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Radical Anions of Aromatic Carbonitriles as Reagents for Arylation of Fluorinated Benzonitriles

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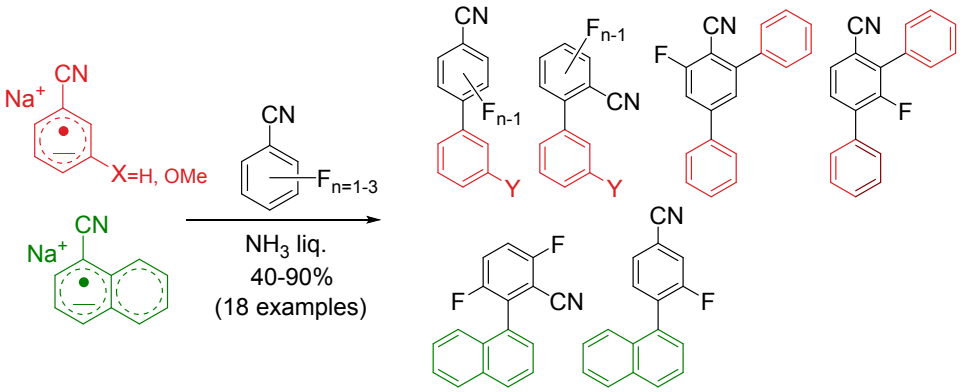
Abstract

The first example of phenylation of fluorobenzonitriles with the sodium salt of a benzonitrile radical anion in liquid ammonia is presented. The reaction regioselectivity corresponds to the *ortho*- and *para*-fluorine atom substitution in fluorobenzonitrile with the phenyl moiety of the benzonitrile radical anion and affords 2- and 4-cyanobiphenyls in 40–90% yields. 3-Methoxybenzonitrile as well as 1-cyanonaphthalene radical anions were also successfully subjected to this interaction forming 3′-methoxycyanobiphenyls and (1-naphthyl)benzonitriles, respectively. The radical anion acts as an *ipso*-C-nucleophile with consequent loss of the cyano group. The revealed new type of radical anion reactivity opens up the prospect of developing a general approach to fluorinated cyanobisarenes on the basis of an interaction of the cyanoarene radical anion with fluorinated substrates activated to aromatic nucleophilic substitution.

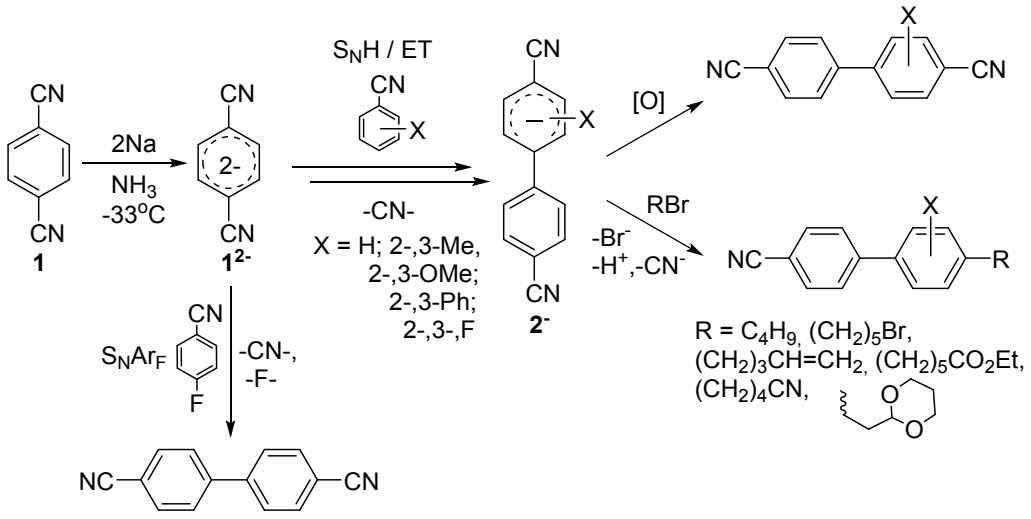


Keywords: fluorinated cyanobiphenyls; cyanoarene radical anion; aromatic substitution of fluorine

Introduction

Cyanoarenes are known to yield long-living anionic species (radical anions, dianions, and cyclohexadienyl anions) in preparative amounts via reduction by alkali metals in liquid ammonia.[1] A common feature of these anionic forms is the HOMO localization mostly on the aromatic ring, not in the cyano group.[2,3] That is why alkylation occurs at the *ipso*- or unsubstituted (predominantly *para*-) position of the aromatic fragment thus producing alkylarenes, alkylcyanoarenes, or dihydro derivatives in good-to-high yields.[1] In addition to high productivity of cyanoarenes in Birch reductive alkylation, we uncovered the possibility of arylation of neutral aromatic substrates (benzonitrile,[4] tolunitrile, methoxy- and fluorobenzonitrile,[5,6] or 2- and 3-cyanobiphenyl[7]) with terephthalonitrile dianion $\mathbf{1}^{2-}$. The coupling of dianion $\mathbf{1}^{2-}$ with neutral cyanoarenes proceded predominantly as a nucleophilic substitution of the substrate *para*-hydrogen atom with the *para*-cyanophenyl moiety of dianion (S_NH) and/or one electron transfer followed by recombination of radical anions in a primary cage (*ET*). Oxidation or alkylation of thus formed long-living dimeric anion $\mathbf{2}^{-}$ provided the corresponding biphenyl- and terphenylcarbonitriles and their alkylated derivatives in a one-pot manner (Scheme 1). Nevertheless, there was one example of a fluorine atom substitution (S_NAr_f) when dianion $\mathbf{1}^{2-}$ reacted with 4-fluorobenzonitrile and formed 4,4′-dicyanobiphenyl[5].

Scheme 1. *para*-Cyanophenylation of cyanoarenes with terephthalonitrile dianion



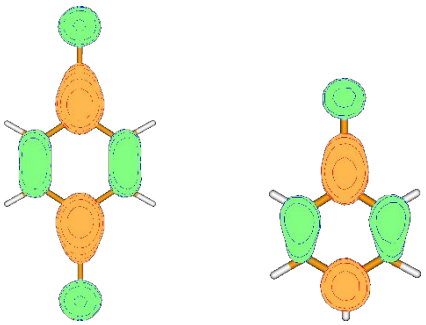
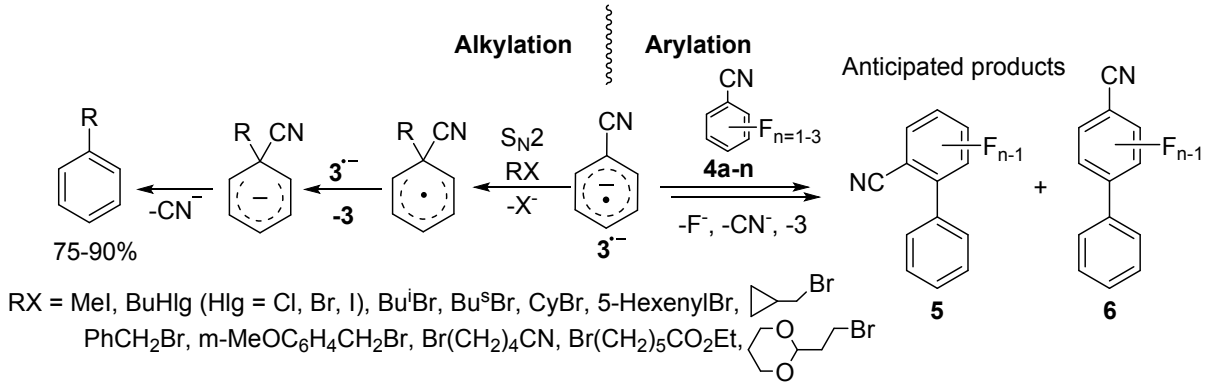


Figure 1. A HOMO view of dianion $\mathbf{1}^{2-}$ (left) and SOMO of radical anion $\mathbf{3}^{\bullet-}$ (right) (DFT (U)M06-2X/6-31G(d), US GAMESS).[8]

The development of the synthetic approach to bisarenes utilizing the anionic forms of cyanarenes requires clarification of the possibility of involving an anionic form other than dianion $\mathbf{1}^{2-}$ in aromatic cross-coupling. Our attention was drawn to benzonitrile radical anion $\mathbf{3}^{\bullet-}$ for the following reasons: it closely resembles dianion $\mathbf{1}^{2-}$ in terms of electronic structure (Figure 1); its reactivity toward alkyl halides has proved to be nucleophilic only and results in selective *ipso*-alkylation of $\mathbf{3}^{\bullet-}$[9–11] giving alkylbenzenes in high yields (Scheme 2, Alkylation). We assumed the nucleophilic reactivity of $\mathbf{3}^{\bullet-}$ to be a promising feature that could be responsible for the fluorine atom substitution in fluorinated benzonitriles. These compounds are commonly used as universal structural blocks activated to aromatic nucleophilic substitution with various nucleophiles, thereby affording products that are prone to further modifications via substitution of fluorine atoms as well as transformations in the cyano group.[12–15] We chose mono-, di-, and trifluorobenzonitriles **4a–n** as neutral substrates for testing $\mathbf{3}^{\bullet-}$ because substrates that are more fluorinated cannot be used in a liquid ammonia medium owing to rapid aminodefluorination. In case of success, the arylation of fluorobenzonitriles by the radical anion $\mathbf{3}^{\bullet-}$ would lead to the selective one-pot synthesis of fluorinated 2- (**5**) and 4-cyanobiphenyls (**6**) (Scheme 2, Arylation). It should be noted that fluorinated cyanbiphenyls are valuable *p*-deficient building blocks on both supramolecular chemistry[16] and materials science[17] as well as precursors of biologically active substances,[18,19] including agrochemicals.[20]

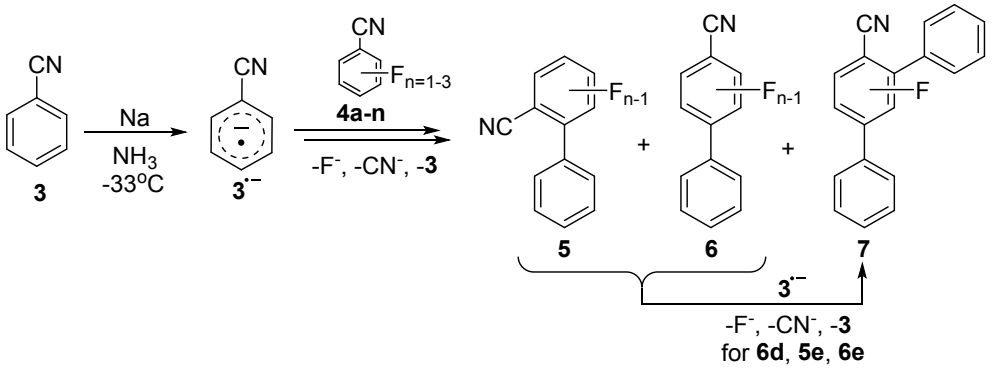
Scheme 2. Benzonitrile radical anion alkylation products formation and anticipated arylation products

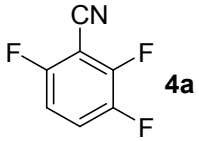
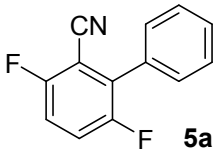


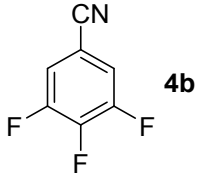
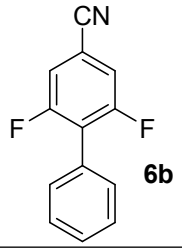
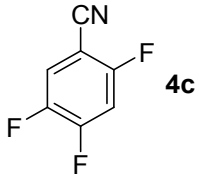
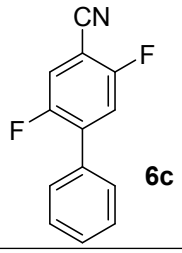
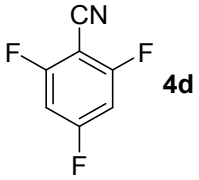
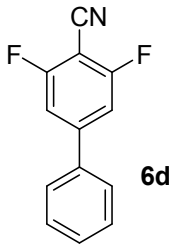
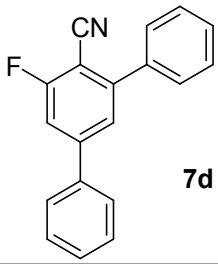
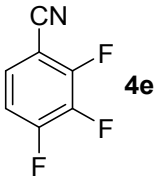
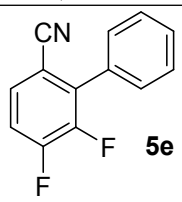
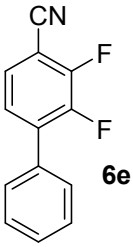
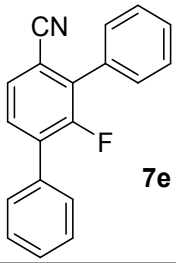
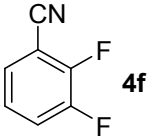
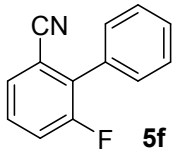
Results and Discussion

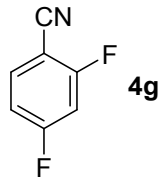
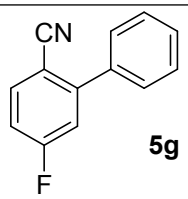
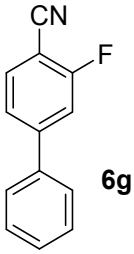
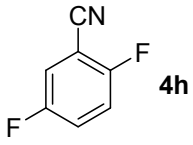
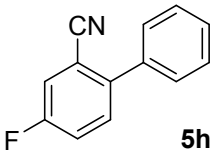
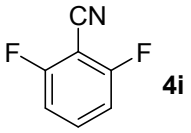
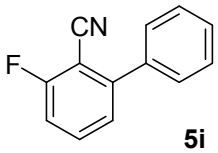
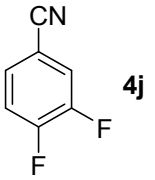
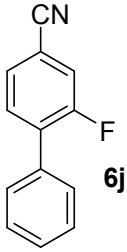
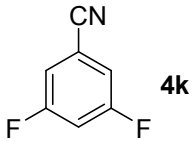
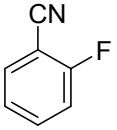
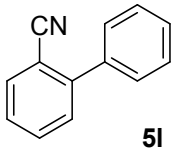
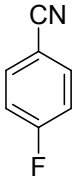
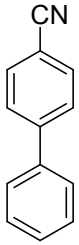
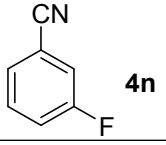
We began with trifluorobenzonitriles **4a–e** as the most reactive substrates. Radical anion **3**$^{\bullet-}$ was generated by the reduction of benzonitrile 3 with sodium in liquid ammonia. Because of the stoichiometry of the radical anionic transformations, half the amount of trifluorobenzonitrile **4a–e** was employed with respect to the salt of radical anion **3**$^{\bullet-}$. The expected difluorocyanobiphenyls **5a**,**e** and **6b–e** formed in all cases with good total yields (Entries 1–5, Table 1).

Table 1: Interaction of radical anion **3**$^{\bullet-}$ sodium salt with fluorinated benzonitriles in liquid ammonia at –33 ºC[a]



Entry	Fluorobenzonitrile	Products	Product yield[b]
1	 **4a**	 **5a**	50 (41)

2	 **4b**	 **6b**	62 (56)
3	 **4c**	 **6c**	72 (68)
4	 **4d**	 **6d**  **7d**	8 (7) 56 (50)
5	 **4e**	 **5e**  **6e**  **7e**	15[21] 21 (20) 30 (25)
6[b]	 **4f**	 **5f**	37 (25)[22]

7	 **4g**	 **5g**  **6g**	2^{23} 85 (65)[24]
8	 **4h**	 **5h**	13^{25}
9	 **4i**	 **5i**	69 (51)[26]
10	 **4j**	 **6j**	75 (60)
11	 **4k**	---	
12	 **4l**	 **5l**	35
13	 **4m**	 **6m**	93
14	 **4n**	---	

[a] Benzonitrile (4.0 mmol), sodium (3.0 mmol), fluorinated benzonitrile (1.5 mmol), liquid ammonia ~40 mL, duration of the reaction: 1–2 h.

[b] NMR yield, % (isolated yield, %) calculated as mean values from no fewer than two runs. Deviation does not exceed 5%

Utilization of benzonitriles **4d** and **4e** provided *m*-terphenyls [5′-fluoro- (**7d**) and 2′-fluoro-[1,1′:3′,1″-terphenyl]-4′-carbonitrile (**7e**), respectively] along with biphenyls **6d**, **5e**, and **6e** (Entries 4 and 5, Table 1). The formation of terphenyls **7d** and **7e** is obviously caused by the involvement of initially formed biphenyls **6d** and **5e**, **6e** into further arylation. According to this notion, an increase in the molar ratio of $\mathbf{3}^{\bullet-}$ to **4e** from 2/1 to 8/1 led to an increase in the terphenyl **7e** yield from 30% to 58%, with the yield of *para*-cyanobiphenyl **6e** being only 2%, whereas the *ortho*-isomer **5e** was almost absent. It should be mentioned that in addition to the target products **5**, **6**, and **7**, the reaction mixtures always contained some amount of starting benzonitriles **3** and **4** (10–50% of the initial amount), as well as minor components whose molecular weights corresponded to di- and tetrafluorodicyanobiphenyls (~5% in total), aminofluorocyanobiphenyls (1–3%), and difluorinated 4-amino-2-phenylquinazolines (2–10%, their formation is discussed below). All the synthesized difluorobiphenylcarbonitriles were readily isolated from reaction mixtures via preparative TLC.

The involvement of difluorobenzonitriles **4f–k** in the interaction with $\mathbf{3}^{\bullet-}$ was successful for substrates containing *ortho*- and *para*-fluorine atoms, activated to substitution (Entries 6, 7, 9, and 10 in Table 1). In the case of 2,5-difluorobenzonitrile **4h**, cyanobiphenyl **5h** formed in a low yield, whereas phenylation of 3,5-difluorobenzonitrile **4k** did not take place at all (Entries 8 and 11 in Table 1). Unlike transformations involving trifluorobenzonitriles **4d** and **4e**, reactions with difluorobenzonitriles **4g** and **4i** did not lead to the formation of terphenylcarbonitriles. Probably, monofluorinated cyanobiphenyls **6g** and **5i** are less activated to phenylation by $\mathbf{3}^{\bullet-}$ than their difluorinated analogs are. Data on 5-fluoro-2-cyanobiphenyl **5g**[23] and 4-fluoro-2-cyanobiphenyl **5h**[25] can be found in the literature (catalytic cross-coupling was conducted for their synthesis). Because of their small content in the reaction mixtures, we did not isolate these products.

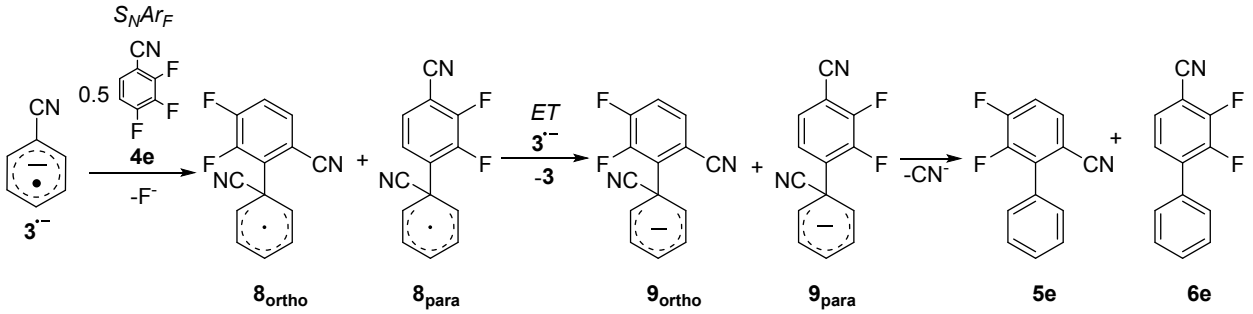
With respect to monofluorobenzonitriles **4l–n**, only 4-fluorobenzonitrile **4m** converted into corresponding 4-cyanobiphenyl **6m** almost completely (Entry 13, Table 1). 2-Fluorobenzonitrile **4l** resulted in the formation of 2-cyanobiphenyl **5l** with a significantly lower yield (Entry 12, Table 1). In the case of 3-fluorobenzonitrile **4n**, no phenylation occurred, and the reaction mixture contained mainly benzonitriles **3** and **4n** (46% and 31%), a small amount (~5%) of benzamides, and phenylated 1,3,5-triazines, being products of starting nitriles alkaline hydrolysis and trimerization, respectively.

The above results indicate well-pronounced productivity of radical anion $\mathbf{3}^{\bullet-}$ as a reagent for the phenylation of fluorobenzonitriles regardless of the number of fluorine atoms in substrates **4**. The substitution of fluorine occurs at positions *ortho*- and *para*- toward the cyano group of **4**, in agreement with the orientation observed in the reactions of these compounds with carbon-

centered and heteroatomic nucleophiles proceeding via the S_NAr mechanism[12–14,27–30]. Taking these data into account, it could be assumed that radical anion **3**$^{\bullet-}$ has the properties of a nucleophile rather than a one-electron donor toward fluorinated benzonitriles **4**. At the same time, the detection of fluorinated dicyanobiphenyls as minor byproducts does not allow us to completely eliminate some *ET*-share of the **3**$^{\bullet-}$ reactivity. Dicyanobiphenyls can arise as a result of the *ET* from **3**$^{\bullet-}$ to fluorobenzonitriles **4** affording radical anions prone to dimerization followed by the departure of fluoride.[31,32]

Scheme 3 illustrates the reaction pathway proposed for the phenylation of fluorinated benzonitriles **4** by radical anion **3**$^{\bullet-}$, with trifluorobenzonitrile **4e**. At the first stage, the substitution of the *ortho*- and *para*-fluorine atom in benzonitrile **4e** by the **3**$^{\bullet-}$ *ipso*-carbon atom bearing the maximum electron density (see Figure 1) takes place, leading to the corresponding biphenyl radicals $\mathbf{8}_{ortho}$ and $\mathbf{8}_{para}$. Further reduction of these radicals with radical anion **3**$^{\bullet-}$ yields anions $\mathbf{9}_{ortho}$ and $\mathbf{9}_{para}$ (containing a geminal cyano group), which rapidly undergo decyanation, thus restoring aromaticity and providing cyanobiphenyls **5e** and **6e**.

Scheme 3. Phenylation of fluorobenzonitrile 4e with benzonitrile radical anion

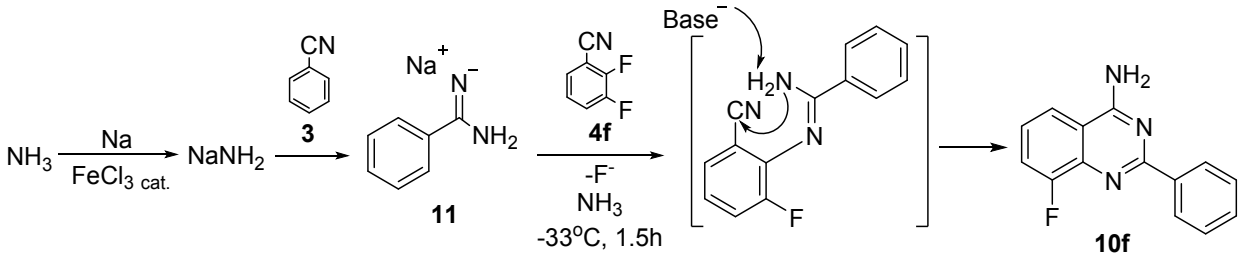


Evaluating the synthetic productivity of the reaction under investigation, it should be noted that all the product mixtures obtained in the reactions of *ortho*-fluorinated benzonitriles contained corresponding 4-amino-2-phenylquinazolines (**10**) in substantial amounts along with target cyanobiphenyls **5** and **6**. The highest content (33%) was found for 4-amino-2-phenyl-8-fluoroquinazoline (**10f**) formed in the reaction of 2,3-difluorobenzonitrile **4f**. This new quinazoline was isolated (yield 27%), and its structure was confirmed by X-ray analysis (Figure 1 in SI).

Probably, the formation of aminoquinazolines **10** is due to some processes initiated by the amide anion and proceeding in parallel with the main reaction (the presence of the amide ion is quite likely under the conditions employed). This assumption was confirmed by counter-synthesis (alike[33]) involving the formation of amidine **11** sodium salt from benzonitrile **3** under the action of sodium amide, and subsequent interaction with difluorobenzonitriles **4f** or **4i**

accomplished by the cyclization into quinazolines **10f** or **10i**, respectively, with a yield of 40% and 42% (Scheme 4). For **10i**, a crystal suitable for XRD analysis was obtained (Figure 2 in SI). Quinazolines are among privileged structures with a wide spectrum of biological activities[34–37]; therefore, the demonstrated simplicity and ease of preparation of fluorinated 4-amino-2-phenyl derivatives **10** according to the proposed scheme in liquid ammonia has synthetic value, but beyond the scope of the present work.

Scheme 4. The way assumed for 4-amino-2-quinazolines 10 formation



Regarding the phenylation of fluorinated benzonitriles **4** by radical anion **3**$^{\bullet-}$, we have every reason to suppose that the revealed new type of reactivity could also be inherent in radical anions of other cyanoarenes, characterized by a common type of electronic structure. To determine whether the revealed reaction is of a general nature, radical anions of 3-methoxybenzonitrile (**12**$^{\bullet-}$) and 1-cyanonaphthalene (**13**$^{\bullet-}$, Figure 2) were subjected to the interaction with fluorinated benzonitriles **4a**, **4c**, **4j**, and **4l**.

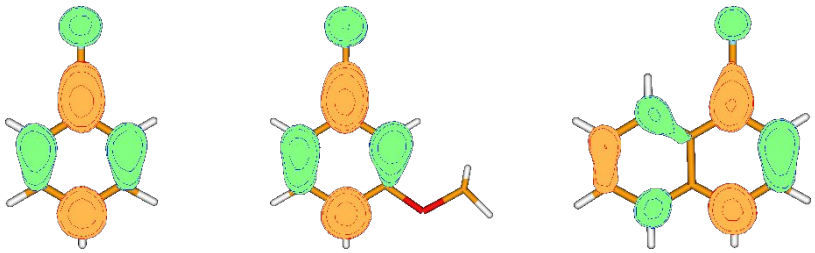
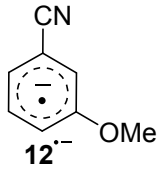
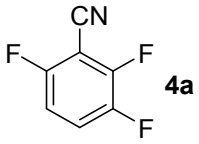
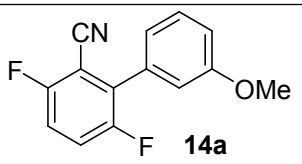
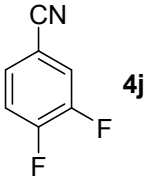
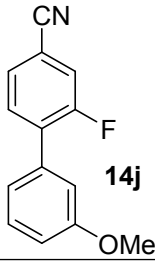
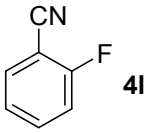
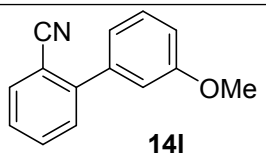
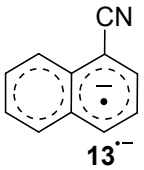
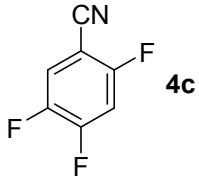
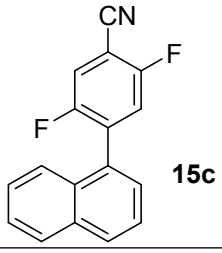
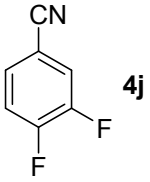
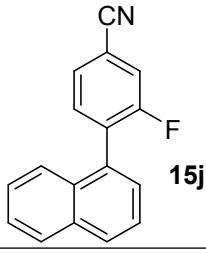
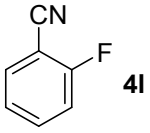
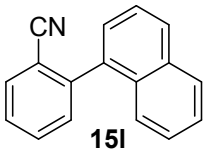


Figure 2. A SOMO view of radical anions **3**$^{\bullet-}$ (left), **12**$^{\bullet-}$ (middle), and **13**$^{\bullet-}$ (right) (DFT UM06-2X/6-31G(d), US GAMESS).

Generation of radical anions **12**$^{\bullet-}$ and **13**$^{\bullet-}$ and their reactions with fluorinated benzonitriles were carried out under the conditions analogous to phenylation with radical anion **3**$^{\bullet-}$. As expected, target cyanobisaryls **14** and **15** were detected for both radical anions; **12**$^{\bullet-}$ proved to be more productive (Table 2). Radical anion **13**$^{\bullet-}$ provided naphthylbenzonitriles **15** with the yields decreasing markedly with the diminishing number of fluorine atoms in substrate **4**.

Table 2: Interaction of radical anion **12**$^{\bullet-}$ and **13**$^{\bullet-}$ sodium salts with fluorinated benzonitriles in liquid ammonia at –33 ºC[a]

Entry	Radical anion	Fluorobenzonitrile	Product	Product yield[b]
1	 **12**$^{\bullet-}$	 **4a**	 **14a**	60 (38)
2		 **4j**	 **14j**	85 (56)
3		 **4l**	 **14l**	83
4	 **13**$^{\bullet-}$	 **4c**	 **15c**	43 (31)
5		 **4j**	 **15j**	35 (28)
6		 **4l**	 **15l**	traces

[a] Nitrile **12** or **13** (4.0 mmol), sodium (3.0 mmol), fluorinated benzonitrile (1.5 mmol), and liquid ammonia ~40 mL; duration of the reaction 1–2 h.

[b] NMR yield, % (isolated yield, %) calculated as mean values of no fewer than two runs. Deviation does not exceed 5%

The known 3′-methoxy-[1,1′-biphenyl]-2-carbonitrile **14l**[38] and 2-(naphthalen-1-yl)benzonitrile **15l**,[39] which formed in the reactions of **12**$^{\bullet-}$ and **13**$^{\bullet-}$ with fluorobenzonitrile **4l**, were not isolated from the reaction mixtures. Fluorinated methoxycyanobiphenyls **14a** and **14j** as well as naphthylbenzonitriles **15c** and **15j** are novel compounds, in addition to the spectral characteristics, a single crystal was grown from products **14j** and **15c** for structural verification by the X-ray diffraction analyses (Figures 3, 4 in SI, respectively).

The localization of the methoxy group at the 3′-position of the biphenyl core in all the products **14** indicated that radical anion **12**$^{\bullet-}$ behaved as the *ipso*-localized nucleophile. On the contrary, the *para*-localization of the nucleophilic center should lead to the formation of 2′-methoxylated isomers of **14**, which were not observed. Thus, the experimental evidence has been obtained in favor of validity of the reaction pathway suggested above, which involves formation of the new bond between the *ipso*-atom of the cyanoarene radical anion and the fluorinated carbon atom of the substrate activated to nucleophilic substitution (Scheme 3).

Conclusion

For the first time, we propose a convenient one-pot synthesis of cyanobisarenes using the benzo- and naphthonitrile radical anions in liquid ammonia as nucleophilic reagents effectively substituting the aromatic fluorine atoms. We obtained 11 new fluorinated cyanoarenes with a biphenylic, terphenylic, and phenylnaphthylic framework.

Recently, Zhang and collegues[40] described the selective C-F bond arylation through palladium-catalyzed cross-coupling of polyfluoroarenes with arylboronic acids. It is worth noting that the authors link the high reaction regioselectivity with the significant nucleophilic character of chosen electron-rich palladium complex (Pd(0)BrettPhos) which facilitates the oxidative addition of the Pd center to the C−F bond.

As for the the synthetic utilization of the cross-coupling of radical anions with neutral fluoroaromatic substrates, that is an almost unexplored area. The synthetically significant reactions of the benzophenone radical anion with naphthalene[41] and also with *N*-oxides of azaheterocycles are known.[42–44] In all these cases, the S_NH reactions formed a new bond at the benzophenone carbonyl carbon atom, and thus provided aryldiphenylcarbinols. The products of the coupling between the reagent and substrate aromatic rings were not mentioned in the cited articles. The ability of the monocyanoarene radical anion to arylate substrates activated to aromatic fluorine substitution, as discovered in the present work, opens up the prospect of developing a new general approach to the directed synthesis of functionalized cyanobisaryls, which are widely used as valuable structural blocks for the synthesis of bioactive compounds and new materials.[18] Productivity of the proposed reaction is comparable to that of cross-coupling catalyzed by transition metals that is currently utilizing as common approach to such compounds.[45-47] The advantages of the method proposed can be attributed primarily to the absence of the need to use catalityc systems and pre-activated reagents.

Experimental

General information: Liquid ammonia was purified just before use by dissolving metallic sodium in it, followed by distillation into a reaction vessel cooled to ca. 80ºC. Metallic sodium was freed from oxide film under dry hexane. Commercial benzonitrile was purified by distillation over P_2O_5. Commercially available 3-methoxybenzonitrile, 1-cyanonaphthalene and fluorinated benzonitriles **4a**–**n** were used without further purification. Melting points of products **5–7**, **10f**, **14**, **15** are uncorrected.

^1H, $^{13}C\{^1H\}$ and ^{19}F NMR spectra of all compounds were acquired with a Bruker Avance III 500 instrument at 500.03, 125.76 and 470.50 MHz, respectively, in [D_6]acetone (except **14a** acquired in [D_6]DMSO); chemical shifts (δ) of ^1H and $^{13}C\{^1H\}$ are given in ppm relative to TMS using the solvent signals as the internal standard (δH = 2.05 ppm, δC = 29.8 and 206.3 ppm), the internal standard for ^{19}F spectra was C_6F_6 (δ= –162.9 ppm). Signal assignment and structure justification were carried out based on the HSQC and HMBC data and on analysis of the C–F spin–spin coupling constants.

IR spectra were recorded with a Vector-22 instrument for samples pelleted with KBr (0.25 %).

GC–MS analysis was performed with a Hewlett–Packard G1081A instrument consisting of an HP-5890 Series II gas chromatograph and an HP-5971 mass-selective detector (IE, 70 eV) with an HP5 capillary column.

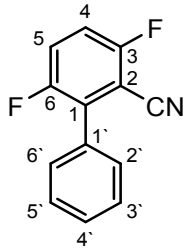
High resolution mass-spectra and exact masses were obtained using Thermo Fischer Scientific Double Focusing System (DFS) magnetic sector high resolution mass-spectrometer (Bremen, Germany). Samples were introduced into mass-spectrometer by direct inlet. The mass spectrometer used electron ionization with 70 eV ionization energy. Measurements of the exact masses of the ions were performed with respect to the standard lines of perfluorokerosene (PFK).

XRD data were obtained at room temperature on a Bruker Kappa Apex II CCD diffractometer using φ, ω scans of narrow (0.5°) frames with Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator. Absorption corrections were applied empirically using *SADABS* programs.[48] The structures were solved by direct methods and refined by full-matrix least-squares method against all F^2 in anisotropic approximation (beside the atoms H) using the *SHELX-97* programs set[49]. The H atoms positions were calculated with the riding model except for the hydrogens of amino group in **10f** refined independently. The asymmetric part of **10i** includes two independent molecules. The crystallographic data of **10f**, **10i**, **14j** and **15c** are listed in SI. CCDC 1875478-1875481 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi, or

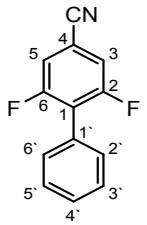
from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

Quantum-chemical calculations were performed using the GAMESS[8] package within (U)MP2/6-31+G(d) level of theory. All stationary points were proved to be minima via analysis of normal vibrations (no imaginary frequencies found). HOMO (SOMO) views were obtained with MOLDEN[50,51] utility.

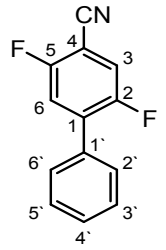
General Procedure: Metallic sodium (0.070 g, 3.0 mmol) and aromatic carbonitrile **3**, **12** or **13** (4.0 mmol) were successively added to liquid NH_3 (30-40 mL) under an atmosphere of evaporating NH_3 at -33÷-45 ºC. To thus obtained sodium salt of radical anion $\mathbf{3}^{\bullet-}$, $\mathbf{12}^{\bullet-}$ or $\mathbf{13}^{\bullet-}$ fluorinated benzonitrile **4a-n** (1.5 mmol) was added. The reaction mixture was stirred under an atmosphere of evaporating NH_3 at -33ºC for 1÷1.5 h. The reaction mixture was brought into contact with air, Et_2O (25 mL) was added and stirring continued until the NH_3 completely evaporated. H_2O (25 ml) was added to the residue, the organic products were extracted with Et_2O (3 × 30 mL). The combined ether extract was successively washed with H_2O, a saturated NaCl solution, dried with $MgSO_4$. The composition of the reaction mixtures obtained after distillation of the Et_2O was analyzed by ^1H, ^{19}F NMR and GC-MS. The products **5÷7**, **14** and **15** were separated by TLC on plates with a fixed layer of silica gel (Silica gel 60 PF_{254} containing gypsum, Merck) and n-hexane/Et_2O mixture (10/1 v/v ratio) as eluent, and recrystallized from hexane. Yields refer to analytically pure samples.



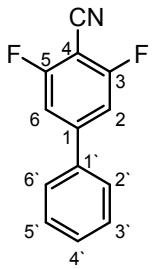
3,6-Difluoro-[1,1'-biphenyl]-2-carbonitrile (5a): Yield: 132 mg (41%), light fine needles, mp 89.6–90.1 °C (hexane). ^1H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.68 (td, J = 9.2, 9.2, 4.7 *Hz*, H^5, 1H), 7.58-7.52 (m, $H^{2',3',4',5',6'}$, 5H), 7.50 (ddd, J = 9.3, 8.4, 3.9 *Hz*, H^4, 1H). $^{13}C\{^1H\}$ NMR (125.73 MHz, $(CD_3)_2CO$, δ): 161.0 (dd, J = 253, 2.8 *Hz*, C^3, 1C), 156.4 (dd, J = 244, 2.6 *Hz*, C^6, 1C), 134.7 (d, J = 20.8 *Hz*, C^1, 1C), 132.0 (d, J = 1.5 *Hz*, $C^{1'}$, 1C), 130.6 (d, J = 1.8 *Hz*, $C^{2',6'}$, 2C), 130.5 (s, $C^{4'}$, 1C), 129.6 (s, $C^{3',5'}$, 2C), 123.5 (dd, J = 26.1, 9.3 *Hz*, C^5, 1C), 117.7 (dd, J = 22.7, 9.0 *Hz*, C^4, 1C), 113.0 (d, J = 3.4 *Hz*, C^{CN}, 1C), 103.7 (d, J = 17.7, 5.0 *Hz*, C^2, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 51.3 (ddd, J = 16.8, 8.3, 4.4 *Hz*, $F^{3\text{ or }6}$, 1F), 44.4 (ddd, J = 16.8, 9.0, 3.9 *Hz*, $F^{6\text{ or }3}$, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2237 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 216 (15.1), 215 (100.0) [M^+], 214 (11.0), 213 (5.0), 195 (13.3), 188 (14.8), 187 (5.6), 168 (6.2). HRMS: calcd. for $C_{13}H_7F_2N$ [M+] 215.0541; found 215.0544.



2,6-Difluoro-[1,1'-biphenyl]-4-carbonitrile (6b): Yield: 181 mg (56%), white powder, mp 135.6–137.2°C (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.71-7.64 (m, $H^{3,5}$, 2H), 7.57-7.49 (m, H1',2',3',4',5', 5H). $^{13}C\{^{1}H\}$ (125.73 MHz, $(CD_3)_2CO$ δ): 160.8 (dd, J = 7.9, 250 *Hz*, $C^{2,6}$, 2C), 131 (t, J = 1.9 *Hz*, $C^{2',6'}$, 2C), 130.2 (s, $C^{4'}$, 1C), 129.5 (s, $C^{3',5'}$, 2C), 128.4 (s, $C^{1'}$, 1C), 124.8 (t, J = 19.2 *Hz*, C^{1}, 1C), 117.3 (t, J = 3.5 *Hz*, C^{CN}, 1C), 117.1 (dd, J = 22.7, 9.0 *Hz*, $C^{3,5}$, 2C), 113.6 (t, J = 12.5 *Hz*, C^{4}, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 52.3 (d, J = 6.5 *Hz*, $F^{2.6}$, 2F). IR (KBr) $\tilde{\nu}_{max}$: 2239 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 216 (14.8), 215 (100.0) [M^+], 214 (11.4), 195 (7.4), 189 (5.4), 176 (6.2), 163 (6.6). HRMS: calcd. for $C_{13}H_7F_2N$ [M+] 215.0541; found 215.0544. Anal. calcd for $C_{13}H_7F_2N$ (215.054): C,72.56; H, 3.28; F, 17.66; N, 6.51; found: C,72.77; H, 3.59; F, 17.53; N, 6.41.

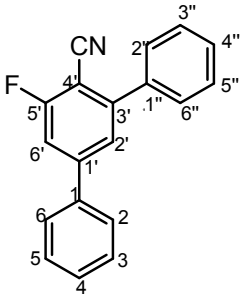


2,5-Difluoro-[1,1'-biphenyl]-4-carbonitrile (6c): Yield: 219 mg (68%), white powder, mp. 56.5–59.2°C (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.82 (dd, J = 9.7, 5.4 *Hz*, H^{3}, 1H), 7.67-7.64 (m, $H^{2',6'}$, 2H), 7.62 (dd, J = 9.7, 6.1 *Hz*, H^{6}, 1H), 7.56-7.49 (m, $H^{3',4',5'}$, 3H). $^{13}C\{^{1}H\}$ NMR (125.73 MHz, $(CD_3)_2CO$ δ): 160.3 (dd, J = 253, 2.7 *Hz*, C^{5}, 1C), 156.2 (dd, J = 244, 2.6 *Hz*, C^{2}, 1C), 137.3 (dd, J = 15.9, 8.4 *Hz*, C^{1}, 1C), 134.0 (t, J = 1.7 *Hz*, $C^{1'}$, 1C), 130.4 (s, $C^{4'}$, 1C), 129.9 (d, J = 3.5 *Hz*, $C^{2',6'}$, 2C), 129.8 (s, $C^{3',5'}$, 2C), 121.7 (dd, J = 29.6, 1.3 *Hz*, C^{3}, 1C), 119.2 (dd, J = 22.9, 4.1 *Hz*, C^{6}, 1C), 113.5 (d, J = 2.2 *Hz*, C^{CN}, 1C), 101.4 (dd, J = 18.3, 10.4 *Hz*, C^{4}, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 50.0 (ddd, J = 16.3, 9.6, 5.7 *Hz*, $F^{5 \text{ or } 2}$, 1F), 42.8 (ddd, J = 16.2, 8.9, 6.6 *Hz*, $F^{2 \text{ or } 5}$, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2237 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 216 (15.1), 215 (100.0) [M^+], 214 (14.8), 213 (6.8), 195 (8.4), 194 (6.1), 189 (8.7), 188 (5.1), 187 (5.9), 176 (6.0). HRMS: calcd. for $C_{13}H_7F_2N$ [M+] 215.0541; found 215.0543.

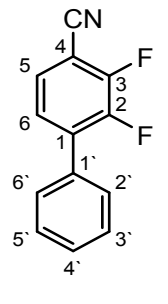


3,5-Difluoro-[1,1'-biphenyl]-4-carbonitrile (6d): Yield: 23 mg (7%), white powder, mp. 88.8–92.6°C (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.83-7.79 (m, $H^{2',6'}$, 2H), 7.64 (d, J = 9.3 *Hz*, $H^{2,6}$, 2H), 7.57-7.49 (m, $H^{3',4',5'}$, 3H). $^{13}C\{^{1}H\}$ NMR (125.73 MHz, $(CD_3)_2CO$ δ): 164.2 (dd, J = 5.5, 257 *Hz*, $C^{3,5}$, 2C), 150.4 (t, J = 10.1 *Hz*, C^{1}, 1C), 137.7 (t, J = 2.4 *Hz*, $C^{1'}$, 1C), 130.8 (s, $C^{4'}$, 1C), 130.2 (s, $C^{3',5'}$, 2C), 128.2 (s, $C^{2',6'}$, 2C), 111.4 (dd, J = 3.4, 20.8 *Hz*, $C^{2,6}$, 2C), 110 (s, C^{CN}, 1C), 90.9 (t, J = 19.8 *Hz*, C^{4}, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 57.9 (d, J = 9.7 *Hz*, $F^{3,5}$, 2F). IR (KBr) $\tilde{\nu}_{max}$: 2237 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 216 (15.3), 215 (100.0) [M^+], 214 (15.6), 213 (8.4), 195 (6.7), 194 (5.4), 189 (6.5), 187 (5.6). HRMS: calcd. for $C_{13}H_7F_2N$ [M+] 215.0541; found 215.0544.

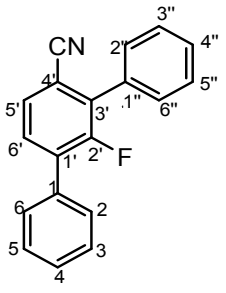
5'-Fluoro-[1,1':3',1''-terphenyl]-4'-carbonitrile (7d): Yield: 205 mg (50%), white small needles, mp. 107.4–108.1°C (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.87-7.83 (m, $H^{2,6}$, 2H), 7.75-7.70 (m, $H^{2',6',(3",5") \text{ or } (2",6")}$, 4H), 7.60-7.47 (m, $H^{3,4,5,(3",5") \text{ or } (2",6")}$, 4", 6H). ^{13}C{^{1}H} NMR (125.73 MHz, $(CD_3)_2CO$ δ): 165.3 (d, J = 251 *Hz*, $C^{5'}$, 1C), 148.7 (d, J = 9.1 *Hz*, $C^{1'}$, 1C), 148.3 (d, J = 0.9 *Hz*, $C^{3'}$, 1C), 138.8 (d, J = 2.5 *Hz*, C^{1}, 1C), 138.3 (d, J = 2.5 *Hz*, $C^{1"}$, 1C), 130.3 (s, C^{4}, 1C), 130.1 (s, $C^{3,5,4"}$, 3C), 129.8 (s, $C^{(2",6") \text{ or } (3",5")}$, 2C), 129.7 (s, $C^{(3",5") \text{ or } (2",6")}$, 2C), 128.3 (s, $C^{2,6}$, 2C), 125.2 (d, J = 2.7 *Hz*, $C^{2'}$, 1C), 114.2 (s, C^{CN}, 1C), 113.8 (d, J = 21.3 *Hz*, $C^{6'}$, 1C), 99.7 (d, J = 16 *Hz*, $C^{4'}$, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 56.4 (d, J = 11 *Hz*, $F^{5'}$, 1C). IR (KBr) $\tilde{\nu}_{max}$: 2231 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 274 (21.2), 273 (100.0), 272 (28.0), 271 (7.7), 251 (6.9), 245 (5.1), 244 (6.8). HRMS: calcd. for $C_{19}H_{12}FN$ [M+] 273.0948; found 273.0944.



2,3-Difluoro-[1,1'-biphenyl]-4-carbonitrile (6e): Yield: 64 mg (20%), small yellowish crystals, mp. 91.4–93.3 °C (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.73 (ddd, J = 8.2, 5.9, 1.9 *Hz*, H^{5}, 1H), 7.66-7.64 (m, $H^{2',6'}$, 2H), 7.58-7.50 (m, $H^{6,3',4',5'}$, 4H). ^{13}C{^{1}H} NMR (125.73 MHz, $(CD_3)_2CO$ δ): 152.0 (dd, J = 258, 15.9 *Hz*, C^{3}, 1C), 147.6 (dd, J = 251, 11.7 *Hz*, C^{2}, 1C), 136.5 (dd, J = 10.3, 1.0 *Hz*, C^{1}, 1C), 133.0 (dd, J = 2.6, 1.3 *Hz*, $C^{1'}$, 1C), 129.4 (s, $C^{4'}$, 1C), 128.9(3) (d, J = 3.2 *Hz*, $C^{2',6'}$, 2C), 128.9(0) (s, $C^{3',5'}$, 2C), 128.3 (d, J = 4.7 *Hz*, C^{5}, 1C), 126.5 (dd, J = 4.0, 2.8 *Hz*, C^{6}, 1C), 112.6 (d, J = 3.8 *Hz*, C^{CN}, 1C), 101.5 (dd, J = 12.3, 1.5 *Hz*, C^{4}, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 30.8 (dd, J = 19.8, 5.7 *Hz*, $F^{3 \text{ or } 2}$, 1F), 22.4 (dd, J = 19.7, 6.7 *Hz*, $F^{2 \text{ or } 3}$, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2237 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 216 (14.7), 215 (100.0), 214 (13.7), 213 (6.4), 195 (7.0), 189 (5.8), 188 (5.2), 187 (5.6). HRMS: calcd. for $C_{13}H_7F_2N$ [M+] 215.0541; found 215.0543.



2'-Fluoro-[1,1':3',1''-terphenyl]-4'-carbonitrile (7e): Yield: 102 mg (25%), white powder, mp. 95.7 °C with decomposition (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.81 (d, J = 8.0, 0.9 *Hz*, $H^{5'}$, 1H), 7.73 (d, J = 8.0, 7.3 *Hz*, $H^{6'}$, 1H), 7.68-7.64 (m, 2H), 7.62-7.59 (m, 2H), 7.58-7.54 (m, 2H), 7.54-7.51 (m, 3H), 7.70-7.44 (m, 1H). ^{13}C{^{1}H} NMR (125.73 MHz, $(CD_3)_2CO$ δ): 157.2 (d, J = 249 *Hz*, $C^{2'}$, 1C), 135.2(2) (d, J = 15.2 *Hz*, 1C), 135.2(0) (d, J = 1.2 *Hz*, 1C), 134.5 (d, J = 20.4 *Hz*, 1C), 133.1 (s, $C^{6'}$, 1C), 131.7 (d, J = 4.3 *Hz*, 1C), 130.8 (d, J = 1.7 *Hz*, 2C), 130.3 (d, J = 4.6 *Hz*, $C^{5'}$, 1C), 130.0(3) (s, 2C), 130.0(1) (s, 1C), 129.8 (s, 1C), 129.6 (s, 2C), 129.4 (s, 2C), 117.8 (d, J = 3.9 *Hz*, C^{CN}, 1C), 113.9 (d, J = 4.5 *Hz*, $C^{4'}$, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 45.4 (d, J = 6.7 *Hz*, F^{2}, 1F). IR (KBr)

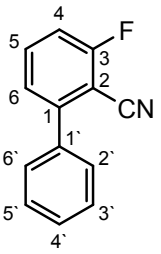


$\tilde{\nu}_{max}$: 2231 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 274 (21.1), 273 (100.0), 272 (18.3), 271 (5.8), 251 (7.4), 244 (6.1). HRMS: calcd. for $C_{19}H_{12}FN$ [M+] 273.0948; found 273.0950.

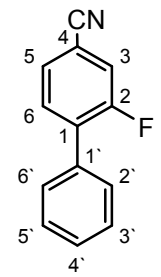
6-Fluoro-[1,1'-biphenyl]-2-carbonitrile (5f)[22]: Yield: 74 mg (25%), yellowish powder, mp. 107.4–110.5°C (TLC).

3-Fluoro-[1,1'-biphenyl]-4-carbonitrile (6g)[24]: Yield: 192 mg (65%), colorless needles, mp. 78.7–79.0°C (hexane).

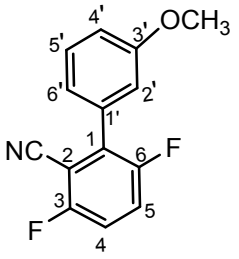
3-Fluoro-[1,1'-biphenyl]-2-carbonitrile (5i)[26]: Yield: 151 mg (51%), yellowish powder, mp. 78.2–78.9°C (TLC). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.83 (ddd, J = 8.4, 7.8, 6.0 *Hz*, H^5, 1H), 7.65-7.62 (m, $H^{2',6'}$, 2H), 7.58-7.50 (m, $H^{3',4',5'}$, 3H), 7.47 (ddd, J = 7.8, 1.0, 0.4 *Hz*, H^6, 1H), 7.43 (ddd, J = 9.3, 8.5, 1.0 *Hz*, H^4, 1H). $^{13}C\{^1H\}$ NMR (125.73 MHz, $(CD_3)_2CO$ δ): 164.9 (d, J = 256 *Hz*, C^3, 1C), 148.1 (s, C^1, 1C), 138.2 (d, J = 2.2 *Hz*, $C^{1'}$, 1C), 136.0 (d, J = 9.5 *Hz*, C^5, 1C), 130.0 (s, $C^{4'}$, 1C), 129.6(9) (s, $C^{2',6'}$, 2C), 129.6(6) (s, $C^{3',5'}$, 2C), 126.9 (d, J = 3.2 *Hz*, C^6, 1C), 115.7 (d, J = 20.2 *Hz*, C^4, 1C), 114.0 (d, J = 1 *Hz*, C^{CN}, 1C), 101.3 (d, J = 15.6 *Hz*, C^2, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 56.2 (dd, J = 9.2, 6.0 *Hz*, F^3, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2231 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 198 (14.7), 197 (100.0) [M^+], 196 (19.7), 195 (7.4), 177 (9.1), 171 (5.7), 170 (13.6), 169 (10.2), 85 (6.7). HRMS: calcd. for $C_{13}H_8FN$ [M+] 197.0635; found 197.0634.



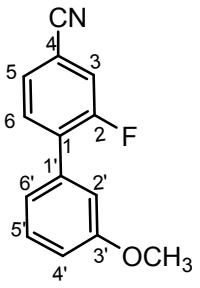
2-Fluoro-[1,1'-biphenyl]-4-carbonitrile (6j): Yield: 178 mg (60%), colorless layered crystals, mp. 78.1°C with decomposition (TLC). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ):7.76-7.70 (m, $H^{3,5,6}$, 3H), 7.64-7.61 (m, $H^{2',6'}$, 2H), 7.55-7.51 (m, $H^{3',5'}$, 2H), 7.49-7.46 (m, $H^{4'}$, 1H). $^{13}C\{^1H\}$ NMR (125.73 MHz, $(CD_3)_2CO$ δ): 160.1 (d, J = 250 *Hz*, C^2, 1C), 135.0 (d, J = 13.5 *Hz*, C^1, 1C), 134.9 (d, J = 1.3 *Hz*, $C^{1'}$, 1C), 133.0 (d, J = 4 *Hz*, C^6, 1C), 129.9 (d, J = 3.2 *Hz*, $C^{2',6'}$, 1C), 129.8 (s, $C^{4'}$, 2C), 129.7 (s, $C^{3',5'}$, 2C), 129.6 (d, J = 4 *Hz*, C^5, 1C), 120.8 (d, J = 27 *Hz*, C^3, 1C), 118.2 (d, J = 2.8 *Hz*, C^{CN}, 1C), 113.4 (d, J = 9.8 *Hz*, C^4, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 48.1 (t, J = 8.5 *Hz*, F^2, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2241 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 198 (15.1), 197 (100.0) [M^+], 196 (21.2), 195 (8.2), 171 (7.1), 170 (7.4), 169 (11.1), 85 (6.7). HRMS: calcd. for $C_{13}H_8FN$ [M+] 197.0635; found 197.0637.



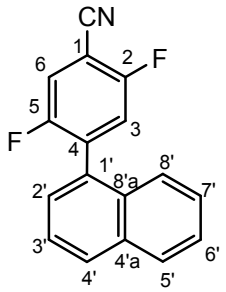
3,6-Difluoro-3'-methoxy-[1,1'-biphenyl]-2-carbonitrile (14a): Yield: 140 mg (38%), white powder, mp. 103.1–103.5°C (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2SO$, δ): 7.80 (td, J = 9.2, 9.2, 4.7 *Hz*, H^5, 1H), 7.65 (ddd, J = 9.2, 8.7, 4.0 *Hz*, H^4, 1H), 7.48 (ddd, J = 8.2, 7.6, 0.6 *Hz*, $H^{5'}$, 1H), 7.14-7.08 (m, $H^{2',4',6'}$, 3H), 3.81 (s, OCH_3, 3H). $^{13}C\{^1H\}$ NMR (125.73 MHz, $(CD_3)_2SO$ δ): 159.4 (dd, J = 253, 2.6 *Hz*, C^3, 1C), 159.1 (s, $C^{3'}$, 1C), 154.8 (dd, J = 243, 2.5 *Hz*, C^6, 1C), 132.8 (d, J = 21.0 *Hz*, C^1, 1C), 131.6 (d, J = 1.5 *Hz*, $C^{1'}$, 1C), 129.8



(s, $C^{5'}$, 1C), 123.0 (dd, J = 25.9, 9.5 *Hz*, C^{5}, 1C), 121.7 (d, J = 1.7 *Hz*, $C^{6'}$, 1C), 117.1 (dd, J = 22.5, 9.1 *Hz*, C^{4}, 1C), 115.2 (d, J = 1.6 *Hz*, $C^{2'}$, 1C), 115.1 (s, $C^{4'}$, 1C), 112.4 (d, J = 3.4 *Hz*, C^{CN}, 1C), 101.9 (dd, J = 17.5, 5.1 *Hz*, C^{2}, 1C), 55.2 (s, C^{OCH3}, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2SO$, rel. C_6F_6, δ): 50.6 (ddd, J = 16.8, 8.5, 4.6 *Hz*, $F^{3 \text{ or } 6}$, 1F), 43.8 (ddd, J = 16.6, 9.2, 3.9 *Hz*, $F^{6 \text{ or } 3}$, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2231 (C≡N), 1248, 1043 (C–O–C) cm^{-1}. EIMS (70 eV) *m/z*: 246 (16.0), 245 (100.0), 217 (24.6), 216 (24.5), 215 (24.6), 202 (46.0), 188 (18.0), 176 (33.7), 175 (16.9), 39 (19.7). HRMS: calcd. for $C_{14}H_9F_2NO$ [M+] 245.0647; found 245.0645.

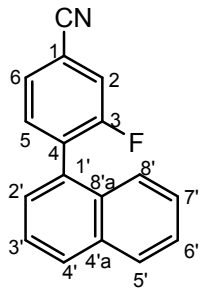


2-Fluoro-3'-methoxy-[1,1'-biphenyl]-4-carbonitrile (14j): Yield: 190 mg (56%), white crystalls, mp. 88.3°C with decomposition°C (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 7.76 (ddd, J = 8.1, 7.6, 0.9 *Hz*, H^{6}, 1H), 7.74-7.71 (m, H^{3}, 1H), 7.70 (dd, J = 7.9, 1.6 *Hz*, H^{5}, 1H), 7.43 (ddd, J = 8.2, 7.5, 0.5 *Hz*, $H^{5'}$, 1H), 7.20-7.15 (m, $H^{2',6'}$, 2H), 7.05 (ddd, J = 8.3, 2.6, 0.9 *Hz*, $H^{4'}$, 1H), 3.87 (s, OCH_3, 3H). $^{13}C\{^{1}H\}$ NMR (125.73 MHz, $(CD_3)_2CO$ δ): 161.0 (s, $C^{3'}$, 1C), 160.1 (d, J = 250 *Hz*, C^{2}, 1C), 136.2 (d, J = 1.4 *Hz*, $C^{1'}$, 1C), 134.9 (d, J = 13.4 *Hz*, C^{1}, 1C), 133.0 (d, J = 4.0 *Hz*, C^{6}, 1C), 130.7 (s, $C^{5'}$, 1C), 129.6 (d, J = 4.0 *Hz*, C^{5}, 1C), 122.1 (d, J = 3.2 *Hz*, $C^{6'}$, 1C), 120.8 (d, J = 27.0 *Hz*, C^{3}, 1C), 118.2 (d, J = 2.8 *Hz*, C^{CN}, 1C), 115.5 (d, J = 3.1 *Hz*, $C^{2'}$, 1C), 115.4 (s, $C^{4'}$, 1C), 113.4 (d, J = 9.9 *Hz*, C^{4}, 1C), 55.6 (s, C^{OCH3}, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 48.6 (t, J = 8.8 *Hz*, F^{2}, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2233 (C≡N), 1217, 1022 (C–O–C) cm^{-1}. EIMS (70 eV) *m/z*: 228 (16.3), 227 (100.0), 198 (8.5), 197 (29.0), 196 (12.4), 184 (29.5), 182 (5.3), 158 (23.1), 157 (5.2). HRMS: calcd. for $C_{14}H_{10}FNO$ [M+] 227.0741; found 227.0743.

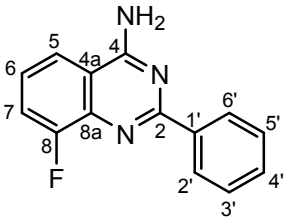


2,5-Difluoro-4-(naphthalen-1-yl)benzonitrile (15c): Yield: 123 mg (31%), white crystalls, mp. 107.9°C with decomposition°C (hexane). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 8.07 (dm, J = 8.3 *Hz*, $H^{8'}$, 1H), 8.03 (dm, J = 8.1 *Hz*, $H^{5'}$, 1H), 7.90 (ddd, J = 8.5, 5.4, 0.4 *Hz*, H^{3}, 1H), 7.64(4) (dm, J = 8.3 *Hz*, $H^{4'}$, 1H), 7.64(2) (dd, J = 8.3, 7.0 *Hz*, $H^{3'}$, 1H), 7.59 (ddd, J = 8.1, 6.8, 1.4 *Hz*, $H^{7'}$, 1H), 7.58 (ddd, J = 9.1, 5.7, 0.4 *Hz*, H^{6}, 1H), 7.55 (dm, J = 7.0 *Hz*, $H^{2'}$, 1H), 7.54 (ddd, J = 8.3, 6.8, 1.5 *Hz*, $H^{6'}$, 1H). $^{13}C\{^{1}H\}$ NMR (125.73 MHz, $(CD_3)_2CO$ δ): 160.2 (dd, J = 254, 2.8 *Hz*, $C^{2 \text{ or } 5}$, 1C), 156.7 (dd, J = 243, 2.6 *Hz*, $C^{5 \text{ or } 2}$, 1C), 136.7 (dd, J = 19.5, 8.5 *Hz*, C^{4}, 1C), 134.6 (s, $C^{4'a}$, 1C), 132.1 (d, J = 1.3 *Hz*, $C^{1'}$, 1C), 131.9 (d, J = 0.8 *Hz*, $C^{8'a}$, 1C), 130.6 (s, $C^{8'}$, 1C), 129.4 (s, $C^{5'}$, 1C), 128.7 (d, J = 1.1 *Hz*, $C^{2'}$, 1C), 127.9 (s, $C^{6'}$, 1C), 127.3 (s, $C^{7'}$, 1C), 126.2 (s, $C^{3'}$, 1C), 125.8 (d, J = 1.6 *Hz*, $C^{4'}$, 1C), 121.2 (dd, J = 29.0, 1.3 *Hz*, C^{3}, 1C), 121.0 (dd, J = 22.4, 4.0 *Hz*, C^{6}, 1C), 113.6 (d, J = 2.2 *Hz*, C^{CN}, 1C), 102.2 (dd, J = 18.1, 10.1 *Hz*, C^{1}, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 49.8 (ddd, J = 16.5, 9.2, 5.4 *Hz*, $F^{2 \text{ or } 5}$, 1F), 49.6 (ddd, J = 15.3, 6.2, 2.3 *Hz*, $F^{5 \text{ or } 2}$, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2237 (C≡N)

cm^{-1}. EIMS (70 eV) *m/z*: 266 (18.0), 265 (100.0), 264 (62.1), 263 (28.2), 246 (11.3), 245 (20.7), 244 (12.0), 119 (13.4). HRMS: calcd. for $C_{17}H_9F_2N$ [M+] 265.0700; found 265.0702.



3-Fluoro-4-(naphthalen-1-yl)benzonitrile (15j). Yield: 103 mg (28%), white solid (TLC). ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 8.05 (d, J = 8.3 *Hz*, H, 1H), 8.02 (d, J = 8.2 *Hz*, H, 1H), 7.82 (dd, J = 9.5, 1.5 *Hz*, H, 1H), 7.80 (dd, J = 7.7, 1.6 *Hz*, H, 1H), 7.68 (dd, J = 7.8, 7.3 *Hz*, H, 1H), 7.63 (dd, J = 8.2, 7.1 *Hz*, H, 1H), 7.60-7.55 (m, H, 2H), 7.54-7.50 (m, H, 2H). ^{13}C{^{1}H} NMR (125.73 MHz, $(CD_3)_2CO$ δ): 160.6 (d, J = 249 *Hz*, C^3, 1C), 134.6(2) (s, C, 1C), 134.6(0) (d, J = 4.1 *Hz*, C^5, 1C), 134.3 (d, J = 16.7 *Hz*, C^4, 1C), 133.0 (s, C, 1C), 132.1 (s, C, 1C), 130.2 (s, C, 1C), 129.5 (d, J = 3.9 *Hz*, C^6, 1C), 129.4 (s, C, 1C), 128.6 (d, J = 1.1 *Hz*, C, 1C), 127.7 (s, C, 1C), 127.2 (s, C, 1C), 126.3 (s, C, 1C), 125.9 (d, J = 1.5 *Hz*, C, 1C), 120.4 (d, J = 26.4 *Hz*, C^2, 1C), 118.0 (d, J = 2.9 *Hz*, C^{CN}, 1C), 114.1 (d, J = 9.6 *Hz*, C^1, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 52.4 (ddd, J = 9.4, 6.8, 2.7 *Hz*, F^3, 1F). IR (KBr) $\tilde{\nu}_{max}$: 2237 (C≡N) cm^{-1}. EIMS (70 eV) *m/z*: 248 (18.5), 247 (100.0), 246 (64.8), 245 (31.9), 227 (11.1), 226 (8.1), 219 (7.7), 110 (10.7). HRMS: calcd. for $C_{17}H_{10}FN$ [M+] 247.0792; found 247.0794.



4-Amino-2-phenyl-8-fluoroquinazoline (10f). Metallic sodium (33 mg, 1.4 mmol) was dissolved in liquid ammonia (30-40 ml). $FeCl_3$ (a drop) was put into metal-ammonia solution, benzonitrile **3** (1.3 mmol) was added after the formation of $NaNH_2$, and the resulting mixture was maintained under an atmosphere of evaporating NH_3 at -33ºC for ca. 0.5 h. 2,3-Difluorobenzonitrile **4f** (1.4 mmol) was added to the thus obtained suspension of the amidine **11** sodium salt and stirring was continued for 1.5 h. The reaction mixture was brought into contact with air, Et_2O (25 mL) was added and stirring continued until NH_3 was completely evaporated. To the residue H_2O (25 ml) was added, the organic products were extracted with Et_2O (3 × 25 mL). The combined ether extract was successively washed with H_2O, a saturated NaCl solution, dried with $MgSO_4$. The composition of the reaction mixture obtained after distillation of the Et_2O was analyzed by ^{1}H, ^{19}F NMR and GC-MS. Quinazoline **10f** was isolated by crystallization of the reaction mixture from acetone. Yield: 124 mg (40%), white crystals, mp 179.4-179.6°C. ^{1}H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 8.61-8.57 (m, $H^{2',6'}$, 2H), 8.02 (ddd, J = 8.3, 1.1, 0.9 *Hz*, H^5, 1H), 7.55 (ddd, J = 10.6, 7.8, 1.2 *Hz*, H^7, 1H), 7.51-7.46 (m, $H^{3',4',5'}$, 3H), 7.44 (ddd, J = 8.2, 7.9, 4.9 *Hz*, H^6, 1H), 7.35-7.22 (br.s, NH_2, 2H). ^{13}C{^{1}H} NMR (125.73 MHz, $(CD_3)_2CO$ δ): 162.9 (d, J = 3.7 *Hz*, C^4, 1C), 161.4 (d, J = 1.1 *Hz*, C^2, 1C), 158.6 (d, J = 254 *Hz*, C^8, 1C), 142.4 (d, J = 12.4 *Hz*, C^{8a}, 1C), 139.7 (s, $C^{1'}$, 1C), 131.0 (s, $C^{4'}$, 1C), 129.2 (s, $C^{2',6'}$, 2C), 128.9 (s, $C^{3',5'}$, 2C), 125.6 (d, J = 7.8 *Hz*, C^6, 1C), 119.6 (d, J = 4.7 *Hz*, C^5, 1C), 118.0 (d, J = 18.7 *Hz*, C^7, 1C), 116.0 (d, J = 3.5 *Hz*, C^{4a}, 1C). ^{19}F NMR (470.50 MHz,

$(CD_3)_2CO$, rel. C_6F_6, δ): 55.3 (dd, J = 10.6, 4.9 *Hz*, F^8, 1F). IR (KBr) $\tilde{\nu}_{max}$: 3475, 3311, 3174 (NH_2) cm^{-1}. EIMS (70 eV) *m/z*: 239 (100.0), 223 (39.6), 136 (58.0), 108 (34.2), 104 (24.6), 94 (31.2), 77 (85.9). HRMS: calcd. for $C_{14}H_{10}FN_3$ [M+] 239.0853; found 239.0854.

4-Amino-2-phenyl-5-fluoroquinazoline (10i). Yield: 130 mg (42%), white crystals, mp 158.7-159.8°C. ^1H NMR (500.03 MHz, $(CD_3)_2CO$, δ): 8.57-8.53 (m, $H^{2',6'}$, 2H), 7.75 (ddd, J = 8.4, 8.0, 6.2 *Hz*, H^7, 1H), 7.65 (dd, J = 8.4, 1.0 *Hz*, H^8, 1H), 7.48-7.46 (m, $H^{3',4',5'}$, 3H), 7.19 (ddd, J = 11.9, 7.9, 1.1 *Hz*, H^6, 1H), 7.32-7.86 (br.s, NH_2, 2H). $^{13}C\{^1H\}$ NMR (125.73 MHz, $(CD_3)_2CO$ δ): 162.1 (d, J = 1.7 *Hz*, C^2, 1C), 160.1 (d, J = 252.0 *Hz*, C^5, 1C), 161.0 (d, J = 4.1 *Hz*, C^4, 1C), 154.5 (s, C^{8a}, 1C), 139.3 (s, $C^{1'}$, 1C), 133.8 (d, J = 11.1 *Hz*, C^7, 1C), 131.1 (s, $C^{3',5'}$, 2C), 129.2 (s, $C^{2',6'}$, 2C), 128.9 (s, $C^{4'}$, 1C), 125.3 (d, J = 3.9 *Hz*, C^8, 1C), 111.0 (d, J = 22.9 *Hz*, C^6, 1C), 104.52 (d, J = 11.2 *Hz*, C^{4a}, 1C). ^{19}F NMR (470.50 MHz, $(CD_3)_2CO$, rel. C_6F_6, δ): 51.8-51.5 (m, F^5, 1F). IR (KBr) $\tilde{\nu}_{max}$: 3523, 3300, 3196 (NH_2) cm^{-1}. EIMS (70 eV) *m/z*: 240 (16.6), 239 (100.0), 238 (21.8), 223 (25.1), 136 (22.1), 120 (8.2), 108 (7.0), 104 (10.9), 94 (6.8), 77 (20.4). HRMS: calcd. for $C_{14}H_{10}FN_3$ [M+] 239.0853; found 239.0854.

Associated content

Supporting Information includes:

^1H, $^{13}C\{^1H\}$ and ^{19}F spectra of synthesized compounds, XRay data, Cartesian coordinates and total energies of calculated structures (PDF).

X-ray crystallographic data of compounds **10i**, **10f**, **14j** and **15c** (CIF).

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