Efficient Preparation of Tetrasubstituted Pyrazines Starting from Pyrazin-2(1*H*)-ones

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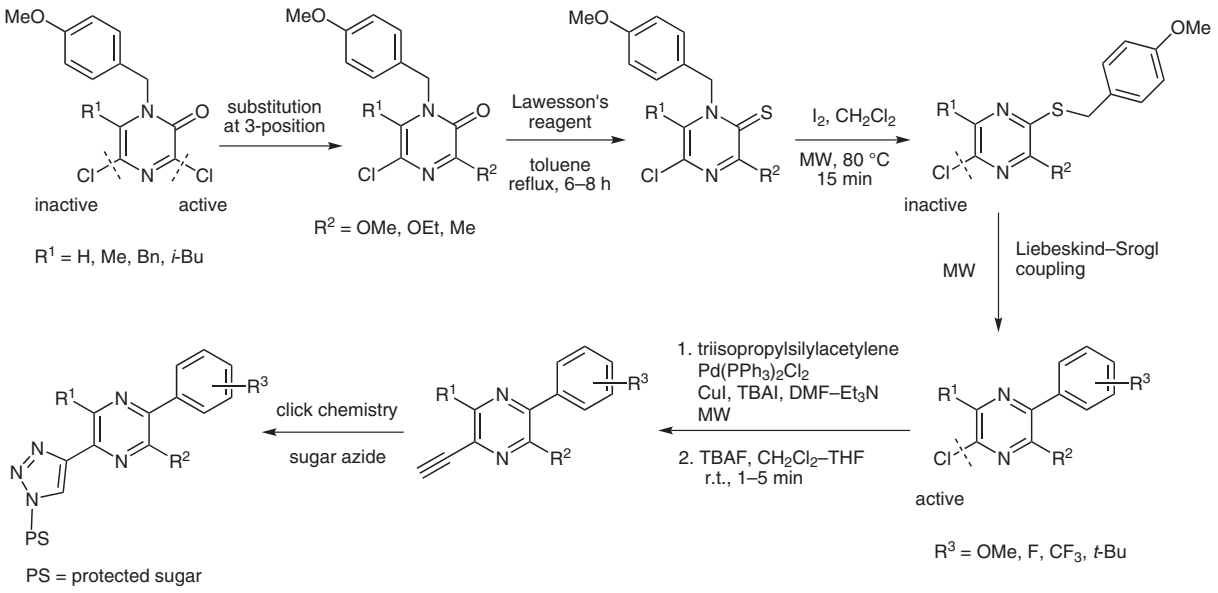
Abstract: An efficient methodology for the synthesis of tetrasubstituted pyrazines starting from pyrazin-2(1*H*)-ones has been elaborated. Diversity in the functionalization and the beneficial effect of microwave irradiation throughout the methodology has been demonstrated.

Key words: palladium catalysis, copper catalysis, pyrazines, 3,5-dichloropyrazin-2(1*H*)-ones, microwaves, nucleosides



Scheme 1

Even though a number of important, natural as well as synthetic, heterocyclic compounds possess a tetrasubstituted pyrazine core structure,[1] there are only a limited number of synthetic methodologies described for their synthesis.[2] We have previously reported 3,5-dichloropyrazin-2(1*H*)-ones as attractive starting materials for the synthesis of different heterocyclic compounds.[3] Recently we have described a new methodology, starting from pyrazin-2(1*H*)-ones, for the synthesis of tetrasubstituted pyrazines coupled with a sugar moiety via a triazole linkage (Scheme 1).[4] Using our optimized conditions[5] 3,5-dichloropyrazin-2(1*H*)-ones can be synthesized in the laboratory on a 40–50-gram scale. Herein we report an efficient methodology for the synthesis of tetrasubstituted pyrazines starting from these readily available pyrazin-2(1*H*)-ones.

Alkoxylation of pyrazin-2(1*H*)-ones **1a**–**c** at the C3-position gave quantitative yields of **2a**–**c** (Scheme 2). When treated with tetramethylstannane under Stille conditions, **1d** gave methylated compound **2d** in 95% yield. All C3-substituted pyrazine-2(1*H*)-ones **2a**–**d** were reacted with Lawesson's reagent to afford the corresponding thioamides **3a**–**d** in good yields (Scheme 2).

A mixture of compound **3a**, methyl iodide (5 equiv) and iodine (10 mol%) in toluene was refluxed for 12 hours yielding 72% of the expected methyl thioether **4a** together with 20% of *p*-methoxybenzyl thioether **5a** as the main byproduct (Table 1, entry 1).[6] The formation of **5a** might

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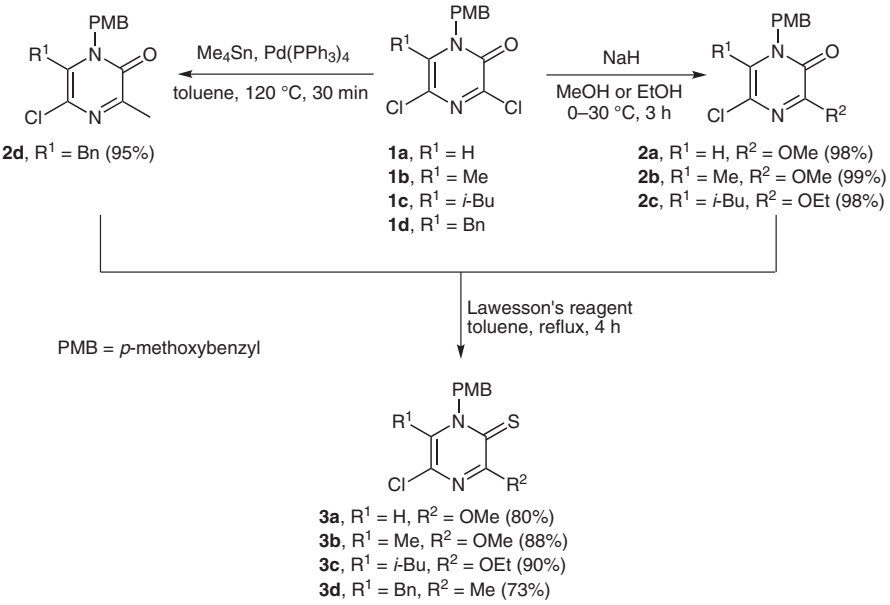
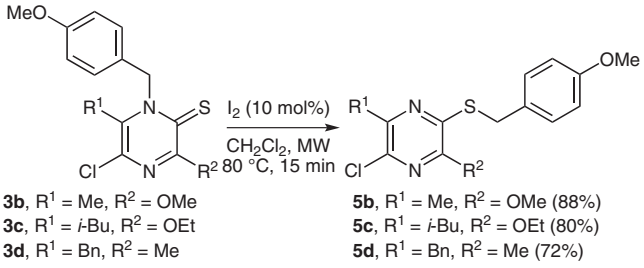


Scheme 2

be explained by the competitive reaction of the in situ formed *p*-methoxybenzyl iodide. During the scale-up of the reaction we noticed that it was rather difficult to separate the desired methyl thioether **4a** from compound **5a** due to their similar polarity. Therefore efforts were made to make this reaction more selective. However, under microwave irradiation at a temperature of 130 °C for 30 minutes under the same conditions, the amount of byproduct **5a** increased (entry 2). The reaction was rather slow in the absence of iodine, still giving both **4a** and **5a**, but with decreased yields (entry 3). This observation was interesting as only salt formation was expected with methyl iodide. Clearly upon heating[7] the intermediate salt loses *p*-methoxybenzyl iodide, forming **4a**, and the in situ formed *p*-methoxybenzyl iodide reacts with another molecule of starting material **3a** to give **5a**.

As it was impossible to minimize the competition between methyl iodide and the in situ formed *p*-methoxybenzyl iodide, it was decided to exclude methyl iodide from the reaction mixture. This should result in the sole formation of *p*-methoxybenzyl thioether **5a**. As a proof of concept **3a** was refluxed in toluene with iodine (10 mol%). To our satisfaction only **5a** was formed in 45% yield (entry 4). Interestingly when the solvent was changed to dichloromethane, the yield increased to 65% (entry 5). When the reaction was run at room temperature with 5, 10, 50, and 80 mol% of iodine, respectively, there was no important change in yields, but a dramatic difference in reaction time was observed ranging from 40 hours to 0.15 hours (entries 7–10). The best results were obtained when the reaction was carried out with 10 mol% iodine in dichloromethane under microwave irradiation at 80 °C and 150-W maximum power for 15 minutes yielding compound **5a** in 83% yield (entry 6).

This optimized protocol was applied to convert the pyrazine-2(1*H*)-thiones **3b–d** into the corresponding *p*-methoxybenzyl thioethers **5b–d** (Scheme 3).



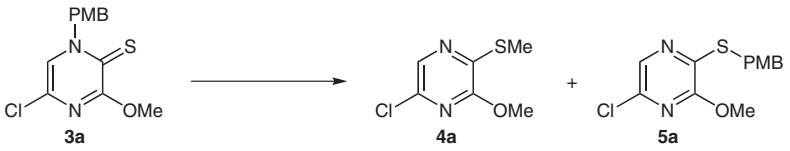
Scheme 3

A plausible mechanism for the transfer of the *p*-methoxybenzyl group is shown in Scheme 4. Iodine first reacts with the sulfur atom of thioamide **3a** to give intermediate **A**. This loses the *p*-methoxybenzyl group to form the unstable intermediates **B** and **C** that directly react with each other to give the *p*-methoxybenzyl thioethers **5**, while iodine goes back into the catalytic cycle. It is interesting to note that the reaction, which is rather slow at room temperature, is rapid under microwave irradiation.

To our surprise, all efforts to perform a Sonogashira reaction on compound **5**, met with failure. This is in sharp contrast with our previously published work,[6] where the reaction went smoothly when a methylthio group was present instead of a *p*-methoxybenzylthio group at the C2-position of the pyrazine. Probably the *p*-methoxybenzyl thioether renders the chlorine less susceptible to nucleophilic substitution by the palladium (Scheme 5).

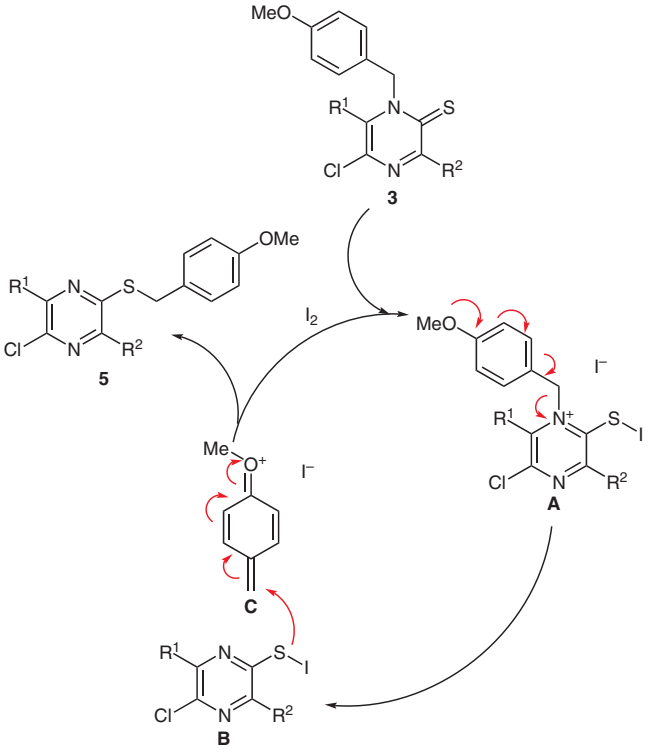
Hence we considered whether the *p*-methoxybenzylthio group would be sufficiently reactive under standard Liebeskind–Srogl conditions. When pyrazine **5a** was reacted

Table 1 Optimization Study for Thioether Formation[a]

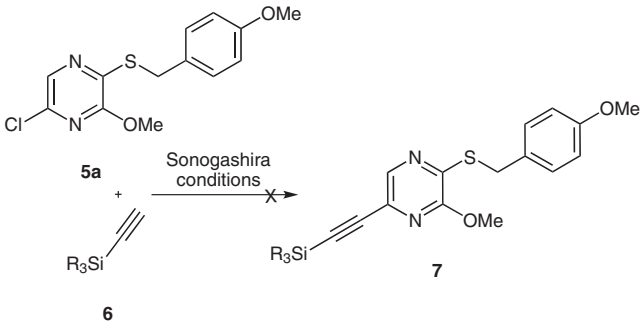


Entry	Reagent (equiv)	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%) **4a**	Yield (%) **5a**
1[b]	MeI (5)	I_2 (10)	toluene	reflux	12	72	20
2[c]	MeI (5)	I_2 (10)	toluene	130	0.5	55	30
3	MeI (5)	–	toluene	reflux	1	40	15
4	–	I_2 (10)	toluene	reflux	12	0	45
5	–	I_2 (10)	CH_2Cl_2	reflux	6	0	65
6[d]	–	I_2 (10)	CH_2Cl_2	80	0.25	0	83
7	–	I_2 (10)	CH_2Cl_2	r.t.	24	0	79
8	–	I_2 (5)	CH_2Cl_2	r.t.	40	0	73
9	–	I_2 (50)	CH_2Cl_2	r.t.	6	0	80
10	–	I_2 (80)	CH_2Cl_2	r.t.	0.15	0	85

[a] All reactions: **3a** (0.1 mmol), conventional heating, unless otherwise stated.
[b] Scale-up of the reaction with 5 mmol of **3a** also resulted in full conversion, but it was not possible to separate **4a** from **5a** by column chromatography.
[c] The mixture was irradiated using 400 W maximum power in a multimode microwave apparatus.
[d] The mixture was irradiated using 150 W maximum power in a multimode microwave apparatus.



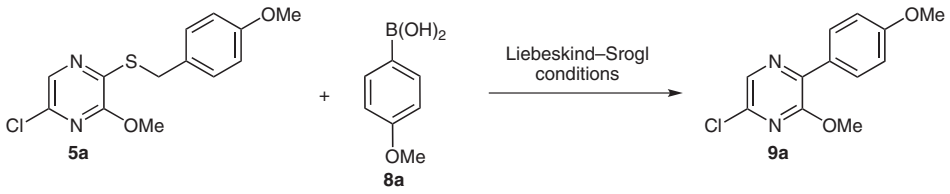
Scheme 4



Scheme 5

with boronic acid **8a** in the presence of copper(I) thiophene-2-carboxylate (CuTC) and $Pd(PPh_3)_4$ in tetrahydrofuran under conventional heating as well as under microwave irradiation (Table 2, entries 1–3, 5, and 6) poor to average yields were obtained. As the reaction was rather sluggish it was assumed that the reagents decomposed during the long reaction time at high temperature. To overcome this difficulty, the reagents were added in two portions and, to our satisfaction, the reaction was complete in one hour under microwave irradiation at 120 °C yielding **9a** in 84% (entry 4).[8] This optimized protocol was then applied for the conversion of **5a–d** into **9b–j** in good to excellent yields (Table 3).

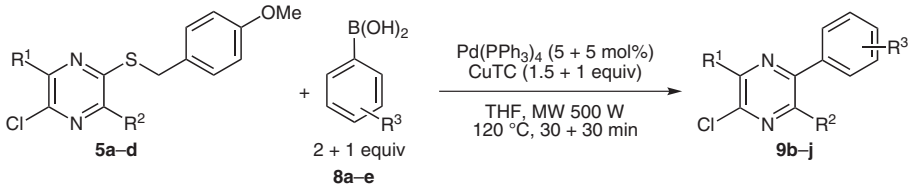
Table 2 Optimization Study of the Liebeskind–Srogl Cross-Coupling Reaction on the *p*-Methoxybenzylthio Group[a]



Entry	Boronic acid (equiv)	CuTC (equiv)	$Pd(PPh_3)_4$ (mol%)	Temp (°C) (MW^b/ΔT)	Time (h)	Ratio[c] **9a**/**5a**
1	3	3	5	100 (MW)	0.8	40:30
2	5	5	10	120 (MW)	1.3	57:25
3	1.1	1.2	3	100 (MW)	0.8	30:62
4[d]	2 + 1	1.5 + 1	5 + 5	120 (MW)	0.5 + 0.5	84:08
5	3	3	5	reflux (ΔT)	10	30:65
6[d]	2 + 1	1.5 + 1	5 + 5	reflux (ΔT)	4 + 4	45:50

[a] All reactions were run using **5a** (0.2 mmol) in THF in a sealed tube.
[b] A maximum power of 500 W in a multimode microwave apparatus was used.
[c] Ratio determined by GC-MS.
[d] A fresh batch of reagents was added at the stipulated time.

Table 3 Liebeskind–Srogl Cross-Coupling on Pyrazines **5**[a]



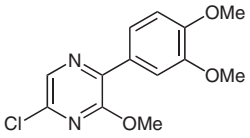
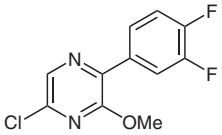
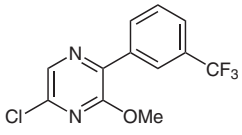
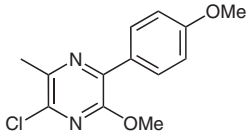
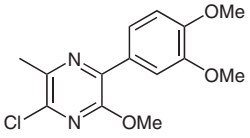
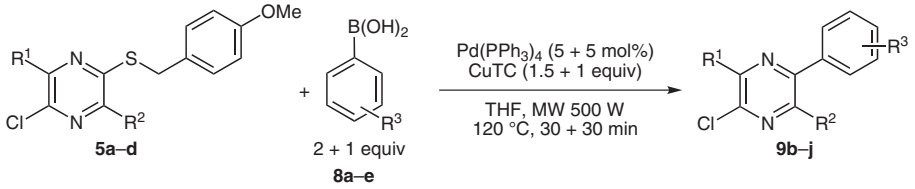
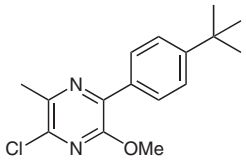
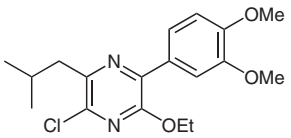
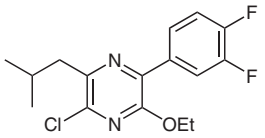
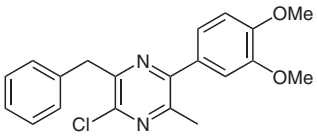
Entry	Product	Structure	Yield (%)
1	**9b**		69
2	**9c**		75
3	**9d**		80
4[b]	**9e**		86
5[b]	**9f**		93

Table 3 Liebeskind–Srogl Cross-Coupling on Pyrazines **5**[a] (continued)



Entry	Product	Structure	Yield (%)
6	**9g**		92
7[b]	**9h**		79
8	**9i**		72
9	**9j**		80

[a] Reactions conditions: **5a–d** (0.5 mmol), boronic acids (2 + 1 equiv), $Pd(PPh_3)_4$ (5 + 5 mol%), CuTC (1.5 + 1 equiv), THF (4 mL), sealed tube, MW (multimode microwave apparatus, max. 120 °C and 500 W, 60 min; reagents were added in 2 portions as stipulated; the second portion was added at half reaction time (i.e., 30 min).
[b] Using **5a–c** (5 mmol).

As we were able to substitute the *p*-methoxybenzylthio group of compound **5** by an aryl group in compound **9**, the reactivity of the chlorine towards Sonogashira reaction was reinvestigated (Table 4). To our delight when a mixture of compound **9** with triisopropylsilylacetylene (TIPSA, 1.5 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol%), copper(I) iodide (10 mol%), and tetrabutylammonium iodide (1.2 equiv) in *N*,*N*-dimethylformamide–triethylamine (1:1) was irradiated for 20 minutes at a ceiling temperature of 80 °C, a smooth reaction took place. Subsequent desilylation upon treatment of the crude compound with 1 M tetrabutylammonium fluoride in tetrahydrofuran at room temperature yielded the desired terminal acetylenes **10a–d** (Table 4), which were purified by simple filtration over silica gel.

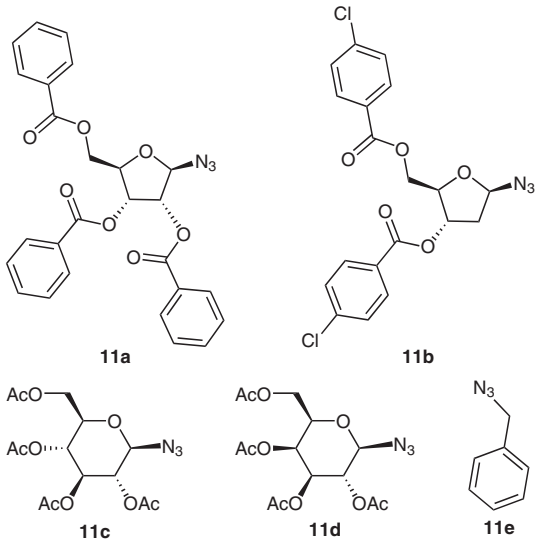
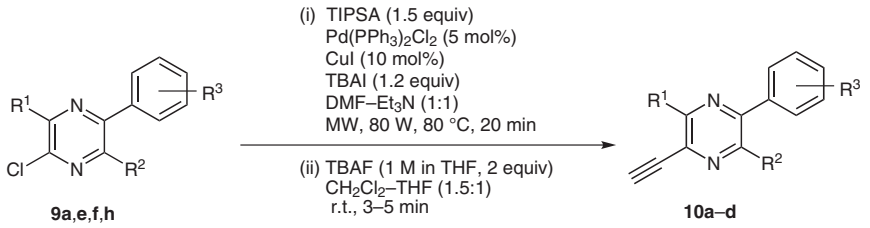
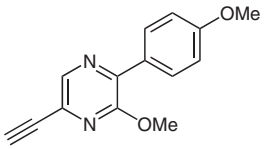
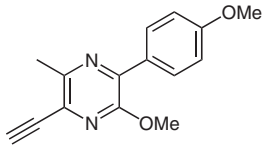
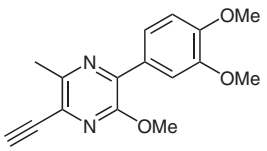
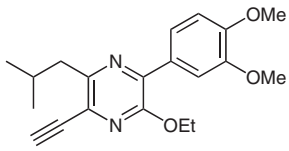


Figure 1 Structure of azides **11a–e**

For the final step, the protected sugar azides[9] and benzyl azide[10] **11a–e** (Figure 1) were all synthesized according to literature procedures. Then, the coupling of azides **11a–d** with the generated pyrazines **10a–d** was investigated. A mixture of pyrazine **10** with protected sugar azide **11** (1.2 equiv), copper turnings (2 equiv), copper sulfate (5 mol%), tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine ligand (TBTA, 5 mol%) in tetrahydrofuran–isopropyl alcohol–water (3:1:1, 5 mL) was irradiated at 90 °C ceiling temperature using 200-W maximum power for 20 minutes (Table 5). The copper(I)-catalyzed [3+2] dipolar cycloaddition reaction occurred with full regioselectivity, resulting in the formation of the corresponding 1,4-disubstituted 1,2,3-triazoles **12a–h** in good yields (entries 1–8). Reacting pyrazine **10d** with benzyl azide **11e** apply-

Table 4 Sonogashira Cross-Coupling of Pyrazines **9a**,**e**,**f**,**h**[a]



Entry	Product	Structure	Yield[b] (%)
1	**10a**		78
2	**10b**		91
3	**10c**		80
4	**10d**		59

[a] Using **9a**,**e**,**f**,**h** (2.0 mmol) in a multimode microwave apparatus.
[b] Yields over two steps.

ing similar conditions afforded 1,2,3-triazole compound **12i** in good yield (entry 9). Interestingly when pyrazine **10d** was reacted with trimethylsilyl azide, the corresponding desilylated 1,2,3-triazole product **12j** was obtained in 80% yield.

In summary, we have developed a new and efficient protocol for the synthesis of tetrasubstituted pyrazines starting from 3,5-dichloro-1-(4-methoxybenzyl)pyrazin-2(1*H*)-ones. A small library of pyrazine-containing nucleoside analogues was generated. The application of microwave irradiation during the different steps of the sequence has been shown to be highly valuable for speeding up reactions.

NMR spectra were recorded on a 300 MHz instrument using $CDCl_3$ and DMSO-d_6 as solvent unless otherwise stated, relative to TMS as internal standard. For mass spectrometry, the ion source temperature was 150–250 °C, as required. For chromatography, analytical TLC plates and 70–230 mesh silica gel were used. All solvents and chemicals were purchased and used as available.

All microwave irradiation experiments were carried out in a multimode Milestone MicroSYNTH microwave reactor (Laboratory Microwave Systems). This apparatus was used in the standard configuration as delivered, including proprietary software. Reactions were carried out in sealed microwave process vials (15, 50 mL) and temperature control was performed using both, external infrared and internal fiber optic sensors. The ramp time (time required to reach the expected temperature) was always between 1 to 2 min and is included in the total reaction time. The reaction mixture was continuously stirred during reaction. After irradiation, the reaction vessel was rapidly cooled by air jet cooling to ambient temperature.

3,5-Dichloro-1-(4-methoxybenzyl)pyrazin-2(1*H*)-ones 1a–d; General Procedure

General procedure for the preparation of **1a–d** is the same as previously described by our group.[5] Data for compounds **1a**,**b**,**d**[5] and **1d**[6] are in accordance with previously published work.

3-Alkoxy-5-chloro-1-(4-methoxybenzyl)pyrazin-2(1*H*)-ones 2a–c; General Procedure

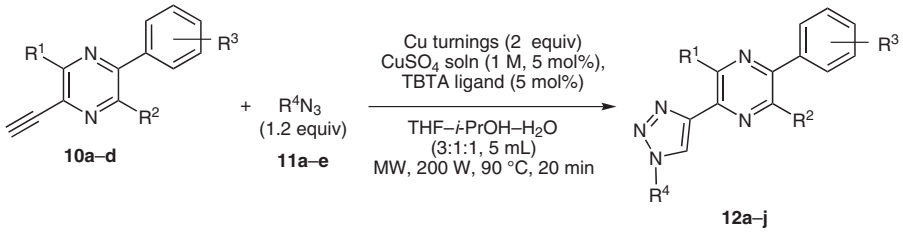
General procedure for the preparation of **2a–c** is the same as previously described by our group.[6] Data for the compounds **2a**[6] and **2b**[11] are in accordance with the previously published work.

5-Chloro-3-ethoxy-6-isobutyl-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (2c)

White solid; yield: 2.8 g (7.92 mmol, 98%); mp 86–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8.67 Hz, 2 H), 6.84 (d, *J* = 8.64 Hz, 2 H), 5.25 (s, 2 H), 4.39 (q, *J* = 7.14 Hz, 2 H), 3.77 (s, 3 H), 2.59 (d, *J* = 7.35 Hz, 2 H), 1.99 (m, 1 H), 1.46 (t, *J* = 6.96 Hz, 3 H), 1.01 (d, *J* = 6.60 Hz, 6 H).

Table 5 Synthesis of Triazoles **12a–j**[a]



Entry	Substrate	Azide R^4N_3	Product	Yield (%)
1	**10a**	**11a**	**12a**	82
2	**10b**	**11b**	**12b**	69
3	**10b**	**11c**	**12c**	56
4	**10b**	**11d**	**12d**	38
5	**10c**	**11a**	**12e**	92
6	**10c**	**11b**	**12f**	71
7	**10d**	**11a**	**12g**	73
8	**10d**	**11b**	**12h**	63
9	**10d**	**11e**	**12i**	78
10[b]	**10d**	$TMSN_3$	**12j** (R^4 = H)	80

[a] Using **10a–d** (0.1 mmol) in a multimode microwave apparatus.
[b] The protective group (TMS) was cleaved in situ.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 152.9, 151.6, 129.5, 128.2, 127.4, 123.2, 114.2, 63.9, 55.2, 47.6, 37.3, 28.9, 22.3, 14.0.

HRMS (EI): *m*/*z* [M] calcd for $C_{18}H_{23}ClN_2O_3$: 350.1397; found: 350.1389.

6-Benzyl-5-chloro-1-(4-methoxybenzyl)-3-methylpyrazin-2(1*H*)-one (2d)

The preparation of **2d** is the same as previously described by our group;[6] white solid; yield: 2.7 g (7.6 mmol, 95%); mp 152–154 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 3 H), 7.11 (d, *J* = 6.78 Hz, 2 H), 7.05 (d, *J* = 8.67 Hz, 2 H), 6.87 (d, *J* = 8.85 Hz, 2 H), 5.05 (s, 2 H), 4.11 (s, 2 H), 3.79 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 156.4, 155.9, 134.7, 134.6, 129.3, 127.8, 127.5 (2 C), 127.0, 114.4, 55.3, 47.6, 35.2, 20.9.

HRMS (EI): *m*/*z* [M] calcd for $C_{20}H_{19}ClN_2O_2$: 354.1135; found: 354.1134.

5-Chloro-1-(4-methoxybenzyl)pyrazine-2(1*H*)-thiones 3a–d; General Procedure

General procedure for the preparation of **3a-d** is the same as previously described by our group.[6] Data for compounds **3a** are in accordance with previously published work.[6]

5-Chloro-3-methoxy-1-(4-methoxybenzyl)-6-methylpyrazine-2(1*H*)-thione (3b)

Yellow solid; yield: 2.18 g (7.04 mmol, 88%); mp 127–129 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 8.67 Hz, 2 H), 6.84 (d, *J* = 8.76 Hz, 2 H), 6.00 (s, 2 H), 4.05 (s, 3 H), 3.77 (s, 3 H), 2.45 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 159.2, 159.0, 131.0, 129.9, 127.6, 124.9, 114.4, 56.1, 55.3, 17.0.

HRMS (EI): *m*/*z* [M] calcd for $C_{14}H_{15}ClN_2O_2S$: 310.0543; found: 310.0547.

5-Chloro-3-ethoxy-6-isobutyl-1-(4-methoxybenzyl)pyrazine-2(1*H*)-thione (3c)

Yellow liquid; yield: 2.6 g (7.2 mmol, 90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (d, *J* = 8.49 Hz, 2 H), 6.84 (d, *J* = 8.46 Hz, 2 H), 5.99 (br s, 2 H), 4.46 (q, *J* = 7.14 Hz, 2 H), 3.77 (s, 3 H), 2.71 (d, *J* = 7.14 Hz, 2 H), 2.10–1.96 (m, 1 H), 1.49 (t, *J* = 6.99 Hz, 3 H), 1.01 (d, *J* = 6.60 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 158.0, 133.5, 130.2, 130.0, 127.6, 127.2, 125.3, 114.3, 65.0, 55.2, 49.5, 38.1, 29.2, 24.6, 22.3, 15.6, 14.0.

HRMS (EI): *m*/*z* [M] calcd for $C_{18}H_{23}ClN_2O_2S$: 366.1169; found: 366.1156.

6-Benzyl-5-chloro-1-(4-methoxybenzyl)-3-methylpyrazine-2(1*H*)-thione (3d)

Yellow solid; yield: 2.16 g (5.84 mmol, 73%); mp 125–127 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 3 H), 7.08 (d, *J* = 6.6 Hz, 2 H), 7.00 (d, *J* = 8.1 Hz, 2 H), 6.88 (d, *J* = 8.07 Hz, 2 H), 5.81 (br s, 2 H), 4.20 (s, 2 H), 3.79 (s, 3 H), 2.79 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 163.8, 159.2, 138.4, 134.3, 134.1, 133.4, 132.3, 132.2, 132.1, 131.5 (2 C), 129.4, 128.5, 128.4, 127.7, 127.4, 127.2, 124.9, 114.5, 55.3, 36.0, 26.8.

HRMS (EI): *m*/*z* [M] calcd for $C_{20}H_{19}ClN_2OS$: 370.0907; found: 370.0912.

5-Chloro-2-(4-methoxybenzylthio)pyrazines 5a–d; General Procedure

Thioamide **3** (5 mmol) and I_2 (10 mol%) were successively added to CH_2Cl_2 (15 mL) in a 50-mL glass vial. The resulting soln was irradiated at 80 °C ceiling temperature for 15 min using maximum 150-W microwave power. After completion of the reaction, the mixture was diluted with EtOAc (200 mL) and washed with 5% aq $Na_2S_2O_3$ (100 mL) to remove I_2, followed by H_2O (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 0–10% EtOAc–heptane) to afford compounds **5a**–**d**.

5-Chloro-3-methoxy-2-(4-methoxybenzylthio)pyrazine (5a)

Light-yellow solid; yield: 1.23 g (4.15 mmol, 83%); mp 79–81 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.31 (d, *J* = 8.46 Hz, 2 H), 6.82 (d, *J* = 8.46 Hz, 2 H), 4.32 (s, 2 H), 4.00 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 155.1, 144.2, 140.0, 133.8, 130.2, 128.9, 113.9, 55.2, 54.7, 32.8.

HRMS (EI): *m*/*z* [M] calcd for $C_{13}H_{13}ClN_2O_2S$: 296.0386; found: 296.0394.

5-Chloro-3-methoxy-2-(4-methoxybenzylthio)-6-methylpyrazine (5b)

Off white; yield: 1.36 g (4.4 mmol, 88%); mp 73–75 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.67 Hz, 2 H), 6.82 (d, *J* = 8.67 Hz, 2 H), 4.32 (s, 2 H), 3.96 (s, 3 H), 3.78 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 153.5, 142.6, 141.6, 138.4, 130.3, 129.3, 113.8, 55.2, 54.5, 32.8, 20.5.

HRMS (EI): *m*/*z* [M] calcd for $C_{14}H_{15}ClN_2O_2S$: 310.0543; found: 310.0558.

5-Chloro-3-ethoxy-6-isobutyl-2-(4-methoxybenzylthio)pyrazine (5c)

Colorless oil; yield: 1.46 g (4 mmol, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.46 Hz, 2 H), 6.82 (d, *J* = 8.46 Hz, 2 H), 4.38 (q, *J* = 6.96 Hz, 2 H), 4.32 (s, 2 H), 3.77 (s, 3 H), 2.71 (d, *J* = 7.17 Hz, 2 H), 2.23–2.12 (m, 1 H), 1.39 (t, *J* = 7.14 Hz, 3 H), 0.96 (d, *J* = 6.57 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 152.9, 144.3, 142.7, 138.6, 130.2, 129.4, 113.8, 63.4, 55.2, 42.1, 32.7, 28.1, 22.4, 14.2.

HRMS (EI): *m*/*z* [M] calcd for $C_{18}H_{23}ClN_2O_2S$: 366.1169; found: 366.115.

6-Benzyl-5-chloro-2-(4-methoxybenzylthio)-3-methylpyrazine (5d)

Colorless oil; yield: 1.33 g (3.6 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.27 (m, 5 H), 7.19 (d, *J* = 8.49 Hz, 2 H), 6.77 (d, *J* = 8.46 Hz, 2 H), 4.29 (s, 2 H), 4.24 (s, 2 H), 3.77 (s, 3 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 152.6, 149.9, 148.6, 142.0, 137.5, 130.1, 129.2, 128.4, 126.6, 113.8, 55.2, 40.3, 33.5, 20.6.

HRMS (EI): *m*/*z* [M] calcd for $C_{20}H_{19}ClN_2OS$: 370.0907; found: 370.0888.

2-Aryl-5-chloropyrazines 9a–j; General Procedure

A mixture of pyrazine **5** (0.5 mmol), boronic acid **8** (2 equiv), $Pd(PPh_3)_4$ (5 mol%), and CuTC (1.5 equiv) in THF (4 mL) was irradiated in a 15-mL sealed tube at a ceiling temperature of 120 °C using 500-W maximum power for 30 min. After 30 min more of the above reactants, boronic acid **8** (1 equiv), $Pd(PPh_3)_4$ (5 mol%), and CuTC (1 equiv) were added and the reaction was run for a further 30 min under the same conditions. After completion of the reaction, the mixture was filtered through celite and the filtrate was diluted with EtOAc (200 mL), and washed with H_2O (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 0–30% EtOAc–heptane) to afford compounds **9a**–**j**.

5-Chloro-3-methoxy-2-(4-methoxyphenyl)pyrazine (9a)

The reaction was carried out on a 5-mmol scale; light-yellow solid; yield: 1.05 g (4.2 mmol, 84%); mp 69–71 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.09 (d, *J* = 8.85 Hz, 2 H), 6.98 (d, *J* = 8.85 Hz, 2 H), 4.06 (s, 3 H), 3.97 (s, 3 H).

HRMS (EI): *m*/*z* [M] calcd for $C_{12}H_{11}ClN_2O_2$: 250.0509; found: 250.0514.

5-Chloro-2-(3,4-dimethoxyphenyl)-3-methoxypyrazine (9b)

White solid; yield: 96 mg (0.35 mmol, 69%); mp 118–120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.74 (d, *J* = 8.46 Hz, 1 H), 7.65 (s, 1 H), 6.95 (d, *J* = 8.46 Hz, 1 H), 4.07 (s, 3 H), 3.96–3.94 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 150.2, 148.7, 142.3, 140.5, 134.5, 127.4, 122.2, 111.8, 110.4, 55.9, 54.5.

HRMS (EI): *m*/*z* [M] calcd for $C_{13}H_{13}ClN_2O_3$: 280.0615; found: 280.0578.

5-Chloro-2-(3,4-difluorophenyl)-3-methoxypyrazine (9c)

White solid; yield: 96 mg (0.37 mmol, 75%); mp 113–115 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 8.01–7.88 (m, 2 H), 7.28–7.19 (m, 1 H), 4.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 151.7, 151.6, 149.4, 149.3, 148.5, 148.3, 143.7, 138.3, 134.9, 131.7, 131.6, 129.9, 125.4 (2 C), 125.3 (2 C), 118.3, 118.0, 117.1, 116.9, 113.9, 54.7.

HRMS (EI): *m*/*z* [M] calcd for $C_{11}H_7ClF_2N_2O$: 256.0215; found: 256.0227.

5-Chloro-3-methoxy-2-[3-(trifluoromethyl)phenyl]pyrazine (9d)

White solid; yield: 115 mg (0.4 mmol, 80%); mp 38–40 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.27–8.25 (m, 2 H), 7.69 (d, *J* = 7.53 Hz, 1 H), 7.58 (t, *J* = 7.74 Hz, 1 H), 4.10 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9, 144.1, 139.1, 135.5, 135.1, 132.1, 130.9, 130.5, 128.7, 126.0, 125.9 (2 C), 125.8, 122.2, 54.7.

HRMS (EI): *m*/*z* [M] calcd for $C_{12}H_8ClF_3N_2O$: 288.0277; found: 288.0276.

2-Chloro-6-methoxy-5-(4-methoxyphenyl)-3-methylpyrazine (9e)

The reaction was carried out on a 5-mmol scale, white solid; yield: 1.14 g (4.3 mmol, 86%); mp 71–73 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.85 Hz, 2 H), 6.98 (d, *J* = 8.85 Hz, 2 H), 4.03 (s, 3 H), 3.86 (s, 3 H), 2.60 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 164.9, 142.1, 140.9, 139.7, 130.4, 127.5, 113.6, 55.3, 54.3, 20.7.

HRMS (EI): *m*/*z* [M] calcd for $C_{13}H_{13}ClN_2O_2$: 264.0666; found: 264.0663.

2-Chloro-5-(3,4-dimethoxyphenyl)-6-methoxy-3-methylpyrazine (9f)

The reaction was carried out on a 5-mmol scale; light-yellow solid; yield: 1.37 g (4.65 mmol, 93%); mp 94–96 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.46 Hz, 1 H), 7.65 (d, *J* = 1.14 Hz, 1 H), 6.94 (d, *J* = 8.46 Hz, 1 H), 4.03 (s, 3 H), 3.96 (s, 3 H), 3.93 (s, 3 H), 2.61 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.9, 150.0, 148.7, 142.1, 139.4, 129.6, 127.6, 122.2, 113.8, 111.9, 110.5, 55.9 (2 C), 54.4, 20.7.

HRMS (EI): *m*/*z* [M] calcd for $C_{14}H_{15}ClN_2O_3$: 294.0771; found: 294.0765.

2-(4-*tert*-Butylphenyl)-5-chloro-3-methoxy-6-methylpyrazine (9g)

Colorless liquid; yield: 133 mg (0.46 mmol, 92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.46 Hz, 2 H), 7.48 (d, *J* = 8.67 Hz, 2 H), 4.02 (s, 3 H), 2.60 (s, 3 H), 1.34 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 152.4, 142.3, 141.4, 140.0, 132.1, 128.6, 125.2, 54.3, 34.7, 31.2, 20.7.

HRMS (EI): *m*/*z* [M] calcd for $C_{16}H_{19}ClN_2O$: 290.1186; found: 290.1186.

2-Chloro-5-(3,4-dimethoxyphenyl)-6-ethoxy-3-isobutylpyrazine (9h)

The reaction was carried out on a 5-mmol scale; off-white solid; yield: 1.39 g (3.95 mmol, 79%); mp 72–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.79 (m, 2 H), 6.95 (d, *J* = 8.28 Hz, 1 H), 4.47 (q, *J* = 6.99 Hz, 2 H), 3.95–3.94 (m, 6 H), 2.80 (d, *J* = 7.17 Hz, 2 H), 2.29–2.20 (m, 1 H), 1.47 (t, *J* = 6.99 Hz, 3 H), 1.00 (d, *J* = 6.57 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 149.9, 148.4, 144.7, 141.0, 138.9, 128.0, 122.2, 112.0, 110.6, 63.1, 55.9, 55.7, 42.1, 28.1, 22.4, 14.4.

HRMS (EI): *m*/*z* [M] calcd for $C_{18}H_{23}ClN_2O_3$: 350.1397; found: 350.1387.

2-Chloro-5-(3,4-difluorophenyl)-6-ethoxy-3-isobutylpyrazine (9i)

White solid; yield: 117 mg (0.36 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07–7.94 (m, 2 H), 7.20 (t, *J* = 8.46 Hz, 1 H), 4.49 (q, *J* = 7.14 Hz, 2 H), 2.79 (d, *J* = 7.14 Hz, 2 H), 2.30–2.16 (m, 1 H), 1.47 (t, *J* = 7.17 Hz, 3 H), 0.99 (d, *J* = 6.60 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 152.6, 152.4, 151.7, 151.5, 149.2, 149.1, 148.4, 148.3, 145.2, 142.5, 136.8, 132.3 (2 C), 132.1, 125.4 (2 C), 125.3 (2 C), 118.2, 118.0, 117.0, 116.8, 63.5, 42.1, 29.7, 28.1, 22.4, 14.4.

HRMS (EI): *m*/*z* [M] calcd for $C_{16}H_{17}ClF_2N_2O$: 326.0997; found: 326.1014.

2-Benzyl-3-chloro-6-(3,4-dimethoxyphenyl)-5-methylpyrazine (9j)

Colorless oil; yield: 111 mg (0.4 mmol, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 5 H), 7.18–7.14 (m, 2 H), 6.96 (d, *J* = 7.92 Hz, 1 H), 4.32 (s, 2 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 2.61 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 150.4, 149.7, 149.0, 148.8, 144.9, 137.5, 130.0, 129.1, 128.4, 126.6, 121.8, 112.4, 110.7, 55.9 (2 C), 40.6, 22.6.

HRMS (EI): *m*/*z* [M] calcd for $C_{20}H_{19}ClN_2O_2$: 354.1135; found: 354.1145.

2-Aryl-5-ethynylpyrazines 10a–d; General Procedure

A mixture of pyrazine **9** (2.0 mmol), triisopropylsilylacetylene (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), and TBAI (1.2 equiv) in DMF–Et_3N (1:1, 4 mL) was irradiated in a 15-mL sealed tube at a ceiling temperature of 80 °C using 80-W maximum power for 20 min. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (200 mL) and washed with H_2O (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and distilled under reduced pressure. The obtained residue was dissolved in CH_2Cl_2–THF (1.5:1, 5 mL) and 1 M TBAF in THF (2 equiv) was added dropwise. The mixture was stirred at r.t. for 3–5 min. After completion of the reaction, the solvents were removed under reduced pressure and the residue was directly subjected to flash column chromatography (short silica gel pad, 0–30% EtOAc–heptane) to afford the desired terminal acetylenes **10a–d** in good yields.

5-Ethynyl-3-methoxy-2-(4-methoxyphenyl)pyrazine (10a)

Light-yellow solid; yield: 374 mg (1.56 mmol, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.10 (d, *J* = 8.85 Hz, 2 H), 6.99 (d, *J* = 8.88 Hz, 2 H), 4.06 (s, 3 H), 3.87 (s, 3 H), 3.29 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 156.7, 142.7, 139.6, 131.7, 130.8, 127.7, 113.6, 80.5, 79.8, 55.3, 54.0.

HRMS (EI): *m*/*z* [M] calcd for $C_{14}H_{12}N_2O_2$: 240.0899; found: 240.0897.

2-Ethynyl-6-methoxy-5-(4-methoxyphenyl)-3-methylpyrazine (10b)

Dark-brown solid; yield: 462 mg (1.82 mmol, 91%); mp 128–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.85 Hz, 2 H), 6.98 (d, *J* = 8.85 Hz, 2 H), 4.03 (s, 3 H), 3.86 (s, 3 H), 3.45 (s, 1 H), 2.65 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 155.1, 147.7, 141.5, 130.8, 130.0, 127.9, 113.6, 82.1, 80.9, 55.3, 53.9, 20.9.

HRMS (EI): *m*/*z* [M] calcd for $C_{15}H_{14}N_2O_2$: 254.1055; found: 254.1065.

5-(3,4-Dimethoxyphenyl)-2-ethynyl-6-methoxy-3-methylpyrazine (10c)

Light-brown solid; yield: 454 mg (1.6 mmol, 80%); mp 145–147 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 1.71, 8.47 Hz, 1 H), 7.71 (d, *J* = 1.50 Hz, 1 H), 6.94 (d, *J* = 8.46 Hz, 1 H), 4.04 (s, 3 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.46 (s, 1 H), 2.66 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 150.3, 148.6, 147.7, 141.2, 130.1, 128.0, 122.6, 112.1, 110.5, 82.2, 80.8, 55.9, 53.9, 20.9.

HRMS (EI): *m*/*z* [M] calcd for $C_{16}H_{16}N_2O_3$: 284.1161; found: 284.1170.

3-(3,4-Dimethoxyphenyl)-2-ethoxy-6-ethynyl-5-isobutylpyrazine (10d)

Pink solid; yield: 401 mg (1.18 mmol, 59%); mp 108–110 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.86 (m, 2 H), 6.95 (d, *J* = 8.28 Hz, 1 H), 4.48 (q, *J* = 6.96 Hz, 2 H), 3.95–3.94 (m, 6 H), 3.39 (s, 1 H), 2.86 (d, *J* = 7.14 Hz, 2 H), 2.31–2.18 (m, 1 H), 1.47 (t, *J* = 7.14 Hz, 3 H), 0.99 (d, *J* = 6.78 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.7, 150.5, 150.2, 148.4, 140.7, 130.2, 128.4, 122.7, 112.3, 110.5, 81.5, 81.0, 62.5, 55.9, 55.7, 42.7, 28.8, 22.4, 14.5.

HRMS (EI): *m*/*z* [M] calcd for $C_{20}H_{24}N_2O_3$: 340.1787; found: 340.1775.

Azides 11a–e; General Procedure

All protected sugar azides[9] **11a–d** and benzyl azide[10] **11e** were synthesized according to literature procedures.

4-(5-Arylpyrazin-2-yl)-1,2,3-triazoles 12a–j; General Procedure

A mixture of pyrazine **10** (0.1 mmol), azide **11** (1.2 equiv), Cu turnings (2 equiv), aq 1 M $CuSO_4$ (5 mol%), and TBTA (5 mol%) in THF–*i*-PrOH–H_2O (3:1:1, 5 mL) was irradiated in a 15-mL sealed tube at a ceiling temperature of 90 °C using 200 W maximum power for 20 min. After completion of the reaction, the mixture was diluted with EtOAc (100 mL), and washed with H_2O (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The obtained residue was subjected to column chromatography (silica gel, 0–50% EtOAc–heptane) to afford desired compounds **12a–j**.

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-{4-[6-methoxy-5-(4-methoxyphenyl)pyrazin-2-yl]-1*H*-1,2,3-triazol-1-yl}tetrahydrofuran-3,4-diyl Dibenzoate (12a)

White solid; yield: 119 mg (0.16 mmol, 82%); mp 77–79 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.96 (s, 1 H), 8.30 (s, 1 H), 8.11 (d, *J* = 8.49 Hz, 2 H), 8.03–7.96 (m, 6 H), 7.62–7.34 (m, 9 H), 7.00 (d, *J* = 8.46 Hz, 2 H), 6.54 (d, *J* = 3.03 Hz, 1 H), 6.37 (br s, 1 H), 6.18 (t, *J* = 5.25 Hz, 1 H), 4.94–4.88 (m, 2 H), 4.63 (dd, *J* = 3.39, 11.97 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 165.1 (2 C), 160.5, 156.8, 146.7, 141.9, 138.9, 133.9, 133.7, 133.3, 132.8, 130.6, 129.9, 129.8, 129.6, 129.1, 128.6, 128.5, 128.4, 128.2, 121.5, 113.6, 90.5, 81.4, 75.3, 71.5, 63.5, 55.3, 53.4.

MS (ESI$^+$): *m*/*z* [M] calcd for $C_{40}H_{33}N_5O_9$: 727.7; found: 750.3 [M + Na]$^+$, 1478.2 [2 M + Na]$^+$.

[(2*R*,3*S*,5*R*)-3-(4-Chlorobenzoyloxy)-5-{4-[6-methoxy-5-(4-methoxyphenyl)-3-methylpyrazin-2-yl]-1*H*-1,2,3-triazol-1-yl}tetrahydrofuran-2-yl]methyl 4-Chlorobenzoate (12b)

Yellow solid; yield: 95 mg (0.14 mmol, 69%); mp 66–67 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 8.14 (d, *J* = 8.67 Hz, 2 H), 8.01 (d, *J* = 8.46 Hz, 2 H), 7.85 (d, *J* = 8.46 Hz, 2 H), 7.47 (d, *J* = 8.31 Hz, 2 H), 7.31 (d, *J* = 8.49 Hz, 2 H), 7.00 (d, *J* = 8.64 Hz, 2 H), 6.52 (t, *J* = 5.85 Hz, 1 H), 5.87 (br s, 1 H), 4.75–4.69 (m, 2 H), 4.54–4.51 (m, 1 H), 3.96 (s, 3 H), 3.87 (s, 3 H), 3.51–3.42 (m, 1 H), 2.98–2.89 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 164.9, 160.4, 154.7, 148.3, 142.2, 140.2, 139.8, 136.2, 131.1, 130.9, 130.6, 128.9, 128.2, 127.6, 127.4, 123.2, 113.6, 88.7, 83.5, 74.8, 63.9, 55.3, 53.3, 37.8, 22.4.

MS (ESI$^+$): *m*/*z* [M] calcd for $C_{34}H_{29}Cl_2N_5O_7$: 690.5; found: 691.2 [M]$^+$, 1403.4 [2 M + Na]$^+$.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-{4-[6-methoxy-5-(4-methoxyphenyl)-3-methylpyrazin-2-yl]-1*H*-1,2,3-triazol-1-yl}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (12c)

White solid; yield: 70 mg (0.11 mmol, 56%); mp 182–185 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 8.14 (d, *J* = 8.85 Hz, 2 H), 7.00 (d, *J* = 8.85 Hz, 2 H), 5.98 (d, *J* = 9.42 Hz, 1 H), 5.58 (t, *J* = 9.42 Hz, 1 H), 5.46 (t, *J* = 9.42 Hz, 1 H), 5.30 (t, *J* = 9.78 Hz, 1 H), 4.37–4.31 (m, 1 H), 4.18 (d, *J* = 12.63 Hz, 1 H), 4.08–4.04 (m, 4 H), 3.87 (s, 3 H), 2.96 (s, 3 H), 2.09 (s, 6 H), 2.04 (s, 3 H), 1.91 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 169.9, 169.4, 169.0, 160.4, 154.9, 148.5, 142.3, 140.5, 136.0, 130.6, 128.2, 122.3, 113.6, 85.8, 75.2, 70.3, 67.7, 61.6, 55.3, 53.5, 22.4, 20.7, 20.5 (2 C), 20.2.

MS (ESI$^+$): *m*/*z* [M] calcd for $C_{29}H_{33}N_5O_{11}$: 627.5; found: 628.8 [M]$^+$, 1277.8 [2 M + Na]$^+$.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-{4-[6-methoxy-5-(4-methoxyphenyl)-3-methylpyrazin-2-yl]-1*H*-1,2,3-triazol-1-yl}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (12d)

White solid; yield: 48 mg (0.08 mmol, 38%); mp 81–83 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 8.14 (d, *J* = 8.85 Hz, 2 H), 7.00 (d, *J* = 8.85 Hz, 2 H), 5.93 (d, *J* = 9.21 Hz, 1 H), 5.69 (t, *J* = 9.78 Hz, 1 H), 5.59 (br s, 1 H), 5.30 (dd, *J* = 3.39, 10.33 Hz, 1 H), 4.28–4.20 (m, 3 H), 4.10 (s, 3 H), 3.87 (s, 3 H), 2.96 (s, 3 H), 2.25 (s, 3 H), 2.06 (s, 3 H), 2.02 (s, 3 H), 1.93 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 170.0, 169.8, 169.2, 160.4, 154.9, 148.4, 142.4, 140.4, 136.2, 130.6, 128.2, 122.3, 113.6, 86.3, 74.2, 70.8, 67.8, 66.8, 61.2, 55.3, 53.6, 22.4, 20.7, 20.6, 20.5, 20.3.

MS (ESI$^+$): *m*/*z* [M] calcd for $C_{29}H_{33}N_5O_{11}$: 627.5; found: 628.9 [M]$^+$, 1277.6 [2 M + Na]$^+$.

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-{4-[5-(3,4-dimethoxyphenyl)-6-methoxy-3-methylpyrazin-2-yl]-1*H*-1,2,3-triazol-1-yl}tetrahydrofuran-3,4-diyl Dibenzoate (12e)

White solid; yield: 151 mg (0.19 mmol, 98%); mp 83–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.03–7.96 (m, 6 H), 7.82 (d, *J* = 8.46 Hz, 1 H), 7.77 (s, 1 H), 7.62–7.55 (m, 2 H), 7.50–7.35 (m, 7 H), 6.96 (d, *J* = 8.46 Hz, 1 H), 6.54 (d, *J* = 1.14 Hz, 1 H), 6.38 (t, *J* = 4.14 Hz, 1 H), 6.22 (t, *J* = 5.28 Hz, 1 H), 4.96–4.87 (m, 2 H), 4.63 (dd, *J* = 3.96, 12.24 Hz, 1 H), 3.99 (s, 3 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.97 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.1, 154.7, 150.0, 148.7, 148.3, 142.2, 139.9, 136.2, 13.9, 133.7, 133.3, 129.9, 129.8, 129.6, 129.1, 128.6 (2 C), 128.5, 128.4 (2 C), 123.3, 122.4, 112.0, 110.5, 90.4, 81.3, 75.4, 71.5, 63.5, 55.9, 53.4, 35.4, 31.8, 26.4, 22.6, 22.5, 14.1.

MS (ESI$^+$): *m*/*z* [M] calcd for $C_{42}H_{37}N_5O_{10}$: 771.7; found: 772.4 [M]$^+$, 1565.0 [2 M + Na]$^+$.

[(2*R*,3*S*,5*R*)-3-(4-Chlorobenzoyloxy)-5-{4-[5-(3,4-dimethoxyphenyl)-6-methoxy-3-methylpyrazin-2-yl]-1*H*-1,2,3-triazol-1-yl}tetrahydrofuran-2-yl]methyl 4-Chlorobenzoate (12f)

Yellow solid; yield: 102 mg (0.14 mmol, 71%); mp 99–101 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 8.01 (d, *J* = 8.46 Hz, 2 H), 7.86–7.81 (m, 3 H), 7.78 (s, 1 H), 7.47 (d, *J* = 8.31 Hz, 2 H), 7.31 (d, *J* = 8.46 Hz, 2 H), 6.96 (d, *J* = 8.46 Hz, 1 H), 6.52 (t, *J* = 5.82 Hz, 1 H), 5.87 (br s, 1 H), 4.76–4.69 (m, 2 H), 4.53 (d, *J* = 7.53 Hz, 1 H), 3.99–3.95 (m, 9 H), 3.51–3.43 (m, 1 H), 3.02–2.89 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 164.9, 154.7, 150.0, 148.7, 148.2, 142.2, 140.3, 139.9, 139.8, 136.3, 131.1, 130.9, 128.9, 128.7, 128.4, 127.6, 127.4, 123.2, 122.4, 112.0, 110.5, 88.7, 83.5, 74.8, 63.9, 55.9, 53.4, 37.8, 35.4, 31.8, 26.4, 26.3, 22.6, 22.4, 14.1.

MS (ESI$^+$): *m*/*z* [M] calcd for $C_{35}H_{31}Cl_2N_5O_8$: 720.5; found: 721.7 [M]$^+$, 1463.2 [2 M + Na]$^+$.

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-{4-[5-(3,4-dimethoxyphenyl)-6-ethoxy-3-isobutylpyrazin-2-yl]-1*H*-1,2,3-triazol-1-yl}tetrahydrofuran-3,4-diyl Dibenzoate (12g)

Light-yellow solid; yield: 121 mg (0.15 mmol, 73%); mp 70–72 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (s, 1 H), 8.03–7.92 (m, 8 H), 7.59–7.54 (m, 2 H), 7.47–7.32 (m, 7 H), 6.97 (d, *J* = 8.46 Hz, 1 H), 6.50 (s, 1 H), 6.38 (s, 1 H), 6.22 (t, *J* = 4.89 Hz, 1 H), 4.96–4.84 (m, 2 H), 4.67–4.63 (m, 1 H), 4.35 (t, *J* = 6.57 Hz, 2 H), 3.98–3.95 (m, 6 H), 3.41–3.21 (m, 2 H), 2.33–2.29 (m, 1 H), 1.44 (t, *J* = 6.03 Hz, 3 H), 1.01 (d, *J* = 6.03 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.1, 154.1, 149.8, 148.4 (2 C), 145.3, 139.3, 136.2, 133.9, 133.7, 133.3, 129.9, 129.7, 129.1, 128.8, 128.6, 128.5, 128.4, 123.6, 122.4, 112.2, 110.6, 90.4, 81.1,

75.4, 71.5, 63.6, 62.0, 55.9, 55.7, 42.4, 35.4, 30.9, 28.5, 26.4, 22.6, 22.5 (2 C), 14.5.

MS (ESI$^+$): *m*/*z* [M] calcd for $C_{46}H_{45}N_5O_{10}$: 827.8; found: 828.3 $[M]^+$, 1677.1 $[2\ M + Na]^+$.

[(2*R*,3*S*,5*R*)-3-(4-Chlorobenzoyloxy)-5-{4-[5-(3,4-dimethoxyphenyl)-6-ethoxy-3-isobutylpyrazin-2-yl]-1*H*-1,2,3-triazol-1-yl}tetrahydrofuran-2-yl]methyl 4-Chlorobenzoate (12h)

Light-yellow solid; yield: 98 mg (0.13 mmol, 63%); mp 59–61 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 8.00 (d, *J* = 7.74 Hz, 2 H), 7.92–7.86 (m, 4 H), 7.45 (d, *J* = 7.92 Hz, 2 H), 7.32 (d, *J* = 7.92 Hz, 2 H), 6.98 (d, *J* = 8.67 Hz, 1 H), 6.51 (t, *J* = 5.64 Hz, 1 H), 5.87 (br s, 1 H), 4.70–4.67 (m, 2 H), 4.57–4.51 (m, 1 H), 4.41 (q, 6.39 Hz, 2 H), 3.98 (s, 3 H), 3.95 (s, 3 H), 3.54–3.45 (m, 1 H), 3.39–3.21 (m, 2 H), 2.95–2.90 (m, 1 H), 2.34–2.25 (m, 1 H), 1.47 (t, *J* = 6.96 Hz, 3 H), 1.01 (d, *J* = 6.57 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 164.9, 154.2, 149.8, 148.4 (2 C), 145.2, 140.2, 139.8, 138.3, 136.3, 131.1, 128.9, 128.8, 127.7, 127.5, 123.5, 122.4, 112.2, 110.6, 88.7, 83.5, 74.9, 64.0, 62.0, 55.9, 55.7, 42.4, 37.6, 35.4, 31.8, 30.9, 28.5, 26.4, 22.6, 22.5 (2 C), 14.6, 14.1.

MS (ESI$^+$): *m*/*z* [M] calcd for $C_{39}H_{39}Cl_2N_5O_8$: 776.6; found: 777.2 $[M]^+$, 1575.6 $[2\ M + Na]^+$.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-5-(3,4-dimethoxyphenyl)-6-ethoxy-3-isobutylpyrazine (12i)

Yellow solid; yield: 74 mg (0.16 mmol, 78%); mp 137–139 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.91–7.89 (m, 2 H), 7.41–7.33 (m, 5 H), 6.96 (d, *J* = 9.03 Hz, 1 H), 5.61 (s, 2 H), 4.44 (q, *J* = 7.23 Hz, 2 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.32 (d, *J* = 6.96 Hz, 2 H), 2.33–2.22 (m, 1 H), 1.46 (t, *J* = 6.99 Hz, 3 H), 0.99 (d, *J* = 6.60 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 149.8, 148.4, 148.3, 145.3, 139.0, 136.8, 134.7, 129.1, 128.8, 128.7, 128.0, 124.0, 122.3, 112.2, 110.6, 62.0, 55.9, 55.7, 54.1, 42.5, 28.5, 22.5, 14.5.

HRMS (EI): *m*/*z* [M] calcd for $C_{27}H_{31}N_5O_3$: 473.2427; found: 473.2420.

3-(3,4-Dimethoxyphenyl)-2-ethoxy-5-isobutyl-6-(1*H*-1,2,3-triazol-4-yl)pyrazine (12j)

Green solid; yield: 61 mg (0.16 mmol, 80%); mp 202–204 °C.

^{1}H NMR (400 MHz, DMSO): δ = 15.3 (br s, 1 H), 8.38 (br s, 1 H), 7.86 (d, *J* = 1.50 Hz, 1 H), 7.82 (dd, *J* = 1.50, 6.33 Hz, 1 H), 7.09 (d, *J* = 6.42 Hz, 1 H), 4.52 (q, *J* = 5.28 Hz, 2 H), 3.83–3.82 (m, 6 H), 2.50 (merged in solvent peak, 2 H), 2.21–2.13 (m, 1 H), 1.44 (t, *J* = 5.28 Hz, 3 H), 0.93 (d, *J* = 4.92 Hz, 6 H).

^{13}C NMR (75 MHz, DMSO): δ = 153.8, 149.7, 148.0, 127.8, 121.9, 112.1, 111.2, 61.9, 55.4, 55.2, 54.8, 41.9, 27.8, 22.2, 14.3.

HRMS (EI): *m*/*z* [M] calcd for $C_{20}H_{25}N_5O_3$: 383.1957; found: 383.1973.

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