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## [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. © 1998 Elsevier Science Ltd. All rights reserved.

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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  $\underline{1}$  when the reaction is performed in the presence of silver carbonate, while 2-phenyl 2,3-dihydrofuran  $\underline{2}$  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  $\underline{1}$  or 2-phenyl 2,3-dihydrofuran  $\underline{2}$  can be achieved using tetraalkylammonium salts (Scheme 1 and Table 1).

As shown in Table 1, formation of a mixture of compounds  $\underline{1}$  and  $\underline{2}$  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  $\underline{2}$  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 <sup>a)</sup>



| Entry | Base                                  | QX   | PPh <sub>3</sub><br>(equiv.) | Temperature<br>/Time <sup>b)</sup> | Conversion (%) <sup>c)</sup> | Yield<br>(%) <sup>c)</sup> | <u>2</u> / <u>1</u><br>Ratio <sup>d)</sup> |
|-------|---------------------------------------|--|------------------------------|------------------------------------|------------------------------|----------------------------|--|
| 1     | KOAc                                  | nBu <sub>4</sub> NC1,xH <sub>2</sub> O<br>(1 equiv.) | 0.1                          | 80 °C / 3 h                        | 100                          | 90                         | 56 / 44                                    |
| 2     | KOAc                                  | nBu <sub>4</sub> NCl<br>(1 equiv.)                   | 0.1 <sup>e)</sup>            | 80 °C / 3 h                        | 100                          | 90                         | 51 / 49                                    |
| 3     | KOAc                                  | nBu <sub>4</sub> NCl<br>(1 equiv.)                   | -                            | 20 °C / 40h                        | 82                           | 66                         | 90 / 10                                    |
| 4     | KOAc                                  | nBu₄NCl<br>(2.5 equiv.)                              | -                            | 20 °C / 16h                        | 100                          | 100                        | 92 / 8                                     |
| 5     | KOAc                                  | nBu <sub>4</sub> NCl<br>(2.5 equiv.)                 | -                            | 40 °C / 16h                        | 100                          | 100                        | 88 / 12                                    |
| 6     | KOAc                                  | nBu₄NBr<br>(2.5 equiv.)                              | -                            | 20 °C / 40h                        | 94                           | 63                         | 97 / 3                                     |
| 7     | KOAc                                  | nBu₄NOAc<br>(1 equiv.)                               | -                            | 20 °C / 40h                        | 85                           | 85                         | 44 / 56                                    |
| 8     | nBu <sub>4</sub> NOAc<br>(1.5 equiv.) | nBu <sub>4</sub> NOAc <sup>î)</sup><br>(1 equiv.)    | -                            | 20 °C / 6h                         | 100                          | 97                         | 3 / 97                                     |

<sup>a)</sup> 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<sub>3</sub> (as indicated) and Pd(OAc)<sub>2</sub> (0.05 equiv.).

<sup>b)</sup> Reaction times were not optimized.

<sup>c)</sup> Determined by GLC against an internal standard.

<sup>d)</sup> Determined by GLC.

<sup>e)</sup> Selective formation of  $\underline{2}$  has been reported [17, 18] in reaction performed at 80 °C, in the presence of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> (Pd / L= 1).

<sup>n</sup> in N,N-dimethylformamide or acetonitrile.

 Table 2

 Palladium-catalysed arylation of 2,3-dihydrofuran.<sup>a), b)</sup>

| ArX       | Conditions      | Product        | Yield (%) <sup>c), d)</sup>         |
|-----------|-----------------|----------------|-------------------------------------|
| <u></u> ı | A <sup>a)</sup> | ()<br>()<br>() | 78 <sup>e)</sup> (94) <sup>e)</sup> |
| n         | B <sup>bì</sup> | o              | 77 (92)                             |
| MeO       | A <sup>a)</sup> | MeO            | 75 °)                               |
| v         | B <sup>b)</sup> | MeO            | 75                                  |
|           | A <sup>a)</sup> | CH,<br>O       | 77 (95)                             |
| n         | B <sup>b)</sup> | OH,<br>OCH,    | 80                                  |
|           | A <sup>a)</sup> | o              | 92                                  |
| n         | B <sup>b</sup>  | o              | 90                                  |

- <sup>a)</sup> General procedure (conditions A): To a well-stirrred suspension of n-Bu<sub>4</sub>NOAc (2 2.5 equiv.) and 4A 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<sub>4</sub>), the solvent evaporated under reduced pressure and the crude product purified by flash chromatography.
- <sup>b)</sup> General procedure (conditions B): To a well-stirred suspension of KOAc (2 2.5 equiv.), nBu<sub>4</sub>NCl (2.5 equiv.) and 4A 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.

<sup>&</sup>lt;sup>c)</sup> Non optimised yields of isolated products.

<sup>&</sup>lt;sup>d)</sup> 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-nbutylammonium 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-nbutylammonium 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).

$$ArI + \begin{pmatrix} O \\ M \end{pmatrix} \xrightarrow{\text{Cat. Pd(OAc)_2}} Ar \xrightarrow{\text{O}} 75\% - 95\%$$

$$ArI + \begin{pmatrix} O \\ M \end{pmatrix} \xrightarrow{\text{Cat. Pd(OAc)_2}} Ar \xrightarrow{\text{O}} 75\% - 95\%$$

$$Cat. Pd(OAc)_2 \xrightarrow{\text{KOAc, n-Bu_4NCl}} Ar \xrightarrow{\text{O}} 75\% - 92\%$$
Scheme 2
$$DMF, 20 \circ C \xrightarrow{\text{O}} 75\% - 92\%$$

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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