Transition Metal-Catalyzed Orthogonal Solid-Phase Decoration of the 2(1*H*)-Pyrazinone Scaffold Using a Sulfur Linker

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A new transition metal-catalyzed orthogonal solid-phase protocol for the synthesis of highly substituted 2(1*H*)-pyrazinones was developed, on the basis of Chan−Lam arylation and Liebeskind−Srogl cross-coupling reactions. This strategy opens the way for the generation of small libraries of 2(1*H*)-pyrazinone analogues for biological screening.

Introduction

Combinatorial chemistry, along with high-throughput screening, has emerged as a powerful tool for the development of new drug candidates.[1] One of the most widely used strategies for library generation is solid-phase organic synthesis (SPOS), the growing popularity of which is based on the ability to drive reactions to completion using an excess of reagents and then removing them, together with byproducts, by simple filtration, to yield target molecules in high purities. However, to adapt a well-established solution-phase method to solid-phase format, two additional steps, attachment to the resin and cleavage of the final compound, should be added to the protocol. The chosen linker should be orthogonal to the reaction scheme; in other words, it should be stable through the whole synthetic sequence and should be able to be rapidly cleaved to release clean reaction products. Among the strategies applied for SPOS of combinatorial libraries of heterocyclic compounds is traceless cleavage which forms compounds without a link to the solid support.[2]

In addition to their broad biological activities, 2(1*H*)-pyrazinones can be used as building blocks for the synthesis of a variety of highly substituted heterocycles.[3] Recently, we adapted some of those solution-phase protocols to solid phase, opening a way for the generation of libraries of pharmacologically interesting heterocycles. The "traceless linking" strategy was successfully applied for the synthesis of diversely substituted 2-chloropyridines **5** and pyridinones **7** via Diels−Alder reactions of resin-bound pyrazinones **2**[4] (Scheme 1). Solid-phase synthesis of 3,5-dichloro-2(1*H*)-pyrazinones **1**, followed by microwave-assisted decoration of this useful scaffold and subsequent cleavage of the final products, provided desired compounds **3** in good yields and purities.[5] However, for the synthesis of **3** and **7**, one important point of diversification is lost because the cleavage of pyrazinones **3** and pyridinones **7** from the resin results in an unsubstituted N1 position (Scheme 1).

As part of our ongoing research to develop new methods for the derivatization of the 2(1*H*)-pyrazinone scaffold, we searched for a linker which can allow further diversification at position N1 of the pyrazinone ring. In general for SPOS, considerable attention has been paid to sulfide linkers[6] which have been extensively used in "safety-catch" strategies.[6a−c] These linkers are stable under diverse reaction conditions and are selectively activated by oxidation to their corresponding sulfones. Subsequent treatment with nucleophiles (e.g., amines and alcohols) release products from the linker. In another approach,[6d] the final compounds were released from the thiophenol support by direct cleavage upon treatment with nucleophilic amines, without prior oxidation of the thioether bond to the sulfone. It should be noted that both methods form a carbon−heteroatom bond in the final products.

We now wish to report a new application of thioether linkers for the formation of a carbon−carbon bond in the final pyrazinones, via Liebeskind−Srogl cross-coupling conditions using various arylboronic acids.[7] Because of the high selectivity of the Cu(I) catalyst to the thioether moiety, selective functional transformations can be carried out in the presence of groups that are otherwise reactive under other cross-coupling reaction conditions. A new transition metal-catalyzed orthogonal solid-phase protocol, based on sequential Chan−Lam arylation[8,9] and a Liebeskind−Srogl cross-coupling reaction,[7] allows for the selective decoration of the 2(1*H*)-pyrazinone scaffold, affording products bearing substituents at position N1 and C3.

Results and Discussion

Preliminary studies in solution phase and on the solid phase were conducted to determine the robustness and

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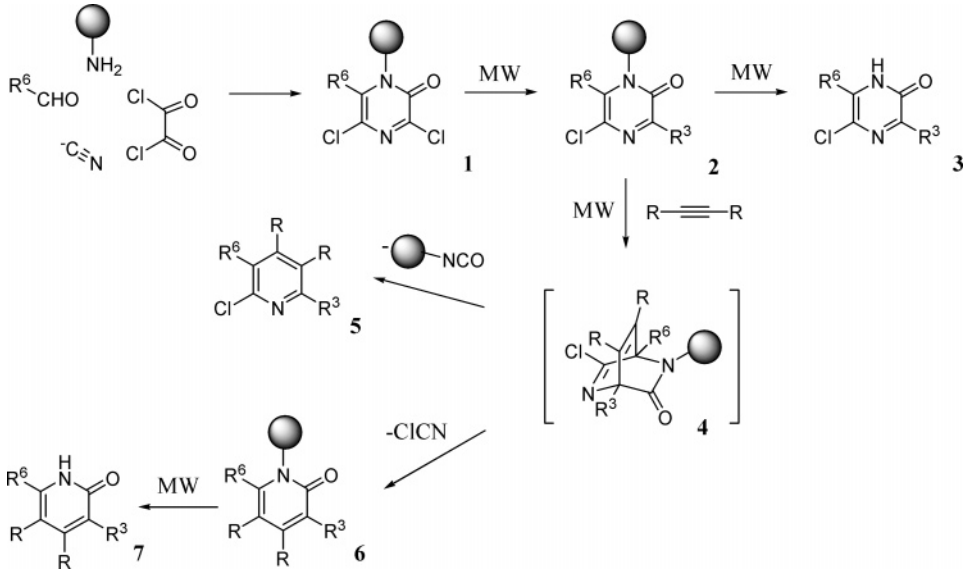
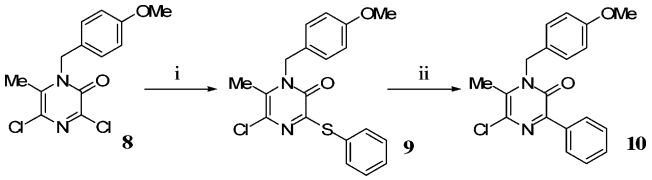
Scheme 1. Microwave-Assisted Solid-Phase Chemistry of 2(1*H*)-Pyrazinones



Scheme 2. Proof of Concept of Solution-Phase Methodology[a]



[a] Reagents and conditions: (i) PhSH (1.5 equiv), Hünig's Base (2.5 equiv), THF, RT, 40 min, 85%; (ii) $PhB(OH)_2$ (1.2 equiv), CuTC (3 equiv), $Pd(PPh_3)_4$ (6 mol %), THF, Δ, 50 °C, 2 days, 62% or MW, 130 °C, 250 W, 30 min, 54%.

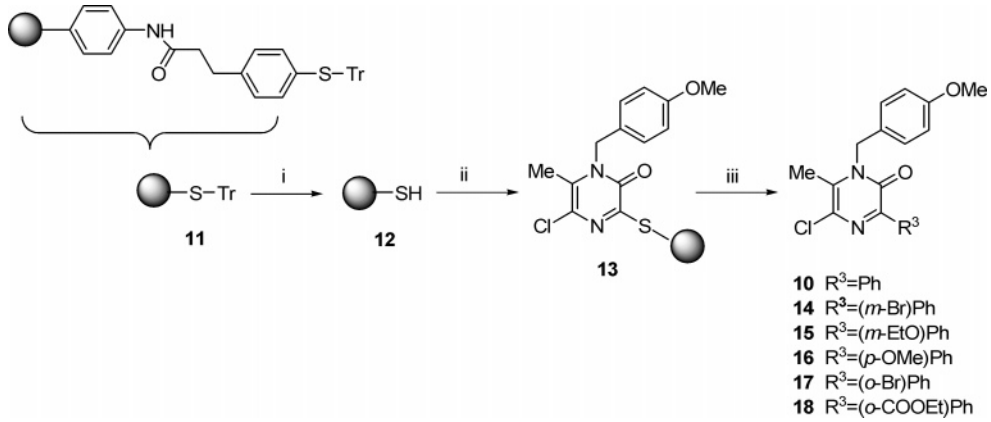
limitations of the reaction conditions. For initial experiments in solution phase, as a "proof of concept", we mimicked the sulfur linker with a thiophenol substituent at position C3 of the pyrazinone scaffold (Scheme 2).

Pyrazinone **8** was treated with thiophenol (1.5 equiv) in the presence of Hünig's base (2.5 equiv) in THF, as solvent, for 40 min to give compound **9** in an 85% yield. Next we investigated the reactivity of the thioether moiety in **9** with phenylboronic acid under Liebeskind−Srogl conditions.[7] The best results were obtained with pyrazinone **9**, phenyl boronic acid (1.2 equiv), copper(I)-thiophene-2-carboxylate (CuTC) (3 equiv), and $Pd(PPh_3)_4$ (6 mol %) heated at 50 °C for 2 days, affording the C3-arylated pyrazinone **10** in a 62% yield. Application of controlled microwave irradiation at 130 °C for 30 min gave pyrazinone **10** in a 54% yield. The use of $Zn(OAc)_2$, which has been shown to have a beneficial effect in the cross-coupling reactions of thioether substituted pyrazines,[7] did not provide any further improvement in the reaction yields.

To develop our new solid-phase approach, we have chosen commercially available 3-(4-(tritylmercapto)phenylpropionyl AM resin **11** (Scheme 3), which must be deprotected prior to use by treatment with a mixture of TFA and triethylsilane (TES) (95:5).

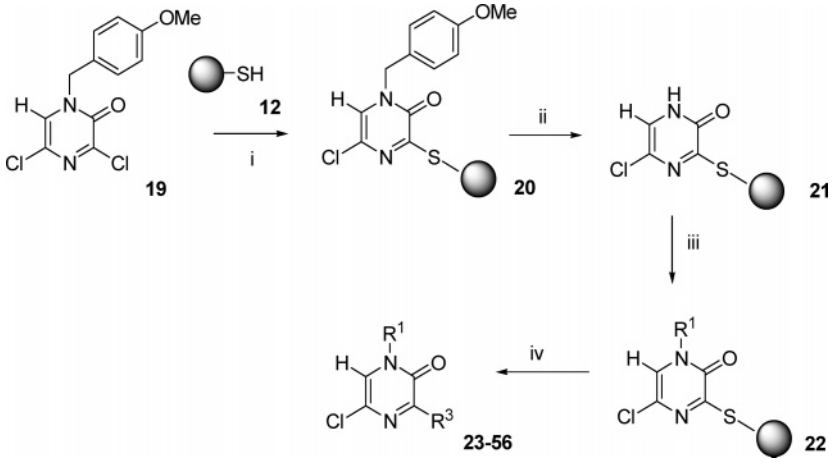
First, the reaction of pyrazinone **8** with the deprotected resin **12** was investigated as function of time, by application of the optimized reaction conditions for the solution phase. The substitution was monitored by FT-IR (disappearance of specific absorption of SH bond at 2560 cm^{-1}). The optimal result was obtained when the resin was shaken with pyrazinone **8** in THF in the presence of Hünig's base (10 equiv) for 12 h at room temperature. A further increase of the reaction time provided no substantial improvement. The

Scheme 3. Liebeskind−Srogl Cross-Coupling Reaction of Resin-Bound Pyrazinone **13**[a]



[a] Reagents and conditions: (i) TFA−TES (95:5), RT., 1 h; (ii) pyrazinone **8** (4 equiv), Hünig's base (10 equiv), THF, RT, 12 h or MW, 100 °C, 100 W, 30 min; (iii) $R^3B(OH)_2$ (2 equiv), CuTC (3 equiv), $Pd(PPh_3)_4$ (6 mol %), THF, Δ, 50 °C, 2 days (for yields see Table 1).

Scheme 4. Transition Metal-Catalyzed Solid-Phase Protocol for the Decoration of the 2(1*H*)-Pyrazinone Scaffold[a]



[a] Reagents and conditions: (i) pyrazinone **19** (4 equiv), Hünig's base (10 equiv), THF, RT, 12 h or MW, 100 °C, 100 W, 30 min; (ii) TFA−DCM (1:2), MW, 120 °C, 120 W, 40 min; (iii) $R^1B(OH)_2$ (3 equiv), $Cu(OAc)_2$ (3 equiv), TEA-Py (1:2), DCM, air, RT, 24 h; (iv) $R^3B(OH)_2$ (2 equiv), CuTC (3 equiv), $Pd(PPh_3)4$ (6 mol %), THF, Δ, 50 °C, 2 days (for the yields see Table 2).

Table 1. Liebeskind−Srogl Reaction of Resin-Bound Pyrazinone **13** with Boronic Acids[a]

entry	R^3	catalyst[b]	product	yield[c] (%)
1	(*m*-Br)phenyl	$Pd(PPh_3)_4$	**14**	55
2	(*m*-EtO)phenyl	$Pd(PPh_3)_4$	**15**	22
3	(*p*-MeO)phenyl	$Pd(PPh_3)_4$	**16**	35
4	(*p*-MeO)phenyl	Pd_2dba_3	**16**	22
5	(*o*-Br)phenyl	$Pd(PPh_3)_4$	**17**	traces[d]
6	(*o*-COOEt)phenyl	$Pd(PPh_3)_4$	**18**	traces[d]

[a] All reactions were performed on a 0.176 mmol scale. [b] 6 mol %. [c] Isolated yields based on the loading of trityl-protected resin **11**. [d] Determined by CI-MS.

application of microwave irradiation was found to speed up reaction times dramatically: upon treatment with an excess of pyrazinone **8**, all resin reacted in 30 min when heated at 100 °C. The addition of DMAP to the reaction mixture or a change of the solvent from THF to toluene and Hünig's base to Cs_2CO_3 did not have any positive influence on the outcome of the reaction.

Resin-bound pyrazinone **13** underwent cleavage from the resin upon treatment with 2 equiv of phenyl boronic acid under Liebeskind−Srogl conditions, as optimized for the solution phase but with the application of a greater excess of 2 equiv of the boronic acid. The resin was washed with a mixture of THF−MeOH (9:1); the combined filtrate was absorbed on silica gel, and pyrazinone **10** was eluted with a mixture of DCM−hexane (9:1), selectively leaving all polar reagents. The byproducts stayed on the sorbent. After recrystallization, compound **10** was obtained in analytical purity.

To investigate the scope and limitations of our approach, resin-bound pyrazinone **13** was reacted with ortho-, meta- and para-substituted boronic acids to afford 3-aryl pyrazinones **14**−**18** (Scheme 3, Table 1). Because of steric hindrance, the ortho-substituted boronic acids gave only traces of desired products (entries 5 and 6, Table 1). When Pd_2dba_3 was used as catalyst,[7] pyrazinone **16** was obtained in a 22% yield (entry 4, Table 1) compared to the 35% yield obtained in the presence of $Pd(PPh_3)_4$ (entry 3, Table 1). It should be noted that all yields are calculated based on the loading of the starting trityl-protected resin **11**.

In our previous work, we demonstrated that the (*p*-methoxy)benzyl group in position N1 of the pyrazinone scaffold can easily be cleaved upon treatment with a TFA−DCM mixture under microwave irradiation,[4] opening a way for the further derivatization of the 2(1*H*)-pyrazinone skeleton. We recently described the usefulness of the copper-(II)-mediated Chan−Lam cross-coupling protocol for the N-arylation of the 2(1*H*)-pyrazinone scaffold in solution phase.[8] The classical Chan−Lam reaction[9] allows carbon−heteroatom bond formation via an oxidative coupling of arylboronic acids with amines, alcohols, or thiols, induced by a stoichiometric amount of copper(II) or a catalytic amount of this catalyst which can be reoxidized by oxygen or by an oxidant added to the reaction mixture.[10] Chan−Lam reactions can be conducted at room temperature in air, which provides a practical advantage over the Buchwald−Hartwig cross-coupling reaction.[11]

Pyrazinone **19** (Scheme 4) was chosen as the starting compound for the investigation of the Chan−Lam arylation on solid support. After microwave-assisted linkage with deprotected resin **12** under the conditions optimized for compound **8**, the (*p*-methoxy)benzyl group was removed by irradiation of a suspension of resin-bound pyrazinone **20** in a mixture of TFA−DCM (1:2) at 120 °C for 40 min. The resulting N1-unsubstituted compound, **21**, was subjected to Chan−Lam coupling with a series of boronic acids (Scheme 4 and Table 2) using $Cu(OAc)_2$ as catalyst and Et_3N/Py (1:2) as the base in dichloromethane at room temperature (RT).[8]

The final products **23**−**56** were released from the resin under Liebeskind−Srogl conditions. As for compounds **10** and **14**−**18**, the products were absorbed on silica gel and eluted with DCM−hexane (9:1) to provide the desired products in high purity. As before, isolated yields (Table 2) were calculated based on the loading of the trityl-protected starting resin **11**. The performance of the synthesis on the solid phase avoids several laborious purifications. However, probably because of steric hindrance, Chan−Lam coupling

Table 2. Cleavage of Pyrazinones **23**−**56** from the Solid Support[a]

entry	R^1	R^3	product	yield[b] (%)
1	(*m*-CF_3)C_6H_4	Ph	**23**	29
2	(*m*-CF_3)C_6H_4	(*m*-EtO)C_6H_4	**24**	31
3	(*m*-CF_3)C_6H_4	(*m*-Cl)C_6H_4	**25**	29
4	(*m*-CF_3)C_6H_4	(*p*-MeO)C_6H_4	**26**	38
5	(*m*-CF_3)C_6H_4	(*m*-Br)C_6H_4	**27**	31
6	(*m*-CF_3)C_6H_4	(*p*-PhO)C_6H_4	**28**	37
7	(*m*-CF_3)C_6H_4	(*m*-CF_3)C_6H_4	**29**	41
8	(*m*-Cl)C_6H_4	Ph	**30**	28
9	(*m*-Cl)C_6H_4	(*m*-EtO)C_6H_4	**31**	34
10	(*m*-Cl)C_6H_4	(*m*-Cl)C_6H_4	**32**	31
11	(*m*-Cl)C_6H_4	(*p*-MeO)C_6H_4	**33**	45
12	(*m*-Cl)C_6H_4	(*m*-Br)C_6H_4	**34**	25
13	(*m*-Cl)C_6H_4	(*p*-PhO)C_6H_4	**35**	29
14	(*m*-Cl)C_6H_4	(*m*-CF_3)C_6H_4	**36**	31
15	(*m*-EtO)C_6H_4	Ph	**37**	32
16	(*m*-EtO)C_6H_4	(*m*-EtO)C_6H_4	**38**	30
17	(*m*-EtO)C_6H_4	(*m*-Cl)C_6H_4	**39**	32
18	(*m*-EtO)C_6H_4	(*p*-MeO)C_6H_4	**40**	41
19	(*m*-EtO)C_6H_4	(*m*-Br)C_6H_4	**41**	28
20	(*m*-EtO)C_6H_4	(*p*-PhO)C_6H_4	**42**	30
21	(*p*-EtO)C_6H_4	(*m*-CF_3)C_6H_4	**43**	32
22	Ph	(*m*-EtO)C_6H_4	**44**	34
23	Ph	(*m*-Cl)C_6H_4	**45**	46
24	Ph	(*p*-MeO)C_6H_4	**46**	39
25	Ph	(*m*-Br)C_6H_4	**47**	31
26	Ph	(*p*-PhO)C_6H_4	**48**	38
27	Ph	(*m*-CF_3)C_6H_4	**49**	37
28	(*p*-MeO)C_6H_4	Ph	**50**	32
29	(*p*-MeO)C_6H_4	(*m*-EtO)C_6H_4	**51**	37
30	(*p*-MeO)C_6H_4	(*m*-Cl)C_6H_4	**52**	28
31	(*p*-MeO)C_6H_4	(*p*-MeO)C_6H_4	**53**	38
32	(*p*-MeO)C_6H_4	(*m*-Br)C_6H_4	**54**	35
33	(*m*-Br)C_6H_4	Ph	**55**	29
34	(*m*-Br)C_6H_4	(*m*-EtO)C_6H_4	**56**	24

[a] All reaction were performed on a 0.176 mmol scale. [b] Isolated yields based on the loading of trityl-protected resin **11**.

did not work well when the 2(1*H*)-pyrazinone scaffold has a methyl substituent at position C6.

In summary, we have developed a new transition metal-catalyzed orthogonal solid-phase protocol based on sequential Chan−Lam arylation and Liebeskind−Srogl cross-coupling reaction for the derivatization of the 2(1*H*)-pyrazinone scaffold. The final compounds were released from the solid support by application of a new traceless linking strategy where the sulfur linker is cleaved without prior oxidation resulting in the formation of a new C−C bond. This strategy opens a way for the generation of libraries of 2(1*H*)-pyrazinone analogues.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on Bruker Avance 300 instrument, using $CDCl_3$ as solvent unless otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane, using the residual solvent signal as an internal reference. Mass spectra were recorded with a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150−250 °C, as required. High-resolution EI-mass spectra were performed with a resolution of 10 000. The low-resolution spectra were obtained with a HP5989A MS instrument. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70−230 mesh silica gel (E. M. Merck)) were used. All reagents purchased from commercial sources were used without further purification.

Microwave Irradiation Experiments. All microwave experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus,[12a] with the exception of the removal of the (*p*-methoxy)benzyl group of resin-bound pyrazinone **20** which was done in a MicroSYNTH multimode microwave apparatus (Milestone).[12b] The reactions were carried out in sealed microwave process vials with temperature measurement using an IR sensor on the outer surface of the process vial (CEM) or a fiber optic one (Milestone).

Synthesis of 3,5-Dichloro-2(1*H*)-pyrazinones. The synthesis of the ¸dichloro-2(1*H*)-pyrazinones was carried out according to the procedure described earlier.[13]

3,5-Dichloro-1-(4-methoxybenzyl)-6-methyl-2(1*H*)-pyrazinone (8). mp: 112 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 7.15 (d, 2H, J = 8 Hz), 6.84 (d, 2H, J = 8 Hz), 5.27 (s, 2H), 3.77 (s, 3H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.97, 153.57, 143.98, 136.59, 129.04, 126.31, 124.22, 114.89, 55.73, 50.15, 17.24. MS (EI): *m/z (%)* 298 (4) [MH^+], 121-(100). HRMS (EI) Calcd for $C_{13}H_{12}Cl_2N_2O_2$: 298.0276. Found: 298.0280.

3,5-Dichloro-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (19). The spectral data were reported earlier.[13]

Reaction of 3,5-Dichloropyrazinone 8 with Thiophenol. Thiophenol (1.54 mL, 0.015 mol, 1.5 equiv) and diisopropylethylamine (Hünig's base) (4.13 mL, 0.025 mol, 2.5 equiv) were added to a solution of pyrazinone **8** (2.97 g, 0.01 mmol) in THF (30 mL). The reaction mixture was stirred for 40 min at RT; then the solvent was evaporated under reduced pressure, and the residue was loaded into a column with silica gel and eluted with a *n*-hexane−DCM (1:1) mixture to afford, after concentration in vacuo, 3-(phenylthio)pyrazinone **9**.

5-Chloro-1-(4-methoxybenzyl)-6-methyl-3-(phenylthio)-2(1*H*)-pyrazinone (9). Yield: 3.16 g (85%). mp: 154 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 7.58 (m, 2H), 7.44 (m, 3H), 7.19 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.8 Hz), 5.27 (s, 2H), 3.80 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.82, 155.95, 154.40, 135.51, 130.32, 129.71, 129.51, 129.01, 128.54, 127.18, 127.12, 114.81, 55.73, 48.79, 16.65. HRMS (EI) Calcd for $C_{19}H_{17}O_2N_2SCl$: 372.0699. Found: 372.0694.

Deprotection of 3-(4-(Tritylmercapto)phenylpropionyl AM Resin (11). A suspension of resin **11** (0.2 g, 0.176 mmol, loading 0.88 mmol/g, purchased from NovaBiochem, lot no. A30429), in TFA−TES (95:5) mixture (2 mL) was shaken at RT for 1 h. Then the liquid was filtered off with a polypropylene frit cartridge. The resin was washed with THF (5 mL × 3), THF−MeOH (1:1, v/v, 5 mL × 3), and finally DCM (5 mL × 3) to provide resin **12**, which was used immediately in the next step.

General Procedure for the Coupling of 3,5-Dichloropyrazinones with Thiophenol Resin. 3.5-Dichloropyrazinone (0.70 mmol, 4 equiv) and diisopropylethylamine (Hünig's base) (0.3 mL, 1.76 mol, 10 equiv) were added to a suspension of deprotected resin **12** (0.176 mmol) in THF (3 mL). The reaction mixture was shaken at RT for 12 h or irradiated at 100 °C for 30 min (hold time 2 min, maximum

power 100 W). After the mixture was cooled to ambient temperature, the solvent was filtered off via a polypropylene frit cartridge. The resin was washed as follows: THF (5 mL × 3), THF−MeOH (1:1, v/v, 5 mL × 3), and DCM (5 mL × 3). The obtained resin-bound pyrazinone was dried under vacuum.

Liebeskind−Srogl Cross-Coupling Reaction of 3-(Phenylthio)pyrazinone 9 in Solution Phase. (A) Conventional Conditions. Boronic acid (0.16 mmol, 1.2 equiv), CuTC (0.76 mg, 0.4 mmol, 3 equiv), and $Pd(PPh_3)_4$ (0.009 g, 0.0078 mmol, 6 mol %) were added to a solution of 3-(phenylthio)-pyrazinone **9** (0.048 g, 0.13 mmol) in THF (3 mL). The reaction mixture was heated at 50 °C for 2 days. After it was cooled, the mixture was absorbed on silica gel, and the residue was purified by flash chromatography on silica gel (eluent, DCM) to yield 3-arylpyrazinone **10**.

5-Chloro-1-(4-methoxybenzyl)-6-methyl-3-phenyl-2(1*H*)-pyrazinone (10). Yield: 0.026 g (62%). mp: 113 °C (EtOH). Spectral data were reported earlier.[14]

(B) Microwave Irradiation. Boronic acid (0.16 mmol, 1.2 equiv), CuTC (0.76 mg, 0.4 mmol, 3 equiv), and $Pd(PPh_3)_4$ (0.009 g, 0.0078 mmol, 6 mol %) were added to a solution of 3-(phenylthio)pyrazinone **9** (0.048 g, 0.13 mmol) in THF (3 mL). The reaction mixture was irradiated at 130 °C for 30 min (hold time 2 min, maximum power 250 W). After it was cooled, the mixture was absorbed on silica gel, and the residue was purified by flash chromatography on silica gel (eluent, DCM).

5-Chloro-1-(4-methoxybenzyl)-6-methyl-3-phenyl-2(1*H*)-pyrazinone (10). Yield: 0.023 g (54%).

General Procedure for Liebeskind−Srogl Cross-Coupling Reaction of Resin-Bound Pyrazinones. A boronic acid (0.35 mmol, 2 equiv), CuTC (0.1 g, 0.53 mmol, 3 equiv), and $Pd(PPh_3)_4$ (0.0115 g, 0.01 mmol, 6 mol %) were added to a suspension of resin-bound pyrazinone, obtained from 0.176 mmol of trityl-protected resin **11**, in THF (3 mL). The reaction mixture was shaken at 50 °C for 2 days. After the mixture was cooled to ambient temperature, the solvent was filtered of with a polypropylene frit cartridge, and the resin was washed with THF−MeOH (1:1, v/v, 5 mL × 3) and THF (5 mL x 3). The combined filtrate was absorbed on silica gel. The residue was loaded on a short silica gel plug and eluted with a mixture DCM−*n*-hexane (9:1). The solvent was concentrated in vacuo to provide 3-arylated pyrazinones

3-(3-Bromophenyl)-5-chloro-1-(4-methoxybenzyl)-6-methyl-2(1*H*)-pyrazinone (14). Yield: 0.0405 g (55%). ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H), 8.39 (d, 1H, J = 7.9 Hz), 7.75 (d, 1H, J = 7.9 Hz), 7.32 (m, 1H), 7.18 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 5.36 (s, 2H), 3.78 (s, 3H), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.82, 155.65, 147.06, 137.42, 136.35, 133.43, 132.14, 129.98, 128.78, 127.97, 126.98, 126.87, 122.72, 114.90, 55.73, 49.09, 17.10. MS (EI): *m/z (%)* 418 (2) [MH^+], 121(100).

5-Chloro-3-(3-ethoxyphenyl)-1-(4-methoxybenzyl)-6-methyl-2(1*H*)-pyrazinone (15). Yield: 0.015 g (22%). ^{1}H NMR ($CDCl_3$): δ 8.01 (m, 2H), 7.36 (m, 1H), 7.18 (d, 2H, J = 8.2 Hz), 7.01 (d, 1H, J = 8.2 Hz), 6.87 (d, 2H, J = 8.2 Hz), 5.33 (s, 2H), 4.12 (q, 2H, J = 6.4 Hz), 3.79 (s, 3H), 2.48 (s, 3H), 1.44 (t, 3H, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$): δ 159.71, 159.13, 155.81, 148.60, 136.81, 135.47, 129.43, 128.76, 127.15, 127.14, 121.94, 117.46, 114.93, 114.81, 63.94, 55.72, 48.92, 17.46, 15.26. HRMS (EI) Calcd for $C_{21}H_{21}O_3N_2Cl$: 384.1240. Found: 384.1239.

5-Chloro-1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-6-methyl-2(1*H*)-pyrazinone (16). Yield: 0.023 g (35%). ^{1}H NMR ($CDCl_3$): δ 8.45 (d, 2H, J = 9.1 Hz), 7.19 (d, 2H, J = 9.1 Hz), 6.96 (d, 2H, J = 9.1 Hz), 6.87 (d, 2H, J = 9.1 Hz), 5.35 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 161.72, 159.68, 133.91, 131.20, 129.53, 129.01, 128.73, 128.34, 127.27, 114.81 (×2), 113.87, 55.71, 48.87, 30.10, 17.40. MS (EI): *m/z (%)* 370 (2) [MH^+], 121 (100).

3-Phenyl-5-chloro-1-(3-trifluoromethylphenyl)-2(1*H*)-pyrazinone (23). mp: 133−134 °C (DCM−hexane) (29%). ^{1}H NMR ($CDCl_3$): δ 8.4−8.36 (m, 2H), 7.71−7.67 (m, 4H), 7.48−7.41 (m, 3H), 7.30 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 154.1, 153.9, 139.7, 134.8, 132.9, 132.5, 131.5, 130.7,129.9, 129.8, 128.6, 127.3, 126.7, 125.2, 123.6, 121.8. HRMS (EI) Calcd for $C_{17}H_{10}ClF_3N_2O$: 350.0433. Found: 350.0430.

3-(3-Ethoxyphenyl)-5-chloro-1-(3-triflurometHylphenyl)-2(1*H*)-pyrazinone (24). mp: 119−120 °C (DCM−hexane) (31%). ^{1}H NMR ($CDCl_3$): δ 8.0−7.97 (m, 2H), 7.78−7.64 (m, 4H), 7.45−7.37 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 159.1, 153.4, 139.7, 136.0, 132.9, 130.8, 129.9, 129.5, 127.2, 126.7, 125.3, 123.7, 123.6, 122.3, 121.8, 118.6, 115.1, 63.9, 15.1. HRMS (EI) Calcd for $C_{19}H_{14}ClF_3N_2O_2$: 394.0695. Found: 394.0684.

3-(3-Chlorophenyl)-5-chloro-1-(3-triflurometHylphenyl)-2(1*H*)-pyrazinone(25). mp: 100−101 °C (DCM−hexane) (29%). ^{1}H NMR ($CDCl_3$): δ 8.4 (s, 1H), 8.33−8.30 (d, J = 8.2 Hz, 1H), 7.71−7.67 (m, 4H), 7.48−7.41 (m, 3H), 7.30 (s, 1H). ^{13}C NMR ($CDCl_3$): 153.9, 152.0, 139.5, 136.4, 134.7, 133.0, 132.5, 131.5, 130.8, 129.9, 129.6, 127.9, 127.3, 126.8, 125.3, 123.5, 121.7. HRMS (EI) Calcd for $C_{17}H_9Cl_2F_3N_2O$: 384.0040. Found: 384.0037.

3-(4-Methoxyphenyl)-5-chloro-1-(3-triflurometHylphenyl)-2(1*H*)-pyrazinone (26). mp: 157−158 °C (DCM−hexane) (38%). ^{1}H NMR ($CDCl_3$): δ 8.37−8.34 (m, 2H), 7.66−7.55 (m, 3H), 7.38−7.35 (m, 1H) 7.12 (s, 1H) 6.86−6.83 (m, 2H). ^{13}C NMR ($CDCl_3$): 162.0, 158.6, 152.5, 139.4, 131.9, 131.3, 130.2, 129.5, 127.6, 127.1, 126.8, 126.1, 123.6, 123.2, 123.1, 114.0, 113.5, 55.2. HRMS (EI) Calcd for $C_{18}H_{12}ClF_3N_2O_2$: 380.0539. Found: 380.0523.

3-(3-Boromophenyl)-5-chloro-1-(3-triflurometHylphenyl)-2(1*H*)-pyrazinone (27). mp: 97−98 °C (DCM−hexane) (31%). ^{1}H NMR ($CDCl_3$): δ 8.58−8.57 (m, 1H), 8.38−8.35 (m, 1H), 7.78−7.66 (m, 4H) 7.61−7.58 (m, 1H) 7.33−7.28 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 153.4, 151.4, 139.0, 136.1, 133.9, 132.5, 132.1, 130.3, 129.6, 129.4, 127.8, 126.8, 126.4, 125.6, 123.1, 122.3, 121.3. HRMS (EI) Calcd for $C_{17}H_9ClF_3N_2OBr$: 427.9539. Found: 427.9555.

3-(4-Phenoxyphenyl)-5-chloro-1-(3-triflurometHylphenyl)-2(1*H*)-pyrazinone (28). mp: 131−132 °C (DCM−hexane) (37%). ^{1}H NMR ($CDCl_3$): δ 8.43−8.40 (m, 1H), 7.74−7.64 (m, 3H), 7.55−7.41 (m, 2H), 7.37−7.28 (m, 2H), 7.23−7.22 (m, 1H), 7.17−7.1 (m, 1H), 7.06−6.99 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 161.2, 160.1, 157.0, 156.5, 155.9,

153.6, 152.4, 139.3, 138.6, 131.3, 130.2, 129.8, 129.7, 129.6, 129.4, 129.2, 129.0,128.0, 126.9, 124.2, 123.2, 119.7, 118.8, 117.5. HRMS (EI) Calcd for $C_{23}H_{14}ClF_3N_2O_2$: 442.0696. Found: 442.0695.

3-(3-Trifluromethylphenyl)-5-chloro-1-(3-trifluromethylphenyl)-2(1*H*)-pyrazinone (29). mp: 121−122 °C (DCM−hexane) (41%). ^{1}H NMR ($CDCl_3$): δ 8.74 (s, 1H), 8.62−8.60 (d, J = 8.22 Hz, 1H), 7.79−7.68 (m, 5H), 7.59−7.54 (m, 1H), 7.37 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 153.5, 151.5, 139.0, 134.9, 134.4, 130.9, 130.4, 129.4, 128.6, 127.4, 126.9, 126.5, 126.2, 125.9, 125.7, 124.9, 123.1, 122.0, 121.3. HRMS (EI) Calcd for $C_{18}H_9ClF_6N_2O$: 418.0308. Found: 418.0313.

3-Phenyl-5-chloro-1-(3-chlorophenyl)-2(1*H*)-pyrazinone (30). mp: 114−115 °C (DCM−hexane) (28%). ^{1}H NMR ($CDCl_3$): δ 8.39−8.36 (m, 2H), 7.49−7.27 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 154.0, 153.7, 140.2, 135.7, 134.9, 131.5, 131.0, 130.1, 129.8, 128.6, 127.2, 126.8, 125.5, 124.6. HRMS (EI) Calcd for $C_{16}H_{10}Cl_2N_2O$: 316.0170. Found: 316.0159.

3-(3-Chlorophenyl)-5-chloro-1-(3-chlorophenyl)-2(1*H*)-pyrazinone (31). mp: 117 °C (DCM−hexane) (31%). ^{1}H NMR ($CDCl_3$): δ 8.44 (s, 1H), 8.34−8.31 (d, J = 8.22, 1H), 7.49−7.25 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 153.9, 151.9, 140.0, 136.4, 135.8, 134.7, 131.4, 131.1, 130.3, 129.8, 129.7, 127.9, 127.1, 126.8, 126.2, 124.6. HRMS (EI) Calcd for $C_{16}H_9Cl_3N_2O$: 349.9780. Found: 349.9787.

3-(3-Ethoxyphenyl)-5-chloro-1-(3-chlorophenyl)-2(1*H*)-pyrazinone (32). mp: 145−146 °C (DCM−hexane) (34%). ^{1}H NMR ($CDCl_3$): δ 8.0−7.9 (m, 2H), 7.47−7.27 (m, 5H), 7.03−7.0 (m, 2H), 4.1−4.0 (q, J = 7.3 Hz, 2H,), 1.44−1.39 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 158.8, 153.8, 153.0, 139.9, 135.8, 135.5, 130.8,129.9, 129.2, 126.8, 126.6, 125.3, 124.4, 122.0, 118.3, 114.7, 63.7, 14.9. HRMS (EI) Calcd for $C_{18}H_{14}Cl_2N_2O_2$: 360.0432. Found: 360.0438.

3-(4-Methoxyphenyl)-5-chloro-1-(3-chlorophenyl)-2(1*H*)-pyrazinone (33). mp: 123−124 °C (DCM−hexane) (45%). ^{1}H NMR ($CDCl_3$): δ 8.44−8.43 (m, 2H), 7.55−7.19 (m, 5H), 6.98−6.92 (m, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 162.0, 153.7, 139.9, 135.2, 131.3, 130.6,129.6, 128.7, 128.1, 127.7, 127.3, 126.5, 124.3, 123.9, 114.1, 113.5, 55.3. HRMS (EI) Calcd for $C_{17}H_{12}Cl_2N_2O_2$: 346.0275. Found: 346.0274.

3-(3-Bromophenyl)-5-chloro-1-(3-chlorophenyl)-2(1*H*)-pyrazinone (34). mp: 132−133 °C (DCM−hexane) (25%). ^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1H), 8.38−8.36 (d, J = 8.2, 1H), 7.6−7.57 (d, J = 8.2, 1H), 7.49−7.46 (m, 3H), 7.35−7.28 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 153.6, 151.5, 139.7, 136.4, 135.5, 134.0, 132.2, 130.8, 130.1, 129.8, 128.0, 126.8, 126.5, 125.9, 124.3, 122.5. HRMS (EI) Calcd for $C_{16}H_9ClN_2$-OBr: 393.9275. Found: 393.9274.

3-(4-Phenoxyphenyl)-5-chloro-1-(3-chlorophenyl)-2(1*H*)-pyrazinone (35). mp: 88−89 °C (DCM−hexane) (29%). ^{1}H NMR ($CDCl_3$): δ 8.44 (s, 1H), 8.41(s, 1H), 7.47−7.46 (m, 4H), 7.39−7.33 (m, 3H), 7.18−7.13 (m, 1H), 7.08−1.0 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 160.3, 156.2, 153.9, 152.6, 140.0, 135.4, 131.5, 130.8, 130.0, 129.9, 129.4, 126.9, 126.6, 124.6, 124.4, 124.2, 119.9, 117.7. HRMS (EI) Calcd for $C_{22}H_{14}Cl_2N_2O_2$: 408.0432. Found: 408.0429.

3-(3-Trifluromethylphenyl)-5-chloro-1-(3-chlorophenyl)-2(1*H*)-pyrazinone (36). mp: 82−83 °C (DCM−hexane) (31%). ^{1}H NMR ($CDCl_3$): δ 8.75 (s, 1H), 8.63−8.6 (d, J = 7.2, 1H), 7.73−7.71 (d, J = 7.2, 1H), 7.59−7.54 (m, 1H), 7.5 (s, 3H), 7.48 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 153.9, 151.8, 139.9, 135.8, 135.4, 132.8, 131.2, 130.8, 130.4, 129.0, 127.8, 127.2, 126.8, 126.6, 126.4, 126.1, 124.6. HRMS (EI) Calcd for $C_{17}H_9Cl_2N_2OF_3$: 384.0044. Found: 384.0025.

3-Phenyl-5-chloro-1-(3-ethoxyphenyl)-2(1*H*)-pyrazinone (37). mp: 101−103 °C (DCM−hexane) (32%). ^{1}H NMR ($CDCl_3$): δ 8.41−8.38 (m, 2H), 7.44−7.37 (m, 4H), 7.3 (s, 1H), 7.0−6.94 (m, 3H) 4.08−4.01 (q, J = 7.3 Hz, 2H,), 1.44−1.39 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): 159.7, 153.9, 153.0, 139.9, 134.7,130.8, 130.4, 129.3, 128.1, 126.3, 125.8, 117.7, 115.8, 112.2, 63.9, 14.6. HRMS (EI) Calcd for $C_{18}H_{15}ClN_2O_2$: 326.0821. Found: 326.0829.

3-(3-Ethoxyphenyl)-5-chloro-1-(3-ethoxyphenyl)-2(1*H*)-pyrazinone (38). mp: 119−120 °C (DCM−hexane) (30%). ^{1}H NMR ($CDCl_3$): δ 8.01 (m, 2H), 7.44−7.30 (m, 3H), 7.01−6.94 (m, 4H), 4.09−4.04 (q, J = 7.3 Hz, 2H,), 1.44−1.38 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): 159.8, 158.7, 153.9, 152.6, 140.0, 135.9,130.4, 129.0, 126.3, 125.8, 121.9, 118.1, 117.7, 115.8, 114.5, 112.2, 63.9, 63.6, 14.8, 14.6. HRMS (EI) Calcd for $C_{20}H_{19}ClN_2O_3$: 370.1084. Found: 370.1088.

3-(3-Chlorophenyl)-5-chloro-1-(3-ethoxyphenyl)-2(1*H*)-pyrazinone (39). mp: 99−100 °C (DCM−hexane) (32%). ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H), 8.35−8.34 (d, J = 8.2, 1H), 7.44−7.32 (m, 4H), 7.0−6.9 (m, 3H), 4.08−4.01 (q, J = 7.3 Hz, 2H,), 1.44−1.39 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 160.2, 154.1, 151.5, 140.1, 136.7, 134.6, 131.1, 130.8, 129.7, 129.6, 127.8, 126.9, 126.7, 118.0, 116.3, 112.6, 64.3, 15.0. HRMS (EI) Calcd for $C_{18}H_{14}Cl_2N_2O_2$: 360.0432. Found: 360.0435.

3-(4-Methoxyphenyl)-5-chloro-1-(3-ethoxyphenyl)-2(1*H*)-pyrazinone (40). mp: 111−112 °C (DCM−hexane) (41%). ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H), 8.44 (s, 1H), 7.42−7.37 (m, 1H), 7.0 (s, 1H) 6.99−6.91 (m, 5H), 4.08−4.01 (q, J = 7.3 Hz, 2H), 3.84 (s, 3H), 1.43−1.38 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.2, 160.1, 154.3, 152.6, 140.5, 131.7,130.7 127.9, 126.8, 125.0, 118.2, 116.1, 113.9, 112.7, 64.2, 55.7, 15.0. HRMS (EI) Calcd for $C_{19}H_{17}ClN_2O_3$: 356.0927. Found: 356.0911.

3-(3-Bromophenyl)-5-chloro-1-(3-ethoxyphenyl)-2(1*H*)-pyrazinone (41). mp: 85−86 °C (DCM−hexane) (28%). ^{1}H NMR ($CDCl_3$): δ 8.6 (s, 1H), 8.6−8.4 (d, J = 8.2, 1H), 7.59−7.56 (d, J = 8.2, 1H), 7.44−7.39 (m, 1H), 7.34−7.32 (m, 1H), 7.3 (s, 1H), 7.02−6.9 (m, 3H), 4.09−4.02 (q, J = 7.3 Hz, 2H,), 1.44−1.40 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 160.2, 154.1, 151.5, 140.1, 136.9, 134.0, 132.5, 130.8, 130.0, 128.3, 126.9, 126.7, 118.0, 116.3, 112.6, 64.3, 15.0. HRMS (EI) Calcd for $C_{18}H_{14}ClBrN_2O_2$: 403.9927. Found: 403.9926.

3-(4-Phenoxyphenyl)-5-chloro-1-(3-ethoxyphenyl)-2(1*H*)-pyrazinone (42). mp: 85−86 °C (DCM−hexane) (30%). ^{1}H NMR ($CDCl_3$): δ 8.46−8.43 (m, 2H), 7.58−7.56 (m, 1H), 7.45−7.33 (m, 3H), 7.26 (s, 1H), 7.16−7.14 (m, 1H), 7.02−6.9 (m, 6H), 4.08−4.01 (q, J = 7.3 Hz, 2H,), 1.44−1.39 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): 160.7, 159.8, 159.7, 159.6, 156.1, 153.9, 152.1, 139.9, 135.0, 131.3, 130.3, 129.8, 129.5, 129.1, 126.3, 125.1, 123.9, 121.5, 119.6, 117.5,

115.7, 112.2, 63.8, 14.6. HRMS (EI) Calcd for $C_{24}H_{19}ClN_2O_3$: 418.1084. Found: 418.1070.

3-(3-Trifluromethylphenyl)-5-chloro-1-(3-ethoxyphenyl)-2(1*H*)-pyrazinone (43). mp: 90−91 °C (DCM−hexane) (32%). ^{1}H NMR ($CDCl_3$): δ 8.46−8.42 (d, J = 9.12 Hz, 1H), 7.45−7.33 (m, 3H), 7.16−7.12 (m, 1H), 7.07−6.94 (m, 4H), 4.08−4.01 (q, J = 7.3 Hz, 2H,), 1.43−1.39 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 159.7, 156.1, 153.9, 152.1, 140.0, 135.0, 131.3, 130.4, 129.8, 129.5, 129.2, 126.4, 125.2, 123.9, 119.6, 117.6, 117.4, 115.7, 112.2, 63.9, 14.6. HRMS (EI) Calcd for $C_{19}H_{14}ClF_3N_2O_2$: 394.0695. Found: 394.0699.

3-(3-Ethoxyphenyl)-5-chloro-1-phenyl-2(1*H*)-pyrazinone (44). mp: 124−125 °C (DCM−hexane) (34%). ^{1}H NMR ($CDCl_3$): δ 8.01−7.99 (m, 2H), 7.55−7.30 (m, 6H), 7.02−6.98 (m, 1H), 4.11−4.04 (q, J = 7.3 Hz, 2H,), 1.42−1.38 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 158.2, 153.5, 152.1, 138.5, 135.4,129.2, 129.1 129.0, 128.6, 125.9, 125.4, 125.3 121.4, 117.6, 114.1, 63.1, 14.3. HRMS (EI) Calcd for $C_{18}H_{15}ClN_2O_2$: 326.0822. Found: 326.0816.

3-(3-Chlorophenyl)-5-chloro-1-phenyl-2(1*H*)-pyrazinone (45). mp: 142−143 °C (DCM−hexane) (46%). ^{1}H NMR ($CDCl_3$): δ 8.46−8.45 (m, 1H), 8.35−8.32 (d, J = 8.22 Hz, 1H) 7.55−7.48 (m, 3H), 7.45−7.40 (m, 3H), 7.37−7.32 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 153.4, 150.7, 138.3, 135.7,133.7, 130.3, 129.2, 129.1, 128.9, 128.8, 126.9, 126.0, 125.4. HRMS (EI) Calcd for $C_{16}H_{10}Cl_2N_2O$: 316.0170. Found: 316.0167.

3-(4-Methoxyphenyl)-5-chloro-1-phenyl-2(1*H*)-pyrazinone (46). mp: 171−172 °C (DCM−hexane) (39%). ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1H), 8.45 (s, 1H) 7.52−7.46 (m, 3H), 7.42−7.40 (m, 2H), 6.94 (d, J = 9.15 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 161.4, 153.5, 151.8, 138.7, 130.8, 129.1, 128.8, 127.0, 126.0, 125.5, 124.1 113.0, 54.9. HRMS (EI) Calcd for $C_{17}H_{13}ClN_2O_2$: 312.0666. Found: 312.0660.

3-(3-Bromophenyl)-5-chloro-1-phenyl-2(1*H*)-pyrazinone (47). mp: 120−121 °C (DCM−hexane) (31%). ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H), 8.39−8.36 (d, J = 8.22 Hz, 1H) 7.57−7.48 (m, 4H), 7.42−7.39 (m, 2H), 7.33−7.28 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 153.3, 150.5, 138.3, 136.0, 133.2, 131.6, 129.2, 129.1, 127.4, 126.0, 125.9, 125.3, 121.8. HRMS (EI) Calcd for $C_{16}H_{10}ClBrN_2O$: 359.9665. Found: 356.9673.

3-(4-Phenoxyphenyl)-5-chloro-1-phenyl-2(1*H*)-pyrazinone (48). mp: 98−99 °C (DCM−hexane) (38%). ^{1}H NMR ($CDCl_3$): δ 8.37 (s, 1H), 8.34 (s, 1H) 7.49−7.45 (s, 1H), 7.43−7.27 (m, 6H), 7.17 (s, 2H) 7.08−7.02 (m, 1H), 6.98−6.91 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 159.8, 156.0, 153.9, 152.1, 138.9, 138.3, 135.0, 131.3, 129.8, 129.6, 129.4, 129.1, 127.6, 126.8, 126.4, 125.8, 125.6, 125.1, 123.9, 119.6, 117.5. HRMS (EI) Calcd for $C_{22}H_{15}ClN_2O_2$: 374.0822. Found: 374.0813.

3-(3-Trifluromethylphenyl)-5-chloro-1-phenyl-2(1*H*)-pyrazinone (49). mp: 161−162 °C (DCM−hexane) (37%). ^{1}H NMR ($CDCl_3$): δ 8.78 (s,1H), 8.63−8.61 (d, J = 7.29 Hz, 1H), 7.71−7.69 (1, J = 8.22 Hz, 1H) 7.57−7.46 (m, 4H), 7.43−7.37 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 153.4, 150.6, 138.3, 134.8, 131.9, 130.3, 129.9, 129.3, 128.1, 126.8, 126.7, 126.3, 126.0, 125.8, 125.3, 125.2, 121.7,121.1. HRMS (EI) Calcd for $C_{17}H_{10}ClF_3N_2O$: 350.0434. Found: 350.0428.

3-Phenyl-5-chloro-1-(4-methoxyphenyl)-2(1*H*)-pyrazinone (50). mp: 165−166 °C (DCM−hexane) (31%). ^{1}H NMR ($CDCl_3$): δ 8.46 (d, 2H, J = 9.0 Hz), 7.58−7.40 (m, 5H), 7.00−6.91 (m, 3H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 160.5, 153.3, 152.9, 140.5, 130.4, 129.7, 129.2 (×2), 128.6, 128.3 (×2), 127.0, 126.4 (×2), 111.2 (×2), 54.6. HRMS (EI) Calcd for $C_{17}H_{13}N_2O_2Cl$: 312.0666. Found: 312.0666.

3-(3-Ethoxyphenyl)-5-chloro-1-(4-methoxyphenyl)-2(1*H*)-pyrazinone (51). mp: 129−130 °C (DCM−hexane) (37%). ^{1}H NMR ($CDCl_3$): δ 8.45−8.42 (m, 2H), 7.38 (m, 1H), 7.07 (s, 1H), 7.0 (m, 5H), 4.09−4.03 (q, 2H, J = 7.3 Hz), 3.81 (s, 3H), 1.43−1.37 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 161.9, 159.7, 154.5, 152.8, 139.8, 131.2 (×2), 130.3, 129.6, 126.8, 124.1, 118.4, 116.3, 113.5, 112.8 (×2), 63.7, 55.6, 14.8. HRMS (EI) Calcd for $C_{19}H_{17}N_2O_3Cl$: 356.0928. Found: 356.0913.

3-(3-Chlorophenyl)-5-chloro-1-(4-methoxyphenyl)-2(1*H*)-pyrazinone (52). mp: 134−135 °C (DCM−hexane) (28%). ^{1}H NMR ($CDCl_3$): δ 8.48 (d, 2H, J = 8.7 Hz), 7.52−7.70 (m, 3H), 7.30 (m, 1H), 7.12 (s, 1H), 6.85 (m, 2H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 162.2, 159.5, 153.6, 151.9, 139.8, 135.9, 131.2, 130.1, 129.6, 128.4, 128.1, 127.9, 126.7 (×2), 113.8 (×2), 55.4. HRMS (EI) Calcd for $C_{17}H_{12}N_2O_2Cl_2$: 346.0276. Found: 346.0273.

3-(3-Methoxyphenyl)-5-chloro-1-(4-methoxyphenyl)-2(1*H*)-pyrazinone (53). mp: 147−148 °C (DCM−hexane) (38%). ^{1}H NMR ($CDCl_3$): δ 8.47 (m, 2H), 7.42 (d, 2H, J = 9.1 Hz), 7.12−6.98 (m, 5H), 3.86 (s, 3H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 161.2, 159.7, 153.7, 153.0, 149.4, 138.7, 130.1 (×2), 128.5, 126.7 (×2), 124.6, 115.1 (×2), 113.2 (×2), 55.6, 54.9. HRMS (EI) Calcd for $C_{18}H_{15}N_2O_3Cl$: 342.0771. Found: 342.0770.

3-(3-Bromophenyl)-5-chloro-1-(4-methoxyphenyl)-2(1*H*)-pyrazinone (54). mp: 171−172 °C (DCM−hexane) (35%). ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1H), 8.37 (d, 2H, J = 8.9 Hz), 7.55−7.40 (3H), 7.12 (m, 3H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 160.1, 153.4, 153.0, 150.7, 138.1, 132.8, 131.5, 130.3, 129.1, 128.7, 128.3, 127.6 (×2), 125.3, 124.2, 112.3 (×2), 55.7. HRMS (EI) Cacd for $C_{17}H_{12}N_2O_2BrCl$: 389.9771. Found: 389.9767.

3-Phenyl-5-chloro-1-(3-bromophenyl)-2(1*H*)-pyrazinone (55). mp: 132−133 °C (DCM−hexane) (29%). ^{1}H NMR ($CDCl_3$): δ 8.62 (s, 1H), 8.40 (m, 1H), 7.47−7.13 (m, 6H), 7.09 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 153.2, 150.9, 148.0, 139.4, 130.6, 130.1, 129.8 (×2), 129.5, 128.6 (×2), 127.4, 126.5, 125.7, 122.4, 121.1. HRMS (EI) Calcd for $C_{16}H_{10}N_2OBrCl$: 359.9665. Found: 359.9670.

3-(3-Ethoxyphenyl)-5-chloro-1-(3-bromophenyl)-2(1*H*)-pyrazinone (56). mp: 143−145 °C (DCM−hexane) (24%). ^{1}H NMR ($CDCl_3$): δ 8.58 (s, 1H), 8.35 (m, 1H), 7.70 (d, 1H, J = 8.3 Hz), 7.44−19 (m, 4H), 7.12 (m, 2H), 4.15−4.09 (q, 2H, J = 7.2 Hz), 1.41−1.35 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 161.3, 153.2, 152.2, 142.1, 132.2, 130.7, 130.5, 129.8, 128.3, 127.4, 126.7, 125.0, 121.6, 117.9, 116.2, 113.6. HRMS (EI) Calcd for $C_{18}H_{14}N_2O_2BrCl$: 403.9927. Found: 403.9921.

General Procedure for the Deprotection of the (*p*-Methoxy)benzyl Group at Position N1 of the Pyrazinone Ring on the Solid Support. A suspension of pyrazinone **20**, obtained from 0.176 mmol of trityl protected resin **11**, in a mixture of DCM−TFA (2:1, v/v) was irradiated at 120

°C for 40 min (hold time 2 min, maximum power 120 W). After the mixture was cooled to ambient temperature, the solvent was filtered off with a polypropylene frit cartridge, and the resin was washed with DCM (5 mL × 3), MeOH (5 mL × 3), and DCM (5 mL × 3). The resulting resin **21** was dried under vaccum.

General Procedure of Chan−Lam Coupling of Pyrazinone 21 with Boronic Acids On Solid Support. Boronic acid (0.53 mmol, 3 equiv), $Cu(OAc)_2$ (0.096 g, 0.53 mmol, 3 equiv), triethylamine (0.073 mL, 0.53 mmol, 3 equiv), and pyridine (0.087 mL, 1.06 mmol, 6 equiv) were added to a suspension of resin-bound pyrazinone **21**, obtained starting from 0.176 mmol of trityl-protected resin **11**, in DCM (3 mL). The reaction mixture was shaken at RT for 24 h in an ambient atmosphere; the solvent was then filtered off with a polypropylene frit cartridge, and the resin was washed with DCM (5 mL × 3), THF−(aq) NH_3 (1:1, v/v, 5 mL × 3), THF−H_2O (1:1, v/v, 5 mL × 3), THF (5 mL × 3), and DCM (5 mL × 3). The whole procedure was repeated once. The resulting resin-bound pyrazinone **22** was dried under vacuum.

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Supporting Information Available. ^{1}H NMR spectra for compounds **23**−**52**. This material is available free of charge via the Internet at http://pubs.acs.org.

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