Abstract: A systematic study of the cross-coupling capability of the 4- and 5-positions of 2-phenylthiazoles and -oxazoles under Stille conditions is presented. The azoles were both applied as stannanes and as the halide component. The obtained results were compared regarding the position of the halide and Bu$_3$Sn group. In order to establish a general reactivity platform for those heterocyclic systems, a broad variety of aromatic and heteroaromatic halides were coupled and some significant differences concerning the coupling properties of the investigated systems were observed.

Key words: cross-coupling, heterocycles, Stille reaction, oxazole, thiazole

Both, substituted thiazoles and oxazoles are interesting building blocks and frequently encountered structural motifs in a variety of natural products and synthetic bioactive compounds useful as pharmaceuticals or plant protection agents. In general, both heterocycles can be obtained via cyclization reactions. In the case of thiazole and its derivatives, the Hantzsch reaction (condensation of α-halo ketones with appropriate thioureas) is the most frequently encountered route whereas various cyclization methodologies exist leading to interesting oxazole or oxazoline derivatives. The described methods are useful and usually deliver satisfying results only when a small number of products has to be prepared. Nevertheless, substituted starting materials have to be prepared for each single compound and sometimes unwanted side reactions can lower the obtained yields. Therefore, an alternative approach is preferable by introducing the required substituents into the already preformed thiazoles and oxazoles when a larger number of differently substituted azoles are envisaged. In this regard, transition-metal-catalyzed cross-coupling reactions represent a very attractive alternative since similar number of differently substituted azoles are envisaged. The azoles were both applied as stannanes and as the halide component. The obtained results were compared regarding the position of the halide and Bu$_3$Sn group. In order to establish a general reactivity platform for those heterocyclic systems, a broad variety of aromatic and heteroaromatic halides were coupled and some significant differences concerning the coupling properties of the investigated systems were observed.

In the thiazole series, 2-phenylthiazole (1) was obtained via a Hantzsch cyclization. Functionalization of the 5-position was easily achieved via direct bromination or lithiation and subsequent quenching with Bu$_3$SnCl. By applying the conditions specified in Scheme 1, 5-bromo-2-phenylthiazole (2) as well as 5-tributylstannyl-2-phenylthiazole (3) were obtained in good yields. The desired 4-bromo-2-phenylthiazole (4) was obtained via a halogen dance reaction and subsequent quenching of the reaction mixture with water. The isolated product was not only used as coupling partner, but also as starting material for the synthesis of 4-tributylstannyl-2-phenylthiazole (5), which was prepared via metal–halogen exchange using t-BuLi followed by addition of Bu$_3$SnCl.

In the oxazole series 5-bromo-2-phenyloxazole (6) was prepared according to a literature procedure and subsequently converted into the other desired coupling partners under similar conditions as in the thiazole series. 5-Tributylstannyl-2-phenyloxazole (7) was obtained after metal–halogen exchange and subsequent quenching with Bu$_3$SnCl. 4-Bromo-2-phenyloxazole (8) was again prepared via a halogen dance reaction and trapping of the 4-bromo-5-lithio species with water or MeOH. The obtained product could then be transformed into the corresponding 4-tributylstannyl-2-phenyloxazole (9).

In both series all coupling partners were obtained in good yields. Under halogen dance conditions the lithiated oxazole species turned out to be less stable than the corresponding thiazoles and in some cases ring opening was observed as well. All stannanes 3, 5, 7, and 9 were purified by Kugelrohr distillation. A major difference in reactivity of thiazoles vis-à-vis oxazoles was observed during the metal–halogen exchange in the 4-position. In the oxazole

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series it was sufficient to use n-BuLi leading to full conversion to 9, whereas a mixture consisting of unreacted starting material 4, product 5, and dehalogenated starting material 1 was obtained in the thiazole series under the same reaction conditions. Therefore, it was necessary to use t-BuLi instead of n-BuLi in order to obtain 4-tributylstannyl-2-phenylthiazole (5) in satisfactory yields (Scheme 1).

![Scheme 1 Synthesis of cross-coupling reaction partners. Reagents and conditions: (a) Br₂, CHCl₃, r.t.; (b) n-BuLi, Bu₃SnCl, THF, –80 °C; (c) LDA, H₂O–THF, –80 °C; (d) t-BuLi, Bu₃SnCl, THF, –80 °C.](image)

In order to compare the results of the coupling reactions of the two heterocyclic systems, standard conditions regarding solvent, reaction temperature and catalyst had to be defined. Toluene turned out to be a good solvent in test reactions and reaction mixtures were refluxed until complete consumption of the halide (2–48 h) was observed by TLC or GC/MS analysis. Pd(PPh₃)₄ was chosen as the catalyst since it is commercially available or can easily be prepared freshly in the laboratory. In order to avoid purification problems often encountered in cross-coupling reactions under Stille conditions, we followed a literature procedure where addition of CsF was suggested. This reagent not only activates the applied stannane, but also simplifies the purification due to generation of insoluble Bu₃SnF.

Initially, the cross-coupling capability of stannane 3 and 5 was investigated by using iodo- or bromobenzene as coupling partners. In all cases good yields of 10a and 11a (Table 1, entries 1 and 4–6) were obtained. The results showed that essentially the same yields were obtained independent of the position of the Bu₃Sn group (positions 4 or 5), indicating similar coupling capabilities of these two positions in the thiazole system. In the case of iodobenzene as reaction partner the yield could even be improved to 84% (entry 2) or 89% (entry 3) by increasing the amount of the halide to 1.5 or 2 equivalents. However, costs and complexity of the aryl or hetaryl halide might determine if such an excess of one reagent can be justified. Steric and electronic effects were also explored by applying substituted coupling partners such as 2-bromo- toluene, 4-bromoanisole and 4-nitrobromobenzene. Neither coupling partners with sterical hindrance nor electron-withdrawing substituents led to a significant decrease in yield. When 2-bromo- toluene was used the yield was lowered by approximately 10% (entries 7 and 8) compared to unhindered iodo- or bromobenzene, but the investigated positions still showed similar behavior. Applying electron-poor 4-nitrobromobenzene in the coupling process (entries 11 and 12) yielded 69 and 78% of the desired coupling products 10d and 11d. In these cases, slightly higher yields were obtained in 4- than in 5-position. On the other hand, coupling reactions with electron-rich 4-bromoanisole resulted in significantly lower yields of 38% for cross-coupling in 5-position and 41% in 4-position (entries 9 and 10). Apart from the desired compound 10c, 16% of starting material as well as 25% of 2,5-diphenylthiazole (as a result of a ligand-exchange reaction) were obtained when coupling 4-bromoanisole into the 5-position (entry 9). When performing the reaction in 4-position the formation of considerable amounts (>10%) of 2,4-diphenylthiazole was observed.

To further broaden the substrate scope of this transformation a series of hetaryl halides was selected as coupling partners. As before, the coupling capabilities of position 5 as well as 4 were investigated. When 3-bromopyridine (entries 15 and 16), 2-fluoro-4-iodopyridine (entries 17 and 18), and 4-chloro-2-methylsulanylpuridine (entries 19 and 20) were used similar yields compared to iodo- and bromobenzene were obtained. Satisfying results were also achieved with 2-bromothiophene (entries 13 and 14), but lower yields were obtained when 2,4-dichloropyrimidine was applied (entries 21 and 22). Since some biologically active natural products contain differently joined bisazole fragments, compound 3 was also coupled with 5-iodo-2-phenylthiazole, 2 as well as 6 and in all cases (entries 23–25) satisfactory yields of the coupled products were obtained. Among the three coupling partners, 5-iodo-2-phenylthiazole (entry 23) provided the highest yield (81%) of the product, but due to decomposition under the applied conditions it had to be separated from 13% of the dehalogenated starting material. In the course of these reactions some side products were generated: the formation of the homocoupling product 2,2'-bithiazole was observed with 2-bromothiophene and in many cases 2.5- and 2,4-diphenylthiazole were isolated (4–25%). The highest amount of the latter side product was obtained when the cross-coupling reaction was performed at the 5-position with 4-bromoanisole and 3-bromopyridine. The formation of 2,2'-diphenyl[5,5'-bithiazolyl (10j) and 2,2'-diphenyl[4,4'-bithiazolyl (11j) was also observed in the yield range of 2–11%.

Taken together, we have found that cross-coupling of thi/azoles 3 and 5 with aryl and hetaryl halides can be per-
formed in very similar yields indicating that the coupling capabilities of positions 4 and 5 are comparable. Electron-poor and also sterically demanding halides can be applied and good yields are obtained, both in the carbocyclic and heterocyclic series. Only with electron-rich halides significantly lower yields are encountered as it is known from the literature. In the 5- and the 4-position of 2-phenylthiazole no significant differences in cross-coupling capability were detected. Subsequently, an additional survey on the analogous oxazole system was carried out to determine any related trends true for this ring system.

In the oxazole series, the conditions regarding solvent, reaction temperature, and catalyst were the same as in the thiazole series and an initial experiment iodobenzene was coupled with both 7 and 9 (Table 2, entries 1 and 2). Results of the two conversions were in accordance with the thiazole series and again very similar yields were obtained for reactions in the 4- and in 5-positions suggesting that differences in coupling capability of these positions are minor. When four additional experiments were carried out in order to support this observation some very unexpected and interesting results were obtained. 2-Fluoro-4-

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**Table 1** Stille Cross-Coupling Reactions of 3 and 5 with Various Halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>Z</th>
<th>ArX</th>
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<th>Ar</th>
<th>Yield (%)</th>
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<td>phenyl</td>
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<td>H</td>
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<td>2-bromotoluene</td>
<td>11b</td>
<td>2-methylphenyl</td>
<td>66</td>
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<td>SnBu3</td>
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<td>10d</td>
<td>4-nitrophenyl</td>
<td>69</td>
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<tr>
<td>12</td>
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<td>4-nitrobromobenzene</td>
<td>11d</td>
<td>4-nitrophenyl</td>
<td>78</td>
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<td>10e</td>
<td>2-thienyl</td>
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<td>2-thienyl</td>
<td>51</td>
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<td>H</td>
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<tr>
<td>20</td>
<td>H</td>
<td>SnBu3</td>
<td>4-chloro-2-methylsulfonylpyrimidine</td>
<td>11h</td>
<td>2-methylsulfonyl-4-pyrimidinyl</td>
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<td>48</td>
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<td>2,4-dichloropyrimidine</td>
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<td>2-chloro-4-pyrimidinyl</td>
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<tr>
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<td>SnBu3</td>
<td>H</td>
<td>5-iodo-2-phenylthiazole</td>
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<td>2-phenyl-5-thiazolyl</td>
<td>81</td>
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<td>SnBu3</td>
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<td>10j</td>
<td>2-phenyl-5-thiazolyl</td>
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<tr>
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<td>H</td>
<td>6</td>
<td>10k</td>
<td>2-phenyl-5-oxazolyl</td>
<td>70</td>
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iodopyridine and 4-chloro-2-methylsulfanylpyrimidine were chosen as coupling partners and when they were coupled into the 5-position almost identical yields (entries 3 and 5) as in the thiazole series were obtained. But when coupling the two heterocyclic coupling partners into the 4-position (entries 4 and 6) the obtained yields were significantly lower than in the 5-position. It seems that the coupling capability of 5-tributylstannyl-2-phenyloxazole (7) is comparable to that of 5-tributylstannyl-2-phenylthiazole (3) and 4-tributylstannyl-2-phenylthiazole (5) whereas the coupling capability of 4-tributylstannyl-2-phenyloxazole (9) is definitely lower, which can be observed when more demanding coupling partners are applied.

Especially when a great number of differently substituted thiazoles or oxazoles have to be synthesized (e.g., for a compound library) it is beneficial to introduce the tin on the azole system and couple it with different aryl or heteraryl halides since a large number of halides are commercially available and often inexpensive. But since the synthetic route could make it necessary to apply the azole as a halide we wanted to conclude our investigations by coupling 2, 4, 6, and 8 with commercially available tributylphenylstannane (Table 3). In the thiazole as well as in the oxazole series the obtained yields (74–82%) were comparable or slightly better than when applying the thiazole or oxazole as tin compound. Since previous experiments showed that at least iodothiazoles favor the formation of bithiazoles17 we only considered the bromo compounds within the scope of the present study.

Finally, a set of competition experiments was also set up in order to establish the direct ranking of coupling efficiencies of the various positions in the heterocyclic systems: 1 equivalent of 5-tributylstannyl-2-phenylthiazole (3) or 5-tributylstannyl-2-phenyloxazole (7), and 1 equivalent of 4-tributylstannyl-2-phenylthiazole (5) or 4-tributylstannyl-2-phenyloxazole (9) were put forward simultaneously and coupled with 1 equivalent of bromobenzene under standard conditions (Table 4). The reactions were run overnight and the composition of the reaction mixture was determined after consumption of the halide via GC/MS.

In the thiazole series, the ratio of 2,5-diphenylthiazole (10a) to 2,4-diphenylthiazole (11a) was 71:29 (Table 4, entry 1) whereas in the oxazole series 2,5-diphenyloxazole (12a) was formed exclusively (entry 2). These results are comparable to what was observed in the competition experiments with tin-halide coupling.

### Table 2: Stille Cross-Coupling Reactions of 7 and 9 with Various Halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>Z</th>
<th>X</th>
<th>Product Ar</th>
<th>Yield (%)</th>
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<td>SnBu3</td>
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<td>iodobenzene</td>
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<td>SnBu3</td>
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<td>H</td>
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### Table 3: Stille Cross-Coupling Reactions with Tributylphenylstannane

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<th>Starting material</th>
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<th>Y</th>
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<td>O</td>
<td>H</td>
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### Table 4: Competition Experiments

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<th>Z</th>
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<td>SnBu3</td>
<td>Br</td>
<td>10a, 11a</td>
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<td>Br</td>
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<td>SnBu3</td>
<td>12a, 13a</td>
<td>96:4</td>
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</table>
sults support the observed trend, indicating that the difference in coupling reactivity between 7 and 9 is much more pronounced than for the analogous thiazole compounds 3 and 5. When the experiments were carried out with 1 equivalent of 5-bromo-2-phenyliodazole 2 or 5-bromo-2-phenyloxazole (6), and 1 equivalent of 4-bromo-2-phenyliodazole (4) or 4-bromo-2-phenyloxazole (8) and 1 equivalent of tributylphosphinestannane very similar results were obtained and the ratio in the thiazole series was 82:18 favoring 2,5-diphenylthiazole (10a) (entry 3) and in the oxazole series again almost no 2,4-diphenyloxazole (13a) was formed (entry 4).

The results of this study show that the Stille cross-coupling reaction is generally applicable for the introduction not only of aromatic but also various heteroaromatic substituents in the 5-position as well as the 4-position of thiazoles and oxazoles. Even with heterocyclic coupling partners moderate to good yields were obtained. In the case of thiazoles no difference concerning the coupling capability of the 4- and 5-position could be observed whereas significantly lower yields were obtained in the oxazole series when heterocyclic halides were coupled into the 4-position instead of the 5-position. Still the thiazolestannanes 3 and 5 as well as the oxazolestannanes 7 and 9 are very useful building blocks for the synthesis of arylated derivatives and especially appealing when a number of differently substituted thiazoles or oxazoles is needed. Additionally, it has to be mentioned that the halogen dance reaction proved to be a very useful tool for the synthesis of the 4-substituted starting materials, both, halides and metal organyls.

All reactions were conducted under N₂ or argon using dried glassware and magnetic stirring. Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. All solvents were dried over Al₂O₃ cartridges prior to use. Flash column chromatography was performed on silica gel 60 from Merck (40–63 μm) using a Büchi Sepacore preparative column. The ratio of crude product to silica gel was 1:30 and in case of cross-coupling products cartridges with 45 g of SiO₂ were used. Kugelrohr distillation was carried out using a Büchi GKR-51 apparatus. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. NMR-spectra were recorded from CDCl₃ solution on a Bruker AC 200 (200 MHz) and chemical shifts are reported in ppm using TMS as internal standard. Elemental analyses were carried out in the Microanalytical Laboratory, Institute of Physical Chemistry, Vienna University.

Stannanes of Azoles; General Procedure

The appropriate starting material was lithiated with n- or t-BuLi (1.1–1.25 equiv) under argon at -80 °C. After complete addition, the mixture was warmed to -50 °C and held at that temperature for 30 min. The mixture was again cooled to -80 °C and Bu₃SnCl (1.1–1.4 equiv) was added dropwise at that temperature. The mixture was warmed to r.t. and diluted with Et₂O (5 x reaction volume). The organic layer was washed with aq 2 N HCl (5 x reaction volume), H₂O (5 x reaction volume), and brine (5 x reaction volume), dried (Na₂SO₄), filtered, and evaporated. The crude material was purified by Kugelrohr distillation.

5-Tributylstannyl-2-phenyliodazole (3)

Compound 3 was prepared from 1 (1 equiv, 6.66 mmol, 1.07 g) according to the general procedure for the preparation of stannanes using anhyd THF (20 mL), n-BuLi (1.25 equiv, 8.33 mmol, 3.33 mL, 2.5 M in hexane), and Bu₃SnCl (1.15 equiv, 7.66 mmol, 2.08 mL). yield: 2.53 g (84%); yellow oil; bp 200 °C/0.1 mbar; Rf = 0.70 (PE–EtOAc, 10:1).

1H NMR (200 MHz, CDCl₃): δ = 0.91 (t, J = 7.1 Hz, 9 H, CH₃), 1.16 (t, J = 7.8 Hz, 6 H, SnCH₂), 1.35 (sext, J = 7.1 Hz, 6 H, CH₂CH₂CH₂), 1.50–1.68 (m, 6 H, CH₂CH₂CH₂), 7.34–7.48 (m, 3 H, ArH), 7.81 (s, 1 H, H-4), 7.94–8.16 (m, 2 H, ArH).

13C NMR (50 MHz, CDCl₃): δ = 20.9 (t), 22.2 (t), 29.1 (t), 125.3 (d, C-5), 127.1 (d), 128.8 (d), 129.4 (d, C-4), 132.4 (s, C-4¢), 150.3 (d, C-3), 173.3 (s, C-2).

4-Tributylstannyl-2-phenyloxazole (5)

Compound 5 was prepared from 4 (1 equiv, 1.25 mmol, 300 mg) according to the general procedure for the preparation of stannanes using anhyd Et₂O (15 mL), t-BuLi (1.2 equiv, 1.50 mmol, 0.92 mL, 1.63 M in pentane), and Bu₃SnCl (1.4 equiv, 1.75 mmol, 0.47 mL). Since the boiling point of the product was too high, the excess of Bu₃Sn was distilled off and the then-pure residue could be used for further reactions; yield: 466 mg (83%); yellow oil; Rf = 0.64 (PE–THF, 50:1).

1H NMR (200 MHz, CDCl₃): δ = 0.71–1.83 [m, 27 H, (CH₂)₃CH₃], 7.33 (s, 1 H, H-5), 7.38–7.51 (m, 3 H, ArH), 7.98–8.08 (m, 2 H, ArH).

13C NMR (50 MHz, CDCl₃): δ = 10.4 (t), 13.7 (q, CH₃), 27.3 (t), 29.1 (t), 125.3 (d, C-5), 127.1 (d), 128.8 (d), 129.4 (d, C-4¢), 134.2 (s, C-4¢), 160.9 (s, C-4), 168.3 (s, C-2).

5-Tributylstannyl-2-phenyloxazole (7)

Compound 7 was prepared from 6 (1 equiv, 2.23 mmol, 500 mg) according to the general procedure for the preparation of stannanes using anhyd THF (25 mL), n-BuLi (1.1 equiv, 2.45 mmol, 1.34 mL, 1.83 M in hexane) and Bu₃SnCl (1.1 equiv, 2.45 mmol, 0.89 mL); yield: 830 mg (86%); colorless oil; bp 180–185 °C/0.05 mbar; Rf = 0.29 (PE–EtOAc, 10:1).

1H NMR (200 MHz, CDCl₃): δ = 0.88 (t, J = 7.2 Hz, 9 H, CH₃), 1.12 (t, J = 7.9 Hz, 6 H, SnCH₃), 1.34 (sext, J = 7.2 Hz, 6 H, CH₂CH₂CH₂), 1.47–1.68 (m, 6 H, CH₃CH₂CH₂), 7.23 (s, 1 H, H-4), 7.33–7.54 (m, 3 H, ArH), 7.96–8.13 (m, 2 H, ArH).

13C NMR (50 MHz, CDCl₃): δ = 10.3 (t), 13.6 (q, CH₃), 27.1 (t), 28.9 (t), 126.3 (d), 128.1 (s, C-1‘), 128.6 (d, C-5), 129.8 (d, C-4‘), 138.7 (d, C-4‘), 155.5 (s, C-5), 161.9 (s, C-2).

4-Tributylstannyl-2-phenyloxazole (9)

Compound 9 was prepared from 8 (1 equiv, 0.89 mmol, 200 mg) according to the general procedure for the preparation of stannanes using anhyd THF (20 mL), n-BuLi (1.1 equiv, 0.99 mmol, 0.42 mL, 2.4 M in hexane), and Bu₃SnCl (1.1 equiv, 0.99 mmol, 0.27 mL); yield: 260 mg (67%); colorless oil; bp 220–225 °C/0.35 mbar; Rf = 0.31 (PE–EtOAc, 40:1).

1H NMR (200 MHz, CDCl₃): δ = 0.92 (t, J = 7.1 Hz, 9 H, CH₃), 1.07–1.67 [m, 18 H, (CH₃)₂], 7.36–7.51 (m, 3 H, ArH), 7.55 (s, 1 H, H-5), 7.99–8.15 (m, 2 H, ArH).

13C NMR (50 MHz, CDCl₃): δ = 9.8 (t), 13.7 (q, CH₃), 27.2 (t), 29.0 (t), 126.5 (d), 128.1 (s, C-1′), 128.6 (d, C-4′), 138.7 (s, C-4′), 144.7 (d, C-5), 162.6 (s, C-2).
Halogen Dance Reaction; General Procedure
A freshly prepared solution of LDA (1 equiv) in anhyd THF (10%) was added to a solution of the halide (1 equiv) in anhyd THF (20%) at –80 °C under argon. When TLC control showed complete HD reaction, the mixture was quenched with H2O (10 mL) or MeOH (10 mL), and allowed to warm to r.t. Brine (10 mL) was added and 2/3 of the THF was removed under reduced pressure. The mixture was extracted with CH2Cl2 [3 × (5 × reaction volume)] and the combined organic layers were washed with aq sat. NaHCO3 (5 × reaction volume) and brine (5 × reaction volume). The organic layer was dried (Na2SO4), filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

4-Bromo-2-phenylthiazole (4)
Compound 4 was prepared from 2 (1 equiv, 12.49 mmol, 3.00 g) according to the general procedure for the halogen dance reaction; yield: 2.34 g (78%); colorless solid; mp 65–67 °C (Lit.18 mp 65 °C); \( R_f = 0.63 \) (PE–THF, 10:1).

1H NMR (200 MHz, CDCl3): \( \delta = 7.20 \) (s, 1 H, H-5), 7.33–7.48 (m, 3 H, ArH), 7.82–7.99 (m, 2 H, ArH).

13C NMR (50 MHz, CDCl3): \( \delta = 117.0 \) (s, C-4), 126.3 (s, C-1¢), 132.5 (s, C-1′), 169.0 (s, C-2).

4-Bromo-2-phenylazole (8)
Compound 8 was prepared from 6 (1 equiv, 2.23 mmol, 500 mg) according to the general procedure for the halogen dance reaction; yield: 365 mg (78%); colorless oil; \( R_f = 0.40 \) (PE–EtOAc, 20:1).

1H NMR (200 MHz, CDCl3): \( \delta = 7.75–7.50 \) (m, 3 H, ArH), 7.65 (s, 1 H, H-5), 7.90–8.10 (m, 2 H, ArH).

13C NMR (50 MHz, CDCl3): \( \delta = 117.0 \) (s, C-4), 126.3 (s, C-1¢), 126.4 (d), 128.8 (d), 131.0 (d, C-4′), 136.6 (d, C-5′), 162.1 (s, C-2).

Stille Cross-Coupling Reaction of Azoles; General Procedure
The stannane (1 equiv), the halide (1.1–2 equiv), CsF (2.2 equiv), Pd(PPh3)4 (0.05 equiv) were dissolved in anhyd toluene (12 mL), and allowed to warm to r.t. Brine (10 mL) was added and 2/3 of the THF was removed under reduced pressure. The mixture was extracted with CH2Cl2 [3 × (5 × reaction volume)] and the combined organic layers were washed with aq sat. NaHCO3 (5 × reaction volume) and brine (5 × reaction volume). The organic layer was dried (Na2SO4), filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

2,5-Diphenylthiazole (10a)
Yield: see Table 1 (entries 1–3 and entry 5) and Table 3 (entry 1); colorless solid; mp 103–104 °C (Lit.19 mp 103–104 °C); \( R_f = 0.83 \) (PE–EtOAc, 10:1).

NMR data of the obtained product were in agreement with the literature.23

5-(4-Methoxyphenyl)-2-phenylthiazole (10c)
Reaction time: 48 h; yield: 38 mg (38%); colorless solid; mp 98–100 °C (Lit.21 mp 103–105 °C); \( R_f = 0.35 \) (PE–EtOAc, 10:1). NMR data of the obtained product were in agreement with the literature.21

4-(4-Methylphenyl)-2-phenylthiazole (10e)
Reaction time: 18 h; yield: 69 mg (69%); colorless solid; mp 130–132 °C (Lit.21 mp 134–135 °C); \( R_f = 0.49 \) (PE–EtOAc, 30:1).

1H NMR data of the obtained product was in agreement with the literature.21

13C NMR (50 MHz, CDCl3): \( \delta = 55.3 \) (q, CH3), 110.9 (d, C-5), 114.1 (d), 126.6 (d), 127.5 (s, C-1′), 127.7 (d), 128.9 (d), 129.9 (d, C-4′), 133.8 (s, C-1′), 156.1 (s, C-4), 159.6 (s, C-4′), 167.7 (s, C-2).

5-(4-Nitrophenyl)-2-phenylthiazole (10d)
Reaction time: 18 h; yield: 67 mg (67%); pale yellow solid; mp 191–194 °C (Lit.22 mp 173 °C); \( R_f = 0.32 \) (PE–EtOAc, 10:1).

NMR data of the obtained product were in agreement with the literature.22

2,4-Diphenylthiazolium chloride (11a)
Yield: see Table 1 (entries 4 and 6) and Table 3 (entry 2); colorless solid; mp 75–78 °C (Lit.19 mp 93–94 °C); \( R_f = 0.56 \) (PE–EtOAc, 15:1).

1H NMR data of the obtained product were in agreement with the literature.19

13C NMR (50 MHz, CDCl3): \( \delta = 112.7 \) (d, C-5), 126.5 (d), 126.6 (d), 128.2 (d), 128.8 (d), 130.0 (d), 133.8 (s), 134.5 (s), 156.3 (s, C-4), 167.9 (s, C-2).

2-Phenyl-5-(2-thienyl)thiazole (10b)
Reaction time: 18 h; yield: 68 mg (68%); colorless oil; \( R_f = 0.64 \) (PE–EtOAc, 10:1).

1H NMR (200 MHz, CDCl3): \( \delta = 2.51 \) (s, 3 H, CH3), 7.27–7.39 (m, 3 H, ArH), 7.46–7.55 (m, 4 H, ArH), 7.86 (s, 1 H, H-4), 8.00–8.10 (m, 2 H, ArH).
9.24 (m, 1 H, H-2).
7.29–7.35 (m, 2 H), 7.41–7.51 (m, 3 H, ArH), 7.53 (dd, J = 3.7, 1.2 Hz, 1 H), 7.97–8.08 (m, 2 H, ArH).
11C NMR (50 MHz, CDCl3): δ = 111.4 (d), 124.3 (d), 125.5 (d), 126.7 (d), 127.7 (d), 128.9 (d), 130.2 (d), 133.4 (s), 138.4 (s), 150.8 (s), 168.0 (s, C-2).

3-(2-Phenylthiazol-5-yl)pyridine (10f)
Reaction time: 24 h; yield: 80 mg (75%); colorless solid; mp 90–92 °C (Lit.22 mp 90–91 °C); Rf = 0.25 (PE–EtOAc, 1:1).

NMR data of the obtained product were in agreement with the literature.22

3-(2-Phenylthiazol-4-yl)pyridine (11f)
Reaction time: 24 h; yield: 67 mg (67%); beige solid; mp 81–83 °C; Rf = 0.16 (PE–EtOAc, 3:1).

1H NMR (200 MHz, CDCl3): δ = 7.33 (dd, J = 4.7, 7.8 Hz, 1 H, H-5), 7.38–7.47 (m, 3 H, ArH), 7.51 (s, 1 H, H-5’), 7.96–8.04 (m, 2 H, ArH), 8.24 (m, 1 H, H-4), 8.56 (dd, J = 4.7, 1.4 Hz, 1 H, H-6), 9.13–9.24 (m, 1 H, H-2).
11C NMR (50 MHz, CDCl3): δ = 113.8 (d), 123.6 (d), 126.6 (d), 129.0 (d), 130.3 (d), 133.3 (s, C-3), 133.7 (d), 147.7 (d), 149.1 (d), 153.1 (s, C-4’), 165.8 (s, C-2’).

Anal. Calcd for C14H9FN2S: C, 65.61; H, 3.54; N, 10.93. Found: C, 64.89; H, 3.48; N, 10.93.

2-Methylsulfanyl-4-(2-phenylthiazol-4-yl)pyrimidine (11h)
Reaction time: overnight; yield: 61 mg (61% mg); yellow solid; mp 127–128 °C; Rf = 0.31 (PE–EtOAc, 10:1).

1H NMR (200 MHz, CDCl3): δ = 2.63 (s, 3 H, SCH3), 7.40–7.52 (m, 3 H, ArH), 7.82 (d, J = 5.1 Hz, 1 H, H-5), 7.94–8.08 (m, 2 H, ArH), 8.29 (s, 1 H, H-5’), 8.61 (d, J = 5.1 Hz, 1 H, H-6).
11C NMR (50 MHz, CDCl3): δ = 14.2 (q, SCH3), 112.8 (d), 120.9 (d), 126.6 (d), 129.0 (d), 130.5 (d), 133.2 (s), 153.9 (s), 158.3 (d), 158.9 (s), 168.7 (s), 172.3 (s).


2-Chloro-4-(2-phenylthiazol-5-yl)pyrimidine (10i)
Reaction time: overnight; yield: 59 mg (48%); pale yellow solid; mp 180–183 °C; Rf = 0.33 (PE–EtOAc, 3:1).

1H NMR (200 MHz, CDCl3): δ = 7.42–7.56 (m, 4 H, ArH, H-5), 7.93–8.09 (m, 2 H, ArH), 8.47 (s, 1 H, H-4’), 8.58 (d, J = 5.3 Hz, 1 H, H-6).

11C NMR (50 MHz, CDCl3): δ = 114.2 (d), 126.8 (d), 129.2 (d), 131.2 (d), 132.9 (s), 135.8 (d), 144.9 (d), 159.6 (d), 160.2 (s), 161.7 (s), 172.6 (s).

Anal. Calcd for C14H11ClN3S: C, 57.04; H, 2.95; N 15.35. Found: C, 56.84; H, 2.81; N, 14.96.

2-Chloro-4-(2-phenylthiazol-4-yl)pyrimidine (11i)
Reaction time: 24 h; yield: 30 mg (30%); colorless solid; mp 188–190 °C; Rf = 0.68 (PE–EtOAc, 5:1).

1H NMR (200 MHz, CDCl3): δ = 7.43–7.53 (m, 3 H, ArH), 8.00–8.07 (m, 2 H, ArH), 8.12 (d, J = 5.1 Hz, 1 H, H-5), 8.39 (s, 1 H, H-5’), 8.69 (d, J = 5.1 Hz, 1 H, H-6).
11C NMR (50 MHz, CDCl3): δ = 114.4 (d), 120.8 (d), 125.1 (d), 127.5 (d), 129.1 (d), 131.3 (s), 150.9 (s), 158.9 (s), 159.8 (s), 160.1 (s), 167.5 (s).

Anal. Calcd for C14H10ClN3S: C, 57.04; H, 2.95; N, 15.35. Found: C, 57.12; H, 3.01; N 14.93.

2,2’-Diphenyl[5,5’]bithiazolyl (10j)

Yield: see Table 1, entries 23, 24; yellow solid; mp 195–197 °C (Lit.23 mp 182 °C); Rf = 0.29 (PE–EtOAc, 10:1).

NMR data of the obtained product were in agreement with the literature.22

2,2’-Diphenyl[4,4’]bithiazolyl (11j)

Yield: isolated as by-product in varying trace amounts; colorless solid; mp 179–182 °C (Lit.24 mp 185 °C); Rf = 0.65 (CH2Cl2).

1H NMR (200 MHz, CDCl3): δ = 7.38–7.56 (m, 6 H, ArH), 7.92 (s, 2 H, H-5, H-5’), 7.97–8.13 (m, 4 H, ArH).
13C NMR (50 MHz, CDCl3): δ = 115.3 (d, C-5, C-5’), 126.6 (d), 128.9 (d), 130.1 (d), 133.6 (s), 151.6 (s, C-4, C-4’), 168.3 (s, C-2, C-2’).

5-Phenyl-2-(2-phenylthiazol-5-yl)oxazole (10k)
Reaction time: 24 h; yield: 70 mg (70%); yellow solid; mp 121–124 °C; Rf = 0.05 (CH2Cl2).

1H NMR (200 MHz, CDCl3): δ = 7.37 (s, 1 H, H-4), 7.40–7.59 (m, 6 H, ArH), 7.89–8.01 (m, 2 H, ArH), 8.02–8.19 (m, 3 H, ArH, H-4’).

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2,5-Diphenyloxazole (12a) 
Yield: see Table 2 (entry 1) and Table 3 (entry 3); yellow solid; mp 72–75 °C (Lit. 24 mp 74 °C); \( R_f = 0.28 \) (PE–EtOAc; 10:1).

NMRI data of the obtained product were in agreement with the literature. 27

2,4-Diphenyloxazole (12a) 
Yield: see Table 2 (entry 2 and Table 3 (entry 4); beige solid; mp 102–104 °C (Lit. 25 mp 101–102 °C); \( R_f = 0.18 \) (PE–EtOAc; 30:1).

NMRI data of the obtained product were in agreement with the literature. 28

2-Fluoro-4-(2-phenyloxazol-5-yl)pyrimidine (12b) 
Reaction time: 17 h; yield: 80 mg (80%); colorless solid; mp 114 °C; \( R_f = 0.28 \) (PE–EtOAc, 8:1).

Anal. Calcd for C14H9FN2O·0.3 H2O: C, 68.46; H, 3.94; N, 11.40. Found: C, 68.32; H, 3.83; N, 11.32.

2-Fluoro-4-(2-phenyloxazol-4-yl)pyrimidine (12b) 
Reaction time: 20 h; yield: 23 mg (46%); colorless solid; mp 138–140 °C; \( R_f = 0.17 \) (PE–EtOAc; 8:1).

1H NMR (200 MHz, CDCl3): \( \delta = 7.38 \) (br s, 1 H, H-3), 7.43–7.60 (m, 3 H, ArH), 7.53 (d, \( J = 4.2 \) Hz, C-5), 126.6 (d), 128.9 (d), 131.0 (d), 136.1 (d), 144.0 (d, \( J = 39.9 \) Hz, C-6), 162.9 (s, C-2).


2-Methylsulfanyl-4-(2-phenyloxazol-5-yl)pyrimidine (12c) 
Reaction time: 18 h; yield: 125 mg (75%); colorless solid; mp 122–124 °C; \( R_f = 0.14 \) (PE–EtOAc, 20:1).

1H NMR (200 MHz, CDCl3): \( \delta = 2.56 \) (s, 3 H, SCH3), 7.24 (d, \( J = 5.1 \) Hz, 1 H, H-5), 7.40–7.50 (m, 3 H, ArH), 7.91 (s, 1 H, H-4'), 8.01–8.13 (m, 2 H, ArH), 8.52 (d, \( J = 5.1 \) Hz, 1 H, H-6).

13C NMR (50 MHz, CDCl3): \( \delta = 14.1 \) (q, SCH3), 110.1 (d, C-5), 126.7 (s), 126.8 (d), 128.9 (d), 130.7 (d), 131.3 (d, C-4'), 148.8 (s, C-4'), 153.6 (s, C-5'), 157.9 (d, C-6), 163.4 (s, C-2'), 173.1 (s, C-2).

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