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Note

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Synthesis of Phenanthrothiazoles and 1,2-Di(heteroaryl)benzenes Through Successive Pd-Catalyzed Direct Arylations

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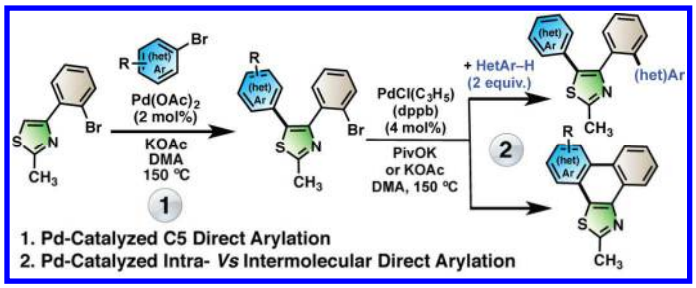


Abstract: Palladium-catalyzed direct arylation of 4-(2-bromophenyl)-2-methylthiazole proceeds in high efficiency at the thiazolyl C5 position using aryl bromides as aryl source. This transformation provides a simple access to 4-(2-bromophenyl)-2-methyl-5-arylthiazoles, which could be further converted into phenanthrothiazoles *via* palladium-catalyzed intramolecular direct arylation. When the direct arylation of 4-(2-bromophenyl)-2-methyl-5-arylthiazoles is conducted in the presence of an external heteroarene such as thiazoles, thiophenes, or imidazo[1,2-a]pyridines, the intermolecular arylation of such external heteroarenes proceeds faster than the intramolecular reaction, allowing the formation of 1,2-di(heteroaryl)benzene derivatives.

Polyaromatic hydrocarbons are an important class of molecules that find applications in organic electronics and optoelectronics due to their unique π–π stacking features in solid states.[1] The incorporation of heteroatoms such as sulfur or nitrogen, in such polyaromatic hydrocarbon structures induces a positive switch of their chemical and/or physical properties. As examples, some thiophene-analogues of polyaromatic hydrocarbons found applications in solar cell systems,[2] as motifs in helicenes,[3]

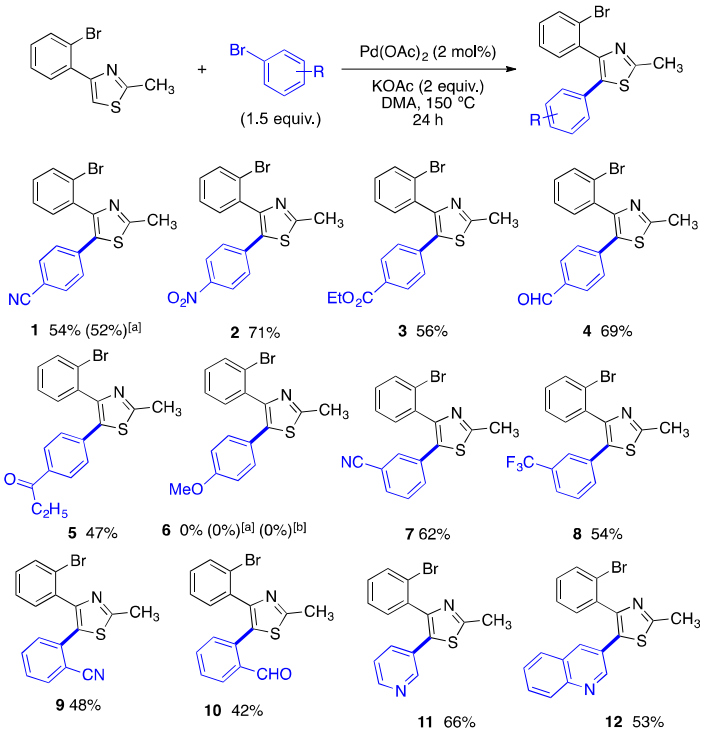
and in nanographenes.[4] Some nitrogen-containing polycyclic aromatic hydrocarbons displayed unprecedented luminescence properties and represent promising candidates for fabricating organic optoelectronic devices.[5] On the other hand, the thiazole moiety is present in a number of important natural products with high pharmacological activities.[6] The synthesis of phenanthroid-fused thiazoles is poorly developed, albeit some phenanthrothiazoles display interesting potential pharmacological activity.[7] One of the major reason of the limited information concerning phenanthrothiazole derivatives probably arises from the scarce synthetic routes described in the literature. Therefore, the discovery of straightforward synthetic routes for access to phenanthrothiazoles remains an important challenge for both academic research groups and for chemical companies.

Domínguez, Tellitu and co-worker reported the synthesis of phenanthrothiazoles through the oxidative cyclization of 4,5-diarylthiazole using a stoichiometric amount of phenyliodine(III)*bis*(trifluoroacetate) reagent.[8] A few example of phenanthrothiazoles synthesis by pyrolysis of 1,2,4-triazine ring under hash reaction conditions (i.e. up to 350 ºC) were also reported.[9] However, with these two procedures, the substrate scope remains very limited due to both challenging access to starting materials and poor functional group tolerance. During the last decades, transition-metal catalyzed direct C–H bond functionalization has emerged as a powerful methodology for the formation of C–C bonds,[10] including direct arylations,[11] C–heteroatom bonds,[12] using palladium catalysis,[13] ruthenium,[14] or other metals,[15] directed C–H bonds,[16] oxidative couplings,[17] and it was also apply to the straightforward synthesis and the easy modifications of organic molecules.[18] In 2013, Nishihara and co-workers reported the synthesis of polyaromatic hydrocarbon such as triphenylenes through cross-coupling followed by annulation reaction of *ortho*-bromobenzylalcohols.[19] A similar strategy was employed by Greaney and co-workers using 2-bromophenylboronic esters.[20] C–H bond arylation was recently transfer to the synthesis of polyaromatic hydrocarbons containing heteroatoms. As example, phenanthro[9,10-*b*]thiophene were synthetized by palladium-catalyzed oxidative intramolecular C–H bond arylation.[21] In 2014, Bach and co-workers reported a novel synthetic route for the preparation of phenanthro[9,10-*c*]thiophenes involving C–H bond activation, Suzuki cross-coupling and photocyclization.[22] Recently, we have reported the

synthesis of thiophene-analogues of polyaromatic hydrocarbons in two operations from thiophenes, 2-bromobenzenesulfonyl chlorides and aryl bromides.[23] The C3-desulfitative arylation of thiophenes provides a straightforward access to 4-(2-bromophenyl)thiophene derivatives,[24] which could react with activated aryl bromides in Pd-promoted two-fold C–H bond arylation to allow to the formation of phenanthro[9,10-*b*]thiophenes. We employed a similar synthetic scheme for the elaboration of medium-size heterocycles with a bridgehead nitrogen atom.[25] However, to the best of our knowledge, there is no example of palladium-catalyzed successive C–H bond arylation reactions for the formation of phenanthrothiazoles.

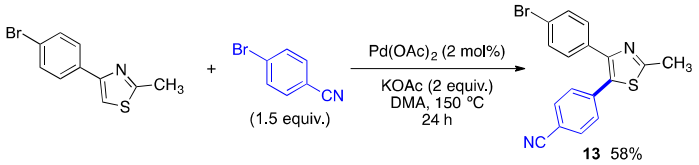
Our investigations started with the evaluation of the reactivity of commercially available 4-(2-bromophenyl)-2-methylthiazole in the presence of 4-bromobenzonitrile under our previously optimized reaction conditions for the synthesis of C5-arylated thiophenes[23, 26] (*i.e.,* 2 mol% $PdCl(C_3H_5)$(dppb) as catalyst in the presence of PivOK as base in DMA at 150 ºC). Interestingly, the intermolecular palladium-catalyzed direct arylation proceeded to give **1** in good yield, without the cleavage of the phenyl C–Br bond. However, under these conditions, no formation of phenanthrothiazole **14**, which would result from a palladium-catalyzed one-pot two-fold direct arylation was observed. This reactivity might be explained by a slower oxidative addition rate to palladium(0) of a bromobenzene bearing a thiazole substituent than a bromobenzene bearing a nitrile group. The use of $Pd(OAc)_2$ as catalyst instead of $PdCl(C_3H_5)$(dppb) and KOAc as base provided **1** in a similar yield. Consequently, this phosphine-free catalytic system was selected to evaluate the reactivity of 4-(2-bromophenyl)-2-methylthiazole with other aryl bromides. All the aryl bromides that we selected displayed a similar reactivity, and only the C5-arylated thiazole derivatives were obtained. Good yields in the desired 4-(2-bromophenyl)-2-methyl-5-arylthiazoles **2-5** were obtained with bromobenzenes substituted at *para*-position by nitro-, ester-, formyl-, or propionyl-substituents in the presence of 2 mol% of phosphine-free $Pd(OAc)_2$. A complex mixture was formed when 4-bromonanisole was used as the aryl source, even using $PdCl(C_3H_5)$(dppb) catalyst. We also investigated the reactivity of 4-iodoanisole, but the desired product **6** was observed in only trace amount

by GC/MS analysis of the crude mixture with other side-products. Among them a huge amount of 4-iodoanisole homocoupling prevents the isolation of **6** in a pure form. The *meta*-substituted electron-deficient aryl bromides, 3-bromobenzonitrile and 1-bromo-3-(trifluoromethyl)benzene, were also found to be suitable reactants, affording **7** and **8** in 62% and 54% yields, respectively. The reaction was found to be slightly sensitive to steric hindrance as the *ortho*-substituted electron-deficient aryl bromides 2-bromobenzonitrile and 2-bromobenzaldehyde delivered the desired 4-(2-bromophenyl)-2-methyl-5-arylthiazoles **9** and **10** in moderate yields of 42% and 48%, respectively. The *N*-containing heteroaryl bromides, 3-bromopyridine and 3-bromoquinoline, were also successfully employed as coupling partners to afford the C5 arylated thiazoles **11** and **12** in 66% and 53% yields, respectively. It is important to mention that, in all the examples mentioned above, the C–Br bond of 4-(2-bromophenyl)-2-methylthiazole remained untouched under these reaction conditions.



Scheme 1. Palladium-Catalyzed Direct Intermolecular C5-Arylation of 4-(2-bromophenyl)-2-methylthiazole. [a] $PdCl(C_3H_5)(dppb)$ and PivOK were used instead of $Pd(OAc)_2$ and KOAc. [b] The reaction is performed with 4-iodoanisole instead of 4-bromoanisole and Ag_2CO_3 as base.

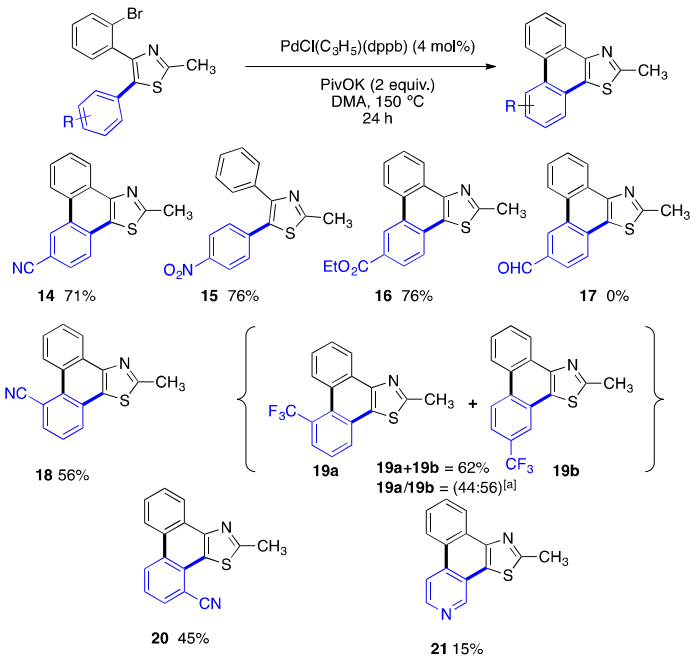
We also investigated the C–Br bond cleavage selectivity using 4-(4-bromophenyl)-2-methylthiazole (Scheme 2). In the presence of 4-bromobenzonitrile, under the optimized reaction conditions (i.e., 2 mol% $Pd(OAc)_2$, KOAc as base in DMA at 150 ºC), we obtained the formation of the C5 arylated product **13** without cleavage of the 4-(4-bromophenyl)-2-methylthiazole C–Br bond. This result suggests that the selectivity of the oxidative addition to palladium(0) is due to electronic effects rather than to steric effects.



Scheme 2. Palladium-Catalyzed Direct Intermolecular C5-Arylation of 4-(4-bromophenyl)-2-methylthiazole.

In a second step, we investigated the reactivity of some of the 5-(2-bromophenyl)-2-methyl-4-arylthiazoles prepared in the Scheme 1 for intramolecular direct arylation (Scheme 3).[27] As expected, the compound **1** did not react in the presence of 4 mol% of $Pd(OAc)_2$ as catalyst associated to PivOK as base in DMA. But, we were pleased to find that **1** was cyclized into the desired phenanthrothiazole **14** using 4 mol% $PdCl(C_3H_5)$(dppb) as catalyst. The use of this palladium catalyst which contains a phosphine ligand, promote the oxidative addition of the 2-bromophenyl moiety. However, the use of a lower catalyst loading of 2 mol% resulted in a partial conversion of **1**. It is important to note that under these conditions, the reaction between 4-(2-bromophenyl)-2-methylthiazole and 4-bromobenzonitrile did not afford the product **12** resulting from a palladium-catalyzed one-pot two-fold direct arylation. Then, we evaluated, under these reaction conditions, the cyclization of few other 4-(2-bromophenyl)-2-methyl-5-arylthiazoles previously prepared. No cyclization occurred using more electron-deficient 4-(2-bromophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (**2**), and only the product **15** resulting from a debromination reaction was isolated in 76% yield. This result might be explained by the formation of "palladium black" due to the presence of a nitro group in the reaction mixture. Such palladium species could catalyze the debromination reaction. On the contrary, the cyclization reaction was found to be operative when the C5 aryl group on thiazole is substituted at the *para* position by an ester group (product **3**) allowing the

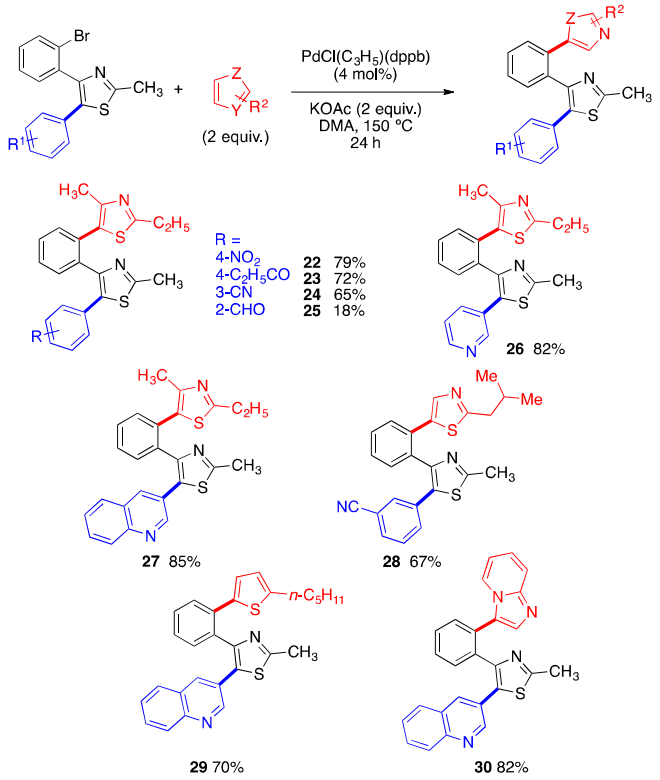
synthesis of the desired phenanthrothiazole **16** in 76% yield. The intramolecular direct arylation does not occur using 4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (**4**), but only the degradation of **4** was observed by GC-MS and NMR analysis, including its deformylation. The cyclization of 3-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzonitrile (**7**), containing a *meta*-substituent on the benzonitrile unit, lead to the single regioisomer **18** in 56% yield. The cyclization occurred at the more sterically hindered *ortho*-position of the cyano group. This regioselectivity is similar to our previous observations for the cyclization of 4-(2-bromophenyl)thiophene in the presence of 3-bromobenzonitrile.[23] This regioselectivity might be explained by electronic factors, such as repulsing effect between sulfur atom and CN group,[28] or a directing group effect of the cyano group. In contrast, the *meta*-substituted 4-(2-bromophenyl)-2-methyl-5-(3-(trifluoromethyl)phenyl)thiazole (**8**) gave a mixture of the two phenanthrothiazole regioisomers **19a** and **19b** in 44:56 ratio. The major product **19b** results from the functionalization of the less sterically hindered C–H bond (at *para* position of the CF_3) and the minor product **19a** arises from the cyclization at the *ortho*-position of the CF_3 substituent, which is the most electron-deficient C–H bond. A cyano substituent at *ortho*-position of the C5-aryl group on thiazole decreases the yield in cyclization product, as desired phenanthrothiazole **20** was isolated in only 45% yield. Finally, the reactivity of the compound **11**, which bears a pyridine at the thiazolyl C5 position was examined in cyclization reaction. Very few examples of or intramolecular palladium-catalyzed direct arylations of substrates containing a pyridine motif have been reported.[29] Using the standard reaction conditions, the cyclization reaction allowed the formation of the desired phenanthrothiazole derivative **21** as a single regioisomer, resulting from the activation of the C4–H bond of the pyridine unit, but in a very low yield.



Scheme 3. Synthesis of Phenanthrothiazole Derivatives *via* Palladium-Catalyzed Direct Intramolecular Arylation of 5-(2-Bromophenyl)-2-methyl-4-arylthiazoles **1-3**, **8-9** and **11**. [a] ratio determined by NMR.

Next, we investigated the reactivity of some 4-(2-bromophenyl)-2-methyl-5-arylthiazoles prepared in the Scheme 1 in intermolecular direct arylation in the presence of heteroarenes (Scheme 4). Under the quite similar conditions than those employed for intramolecular direct arylation in the Scheme 2, namely, 4 mol% $PdCl(C_3H_5)$(dppb) associated to KOAc as base in DMA, we found that 4-(2-bromophenyl)-2-methyl-5-arylthiazole **2** in the presence of 1.5 equivalents of 2-ethyl-4-methylthiazole lead exclusively to the polyaromatic compound **22** in 79% yield, without formation of the phenanthrothiazole **14**. This result indicates that the palladium-catalyzed intermolecular arylation proceeds faster than the intramolecular reaction. It confirms that the thiazolyl C–H bond is more reactive than the C–H bond of the nitrobenzene in palladium-catalyzed direct arylation. Similar results were obtained with the other 4-(2-bromophenyl)-2-methyl-5-arylthiazoles **5**, **7** to furnish the products **23** and **24** in good yields. Starting from 2-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (**10**) and 2-ethyl-4-methylthiazole, the intermolecular direct arylation reaction proceeded in low yield without formation of intramolecular cyclizing product, but the presence of a huge amount of degradation product including one coming from a deformylation was observed. In contrast to the cyclization reaction, in which pyridine or quinoline substituents as C5

position of the thiazole decreased drastically their reactivity, such *N*-containing heteroaryls does not affect the yields for the formation of the derivatives **26** and **27,** which were obtained in 82% and 85% yields from the compounds **11** and **12**, respectively. Using 2-isobutylthiazole, the intermolecular reaction also proceeded faster than the cyclization reaction to afford the compound **28** in good yield. When *n*-pentylthiophene was used as heteroarene with **12**, again only the intermolecular reaction was observed to afford the C5-arylated thiophene **29** in 70% yield. Finally, using imidazo[1,2-*b*]pyridine, which is also a very reactive substrate in palladium-catalyzed C–H bond arylation, again only the intermolecular coupling was observed allowing the formation of **30** in 82% yield.



Scheme 4. Synthesis of 1,2-Dithiazolyarenes Derivatives *via* Palladium-Catalyzed Direct Intermolecular Arylation of 4-(2-Bromophenyl)-2-methyl-5-arylthiazoles **2**, **5**, **7**, and **10**-**12**.

In summary, we have discovered that in contrast to the reaction between 4-(2-bromophenyl)thiophene and electron-deficient aryl bromides, in which palladium-catalyzed one-pot cascade two-fold direct arylations to allow the synthesis of phenanthro[9,10-*b*]thiophenes, the reaction with 4-(2-bromophenyl)-2-methylthiazole stopped after the first direct arylation. This procedure tolerates a wide variety of

substituents on the aryl bromide such as nitro, cyano, ester, ketone, formyl, trifluoromethyl and also pyridine derivatives. The cyclization occurred in a second step using $PdCl(C_3H_5)$(dppb) as catalyst. We also demonstrated that $PdCl(C_3H_5)$(dppb) catalyst preferentially promotes the intermolecular arylation between 4-(2-bromophenyl)-2-methyl-5-arylthiazoles and heteroarenes such as thiazoles, thiophenes, and imidazo[1,2-*a*]pyridines. These two steps procedures from commercially aivalable strating materials represent an economically attractive, and straightforward route for the preparation of a wide range of phenanthro-fused thiazoles and polyaryl derivatives, which could inspire the preparation of structures with applications in electronic devices or potent pharmaceuticals.

EXPERIMENTAL SECTION

All reactions were carried out under argon atmosphere with standard Schlenk techniques. DMA was was not purified before use. ^{1}H NMR spectra were recorded on 400 MHz spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H; 77.0 ppm for ^{13}C), constants were reported in Hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ^{13}C NMR spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

Preparation of the $PdCl(C_3H_5)$(dppb) catalyst:[30] An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The powder was used without purification. (^{31}P 381 MHz, $CDCl_3$) δ = 19.3 (s).

General Procedure A (Palladium-catalyzed direct intermolecular arylation): To a 25 mL oven dried Schlenk tube 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol), aryl bromides (1.5 mmol, 1.5 equiv.), KOAc (196 mg, 2 mmol, 2 equiv.), DMA (4 mL) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and

stirred at 150 °C (oil bath temperature) for 24 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by flash chromatography to afford the desired arylated products.

General Procedure B (Palladium-catalyzed direct intramolecular arylation): To a 25 mL oven dried Schlenk tube 5-(2-bromophenyl)-2-methyl-4-arylthiazole (0.5 mmol), PivOK (140 mg, 1 mmol, 2 equiv.), DMA (4 mL) and $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol, 4 mol%) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 24 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by flash chromatography to afford the desired arylated products.

General Procedure C (Palladium-catalyzed direct intermolecular arylation): To a 25 mL oven dried Schlenk tube 5-(2-bromophenyl)-2-methyl-4-arylthiazole (0.5 mmol), heteroarenes (1 mmol, 2 equiv.), KOAc (98 mg, 1 mmol, 2 equiv.) DMA (4 mL) and $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol, 4 mol%) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 24 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by flash chromatography to afford the desired arylated products.

4-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzonitrile (1): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 4-bromobenzonitrile (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **1** (192 mg, 54%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 4.2 Hz, 2H), 7.28 – 7.24 (m, 3H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.2, 150.2, 136.4, 136.0, 133.3, 132.8, 132.4, 131.8, 130.4, 128.8, 127.7, 123.6, 118.5, 111.2, 19.4. Elemental analysis: calcd (%) for $C_{17}H_{11}BrN_2S$ (355.25): C 57.48, H 3.12; found: C 57.56, H 3.01. MS (IE) = (M+1) 356 m/z.

4-(2-Bromophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (2): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 1-bromo-4-nitrobenzene (303 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **2** (266 mg, 71%) as brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm). 8.08 (d, *J* = 8.9 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.33 – 7.25 (m, 3H), 2.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.5, 150.7, 146.8, 138.4, 135.9, 133.4, 132.4, 131.9, 130.5, 128.9, 127.8, 124.0, 123.6, 19.6. Elemental analysis: calcd (%) for $C_{16}H_{11}BrN_2O_2S$ (375.24): C 51.21, H 2.95; found: C 51.38, H 3.21. MS (IE) = (M+1) 376 m/z.

Ethyl 4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzoate (3): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and ethyl 4-bromobenzoate (344 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **3** (225 mg, 56%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.27 – 7.18 (m, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.0, 164.4, 149.7, 136.4, 136.2, 133.8, 133.2, 131.9, 130.0, 129.8, 129.5, 128.2, 127.6, 123.8, 61.0, 19.4, 14.3. Elemental analysis: calcd (%) for $C_{19}H_{16}BrNO_2S$ (402.31): C 56.73, H 4.01; found: C 56.89, H 4.22. MS (IE) = (M+1) 403 m/z.

4-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (4): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 4-bromobenzaldehyde (278 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **4** (247 mg, 69%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.92 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.27 (m, 4H), 7.27 – 7.20 (m, 1H), 2.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 191.4, 165.0, 150.1, 137.8, 136.3, 135.2, 133.5, 133.3, 131.9, 130.2, 130.0, 128.8, 127.7, 123.7, 19.5. Elemental analysis: calcd (%) for $C_{17}H_{12}BrNOS$ (358.25): C 57.00, H 3.38; found: C 56.87, H 3.59. MS (IE) = (M-1) 357 m/z.

1-(4-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)phenyl)propan-1-one (5): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 4-bromopropiophenone (320 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 85-15) to afford the desired compound **5** (181 mg, 47%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.81 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.29 (m, 2H), 7.28 – 7.19 (m, 3H), 2.93 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 200.0, 164.5, 149.7, 136.5, 136.2, 135.7, 133.7, 133.2, 131.9, 130.1, 128.4, 128.3, 127.6, 123.8, 31.7, 19.4, 8.2. Elemental analysis: calcd (%) for $C_{19}H_{16}BrNOS$ (386.31): C 59.07, H 4.17; found: C 59.21, H 4.02. MS (IE) = (M+1) 387 m/z.

3-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzonitrile (7): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 3-bromobenzonitrile (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **7** (220 mg, 62%) as brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.40 – 7.28 (m, 4H), 7.25 (d, *J* = 8.1 Hz, 1H), 2.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 164.7, 149.9, 135.8, 133.3, 133.2, 132.6, 132.2, 131.9, 131.7, 131.1, 130.4, 129.5, 127.7, 123.6, 118.2, 112.9, 19.4. Elemental analysis: calcd (%) for $C_{17}H_{11}BrN_2S$ (355.25): C 57.48, H 3.12; found: C 57.24, H 2.95. MS (IE) = (M-1) 354 m/z.

4-(2-Bromophenyl)-2-methyl-5-(3-(trifluoromethyl)phenyl)thiazole (8): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 1-bromo-3-(trifluoromethyl)benzene (338 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 90-10) to afford the desired compound **8** (215 mg, 54%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.43 (s, 1H), 7.37 – 7.29 (m, 4H), 7.27 – 7.20 (m, 1H), 2.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 164.3, 149.7, 136.1, 133.2, 133.1, 132.6, 131.9, 131.5, 130.9 (q, *J* = 32.1Hz), 130.1, 129.1, 127.6, 125.2 (q, *J* = 3.9 Hz), 124.4 (q, *J* =

3.7 Hz), 123.9 (q, J = 272.7 Hz), 123.8, 19.4. Elemental analysis: calcd (%) for $C_{17}H_{11}BrF_3NS$ (398.24): C 51.27, H 2.78; found: C 51.33, H 2.89. MS (IE) = (M+1) 399 m/z.

2-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzonitrile (9): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 2-bromobenzonitrile (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **9** (170 mg, 48%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (dd, J = 1.3, 7.5 Hz, 1H), 7.50 (dd, J = 1.0, 8.0 Hz, 1H), 7.45 – 7.32 (m, 3H), 7.32 – 7.21 (m, 2H), 7.14 (td, J = 1.8, 7.8 Hz, 1H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.8, 151.8, 135.4, 135.3, 133.5, 133.0, 132.5, 132.4, 131.7, 130.0, 129.8, 128.6, 127.3, 123.6, 117.8, 113.2, 19.4. Elemental analysis: calcd (%) for $C_{17}H_{11}BrN_2S$ (355.25): C 57.48, H 3.12; found: C 57.21, H 3.32. MS (IE) = (M+1) 356 m/z.

2-(4-(2-Bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (10): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 2-bromobenzaldehyde (278 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **10** (150 mg, 42%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.04 (s, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.44 – 7.33 (m, 2H), 7.23 – 7.16 (m, 2H), 7.14 – 7.06 (m, 1H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 190.8, 165.7, 152.0, 134.9, 134.3, 134.3, 133.6, 133.2, 132.4, 132.4, 130.1, 129.8, 129.0, 127.9, 127.3, 123.6, 19.4. Elemental analysis: calcd (%) for $C_{17}H_{12}BrNOS$ (358.25): C 57.00, H 3.38; found: C 57.11, H 3.61. MS (IE) = (M-1) 357 m/z.

4-(2-Bromophenyl)-2-methyl-5-(pyridin-3-yl)thiazole (11): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 3-bromopyridine (237 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **11** (218 mg, 66%) as brown oil: ^{1}H NMR (400 MHz, THF-d_8) δ (ppm) 8.57 – 8.31 (m, 2H), 7.60 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 5.2 Hz, 1H), 7.41 – 7.10 (m, 4H), 2.71 (s, 3H). ^{13}C NMR (75 MHz, THF-d_8) δ (ppm) 164.9, 151.0, 149.8, 149.6, 137.5, 136.1, 133.9, 133.1, 131.9, 130.9, 129.2, 128.3, 124.4,

124.2, 19.2. Elemental analysis: calcd (%) for $C_{15}H_{11}BrN_2S$ (331.23): C 54.39, H 3.35; found: C 54.67, H 3.19. MS (IE) = (M+1) 332 m/z.

4-(2-Bromophenyl)-2-methyl-5-(quinolin-3-yl)thiazole (12): Following the general procedure **A** using 4-(2-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 3-bromoquinoline (312 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **12** (202 mg, 53%) as brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.69 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 1.9 Hz, 1H), 7.65 (s, 2H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.30 (td, *J* = 1.0, 7.1 Hz, 1H), 7.21 (td, *J* = 1.7, 7.8 Hz, 1H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 164.7, 150.1, 149.8, 147.0, 136.1, 134.7, 133.3, 132.0, 131.3, 130.3, 129.9, 129.2, 127.9, 127.7, 127.5, 127.2, 125.3, 123.8, 19.5. Elemental analysis: calcd (%) for $C_{19}H_{13}BrN_2S$ (381.29): C 59.85, H 3.44; found: C 60.13, H 3.58. MS (IE) = (M+1) 382 m/z.

4-(4-(4-Bromophenyl)-2-methylthiazol-5-yl)benzonitrile (13): Following the general procedure **A** using 4-(4-bromophenyl)-2-methylthiazole (254 mg, 1 mmol) and 4-bromobenzonitrile (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **13** (206 mg, 58%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 2.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6, 149.8, 136.8, 133.2, 132.6, 131.8, 130.7, 130.6, 130.0, 122.6, 118.4, 111.7, 19.3. Elemental analysis: calcd (%) for $C_{17}H_{11}BrN_2S$ (355.25): C 57.48, H 3.12; found: C 57.21, H 2.89. MS (IE) = (M+1) 356 m/z.

2-Methylphenanthro[9,10-*d*]thiazole-9-carbonitrile (14): Following the general procedure **B** using 4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzonitrile (**1**) (178 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et_2O, 85-15) to afford the desired compound **14** (97 mg, 71%) as a white solid (mp = 251-254 ºC): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.99 (s, 1H), 8.82 (d, *J* = 8.9 Hz, 1H), 8.62 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.83 – 7.73 (m, 3H), 2.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.7, 150.7, 129.8, 129.7, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3,

127.6, 126.7, 125.0, 123.0, 119.3, 109.5, 20.3. Elemental analysis: calcd (%) for $C_{17}H_{10}N_2S$ (274.34): C 74.43, H 3.67; found: C 74.59, H 3.72. MS (IE) = (M) 274 m/z.

2-Methyl-5-(4-nitrophenyl)-4-phenylthiazole (15) Following the general procedure **B** using 4-(2-bromophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (**2**) (188 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et_2O, 80-20) to afford the desired compound **15** (112 mg, 76%) as a yellow solid (mp = 133-136 ºC): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.14 (d, *J* = 8.9 Hz, 2H), 7.48-7.46 (m, 2H), 7.46 – 7.43 (m, 2H), 7.36 – 7.30 (m, 3H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.6, 151.7, 147.0, 139.1, 134.2, 130.0, 129.8, 129.1, 128.7, 128.5, 124.0, 19.4. Elemental analysis: calcd (%) for $C_{16}H_{12}N_2O_2S$ (296.34): C 64.85, H 4.08; found: C 65.11, H 4.23. MS (IE) = (M) 296 m/z.

Ethyl 2-methylphenanthro[9,10-*d*]thiazole-9-carboxylate (16): Following the general procedure **B** using 4 ethyl 4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzoate (**3**) (201 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH_2Cl_2, 40-60) to afford the desired compound **16** (122 mg, 76%) as a yellow solid (mp = 175-178 ºC):: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.40 (s, 1H), 8.86 – 8.66 (m, 2H), 8.21 (dd, *J* = 1.4, 8.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.81 – 7.63 (m, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 2.97 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.9, 166.6, 150.1, 130.2, 130.1, 129.8, 128.2, 128.1, 127.9, 127.8, 127.4, 127.2, 125.9, 125.8, 124.8, 123.3, 61.3, 20.2, 14.5. Elemental analysis: calcd (%) for $C_{19}H_{15}NO_2S$ (321.39): C 71.01, H 4.70; found: C 70.87, H 4.65. MS (IE) = (M+1) 322 m/z.

2-Methylphenanthro[9,10-*d*]thiazole-8-carbonitrile (18): Following the general procedure **B** using 3-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzonitrile (**7**) (178 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH_2Cl_2, 20-80) to afford the desired compound **18** (77 mg, 56%) as a white solid (mp = 231-234 ºC):: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.77 (d, *J* = 8.8 Hz, 1H), 8.85 (dd, *J* = 1.5, 7.9 Hz, 1H), 8.11 (dd, *J* = 1.3, 8.0 Hz, 1H), 8.03 (dd, *J* = 1.3, 7.4 Hz, 1H), 7.86 – 7.71 (m, 2H), 7.63 (t, *J* = 7.7 Hz, 1H), 2.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.7, 149.5, 135.5,

131.0, 130.3, 128.9, 128.9, 128.4, 128.4, 128.0, 127.2, 126.3, 125.2, 124.9, 121.3, 108.4, 20.2. Elemental analysis: calcd (%) for $C_{17}H_{10}N_2S$ (274.34): C 74.43, H 3.67; found: C 74.63, H 3.55. MS (IE) = (M) 274 m/z.

2-Methyl-8-(trifluoromethyl)phenanthro[9,10-*d*]thiazole (19a) and **2-Methyl-10-(trifluoromethyl)phenanthro[9,10-*d*]thiazole (19b):** Following the general procedure **B** using 3-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzonitrile (**8**) (199 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH_2Cl_2, 60-40) to afford the desired compound **19** (98 mg, 62%) as a mixture of the two regioisomers in 44:56 ratio as a white solid (mp = 111-115 ºC):: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.80 (dd, *J* = 1.3, 8.0 Hz, 1H, **19b**), 8.78 – 8.71 (m, 2H, **19a**+**19b**), 8.67 (d, *J* = 8.7 Hz, 1H, **19b**), 8.57 (d, *J* = 8.0 Hz, 1H, **19b**), 8.06 (s, 1H, **19b**), 8.04 (d, *J* = 8.2 Hz, 1H, **19a**), 7.99 (d, *J* = 7.9 Hz, 1H, **19a**), 7.78 – 7.66 (m, 5H, **19a**+**19b**), 7.64 – 7.57 (m, 1H, **19a**), 2.93 (s, 3H, **19b**), 2.92 (s, 3H, **19a**). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm). 166.3, 166.2, 149.4, 149.1, 130.7 (q, *J* = 2.1 Hz), 130.5 (q, *J* = 30,1 Hz), 130.0, 129.5, 129.1, 128.9, 128.9 (q, *J* = 32.1 Hz), 128.8, 128.7, 128.5, 128.4, 128.1, 127.9, 127.3, 127.1 (q, *J* = 8.2 Hz), 127.1, 126.6, 126.0, 125.9, 125.4 (q, *J* = 271.5 Hz), 124.8, 124.4, 124.2, 124.1 (q, *J* = 271.5 Hz), 123.3, 122.8 (q, *J* = 4.0 Hz), 122.1 (q, *J* = 4.0 Hz), 20.1, 20.1. Elemental analysis: calcd (%) for $C_{17}H_{10}F_3NS$ (317.33): C 64.35, H 3.18; found: C 64.49, H 3.11. MS (IE) = (M) 317 m/z.

2-Methylphenanthro[9,10-*d*]thiazole-11-carbonitrile (20): Following the general procedure **B** using 2-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzonitrile (**9**) (178 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH_2Cl_2, 10-90) to afford the desired compound **20** (61 mg, 45%) as a yellow solid (mp = 150-153 ºC):: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.24 (d, *J* = 8.3 Hz, 1H), 8.89 (d, *J* = 7.5 Hz, 1H), 8.71 (d, *J* = 7.5 Hz, 1H), 8.25 (d, *J* = 7.4 Hz, 1H), 7.91 – 7.73 (m, 3H), 2.96 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 168.8, 151.1, 135.4, 130.1, 129.3, 129.2, 129.1, 128.4, 127.8, 127.5, 127.4, 126.7, 124.9, 124.3, 119.9, 107.4, 19.9. Elemental analysis: calcd (%) for $C_{17}H_{10}N_2S$ (274.34): C 74.43, H 3.67; found: C 74.59, H 3.72. MS (IE) = (M) 274 m/z.

2-Methylbenzo[*f*]thiazolo[4,5-*h*]isoquinoline (21): Following the general procedure **B** using 4-(2-Bromophenyl)-2-methyl-5-(pyridin-3-yl)thiazole (**11**) (166 mg, 0.5 mmol, 1 equiv.) the residue was purified by flash chromatography on silica gel (pentane-Et_2O, 50-50) to afford the desired compound **21** (19 mg, 15%) as a brown solid (mp = 45-50 ºC):: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.34 (d, *J* = 8.0 Hz, 1H), 9.02 (d, *J* = 3.3 Hz, 1H), 8.80 (d, *J* = 7.9 Hz, 1H), 8.27 (d, *J* = 7.7 Hz, 1H), 7.89 – 7.75 (m, 2H), 7.58 (dd, *J* = 4.4, 8.1 Hz, 1H), 3.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.3, 148.3, 145.2, 133.0, 130.9, 130.8, 129.3, 129.0, 127.1, 125.1, 124.0, 122.2, 122.1, 118.6, 20.2. Elemental analysis: calcd (%) for $C_{15}H_{10}N_2S$ (250.31): C 71.97, H 4.03; found: C 72.08, H 4.34. MS (IE) = (M) 250 m/z.

2-Ethyl-4-methyl-5-(2-(2-methyl-5-(4-nitrophenyl)thiazol-4-yl)phenyl)thiazole (22): Following the general procedure **C** using 4-(2-bromophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (**2**) (188 mg, 0.5 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 50-50) to afford the desired compound **22** (172 mg, 79%) as a brown solid (mp = 99-102 ºC): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.98 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.26-7.24 (m, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 2.87 – 2.69 (m, 2H), 2.77 (s, 3H), 1.74 (s, 3H), 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.9, 150.5, 147.9, 146.9, 138.6, 134.7, 132.0, 131.9, 131.3, 131.2, 129.2, 129.2, 129.1, 129.0, 128.9, 123.9, 26.8, 19.5, 15.2, 14.6. Elemental analysis: calcd (%) for $C_{22}H_{19}N_3O_2S_2$ (421.53): C 62.69, H 4.54; found: C 62.79, H 4.31. MS (IE) = (M) 421 m/z.

1-(4-(4-(2-(2-Ethyl-4-methylthiazol-5-yl)phenyl)-2-methylthiazol-5-yl)phenyl)propan-1-one (23): Following the general procedure **C** using 1-(4-(4-(2-bromophenyl)-2-methylthiazol-5-yl)phenyl)propan-1-one (**5**) (193 mg, 0.5 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 50-50) to afford the desired compound **23** (156 mg, 72%) as a brown solid (mp = 64-49 ºC): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 – 7.68 (m, 3H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.43 (td, *J* = 1.3, 7.5 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 2H), 2.95 (q, *J* = 7.2 Hz, 2H), 2.89 – 2.81 (m, 2H), 2.78 (s, 3H), 1.75 (s, 3H), 1.27 (d, *J* = 7.3

Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 200.0, 164.8, 149.4, 147.7, 136.5, 136.5, 136.3, 135.6, 135.2, 134.4, 133.3, 131.7, 131.2, 129.2, 128.6, 128.3, 128.2, 31.8, 26.6, 19.3, 15.1, 14.5, 8.2. Elemental analysis: calcd (%) for $C_{25}H_{24}N_2OS_2$ (432.60): C 69.41, H 5.59; found: C 69.49, H 5.21. MS (IE) = (M) 432 m/z.

3-(4-(2-(2-Ethyl-4-methylthiazol-5-yl)phenyl)-2-methylthiazol-5-yl)benzonitrile (24): Following the general procedure **C** using 3-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzonitrile (**7**) (178 mg, 0.5 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 50-50) to afford the desired compound **24** (130 mg, 65%) as a brown solid (mp = 47-50 ºC): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (dd, J = 1.4, 7.6 Hz, 1H), 7.46 (d, J = 7.2, 16.6 Hz, 3H), 7.30 – 7.19 (m, 2H), 7.10 (s, 1H), 7.05 (d, J = 7.9 Hz, 1H), 2.84 (q, J = 7.5 Hz, 2H), 2.76 (s, 3H), 1.74 (s, 3H), 1.28 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.2, 149.7, 147.9, 134.5, 133.4, 132.5, 131.9, 131.7, 131.6, 131.4, 131.1, 131.0, 129.5, 129.2, 129.0, 128.9, 118.2, 112.9, 26.8, 19.5, 15.3, 14.5. Elemental analysis: calcd (%) for $C_{23}H_{19}N_3S_2$ (401.55): C 68.80, H 4.77; found: C 68.79, H 5.03. MS (IE) = (M) 401 m/z.

2-(4-(2-(2-Ethyl-4-methylthiazol-5-yl)phenyl)-2-methylthiazol-5-yl)benzaldehyde (25): Following the general procedure **C** using 2-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzaldehyde (**10**) (179 mg, 0.5 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 50-50) to afford the desired compound **25** (37 mg, 18%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.75 (dd, J = 3.4, 5.9 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.0 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.13 (d, J = 7.7 Hz, 1H), 6.78 (dd, J = 3.2, 5.7 Hz, 1H), 2.86 (q, J = 7.5 Hz, 2H), 2.82 (s, 3H), 1.67 (s, 3H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 190.1, 166.2, 151.6, 135.8, 134.3, 133.8, 133.4, 133.3, 132.2, 131.8, 131.5, 131.2, 129.4, 129.1, 128.8, 128.7, 128.6, 127.8, 125.5, 26.6, 19.3, 15.2, 14.2. Elemental analysis: calcd (%) for $C_{23}H_{20}N_2OS_2$ (404.54): C 68.29, H 4.98; found: C 68.12, H 5.21. MS (IE) = (M) 404 m/z.

2-Ethyl-4-methyl-5-(2-(2-methyl-5-(pyridin-3-yl)thiazol-4-yl)phenyl)thiazole (26): Following the general procedure **C** using 4-(2-Bromophenyl)-2-methyl-5-(pyridin-3-yl)thiazole (**11**) (166 mg, 0.5 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (EtOAc, 100) to afford the desired compound **26** (155 mg, 82%) as brown oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) δ 8.40 (d, J = 3.8 Hz, 1H), 7.97 (s, 1H), 7.67 (d, J = 6.4 Hz, 1H), 7.59 – 7.40 (m, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.24 (d, J = 4.7 Hz, 1H), 7.20 – 7.14 (m, 1H), 2.76 (q, J = 7.4 Hz, 2H), 2.72 (s, 3H), 1.64 (s, 3H), 1.18 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 170.2, 165.2, 149.4, 148.8, 148.1, 147.8, 135.5, 134.9, 131.9, 131.7, 131.0, 130.7, 129.3, 129.0, 128.8, 128.0, 124.2, 26.3, 19.4, 15.4, 14.5. Elemental analysis: calcd (%) for $C_{21}H_{19}N_3S_2$ (377.52): C 66.81, H 5.07; found: C 67.06, H 4.85. MS (IE) = (M+1) 378 m/z.

2-Ethyl-4-methyl-5-(2-(2-methyl-5-(quinolin-3-yl)thiazol-4-yl)phenyl)thiazole (27): Following the general procedure **C** using 4-(2-bromophenyl)-2-methyl-5-(quinolin-3-yl)thiazole (**12**) (191 mg, 0.5 mmol, 1 equiv.) and 2-ethyl-4-methylthiazole (127 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 40-60) to afford the desired compound **27** (182 mg, 85%) as brown oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) δ 8.19 (d, J = 1.9 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.78 – 7.72 (m, 3H), 7.63 – 7.53 (m, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 2.76 (s, 3H), 2.59 (q, J = 7.5 Hz, 2H), 1.41 (s, 3H), 1.00 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 170.2, 165.4, 149.5, 149.0, 147.6, 146.8, 134.9, 134.5, 132.1, 131.8, 130.9, 130.4, 129.3, 129.0, 128.9, 128.8, 128.5, 127.7, 125.2, 26.2, 19.5, 15.1, 14.0. Elemental analysis: calcd (%) for $C_{25}H_{21}N_3S_2$ (427.58): C 70.23, H 4.95; found: C 70.29, H 5.12. MS (IE) = (M) 427 m/z.

3-(4-(2-(2-Isobutylthiazol-5-yl)phenyl)-2-methylthiazol-5-yl)benzonitrile (28): Following the general procedure **C** using 3-(4-(2-bromophenyl)-2-methylthiazol-5-yl)benzonitrile (**7**) (178 mg, 0.5 mmol, 1 equiv.) and 2-isobutylthiazole (141 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **28** (139 mg, 67%) as brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.51 (dd, J = 2.4, 5.1 Hz, 1H), 7.46 – 7.37 (m, 4H),

7.21 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 5.4 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.02 (s, 1H), 2.75 (s, 3H), 2.73 (d, J = 7.1 Hz, 2H), 2.08 – 1.89 (m, 1H), 0.94 (d, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.4, 165.1, 149.8, 139.9, 136.1, 133.2, 132.9, 132.4, 132.1, 131.6, 131.2, 131.0, 130.9, 130.3, 129.3, 129.3, 128.7, 118.1, 112.7, 42.1, 29.7, 22.2, 19.4. Elemental analysis: calcd (%) for $C_{24}H_{21}N_3S_2$ (415.57): C 69.37, H 5.09; found: C 69.44, H 5.21. MS (IE) = (M) 415 m/z.

2-Methyl-4-(2-(5-pentylthiophen-2-yl)phenyl)-5-(quinolin-3-yl)thiazole (29): Following the general procedure **C** using 4-(2-bromophenyl)-2-methyl-5-(quinolin-3-yl)thiazole (**12**) (191 mg, 0.5 mmol, 1 equiv.) and 2-*n*-pentylthiophene (155 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **29** (159 mg, 70%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.64 (dd, J = 1.5, 6.8 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.39 – 7.32 (m, 3H), 6.36 (d, J = 3.5 Hz, 1H), 6.24 (d, J = 3.5 Hz, 1H), 2.81 (s, 3H), 2.55 (t, J = 7.6 Hz, 2H), 1.53 – 1.40 (m, 2H), 1.35 – 1.20 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.6, 150.6, 149.9, 146.7, 139.6, 134.6, 134.5, 132.8, 131.2, 130.8, 130.0, 129.5, 129.1, 129.0, 127.7, 127.7, 127.5, 126.9, 125.5, 125.2, 123.8, 31.3, 31.2, 29.9, 22.4, 19.5, 14.0. Elemental analysis: calcd (%) for $C_{28}H_{26}N_2S_2$ (454.65): C 73.97, H 5.76; found: C 74.11, H 5.69. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{26}N_2NaS_2$ 477.14351; Found 477.1435.

4-(2-(Imidazo[1,2-*a*]pyridin-3-yl)phenyl)-2-methyl-5-(quinolin-3-yl)thiazole (30): Following the general procedure **C** using 4-(2-bromophenyl)-2-methyl-5-(quinolin-3-yl)thiazole (**12**) (191 mg, 0.5 mmol, 1 equiv.) and imidazo[1,2-*a*]pyridazine (118 mg, 1 mmol, 2 equiv.), the residue was purified by flash chromatography on silica gel (CH_2Cl_2-MeOH, 95-5) to afford the desired compound **30** (172 mg, 82%) as brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (d, J = 2.2 Hz, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.58 – 7.49 (m, 3H), 7.47 – 7.40 (m, 1H), 7.37 – 7.32 (m, 2H), 7.31 – 7.24 (m, 2H), 7.20 (d, J = 8.8 Hz, 1H), 7.12 (s, 1H), 6.54 (t, J = 7.0, 7.7 Hz, 1H), 5.91 (t, J = 6.1, 7.4 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.3, 149.5, 149.0, 146.8, 144.7, 134.9, 134.1, 133.0,

132.0, 130.3, 129.7, 129.5, 129.1, 129.1, 128.8, 127.8, 126.8, 126.8, 124.4, 123.5, 123.3, 121.8, 116.7, 111.3, 19.4. Elemental analysis: calcd (%) for $C_{26}H_{18}N_4S$ (418.52): C 74.62, H 4.34; found: C 74.37, H 4.22. MS (IE) = (M) 418 m/z.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Characterization data, ^{1}H and ^{13}C NMR spectra for all new compounds.

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