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Synthesis of Fluorinated and Non-Fluorinated Bicyclic Amidines through Ring-Closing Metathesis

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An efficient method for the synthesis of fluorinated and non-fluorinated imidazoazepines by a ring-closing metathesis reaction as the key step is described. The influence of the fluorine atoms on the preparation of these bicyclic systems is also studied.

Introduction

The amidine group constitutes a relevant moiety in organic and medicinal chemistry, as it can be found in the structures of numerous natural products,[1] many of which display biological activity against different pathogens.[2] It can also be found in compounds with tumor suppressor properties, which act as protein–protein interaction inhibitors, as in the family of *cis*-imidazolines known as Nutley inhibitors or Nutlins[3] (Figure 1). On the other hand, amidines as well as guanidines are considered strong organic bases thanks to the resonance stabilization of the amidinium ion that results from protonation of the imino nitrogen atom.[4] This feature turns the amidine structure into a desirable moiety for potential drug design as arginine mimics.[5] Apart from this basic character, neutral amidines may be considered as N-based donor ligands in coordination chemistry[6] and have also been used as synthetic intermediates in the preparation of heterocyclic compounds.[4]

Due to the importance of this substructure, several methods for the preparation of amidines have been devised.[7] However, very few of them have dealt with the synthesis of its bicyclic counterpart.[8] In this sense, lactams appeared as suitable starting materials for an intramolecular attack of an azido group on a lactam function.[9] Imidazolines are also synthetic precursors of bicyclic amidines through transition-metal-catalyzed microwave-assisted intramolecular

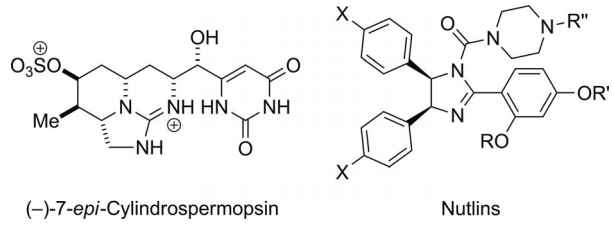

Figure 1. Amidines with pharmacological activity.

C-2 alkylation through C–H bond activation.[10] Alternatively, intramolecular bromoamination of amidine-containing olefin functionalities allows the creation of tricyclic amidines.[11] Additionally, a thermally generated imidazoline-derived carbene was also employed to obtain bicyclic amidines by insertion into olefins.[12] More recently, proline has been used as a starting material for the preparation of chiral bicyclic imidazolines through carboxylic amide derived imidoyl chlorides.[13]

We envisioned the possibility of using imidazolines bearing two pendant olefins as starting materials, which upon ring-closing metathesis (RCM) should establish the bicyclic system. With the increasing accessibility of fluorinated building blocks, the CF_2-synthon approach has emerged as a convenient strategy to synthesize a variety of fluorinated derivatives.[14] This *gem*-difluoro moiety, frequently used in medicinal chemistry due to its synthetic accessibility and its inertness in biological systems, can provide the resulting products with modified physicochemical and biological properties, as well as new interactions with the drug target, often leading to improved pharmacological features.[14,15]

Herein, we report a versatile strategy for the preparation of bicyclic amidines, particularly imidazo[1,2-*a*]azepines, by using RCM as the key step. The correct choice of starting materials would allow for the control of the ring size, as outlined in Scheme 1. Both, fluorinated and non-fluorinated amidines were prepared to study the influence of a *gem*-difluoro moiety in this type of heterocycle.

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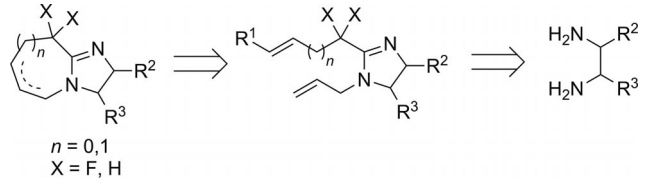


Scheme 1.

Results and Discussion

Synthesis of Imidazolines 3

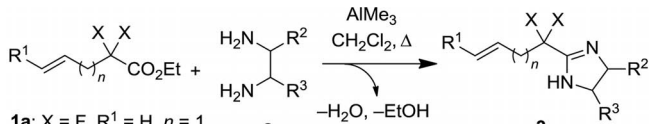
The first step of our study was the preparation of imidazolines **3** (Table 1). We first evaluated one of the usual conditions employed to generate the imidazoline unit, which involved treatment of the corresponding nitriles and diamines in basic media or, alternatively, with 4 N HCl in dioxane. However, the use of fluorinated nitriles under these conditions gave complex reaction mixtures. We decided then to apply a different methodology by treatment of unsaturated esters **1**[16] and diamines **2** with trialkylaluminum derivatives.[17] By using ester **1a** and diamine **2c** as model substrates, the reactions were initially performed in refluxing toluene in the presence of trimethylaluminum (2.0 equiv.), but only a low yield of the desired product was isolated. However, we found that when the reaction was performed in refluxing dichloromethane, the corresponding imidazoline **3c** was obtained in 86% yield (Table 1, Entry 3). The extension of these optimized conditions to different esters **1** and diamines **2** led us to obtain a new family of imidazolines **3** in moderate to good yields (Table 1).

cis-1,2-Cyclohexanediamine (*cis*-**2c**; Table 1, Entries 3, 6, and 9), *meso*-1,2-diphenylethylendiamine (*cis*-**2d**; Table 1, Entries 4, 7, and 10), and (1*R*,2*R*)-(+)-1,2-diphenylethylendiamine (*trans*-**2d**; Table 1, Entry 5) successfully led to the corresponding imidazolines **3** in good yields.[18] With ethylenediamine (**2a**; Table 1, Entries 1 and 8) and 1,2-propanediamine (**2b**; Table 1, Entry 2) the isolated yield of the final imidazolines dropped off due to the hydrolysis of the imidazoline moiety to the corresponding amide during the purification conditions.[19] This process is especially important with ester **1c** and amine **2a**, where the amide arising from the hydrolysis of imidazoline **3g** was the only product detected (Table 1, Entry 8).[20]

It is known that imidazolines are susceptible to slow hydrolysis towards the corresponding amides upon exposure to air, although they are quite stable when handled under an atmosphere of nitrogen.[21] In this study, hydrolysis was observed to be more favorable with imidazolines derived from 1,2-propanediamine (**2b**) and, particularly, ethylenediamine (**2a**) probably due to their decreased steric requirements compared to those of amines **2c** and **2d**.

Regarding the influence of the *gem*-difluoro moiety in the process, although the chemical yields of the fluorinated and non-fluorinated imidazolines were comparable, the non-fluorinated counterparts required longer reaction times to go to completion (Table 1, Entries 6–8). On the other hand, the non-fluorinated analogues tended to undergo an aromatization event to yield the corresponding imidazole during the purification process. Thus, during the isolation of compound *cis*-**3f**, small amounts of the corresponding imidazole (ca. 10%) were observed. However, in the case of their fluorinated analogues, for example, *cis*-**3d** and *cis*-**3i**, imidazole formation was not observed, as could be expected by the electron-withdrawing effect of the fluorine atoms.

Table 1. Synthesis of imidazolines **3**.



1a: X = F, R^1 = H, *n* = 1
1b: X = H, R^1 = H, *n* = 1
1c: X = F, R^1 = Ph, *n* = 0

2 **3**

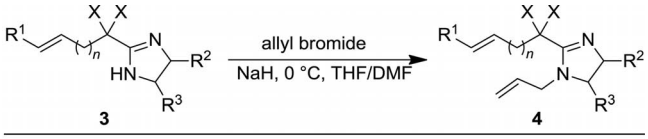
Entry	Ester	X	Amine **2**	R^2	R^3	Time [h]	Product **3** (% yield)
1	**1a**	F	**2a**	H	H	3	**3a** (23)[a]
2	**1a**	F	**2b**	Me	H	3	**3b** (61)[a]
3	**1a**	F	*cis*-**2c**	–$(CH_2)_4$–		3	**3c** (86)[a]
4	**1a**	F	*cis*-**2d**	Ph	Ph	3	*cis*-**3d** (74)[a]
5	**1a**	F	*trans*-**2d**	Ph	Ph	3	*trans*-**3d** (76)[a]
6	**1b**	H	*cis*-**2c**	–$(CH_2)_4$–		12	**3e** (86)[b]
7	**1b**	H	*cis*-**2d**	Ph	Ph	12	*cis*-**3f** (76)[b]
8	**1c**	F	**2a**	H	H	3	**3g** (0)[c]
9	**1c**	F	*cis*-**2c**	–$(CH_2)_4$–		3	**3h** (83)[b]
10	**1c**	F	*cis*-**2d**	Ph	Ph	3	*cis*-**3i** (78)[b]

[a] Isolated yield after flash column chromatography. [b] Crude yield determined by ^{1}H NMR spectroscopy. [c] See ref.[19]

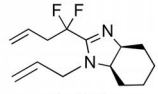
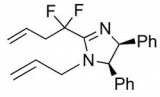
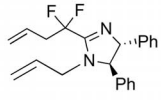
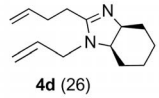
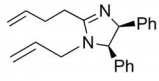
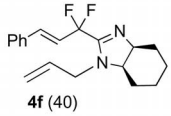
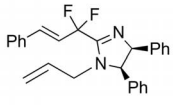
Taking into account that 4,5-diarylimidazolines are relevant structures in medicinal chemistry and are present in hormone modulators[22] and antitumor therapy agents,[3] the methodology described herein would allow for the preparation of fluorinated analogues of these biologically important derivatives (see Table 1, Entries 4, 5, and 11).

At this point, the special spectral features of some imidazolines **3** should be mentioned. These compounds are in equilibrium with their tautomeric form,[23] as shown by the ^{1}H and ^{13}C NMR spectra of some products (some signals appear broad or obscured).[24] For asymmetric 1,2-diaminopropane, both imidazoline regioisomers are possible. In this case, the tautomeric equilibrium was so rapidly established at room temperature that average NMR signals were observed for the unique imidazoline compound isolated after purification (see the Experimental Section).

Table 2. Synthesis of *N*-allylated imidazolines **4**.



3 **4**

Entry	X	3	Product 4 (% yield)[a]
1	F	**3c**	 **4a** (63)
2	F	*cis*-**3d**	 *cis*-**4b** (90)
3	F	*trans*-**3d**	 *trans*-**4c** (62)
4	H	**3e**	 **4d** (26)
5	H	*cis*-**3f**	 *cis*-**4e** (26)
6	F	**3h**	 **4f** (40)
7	F	*cis*-**3i**	 *cis*-**4g** (43)

[a] Isolated yield after flash column chromatography.

Preparation of *N*-Allylated Imidazolines 4

The next step of our synthetic strategy was the generation of the dienic system by *N*-allylation of imidazolines **3**. Due to the problems encountered in the isolation of imidazolines **3**, the allylation process was carried out by employing, in most cases, the crude reaction mixture obtained in their formation. Thus, the reaction was performed under standard conditions by treatment of a solution of imidazolines **3** (crude product without purification) and allyl bromide in THF/DMF (3:1) with sodium hydride. After the workup, desired *N*-allylated imidazolines **4** were obtained in moderate to good yields (Table 2).[25]

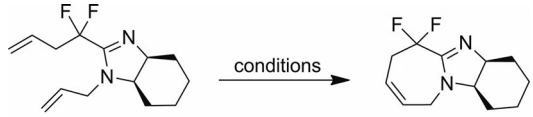
The allylation reaction took place with moderate to good yield for the fluorinated imidazolines derived from esters **1a** and **1c** (Table 2, Entries 1–3, 6, and 7). However, the yields of non-fluorinated products **4d** and **4e** dropped dramatically (Table 2, Entries 4 and 5). Again, we observed better behavior of the fluorinated derivatives, which were obtained in a more efficient manner than their non-fluorinated analogues.

Ring-Closing Metathesis (RCM) of Imidazolines 4

The last step of our synthetic strategy was the RCM reaction of dienic imidazolines **4**. In this context, the metathesis reaction has become a very useful synthetic tool for the preparation of olefins.[26] Moreover, the presence of heterocyclic groups in potentially active substrates has increased the interest in this reaction. The protection of nitrogen-containing groups and, alternatively, the addition of acids as additives are the current strategies to achieve ring closure in heterocyclic systems and prevent catalyst deactivation.[27,28]

Using compound **4a** as a model substrate, we initially performed the optimization of the RCM reaction to find suitable conditions for this process. The obtained results are depicted in Table 3.

Table 3. Optimization conditions of the RCM reaction.



4 **5**

Entry	Catalyst (mol-%)	Additive	Solvent[a]	Product	% Yield[b]
1	G1 (5)	–	DCM	SM[c]	–
2	G2 (5)	–	DCM	SM[c]	–
3	HG (5)	–	toluene	SM[c]	–
4	G2 (5)	$Ti(OiPr)_4$	DCM	SM[c]	–
5	G1 (5)	*p*TSA[d]	DCM	**5a**	30
6	G2 (5)	*p*TSA[d]	DCM	**5a**	99
7	G2 (10)	*p*TSA[d]	DCM	**5a**	45
8	HG2 (5)	*p*TSA[d]	DCM	**5a**	80

[a] All reactions were conducted under reflux for 30 min. [b] Isolated yield. [c] Starting material. [d] *p*TSA: *p*-toluenesulfonic acid.

As expected by previous work with related aromatic imidazole derivatives, the reaction without additives did not take place, recovering the starting material unaltered with all the catalysts employed (Figure 2) either in refluxing DCM or toluene (Table 3, Entries 1–3). Likewise, the use of $Ti(OiPr)_4$ as additive, to avoid the formation of chelates between the basic nitrogen atoms of the imidazolines and the catalyst, did not produce any change in the reaction (Table 3, Entry 4). Finally, the use of *p*-toluenesulfonic acid (*p*TSA) as additive to generate the imidazolium ion and prevent the inactivation of the Grubbs catalyst by the lone pair of the imidazole nitrogen atom[28b] led to the metathesis products. By employing the first-generation Grubbs catalyst (G1), **5a** was obtained in 30% yield (Table 4, Entry 5). The best result was obtained with 5 mol-% of the second-generation Grubbs catalyst (G2; Table 3, Entry 6) in refluxing DCM. The use of higher catalyst loadings (Table 3, Entry 7) or the use of Hoveyda–Grubbs second-generation catalyst (HG2; Table 3, Entry 8) provided lower yields of final imidazoline **5a**.[29]

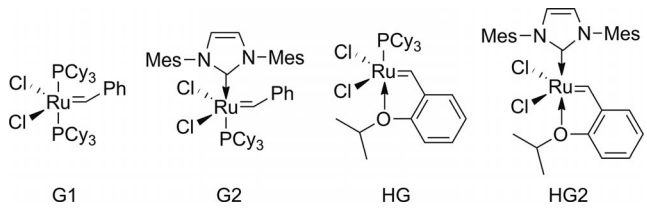


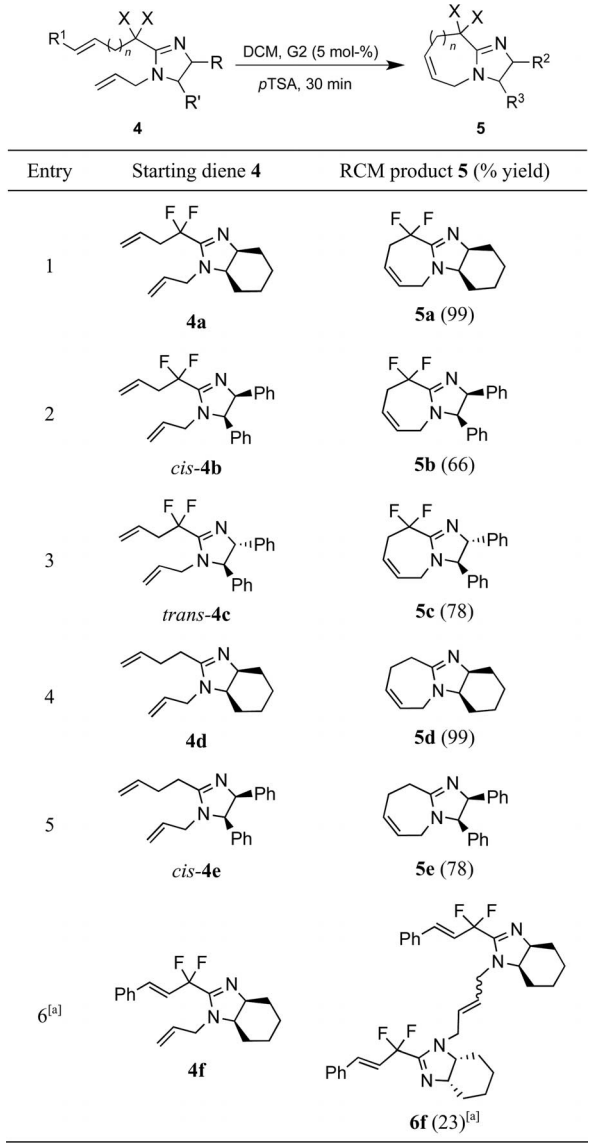
Figure 2. Catalyst employed.

The optimized conditions involved the pretreatment of imidazoline **4a** with *p*TSA (1.1 equiv.) in DCM for 30 min. After adding catalyst G2 (5 mol-%), the mixture was heated at reflux for another 30 min. These conditions were then applied to the rest of imidazolines **4** (Table 4).

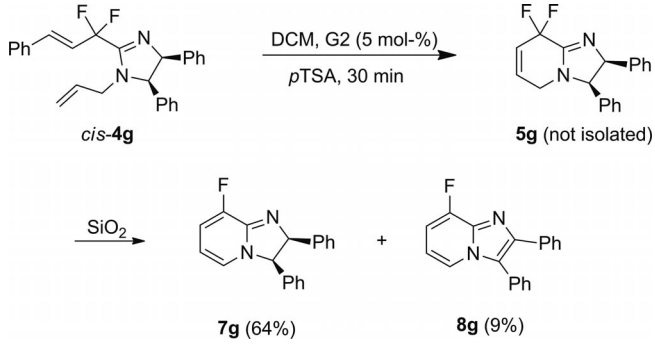
Under the optimized conditions, imidazolines **4a**–**e** cyclized to afford the desired bicyclic and tricyclic imidazolines **5a**–**e** in moderate to good yields (Table 4, Entries 1–5).[30,31] The slightly lower yields observed for imidazolines **5b**,**e** (Table 4, Entries 2 and 5) are due to the partial aromatization of the imidazoline ring towards the corresponding imidazole under the purification conditions. Substrate **4f** was inert under the optimized conditions, and when the reaction was performed in refluxing toluene, cross-metathesis product **6f** (Table 4, Entry 6) was obtained in 23% yield.[32]

RCM of compound **4g** took place in an efficient manner, giving rise to the corresponding six-membered ring. However, although in the crude reaction mixture bicyclic product **5g** could clearly be identified as the major product (by ^1H and ^{19}F NMR spectroscopy, see the Experimental Section), during purification HF elimination occurred, and the major isolated product was **7g**, in 64% yield, together with a small amount of benzimidazole **8g** arising from the aromatization of the imidazoline unit (ca. 9% yield, Scheme 2).

Table 4. RCM reaction of imidazolines **4**.



[a] The reaction was performed in refluxing toluene.



Scheme 2.

Conclusions

We have developed a new synthetic procedure for the preparation of fluorinated and non-fluorinated imidazolines **3** from readily available esters **1** and commercially available diamines **2** in the presence of trimethylaluminum as a catalyst. These imidazolines were *N*-allylated to afford dienic intermediates **4**, which were subjected to RCM to afford bicyclic and tricyclic amidines **5** in moderate to good yields. Both amidines **4** and **5** are structurally interesting compounds, and the application of this synthetic sequence to study the reactivity of these derivatives and the preparation of biologically active derivatives are currently underway in our laboratories.

Experimental Section

General Experimental Techniques: All melting points were determined by using a Kofler hot-stage apparatus. Optical rotations were determined by using a 10-cm path length cell. High-resolution mass spectra were recorded with a VG AutoSpec spectrometer by employing electron impact (EI, 70 eV) or fast atom bombardment (FAB) techniques and with a Q-TOF premier mass spectrometer with an electrospray source by using electrospray ionization technique (ESI). ^{1}H NMR spectra were recorded with Avance Bruker spectrometers, in the solvent indicated, at 300 or 400 MHz and ^{13}C NMR spectra at 75 or 100 MHz. ^{19}F NMR spectra were acquired at 282 MHz with high-power proton decoupling. ^{1}H NMR spectra were referenced to residual $CHCl_3$ (δ = 7.26 ppm), ^{13}C NMR spectra to the central component of the $CDCl_3$ triplet at δ = 77.0 ppm, and ^{19}F NMR spectra to $CFCl_3$ as the internal reference, which was set at δ = 0.00 ppm. Carbon substitution degrees were established by DEPT pulse sequences. Reaction progress was monitored by thin-layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by immersion with ethanolic ceric ammonium molybdate and heating. Flash column chromatography was performed, as indicated in each case, by using silica gel 60 (0.040–0.063 mm) or silica gel Sepra NH_2 (50 μm, 64 Å). All operations involving air-sensitive reagents were performed under an inert atmosphere of dry nitrogen by using syringe techniques, oven-dried glassware, and freshly distilled and dried solvents. Solvents and reagents were purified by standard methods.[33]

General Procedure for the Preparation of Imidazolines 3: Trimethylaluminum (2 M in hexane, 2.44 mmol) was added dropwise at 0 °C to a solution of diamine **2** (1.22 mmol) in dichloromethane (0.6 mL). The mixture was stirred at room temperature for 1 h. The reaction was cooled down again to 0 °C, and a solution of ethyl ester **1** (1.22 mmol) in dichloromethane (0.9 mL) was added. The resulting mixture was heated at 70 °C for 3 h (overnight for non-fluorinated compounds). The reaction mixture was cooled down to room temperature and quenched with methanol (1.0 mL). The crude mixture was filtered through a Celite pad, washed with DCM, and concentrated in vacuo. The oily residue was subjected to flash column chromatography.

***cis*-2-(1,1-Difluoro-3-butenyl)-3a,4,5,6,7,7a-hexahydrobenzoimidazole (3c):** According to the general procedure described above, ethyl ester **1a** (200.0 mg, 1.22 mmol) afforded imidazoline **3c** (223.0 mg) as a white solid in 86% yield after flash chromatography (*n*-hexane/ethyl acetate, 2:1) on silica gel. M.p. 67–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.89 (m, 8 H), 2.93 (td, J = 16.9, 7.1 Hz, 2 H), 3.78 (br. s, 2 H), 4.78 (br. s, 1 H), 5.24 (d, J = 10.2 Hz, 1 H), 5.26 (d, J = 17.2 Hz, 1 H), 5.81 (ddt, J = 17.2, 10.2, 7.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 20.8, 28.0, 28.0, 39.9 (t, J = 24.6 Hz), 57.3, 64.4, 117.0 (t, J = 241.9 Hz), 121.1, 127.9 (J = 5.1 Hz), 161.2 (t, J = 30.3 Hz) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –102.4 (dt, J_{FF} = 267.0 Hz, J_{HF} = 16.9 Hz, 1 F), –100.9 (dt, J_{FF} = 267.0 Hz, J_{HF} = 16.9 Hz, 1 H) ppm. HRMS (EI): calcd. for $C_{11}H_{16}F_2N_2$ $[M]^+$ 214.1281; found 214.1275.

General Procedure for the Synthesis of *N*-Allylimidazolines 4: Sodium hydride (0.77 mmol) was added to a solution of imidazoline (0.61 mmol) and allyl bromide (1.02 mmol) in a mixture of THF/DMF (3:1, 4 mL) at 0 °C. When TLC showed total consumption of the starting material, the mixture was diluted with diethyl ether (5.0 mL) and washed with water (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried with anhydrous Na_2SO_4. The oily residue was subjected to flash column chromatography as detailed below.

***cis*-*N*-Allyl-2-(1,1-difluoro-3-butenyl)-4,5-dihydro-4,5-diphenylimidazole (4b):** According to the general procedure described above, imidazoline *cis*-**3d** (190.0 mg, 0.61 mmol) afforded *N*-allylimidazoline **4b** (191.0 mg) as a yellowish oil in 90% yield after flash column chromatography (*n*-hexane/ethyl acetate, 2:1) on silica gel deactivated by treatment with 2% triethylamine in hexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.07–3.36 (m, 2 H), 3.29 (dd, J = 15.8, 8.1 Hz, 1 H), 4.40 (dd, J = 15.8, 3.2 Hz, 1 H), 4.99 (d, J = 17.2 Hz, 1 H), 5.11 (d, J = 11.7 Hz, 1 H), 5.16 (d, J = 10.0 Hz, 1 H), 5.35 (d, J = 17.2 Hz, 1 H), 5.37 (d, J = 10.2 Hz, 1 H), 5.50 (d, J = 11.7 Hz, 1 H), 5.80 (dddd, J = 17.2, 10.0, 8.1, 3.2 Hz, 1 H), 6.05 (ddt, J = 17.2, 10.2, 7.0 Hz, 1 H), 6.81 (dd, J = 7.3, 3.9 Hz, 2 H), 6.86 (dd, J = 7.7, 2.1 Hz, 2 H), 6.97 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.1 (t, J = 23.6 Hz), 47.1 (t, J = 4.1 Hz), 69.2, 72.6, 117.9 (t, J = 241.6 Hz), 118.3, 120.9, 126.5, 127.2, 127.4, 127.7, 127.8, 127.9, 128.6 (t, J = 5.0 Hz), 133.0, 135.5, 138.2, 159.8 (t, J = 30.3 Hz) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –100.9 (ddd, J_{FF} = 282.3 Hz, J_{HF} = 24.6 Hz, J_{HF} = 14.6 Hz, 1 F), –99.3 (dddd, J_{FF} = 282.3 Hz, J_{HF} = 18.9 Hz, J_{HF} = 15.0 Hz, J_{HF} = 3.0 Hz, 1 F) ppm. HRMS (EI) calcd. for $C_{22}H_{22}F_2N_2$ $[M]^+$ 352.1751; found 352.1741.

General Procedure for the Preparation of Compounds 5 by Ring-Closing Metathesis: *p*TSA (0.044 mmol) was added to a stirred solution of dienic imidazolines **4** (0.04 mmol) in anhydrous dichloromethane (2.0 mL), and the solution was heated at reflux for 30 min. After cooling down to room temperature, the second-generation Grubbs catalyst (5 mol-%) was added, and the mixture was heated at reflux for another 30 min. The obscured solution was quenched with 10% aqueous $NaHCO_3$ (5.0 mL) and extracted with dichloromethane (3 × 5.0 mL). The combined organic layers were washed with brine (5.0 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was subjected to flash column chromatography.

6,6-Difluoro-1,3,4,4a,6,7,10,11a-octahydro-2*H*-azepino[1,2-*a*]benzimidazole (5a): According to the general procedure described above, *N*-allylimidazoline **4a** (10.0 mg, 0.47 mmol) afforded tricyclic amidine **5a** (9.0 mg) as a yellowish solid in 99% yield after flash chromatography (*n*-hexane/ethyl acetate, 1:1) on silica gel Sepra NH_2 (50 μm, 64 Å). Mp 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.94 (m, 8 H), 2.79–2.94 (m, 2 H), 3.48 (dt, J = 8.1, 5.6 Hz, 1 H), 3.55–3.75 (m, 2 H), 3.78–3.86 (m, 1 H), 5.54–5.62 (m, 1 H), 5.77–5.84 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 21.4, 24.5, 28.1, 36.4 (t, J = 26.8 Hz), 42.4, 62.1, 63.8, 116.2 (t, J = 241.9 Hz), 122.5 (t, J = 6.3 Hz), 126.3, 160.8 (t, J = 27.6 Hz) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –100.5 (dt, J_{HF} =

14.6 Hz, J_{HF} = 4.7 Hz, 2 F) ppm. HRMS (EI): calcd. for $C_{12}H_{16}F_2N_2$ $[M]^+$ 226.1282; found 226.1284.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data for new products, and complete details about the synthesis of new products.

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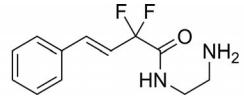
[1] R. G. S. Berlinck, A. C. B. Burtuloso, M. H. Kossuga, *Nat. Prod. Rep.* **2008**, *25*, 919–954.
[2] M. Silva Dos Santos, A. M. R. Bernardino, M. Costa de Souza, *Quim. Nova* **2006**, *29*, 1301–1306.
[3] L. T. Vassilev, B. T. Vu, B. Graves, D. Carvajal, F. Podlaski, Z. Filipovic, N. Kong, U. Kammlott, C. Lucacs, C. Klein, N. Fotouhi, E. A. Liu, *Science* **2004**, *303*, 844–848.
[4] a) T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, *5*, 737–752; b) T. Ishikawa, K. Takuya, "Amidines in Organic Synthesis" in *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts* (Ed.: T. Ishikawa), Wiley, Chichester, U.K., **2009**, pp. 49–91.
[5] L. Peterlin-Masic, D. Kikelj, *Tetrahedron* **2001**, *57*, 7073–7105.
[6] M. P. Coles, *Dalton Trans.* **2006**, 985–1001.
[7] See, for example: a) A. A. Aly, A. M. Tour-ElDin, *ARKIVOC* **2008**, *1*, 153–194; b) H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2009**, *351*, 489–519.
[8] Bicyclic amidines, which include common organic bases such as DBU and DBN, are frequently used in many base-promoted transformations: C. Joannesse, C. Simal, C. Concellón, J. E. Thomsom, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 2900–2907.
[9] N. Kumagai, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2004**, *116*, 484; *Angew. Chem. Int. Ed.* **2004**, *43*, 478–482.
[10] K. L. Tan, A. Vasudevan, R. G. Bergman, J. A. Ellman, A. J. Souers, *Org. Lett.* **2003**, *5*, 2131–2134.
[11] H. Fujioka, K. Murai, Y. Ohba, H. Hirose, Y. Kita, *Chem. Commun.* **2006**, 832–834.
[12] K. L. S. Hehir, L. O'Donovan, M. P. Carty, F. Aldabbagh, *Tetrahedron* **2008**, *64*, 4196–4203.
[13] Q. Zhu, Y. Yu, *Org. Lett.* **2010**, *12*, 4156–4159 and references cited therein.
[14] For reviews, see: a) R. Smits, C. D. Cadicamo, K. Burger, B. Koksch, *Chem. Soc. Rev.* **2008**, *37*, 1727–173; b) W.-D, Meng, F.-L Qing, "Synthesis of *gem*-Difluoromethylenated Nucleosides" in *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, UK, **2009**, chapter 8, pp. 201–212; c) J. L. Aceña, A. Simón-Fuentes, S. Fustero, *Curr. Org. Chem.* **2010**, *14*, 928–949; d) S. Fustero, J. F. Sanz-Cervera, J. L. Aceña, M. Sánchez-Roselló, *Synlett* **2009**, 525–549; See, also: e) S. Fustero, M. Sánchez-Roselló, V. Rodrigo, J. F. Sanz-Cervera, J. Piera, A. Simón-Fuentes, C. del Pozo, *Chem. Eur. J.* **2008**, *14*, 7019–7029; f) S. Fustero, M. Sánchez-Roselló, J. L. Aceña, B. Fernández, A. Asensio, J. F. Sanz-Cervera, C. del Pozo, *J. Org. Chem.* **2009**, *74*, 3414–3423; g) S. Fustero, S. Catalán, M. Sánchez-Roselló, A. Simón-Fuentes, C. del Pozo, *Org. Lett.* **2010**, *12*, 3484–3487; h) N. M. Cerqueira, P. A. Fernandes, M. J. Ramos, *Chem. Eur. J.* **2007**, *13*, 8507–8515; i) J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli, C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16793–16797; j) Ch. Fäh, L. A. Hardegger, L. Baitsch, W. B. Schweizer, S. Meyer, D. Bur, F. Diederich, *Org. Biomol. Chem.* **2009**, *7*, 3947–3957; k) S. N. Crane, W. C. Black, J. T. Palmer, D. E. Davis, E. Setti, J. Robichaud, J. Paquet, R. M. Oballa, Ch. I. Bayly, D. J. McKay, J. R. Somoza, N. Chauret, C. Seto, J. Scheigetz, G. Wesolowski, F. Masse, S. Desmarais, M. Ouellet, *J. Med. Chem.* **2006**, *49*, 1066–1079.
[15] a) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, U.K., **2009**; See also: b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; c) K. Müller, Ch. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; e) J.-P. Bégué, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, *127*, 992–1012.
[16] a) W. Ghattas, C. R. Hess, G. Lacazio, R. Hardré, J. P. Klinman, M. Réglier, *J. Org. Chem.* **2006**, *71*, 8618–8621; b) K. Tsuda, E. Ohki, S. Nozoe, *J. Org. Chem.* **1963**, *28*, 783–785.
[17] a) P. A. Crassous, C. Cardinaletti, A. Carrieri, B. Bruni, M. D. Vaira, F. Gentili, F. Ghelfi, M. Giannella, H. Paris, A. Piergentili, W. Quaglia, S. Schaaak, C. Vesprini, M. Pigini, *J. Med. Chem.* **2007**, *50*, 3964–3968 and references cited therein; b) C. A. Busacca, Y. Dong, E. M. Spinelli, *Tetrahedron Lett.* **1996**, *37*, 2935–2938.
[18] Aromatic diamines such as *o*-phenylendiamine afforded a complex mixture of compounds.
[19] Imidazoline hydrolysis is clearly accelerated during purification by column chromatography, where significant cleavage of the imidazolines to afford the corresponding amides was observed. The use of alumina or deactivated silica gel as stationary phases (see the Experimental Section) also failed to reduce the hydrolysis.
[20] Spectroscopic data for the amide derived from the hydrolysis of **3g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (t, J = 9.0 Hz, 2 H), 3.42 (dt, J = 9.0 Hz, 2 H), 6.44 (dt, J = 16.1, 11.2 Hz, 1 H), 7.12 (dt, J = 16.1, 2.8 Hz, 1 H), 7.29–7.35 (m, 3 H), 7.48–7.52 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.7, 41.8, 114.3 (t, J = 249.8 Hz), 118.8 (J = 24.8 Hz), 127.4, 128.7, 129.5, 134.2, 136.5 (t, J = 11.3 Hz), 164.1 (t, J = 22.5 Hz) ppm.



[21] a) V. V. Lisitskii, Z. A. Akhmetchenko, I. E. Alekhina, Y. I. Murinov, *Russ. J. Appl. Chem.* **2007**, *80*, 761–766; b) N. A. Boland, M. Casey, S. J. Hynes, J. W. Matthews, M. P. Smyth, *J. Org. Chem.* **2002**, *67*, 3919–3922 and references cited therein.
[22] M. von Rauch, S. Busch, R. Gust, *J. Med. Chem.* **2005**, *48*, 466–474.
[23] E. D. Raczynska, R. Gawinecki, *Trends Org. Chem.* **1998**, *7*, 85–93.
[24] a) P. Seckarova, R. Marek, K. Malinakova, E. Kolehmainen, D. Hockva, M. Hocek, V. Sklenar, *Tetrahedron Lett.* **2004**, *45*, 6259–6263; b) A. F. Pozharskii, E. A. Filatova, I. V. Borovlev, N. V. Vistorovskii, *Chem. Heterocycl. Compd.* **2001**, *37*, 733–742.
[25] Bussaca et al. reported that strong bases, in combination with high temperatures, favor epimerization of chiral imidazolines. In our case, however, careful manipulation allowed the preparation of allylated compounds as unique *cis* diastereoisomers, as indicated by their NMR spectra. C. A. Busacca, T. Bartholomeyzik, S. Cheekoori, N. Grinberg, H. Lee, S. Ma, A. Saha, S. Shen, C. H. Senanayake, *J. Org. Chem.* **2008**, *73*, 9756–9761.
[26] A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243–251.
[27] a) A. J. Phillips, A. D. Abell, *Aldrichim. Acta* **1999**, *32*, 75–89; b) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199–2238; c) P. Compain, *Adv. Synth. Catal.* **2007**, *349*, 1829–1846.
[28] a) T. J. Donohhoe, L. P. Fishlock, P. A. Procopiou, *Chem. Eur. J.* **2008**, *14*, 5716–5726; b) V. Gracias, A. F. Gasiecki, S. W. Djuric, *Org. Lett.* **2005**, *7*, 3183–3186.
[29] When the reaction was performed with an excess amount of G2 or with HG2 catalysts, a tandem RCM–double-bond isomerization occurred, decreasing the final yield of the desired product. a) B. Schmidt, *J. Org. Chem.* **2004**, *69*, 7672–7687; b) this fact has been previously observed in other RCM reactions

in our laboratories: S. Fustero, M. Sánchez-Roselló, D. Jiménez, J. F. Sanz-Cervera, C. del Pozo, J. L. Aceña, *J. Org. Chem.* **2006**, *71*, 2706–2714.

[30] In this study, the presence of fluorine atoms seems to have no significant effect, for example, on the final chemical yield. In this context, several examples where the presence of fluorine atoms plays an important role have recently been described. See, for example: a) Ch. Audouard, J. Fawcett, G. A. Griffiths, J. M. Percy, *Org. Biomol. Chem.* **2004**, *2*, 528–541; b) Y.-Y. Yang, J. Xu, Z.-W. You, X. Xu, X.-L. Qiu, F.-L. Qing, *Org. Lett.* **2007**, *9*, 5437–5440; c) S. Fustero, B. Fernández, J. F. Sanz-Cervera, N. Mateu, S. Mosulen, R. J. Carbajo, A. Pineda-Lucena, C. Ramírez de Arellano, *J. Org. Chem.* **2007**, *72*, 8716–8723; d) see, also ref.[29]

[31] It is important to mention that in all the aforementioned cases (see, ref.[30]), the RCM process was performed in the absence of a co-catalyst. Considering the lowering in nitrogen basicity induced by the fluorine atoms, it is reasonable to think that the RCM process would work better in those cases. However, in our study the nitrogen atom was previously protonated by treatment with TsOH, and therefore, the nitrogen lone pair does not operate in this case, which may explain the small difference found between the fluorinated and the non-fluorinated derivatives.

[32] When the reaction was performed with the G2 catalyst in refluxing toluene an equimolecular mixture of starting material **4f** and compound **6f** was obtained.

[33] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, 4th ed., Butterworth Heinemann Press, Oxford, **1996**.

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