# Efficient Palladium-Catalyzed Synthesis of Unsymmetrical (Het)aryl-tetrazines

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**Abstract:** Palladium-catalyzed copper(I)-mediated cross-coupling reaction of 3-methylthio-6-(morpholin-4-yl)-1,2,4,5-tetrazine with a wide range of boronic acids and organotin derivatives led to new unsymmetrical aryl- and hetaryl-substituted tetrazines in moderate to good yields. These results represent the first cross-coupling reactions of readily available 3-methylthiotetrazine under Suzuki-like and Stille-like conditions and could extend the scope of tetrazine chemistry.

**Key words:** 3-methylthio-1,2,4,5-tetrazine, Pd-catalyzed, Cu(I)-assisted, Suzuki-like reactions, Stille-like reactions

Over the past two decades, the chemistry of tetrazines has received a growing interest,[1] in particular in the fields of organic synthesis,[2] pesticides[3] and pyrotechnics.[4] Their specific reactivity properties, due to an extremely electron-deficient core, make them a partner of choice in the inverse-electron demand Diels–Alder reaction[5] and open the way to the synthesis of the core of various natural products[5b,e] as well as heterocyclic rings such as pyridazines[5c–f,6] or 1,2,4-triazines.[7]

The use of these compounds is weakened by the lack of synthetic methods providing unsymmetrical tetrazines. Nucleophilic substitution remains the most common way, generally by using 3,6-dichloro-, 3,6-bis(3,5-dimethylpyrazol-1-yl)- or 3,6-bis(methylthio)-1,2,4,5-tetrazines.[8] The use of amines, thiols or alkoxide derivatives as nucleophiles often leads to the desired substituted products in good yields.[8] However, this subtitution pathway has deficiencies since the carbon–carbon bond formation is poorly represented in literature and is restricted to few carbon nucleophiles such as cyanides or malonic acid derivatives.[5c,e,9]

Recently, Kotschy's group[10] reported the synthesis of unsymmetrical tetrazines from cross-coupling reactions of 6-substituted 3-chloro-1,2,4,5-tetrazines with different alkynes with encouraging yields. The authors have shown that the reactivity of chlorotetrazines depends on the nature of the ring substituent and that electron-deficient tetrazines are unstable under the required experimental conditions.

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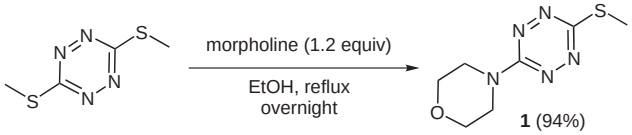
During the course of our investigations on carbon–carbon bond formation between a 1,2,4,5-tetrazine core and aromatic or heteroaromatic derivatives, we thought about well-established Suzuki or Stille cross-coupling reactions.[11] Kotschy's group has reported an unsuccessful Suzuki cross-coupling reaction[10] suggesting that boronic acids initiate unexpected side reactions under alkaline conditions. Furthermore, other reactive organometallic species such as organolithium, Grignard or arylzinc reagents were unsuccessfull along with an attempted Heck reaction.[10]

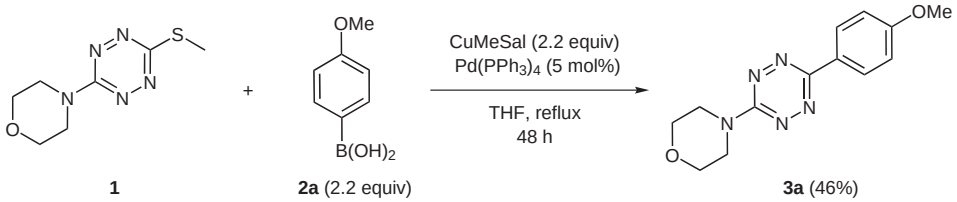



**Scheme 1** Preparation of 3-methylthio-6-(morpholin-4-yl)-1,2,4,5-tetrazine **1**

An overall view of tetrazine chemistry clearly indicates that the 3,6-bis(methylthio)-1,2,4,5-tetrazine is readily accessible[6c,12] on a large scale. Liebeskind and co-workers,[13] as well as we, have recently developed copper(I)-mediated palladium-catalyzed cross-coupling reactions between heteroaromatic thioethers and organoborons[14] and organostannanes.[15] These methods have been extended to various thioether substrates.[16] We decided to apply this cross-coupling approach to methylthiotetrazines.

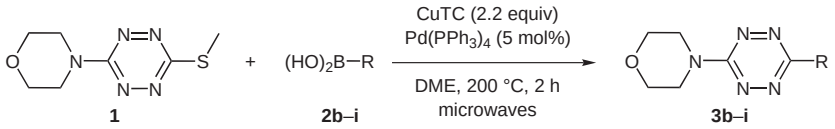
According to Kotschy et al. (vide infra),[10] 3-chloro-1,2,4,5-tetrazine bearing a morpholino substituent is one of the more stable substrates when involved in Sonogashira cross-coupling. Therefore, we decided to start our investigations with the 3-methylthio-6-(morpholin-4-yl)-1,2,4,5-tetrazine (**1**). This compound was readily obtained by nucleophilic displacement of one methylthio group of 3,6-bis(methylthio)-1,2,4,5-tetrazine with morpholine (Scheme 1).[17]

The first cross-coupling attempt was performed with the commercially available 4-methoxyphenylboronic acid (**2a**) under standard conditions using copper(I) methylsalicylate (CuMeSal) and tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$, (5 mol%)] in refluxing tetrahydrofuran (Scheme 2). After 48 hours, the coupled product **3a** was isolated with a promising 46% yield. No degradation of the starting material was observed, which was recovered (42%; Table 1, entry 1).




**1** **2a** (2.2 equiv) **3a** (46%)

**Scheme 2** Pd-catalyzed cross-coupling reaction between tetrazine **1** and boronic acid **2a**




**1** **2b–i** **3b–i**

**Scheme 3** Extension of the reaction to various boronic acid derivatives

In a second set of experiments (Table 1), the nature of the copper cofactor was investigated. Among the copper(I) carboxylates examined, copper(I) thiophene-2-carboxylate (CuTC) gave the best results (Table 1, entry 2). As to the solvent, no significant difference was observed between tetrahydrofuran and 1,2-dimethoxyethane (DME; Table 1, entry 3). However, the yield dramatically decreased when a non-polar aprotic solvent like toluene was used (Table 1, entry 4).

Increasing the charge of the palladium catalyst brought no improvement (Table 1, entry 5), no more and no less than a progressive addition of the boronic acid **2a** and CuTC (Table 1, entry 6). We then decided to take advantage of microwave activation on this copper-promoted reaction.[16b] After few attempts of optimizing the temperature (Table 1, entries 7 and 8), the reaction time (Table 1, entries 8 and 9) or the amount of Pd catalyst (Table 1, entries 8 and 10), the best reaction conditions were achieved in DME at 200 °C (microwave irradiation) over two hours (Table 1, entry 9).[18]

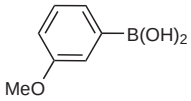
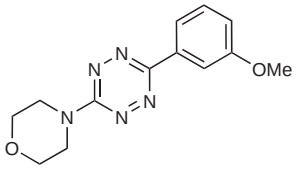
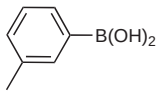
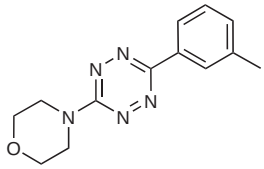
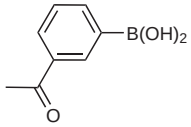
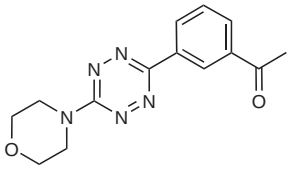
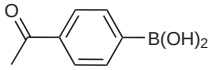
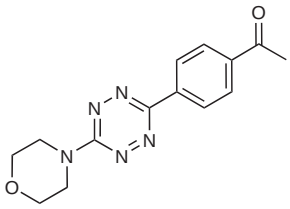
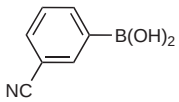
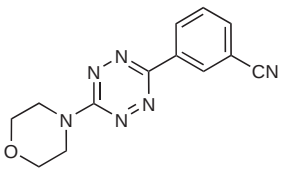
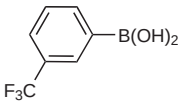
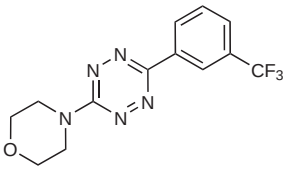
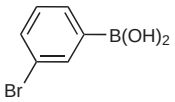
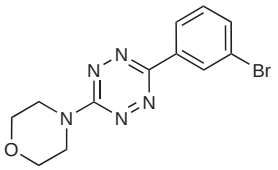
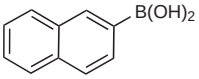
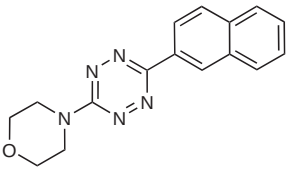
Different boronic acids were evaluated under the previous conditions (Scheme 3). Results are summarized in Table 2. Methylthiotetrazine **1** proved to react readily with electron-rich arylboronic acids in good yields (Table 2, entries 1 and 2). On using electron-poor arylboronic acids **2d**, **2e** and **2f**, the corresponding products were isolated in 56%, 54% and 28% yields respectively (Table 2, entries 3–5). Nevertheless, the reaction with boronic acids **2g**–**i** gave the resulting products **3g**–**i** which were first isolated as mixtures with the starting material **1**. A treatment with *m*-chloroperoxybenzoic acid (MCPBA) in dichloromethane converted tetrazine **1** into the more polar 3-methylsulfinyl-6-(morpholin-4-yl)-1,2,4,5-tetrazine and 3-methylsulfonyl-6-(morpholin-4-yl)-1,2,4,5-tetrazine (Table 2, entries 6–8),[5f,19] which were easily removed after purification. However, this oxidation step probably initiated side reactions responsible for low yields.

**Table 1** Optimization of the Pd-Catalyzed Cross-Coupling Conditions between Tetrazine **1** and Boronic Acid **2a**

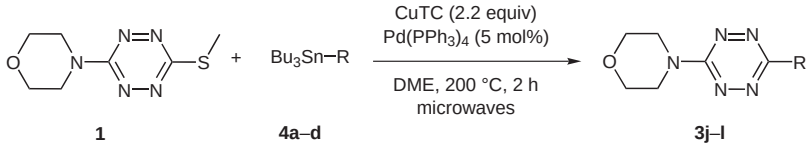
| Entry | $Pd(PPh_3)_4$ | 'Cu' | Solvent | Heating, Time | Yield (%)[a] | Recovered tetrazine **1** (%) |
|---|---|---|---|---|---|---|
| 1 | 5 mol% | CuMeSal | THF | Reflux, 48 h | 46 | 42 |
| 2 | 5 mol% | CuTC | THF | Reflux, 48 h | 68 | 20 |
| 3 | 5 mol% | CuTC | DME | Reflux, 48 h | 66 | 14 |
| 4 | 5 mol% | CuTC | Toluene | Reflux, 48 h | 14 | 75 |
| 5 | 15 mol% | CuTC | DME | Reflux, 48 h | 61 | 16 |
| 6[b] | 5 mol% | CuTC | DME | Reflux, 48 h | 46 | 31 |
| 7 | 5 mol% | CuTC | DME | Microwaves,[c] 180 °C, 2 h | 62 | 23 |
| 8 | 5 mol% | CuTC | DME | Microwaves,[c] 200 °C, 2 h | 71 | 20 |
| 9 | 5 mol% | CuTC | DME | Microwaves,[c] 200 °C, 4 h | 67 | 20 |
| 10 | 10 mol% | CuTC | DME | Microwaves,[c] 200 °C, 2 h | 71 | 21 |

[a] Isolated yield of the pure product.
[b] Run performed with progressive addition of boronic acid and CuTC quantities.
[c] Run performed with a Biotage Initiator microwave apparatus (control by means of temperature).

**Table 2** Copper(I)-Promoted Palladium-Catalyzed Cross-Coupling of Boronic Acids **2b–i** with 3-Methylthio-6-(morpholin-4-yl)-1,2,4,5-tetrazine **1**

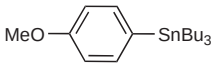
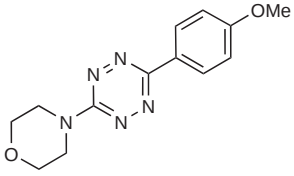
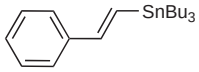
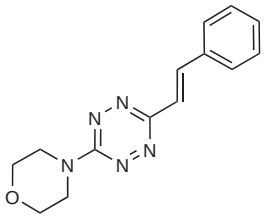
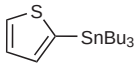
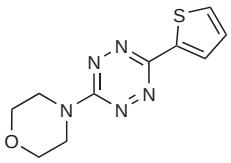
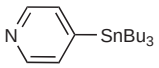
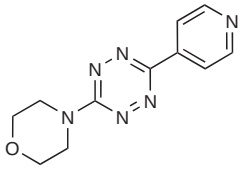
| Entry | $RB(OH)_2$ | Product | Yield (%)[a] | Recovered **1** (%) |
|---|---|---|---|---|
| 1 |  **2b** |  **3b** | 67 | 21 |
| 2 |  **2c** |  **3c** | 58 | 21 |
| 3 |  **2d** |  **3d** | 56 | 23 |
| 4 |  **2e** |  **3e** | 54 | 27 |
| 5 |  **2f** |  **3f** | 28 | 49 |
| 6[b] |  **2g** |  **3g** | 31 | n.d. |
| 7[b] |  **2h** |  **3h** | 42 | n.d. |
| 8[b] |  **2i** |  **3i** | 60 | n.d. |

[a] Isolated yield of the pure product.
[b] An oxidative treatment with MCPBA was required after completion of the cross-coupling reaction.




**Scheme 4** Extension of the reaction to organostannanes derivatives

**Table 3** Copper(I)-Promoted Palladium-Catalyzed Cross-Coupling of Stannanes **4a**–**d** with 3-Methylthio-6-(morpholin-4-yl)-1,2,4,5-tetrazine **1** under Microwave Irradiation

| Entry | $RSnBu_3$ | Product | Yield (%)[a] | Recovered **1** (%) |
|---|---|---|---|---|
| 1 |  **4a** |  **3a** | 49 | 28 |
| 2[b] |  **4b** |  **3j** | 34 | n.d. |
| 3 |  **4c** |  **3k** | 35<br>52[c] | 31<br>29[c] |
| 4 |  **4d** |  **3l** | 8<br>30[c] | 38<br>28[c] |

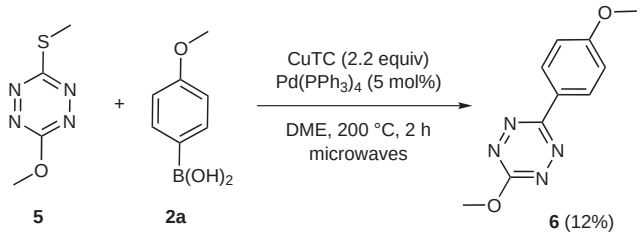
[a] Isolated yield of the pure product.
[b] An oxidative treatment with MCPBA was required after completion of the cross-coupling reaction.
[c] Reactions carried out in refluxing DME for 48 h.

The cross-coupling method was then extended to organotin derivatives (Scheme 4). Different organostannanes were evaluated using $Pd(PPh_3)_4$ and CuTC in DME under microwave irradiation for two hours (Table 3).[20]

The reaction of methylthiotetrazine **1** with organostannane **4a**[21] was performed (Table 3, entry 1) and compared to the cross-coupling between **1** and organoboron **2a** (Scheme 2). A lower yield of the desired product **3a** and degradation products were observed in the former reaction.

Once **1** reacted with styryl derivative **4b**,[22] the crude mixture underwent an oxidative treatment with MCPBA,[19] which affected the isolated yield of the product **3j** (Table 3, entry 2). The high sensitivity of the organotin derivatives towards the cross-coupling reaction conditions was also demonstrated through two additional experiments (Table 3, entries 3 and 4). Reactions of **1** with organostannanes **4c** and **4d**[23] were performed in DME under microwave irradiation and in refluxing DME. It is noteworthy that desired tetrazines **3k** and **3l** were isolated in higher yields in refluxing DME.[24]

Lastly, when the electron-deficient 3-methylthio-6-methoxy-1,2,4,5-tetrazine (**5**)[6c] was reacted with **2a** at 200 °C under microwave irradiation, the coupled product **6** was isolated in 12% yield among degradation products (Scheme 5).[25] Under the same experimental conditions, the 3-chloro-6-methylthio-1,2,4,5-tetrazine, unfortunately, degraded completely.




**Scheme 5** Pd-catalyzed cross-coupling reaction of 3-methylthio-6-methoxy-1,2,4,5-tetrazine (**5**) and boronic acid **2a**

In conclusion, we have demonstrated the cross-coupling of a 3-methylthio-1,2,4,5-tetrazine with boronic acids and organostannane derivatives. Microwave irradiation allows shorter reaction times. This reaction constitutes a very efficient way for the synthesis of unsymmetrical tetrazines with vinyl, aryl and heteroaryl substituents. Work is in progress to increase the diversity of both substituents on tetrazines.

## Acknowledgment

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(17) (17) **3-Methylthio-6-(morpholin-4-yl)-1,2,4,5-tetrazine (1)**: To a suspension of 3,6-bis(methylthio)-1,2,4,5-tetrazine (1.08 g, 6.2 mmol) in EtOH (20 mL) at 25 °C, morpholine (660 μL, 7.5 mmol) was added. After the mixture was refluxed for 15 h, it was allowed to cool to r.t. and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane–EtOAc = 95:5 to 8:2). 3-Methylthiotetrazine **1** (1.24 g, 94%) was obtained as a red solid; mp 131–132 °C. MS (Ionspray®): *m*/*z* = 214 $[M + H]^+$. $^1$H NMR (250 MHz, $CDCl_3$): δ = 3.94 (dt, *J* = 1.0, 4.8 Hz, 4 H), 3.84 (dt, *J* = 1.0, 4.8 Hz, 4 H), 2.67 (s, 3 H). $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ = 166.6 (C), 160.5 (C), 66.5 ($CH_2$), 43.9 ($CH_2$), 13.7 ($CH_3$). IR: 2965, 2908, 1524, 1441, 1267, 1113, 920, 847, 791 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_7H_{11}N_5OS$: 213.0684; found: 213.0687.

(18) **Palladium-Catalyzed Cross-Coupling Reaction of Compound 1 with Boronic Acids 2a–i; General Procedure**: 3-Methylthio-6-(morpholin-4-yl)-1,2,4,5-tetrazine (**1**; 100 mg, 0.5 mmol), boronic acid (1.1 mmol) and CuTC (197 mg, 1.1 mmol) were dissolved in anhyd DME (5 mL) in a sealed reaction vessel under argon. After the mixture was degassed, $Pd(PPh_3)_4$ (27 mg, 0.025 mmol) was added and the reaction mixture was stirred under microwave irradiation at 200 °C (14–16 bars) for 2 h. The reaction mixture was then allowed to cool to r.t., poured into sat. aq $Na_2CO_3$ and extracted with $CH_2Cl_2$. The organic phases were collected, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Desired compounds were purified by chromatography on silica gel (PE–EtOAc = 95:5 to 7:3).

**3-(Morpholin-4-yl)-6-(4-methoxyphenyl)-1,2,4,5-tetrazine (3a)**: 4-Methoxyphenylboronic acid (**2a**; yield: 71%) and 1-methoxy-4-tributylstannylbenzene (**4a**; yield: 49%) were used as the boronic acid and the organostannane derivatives, respectively; red solid; mp 176–178 °C. MS (Ionspray®): *m*/*z* = 274 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 9.0 Hz, 2 H), 7.05 (d, *J* = 9.0 Hz, 2 H), 4.04 (t, *J* = 4.5 Hz, 4 H), 3.89 (s, 3 H), 3.87 (t, *J* = 4.5 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 162.0 (C), 160.6 (C), 159.5 (C), 128.0 (CH), 125.3 (C), 114.6 (CH), 66.6 ($CH_2$), 55.6 ($CH_3$), 43.9 ($CH_2$). IR: 2917, 1607, 1512, 1438, 1244, 1116, 1034, 936, 837 $cm^{-1}$. Anal. Calcd for $C_{13}H_{15}N_6O_2$ (273): C, 57.13; H, 5.53; N, 25.63. Found: C, 57.34; H, 5.52; N, 24.48.

**3-(Morpholin-4-yl)-6-(3-methoxyphenyl)-1,2,4,5-tetrazine (3b)**: 3-Methoxyphenylboronic acid (**2b**) was used as the boronic acid derivative; yield: 67%; red solid; mp 140–142 °C. MS (Ionspray®): *m*/*z* = 274 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 7.99 (dt, *J* = 1.0, 8.0 Hz, 1 H), 7.93 (dd, *J* = 1.0, 2.6 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.05 (ddd, *J* = 1.0, 2.6, 8.0 Hz, 1 H), 4.05 (t, *J* = 4.5 Hz, 4 H), 3.89 (s, 3 H), 3.87 (t, *J* = 4.5 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.5 (C), 160.2 (C), 159.3 (C), 134.0 (C), 130.1 (CH), 118.8 (CH), 117.4 (CH), 110.7 (CH), 66.5 ($CH_2$), 55.5 ($CH_3$), 43.8 ($CH_2$). IR: 2927, 2857, 1598, 1522, 1448, 1262, 1229, 1119, 963, 786 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{13}H_{15}N_5O_2$: 273.1226; found: 273.1220.

**3-(Morpholin-4-yl)-6-(3-methylphenyl)-1,2,4,5-tetrazine (3c)**: 3-Methylphenylboronic acid (**2c**) was used as the boronic acid derivative; yield 58%; red solid; mp 127–129 °C. MS (Ionspray®): *m*/*z* = 258.5 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 8.20 (d, *J* = 7.8 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 4.06 (t, *J* = 4.7 Hz, 4 H), 3.88 (t, *J* = 4.7 Hz, 4 H), 2.46 (s, 3 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.6 (C), 159.7 (C), 139.9 (C), 132.6 (C), 131.6 (CH), 129.1 (CH), 127.1 (CH), 123.6 (CH), 66.6 ($CH_2$), 43.9 ($CH_2$), 21.7 ($CH_3$). IR: 2965, 2860, 2362, 2338, 1521, 1451, 1252, 1116, 941, 784 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{13}H_{15}N_5O$: 257.1277; found: 257.1288.

**3-(Morpholin-4-yl)-6-(3-acetylphenyl)-1,2,4,5-tetrazine (3d)**: 3-Acetylphenylboronic acid (**2d**) was used as the boronic acid derivative; yield: 56%; red solid; mp 174–176 °C. MS (Ionspray®): *m*/*z* = 286 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.98 (s, 1 H), 8.60 (d, *J* = 7.9 Hz, 1 H), 8.12 (d, *J* = 7.9 Hz, 1 H), 7.65 (t, *J* = 7.9 Hz, 1 H), 4.09 (t, *J* = 4.4 Hz, 4 H), 3.89 (t, *J* = 4.4 Hz, 4 H), 2.70 (s, 3 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 197.7 (C), 160.5 (C), 158.7 (C), 137.9 (C), 133.2 (C), 130.5 (CH), 130.1 (CH), 129.5 (CH), 126.4 (CH), 66.5 ($CH_2$), 43.8 ($CH_2$), 26.9 ($CH_3$). IR: 2981, 2906, 2359, 2340, 1692, 1536, 1262, 1111, 967, 946 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{14}H_{15}N_5O_2$: 285.1226; found: 285.1213.

**3-(Morpholin-4-yl)-6-(4-acetylphenyl)-1,2,4,5-tetrazine (3e)**: 4-Acetylphenylboronic acid(**2e**) was used as the boronic acid derivative; yield: 54%; red solid; mp 194–197 °C. MS (Ionspray®): *m*/*z* = 286 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 8.8 Hz, 2 H), 8.11 (d, *J* = 8.8 Hz, 2 H), 4.09 (t, *J* = 4.6 Hz, 4 H), 3.89 (t, *J* = 4.6 Hz, 4 H), 2.41 (s, 3 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 197.7 (C), 160.2 (C), 158.7 (C), 138.6 (C), 136.9 (C), 129.1 (CH), 126.4 (CH), 66.6 ($CH_2$), 43.9 ($CH_2$), 26.9 ($CH_3$). IR: 2975, 2874, 2324, 1676, 1536, 1269, 1114, 943, 849 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{14}H_{15}N_5O_2$: 285.1226; found: 285.1216.

**3-(Morpholin-4-yl)-6-(3-cyanophenyl)-1,2,4,5-tetrazine (3f)**: 3-Cyanophenylboronic acid (**2f**) was used as the boronic acid derivative; yield: 28%; red solid; mp 197–198 °C. MS (Ionspray®): *m*/*z* = 269 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.71 (dt, *J* = 0.5, 1.5 Hz, 1 H), 8.63 (dt, *J* = 1.5, 8.0 Hz, 1 H), 7.79 (dt, *J* = 1.5, 8.0 Hz, 1 H), 7.65 (dt, *J* = 0.5, 8.0 Hz, 1 H), 4.09 (t, *J* = 4.7 Hz, 4 H), 3.89 (t, *J* = 4.7 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.4 (C), 157.8 (C), 134.1 (C), 133.8 (CH), 130.1 (CH), 130.0 (CH), 129.8 (CH), 118.5 (C), 113.5 (C), 66.5 ($CH_2$), 43.9 ($CH_2$). IR: 2872, 2235, 1536, 1446, 1255, 1117, 1034, 966 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{13}H_{12}N_6O$: 268.1073; found: 268.1079.

**3-(Morpholin-4-yl)-6-(3-trifluoromethylphenyl)-1,2,4,5-tetrazine (3g)**: 3-Trifluoromethylphenylboronic acid (**2g**) was used as the boronic acid derivative; yield: 31%; red solid; mp 144 °C. MS (Ionspray®): *m*/*z* = 311.5 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.69 (s, 1 H), 8.58 (d, *J* = 7.8 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.66 (t, *J* = 7.8 Hz, 1 H), 4.08 (t, *J* = 4.5 Hz, 4 H), 3.89 (t, *J* = 4.5 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.5 (C), 158.4 (C), 133.6 (C), 131.6 ($^2J_{C-F}$ = 33 Hz, C), 129.7 (CH), 129.3 (CH), 127.3 ($^3J_{C-F}$ = 4 Hz, CH), 124.1 ($^1J_{C-F}$ = 271 Hz, C), 123.2 ($^3J_{C-F}$ = 4 Hz, CH), 66.5 ($CH_2$), 43.9 ($CH_2$). IR: 2917, 2850, 1530, 1446, 1302, 1268, 1166, 1120, 1066, 1034, 963, 945, 695 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{13}H_{12}N_5OF_3$: 311.0994; found: 311.0991.

**3-(Morpholin-4-yl)-6-(3-bromophenyl)-1,2,4,5-tetrazine (3h)**: 3-Bromophenylboronic acid (**2h**) was used as the boronic acid derivative; yield: 42%; red solid; mp 141–142 °C. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.56 (t, *J* = 1.5 Hz, 1 H), 8.33 (ddd, *J* = 1.0, 1.5, 8.0 Hz, 1 H), 7.64 (ddd, *J* = 1.0, 1.5, 8.0 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 4.07 (t, *J* = 4.4 Hz, 4 H), 3.88 (t, *J* = 4.4 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.5 (C), 158.4 (C), 134.8 (C), 133.7 (CH), 130.6 (CH), 129.4 (CH), 124.8 (CH), 123.4 (C), 66.6 ($CH_2$), 43.9 ($CH_2$). IR: 2361, 2337, 1530, 1447, 1254, 1123, 1031, 944, 780, 733 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{12}H_{12}N_5O^{79}Br$: 321.0225; found: 321.0211.

**3-(Morpholin-4-yl)-6-(naphtalen-2-yl)-1,2,4,5-tetrazine (3i)**: Naphthalen-2-ylboronic acid (**2i**) was used as boronic acid derivative; yield: 60%; red solid; mp 172–173 °C. MS (Ionspray®): *m*/*z* = 294 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.93 (s, 1 H), 8.48 (dd, *J* = 1.8, 8.5 Hz, 1 H), 7.99 (d, *J* = 8.5 Hz, 2 H), 7.89 (t, *J* = 5.0 Hz, 1 H), 7.54 (m, 2 H), 4.08 (t, *J* = 4.5 Hz, 4 H), 3.89 (t, *J* = 4.5 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.5 (C), 159.7 (C), 134.7 (C), 133.5 (C), 130.0 (C), 129.2 (CH), 129.0 (CH), 128.0 (CH), 127.4 (CH), 126.8 (CH), 126.5 (CH), 123.3 (CH), 66.6 ($CH_2$), 43.9 ($CH_2$). IR: 2960, 2869, 2359, 1522, 1451, 1336, 1262, 1119, 953 $cm^{-1}$. Anal. Calcd for $C_{16}H_{15}N_5O$(293): C, 65.52; H, 5.15; N, 23.88. Found: C, 65.64; H, 5.07; N, 23.26.

(19) **Cross-Coupling Reaction Followed by an Oxidative Treatment (Compounds 3g–j)**: Same procedure as in ref. 18 was used with an extra oxidative step, described as follows. The crude product was dissolved in $CH_2Cl_2$. After

the temperature was adjusted to 5 °C with an ice bath, MCPBA (81 mg, 0.47 mmol) was added and the mixture was stirred for 30 min at 5 °C. The reaction was then hydrolyzed with sat. aq $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic phases were collected, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Desired compounds were purified by chromatography on silica gel (PE–EtOAc: 95:5 to 7:3).

(20) **Palladium-Catalyzed Cross-Coupling Reaction of Compound 1 with Organostannanes 4a–d; General Procedure**: Same procedure as in ref. 18 was used except that the reaction was carried out with organotin derivatives.
**3-(Morpholin-4-yl)-6-[(*E*)-styryl]-1,2,4,5-tetrazine (3j)**: 3-[(*E*)-2-Phenylethenyl]tributyltin (**4b**) was used as the organostannane derivative; yield: 34%; red solid; mp 126 °C. MS (Ionspray®): *m*/*z* = 270 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 16.3 Hz, 1 H), 7.62 (dd, *J* = 1.5, 8.3 Hz, 2 H), 7.41 (m, 3 H), 7.35 (d, *J* = 16.3 Hz, 1 H), 4.03 (t, *J* = 4.5 Hz, 4 H), 3.86 (t, *J* = 4.5 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.1 (C), 160.0 (C), 136.0 (C), 135.7 (CH), 129.3 (CH), 129.0 (CH), 127.6 (CH), 121.1 (CH), 66.6 ($CH_2$), 43.8 ($CH_2$). IR: 2956, 2863, 1637, 1521, 1450, 1341, 1254, 1119, 1056, 949, 848, 751, 693 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{14}H_{15}N_5O$: 269.1277; found: 269.1274.
**3-(Morpholin-4-yl)-6-(thien-2-yl)-1,2,4,5-tetrazine (3k)**: 2-Tributylstannylthiophene (**4c**) was used as the organostannane derivative; yield: 42%; red solid; mp 187–191 °C. MS (Ionspray®): *m*/*z* = 250 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 1.0, 3.8 Hz, 1 H), 7.50 (dd, *J* = 1.0, 5.0 Hz, 1 H), 7.19 (dd, *J* = 3.8, 5.0 Hz, 1 H), 4.03 (t, *J* = 4.4 Hz, 4 H), 3.87 (t, *J* = 4.4 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.4 (C), 157.8 (C), 136.7 (C), 129.2 (CH), 128.5 (CH), 127.6 (CH), 66.6 ($CH_2$), 43.9 ($CH_2$). IR: 2965, 2907, 2866, 2362, 2341, 1529, 1433, 1259, 1112, 941, 718 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{10}H_{11}N_5OS$: 249.0684; found: 249.0693.
**3-(Morpholin-4-yl)-6-(pyridin-4-yl)-1,2,4,5-tetrazine (3l)**: 4-Tributylstannylpyridine (**4d**) was used as the organostannane derivative; yield: 30%; red solid; mp 198–199 °C. MS (Ionspray®): *m*/*z* = 245.5 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.81 (br s, 2 H), 8.26 (d, *J* = 4.1 Hz, 2 H), 4.11 (t, *J* = 4.7 Hz, 4 H), 3.89 (t, *J* = 4.7 Hz, 4 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.4 (C), 157.9 (C), 150.9 (C), 140.1 (CH), 66.6 ($CH_2$), 43.9 ($CH_2$); $C_9$ was not observed. IR: 2989, 2902, 1593, 1520, 1443, 1340, 1250, 1117, 1037, 966, 942, 846 $cm^{-1}$. Anal. Calcd for $C_{11}H_{12}N_6O$(244): C, 54.09; H, 4.95; N, 34.41. Found: C, 54.41; H, 4.93; N, 34.55.

(21) For preparation of compound **4a**, see: Morita, Y.; Kashiwagi, A.; Nakasuji, K. *J. Org. Chem.* **1997**, *62*, 7464.

(22) For preparation of compound **4b**, see ref. 15b.

(23) For preparation of compound **4d**, see: Peters, D.; Hörnfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1990**, *27*, 2165.

(24) The same experimental procedure as described in ref. 18 was used, except that the reaction was carried out in a 10 mL round-bottomed flask and stirred in refluxing DME for 48 h.

(25) In refluxing DME after 48 hours, only traces of the cross-coupling product **6** were observed.
**3-Methoxy-6-(4-methoxyphenyl)-1,2,4,5-tetrazine (6)**: 3-Methylthio-6-methoxy-1,2,4,5-tetrazine (**5**; 129 mg, 0.8 mmol), 4-methoxyphenylboronic acid (**2a**; 277 mg, 1.8 mmol) and CuTC (342 mg, 1.8 mmol) were dissolved in anhyd DME (6 mL) in a sealed reaction vessel under argon. After the mixture was degassed, $Pd(PPh_3)_4$ (47 mg, 0.04 mmol) was added and the reaction mixture was stirred under microwave irradiation at 200 °C for 2 h. The reaction mixture was then allowed to cool to r.t., poured into sat. $Na_2CO_3$ and extracted with $CH_2Cl_2$. The organic phases were collected, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by chromatography on silica gel (PE–EtOAc: 1:0 to 9:1) afforded compound **7** (22 mg, 12%) as a red solid; mp 119–120 °C. MS (Ionspray®): *m*/*z* = 219 $[M + H]^+$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 9.0 Hz, 2 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 4.34 (s, 3 H), 3.91 (s, 3 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 166.8 (C), 163.1 (C), 162.9 (C), 129.3 (CH), 124.3 (C), 114.8 (CH), 56.6 ($CH_3$), 55.6 ($CH_3$). IR: 2923, 2854, 1602, 1488, 1453, 1376, 1249, 1179, 1117, 1041, 940, 848 $cm^{-1}$. HRMS: *m*/*z* $[M^+\cdot]$ calcd for $C_{10}H_{10}N_4O_2$: 218.0804; found: 218.0797.