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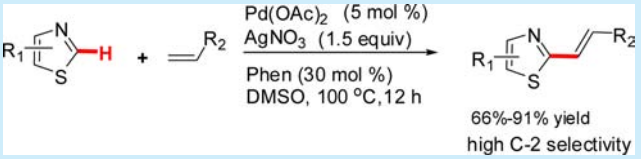
Palladium-Catalyzed C-2 Selective Olefination of Thiazoles

Wei Liu, Xin Yu, and Chunxiang Kuang*

Department of Chemistry, Tongji University, Siping Road 1239, Shanghai 200092, P. R. China and Key Laboratory of Yangtze River Water Environment, Ministry of Education, Siping Road 1239, Shanghai 200092, P. R. China

Supporting Information

ABSTRACT: A highly efficient protocol for C2 selective alkenylation of electron-deficient thiazoles is developed. High C2 position selectivity for alkenylation products is achieved at a neutral environment, and a possible pathway of oxidative alkenylation is discussed. This methodology provides a simple way to construct a 2-alkenyl-thiazole moiety.



Since the discovery of the transition-metal-catalyzed oxidative olefination of benzene by Fujiwara, significant progress has been made to improve the efficiency and practicality of the oxidative Heck reaction.[1] The scope of direct alkenylation partners has broadened to include various directing groups,[2] electron-rich (hetero)arenes,[3] and even some examples for the site-selective C−H olefination of electron-deficient (hetero)arenes.[4]

A thiazole-containing structural motif is frequently featured at the core of pharmaceuticals and organic materials.[5] Considering their importance, great successes have been accomplished regarding transition-metal-catalyzed direct arylation[6] and alkylation[7] of thiazoles, including oxidative C−H/C−H coupling reactions. To our knowledge, the most direct olefination of thiazoles still relies on the use of alkenyl bromides as coupling partners,[8] but commercially available alkenyl halide are still limited. However, in sharp contrast to those extensive studies, the C−H/C−H oxidative olefination of thiazoles has rarely been reported because of their tendency to undergo homocoupling toward oxidative environments. Moreover, direct olefination of thiazoles remains a daunting challenge in the selectivity inversion between C2 and C5 positions.[9]

Based on our ongoing interest in exploring C−C bond formations through cross-dehydrogenative coupling reactions,[2b,10] we report in this paper an efficient and highly regioselective protocol for oxidative olefination at the C2 position of electron-deficient thiazoles. This simple and novel method provides access to 2-alkenylthiazole derivatives that are closely related to a variety of biologically active natural products, like artemisinin, and drug molecules such as epothilone C (Figure 1).

We initially employed reported conditions[4c,10] for the oxidative Heck reaction of 4,5-dimethylthiazole (**1a**) and methyl acrylate (**2a**), but no desired product was observed (Table 1, entry 1). As shown in Table 1, a few types of simple silver and copper salts were tested (entries 1 to 5), where all incomplete ionization silver and copper salts (Ag_2CO_3, $Cu(OAc)_2$, and AgOAc) failed to obtain any desired product; in the case of complete ionization of silver salts ($AgNO_3$ and Ag_2SO_4), the corresponding products were obtained with low yields. $AgNO_3$ was found to be the optimal oxidant for this reaction.

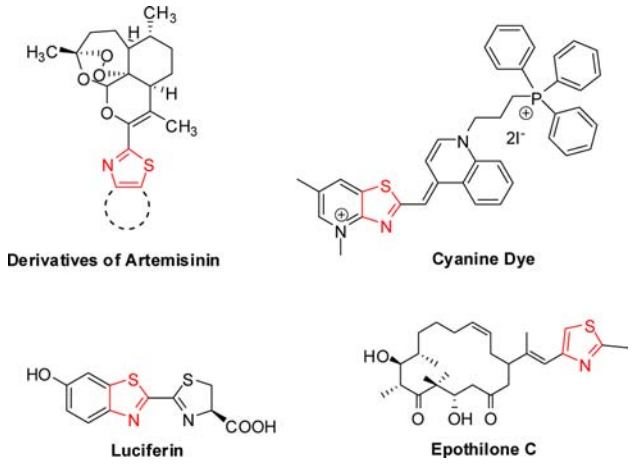


Figure 1. Representatives of thiazole-containing compounds.

Encouraged by this preliminary result, a variety of solvents were screened (entries 5 to 8); as a result, DMSO was selected as the most effective solvent compared to others such as 1,4-dioxane, DMF, and toluene. An improved yield (89%) was obtained by lowering the reaction temperature from 125 to 100 °C (entries 9 to 11). In addition, the yield of this reaction could be slightly diminished when no 1,10-phenanthroline was used. Thus, the optimal reaction conditions were obtained when 5 mol % of $Pd(OAc)_2$ was used in combination with 1,10-phenanthroline (30 mol %) and $AgNO_3$ (1.5 equiv) at 100 °C in DMSO (entry 9). Furthermore, this Heck reaction proceeded with complete stereoselectivity and generated (*E*)-**3a** exclusively.

With the optimized conditions identified (Table 1, entry 9), we further examined the scope of other thiazole derivatives and alkenes for C-2 alkenylation reactions (Scheme 1). We first

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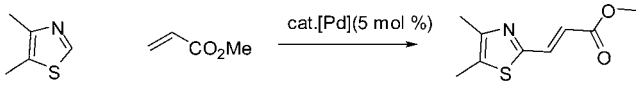
Table 1. Optimization of Typical Reaction Conditions[a]

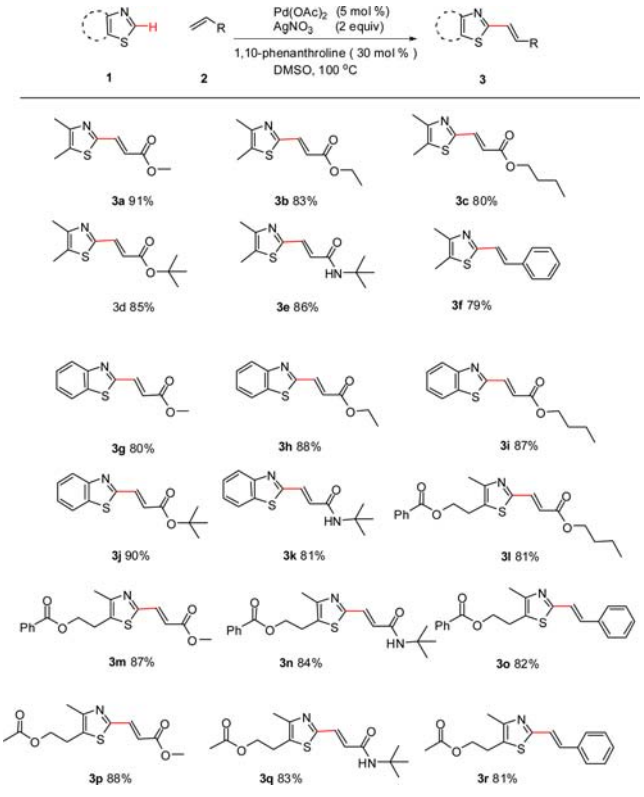


1a 2a 3a

entry	oxidant	solvent	t (°C)	yield (%)[c]
1	Ag_2CO_3	dioxane	125	trace
2	AgOAc	dioxane	125	trace
3	$Cu(OAc)_2$	dioxane	125	trace
4	Ag_2SO_4	dioxane	125	18
5	$AgNO_3$	dioxane	125	31
6	$AgNO_3$	DMF	125	65
7	$AgNO_3$	DMSO	125	81
8	$AgNO_3$	toluene	125	48
9	**$AgNO_3$**	**DMSO**	**100**	**89**
10	$AgNO_3$	DMSO	75	53
11	$AgNO_3$	DMSO	50	12
12[b]	$AgNO_3$	DMSO	100	69

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.65 mmol), $Pd(OAc)_2$ (5 mol %), 1,10-phenanthroline (30 mol %) and oxidant (1.5 equiv), solvent (1.5 mL), 12 h. [b]No 1,10-phenanthroline was added. [c]Isolated yields.

Scheme 1. Substrate Scope[a,b]

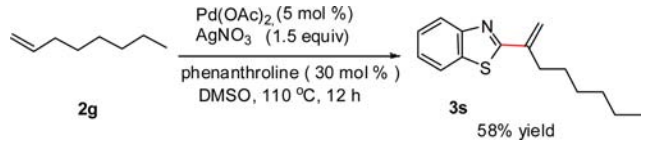


[a]Reaction conditions: **1** (0.5 mmol), **2** (0.65 mmol), $Pd(OAc)_2$ (5 mol %), 1,10-phenanthroline (30 mol %), and $AgNO_3$ (1.5 equiv), DMSO (1.5 mL), 100 °C, 12 h. [b] Isolated yields.

examined the compatibility of the olefin coupling partners. Gratifyingly, terminal olefin coupling partners containing ester, amide, and aryl moieties were found to be suitable reactants (Scheme 1, compounds **3a**–**3f**). Further reactions of differently 4,5-disubstituted thiazoles show the versatility of this oxidative olefination methodology in high yields (Scheme 1, compounds **3g**–**3r**) without any observable homocoupling products.

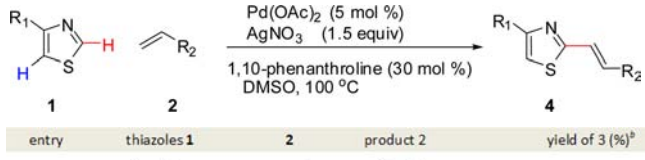
Interestingly, 1-octene was applied to the standard conditions, affording the branched product **3s** in moderate yield (58%) (Scheme 2). Notably, no desired product was observed under the above conditions when vinyl acetate and allyl acetate were used as substrates.

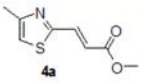
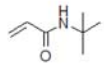
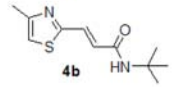
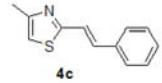
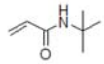
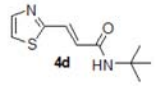
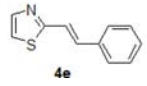
Scheme 2. Reaction of 3a with 1-Octene



The C2 position of the thiazole moiety is known to possess lower electron density than the C5 position, whereas it has higher electron density than the C4 position.[6d] However, we found that the only C2 alkenylation products were obtained in high yields when 4-methylthiazole as coupling partner was applied to the alkenylation reaction under the above reaction conditions (Table 2, compounds **4a**, **4b**, and **4c**). It was found

Table 2. C2-Selective Alkenylation of 4-Methylthiazole and Thiazole[a]



entry	thiazoles 1	2	product 2	yield of 3 (%)[b]
1				88 (35)[c]
2	1e			86 (31)[c]
3	1e			79 (25)[c]
4				63 (0)[c]
5				66 (0)[c]

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.65 mmol), $Pd(OAc)_2$ (5 mol %), 1,10-phenanthroline (30 mol %), and $AgNO_3$ (1.5 equiv), DMSO (1.5 mL), 100 °C, 12 h. [b]Isolated yields. [c]No 1,10-phenanthroline was added.

that the yield of the desired product was significantly diminished without 1,10-phenanthroline in the system. No C5 alkenylation or dialkenylation products were observed.

To further illustrate the regioselective control of our methodology, we investigated the site-selective oxidative olefination of a more challenging substrate of the thiazole moiety. Under the optimal reaction conditions, terminal olefin coupling partners could couple with the C2 position of thiazole in moderate yields whereas the C4 and C5 positions of thiazole cannot undergo the alkenylation reaction with the excessive alkene (Table 2, compounds **4d**, **4e**). No desired product was

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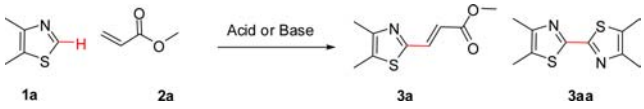
observed without 1,10-phenanthroline in the reaction system. The result from the above experiment indicates that, relative to the C4 and C5 positions in thiazoles, the C2 position should have higher reactivity in the formation of the alkenylation product under the optimal conditions and 1,10-phenanthroline played an important role in the C2 selectivity inversion.

To gain insight into the reaction mechanism, we investigated the effect of an acidic or alkaline environment on the olefination reaction. Trifluoroacetic acid or acetic acid was shown to be an efficient additive in the C-5 alkenylation of electron-deficient (hetero)arenes.[9,4a] Unexpectedly, though, no desired C-2 alkenylation product **3a** was observed with the addition of trifluoroacetic acid or acetic acid to the $Pd(OAc)_2$/$AgNO_3$ system, whereas homocoupling product **3aa** was produced (Table 3, entries 1 to 3). Bases are reportedly used

Table 3. Effect of Acidic or Alkaline Environment[a]



1a 2a 3a 3aa

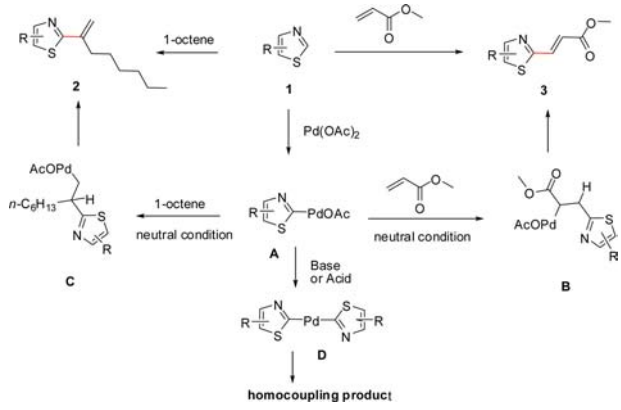
entry	acid	base	yield of **3a** (%)[b]	yield of **3aa** (%)[b]
1	CH_3COOH (1.0 equiv)	–	trace	28
2	CF_3COOH (1.0 equiv)	–	trace	33
3	CF_3COOH (0.1 equiv)	–	trace	15
4	–	pyridine (1.0 equiv)	trace	trace
5	–	K_3PO_4 (1.0 equiv)	trace	24
6	–	LiO*t*-Bu (1.0 equiv)	trace	44

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.65 mmol), $Pd(OAc)_2$ (5 mol %), 1,10-phenanthroline (30 mol %), and $AgNO_3$ (1.5 equiv), DMSO (1.5 mL), 100 °C, 12 h. [b]Isolated yields.

extensively in C−H/C−H oxidative coupling reactions of thiazoles and enhance the efficiency of C−C bond formation.[11−14] However, the addition of 1 equiv of base such as LiO*t*Bu,[11] pyridine,[12] and K_3PO_4[13] was detrimental to the reaction and resulted in the lack of any observable desired thiazole olefination product. Additionally, the homocoupling product **3aa** formed when a strong base (LiO*t*Bu and K_3PO_4) was applied to the reaction system (Table 3, entries 4 to 6). The above findings indicate that a neutral environment may be the preferred condition for this oxidative Heck reaction of thiazoles at the C2 position. Additionally, different results in Table 1 between incomplete ionization salts and complete ionization salts should be presently well understood. Moreover, the H/D exchange control experiments for benzothiazole **1b** was performed and moderate deuterium incorporation at the C-2 position was observed. However, no deuterium incorporation occurred when no Pd-catalyst was used (Scheme S1). The results indicate that the thiazoles should undergo a substitution reaction with the Pd-catalyst to generate a thiazolylpalladium intermediate.

Despite the rather fragmented information on the mechanism at present, we propose that the Pd-catalyzed vinylation proceeds through a plausible catalytic mechanism. As shown in Scheme 3, the thiazoles should undergo C2 selective electrophilic C−H substitution of Pd $(OAc)_2$ to generate the

Scheme 3. Proposed Mechanism



palladium(II) intermediate **A**. Next, the resulting Pd−C bond of **A** adds to the carbon−carbon double bond of the terminal olefin coupling partners, such as methyl acrylate, to form the Pd complexes **B**. Later, product **3** was formed when *β*-H elimination of **B** occurred. However, for 1-octene,[2b] complexes **C** may be the predominant intermediate after the formation of intermediate **A** and branched product **2** was obtained. Thiazole homocoupling proceeded through the formation of intermediate **D** when an acid or base was applied to the reaction system. Further studies are needed to understand the mechanism of selectivity between the C2 and C5 positions in a Pd-catalyzed oxidative Heck reaction.

In summary, we have developed an efficient and highly C2 selective oxidative olefination of thiazole derivatives. The broad substrate scope made this method synthetically useful. Further investigations to gain insight into the reaction mechanism and to apply this methodology to the synthesis of biologically active molecules are underway.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kuangcx@tongji.edu.cn.

Notes

The authors declare no competing financial interest.

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