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# Ru-catalyzed direct C–H amidation of 2-arylbenzo[*d*]thiazoles with sulfonyl azides

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ABSTRACT

Ru-catalyzed direct C–H amidation of 2-arylbenzo[*d*]thiazoles was developed using sulfonyl azides as the amino source under no external oxidants and free-base conditions to release $N_2$ gas as the single byproduct. The present protocol shows good functional group tolerance and high regioselectivity, providing various structurally versatile amidated 2-arylbenzothiazoles with potential biological and therapeutic activities in moderate to good yields.



## 1. Introduction

Fundamental importance has been given to the C–N bond-forming reactions for developing a series of arylamine compounds. As a result, significant progress has been made to introduce nitrogen-containing groups into arene molecules. Among these, Pd-catalyzed Buchwald–Hartwig coupling[1] and copper-catalyzed Ullmann and Goldberg couplings[2] made great contribution to transition metal-catalyzed amination, wherein pre-functionalized aryl halides were treated with amines. However, stoichiometric amounts of byproducts such as hydrogen halides and their base salts were generated following this procedure. In the last decade, great efforts have been made to form C–N bond via direct C–H amination in environmentally benign ways. Metal-mediated intramolecular[3] and intermolecular[4] oxidative C–N bond-forming reactions were developed using amines as substrates in the presence of external oxidants. Recently, a range of pre-activated amino precursors, such as hydroxylamines,[5] halogenated amines,[6] and azides[7] were used as amino source under oxidant-free conditions. For example, Yu and co-workers reported the synthesis of tertiary and secondary arylalkyl amines via Pd-catalyzed intermolecular C–H activation/C–N bond-forming reactions,[5e] and the preparation of β-, γ-, and δ-lactams via Pd-catalyzed intramolecular C–H activation/lactamization starting from hydroxylamines.[5g] Ritter and co-workers described Pd-catalyzed intermolecular C–H imidation of arenes from *N*-fluorobenzenesulfonimide.[6a] Chang group also reported a range of direct C–H amination of arenes using various azides (including sulfonyl,[7c,f,n–p] acyl,[7m] aryl,[7b,n,q] and alkyl azides[7a]).

2-Arylbenzo[*d*]thiazoles are widely presented in biologically active natural products and pharmaceuticals that exhibit remarkable therapeutic activities, such as antitumor, antiviral, and antimicrobial activities.[8] Recently, we reported various C–H functionalization reactions of 2-arylbenzo[*d*]-thiazoles, including arylation,[9] acylation,[10] acyloxation,[11] and fluorination,[12] showing favorable activity and good compatibility. Inspired by our previous results,[9–12] our interest in looking for small molecules for inhibition of anti-proliferative activity against cancer cells, and the well-documented studies[5–7] on transition metal-catalyzed C–N bond formation, herein we describe the Ru-catalyzed direct C–H amidation of 2-arylbenzo[*d*]thiazoles using organic azides as the unique amino source.

## 2. Results and discussion

Inspired by previous research developed by Chang's group for rhodium-catalyzed intermolecular amidation of arenes with sulfonyl azides,[7f] we attempted to explore an effective catalytic system for the direct C–H amidation of 2-arylbenzo[*d*]thiazoles **1** with

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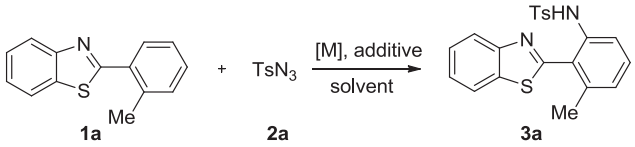
sulfonyl azides **2**. Initially, 2-(*o*-tolyl)benzo[*d*]thiazole **1a** and *p*-tolylsulfonyl azide **2a** were treated with 4 mol % catalytic $[RhCp^*Cl_2]_2$ and 16 mol % additive ($AgSbF_6$) in 1,2-dichloroethane at 80 °C for 12 h. The desired C–H aminated product **3a** was obtained in 13% yield (Table 1, entry 1). Subsequently, catalyst screening (RhOAc, $[Ir(COD)Cl]_2$, $[Ru(p\text{-cymene})Cl_2]_2$) indicated that $[Ru(p\text{-cymene})Cl_2]_2$ is the optimal catalyst, which provided the desired product in satisfied yield 73% (Table 1, entries 2–4). In order to advance the process further, a variety of silver salts as additive were examined, including AgI, $Ag_2CO_3$, $AgNO_3$, AgOAc, AgF, $AgCO_2CF_3$, and AgOTf (Table 1, entries 5–11). Results demonstrated that $AgSbF_6$ was the most suitable additive. Optimization of the solvent showed that 1,2-dichloroethane was the best choice compared to other solvents (Table 1, entry 4 vs entries 12–15). Reaction temperature is essential for the amidation process since raising or lowering the temperature to 100 and 60 °C would decrease the yields of product to 57% and 40%, respectively (Table 1, entries 16 and 17). The use of 1.0 or 1.5 equiv of *p*-tolylsulfonyl azide **2a** reduced the yields to 50% and 65%, respectively (Table 1, entries 18 and 19). Further studies showed that increasing the loading of $[Ru(p\text{-cymene})Cl_2]_2/AgSbF_6$ led to no obviously changes in yield (Table 1, entry 20).

**Table 1**
Optimization of the reaction conditions[a]




| Entry | [M] | Additive | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $[RhCp^*Cl_2]_2$ | $AgSbF_6$ | DCE | 13 |
| 2 | RhOAc | $AgSbF_6$ | DCE | nr |
| 3 | $[Ir(COD)Cl]_2$ | $AgSbF_6$ | DCE | 13 |
| 4 | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | DCE | 73 |
| 5 | $[Ru(p\text{-cymene})Cl_2]_2$ | AgI | DCE | nr |
| 6 | $[Ru(p\text{-cymene})Cl_2]_2$ | $Ag_2CO_3$ | DCE | nr |
| 7 | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgNO_3$ | DCE | nr |
| 8 | $[Ru(p\text{-cymene})Cl_2]_2$ | AgOAc | DCE | nr |
| 9 | $[Ru(p\text{-cymene})Cl_2]_2$ | AgF | DCE | nr |
| 10 | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgCO_2CF_3$ | DCE | 19 |
| 11 | $[Ru(p\text{-cymene})Cl_2]_2$ | AgOTf | DCE | 26 |
| 12 | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | DCM | Trace |
| 13 | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | THF | 36 |
| 14 | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | PhCl | 43 |
| 15 | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | Toluene | 34 |
| 16[c] | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | DCE | 57 |
| 17[d] | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | DCE | 40 |
| 18[e] | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | DCE | 50 |
| 19[f] | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | DCE | 65 |
| 20[g] | $[Ru(p\text{-cymene})Cl_2]_2$ | $AgSbF_6$ | DCE | 70 |

[a] Reaction conditions: 2-(*o*-tolyl)benzo[*d*]thiazole **1a** (0.2 mmol), $TsN_3$ **2a** (0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), 80 °C, 2 mL of solvent, 12 h.
[b] Isolated yield based on **1a**, nr=no reaction.
[c] At 100 °C.
[d] At 60 °C.
[e] $TsN_3$ (1.0 equiv).
[f] $TsN_3$ (1.5 equiv).
[g] $[Ru(p\text{-cymene})Cl_2]_2/AgSbF_6$ (8 mol %/32 mol %).

With the optimized conditions in hand, we next investigated the substrate scope for the Ru-catalyzed amidation of 2-arylbenzo[*d*]thiazoles **1** with *p*-tolylsulfonyl azide **2a**, as summarized in Table 2. In most cases, substrate **2a** reacted with various 2-arylbenzo[*d*]thiazoles **1** containing substituents on the 2-phenyl ring leading to the corresponding *ortho*-amidated products in moderate to good yields (Table 2, entries 1–5). For instance, the reaction of 2-(2-methoxyphenyl)benzo[*d*]thiazole **1b** possessing a strong electron-donating group (methoxyl) under the standard conditions afforded the desired product **3b** in moderate yield 55% (Table 2, entry 2). Good yields were obtained when 2-arylbenzo[*d*]thiazoles (**1c** and **1d**) with moderate electron-withdrawing groups (such as Cl and F) on the *ortho*-position of 2-phenyl ring were utilized in the reaction (80% and 88% yields, respectively) (Table 2, entries 3 and 4). However, low yield was observed when substrate **1e** bearing a strong electron-withdrawing group ($NO_2$) reacted with **2a** (Table 2, entry 5). We next investigated the effects of substituents on the benzothiazole parts under the present conditions. It was observed that the reaction exhibited good functional group tolerance with acceptable yield (65–85%) and high selectivity (Table 2, entries 6–11). For instance, 2-(2-chlorophenyl)-6-methylbenzo[*d*]thiazole **1f** reacted with **2a** leading to the formation of amidated product **3f** in 72% yield (Table 2, entry 6). The reaction of 6-chloro-2-(*o*-tolyl)benzo[*d*]thiazolesubstrates **1j** under the standard conditions afforded **3j** in 78% yield (Table 2, entry 10). Regrettably, to 2-(*m*-tolyl)benzo[*d*]thiazole **1l** with a substituent at the *meta*-position of 2-phenyl ring gave relatively lower yield (46%) of *mono*-amidated product **3l** at the less sterically hindered position without detecting any bis-amidated product (Table 2, entry 12). To those unsubstituted 2-phenylbenzo[*d*]thiazoles **1m** and **1n** also reacted with sulfonyl azide **2a** smoothly under the present conditions and led to moderate *mono*-amidated products **3m** and **3n**, and no bis-amidated products were observed (Table 2, entries 13 and 14). Unfortunately, heterocyclic ring substituted substrates 2-(furan-2-yl)benzo[*d*]thiazole **1o** and 2-(pyridin-4-yl)benzo[*d*]thiazole **1p** failed to supply the desired amidated products **2o**,**p** under the standard conditions (Table 2, entries 15 and 16). In addition, the present protocol can tolerate aldehyde and ketone groups with relatively lower yields (Table 2, entries 17 and 18).

Encouraged by the successful results in the amidation reaction of 2-arylbenzothiazoles, we continued to examine the scope of azides to obtain structurally versatile amidated 2-arylbenzothiazoles (Table 3). It is pleased to observe that different substituted sulfonyl azides can be applied to the protocol. For the reaction of 2-arylbenzothiazole **1g** with sulfonyl azides **2**, the results show that sulfonyl azides **2** with electron-donating group at the phenyl ring afforded the product in a little higher yield. For example, 91% yield of the target product **3s** was attained for 4-methoxybenzenesulfonyl azide **2b**, compared to 81% and 75% for *p*-nitro and *p*-chlorobenzenesulfonyl azide (Table 3, entries 2, 4, and 5).

Based on the recent reports of transition metal-catalyzed direct using azides as the amine source[7a–d,f–i,l–q] and the functionalization of 2-arylbenzothiazole[9–12] via C–H activation, a plausible mechanistic pathway of the present Ru-catalyzed direct is shown in Scheme 1. Initially, the additive $AgSbF_6$ promotes the generation of an active cationic Ru(II) species from neutral ruthenium precursor $[RuCl_2(p\text{-cycmene})]_2$. Ru(II) species facilitates the formation of a five-membered ruthenacycle species **I** via C–H bond activation. Subsequently, a reversible coordination of azide to the Ru(II) species **I** leads to Ru intermediate **II**. Then, insertion of an amido moiety into the ruthenacycle releases a molecule $N_2$ gas to afford six-membered ruthenacycle species **III**. Finally, protonolysis of **III** generates the desired product **3** and provides the active cationic Ru(II) species for the following catalytic cycle.

## 3. Conclusion

In summary, we have successfully developed a method for the insertion of an amino group into 2-arylbenzo[*d*]thiazole C–H bonds by using sulfonyl azides as the nitrogen source. The reaction requires no external oxidants, base-free, and releases $N_2$ as the single byproduct, thus offering a favorable and environmentally benign method for C–N bond formation. A variety of structurally versatile amidated 2-arylbenzothiazoles were obtained by the present