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Graphical Abstract

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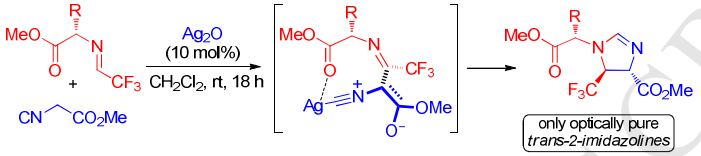

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ABSTRACT

Trifluoromethyl aldimines derived from α-amino esters have proven to be very good starting materials to obtain the title compounds. A Ag_2O-catalyzed Mannich-type/cyclization cascade reaction starting from suitable α-isocyano acetates leads to enantiopure valuable *trans*-carboxylic trifluoromethyl substituted 2-imidazolines by a highly stereoselective addition without the need to add organocatalysts.

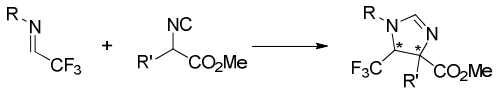
1. Introduction

2-Imidazolines are an important class of heterocyclic compounds due to their wide applications in different chemistry fields. They can be found in natural product chemistry, pharmaceutical chemistry, organic synthesis, coordination chemistry, and homogeneous catalysis.[1] Furthermore, carboxylic substituted 2-imidazolines are cyclic analogues of α,β-diamino acids,[2] key structural units of several natural products, having great relevance in the synthesis of bioactive compound derivatives characterized by exclusive pharmacological profiles. α,β-Diamino acids have also been used to induce specific conformations in peptide segments, or as precursors of imidazoline derivatives with therapeutic activity, increasing the resistance to hydrolysis.[3]

Many new efficient methods to synthesize 2-imidazolines as well as modifications of traditional methods have been reported. Among these, a remarkable example is the reaction between imines and both unactivated or activated isocyanides[4] to give racemic 2-imidazolines. In addition, starting from α-isocyano acetates,[5] carboxylic substituted 2-imidazolines can be obtained. These Mannich-type/cyclization cascade reactions are usually base[5g] or metal catalyzed, but the simultaneous use of both have also been reported.[6]

In particular, the development of transition metal-catalyzed processes provides access to both *cis* or *trans* isomers, under mild conditions and starting from the same materials.[1,7] Moreover, since the first asymmetric form of this reaction was reported,[4] a variety of enantioselective approaches have been widely investigated.[5] The structural diversity introduced on the imidazoline ring are many, but only one example of a CF_3-substitued 2-imidazoline is reported,[8] despite the relevance of the trifluoromethyl group on the molecular behaviour.[9] As is well known, the incorporation of fluorine-containing groups into an organic molecule often drastically perturbs the chemical, physical, and biological properties of the parent compound.[10]

Given the broad utility of trifluoromethyl heterocycle compounds in medicinal chemistry,[11] our attention was directed towards the synthesis of carboxylic trifluoromethyl-substituted 2-imidazolines (Scheme 1) by a Mannich-type addition/cyclization cascade reaction between trifluoromethyl aldimines[12] and suitable α-isocyano acetates.[13]



Scheme 1. Synthesis of carboxylic trifluoromethyl substituted 2-imidazolines.

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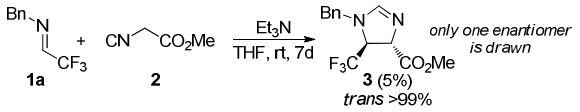
2. Results and discussion

First, the addition was tested by reaction of an equimolar mixture of trifluoromethyl aldimine **1a** and methyl 2-isocyanoacetate (**2**) in THF at rt without catalyst,[14] but no reaction occurred and both reagents were quantitatively recovered (48 h). Even when changing the reaction conditions (solvent, temperature, molar ratios), no addition product was observed. Then, a base-promoted Mannich-type reaction was attempted and several tertiary amines (Et_3N, DBU, DMAP, DABCO) have been examined. Only performing the reaction in THF using a stoichiometric amount of Et_3N, 2-imidazoline *trans*-**3**[7b,15] was obtained, although in long reaction times and low yields (Scheme 2).

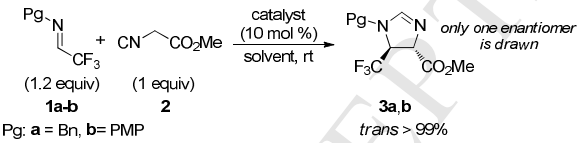


Scheme 2. Base-promoted Mannich-type reaction.

Next, we focused our attention on a metal-catalyzed addition/cyclization cascade reaction. Given our success in the $ZrCl_4$-catalyzed additions of nucleophiles to trifluoromethyl aldimines,[16] zirconium tetrachloride was considered as a suitable Lewis acid, also because it is easy to handle, cheap and environmentally friendly.[17] However, its catalytic use at room temperature failed in the reaction between α-isocyano acetate **2** and aldimine **1a** and only a complex crude mixture was recovered, even working at lower temperature (0 °C). Furthermore, other different Lewis acids such as $CuCl_2$, Cu_2O and $ZnCl_2$ were tested by us under different conditions, but with no results in any case.

Finally, we envisioned the catalytic activity of silver(I) derivatives, considering their efficiency in the 2-imidazoline formation.[5a-e,14c] Working in THF at room temperature, Ag_2O (10 mol %) provided the best result, affording the desired product *trans*-**3a** in higher yield and in shorter reaction time (Table 1, entry 3).

Table 1. Optimization of the addition/cyclization cascade reaction of **2** on achiral trifluoromethyl aldimines

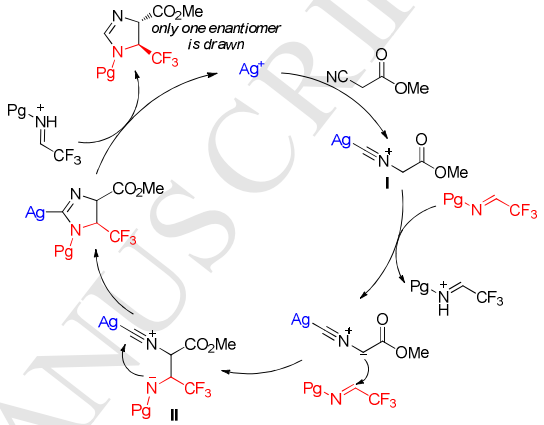


Entry	Pg	**3**	Catalyst	Solvent	Time (h)	Yield[a] (%)
1	Bn	**a**	AgOAc	THF	22	46
2	Bn	**a**	$AgNO_3$	THF	24	52
3	Bn	**a**	Ag_2O	THF	18	60
4	Bn	**a**	Ag_2O	CH_2Cl_2	20	62
5	Bn	**a**	Ag_2O	DMSO	15	66
6	Bn	**a**	Ag_2O	NMP	15	63
7	Bn	**a**	Ag_2O	DMF	15	65
8	Bn	**a**	Ag_2O	EtOH	16	45
9	Bn	**a**	Ag_2O	iPrOH	15	40
10	Bn	**a**	Ag_2O	–	5	85
11[b]	PMP	**b**	Ag_2O	–	5	88

[a] After flash chromatography on silica gel. [b] No reaction occurred without catalyst

Further examination of the solvent effect, ranging from aprotic polar (entries 4−7) to protic polar (entries 5−9), revealed that the performance of the silver oxide-catalyzed addition does not seem to be influenced by the solvent; we observed a slight decrease of the yield only by using EtOH or iPrOH. The best result was achieved working under solvent-free conditions (entry 10) and *trans*-**3a** was successfully obtained within 5 h (*vs* 15 h, entries 5-7) with higher yield and purity. Varying the aldimine *N*-protecting group and working under the same solvent-free conditions of entry 10, the expected *trans* 2-imidazoline **3b** was found in good yield (entry 11).

On the basis of the collected results and supported by the data reported in the literature,[13,14a,b,18] a mechanism for the silver(I)-catalyzed Mannich-type reaction is depicted in Scheme 3.

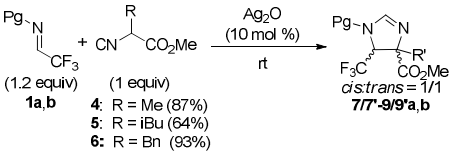


Scheme 3. Proposed mechanism for the silver(I)-catalyzed Mannich-type addition/cyclization cascade reaction.

After deprotonation of the activated isocyanide **I**, the formed enolate leads to **II**. The ring closure reaction followed by silver(I) cation/proton exchange provides the *trans* 2-imidazoline, as has been widely reported for the analogous reaction on unfluorinated aldimines.[4b,c,f,5c,g,f]

Next, three different α-substituted isocyano acetates **4**-**6** were synthesized starting from α-amino acid methyl ester hydrochlorides, through slight modifications of the standard protocol,[14a,19] and then tested in the reaction with **1a**,**b** and aldimine **1c** derived from β-alanine (Table 2).

Table 2. Silver(I)-catalyzed Mannich-type reactions of α-isocyano methyl esters **4**-**6** to achiral aldimines



Entry	R	R'	Product	Solvent	Time (h)	Yield[b] (%)
1	Bn	Me	**7/7'a**	–	4	60
2	PMP		**7/7'b**	–	4	58
3	Bn	iBu	**8/8'a**	CH_2Cl_2	16	54
4	PMP		**8/8'b**	CH_2Cl_2	16	56
5	Bn	Bn	**9/9'a**	CH_2Cl_2	12	48
6	PMP		**9/9'b**	CH_2Cl_2	10	50

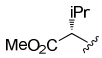
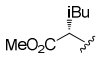
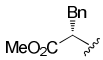
[a] After flash chromatography on silica gel.

While the reactions involving **4** proceeded as expected under solvent-free conditions (entries 1–2), starting from **5** or **6** the use of CH_2Cl_2 was specifically required to afford the desired products

(entries 3–6).[20] The data reported in Table 2 seems to show that the presence of a steric hindrance on the pronucleophile carbon only partially influence the reaction yields, but significantly controls the reaction diastereoselectivity.[21] Actually, the substituent on the nucleophile carbon could be responsible for the similar energy between *E*/*Z* enolates, resulting in a total loss of geometric selectivity.[22]

Once better conditions were identified, we focused our efforts on obtaining asymmetric induction in the model reaction. Thus, we decided to perform the silver oxide catalyzed Mannich-type addition starting from optically pure trifluoromethyl aldimines, hoping that the presence of a chiral resident center on the electrophilic aldimine could control the facially stereoselective addition.[5] Therefore, aldimine **1c**, derived from (*R*)-α-methyl benzylamine,[23] and aldimines **1d-f**, deriving from L-α-amino esters[24] were considered in the addition reactions with **2** (Table 3).

Table 3. Reactions of **2** on chiral trifluoromethyl aldimines

Entry	1	R	Solvent	Product	Dr[a]	Yield[b] (%)
1	**c**		–	**10/10'**	0.6:0.4	50
2	**d**		CH_2Cl_2	**11**	>0.99:0.1	49
3	**e**		CH_2Cl_2	**12**	>0.99:0.1	45
4	**f**		CH_2Cl_2	**13**	>0.99:0.1	38

[a] Determined by ^1H and ^{19}F NMR spectroscopy performed on the crude mixtures. [b] After flash chromatography on silica gel.

The Mannich-type reaction between methyl 2-isocyanoacetate (**2**) and aldimine **1c** took place under solvent-free conditions but afforded *trans*-2-imidazolines **10/10'** with a very low diastereomeric ratio (entry 1), even when the addition was attempted at lower temperatures (from −20 to 0 °C). However, pure diastereomerically compounds **10** (major) and **10'** (minor) were obtained by HPLC purification. So, following our already reported methodology,[16b,c] two-dimensional nuclear Overhauser spectroscopic analyses (2D NOESY) coupled with computational studies (see SI) allowed us to assign the *S,S* and the *R,R* absolute configurations to the new chiral centers of **10** and **10'**, respectively.

Unexpectedly, the reactions starting from aldimines **1d-f** did not occur under solvent-free conditions but required the use of CH_2Cl_2 as the best solvent (entries 2-4).

Under these conditions, the Ag_2O-catalyzed Mannich-type addition/cyclization cascade reactions occurred with very high diastereoselectivity, forming in all cases only the configured *S,R,R* diastereomer.[25]

A possible explanation for the stereochemical results[27] seems to be the presence of the ester moiety on the aldimine. An interaction could be generated between the silver-isocyano acetate complex and aldimines deriving from L-α-amino esters (Figure 1, **III**), making for a greater discrimination of aldimine enantiotopic faces. In fact, this interaction could create a well-defined chiral pocket that can readily favor the enolate attack preferentially on the *Re* imine face so giving enantiopure valuable trifluoromethyl imidazolidines. Obviously, a similar interaction cannot be proposed for aldimine **1c** (Figure 1, **IV**). In fact, starting from the latter, a low induction was observed.

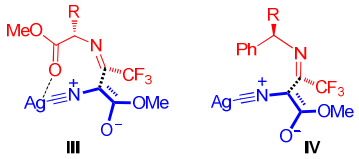


Fig 1. Model for preferred face-selective addition reaction.

3. Conclusions

In conclusion, we have reported the first example of a Ag_2O-catalyzed Mannich-type/cyclization cascade reaction between trifluoromethyl aldimines and α-isocyano acetates. The process offers a simple and efficient route for the synthesis of *trans*-carboxylic trifluoromethyl substituted 2-imidazolines without it being necessary to add a base.[6] The methodology works very well under solvent-free conditions starting from methyl isocyano acetate (**2**) and the use of silver oxide as catalyst leads to total geometric stereoselective control. In addition, large-scale (250 mg) synthesis of **3a** was realized in good yields and high selectivity (see SI).

Moreover, the reactivity of α-substituted isocyano acetates was also studied, for which few examples are reported in the literature.[5h,28] The results showed that the presence of an alkyl group on the nucleophilic site is responsible of the total loss of geometric selectivity.

Finally, starting from α-amino ester functionalized chiral aldimines, a complete stereoselective induction without the need for other added organocatalysts was observed, and enantiopure valuable *trans*-carboxylic trifluoromethyl 2-imidazolines, enriched by an α-amino ester residue, were obtained.

4. Experimental section

4.1. General information

IR spectra were recorded on a Fourier transform infrared (FT/IR) spectrophotometer in $CHCl_3$ as solvent and are reported in reciprocal centimeters. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian-Mercury 300 instrument and on a Bruker Avance III 400 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) and C_6F_6 (δ = −164.9 for ^{19}F NMR) were used as internal standard. The NOESY experiments were performed by a 400 MHz instrument using $CDCl_3$ as the solvent and $CHCl_3$ as the internal standard and used to assist in structure elucidation.[29] 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-f** were prepared by reaction of trifluoroacetaldehyde ethyl hemiacetal and an the relevant primary amine, following the reported procedures.[24,30] Methyl 2-isocyanoacetate (**2**) is commercially available and used as received.

*4.2. General procedure for the synthesis of α-isocyano acetates **4-6**.*

The methyl ester·HCl salt (100 mmol) was added to a semi-saturated Na_2CO_3 (aq) (100 mL) solution and the mixture was extracted with CH_2Cl_2 (4 × 100 mL). The organic layers were combined and dried over $MgSO_4$. Removal of the solvent under reduced pressure allowed isolation of the corresponding methyl ester. Acetic formic anhydride (110 mmol), prepared by stirring 1

equiv of acetic anhydride (10.4 mL) and 1.1 equiv of formic acid (4.6 ml) for 2 h at 55 °C, was added dropwise at 0 °C to a stirred solution of the appropriate methyl ester (50 mmol) in CH_2Cl_2 (135 mL), and the mixture was stirred for 2 h at room temperature. All volatiles were evaporated under reduced pressure, and the corresponding formamides were isolated (68-95%). Then, a solution of $POCl_3$ (2.9 mL, 4.8 g, 31 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of formamide (25 mmol) in Et_3N (17 mL) and CH_2Cl_2 (60 mL) at –25 °C. The reaction mixture was stirred for 5 h at the same temperature, and the resulting red mixture was added to cold H_2O (60 mL) and extracted with Et_2O (3 × 60 mL). The organic layers were combined, washed with H_2O (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo* to yield the desired α-isocyano acetates **4-6**[14c] (64-93%), which were obtained as pure compounds and directly used in follow-up chemistry.

4.3. General procedure for the Ag_2O-catalyzed Mannich-type reactions.

Method A: To a mixture of trifluoromethyl aldimines **1a-c** (0.18 mmol) and Ag_2O (0.015 mmol), α-isocyano acetates **2** or **4** (0.15 mmol) were added. The reactions were performed under solvent-free conditions and stirred at room temperature (3-5 h, see Tables 1 and 2). EtOAc was added and the mixtures were filtered through a pad of celite. After solvent evaporation, the crude mixtures were purified by flash chromatography on silica gel or by HPLC.

Method B: To a mixture of trifluoromethyl aldimines **1a-b** or **1d-f** (0.18 mmol) and Ag_2O (0.018 mmol) in CH_2Cl_2, α-isocyano acetates (0.18 mmol) were added. The reactions were stirred at room temperature (see Tables 2 and 3). EtOAc was added and the mixtures were filtered through a pad of celite. After solvent evaporation, the crude mixtures were purified by flash chromatography on silica gel or by HPLC.

4.3.1. Methyl 1-benzyl-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*trans-**3a***). ***Method A***.

Colorless oil (36 mg, 85%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 3:7). ^{1}H NMR ($CDCl_3$): δ 7.41–7.22 (m, 6H), 4.77 (d, *J* = 15.1 Hz, 1H), 4.70 (d, *J* = 7.0, 1H), 4.36−4.27 (m, 2H), 3.77 (s, 3H). ^{19}F NMR ($CDCl_3$): δ –74.6 (d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 169.9, 157.4, 134.5, 129.0 (2C), 128.4, 128.0 (2C), 124.8 (q, *J* = 280.3 Hz), 70.3, 60.9 (q, *J* = 31.9 Hz), 52.9, 50.6. IR: 3019, 2869, 1754, 1588 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{13}H_{14}F_3N_2O_2$ 287.1007, found 287.1068.

4.3.2. Methyl 1-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*trans-**3b***). ***Method A***.

Red oil (40 mg, 88%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 3:7) ^{1}H NMR ($CDCl_3$): δ 7.17 (s, 1H), 7.11 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.96−4.89 (m, 2H), 3.84 (s, 3H), 3.78 (s, 3H). ^{19}F NMR ($CDCl_3$): δ –74.8 (d, *J* = 6.1 Hz). ^{13}C NMR ($CDCl_3$): δ 170.0, 158.1, 155.5, 131.3, 124.4 (q, *J* = 281.2 Hz), 123.8 (2C), 114.9 (2C), 70.3, 63.1 (q, *J* = 31.7 Hz), 55.5, 53.2. IR: 3030, 2973, 1750, 1499 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{13}H_{14}F_3N_2O_3$ 303.0957, found 303.0905.

4.3.3. Methyl 1-benzyl-4-methyl-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*cis-**7a***). ***Method A***.

Yellow oil (12 mg, 27 %). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^{1}H NMR ($CDCl_3$): δ 7.39–7.19 (m, 5H), 6.94 (s, 1H), 4.59 (d, *J* = 15.0 Hz, 1H), 4.37 (q, *J* = 7.6 Hz, 1H), 4.25 (d, *J* = 15.1 Hz, 1H), 3.71 (s, 3H), 1.59 (s, 3H). ^{19}F NMR ($CDCl_3$): δ –67.0 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 173.0, 155.5, 134.8, 128.9 (2C), 128.3, 128.1 (2C), 124.9 (q, *J* = 282.4 Hz), 76.8, 62.9 (q, *J* = 30.5 Hz), 53.0, 50.7, 19.8 (q, *J* =3.0 Hz). IR: 3201, 2875, 1747, 1594 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{14}H_{16}F_3N_2O_2$ 301.1164, found 301.1189.

4.3.4. Methyl 1-benzyl-4-methyl-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*trans-**7'a***). ***Method A***.

Yellow oil (14 mg, 31%). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^{1}H NMR ($CDCl_3$): δ 7.42–7.14 (m, 6H), 4.65 (d, *J* = 14.5 Hz, 1H), 4.23 (d, *J* = 14.7 Hz, 1H), 3.74 (s, 3H), 3.51 (q, *J* = 7.1 Hz, 1H), 1.41 (s, 3H). ^{19}F NMR ($CDCl_3$): δ –69.3 (d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 171.5, 156.5, 134.4, 129.1 (2C), 128.6, 128.2 (2C), 124.2 (q, *J* = 279.4 Hz), 77.2, 67.9 (q, *J* = 31.1 Hz), 52.8, 50.7, 27.5. IR. 3199, 2835, 1751, 1253 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{14}H_{16}F_3N_2O_2$ 301.1164, found 301.1145.

*4.3.5. Methyl 1-(4-methoxyphenyl)-4-methyl-5-(trifluoromethyl)-4,5 dihydro-1H-imidazole-4-carboxylate (cis-**7b**). **Method A**.*

Red oil (14 mg, 29%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 3:7). ^{1}H NMR ($CDCl_3$): 7.13 (d, *J* = 8.8 Hz, 2H), 7.01 (s, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.08 (q, *J* = 7.3 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 1.71 (s, 3H). ^{19}F NMR ($CDCl_3$): –67.8 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 173.2, 158.3, 154.1, 131.7, 124.9 (2C), 124.5 (q, *J* = 281.2 Hz), 114.8 (2C), 65.4 (q, *J* = 30.2 Hz), 60.3, 55.5, 53.3, 19.5 (q, *J* = 2.9 Hz). IR: 3256, 2917, 1769, 1240, 1150 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{14}H_{16}F_3N_2O_3$ 317.1113, found 317.1154.

4.3.6. Methyl 1-(4-methoxyphenyl)-4-methyl-5-(trifluoromethyl)-4,5 dihydro-1H-imidazole-4-carboxylate (*trans-**7'b***). ***Method A***.

Red oil (14 mg, 29%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 3:7). ^{1}H NMR ($CDCl_3$): 7.17 (s, 1H), 7.09 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 4.23 (q, *J* = 6.9 Hz, 1H), 3.81 (s, 6H), 1.68 (s, 3H). ^{19}F NMR ($CDCl_3$): –69.5 (d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$): 170.7, 158.0, 153.9, 131.7, 124.1 (2C), 123.8 (q, *J* = 282.3 Hz), 114.9 (2C), 76.0, 70.8 (q, *J* = 30.4 Hz), 55.5, 53.0, 27.6. IR. 3189, 2850, 1735, 1256, 1140 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{14}H_{16}F_3N_2O_3$ 317.1113, found 317.1137.

4.3.7. Methyl 1-benzyl-4-isobutyl-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*cis-**8a***). ***Method B***.

Colorless oil (18 mg, 29 %). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^{1}H NMR ($CDCl_3$): 7.37–7.28 (m, 3H), 7.15 (d, *J* = 6.6, 2H), 7.06 (s, 1H), 4.58 (d, *J* = 15.2 Hz, 1H), 4.21 (d, *J* = 15.2 Hz, 1H), 3.84 (q, *J* = 7.6 Hz, 1H), 3.62 (s, 3H), 2.02 (dd, *J* = 5.7, 13.5 Hz, 1H), 1.92–1.83 (m, 1H), 1.72 (dd, *J* = 5.2, 13.9 Hz, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H). ^{19}F NMR ($CDCl_3$): –66.9 (d, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$): 174.1, 155.7, 135.1, 128.9 (2C), 128.3, 128.0 (2C), 124.8 (q, *J* = 283.7 Hz), 80.2, 52.6, 64.6 (q, *J* = 30.0 Hz), 50.6 (q, *J* = 1.4 Hz), 41.3 (q, *J* = 2.5 Hz), 25.3, 24.5, 23.4. IR: 3027, 2834, 1764, 1413, 1115 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{17}H_{22}F_3N_2O_2$ 343.1633, found 343.1659.

4.3.8. Methyl 1-benzyl-4-isobutyl-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*trans-**8'a***). ***Method B.***

Colorless oil (15.6 mg, 25%). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^{1}H NMR ($CDCl_3$): 7.45–7.29 (m, 3H), 7.21 (d, *J* = 6.6, 2H), 7.09 (s, 1H), 4.61 (d, *J* = 15.0 Hz, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.74 (s, 3H), 3.45 (q, *J* = 7.2 Hz, 1H), 1.93 (dd, *J* = 6.6, 13.6 Hz, 1H), 1.70–1.66 (m, 1H), 1.19 (dd, *J* = 5.3, 13.5 Hz, 1H), 0.83 (d, *J*=6.7 Hz, 3H), 0.81 (d, *J*=6.7 Hz, 3H). ^{19}F NMR ($CDCl_3$): –69.2 (d, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$): 170.8, 156.0, 134.6, 129.0 (2C), 128.5 (3C), 124.5 (q, *J* = 283.2 Hz), 79.7, 67.4 (q, *J* = 30.4 Hz), 52.6, 50.9, 49.8, 24.6, 24.2, 23.1.

IR: 3157, 2765, 1758, 1456, 1200 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{22}F_3N_2O_2$ 343.1633, found 343.1602.

4.3.9. Methyl 4-isobutyl-1-(4 methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*cis*-***8b***). ***Method B.***

Brown oil (17.6 mg, 27%). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^1H NMR ($CDCl_3$): 7.16 (s, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 4.67 (q, *J* = 7.1 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.11 (dd, *J* = 5.1, 13.3 Hz, 1H), 2.00–1.89 (m, 1H), 1.85–1.83 (m, 1H), 1.04 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.5 Hz, 3H). ^{19}F NMR ($CDCl_3$): –67.2 (d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$): 174.2, 157.9, 153.6, 131.9, 124.3 (q, *J* = 284.9 Hz), 124.2 (2C), 114.8 (2C), 80.3, 67.4 (q, *J* = 29.4 Hz), 55.5, 52.9, 41.5, 25.2, 24.5, 23.7. IR: 3076, 2748, 1765, 1433 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{22}F_3N_2O_3$ 359.1583, found 359.1553.

4.3.10. Methyl 4-isobutyl-1-(4 methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*trans*-***8′b***). ***Method B***.

Brown oil (19 mg, 29%). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^1H NMR ($CDCl_3$): 7.20 (s, 1H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.20 (q, *J* = 7.3 Hz, 1H), 3.81 (s, 6H), 2.21 (dd, *J* = 13.4, 6.7 Hz, 1H), 1.99–1.90 (m, 1H), 1.67 (dd, *J* = 5.1, 13.3 Hz, 1H), 1.00 (d, *J*=6.7 Hz, 3H), 0.94 (d, *J*=6.7 Hz, 3H). ^{19}F NMR ($CDCl_3$): –69.5 (d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 170.7, 157.7, 153.3, 132.1, 123.4 (q, *J* = 284.3 Hz), 123.4 (2C), 114.9 (2C), 79.6, 70.4 (q, *J* = 29.9 Hz), 55.5, 52.7, 50.2, 24.7, 24.5, 23.2. IR: 3189, 2753, 1763, 1421 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{22}F_3N_2O_3$ 359.1583, found 359.1565.

4.3.11. Methyl 1,4-dibenzyl-5-(trifluoromethyl) 4,5-dihydro-1H-imidazole-4-carboxylate (*cis*-***9a***). ***Method B***.

Yellow oil (17 mg, 24%). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^1H NMR ($CDCl_3$): 7.51 (s, 1H), 7.33–7.14 (m, 10H), 4.75 (d, *J* = 15.2 Hz, 1H), 4.30 (d, *J* = 15.1 Hz, 1H), 4.13 (q, *J* = 7.5 Hz, 1H), 3.37–3.34 (m, 4H), 3.13 (d, *J*=13.1 Hz, 1H). ^{19}F NMR ($CDCl_3$): –67.3 (d, *J* = 9.9 Hz). ^{13}C NMR ($CDCl_3$): 172.6, 156.6, 135.2, 134.6, 130.4 (2C), 129.0 (2C), 128.4, 128.1 (2C), 128.0 (2C), 127.1, 124.6 (q, *J* = 284.0 Hz), 80.2, 64.2 (q, *J* = 30.5 Hz), 52.5, 51.0, 39.2. IR: 3065, 2734, 1748, 1548, 1400, 1213 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_2$ 377.1477, found 377.1405.

4.3.12. Methyl 1,4-dibenzyl-5-(trifluoromethyl) 4,5-dihydro-1H-imidazole-4-carboxylate (*trans*-***9′a***). ***Method B***.

Yellow oil (17 mg, 24%). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^1H NMR ($CDCl_3$): 8.03 (s, 1H), 7.37–7.18 (m, 10H), 4.95 (d, *J* = 14.8 Hz, 1H), 4.39 (d, *J* = 15.0 Hz, 1H), 4.30 (q, *J* = 7.3 Hz, 1H), 3.40–3.39 (m, 4H), 3.20 (d, *J* = 13.3 Hz, 1H). ^{19}F NMR ($CDCl_3$): –68.5 (d, *J* = 9.9 Hz). ^{13}C NMR ($CDCl_3$): 171.8, 157.7, 134.3, 133.9, 130.3 (2C), 129.1 (2C), 128.7, 128.4 (2C), 128.2 (2C), 127.4, 124.2 (q, *J* = 284.2 Hz), 78.8, 64.6 (q, *J* = 30.8 Hz), 52.9, 51.4, 38.8. IR: 3065, 2734, 1748, 1545, 1400, 1213 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_2$ 377.1477, found 377.1428.

4.3.13. Methyl 4-benzyl-1-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*cis*-***9b***). ***Method B.***

Brown oil (16 mg, 23%). Separated by HPLC (eluent: hexane/ethyl acetate = 7:3). ^1H NMR ($CDCl_3$): 7.35–7.22 (m, 6H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.93 (br, 1H), 3.80 (s, 3H), 3.52 (s, 3H), 3.45 (d, *J*=13.2 Hz, 1H), 3.26 (d, *J*=12.6 Hz, 1H). ^{19}F NMR ($CDCl_3$): –67.4 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 173.2, 158.0, 153.7, 135.5, 131.5, 130.3 (2C), 128.2 (2C), 127.1, 124.3 (q, *J* = 286.0 Hz), 124.0 (2C), 114.8 (2C), 80.9, 66.8 (br), 55.5, 52.7, 39.5. IR: 3010, 2900, 1787, 1533, 1416 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_3$ 393.1426, found 393.1432.

4.3.14. Methyl 4-benzyl-1-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*trans*-***9′b***). ***Method B***.

Brown oil (19 mg, 27%). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). ^1H NMR ($CDCl_3$): 7.33–7.22 (m, 6H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.40 (d, *J* = 8.8 Hz, 2H), 4.39 (q, *J* = 6.8 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.46 (d, *J*=13.7 Hz, 1H), 3.34 (d, *J*=13.9 Hz, 1H). ^{19}F NMR ($CDCl_3$): –68.7 (d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 170.2, 158.4, 155.3, 134.4, 130.0, 131.3 (2C), 128.5 (2C), 127.5, 125.2 (2C), 123.8 (q, *J* = 287.7 Hz), 114.5 (2C), 79.1, 67.6 (q, *J*=30.8 Hz,), 55.4, 53.2, 44.2. IR: 2900, 1765, 1516 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_3$ 393.1426, found 393.1468.

4.3.15. Methyl (4S,5S)-1-[(R)-1-phenylethyl]-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (***10***). ***Method A.***

Colorless oil (12 mg, 26%). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). $[\alpha]_D$ = +33.9 (*c* = 2 g/100 mL, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.43–7.34 (m, 5H), 6.91 (s, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.69 (q, *J* = 6.8 Hz, 1H), 4.60−4.51 (m, 1H), 3.82 (s, 3H), 1.62 (d, *J* = 6.9 Hz, 3H). ^{19}F NMR ($CDCl_3$): –75.0 (d, *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$): 169.5. 156.4, 138.6, 129.1 (2C), 128.6, 127.2 (2C), 124.6 (q, *J* = 280.7 Hz), 68.9, 61.7 (q, *J* = 31.5 Hz), 56.2, 53.3, 18.4. IR: 3076, 2750, 1762, 1567 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{16}F_3N_2O_2$ 301.1164, found 301.1103.

4.3.16. Methyl (4R,5R)-1-[(R)-1-phenylethyl]-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (***10′***). ***Method A.***

Colorless oil (11 mg, 24 %). Purified by HPLC (eluent: hexane/ethyl acetate = 7:3). $[\alpha]_D$ = +23.6 (*c* = 2 g/100 mL, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.39–7.15 (m, 6H), 4.73 (d, *J* = 5.9 Hz, 1H), 4.57 (q, *J* = 6.8 Hz, 1H), 4.12−4.09 (m, 1H), 3.72 (s, 3H), 1.71 (d, *J* = 7.0 Hz, 3H). ^{19}F NMR ($CDCl_3$): –74.9 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 160.5, 154.5, 137.7, 129.1 (2C), 128.4, 126.2 (2C), 69.8, 61.3 (q, *J* = 34.5 Hz), 56.8, 52.9, 22.1 [note: the CF_3 signal was obscured due to its low intensity.]. IR: 3056, 2754, 1759, 1557 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{16}F_3N_2O_2$ 301.1164, found 301.1153.

4.3.17. Methyl (4R,5R)-1-[(S)-1-methoxy-3-methyl-1-oxobutan-2-yl]-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (***11***). *Method B.*

Colorless oil (27.6 mg, 49 %). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 3:7). $[\alpha]_D$ = +38.6 (*c* = 1 g/100 mL, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.14 (s, 1H), 4.70 (dd, *J* = 1.97, 6.5 Hz, 1H), 4.35–4.29 (m, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.52 (d, *J* = 10.4 Hz, 1H), 2.29−2.20 (m, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H). ^{19}F NMR ($CDCl_3$): –75.3 (d, *J* = 6.4 Hz). ^{13}C NMR ($CDCl_3$): 171.1, 169.9, 154.7, 124.8 (q, *J* = 279.9 Hz), 69.9, 67.3, 62.7 (q, *J* = 31.8 Hz), 53.1, 52.4, 29.8, 19.6, 19.2. IR: 3056, 2830, 1765, 1745, 1178 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{18}F_3N_2O_4$ 311.1219, found 311.1274.

4.3.18. Methyl (4R,5R)-1-[(S)-1-methoxy-4-methyl-1-oxopentan-2-yl]-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (***12***). *Method B.*

Colorless oil (15.5 mg, 45 %). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 3:7). $[\alpha]_D$ = +20.6 (*c* = 2 g/100 mL, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.07 (s, 1H), 4.74 (dd, *J* = 6.9, 1.9 Hz, 1H), 4.38 (quintet, *J* = 6.6 Hz, 1H), 4.03 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 1.76−1.87 (m, 3H), 0.99 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.1 Hz,

3H). ^{19}F NMR ($CDCl_3$): –75.2 (d, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$): 171.6, 169.3, 155.3, 124.6 (q, *J* = 279.6 Hz), 68.8, 62.8 (q, *J* = 31.5 Hz), 58.5, 53.3, 52.8, 39.5, 24.5, 22.8, 21.0. IR: 2945, 2830, 1784, 1747, 1156 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{20}F_3N_2O_4$ 325.1375, found 325.1342.

4.3.19. Methyl (4R,5R)-1-[(S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (***13***). ***Method B***.

Colorless oil (14.4 mg, 38 %). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 3:7). $[\alpha]_D$ = +19.3 (*c* = 1 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 7.28–7.12 (m, 5H), 6.98 (s, 1H), 4.61 (dd, *J* = 2.0, 6.7 Hz, 1H), 4.33 (quintet, *J* = 6.5 Hz, 1H), 4.20 (dd, *J* = 6.7, 8.6 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 3.31 (d, *J* = 6.6, 14.2 Hz, 1H), 3.10 (dd, *J* = 8.6, 14.2 Hz, 1H). ^{19}F NMR ($CDCl_3$): –75.6 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 170.8, 169.9, 154.3, 135.5, 128.9 (2C), 128.7 (2C), 127.3, 124.6 (q, *J* = 279.9 Hz), 70.1, 62.6 (q, *J* = 31.6 Hz), 58.6, 53.1, 52.7, 37.2. IR: 3100, 2838, 1768, 1747, 1589, 1156 cm^{-1}. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{18}F_3N_2O_4$ 359.1219, found 359.1258.

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Supplementary Material

Supplementary data related to this article can be found at http://dx.doi.org/