2,4-Disubstituted Thiazoles by Regioselective Cross-Coupling or Bromine–Magnesium Exchange Reactions of 2,4-Dibromothiazole

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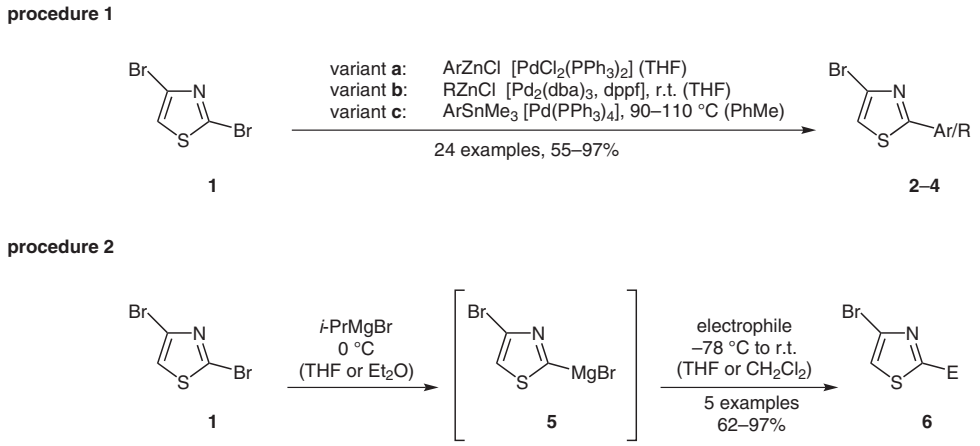
Received 25 November 2010

PSP No 199

Abstract: Cross-coupling reactions occur on 2,4-dibromothiazole preferentially at the more electron-deficient 2-position. This fact can be favorably used to prepare 2-substituted 4-bromothiazoles, which serve as precursors for 2,4-disubstituted thiazoles. Protocols for regioselective Negishi and Stille cross-coupling reactions are provided. Alternatively, the title compound can be metalated in 2-position by a halogen–metal exchange reaction. As a supplement to the well-established bromine–lithium exchange, the regioselective bromine–magnesium exchange reaction is presented.

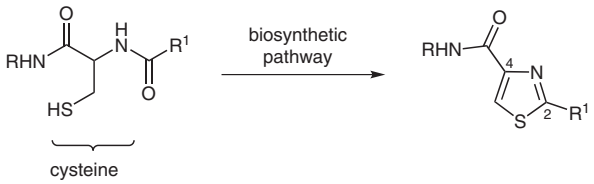
Key words: catalysis, cross-coupling, heterocycles, palladium, regioselectivity, thiazoles



Scheme 1 Introduction of substituents at the 2-position of 2,4-dibromothiazole (**1**)

Introduction

The thiazole ring occurs in many natural products of medicinal relevance.[4] Examples include epothilone,[5] thiostreptone,[6] and the amythiamicins,[7] to name only a few. Biosynthetically, the thiazole ring is formed by the condensation of a cysteine-containing peptide and subsequent oxidation as shown in Scheme 2.[8] As a consequence, most naturally occurring thiazoles are 2,4-disubstituted and display various substitution patterns at the two different sites (R, R^1). If another cysteine resides at the C-terminal position of the cysteine, which forms the thiazole ring, a second thiazole ring formation can occur biosynthetically leading to an important subclass of naturally occurring thiazoles, the 2′,4-disubstituted 2,4′-bithiazoles.



Scheme 2 Biosynthetic formation of thiazole rings explaining the abundance of naturally occurring 2,4-disubstituted thiazoles

Synthetic access to 2,4-thiazoles is achieved by several ring-closing methods, of which the classic Hantzsch[9] and Gabriel synthesis[10] are most extensively employed. Another possible route to 2,4-thiazoles aims at the introduction of substituents in the 2- and 4-position of a preformed thiazole. A key discovery along these lines was the regioselective bromine–lithium exchange reaction at the 2-position[11] of readily available 2,4-dibromothiazole (**1**),[12] which has been used in several synthetic applications.[13] The first cross-coupling reaction of 2,4-dibromothiazole was reported in 1995 by Gronowitz et al., who employed

SYNTHESIS 2011, No. 2, pp 0199–0206
Advanced online publication: 20.12.2010
DOI: 10.1055/s-0030-1258373; Art ID: Z29310SS

the Suzuki protocol to prepare a 5-(4′-bromothiazol-2′-yl)-substituted uracil in low yield (15%).[14] Nicolaou et al. utilized the regioselective Sonogashira cross-coupling and the Stille cross-coupling of tributylvinylstannane to access analogues of epothilone E.[13c,15] At the same time, first attempts were undertaken in our group to assemble 2-substituted 4-bromothiazoles by Negishi cross-coupling. Eventually, our investigations led to three protocols (procedure 1, Scheme 1) for the regioselective cross-coupling of 2,4-dibromothiazole (**1**). In addition, we employed a bromine–magnesium exchange reaction[16] to functionalize the title compound selectively at C2 (procedure 2, Scheme 1).

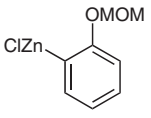
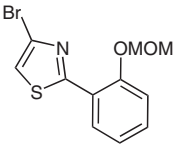
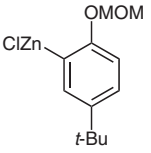
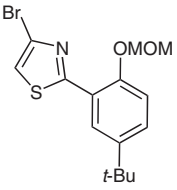
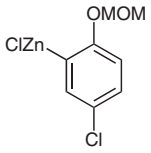
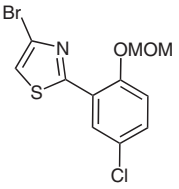
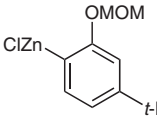
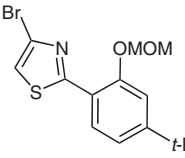
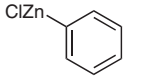
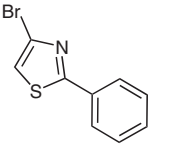
Scope and Limitations

High regioselectivity in cross-coupling reactions is achieved in multiple halogen-substituted hetarenes if the reactive positions are significantly different in their electronic properties.[17,18] 2,4-Dibromothiazole (**1**) exhibits a more electron-deficient position at C2, which should be preferably attacked by a nucleophilic Pd(0) intermediate in the event of a cross-coupling reaction. High selectivity is expected for reactions, in which the oxidative addition event is rate determining. In this respect, the Negishi cross-coupling is particularly well suited. Indeed, a broad variety of arylzinc halides were shown to be superior reaction partners in regioselective cross-coupling reactions (procedure 1, variant a). Table 1 provides some results achieved with arylzinc compounds prepared by directed lithiation and subsequent transmetalation.[19] In the course of this study, it was shown for the first time that after an initial cross-coupling at C2, a second cross-coupling at C4 was feasible. 4-Bromothiazoles **2a–d** underwent a clean Suzuki cross-coupling with various arylboronic acids yielding 2,4-diarylthiazoles.[19]

In a similar fashion, access to 4-bromo-2,4′-bithiazoles **3a–g** was possible by a regioselective Negishi cross-coupling of 4-zincated thiazoles (Table 2).[20] Zincation was achieved in this case by a halogen–metal exchange reaction from the corresponding 4-bromothiazole. The cross-coupling reaction was performed in THF using $PdCl_2(PPh_3)_2$ as the catalyst. In contrast to the reactions outlined in Table 1, which were performed at ambient temperature, the reactions with the zincated thiazoles were performed in refluxing THF.

The brominated starting materials **4** for the preparation of 2-substituted 4-thiazolylzinc reagents as employed in the reactions discussed above were obtained by another regioselective Negishi cross-coupling reaction of 2,4-dibromothiazole (**1**).[20–22] The alkylzinc reagents, which were used in this reaction (Procedure 1, variant b) (Table 3), all bear a β-hydrogen atom. It was therefore necessary to modify the catalyst such that the rate of the reductive elimination step was enhanced and β-hydride elimination was avoided. 1,1′-Bis(diphenylphosphino)ferrocene (dppf) as ligand[23] and $Pd_2(dba)_3$ (dba = dibenzylideneacetone) as catalyst precursor turned out to be an ideal combination to conduct the desired transformation at room temperature. The organozinc compounds were accessible by transmetalation from the respective organolithium reagents, which were either commercially available or generated by an iodine–lithium exchange reaction.

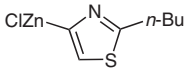
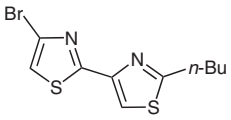
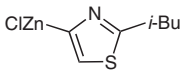
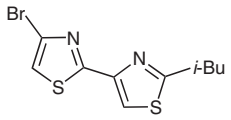
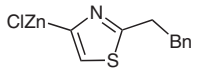
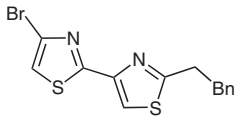
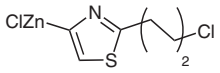
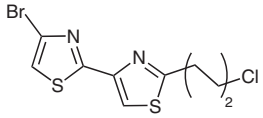
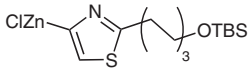
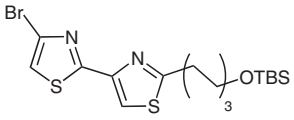
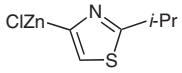
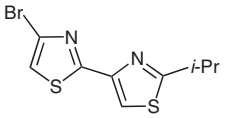
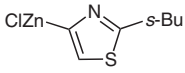
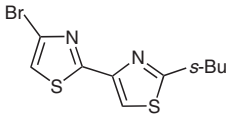
Table 1 Regioselective Negishi Cross-Coupling of 2,4-Dibromothiazole (**1**) with Arylzinc Reagents (Scheme 1, Procedure 1a)

Entry	ArZnCl	Product	Yield (%)[a]
1[b]		 **2a**	58
2[b]		 **2b**	55
3[b]		 **2c**	62
4[b]		 **2d**	55
5[c]		 **2e**	83

[a] Yield of isolated product. MOM = methoxymethyl.
[b] The organozinc reagent was prepared by directed *ortho*-metalation of the corresponding arene with *t*-BuLi and subsequent transmetalation with $ZnCl_2$.
[c] Commercially available PhLi was used for the transmetalation step.[20]

The utility of the presented strategy for accessing 2,4-disubstituted thiazoles and 2′,4-disubstituted 2,4′-bithiazoles was shown in total synthetic approaches towards the naturally occurring endothelin converting enzyme inhibitor WS 75624 A (**7**)[21] and the antifungal fermentation product cystothiazole E (**8**)[22] (Figure 1). In the former case the Negishi cross-coupling product **4h** (Table 3, entry 8) was converted into the respective 4-stannylated thiazole and coupled to an appropriately functionalized iodopyridine

Table 2 Regioselective Negishi Cross-Coupling of 2,4-Dibromothiazole (**1**) with 4-Thiazolylzinc Reagents (Scheme 1, Procedure 1a)

Entry	ArZnCl	Product	Yield (%)[a]
1[b]		 **3a**	96
2[b]		 **3b**	88
3[b]		 **3c**	89
4[b]		 **3d**	91
5[b]		 **3e**	94
6[b]		 **3f**	97
7[b]		 **3g**	95

[a] Yield of isolated product. TBS = *tert*-butyldimethylsilyl.
[b] The organozinc reagent was prepared by bromine–lithium exchange with *t*-BuLi and subsequent transmetalation with $ZnCl_2$.

to generate the key precursor for compound **7**. In the latter case, 4-bromothiazole **4f** (Table 3, entry 6) was converted into bithiazole **3f** (Table 2, entry 6). The final cross-coupling was achieved using an alkenylboronic acid, which was in turn obtained from the respective alkyne by hydroboration.[22]

Since it turned out that the Negishi cross-coupling was not suitable for the cross-coupling of 2-aryl- and 2-alkynyl-substituted 4-thiazolylzinc reagents, other cross-coupling reactions were evaluated in particular regarding the synthesis of bithiazoles **3**. It was found that a selective Stille cross-coupling was possible at C2 using a stannane as nucleophile and $Pd(PPh_3)_4$ as the catalyst (Scheme 1, Procedure 1c, Table 4).[20]

The high stability of tin compounds and their high functional group tolerance make stannanes also ideal reaction partners in the cross-coupling of functionalized nucleophiles with 2,4-dibromothiazole (**1**). As an example the reaction of the enantiomerically pure stannane **9** is depicted in Scheme 3, which proceeded smoothly to deliver

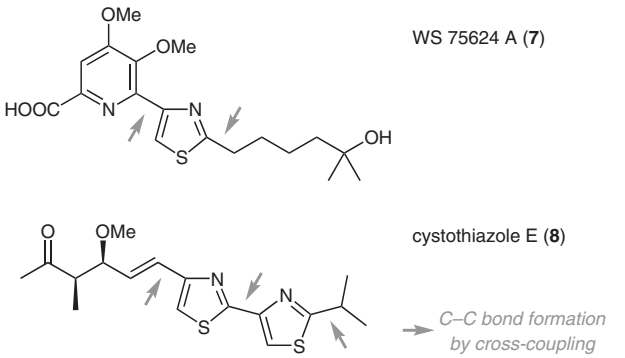
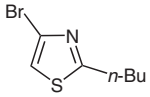
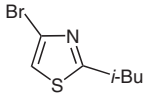
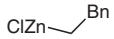
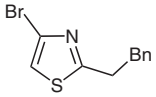
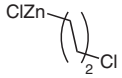
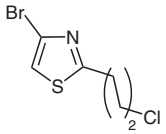
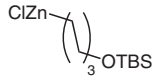
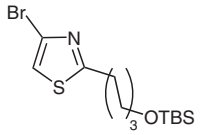
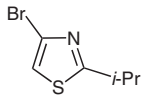
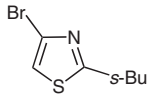
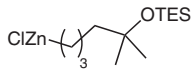
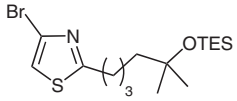


Figure 1 Natural products WS 75624 A (**7**) and cystothiazole E (**8**) obtained by cross-coupling reactions at the indicated positions

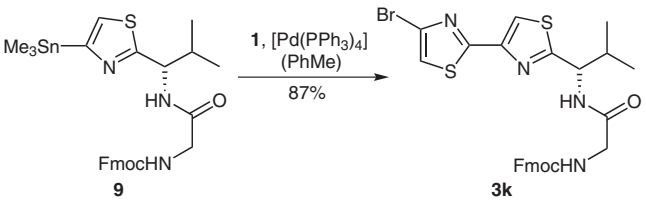
Table 3 Regioselective Negishi Cross-Coupling of 2,4-Dibromothiazole (**1**) with Alkylzinc Reagents (Scheme 1, Procedure 1b)

Entry	RZnCl	Product	Yield (%)[a]
1[b]	*n*-BuZnCl	 **4a**	85
2[c]	*i*-BuZnCl	 **4b**	73
3[c]		 **4c**	79
4[c]		 **4d**	80
5[c]		 **4e**	85
6[b]	*i*-PrZnCl	 **4f**	72
7[b]	*s*-BuZnCl	 **4g**	76
8[c]		 **4h**	85

[a] Yield of isolated product. TES = triethylsilyl.
[b] The organozinc reagent was prepared by transmetalation of commercially available organolithium reagent with $ZnCl_2$.
[c] The organolithium reagent was prepared from the corresponding iodide and *t*-BuLi and was subsequently transmetalated with $ZnCl_2$.

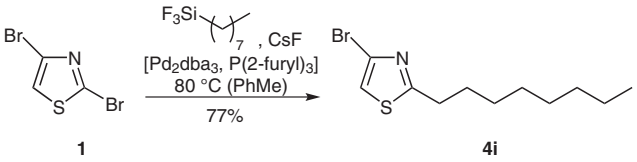
bithiazole **3k**, the eastern bithiazole fragment of the amythiamicins.[24] In a similar fashion the eastern bithiazole fragment of the GE factors could be prepared.[25]

Other regioselective coupling reactions of 2,4-dibromothiazole (**1**) have been reported, which employ a similar approach for the synthesis of 2-substituted 4-bromothiazoles.[26] The Suzuki reaction, which was – as mentioned earlier – the first regioselective cross coupling reaction of 2,4-dibromothiazole ever been conducted,[14] has been investigated more closely in two recent studies.[27]



Scheme 3 Regioselective Stille cross-coupling of functionalized stannane **9** and 2,4-dibromothiazole (**1**) to produce the eastern bithiazole fragment of the amythiamicins (Fmoc = 9-fluorenylmethoxycarbonyl)

Under optimized conditions, the reaction also proceeds selectively in the 2-position. Even the Hiyama cross-coupling reaction, which requires relative harsh conditions (heat, base), was shown to proceed with very good regioselectivity and in decent yield (Scheme 4).[28]

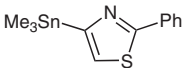
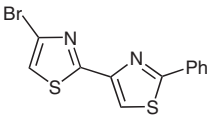
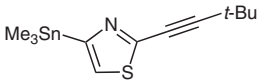
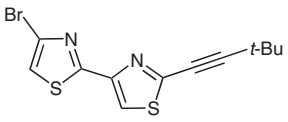
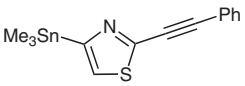
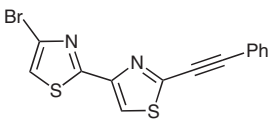


Scheme 4 Regioselective Hiyama cross-coupling of *n*-octyltrifluorosilane and 2,4-dibromothiazole (**1**)

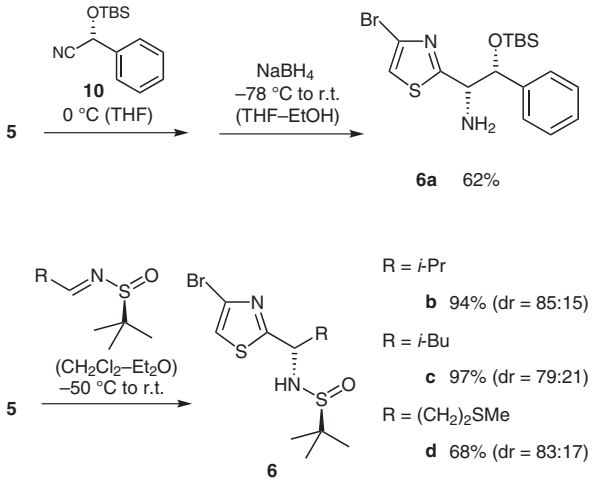
A different route to 2,4-dithiazoles relies on halogen–metal exchange reaction. In this context, we found the bromine–magnesium exchange as described by Knochel et al.[16] particularly useful. The corresponding reagent **5** (Scheme 1) can be generated from 2,4-dibromothiazole (**1**) by treatment with *i*-PrMgBr or *s*-BuMgCl in an ethereal solvent. Trapping with simple nitriles leads upon hydrolysis to the respective ketones.[29] The intermediate imine adduct can also be reduced to an amine. In the example shown in Scheme 5, the *tert*-butyldimethylsilyl (TBS)-protected (*R*)-mandelonitrile **10** was used as the electrophile.[30] Diastereoselective reduction (dr = 79:21) delivered the O-protected amino alcohol **6a** in 62% yield after separation from the minor diastereoisomer. The magnesium reagent **5** was shown to react also with chiral imines,[31] which opened a stereoselective pathway to chiral 2-(α-aminoalkyl)-substituted thiazoles. Optimal diastereoselectivities in these reactions were achieved in dichloromethane as the solvent with as little diethyl ether as co-solvent as possible. Diastereomerically pure products are available upon recrystallization. Product **6b**, which was required for the synthesis of stannane **9** (Scheme 3) for example was obtained in 72% yield.[24] Removal of the chiral auxiliary was easily achieved upon treatment with HCl in MeOH–1,4-dioxane.

In summary, 2,4-dibromothiazole (**1**) has emerged as an extremely useful building block for the synthesis of 2,4-disubstituted thiazoles. The two major regioselective functionalization pathways rely on a regioselective reaction at C2. A bromine–metal exchange reaction – the magnesium version of which was presented in this manuscript – allows to convert 2,4-dibromothiazole (**1**) into a potent

Table 4 Regioselective Stille Cross-Coupling of 2,4-Dibromothiazole (**1**) with 4-Thiazolylstannanes (Scheme 1, Procedure 1c)

Entry	$ArSnMe_3$	Product	Yield (%)[a]
1[b]		 **3h**	61
2[b]		 **3i**	58
3[b]		 **3j**	58

[a] Yield of isolated product.
[b] 4-Thiazolylstannanes were prepared by bromine–lithium exchange from the respective bromide with *t*-BuLi and subsequent electrophilic substitution by Me_3SnCl.



Scheme 5 Reaction of various electrophiles with the 2-thiazolylmagnesium reagent **5** derived from 2,4-dibromothiazole (**1**)

nucleophile. Cross-coupling reactions facilitate the direct carbon–carbon bond formation at C2 with a variety of organometallic compounds. The Negishi and Stille cross-coupling reactions were found particularly useful for many synthetic purposes.

Herein we describe two typical procedures for different substrate classes depicted in Scheme 1 and in Tables 1– 4. Procedure 1 is subdivided into three variants (1a–1c), which require modification of the catalyst and the solvent. Since the zinc reagents required in variant 1b can be generated either from commercial alkyllithium reagents or from iodides by an iodine–lithium exchange two modifications are reported for this procedure.

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Tetrahydrofuran (THF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were purified using a SPS-800 solvent purification system (M. Braun). Chemicals were either commercially available or prepared according to the cited references. TLC was performed on silica-coated glass plates (0.25 mm silica gel 60 F254) with detection by UV (254 nm) or $KMnO_4$ (0.5% in water) with subsequent heating. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) with the indicated eluent. Common solvents for chromatography such as pentane, ethyl acetate (EtOAc), diethyl ether, dichloromethane and methyl *tert*-butyl ether (*t*-BuOMe) were distilled prior to use. IR: JASCO IR-4100 (ATR). MS and HRMS: Finnigan MAT 8200 (MS-EI) and Finnigan MAT 95S (HRMS-EI). ^1H and ^{13}C NMR: Bruker AV-200 and Bruker AV-360, recorded at 296 K. Chemical shifts are reported relative to tetramethylsilane. The multiplicities of the ^{13}C NMR signal were determined by DEPT experiments, assignments are based on COSY, HMBC and HMQC experiments. Optical rotations were measured using a Perkin-Elmer 241 MC Polarimeter.

Procedure 1a (Table 1)[19]

A solution of *t*-BuLi (4.15 mL, 5.55 mmol, 1.34 M in pentane) was added dropwise to a stirred solution of the corresponding *O*-methoxymethyl (MOM)-protected phenol (5.00 mmol) in Et_2O (25 mL) at 0 °C. The mixture was then stirred for another 10 min at 0 °C. A solution of $ZnCl_2$ (15.0 mL, 7.50 mmol, 0.5 M in THF) was subsequently added and the resulting mixture was warmed to r.t. After another 30 min, the above solution of the arylzinc reagent was added dropwise to a suspension of 2,4-dibromothiazole (**1**; 1.22 g, 5.00 mmol) and $PdCl_2(PPh_3)_2$ (175 mg, 0.25 mmol) in THF (25 mL). The mixture was stirred at r.t. for 16 h and subsequently quenched with sat. aq NH_4Cl (50 mL). After extraction with Et_2O (3×50 mL), the organic layers were combined, washed with brine (50 mL), and dried (Na_2SO_4). After removal of the solvent, the residue was purified by flash chromatography over silica gel (pentane–*t*-BuOMe, 50:1), yielding 4-bromothiazoles **2a–e**.

Analytical data for 4-bromothiazoles **2b–d** are provided below. Data for compound **2a**[19] as well as a procedure and analytical data for compound **2e**[20] can be found in the corresponding references.

4-Bromo-2-[5-(*tert*-butyl)-2-(methoxymethoxy)phenyl]thiazole (2b)

Yield: 984 mg (2.76 mmol, 55%); $R_f = 0.53$ (pentane–*t*-BuOMe, 3:1, UV); mp 64 °C.

IR (KBr): 3091 (m, $C_{ar}H$), 2954 (s, CH), 1603 (m, ar C=C), 1585 (s, ar C=C), 1504 (s, ar C=C), 1450 (s, ar C=C), 1138 (s), 895 cm^{-1} (s).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, $C(CH_3)_3$], 3.40 (s, 3 H, OCH_3), 5.24 (s, 2 H, OCH_2O), 7.04–8.34 (m, 4 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.8 [q, $C(CH_3)_3$], 34.8 [s, $C(CH_3)_3$], 56.7 (q, OCH_3), 94.6 (t, OCH_2O), 114.3 (d, $C_{ar}H$), 117.9 (d, $C_{ar}H$), 121.6 (s, C_{ar}), 125.6 (d, $C_{ar}H$), 128.6 (d, $C_{ar}H$), 128.7 (s, $C_{ar}Br$), 145.3 (s, C_{ar}), 152.5 (s, C_{ar}), 164.1 (s, C_{ar}).

MS (EI, 70 eV): *m*/*z* (%) = 357 (21, [M ($^{81}Br)^+$]), 355 (20, [M ($^{79}Br)^+$]), 312 (41, [(M (^{81}Br) – $C_2H_4O)^+$]), 310 (40, [(M (^{79}Br) – $C_2H_4O)^+$]), 45 (100, [$C_2H_5O^+$]).

Anal. Calcd for $C_{15}H_{18}BrNO_2S$: C, 50.57; H, 5.09; N, 3.93. Found: C, 50.31; H, 4.82, N, 4.02.

4-Bromo-2-[5-chloro-2-(methoxymethoxy)phenyl]thiazole (2c)
The reaction was carried out on a 3.00 mmol scale; yield: 620 mg (1.85 mmol, 62%); R_f = 0.37 (pentane–*t*-BuOMe, 3:1, UV); mp 82 °C.

IR (KBr): 3120 (m, $C_{ar}H$), 2959 (m, CH), 1594 (m, ar C=C), 1575 (s, ar C=C), 1489 (s, ar C=C), 1450 (s, ar C=C), 1260 (s), 984 cm^{-1} (s).

^1H NMR (200 MHz, $CDCl_3$): δ = 3.52 (s, 3 H, OCH_3), 5.37 (s, 2 H, OCH_2O), 7.15–8.39 (m, 4 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 57.1 (q, OCH_3), 94.9 (t, OCH_2O), 116.1 (d, $C_{ar}H$), 118.9 (d, $C_{ar}H$), 123.4 (s, C_{ar}), 125.9 (s, $C_{ar}Br$), 127.9 (s, $C_{ar}Cl$), 128.3 (d, $C_{ar}H$), 131.2 (d, $C_{ar}H$), 152.9 (s, C_{ar}), 162.3 (s, C_{ar}).

MS (EI, 70 eV): *m*/*z* (%) = 337 (9, [M ($^{81}Br^{37}Cl)^+$]), 335 (31, [M ($^{81}Br^{35}Cl)^+$]), 335 (31, [M ($^{79}Br^{37}Cl)^+$]), 333 (14, [M ($^{79}Br^{35}Cl)^+$]), 45 (100, [$C_2H_5O^+$]).

Anal. Calcd for $C_{11}H_9BrClNO_2S$: C, 39.48; H, 2.71; N, 4.19. Found: C, 39.29; H, 2.69, N, 4.22.

4-Bromo-2-[4-(*tert*-butyl)-2-(methoxymethoxy)phenyl]thiazole (2d)
Yield: 987 mg (2.77 mmol, 55%); R_f = 0.67 (pentane–*t*-BuOMe, 3:1, UV); yellow oil.

IR (NaCl): 3121 (m, $C_{ar}H$), 2964 (s, CH), 1608 (m, ar C=C), 1570 (s, ar C=C), 1506 (s, ar C=C), 1456 (s, ar C=C), 993 cm^{-1} (s).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 [s, 9 H, $C(CH_3)_3$], 3.42 (s, 3 H, OCH_3), 5.27 (s, 2 H, OCH_2O), 7.00–8.21 (m, 4 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.1 [q, $C(CH_3)_3$], 34.1 [s, $C(CH_3)_3$], 55.6 (q, OCH_3), 93.3 (t, OCH_2O), 110.3 (d, $C_{ar}H$), 116.2 (d, $C_{ar}H$), 118.1 (s, C_{ar}), 118.3 (d, $C_{ar}H$), 124.0 (s, $C_{ar}Br$), 126.9 (d, $C_{ar}H$), 153.1 (s, C_{ar}), 154.2 (s, C_{ar}), 162.4 (s, C_{ar}).

MS (EI, 70 eV): *m*/*z* (%) = 357 (7, [M ($^{81}Br)^+$]), 355 (8, [M ($^{79}Br)^+$]), 45 (100, [$C_2H_5O^+$]).

Anal. Calcd for $C_{15}H_{18}BrNO_2S$: C, 50.57; H, 5.09; N, 3.93. Found: C, 50.24; H, 4.21, N, 5.14.

Procedure 1a (Table 2)[20]
A solution of *t*-BuLi (1.15 mL, 1.73 mmol, 1.5 M in pentane) was added at –78 °C to a solution of the corresponding 4-bromothiazole (0.82 mmol) in THF (4 mL). After stirring the mixture at –78 °C for 10 min, $ZnCl_2$ (2.40 mL, 1.20 mmol, 0.5 M in THF) was added. The resulting mixture was stirred at r.t. for 30 min and a mixture of 2,4-dibromothiazole (**1**; 153 mg, 0.63 mmol) and $PdCl_2(PPh_3)_2$ (22.0 mg, 32.0 μmol) in THF (4 mL) was added via a syringe. After refluxing for 16 h, the reaction was quenched with sat. aq NH_4Cl (10 mL), and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL). After drying (Na_2SO_4) and filtration, the solvent was removed and the residue was purified by flash chromatography over silica gel (pentane–Et_2O, 50:1–4:1), yielding bithiazoles **3a–g**.

Representative analytical data for bithiazole **3a**[20] are provided below. Data for compounds **3b–g**[20] can be found in the corresponding reference.

4-Bromo-2′-butyl-2,4′-bithiazole (3a)
Yield: 183 mg (0.60 mmol, 96%).

^1H NMR (360 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.44 (virt. sext, *J* ≈ 7.4 Hz, 2 H, CH_2), 1.78 (virt. quint, *J* ≈ 7.7 Hz, 2 H, CH_2), 3.01 (t, *J* = 7.7 Hz, 2 H, ArCH_2), 7.19 (s, 1 H, ArH), 7.85 (s, 1 H, ArH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 13.7 (q, CH_3), 22.2 (t, CH_2), 31.9 (t, CH_2), 33.1 (t, CH_2), 116.0 (d, $C_{ar}H$), 117.1 (d, $C_{ar}H$), 125.9 (s, $C_{ar}Br$), 147.7 (s, C_{ar}), 167.7 (s, C_{ar}), 172.6 (s, C_{ar}).

Procedure 1b (Table 3)
By Direct Zincation of Commercially Available Organolithium Reagents:[20] A solution of the commercially available organolithium compound (5.00 mmol) was added at –78 °C to a solution of $ZnCl_2$ (15.0 mL, 7.50 mmol, 0.5 M in THF). The resulting mixture was stirred at r.t. for 30 min and was then added via a syringe to a solution of 2,4-dibromothiazole (**1**; 486 mg, 2.00 mmol), $Pd_2(dba)_3$ (46.0 mg, 0.10 mmol), and dppf (56.0 mg, 0.10 mmol) in THF (10 mL). After stirring for 16 h at r.t., the reaction was quenched with sat. aq NH_4Cl (10 mL), and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL). After drying (Na_2SO_4) and filtration, the solvent was removed and the residue was purified by flash chromatography over silica gel (pentane–Et_2O, 30:1–20:1), yielding 4-bromothiazoles **4a**, **4f**, and **4g**.

By Lithiation of Alkyl Iodides and Subsequent Zincation:[20] A solution of *t*-BuLi (6.90 mL, 10.4 mmol, 1.5 M in pentane) was added at –78 °C to a solution of the corresponding primary alkyl iodide (5.00 mmol) in Et_2O (8 mL). After stirring the mixture at –78 °C for 1 h, $ZnCl_2$ (15.0 mL, 7.50 mmol, 0.5 M in THF) was added. The resulting mixture was stirred at r.t. for 30 min and was then added via a syringe to a solution of 2,4-dibromothiazole (**1**; 486 mg, 2.00 mmol), $Pd_2(dba)_3$ (46.0 mg, 0.10 mmol), and dppf (56.0 mg, 0.10 mmol) in THF (10 mL). After stirring for 16 h at r.t., the reaction was quenched with sat. aq NH_4Cl (10 mL), and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL). After drying (Na_2SO_4) and filtration, the solvent was removed and the residue was purified by flash chromatography over silica gel (pentane–Et_2O, 30:1–20:1), yielding 4-bromothiazoles **4b–e** and **4h**.

Representative analytical data for 4-bromothiazole **4a**[20] are provided below. Data for compounds **4b–g**[20] and **4h**[21] can be found in the corresponding references.

4-Bromo-2-butylthiazole (4a)
Yield: 375 mg (1.70 mmol, 85%).

^1H NMR (360 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.38 (virt. sext, *J* ≈ 7.5 Hz, 2 H, CH_2), 1.73 (virt. quint, *J* ≈ 7.6 Hz, 2 H, CH_2), 2.96 (t, *J* = 7.7 Hz, 2 H, ArCH_2), 7.03 (s, 1 H, ArH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 13.6 (q, CH_3), 22.1 (t, CH_2), 31.8 (t, CH_2), 33.2 (t, CH_2), 115.5 (d, $C_{ar}H$), 124.1 (s, $C_{ar}Br$), 172.7 (s, C_{ar}).

Procedure 1c (Table 4)
A solution of *t*-BuLi (0.60 mL, 0.90 mmol, 1.5 M in pentane) was added at –78 °C to a solution of the corresponding 4-bromothiazole (0.43 mmol) in Et_2O (2 mL). After stirring the mixture at –78 °C for 10 min, Me_3SnCl (0.43 mL, 0.43 mmol, 1.0 M in THF) was added. The resulting mixture was stirred at r.t. for 2 h, then Et_2O (8 mL)

and H_2O (2 mL) were added. The organic layer was dried (Na_2SO_4) and after filtration the solvent was removed. The residue was dissolved in toluene (3.5 mL) to which 2,4-dibromothiazole (**1**; 104 mg, 0.42 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 22.0 μmol) were added and the solution was degassed. After refluxing for 16 h, H_2O (5 mL) was added, and the aqueous layer was extracted with Et_2O (3 × 8 mL). The combined organic layers were washed with brine (8 mL). After drying (Na_2SO_4) and filtration, the solvent was removed and the residue was purified by flash chromatography over silica gel (pentane–Et_2O, 20:1) to yield bithiazoles **3h–j**.

Representative analytical data for bithiazole **3h**[20] are provided below. Data for compounds **3i–j**[20] can be found in the corresponding references. A procedure and complete analytical data for compound **3k**[24] are given in the corresponding reference.

4-Bromo-2′-phenyl-2,4′-bithiazole (3h)
Yield: 85.0 mg (0.26 mmol, 61%).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.24 (s, 1 H, ArH), 7.44–7.46 (m, 3 H, C_6H_5), 7.98–8.00 (m, 2 H, C_6H_5), 7.99 (s, 1 H, ArH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 116.5 (d, $C_{ar}H$), 117.5 (d, $C_{ar}H$), 126.0 (s, $C_{ar}Br$), 126.7 (d, $C_{ar}H$), 129.1 (d, $C_{ar}H$), 130.7 (d, $C_{ar}H$), 132.8 (s, C_{ar}), 149.0 (s, C_{ar}), 163.6 (s, C_{ar}), 168.9 (s, C_{ar}).

Procedure 2 (Scheme 5)[24]
To a suspension of 2,4-dibromothiazole (**1**; 4.01 g, 16.5 mmol) in Et_2O (1.8 mL) was added dropwise *i*-PrMgBr (4.80 mL, 16.5 mmol, 3.45 M in Et_2O) at 0 °C. The mixture was stirred for 30 min at 0 °C to yield the Grignard reagent **5**. A solution of the corresponding sulfoximine (8.25 mmol) in CH_2Cl_2 (50 mL) was cooled to –50 °C and the Grignard reagent **5** was added dropwise. The resulting mixture was stirred for another 2 h at –50 °C before it was allowed to reach r.t. within 12 h. The reaction was quenched by the addition of sat. aq NH_4Cl (50 mL) and diluted with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvents were removed under reduced pressure and the residue was purified by flash chromatography over silica gel (pentane–EtOAc, 2:1–1:2) to yield the corresponding sulfinamides **6b–d**.

A procedure and complete analytical data for compound **6a** are provided in the corresponding references.[29,30b] Analytical data for sulfinamide **6b** can also be found in the corresponding reference.[24] Complete analytical data for sulfinamides **6c** and **6d** are given below.

(*S*)-*N*-[(*S*)-1-(4-Bromothiazol-2yl)-3-methylbutyl]-2-methylpropane-2-sulfinamide (6c)
The reaction was carried out on a 0.64 mmol scale; yield: 218 mg (0.62 mmol, 97%); dr = 79:21; R_f = 0.47 (pentane–EtOAc, 1:1, UV); mp 82 °C; $[\alpha]_D^{20}$ +31.4 (*c* = 1.05, $CHCl_3$).

IR (ATR): 3258 (m, NH), 3069 (s), 2918 (m, CH_2), 2361 (m), 1469 (m, CH), 1413 (w), 1386 (w, CH_3), 1364 (w), 1255 (w), 1170 (w), 1092 (w), 1047 (vs, SO), 885 (w), 834 (w), 732 cm^{-1} (w).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.92 [d, *J* = 6.4 Hz, 3 H, $CH(CH_3)(CH_3)$], 0.94 [d, *J* = 6.4 Hz, 3 H, $CH(CH_3)(CH_3)$], 1.24 [s, 9 H, $C(CH_3)_3$], 1.73–2.04 [m, 3 H, $CH_2CH(CH_3)_2$], 3.92 (d, *J* = 8.2 Hz, 1 H, NH), 4.61–4.69 (m, 1 H, $NHCHCH_2$), 7.16 (s, 1 H, ArH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 21.8 [q, $CH(CH_3)_2$], 22.6 [q, $C(CH_3)_3$], 22.7 [q, $CH(CH_3)_2$], 24.6 [d, $CH(CH_3)_2$], 46.4 [t, $CH_2CH(CH_3)_2$], 56.4 (d, CHNH), 56.6 [s, $C(CH_3)_3$], 116.8 (d, $C_{ar}H$), 124.9 (s, $C_{ar}Br$), 173.8 (s, C_{ar}).

MS (EI, 70 eV): *m*/*z* (%) = 298 (32, [(M (^{81}Br) – C_4H_8)$^+$]), 296 (31, [(M (^{79}Br) – C_4H_8)$^+$]), 235 (54, [$C_8H_{12}{}^{81}BrNS^+$]), 233 (52, [$C_8H_{12}{}^{79}BrNS^+$]), 192 (70), 190 (68), 57 (100, [$C_4H_9^+$]), 41 (34, [$C_2H_3N^+$]).

HRMS-EI: *m*/*z* calcd for $C_8H_{13}{}^{79}BrN_2S_2$ [(M (^{79}Br) – 56)$^+$]: 295.9652; found: 295.9652.

(*S*)-*N*-[(*S*)-1-(4-Bromthiazol-2-yl)-3-(methylthio)propyl]-2-methylpropan-2-sulfinamide (6d)
The reaction was carried out on a 0.75 mmol scale; yield: 189 mg (0.51 mmol, 68%); dr = 83:17 (diastereoisomers were not separable); R_f = 0.28 (pentane–EtOAc, 1:1, UV); mp 103 °C.

IR (ATR): 3247 (w, NH), 3062 (m, C=CH), 2958 (w, CH_2), 1471 (s, CH), 1406 (w), 1363 (w, CH_3), 1277 (m), 1047 (vs, SO), 1016 (w), 884 (m), 841 (s), 801 cm^{-1} (w).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.25 [s, 9 H, $C(CH_3)_3$], 2.10 (s, 3 H, SCH_3), 2.15–2.33 (m, 2 H, CH_2CH_2S), 2.57–2.61 (m, 2 H, CH_2CH_2S), 4.19 (d, *J* = 7.8 Hz, 1 H, NH), 4.84 (m, 1 H, NHC*H*), 7.19 (s, 1 H, ArH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 15.4 (q, SCH_3), 22.7 [q, $C(CH_3)_3$], 30.0 (s, CH_2CH_2S), 35.8 (s, CH_2CH_2S), 56.5 [s, $C(CH_3)_3$], 56.7 (d, CHNH), 117.3 (d, $C_{ar}H$), 125.0 (s, $C_{ar}Br$), 172.6 (s, C_{ar}).

MS (EI, 70 eV): *m*/*z* (%) = 316 (13, [(M (^{81}Br) – C_4H_8)$^+$]), 314 (12, [(M (^{79}Br) – C_4H_8)$^+$]), 279 (10), 253 (9, [$C_7H_{10}{}^{81}BrNS_2^+$]), 251 (10, [$C_7H_{10}{}^{79}BrNS_2^+$]), 191 (24), 190 (22), 167 (18), 149 (32), 104 (25), 83 (19), 57 (100, [$C_4H_9^+$]), 41 (37, [$C_2H_3N^+$]).

HRMS-EI: *m*/*z* calcd for $C_7H_{11}{}^{79}BrN_2OS_3$ [(M (^{79}Br) – 56)$^+$]: 313.9217; found: 313.9218.

Acknowledgment

Our own work in this area was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, BASF SE, and the TUM Graduate School. We thank Wacker Chemie (Munich) and Umicore (Hanau) for the donation of chemicals.

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