Electronic supplementary materials *Mendeleev Commun.*, 2024, **34**, 181–184

Assessing the contribution of reaction components to the overall toxicity of synthesis of 4-methoxy-4′-nitro-1,1′-biphenyl

Ksenia S. Egorova, Alexandra V. Posvyatenko, Alexey S. Galushko and Andrey E. Kolesnikov

Contents

Building of bio-Strips and calculation of BFs and CPs

A bio-Strip is a visual representation of a chemical reaction in accordance with amounts (*n*, mmol) and half-maximal cytotoxicity concentrations (CC_{50}, $mmol \cdot L^{-1}$ or mM) of all its participant substances. In the bio-Strip, the length of each section corresponds to the "normalized cytotoxicity" (NC, see equation 1) of the corresponding substance (starting material (SM), catalyst (CT), additional reagent (R), solvent (S), product (P), or byproduct (BP).

$$\mathrm{NC} = \frac{\mathrm{n}}{\mathrm{CC_{50}}} (1)$$

The color of the sections reflects the CC_{50} of the corresponding compounds measured in a particular cell line. The lowest CC_{50} value (highest cytotoxicity) is red, while the highest CC_{50} value (lowest cytotoxicity) is green.

For each reaction, the following metrics are calculated: the bio-Factor (BF), which shows the change in the "overall cytotoxicity" upon the reaction course (see equation 2), and three cytotoxicity potentials (CPs): the initial CP (CP_i), which characterizes the compounds entering the reaction (SM, CT, S, R; see equation 3); the final CP (CP_f), which characterizes the compounds leaving the reaction (P, BP and compounds that can be recycled or regenerated, such as CT and S; see equation 4), and the relative final CP (CP_{f_rel}), which characterizes the compounds leaving the reaction except for the target product (BP and compounds that can be recycled or regenerated; see equation 5).

$$\mathrm{BF} = \frac{\sum \mathrm{NC}_{out}}{\sum \mathrm{NC}_{in}} = \frac{\sum \frac{n}{CC_{50}}(out)}{\sum \frac{n}{CC_{50}}(in)} (2),$$

$$\mathrm{CP}_i = \sum \mathrm{NC}_{in} (3),$$

$$\mathrm{CP}_f = \sum \mathrm{NC}_{out} (4),$$

$$\mathrm{CP}_{f\_rel} = \sum \mathrm{NC}_{out} - \mathrm{NC}_{product} (5),$$

where *in* and *out* mark the compounds entering or leaving the reaction, respectively.

In essence, CPs show the quantity of the liters of the cultural media that can be "poisoned" by the substances participating in a given reaction. Therefore, lower CP values correspond to reactions with lower "overall cytotoxicity". According to the equations, reactions at larger scales are characterized by higher CPs, as compared to the same reactions at smaller scales.

Table S1. Experimental data used in this work.

Substance	Mw, g·mol^{-1}	Amount in reaction, mmol[a]	24-h CC_{50}, mM[b]		
			CaCo-2	FRSN	HEK293T
Starting materials					
4-Methoxyphenylboronic acid	151.96	1.00	4.108 (3.929-4.287)	5.563 (3.362-7.763)	4.309 (1.932-6.686)
1-Iodo-4-nitrobenzene	249.01	1.00	>20[c]	>20[c]	>35[c]
1-Bromo-4-nitrobenzene	202.01	1.00	>2[c]	>10[c]	>4[c]
Catalysts					
$Pd(OAc)_2$	224.50	0.01	1.035 (0.421-1.650)	0.709 (0.510-0.908)	1.096 (0.640-1.553)
$PdCl_2$	177.33	0.01	0.698 (0.522-0.875)	0.385 (0.305-0.465)	0.724 (0.347-1.102)
$Pd(acac)_2$	304.64	0.01	0.037 (0.026-0.049)	0.007 (0.005-0.009)	0.014 (0.009-0.019)
Reagents					
Na_2CO_3	105.988	1.00	45.423 (31.753-59.094)	46.313 (39.130-53.497)	32.063 (24.104-40.022)
K_2CO_3	138.205	1.00	29.997 (23.581-36.413)	49.953 (24.034-75.873)	32.360 (25.446-39.274)
Cs_2CO_3	325.82	1.00	18.278 (13.713-22.842)	27.244 (18.986-35.502)	7.113 (5.302-8.923)
Solvents					
Ethanol	46.07	1.263	598.875 (456.787-740.963)	1266.750 (895.474-1638.026)	607.700 (504.107-711.293)
NMP	99.13	1.648	144.300 (108.218-180.382)	118.167 (86.989-149.345)	192.500 (161.918-223.082)
Products					
4-Methoxy-4'-nitro-1,1'-biphenyl	229.24	1.00	>13[c]	>10[c]	>10[c]
Byproducts					
NaI	149.8940	<1.00	184.733 (167.782-201.684)	127.267 (89.611-164.922)	80.103 (77.624-82.583)
NaBr	102.8900	<1.00	185.880 (107.519-264.241)	163.100 (137.261-188.939)	80.040 (64.682-95.398)
KI	166.0030	<1.00	112.300 (103.109-121.491)	64.477 (57.074-71.880)	55.627 (49.419-61.835)
KBr	119.0100	<1.00	314.733 (256.230-373.237)	89.727 (55.567-123.886)	67.760 (42.527-92.993)
CsI	259.81	<1.00	27.293 (14.467-41.118)	83.138 (75.238-91.037)	40.437 (27.602-53.272)
CsBr	212.81	<1.00	34.535 (30.465-38.605)	84.757 (62.806-106.707)	58.418 (47.685-69.150)
$Na_2B_4O_7$[d]	381.37	<0.20	37.453 (23.232-51.674)	43.623 (26.873-60.374)	46.313 (39.594-53.033)
$K_2B_4O_7$[d]	305.5	<0.20	13.213 (6.274-20.152)	32.343 (20.201-44.486)	24.583 (22.180-26.985)
$Cs_2B_4O_7$[d]	511	<0.20	9.755 (4.995-14.514)	28.133 (22.383-33.882)	13.927 (8.258-19.595)
H_3BO_3	61.84	<0.97	246.075 (165.622-326.528)	120.067 (76.847-163.287)	115.788 (75.313-156.262)

[a] 100% conversion is considered. For clarity, maximal possible amounts of byproducts were used in calculations. [b] 95% confidence intervals are shown in parentheses. [c] The exact value could not be measured due to technical difficulties (insufficient solubility in the cultural media). [d] $K_2B_4O_7{\cdot}4H_2O$, $Na_2B_4O_7{\cdot}10H_2O$, and $Cs_2B_4O_7{\cdot}5H_2O$ were tested.

Table S2. bio-Factors and cytotoxicity potentials for synthesis of 4-methoxy-4'-nitro-1,1'-biphenyl.

Reaction	SM2 (ArX)	CT (PdA_2)	R (M_2CO_3)	S	BP1 (MX)	BP2 ($M_2B_4O_7$)	CaCo-2				FRSN				HEK293T			
							BF	CP_i	CP_f	CP_{f_rel}	BF	CP_i	CP_f	CP_{f_rel}	BF	CP_i	CP_f	CP_{f_rel}
A-A-A-A	I	OAc	Na	EtOH	NaI	Na	0.4	0.37	0.15	0.07	0.54	0.29	0.16	0.06	0.52	0.35	0.18	0.08
A-A-A-B	I	OAc	Na	NMP	NaI	Na	0.49	0.44	0.22	0.14	0.68	0.41	0.28	0.18	0.57	0.39	0.22	0.12
A-A-B-A	I	OAc	K	EtOH	KI	K	0.42	0.38	0.16	0.08	0.58	0.29	0.17	0.07	0.55	0.35	0.19	0.09
A-A-B-B	I	OAc	K	NMP	KI	K	0.51	0.45	0.23	0.15	0.7	0.4	0.28	0.18	0.59	0.39	0.23	0.13
A-A-C-A	I	OAc	Cs	EtOH	CsI	Cs	0.48	0.4	0.19	0.12	0.54	0.3	0.16	0.06	0.44	0.46	0.2	0.1
A-A-C-B	I	OAc	Cs	NMP	CsI	Cs	0.55	0.47	0.26	0.19	0.67	0.42	0.28	0.18	0.49	0.5	0.24	0.14
A-B-A-A	I	Cl	Na	EtOH	NaI	Na	0.4	0.38	0.15	0.07	0.56	0.3	0.17	0.07	0.52	0.35	0.18	0.08
A-B-A-B	I	Cl	Na	NMP	NaI	Na	0.5	0.45	0.22	0.14	0.69	0.42	0.29	0.19	0.57	0.39	0.23	0.13
A-B-B-A	I	Cl	K	EtOH	KI	K	0.43	0.39	0.16	0.09	0.6	0.3	0.18	0.08	0.55	0.35	0.19	0.09
A-B-B-B	I	Cl	K	NMP	KI	K	0.51	0.46	0.23	0.16	0.71	0.42	0.3	0.2	0.6	0.39	0.23	0.13
A-B-C-A	I	Cl	Cs	EtOH	CsI	Cs	0.48	0.41	0.2	0.12	0.56	0.31	0.17	0.07	0.45	0.46	0.21	0.11
A-B-C-B	I	Cl	Cs	NMP	CsI	Cs	0.56	0.48	0.27	0.19	0.68	0.43	0.29	0.19	0.49	0.5	0.25	0.15
A-C-A-A	I	acac	Na	EtOH	NaI	Na	0.65	0.63	0.41	0.33	0.92	1.7	1.57	1.47	0.84	1.05	0.88	0.78
A-C-A-B	I	acac	Na	NMP	NaI	Na	0.68	0.7	0.48	0.4	0.93	1.82	1.69	1.59	0.85	1.09	0.93	0.83
A-C-B-A	I	acac	K	EtOH	KI	K	0.65	0.64	0.42	0.34	0.93	1.7	1.58	1.48	0.85	1.05	0.89	0.79
A-C-B-B	I	acac	K	NMP	KI	K	0.69	0.71	0.49	0.41	0.93	1.82	1.7	1.6	0.86	1.09	0.93	0.83
A-C-C-A	I	acac	Cs	EtOH	CsI	Cs	0.68	0.66	0.45	0.38	0.92	1.72	1.58	1.48	0.78	1.16	0.91	0.81
A-C-C-B	I	acac	Cs	NMP	CsI	Cs	0.71	0.73	0.52	0.45	0.92	1.84	1.7	1.6	0.79	1.2	0.95	0.85
B-A-A-A	Br	OAc	Na	EtOH	NaBr	Na	0.18	0.82	0.15	0.07	0.46	0.34	0.15	0.05	0.32	0.57	0.18	0.08
B-A-A-B	Br	OAc	Na	NMP	NaBr	Na	0.24	0.89	0.22	0.14	0.6	0.46	0.27	0.17	0.36	0.61	0.22	0.12
B-A-B-A	Br	OAc	K	EtOH	KBr	K	0.19	0.83	0.15	0.08	0.48	0.34	0.16	0.06	0.33	0.57	0.19	0.09
B-A-B-B	Br	OAc	K	NMP	KBr	K	0.25	0.9	0.22	0.15	0.62	0.45	0.28	0.18	0.37	0.61	0.23	0.13
B-A-C-A	Br	OAc	Cs	EtOH	CsBr	Cs	0.22	0.85	0.19	0.11	0.46	0.35	0.16	0.06	0.29	0.68	0.19	0.09
B-A-C-B	Br	OAc	Cs	NMP	CsBr	Cs	0.28	0.92	0.26	0.18	0.6	0.47	0.28	0.18	0.33	0.72	0.24	0.14
B-B-A-A	Br	Cl	Na	EtOH	NaBr	Na	0.18	0.83	0.15	0.07	0.48	0.35	0.17	0.07	0.32	0.57	0.18	0.08
B-B-A-B	Br	Cl	Na	NMP	NaBr	Na	0.25	0.9	0.22	0.14	0.61	0.47	0.29	0.19	0.37	0.61	0.23	0.13
B-B-B-A	Br	Cl	K	EtOH	KBr	K	0.19	0.84	0.16	0.08	0.5	0.35	0.17	0.07	0.33	0.57	0.19	0.09
B-B-B-B	Br	Cl	K	NMP	KBr	K	0.25	0.91	0.23	0.15	0.63	0.47	0.29	0.19	0.38	0.61	0.23	0.13
B-B-C-A	Br	Cl	Cs	EtOH	CsBr	Cs	0.22	0.86	0.19	0.11	0.48	0.36	0.17	0.07	0.29	0.68	0.2	0.1
B-B-C-B	Br	Cl	Cs	NMP	CsBr	Cs	0.28	0.93	0.26	0.18	0.61	0.48	0.29	0.19	0.33	0.72	0.24	0.14
B-C-A-A	Br	acac	Na	EtOH	NaBr	Na	0.38	1.08	0.41	0.33	0.9	1.75	1.57	1.47	0.7	1.27	0.88	0.78
B-C-A-B	Br	acac	Na	NMP	NaBr	Na	0.41	1.15	0.48	0.4	0.9	1.87	1.69	1.59	0.7	1.31	0.93	0.83
B-C-B-A	Br	acac	K	EtOH	KBr	K	0.38	1.09	0.41	0.34	0.9	1.75	1.58	1.48	0.7	1.27	0.89	0.79
B-C-B-B	Br	acac	K	NMP	KBr	K	0.42	1.16	0.48	0.41	0.91	1.87	1.69	1.59	0.71	1.31	0.93	0.83
B-C-C-A	Br	acac	Cs	EtOH	CsBr	Cs	0.4	1.11	0.45	0.37	0.89	1.77	1.58	1.48	0.65	1.38	0.9	0.8
B-C-C-B	Br	acac	Cs	NMP	CsBr	Cs	0.44	1.18	0.52	0.44	0.9	1.89	1.7	1.6	0.66	1.42	0.94	0.84

Target product P (4-methoxy-4'-nitro-1,1'-biphenyl) and starting material SM1 (4-methoxyphenylboronic acid) are not shown. ArI, 1-iodo-4-nitrobenzene; ArBr, 1-bromo-4-nitrobenzene; EtOH, ethanol; NMP, *N*-methylpyrrolidone; SM, starting material; CT, catalyst; R, reagent; S, solvent; BP, byproduct; BF, bio-Factor; CP_i, initial cytotoxicity potential; CP_f, final cytotoxicity potential; CP_{f_rel}, relative final cytotoxicity potential. The five lowest CPs in each cell line are highlighted with green, whereas the names of the reactions with the lowest CPs in all cell lines are highlighted with blue.

Table S3. bio-Factors and cytotoxicity potentials for synthesis of 4-methoxy-4'-nitro-1,1'-biphenyl at 75% conversion.

Reaction	SM2 (ArX)	CT (PdA_2)	R (M_2CO_3)	S	BP1 (MX)	BP2 ($M_2B_4O_7$)	CaCo-2				FRSN				HEK293T			
							BF	CP_i	CP_f	CP_{f_rel}	BF	CP_i	CP_f	CP_{f_rel}	BF	CP_i	CP_f	CP_{f_rel}
A-A-A-A	I	OAc	Na	EtOH	NaI	Na	0.55	0.37	0.2	0.15	0.66	0.29	0.19	0.11	0.64	0.35	0.22	0.15
A-A-A-B	I	OAc	Na	NMP	NaI	Na	0.62	0.44	0.27	0.21	0.76	0.41	0.31	0.23	0.68	0.39	0.26	0.19
A-A-B-A	I	OAc	K	EtOH	KI	K	0.56	0.38	0.22	0.16	0.68	0.29	0.2	0.12	0.66	0.35	0.23	0.15
A-A-B-B	I	OAc	K	NMP	KI	K	0.63	0.45	0.28	0.23	0.78	0.4	0.31	0.24	0.7	0.39	0.27	0.19
A-A-C-A	I	OAc	Cs	EtOH	CsI	Cs	0.61	0.4	0.25	0.19	0.65	0.3	0.2	0.12	0.58	0.46	0.27	0.19
A-A-C-B	I	OAc	Cs	NMP	CsI	Cs	0.67	0.47	0.31	0.26	0.75	0.42	0.32	0.24	0.62	0.5	0.31	0.23
A-B-A-A	I	Cl	Na	EtOH	NaI	Na	0.55	0.38	0.21	0.15	0.67	0.3	0.2	0.13	0.64	0.35	0.23	0.15
A-B-A-B	I	Cl	Na	NMP	NaI	Na	0.62	0.45	0.28	0.22	0.76	0.42	0.32	0.24	0.68	0.39	0.27	0.19
A-B-B-A	I	Cl	K	EtOH	KI	K	0.57	0.39	0.22	0.16	0.7	0.3	0.21	0.13	0.66	0.35	0.23	0.16
A-B-B-B	I	Cl	K	NMP	KI	K	0.63	0.46	0.29	0.23	0.78	0.42	0.33	0.25	0.7	0.39	0.27	0.2
A-B-C-A	I	Cl	Cs	EtOH	CsI	Cs	0.61	0.41	0.25	0.19	0.67	0.31	0.21	0.13	0.59	0.46	0.27	0.19
A-B-C-B	I	Cl	Cs	NMP	CsI	Cs	0.67	0.48	0.32	0.26	0.76	0.43	0.33	0.25	0.62	0.5	0.31	0.24
A-C-A-A	I	acac	Na	EtOH	NaI	Na	0.73	0.63	0.46	0.41	0.94	1.7	1.6	1.53	0.88	1.05	0.93	0.85
A-C-A-B	I	acac	Na	NMP	NaI	Na	0.76	0.7	0.53	0.48	0.95	1.82	1.72	1.65	0.89	1.09	0.97	0.89
A-C-B-A	I	acac	K	EtOH	KI	K	0.74	0.64	0.48	0.42	0.95	1.7	1.61	1.53	0.89	1.05	0.93	0.86
A-C-B-B	I	acac	K	NMP	KI	K	0.77	0.71	0.55	0.49	0.95	1.82	1.73	1.65	0.89	1.09	0.97	0.9
A-C-C-A	I	acac	Cs	EtOH	CsI	Cs	0.76	0.66	0.51	0.45	0.94	1.72	1.61	1.54	0.84	1.16	0.97	0.9
A-C-C-B	I	acac	Cs	NMP	CsI	Cs	0.78	0.73	0.58	0.52	0.94	1.84	1.73	1.66	0.84	1.2	1.01	0.94
B-A-A-A	Br	OAc	Na	EtOH	NaBr	Na	0.38	0.82	0.32	0.26	0.59	0.34	0.2	0.13	0.49	0.57	0.28	0.2
B-A-A-B	Br	OAc	Na	NMP	NaBr	Na	0.43	0.89	0.38	0.33	0.7	0.46	0.32	0.24	0.52	0.61	0.32	0.24
B-A-B-A	Br	OAc	K	EtOH	KBr	K	0.39	0.83	0.32	0.27	0.61	0.34	0.2	0.13	0.49	0.57	0.28	0.21
B-A-B-B	Br	OAc	K	NMP	KBr	K	0.44	0.9	0.39	0.34	0.71	0.45	0.32	0.25	0.53	0.61	0.32	0.25
B-A-C-A	Br	OAc	Cs	EtOH	CsBr	Cs	0.41	0.85	0.35	0.3	0.6	0.35	0.21	0.14	0.46	0.68	0.31	0.24
B-A-C-B	Br	OAc	Cs	NMP	CsBr	Cs	0.46	0.92	0.42	0.36	0.7	0.47	0.33	0.25	0.5	0.72	0.36	0.28
B-B-A-A	Br	Cl	Na	EtOH	NaBr	Na	0.39	0.83	0.32	0.26	0.61	0.35	0.21	0.14	0.49	0.57	0.28	0.21
B-B-A-B	Br	Cl	Na	NMP	NaBr	Na	0.44	0.9	0.39	0.33	0.71	0.47	0.33	0.26	0.53	0.61	0.32	0.25
B-B-B-A	Br	Cl	K	EtOH	KBr	K	0.39	0.84	0.33	0.27	0.62	0.35	0.22	0.14	0.5	0.57	0.29	0.21
B-B-B-B	Br	Cl	K	NMP	KBr	K	0.44	0.91	0.4	0.34	0.72	0.47	0.34	0.26	0.53	0.61	0.33	0.25
B-B-C-A	Br	Cl	Cs	EtOH	CsBr	Cs	0.42	0.86	0.36	0.3	0.61	0.36	0.22	0.15	0.47	0.68	0.32	0.24
B-B-C-B	Br	Cl	Cs	NMP	CsBr	Cs	0.46	0.93	0.43	0.37	0.71	0.48	0.34	0.27	0.5	0.72	0.36	0.29
B-C-A-A	Br	acac	Na	EtOH	NaBr	Na	0.53	1.08	0.58	0.52	0.92	1.75	1.61	1.54	0.77	1.27	0.98	0.91
B-C-A-B	Br	acac	Na	NMP	NaBr	Na	0.56	1.15	0.65	0.59	0.93	1.87	1.73	1.66	0.78	1.31	1.02	0.95
B-C-B-A	Br	acac	K	EtOH	KBr	K	0.53	1.09	0.58	0.53	0.93	1.75	1.62	1.54	0.77	1.27	0.99	0.91
B-C-B-B	Br	acac	K	NMP	KBr	K	0.56	1.16	0.65	0.6	0.93	1.87	1.74	1.66	0.78	1.31	1.03	0.95
B-C-C-A	Br	acac	Cs	EtOH	CsBr	Cs	0.55	1.11	0.61	0.56	0.92	1.77	1.62	1.55	0.74	1.38	1.02	0.94
B-C-C-B	Br	acac	Cs	NMP	CsBr	Cs	0.58	1.18	0.68	0.63	0.92	1.89	1.74	1.67	0.75	1.42	1.06	0.99

Target product P (4-methoxy-4'-nitro-1,1'-biphenyl) and starting material SM1 (4-methoxyphenylboronic acid) are not shown. ArI, 1-iodo-4-nitrobenzene; ArBr, 1-bromo-4-nitrobenzene; EtOH, ethanol; NMP, *N*-methylpyrrolidone; SM, starting material; CT, catalyst; R, reagent; S, solvent; BP, byproduct; BF, bio-Factor; CP_i, initial cytotoxicity potential; CP_f, final cytotoxicity potential; CP_{f_rel}, relative final cytotoxicity potential.

Table S4. bio-Factors and cytotoxicity potentials for synthesis of 4-methoxy-4'-nitro-1,1'-biphenyl at 50% conversion.

Reaction	SM2 (ArX)	CT (PdA_2)	R (M_2CO_3)	S	BP1 (MX)	BP2 ($M_2B_4O_7$)	CaCo-2				FRSN				HEK293T			
							BF	CP_i	CP_f	CP_{f_rel}	BF	CP_i	CP_f	CP_{f_rel}	BF	CP_i	CP_f	CP_{f_rel}
A-A-A-A	I	OAc	Na	EtOH	NaI	Na	0.7	0.37	0.26	0.22	0.77	0.29	0.22	0.17	0.76	0.35	0.26	0.21
A-A-A-B	I	OAc	Na	NMP	NaI	Na	0.75	0.44	0.33	0.29	0.84	0.41	0.34	0.29	0.78	0.39	0.3	0.25
A-A-B-A	I	OAc	K	EtOH	KI	K	0.71	0.38	0.27	0.23	0.79	0.29	0.23	0.18	0.77	0.35	0.27	0.22
A-A-B-B	I	OAc	K	NMP	KI	K	0.75	0.45	0.34	0.3	0.85	0.4	0.34	0.29	0.8	0.39	0.31	0.26
A-A-C-A	I	OAc	Cs	EtOH	CsI	Cs	0.74	0.4	0.3	0.26	0.77	0.3	0.23	0.18	0.72	0.46	0.33	0.28
A-A-C-B	I	OAc	Cs	NMP	CsI	Cs	0.78	0.47	0.37	0.33	0.83	0.42	0.35	0.3	0.74	0.5	0.37	0.32
A-B-A-A	I	Cl	Na	EtOH	NaI	Na	0.7	0.38	0.26	0.23	0.78	0.3	0.23	0.18	0.76	0.35	0.27	0.22
A-B-A-B	I	Cl	Na	NMP	NaI	Na	0.75	0.45	0.33	0.29	0.84	0.42	0.35	0.3	0.79	0.39	0.31	0.26
A-B-B-A	I	Cl	K	EtOH	KI	K	0.71	0.39	0.28	0.24	0.8	0.3	0.24	0.19	0.78	0.35	0.27	0.22
A-B-B-B	I	Cl	K	NMP	KI	K	0.76	0.46	0.35	0.31	0.86	0.42	0.36	0.31	0.8	0.39	0.31	0.26
A-B-C-A	I	Cl	Cs	EtOH	CsI	Cs	0.74	0.41	0.3	0.26	0.78	0.31	0.24	0.19	0.72	0.46	0.33	0.28
A-B-C-B	I	Cl	Cs	NMP	CsI	Cs	0.78	0.48	0.37	0.33	0.84	0.43	0.36	0.31	0.75	0.5	0.37	0.32
A-C-A-A	I	acac	Na	EtOH	NaI	Na	0.82	0.63	0.52	0.48	0.96	1.7	1.64	1.59	0.92	1.05	0.97	0.92
A-C-A-B	I	acac	Na	NMP	NaI	Na	0.84	0.7	0.59	0.55	0.96	1.82	1.76	1.71	0.92	1.09	1.01	0.96
A-C-B-A	I	acac	K	EtOH	KI	K	0.83	0.64	0.53	0.49	0.96	1.7	1.64	1.59	0.93	1.05	0.97	0.92
A-C-B-B	I	acac	K	NMP	KI	K	0.84	0.71	0.6	0.56	0.97	1.82	1.76	1.71	0.93	1.09	1.01	0.96
A-C-C-A	I	acac	Cs	EtOH	CsI	Cs	0.84	0.66	0.56	0.52	0.96	1.72	1.65	1.6	0.89	1.16	1.03	0.98
A-C-C-B	I	acac	Cs	NMP	CsI	Cs	0.86	0.73	0.63	0.59	0.96	1.84	1.77	1.72	0.89	1.2	1.07	1.03
B-A-A-A	Br	OAc	Na	EtOH	NaBr	Na	0.59	0.82	0.48	0.45	0.73	0.34	0.25	0.2	0.66	0.57	0.37	0.32
B-A-A-B	Br	OAc	Na	NMP	NaBr	Na	0.62	0.89	0.55	0.51	0.8	0.46	0.36	0.31	0.68	0.61	0.41	0.36
B-A-B-A	Br	OAc	K	EtOH	KBr	K	0.59	0.83	0.49	0.45	0.74	0.34	0.25	0.2	0.66	0.57	0.38	0.33
B-A-B-B	Br	OAc	K	NMP	KBr	K	0.62	0.9	0.56	0.52	0.81	0.45	0.37	0.32	0.69	0.61	0.42	0.37
B-A-C-A	Br	OAc	Cs	EtOH	CsBr	Cs	0.61	0.85	0.52	0.48	0.73	0.35	0.26	0.21	0.64	0.68	0.44	0.39
B-A-C-B	Br	OAc	Cs	NMP	CsBr	Cs	0.64	0.92	0.59	0.55	0.8	0.47	0.38	0.33	0.66	0.72	0.48	0.43
B-B-A-A	Br	Cl	Na	EtOH	NaBr	Na	0.59	0.83	0.49	0.45	0.74	0.35	0.26	0.21	0.66	0.57	0.38	0.33
B-B-A-B	Br	Cl	Na	NMP	NaBr	Na	0.62	0.9	0.56	0.52	0.8	0.47	0.38	0.33	0.68	0.61	0.42	0.37
B-B-B-A	Br	Cl	K	EtOH	KBr	K	0.59	0.84	0.5	0.46	0.75	0.35	0.26	0.21	0.67	0.57	0.38	0.33
B-B-B-B	Br	Cl	K	NMP	KBr	K	0.63	0.91	0.57	0.53	0.81	0.47	0.38	0.33	0.69	0.61	0.42	0.37
B-B-C-A	Br	Cl	Cs	EtOH	CsBr	Cs	0.61	0.86	0.52	0.49	0.74	0.36	0.27	0.22	0.65	0.68	0.44	0.39
B-B-C-B	Br	Cl	Cs	NMP	CsBr	Cs	0.64	0.93	0.59	0.56	0.8	0.48	0.39	0.34	0.67	0.72	0.48	0.43
B-C-A-A	Br	acac	Na	EtOH	NaBr	Na	0.69	1.08	0.74	0.71	0.95	1.75	1.66	1.61	0.85	1.27	1.08	1.03
B-C-A-B	Br	acac	Na	NMP	NaBr	Na	0.71	1.15	0.81	0.78	0.95	1.87	1.78	1.73	0.85	1.31	1.12	1.07
B-C-B-A	Br	acac	K	EtOH	KBr	K	0.69	1.09	0.75	0.72	0.95	1.75	1.66	1.61	0.85	1.27	1.08	1.03
B-C-B-B	Br	acac	K	NMP	KBr	K	0.71	1.16	0.82	0.78	0.95	1.87	1.78	1.73	0.85	1.31	1.12	1.07
B-C-C-A	Br	acac	Cs	EtOH	CsBr	Cs	0.7	1.11	0.78	0.74	0.95	1.77	1.67	1.62	0.83	1.38	1.14	1.09
B-C-C-B	Br	acac	Cs	NMP	CsBr	Cs	0.72	1.18	0.85	0.81	0.95	1.89	1.79	1.74	0.83	1.42	1.18	1.13

Target product P (4-methoxy-4'-nitro-1,1'-biphenyl) and starting material SM1 (4-methoxyphenylboronic acid) are not shown. ArI, 1-iodo-4-nitrobenzene; ArBr, 1-bromo-4-nitrobenzene; EtOH, ethanol; NMP, *N*-methylpyrrolidone; SM, starting material; CT, catalyst; R, reagent; S, solvent; BP, byproduct; BF, bio-Factor; CP_i, initial cytotoxicity potential; CP_f, final cytotoxicity potential; CP_{f_rel}, relative final cytotoxicity potential.

Table S5. bio-Factors and cytotoxicity potentials for synthesis of 4-methoxy-4'-nitro-1,1'-biphenyl at 25% conversion.

Reaction	SM2 (ArX)	CT (PdA_2)	R (M_2CO_3)	S	BP1 (MX)	BP2 ($M_2B_4O_7$)	CaCo-2				FRSN				HEK293T			
							BF	CP_i	CP_f	CP_{f_rel}	BF	CP_i	CP_f	CP_{f_rel}	BF	CP_i	CP_f	CP_{f_rel}
A-A-A-A	I	OAc	Na	EtOH	NaI	Na	0.85	0.37	0.31	0.3	0.89	0.29	0.25	0.23	0.89	0.88	0.35	0.3
A-A-A-B	I	OAc	Na	NMP	NaI	Na	0.87	0.44	0.38	0.37	0.92	0.41	0.37	0.35	0.92	0.89	0.39	0.35
A-A-B-A	I	OAc	K	EtOH	KI	K	0.85	0.38	0.33	0.31	0.89	0.29	0.26	0.23	0.89	0.89	0.35	0.31
A-A-B-B	I	OAc	K	NMP	KI	K	0.88	0.45	0.4	0.38	0.93	0.4	0.37	0.35	0.93	0.9	0.39	0.35
A-A-C-A	I	OAc	Cs	EtOH	CsI	Cs	0.87	0.4	0.35	0.33	0.88	0.3	0.27	0.24	0.88	0.86	0.46	0.39
A-A-C-B	I	OAc	Cs	NMP	CsI	Cs	0.89	0.47	0.42	0.4	0.92	0.42	0.39	0.36	0.92	0.87	0.5	0.43
A-B-A-A	I	Cl	Na	EtOH	NaI	Na	0.85	0.38	0.32	0.3	0.89	0.3	0.27	0.24	0.89	0.88	0.35	0.31
A-B-A-B	I	Cl	Na	NMP	NaI	Na	0.87	0.45	0.39	0.37	0.92	0.42	0.39	0.36	0.92	0.89	0.39	0.35
A-B-B-A	I	Cl	K	EtOH	KI	K	0.86	0.39	0.33	0.31	0.9	0.3	0.27	0.24	0.9	0.89	0.35	0.31
A-B-B-B	I	Cl	K	NMP	KI	K	0.88	0.46	0.4	0.38	0.93	0.42	0.39	0.36	0.93	0.9	0.39	0.35
A-B-C-A	I	Cl	Cs	EtOH	CsI	Cs	0.87	0.41	0.36	0.34	0.89	0.31	0.28	0.25	0.89	0.86	0.46	0.4
A-B-C-B	I	Cl	Cs	NMP	CsI	Cs	0.89	0.48	0.42	0.41	0.92	0.43	0.4	0.37	0.92	0.87	0.5	0.44
A-C-A-A	I	acac	Na	EtOH	NaI	Na	0.91	0.63	0.58	0.56	0.98	1.7	1.67	1.64	0.98	0.96	1.05	1.01
A-C-A-B	I	acac	Na	NMP	NaI	Na	0.92	0.7	0.64	0.63	0.98	1.82	1.79	1.76	0.98	0.96	1.09	1.05
A-C-B-A	I	acac	K	EtOH	KI	K	0.91	0.64	0.59	0.57	0.98	1.7	1.67	1.65	0.98	0.96	1.05	1.01
A-C-B-B	I	acac	K	NMP	KI	K	0.92	0.71	0.66	0.64	0.98	1.82	1.79	1.76	0.98	0.96	1.09	1.05
A-C-C-A	I	acac	Cs	EtOH	CsI	Cs	0.92	0.66	0.61	0.59	0.98	1.72	1.68	1.66	0.98	0.95	1.16	1.1
A-C-C-B	I	acac	Cs	NMP	CsI	Cs	0.93	0.73	0.68	0.66	0.98	1.84	1.8	1.78	0.98	0.95	1.2	1.14
B-A-A-A	Br	OAc	Na	EtOH	NaBr	Na	0.79	0.82	0.65	0.63	0.86	0.34	0.29	0.27	0.86	0.83	0.57	0.47
B-A-A-B	Br	OAc	Na	NMP	NaBr	Na	0.81	0.89	0.72	0.7	0.9	0.46	0.41	0.39	0.9	0.84	0.61	0.51
B-A-B-A	Br	OAc	K	EtOH	KBr	K	0.8	0.83	0.66	0.64	0.87	0.34	0.29	0.27	0.87	0.83	0.57	0.47
B-A-B-B	Br	OAc	K	NMP	KBr	K	0.81	0.9	0.73	0.71	0.9	0.45	0.41	0.39	0.9	0.84	0.61	0.51
B-A-C-A	Br	OAc	Cs	EtOH	CsBr	Cs	0.8	0.85	0.69	0.67	0.87	0.35	0.3	0.28	0.87	0.82	0.68	0.56
B-A-C-B	Br	OAc	Cs	NMP	CsBr	Cs	0.82	0.92	0.76	0.74	0.9	0.47	0.42	0.4	0.9	0.83	0.72	0.6
B-B-A-A	Br	Cl	Na	EtOH	NaBr	Na	0.8	0.83	0.66	0.64	0.87	0.35	0.3	0.28	0.87	0.83	0.57	0.48
B-B-A-B	Br	Cl	Na	NMP	NaBr	Na	0.81	0.9	0.73	0.71	0.9	0.47	0.42	0.4	0.9	0.84	0.61	0.52
B-B-B-A	Br	Cl	K	EtOH	KBr	K	0.8	0.84	0.67	0.65	0.87	0.35	0.3	0.28	0.87	0.83	0.57	0.48
B-B-B-B	Br	Cl	K	NMP	KBr	K	0.81	0.91	0.74	0.72	0.91	0.47	0.42	0.4	0.91	0.84	0.61	0.52
B-B-C-A	Br	Cl	Cs	EtOH	CsBr	Cs	0.81	0.86	0.69	0.67	0.87	0.36	0.32	0.29	0.87	0.82	0.68	0.56
B-B-C-B	Br	Cl	Cs	NMP	CsBr	Cs	0.82	0.93	0.76	0.74	0.9	0.48	0.44	0.41	0.9	0.83	0.72	0.6
B-C-A-A	Br	acac	Na	EtOH	NaBr	Na	0.84	1.08	0.91	0.89	0.97	1.75	1.71	1.68	0.97	0.92	1.27	1.18
B-C-A-B	Br	acac	Na	NMP	NaBr	Na	0.85	1.15	0.98	0.96	0.98	1.87	1.82	1.8	0.98	0.93	1.31	1.22
B-C-B-A	Br	acac	K	EtOH	KBr	K	0.84	1.09	0.92	0.9	0.98	1.75	1.71	1.68	0.98	0.92	1.27	1.18
B-C-B-B	Br	acac	K	NMP	KBr	K	0.85	1.16	0.99	0.97	0.98	1.87	1.83	1.8	0.98	0.93	1.31	1.22
B-C-C-A	Br	acac	Cs	EtOH	CsBr	Cs	0.85	1.11	0.95	0.93	0.97	1.77	1.72	1.69	0.97	0.91	1.38	1.26
B-C-C-B	Br	acac	Cs	NMP	CsBr	Cs	0.86	1.18	1.02	1	0.97	1.89	1.84	1.81	0.97	0.92	1.42	1.3

Target product P (4-methoxy-4'-nitro-1,1'-biphenyl) and starting material SM1 (4-methoxyphenylboronic acid) are not shown. ArI, 1-iodo-4-nitrobenzene; ArBr, 1-bromo-4-nitrobenzene; EtOH, ethanol; NMP, *N*-methylpyrrolidone; SM, starting material; CT, catalyst; R, reagent; S, solvent; BP, byproduct; BF, bio-Factor; CP_i, initial cytotoxicity potential; CP_f, final cytotoxicity potential; CP_{f_rel}, relative final cytotoxicity potential.

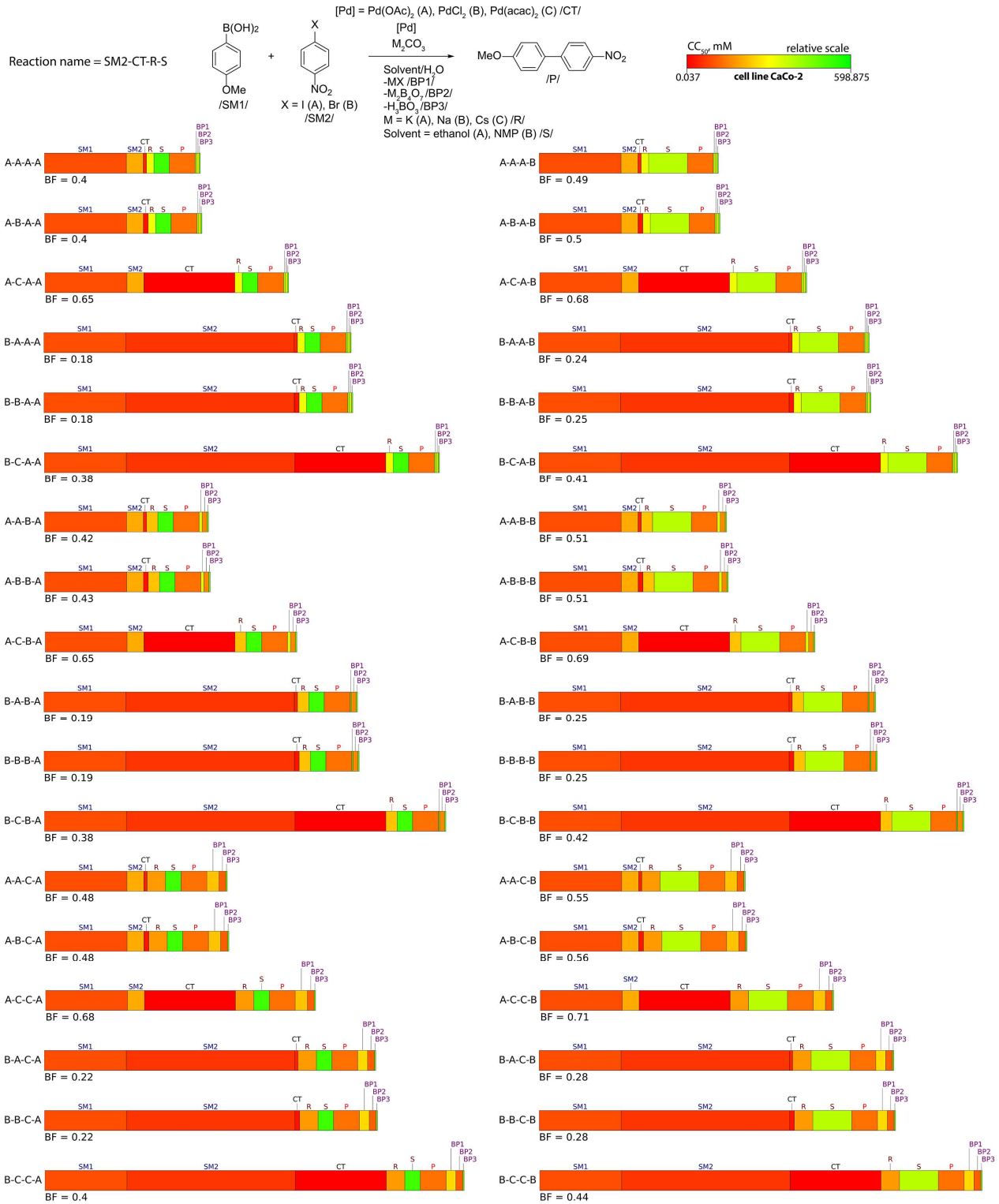

Figure S1. bio-Strips of 36 synthetic routes for 4-methoxy-4'-nitro-1,1'-biphenyl based on 24-h CC_{50} values measured in CaCo-2 cells. The 1st, 2nd, 3rd, and 4th letters in the reaction names correspond to the types of starting material (SM2: 1-iodo-4-nitrobenzene (A), 1-bromo-4-nitrobenzene (B)), catalyst (CT: $Pd(OAc)_2$ (A), $PdCl_2$ (B), or $Pd(acac)_2$ (C)), reagent (R: Na_2CO_3 (A), K_2CO_3 (B), Cs_2CO_3 (C)), and solvent (S: ethanol (A), NMP (B)), respectively. The color of the strip sections corresponds to the CC_{50} of a particular substance in CaCo-2 cells (see the cytotoxicity scale above the bio-Strips). bio-Factors are shown below the strips.

Figure S2. bio-Strips of 36 synthetic routes for 4-methoxy-4'-nitro-1,1'-biphenyl based on 24-h CC_{50} values measured in FRSN cells. The 1st, 2nd, 3rd, and 4th letters in the reaction names correspond to the types of starting material (SM2: 1-iodo-4-nitrobenzene (A), 1-bromo-4-nitrobenzene (B)), catalyst (CT: $Pd(OAc)_2$ (A), $PdCl_2$ (B), or $Pd(acac)_2$ (C)), reagent (R: Na_2CO_3 (A), K_2CO_3 (B), Cs_2CO_3 (C)), and solvent (S: ethanol (A), NMP (B)), respectively. The color of the strip sections corresponds to the CC_{50} of a particular substance in FRSN cells (see the cytotoxicity scale above the bio-Strips). bio-Factors are shown below the strips.

Figure S3. bio-Strips of 36 synthetic routes for 4-methoxy-4'-nitro-1,1'-biphenyl based on 24-h CC_{50} values measured in HEK293T cells. The 1st, 2nd, 3rd, and 4th letters in the reaction names correspond to the types of starting material (SM2: 1-iodo-4-nitrobenzene (A), 1-bromo-4-nitrobenzene (B)), catalyst (CT: $Pd(OAc)_2$ (A), $PdCl_2$ (B), or $Pd(acac)_2$ (C)), reagent (R: Na_2CO_3 (A), K_2CO_3 (B), Cs_2CO_3 (C)), and solvent (S: ethanol (A), NMP (B)), respectively. The color of the strip sections corresponds to the CC_{50} of a particular substance in HEK293T cells (see the cytotoxicity scale above the bio-Strips). bio-Factors are shown below the strips.