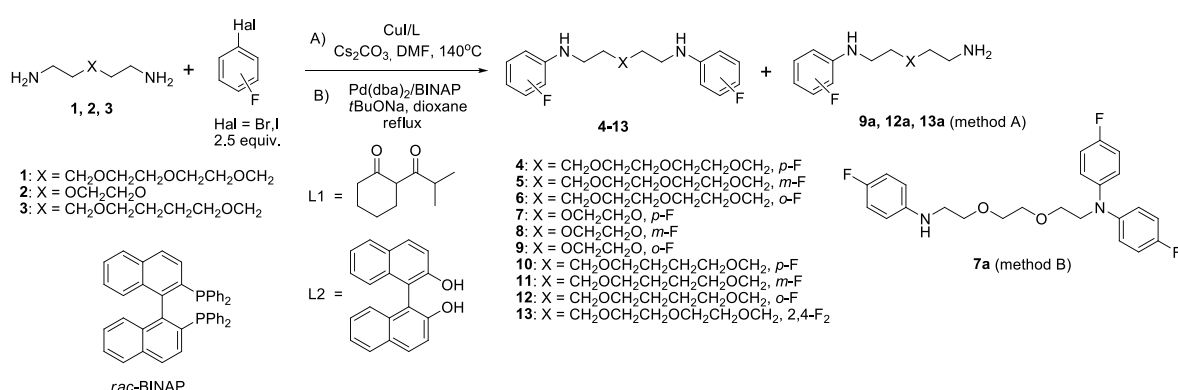


Cu(I)- and Pd(0)-Catalyzed Arylation of Oxadiazines with Fluorinated Halogenobenzenes: Comparison of Efficiency

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Supporting Information



Scheme S1.

Table S1. Cu(I)-catalyzed arylation of oxadiazines 1–3 with fluoroiodo- and bromofluorobenzenes.

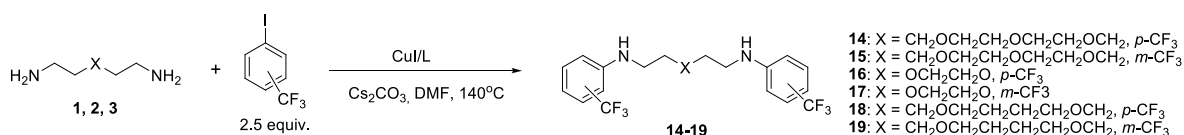
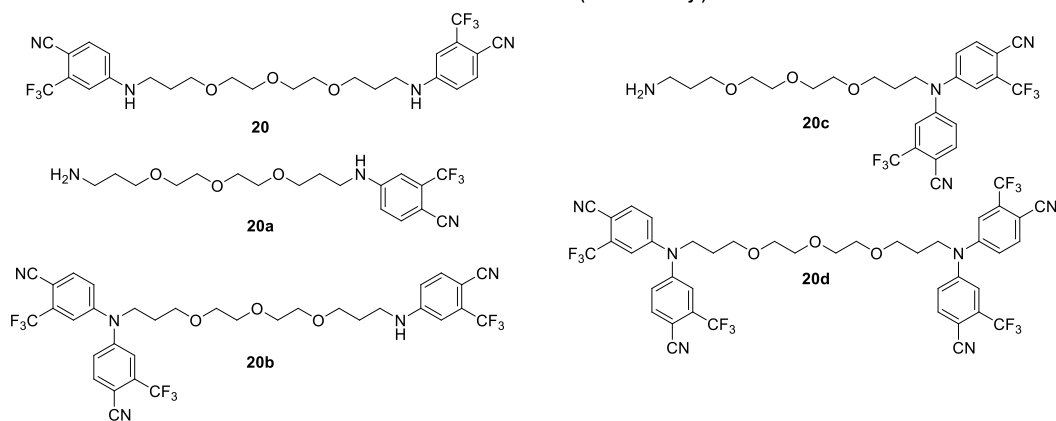
Aryl halide	Amine	L (CuI/L, mol%)	Product	Yield, %
4-Fluoroiodobenzene	1	L1 (20/40)	4	24
4-Fluoroiodobenzene	1	L2 (10/20)	4	18
4-Bromofluorobenzene	1	L1 (20/40)	4	35
3-Fluoroiodobenzene	1	L1 (20/40)	5	82
2-Fluoroiodobenzene	1	L1 (20/40)	6	77
2-Bromofluorobenzene	1	L1 (20/40)	6	40 ^{a)}
2,4-Difluoroiodobenzene	1	L1 (20/40)	13	20
			13a	19
4-Fluoroiodobenzene	2	L1 (20/40)	7	34
4-Fluoroiodobenzene	2	L2 (10/20)	7	62
4-Bromofluorobenzene	2	L1 (20/40)	7	54
3-Fluoroiodobenzene	2	L1 (20/40)	8	70
2-Fluoroiodobenzene	2	L1 (20/40)	9	58
			9a	16
2-Bromofluorobenzene	2	L1 (20/40)	9	52 ^{a)}
4-Fluoroiodobenzene	3	L1 (20/40)	10	58
4-Fluoroiodobenzene	3	L2 (10/20)	—	— ^{b)}
4-Bromofluorobenzene	3	L1 (20/40)	10	48
3-Fluoroiodobenzene	3	L1 (20/40)	11	77
2-Fluoroiodobenzene	3	L1 (20/40)	12	30
			12a	8
2-Bromofluorobenzene	3	L1 (20/40)	12	60 ^{a)}

^{a)} Total conversion of NH₂ into NHAr is shown which was estimated from ¹H NMR spectrum of the reaction mixture. ^{b)} Conversion was low, it could not be estimated from ¹H NMR spectrum of the reaction mixture.

Table S2. Pd(0)-catalyzed arylation of oxadiazines 1–3 with bromofluorobenzenes.

Aryl halide	Amine	Pd(dba) ₂ /BINAP, mol%	Product	Yield, %
4-Bromofluorobenzene	1	1/1.5	4	72
3-Bromofluorobenzene	1	1/1.5	5	78
2-Bromofluorobenzene	1	1/1.5	6	74 ^{a)}
2-Bromofluorobenzene	1	4/4.5	6	98
4-Bromofluorobenzene	2	1/1.5	7	77 ^{a)}
4-Bromofluorobenzene	2	2/2.5	7	73
4-Bromofluorobenzene	2	2/2.5	7a	11
3-Bromofluorobenzene	2	2/2.5	8	98
2-Bromofluorobenzene	2	1/1.5	9	63
4-Bromofluorobenzene	3	1/1.5	10	60
3-Bromofluorobenzene	3	1/1.5	11	73
2-Bromofluorobenzene	3	1/1.5	12	49

^{a)} Total conversion of NH₂ into NHAr is shown which was estimated from ¹H NMR spectrum of the reaction mixture.

**Products in the reaction with 4-iodo-2-(trifluoromethyl)benzonitrile:****Scheme S2.****Table S3.** Cu(I)-catalyzed arylation of oxadiazines 1–3 with iodo(trifluoromethyl)benzenes.

Entry	Aryl halide	Amine	L (CuI/L, mol%)	Product	Yield, %
1	1-Iodo-4-(trifluoromethyl)benzene	1	L1 (20/40)	14	25
2	1-Iodo-4-(trifluoromethyl)benzene	1	L2 (10/20)	14	14
3	1-Iodo-3-(trifluoromethyl)benzene	1	L1 (20/40)	15	21
4	1-Iodo-4-(trifluoromethyl)benzene	2	L1 (20/40)	16	14
5	1-Iodo-4-(trifluoromethyl)benzene	2	L2 (10/20)	—	—
6	1-Iodo-3-(trifluoromethyl)benzene	2	L1 (20/40)	17	98
7	1-Iodo-4-(trifluoromethyl)benzene	3	L1 (20/40)	18	28
8	1-Iodo-4-(trifluoromethyl)benzene	3	L2 (10/20)	18	10
9	1-Iodo-3-(trifluoromethyl)benzene	3	L1 (20/40)	19	91
				20	17
10	4-Iodo-2-(trifluoromethyl)benzonitrile	1	L1 (20/40)	20a	44
				20b	4
				20c	12
11	4-Iodo-2-(trifluoromethyl)benzonitrile ^{a)}	1	L1 (20/40)	20b	12
				20d	9
				20	9
12	4-Iodo-2-(trifluoromethyl)benzonitrile	1	L1 (10/20)	20b	5
				20c	5

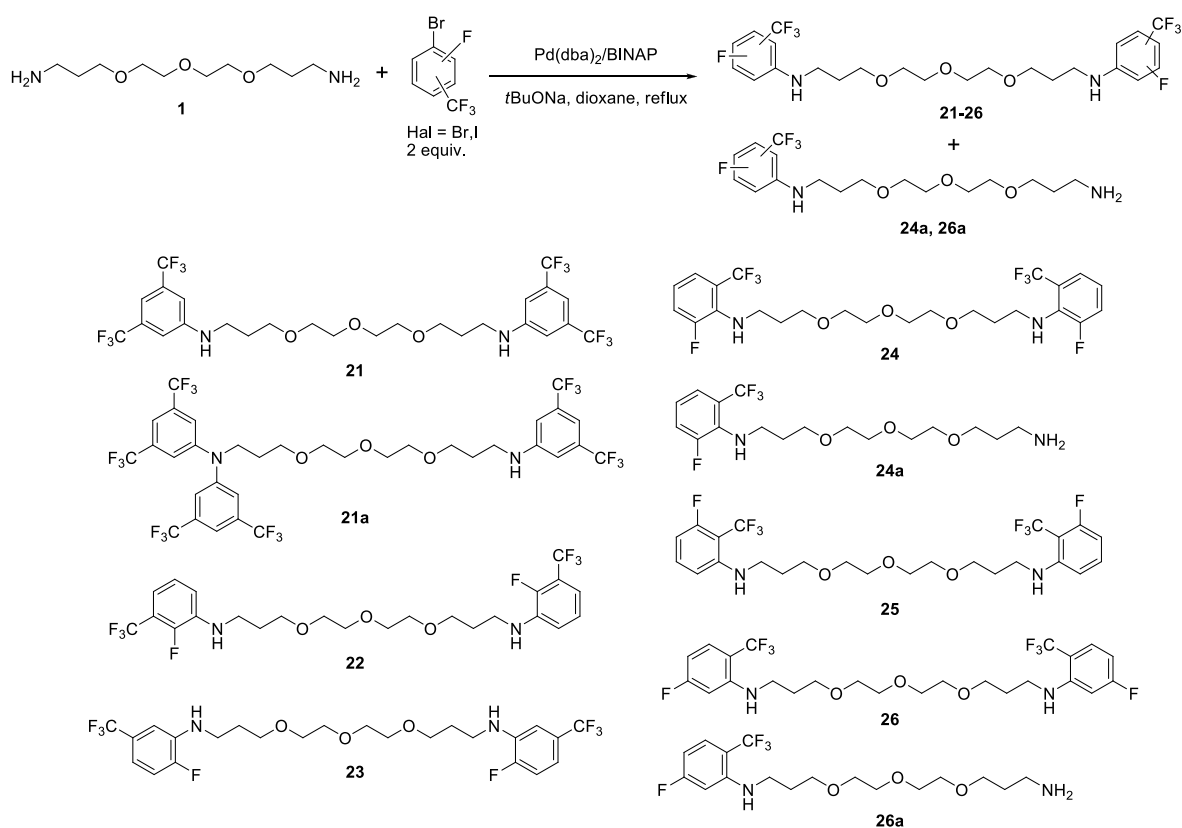
a) 4 Equiv. of 4-Iodo-2-(trifluoromethyl)benzonitrile were used.

4-((3-(2-(2-(3-Aminopropoxy)ethoxy)ethoxy)propyl)amino)-2-(trifluoromethyl)benzonitrile (**20a**). Obtained as one of several products according to method A from trioxadamine **1** (0.5 mmol, 110 mg), 4-iodo-2-(trifluoromethyl)benzonitrile (1.25 mmol, 371 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (34 mg). Eluent CH₂Cl₂–MeOH 20:1. Yield 86 mg (44%). ¹H-NMR (400 MHz, CDCl₃) δ 1.74 (quintet, 2H, ³J = 6.0 Hz, OCH₂CH₂CH₂NH₂), 1.88 (quintet, 2H, ³J = 5.8 Hz, OCH₂CH₂CH₂NHAr), 3.27 (q, 2H, ³J = 5.9 Hz, CH₂NH₂), 3.36 (q, 2H, ³J = 5.9 Hz, CH₂NAr), 3.54–3.60 (m, 8H, OCH₂), 3.61–3.64 (m, 4H, OCH₂), 5.69 (t, 1H, ³J = 5.0 Hz, NH), 6.65 (dd, 1H, ³J = 8.6 Hz, ⁴J = 2.0 Hz, H5 (Ph)), 6.82 (d, 1H, ⁴J = 2.0 Hz, H2 (Ph)), 7.48 (d, 1H, ³J = 8.6 Hz, H5 (Ph)). NH₂ protons were not unambiguously assigned. ¹³C-NMR (100.6 MHz, CDCl₃) δ 28.2 (1C, OCH₂CH₂CH₂NH), 28.3 (1C, OCH₂CH₂CH₂NHAr), 36.7 (1C, CH₂NH₂), 41.2 (1C, CH₂NHAr), 69.4 (1C, OCH₂), 69.6 (1C, OCH₂), 70.0 (1C, OCH₂), 70.1 (1C, OCH₂), 70.2 (1C, OCH₂), 70.3 (1C, OCH₂), 94.0 (1C, C4 (Ph)), 110.0 (1C, C6 (Ph)), 113.3 (1C, C2 (Ph)), 118.5 (1C, CN), 122.7 (q, 1C, ¹J_{CF} = 273.5 Hz, CF₃), 133.8 (1C, ²J_{CF} = 32.1 Hz, C3 (Ph)), 136.0 (1C, C5 (Ph)), 151.5 (1C, C1 (Ph)). MS (MALDI-TOF+): Calculated for C₁₈H₂₇F₃N₃O₃ [M + H] 390.2005, found 390.2026.

4,4'-((3-(2-(2-(3-((4-Cyano-3-(trifluoromethyl)phenyl)amino)propoxy)ethoxy)ethoxy)propyl)-azandiyl)bis(2-(trifluoromethyl)benzonitrile) (**20b**). Obtained as one of several products according to method A from trioxadamine **1** (0.5 mmol, 110 mg), 4-iodo-2-(trifluoromethyl)benzonitrile (2 mmol, 594 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (34 mg). Eluent CH₂Cl₂–MeOH 200:1. Yield 44 mg (12%). ¹H-NMR (400 MHz, CDCl₃) δ 1.87–1.94 (m, 4H, OCH₂CH₂CH₂N), 3.27 (t, 2H, ³J = 6.0 Hz, CH₂NAr), 3.59–3.62 (m, 8H, OCH₂), 3.65–3.68 (m, 4H, OCH₂), 4.05 (t, 2H, CH₂NAr₂), 5.90 (br. s, 1H, NH), 6.65 (d, 1H, ³J = 8.1 Hz, H6 (Ph)), 6.81 (s, 1H, H2 (Ph)), 7.35 (d, 2H, ³J = 8.0 Hz, ⁴J = 2.0 Hz, H6 (2Ph)), 7.44 (d, 2H, ⁴J = 2.2 Hz, H2 (2Ph)), 7.50 (d, 1H, ³J = 8.1 Hz, H5 (Ph)), 7.67 (d, 2H, ³J = 8.0 Hz, H5 (2Ph)).

4,4'-((3-(2-(2-(3-Aminopropoxy)ethoxy)ethoxy)propyl)azanediyl)bis(2-(trifluoromethyl)benzonitrile) (**20c**). Obtained as one of several products according to method A from trioxadamine **1** (0.5 mmol, 110 mg), 4-iodo-2-(trifluoromethyl)benzonitrile (2 mmol, 594 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (34 mg). Eluent CH₂Cl₂–MeOH 50:1. Yield 35 mg (12%). ¹H-NMR (400 MHz, CDCl₃) δ 1.80 (quintet, 2H, ³J = 5.8 Hz, OCH₂CH₂CH₂NH₂), 1.92 (quintet, 2H, ³J = 5.7 Hz, OCH₂CH₂CH₂NAr₂), 3.34 (t, 2H, ³J = 5.5 Hz, CH₂NH₂), 3.49 (t, 2H, ³J = 5.7 Hz, CH₂O), 3.56–3.68 (m, 10 H, OCH₂), 4.05 (t, 2H, ³J = 7.0 Hz, CH₂NAr₂), 7.38 (dd, 2H, ³J = 8.6 Hz, ⁴J = 2.5 Hz, H6 (Ph)), 7.46 (d, 2H, ⁴J = 2.5 Hz, H2 (Ph)), 7.77 (dd, 2H, ³J = 8.6 Hz, ⁴J = 2.0 Hz, H5 (Ph)). NH₂ protons were not unambiguously assigned. MS (MALDI-TOF+): Calculated for C₂₆H₂₉F₆N₄O₃ [M + H] 559.214, found 559.202.

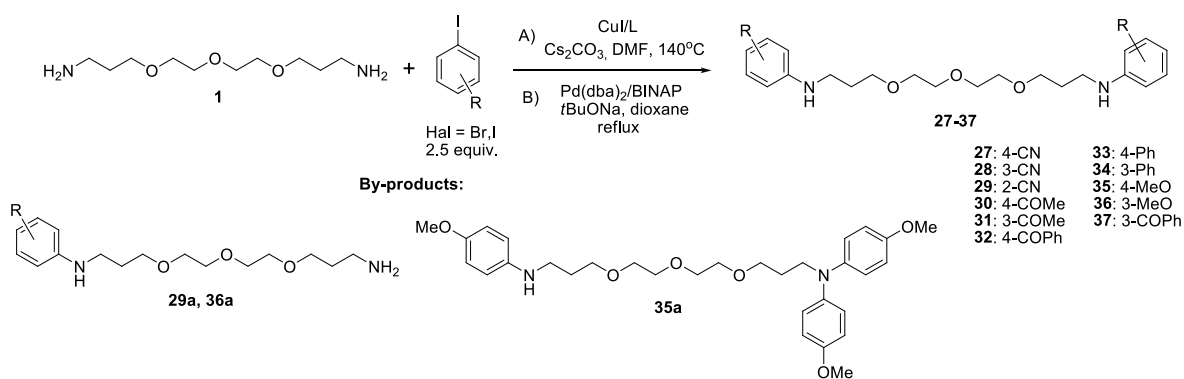
4,4',4'',4'''-((((Oxybis(ethane-2,1-diyl))bis(oxy))bis(propane-3,1-diyl))bis(azanetriyl))tetrakis(2-(trifluoromethyl)benzonitrile) (**20d**). Obtained as one of several products according to method A from trioxadamine **1** (0.5 mmol, 110 mg), 4-iodo-2-(trifluoromethyl)benzonitrile (2 mmol, 594 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (34 mg). Eluent CH₂Cl₂–MeOH 200:1. Yield 40 mg (9%). ¹H-NMR (400 MHz, CDCl₃) δ 1.94 (quintet, 4H, ³J = 5.8 Hz, OCH₂CH₂CH₂N), 3.52 (t, 4H, ³J = 5.5 Hz, CH₂O), 3.59–3.62 (m, 4H, OCH₂), 3.68–3.71 (m, 4H, OCH₂), 4.05 (t, 4H, ³J = 6.9 Hz, CH₂N), 7.37 (dd, 4H, ³J = 8.5 Hz, ⁴J = 2.1 Hz, H6 (Ph)), 7.48 (d, 4H, ⁴J = 2.1 Hz, H2 (Ph)), 7.76 (dd, 4H, ³J = 8.6 Hz, ⁴J = 2.1 Hz, H5 (Ph)). ¹³C-NMR (100.6 MHz, CDCl₃) δ 27.2 (2C, OCH₂CH₂CH₂NH), 49.2 (2C, CH₂N), 67.2 (2C, CH₂O), 70.3 (2C, CH₂O), 70.4 (2C, CH₂O), 103.0 (4C, C4 (Ph)), 115.5 (4C, CN), 118.7 (q, 4C, ³J_{CF} = 4.2 Hz, C2 (Ph)), 122.0 (q, 4C, ¹J_{CF} = 274.0 Hz, CF₃), 123.5 (4C, C6 (Ph)), 134.7 (q, 4C, ²J_{CF} = 32.2 Hz, C3 (Ph)), 136.4 (4C, C5 (Ph)), 149.4 (4C, C1 (Ph)).



Scheme S3.

Table S4. Pd(0)-catalyzed arylation of trioxadiazamine **1** with bromofluoro(trifluoromethyl)benzenes.

Entry	Aryl halide	$\text{Pd}(\text{dba})_2/\text{BINAP}$, mol%	Product	Yield, %
1	1-Bromo-3,5-di(trifluoromethyl)benzene	1/1.5	21	80
			21a	7
2	3-Bromo-2-fluorobenzotrifluoride	1/1.5	22	65
3	3-Bromo-4-fluorobenzotrifluoride	1/1.5	23	70
4	2-Bromo-3-fluorobenzotrifluoride	1/1.5	—	—
5	2-Bromo-3-fluorobenzotrifluoride	8/8.5	24	18
			24a	7
6	2-Bromo-6-fluorobenzotrifluoride	1/1.5	—	—
7	2-Bromo-6-fluorobenzotrifluoride	8/8.5	25	17
8	2-Bromo-4-fluorobenzotrifluoride	1/1.5	—	—
9	2-Bromo-4-fluorobenzotrifluoride	4/4.5	26a	12
10	2-Bromo-4-fluorobenzotrifluoride	8/8.5	26	29



Scheme S4.

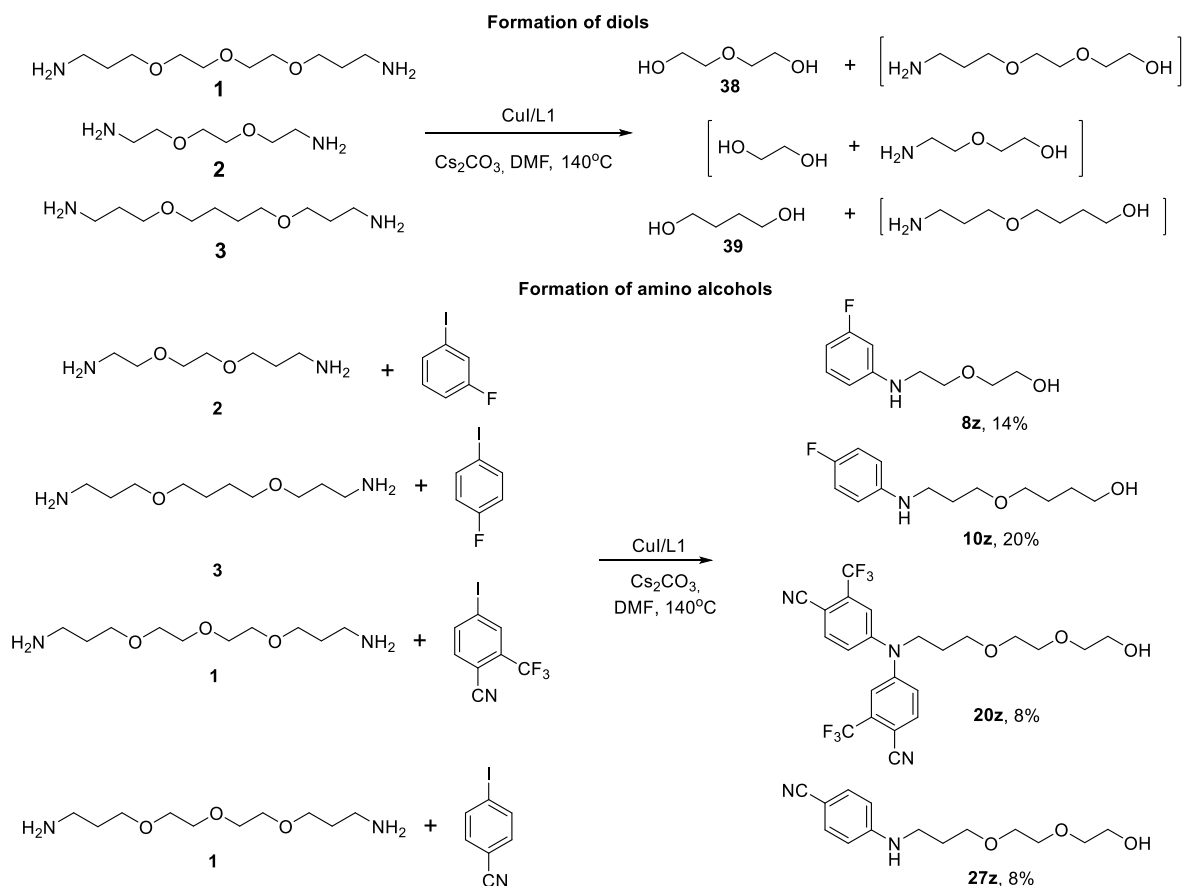
Table S5. Cu(I)-catalyzed arylation of trioxadiazine **1** with various aryl iodides (CuI/L1, 20/40 mol%).

Entry	Aryl halide	Product	Yield, %
1	4-Iodobenzonitrile	27	91
2	3-Iodobenzonitrile	28	78
3	2-Iodobenzonitrile	29 29a	40 38
4	4-Iodoacetophenone	30	85
5	3-Iodoacetophenone	31	45
6	4-Iodobenzophenone	32	71
7	4-Iodobiphenyl	33	65
8	3-Iodobiphenyl	34	50
9	4-Iodoanisole	35	43
10	3-Iodoanisole	36 36a	64 17

Table S6. Pd(0)-catalyzed arylation of trioxadiazine **1** with various aryl iodides.

Entry	Aryl halide	Pd(dba) ₂ /BINAP, mol%	Product	Yield, %
1	4-Bromobenzonitrile	1/1.5	27	84
2	3-Bromobenzonitrile	1/1.5	28	55 ^{a)}
3	3-Bromobenzonitrile	4/4.5	28	94
4	2-Bromobenzonitrile	1/1.5	29	69 ^{a)}
5	2-Bromobenzonitrile	4/4.5	29	40
6	4-Bromoacetophenone	1/1.5	— ^{b)}	—
7	3-Bromoacetophenone	1/1.5	— ^{b)}	—
8	4-Bromobenzophenone	1/1.5	32	96
9	4-Bromobiphenyl	1/1.5	33	65
10	3-Bromobiphenyl	1/1.5	34	79
11	4-Bromoanisole	1/1.5	35 35a	41 6
12	3-Bromoanisole	1/1.5	36	73
13	3-Bromobenzophenone	1/1.5	37	82

^{a)} Total conversion of NH₂ into NHAr is shown which was estimated from ¹H NMR spectrum of the reaction mixture; ^{b)} Starting compound was unstable under reaction conditions.



Scheme S5.

2-((2-((3-Fluorophenyl)amino)ethoxy)ethan-1-ol (8z). Obtained as the second product in the synthesis of compound **8** using method A. Eluent CH₂Cl₂–MeOH 50:1. Yield 14 mg (14%). ¹H-NMR (400 MHz, CDCl₃) δ 3.29 (t, 2H, ³J = 5.6 Hz, CH₂N), 3.59 (t, 2H, ³J_{HH} = 4.5 Hz, OCH₂), 3.70 (t, 2H, ³J = 5.3 Hz, OCH₂), 3.70 (t, 2H, ³J = 5.3 Hz, OCH₂), 6.31 (dt, 1H, ³J_{HF} = 11.5 Hz, ⁴J_{HH} = 2.1 Hz, H2 (Ph)), 6.36–6.41 (m, 2H, H4, H6 (Ph)), 7.09 (td, 1H, ³J_{HH} = 8.0 Hz, ⁴J_{HF} = 6.8 Hz, H5 (Ph)). NH and OH were not unambiguously assigned. ¹³C-NMR (100.6 MHz, CDCl₃) δ 43.5 (1C, CH₂N), 61.8 (1C, OCH₂), 69.4 (1C, OCH₂), 72.1 (1C, CH₂OH), 99.6 (d, 2C, ²J_{CF} = 25.1 Hz, C2 (Ph)), 104.0 (d, 1C, ²J_{CF} = 21.4 Hz, C4 (Ph)), 108.9 (1C, C6 (Ph)), 130.2 (d, 1C, ³J_{CF} = 10.3 Hz, C5 (Ph)), 149.9 (d, 1C, ³J_{CF} = 10.3 Hz, C1 (Ph)), 158.7 (d, 1C, ¹J_{CF} = 242.2 Hz, C3 (Ph)). MS (MALDI-TOF+): Calculated for C₁₀H₁₃FN₂O₂ [M – H₂ + H] 198.0930, found 198.0911.

4-(3-((4-Fluorophenyl)amino)propoxy)butan-1-ol (10z). Obtained as the second product in the synthesis of compound **10** using method A. Eluent CH₂Cl₂–MeOH 50:1. Yield 24 mg (20%). ¹H-NMR (400 MHz, CDCl₃) δ 1.64–1.70 (m, 4H, OCH₂CH₂CH₂CH₂OH), 1.89 (quintet, 2H, ³J = 6.2 Hz, OCH₂CH₂CH₂N), 3.20 (t, 2H, ³J = 6.5 Hz, CH₂N), 3.47 (t, 2H, ³J = 5.7 Hz, OCH₂), 3.56 (t, 2H, ³J = 5.8 Hz, OCH₂), 3.65 (t, 2H, ³J = 5.7 Hz, CH₂O), 6.61 (dd, 2H, ³J_{HH} = 8.8 Hz, ⁴J_{HF} = 4.3 Hz, H2, H2' (Ph)), 7.85–7.89 (dd, 2H, ³J_{HH} = 8.8 Hz, ³J_{HF} = 8.8 Hz, H3, H3' (Ph)). ¹³C-NMR (100.6 MHz, CDCl₃) δ 26.5 (1C, CH₂CH₂CH₂CH₂OH), 28.0 (1C, CH₂CH₂CH₂CH₂OH), 29.9 (1C, NCH₂CH₂CH₂O), 45.3 (1C, CH₂N), 62.5 (1C, CH₂O), 69.0 (1C, OCH₂), 71.1 (1C, OCH₂), 116.0 (d, 2C, ²J_{CF} = 22.5 Hz, C3, C3' (Ph)), 117.1 (d, 2C, ³J_{CF} = 7.5 Hz, C2, C2' (Ph)), 149.8 (1C, C1 (Ph)), 157.8 (d, 1C, ¹J_{CF} = 240.5 Hz, C4 (Ph)). MS (MALDI-TOF+): Calculated for C₁₃H₂₁FN₂O₂ [M – H₂ + H] 242.156, found 242.173.

4-((3-(2-(2-Hydroxyethoxy)ethoxy)propyl)amino)-2-(trifluoromethyl)benzonitrile (20z). Obtained as one of several products according to method A from trioxadiazine **1** (0.5 mmol, 110 mg), 4-iodo-2-(trifluoromethyl)benzonitrile (2 mmol, 594 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (34 mg). Eluent CH₂Cl₂–MeOH 100:1. Yield 20 mg (8%). ¹H-NMR (400 MHz, CDCl₃) δ 1.94 (quintet, 2H, ³J = 6.2 Hz, OCH₂CH₂CH₂N), 3.52 (t, 2H, ³J = 6.9 Hz, CH₂NPh₂),

3.59–3.63 (m, 4H, OCH₂), 3.66–3.79 (m, 2H, OCH₂), 3.74 (t, 2H, ³J = 4.5 Hz, CH₂OH), 4.05 (t, 2H, ³J = 6.9 Hz, CH₂NPh₂), 7.36 (dd, 4H, ³J = 8.6 Hz, ⁴J = 2.3 Hz, H₆ (Ph)), 7.47 (d, 4H, ⁴J = 2.3 Hz, H₂(Ph)), 7.76 (d, 4H, ³J = 8.6 Hz, H₅(Ph)). OH proton was not unambiguously assigned. ¹³C-NMR (100.6 MHz, CDCl₃) δ 27.2 (1C, OCH₂CH₂CH₂N), 49.2 (1C, CH₂N), 61.7 (1C, CH₂OH), 67.2 (1C, OCH₂), 70.3 (1C, OCH₂), 70.4 (1C, OCH₂), 72.3 (1C, CH₂O), 103.0 (2C, C₄ (Ph)), 115.5 (2C, CN), 118.7 (2C, C₂ (Ph)), 122.0 (q, 2C, ¹J_{CF} = 274.4 Hz, CF₃), 123.5 (2C, C₆ (Ph)), 134.8 (q, 2C, ²J_{CF} = 32.5 Hz, C₃ (Ph)), 136.4 (2C, C₅ (Ph)), 149.4 (2C, C₁ (Ph)). ¹⁹F-NMR (376.4 MHz, CDCl₃) δ –62.33 (6F, CF₃). MS (MALDI-TOF+): Calculated for C₂₃H₂₂F₆N₃O₃ [M + H] 502.1565, found 502.1530.

4-((3-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)amino)benzonitrile (**27z**). Obtained as the second product in the synthesis of compound **27**. Eluent CH₂Cl₂/MeOH 20:1 Yield 11 mg (8%). ¹H-NMR (400 MHz, CDCl₃) δ 1.89 (quintet, 2H, ³J = 5.9 Hz, OCH₂CH₂CH₂N), 3.26 (q, 2H, ³J = 6.3 Hz CH₂N), 3.58–3.62 (m, 6H, OCH₂), 3.65–3.68 (m, 2H, OCH₂), 3.73 (t, 2H, ³J = 4.4 Hz, CH₂O), 4.90 (br. s, 1H, NH), 6.53 (d, 2H, ³J_{obs} = 8.7 Hz, H₂, H₂'(Ph)), 7.37 (d, 4H, ³J_{obs} = 8.7 Hz, H₃, H₃'(Ph)). OH proton was not unambiguously assigned. MS (MALDI-TOF+): Calculated for C₁₄H₂₇N₂O₃ [M + H] 265.1552, found 265.1524.