JOC The Journal of Organic Chemistry

Article

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Chemo- and Stereoselective Synthesis of Fluorinated Enamides from Ynamides in HF/Pyridine: Second-Generation Approach to Potent Ureas Bioisosteres

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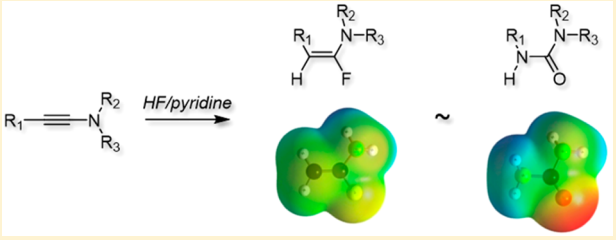
Supporting Information

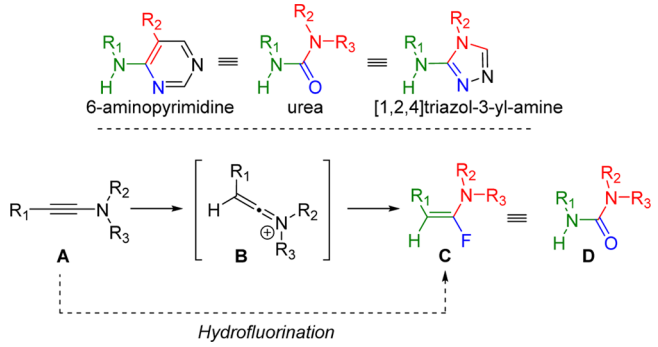
ABSTRACT: (*E*)- and (*Z*)-α-fluoroenamides could be easily prepared with high levels of chemo- and regioselectivities by hydrofluorination of readily available ynamides with HF/pyridine. The scope and limitations of this new process for the hydrofluorination of ynamides, as well as the stability of the resulting α-fluoroenamides, have been extensively studied. Theoretical calculations at the MP2 and B3LYP levels of theory showed that the resulting fluoroenamides exhibit geometrical and electronic properties that partially mirror those of ureas, therefore demonstrating that the hydrofluorination of ynamides provides a general, straightforward, and user-friendly approach to bioisosteres of ureas, potent building blocks for biological studies and medicinal chemistry.



INTRODUCTION

Over the past decade, the chemistry of urea has undergone nothing short of a renaissance with remarkable applications in many fields of chemistry. The unique structural properties of ureas (planarity of the urea linkage, hydrogen-bonding ability, coordination to metals, etc.)[1] have indeed been elegantly used, for example, in the preparation of noncovalent organocatalysts,[2−4] in the development of selective anion chemosensors,[5,6] and, recently, in the design of imidazole quartet for (water)proton-channel systems.[7,8] In addition, and besides the historical use of ureas (and more specifically sulfonyl ureas) as antidiabetic agents,[9,10] the recent development of urea-based anticancer and antiinfective molecules[11−13] unambiguously demonstrated their strong potential as key structural elements and/or pharmacophores in medicinal chemistry. Although the modification of structural properties of ureas is now a common strategy in the design of new bioactive molecules or lead optimization, as recently shown for selective enzyme inhibitors,[14,15] little attention has been paid to their replacement with rigid, stable, and adjustable bioisosteres, which might represent an interesting strategy in medicinal chemistry and chemical biology as well.[16,17] Indeed, and to the best of our knowledge, only triazoles and aminopyrimidines have been evaluated as urea bioisosteres in SAR studies (Scheme 1).[18−20] Based on the well-known bioisosterism between fluoroolefins and amides, which has been extensively used in medicinal chemistry,[21−24] we envisioned that, in analogy, fluoroenamines **C** might be an especially versatile class of ureas **D** isosteres (Scheme 1).

Scheme 1. Previously Reported and Targeted Urea D Bioisosteres and Synthesis of α-Fluoroenamines C



Received: November 27, 2014
Published: January 8, 2015

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

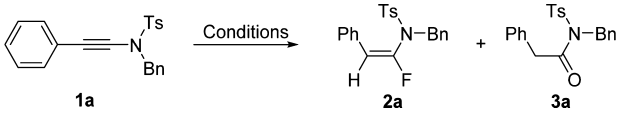
Since this class of enamides is virtually unknown, we recently reported the first general synthesis of α-fluoroenamides via a superacid-catalyzed[25] hydrofluorination[26] of ynamides **A**[27−31] through the intermediacy of a keteniminium ion **B** (Scheme 1).[32] Although this method was shown to have a rather broad substrate scope, some acid-sensitive and chiral ynamides were not well tolerated under these conditions. In addition, the necessary safety arrangements and procedure for handling pure liquid hydrogen fluoride could be considered as a major limitation to the use of this method. To address this drawback and develop a more user-friendly second-generation procedure, we considered using less volatile solutions of HF with an organic base[33−35] or other sources of fluoride ions in the hydrofluorination process.

Herein, we report a general and more practical process for the stereo- and regioselective synthesis of α-fluoroenamides. This second-generation hydrofluorination process enables the synthesis of a wider range of fluorinated enamides and allows the hydrofluorination of ynamides that could not be cleanly fluorinated in liquid hydrogen fluoride. We therefore report in this manuscript the results obtained with our second-generation procedure as well as a full account on the hydrofluorination of ynamides in neat hydrogen fluoride. A mechanistic investigation and a study of the stability of the fluoroenamides allowed us to propose a hypothesis to explain the substrate dependence of the stereoselectivity. In addition, and in order to validate our hypothesis on the potential use of fluoroenamides as new potent isosteres of ureas, calculations at the theoretical level were conducted on selected representative fluoroenamides and the corresponding ureas.

RESULTS AND DISCUSSION

Screening of Reagents and Conditions for the Second-Generation Hydrofluorination Process. In order to extend the scope of the reaction and avoid the use of pure fluorhydric acid, other fluorinating agents were tested using ynesulfonamide **1a** as a model substrate (Table 1). $BF_3{\cdot}OEt_2$ was first evaluated at low temperature, but unfortunately, only traces of the desired fluorinated product could be detected in the crude reaction mixture, the major product formed being amide **3a** resulting from the hydrolysis of the intermediate keteniminium ion (Table 1, entry 1). No improvement was observed at higher temperature, and the competitive formation of amide **3a**, which was still formed as the main product, could not be avoided (Table 1, entry 2). To evaluate whether superacidic conditions were needed to perform the hydrofluorination reaction, the use of trifluoromethanesulfonic acid was tested. While the keteniminium ion must definitely be formed under these conditions,[36−39] the subsequent addition of tetrabutylammonium fluoride did not, however, allow trapping of this highly reactive intermediate. The amide **3a** was once again predominantly formed under these conditions, which can be attributed to a competitive trapping of the intermediate *N*-sulfonylketeniminium ion by the triflate counterion yielding an unstable ketene *N*,*O*-acetal that would next decompose under the reaction conditions (Table 1, entry 3).[40]

Table 1. Screening of Fluorinating Agents for the Hydrofluorination of Model Ynamide 1a



1a **2a** **3a**

				products[b] (%)		
entry	conditions[a]	temp (°C)	time	**1a**	**2a**[c]	**3a**
1	$BF_3{\cdot}OEt_2$	−10	15 min	0	5	95[d]
2	$BF_3{\cdot}OEt_2$	20	15 min	0	7	93[d]
3	CF_3SO_3H/Bu_4NF	−10	15 min	37	0	63
4	HF/Et_3N[e]	−10	15 min	>95	0	0
5	HF/Et_3N[e]	20	15 min	>95	0	0
6	HF/pyridine[f]	−78	5 min	>95	0	0
7	HF/pyridine[f]	−50	5 min	78	22	0
8	HF/pyridine[f]	−20	95 h	4	84	12
9	HF/pyridine[f]	20	5 min	5	65	30
10	HF/pyridine[g]	20	5 min	>95	0	0
11	HF/pyridine[f]	−10	15 min	0	98	2

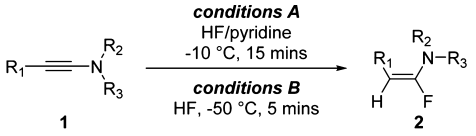
[a]Reaction media. [b]Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Only the (*E*)-α-fluoroenamide was detected and no traces of the (*Z*)-isomer could be detected. [d]Side product formation. [e]37/63, w/w. [f]70/30, w/w. [g]50/50, w/w.

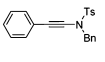
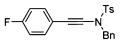
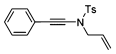
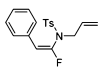
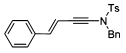
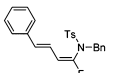
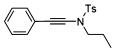
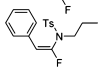
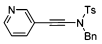
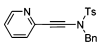
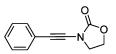
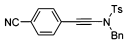
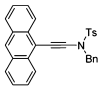
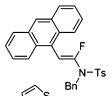
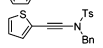
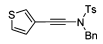
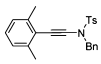
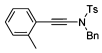
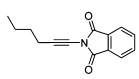
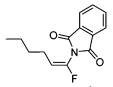
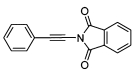
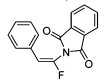
In order to avoid the presence of other counteranions for the keteniminium that could competitively trap this highly reactive intermediate and, therefore, increase the amount of fluoroenamide formed, we decided to switch to HF/base reagents.[41,42] We first evaluated the use of HF/Et_3N but, whatever the conditions used, this fluorinating agent was found not to be acidic enough to generate a keteniminium ion or to allow the hydrofluorination process, as only starting material was recovered with this reagent (Table 1, entries 4 and 5). Then the use of HF/pyridine was evaluated as the reaction media for the hydrofluorination of the ynesulfonamide **1a**. While no reaction occurred at −78 °C, due to the mixture freezing under these conditions, the desired (*E*)-α-fluoroenesulfonamide **2a** was, gratifyingly, formed at −50 °C (Table 1, entries 6 and 7). However, 95 h at −20 °C was needed to fully convert the ynesulfonamide under these conditions, and the formation of the undesired amide **3a** could not be fully avoided (Table 1, entry 8). Considering that the amide could result from partial hydrolysis of the remaining ynamide when the reaction time was too long, the reaction was next tested at higher temperature. At 20 °C, the ynamide was almost fully converted after 5 min, but amide formation could still not be avoided (Table 1, entry 9). Since pyridine concentration of Olah's reagent is known to influence the selectivity of addition reaction,[43] we therefore evaluated the influence of this parameter on the hydrofluorination reaction. When the pyridine concentration increased, no reaction occurred (Table1, entry 10), confirming the necessity of sufficiently acidic conditions for the hydrofluorination reaction. It was finally found that when the reaction was performed in HF/pyridine (70/30, w/w) for 15 min at −10 °C, the ynesulfonamide **1a** was fully converted to the desired (*E*)-α-fluoroenesulfonamide **2a**, which was formed as a single regio- and stereoisomer and could be isolated in 86% yield (Table 1, entry 11).

Second-Generation Hydrofluorination of Ynamides. With these new optimized conditions in hand based on the use of the classical fluorinating agent HF/pyridine, the effect of pyridine−(poly) hydrogen fluoride complexes on the efficiency, regioselectivity, and stereoselectivity of the hydrofluorination of a set of representative ynamides was evaluated (Table 2).[44] For all substrates tested, including aryl- and alkyl- substituted ynesulfonamides, ynecarbamates, and ynimides, the hydrofluorination reaction in HF/pyridine allowed the synthesis of the desired nitrogen-substituted fluoroolefins. Aryl- and alkyl-substituted ynesulfonamides **1a**−**i** and ynecarbamate **1j** led to the corresponding fluorinated enamides with similar yields under liquid HF (conditions B) and HF/pyridine (conditions A)

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

Table 2. Hydrofluorination of Ynamides: Scope and Limitations



Entry		Substrate	Conditions		Product	Yield[a]	E:Z[b]
1	1a		A	2a		86%	98:2
			B			96%	99:1
2	1b		A	2b		85%	98:2
			B			97%	99:1
3	1c		A	2c		42%	91:9
			B			52%[c]	93:7
4	1d		A	2d		46%	97:3
			B			44%[c]	93:7
5	1e		A	2e		81%	99:1
			B			77%	99:1
6	1f		A[d,e]	2f		46%	80:20
			B			48%	77:23
7	1g		A[d,e]	2g		22%	99:1
			B			50%	99:1
8	1h		A	2h		79%[c]	90:10
			B			86%	92:8
9	1i		A	2i		84%[c]	18:82
			B			80%[c]	32:68
10	1j		A	2j		89%	97:3
			B			73%[f]	98:2
11	1k		A	2k		28%	99:1
			B			/[g]	/
12	1l		A[e,h]	2l		10%	1:99
			B			/[g]	/
13	1m		A[e]	2m		53%	41:59
			B			/[g]	/
14	1n		A[d,e]	2n		34%	33:67
			B			/[g]	/
15	1o		A[d,e]	2o		63%	3:97
			B			/[g]	/
16	1p		A	2p		82%	96:4
			B			/[i]	/
17	1q		A[e]	2q		66%[d]	66:34
			B			/[i]	/
18	1r		A[e]	2r		30%	93:7
			B			/[i]	/

[a]Yields of pure, isolated fluoroenamides (E/Z) . [b]E/Z ratio determined by ^{1}H NMR analysis of crude reaction mixtures. [c]E and Z isomers were separated. [d]0 °C. [e]60 min. [f]Addition of HF/pyridine to reaction media. [g]Complex mixture. [h]20 °C. [i]Not evaluated.

(Table 2, entries 1−10).[45] In these cases, the possibility to access to the same α-fluoroenamides in good yields using HF/pyridine, a widely used and practical reagent, instead of neat hydrogen fluoride reinforces the potential of the method which can now be performed much more easily. In addition, when substrates **1k−o** only led to complex mixtures when hydrofluoric acid was used, these ynamides could be converted to the corresponding desired α-fluoroenamides **2k−o** by using HF/pyridine (Table 2, entries

DOI: 10.1021/jo502699y
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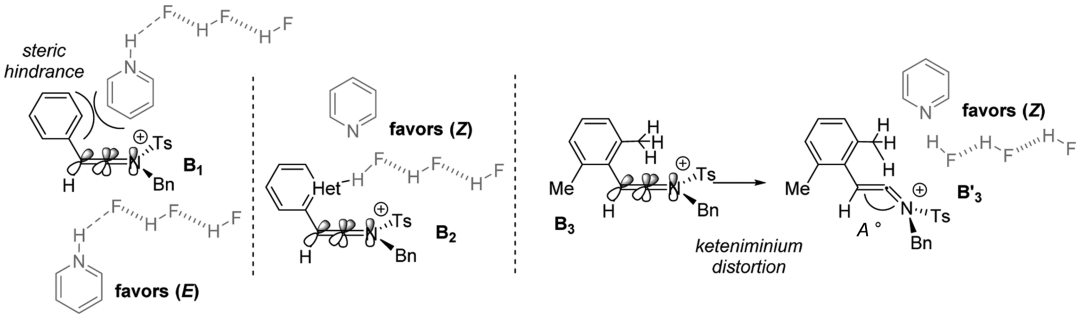
Scheme 2. Possible Keteniminium Intermediates and Basis for Observed Stereoselectivity



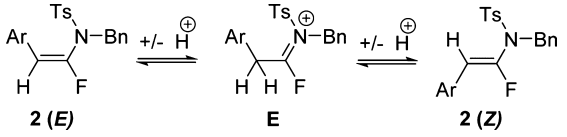
11−15). When the hydrofluorination process could not be achieved by using our previous procedure, our second-generation conditions allowed the synthesis of the desired heteroaromatic fluorinated products. Starting from these substrates, the stereoselectivity of the reaction dramatically decreased. To check whether the stereochemical outcome of the reaction could also be influenced by a steric effect, the behavior of xylyl-substituted ynamide **1o** was evaluated (Table 2, entry 15). To our surprise, the reaction turned out to be completely *Z* selective in this case, and *α*-fluoroenesulfonamide **2o** could be isolated in 63% yield after 1 h of reaction at 0 °C. It has to be noted that the tolyl analogue **1p** selectively yielded the (*E*)-*α*-fluoroenesulfonamide **2p** after 5 min reaction at −10 °C (Table 2, entry 16).

Finally, to evaluate whether these conditions could be extended to the synthesis of *α*-fluoroenimides, ynimides **1q** and **1r** were tested as substrates using our second-generation optimized procedure. To our delight, the hydrofluorination also occurred from these ynimides, allowing the synthesis of original fluoroenimides such as **2q** and **2r** (Table 2, entries 17 and 18).

Stereochemical Outcome of the Keteniminium Ion Fluorination. As previously mentioned, the nature of the substituent of the ynamides strongly influences the stereochemical outcome of their hydrofluorination. To rationalize the observed differences in stereoselectivity, we proposed the involvement of the following intermediates in the mechanism (Scheme 2). After protonation, the aryl-substituted ynesulfonamides should lead to the formation of keteniminium ion intermediates such as ion $\mathbf{B}_1$, with an upper face being sterically hindered by the phenyl group, thus favoring the pyridinium (poly)hydrogen fluoride complexes to approach *syn* to the H atom (formation of the *E* isomer). For alkyl- and styryl-substituted ynamides, the smaller steric hindrance would disfavor the selectivity of the reaction. As expected, a similar impact of the substituent is also observed for ynimide derivatives (Table 2, entries 17 and 18). For heteroaryl-substituted ynamides, the position of the heteroatom strongly influences the stereochemical outcome of the reaction. When starting from 3-pyridinyl-substituted ynesulfonamide **1h**, the hydrofluorination process led selectively to the formation of the (*E*)-*α*-fluoroenesulfonamide **2h**; under the same conditions, the 2-pyridinyl substrate **1i** led mainly to the formation of the *Z* product **2i**. Analogously, for thiofuranyl-substituted ynamides **1m** and **1n**, the reaction led selectively to the (*Z*)-fluoroenamide products, the stereoselectivity being lower in these cases. To explain the behavior of these substrates, it could be postulated that an intermediate ion $\mathbf{B}_2$ could be formed through competitive hydrogen bonds with the heteroatom of the aromatic ring of the ynamide forcing the attack of the fluoride ions by the face that promotes the *Z* isomer formation (Scheme 2).[46,47] The dramatic effect of methyl substitution of the aromatic ring on the selectivity of the process led us to propose the following rationalization (Table 2, entries 15 and 16). It first has to be noted that substrate **1o** possessing a xylyl group is by far less reactive than its tolyl analogue **1p**. By analogy to the elucidated mechanism involving a [1,5] sigmatropic methyl hydrogen shift from keteniminium ions,[38] it could be postulated that a partial stabilization of the keteniminium ion $\mathbf{B}_3$ through a hyperconjugation effect could account for the stereoselectivity of the process. The partial stabilization of the charge must distort the keteniminium ion (decrease of angle *A*°) favoring the nucleophilic attack of HF/pyridine complex by the upper face of the distorted ion $\mathbf{B'}_3$ and leading to the formation of the *Z* isomer. In the case of the tolyl analogue, the strong reactivity of the keteniminium ion toward the fluoride ions (immediate reaction) would prevent such a process, resulting in a "classical" stereoselectivity for the reaction. For substrate **1l**, which also led to the (*Z*) isomer, a similar behavior could be postulated.

Study of the Fluoroenamide Stability. The strong substrate dependency of the stereochemical outcome of the hydrofluorination reaction also could have been attributed to thermodynamic control. An equilibrium between (*E*)- and (*Z*)-*α*-fluoroenamides, through the intermediate formation of a fluoroiminium ion **E**, could indeed account for the formation of the *Z* isomers in some cases and therefore needed to be evaluated (Scheme 3).

Scheme 3. Possible Isomerization of *α*-Fluoroenamides under Acidic Conditions



Although X-ray diffraction analyses of crystals of (*E*)-*α*-fluoroenamide **2b** and (*Z*)-*α*-fluoroenamide **2i** showed a partial pyramidalization of the sulfonamide nitrogen atom (Figure 1),[32] which is not favorable for the formation of the fluoroiminium ions due to nonoptimal conjugation between the nitrogen lone pair and the double bond, the intermediacy of such fluoroiminium species could, however, not be ruled out on this basis. The conformation of the fluoroenamides being indeed most certainly different in solution, the possibility of a thermodynamic control through the formation of a fluoroiminium ion needed to be assessed.

Toward this end, a set of fluoroalkenes were subjected to the reaction conditions to check whether an isomerization could be

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

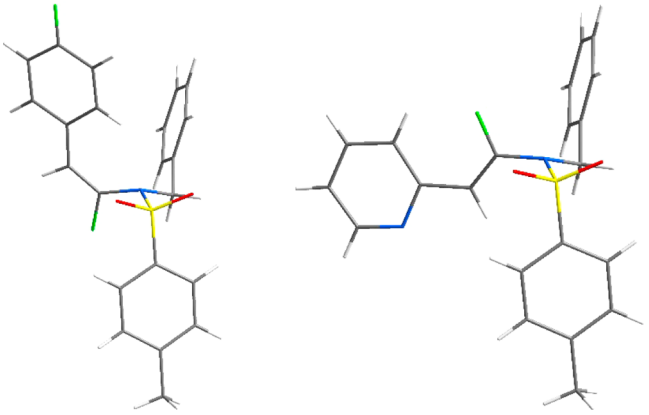
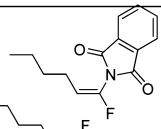
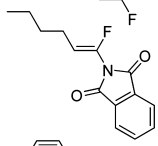
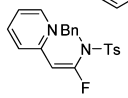
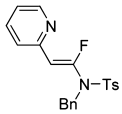
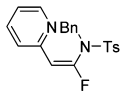
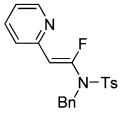
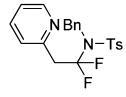
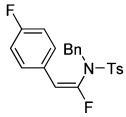


Figure 1. X-ray crystal structures of fluoroenesulfonamides (*E*)-**2b** and (*Z*)-**2i**.[32]

observed or not. Under our defined reaction conditions in HF/pyridine, both (*E*) and (*Z*) isomers of the enimide **2q** were found to be perfectly stable and no isomerization could be detected from ^{1}H NMR analysis of crude reaction mixtures (Table 3, entries 1 and 2).

These two substrates could be completely recovered, even after 1 h under the reaction conditions, therefore confirming the chemical and stereochemical stability of these fluoroenimides under the reaction conditions. A similar observation could be made starting from both *E* and *Z* isomers of 2-pyridyl-substituted fluoroenamide **2i**. When the conditions were forced by increasing the temperature, the *E* isomer **2i** was also recovered at the end of the reaction, while surprisingly, the corresponding *Z* isomer **2i** led to the exclusive formation of the difluorinated product **4** after 20 min at 20 °C. In this case, the intermediate formation of a highly reactive fluoroiminium ion intermediate could favor the difluorination process but not the equilibration between both double-bond isomers. All together, these experiments are in strong agreement with a kinetic control instead of a thermodynamic control of the hydrofluorination reaction in HF/pyridine. As previously mentioned, α-fluoroenamides could be potentially used as novel isosteres of ureas. Taking into account the recently reported potential of *N*-sulfonyl-substituted ureas as anticancer agents,[14,15] the synthesis of potent α-fluoroenesulfonamide bioisosteres could offer further advances in this field, provided that these compounds would be stable enough. With this goal in mind, we briefly tested the chemical stability of (*E*)-α-fluoroenamide **2b**. To our delight, this fluorinated enamide was found to be perfectly stable not only in water or methanol (Table 3, entries 7 and 8) but also under basic or acidic aqueous conditions (Table 3, entries 9 and 10), with **2b** being totally recovered in all trials. This stability confirms that these potential urea isosteres should definitely be stable under physiological conditions, making them good candidates for further biological studies.

Table 3. Study of the Chemical and Stereochemical Stability of α-Fluoroenamides

Entry	Substrate	Conditions	Products (Yield)[a]
1	**2q** *(E)* 	HF/pyridine[d]	/[c]
2	**2q** *(Z)* 	HF/pyridine[d]	/[c]
3	**2i** *(E)* 	HF/pyridine[b]	/[c]
4	**2i** *(Z)* 	HF/pyridine[b]	/[c]
5	**2i** *(E)* 	HF/pyridine[e]	/[c]
6	**2i** *(Z)* 	HF/pyridine[e]	**4** (93%) 
7		H_2O[f]	/[c]
8		MeOH[f]	/[c]
9	**2d** *(E)* 	$NaOH_{aq}$ (2M)[f]	/[c]
10		HCl_{aq} (2M)[f]	/[c]

[a]Yields obtained after purification. [b]HF/pyridine (70/30, w/w), 15 min, −20 °C. [c]No reaction. [d]HF/pyridine (70/30, w/w), 60 min, −10 °C. [e]HF/pyridine (70/30, w/w), 20 min, 20 °C. [f]24 h, rt.

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

Evaluation of the Fluoroenamine Mimetic Character. Besides their chemical stability, which clearly is a prerequisite for the potential use of fluorinated enamides as urea bioisosteres, we next focused our attention on getting further insights on the analogy between these two functional groups. With this goal in mind, theoretical calculations were carried out on selected and representative substituted ureas (urea **D1**, *N*-methylurea **D2**, *N*-*tert*-butylurea **D3**, and *N*-phenylurea **D4**) and their proposed isosteres.[48−50] As an initial evaluation of the ability for a fluoroenamine to mimic a urea, the comparison between the simplest existing models, urea **D1** and its fluoroenamine analogue **C1**, was first performed. Equilibrium structures and transition structures for internal rotations are depicted in Figure 2. Selected geometrical parameters, NBO charges, and free energies of solvation in water are reported in Table 4.

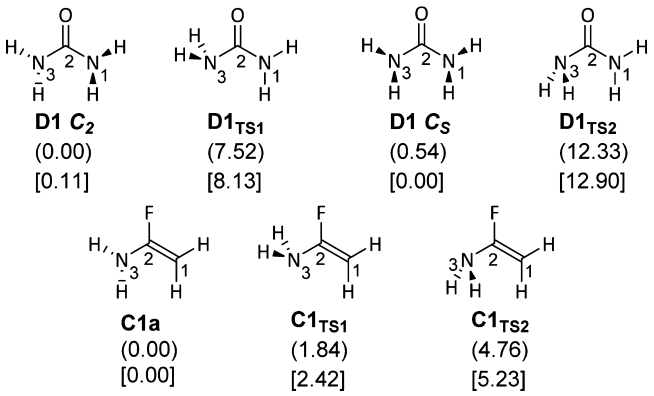


Figure 2. Equilibrium structures and internal rotation transition structures for urea **D1** and fluoroenamine **C1**. ZPE-corrected relative energies (kcal·mol^{-1}) are indicated in parentheses (MP2/cc-pVDZ) and in square brackets [B3LYP/cc-pVDZ].[51]

*Comparison of Urea **D1** and Its Fluoroolefin Mimic **C1**.* For urea **D1**, in accordance with recently reported calculations,[52−55] MP2 calculations led to the identification of two equilibrium structures and two transition states corresponding to internal rotations. The two minima of **D1** correspond to conformations in which the NH_2 groups are pyramidalized on opposite sides with C_2 symmetry (**D1** C_2) and on the same sides with C_s symmetry (**D1** C_s). The rotation around the C_2-N_3 urea bond breaks the conjugation, which must destabilize the resulting transition state, a result that is in agreement with reported data. Moreover, two transition structures were located owing to the two possible orientations of the nitrogen lone pair. Assuming that during rotation the inversion of the nitrogen atom occurs with a lower barrier height than the rotation around the C−N bond, the rotational barrier was calculated as the difference between the lowest transition structure and the lowest equilibrium structure (7.5 kcal mol^{-1} at the MP2/cc-pVDZ level). It has to be noted that similar optimized geometries and values were obtained by conducting calculations at the DFT level of theory.[51] For fluoroenamine **C1**, similar calculations led to the identification of one minimum **C1a** and two transition states $\mathbf{C1}_{TS1}$ and $\mathbf{C1}_{TS2}$. Going from **C1a** to $\mathbf{C1}_{TS1}$ through a rotation around the N_3-C_2 bond requires 1.84 kcal mol^{-1}. At this stage, it is noteworthy that rotation around the N_3-C_2 bond affect the stabilities of the conformers, this effect being smaller in the case of fluoroenamine compared to the corresponding urea. This variation of stabilities could be attributed to the absence of conjugation breaking in this case. It could also be envisaged that the nitrogen lone pair could participate to the stabilization of the transition state $\mathbf{C1}_{TS1}$ through an electron-density donation to the antibonding σ^*_{C-F} orbital.

Calculated geometrical parameters for the urea minima conformers were also shown to correlate well with the reported ones (Table 4), whatever the calculation methods used. For further comparison, charges derived from Mulliken population analyses and NBO charges have also been determined, the former calculations correlating well with the second but showing lower values.[51] Solvation free energies of ureas and their potent isosteres in aqueous phase were also determined by using an implicit solvation method and compared.[51] The comparison of the geometrical parameters of the simplest ureido derivative and its fluoroenamine hypothetical isostere was needed to evaluate the steric characteristics of the two, a special attention being paid to selected parameters, summarized in Table 4. For clarity, the following discussion will be focused on the data extracted from calculations at the MP2 level. Geometrical parameters and charges of the global minimum structures **D1** $\mathbf{C}_2$ and **D1** $\mathbf{C}_s$ can be compared to the fluoroenamine minimum **C1a** values (Figure 3). The results indicate that while the C−F bond (1.366 Å) is longer than the C═O bond (1.230 Å) and the C═C bond (1.347 Å) is shorter than the N_1-C_2 bond (1.394 Å), the N_3-C_2 bonds for urea and fluoroenamine are very close (1.394 and 1.392 Å). The angle $C_1{=}C_2{-}F$ (120.1°) is very close to the $N_1-C_2{=}O$ one (123.3°). However, the N_3-C_2-F angle (109.7°) is smaller than the $N_3-C_2{=}O$ angle (123.3°). The studied geometric values seem to indicate an overall steric similarity between urea **D1** and its analogous fluoroenamine **C1a**.

We were also particularly interested in comparing the electronic distribution between the atoms of the compared functions and thus especially to evaluate the ability to use these isosteres for synthetic purposes (H bond donor ability, original dipoles). The set of charges all depict larger charge separations between urea elements than for the fluoroenamine one. However, it is really interesting to note that the same trends are observed. Respective NBO charges are for example of −0.42 and −0.63 for the fluorine and carbon atom C_1 of the fluoroenamine, and the corresponding oxygen and nitrogen atom charge values for the urea are −0.76 and −0.94. In addition, the central carbon atom charge is positive in both cases (+1.06 for $\mathbf{D1C}_2$ and $\mathbf{D1C}_s$ and +0.75 for **C1a**), confirming an overall identical variation of charges. It is also worth noting that the substitution of the N−C═O by the fluoroolefin C═C−F did not impact the negative charge on the second nitrogen atom, the negative charge on N_3 being almost identical in **D1** (−0.94) and **C1** (−0.91). In addition, the vinylic hydrogen charge of +0.21 is close to the H_1 charge value in the urea (+0.39), and H_3 values were identical between fluoroenamine **C1a** (+0.39) and ureas $\mathbf{D1C}_2$ (+0.39) and $\mathbf{D1C}_s$ (+0.38), results which suggest a similar ability of the fluoroenamine to participate in hydrogen bonding.

To gain further insight into the evaluation of the ability of fluoroenamines to act as hydrogen-bonding donors and acceptors, the solvation free energies in the aqueous phase were calculated (ΔG_s, Table 4). As for urea **D1**, the solvation free energy of fluoroenamine **C1** was negative (−10.1 and −11.96 kcal mol^{-1} for $\mathbf{D1C}_2$ and $\mathbf{D1C}_s$ and −3.27 for **C1**), confirming the strong interactions between the ureas and water molecules and a similar, but lower, aptitude of fluoroenamine to be stabilized in a water environment.

This initial promising comparison between fluoroenamines and ureas prompted us to extend this study to substituted ureido analogues, especially considering the impact of the nitrogen

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

Table 4. Selected Geometric Parameters, Charges, and Energies of Solvation in the Aqueous Phase for Optimized Minima

	Geometric parameters					NBO Charges						ΔG_S (kcal.mol^{-1})
	Distances (Å)			Bond angles (°)								
In ***D***	N_1-C_2	C_2=O	N_3-C_2	N_1-C_2=O	N_3-C_2=O	O	C_2	N_1	N_3	H_1	H_3	
In **C**	C_1=C_2	C_2-F	N_3-C_2	C_1=C_2-F	N_3-C_2-F	F	C_2	C_1	N_3	H_1	H_3	
In **C'**	N_1-C_2	C_2-F	C_3=C_2	N_1-C_2-F	C_3=C_2-F	F	C_2	N_1	C_3	H_1	H_3	
Compound												
D1 C$_2$	*1.394*	*1.230*	*1.394*	*123.3*	*123.3*	*-0.76*	*+1.06*	*-0.94*	*-0.94*	*+0.39*	*+0.39*	*-10.01*
D1 C$_S$	*1.390*	*1.231*	*1.389*	*122.6*	*122.6*	*-0.76*	*+1.06*	*-0.93*	*-0.93*	*+0.38*	*+0.38*	*-11.96*
C1a	1.347	1.366	1.392	120.1	109.7	-0.42	+0.75	-0.63	-0.91	+0.21	+0.39	-3.27
D2$_{cis}$	*1.386*	*1.232*	*1.400*	*123.3*	*123.0*	*-0.76*	*+1.06*	*-0.80*	*-0.94*	*+0.39*	*+0.39*	*-9.31*
C2$_{cis}$	1.348	1.369	1.398	120.6	109.6	-0.42	+0.73	-0.40	-0.91	+0.21	+0.39	-3.02
C'2$_{cis}$	1.388	1.368	1.349	110.8	119.5	-0.42	+0.74	-0.77	-0.62	+0.39	+0.21	-2.46
D2$_{trans}$	*1.384*	*1.234*	*1.395*	*122.8*	*122.6*	*-0.77*	*+1.07*	*-0.79*	*-0.94*	*+0.41*	*+0.39*	*-9.67*
C2$_{trans}$	1.347	1.369	1.397	120.3	110.0	-0.42	+0.74	-0.41	-0.91	+0.22	+0.39	-3.18
C'2$_{trans}$	1.381	1.368	1.350	110.1	120.0	-0.42	+0.75	-0.77	-0.64	+0.39	+0.21	-2.42
D3$_{cis}$	*1.384*	*1.234*	*1.404*	*124.7*	*122.2*	*-0.77*	*+1.07*	*-0.82*	*-0.94*	*+0.39*	*+0.39*	*-7.97*
C3$_{cis}$	1.351	1.368	1.399	122.7	108.9	-0.42	+0.74	-0.41	-0.90	+0.21	+0.39	-2.43
C'3$_{cis}$	1.389	1.370	1.349	111.7	118.9	-0.42	+0.74	-0.79	-0.61	+0.39	+0.21	-2.56
D3$_{trans}$	*1.394*	*1.235*	*1.396*	*122.0*	*122.1*	*-0.76*	*+1.07*	*-0.82*	*-0.95*	*+0.40*	*+0.39*	*-7.94*
C3$_{trans}$	1.351	1.371	1.393	119.4	109.2	-0.42	+0.76	-0.43	-0.92	+0.23	+0.39	-3.46
C'3$_{trans}$	1.381	1.375	1.351	108.4	117.9	-0.42	+0.74	-0.79	-0.61	+0.39	+0.21	-1.31
D4$_{cis}$	*1.390*	*1.230*	*1.401*	*125.0*	*122.8*	*-0.76*	*+1.07*	*-0.77*	*-0.93*	*+0.41*	*+0.39*	*-8.46*
C4$_{cis}$	1.357	1.364	1.391	121.9	109.6	-0.42	+0.77	-0.42	-0.90	+0.22	+0.39	-4.03
C'4$_{cis}$	1.388	1.368	1.347	111.6	119.7	-0.41	+0.73	-0.76	-0.58	+0.41	+0.21	-2.00
D4$_{trans}$	*1.396*	*1.233*	*1.388*	*121.1*	*123.1*	*-0.76*	*+1.07*	*+0.78*	*-0.94*	*+0.42*	*+0.40*	*-7.80*
C4$_{trans}$	1.356	1.366	1.388	119.3	110.2	-0.41	+0.78	-0.44	-0.92	+0.24	+0.40	-3.93
C'4$_{trans}$	1.391	1.368	1.347	109.1	120.2	-0.42	+0.75	-0.76	-0.62	+0.41	+0.22	-2.82

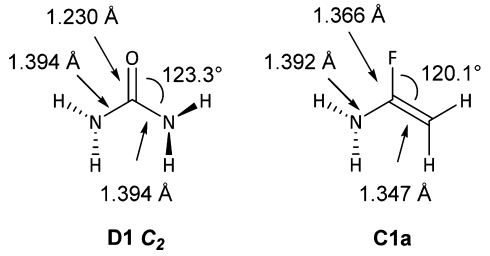


Figure 3. Comparison of geometrical parameters of urea **D1C$_2$** and fluoroenamine **C1a**.

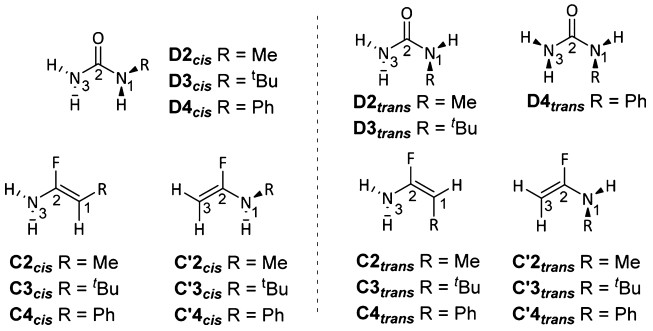


Figure 4. Compared optimized minima (MP2/cc-pVDZ) for ureas **D2**−**4** and fluoroenamine **C2**−**4** and **C′2**−**4**.

substituents on the conformational preference of the ureido derivatives.

*Comparison of Substituted Ureas **D2**−**4** and Fluorolefin Proposed Isosteres **C2**−**4**.* In this context, and by using the same procedures than the ones described above, conformational analyses, charges, and solvation free energies of methyl **D2**, *tert*-butyl **D3**, and phenyl ureas **D4** were compared to those of their fluoroenamine analogues **C2**, **C3**, and **C4** (Figure 4).

For the purpose of clarity, Figure 4 presents only the optimized minima obtained from MP2 calculations. It is also important to mention at this stage that equilibrium structures were identified for all the calculated ureas, and all the parameters of these species were found to be almost identical to the ones reported in the literature, with the substituent group pointing in the direction of the carbonyl group (*s-cis* derivative **Di$_{cis}$**) or in the opposite direction (*s-trans* derivative **Di$_{trans}$**). For substituted enamines (**Ci**), two families of potent mimics were calculated, the ones presenting the substituent located on the olefin (**Ci**) and the ones with the R group located on the nitrogen atom (**C′i**). In all cases, two minima were identified and called *cis* and *trans* (for derivatives **C′i**, the *cis* and *trans* terms refer to the orientation of the R group in the same direction than the C−F bond or opposite to this bond). In addition to these minima, transitions structures were also identified to connect to the minima.[51]

To focus on one significant derivative, the extrema of the MP2 rotational energy profile of the *tert*-butyl urea **D3** and of its fluoroenamine postulated isostere **C′3** was evaluated (Figure 5). For this urea derivative, the **D3$_{cis}$** conformer was shown to be more stable than its *trans* conformer by 2.93 kcal mol^{-1}, a result in accordance with the classically observed *cis*-preferred

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

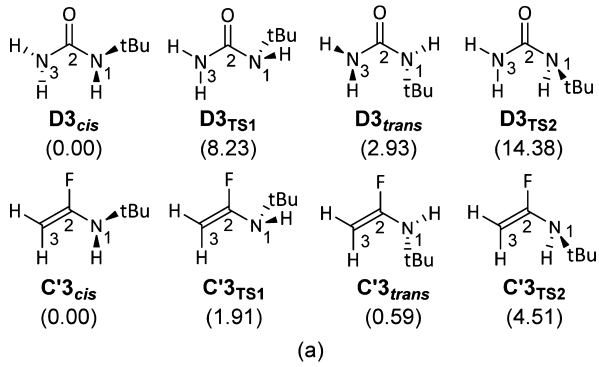


Figure 5. Equilibrium structures and internal rotation transition structures for urea **D3** and fluoroenamine **C′3**. ZPE corrected relative energies (kcal mol^{-1}) are indicated in brackets (MP2/cc-pVDZ).[51]

orientation of urea derivatives.[54,55] Two different transition states ($\mathbf{D3}_{TS1}$ and $\mathbf{D3}_{TS2}$) have also been identified to connect the two minima by rotation around the N_1-C_2 bond. This rotation from $\mathbf{D3}_{cis}$ gives rise to $\mathbf{D3}_{TS1}$ (relative energy of +8.23 kcal. mol^{-1}). A rotation from $\mathbf{D3}_{trans}$ leading to the same transition state requires 5.30 kcal mol^{-1} (Figure 5). It has to be noted that the effect of the substitution of the urea with a *tert*-butyl group is present but did only affect slightly the rotational energy profile (destabilization of the *trans* isomer). For the proposed fluoroenamine **C′3** mimic, four stable geometries were identified, two minima which are symmetrical and show similar parameters ($\mathbf{C'3}_{cis}$ and $\mathbf{C'3}_{trans}$) and two transition states $\mathbf{C'3}_{TS1}$ and $\mathbf{C'3}_{TS2}$. Going from $\mathbf{C'3}_{cis}$ to $\mathbf{C'3}_{TS1}$ through a rotation around the N_1-C_2 bond requires 1.91 kcal mol^{-1}. As for urea, it is interesting to note that rotation around the N_1-C_2 bond also affect the stability of the fluoroenamine, but has a lower impact. This can be attributed to the fact that compared to the urea, no conjugation is broken, in addition to the fact that the C−F bond is longer than the C═O one, the small fluorine atom therefore not sterically interacting with the alkyl group.

Calculated geometrical parameters for the urea minima conformers reported in Table 4 were also compared to the parameters of the proposed isosteres, and the following general comments can be extracted from the selected data:

For all the calculated geometries, the results indicate that the C═C bond of the fluoroolefin is shorter than the corresponding C−N bonds of the ureas and that the C−F bond is longer than the C═O bond. No effects of the substituents were observed. The N−C═O and C═C−F bond angles were shown to be very close for all of the calculated urea/fluoroenamine couples (around 120°). However, the comparison of the N−C═O to the corresponding N−C−F bond in the mimetic revealed a shorter angle regardless the relative stereochemistry of the fluoroalkene or the nature of the substituent.

Then, special attention was paid to the comparison of electronic distribution between ureas elements and fluoroenamine ones. As for the unsubstituted derivatives, a larger charge separation was observed for urea elements than for the proposed isosteres, but a similar trend was observed with the expected negative charges on fluorine atom and carbon C_1, as for O and N_1 in the ureas. Even more interesting was the similarity of the positive charges located on the hydrogen atoms, revealing a potential ability of the isosteres to act as hydrogen bond donor (Figure 6).

To further explore this aspect, the solvation free energies in the aqueous phase of the ureas and the fluoroenamines were

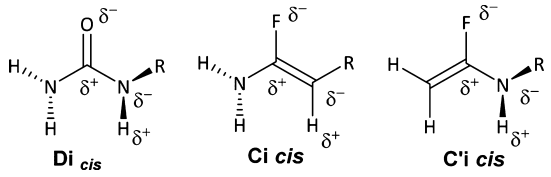


Figure 6. Polarization of urea **Di** and fluoroenamines **Ci** and **C′i**.

calculated and compared. First, solvation free energies show strong negative values for urea derivatives confirming the strong ability of ureas to interact with polarized molecules through hydrogen bonding. Then, it is noteworthy that the impact of the substitution of one hydrogen with an alkyl or aromatic group is dramatic for the solvation properties of the molecule. For the *cis* minima (with **D1*Cs*** as a reference), the ability to solvate water molecules decreases in the following order H > Me > Ph > ^{t}Bu with a variation of solvation free energies going from 2.65 to 3.99 kcal mol^{-1} (similar variation were obtained when calculations were performed at the DFT level).[51] For the *trans*-optimized geometries, the negative impact of the substituent is also predominant with a variation of solvation free energies going from 2.29 to 4.16 kcal mol^{-1}. However, it has to be noted that the impact of the phenyl and *tert*-butyl groups are similar for the *trans* ureas. This variation probably comes from the increase of the hydrophobicity of the molecule resulting of the addition of lipophilic alkyl chains, even if it could also be due to the removal of a hydrogen that could participate in a hydrogen bond. As already observed when comparing electronic distribution, similar trends can be highlighted by analyzing the solvation free energies of substituted fluoroenamines. The energies were shown to be lower than for ureas, a result which confirms that the proposed isosteres are less prone to solvation than their corresponding ureas. However, the observed substitution negative effect is smaller for fluoroenamines than for ureas. For the **C′i** isosteres the decrease of these energies goes from 0.81 to 1.27 kcal mol^{-1} for the *cis* derivatives and from 0.45 to 1.96 kcal mol^{-1} for the *trans* ones. It also has to be noted that for $\mathbf{C'i}_{cis}$ derivatives substituting a hydrogen with a phenyl group has the strongest impact. An original behavior of the **Ci** isosteres was also observed. When the negative impact of an additional substituent on the water solvation was also shown, and thus for *cis* and *trans* derivatives, for the phenyl substituted *cis* isomers, the substitution was in favor of an increase of the solvation enthalpies, a result which could probably come from electronic delocalization of the π electrons. More interestingly, comparing the solvation energies between **Ci** and **C′i** isosteres revealed a stronger ability of the **Ci** isosteres than the **C′i** ones to interact with water. The free NH bond available to act as hydrogen donor could account for this difference of behavior.

In light of these discussions, the following general remarks can be made. Structurally speaking, the fluoroenamine unit is found to be similar in terms of steric demand to an ureido unit. The charge distribution, as evaluated by calculating the NBO and Mulliken charges, in addition to the calculated solvation free energies indicate that the fluoroenamine moiety imparts the proper polarity to mimic that of a urea, with a lowest magnitude of charge separation. Evaluating the electronic deficiency on the hydrogen atoms also revealed interesting similarities between the substituted ureas and their proposed isosteres, similarities that could find interesting applications in term of hydrogen-bonding interactions, and thus especially considering the partial rigidity of the proposed isosteres.[4] To further explore this assumption, the

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

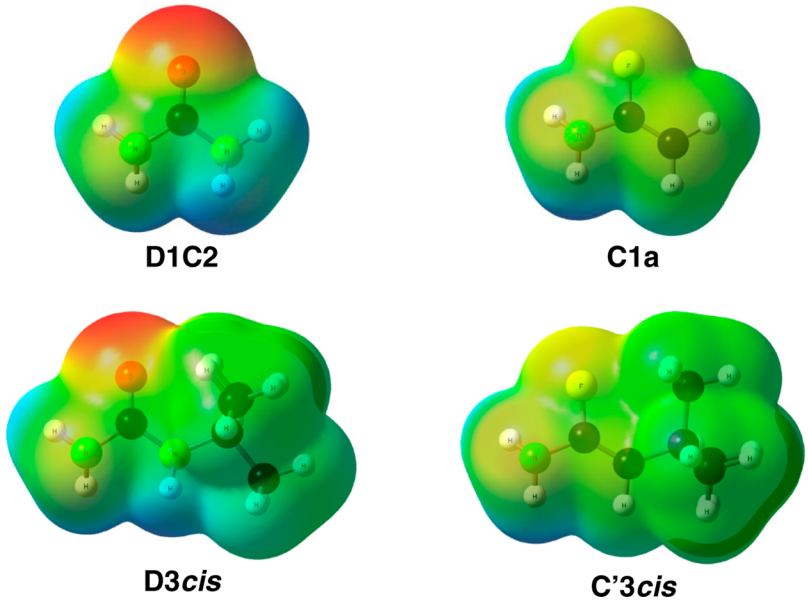


Figure 7. Electrostatic potential of the ureas **D1C2** and **D3cis** and their fluoroenamines isosteres **C1a** and **C′3cis** (color alteration from red to blue describes the shift of the electronically rich to deficient circumstance).

comparison of the electrostatic potential profiles was performed for ureas **D1*C2*** and **D3*cis*** and fluoroenamines **C1a** and **C′3*cis*** minima (Figure 7).

As already anticipated, the ureas have a very negative oxygen, a highly positive carbonyl carbon, and very positive NH hydrogens. The evaluated isosteres have an appropriately polarized C═C double bond, a negative fluorine atom in place of the oxygen atom of the urea, and a positive CH in place of one NH moiety of ureas, the enamide free NH_2 group showing close electronic distribution to the corresponding NH_2 group of the urea. Thus, the fluoroenamines indeed mimic the ureas electronically, with analogous continuous charge distribution.

Finally, the question remains to the overall effectiveness of the fluorenamines as ureido bioisosteres. It could be considered that there are a lot of effects that determine or influence the effect of a group to act as a bioisostere, and the ideal evaluation would come from bioactivities comparison of fluoroenamine-containing bioactive derivatives. However, in a pharmaceutical context where new molecular frameworks are needed,[56] this work sets the stage for further evaluation in this field. In addition, taking into account the similarity of charge distribution between the proposed isosteres and their ureido analogues, these results would find great interest in the field of homogeneous catalysis and organic synthesis, with the proposed synthetic procedure for the preparation of their analogues offering a straightforward access to these derivatives.

CONCLUSION

In conclusion, a new, improved procedure for the synthesis of α-fluoroenamides has been developed. This second-generation procedure displays a broader scope than the previously reported procedure on the basis of the use of neat HF, therefore circumventing the problem of handling pure HF superacid, and can be applied to the synthesis of *E* and *Z* isomers. These new conditions also allowed a better understanding of the mechanism of the hydrofluorination process and its substrate-dependent stereoselectivity. Stability studies and calculations tend to confirm that these new fluorinated building blocks could be exploited in SAR studies and could be used as potent isosteres of urea derivatives.

EXPERIMENTAL SECTION

Reactions performed in HF/pyridine media were carried out in a sealed Teflon flask with a magnetic stirrer. No further precautions have to be taken to keep the mixture from moisture (a test reaction performed in anhydrous conditions leads to the same results, as expected). Yields refer to isolated pure products. ^{1}H, ^{13}C, and ^{19}F NMR were recorded on a 400 MHz spectrometer using $CDCl_3$ as solvent. DEPT 135, COSY $^{1}H-^{1}H$, and $^{1}H-^{13}C$ experiments were used to confirm the NMR peaks assignments. Melting points were determined in a capillary tube. All separations were done under flash chromatography conditions on silica gel (15−40 μm). High-resolution mass spectra were obtained on a Qtof spectrometer. All reactions for ynamide synthesis were carried out in oven-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. Copper-catalyzed reactions were carried out in resealable pressure tubes. All solvents were reagent grade. 1,4-Dioxane was freshly distilled from sodium/benzophenone under argon and degassed immediately prior to use. Copper(I) iodide (99.999% purity) was purchased from Aldrich and used as supplied. Finely powdered cesium carbonate was used for copper-mediated coupling reactions. All other reagents were used as supplied. Unless otherwise noted, reactions were magnetically stirred and monitored by thin-layer chromatography using Merck-Kiesegel 60F254 plates. Flash chromatography was performed with silica gel 60 (particle size 35−70 μm) supplied by SDS. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext = sextuplet, sept = septuplet, m = multiplet, br = broad), integration, and coupling constant (*J*/Hz).

Procedure A: General Procedure for the Synthesis of Ynamides from 1,1-Dibromo-1-alkenes. A 15 mL pressure tube was charged with the sulfonamide, amide, or oxazolidinone (3.2 mmol, 1 equiv), the 1,1-dibromo-1-alkene (3.8 mmol, 1.2 equiv), Cs_2CO_3 (12.8 mmol, 4 equiv), and copper(I) iodide (0.4 mmol, 0.12 equiv). The tube was fitted with a rubber septum, evacuated under high vacuum, and backfilled with argon. Dry and degassed 1,4-dioxane or DMF (6 mL) and *N*,*N*′-dimethylethylenediamine (60 μL, 0.6 mmol, 0.18 equiv) were next added, the rubber septa was replaced by Teflon-coated screw cap, and the light blue-green suspension was heated at 80 °C for 1 or 2 days. The brownish suspension was cooled to rt. When the reaction was run in

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

1,4-dioxane, the crude reaction mixture was filtered over a plug of silica gel (washed with EtOAc) and concentrated. When the reaction was run in DMF, the crude reaction mixture was diluted with water and extracted with diethyl ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel.

*N-Benzyl-2-(thiophen-3-yl)-N-tosylethynamine (**1n**).* This compound was obtained from *N*-benzyl-*N*-tosylamine (846 mg, 3.2 mmol) and 3-(2,2-dibromovinyl)thiophene (1.04 g, 3.8 mmol) following general procedure A. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 90/10 as the eluent, thereby obtaining compound **1n** (1.03 g, 87%). Orange solid. Mp: 97.5−99.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.78 (d, 2 H, J = 8.3 Hz), 7.33−7.29 (m, 7 H), 7.27 (dd, 1 H, J = 3.0 Hz, J = 1.1 Hz), 7.27 (dd, 1 H, J = 3.0 Hz, J = 1.1 Hz), 7.20 (dd, 1 H, J = 5.0 Hz, J = 3.0 Hz), 6.95 (dd, 1 H, J = 5.0 Hz, J = 1.1 Hz), 4.57 (s, 2 H), 2.45 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 144.7, 134.9, 134.6, 130.2 (CH), 129.8 (CH), 128.9 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 125.2 (CH), 121.6, 82.1, 66.5, 55.8 (CH_2), 21.8 (CH_3). HRMS (Q-TOF, ES$^+$, CH_3CN): m/z calcd for $C_{20}H_{17}NO_2S_2$ [M + H]$^+$ 368.0779, m/z found 368.0777.

All other ynamides synthesized using this method were previously reported.[57]

Ynamide **1j** was prepared by copper-catalyzed cross-coupling between oxazolidinone and potassium (1-phenylethynyl) trifluoroborate and previously reported.[58]

Ynamides **1q** and **1r** were prepared by copper-catalyzed coupling reaction between alkynyl(triaryl)bismuthonium salts and five membered imides.[59]

Procedure B: General Procedure for the Synthesis of Fluoroenamides from Ynamides. To a mixture of hydrofluoric acid and pyridine (4 mL, 70/30 w/w) maintained at the required temperature was added the starting ynamide. The mixture was magnetically stirred at the same temperature during the required time. The reaction mixture was then neutralized with water−ice−sodium carbonate solution and extracted with dichloromethane (×3). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Products were isolated by column chromatography over silica gel.

*(E)-N-Benzyl-1-fluoro-2-phenyl-N-tosylethenamine (**2a**).* This compound was obtained from *N*-benzyl-2-phenyl-*N*-tosylethynamine (**1a**) (80 mg, 0.221 mmol) following general procedure B at −10 °C during 15 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 97/3 as the eluent, thereby obtaining compound **2a** (73 mg, 86%). White solid. Mp: 70−72 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.84 (d, 2 H, J = 8.1 Hz), 7.34 (m, 4 H), 7.27 (m, 3 H), 7.16 (m, 3 H), 7.08 (m, 2 H), 6.17 (d, 1 H, J = 8.7 Hz), 4.40 (s, 2 H), 2.48 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 147.0 (d, J = 273 Hz), 144.6, 136.0, 133.7, 131.2 (d, J = 8 Hz), 129.9 (2 CH), 129.5 (2 CH), 128.4 (9 CH), 128.0 (CH), 111.5 (d, CH, J = 42 Hz), 52.2 (CH_2), 21.8 (CH_3). ^{19}F {1H} NMR ($CDCl_3$, 376 MHz, ppm) δ: −87.13. HRMS (Q-TOF, ES$^+$, CH_3OH): m/z calcd for $C_{22}H_{20}FNO_2S$ [M + Na]$^+$ 404.1097, m/z found 404.1098.

*N-Benzyl-2-phenyl-N-tosylacetamide (**3a**).* This compound is the byproduct obtained when the reaction conditions are optimized. It was purified over silica gel with petroleum ether/ethyl acetate 95/5 as the eluent. White solid. Mp: 70−72 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.65 (d, 2 H, J = 8.4 Hz), 7.33 (m, 5 H), 7.25 (m, 5 H), 6.99 (dd, 2 H, J = 7.0 Hz, J = 2.5 Hz), 5.08 (s, 2 H), 3.87 (s, 2 H), 2.43 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 171.4, 145.1, 136.7, 136.7, 133.3, 129.8 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 127.3 (CH), 49.8 (CH_2), 43.0 (CH_2), 21.8 (CH_3). HRMS (ESI, CH_3OH): m/z calcd for $C_{22}H_{21}NO_3S$ [M + Na]$^+$ 402.1140, m/z found 402.1136.

*(E)-N-Benzyl-1-fluoro-2-(4-fluorophenyl)-N-tosylethenamine (**2b**).* This compound was obtained from ynamide **1b** (70 mg, 0.184 mmol) following the general procedure B at −10 °C during 15 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 97/3 as the eluent, thereby obtaining compound **2b** (63 mg, 85%). White solid. Mp: 107−109 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.84 (d, 2 H, J = 7.9 Hz), 7.34 (d, 2 H, J = 8.0 Hz), 7.28 (dd, 2 H, J = 8.6 Hz, J = 5.4 Hz), 7.15 (m, 5 H), 6.92 (dd, 2 H, J = 8.8 Hz, J = 8.8 Hz), 6.13 (d, 1 H, J = 8.6 Hz), 4.38 (s, 2 H), 2.46 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 162.4 (d, J = 248 Hz), 146.8 (d, J = 274 Hz), 144.7, 135.7, 133.5, 130.1 (dd, CH, J = 8 Hz, J = 4 Hz), 129.9 (CH), 129.5 (CH), 128.4 (5 CH), 127.2 (dd, J = 8 Hz, J = 3 Hz), 115.3 (d, CH, J = 22 Hz), 110.9 (d, CH, J = 42 Hz), 52.1 (CH_2), 21.7 (CH_3). ^{19}F {1H} NMR ($CDCl_3$, 376 MHz, ppm) δ: −113.51, −89.09. HRMS (ESI, CH_3OH): m/z calcd for $C_{22}H_{19}NO_2F_2S$ [M + H]$^+$ 400.1183, m/z found 400.1179.

*(E)-N-Benzyl-1-fluoro-N-tosylbut-1-en-1-amine (**2c**).* This compound was obtained from ynamide **1c** (84 mg, 0.267 mmol) following general procedure B at −10 °C during 15 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 92/8 as the eluent, thereby obtaining compound **2c** (37 mg, 42%). White solid. Mp: 74−75 °C. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.84 (d, 2 H, J = 8.3 Hz), 7.48 (d, 2 H, J = 8.0 Hz), 7.34 (m, 5 H), 5.13 (dd, 1 H, J = 7.7 Hz, J = 7.7 Hz), 4.40 (s, 2 H), 2.47 (s, 3 H), 1.78 (dqd, 2 H, J = 7.6 Hz, J = 7.6 Hz, J = 1.7 Hz), 0.61 (td, 3 H, J = 7.5 Hz, J = 0.9 Hz). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 146.9 (d, J = 267 Hz), 145.3, 137.4, 135.9, 130.8 (CH), 130.1 (CH), 129.3 (CH), 129.0 (CH), 128.6 (CH), 113.6 (d, CH_2, J = 32 Hz), 52.0 (CH_2), 21.5 (CH_3), 20.1 (d, CH_2, J = 4 Hz), 13.4 (d, CH_3, J = 3 Hz). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −99.15. HRMS (ESI, CH_3OH): m/z calcd for $C_{18}H_{20}NO_2FS$ [M + Na]$^+$ 356.1096, m/z found 356.1097.

*(E)-N-Benzyl-1-fluoro-N-tosyldec-1-en-1-amine (**2d**).* This compound was obtained from ynamide **1d** (52 mg, 0.130 mmol) following general procedure B at −10 °C during 15 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 96/4 as the eluent, thereby obtaining compound **2d** (25 mg, 46%). White solid. Mp: 40−42 °C. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.84 (d, 2 H, J = 8.2 Hz), 7.48 (d, 2 H, J = 8.5 Hz), 7.34 (m, 5 H), 5.16 (dd, 1 H, J = 7.7 Hz, J = 7.7 Hz), 4.41 (s, 2 H), 2.47 (s, 3 H), 1.76 (dtd, 2 H, J = 7.9 Hz, J = 7.9 Hz, J = 1.7 Hz), 1.11−1.36 (m, 8 H), 1.05 (m, 2 H), 0.92 (m, 2 H), 0.89 (t, 3 H, J = 7.1 Hz). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 147.1 (d, J = 267 Hz), 145.3, 137.4, 135.9, 130.8 (CH), 130.2 (CH), 129.3 (CH), 129.0 (CH), 128.6 (CH), 112.3 (d, CH, J = 32 Hz), 52.0 (CH_2), 32.6 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.5 (d, CH_2, J = 2 Hz), 26.8 (d, CH_2, J = 3 Hz), 23.3 (2 CH_2), 21.5 (CH_3), 14.4 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −98.44. HRMS (ESI, CH_3OH): m/z calcd for $C_{24}H_{32}NO_2FS$ [M + Na]$^+$ 440.2035, m/z found 440.2031.

*N-((E)-1-Fluoro-2-phenylvinyl)-N-tosylprop-2-en-1-amine (**2e**).* This compound was obtained from ynamide **1e** (80 mg, 0.257 mmol) following general procedure B at −10 °C during 5 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 95/5 as the eluent, thereby obtaining compound **2e** (69 mg, 81%). White solid. Mp: 52−53 °C. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.81 (d, 2 H, J = 7.9 Hz), 7.55 (d, 2 H, J = 7.1 Hz), 7.26−7.36 (m, 5 H), 6.29 (d, 1 H, J = 8.5 Hz), 5.63 (tdd, 1 H, J = 17.0 Hz, J = 10.1 Hz, J = 6.7 Hz), 5.12 (dd, 1 H, J = 16.6 Hz, J = 2.3 Hz), 5.08 (dd, 1 H, J = 10.1 Hz, J = 2.2 Hz), 3.91 (d, 2 H, J = 6.9 Hz), 2.44 (s, 3 H). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 147.2 (d, J = 275 Hz), 144.6, 135.9, 131.4 (d, J = 8 Hz), 130.8 (CH), 129.8 (CH), 128.7 (CH), 128.5 (d, 2CH, J = 4 Hz), 128.3 (CH), 128.2 (CH), 120.6 (CH_2), 111.3 (d, CH, J = 42 Hz), 51.4 (d, CH_2, J = 2 Hz), 21.7 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −85.58. HRMS (ESI, CH_3OH): m/z calcd for $C_{18}H_{18}NO_2FS$ [M + Na]$^+$ 354.0940, m/z found 354.0934.

*(3E)-N-Benzyl-1-fluoro-4-phenyl-N-dien-1-amine (**2f**).* This compound was obtained from ynamide **1f** (33 mg, 0.085 mmol) following general procedure B at 0 °C during 2 h. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 95/5 as the eluent, thereby obtaining compound **2f** (16 mg, 46%). White solid. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.88 (d, 2 H, J = 8.3 Hz), 7.85 (d, 2 H, J = 8.4 Hz), 7.20−7.53 (m, 12 H), 6.83 (ddd, 1 H, J = 15.9 Hz, J = 10.9 Hz, J = 1,0 Hz), 6.62 (d, 1 H, J = 15.9 Hz), 6.50 (d, 1 H, J = 15.8 Hz), 6.32 (ddd, 1 H, J = 15.8 Hz, J = 10.8 Hz, J = 1.1 Hz), 6.04 (ddd, 1 H, J = 10.8 Hz, J = 5.1 Hz, J = 0.5 Hz), 5.64 (ddd, 1 H, J = 27.2 Hz, J = 10.9 Hz, J = 0.5 Hz), 4.60 (s, 2 H), 4.59 (s, 2 H), 2.48 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 149.1 (d, J = 276 Hz), 147.7 (d, J =

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

280 Hz), 145.7, 145.5, 137.8, 137.6, 137.3, 136.9, 136.2, 135.9, 134.8 (d, CH, J = 4 Hz), 134.4 (d, CH, J = 11 Hz), 130.9 (CH), 130.9 (CH), 130.1 (CH), 129.5 (CH), 129.5 (CH), 129.4 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.4 (CH), 127.2 (CH), 122.2 (d, CH, J = 4 Hz), 120.3 (d, CH, J = 1 Hz), 113.0 (d, CH, J = 40 Hz), 111.4 (d, CH, J = 25 Hz), 53.0 (CH_2), 52.6 (CH_2), 21.5 (CH_3), 21.5 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −94.53 (d, J = 27.3 Hz), −92.84 (d, J = 4.8 Hz). HRMS (ESI, CH_3OH): m/z calcd for $C_{24}H_{22}NO_2FS$ $[M + H]^+$ 408.1428, m/z found 408.1436.

*N-((E)-1-Fluoro-2-phenylvinyl)-N-tosylpropan-1-amine (**2g**).* This compound was obtained from ynamide **1g** (105 mg, 0.336 mmol) following general procedure B at −10 °C during 1 h. The crude reaction mixture was purified over silica gel with the eluent petroleum ether/ethyl acetate 96/4 as the eluent, thereby obtaining compound **2g** (25 mg, 22%). Light yellow oil. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.83 (d, 2 H, J = 8.0 Hz), 7.64 (m, 2 H), 7.46 (d, 2 H, J = 8.6 Hz), 7.36 (m, 2 H), 7.30 (m, 1 H), 6.44 (d, 1 H, J = 8.9 Hz), 3.27 (td, 2 H, J = 7.6 Hz, J = 1.7 Hz), 2.45 (s, 3 H), 1.48 (tq, 2 H, J = 7.6 Hz, J = 7.4 Hz), 0.76 (t, 3 H, J = 7.4 Hz). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 148.4 (d, J = 273 Hz), 145.5, 137.0, 132.5 (d, J = 8 Hz), 130.7 (CH), 129.3 (d, CH, J = 4 Hz), 129.3 (CH), 128.9 (3 CH), 111.8 (d, CH, J = 43 Hz), 50.9 (CH_2), 21.9 (CH_2), 21.5 (CH_3), 11.4 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −86.35. HRMS (ESI, CH_3OH): m/z calcd for $C_{18}H_{20}NO_2FS$ $[M + Na]^+$ 356.1097, m/z found 356.1092.

*Compounds **2h**.* These compounds were obtained from ynamide **1h** (108 mg, 0.298 mmol) following general procedure B at −20 °C during 20 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 85/15 as the eluent, thereby obtaining compounds **2h** (90 mg, 79%). The isomers can be separated through a subsequent flash chromatography with eluent petroleum ether/CH_2Cl_2/MeOH 50/48/2 as the eluent.

*(E)-N-Benzyl-1-fluoro-2-(pyridin-3-yl)-N-tosylethenamine (**2h-E**).* Light brown solid. Mp: 89−92 °C. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 8.48 (d, 1 H, J = 2.1 Hz), 8.40 (dd, 1 H, J = 4.8 Hz, J = 1.6 Hz), 7.88 (d, 2 H, J = 8.0 Hz), 7.79 (ddd, 1 H, J = 8.0 Hz, J = 1.7 Hz, J = 0.5 Hz), 7.49 (d, 2 H, J = 8.6 Hz), 7.18 (m, 6 H), 6.31 (d, 1 H, J = 8.3 Hz), 4.48 (s, 2 H), 2.47 (s, 3 H). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 150.4 (d, CH, J = 4 Hz), 149.6 (CH), 148.9 (d, J = 276 Hz), 145.9, 136.6, 135.2 (d, CH, J = 3 Hz), 134.6, 130.9 (CH), 130.4 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.4 (d, J = 8 Hz), 123.8 (CH), 109.5 (d, CH, J = 44 Hz), 52.7 (CH_2), 21.5 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −87.08. HRMS (ESI, CH_3OH): m/z calcd for $C_{21}H_{19}N_2O_2FS$ $[M + H]^+$ 383.1230, m/z found 383.1229.

*(Z)-N-Benzyl-1-fluoro-2-(pyridin-3-yl)-N-tosylethenamine (**2h-Z**).* White solid. Mp: 135−137 °C. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 8.52 (d, 1 H, J = 2.0 Hz), 8.44 (dd, 1 H, J = 4.8 Hz, J = 1.5 Hz), 7.88 (d, 2 H, J = 8.3 Hz), 7.77 (dd, 1 H, J = 8.0 Hz, J = 1.8 Hz), 7.52 (d, 2 H, J = 8.6 Hz), 7.33 (m, 6 H), 5.82 (d, 1 H, J = 30.3 Hz), 4.64 (d, 2 H, J = 0.8 Hz), 2.49 (s, 3 H). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 150.5 (d, CH, J = 7 Hz), 149.7 (CH), 149.1 (d, J = 282 Hz), 145.7, 136.7, 136.1, 135.9 (d, CH, J = 9 Hz), 131.0 (CH), 129.6 (CH), 129.4 (CH), 129.1 (d, J = 5 Hz), 129.0 (CH), 128.7 (2CH), 124.4 (CH), 107.6 (d, CH, J = 22 Hz), 52.9 (CH_2), 21.5 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −87.08. HRMS (ESI, CH_3OH): m/z calcd for $C_{21}H_{19}N_2O_2FS$ $[M + H]^+$: 383.1230, m/z found 383.1229.

*Compounds **2i**.* These compounds were obtained from ynamide **1i** (103 mg, 0.285 mmol) following general procedure B at −20 °C during 20 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 85/15 as the eluent, thereby obtaining compounds ***2i-E*** (17 mg, 16%) and **2i-*Z*** (74 mg, 68%).

*(E)-N-Benzyl-1-fluoro-2-(pyridin-2-yl)-N-tosylethenamine (**2i-E**).* Beige solid. Mp: 73−76 °C. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 8.34 (dm, 1 H, J = 4.8 Hz), 7.83 (d, 2 H, J = 8.3 Hz), 7.64 (ddd, 1 H, J = 7.8 Hz, J = 7.8 Hz, J = 1.8 Hz), 7.53 (d, 2 H, J = 8.0 Hz), 7.40 (d, 2 H, J = 8.5 Hz), 7.23 (m, 5 H), 7.15 (ddd, 1 H, J = 7.4 Hz, J = 4.8 Hz, J = 0.9 Hz), 6.30 (d, 1 H, J = 8.4 Hz), 4.67 (d, 2 H, J = 1.9 Hz), 2.44 (s, 3 H). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 152.1 (d, J = 12 Hz), 150.7 (d, J = 274 Hz), 150.0 (CH), 145.4, 137.4, 136.8 (CH), 135.6, 130.6 (CH), 130.1 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 124.0 (d, CH, J = 4 Hz), 123.0 (CH), 112.1 (d, CH, J = 43 Hz), 53.5 (CH_2), 21.5 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −78.64. HRMS (ESI, CH_3OH): m/z calcd for $C_{21}H_{19}N_2O_2FS$ $[M + H]^+$ 383.1230, m/z found 383.1233.

*(Z)-N-Benzyl-1-fluoro-2-(pyridin-2-yl)-N-tosylethenamine (**2i-Z**).* Brown solid. Mp: 118−121 °C. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 8.50 (dm, 1 H, J = 4.8 Hz), 7.88 (d, 2 H, J = 8.4 Hz), 7.71 (ddd, 1 H, J = 7.8 Hz, J = 7.8 Hz, J = 1.8 Hz), 7.54 (d, 1 H, J = 8.0 Hz), 7.50 (d, 2 H, J = 8.5 Hz), 7.39 (m, 2 H), 7.34 (m, 2 H), 7.28 (m, CH), 7.20 (dd, 1 H, J = 7.5 Hz, J = 4.8 Hz), 5.87 (d, 1 H, J = 29.9 Hz), 4.69 (s, 2 H), 2.47 (s, 3 H). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 152.5 (d, J = 8 Hz), 150.4 (CH), 149.8 (d, J = 285 Hz), 145.7, 137.2 (CH), 136.7, 136.1, 130.9 (CH), 129.5 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 124.3 (d, CH, J = 13 Hz), 123.3 (CH), 111,6 (d, CH, J = 20 Hz), 52.9 (CH_2), 21.5 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −84.70. HRMS (ESI, CH_3OH): m/z calcd for $C_{21}H_{19}N_2O_2FS$ $[M + H]^+$ 383.1230, m/z found 383.1232.

*3-((E)-1-Fluoro-2-phenylvinyl)oxazolidin-2-one (**2j**).* This compound was obtained from ynamide **1j** (100 mg, 0.534 mmol) following general procedure B at −20 °C during 5 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 80/20 as the eluent, thereby obtaining compound **2j** (99 mg, 89%). White solid. Mp: 57−59 °C. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.37 (m, 4 H), 7.27 (t, 1 H, J = 6.9 Hz), 6.34 (d, 1 H, J = 8.6 Hz), 4.57 (dd, 1 H, J = 8.6 Hz, J = 7.2 Hz), 3.97 (ddd, 2 H, J = 9.4 Hz, J = 7.2 Hz, J = 2.7 Hz). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 155.5 (d, J = 3 Hz), 147.5 (d, J = 263 Hz), 132.6 (d, J = 8 Hz), 129.5 (CH), 128.8 (d, CH, J = 4 Hz), 128.5 (CH), 107.5 (d, CH, J = 40 Hz), 64.1 (CH_2), 44.7 (d, CH_2, J = 2 Hz). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −92.38. HRMS (ESI, CH_3OH): m/z calcd for $C_{11}H_{10}NO_2F$ $[M + H]^+$ 208.0774, m/z found 208.0779.

*(E)-N-Benzyl-1-fluoro-2-(4-cyano)phenyl-N-tosylethenamine (**2k**).* This compound was obtained from ynamide **1k** (96 mg, 0.248 mmol) following general procedure B at 0 °C during 30 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 90/10 as the eluent, thereby obtaining compound **2k** (28 mg, 28%). Pale yellow visquous solid. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.82 (d, 2 H, J = 7.9 Hz), 7.48 (d, 2 H, J = 8.4 Hz), 7.36 (m, 4 H), 7.15 (m, 5 H), 6.15 (d, 1 H, J = 8.0 Hz), 4.36 (s, 2 H), 2.48 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 148.6 (d, J = 279 Hz), 145.1, 136.3 (d, J = 9 Hz), 135.4, 133.1, 132.0 (CH), 130.1 (CH), 129.7 (CH), 128.9 (d, CH, J = 4 Hz), 128.7 (CH), 128.6 (CH), 128.4 (CH), 118.9, 111.3, 110.9 (d, CH, J = 43 Hz), 52.2 (CH_2), 21.8 (CH_3). ^{19}F {1H} NMR ($CDCl_3$, 376 MHz, ppm) δ: −84.82. HRMS (ESI, CH_3OH): m/z calcd for $C_{23}H_{19}N_2O_2FS$ $[M + H]^+$ 407.1230, m/z found 407.1227.

*(Z)-N-Benzyl-1-fluoro-2-(9-anthracyl)-N-tosylethenamine (**2l**).* This compound was obtained from ynamide **1l** (81 mg, 0.176 mmol) following general procedure B at 0 °C during 1h. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 92/8 as the eluent, thereby obtaining compound **2l** (9 mg, 10%). White viscous solid. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.37 (s, 1 H), 7.92 (d, 2 H, J = 8.5 Hz), 7.90 (d, 2 H, J = 8.3 Hz), 7.58 (d_{broad}, 2 H, J = 8.6 Hz), 7.50 (m, 5 H) 7.42 (tm, 2 H, J = 7.2 Hz), 7.34 (tm, 4 H, J = 8.1 Hz), 6.48 (d, 1 H, J = 29.2 Hz), 4.61 (s, 2 H), 2.42 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 146.7 (d, J = 280 Hz), 144.6, 135.8, 134.5, 131.3, 130.1 (CH), 129.9 (CH), 129.8, 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.4 (CH), 126.0 (CH), 125.9 (CH), 125.3 (CH), 108.5 (d, J = 28 Hz), 51.6 (CH_2), 21.8 (CH_3). ^{19}F {1H} NMR ($CDCl_3$, 376 MHz, ppm) δ: −92.23. HRMS (ESI, CH_3OH): m/z calcd for $C_{30}H_{24}NO_2FS$ $[M + H]^+$ 482.1590, m/z found 482.1589.

*(Z)-N-Benzyl-1-fluoro-2-(2-thiofuranyl)-N-tosylethenamine (**2m**).* These compounds were obtained from ynamide **1m** (100.4 mg, 0.274 mmol) following general procedure B at −20 °C during 1 h. The crude reaction mixture was purified over silica gel with petroleum ether/diethylamine 95/5 as the eluent, thereby obtaining compounds **2m** (55.9 mg, 53%). Only the main isomer ***Z*** is described. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.77 (d, 2 H, J = 8.3 Hz), 7.36−7.26 (m, 8 H), 7.01 (d_{broad}, 1 H, J = 3.5 Hz), 6.98−6.94 (m, 1 H), 5.96 (d, 1 H, J = 29.4 Hz), 4.54 (s, 2 H), 2.46 (s, 3 H). For the *E* isomer, among others: 6.38 (d, 1 H, J = 6.2 Hz). ^{19}F {1H} NMR ($CDCl_3$, 376 MHz,

DOI: 10.1021/jo502699y
J. Org. Chem. 2015, 80, 3397−3410

ppm) δ: −91.37. For the *E* isomer, among others: −93.15. HRMS (Q-TOF, ES$^+$, CH_3OH): *m*/*z* calcd for $C_{20}H_{18}FNO_2S_2$ $[M + H]^+$ 388.0841, *m*/*z* found 388.0847.

*N-Benzyl-1-fluoro-2-(3-thiofuranyl)-N-tosylethenamine (**2n**).* This compound was obtained from ynamide **1n** (83.7 mg, 0.228 mmol) following general procedure B at 0 °C during 1 h. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 90/10 as the eluent, thereby obtaining compound **2n** (29.8 mg, 34%), which is a mixture of *E* and *Z* isomers. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.84 (d, 0.56 H, *J* = 8.1 Hz), 7.78 (d, 1.44 H, *J* = 8.3 Hz), 7.34 (d, 2 H, *J* = 8.1 Hz), 7.32−7.11 (m, 8 H), 6.20 (d, 0.28 H, *J* = 7.6 Hz), 5.74 (d, 0.72 H, *J* = 30.0 Hz), 4.53 (s, 1.44 H), 4.39 (s, 0.56 H), 2.46 (s, 3 H). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 144.3, 144.2, 136.9, 136.7, 134.7, 133.5, 132.7 (d, *J* = 7 Hz), 131.8 (d, *J* = 8 Hz), 130.1 (CH), 129.8 (CH), 129.7 (CH), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 125.4 (CH), 125.3 (CH), 124.9 (CH), 124.5 (CH), 106.9 (d, CH, *J* = 43 Hz), 105.5 (d, CH, *J* = 24 Hz), 52.0 (CH_2), 51.7 (CH_2), 21.6 (CH_3). ^{19}F {1H} NMR ($CDCl_3$, 376 MHz, ppm) δ: −92.69, −92.78. HRMS (Q-TOF, ES$^+$, CH_3OH): *m*/*z* calcd for $C_{20}H_{18}FNO_2S_2$ $[M + H]^+$ 388.0841, *m*/*z* found 388.0847.

*(Z)-N-Benzyl-1-fluoro-2-(2,6-dimethylphenyl)-N-tosylethenamine (**2o**).* This compound was obtained from ynamide **1o** (80 mg, 0.226 mmol) following general procedure B at 0 °C during 2 h. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 95/5 as the eluent, thereby obtaining compound **2o** (53 mg, 63%). White viscous solid. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.83 (d, 2 H, *J* = 8.3 Hz), 7.34 (m, 7 H) 7.04 (t, 1 H, *J* = 7,5 Hz), 6.94 (d, 2 H, *J* = 7.5 Hz), 5.70 (d, 1 H, *J* = 30.5 Hz), 4.52 (s, 2 H), 2.46 (s, 3 H), 1.97 (s, 6 H). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 146.7 (d, *J* = 276 Hz), 145.5, 137.5, 137.0, 136.0, 131.0 (d, *J* = 3 Hz), 130.9 (CH), 129.9 (CH), 129.5 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 109.9 (d, CH, *J* = 29 Hz), 52.5 (CH_2), 21.5 (CH_3), 20.2 (CH_3). ^{19}F {1H} NMR ($CDCl_3$, 376 MHz, ppm) δ: −93.34. HRMS (ESI, CH_3OH): *m*/*z* calcd for $C_{24}H_{24}NO_2FS$ $[M + H]^+$ 410.1590, *m*/*z* found 410.1587.

*(E)-N-Benzyl-1-fluoro-2-(2-methylphenyl)-N-tosylethenamine (**2p**).* This compound was obtained from ynamide **1p** (100 mg, 0.266 mmol) following general procedure B at −10 °C during 10 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 95/5 as the eluent, thereby obtaining compound **2p** (86 mg, 82%). White viscous solid. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.80 (d, 2 H, *J* = 8.0 Hz), 7.42 (m, 1 H) 7.32 (d, 2 H, *J* = 8.0 Hz), 7.15 (m, 5 H), 7.03 (m, 1 H), 6.90 (m, 2 H), 6.21 (d, 1 H, *J* = 8.3 Hz), 4.28 (s, 2 H), 2.46 (s, 3 H), 1.93 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 147.4 (d, *J* = 272 Hz), 144.5, 136.6 (d, *J* = 4 Hz), 135.9, 133.7, 130.2 (d, *J* = 8 Hz), 129.8 (CH), 129.6 (CH), 129.2 (CH), 128.5 (CH), 128.4 (2 CH), 128.3 (CH), 128.2 (CH), 126.0 (CH), 109.2 (d, CH, *J* = 40 Hz), 52.1 (CH_2), 21.8 (CH_3), 19.9 (CH_3). ^{19}F {1H} NMR ($CDCl_3$, 376 MHz, ppm) δ: −86.69. HRMS (ESI, CH_3OH): *m*/*z* calcd for $C_{23}H_{22}NO_2FS$ $[M + H]^+$ 396.1428, *m*/*z* found 396.1428.

*Compounds **2q**.* These compounds were obtained from ynamide **1q** (33.8 mg, 0.149 mmol) following general procedure B at −10 °C during 1 h. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 92/8 as the eluent, thereby obtaining compounds **2q-*E*** (24 mg, 66%) and **2q-*Z*** (12 mg, 34%).

*2-((E)-1-Fluorohex-1-enyl)isoindoline-1,3-dione (**2q-E**).* White solid. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.97−7.94 (m, 2 H), 7.84−7.80 (m, 2 H), 5.62 (d, 1 H, *J* = 7.9 Hz), 1.90 (qd, 2 H, *J* = 7.6 Hz, J = 1.9 Hz), 1.43−1.35 (m, 2 H), 1.32−1.24 (m, 2 H), 0.84 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 165.5, 165.4, 139.9 (d, *J* = 260 Hz), 135.1 (CH), 131.7, 124.5 (CH), 110.9 (d, CH, *J* = 26 Hz), 31.2 (CH_2), 25.3 (d, CH_2, *J* = 3 Hz), 22.3 (CH_2), 13.9 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −93.67. HRMS (Q-TOF, ES$^+$, CH_3OH): *m*/*z* calcd for $C_{14}H_{14}FNO_2$ $[M + H]^+$ 248.1087, *m*/*z* found 248.1087.

*2-((Z)-1-Fluorohex-1-enyl)isoindoline-1,3-dione (**2q-Z**).* White solid. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.95−7.92 (m, 2 H), 7.82−7.78 (m, 2 H), 5.01 (dt, 1 H, *J* = 28.9 Hz, J = 7.7 Hz), 2.31 (qd, 2 H, *J* = 7.3 Hz, *J* = 2.4 Hz), 1.53−1.37 (m, 4 H), 0.94 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 165.8, 165.8, 139.5 (d, *J* = 263 Hz), 135.0 (CH), 131.6, 124.3 (CH), 111.2 (d, CH, *J* = 23 Hz), 31.1 (CH_2), 24.1 (CH_2), 22.3 (CH_2), 13.9 (CH_3). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −98.60. HRMS (Q-TOF, ES$^+$, CH_3OH): *m*/*z* calcd for $C_{14}H_{14}FNO_2$ $[M + H]^+$ 248.1087, *m*/*z* found 248.1089.

*2-((E)-1-Fluoro-2-phenylvinyl)isoindoline-1,3-dione (**2r**).* This compound was obtained from ynamide **1r** (22.2 mg, 0.090 mmol) following general procedure B at −10 °C during 1 h. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 80/20 as the eluent, thereby obtaining compound **2r** (7 mg, 30%). White solid. ^{1}H NMR (C_3D_6O, 400 MHz, ppm) δ: 7.96−7.93 (m, 2 H), 7.84−7.81 (m, 2 H), 7.24−7.16 (m, 5 H), 7.73 (d, 1 H, *J* = 8.1 Hz). ^{13}C NMR (C_3D_6O, 100 MHz, ppm) δ: 165.3, 165.2, 140.6 (d, *J* = 265 Hz), 135.2 (CH), 131.6, 131.1 (d, *J* = 7 Hz), 128.9 (CH), 128.3 (CH), 127.7 (d, CH, *J* = 4 Hz), 124.7 (CH), 112.3 (d, CH, *J* = 34.0 Hz). ^{19}F {1H} NMR (C_3D_6O, 376 MHz, ppm) δ: −87.61. HRMS (Q-TOF, ES$^+$, CH_3OH): *m*/*z* calcd for $C_{16}H_{10}FNO_2$ $[M + H]^+$ 268.0774, *m*/*z* found 268.0768.

*N-Benzyl-1,1-difluoro-2-(pyridin-2-yl)-N-tosylethanamine (**4**).* This compound was obtained from (*Z*)-*N*-benzyl-1-fluoro-2-(pyridin-2-yl)-*N*-tosylethenamine (**2i-*Z***) (7.5 mg, 0.020 mmol) following general procedure B, at +20 °C during 20 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate 80/20 as the eluent, thereby obtaining compound **4** (7.3 mg, 93%). White viscous solid. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.50 (d, 1 H, *J* = 4.1 Hz), 7.64−7.58 (m, 3 H), 7.33 (d, 1 H, *J* = 7.7 Hz), 7.23−7.15 (m, 8 H), 4.51 (s, 2 H) 3.85 (t, 2 H, *J* = 15.3 Hz), 2.40 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 152.4 (t, *J* = 3 Hz), 149.4 (CH), 144.0, 137.5, 137.5, 136.4 (CH), 129.5 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 125.4 (CH), 122.5 (CH), 49.5 (CH_2), 46.5 (t, CH_2, *J* = 30 Hz), 21.5 (CH_3). Due to low stability of the compound **4**, long time carbon NMR acquisition could not have been performed, and so the carbons of CF_2 group did not appear. ^{19}F {1H} NMR ($CDCl_3$, 376 MHz, ppm) δ: −71.41. HRMS (Q-TOF, ESI, CH_3CN): *m*/*z* calcd for $C_{21}H_{20}F_2N_2O_2S$ $[M + H]^+$ 403.1286, *m*/*z* found 403.1286.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Cartesian coordinates and energies (hartrees) for the MP2/cc-pVDZ- and B3LYP/cc-pVDZ-optimized geometries and ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Université Libre de Bruxelles, the Université de Poitiers, the Université de Versailles, the CNRS, and the ANR (project VINFLUSUP ANR-11-JS07-003-01) for financial support. B.M., G.C., and K.J., respectively, acknowledge the ANR, the Région Poitou-Charentes, and the University of Versailles for graduate fellowships. We also deeply thank Prof. Sueda for a generous gift of ynimides.

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