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First Palladium-Catalyzed Direct Regioselective C-5 (Het)Arylation of Mono- or Disubstituted Thiazolo[3,2-*b*][1,2,4]triazoles

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Keywords: C–H activation / Regioselectivity / Nitrogen heterocycles / Sulfur heterocycles / Palladium

An efficient and convenient method was developed for the formation of polysubstituted thiazolo[3,2-*b*][1,2,4]triazoles through C-5 (het)arylation. The direct C–H activation protocol giving access to di- and trisubstituted derivatives in excellent yields was optimized. The method is suitable for use with a wide range of (hetero)aryl bromides, and allows access to a collection of C-5,6 bis(het)aryl derivatives with full regioselectivity. The results are supported by a full description of all final compounds, and X-ray crystallographic data confirmed that the spectroscopic analyses were interpreted correctly.

Introduction

Innovation in the design, synthesis, and production of original molecules that have value as human therapeutic agents remains one of the major objectives of organic and medicinal chemistry programs. During the past decades, research in heterocyclic chemistry has provided access to libraries based on the exploration of chemical space and the creation of privileged and rare heterocyclic structures.[1] Considerable effort has been devoted to developing new methodologies that can be used to furnish molecular innovation in newly built collections.

Lately, the fusion of two heterocycles containing five atoms has attracted much attention. Systems containing both nitrogen and sulfur atoms in the same cycle showed remarkable properties and have proved to be suitable for the development of functional organic materials as well as pharmaceutically important molecules.[2]

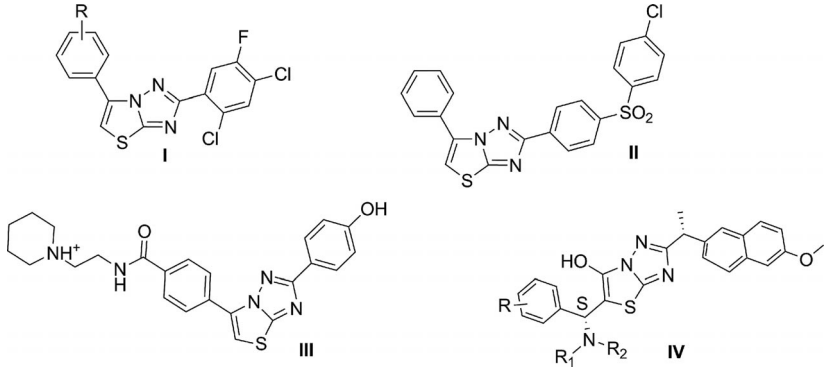

Figure 1. Examples of thiazolo[3,2-*b*][1,2,4]triazoles with biological and medicinal activities.

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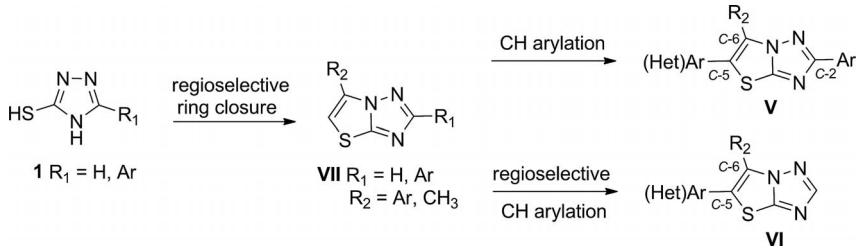
In connection with an ongoing project based on the development of efficient methodologies to generate original collections of small nitrogen-containing heterocycles,[3] we turned our attention to thiazolo[3,2-*b*][1,2,4]triazole. This highly attractive unit has seldom been described, despite the fact that some of its representatives have shown versatile biological activities (Figure 1).[4–8] The thiazolo[3,2-*b*]-[1,2,4]triazole core is found in structures possessing antimi-



Scheme 1. Optimization of the C–H arylation.

crobial **I**,[4] antibacterial **II**,[5] G-quadruplex stabilizing **III**,[6] and anti-inflammatory **IV**[7,8] activities.

We considered that it would be of great interest to develop a versatile method based on the building of thiazolo[3,2-*b*][1,2,4]triazole derivatives that could take advantage of novel C–H arylation instead of the commonly used but laborious method that only assembles intermediates possessing the desired substituents in advance.

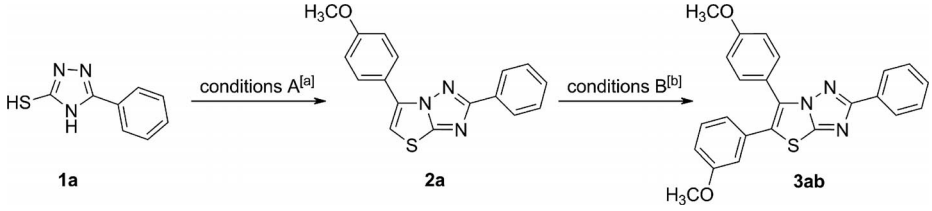
Transition-metal-catalyzed functionalization has always been an attractive alternative and a greener method than other catalyzed reactions because it avoids the preliminary preparation of the requisite organometallic and/or halogenated arenes.[9] As a result, the number of steps, the amount of waste, the amount of solvent, and the reaction time are all usually reduced. We therefore developed a versatile strategy with which to assess the feasibility of C-5 (het)arylation in the thiazolo[3,2-*b*][1,2,4]triazoles series. In particular, our method was designed to allow the construction of C-2,5,6 (**V**), and C-5,6 (**VI**) tri- and disubstituted collections from C-2,6 and C-6 derivatives **VII** including quantitative regioselectivity in the latter case (Scheme 1).

Results and Discussion

Although a survey of the literature indicated that C-5 arylation is efficient when using aryl iodides and copper catalysis,[10] in our hands, this copper-catalyzed reaction was unsuccessful using **2a** (Table 1, entry 1) and 4-bromoanisole. In similar work to ours, the arylation of some C-2,6 disubstituted thiazolotriazoles under ligandless palladium catalysis and microwave irradiation was reported.[11] However, the method, involving Cs_2CO_3 as base, appeared to be compatible only with activated bromobenzene derivatives and no mention was made of any selective reactions. Indeed, under the conditions developed by Tian et al., starting from **2e** and 4-bromoanisole, only starting material with traces of the desired compound was recovered.

These two interesting reports prompted us to investigate an alternative sequence. We began our study with a reaction model involving **2a**, which was obtained in 81% yield by using commercially available 3-phenyl-1*H*-1,2,4-triazole-5-thiol (**1a**) and 4-methoxyphenacyl bromide in a hydrochloric acid solution. As reported in Table 1, several condi-

Table 1. Optimization of direct Pd-catalyzed arylation.



Entry	Catalyst	Ligand	Base	Solvent	Yield [%][c]
1	$Cu(acac)_2$	–	*t*BuOLi	DMF/xylene	–[e]
2	CuI	–	*t*BuOLi	DMF	–[e]
3	$Pd(OAc)_2$	–	KOAc	DMA	–[e]
4	$Pd(PPh_3)_4$	–	Cs_2CO_3	1,4-dioxane	32
5	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	K_2CO_3	DMA	57[d]
6	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	K_2CO_3	1,4-dioxane	90
7	$Pd(OAc)_2$	PCy_3	K_2CO_3	1,4-dioxane	83
8	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	1,4-dioxane	98
9	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	1,4-dioxane	83
10	$Pd(OAc)_2$	$P(tBu)_3{\cdot}HBF_4$	Cs_2CO_3	1,4-dioxane	89

[a] Reaction conditions A: (i) 4-methoxyphenacyl bromide, aq. HCl (37% w/w), EtOH, reflux, 15 h; (ii) satd. aq. Na_2CO_3, room temp. [b] Reaction conditions B: sealed vial, **2a** (0.33 mmol, 1.0 equiv.), 4-bromoanisole (1.5 equiv.), catalyst (10 mol-%), ligand (20 mol-%), base (2.0 equiv.), solvent (2 mL), 130 °C, 15 h. [c] Yield of isolated product. [d] Addition of PivOH (30 mol-%) required. [e] Starting material was fully recovered.

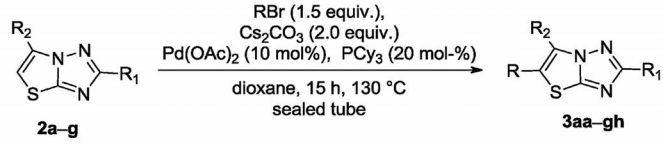
tions were tried before a suitable and near quantitative method to obtain **3ab** was achieved.

Some previously published copper and palladium conditions were first evaluated, but no conversion was observed in our case.[12–14] A small amount of product was observed using $Pd(PPh_3)_4$ and Cs_2CO_3 in dioxane, whereas a significant increase in yield was observed by using $Pd(OAc)_2/PCy_3$ or $PtBu_3{\cdot}HBF_4$ as the catalytic system and K_2CO_3 as base. Dioxane proved to be better than DMA (entries 5 and 6) as solvent. Switching the base to Cs_2CO_3 led to optimal conditions (entry 8), and full conversion and a near quantitative yield were obtained. Further changes to solvent and carbonate source led to less efficient reactions. With half the amount of catalyst, compound **3ab** was isolated in only 81% yield. Changing the heating mode to microwave irradiation did not afford any benefit.

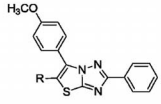
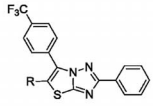
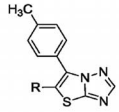
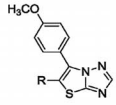
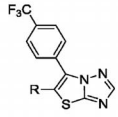
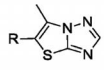
Thiazolotriazoles **2b**–**g** were developed by following the same procedure as that described for **2a**. C–H arylation was next carried out between various brominated (het)aryls and each prebuilt thiazolotriazole derivative (Table 2).

Irrespective of the starting material used, i.e., C-2,6 or C-6 substituted derivatives **2a**–**g**, the catalytic C–H (het) arylation smoothly afforded products **3aa**–**gh**. Complete conversion as judged by TLC analysis was reached before stopping the reaction, and ^1H NMR analysis of the crude material showed only one single product formed, without degradation. Steric enhancement (exemplified by C–H arylation from derivatives of type **2** and 2-methoxybromobenzene) did not affect the yield of the reactions. Substrates with either electron-donating (Me, OMe) or electron-withdrawing (CF_3, CO_2Me) groups on the bromo aryl groups were broadly applicable for direct arylation. The only case

Table 2. C-5 C–H arylation leading to derivatives of type **V** and **VI**.



2a–g → **3aa–gh**

Entry	Starting material	Type **3** products		Yield[a]
1	**2a** $R_1 = C_6H_5$, R_2 = 4-$MeOC_6H_4$		**3aa** R = 2-$MeOC_6H_4$	89%
			3ab R = 3-$MeOC_6H_4$	98%
			3ac R = 4-$MeOC_6H_4$	93%
			3ad R = 4-$CF_3C_6H_4$	82%
			3ae R = 5-pyrimidinyl	88%
2	**2b**[c] $R_1 = C_6H_5$ R_2 = 4-$CF_3C_6H_4$		**3ba** R = 3-$MeOC_6H_4$	84%
			3bb R = 4-$CF_3C_6H_4$	92%
			3bc R = 5-pyrimidinyl	94%
3	**2c**[c] R_1 = H $R_2 = C_6H_5$		**3ca** R = 3-$MeOC_6H_4$	92%
			3cb R = 4-$CF_3C_6H_4$	82%
			3cc R = 5-pyrimidinyl	90%
4	**2d**[c] R_1 = H R_2 = 4-$CH_3C_6H_4$		**3da** R = 3-$MeOC_6H_4$	96%
			3db R = 4-$CF_3C_6H_4$	75%[b]
			3dc R = 5-pyrimidinyl	87%
5	**2e**[c] R_1 = H R_2 = 4-$MeOC_6H_4$		**3ea** R = 2-$MeOC_6H_4$	80%
			3eb R = 3-$MeOC_6H_4$	87%
			3ec R = 4- $MeOC_6H_4$	53%[b]
			3ed R = 4-$CF_3C_6H_4$	89%
			3ee R = 5-pyrimidinyl	92%
6	**2f**[c] R_1 = H R_2 = 4-$CF_3C_6H_4$		**3fa** R = 3-$MeOC_6H_4$	86%
			3fb R = 4-$CF_3C_6H_4$	75%[b]
			3fc R = 5-pyrimidinyl	89%
7	**2g**[c] R_1 = H $R_2 = CH_3$		**3ga** R = 2-$MeOC_6H_4$	88%
			3gb R = 3-$MeOC_6H_4$	96%
			3gc R = 4-$MeOC_6H_4$	67%
			3gd R = 4-$CF_3C_6H_4$	84%[b]
			3ge R = 5-pyrimidinyl	95%
			3gf R = 4-pyridinyl	81%[b]
			4gg R = 4-MeC_6H_4	76%
			3gh R = 4-$MeO_2CC_6H_4$	99%[b]

[a] Yield of isolated product. [b] Reaction performed at 160 °C. [c] Compounds **2b**–**g** were prepared as described for **2a** from the corresponding 1,2,4-triazole-5-thiols of type **1** in yields of 76 (**2b**), 62 (**2c**), 61 (**2d**), 77 (**2e**), 58 (**2f**), and 71% (**2g**).

in which we were unable to obtain full conversion, starting from substrate **2e** and 4-bromoanisole, was compound **3ec**. In this case, no improvement was observed by increasing the reaction time or the reaction temperature.

Activated as well as deactivated (het)aryl bromide derivatives can now be used in C-5 arylation without discrimination. Moreover, reactions with thiazolotriazoles free of C-2 substituents lead to a fully regioselective C–H (het)arylation at C-5 (entries 3–7).

X-ray analysis of crystals of **3ee** formally confirmed that the spectroscopic analyses were interpreted correctly, particularly with respect to the regioselectivity of the C–H activation in C-5 vs. C-2. As clearly shown in Figure 2, the three (het)aryl groups are not coplanar. Thiazolotriazole forms a 72.4° angle with the pyrimidine in C-5 and a dihedral angle of 23.9° with methoxybenzyl in C-6. Two hydrogen bonds were also identified. The first being an intramolecular H bond between N-1 and the hydrogen of C-20, whereas the second is an intermolecular H bond between the N-1 and the hydrogen of C-2 from a homologous molecule with the following symmetry code: x, 1/2 – y, 1/2 + z.

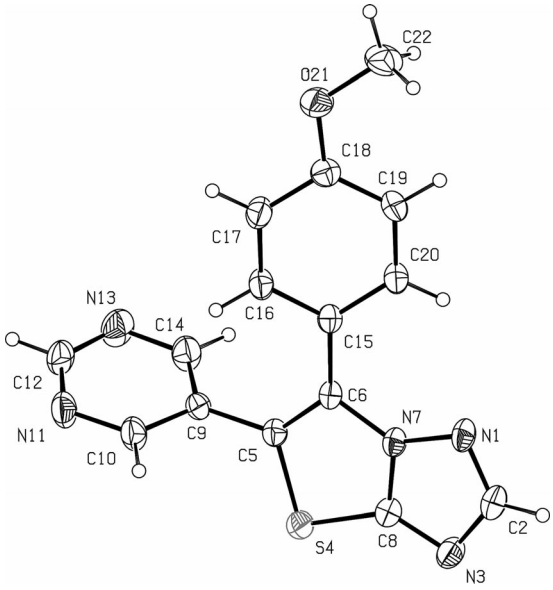
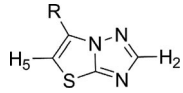


Figure 2. ORTEP representation of **3ee**.

To understand why (het)arylation takes place only in the C-5 position (vs. C-2), pKa calculations were run using the Jaguar software from Schrodinger (Table 3; for details see the Supporting Information). A large pKa difference between the H-2 and H-5 hydrogen atoms was observed. The pKa of H-2 was always around 36 and does not seem be affected by the nature of the C-3 substituent. This acidity is higher (ca. 8 units) than that observed at the H-5 position, which confirms our experimental observations and the sensitivity to basic conditions.

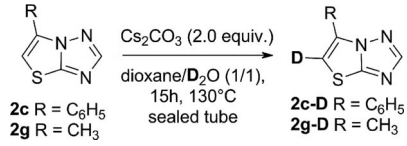
The large difference in acidity between the two hydrogen atoms H-2 and H-5 prompted us to investigate the reaction mechanism of the previously optimized Pd-catalyzed direct arylation reaction and its regioselectivity. Deuterium-incorporation experiments were carried out starting from **2c** and **2g** in the presence of Cs_2CO_3 (Scheme 2). Under these conditions, the C-5 proton exchanged exclusively. Deuterated derivatives were isolated in quantitative yields after one hour of reaction in a sealed tube.

Table 3. Calculation of pK_a for hydrogen atoms H-2 and H-5.



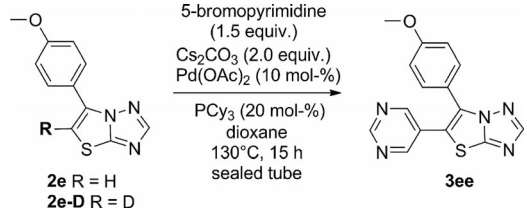
Entry	Product	R	H-2 pKa[a]	H-5 pKa[a]
1	**2c**	Ph	36.8	28.3
2	**2d**	4-MeC_6H_4	37	28.7
3	**2e**	4-MeOC_6H_4	37.2	29.2
4	**2f**	4-$CF_3C_6H_4$	36.2	26.7
5	**2g**	CH_3	36.3	28.7

[a] pKa predicted by using the B3LYP/6-31G** level of theory within Jaguar.



Scheme 2. Deuterium incorporation; each reaction was quantitative.

Additionally, the kinetic isotope effect (KIE) with both non-deuterated **2e** and its deuterated analogue **2e**-D was determined with 5-bromopyrimidine to form **3ee** (Scheme 3). The k_H/k_D ratio for the C-H/C-D bond activations was found to be around 1, because the two reactions reached completion in the same time. This indicates that the palladium(II)-catalyzed C–H bond cleavage did not occur in the rate-determining step.[15] Consequently, several mechanistic scenarios remain possible.[16]



Scheme 3. Determination of KIE of regioselective C–H arylation.

Conclusions

We have developed a novel and efficient direct C–H activation protocol that gives access to di- and trisubstituted thiazolo[3,2-*b*][1,2,4]triazoles based on a palladium-metal catalyst. Excellent yields were obtained with a wide range of (hetero)aryl halides with either electron-withdrawing or electron-rich substituents. The method was used to generate a collection of C-5,6 bis(het)aryl with full regioselectivity. Further investigations involving the orchestration of such

palladium-catalyzed cross-coupling reactions with the additional aim of preparing focused libraries of biologically active compounds are in progress in our laboratory.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DPX 250 MHz or 400 MHz instrument using $CDCl_3$ or [D_6]DMSO; chemical shifts are reported in parts per million (δ scale) and all coupling constant (J) values are in Hertz [Hz]. The following abbreviations are used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet) and ddd (double double doublet). Melting points are uncorrected. IR absorption spectra were obtained with a Perkin–Elmer Paragon 1000 PC and values are reported in cm^{-1}. HRMS were recorded with a Bruker maXis mass spectrometer. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F254). Spots were visualized by UV light at 254 and 356 nm. Column chromatography was performed using silica gel 60 (0.063–0.200 mm, Merck). Reactions requiring anhydrous conditions were performed under argon. All solvents were freshly distilled under argon prior to use. Chemicals were purchased from Aldrich and Acros organics as commercial sources. Microwave irradiations were carried out in sealed 2–5 mL vessels placed in a Biotage Initiator system using a standard absorbance level (300 W maximum power). The temperatures were externally measured by an IR probe that determined the temperature on the surface of the vial and could be read directly from the instrument. The reaction time was measured from when the reaction mixture reached the stated temperature for temperature-controlled experiments. Pressure was measured by a noninvasive sensor integrated into the cavity lid.

6-(4-Methoxyphenyl)-2-phenylthiazolo[3,2-*b*][1,2,4]triazole (2a): A mixture of 5-phenyl-1*H*-1,2,4-triazole-3-thiol (1.0 g, 5.64 mmol, 1.0 equiv.), 4-methoxyphenacyl bromide (1.42 g, 6.21 mmol, 1.1 equiv.), EtOH (50 mL) and aqueous concentrated HCl solution (37%, 2 mL) was heated at reflux for 15 h. The mixture was then cooled to room temperature, and volatiles were evaporated under reduced pressure. An aqueous saturated solution of sodium carbonate (20 mL) was added to the residue. After extraction with CH_2Cl_2 (3× 30 mL), the combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting solid was washed with Et_2O (2× 20 mL) to afford **2a** (1.40 g, 81%), which was fully characterized without any further purification, m.p. 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 6.9 Hz, 2 H), 8.14 (d, J = 8.8 Hz, 2 H), 7.46 (m, 3 H), 7.07 (d, J = 8.8 Hz, 2 H), 6.96 (s, 1 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.9 (C_q), 160.7 (C_q), 157.7 (C_q), 133.0 (C_q), 131.3 (C_q), 129.6 (CH_{Ar}), 128.6 ($2CH_{Ar}$), 128.2 ($2CH_{Ar}$), 126.8 ($2CH_{Ar}$), 120.7 (C_q), 114.4 ($2CH_{Ar}$), 105.6 (CH_{Ar}), 55.4 (CH_3) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3065, 1608, 1505, 1440, 1324, 1273, 1182, 1114, 813, 722 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{17}H_{14}N_3OS$ $[M + H]^+$ 308.085210; found 308.085393.

2-Phenyl-6-[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*][1,2,4]triazole (2b): A mixture of 5-phenyl-1*H*-1,2,4-triazole-3-thiol (2.0 g, 11.28 mmol, 1.0 equiv.) and 4-(trifluoromethyl)phenacyl bromide (1.42 g, 12.41 mmol, 1.1 equiv.) in EtOH (50 mL) was heated to reflux for 3 h. The resulting suspension was filtered and washed successively with EtOH (2× 10 mL) and Et_2O (2× 10 mL). The resulting solid was then added to concentrated sulfuric acid solution (10 mL) at 0 °C and stirred for 1 h. The temperature was allowed to rise to room temperature. After full conversion, a saturated solution of sodium carbonate was slowly added until pH 7. The resulting solution was extracted with EtOAc (2× 50 mL) and the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting precipitate was washed with Et_2O (2× 10 mL) to afford **2b** (2.98 g, 76%) as a white solid. The product was fully characterized without any further purification due to its high insolubility; only a 135DEPT was furnished, m.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, J = 8.2 Hz, 2 H), 8.24 (d, J = 8.2 Hz, 2 H), 7.81 (d, J = 8.2 Hz, 2 H), 7.52–7.40 (m, 3 H), 7.23 (s, 1 H) ppm. 135 DEPT ^{13}C NMR (101 MHz, $CDCl_3$): δ = 129.9 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 126.8 ($2CH_{Ar}$), 126.8 ($2CH_{Ar}$), 126.0 (q, J = 3.9 Hz, CH_{Ar}), 109.5 (CH_{Ar}) ppm. IR (neat): $\tilde{\nu}$ = 3122, 1470, 1443, 1323, 1167, 1069, 1017, 848, 707, 692 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{17}H_{11}F_3N_3S$ $[M + H]^+$ 346.062029; found 346.062351.

6-Phenylthiazolo[3,2-*b*][1,2,4]triazole (2c): A mixture of 1*H*-1,2,4-triazole-3-thiol (2.0 g, 19.80 mmol, 1.0 equiv.) and phenacyl bromide (4.33 g, 21.78 mmol, 1.1 equiv.) in EtOH (200 mL) was heated to reflux for 15 h. The solution was then cooled to room temperature and evaporated under reduced pressure. The solid was then added to concentrated sulfuric acid solution (10 mL) at 0 °C and stirred for 3 h at room temperature. After full conversion, a saturated solution of sodium carbonate was slowly added until pH 7. The resulting solution was extracted with EtOAc (2× 50 mL) and the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (EtOAc/petroleum ether, 1:3) to afford **2c** (2.47 g, 62%) as a white solid, m.p. 88–90 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.26 (d, J = 1.4 Hz, 1 H), 8.11 (d, J = 8.3 Hz, 2 H), 7.60–7.46 (m, 3 H), 7.16 (d, J = 1.4 Hz, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 158.6 (C_q), 157.5 (CH_{Ar}), 134.6 (C_q), 131.3 (CH_{Ar}), 130.4 ($2CH_{Ar}$), 129.4 (C_q), 128.1 ($2CH_{Ar}$), 109.9 (CH_{Ar}) ppm. IR (neat): $\tilde{\nu}$ = 3117, 1473, 1447, 1402, 1237, 1189, 1172, 740, 689, 641 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{10}H_8N_3S$ $[M + H]^+$ 202.043345; found 202.043394.

6-(*p*-Tolyl)thiazolo[3,2-*b*][1,2,4]triazole (2d): A mixture of 1*H*-1,2,4-triazole-3-thiol (2.0 g, 19.80 mmol, 1.0 equiv.), *p*-tolylphenacyl bromide (4.64 g, 21.78 mmol, 1.1 equiv.), EtOH (200 mL), and concentrated HCl (37%, 8 mL) was heated to reflux for 72 h. The solution was then cooled to room temperature, and evaporated under reduced pressure. A saturated solution of sodium carbonate was slowly added until pH 7. The resulting solution was extracted with EtOAc (2× 50 mL) and the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (EtOAc/petroleum ether, 1:3) to afford **2d** (2.6 g, 61%) as a white solid, m.p. 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.97 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.07 (s, 1 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.1 (C_q), 156.0 (CH_{Ar}), 140.1 (C_q), 133.3 (C_q), 129.7 ($2CH_{Ar}$), 126.5 ($2CH_{Ar}$), 125.2 (C_q), 107.6 (CH_{Ar}), 21.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3109, 1475, 1248, 1180, 1018, 856, 821, 732, 690, 644 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{11}H_{10}N_3S$ $[M + H]^+$ 216.058995; found 216.059289.

6-(4-Methoxyphenyl)thiazolo[3,2-*b*][1,2,4]triazole (2e): A mixture of 1*H*-1,2,4-triazole-3-thiol (2.0 g, 19.80 mmol, 1.0 equiv.), 4-methoxyphenacyl bromide (4.99 g, 21.78 mmol, 1.1 equiv.), EtOH (200 mL), and concentrated HCl (37%, 8 mL) was heated to reflux for 72 h. The mixture was then cooled to room temperature, and evaporated under reduced pressure. A saturated solution of sodium carbonate was slowly added until pH 7. The resulting solution was

extracted with EtOAc (2× 50 mL) and the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (EtOAc/petroleum ether, 1:1) to afford **2c** (3.52 g, 77%) as a white solid, m.p. 132–134 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.42 (s, 1 H), 8.16 (d, J = 9.0 Hz, 2 H), 7.80 (s, 1 H), 7.12 (d, J = 9.0 Hz, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.6 (C_q), 157.1 (C_q), 156.5 (CH_{Ar}), 131.9 (C_q), 128.3 ($2CH_{Ar}$), 120.7 (C_q), 114.8 ($2CH_{Ar}$), 109.2 (CH_{Ar}), 55.8 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 3106, 1609, 1507, 1474, 1295, 1184, 1020, 831, 732, 691 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{11}H_{10}N_3OS$ [M + H]$^+$ 232.053909; found 232.054069.

6-[4-(Trifluoromethyl)phenyl]thiazolo[3,2-*b*][1,2,4]triazole (2f): A mixture of 1*H*-1,2,4-triazole-3-thiol (2.0 g, 19.8 mmol, 1.0 equiv.) and 4-(trifluoromethyl)phenacyl bromide (5.81 g, 21.78 mmol, 1.1 equiv.) in EtOH (200 mL) was hated to reflux for 15 h. The solution was then cooled to room temperature, and evaporated under reduced pressure. The solid was then added to concentrated sulfuric acid solution at 0 °C and stirred for 3 h at room temperature. The temperature was allowed to rise to room temperature. After full conversion, a saturated solution of sodium carbonate was slowly added until pH 7. The resulting solution was extracted with CH_2Cl_2 (2× 50 mL) and the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (CH_2Cl_2) to afford **2d** (3.09 g, 58%) as a white solid, m.p. 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 8.3 Hz, 2 H), 8.25 (s, 1 H), 7.78 (d, J = 8.3 Hz, 2 H), 7.27 (s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.2 (C_q), 156.2 (CH_{Ar}), 131.7 (C_q), 131.6 (q, J = 32.6 Hz, C_q), 131.1 (d, J = 32.6 Hz, C_q), 126.8 ($2CH_{Ar}$), 126.0 (q, J = 3.8 Hz, $2CH_{Ar}$), 123.8 (q, J = 272.4 Hz), 110.5 (CH_{Ar}) ppm. IR (neat): $\tilde{\nu}$ = 1470, 1319, 1248, 1178, 1113, 1015, 849, 767, 704, 642 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{11}H_7F_3N_3S$ [M + H]$^+$ 270.030729; found 270.031073.

6-Methylthiazolo[3,2-*b*][1,2,4]triazole (2g): 3-Mercapto-1,2,4-triazole (**1b**, 2.0 g, 19.80 mmol, 1.0 equiv.) was dissolved in EtOH (50 mL) and chloroacetone (2.19 g, 23.8 mmol, 1.2 equiv.) was added dropwise. The mixture was heated to reflux for 3 h. After evaporation of solvent under reduced pressure, a saturated solution of sodium carbonate was added to the mixture until pH 7. The resulting solution was extracted with EtOAc (2× 50 mL) and the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained product **2g** (1.95 g, 71%), which was obtained as a white solid, was sufficiently pure to be fully characterized, m.p. 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 6.62 (s, 1 H), 2.55 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.3 (C_q), 156.1 (CH_{Ar}), 129.6 (C_q), 107.8 (CH_{Ar}), 12.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3077, 1472, 1407, 1351, 1241, 1172, 1138, 986, 810, 783 cm^{-1}. HRMS (ESI): m/z calcd. for $C_5H_6N_3S$ [M + H]$^+$ 140.027695; found 140.027864.

General Procedure A: A 2–5 mL vial containing a stirring bar was loaded with the desired thiazolo[3,2-*b*][1,2,4]triazole synthon (1.0 equiv.), (hetero)aryl bromide (1.5 equiv.), Cs_2CO_3 (2.0 equiv.), PCy_3 (20 mol-%), and $Pd(OAc)_2$ (10 mol-%) in 1,4-dioxane (2 mL). The tube was degassed for 10 min under argon, sealed, and then heated at 130 °C for 15 h. The resulting mixture was cooled to room temperature, 1,4-dioxane was removed under reduced pressure, and the residue was purified by flash chromatography to afford the desired product.

5-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-2-phenylthiazolo[3,2-*b*]-[1,2,4]triazole (3aa): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2a**, 100.0 mg, 0.325 mmol), palladium acetate (7.3 mg, 0.033 mmol), tricyclohexylphosphine (18.2 mg, 0.065 mmol), cesium carbonate (212.7 mg, 0.651 mmol), and 2-bromoanisole (91.3 mg, 0.488 mmol). Standard workup followed by flash chromatography (CH_2Cl_2) gave **3aa** (120 mg, 89%) as a white solid, m.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 6.7 Hz, 2 H), 7.63 (d, J = 8.8 Hz, 2 H), 7.27–7.48 (m, 5 H), 6.96–6.88 (m, 4 H), 3.83 (s, 3 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.8 (C_q), 160.2 (C_q), 157.3 (C_q), 156.2 (C_q), 132.4 (CH_{Ar}), 131.5 (C_q), 130.8 (CH_{Ar}), 130.5 ($2CH_{Ar}$), 129.4 (CH_{Ar}), 129.2 (C_q), 128.5 ($2CH_{Ar}$), 126.8 ($2CH_{Ar}$), 121.1 (C_q), 120.9 (CH_{Ar}, C_q), 120.2 (C_q), 113.9 ($2CH_{Ar}$), 111.5 (CH_{Ar}), 55.5 (OCH_3), 55.3 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 2935, 1638, 1246, 1164, 1021, 806, 717, 695 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{24}H_{20}N_3O_2S$ [M + H]$^+$ 414.120774; found 414.127340.

5-(3-Methoxyphenyl)-6-(4-methoxyphenyl)-2-phenylthiazolo[3,2-*b*]-[1,2,4]triazole (3ab): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2a**, 100.0 mg, 0.325 mmol), palladium acetate (7.3 mg, 0.033 mmol), tricyclohexylphosphine (18.2 mg, 0.065 mmol), cesium carbonate (212.7 mg, 0.651 mmol), and 3-bromoanisole (91.3 mg, 0.488 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/petroleum ether, 3:1) gave **3ab** (132 mg, 98%) as a white solid, m.p. 182–184 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.23 (d, J = 6.7 Hz, 2 H), 7.68 (d, J = 8.9 Hz, 2 H), 7.52–7.42 (m, 3 H), 7.23–7.29 (m, 1 H), 6.90–7.00 (m, 5 H), 3.90 (s, 3 H), 3.76 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.4 (C_q), 161.9 (C_q), 161.3 (C_q), 156.6 (C_q), 134.3 (C_q), 132.8 ($2CH_{Ar}$), 132.7 (C_q), 131.5 (CH_{Ar}), 131.0 (CH_{Ar}), 130.0 ($2CH_{Ar}$), 129.7 (C_q), 128.2 ($2CH_{Ar}$), 126.2 (C_q), 123.1 (CH_{Ar}), 121.5 (C_q), 116.1 (CH_{Ar}), 116.0 (CH_{Ar}), 115.6 ($2CH_{Ar}$), 56.8 (OCH_3), 56.7 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 1602, 1511, 1468, 1439, 1292, 1233, 1177, 1026, 778 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{24}H_{20}N_3O_2S$ [M + H]$^+$ 414.120774; found 414.127172.

5-(4-Methoxyphenyl)-6-(4-methoxyphenyl)-2-phenylthiazolo[3,2-*b*]-[1,2,4]triazole (3ac): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2a**, 100.0 mg, 0.325 mmol), palladium acetate (7.3 mg, 0.033 mmol), tricyclohexylphosphine (18.2 mg, 0.065 mmol), cesium carbonate (212.7 mg, 0.651 mmol), and 4-bromoanisole (91.3 mg, 0.488 mmol). Standard workup followed by flash chromatography (CH_2Cl_2) gave **3ac** (125 mg, 93%) as a white solid, m.p. 198–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 6.6 Hz, 2 H), 7.64 (d, J = 8.9 Hz, 2 H), 7.48–7.39 (m, 3 H), 7.30 (d, J = 8.8 Hz, 2 H), 6.96 (d, J = 8.9 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.8 (C_q), 160.4 (C_q), 160.0 (C_q), 155.0 (C_q), 131.3 (C_q), 131.2 ($2CH_{Ar}$), 130.6 ($2CH_{Ar}$), 129.5 (CH_{Ar}), 128.5 ($2CH_{Ar}$), 127.5 (C_q), 126.7 ($2CH_{Ar}$), 125.0 (C_q), 123.8 (C_q), 120.2 (C_q), 114.5 ($2CH_{Ar}$), 114.2 ($2CH_{Ar}$), 55.4 (OCH_3), 55.3 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 2963, 1505, 1441, 1294, 1267, 1174, 1023, 830, 786, 693 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{24}H_{20}N_3O_2S$ [M + H]$^+$ 414.120774; found 414.127241.

6-(4-Methoxyphenyl)-2-phenyl-5-[4-(trifluoromethyl)phenyl]thiazolo-[3,2-*b*][1,2,4]triazole (3ad): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2a**, 100.0 mg, 0.325 mmol), palladium acetate (7.3 mg, 0.033 mmol), tricyclohexylphosphine (18.2 mg, 0.065 mmol), cesium carbonate (212.7 mg, 0.651 mmol), and 1-bromo-4-(trifluoromethyl)benzene (109.8 mg, 0.488 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/petroleum ether, 3:1) gave **3ad** (120 mg, 82%) as a yellow solid, m.p. 204–206 °C. ^{1}H NMR (250 MHz,

$CDCl_3$): δ = 8.21–8.18 (m, 2 H), 7.63–7.59 (m, 4 H), 7.51–7.51 (m, 5 H), 6.98 (d, J = 8.8 Hz, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.8 (C_q), 162.3 (C_q), 156.7 (C_q), 136.9 (d, J = 1.6 Hz, C_q), 132.8 ($2CH_{Ar}$), 132.5 (C_q), 132.0 (d, J = 32.8 Hz, C_q), 131.2 (CH_{Ar}), 130.9 ($2CH_{Ar}$), 130.8 (C_q), 130.0 ($2CH_{Ar}$), 128.2 ($2CH_{Ar}$), 127.4 (q, J = 3.7 Hz, $2CH_{Ar}$), 123.0 (C_q), 122.6 (q, J = 227.4 Hz, C_q), 120.8 (C_q), 115.9 ($2CH_{Ar}$), 56.8 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 1611, 1471, 1441, 1323, 1251, 1167, 1068, 841, 781, 695 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{17}F_3N_3OS$ $[M + H]^+$ 452.103894; found 452.104055.

6-(4-Methoxyphenyl)-2-phenyl-5-(pyrimidin-5-yl)thiazolo[3,2-*b*]-[1,2,4]triazole (3ae): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2a**, 100.0 mg, 0.325 mmol), palladium acetate (7.3 mg, 0.033 mmol), tricyclohexylphosphine (18.2 mg, 0.065 mmol), cesium carbonate (212.7 mg, 0.651 mmol), and 5-bromopyrimidine (77.6 mg, 0.488 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/petroleum ether, 3:1) gave **3ae** (110 mg, 88%) as a white solid, m.p. 216–218 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 8.76 (s, 2 H), 8.22 (m, 2 H), 7.61 (d, J = 8.3 Hz, 2 H), 7.53–7.44 (m, 3 H), 7.04 (d, J = 8.3 Hz, 2 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.9 (C_q), 161.3 (C_q), 158.0 (CH_{Ar}), 156.4 ($2CH_{Ar}$), 155.4 (C_q), 131.3 ($2CH_{Ar}$), 130.8 ($2C_q$), 129.9 (CH_{Ar}), 128.6 ($2CH_{Ar}$), 127.1 (C_q), 126.9 ($2CH_{Ar}$), 118.5 (C_q), 116.8 (C_q), 114.9 ($2CH_{Ar}$), 55.4 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 1511, 1466, 1443, 1418, 1262, 1178, 1026, 810, 717, 695 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{16}N_5OS$ $[M + H]^+$ 386.107008; found 386.107116.

5-(3-Methoxyphenyl)-2-phenyl-6-[4-(trifluoromethyl)phenyl]thiazolo-[3,2-*b*][1,2,4]triazole (3ba): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2b**, 100.0 mg, 0.290 mmol), palladium acetate (6.5 mg, 0.029 mmol), tricyclohexylphosphine (16.2 mg, 0.058 mmol), cesium carbonate (188.7 mg, 0.580 mmol), and 3-bromoanisole (81.2 mg, 0.434 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/petroleum ether, 1:1) gave **3ba** (110 mg, 84%) as a white solid. Due to high insolubility, only a 135DEPT was obtained, m.p. 224–226 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.25–8.15 (m, 2 H), 7.87 (d, J = 8.2 Hz, 2 H), 7.70 (d, J = 8.2 Hz, 2 H), 7.54–7.39 (m, 3 H), 7.30 (t, J = 8.0 Hz, 1 H), 6.98–6.86 (m, 3 H), 3.74 (s, 3 H) ppm. 135 DEPT ^{13}C NMR (63 MHz, $CDCl_3$): δ = 130.4 (CH_{Ar}), 130.2 ($2CH_{Ar}$), 129.8 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 126.8 ($2CH_{Ar}$), 125.7 (q, J = 3.6 Hz, $2CH_{Ar}$), 121.8 (CH_{Ar}), 115.1 (CH_{Ar}), 114.9 (CH_{Ar}), 55.3 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 1596, 1472, 1322, 1298, 1121, 1020, 849, 784, 715, 692 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{17}F_3N_3OS$ $[M + H]^+$ 452.103894; found 452.103943.

2-Phenyl-5,6-bis[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*][1,2,4]triazole (3bb): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2b**, 100.0 mg, 0.290 mmol), palladium acetate (6.5 mg, 0.029 mmol), tricyclohexylphosphine (16.2 mg, 0.058 mmol), cesium carbonate (188.7 mg, 0.580 mmol), and 1-bromo-4-(trifluoromethyl)benzene (97.7 mg, 0.434 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/petroleum ether, 1:1) gave **3bb** (130 mg, 92%) as a white solid, m.p. 232–234 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.0 Hz, 2 H), 7.82 (d, J = 8.2 Hz, 2 H), 7.73 (d, J = 8.2 Hz, 2 H), 7.65 (d, J = 8.0 Hz, 2 H), 7.51–7.46 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6 (C_q), 155.4 (C_q), 134.5 (d, J = 1.7 Hz, C_q), 131.9 (q, J = 32.9 Hz, C_q), 131.4 (q, J = 33.1 Hz, C_q), 130.8 (d, J = 1.7 Hz, C_q), 130.7 (C_q), 130.3 ($2CH_{Ar}$), 130.0 (CH_{Ar}), 129.7 ($2CH_{Ar}$), 128.7 ($2CH_{Ar}$), 127.8 (C_q), 126.8 ($2CH_{Ar}$), 126.3 (q, J = 3.7 Hz, $2CH_{Ar}$), 126.0 (q, J = 3.7 Hz, $2CH_{Ar}$, C_q), 123.7 (q, J = 272.5 Hz, C_q), 123.6 (q, J = 272.4 Hz, C_q) ppm. IR (neat): $\tilde{\nu}$ = 1442, 1320, 1270, 1167, 1127, 1067, 1015, 844, 818, 696 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{14}F_6N_3S$ $[M + H]^+$ 490.080714; found 490.080617.

2-Phenyl-5-(pyrimidin-5-yl)-6-[4-(trifluoromethyl)phenyl]thiazolo-[3,2-*b*][1,2,4]triazole (3bc): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2b**, 100.0 mg, 0.290 mmol), palladium acetate (6.5 mg, 0.029 mmol), tricyclohexylphosphine (16.2 mg, 0.058 mmol), cesium carbonate (188.7 mg, 0.580 mmol), and 5-bromopyrimidine (69.1 mg, 0.434 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99.7:0.3) gave **3bc** (115 mg, 94%) as a white solid, m.p. 234–236 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.74 (s, 2 H), 8.21–8.15 (m, 2 H), 7.79 (2d, J = 8.4 Hz, 4 H), 7.52–7.41 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.1 (C_q), 158.7 (CH_{Ar}), 156.6 ($2CH_{Ar}$), 155.6 (C_q), 132.4 (q, J = 33.1 Hz, C_q), 130.5 (C_q), 130.2 ($2CH_{Ar}$), 130.2 (CH_{Ar}), 130.1 (d, J = 1.4 Hz, C_q), 129.2 (C_q), 128.7 ($2CH_{Ar}$), 126.9 ($2CH_{Ar}$), 126.4 (q, J = 3.6 Hz, $2CH_{Ar}$), 126.2 (C_q), 123.5 (q, J = 272.6 Hz, C_q), 119.6 (C_q) ppm. IR (neat): $\tilde{\nu}$ = 1444, 1320, 1270, 1185, 1108, 1066, 814, 716, 696, 628 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{13}F_3N_5S$ $[M + H]^+$ 424.083828; found 424.083990.

5-(3-Methoxyphenyl)-6-phenyl-thiazolo[3,2-*b*][1,2,4]triazole (3ca): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2c**, 100.0 mg, 0.497 mmol), palladium acetate (11.2 mg, 0.050 mmol), tricyclohexylphosphine (27.9 mg, 0.100 mmol), cesium carbonate (323.8 mg, 0.994 mmol), and 3-bromoanisole (139.4 mg, 0.745 mmol). Standard workup followed by flash chromatography (CH_2Cl_2) gave **3ca** (140 mg, 92%) as a white solid. M.p 74–76 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.64–7.60 (m, 2 H), 7.42 (m, 3 H), 7.24 (t, J = 7.8 Hz, 1 H), 6.94 (d, J = 7.8 Hz, 1 H), 6.90–6.85 (m, 2 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8 (C_q), 155.2 (CH_{Ar}), 154.5 (C_q), 132.4 (C_q), 130.2 (CH_{Ar}), 129.8 (CH_{Ar}), 129.8 ($2CH_{Ar}$), 128.8 ($2CH_{Ar}$), 128.3 (C_q), 127.8 (C_q), 127.1 (C_q), 121.6 (CH_{Ar}), 115.0 (CH_{Ar}), 114.6 (CH_{Ar}), 55.2 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 1602, 1568, 1406, 1354, 1288, 1153, 1050, 790, 706, 690 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{14}N_3OS$ $[M + H]^+$ 308.085210; found 308.085585.

6-Phenyl-5-[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*][1,2,4]triazole (3cb): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2c**, 100.0 mg, 0.497 mmol), palladium acetate (11.2 mg, 0.050 mmol), tricyclohexylphosphine (27.9 mg, 0.100 mmol), cesium carbonate (323.8 mg, 0.994 mmol), and 1-bromo-4-(trifluoromethyl)benzene (167.7 mg, 0.745 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99.5:0.5) gave **3cb** (140 mg, 82%) as a yellow solid, m.p. 150–152 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.61–7.58 (m, 4 H), 7.48–7.42 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.6 (CH_{Ar}), 154.6 (C_q), 134.9 (d, J = 1.4 Hz, C_q), 130.9 (q, J = 32.9 Hz, C_q), 130.2 (CH_{Ar}), 129.8 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 129.4 (C_q), 129.1 ($2CH_{Ar}$), 127.2 (C_q), 126.1 (q, J = 3.8 Hz, $2CH_{Ar}$), 125.3 (C_q), 123.7 (q, J = 272.3 Hz, C_q) ppm. IR (neat): $\tilde{\nu}$ = 2923, 1473, 1323, 1163, 1019, 847, 768, 705, 693 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{11}F_3N_3S$ $[M + H]^+$ 346.062029; found 346.062233.

6-Phenyl-5-pyrimidin-5-yl-thiazolo[3,2-*b*][1,2,4]triazole (3cc): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2c**, 100.0 mg, 0.497 mmol), palladium acetate (11.2 mg, 0.050 mmol), tricyclohexylphosphine (27.9 mg, 0.100 mmol), cesium carbonate (323.8 mg, 0.994 mmol), and 5-bromopyrimidine (118.5 mg, 0.745 mmol). Standard workup followed by flash chromatography (EtOAc/petroleum ether, 3:1) gave **3cc** (125 mg, 90%) as a yellow solid, m.p. 170–172 °C. ^1H NMR

(250 MHz, $CDCl_3$): δ = 9.17 (s, 1 H), 8.70 (s, 2 H), 8.19 (s, 1 H), 7.59–7.44 (m, 5 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.8 (CH_{Ar}), 157.9 ($2CH_{Ar}$), 157.4 (CH_{Ar}), 156.2 (C_q), 132.2 (C_q), 132.2 (CH_{Ar}), 131.0 ($2CH_{Ar}$), 130.9 ($2CH_{Ar}$), 127.9 (C_q), 127.8 (C_q), 120.6 (C_q) ppm. IR (neat): $\tilde{\nu}$ = 3090, 1549, 1475, 1416, 1360, 1171, 878, 759, 705, 630 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{14}H_{10}N_5S$ $[M + H]^+$ 280.065143; found 280.065371.

5-(3-Methoxyphenyl)-6-(*p*-tolyl)thiazolo[3,2-*b*][1,2,4]triazole (3da): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2d**, 100.0 mg, 0.465 mmol), palladium acetate (10.4 mg, 0.046 mmol), tricyclohexylphosphine (26.1 mg, 0.093 mmol), cesium carbonate (302.7 mg, 0.929 mmol), and 3-bromoanisole (130.3 mg, 0.697 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99.5:0.5) gave **3da** (143 mg, 96%) as a yellow solid, m.p. 118–120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.23 (m, 3 H), 6.95–6.88 (m, 3 H), 3.69 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8 (C_q), 155.2 (CH_{Ar}), 154.5 (C_q), 140.0 (C_q), 132.5 (C_q), 130.1 (CH_{Ar}), 129.6 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 128.5 (C_q), 126.5 (C_q), 124.8 (C_q), 121.6 (CH_{Ar}), 114.8 (CH_{Ar}), 114.6 (CH_{Ar}), 55.2 (OCH_3), 21.49 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3111, 2917, 1469, 1414, 1236, 1164, 1042, 798, 766, 690 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{18}H_{16}N_3OS$ $[M + H]^+$ 322.100860; found 322.101096.

6-(*p*-Tolyl)-5-[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*][1,2,4]triazole (3db): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2d**, 100.0 mg, 0.465 mmol), palladium acetate (10.4 mg, 0.0465 mmol), tricyclohexylphosphine (26.1 mg, 0.093 mmol), cesium carbonate (302.7 mg, 0.929 mmol), and 1-bromo-4-(trifluoromethyl)benzene (156.8 mg, 0.697 mmol). The mixture was heated at 160 °C. Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99.5:0.5) gave **3db** (145 mg, 87%) as a yellow solid, m.p. 146–148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.60 (d, *J* = 8.2 Hz, 2 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.5 (CH_{Ar}), 154.6 (C_q), 140.6 (C_q), 135.1 (d, *J* = 1.2 Hz, C_q), 130.8 (q, *J* = 33.0 Hz, C_q), 129.8 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 126.6 (C_q), 126.0 (q, *J* = 3.8 Hz, $2CH_{Ar}$), 124.7 (C_q), 124.2 (C_q),123.7 (q, *J* = 272.3 Hz, C_q), 21.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1616, 1469, 1324, 1109, 1067, 1016, 883, 852, 781, 646 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{18}H_{13}F_3N_3S$ $[M + H]^+$ 360.077680; found 360.077999.

6-(*p*-Tolyl)-5-pyrimidin-5-yl-thiazolo[3,2-*b*][1,2,4]triazole (3dc): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2d**, 100.0 mg, 0.465 mmol), palladium acetate (10.4 mg, 0.0465 mmol), tricyclohexylphosphine (26.1 mg, 0.093 mmol), cesium carbonate (302.7 mg, 0.929 mmol), and 5-bromopyrimidine (110.8 mg, 0.697 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99:1) gave **3dc** (118 mg, 87%) as a yellow solid, m.p. 198–200 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 8.74 (s, 2 H), 8.22 (s, 1 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.3 (CH_{Ar}), 156.4 ($2CH_{Ar}$), 156.0 (CH_{Ar}), 154.8 (C_q), 141.2 (C_q), 131.0 (C_q), 130.2 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 126.7 (C_q), 123.4 (C_q), 118.6 (C_q), 21.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3099, 1550, 1474, 1360, 1168, 911, 876, 717, 658, 624 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{15}H_{12}N_5S$ $[M + H]^+$ 294.080793; found 294.080990.

5-(2-Methoxyphenyl)-6-(4-methoxyphenyl)thiazolo[3,2-*b*][1,2,4]triazole (3ea): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2e**, 100.0 mg, 0.432 mmol), palladium acetate (9.7 mg, 0.043 mmol), tricyclohexylphosphine (24.2 mg, 0.086 mmol), cesium carbonate (281.8 mg, 0.865 mmol), and 2-bromoanisole (121.3 mg, 0.649 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99.7:0.3) gave **3ea** (116 mg, 80%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.53 (d, *J* = 8.9 Hz, 2 H), 7.36 (td, *J* = 8.2, 1.7 Hz, 2 H), 7.24 (dd, *J* = 8.2, 1.7 Hz, 1 H), 6.94–6.87 (m, 4 H), 3.80 (s, 3 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.2 (C_q), 157.3 (C_q), 155.5 (C_q), 155.0 (CH_{Ar}), 132.4 (CH_{Ar}), 130.9 (CH_{Ar}), 130.5 ($2CH_{Ar}$), 129.2 (C_q), 121.9 (C_q), 120.9 (C_q, CH_{Ar}), 120.0 (C_q), 114.0 ($2CH_{Ar}$), 111.5 (CH_{Ar}), 55.5 (OCH_3), 55.3 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 2931, 1511, 1488, 1358, 1290, 1167, 1023, 816, 752, 632 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{18}H_{16}N_3O_2S$ $[M + H]^+$ 338.095774; found 338.095850.

5-(3-Methoxyphenyl)-6-(4-methoxyphenyl)thiazolo[3,2-*b*][1,2,4]triazole (3eb): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2e**, 100.0 mg, 0.432 mmol), palladium acetate (9.7 mg, 0.043 mmol), tricyclohexylphosphine (24.2 mg, 0.086 mmol), cesium carbonate (281.8 mg, 0.865 mmol), and 3-bromoanisole (121.3 mg, 0.649 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/petroleum ether, 3:1) gave **3eb** (127 mg, 87%) as a yellow solid, m.p. 124–126 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.60 (d, *J* = 8.9 Hz, 2 H), 7.32–7.25 (m, 1 H), 7.03–6.89 (m, 5 H), 3.87 (s, 3 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.0 (C_q), 161.3 (C_q), 156.6 (CH_{Ar}), 155.8 (C_q), 134.1 (C_q), 132.6 ($2CH_{Ar}$), 131.6 (CH_{Ar}), 129.6 (C_q), 127.2 (C_q), 123.0 (CH_{Ar}), 121.4 (C_q), 116.1 (CH_{Ar}), 116.1 (CH_{Ar}), 115.7 ($2CH_{Ar}$), 56.8 (CH_3), 56.7 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2951, 1595, 1406, 1357, 1290, 1164, 1025, 857, 770, 689 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{18}H_{16}N_3O_2S$ $[M + H]^+$ 338.095774; found 338.095774.

5-(4-Methoxyphenyl)-6-(4-methoxyphenyl)thiazolo[3,2-*b*][1,2,4]-triazole (3ec): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2e**, 100.0 mg, 0.432 mmol), palladium acetate (9.7 mg, 0.043 mmol), tricyclohexylphosphine (24.2 mg, 0.086 mmol), cesium carbonate (281.8 mg, 0.865 mmol), and 4-bromoanisole (121.3 mg, 0.649 mmol). The mixture was heated at 160 °C. Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99.5:0.5) gave **3cc** (77 mg, 53%) as a white solid, m.p. 138–140 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.55 (d, *J* = 8.9 Hz, 2 H), 7.29 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 8.9 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 3.84 (s, 3 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.4 (C_q), 160.1 (C_q), 154.9 (CH_{Ar}), 154.2 (C_q), 131.1 ($2CH_{Ar}$), 130.6 ($2CH_{Ar}$), 127.4 (C_q), 126.0 (C_q), 123.6 (C_q), 120.1 (C_q), 114.5 ($2CH_{Ar}$), 114.3 ($2CH_{Ar}$), 55.4 (OCH_3), 55.3 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 3062, 2933, 1518, 1442, 1295, 1166, 1024, 837, 766, 648 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{18}H_{16}N_3O_2S$ $[M + H]^+$ 338.095774; found 338.096112.

6-(4-Methoxyphenyl)-5-[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*]-[1,2,4]triazole (3ed): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2e**, 100.0 mg, 0.432 mmol), palladium acetate (9.7 mg, 0.043 mmol), tricyclohexylphosphine (24.2 mg, 0.086 mmol), cesium carbonate (281.8 mg, 0.865 mmol), and 1-bromo-4-(trifluoromethyl)benzene (145.9 mg, 0.649 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99.6:0.4) gave **3ed** (144 mg, 89%) as a yellow solid, m.p. 132–134 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.59 (d, *J* = 8.2 Hz, 2 H), 7.53 (d, *J* = 8.8 Hz, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.9 (C_q), 155.5 (CH_{Ar}), 154.5 (C_q), 135.2 (d, *J* = 1.6 Hz, C_q), 131.2 ($2CH_{Ar}$), 130.7 (q, *J* = 32.9 Hz, C_q), 129.5 ($2CH_{Ar}$), 129.3 (C_q), 126.0 (q, *J* = 3.7 Hz, $2CH_{Ar}$), 124.0

(C_q), 123.7 (q, J = 272.3 Hz, C_q), 119.3 (C_q), 114.6 ($2CH_{Ar}$), 55.4 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 1465, 1324, 1252, 1165, 1116, 1067, 1026, 841, 804 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{13}F_3N_3OS$ $[M + H]^+$ 376.072594; found 376.072723.

6-(4-Methoxyphenyl)-5-pyrimidin-5-yl-thiazolo[3,2-*b*][1,2,4]triazole (3ee): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2e**, 100.0 mg, 0.432 mmol), palladium acetate (9.7 mg, 0.043 mmol), tricyclohexylphosphine (24.2 mg, 0.086 mmol), cesium carbonate (281.8 mg, 0.865 mmol), and 5-bromopyrimidine (103.1 mg, 0.649 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 98.8:1.2) gave **3ee** (123 mg, 92%) as a white solid, m.p. 208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.73 (s, 2 H), 8.20 (s, 1 H), 7.52 (d, J = 8.8 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.3 (C_q), 158.2 (CH_{Ar}), 156.4 ($2CH_{Ar}$), 155.9 (CH_{Ar}), 154.7 (C_q), 131.1 ($2CH_{Ar}$), 130.8 (C_q), 126.8 (C_q), 118.3 (C_q), 117.9 (C_q), 115.0 ($2CH_{Ar}$), 55.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3105, 1548, 1411, 1360, 1251, 1176, 1025, 877, 701, 622 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{12}N_5OS$ $[M + H]^+$ 310.075707; found 310.075723.

5-(3-Methoxyphenyl)-6-[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*]-[1,2,4]triazole (3fa): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2f**, 100.0 mg, 0.371 mmol), palladium acetate (8.30 mg, 0.037 mmol), tricyclohexylphosphine (20.8 mg, 0.074 mmol), cesium carbonate (242.0 mg, 0.743 mmol), and 3-bromoanisole (104.2 mg, 0.557 mmol). Standard workup followed by flash chromatography (CH_2Cl_2) gave **3fa** (120 mg, 86%) as a yellow solid, m.p. 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.78 (d, J = 8.2 Hz, 2 H), 7.67 (d, J = 8.2 Hz, 2 H), 7.28 (t, J = 8.1 Hz, 1 H), 6.94–6.86 (m, 3 H), 3.72 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0 (C_q), 155.3 (CH_{Ar}), 154.6 (C_q), 131.7 (C_q), 131.4 (q, J = 32.8 Hz, C_q), 131.3 (d, J = 1.0 Hz, C_q), 130.5 (CH_{Ar}), 130.0 ($2CH_{Ar}$), 128.9 (C_q), 126.7 (C_q), 125.7 (q, J = 3.8 Hz, $2CH_{Ar}$), 123.7 (q, J = 272.4 Hz, C_q), 121.7 (CH_{Ar}), 115.2 (CH_{Ar}), 114.9 (CH_{Ar}), 55.3 (OCH_3) ppm. IR (neat): $\tilde{\nu}$ = 1596, 1465, 1325, 1245, 1163, 1038, 1022, 858, 775, 690 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{13}F_3N_3OS$ $[M + H]^+$ 376.072594; found 376.072732.

5,6-Bis[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*][1,2,4]triazole (3fb): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2f**, 100.0 mg, 0.371 mmol), palladium acetate (8.30 mg, 0.037 mmol), tricyclohexylphosphine (20.8 mg, 0.074 mmol), cesium carbonate (242.0 mg, 0.743 mmol), and 1-bromo-4-(trifluoromethyl)benzene (125.3 mg, 0.557 mmol). The mixture was heated at 160 °C. Standard workup followed by flash chromatography (CH_2Cl_2) gave **3fb** (115 mg, 75%) as a white solid. Due to high insolubility, only a 135 DEPT ^{13}C was obtained, m.p. 160–162 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 7.79 (d, J = 8.5 Hz, 2 H), 7.74 (d, J = 8.5 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H), 7.52 (d, J = 8.2 Hz, 2 H) ppm. 135 DEPT ^{13}C NMR (63 MHz, $CDCl_3$): δ = 155.7 (CH_{Ar}), 130.1 ($2CH_{Ar}$), 129.7 ($2CH_{Ar}$), 126.4 (q, J = 3.7 Hz, $2CH_{Ar}$), 126.1 (q, J = 3.7 Hz, $2CH_{Ar}$) ppm. IR (neat): $\tilde{\nu}$ = 1618, 1474, 1320, 1162, 1065, 1017, 882, 807, 703, 643 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{10}F_6N_3S$ $[M + H]^+$ 414.049414; found 414.049309.

5-Pyrimidin-5-yl-6-[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*][1,2,4]-triazole (3fc): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2f**, 100.0 mg, 0.371 mmol), palladium acetate (8.30 mg, 0.037 mmol), tricyclohexylphosphine (20.8 mg, 0.074 mmol), cesium carbonate (242.0 mg, 0.743 mmol), and 5-bromopyrimidine (88.6 mg, 0.557 mmol). Standard workup followed by flash chromatography (CH_2Cl_2) gave **3fc** (115 mg, 89%) as a white solid. Due to high insolubility, only a 135 DEPT was obtained, m.p. 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (s, 1 H), 8.74 (s, 2 H), 8.22 (s, 1 H), 7.75 (m, 4 H) ppm. 135 DEPT ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.83 (CH_{Ar}), 156.58 ($2CH_{Ar}$), 156.09 (CH_{Ar}), 130.08 ($2CH_{Ar}$), 126.46 (q, J = 3.8 Hz, $2CH_{Ar}$) ppm. IR (neat): $\tilde{\nu}$ = 1550, 1419, 1321, 1162, 1124, 1018, 881, 811, 724, 633 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_9F_3N_5S$ $[M + H]^+$ 348.052527; found 348.052797.

5-(2-Methoxyphenyl)-6-methyl-thiazolo[3,2-*b*][1,2,4]triazole (3ga): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol), palladium acetate (16.1 mg, 0.072 mmol), tricyclohexylphosphine (40.3 mg, 0.144 mmol), cesium carbonate (468.2 mg, 1.437 mmol), and 2-bromoanisole (201.5 mg, 1.078 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99:1) gave **3ga** (155 mg, 88%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.35 (t, J = 7.7 Hz, 1 H), 7.28 (d, J = 7.7 Hz, 1 H), 7.00–6.93 (m, 2 H), 3.79 (s, 3 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.1 (C_q), 155.1 (C_q), 154.9 (CH_{Ar}), 132.0 (CH_{Ar}), 130.9 (CH_{Ar}), 126.4 (C_q), 121.3 (C_q), 120.8 (CH_{Ar}), 119.2 (C_q), 111.4 (CH_{Ar}), 55.5 (CH_3), 11.81 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2929, 1466, 1411, 1358, 1266, 1241, 1166, 1023, 752, 652 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{12}N_3OS$ $[M + H]^+$ 246.069559; found 246.069815.

5-(3-Methoxyphenyl)-6-methylthiazolo[3,2-*b*][1,2,4]triazole (3gb): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol), palladium acetate (16.1 mg, 0.072 mmol), tricyclohexylphosphine (40.3 mg, 0.144 mmol), cesium carbonate (468.2 mg, 1.437 mmol), and 3-bromoanisole (201.5 mg, 1.078 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99.5:0.5) gave **3gb** (170 mg, 96%) as a yellow solid, m.p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.41 (t, J = 7.9 Hz, 1 H), 7.08 (d, J = 7.9 Hz, 1 H), 7.10–6.97 (m, 2 H), 3.88 (s, 3 H), 2.66 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0 (C_q), 155.2 (CH_{Ar}), 154.3 (C_q), 132.4 (C_q), 130.2 (CH_{Ar}), 125.4 (C_q), 125.2 (C_q), 121.4 (CH_{Ar}), 114.9 (CH_{Ar}), 114.3 (CH_{Ar}), 55.4 (OCH_3), 11.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1602, 1571, 1467, 1359, 1240, 1129, 1044, 876, 781, 694 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{12}N_3OS$ $[M + H]^+$ 246.069559; found 264.069813.

5-(4-Methoxyphenyl)-6-methylthiazolo[3,2-*b*][1,2,4]triazole (3gc): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol), palladium acetate (16.1 mg, 0.072 mmol), tricyclohexylphosphine (40.3 mg, 0.144 mmol), cesium carbonate (468.2 mg, 1.437 mmol), and 4-bromoanisole (201.5 mg, 1.078 mmol). Standard workup followed by flash chromatography (CH_2Cl_2) gave **3gc** (118 mg, 67%) as a yellow solid, m.p. 110–112 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.42 (d, J = 8.7 Hz, 2 H), 7.02 (d, J = 8.7 Hz, 2 H), 3.88 (s, 3 H), 2.61 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 161.5 (C_q), 156.4 (CH_{Ar}), 155.5 (C_q), 131.8 ($2CH_{Ar}$), 126.9 (C_q), 125.8 (C_q), 124.7 (C_q), 116.0 ($2CH_{Ar}$), 56.9 (OCH_3), 13.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3094, 1601, 1509, 1408, 1361, 1247, 1140, 1032, 800, 700, 652 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{12}N_3OS$ $[M + H]^+$ 246.069559; found 246.069875.

6-Methyl-5-[4-(trifluoromethyl)phenyl]thiazolo[3,2-*b*][1,2,4]triazole (3gd): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol), palladium acetate (16.1 mg, 0.072 mmol), tricyclohexylphosphine (40.3 mg, 0.144 mmol), cesium carbonate (468.2 mg, 1.437 mmol), and 1-bromo-4-(trifluoromethyl)benzene (242.5 mg, 1.078 mmol).

The mixture was heated at 160 °C. Standard workup followed by flash chromatography (CH_2Cl_2) gave **3gd** (171 mg, 84%) as a yellow solid, m.p. 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.75 (d, J = 8.2 Hz, 2 H), 7.61 (d, J = 8.2 Hz, 2 H), 2.66 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.5 (CH_{Ar}), 154.5 (C_q), 134.8 (d, J = 1.4 Hz, C_q), 130.9 (q, J = 32.9 Hz, C_q), 129.3 ($2CH_{Ar}$), 126.3 (C_q), 126.2 (q, J = 3.7 Hz, $2CH_{Ar}$), 123.9 (C_q), 123.7 (q, J = 272.4 Hz, C_q), 11.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2922, 1614, 1405, 1321, 1172, 1109, 1007, 835, 701, 652 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{12}H_9F_3N_3S$ $[M + H]^+$ 284.046379; found 284.046540.

6-Methyl-5-(pyrimidin-5-yl)thiazolo[3,2-*b*][1,2,4]triazole (3ge): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol), palladium acetate (16.1 mg, 0.072 mmol), tricyclohexylphosphine (40.3 mg, 0.144 mmol), cesium carbonate (468.2 mg, 1.437 mmol), and 4-bromopyrimidine (171.4 mg, 1.078 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 98.7:1.3) gave **3ge** (148 mg, 95%) as a yellow solid, m.p. 224–226 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.25 (s, 1 H), 9.03 (s, 2 H), 8.32 (s, 1 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (63 MHz, [D$_6$]DMSO): δ = 158.5 (CH_{Ar}), 156.8 ($2CH_{Ar}$), 156.1 (CH_{Ar}), 154.6 (C_q), 128.5 (C_q), 126.4 (C_q), 118.0 (C_q), 11.7 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3105, 3031, 1478, 1409, 1388, 1240, 1180, 906, 723, 651 cm^{-1}. HRMS (ESI): m/z calcd. for $C_9H_8N_5S$ $[M + H]^+$ 218.049493; found 218.049799.

6-Methyl-5-(pyridin-4-yl)thiazolo[3,2-*b*][1,2,4]triazole (3gf): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol), palladium acetate (16.1 mg, 0.072 mmol), tricyclohexylphosphine (40.3 mg, 0.144 mmol), cesium carbonate (468.2 mg, 1.437 mmol), and 4-bromopyridine hydrochloride (209.6 mg, 1.078 mmol). The mixture was heated at 160 °C. Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 98:2) gave **3gf** (126 mg, 81%) as a white solid, m.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, J = 6.1 Hz, 2 H), 8.18 (s, 1 H), 7.40 (d, J = 6.1 Hz, 2 H), 2.72 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.8 (CH_{Ar}), 154.5 (C_q), 150.7 ($2CH_{Ar}$), 139.1 ($2C_q$), 127.3 (C_q), 122.8 ($2CH_{Ar}$), 12.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3097, 1600, 1476, 1408, 1362, 1240, 1168, 1159, 817, 648 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{10}H_9N_4S$ $[M + H]^+$ 217.054244; found 217.054514.

6-Methyl-5-(*p*-tolyl)thiazolo[3,2-*b*][1,2,4]triazole (3gg): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol), palladium acetate (16.1 mg, 0.072 mmol), tricyclohexylphosphine (40.3 mg, 0.144 mmol), cesium carbonate (468.2 mg, 1.437 mmol), and 4-bromotoluene (184.3 mg, 1.078 mmol). Standard workup followed by flash chromatography (CH_2Cl_2/petroleum ether, 3:1) gave **3gg** (125 mg, 76%) as a white solid, m.p. 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 2.61 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1 (CH_{Ar}), 154.3 (C_q), 139.1 (C_q), 129.8 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 128.2 (C_q), 125.7 (C_q), 124.7 (C_q), 21.3 (CH_3), 11.6 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2921, 1470, 1407, 1361, 1235, 1170, 1139, 813, 653 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{12}H_{12}N_3S$ $[M + H]^+$ 230.074645; found 230.075020.

Methyl 4-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)benzoate (3gh): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol), palladium acetate (16.1 mg, 0.072 mmol), tricyclohexylphosphine (40.3 mg, 0.144 mmol), cesium carbonate (468.2 mg, 1.437 mmol), and methyl 4-bromobenzoate (231.7 mg, 1.078 mmol). The mixture was heated at 160 °C. Standard workup followed by flash chromatography (CH_2Cl_2/MeOH, 99:1) gave **3gh** (194 mg, quant.) as a white solid, m.p. 164–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.2 Hz, 2 H), 8.12 (s, 1 H), 7.55 (d, J = 8.2 Hz, 2 H), 3.94 (s, 3 H), 2.65 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.2 (C_q), 155.4 ($2C_q$), 154.5 (C_q), 135.6 (C_q), 130.4 ($2CH_{Ar}$), 128.8 ($2CH_{Ar}$), 126.1 (C_q), 124.5 (C_q), 52.4 (OCH_3), 11.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3109, 1719, 1476, 1402, 1269, 1236, 1114, 850, 700, 693 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{13}H_{12}N_3O_2S$ $[M + H]^+$ 274.064474; found 274.064676.

5-[^{2}H]-6-Phenylthiazolo[3,2-*b*][1,2,4]triazole (3c-D): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2c**, 100.0 mg, 0.497 mmol) and cesium carbonate (323.8 mg, 0.994 mmol) in a mixture of 1,4-dioxane/D_2O (4 mL, 1:1). Standard workup followed by flash chromatography (dichloromethane) gave **3c**-D (100 mg, quant.) as a white solid, m.p. 90–92 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 8.08–8.03 (m, 2 H), 7.54–7.41 (m, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 158.4 (C_q), 157.4 (CH_{Ar}), 134.5 (C_q), 131.3 (CH_{Ar}), 130.4 ($2CH_{Ar}$), 129.3 (C_q), 128.0 ($2CH_{Ar}$), 109.7 (m, C_q) ppm. IR (neat): $\tilde{\nu}$ = 3113, 2920, 2303, 1406, 1351, 1240, 1185, 732, 653, 612 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{10}H7N_3SD$ $[M + H]^+$ 203.049621; found 203.050209.

5-[^{2}H]-6-Methylthiazolo[3,2-*b*][1,2,4]triazole (3g-D): The reaction was carried out as described in General Procedure A using thiazolo[3,2-*b*]triazole (**2g**, 100.0 mg, 0.718 mmol) and cesium carbonate (468.2 mg, 1.437 mmol) in a mixture of 1,4-dioxane/D_2O (4 mL, 1:1). Standard workup followed by flash chromatography (dichloromethane) gave **3g**-D (100 mg, quant.) as a white solid, m.p. 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.2 (C_q), 156.1 (CH_{Ar}), 129.5 (C_q), 107.9 (C_q), 127.6 (m, C_q), 14.4 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3113, 2920, 1472, 1406, 1351, 1240, 1162, 732, 637, 612 cm^{-1}. HRMS (ESI): m/z calcd. for $C_5H_5N_3SD$ $[M + H]^+$ 141.033971; found 141.034161.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR or ^{13}C DEPT NMR spectra for all compounds; pK_a determination method.

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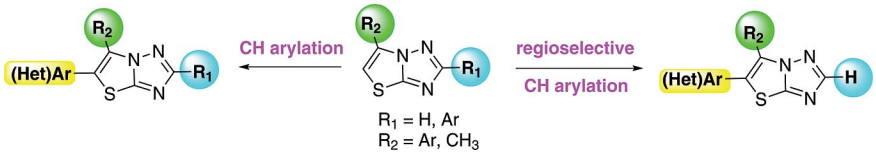

An efficient and convenient method has been developed for the formation of polysubstituted thiazolo[3,2-*b*][1,2,4]triazoles through C-5 (het)arylation. The direct C–H activation protocol giving access to di- and trisubstituted derivatives in excellent yields, and the method enables access to a collection of C-5,6 bis(het)aryl derivatives with full regioselectivity.

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First Palladium-Catalyzed Direct Regioselective C-5 (Het)Arylation of Mono- or Disubstituted Thiazolo[3,2-*b*][1,2,4]triazoles

Keywords: C–H activation / Regioselectivity / Nitrogen heterocycles / Sulfur heterocycles / Palladium

