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Palladium-catalyzed alkenation of thiophenes and furans by regioselective C–H bond functionalization

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ABSTRACT

A palladium-catalyzed direct alkenation of thiophenes and furans has been developed in the presence of AgOAc and pyridine. A variety of olefinic substrates such as acrylates, acrylamides, and acrylonitrile can perform the direct oxidative coupling reactions with various thiophenes and furans to give the mono-alkenylated products in good yields. In most cases, the (*E*)-isomers were isolated as the major products.

Thiophenes and furans are important aromatic heterocycles that serve as key components of a variety of biologically active molecules and functional materials.[1] The traditional alkenation of these heterocycles often involves the formylation and subsequent Wittig reactions.[2] Recently, the development of transition metal-catalyzed cross-coupling reactions between the functionalized heterocycles and olefins has provided the versatile tools for the synthesis of alkenylated heteroaromatic rings in the presence of phosphine ligands.[3] Although these reactions are very useful, they often suffered from disadvantages of prefunctionalization of heterocycles and formation of undesired waste salts. Therefore, the exploration of catalytic reactions involving Csp^2–Csp^2 bond formation via C–H bond activation rather than C–X or C–M bond cleavage aroused much attention currently.[4] Fujiwara and co-workers pioneered the palladium-assisted oxidative coupling of arenes and aromatic heterocycles with olefins.[5] They found that both aromatic and olefinic C–H bonds in acetic acid could be activated by stoichiometric or catalytic amount of palladium to give the alkenylated aromatic compounds.[6] Ishii and co-workers reported the direct oxidative coupling reactions of arenes with olefins catalyzed by $Pd(OAc)_2$ in acetic acid combined with heteropolyoxometalate under dioxygen.[7] Under their reaction conditions, furan and substituted thiophenes could be converted to the heterocycle-substituted olefins.[8] Quite recently, the lithium salts were found to have special effect on the reactions of $Pd(OAc)_2$–$Cu(OAc)_2$ catalyzed direct alkenation of thiophenes and furans with olefins.[9] In addition, the palladium-catalyzed decarbonylative olefination has also been utilized in the olefination of aromatic compounds.[10] Herein, we report the development of palladium-catalyzed direct oxidative reactions of thiophenes and furans with olefins in the presence of AgOAc and pyridine. The reactions are regio- and stereoselective, giving the products substituted at 2-position with (*E*)-isomers as major products in one step.

We initially studied the effects of catalysts, solvents, and bases on the alkenation reaction of thiophene and *n*-butyl acrylate at 120 °C in DMF for 12 h. It was found that the reaction was sluggish when 10 mol % $Pd(OAc)_2$ was used as the catalyst (Table 1, entry 1). However, the addition of silver(I) compounds such as Ag_2O, $AgNO_3$, Ag_2CO_3, and AgOAc, improved the efficiency of the coupling reaction significantly (Table 1, entries 2–5), and an 83% isolated yield was obtained by using 1 equiv of AgOAc (Table 1, entry 5). Silver compounds presumably functioned as stoichiometric oxidants.

These results are better than that using $Pd(OAc)_2$ (5 mol %)–$Cu(OAc)_2$ (2 equiv) system in acetic acid,[6c] in which a 3% yield was obtained for the reaction of thiophene and methyl acrylate at 100 °C for 8 h. The combined catalytic system of $Pd(OAc)_2$ with $Cu(OAc)_2$ was less effective under the reaction conditions (Table 1, entry 8), and $Pd(OAc)_2$ was superior to $PdCl_2$ and $Pd(PPh_3)_4$ (Table 1, entries 5–7). A number of solvents that are routinely used in the palladium-catalyzed C–H bond activation reactions were tested, including 1,4-dioxane, toluene, acetic acid, NMP, DMF, and DMSO (Table 1, entries 14–18). The best result was obtained by DMF that was used in all subsequent reactions. Poor yield was observed in acetic acid (Table 1, entry 16). The bases influenced the reaction markedly (Table 1, entries 5, and 9–13). Pyridine turned out to

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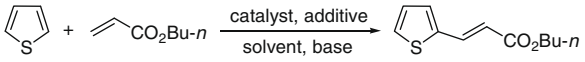
Table 1
Effect of catalysts, solvents, and bases[a]



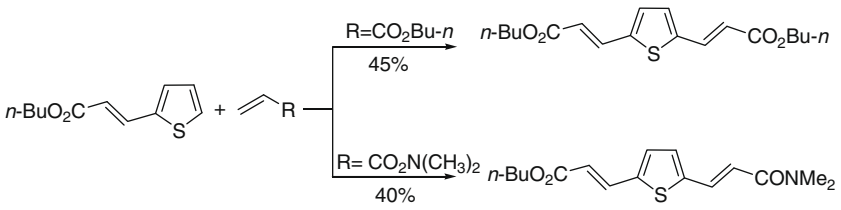
Entry	Catalyst (mol %)/oxidant	Solvent	Base	Yield[b] (%)
1	$Pd(OAc)_2$ (10%)	DMF	Pyridine	23
2	$Pd(OAc)_2$ (10%)/Ag_2O	DMF	Pyridine	76.
3	$Pd(OAc)_2$ (10%)/$AgNO_3$	DMF	Pyridine	41
4	$Pd(OAc)_2$ (10%)/Ag_2CO_3	DMF	Pyridine	82
5	$Pd(OAc)_2$ (10%)/AgOAc	DMF	Pyridine	83
6	$PdCl_2$ (10 %)/AgOAc	DMF	Pyridine	67
7	$Pd(PPh_3)_4$ (10%)/AgOAc	DMF	Pyridine	42
8	$Pd(OAc)_2$(10%)/$Cu(OAc)_2$	DMF	Pyridine	Trace
9	$Pd(OAc)_2$ (10%)/AgOAc	DMF	TEA	44
10	$Pd(OAc)_2$ (10%)/AgOAc	DMF	DABCO	77
11	$Pd(OAc)_2$ (10%)/AgOAc	DMF	DMAP	61
12	$Pd(OAc)_2$ (10%)/AgOAc	DMF	K_2CO_3	38
13	$Pd(OAc)_2$ (10%)/AgOAc	DMF	KOH	32
14	$Pd(OAc)_2$ (10%)/AgOAc	Dioxane	Pyridine	59
15	$Pd(OAc)_2$ (10%)/AgOAc	Toluene	Pyridine	77
16	$Pd(OAc)_2$ (10%)/AgOAc	AcOH	Pyridine	29
17	$Pd(OAc)_2$ (10%)/AgOAc	NMP	Pyridine	66
18	$Pd(OAc)_2$ (10%)/AgOAc	DMSO	Pyridine	57

[a] Reaction conditions: thiophene (2.0 mmol), *n*-butyl acrylate (0.5 mmol, 1 equiv), 2 equiv of oxidant, additive (2.0 mmol), $Pd(OAc)_2$ (10 mol %), 120 °C, 12 h.
[b] Isolated yields based on *n*-butyl acrylate.

be better than DBACO or DMAP, but the inorganic bases such as K_2CO_3 and KOH were ineffective.

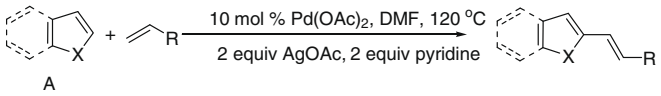
Dialkenation was observed when 0.5 mmol thiophene was treated with 0.5 mmol *n*-butyl acrylate under the reaction conditions, but the excessive thiophene could retard the dialkenation efficiently. When 2 mmol thiophene was used, only monoalkenylated (*E*)-isomer was obtained, leading to good regio- and stereoselectivity. The dialkenation product could be produced further by using the monoalkenylated products as substrates (Scheme 1).

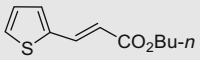
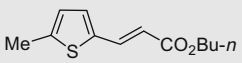
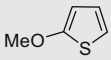
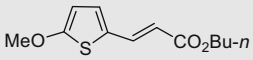
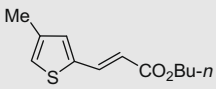
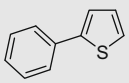
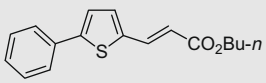
With the optimized conditions in hand (10 mol % $Pd(OAc)_2$, 2 equiv of AgOAc, 2 equiv of pyridine, 120 °C in DMF), we then examined the scope and limitation of the method. The results are summarized in Table 2. A variety of thiophenes were examined. The reaction of thiophene and *n*-butyl acrylate furnished the direct coupling product in 83% yield (Table 2, entry 1). Thiophenes bearing electron-donating substituents such as 2-methyl and 2-methoxyl derivatives gave the products in good yields (Table 2, entries 2 and 3). A mixture of (*E*)-butyl 3-(4-methylthiophen-2-yl)acrylate and (*E*)-butyl 3-(3-methylthiophen-2-yl)acrylate was obtained with 3-methylthiophene and the ratio of two regio-isomers was approximately 4:5 (Table 2, entry 4). The aryl-substituted thiophenes showed relatively lower reactivity, and the high yields were obtained after the treatment of excessive olefins (Table 2, entries 5–9, and 12). The substituents in the aryl ring showed little



Scheme 1. Reaction conditions: thiophenes (0.5 mmol), acrylates or acrylamide (2 mmol), pyridine (2.0 mmol), AgOAc (200 mol %), Pd(OAc)2 (10 mol %), 120 °C, 12 h.

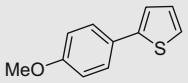
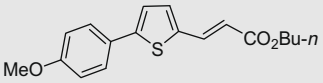
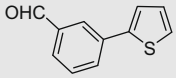
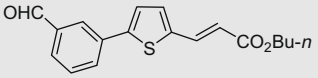
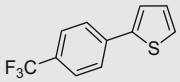
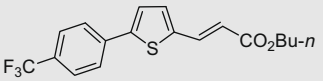
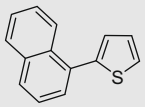
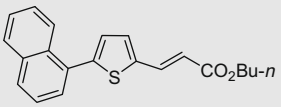
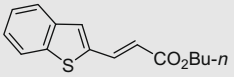
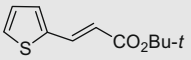
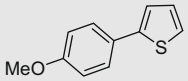
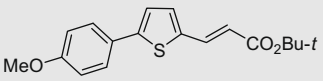
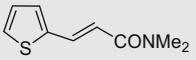
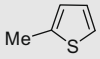
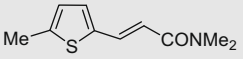
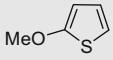
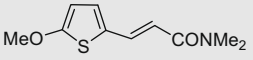
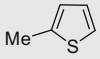
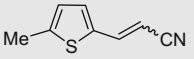
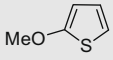
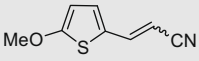
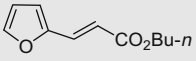
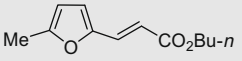
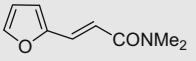
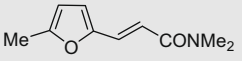
Table 2
Palladium-catalyzed direct alkenylation[a]



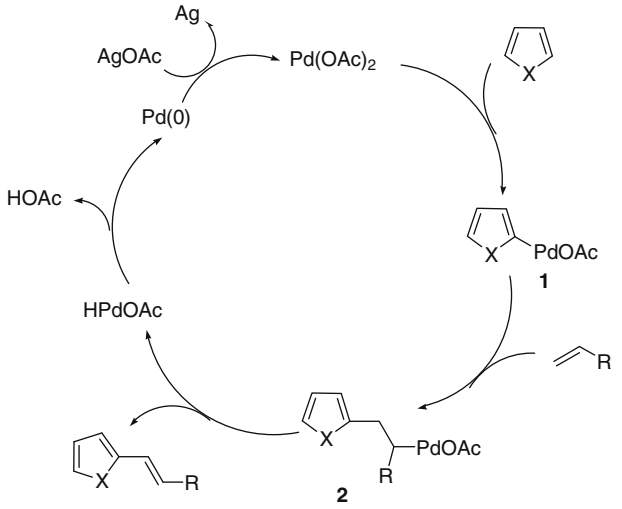
Entry	A	R	Product	Yield[b] (%)
1		CO_2Bu-*n*		83
2		CO_2Bu-*n*		87
3		CO_2Bu-*n*		62
4		CO_2Bu-*n*		89 (4:5)
5		CO_2Bu-*n*		80[c]

(*continued on next page*)

Table 2 (*continued*)

Entry	A	R	Product	Yield[b] (%)
6		CO_2Bu-*n*		87[c]
7		CO_2Bu-*n*		75[c]
8		CO_2Bu-*n*		76[c]
9		CO_2Bu-*n*		80[c]
10		CO_2Bu-*n*		84
11		CO_2Bu-*t*		90
12		CO_2Bu-*t*		78[c]
13		$CONMe_2$		85
14		$CONMe_2$		90
15		$CONMe_2$		70
16		CN		38 (1:2)[d,e]
17		CN		46 (1:2)[e]
18		CO_2Bu-*n*		76
19		CO_2Bu-*n*		90
20		$CONMe_2$		64
21		$CONMe_2$		76

[a] Reaction conditions: thiophene (2.0 mmol), *n*-butyl acrylate (0.5 mmol, 1 equiv), 2 equiv of AgOAc, pyridine (2.0 mmol), $Pd(OAc)_2$ (10 mol %), 120 °C, 12 h.
[b] Isolated yields.
[c] Thiophenes (0.5 mmol), acrylates, or acrylamide (2.0 mmol).
[d] Thiophenes (2.0 mmol), acrylnitrile (2.0 mmol).
[e] The ratio of *Z*- to *E*-isomers in parentheses.



Scheme 2.

effect on the reactions and good yields were obtained with both electron-withdrawing and electron-donating groups under the reaction conditions (Table 2, entries 5–8). 2-(Naphthalen-1-yl)thiophene gave the corresponding coupling product in 80% yield (Table 2, entry 9). It should be noted that benzo[*b*]thiophene reacted equally efficiently to yield the expected product in very good yield (Table 2, entry 10). The coupling reaction worked smoothly with the diverse acrylate such as *t*-butyl acrylate (Table 2, entries 11 and 12). *N*,*N*-ɒimethylacrylamide was also found to be compatible with the coupling reaction, and gave the desired products in good yields (Table 2, entries 13–15). In the case of acrylnitrile, the yields decreased (Table 2, entries 16 and 17). In addition, *Z* and *E* isomers were produced at a ratio of 1:2, which is possibly because CN group is relatively small and makes the energy of *Z*- and *E*-isomer transition state of β-hydro elimination closer.[5,11] However, the reactions of thiophene bearing electron-withdrawing substitutes such as acyl and ester groups were sluggish, indicating that the reaction might undergo an electrophilic metalation processes.[12]

The coupling reaction works well with furans (Table 2, entries 18–21). Furan and 2-methyl furan reacted with *n*-butyl acrylate efficiently and afforded the expected coupling products in high yields. *N*,*N*-ɒimethylacrylamide was also a good coupling partner and good yields were delivered.

Because the thiophenes bearing electron-withdrawing groups are inactive under the reaction conditions, we suppose that an electrophilic metalation mechanism is favored as shown in Scheme 2.[5,9,13] Initially, the electronic attack of Pd(II) into thiophene forms the intermediate 1, which inserts into olefins to afford the intermediate 2. The subsequent *β*–hydro elimination results in the product and liberates Pd(0) as well as acetic acid. The Pd(II) is regenerated from the oxidation of Pd(0) by silver(I) compounds.

In conclusion, we have developed an efficient and new method for the coupling of thiophenes and furans with various olefins through palladium-mediated direct alkenation in conjunction with AgOAc and pyridine.[14] The method provides the desired products in good yields, and in most cases, high regio- and stereoselectivities are presented. Studies to expand the substrate scope of the method are currently in progress in our laboratory.

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References and notes

1. (a) Roncali, J. *Chem. Rev.* **1997**, *97*, 173–205; (b) Mitschke, U.; Bauerle, P. J. *Mater. Chem.* **2000**, *10*, 1471–1507; (c) Katz, H. E.; Bao, Z.; Gilat, S. L. *Acc. Chem. Res.* **2001**, *34*, 359–369; (d) Nesterov, E. E.; Skoch, J.; Hyman, B. T.; Klunk, W. E.; Bacskai, B. J.; Swager, T. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5452–5456.
2. (a) Jiang, B.; Dou, Y.; Xu, X. Y.; Xu, M. *Org. Lett.* **2008**, *10*, 593–596; (b) Molander, G. A.; Oliveira, R. A. *Tetrahedron Lett.* **2008**, *49*, 1266–1268; (c) El-Batta, A.; Jiang, C. C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. *J. Org. Chem.* **2007**, *72*, 5244–5259; (d) Thiemann, T.; Watanabe, M.; Tanaka, Y.; Mataka, S. *New J. Chem.* **2006**, *30*, 359–369.
3. (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963; (b) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, 1589–1592; (c) Morales-Morales, D.; Redon, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619–1620; (d) Ostermeier, M.; Prieb, J.; Helmchen, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 612–614; (e) Schnyder, A.; Aemmer, T.; Indolese, A. F.; Pittelkow, U.; Studer, M. *Adv. Synth. Catal.* **2002**, *344*, 495–498; (f) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.
4. (a) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666–7673; (b) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am.Chem. Soc.* **2002**, *124*, 1586–1587; (c) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156–4157; (d) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512–3515.
5. Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851–855.
6. (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639; (b) Fujiwara, Y.; Asano, R.; Moritani, I.; Teranishi, S. *J. Org. Chem.* **1976**, *41*, 1681–1683; (c) Akiyama, F.; Miyazaki, H.; Kaneda, K.; Teranishi, S.; Fujiwara, Y.; Abe, M.; Taniguchi, H. *J. Org. Chem.* **1980**, *45*, 2359–2361; (d) Fujiwara, Y.; Noritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169; (e) Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674–11679.
7. (a) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623–4625; (b) Yamada, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 5471–5474; (c) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476–1477.
8. Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221–1226.
9. Maehara, A.; Satoh, T.; Miura, M. *Tetrahedron* **2008**, *64*, 5982–5986.
10. (a) GooBen, L. J.; Paetzold, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1237–1241; (b) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159–1162; (c) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251.
11. (a) Beletskay, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (b) Moreno-Manas, M.; Perea, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449–7452; (c) Guertler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107–3112.
12. (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473; (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529; (c) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552–9553; (d) Zhang, H. M.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144–6148.
13. (a) Grimster, N. P.; Godfrey, C. D.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125–3129; (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.
14. *General procedure*: A mixture of acrylates or acrylamide (0.5 mmol), $Pd(OAc)_2$ (11 mg, 10 mol%), thiophenes or furans (2 mmol), AgOAc (1 mmol), pyridine (2 mmol), DMF (1 mL) was sealed with lined cap and stirred at 120 °C for 12 h. Afterward, CH_2Cl_2 (45 mL) was added to the reaction mixture, and then washed with deionized water (3 × 15 mL), dried with Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to afford the corresponding products (*E*)-butyl 3-(5-methoxythiophen-2-yl)acrylate. The product was obtained as brown oil (R_f = 0.33 in 91% petroleum ether/9% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.62 (d, 1H, *J* = 15.6 Hz), 6.92 (d, 1H, *J* = 4.0 Hz), 6.15 (d, 1H, *J* = 4.0 Hz), 5.93 (d, 1 H, *J* = 15.6 Hz), 4.16 (t, 2H, *J* = 6.6 Hz), 3.92 (s, 3H), 1.62–1.70 (m, 2H), 1.37–1.47 (m, 2H), 0.95 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 167.2, 138.1, 130.9, 126.2, 113.1, 104.8, 64.1, 60.1, 30.8, 19.1, 13.7. MS (EI): *m/z* (%): 242 (7) [M^++2], 241 (15) [M^++1], 240 (100) [M^+], 184 (69), 167 (82), 140 (61). HRMS (EI): Calcd for $C_{12}H_{16}O_3S$: [M^+] 240.0816. Found: 240.0820.