Synthesis of Aryltrifluoromethylpyridazines Application to the Synthesis of Rod-like Molecules as Liquid Crystals Diazines Part 46

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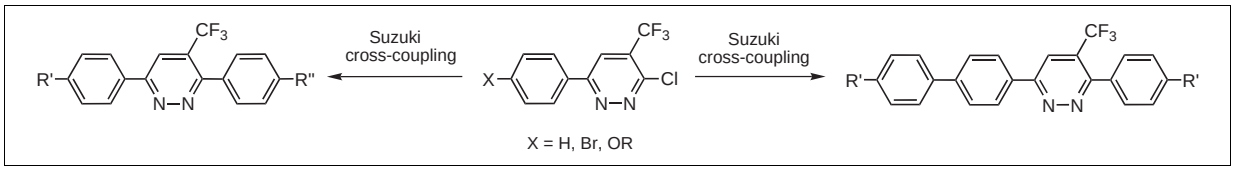

Conjugated oligomers with a trifluoromethylpyridazine unit have been synthesized by Suzuki cross-coupling reaction. These oligomers could be used as building block for construction of supramolecules or as liquid crystals when they are substituted by long chain alkoxy groups.

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Introduction.

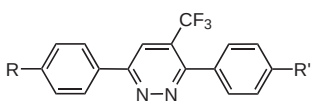
There is a widespread interest in the synthesis of new conjugated oligoarenes containing electron-deficient heterocycles in their backbone. Oligomers incorporating pyridine, bipyridine, quinoline, triazine and more recently pyrazine moieties have been previously described mainly for the elaboration of electronic devices [1-5].

Since the last two decades such structures have received considerable attention due to their role in the design and generation of new materials which are used in various fields such as electroluminescent materials [6], organic conductors [7], optoelectronic devices [8], nonlinear optic (NLO) materials [9], liquid crystals [10]. They are also used as building blocks for supramolecules [11]. In such molecules, azaheterocycles can be used as the electron-deficient units and fluorine atoms to increase the electron deficiency of these π-conjugated moieties.

Incorporation of a heteroaryl moiety such as pyridine, pyrimidine or pyrazine into the π-conjugated system have been investigated to synthesize liquid crystals [10f,12].

With the aim to synthesize new conjugated structures containing a π-deficient aromatic, we report here the synthesis of a new family of rod-like oligomers including a trifluoromethyl-pyridazine as central unit and substi–tuted by benzene rings with various electron-donor groups at the *para* position (Scheme 1).

Scheme 1



Several applications could be envisaged according to the nature of the *para*-substituents. Long chain alkoxy groups would bring liquid crystal properties to these rod-like core compounds, whereas hydroxyl groups would allow further functionalization and their incorporation into supramolecules.

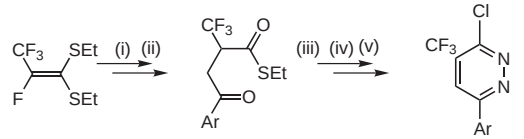
Results and Discussion.

For the synthesis of such oligomers, 6-aryl-3-chloro-4-trifluoromethylpyridazines were chosen as central unit. Substituted phenyl moieties with long terminal alkyl- or alkoxy chains were introduced by cross-coupling reactions and should induce liquid crystallinity.

The synthetic methods to access to 6-aryl-3-chloro-4-trifluoromethylpyridazines, include either forming the heterocycle moiety by using fluorinated precursors or introducing the trifluoromethyl group into the preformed pyridazine.

Using the first strategy, the synthesis of 6-(*p*-bromo-phenyl)-3-chloro-4-trifluoromethylpyridazine **1** has been previously described from perfluoroketene dithioacetal as

Scheme 2



(i) ArCOMe, KH, THF, 0-25°, 10h
(ii)TFA, H_2O, reflux, 10h
(iii) NH_2NH_2, PTSA, PhMe, reflux
(iV) $CuCl_2$, MeCN, reflux, 7h
(V) $POCl_3$, 70-80°, 4h

1 Ar = *p*-Br-C_6H_4 52%
2 Ar = Ph 28%
3 Ar = *p*-$C_7H_{15}O$-C_6H_4 29%

starting material [13a,b]. According to this methodology, two 6-aryl-3-chloro-4-trifluoromethylpyrid-azines **2**, **3** were obtained in five steps with 28-52% overall yields (Scheme 2). A recent paper reports a new procedure to prepare 4-trifluoromethyl-4,5-dihydro-pyridazin-3-ones, which can be an interesting alternative to the first three steps depicted in Scheme 2 [13c].

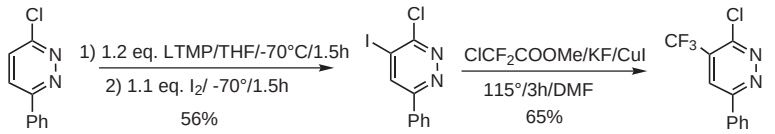
Using the second strategy, compound **2** has been obtained by reaction of 3-chloro-4-iodo-6-phenyl-pyridazine **4** with methyl chlorodifluoroacetate as trifluoromethylating agent [14]. This methodology has been previously used to access to trifluoromethyl pyrazines and pyrimidines [15]. The metallation of commercial 3-chloro-6-phenylpyridazine was carried out with 1.2 equivalent of lithium 2,2,6,6-tetramethyl-piperidide (LTMP) at -70° for 1.5 hour, followed by reaction with iodine (1.1 eq.) as the electrophile and gave regioselectively the 4-iodo derivative **4** in 56% yield. Heating methyl chlorodifluoroacetate with **4** in the presence of anhydrous potassium fluoride and copper (I) iodide in dimethylformamide led to the corresponding trifluoromethyl compound **2** in moderate yield with simultaneous elimination of carbone dioxide and methyl iodide (Scheme 3).

would induce a difference in reactivity. In the Suzuki cross-coupling reaction, the bromine atom is known to be more reactive than the chlorine, however in this case, the chlorine atom is attached to the π-deficient pyridazine, substituted by a very strong electron-withdrawing group such as the trifluoromethyl group. Thus the reactivity could be reversed between the chlorine and the bromine atom. To test this reactivity we have investigated the coupling reaction of **1** with *p*-methoxyphenyl boronic acid.

When 1 equivalent of *p*-methoxyphenyl boronic acid was used, we obtained a mixture of compounds resulting from bicoupling and monocoupling either with the bromine or the chlorine atom. All attempts to control the selectivity of this reaction using various experimental conditions were unsuccessful.

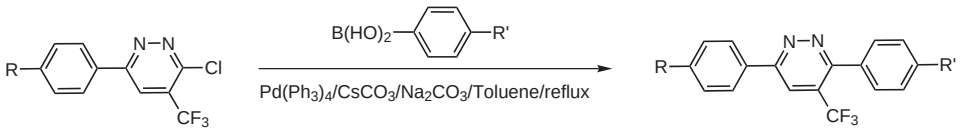
In order to improve the reactivity, we have attempted the replacement of the chlorine atom by an iodine atom. Treatment of **1** with acetic acid, sulphuric acid and sodium iodide under reflux of acetonitrile did not lead to the expected iodo derivative but gave the reduction of the carbon chlorine bond, affording **8** in good yield (Scheme 5).

Scheme 3



4 **2**

Scheme 4



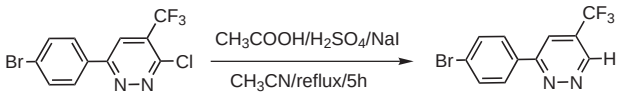
2 R = H
3 R = OC_7H_{15}

5	R = H	R' = H	65%
6	R = H	R' = OMe	95%
7	R = OC_7H_{15}	R' = OMe	75%

The coupling reaction of **2** and **3** with aryl boronic acids was carried out under standard aqueous Suzuki cross coupling conditions to afford **5-7** in good yields (Scheme 4).

For the synthesis of longer oligomers problems would arise from use of compound **1** as a building block. This compound bears two different halogen atoms which

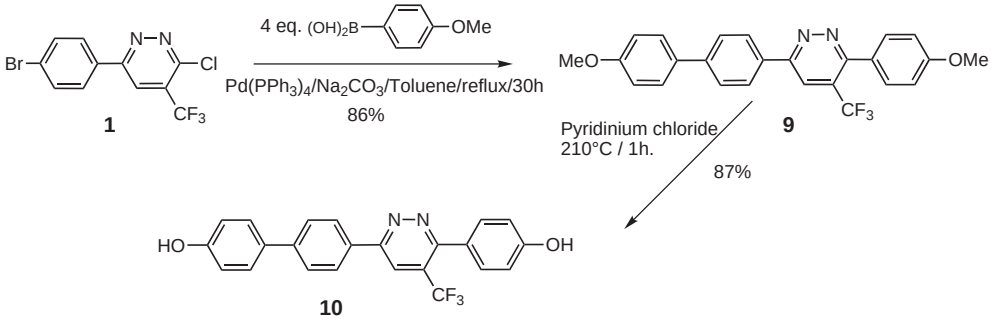
Scheme 5



1 78% **8**

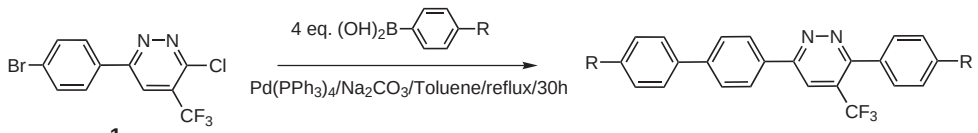
When a four-fold excess of boronic acid was used, the compound **9** was obtained in good yield (86%). A further cleavage of the methoxy group using pyridinium chloride at 210° for 1 hour led to the dihydroxy compound **10** in 87% yield (Scheme 6).

Scheme 6



In order to synthesize rod-like molecules, which could have liquid crystalline properties and to evaluate the influence of various terminal chains, we have investigated the coupling reaction of **1** with alkyl- or alkoxyphenylboronic acids leading to compounds **11-15** with good yields (Scheme 7).

Scheme 7



11 R = C_4H_9 74%
12 R = $C_{12}H_{25}$ 83%
13 R = C_8H_{13} 71%
14 R = OC_8H_{17} 78%
15 R = $OC_{12}H_{25}$ 83%

The synthesis of compound **13** has been achieved by coupling reaction of **1** with the 4-(oct-1-ynyl)-phenylboronic acid **16** obtained from the corresponding bromo derivative in 71% yield. Compounds **14** and **15** were synthesized either by coupling reaction of the corresponding alkoxyboronic acid or by a Williamson reaction from the dihydroxy derivative **10** (yield: 91%).

Then the liquid crystalline property of these oligomers was investigated, their melting behaviour was examined by differential scanning calorimetry (DSC) and polarization microscopy [16].

Despite the nature and the lengh of the terminal alkyl group, compounds **11-13** revealed no liquid crystalline behaviour; they featured only a crystalline to isotropic transition. During the cooling run, the smallest oligomer **14** exhibited a nematic mesophase, indicated by the typical Schlieren texture from 86.9° (ΔH = 17.70 kJ mol^{-1}) to the clearing temperature determined for 117.3° (ΔH = 0.53 kJ mol^{-1}). Oligomer **15** showed also a crystalline nematic mesophase; the melting peak was observed at 99.46° (ΔH = 11.73 kJ mol^{-1}) and clearing temperature at 117.9° (ΔH = 0.10 kJ mol^{-1}) during the heating run, while the cooling run revealed the crystallization peak at 86.64° (ΔH = 7.40 kJ mol^{-1}).

Conclusion.

Starting from 6-aryl-3-chloro-4-trifluoromethylpyridazines as building blocks, we have described, using palladium-catalyzed cross-coupling reactions, a general synthetic route to access to various trifluoromethylated polyarylpyridazines. These oligomers could find applications in the construction of supramolecules, or as crystal liquids when they are substituted in terminal position by long chain alkoxy groups.

EXPERIMENTAL

Melting points were determined on a Electrothermal 1100 instrument. The ^1H, ^{13}C and ^{19}F nmr spectra were recorded on a Bruker AC 300 (300 MHz ^1H, 75 MHz ^{13}C, 282.5 MHz ^{19}F)

instrument. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin-Elmer 16 PC FT-IR spectrometer. Mass spectra were recorded on an ATI-Unicam Automass® apparatus.

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General Procedure A for Synthesis of 3-Chloro-4-trifluoromethylpyrazines.

A mixture of (2*H*)-pyridazin-3-one prepared according to procedures reported in the literature [13a], (4 mmoles, 1 equiv.) and phosphorus oxychloride (40 mmoles, 10 equiv.) was heated at 70-80° for 4 hours, under argon atmosphere. After cooling, the excess of phosphorus oxychloride was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (eluent petroleum ether:ethyl acetate (95:5)) to give the 3-chloro-4-trifluoromethylpyridazines **1**-**3**.

General Procedure B for Cross-coupling of 3-Chloro-4-trifluoromethyl-pyrazines with Arylboronic Acids Under Suzuki Conditions.

A mixture of 3-chloro-4-trifluoromethylpyrazine, arylboronic acid (n equiv.), tetrakis(triphenylphosphine)palladium(0) (0.1 equiv.), Cesium carbonate (1 equiv.), aqueous 2 *M* potassium carbonate (1 equiv.) and ethanol (1 mL) in degassed toluene (15 mL) was heated to reflux under nitrogen for 30 hours. The reaction mixture was cooled, diluted with 20 mL of a mixture of water and ethyl acetate (1:1) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic extracts were dried over magnesium sulfate and evaporated.

6-(*p*-Bromophenyl)-3-chloro-4-trifluoromethylpyridazine (**1**). [13a]

Preparation of **1** according to the general procedure A was described in the literature.

3-Chloro-6-phenyl-4-trifluoromethylpyridazine (**2**) [13b].

Method 1.

Preparation of **2** according to the general procedure A gave after purification 2.20 g of **2** (85%) as a colorless solid, mp 159-160° (litt. 152°). [13b]

Method 2.

A mixture of **4** (0.50 g, 1.58 mmoles), methyl chlorodifluoroacetate (0.46 g, 3.16 mmoles), potassium fluoride (0.18 g, 3.16 mmoles), and copper(I) iodide (0.45 g, 2.37 mmoles) in DMF (4 mL) under nitrogen atmosphere was heated at 115° for 3 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The organic extract was washed with water, dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent cyclohexane:ethyl acetate (7:3)) to give 224 mg (65%) of **2** as a colorless solid, mp 159-160°. ^{1}H nmr (deuteriochloroform): δ 7.59 (m, 3H, H_{Ph}), 8.10 (m, 3H, H_{Ph} + H_5); ^{13}C nmr (deuteriochloroform): δ 121.1, 122.5, 127.2, 129.3, 129.3, 131.3, 133.7, 151.0, 159.3; ^{19}F nmr (deuteriochloroform): δ -66.1; ir (potassium bromide) 1151, 1396, 1449, 1520, 3054, 3074 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_7ClF_3N_2$ *m/e* = 259.0250; found 259.0244.

3-Chloro-6-(4-heptyloxyphenyl)-4-trifluoromethylpyridazine (**3**).

Preparation of **3** according to the general procedure A gave after purification 3.47 g of **3** (93%) as a colorless solid, mp 84-85°; ^{1}H nmr (deuteriochloroform): δ 0.91 (t, J = 6.6 Hz, 3H, CH_3), 1.3-1.6 (m, 8H, 4 x CH_2), 1.84 (m, 2H, OCH_2CH_2), 4.05 (t, J = 6.6 Hz, 2H, OCH_2), 7.06 (d, J = 9.0 Hz, 2H, 2 x CH), 8.02 (q, $^4J_{H,F}$ = 0.7 Hz, 1H, H_5), 8.06 (d, J = 9.0 Hz, 2H, 2 x CH); ^{13}C nmr (deuteriochloroform): δ 14.0, 22.6, 25.9, 29.0, 29.1, 31.7, 68.2, 115.2, 121.1, 121.6, 125.8, 128.6, 128.7, 149.9, 158.7, 161.9; ^{19}F nmr (deuteriochloroform): δ -66.1; GC-MS: m/e (%) = 374 [M^++1], 372, 276, 274 (100), 246, 118, 57.

Anal. Calcd. for $C_{18}H_{20}ClF_3N_2O$: C, 57.99; H, 5.41; N, 7.51. Found: C, 58.30; H, 5.52; N, 7.34.

3-Chloro-4-iodo-6-phenylpyridazine (**4**).

A solution of 3.93 mL of *n*-butyllithium (1.6 *M* in hexane, 6.29 mmoles, 1.2 equiv.) was added to a cold (–30°), stirred and anhydrous mixture of THF (40 mL) and 1.19 mL of 2,2,6,6-tetramethylpiperidine (TMPH) (7.1 mmoles, 1.3 equiv.) under an atmosphere of dry nitrogen. The mixture was warmed to 0°. After 30 minutes, the mixture was cooled to -78° and added to a cold (-78°) solution of 3-chloro-6-phenylpyridazine (1 g, 5.24 mmoles) dissolved in THF (5 mL). Then, the mixture was stirred for 90 minutes. At -70°, iodine (1.50 g, 5.91 mmoles, 1.1 equiv.) was introduced and stirring was continued for 90 minutes at this temperature. Hydrolysis was then carried out at -70° using a solution of THF:EtOH:HCl (4:1:1). Temperature was raised to room temperature, the mixture was made slightly basic with saturated sodium hydrogen carbonate solution. The solution was decolorized with sodium thiosulfate and evaporated nearly to dryness. The residue was extracted with dichloromethane (3x20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The product was purified by column chromatography (silica gel, eluent: cyclohexane: ethylacetate (1:1)) to give 0.93 g of 4 (56%) as a colorless solid, mp 138-139°. ^{1}H nmr (deuteriochloroform): δ 7.54 (m, 3H, H_{Ph}), 8.02 (m, 2H, H_{Ph}), 8.36 (s, 1H, H_5); ^{13}C nmr (deuteriochloroform): δ 104.9, 127.6, 129.6, 131.2, 134.1, 136.9, 158.2, 159.2; ir (potassium bromide) 603, 696, 771, 808, 1039, 1156, 1362, 1440, 1541 cm^{-1}.

Anal. Calcd. for $C_{10}H_6ClIN_2$ (316.4) C, 37.95 H, 1.91 N, 8.85. Found C, 38.05 H, 1.97 N, 8.92.

3,6-Diphenyl-4-trifluoromethylpyridazine (**5**).

Cross-coupling reaction of **2** (50 mg, 0.2 mmole) with phenylboronic acid (100 mg, 0.52 mmole) according to general procedure B (t = 30 hours) gave after purification by column chromatography (silica gel, eluent dichloromethane:ethyl acetate (1:1)) 101 mg (65%) of **5** as a colorless solid, mp 108-109°. ^{1}H nmr (deuteriochloroform): δ 7.55 (m, 6H, H_{Ph}), 7.65 (m, 2H, H_{Ph}), 8.15 (s, 1H, H_5), 8.19 (m, 2H, H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 115.9, 121.0, 121.2, 124.8, 127.6, 128.5, 128.7, 130.1, 131.3, 135.2, 136.0, 157.4, 158.7; ^{19}F nmr

(deuteriochloroform): δ -60.3; ir (potassium bromide) 1452, 1403, 1377, 1263, 1136, 1092, 1047, 910, 763, 695, 674 cm^{-1}.

Anal. Calcd. for $C_{17}H_{11}F_3N_2$ (300.09) C, 68.00 H, 3.69 N, 9.33. Found: C, 67.79 H, 3.61 N, 9.21.

3-(4-Methoxyphenyl)-6-phenyl-4-trifluoromethylpyridazine (**6**).

Cross-coupling reaction of **2** (78 mg, 0.3 mmole) with 4-methoxyphenylboronic acid (100 mg, 0.66 mmole) according to the general procedure B (t = 30 hours) gave after purification by column chromatography (silica gel, eluent dichloromethane) 95 mg (95%) of **6** as a pale yellow solid, mp 112-113°. ^{1}H nmr (deuteriochloroform): δ 3.81 (s, 3H, OCH_3), 7.07 (d, J = 8.7 Hz, 2H, H_{Ph}), 7.60 (m, 3H, H_{Ph}), 7.66 (d, J = 8.7 Hz, 2H, H_{Ph}), 8.14 (s, 1H, H_5), 8.20 (m, 2H, H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 55.8, 114.2, 116.5, 121.1, 121.3, 124.9, 127.5, 128.3, 129.7, 131.2, 135.3, 157.0, 158.3, 161.3; ir (potassium bromide) 696, 771, 833, 1024, 1151, 1242, 1378, 1404, 1510, 1609 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}F_3N_2O$ (330.10) C, 65.45 H, 3.97 N, 8.48. Found: C, 65.31 H, 3.82 N, 8.40.

6-(4-Heptyloxyphenyl)-3-(4-methoxyphenyl)-4-trifluoromethylpyridazine (**7**).

Cross-coupling reaction of **3** (50 mg, 0.13 mmole) with 4-methoxyphenylboronic acid (50 mg, 0.33 mmole) according to the general procedure B (t = 30 hours) gave after purification by column chromatography (silica gel, eluent dichloromethane:ethyl acetate (4:1)) 89 mg (75%) of **7** as a yellow solid, mp 88-89°. ^{1}H nmr (deuteriochloroform): δ 0.84 (t, J = 7.5 Hz, 3H, CH_3), 1.30 (m, 8H, 4xCH_2), 1.74 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.97 (t, J = 6.4 Hz, 2H, OCH_2), 6.98 (m, 4H, H_{Ph}), 7.54 (d, J = 8.3 Hz, 2H, H_{Ph}), 7.98 (s, 1H, H_5), 8.06 (d, J = 8.3 Hz, 2H, H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 14.5, 23.0, 26.4, 29.5, 29.6, 32.2, 55.7, 68.6, 114.2, 115.6, 120.2, 121.3, 127.4, 128.5, 128.9, 131.1, 143.7, 156.2, 157.9, 162.2, 161.9; ir (potassium bromide) 828, 1077, 1135, 1179, 1247, 1267, 1392, 1418, 1506, 1608, 2856, 2931 cm^{-1}.

Anal. Calcd. for $C_{25}H_{27}F_3N_2O_2$ (442.22) C, 67.55 H, 6.12 N, 6.30. Found C, 67.75 H, 6.21 N, 6.42.

3-(4-Bromophenyl)-5-trifluoromethylpyridazine (**8**).

A stirred solution of **1** (100 mg, 0.3 mmole), Sodium iodide (150 mg, 1.0 mmole), acetic acid (0.5 mL), concentrated sulphuric acid (2 μL) in acetonitrile (5 mL) was refluxed for 5 hours. After cooling, acetonitrile was evaporated under reduced pressure and the residue partitioned between dichloromethane (20 mL) and water (20 mL). The mixture was made slightly basic with saturated sodium hydrogen carbonate solution. The aqueous solution was extracted with dichloromethane (3 x 20 mL). The extracts were dried over magnesium sulfate, filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, eluent dichloromethane) to give 69 mg (78%) of **8** as a colorless solid, mp 174-175°. ^{1}H nmr (deuteriochloroform): δ 7.73 (d, J = 8.8 Hz, 2H, H_{Ph}), 8.03 (s, 1H, H_4), 8.05 (d, J = 8.8 Hz, 2H, H_{Ph}), 9.42 (s, 1H, H_6); ^{13}C nmr (deuteriochloroform): δ 118.1 (2C), 123.0, 125.0, 127.8, 129.0, 131.6, 144.1, 157.9; ir (potassium bromide) 829, 1041, 1072, 1101, 1113, 1138, 1180, 1272, 1342, 1400, 1591 cm^{-1}.

Anal. Calcd. for $C_{11}H_6BrF_3N_2$ (303.08) C, 43.59 H, 2.00 N, 9.24. Found C, 43.68 H, 2.15 N, 8.89.

6-(4'-Methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-4-trifluoromethylpyridazine (**9**).

Cross-coupling reaction of **1** (100 mg, 0.13 mmole) with 4-methoxyphenylboronic acid (200 mg, 1.32 mmoles) according to the general procedure B (t = 30 hours) gave after purification by column chromatography (silica gel, eluent dichloromethane:ethyl acetate (4:1)) 114 mg (86%) of **9** as a yellow solid, mp 106-107°. ^{1}H nmr (deuteriochloroform): δ 8.18 (d, J = 7.9 Hz, 2H, H_{Ph}), 8.08 (s, 1H, H_5), 7.70 (d, J = 7.9 Hz, 2H, H_{Ph}), 7.56 (m, 4H, H_{Ph}), 6.97 (m, 4H, H_{Ph}), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): δ 55.7, 55.8, 114.2, 114.8, 116.5, 120.8, 121.3, 125.0, 127.8, 128.1, 128.6, 131.2, 132.8, 133.4, 143.5, 156.8, 157.9, 160.1, 161.2; ir (potassium bromide) 714, 822, 918, 1010, 1031, 1133, 1178, 1256, 1394, 1496, 1602 cm^{-1}.

Anal. Calcd for $C_{25}H_{19}F_3N_2O_2$ (436.14) C, 78.51 H, 5.80 N, 7.32. Found C, 78.30 H, 5.81 N, 7.25.

3-(4-Hydroxyphenyl)-6-(4'-hydroxybiphenyl-4-yl)-4-trifluoromethylpyridazine (**10**).

Pyridine hydrochloride (10 g) heated at 220° for 15 minutes was added to **9** (80 mg, 0.18 mmol). The mixture was maintained at this temperature for 1 hour then poured on to ice. The solution was extracted with ether (3x20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. After purification by column chromatography (silica gel, eluent dichloromethane) 67 mg (87%) of **10** was obtained as a pale yellow solid, mp > 250°. ^{1}H nmr (acetone-d_6): δ 6.85 (d, J = 8.7 Hz, 2H, H_{Ph}), 6.90 (d, J = 8.7 Hz, 2H, H_{Ph}), 7.42 (d, J = 8.7 Hz, 2H, H_{Ph}), 7.51 (d, J = 8.7 Hz, 2H, H_{Ph}), 7.70 (d, J = 8.7 Hz, 2H, H_{Ph}), 8.26 (d, J = 8.7 Hz, 2H, H_{Ph}), 8.37 (s, 1H, H_5), 8.55 (s, 1H, OH), 8.80 (s, 1H, OH); ^{13}C nmr (acetone-d_6): δ 116.4, 117.2, 121.9 (2C), 122.7, 128.1, 128.3, 128.8, 128.9, 129.4, 132.1, 134.4, 144.3, 157.8, 158.7, 159.1, 160.1.

This compound was used without further purification for the synthesis of **14**.

6-(4'-Butylbiphenyl-4-yl)-3-(4-butylphenyl)-4-trifluoromethylpyridazine (**11**).

Cross-coupling reaction of **1** (150 mg, 0.47 mmole) with 4-butylphenylboronic acid (356 mg, 0.80 mmole) according to the general procedure B (t = 30 hours) gave after purification by column chromatography (silica, eluent dichloromethane) 169 mg (74%) of **11** as a colorless solid, mp 118-119°. ^{1}H nmr (deuteriochloroform): δ 0.87 (m, 6H, 2 x CH_3), 1.32 (m, 4H, 2 x CH_2), 1.58 (m, 4H, 2 x CH_2), 2.61 (m, 4H, 2 x CH_2), 7.23 (m, 4H, H_{Ph}), 7.51 (m, 4H, H_{Ph}), 7.71 (d, J = 7.1 Hz, 2H, H_{Ph}), 8.07 (s, 1H, H_5), 8.17 (d, J = 7.1 Hz, 2H, H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 14.4 (2C), 22.8, 33.8, 34.0, 35.7, 35.9, 120.7, 120.8, 127.4, 127.9, 128.1, 128.8, 129.5, 129.6, 133.4, 133.7, 137.6, 143.4, 144.0, 145.2, 157.3, 158.1; ^{19}F nmr (deuteriochloroform): δ -60.3; ir (potassium bromide) 807, 1048, 1139, 1172, 1260, 1396, 1605, 2855, 2928, 2958 cm^{-1}.

Anal. Calcd for $C_{31}H_{31}F_3N_2$ (488.24) C, 76.21 H, 6.40 N, 5.73 Found C, 75.88 H, 6.06 N, 5.23.

6-(4'-Dodecylbiphenyl-4-yl)-3-(4-dodecylphenyl)-4-trifluoromethylpyridazine (**12**).

Cross-coupling reaction of **1** (130 mg, 0.38 mmole) with 4-dodecylphenylboronic acid (440 mg, 1.52 mmoles) according to

the general procedure B (t = 30 hours) gave after purification by column chromatography (silica, eluent petrolueum ether:ethyl acetate (95:5)) 224 mg (83 %) of **12** as a pale yellow solid, mp 82-83°. ^{1}H nmr (deuteriochloroform): δ 0.87 (m, 6H, 2 x CH_3), 1.26 (m, 36H, 18 x CH_2), 1.64 (m, 4H, 2 x CH_2), 2.64 (m, 4H, 2 x CH_2), 7.23 (m, 4H, H_{Ph}), 7.51 (m, 4H, H_{Ph}), 7.71 (d, J = 7.1 Hz, 2H, H_{Ph}), 8.07 (s, 1H, H_5), 8.17 (d, J = 7.1 Hz, 2H, H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 14.5, 23.1, 29.8, 29.9, 30.0, 30.1, 31.7, 31.9; 32.4, 36.1, 36.3, 36.4, 120.7, 120.8, 126.1, 128.3, 128.6, 129.8, 130.2, 130.6, 133.4, 133.7, 137.6, 143.5, 144.0, 145.2, 157.3, 158.1; ^{19}F nmr (deuteriochloroform): δ -60.3; ir (potassium bromide) 808, 842, 1048, 1155, 1182, 1260, 1396, 1467, 1606, 2850, 2918 cm^{-1}.

Anal. Calcd. for $C_{47}H_{63}F_3N_2$ (713.01) C, 79.17 H, 8.91 N, 3.93. Found C, 78.83 H, 8.62 N, 3.65

6-(4'-(Oct-1-ynyl)biphenyl-4-yl)-3-(4-(oct-1-ynyl)phenyl)-4-trifluoromethyl-pyridazine (**13**).

Cross-coupling reaction of **1** (60 mg, 0.18 mmole) with 4-oct-1-ynyl-phenylboronic acid (207 mg, 0.9 mmole) according to the general procedure B (t = 30 hours) gave after purification by column chromatography (silica, eluent petroleum ether: dichloromethane (4:1)) 75 mg (71%) of **13** as a colorless solid, mp 115-116°. ^{1}H nmr (deuteriochloroform): δ 0.94 (t, J = 5.4 Hz, 6H, 2 x CH_3), 1.47 (m, 16H, 8 x CH_2), 2.47 (t, J = 6.8 Hz, 4H, 2 x CH_2), 7.54 (m, 8H, H_{Ph}), 7.81 (d, J = 8.3 Hz, 2H, H_{Ph}), 8.19 (s, 1H, H_5) 8.28 (d, J = 8.2 Hz, 2H, H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 13.1, 18.5, 21.6, 27.6, 30.4, 79.1, 79.2, 90.9, 91.6, 122.9, 124.8, 125.8, 126.6, 126.7, 128.1, 130.4, 131.1, 132.6, 133.5, 137.7, 142.0; ^{19}F (deuteriochloroform): δ -60.3; ir (potassium bromide) 819, 1048, 1086, 1159, 1260, 1404, 2341, 2352, 2856, 2930, 2957cm^{-1}.

Anal. Calcd. for $C_{39}H_{39}F_3N_2$ (592.31) C, 79.03 H, 6.63 N, 4.73. Found C, 79.26 H, 6.36 N, 4.59.

6-(4'-Octyloxybiphenyl-4-yl)-3-(4-octyloxyphenyl)-4-trifluoromethylpyridazine (**14**).

Method 1.

A solution of 1-bromooctane (66 mg, 0.34 mmole, 2.1 equiv.) in acetone (2 mL) was added to a mixture of **10** (67 mg, 0.16 mmole, 1 equiv.) in acetone (5 mL). The mixture was stirred and heated under reflux for 48 hours. After cooling at room temperature acetone was evaporated, then the residue was extracted with diethyl ether (3x10 mL). The organic phase was washed with water (5 mL), then with a 5% aqueous sodium hydroxide solution (5 mL) and finally with water (5 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent dichloromethane) to give 94 mg (91%) of **14** as a pale yellow solid.

Method 2.

Cross-coupling reaction of **1** (50 mg, 0.15 mmole) with 4-octyloxyphenylboronic acid (150 mg, 0.6 mmole) according to the general procedure B (t = 30 hours) gave after purification by column chromatography (silica, eluent dichloromethane) 73 mg (78%) of **14** as a pale yellow solid, mp 115-144°. ^{1}H nmr (deuteriochloroform): δ 0.92 (m, 6H, 2xCH_3), 1.4 (m, 20H, 10xCH_2), 1.85 (m, 4H, 4xCH_2), 4.05 (m, 4H, 2xOCH_2), 7.05 (m, 4H, H_{Ph}), 7.65 (m, 4H, H_{Ph}), 7.79 (d, J = 8.7 Hz, 2H, Ph), 8.16 (s, 1H, H_5), 8.27 (d, J = 8.2 Hz, 2H, H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 14.5, 23.1, 26.5, 29.7, 29.8, 32.2, 68.5, 95.7, 114.7, 115.3, 118.8, 122.7, 127.7, 127.9, 128.2, 128.6, 131.2, 132.5, 133.3, 143.6, 156.9, 157.9, 159.7, 160.9; ^{19}F NMR (deuteriochloroform): δ -60.3.

Anal. Calcd. for $C_{39}H_{47}F_3N_2O_2$ (632.36) C, 74.02 H, 7.49 N, 4.43. Found C, 73.65 H, 7.63 N, 4.20.

6-(4'-Dodecyloxybiphenyl-4-yl)-3-(4-dodecyloxyphenyl)-4-trifluoromethyl-pyridazine (**15**).

Cross-coupling reaction of **1** (68 mg, 0.2 mmole) with 4-dodecyloxyphenylboronic acid (244 mg, 0.8 mmole) according to the general procedure B (t = 30 hours) gave after purification by column chromatography (silica, eluent dichloromethane) 123 mg (83%) of **15** as a pale yellow solid, mp 95°. ^{1}H nmr (deuteriochloroform): δ 0.91 (t, J = 5.6 Hz, 6H, 2xCH_3), 1.4 (m, 36H, 18 x CH_2), 1.85 (m, 4H, 2 x CH_2), 4.06 (m, 4H, 2 x CH_2), 7.06 (m, 4H, H_{Ph}), 7.64 (m, 4H, H_{Ph}), 7.79 (d, J = 8.7 Hz, 2H, H_{Ph}), 8.16 (s, 1H, H_5), 8.27 (d, J = 8.2 Hz, 2H, H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 14.5, 23.1, 26.5, 29.7, 29.8, 30.0, 30.1, 32.3, 68.5, 114.7, 115.3, 120.7, 122.7, 127.7, 127.9, 128.2, 128.6, 131.1, 132.5, 133.3, 143.6, 156.9, 157.9, 159.7, 160.9, 161.8; ^{19}F nmr (deuteriochloroform): δ -60.3.

Anal. Calcd for $C_{47}H_{63}F_3N_2O_2$ (744.48) C, 75.77 H, 8.52 N, 3.76. Found C, 75.72 H, 8.72 N, 3.73.

4-(Oct-1-ynyl)phenylboronic acid (**16**).

1-Bromo-4-(oct-1-ynyl)benzene (1.68 g, 6.35 mmoles) synthesized according to the literature [17] was dissolved in 20 mL of anhydrous THF in a 100 mL flask equiped with a nitrogen inlet-outlet. The solution was cooled to -78° with a dry ice-acetone bath. *n*-Butyllithium (2.5 *M* in hexane, 3.05 mL, 7.6 mmoles) was added dropwise to the stirring mixture, maintaining the temperature below -65°. After 30 min, triisopropylborate (4.39 mL, 19.0 mmoles) was added dropwise. The temperature was maintained at -78° during 30 min. The reaction mixture was subsequently warmed to room temperature and stirred overnight. 10 mL of a mixture THF:HCl:EtOH (4:1:1) was added then the solution was neutralised with a saturated sodium hydrogen carbonate solution. The solution was extracted with diethylether (3 x 10 mL), dried over magnesium sulfate, filtered and the solvent was evaporared. The bown powder was washed with dichloromethane to yield 1.46 g (71%) of a brown solid, mp 118°. ^{1}H nmr (DMSO-d_6): δ 0.88 (m, 3H, CH_3), 1.30 (m, 8H, 4 x CH_2), 2.43 (t, J = 6.8 Hz, 2H, CH_2), 7.33 (d, J = 7.9 Hz, 2H, H_{Ph}), 7.74 (d, J = 7.9 Hz, 2H, H_{Ph}), 8.13 (s, 2H, OH); ^{13}C nmr (DMSO-d_6): δ 14.3, 19.0, 22.4, 28.3, 28.4, 31.1, 81.1, 91.9, 125.2, 130.5, 134.5; ir (potassium bromide) 690, 750, 841, 1179, 1306, 1343, 1401, 1464, 1605, 2857, 2929, 2947 cm^{-1}; MS (EI) m/z 229 (M^+, 100).

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