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Ethyl Nitroacetate in Aza-Henry Addition on Trifluoromethyl Aldimines: A Solvent-Free Procedure To Obtain Chiral Trifluoromethyl α,β-Diamino Esters

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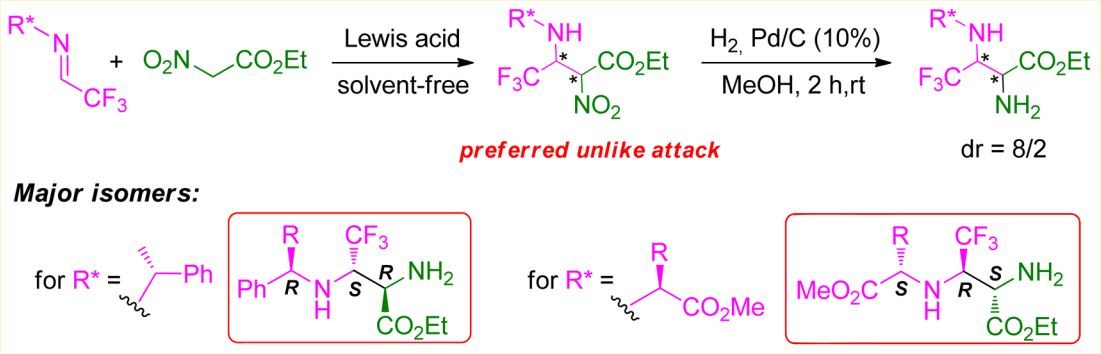
Supporting Information



ABSTRACT: A self-catalyzed aza-Henry addition of ethyl nitroacetate on *N*-alkyl trifluoromethyl aldimines was reported to synthesize β-amino α-nitro trifluoromethyl esters, precursors of α,β-diamino acid derivatives. In the presence of a resident chiral center on the imine nitrogen, the use of a suitable Lewis acid leads to a good stereofacial control, always resulting from a nucleophilic unlike attack. By starting from optically pure *N*-protected trifluoromethyl aldimines or directly from *N*-α-amino ester trifluoromethyl aldimines, small ψ[CH(CF_3)NH]-peptidomimetic backbones can be achieved in which a new primary amine function represents a possible center for synthetic extension. Finally, a very interesting, and never observed before, palladium-catalyzed *syn* β-elimination occurred, leading to the selective nitro group reduction reaction on the *syn*-α-amino ester functionalized aza-Henry adducts and obtaining more stable optically pure trifluoromethyl conjugated imines.

INTRODUCTION

The addition of carbanions to C = X bonds represents one of the most important processes of formation of carbon−carbon bonds. Among these reactions, the Henry addition[1] has been studied extensively, while its modification, known as the nitro-Mannich or aza-Henry reaction,[2] which uses an imine as electrophilic species, was much less investigated. Nucleophilic addition of nitro compounds to suitable imines represents a powerful synthetic method for C−C bond formation that leads to β-nitro amine derivatives, efficient building blocks for organic synthesis.[3]

In this field, we have reported a $ZrCl_4$-catalyzed Henry reaction[4] leading directly to functionalized nitro alkenes and, most recently, a $ZrCl_4$-catalyzed aza-Henry reaction on trifluoromethyl aldimines, giving the corresponding β-nitro amine derivatives, useful starting materials for the construction of small trifluoromethyl-modified dipeptides.[5]

Continuing our studies, $ZrCl_4$-catalyzed aza-Henry reaction of ethyl nitroacetate[2a] on trifluoromethyl aldimines[6] was considered to obtain β-amino α-nitro trifluoromethyl esters, precursors of the corresponding α,β-diamino acid derivatives.

RESULTS AND DISCUSSION

Reactivity of Ethyl Nitroacetate with *N*-Alkyl Trifluoromethyl Aldimines. Ethyl nitroacetate (**2**) reactivity in the aza-Henry addition[7] was tested using (*E*)-*N*-(2,2,2-trifluoroethylidene)cyclohexanamine (**1a**) as a suitable substrate.

Following the previously reported procedure,[4] a first reaction was performed in the presence of $ZrCl_4$ as catalyst (10%mol), and compounds *syn*-**3a** and *anti*-**3′a**, determined by ^{1}H NMR spectra, were obtained in satisfactory yields (Scheme 1, pathway A) after only 1 h of stirring at room temperature, but undesired polymerization reactions were observed. To avoid side reactions, the aza-Henry addition was attempted without catalyst, hoping for a self-catalyzed reaction, considering the acidity of the nitroacetate methylene protons. In effect, the expected β-amino α-nitro esters were obtained in very high yields and purity (Scheme 1, pathway B), working under

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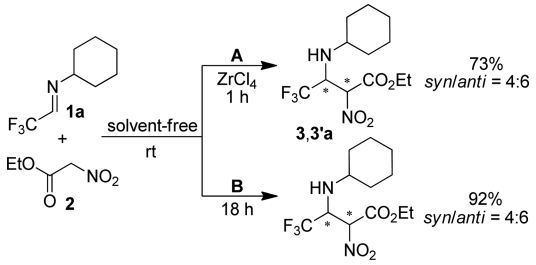
Scheme 1. Comparison between the $ZrCl_4$-Catalyzed (A) and the Self-Catalyzed Aza-Henry Addition (B) on 1a



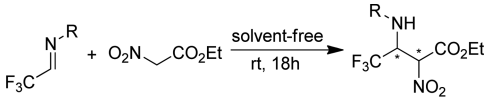
solvent-free conditions, at room temperature, although for longer times (18 h).

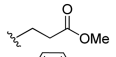
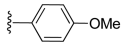
While the yield increased satisfactorily when no catalyst was employed, no difference in the *syn*/*anti* ratio was observed between the two procedures, with the $ZrCl_4$ influencing the reaction rate but not the *syn*/*anti* selectivity. This is probably due to a lower steric hindrance of the $-CO_2Et$ group compared to those of the alkyl residues present in the other reported $ZrCl_4$-catalyzed additions of nitro alkanes.[4]

The aza-Henry reaction performed following pathway B of Scheme 1 can be considered a good example of green chemistry, the reaction taking place at room temperature, with no or very low environmental impact since no solvent or catalyst was used. Moreover, no workup was needed, and a total atom economy was obtained.

The green aza-Henry reaction conditions have been extended to different trifluoromethyl (*E*)-aldimines **1b–f** to obtain the corresponding *β*-amino *α*-nitro trifluoromethyl esters *syn*-**3b–f** and *anti*-**3′b–f**. The results are reported in Table 1.

Table 1. Green Aza-Henry Reaction on Different (*E*)-*N*-Alkyl Trifluoromethyl Aldimines

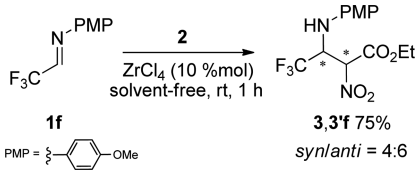


entry	1	R	3,3'	yield[a] (%)
1	**a**		**a**	92
2	**b**		**b**	88
3	**c**		**c**	87
4	**d**		**d**	80
5	**e**		**e**	95
6	**f**		**f**	55[b]

[a]After 18 h of stirring followed by a fast filtration through a plug filled with Celite. [b]After 30 d of stirring followed by a fast filtration through a plug filled with Celite.

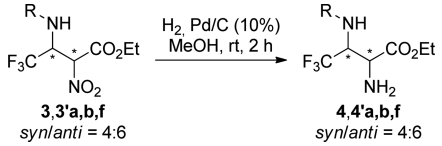
The expected compounds were obtained in high yields and very high chemical purity for all of the tested substrates, except for the imine **1f** (entry 6), in which the presence of an aromatic residue directly bonded to the imine nitrogen atom can modify the substrate reactivity. In fact, in this case, the addition took place only after 30 d and even in low yields. To decrease reaction time, the aza-Henry addition on **1f** was successfully repeated in the presence of $ZrCl_4$,[4] obtaining *β*-amino *α*-nitro esters **3** and **3′f** in higher yields and shorter times (Scheme 2). Once again, the presence of catalyst did not change the selectivity of the reaction.

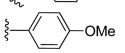
Scheme 2. $ZrCl_4$-Catalyzed Aza-Henry Reaction on the (*E*)-*N*-Aryl Trifluoromethyl Aldimine 1f



Unfortunately, all attempts [flash chromatography on silica gel, fast filtration on a short column (3 cm) of acidic Al_2O_3 or of HCl-washed SiO_2, HPLC used both in normal and in reversal-phase or coupled with a chiral solid phase[8]] to obtain the *β*-amino *α*-nitro esters *syn*-**3a–f** and *anti*-**3′a–f** as purified diastereomers failed, due to the fast and uncontrollable epimerization of compounds, and products were always obtained as *syn*/*anti* racemates. To overcome this problem, the crude mixtures of **3,3′a,b,f** were directly subjected to a selective nitro group reduction reaction using MeOH as solvent and 10% Pd/C as catalyst,[4,9] obtaining in the good yields the corresponding primary *α*,*β*-diamino esters *syn*-**4a,b,f** and *anti*-**4′a,b,f** (Table 2) that were then obtained as pure compounds after flash chromatography on silica gel (see the Experimental Section).

Table 2. Selective Nitro Group Reduction Reaction



entry	3,3'	R	4,4'	yield[a] (%)
1	**a**		**a**	90
2	**b**		**b**	83
3	**f**		**f**	86

[a]After 2 h of stirring followed by a fast filtration through a plug filled with Celite.

Then, we explored the possibility to gain an asymmetric aza-Henry addition by adding a suitable chiral organometallic catalyst, such as Zr/BINOL Lewis acid, prepared in situ starting from zirconium(IV) *tert*-butoxide [$Zr(O\text{-}t\text{-}Bu)_4$], that was reported as an efficient catalyst in some addition reactions.[10,11]

First, the reactions on imines **1b** and **1f**, having two easily removable protecting groups,[12] were performed using directly the commercially available $Zr(O\text{-}t\text{-}Bu)_4$ as Lewis acid, but no reactions were observed. Assuming that probably the *t*-Bu electron-donating groups on the metal-coordinating oxygens can lower the catalyst chelating activity, the reactions on the same imines were performed by using two different Zr/BINOL chiral Lewis acids[10] (Figure 1), hoping that the naphthyl residues on oxygen atoms could dramatically change the reaction.

Unfortunately, in the catalyzed additions on **1b**, performed either with Zr/BINOL-A or B, the products were obtained as a racemate after 18 h of stirring, as shown by the HPLC analyses

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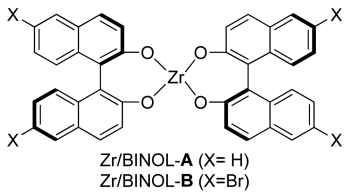
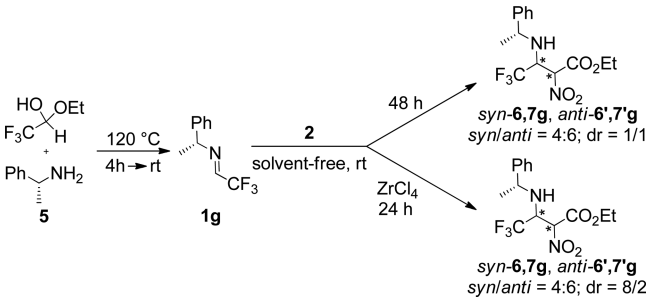


$C_6H_{10}F_3N_2O_4$

Figure 1. Different Zr/BINOL chiral Lewis acids.

performed on a chiral solid phase, suggesting that the chiral catalysts did not influence the reactions. Therefore, we considered imine **1f**, which reacted very slowly (30 d) without catalyst (Table 1, entry 6) but quickly (1 h) in the presence of $ZrCl_4$ (Scheme 3). However, once again, 30 d was needed to

Scheme 3. Comparison between the Self-Catalyzed and the $ZrCl_4$-Catalyzed Aza-Henry Addition on Optically Pure 1g



observe the disappearance of starting materials and the formation of products, by NMR analyses, always as a racemate in low yields, suggesting that also in the presence Zr/BINOL chiral Lewis acids the aza-Henry additions took place through a self-catalytic process.

The collected data clearly indicate that also the presence of electron-withdrawing aryl residues in the place of *t*-Bu electron-donating groups on oxygen atoms dramatically lower the zirconium coordinating activity.

Hoping for more success and also to achieve asymmetric reactions at low cost and high atom economy, the stereoselective studies were continued considering the reactivity of the chiral imine **1g** derived from (*R*)-1-phenylethylamine (**5**) both in a catalyzed and in an uncatalyzed one-pot aza-Henry reaction with ethyl nitroacetate. Thus, trifluoroacetaldehyde ethyl hemiacetal was added in an equimolar ratio to commercial amine **5**, heated to 120 °C (4 h), and after the reaction mixture was brought to room temperature, only ethyl nitroacetate (1 equiv) or $ZrCl_4$ (20 mol %) and ethyl nitroacetate (**2**, 1 equiv) were added (Scheme 3).

By comparison of the ^1H and ^{19}F NMR spectra performed on the crude mixtures, while as expected no difference between the two reaction data was obtained in the diastereomeric *syn*/*anti* ratio, the facial selectivity of the attack was deeply influenced by the presence of catalyst (dr 1/1 vs 8/2), suggesting the crucial role of $ZrCl_4$ on the facial selectivity control. To explain this, one can suppose that only when Zr(IV) coordinates both carbonyl and nitro group oxygen atoms, forming an octahedral-like intermediate **I** (Figure 2) and so constraining the nitronate in a planar geometric disposition, the nucleophilic attack takes place preferentially on one of the two imine prochiral faces.

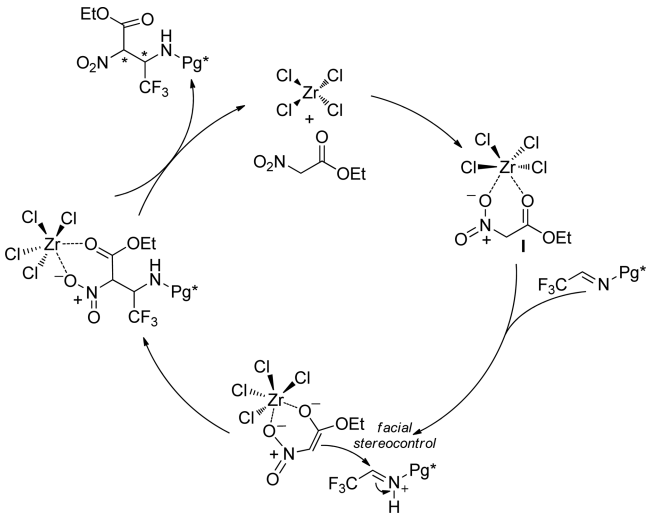
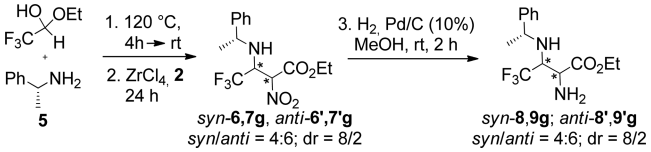


Figure 2. Possible pathway of $ZrCl_4$-catalyzed aza-Henry addition.

Here again, it proved impossible to separate the *β*-amino *α*-nitro esters *syn*-**6,7g** and *anti*-**6′,7′g** as pure diastereomers by flash chromatography, which is why the crude mixtures were subjected to the selective nitro group reduction reaction[9] under the conditions reported above. The obtained corresponding trifluoromethyl *α,β*-diamino esters *syn*-**8,9g** and *anti*-**8′,9′g** (Scheme 4) were successfully purified by flash chromatography on silica gel and obtained as optically pure compounds.

Scheme 4. Synthesis of Trifluoromethyl *α,β*-Diamino Esters



As determined by 2D NMR spectra coupled with minimization geometries[5,13] (see the Supporting Information), the major isomer showed the *R,S,R* configuration,[4] resulting from a nucleophilic unlike attack of the nitronate *Re* face on the prochiral *Si* face of the activated imine **1g** (Figure 3).

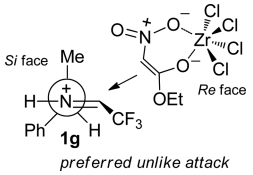


Figure 3. Nucleophilic attack of the nitronate *Re* face on the prochiral *Si* face of activated imine **1g**.

Reactivity of Ethyl Nitroacetate with *N*-*α*-Amino Ester Trifluoromethyl Aldimines. Extending our studies aimed at obtaining interesting peptidomimetic structures, trifluoromethyl aldimines derived from L-*α*-amino esters[14] were considered as useful substrates in the asymmetric aza-Henry reaction, even for potential chemical transformations of easily achievable multifunctionalized structures.

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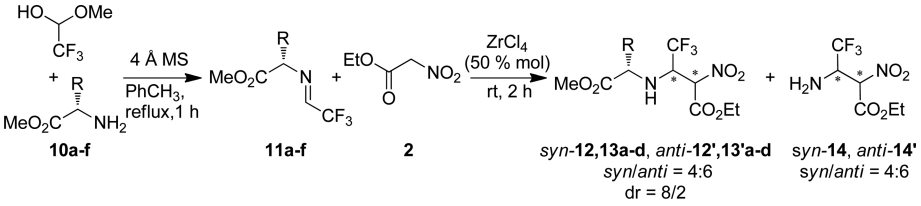
Table 3. $ZrCl_4$-Catalyzed Aza-Henry Reaction on the *N*-α-Amino Ester Substituted Trifluoromethyl (*E*)-Aldimines



entry	11	R	yield[a] (%)	*syn*-12,13/*anti* 12′,13′ (% conv)[b]	*syn*-14/*anti*-14′ (% conv)[b]
1	**a**	$CH(CH_3)_2$	75	55	45
2	**b**	$CH(CH_3)CH_2CH_3$	72	50	50
3	**c**	$CH_2CH(CH_3)_2$	74	trace	>90
4	**d**	$CH_2CH_2SCH_3$	70	trace	>90
5	**e**	CH_2Ph	73		99
6	**f**	CH(O-*t*-Bu)CH_3	74		>95

[a]Determined after rapid filtration through a plug filled with Celite. [b]Determined by ^1H and ^{19}F NMR spectra performed on the crude mixtures.

Following the reaction conditions recently reported by us,[14] starting from α-amino esters **10a−f**, the corresponding trifluoromethyl aldimines **11a−f** were obtained in good yields and very high purity and directly used without purification in the subsequent asymmetric aza-Henry reaction. First, the reactions were attempted without catalyst and solvent, but no addition products were obtained, even after a long time. In effect, the presence of an ester group on the aminic residue may decrease the imine lone pair availability, thus inhibiting the self-catalyzed reaction. A slow disappearance of imine was observed by spectroscopy, likely due to hydrolysis.

Ethyl nitroacetate was then reacted under solvent-free $ZrCl_4$-catalyzed asymmetric aza-Henry reactions in an equimolar ratio with aldimines **11a−f** (Table 3), and the addition outcome was followed by ^1H and ^{19}F NMR analyses.

Compared to similar additions carried out on *N*-alkyl aldimines ($ZrCl_4$ 10% mol), in all cases a greater amount of catalyst (50% mol) was required to bring the reactions to completion. Furthermore, starting from aldimines **11a−d**, surprisingly the NMR analyses performed on the crude mixtures showed, after only 2 h, the formation of six different compounds (entries 1−4), and was then possible to assign the structures of the expected *syn*-**12,13**/*anti*-**12′,13′a−d** and the unexpected *syn*-**14**/*anti*-**14′**. In the latter compounds, the $RCHCO_2Me$ groups were lost and the primary amine functions restored. Moreover, the compounds *syn*-**14**/*anti*-**14′** were the only products obtained in the aza-Henry reactions performed on aldimines **11e,f** (entries 5 and 6), perhaps depending on the greater or lesser inductive effect of the R residue.

In order to limit and/or avoid the formation of **14,14′**, the addition of **2** on the imine **11a** was performed by changing some reaction parameters [temperature (up to −20 °C), time, and molar ratio], but no significant differences were found.

While it is possible to propose a catalytic cycle to explain the synthesis of the expected products (Figure 4, A), it is very difficult to explain the formation of the unexpected primary amines (Figure 4, B).

Considering the reagent structures, $ZrCl_4$ probably coordinates both imine and ethyl nitroacetate, forming first the cyclic complex **I** and, after deprotonation, the cyclic complex **II**, respectively. As a consequence, the aza-Henry reaction occurs through an intermolecular attack of **II** on **I**, leading to the key tetrahedral intermediate **III**. The latter can lead to the desired products *syn*-**12,13** and *anti*-**12′,13′**, restoring the cycle (A), or

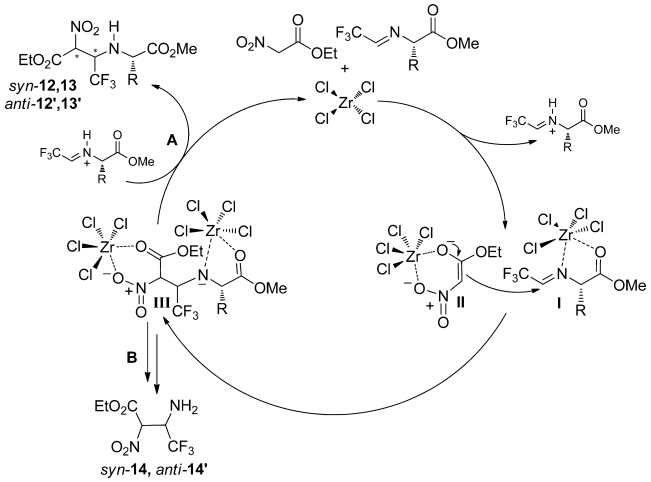


Figure 4. Possible pathway of $ZrCl_4$-catalyzed aza-Henry addition on *N*-α-amino ester substituted trifluoromethyl (*E*)-aldimines.

undergoes an unexpected never before observed C−N bond cleavage (B), leading to the primary amines *syn*-**14**/*anti*-**14′**.

To avoid or limit the formation of these last compounds, the use of different catalysts was considered. Unfortunately, in the presence of Cu(I or II) or monodentate boron no reaction occurred, as already happened starting from nitro alkanes.[4] On the contrary, the use of $AlCl_3$ as catalyst lead successfully to the only expected addition products in high yields and in satisfactory diastereoselectivity[15] (Table 4).

By starting from imine **11e** (entry 5), the desired compounds were not achieved and compounds *syn*-**14**/*anti*-**14′** were the only products of the reaction, suggesting a very strong influence of the L-α-amino ester residue on the reaction outcome.

Completely different but very interesting was the behavior of imine **11f** which, in the presence of $AlCl_3$ as catalyst, did not undergo the expected addition reaction (Table 4, entry 6) but surprisingly led in only 30 min to the oxazolidine **11′f**, probably through an intramolecular nucleophilic attack, to our knowledge never observed before (Scheme 5).[16]

The success of $AlCl_3$-catalyzed aza-Henry reactions on imines **11a−d** can be due to the different coordinating capacity of considered metals. In fact, the aluminum coordination to the nitro compound leads to a linear activated ethyl nitroacetate. After generation of nucleophilic specie **V**, an intermolecular attack on activated imine (**VI**) gives **VII** that leads to the

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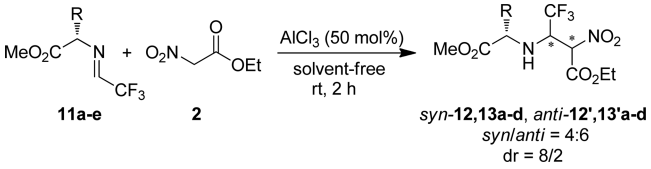
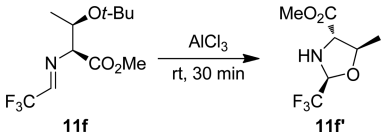
Table 4. $AlCl_3$-Catalyzed Aza-Henry Reaction on the *N*-α-Amino Ester Substituted Trifluoromethyl (*E*)-Aldimines



entry	11	R	*syn*-12,13/*anti*-12′,13′	yield[a] (%)
1	a	$CH(CH_3)_2$	a	80
2	b	$CH(CH_3)CH_2CH_3$	b	75
3	c	$CH_2CH(CH_3)_2$	c	72
4	d	$CH_2CH_2SCH_3$	d	70
5	e	CH_2Ph		
6	f	CH(O-*t*-Bu)CH_3		

[a]After flash chromatography on silica gel (obtained as diastereomeric mixtures, due to isomerization during the purification step).

Scheme 5. Reactivity of 11f in the Presence of $AlCl_3$



primary amines **14,14′** only when R is a benzylic residue (Table 4, entry 5).

In fact, starting from the other aldimines **11a−d**, the nucleophilic attack was followed by protonation, giving the desired products **12,13/12′,13′** and restoring the catalytic cycle (Figure 5).

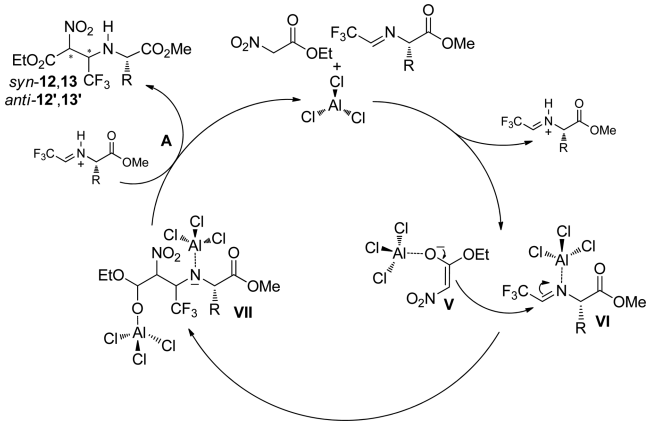
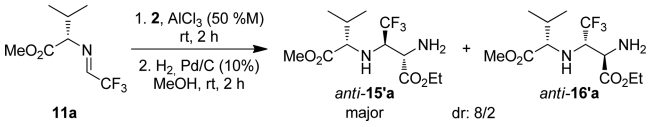


Figure 5. Possible pathway of $AlCl_3$-catalyzed aza-Henry addition on *N*-α-amino ester substituted trifluoromethyl (*E*)-aldimines.

Also for these compounds, after 12 h, complete isomerization of the obtained diastereomers was observed; therefore, we decided to repeat the $AlCl_3$-catalyzed reactions and perform the nitro group reduction reaction directly on the crude mixtures.

The nitro reduction was tested on the aza-Henry crude mixture obtained from aldimine **11a**, working at room temperature in MeOH as solvent, in the presence of Pd/C (10%M) as catalyst and using H_2 as hydrogen source at atmospheric pressure. After 2 h, NMR analyses showed the substrate disappearance but, surprisingly, after purification by flash chromatography only the *anti* isomers **15′,16′a** (Scheme 6) were collected as determined by 2D NMR analyses.

Scheme 6. Aza-Henry Addition on 11a and Selective Nitro Group Reduction Performed Directly on the Crude



The reduction was then repeated by changing some parameters (MeOH at reflux, 10% Pd/C, ammonium formate as hydrogen source), but only a decrease in the yields was observed, with only products *anti*-**15′,16′a** in the same dr (8/2) being obtained.

By comparison of energy minimization studies and 2D NMR analyses on purified compounds, the *S,R,S* absolute configuration was assigned to the major diastereomer *anti*-**15a′**, the unlike nucleophilic attack occurring preferentially on the *Re* face of $AlCl_3$-activated imine chiral complex (Figure 6).

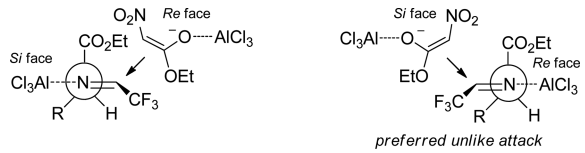


Figure 6. Two possible nucleophilic attack of nitronate on the prochiral face of activated *N*-α-amino ester substituted trifluoromethyl (*E*)-aldimines.

The obtained optically pure compounds can be considered new ψ[$CH(CF_3)NH$]-peptidomimetics,[17] already enriched by the presence of a natural α-amino ester residue and therefore a useful small building block for the synthesis of more complex systems.

The nitro group reduction was then performed on the other crude mixtures obtained starting from aldimines **11b−d**, and all results are collected in Table 5.

Once again, after the reduction reaction only the *anti* primary amines **15′** and **16′a−c** with the same diastereomeric ratio (8/2) were obtained, as determined by comparison of NMR analyses performed on the starting aza-Henry crude mixtures. Starting from aldimine **11d** (entry 4) no reduction products were observed, even when the reaction conditions were changed (50% M of catalyst and/or ammonium formate as hydrogen source in MeOH at reflux), probably due to the presence of a sulfur atom in the R group.

Obviously, the unexpected presence of new conjugated imine **17,18a,b** as purified optically pure chiral compounds coupled with the absence of *syn* primary amine isomers expected as reduction products of corresponding *syn*-**12,13a−c** nitro adducts have drawn our attention.

Although we expected a complete racemization still hoping to gain more information, we decided to perform the reduction on a nitro derivative purified mixture after flash chromatography of the crude mixture obtained from aldimine **11a**. Unexpectedly, only the nitro compounds *syn*-**12,13a** (dr = 8/2) were collected in very low yields (<10%). Moreover, the reduction, performed on obtained purified *syn* isomers, gives the previously observed conjugated imine structures **17,18a** (Scheme 7).

Considering the collected data, compounds **17,18a−c** should result only via the *syn* nitro compounds **12,13a−c** during the Pd-catalyzed hydrogenation reaction, whereas with the use of

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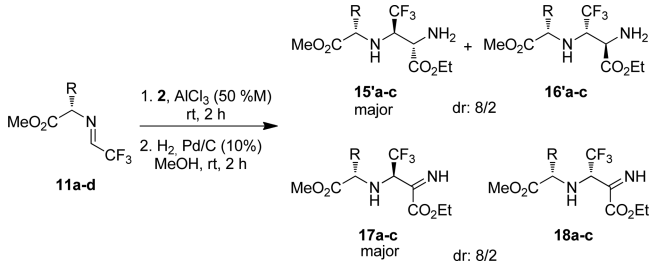
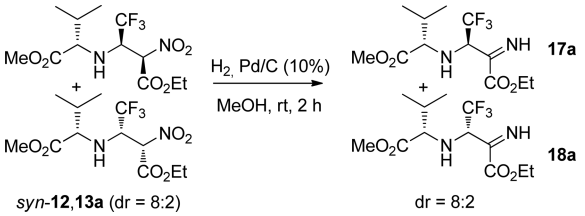
Table 5. Selective Nitro Group Reduction



entry	R	15′	yield[a] (%)	16′	yield[a] (%)	17	yield[a] (%)	18	yield[a] (%)
1	$CH(CH_3)_2$	**a**	36	**a**	9	**a**	29	**a**	7
2	$CH(CH_3)CH_2CH_3$	**b**	37	**b**	9	**b**	30	**b**	8
3	$CH_2CH(CH_3)_2$	**c**	31	**c**	8	**c**	25	**c**	6
4	$CH_2CH_2SCH_3$								

[a]After flash chromatography on silica gel.

Scheme 7. Selective Nitro Group Reduction Performed on the Purified *syn*-12,13a



Pd as catalyst the *syn*-geometry of the starting compounds could be responsible for the synthesis of the new highly functionalized imines as they may be formed through a palladium-catalyzed *syn* β-elimination[18] of the corresponding unisolated hydroxylamines,[19] well-known intermediates in the nitro group reduction reaction.

CONCLUSION

In this paper, $ZrCl_4$- or $AlCl_3$-catalyzed aza-Henry reactions of ethyl nitroacetate on trifluoromethyl aldimines were reported. While the most green zirconium catalyst was very efficient in promoting the addition on different *N*-alkyl-substituted CF_3-aldimines, starting from α-amino ester functionalized aldimines, the same $ZrCl_4$ promoted an uncontrollable side reaction, leading to primary β-nitro amines wherein the alkyl α-amino ester residue is lost. In these cases, the use of $AlCl_3$ was needed to obtain the desired compounds that, after reduction of nitro group, can be considered as interesting ψ[CH(CF_3)NH]-peptidomimetics after the reduction of nitro group. Small ψ[CH(CF_3)NH]-peptidomimetic backbones can be achieved even from the chiral diamines obtained starting from an optically pure *N*-benzyl-protected trifluoromethyl aldimine **1g**, first through a functionalization of the $-NH_2$ residue in the α position to the ester moiety and then by hydrogenolysis of the chiral benzyl group, restoring a new primary amine function like a possible center of molecular growth.

Finally, a never before observed palladium-catalyzed *syn* β-elimination occurs on the *syn*-α-amino ester functionalized aza-Henry adducts during the reduction reaction of the nitro group. Starting from these isomers, more stable trifluoromethyl-conjugated imines were obtained as interesting new compounds.

EXPERIMENTAL SECTION

IR spectra were recorded on an FT/IR spectrophotometer in $CHCl_3$ as the solvent and reported in cm^{-1}. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a 300 or a 400 MHz instrument and reported in δ units. $CDCl_3$ was used as the solvent, and $CHCl_3$ (δ = 7.26 ppm for ^1H NMR), $CDCl_3$ (δ = 77.0 ppm for ^{13}C NMR), or C_6F_6 (δ = −164.9 for ^{19}F NMR) was used as internal standard. The NOESY experiments were performed on a 400 MHz instrument using $CDCl_3$ as the solvent and $CHCl_3$ as the internal standard and used to assist in structure elucidation.[20] ESI MS analyses were performed using a quadrupole-time-of-flight (Q-TOF) mass spectrometer equipped with an ESI source and a syringe pump. The experiments were conducted in the positive-ion mode. Optical rotation was determined at 25 °C at a wavelength of 589 nm, using a quartz cell of 1 cm length. Imines **1a−g**,[6] **11a,b,c,e**,[14] and **11d**[21] were prepared by reaction of trifluoroacetaldehyde ethyl hemiacetal and an opportune primary amine following the reported procedure. All of the optimized geometries were located using hybrid functional theory (B3LYP)[22] and the 6-31G(d, p)[23] basis set using the continuum solvation model[24] with chloroform (ε = 4.81) as the solvent, conforming to the experimental conditions. All calculations were carried out using the Gaussian 09 program.[25]

Synthesis of Trifluoromethyl β-Amino α-Nitro Esters *syn*-3a−f and *anti*-3′a-f. A mixture of trifluoromethyl (*E*)-aldimine **1a−f** (1.1 mmol) and ethyl nitroacetate (1 mmol) was kept stirring overnight under solvent-free conditions at room temperature. The obtained crude mixtures were recovered and used without any further purification in the subsequent reaction.

*Ethyl 3-(Cyclohexylamino)-4,4,4-trifluoro-2-nitrobutanoate (syn-**3a** and anti-**3′a**).* Yellow-brown oil. Yield 95% (0.295 g). IR ν_{max} cm^{-1}: 3371; 1755; 1571. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.90−1.28 (m, 12H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.51−1.85 (m, 9H), 1.99 (d, *J* = 11.5 Hz, 1H), 2.65−2.71 (m, 2H), 4.13−4.44 (m, 6H), 5.22 (d, *J* = 6.8, 1H, *syn* isomer), 5.36 (d, *J* = 5.9 Hz, 1H, *anti* isomer). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.7 (2C), 24.2 (2C), 24.4 (2C), 25.7 (2C), 32.4, 32.6, 33.9 (2C), 54.7, 55.0, 57.2 (q, *J* = 29.5 Hz), 57.5 (q, *J* = 29.4 Hz), 63.3, 63.7, 86.1, 87.0, 124.7 (q, *J* = 286.0 Hz), 124.8 (q, *J* = 285.2 Hz), 161.7, 162.0. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −70.89 (d, *J* = 7.0 Hz), −72.41 (d, *J* = 7.5 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{20}F_3N_2O_4$ 313.1375, found 313.1378.

*Ethyl 3-(Benzylamino)-4,4,4-trifluoro-2-nitrobutanoate (syn-**3b** and anti-**3′b**).* Yellow oil. Yield 95% (0.305 g). IR ν_{max} cm^{-1}: 3381; 1754; 1574. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 2.26 (br, 1H), 2.56 (br, 1H), 3.83−3.99 (m, 3H), 4.02−4.17 (m, 3H),), 4.34 (q, *J* = 7.1 Hz, 4H), 5.31 (d, *J* = 6.4 Hz, 1H, *syn* isomer), 5.46 (d, *J* = 5.5 Hz, 1H, *anti* isomer), 7.24−7.39 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.6 (2C), 52.2, 52.3, 59.3 (q, *J* = 29.5 Hz), 59.5 (q, *J* = 29.5 Hz), 63.4, 63.7, 85.4, 86.6, 124.7 (q, *J* = 286.7 Hz), 124.8 (q, *J* = 285.9 Hz), 127.5, 127.6, 128.1, 128.2,

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128.4 (2C), 128.5 (2C), 128.7 (2C), 138.1, 138.2, 161.6, 161.7. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −70.37 (d, J = 6.9 Hz), −71.43 (d, J = 7.0 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{16}F_3N_2O_4$ 321.1062, found 321.1053.

*Ethyl 3-(Cyclopentylamino)-4,4,4-trifluoro-2-nitrobutanoate (**syn-3c** and **anti-3′c**).* Yellow-brown oil. Yield 90% (0.265 g). IR ν_{max} cm^{-1}: 3380; 1743; 1565. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (t, J = 7.2, 6H), 1.43−1.95 (m, 16H), 2.09 (d, J = 11.2, 1H), 3.26−3.38 (m, 2H), 3.38−3.51 (m, 1H), 4.03−4.15 (m, 2H), 4.26 (q, J = 7.2, 4H), 5.19 (d, J = 6.8 Hz, 1H, *syn* isomer), 5.35 (d, J = 5.6 Hz, 1H, *anti* isomer). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.6 (2C), 23.2, 23.3 (2C), 23.8, 30.8 (2C), 33.8, 33.9, 52.2 (2C), 57.8 (q, J = 26.3 Hz), 58.9 (q, J = 29.3 Hz), 63.2, 63.6, 85.9, 86.9, 124.7 (q, J = 286.6 Hz), 124.9 (q, J = 285.7 Hz), 161.7, 161.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −70.19 (d, J = 8.1 Hz), −72.01 (d, J = 8.2 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{11}H_{18}F_3N_2O_4$ 299.1219, found 299.1216.

*Ethyl 4,4,4-Trifluoro-2-nitro-3-(pentylamino)butanoate (**syn-3d** and **anti-3′d**).* Yellow-brown oil. Yield 80% (0.238 g). IR ν_{max} cm^{-1}: 3373; 1755; 1553. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.86 (t, J = 6.7, 6H), 1.19−1.34 (m, 10H), 1.35−1.48 (m, 4H), 1.48−1.72 (m, 4H), 1.94 (br, 1H), 2.56−2.73 (m, 2H), 2.81−2.92 (m, 3H), 3.99−4.08 (m, 1H, *syn* isomer), 4.09−4.19 (m, 1H, *anti* isomer), 4.30 (q, J = 7.1, 2H, *syn* isomer), 4.31 (q, J = 7.1 Hz, 2H, *anti* isomer), 5.21 (d, J = 6.8 Hz, 1H, *syn* isomer), 5.36 (d, J = 6.0 Hz, 1H, *anti* isomer). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.7 (2C), 13.8 (2C), 22.3 (2C), 28.9 (2C), 29.9 (2C), 48.8, 48.9, 60.3 (q, J = 28.0 Hz), 60.7 (q, J = 29.3 Hz), 63.3, 63.7, 85.8, 86.8, 124.7 (q, J = 286.3 Hz), 124.9 (q, J = 285.7), 161.6, 161.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −71.49 (d, J = 6.8 Hz), −71.86 (d, J = 7.0 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{11}H_{20}F_3N_2O_4$ 301.1375, found 301.1368.

*Ethyl 4,4,4-Trifluoro-3-[(3-methoxy-3-oxopropyl)amino]-2-nitrobutanoate (**syn-3e** and **anti-3′e**).* Yellow-brown oil. Yield 95% (0.302 g). IR ν_{max} cm^{-1}: 3364; 1743; 1684; 1571. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.30 (t, J = 7.2, 6H), 2.27 (br, 1H), 2.74 (br, 1H), 2.81−3.00 (m, 4H), 3.16−3.29 (m, 4H), 3.66 (s, J = 4.2 Hz, 6H), 4.01−4.16 (m, 2H), 4.30 (d, J = 7.1 Hz, 2H, *syn* isomer), 4.31 (q, J = 7.1 Hz, 2H, *anti* isomer), 5.21 (d, J = 6.6 Hz, 1H, *syn* isomer), 5.34 (d, J = 6.3 Hz, 1H, *anti* isomer).^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.7 (2C), 35.0, 35.1, 44.4 (2C), 51.6 (2C), 60.5 (q, J = 29.7 Hz), 60.8 (q, J = 29.7 Hz), 63.4, 63.8, 85.5, 86.7, 124.5 (q, J = 286.1 Hz), 124.6 (q, J = 285.4 Hz), 161.5, 161.7, 171.9, 172.4. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.52 (d, J = 8.3 Hz), −73.14 (d, J = 7.9 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{10}H_{16}F_3N_2O_6$ 317.0960, found 317.0954.

*Ethyl 4,4,4-Trifluoro-3-[(4-methoxyphenyl)amino]-2-nitrobutanoate (**syn-3f** and **anti-3′f**).* Brown oil. Yield 80% (0.269 g). IR ν_{max} cm^{-1}: 3364; 1758; 1563. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.17 (t, J = 7.2 Hz, 3H, *anti* isomer), 1.26 (t, J = 7.2 Hz, 3H, *syn* isomer), 3.75 (s, 6H), 4.12−4.37 (m, 4H), 4.60 (d, J = 11.1 Hz, 2H), 4.70−4.88 (m, 1H), 5.00−5.14 (m, 1H), 5.38 (d, J = 5.9 Hz, 1H, *syn* isomer), 5.60 (d, J = 4.4 Hz, 1H, *anti* isomer), 6.69−6.85 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.6 (2C), 55.5 (2C), 58.3 (q, J = 31.0, Hz), 58.7 (q, J = 31.2 Hz), 63.8, 64.2, 84.3, 85.4, 114.8 (2C), 114.9 (2C), 116.3 (2C), 116.6 (2C), 123.83 (q, J = 285.3 Hz), 124.0 (d, J = 284.7 Hz), 138.2, 138.5, 154.1, 154.2, 161.4, 161.6. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −70.13 (d, J = 7.1 Hz), −72.32 (d, J = 6.6 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{16}F_3N_2O_5$ 337.1011, found 337.1008.

Nitro Group Reduction: Synthesis of Compounds *syn*-4a,b,f and *anti*-4′a,b,f. In a two-neck flask, the crude mixtures of trifluoromethyl β-amino α-nitro esters ***syn*-3a,b,f** and ***anti*-3′a,b,f** were dissolved in 5 mL of anhydrous MeOH, and 10% Pd/C (120 mg/mmol of nitro compound) was added. The reaction mixtures were hydrogenated under atmospheric pressure at room temperature for 2 h, after which time the crude mixtures were filtered off to remove the catalyst and the solvent was removed by evaporation at reduced pressure. The obtained compounds were separated by flash chromatography on silica gel.

*Ethyl 2-Amino-3-(cyclohexylamino)-4,4,4-trifluorobutanoate (**syn-4a**).* Pale yellow oil. Yield 40% (0.113 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). IR ν_{max} cm^{-1}: 3385; 3314; 1745. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.23−1.07 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H), 1.85−1.56 (m, 9H), 2.65−2.56 (m, 1H), 3.64−3.56 (m, 2H), 4.26−4.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 24.5, 24.6, 25.9, 33.5, 33.7, 54.5, 54.6, 58.7 (q, J = 26.5 Hz), 61.4, 125.91 (q, J = 284.7 Hz), 172.8. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.8 (d, J = 6.7 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{12}H_{22}F_3N_2O_2$ 283.1633, found 283.1623.

*Ethyl 2-Amino-3-(cyclohexylamino)-4,4,4-trifluorobutanoate (**anti-4′a**).* Pale yellow oil. Yield 43% (0.115 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). IR ν_{max} cm^{-1}: 3380; 3302; 1730. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.21−0.89 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H), 1.87−1.51 (m, 9H), 2.59−2.50 (m, 1H), 3.71 (dq, J = 2.3 Hz, 7.9 Hz, 1H), 3.86 (d, J = 2.3 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.1, 24.4, 24.6, 25.9, 33.1, 34.0, 53.5 (q, J = 2.0 Hz), 54.3, 57.8 (q, J = 26.3 Hz), 61.7, 126.3 (q, J = 285.5 Hz), 172.6. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.8 (d, J = 6.8 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{12}H_{22}F_3N_2O_2$ 283.1633, found 283.1630.

*Ethyl 2-Amino-3-(benzylamino)-4,4,4-trifluorobutanoate (**syn-4b**).* Pale yellow oil. Yield 36% (0.099 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate =75:25). IR ν_{max} cm^{-1}: 3388; 3315; 1755. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (t, J = 7.1 Hz, 3H), 2.05 (br, 3H), 3.48−3.61 (m, 1H), 3.70 (d, J = 3.9 Hz, 1H), 3.90 (d, J = 12.0 Hz, 1H), 4.00 (d, J = 12.0 Hz, 1H), 4.19 (ddd, J = 14.2 Hz, 7.1 Hz, 2.2 Hz, 2H), 7.26−7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 51.7, 54.0, 60.9 (q, J = 25.8 Hz), 61.5, 124.0 (q, J = 281.7 Hz), 127.3, 128.2 (2C), 128.4 (2C), 139.2, 172.1. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −70.0 (d, J = 7.6 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{18}F_3N_2O_2$ 291.1320, found 291.1313.

*Ethyl 2-Amino-3-(benzylamino)-4,4,4-trifluorobutanoate (**anti-4′b**).* Pale yellow oil. Yield 42% (0.103 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). IR ν_{max} cm^{-1}: 3376; 3357; 1736. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.24 (t, J = 7.1 Hz, 3H), 2.43 (br, 3H), 3.78−3.96 (m, 3H), 4.10 (d, J = 1.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 7.11−7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 55.7, 61.0, 61.8, 65.1 (q, J = 30.9 Hz), 122.3 (q, J = 286.6 Hz), 127.7, 128.1, 128.5 (2C), 129.7, 138.9, 170.8. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −75.7 (d, J = 7.4 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{18}F_3N_2O_2$ 291.1320, found 291.1317.

*Ethyl 2-Amino-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]-butanoate (**syn-4f**).* Pale yellow oil. Yield 39% (0.096 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). IR ν_{max} cm^{-1}: 3396; 3343; 1755. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (t, J = 7.1, 3H), 2.24 (br, 2H), 3.74 (m, 4H), 4.16−4.36 (m, 3H), 4.48 (d, J = 8.8 Hz, 1H), 6.69−6.76 (m, 2H), 6.77−6.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 14.0, 54.0, 55.6, 59.0 (q, J = 27.7 Hz), 61.8, 115.0 (2C), 116.1 (2C), 125.32 (q, J = 284.3 Hz), 139.4, 153.4, 172.3. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −71.2 (d, J = 7.7 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{18}F_3N_2O_3$ 307.1270, found 307.1261.

*Ethyl 2-Amino-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]-butanoate (**anti-4′f**).* Pale yellow oil. Yield 42% (0.103 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate =75:25). IR ν_{max} cm^{-1}: 3376; 3357; 1736. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.08 (t, J = 7.1 Hz, 3H), 2.18 (br, 2H), 3.73 (s, 3H), 4.04 (q, J = 7.1, 2H), 4.13 (s, 1H), 4.37−4.42 (m, 1H), 4.59 (d, J = 7.5, 1H), 6.64−6.70 (m, 2H), 6.72−6.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.8, 52.7, 55.7, 58.4 (q, J = 28.4 Hz), 62.1, 114.7 (2C), 116.0 (2C), 125.7 (q, J = 284.6 Hz), 140.1, 153.2, 171.0. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −73.4 (d, J = 7.4 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{18}F_3N_2O_3$ 307.1270, found 307.1267.

Synthesis of Trifluoromethyl β-Amino α-Nitro Esters *syn*-6,7g and *anti*-6′,7′g. The same procedure reported to obtain **3,3′a−f** was followed.

*Ethyl 4,4,4-Trifluoro-2-nitro-3-[[(1R)-1-phenylethyl]amino]-butanoate (**syn-6,7g, anti-6′,7′g**).* Yellow oil. Yield 85% (0.284 g). IR ν_{max} cm^{-1}: 3378; 1748; 1554. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20 (t, J = 7.1 Hz, 3H, *anti* minor isomer), 1.28−1.40 (m, 21H), 2.27 (br, 4H), 3.74−3.82 (m, 1H), 3.94−4.23 (m, 7H), 4.26−4.45 (m, 8H), 5.15 (d, J = 5.6 Hz, 1H, *syn* minor isomer), 5.28 (d, J = 5.7 Hz, 1H, *syn* major isomer), 5.34 (d, J = 4.6 Hz, 1H, *anti* minor isomer), 5.42 (d, J =

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4.9 Hz, 1H, *anti* major isomer), 7.19−7.39 (m, 20H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.6 (2C), 13.7 (2C), 23.1 (2C), 24.7, 24.8, 55.6, 55.7 (2C), 55.9, 57.4 (q, J = 29.5 Hz, 2C), 57.5 (q, J = 29.8 Hz, 2C), 63.3, 63.5, 63.7, 63.9, 85.3 (2C), 86.0, 86.4, 124.6 (q, J = 252.2 Hz, 2C), 124.7 (q, J = 247.5 Hz, 2C), 126.6 (3C), 126.7, 127.1 (2C), 127.3 (2C), 127.7 (2C), 127.8 (2C), 128.4 (2C), 128.6 (4C), 128.8 (2C), 142.2, 142.5, 143.6, 143.9, 161.6 (2C), 162.0 (2C). ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −69.92 (d, J = 6.8 Hz), −70.41 (d, J = 7.0 Hz), −71.02 (d, J = 6.5 Hz), −71.98 (d, J = 7.4 Hz). HRMS: m/z [M + H]$^+$ calcd for $C_{14}H_{18}F_3N_2O_4$ 335.1219, found 335.1217.

Nitro Group Reduction: Synthesis of Compounds *syn*-8,9g, *anti*-8′,9′g. The same reported procedure to obtain **4,4′a−f** was followed.

*Ethyl (2S,3S)-2-Amino-4,4,4-trifluoro-3-[[(1R)-1-phenylethyl]-amino]butanoate (**syn-8g**).* Pale yellow oil. Yield 30% (0.077 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). IR ν_{max} cm^{-1}: 3375; 3338; 1762. $[\alpha]_D^{25}$ +21.4 (c = 1.4, $CHCl_3$).^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.33 (t, J = 7.1, 3H), 1.41 (d, J = 6.5, 3H), 3.26−4.32 (br, 3H), 3.43−3.34 (m, 1H), 3.82 (d, J = 3.1, 1H), 4.13 (q, J = 6.5 Hz, 1H), 4.21−4.32 (m, 2H), 7.28−7.47 (m, 5H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.9, 24.9, 55.7 (q, J = 27.7 Hz), 55.8, 61.6, 64.2, 125.7 (q, J = 287.8 Hz), 127.1 (2C), 127.7, 128.7 (2C), 143.2, 170.1. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −70.8 (d, J = 7.5 Hz). HRMS: m/z [M + H]$^+$ calcd for $C_{14}H_{20}F_3N_2O_2$ 305.1477, found 305.1472.

*Ethyl (2R,3S)-2-Amino-4,4,4-trifluoro-3-[[(1R)-1-phenylethyl]-amino]butanoate (**anti-8′g**).* Pale yellow oil. Yield 37% (0.096 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). IR ν_{max} cm^{-1}: 3388; 3346; 1772. $[\alpha]_D^{25}$ +29.7 (c = 3.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24 (t, J = 7.2 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3H), 3.49−4.21 (br, 3H), 3.52−3.62 (m, 1H), 4.01 (d, J = 4.1 Hz, 1H), 4.04 (q, J = 6.4 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 7.26−7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.9, 23.6, 55.6, 56.5 (q, J = 28.0 Hz), 61.7, 63.5, 125.3 (q, J = 283.9 Hz), 126.8 (2C), 127.5, 128.6 (2C), 144.2, 170.3. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −71.8 (d, J = 8.0 Hz). HRMS: m/z [M + H]$^+$ calcd for $C_{14}H_{20}F_3N_2O_2$ 305.1477, found 305.1476.

*Ethyl (2R,3R)-2-Amino-4,4,4-trifluoro-3-[[(1R)-1-phenylethyl]-amino]butanoate (**syn-9g**).* Pale yellow oil. Yield 7% (0.018 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). IR ν_{max} cm^{-1}: 3365; 3342; 1758. $[\alpha]_D^{25}$ +31.3 (c = 6, $CHCl_3$).^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (t, J = 7.1, 3H), 1.34 (d, J = 6.4 Hz, 3H), 3.30−4.35 (br, 3H), 3.33−3.38 (m, 1H), 3.78 (d, J = 4.1 Hz, 1H), 4.08 (q, J = 6.5 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 7.28−7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.9, 24.8, 55.8, 56.7 (q, J = 27.3), 62.0, 63.6, 123.9 (q, J = 281.4 Hz), 127.1 (2C), 127.4, 128.5 (2C), 143.5, 170.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −70.6 (d, J = 7.3 Hz). HRMS: m/z [M + H]$^+$ calcd for $C_{14}H_{20}F_3N_2O_2$ 305.1477, found 305.1478.

*Ethyl (2S,3R)-2-Amino-4,4,4-trifluoro-3-[[(1R)-1-phenylethyl]-amino]butanoate (**anti-9′g**).* Pale yellow oil. Yield 9% (0.025 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). IR ν_{max} cm^{-1}: 3366; 3335; 1743. $[\alpha]_D^{25}$ +26.8 (c = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.23−1.31 (m, 6H), 3.49−4.40 (br, 3H), 3.67 (m, 1H), 3.96 (d, J = 3.4 Hz, 1H), 4.04 (q, J = 6.8 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 7.21−7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.9, 23.4, 55.6, 56.7 (q, J = 27.5 Hz), 62.1, 63.6, 123.9 (q, J = 285.0 Hz), 126.7, 127.1 (2C), 128.5 (2C), 144.2, 170.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.3 (d, J = 8.0 Hz). HRMS: m/z [M + H]$^+$ calcd for $C_{14}H_{20}F_3N_2O_2$ 305.1477, found 305.1478.

Synthesis of 11f′. To imine **11f** (1 mmol), obtained following the reported procedure,[14] was added $AlCl_3$ (0.5 mmol), and the mixture was stirred during 30 min at room temperature. Then 5 mL of water was added, and the crude mixtures were extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The obtained crude was filtrated through a plug filled with Celite.

*Methyl (2S,3R)-3-tert-Butoxy-2-[(E)-(2,2,2-trifluoroethylidene)-amino]butanoate (**11f**).* Pale yellow oil. Yield 72% (0.193 g). IR ν_{max} cm^{-1}: 1738; 1686; 1743. $[\alpha]_D^{25}$ +68.2 (c = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.12 (s, 9H), 1.21 (d, J = 6.7 Hz, 3H), 3.77 (s, 3H), 3.82 (d, J = 6.8, 1H), 4.04−4.13 (m, 1H), 7.62 (q, J = 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 20.4, 2.8 (3C), 52.4, 67.3, 74.7, 78.2, 122.6 (q, J = 282.6 Hz); 152.8 (q, J = 28.9 Hz), 169,5. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −71.5 (d, J = 7.4 Hz). HRMS: m/z [M + H]$^+$ calcd for $C_{11}H_{19}F_3NO_3$ 270.1317, found 270.1316.

*Methyl (2S,4S,5R)-5-Methyl-2-(trifluoromethyl)-1,3-oxazolidine-4-carboxylate (**11f′**).* Yellow oil. Yield 65% (0.139 g). IR ν_{max} cm^{-1}: 3396; 1774; 1587. $[\alpha]_D^{25}$ +23.3 (c = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.43 (d, J = 6.0, 3H), 1.79 (br, 1H), 3.56 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H), 3.85−3.91 (m, 1H), 5.04 (q, J = 5.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 18.1, 52.4, 64.7, 78.7, 87.4 (q, J = 34.3 Hz), 123.0 (q, J = 282.0 Hz), 170.3. ^{19}F NMR ($CDCl_3$, 282 MHz,) δ: −82.4 (d, J = 5.3 Hz). HRMS: m/z [M + H]$^+$ calcd for $C_7H_{11}F_3NO_3$ 214.0691, found 214.0688.

$ZrCl_4$-Catalyzed Synthesis of *syn*-12,13a−d, *anti*-12′,13′a−d, *syn*-14, and *anti*-14′. To a mixture of trifluoromethyl (*E*)-aldimine **1f** (1.1 mmol) and ethyl nitroacetate (1 mmol) was added $ZrCl_4$ (0.5 mmol). The reaction was performed under solvent-free conditions and stirred at room temperature (1.5−24 h). After addition of water (5 mL), the crude mixture was extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The obtained crude mixture was used without any further purification in the subsequent nitro reduction reaction.

$AlCl_3$-Catalyzed Synthesis of *syn*-12,13a−d and *anti*-12′,13′a−d. To a mixture of trifluoromethyl (*E*)-aldimine **11a−d** (1.3 mmol) and ethyl nitroacetate (1 mmol) was added $AlCl_3$ (0.5 mmol). The reactions were performed under solvent-free conditions and stirred at room temperature during 2 h. Then, after addition of water (5 mL), the crude mixtures were extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The obtained crude mixtures were used without any further purification in the subsequent nitro reduction reaction.

*Ethyl 4,4,4-Trifluoro-3-[[(2S)-1-methoxy-3-methyl-1-oxobutan-2-yl]amino]-2-nitrobutanoate (**syn-12,13a** and **anti-12′,13′a**).* Yellow-brown oil. Yield 80% (0.276 g). IR ν_{max} cm^{-1}: 3373; 1743; 1573. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (d, J = 3.2 Hz, 6H, minor isomers), 0.91 (d, J = 3.2 Hz, 6H, minor isomers), 0.95 (d, J = 6.8 Hz, 12H, major isomers), 1.33 (t, J = 7.2 Hz, 6H, major isomers), 1.34 (t, J = 7.2 Hz, 6H, minor isomers), 1.78−1.91 (m, 2H, minor isomers), 1.91−2.05 (m, 2H, major isomers), 2.66 (br, 2H), 2.79 (br, 2H), 3.06−3.14 (m, 1H, minor isomer), 3.14−3.22 (m, 1H, minor isomer), 3.23−3.33 (m, 2H, major isomers), 3.70 (s, 6H, major isomers), 3.72 (s, 6H, minor isomers), 3.98−4.14 (m, 2H), 4.19−4.42 (m, 10H), 5.24 (d, J = 6.2 Hz, 1H, *syn* minor isomer), 5.28 (d, J = 4.9 Hz, 1H, *syn* major isomer), 5.35 (d, J = 6.4 Hz, 1H, *anti* minor isomer), 5.46 (d, J = 4.3 Hz, 1H, *anti* major isomer). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.60 (2C, major isomer), 13.7 (minor isomer), 13.8 (minor isomer), 17.5 (minor isomer), 17.6 (2C, major isomer), 17.7 (minor isomer), 18.8 (2C), 18.9 (2C), 31.9 (major isomer), 32.1 (major isomer), 32.62 (2C, minor isomer), 51.6 (major isomer), 51.7 (2C), 51.8 (minor isomer), 60.18 (q, J = 30.2 Hz, major isomer), 60.2 (q, J = 30.1 Hz, major isomer), 60.95 (q, J = 29.8 Hz, minor isomer), 61.1 (q, J = 29.8 Hz, minor isomer), 63.4 (major isomer), 63.7 (major isomer), 63.8 (minor isomer), 64.0 (minor isomer), 66.8 (major isomer), 66.9 (minor isomer), 67.0 (minor isomer), 67.4, 84.8 (major isomer), 85.7 (2C), 86.9 (minor isomer), 124.21 (q, J = 284.4 Hz, 4C), 161.4 (minor isomer), 161.6 (minor isomer), 161.7 (major isomer) 161.8 (major isomer), 173.7 (2C), 173.8 (2C). ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.5 (d, J = 6.8 Hz, minor isomer), −73.5 (d, J = 6.6 Hz, minor isomer), −73.6 (d, J = 6.8 Hz, major isomer), −74.0 (d, J = 7.0, major isomer). HRMS: m/z [M + H]$^+$ calcd for $C_{12}H_{20}F_3N_2O_6$ 345.1273, found 345.1265.

*Methyl (2S,3S)-2-[[4-Ethoxy-1,1,1-trifluoro-3-nitro-4-oxobutan-2-yl]amino]-3-methylpentanoate (**syn-12,13b** and **anti-12′,13′b**).* Yellow-brown oil. Yield 75% (0.276 g). IR ν_{max} cm^{-1}: 3385; 1756; 1568. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.78−0.96 (m, 24H), 1.05−1.25 (m, 4H), 1.29−1.37 (m, 12H), 1.38−1.52 (m, 4H), 1.53−1.67

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(m, 2H), 1.67−1.80 (m, 2H), 2.59−2.71 (m, 2H), 2.72−2.82 (m, 2H), 3.17−3.28 (m, 2H), 3.33−3.41 (m, 2H), 3.70 (s, 6H, major isomers), 3.72 (s, 6H, minor isomers), 3.99−4.12 (m, 2H), 4.18−4.29 (m, 2H), 4.29−4.42 (m, 8H), 5.24 (d, J = 6.3 Hz, 1H, *syn* minor isomer), 5.29 (d, J = 4.9, 1H, *syn* major isomer), 5.34 (d, J = 6.4 Hz, 1H, *anti* minor isomer), 5.46 (d, J = 4.3 Hz, 1H, *anti* major isomer). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.3 (2C, minor isomers), 11.4 (2C, major isomers), 13.6 (major isomers), 13.7 (minor isomers), 13.8 (2C), 15.2 (2C, minor isomers), 15.4 (2C, major isomers), 24.5 (minor isomers), 24.6 (minor isomers), 24.7 (2C, major isomers), 38.6 (major isomers), 38.9 (major isomers), 39.4 (2C, minor isomers), 51.8 (3C), 51.9 (minor isomers), 59,9 (q, J = 30.3 Hz, major isomers), 60.0 (q, J = 30.2 Hz, major isomers), 60.4 (q, J = 29.7, minor isomers), 61.0 (q, J = 29.9 Hz, minor isomers), 63.5 (minor isomers), 63.8 (major isomers), 64.0 (minor isomers), 64.1 (major isomers), 65.8 (2C, major isomers), 66.0 (minor isomers), 66.2 (minor isomers), 84.6 (major isomers), 85.6 (major isomers), 86.6 (minor isomers), 86.8 (minor isomers), 124.17 (q, J = 287.3 Hz, 4C), 161.7 (major isomers), 161.8 (2C, minor isomers), 161.9 (major isomer), 174.0 (4C). ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.5 (d, J = 6.7 Hz, minor isomer), −73.4 (d, J = 6.3 Hz, minor isomer), −73.5 (d, J = 6.4 Hz, major isomer), −74.0 (d, J = 6.7 Hz, major isomer). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{22}F_3N_2O_6$ 359.1430, found 359.1427.

*Methyl (2S)-2-[[4-Ethoxy-1,1,1-trifluoro-3-nitro-4-oxobutan-2-yl]amino]-4-methylpentanoate (**syn-12,13c** and **anti-12′,13′c**).* Yellow-brown oil. Yield 72% (0.258 g). IR ν_{max} cm^{-1}: 3365;1758; 1555. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.80−0.91 (m, 24H), 1.20−1.77 (m, 24H), 2.42−2.57 (m, 2H), 2.59−2.70 (m, 2H), 3.26−3.41 (m, 2H), 3.47−3.56 (m, 2H), 3.67 (s, 6H, major isomers), 3.68 (s, 6H, minor isomers), 3.98−4.15 (m, 4H), 4.21−4.37 (m, 8H), 5.23 (d, J = 6.1 Hz, 1H, *syn* minor isomer), 5.28 (d, J = 5.0 Hz, 1H, *syn* major isomer), 5.35 (d, J = 6.2 Hz, 1H, *anti* minor isomer), 5.44 (d, J = 4.5 Hz, 1H, *anti* major isomer). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.8 (4C), 21.8 (2C, major isomers), 21.9 (minor isomers), 22.0 (minor isomers), 22.7 (4C), 24.4 (major isomers), 24.5 (2C), 24.6 (minor isomers), 41.6 (2C, minor isomers), 43.8 (2C, major isomers), 51.8 (2C, major isomers), 51.9 (minor isomers), 53.0 (minor isomers), 58.8 (q, J = 28.4 Hz, 2C, major isomers), 57.9 (2C, minor isomers), 59.0 (d, J = 27.3 Hz, 2C, minor isomers), 59.3 (2C, major isomers), 61.5 (minor isomers), 61.7 (major isomers), 62.2 (minor isomers), 62.3 (major isomers), 84.6 (major isomers), 85.9 (2C), 86.7 (minor isomers), 123.91 (q, J = 283.7 Hz, 2C), 125.1 (q, J = 285.1 Hz, 2C), 162.4 (4C), 174.4 (4C). ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.5 (d, J = 7.2 Hz, minor isomer), −73.3 (d, J = 6.8 Hz, minor isomer), −73.4 (d, J = 7.2 Hz, major isomer), −73.7(d, J = 7.0 Hz, major isomer). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{22}F_3N_2O_6$ 359.1430, found 359.1422.

*Ethyl 4,4,4-Trifluoro-3-[[(2S)-1-methoxy-4-(methylsulfanyl)-1-oxobutan-2-yl]amino]-2-nitrobutanoate (**syn-12,13d** and **anti-12′,13′d**).* Brown oil. Yield 70% (0.265 g). IR ν_{max} cm^{-1}: 3395; 1765; 1568. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.21−1.33 (m, 12H), 1.62−1.98 (m, 8H), 1.98−2.06 (m, 12H), 2.42 (t, J = 7.0 Hz, 4H, major isomers), 2.46−2.60 (m, 4H, minor isomers), 2.66−2.91 (m, 4H), 3.49−3.62 (m, 4H), 3.65 (s, 3H, major isomers), 3.66 (s, 3H, major isomers), 3.68 (s, 6H, minor isomers), 3.96−4.11 (m, 4H), 4.17−4.35 (m, 8H), 5.19 (d, J = 5.8 Hz, 1H, *syn* minor isomers), 5.24 (d, J = 4.8 Hz, 1H, *syn* major isomers), 5.29 (d, J = 6.4 Hz, 1H, *anti* minor isomers), 5.41 (d, J = 4.4 Hz, 1H, *anti* major isomers). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.8 (2C), 13.9 (2C), 15.0 (2C, major isomers), 15.1 (minor isomers), 15.3 (minor isomers), 29.9 (2C, major isomers), 30.1 (minor isomers), 30.2 (minor isomers), 31.2 (2C, major isomers), 32.1 (minor isomers), 32.3 (minor isomers), 51.8 (major isomers), 51.9 (minor isomers), 52.1 (minor isomers), 52.6 (major isomers), 61.1 (q, J = 29.8 Hz, 2C), 61.3 (q, J = 29.8 Hz, 2C), 63.6 (major isomers), 63.8 (minor isomers), 64.0 (major isomers), 64.2 (minor isomers), 67.0 (minor isomers), 67.1 (minor isomers), 67.2 (major isomers), 67.6 (major isomers), 84.9 (major isomers), 85.9 (2C), 87.1 (minor isomers), 124.5 (q, J = 286.4 Hz, 2C), 124.6 (q, J = 286.2 Hz, 2C), 161.6 (2C), 161.8 (2C), 173.9 (2C, major isomers), 174.9 (2C, minor isomers). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −71.54 (d, J = 6.7 Hz), −72.08 (d, J = 6.9 Hz), −72.60 (d, J = 7.1 Hz), −73.59 (d, J = 7.4 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{12}H_{20}F_3N_2O_6S$ 377.0994, found 377.0991.

*Ethyl 3-Amino-4,4,4-trifluoro-2-nitrobutanoate (**syn-14** and **anti-14′**).* Yellow oil. Yield 75% (0.258 g). IR ν_{max} cm^{-1}: 3396; 3343; 1755; 1555. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.29−1.36 (m, 6H), 3.69−3.75 (m, 4H), 4.30−4.41 (m, 4H), 4.81−4.91 (m, 1H), 4.95−5.25 (m, 1H), 5.30 (d, J = 4.5 Hz, 1H, *syn* isomer), 5.40 (d, J = 5.7 Hz, 1H, *anti* isomer). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.6, 13.7, 64.3, 64.4, 69.6 (q, J = 33.5 Hz), 70.0 (q, J = 33.3 Hz), 83.9, 85.7, 122.7 (q, J = 282.7 Hz), 122.8 (q, J = 282.5 Hz), 161.9, 162.2. ^{19}F NMR ($CDCl_3$, 282 MHz,) δ: −76.9 (d, J = 6.2 Hz), −77.3 (d, J = 6.5 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_6H_{10}F_3N_2O_4$ 231.0593, found 231.0591.

Nitro Group Reduction: Synthesis of Compounds *anti*-15′a−c,16′a−c, and 17,18a−c. The same reported procedure to obtain ***syn*-4a-f**, ***anti*-4′a-f**, ***syn*-8,9g**, and ***anti*-8′,9′g** was followed.

*Ethyl (2S,3R)-2-Amino-4,4,4-trifluoro-3-[[(2S)-1-methoxy-3-methyl-1-oxobutan-2-yl]amino]butanoate (**anti-15′a**).* Pale yellow oil. Yield 36% (0.090 g). $[\alpha]_D^{25}$ −6.5 (c = 7, $CHCl_3$). IR ν_{max} cm^{-1}: 3545; 3391; 1733. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 2.01−2.10 (m, 1H), 3.06 (d, J = 5.3 Hz, 3H), 3.30 (d, J = 5.0 Hz, 1H), 3.54−3.61 (m, 1H), 3.75 (s, 3H), 4.02 (d, J = 3.5 Hz, 1H),: 4.26 (q, J = 7.1, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 14.0, 17.8, 19.3, 32.6, 51.6, 58.7 (q, J = 28.1 Hz), 61.9, 64.5, 66.9, 125.9 (q, J = 285.9 Hz), 169.5, 174.4. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.75 (d, J = 7.7 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{12}H_{22}F_3N_2O_4$ 315.1532, found 315.1544.

*Ethyl (2R,3S)-2-Amino-4,4,4-trifluoro-3-[[(2S)-1-methoxy-3-methyl-1-oxobutan-2-yl]amino]butanoate (**anti-16′a**).* Pale yellow oil. Yield 9% (0.025 g). $[\alpha]_D^{25}$ +6.8 (c = 7, $CHCl_3$). IR ν_{max} cm^{-1}: 3498; 3357; 1754. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.30 (t, J = 7.1, 3H), 1.99−2.08 (m, 1H), 3.13 (d, J = 5.6 Hz, 1H), 3.53−3.62 (m, 4H), 3.71 (s, 3H), 3.93 (d, J = 4.6 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 14.0, 17.7, 19.2, 32.7, 51.8, 59.6 (q, J = 28.0 Hz), 61.7, 64.1, 66.6, 124.0 (q, J = 284.4 Hz), 169.7, 174.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.10 (d, J = 8.7 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{12}H_{22}F_3N_2O_4$ 315.1532, found 315.1540.

*Methyl (2S,3S)-2-[[(2R,3S)-3-Amino-4-ethoxy-1,1,1-trifluoro-4-oxobutan-2-yl]amino]-3-methylpentanoate (**anti-15′b**).* Pale yellow oil. Yield 37% (0.092 g). $[\alpha]_D^{25}$ −5.25 (c = 2, $CHCl_3$). IR ν_{max} cm^{-1}: 3432; 3321; 1748. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 1.13−1.24 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.43−1.52 (m, 1H), 1.73 (br, 3H), 3.34 (d, J = 5.0 Hz, 1H), 3.46−3.56 (m, 1H), 3.73 (s, 3H), 3.96 (d, J = 3.5 Hz, 1H), 4.24 (qd, J = 7.1 Hz, 2.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 11.4, 13.9, 15.7, 24.9, 38.2, 51.5, 58.5 (q, J = 28.7 Hz), 62.2, 63.3, 66.9, 123.8 (q, J = 281.8 Hz), 169.6, 174.9.^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.8 (d, J = 8.1). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{24}F_3N_2O_4$ 329.1688, found 329.1688.

*Methyl (2S,3S)-2-[[(1S,2R)-2-Amino-4-ethoxy-1,1,1-trifluoro-4-oxobutan-2-yl]amino]-3-methylpentanoate (**anti-16′b**).* Pale yellow oil. Yield 9% (0.022 g). $[\alpha]_D^{25}$ +4.8 (c = 7, $CHCl_3$). IR ν_{max} cm^{-1}: 3432; 3321; 1748. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (d, J = 6.9 Hz, 6H), 1.08−1.22 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.40−1.52 (m, 2H), 1.65 (br, 2H), 3.19 (d, J = 5.6 Hz, 1H), 3.50−3.60 (m, 1H), 3.69 (s, 3H), 3.90 (d, J = 4.6 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 11.3, 13.8, 15.4, 24.7, 39.5, 51.6, 59.3 (q, J = 28.3 Hz), 61.7, 63.8, 65.5, 125.2 (q, J = 286.0 Hz), 169.7, 174.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.2 (d, J = 7.9 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{24}F_3N_2O_4$ 329.1688, found 329.1685.

*Methyl (2S)-2-[[(2R,3S)-3-Amino-4-ethoxy-1,1,1-trifluoro-4-oxobutan-2-yl]amino]-4-methylpentanoate (**anti-15′c**).* Pale yellow oil. Yield 31% (0.073 g). $[\alpha]_D^{25}$ −8.8 (c = 3, $CHCl_3$). IR ν_{max} cm^{-1}: 3482; 3331; 1762. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.29 (t, J = 7.1, 3H), 1.42−1.56 (m, 4H), 1.66−1.87 (m, 2H), 3.50−3.58 (m, 2H), 3.74 (s, 3H), 3.99 (d, J = 3.6 Hz, 1H), 4.24 (qd, J = 7.0 Hz, 1.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.8, 22.0, 22.7, 24.5, 43.8, 52.0, 58.6 (q, J = 29.7 Hz), 59.3, 62.1, 63.3, 124.9 (q, J = 290.9 Hz), 168.7, 175.2. ^{19}F NMR

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($CDCl_3$, 282 MHz) δ: −72.6 (d, J = 8.0 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{24}F_3N_2O_4$ 329.1688, found 329.1681.

*Methyl (2S)-2-[[(1S,2R)-2-Amino-3-ethoxy-3-oxo-1-(trifluoromethyl)propyl]amino]-4-methylpentanoate (**anti-16′c**).* Pale yellow oil. Yield 8% (0.019 g). $[\alpha]_D^{25}$ +5.7 (c = 8, $CHCl_3$). IR ν_{max} cm^{-1}: 3530; 3344; 1746. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H), 1.23−1.36 (m, 5H), 1.40−1.54 (m, 3H), 1.70−1.80 (m, 1H), 3.35−3.41 (m, 1H), 3.63−3.68 (m, 1H), 3.71 (s, 3H), 3.97 (d, J = 4.3 Hz, 1H), 4.25 (qd, J = 7.1 Hz, 1.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.9, 21.9, 22.8, 24.5, 43.8, 51.9, 58.7 (q, J = 29.0 Hz), 59.3, 61.9, 63.5, 125.0 (q, J = 285.6 Hz), 169.1, 175.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −71.9 (d, J = 8.8 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{24}F_3N_2O_4$ 329.1688, found 329.1684.

*Ethyl (3R)-4,4,4-Trifluoro-2-imino-3-[[(2S)-1-methoxy-3-methyl-1-oxobutan-2-yl]amino]butanoate (**17a**).* Pale yellow oil. Yield 29% (0.074 g). $[\alpha]_D^{25}$ −34.8 (c = 16, $CHCl_3$). IR ν_{max} cm^{-1}: 3545; 3388; 1734; 1684. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.93 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.91−2.01 (m, 1H), 2.67 (br, 2H), 3.07 (d, J = 5.4 Hz, 1H), 3.62 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 4.70−4.83 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.9, 17.9, 19.1, 31.8, 51.6, 55.9 (q, J = 32.8 Hz), 62.3, 67.8, 123.8 (q, J = 281.7 Hz), 145.6, 162.2, 174.9. ^{19}F NMR ($CDCl_3$, 282 MHz,) δ: −72.06 (d, J = 7.2). HRMS: m/z $[M + H]^+$ calcd for $C_{12}H_{20}F_3N_2O_4$ 313.1375, found 313.1381.

*Ethyl (3S)-4,4,4-Trifluoro-2-imino-3-[[(2S)-1-methoxy-3-methyl-1-oxobutan-2-yl]amino]butanoate (**18a**).* Pale yellow oil. Yield 7% (0.006 g). $[\alpha]_D^{25}$ −5.5 (c = 6, $CHCl_3$). IR ν_{max} cm^{-1}: 3545; 3388; 1734; 1684. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (d, J = 6.8 Hz, 6H), 1.36 (t, J = 7.1 Hz, 3H), 1.28 (br, 1H), 1.92−2.01 (m, 1H), 3.13 (d, J = 6.0 Hz, 1H), 3.54 (br, 1H), 3.73 (s, 3H), 4.34 (q, J = 7.1 Hz, 2H), 4.86 (q, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.9, 18.0, 19.0, 31.6, 51.8, 55.3 (q, J = 31.9 Hz), 62.4, 66.1, 124.0 (q, J = 284.3 Hz), 145.2, 162.0, 173.7. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −71.53 (d, J = 7.8 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{12}H_{20}F_3N_2O_4$ 313.1375, found 313.1371.

*Methyl (2S,3S)-2-[[(2R)-4-Ethoxy-1,1,1-trifluoro-3-imino-4-oxobutan-2-yl]amino]-3-methylpentanoate (**17b**).* Pale yellow oil. Yield 30% (0.074 g). $[\alpha]_D^{25}$ −51.3 (c = 3, $CHCl_3$). IR ν_{max} cm^{-1}: 3556; 3395; 1762; 1679. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.86−0.90 (m, 6H), 1.13−1.25 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.43−1.59 (m, 1H), 1.72 (br, 2H), 3.13 (br, 2H), 3.61 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 4.69−4.82 (m, 1H).^{13}C NMR ($CDCl_3$, 101 MHz) δ: 11.2, 13.9, 15.6, 24.7, 38.5, 52.0, 55.9 (q, J = 32.3 Hz), 61.8, 65.8, 125.4 (q, J = 283.6 Hz), 145.6, 162.0, 176.0. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.1 (d, J = 7.8 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{22}F_3N_2O_4$ 327.1532, found 327.1523.

*Methyl (2S,3S)-2-[[(1S)-3-Ethoxy-2-imino-3-oxo-1-(trifluoromethyl)propyl]amino]-3-methylpentanoate (**18b**).* Pale yellow oil. Yield 8% (0.020 g). $[\alpha]_D^{25}$ −6.3 (c = 2, $CHCl_3$). IR ν_{max} cm^{-1}: 3449; 3388; 1757; 1682. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.83−0.86 (m, 6H), 1.13−1.21 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.58−1.75 (m, 3H), 3.15 (d, J = 5.7 Hz, 1H), 3.70 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.85 (q, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 11.2, 13.8, 15.3, 24.9, 38.2, 51.6, 55.0 (q, J = 32.1 Hz), 62.2, 65.0, 124.0 (q, J = 284.4 Hz), 145.2, 162.1, 173.6. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −71.1 (d, J = 7.8). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{22}F_3N_2O_4$ 327.1532, found 327.1527.

*Methyl (2S)-2-[[(2R)-4-ethoxy-1,1,1-trifluoro-3-imino-4-oxobutan-2-yl]amino]-4-methylpentanoate (**17c**).* Pale yellow oil. Yield 25% (0.059 g). $[\alpha]_D^{25}$ −54.7 (c = 8, $CHCl_3$). IR ν_{max} cm^{-1}: 3449; 3385; 1758; 1687. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.5, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.43−1.56 (m, 3H), 1.75−1.88 (m, 2H), 3.37 (t, J = 7.2 Hz, 1H), 3.61 (s, 3H), 4.35 (q J = 7.1 Hz, 2H), 4.8 (q, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 14.1, 22.0, 23.0, 24.6, 41.8, 52.2, 54.2 (q, J = 31.7 Hz), 58.1, 62.6, 124.0 (q, J = 285.5 Hz), 145.6, 162.3, 174.6. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.2 (d, J = 7.1 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{22}F_3N_2O_4$ 327.1532, found 327.1528.

*Methyl (2S)-2-[[(2S)-4-Ethoxy-1,1,1-trifluoro-3-imino-4-oxobutan-2-yl]amino]-4-methylpentanoate (**18c**).* Pale yellow oil. Yield 6% (0.014 g). $[\alpha]_D^{25}$ −4.7 (c = 5, $CHCl_3$). IR ν_{max} cm^{-1}: 3478; 3352; 1764; 1689. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.44−1.59 (m, 3H), 1.63−1.78 (m, 2H), 3.37−3.43 (m, 1H), 3.70 (s, 3H), 4.34 (q, J = 7.1 Hz, 2H), 4.93 (q, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 13.9, 21.8, 22.8, 24.5, 41.6, 51.9, 54.0 (q, J = 32.2 Hz), 57.9, 62.4, 123.8 (q, J = 283.2 Hz), 145.4, 162.1, 174.4. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −71.3 (d, J = 7.4 Hz). HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{22}F_3N_2O_4$ 327.1532, found 327.1529.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00136.

Complete characterization data (^1H, ^{13}C, and ^{19}F NMR data) for all new compounds, computational details, 2D NMR spectra, and optimized geometries to determine the absolute configuration of the new chiral centers (PDF)

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Notes

The authors declare no competing financial interest.

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