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LETTERS

[Pd/Base/QX] catalyst systems for directing Heck-type reactions

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Abstract:
Palladium-catalyzed arylation of 2,3-dihydrofuran can be *directed at will* by an appropriate selection of the [Pd/Base/QX] catalyst systems.

Keywords: Ammonium salts, Arylation, Heck reactions, Palladium and compounds.

Within the past decade, the extensive study of Heck-type reactions [1-3] and their application in organic synthesis has led to the introduction of various improvements [4-6]. In particular, addition of a tetraalkylammonium salt (QX) has proved useful in enhancing the reaction rate [4, 6] whatever the anion [7, 8] and appropriate reaction conditions have been determined to obtain the optimum accelerating effect of QX [9]. Tetraalkylammonium salts have also been found to enhance the selectivity of Heck-type reactions [4, 6, 10-16]. We now wish to report that variations in the nature of the [Pd/Base/QX] catalyst system can allow to *direct at will* the outcome of the reactions.

In some cases, silver salts have been shown to be complementary to tetraalkylammonium salts in controlling the selectivity of the reactions [6]. In particular, treatment of iodobenzene with 2,3-dihydrofuran [17, 18] gives rise to the formation of 2-phenyl 2,5-dihydrofuran 1 when the reaction is performed in the presence of silver carbonate, while 2-phenyl 2,3-dihydrofuran 2 is formed in the presence of a mixture of potassium acetate and tetra-n-butylammonium chloride.

The results reported herein show that a highly selective formation of *either* 2-phenyl 2,5-dihydrofuran 1 *or* 2-phenyl 2,3-dihydrofuran 2 can be achieved using tetraalkylammonium salts (Scheme 1 and Table 1).

As shown in Table 1, formation of a mixture of compounds 1 and 2 was observed when iodobenzene was reacted with 2,3-dihydrofuran at 80 °C in N,N-dimethylformamide, in the presence of potassium acetate, tetra-n-butylammonium chloride (hydrated or not), and catalytic amounts of palladium acetate and triphenylphosphine (entries 1 and 2). In net contrast, compound 2 was obtained with high selectivity (entries 3-6) and in high yield (entries 4 and 5) when triphenylphosphine was omitted and when the reaction was performed at room temperature (20 °C). It is noteworthy that the reaction yield can be substantially increased (entry 4 compared to entry 3) by using an excess of tetraalkylammonium chloride which

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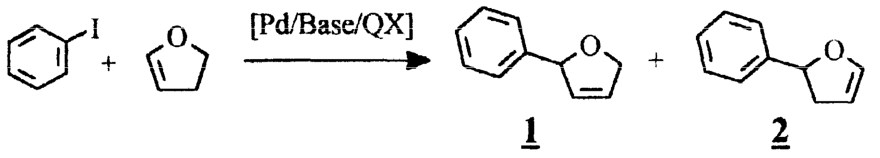
Table 1
Influence of [Pd/Base/QX] catalyst system on the phenylation of 2,3-dihydrofuran [a)]



(Scheme 1)

Entry	Base	QX	PPh_3 (equiv.)	Temperature /Time [b)]	Conversion (%) [c)]	Yield (%) [c)]	2 / 1 Ratio [d)]
1	KOAc	nBu_4NCl,xH_2O (1 equiv.)	0.1	80 °C / 3 h	100	90	56 / 44
2	KOAc	nBu_4NCl (1 equiv.)	0.1 [e)]	80 °C / 3 h	100	90	51 / 49
3	KOAc	nBu_4NCl (1 equiv.)	-	20 °C / 40h	82	66	90 / 10
4	**KOAc**	**nBu_4NCl (2.5 equiv.)**	-	**20 °C / 16h**	**100**	**100**	**92 / 8**
5	KOAc	nBu_4NCl (2.5 equiv.)	-	40 °C / 16h	100	100	88 / 12
6	KOAc	nBu_4NBr (2.5 equiv.)	-	20 °C / 40h	94	63	97 / 3
7	KOAc	nBu_4NOAc (1 equiv.)	-	20 °C / 40h	85	85	44 / 56
8	**nBu_4NOAc (1.5 equiv.)**	**nBu_4NOAc [f)] (1 equiv.)**	-	**20 °C / 6h**	**100**	**97**	**3 / 97**

[a)] To a well-stirred mixture of KOAc (2.5 equiv. when indicated), QX (as indicated) and 4Å molecular sieves in DMF (1 ml/ 1 mmol of PhI) were successively added iodobenzene (1 equiv.), 2,3-dihydrofuran (10 equiv.), PPh_3 (as indicated) and $Pd(OAc)_2$ (0.05 equiv.).

[b)] Reaction times were not optimized.

[c)] Determined by GLC against an internal standard.

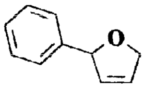
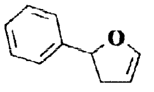
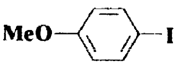
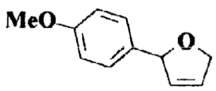
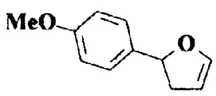
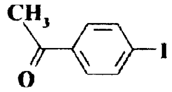
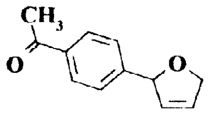
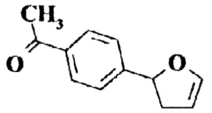
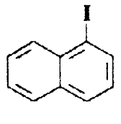
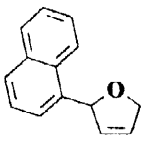
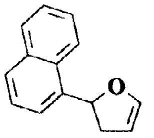
[d)] Determined by GLC.

[e)] Selective formation of 2 has been reported [17, 18] in reaction performed at 80 °C, in the presence of $Pd(OAc)_2$ and PPh_3 (Pd / L= 1).

[f)] in N,N-dimethylformamide or acetonitrile.

Table 2

Palladium-catalysed arylation of 2,3-dihydrofuran.[a), b)]

ArX	Conditions	Product	Yield (%)[c), d)]
	A[a)]		78[e)] (94)[e)]
"	B[b)]		77 (92)
	A[a)]		75[e)]
"	B[b)]		75
	A[a)]		77 (95)
"	B[b)]		80
	A[a)]		92
"	B[b)]		90

[a)] General procedure (conditions A): To a well-stirrred suspension of n-Bu$_4$NOAc (2 - 2.5 equiv.) and 4Å molecular sieves in dry DMF were successively added the aryl iodide (1 equiv.), 2,3-dihydrofuran (10 equiv.) and palladium acetate (0.05 equiv.). The reaction mixture was then stirred at room temperature (20 °C) overnight (for convenience) unless otherwise stated. Diethyl ether was then added and the mixture filtered over celite. The filtrate was washed with water, dried (MgSO$_4$), the solvent evaporated under reduced pressure and the crude product purified by flash chromatography.

[b)] General procedure (conditions B): To a well-stirrred suspension of KOAc (2 - 2.5 equiv.), nBu$_4$NCl (2.5 equiv.) and 4Å molecular sieves in dry DMF were successively added the aryl iodide (1 equiv.), 2,3-dihydrofuran (10 equiv.), and palladium acetate (0.05 equiv.). For convenience, the reaction mixture was then stirred overnight at room temperature (20 °C), unless otherwise stated. Work-up was performed as detailed in conditions A.

[c)] Non optimised yields of isolated products.

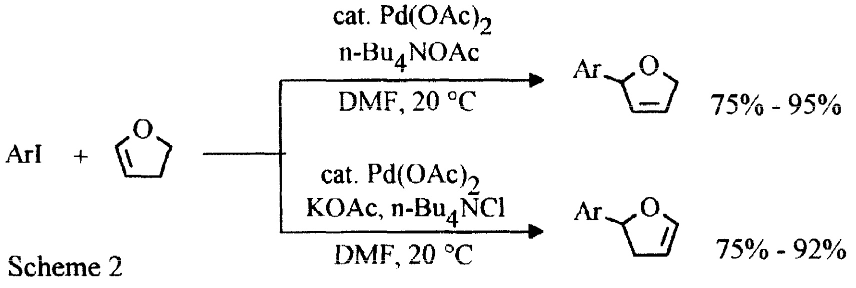
[d)] Yields in parentheses were determined by GLC against an internal standard.

[e)] Reaction time: 5h - 6h.

might stabilize the palladium catalyst in the absence of ligand phosphine. On the other hand, the selectivity of the reaction was lowered as the temperature increased (entry 5 compared to entry 4).

Although detrimental to the reaction yield, use of tetra-n-butylammonium bromide was beneficial for the selectivity (entry 6). Surprisingly, tetra-n-butylammonium acetate was far less efficient than tetra-n-butylammonium chloride or bromide when used in conjunction with potassium acetate, as a mixture of compounds 1 and 2 was obtained (entry 7). Interestingly however, when KOAc was omitted, i. e. when tetra-n-butylammonium acetate was used both as base and tetraalkylammonium salt, phenylation of 2,3-dihydrofuran led to the formation of compound 1, in high yield and with a high selectivity (entry 8).

Optimum conditions (Table 1, entries 4 and 8) have thus been found to synthesize 2-aryl 2,5-dihydrofuran and 2-aryl 2,3-dihydrofuran conveniently, under mild conditions (room temperature) and in high yields (Table 2 and Scheme 2).



Scheme 2

These results clearly show that selectivity of the arylation of 2,3-dihydrofuran can be highly controlled by an appropriate selection of the [Pd/Base/QX] catalyst system (very probably by efficiently preventing or promoting the migration of the double bond formed).

In conclusion, the procedure using tetraalkylammonium salts can be highly *flexible*. It can be effective, not only for enhancing the rate and selectivity of Heck-type reactions, but moreover, for *directing at will* the outcome of the reactions in order to perform them with the desired selectivity.

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