Angewandte Chemie

DOI: 10.1002/ange.200800966

Heck Reaction

Ligand-Free Pd-Catalyzed Highly Selective Arylation of Allylic Esters with Retention of the Traditional Leaving Group**

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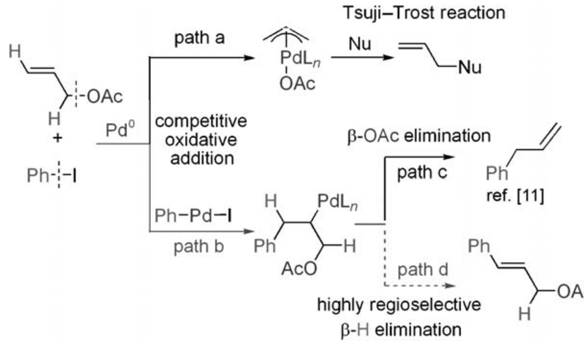
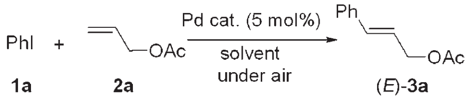
The Heck reaction[1] has been studied in detail as a powerful tool for the construction of C–C bonds in organic synthesis.[2] Over the past several decades, the scope of the Heck reaction has been expanded significantly to include aryl chlorides[3] and tosylates,[4] alkyl halides,[5] and arenes (through C–H activation) as suitable substrates.[6] The Heck reaction can also be carried out regioselectively with electron-rich olefins.[7] However, Pd-catalyzed Heck reactions between organic halides and allylic esters have not been well developed. Such reactions are challenging from a mechanistic point of view for two reasons: 1) The allylic ester could readily undergo C–O cleavage through oxidative addition to Pd^0 to form a π-allyl palladium species (Scheme 1, path a), which is the key intermediate in the Tsuji–Trost reaction.[8,9] This process competes with the desired oxidative addition of an aryl halide to Pd^0 (Scheme 1, path b). 2) After the insertion in path b, β-OAc elimination[10] (Scheme 1, path c) competes with the desired β-hydride elimination (Scheme 1, path d). Lautens and co-workers developed a reductive coupling of allylic acetates that involves β-OAc elimination (Scheme 1, path c).[11] Although products formed through β-H elimination were observed by Lautens and others,[11b,12] they were produced in low yield with low selectivity. We now demonstrate an efficient and highly selective Heck reaction of organic halides with allylic esters by avoiding β-acetate (Scheme 1, path d) or β-carbonate elimination. The resulting substituted allylic esters are amenable to further functional-group transformations.



Scheme 1. Competitive processes in the Pd-catalyzed reaction of iodobenzene and allyl acetate.

Our initial efforts focused on the Heck reaction between PhI (**1a**) and allyl acetate (**2a**). Only a trace amount of the expected product **3a** was formed when **1a** and **2a** were treated with $[Pd(PPh_3)_4]$ (5 mol%; Table 1, entry 1). However, (*E*)-**3a** was produced in 7% yield when $Pd(OAc)_2$ was

Table 1: Unexpected Pd-catalyzed Heck reaction between iodobenzene (**1a**) and allyl acetate (**2a**).[a,b]



Entry	Catalyst	Additive(s) (equiv)	Base[c]	Solvent	*t* [h]	Yield [%]
1	$[Pd(PPh_3)_4]$		K_2CO_3	benzene	48	trace
2	$Pd(OAc)_2$		K_2CO_3	benzene	48	trace
3	$Pd(OAc)_2$		K_2CO_3	DMF[d]	15	7
4	$Pd(OAc)_2$	Ag_2CO_3 (0.6)		DMF[d]	12	55
5	**$Pd(OAc)_2$**	**Ag_2CO_3 (0.6)**		**benzene**	**10**	**94**
6	$Pd(OAc)_2$	Ag_2CO_3 (1.0)		benzene	10	82
7	$Pd(OAc)_2$	Ag_2CO_3 (0.2)		benzene	48	35
8[e]	$Pd(OAc)_2$	Ag_2CO_3 (0.6)		toluene	24	67
9[e]	$Pd(OAc)_2$	Ag_2CO_3 (2.0)		toluene	24	18
10[e]	$Pd(OAc)_2$ PPh_3	Ag_2CO_3 (0.6)		toluene	24	10
11[e]	$Pd(OAc)_2$	Ag_2CO_3 (0.6)	K_2CO_3	toluene	24	<5
12[e]	$Pd(OAc)_2$	$AgNO_3$ (1.2)		toluene	24	0
13[e]	$Pd(OAc)_2$	$AgNO_3$ (1.2)	K_2CO_3	toluene	16	35
14[e,f]	$Pd(OAc)_2$	Ag_2CO_3 (0.6)		toluene	24	32
15[e,f]	$Pd(OAc)_2$	Ag_2CO_3 (0.6) H_2O (4.0)		toluene	16	76

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), solvent (3 mL), reflux in air. [b] Trace amounts of di- and triphenylated products were observed for some reactions. [c] The amount of K_2CO_3 used (when applicable) was 2.0 equivalents. [d] The reaction was carried out at 120°C; DMF = *N*,*N*-dimethylformamide. [e] PhBr (**1b**, 1.0 mmol) and **2a** (0.5 mmol) were used as the substrates; the reaction mixture was heated at reflux in toluene. [f] The reaction was carried out under N_2.

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[**] Financial support from Peking University and the National Science Foundation of China (No. 20742001 and No. 20702002) is greatly appreciated.

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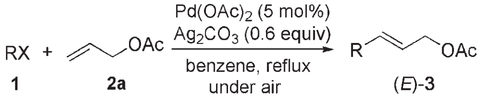
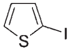
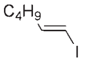
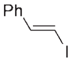
used as the catalyst in DMF at 120 °C (Table 1, entry 3), and the presence of Ag_2CO_3 in the absence of another base led to a dramatic improvement in the yield to 55 % (Table 1, entry 4). It seems that Ag_2CO_3 serves not only as a source of silver to scavenge the halide,[13] but also as a base. Allylbenzene, the product of β-OAc elimination, was not observed in these reactions.

Further investigations indicated that the desired product was formed in the highest yield with only 0.6 equivalents of Ag_2CO_3 in the absence of an additional base and a ligand. The yields decreased with a higher or lower concentration of Ag_2CO_3 (compare entries 5–7 and entries 8 and 9 of Table 1). An additional base greatly inhibited the reaction (compare entries 8 and 11 of Table 1 and see the Supporting Information). In contrast, no product was observed when other silver salts, such as $AgNO_3$, were used in the absence of an additional base (Table 1, entry 12). However, (*E*)-**3a** was produced in 35 % yield when $AgNO_3$ was used together with K_2CO_3 (2.0 equiv; compare entries 12 and 13 of Table 1).

Table 2: Pd-catalyzed Heck reaction of allyl acetate (**2a**) with different organic halides.[a]



Entry	1	Yield [%]	Entry	1	Yield [%]
1	PhI (**1a**)	94/(*E*)-**3a**	10[c]	PhBr (**1b**)	65/(*E*)-**3a**
2	4-Me-C_6H_4-I (**1c**)	98/(*E*)-**3b**	11[c]	2-Me-C_6H_4-Br (**1k**)	71/(*E*)-**3c**
3[b]	2-Me-C_6H_4-I (**1d**)	86/(*E*)-**3c**	12[d,e]	4-CO_2Me-C_6H_4-Br (**1l**)	65/(*E*)-**3d**
4	4-CO_2Me-C_6H_4-I (**1e**)	80/(*E*)-**3d**	13[d,f]	4-NO_2-C_6H_4-Br (**1m**)	62/(*E*)-**3e**
5	4-NO_2-C_6H_4-I (**1f**)	81/(*E*)-**3e**	14	 (**1n**)	75/(*E*)-**3j**
6	4-F-C_6H_4-I (**1g**)	80/(*E*)-**3f**			
7	4-Ph-C_6H_4-I (**1h**)	79/(*E*)-**3g**	15[g]	 (**1o**)	55/(*E*)-**3k**
8	4-MeCO-C_6H_4-I (**1i**)	82/(*E*)-**3h**			
9[b]	4-OMe-C_6H_4-I (**1j**)	81/(*E*)-**3i**	16[g]	 (**1p**)	60/(*E*)-**3i**

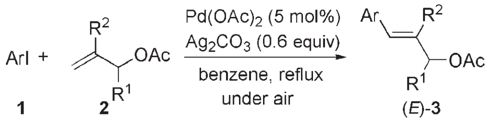
[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), Ag_2CO_3 (0.3 mmol), benzene (3 mL), reflux in air. [b] The reaction mixture was heated at reflux in toluene. [c] The reaction mixture was heated at reflux in toluene (**1**: 0.6 mmol; **2a**: 0.5 mmol). [d] The reaction mixture was heated at reflux in toluene (**2a**: 3.0 equiv). [e] Some of the starting material **1l** (7 %) was recovered. [f] Some of the starting material **1m** (19 %) was recovered. [g] The amount of **2a** used was 3.0 equivalents.

The yield of (*E*)-**3a** decreased to 10 % in the presence of PPh_3 (20 mol %; Table 1, entry 10). With other ligands, such as dppe, the yield was even lower (see the Supporting Information). Surprisingly, (*E*)-**3a** was obtained in only 32 % yield when the reaction was carried out in toluene under N_2 (compare entries 8 and 14 of Table 1). The presence of water (4.0 equiv) led to a dramatic improvement in the yield of (*E*)-**3a** to 76 % (compare entries 14 and 15 of Table 1). $Pd(OAc)_2$ was more effective than other palladium catalysts, such as $PdCl_2$ and $Pd(O_2CCF_3)_2$ (see the Supporting Information). After extensive screening of the other reaction parameters (see the Supporting Information), we concluded that the reaction proceeded most efficiently in the presence of $Pd(OAc)_2$ (5 mol %) and Ag_2CO_3 (0.6 equiv) and in the absence of a ligand at reflux in benzene (Table 1, entry 5), or in toluene in air when bromobenzene (**1b**) was used as the substrate.

The scope of the Heck reaction was expanded to a variety of organic halide substrates (Table 2). Substituted *E*-allylic acetates (*E*)-**3** were formed with high stereoselectivity in these reactions. Reactions of aryl iodides with electron-withdrawing or electron-donating groups proceeded efficiently (Table 2, entries 2–9; 79–98 %). The heterocyclic iodide 2-iodothiophene (**1n**) was coupled with **2a** to give (*E*)-**3j** in 75 % yield (Table 2, entry 14). Even vinyl iodides reacted well with **2a** to give the desired products in moderate yields (Table 2, entries 15 and 16). The wide applicability of this reaction is also demonstrated by the good reactivity of aryl bromide substrates (Table 2, entries 10–13).

A series of substituted allylic acetates **2** were investigated as substrates (Table 3). Certain allylic acetates substituted at the 1- or 2-position were found to be viable for the stereoselective construction of aryl-substituted *E*-allylic acetates (*E*)-**3** in good yields (Table 3, entries 2–7). When the 2-position of the substrate was substituted, the *E*/*Z* selectivity decreased as a result of steric hindrance (Table 3, entries 5 and 6).

Table 3: Pd-catalyzed Heck reaction of aryl iodides **1** with substituted allylic acetates **2**.[a]

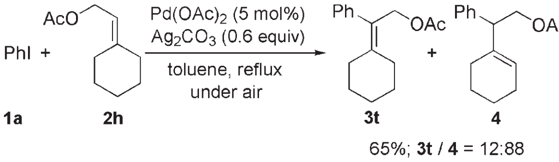


Entry	Ar (**1**)	**2**	R^1	R^2	*t* [h]	Yield [%]
1	Ph (**1a**)	**2b**	Me	H	12	45/(*E*)-**3m**
2	Ph (**1a**)	**2c**	Et	H	10	87/(*E*)-**3n**
3	Ph (**1a**)	**2d**	*i*Pr	H	10	98/(*E*)-**3o**
4[b]	Ph (**1a**)	**2e**	Ph	H	15	80/(*E*)-**3p**
5	Ph (**1a**)	**2f**	H	Me	15	73[c]/**3q**
6	4-NO_2-C_6H_4 (**1f**)	**2g**	H	Ph	12	92[d]/**3r**
7	4-NO_2-C_6H_4 (**1f**)	**2e**	Ph	H	12	87/(*E*)-**3s**

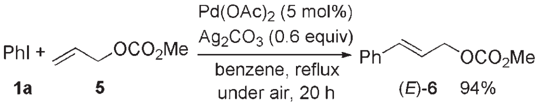
[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), Ag_2CO_3 (0.3 mmol), benzene (3 mL), reflux in air. [b] The amount of **1a** used was 2.0 mmol; the amount of **2e** used was 1.05 equivalents. [c] (*E*)-**3q**/(*Z*)-**3q** 80:20. [d] (*E*)-**3r**/(*Z*)-**3r** 19:81.

The allylic acetate **2h**, in which the 3-position is substituted, reacted with **1a** to give **3t** and **4** in 65 % combined yield [**3t**/**4** 12:88; Eq. (1)].

These results inspired us to consider allylic substrates with other leaving groups. We were pleased to find that even the Heck reaction of relatively active allyl methyl carbonate (**5**)



(1)

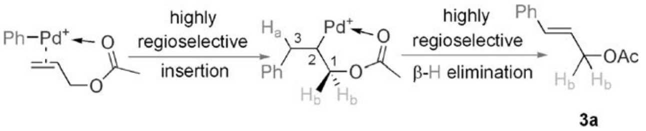


(2)

with **1a** was successful, with (*E*)-**6** produced in 94% yield [Eq. (2)].

The high regioselectivities observed in these reactions can be explained reasonably on the basis of chelation between the carbonyl O atom and the Pd atom, as described previously (Scheme 2).[14] Rotation about the C1−C2 bond is impeded as a result of this chelation, and therefore H_a is favored to adopt a *syn* relationship with Pd for subsequent β-H elimination.

In conclusion, we have developed a $Pd(OAc)_2$-catalyzed highly selective Heck reaction between organic halides and allylic esters. The β elimination of the OAc or OCO_2Me group is avoided in this reaction, which could serve as a useful supplement to the traditional Heck reaction and the Tsuji–Trost allylation. The reaction conditions are mild, the reaction can be carried out in a straightforward manner in air, and no ligand is required. Although cinnamyl acetate can be prepared from cinnamaldehyde, some substituted cinnamaldehydes are not commercially available. Furthermore, the selectivity of Heck reactions with allylic alcohols is complicated.[15] This method could provide a useful tool for the synthesis of substituted allylic alcohols. Further studies on the mechanism of the reaction and synthetic applications are ongoing in our laboratory.



3a

Scheme 2. Source of the high regioselectivity of the present Heck reaction.

Experimental Section

Typical procedure: Iodobenzene (**1a**; 102 mg, 0.5 mmol) and then **2a** (100 mg, 1.0 mmol) were added to a mixture of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and Ag_2CO_3 (83 mg, 0.3 mmol) in benzene (3 mL), and the resulting mixture was heated at reflux for 10 h. The reaction mixture was then concentrated by evaporation, and the residue was purified carefully by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether 10:1) to afford (*E*)-**3a**[16] (83 mg, 94%) as a liquid. IR (neat): $\tilde{\nu} = 1739, 1653, 1236, 1027\ \mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.20$–7.43 (m, 5H), 6.66 (d, $J = 15.6$ Hz, 1H), 6.29 (dt, $J = 15.6$, 6.3 Hz, 1H), 4.73 (d, $J = 6.3$ Hz, 2H), 2.11 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta = 170.8$, 136.2 134.2, 128.6, 128.0, 126.6, 123.1, 65.1, 21.0 ppm; MS (70 eV): m/z (%): 176.2 (17) [M^+], 43 (100).

Received: February 28, 2008

Keywords: allylic compounds · Heck reaction · palladium · regioselectivity · silver

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