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Polyarylated Thiazoles via a Combined Halogen Dance – Cross-Coupling Strategy

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The application of the halogen dance reaction for the synthesis of starting materials for cross-coupling reactions is reported. The obtained compounds were then successfully applied in sequential Stille and Suzuki–Miyaura cross-coupling reactions to obtain novel thiazole derivatives.

Introduction

Simple and convenient methods for the synthesis and decoration of heterocycles are always desirable due to the importance of heterocyclic compounds as agrochemicals, pharmaceuticals, natural products, materials and in many other areas of interest.[1] Thiazole can be considered as an important member of the heterocyclic family and substituted thiazoles can be found in a number of molecules with interesting properties.[2,3] Principally, substituted thiazoles can be prepared by two methods: directly via cyclization reactions[4] or via decoration of simple thiazole building blocks. For the synthesis of complex thiazole derivatives, the latter approach is usually the more convenient one, especially, when libraries of compounds have to be prepared. Transition metal catalyzed cross-coupling reactions have proved to be very useful for developing syntheses of complex heterocyclic compounds.[5] They are nowadays well established methods for the formation of C–C and C–X (X = N, O, and S) bonds.[6] In cross-coupling reactions thiazole building blocks can either be used as the organometallic species[7] or as the halogenated counterpart. Therefore, developing methods for the efficient synthesis of halogenated/metallated thiazoles, as valuable building blocks, are highly desirable. Within this contribution, transition metal-catalyzed cross-coupling strategies were applied to decorate the thiazole building block **1**, obtained via a cyclization strategy, with various aryl and heteroaryl substituents. In the present case a cyclization strategy would not be versatile enough since only a limited number of substituents can be introduced and for each substitution pattern different thioamides and α-halo ketones have to be prepared.

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The halogen dance (HD) reaction for the synthesis of various di- and trisubstituted heterocycles was reported in the literature.[8] It represents a base-induced reaction of a haloaromatic compound in which the position of the halogen atom differs from its position in the starting material. Additionally, quenching the intermediate with different electrophiles leads to the introduction of a new functionality at the position where the halogen was present initially. In summary, the big advantage of the HD methodology is that the number of reactive centers is increased and further manipulations on the molecule are facilitated. HD reactions were successfully performed on a number of heterocyclic systems[8] but only recently oxazole[9] and thiazole have been added to this list. The first HD on thiazole was performed by Stangeland and Sammakia[10] and recently two more examples, from our group, were published.[11] In a very recent example, we reported preliminary data on the formation of polyhalogenated thiazoles via the HD reaction as starting materials for cross-coupling reactions. Within this contribution we have extended our investigations and significantly broadened the substrate scope of the methodology.[12]

In the present contribution the HD reaction on 2-anilinothiazole was investigated. Additionally, the 4-halogenated and 4,5-dihalogenated/metallated thiazoles, obtained after a HD on thiazole **2**, were then cross-coupled with different aromatic systems in a sequential manner leading finally to

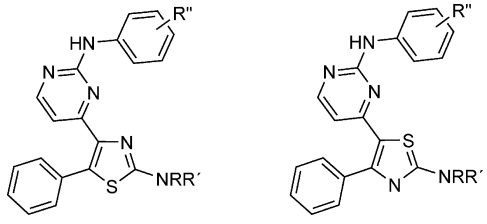


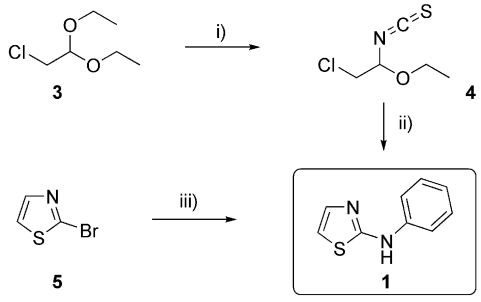
Figure 1. Related protein kinase inhibitors.

a variety of 2,4,5-trisubstituted thiazoles. These compounds are of interest since they are structurally related to substances reported as potential protein kinase inhibitors (PKIs, Figure 1).[13]

Results and Discussion

Synthesis of Starting Materials

2-Anilinothiazole (**1**) was first prepared according to the method reported in the literature starting from **3** (Scheme 1).[14] Although the starting materials were cheap, this method has the disadvantage that it is a two step process leading to only 48% of **1**, a yield which was considered as unsatisfactory especially for the first step of a reaction sequence. Therefore, two alternative strategies for the synthesis of **1** were investigated: a) nucleophilic substitution b) Hantzsch synthesis[15] with *N*-phenylthiourea.

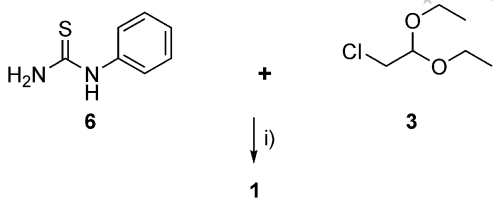


i) NH_4SCN, $SiCl_4$, 1,2-dichloroethane, 53% ii) a.) aniline, K_2CO_3, CH_3CN; b.) *p*TsOH, 50°C, 1h, 91%. iii) aniline, *p*TsOH, 24h, refluxing, *i*PrOH, 60%.

Scheme 1. Synthesis of **1**.

Commercially available 2-bromothiazole (**5**) was selected for nucleophilic substitution with aniline. Due to the low nucleophilicity of aniline, activation of **5** via protonation was necessary. Consequently, *p*TosOH was used as acid and an appreciable yield of 60% was obtained when equimolar amounts of *p*TosOH were used (*i*PrOH as solvent). Incomplete conversion was observed when substoichiometric amounts of *p*TosOH were used and in the absence of *p*TosOH no product was formed. Unfortunately, the expectation that the higher boiling solvent *sec*-BuOH would lead to higher product yields was not fulfilled and 56% of the product was isolated in that case. Although higher yielding, we did not consider this process as ideal due to the rather expensive starting material **5**.

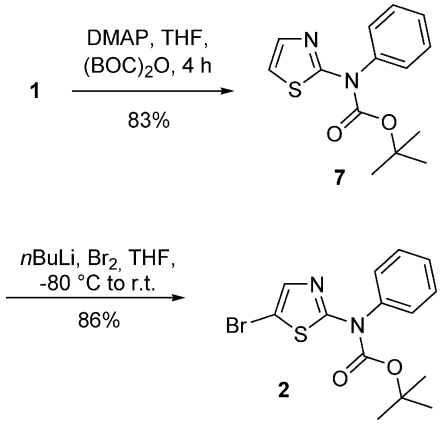
The Hantzsch synthesis was used by Kaye et al.[16] for the synthesis of various thiazole derivatives with yields up to 94%. When this method was applied for the synthesis of **1**, using commercially available *N*-phenylthiourea (**6**) and 2-chloro-1,1-diethoxyethane, 84% of the desired product was obtained (Scheme 2). Therefore, this cyclization strategy became ultimately the method of choice for the synthesis of starting material **1**.



i) 2-chloro-1,1-diethoxyethane, H_2O, reflux, 4 h, HCl, 60%

Scheme 2. Synthesis of **1** via Hantzsch cyclization.

Due to its possible interference in forthcoming reactions the free amine functionality had to be protected. The BOC group was chosen[11a] due to its lower tendency to migrate under lithiation conditions compared to the pivaloyl group.[17] Compound **7** was prepared via a standard protocol.[11a] Introduction of bromine in the 5-position of thiazoles was achieved via lithiation using *n*BuLi and quenching with Br_2 (Scheme 3). Lithiation conditions were used as bromination under conventional bromination conditions (i.e. Br_2 in $CHCl_3$) resulted in partial removal of the BOC group and only 53% yield of product **2** were isolated. However, under lithiation conditions the desired product **2** was obtained in 86% yield.

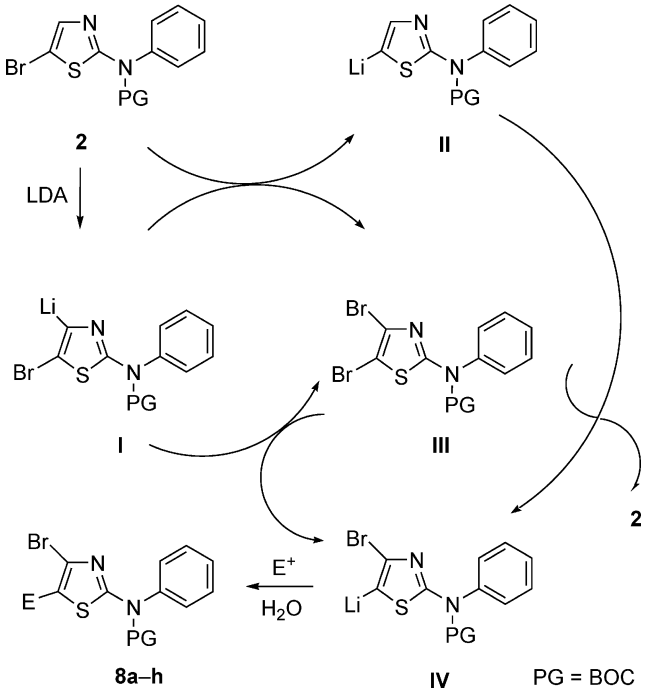


Scheme 3. Synthesis of precursor **2**.

Halogen Dance Reaction

Compound **2** was then used as starting material for HD reactions. The reason why an HD takes place on **2** can be explained on the basis of differences in acidity. The 5-position, in this particular case, is more acidic than the 4-position therefore favoring lithiation at the 5-position rather than in 4-position. However, when LDA is used as base the initially formed lithiated species is **I**. This intermediate **I** can react by itself as a lithiating reagent but in contrast to LDA it gives a metal–halogen exchange starting a cascade of metal–halogen exchange reactions which ultimately leads to the most stable lithiated species **IV**: First, **I** reacts with still present starting material **2** which leads to the intermediates **II** and **III**. Then again, these two species can react with each other and metal–halogen exchange on **III** takes place in 5-

position leading to the most stable lithiated species **IV** on the one hand and on the other hand starting material **2** is recovered. Key intermediate **IV** can also be formed upon reaction of intermediate **I** with intermediate **III** whereby **I** is transformed to **III** and **III** into **IV**. It can be seen that all lithiated intermediates (**I**, **II**, **IV**) can react with the intermediate halide species (**2**, **III**) ultimately leading to the thermodynamically most stable compound **IV**. The suggested mechanism is summarized in Scheme 4.



Scheme 4. The mechanism of the HD reaction. Structures with roman numbers are not isolated reaction intermediates.

To optimize HD reaction conditions, the conversion of the 5-bromo compound **2** to the 4-bromo compound **8a** was investigated in detail (Table 1). In first attempts 1.1 equiv. of LDA were added dropwise to a solution of **2** at –80 °C over a period of 15 min. Then the reaction mixture was stirred for 1 h keeping the temperature below –70 °C. Quenching the reaction with H_2O (1.1 equiv.) in 5 mL of THF gave only 10% of the desired product with 80% recovery of starting material. When the temperature was elevated to –50 °C, decomposition of the product was observed and no product was obtained after workup. By using an excess of LDA (2.2 equiv.), an improvement in the yield was observed and 60% of product **8a** was obtained. Further increasing the amount of LDA to 3.3 equiv. resulted in the complete conversion of the starting material and 97% of the product **8a** was obtained. These results were comparable to the previously reported[11a] HD reaction on a thiazole derivative, where 3.3 equiv. of base (LDA) were required as well to give complete HD. We also observed that "inverse"[8b] addition of base was not necessary and similar yields were obtained when the halide was added to the LDA solution.

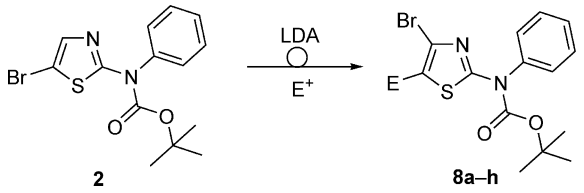
Table 1. Optimization of HD conditions.

Entry	Temperature	LDA [equiv.]	% of **2**	% of **8a**
1	–85 °C to –70 °C	1.1	80	10
2	–85 °C to –50 °C	1.1	–	–
3	–85 °C to –60 °C	2.2	35	60
4	–85 °C to –60 °C	3.3	–	97

These optimized conditions were then used to obtain different 4,5-disubstituted thiazoles. 4-Bromo-5-lithiated intermediate **IV** was trapped with various electrophiles and several substituents were introduced at 5-position in good yields (43–97%; Table 2, Scheme 5). The highest yield was obtained when intermediate **IV** was quenched with water (H_2O) leading to 97% of 4-bromo compound **8a** (entry 1). Also iodine (70% with I_2, entry 4) and chlorine (70% with hexachloroethane, entry 5) were introduced with good yields. Especially the 5-iodo-4-bromo compound **8c** is an interesting substrate for further cross-coupling reactions. Unfortunately, the introduction of bromine to obtain 4,5-dibrominated product **8b** worked only in comparably moderate yields (50%). Even by applying 1,2-dibromo-1,1,2,2-tetrachloroethane instead of Br_2, a method successful in the oxazole series,[10] did not improve the yield (30%). On the other hand, the introduction of tributyltin (with Bu_3SnCl) worked well and the desired compound **8e** was isolated in 65% yield (entry 6). Compound **8e** is another interesting starting material for sequential cross-coupling reactions since it enables a potential Stille reaction in 5-position followed by any other cross-coupling method in the 4-position. However, attempts to introduce a boronic acid or ester via this methodology were unsuccessful. This is not too surprising since in our previous research we already found a very limited stability of thiazole-boron compounds. We could never isolate a free boronic acid and only pinacol esters, obtained via immediate transesterification with pinacol proved to be accessible in some cases.[18] Introduction of an alcohol with benzophenone resulted in the formation of product **8g** in 43% yield. The lower yield in the case of benzophenone compared to other electrophiles can be explained by steric reasons. A formyl group could also be introduced by using DMF as an electrophile (**8f**, 97% yield) as well as TMS using TMSCl (**8h**, 97%), which provides an interesting option to block position 5 temporarily.

Table 2. Electrophiles introduced at 5-position of thiazole.

Entry	E	Electrophile	Product	Yield (%)
1	H	H_2O	**8a**	97
2	Br	Br_2	**8b**	50
3	Br	$C_2Br_2Cl_4$	**8b**	30
4	I	I_2	**8c**	70
5	Cl	C_2Cl_6	**8d**	70
6	$SnBu_3$	Bu_3SnCl	**8e**	65
7	Bpin/$B(OH)_2$	$B(OiPr)_3$	–	–
8	CHO	DMF	**8f**	97
9	$C(OH)(C_6H_5)_2$	benzophenone	**8g**	43
10	TMS	TMSCl	**8h**	97



Scheme 5. Introduction of electrophiles via HD.

Cross-Coupling Reactions

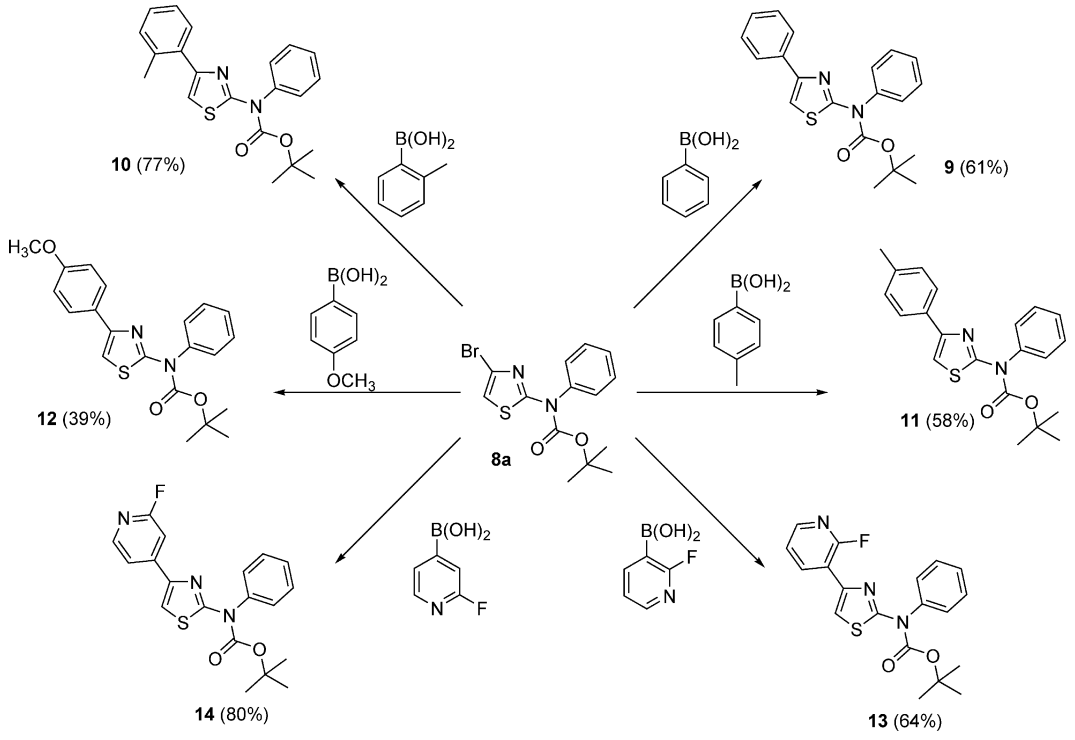
As already mentioned above, heterocyclic compounds, especially polyarylated ones, are of considerable interest in many different research fields.[1] Therefore, compounds **8a**, **8c**, and **8e** were then used in Pd-catalyzed cross-coupling reactions with aromatic and heteroaromatic systems (see Schemes 6, 7 and 9).

Initially, **8a** was cross-coupled with either phenylboronic acid or tributyl(phenyl)stannane. Both, the Stille[19–21] [$Pd(PPh_3)_4$, CsF, toluene] and Suzuki–Miyaura[22] protocols [$Pd(PPh_3)_4$, $NaHCO_3$, DME, H_2O] gave the same result (product **9** in 60% and 61%, respectively). Additionally, we also investigated the effect of different substituents on the benzene ring on the outcome of Suzuki–Miyaura cross-coupling reactions. The Stille protocol was excluded from this survey due to the high toxicity of tin compounds and the limited commercial availability of arylstannanes in comparison to aryl boronic acids. (4-Methoxyphenyl)boronic acid, (4-methylphenyl)boronic acid and (2-methylphenyl)-boronic acid were selected as aryl donors. The best yields were obtained in the case of (2-methylphenyl)boronic acid i.e. 77%. (4-Methylphenyl)boronic acid gave a yield of 58%, however, in case of (4-methoxyphenyl)boronic acid only 39% of the desired compound **12** was obtained. However, similar observations were reported in the literature[18,23] for aryl-donors with electron donating substituents. Somewhat remarkable was that the sterically demanding (2-methylphenyl)boronic acid gave the best yield, even better than the simple phenylboronic acid. An explanation for that might be the lower tendency to form a biphenyl by-product than in the other cases.

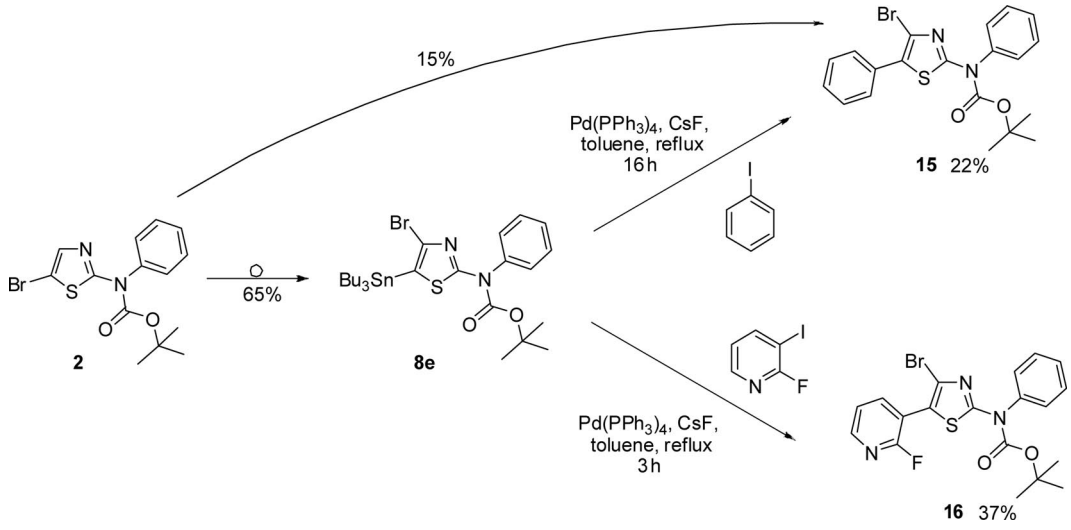
After investigating aryl coupling partners, the cross-coupling of heteroaryl donors with **8a** was investigated. (2-Fluoropyridin-3-yl)- and (2-fluoropyridin-4-yl)boronic acid were chosen for cross-couplings since those compounds were available in our lab and of interest in the context of potential PKIs. These two boronic acids were prepared from 2-fluoropyridine by following the literature procedure.[24] Applying these compounds in the cross-coupling protocol, (2-fluoropyridin-3-yl)boronic acid gave a good yield of 64% of **13**, and in the case of (2-fluoropyridin-4-yl)boronic acid an excellent yield of 80% of **14** was obtained. The higher yields in the case of heteroaromatic partners are quite encouraging as heteroaromatic moieties are key structural features of many biologically active compounds.

Sequential Cross-Coupling Reactions

Subsequently, starting materials **8c** and **8e** were used in sequential cross-coupling reactions. Initially, **8e** a vicinal bromostannane, was selected for cross-coupling reactions. It represents a challenging compound for cross-coupling re-

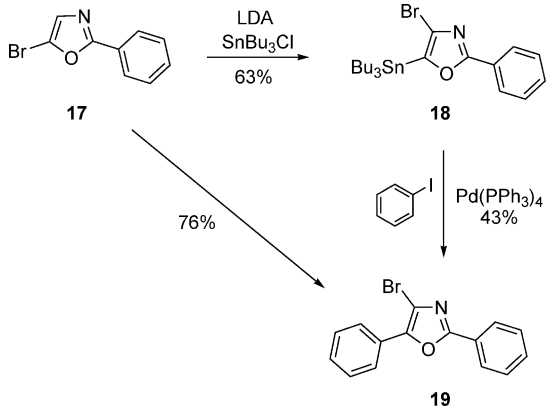


Scheme 6. Suzuki–Miyaura cross-coupling reactions with **8a**.



Scheme 7. Cross-couplings with vicinal (bromostannyl)thiazole **8e**.

actions since an organometal and a halide-species are present in the same molecule (tributyltin in 5-position and Br in 4-position). Therefore, there are more possibilities for side reactions since **8e** can potentially react with itself. When the cross-coupling reaction of iodobenzene with **8e** was performed only 22% of product **15** (Scheme 7) was isolated. Compound **8a** was obtained as a major side product (39%) which shows the instability of **8e** under the reaction conditions. In another project a similar reaction was performed on the oxazole derivative **18** (Scheme 8). There, 43% of the desired product **19** was obtained upon cross-coupling with iodobenzene. However, performing the reaction in one-pot

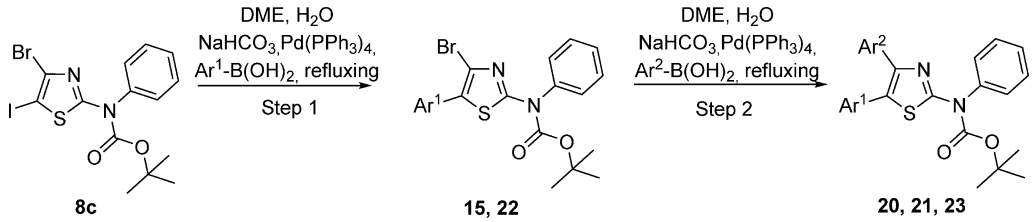


Scheme 8. Cross-coupling with vicinal (bromostannyl)oxazole **17**.

i.e. starting from **17**, improved the yield and the required product **19** was obtained in 76% overall yield over two steps (Scheme 8).[25] However, when this strategy was applied to **8e**, an overall yield of 15% was obtained. These lower yields with vicinal bromostannanes of azoles were not surprising. Revesz and co-workers[26] reported imidazole examples which gave similar low yields (24–55%). Only in one case the desired product was obtained in 74% yield.

It was mentioned above that better yields were obtained in cross-coupling reactions of **8a** with heterocyclic boronic acids. Therefore, also in the sequential case 2-fluoro-3-iodopyridine was cross-coupled with **8e**. The yields were slightly better but again not more than 37% of the desired product **16** (Scheme 7) was obtained along with 30% of side product **8a**.

In comparison to **8e**, starting material **8c** is actually well set up for sequential cross-coupling reactions as it was found that the 5-position is slightly favored over the 4-position in cross-coupling reactions.[19] The iodine in 5-position should further increase the selectivity in cross-coupling reactions. Indeed, when the cross-coupling was performed between **8c** and phenylboronic acid, the 5-position was selectively cross-coupled to give 80% of the desired product **15** (Scheme 9). The second cross-coupling step was then performed on **15** at 4-position and 90% of product **20** were obtained. When sterically hindered (2-methylphenyl)boronic acid was used in the second cross-coupling step 50% of the desired product **21** were isolated. This lower yield



Scheme 9. Sequential cross-couplings with thiazole **8c**.

Table 3. Sequential cross-couplings with thiazole **8c**.

Entry	Step 1 Coupling partner	Product	Yield (%)	Step 2 Coupling partner	Product	Yield (%)	Overall Yield (%)
1	phenylboronic acid	**15**	80	phenylboronic acid	**20**	90	72
2	phenylboronic acid	**15**	80	(2-methylphenyl)boronic acid	**21**	50	40
3	(2-methylphenyl)boronic acid	**22**	59	phenylboronic acid	**23**	90	53

can be explained by steric reasons. A slightly better yield was obtained when (2-methylphenyl)boronic acid was used in the first cross-coupling step on **8c** (59% yield of **22**). Compound **22** was then again cross-coupled in 4-position with phenylboronic acid to give product **23** in an excellent yield of 90%. In summary, compound **20** was prepared in 72% yield over two cross-coupling steps starting from **8c**. The synthesis of **21** and **23** was not as efficient but still 40% resp. 53% were obtained. In both cases cross-coupling with (2-methylphenyl)boronic acid was the step which lowered the yield of the overall process (Table 3).

Conclusions

In conclusion we found that the HD reaction can be used as an efficient method for the synthesis of starting materials for sequential cross-coupling reactions. Additionally, a series of electrophiles can be introduced in 5-position. HD reactions were performed on 1,1-dimethylethyl *N*-(5-bromothiazol-2-yl)-*N*-phenylcarbamate (**2**), which in turn was synthesized from commercially available 2-phenylthiourea **6** in three steps with an overall yield of 60%, improving previous routes significantly. Depending on the nature of the electrophile, moderate to excellent yields were obtained (43–97%). Subsequently, cross-coupling reactions were then performed on products **8a**, **8c** and **8e**. Reactions with **8a** gave yields in the range of 40–77% when cross-coupled with aryl systems. In case of heteroaryl systems slightly better yields were obtained (64–80%). Compound **8c** also proved to be a good substrate for sequential cross-coupling reactions and different aryl groups were introduced selectively at 5- and subsequently at 4-position in good yields (60–90%). Compound **8e** on the other hand gave only low yields in sequential reactions, which was somehow expected since the compound was challenging due to its "bivalent" nature as halide and organometal species.

Experimental Section

General Methods: All lithiation reactions were conducted under argon using dried glassware and magnetic stirring. Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were dried with Al_2O_3 cartridges prior to use. Flash column chromatography was performed on silica gel 60 from Merck (40–63 μm) using a Büchi Sepacore preparative column. The ratio of crude product to silica gel was 1:30. For thin-layer chromatography (TLC) aluminum backed silica gel was used. The solvent mixture used for TLC was also used for column chromatography. Kugelrohr distillation was carried out using a Büchi GKR-51 apparatus. Melting points were determined using a Kofler-type Leica Galen III micro hot-stage microscope and are uncorrected. NMR spectra were recorded from $CDCl_3$ solution on a Bruker AC 200 (200 MHz) and chemical shifts are reported in ppm using TMS as internal standard. Elemental analyses were carried out in the Microanalytical Laboratory, Institute of Physical Chemistry, Vienna University.

***N*-Phenylthiazol-2-amine (1). Method I:** 2-Bromothiazole (1 equiv., 3.00 g, 18.2 mmol) was dissolved in *i*PrOH (50 mL). Then aniline (1.5 equiv., 2.54 g, 27.3 mmol) and *p*TosOH (1.0 equiv., 3.12 g, 18.2 mmol) were added to the reaction mixture. After refluxing for 60 h the reaction mixture was diluted with EtOAc and washed with satd. $NaHCO_3$, water and brine. The organic layer was dried with Na_2SO_4, filtered and the solvent was evaporated. Recrystallization from DIPE gave pure **1** (yield 60%, 1.93 g, 1.09 mmol, yellow solid).

Method II: *N*-Phenylthiourea (1 equiv., 1.00 g, 6.57 mmol), 2-chloro-1,1-diethoxyethane (1 equiv., 0.82 g, 6.57 mmol) and few drops of concd. aqueous HCl were mixed in water (100 mL). After refluxing for 4 h the reaction mixture was diluted with water (100 mL) followed by aq. NaOH (2 N) to make the solution alkaline. The resulting precipitate was collected by filtration, washed with water and dried at 80 °C. Recrystallization from DIPE gave **1** (yield 84%, 0.97 g, 0.55 mmol, yellow solid).

Melting point and NMR spectroscopic data matched literature reports.[27]

1,1-Dimethylethyl *N*-(5-Bromothiazol-2-yl)-*N*-phenylcarbamate (2): *n*BuLi (1.1 equiv., 2.38 M in hexane, 5.03 mL) was added dropwise to a stirred solution of **3** (1.0 equiv., 3.00 g, 10.9 mmol) in dry THF (50 mL) under argon atmosphere at –80 °C. Stirring at –80 °C was continued for 30 min, then Br_2 (1.1 equiv., 1.91 g, 11.94 mmol) was added below –70 °C. The reaction mixture was stirred for additional 30 min at –80 °C and then slowly warmed to ambient temperature. The reaction solution was then poured onto water, diluted with EtOAc, washed with water and brine. The organic layer was dried with Na_2SO_4, filtered and the solvent was evaporated to give **2**. The crude product was purified by MPLC (LP:EtOAc 10:1) to give 86% yield (3.32 g, 9.3 mmol) of **2** as colorless crystals.

Melting point and NMR spectroscopic data match with corresponding values in the literature.[11a] $C_{14}H_{15}BrN_2O_2S$ (355.2): C 47.33, H 4.26, N 7.89; found C 47.55, H 4.11, N 7.87.

General Procedure for the Halogen Dance: Freshly prepared LDA (3.3 equiv. as 10% solution in THF) was added dropwise to the halide (200 mg) in dry THF (10 mL) at –85 °C. The reaction mixture was warmed to –70 °C and stirred at this temperature until TLC showed complete HD reaction. The corresponding electrophile (3.3 equiv.) [15% sol. in THF in case of solids and neat in case of liquid] was added at –90 °C and the reaction mixture was allowed to reach ambient temperature within 1 h. The reaction mixture was diluted with EtOAc, washed with 2 N HCl, water, and brine and the organic phase dried with Na_2SO_4. The solvent was evaporated and the crude product was purified by MPLC or recrystallization.

1,1-Dimethylethyl *N*-(4-Bromothiazol-2-yl)-*N*-phenylcarbamate (8a): M.p. 117–119 °C; yield 97% (194 mg, 0.54 mmol, colorless crystals) MPLC LP/DIPE, 10:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.42 (s, 9 H), 6.85 (s, 1 H), 7.19–7.24 (m, 2 H), 7.33–7.45 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.9 (q), 83.8 (s), 111.8 (d), 120.9 (s), 128.2 (d), 128.3 (d), 129.1 (d), 138.6 (s), 152.7 (s), 162.2 (s) ppm. $C_{14}H_{15}BrN_2O_2S$ (355.25): calcd. C 47.33, H 4.26, N 7.89; found C 47.40, H 4.12, N 7.79.

1,1-Dimethylethyl *N*-(4,5-Dibromothiazol-2-yl)-*N*-phenylcarbamate (8b): M.p. 106–109 °C; yield 50% (121 mg, 0.28 mmol, colorless crystals) MPLC LP/DIPE, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.41 (s, 9 H), 7.16–7.21 (m, 2 H), 7.39–7.45 (m) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.9 (q), 84.3 (s), 101.8 (s), 123.9 (s), 128.4 (d), 128.5 (d), 129.2 (d), 137.6 (s), 152.8 (s), 161.3 (s) ppm. $C_{14}H_{14}Br_2N_2O_2S$ (434.15): calcd. C 38.73, H 3.25, N 6.45; found C 38.93, H 3.30, N 6.34.

1,1-Dimethylethyl *N*-(4-Bromo-5-iodothiazol-2-yl)-*N*-phenylcarbamate (8c): M.p. 144–147 °C; yield 70% (189 mg, 0.39 mmol, colorless crystals) MPLC LP/DIPE, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.41 (s, 9 H), 7.16–7.21 (m, 2 H), 7.35–7.48 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.9 (q), 67.1 (s), 84.3 (s), 128.3 (d), 128.4 (d), 129.2 (d), 130.2 (s), 137.9 (s), 152.8 (s), 165.7 (s) ppm. $C_{14}H_{14}BrIN_2O_2S$ (481.15): calcd. C 34.95, H 2.93, N 5.82; found C 34.94, H 2.76, N 5.75.

1,1-Dimethylethyl *N*-(4-Bromo-5-chlorothiazol-2-yl)-*N*-phenylcarbamate (8d): M.p. 136–138 °C; yield 70% (153 mg, 0.39 mmol, yellow crystals) MPLC LP/DIPE, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.35 (s, 9 H), 7.10–7.14 (m, 2 H), 7.31–7.38 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.0 (q), 84.3 (s), 117.2 (s), 120.7 (s), 128.4 (d), 128.5 (d), 129.2 (d), 137.4 (s), 152.8 (s), 158.8 (s) ppm. $C_{14}H_{14}BrClN_2O_2S$ (389.70): calcd. C 43.15, H 3.62, N 7.19; found C 43.14, H 3.53, N 6.99.

1,1-Dimethylethyl *N*-[4-Bromo-5-(tributylstannyl)thiazol-2-yl]-*N*-phenylcarbamate (8e): M.p. 35–37 °C; yield 65% (235 mg, 0.36 mmol, colorless crystals) MPLC LP/DIPE, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (t, J = 7 Hz, 3 H), 1.15–1.23 (m, 6 H), 1.27–1.38 (m, 6 H), 1.42 (s, 9 H) 1.44–1.52 (m, 6 H), 7.19–7.25 (m, 2 H), 7.35–7.47 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 11.0 (t), 13.6 (q), 27.2 (t), 28.0 (t), 28.9 (q), 83.4 (s), 121.7 (s), 128.0 (s), 128.3 (d), 129.0 (d), 139.2 (s), 152.8 (s), 166.7 (s) ppm.

1,1-Dimethylethyl *N*-(4-Bromo-5-formylthiazol-2-yl)-*N*-phenylcarbamate (8f): M.p. 152–154 °C; yield 97% (215 mg, 0.56 mmol, colorless crystals) MPLC LP/DIPE, 4:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.35 (s, 9 H), 7.10–7.14 (m, 2 H), 7.31–7.38 (m, 3 H), 9.88 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.8 (q), 85.2 (s), 126.9 (s), 128.1 (d), 128.7 (d), 129.3 (d), 133.1 (s), 137.4 (s), 152.3 (s), 167.0 (s), 183.7 (d) ppm. $C_{15}H_{15}BrN_2O_3S$ (383.26): calcd. C 47.01, H 3.94, N 7.31; found C 46.95, H 3.82, N 7.15.

1,1-Dimethylethyl *N*-[4-Bromo-5-(hydroxydiphenylmethyl)thiazol-2-yl]-*N*-phenylcarbamate (8 g): M.p. 184–187 °C; yield 43% (130 mg, 0.24 mmol, colorless crystals) MPLC LP:EtOAc 10:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.35 (s, 9 H), 3.82 (br. s, 1 H), 7.17–7.22 (m, 2 H), 7.31–7.38 (m, 13 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.9 (q), 78.1 (s), 83.8 (s), 119.1 (s), 127.9 (d), 126.5 (d), 127.4 (d), 127.5 (s), 128.0 (d), 128.1 (d), 128.2 (d), 128.4 (d), 129.1 (d), 133.9 (s), 138.2 (s), 143.8 (s), 144.8 (d) 152.5 (s), 160.3 (s) ppm. $C_{27}H_{25}BrN_2O_3S$ (537.47): calcd. C 60.34, H 4.69, N 5.21; found C 60.09, H 4.52, N 5.15.

1,1-Dimethylethyl *N*-[4-Bromo-5-(trimethylsilyl)thiazol-2-yl]-*N*-phenylcarbamate (8h): Yield 97% (233 mg, 0.54 mmol, yellow powder) Data matched with the literature.[18]

General Procedure for Cross-Coupling Reactions

Stille Cross-Coupling: The stannane (1 equiv.) and corresponding halide (1 equiv.) were refluxed in dry toluene (15 mL) with the catalyst [$Pd(PPh_3)_4$, 0.05 equiv.] and CsF (2.2 equiv.). The reaction was monitored by TLC.

Suzuki–Miyaura Cross-Coupling: The boronic acid (1 equiv.), the halide (1 equiv.), the catalyst [$Pd(PPh_3)_4$, 0.05equiv] and the base $NaHCO_3$ (3.3 equiv.) were refluxed in a mixture of DME and H_2O (2:1, 10% solution) until the TLC showed the completion of the reaction.

General Workup Procedure for Cross-Coupling Reactions: The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude mixture was purified by MPLC. The product fractions were collected and the solvent evaporated to obtain pure compound.

1,1-Dimethylethyl *N*-(4-Phenylthiazol-2-yl)-*N*-phenylcarbamate (9): M.p. 128–130 °C; yield 61% (120 mg, 0.34 mmol, colorless crystals), MPLC LP/DIPE, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.43 (s, 9 H), 7.15 (s, 1 H), 7.22–7.32 (m, 5 H), 7.40–7.46 (m, 3 H), 7.61–7.65 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.6 (q), 83.8 (s), 108.4 (d), 126.4 (d), 128.1 (d), 128.3 (d), 129.0 (d), 129.1 (d), 129.3 (d), 135.1 (s), 140.1 (s), 150.4 (d), 153.4 (s), 162.0 (s) ppm. $C_{20}H_{20}N_2O_2S$ (352.45): calcd. C 68.16, H 5.72, N 7.95; found C 68.07, H 5.60, N 7.78.

1,1-Dimethylethyl *N*-[4-(2-Methylphenyl)thiazol-2-yl]-*N*-phenylcarbamate (10): M.p. 80–82 °C; yield 77% (158 mg, 0.43 mmol, colorless powder), MPLC LP/DIPE, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.45 (s, 9 H), 2.97 (s, 3 H), 6.94 (s, 1 H), 7.10–7.14 (m, 3 H), 7.22–7.44 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.3 (q), 28.6 (q), 83.2 (s), 110.9 (d), 125.6 (d), 127.6 (d) 127.7 (d), 128.5 (d), 128.8 (d), 129.3 (d), 130.8 (d) 134.7 (s), 136.3 (s), 139.7 (s), 150.7 (s), 152.9 (s), 160.6 (s) ppm. $C_{21}H_{22}N_2O_2S$ (366.48): calcd. C 68.82, H 6.05, N 7.64; found C 68.87, H 5.87, N 7.69.

1,1-Dimethylethyl *N*-[4-(4-Methylphenyl)thiazol-2-yl]-*N*-phenylcarbamate (11): M.p. 96–98 °C, yield 58% (119 mg, 0.32 mmol, colorless powder), MPLC LP/DIPE, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.49 (s, 9 H), 2.32 (s, 3 H), 7.27–7.31 (m, 3 H), 7.32–7.58 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.2 (q), 28.1 (q), 83.2 (s), 107.1 (d), 125.8 (d), 127.7 (d) 128.6 (d), 128.7 (d), 129.1 (d), 131.9 (s), 137.3 (s), 139.7 (s), 150.0 (s), 152.9 (s), 161.4 (s) ppm. $C_{21}H_{22}N_2O_2S$ (366.48): calcd. C 68.82, H 6.05, N 7.64; found C 68.37, H 5.86, N 7.65.

1,1-Dimethylethyl *N*-[4-(4-Methoxyphenyl)thiazol-2-yl]-*N*-phenylcarbamate (12): M.p. 124–126 °C; yield 39% (83 mg, 0.22 mmol, colorless powder), MPLC LP/DIPE, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.45 (s, 9 H), 3.77 (s, 3 H), 6.78–6.84 (m, 2 H), 7.01 (s, 1 H), 7.27–7.60 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.0 (q), 55.2 (q), 83.2 (s), 106.0 (d), 113.7 (d), 127.1 (d) 127.6 (s), 127.7 (d), 128.5 (d), 128.7 (d), 139.6 (s), 149.6 (s), 152.8 (s), 159.1 (s), 161.4 (s) ppm. $C_{21}H_{22}N_2O_3S$ (382.48): calcd. C 65.95, H 5.80, N 7.32; found C 65.72, H 5.64, N 7.40.

1,1-Dimethylethyl *N*-[4-(2-Fluoropyridin-3-yl)thiazol-2-yl]-*N*-phenylcarbamate (13): M.p. 159–161 °C, yield 64% (134 mg, 0.37 mmol, colorless powder) MPLC LP/EtOAc, 15:1, ^{1}H NMR ($CDCl_3$, 50 MHz): δ = 1.39 (s, 9 H), 6.98–7.05 (m, 1 H), 7.19–7.24 (m, 2 H), 7.33–7.47 (m, 4 H), 7.92–7.96 (m), 7.98–8.07 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.0 (q), 83.6 (s), 114.1 (d, $^4J_{C,F}$ = 14.8 Hz), 117.6 (d, $^2J_{C,F}$ = 26.5 Hz), 121.7 (d, $^4J_{C,F}$ = 4.2 Hz), 127.9 (d), 128.5 (d), 128.9 (d), 139.4 (s), 139.6 (d, $^3J_{C,F}$ = 4.2 Hz), 141.7 (d, $^3J_{C,F}$ = 7.1 Hz), 145.3 (d, $^3J_{C,F}$ = 15.2 Hz), 152.8 (s), 160.2

(d, $^1J_{C,F}$ = 240.9 Hz), 161.3 (s) ppm. $C_{19}H_{18}FN_3O_2S$ (371.43): calcd. C 61.44, H 4.88, N 11.31; found C 61.29, H 4.84, N 11.03.

1,1-Dimethylethyl *N*-[4-(2-Fluoropyridin-4-yl)thiazol-2-yl]-*N*-phenylcarbamate (14): M.p. 126–128 °C, yield 80% (167 mg, 0.45 mmol, yellow powder). MPLC LP/EtOAc, 5:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.38 (s, 9 H), 7.03 (s, 1 H), 7.19–7.22 (m, 3 H), 7.29 (dd, J_{HF} = 1.4, $J_{H5'''}$ = 4.8 Hz, 1 H), 7.34–7.42 (m, 3 H), 8.03 (d, $J_{H5'''}$ = 5.3 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.0 (q), 83.8 (s), 105.7 (d, $^2J_{C,F}$ = 39.0 Hz), 112.6 (d), 117.9 (d, $^4J_{C,F}$ = 3.8 Hz), 128.1 (d), 128.4 (d), 128.9 (d), 139.0 (s), 146.3 (d, $^4J_{C-F}$ = 3.9 Hz), 146.9 (d, $^3J_{C,F}$ = 8.7 Hz), 147.7 (d, $^3J_{C,F}$ = 15.4 Hz), 152.9 (s), 162.1 (s), 164.5 (d, $^1J_{C,F}$ = 234.6 Hz) ppm. $C_{19}H_{18}FN_3O_2S$ (371.43): calcd. C 61.44, H 4.88, N 11.31, S 8.63; found C 61.21, H 5.03, N 10.81, S 8.30.

1,1-Dimethylethyl *N*-(4-Bromo-5-phenylthiazol-2-yl)-*N*-phenylcarbamate (15): M.p. 173–176 °C; yield 80% (143 mg, 0.33 mmol, colorless powder), ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.18 (s, 9 H), 7.24–7.30 (m, 2 H), 7.39–7.44 (m, 4 H) 7.50–7.54 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.0 (q), 83.9 (s), 117.9 (s), 128.1 (d), 128.2 (d), 128.5 (d), 128.6 (d), 128.9 (d), 129.1 (d), 130.7 (s), 138.3 (s), 152.8 (s) ppm. $C_{20}H_{19}BrN_2O_2S$ (431.35): calcd. C 55.69, H 4.44, N 6.49; found C 55.96, H 4.44, N 6.36.

1,1-Dimethylethyl *N*-[4-Bromo-5-(2-fluoropyridin-3-yl)thiazol-2-yl]-*N*-phenylcarbamate (16): M.p. 156–158 °C, yield 37% (69 mg, 0.15 mmol, yellow powder), MPLC LP/EtOAc, 4:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.43 (s, 9 H), 7.23–7.31 (m, 3 H), 7.37–7.52 (m, 3 H), 8.04 (dt, $J_{H6''}$ = 7.4, $J_{H4''}$ = 1.9 Hz, 1 H), 8.24 (d, J_{H5} = 4.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.9 (q), 84.3 (s), 114.0 (d, $^2J_{C,F}$ = 30.3 Hz), 119.0 (d, $^3J_{C,F}$ = 6.4 Hz), 121.4 (d, $^4J_{C,F}$ = 4.3 Hz), 121.9 (s), 128.4 (d), 128.4 (d), 129.1 (d), 138.1 (s), 142.3 (d, $^3J_{C,F}$ = 3.5 Hz), 147.6 (d, $^3J_{C,F}$ = 14.4 Hz), 152.7 (s), 160.0 (d, $^1J_{C,F}$ = 241.6 Hz), 162.2 (s) ppm.

1,1-Dimethylethyl *N*-(4,5-Diphenylthiazol-2-yl)-*N*-phenylcarbamate (20): M.p. 168–172 °C, yield 90% (160 mg, 0.37 mmol, colorless powder), MPLC LP/EtOAc, 20:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.45 (s, 9 H), 7.09–7.16 (m, 3 H), 7.27–7.48 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.0 (q), 83.3 (s), 127.2 (d), 127.6 (d), 127.7 (d), 127.9 (d), 128.6 (d), 128.7 (d), 128.8 (d), 129.6 (d) 132.3 (s), 135.0 (s), 139.2 (s), 144.2 (s), 152.9 (s), 159.3 (s) ppm.

1,1-Dimethylethyl *N*-[4-(2-Methylphenyl)-5-(phenyl)thiazol-2-yl]-*N*-phenylcarbamate (21): M.p. 158–161 °C; yield 50% (91 mg, 0.20, colorless powder) MPLC LP/DIPE, 15:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.46 (s, 9 H), 2.02 (s, 3 H) 6.01–7.41 (m, 14 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.1 (q), 28.0 (q), 83.3 (s), 125.3 (d), 127.0 (s), 127.7 (d), 127.8 (d), 128.4 (d), 128.5 (d), 128.8 (d), 130.3 (d), 130.6 (d), 132.3 (s), 135.1 (s), 137.4 (s), 139.2 (s), 145.3 (s), 152.9 (s), 158.8 (s) ppm. $C_{27}H_{26}N_2O_2S$ (442.57): calcd. C 73.27, H 5.92, N 6.33; found C 72.73, H 5.57, N 6.16.

1,1-Dimethylethyl *N*-[4-Bromo-5-(2-methylphenyl)thiazol-2-yl]-*N*-phenylcarbamate (22): M.p. 160–162 °C; yield 59% (109 mg, 0.24 mmol, colorless powder) MPLC LP/DIPE, 15:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.42 (s, 9 H), 2.32 (s, 3 H) 7.25–7.50 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.3 (q), 28.0 (q), 83.9 (s), 120.2 (s), 125.7 (d), 126.8 (s), 128.2 (d), 128.5 (d), 129.1 (d), 129.2 (d), 129.6 (s), 130.3 (d), 131.4 (d), 138.2 (s), 138.4 (s), 152.7 (s), 161.2 (s) ppm. $C_{21}H_{21}BrN_2O_2S$ (445.37): calcd. C 56.63, H 4.75, N 6.29; found C 57.17, H 4.63, N 6.30.

1,1-Dimethylethyl *N*-[5-(2-Methylphenyl)-4-phenylthiazol-2-yl]-*N*-phenylcarbamate (23): M.p. 177–179 °C; yield 90% (83 mg, 0.19 mmol, colorless powder) MPLC LP/DIPE, 15:1, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.45 (s, 9 H), 2.11 (s, 3 H) 7.03–7.10 (m, 3 H), 7.21–7.48 (m, 11 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.1 (q), 28.0 (q), 83.3 (s), 126.0 (d), 126.2 (s), 127.0 (d), 127.3 (d), 127.7 (d), 127.9 (d), 128.5 (d), 128.6 (d), 128.8 (d), 130.4 (d), 131.4 (d), 131.5 (s), 135.1 (s), 138.0 (s), 139.3 (s), 144.2 (s), 152.9 (s), 159.5 (s) ppm.

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