ChemPubSoc Europe

DOI: 10.1002/ejoc.201700470

EurJOC European Journal of Organic Chemistry

Full Paper

Radical Difluoromethylation

Ag^{I}-Promoted Difluoromethylation of Isocyanides To Give Difluoromethylated Phenanthridines

Wen Wan*[a] Xiaochen Xu,[a] Yunrong Chen,[a] Haizhen Jiang,[a] Yong Wang,[a] Hongmei Deng,[b] and Jian Hao*[a,c]

Abstract: An Ag^{I}-mediated ethoxycarbonyldifluoromethylation of isocyanides has been developed. This radical cascade reaction involves the addition of difluoromethylene radical to the isocyanide functionality, and subsequent homolytic aromatic substitution to give difluoromethylated phenanthridines with a good functional-group tolerance.

Introduction

It is well known that the incorporation of a fluorine-containing functional group into organic molecules such as pharmaceuticals and agrochemicals has been considered to be a good strategy in drug design. Such modifications can enhance the binding interactions and metabolic stabilities of the molecules, and change their physical properties and reactivities.[1] The *gem*-difluoromethylene unit (CF_2) is of particular interest due to its unique behaviour as a bioisostere, mimicking the steric and electronic features of an oxygen atom or a carbonyl group. This can often lead to increased dipole moments, enhanced acidity of neighbouring groups and conformational changes.[2] Recently, significant progress has been made in the difluoromethylation of aromatic compounds.[3] Among the functionalized difluoro moieties that have been reported, the CF_2CO_2Et moiety is extremely appealing. It can be transformed into a variety of other difluoromethylene-containing functional groups, which overcomes the drawbacks of the recently reported perfluoroalkyl groups.

Phenanthridines are biologically important compounds that occur in nature and are used as drugs or as drug candidates in medicinal chemistry.[4] These heterocycles show antibacterial, antitumoral, cytotoxic and antileukemic activities.[5] Fluorine-containing phenanthridines have received great attention in recent years. However, to the best of knowledge, only a handful of examples have been developed to date in which a difluoromethylene moiety is incorporated into the phenanthridine.[6]

With respect to the CF_2CO_2Et moiety, to date, only Yu's group has reported a method for the ethoxycarbonyldifluoromethylation of isocyanides; they used $BrCF_2CO_2Et$ as a fluoroalkylating reagent and *fac*-Ir(ppy)$_3$ (ppy = 2-phenylpyridinato) as a photoredox catalyst.[7] Despite these important advances, current strategies for the ethoxycarbonyldifluoromethylation of phenanthridines still suffer from the disadvantages that they require expensive photoredox catalysts, and have limited substrate scope. This greatly limits their use on a large scale in synthesis and in the industry. Therefore, it is highly desirable to develop a simple, convenient, efficient and alternative strategy to address the synthesis of more diverse CF_2CO_2Et-containing phenanthridines through the difluoromethylation of biaryl isocyanides.

Our group has always been interested in difluoromethylation. We reported an Ag^{I}-mediated ethoxycarbonyldifluoromethylation of terminal unactivated or activated alkenes and aromatic rings, and constructed a wide range of complex oxindoles with a terminal CF_2CO_2Et group through a radical process.[8] Inspired by recent reports on cascade radical addition/cyclization reactions to form functionalized phenanthridines, we decided to investigate the modular synthesis of phenanthridines bearing a terminal CF_2CO_2Et group.

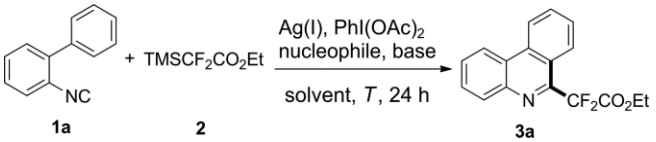
Results and Discussion

The reaction was optimized by using biaryl isocyanide **1a** in combination with $Me_3SiCF_2CO_2Et$ (**2**) as a difluoromethyl radical precursor in the presence of an Ag^{I} salt, $PhI(OAc)_2$ as an oxidant and NaOAc as an initiator, at ambient temperature (Table 1). To our delight, the target phenanthridine **3a** was obtained in 6 % yield, as determined by ^{19}F NMR spectroscopy (Table 1, entry 1). A variety of silver(I) salts, including Ag_2CO_3, $AgBF_4$, AgOTf, AgF, AgOAc and $AgNO_3$, were evaluated, and we found that Ag_2CO_3 gave a somewhat better yield (Table 1, entries 1–6). A solvent screen revealed that the use of 1,4-dioxane improved the yield to 15 % (Table 1, entries 7–11). Different bases were tested, including K_2CO_3, KOH, Et_3N, *t*BuONa and K_3PO_4, and we found that the yield of the reaction improved marginally to 47 %

[a] *Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shangda Road 99, Shanghai, China*
E-mail: wanwen@shu.edu.cn; jhao@shu.edu.cn
http://www.chem.shu.edu.cn
[b] *Laboratory of Microstructures, Shanghai University, China*
[c] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Ling Ling Road 345, Shanghai, China*
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201700470.

when K_2CO_3 (0.5 equiv.) was used (Table 1, entries 12–17). A higher loading of K_2CO_3 (3.0 equiv.) improved the efficiency of the reaction, giving a yield of 72 % (Table 1, entry 13). Extension of the reaction time to 48 h resulted in a lower yield and the formation of a complex mixture (Table 1, entry). Increasing the temperature to 50 °C resulted in a lower conversion to the expected product, and a 52 % yield (Table 1, entry 19). Replacement of the nucleophilic reagent NaOAc with LiOAc or KOAc did not improve the efficiency of the reaction (Table 1, entries 20 and 21). Decreasing the amount of $Me_3SiCF_2CO_2Et$ resulted in lower yields of the target compound **3a** (Table 1, entries 22 and 23).

Table 1. Survey of reaction conditions.[a]



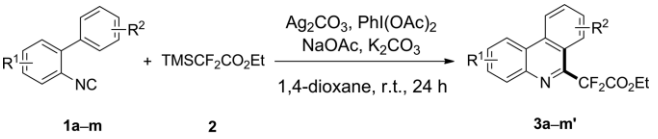
1a 2 3a

Entry	Ag^I salt (2.5 equiv.)	Nucleophile (3.0 equiv.)	Base (equiv.)	Solvent	Temp [°C]	Yield [%][b]
1	Ag_2CO_3	NaOAc	–	NMP	r.t.	6
2	$AgBF_4$	NaOAc	–	NMP	r.t.	1
3	AgOTf	NaOAc	–	NMP	r.t.	4
4	AgF	NaOAc	–	NMP	r.t.	1
5	AgOAc	NaOAc	–	NMP	r.t.	4
6	$AgNO_3$	NaOAc	–	NMP	r.t.	3
7	Ag_2CO_3	NaOAc	–	DMSO	r.t.	3
8	Ag_2CO_3	NaOAc	–	DMF	r.t.	3
9	Ag_2CO_3	NaOAc	–	CH_3CN	r.t.	0
10	Ag_2CO_3	NaOAc	–	THF	r.t.	2
11	Ag_2CO_3	NaOAc	–	1,4-dioxane	r.t.	15
12	Ag_2CO_3	NaOAc	K_2CO_3 (0.5)	1,4-dioxane	r.t.	47
13	Ag_2CO_3	NaOAc	K_2CO_3 (3)	1,4-dioxane	r.t.	72
14	Ag_2CO_3	NaOAc	Et_3N (3)	1,4-dioxane	r.t.	26
15	Ag_2CO_3	NaOAc	K_3PO_4 (3)	1,4-dioxane	r.t.	36
16	Ag_2CO_3	NaOAc	NaOH (3)	1,4-dioxane	r.t.	45
17	Ag_2CO_3	NaOAc	*t*BuONa (3)	1,4-dioxane	r.t.	12
18	Ag_2CO_3	NaOAc	K_2CO_3 (3)	1,4-dioxane	r.t.[c]	65
19	Ag_2CO_3	NaOAc	K_2CO_3 (3)	1,4-dioxane	50	52
20	Ag_2CO_3	LiOAc	K_2CO_3 (3)	1,4-dioxane	r.t.	61
21	Ag_2CO_3	KOAc	K_2CO_3 (3)	1,4-dioxane	r.t.	58
22	Ag_2CO_3	NaOAc	K_2CO_3 (3)	1,4-dioxane	r.t.[d]	43
23	Ag_2CO_3	NaOAc	K_2CO_3 (3)	1,4-dioxane	r.t.[e]	39

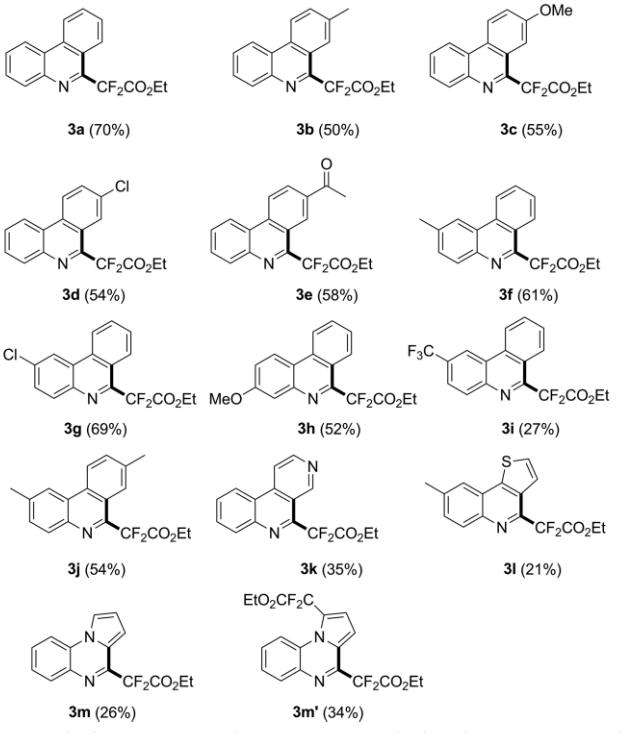
[a] Reaction conditions: 2-isocyanobiphenyl (**1a**; 0.2 mmol), $TMSCF_2CO_2Et$ (**2**; TMS = trimethylsilyl; 1 mmol), Ag^I salt (2.5 equiv.), $PhI(OAc)_2$ oxidant (2.0 equiv.), initiator (3.0 equiv.) and base in solvent (3.0 mL) for 24 h under a nitrogen atmosphere. [b] Yields determined by ^{19}F NMR spectroscopic analysis with $PhCF_3$ as the internal standard. [c] Reaction time: 48 h. [d] Ratio of **1a**/**2** was 1:2. [e] Ratio of **1a**/**2** was 1:1.

Encouraged by these results, a variety of biphenyl isocyanides **1a**–**1m** were used to react with $Me_3SiCF_2CO_2Et$ (**2**) under the optimized reaction conditions (Table 1, entry 13), in order to study the scope and limitations of this transformation. As shown in Table 2, the corresponding 6-difluoromethylated phenanthridine derivatives were formed in moderate to good yields. The substituents on both benzene rings did not affect this transformation significantly. Electron-withdrawing substituents, such as chloro or acetyl groups, on the aryl rings proved to be well tolerated under the standard conditions, and the difluoromethylated phenanthridines **3d**, **3e** and **3g** were formed. These could then be subjected to further modification at the substituted positions. Notably, aromatic heterocycles could be incorporated into the phenanthridine scaffold in reasonable yields, which makes this approach more useful for the preparation of pharmaceuticals and *gem*-difluoromethylene-linked identical or nonidentical twin drugs twin drugs. For instance, replacement of a benzene ring from the biaryl isocyanides with pyridine or thiophene moiety was compatible with these cyclization reaction conditions. A substrate bearing an electron-deficient pyridine moiety instead of a phenyl ring was cyclized to give a benzo[*c*][2,7]naphthyridine scaffold **3k** in a reasonable yield (35 %). A substrate containing an electron-rich thienyl moiety instead of a phenyl ring, 2-(2-thienyl)phenyl isocyanide (**1k**), was also found to be a suitable substrate for this annulation reaction, and thieno[3,2-*c*]quinoline system **3l** was formed in 17 % yield. Interestingly, when 1-(2-isocyanophenyl)-1*H*-pyrrole (**1m**) was used in this annulation, a mixture of mono- and bis-ethoxycarbonyldifluoromethylated pyrrolo[1,2-*a*]quinoxalines was obtained in 26 % (**3m**) and 34 % (**3m′**) yields.

Table 2. Scope of the difluoromethylenation reaction of biaryl isocyanides with **2**.[a,b]



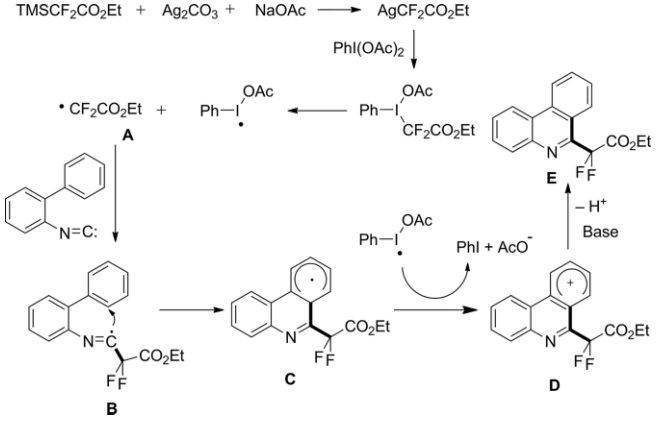
1a–m 2 3a–m'



[a] Standard reaction conditions: 2-isocyanobiphenyl (**1a**; 0.2 mmol), $TMSCF_2CO_2Et$ (**2**; 1 mmol), Ag_2CO_3(2.5 equiv.), $PhI(OAc)_2$ (2.0 equiv.), NaOAc (3.0 equiv.) K_2CO_3 (3.0 equiv.) in 1,4-dioxane (3.0 mL) for 24 h under a nitrogen atmosphere. [b] Isolated yield.

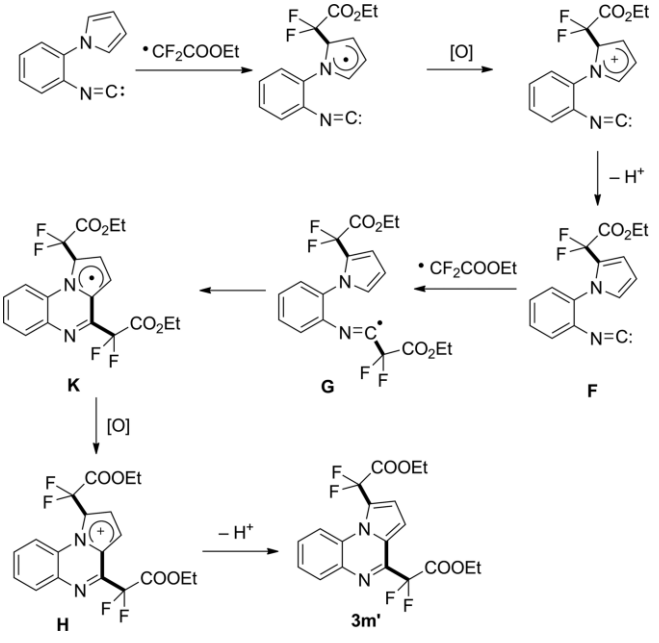
To test whether an in-situ-generated (ethoxycarbonyl)difluoromethyl radical species ($^{\cdot}CF_2CO_2Et$) was involved in the reaction, we carried out an inhibition experiment on the reaction of **1a** through the addition of the known radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy; 2.0 equiv.) under the standard reaction conditions (see Supporting Information). Complete suppression of the desired reaction was observed, and the formation of TEMPO-CF_2CO_2Et was detected by ^{19}F NMR spectroscopy. This suggests that a $^{\cdot}CF_2CO_2Et$ radical species is involved in this reaction and initiates the cascade sequence through addition to the isocyanide, which is consistent with literature precedent.[8c,9]

An annulation was proposed as the mechanism of these reactions (Scheme 1). Firstly, $^{\cdot}CF_2CO_2Et$ radical intermediate **A** is generated and further stabilized by the combination of Ag^I and $PhI(OAc)_2$. Addition of the $^{\cdot}CF_2CO_2Et$ radical intermediate to the isocyanide generates the imidoyl radical **B**, which cyclizes onto the arene to give cyclohexadienyl radical **C**. Oxidation of **C** produces the corresponding carbocation **D**. Finally, intermediate **D** is deprotonated, which leads to rearomatization to give the desired *gem*-difluoromethylenated phenanthridine **E**.



Scheme 1. Proposed reaction mechanism for the formation of **3a**–**3m**.

As noted above, aromatic heterocycles, such as pyridine, thiophene and pyrrole, were successfully incorporated into the phenanthridine scaffold. However, an exception was found when bis-ethoxycarbonyldifluoromethylated phenanthridine **3m′** was obtained from an *N*-pyrrole-substituted isocyanide derivative. To study the formation of this bis-ethoxycarbonyldifluoromethylated phenanthridine, we carried out the reaction of monoethoxycarbonyl difluoromethylated phenanthridine **3m** with an excess of $TMSCF_2CO_2Et$ under the standard reaction conditions. Unfortunately, a conversion of the substrate **3m** into **3m′** of less than 10 % was obtained, even when the reaction time was extended to 72 h. This indicates that **3m′** was not formed by direct difluoromethylation of the pyrrole ring from pyrrolo[1,2-*a*]quinoxaline derivative **3m**. These results suggest that a C–H difluoromethylation of the pyrrole ring takes place before difluoromethylation of the isocyanide functionality.[10] Thus, a more reasonable mechanism for the formation of **3m′** is proposed as shown in Scheme 2. Firstly, the in-situ-generated $^{\cdot}CF_2CO_2Et$ radical intermediate undergoes direct C–H difluoromethylation at the α position of the electron-rich pyrrole ring to generate isocyanide derivative **F** containing a difluoromethylated pyrrole moiety. Subsequent addition of a second $^{\cdot}CF_2CO_2Et$ radical to isocyanide **F** produces the imidoyl radical **G**. This then cyclizes onto the pyrrole to give dihydropyrrole radical **K**. Oxidation of **K** and further rearomatization gives pyrrolo[1,2-*a*]quinoxaline **3m′**, which bears two CF_2CO_2Et groups on its heterocyclic scaffold.



Scheme 2. Proposed reaction mechanism for the formation of **3m′**.

Conclusions

An efficient and convenient method for the synthesis of ethoxycarbonyldifluoromethylated phenanthridines has been developed by means of an Ag^I-mediated cascade *gem*-difluoromethylenation/cyclization of isocyanides with $TMSCF_2CO_2Et$ under mild reaction conditions. This provides an alternative strategy for the synthesis of structurally diverse CF_2CO_2Et-containing *gem*-difluoromethylenated phenanthridines. These compounds offer a range of possibilities for synthetic post-functionalization for the preparation of pharmaceutically and biologically active phenanthridine derivatives, as well as functional materials.

Experimental Section

General Remarks: ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ with a Bruker AV-500 spectrometer. Chemical shifts for ^1H NMR spectra are reported in ppm downfield from tetramethylsilane, and residual $CHCl_3$ was used as an internal reference (δ = 7.26 ppm for ^1H). Chemical shifts for ^{13}C NMR spectra are reported in ppm, and internal $CDCl_3$ (δ = 77.16 ppm for ^{13}C) was used as an internal reference. Chemical shifts for ^{19}F NMR spectra are reported in ppm downfield from internal fluorotrichloromethane ($CFCl_3$). Coupling constants (*J*) are given in Hertz (Hz). The terms m, s, d, t and q refer to multiplet, singlet, doublet, triplet and quartet, respectively; br. refers to a broad signal. Infrared spectra (IR) were recorded with an Avatar 370 FTIR spectrometer, absorbance frequencies are given at

maximum intensity in cm^{-1}. Melting points were obtained with an X-4 digital melting-point apparatus. High-resolution mass spectra (HRMS) and mass spectra (MS) were recorded using the electron impact (EI) or electrospray ionization (ESI) techniques.

General Procedure for Synthesis of Substrates (Derivatives of Isocyanides):[11] 2-Bromoaniline (20 mmol), phenylboronic acid (24 mmol), K_2CO_3 (2 M aq.; 45 mL) and DME (40 mL) were added to an oven-dried three-necked flask under a gentle stream of nitrogen. The mixture was stirred for 30 min at room temperature under a nitrogen atmosphere. $PdCl_2(PPh_3)_2$ (280 mg, 0.40 mmol) was then added at room temperature, and the mixture was stirred overnight at 80 °C under nitrogen. The reaction mixture was then cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and dried with $MgSO_4$, and the volatiles were removed in vacuo. The residue was subjected to column chromatography on silica gel (petroleum ether/EtOAc, 30:1) to give [1,1′-biphenyl]-2-amine (89 %).

[1,1′-Biphenyl]-2-amine (18 mmol) and THF (30 mL) were added to an oven-dried three-necked flask equipped with a dropping funnel under a nitrogen atmosphere, and the solution was cooled to 0 °C. Acetic formic anhydride [prepared from the reaction of acetic anhydride (3.8 mL) with formic acid (1.7 mL) at 55 °C for 2 h] was transferred to the dropping funnel and added to the solution of [1,1′-biphenyl]-2-amine dropwise at 0 °C. After the addition was complete, the mixture was warmed to room temperature and stirred for 2 h. After this time, the reaction was quenched with sat. aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (3 ×). The organic extract was dried with Na_2SO_4 and concentrated under reduced pressure to give the formamide as a pale yellow oil. This material was used in the subsequent dehydration without further purification.

THF (30 mL), NEt_3 (150 mmol) and all of the formamide obtained above were added to an oven-dried three-necked flask equipped with a dropping funnel under a nitrogen atmosphere. The resulting solution was cooled to 0 °C. $POCl_3$ (36 mmol) was added dropwise, and the mixture was stirred for 2 h at 0 °C after the addition was complete. After this time, the reaction was quenched with sat. aqueous Na_2CO_3, and the mixture was stirred for 1 h. The mixture was extracted with CH_2Cl_2 (3 ×). The organic phase was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc, 40:1) to give **1a** (78 %) as a green oil.

2-Isocyano-1,1′-biphenyl (1a): Green oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.51 (m, 2 H), 7.51–7.47 (m, 3 H), 7.47–7.41 (m, 3 H), 7.38 (ddd, J = 7.9, 6.9, 2.0 Hz, 1 H) ppm.

2-Isocyano-4′-methyl-1,1′-biphenyl (1b): This compound was prepared by the same procedure described for **1a**, except that *p*-tolylboronic acid was used instead of phenylboronic acid. Compound **1b** was obtained (84 % over two steps) as a green oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (dd, J = 7.9, 1.3 Hz, 1 H), 7.49–7.42 (m, 4 H), 7.38 (ddd, J = 7.9, 6.9, 2.1 Hz, 1 H), 7.32 (d, J = 7.9 Hz, 2 H), 2.45 (s, 3 H) ppm.

2-Isocyano-4′-methoxy-1,1′-biphenyl (1c): This compound was prepared by the same procedure described for **1a**, except that (4-methoxyphenyl)boronic acid was used instead of phenylboronic acid. Compound **1c** was obtained (85 % over two steps) as a pale green solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.41 (m, 3 H), 7.41–7.34 (m, 2 H), 7.23 (dd, J = 7.4, 1.7 Hz, 1 H), 7.09–6.99 (m, 2 H), 3.84 (s, 3 H) ppm.

4′-Chloro-2-isocyano-1,1′-biphenyl (1d): This compound was prepared by the same procedure described for **1a**, except that (4-chlorophenyl)boronic acid was used instead of phenylboronic acid. Compound **1d** was obtained (88 % over two steps) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.42 (m, 6 H), 7.39 (dd, J = 7.9, 6.5 Hz, 2 H) ppm.

1-(2′-Isocyano-[1,1′-biphenyl]-4-yl)ethan-1-one (1e): This compound was prepared by the same procedure described for **1a**, except that (4-acetylphenyl)boronic acid was used instead of phenylboronic acid. Compound **1e** was obtained (82 % over two steps) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 2 H), 7.65–7.59 (m, 2 H), 7.55–7.47 (m, 2 H), 7.47–7.40 (m, 2 H), 2.66 (s, 3 H) ppm.

2-Isocyano-5-methyl-1,1′-biphenyl (1f): This compound was prepared by the same procedure described for **1a**, except that 2-bromo-4-methylaniline was used instead of 2-bromoaniline. Compound **1f** was obtained (88 % over two steps) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2 H), 7.48–7.45 (m, 2 H), 7.45–7.39 (m, 1 H), 7.37 (d, J = 8.1 Hz, 1 H), 7.23 (d, J = 2.0 Hz, 1 H), 7.17 (dd, J = 8.2, 1.9 Hz, 1 H), 2.41 (s, 3 H) ppm.

5-Chloro-2-isocyano-1,1′-biphenyl (1g): This compound was prepared by the same procedure described for **1a**, except that 2-bromo-4-chloroaniline was used instead of 2-bromoaniline. Compound **1g** was obtained (87 % over two steps) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.45 (m, 5 H), 7.43 (dd, J = 5.4, 3.1 Hz, 2 H), 7.35 (dd, J = 8.5, 2.3 Hz, 1 H) ppm.

2-Isocyano-4-methoxy-1,1′-biphenyl (1h): This compound was prepared by the same procedure described for **1a**, except that 2-bromo-5-methoxyaniline was used instead of 2-bromoaniline. Compound **1h** was obtained (86 % over two steps) as a green solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.43 (m, 4 H), 7.42–7.37 (m, 1 H), 7.34 (dd, J = 8.4, 0.6 Hz, 1 H), 7.07–6.96 (m, 2 H), 3.86 (s, 3 H) ppm.

2-Isocyano-5-trifluoromethyl-1,1′-biphenyl (1i): This compound was prepared by the same procedure described for **1a**, except that 2-bromo-4-trifluoromethyl-phenylamine was used instead of 2-bromoaniline. Compound **1i** was obtained (56 % over two steps) as a dark blue solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, J = 2.0 Hz, 1 H), 7.67–7.60 (m, 2 H), 7.52 (d, J = 4.4 Hz, 4 H), 7.50–7.44 (m, 1 H) ppm.

2-Isocyano-4′,5-dimethyl-1,1′-biphenyl (1j): This compound was prepared by the same procedure described for **1a**, except that 2-bromo-4-methylaniline was used instead of 2-bromoaniline, *p*-tolylboronic acid was used instead of phenylboronic acid. Compound **1j** was obtained (82 % over two steps) as a pale green solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.38 (m, 2 H), 7.36 (d, J = 8.1 Hz, 1 H), 7.30–7.26 (m, 2 H), 7.21 (d, J = 1.9 Hz, 1 H), 7.14 (ddd, J = 8.0, 2.0, 0.8 Hz, 1 H), 2.41 (s, 3 H), 2.40 (s, 3 H) ppm.

4-(2-Isocyanophenyl)pyridine (1k): This compound was prepared by the same procedure described for **1a**, except that pyridin-4-ylboronic acid was used instead of phenylboronic acid. Compound **1k** was obtained (70 % over two steps) as a brown solid. M.p. 61–63 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.79–8.69 (m, 2 H), 7.58–7.39 (m, 6 H) ppm.

2-(2-Isocyano-5-methylphenyl)thiophene (1l): This compound was prepared by the same procedure described for **1a**, except that 2-Bromo-4-methyl-phenylamine and thiophen-2-ylboronic acid was used instead of 2-Bromo-phenylamine and phenylboronic acid. Compound **1l** was obtained (50 % over two steps) as a dark yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (dd, J = 3.6, 1.2 Hz, 1 H), 7.42 (dd, J = 5.2, 1.2 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 2 H), 7.15 (dd, J = 5.2, 3.6 Hz, 1 H), 7.12 (dd, J = 8.0, 1.9 Hz, 1 H), 2.40 (s, 3 H) ppm.

1-(2-Isocyano-phenyl)-1*H*-pyrrole (1m): 2-Iodoaniline (20 mmol), pyrrole acid (24 mmol), CuI (2 mmol), DMEDA (*N*,*N*′-dimethylethyl-

enediamine; 4 mmol), K_3PO_4 (44 mmol) and toluene (50 mL) were added to an oven-dried three-necked flask under a gentle stream of nitrogen, and the mixture was stirred for 2 h at 110 °C. The reaction mixture was then cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and dried with $MgSO_4$. The volatiles were removed in vacuo, and the residue was subjected to column chromatography on silica gel to give 2-(1*H*-pyrrol-1-yl)aniline. Compound **1m** was then prepared as described above to give **1m** (42 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.44 (m, 2 H), 7.42–7.31 (m, 2 H), 7.02 (t, *J* = 2.2 Hz, 2 H), 6.39 (t, *J* = 2.2 Hz, 2 H) ppm.

General Procedure for Synthesis of 6-Difluoromethyl Phenanthridines:[6e,7] A Schlenk tube (10 mL) was loaded with Ag_2CO_3 (1.25 mmol), NaOAc (1.5 mmol), PhIOAc (1 mmol), K_2CO_3 (1.5 mmol), biarylisonitrile (0.5 mmol) and preactivated powdered molecular sieves (4 Å; 60 mg). $TMSCF_2CO_2Et$ (2.5 mmol) and 1,4-dioxane (5 mL) were then added under the protection of N_2. The mixture was stirred at ambient temperature for 24 h. Th reaction was quenched with water, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and the solvents were evaporated under vacuum. The residue was purified by flash column chromatography on silica gel to give the desired phenanthridines **3**.

Ethyl Difluoro(phenanthridin-6-yl)acetate (3a): Purification by silica gel chromatography (petroleum ether/EtOAc, 20:1) gave compound **3a** (70 %) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 8.5 Hz, 1 H), 8.54 (ddt, *J* = 9.7, 7.6, 2.4 Hz, 2 H), 8.13–8.07 (m, 1 H), 7.87 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.78–7.69 (m, 3 H), 4.60 (q, *J* = 7.1 Hz, 2 H), 1.51 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –98.71 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.7 (t, *J* = 30.9 Hz), 150.1 (t, *J* = 29.0 Hz), 141.7, 133.8, 131.2, 130.8, 128.9, 128.8, 127.8, 126.2 (t, *J* = 4.9 Hz), 124.8, 122.4, 122.2 (t, *J* = 2.1 Hz), 122.0, 115.8 (t, *J* = 254.0 Hz), 63.0, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2993, 1715, 1446, 1364, 1299, 1153, 1099, 1012, 937, 822, 769, 728, 678 cm^{-1}.

Ethyl Difluoro-(8-methylphenanthridin-6-yl)acetate (3b): Purification by silica gel chromatography (petroleum ether/EtOAc, 20:1) gave compound **3b** (50 %) as a pale yellow solid. M.p. 85–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.51–8.45 (m, 2 H), 8.35–8.27 (m, 1 H), 8.15–8.04 (m, 1 H), 7.73–7.69 (m, 2 H), 7.68 (dd, *J* = 8.5, 1.7 Hz, 1 H), 4.61 (q, *J* = 7.2 Hz, 2 H), 2.61 (s, 3 H), 1.52 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –98.83 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.8 (t, *J* = 30.8 Hz), 149.8 (t, *J* = 28.9 Hz), 141.4, 137.9, 132.9, 131.7, 130.7, 128.7, 128.5, 125.4 (t, *J* = 4.6 Hz), 124.9, 122.4, 122.3, 121.8, 116.0 (t, *J* = 254.0 Hz), 62.9, 21.9, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2986, 2916, 1768, 1449, 1374, 1291, 1152, 1097, 1019, 953, 858, 776, 738 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{16}F_2NO_2$ [M + H]$^+$ 316.1144; found 316.1147.

Ethyl Difluoro-(8-methoxyphenanthridin-6-yl)acetate (3c): Purification by silica gel chromatography (petroleum ether/EtOAc, 50:1) gave compound **3c** (55 %) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 9.1 Hz, 1 H), 8.50 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.12–8.06 (m, 1 H), 7.87 (q, *J* = 2.2 Hz, 1 H), 7.76–7.64 (m, 2 H), 7.53 (dd, *J* = 9.1, 2.6 Hz, 1 H), 4.56 (q, *J* = 7.1 Hz, 2 H), 4.01 (s, 3 H), 1.47 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –99.95 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.7 (t, *J* = 31.2 Hz), 158.7, 149.0 (t, *J* = 28.8 Hz), 140.9, 130.7, 128.8, 128.2, 127.9, 124.9, 124.0, 123.6, 122.2, 121.5, 115.9 (t, *J* = 253.7 Hz), 105.7 (t, *J* = 5.1 Hz), 63.0, 55.5, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2998, 2928, 2852, 1770, 1617, 1574, 1530, 1457, 1379, 1292, 1224, 1096, 892 cm^{-1}.

Ethyl (8-Chlorophenanthridin-6-yl)difluoroacetate (3d): Purification by silica gel chromatography (petroleum ether/EtOAc, 50:1) gave compound **3d** (54 %) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 8.9 Hz, 1 H), 8.58 (d, *J* = 2.0 Hz, 1 H), 8.49–8.46 (m, 1 H), 8.08 (dd, *J* = 6.1, 3.4 Hz, 1 H), 7.82 (dd, *J* = 8.9, 2.1 Hz, 1 H), 7.75 (dd, *J* = 6.2, 3.3 Hz, 2 H), 4.60 (q, *J* = 7.1 Hz, 2 H), 1.51 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –98.76 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.3 (t, *J* = 30.9 Hz), 149.1 (t, *J* = 29.5 Hz), 141.6, 134.0, 132.2, 131.9, 130.9, 129.3, 129.3, 125.5 (t, *J* = 5.4 Hz), 124.2, 124.1, 123.0, 121.9, 115.5 (t, *J* = 254.4 Hz), 63.1, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2992, 2955, 2907, 1771, 1571, 1516, 1471, 1366, 1150, 1098, 1019, 945 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{12}ClF_2NO_2$ [M + H]$^+$ 336.0603; found 336.0598.

Ethyl (8-Acetylphenanthridin-6-yl)difluoroacetate (3e): Purification by silica gel chromatography (petroleum ether/EtOAc, 5:1) gave compound **3e** (58 %) as a pale yellow solid. M.p. 129–133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.05 (d, *J* = 1.9 Hz, 1 H), 8.63 (d, *J* = 8.7 Hz, 1 H), 8.51 (dd, *J* = 7.5, 2.1 Hz, 1 H), 8.38 (dd, *J* = 8.7, 1.7 Hz, 1 H), 8.11–8.04 (m, 1 H), 7.81–7.71 (m, 2 H), 4.58 (q, *J* = 7.1 Hz, 2 H), 2.76 (s, 3 H), 1.49 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –98.08 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.9, 163.3 (t, *J* = 30.8 Hz), 150.4 (t, *J* = 28.8 Hz), 142.4, 136.6, 135.7, 130.9, 130.2, 129.4, 129.3, 127.4 (t, *J* = 5.0 Hz), 124.0, 123.0, 122.6, 121.7, 115.5 (t, *J* = 254.3 Hz), 63.2, 26.6, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2990, 2927, 2859, 1771, 1683, 1615, 1528, 1404, 1361, 1298, 1256, 1148, 1095, 1010, 950 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{16}F_2NO_3$ [M + H]$^+$ 344.1093; found 344.1091.

Ethyl Difluoro-(2-methylphenanthridin-6-yl)acetate (3f): Purification by silica gel chromatography (petroleum ether/EtOAc, 50:1) gave compound **3f** (61 %) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 8.1 Hz, 1 H), 8.53–8.49 (m, 1 H), 8.22 (d, *J* = 6.8 Hz, 1 H), 7.94 (dd, *J* = 8.4, 2.9 Hz, 1 H), 7.80 (tdd, *J* = 8.5, 4.0, 1.5 Hz, 1 H), 7.67 (dddd, *J* = 8.3, 6.9, 3.1, 1.2 Hz, 1 H), 7.50 (dt, *J* = 8.5, 2.6 Hz, 1 H), 4.59 (dt, *J* = 7.8, 6.7 Hz, 2 H), 2.61 (s, 3 H), 1.51 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –98.54 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.8 (t, *J* = 30.6 Hz), 149.1 (t, *J* = 28.9 Hz), 140.0, 139.0, 133.4, 130.8, 130.6, 130.4, 127.6, 126.0 (t, *J* = 4.9 Hz), 124.6, 122.3, 122.3 (t, *J* = 2.0 Hz), 121.5, 116.0 (t, *J* = 253.7 Hz), 62.9, 22.0, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2989, 1766, 1446, 1371, 1295, 1153, 1093, 1023, 936, 830, 759, 725, 673 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{16}F_2NO_2$ [M + H]$^+$ 316.1144; found 316.1145.

Ethyl (2-Chlorophenanthridin-6-yl)difluoroacetate (3g): Purification by silica gel chromatography (petroleum ether/EtOAc, 50:1) gave compound **3g** (69 %) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52–8.45 (m, 2 H), 8.42 (d, *J* = 2.3 Hz, 1 H), 7.99 (d, *J* = 8.7 Hz, 1 H), 7.85 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1 H), 7.73 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1 H), 7.64 (dd, *J* = 8.7, 2.2 Hz, 1 H), 4.57 (q, *J* = 7.1 Hz, 2 H), 1.48 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –98.71 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.4 (t, *J* = 30.8 Hz), 150.3 (t, *J* = 29.1 Hz), 139.9, 135.0, 132.7, 132.1, 131.5, 129.6, 128.5, 126.2 (t, *J* = 4.9 Hz), 125.8, 122.4, 122.3, 121.7, 115.6 (t, *J* = 254.1 Hz), 63.1, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2991, 2934, 1764, 1605, 1565, 1520, 1483, 1372, 1295, 1154, 1096, 1016, 937 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{13}ClF_2NO_2$ [M + H]$^+$ 336.0597; found 336.0594.

Ethyl Difluoro-(3-methoxyphenanthridin-6-yl)acetate (3h): Purification by silica gel chromatography (petroleum ether/EtOAc, 50:1) gave compound **3h** (52 %) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52–8.45 (m, 2 H), 8.40 (d, *J* = 9.0 Hz, 1 H), 7.81 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1 H), 7.64 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.46 (d, *J* = 2.7 Hz, 1 H), 7.34 (dd, *J* = 9.0, 2.7 Hz, 1 H), 4.57 (q, *J* = 7.1 Hz, 2 H), 3.95 (s, 3 H), 1.46 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –98.75 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.7 (t, *J* = 31.1 Hz), 160.2, 150.4 (t, *J* = 28.6 Hz), 143.4, 134.0, 131.2, 126.7, 126.1 (t, *J* = 4.8 Hz), 123.2, 121.9, 121.4, 120.0, 118.9, 115.6 (t, *J* =

254.1 Hz), 110.3, 63.0, 55.6, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2990, 2936, 2844, 1767, 1615, 1478, 1374, 1302, 1252, 1210, 1095, 1031, 931, 829 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{16}F_2NO_3$ $[M + H]^+$ 332.1093; found 332.1095.

Ethyl Difluoro-(2-trifluoromethylphenanthridin-6-yl)acetate (3i): Purification by silica gel chromatography (petroleum ether/EtOAc, 50:1) gave compound **3i** (27 %) as a dark red solid. M.p. 93–95 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.89 (s, 1 H), 8.72 (d, *J* = 8.3 Hz, 1 H), 8.60 (dd, *J* = 6.4, 4.2 Hz, 1 H), 8.24 (d, *J* = 8.5 Hz, 1 H), 7.99 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1 H), 7.95 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.84 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1 H), 4.60 (q, *J* = 7.1 Hz, 2 H), 1.50 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.08, –98.95 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.3 (t, *J* = 30.7 Hz), 152.3 (t, *J* = 29.3 Hz), 143.0, 133.5, 132.0, 131.7, 130.4 (q, *J* = 32.7 Hz), 129.1, 128.8, 126.5 (t, *J* = 4.9 Hz), 125.0 (q, *J* = 3.4 Hz), 124.5, 124.0 (q, *J* = 272.7 Hz), 122.5, 119.9 (q, *J* = 4.3 Hz), 115.4 (t, *J* = 254.6 Hz), 63.1, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2996, 2949, 1762, 1430, 1368, 1306, 1230, 1175, 1124, 1016, 934 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{13}F_5NO_2$ $[M + H]^+$ 370.0861; found 370.0864.

Ethyl (2,8-Dimethylphenanthridin-6-yl)difluoroacetate (3j): Purification by silica gel chromatography (petroleum ether/EtOAc, 20:1) gave compound **3j** (54 %) as a pale yellow solid. M.p. 113–116 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 8.5 Hz, 1 H), 8.26 (s, 1 H), 8.21 (s, 1 H), 7.93 (d, *J* = 8.3 Hz, 1 H), 7.61 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.48 (dd, *J* = 8.4, 1.8 Hz, 1 H), 4.58 (q, *J* = 7.1 Hz, 2 H), 2.59 (s, 3 H), 2.57 (s, 3 H), 1.49 (t, *J* = 7.2 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –98.71 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.8 (t, *J* = 30.9 Hz), 148.7 (t, *J* = 29.1 Hz), 139.7, 138.9, 137.7, 132.6, 131.3, 130.3, 130.2, 125.3 (t, *J* = 4.6 Hz), 124.7, 122.5, 122.2, 121.4, 116.1 (t, *J* = 253.7 Hz), 62.9, 22.1, 21.8, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 1715, 1425, 1362, 1222, 1091, 902, 736 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{18}F_2NO_2$ $[M + H]^+$ 330.1300; found 330.1302.

Ethyl (Benzo[*c*][2,7]naphthyridin-5-yl)difluoroacetate (3k): Purification by silica gel chromatography (petroleum ether/EtOAc, 3:1) gave compound **3k** (35 %) as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.88 (s, 1 H), 8.97 (d, *J* = 5.8 Hz, 1 H), 8.52 (dd, *J* = 8.0, 1.4 Hz, 1 H), 8.39 (d, *J* = 5.7 Hz, 1 H), 8.11 (dd, *J* = 8.2, 1.4 Hz, 1 H), 7.92–7.71 (m, 2 H), 4.57 (q, *J* = 7.1 Hz, 2 H), 1.47 (t, *J* = 7.2 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –97.49 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.0 (t, *J* = 30.5 Hz), 150.1 (t, *J* = 29.5 Hz), 150.0, 148.9, 142.8, 138.5, 131.3, 131.0, 129.6, 122.7, 122.5, 117.6, 115.6, 115.1 (t, *J* = 254.0 Hz), 63.2, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2987, 2933, 2866, 1777, 1603, 1569, 1515, 1471, 1414, 1371, 1304, 1155, 1104, 937 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{13}F_2N_2O_2$ $[M + H]^+$ 303.0940; found 303.0943.

Ethyl Difluoro-(8-methyl-thieno[3,2-*c*]quinolin-4-yl)acetate (3l): Purification by silica gel chromatography (petroleum ether/EtOAc, 3:1) gave compound **3l** (21 %) as a yellow solid. M.p. 63–65 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.5 Hz, 1 H), 7.93–7.86 (m, 2 H), 7.64 (d, *J* = 5.4 Hz, 1 H), 7.55 (dd, *J* = 8.5, 1.9 Hz, 1 H), 4.52 (q, *J* = 7.1 Hz, 2 H), 2.63 (s, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –101.56 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.4 (t, *J* = 31.6 Hz), 146.9, 145.6 (t, *J* = 29.9 Hz), 140.3, 139.1, 131.1, 130.5, 128.8, 126.9, 124.7, 123.4 (t, *J* = 3.9 Hz), 122.3, 114.3 (t, *J* = 251.9 Hz), 63.1, 21.8, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 2857, 1771, 1656, 1513, 1458, 1380, 1280, 1177, 1106, 1024, 827, 744 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{14}F_2NO_2S$ $[M + H]^+$ 322.0708; found 322.0711.

Ethyl Difluoro(pyrrolo[1,2-*a*]quinoxalin-4-yl)acetate (3m): Compound **3m** was synthesized in the same way, except that 1-(2-isocyano-phenyl)-1*H*-pyrrole (**1m**; 1.0 mmol, 2 equiv.) and $TMSCF_2CO_2Et$ (**2**; 0.5 mmol, 1 equiv.) were used. Purification by silica gel chromatography (petroleum ether/EtOAc, 50:1) gave compound **3m** (26 %) as a dark yellow solid. M.p. 70–71 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 2.7, 1.2 Hz, 1 H), 7.97 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.87 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.63–7.56 (m, 1 H), 7.50–7.40 (m, 1 H), 7.24–7.15 (m, 1 H), 6.96 (dd, *J* = 4.2, 2.7 Hz, 1 H), 4.48 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –105.83 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.9 (t, *J* = 31.7 Hz), 146.1 (t, *J* = 29.5 Hz), 134.1, 130.9, 129.5, 127.8, 125.5, 121.8, 115.2, 114.7, 113.7, 113.0 (t, *J* = 253.5 Hz), 108.1 (t, *J* = 3.3 Hz), 63.2, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 2859, 1768, 1612, 1544, 1467, 1374, 1308, 1106, 767, 715 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{13}F_2N_2O_2$ $[M + H]^+$ 291.0940; found 291.0945.

Ethyl [1-(Ethoxycarbonyldifluoromethyl)pyrrolo[1,2-*a*]quinoxalin-4-yl]difluoroacetate (3m′): Compound **3m′** was synthesized in the same way except that the reaction time was 72 h. Purification by silica gel chromatography (petroleum ether/EtOAc, 50:1) gave compound **3m′** (34 %) as a bright yellow solid. M.p. 78–81 °C. ^1H NMR (500 MHz, CD_2Cl_2): δ = 8.23 (d, *J* = 8.6 Hz, 1 H), 8.07 (dd, *J* = 8.0, 1.7 Hz, 1 H), 7.72 (ddd, *J* = 8.8, 7.2, 1.7 Hz, 1 H), 7.62 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1 H), 7.31 (d, *J* = 1.1 Hz, 2 H), 4.51 (q, *J* = 7.1 Hz, 2 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 1.42 (dd, *J* = 7.6, 6.7 Hz, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (471 MHz, CD_2Cl_2): δ = –93.01, –105.45 ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.9 (t, *J* = 33.7 Hz), 162.5 (t, *J* = 31.3 Hz), 145.9 (t, *J* = 29.5 Hz), 135.1, 131.5, 130.0, 128.0, 126.3, 125.6, 122.4 (t, *J* = 31.0 Hz), 118.7 (t, *J* = 6.8 Hz), 116.8 (t, *J* = 7.8 Hz), 113.0 (t, *J* = 253.9 Hz), 111.0 (t, *J* = 247.2 Hz), 107.3 (t, *J* = 3.7 Hz), 64.0, 63.4, 14.0, 13.7 ppm. IR (KBr): $\tilde{\nu}$ = 2991, 2924, 2860, 1769, 1622, 1550, 1463, 1380, 1301, 1246, 1110, 1060, 755 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{19}H_{17}F_4N_2O_4$ $[M + H]^+$ 413.1119; found 413.1124.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Nos. 21572128, 21672139) and the Science Foundation of Shanghai Municipal Commission of Sciences and Technology (No. 15230724800). The authors thank the Laboratory of Micro-structures of Shanghai University for structure analysis.

Keywords: Fluorinated compounds · Fluorine · Radicals · Cyclization · Isocyanides · Nitrogen heterocycles

[1] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) J. P. Begue, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, **2008**; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308; d) Ojima, I., *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley–Blackwell, Chichester, **2009**; e) J. Wang, M. Sánchez-Roselló, J. Aceña, C. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[2] a) G. M. Blackburn, D. A. England, F. Kolkmann, *Chem. Soc. Chem. Commun.* **1981**, 930–932; b) Y. Xu, J. Aoki, K. Shimizu, M. Umezu-Goto, K. Hama, Y. Takanezawa, S. Yu, G. B. Mills, H. Arai, L. Qian, G. D. Prestwich, *J. Med. Chem.* **2005**, *48*, 3319–3327; c) T. Hakogi, T. Yamamoto, S. Fujii, K. Ikeda, S. Katsumura, *Tetrahedron Lett.* **2006**, *47*, 2627–2630; d) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319; e) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; f) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

[3] a) W. Qiu, D. J. Burton, *Tetrahedron Lett.* **1996**, *37*, 2745–2748; b) T. Yokomatsu, T. Murano, K. Suemune, S. Shibuya, *Tetrahedron* **1997**, *53*, 815–822; c) M. K. Schwaebe, J. R. McCarthy, J. P. Whitten, *Tetrahedron Lett.* **2000**, *41*, 791–794; d) J. Zhu, W. Zhang, L. Zhang, J. Liu, J. Zheng, J. Hu, *J. Org. Chem.* **2010**, *75*, 5505–5512; e) Z. Feng, F. Chen, X. Zhang, *Org.*

Lett. **2012**, *14*, 1938–1941; f) Q. Qi, Q. Shen, L. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 6548–6551; g) M. Belhomme, T. Poisson, X. Pannecouke, *Org. Lett.* **2013**, *15*, 3428–3431; h) Z. Feng, Y. Xiao, X. Zhang, *Org. Chem. Front.* **2014**, *1*, 113–116; i) Z. Feng, Q. Min, Y. Xiao, B. Zhang, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1669–1673; *Angew. Chem.* **2014**, *126*, 1695–1699; j) Q. Min, Z. Yin, Z. Feng, W. Guo, X. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 1230–1233.

[4] a) T. Nakanishi, J. Suzuki, *J. Nat. Prod.* **1998**, *61*, 1263–1267; b) T. Nakanishi, M. Suzuki, A. Saimoto, T. Kabasawa, *J. Nat. Prod.* **1999**, *62*, 864–867; c) T. Ishikawa, *Med. Res. Rev.* **2001**, *21*, 61–67; d) W. A. Denny, *Curr. Med. Chem.* **2002**, *9*, 1655–1665; e) S. Zhu, A. L. Ruchelman, N. Zhou, A. Liu, L. F. Liu, E. LaVoie, *Bioorg. Med. Chem.* **2005**, *13*, 6782–6794; f) P. H. Bernardo, K. F. Wan, T. Sivaraman, J. Xu, F. K. Moore, A. W. Hung, H. Y. K. Mok, V. C. Yu, C. L. L. Chai, *J. Med. Chem.* **2008**, *51*, 6699–6710; g) E. Dubost, N. Dumas, C. Fossey, R. Magnelli, S. Butt-Gueulle, C. Balladonne, D. H. Caignard, F. Dulin, J. S. d.-O. Santos, P. Millet, Y. Charnay, S. Rault, T. Cailly, F. Fabis, *J. Med. Chem.* **2012**, *55*, 9693–6707.

[5] a) S. D. Phillips, R. N. Castle, *J. Heterocycl. Chem.* **1981**, *18*, 223–232; b) S. Simeon, J. L. Rios, A. Villar, *Pharmazie* **1989**, *44*, 593–597; c) O. B. Abdel-Halim, T. Morikawa, S. Ando, H. Matsuda, M. Yoshikawa, *J. Nat. Prod.* **2004**, *67*, 1119–1124; d) L. Sripada, J. A. Teske, A. Deiters, *Org. Biomol. Chem.* **2008**, *6*, 263–265.

[6] a) Z. Zhang, X. Tang, W. R. Dolbier Jr., *Org. Lett.* **2015**, *17*, 4401–4403; b) J.-W. Gu, X. Zhang, *Org. Lett.* **2015**, *17*, 5384–5387; c) W. Wan, G. Ma, J. Li, Y. Chen, Q. Hu, M. Li, H. Jiang, H. Deng, J. Hao, *Chem. Commun.* **2016**, *52*, 1598–1601; d) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu, J. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2743–2747; *Angew. Chem.* **2016**, *128*, 2793–2797; e) P. Xiao, J. Rong, C. Ni, J. Guo, X. Li, D. Chen, J. Hu, *Org. Lett.* **2016**, *18*, 5912–5915.

[7] X. Sun, S. Yu, *Org. Lett.* **2014**, *16*, 2938–2941.

[8] a) G. Ma, W. Wan, Q. Hu, H. Jiang, J. Wang, S. Zhu, J. Hao, *Chem. Commun.* **2014**, *50*, 7527–7530; b) H. Jiang, W. Lu, K. Yang, G. Ma, M. Xu, J. Li, J. Yao, W. Wan, H. Deng, S. Wu, S. Zhu, J. Hao, *Chem. Eur. J.* **2014**, *20*, 10084–10092; c) G. Ma, W. Wan, J. Li, Q. Hu, H. Jiang, S. Zhu, J. Wang, J. Hao, *Chem. Commun.* **2014**, *50*, 9749–9752.

[9] a) J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc.* **1970**, *92*, 1651–1659; b) J. M. Anderson, J. K. Kochi, *J. Org. Chem.* **1970**, *35*, 986–989; c) S. Seo, J. B. Taylor, M. F. Greaney, *Chem. Commun.* **2012**, *48*, 8270–8272; d) M. Tobisu, K. Koh, T. Furukawa, N. Chatani, *Angew. Chem. Int. Ed.* **2012**, *51*, 11363–11366; *Angew. Chem.* **2012**, *124*, 11525–11528; e) Q. Wang, X. Dong, T. Xiao, L. Zhou, *Org. Lett.* **2013**, *15*, 4846–4849.

[10] a) Y. Ye, S. H. Lee, M. S. Sanford, *Org. Lett.* **2011**, *13*, 5464–5467; b) Q. Lin, L. Chu, F.-L. Qing, *Chin. J. Chem.* **2013**, *31*, 885–891; c) J. Jung, E. Kim, Y. You, E. J. Cho, *Adv. Synth. Catal.* **2014**, *356*, 2741–2748; d) J. Li, W. Wan, G. Ma, Y. Chen, Q. Hu, K. Kang, H. Jiang, J. Hao, *Eur. J. Org. Chem.* **2016**, 4916–4921.

[11] a) K. Uneyama, G. Mizutani, K. Maeda, T. Kato, *J. Org. Chem.* **1999**, *64*, 6717–6723; b) Y. Cheng, H. Jiang, Y. Zhang, S. Yu, *Org. Lett.* **2013**, *15*, 5520–5523; c) L. Wang, W. Sha, Q. Dai, X. Feng, W. Wu, H. Peng, B. Chen, J. Cheng, *Org. Lett.* **2014**, *16*, 2088–2091; d) B. Zhang, C. Mück-Lichtenfeld, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.* **2013**, *52*, 10792–10795; *Angew. Chem.* **2013**, *125*, 10992–10995; e) J. C. Antilla, J. M. Baskin, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 5578–5587; f) see ref.[9e].

Received: April 5, 2017