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Aerobic Dehydrogenative Heck Reactions of Heterocycles with Styrenes: A Negative Effect of Metallic Co-Oxidants

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Abstract: The aerobic *dehydrogenative Heck reaction* (DHR) of heterocycles with styrenes was found to be more efficient in the absence of metallic cooxidants. According to a study of the isotope effect, the C-H cleavage was the rate-determining step of the catalytic cycle. Electrospray ionization mass spectrometry, subsequent MS/MS, and high-resolution mass spectrometry were used to detect and characterize catalytic intermediates and species formed in the presence of metallic co-oxidants.

Keywords: C–H activation; Heck reaction; homogeneous catalysis; mass spectrometry; reaction mechanisms

The intermolecular dehydrogenative Heck reactions (DHRs) are of interest in term of atom economy, since the result of a DHR is the formation of a C-C bond from two C-H bonds.^[1] However, most procedures require the use of stoichiometric oxidants such as copper and silver salts or quinones which decrease the "green" aspect of these transformations. Catalytic amounts of these species with molecular oxygen as the terminal oxidant have been used in some studies,^[2] but only a few reports concern oxygen as the sole oxidant.^[2b,c,e,j,k,o,q,t] In addition, the substrate scope is often restricted to olefins bearing an electron-withdrawing group as the coupling partners, and few examples have been described with heterocycles, which limits the applications of these reactions.^[3] Herein, we report an efficient method for the DHR of heterocycles with styrenes using O_2 as the sole oxidant, and an investigation of the mechanism using electrospray ionization mass spectrometry (ESI-MS). ESI-MS is well adapted for the observation of protonated, deprotonated, or cationized forms of short-lived molecules produced from catalyzed reactions. The technique thus provides continuous snapshots of the composition of the reaction solution and hence insights into its mechanism.^[4] The influence of metallic co-oxidants on the efficiency of the reaction is also discussed.

We have reported the DHR of furans with styrenes under aerobic conditions.^[5] However, the methodology required the presence of 10% of benzoquinone (BO), 50% of Cu(II) and 40-60°C for an efficient coupling. We have recently presented the DHR of furans and thiophenes with styrenes at room temperature.^[6] The method involves the use of DMSO as cosolvent and BQ as stoichiometric oxidant, which both have a positive influence on the process efficiency. We have explored the possibility to perform the reaction using DMSO as solvent under an oxygen atmosphere in the absence of a stoichiometric organic oxidant. Since catalytic amounts of metallic co-oxidants are often useful for the reoxidation of palladium in DHRs, we have first studied their influence on the efficiency of the process. Thus, the coupling of 2-methylfuran (1a) with styrene (2a) was carried out at room temperature using Pd(OAc)₂ as catalyst, DMSO/ AcOH as solvent, various metallic co-oxidants, and O_2 (Table 1).

With the typical co-oxidants of oxidative palladocatalyzed reactions, AgOAc and Cu(OAc)₂, low yields were obtained after 4 h at room temperature (Table 1, entries 1 and 2). The yield with AgOAc was scarcely improved after 24 h (entry 1), while a medium yield was obtained with Cu(OAc)₂ (entry 2). While Cu₂O and Fe₃O₄ did not improve the results (entries 3 and 4), we were then delighted to find that manganese salts and oxides led to 39–45% only after 4 h (entries 5–9). To our surprise, when the coupling was performed in the absence of a co-oxidant, the yield in 4 h was improved to 50%, and **3aa** could be isolated in 68% yield when the reaction time was prolonged to 24 h (entry 10). The scope of the process was then examined. After slight modifications of the original pro-



Entry	M,%	Yield [%] ^[b]				
		4 h	24 h			
1	AgOAc, 10	8.1 ± 0.2	8.9 ± 0.3			
2	$Cu(OAc)_{2}, 10$	27.8 ± 0.6	50.4 ± 1.0			
3	Cu ₂ O, 10	17.0 ± 0.5	23.5 ± 1.2			
4	$Fe_{3}O_{4}, 10$	19.0 ± 1.0	32.9 ± 1.1			
5	$Mn(OAc)_3, 10$	40.5 ± 0.8	67.6 ± 1.5			
6	$Mn(OAc)_2, 10$	44.1 ± 1.1	78.1 ± 1.0			
7	MnO, 10	43.4 ± 1.5	77.7 ± 1.2			
8	Mn_2O_3 , 10	44.5 ± 1.0	78.1±1.7 (64)			
9	$MnO_2, 10$	40.2 ± 1.5	76.5 ± 1.5			
10	-	49.4 ± 1.4	81.5 ± 1.0 (68)			

^[a] Conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), M (0 or 0.1 mmol), AcOH (2 mL), DMSO (2 mL), O₂ (gas bag), room temperature, 4–24 h.

^[b] GC yield averaged from two reactions (PhNO₂ was used as standard), isolated yield in parenthesis.

cedure (Table 1, entry 10), furans, thiophenes, and indoles 1 were successfully coupled with styrenes 2 to give Heck-type products in medium to high yields (Table 2). Some reactions required a 10% catalyst loading to achieve the total conversion of 2. The reactions were performed between room temperature and 60°C, and all compounds were isolated as the E-isomers. As previously observed,^[5,6] 2-substituted furans and thiophenes (1a, 1b, 1c, 1e) reacted at the C-5 position (Table 2, entries 1-13, 18, 20, 22, 24). 3-Methylthiophene (1f) reacted mainly at C-5 (entries 19, 21, 23, 25). Furan (1d) led to a mixture of styrylfurans (3da, 3db, 3dc, 3dd) as major compounds and bis-(styryl)furans (4da, 4db, 4dc, 4dd, entries 14–17), while thiophene (1g) provided only the monosubstituted product (**3ga**, entry 26). 1-Methylindole (**1h**) and 1,2-methylindole (1i) were coupled with 2a in medium yields (entries 27 and 28). The coupling of chlorinated and fluorinated styrenes (2b-2d) left the carbon-halogen bond intact (entries 2–7, 11–13, 15–17, 20–25). The method is also compatible with the use of *p*-acetoxystyrene (**2e**, entries 8–9).

To learn about the C–H activation step, we have performed a kinetic study using **1e** and monodeuterated thiophene *d*-**1e** for the DHR with **2a** (Figure 1). The isotope effect ($k_{H/D}$ =4.4±0.5) shows that the C– H cleavage was the rate-determining step of the catalytic cycle, as previously observed with two equivalents of BQ to regenerate the catalyst,^[6] and in other oxidative Pd-catalyzed reactions.^[7]



Figure 1. Kinetic isotope effect. *Conditions:* 1 (1.0 mmol), 2a (1.0 mmol), Pd(OAc)₂ (0.1 mmol), AcOH (2 mL), DMSO (2 mL), O₂ (gas bag), 40° C.

We have then used ESI-MS to further study the mechanism of the reaction. We have first monitored by ESI(+)-MS a mixture of Pd(OAc)₂ in AcOH/ DMSO (1:1) under an oxygen atmosphere. After 5 min of stirring at room temperature, five clusters were detected and attributed to [Pd(OAc)(DMSO)]⁺, [Pd(DMSO-H)(DMSO)]⁺, $[Pd(OAc)(DMSO)_2]^+$, $[Pd_2(OAc)_3(DMSO)]^+$, and $[Pd_2(OAc)_3(DMSO)_2]^+$ (Figure 2). Such species were identical to those observed previously in DHRs performed in the presence BQ.^[8] [Pd(OAc)(DMSO)]⁺ and [Pd(OAc)of (DMSO)₂]⁺ originate from the solvated species $[Pd_2(OAc)_3(DMSO)]^+$ $Pd(OAc)_2(DMSO)_2$. and $[Pd_2(OAc)_3(DMSO)_2]^+$ are connected to the dinuclear analogue $Pd_2(OAc)_4(DMSO)_2$. Finally, [Pd(DMSO-H)(DMSO)]⁺ associated is to Pd(DMSO-H)(DMSO)(OAc) and the activation of DMSO by Pd(OAc)₂(DMSO)₂.

The monitoring of an AcOH/DMSO solution of Pd(OAc)₂, **1a** and **2a** under an oxygen atmosphere at rt by ESI(+)-MS led to complex spectra which proved difficult to analyze. Fortunately, the use of nbutylfuran (1j) instead of 1a led to the simplification of the spectra. Indeed, the main feature of the corresponding ESI(+)-MS obtained after 1.5 h (Figure 3, top) is the observation of an intense peak at m/z411.1, attributed to [Pd(3ja+H)(DMSO)]⁺. This structure was confirmed by HR-MS, and the ESI(+)-MS/ MS has shown the loss of Pd and DMSO (Figure S1 in the Supporting Information). In addition, when 2ethylfuran (1k) was used instead of 1j, a shift of 28 mass units was observed, and when tert-butylstyrene (2f) was used instead of 2a in conjunction with 1k, the shift was of 28 mass units as expected (Table 3). The neutral intermediate Pd(3ia+H)(DMSO)(OAc)results from the insertion of 2a into the furyl-Pd(II) bond of Pd(1j-H)(DMSO)₂(OAc). The latter was observed at m/z 389.1 as $[Pd(1j-H)(DMSO)(OAc)Na]^+$ (Figure 3, *bottom*). This structure was confirmed by

		3 [%] ^[b]	6 C C C C C C C C C C C C C C C C C C C	adc, 37 dc, 37 dc, 12 dc, 12	add, 35 F	S 3ea, 69	S 3fa, 66 ^[c]
Ĺ	z-	Time [h]	24	24	48	24	24
+		Temp. [°C]	40	40	40	40	40
e l	S 1g 1h), <i>p</i> -OAc (2e)	2 Pd [%]	2b 10	2c 10	2d 5	2a 10	2a 5
-10%) H (1:1) -48 h	S 1f (2c), <i>p</i> -F (2d)	1 (equiv.)	1d (8.0)	1d (8.0)	1d (8.0)	1e (1.0)	1f (5.0)
od(OAc) ₂ (5- MSO, AcOl O ₂ (1 atr .t60°C, 24	S 1e I (2b), <i>m</i> -CI	Entry	15	16	17	18	19
ArH + ArH + MeO	1b 1c 1d R: H (2a), PC	3 [%] ^[b]	3ba, 61	3ab, 88	3bb, 56	3ac, 74	3bc, 51
h styrenes	a	Time [h]	24	24	24	24	48
cycles 1 wit		Temp. [°C]	40	40	40	40	40
g of hetero		2 Pd [%]	2a 5	2 b 5	2 b 5	2c 5	2c 10
2. Couplin _i		1 (equiv.)	1b (2.0)	1a (2.0)	1b (2.0)	1a (2.0)	1b (2.0)
Table		Entry	1	0	ς	4	S.

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62	Table	2. (Continu	(pən										
	Entry	1 (equiv.)	7	Pd [%]	Temp. [°C]	Time [h]	3 [%] ^[b]	Entry	1 (equiv.)	2 Pd [%]	Temp. [°C]	Time [h]	3 [%] ^[b]
asc.wile	6	1a (2.0)	2d	5	Ľ	24	3ad, 82	20	1e (1.0)	2b 10	60	48	S 3eb, 60
y-vch.de	Γ	1b (2.0)	2d	S	40	24	3bd, 58	21	1f (5.0)	2b 5	40	48	S 31b, 72 ^[c]
©	8	1a (2.0)	2e	Ś	11	24	Sae, 77 OAc	22	1e (1.0)	2c 10	60	48	S
2013 Wiley-V	6	1b (2.0)	2e	Ś	40	48	DAC OAC 3be, 50	23	1f (5.0)	2c 5	40	48	s ster, 67 ^[e]
CH Verlag G	10	1c (2.0)	2a	S	40	24	MeO O O O O O O O O O O O O O O O O O O	24	1e (1.0)	2d 10	40	48	S 3ed, 55
mbH & Co. K	11	1c (2.0)	2b	10	40	48	Me0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	25	1f (5.0)	2d 5	40	24	S 3fd. 64 ^[c]
GaA, Weinho	12	1c (2.0)	2c	10	40	48	Me0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	26	1g (5.0)	2a 10	40	24	S 3ga, 50
eim	13	1c (2.0)	2d	5	40	48	MeO O F	27	1h (2.0)	2a 5	r.t.	24	N 3ha, 57
Adv. Synth. Catal.	14	1d (8.0)	2a	10	t	24	3da, 35 3da, 35 4da, 28	28	1i (2.0)	2a 5	r.t.	24	N 31a, 42
2013 , 355,	$[b] \frac{[a]}{[b]} \frac{Co}{Iso}$	<i>nditions:</i> 1 lated yield.	(1.0-) Co	8.0 mm ntamin	ol), 2 (1.0 m ated with ~	mol), Pd(10% of 3-	OAc) ₂ (0.05–0.1 mmol), AcC methyl-2-styrylthiophene der	H (2 m ivatives	L), DMSO	(2 mL), O ₂	(gas bag), r	oom temp	oerature to 60°C, 24-48 h.

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Figure 2. ESI(+)-MS of an AcOH/DMSO solution of $Pd(OAc)_2$ after 5 min. *Conditions:* $Pd(OAc)_2$ (0.05 mmol), AcOH (2 mL), DMSO (2 mL), O₂ (gas bag), room temperature, 5 min.



Figure 3. *Top:* ESI(+)-MS of an AcOH/DMSO solution of **1j**, **2a**, Pd(OAc)₂. *Conditions:* **1j** (2.0 mmol), **2a** (1.0 mmol), Pd(OAc)₂ (0.05 mmol), AcOH (2 mL), DMSO (2 mL) O₂ (gas bag), room temperature, 1.5 h. *Bottom:* extension of the spectra between m/z 200–400.

HR-MS, and the ESI(+)-MS/MS has shown the loss of 1j and DMSO (Figure S2 in the Supporting Information). The use of 1k also confirms the proposed

structure (Table 3). Unsolvated and hydrated species, $[Pd(3ja+H)]^+$ and $[Pd(3ja+H) (H_2O)]^+$, were observed at m/z 333.1 and 351.1, respectively (Figure 3,

Table 3. Comparison of detected species for the coupling of1j with 2a, 1k with 2a, and 1k with 2f.

Proposed Structures		m/z	
1	1j, 2a	1k, 2a	1k, 2f
[Pd(3 +H)(DMSO)] ⁺	411.1	383.1	439.2
$[Pd(3+H)]^+$	333.1	305.0	361.1
$[Pd(3+H)(H_2O)]^+$	351.1	323.0	379.1
[Pd(1-H)(DMSO)(OAc)Na]+	389.1	361.0	361.1

bottom), and their structures were confirmed by HR-MS. The ESI(+)-MS/MS of both species has shown the loss of Pd, while the ESI(+)-MS/MS of the m/z 351 complex agreed with the presence of H₂O (Figure S3 in the Supporting Information). The couplings with **1k** and **2f** also led to the confirmation of the proposed structures (Table 3).

No clusters connected to 1, 2 or 3 were observed above m/z 400, whereas active dinuclear species were detected in the presence of BQ.^[8] The latter has therefore an influence on the structure of the active species. However BQ adducts are usually difficult to detect by ESI-MS, and their plausible role in the formation of dinuclear species has not been determined.^[8] The hydrated adduct $[Pd(3ja+H)(H_2O)]^+$ was not observed in the presence of BQ.^[8] It is known that the reoxidation of Pd(0) under O_2 can lead to the formation of H_2O_2 and subsequently to H_2O ,^[9] thus explaining probably the presence of $[Pd(3ja+H)-(H_2O)]^+$.

In view of the ESI-MS data, the following mechanism is proposed. The inactive trimer $[Pd(OAc)_2]_3 A$, reacts with DMSO leading to the inactive or low active dimer **B** and to the active monomer **C** (Scheme 1). **C** activates a C–H bond of DMSO and **1**, leading to PdL₂(DMSO–H)(OAc) and the furyl-Pd complex **D**. The insertion of **2** furnishes **E**, which suffers β -hydride elimination to give **F**. Species **F** would react directly with O₂ and AcOH to regenerate the catalyst, or would lead through reductive elimination to the Pd(0) complex **G**. In the latter case, the reoxidation of **G** by O₂/AcOH would finish the catalytic cycle.^[10]

Finally, we have studied the influence of metallic co-oxidants on the kinetic profile of the reactions. The monitoring by GC of the DHR of **1e** with **2a** performed under O_2 as the sole oxidant or with addition of $Cu(OAc)_2$ (10%) or AgOAc (10%), has shown that the initial rate is not affected by these co-oxidants (Figure 4). AgOAc has however a negative influence on the rate after the initial stage of the reaction. The



Scheme 1. Proposed catalytic cycle and species detected by ESI(+)-MS for the DHR of 1j with 2a.



Figure 4. Dependence of the yield of **3ea** on the presence of a co-oxidant. *Conditions:* **1e** (1.0 mmol), **2a** (1.0 mmol), Pd(OAc)₂ (0.1 mmol), Cu(OAc)₂ or AgOAc (0 or 0.1 mmol), AcOH (2 mL), DMSO (2 mL), O₂ (gas bag), 40 °C. Data are averaged from two reactions.



Figure 5. Dependence of the conversion of **2a** on the presence of a co-oxidant for the DHR of **1e**. *Conditions:* **1e** (1.0 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol), $Cu(OAc)_2$ or AgOAc (0 or 0.1 mmol), AcOH (2 mL), DMSO (2 mL), O₂ (gas bag), 40 °C. Data are averaged from two reactions.

comparison of the conversion and yield curves in the presence of AgOAc shows that secondary reactions occur, probably through polymerization or oxidation of 2a, but the conversion follows the trend observed for the formation of **3ea**, suggesting that the metallic co-oxidants act as poisons of the catalyst (Figure 5). This observation was also noticed for the DHR of 1a with 2a, but in greater proportions (Figure 6 and Figure 7). Indeed, the presence of 10% of $Cu(OAc)_2$ had a strong negative influence on the rate after the initial stage of this reaction, while the presence of 10% of AgOAc completely prevented the progression of the transformation after few minutes of stirring. On the opposite, the influence of $Mn(OAc)_3$ on the reaction profile of the DHRs of 1a with 2a and 1e with 2a was not significant (Figure S4 and Figure S5 in the Supporting Information).

The ESI(+)-MS of an AcOH/DMSO solution of $Pd(OAc)_2$ and AgOAc has, after 5 min of stirring, shown several silver clusters and mixed species,



Figure 6. Dependence of the yield of **3aa** on the presence of a co-oxidant. *Conditions:* **1a** (2.0 mmol), **2a** (1.0 mmol), Pd(OAc)₂ (0.05 mmol), Cu(OAc)₂ or AgOAc (0 or 0.1 mmol), AcOH (2 mL), DMSO (2 mL), O₂ (gas bag), room temperature. Data are averaged from two reactions.



Figure 7. Dependence of the conversion of **2a** on the presence of a co-oxidant for the DHR of **1a**. *Conditions:* **1a** (2.0 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), $Cu(OAc)_2$ or AgOAc (0 or 0.1 mmol), AcOH (2 mL), DMSO (2 mL), O₂ (gas bag), room temperature. Data are averaged from two reactions.

 $(Ag)_a(Pd)_b(DMSO)_c(OAc)_d$ (a, b, c=1-2; d=3-5), which were confirmed by HR-MS (Figure S6 in the Supporting Information).

Only two clusters of Figure 2, $[Pd(OAc)(DMSO)_2]^+$ and $[Pd_2(OAc)_3(DMSO)_2]^+$, were detected under these conditions. We have proposed that the trinuclear complex $[Pd(OAc)_2]_3$ is an inactive species for DHRs, since the $Pd(OAc)_2$ units are joined by double OAc bridges, and no acetate ligand can participate in a C-H bond activation.^[8] Similarly, we suspect that the acetates form bridges between the Pd and Ag atoms in the mixed complexes $(Ag)_a(Pd)_b(DMSO)_c$ - $(OAc)_d$, leading to inactive species. An AcOH/DMSO solution of Pd(OAc)_2, AgOAc, **1j** and **2a** under an oxygen atmosphere was then monitored by ESI(+)-MS. After 10 min, a simple spectrum was obtained and two clusters were easily detected at m/z 333.0 and 411.0, which were previously attributed to $[Pd(3ja+H)]^+$ and $[Pd(3ja+H)(DMSO)]^+$ (Figure S7 in the Supporting Information). After 45 min, $[Pd(3ja+H)]^+$ was almost not present, while $[Pd-(3ja+H)(DMSO)]^+$ was not detected. $[Ag(DMSO)]^+$ and

 $[Ag(DMSO)_2]^+$ were still present, and mononuclear Pd species were observed at m/z 649 and 727 but could not be characterized. (Figure S8 in the Supporting Information). The kinetic profile of the DHR of 1a with 2a has shown that the reaction does not progress after 30 min almost (Figure 6 and Figure 7).^[11] This observation and the disappearance of [Pd(3ja+H)]⁺ and [Pd(3ja+H)(DMSO)]⁺ confirm that such intermediates are involved as active species. The simple spectrum obtained after 45 min (Figure S8 in the Supporting Information) showing that most of the palladium species are not present, suggests that the inactivation of the catalyst is probably due to the formation of insoluble clusters or particles.

In conclusion, the present study shows that co-oxidants usually used to regenerate Pd(II) species are not always beneficial to DHRs. Indeed, oxygen as the sole oxidant led to a more active catalytic system than $Cu(OAc)_2$ and AgOAc in conjunction with oxygen, for the Pd(II)-catalyzed coupling of heteroarenes with styrenes. ESI(+)-MS has led to the identification of four intermediates involved in the C–H activation of the arene and the insertion of the alkene into the Pd– Ar bond. The catalytic species are mononuclear complexes. The presence of co-oxidants can lead to the formation of insoluble or inactive mixed species.

Experimental Section

Typical Procedure

A round-bottom flask was charged with $Pd(OAc)_2$ (11.2–22.4 mg, 0.05–0.1 mmol), AcOH (2 mL), DMSO (2 mmol), **1** (1.0–8.0 mmol) and **2** (1.0 mmol). A gas bag filled with O₂ was adapted, and the mixture was stirred at rt-60 °C for 24 h to 48 h. Et₂O (20 mL) was then added, and a saturated aqueous solution of NaHCO₃ (20 mL) was slowly added with rapid stirring. The organic phase was washed with 2M NaOH (20 mL) and H₂O (20 mL). The combined aqueous phases were extracted with Et₂O (20 mL). The combined organic phases were dried over MgSO₄, and then evaporated to dryness. Product **3** was isolated from flash chromatography (SiO₂, petroleum ether 100% or petroleum ether/ EtOAc, 98:2–70:30).

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