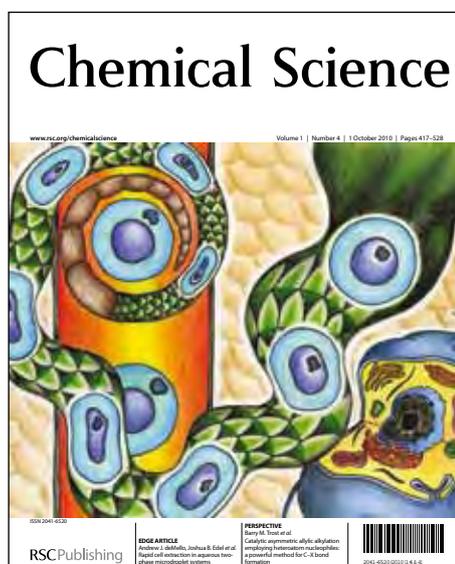


# Chemical Science

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EDGE ARTICLE

# Programmed Synthesis of Arylthiazoles through Sequential C–H Couplings

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A programmed synthesis of privileged arylthiazoles via sequential C–H couplings catalyzed by palladium or nickel catalysts has been accomplished. This versatile protocol can supply all possible arylthiazole substitution patterns (2-aryl, 4-aryl, 5-aryl, 2,4-diaryl, 2,5-diaryl, 4,5-diaryl, and 2,4,5-triaryl) from an unfunctionalized thiazole platform by 11 distinct synthetic routes. We have generated over 150 arylthiazoles by using this methodology. We have applied this method to the rapid synthesis of fatostatin (SREBP inhibitor), and the 10 gram-scale synthesis of triarylthiazoles has been demonstrated.

## Introduction

Thiazoles attached with aryl or heteroaryl groups (arylthiazoles) represent privileged structural motifs that are frequently utilized in functional organic materials including 15 organic electroluminescent devices, as well as in bioactive compounds and pharmaceuticals (Figure 1).<sup>1</sup> Thus, an efficient synthetic methodology that allows cost- and step-efficient production of arylthiazoles is in high demand. Moreover, in a situation where the structure-property relationships are not 20 predictable, a uniform and programmable design that allows the synthesis of all possible arylthiazoles (2-aryl, 4-aryl, 5-aryl, 2,4-diaryl, 2,5-diaryl, 4,5-diaryl, and 2,4,5-triaryl) would help accelerate identifying and optimizing the “functional” arylthiazole structures. Therefore, both step economy and 25 programmability need to be implemented in the next-generation synthesis of privileged arylthiazoles.

To date, the majority of arylthiazoles are synthesized by the classical Hantzsch thiazole synthesis, connecting  $\alpha$ -haloketones and thioamides in a convergent manner.<sup>2</sup> The advantage of this 30 method is that it is possible to synthesize large amounts of arylthiazoles from inexpensive starting materials. However, the syntheses of both  $\alpha$ -haloketones and thioamides typically require several steps from commercially available compounds, rendering the rapid construction of arylthiazole libraries difficult. To 35 address this drawback, various cyclization methods for the synthesis of arylthiazoles have been developed.<sup>3</sup> As an alternative and newer method, palladium-catalyzed cross-coupling reactions allow the divergent synthesis of arylthiazoles.<sup>4,5</sup> However, superfluous steps are required prior to the cross-coupling; the parent thiazole must be pre-functionalized with a halogen or a metal group at the position where aryl groups are to be installed.

In pursuit of developing a step-economical and programmable arylthiazole synthesis, we have been attracted by the potential of catalytic C–H arylation reactions of thiazoles.<sup>6–9</sup> Unlike the cross-coupling method, aryl groups can be installed onto the thiazole 45 core directly in C–H arylation (step economy). Moreover, as the three C–H bonds on thiazole (C2, C4, C5) are chemically nonequivalent, it is in principle possible to acquire bond selectivity (regioselectivity) in aryl-installing reactions and to

50 strategically utilize them in orthogonal functionalization (programmability).

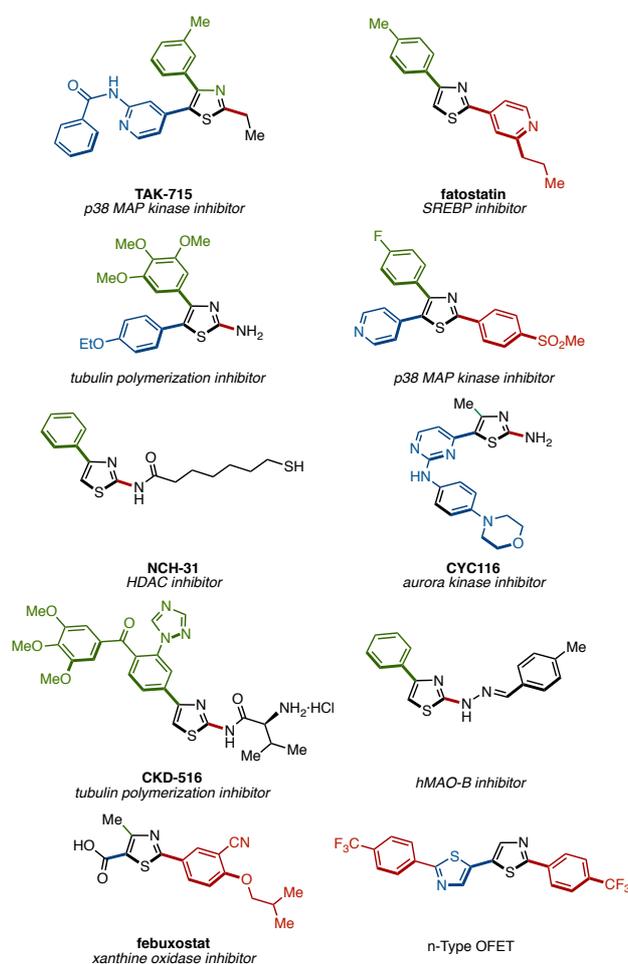


Fig 1. Selected examples of functional arylthiazoles.

Herein, we report a general and programmable synthetic scheme that can synthesize all possible arylthiazole substitution patterns (2-aryl, 4-aryl, 5-aryl, 2,4-diaryl, 2,5-diaryl, 4,5-diaryl, and 2,4,5-triaryl) from an unfunctionalized thiazole platform (Figure 2).<sup>10</sup> In this article, an application to the rapid synthesis of fatostatin (SREBP inhibitor), a re-optimization of C4-selective arylation of 2-substituted thiazoles, and a gram-scale synthesis of triarylthiazole are also described. Noteworthy features of the present methodology are that (i) all aryl groups assembled stem from readily available aryl halides or arylboronic acids, (ii) the aryl-group-installation at the desired position can be achieved by the choice of catalytic systems, and (iii) due to the regiodivergent nature of established catalytic conditions, 11 distinct pathways for 7 arylthiazoles has been established.

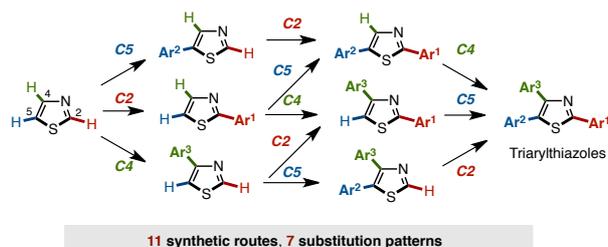


Fig 2. Programmed synthesis of arylthiazoles.

In order to achieve fully programmed synthesis of arylthiazoles as shown in Figure 2, it is essential to acquire regiodivergency in thiazole C–H arylation by *catalyst control*.<sup>11</sup> This is conceptually different from the previously reported procedures for the selective synthesis of multiply arylated thiazoles, which are mainly based on the inherent reactivity difference of three thiazole C–H bonds (*substrate control*).<sup>12</sup> In 2008, Fagnou and coworkers reported a pioneering work on the regioselective synthesis of arylthiazoles via Pd-catalyzed C–H couplings to install three different aryl groups (Figure 3; i).<sup>11a</sup> Their method, wherein a thiazole was first oxidized to a thiazole *N*-oxide, involved C–H arylations of thiazole *N*-oxides with aryl halides in the order of C2, C5 then C4; these reactions all proceeded regioselectively to give the desired triarylthiazole *N*-oxides. Finally, reduction of the *N*-oxides was conducted to afford the target triarylthiazoles. In 2011, Murai, Shibahara, and coworkers reported a sequential C–H arylation of thiazoles using their own Pd catalyst (Figure 3; ii).<sup>11b</sup> Thiazoles were coupled with aryl halides in the order of C5, C2, then C4 to afford triarylthiazoles. Although these two protocols successfully provide arylthiazoles in a regioselective manner, only one pathway en route to triarylthiazoles has been developed. Moreover, these protocols allow access to only 3 arylthiazole substitution patterns and the pathways leading to 4 remaining substitution patterns have not been developed (4-aryl, 5-aryl, 2,4-diaryl, and 4,5-diaryl for the Fagnou method, and 2-aryl, 4-aryl, 2,4-diaryl, and 4,5-diaryl for the Murai-Shibahara method). Similar limitation was also observed in our previous work on the regioselective synthesis of multiply arylated thiophenes.<sup>13a</sup>

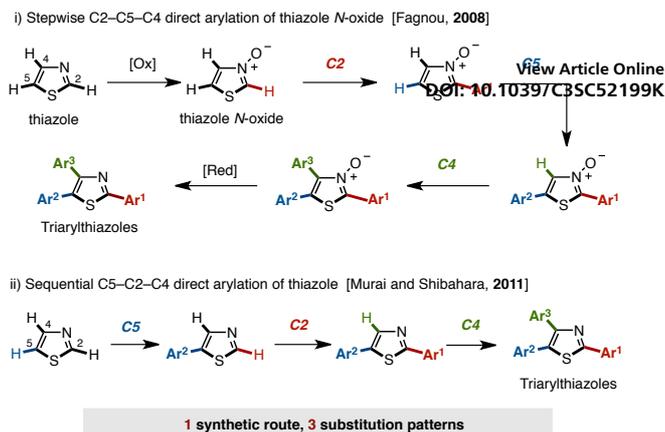
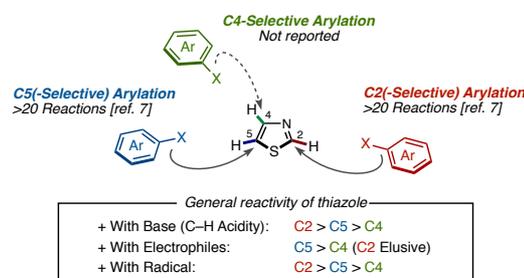


Fig 3. Selective synthesis of multiply arylated thiazoles by Fagnou and Murai/Shibahara.

These seminal works clearly show the limitation of relying solely on substrate control (reactivity difference of C–H bonds of thiazole). Catalyst-controlled regioselectivity (regiodivergency) and selective C–H arylation at the least reactive C4 position have to be established to realize the programmed synthesis of arylthiazoles. The latter issue is evident from the previous reports by Fagnou and Murai/Shibahara as they both conducted the C4 arylation in the last step.

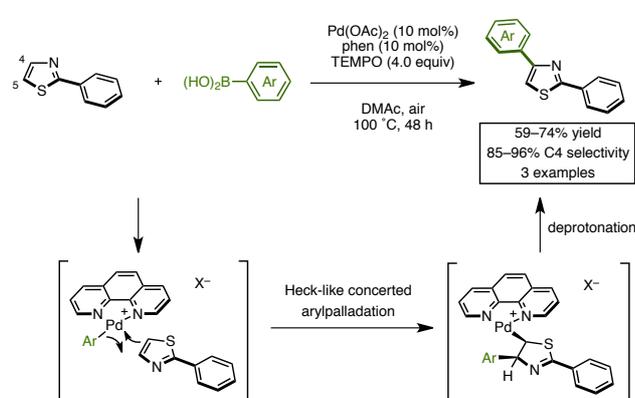
Although the catalyst-controlled C4-selective thiazole arylation is critically needed, it has been well documented that C2 and/or C5 positions are preferentially arylated over the C4 position under transition-metal-catalyzed C–H arylation conditions (Figure 4).<sup>7</sup> Under forcing conditions, diarylation occurs at the C2 and C5 positions under the influence of palladium catalysts.<sup>7b,8</sup> The reactivity of three positions of thiazole in C–H arylation (C2, C5 >> C4) is in line with the typical reactivity profile of the thiazole ring (Figure 4). For example, the deprotonation of thiazoles occurs preferentially at the C2 position. Thus, under the C–H arylation conditions using a strong base, C2 arylation tends to take place preferentially. On the other hand, thiazoles react with electrophiles preferentially at the C5 position. Thus, under the C–H arylation conditions where the nucleophilicity of thiazole plays a key role, C5 arylation tends to predominate. Radical reactions of thiazoles are also known, but the C4 position is least reactive. Only one example of reactivity preference for the C4 position of thiazoles is known, but the C2 position has to be substituted and some C5 substitution is also observed.<sup>14</sup> Thus, the introduction of an aryl group at the C4 position of a thiazole derivative required a number of synthetic steps.<sup>15</sup>



**Fig 4.** Paucity of C4-selective thiazole C–H arylation and the general reactivity of thiazole.

Recently, we discovered the first C4-selective C–H arylation of 2-phenylthiazole with arylboronic acids, catalyzed by a Pd(OAc)<sub>2</sub>/phen (1,10-phenanthroline)/TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) system (Scheme 1).<sup>9</sup> This previously inaccessible regiochemical outcome and the hitherto unrecognized regiocontrolling elements that have been uncovered in this study should provide a deeper understanding of the reactivity of thiazoles. Although a full understanding of the mechanism is still ongoing, our preliminary experiments and theoretical calculations of related reactions indicated that our C4-selective arylation occurs by a mechanism involving Heck-like concerted arylpalladation across the C=C bond of thiazoles.<sup>16</sup> Although we did not fully explore the scope of this reaction in our previous communication (only three reactions of 2-phenylthiazole were examined), this breakthrough finding finally opened the door for the programmed synthesis of arylthiazoles, providing access to 7 arylthiazole substitution patterns by 11 different synthetic routes.

**Scheme 2** C4-Selective C–H arylation of 2-phenylthiazole.



## Results and Discussion

Transition-metal-catalyzed C–H arylation of thiazoles at the C2 position has already been reported by several groups including our own.<sup>7</sup> After extensive screening of various reaction conditions for the preparation of 2-arylthiazoles,<sup>17</sup> we came to the conclusion that Rossi's Pd/Cu-based protocol (Method A),<sup>7g</sup> our Ni-based protocol (Method B),<sup>7k,7r</sup> and Mori's Pd-based protocol (Method C)<sup>7n</sup> can effectively convert thiazole (**1**) to 2-arylthiazoles (**3**) using aryl halides (**2**) as an aryl source (Table 1). It should be noted, however, that there is no single, universal catalytic system; all three systems have pros and cons.

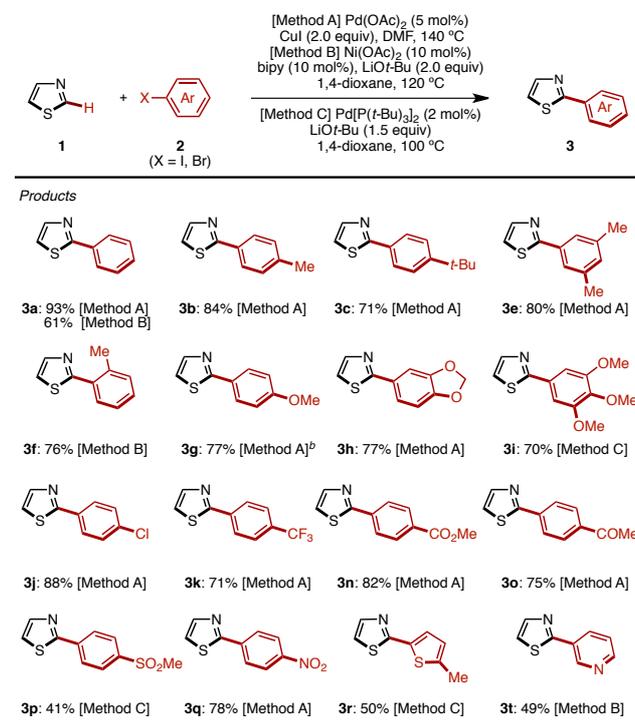
It was found that Rossi's palladium catalyst system [Method A: Pd(OAc)<sub>2</sub> and CuI in DMF at 140 °C] was generally preferred for the synthesis of 2-arylthiazole **3** from **1**. When a sterically hindered aryl iodide such as 2-methyl-1-iodobenzene (**2f**) and an electron-deficient heteroaryl iodide such as 3-iodopyridine (**2t**) were used, our nickel catalytic system [Method B: Ni(OAc)<sub>2</sub>, bipy (2,2'-bipyridyl) and LiOt-Bu in 1,4-dioxane at 85 °C] was most effective and gave higher yields than Method A (76% for **3f** and 49% for **3t**). In the synthesis of 2-arylthiazoles **3j**, **3p** and **3r**, Mori's palladium catalyst system [Method C: Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub>, LiOt-Bu and 1,4-dioxane at 100 °C] was most effective, affording

the corresponding coupling product with complete regioselectivity at the C2 position.

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**Table 1** Synthesis of 2-arylthiazoles by C2-selective arylation of thiazole.<sup>a</sup>

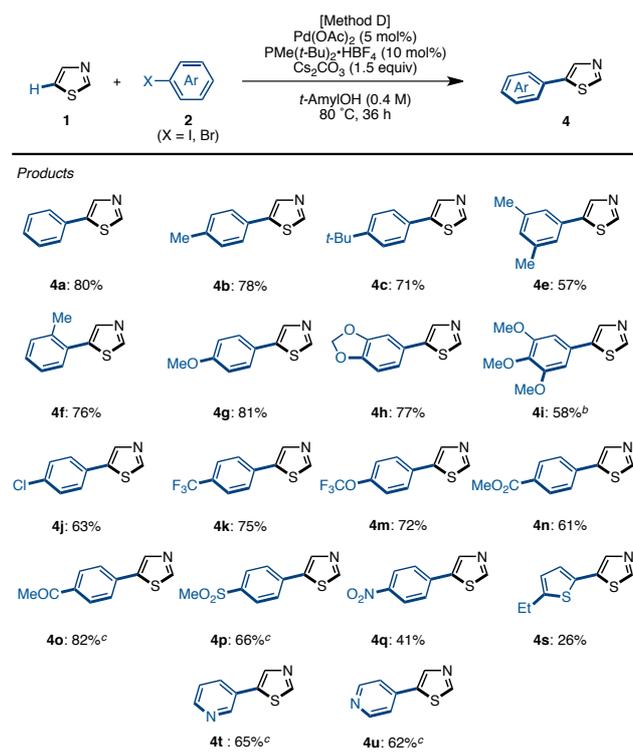


<sup>a</sup> Reaction conditions. Method A: **1** (0.8 mmol), **2** (X = I, 0.4 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), CuI (0.8 mmol), DMF (1.0 mL), 140 °C, 40 h. Method B: **1** (0.6 mmol), **2** (X = I, 0.4 mmol), Ni(OAc)<sub>2</sub> (0.04 mmol), bipy (0.04 mmol), LiOt-Bu (0.8 mmol), 1,4-dioxane (1.0 mL), 120 °C, 36 h. Method C: **1** (0.6 mmol), **2** (X = Br, 0.4 mmol), Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> (0.008 mmol), LiOt-Bu (0.6 mmol), 1,4-dioxane (1.2 mL), 100 °C, 12 h. <sup>b</sup> The reaction was performed for 16 h.

The synthesis of 5-arylthiazoles **4** via C–H arylation of thiazoles has already been reported under various reaction conditions.<sup>7</sup> However, these conditions had not been optimized for unfunctionalized thiazole (**1**). Therefore, we began by optimizing the conditions for C5-selective C–H arylation of **1**, based on our protocol [PdCl<sub>2</sub>, bipy in DMF at 120 °C]<sup>7q</sup> and Fagnou's protocol [Pd(OAc)<sub>2</sub>, PMe(*t*-Bu)<sub>2</sub>-HBF<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub> in *t*-AmylOH].<sup>7m</sup> As a result, optimal conditions for the coupling of thiazole (**1**) and aryl halides **2** have been determined.<sup>17</sup> Treatment of iodobenzene (**2**; X = I) with thiazole (**1**: 1.5 equiv) in the presence of Pd(OAc)<sub>2</sub> (5 mol%), PMe(*t*-Bu)<sub>2</sub>-HBF<sub>4</sub> (10 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv) in *t*-AmylOH at 80 °C for 36 h afforded the desired C5-phenylated product **4a** in 80% yield with virtually complete regioselectivity (Method D). Under these conditions, we examined the substrate scope of C5-selective C–H arylation of thiazole with aryl halides as shown in Table 2. Aryl iodides bearing an alkyl group at the *para*, *meta* and even *ortho* position underwent C5-selective arylation to give the corresponding products (**4b–4f**) in good yields. Aryl iodides bearing electron-rich substituents (resulting in products **4g–4i**) and electron-deficient substituents (resulting in products **4j–4q**) as well as heteroaryl iodides (resulting in products **4s–4u**) gave the desired products. However, when 2-iodo-5-ethylthiophene (**2i**) was used

as the coupling partner, the yield of product **4i** was low (26%) due to the occurrence of homocoupling of **2i** as a side reaction. In some cases, aryl bromides were also applicable to give the corresponding coupling products (**4i**, **4o**, **4t** and **4u**) in good to excellent yields. Since 4'-bromoacetophenone (**2o**), bromo-4-(methylsulfonyl)benzene (**2p**), and bromopyridines (**2t** and **2u**) were less reactive under Method D, we changed the reaction conditions to those reported by Doucet and coworkers [Method E: Pd(OAc)<sub>2</sub>, KOAc in DMAc, 130 °C].<sup>71</sup> As a result, these coupling reactions performed well to give the desired products (**4o**, **4p**, **4t**, and **4u**).

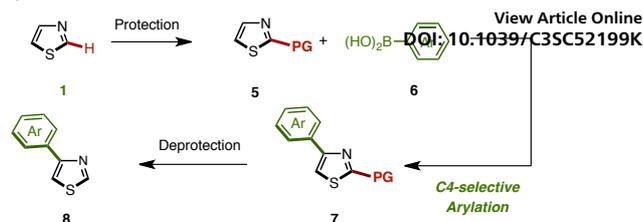
**Table 2** Synthesis of 5-arylthiazoles by C5-Selective Arylation of Thiazole.<sup>a</sup>



<sup>a</sup> Reaction conditions. Method D: **1** (0.6 mmol), **2** (X = I, 0.4 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), PMe(t-Bu)<sub>2</sub>·HBF<sub>4</sub> (0.04 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.6 mmol), *t*-AmylOH (1.0 mL), 80 °C, 36 h. <sup>b</sup> Bromobenzene (0.4 mmol) was used instead of iodobenzene, and the reaction was performed at 100 °C for 18 h. <sup>c</sup> Method E: **1** (0.8 mmol), **2** (X = Br, 0.4 mmol), Pd(OAc)<sub>2</sub> (0.004 mmol), KOAc (0.8 mmol), DMAc (1.0 mL), 130 °C, 20 h.

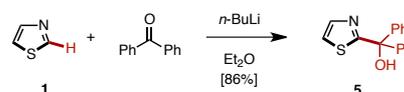
As already described, we have developed a palladium-catalyzed C4-selective C–H arylation of 2-arylthiazoles with arylboronic acids under Pd(OAc)<sub>2</sub>/phen/TEMPO system (Scheme 1).<sup>9</sup> However, when we applied this first-generation protocol to the C–H arylation of an unfunctionalized thiazole (**1**) with phenylboronic acid (**6a**), the yield of the desired coupling product **8a** was abysmal (<10% yield). We envisioned that some form of protecting group at the C2 position was necessary. Namely, it was thought that the C4-arylation product **8** could be synthesized by a sequence of (i) protection of **1**, (ii) C4-arylation of 2-substituted thiazole **5** with an arylboronic acid **6**, and (iii) removal of the C2 substituent from the resulting C4-arylated thiazole **7** (Scheme 2).

**Scheme 2** Protection-arylation-deprotection sequence for the synthesis of 4-Arylthiazoles **8**.



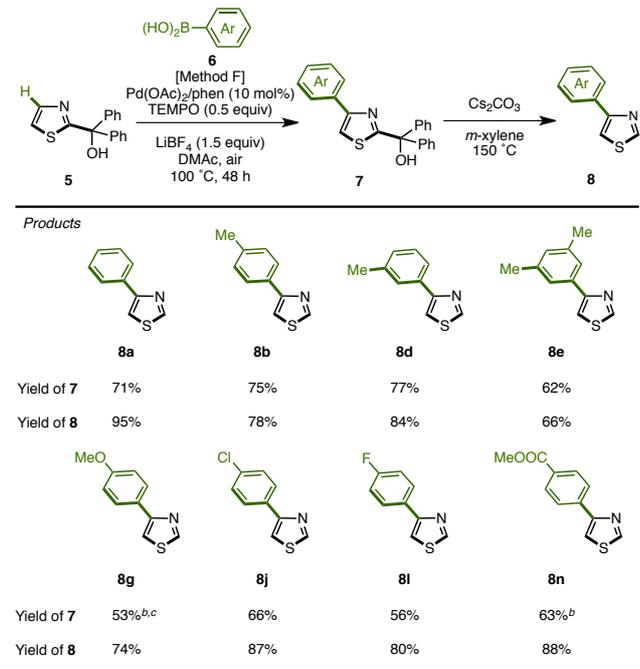
Among many possible protecting groups at the C2-position of thiazole, we decided to apply Mori's procedure using a diphenylmethanol group.<sup>18</sup> The protected thiazole **5** was readily prepared by the treatment of **1** with *n*-BuLi, followed by the reaction with benzophenone in 86% yield (Scheme 3).

**Scheme 3** "Protection" of thiazole at C2-position.



The protected thiazole **5** was then reacted with arylboronic acid under the influence of Pd(OAc)<sub>2</sub>/phen/TEMPO. During these studies, we re-optimized our C4-selective arylation conditions, employing less amounts of TEMPO but using LiBF<sub>4</sub> as an additive (Method F). Details of these conditions are discussed later in the manuscript (Table 7). Thus, the treatment of **5** (1.0 equiv) and phenylboronic acid (**6a**: 4.0 equiv) in the presence of Pd(OAc)<sub>2</sub> (10 mol%), phen (10 mol%), TEMPO (50 mol%), and LiBF<sub>4</sub> (1.5 equiv) in DMAc under air at 100 °C afforded the C4-phenylated thiazole **7a** in 71% yield with complete regioselectivity (Table 3). Deprotection of the diphenylmethanol group of **7a** was accomplished by treatment with Cs<sub>2</sub>CO<sub>3</sub> at 150 °C<sup>18</sup> to afford 4-phenylthiazole (**8a**) in 95% yield. The scope of C4-selective C–H arylation of thiazole **5** with respect to various arylboronic acids **6** (followed by diphenylmethanol group removal) is summarized in Table 3. A variety of arylboronic acids reacted smoothly to furnish the coupling products (**7b–7n**), and the desired 4-arylthiazoles (**8b–8n**) were obtained in good yields after deprotection.

**Table 3** Synthesis of 4-arylthiazoles by C–H arylation.<sup>a</sup>



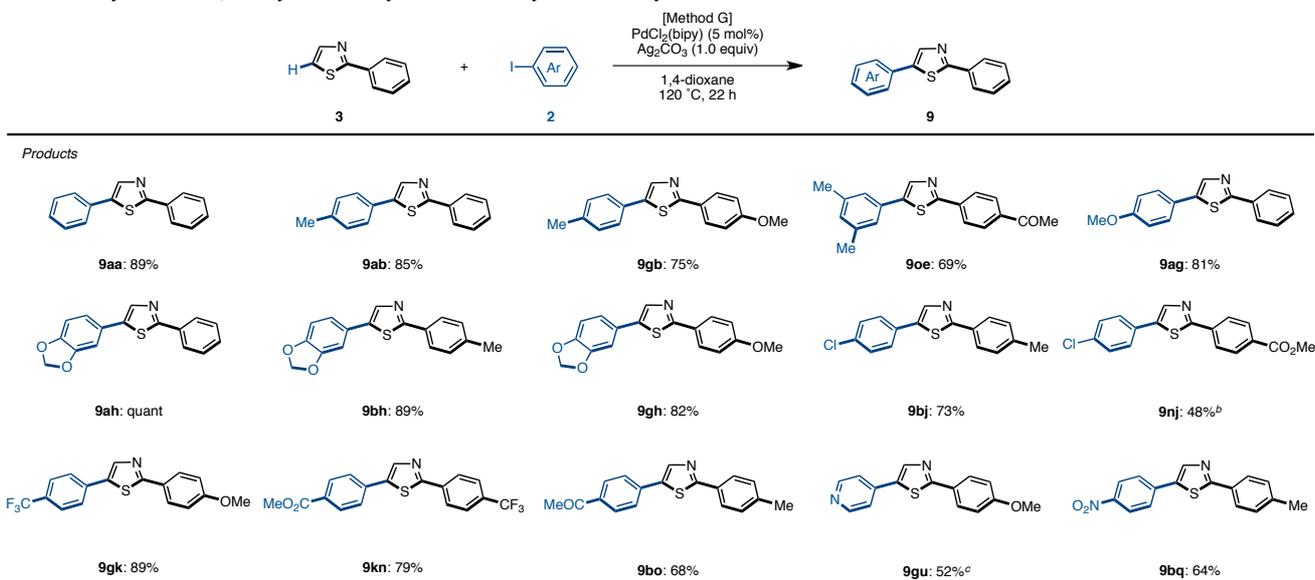
<sup>a</sup> Reaction conditions. Method F: **5** (0.25 mmol), **6** (1.0 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), phen (0.025 mmol), TEMPO (0.125 mmol), LiBF<sub>4</sub> (0.38 mmol), DMAc (0.5 mL), air, 100 °C, 48 h; then **7** (0.1–0.2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (1.0 mmol), *m*-xylene (0.8 mL), 150 °C, 40 h. <sup>b</sup> TEMPO (0.25 mmol) was used. <sup>c</sup> The yield was determined by <sup>1</sup>H-NMR.

We have established methods for the first arylation of thiazole (**1**) to obtain mono-arylated thiazoles of three different substitution patterns (**3**, **4**, and **8**) with complete regioselectivity. Thus, we then carried out the second arylation, in which the mono-arylated thiazoles were coupled with another aryl coupling

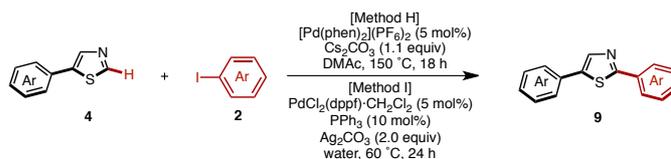
partner to obtain diarylthiazoles. We first performed the C5-selective arylation of 2-arylthiazoles **3** with aryl iodides **2** under our developed conditions [PdCl<sub>2</sub>(bipy), Ag<sub>2</sub>CO<sub>3</sub> in 1,4-dioxane at 120 °C].<sup>7q</sup> After a slight modification of reaction conditions (Method G), we turned our attention to defining the scope and functional group tolerance of the aryl iodide coupling partner in the synthesis of 2,5-diarylthiazoles **9** from 2-arylthiazoles **3** (Table 4). Numerous aryl iodides and 2-arylthiazoles were coupled with each other to give 2,5-diarylthiazole products **9** in excellent yields. When coupling reactions between 4-iodopyridine (**2u**) and 2-(4-methoxyphenyl)thiazole (**3g**) as well as chloropyridine (**2j**) and methyl 4-(2-thiazolyl)benzoate (**3n**) were conducted, the yields of the resulting diarylthiazoles (**9gu** and **9nj**) were low under our standard conditions (Method G). After increasing the reaction temperature and time, these yields were rendered moderate (48% and 52% yield, respectively).

Starting from 5-arylthiazoles **4**, we found that C2-selective arylation was possible using two different methods, namely the protocols originally developed by Murai/Shibahara<sup>8d</sup> and Greaney.<sup>7h</sup> For example, when Murai's protocol [Method H: Pd(phen)<sub>2</sub>(PF<sub>6</sub>)<sub>2</sub>, Cs<sub>2</sub>CO<sub>3</sub>, DMAc, 150 °C] was used for the coupling of 2-phenylthiazole (**3a**) with iodobenzene, 2,5-diphenylthiazole (**9aa**) was obtained in 83% yield, whereas Greaney's protocol [Method I: PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub>, Ph<sub>3</sub>P, Ag<sub>2</sub>CO<sub>3</sub>, water, 60 °C] gave a 96% yield. Employing these conditions, the C2-selective arylation of **4** was conducted with various aryl iodides (Table 5). Although most of the coupling reactions proceeded by Method H to give the corresponding products in good yields, the yields of **9an**, **9hg**, **9qa**, and **9vb** were low due to competing hydrolysis of the substituents or functional group intolerance. After changing the reaction conditions to Method I, these products were generated in moderate yields. In the case of **9bg**, **9ga**, **9gb** and **9jb**, the yields were better at lower temperatures (130 °C) to prevent decomposition of the product.

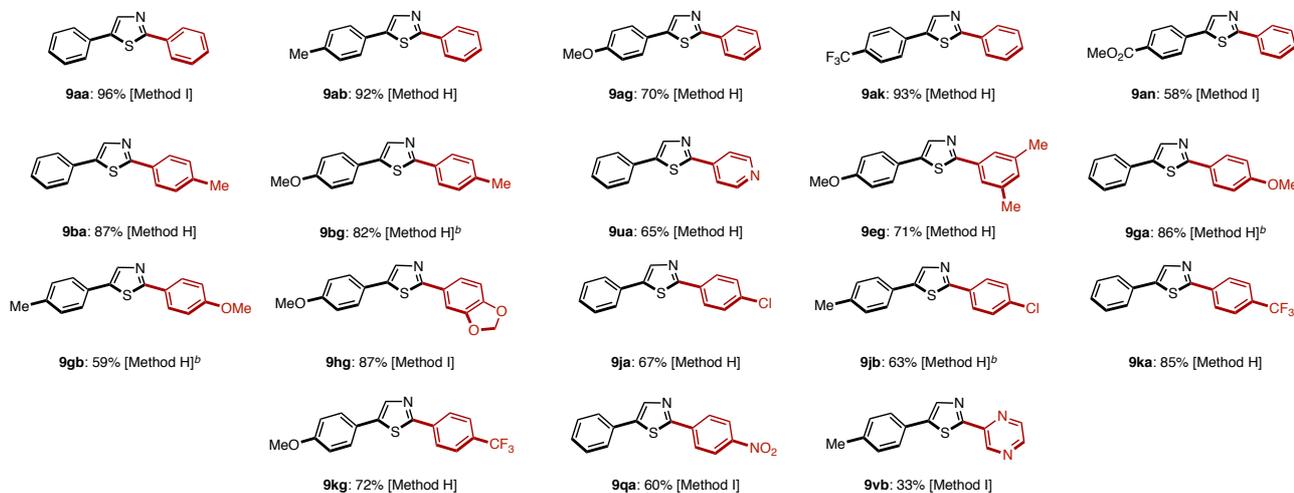
**Table 4** Synthesis of 2,5-diarylthiazoles by C5-selective arylation of 2-arylthiazoles.<sup>a</sup>



<sup>a</sup> Reaction conditions. Method G: **3** (0.375 mmol), **2** (0.25 mmol), PdCl<sub>2</sub>(bipy) (0.0125 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.25 mmol), 1,4-dioxane (1.0 mL) at 120 °C, 22 h. <sup>b</sup> The reaction was performed over 36 h. <sup>c</sup> The reaction was performed at 150 °C.

**Table 5** Synthesis of 2,5-diarylthiazole by C2-selective arylation of 5-arylthiazoles.<sup>a</sup>View Article Online  
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## Products

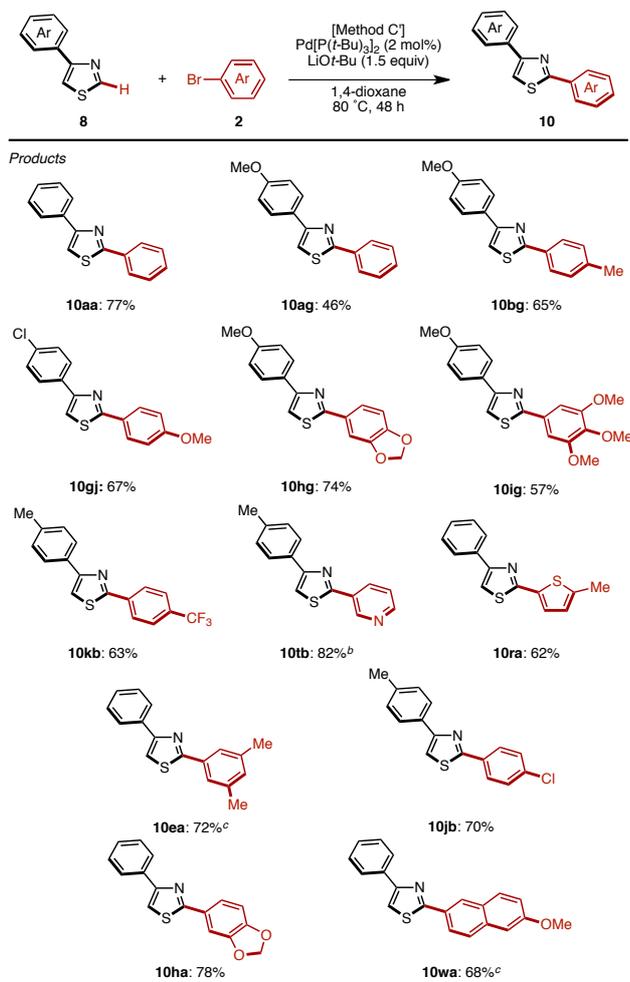


<sup>a</sup> Reaction conditions. Method H: **4** (0.2 mmol), **2** (0.22 mmol), Pd(phen)<sub>2</sub>(PF<sub>6</sub>)<sub>2</sub> (0.01 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.22 mmol), DMAc (0.8 mL), 150 °C, 18 h. Method I: **4** (0.2 mmol), **2** (0.24 mmol), PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (0.01 mmol), PPh<sub>3</sub> (0.02 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.4 mmol), water (1.0 mL), 60 °C, 24 h. <sup>b</sup> The reaction was performed at 130 °C.

The C2-selective C–H arylation of 4-arylthiazoles **8** has not been reported thus far. Thus, without literature precedent, we attempted the coupling under several reaction conditions.<sup>17</sup> When the coupling reaction between 4-phenylthiazole (**8a**) and iodobenzene was conducted with our Ni catalyst<sup>7k,7r</sup> or under Pd catalysis reported by Rossi<sup>7g</sup> and Hoarau<sup>7j</sup>, the coupling product **10aa** was obtained in low yield (22% and 6% yield, respectively). We then found that Mori's protocol [Method C: Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> and LiOt-Bu in 1,4-dioxane]<sup>7n</sup> was superior to others for the C–H arylation; 2,4-diphenylthiazole (**10aa**) was obtained in 55% yield from **8a** and bromobenzene, and the yield was increased to 77% after the slight modification of conditions (Method C': reaction temperature was lowered to 80 °C).<sup>17</sup> Using these optimal conditions, we further investigated the coupling of various 4-arylthiazoles and bromoarenes as shown in Table 6. Gratifyingly, we found that a relatively broad range of 4-arylthiazoles and bromoarenes can couple with complete C2 selectivity and in good yields.

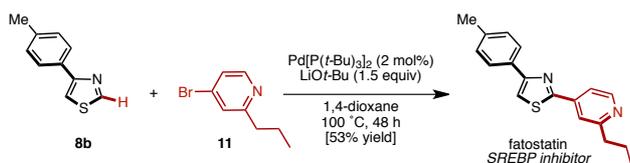
We subsequently applied this protocol to the synthesis of fatostatin, which was reported as a sterol regulatory element-binding protein (SREBP) by Uesugi and coworkers.<sup>19</sup> 4-(*p*-Tolyl)thiazole (**8b**) was reacted with 4-bromo-2-propylpyridine (**11**)<sup>20</sup> under the influence of Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub>/LiOt-Bu (Method C) to give fatostatin in 53% yield (Scheme 4). Although this synthesis is not shorter than that of the original report,<sup>19</sup> it could easily bring structural diversity to the aryl substituent at the C2 position of the thiazole core.

**Table 6.** Synthesis of 2,4-Diarylthiazoles by C2-Selective Arylation of 4-Arylthiazoles.<sup>a</sup>



<sup>a</sup> Reaction conditions. Method C: **8** (0.2 mmol), **2** (0.24 mmol), Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> (0.004 mmol), LiO*t*-Bu (0.3 mmol), 1,4-dioxane (0.6 mL), 80 °C, 48 h. <sup>b</sup> **8** (0.3 mmol), **2** (0.2 mmol), LiO*t*-Bu (0.4 mmol), 100 °C. <sup>c</sup> The reaction was performed at 100 °C.

#### Scheme 4 Synthesis of Fatostatin by C-H Arylation.



Next, a C4-selective C-H arylation of 2-arylthiazoles **3** was investigated. Following our previously reported conditions for the C4-selective arylation of 2-arylthiazoles,<sup>9</sup> 2-phenylthiazole (**3a**) was treated with 4.0 equiv of phenylboronic acid (**2a**) in the presence of Pd(OAc)<sub>2</sub>/phen catalyst and TEMPO (4.0 equiv) to give diphenylthiazole in 85% combined yield (**10aa** and its regioisomer) with 86% regioselectivity at the C4 position of **3a** (74% isolated yield; Table 7, entry 1). Although **10aa** could be synthesized, the reaction requires an excess amount of TEMPO (4.0 equiv to thiazole substrate), and the regioselectivity was not perfect. Therefore, a re-optimization of the coupling reaction was conducted (Table 7). The amount of TEMPO was eventually reduced to 0.5 equiv (entry 2) as well as to 0.2 equiv (entry 3)

under an atmosphere of air. Surprisingly, the coupling reaction proceeded well without TEMPO to give the corresponding coupling product **10aa** in 71% isolated yield (entry 4). We hypothesized that the oxidation of Pd(0) to Pd(II) might not always require any co-oxidants, and also worked under air (molecular oxygen) as a terminal oxidant in the case of 2-phenylthiazole (**3a**). However, we continued to use 0.5 equiv of TEMPO, since it was often effective for the C-H arylation of 2-arylthiazoles **3** (see Table 8). It should be noted that C4-selective C-H arylation of thiophenes necessitates the use of TEMPO as a co-oxidant under air; otherwise the products were produced in low yield.<sup>9</sup> Next, after screening additives, LiBF<sub>4</sub> (1.5 equiv) was identified as the optimal additive; both the reaction yield (77%) and regioselectivity (90%) were slightly improved (entry 5). Although the role of LiBF<sub>4</sub> remains unclear, we assume that the lithium cation coordinates with the nitrogen atom of 2-arylthiazole to prevent over-arylation as well as to increase regioselectivity. In contrast, the use of lithium base additives such as LiOAc (entry 6) and LiOH (entry 7) decreased the yield and regioselectivity.

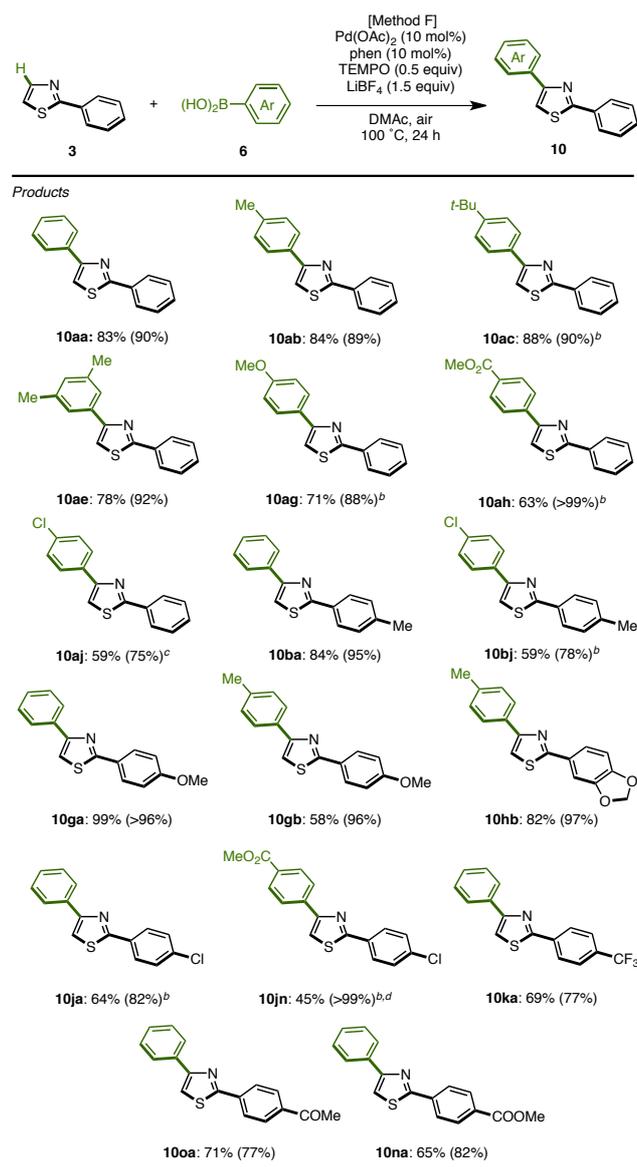
Table 7 Optimization of C4-selective C-H arylation of 2-phenylthiazole.<sup>a</sup>

Reaction scheme showing the optimization of C4-selective C-H arylation of 2-phenylthiazole (**3a**) with phenylboronic acid (**6**) to form 10aa. The reaction conditions are: Pd(OAc)<sub>2</sub> (10 mol%), phen (10 mol%), TEMPO (X equiv), additive (1.5 equiv), DMAc, air, 100 °C, 24 h.

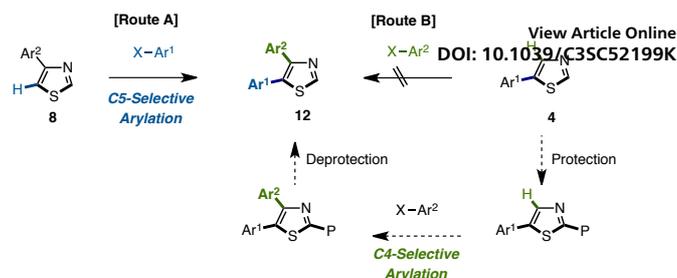
| entry | TEMPO/equiv | additive          | C4/C5 | yield (%) <sup>b</sup> |
|-------|-------------|-------------------|-------|------------------------|
| 1     | 4.0         | –                 | 86:14 | 85 (74)                |
| 2     | 0.5         | –                 | 86:14 | 85 (74)                |
| 3     | 0.2         | –                 | 88:12 | 77                     |
| 4     | –           | –                 | 88:12 | 83 (71)                |
| 5     | 0.5         | LiBF <sub>4</sub> | 90:10 | 93 (83)                |
| 6     | 0.5         | LiOAc             | 58:42 | 40                     |
| 7     | 0.5         | LiOH              | 9:91  | 68                     |

<sup>a</sup> Reaction conditions: **3a** (0.25 mmol), **6** (1.0 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), phen (0.025 mmol), TEMPO (none to 1.0 mmol), additive (0.38 mmol), DMAc (0.5 mL), air, 100 °C, 24 h. <sup>b</sup> The combined yield of regioisomers is given. Isolated yield of **10aa** is given in parenthesis.

With these optimal conditions in hand (Method F), a range of 2,4-diarylthiazoles **10** were synthesized from 2-arylthiazoles **3** (Table 8). 2-Arylthiazoles bearing electron-donating groups (such as 4-methyl, 4-*tert*-butyl, 3,5-dimethyl, and 4-methoxy groups) on the aryl substituent were coupled with various arylboronic acids **6** to give the corresponding products **10aa–10ag** in good yields. 2-Arylthiazoles with electron-deficient groups (such as 4-methylester and 4-chloro groups) on the aryl substituent also gave products **10ah–10aj** in moderate to good yields after slight modification of our standard conditions. Additionally, a broad range of arylboronic acids **6** was also successfully employed in the C4-selective arylation. Although some reactions displayed incomplete regioselectivity, it is noteworthy that 2,4-diarylthiazoles **10** can be readily separated from the minor regioisomer (2,5-diarylthiazoles) by flash column chromatography.

**Table 8** Synthesis of 2,4-diarylthiazoles by C4-selective arylation of 2-arylthiazoles.<sup>a</sup>

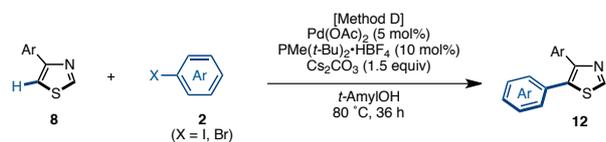
<sup>a</sup> Reaction conditions. Method F: **3** (0.25 mmol), **6** (1.0 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), phen (0.025 mmol), TEMPO (0.125 mmol), LiBF<sub>4</sub> (0.38 mmol), DMAc (0.5 mL), air, 100 °C, 24 h. Yield of the isolated product and regioselectivity (in parenthesis) are given. <sup>b</sup> The reaction was performed for 48 h. <sup>c</sup> 4-MeO-TEMPO (0.125 mmol) was used instead of TEMPO. <sup>d</sup> TEMPO (0.25 mmol) was used.

**Scheme 5** Two possible routes for the synthesis of 2,5-diarylthiazoles.

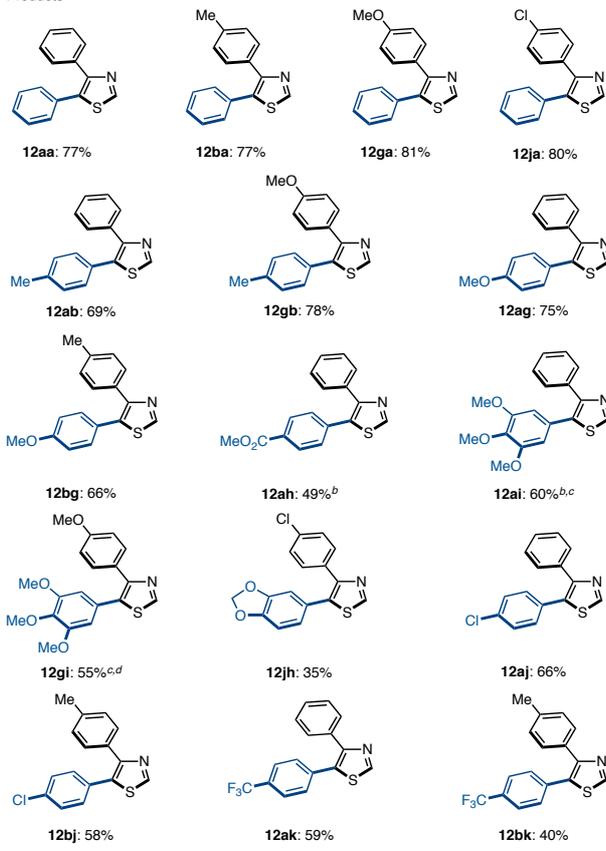
25 Thus, we investigated coupling reaction conditions for the synthesis of 2,5-diarylthiazoles via route A. As described in Table 2, we had already optimized the reaction conditions (Method D) for the C5-selective C–H arylation of thiazole (**1**). Using those conditions with slight modifications,<sup>17</sup> the coupling reaction of 4-phenylthiazole (**8a**) with iodobenzene (**2**) in the presence of Pd(OAc)<sub>2</sub> (10 mol%), PMe(*t*-Bu)<sub>2</sub>·HBF<sub>4</sub> (10 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv) in *t*-AmylOH at 80 °C for 36 h afforded 4,5-diphenylthiazole (**12aa**) in 77% yield. Under these conditions, an over-arylation product (triphenylthiazole) was obtained in 14% yield. The substrate scope for the C5-selective C–H arylation of 4-arylthiazoles was further investigated as shown in Table 9. Although each reaction produced triarylthiazoles in less than 10% yield, the desired 2,5-diarylthiazoles **12** were only obtained in moderate yields, since the reactivity was similar to the C5-selective C–H arylation of unfunctionalized thiazole (see Table 2). To obtain **12ah**, **12ai**, and **12gi** in better yields, higher temperatures were required, and in the case of an electron-rich aryl coupling partner such as 3,4,5-trimethoxyphenyl halide, the use of the aryl bromide instead of the aryl iodide provided a better result to give **12gi** in 55% yield.

**Table 9** Synthesis of 4,5-diarylthiazoles by C5-selective arylation of 4-arylthiazoles.<sup>a</sup>

10 The synthesis of 4,5-diarylthiazoles **12** by direct arylation has also not been reported thus far. For the synthesis of this motif using C–H coupling methodology, it is possible to select two synthetic routes: (i) C5-selective C–H arylation of 4-arylthiazoles **8** (route A, Scheme 5) and (ii) C4-selective C–H arylation of 5-arylthiazoles **4** (route B; Scheme 5). However, we only attempted route A since route B has synthetic problems in that 5-substituted thiazoles show a low reactivity at the C4 position due to steric reasons. Since the C2-arylation of 5-arylthiazoles is preferred, the substrate might need to be protected at C2, reacted at C4, and subsequently deprotected (see Table 3).



Products

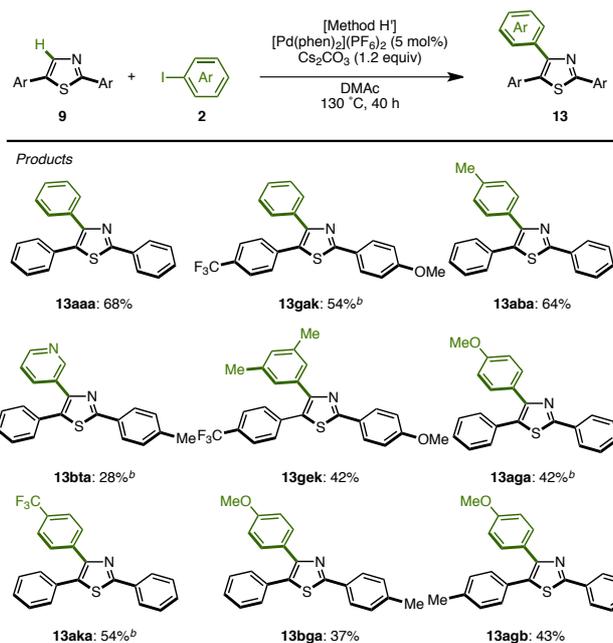


<sup>a</sup> Reaction conditions. Method D: **8** (0.2 mmol), **2** (X = I, 0.2 mmol), Pd(OAc)<sub>2</sub> (0.01 mmol), PMe(*t*-Bu)<sub>2</sub>·HBF<sub>4</sub> (0.02 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.3 mmol), *t*-AmylOH (0.5 mL), 80 °C, 36 h. <sup>b</sup> The reaction was performed at 100 °C for 18 h. <sup>c</sup> **2** (X = Br, 0.2 mmol) was used. <sup>d</sup> The reaction was performed at 100 °C for 36 h.

C–H arylation of 2,5-diarylthiazoles at the C4 position has only been reported by Shibahara, Murai and co-workers, which

uses Pd(phen)<sub>2</sub>(PF<sub>6</sub>)<sub>2</sub> as a catalyst, and Cs<sub>2</sub>CO<sub>3</sub> as a base in DMAC.<sup>8d</sup> These reaction conditions were modified with respect to temperature, time, and equivalents of aryl iodide. View Article Online  
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 results were obtained at 130 °C for 40 h using 1.5 equiv of aryl iodide (68% isolated yield of **13aaa**). Under the optimized conditions (Method H<sup>†</sup>), we carried out a direct C4-arylation using various 2,5-diarylthiazoles **9** and aryl iodides **2** (Table 10). Not only were triarylthiazoles generated using iodobenzene (**2**; to give **13aaa** and **13gak**), but also substituted iodobenzenes (methyl, dimethyl, methoxy, trifluoromethyl substituents) and even heteroaromatics led to the corresponding triarylthiazoles **13aba**, **13gek**, **13aga**, **13aka**, and **13bea**.

**Table 10** Synthesis of triarylthiazoles by C4-arylation of 2,5-diarylthiazoles.<sup>a</sup>

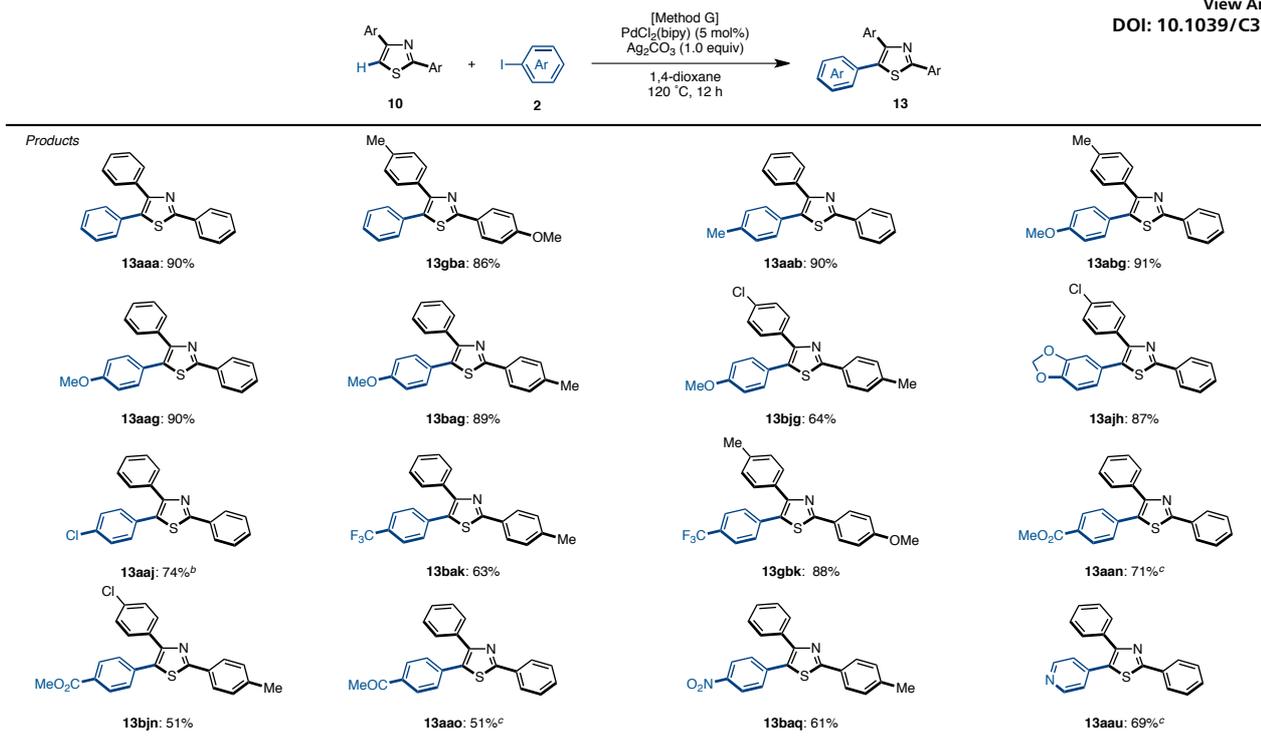


<sup>a</sup> Reaction conditions. Method H<sup>†</sup>: **9** (0.2 mmol), **2** (0.22 mmol), Pd(phen)<sub>2</sub>(PF<sub>6</sub>)<sub>2</sub> (0.01 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.24 mmol), DMAC (0.8 mL), 130 °C, 40 h. <sup>b</sup> The reaction was performed at 150 °C, 18 h using Pd(phen)<sub>2</sub>(PF<sub>6</sub>)<sub>2</sub> (0.02 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (0.30 mmol).

**Table 11** Synthesis of triarylthiazoles by C5-arylation of 2,4-diarylthiazoles.

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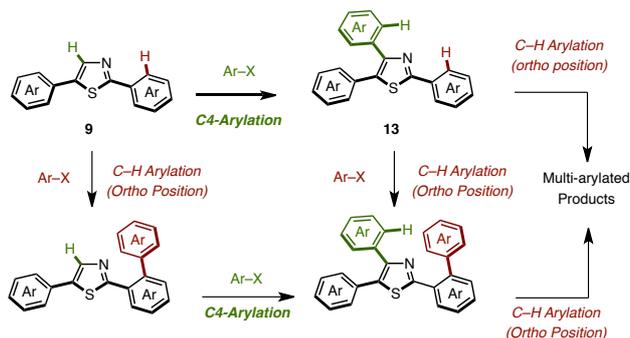
DOI: 10.1039/C3SC52199K



<sup>a</sup> Reaction conditions. Method G: **2** (0.375 mmol), **10** (0.25 mmol), PdCl<sub>2</sub>(bipy) (0.0125 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.25 mmol), 1,4-dioxane (1.0 mL), 120 °C, 12 h. <sup>b</sup> The reaction was performed for 22 h. <sup>c</sup> The reaction was performed at 140 °C for 22 h.

The somewhat lower yields of the coupling reaction were analyzed by GC analysis, and it was found that the arylation at the aryl groups on the thiazole cores took place in these particular reactions (Scheme 6). Thus, the possible side reactions are (i) overarylation of triarylthiazole **13** at the *ortho* position of the C2- or C4-aryl substituents after/before C4-arylation of **9** and (ii) further C–H arylation from 2,5-diarylthiazoles at the C4 or C2 position to give multi-arylated products.

**Scheme 6** Potential side reactions in the C4-arylation of 2,5-diarylthiazoles.

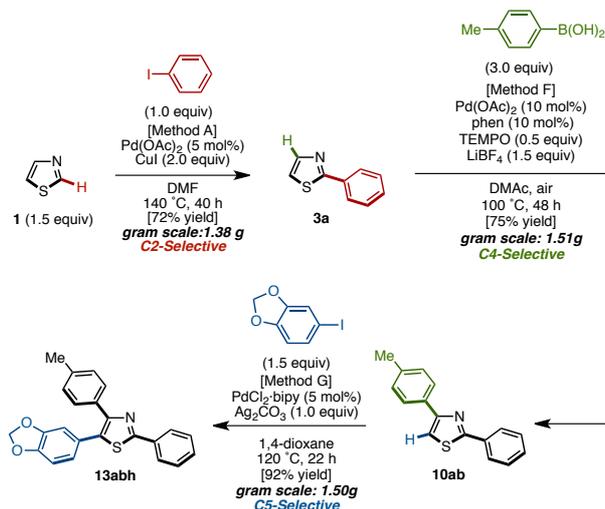


When the reaction conditions of C5-selective C–H arylation of 2-arylthiazoles were optimized (see Table 4), the best results were obtained using our previous conditions for palladium catalysis, PdCl<sub>2</sub>(bipy)/Ag<sub>2</sub>CO<sub>3</sub> in 1,4-dioxane (Method G).<sup>74</sup> We were pleased to find that a wide range of 2,4-diarylthiazoles **10** and

aryl iodides **2** can be coupled to give triarylthiazoles **13** under those conditions (Table 11). Both electron-poor and electron-rich aryl iodides can be used in the C–H coupling reaction, but the reactions using more electron-poor aryl iodides (those containing chloro, ester and acetyl groups) as well as iodopyridine required longer reaction times and higher temperatures. When electron-deficient 2,4-diarylthiazoles were used, the corresponding triarylthiazoles were formed in relatively low yields (**13bjg** and **13ajn**). To improve the yields of **13aaj**, **13aan**, **13aao** and **13aau**, the reactions were conducted over longer time periods (12 h to 22 h) and/or at elevated temperatures (120 °C to 140 °C).

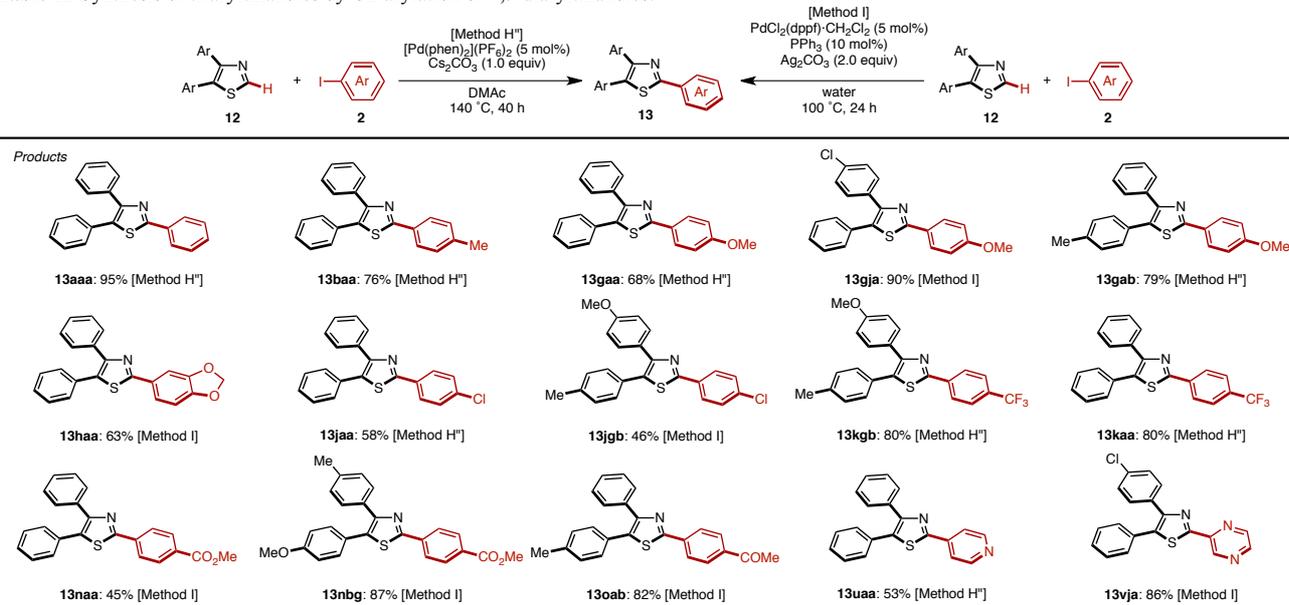
To demonstrate the utility of the C5-arylation of 2,4-diarylthiazoles, a gram-scale synthesis of triarylthiazole **13abh** was undertaken (Scheme 7). Thiazole (**1**) was coupled with iodobenzene under Pd(OAc)<sub>2</sub>/CuI catalysis (Method A) to give 2-phenylthiazole (**3a**) in 72% yield (1.38 g). Afterwards, palladium-catalyzed C4-selective C–H arylation of **3a** with *p*-tolylboronic acid was conducted under the influence of Pd(OAc)<sub>2</sub>/phen/TEMPO/LiBF<sub>4</sub> (Method F) to furnish the corresponding 2,4-diarylthiazole **10ab** in 75% yield with >95% regioselectivity (1.51 g). Finally, the C–H arylation of **10ab** at the C5-position with aryl iodide in the presence of PdCl<sub>2</sub>(bipy)/Ag<sub>2</sub>CO<sub>3</sub> catalyst (Method G) gave triarylthiazole **13abh** in 92% yield (1.50 g).

**Scheme 7** Gram-scale synthesis of triarylthiazole by sequential C–H arylations.



We first selected two representative catalyst systems [our own conditions (Method G)<sup>7a</sup> and Murai's conditions (Method H)<sup>8d</sup>] for the C–H arylation of 4,5-diarylthiazoles to provide triarylthiazoles **13** (Table 12). The coupling of 4,5-diphenylthiazole (**12aa**) with iodobenzene (**2**) under these two conditions gave an identical yield (66% yield) of the desired triphenylthiazole (**13aaa**). However, the starting material **12aa** still remained under Murai's conditions, whereas **12aa** was consumed using our protocol. After some modification of Murai's conditions with respect to the equivalents of base and iodobenzene (Method H<sup>''</sup>), the yield of **13aaa** was increased to 85% (isolated yield). When the same reaction was performed under Greaney's conditions (Method I),<sup>7h</sup> **13aaa** was obtained in 95% yield. These two different conditions for the C–H arylation of **12aa** led to an extension of the reaction scope with respect to the 4,5-diarylthiazoles and aryl halide substrates (Table 12).

**Table 12** Synthesis of triarylthiazoles by C2-arylation of 4,5-diarylthiazoles.



<sup>a</sup> Reaction conditions. Method H<sup>''</sup>: **12** (0.2 mmol), **2** (0.3 mmol), Pd(phen)<sub>2</sub>(PF<sub>6</sub>)<sub>2</sub> (0.01 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.20 mmol), DMAc (0.8 mL), 140 °C, 40 h. Method I: **12** (0.125–0.15 mmol), **2** (0.15–0.18 mmol), PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (5 mol%), Ph<sub>3</sub>P (10 mol%), Ag<sub>2</sub>CO<sub>3</sub> (0.25–0.3 mmol), water (1.0 mL), 100 °C, 24 h.

## Conclusions

In summary, we have developed a programmed synthesis of all substitution patterns of arylthiazoles (2,4-diaryl, 2,5-diaryl, 4,5-diaryl, and 2,4,5-triaryl) via sequential C–H arylation. Representative reaction conditions are summarized in Scheme 8. Noteworthy features of our method are: (i) the synthetic expediency in introducing aryl groups by step-economical, direct C–H arylation, (ii) all aryl groups assembled stem from readily available aryl halides or arylboronic acids, (iii) the aryl-group-installation at the desired position can be achieved by the choice of catalytic systems, and (iv) the possibility of synthesizing all substitution patterns of arylthiazoles by 11 distinct pathways. Using this protocol, we have accomplished the synthesis of over 150 different arylthiazoles, among which exists fatostatin, known as a SREBP inhibitor. This method can be applied to a gram-scale synthesis of triarylthiazoles. Testing the biological activity of the generated library of arylthiazoles for agrochemical and pharmaceutical research is now the focus of our ongoing efforts.

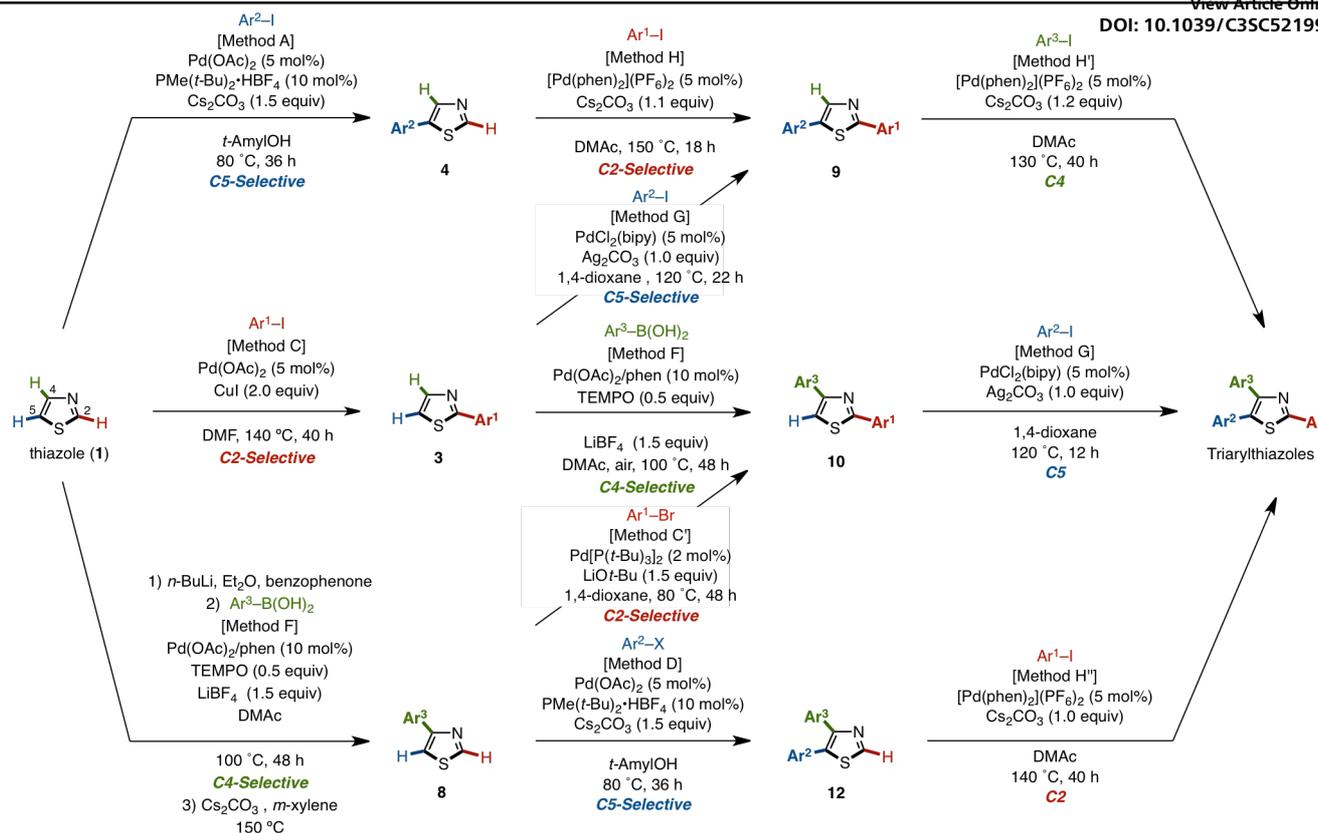
## Supporting Information Available

Detailed experimental procedures and spectral data for all compounds, including scanned image of <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://www.rsc.org>.

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Scheme 8 Programmed synthesis of all substitution patterns of thiazoles.

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## Notes and References

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† Electronic Supplementary Information (ESI) available: experimental procedures, characterization of data for all new compounds, details of modification of reaction conditions.

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