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Pd/Cu-Cocatalyzed Regioselective Arylation of Thiazole Derivatives at 2-Position under Ligand-Free Conditions

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

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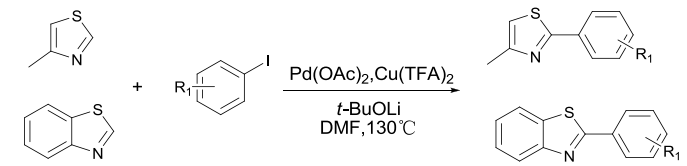
An efficient protocol for regioselective arylation of thiazole derivatives at 2-position via palladium- and copper- catalyzed C-H bond activation under ligand-free conditions has been developed. Reaction proceeds smoothly with 1% palladium catalyst in the presence of 20% Cu(TFA)$_2$ to furnish the desired products. The direct C-H arylation and no ligand used made this method synthetically useful for the arylation of thiazoles at the 2-position.

As an efficient and green method, direct C-H functionalization has been focused on because of its high atom efficiency and minimized wasteful byproducts compared to the reported cross-coupling reactions and its wide range of applications in the synthesis of biologically active compounds and organic intermediates. Transition-metal-catalyzed C−H functionalizations are some of the most convenient and efficient procedures available for the construction of complex heterocycles from simple starting materials.[1] At the same time, arylation of heterocycles has received significant attention in recent years because the heteroarenes are important structural units frequently found in biologically active molecules, organic materials, and pharmaceuticals.[2] Consequently, there has been significant effort at achieving efficient, high yielding, and highly selective functionalization of these types of molecules.[3] Traditional cross-coupling methodologies are highly versatile, but they need preactivation of heterocycles.[4] Therefore, the more efficient routes to these compounds involve direct functionalization of heterocycle C-H bonds were applied for the arylation reactions.

However the selectivity of C-H bond is one of the eternal research topics in organic synthesis.[5] Current solutions to achieve the selective functionalization among multiple C-H bonds that exist in the substrates and products usually are constructing a directing group or distinguishing C-H bonds by their inherent electronic nature.[6] However, there are some disadvantages of directing group strategy, for example, the directing groups are not always desirable in the target molecule and the removal of them is obligatory.[7] Therefore, regioselective arylation of heterocycles is highly desirable for practical synthetic application.To solve the problem, significant developments to carry out C-H activations have enabled direct arylation of thiazole-containing structural motifs and even some examples have been achieved in a regioselective manner.[8] In general, 2-blocked thiazoles were used to get the selective 5-arylated thioazoles, and the 5-substituted thiazoles were employed to achieve 2-arylated thiazole derivatives.[9] Moreover, the reported protocols have some drawbacks such as the use of air- and moisture-sensitive $Pd(PPh_3)_4$ or an additional ligand.[10] Many groups have accomplished excellent results that address the drawbacks mentioned above in the arylation of thiazoles.[11] In these methods, 4-methylthiazole was rarely used because 4-methylthiazole dimer was more easily formed than thiazole dimer.[12] 5-arylated thioazole and 4-methylthiazole dimer should be reduced simultaneously to get the selective 2-arylated thioazole. On the basis of the above excellent works, our attention was drawn to the observation that copper salts can affect the regioselectivity of palladium-catalyzed electron-rich heterocycle arylation. To our delight, we found that when a combination of catalytic Pd and Cu was used, the main products were 2-arylated thiazole derivatives.



Scheme 1 Pd/Cu-Cocatalyzed Regioselective Arylation of Thiazole Derivatives

The Pd/Cu-cocatalyzed regioselective C-H arylation of 4-methylthiazole (**1**) with iodobenzene (**2a**) was chosen as model reaction for the purpose of optimization of reaction conditions. Since the reaction proceeded smoothly to afford the desired 2-phenylated 4-methylthiazole (**3a**) in the presence of a combination of catalytic Pd and Cu, various palladium and copper catalysts were screened for the selective C-H arylation reaction. It has been observed that, **5a** and **6a** increased as the main byproduct respectively when CuI or the combination of CuI and $Pd(OAc)_2$ was used as the catalyst (Table 1, entries 10 and 11). The yield of **3a** decreased dramaticly in the absence of copper or palladium source, indicating that copper

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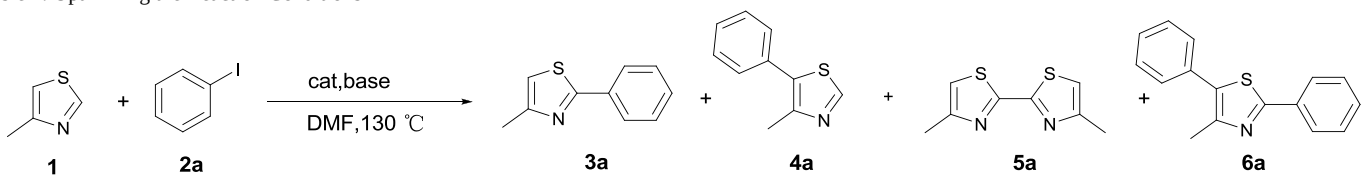
and palladium sources were crucial for the reaction (Table 1,entries 8-9). Therefore, the combination of $Pd(OAc)_2$ and $Cu(TFA)_2$ has shown a good catalytic activity among all the above catalysts combination, providing the desired product in up to 81% yield (Table 1, entry 6). When the loading of $Pd(OAc)_2$ increased from 1% to 5%, the yield of **3a** decreased because **4a**, **5a** and **6a** were produced simultaneously as byproducts (Table 1, entries 6 and 7). Therefore, 1% $Pd(OAc)_2$ with 20% $Cu(TFA)_2$ was the optimal amount for the catalysts. Subsequent experiments revealed that 3h was ideal reaction time to reach better yield of **3a**. (Table 1, entries 1-6). The addition of 2.0 equiv *t*-BuOLi greatly improved the reaction yield from 40% to 81% yield (Table 1, entries 6 and 15). Other inorganic bases such as, *t*-BuONa, *t*-BuOK, Cs_2CO_3 and KOH were less effective than *t*-BuOLi (Table 1, entries 16-19). Solvent screening indicated that polar aprotic DMF was the best choice (Table 1, entries 13-14).

Table 1. Optimizing the Reaction Conditions[a]



1 **2a** **3a** **4a** **5a** **6a**

Entry	Time/h	Catalyst (mol %)	Solvent	Base	Yield/(%)			
					3a	4a	5a	6a
1	0.5	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	*t*-BuOLi	54	1	--	--
2	1	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	*t*-BuOLi	68	5	2	--
3	1.5	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	*t*-BuOLi	70	9	2	--
4	2	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	*t*-BuOLi	73	10	2	--
5	2.5	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	*t*-BuOLi	80	12	3	--
6	3	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	*t*-BuOLi	81	13	3	--
7	3	$Pd(OAc)_2$ (5), $Cu(TFA)_2$ (20)	DMF	*t*-BuOLi	20	28	18	10
8	3	$Pd(OAc)_2$(1)	DMF	*t*-BuOLi	5	31	--	--
9	3	$Cu(TFA)_2$ (20)	DMF	*t*-BuOLi	--	--	--	--
10	3	CuI (20)	DMF	*t*-BuOLi	30	--	33	--
11	3	$Pd(OAc)_2$ (1), CuI (20)	DMF	*t*-BuOLi	63	--	--	17
12	3	$Pd(OAc)_2$ (1), $Cu(OAc)_2$ (20)	DMF	*t*-BuOLi	46	10	15	--
13	3	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMSO	*t*-BuOLi	68	15	8	--
14	3	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	toluene	*t*-BuOLi	31	--	--	--
15	3	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	--	40	--	20	--
16	3	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	*t*-BuOK	34	--	--	--
17	3	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	*t*-BuONa	18	30	--	--
18	3	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	Cs_2CO_3	6	13	--	--
19	3	$Pd(OAc)_2$ (1), $Cu(TFA)_2$ (20)	DMF	KOH	--	--	--	--

[a] Reaction condition: 1a (1.0 mmol), 2a (1.0 mmol), base(2 equiv), in solvent(3 mL). The yields were determined by GC.

Under the optimized conditions, the scope of this selective C-H arylation reaction was investigated with different aryl iodide. Either electron-withdrawing or electron-donating groups on the phenyl ring of the aryl iodide were well tolerated, affording the desired products with satisfactory yields. It is noteworthy that the para-methyl, para-chloro, para-nitro groups were very compatible, producing the corresponding products in good yields (**3d**-**3g**). However, when sterically hindered substrates such as ortho-methyl iodobenzene,

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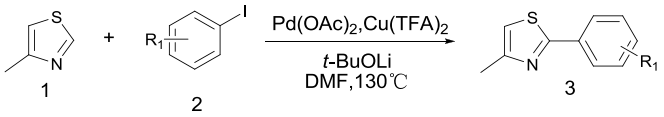
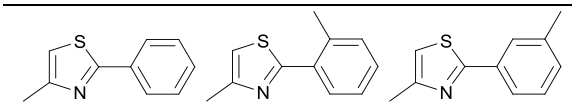
ortho- carboxyl iodobenzene were employed in the reaction, the yield of **3b** and **3i** dramatic declined, and the significant differences between the yields of **3b** and **3i** may be due not only steric hindrance but also the electron-donating or electron-withdrawing characters of the substituents. Di-4-methylthiazole compound **3h** was obtained as main product when 1,4-diiodobenzene was used. Unfortunately, no desired products were obtained when bromobenzene and chlorobenzene were employed under the optimal reaction conditions.

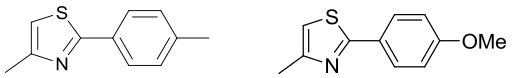
Table 2. Substrate Scope of Regioselective Arylation of 4-methylthiazole [a]



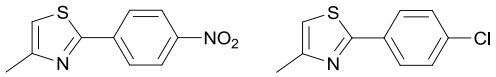
1 2 3



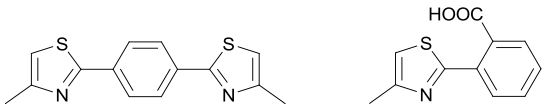
3a,75% **3b**[b]**,**56% **3c,**71%



3d,70% **3e,**68%



3f,85% **3g,**88%



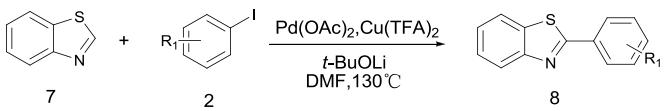
3h[c]**,**70% **3i,**trace

[a] Reaction condition: 1 (1.0 mmol), 2 (1.0 mmol),$Pd(OAc)_2$ (1 mol%), $Cu(TFA)_2$ (20 mol%), *t*-BuOLi (2 equiv), in DMF(3.0 mL), 3 h. Isolated yield.[b] Reaction time was 5 h. [c] 2 equiv 4-methylthiazole was used.

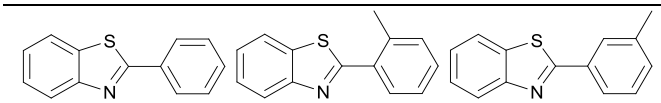
To expand the substrate scope, benzothiazole was examined with different iodobenzene under the optimized conditions. The steric effect and electronic effect were the same as 4-methylthiazole. However, the yield of benzothiazole was generally higher than 4-methylthiazole because of the less byproduct. However when 1,4-diiodobenzene was employed in the reaction, **8a** was obtained rather than the corresponding monosubstituted or disubstituted product. It may be due to the formation of monosubstituted product which can easily dehalogenate in alkalis condition.

Based on our investigations and previous study by some groups[11b,13], the catalytic pathway is considered to proceed as shown in Figure 1. 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. Because of the ability of Cu salts to metallate acidic C-H bonds and in particular the C-2 position of thiazole moiety, in the presence of a base , organocopper derivatives **10** will be produced and CuX oxidized to Cu(II) in the presence of air, might then undergo transmetallation with the aryl palladium(II) halide species **9**, reductive elimination occurs to afford the desired biaryl product **3** by releasing the Pd(0) species to complete the catalytic cycle.

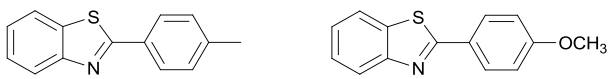
Table 3. Substrate Scope of Regioselective Arylation of Benzothiazole [a]



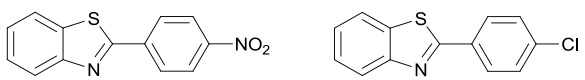
7 2 8



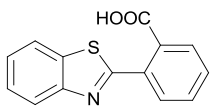
8a,78% **8b**[b]**,**64% **8c,**76%



8d,92% **8e**[b]**,**74%



8f,90% **8g,**78%



8i,trace

[a] Reaction condition: 1 (1.0 mmol), 2 (1.0 mmol),$Pd(OAc)_2$ (1 mol%), $Cu(TFA)_2$ (20 mol%), *t*-BuOLi (2 equiv), in DMF(3.0 mL), 3 h. Isolated yield.[b] Reaction time was 5 h.

Conclusions

In summary, an efficient protocol for regioselective arylation of electron-rich thiazole derivatives at 2-position via palladium- and copper- catalyzed C-H bond activation has been developed. The less usage of palladium and ligand-free conditions make this C-H arylation protocol more resourceful for future applications and provide a powerful tool for the synthesis of substituted arylthiazole derivatives.

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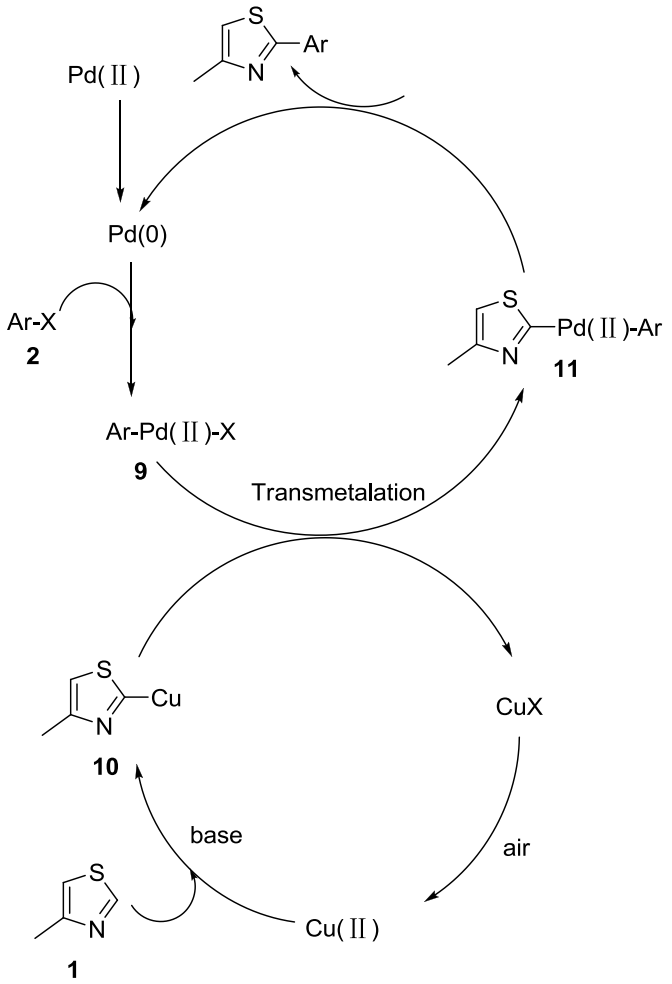

Figure 1. Proposed mechanism for regioselective arylation of thiazole derivatives.

Notes and references

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