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Reigoselective Arylation of Thiazole Derivatives at 5-Position via Pd Catalysis under Ligand-Free Conditions

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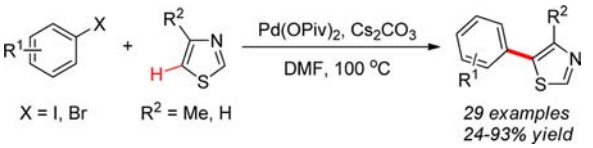
ABSTRACT



An efficient regioselective arylation of thiazole derivatives *via* Pd-catalyzed C−H activation is reported. The transformation was hypothesized through a Pd(0/II) catalytic cycle in the absence of special ligand sets. This method provided an efficient process to direct arylation of thiazoles at the 5-position.

Selectivity is one of the perpetual research topics in organic synthesis.[1] Direct functionalization of C−H bonds *via* transition-metal catalysis has recently emerged as a powerful and practical alternative to the well-applied Pd-catalyzed cross-coupling reactions (e.g., Suzuki−Miyaura, Stille, and Negishi couplings) owing to the ubiquity of C−H bonds and the avoidance of prefunctionalization of the starting materials; thus, considerable interest has been instigated in the synthetic community.[2] To realize the selective functionalization among multiple C−H bonds that exist in the substrates and products, current solutions involved either a certain directing group[2d,j,3] or an inherent distinguished C−H bond exerted by the electronic nature.[4] Especially, the directing group strategy has exhibited its advantages in the past decades. However, the directing groups are not always desirable in the target molecule, and the removal of them is usually indispensible, thus obviously limiting their synthetic utility.[5] Alternatively, the use of electronically activated substrates to enable the selective C−H bond activation/functionalizaiton was preferable, especially for the derivatization of heterocyclic aromatics.

A thiazole-containing structural motif is frequently found in biologically active molecules, organic materials, and pharmaceuticals (Figure 1).[4o] In fact, the elaboration of thiazole has been well documented.[6] Recently, significant developments to carry out C−H activations have enabled direct arylation of heterocyclics and some beautiful

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examples have been achieved in a regioselective manner.[7] Generally, 2-blocked thiazoles were used to ensure the selective 5-arylated thioazoles,[4o] and conversely, the 5-substituted thiazoles were adopted to facilitate the formation of 2-arylated thiazole derivatives.[8] Notably, for all the successful examples, either the air- and moisture-sensitive $Pd(PPh_3)_4$ or an additional ligand set was used to promote both efficacy and selectivity.[9] Therefore, the development of sustainable processes for direct functionalization of the thiazole moiety in a regioselective fashion is still highly desirable for practical synthetic application. Herein we

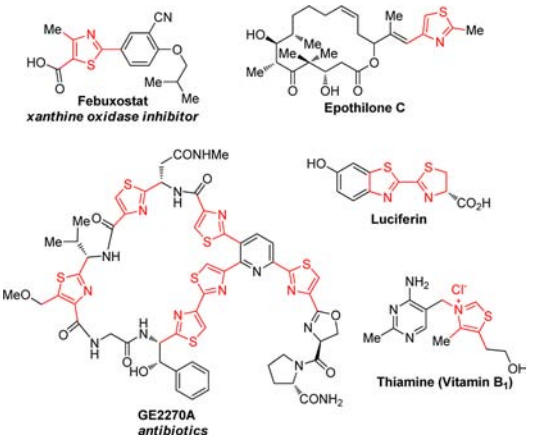

Figure 1. Representatives of thiazole-containing compounds.

demonstrated a new development in the regioselective arylation of thiazole derivatives *via* Pd catalysis under ligand-free conditions.

It is known that the C-5 position of the thiazole moiety possesses high electron density. Therefore, electrophilic palladation usually occurred at this site. Subsequent reductive elimination based on this prediction would deliver the 5-selective functionalization of the thiazole scaffold. Based on this concept, $Pd(OAc)_2$ was initially examined as a catalyst for the reaction of 4-methylthiazole (**2a**) with phenyl iodide (**1a**) in the presence of 1.0 equiv of Cs_2CO_3 in DMF (2.0 mL) at 140 °C. To our delight, in the presence of 10 mol % of $Pd(OAc)_2$, the reaction proceeded smoothly to afford the desired 5-phenylated 4-methylthiazole (**3aa**) in 54% yield, together with a detectable 2,5-diphenylated 4-methylthiazole as a byproduct (Table 1, entry 1).

Encouraged by this preliminary result, a variety of Pd(II) species were evaluated (see Supporting Information, Table S1). We found that $Pd(OPiv)_2$ was the optimal catalyst, providing the desired product in 80% yield. Using other inorganic bases led to no improvement in the reaction performance. It is noteworthy that, in the absence of the base, the reaction did work while delivering the 5-phenylated product with a negligible yield (only 5%). Obviously, no reaction took place in the absence of Pd species (Table 1, entries 7 and 14). Solvent screening indicated that

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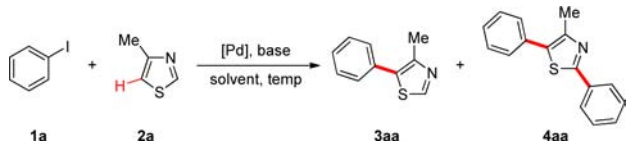
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa 4aa

entry	[Pd] (mol %)	base (equiv)	solvent (mL)	temp (°C)	yield (%)[b] 3aa	4aa
1	$Pd(OAc)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	140	54	5
2	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	140	80	3
3	$Pd(OPiv)_2$ (10)	K_3PO_3 (1.0)	DMF (2.0)	140	65	4
4	$Pd(OPiv)_2$ (10)	CsOAc (1.0)	DMF (2.0)	140	65	4
5	$Pd(OPiv)_2$ (10)	CsF (1.0)	DMF (2.0)	140	38	2
6	$Pd(OPiv)_2$ (10)	CsOPiv (1.0)	DMF (2.0)	140	66	3
7	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (0)	DMF (2.0)	140	5	1
8	$Pd(OAc)_2$ (10) + PivOH (10)	Cs_2CO_3 (1.0)	DMF (2.0)	140	42	2
9	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMAc (2.0)	140	64	2
10	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	*o*-xylene (2.0)	140	67	4
11	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	mesitylene (2.0)	140	53	5
12	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	$^nBu_2O$ (2.0)	140	44	4
13	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	CH_3NO_2 (2.0)	140	NR	NR
14	$Pd(OPiv)_2$ (0)	Cs_2CO_3 (1.0)	DMF (2.0)	140	NR	NR
15	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	140	77	3
16	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	140	77	3
17[d]	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	140	72	2
18[e]	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	140	69	3
19	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	120	81	2
20	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	**100**	**84 (75)**[c]	**3**
21	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	80	53	1
22	$Pd(OPiv)_2$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	60	3	–
23	$Pd_2(dba)_3$ (10)	Cs_2CO_3 (1.0)	DMF (2.0)	100	3	–

[a] Unless otherwise noted, all reactions were carried out in 0.2 mmol scale in 2 mL of solvent for 24 h. NR = No Reaction. [b] NMR yields with methylene bromide as an internal standard. [c] Isolated yield in the parentheses. [d] The reaction was performed for 12 h. [e] The reaction was performed for 6 h.

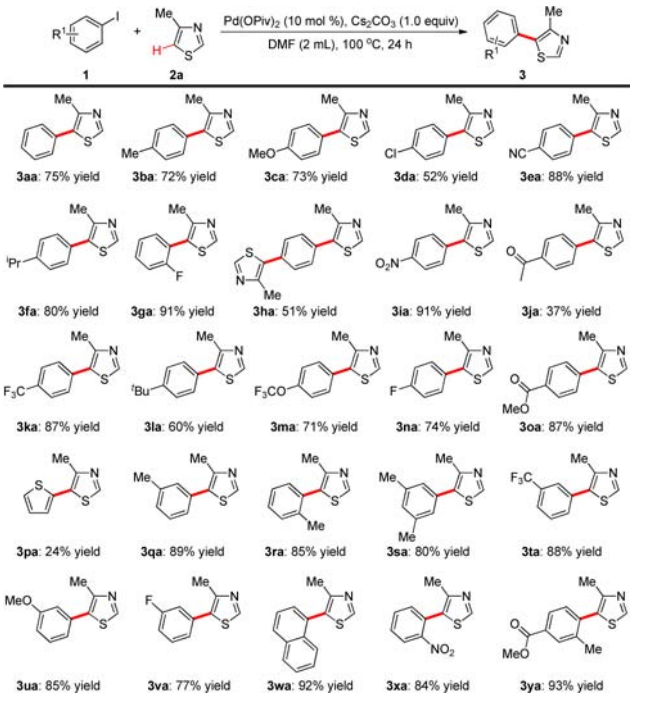
polar aprotic DMF was the best choice. Interestingly, the replacement of $Pd(OPiv)_2$ by an equimolar amount of $Pd(OAc)_2$ and PivOH as the catalyst dramatically decreased the yield (Table 1, entry 8). Furthermore, the concentration of the reaction mixture was also examined, and either decreasing or increasing the concentration deteriorated the reaction efficiency to some extent. Shortening the reaction time from 24 to 12 h also led to a lowered yield (72%). To our delight, a further improved yield (84%) was obtained by lowering the reaction temperature from 140 to 100 °C. It is noteworthy that in the presence of Pd(0) species, such as $Pd_2(dba)_3$, the reaction did proceed but delivered the desired product in only 3% yield (Table 1, entry 23).

With the optimized conditions in hand, we further examined the scope of aryl iodide as coupling partners for the C-5 arylation of 4-methylthiazole (Scheme 1). Gratifyingly, a wide variety of aryl iodides, regardless of the electron-deficient to -rich nature, were successfully applied for this regioselective arylation. It is noteworthy that the *para*-cyano, ester, and nitro groups were very compatible (**3ea**, **3ia**, and **3oa**), producing the corresponding desired products in good to excellent yields (87−91%). Sterically hindered substrates, such as *ortho*-methyl and *ortho*-nitro phenyl iodide and 1-naphthyl iodide, were also well tolerated and to some extent enhanced the efficacy, leading to an up to 92% isolated yield of **3** (**3ra**, **3xa**, and **3wa**). To our satisfaction, the integration of the transformable ester group and sterically hindered *ortho*-methyl group on the phenyl iodide could also be utilized as a qualified partner, furnishing the highly functionalized molecule (**3ya**) in 93% yield. In this transformation, both fluoro- and trifluoromethyl-containing aryl iodides worked well, affording the pharmaceutically important fluoro-containing thiazole derivatives (**3ga**, **3ka**, **3na**, **3ta**, and **3va**) in 74−91% yields. The *para*-acetyl phenyl iodide and even 2-iodothiophene could also be used as substrates (**3ja**, **3pa**), albeit only synthetically useful yields were obtained under the current reaction conditions. When *p*-bromoiodobenzene was used as a substrate, 1,4-bis(4-methylthiazol-5-yl)benzene (**3ha**) was obtained in 51% yield.

Subsequently, aryl bromide representatives (**5**), including phenyl bromide, *p*-methoxyphenyl bromide and *p*-fluorophenyl bromide have been applied to the optimized reaction conditions (Scheme 2). It was found that all the reactions proceeded smoothly to afford the corresponding regioselective arylated products in moderate to good yields (47−71%). These results further extended the application of this method.

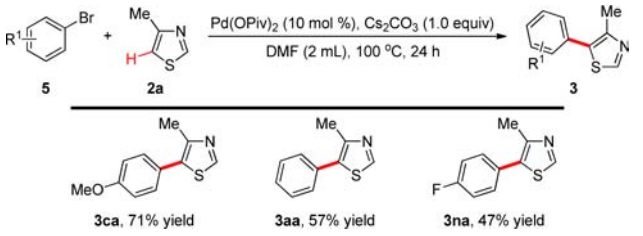
Later, we investigated the regioselective arylation of a more challenging substrate of the thiazole moiety

Scheme 1. Substrate Scope of Regioselective Arylation of 4-Methylthiazole[a]



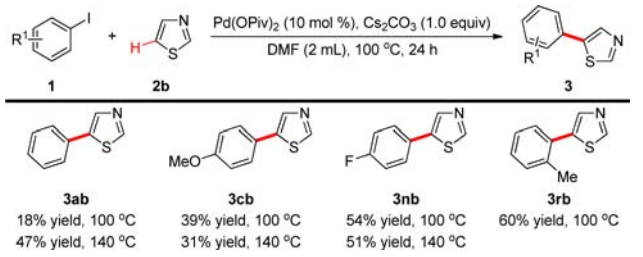
[a] Unless otherwise noted, all reactions were carried out in 0.2 mmol scale in 2 mL of solvent at 100 °C. Isolated yields are given.

Scheme 2. Substrate Scope of Regioselective Arylation of 4-Methylthiazole Using Aryl Bromides[a]



[a] Unless otherwise noted, all reactions were carried out in 0.2 mmol scale in 2 mL of solvent at 100 °C. Isolated yields are given.

Scheme 3. Substrate Scope of Regioselective Arylation of Thiazole[a]



[a] Unless otherwise noted, all reactions were carried out in 0.2 mmol scale in 2 mL of solvent at 100 °C. Isolated yields are given.

(Scheme 3). Under the optimal reaction conditions, phenyl iodide could couple with thiazole but in only 18% yield, whereas the yield can be improved to 47% by elevating the reaction temperature from 100 to 140 °C. In comparison, the *p*-fluorophenyl iodide and *p*-methoxyphenyl iodide were compatible under standard conditions, affording the 5-arylated thiazole derivatives in moderate yields (54% and 39%, respectively). However, we failed to improve the reaction efficiency further at an even higher reaction temperature (140 °C). Unexpectedly, the sterically hindered *ortho*-methyl phenyl iodide coupled more efficiently with thiazole specifically at the C-5 position in up to 60% isolated yield. Futher studies to promote the efficacy is underway.

To further illustrate the regioselective control of our current methodology, an experiment using 2-phenylthiazole **6** as the substrate was carried out (Scheme 4). As expected, the corresponding 5-phenylated product **7**[10] was exclusively obtained in 44% isolated yield and the *otho*-phenylated product **8** on the phenyl ring was not observed.

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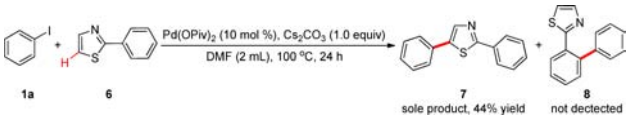
(12) To investigate whether the reaction was catalyzed homo- or heterogeneously, a further Hg drop test was performed. It was found that, in the presence of an additional 400 mg Hg, the reaction proceeded also smoothly, affording the desired product in 50% isolated yield. This result umbiguously demonstrated that this catalytic process was homogeneous. Refer to: Whitesides, G. M.; Hackett, M.; Brainard, R. L.; Lavalleye, J. P. P. M.; Sowinski, A. F.; Izumi, A. N.; Moore, S. S.; Brown, D. W.; Staudt, E. M. *Organometallics* **1985**, *4*, 1819.

Scheme 4. Evaluation of the Regioselective Arylation *versus* Directed *ortho*-C−H Functionalization of 2-Phenylthiazole



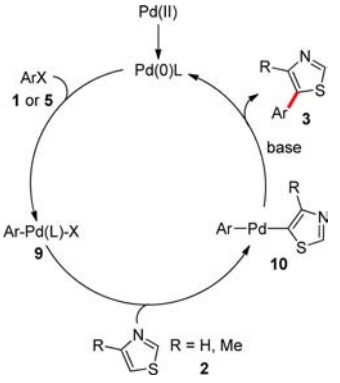


Figure 2. Proposed mechanism for regioselective arylation of thiazole derivatives.

Based on our investigations and previous theoretical calculations by Gorelsky,[6a,11] the catalytic pathway is considered to proceed as shown in Figure 2. After the reduction of the Pd(II) species to a Pd(0) species (this might be stabilized by the starting thiazole moiety or the corresponding product), arylpalladium species **9** is generated through the oxidative addition by aryl iodide (bromide). After the regioselective C−H activation of thioazole to form biaryl Pd(II) species **10**, reductive elimination occurs to afford the desired biaryl product **3** by releasing the Pd(0) species to complete the catalytic cycle.[12]

In conclusion, we have developed an efficient, ligand-free, and highly regioselective Pd(II)-catalyzed arylation of thiazole derivatives. The broad substrate scope and ligand-free conditions made this method synthetically useful. Further investigations to gain insight into the reaction mechanism, to promote the efficacy for other thioazle derivatives, and to apply this methodology to the synthesis of biologically active molecules are underway.

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Supporting Information Available. Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.