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Palladium-Catalyzed Direct Oxidative Alkenylation of Azoles

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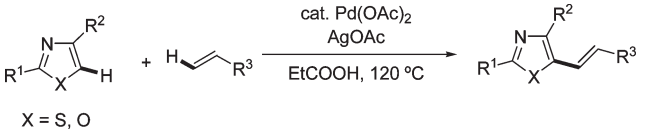

The direct heteroaromatic sp^2 C−H alkenylation of 2-substituted azole compounds with alkenes proceeds in the presence of $Pd(OAc)_2$ and AgOAc as catalyst and oxidant, respectively, to afford the corresponding 5-alkenylated azoles in good yields.

Transition-metal-catalyzed direct C−C bond-forming reactions via C−H bond cleavage have attracted much attention in modern organic synthesis because they require no prefunctionalization step of the starting materials and provide a potentially more efficient alternative to the conventional methodologies using organic halides and organometallic reagents.[1] In particular, the palladium-catalyzed oxidative cross-coupling of arenes and alkenes via C−H bond cleavage of both the substances, the so-called Fujiwara−Moritani reaction, is quite attractive from the viewpoint of step economy and enables a rapid increase of molecular complexity in various arenes and heteroarenes.[2] For example, the reactions of six-membered arenes having a directing group[3] such as benzoic acid, anilide, or benzylamine and electron-rich heteroarenes[4] including indole, thiophene, furan, and indolizine have been developed. Previously, we also reported the palladium-catalyzed direct site-selective alkenylation of thiophenes and furans as well as heteroarenecarboxylic acids with concomitant decarboxylation.[5] In addition, the direct alkenylation of unactivated electron-deficient arenes like pyridine *N*-oxide and perfluoroarene has been achieved.[6] However, less attention has so far been focused on azoles, which are useful heteroaromatic cores in pharmaceutical and material chemistry.[7] Most direct alkenylations of azoles still rely on use of the corresponding alkenyl halides[8] due to the problematic homocoupling under the oxidative conditions.[9] Herein, we report a palladium-based catalyst system for the direct C−H alkenylation of azoles with a number of alkenes.

As an initial attempt, treatment of isobutylthiazole (**1a**) with *n*-butyl acrylate (**2a**) in the presence of 10 mol % of $Pd(OAc)_2$ and 3.0 equiv of AgOAc as an oxidant in mesitylene (2.5 mL) at 120 °C for 8 h afforded the corresponding 5-alkenylated product **3aa** albeit in 29% yield (Table 1, entry 1). While an acidic additive, PivOH, was found to accelerate the direct alkenylation, a small but significant amount of alkenylated mesitylene was also detected as byproduct (entry 2). Thus, nonaromatic solvents were tested. Aprotic polar solvents such as DMAc and DMSO were ineffective (entries 3 and 4). On the other hand, the reaction in PivOH itself gave **3aa** in high yield, and no byproduct was formed (entry 5). EtCOOH further improved the yield of **3aa** (entry 6). The use of $Cu(OAc)_2$ in place of AgOAc or lower temperature decreased the reaction efficiency (entries 7 and 8). The lower catalyst loading had no negative influence on the yield (entry 9).

With the effective reaction conditions in hand (Table 1, entry 9), a variety of alkenes were tested for the direct alkenylation of **1a** (Table 2). Acrylate esters bearing bulky

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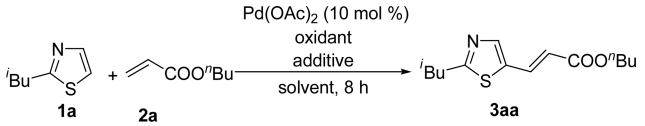
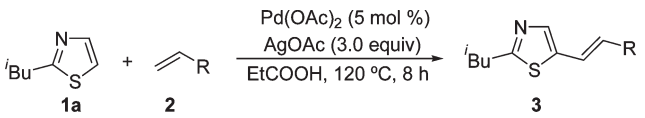
TABLE 1. Optimization for Palladium-Catalyzed Reaction of 2-Isobutylthiazole (1a) with *n*-Butyl Acrylate (2a)[a]



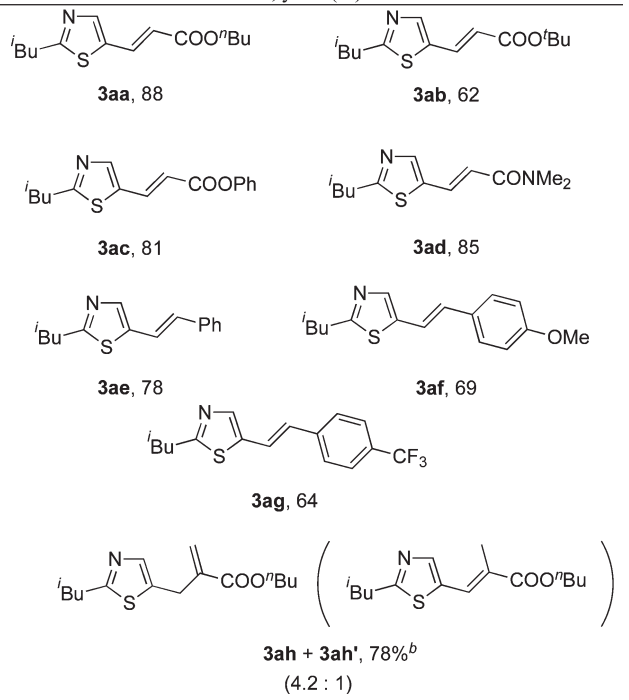
entry	oxidant	additive	solvent	temp (°C)	**3aa**, yield[b] (%)
1	AgOAc		mesitylene	120	(29)
2	AgOAc	PivOH	mesitylene	120	(88)
3	AgOAc	PivOH	DMSO	120	(15)
4	AgOAc	PivOH	DMAc	120	(49)
5	AgOAc		PivOH	120	(88)
6	AgOAc		EtCOOH	120	(93)
7	$Cu(OAc)_2$		EtCOOH	120	(54)
8	AgOAc		EtCOOH	90	(30)
9[c]	AgOAc		EtCOOH	120	(93) 88

[a]A mixture of **1a** (0.2 mol), **2a** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), additive (0.2 mmol), and oxidant (0.6 mmol) was stirred in solvent (1 mL) for 8 h. [b]GC yield is in parentheses. [c]$Pd(OAc)_2$ (0.01 mmol) was used.

TABLE 2. Palladium-Catalyzed Alkenylation of 2-Isobutylthiazole (1a) with Various Alkenes 2[a]



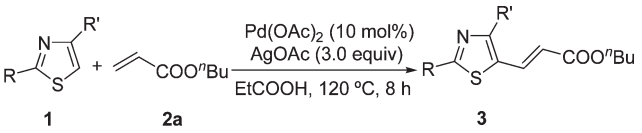
3, yield (%)



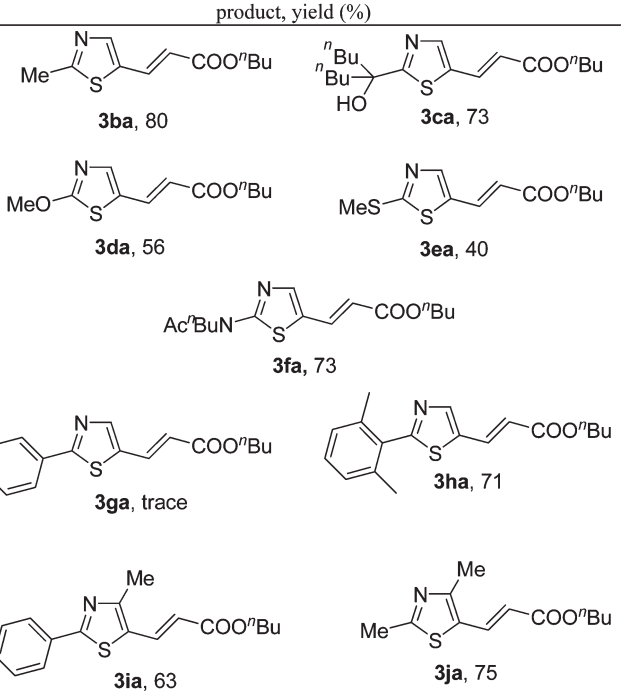
[a]A mixture of **1a** (0.50 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), and AgOAc (1.5 mmol) was stirred in EtCOOH (2.5 mL) at 120 °C for 8 h. Key: **2a**, R = COO^nBu; **2b**, R = COO^tBu; **2c**, R = COOPh; **2d**, R = $CONMe_2$; **2e**, R = Ph; **2f**, R = 4-$MeOC_6H_4$; **2g**, R = 4-FC_6H_4. [b]Butyl methacrylate (**2h**) was used as alkene.

tert-butyl **2b** and aromatic phenyl groups **2c** resulted in the formation of **3ab** and **3ac** in 62% and 81% yields, respectively. Acrylamide **2d** showed a similar reactivity. Styrenes also could be employed for the oxidative coupling. Not only simple styrene (**2e**) but also electron-rich and -deficient styrenes **2f** and **2g** reacted with **1a** smoothly to furnish **3ae**−**ag** in good yields. Interestingly, methacrylate ester **2h** provided the unconjugated (to azole) product **3ah** as the major product (**3ah**/**3ah**′ = 4.2:1). In contrast, internal or aliphatic alkenes such as methyl cinnamate and 1-hexene gave the corresponding coupled products in low yields (ca. < 10% by GC−MS).

TABLE 3. Palladium-Catalyzed Alkenylation of Various Thiazoles 1 with *n*-Butyl Acrylate (2a)[a]



product, yield (%)



[a]A mixture of **1** (0.50 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), and AgOAc (1.5 mmol) was stirred in EtCOOH (2.5 mL) at 120 °C for 8 h. Key: **1b**, R = Me, R′ = H; **1c**, R = $^nBu_2COH$, R′ = H; **1d**, R = MeO, R′ = H; **1e**, R = MeS, R′ = H; **1f**, R = N^nBuAc, R′ = H; **1g**, R = Ph, R′ = H; **1h**, R = 2,6-$Me_2C_6H_3$, R′ = H; **1i**, R = Ph, R′ = Me; **1j**, R, R′ = Me.

The oxidative coupling reaction was further extended to various thiazoles **1** as shown in Table 3. A smaller methyl-substituted thiazole **1b** also afforded the desired product **3ba** in 80% yield. Thiazole having a free hydroxyl group **1c** reacted with **2a** without any difficulties. Moreover, thiazoles bearing heteroatom substituents at the 2-position **1d**−**f** gave **3da**, **3ea**, and **3fa** in moderate to good yields. On the other hand, 2-phenylthiazole showed less activity toward the reaction. This is probably because of the catalyst deactivation arising from a competitive cyclopalladation on benzene ring.[10] Therefore, we tested 2-(2,6-dimethylphenyl)thiazole (**1h**) as the reactant to suppress the unfavorable palladation mentioned above. As

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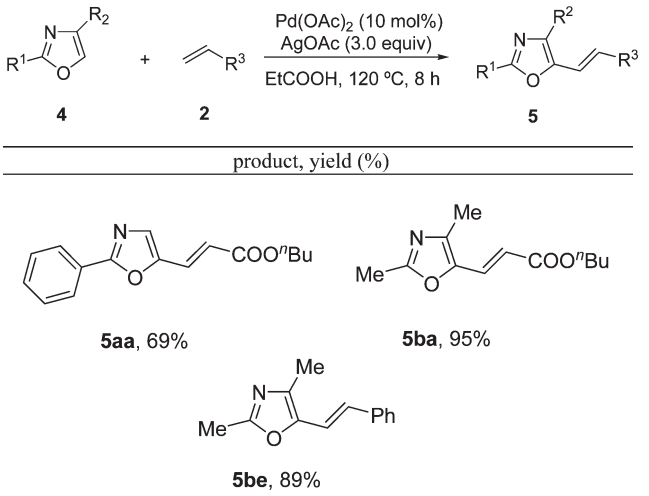
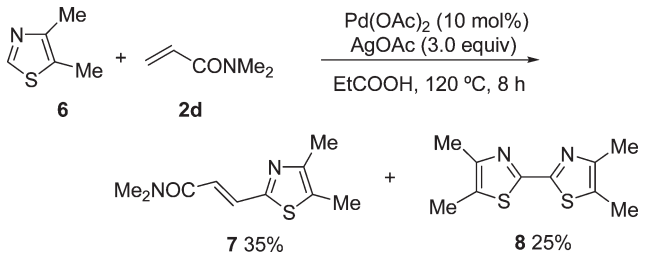
TABLE 4. Palladium-Catalyzed Alkenylation of Oxazoles 4 with Alkenes 2[a]



[a]A mixture of **4** (0.50 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), and AgOAc (1.5 mmol) was stirred in EtCOOH (2.5 mL) at 120 °C for 8 h. Key: **4a**, R^1 = Ph, R^2 = H; **4b**, R^1, R^2 = Me.

SCHEME 1. Palladium-Catalyzed Alkenylation of 4,5-Dimethylthiazole (6) with 2d



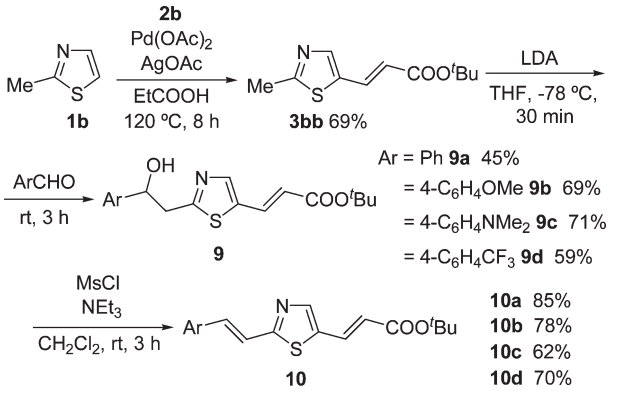
expected, **1h** could be transformed to **3ha** in 71% yield. Notably, the introduction of a methyl group to the 4-position of thiazole significantly accelerated the reaction despite the presence of a phenyl substituent at the 2-position (**3ja**).[11] Furthermore, the coupling of 2,4-dimethylthiazole (**1j**) proceeded smoothly under the standard conditions.

2-Substituted oxazoles instead of thiazoles **1** were also available for use (Table 4). Interestingly, 2-phenyloxazole (**4a**) gave 5-alkenyled product **5aa** in 69% yield, which is in marked contrast to the trend of thiazole (Table 2, **3ga**). 2,4-Dimethyloxazole (**4b**) also reacted with **2a** and **2e** smoothly to afford excellent yields of **5ba** and **5be**, respectively.

Next, we attempted the direct C2 alkenylation of 4,5-dimethylthiazole (**6**) (Scheme 1). Under the standard conditions, we obtained the desired **7** albeit in 35% yield, contaminated with the conceivable homocoupling product **8**.

π-Extended 2,5-disubstituted thiazoles are known to show unique optical properties.[12] Inspired by the literature, we synthesized some 2,5-dialkenylated thiazoles **10** and investigated their fluorescence in the solid state (Scheme 2). The monoalkenylated thiazole **3bb** was first prepared by our palladium-catalyzed direct alkenylation of 2-methylthiazole (**1b**). The deprotonation of **3bb** with LDA at −78 °C in THF and addition of the resultant lithium reagent to aromatic aldehydes at room temperature gave aldol-type products **9a**−**d**. Finally, we obtained the desired 2,5-dialkenylthiazoles **10** by dehydration of **9** upon treatment with mesyl chloride and triethylamine.

SCHEME 2. Synthesis of 2,5-Dialkenylthiazoles 10



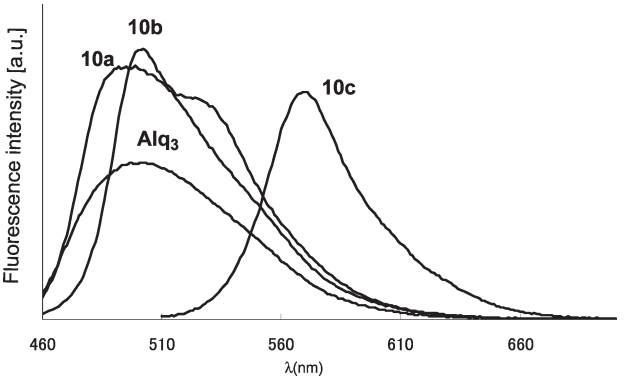


FIGURE 1. Fluorescence spectra of **10a**,[a] **10b**,[a] **10c**,[b] and Alq_3[c] in the solid state. [a]Excited at 430 nm. [b]Excited at 500 nm. [c] Excited at 380 nm.

Dialkenylthiazoles **10** except for **10d** showed solid-state fluorescence (Figure 1). The emission spectra of styryl-substituted **10a** exhibited the major band with maximum emission λ_{em} at 492 nm. By installation of the strongly electron-donating dimethylamino group to the benzene ring, this peak was red-shifted by 78 nm (**10c**). The methoxy substituent caused a similar shift, although the effect was considerably small (**10b**). These compounds exhibited similar or relatively strong emissions compared to a typical emitter, tris(8-hydroxyquinolinato)aluminum (Alq_3).

In summary, we have described an effective palladium catalyst system for the direct alkenylation of thiazoles and oxazoles with alkenes.[13] In addition, with the catalysis as the key transformation, we succeeded in the synthesis of π-conjugated 2,5-dialkenylated thiazoles with interesting optical properties.

Experimental Section

Typical Procedure for Palladium-Catalyzed Alkenylation of Azoles 1 or 4 with Alkenes 2. In a 20 mL two-necked flask were

(11) This is probably because the methyl group at 4-position in thiazole inhibited the unfavorable coordination of nitrogen to the palladium center necessary for the competitive cyclopalladation.

(12) Selected examples: (a) Shu, C.-F.; Wang, Y.-K. *J. Mater. Chem.* **1998**, *8*, 833. (b) Eckert, K.; Schröder, A.; Hartmann, H. *Eur. J. Org. Chem.* **2000**, 1327.

(13) The fact that the alkenylation of azoles **1** and **4a** occurs selectively at the relatively electrophile-susceptible 5-position rather than the 4-position is consistent with the relevant Pd-catalyzed direct arylation chemistry.[1a−e]

added 2-isobutylthiazole (**1a**, 0.5 mmol, 71 mg), *n*-butyl acrylate (**2a**, 1 mmol, 128 mg), $Pd(OAc)_2$ (0.03 mmol, 5.6 mg), AgOAc (1.5 mmol, 250 mg), dibenzyl (ca. 50 mg) as internal standard, and propionic acid (2.5 mL). The resulting mixture was stirred under nitrogen at 120 °C (bath temperature) for 8 h. After the suspension was allowed to cool to room temperature, analysis of the mixture by GC confirmed the formation of the desired compound. The reaction mixture was poured into satd aq $NaHCO_3$ and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product **3aa** (0.44 mmol, 118 mg, 88%) was also isolated by chromatography on silica gel using hexane−ethyl acetate (95:5, v/v). **3aa**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.00 (d, J = 6.9 Hz, 6H), 1.39−1.45 (m, 2H), 1.64−1.69 (m, 2H), 2.09−2.16 (m, 1H), 2.87 (d, J = 7.0 Hz, 2H), 4.19 (t, J = 7.0 Hz, 2H), 6.13 (d, J = 15.7 Hz, 1H), 7.74 (d, J = 15.7 Hz, 1H), 7.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.1, 22.2, 29.7, 30.7, 42.7, 64.5, 119.6, 134.0, 134.3, 145.4, 166.3, 172.8; HRMS m/z (M^+) calcd for $C_{14}H_{21}NO_2S$ 267.1293, found 267.1297.

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