Preparation of 2- and 5-Aryl Substituted Thiazoles via Palladium-Catalyzed Negishi Cross-Coupling

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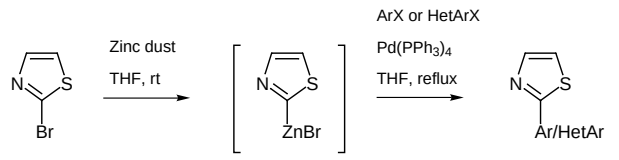
Abstract: 2-Aryl substituted thiazoles **3a−k** were prepared by oxidative insertion of zinc into 2-bromothiazole (**1**) followed by palladium(0)-catalyzed Negishi cross-coupling in a one-pot procedure. 5-Aryl substituted thiazoles **6a−i** were prepared by regioselective C-5 lithiation of 2-(trimethylsilyl)thiazole (**4**) followed by transmetalation with zinc chloride and palladium(0)-catalyzed Negishi cross-coupling in a one-pot procedure. The synthetic sequences were combined to give 2,5-diaryl substituted thiazoles **8a**,**b** and **10** via stepwise C-2 and C-5 arylation and vice versa.

Key words: thiazoles, cross-coupling, arylation, zinc, lithiation

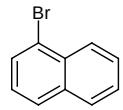
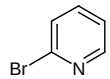
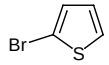
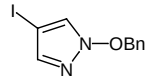
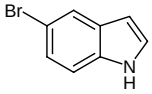
Thiazole is an important heterocycle found in various natural products, notably thiamine (vitamin B). Numerous thiazole derivatives, including penicillins and antibiotics, exhibit pharmacological activity.[1] In addition to this, 2-(trimethylsilyl)thiazole (2-TST) (**4**) can be considered as a formyl anion equivalent thereby representing an important synthetic building block.[2] Therefore the generation of thiazole derivatives has several important applications, and methods for regioselective introduction of aromatic and heteroaromatic substituents are desirable. Thiazoles have traditionally been prepared by the Hantzsch synthesis,[3] a cyclocondensation of α-halocarbonyl compounds with thioamides. Several variations of this theme have been developed for the preparation of substituted thiazoles.[4−6] Methods for the assembly on solid support have also been devised.[7,8] Apart from the synthesis of aryl- and heteroarylated thiazoles by ring closure, diazotization methods have been described.[9] In the first systematic investigation of the properties of metalated thiazole species, Dondoni et al. have synthesized 2-, 4- and 5-trimethylstannyl substituted thiazoles[10] and prepared various di- and trimers of thiazoles in good yields using the Stille cross-coupling reaction.[11] Furthermore, the Stille cross-coupling has been used to synthesize arylated and heteroarylated thiazoles both via reaction of stannylated thiazoles[12-18] with organohalides and via stannylated aryl- and heteroaryls with brominated thiazoles.[14,15,18] In contrast to trialkylstannyl thiazoles, thiazoleboronic acids are, to the best of our knowledge, not known, therefore aryl- and heteroaryl thiazoles have only been prepared by Suzuki cross-coupling via thiazole halides.[14−17,19] Recently, 2- and 5-substituted arylated thiazoles have been prepared by base promoted reaction between arylpalladium(II) halides and the parent thiazole, presumably occurring by electrophilic attack of the arylpalladium(II) halide.[20−22]

Knochel and co-workers[23,24] have prepared 2-thiazolezinc bromide (**2**) by oxidative insertion of zinc into 2-bromothiazole (**1**) and used it for the preparation of a few 2-aryl substituted thiazoles. Regioselective conversion of heterocycles into the corresponding organozinc compounds provides a viable method for regioselective aromatic and heteroaromatic substitution of the respective heterocycle. The organozinc intermediates generally tolerate a broad range of functional groups and do not involve the use of toxic trialkyltin compounds.[25] We now report methods for selective introduction of aromatic and heteroaromatic substituents into the 2-and 5-position of thiazoles using the Negishi cross-coupling reaction affording otherwise inaccessible aromatic systems. Scopes and limitations of these methods are described.

2-Thiazolezinc bromide (**2**) was prepared by oxidative insertion of zinc dust to 2-bromothiazole (**1**) as previously described by Knochel et al.[23] (Scheme 1). The reaction was performed in THF using three equivalents of zinc dust and 1,2-dibromoethane and trimethylsilyl chloride as activating agents.[23,26] 2-Thiazolezinc bromide (**2**) was subsequently refluxed in THF for 24 hours, with the proper aryl halide or heteroaryl halide in the presence of 1-2 mol% $Pd(PPh_3)_4$ in a one-pot procedure, producing 2-aryl and 2-heteroaryl substituted thiazoles **3a−k** in modest to good yields. A number of functional groups were tolerated under the reaction conditions (Scheme 1), demonstrating the weakly basic and nucleophilic character of the organozinc compound, and both aryl halides with electron-donating (Scheme 1, Entries 2, 4 and 5) and -withdrawing groups (Entries 3 and 6) reacted. Furthermore cross-coupling with both π-excessive (Entries 9-11) and the π-deficient 2-bromopyridine (Entry 8) produced 2-heteroaryl thiazoles **3h−k** in modest to good yields. The yields of the cross-coupled products were found to be dependent on the reaction temperature, since the isolated yields of **3h** and **3i** increased from 11% to 45% and from 27% to 68%, respectively upon raising the temperature from room temperature to reflux. Negishi cross-coupling reactions with acyl chlorides have been reported,[27−29] but attempts to acylate 2-thiazolezinc bromide (**2**) under the same reaction conditions as above, using acetyl chloride and benzoyl chloride, failed.



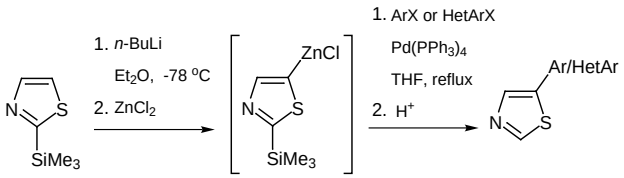
1 **2** **3a-k**

Entry	Sub—Hal	Product	Yield[a] (%)
1	Sub = 4-Me	**3a**	78
2	4-NH_2	**3b**	49
3	4-Ac	**3c**	72
4	4-OH	**3d**	29
5	2-OMe	**3e**	57
6	2-CHO	**3f**	42
7		**3g**	68
8		**3h**	45
9		**3i**	68
10		**3j**	27
11		**3k**	64

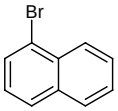
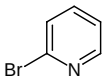
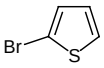
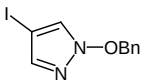
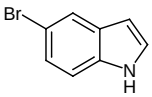
[a] Yields of chromatographically pure products

Scheme 1

Lithiation of 2-(trimethylsilyl)thiazole (2-TST) (**4**) occurs regioselectively in the 5-position (Scheme 2).[30] Subsequent transmetalation with zinc chloride followed by cross-coupling with an aryl- or heteroaryl halide, provided a general one-pot procedure for the introduction of aromatic and heteroaromatic substituents into the 5-position of thiazole. The 2-trimethylsilyl group of the cross-coupled products was cleaved off quantitatively under acidic workup. The lithiation and transmetalation was performed in diethyl ether, since it appeared that 5-lithio-2-(trimethylsilyl)thiazole is unstable in THF at −78 °C.[31] In order to perform the cross-couplings in refluxing THF the diethyl ether was removed by evaporation prior to addition of the organohalide and the catalyst. Three equivalents of zinc chloride were used, as the isolated yield of **6a** was 79% compared to 48% when one equivalent of zinc chloride was employed. A comparison between 2-(trimethylsilyl)-5-thiazolezinc chloride (**5**) and 2-thiazolezinc bromide (**2**) revealed that the former produced better yields of corresponding arylated thiazoles in the cross-coupling with 4-iodoaniline, 4-iodoanisole, 1-bromonaphthalene, 2-bromopyridine and 4-iodo-1-(benzyloxy)pyrazole (Scheme 1, Entries 2, 5, 7, 8 and 10; Scheme 2 Entries 2, 4, 6, 7 and 9). However, **5** gave significantly lower yields than **2** in the cross-coupling with 4-bromoacetophenone and 5-bromoindole and moreover **5** failed to give the desired product upon reaction with 2-bromobenzaldehyde (Scheme 1, Entries 3, 6 and 11; Scheme 2 Entries 3, 5 and 10). These observations may be due to a higher nucleophilicity/basicity of 2-(trimethylsilyl)-5-thiazolezinc chloride (**5**) than the corresponding 2-thiazolezinc bromide (**2**).



4 **5** **6a-i**

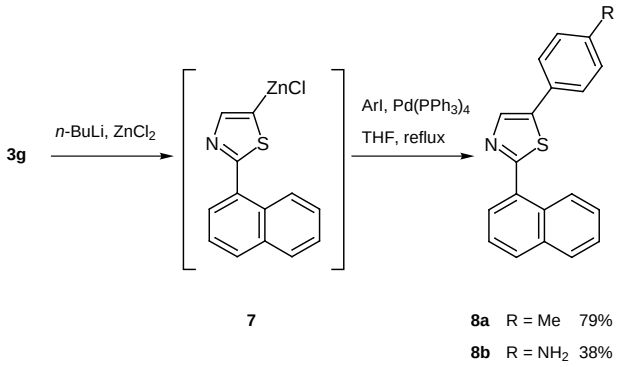
Entry	Sub—Hal	Product	Yield[a] (%)
1	Sub = 4-Me	**6a**	79
2	4-NH_2	**6b**	88
3	4-Ac	**6c**	26
4	2-OMe	**6d**	67
5	2-CHO	-	[b]
6		**6e**	83
7		**6f**	68
8		**6g**	48
9		**6h**	58
10		**6i**	26

[a] Yields of chromatographically pure products; [b] Complicated mixture

Scheme 2

The methodology developed above was combined for the preparation of 2,5-diaryl substituted thiazoles via repeated metalation/cross-coupling. The order of introducing the aryl substituents could be C-2 followed by C-5 arylation or alternatively C-5 followed by C-2 arylation. This

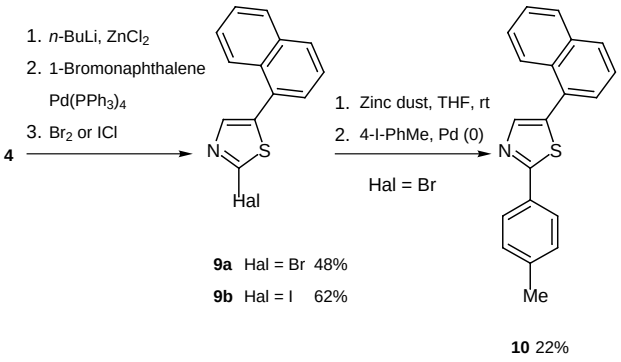
should allow the presence of one aryl substituent possessing e.g. a base sensitive group if this aryl substituent is introduced in the second cross-coupling. Thus, 5-(4-methylphenyl)-2-(1-naphthyl)thiazole (**8a**) and 5-(4-aminophenyl)-2-(1-naphthyl)thiazole (**8b**) were prepared in 79% and 38% yield by cross-coupling of 2-(1-naphthyl)thiazole (**3g**) with 4-iodotoluene or 4-iodoaniline, respectively (Scheme 3).



Scheme 3

Although, **8b** is only formed in 38% yield this method demonstrates the advantages of introducing the 4-aminophenyl substituent in the final cross-coupling, since attempted bromodesilylation (see below) on 5-(4-aminophenyl)-2-(trimethylsilyl)thiazole (intermediate in the synthesis of **6b**) led to extensive bromination of the 4-aminophenyl substituent. Arylation at C-5 succeeded by C-2 arylation was demonstrated by the preparation of 2-(4-methylphenyl)-5-(1-naphthyl)thiazole (**10**). The required 2-halo-5-(1-naphthyl)thiazoles **9a**,**b** were obtained by in situ halodesilylation of the intermediate 5-(1-naphthyl)-2-(trimethylsilyl)thiazole using bromine or iodine mono chloride. In contrast to 2-bromothiazole (**1**), which underwent complete zinc insertion within 15 minutes at room temperature, 2-bromo-5-(1-naphthyl)thiazole (**9a**) required 24 hours at room temperature and surprisingly 2-iodo-5-(1-naphthyl)thiazole (**9b**) failed to react. Subsequent treatment of 5-(1-naphthyl)thiazol-2-ylzinc bromide with 4-iodotoluene in the presence of 2 mol% $Pd(PPh_3)_4$ afforded 2-(4-methylphenyl)-5-(1-naphthyl)thiazole (**10**) in 22% yield (Scheme 4).

In conclusion, palladium(0)-catalyzed Negishi cross-coupling using the thiazolezinc intermediates **2** and **5** proved to be an efficient method for the preparation of 2- and 5-arylsubstituted thiazoles possessing a broad range of functional groups. The methods for C-2 and C-5 arylation were combined to give 2,5-diaryl substituted thiazoles. In these reactions the yields were strongly dependent on the nature of the aryl substituents.



Scheme 4

All reactions involving air-sensitive reagents were performed under argon using syringe-septum cap techniques. All glassware was flame dried prior to use. All chemicals were used as purchased without further purification unless otherwise stated. THF was freshly distilled over sodium/benzophenone under N_2·Et_2O was dried and stored over 3 Å sieves. DMF was dried and stored over 3 Å sieves. BuLi was titrated prior to use.[32] 1 M solutions of anhyd. $ZnCl_2$ in Et_2O were prepared by melting the salt in vacuo before dissolving it in Et_2O. TLC was performed using Merck 60 F_{254} sheets. All sheets were visualized under UV-light, 254 nm. Column Chromatography (CC) was performed on silica gel (Merck 0.063−0.200 mm). Preparative HPLC was performed on a conventional reverse-phase Luna C_{18} silica preparative column using a gradient (20−100% B) flow of 9 mL/min. Solvent A was 0.1% aq trifluoroacetic acid, solvent B was 80% MeCN/H_2O containing 0.1% trifluoroacetic acid. Sample absorbance was recorded at 254 nm. In cases where ordinary chromatography did not suffice to obtain the required purity for microanalysis, the oily products were purified by preparative HPLC and crystalline compounds were purified by crystallization or HPLC. All compounds were colorless unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 MHz and a Varian 400 MHz instrument at 300.07/75.46 MHz and 400.45/100.70 MHz respectively with TMS as internal standard. Aromatic ^{1}H NMR signals from thiazoles are referred to as H-2, H-4 and H-5. Melting points were determined in capillary tubes and are uncorrected. HRMS was performed at Department of Chemistry, University of Odense. The spectrofotometer was a Ionspec Fourir Transform Mass Spectrofotometer with a matrix assisted laser desorption ionisation. Elemental analyses were performed at Department of Chemistry, University of Copenhagen.

2-Aryl Substituted Thiazoles; General Procedure I

To a stirred suspension of zinc dust (< 10 micron, 98+%, Aldrich, 196 mg, 3 mmol) in THF (0.5 mL) was added 1,2-dibromoethane (50 mg, 0.27 mmol). Heating with a heat gun until the evolution of ethylene gas was done twice. Trimethylsilyl chloride (15 µL, 0.12 mmol) and a solution of 2-bromothiazole (**1**; 164 mg, 1 mmol) in THF (0.4 mL) were added. After 15 min the proper aryl- or heteroaryl halide (1.5 equiv) and $Pd(PPh_3)_4$ (ca 15 mg, 1-2 mol%) dissolved in THF (2 mL) were added and the mixture was stirred for 24 h at reflux, before quenching with a sat aq solution of NaCl (10 mL). Extraction with CH_2Cl_2 (3 × 15 mL), drying ($MgSO_4$) of the combined organic phases, filtration and evaporation in vacuo provided the crude material, which was purified by column chromatography (CC).

2-(4-Methylphenyl)thiazole (3a)

Prepared by following the general procedure I using 4-iodotoluene as the aryl halide.

CC (10% EtOAc in heptane) gave 253 mg (78%) of **3a** as an oil. An analytically pure sample of **3a** was obtained by preparative HPLC; R_f 0.35 (10% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 7.25 (d, 2 H, *J* = 8.1 Hz), 7.29 (d, 1 H, *J* = 3.3 Hz, H-5), 7.84 (d, 1 H, *J* = 3.3 Hz, H-4), 7.86 (d, 2 H, *J* = 8.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 21.3, 118.4, 126.6, 129.7, 130.9, 140.4, 143.5, 168.8.

Anal. calcd for $C_{10}H_9NS$: C, 68.54; H, 5.18; N, 7.99. Found C, 68,26; H, 5.23; N, 7.96.

2-(4-Aminophenyl)thiazole (3b)
Prepared by following the general procedure I using 4-iodoaniline as the aryl halide.

CC (40% EtOAc in heptane) gave 86 mg (49%) of **3b** as yellow crystals. An analytically pure sample of **3b** was obtained by preparative HPLC; mp 129−130 °C (Lit.[33] mp 123−124 °C); R_f 0.25 (40% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 5.63 (br s, 2 H, NH_2), 6.60 (d, 2 H, *J* = 8.7 Hz), 7.49 (d, 1 H, *J* = 3.3 Hz, H-5), 7.60 (d, 2 H, *J* = 8.7 Hz), 7.71 (d, 1 H, *J* = 3.3 Hz, H-4).

^{13}C NMR (DMSO-d_6): δ = 114.1, 117.8, 121.4, 128.0, 143.6, 151.5, 168.9.

2-(4-Acetylphenyl)thiazole (3c)
Prepared by following the general procedure I using 4-bromoacetophenone as the aryl halide.

CC (15−20% EtOAc in heptane) gave 146 mg (72%) of **3c**. An analytically pure sample of **3c** was obtained by preparative HPLC; mp 112−113 °C (Lit.[34] mp 41.5 °C); R_f 0.10 (20% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 2.64 (s, 3 H, CH_3) 7.43 (d, 1 H, *J* = 3.3 Hz, H-5), 7.94 (d, 1 H, *J* = 3.3 Hz, H-4), 8.01−8.09 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 26.6, 120.2, 126.7, 127.5, 129.1, 137.9, 144.2, 167.0, 197.5.

2-(4-Hydroxyphenyl)thiazole (3d)
Prepared by following the general procedure I using 4-iodophenol as the aryl halide.

CC (30% EtOAc in heptane) gave 52 mg (29%) **3d**; mp 172−173 °C (heptane/EtOAc) (Lit.[35] mp 163−165 °C); R_f 0.15 (30% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 4.91 (br s, 1 H, OH), 6.85−6.88 (m, 2 H), 7.43 (d, 1 H, *J* = 3.3 Hz, H-5), 7.74 (d, 1 H, *J* = 3.3 Hz, H-4), 7.74−7.78 (m, 2 H)

^{13}C NMR ($CDCl_3$): δ = 115.5, 118.0, 124.7, 127.9, 142.4, 159.7, 169.5.

2-(2-Methoxyphenyl)thiazole (3e)
Prepared by following the general procedure I using 2-iodoanisole as the aryl halide.

CC (15% EtOAc in heptane) gave 109 mg (57%) **3e** as an oil; R_f 0.45 (15% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 4.02 (s, 3 H, OCH_3), 7.03 (dd, 1 H, *J* = 7.8, 0.9 Hz), 7.10 (dt, 1 H, *J* = 0.9, 7.8 Hz), 7.39 (d, 1 H, *J* = 3.3 Hz, H-5), 7.39 (dt, 1 H, *J* = 1.8, 7.8 Hz), 7.92 (d, 1 H, *J* = 3.3 Hz, H-4), 8.42 (dd, 1 H, *J* = 1.8, 7.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 55.5, 111.4, 119.8, 121.1, 122.3, 128.4, 130.7, 141.8, 156.3, 162.5.

Anal. calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found C, 62.71; H, 4.61; N, 7.21.

2-(2-Formylphenyl)thiazole (3f)
Prepared by following the general procedure I using 2-bromobenzaldehyde as the aryl halide.

CC (15% EtOAc in heptane) gave 80 mg (42%) of **3f**; R_f 0.15 (15% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.49 (d, 1 H, *J* = 3.3 Hz, H-5), 7.55−7.57 (m, 1 H), 7.64−7.66 (m, 1 H), 7.74−7.76 (m, 1 H), 7.98 (d, 1 H, *J* = 3.3 Hz, H-4), 8.21−8.23 (m, 1 H), 10.52 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$): δ = 120.8, 128.2, 128.3, 129.9, 130.0, 130.2, 133.9, 143.9, 164.4, 192.2.

The compound was slightly unstable and a correct microanalysis could not be obtained.

2-(1-Naphthyl)thiazole (3g)
Prepared by following the general procedure I using 1-bromonaphthalene as the aryl halide.

CC (5−10% EtOAc in heptane) gave 143 mg (68%) of **3g** as an oil. An analytically puresample of **3g** was obtained by preparative HPLC; R_f 0.20 (5% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.46 (d, 1 H, *J* = 3.3 Hz, H-5), 7.51−7.62 (m, 3 H), 7.82−7.84 (m, 1 H), 7.91−7.96 (m, 2 H), 8.05 (d, 1 H, *J* = 3.3 Hz, H-4), 8.79−8.81 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 119.9, 125.2, 125.9, 126.5, 127.5, 128.5, 128.8, 130.5, 130.7, 130.9, 134.1, 143.6. One carbon signal overlapped.

Anal. calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63. Found C, 73.77; H, 4.30; N, 6.59.

2-(2-Pyridyl)thiazole (3h)
Prepared by following the general procedure I using 2-bromopyridine as the heteroaryl halide.

CC (15−20% EtOAc in heptane) gave 73 mg (45%) of **3h**; mp 59−60 °C (heptane/EtOAc); R_f 0.10 (15% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.31 (dt, 1 H, *J* = 1.1, 7.6 Hz), 7.43 (d, 1 H, *J* = 3.3 Hz, H-5), 7.79 (ddd, 1 H, *J* = 8.0, 7.6, 1.8 Hz), 7.91 (d, 1 H, *J* = 3.3 Hz, H-4), 8.19 (dt, 1 H, *J* = 8.0, 1.1 Hz), 8.60 (ddd, 1 H, *J* = 1.0, 1.8, 4.8 Hz)

^{13}C NMR ($CDCl_3$): δ = 119.7, 121.4, 124.5, 137.2, 144.0, 149.5, 151.4, 169.3.

Anal. calcd for $C_8H_6N_2S$: C, 59.27; H, 3.73; N, 17.28. Found C, 58.93; H, 3.41; N, 17.03.

2-(2-Thienyl)thiazole (3i)
Prepared by following the general procedure I using 2-bromothiophene as the heteroaryl halide.

CC (10−15% EtOAc in heptane) gave 113 mg (68%) of **3i** as a yellow oil. (Lit.[36] mp 30−31°C); R_f 0.35 (15% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.07 (dd, 1 H, *J* = 5.1, 3.7 Hz), 7.24 (d, 1 H, *J* = 3.3 Hz, H-5), 7.38 (dd, 1 H, *J* = 5.1, 1.2 Hz), 7.52 (dd, 1 H, *J* = 1.2, 3.7 Hz), 7.76 (d, 1 H, *J* = 3.3 Hz, H-4).

^{13}C NMR ($CDCl_3$): δ = 118.1, 126.7, 127.9, 127.1, 137.2, 143.2, 162.1.

2-(4-[1-Benzyloxypyrazolyl])thiazole (3j)
Prepared by following the general procedure I using 1-(benzyloxy)-4-iodopyrazole[37] as the heteroaryl halide.

CC (20−30% EtOAc in heptane) gave 69 mg (27%) **3j** as yellow crystals. An analytically pure sample of **3j** was obtained by preparative HPLC; mp 59−60 °C; R_f 0.40 (50% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 5.34 (s, 2 H), 7.19 (d, 1 H, *J* = 3.3 Hz, H-5), 7.31−7.38 (m, 5 H), 7.54 (d, 1 H, *J* = 1.2 Hz), 7.71 (d, 1 H, *J* = 3.3 Hz), 7.72 (d, 1 H, *J* = 1.2 Hz)

^{13}C NMR ($CDCl_3$): δ = 80.8, 114.9, 117.2, 121.5, 128.9, 129.6, 129.7, 132.0, 133.3, 142.9, 160.1.

Anal. calcd For $C_{13}H_{11}N_3OS$: C, 60.82; H, 4.32; N, 16.37. Found C, 60.62; H, 4.19; N, 16.26.

2-(5-Indolyl)thiazole (3k)
Prepared by following the general procedure I using 5-bromoindole as the heteroaryl halide.

CC (15−40% EtOAc in heptane) gave 128 mg (64%) of **3k**; mp 123−124 °C (heptane/EtOAc) (Lit.[38] mp 119−121 °C); R_f 0.15 (30% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 6.62−6.63 (m, 1 H), 7.24−7.26 (m, 1 H), 7.28 (d, 1 H, *J* = 3.3 Hz, H-5), 7.42 (d, 1 H, *J* = 8.5 Hz), 7.86 (d, 1 H, *J* = 3.3 Hz, H-4), 7.84−7-88 (m, 1 H), 8.28−8.29 (m, 1 H), 8.73 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 103.3, 111.5, 117.7, 119.5, 120.9, 125.6, 125.8, 128.1, 136.9, 143.1, 170.5.

Anal. calcd for $C_{11}H_8N_2S$: C, 65.97; H, 4.03; N, 13.99. Found C, 66.22; H, 3.91; N, 13.75.

5-Aryl Substituted Thiazoles; General Procedure II
To a stirred solution of BuLi (0.69 mL, 1.6 M in hexanes, 1.1 mmol) in Et_2O (1 mL) at –78 °C was added dropwise a solution of 2-TST (**4**; 0.16 mL, 1.0 mmol) in Et_2O (1 mL) over a period of 30 min. After an addition period of 30 min, a 1.0 M solution of anhyd $ZnCl_2$ in Et_2O (3 mL, 3.0 mmol) was added and the solution was allowed to warm to r.t. over 30 min. The organozinc compound was concentrated in vacuo and a solution of $Pd(PPh_3)_4$ (ca 15 mg, 1-2 mol%) and the proper aryl- or heteroaryl halide (1.5 equiv) in THF (4 mL) was added. The reaction mixture was refluxed for 24 h before quenching with an aq solution of HCl (5%, 5 mL). The pH was adjusted to 10 with 2 M aq NaOH solution. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude products were purified by column chromatography (CC).

5-(4-Methylphenyl)thiazole (6a)
Prepared by following the general procedure II using 4-iodotoluene as the aryl halide.

CC (5−30% EtOAc in heptane) gave 138 mg (79%) of **6a** as pale yellow crystals; mp 83−84 °C (heptane/EtOAc) (Lit.[4] mp 87 °C); R_f 0.25 (20% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3 H), 7.23 (d, 2 H, *J* = 8.0 Hz), 7.48 (d, 2 H, *J* = 8.0 Hz), 8.04 (s, 1 H, H-4), 8.73 (s, 1 H, H-2)

^{13}C NMR ($CDCl_3$): δ = 20.7, 126.2, 127.5, 129.1, 137.6, 137.9, 138.9, 151.0.

5-(4-Aminophenyl)thiazole (6b)
Prepared by following the general procedure II using 4-iodoaniline as the aryl halide.

CC (40−60% EtOAc in heptane) gave 155 mg (88%) of **6b** as yellow crystals; mp 158−159 °C (heptane/EtOAc) (Lit.[39] mp 149−150 °C); R_f 0.15 (50% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 3.82 (br s, 2 H, NH_2), 6.71 (d, 2 H, *J* = 8.8 Hz), 7.38 (d, 2 H, *J* = 8.8 Hz), 7.93 (s, 1 H, H-4), 8.65 (s, 1 H, H-5).

^{13}C NMR ($CDCl_3$): δ = 114.6, 120.6, 127.5, 136.6, 139.2, 146.2, 149.9.

5-(4-Acetylphenyl)thiazole (6c)
Prepared by following the general procedure II using 4-bromoacetophenone as the aryl halide and DMF instead of THF in the cross-coupling step.

CC (20−40% EtOAc in heptane) gave 52 mg (26%) of **6c**.[40] An analytically pure sample of **6c** was obtained by preparative HPLC; mp 94−95 °C; R_f 0.15 (30% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 2.65 (s, 3 H), 7.70 (d, 2 H, *J* = 8.4 Hz), 8.04 (d, 2 H, *J* = 8.4 Hz), 8.26 (s, 1 H, H-4), 9.04 (s, 1 H, H-2).

^{13}C NMR ($CDCl_3$): δ = 27.0, 115.1, 127.2, 129.6, 134.7, 137.4, 138.1, 154.0, 197.3.

HRMS: *m*/*z* calcd: 204.0478; found 204.0479.

5-(2-Methoxyphenyl)thiazole (6d)
Prepared by following the general procedure II using 2-iodoanisole as the aryl halide.

CC (20−40% EtOAc in heptane) gave 129 mg (67%) of **6d** as a yellow oil; R_f 0.25 (30% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 3.88 (s, 3 H), 7.00−7.06 (m, 2 H), 7.32 (dt, 1 H, *J* = 1.6, 7.6 Hz), 7.66 (dd, 1 H, *J* = 1.6, 7.6 Hz), 8.29 (s, 1 H, H-4), 8.81 (s, 1 H, H-2)

^{13}C NMR ($CDCl_3$): δ = 54.9, 110.8, 119.4, 120.4, 128.0, 128.7, 133.3, 140.2, 152.1, 154.7.

Anal. calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found C, 62.89; H, 4.52; N, 7.14.

5-(1-Naphthyl)thiazole (6e)
Prepared by following the general procedure II using 1-bromonaphthalene as the aryl halide.

CC (10−30% EtOAc in heptane) gave 175 mg (83%) of **6e** as an oil; R_f 0.10 (20% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.53−7.57 (m, 4 H), 7.91−7.93 (m, 2 H), 8.03 (d, 1 H, *J* = 0.8 Hz, H-4), 8.06−8.08 (m, 1 H), 8.94 (d, 1 H, *J* = 0.8 Hz, H-2).

^{13}C NMR ($CDCl_3$): δ = 125.4, 125.5, 126.6, 127.2, 128.5, 128.7, 129.1, 129.6, 132.2, 134.0, 136.5, 142.6, 153.5.

Anal. calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63. Found C, 73.55; H, 4.34; N, 6.58.

5-(2-Pyridyl)thiazole (6f)
Prepared by following the general procedure II using 2-bromopyridine as the heteroaryl halide.

CC (20−50% EtOAc in heptane) gave 111 mg (68%) of **6f** as a yellow oil. (Lit.[41] mp 63−64 °C); R_f 0.20 (50% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.18−7.21 (m, 1 H, H-5'), 7.65−7.74 (m, 2 H, H-3' and H-4'), 8.32 (s, 1 H, H-4), 8.57−8.59 (m, 1 H, H-6'), 8.82 (s, 1 H, H-2).

^{13}C NMR ($CDCl_3$): δ = 121.0, 123.9, 138.0, 141.4, 141.6, 151.1, 151.5, 155.7.

HRMS: *m*/*z* calcd 163.0324; found 163.0325.

5-(2-Thienyl)thiazole (6g)
Prepared by following the general procedure II using 2-bromothiophene as the aryl halide.

CC (10−30% EtOAc in heptane) gave 81 mg (48%) of **6g** as a yellow oil. An analytically pure sample of **6g** was obtained by preparative HPLC; R_f 0.20 (20% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.07 (dd, 1 H, *J* = 3.6, 4.8 Hz), 7.22 (dd, 1 H, *J* = 3.6, 1.2 Hz), 7.32 (dd, 1 H, *J* = 1.2, 4.8 Hz), 7.98 (s, 1 H, H-4), 8.72 (s, 1 H, H-2).

^{13}C NMR ($CDCl_3$): δ = 125.1, 125.3, 126.5, 131.9, 132.1, 138.6, 150.8.

Anal. calcd for $C_7H_5NS_2$: C, 50.27; H, 3.01; N, 8.38. Found C, 50.03; H, 2.79; N, 8.31.

5-(4-[1-Benzyloxypyrazolyl])thiazole (6h)
Prepared by following the general procedure II using 1-(benzyloxy)-4-iodopyrazole[37] as the heteroaryl halide.

CC (30−40% EtOAc in heptane) gave 150 mg (58%) of **6h** as yellow crystals. An analytically pure sample of **6h** was obtained by preparative HPLC; mp 39−40 °C; R_f 0.30 (50% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 5.32 (s, 2 H), 7.20 (d, 1 H, *J* = 1.2 Hz), 7.32−7.40 (m, 5 H), 7.47 (d, 1 H, *J* = 1.2 Hz), 7.79 (s, 1 H, H-4), 8.66 (s, 1 H, H-2).

^{13}C NMR ($CDCl_3$): δ = 80.8, 109.3, 119.8, 127.8, 128.5, 128.8, 130.6, 132.4, 137.6, 149.9.

Anal. calcd for $C_{13}H_{11}N_3OS$: C, 60.82; H, 4.32; N, 16.37. Found C, 60.36; H, 4.08; N, 16.05.

5-(5-Indolyl)thiazole (6i)
Prepared by following the general procedure II using 5-bromoindole as the heteroaryl halide.

CC (20−40% EtOAc in heptane) gave 52 mg (26%) of **6i** as pale yellow crystals; mp 184−185 °C (heptane/EtOAc); R_f 0.25 (50% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 6.60−6.61 (m, 1 H), 7.26−7.28 (m, 1 H), 7.43−7.44 (m, 2 H), 7.86 (s, 1 H, H-4), 8.06 (s, 1 H), 8.34 (br s, 1 H), 8.73 (1 H, s, H-2)

^{13}C NMR ($CDCl_3$): δ = 103.3, 111.9, 119.8, 121.8, 123.1, 125.7, 128.6, 136.0, 138.0, 141.3, 151.3.

Anal. calcd for $C_{11}H_8N_2S$: C, 65.97; H, 4.03; N, 13.99. Found C, 65.43; H, 4.11; N, 13.60.

5-(4-Methylphenyl)-2-(1-naphthyl)thiazole (8a)
The general procedure II using **3g** (211 mg, 1 mmol) (instead of 2-TST (**4**)) and 4-iodotoluene as the aryl halide was followed.

CC (0−15% EtOAc in heptane) gave 239 mg (79%) of **8a** as yellow crystals; mp 118−119 °C (heptane/EtOAc); R_f 0.20 (10% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 7.29 (d, 2 H, *J* = 8 Hz), 7.51−7.57 (m, 3 H), 7.60−6.62 (m, 1 H), 7.90−7.95 (m, 2 H), 7.91 (d, 2 H, *J* = 8 Hz), 7.95 (s, 1 H, H-4), 8.20−8.22 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 21.1, 124.9, 125.7, 126.2, 126.5, 127.2, 128.2, 129.3, 129.6, 130.2, 130.3, 130.6, 133.8, 138.2, 138.4, 139.9, 165.9.

Anal. calcd for $C_{20}H_{15}NS$: C, 79.70; H, 5.02; N, 4.65. Found C, 79.68; H, 4.99; N, 4.64.

5-(4-Aminophenyl)-2-(1-naphthyl)thiazole (8b)
The general procedure II using **3g** (211 mg, 1 mmol) (instead of 2-TST (**4**)) and 4-iodoaniline as the aryl halide was followed.

CC (40−50% EtOAc in heptane) gave 116 mg (38%) of **8b** as yellow crystals; mp 124−125 °C (heptane/EtOAc); R_f 0.30 (50% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 3.84 (br s, 2 H, NH_2), 6.72−6.76 (m, 2 H), 7.44−7.48 (m, 2 H), 7.51−7.62 (m, 3 H), 7.83−7.94 (m, 3 H), 8.04 (s, 1 H, H-4), 8.87−8.89 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 115.2, 121.4, 124.9, 125.8, 126.2, 127.1, 127.9, 128.2, 130.0, 130.4, 130.9, 133.9, 137.2, 140.5, 146.6, 164.7.

Anal. calcd for $C_{19}H_{14}N_2S$: C, 75.47; H, 4.67; N, 9.26. Found C, 75.29; H, 4.69; N, 9.16.

2-Bromo-5-(1-naphthyl)thiazole (9a)
The general procedure II was followed using 2-TST (**4**; 0.63 mL, 4 mmol) and 1-bromonaphthalene (6 mmol) as the aryl halide. After cross-coupling for 24 h at reflux, the mixture was cooled to r.t. and Br_2 (0.205 mL, 4 mmol) was added and stirring was continued for 48 h. The mixture was quenched with a 1 M aq solution of Na_2SO_3 (10 mL) and worked up as described in general procedure II.

CC (0−10% EtOAc in heptane) gave 563 mg (48%) of **9a**; mp 61−62 °C (heptane/EtOAc). Compound **9a** was used in the next step without further purification; R_f 0.45 (20% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.49−7.56 (m, 4 H), 7.67 (s, 1 H, H-4), 7.90−7.93 (m, 2 H), 8.05−8.08 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 125.1, 125.4, 126.7, 127.4, 127.5, 128.8, 129.1, 130.1, 132.0, 134.0, 136.0, 140.6, 141.7.

2-Iodo-5-(1-naphthyl)thiazole (9b)
The procedure described for preparation of **9a** was followed using iodine monochloride (0.65 g, 4 mmol) instead of bromine.

CC (0−10% EtOAc in heptane) gave 0.84 g (62%) of **9b** as a yellow oil; R_f 0.25 (20% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 7.50−7-56 (m, 4 H), 7.70 (s, 1 H, H-4), 7.90−7.94 (m, 2 H), 8.03−8.05 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 100.5, 124.9, 125.2, 126.4, 127.1, 127.3, 128.6, 128.8, 129.8, 131.7, 133.7, 142.8, 143.5.

HRMS: *m*/*z* calcd 337.9495; found 337.9492.

2-(4-Methylphenyl)-5-(1-naphthyl)thiazole (10)
The general procedure I using **9a** (290 mg, 1 mmol) (instead of 2-bromothiazole (**1**)) and 4-iodotoluene as the aryl halide with the exception of performing the oxidative insertion of zinc for 24 h at r.t.

CC (10−40% EtOAc in heptane) followed by preparative HPLC gave 66 mg (22%) of **10** as crystals; mp 75−76 °C; R_f 0.45 (20% EtOAc in heptane).

^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H), 7.28−7.30 (m, 2 H), 7.50−7.56 (m, 3 H), 7.56−7.62 (m, 1H), 7.89−7.93 (m, 4 H); 7.94 (s, 1 H, H-4), 8.18−8.22 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 21.8, 125.5, 125.5, 126.5, 126.6, 127.1, 128.7, 128.8, 128.9, 129.5, 130.0, 131.0, 132.1, 134.0, 136.1, 140.8, 142.4, 169.0.

HRMS: *m*/*z* calcd 302.0998; found 302.0985.

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