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Palladium-Catalyzed Dehydrogenative Coupling of Furans with Styrenes

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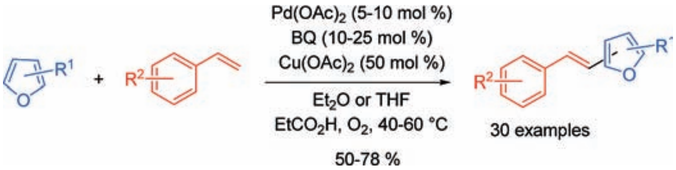
ABSTRACT



Under palladium(II)-catalyzed and oxidative conditions, the coupling of furans with styrenes leads to the formation of Heck-type products in medium to good yields. The reaction is highly regio- and stereoselective, giving *trans*-olefins predominantly.

The formation of C−C bonds plays an important role in organic synthesis but usually requires prefunctionalized starting materials. Dehydrogenative couplings,[1] in which two C−H bonds react to form C−C bonds, have the potential to lead to mild, general, and selective methodologies able to make already known or new chemical transformations environmentally sustainable. Among such transformations, the intermolecular coupling of arenes and alkenes, also called "oxidative Heck reaction", introduced by Fujiwara,[2] has gain interest these past years.[3] Progress has been achieved on the regioselectivity,[4] the use of oxygen as the reoxidant,[4b,c,5] the heterogenization of the catalyst,[6] and the functionalization of acid-sensitive arenes,[4c,f,6a,c] or unactivated arenes.[7] Despite these advances, the use of olefins bearing an electron-withdrawing group, such as acrylates, acrylamides, acrylonitriles, and α,β-unsaturated carbonyl derivatives, is generally required to achieve fair yields. Styrenes are more electron-rich compounds than acrylates and are a notoriously difficult substrate class due to facile polymerization and cleavage under palladium oxidative conditions.[8] Examples of oxidative Heck reactions have been reported using styrenes, but with low yields (<40%)[4a,b,5b,c,9] or with poor substrates scope.[4f,7b,10] Among the arenes studied, furans have received less attention, probably because of their high sensitivity to protic conditions, which are generally used for

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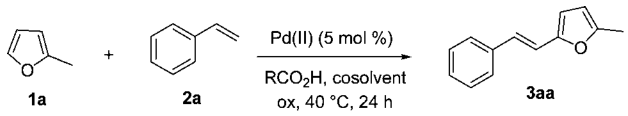
Table 1. Optimization of the Coupling of 2-Methylfuran (**1a**) with Styrene (**2a**)[a]



entry	R	cosolvent	Pd(II)	oxidant	yield (%)[b]
1	Me		$Pd(OAc)_2$	BQ (2.0 equiv)	<5
2	Me	CH_2Cl_2	$Pd(OAc)_2$	BQ (2.0 equiv)	43
3	Me	EtOAc	$Pd(OAc)_2$	BQ (2.0 equiv)	40
4	Me	Et_2O	$Pd(OAc)_2$	BQ (2.0 equiv)	55
5	Me	Et_2O	$Pd(OCOCF_3)_2$	BQ (2.0 equiv)	51
6	Me	Et_2O	$Pd(OAc)_2$	BQ (10 mol %), $Cu(OAc)_2$ (50 mol %), air[d]	43−54
7	Et	Et_2O	$Pd(OAc)_2$	BQ (10 mol %),$Cu(OAc)_2$ (50 mol %), O_2[d]	65[c]
8	Et	Et_2O	$Pd(OAc)_2$	$Cu(OAc)_2$ (50 mol %), O_2[d]	60
9	Et	THF	$Pd(OAc)_2$	BQ (10 mol %), $Cu(OAc)_2$ (50 mol %), O_2[d]	56
10	Et	dioxane	$Pd(OAc)_2$	BQ (10 mol %), $Cu(OAc)_2$ (50 mol %), O_2[d]	55

[a] **1a** (1.1 mmol), **2a** (1.0 mmol), Pd(II) (0.05 mmol), RCO_2H (2 mL), cosolvent (2 mL), 40 °C, 24 h. [b] Isolated yield. [c] *E*/*Z* > 99.9, determined by GC. [d] Gas bag.

oxidative Heck reactions. Only few examples are reported, and they generally require the use of electron-poor alkenes.[9a,c,11] We have recently reported the synthesis of difurylalkanes through the bis-coupling of 2-alkylfurans with various alkenes, including styrenes.[12] We report herein a dehydrogenative coupling of furans and styrenes leading to Heck-type products.

The coupling of 2-methylfuran (**1a**, 1.1 equiv) with styrene (**2a**) in the presence of 0.05 equiv of $Pd(OAc)_2$ and 2.0 equiv of benzoquinone (BQ) was first attempted in AcOH, but less than 5% yield was obtained (Table 1, entry 1). Cosolvents can affect strongly the course of the reaction, since acetone and acetonitrile led to the formation of difurylalkanes.[12] We have focused our attention on the influence of less coordinating solvents. CH_2Cl_2, EtOAc, and Et_2O improved the efficiency of the process, leading to **3aa** in up to 55% yield (entries 2−4). $Pd(OCOCF_3)_2$ led to a slighty lower yield (entry 5). The association of air with catalytic amounts of both BQ and $Cu(OAc)_2$ as the oxidizing system afforded **3aa** in up to 54% yield, but the results were inconsistent (entry 6). In contrast, reproducible results were obtained in $EtCO_2H$ instead of AcOH and with O_2 instead of air, affording **3aa** in fair yield and high stereoselectivity (entry 7). Yields were lower in the absence of benzoquinone or with THF or dioxane as the cosolvent (entries 8−10).

The scope of the process was then examined. After slight modifications of the original procedure, mono-, di-, and trisubstituted furans react with various styrenes bearing electron-withdrawing or -donating groups on the aromatic ring, to give Heck-type products in medium to good yields (Table 2). α,β-Methyl styrenes were reluctant to react. Crude mixtures have shown good stereoselectivity, and in most cases, the isolated compounds were obtained as *E*-isomers. The formation of palladium black, in certain cases, leads to partial conversions. π-Acidic alkene ligands, such as dibenzylidene acetone (dba), can influence Pd-catalyzed cross-coupling reactions, interacting with both palladium(0) and palladium(II) intermediates.[13] Indeed, we have observed less formation of Pd black and full conversion in the presence of dba as additive (**3ab**, **3ac**). Such compound probably stabilizes Pd(0) species[13] and prevents their agglomeration leading to insoluble Pd(0). We suspect that when the Pd deposit was not observed, compounds **3** play a similar role and act as efficient ligands for Pd(0). The use of 25% BQ also prevented the formation of Pd black and led to quantitative conversions and fair yields (**3cb**, **3cc**, **3cd**, **3ce**, **3da**, **3dg**, **3ea**, **3eb**, **3ec**). BQ acts probably as an electron-transfer mediator between the catalyst and the oxidant and facilitates the overall transformation.[14] As observed earlier with acrylates, in the reaction of 2-substituted furans bearing either an electron-donating group (**1a**, **1b**) or an electron-withdrawing group (**1e**), the coupling takes place at C_5.[11a] Chlorinated and fluorinated styrenes undergo coupling leaving the carbon−halogen bond intact (**3ab**, **3ac**, **3af**, **3bf**, **3cb**, **3cc**, **3eb**, **3ec**, **3fb**, **3fc**), while brominated derivatives were more reluctant to react. Bis(styryl)-furans **4ha** and **4hh** were obtained from furan **1h**. The monosubstituted intermediates **3ha** and **3hh** were always obtained as traces, even in the presence of an excess of **1**, suggesting that these intermediates react faster than **1**. It should be noted that **4ha** has been recently described as a potentail organic fluorophore for various applications.[15]

The kinetic profiles of the formation of **3aa** and **3ea**, under similar conditions, have shown an induction period depending on the nature of **1** (Figure 1); such transformation being faster with **1a**.

Palladium acetate exists as a trimer in the solid state, in which the $Pd(OAc)_2$ units are joined by double OAc bridges.[16] In AcOH, such structure is maintained, characterized by a UV−vis absorption at 370−450 nm.[17] The UV−vis spectra of palladium acetate in $EtCO_2H$ and in a mixture of

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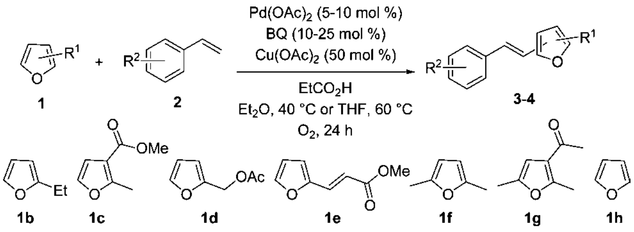
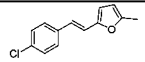
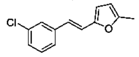
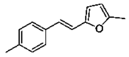
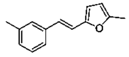
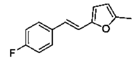
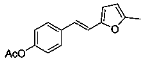
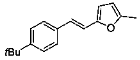
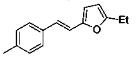
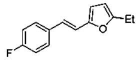
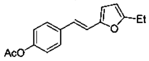
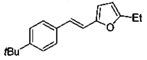
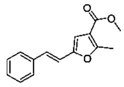
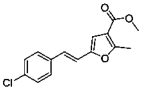
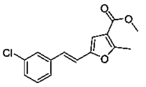
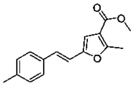
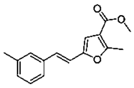
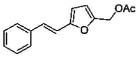
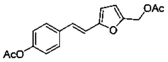
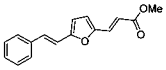
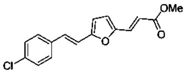
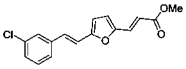
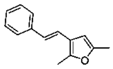
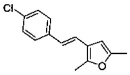
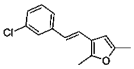
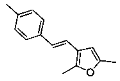
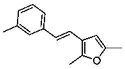
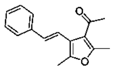
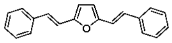
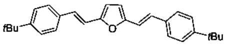
Table 2. Coupling of Furan **1** with Styrene **2**[a]



R^2 = *p*-Cl (**2b**), *m*-Cl (**2c**), *p*-Me (**2d**), *m*-Me (**2e**), *p*-F (**2f**), *p*-AcO (**2g**), *p*-*t*Bu (**2h**)

entry	1, equiv	2	Pd (%)	BQ (%)	temp (°C)	3-4, yield (%)[b]
1[c,d]	**1a**, 1.1	**2b**	5	10	40	 **3ab**, 68
2[c,d]	**1a**, 1.1	**2c**	5	10	40	 **3ac**, 64
3	**1a**, 2.0	**2d**	5	10	40	 **3ad**, 71
4	**1a**, 2.0	**2e**	5	10	40	 **3ae**, 63
5	**1a**, 1.1	**2f**	5	10	40	 **3af**, 64
6	**1a**, 1.1	**2g**	5	10	40	 **3ag**, 62
7	**1a**, 1.1	**2h**	5	10	40	 **3ah**, 56
8	**1b**, 2.0	**2d**	5	10	60	 **3bd**, 64
9	**1b**, 2.0	**2f**	10	10	60	 **3bf**, 78
10	**1b**, 2.0	**2g**	10	10	60	 **3bg**, 60
11	**1b**, 1.1	**2h**	5	10	40	 **3bh**, 63
12	**1c**, 2.0	**2a**	10	10	60	 **3ca**, 68
13	**1c**, 2.0	**2b**	10	25	60	 **3cb**, 72
14	**1c**, 2.0	**2c**	10	25	60	 **3cc**, 71
15	**1c**, 2.0	**2d**	10	25	60	 **3cd**, 65
16	**1c**, 2.0	**2e**	10	25	60	 **3ce**, 66
17	**1d**, 2.0	**2a**	10	25	60	 **3da**, 50
18	**1d**, 2.0	**2g**	10	25	60	 **3dg**, 53
19	**1e**, 2.0	**2a**	10	25	60	 **3ea**, 60
20	**1e**, 2.0	**2b**	10	25	60	 **3eb**, 64
21	**1e**, 2.0	**2c**	10	25	60	 **3ec**, 62
22	**1f**, 2.0	**2a**	10	10	60	 **3fa**, 64
23	**1f**, 2.0	**2b**	10	10	60	 **3fb**, 66
24	**1f**, 2.0	**2c**	10	10	60	 **3fc**, 66
25	**1f**, 2.0	**2d**	10	10	60	 **3fd**, 52
26	**1f**, 2.0	**2e**	10	10	60	 **3fe**, 55
27[d]	**1g**, 2.0	**2a**	10	10	60	 **3ga**, 57
28	**1h**, 0.45	**2a**	10	10	40	 **4ha**, 50
29	**1h**, 0.45	**2h**	10	10	40	 **4hh**, 60

[a] **1** (0.45−2.0 mmol), **2** (1.0 mmol), BQ (0.1−0.25 mmol), Cu(OAc)$_2$ (0.5 mmol), O$_2$ (gas bag), EtCO$_2$H (2 mL), cosolvent (2 mL), Et$_2$O/40 °C or THF/60 °C, conv 100%, 24 h. [b] Isolated yield. [c] Dibenzylidene acetone (dba) as additive (0.2 mmol). [d] 48 h.

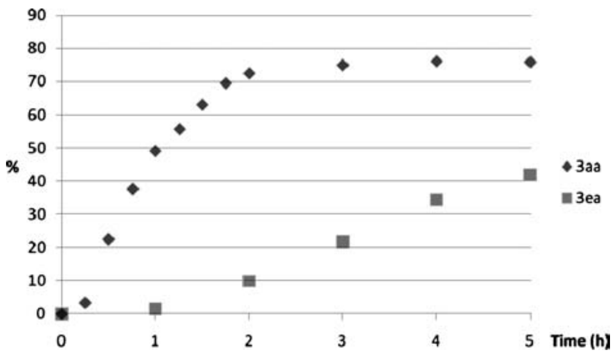
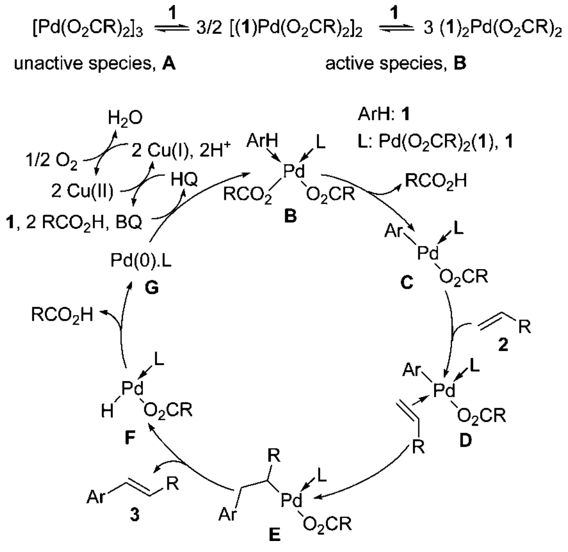


Figure 1. Kinetic profiles of the formation of **3aa**, and **3ea**. Conditions: **1** (2.0 mmol), **2a** (1.0 mmol), Pd(OAc)$_2$ (0.1 mmol), BQ (0.1 mmol), Cu(OAc)$_2$ (0.5 mmol), O$_2$ (gas bag), EtCO$_2$H (2 mL), THF (2 mL), 60 °C. Data are averaged from two reactions.

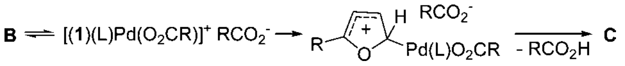
EtCO$_2$H/THF show such similar absorptions, signifying that Pd(II) is also a trimer in these solvents (Figure S1, Supporting Information). We propose that the trimer **A** is an inactive catalytic species and that the induction period is associated to the complexation of **A** by **1**, leading to dimer or monomer derivatives **B** as active catalysts (Scheme 1). Such steps are promoted by electron rich arenes, such as **1a**. The overall transformation is then considered to proceed via a reaction path similar to that proposed by Fujiwara et al. (Scheme 1).[18]

Scheme 1. Proposed Mechanism



The formation of **C** involves probably an electrophilic aromatic palladation. Such transformation is usually the rate-determining step in intermolecular oxidative Heck reactions.[4g,5b,d,9c] The kinetics have shown that the nature of **1** has a strong influence on the rate of the transformation (**1a** > **1e**, Figure 1). Such results are compatible with an electrophilic palladium pathway for the formation of **C**, since electron-rich arene **1a** reacts faster than electron-poor arene **1e** (Scheme 2). In addition, the most thermodynamically favored cation will result in the addition of [(L)Pd(O$_2$CR)]$^+$ on C$_5$ of **1a** rather than on C$_5$ of **1e**. The coordination of alkene **2** to **C** leads to **D**, followed by the insertion of the C=C bond into the Ar–Pd bond affording the σ-alkyl-palladium(II) complex **E**. β-Hydride elimination leads to product **3**, and HPd(L)O$_2$CR. The elimination of RCO$_2$H affords Pd(0), which is stabilized by either **3** or an additive such as dba.[13] Finally Pd(0) is reoxidized to Pd(II) by the multistep electron transfer system BQ/Cu(II)/RCO$_2$H.

Scheme 2. Electrophilic Palladation



In summary, we have developed a palladium-catalyzed dehydrogenative coupling of furans and styrenes. The transformation occurs under mild conditions and is compatible with various substituted furans and styrenes. The method provides Heck-type products in medium to good yields and with high regio- and stereoselectivities. Kinetic investigations have shown an induction period that depends on the nature of the furan.

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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