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A novel base-mediated intramolecular hydroamination to build fused heteroaryl pyrazinones

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ABSTRACT

Functionalized fused heteroaryl pyrazinones were built up through a novel DBU-catalyzed intramolecular hydroamination reaction of aryl(prop-2-yn-1-yl)-1*H*-heteroaryl-2-carboxamides. The nucleophilic addition afforded three isomers; two with an *exo*-cyclic double bond [cis (*Z*), trans (*E*)], and a third one with an *endo*-cyclic double bond. After the carboxamide deprotection, isomerization of the mixture under acidic conditions resulted in a unique isomer.

The catalytic hydroamination of C–C multiple bonds has been extensively explored in organic chemistry for being a very powerful and atom-efficient method to create C–N bonds.[1] The intramolecular version of this reaction generates, in a straightforward manner, nitrogen-containing heterocycles, which are key intermediates for the syntheses of biologically active substances, dyes, and fine chemicals. The wide number of methods (catalytic and non-catalytic ones) reported in the literature for this transformation reflects its synthetic value.[2] In general, they involve the presence of alkali metals (Li, K), early or late transition metals (Sc,[3] Ti, Zr, Pd,[4] Au,[5] Ru,[6] Zn[7]), and lanthanide complexes.[8] Non-metal assisted procedures have been published as well, intermolecular hydroaminations were described with strong inorganic bases (e.g., CsOH, KOH),[9a,b] while TBAF has been used to synthesize γ-lactams from carboxamides containing electron-deficient triple bonds.[9c]

All these synthetic approaches are substrate-dependent, and a general and simple method is lacking. Herein, we present a novel and robust methodology to obtain new 5,6-bicyclic systems by a simple base-catalyzed intramolecular hydroamination of a wide range of *NH*-heterocycle-containing alkynes.

As part of a medicinal chemistry project, we needed a general and rapid synthetic method amenable to synthesize diversely substituted 4-benzylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones. The only literature precedent was by Becalli et al., who described a hydroamination/cyclization reaction using a Pd(II) catalyst to synthesize the *N*-alkyl-pyrrolo[1,2-*a*]pyrazinone skeleton from *N*-alkyl-*N*-allyl-pyrrolo-2-carboxamides (Scheme 1).[4d] However, their reaction worked only with *N*-substituted compounds.

Following the same procedure, the synthesis of the simple 4-benzylpyrrolo[1,2-*a*]pyrazinone from the precursor **I** (Scheme 1) was attempted. In our hands, the reaction gave the reduced 3,4-dihydropyrrolo[1,2-*a*]pyrazinone system (**II**) in modest yield. In order to obtain the desired pyrrolo[1,2-*a*]pyrazinone scaffold, several oxidative conditions were tried on the unprotected adduct without any success (i.e., MnO_2, DMP, DDQ). Similar negative results were obtained from the protected material (**II**). At that point, we decided to circumvent the need for the oxidation reaction by incorporating an alkyne in the starting material (**III**) (Scheme 2). Due to cleavage problems of the *p*-methoxyphenyl and benzyl protecting groups, 2,4-dimethoxybenzyl (DMB) was chosen, as it is easily removed under acidic conditions.

Pleasingly, the cyclization reaction of the propynyl derivative (**III**) gave the desired product in a 63% yield. Microwave heating was employed to shorten the reaction time to some minutes compared to the 3-day reaction of Becalli. The reaction did not work when the carboxamide moiety was unprotected.

When the set conditions were applied to our carboxamide of interest, **1a**, the yield dropped drastically to 12%. Furthermore, an isomeric mixture was obtained: two isomers were identified as 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, with an *exo*-cyclic double bond [cis (*Z*), trans (*E*)], and a third one was a

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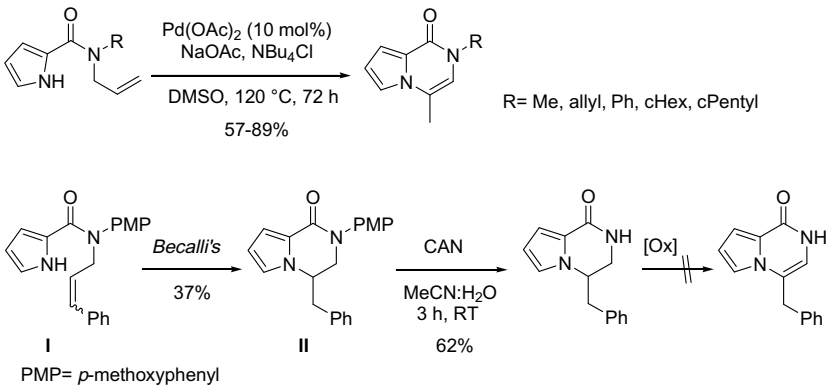
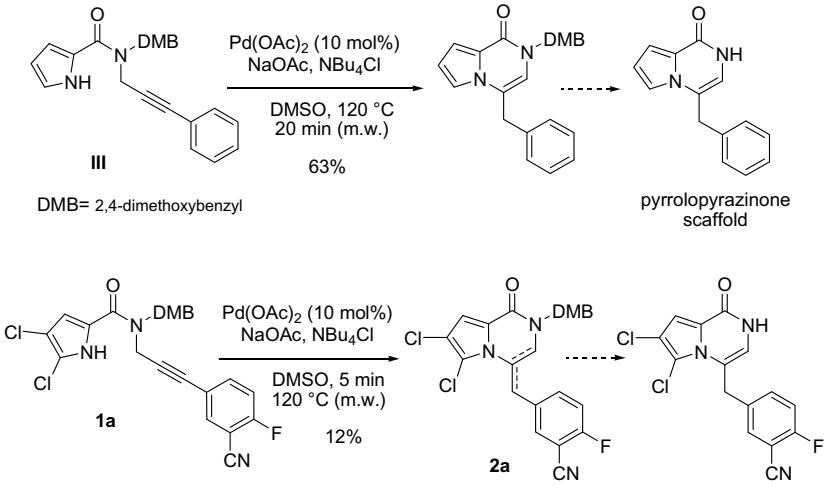


Scheme 1.



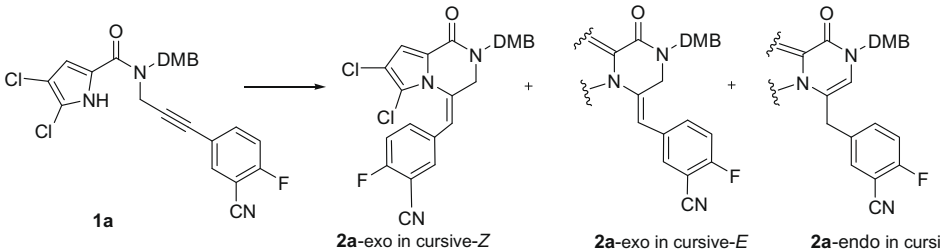
Scheme 2.

pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one with an *endo*-cyclic double bond. The stereochemical assignments for isomers *exo-E* and *exo-Z* were based on ^{1}H–^{1}H NOESY analysis.[10]

This result prompted us to investigate other synthetic approaches that could allow a wide range of substituents to be tolerated on the scaffold. Given the precedent for base-catalyzed addition of 5-membered heterocycles onto alkynes, we focused on non-metal conditions (Table 1).[10]

Unsurprisingly under neutral condition, the cyclization of carboxamide **1a** was poor and resulted in a complex mixture of products (entry 1). We then decided to attempt the base-mediated activation of the pyrrolic nitrogen to induce the cyclization. The

Table 1
Hydroamination/cyclization reaction with carboxamide **1a**



Entry	Reaction conditions	Results
1	DMF, 120 °C, 20 min (m.w.)	Complex mixture
2	Et_3N, DCM, reflux, 2 days	20% conversion
3	KOH (1 equiv), DMSO, rt, 2 h	Complex mixture
4	DBU (1 equiv), DCM, rt, 2 h	Complete conversion (**2a**-*exo-Z* only)
5	DBU (0.3 equiv), DCM, rt, 2 h	Complete conversion (**2a**-*exo-Z* only)
6	DBU (0.3 equiv), DCM, reflux, 30 min	Complete conversion (**2a**-*exo-Z* only)
7	TBAF (1 equiv), THF, rt, 1 h	**2a**-*exo-Z*:**2a**-*endo* (10:1)

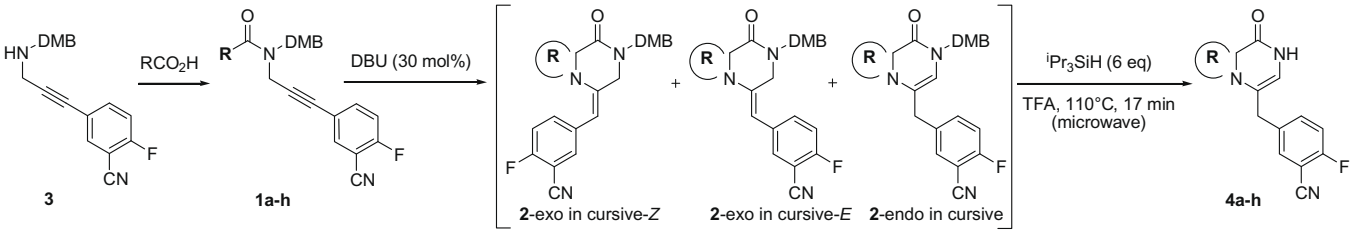
reaction with Et_3N was slow, and after 48 h there was only a 20% conversion (entry 2). With KOH, the reaction was much faster but it was not efficient (entry 3). To our delight, the hydroamination/cyclization of **1a** proceeded cleanly and smoothly with DBU as base (entries 4–6). Complete conversion to **2a**-*exo*-*Z* isomer was seen within 2 h using 1 equiv of DBU in DCM at rt (entry 4). Considering that this reaction is a rearrangement, a sub-stoichiometric amount of DBU (0.3 equiv) was used and complete conversion was seen in the identical timeframe (entry 5). The reaction could be accelerated by heating at reflux, whereby complete conversion was observed in 30 min (entry 6). When TBAF was used as base, although **2a**-*exo*-*Z* was the major product, 10% of the **2a**-*endo* isomer was obtained (entry 7).

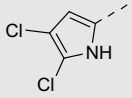
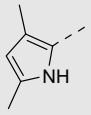
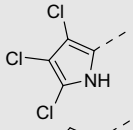
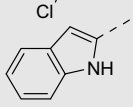
Based on this promising result with a sub-stoichiometric amount of DBU, we were interested in further understanding the scope of this reaction.

To study the relevance of the *NH*-containing heterocycle on the reaction, we held the 3-cyano-4-fluorophenyl-substituted alkyne constant. Carboxamides **1a–h** were synthesized by amide coupling reaction of the DMB-protected amine **3**[11] with a series of heteroaryl-carboxylic acids.[12] The amide coupling reactions proceeded in good yields using TBTU or HATU as coupling reagents. Carboxamides **1a–h** were then treated with a substoichiometric amount of DBU (30 mol %) to afford the desired heteroarylpyrazinone analogues (**2a–h**),[13,14] as summarized in Table 2. In general, the hydroamination/cyclization reaction took place under mild conditions (method *A*, entries 1, 2, 4–7).

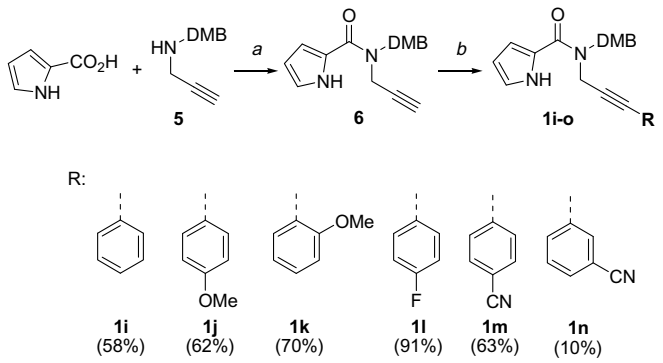
The microwave heating accelerated the reaction compared to the conventional refluxing method (method *A vs B*, entry 1). Complete cyclization of carboxamide **1a** was achieved in 3 min under microwave heating in DMF, while it required 30 min under refluxing of dichloromethane. Furthermore, similar yields (67% and 71%,

Table 2
Amide coupling reaction of **3** with RCO2H, hydroamination/cyclization of carboxamides **1a–h** and deprotection/isomerization



Entry	R	1[a] (%)[b]	Method[c] (%)[d]	t_R[e]	Isomeric mixture (mol/mol %)[f]			**4** (%)
					2-*exo*-Z	**2**-*exo*-E	**2**-*endo*	
1		**a** (50)[g]	*A* (67) *B* (71)	30 min 3 min	100 63	– –	– 37	70
2		**b** (65)	*A* (80)	3 h 30 min	27	5	68	94
3		**c** (30)	*A* (0) *B* (85)	10 min	10	5	85	Degradation
4		**d** (56)[g]	*A* (69)	2 h	60	12	28	75
5		**e** (55)	*A* (85)	1 h	42	8	50	54
6		**f** (42)[g]	*A* (18)	30 min	89	11	–	83
7		**g** (68)[g]	*A* (34)	2 h	–	–	100	85
8		**h** (42)[g]	*A* (0) *B* (85)	10 min	–	–	100	Degradation

[a] Coupling conditions: RCO_2H (1 equiv), **3** (1 equiv), TBTU (1 equiv), TEA (2 equiv), DMF, rt.
[b] Isolated yields.
[c] Method *A*: DBU (30 mol %), DCM, reflux. Method *B*: DBU (30 mol %), DMF, 120 °C (microwave).
[d] Isolated yield of the isomeric mixture.
[e] The reaction time of the hydroamination/cyclization (t_R) was the time when there was no more presence of **1** (monitored by UPLC/MS).
[f] Ratio (mol/mol %) calculated from ^1H NMR, COSY and NOESY spectra on purified product.
[g] HATU as coupling reagent.



Scheme 3. Reagents and conditions: (a) TBTU, TEA, DMF, ON, rt (56%); (b) RI, $Pd(PPh_3)_4$ (10 mol %), CuI (20 mol %), TEA, DMF, rt, ON (10–91%).

respectively) were obtained in both cases but while the thermal reaction gave only the **2a**-*exo*-*Z*, the microwave one gave a ratio 2:1 of **2a**-*exo*-*Z*:**2a**-*endo* isomers.

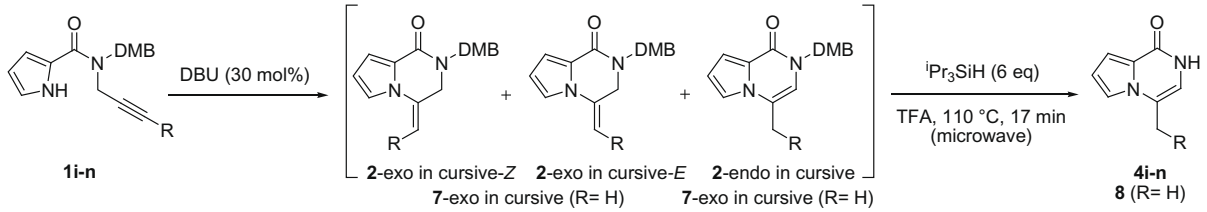
As expected, the substitution of the pyrrole ring played an important role on the cyclization reaction. While the presence of electron-withdrawing groups accelerated the reaction (**1a**,**d**, entries 1 and 4), the absence of substituents (**1b**, entry 2) or even the presence of electron-donating ones (**1c**, entry 3) slowed down the cyclization rate. In the case of the trichloro-substituted pyrrole **1d**, the reaction rate was decreased, probably due to a counteracting steric effect.

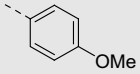
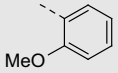
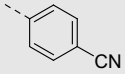
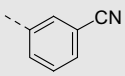
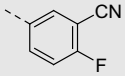
With regard to the dimethyl-substituted **1c,** microwave heating (method *B*) was required to drive the reaction to completion, since no conversion was seen after 12 h at reflux (method *A*). Both the hindered dimethylpyrrole and the electron-donating nature of the methyl groups, significantly deactived the pyrrolic N–H for intramolecular cyclization.

This cyclization reaction also worked well with other *NH*-containing heterocycles (entries 5–8), although the triazole **1h** (entry 8) required harsh conditions (10 min at microwave, method *B*). In all the cases, the cyclization reaction resulted into a mixture of up to three isomers, except for dichloropyrrole **1a**, pyrazole **1g**, and triazole **1h**.[15]

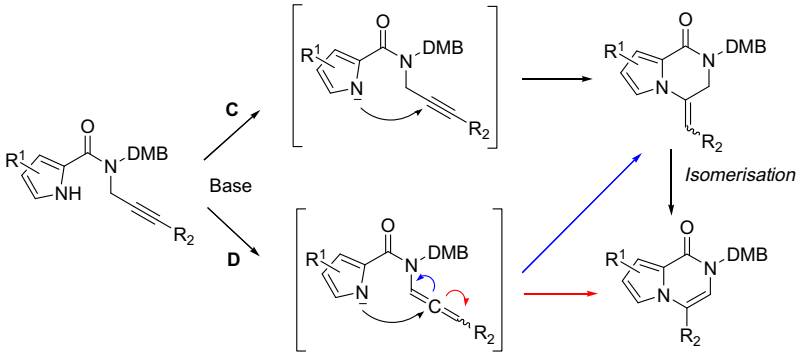
Attempts to isomerize these mixture to a unique isomer under the basic conditions, even after longer reaction times, failed. Fortunately, a solution was found under acidic conditions, sulfuric acid converted all the isomers into the thermodynamically most stable **4**-*endo* isomer with the concomitant DMB-cleavage; however, nitrile hydrolysis was observed as well (50% H_2SO_4, 110 °C, 24 h, *Y* = 22%). This side-reaction was successfully suppressed in neat TFA (RT, 20 h, 50% conversion). The addition of 6 equiv of triisopropylsilane and microwave heating at 110 °C gave full deprotection and complete conversion to the *endo*-isomer in excellent yields.[16]

Table 3
Hydroamination/cyclization of carboxamides **1i–n** and deprotection/isomerization reaction



Entry	R	Carboxamides	Method[a] (%)[b]	t_R[c]	Isomeric mixture (mol/mol %)[d]			**4** (%)
					2-*exo*-*Z*	**2**-*exo*-*E*	**2**-*endo*	
1	H	**6**	*B* (78)[e]	25 min	75	25	62	
2		**1i**	*B* (94)[e]	10 min	—	60	40	78
3		**1j**	*B* (66)[e]	10 min	5	65	30	87
4		**1k**	*B* (88)[e]	10 min	13	80	7	55
5		**1l**	*B* (60)[e]	10 min	27	73	—	68
6		**1m**	*A* (67)	3 h	—	—	100	82
7		**1n**	*A* (91)	5 h	—	38	62	70
8		**1b**	*A* (80)	3 h 30 min	27	5	68	94

[a] Method *A*: DBU (30 mol %), DCM, reflux. Method *B*: DBU (30 mol %), DMF, 120 °C (microwave).
[b] Isolated yield of the isomeric mixture.
[c] The reaction time of the hydroamination/cyclization (t_R) was the time when there was no more presence of **1** (monitored by UPLC/MS).
[d] Ratio (mol/mol %) calculated from 1H NMR, COSY and NOESY spectra on purified product.
[e] No reaction after 12 h at reflux (method *A*).



Scheme 4.

This reaction was applicable to a broad range of substituents, thereby enabling the acyclic substrates (**1a–h**) to be converted into a single desired bicyclic system by two simple high-yielding reactions.

The exploration on the alkyne substituent was carried out keeping the unsubstituted pyrrole constant. Carboxamides **1i–o** were obtained by Sonogashira coupling of diverse aryl iodides and acetylene **6**, resulting from the reaction of acetylene **5**[11] and 2-pyrrole carboxylic acid using TBTU as coupling reagent (Scheme 3). In the optimization of the Sonogashira cross-coupling reaction, several Pd(0) and Pd(II) catalysts [$Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$], and Cu(I) co-catalysts [CuI, CuBr] were tried. The best results were obtained with a mixture of a 10 mol % $Pd(PPh_3)_4$ and 20 mol % CuI. The reaction worked well with aryl iodides, but failed with aryl bromides. Modest to high conversions were observed in both electron-rich and electron-poor aryl groups.

Carboxamides **1i–n** were subjected to cyclization conditions. The results were summarized in Table 3.

The cyclization reaction of acetylene **6** (entry 1) required harsh conditions (method *B*) and longer reaction time compared to the rest of the analogues. Despite being a completely deactivated system (terminal acetylene), the reaction occurred in good yield. Electron-rich alkynes (entries 2 and 3), which bore *o*/*p*-substituted aryl with electron-donating groups, needed microwave heating (method *B*) to get total conversion but good yields were still obtained. On the other hand, electron-poor alkynes (entries 6–8) proceeded in milder conditions (method *A*). The cyano-derivatives **1m** and **1n** (entries 6 and 7) confirmed that the *para*-substitution with an electron-withdrawing group accelerated the cyclization reaction compared to *meta*-one [t_R (*para*, **1m**) = 3h vs t_R (*meta*, **1n**) = 5h]. With regard to the fluoro-derivative **1l** (entry 5), the cyclization required microwave condition (method *B*). However, the introduction of cyano group in *meta* position (**1b**, entry 8) activated the alkyne, and cyclization took place at lower temperature (method *A*). The cyclization reaction afforded up to three isomers (*exo-Z*, *exo-E*, and *endo*), except for **1m** (entry 6), which gave **2m**-*endo* as unique isomer. The DMB-removal and isomerization of the isomeric mixtures (**2b,i–n** and **7**) were achieved in high yields.

No mechanistic studies were performed but two possible pathways could be considered (Scheme 4).

The first would involve the nucleophilic addition of a pyrrolide onto the alkyne, as precedented by the intermolecular reactions of Tzalis and Trofimov[10a,b] followed by DBU-mediated double bond isomerization to give the isomeric product mixture (pathway 'C', Scheme 4). The second conceivable pathway would involve DBU-mediated alkyne–allene isomerization, where there is a growing body of evidence in several intramolecular cyclization reactions,[17] followed by 6-*exo*-dig or 6-*endo*-dig processes, and any subsequent double bond migration (pathway 'D', Scheme 4).

In summary, we have developed an entirely novel procedure for the synthesis of polyfunctionalized 4-(arylmethyl)pyrrolo[1,2-*a*]-pyrazinones by DBU-mediated hydroamination/cyclization of aryl(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide. The resulting isomeric mixture was isomerized to a unique isomer (**4**-*endo*) and concomitant DMB-cleavage under acidic conditions. The cyclization rate was demonstrated to be influenced by both the electronic nature of the pyrrole ring and the substituted alkyne. This methodology has been shown to be applicable to a wide range of other bicyclic frameworks and substituents.

Acknowledgments

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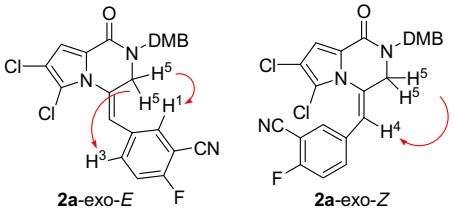
References and notes

1. (a) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579–1593 and references cited therein; (b) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420 and references cited therein.
2. Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159 and references cited therein.
3. Lauterwasser, F.; Hayes, P. G.; Bräse, S.; Piers, W. E.; Schafer, L. L. *Organometallics* **2004**, *23*, 2234–2237.
4. (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581–2584; (b) Cacchi, S.; Fabrizi, G.; Carangio, A. *Synlett* **1997**, 959–961; (c) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853–7861; (d) Becalli, E. M.; Broggini, G.; Martinelli, M.; Paladino, G. *Tetrahedron* **2005**, *61*, 1077–1082.
5. Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun. (Camb.)* **2006**, 661–662.
6. Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366–12367.
7. Zulys, A.; Dochnahl, M.; Hollmann, D.; Lohnwitz, K.; Herrmann, J. S.; Roesky, P. W.; Blechert, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7794–7798.
8. (a) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295–9306; (b) Motta, A.; Fragalà, I. L.; Marks, T. J. *Organometallics* **2006**, *25*, 5533–5539.
9. (a) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193–6195; (b) Trofimov, B. A.; Tarasova, O. A.; Shemetova, M. A.; Afonin, A. V.; Klyba, L. V.; Baikalova, L. V.; Mikhaleva, A. I. *Russ. J. Org. Chem.* **2003**, *39*, 408–414; (c) Fustero, S.; Fernandez, B.; Bello, P.; Pozo, C. D.; Arimitsu, S.; Hammond, G. B. *Org. Lett.* **2007**, *9*, 4251–4253.
10. It was detected the NOEs between H^5/H^1 and H^5/H^3 for the *E* conformation, and the key NOE between H^5 and H^4 for the *Z* conformation.



11. Jones, P.; Kinzel, O. D.; Llauger Bufi, L.; Muraglia, E.; Pescatore, G.; Torrisi, C. WO 2007/138355, 2007.
12. *A typical procedure is as follows*: A mixture of pyrrole-2-carboxylic acid (0.3 g, 3 mmol), TBTU (0.96 g, 3 mmol), and TEA (0.3, 3 mmol) in dry DMF (6 mL) was

stirred for 15 min at rt. A solution of **3** (1 g, 3 mmol) and TEA (0.3 g, 3 mmol) in DMF (4 mL) was then added, and the mixture was left for 6 h. The reaction mixture was diluted with DCM and washed sequentially with a saturated aqueous $NaHCO_3$ solution and brine. The pooled organics were dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. Compound **1b** was isolated by silica gel chromatography (biotage system, eluent: petroleum ether/EtOAc, 7:3) as a yellow powder. Yield, 65% (0.81 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (br s, 1H, *NH*), 7.94–7.93 (m, 1H), 7.79–7.76 (m, 1H), 7.55 (dd, 1, H, J = 9.0 Hz), 7.17 (d, 1H, J = 8.3 Hz), 6.97 (s, 1H), 6.63 (s, 1H), 6.56 (d, 1H, J = 8.3 Hz), 6.53–6.48 (m, 1H), 6.14 (s, 1H), 4.82 (s, 2H, CH_2), 4.54 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.0, 46.6, 56.1, 56.4, 81.0, 88.8, 99.3, 101.9, 105.5, 109.7, 112.8, 114.1, 117.6, 118.1, 118.3, 120.7, 122.8, 124.7, 129.5, 137.5, 139.7, 159.0, 161.0, 163.2, 164.1. MS (ES) $C_{24}H_{20}FN_3O_3$ required: 417, found: 418 $(M+H)^+$.

13. *Method A*: To a solution of carboxamide **1b** (100 mg, 0.24 mmol) in dry DCM (0.8 mL) was added DBU (11 mg, 0.072 mmol). The mixture was heated at reflux for 5 h. The reaction solution was diluted in DCM, and then washed with 0.5 N HCl solution and brine. The organic extracts were dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. After purification by silica gel chromatography (biotage system, eluent: petroleum ether/EtOAc, 7:3), the three isomers (α:β:γ) were quantified (27:5:68 mol/mol %, respectively). Yield, 80% (80 mg). The most relevant signals on the ^{1}H NMR (500 MHz, DMSO-d_6) data were: **2b**-*exo-Z*, δ 11.64 (bs, 1H, *NH*), 7.81–7.78 (m, 1H$_{Ar}$), 7.60–7.58 (m, 1H$_{Ar}$), 7.55–7.52 (m, 1H$_{Ar}$), 7.18 (d, 1H$_{Ar}$, J = 8.4 Hz), 6.97 (s, 1H), 6.80 (dd, 1H$_{pyr}$, J = 3.8 and 1.5 Hz), 6.61 (d, 1H$_{Ar}$, J = 2.3 Hz), 6.58 (overlapped, 1H$_{pyr}$), 6.54 (dd, 1H$_{Ar}$, J = 8.3 and 2.5 Hz), 6.24–6.23 (m, 1H$_{pyr}$), 6.14 (s, 1H), 4.56 (s, 2H, CH_2), 4.24 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3)]; **2b**-*exo-E*, δ 7.70–7.68 (m, 1H$_{Ar}$), 7.11 (d, 1H$_{Ar}$, J = 8.3 Hz), 6.86 (dd, 1H$_{pyr}$, J = 3.8 and 1.5 Hz), 4.50 (s, 2H, CH_2), 4.49 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3)]; **2b**-*endo*, δ 7.97 (dd, 1H$_{Ar}$, J = 6.2 and 2.1 Hz), 7.81–7.78 (m, 1H$_{Ar}$), 7.55–7.52 (m, 1H$_{Ar}$), 7.41–7.40 (m, 1H$_{pyr}$), 7.06 (d, 1H$_{Ar}$, J = 8.3 Hz), 6.96 (dd, 1H$_{pyr}$, J = 3.8 and 1.5 Hz), 6.62 (d, 1H$_{Ar}$, J = 2.3 Hz), 6.60 (overlapped, 1H$_{pyr}$), 6.58 (s, C*H*), 6.51 (dd, 1H$_{Ar}$, J = 8.3 and 2.5 Hz), 4.87 (s, 2H, CH_2), 4.08 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3)]. ^{19}F NMR (500 MHz, DMSO-d_6) δ −110.8 (**2b**-*exo-Z*), -112.3 (**2b**-*endo*). MS (ES) $C_{24}H_{20}FN_3O_3$ required: 417, found: 418 $(M+H)^+$.
14. *Method B*: A mixture of carboxamide **1c** (100 mg, 0.22 mmol) and DBU (10.2 mg, 0.067 mmol) in dry DMF (0.75 mL) was sealed in a microwave tube and irradiated in a microwave reactor (Emrys Optimizer) for 10 min at 120 °C. The solution was concentrated under reduced pressure and the crude diluted with DCM. The solution was washed with 0.5 N HCl solution and brine. The organic extracts were dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. After purification by silica gel chromatography (biotage system, eluent: petroleum ether/EtOAc, 7:3), the three isomers (α:β:γ) were quantified (10:5:85 mol/mol %, respectively). Yield, 85% (85 mg). The major isomer, **2c-**endo, was characterized. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.76 (dd, 1H$_{Ar}$, J = 6.1 and 2.1 Hz), 7.61–7.58 (m, 1H$_{Ar}$), 7.54 (dd, 1H$_{Ar}$, J = 8.9 Hz), 7.05 (d, 1H$_{Ar}$, J = 8.3 Hz), 6.57 (d, 1H$_{Ar}$, J = 2.5 Hz), 6.50 (dd, 1H$_{Ar}$, J = 8.3 and 2.5 Hz), 6.12 (s, 1H$_{pyr}$), 6.06 (s, C*H*), 4.76 (s, 2H, CH_2), 4.27 (s, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 3.76 (s, 3H, OCH_3)]. MS (ES) $C_{26}H_{24}FN_3O_3$ required: 445, found: 446 $(M+H)^+$.
15. The molar ratio of the three isomers remained the same before and after silica gel purification (confirmed by ^{19}F NMR spectra).
16. *A typical procedure is as follows*: A mixture of **2b** (65 mg, 0.15 mmol), ^{i}Pr$_3$SiH (0.19 mL, 0.93 mmol) and TFA (0.7 mL) was irradiated in a microwave reactor (Emrys Optimizer) for 17 min at 110 °C. After cooling down to room temperature, the mixture was purified by silica gel chromatography (biotage system, eluent: petroleum ether/EtOAc, 3:2) to afford **4b** as a white powder. Yield, 94% (42 mg). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.51 (d, 1H, J = 2.1 Hz, N*H*), 7.92–8.00 (m, 1H$_{Ar}$), 7.71–7.79 (m, 1H$_{Ar}$), 7.47 (t, 1H$_{Ar}$, J = 9 Hz), 7.29–7.32 (m, 1H$_{pyr}$), 6.89–6.92 (m, 1H$_{pyr}$), 6.43–6.53 (m, 2H, H$_{pyr}$ and C*H*), 4.08 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.0, 99.9, 109.4, 111.5, 113.2, 113.8, 116.4, 116.6, 117.0, 124.1, 133.5, 134.7, 135.9, 155.2, 161.2. MS (ES) $C_{15}H_{10}FN_3O$ required: 267, found: 268 $(M+H)^+$.
17. (a) Grigg, R.; Loganathan, V.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1996**, *52*, 11479–11502; (b) Le Strat, F.; Harrowven, D. C.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 489–498.