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Regio- and Chemoselective Zincation of Sensitive and Moderately Activated Aromatics and Heteroaromatics Using TMPZnCl·LiCl

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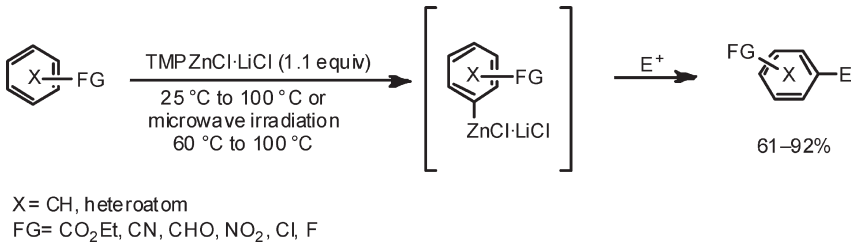

A broad range of functionalized aryl- and heteroarylzinc reagents were prepared via directed zincation of sensitive and moderately activated aromatics and heteroaromatics using TMPZnCl·LiCl under various reaction conditions. Diverse sensitive functional groups such as a nitro group, an aldehyde, an ester, and a nitrile are readily tolerated and are compatible with high metalation temperatures. Furthermore, the resulting zinc organometallics display an excellent reactivity toward various classes of electrophiles providing functionalized aromatics and heteroaromatics in high yields.

1. Introduction

The metalation of aromatics and heteroaromatics is an important tool since it allows a versatile functionalization of these molecules. A range of new bases for regio- and chemoselective metalation have already been developed.[1] In particular, mixed Zn/Li bases[2] and other ate reagents have found useful applications.[3] However, the use of highly reactive zincates or related ate bases is not always compatible with sensitive groups. Recently, we have reported that magnesium bases such as TMPMgCl·LiCl[4] (TMP = 2,2,6,6-tetramethylpiperidyl) or $TMP_2Mg·2LiCl$[5] proved to be highly active and selective bases for the magnesiation of various aromatic ring systems. Remarkably, these bases are also compatible with several important functional groups such as an ester, a nitrile, or an aryl ketone. However, more sensitive functionalities such as an aldehyde or a nitro group are not tolerated. Therefore, we have prepared the chemoselective base $TMP_2Zn·2MgCl_2·2LiCl$[6a,b] for the direct zincation of sensitive aromatics and heteroaromatics. Nevertheless, with this reagent some electron-poor functionalized arenes and heteroarenes still give unsatisfactory results in terms of yields and reaction selectivity. Moreover, several activated aromatics bearing a nitro group or heterocycles like pyridazines require

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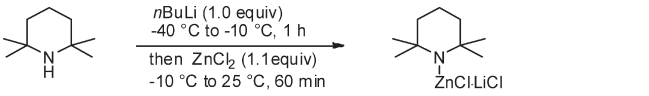
SCHEME 1. Preparation of TMPZnCl·LiCl (1)



1: TMPZnCl·LiCl > 95%, 1.3 M in THF

metalation temperatures below −50 °C, which is not convenient for reaction upscaling.[6c] Thus, we have developed a highly selective and mild base TMPZnCl·LiCl[7,4d] that allows chemoselective metalations at 25 °C for the directed zincation of molecules containing sensitive functional groups such as an aldehyde or a nitro group. Its higher selectivity is due to the absence of magnesium salts ($MgCl_2$) and to a different stoichiometry (TMPZnX instead of TMP_2ZnX). The mild base TMPZnCl·LiCl (**1**) is conveniently prepared in a one-pot procedure in quantitative yield as shown in Scheme 1.

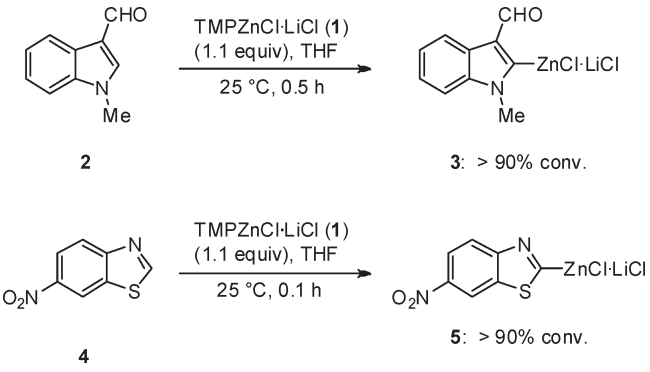
Whereas activated arenes and heteroarenes are smoothly metalated at 25 °C using TMPZnCl·LiCl (**1**), low activated systems bearing weak or electron-withdrawing groups do not react at 25 °C with the base **1**. However, they undergo smooth metalation by heating (65−100 °C) or using microwave irradiation.[8] Herein, we give a full report on the zincation of sensitive and moderately activated aromatics and heteroaromatics at room temperature as well as under thermic conditions or with microwave activation.

2. Results and Discussion

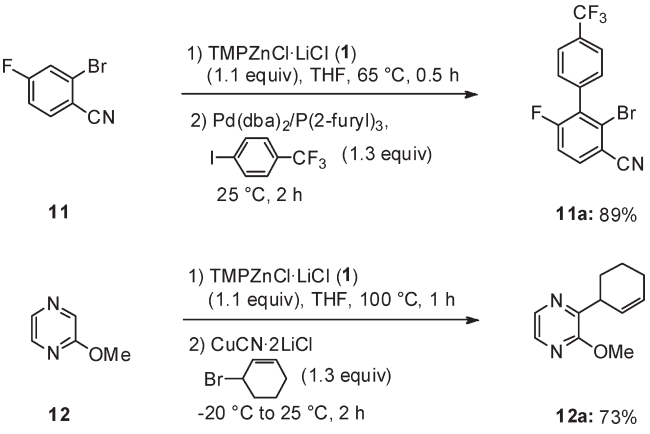
Thus, the directed zincation of *N*-methylindole-3-carboxyaldehyde (**2**) provides the desired zinc species **3** at 25 °C within 30 min (Scheme 2). In the case of 6-nitro-1,3-benzothiazole (**4**) the metalation to **5** at 25 °C requires only 10 min (Scheme 2). The resulting zinc reagents **3** and **5** readily undergo an iodination, a copper-mediated allylation,[9] as well as a Neghishi cross-coupling reaction[10] leading to new substituted heteroaromatics **2a**,**b** and **4a**, which can be obtained in 66−84% yield (Table 1, entries 1−3).

Similarly, 1-benzofuran-3-carbaldehyde (**6**) was smoothly zincated at 25 °C within 30 min leading to a zinc reagent which undergoes an allylation with 3-bromocyclohexene[9] (in the presence of a catalytic amount of CuCN·2LiCl) leading to the allylated aldehyde **6a** in 61% yield (entry 4). A Pd(0)-catalyzed cross-coupling reaction with 4-iodoanisole[10] gives the benzofuran derivative **6b** in 65% yield (entry 5). In the case of 2,4,6-trichloropyrimidine (**7**), the metalation is completed within 45 min at 25 °C. Further iodination, allylation, and acylation[9] give the pyrimidines **7a**−**c** in 83−90% yield (entries 6−8). 2,4- Difluoronitrobenzene (**8**) was reacted with **1** at 25 °C and fully metalated within 1 h. The resulting

SCHEME 2. Zincation of *N*-Methylindole-3-carboxyaldehyde (2) and 6-Nitro-1,3-benzothiazole (4) Using TMPZnCl·LiCl (1) at 25 °C



SCHEME 3. Zincation of 4-Fluoro-2-bromobenzonitrile (11) and 2-Methoxypyrazine (12) Using TMPZnCl·LiCl (1) and Heating



zinc species can be acylated with ethyl chloroformate[11] in the presence of catalytic amounts of $Pd(PPh_3)_4$ to give the nitroarene **8a** in 63% yield (entry 9). In addition, 2,6- and 2,5-dichloropyrazine (**9**) and (**10**) are smoothly zincated at 25 °C within 30 min. After the reaction mixture was quenched with allyl bromide (in the presence of CuCN·2LiCl (5 mol %))[9] and Negishi[10] or Sonogashira[12] cross-coupling reactions, the resulting functionalized heteroarenes **9a**−**d** and **10a**,**b** were provided in 75−83% yield (entries 10−15).

Aromatics and heteroaromatics which cannot be fully metalated at 25 °C were reacted with TMPZnCl·LiCl (**1**) by heating in an oil bath (65−100 °C). Thus, the treatment of 4-fluoro-2-bromobenzonitrile (**11**) with **1** (1.1 equiv, 65 °C, 30 min) leads to the zincated species which readily undergoes a Neghishi cross-coupling[10] (Scheme 3) or a Cu-catalyzed allylation to the expected products **11a** and **11b** in 88−89% yield (Scheme 3 and Table 2, entry 1). Interestingly, 2-methoxypyrazine (**12**) can be converted to the corresponding Zn compound with TMPZnCl·LiCl (**1**) at 100 °C within 60 min (Scheme 3). Allylation with 3-bromocyclohexene affords the new pyrazine derivative **12a** in 73% yield (Scheme 3). Similarly, 4,6-dichloro-2-(methylthio)-pyrimidine (**13**) reacts with TMPZnCl·LiCl (**1**: 1.1 equiv, 65 °C,

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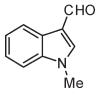
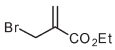
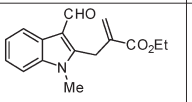
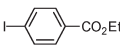
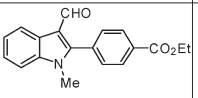
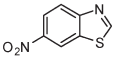
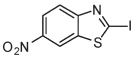
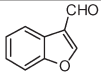
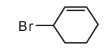
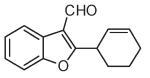
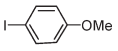
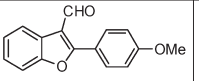
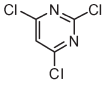
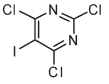
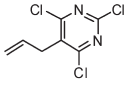
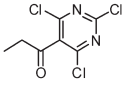
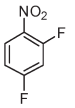
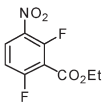
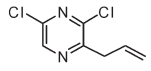
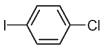
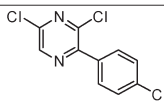
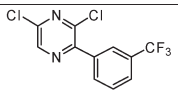
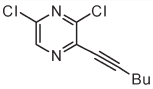
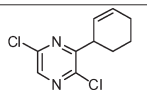
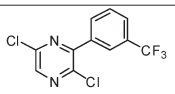
TABLE 1. Products Obtained by Regio- and Chemoselective Zincation Using TMPZnCl·LiCl (1) at 25 °C and Quenching with Electrophiles

entry	substrate	electrophile	product	yield [%][a]
1	 **2** (25 °C, 0.5 h)[b]		 **2a**	66[c]
2	**2**		 **2b**	73[d]
3	 **4** (25 °C, 0.1 h)[b]	I_2	 **4a**	84
4	 **6** (25 °C, 0.5 h)[b]		 **6a**	61[c]
5	**6**		 **6b**	65[d]
6	 **7** (25 °C, 0.7 h)[b]	I_2	 **7a**	83
7	**7**		 **7b**	90[c]
8	**7**		 **7c**	84[e]

entry	substrate	electrophile	product	yield [%][a]
9	 **8** (25 °C, 1.0 h)[b]		 **8a**	63[f]
10	 **9** (25 °C, 0.5 h)[b]		 **9a**	78[c]
11	**9**		 **9b**	81[d]
12	**9**		 **9c**	83[d]
13	**9**		 **9d**	83[d]
14	 **10** (25 °C, 0.5 h)[b]		 **10a**	78[c]
15	**10**		 **10b**	75[d]

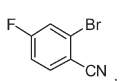
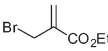
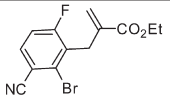
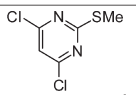
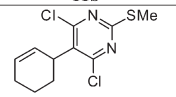
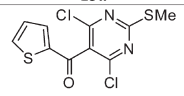
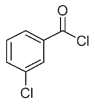
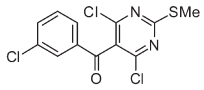
[a]Yield of analytically pure product. [b]Conditions for the zincation with TMPZnCl·LiCl. [c]5 mol % of CuCN·2LiCl was added. [d]3 mol % of $Pd(dba)_2$ and 6 mol % of P(2-furyl)$_3$ were added. [e]1.1 equiv of CuCN·2LiCl was added. [f]5 mol % of $Pd(PPh_3)_4$ was added.

30 min). Acylations and an allylation[9] give the functionalized pyrimidines **13a**−**c** in 88−90% yield (Table 2, entries 2−4).

In cases of less activated substrates, microwave irradiation turns out to be essential since conventional heating gives unsatisfactory conversions to the corresponding zinc reagents. Therefore, 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (**14**) is zincated at 100 °C (200 W) for 1 h (Scheme 4). Acylation with 2-thienyl chloride and benzoyl chloride (after transmetalation with CuCN·2LiCl)[9] afford the fully substituted pyrazines **14a** and **14b** in 78−90% yield (Scheme 4, Table 3, entry 1). 5-Bromo-2,4-dimethoxypyrimidine (**15**) is metalated at 60 °C (100 W) within 30 min to the expected zinc intermediate. Pd(0)-catalyzed cross-coupling reactions[10] lead to the new substituted pyrimidines **15a**,**b** in 86−92% (Scheme 4, Table 3, entry 2). Interestingly, the use of $TMP_2Zn·2MgCl_2·2LiCl$[6] for the zincation of 3-chloro-6-methoxypyridazine (**16**) leads to a mixture of regioisomers (metalation in positions 4 and 5). However, by using TMPZnCl·LiCl (**1**; 1.1 equiv, 80 °C, 100 W, 1 h), 3-chloro-6-methoxypyridazine (**16**) is regioselectively metalated in the *ortho*-position to the methoxy group[13] (metalation in position 4). The resulting zinc species

(13) The regioselectivity has been established by quenching the zinc organometallic with D_2O.

TABLE 2. Products Obtained by Regio- and Chemoselective Zincation Using TMPZnCl·LiCl (1), Conventional Heating, and Quenching with Electrophiles

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **11** (65 °C, 0.5 h)[b]		 **11b**	88[c]
2	 **13** (65 °C, 0.5 h)[b]		 **13a**	90[c]
3	**13**		 **13b**	88[d]
4	**13**		 **13c**	88[d]

[a]Yield of analytically pure product. [b]Conditions for the zincation with TMPZnCl·LiCl. [c]5 mol % of CuCN·2LiCl was added. [d]1.1 equiv of CuCN·2LiCl was added.

readily undergoes after transmetalation with CuCN·2LiCl[9] an acylation with benzoyl chloride or Pd(0)-catalyzed cross-coupling reactions leading to the new substituted pyridazines **16a**,**b** in 80−89% yield (entries 3 and 4). The zincation of 3,6-dimethoxypyridazine (**17**) with TMPZnCl·LiCl (**1**) (90 °C, 100 W, 1 h) and subsequent iodination as well as a Neghishi cross-coupling reaction[10] afforded the desired pyridazines **17a**, **b** in 76−88% yield (entries 5 and 6).

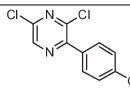
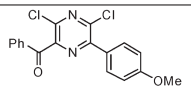
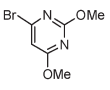
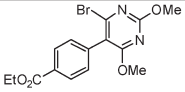
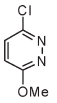
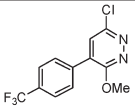
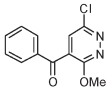
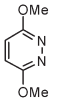
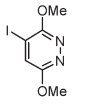
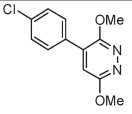
3. Conclusion

In summary, we have reported that aromatic and heterocyclic substrates, bearing electron-withdrawing groups or several heterocyclic nitrogen atoms, undergo smooth and selective zincations at room temperature using TMPZnCl·LiCl (**1**). On the other hand, the metalation of moderately activated arenes and heteroarenes occurs only by conventional heating (65−100 °C) or microwave irradiation, allowing a regio- and chemoselective zincation in excellent yield. Remarkably, sensitive functionalities like an ester or a nitrile are tolerated at these high temperatures. Further applications of this method are currently being investigated in our laboratories.

4. Experimental Section

General Considerations. All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR (25 °C) and capillary GC. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.25 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. Column chromatographical purification was performed using SiO_2 (0.040−0.063 mm, 230−400 mesh ASTM) if not indicated otherwise. TMPH and liquid acid chlorides were distilled prior to use. The given watt numbers refer to the maximum magnetron power output.

TABLE 3. Products Obtained by Regio- and Chemoselective Zincation Using TMPZnCl·LiCl (1), Microwave Activation, and Quenching with Electrophiles

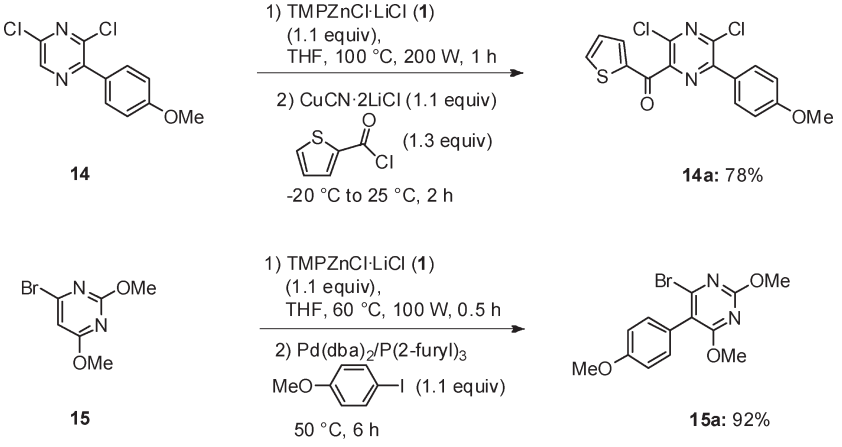
entry	substrate	electrophile	product	yield [%][a]
1	 **14** (100 °C, 1.0 h)[b]		 **14b**	90[c]
2	 **15** (60 °C, 0.5 h)[b]		 **15b**	86[d]
3	 **16** (90 °C, 1.0 h)[b]		 **16a**	89[d]
4	**16**		 **16b**	80[c]
5	 **17** (90 °C, 1 h)[b]	I_2	 **17a**	76
6	**17**		 **17b**	88[d]

[a]Yield of analytically pure product. [b]Conditions for the zincation with TMPZnCl·LiCl. [c]1.1 equiv of CuCN·2LiCl was added. [d]3 mol % of $Pd(dba)_2$ and 6 mol % of P(2-furyl)$_3$ were added.

Typical Procedure for the Preparation of the Reagent TMPZnCl·LiCl (1) (TP1). A dry and argon-flushed 250 mL Schlenk flask equipped with a magnetic stirring bar and a rubber septum was charged with freshly distilled TMP-H (10.2 mL, 60 mmol) dissolved in THF (60 mL). This solution was cooled to −40 °C, and *n*-BuLi (2.4 M in hexane, 25 mL, 60 mmol) was dropwise added. After the addition was complete, the reaction mixture was allowed to warm slowly to −10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 66 mL, 66 mmol) was dropwise added, and the resulting solution was stirred for 30 min at −10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum to afford a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared TMPZnCl·LiCl (**1**) solution was titrated prior to use at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.3 M in THF was obtained.

Typical Procedure for the Zincation of Polyfunctionalized Aromatics and Heterocycles with TMPZnCl·LiCl (1) at 25 °C (TP2). A dry and argon-flushed flask equipped with a magnetic

SCHEME 4. Zincation of 3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (14) and 5-Bromo-2,4-dimethoxypyrimidine (15) Using TMPZnCl·LiCl (1) and Microwave Irradiation



stirring bar was charged with a solution of the corresponding arene or heteroarene (1.0 mmol) in dry THF (1−2 mL). The zinc base (1.1 mmol) was added, and the reaction mixture was stirred at 25 °C for the indicated times. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in dry THF. The subsequent reactions with electrophiles were carried out with the indicated conditions.

Typical Procedure for the Zincation of Polyfunctionalized Aromatics and Heterocycles with TMPZnCl·LiCl (1) using Conventional Heating or Microwave Irradiation (TP3). A 10-mL pressurized vial equipped with a magnetic stirring bar was charged with a solution of the corresponding arene or heteroarene (1.0 mmol) in dry THF (1−2 mL). The zinc base (1.1 mmol) was added, and the reaction mixture was heated at the corresponding temperatures by using an oil bath or by using a Discover Bench-Mate Microwave system under the indicated conditions. After the desired reaction conditions were set up, the reaction mixture temperatures were displayed on the microwave screen during irradiation. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in dry THF. The subsequent reactions with electrophiles were carried out with the indicated conditions.

Ethyl 2-[(3-Formyl-1-methyl-1*H*-indol-2-yl)methyl]acrylate (2a). To a solution of 1-methylindole-3-carboxyaldehyde (**2**) (159 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 30 min according to TP2. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 5 min of stirring at the same temperature, the mixture was cooled to −60 °C, ethyl 2-(bromomethyl)acrylate (290 mg, 1.5 mmol) was added, and the resulting mixture was allowed to warm slowly to −20 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (Et_2O/pentane 3:7) furnished the compound **2a** (179 mg, 66%) as a yellowish solid: mp 121.3−123.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.12 (s, 1H), 8.30−8.26 (m, 1 H), 7.35−7.38 (m, 3 H), 6.31 (s, 1 H), 5.24 (s, 1 H), 4.30−4.32 (q, J = 7.0 Hz, 2 H), 4.12 (s, 2 H), 3.66−3.65 (m, 3 H), 1.33 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.1, 166.0, 146.9, 137.2, 136.7, 126.9, 125.6, 123.5, 123.0, 121.1, 115.0, 109.5, 61.4, 29.9, 26.5, 14.2; IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3061, 2980, 1912, 1720, 1707, 1631, 1608, 1579, 1533, 1472, 1442, 1420, 1395, 1374, 1328, 1252, 1202, 1186, 1174, 1137, 1095, 1043, 1018, 968, 948, 911, 868, 854, 815, 782, 765, 757, 750, 730, 668, 658; HRMS (ESI) calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1282.

Ethyl 4-(3-Formyl-1-methyl-1*H*-indol-2-yl)benzoate (2b). To a solution of 1-methylindole-3-carboxyaldehyde (**2**) (159 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 30 min according to TP2. $Pd(dba)_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) mixed with ethyl-4-iodobenzoate (360 mg, 1.3 mmol) were then added via cannula, and the resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (Et_2O/pentane 1:1) furnished the compound **2b** (224 mg, 73%) as a colorless solid: mp 162.0−163.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.72 (s, 1 H), 8.43−8.41 (m, 1 H), 8.22 (d, J = 8.3 Hz, 2 H), 7.57 (d, J = 6.8 Hz, 2 H), 7.41−7.32 (m, 3 H), 4.44 (q, d, J = 7.3 Hz, 2 H), 3.68−3.66 (m, 3 H), 1.43 (t, d, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.0, 165.8, 149.8, 137.5, 133.0, 131.8, 130.9, 129.7, 125.1, 124.4, 123.5, 122.3, 116.0, 109.8, 61.4, 31.1, 14.3; IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3025, 2978, 2926, 2803, 2768, 2730, 1711, 1649, 1608, 1577, 1568, 1537, 1493, 1466, 1442, 1416, 1372, 1326, 1312, 1278, 1182, 1156, 1127, 1106, 1071, 1029, 1018, 991, 951, 883, 861, 848, 812, 759, 741, 710, 693, 628, 613; HRMS (ESI) calcd for $C_{19}H_{17}NO_3$ 307.1208, found 307.1281.

2-Iodo-6-nitro-1,3-benzothiazole (4a). To a solution of 6-nitro-1,3-benzothiazole (**4**) (159 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 10 min according to TP2. Iodine (381 mg, 1.5 mmol) in 2 mL of THF was then added, and the mixture was stirred for 1 h. The reaction mixture was then quenched with a satd aq $Na_2S_2O_3$ (30 mL) and NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (Et_2O/pentane 1:4) furnished the compound **4a** (257 mg, 84%) as a yellowish solid: mp 179.0−181.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (dd, J = 2.0 Hz, J = 0.4 Hz, 1 H), 8.31 (dd, J = 6.6 Hz, J = 2.3 Hz, 1 H), 8.13 (dd, J = 8.4 Hz, J = 0.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 145.2, 139.5, 122.8, 121.9, 116.9, 112.1; MS (70 eV, EI) m/z 306 [M$^+$] (100), 276 (31), 133 (31), 69 (5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3104, 3054, 1598, 1567, 1505, 1425, 1398, 1332, 1260, 1232, 1120, 1045, 957, 881, 844, 844, 823, 750, 744, 720, 637; HRMS (EI) calcd for $C_7H_3IN_2O_2S$ 305.8960, found 305.8920.

2-Cyclohex-2-en-1-yl-1-benzofuran-3-carbaldehyde (6a). To a solution of 1-benzofuran-3-carbaldehyde (**6**) (146 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 30 min according to TP2. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 5 min of stirring at the same temperature, the mixture was cooled to −60 °C, 3-bromocyclohexene (242 mg, 1.5 mmol) was added, and the resulting mixture was allowed to warm slowly to −20 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (Et_2O/pentane 5:95) furnished the compound **6a** (138 mg, 61%) as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.18−8.12 (m, 1 H), 7.49−7.43 (m, 1 H), 7.35−7.29 (m, 2 H), 6.06−6.00 (m, 1 H), 5.78−5.73 (m, 1 H), 4.18−4.10 (m, 1 H), 2.29−2.09 (m, 3 H), 2.04−1.88 (m, 2 H), 1.81−1.67 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 172.3, 153.8, 130.6, 125.2, 124.5, 122.0, 117.3, 111.0, 35.3, 29.1, 24.5, 21.1; MS (70 eV, EI) *m*/*z* 226 [M^+] (100), 209 (16), 197 (20), 183 (20), 169 (32), 141 (13), 115 (20); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3326, 3060, 3024, 2935, 2859, 2835, 2755, 1786, 1667, 1573, 1478, 1451, 1432, 1402, 1377, 1342, 1278, 1251, 1222, 1180, 1150, 1095, 1060, 1044, 1027, 1010, 952, 925, 892, 872, 857, 814, 799, 741, 724, 652, 632; HRMS (EI) calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.0982.

2-(4-Methoxyphenyl)-1-benzofuran-3-carbaldehyde (6b). To a solution of 1-benzofuran-3-carbaldehyde (**6**) (146 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 30 min according to TP2. $Pd(dba)_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) mixed with 4-iodoanisole (304 mg, 1.3 mmol) were then added via cannula, and the resulting mixture was stirred at 25 °C overnight. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (Et_2O/pentane 15:85) furnished the compound **6b** (164 mg, 65%) as a yellowish solid: mp 116.3−118.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1 H), 8.26−8.22 (m, 1 H), 7.83−7.79 (m, 2 H), 7.55−7.49 (m, 1 H), 7.40−7.33 (m, 2 H), 7.08−7.03 (m, 2 H), 3.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.5, 165.5, 161.2, 152.7, 130.7, 125.6, 124.7, 122.4, 121.0, 116.5, 114.6, 110.9, 55.5; MS (70 eV, EI) *m*/*z* 252 [M^+] (100), 237 (13), 221 (19), 209 (21), 181 (20), 152 (20); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3059, 2915, 2822, 2037, 1948, 1651, 1606, 1578, 1501, 1477, 1446, 1399, 1374, 1342, 1309, 1259, 1247, 1176, 1135, 1107, 1075, 1029, 934, 912, 834, 787, 742; HRMS (EI) calcd for $C_{16}H_{12}O_3$ 252.0786, found 252.0775.

2,4,6-Trichloro-5-iodopyrimidine (7a). To a solution of 2,4,6-trichloropyrimidine (**7**) (186 mg, 1.0 mmol) in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 45 min according to TP2. Iodine (381 mg, 1.5 mmol) in THF (2 mL) was then added, and the mixture was stirred for an additional 1 h. The reaction mixture was then quenched with a satd aq $Na_2S_2O_3$ (30 mL) and NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:7) furnished the compound **7a** (256 mg, 83%) as a colorless solid: mp 97.0−98.0 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 159.3, 96.5; MS (70 eV, EI) *m*/*z* 308 (100) [^{35}Cl-M^+], 273 (25), 127 (18), 85 (11); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 1477, 1270, 1208, 1182, 1009, 851, 806, 752; HRMS (EI) calcd for $C_4Cl_3IN_2$ 307.8172, found 307.8162.

5-Allyl-2,4,6-trichloropyrimidine (7b). To a solution of 2,4,6-trichloropyrimidine (**7**) (186 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 45 min according to TP2. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 5 min of stirring at the same temperature, the mixture was cooled to −60 °C, allyl bromide (240 mg, 2.0 mmol) was added, and the resulting mixture was allowed to warm slowly to 20 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:6) furnished the compound **7b** (201 mg, 90%) as a colorless solid: mp 39.2−40.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75−5.88 (m, 1H), 5.08−5.18 (m, 2H), 3.61 (dt, J = 6.4 Hz, J = 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 157.1, 130.2, 129.3, 118.5, 33.5; MS (70 eV, EI) *m*/*z* 222 (100) [^{35}Cl-M^+], 187 (33), 151 (62), 125 (35), 90 (43); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3087, 2934, 1635, 1533, 1501, 1435, 1330, 1287, 1215, 1185, 1123, 1095, 993, 930, 875, 790; HRMS (EI) calcd for $C_7H_5Cl_3N_2$ 221.9518, found 221.9494.

1-(2,4,6-Trichloropyrimidin-5-yl)propan-1-one (7c). To a solution of 2,4,6-trichloropyrimidine (**7**) (186 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 45 min according to TP2. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, propanoyl chloride (231 mg, 2.0 mmol) was added, and the resulting mixture was allowed to warm slowly to 25 °C overnight. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and aq NH_3, and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished the compound **7c** (201 mg, 84%) as a colorless solid: mp 74.3−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (q, J = 7.2 Hz, 2 H), 1.19 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 159.2, 158.3, 131.7, 36.8, 7.2; MS (70 eV, EI) *m*/*z* 238 (2) [^{35}Cl-M^+], 209 (100), 120 (8); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 2987, 2941, 2894, 1718, 1538, 1501, 1403, 1305, 1210, 1155, 1065, 946, 835, 657; HRMS (EI) calcd for $C_7H_5Cl_3N_2O$ 237.9467, found 237.9482.

Ethyl 2,6-Difluoro-3-nitrobenzoate (8a). To a solution of 2,4-fluoronitrobenzene (**8**) (776 mg, 5.0 mmol) dissolved in THF (5 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred for 1 h according to TP2. $Pd(PPh_3)_4$ (5 mol %, 290 g) dissolved in THF (7 mL) and mixed with ethyl chloroformate (1.36 g, 10 mmol) was then added via cannula to the reaction mixture. The resulting mixture was allowed to stir at 25 °C overnight. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (Et_2O/pentane 15:85) furnished the compound **8a** (728 mg, 63%) as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21−8.16 (m, 1H), 7.13−7.07 (m, 1H), 4.48−4.40 (m, 2H), 1.41−1.35 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 (dd, J = 266.3 Hz, J = 5.9 Hz), 159.4, 154.4, (dd, J = 274.0 Hz, J = 7.7 Hz), 134.2 (m), 129.15 (d, J = 12.6 Hz), 114.0 (t, J = 20.4 Hz), 112.4 (dd, J = 23.7 Hz, J = 4.7 Hz), 63.0, 14.0; MS (70 eV, EI) *m*/*z* 231 (3) [M^+], 203 (35), 186 (100), 171 (38), 140 (65), 112 (44), 62 (13); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3104, 2988, 1734, 1624, 1599, 1537, 1474, 1449, 1369, 1351, 1291, 1261, 1221, 1174, 1151, 1128, 1036, 1011, 860, 833, 791, 747, 654, 617; HRMS (EI) calcd for $C_9H_7F_2NO_4$, 231.0343, found 231.0345.

2-Allyl-3,5-dichloropyrazine (9a). To a solution of 2,6-dichloropyrazine (**9**) (149 mg, 1.0 mmol) dissolved in THF

(1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred at this temperature for 30 min according to TP2. After the mixture was cooled to −30 °C, CuCN·2LiCl (1 M solution in THF, 5 drops) was added, and the reaction mixture was then cooled to −60 °C. Allyl bromide (181 mg, 1.5 mmol) was added dropwise at −60 °C, and the reaction mixture was allowed to warm slowly to 0 °C for 1.5 h. The resulting mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:6) furnished the compound **9a** (148 mg, 78%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 6.07−5.93 (m, 1 H), 5.22−5.14 (m, 2 H), 3.70 (dt, J = 6.6 Hz, 1.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 146.8, 145.1, 141.8, 132.2, 118.3, 38.6; MS (70 eV, EI) m/z 188 (36) [^{35}Cl-M$^+$], 187 (100), 153 (13), 86 (2); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3453, 3081, 3055, 2985, 2938, 2680, 1722, 1646, 1533, 1516, 1455, 1419, 1377, 1323, 1289, 1250, 1142, 1101, 1058, 1023, 965, 931, 893, 877, 801, 746; HRMS (EI) calcd for $C_7H_6Cl_2N_2$ 187.9908, found 187.9888.

3,5-Dichloro-2-(4-chlorophenyl)pyrazine (9b). To a solution of 2,6-dichloropyrazine (**9**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred at this temperature for 30 min according to TP2. Pd(dba)$_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL) and mixed with 1-chloro-4-iodobenzene (310 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h and then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **9b** (210 mg, 81%) as a colorless solid: mp 122.6−124.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1 H), 7.75 (d, J = 9.0 Hz, 2 H), 7.47 (d, J = 9.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 145.6, 145.3, 142.0, 136.3, 133.4, 130.8, 128.6; MS (70 eV, EI) m/z 258 (100) [^{35}Cl-M$^+$], 225 (39), 223 (55), 137 (22), 85 (8); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3075, 2924, 1903, 1656, 1597, 1536, 1500, 1416, 1401, 1312, 1289, 1258, 1173, 1143, 1113, 1103, 1088, 1021, 1007, 959, 912, 865, 834, 825, 772, 737, 712, 657, 631, 620, 615, 602; HRMS (EI) calcd for $C_{10}H_5Cl_3N_2$ 257.9518, found 257.9353.

3,5-Dichloro-2-[3-(trifluoromethyl)phenyl]pyrazine (9c). To a \ solution of 2,6-dichloropyrazine (**9**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred at this temperature for 30 min according to TP2. Pd(dba)$_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL) and mixed with 3-iodobenzotrifluoride (354 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h and then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **9c** (242 mg, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.61 (s, 1 H), 8.07 (s, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 7.75 (d, J = 7.8 Hz, 1 H), 7.63 (t, J = 7.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.6, 146.1, 145.5, 142.2, 135.7, 132.6 (q, J = 2.7 Hz), 131.0 (q, J = 32.6 Hz), 128.9, 126.6 (q, J = 3.9 Hz), 126.5 (q, J = 3.9 Hz), 123.7 (q, J = 272.7 Hz); MS (70 eV, EI) m/z 292 (100) [^{35}Cl-M$^+$], 257 (66), 171 (18), 145 (10); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 2340, 1615, 1534, 1504, 1411, 1332, 1296, 1275, 1256, 1166, 1112, 1094, 1072, 1023, 1002, 903, 867, 807, 793, 772, 705, 697, 662, 653, 646, 620, 610, 604; HRMS (EI) calcd for $C_{11}H_5Cl_2F_3N_2$ 291.9782, found 291.9782.

3,5-Dichloro-2-hex-1-yn-1-ylpyrazine (9d). To a solution of 2,6-dichloropyrazine (**9**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred at this temperature for 30 min according to TP2. Iodine (381 mg, 1.5 mmol) dissolved in THF (2 mL) was added dropwise, and the resulting mixture was stirred for 1 h at 25 °C. To the solution of freshly generated in situ 2,3-chloro-5-iodopyrazine were successively slowly added NEt_3 (7 mL), CuI (8 mg, 4 mol %), Pd(dba)$_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) in THF (2 mL), and 1-hexyne (115 mg, 1.4 mmol). The reaction mixture was stirred at 25 °C for 1 h. The resulting mixture was quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **9d** (189 mg, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 2.51 (t, J = 7.1 Hz, 2 H), 1.40−1.68 (m, 4 H), 2.51 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 144.6, 141.7, 137.5, 101.6, 75.7, 29.9, 21.9, 19.4, 13.5; MS (70 eV, EI) m/z 228 (47) [^{35}Cl-M$^+$], 213 (92), 199 (100), 186 (39), 165 (31), 149 (72), 57 (44), 43 (50); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 2958, 2932, 2872, 2231, 1494, 1465, 1418, 1308, 1274, 1249, 1166, 1141, 1091, 1051, 1007, 948, 903, 875, 851, 829, 767, 743, 669, 654, 648, 638, 633, 628, 623, 618, 612, 601; HRMS (EI) calcd for $C_{10}H_{10}Cl_2N_2$ 228.0221, found 228.0213.

2,5-Dichloro-3-cyclohex-2-en-1-ylpyrazine (10a). To a solution of 2,6-dichloropyrazine (**10**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred at this temperature for 30 min according to TP2. After the mixture was cooled to −30 °C, CuCN·2LiCl (1 M solution in THF, 5 drops) was added, and the reaction mixture was then cooled to −60 °C. 3-Bromocyclohexene (242 mg, 1.5 mmol) was then added dropwise, and the reaction mixture was allowed to warm slowly to −20 °C for 2 h. The resulting mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **10a** (178 mg, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.44 (s, 1 H), 5.99−5.95 (m, 1 H), 5.65 (d, J = 10.0 Hz, 1 H), 4.00−3.98 (m, 1H), 2.16−206 (m, 3H), 1.86−1.83 (m, 1 H), 1.71−160 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.6, 146.2, 144.4, 141.7, 129.3, 126.2, 39.1, 27.9, 24.3, 21.0; MS (70 eV, EI) m/z 228 (100) [^{35}Cl-M$^+$], 215 (15), 201 (76), 199 (100), 187 (20), 174 (27), 164 (26), 79 (12), 67 (46); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3661, 3319, 3026, 2934, 2860, 2835, 1807, 1656, 1533, 1512, 1446, 1414, 1349, 1330, 1268, 1252, 1145, 1071, 1041, 987, 890, 861, 822, 786, 768, 721, 666, 633, 618, 611, 601; HRMS (EI) calcd for $C_{10}H_{10}Cl_2N_2$ 228.0221, found 228.0209.

2,5-Dichloro-3-[3-(trifluoromethyl)phenyl]pyrazine (10b). To a solution of 2,6-dichloropyrazine (**10**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was stirred at this temperature for 30 min according to TP2. Pd(dba)$_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL) and mixed with 3-iodobenzotrifluoride (354 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h and then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:9) furnished the compound **10b** (219 mg, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.61 (s, 1H), 8.07 (s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 149.6, 146.1, 145.4, 142.1,

135.8, 132.6 (d, J = 1.1 Hz), 131.5 (q, J = 32.8 Hz), 128.9, 126.5, (dq, J = 24.4 Hz, J = 3.9 Hz), 123.8 (d, J = 272.3 Hz); MS (70 eV, EI) m/z 292 (100) [^{35}Cl-M$^+$], 259 (25), 257 (72), 230 (17), 172 (19), 165 (11), 145 (15); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3079, 2357, 1810, 1615, 1534, 1505, 1443, 1411, 1332, 1305, 1296, 1275, 1256, 1221, 1166, 1112, 1094, 1072, 1023, 1002, 903, 867, 807, 793, 772, 734, 705, 697, 662, 653, 646, 635, 629, 625, 617, 608; HRMS (EI) calcd for $C_{11}H_5Cl_2F_3N_2$ 291.9782, found 291.9777.

2-Bromo-6-fluoro-4′-trifluoromethylbiphenyl-3-carbonitrile (11a). To a solution of 2-bromo-4-fluorobenzonitrile (**11**) (200 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 65 °C and for 30 min according to TP3. Pd(dba)$_2$ (14 mg, 2 mol %), P(2-furyl)$_3$ (10 mg, 4 mol %), and 4-iodo-benzotrifluoride (353 mg, 1.3 mmol) were then added, and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **11a** (305 mg, 89%) as a colorless solid: mp 145.3−147.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.71 (m, 3 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.28 (t, J = 8.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, J = 259.8 Hz), 136.4 (q, J = 1.6 Hz), 135.3, (d, J = 10.1 Hz), 131.8 (d, J = 19.6 Hz), 131.2 (q, J = 32.7 Hz), 130.2 (d, J = 1.0 Hz), 128.0 (d, J = 3.6 Hz), 123.8 (q, J = 272.5 Hz), 125.5 (q, J = 3.6 Hz), 116.7 (d, J = 1.2 Hz), 116.1 (d, J = 24.5 Hz), 113.3 (d, J = 3.9 Hz); MS (70 eV, EI) m/z 343 (100) [^{79}Br-M$^+$], 264 (10), 244 (30), 195 (35), 168 (7); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3065, 2924, 2230, 1921, 1619, 1592, 1569, 1520, 1463, 1408, 1392, 1322, 1278, 1257, 1191, 1160, 1109, 1071, 1053, 1020, 955, 905, 847, 834, 813, 766, 739, 696, 677; HRMS (EI) calcd for $C_{14}H_6BrF_4N$ 342.9620, found 342.9610.

2-(2-Bromo-3-cyano-6-fluorobenzyl)acrylic Acid Ethyl Ester (11b). To a solution of 2-bromo-4-fluorobenzonitrile (**11**) (200 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 65 °C for 30 min according to TP3. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 15 min of stirring at the same temperature, ethyl (2-bromomethyl)acrylate (250 mg, 1.3 mmol) was added, and the resulting mixture was allowed to warm slowly to 20 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **11b** (273 mg, 88%) as a colorless solid: mp 39.8−40.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.58 (m, 1 H), 7.16 (t, J = 8.6 Hz, 1 H), 6.22 (t, J = 1.7 Hz, 1 H), 5.07 (t, J = 1.7 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.84 (q, J = 1.9 Hz, 2 H), 1.3 (q, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 163.3 (d, J = 259.8 Hz), 135.7, 134.1 (d, J = 10.6 Hz), 129.6 (d, J = 5.4 Hz), 129.2 (d, J = 18.8 Hz), 125.6, 116.9 (d, J = 1.3 Hz), 115.6 (d, J = 24.8 Hz), 113.0 (d, J = 3.9 Hz), 61.1, 31.2 (d, J = 3.1 Hz), 14.1; MS (70 eV, EI) m/z 311 (4) [^{79}Br-M$^+$], 268 (19), 232 (100), 205 (26), 204 (62), 176 (63), 159 (96), 158 (67), 133 (22), 132 (17); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3078, 2985, 2938, 2235, 1926, 1704, 1635, 1579, 1469, 1432, 1403, 1369, 1348, 1280, 1256, 1207, 1170, 1136, 1094, 1025, 956, 864, 832, 755, 700, 685; HRMS (EI) calcd for $C_{13}H_{11}BrFNO_2$ 310.9957, found 310.9997.

2-Cyclohex-2-enyl-3-methoxypyrazine (12a). To a solution of 2-methoxypyrazine (**12**) (110 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 100 °C for 1 h according to TP3. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 15 min of stirring at the same temperature, 3-bromocyclohexene (209 mg, 1.3 mmol) was added, and the resulting mixture was allowed to warm slowly to 25 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2) furnished the compound **12a** (139 mg, 73%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−8.04 (m, 1 H), 7.90−7.89 (m, 1 H), 5.96−5.90 (m, 1 H), 5.75−5.71 (m, 1 H), 3.94 (s, 3 H), 3.92−3.89 (m, 1 H), 2.14−1.99 (m, 3 H), 1.84−1.57 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 150.6, 138.0, 135.7, 128.8, 128.0, 53.4, 37.3, 27.9, 24.8, 21.4; MS (70 eV, EI) m/z 190 (72) [^{35}Cl-M$^+$], 189 (26), 175 (25), 162 (26), 161 (100), 149 (11), 124 (61); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3052, 3025, 2983, 2934, 1836, 1893, 1787, 1685, 1651, 1574, 1540, 1457, 1444, 1394, 1378, 1345, 1328, 1314, 1266, 1248, 1223, 1184, 1167, 1138, 1127, 1076, 1062, 1043, 1009, 988, 932, 891, 863, 840, 804, 780, 768, 721, 703, 679; HRMS (EI) calcd for $C_{11}H_{14}N_2O$, 190.1106, found 190.1106.

4,6-Dichloro-5-cyclohex-2-enyl-2-methylsulfanylpyrimidine (13a). To a solution of 4,6-dichloro-2-methylsulfanylpyrimidine (**13**) (196 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 65 °C for 30 min according to TP3. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 15 min of stirring at the same temperature, 3-bromocyclohexene (209 mg, 1.3 mmol) was added, and the resulting mixture was allowed to warm slowly to 25 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished the compound **13a** (241 mg, 90%) as a colorless solid: mp 99.9−101.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87−5.80 (m, 1 H), 5.53−5.47 (m, 1 H), 4.13−4.03 (m, 1 H), 2.53 (s, 3 H), 2.14−2.06 (m, 2 H), 1.99−1.83 (m, 3 H), 1.76−1.63 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 161.3, 129.0, 128.2, 127.0, 37.9, 26.0, 24.2, 22.6, 14.3; MS (70 eV, EI) m/z 274 (100) [^{35}Cl-M$^+$], 248 (17), 246 (26), 220 (13), 211 (11), 208 (11), 150 (10); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 2926, 1534, 1480, 1337, 1309, 1258, 1181, 1119, 1043, 979, 882, 856, 825, 803, 769, 757, 717; HRMS (EI) calcd for $C_{11}H_{12}Cl_2N_2S$ 274.0098, found 274.0086.

(4,6-Dichloro-2-methylsulfanylpyrimidin-5-yl)thiophene-2-ylmethanone (13b). To a solution of 4,6-dichloro-2-methylsulfanylpyrimidine (**13**) (196 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 65 °C for 30 min according to TP3. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, 2-thiophenecarbonyl chloride (293 mg, 2.0 mmol) was added, and the resulting mixture was allowed to warm slowly to 25 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and aq NH_3, and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **13b** (268 mg, 88%) as a colorless solid: mp 126.1−127.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 4.8 Hz, 1 H), 7.49 (d, J = 3.8 Hz, 1 H), 7.17 (t, J = 4.3 Hz, 1 H), 2.60 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.0, 174.5, 157.9, 142.1, 137.0, 135.5, 128.8, 125.7, 14.5; MS (70 eV, EI) m/z 304 (78) [^{35}Cl-M$^+$], 110 (100); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3115, 3088, 2462, 2154, 2161, 1657, 1639, 1540, 1478, 1409, 1356, 1345, 1321, 1283,

1245, 1181, 1098, 1086, 1077, 1055, 976, 907, 884, 859, 826, 819, 768, 744, 740, 729, 686; HRMS (EI) calcd for $C_{10}H_6Cl_2N_2OS_2$ 303.9299, found 303.9288.

(3-Chlorophenyl)[4,6-dichloro-2-(methylthio)pyrimidin-5-yl]methanone (13c). To a solution of 4,6-dichloro-2-methylsulfanylpyrimidine (**13**) (590 mg, 3.0 mmol) dissolved in THF (3 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 65 °C for 30 min according to TP3. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, 2-chlorobenzoyl chloride (787 mg, 4.5 mmol) was added, and the resulting mixture was allowed to warm slowly to 25 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and NH_3, and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished the compound **13c** (880 mg, 88%) as a colorless solid: mp 158.4−160.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.82 (s, 1 H), 7.68 (d, J = 8.6 Hz, 1 H), 7.64−7.62 (m, 1 H), 7.47−7.44 (m, 1), 2.62 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 188.4, 175.0, 158.1, 136.7, 135.9, 135.0, 130.7, 129.4, 127.9, 125.3, 14.8; MS (70 eV, EI) m/z 332 (35) [^{35}Cl-M$^+$], 221 (16), 139 (100), 111 (58), 75 (44), 50 (20); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 2955, 2920, 2851, 1728, 1672, 1582, 1569, 1548, 1467, 1399, 1346, 1321, 1286, 1244, 1230, 1218, 1177, 1091, 1077, 1012, 968, 919, 847, 814, 747, 721, 664; HRMS (EI) calcd for $C_{12}H_7Cl_3N_2OS$ 331.9345, found 331.9334.

[3,5-Dichloro-6-(4-methoxyphenyl)pyrazin-2-yl](2-thienyl)methanone (14a). To a solution of 3,5-dichloro-2-(4-methoxyphenyl)-pyrazine (**14**) (256 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 100 °C (200 W) for 1 h in the microwave according to TP3. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, 2-thiophenecarbonyl chloride (293 mg, 2.0 mmol) was added, and the resulting mixture was allowed to warm slowly to 25 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and aq NH_3, and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **14a** (284 mg, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91−7.86 (m, 2 H), 7.81−7.78 (m, 2 H), 7.18−7.15 (m, 1 H), 7.03−6.98 (m, 2 H), 3.87 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.4, 161.3, 149.4, 145.6, 142.1, 140.9, 136.8, 131.3, 128.4, 126.2, 113.9, 55.4; MS (70 eV, EI) m/z 364 (15) [^{35}Cl-M$^+$], 111 (100); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3111, 3002, 2944, 2840, 2045, 1737, 1642, 1603, 1513, 1491, 1453, 1414, 1364, 1348, 1301, 1258, 1233, 1183, 1154, 1123, 1114, 1085, 1073, 1048, 1024, 1010, 946, 928, 869, 847, 834, 816, 796, 781, 753, 740, 724, 705, 662, 642, 633, 622, 611, 604; HRMS (EI) calcd for $C_{16}H_{10}Cl_2N_2O_2S$ 363.9840, found 363.9832.

[3,5-Dichloro-6-(4-methoxyphenyl)pyrazin-2-yl](phenyl)methanone (14b). To a solution of 3,5-dichloro-2-(4-methoxyphenyl-)pyrazine (**14**) (256 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 100 °C (200 W) for 1 h in the microwave according to TP3. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, benzoyl chloride (280 mg, 2.0 mmol) was added, and the resulting mixture was allowed to warm slowly to 25 °C within 2 h. The reaction mixture was then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and aq NH_3, and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **14b** (347 mg, 90%) as a colorless solid: mp 93.8−95.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91−7.81 (m, 4 H), 7.68−7.62 (m, 1 H), 7.53−7.48 (m, 2 H), 7.00−6.96 (m, 2 H), 3.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3, 161.3, 150.0, 147.6, 145.3, 141.4, 134.5, 131.2, 130.3, 128.8, 126.4, 113.8, 55.4; MS (70 eV, EI) m/z 358 (16) [^{35}Cl-M$^+$], 105 (100), 77 (34); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3005, 2356, 1748, 1664, 1605, 1594, 1579, 1512, 1501, 1441, 1420, 1370, 1298, 1266, 1253, 1216, 1179, 1153, 1121, 1087, 1029, 1012, 954, 864, 835, 810, 794, 778, 734, 711, 684, 661; HRMS (EI) calcd for $C_{18}H_{12}Cl_2N_2O_2$ 358.0276, found 358.0270.

5-Bromo-2,4-dimethoxy-6-(4-methoxyphenyl)pyrimidine (15a). To a solution of 5-bromo-2,4-dimethoxypyrimidine (**15**) (219 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 60 °C (100 W) for 30 min according to TP3. $Pd(dba)_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL) and mixed with 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 6 h and then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (pentane/ether 78:22) furnished the compound **15a** (300 mg, 92%) as a white solid: mp 114.1−115.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 8.8 Hz, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 4.07 (s, 3 H), 4.00 (s, 3 H), 3.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 165.3, 163.3, 160.8, 131.2, 130.0, 113.3, 96.3, 55.4, 55.3, 55.1; MS (EI, 70 eV) m/z 324 (100) [^{79}Br-M$^+$], 323 (47), 310 (14), 309 (15), 297 (22), 296 (39), 295 (26), 294 (36), 265 (12), 215 (38), 158 (16), 157 (12); IR (ATR) (cm^{-1}) 2989, 2940, 2836, 1615, 1583, 1565, 1543, 1519, 1482, 1447, 1416, 1380, 1352, 1309, 1300, 1258, 1201, 1194, 1188, 1177, 1150, 1109, 1030, 1019, 1008, 946, 930, 866, 836, 824, 808, 785, 740, 728, 705, 676, 660, 627; HRMS (EI) calcd for $C_{13}H_{13}BrN_2O_3$ 324.0110, found 324.0114.

4-(5-Bromo-2,6-dimethoxypyrimidin-4-yl)benzoic Acid Ethyl Ester (15b). To a solution of 5-bromo-2,4-dimethoxypyrimidine (**15**) (219 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 60 °C (100 W) for 30 min according to TP3. $Pd(dba)_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL) and mixed with ethyl 4-iodobenzoate (304 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 6 h and then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (pentane/ether 75:25) furnished the compound **15b** (314 mg, 86%) as a white solid: mp 128.9−130.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 8.4 Hz, 2 H), 7.80 (d, J = 8.4 Hz, 2 H), 4.40 (q, J = 7.1 Hz, 2 H), 4.09 (s, 3 H), 4.01 (s, 3 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 166.1, 165.2, 163.5, 141.8, 131.4, 129.4, 129.1, 97.0, 61.2, 55.4, 55.3, 14.3; MS (70 eV, EI) m/z 366 (90) [^{79}Br-M$^+$], 365 (55), 339 (29), 338 (56), 337 (32), 336 (47), 323 (36), 321 (35), 223 (16), 221 (15); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 2997, 2941, 1943, 1714, 1664, 1560, 1539, 1509, 1481, 1452, 1408, 1379, 1349, 1311, 1282, 1238, 1193, 1178, 1153, 1127, 1112, 1104, 1030, 1022, 1006, 938, 877, 865, 843, 788, 775, 732, 719, 702, 688, 688, 669, 656, 628; HRMS (EI) calcd for $C_{15}H_{15}BrN_2O_4$ 366.0215, found 366.0195.

6-Chloro-3-methoxy-4-[4-(trifluoromethyl)phenyl]pyridazine (16a). To a solution of 3-chloro-6-methoxypyridazine (**16**) (145 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 80 °C (100 W) for 60 min according to TP3. $Pd(dba)_2$ (17 mg, 3 mol %) and P(2-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL) and mixed with

1-iodo-4-trifluoromethylbenzene (300 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 6 h and then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2) furnished the compound **16a** (257 mg, 89%) as a white solid: mp 139.8−141.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76−7.70 (m, 4 H), 7.41 (s, 1 H), 4.17 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.5, 151.5, 135.9, 131.8 (q, J = 32.8 Hz), 131.3, 129.5, 128.9, 125.7 (q, J = 3.6 Hz), 123.7 (q, J = 272.4 Hz), 55.7; MS (70 eV, EI) m/z 288 (36) [^{35}Cl-M$^+$], 287 (100), 271 (13), 217 (16), 203 (22); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3029, 2991, 2950, 2894, 2863, 2349, 2234, 1928, 1738, 1620, 1574, 1526, 1460, 1454, 1412, 1377, 1324, 1296, 1259, 1236, 1166, 1109, 1070, 1043, 1017, 961, 930, 864, 842, 778, 743, 730, 678; HRMS (EI) calcd for $C_{12}H_8ClF_3N_2O$ 288.0277, found 288.0250.

(6-Chloro-3-methoxypyridazin-4-yl)phenylmethanone (16b). To a solution of 3-chloro-6-methoxypyridazine (**16**) (145 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 80 °C (100 W) for 60 min according to TP3. The reaction mixture was cooled to −20 °C, and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, benzoyl chloride (155 mg, 1.1 mmol) was added, and the resulting mixture was allowed to warm slowly within 2 h. The reaction mixture was quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (pentane/ether 65:35) furnished the compound **16b** (200 mg, 80%) as yellowish white solid: mp 97.1−98.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77−7.74 (m, 2 H), 7.68−7.63 (m, 1 H), 7.50 (t, J = 7.7 Hz, 2 H), 7.38 (s, 1 H), 4.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.4, 160.8, 151.3, 135.0, 134.8, 130.4, 129.7, 128,9, 128.5, 55.7; MS (70 eV, EI) m/z 248 (21) [^{35}Cl-M$^+$], 219 (6), 183 (7), 105 (100), 91 (38), 77 (69), 51 (18); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3080, 3026, 2955, 1810, 1668, 1595, 1579, 1530, 1489, 1458, 1449, 1371, 1327, 1308, 1287, 1268, 1192, 1173, 1161, 1124, 1096, 1078, 1023, 994, 965, 902, 832, 802, 778, 731, 709, 682, 670, 651, 623, 614; HRMS (ESI) calcd for $C_{12}H_9ClN_2O_2$ 249.0432, found 249.0425.

4-Iodo-3,6-dimethoxypyridazine (17a). To a solution of 3,6-dimethoxypyridazine (**17**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 90 °C (100 W) for 1 h according to TP3. Iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added, and the resulting mixture was stirred for 0.5 h. The reaction mixture was quenched with a satd aq $Na_2S_2O_3$ solution (10 mL) and with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (pentane/ether, 8:2) furnished the compound **17a** (201 mg, 76%) as a white solid: mp 154.1−156.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (s, 1 H), 4.01 (s, 3 H), 4.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3, 160.1, 130.8, 93.9, 55.9, 54.9; MS (70 eV, EI) m/z 266 (100) [M$^+$], 265 (66), 237 (29), 109 (12), 85 (14), 71 (22), 57 (25), 53 (23); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3069, 3008, 2996, 2984, 2960, 2948, 2890, 2859, 2667, 2568, 2197, 1996, 1908, 1793, 1576, 1535, 1512, 1458, 1443, 1371, 1346, 1298, 1230, 1186, 1134, 1058, 1019, 1003, 896, 856, 800, 771, 748, 667; HRMS (EI) calcd for $C_6H_7IN_2O_2$ 265.9552, found 265.9553.

4-(4-Chlorophenyl)-3,6-dimethoxypyridazine (17b). To a solution of 3,6-dimethoxypyridazine (**17**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C, and the resulting mixture was heated at 90 °C (100 W) for 1 h according to TP3. Pd(dba)$_2$ (17 mg, 3 mol %) and P(o-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL) and mixed with 1-chloro-4-iodobenzene (262 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 6 h and then quenched with a satd aq NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2) furnished the compound **17b** (220 mg, 88%) as a white solid: mp 117.1−118.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50 (dt, J = 6.6, 2.2 Hz, 2 H), 7.38 (dt, J = 6.8, 2.2 Hz, 2 H), 6.87 (s, 1 H), 4.05 (s, 3 H), 4.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.6, 159.1, 135.6, 132.8, 131.8, 130.3, 128.7, 119.0, 54.8, 54.6; MS (70 eV, EI) m/z 249 (100) [^{35}Cl-M$^+$], 233 (11), 221 (16), 136 (21); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 3047, 3023, 2992, 2953, 2865, 1910, 1737, 1657, 1612, 1536, 1494, 1462, 1446, 1405, 1375, 1356, 1302, 1273, 1253, 1221, 1192, 1143, 1108, 1091, 1017, 1013, 995, 963, 909, 876, 835, 827, 821, 774, 769, 744, 718, 669, 658, 629, 612; HRMS (EI) calcd for $C_{12}H_{11}ClN_2O_2$ 249.0430, found 249.0428.

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Note Added after ASAP Publication. There were errors in the version published ASAP June 17, 2010. The supporting information and structure **11b** in Table 2 have been replaced; the corrected version reposted on June 23, 2010.

Supporting Information Available: NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.