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Pd-Catalyzed Olefination of Furans and Thiophenes with Allyl Esters

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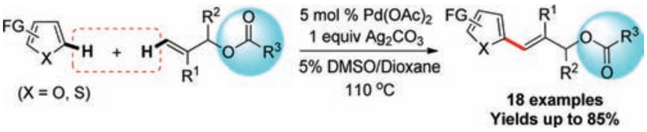
ABSTRACT



A direct Pd(II)-catalyzed olefination of furans and thiophenes with allyl esters is demonstrated. Under the typical conditions, the dehydrogenative Heck coupling reactions of heteroarenes with allylic esters proceeded via a β-H elimination rather than a β-OAc elimination to give the corresponding γ-substituted allylic esters.

The Pd-catalyzed direct cross-couplings of arenes with alkenes, which are called an oxidative Heck reaction,[1] an intermolecular dehydrogenative Heck reaction (DHR),[2] or a Fujiwara–Moritani reaction,[3] have drawn much attention in recent years. Among them, several efficient olefinations of heteroarenes with alkenes have also been developed by Fujiwara,[4] Itahara,[5] Gaunt,[6] Yu,[7] Le Bras and Muzart,[8] Zhang,[9] Satoh and Miura,[10] and Jiang[11] et al.[12] Despite significant progress in DHRs, most of them suffer from limited substrate scope to electron-deficient olefins and styrenes as the coupling partners. Thus, new systems with a broad substrate scope would be highly desirable. Herein, we wish to report the first example of a Pd-catalyzed direct oxidative olefination of furans and thiophenes with electron-rich alkenes such as allyl esters and ethers.

Allyl esters have been widely applied as allylation reagents to form a C–C bond in organic synthesis.[13]

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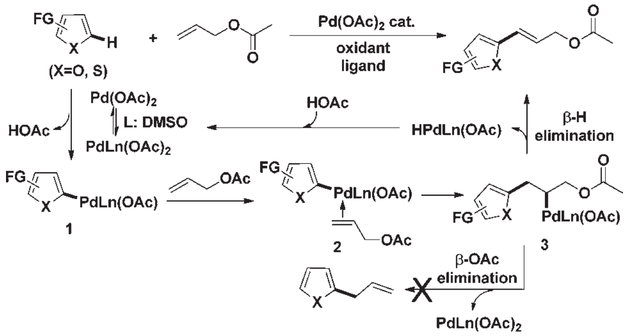
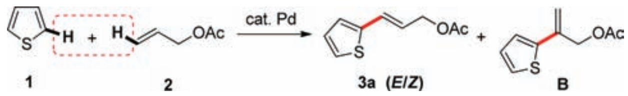
Scheme 1. β-H Elimination vs β-OAc Elimination in Heck-Type Reactions of Allylic Esters with Furans and Thiophenes



However, among these systems, Pd-catalyzed Heck cross-coupling reactions of allyl esters used as the coupling partners with aryl halides and boronic acids have rarely been achieved.[14] As expected from the mechanism for the DHR, the β-H elimination may be promoted by the electron-rich arene to stabilize the positively charged benzylic carbon in the four-membered transition state. Otherwise, the β-OAc elimination may occur.[3] Inspired by previous work in DHRs,[2] we pondered the possibility of the direct oxidative cross-coupling of heteroarenes with allylic esters. Fortunately, we successfully accomplished an efficient olefination of furans and thiophenes with allyl esters via a highly selective β-H elimination process in the Fujiwara–Moritani reaction (Scheme 1).[15]

Initially, we chose thiophene and allyl acetate as the model substrates to optimize suitable conditions for this reaction (Table 1). It was found that the solvent, catalysts, and additives critically affect the efficiency of this reaction. No products were observed in DMSO (entry 1). Only 15% yield of product was obtained in 1,4-dioxane (entry 2). The yields of the desired products increased significantly by the addition of 5% (v) DMSO as cosolvent into DCE, THF, DMF, and 1,4-dioxane (entries 3–6). The yield slightly decreased by using 10% DMSO/Dioxane (v/v) as the solvent (entry 7). The solvent effect indicates that a specified volume of DMSO plays an important role in this system. Catalysts were screened (entries 8–11), and as a result, Pd(OAc)$_2$ was selected as the most effective catalyst. The additive Ag$_2$CO$_3$ was the best compared to others such as Ag$_2$O, Ag$_2$SO$_4$, AgNO$_3$, and Cu(OAc)$_2$ (entries 12–16). Interestingly, NaIO$_4$ gave a 42% yields of the products (entry 17). Moreover, the yield decreased with decreasing amounts of Ag$_2$CO$_3$ (entry 18). A very slightly increased yield was gained by using 1.5 equiv of Ag$_2$CO$_3$ (entry 19). The yield increased to 66% with increasing amounts of thiophene (entry 20).

Table 1. Modification of the Typical Reaction Conditions[a]



entry	catalyst	additive	solvent (v/v)	yield (%)[b]
1	Pd(OAc)$_2$	AgOAc	DMSO	0
2	Pd(OAc)$_2$	AgOAc	Dioxane	15
3	Pd(OAc)$_2$	AgOAc	5% DMSO/DCE	38
4	Pd(OAc)$_2$	AgOAc	5% DMSO/THF	42
5	Pd(OAc)$_2$	AgOAc	5% DMSO/DMF	43
6	Pd(OAc)$_2$	AgOAc	5% DMSO/ Dioxane	43
7	Pd(OAc)$_2$	AgOAc	10% DMSO/ Dioxane	35
8	PdCl$_2$	AgOAc	5% DMSO/ Dioxane	40
9	Pd(TFA)$_2$	AgOAc	5% DMSO/ Dioxane	43
10	Pd(PCy$_3$)$_2$Cl$_2$	AgOAc	5% DMSO/ Dioxane	30
11	Pd(acac)$_2$	AgOAc	5% DMSO/ Dioxane	41
12	**Pd(OAc)$_2$**	**Ag$_2$CO$_3$**	**5% DMSO/ Dioxane**	**60**
13	Pd(OAc)$_2$	Ag$_2$O	5% DMSO/ Dioxane	16
14	Pd(OAc)$_2$	Ag$_2$SO$_4$	5% DMSO/ Dioxane	10
15	Pd(OAc)$_2$	AgNO$_3$	5% DMSO/ Dioxane	0
16	Pd(OAc)$_2$	Cu(OAc)$_2$	5% DMSO/ Dioxane	19
17	Pd(OAc)$_2$	NaIO$_4$	5% DMSO/ Dioxane	42
18[c]	Pd(OAc)$_2$	Ag$_2$CO$_3$	5% DMSO/ Dioxane	53
19[d]	Pd(OAc)$_2$	Ag$_2$CO$_3$	5% DMSO/ Dioxane	61
20[e]	**Pd(OAc)$_2$**	**Ag$_2$CO$_3$**	**5% DMSO/ Dioxane**	**66**

[a] Reaction conditions: thiophene (1.5 mmol), allyl acetate (0.5 mmol), additive (1 equiv), catalyst (5 mol %), 110 °C, 12 h, unless otherwise noted. [b] Isolated yields of the *E*/*Z* and B isomers. [c] Ag$_2$CO$_3$ (0.5 equiv). [d] Ag$_2$CO$_3$ (1.5 equiv). [e] Thiophene (2.5 mmol).

To investigate the substrate scope of this reaction, the direct olefination of various thiophenes, benzothiophene, furans, and benzofurans with substituted allylic esters and ethers are summarized in Table 2. Alkyl-substituted thiophenes give moderate to good yields of the corresponding products under the typical conditions (**3a**–**3d**). Surprisingly, olefination of 3-methylthiophene with allyl acetate occurs at a more sterically hindered position (**3c**). However, 2-thienyl halides give relatively low yields of the oxidative vinylic C–H/C–H cross-coupling products (**3e** and **3f**). Thiophenes with an electron-withdrawing acyl group could also be coupled with allyl acetate in moderate yields (**3g** and **3h**). Moreover, benzothiophene, furan, and benzofuran could also give moderate yields of the desired products (**3i**, **3j**, and **3k**). However, nitrogen-based heteroarenes such as indoles, azoles, and thiazoles do not work in this

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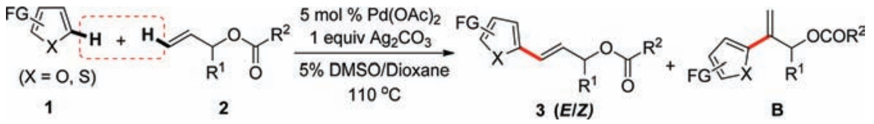
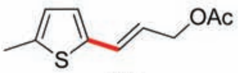
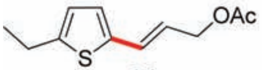
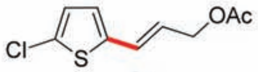
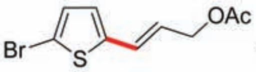
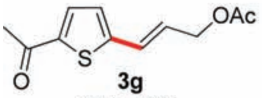
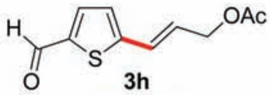
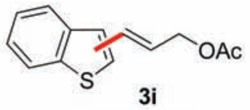
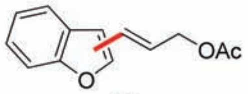
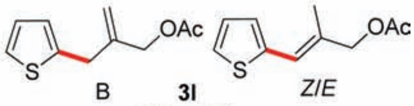
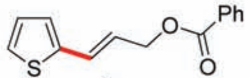
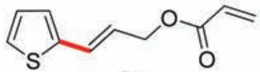
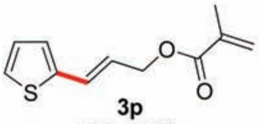
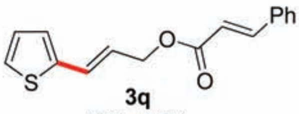
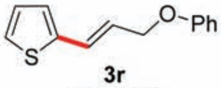
Table 2. Pd-Catalyzed Oxidative Heck Reaction of Thiophenes and Furans with Allyl Esters and Ethers[a]



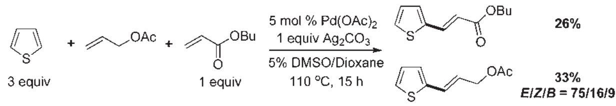
product time, yield *E*/*Z*/*B*	product time, yield *E*/*Z*/*B*	product time, yield *E*/*Z*/*B*
 **3a** 12 h,[b] 66%[c] 78/15/7[d]	 **3b** 12 h, 83% 75/9/16	 **3c** 14 h, 58% 93/6/1
 **3d** 12 h, 73% 77/8/15	 **3e** 21.5 h, 45% 70/20/10	 + **3a** **3f** 20 h, 30% 86/8/6 33%
 **3g** 12 h, 50% 93/5/2	 **3h** 20 h, 52% 89/9/2	 **3i** 21 h, 53% 2': 61/6/5; 3': 20/4/4
 **3j** 15 h, 60% 75/17/8	 **3k** 25 h, 55% 2': 54/13/6; 3': 21/4/2	 **3l** 13 h, 45% 63/24/13
 **3m** 12 h, 53% 88/4/8	 **3n** 23 h, 85% 62/26/12	 **3o** 15 h, 33% 72/14/14
 **3p** 22 h, 57% 68/20/12	 **3q** 23 h, 83% 82/12/6	 **3r** 12 h, 73% 80/8/12

[a] Reaction conditions: heteroarene (2.5 mmol, 5 equiv), allyl esters or ethers (0.5 mmol, 1 equiv), Ag$_2$CO$_3$ (1 equiv), Pd(OAc)$_2$ (5 mol %), 5% DMSO/Dioxane (2 mL, v/v), 110 °C, unless otherwise noted. [b] Reaction time, indicated by TLC. [c] Isolated overall yields of the *E*/*Z* and B isomers. [d] Ratio of *E*/*Z*/*B* determined by crude ^{1}H NMR.

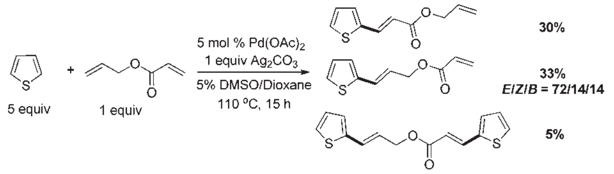
procedure. It might be attributed to the lower electrophilicity of the intermediate Ar-PdLn-OAc which could not chelate with the electron-rich olefins efficiently.[3,15]

Various substituted allylic esters give moderate to high yields of the coupling products in this reaction (Table 2, **3l**–**3q**). A branched cross-coupling product is obtained as the major product which might proceed via a β-elimination of the H-atom from the methyl group (**3l**). Both allyl benzoate and allyl cinnamate give high yields of the products (**3n** and **3q**). In addition, allyl acrylate and allyl methacrylate give the corresponding products in 33% and 57% yields, respectively (**3o** and **3p**). It is noteworthy that allylic ether is also used successfully as the olefination partner under these reaction conditions (**3r**).

There may be a competing cross-coupling of a heteroarene between the allylic and the acrylic double bonds. The alkyl-Pd-intermediate might be stabilized by chelation of a Pd-atom with the carbonyl O-atom which was previously proposed.[13f,16] As expected from the chelation effect, the yields of olefination of thiophene with allyl acetates would be much higher than that with acrylates. However, as a matter of fact, the difference is not remarkable. An intermolecular competing reaction was carried out (eq 1), which indicates that the difference between allyl acetate and butyl acrylate in the olefination of thiophene is not obvious. The same conclusion can be obtained from an intramolecular competing reaction of an allyl acrylate with thiophene under the typical conditions (eq 2). Additionally, coupling of thiophene with 1-octene gives a 64% yield of the desired products (eq 3), which provides further evidence suggesting the chelation effect was not significant.



(1)



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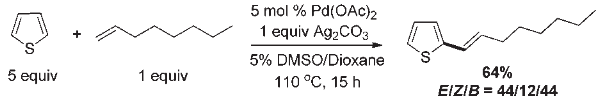

(3)

In summary, we developed a convenient and direct Pd(II)-catalyzed olefination of thiophenes and furans by using allylic esters and ethers. In the present system, electron-rich olefins such as allyl esters and ethers are used as the olefination partners in the oxidative Heck coupling of heteroarenes for the first time. A variety of γ-substituted allylic esters have been prepared by an oxidative Heck-type reaction via β-H elimination rather than β-OAc elimination. Additionally, a series of allylic esters even bearing another C=C bond such as allyl methacrylate and allylic ether give moderate to good yields of the desired products. Further investigation of this procedure is underway in our laboratory.

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Supporting Information Available. Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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