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Synthesis of 2′-Substituted 4-Bromo-2,4′-bithiazoles by Regioselective Cross-Coupling Reactions

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The synthesis of the title compounds (**1**) was achieved in two steps starting from readily available 2,4-dibromothiazole (**2**). In a regioselective Pd(0)-catalyzed cross-coupling step, compound **2** was converted into a variety of 2-substituted 4-bromothiazoles **3** (10 examples, 65−85% yield). Alkyl and aryl zinc halides were employed as nucleophiles to introduce an alkyl or aryl substituent. The Sonogashira protocol was followed to achieve an alkynyl-debromination. Bromo−lithium exchange at carbon atom C-4 and subsequent transmetalation to zinc or tin converted the 4-bromothiazoles **3** into carbon nucleophiles which underwent a second regioselective cross-coupling with another equivalent of 2,4-dibromothiazole (**2**). The Negishi cross-coupling gave high yields of the 2′-alkyl-4-bromo-2,4′-bithiazoles **1a**−**g** (88−97%). The synthesis of the 2′-phenyl- and 2′-alkynyl-4-bromo-2,4′-bithiazoles **1h**−**j** required a Stille cross-coupling that did not proceed as smoothly as the Negishi cross-coupling (58−62% yield). The title compounds which were accessible in total yields of 38−82% are versatile building blocks for the synthesis of 2,4′-bithiazoles.

Introduction

2′,4-Disubstituted 2,4′-bithiazoles represent an important class of natural products which exhibit an intriguing and diversified spectrum of biological acitivities. Structurally, one can distinguish the less complex cystothiazoles,[1] melithiazoles,[2] and myxothiazoles[3] which contain the bithiazole unit as the only heterocyclic element and the more complex macrocyclic bithiazole antibiotics (e.g., amithiamicines,[4] cyclothiazomycin,[5] micrococcin P,[6] GE 2270,[7] and GE 37468[8]) which contain additional thiazole and pyridine heterocycles as substructures. As a third class of natural occurring 2,4′-bithiazoles, bleomycins[9] and tallysomycins[10] are glycopeptide antibiotics which carry a bithiazole amino acid at their C-terminal position. In addition to their immediate biological relevance, 2′,4-disubstituted bithiazoles have attracted synthetic interest based on the biological properties of their complexes.[11]

The common approach toward the synthesis of 2′,4-disubstituted 2,4′-bithiazoles relies on the classical Hantzsch reaction to establish at least one thiazole ring. This strategy has been employed in several syntheses of biologically active bithiazoles, e.g., cystothiazoles A and C,[12] myxothiazol,[13] micrococcin P,[14] and bleomycins.[9c] In the synthesis of micrococcinic acid, a degradation product of the micrococcins, Kelly et al. successfully used the selective lithium−halogen metal exchange reaction at 2,4-dibromothiazole to establish the substitution pattern in one ring of a 2′,4-disubstituted 2,4′-bithiazole.[15] The second thiazole ring was formed by a Hantzsch reaction. Dondoni et al. employed the regioselective functionalization of a 2,4-distubstituted thiazole for the synthesis of bithiazoles.[16] In addition, they showed that a regioselective cross-coupling on a 2,5-dibromothiazole is possible.[16b]

Our strategy for the synthesis of biologically relevant five-membered heterocyclic rings centers on regioselective

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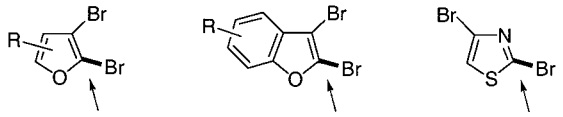
SCHEME 1. Preferred Sites for a Cross-Coupling on Dibrominated Furans, Benzofurans, and Thiazoles



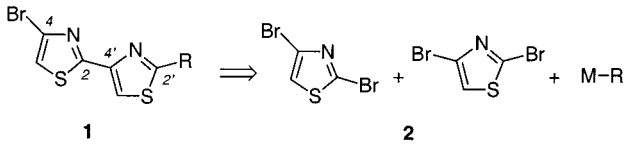
Pd(0)- or Ni(0)-catalyzed cross-coupling reactions.[17,18] In dibromo- and tribromohetarenes, a regioselective cross-coupling can be achieved at the most electron deficient position because the transition metal acts as a nucleophile in the oxidative addition step. Cross-coupling reactions which proceed via fast transmetalation and reductive elimination steps are particularly sensitive toward this electronic requirement. The regioselective cross-coupling strategy was successfully applied to furans,[19] thiazoles,[20] and benzofurans[21] (Scheme 1) and it appeared as if it was also applicable for the construction of bithiazoles.[22]

In this context, the title compounds, 2′-substituted 4-bromo-2,4′-bithiazoles (**1**), were considered to be attractive target compounds. Their electrophilicity at the 4-position can be favorably used for reactions with a variety of nucleophiles. The polarity at C-4 can be readily reversed by bromo−metal exchange to allow for a reaction with electrophiles.

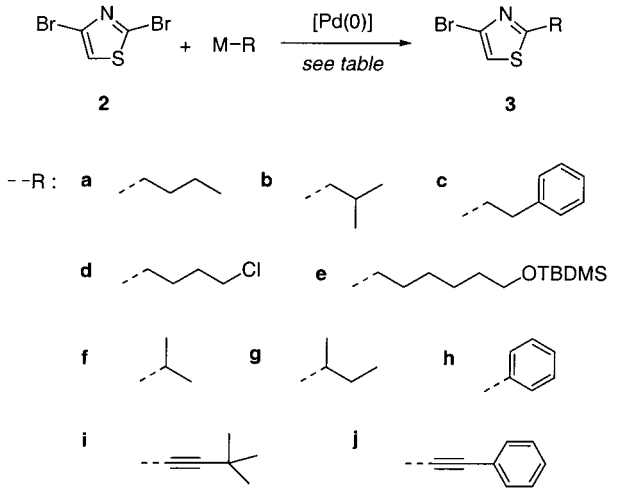
Results and Discussion

The general scheme for the synthesis of the title compounds is outlined below (Scheme 2). Cross-coupling of an organometallic reagent (RM) with 2,4-dibromothiazole (**2**)[23] should occur at the 2-position. Subsequent bromo−lithium exchange generates a carbon nucleophile

SCHEME 2. General Strategy for the Syntheses of the Title Compounds (1)



SCHEME 3. Cross-Coupling at Carbon Atom C-2 of Thiazole 2 (Cf. Table 1)



that can react in a second step with another molecule of compound **2** to the desired product. Only two reaction steps are necessary to establish the desired carbon framework.

In the following sections the above-mentioned reactions are described in more detail. It turned out that the Sonogashira and the Neghishi cross-coupling reactions are well-suited for the first C−C bond-forming step. For the second C−C bond formation Negishi and Stille cross-coupling reactions were employed depending on the primary substitution pattern.

Experiments toward a C−C bond formation between an alkylmetal reagent and the C-2 position of 2,4-dibromothiazole were conducted with the corresponding zinc reagents in THF solutions at room temperature (Scheme 3, Table 1, entries 1−7). The organozinc compounds were prepared by transmetalation of the organolithium reagents which were either commercially available (procedure A) or generated by an iodine−lithium exchange reaction (procedure B). They were used in excess (2.5 equiv) relative to 2,4-dibromothiazole. To avoid β-hydride elimination and isomerization, 1,1′-bis-(diphenylphosphino)ferrocene (dppf)[24] was used as the ligand in all instances. The in situ preparation of the metal−ligand complex from $Pd_2(dba)_3$ (dba = dibenzylidene acetone) and dppf was preferable as compared to the use of the preformed $PdCl_2$(dppf) complex.

In the synthesis of thiazole **3d** (entry 4), for example, the yield obtained with the latter catalyst was 65% as compared to 80% achieved with $Pd_2(dba)_3$/dppf. In general, the yields for the cross-coupling of the primary alkyl zinc reagents (entries 1−5) were slightly higher than those for the secondary alkyl zinc reagents (entries 6−7).

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TABLE 1. Details for a Set of Regioselective Cross-Coupling Reactions Conducted with Bithiazole 2 (Cf. Scheme 3)

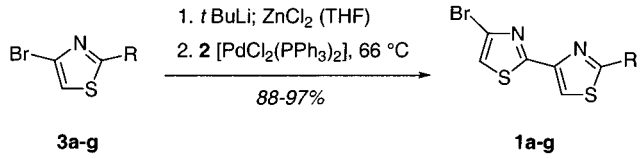
entry	procedure[a]	catalyst	product	yield [%][b]
1	A[c]	$Pd_2(dba)_3$/dppf	**3a**	85
2	B[d]	$Pd_2(dba)_3$/dppf	**3b**	73
3	B	$Pd_2(dba)_3$/dppf	**3c**	79
4	B	$Pd_2(dba)_3$/dppf	**3d**	80
5	B	$Pd_2(dba)_3$/dppf	**3e**	85
6	A	$Pd_2(dba)_3$/dppf	**3f**	72
7	A	$Pd_2(dba)_3$/dppf	**3g**	76
8	A	$PdCl_2(PPh_3)_2$	**3h**	83
9	C[e]	$Pd(PPh_3)_4$/CuI	**3i**	65
10	C	$Pd(PPh_3)_4$/CuI	**3j**	81

[a] The cross-coupling reactions were conducted at room temperature in THF as the solvent employing substrate **2** (1 equiv) and 5 mol % of the given catalyst. [b] Yield of isolated product. [c] Procedure A: Commercially available organolithium reagent (2.5 equiv) was transmetalated with $ZnCl_2$ (3.75 equiv). [d] Procedure B: The organolithium reagent was prepared from the corresponding iodide (2.5 equiv) and *tert*-butyllithium (5.2 equiv) and was subsequently transmetalated with $ZnCl_2$ (3.75 equiv). [e] Procedure C: The alkyne (1.5 equiv) and *N*,*N*-diisopropylamine (1.5 equiv) were employed as precursors for the alkynylmetal species. 10 mol % of CuI was used.

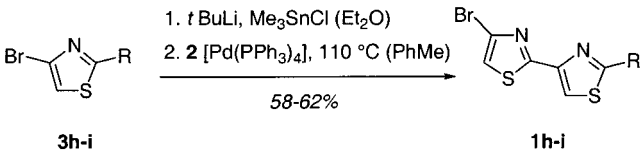
The functional group tolerance was limited by the preparation of the alkyllithium reagents. An organozinc reagent that was prepared directly[25] from ethyl 5-iodopentanoate did not give a clean and complete conversion under a variety of conditions. Further studies in this direction have not yet been undertaken. The amount of catalyst in the reaction **2** → **3a** was varied. A satisfactory conversion was achieved with a catalyst:substrate ratio as low as 1:200 (0.5 mol %) without significant deterioration of the product yield. With less catalyst the reaction remained incomplete. For the cross-coupling of compounds which did not contain a β-hydrogen atom, the use of $PdCl_2(PPh_3)_2$ was sufficient (entry 8). 2-Alkynylthiazoles **3i** and **3j** (entries 9 and 10) were obtained by a regioselective Sonogashira cross-coupling. In the former case, the use of $PdCl_2(PPh_3)_2$ resulted in some homocoupling, which let us employ $Pd(PPh_3)_4$ as the catalyst. All reactions were complete overnight at room temperature (16 h). The regioselective Sonogashira cross-coupling for which literature precedence existed[18k] proceeded even faster (3−4 h). Side reactions (cross-coupling at C-4 or disubstitution) were not observed by GC/MS. In some runs, however, a hydrodebromination of the starting material **2** to 4-bromothiazole occurred. Spectroscopically, the regioselectivity of the cross-coupling can be nicely checked by ^{13}C NMR. The carbon atom at which the substitution takes place is significantly deshielded ($\Delta\delta$ = 35−40 ppm if R = alkyl, aryl; $\Delta\delta$ = ca. 15 ppm if R = alkynyl). To provide an example, the carbon atom C-2 of 2,4-dibromothiazole (**2**) resonates at 137.6 ppm whereas the carbon atom C-2 of 2-butyl-4-bromothiazole (**3a**) is responsible for the signal at 172.7 ppm. The signal for the carbon atom C-4 (δ = 123.4 ppm) remains essentially unchanged.

The intermediates **3** obtained in the first coupling step were transformed into 4-thiazolyllithium compounds by bromo−lithium exchange. Transmetalation to zinc provided potential carbon nucleophiles which were ready to be used in Negishi cross-coupling reactions with another equivalent of 2,4-dibromothiazole (**2**). As previously stated, $PdCl_2(PPh_3)_2$ is a satisfactory catalyst for these $C_{sp^2}-C_{sp^2}$ type cross-coupling reactions. They proceeded cleanly as long as the substituent at the 2-position of the 4-thiazolyl zinc reagent was an alkyl group (Scheme 4). The products **1a**−**g** were obtained in excellent yields (88−97%). In contrast to the first cross-coupling that was conducted at ambient temperature, the second cross-coupling was performed in THF at reflux. Still, there was no complication with regard to functional groups nor with regard to the regioselectivity of the cross-coupling. The total yield of compounds **1a**−**g** over two steps varied between 64% and 82%. Compound **1f** was used as the pivotal intermediate in our synthesis of cystothiazole E.[22] An analogous triflate was later mentioned in another report on cystothiazole syntheses[26] but its synthesis was not disclosed.

SCHEME 4. Negishi Cross-Coupling of 2-Alkylthiazolyl Zinc Reagents and Thiazole 2



SCHEME 5. Stille Cross-Coupling of 4-(2-Alkynyl)- and 4-(2-Phenyl)thiazolylstannanes and Thiazole 2



The 2-phenyl- and 2-alkynylthiazolyl zinc reagents derived from compounds **3h**−**j** did not undergo a Negishi cross-coupling with thiazole **2** as the electrophile. A variation of reaction conditions (catalyst, solvent, temperature) remained unsuccessful. Among others, $PdCl_2(PPh_3)_2$, $PdCl_2$(dppf), and $NiCl_2$(dppp) were used as catalysts. Only unreacted thiazole **2** and debrominated thiazoles derived from **3h**−**j** were recovered. In search for other possible reactions the Suzuki and Stille cross-coupling were considered. The synthesis of aryl boronic esters is more tedious and often less efficient than the synthesis of arylstannanes. In addition, there was literature precedence for an unsatisfactory and low-yielding (15%) Suzuki cross-coupling on 2,4-dibromothiazole.[18j] We consequently started to study the Stille cross-coupling. The required 4-trimethylstannylthiazoles were prepared from the bromides **3h**−**j** by bromo−lithium exchange and subsequent quench with chlorotrimethylstannane. They were obtained as yellow oils which were not purified but directly taken into the cross-coupling step (Scheme 5). The cross-coupling proceeded (Scheme 5) regioselectively but the yields were lower than in the Negishi cross-coupling of the 2-alkylthiazolyl zinc reagents. The total yield in which compounds **1h**−**j** were synthesized from **2** varied between 38% and 51%.

In summary, we have explored a useful and versatile approach to 2′-substituted 4-bromo-2,4′-bithiazoles. The

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examples we presented demonstrate that the strategy is general and should be applicable to the synthesis of a broad variety of bithiazoles. Further reactions at the carbon atom C-4 have not been studied further. Precedence for a successful Suzuki cross-coupling exists[22] and there is no doubt that other commonly used transformations of 4-bromothiazoles[27] are also suited for the products **1a**−**j**. Further work in our research group centers on the application of the described method to more complex, biologically relevant bithiazoles.

Experimental Section

General. All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium immediately prior to use. *N*,*N*-Disopropylamine was distilled from calcium hydride. The employed alkynes were distilled immediately prior to use. $Pd(PPh_3)_4$,[28] $PdCl_2(PPh_3)_2$,[29] $PdCl_2$(dppf),[30] $Pd_2(dba)_3$,[31] and dppf were prepared according to literature procedures. All other chemicals were either commercially available or prepared according to the cited references. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent at 303 K. Chemical shifts are reported relative to tetramethylsilane as an internal standard or to distinguished solvent signals. Apparent multiplets which occur as a result of the accidental equality of coupling constants of magnetically nonequivalent protons are marked as virtual (virt.). Combustion analyses were conducted by the microanalytical laboratory Beller (Göttingen). MS spectra were recorded in the EI mode at an ionization energy of 70 eV. TLC was performed on aluminum sheets (0.2 mm silica gel 60 F_{254}). Detection was done by UV or coloration with ceric ammonium molybdate (CAM). Flash chromatography was performed on silica gel 60 (230−400 mesh) (ca. 100 g for 1 g of material to be separated) with the eluent given in brackets. Common solvents [THF, Et_2O, ethyl acetate (EtOAc), and pentane (P)] were distilled prior to use.

General Procedure A for Negishi Cross-Coupling Reactions to 2-Substituted 4-Bromothiazoles. A solution of the commercially available organolithium compound (5.0 mmol) was added at −78 °C to 15 mL of a 0.5 M solution of $ZnCl_2$ (7.5 mmol) in THF. The resulting mixture was stirred at room temperature for 30 min and was added via syringe to a solution of 486 mg of 2,4-dibromothiazole (**2**) (2.0 mmol), 46 mg of $Pd_2(dba)_3$ (0.1 mmol), and 56 mg of dppf (0.1 mmol) in 10 mL of THF. After being stirred for 16 h at room temperature the reaction was quenched with 10 mL of saturated NH_4Cl solution and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL). After drying over Na_2SO_4 and filtration, the solvent was removed and the residue was purified by flash chromatography.

4-Bromo-2-butylthiazole (3a). The reaction was carried out on the same scale as described for general procedure A employing 2.0 mL of a *n*-butyllithium solution (2.5 M in hexanes) (5.0 mmol). A total of 375 mg (85%) of **3a** was obtained as a yellow oil (P/Et_2O = 97/3 as eluent). R_f 0.43 (P/Et_2O = 95/5). IR (film): $\tilde{\nu}$ 3123 cm^{-1} (m, CH_{ar}), 2957 (s, CH_{al}), 2871 (s, CH_{al}). ^1H NMR: δ 0.91 (t, J = 7.3 Hz, 3 H), 1.38 (virt. sext, $J \cong$ 7.5 Hz, 2 H), 1.73 (virt. quin, $J \cong$ 7.6 Hz, 2 H), 2.96 (t, J = 7.7 Hz, 2 H), 7.03 (s, 1 H). ^{13}C NMR: δ 13.6, 22.1, 31.8, 33.2, 115.5, 124.1, 172.7. MS, *m*/*z* (%): 221 (6) [$M^+(^{81}Br)$], 219 (7) [$M^+(^{79}Br)$], 206 (5) [$M^+(^{81}Br) - CH_3$], 204 (4) [$M^+(^{79}Br) - CH_3$], 192 (25) [$M^+(^{81}Br) - C_2H_5$], 190 (23) [$M^+(^{79}Br) - C_2H_5$], 179 (100) [$M^+(^{81}Br) - C_3H_6$], 177 (99) [$M^+(^{79}Br) - C_3H_6$], 138 (9) [$^{81}BrCCHS^+$], 136 (7) [$^{79}BrCCHS^+$]. Anal. Calcd for $C_7H_{10}BrNS$ (220.13): C, 38.19; H, 4.58. Found: C, 37.98; H, 4.50.

4-Bromo-2-isopropylthiazole (3f). The reaction was carried out on the same scale as described for general procedure A employing 7.1 mL of an isopropyllithium solution (0.7 M in pentane) (5.0 mmol). A total of 295 mg (72%) of **3f** was obtained as a colorless oil (P/Et_2O = 95/5 as eluent). R_f 0.30 (P/Et_2O = 95/5). IR (film): $\tilde{\nu}$ 3122 cm^{-1} (m, CH_{ar}), 2968 (s, CH_{al}). ^1H NMR: δ 1.37 (d, J = 7.0 Hz, 6 H), 3.28 (sept, J = 7.0 Hz, 1 H), 7.05 (s, 1 H). ^{13}C NMR: δ 22.8, 33.4, 115.2, 124.1, 180.0. MS, *m*/*z* (%): 207 (46) [$M^+(^{81}Br)$], 205 (43) [$M^+(^{79}Br)$], 192 (100) [$M^+(^{81}Br) - CH_3$], 190 (98) [$M^+(^{79}Br) - CH_3$], 138 (14) [$^{81}BrCCHS^+$], 136 (13) [$^{79}BrCCHS^+$], 126 (50) [$M^+ - Br$]. Anal. Calcd for C_6H_8BrNS (206.10): C, 34.94; H, 3.91. Found: C, 34.79; H, 4.01.

4-Bromo-2-*sec*-butylthiazole (3g). The reaction was carried out as described for general procedure A starting with 972 mg of 2,4-dibromothiazole (**2**) (4.0 mmol), 7.6 mL of a *sec*-butyllithium solution (1.3 M in pentane) (10.0 mmol), 30 mL of a $ZnCl_2$ solution (0.5 M in THF) (15 mmol), 92 mg of $Pd_2(dba)_3$ (0.2 mmol), and 112 mg of dppf (0.2 mmol). A total of 667 mg (76%) of **3g** was obtained as a yellow oil (P/Et_2O = 98/2 as eluent). R_f 0.37 (P/Et_2O = 97/3). IR (film): $\tilde{\nu}$ 3123 cm^{-1} (w, CH_{ar}), 2965 (s, CH_{al}), 2930 (m, CH_{al}). ^1H NMR: δ 0.90 (t, J = 7.4 Hz, 3 H), 1.33 (d, J = 7.0 Hz, 3 H), 1.65 (virt. dquin, $J \cong$ 7.0 Hz, $J \cong$ 14.0 Hz, 1 H), 1.78 (virt. dquin, $J \cong$ 7.0 Hz, $J \cong$ 14.0 Hz, 1 H), 3.06 (virt. sext, $J \cong$ 7.0 Hz, 1 H), 7.05 (s, 1 H). ^{13}C NMR: δ 11.6, 20.4, 30.5, 40.3, 115.2, 124.0, 178.1. MS, *m*/*z* (%): 221 (21) [$M^+(^{81}Br)$], 219 (19) [$M^+(^{79}Br)$], 206 (33) [$M^+(^{81}Br) - CH_3$], 204 (30) [$M^+(^{79}Br) - CH_3$], 193 (100) [$M^+(^{81}Br) - C_2H_4$], 191 (96) [$M^+(^{79}Br) - C_2H_4$], 179 (12) [$M^+(^{81}Br) - C_3H_6$], 177 (10) [$M^+(^{79}Br) - C_3H_6$]. Anal. Calcd for $C_7H_{10}BrNS$ (220.13): C, 38.19; H, 4.58. Found: C, 38.23; H, 4.60.

4-Bromo-2-phenylthiazole (3h). The reaction was carried out on the same scale as described for general procedure A employing 2.8 mL of a phenyllithium solution (1.8 M in cyclohexan/Et_2O = 70/30) (5.0 mmol) and 70 mg of $PdCl_2(PPh_3)_2$ (0.1 mmol) as the catalyst instead of $Pd_2(dba)_3$/dppf. A total of 398 mg (83%) of **3h** was obtained as a red solid (P/Et_2O = 96/4 as eluent). R_f 0.22 (P/Et_2O = 97/3). Mp: 65 °C. IR (KBr): $\tilde{\nu}$ 3120 cm^{-1} (w, CH_{ar}). ^1H NMR: δ 7.19 (s, 1 H), 7.42−7.43 (m, 3 H), 7.90−7.93 (m, 2 H). ^{13}C NMR: δ 116.4, 126.1, 126.4, 129.0, 130.7, 132.6, 169.0. MS, *m*/*z* (%): 241 (100) [$M^+(^{81}Br)$], 239 (98) [$M^+(^{79}Br)$], 138 (62) [$^{81}BrCCHS^+$], 136 (58) [$^{79}BrCCHS^+$]. HRMS *m*/*z* calcd for C_9H_6BrNS (M^+) 238.9404, found 238.9406.

General Procedure B for Negishi Cross-Coupling Reactions to 2-Substituted 4-Bromothiazoles. A 6.9-mL sample of a 1.5 M solution of *tert*-butyllithium in pentane (10.4 mmol) was added at −78 °C to a solution of a primary alkyl iodide (5.0 mmol) in 8 mL of Et_2O.[32] After the mixture was stirred at −78 °C for 1 h, 15 mL of a 0.5 M solution of $ZnCl_2$ (7.5 mmol) in THF was added. The resulting mixture was stirred at room temperature for 30 min and was added via syringe to a solution of 486 mg of 2,4-dibromothiazole (**2**) (2.0 mmol), 46 mg of $Pd_2(dba)_3$ (0.1 mmol), and 56 mg of dppf (0.1 mmol) in 10 mL of THF. After being stirred for 16 h at room temperature the reaction was quenched with 10 mL of saturated NH_4Cl solution and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL). After drying over Na_2SO_4 and

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filtration, the solvent was removed and the residue was purified by flash chromatography.

4-Bromo-2-isobutylthiazole (3b). The reaction was carried out on the same scale as described for general procedure B employing 920 mg of isobutyl iodide (5.0 mmol) and 6.9 mL of a *tert*-butyllithium solution (1.5 M in pentane) (10.4 mmol). A total of 320 mg (73%) of **3b** was obtained as a red oil (P/Et_2O = 97/3 as eluent). R_f 0.44 (P/Et_2O = 95/5). IR (film): $\tilde{\nu}$ 3123 cm^{-1} (w, CH_{ar}), 2958 (s, CH_{al}), 2869 (m, CH_{al}). ^1H NMR: δ 0.97 (d, J = 6.6 Hz, 6 H), 2.09 (virt. nonet, $J \cong$ 6.8 Hz, 1 H), 2.84 (d, J = 7.0 Hz, 2 H), 7.05 (s, 1 H). ^{13}C NMR: δ 22.2, 29.7, 42.5, 115.7, 124.2, 171.5. MS, *m/z* (%): 221 (12) [$M^+(^{81}Br)$], 219 (11) [$M^+(^{79}Br)$], 206 (15) [$M^+(^{81}Br) - CH_3$], 204 (15) [$M^+(^{79}Br) - CH_3$], 179 (100) [$M^+(^{81}Br) - C_3H_6$], 177 (98) [$M^+(^{79}Br) - C_3H_6$]. HRMS *m/z* calcd for $C_7H_{10}BrNS$ (M^+) 220.9697, found 220.9702.

4-Bromo-2-phenylethylthiazole (3c). The reaction was carried out on the same scale as described for general procedure B employing 1.16 g of 2-iodoethylbenzene (5.0 mmol) and 6.9 mL of a *tert*-butyllithium solution (1.5 M in pentane) (10.4 mmol). A total of 424 mg (79%) of **3c** was obtained as a white solid (P/Et_2O = 95/5 as eluent). R_f 0.30 (P/Et_2O = 95/5). Mp: 82 °C. IR (KBr): $\tilde{\nu}$ 3078 cm^{-1} (s, CH_{ar}), 2931 (w, CH_{al}). ^1H NMR: δ 3.10 (t, J = 8.2 Hz, 2 H), 3.31 (t, J = 8.2 Hz, 2 H), 7.07 (s, 1 H), 7.19−7.29 (m, 5 H). ^{13}C NMR: δ 35.2, 35.7, 115.9, 124.3, 126.5, 128.4, 128.6, 139.9, 171.2. MS, *m/z* (%): 269 (43) [$M^+(^{81}Br)$], 267 (41) [$M^+(^{79}Br)$], 188 (18) [$M^+ - Br$], 91 (100) [$C_7H_7^+$]. Anal. Calcd for $C_{11}H_{10}BrNS$ (268.17): C, 49.27; H, 3.76. Found: C, 49.16; H, 3.65.

4-Bromo-2-(4-chlorobutyl)thiazole (3d). The reaction was carried out on the same scale as described for general procedure B employing 1.09 g of 4-chloro-1-iodobutane (5.0 mmol) and 6.9 mL of a *tert*-butyllithium solution (1.5 M in pentane) (10.4 mmol). A total of 407 mg (80%) of **3d** was obtained as a red oil (P/Et_2O = 90/10 as eluent). R_f 0.30 (P/Et_2O = 90/10). IR (film): $\tilde{\nu}$ 3121 cm^{-1} (m, CH_{ar}), 2953 (m, CH_{al}). ^1H NMR: δ 1.81−1.98 (m, 4 H), 3.02 (t, J = 7.4 Hz, 2 H), 3.54 (t, J = 6.3 Hz, 2 H), 7.07 (s, 1 H). ^{13}C NMR: δ 26.9, 31.6, 32.7, 44.3, 115.9, 124.4, 171.6. MS, *m/z* (%): 257 (7) [$M^+(^{81}Br^{37}Cl)$], 255 (30) [$M^+(^{81}Br)$, $M^+(^{79}Br^{37}Cl)$], 253 (22) [$M^+(^{79}Br^{35}Cl)$], 220 (100) [$M^+(^{81}Br) - Cl$], 218 (98) [$M^+(^{79}Br) - Cl$], 206 (12) [$M^+(^{81}Br) - CH_2Cl$], 204 (13) [$M^+(^{79}Br) - CH_2Cl$], 192 (84) [$M^+(^{81}Br) - (CH_2)_2Cl$], 190 (87) [$M^+(^{79}Br) - (CH_2)_2Cl$], 178 (46) [$M^+(^{81}Br) - (CH_2)_3Cl$], 176 (45) [$M^+(^{79}Br) - (CH_2)_3Cl$]. Anal. Calcd for $C_7H_9BrClNS$ (254.58): C, 33.03; H, 3.56. Found: C, 33.18; H, 3.55.

4-Bromo-2-[6-(*tert*-butyldimethylsiloxy)hexyl]thiazole (3e). The reaction was carried out on the same scale as described for general procedure B employing 1.71 g of 1-iodo-6-(*tert*-butyldimethylsiloxy)hexane[33] (5.0 mmol) and 6.9 mL of a *tert*-butyllithium solution (1.5 M in pentane) (10.4 mmol). A total of 642 mg (85%) of **3e** was obtained as a red oil (P/Et_2O = 98/2 as eluent). R_f 0.53 (P/Et_2O = 95/5). IR (film): $\tilde{\nu}$ 3124 cm^{-1} (w, CH_{ar}), 2979 (s, CH_{al}). ^1H NMR: δ 0.02 (s, 6 H), 0.87 (s, 9 H), 1.34−1.38 (m, 4 H), 1.49 (quin, J = 6.5 Hz, 2 H), 1.77 (quin, J = 7.5 Hz, 2 H), 2.97 (t, J = 7.8 Hz, 2 H), 3.57 (t, J = 6.3 Hz, 2 H), 7.05 (s, 1 H). ^{13}C NMR: δ −5.3, 18.3, 25.5, 26.0, 28.8, 29.8, 32.6, 33.5, 63.0, 115.6, 124.1, 172.7. MS, *m/z* (%): 364 (3) [$M^+(^{81}Br) - CH_3$], 362 (3) [$M^+(^{79}Br) - CH_3$], 322 (100) [$M^+(^{81}Br) - {}^t$Bu], 320 (96) [$M^+(^{79}Br) - {}^t$Bu]. HRMS *m/z* calcd for $C_{11}H_{18}BrNOSSi$ ($M^+ - {}^t$Bu) 320.0140, found 320.0135.

General Procedure C for Sonogashira Cross-Coupling Reactions to 2-Substituted 4-Bromothiazoles. A solution of 3.0 mmol of the alkyne in 1 mL of THF was added via syringe to a mixture of 486 mg of 2,4-dibromothiazole (**2**) (2.0 mmol), 304 mg of *N*,*N*-diisopropylamine (3.0 mmol), 38 mg of CuI (0.2 mmol), and 114 mg of $Pd(PPh_3)_4$ (0.1 mmol) in 5 mL of THF during 1 h via syringe pump. After the mixture was stirred for 3 h at room temperature, 5 mL of H_2O and 30 mL of Et_2O were added and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL). After drying over Na_2SO_4 and filtration, the solvent was removed and the residue was purified by flash chromatography.

4-Bromo-2-(3,3-dimethyl-1-butynyl)thiazole (3i). The reaction was carried out on the same scale as described for general procedure C employing 246 mg of 3,3-dimethyl-1-butyne (3.0 mmol). A total of 317 mg (65%) of **3i** was obtained as a yellow solid (P/Et_2O = 98.5/1.5 as eluent). R_f 0.45 (P/Et_2O = 97/3). Mp: 67 °C. IR (KBr): $\tilde{\nu}$ 3118 cm^{-1} (m, CH_{ar}), 2971 (m, CH_{al}). ^1H NMR: δ 1.31 (s, 9 H), 7.11 (s, 1 H). ^{13}C NMR: δ 28.3, 30.2, 72.1, 105.5, 117.6, 125.2, 150.5. MS, *m/z* (%): 244 (100) [$M^+(^{81}Br) - H$], 242 (98) [$M^+(^{79}Br) - H$], 230 (77) [$M^+(^{81}Br) - CH_3$], 228 (73) [$M^+(^{79}Br) - CH_3$]. Anal. Calcd for $C_9H_{10}BrNS$ (244.15): C, 44.28; H, 4.13. Found: C, 44.60; H, 4.33.

4-Bromo-2-phenylethynylthiazole (3j). The reaction was carried out on the same scale as described for general procedure C employing 306 mg of phenylethyne (3.0 mmol). A total of 428 mg (81%) of **3j** was obtained as a yellow solid (P/Et_2O = 95/5 as eluent). R_f 0.29 (P/Et_2O = 95/5). Mp: 74 °C. IR (KBr): $\tilde{\nu}$ 3118 cm^{-1} (w, CH_{ar}), 2208 (m, C≡C). ^1H NMR: δ 7.22 (s, 1 H), 7.32−7.39 (m, 3 H), 7.54−7.57 (m, 2 H). ^{13}C NMR: δ 81.4, 95.4, 118.6, 120.9, 125.9, 128.5, 129.5, 132.0, 149.7. MS, *m/z* (%): 265 (98) [$M^+(^{81}Br)$], 263 (100) [$M^+(^{79}Br)$], 138 (33) [$^{81}BrCCHS^+$], 136 (30) [$^{79}BrCCHS^+$]. HRMS *m/z* calcd for $C_{11}H_6BrNS$ (M^+) 264.9384, found 264.9384.

General Procedure D for Negishi Cross-Coupling Reactions to 2′-Substituted 4-Bromo-2,4′-bithiazoles. A 1.4-mLsample of a 1.5 M solution of *tert*-butyllithium in pentane (2.1 mmol) was added at −78 °C to a solution of 1.0 mmol of bromothiazole **3** in 5 mL of THF. After the mixture was stirred at −78 °C for 10 min, 3.0 mL of a 0.5 M solution of $ZnCl_2$ (1.5 mmol) in THF was added. The resulting mixture was stirred at room temperature for 30 min and a mixture of 187 mg of 2,4-dibromothiazole (**2**) (0.77 mmol) and 27 mg of $PdCl_2(PPh_3)_2$ (38.5 μmol) in 5 mL of THF was added via syringe. After refluxing for 16 h the reaction was quenched with 10 mL of saturated NH_4Cl solution and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL). After drying over Na_2SO_4 and filtration, the solvent was removed and the residue was purified by flash chromatography.

4-Bromo-2′-butyl-2,4′-bithiazole (1a). The reaction was carried out as described for general procedure D starting with 180 mg of bromothiazole **3a** (0.82 mmol), 153 mg of 2,4-dibromothiazole (**2**) (0.63 mmol), 1.15 mL of a *tert*-butyllithium solution (1.5 M in pentane) (1.72 mmol), 2.4 mL of a $ZnCl_2$ solution (0.5 M in THF) (1.2 mmol), and 22 mg of $PdCl_2(PPh_3)_2$ (32 μmol). A total of 183 mg (96%) of **1a** was obtained as a yellow solid (P/Et_2O = 95/5 as eluent). R_f 0.17 (P/Et_2O = 95/5). Mp: 66 °C. IR (KBr): $\tilde{\nu}$ 3120 cm^{-1} (w, CH_{ar}), 2950 (m, CH_{al}). ^1H NMR: δ 0.95 (t, J = 7.4 Hz, 3 H), 1.44 (virt. sext, $J \cong$ 7.4 Hz, 2 H), 1.78 (virt. quin, $J \cong$ 7.7 Hz, 2 H), 3.01 (t, J = 7.7 Hz, 2 H), 7.19 (s, 1 H), 7.85 (s, 1 H). ^{13}C NMR: δ 13.7, 22.2, 31.9, 33.1, 116.0, 117.1, 125.9, 147.7, 167.7, 172.6. MS, *m/z* (%): 304 (22) [$M^+(^{81}Br)$], 302 (20) [$M^+(^{79}Br)$], 275 (23) [$M^+(^{81}Br) - C_2H_5$], 273 (20) [$M^+(^{79}Br) - C_2H_5$], 262 (100) [$M^+(^{81}Br) - C_3H_6$], 260 (96) [$M^+(^{79}Br) - C_3H_6$], 138 (8) [$^{81}BrCCHS^+$], 136 (7) [$^{79}BrCCHS^+$]. HRMS *m/z* calcd for $C_{10}H_{11}BrN_2S_2$ (M^+) 301.9547, found 301.9553.

4-Bromo-2′-isobutyl-2,4′-bithiazole (1b). The reaction was carried out as described for general procedure D starting with 120 mg of bromothiazole **3b** (0.55 mmol), 102 mg of 2,4-dibromothiazole (**2**) (0.42 mmol), 0.76 mL of a *tert*-butyllithium solution (1.5 M in pentane) (1.1 mmol), 1.6 mL of a $ZnCl_2$ solution (0.5 M in THF) (0.8 mmol), and 15 mg of $PdCl_2(PPh_3)_2$ (21 μmol). A total of 111 mg (88%) of **1b** was obtained as a yellow solid (P/Et_2O = 95/5 as eluent). R_f 0.17 (P/Et_2O = 95/5). Mp: 95 °C. IR (KBr): $\tilde{\nu}$ 3120 cm^{-1} (w, CH_{ar}), 2950 (m, CH_{al}). ^1H NMR: δ 1.02 (d, J = 6.6 Hz, 6 H), 2.15 (virt. nonet, $J \cong$ 6.8

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Hz, 1 H), 2.91 (d, J = 7.2 Hz, 2 H), 7.24 (s, 1 H), 7.90 (s, 1 H). ^{13}C NMR: δ 22.2, 29.7, 42.1, 116.2, 117.2, 125.8, 147.6, 163.7, 171.4. MS, m/z (%): 304 (25) [M^+(^{81}Br)], 302 (24) [M^+(^{79}Br)], 289 (16) [M^+(^{81}Br) − CH_3], 287 (15) [M^+(^{79}Br) − CH_3], 262 (100) [M^+(^{81}Br) − C_3H_6], 260 (95) [M^+(^{81}Br) − C_3H_6], 138 (9) [^{81}BrCCHS$^+$], 136 (8) [^{79}BrCCHS$^+$]. HRMS m/z calcd for $C_{10}H_{11}BrN_2S_2$ (M^+) 301.9547, found 301.9549.

4-Bromo-2′-phenylethyl-2,4′-bithiazole (1c). The reaction was carried out as described for general procedure D starting with 216 mg of bromothiazole **3c** (0.81 mmol), 151 mg of 2,4-dibromothiazole (**2**) (0.62 mmol), 1.13 mL of a *tert*-butyllithium solution (1.5 M in pentane) (1.69 mmol), 2.4 mL of a $ZnCl_2$ solution (0.5 M in THF) (1.2 mmol), and 22 mg of $PdCl_2(PPh_3)_2$ (32 μmol). A total of 193 mg (89%) of **1c** was obtained as a white solid (P/Et_2O = 92/8 as eluent). R_f 0.21 (P/Et_2O = 90/10). Mp: 126 °C. IR (KBr): $\tilde{\nu}$ 3122 cm^{-1} (m, CH_{ar}), 2925 (w, CH_{al}). ^{1}H NMR: δ 3.15 (t, J = 7.9 Hz, 2 H), 3.36 (t, J = 7.9 Hz, 2 H), 7.23 (s, 1 H), 7.21−7.32 (m, 5 H), 7.87 (s, 1 H). ^{13}C NMR: δ 35.0, 35.6, 116.2, 117.2, 125.9, 126.5, 128.5, 128.6, 140.0, 147.7, 163.6, 171.2. MS, m/z (%): 352 (100) [M^+(^{81}Br)], 350 (96) [M^+(^{79}Br)], 275 (27) [M^+(^{81}Br) − C_6H_5], 273 (25) [M^+(^{79}Br) − C_6H_5], 261 (12) [M^+(^{81}Br) − $CH_2C_6H_5$], 259 (10) [M^+(^{79}Br) − $CH_2C_6H_5$], 91 (97) [C_7H_7+]. Anal. Calcd for $C_{14}H_{11}BrN_2S_2$ (351.29): C, 47.87; H, 3.16. Found: C, 47.68; H, 3.22.

4-Bromo-2′-(4-chlorobutyl)-2,4′-bithiazole (1d). The reaction was carried out as described for general procedure D starting with 414 mg of bromothiazole **3d** (1.63 mmol), 304 mg of 2,4-dibromothiazole (**2**) (1.25 mmol), 2.28 mL of a *tert*-butyllithium solution (1.5 M in pentane) (3.42 mmol), 4.9 mL of a $ZnCl_2$ solution (0.5 M in THF) (2.45 mmol), and 45 mg of $PdCl_2(PPh_3)_2$ (64 μmol). A total of 383 mg (91%) of **1c** was obtained as a white solid (P/EtOAc = 80/20 as eluent). R_f 0.17 (P/EtOAc = 80/20). Mp: 49 °C. IR (KBr): $\tilde{\nu}$ 3082 cm^{-1} (w, CH_{ar}), 2955 (w, CH_{al}). ^{1}H NMR: δ 1.86−2.01 (m, 4 H), 3.05 (t, J = 7.6 Hz, 2 H), 3.57 (t, J = 6.5 Hz, 2 H), 7.20 (s, 1 H), 7.87 (s, 1 H). ^{13}C NMR: δ 26.9, 31.7, 32.5, 44.4, 116.2, 117.3, 125.9, 147.8, 163.5, 171.4. MS, m/z (%): 340 (10) [M^+(^{81}Br^{37}Cl)], 338 (33) [M^+(^{81}Br^{35}Cl), M^+(^{79}Br^{37}Cl)], 336 (24) [M^+(^{79}Br^{35}Cl)], 303 (100) [M^+(^{81}Br) − Cl], 301 (98) [M^+(^{79}Br) − Cl], 275 (74) [M^+(^{81}Br) − CH_2CH_2Cl], 273 (69) [M^+(^{79}Br) − CH_2CH_2Cl], 138 (17) [^{81}BrCCHS$^+$], 136 (18) [^{79}BrCCHS$^+$]. HRMS m/z calcd for $C_{10}H_{10}BrClN_2S_2$ (M^+) 335.9157, found 335.9155.

4-Bromo-2′-[6-(*tert*-butyldimethylsiloxy)-hexyl]-2,4′-bithiazole (1e). The reaction was carried out as described for general procedure D starting with 73 mg of bromothiazole **3e** (193 μmol), 36 mg of 2,4-dibromothiazole (**2**) (149 μmol), 270 μL of a *tert*-butyllithium solution (1.5 M in pentane) (405 μmol), 580 μL of a $ZnCl_2$ solution (0.5 M in THF) (290 μmol), and 5.2 mg of $PdCl_2(PPh_3)_2$ (7.5 μmol). A total of 65 mg (94%) of **1e** was obtained as a white solid (P/Et_2O = 97/3 as eluent). R_f 0.37 (P/Et_2O = 95/5). Mp: 57 °C. IR (KBr): $\tilde{\nu}$ 3125 cm^{-1} (m, CH_{ar}), 2931 (s, CH_{al}). ^{1}H NMR: δ 0.02 (s, 6 H), 0.87 (s, 9 H), 1.36−1.45 (m, 4 H), 1.52 (quin, J = 6.7 Hz, 2 H), 1.82 (quin, J = 7.5 Hz, 2 H), 3.01 (t, J = 7.7 Hz, 2 H), 3.59 (t, J = 6.5 Hz, 2 H), 7.19 (s, 1 H), 7.85 (s, 1 H). ^{13}C NMR: δ −5.3, 18.4, 25.5, 26.0, 28.9, 29.9, 32.7, 33.3, 63.1, 116.0, 117.2, 125.9, 147.7, 163.7, 172.7. MS, m/z (%): 449 (4) [M^+(^{81}Br)], 447 (3) [M^+(^{79}Br)], 405 (100) [M^+(^{81}Br) − ^{t}Bu], 403 (85) [M^+(^{79}Br) − ^{t}Bu], 75 (44). Anal. Calcd for $C_{18}H_{29}BrN_2OS_2Si$ (461.56): C, 46.84; H, 6.33. Found: C, 46.89; H, 6.30.

4-Bromo-2′-isopropyl-2,4′-bithiazole (1f). The reaction was carried out as described for general procedure D starting with 268 mg of bromothiazole **3f** (1.3 mmol), 243 mg of 2,4-dibromothiazole (**2**) (1.0 mmol), 1.8 mL of a *tert*-butyllithium solution (1.5 M in pentane) (2.7 mmol), 4.0 mL of a $ZnCl_2$ solution (0.5 M in THF) (2.0 mmol), and 35 mg of $PdCl_2(PPh_3)_2$ (50 μmol). A total of 281 mg (97%) of **1c** was obtained as a white solid (P/Et_2O = 97/3 as eluent). R_f 0.67 (P/EtOAc = 75/25). Mp: 41 °C. IR (KBr): $\tilde{\nu}$ 3114 cm^{-1} (m, CH_{ar}), 2955 (w, CH_{al}). ^{1}H NMR: δ 1.36 (d, J = 6.8 Hz, 6 H), 3.28 (sept, J = 6.8 Hz, 1 H), 7.16 (s, 1 H), 7.80 (s, 1 H). ^{13}C NMR: δ 23.5, 33.7, 116.1, 117.6, 126.2, 147.9, 164.3, 179.3. MS, m/z (%): 290 (85) [M^+(^{81}Br)], 288 (100) [M^+(^{79}Br)], 275 (80) [M^+(^{81}Br) − CH_3], 273 (76) [M^+(^{79}Br) − CH_3], 138 (26) [^{81}BrCCHS$^+$], 136 (24) [^{79}BrCCHS$^+$]. Anal. Calcd for $C_9H_9N_2S_2$ (289.22): C, 37.38; H, 3.14. Found: C, 37.48; H, 3.03.

4-Bromo-2′-*sec*-butyl-2,4′-bithiazole (1g). The reaction was carried out as described for general procedure D starting with 398 mg of bromothiazole **3g** (1.81 mmol), 340 mg of 2,4-dibromothiazole (**2**) (1.40 mmol), 2.5 mL of a *tert*-butyllithium solution (1.5 M in pentane) (3.75 mmol), 5.5 mL of a $ZnCl_2$ solution (0.5 M in THF) (2.75 mmol), and 49 mg of $PdCl_2(PPh_3)_2$ (70 μmol). A total of 403 mg (95%) of **1g** was obtained as a yellow solid (P/Et_2O = 97/3 as eluent). R_f 0.21 (P/Et_2O = 97/3). Mp: 36 °C. IR (KBr): $\tilde{\nu}$ 3120 cm^{-1} (m, CH_{ar}), 2956 (m, CH_{al}). ^{1}H NMR: δ 0.94 (t, J = 7.4 Hz, 3 H), 1.38 (d, J = 6.8 Hz, 3 H), 1.70 (virt. dquin, $J \cong$ 7.0 Hz, $J \cong$ 14.0 Hz, 1 H), 1.84 (virt. dquin, $J \cong$ 7.0 Hz, $J \cong$ 14.0 Hz, 1 H), 3.12 (virt. sext, $J \cong$ 7.0 Hz, 1 H), 7.19 (s, 1 H), 7.86 (s, 1 H). ^{13}C NMR: δ 11.6, 20.6, 30.6, 40.1, 115.6, 117.1, 125.8, 147.5, 163.9, 178.1. MS, m/z (%): 304 (45) [M^+(^{81}Br)], 302 (43) [M^+(^{79}Br)], 289 (33) [M^+(^{81}Br) − CH_3], 287 (31) [M^+(^{79}Br) − CH_3], 276 (100) [M^+(^{81}Br) − C_2H_4], 274 (96) [M^+(^{79}Br) − C_2H_4], 138 (18) [^{81}BrCCHS$^+$], 136 (17) [^{79}BrCCHS$^+$]. Anal. Calcd for $C_{10}H_{11}BrN_2S_2$ (303.24): C, 39.61; H, 3.66. Found: C, 39.48; H, 3.53.

General Procedure E for Stille Cross-Coupling Reactions to 2'-Substituted 4-Bromo-2,4'-bithiazoles. A 1.4-mL sample of a 1.5 M solution of *tert*-butyllithium in pentane (2.1 mmol) was added at −78 °C to a solution of 1.0 mmol of bromothiazole **3** in 5 mL of Et_2O. After the mixture was stirred at −78 °C for 10 min, 1 mL of a 1.0 M solution of Me_3SnCl (1.0 mmol) in THF was added. The resulting mixture was stirred at room temperature for 2 h and 20 mL of Et_2O and 5 mLof H_2O were added. The organic layer was dried over Na_2SO_4 and after filtration, the solvent was removed and the residue was dissolved in 8 mL of toluene to which 243 mg of 2,4-dibromothiazole (**2**) (1.0 mmol) and 58 mg of $Pd(PPh_3)_4$ (50 μmol) were added, and the solution was degassed. After refluxing for 16 h, 5 mL of H_2O was added and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL). After drying over Na_2SO_4 and filtration, the solvent was removed and the residue was purified by flash chromatography.

4-Bromo-2′-phenyl-2,4′-bithiazole (1h). The reaction was carried out as described for general procedure E starting with 103 mg of bromothiazole **3h** (429 μmol), 104 mg of 2,4-dibromothiazole (**2**) (429 μmol), 0.6 mL of a *tert*-butyllithium solution (1.5 M in pentane) (901 μmol), 429 μL of a Me_3SnCl solution (1 M in THF) (429 μL), and 24 mg of $Pd(PPh_3)_4$ (22 μmol). A total of 85 mg (61%) of **1h** was obtained as a white solid (P/Et_2O = 95/5 as eluent). R_f 0.24 (P/Et_2O = 93/7). Mp: 164 °C. IR (KBr): $\tilde{\nu}$ 3112 cm^{-1} (m, CH_{ar}). ^{1}H NMR: δ 7.24 (s, 1 H), 7.44−7.46 (m, 3 H), 7.98−8.00 (m, 2 H), 7.99 (s, 1 H). ^{13}C NMR: δ 116.5, 117.5, 126.0, 126.7, 129.1, 130.7, 132.8, 149.0, 163.6, 168.9. MS, m/z (%): 324 (100) [M^+(^{81}Br)], 322 (96) [M^+(^{79}Br)], 138 (15) [^{81}BrCCHS$^+$], 136 (14) [^{79}BrCCHS$^+$]. Anal. Calcd for $C_{12}H_7BrN_2S_2$ (323.23): C, 44.59; H, 2.18. Found: C, 44.65; H, 2.13.

4-Bromo-2′-(3,3-dimethylbut-1-ynyl)-2,4′-bithiazole (1i). The reaction was carried out as described for general procedure E starting with 100 mg of bromothiazole **3i** (410 μmol), 100 mg of 2,4-dibromothiazole (**2**) (410 μmol), 0.57 mL of a *tert*-butyllithium solution (1.5 M in pentane) (860 μmol), 410 μL of a Me_3SnCl solution (1 M in THF) (410 μL), and 24 mg of $Pd(PPh_3)_4$ (22 μmol). A total of 85 mg (58%) of **1i** was obtained as a white solid (P/Et_2O = 95/5 as eluent). R_f 0.23 (P/Et_2O = 95/5). Mp: 136 °C. IR (KBr): $\tilde{\nu}$ 3122 cm^{-1} (m, CH_{ar}), 2968 (m, CH_{al}), 2221 (s, C═C). ^{1}H NMR: δ 1.36 (s, 9 H), 7.24 (s, 1 H), 7.95 (s, 1H). ^{13}C NMR: δ 28.3, 30.3, 72.3, 105.4, 117.6, 117.7, 126.0, 148.3, 150.5, 162.9. MS, m/z (%): 328 (100) [M^+(^{81}Br)], 326 (96) [M^+(^{79}Br)], 313 (84) [M^+(^{81}Br) − CH_3], 311 (78) [M^+(^{79}Br) − CH_3], 138 (13) [^{81}BrCCHS$^+$], 136 (11) [^{79}BrCCHS$^+$].

Anal. Calcd for $C_{12}H_{11}BrN_2S_2$ (327.27): C, 44.04; H, 3.39. Found: C, 44.01; H, 3.30.

4-Bromo-2′-phenylethynyl-2,4′-bithiazole (1j). The reaction was carried out as described for general procedure E starting with 100 mg of bromothiazole **3j** (379 μmol), 93 mg of 2,4-dibromothiazole (**2**) (379 μmol), 0.53 mL of a *tert*-butyllithium solution (1.5 M in pentane) (795 μmol), 379 μL of a Me_3SnCl solution (1 M in THF) (379 μmol), and 22 mg of $Pd(PPh_3)_4$ (19 μmol). A total of 82 mg (58%) of **1j** was obtained as a white solid (P/Et_2O = 95/5 as eluent). R_f 0.13 (P/Et_2O = 95/5). Mp: 178 °C. IR (KBr): $\tilde{\nu}$ 3113 cm^{-1} (w, CH_{ar}), 2210 (m, C═C). ^{1}H NMR: δ 7.25 (s, 1 H), 7.35−7.42 (m, 3 H), 7.59−7.61 (m, 2 H), 8.04 (s, 1 H). ^{13}C NMR: δ 81.6, 95.4, 117.9, 118.3, 121.0, 126.1, 128.6, 129.9, 132.1, 148.8, 149.7, 162.8. MS, *m*/*z* (%): 348 (100) [M^+(^{81}Br)], 346 (96) [M^+(^{79}Br)], 138 (24) [^{81}BrCCHS$^+$], 136 (22) [^{79}BrCCHS$^+$]. Anal. Calcd for $C_{14}H_7BrN_2S_2$ (347.26): C, 48.42; H, 2.03. Found: C, 48.29; H, 2.00.

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Supporting Information Available: Spectra of compounds **1a**−**j** and **3a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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