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Tetrahedron Letters 47 (2006) 2573–2576

Tetrahedron Letters

An efficient palladium-catalyzed Heck coupling of aryl chlorides with alkenes

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Received 16 December 2005; revised 7 February 2006; accepted 8 February 2006
Available online 24 February 2006

Abstract—Catalyst system $PdCl_2(PCy_3)_2/Cs_2CO_3$ in dioxane was found to be the efficient catalyst system for Heck cross-coupling reactions of deactivated, neutral, and activated aryl chlorides with a variety of alkenes under mild conditions to afford selectively *E*-arylated alkenes in good to excellent yields.

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Palladium-catalyzed Heck reactions of aryl halides with alkenes have become one of the most powerful tools in organic synthesis for the construction of carbon–carbon bond. Generally, aryl bromides, iodides, and activated alkenes are typically employed as the cross-coupling reactants, and a variety of the efficient palladium catalyst systems have been developed.[1] Aryl chlorides are cheaper and more easily available than bromides and iodides, but less reactive. Recent years attempts to establish the efficient catalyst systems for the Heck reactions of aryl chlorides have been made extensively, but among the reported catalytic procedures, in order to achieve the satisfactory yields of the cross-coupling reactions, either the activated aryl chlorides, or the activated alkenes were employed.[2] The catalyst systems which show the high catalytic activity in Heck reactions of deactivated aryl chlorides are still few.[3] The aim of our research work is to develop the efficient catalyst system for the cross-coupling of deactivated, neutral and activated aryl chlorides with both activated and deactivated alkenes.

We chose the reaction of chlorobenzene **1a** with styrene **2a** as the model reaction to screen the catalyst and optimize the reaction conditions (Table 1). Initial studies revealed that in the presence of Cs_2CO_3 and in toluene at 120 °C (sealed tube, oil bath temperature) for 12 h, complexes $PdCl_2(PPh_3)_2$ and $NiCl_2(dppp)$ showed no catalytic activity at all, and $Pd(PPh_3)_4$ catalyzed the cross-coupling reaction to give a small amount of stilbene **3a** (entries 1–3). Complex $PdCl_2(PEt_3)_2$, which contains the electron-rich phosphine ligands of PEt_3, displayed the mild catalytic activity to afford the coupled products in 55% GC yield (entry 4). In this case, the analysis of the reaction mixture by GC–MS disclosed that the cross-coupling reaction produced three coupled products, and the selectivity of the major product **3a** was 85%. Further investigation found that $PdCl_2(PPCy_3)$, which bears the electron-rich and bulky phosphine ligands of PCy_3, catalyzed the cross-coupling reaction with high activity and selectivity to furnish the cross-coupled products in 80% GC yield with 90% selectivity of **3a** (entry 5). Dioxane could promote the reaction greatly when it was used as the solvent. In this case, cross-coupled products were formed in quantitative yield, and the selectivity of **3a** was in 93% (entry 6). As revealed in Table 1, under the solvent-free condition, the cross-coupling of **1a** with **2a** also proceeded smoothly, but the selectivity of **3a** was decreased (entry 7 vs entries 5 and 6). In addition, the use of DMF to replace dioxane as solvent resulted in decreasing the catalytic activity of $PdCl_2(PCy_3)_2$ (entry 8), and in $CHCl_2CHCl_2$, the formation of **3a** could not be determined at all (entry 9). Among the base chosen, Cs_2CO_3 is the best one. $PdCl_2(PCy_3)_2$ showed very low or no catalytic activity when K_2CO_3, Na_3PO_4, piperidine, or Et_3N were used as bases, or in the absence of base (entries 10–14). Therefore, we carried out the reactions of **1a** with a variety of alkenes, and a number of aryl chlorides with ethyl acrylate in the presence of $PdCl_2(PCy_3)_2$ in dioxane with the use of Cs_2CO_3 as base to examine the scope of the present catalyst system for the Heck

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Keywords: Alkene; Aryl chloride; Catalysis; Heck coupling; Palladium.

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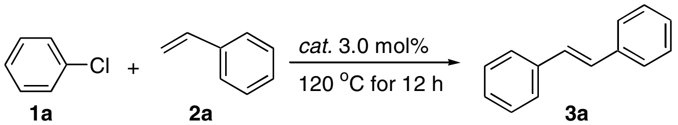
doi:10.1016/j.tetlet.2006.02.040

Table 1. Palladium-catalyzed Heck coupling of chlorobenzene with styrene[a]



1a **2a** **3a**

Entry	Catalyst	Solvent	Base	Yield[b] (%)	Selectivity[c] (%)
1	$PdCl_2(PPh_3)_2$	Toluene	Cs_2CO_3	NR	
2[d]	$NiCl_2(dppp)$	Toluene	Cs_2CO_3	NR	
3	$Pd(PPh_3)_4$	Toluene	Cs_2CO_3	<5	
4	$PdCl_2(PEt_3)_2$	Toluene	Cs_2CO_3	55	85
5	$PdCl_2(PCy_3)_2$	Toluene	Cs_2CO_3	80	90
6	$PdCl_2(PCy_3)_2$	Dioxane	Cs_2CO_3	>99(90)	93
7	$PdCl_2(PCy_3)_2$	—	Cs_2CO_3	90	81
8	$PdCl_2(PCy_3)_2$	DMF	Cs_2CO_3	60	95
9	$PdCl_2(PCy_3)_2$	$CHCl_2CHCl_2$	Cs_2CO_3	NR	
10	$PdCl_2(PCy_3)_2$	Dioxane	K_2CO_3	30	92
11	$PdCl_2(PCy_3)_2$	Dioxane	Na_3PO_4	10	
12	$PdCl_2(PCy_3)_2$	Dioxane	Piperidine	<5	
13	$PdCl_2(PCy_3)_2$	Dioxane	Et_3N	NR	
14	$PdCl_2(PCy_3)_2$	Dioxane	—	NR	

[a] Reactions were carried out at 120 °C for 12 h using 0.66 mmol of **1a**, 0.6 mmol of **2a**, 0.66 mmol of base and 0.018 mmol of catalyst in 0.8 mL of solvent.

[b] GC yields are based on the amount of **2a** used. Number in parentheses is isolated yield.

[c] By GC.

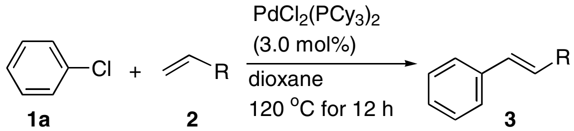
[d] DPPP = 1,3-bis(diphenylphosphino)propane.

reaction of aryl chlorides with alkenes as summarized in Tables 2 and 3.

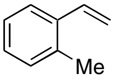
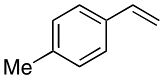
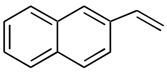
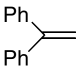
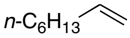
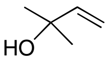
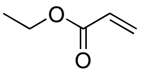
The results of the cross-coupling of chlorobenzene with deactivated (electron-rich) and activated (electron-deficient) alkenes are shown in Table 2, and the catalytic reactions appeared quite general with respect to the nature of the alkenes. For example, the cross-coupling of chlorobenzene with 2-methylstyrene **2b**, 4-methylstyrene **2c**, 2-vinylnaphthalene **2d**, and 1,1-diphenylethylene **2e** afforded the desired product in good to high yields with high selectivity of **3b–e** (entries 1–4). The formation of **3e** in moderate yield might be due to the existence of two bulky phenyl groups in **3e**. It was worthy to note that the normally inactive 1-octene **2f** and 2-methyl-3-butyn-2-ol **2g** could also proceed the cross-coupling reaction smoothly under the same reaction conditions to afford the cross-coupled products in quantitative yields (entries 5–6). In the case of **2f** used, the selectivity of **3f** was in only 60% arising from the cross-coupling reactions occurring not only at the alkenic C–H bond, but also at C–H bond of α-CH_2 of alkene.[4] The successful cross-coupling of **2g** with chlorobenzene indicated that hydroxyl group was tolerated under the reaction conditions. As expected, the activated alkene ethyl acrylate **2h** reacted with **2a** produced quantitatively the desired cross-coupling product **3h** as an exclusive coupled product (entry 7).

In order to assess the scope of $PdCl_2(PCy_3)_2$-catalyzed Heck reaction, the cross-coupling of a variety of aryl chlorides, deactivated as well as activated aryl chlorides with **2h** was investigated. As seen from Table 3, both electron-rich and electron-deficient aryl chlorides were compatible with the coupling reaction to afford arylated alkenes **3i–m** in high yields with high selectivity.

Table 2. Palladium-catalyzed Heck coupling of chlorobenzene with alkenes[a]



1a **2** **3**

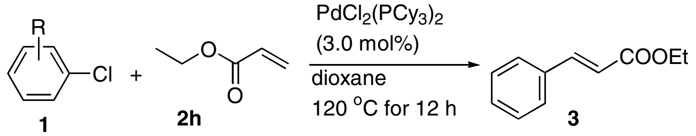
Entry	Alkene		Yield[b] (%)		Selectivity[c] (%)
1		**2b**	90(81)	**3b**	93
2		**2c**	94(89)	**3c**	95
3		**2d**	95(90)	**3d**	95
4		**2e**	65(59)	**3e**	95
5		**2f**	>99(83)	**3f**	60
6		**2g**	>99(96)	**3g**	100
7		**2h**	>99(93)	**3h**	100

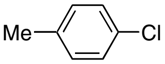
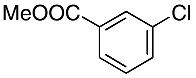
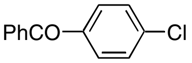
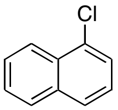
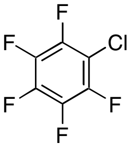
[a] Reactions were carried out at 120 °C for 12 h using 0.66 mmol of **1a**, 0.6 mmol of **2**, 0.66 mmol of Cs_2CO_3 and 0.018 mmol of catalyst in 0.8 mL of solvent.

[b] GC yields are based on the amount of **2** used. Numbers in parentheses are isolated yields.

[c] By GC.

Table 3. Palladium-catalyzed Heck coupling of aryl chlorides with ethyl acrylate[a]



Entry	Aryl chlorides		Yield[b] (%)		Selectivity[c] (%)
1		**1b**	>99(94)	**3i**	97
2		**1c**	98(93)	**3j**	97
3		**1d**	96(89)	**3k**	97
4		**1e**	92(85)	**3l**	98
5		**1f**	94(87)	**3m**	97

[a] Reactions were carried out at 120 °C for 12 h using 0.66 mmol of **1**, 0.6 mmol of **2h**, 0.66 mmol of Cs_2CO_3 and 0.018 mmol of catalyst in 0.8 mL of solvent.

[b] GC yields are based on the amount of **2h** used. Numbers in parentheses are isolated yields.

[c] By GC.

The mechanism of Heck reaction has been well documented.[5] The high catalytic activity of the present catalyst system for aryl chlorides was considered to be the use of the electron-rich and bulky phosphine ligand of PCy_3,[5b] combined with the choice of Cs_2CO_3 as the base, as well as dioxane as the solvent.

In summary, we developed a practical and efficient $PdCl_2(PCy_3)_2$-catalyzed cross-coupling of aryl chlorides with alkenes at 120 °C in dioxane using Cs_2CO_3 as base. The advantages of this catalyst system include its generality and high catalytic activity for not only electron-deficient (activated), but also electron-neutral and electron-rich (deactivated) aryl chlorides under mild and convenient conditions.

A typical experimental procedure for cross-coupling of 4-chlorobenzophenone **1d** with ethyl acrylate (Table 3, entry 3): A mixture of **1d** (143 mg, 0.66 mmol), ethyl acrylate (60 mg, 0.60 mmol), Cs_2CO_3 (215 mg, 0.66 mmol) and $PdCl_2(PCy_3)_2$ (14.5 mg, 0.018 mmol) in dioxane (0.8 mL) under nitrogen in a sealed tube was heated with stirring at 120 °C (oil bath temperature) for 12 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 to 2.0 mL and octadecane (51.0 mg, 0.2 mmol) was added as internal standard for GC analysis. After GC and GC–MS analyses, removing the solvents and volatiles under vacuum, the residue was subjected to preparative TLC isolation (silica, eluted with cyclohexane) to give **3k** as colorless oil (150 mg, 0.54 mmol, 89%). The results of GC analysis of the reaction mixture revealed that the cross-coupling reaction gave three products in a ratio of 2:1:97 (**3k**) in 96% GC yield. Ethyl (*E*)-4-benzoyl-cinnamate **3k:** ^1H NMR (300 MHz, $CDCl_3$): δ 7.95–7.43 (m, 10H), 6.54 (d, 1H, $J = 16.1$ Hz), 4.27 (q, 2H, $J = 7.2$ Hz), 1.35 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 195.9, 166.6, 143.2, 138.3, 138.2, 138.0, 132.7, 130.6, 130.0, 128.4, 127.9, 120.7, 60.8, 14.3; GCMS *m*/*z* (% rel. inten.) 280(M^+, 42), 252(9), 235(18), 203(56), 175(25), 129(11), 105(100), 91(12), 77(76). HRMS calcd for $C_{18}H_{16}O_3$ 280.1099, found 280.1097.

Other products are known compounds and were characterized by ^1H, ^{13}C NMR, ^{19}F NMR (for **3m**) and mass spectra.

Acknowledgements

This project (20573061) was supported by National Natural Science Foundation of China.

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