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Halogenated 2′-Chlorobithiazoles via Pd-Catalyzed Cross-Coupling Reactions

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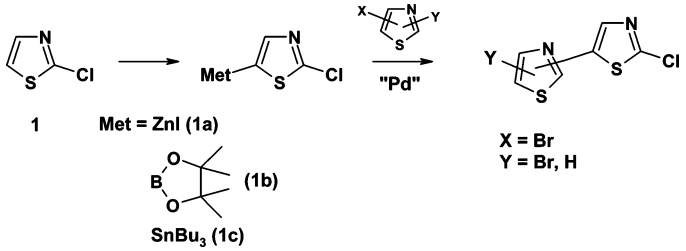

Halogenated bithiazoles allow facile further functionalization and are, therefore, suitable intermediates for the synthesis of compounds with interesting biological activity or material science properties. The applicability of three coupling methods (Negishi, Suzuki, and Stille) for the synthesis of the title compounds was compared. The Negishi method proved to be troublesome, and side reactions were predominant. The synthesis of the first thiazoleboronic acid ester offered a new method for the formation of bithiazoles, not generally applicable so far. The lower toxicity compared to that of tin organyls make this method an approach with interesting perspectives. The Stille coupling proved to be superior to the other methods and enabled the synthesis of the title compounds with diverse connectivity.

Introduction

The bithiazole motif can be found in a number of molecules with interesting properties. Besides compounds with biological activities in various fields,[1] a number of compounds with attractive qualities in material sciences were reported in the literature (Figure 1).[2] We, therefore, consider the availability of versatile methods for the efficient synthesis of bithiazole building blocks, which can further be functionalized to more complex molecules, as an important contribution to this field of research. Additionally, starting materials should be cheap and readily available, either from commercial sources or via well-established transformations. Two principle methods for the synthesis of bithiazoles are reported—cyclization strategies and cross-coupling protocols—whereby the first method is predominating. In the cases of **I**, **II**, **IV**, and **V**, cyclization strategies were applied, although **I** was also prepared via cross-coupling methods, as was the case for the bithiazole motif in **III**.

In contrast to cyclization reactions, palladium-catalyzed cross-coupling reactions[3] offer the possibility to prepare a wide range of compounds from a small number of selected starting materials. Cross-coupling reactions are, nowadays, a well-established method for the formation of C−C and even C−X (X = N, O, S) bonds. Especially, cross-coupling reactions to biphenyl compounds are extensively investigated, and a still-growing number of efficient catalysts with various ligands are available for these transformations.[4] Heterocyclic substrates on

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(1) Selected examples: (a) Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka S. *J. Antibiot.* **1998**, *51*, 275−281. (b) Dube, D.; Dube, L.; Gallant, M.; Lacombe, P.; Deschenes, D.; MacDonald, D. PCT Int. Appl. WO 2004096220, 2004; *Chem. Abstr.* 141:410960. (c) Beachy, P. A.; Chen, J. K.; Taipale, A. J. PCT Int. Appl. WO 2005033288, 2005; *Chem. Abstr.* 142:367707. (d) Riego, E.; Hernandez, D.; Albericio, F.; Alvarez, M. *Synthesis* **2005**, 1907−1922.

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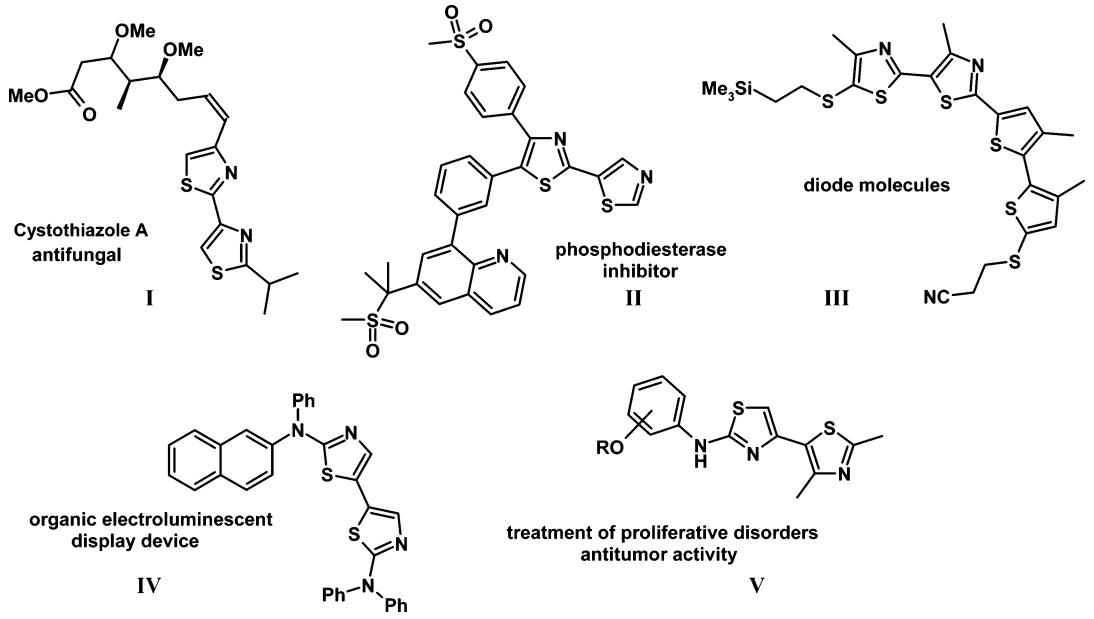

FIGURE 1. Selected bithiazole compounds with interesting biological activity or material science properties.

the other hand are by far less represented in the literature, and hardly any systematic studies of various ring-systems are available.[5] Often, efficient reaction conditions for biphenyl formation give lower or unsuccessful results on heterocyclic systems. Cross-coupling reactions leading to biheteroaryl compounds are even less investigated.[6]

We, therefore, embarked in a systematic research program focused on the formation of such biheteroaryl systems and started with the synthesis of bithiazole compounds. Dondoni and co-workers[7] reported the formation of all possible bithiazole compounds via a Stille reaction, but this work was limited with one exception only to the parent systems bearing no substituents for subsequent functionalizations. Additionally, the Negishi[8] and Stille[9] reactions already proved to be efficient in the synthesis of selected functionalized bithiazole systems.[10,11] In this study, we compared three cross-coupling methodologies (Negishi, Stille, and Suzuki−Miyaura[12]) in the formation of bithiazoles. For Suzuki−Miyaura reactions, we had to establish thiazoleboronic acids or esters as cross-coupling partners, a compound class not known in the literature, so far. Although 2-thiazoleboronic acid was claimed in patents, its actual preparation remains doubtful.[13] The only nonpatent reference indirectly claimed the formation of 2-thiazoleboronic acid, but no preparation procedure is given.[14]

As starting material, we chose 2-chlorothiazole (**1**), because it is readily available from commercial 2-aminothiazole via a Sandmeyer reaction.[15] The formation of the metal organyl in

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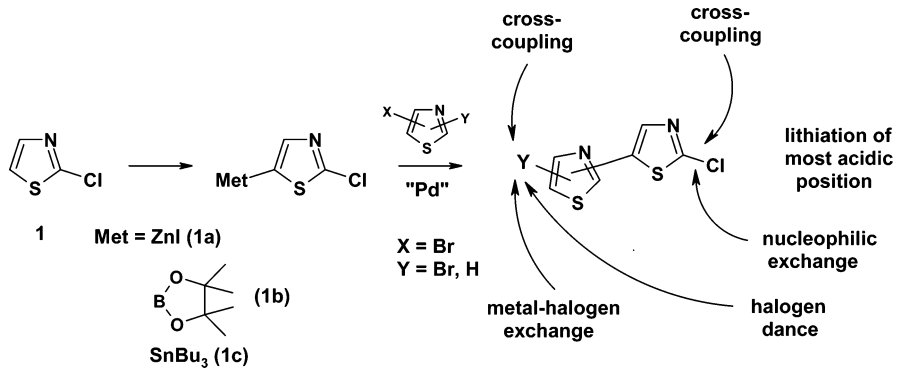
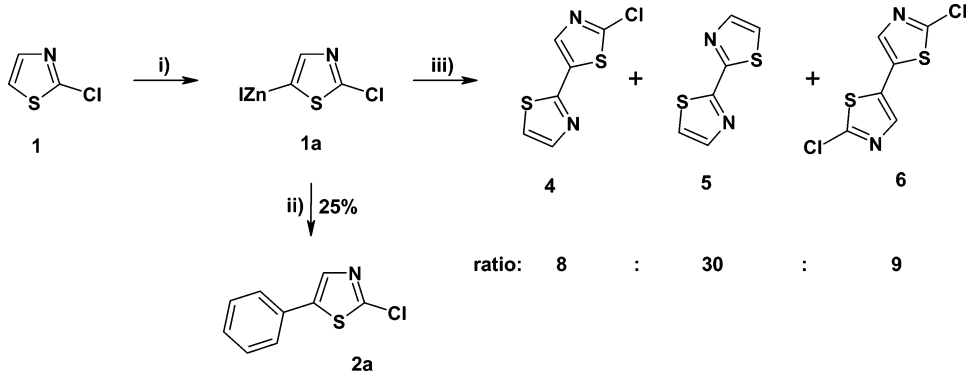


FIGURE 2. Applied cross-coupling strategy for the formation of bithiazoles and possible further transformations.

SCHEME 1. Negishi Attempts toward Bithiazoles[a]



[a] (i)*n*-BuLi, ZnI_2, THF, −80 °C; (ii) iodobenzene, $Pd(PPh_3)_4$, THF, 120 °C, mw; (iii) 2-bromothiazole, $Pd(PPh_3)_4$, THF, 170 °C, mw.

the 5-position and subsequent cross-coupling with various halothiazoles should give the desired bithiazoles, maintaining the chlorine and the introduced thiazole ring for various subsequent transformations (Figure 2).

Results and Discussion

Initially, we investigated the Negishi protocol, because it gave excellent results in the formation of 2,4′-bithiazoles in the synthesis of cystothiazoles.[10,11] Additionally, toxicity is less problematic compared to that of the Stille reaction, and preparation of the organometal species should be less elaborate as was expected for thiazoleboronic acids. In a test reaction, the metal organyl was prepared from **1** via lithiation at the 5-position with LDA and subsequent quenching with ZnI_2. Cross-coupling with iodobenzene under thermal conditions and $Pd(PPh_3)_4$ catalysis gave no conversion to the desired 2-chloro-5-phenylthiazole (**2**). When the cross-coupling reaction was performed under microwave conditions (120 °C, THF, 10 min) 25% of **2a** was formed (Scheme 1) and only minor amounts of **1** were recovered as a result of its volatility. This is consistent with the literature to a certain extent, because Bach reported successful Negishi reactions only for 4-thiazolyl zinc reagents bearing alkyl substituents in the 2-position. This is, of course, the case for cystothiazoles with an isopropyl group in that position, but even phenyl or alkynyl substituents in the 2-position did not give any conversion.[10b]

Nevertheless, 2-bromothiazole (**3**) was also applied to Negishi cross-coupling conditions with **1a**, and the conversion was monitored by GC-MS analysis. We found that under reflux conditions no conversion was observed. Initial microwave experiments (130 °C, 20min) gave the same results. When the temperature was raised to 170 °C (15bar, 20min), three different products were formed besides starting material **3** as the major component, indicating a slow cross-coupling process (Scheme 1). The new compounds included the desired bithazole **4**, however, in the lowest amount of all reaction products. The major new compound was 2,2′-bithiazole (**5**),[8b,16] derived from a homo coupling of **3**. 2,2′-Dichloro-5,5′-bithiazole (**6**) was detected as another homocoupling product derived from the organozinc intermediate **1a**. As a result of their similar properties, the three compounds could not be separated on preparative scale, but their relative ratio was determined by GC-MS analysis (Scheme 1). The structures of compounds **5** and **6** were assigned, because GC-MS data of the pure compounds were available in our laboratory. Significant hydrolysis of **1a** could be ruled out, because additional heating under the same conditions gave further conversion to the three initially observed compounds. Obviously, high temperatures are required for a successful cross-coupling, but then side reactions leading to homocoupling products are dominant. We, therefore, did not investigate the Negishi method further.

As a result of the high toxicity of the tin compounds, we decided to investigate the Suzuki−Miyaura reaction next. The

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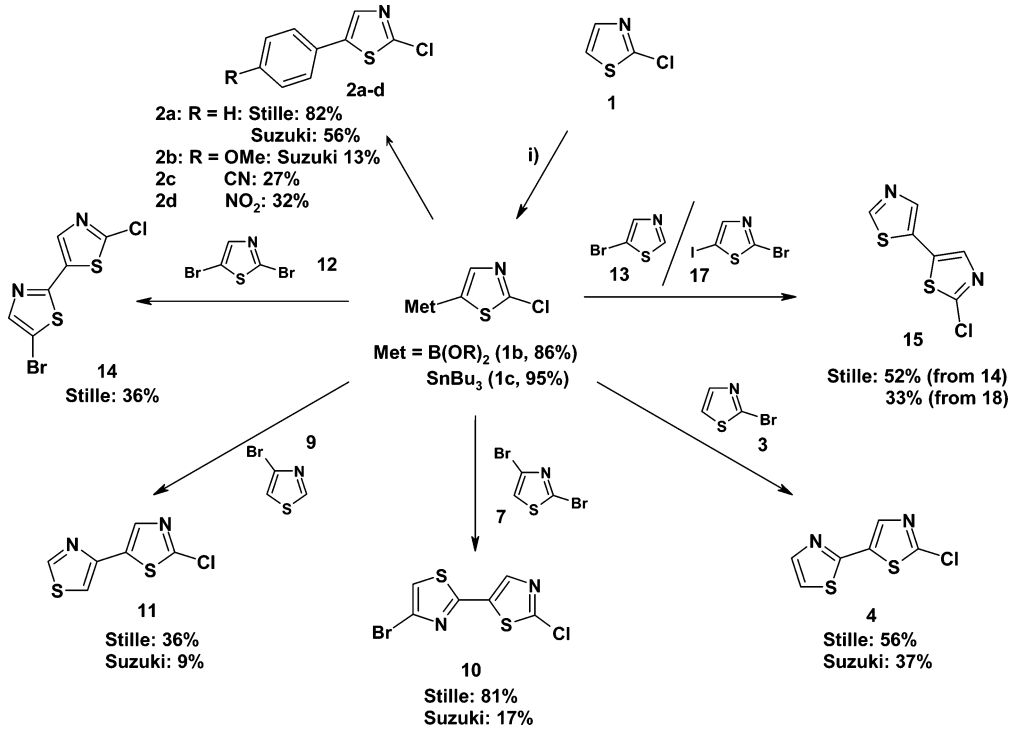
SCHEME 2. Formation of Bithiazoles via Suzuki−Miyaura or Stille Reactions[a]



[a] (i) (1) LDA, B(O-*i*Pr)$_3$, THF, −80 °C to room temperature; (2) pinacol, CH_3COOH. Cross-coupling conditions: halide, dry dioxane, $Pd(PPh_3)_4$, Cs_2CO_3, mw or thermal.

formation of bithiazoles via this method initially required a protocol for the formation of the corresponding thiazoleboronic acid or ester. Therefore, 2-chlorothiazole **1** was added to a mixture of LDA and B(O-*i*Pr)$_3$ at −80 °C. Via this method, the initially lithiated species should be trapped by the boron electrophile in the moment of formation. Nevertheless, isolation of the resulting boronic acid proved to be impossible due to the very limited stability of this species. A workup protocol developed for the formation of 2-pyridineboronic acid,[17] which is sensitive to deboronation, failed in our hands, and only starting material **1** was recovered. This result indicated a strong tendency of initially formed 5-thiazoleboronic acid to decompose in a deboronation reaction. We, therefore, decided to synthesize the corresponding 5-thiazoleboronic acid pinacol ester (**1b**), for which a higher stability was expected, by adding a transesterification step to the reaction protocol. After aqueous workup and purification by Kugelrohr distillation, **1b** was obtained in 30% yield (Scheme 2). In scale-up experiments, considerably lower yields (<10%) were obtained independent of concentration effects. A modification of the workup procedure toward a water-free protocol[18] drastically improved the result. A simple filtration of the reaction mixture through a pad of Celite and evaporation of the solvent gave **1b** in excellent 86% yield after Kugelrohr distillation. This is also an indication for the very low stability of thiazoleboronic acids under aqueous conditions. To the best of our knowledge, **1b** is the first successfully synthesized and characterized thiazoleboronic acid ester.

As a result of the instability of **1b** under aqueous conditions, a water-free cross-coupling protocol was required. First we used solid Na_2CO_3 in DME and $Pd(PPh_3)_4$ as catalyst. The reaction mixture was heated under microwave conditions to 150 °C for 30 min, but no conversion to the desired product was observed. When the temperature was increased to 170 °C for 120 min, again no product was formed, but **1b** obviously decomposed. We changed the base and followed a literature reference[19] to identify Cs_2CO_3 as an efficient base to give a cross-coupling reaction with iodobenzene to compound **2a**. Elevated temperatures facilitated the transformation, and the best results were obtained using microwave irradiation (130 °C, dioxane, $Pd(PPh_3)_4$), providing efficient conversion and minimizing the decomposition of **1b** under the reaction conditions. GC-MS analysis after 20 min of microwave irradiation indicated that **1b** has either reacted to the product or is decomposed to **1**. Compound **2a** was isolated in 56% yield. Thoroughly dried dioxane (over Na) and Cs_2CO_3 (160 °C, drying pistol) improved the stability of **1b** considerably in the reaction mixture. We found that the boronic ester was now stable for several hours at high temperatures but, interestingly, reacted at lower rates than in the presence of traces of water. Instead of 20 min at 130 °C, now almost 3 h at 170 °C were necessary to obtain 78% (GC-MS) conversion to **2a**. Similar results indicating a catalytic effect of trace amounts of water have been reported in the literature.[20]

Further attempts to improve the cross-coupling yield were performed. The addition of ionic liquids to the reaction mixture to increase the temperature only led to the fast deboronation of **1b**, and no cross-coupling product **2a** was observed. Using graphite, another good microwave absorber, instead gave about 50% conversion to **2a** after 20 min, according to GC-MS analysis, but decomposition of the remaining **1b** to 2-chlorothiazole, therefore, did not lead to an improvement in the yield.

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TABLE 1. Cross-Coupling Results of 1b and 1c with Various Halothiazoles under Microwave Irradiation

entry	halide	method	base	*T* (°C)	time (min)	product	yield (%)
1	**3**	Suzuki (**1b**)	Cs_2CO_3	170	20	4	37[a]
2	**3**	Suzuki (**1b**)	KOAc	170	70	4	32[a]
3	**3**	Suzuki (**1b**)	Cs_2CO_3	130	20	4	19[c]
4	**3**	Stille (**1c**)		170	110	4	6[b]
5	**3**	Stille (**1c**)		170	150	4	44[c]
6	**3**	Stille (**1c**)		170	20	4	56[a]
7	**7**	Suzuki (**1b**)	Cs_2CO_3	170	40	10	17[a]
8	**7**	Stille (**1c**)		170	20	10	69[b]
9	**7**	Stille (**1c**)		170[d]	20	10	81[a]
10	**9**	Suzuki (**1b**)	Cs_2CO_3	170	60	11	9[a,e]
11	**9**	Suzuki (**1b**)	NEt_3	170	60	11	0[a]
12	**9**	Stille (**1c**)		125	120	11	36[a]
13	**12**	Stille (**1c**)		170	30	4	14[a]
14	**12**	Stille (**1c**)		170	60	14	36[c]
15	**13**	Stille (**1c**)		125	120	15	52[a]
16	**17**	Stille (**1c**)		170	30	15	33[a]

[a] Freshly prepared $Pd(PPh_3)_4$. [b] Commercially available $Pd(PPh_3)_4$. [c] $PdCl_2(PhCN)_2$. [d] Alternatively under reflux. [e] Traces of water present.

Attempts to improve the yields by switching to other catalytic entities are currently under way in our laboratory.

Additionally, we investigated the influence of electron-donating and electron-withdrawing substituents on the outcome of the Suzuki−Miyaura cross-coupling reaction. Therefore, 4-iodoanisole, 4-iodonitrobenzene, and 4-iodobenzonitrile were tested as halides. We found that in all three cases similar results were obtained. With 4-iodonitrobenzene and 4-iodobenzonitrile, 32% (**2d**) and 27% (**2c**) of the cross-coupling product were isolated. 4-Iodoanisole gave only 13% of the desired compound **2b**, accompanied by another 13% of **2a**, derived from a ligand exchange from $Pd(PPh_3)_4$, a phenomenon already described in the literature.[21] Therefore, also in this case, 26% of cross-coupling products were obtained, which lies within the range of the other two investigated halides. The results remained the same, no matter if the boronic acid ester or the halide were used in excess. Because with Cs_2CO_3 a heterogeneous base was used, we also added, in one experiment (4-iodonitrobenzene as halide), 2 equiv of EDTA to the reaction mixture to get the base in solution through complexation. In this case, no cross-coupling product **2d** was detected, and only starting material was recovered.

Optimized cross-coupling reaction conditions were then applied to conversions of **1b** with several bromothiazoles (Table 1). The best yield (37%) was obtained using 2-bromothiazole (**3**) at 170 °C. At 130 °C, only 19% of **4** was obtained. Again, 2,2′-bithiazole (**5**), derived from a homocoupling of the applied halide, was isolated as byproduct (13%; entry 1). When the weaker base KOAc was used instead of Cs_2CO_3, slightly lower yields (32%) were obtained, but no **5** was formed (entry 2). Dibromide **7** gave even lower yields (17%) of the desired product **10** (entry 7), and a number of additional side reactions were observed. Surprisingly, 4-bromo-2-chlorothiazole (**8**) was formed as a byproduct, according to GC-MS analysis. To prove the structure of compound **8**, it was alternatively synthesized from **7** via a lithiation with *n*-BuLi in the 2-position and subsequent quenching with hexachloroethane (see experimental part). Eventually, reductive elimination from a Pd species formed in the course of the reaction can proceed to this side product. Because only small amounts were detected, no further investigations into this direction were undertaken. Minor amounts of 4-bromothiazole (**9**) were detected, which must be formed by the reduction of the administered halide in the 2-position. The least reactive bromothiazole **9** gave the lowest yield (9%). In this case, dry conditions did not give any conversion, and only in the presence of traces of water was conversion achieved (entry 10). Under such conditions, **1b** has a very limited stability and, therefore, the yield could not be improved. When Et_3N was used as the homogeneous base instead of Cs_2CO_3, no conversion was observed at all (entry 11). Based on the poor yields even for the most reactive bromothiazoles and as a result of the side reactions encountered, we moved on to investigate the Stille reaction as a final alternative.

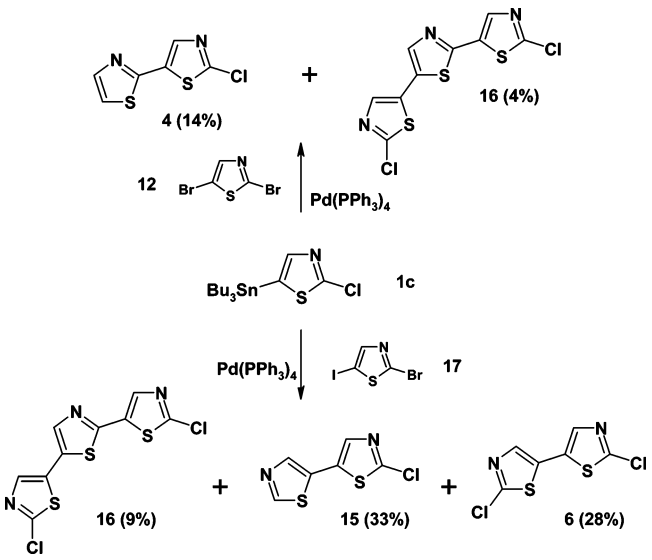
The starting material, 2-chloro-5-tributylstannylthiazole (**1c**) was prepared in 96% yield from **1** via lithiation with LDA at −70 °C in dry THF and subsequent quenching with Bu_3SnCl. Again, cross-coupling with iodobenzene was used as the test reaction under microwave conditions (170 °C, benzene, $Pd(PPh_3)_4$, 20 min) and afforded **2a** in a promising 82% yield. However, when **3** was used as the halide, only 6% of product **4** was obtained under the same reaction conditions (entry 4). The yield could be improved to 44% by using a different catalyst ($PdCl_2(PhCN)_2$; entry 5). When freshly prepared $Pd(PPh_3)_4$ was used, even better results (56% of **4**, entry 6) were obtained, which confirmed our experience that commercially available $Pd(PPh_3)_4$ is of varying quality. A similar trend was observed with thiazole halide **7**. With commercially available $Pd(PPh_3)_4$, 69% of **10** was obtained (Table 1, entry 8), whereby the freshly prepared catalyst gave 81% of **10** even under reflux conditions without microwave irradiation (entry 9)

Subsequently, other halothiazoles were submitted to the cross-coupling conditions (Table 1). The least-reactive 4-bromothiazole **9** gave 36% of the cross-coupling product (entry 12). 2,5-Dibromothiazole (**12**) was converted to the desired cross-coupling product **14** in 36% yield under $PdCl_2(PhCN)_2$ catalysis (entry 14). When $Pd(PPh_3)_4$ was used, dehalogenated product **4** and 2,5-bis-coupled compound **17** were obtained instead of the desired product (entry 13 and Scheme 3). It seems that $Pd(PPh_3)_4$ is reactive enough to insert into the C−Br bond in the 5-position of the initially cross-coupled product with subsequent cross-coupling to **16** (4%) or debromination to **4** (14%), and byproducts were not observed under $PdCl_2(PhCN)_2$ catalysis. This is in contrast to Dondonis work, who reported that $Pd(PPh_3)_4$-catalyzed Stille cross-coupling of **12** with 2-trimethylsilyl-4-trimethylstannylthiazole gave 4-bromo-2′-trimethylsilyl-2,4′-thiazole in 76% yield without this side reaction.[8b] A similar result was obtained when 2-bromo-5-iodothiazole (**17**) was used (entry 16 and Scheme 3). In this case, the initial cross-coupling took place in the 5-position, followed by a second cross-coupling in the 2-position to give **16** (9%) or dehalogenation to **15** (33%). Desired 5-bromo-2′-chloro-2,5′-bithiazole was not observed. In the reaction with **17**, a homocoupling product **6** (28%), derived from **1c**, was also obtained. This was not observed in any other case. Finally, 5-bromothiazole (**13**) was cross-coupled to **15** in 52% yield (entry 15) without any side reactions.

In the cases of halides **9** and **13** (entries 11 and 14), lower temperatures proved to be superior, whereby in all other examples, higher temperatures gave the best results. This might be due to a limited stability of **1c** in the presence of a Pd catalyst.

(21) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12−13.

SCHEME 3. Byproduct Formations in Stille Cross-Coupling Reactions of 1c[a]



[a] Conditions: halide, benzene or toluene, $Pd(PPh_3)_4$, 125 °C, mw.

In a blind experiment, **1c** was heated in benzene to 170 °C for 20 min without addition of the halide and catalyst. GC-MS analysis showed that no decomposition occurred, and thermal instability could be ruled out. In contrast, complete decomposition was observed after 20 min when the experiment was repeated in the presence of the Pd catalyst (without any coupling partner). It seems that considerable decomposition takes place in the presence of the Pd catalyst, besides cross-coupling. While the reaction rate increases at high temperatures, the stability of the reagent is decreased. At lower temperatures, the stability of **1c** is increased, on the other hand, but the reaction is considerably slower. We found 125 °C to be the optimum temperature in these two cases. Other solvents (DMF, acetone) were used but gave considerably lower conversion, or no conversion at all, in Stille cross-coupling attempts.

Conclusion

According to the data obtained in this comparative study, the Stille reaction represents the superior cross-coupling method for obtaining bithiazoles. It was successful for the cross-coupling of **1c** with a series of halothiazoles to bithiazoles. Here, side reactions were only detected when dihalides with two positions of similar reactivity were applied. In summary, new bithiazoles were formed in moderate to good yields (36−81%) in three steps starting from 2-aminothiazole. These bithiazoles can be easily further functionalized and might be useful in the synthesis of interesting compounds. Reactions applying a Negishi cross-coupling protocol suffered from substantial side reactions, leading to an inseparable mixture of products. Within this study, we have synthesized the first thiazoleboronic acid ester and successfully demonstrated its principal applicability for cross-coupling reactions. These results may open up a potential alternative to existing strategies, although the procedures have to be optimized and much more has to be learned about the behavior of this new compound class in cross-coupling reactions to gain general applicability. In light of the toxicity of tin organyls, further research toward a Suzuki−Miyaura strategy in thiazole chemistry may prove highly desirable and is currently addressed in our laboratory.

Experimental Section

General Cross-Coupling Procedures. Stille: The stannane **1c** (1 equiv), the halide (1 equiv), and the catalyst (0.05 equiv) were dissolved in benzene or toluene and heated in a CEM Explorer PLS microwave unit under nitrogen. The temperature in all microwave experiments was measured with an external IR sensor. Alternatively, in the case of iodobenzene, refluxing overnight gave similar results.

Suzuki−Miyaura: Boronic acid ester **1b** (1 equiv) and the corresponding halide (1 equiv) were heated in thoroughly dried dioxane (distilled from Na) with the corresponding catalyst (0.05 equiv, Table 1) and Cs_2CO_3 as base (2 equiv) to 170 °C under microwave conditions until complete consumption of **1b**, according to GC-MS analysis.

General Workup Procedure for Cross-Coupling Reactions: The reaction mixture was filtered, the solvent evaporated, and the residue purified by MPLC (LP/EtOAc, 15:1). The product fractions were united, and the solvent was evaporated. In the case of Stille examples, the residue was then treated with light petroleum (LP) to remove the remaining stannane fragments.

2-Chloro-5-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)thiazole (1b): To a solution of LDA (1.1 equiv, 9.20 mmol) and B(O-*i*-Pr)$_3$ (1.3 equiv, 2.04 g, 10.87 mmol) in dry diethyl ether (100 mL) **1** (1 equiv, 1.0 g, 8.36 mmol) was added at −90 °C. The reaction mixture was slowly warmed to room temperature before pinacol (1.4 equiv, 1.38 g, 11.71 mmol) in diethyl ether (10 mL) was added. After 15 min, AcOH (1.1 equiv, 0.55 g, 9.20 mmol) in 0.5 mL of diethyl ether was added, and the reaction mixture was immediately filtered through Celite. The solvent was evaporated, and the crude material was purified by Kugelrohr distillation to give 86% (1.76 g, 7.16 mmol) of **1b** as a colorless liquid: bp 100 °C (0.15 mbar). Compound **1b** decomposes on silica gel and alumina. ^{1}H NMR (DMSO, 200 MHz): δ 1.33 (s, 12H), 7.96 (s, 1H). ^{13}C NMR (DMSO, 50 MHz): δ 24.7 (q), 84.8 (s), 150.7 (d), 157.5 (s). The boron-carrying C5 did not appear. MS (EI) *m*/*z* (relative intensity): 245.2 (33); 230.1 (47); 210.2 (100); 146.1 (39); 85.1 (36).

2-Chloro-5-(tributylstannyl)thiazole (1c): To a stirred solution of DIPA (1.2 equiv, 0.71 g, 7.03 mmol) in dry THF (50 mL) under argon *n*-BuLi (1.2 equiv, 2.90 mL, 7.03 mmol, 2.42M in hexane) was added at −80 °C. The reaction mixture was warmed to 0 °C and stirred at that temperature for 20 min. Then **1** (1 equiv, 0.70 g, 5.85 mmol) was added dropwise at −80 °C, and the reaction mixture was stirred for 30 min and allowed to warm to −50 °C. Subsequently, Bu_3SnCl (1.3 equiv, 2.48 g, 7.61 mmol) was added dropwise at −80 °C. The reaction solution was warmed to room temperature and diluted with diethyl ether, and the organic layer was washed with 2 N HCl, water, and brine, dried over Na_2SO_4, filtered, and evaporated. The crude material was purified by Kugelrohr distillation to give 95% (2.27 g, 5.5 mmol) of **1c** as a colorless liquid: bp 190 °C (0.2 mbar). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.93 (t, J = 7.1 Hz, 9H), 1.17 (m, 6H), 1.35 (sext, J = 7.1 Hz, 6H), 1.55 (m, 6H), 7.47 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 10.9 (t), 13.5 (q), 27.1 (t), 28.8 (t), 132.1 (s), 147.8 (d), 156.1 (s). MS (EI) *m*/*z* (relative intensity): 352.4 (100), 350.4 (70), 296.2 (81), 240.0 (78), 238.0 (70).

2-Chloro-5-phenylthiazole (2a):[22] Compound **2a** was prepared according to the general Stille procedure. Reaction parameters: 20 min; 175 °C; $Pd(PPh_3)_4$; benzene. Yield: 82% (79 mg, 0.40 mmol) colorless solid; mp 40−42 °C. Compound **2a** was alternatively prepared according to the general Suzuki−Miyaura procedure in 56% yield. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.34−7.55 (m, 5H), 7.71 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 126.6 (d), 128.9 (d), 129.2 (d), 130.4 (s), 136.5 (d), 141.4 (s), 150.3 (s). MS (EI) *m*/*z*

(22) Hafez, E. A. A.; Abed, N. M.; Elsakka, I. A. *J. Heterocycl. Chem.* **1983**, *20*, 285−288.

(relative intensity): 197.09 (33), 195.07 (100), 160.11 (24), 134.03 (76), 89.07 (18).

2-Chloro-5-(4-methoxyphenyl)thiazole (2b): Compound **2b** was prepared according to the general Suzuki−Miyaura procedure (170 °C, 20 min). Purification: MPLC (LP/EtOAc, 25:1). Yield: 13% (18 mg, 0.08 mmol) beige solid; mp 82−84 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.84 (s, 3H), 6.93 (d, J = 8.9 Hz, 2H), 7.40 (d, J = 8.9 Hz, 2H), 7.59 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.4 (t), 114.6 (d), 123.0 (s), 127.9 (d), 135.3 (d), 139.0 (d), 141.3 (s), 149.3 (s), 160.1 (s). MS (EI) *m*/*z* (relative intensity): 227.1 (34), 225.1 (100), 210.0 (70), 207.0 (33), 181.9 (31).

4-(2-Chlorothiazol-5-yl)benzonitrile (2c): Compound **2c** was prepared according to the general Suzuki−Miyaura procedure (170 °C, 20 min). Purification: MPLC (LP/EtOAc, 10:1). Yield: 27% (37 mg, 0.17 mmol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.59 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.9 Hz, 2H), 7.82 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 112.3 (s), 118.2 (s), 126.9 (d), 133.0 (d), 134.8 (s), 138.3 (d), 139.2 (s), 152.4 (s). MS (EI) *m*/*z* (relative intensity): 222.1 (27), 221.1 (10), 220.0 (80), 158.8 (100), 113.8 (14).

2-Chloro-5-(4-nitrophenyl)thiazole (2d): Compound **2d** was prepared according to the general Suzuki−Miyaura procedure (170 °C, 20 min). Purification: MPLC (LP/EtOAc, 20:1). Yield: 32% (47 mg, 0.20 mmol) yellow solid; mp 140−143 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.65 (d, J = 8.9 Hz, 2H), 7.87 (s, 1H), 8.28 (d, J = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 124.7 (d), 127.0 (d), 131.1 (s), 136.6 (s), 138.7 (d), 147.6 (s), 152.8 (s). MS (EI) *m*/*z* (relative intensity): 240.1 (100), 210.0 (44), 207.0 (44), 132.6 (62), 88.7 (78).

2′-Chloro-2,5′-bithiazole (4): Compound **4** was prepared according to the general Stille procedure. Reaction parameters: 20 min; 175 °C; $Pd(PPh_3)_4$; benzene. Yield: 56% (70 mg, 0.35 mmol) pale yellow solid; mp 78−80 °C. Compound **4** was alternatively prepared according to the general Suzuki−Miyaura procedure in 32% yield. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35 (d, J = 3.2 Hz, 1H), 7.81 (d, J = 3.2 Hz, 1H), 7.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 119.3 (d), 134.9 (s), 139.2 (d), 143.7 (d), 153.2 (s), 157.4 (s). MS (EI) *m*/*z* (relative intensity): 204.0 (22), 202.0 (55), 167.1 (29), 58.1 (100).

2,2′-Dichloro-5,5′-bithiazole (6): Compound **6** was obtained as a byproduct during the formation of **4** (via a Negishi reaction, not isolated) and **16** (from **1c** and **18** via the general Stille procedure). Yield: 28% (106 mg, 0.447 mmol) pale yellow solid; mp 103−105 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.58 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 129.1 (s), 139.1 (d), 151.9 (s). MS (EI) *m*/*z* (relative intensity): 237.9 (82), 235.9 (100), 200.8 (33), 174.7 (43), 139.7 (34).

2,4-Dibromothiazole (7): 2,4-Thiazolidinedione (1 equiv, 5.38 g (90% from Aldrich), 41.33 mmol) was mixed with $POBr_3$ (7.6 equiv, 100.0 g, 349 mmol) and refluxed for 1.5 h. The reaction mixture was then cooled, poured onto ice water, and neutralized with solid Na_2CO_3. The aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated. The crude material was dissolved in light petroleum, and the remaining solid was removed by filtration. Evaporation of the solvent and subsequent Kugelrohr distillation gave **7** as colorless crystals in 99% (9.94 g, 40.9 mmol) yield; mp 79−80 °C; (lit.:[23] 60% yield; mp 82 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 120.7 (d), 124.3, (s), 136.3 (s). MS (EI) *m*/*z* (relative intensity): 244.9 (66), 242.9 (100), 240.9 (60), 137.9 (50), 57.1 (68).

4-Bromo-2-chlorothiazole (8): A solution of *n*-BuLi (1.05 equiv, 0.91 mL, 2.16 mmol, 2.37 M in hexane) in dry diethyl ether (100 mL) was cooled to −80 °C, and a solution of 2,4-dibromothiazole (1 equiv, 0.5 g, 2.06 mmol) in diethyl ether (5 mL) was added dropwise. After 1 h, a solution of hexachloroethane (1.1 equiv, 536 mg, 2.26 mmol) in diethyl ether (5 mL) was added, and the reaction mixture was slowly warmed to room temperature. The reaction solution was then washed with 2 N HCl, water, and brine, and the aqueous phases were re-extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4. Filtration and evaporation of the solvent gave **8** without further purification in 95% (0.39 g, 1.97 mmol) yield as colorless crystals; mp 59−60 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 118.9 (d), 123.1 (s), 152.5 (s).

4-Bromothiazole (9): Starting material **7** (1 equiv, 3.33 g, 13.71 mmol) was dissolved in dry diethyl ether (100 mL) and cooled to 0 °C. Subsequently, *i*-PrMgCl (1.2 equiv, 8.22 mL, 16.45 mmol) was added at that temperature as a 2 M solution in dry THF. During the addition, a colorless precipitate was formed. After complete addition of the Grignard reagent, the reaction mixture was allowed to warm to room temperature overnight. The organic layer was washed with 2 N HCl solution, water, and brine, dried over Na_2SO_4, and filtered, and the solvent mixture was evaporated. The crude material was purified by Kugelrohr distillation to give 73% (1.65 g, 10.06 mmol) of **9** as colorless liquid; bp 189−190 °C (lit.:[7a] 29% yield, bp 188−190 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.29 (d, J = 2.2 Hz, 1H), 8.73 (d, J = 2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 116.8 (d), 126.5 (s), 153.7 (d). MS (EI) *m*/*z* (relative intensity): 165.0 (100), 163.0 (95), 137.9 (33), 135.9 (31), 57.1 (44).

4-Bromo-2′-chloro-2,5′-bithiazole (10): Compound **10** was prepared according to the general Stille procedure. Reaction parameters: overnight, reflux, $Pd(PPh_3)_4$, benzene (thermal) or 20 min, 170 °C, $Pd(PPh_3)_4$, benzene (microwave). Yield: 81% (112 mg, 0.40 mmol) yellow solid. Compound **10** was alternatively prepared according to the general Suzuki−Miyaura procedure in 17% yield; mp 125−127 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.23 (s, 1H), 7.93 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 116.8 (d), 126.3 (s), 133.7 (s), 139.8 (d), 154.0 (s), 158.2 (s). MS (EI) *m*/*z* (relative intensity): 282.0 (100), 280.0 (67), 137.6 (48), 135.6 (46), 56.6 (52). Anal. Calcd for $C_6H_2BrClN_2S_2$: C, 25.59; H, 0.72; N, 9.95. Found: C, 25.82; H, 1.00; N, 9.87.

2′-Chloro-4,5′-bithiazole (11): Compound **11** was prepared according to the general Stille procedure. Reaction parameters: 120 min, 125 °C, $Pd(PPh_3)_4$, benzene. Yield: 36% (41 mg, 0.20 mmol) pale yellow solid; mp 78−81 °C. Compound **11** was alternatively prepared according to the general Suzuki−Miyaura procedure in 9% yield. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.47 (d, J = 2.0 Hz, 1H), 7.88 (s, 1H), 8.84 (d, J = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 113.6 (d), 135.2 (s), 137.4 (d), 146.7 (s), 151.2 (s), 153.6 (d). MS (EI) *m*/*z* (relative intensity): 204.0 (39), 202.0 (100), 166.9 (51), 113.8 (28), 68.7 (33). Anal. Calcd for $C_6H_3ClN_2S_2$: C, 35.56; H, 1.49; N, 13.82. Found: C, 35.63; H, 1.65; N, 13.56.

2,5-Dibromothiazole (12): 2-Bromothiazole **3** (1 equiv, 1.35 g, 8.23 mmol) was stirred in a mixture of water (10 mL) and 48% aqueous HBr (10 mL). Then Br_2 (4.7 equiv, 6.22 g, 38.9 mmol) was added, and the reaction mixture was refluxed for 3 h. The formed precipitate (the hydrobromide of **12**) was removed by filtration, dissolved in diethyl ether, and neutralized with satd. $NaHCO_3$ solution. The organic layer was washed with water and brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated to give **12**. By extracting the initial filtrate with diethyl ether and repeating the washing procedure for the precipitate, a second fraction of **12** was obtained after Kugelrohr distillation. Overall yield: 55% (1.10 g, 4.53 mmol) as a colorless, slow crystallizing liquid; mp 45−47 °C (lit.:[24] 40% yield, mp 46−47 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.51 (s, 1H).[25] ^{13}C NMR ($CDCl_3$, 50 MHz): δ 110.7 (s), 135.8 (s), 144.0 (d). MS (EI) *m*/*z*

(23) Reynaud, P.; Robba, M.; Moreau, R. C. *Bull. Soc. Chim. Fr.* **1962**, 1735−1738.

(24) Erlenmeyer, H.; Kiefer, H. *Helv. Chim. Acta* **1945**, *28*, 985−991.

(25) Kerdesky, F. A. J.; Seif, L. S. *Synth. Commun.* **1995**, *25*, 4081−4086.

(relative intensity): 244.9 (40), 243.0 (74), 241.0 (35), 164.0 (100), 162.0 (92), 57.1 (77).

5-Bromothiazole (13): Substrate **12** (1 equiv, 683 mg, 2.81 mmol) was cooled to −40 °C in dry diethyl ether (50 mL). At that temperature, *i*-PrMgCl (1.1 equiv, 1.97 mL in dry THF, 3.09 mmol) was added dropwise. After 30 min, the reaction mixture was quenched with MeOH, warmed to room temperature, and washed with 2 N HCl. The organic layer was concentrated, and the crude material was purified by MPLC (first light petroleum, then LP/EtOAc, 10:1) to give 20% (91 mg, 0.55 mmol) of **13** as colorless liquid; bp 70 °C at 20 mbar (lit.:[7a] 16% yield, bp 80−81 °C at 18 Torr).^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.82 (s, 1H), 8.77 (s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 109.1 (s), 144.6 (d), 156.3 (d).[26] MS (EI) *m*/*z* (relative intensity): 164.7 (100), 162.8 (95), 85.7 (16), 83.7 (90), 56.6 (76).

5-Bromo-2′-chloro-2,5′-bithiazole (14): Compound **14** was prepared according to the general Stille procedure. Reaction parameters: 60 min, 170 °C, $Pd(PPh_3)_2Cl_2$, benzene. Yield: 36% (50 mg, 0.178 mmol) pale yellow solid; mp 113−115 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.68 (s, 1H), 7.85 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 109.4 (s), 134.4 (s), 139.4 (d), 144.8 (d), 153.7 (s), 158.5 (s). MS (EI) *m*/*z* (relative intensity): 281.9 (65), 280.0 (44), 203.0 (33), 201.0 (81), 57.0 (100). Anal. Calcd for $C_6H_2BrClN_2S_2$: C, 25.59; H, 0.72; N, 9.95. Found: C, 25.86; H, 0.91; N, 9.73

2-Chloro-5,5′-bithiazole (15): Compound **15** was prepared according to the general Stille procedure. Reaction parameters: 120 min, 125 °C, $Pd(PPh_3)_4$, benzene. Yield: 52% (26 mg, 0.128 mmol) from **13** and 33% (156 mg, 0.77 mmol) from **17**; pale yellow solid; mp 82−84 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.64 (s, 1H), 7.95 (s, 1H), 8.80 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 127.2 (s), 130.0 (s), 138.8 (d), 141.4 (d), 151.3 (s), 153.0 (d). MS (EI) *m*/*z* (relative intensity): 203.8 (65), 201.8 (100), 174.8 (39), 113.6 (29), 68.5 (33).

2,2″-Dichloro-5,2′:5′,5″-terthiazole (16): Compound **16** was obtained as a byproduct during the formation of **4** (from **1c** and **12**; 4%) and **15** (from **1c** and **17**; 9% (67 mg, 0.21 mmol)); pale yellow solid; mp 188−190 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.66 (s, 1H), 7.79 (s, 1H), 7.93 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 127.5 (s), 129.5 (s), 134.2 (s), 139.0 (d), 139.8 (d), 141.3 (d), 151.7 (s), 154.0 (s), 157.1 (s).

2-Bromo-5-iodothiazole (17): 2-Bromothiazole **3** (1 equiv, 1.0 g, 6.10 mmol) in diethyl ether (10 mL) was added dropwise to a solution of LDA (1.1 equiv, 6.70 mmol) in dry diethyl ether (200 mL) at −80 °C. The reaction mixture was kept at that temperature for 30 min before I_2 (1.2 equiv, 1.86 g, 7.32 mmol) in diethyl ether (20 mL) was added dropwise. The reaction mixture was slowly warmed to room temperature and subsequently washed with aqueous satd. $Na_2S_2O_5$, water, and brine. All aqueous phases were re-extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated. MPLC (LP/EtOAc, 10:1) gave **17** in 74% (1.30 g, 4.48 mmol) yield as a yellow solid; mp 108−110 °C (lit.:[7a] 35% yield; mp 110−112 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 72.3 (s), 139.4 (s), 150.6 (d).

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Supporting Information Available: ^{1}H, ^{13}C, and DEPT (where of importance) NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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