faster and gave higher chemical yields (Table 1, entries 1–3, 6–8) than either isopropanol or *tert*-butanol (Table 1, entries 4,5). The easy introduction of chiral protecting groups onto the nitrogen atom (Table 1, entries 6–8) will access to chiral fluorinated α-amino acids.

The next step involved the chemo- and diastereoselective addition of an organometallic allylic reagent to the fluorinated α-imino esters **5**, in which two carbons are prone to nucleophilic attack (Figure 2).

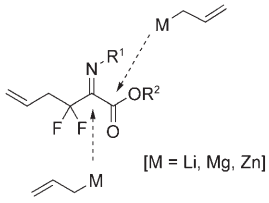


Figure 2. Possible organometallic addition to imino esters **5**.

Nucleophilic additions of organometallic reagents to carbon-nitrogen double bonds is not a trivial task since imines are usually less electrophilic than the corresponding carbonyl derivatives.[22] Nevertheless, additions to ketimines are particularly appealing as these reactions can lead to interesting amino derivatives bearing a quaternary stereocenter.

The stereocontrolled synthesis of nonracemic quaternary α,α-disubstituted α-amino acids represents an attractive target in modern organic chemistry because the incorporation of these compounds into peptides imposes significant constraints on their conformation.[23] As a result, much effort has been directed towards developing new methods for the asymmetric synthesis of quaternary α-amino acids.[24] Many of these methods involve stereoselective nucleophilic additions to carbon–nitrogen double bonds.[22] The asymmetric induction during the addition can be achieved by means of substrate diastereocontrol (imines derived from chiral amines and/or chiral aldehydes), as well as through the use of chiral reagents or catalysts.

In our approach, the formation of the asymmetric quaternary stereocenter takes place through the chemoselective addition of organometallic allylic reagents to the imine moiety of fluorinated α-imino esters **5**. Several authors have carried out this transformation on related processes by using allylic lithium and magnesium organometallic reagents.[10b,18,25] Thus, our first attempt involved a slow addition of a solution of allylmagnesium chloride in THF to the α-imino ester **5a** at 0 °C. The reaction gave the desired product **6a** as well as the over-addition product resulting from the double addition to the iminic and carbonylic carbons in 55% yield and 35:65 ratio. Unfortunately, this result could not be improved by modifying the reaction conditions and similar results were achieved with organolithium reagents.

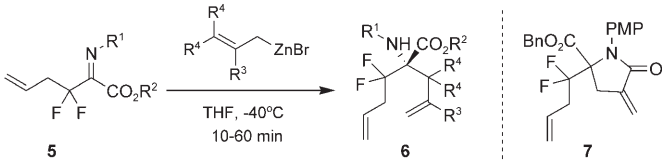
The poor chemoselectivity of the addition of allylmagnesium chloride to imines **5** prompted us to look for more selective allylic organometallic derivatives. We thus tried using organozinc reagents, which react chemo- and regioselectively with α-imino esters on the imine moiety.[26] We found that allylzinc bromides caused the addition to take place exclusively at the iminic carbon of compounds **5** in 10 min at −40 °C (method A), thereby furnishing the desired α-amino esters **6a–i** in almost quantitative yield (Table 2, entries 1–9).[27] For the addition of hindered allylzinc derivatives (Table 2, entries 10–12), a different method involving the preparation of the organometallic reagent under Barbier conditions (method B, see Supporting Information for details) was employed.[28] We found that when a γ-substituted allylzinc derivative was used (Table 2, entry 10), the branched (γ-adduct) product was formed exclusively.

It should be noted that the allylzinc reagent derived from ethyl 2-(bromomethyl)acrylate gave the α-methylene γ-lactam **7** through a tandem addition–ring-closing process.[29]

With regard to the asymmetric version of the process, we decided to evaluate the use of chiral α-imino esters **5f–h** derived from chiral amines. It had previously been reported that the diastereoselective allylation of aldimines derived from phenylethylamine[30] or phenylglycinol[31] could be achieved with good selectivities. Indeed, when (*S*)-1-phenylethylamine was used as a chiral auxiliary, compound **6f** was formed in excellent yield as a 7:3 non-separable mixture of diastereoisomers (Table 2, entry 6). However, much better selectivity was achieved with imino esters **5g,h** derived from (*R*)-phenylglycinol methyl ether (Table 2, entries 7–12). In these reactions a single diastereoisomer was formed, as determined from ^1H and ^{19}F NMR data.

The addition of organometallic reagents to imines generally proceeds through initial coordination of the metal to the nitrogen atom and subsequent carbon–carbon bond formation through a six-membered cyclic transition state. We attribute the excellent selectivity observed in the allylation of **5g,h** to a highly ordered transition state arising from chelation of the imine nitrogen and the oxygen in the chiral auxiliary to the metal, which thus delivers the allylic moiety in a 1,3-like addition from the less-hindered side of the

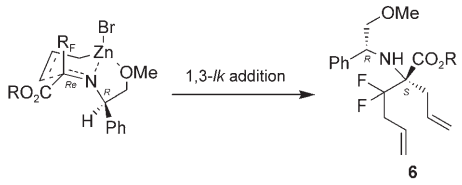
Table 2. Synthesis of α-amino esters **6**.



Entry	**5**	R^1	R^2	Method[a]	R^3	**6** ([%])[b]	*de* [%][c]
1	**5a**	PMP[d]	Et	A	H	**6a** (99)	–
2	**5b**	PMP[d]	Bn	A	H	**6b** (99)	–
3	**5c**	PMP[d]	TMSE[e]	A	H	**6c** (99)	–
4	**5e**	PMP[d]	*t*Bu	A	H	**6d** (99)	–
5	**5b**	PMP[d]	Bn	A	Me	**6e** (99)	–
6	**5f**	(*S*)-PhCH(Me)	Bn	A	H	**6f** (95)	40
7	**5g**	(*R*)-phegly-OMe[f]	Bn	A	H	**6g** (92)	>98
8	**5h**	(*R*)-phegly-OMe[f]	TMSE[e]	A	H	**6h** (95)	>98
9	**5h**	(*R*)-phegly-OMe[f]	TMSE[e]	A	Me	**6i** (91)	>98
10	**5h**	(*R*)-phegly-OMe[f]	TMSE[e]	B	H (R^4=Me)	**6j** (84)	>98
11	**5h**	(*R*)-phegly-OMe[f]	TMSE[e]	B	COO*t*Bu	**6k** (86)	>98
12	**5h**	(*R*)-phegly-OMe[f]	TMSE[e]	B	Ph	**6l** (50)[g]	>98

[a] Method A: Addition of allylzinc bromide solution in THF to the imino ester **5** at −40 °C. Reaction time: 10 min. Method B: Addition of zinc powder to a biphasic solution of **5** and allyl bromide in THF/satd. NH_4Cl. Reaction time: 60 min. [b] Isolated yields. [c] Diastereomeric excess determined from ^{19}F NMR integration. [d] PMP = *p*-$MeOC_6H_4$. [e] TMSE = 2-trimethylsilylethyl. [f] (*R*)-phegly-OMe = (*R*)-PhCH(CH_2OMe). [g] 40% of starting material was recovered unchanged.

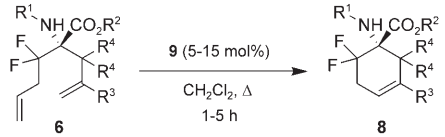
carbon–nitrogen double bond (the side opposite the phenyl group on the *Re* face of the imine; Scheme 3).



Scheme 3. Diastereoselectivity control in the formation of **6**.

With dialkenylic α-amino esters **6** in hand, the final step in our synthetic strategy was the ring-closing metathesis reaction, which was carried out with the second generation Grubbs catalyst [(IHMes)(PCy_3)Cl_2Ru=CHPh] (**9**)[32] in refluxing dichloromethane to afford cyclic protected α-amino esters **8** in excellent yield (Table 3). Although free amines are typically incompatible with ruthenium metathesis catalysts due to catalyst inhibition by the basic nitrogen,[33] in our case, the presence of the electron-withdrawing fluorine atoms favored the cyclization.

Table 3. RCM of α-amino esters **6**.



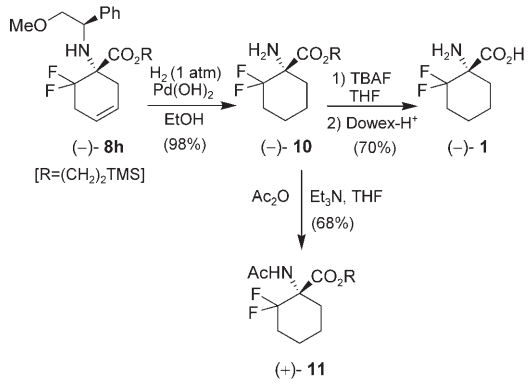
Entry	**6**	R^1	R^2	R^3	**8** ([%])[a]
1	**6a**	PMP[c]	Et	H	**8a** (88)
2	**6b**	PMP[c]	Bn	H	**8b** (93)[b]
3	**6c**	PMP[c]	TMSE[d]	H	**8c** (85)
4	**6d**	PMP[c]	*t*Bu	H	**8d** (75)
5	**6e**	PMP[c]	Bn	Me	**8e** (95)
6	**6f**	(*S*)-PhCH(Me)	Bn	H	**8f** (95)
7	**6g**	(*R*)-phegly-OMe[e]	Bn	H	**8g** (89)
8	**6h**	(*R*)-phegly-OMe[e]	TMSE[d]	H	**8h** (92)
9	**6i**	(*R*)-phegly-OMe[e]	TMSE[d]	Me	**8i** (91)
10	**6j**	(*R*)-phegly-OMe[e]	TMSE[d]	H (R^4=Me)	**8j** (87)
11	**6k**	(*R*)-phegly-OMe[e]	TMSE[d]	COO*t*Bu	**8k** (88)
12	**6L**	(*R*)-phegly-OMe[e]	TMSE[d]	Ph	**8l** (89)

[a] Isolated yields. [b] When the RCM was carried out with first generation Grubbs catalyst (PCy_3)$_2Cl_2$Ru=CHPh, 67% yield was obtained instead. [c] PMP = *p*-$MeOC_6H_4$. [d] TMSE = 2-trimethylsilylethyl. [e] (*R*)-phegly-OMe = (*R*)-PhCH(CH_2OMe).

To complete the synthesis, we undertook the removal of the amino acid protecting groups on compounds **8**. First, we tested the deprotection of the amino group on compound (−)-**8h** by treating it with $Pd(OH)_2$ in ethanol under hydrogen atmosphere (1 atm). The reaction proceeded smoothly, with a simultaneous reduction of the carbon–carbon double bond. Subsequently, the carboxylic group was released through treatment with TBAF in THF to provide the α-amino cyclohexanecarboxylic acid (−)-**1** in good yield after isolation through ion exchange chromatography on Dowex-H^+ (Scheme 4). The absolute configuration of the newly created quaternary stereocenter was determined to be *S* by means of single-crystal X-ray analysis of derivative (+)-**11**, which was prepared through *N*-acetylation of (−)-**10** (Scheme 4).[34]

As a follow up to the synthesis, we were interested in seeing whether our *gem*-difluorinated cyclic α-amino acid derivatives could be incorporated into peptide sequences.

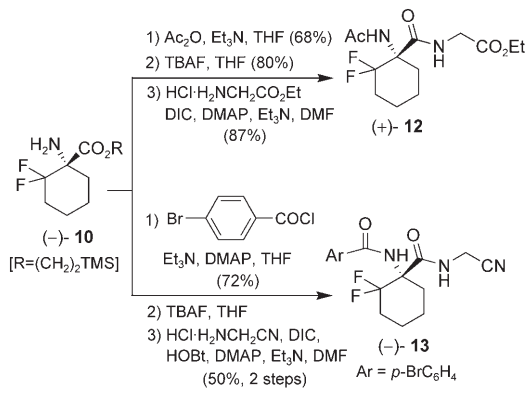
One strategy commonly used to improve the biological properties of bioactive peptides entails the incorporation of α,α-disubstituted non-natural amino acids in a peptide chain.[24] The resulting peptidomimetics show higher stability against proteases, as well as increased levels of lipophilicity



Scheme 4. Amino acid deprotection.

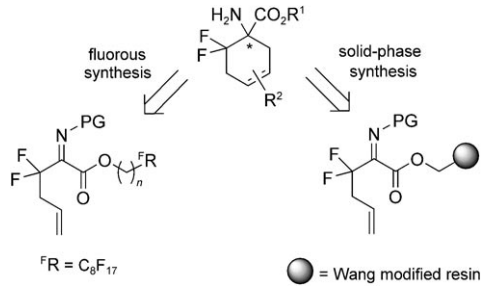
and bioavailability.[35] When these two substituents constitute a cycle, the conformational restriction increases. For this reason, this class of cyclic amino acids has been used in the preparation of peptide-based drugs.[36] In particular, the 1-amino cyclohexanecarboxylic acid framework has been used in the design of cathepsin K inhibitors[37] and V_2 agonists of arginine vasopressin.[38]

Treatment of (−)-**10** with acetic anhydride followed by treatment with TBAF in THF gave the corresponding free carboxylic acid, which in turn was coupled with glycine ethyl ester to afford dipeptide (+)-**12** in good yields (Scheme 5). Currently, we are working on the synthesis of peptidomimetic sequences with potential biological interest that bear the 1-amino 2,2-difluorocyclohexanecarboxylic acid unit. In this context, a number of recent reports on the inhibition of cathepsin K have focused on dipeptide-based nitriles with *para*-substituted benzamides in which a natural amino acid has been replaced with an achiral, conformationally restricted aminocyclohexanecarboxylate moiety. We are thus interested in the preparation of this type of molecules in an enantiomerically pure fashion through incorporation of our difluorinated cyclic α-amino acid derivatives. The preparation of a representative example of this kind of compound is depicted in Scheme 5. Thus, dipeptidomimetic (−)-**13** was prepared by *N*-acylation of (−)-**10** with *p*-bromobenzoyl chloride followed by treatment with TBAF and subsequent coupling with amino-acetonitrile hydrochloride under standard conditions.



Scheme 5. Dipeptide formation.

Solid-phase and fluorous synthesis of difluorinated cyclic α-amino acid derivatives: The increasing practice of combinatorial and parallel synthesis for the discovery of new bioactive compounds has led to improvements in the efficiency of both the reactions and the purification techniques used in organic synthesis. Thus, the development of new synthetic strategies is as important as the design of fast new purification methods of organic compounds. Among these innovations are solid- and fluorous-phase syntheses, which we decided to use in order to obtain fluorinated cyclic α-amino acid derivatives following the same synthetic strategy we had developed in solution (Scheme 6).

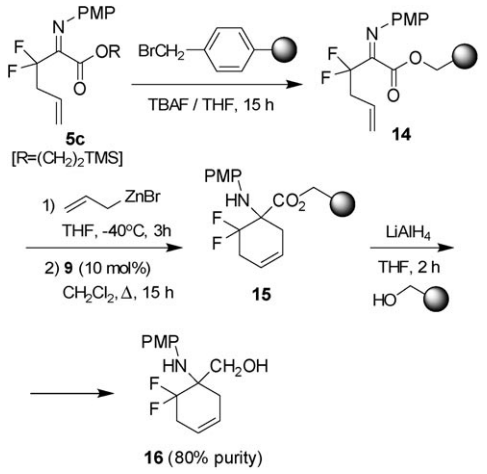


Scheme 6. Solid-phase and fluorous synthesis of fluorinated cyclic α-amino acid derivatives.

The solid-phase methodology facilitates the preparation of compound libraries for high throughput screenings, since separation is reduced to an easy wash and filtration process.[39] In spite of this, the literature contains very few examples of solid-phase parallel synthesis of fluorinated compounds.[40] We therefore decided to adapt our synthetic route to solid-phase conditions in order to prepare small libraries of our compounds.

First, modified Wang-resin bearing bromobenzylic groups was loaded with the fluorinated α-imino ester **5c**, which contains a trimethylsilylethyl group. Ester **5c** was easily transesterified by modified Wang resin in the presence of TBAF. After 15 h at room temperature, washing with CH_2Cl_2 and MeOH afforded the resin-bound imino ester **14**, as determined by means of IR spectroscopy. Next, resin **14** was reacted with an excess of allylzinc bromide (3 equiv) in THF at −40 °C, followed by a ring-closing metathesis reaction in the presence of the second generation Grubbs catalyst **9** to afford the corresponding fluorinated cyclic α-amino ester **15**. Finally, we performed the cleavage of the resin using $LiAlH_4$ reduction, which yielded cyclic amino alcohol **16** with high purity (Scheme 7).

Fluorous synthesis is a relatively new type of synthesis in solution. It is related to solid-phase synthesis in terms of separation strategies, but rather than employing solid supports, perfluoroalkyl chains are used to facilitate the purification of reaction mixtures.[41] This methodology thus combines the advantages of solid-phase separations and solution-phase reactions in that it facilitates the separation of the synthetic intermediates through fluorous solid-phase ex-



Scheme 7. Solid-phase synthesis of fluorinated cyclic α-amino alcohols.

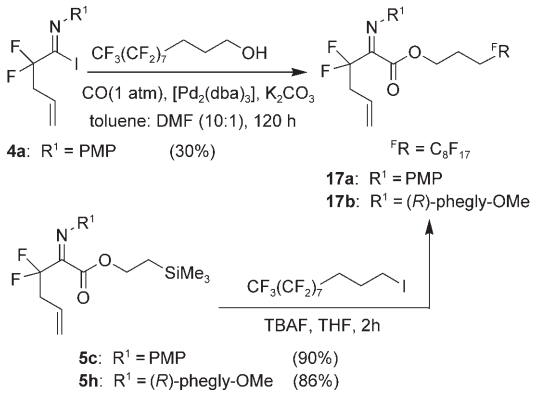
traction techniques (F-SPE)[42] while avoiding some of the limitations of solid-phase chemistry, including the unfavorable kinetics, the high amounts of reagents and long reaction times needed, and the difficult analysis of the reaction mixtures through TLC, NMR spectroscopy, or mass spectrometry.

In general, a fluorous synthesis implies the attachment of a perfluoroalkyl chain (fluorous tag) to an organic molecule within a synthetic route in order to allow for the use of fluorous purification techniques after each step. These fluorous compounds should be equivalent to their non-fluorous counterparts in terms of reactivity. Moreover, the fluorous tag must be compatible with the reaction conditions and it should also be easy to remove at the end of the synthetic sequence.[43]

Our first forays into fluorous chemistry focused on our previous research, making use of previously optimized synthetic routes. Thus, in the last year we have described the fluorous synthesis of both partially modified retropeptides[44] and fluorinated uracils.[45] In this context, our interest in employing fluorous chemistry for the asymmetric synthesis of fluorinated cyclic α-amino acids was to test the scope of this method and to compare the results with those from previously developed solution and solid-phase syntheses.

Following the same strategy used in solution and on solid-phase, we envisioned that the fluorous synthesis should start from fluorous α-imino esters **17**, in which the fluorous tag could be introduced either in the alkoxycarbonylation step from a suitable fluorous alcohol or through displacement of the trimethylsilylethyl moiety with TBAF in the presence of the corresponding fluorous iodide. Both fluorous alcohols and iodides are commercially available.

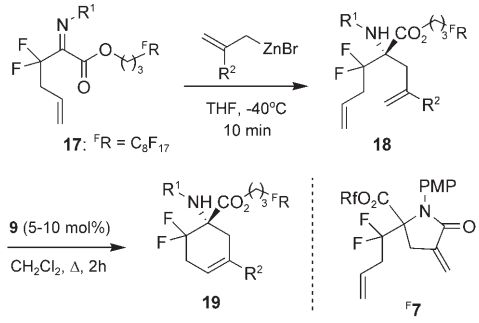
The most direct way to obtain fluorous imino esters **17** is to start from imidoyl iodides **4**. Thus, although the alkoxycarbonylation of iodide **4a** in the presence of 3-(perfluorooctyl)propanol gave the desired α-imino ester **17a**, the reaction took place quite slowly (5 d) and in low yield (30%). However, the transesterification of trimethylsilylethyl α-imino esters **5c**,**h** with 3-(perfluorooctyl) propyl iodide in the presence of TBAF proceeded in only 2 h and in excellent yields (Scheme 8). This second strategy thus leads to the same derivatives as the alkoxycarbonylation reaction, but bypasses the problems derived from the presence of the dibenzalacetone ligand in the reaction mixtures.[20]



Scheme 8. Preparation of fluorous α-imino esters **17**.

As in the solution and on the solid phase, the next step of the synthesis was the reaction of fluorous imino esters **17** with allylzinc bromides (1.5 equiv), followed by cyclization through a ring-closing metathesis reaction. Dialkenylic α-amino esters **18** were obtained in excellent yields through chemoselective addition of allylzinc bromides to the imine moiety of **17**.[46] The addition to chiral imino ester **17b** took place with total diastereoselectivity, as determined from the integration of the ^{1}H and ^{19}F NMR signals. Finally, the RCM reaction in the presence of the second generation Grubbs catalyst (**9**) furnished cyclic derivatives **19** in high yields (Table 4).

Table 4. Fluorous synthesis of cyclic α-amino esters **19**.



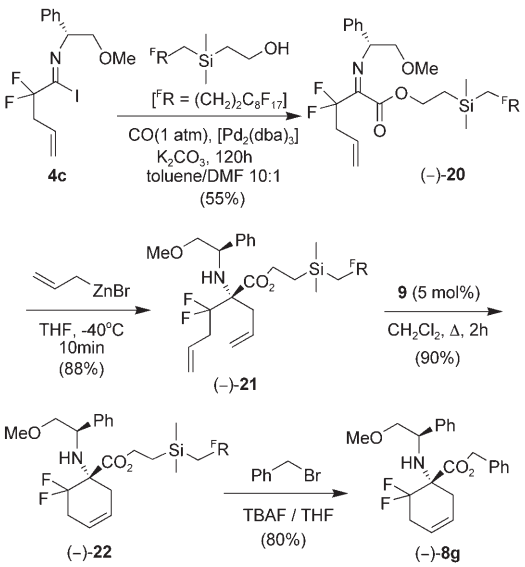
Entry	17	R^1	R^2	18 ([%])[a]	19 ([%])[a]
1	**17a**	PMP[b]	H	**18a** (99)	**19a** (85)
2	**17b**	(*R*)-phegly-OMe[c]	H	**18b** (90) [>98][d]	**19b** (92)
3	**17a**	PMP[b]	Me	**18c** (99)	**19c** (80)
4	**17a**	PMP[b]	CO_2Et	^{F}**7** (90)	–

[a] Isolated yields. [b] PMP = *p*-$MeOC_6H_4$. [c] (*R*)-phegly-OMe = (*R*)-$PhCH(CH_2OMe)$. [d] In brackets [%] diastereomeric excess (*de*) determined from ^{19}F NMR data.

It should be noted that all of the synthetic intermediates (**17**, **18**, **19**) were easily purified through fluorous solid-phase extraction (F-SPE)[42] to remove any excess of non-fluorinated reagents, thereby speeding up and simplifying the purification steps.

The final step of the process involved the removal of the fluorous tag. To this end, we attempted both ester hydrolysis and transesterification reactions on compound **19b**, but our efforts were completely ineffective.[47]

At this point, due to the problems associated with the de-tagging procedures, we decided to change our strategy and use a new fluorous tag that would be easier to remove at the end of the synthesis. In this context, our group has recently described the synthesis and applications of a fluorous analogue of 2-(trimethylsilyl)ethanol[44] that can be easily removed from fluorous esters by a transesterification reaction in the presence of TBAF.[48] Using this new tag, we repeated the synthesis starting from chiral imidoyl iodide **4c**. The perfluoroalkyl chain was introduced as an alcohol in the alkoxycarbonylation step to yield fluorous imino ester (−)-**20**, which was easily purified by means of F-SPE. Next, we carried out the addition of allylzinc bromide (1.5 equiv) followed by the RCM. Both reactions proceeded in excellent yields and with total diastereoselectivity in the addition step (de >98%). Finally, a transesterification reaction with TBAF in the presence of an electrophilic reagent, in this case, benzyl bromide, allowed us to remove the silylated fluorous group successfully, thereby obtaining the cyclic α-amino ester (−)-**8g**, that had been previously prepared in solution phase (Scheme 9).



Scheme 9. Use of fluorous (trimethylsilyl)ethanol for the synthesis of chiral α-amino ester **8g**.

Conclusion

In this paper we have described the asymmetric synthesis of β,β-difluorinated 1-aminocyclohexane-1-carboxylic acids in which the key steps are a chemo-and diastereoselective allylation reaction of α-imino esters **5**, followed by a ring-closing metathesis reaction. The creation of the quaternary stereocenter takes place with a high degree of stereocontrol when the methyl ether of (*R*)-phenylglycinol is used as a chiral auxiliary on the imine nitrogen.

We have also incorporated our *gem*-difluorinated cyclic α-amino acid derivatives into dipeptidic sequences and we are currently studying their biological potential.

In addition, the solution synthesis of these derivatives has been successfully adapted to solid-phase and fluorous-phase methodologies. Both techniques allow for much easier purification as compared to the synthesis in solution. However, fluorous synthesis offers numerous advantages over the solid-phase strategy; the reactions are much faster and more economical because they do not require the excess of reagents that the solid-phase synthesis does. Moreover, fluorous synthesis allows for easier monitoring of the different steps along the synthetic route. In addition, we found that the fluorous trimethylsilylethanol (TMSE) tag was easily removed through treatment with TBAF in a high-yield transesterification process.

Experimental Section

General methods: Reactions were carried out under nitrogen atmosphere unless otherwise indicated. The solvents were purified prior to use: CH_2Cl_2 and CCl_4 were distilled from calcium hydride; hexanes, toluene, and THF from sodium. All reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm E. Merck precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). Fluorous solid-phase extractions were performed on FluoroFlash silica gel cartridges from Fluorous Technologies Inc. (Pittsburgh, Pennsylvania, USA) Melting points were measured on a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1020 polarimeter. IR spectra were recorded on a IR Bruker Equinox 55 spectrometer. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a 300 MHz Bruker AC300 spectrometer and 400 MHz Bruker Avance. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents or fluorotrichloromethane in ^{19}F NMR experiments. Coupling constants (J) are given in Hertz (Hz). High-resolution mass spectra were carried out on VGmAutospec (VG Analytical, Micromass Instruments) by the Universidad de Valencia Mass Spectrometry Service.

General procedure for the preparation of fluorinated α-imino esters 5: NaI (11.6 mmol) was added to a solution of the corresponding imidoyl chloride **3** (3.85 mmol) in dry acetone (10 mL) and the mixture was stirred at room temperature protected from light until the total disappearance of the starting imidoyl chloride (as confirmed by means of GC-MS). The reaction mixture was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (3×15 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of solvents quantitatively gave the corresponding crude imidoyl iodides **4**

as yellow oils; these were subsequently used in the next step of the synthesis with no further purification.

Under CO atmosphere (1 atm), a solution of imidoyl iodide **4** (7.1 mmol) in toluene/DMF (10 mL/1 mL) and the corresponding alcohol (8.5 mmol) were both added to a two-necked flask containing K_2CO_3 (14.2 mmol) and palladium catalyst $[Pd_2(dba)_3]\cdot CHCl_3$ (0.28 mmol). The reaction mixture was stirred at room temperature until the starting material was totally consumed, as confirmed by means of TLC. The crude reaction mixture was then filtered through a silica pad and washed with CH_2Cl_2. The solvents were eliminated under reduced pressure and the mixture was purified by means of flash column chromatography (*n*-hexane/AcOEt 10:1).

***tert*-Butyl 3,3-difluoro-2-[(4-methoxyphenyl)imino]-5-hexenoate (5e)**: By means of the general procedure described above, **5e** was obtained as a yellow oil (137 mg) in 20% yield from **3a** (730 mg). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (s, 9H), 2.90–3.04 (m, 2H), 3.73 (s, 3H), 5.20–5.27 (m, 2H), 5.75–5.88 (m, 1H), 6.78 (d, $J = 9.0$ Hz, 2H), 6.86 ppm (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 27.7 (CH_3), 39.9 (C_t, $^2J(C,F) =$ 24.7 Hz), 55.4 (CH_3), 84.7 (C), 114.0 (CH), 118.6 (C_t, $^1J(C,F) = 245.5$ Hz), 121.1 (CH_2), 121.4 (CH), 128.1 (C_t, $^3J(C,F) = 4.6$ Hz), 140.6 (C), 156.2 (C_t, $^2J(C,F) = 32.8$ Hz), 158.2 (C), 161.3 ppm (C); ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -100.82$ ppm (t, $J(F,H) = 16.4$ Hz, 2F); HRMS: *m*/*z*: calcd for $C_{17}H_{21}F_2NO_3$: 325.1490 $[M]^+$, found 325.1476.

General procedure for the preparation of fluorinated dialkylated α-amino esters 6

Method A

A) Preparation of the allylzinc bromide solutions: Under inert atmosphere, 50 μL of allyl bromide were added to a suspension of activated zinc (1 g, 30.6 mmol) in THF (2.5 mL) and then introduced into a preheated bath at 50 °C with vigorous stirring. After 5 min, the remaining allyl bromide (0.3 mL, 3.4 mmol), which had previously been dissolved in THF (5 mL), was added. Heating was continued for 40 min after the addition was completed; the heating bath was then removed. The reaction mixture was filtered under nitrogen and this freshly prepared solution was used immediately in the next step.

B) Addition of allylzinc solutions to α-imino esters ***5***: The freshly prepared solution (see above) of allylzinc bromide in THF (0.5 mL, 0.51 mmol) was added dropwise to a solution of α-imino ester (0.34 mmol) in THF (5 mL) under inert atmosphere at −40 °C. After 10 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (3×7 mL) and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to afford the desired α-amino esters **6a–i** in almost quantitative yield.

Method B

Activated zinc powder (0.9 mmol) was added slowly to a biphasic solution of **5h** (0.5 mmol) and the corresponding allyl bromide (0.7 mmol) in THF/satd. aq. NH_4Cl (0.5/2 mL) and the reaction mixture was vigorously stirred for 1 h at rt. The crude reaction product was then diluted with EtOAc (5 mL), the layers were separated, and the aqueous layer was extracted twice (2×5 mL) with additional EtOAc. The combined organic layers were washed with brine (3×7 mL) and dried over anhydrous Na_2SO_4. The crude product was subjected to flash chromatography to afford the desired amino esters **6j–l**.

(±)-*tert*-Butyl 2-allyl-3,3-difluoro-2-(4-methoxyphenyl)amino-5-hexenoate (6d): By means of the general procedure described above (Method A), **6d** was obtained as a yellow oil (112 mg) in 99% yield from **5e** (100 mg). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 2.35–2.55 (m, 1H), 2.72–3.06 (m, 3H), 3.68 (s, 3H), 4.71 (br s, 1H), 4.87–4.92 (m, 2H), 5.07–5.15 (m, 2H), 5.26–5.40 (m, 1H), 5.73–5.87 (m, 1H), 6.67 (d, $J =$ 9.0 Hz, 2H), 6.77 ppm (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 27.7$ (CH_3), 31.9 (CH_2), 37.7 (C_t, $^2J(C,F) = 2$ 4.7 Hz), 55.5 (CH_3), 69.3 (C_t, $^2J(C,F) = 25.3$ Hz), 83.6 (C), 114.3 (CH), 119.2 (CH_2), 120.2 (CH_2), 120.5 (CH), 122.8 (C_t, $^1J(C,F) = 254.1$ Hz), 128.8 (C_t, $^3J(C,F) = 4.0$ Hz), 131.6 (CH), 137.9 (C), 153.7 (C), 169.7 ppm (C); ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -103.89$ (ddd, $J(F,F) = 245.5$, $J_1(F,H) = 26.5$, $J_2(F,H) = 9.0$ Hz, 1F), −105.30 ppm (ddd, $J(F,F) = 245.4$, $J_1(F,H) = 27.7$, $J_2(F,H) = 9.3$ Hz, 1F); HRMS: *m*/*z*: calcd for $C_{20}H_{27}F_2NO_3$: 367.1959 $[M]^+$, found 367.1953.

General procedure for the preparation of fluorinated cyclic α-amino esters 8: Under N_2 atmosphere, a solution of second generation Grubbs catalyst [(IMes)(PCy_3)Cl_2Ru=CHPh] (0.037 mmol, 15 mol%) in DCM (1 mL) was added to a solution of α-amino ester **6** (0.1 g, 0.25 mmol) in DCM (2×10^{-2} M). The reaction mixture was stirred at reflux until TLC indicated the total disappearance of the starting material. The solvents were then removed under reduced pressure and the brown residue was purified by means of flash chromatography (*n*-hexane/EtOAc 10:1), with silica gel that had been previously deactivated with a solution of *n*-hexane/Et_3N 2%.

(±)-*tert*-Butyl 6,6-difluoro-1-[(4-methoxyphenyl)amino]-3-cyclohexene-1-carboxylate (8d): By means of the general procedure described above, **8d** was obtained as a white solid (53 mg) in 75% yield from **6d** (76 mg). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (s, 9H), 2.35–2.56 (m, 2H), 2.82–2.89 (m, 2H), 3.69 (s, 3H), 5.51–5.59 (m, 2H), 6.68 (d, $J = 9.0$ Hz, 2H), 6.79 ppm (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 27.8 (CH_3), 31.1 (CH_2), 33.6 (C_t, $^2J(C,F) = 25.3$ Hz), 55.4 (CH_3), 65.7 (C_{dd}, $^2J(C,F) = 24.7$ Hz, $^2J(C,F) = 20.1$ Hz), 82.6 (C), 114.0 (CH), 121.6 (C_{dd}, $^3J(C,F) = 7.5$ Hz, $^3J(C,F) = 3.5$ Hz), 122.4 (C_t, $^1J(C,F) = 250.1$ Hz), 123.9 (CH), 124.1 (CH), 136.8 (C), 155.6 (C), 169.2 ppm (C); ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta =$ −106.51 (ddd, $J(F,F) = 243.4$, $J_1(F,H) = 25.7$, $J_2(F,H) = 14.4$ Hz, 1F), −107.90 ppm (dt, $J(F,F) = 142.3$, $J(F,H) = 9.3$ Hz, 1F); HRMS: *m*/*z*: calcd for $C_{18}H_{23}F_2NO_3$: 339.1646 $[M]^+$, found 339.1648.

(−)-1-Amino-2,2-difluorocyclohexane-1-carboxylic acid [(−)-1]: A solution of (−)-**10** (0.12 mmol) in THF (1.5 mL) was added dropwise to a solution of TBAF in THF (0.15 mmol, 1.0 M in THF). After stirring for 1 h at room temperature, the solvents were removed under reduced pressure and a brown residue was obtained. The crude mixture was purified by means of ion exchange chromatography on Dowex-H^+ to afford the pure fluorinated α-amino acid (−)-**1** as a white solid (15 mg) in 70% yield. $[\alpha]_D^{25} = -18.7$ (*c* 0.5, 6 M HCl); ^{1}H NMR (300 MHz, D_2O): $\delta = 1.45$–1.77 (m, 5H), 2.04–2.12 (m, 2H), 2.36–2.59 ppm (m, 1H); ^{13}C NMR (75.5 MHz, D_2O): $\delta = 20.0$ (CH_2), 21.1 (C_d, $^3J(C,F) = 8.3$ Hz), 30.8 (C_d, $^2J(C,F) = 20.9$ Hz), 31.9 (C_d, $^3J(C,F) = 3.8$ Hz), 64.4 (C_{dd}, $^2J_1(C,F) = 24.7$, $^2J_2(C,F) = 18.7$ Hz), 122.2 (C_{dd}, $^1J_1(C,F) = 249.8$, $^1J_2$ (C,F) = 244.9 Hz), 170.4 ppm (C_d, $^3J(C,F) = 4.9$ Hz); ^{19}F NMR (282.4 MHz, D_2O): $\delta =$ −102.68 (d, $J(F,F) = 243.3$ Hz, 1F), −105.29 ppm (ddd, $J(F,F) = 243.3$, $J_1(F,H) = 37.1$, $J_2(F,H) = 13.4$ Hz, 1F); HRMS: *m*/*z*: calcd for $C_7H_{11}NO_2F_2$: 179.0758 $[M]^+$; found 179.0758.

Loading of imino ester 5c to the modified Wang resin (preparation of resin 14): A solution of α-iminoester **5c** (0.12 g, 0.35 mmol) in THF (1 mL) and TBAF (0.35 mL, 0.35 mmol) was added over a suspension of Wang resin (0.10 g, 1.60 mmol g^{-1}). After 15 h of orbital stirring, the resin was filtered and washed with CH_2Cl_2 (3×5 mL) and MeOH (3×5 mL). Solvents were removed under reduced pressure to afford the α-iminoester **14** supported on the resin as a yellow granulated solid. IR: $\tilde{\nu} =$ 1614 (C=C), 1741 cm^{-1} (C=O).

Preparation of cyclic α-amino ester 15 on solid phase: A freshly prepared solution of allylzinc bromide (1.0 M en THF, 3.0 equiv) was added dropwise to a solution of α-imino ester **14** (0.34 mmol) in THF (5 mL) under inert atmosphere at −40 °C. After 10 minutes, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and filtered. The resin was washed with CH_2Cl_2 (3×5 mL) and MeOH (3×5 mL) and solvents were removed under reduced pressure. Next, a solution of second generation Grubbs catalyst [(IMes)(PCy_3)Cl_2Ru=CHPh] (10 mol%) in DCM (1 mL) was added to a suspension of the dialkenylic resin (1.0 equiv) in dichloromethane (2×10^{-2} M). The reaction mixture was stirred at reflux for 15 h. The resin was then filtered and washed with CH_2Cl_2 (3×5 mL) and MeOH (3×5 mL) and solvents were removed under reduced pressure to afford the cyclic derivative **15**. IR: $\tilde{\nu} =$ 1616 (C=C), 1739 (C=O), 3452 cm^{-1} (N-H).

(*E*)-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl 3,3-difluoro-2-[(4-methoxyphenyl)imino]-5-hexenoate (17a): By means of the general procedure described above for the preparation of fluorinated α-imino esters **5**, **17a** was obtained as a yellow oil (437 mg) in 30% yield

from **4a** (700 mg) and 3-(perfluorooctyl)propanol. ^{1}H NMR (300 MHz, CDCl3): δ = 1.69–1.74 (m, 4H), 2.93–3.07 (m, 2H), 3.71 (s, 3H), 4.11 (t, J = 5.5 Hz, 2H), 5.21–5.28 (m, 2H), 5.74–5.85 (m, 1H), 6.79 (d, J = 9.1 Hz, 2H), 6.85 ppm (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 19.5 (C_t, ^3J(C,F) = 4.0 Hz), 27.4 (C_t, ^2J(C,F) = 24.4 Hz), 39.6 (C_t, ^2J(C,F) = 24.2 Hz), 55.2 (CH_3), 64.3 (CH_2), 114.3 (CH), 118.5 (C_t, ^1J(C,F) = 244.9 Hz), 121.3 (CH), 121.4 (CH_2), 127.8 (C_t, ^3J(C,F) = 4.9 Hz), 140.2 (C), 154.5 (C_t, ^2J(C,F) = 33.9 Hz), 158.7 (C), 162.2 ppm (C) (the signals from the C_8F_{17} group were obscured due to their low intensity); ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ = −83.28 (t, J(F,H) = 9.8 Hz, 2F), −102.4 (t, J(F,H) = 16.5 Hz, 2F), −117.06 (brs, 2F), −124.46 (brs, 6F), −125.27 (brs, 2F), −125.94 (brs, 2F), −128.67 ppm (t, J = 9.3 Hz, 2F); HRMS: m/z: calcd for $C_{24}H_{18}F_{19}NO_3$: 729.0983 $[M]^+$, found 729.1076.

(−)-(*E*)-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl 3,3-difluoro-2-{[(1*R*)-1-phenyl-2-methoxyethyl]imino)}-5-hexenoate (17b): 3-(Perfluorooctil)propil iodide (0.58 mmol) and TBAF (0.35 mmol) were added to a solution of silylated α-imino ester **5h** (0.29 mmol) in dry THF (2 mL) at 0 °C. The reaction mixture was stirred at room temperature until TLC indicated the total disappearance of the starting material. The solvents were then removed under reduced pressure and the residue was purified by means of fluorous solid phase extraction (F-SPE). **17b** was obtained as a yellow oil (190 mg) in 86% yield. $[\alpha]_D^{25}$ = −13.15 (*c* 1.4 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92–2.03 (m, 2H), 2.09–2.18 (m, 2H), 2.85–3.00 (m, 2H), 3.23 (s, 3H), 3.57 (d, J = 6.4 Hz, 2H), 4.27–4.33 (m, 2H), 4.80 (dd, J_1 = 7.5, J_2 = 5.1 Hz, 1H), 5.15 (dd, J_{trans} = 17.1, J_{cis} = 10.2 Hz, 2H), 5.65–5.79 (m, 1H), 7.24–7.28 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.3 (CH_2), 27.9 (C_t, ^2J(C,F) = 23.1 Hz), 39.7 (C_t, ^2J(C,F) = 24.7 Hz), 59.3 (CH), 64.3 (CH_2), 67.7 (CH_3), 77.5 (CH_2), 121.2 (CH_2), 127.4 (CH), 128.2 (CH), 128.3 (CH), 128.9 (CH), 138.5 (C), 161.2 ppm (C), (the signals from the C_8F_{17} and CF_2 groups were obscured due to their low intensity); ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ = −81.23 (t, ^3J(F,F) = 10.3 Hz, 3F), −98.84 (ddd, J(F,F) = 272.4, J_1(F,H) = 17.3, J_2(F,H) = 14.6 Hz, 1F), −100.95 (dt, J(F,F) = 272.4, J(F,H) = 16.4 Hz, 1F), −114.87 (t, ^3J(F,F) = 15.5 Hz, 2F), −122.38 (brs, 6F), −123.19 (brs, 2F), −123.95 (brs, 2F), −126.58 ppm (brs, 2F); HRMS: m/z: calcd for $C_{26}H_{23}NO_3F_{19}$: 758.1376 $[M+H]^+$; found 758.1420.

(*S*)-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl 2-allyl-3,3-difluoro-2-{[(1*R*)-1-phenyl-2-methoxyethyl]amino)}-5-hexenoate (18b): By means of the general procedure described above for the preparation of fluorinated dialkylated α-amino esters **6** (Method A), **18b** was obtained as a pale yellow oil (90 mg) in 90% yield from **17b** (97 mg). $[\alpha]_D^{25}$ = −7.04 (*c* 0.8 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–1.85 (m, 2H), 1.95–2.10 (m, 2H), 2.39–2.67 (m, 2H), 2.77–2.95 (m, 2H), 3.08 (s, 3H), 3.36–3.39 (m, 2H), 3.91–3.96 (m, 2H), 4.12 (t, J = 6.4 Hz, 1H), 4.82 (d, J = 12.2 Hz, 2H), 5.04 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 5.36–5.47 (m, 1H), 5.70 (ddt, J_{trans} = 17.1, J_{cis} = 10.2, J_3 = 7.0 Hz, 1H), 7.18–7.24 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 19.9 (CH_2), 28.0 (C_t, ^2J(C,F) = 22.4 Hz), 34.6 (CH_2), 37.6 (C_t, ^2J(C,F) = 23.6 Hz), 56.8 (CH), 59.2 (CH_3), 64.2 (CH_2), 69.5 (C_t, ^2J(C,F) = 24.1 Hz), 78.1 (CH_2), 118.4 (CH_2), 120.5 (CH_2), 127.6 (CH), 127.9 (CH), 128.4 (CH), 128.9 (C_t, ^3J(C,F) = 4.6 Hz), 132.9 (CH), 142.5 (C), 170.8 ppm (C) (the signals from the C_8F_{17} and CF_2 groups were obscured due to their low intensity); ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ = −81.25 (s, 3F), −100.83 (ddd, J(F,F) = 254.3, J_1(F,H) = 30.2, J_2(F,H) = 8.6 Hz, 1F), −101.05 (ddd, J(F,F) = 254.3, J_1(F,H) = 29.7, J_2(F,H) = 6.9 Hz, 1F), −114.94 (t, ^3J(F,F) = 9.5 Hz, 2F), −122.40 (brs, 6F), −123.21 (brs, 2F), −124.05 (brs, 2F), −126.60 ppm (brs, 2F); HRMS: m/z: calcd for $C_{29}H_{29}NO_3F_{19}$: 800.1844 $[M+H]^+$; found 800.1855.

(*S*)-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl 6,6-difluoro-1-{[(1*R*)-1-phenyl-2-methoxyethyl]amino)}-3-cyclohexene-1-carboxylate (19b): By means of the general procedure described above for the preparation of fluorinated cyclic α-amino esters **8**, **19b** was obtained as a brown oil (57 mg) in 92% yield from **18b** (64 mg). $[\alpha]_D^{25}$ = −16.06 (*c* 1 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.71 (m, 2H), 1.84–1.99 (m, 2H), 2.39–2.47 (m, 2H), 2.72–2.80 (m, 2H), 3.22 (s, 3H), 3.35 (d, J = 6.5 Hz, 2H), 3.56–3.67 (m, 1H), 3.79–3.91 (m, 2H), 5.45–5.58 (m, 2H), 7.16–7.21 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 19.8 (CH_2), 27.8 (C_t, ^2J(C,F) = 22.4 Hz), 30.9 (CH_2), 33.9 (C_t, ^2J(C,F) = 25.3 Hz), 57.5 (CH), 59.1 (CH_3), 63.8 (CH_2), 77.9 (CH_2), 122.1 (C_t, ^3J(C,F) = 5.7 Hz), 122.5 (C_t, ^1J(C,F) = 250.1 Hz), 123.8 (CH), 127.6 (CH), 127.7 (CH), 128.5 (CH), 141.8 (C), 170.5 ppm (C) (the signals from the C_8F_{17} group were obscured due to their low intensity); ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ = −81.25 (d, ^3J(F,F) = 9.5 Hz, 3F), −106.47 (ddd, J(F,F) = 241.4, J_1(F,H) = 20.7, J_2(F,H) = 12.9 Hz, 1F), −107.71 (dt, J(F,F) = 241.4, J(F,H) = 12.9 Hz, 1F), −114.90 (t, ^3J(F,F) = 13.8 Hz, 2F), −122.39 (brs, 2F), −123.21 (brs, 2F), −123.98 (brs, 2F), −126.59 ppm (brs, 2F); HRMS: m/z: calcd for $C_{27}H_{25}NO_3F_{19}$: 772.1531 $[M+H]^+$; found 772.1556.

(−)-(*E*)-2-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl) dimethylsilyl]ethyl 3,3-difluoro-2-{[(1*R*)-1-phenyl-2-methoxyethyl]imino)}-5-hexenoate [(−)-20]: By means of the general procedure described above for the preparation of fluorinated α-imino esters **5**, compound (−)-**20** was obtained as a yellow oil (930 mg) in 55% yield from **4c** (728 mg) and fluorous trimethylsylilethanol (^{F}TMSOH). $[\alpha]_D^{25}$ = −14.62 (*c* 1.6 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6H), 0.52–0.58 (m, 2H), 0.98–1.05 (m, 2H), 1.48–1.60 (m, 2H), 1.92–2.07 (m, 2H), 2.85–3.00 (m, 2H), 3.25 (s, 3H), 3.57 (d, J = 6.4 Hz, 2H), 4.27–4.33 (m, 2H), 4.81 (t, J = 6.4 Hz, 1H), 5.16 (dd, J_{trans} = 17.7, J_{cis} = 9.6 Hz, 2H), 5.74 (ddt, J_{trans} = 17.1, J_{cis} = 10.2, J_3 = 6.9 Hz, 2H), 7.22–7.31 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = −3.6 (CH_3), 14.7 (C_d, ^3J(C,F) = 4 Hz), 15.0 (CH_2), 15.8 (CH_2), 34.4 (C_t, ^2J(C,F) = 21.8 Hz), 39.6 (C_t, ^2J(C,F) = 24.1 Hz), 59.0 (CH), 64.1 (CH_2), 67.2 (CH_3), 77.4 (CH_2), 118.5 (C_t, ^1J(C,F) = 244.9 Hz), 120.9 (CH_2), 127.2 (CH), 127.8 (CH), 128.1 (CH), 128.5 (CH), 156.9 (C_t, ^2J(C,F) = 33.9 Hz), 161.4 ppm (C) (the signals from the C_8F_{17} group were obscured due to their low intensity); ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ = −81.26 (s, 3F), −99.07 (ddd, J(F,F) = 270.5, J_1(F,H) = 17.2, J_2(F,H) = 14.7 Hz, 1F), −101.05 (ddd, J(F,F) = 269.5, J_1(F,H) = 19.0, J_2(F,H) = 16.4 Hz, 1F), −114.93 (t, ^3J(F,F) = 14.6 Hz, 2F), −122.24–(−126.65) ppm (m, 12F); HRMS: m/z: calcd for $C_{30}H_{33}SiO_3NF_{19}$: 844.1926 $[M+H]^+$; found 844.1942.

(*S*)-2-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl) dimethylsilyl]ethyl 2-allyl-3,3-difluoro-2-{[(1*R*)-1-phenyl-2-methoxyethyl]amino)}-5-hexenoate [(−)-21]: By means of the general procedure described above for the preparation of fluorinated dialkylated α-amino esters **6** (Method A), (−)-**21** was obtained as a pale yellow oil (84 mg) in 88% yield from (−)-**20** (88 mg). $[\alpha]_D^{25}$ = −3.4 (*c* 1 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6H), 0.53–0.58 (m, 2H), 0.82–0.90 (m, 2H), 1.50–1.61 (m, 2H), 1.95–2.13 (m, 2H), 2.41–2.71 (m, 2H), 2.84–3.01 (m, 2H), 3.29 (s, 3H), 3.36–3.43 (m, 2H), 3.92–4.02 (m, 2H), 4.15–4.19 (m, 2H), 4.85 (dd, J_1 = 15, J_2 = 12 Hz, 2H), 5.09 (d, J = 17.1 Hz, 1H), 5.15 (d, J = 10.2 Hz, 1H), 5.38–5.49 (m, 1H), 5.79 (ddt, J_{trans} = 17.1, J_{cis} = 10.2, J_3 = 7.0 Hz, 1H), 7.18–7.28 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = −3.3 (CH_3), 15.0 (CH_2), 15.3 (CH_2), 15.8 (CH_2), 34.5 (C_t, ^2J(C,F) = 18.8 Hz), 37.6 (C_t, ^2J(C,F) = 18.0 Hz), 56.7 (CH), 59.2 (CH_2), 64.0 (CH_3), 69.5 (C_t, ^2J(C,F) = 17.4 Hz), 78.2 (CH_2), 118.4 (CH_2), 120.3 (CH_2), 127.5 (CH), 127.9 (CH), 128.4 (CH), 129.2 (CH), 133.0 (CH), 142.8 (C), 170.9 ppm (C) (the signals from the C_8F_{17} and CF_2 groups were obscured due to their low intensity); ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ = −81.28 (d, ^3J(F,F) = 10.3 Hz, 3F), −100.62 (ddd, J(F,F) = 253.4, J_1(F,H) = 30.6, J_2(F,H) = 8.6 Hz, 1F), −104.15 (ddd, J(F,F) = 253.4, J_1(F,H) = 30.6, J_2(F,H) = 6.9 Hz, 1F), −114.92 (t, ^3J(F,F) = 15.5 Hz, 2F), −122.40 (brs, 6F), −123.22 (brs, 2H), −124.11 (brs, 2F), −126.60 ppm (brs, 2F); HRMS: m/z: calcd for $C_{33}H_{39}SiO_3NF_{19}$: 886.2396 $[M+H]^+$; found 886.2350.

(*S*)-2-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl) dimethylsilyl]ethyl 6,6-difluoro-1-{[(1*R*)-1-phenyl-2-methoxyethyl]amino)}-3-cyclohexene-1-carboxylate [(−)-22]: By means of the general procedure described above for the preparation of compounds **8**, (−)-**22** was obtained as a brown oil (54 mg) in 90% yield from (−)-**21** (60 mg). $[\alpha]_D^{25}$ = −7.58 (*c* 0.32 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (S, 6H), 0.52–0.58 (m, 2H), 0.76–0.82 (m, 2H), 1.52–1.63 (m, 2H), 1.98–2.13 (m, 2H), 2.42–2.50 (m, 2H), 2.77–2.88 (m, 2H), 3.28 (s, 3H), 3.42 (d, J = 6.4 Hz, 2H), 3.73–3.98 (m, 3H), 5.51–5.68 (m, 2H), 7.23–7.29 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = −3.7 (CH_3), 14.6 (C_t, ^3J(C,F) = 3.4 Hz), 14.9 (CH_2), 15.2 (CH_2), 29.3 (CH_2), 30.6 (CH_2), 33.3–34.6 (CH_2), 57.1 (CH), 58.7 (CH_3), 63.2 (CH_2), 63.8 (C_t, ^2J(C,F) = 23.0 Hz), 77.6 (CH_2), 121.7 (C_t, ^3J(C,F) = 5.2 Hz), 122.3 (C_t, ^1J(C,F) = 250.1 Hz), 127.1

(CH), 127.3 (CH), 127.8 (CH), 128.1 (CH), 141.9 (C), 170.7 ppm (C) (the signals from the C_8F_{17} group were obscured due to their low intensity); ^{19}F NMR ($CDCl_3$, 282.4 MHz): $\delta = -81.25$ (t, ^3J(F,F) = 9.5 Hz, 3F), −106.42 (ddd, J(F,F) = 243.1, J_1(F,H) = 19.8, J_2(F,H) = 13.8 Hz, 1F), −107.52 (dt, J(F,F) = 242.2, J(F,H) = 13.8 Hz, 1F), −114.79–(−115.02) (m, 2F), −122.39 (brs, 6F), −123.22 (brs, 2F), −124.11 (brs, 2F), −126.60 ppm (brs, 2F); HRMS: m/z: calcd for $C_{31}H_{35}SiO_3NF_{19}$: 858.2083 $[M+H]^+$; found 858.2034.

General procedure for the detagging of the fluorous (trimethylsilyl) ethyl tag: Under N_2 atmosphere, benzyl bromide (0.048 mmol, 0.006 mL) and TBAF (0.03 mmol, 1.0 M in THF) were added to a solution of cyclic α-amino ester (−)-**22** (0.024 mmol) in THF (1 mL) at 0 °C. The reaction mixture was stirred at room temperature until TLC indicated the total disappearance of the starting material. The solvent was removed under reduced pressure and the residue was purified by means of fluorous solid phase extraction to give the previously described compound (−)-**8g** (see ref. [15]).

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[47] Treatment of **19b** with LiOH in THF/H_2O did not work for the fluorous ester hydrolysis. Different transesterification methods such as the reaction with titanium tetraisopropoxide and isopropanol (D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidman, M. Züger, *Synthesis* **1982**,138–141) or the reaction with benzyl bromide in the presence of 3-chloro-1-hydroxytetrabutyldistannoxane (CHTD) [a) J. Otera, T. Yano, R. Okawa, *Organometallics* **1986**, *5*, 1167–1170; b) J. Otera, N. Dan-oh, H. Nozaki, *J. Org. Chem.* **1991**, *56*, 5307–5311] as catalyst also failed to remove the fluorous tag. In all these attempts, only starting material **19b** was recovered unchanged.

[48] The 2-(trimethylsilyl)ethyl group is widely employed for the protection of carboxylic acids because it is easily removed upon treatment with TBAF (See: P. J. Kocienski, *Protecting Groups*, 3rd. ed., Thieme, Stuttgart, **2005**).

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