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Intramolecular Nitrone Cycloaddition of α-(Trifluoromethyl)styrenes. Role of the CF_3 Group in the Regioselectivity

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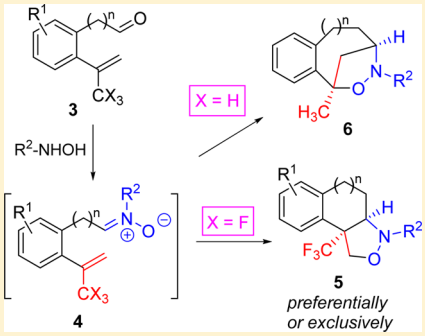
Supporting Information

ABSTRACT: The intramolecular 1,3-dipolar cycloaddition of ortho-substituted 1,1,1-trifluoromethylstyrene-derived nitrones is described. Tricyclic fused isoxazolidines were obtained as major or exclusive products, in contrast to the case for nonfluorinated substrates, which rendered the bridged derivatives. This change in the regioselectivity was attributed to the electronic and, particularly, steric requirements of the trifluoromethyl group in comparison to the methyl group. It is worth mentioning that trifluoromethylstyrenes have been employed for the first time as dipolarophiles in a 1,3-dipolar intramolecular cycloaddition reaction, leading to the corresponding isoxazolidines bearing a quaternary trifluoromethyl moiety. Finally, the synthetic utility of the developed methodology has been illustrated with the synthesis of a family of bicyclic fluorinated 1,3-amino alcohols.



INTRODUCTION

The 1,3-dipolar cycloaddition reaction, initially proposed by Smith,[1] constitutes an outstanding methodology for the synthesis of five-membered-ring-containing heterocycles.[2] It involves the combination of a 1,3-dipole with a multiple bond called a dipolarophile. This methodology, which found widespread application in several fields such as natural product synthesis, materials science, and biological chemistry, started to be recognized as a powerful tool in organic chemistry after the seminal work by Huisgen in the early 1960s.[3]

Among the great variety of 1,3-dipoles described, nitrones are probably the most widely employed in dipolar cycloadditions.[4] This is probably due to the easy access, high stability, and biological significance of these intermediates. Depending on the nature of the dipolarophile moieties, either isoxazole or isoxazolidine skeletons are formed in their reactions with alkenes or alkynes, respectively. These heterocycles are present in a broad variety of alkaloids and natural products, and they can be converted by reductive ring opening into 1,3-amino alcohols, which are precursors of β-amino acids and β-lactams.[5] In addition, nitrone cycloadditions may be involved in the biosynthesis of some alkaloids without enzymatic catalysis.[6]

The regio- and stereochemical issues that arise in intermolecular cycloaddition reactions are minimized in the intramolecular variants of these processes. Thus, when nitrones react with alkenes, fused or bridged isoxazolidines are formed following an exo or endo cyclization mode, often with high levels of stereocontrol. Therefore, intramolecular nitrone cycloaddition reactions are unequaled when it comes to building several stereocenters with high stereoselectivity in one reaction step.[7]

Despite the widespread use of 1,3-dipolar cycloadditions with nitrones as the dipole counterpart, the use of fluorinated substrates lagged behind.[8] Furthermore, while several examples of intermolecular reactions (most of them involving fluorinated dipolarophiles) have been reported in the literature, the intramolecular nitrone cycloaddition reaction (INCR) concerning fluorine-containing substrates remained almost unexplored.[9] In this context, the development of new methodologies that give access to fluorinated isoxazolidine derivatives[10] is highly attractive, since hydrogenolysis of the N−O bond would generate precursors of fluorinated β-amino acids.[11]

With this idea in mind, we focused our attention on an efficient methodology for the preparation of 1-(trifluoromethyl)styrenes, recently disclosed by Valdés and co-workers,[12] and we envisioned the possibility of employing those compounds as dipolarophiles in the intramolecular 1,3-dipolar cycloaddition reaction. Considering the benefits of the introduction of fluorine atoms into biologically active compounds,[13] products arising from this transformation would contain new fluorinated chemical entities bearing a quaternary trifluoromethyl group. The incidence of CF_3 groups in pharmaceuticals and agrochemicals is outstandingly high, which makes this moiety the most widely used among fluorine-containing functional groups.[14] In this context, the generation of novel CF_3-containing scaffolds is always of high interest.

Herein, we present our studies of the INCR on 1-trifluoromethylstyrenes bearing an aldehyde functionality in the ortho position as the precursor of the nitrone moiety

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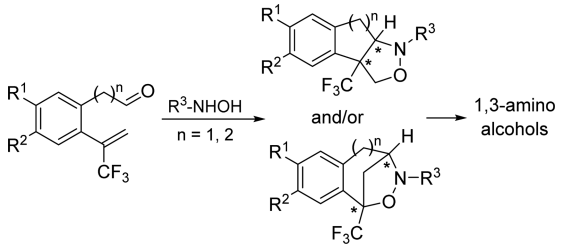
(Scheme 1). The obtained results indicated that the trifluoromethyl group plays a relevant role in the regiochemistry of the

Scheme 1. Intramolecular 1,3-Dipolar Nitrone Cycloaddition of α-Trifluoromethyl Styrenes



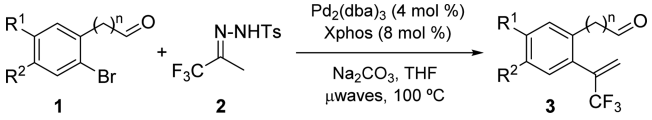
process. Preliminary theoretical studies were also performed in order to shed light on the stereochemical outcome of the reaction. Additionally, the ring opening of the isoxazolidine moiety gave access to new families of fluorinated cyclic 1,3-amino alcohols.

RESULTS AND DISCUSSION

Due to the importance of the incorporation of the trifluoromethyl group into organic molecules, the development of new methodologies that allow for the introduction of this fluorinated one-carbon unit has attracted growing interest.[15] Among the remarkable achievements in this area, a palladium-catalyzed cross-coupling reaction of 1,1,1-trifluoroacetone tosylhydrazone with several aryl halides which gives access to 3,3,3-trifluoromethylstyrenes was recently reported.[12] As we mentioned in the Introduction, we decided to employ this methodology to generate suitable precursors to undergo an intramolecular dipolar cycloaddition. To this end, *o*-bromoacetaldehydes and *o*-bromopropionaldehydes **1** were subjected to slightly modified cross-coupling conditions that involved their reaction with fluorinated hydrazone **2**, $Pd_2(dba)_3$ as the catalyst, Xphos as a ligand, and Na_2CO_3 as a base in THF under microwave irradiation.[16] Under these conditions, moderate to good yields of the corresponding (trifluoromethyl)styrenes **3** were obtained, as depicted in Table 1.

With the starting aldehydes **3** in hand, the next step of our study was the formation of the corresponding nitrones by condensation with hydroxyl amines. The optimization of the reaction conditions was performed with compound **3b** as a

Table 1. Synthesis of the Starting Trifluoromethyl-Containig Aldehydes 3



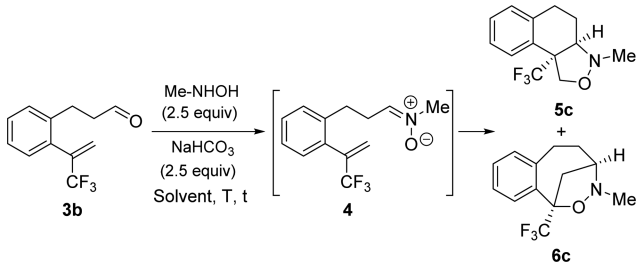
1 2 3

entry	1	*n*	R^1	R^2	3	yield (%)[a]
1	1a	1	H	H	3a	63
2	1b	2	H	H	3b	77
3	1c	1	F	H	3c	44
4	1d	2	F	H	3d	81
5	1e	1	$-OCH_2O-$		3e	41
6	1f	2	$-OCH_2O-$		3f	72

[a]Isolated yield after flash column chromatography. Due to their instability, these aldehydes have to be used immediately after purification.

model substrate and *N*-methylhydroxyl amine. In all cases, intermediate nitrones **4** were not isolated but cyclized under the reaction conditions in the 1,3-dipolar mode, hence rendering the corresponding isoxazolidines **5** and/or **6** (Table 2).

Table 2. Optimization of the Dipolar Cycloaddition Reaction



		yield (%)[b]	
entry	reaction conditions	5c	6c
1	EtOH/H_2O (80/20), room temp, 15 h	*a*	*a*
2	EtOH/H_2O (80/20), reflux, 15 h	14	28
3	EtOH/H_2O (80/20), μwaves, 100 °C, 3 h	14	28
4	DCM, μwaves, 60 °C, 3 h	13	13
5	toluene, μwaves, 120 °C, 30 min	55	29

[a]Complex mixture of products. [b]Isolated yield after flash column chromatography.

The formation of the nitrone and subsequent dipolar cycloaddition were initially tested with hydroxylamine hydrochloride in the presence of sodium bicarbonate in a ethanol/water mixture as the solvent. Unfortunately, after 15 h at room temperature, a complex mixture of products was observed (Table 2, entry 1). Nevertheless, when the reaction mixture was heated at reflux, a mixture of the two regioisomeric cycloadducts **5c** and **6c** was isolated, albeit in low yield (Table 2, entry 2). In order to decrease the reaction time, microwave irradiation was employed and, after 3 h at 100 °C, results comparable to those obtained with conventional heating were obtained (Table 2, entry 3). Changing the solvent to dichloromethane did not improve the efficiency of the process (Table 2, entry 4); however, the use of toluene produced a dramatic change since, after 30 min at 120 °C, 55% of the linear adduct **5c** was obtained together with 29% of the bridged product **6c** (Table 2, entry 5).

The optimized reaction conditions for the INCR were then applied to the rest of the trifluoromethylstyrenes **3**. The results obtained are depicted in Table 3.

In almost all cases, the dipolar cycloaddition leading to fused tricyclic derivatives **5** was preferred over the formation of bridged compounds **6**. On the other hand, starting aldehydes **3** with two methylene groups (n = 2) cyclized more efficiently, probably due to steric reasons.

Substrates unsubstituted in the aromatic ring provided better yields with methyl hydroxylamine, rendering ca. 2:1 mixtures of regioisomers **5** and **6** (Table 3, entries 1 and 3). These reactions with benzyl hydroxylamine gave lower yields of the corresponding cycloadducts, again favoring fused products **5** over bridged ones **6** (Table 3, entries 2 and 4). The presence of an electron-withdrawing group in the aromatic ring such as a fluorine atom led to lower yields and comparable regioselectivities, in general (Table 3, entries 5–8). Alternatively, when

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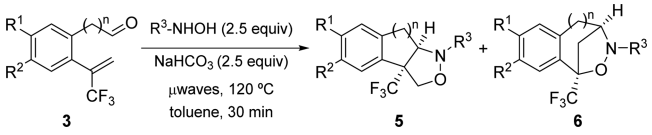
Table 3. Scope of the Dipolar Cycloaddition of Substrates 3



3 5 6

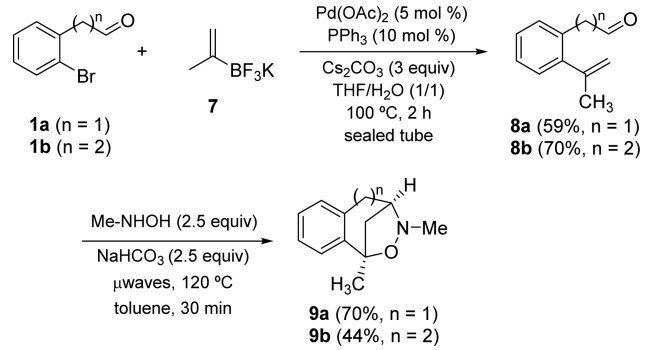
entry	3	n	R^1	R^2	R^3	5, yield (%)[a]	6, yield (%)[a]
1	**3a**	1	H	H	Me	**5a**, 44	**6a**, 25
2	**3a**	1	H	H	Bn	**5b**, 35	0
3	**3b**	2	H	H	Me	**5c**, 55	**6c**, 29
4	**3b**	2	H	H	Bn	**5d**, 46	**6d**, 23
5	**3c**	1	F	H	Me	**5e**, 33	**6e**, 3
6	**3c**	1	F	H	Bn	**5f**, 28	**6f**, 30
7	**3d**	2	F	H	Me	**5g**, 50	**6g**, 13
8	**3d**	2	F	H	Bn	**5h**, 39[b]	**6h**, 16[b]
9	**3e**	1	$-OCH_2O-$		Me	**5i**, 42	0
10	**3e**	1	$-OCH_2O-$		Bn	**5j**, 97	0
11	**3f**	2	$-OCH_2O-$		Me	**5k**, 88	0
12	**3f**	2	$-OCH_2O-$		Bn	**5l**, 79	0

[a]Isolated yield after flash column chromatography. [b]An inseparable mixture of isoxazolidinones **5h** and **6h** was obtained.

electron-donating groups were placed in the aromatic ring, fused compounds **5** were obtained as unique products in generally good yields (Table 3, entries 9−12).

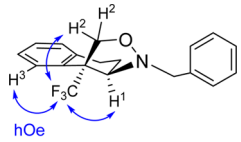
In order to evaluate the influence of the fluorinated moiety in the cycloaddition process, styrenes containing a methyl group instead of the trifluoromethyl group were synthesized. Accordingly, substrates **8** were assembled by Suzuki coupling of the starting bromo-aldehydes **1** and trifluoroalkylborate **7**.[17] After both components were heated in the presence of $Pd(OAc)_2$ in a sealed tube in a THF/H_2O mixture, *ortho*-substituted styrenes **8** were obtained in good yields (Scheme 2). When these substrates were subjected to the optimized

Scheme 2. Intramolecular 1,3-Dipolar Nitrone Cycloaddition of Styrenes 8



INCR conditions (see Table 2, entry 5), bridged products **9** were observed in moderate to good yields together with trace amounts of the corresponding fused products (Scheme 2). Therefore, an inversion of the regioselectivity occurred in comparison to the cyclization of fluorinated derivatives **3**.

The relative stereochemistry of the fused derivatives **5** was determined by means of NMR experiments on compound **5d**. Heteronuclear correlation (HOESY) between the fluorine nuclei and proton H^1 at the fusion of the two aliphatic rings allowed us to assign a *cis* relative stereochemistry between them. Additional correlations with protons H^2 and H^3 were also observed (Figure 1). The same stereochemistry was assumed for all derivatives **5**.



5d

Figure 1. Determination of the relative stereochemistry on compound **5d**.

Regarding the structural elucidation, ^{19}F NMR of bridged compounds **6c,d,g,h** showed broad signals. However, after performing an NMR study at different temperatures on compound **6g**, we found that it was formed as a single product. ^{19}F NMR at high temperature (100 °C) afforded a singlet signal for the CF_3 group whereas three signals corresponding to the three different fluorine atoms were observed at low temperature (−40 °C) (see the Supporting Information).

To gain some insight into the mechanistic details of this transformation, we carried out a preliminary theoretical study by using DFT methods at the B3LYP/6-31G*(d,p) level. The stationary points were characterized by frequency computations in order to verify their nature. Transition structures (TS) were found to have only one imaginary frequency. In order to simplify the results, among 32 possible TSs, only 8 that corresponded to the (*Z*)-nitrone with an endo approach were included, as they were the lowest in energy. The TSs **A**−**D**, related to the methyl derivatives (X = H), indicated that the formation of the bridged cycloadducts is slightly more favorable when n = 2, as TS **D** is 1.10 kcal/mol more stable than TS **C**. Nevertheless, the energy difference is minimum when n = 1 TS **B** being only 0.07 kcal/mol more stable than TS **A** (Scheme 3) (for details see the Supporting Information). In fact, experimental results showed that bridged products **9** were isolated (see Scheme 2) while only traces of the regioisomeric fused products were detected by NMR. This is probably due to the instability of the linear derivatives that decompose under the reaction conditions. The situation is different with fluorinated substrates; *i.e.*, in this case both TS **E** and TS **G**, which lead to fused cycloadducts **5** with n = 1 and n = 2, are 3.63 and 2.71 kcal/mol more stable, respectively, than TS **F** and TS **H** (Scheme 3). These theoretical findings showed the same trend as the experimental results (see Table 3 and Scheme 2).

With these data in hand, it became apparent that both steric and electronic effects play an important role in the cycloaddition process. Steric reasons are always invoked to explain the preferred formation of fused over bridged cycloadducts in intramolecular 1,3-dipolar cycloadditions with nitrones. However, in our case, the regioselectivity of the process is also clearly influenced by the electronic nature of the substituents in the aromatic ring and the presence of the trifluoromethyl moiety.

Regarding the trifluoromethyl group, its electron-withdrawing effect makes the benzylic carbon C1 more electrophilic for the *O*-nitrone attack. However, substrates **3** rendered as major products fused cycloadducts **5**, in contrast to substrates **8** containing a methyl group, which exclusively rendered bridged adducts **9** arising from the C1 attack (Scheme 4). This indicates that the steric requirements of the CF_3 moiety are more important than electronic effects since the preferential nitrone

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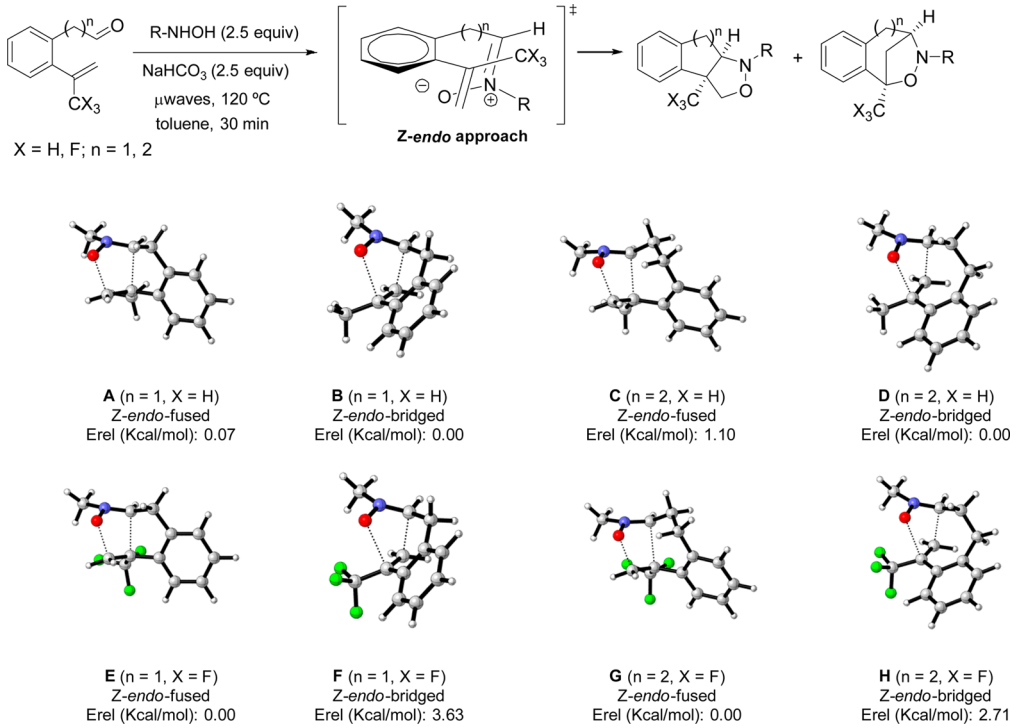
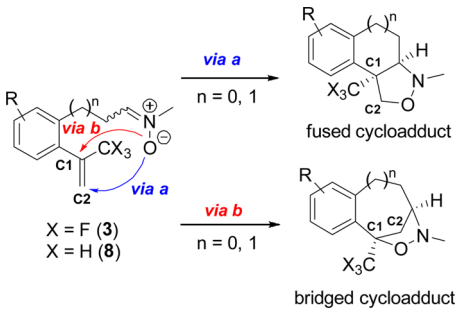
Scheme 3. Transition Structures for a *Z*-endo Approach in the INCR



Scheme 4. Formation of Fused *versus* Bridged Products



approach leads to the C2−O bond (Scheme 4, *via a*). On the other hand, from Table 4 it can be seen that for the bridged transition structures (**B**, **D**, **F**, and **H**), the forming C−C bond lengths (2.065, 2.073, 2.060, and 2.045 Å, respectively) are shorter than the C−O distances. However, the opposite trend is found for fused transition structures (**A**, **C**, **E**, and **G**), with forming C−O bond lengths (2.084, 2.028, 1.986, and 1.929 Å, respectively) being shorter than the C−C distances. Such a reversed situation is in agreement with 1,3-dipolar cycloadditions with electron-deficient dipolarophiles.[18]

The C−O distances are shorter in the TSs leading to fused cycloadducts, and this asynchronicity in the transition states shows that the reaction starts by the addition of the nitrone oxygen to the more electrophilic carbon atom at the benzylic position. Moreover, the bridged TSs, representing a typical asynchronous process, can be considered early transition states, as indicated by the relatively long distance of the forming C−O bonds.[19] Since both CF_3- and CH_3-containing substrates follow the same trend in terms of bond-forming lengths, this indicates that the C2 position does not play an important role in the regioselectivity. Therefore, it seems that steric effects of the trifluoromethyl group are more important than electronic effects.

Regarding the electronic nature of the substituents in the aromatic ring, electron-withdrawing groups would enhance the electrophilicity of the benzylic carbon C1, thereby increasing the preference for the oxygen attack on this carbon (Scheme 4, *via b*), while electron-donating substituents would induce the opposite effect (Scheme 4, *via a*). When both effects operate in the same direction, *i.e.*, substrates bearing a trifluoromethyl group and electron-donating substituents in the aromatic ring, an excellent control of the regioselectivity could be achieved, rendering exclusively the fused adducts **5i−l** (see Table 3, entries 9−12).

Finally, in terms of the synthetic value of the reaction studied, the obtained tricyclic isoxazolidines **5**/**6** can easily be cleaved to the corresponding 1,3-amino alcohols, which represent an interesting moiety for both organic synthesis and medicinal chemistry applications. Among the reductive

Table 4. B3LYP/6-31G* Total (*E*, in au) and Relative[a] (Δ*E*, in kcal/mol) Gas-Phase Energies of Transition States Involved in the Cycloaddition Reactions of Nitrones and Distances for the Two Forming Bonds in the TSs

system	*n*	*E*	Δ*E*	*d*(C−C) (Å)	*d*(C−O) (Å)
			X = H		
TSA	1	−595.922374	0.07	2.167	2.084
TSB	1	−595.92249	0.00	2.065	2.458
TSC	2	−635.198214	1.10	2.276	2.028
TSD	2	−635.199971	0.00	2.073	2.444
			X = F		
TSE	1	−893.675523	0.00	2.226	1.986
TSF	1	−893.669742	3.63	2.060	2.418
TSG	2	−932.951685	0.00	2.361	1.923
TSH	2	−932.947371	2.71	2.045	2.452

[a]Relative to the most stable TS in any series.

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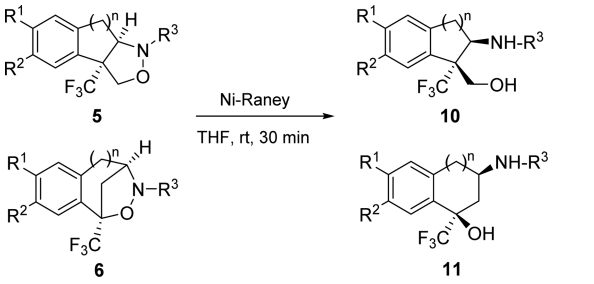
conditions tested for the ring opening of the isoxazolidine ring of compounds **5** and **6** (Zn, Pd/C, $Pd(OH)_2$, $LiAlH_4$, Raney Ni), the best results were obtained with Raney Ni in THF at room temperature (Table 5).

Table 5. Synthesis of Fluorinated Bicyclic γ-Amino Alcohols



5 **10** **6** **11**

entry	5/6	n	R^1	R^2	R^3	10/11, yield (%)[a]
1	**5a**	1	H	H	Me	**10a**, 50
2	**6a**	1	H	H	Me	**11a**, 83
3	**5b**	1	H	H	Bn	**10b**, 75
4	**5c**	2	H	H	Me	**10c**, 89
5	**6c**	2	H	H	Me	**11c**, 57
6	**5d**	2	H	H	Bn	**10d**, 93
7	**6d**	2	H	H	Bn	**11d**, 33
8	**5e**	1	F	H	Me	**10e**, 70
9	**5g**	2	F	H	Me	**10g**, 99
10	**5i**	1	$-OCH_2O-$		Me	**10i**, 57
11	**5k**	2	$-OCH_2O-$		Me	**10k**, 99

[a]Isolated yield after flash column chromatography.

Unsubstituted compounds **5a−d** and **6a,c,d** afforded moderate to very good yields of the corresponding 1,3-amino alcohols (Table 5, entries 1−7). It is important to note that substrates containing the benzyl *N*-protecting group (**5b,d** and **6d**) can be selectively cleaved at the isoxazolidine ring without affecting the benzylic nitrogen (Table 5, entries 3, 6, and 7), provided that the reaction is performed in 30 min. Longer reaction times led to variable mixtures of isoxazolidine ring-opening products with or without debenzylation of the amine functionality.

Substrates **5e,g**, containing the fluorine substituent in the aromatic ring, also gave very good yields of the final products (Table 5, entries 8 and 9) without detection of reductive cleavage of the C−F bond. Finally, compounds **5i,k**, bearing the dioxolane moiety, were efficiently cleaved to the corresponding bicyclic 1,3-amino alcohols (Table 5, entries 10 and 11).

It is worth mentioning that all 1,3-amino alcohols obtained have an interesting structural feature: namely, a quaternary stereocenter bearing a trifluoromethyl group.

SUMMARY

In conclusion, the synthesis of a new family of racemic fluorinated polycyclic isoxazolidines was performed by means of an INCR of *ortho*-substituted α-(trifluoromethyl)styrenes. Despite the widespread applications of intramolecular cycloaddition reactions with nitrones, the use of fluorinated substrates in these types of processes remained almost unprecedented. Additionally, the 1-(trifluoromethyl)vinyl unit was used for the first time as a dipolarophile in intramolecular dipolar cycloaddition reactions. Interestingly, the trifluoromethyl group plays an important role in the regioselectivity of the process; whereas α-methylstyrenes gave rise preferentially to the bridged cycloadducts, with α-(trifluoromethyl)styrenes an inversion of the regioselectivity occurred, affording fused products preferentially or exclusively. It seems that this inversion is due mainly to steric effects of the trifluoromethyl group.

EXPERIMENTAL SECTION

General Methods. Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and PhMe were distilled from sodium, and CH_2Cl_2 was distilled from calcium hydride. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040−0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The designation br indicates that the signal is broad. The abbreviations DCM and THF indicate dichloromethane and tetrahydrofuran, respectively. Microwave reactions were carried out in a 2−5 or 15 mL vial with a Biotage Initiator TM 2.0 microwave synthesizer. The solutions were stirred before the irradiation was started, and the absorbance of the solvent was set as "normal". The reaction time was initiated as soon the system reached the input temperature, although it took approximately 2 min to reach it. A QTOF mass analyzer system has been used for the HRMS measurements.

Synthesis of Isoxazolidines 5 and 6. *Synthesis of Fluorinated Aldehydes 3 (Nitrone Precursors). General Procedure.* A 10 mL microwave glass vial was charged with $Pd_2(dba)_3$ (4 mol %, 0.06 mmol), Xphos (10 mol %, 0.15 mmol), Na_2CO_3 (2.2 equiv, 3.3 mmol), and *N*-tosyl hydrazone **2** (1.5 equiv, 2.25 mmol), which was previously prepared from 1,1,1-trifluoroacetone (1 equiv, 22 mmol) and *N*-tosylhydrazine (1 equiv, 22 mmol) by heating at 70 °C in EtOH (0.5 M) for 5 h and then filtering the precipitate solid at room temperature as a crystalline white solid. The solid reagents were dried together under reduced pressure before being used. The corresponding 2-(2-bromophenyl)acetaldehyde or 3-(2-bromophenyl)-propionaldehyde (1.5 mmol) dissolved in THF (0.3 M) was added. The vial was sealed, and the mixture was heated by microwave irradiation at 100 °C for 2 h. The reaction mixture was cooled to room temperature, opened, filtered through Celite, and concentrated under reduced pressure. The residue obtained was purified by flash chromatography (*n*-hexane/EtOAc (20/1)). The product obtained was used immediately in the next step.[20]

*2-[2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl]acetaldehyde (**3a**).* Starting from 2-(2-bromophenyl)acetaldehyde[21] and following the general procedure indicated above, **3a** was obtained as a yellow oil in 63% yield (202 mg). ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (t, *J* = 1.8 Hz, 1H), 7.51−7.19 (m, 4H), 6.14 (q, *J* = 1.5 Hz, 1H), 5.49 (q, *J* = 1.3 Hz, 1H), 3.74 (d, *J* = 1.8 Hz, 2H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −67.91 (s).

*3-(2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)propanal (**3b**).* Starting from 3-(2-bromophenyl)propanal[22] and following the general procedure indicated above, **3b** was obtained as a yellow oil in 77% yield (264 mg). ^1H NMR (300 MHz, $CDCl_3$): δ 9.70 (t, *J* = 1.3 Hz, 1H), 7.48−7.00 (m, 4H), 6.05 (d, *J* = 1.4 Hz, 1H), 5.44 (d, *J* = 1.4 Hz, 1H), 2.87 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.70−2.56 (m, 2H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −67.46 (s).

*2-(5-Fluoro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)acetaldehyde (**3c**).* Starting from 2-(2-bromo-5-fluorophenyl)acetaldehyde[23] and following the general procedure indicated above, **3c** was obtained as a yellow oil in 44% yield (153 mg). ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (t, *J* = 1.6 Hz, 1H), 7.56−7.31 (m, 1H), 7.11−6.88 (m, 2H), 6.15 (q, *J* = 1.4 Hz, 1H), 5.49 (d, *J* = 1.4 Hz, 1H), 3.73 (d, *J* = 1.6 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.10 (s, 3F), −112.32 (ddd, *J* = 9.1, 8.2, 5.7 Hz, 1F).

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*3-(5-Fluoro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)propanal (**3d**).* Starting from 3-(2-bromo-5-fluorophenyl)propanal[24] and following the general procedure indicated above, **3d** was obtained as a yellow oil in 81% yield (299 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (t, J = 1.1 Hz, 1H), 7.22−7.14 (m, 1H), 7.02−6.88 (m, 2H), 6.16 (q, J = 1.4 Hz, 1H), 5.53 (q, J = 1.3 Hz, 1H), 2.94 (t, J = 7.5 Hz, 2H), 2.80−2.69 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −67.71 (s, 3F), −112.69 (ddd, J = 9.7, 8.2, 5.9 Hz, 1F).

*2-(6-(3,3,3-Trifluoroprop-1-en-2-yl)benzo[d][1,3]dioxol-5-yl)-acetaldehyde (**3e**).* Starting from 2-(6-bromobenzo[d][1,3]dioxol-5-yl)acetaldehyde[25] and following the general procedure indicated above, **3e** was obtained as a yellow oil in 41% yield (159 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (t, J = 1.7 Hz, 1H), 6.75 (s, 1H), 6.70 (s, 1H), 6.11 (q, J = 1.4 Hz, 1H), 6.00 (s, 2H), 5.46 (q, J = 1.4 Hz, 1H), 3.63 (d, J = 1.7 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.07 (s).

*3-(6-(3,3,3-Trifluoroprop-1-en-2-yl)benzo[d][1,3]dioxol-5-yl)-propanal (**3f**).* Starting from 3-(6-bromobenzo[d][1,3]dioxol-5-yl)-propanal[26] and following the general procedure indicated above, **3f** was obtained as a yellow oil in 72% yield (294 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (s, 1H), 6.71 (s, 1H), 6.67 (s, 1H), 6.12 (q, J = 1.4 Hz, 1H), 5.96 (s, 2H), 5.50 (q, J = 1.2 Hz, 1H), 2.86 (t, J = 7.4 Hz, 2H), 2.71−2.63 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −67.67 (s).

*Intramolecular Nitrone Cycloaddition of Fluorinated Aldehydes **3**. General Procedure.* To a solution of the corresponding starting fluorinated aldehyde **3** (0.5 mmol) in toluene (0.2 M) in a 10 mL microwave glass vial were added *N*-alkylhydroxylamine hydrochloride (2.6 equiv) and sodium bicarbonate (2.6 equiv, 109 mg). The vial was sealed, and the mixture was heated by microwave irradiation at 120 °C for 30 min. The reaction mixture was cooled to room temperature, opened, and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography to purify and/or separate the formed regioisomeric isoxazolidines.

Starting from **3a** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **5a** (44%, 54 mg, yellow oil) and **6a** (25%, 30 mg, yellow solid, mp 73−75 °C) was obtained, which were separated by flash chromatography (*n*-hexane/EtOAc (4/1)).

*1-Methyl-3a-(trifluoromethyl)-3,3a,8,8a-tetrahydro-1H-indeno-[2,1-c]isoxazole (**5a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.12 (m, 4H), 4.45 (d, J = 8.9 Hz, 1H), 3.81 (dq, J = 8.9, 1.6 Hz, 1H), 3.41 (d, J = 6.6 Hz, 1H), 3.17 (dd, J = 17.0, 6.6 Hz 1H), 2.80 (d, J = 17.0 Hz, 1H), 2.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 138.5, 129.5, 127.9, 127.2 (CF_3, q, J = 279.9 Hz), 125.6, 125.2, 74.4, 73.3, 71.2 (*C*-CF_3, q, J = 26.2 Hz), 43.4, 35.2. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −72.63 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{12}H_{13}F_3NO$ 244.0944; found 244.0934.

*3-Methyl-1-(trifluoromethyl)-1,3,4,5-tetrahydro-1,4-methanobenzo[e][1,2]oxazepine (**6a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.09 (m, 4H), 3.70 (br s, 1H), 3.35−3.12 (m, 2H), 2.95 (dd, J = 11.3, 5.3 Hz, 1H), 2.81 (s, 3H), 2.36 (d, J = 11.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3, 134.1, 129.8, 129.0, 125.8, 124.9 (CF_3,q, J = 281.1 Hz), 123.3, 83.5 (*C*-CF_3, q, J = 26.7 Hz), 62.7, 46.9, 37.9, 35.2. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −71.70 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{12}H_{13}F_3NO$ 244.0944; found 244.0943.

*1-Benzyl-3a-(trifluoromethyl)-3,3a,8,8a-tetrahydro-1H-indeno-[2,1-c]isoxazole (**5b**).* Starting from **3a** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, **5b** (35%, 56 mg, yellow solid, mp 88−90 °C) was obtained and purified by flash chromatography (*n*-hexane/Et_2O (25/1)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53−7.01 (m, 9H), 4.47 (d, J = 9.0 Hz, 1H), 4.05 (d, J = 13.6 Hz, 1H), 3.99 (d, J = 13.6 Hz, 1H), 3.81 (dq, J = 9.0, 1.6 Hz, 1H), 3.69 (d, J = 7.0 Hz, 1H), 3.12 (dd, J = 17.1, 7.0 Hz, 1H), 2.77 (d, J = 17.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 138.3, 136.8, 129.5, 129.1 (2 × CH), 128.6 (2 × CH), 127.8, 127.7, 127.3 (CF_3,q, J = 279.7 Hz), 125.5, 125.1, 73.1, 72.4, 70.9 (*C*-CF_3, q, J = 26.1 Hz), 61.0, 35.9. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −72.38 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{18}H_{17}F_3NO$ 320.1257; found 320.1255.

Starting from **3b** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **5c** (55%, 71 mg, yellow oil) and **6c** (29%, 37 mg, yellow solid, mp 65−67 °C) was obtained, which were separated by flash chromatography (*n*-hexane/EtOAc (4/1)).

*3-Methyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho-[2,1-c]isoxazole (**5c**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56−6.96 (m, 4H), 4.63 (d, J = 9.2 Hz, 1H), 3.97 (dq, J = 9.2, 1.8 Hz, 1H), 3.17 (dd, J = 7.1, 7.1 Hz, 1H), 2.81 (s, 3H), 2.77−2.73 (m, 2H), 2.32−2.12 (m, 1H), 1.66−1.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 132.1, 129.1, 128.4, 128.1, 127.5 (CF_3, q, J = 282.2 Hz), 126.9, 73.4, 68.2, 58.9 (*C*-CF_3, q, J = 24.2 Hz), 43.6, 26.5, 25.2. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −72.34 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{13}H_{15}F_3NO$ 258.1100; found 258.1105.

*3-Methyl-1-(trifluoromethyl)-3,4,5,6-tetrahydro-1H-1,4-methanobenzo[f][1,2]oxazocine (**6c**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.04 (m, 4H), 3.85−3.59 (m, 2H), 3.09 (ddd, J = 12.6, 7.0, 1.6 Hz, 1H), 2.89 (s, 3H), 2.87−2.77 (m, 1H), 2.63 (dt, J = 14.8, 3.8 Hz, 0H), 2.23−2.13 (m, 2H), 1.63 (tdd, J = 13.6, 3.4, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 137.7, 132.5, 128.5, 126.3, 125.6 (CF_3, q, J = 283.8 Hz), 125.0, 89.0, 66.0, 47.0, 43.2, 34.1, 32.4. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −70.83 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{13}H_{15}F_3NO$ 258.1100; found 258.1099.

Starting from **3b** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **5d** (46%, 77 mg, white solid, mp 95−97 °C) and **6d** (23%, 38 mg, white solid, mp 110−112 °C) was obtained, which were separated by flash chromatography (*n*-hexane/Et_2O (30/1)).

*3-Benzyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho-[2,1-c]isoxazole (**5d**).* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33−7.06 (m, 9 H), 4.56 (d, J = 9.3 Hz, 1H), 4.06 (d, J = 13.7 Hz, 1H), 3.97 (d, J = 13.7 Hz, 1H), 3.92 (dq, J = 9.3, 1.8 Hz, 1H), 3.37 (dd, J = 8.6, 6.3 Hz, 1 H), 2.73−2.58 (m, 2H), 2.04−1.95 (m, 1H), 1.59−1.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.6, 137.1, 132.1, 129.1, 129.0 (2 × CH), 128.5 (2 × CH), 128.3, 128.1, 127.6, 127.6 (CF_3, q, J = 282.3 Hz), 126.9, 73.2, 73.2, 66.3, 61.0, 58.7 (*C*-CF_3, q, J = 24.0 Hz), 26.8, 26.0. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −72.35 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{19}F_3NO$ 334.1413; found 334.1409.

*3-Benzyl-1-(trifluoromethyl)-3,4,5,6-tetrahydro-1H-1,4-methanobenzo[f][1,2]oxazocine (**6d**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−6.95 (m, 9H), 4.33 (d, J = 13.0 Hz, 1H), 3.87 (d, J = 13.0 Hz, 1H), 3.81−3.63 (m, 2H), 3.05 (ddd, J = 12.6, 7.0, 1.5 Hz, 1H), 2.53 (dt, J = 14.8, 3.8 Hz, 1H), 2.16 (d, J = 12.6 Hz, 1H), 2.02−1.86 (m, 1H), 1.62−1.39 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 141.6, 138.0, 137.8, 132.5, 129.3, 128.8, 128.5, 127.8, 125.8 (CF_3, q, J = 283.8 Hz), 125.0, 89.3 (*C*-CF_3, q, J = 25.6 Hz), 63.3, 62.8, 43.4, 34.3, 32.6. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −70.70 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{19}F_3NO$ 334.1413; found 334.1421.

*6-Fluoro-1-methyl-3a-(trifluoromethyl)-3,3a,8,8a-tetrahydro-1H-indeno[2,1-c]isoxazole (**5e**).* Starting from **3c** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **5e** (33%, 43 mg, yellow solid, mp 49−51 °C) was obtained and purified by flash chromatography (*n*-hexane/EtOAc (50/1)). Only trace amounts of the bridged regioisomer could be detected when the reaction was scaled up. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (m, 1H), 7.03−6.91 (m, 2H), 4.51 (d, J = 8.9 Hz, 1H), 3.85 (dq, J = 8.9, 1.6 Hz, 1H), 3.51 (d, J = 6.5 Hz, 1H), 3.23 (dd, J = 17.1, 6.5 Hz, 1H), 2.86 (d, J = 17.1 Hz, 1H), 2.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 162.4, 130.1, 127.0 (CF_3, q, J = 279.6 Hz), 126.5 (d, J = 9.3 Hz), 115.3 (d, J = 23.0 Hz), 112.6 (d, J = 22.5 Hz), 74.9, 73.2, 70.5 (*C*-CF_3, q, J = 26.2 Hz), 43.3, 35.2. ^{19}F NMR (282 MHz, chloroform-*d*): δ −72.89 (s, 3F), −113.45 (ddd, J = 8.8, 8.8, 5.1 Hz, 1F). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{12}H_{12}F_4NO$ 262.0850; found 262.0854.

Starting from **3c** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **5f** (28%, 47 mg, yellow oil) and **6f** (30%, 51 mg, yellow oil) was obtained, which were separated by flash chromatography (*n*-hexane/EtOAc (50/1)). Only **5f** could be completely separated, while **6f** was invariably obtained in a mixture of both regioisomers and the ^{1}H NMR signals

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below were inferred from the spectrum of the mixture by comparison with the spectrum of pure **5f**.

*1-Benzyl-6-fluoro-3a-(trifluoromethyl)-3,3a,8,8a-tetrahydro-1H-indeno[2,1-c]isoxazole (**5f**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.20 (m, 6H), 7.06−6.88 (m, 2H), 4.54 (d, J = 9.0 Hz, 1H), 4.11 (s, 2H), 3.87 (dq, J = 9.0, 1.5 Hz, 1H), 3.81 (dd, J = 7.0, 1.1 Hz, 1H), 3.19 (dd, J = 17.4, 7.0 Hz, 1H), 2.83 (d, J = 17.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 162.4, 145.6 (d, J = 8.7 Hz), 136.6, 128.6, 127.8, 127.1 (CF_3, q, J = 279.9 Hz), 126.4 (d, J = 9.5 Hz), 115.2 (d, J = 23.1 Hz), 112.4 (d, J = 22.5 Hz), 73.1, 72.8, 70.2 (*C*-CF_3,q, J = 26.4 Hz), 60.9, 36.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.62 (s, 3F), −113.47 (ddd, J = 8.8, 8.8, 5.1 Hz, 1F). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{18}H_{16}F_4NO$ 338.1163; found 338.1162.

*3-Benzyl-7-fluoro-1-(trifluoromethyl)-1,3,4,5-tetrahydro-1,4-methanobenzo[e][1,2]oxazepine (**6f**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.27 (m, 6H), 6.91−6.77 (m, 2H), 4.24 (d, J = 12.7 Hz, 1H), 3.89 (d, J = 12.7 Hz, 1H), 3.84 (s, 1H), 3.24−3.05 (m, 2H), 3.03−2.90 (m, 1H), 2.34 (d, J = 11.4 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −71.68 (br s, 3F), −113.46 (ddd, J = 8.8, 8.8, 5.6 Hz, 1F).

Starting from **3d** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **5g** (50%, 69 mg, yellow oil) and **6g** (13%, 18 mg, yellow oil) was obtained, which were separated by flash chromatography (*n*-hexane/EtOAc (50/1)).

*7-Fluoro-3-methyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazole (**5g**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18−7.08 (m, 1H), 7.00−6.86 (m, 2H), 4.61 (d, J = 9.1 Hz, 1H), 3.92 (dq, J = 9.1, 1.7 Hz, 1H), 3.16 (t, J = 6.7 Hz, 1H), 2.80 (s, 3H), 2.74 (m, 4.8 Hz, 2H), 2.25−2.09 (m, 1H), 1.69−1.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 160.5, 141.7, 141.6, 130.8 (d, J = 8.2 Hz), 127.4 (CF_3, q, J = 282.3 Hz), 115.1 (d, J = 21.0 Hz), 114.1 (d, J = 21.5 Hz), 73.5, 68.0, 58.5 (*C*-CF_3, q, J = 23.6 Hz), 43.6, 26.6, 24.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.47 (s, 3F), −114.58 (ddd, J = 8.7, 8.7., 5.5 Hz, 1F). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{13}H_{14}F_4NO$ 276.1006; found 276.1013.

*8-Fluoro-3-methyl-1-(trifluoromethyl)-3,4,5,6-tetrahydro-1H-1,4-methanobenzo[f][1,2]oxazocine (**6g**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.29 (m, 1H), 6.90 (dd, J = 9.7, 3.1 Hz, 1H), 6.87−6.77 (m, 1H), 3.85−3.56 (m, 2H), 3.08 (ddd, J = 12.6, 7.0, 1.6 Hz, 1H), 2.87 (s, 3H), 2.57 (dt, J = 15.0, 3.7 Hz, 1H), 2.25−2.07 (m, 2H), 1.62 (tdd, J = 13.7, 3.3, 1.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 160.2, 144.3, 126.6, 125.3 (CF_3, q, J = 283.6 Hz), 119.0 (d, J = 21.1 Hz), 112.2 (d, J = 20.6 Hz), 88.5 (*C*-CF_3, q, J = 28.4 Hz), 65.6, 46.7, 42.9, 33.6, 32.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −71.17 (br s, 3F), −115.31 (ddd, J = 8.7, 8.7, 5.7 Hz, 1F). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{13}H_{14}F_4NO$ 276.1006; found 276.0999.

Starting from **3d** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **5h** (39%, 69 mg) and **6h** (16%, 28 mg) was obtained as a colorless oil, which was purified but could not be separated by flash chromatography (*n*-hexane/EtOAc (50/1)). The ^{1}H and ^{19}F NMR data were extracted from the spectra of the mixture.

*3-Benzyl-7-fluoro-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazole (**5h**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−6−70 (m, 8H), 4.54 (d, J = 9.2 Hz, 1H), 4.04 (d, J = 13.9 Hz, 1H), 3.96 (d, J = 13.9 Hz, 1H), 3.84 (dq, J = 9.2, 1.8 Hz, 1H), 3.34 (dd, J = 8.4, 6.1 Hz, 1H), 2.71−2.57 (m, 2H), 2.02−1.89 (m, 1H), 1.62−1.41 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.47 (s, 3F), −114.52 (ddd, J = 8.7, 8.7, 5.4 Hz, 1F).

*3-Benzyl-8-fluoro-1-(trifluoromethyl)-3,4,5,6-tetrahydro-1H-1,4-methanobenzo[f][1,2]oxazocine (**6h**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−6−70 (m, 8H), 4.31 (d, J = 13.0 Hz, 1H), 3.86 (d, J = 13.0 Hz, 1H), 3.80−3.62 (m, 2H), 3.05 (ddd, J = 12.6, 7.0, 1.5 Hz, 1H), 2.47 (dt, J = 14.8, 3.7 Hz, 1H), 2.12 (dd, J = 12.6, 0.9 Hz, 1H), 2.02−1.89 (m, 1H), 1.62−1.41 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −70.92 (br s, 3F), −115.28 (ddd, J = 9.4, 8.0, 5.5 Hz, 1F).

*1-Methyl-3a-(trifluoromethyl)-3,3a,9,9a-tetrahydro-1H-[1,3]-dioxolo[4′,5′:5,6]indeno[2,1-c]isoxazole (**5i**).* Starting from **3e** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **5i** (42%, 60 mg, yellow solid, mp 59−61 °C) was obtained and purified by flash chromatography (*n*-hexane/EtOAc (50/1)). The corresponding bridged regioisomer could not been found in the reaction mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.67 (s, 1H), 5.96 (s, 2H), 4.46 (d, J = 8.9 Hz, 1H), 3.84 (dq, J = 8.9, 1.6 Hz, 1H), 3.46 (d, J = 6.6 Hz, 1H), 3.14 (dd, J = 17.0, 6.6 Hz, 1H), 2.79 (s, 3H), 2.75 (d, J = 17.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 147.9, 136.1, 130.8, 127.2 (CF_3, q, J = 280.1 Hz), 105.6, 105.1, 101.7, 75.0, 73.1, 70.7 (*C*-CF_3, q, J = 26.2 Hz), 43.4, 35.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.89 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{13}H_{13}F_3NO_3$ 288.0842; found 288.0848.

*1-Benzyl-3a-(trifluoromethyl)-3,3a,9,9a-tetrahydro-1H-[1,3]-dioxolo[4′,5′:5,6]indeno[2,1-c]isoxazole (**5j**).* Starting from **3e** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, **5j** (97%, 176 mg, yellow oil) was obtained and purified by flash chromatography (*n*-hexane/EtOAc (20/1)). The corresponding bridged regioisomer could not be found in the reaction mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.10 (m, 5H), 6.61 (s, 1H), 6.54 (s, 1H), 5.85 (s, 2H), 4.39 (d, J = 8.9 Hz, 1H), 3.99 (s, 2H), 3.76 (dq, J = 8.9, 1.4 Hz, 1H), 3.66 (d, J = 6.9 Hz, 1H), 2.99 (dd, J = 16.9, 7.0 Hz, 1H), 2.62 (d, J = 16.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 148.2, 137.0, 136.6, 130.4, 129.4, 127.6 (CF_3, q, J = 285.4 Hz), 128.8, 128.0, 105.7, 105.3, 102.0, 73.2, 70.8 (*C*-CF_3, q, J = 26.2 Hz), 61.2, 36.0, 22.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.60 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{17}F_3NO_3$ 364.1155; found 364.1161.

*3-Methyl-10b-(trifluoromethyl)-1,3,3a,4,5,10b-hexahydro-[1,3]-dioxolo[4′,5′:6,7]naphtho[2,1-c]isoxazole (**5k**).* Starting from **3f** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **5k** (88%, 133 mg, white solid, mp 76−78 °C) was obtained and purified by flash chromatography (*n*-hexane/EtOAc (10/1)). Only trace amounts of the bridged regioisomer could be detected when the reaction was scaled up. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (s, 1H), 6.63−6.58 (m, 1H), 5.94 (d, J = 1.4 Hz, 1H), 5.93 (d, J = 1.4 Hz, 1H), 4.56 (d, J = 9.1 Hz, 1H), 3.91 (dq, J = 9.1 Hz, J = 1.8 Hz, 1H), 3.11 (t, J = 6.8 Hz, 1H), 2.79 (s, 3H), 2.70−2.59 (m, 2H), 2.20−2.06 (m, 1H), 1.67−1.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 146.9, 133. 5, 128.9, 127.7 (CF_3, q, J = 282.5 Hz), 124.8, 109.2, 109.1, 108.7, 101.5, 73.8, 68.3, 59.6 (*C*-CF_3, q, J = 23.1 Hz), 43.9, 26.8, 25.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.47 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{14}H_{15}F_3NO_3$ 302.0999; found 302.1007.

*3-Benzyl-10b-(trifluoromethyl)-1,3,3a,4,5,10b-hexahydro-[1,3]-dioxolo[4′,5′:6,7]naphtho[2,1-c]isoxazole (**5l**).* Starting from **3f** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, **5l** (79%, 149 mg, yellow oil) was obtained and purified by flash chromatography (*n*-hexane/EtOAc (10/1)). Only trace amounts of the bridged regioisomer could be detected when the reaction was scaled up. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.06 (m, 5H), 6.65 (s, 1H), 6.63−6.55 (m, 1H), 5.94 (d, J = 1.4 Hz, 1H), 5.93 (d, J = 1.4 Hz, 1H), 4.57 (d, J = 9.2 Hz, 1H), 4.12 (d, J = 13.8 Hz, 1H), 4.03 (d, J = 13.8 Hz, 1H), 3.93 (dq, J = 9.2 Hz, J = 1.7 Hz, 1H), 3.38 (dd, J = 8.4, 6.2 Hz, 1H), 2.73−2.54 (m, 2H), 2.11−1.91 (m, 1H), 1.67−1.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 146.6, 137.0, 133.6, 129.0, 128.5, 127.6, 127.5 (CF_3, q, J = 282.5 Hz), 124.5, 109.0, 108.4, 101.3, 73.3, 66.2, 61.0, 58.7 (*C*-CF_3, q, J = 23.1 Hz), 26.8, 26.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.47 (s). HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{19}F_3NO_3$ 378.1312; found 378.1328.

Synthesis of Nonfluorinated Aldehydes 8 (Nitrone Precursors). *General Procedure.* These substrates were prepared by adapting a known methodology from the literature.[17] A solution of 2-(2-bromophenyl)acetaldehyde **1a** or 3-(2-bromophenyl)-propionaldehyde **1b** (1.5 mmol), palladium(II) acetate (5 mol %, 0.075 mmol), triphenylphosphine (10 mol %, 0.15 mmol), cesium carbonate (3.0 equiv, 4.5 mmol), and potassium isopropenyl trifluoroborate 7 (1.25 equiv, 1.88 mmol) in THF/water 10:1 (0.3 M) was heated in a sealed 10 mL microwave glass vial at 100 °C by microwave irradiation for 2 h. The reaction mixture was cooled to room temperature, opened, filtered through Celite and concentrated

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under reduced pressure. The residue obtained was purified by flash chromatography (*n*-hexane/EtOAc (20:1)]. Due to its instability, the product obtained was used immediately in the next step.

*2-[2-(Prop-1-en-2-yl)phenyl]acetaldehyde (**8a**).* Starting from 2-(2-bromophenyl)acetaldehyde[17] and following the general procedure indicated above, **8a** was obtained as a yellow oil in 59% yield (142 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (t, J = 2.1 Hz, 1H), 7.31−7.15 (m, 4H), 5.23 (dq, J = 1.9, 1.5 Hz, 1H), 4.82 (dq, J = 1.9, 0.9 Hz, 1H), 3.74 (d, J = 2.1 Hz, 2H), 2.02 (dd, J = 1.5, 0.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 144.9, 144.8, 130.7, 129.0, 128.6, 127.6, 127.5, 116.3, 48.3, 25.2.

*3-[2-(Prop-1-en-2-yl)phenyl]propanal (**8b**).* Starting from 3-(2-bromophenyl)propanal[17] and following the general procedure indicated above, **8b** was obtained as a yellow oil in 70% yield (183 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (t, J = 1.4 Hz, 1H), 7.25−6.99 (m, 4H), 5.22−5.19 (m, 1H), 4.86−4.83 (m, 1H), 3.02−2.94 (m, 2H), 2.77−2.69 (m, 2H), 2.06−2.04 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.8, 145.5, 143.9, 136.9, 129.7, 128.5, 127.3, 126.4, 115.4, 45.7, 25.6, 25.3.

Intramolecular Nitrone Cycloaddition of Nonfluorinated Aldehydes 8. *General Procedure.* To a solution of the corresponding starting aldehyde **8** (0.5 mmol) in toluene (0.2 M) in a 10 mL microwave glass vial were added *N*-alkylhydroxylamine hydrochloride (2.6 equiv) and sodium bicarbonate (2.6 equiv, 109 mg). The vial was sealed, and the mixture was heated by microwave irradiation at 120 °C for 30 min. The reaction mixture was cooled to room temperature, opened, and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography to purify the formed isoxazolidines.

*1,3-Dimethyl-1,3,4,5-tetrahydro-1,4-methanobenzo[e][1,2]-oxazepine (**9a**).* Starting from **8a** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **9a** (70%, 66 mg, colorless oil) was obtained and purified by flash chromatography (*n*-hexane/EtOAc (20/1)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.06 (m, 4H), 3.54 (br s, 1H), 3.20 (d, J = 17.1 Hz, 1H), 3.08 (dd, J = 17.1, 3.4 Hz, 1H), 2.77 (s, 3H), 2.44 (dd, J = 11.2, 5.5 Hz, 1H), 2.23 (d, J = 11.2 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9, 133.9, 129.5, 128.1, 125.9, 122.8, 80.1, 63.6, 47.7, 40.3, 38.6, 20.8. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{16}NO$ 190.1226; found 190.1225.

*1,3-Dimethyl-3,4,5,6-tetrahydro-1H-1,4-methanobenzo[f][1,2]-oxazocine (**9b**).* Starting from **8b** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **9b** (44%, 45 mg, white solid, mp 94−96 °C) was obtained and purified by flash chromatography (*n*-hexane/EtOAc (20/1)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−7.07 (m, 4H), 3.70 (td, J = 14.2, 3.6 Hz, 1H), 3.59 (t, J = 6.3 Hz, 1H), 2.91 (s, 3H), 2.75 (ddd, J = 12.4, 6.8, 1.5 Hz, 1H), 2.59 (dt, J = 14.7, 3.8 Hz, 1H), 2.25−2.01 (m, 2H), 1.93 (s, 3H), 1.60 (tdd, J = 13.6, 3.5, 1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 141.1, 131.5, 127.1, 125.8, 123.8, 85.9, 66.3, 47.5, 47.4, 33.9, 32.6, 29.1. HRMS (ESI/Q-TOF) m/z: [M + H - O]+ Calcd for $C_{13}H_{18}N$ 188.1434; found 188.1436.

Reductive Opening of the Isoxazolidines. *General Procedure.* To a solution of the corresponding isoxazolidine **5** or **6** (0.2 mmol) in THF (0.1 M) was added Raney nickel (0.5 mL as a slurry in water), and the resulting mixture was stirred at room temperature for 20 min. The reaction mixture was then filtered through Celite, dried (Na_2SO_4), and concentrated under reduced pressure to afford the corresponding 1,3-amino alcohols **10** or **11**, respectively, without further purification.

*(2-Methylamino-1-(trifluoromethyl)-2,3-dihydro-1H-inden-1-yl)-methanol (**10a**).* Starting from **5a** and following the general procedure indicated above, **10a** was obtained as a white solid (mp 81−83 °C) in 50% yield (25 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23−7.15 (m, 4H), 4.11 (d, J = 12.2 Hz, 1H), 3.84 (dq, J = 12.2, 1.2 Hz, 1H), 3.79 (t, J = 8.0 Hz, 1H), 3.30 (dd, J = 15.8, 8.0 Hz, 1 H), 3.12 (br s, 2H), 2.80 (dd, J = 15.8, 8.0 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.4, 138.3, 129.0, 127.8 (CF_3, q, J = 282.7 Hz), 127.6, 125.0, 124.5, 64.3, 64.1, 60.1 (*C*-CF_3, q, J = 23.3 Hz), 38.5, 35.4. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −70.81 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{15}F_3NO$ 246.1100; found 244.1098.

*3-Methylamino-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (**11a**).* Starting from **6a** and following the general procedure indicated above, **11a** was obtained as a yellow solid (mp 118−120 °C) in 83% yield (41 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79−7.73 (m, 1H), 7.30−7.26 (m, 2H), 7.15−7.09 (m, 1H), 3.33−3.30 (m, 1H), 3.16 (dd, J = 17.2, 4.6 Hz, 1H, 1H), 3.05 (br s, 2H), 2.87−2.78 (m, 1H), 2.47 (s, 3H), 2.42−2.35 (m, 1H), 2.17 (dd, J = 14.2, 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 133.3, 132.5, 128.4, 127.8, 126.8, 126.1, 124.8 (CF_3, q, J = 284.7 Hz), 72.5 (*C*-CF_3, q, J = 28.5 Hz), 51.7, 35.3, 33.1, 32.8. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −78.19 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{15}F_3NO$ 246.1100; found 246.1099.

*(2-Benzylamino-1-(trifluoromethyl)-2,3-dihydro-1H-inden-1-yl)-methanol (**10b**).* Starting from **5b** and following the general procedure indicated above, **10b** was obtained as a white solid (mp 88−90 °C) in 75% yield (48 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−7.12 (m, 9H), 4.13 (d, J = 12.6 Hz, 1H), 3.95−3.77 (m, 4H), 3.26 (dd, J = 15.8, 8.2 Hz, 1H), 3.09 (br s, 2H), 2.84 (dd, J = 15.8, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 139.0, 138.1, 129.1, 128.9 (2 × CH), 128.2 (2 × CH), 127.8 (CF_3, q, J = 282.8 Hz), 127.7, 127.6, 124.9, 124.5, 64.2, 61.6, 60.1 (*C*-CF_3, q, J = 23.2 Hz), 53.0, 39.0. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −71.00 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{19}F_3NO$ 322.1413; found 322.1419.

*(2-Methylamino-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**10c**).* Starting from **5c** and following the general procedure indicated above, **10c** was obtained as a white solid (mp 72−74 °C) in 89% yield (46 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.37 (m, 1H), 7.20−7.13 (m, 2H), 7.10−7.06 (m, 1H), 4.23−4.14 (m, 2H), 3.27 (dd, J = 5.9, 3.4 Hz, 1H), 3.11 (br s, 2H), 2.83−2.78 (m, 2H), 2.46 (s, 3H), 2.23−2.05 (m, 1H), 2.02−1.91 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7, 133.0, 130.0, 129.5, 128.0, 127.3 (CF_3, q, J = 285.4 Hz), 126.6, 64.9, 58.9, 51.1 (*C*-CF_3, q, J = 21.1 Hz), 34.4, 25.0, 22.0. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −69.08 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{17}F_3NO$ 260.1257; found 260.1255.

*7-Methylamino-5-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-benzo-[7]annulen-5-ol (**11c**).* Starting from **6c** and following the general procedure indicated above, **11c** was obtained as a yellow solid (mp 91−93 °C) in 57% yield (30 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.39 (m, 1H), 7.22−7.10 (m, 3H), 4.62 (br s, 2H), 3.80 (t, J = 13.7 Hz, 1H), 3.32−3.26 (m, 1H), 2.74−2.48 (m, 5H), 2.16−2.00 (m, 1H), 1.98−1.87 (m, 1H), 1.82 (d, J = 14.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.7, 139.9, 131.4, 128.0, 126.4 (CF_3, q, J = 286.3 Hz), 126.1, 125.5, 80.0 (*C*-CF_3, q, J = 27.3 Hz), 58.4, 33.9, 33.8, 30.4, 29.9. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −79.52 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{17}F_3NO$ 260.1257; found 260.1248.

*(2-Benzylamino-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**10d**).* Starting from **5d** and following the general procedure indicated above, **10d** was obtained as a colorless oil in 93% yield (62 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57−7.08 (m, 9H), 4.25 (s, 2H), 3.97 (d, J = 12.4 Hz, 1H), 3.84 (d, J = 12.4 Hz, 1H), 3.55 (dd, J = 5.5, 3.4 Hz, 1H), 3.09 (br s, 2H), 2.96−2.87 (m, 2H), 2.25−1.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 137.5, 129.9, 129.6, 129.5, 128.9 (2 × CH), 128.5 (2 × CH), 128.1, 127.8, 127.3 (q, J = 285.5 Hz), 126.6, 64.8, 56.3, 52.2, 51.2 (*C*-CF_3, q, J = 21.2 Hz), 25.0, 22.5. ^{19}F-RMN ($CDCl_3$, 282.4 MHz): δ −67.38 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{21}F_3NO$ 336.1570; found 336.1562.

*7-Benzylamino-5-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-benzo-[7]annulen-5-ol (**11d**).* Starting from **6d** and following the general procedure indicated above, **11d** was obtained as a colorless oil in 33% yield (22 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82−6.94 (m, 9H), 4.08 (d, J = 12.7 Hz, 1H), 3.90−3.70 (m, 2H), 3.52−3.44 (m, 1H), 2.69−2.57 (m, 2H), 2.17−1.78 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.7, 139.7, 138.5, 131.4, 129.0 (2 × CH), 128.5 (2 × CH), 128.1, 127.8, 126.4 (CF_3, q, J = 286.0 Hz), 126.2, 125.8, 80.0, 55.6, 51.4, 34.1, 30.5, 29.9. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −79.01 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{21}F_3NO$ 336.1570; found 336.1566.

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*(5-Fluoro-2-methylamino-1-(trifluoromethyl)-2,3-dihydro-1H-inden-1-yl)methanol (**10e**).* Starting from **5e** and following the general procedure indicated above, **10e** was obtained as a white solid (mp 54−56 °C) in 70% yield (37 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30−7.21 (m, 1H), 7.00−6.89 (m, 2H), 4.18 (d, J = 12.1 Hz, 1H), 3.92−3.81 (m, 2H), 3.35 (dd, J = 15.9, 7.9 Hz, 1H), 2.99 (br s, 2H), 2.87 (dd, J = 16.1, 7.6 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 161.9, 143.8 (d, J = 8.5 Hz), 127.7 (CF_3, q, J = 282.5 Hz), 125.9 (d, J = 9.0 Hz), 114.9 (d, J = 22.8 Hz), 112.0 (d, J = 22.3 Hz), 64.3, 64.2, 59.6 (*C*-CF_3,q, J = 23.5 Hz), 38.6, 35.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −71.75 (s, 3F), −113.77 (ddd, J = 8.8, 8.8, 5.1 Hz, 1F). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{14}F_4NO$ 264.1006; found 264.0999.

*(6-Fluoro-2-methylamino-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**10g**).* Starting from **5g** and following the general procedure indicated above, **10g** was obtained as a white solid (mp 83−85 °C) in quantitative yield (55 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.37 (m, 1H), 7.01−6.90 (m, 1H), 6.86 (dd, J = 9.3, 2.8 Hz, 1H), 4.23 (m, 2H), 3.33 (dd, J = 5.5, 3.5 Hz, 1H), 3.19 (br s, 2H), 3.00−2.74 (m, 2H), 2.53 (s, 3H), 2.26−1.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 160.6, 140.3, 131.6 (d, J = 8.3 Hz), 127.1 (CF_3, q, J = 285.4 Hz), 115.7 (d, J = 20.8 Hz), 114.0 (d, J = 21.4 Hz), 64.8, 58.9, 50.8 (*C*-CF_3, q, J = 21.4 Hz), 34.5, 25.0, 21.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.54 (s, 3F), −115.03 (ddd, J = 8.7, 8.7, 5.7 Hz, 1F). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{16}F_4NO$ 278.1163; found 278.1165.

*(6-Methylamino-5-(trifluoromethyl)-6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)methanol (**10i**).* Starting from **5i** and following the general procedure indicated above, **10i** was obtained as a white solid (mp= 97−99 °C) in 57% yield (33 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.66 (s, 1H), 5.95 (d, J = 1.4 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 4.14 (d, J = 12.0 Hz, 1H), 3.92−3.74 (m, 2H), 3.26 (dd, J = 15.5, 8.1 Hz, 1H), 3.05 (br s, 2H), 2.77 (dd, J = 15.6, 7.4 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 147.6, 134.7, 130.5, 127.8 (CF_3, q, J = 282.9 Hz), 105.2, 104.8, 101.5, 64.3, 64.1, 59.9 (*C*-CF_3,q, J = 23.3 Hz), 38.4, 35.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −71.76 (s, 3F). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{15}F_3NO_3$ 290.0999; found 290.0998.

*(6-Methylamino-5-(trifluoromethyl)-5,6,7,8-tetrahydronaphtho-[2,3-d][1,3]dioxol-5-yl)methanol (**10k**).* Starting from **5k** and following the general procedure indicated above, **10k** was obtained as a white solid (mp 139−141 °C) in quantitative yield (61 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (s, 1H), 6.59 (s, 1H), 5.93 (d, J = 1.4 Hz, 1H), 5.92 (d, J = 1.4 Hz, 1H), 4.18 (m, 2H), 3.29 (dd, J = 5.2, 3.4 Hz, 1H), 2.89−2.68 (m, 2H), 2.51 (s, 3H), 2.04 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 146. 7, 131.6, 127.2 (CF_3, q, J = 285.6 Hz), 122.5, 109.0, 108.8, 101.3, 64.9, 58.7, 51.0 (*C*-CF_3, q, J = 21.2 Hz), 34.4, 24.9, 21.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.27 (s, 3F). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{17}F_3NO_3$ 304.1155; found 304.1160.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02880.

Details of the theoretical calculations and NMR spectra of all new compounds (^{1}H, ^{13}C, and ^{19}F) (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Smith, L. I. *Chem. Rev.* **1938**, *23*, 193.

(2) For recent reviews, see: (a) Singh, S. S.; Chowdhury, S.; Koley, S. *Tetrahedron* **2016**, *72*, 1603. (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366. (c) Kanemasa, S. *Heterocycles* **2010**, *82*, 87. (d) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845. (e) Nájera, C.; Sansano, J. M. *Org. Biomol. Chem.* **2009**, *7*, 4567. (f) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.

(3) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633. (c) Huisgen. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 321.

(4) (a) Mandal, B.; Basu, B. *Top. Heterocycl. Chem.* **2012**, *30*, 85. (b) Yang, J. *Synlett* **2012**, *23*, 2293. (c) Nguyen, T. B.; Martel, A.; Gaulon-Nourry, C.; Dhal, R.; Gilles, D. *Org. Prep. Proced. Int.* **2012**, *44*, 1. (d) Bokach, N. A.; Kuznetsov, M. L.; Kukuskin, V. Y. *Coord. Chem. Rev.* **2011**, *255*, 2946. (e) Nguyen, T. B.; Martel, A.; Gaulon-Nourry, C.; Dhal, R.; Gilles, D. *Org. Prep. Proced. Int.* **2010**, *42*, 387. (f) Bokach, N. A. *Russ. Chem. Rev.* **2010**, *79*, 89. (g) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. - Eur. J.* **2009**, *15*, 7808. (h) Rueck-Braun, K.; Freysoldt, T. H. E; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507.

(5) For the relevance of 1,3-amino alcohols in organic synthesis, see: Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.

(6) Baunach, M.; Hertweck, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 12550.

(7) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247.

(8) In general, the use of fluorinated dipolarophiles in 1,3-dipolar cycloadditions is underdeveloped in comparison with that of their nonfluorinated counterparts. Together with nitrones, azomethine ylides and azides are the most widely used dipoles in those examples. For selected recent references, see: (a) Ponce, A.; Alonso, I.; Adrio, I.; Carretero, J. C. *Chem. - Eur. J.* **2016**, *22*, 4952. (b) Yamada, S.; Higashi, M.; Konno, T.; Ishihara, T. *Eur. J. Org. Chem.* **2016**, *2016*, 4561. (c) Tomaszewska, J.; Kowalska, K.; Koroniak-Szejn, K. *J. Fluorine Chem.* **2016**, *191*, 1. (d) McAlpine, I.; Tran-Dube, M.; Wang, F.; Scales, S.; Matthews, J.; Collins, M. R.; Nair, S. K.; Nguyen, M.; Bian, J.; Martinez Alsina, L.; Sun, J.; Zhong, J.; Warmus, J. S.; O'Neill, B. T. *J. Org. Chem.* **2015**, *80*, 7266. (e) Li, Q.-H.; Wei, L.; Chen, X.; Wang, C.-J. *Chem. Commun.* **2013**, *49*, 6277. (f) Li, Q.-H.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Tetrahedron Lett.* **2012**, *53*, 3650. (g) Yan, D.; Li, Q.; Wang, C.-J. *Chin. J. Chem.* **2012**, *30*, 2714. (h) Li, Q.-H.; Tong, M.-C.; Li, J.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2011**, *47*, 11110. (i) Xie, H.; Zhu, J.; Chen, Z.; Li, S.; Wu, Y. *J. Org. Chem.* **2010**, *75*, 7468.

(9) (a) Jiang, S.; Singh, G.; Batsanov, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3873. (b) Arnone, A.; Broggini, G.; Bruché, L.; Molteni, G.; Zecchi, G. *J. Chem. Res., Synop.* **1998**, *10*, 188. (c) Bandiera, P.; Bravo, P.; Bruché, L.; Zanda, M.; Arnone, M. *Synth. Commun.* **1998**, *28*, 2665. (d) Arnone, A.; Blasco, F.; Resnati, G. *Tetrahedron* **1997**, *53*, 17513. (e) Arnone, A.; Cavicchioli, M.; Donadelli, A.; Resnati, G. *J. Chem. Res. (S)* **1995**, *7*, 282. (f) Arnone, A.; Cavicchioli, M.; Donadelli, A.; Resnati, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1019. (g) Collins, I.; Nadin, A.; Holmes, A. B.; Long, M. E.; Man, J.; Baker, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2205.

(10) Kumar, V.; Kaur, K. *J. Fluorine Chem.* **2015**, *180*, 55.

(11) For the relevance of fluorinated β-amino acids, see: (a) March, T. L.; Johnston, M. R.; Duggan, P. J.; Gardiner, J. *Chem. Biodiversity* **2012**, *9*, 2410. (b) Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Soloshonok, V. A.; Sorochinsky, A. *Synthesis* **2011**, *2011*, 3045. (c) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, *2011*, 3261. (d) Aceña, J. L.; Simón-Fuentes, A.; Fustero, S. *Curr. Org. Chem.* **2010**,

DOI: 10.1021/acs.joc.6b02880
J. Org. Chem. 2017, 82, 2505−2514

14, 928. (e) Sorochinsky, A.; Soloshonok, V. A. *J. Fluorine Chem.* **2010**, *131* (2), 127. (f) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711.
(12) Jiménez-Aquino, A.; Vega, J. A.; Trabanco, A. A.; Valdés, C. *Adv. Synth. Catal.* **2014**, *356*, 1079.
(13) (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
(14) (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (c) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37. (d) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16. (e) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071. (f) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (g) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013.
(15) For recent reviews in trifluoromethylation reactions, see: (a) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (c) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (d) Xu, X.-H.; Matsukazi, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (e) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (f) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (g) Gao, P.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Chem. - Eur. J.* **2015**, *21*, 7648. (h) Wang, S.-M.; Han, J.-B.; Zhang, C.-P.; Qin, H.-L.; Xiao, J.-C. *Tetrahedron* **2015**, *71*, 7949.
(16) Sedgwick, D. M.; Barrio, P.; Simón, A.; Román, R.; Fustero, S. *J. Org. Chem.* **2016**, *81*, 8876.
(17) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107.
(18) Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Romeo, G. *Tetrahedron* **2003**, *59*, 3581.
(19) Aurell, M. J.; Domingo, L. R.; Perez, P.; Contreras, R. *Tetrahedron* **2004**, *60*, 11503.
(20) Due to their instability, HRMS could not be obtained for these derivatives. ^{13}C spectra of freshly purified samples did not account for the right number of signals in the aromatic region, suggesting decomposition in the deuterated solvents in which the samples were dissolved.
(21) Besandre, R.; Jaimes, M.; May, J. A. *Org. Lett.* **2013**, *15*, 1666.
(22) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381.
(23) Baker, S. J.; Zhang, Y.-Z.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R. K.; Sanders, V.; Plattner, J. J. *J. Med. Chem.* **2006**, *49*, 4447.
(24) Pawliczek, M.; Milde, B.; Jones, P. G.; Werz, D. B. *Chem. - Eur. J.* **2015**, *21*, 12303.
(25) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143.
(26) Rochette, E. M.; Lewis, W.; Dossetter, A. G.; Stockman, R. A. *Chem. Commun.* **2013**, *49*, 9395.

DOI: 10.1021/acs.joc.6b02880
J. Org. Chem. 2017, 82, 2505−2514