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Orthogonally Reacting Boron Coupling Reagents: A Novel Multicomponent-Multicatalytic Reaction [(MC)²R] of Dichlorovinylpyrazine

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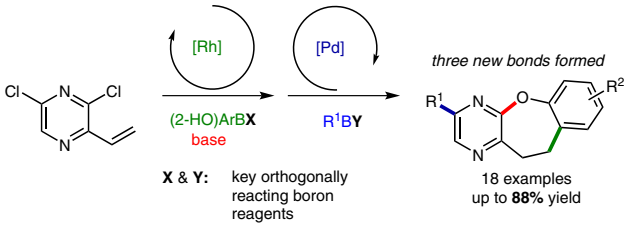

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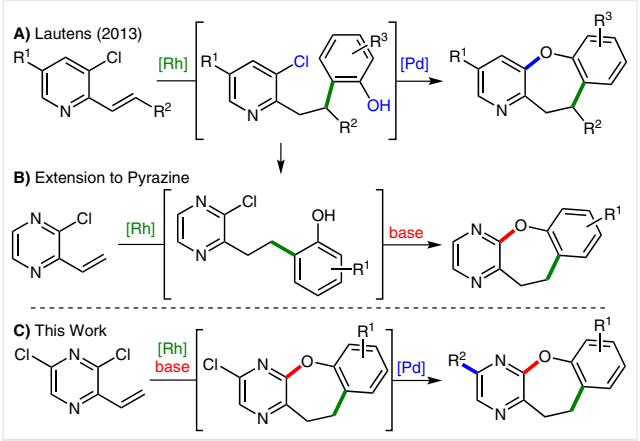
Abstract The results presented herein illustrate the feasibility of two orthogonally reacting boron coupling reagents as a new control strategy in multicomponent-multicatalytic reaction [(MC)²R] chemistry. A process employing dichlorovinylpyrazine merging the rhodium-catalyzed hydroarylation with the Suzuki coupling has been discovered. Three new bonds are formed in a one-pot, one-step process efficiently providing highly substituted diaza-dihydrodibenzoxepine products.

Key words rhodium, palladium, domino reactions, multicomponent reactions, homogeneous catalysis

Multicatalytic reactions are an emerging field in organic synthesis. The combination of transition-metal catalysis with biocatalysis,[1] Brönsted acid catalysis,[2] organocatalysis,[3] and other transition metals[4] have all been demonstrated. Harnessing the power of multiple catalysts leads to rapid generation of molecular complexity and inherent time and cost efficiency due to the lack of isolation/purification of intermediates. A major concern however is the increased chance of unwanted pathways associated with these systems. These reactions thus require exceptional chemoselectivity in order to influence the reactivity. Factors including substrate design such as latent functionality[5] and substrate rigidity,[6] and reactions rates[7] have all served as control strategies in multicomponent-multicatalytic reaction [(MC)²R] chemistry.

To date, (MC)²R chemistry combining metal-catalyzed reactions utilizing nearly identical reagents has not been addressed and reagents have yet to be recognized as viable control elements. Precedence for reagent control can be found in the work of Burke, Molander, and Watson, among others.[8] This work inspired us to develop the first reagent-based control strategy in (MC)²R chemistry.

We herein report a novel (MC)²R of a vinyl pyrazine substrate combining a Rh-catalyzed conjugate addition,[9] a base-mediated S_NAr reaction, and a Pd-catalyzed Suzuki coupling, employing a pair of orthogonally reacting boron coupling reagents. The reaction features three bond-forming processes and readily generates highly substituted pyrazines in one pot.

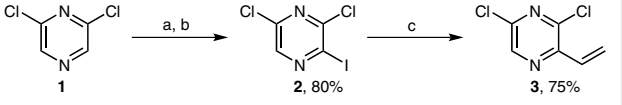


Scheme 1 Previous methodology and new (MC)²R methodology

Motivated by previous work in our group on the domino Rh-catalyzed hydroarylation and Pd-catalyzed C–O coupling of vinyl pyridine (Scheme 1,A),[7] efforts toward the expansion of this methodology revealed the analogous products for pyrazines formed without palladium. The C–O bond formation occurred instead via a base-mediated S_NAr reaction (Scheme 1,B). This spurred efforts toward incorporating a third reaction in the sequence. Due to the presence of the pyrazine scaffold in natural products and the ready availability of halogenated pyrazines (See Scheme 2 for the synthesis of the pyrazine starting material used herein), the

Suzuki coupling has become one of the most versatile and flexible methods for the functionalization of pyrazines and thus was chosen to complete the sequence.[10]

Inclusion of a Suzuki coupling presented substantial additional challenges. The Suzuki coupling and Rh-catalyzed conjugate addition both employ boronic acid coupling partners. A number of selectivity issues arise from the combination of these two reactions. We sought to address this via an investigation of relative reactivities of boron reagents in the conjugate addition (Table 1). We reasoned selectivity would only need to be achieved in the initial Rh-catalyzed reaction, allowing for quick consumption of one boron species, leaving the second for Suzuki coupling. We set up competition experiments to study the relative rates of common boron-based reagents in the conjugate addition to dichlorovinylpyrazine **3**. The investigation revealed some useful trends.



a) LiTMP (1.2 equiv), THF, –78 °C. b) I_2 (1.2 equiv), THF, –78 °C. c) $Pd(dppf)Cl_2$ (5 mol%), vinylBF_3K (1 equiv), Cs_2CO_3 (3 equiv), THF/H_2O (10:1), 40 °C.

Scheme 2 Synthesis of starting material **3**

We initially set out to elucidate the effect of the *ortho*-OH group on the reactivity (Table 1, diagonal entries). We found that the substituent had a slight to modest inhibitory effect on most coupling partners. More interestingly, a moderate acceleration was observed only in the case of pinacol esters. If the BX partner is kept constant, in all cases, we observe a reactivity trend for the BY partner where acid > MIDA > BF_3K. Similarly, when the BY partner is kept constant, the same reactivity trend is observed for the BX partner (Table 1). The BPin esters do not fall neatly into any pattern. The Ph-BPin ester was the least reactive of any species tested whereas the *ortho*-HO-BPin was the most reactive. These findings also show that the *ortho*-OH group plays a significant role in activating the ester. The structures of the boron reagents are shown in Figure 1.

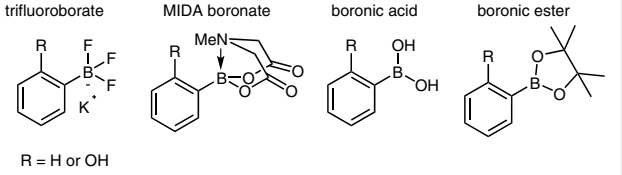
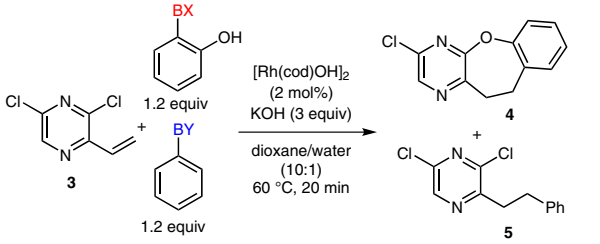


Figure 1 Structures of the boron coupling reagents used

To better understand these trends, we turned to the properties of the boron reagents. It is important to note that MIDA boronates and trifluoroborates are not active coupling reagents, but slowly hydrolyze to give boronic acids in situ.[11] Hence, we can attribute the lower reactivity of these reagents to the initial slow hydrolysis step. The specific activation mode of boronic esters remains elusive, but they are thought to react directly in ester form.[12] We thus focused on the differences between boronic acids and esters.

Table 1 Competition Experiments of Boron Reagents in the Rh-Catalyzed Hydroarylation[a]



BY / BX	BF_3K	BMIDA	$B(OH)_2$	BPin
BF_3K	0.27:1	0.05:1	0.02:1	2.57:1
BMIDA	1:1	0.35:1	0.02:1	1.53:1
$B(OH)_2$	2.30:1	2.04:1	0.59:1	2.62:1
BPin	>25:1	20:1	1.31:1	1.79:1

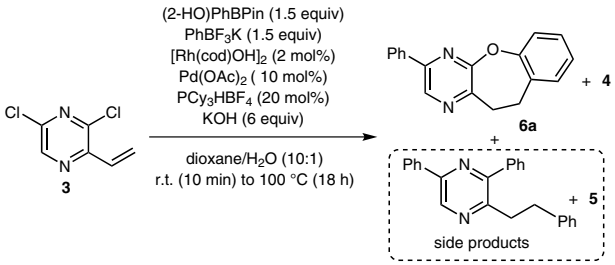
[a] Normalized ratios (given as **4**:**5**) determined by ^1H NMR analysis of the reaction mixture.

The transmetalation step in the hydroarylation, which is rate determining, is known to involve the reaction of the boron reagent with a [Rh]–OH species forming a tetra-coordinate sp^3 boron.[13] This process is accelerated by initial quaternization of boron with a base.[14] The propensity of boron to undergo hybridization from sp^2 to sp^3 thus affects the rate of transmetalation. Increased steric bulk and decreased Lewis acidity of boronic esters pushes the equilibrium toward sp^2 thus disfavoring transmetalation.[15] This may explain the low reactivity of Ph-BPin but does not explain the sharp increase observed for the hydroxy-substituted reagent.

Having established suitable partners, we moved to the combination of all reactions in a one-pot, one-step process. Our initial conditions provided the desired product **6a** in 40% yield. Other species present in appreciable amounts included the product of hydroarylation and cyclization **4** and the two side products shown in Table 2. Each species was distinguishable in the crude ^1H NMR by the unique chemical shifts of the single protons on their pyrazine rings. Interestingly, no product from Suzuki coupling of the excess BPin was ever observed.

Selected optimization experiments are detailed in Table 2, presented as changes from the initial conditions. It should be noted that conditions in bold were adopted for all following entries.

Table 2 Selected Optimization Experiments



Entry	Change	Yield of **6a** (%)[a]	Yield of **4** (%)[a]	Yield of side products (%)[a]
1	N/A	40	0	14
2	Cs_2CO_3 (6 equiv)	5	7	53
3	KOH (3 equiv) + Cs_2CO_3 (3 equiv)	55	0	19
4	CsOH (6 equiv)	58	4	7
5	r.t. (30 min)	60	8	15
6	r.t. (60 min)	60	0	9
7	BF_3K (1.75 equiv)	60	4	17
8	BF_3K (2 equiv)	63	0	15
9	BF_3K (2.5 equiv)	50	0	25
10	$Pd(OAc)_2$ (5%)	64	0	7
11	$Pd(OAc)_2$ (2.5%)	77	0	7
12	$Pd(OAc)_2$ (1%)	18	20	27
13	BPin (1.75 equiv)	80	2	5
14	BPin (2 equiv)	85	0	2

[a] Determined by ^1H NMR analysis of the crude reaction mixture with 3,4,5-trimethoxybenzaldehyde as internal standard.

Optimization began with a screen of palladium catalysts. A variety of Pd(II)/Pd(0) sources, preformed catalysts, and palladacycles were tested. The $Pd(OAc)_2$ catalyst proved most effective. Several phosphine ligands were screened but none proved superior to PCy_3HBF_4. Other factors that were screened included the concentration, Pd/ligand ratio, and Rh loading, though no better alternatives were found.

One important factor influencing the reactivity was the base. We observed a steep decrease in product when switching from KOH to Cs_2CO_3 (Table 2, entry 2), while a combination of KOH and Cs_2CO_3 (Table 2, entry 3) proved better. The presence of a hydroxide base appears to be necessary. Further screening revealed that CsOH was the optimum base (Table 2, entry 4).

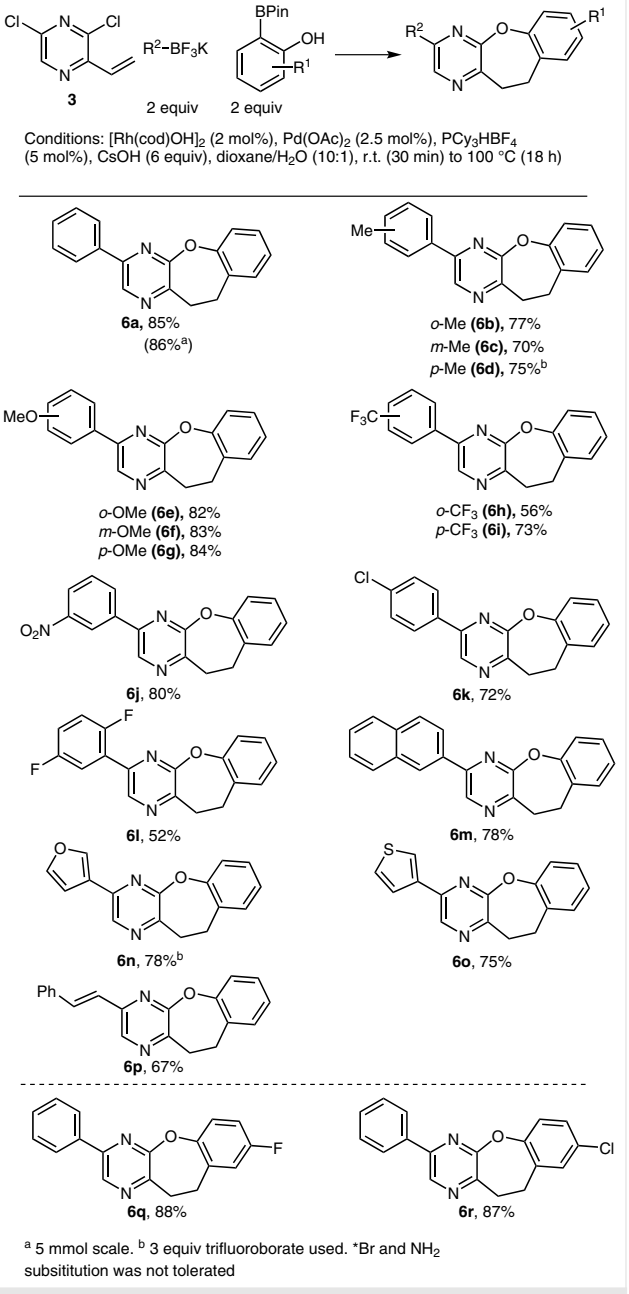
During optimization, many experiments showed a small but significant amount of **4** which was not consumed upon prolonged stirring. We sought to accelerate the Suzuki coupling by increasing the equivalents of trifluoroborate. Two equivalents (Table 2, entry 8) gave a modest increase in product yield with no increase in intermediate formation.

A major concern with any $(MC)^2R$ is if each metal can carry out its function without interference from the other metal or ligands. With this in mind, one of the biggest breakthroughs was realized during a screen of the Pd loading. We observed a steady increase of product yield as we lowered the loading with 2.5 mol% providing a 77% yield of the product (Table 2, entry 11). Further reduction proved unsuccessful (Table 2, entry 12). We attribute this increase not to the lower Pd loading, but rather to the decrease in the amount of phosphine ligand. Probing the hydroarylation step revealed that the presence of phosphine ligand significantly affected yields and reaction times. Phosphine ligands are well-known to coordinate to rhodium and these rhodium–phosphine complexes appear to be inactive for the hydroarylation. With a Pd loading of 2.5 mol%, the ligand loading decreased from 20 mol% to 5 mol%, which would significantly reduce the amount of inactive rhodium–phosphine complex.

The optimization included a screen of the BPin equivalents. As the product arising from the Suzuki coupling with excess BPin was never observed, we reasoned that increasing the amount should reduce the side product, while not influencing the other reactions. In fact, increasing to two equivalents led to an 85% yield (Table 2, entry 14).

Having found satisfactory conditions, the scope of the reaction was explored (Scheme 3). The reaction tolerated a wide range of substitution patterns on the trifluoroborate. Electron-rich, -neutral, and -poor trifluoroborates were all tolerated. Heteroaryl partners and systems with extended conjugation also reacted well under our conditions. Some electron-poor BPin partners were also utilized giving the highest yields observed. Overall, 18 compounds were synthesized giving yields ranging from 52–88%, representing an average yield of 80–96% per step.

In conclusion, we have developed a novel $(MC)^2R$ on a dichlorovinylpyrazine substrate. The reaction generates three new bonds to form diaza-dihydrodibenzoxepine products in a one-pot, one-step process. This reaction represents the first example of employing two orthogonally reacting boron reagents used as a control element in $(MC)^2R$ chemistry. Further studies into the reactivity of boron coupling reagents as well as investigations into the generality of the process are currently underway.



Scheme 3 Reaction scope

Unless otherwise noted, catalytic reactions were carried out under argon atmosphere in sealed 2-dram glass vials with magnetic stirring, while non-catalytic reactions were carried out under argon atmosphere in single-necked round-bottom flasks fitted with a rubber septum, with magnetic stirring. Analytical thin-layer chromatography (TLC) was performed with EMD Millipore™ normal phase silica plates (60 Å pore diameter, F254 indicator). Visualization of developed plates was performed under UV light (254 nm) or by immersion in potassium permanganate ($KMnO_4$) stain, followed by heating with a heat gun. Purification of products was accomplished by silica flash column chromatography with Silicycle Ultra-Pure™ 230–400 mesh silica gel. Unless otherwise noted, starting materials, ligands, and catalysts were purchased from Aldrich, Strem, Combi-Blocks, or VWR and were used without further purification. Dichloromethane and 1,4-dioxane were freshly distilled over calcium hydride before use and tetrahydrofuran was freshly distilled over sodium/benzophenone before use. Trifluoroborate coupling partners were synthesized according to a previously reported literature procedure.[16] Boronic acid pinacol ester,[17] and trifluoroborate[11b,c,18] coupling partners have been previously reported. Product **2** has also been previously reported.[19] Melting point ranges were measured on a Fisher-Johns melting point apparatus and are reported uncorrected. Infrared (IR) spectra were obtained using a Shimadzu FTIR-8400S FT-IR spectrometer as a neat film on a NaCl plate, data are presented as follows: frequency of absorption (cm–1). Proton nuclear magnetic resonance spectra (^1H NMR), carbon nuclear magnetic resonance spectra (^{13}C NMR), and fluorine nuclear magnetic resonance spectra (^{19}F NMR) were recorded at 23 °C with a Bruker Advance III 400 MHz, an Agilent DD2 500 MHz, or a Varian VnmrS 400 NMR spectrometer. Shifts for ^1H NMR spectra are reported in parts per million (δ scale) and are referenced to the residual solvent signal ($CDCl_3$, δ = 7.26 ppm) or tetramethylsilane (δ = 0 ppm). Chemical shifts for carbon resonances are reported in parts per million (δ scale) and are referenced to the carbon resonance of the solvent ($CDCl_3$, δ= 77.16 ppm). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constant (*J*, Hz). High-resolution mass spectra were obtained from a JEOL AccuTOF model JMS-T1000LC mass spectrometer equipped with an IONICS® Direct Analysis in real Time (DART) ion source at Advanced Instrumentation for Molecular Structure (AIMS) in the Department of Chemistry at the University of Toronto.

3,5-Dichloro-2-vinylpyrazine (3)

A round-bottom flask was charged with 3,5-dichloro-2-iodopyrazine (**2**) (3.411 g, 13.7 mmol), potassium vinyl trifluoroborate (2.2 g, 16.44 mmol, 1.2 equiv), Cs_2CO_3 (13.4 g, 41.1 mmol, 3 equiv), and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (559 mg, 0.69 mmol, 5 mol%), and purged with ar-

gon. THF (120 mL) and H_2O (12 mL) were added, and the mixture was heated to 40 °C for 72 h. The crude was partitioned between Et_2O and H_2O, the layers were separated, and the aq layer was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Silica flash column chromatography (hexane/CH_2Cl_2, 9:1) gave the product (1.9180 g, 75%) as an orange-yellow oil.

IR (film): 3020, 2958, 2916, 2848, 1653, 1431, 1296, 1261, 1215, 1149, 1066 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 0.5 Hz, 1 H), 7.12 (ddd, *J* = 17.0, 10.7, 0.5 Hz, 1 H), 6.54 (dd, *J* = 17.0, 1.6 Hz, 1 H), 5.73 (dd, *J* = 10.8, 1.6 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.1, 145.4, 145.2, 142.2, 129.3, 124.5.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_6H_5Cl_2N_2$: 174.9752; found: 174.9829.

3-Chloro-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (4)

A 2-dram vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (1.8 mg, 0.004 mmol, 2 mol%), KOH (33.6 mg, 0.6 mmol, 3 equiv), and 2-hydroxyphenyl boronic acid pinacol ester (52.8 mg, 0.24 mmol, 1.2 equiv) then purged with argon. Another 2-dram vial was charged with **3** (35 mg, 0.2 mmol) and purged with argon. Dioxane (1 mL) was then used to transfer compound **3** to the vial containing the catalyst, base, and boronic acid pinacol ester, rinsing with additional dioxane (2 × 500 µL). Following the addition of H_2O (200 µL), the reaction vial was sealed, and heated at 60 °C for 20 min. After cooling to r.t., the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (CH_2Cl_2/hexane, 7:3) gave the product (44.2 mg, 95%) as an orange-brown oil.

IR (film): 2951, 2916, 2848, 1525, 1489, 1456, 1442, 1356, 1348, 1330, 1311, 1278, 1232, 1170, 1145, 1099, 1084 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 7.31–7.28 (m, 1 H), 7.26–7.21 (m, 2 H), 7.17–7.12 (m, 1 H), 3.31–3.28 (m, 2 H), 3.20–3.16 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.1, 154.7, 143.7, 143.1, 138.2, 132.6, 129.5, 128.1, 125.7, 121.2, 35.2, 28.5.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}ClN_2O$: 233.0403; found: 233.0482.

3,5-Dichloro-2-phenethylpyrazine (5)

A 2-dram vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (1.8 mg, 0.004 mmol, 2 mol%), KOH (33.6 mg, 0.6 mmol, 3 equiv), and phenyl boronic acid pinacol ester (48 mg, 0.24 mmol, 1.2 equiv) then purged with argon. Another 2-dram vial was charged with **3** (35 mg, 0.2 mmol) and purged with argon. Dioxane (1 mL) was then used to transfer compound **3** to the vial containing the catalyst, base, and boronic acid pinacol ester, rinsing with additional dioxane (2 × 500 µL). Following the addition of H_2O (200 µL), the reaction vial was sealed, and stirred at r.t. for 20 min. After cooling to r.t., the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (CH_2Cl_2/hexane, 7:3) gave the product (48.1 mg, 95%) as an orange-brown oil.

IR (film): 2948, 2920, 2867, 1530, 1457, 1432, 1367, 1349, 1330, 1315, 1279, 1236, 1165, 1099, 1085 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 7.23–7.02 (m, 3 H), 6.97–6.65 (m, 2 H), 3.33 (t, *J* = 6.7 Hz, 2 H), 3.13 (t, *J* = 6.7 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.0, 152.8, 147.8, 145.2, 140.7, 130.5, 127.9, 127.0, 120.9, 116.7, 35.0, 25.9.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}Cl_2N_2$: 253.0221; found: 253.0245.

Aryl Boronic Acid Pinacol Esters; General Procedure

A non-flame-dried round-bottom flask was charged with boronic acid, pinacol (2 equiv), and Et_2O (0.1 M) and the mixture allowed to stir at r.t. for 18 h. The solvent was removed in vacuo and the crude was filtered through a plug of silica eluting with Et_2O.

(MC)^{2}R of Dichlorovinylpyrazine; General Procedure

A 2-dram vial was charged with aryl trifluoroborate (2 or 3 equiv), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%), palladium(II) acetate (2.5 mol%), tricyclohexylphosphonium tetrafluoroborate (5 mol%), and cesium hydroxide monohydrate (6 equiv), then purged with argon. Another 2-dram vial was charged with compound **3** (1 equiv) and boronic acid pinacol ester (2 equiv) and purged with argon. Dioxane (1 mL) was used to transfer the vinyl pyrazine and boronic acid pinacol ester to the vial with the remaining reagents, rinsing with additional dioxane (2 × 500 µL). Following the addition of H_2O (200 µL), the vial was sealed with a Teflon cap and the contents allowed to stir at r.t. for 30 min before being heated to 100 °C for 18 h. After cooling to r.t., the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (hexane/EtOAc, 9:1) gave the pure products.

3-Phenyl-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6a)

Synthesized according to the general procedure. Phenyl potassium trifluoroborate (73.6 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH{\cdot}H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (46.6 mg, 85%) as a yellow solid.

Mp 83–85 °C.

IR (film): 3165, 3107, 3061, 3037, 2953, 2926, 2856, 1604, 1585, 1566, 1525, 1489, 1456, 1442, 1427, 1365, 1348, 1330, 1313, 1280, 1232, 1172, 1145, 1101, 1084, 1072, 1028, 1001 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 8.04 (dd, *J* = 8.3, 1.4 Hz, 2 H), 7.52–7.48 (m, 2 H), 7.47–7.43 (m, 1 H), 7.38 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.27–7.23 (m, 2 H), 7.17–7.12 (m, 1 H), 3.37–3.34 (m, 2 H), 3.24 (dd, *J* = 7.3, 4.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 155.3, 148.8, 143.9, 136.2, 135.7, 133.2, 129.9, 129.6, 129.0, 129.0, 128.1, 127.1, 125.5, 121.5, 35.6, 28.9.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_2O$: 275.1106; found: 275.1184.

3-(*o*-Tolyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6b)

Synthesized according to the general procedure. 2-Methylphenyl potassium trifluoroborate (79.2 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH{\cdot}H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (44.4 mg, 77%) as a colorless oil.

IR (film): 3057, 3022, 2953, 2926, 2856, 1581, 1519, 1489, 1448, 1361, 1344, 1329, 1311, 1278, 1234, 1184, 1166, 1147, 1126, 1099, 1072, 1031 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 7.44 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.34–7.22 (m, 6 H), 7.13 (td, *J* = 7.5, 1.3 Hz, 1 H), 3.39–3.35 (m, 2 H), 3.24 (dd, *J* = 7.4, 4.7 Hz, 2 H), 2.42 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.9, 155.4, 151.1, 143.6, 139.4, 136.4, 136.0, 133.2, 131.1, 130.0, 129.6, 129.2, 128.1, 126.2, 125.5, 121.5, 35.6, 28.9, 20.4.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$: 289.1263; found: 289.1346.

3-(*m*-Tolyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6c)

Synthesized according to the general procedure. 3-Methylphenyl potassium trifluoroborate (79.2 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (40.3 mg, 70%) as a white solid.

Mp 67–69 °C.

IR (film): 3057, 3034, 2949, 2922, 2858, 1608, 1683, 1566, 1521, 1489, 1452, 1361, 1278, 1234, 1156, 1099, 1033 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1 H), 7.86 (s, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.40–7.33 (m, 2 H), 7.27–7.21 (m, 3 H), 7.15–7.10 (m, 1 H), 3.34 (dd, *J* = 7.4, 4.4 Hz, 2 H), 3.21 (dd, *J* = 7.4, 4.5 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 155.3, 148.9, 143.7, 138.8, 136.3, 135.6, 133.2, 130.6, 129.5, 128.9, 128.0, 127.8, 125.4, 124.1, 121.5, 35.6, 28.9, 21.6.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$: 289.1263; found: 289.1340.

3-(*p*-Tolyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6d)

Synthesized according to the general procedure. 4-Methylphenyl potassium trifluoroborate (79.2 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (43.2 mg, 75%) as a white solid.

Mp 134–136 °C.

IR (film): 3030, 2949, 2922, 1612, 1525, 1512, 1489, 1452, 1408, 1363, 1344, 1330, 1307, 1276, 1232, 1168, 1145, 1099, 1078 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 1 H), 7.92 (d, *J* = 8.2 Hz, 2 H), 7.36 (dd, *J* = 8.4, 1.3 Hz, 1 H), 7.30–7.27 (m, 2 H), 7.25–7.21 (m, 2 H), 7.12 (ddd, *J* = 7.7, 7.1, 1.3 Hz, 1 H), 3.35–3.31 (m, 2 H), 3.23–3.19 (m, 2 H), 2.40 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 155.3, 148.8, 143.4, 140.0, 136.0, 133.2, 132.8, 129.7, 129.5, 128.0, 126.9, 125.4, 121.5, 35.6, 28.9, 21.4.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$: 289.1263; found: 289.1340.

3-(2-Methoxyphenyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6e)

Synthesized according to the general procedure. 2-Methoxyphenyl potassium trifluoroborate (85.6 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (49.9 mg, 82%) as a yellow solid.

Mp 85–87 °C.

IR (film): 3105, 3005, 2937, 2837, 1601, 1581, 1520, 1489, 1448, 1361, 1348, 1329, 1311, 1290, 1265, 1232, 1182, 1172, 1161, 1143, 1122, 1099, 1080, 1047, 1024 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.86 (s, 1 H), 7.92–7.88 (m, 1 H), 7.41–7.34 (m, 2 H), 7.24–7.19 (m, 2 H), 7.13–7.07 (m, 2 H), 6.99 (dd, *J* = 8.3, 1.0 Hz, 1 H), 3.86 (s, 3 H), 3.36–3.32 (m, 2 H), 3.23–3.20 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 155.4, 147.3, 143.0, 140.7, 133.3, 131.4, 130.9, 129.5, 128.0, 125.3, 125.0, 121.5, 121.3, 111.4, 55.6, 35.5, 28.9.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2$: 305.1212; found: 305.1295.

3-(3-Methoxyphenyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6f)

Synthesized according to the general procedure. 3-Methoxyphenyl potassium trifluoroborate (85.6 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (50.5 mg, 83%) as a white solid.

Mp 83–85 °C.

IR (film): 3057, 2953, 2929, 2854, 2835, 1600, 1585, 1566, 1525, 1489, 1452, 1423, 1363, 1346, 1330, 1311, 1286, 1236, 1184, 1166, 1143, 1099, 1070, 1045 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 1 H), 7.57 (dd, *J* = 8.7, 1.5 Hz, 2 H), 7.37 (t, *J* = 7.9 Hz, 2 H), 7.22 (dd, *J* = 7.2, 6.7, 1.6 Hz, 2 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 6.97 (dd, *J* = 8.2, 2.5 Hz, 1 H), 3.87 (s, 3 H), 3.32 (dd, *J* = 7.5, 4.5 Hz, 2 H), 3.20 (dd, *J* = 7.2, 4.7 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.2, 157.1, 155.2, 148.5, 144.0, 137.0, 136.3, 133.1, 130.0, 129.5, 128.0, 125.4, 121.4, 119.4, 115.8, 112.2, 55.5, 35.5, 28.8.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2$: 305.1212; found: 305.1290.

3-(4-Methoxyphenyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6g)

Synthesized according to the general procedure. 4-Methoxyphenyl potassium trifluoroborate (128.4 mg, 0.6 mmol, 3 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (51.1 mg, 84%) as a pale yellow oil.

IR (film): 3230, 2955, 2926, 2852, 1608, 1525, 1489, 1456, 1440, 1415, 1363, 1348, 1290, 1250, 1232, 1168 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (s, 1 H), 7.98 (d, *J* = 8.9 Hz, 2 H), 7.36 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.24–7.21 (m, 2 H), 7.13 (td, *J* = 7.4, 1.3 Hz, 1 H), 7.01–6.99 (m, 2 H), 3.86 (s, 3 H), 3.32 (dd, *J* = 7.4, 4.1 Hz, 2 H), 3.23–3.19 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.2, 157.2, 155.4, 148.6, 142.8, 135.7, 133.3, 129.6, 128.5, 128.2, 128.0, 125.4, 121.5, 114.5, 55.5, 35.6, 29.0.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2O_2$: 305.1212; found: 305.1295.

3-[2-(Trifluoromethyl)phenyl]-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6h)

Synthesized according to the general procedure. 2-(Trifluoromethyl)phenyl potassium trifluoroborate (100 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH{\cdot}H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (38.3 mg, 56%) as a white solid.

Mp 65–67 °C.

IR (film): 3064, 2953, 2918, 1606, 1581, 1566, 1521, 1489, 1440, 1363, 1346, 1313, 1267, 1234, 1159, 1128, 1112, 1091, 1053, 1035 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (s, 1 H), 7.81–7.78 (m, 1 H), 7.68–7.63 (m, 1 H), 7.60–7.54 (m, 2 H), 7.35 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.28–7.23 (m, 2 H), 7.16 (td, *J* = 7.5, 1.3 Hz, 1 H), 3.42–3.39 (m, 2 H), 3.27 (dd, *J* = 7.3, 4.8 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.8, 155.3, 148.8, 145.1, 139.0 (q, J_{F-C} = 2.82 Hz), 135.6 (q, J_{F-C} = 1.97 Hz), 133.1, 132.0, 131.9 (q, J_{F-C} = 1.03 Hz), 129.6, 129.2, 128.8 (q, J_{F-C} = 30.52 Hz), 128.2, 126.6 (q, J_{F-C} = 5.25 Hz), 125.6, 124.0 (q, J_{F-C} = 273.53 Hz), 121.5, 35.7, 28.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –56.69 (s).

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}F_3N_2O$: 343.0980; found: 343.1067.

3-[4-(Trifluoromethyl)phenyl]-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6i)

Synthesized according to the general procedure. 4-(Trifluoromethyl)phenyl potassium trifluoroborate (100 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH{\cdot}H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (49.9 mg, 73%) as a white solid.

Mp 108–110 °C.

IR (film): 3061, 2965, 2926, 2848, 1618, 1585, 1533, 1516, 1489, 1452, 1410, 1367, 1348, 1325, 1286, 1259, 1234, 1166, 1147, 1124, 1112, 1101, 1082, 1064, 1031, 1016 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 8.14 (d, *J* = 8.1 Hz, 2 H), 7.73 (d, *J* = 8.7 Hz, 2 H), 7.36 (dd, *J* = 8.5, 1.3 Hz, 1 H), 7.26–7.22 (m, 2 H), 7.16–7.11 (m, 1 H), 3.35 (dd, *J* = 7.3, 4.6 Hz, 2 H), 3.22 (dd, *J* = 7.3, 4.7 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 155.1, 147.1, 145.4, 139.0 (q, J_{F-C} = 1.20 Hz), 136.3, 133.1, 131.5 (q, J_{F-C} = 32.56 Hz), 129.6, 128.1, 127.3, 126.0 (q, J_{F-C} = 3.77 Hz), 125.6, 124.0 (q, J_{F-C} = 272.77 Hz), 121.5, 35.7, 28.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.7 (s).

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}F_3N_2O$: 343.0980; found: 343.1058.

3-(3-Nitrophenyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6j)

Synthesized according to the general procedure. 3-Nitrophenyl potassium trifluoroborate (91.6 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH{\cdot}H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (51.1 mg, 80%) as a pale orange solid.

Mp 113–115 °C.

IR (film): 3084, 3028, 2993, 2953, 2926, 2858, 1612, 1581, 1529, 1489, 1448, 1437, 1421, 1365, 1348, 1315, 1298, 1274, 1232, 1182, 1147, 1112, 1099, 1074, 1031 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.86 (t, *J* = 2.0 Hz, 1 H), 8.75 (s, 1 H), 8.35 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1 H), 8.26 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1 H), 7.65 (t, *J* = 8.0 Hz, 1 H), 7.35 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.26–7.22 (m, 2 H), 7.13 (td, *J* = 7.4, 1.3 Hz, 1 H), 3.35 (dd, *J* = 7.4, 4.8 Hz, 2 H), 3.22 (dd, *J* = 7.3, 4.8 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 155.4, 147.3, 143.0, 140.7, 133.3, 131.4, 130.9, 129.5, 128.0, 125.3, 125.0, 121.5, 121.3, 111.4, 55.6, 35.5, 28.9.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}N_3O_3$: 320.0957; found: 320.1035.

3-(4-Chlorophenyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6k)

Synthesized according to the general procedure. 4-Chlorophenyl potassium trifluoroborate (87.3 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH{\cdot}H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (44.4 mg, 72%) as a white solid.

Mp 114–116 °C.

IR (film): 3057, 3037, 3010, 2960, 2928, 2856, 1597, 1581, 1521, 1489, 1452, 1402, 1363, 1344, 1330, 1305, 1298, 1269, 1232, 1170, 1149, 1093, 1076, 1031, 1012 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.66 (s, 1 H), 7.96 (d, *J* = 8.5 Hz, 2 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.37–7.32 (m, 1 H), 7.25–7.21 (m, 2 H), 7.13 (td, *J* = 7.7, 1.2 Hz, 1 H), 3.33 (dd, *J* = 7.6, 4.5 Hz, 2 H), 3.21 (dd, *J* = 7.2, 4.7 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 155.2, 147.5, 144.4, 136.0, 135.9, 134.1, 133.1, 129.6, 129.2, 128.3, 128.1, 125.5, 121.5, 35.6, 28.8.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2O$: 309.0716; found: 309.0749.

3-(2,5-Difluorophenyl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6l)

Synthesized according to the general procedure. 2,5-Difluorophenyl potassium trifluoroborate (88 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (33.2 mg, 52%) as a pale yellow solid.

Mp 53–55 °C.

IR (film): 3126, 3080, 3041, 2951, 2929, 2856, 1626, 1593, 1585, 1558, 1525, 1500, 1489, 1448, 1421, 1363, 1348, 1332, 1305, 1286, 1232, 1217, 1168, 1141, 1099, 1070, 1031 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, *J* = 2.5 Hz, 1 H), 7.82 (ddd, *J* = 9.1, 5.9, 3.1 Hz, 1 H), 7.35 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.24 (dtd, *J* = 7.4, 4.2, 1.8 Hz, 2 H), 7.16–7.04 (m, 3 H), 3.37–3.34 (m, 2 H), 3.24–3.21 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.1 (dd, $J_{F–C}$ = 243.3, 2.22 Hz), 156.6 (dd, $J_{F–C}$ = 243.4, 2.41 Hz), 157.3, 155.2, 145.3 (d, $J_{F–C}$ = 1.27 Hz), 143.5 (dd, $J_{F–C}$ = 4.26, 1.78 Hz), 139.5, 139.4, 133.1, 129.7, 129.6, 128.2, 125.6, 125.0 (dd, $J_{F–C}$ = 14.83, 7.95 Hz), 117.7 (ddd, $J_{F–C}$ = 26.08, 21.41, 8.75 Hz), 117.1 (dd, $J_{F–C}$ = 25.72, 3.53 Hz), 35.7, 28.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –117.9 (m), –120.5 (m).

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}F_2N_2O$: 311.0918; found: 311.1007.

3-(Naphthalen-2-yl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6m)

Synthesized according to the general procedure. 2-Naphthyl potassium trifluoroborate (93.6 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (50.6 mg, 78%) as a yellow oil.

IR (film): 3047, 3007, 2953, 2916, 2359, 2341, 1585, 1519, 1506, 1489, 1467, 1456, 1435, 1392, 1361, 1325, 1305, 1234, 1195, 1182, 1166, 1147, 1122, 1099 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.60 (s, 1 H), 8.16 (dd, *J* = 6.1, 3.6 Hz, 1 H), 7.97–7.90 (m, 2 H), 7.68 (dd, *J* = 7.1, 1.3 Hz, 1 H), 7.58 (dd, *J* = 8.2, 7.1 Hz, 1 H), 7.56–7.50 (m, 2 H), 7.42–7.38 (m, 1 H), 7.29–7.24 (m, 2 H), 7.16 (td, *J* = 7.4, 1.3 Hz, 1 H), 3.47–3.42 (m, 2 H), 3.32–3.26 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.1, 155.3, 150.3, 144.0, 140.0, 133.9, 133.8, 133.0, 131.0, 129.7, 129.5, 128.5, 128.1, 128.0, 126.9, 126.1, 125.4, 125.3, 125.0, 121.4, 35.6, 28.8.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O$: 325.1263; found: 325.1346.

3-(Furan-3-yl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6n)

Synthesized according to the general procedure. 3-Furyl potassium trifluoroborate (104.3 mg, 0.6 mmol, 3 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (41.2 mg, 78%) as a pale orange solid.

Mp 109–111 °C.

IR (film): 3126, 3037, 2951, 2931, 2899, 1600, 1585, 1504, 1489, 1456, 1379, 1340, 1228, 1186, 1157, 1111, 1099, 1070, 1016 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 8.12–8.09 (m, 1 H), 7.52 (t, *J* = 1.7 Hz, 1 H), 7.36 (dd, *J* = 8.4, 1.3 Hz, 1 H), 7.26–7.22 (m, 2 H), 7.16–7.12 (m, 1 H), 6.94 (dd, *J* = 1.9, 0.8 Hz, 1 H), 3.32 (dd, *J* = 7.3, 4.1 Hz, 2 H), 3.21 (dd, *J* = 7.4, 4.3 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 155.2, 144.2, 143.6, 143.4, 142.2, 135.9, 133.2, 129.6, 128.1, 125.5, 123.5, 121.5, 108.5, 35.6, 28.9.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2O_2$: 265.0899; found: 265.0982.

3-(Thiophen-3-yl)-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6o)

Synthesized according to the general procedure. 3-Thiophene potassium trifluoroborate (76.0 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (42.0 mg, 75%) as a pale yellow solid.

Mp 119–121 °C.

IR (film): 3107, 3082, 3063, 3037, 3024, 3014, 2951, 2926, 2848, 1732, 1573, 1537, 1519, 1506, 1489, 1456, 1417, 1379, 1357, 1337, 1327, 1305, 1282, 1234, 1207, 1168, 1143, 1099, 1091, 1072, 1031 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.57 (s, 1 H), 7.98 (d, *J* = 4.2 Hz, 1 H), 7.66 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.39 (dd, *J* = 5.1, 3.1 Hz, 1 H), 7.34 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.24–7.20 (m, 2 H), 7.11 (td, *J* = 7.3, 1.2 Hz, 1 H), 3.30 (dd, *J* = 7.5, 4.3 Hz, 2 H), 3.19 (dd, *J* = 7.3, 4.5 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.1, 155.2, 145.0, 143.4, 138.2, 136.0, 133.2, 129.5, 128.0, 126.8, 126.0, 125.4, 125.0, 121.4, 35.6, 28.8.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2OS$: 281.0670; found: 281.0760.

(*E*)-3-Styryl-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6p)

Synthesized according to the general procedure. (*E*)-Styryl potassium trifluoroborate (84.0 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxyphenyl boronic acid pinacol ester (88 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH·H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (40.2 mg, 67%) as a pale yellow solid.

Mp 103–105 °C.

IR (film): 3101, 3080, 3059, 3037, 3024, 2956, 2926, 2856, 1737, 1732, 1635, 1608, 1597, 1562, 1519, 1489, 1456, 1448, 1429, 1365, 1352, 1329, 1305, 1286, 1259, 1234, 1182, 1161, 1141, 1099, 1074, 1030 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.76 (d, *J* = 16.1 Hz, 1 H), 7.61–7.58 (m, 2 H), 7.42–7.37 (m, 3 H), 7.35–7.30 (m, 1 H), 7.28–7.24 (m, 2 H), 7.17–7.10 (m, 2 H), 3.35–3.29 (m, 2 H), 3.25–3.20 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 155.2, 147.3, 144.0, 137.9, 136.3, 135.1, 133.2, 129.6, 128.97, 128.95, 128.1, 127.3, 125.5, 123.3, 121.5, 35.7, 28.9.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}N_2O$: 301.1263; found: 301.1346.

8-Fluoro-3-phenyl-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6q)

Synthesized according to the general procedure. Phenyl potassium trifluoroborate (73.6 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxy-5-fluorophenyl boronic acid pinacol ester (95.2 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH{\cdot}H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (51.4 mg, 88%) as a white solid.

Mp 74–76 °C.

IR (film): 3061, 3037, 2956, 2929, 1595, 1564, 1525, 1489, 1456, 1442, 1429, 1363, 1342, 1329, 1313, 1274, 1259, 1224, 1197, 1168, 1143, 1097, 1084, 1072, 1028 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (s, 1 H), 7.99 (d, *J* = 6.8 Hz, 2 H), 7.49–7.40 (m, 3 H), 7.30 (dd, *J* = 8.8, 4.8 Hz, 1 H), 6.94–6.85 (m, 2 H), 3.32–3.29 (m, 2 H), 3.18–3.14 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.6, 158.7, 157.1, 151.3 (d, J_{F-C} = 2.70 Hz), 148.8, 143.5, 136.49, 136.47, 135.4, 135.1 (d, J_{F-C} = 8.17 Hz), 129.8, 129.0, 127.0, 122.8 (d, J_{F-C} = 8.75 Hz), 115 (dd, J_{F-C} = 183.4, 23.38 Hz), 35.1, 28.7, 28.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –117.4 (m).

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FN_2O$: 293.1012; found: 293.1090.

8-Chloro-3-phenyl-10,11-dihydrobenzo[6,7]oxepino[2,3-*b*]pyrazine (6r)

Synthesized according to the general procedure. Phenyl potassium trifluoroborate (73.6 mg, 0.4 mmol, 2 equiv), 3,5-dichloro-2-vinylpyrazine (**3**) (34.4 mg, 0.2 mmol, 1 equiv), 2-hydroxy-5-chlorophenyl boronic acid pinacol ester (101.8 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2.5 mol%), PCy_3HBF_4 (3.6 mg, 0.01 mmol, 5 mol%), $[Rh(cod)OH]_2$ (1.8 mg, 0.004 mmol, 2 mol%), and $CsOH{\cdot}H_2O$ (201 mg, 1.2 mmol, 6 equiv) were used giving the product (53.7 mg, 87%) as a colorless oil.

IR (film): 3061, 3037, 2951, 2926, 1521, 1477, 1458, 1442, 1410, 1363, 1340, 1311, 1278, 1265, 1240, 1222, 1168, 1145, 1111, 1085, 1072, 1028 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 8.01–7.98 (m, 2 H), 7.49–7.42 (m, 3 H), 7.29–7.24 (m, 1 H), 7.21–7.15 (m, 2 H), 3.33–3.29 (m, 2 H), 3.15 (dd, *J* = 7.2, 4.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.9, 153.7, 148.9, 143.4, 136.5, 135.4, 134.8, 130.3, 129.9, 129.3, 129.0, 127.9, 127.0, 122.9, 35.1, 28.7.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2O$: 309.0716; found: 309.0799.

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Supporting Information

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