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On the Efficiency of Tetraalkylammonium Salts in Heck Type Reactions

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Abstract: Under appropriate conditions, tetraalkylammonium hydrogensulfate can be just as efficient as tetraalkylammonium chloride or bromide for facilitating Heck-type reactions. Moreover, an appropriate selection of the [Pd / Base / QX] catalyst system can allow this type of reactions to be efficiently realised at will, in a strictly anhydrous medium, in a water-organic solvent mixture or in water alone. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The palladium-catalysed reaction of organic halides with alkenes[1] (Heck reaction) has now become a well-established synthetically important method for forming carbon-carbon bonds. Although it is some time since these reactions were first reported,[2] their application in organic synthesis has become widespread[3] only during the last decade. A number of approaches have been introduced, permitting a great extension of the synthetic applicability of this type of reaction.[3] In particular, tetraalkylammonium salts have been highly successful in enhancing the reactivity and selectivity of inter- and intramolecular Heck-type reactions.[3a,3b,3d] However, while tetraalkylammonium chloride and bromide have been extensively used,[4,5] tetraalkylammonium hydrogensulfate has not been found very effective,[4a,n,o] although its addition has sometimes been beneficial when compared to the reaction performed in the absence of a quaternary ammonium salt.[4w] In our continuing study of the impact of tetraalkylammonium salts in Heck-type reactions, we have undertaken a thorough investigation of the phenylation of methyl acrylate in order to determine the optimal conditions for their use.

Our preliminary observations have been reported.[6] The full results are described in this paper whose objective is to underline the various influences which can greatly affect the efficiency of quaternary ammonium salts in Heck-type reactions.

RESULTS

The reaction of iodobenzene with methyl acrylate (Equation 1) has been systematically studied in the presence of various catalyst systems formed by catalytic amounts of palladium acetate, (with or without triphenylphosphine), and a tetraalkylammonium salt in combination with an inorganic base (an alkali metal hydrogencarbonate, acetate or carbonate) or an organic base (trialkylamine). Although catalytic amounts of tetraalkylammonium salt (QX) can be beneficial, the reaction rate has been shown[4a] to be linearly proportional to the amount of added QX; a stoichiometric quantity of QX has thus been used in all reactions.

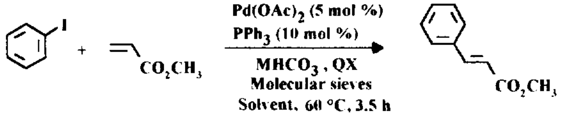
Reaction times have been chosen in order to compare reactions having very different rates; the maximum yields are thus reached well before the indicated reaction times when tetraalkylammonium salt is used in appropriate conditions. Similarly, 5 mole % of palladium catalyst have been used in all reactions although much smaller amounts can be employed when reactions are performed under optimal conditions. Conversion values are not indicated in the various Tables as they are very similar to the yield values: where observed, the low yields are not due to the formation of secondary products.

(1)

A) Reactions performed in the presence of the [Pd / $MHCO_3$ / QX] catalyst system

Results obtained when using an alkali metal hydrogencarbonate as the inorganic base are given in Tables 1 and 2 which detail respectively the reactions performed in the presence and absence of phosphine ligand.

Table 1: Effects of Molecular Sieves and Tetraalkylammonium Salts on Palladium-catalysed Arylation of Methyl Acrylate in the Presence of Alkali Metal Hydrogencarbonate as the Base and Triphenylphosphine as Ligand.[a)]



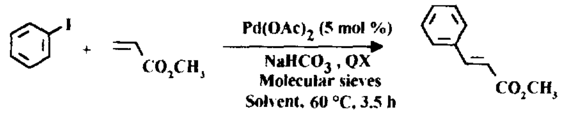
Entry	Base	Solvent [b)]	QX	Molecular sieves	Yield (%) [c)]
1	$NaHCO_3$	CH_3CN	-	no	10
2	$NaHCO_3$	CH_3CN	n-$Bu_4NCl.xH_2O$ [d)]	no	57
3	$NaHCO_3$	CH_3CN	n-Bu_4NCl [e)]	no	70
4	$NaHCO_3$	CH_3CN	n-Bu_4NCl [e)]	yes	99
5	$NaHCO_3$	CH_3CN	n-Bu_4NHSO_4	yes	98
6	$KHCO_3$	CH_3CN	n-Bu_4NHSO_4	yes	99
7	$KHCO_3$	CH_3CN	n-Bu_4NBr	yes	67
8	$NaHCO_3$	DMF	-	yes	16
9	$NaHCO_3$	DMF	n-Bu_4NCl [e)]	yes	99
10	$NaHCO_3$	DMF	n-Bu_4NHSO_4	yes	99
11	$KHCO_3$	DMF	n-Bu_4NHSO_4	yes	93
12	$KHCO_3$	DMF	n-Bu_4NBr	yes	80

a) See General Procedure (Method 1). b) HPLC grade solvents. c) determined by GLC against an internal standard. d)"Tetrabutylammonium chloride hydrate 98%" from Aldrich. e) "Tetra-n-butylammonium chloride 98%" from Lancaster.

Reaction of iodobenzene with methyl acrylate can indeed be improved by addition of hydrated tetra-n-butylammonium chloride[7] (Table 1, entry 2 compared to entry 1), but better results were obtained when using dry tetra-n-butylammonium chloride,[7] and when effecting the reaction in the presence of 4Å molecular sieves, whether the solvent is acetonitrile (entries 3, 4) or N,N-dimethylformamide (entry 9). Under these *strictly unhydrous conditions*, tetra-n-butylammonium hydrogensulfate, generally believed to be inefficient, proved just as effective as tetra-n-butylammonium chloride, whether the inorganic base was sodium or potassium hydrogencarbonate (entries 5, 6, 10 and 11). Remarkably, tetra-n-butylammonium hydrogensulfate can be even more efficient than tetra-n-butylammonium bromide under these conditions, whether the solvent is acetonitrile (entry 6 compared to entry 7) or N,N-dimethylformamide (entry 11 compared to entry 12).

Comparison of Tables 1 and 2 reveals the influence of phosphine ligand. In the absence of triphenylphosphine (Table 2), while tetra-n-butylammonium chloride in association with sodium hydrogencarbonate remains consistently highly efficient for improving the reaction, less predictable results were obtained for tetra-n-butylammonium hydrogensulfate and tetra-n-butylammonium bromide. However, although less successful in acetonitrile (Table 2, entry 3 compared to entry 2), tetra-n-butylammonium hydrogensulfate remains highly effective (as effective as n-Bu$_4$NCl) in N,N-dimethylformamide (entry 7 compared to entry 6). Rather surprisingly, tetra-n-butylammonium bromide is less beneficial than tetra-n-butylammonium hydrogensulfate when it is used in association with an alkali metal hydrogencarbonate, whether the reaction is performed in acetonitrile (entry 4 compared to entry 3) or in DMF (entry 8 compared to entry 7).

Table 2: Effect of Tetraalkylammonium Salts on Palladium-catalysed Arylation of Methyl Acrylate in the Presence of Alkali Metal Hydrogencarbonate as the Base and *in the Absence of Phosphine Ligand.* [a]



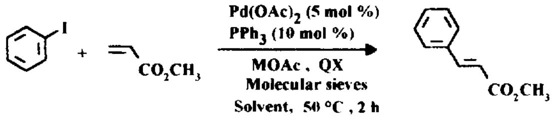
Entry	Solvent	QX	Yield (%) [b]
1	CH$_3$CN	-	3
2	CH$_3$CN	n-Bu$_4$NCl [c]	90
3	CH$_3$CN	n-Bu$_4$NHSO$_4$	45
4	CH$_3$CN	n-Bu$_4$NBr	20
5	DMF	-	5
6	DMF	n-Bu$_4$NCl [c]	99
7	DMF	n-Bu$_4$NHSO$_4$	99
8	DMF	n-Bu$_4$NBr	62

a) See General Procedure (Method I, with 4Å molecular sieves). b) determined by GLC against an internal standard. c) "Tetra-n-butylammonium chloride 98%" from Lancaster.

B) Reactions performed in the presence of the [Pd / MOAc / QX] catalyst system

Results obtained when performing the reactions in the presence of the [Pd / MOAc / QX] catalyst system, with or without triphenylphosphine, are given in Tables 3 and 4. The beneficial effect of molecular sieves on the efficiency of quaternary ammonium salts used in combination with an alkali metal acetate is clearly shown in Table 3. Better yields were obtained when performing the reactions under *strictly anhydrous conditions*, even when tetraalkylammonium chloride is involved (entry 3 compared to entry 2). It is also of interest to note that tetra-n-butylammonium hydrogensulfate can then be quite effective as well, whether the inorganic base is potassium or sodium acetate and whether the solvent is acetonitrile (entries 5-6) or N,N-dimethylformamide (entries 9-10).

Table 3. Effects of Tetraalkylammonium Salts and Molecular Sieves on Palladium-catalysed Arylation of Methyl Acrylate in the Presence of Alkali Metal Acetate as the Base and Triphenylphosphine as Ligand.[a]



Entry	Base	Solvent [b]	QX	4Å Molecular sieves	Yield (%) [c]
1	KOAc	CH$_3$CN	-	no	10
2	KOAc	CH$_3$CN	n-Bu$_4$NCl.xH$_2$O [d]	no	48
3	dried KOAc	CH$_3$CN	n-Bu$_4$NCl [e]	yes	92
4	dried KOAc	CH$_3$CN	n-Bu$_4$NBr	yes	95
5	dried KOAc	CH$_3$CN	n-Bu$_4$NHSO$_4$	yes	86
6	dried NaOAc	CH$_3$CN	n-Bu$_4$NHSO$_4$	yes	80
7	dried KOAc	DMF	-	no	15
8	dried KOAc	DMF	n-Bu$_4$NCl [e]	yes	94
9	dried KOAc	DMF	n-Bu$_4$NHSO$_4$	yes	92
10	dried NaOAc	DMF	n-Bu$_4$NHSO$_4$	yes	80
11	n-Bu$_4$NOAc	DMF	-	no	60
12	n-Bu$_4$NOAc	DMF	-	yes	98
13	KOAc	wet DMF	n-Bu$_4$NCl.xH$_2$O [d]	no	29
14	dried KOAc	DMF	n-Bu$_4$NCl.xH$_2$O [d]	no	94

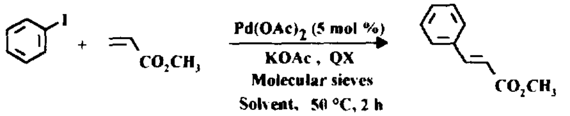
a) See General Procedure (Method I). b) HPLC grade solvents. c) determined by GLC against an internal standard. d) "Tetrabutylammonium chloride hydrate 98%" from Aldrich. e) "Tetrabutylammonium chloride 98%" from Lancaster.

The advantage of *strictly anhydrous conditions* was confirmed when performing the reaction in the presence of commercial tetra-n-butylammonium acetate. This hygroscopic salt proved clearly more effective for accelerating the reaction when used in association with molecular sieves (Table 3, entry 12 compared to entry 11).

Additionally, the inhibiting effect of water has also been evidenced by a net decrease in the reaction yield observed when using hydrated tetra-n-butylammonium chloride[7] and performing the reaction in wet N,N-dimethylformamide (entry 13 compared to entry 8). The fact that good yields can still be obtained when effecting the reaction in dry DMF, in the presence of hydrated tetra-n-butylammonium chloride (entry 14) can be explained by the ability of dried potassium acetate in excess to serve as a dehydrating agent.

In the absence of triphenylphosphine (Table 4), use of tetraalkylammonium chloride or bromide in combination with an alkali metal acetate remains beneficial, particularly in DMF (entries 6-7 compared to entries 1-3) while low yields were obtained with tetraalkylammonium hydrogensulfate (entries 4 and 8).

Table 4. Effect of Tetraalkylammonium Salts on Pd-catalysed Arylation of Methyl Acrylate in the Presence of Potassium Acetate as the Base and *in the Absence of Phosphine Ligand.* [a]



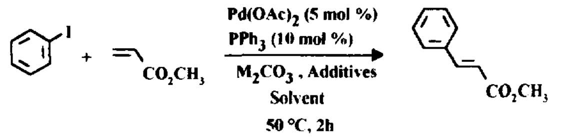
Entry	Solvent	QX	Yield (%) [b]
1	CH_3CN	-	2
2	CH_3CN	n-Bu_4NCl [c]	77
3	CH_3CN	n-Bu_4NBr	68
4	CH_3CN	n-Bu_4NHSO_4	2
5	DMF	-	2
6	DMF	n-Bu_4NCl [c]	99
7	DMF	n-Bu_4NBr	99
8	DMF	n-Bu_4NHSO_4	10

a) See General Procedure (Method I, with 4Å molecular sieves). b) determined by GLC against an internal standard. c) "Tetra-n-butylammonium chloride 98%" from Lancaster.

C) Reactions performed in the presence of the [Pd / M_2CO_3 / QX] catalyst system

Water has been observed to have the opposite effect on the efficiency of quaternary ammonium salts when the latter are used in combination with an alkali metal carbonate, rather than an alkali metal hydrogencarbonate or an alkali metal acetate. As shown in Table 5, the presence of water is necessary for the quaternary ammonium salt to be effective, independently of the nature of its anion. For reactions performed in a dry solvent (acetonitrile or DMF), while hydrated tetra-n-butylammonium chloride[7] showed an important accelerating effect, (Table 5, entries 2 and 14), neither tetra-n-butylammonium hydrogensulfate nor tetra-n-butylammonium bromide had any significant influence (entries 3 and 4). Surprisingly, non hydrated tetra-n-butylammonium chloride[7] was also ineffective (entries 5 and 15). In net contrast, reactions performed in aqueous acetonitrile or aqueous DMF were greatly accelerated upon addition of a quaternary ammonium salt, whether this salt was a chloride, a bromide or a hydrogensulfate (Table 5, entries 7-9 and 16-18).

Table 5. Effect of Water on the Efficiency of the [Pd / M_2CO_3 / QX] Catalyst System in Pd-catalysed Arylation of Methyl Acrylate Performed in the Presence of Phosphine Ligand.[a]



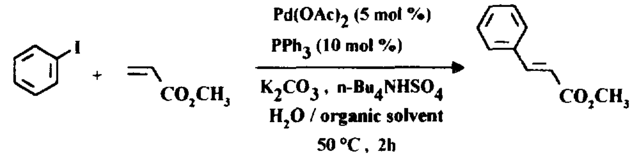
Entry	Base	Solvent	Additives	Yield (%)[b]
1	K_2CO_3	CH_3CN [c]	-	15
2	K_2CO_3	CH_3CN [c]	n-$Bu_4NCl.xH_2O$ [d]	97
3	K_2CO_3	CH_3CN [c]	n-Bu_4NHSO_4	12
4	K_2CO_3	CH_3CN [c]	n-Bu_4NBr	5
5	K_2CO_3	CH_3CN [c]	n-Bu_4NCl [e]	10
6	K_2CO_3	H_2O - CH_3CN [f]	-	5
7	K_2CO_3	H_2O - CH_3CN [f]	n-Bu_4NCl [e]	96
8	K_2CO_3	H_2O - CH_3CN [f]	n-Bu_4NHSO_4	97
9	K_2CO_3	H_2O - CH_3CN [f]	n-Bu_4NBr	96
10	K_2CO_3	H_2O - CH_3CN [f]	LiCl	15
11	K_2CO_3	H_2O - CH_3CN [f]	KCl	15
12	K_2CO_3	CH_3CN [c]	n-$Bu_4NCl.xH_2O$ [d] (+$MgSO_4$)	1
13	K_2CO_3	DMF [c]	-	45
14	K_2CO_3	DMF [c]	n-$Bu_4NCl.xH_2O$ [d]	94
15	K_2CO_3	DMF [c]	n-Bu_4NCl [e]	2
16	K_2CO_3	H_2O - DMF [f]	n-Bu_4NCl [e]	99
17	K_2CO_3	H_2O - DMF [f]	n-Bu_4NBr	99
18	K_2CO_3 or Na_2CO_3	H_2O - DMF [f]	n-Bu_4NHSO_4	98

a) See General Procedure (Method II). b) determined by GLC against an internal standard. c) ACS grade solvents. d) "Tetrabutylammonium chloride hydrate 98%" from Aldrich. e) "Tetra-n-butylammonium chloride 98%" from Lancaster. f) (1:10) mixture of water and organic solvent (CH_3CN or DMF).

The beneficial effect of tetraalkylammonium salt is thus more dependent upon its onium cation than upon its anion. This is consistent with the fact that addition of an alkali metal chloride has no effect (entries 10 and 11).

The crucial role of water is confirmed by the fact that hydrated tetra-n-butylammonium chloride[7] loses completely its effectiveness when it is used in the presence of a dehydrating agent such as magnesium sulfate (entry 12 compared to entry 2). Addition of dry tetra-n-butylammonium chloride[7] can even have an inhibiting effect (entry 15 compared to entry 13). This might be due to a dehydrating effect of tetra-n-butylammonium chloride.[8]

The presence of water is thus necessary for tetraalkylammonium salts to be efficient when they are used in combination with an alkali metal carbonate. A detailed study of the influence of water has been realised for the reaction effected in the presence of a combination of potassium carbonate and tetra-n-butylammonium hydrogensulfate (Equation 2). Water was introduced into the reaction medium in increasing proportions, while the yields were determined after a constant reaction time (2h). As illustrated in Figure 1, very low yields are obtained when reactions are performed in ACS or HPLC grade solvents (either acetonitrile or N,N-dimethylformamide).



(2)

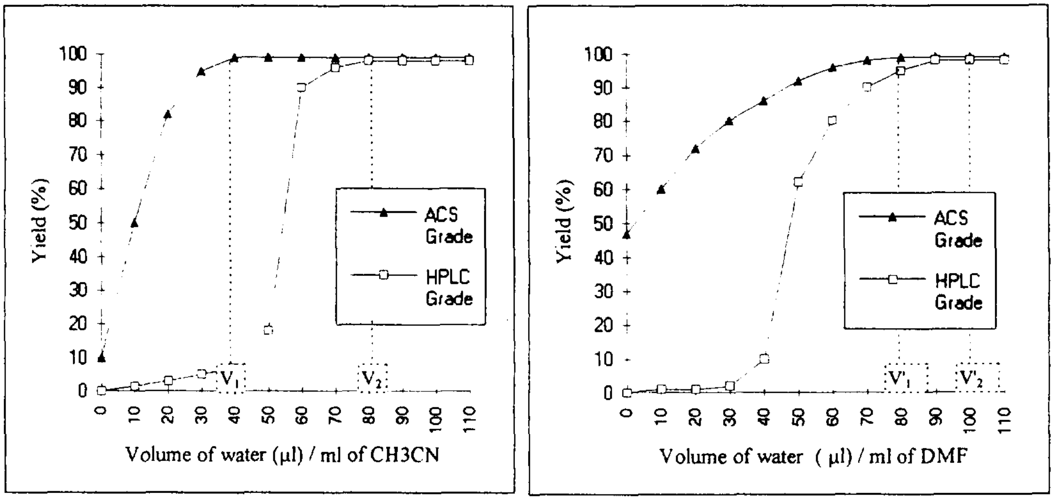


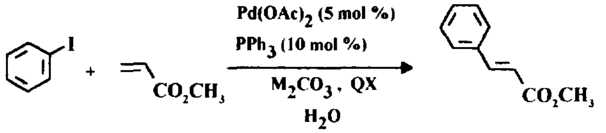
Figure 1. Effect of water on Arylation of Methyl Acrylate in the Presence of the [Pd / K_2CO_3 / n-Bu_4NHSO_4] catalyst system (Equation 2).

Yields are seen to increase with an increasing proportion of water up to the minimum quantity necessary for an optimum yield (v_1 and v'_1 for CH_3CN and DMF respectively).

When more strictly anhydrous solvent is employed (HPLC rather than ACS grade solvents), a greater amount of water ($v_2 > v_1$; $v'_2 > v'_1$) has been found to be necessary.

Results presented in Table 6 clearly show that reactions can even be efficiently realised under mild conditions (50 °C or room temperature), in water, without organic solvent, provided that they are effected in the presence of an alkali metal carbonate and a quaternary ammonium salt, whether QX is a chloride, a bromide or a hydrogensulfate.

Table 6. Pd-catalysed Arylation of Methyl Acrylate in Water, Without Organic Solvent.[a)]

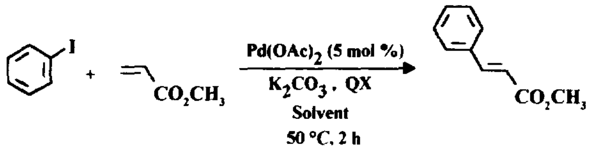


Entry	Base	QX	Temperature / Time	Yield (%)[b)]
1	K_2CO_3	-	50 °C / 2h	5
2	K_2CO_3	n-Bu_4NCl [c)]	50 °C / 2h	98
3	K_2CO_3	n-Bu_4NBr	50 °C / 2h	95
4	K_2CO_3 or Na_2CO_3	n-Bu_4NHSO_4	50 °C / 2h	95 - 98
5	K_2CO_3	n-Bu_4NCl [c)]	25 °C / 24h	98
6	K_2CO_3	n-Bu_4NBr	25 °C / 24h	80
7	K_2CO_3	n-Bu_4NHSO_4	25 °C / 24h	98

a) See General Procedure (Method III). b) determined by GLC against an internal standard. c) hydrated or non hydrated tetra-n-butylammonium chloride.

Comparison of Tables 5 and 7 reveals the influence of phosphine ligand in reactions performed in the presence of the [Pd / M_2CO_3 / QX] catalyst system. In the absence of triphenylphosphine (Table 7), n-Bu_4NCl consistently has an important accelerating effect, whether the solvent employed is aqueous CH_3CN (entry 2), aqueous DMF (entry 6) or neat water (entry 10). In net contrast, the effectiveness of n-Bu_4NBr and n-Bu_4NHSO_4 has been observed to be greatly dependent upon the nature of the solvent. It is particularly noteworthy that addition of n-Bu_4NHSO_4 can still be highly advantageous even when reactions are performed in the absence of phosphine ligand. Its accelerating effect is greater in aqueous CH_3CN (entry 4) than in aqueous DMF (entry 8) or in water (entry 12), while the inverse has been observed for n-Bu_4NBr (entries 3, 7 and 11).

Table 7. Effects of Tetraalkylammonium Salts and Solvent on Pd-catalysed Arylation of Methyl Acrylate in the Presence of Potassium Carbonate as the Base and *in the Absence of Phosphine Ligand.*[a]



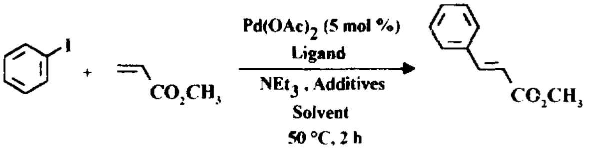
Entry	Solvent	QX	Yield (%)[b]
1	H_2O - CH_3CN[c]	-	2
2	H_2O - CH_3CN[c]	n-Bu_4NCl[d]	77
3	H_2O - CH_3CN[c]	n-Bu_4NBr	55
4	H_2O - CH_3CN[c]	n-Bu_4NHSO_4	94
5	H_2O - DMF[c]	-	0
6	H_2O - DMF[c]	n-Bu_4NCl[d]	98
7	H_2O - DMF[c]	n-Bu_4NBr	98
8	H_2O - DMF[c]	n-Bu_4NHSO_4	44
9	H_2O	-	0
10	H_2O	n-Bu_4NCl[d]	92
11	H_2O	n-Bu_4NBr	92
12	H_2O	n-Bu_4NHSO_4	70

a) See General Procedure (Method II). b) determined by GLC against an internal standard. c) 1:10 mixture of water and organic solvent (CH_3CN or DMF). d) hydrated or non hydrated tetra-n-butylammonium chloride.

D) Reactions performed in the presence of the [Pd / NR_3 / QX] catalyst system

Results obtained when using triethylamine as the base are given in Table 8. Only slightly beneficial effects were observed upon addition of alkali metal chloride (entries 2-3 compared to entry 1) and the presence of triphenylphosphine seems necessary (entry 4 compared to entries 2-3). In contrast, addition of tetraalkylammonium chloride, bromide or hydrogensulfate provokes a net increase of the reaction rate, especially when reactions are conducted in the absence of triphenylphosphine (entries 7-9 compared to entries 5-6). It is worth noting, however, that these increases are generally less important than those observed in reactions using QX in association with an inorganic base (Tables 1-7). Although strictly anhydrous conditions do not seem necessary, conducting the reactions in a mixture of organic solvent and water results in lower yields (Table 8, entry 10 compared to entry 6, entry 11 compared to entries 7 and 8).

Table 8. Pd-catalysed Arylation of Methyl Acrylate in the Presence of Triethylamine as the Base. [a]



Entry	Solvent [b]	Ligand [c]	Additives	Yield (%) [d]
1	CH_3CN or DMF	PPh_3	-	3 - 5
2	CH_3CN	PPh_3	KCl	8
3	CH_3CN	PPh_3	LiCl	22
4	CH_3CN or DMF	-	LiCl or KCl	5
5	CH_3CN	PPh_3	$n\text{-}Bu_4NCl$	55
6	CH_3CN	PPh_3	$n\text{-}Bu_4NHSO_4$	55
7	CH_3CN or DMF	-	$n\text{-}Bu_4NCl$	70 - 75
8	CH_3CN	-	$n\text{-}Bu_4NBr$	74
9	CH_3CN	-	$n\text{-}Bu_4NHSO_4$	79
10	H_2O / CH_3CN [e]	PPh_3	$n\text{-}Bu_4NHSO_4$	35
11	H_2O / CH_3CN [e]	-	$n\text{-}Bu_4NCl$ or $n\text{-}Bu_4NBr$	13 - 15

a) See General Procedure (Method IV). b) HPLC grade solvent. c) 10 mol % of triphenylphosphine is used when indicated. d) determined by GLC against an internal standard. e) 1:10 mixture of water and organic solvent is used.

DISCUSSION

Optimum influence of tetraalkylammonium salts. Appropriate conditions are necessary for obtaining the most efficient use of tetraalkylammonium salts, whatever the nature of their anion. The optimum conditions can be very different (even opposite), depending upon the nature of the base.

The presence of water has been observed to have a crucial influence (which can be highly detrimental or beneficial) when a tetraalkylammonium salt is used in association with an inorganic base. When the latter is an alkali metal hydrogencarbonate or acetate, strictly anhydrous conditions are necessary for obtaining the best yields as shown in Tables 1- 4. In net contrast, the presence of water is necessary when using alkali metal carbonate (Tables 5-7).

When employed in association with an amine, tetraalkylammonium salts have a relatively smaller impact (Table 8 compared to Tables 1-7) although their presence can be advantageous under appropriate conditions.

Comparisons between QCl, QBr and $QHSO_4$ in reactions performed in the presence of phosphine ligand.

The results reported herein clearly show that addition of quaternary ammonium salts can provoke an important increase in the reaction rate, regardless of the nature of their anion. Indeed, tetraalkylammonium hydrogensulfate in association with an alkali metal hydrogencarbonate or acetate can be just as efficient as tetraalkylammonium chloride or bromide in reactions performed in the presence of triphenylphosphine and 4Å molecular sieves (Tables 1 and 3). When the base is an alkali metal carbonate, the beneficial effect of tetraalkylammonium hydrogensulfate is also very similar to that of tetraalkylammonium chloride or bromide in reactions performed in the presence of triphenylphosphine and water (Tables 5 and 6). When amine is used as the base, similar beneficial effects have also been observed using tetraalkylammonium hydrogensulfate or tetraalkylammonium halide (Table 8, entries 5-6).

The accelerating effect of quaternary ammonium salts (QX) in Heck-type reactions is thus due more to their quaternary ammonium cation than to their anion. In accordance with these results, addition of alkali metal chloride (MCl) cannot significantly accelerate these reactions, whether the base involved is an inorganic base ($MHCO_3$, MOAc or M_2CO_3) or an organic base (amine).

Comparisons between QCl, QBr and $QHSO_4$ in reactions performed in the absence of phosphine ligand.

In reactions performed *without phosphine ligand*, tetraalkylammonium chloride proved consistently more effective than tetraalkylammonium bromide or tetraalkylammonium hydrogensulfate whose efficiencies are more variable. However, QBr and $QHSO_4$ can still be quite effective in various cases, and interestingly, their efficiencies can be complementary.

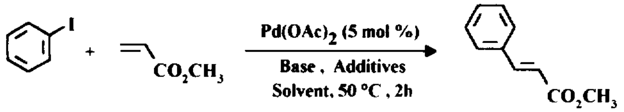
In combination with an alkali metal acetate (Table 4), QBr is preferable to $QHSO_4$, whether the solvent is CH_3CN or DMF. Remarkably, however, when alkali metal hydrogencarbonate is used as base, $QHSO_4$ is largely more effective than QBr, especially in DMF where it is found to be at least as efficient as QCl (Table 2, entry 7 compared to entry 6). When associated with an alkali metal carbonate (Table 7), both $QHSO_4$ and QBr can have an important promoting effect in the appropriate solvent system (entries 3-4, 7-8 and 11-12). In association with an amine (Table 8), QCl, QBr and $QHSO_4$ all have similar beneficial effects (entries 5-6, 7-9).

In net contrast, use of alkali metal chloride (MCl) results only in poor yields, whether MCl is in combination with an organic base (amine) or an inorganic base ($MHCO_3$, MOAc, M_2CO_3), and whatever the nature of the solvent (Tables 8 and 9).

It is worth noting that in cases where $QHSO_4$ is moderately or poorly efficient (Table 2, entry 3; Table 4, entry 8; Table 7, entry 8), use of a combination of LiCl and $QHSO_4$ can provoke a great increase in the reaction rate (Table 9, entries 3, 5 and 7). An exchange such as that outlined in equation (3) may then be involved.

$$Q^+ HSO_4^- + M^+ Cl^- \longrightarrow Q^+ Cl^- + M^+ HSO_4^- \tag{3}$$

Table 9. Pd-catalysed Arylation of Methyl Acrylate: Effect of Additives *in the Absence of Phosphine Ligand.*



Entry	Base	Solvent[a]	Additives[b]	Yield (%)[c]
1	$NaHCO_3$[d]	CH_3CN	-	3
2	$NaHCO_3$[d]	CH_3CN	LiCl	3
3	$NaHCO_3$[d]	CH_3CN	$n\text{-}Bu_4NHSO_4$ / LiCl	84
4	KOAc[d]	DMF	LiCl	3
5	KOAc[d]	DMF	$n\text{-}Bu_4NHSO_4$ / LiCl	82
6	K_2CO_3[e]	H_2O - DMF[f]	LiCl	9
7	K_2CO_3[e]	H_2O - DMF[f]	$n\text{-}Bu_4NHSO_4$ / LiCl	96

a) HPLC grade organic solvent. b) When involved, additives: $n\text{-}Bu_4NHSO_4$ (1 equivalent) and/or LiCl (1.5 equivalent). c) determined by GLC against an internal standard. d) See General Procedure (Method I). e) See General Procedure (Method II). f) 1:10 mixture of water and organic solvent.

Mechanistic Aspects. Although the precise mechanism of the Heck reaction is far from being fully understood, it is well known to result from several elementary steps which are a) oxidative addition, b) double bond insertion, c) β-hydride elimination and d) regeneration of zerovalent palladium catalyst (Figure 2).

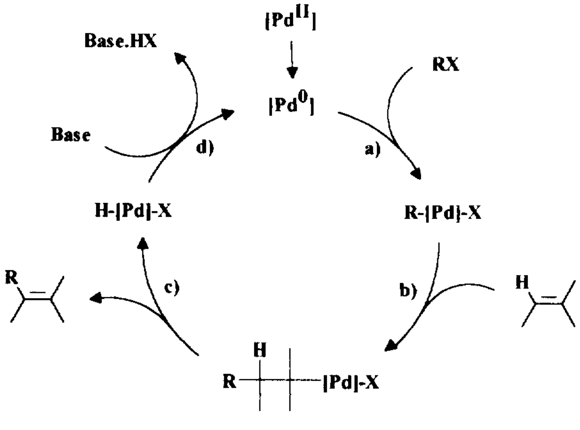


Figure 2. Basic steps of the palladium-catalyzed reaction of aryl- or alkenyl halides with alkenes (Heck reaction).

All the results [3a,3d,4,5] collected to date, which clearly show an important influence of QX on both the rate and selectivity of Heck-type reactions, strongly suggest that QX may interfere in more than one elementary step of this type of reaction.

A tentative rationalization of the *accelerating effect* of QX can be proposed from the results reported herein. The consistently higher promoting efficiency of QCl (compared to QBr and $QHSO_4$), *in the absence of triphenylphosphine*, suggests that QCl might have two roles, in contrast to QBr or $QHSO_4$. It might act (i) as a stabilizing agent by its chloride anion,[9, 10] *when there is no phosphine ligand* in the reaction mixture, and (ii) as an accelerating agent by its onium cation. However, the combined facts that i) alkali metal chlorides are inefficient in enhancing the reaction rate and ii) $QHSO_4$ can be highly effective, even in the absence of phosphine ligand (Tables 2, 4 and 7) indicate that stabilization by chloride anion cannot be the major factor which could explain the important accelerating effect of tetraalkylammonium salts. We propose instead an *assistance of tetraalkylammonium salts in the regeneration of zerovalent palladium catalyst* to explain their promoting influence.

When inorganic base is involved, the results obtained (Tables 1-7) are consistent with the so-called "solid-liquid phase transfer catalysis".[11] The role of water (which can be detrimental or beneficial) can be explained by comparison with many solid-liquid phase transfer catalysed organic processes, in which the importance of water has been well evidenced, and in which solid-liquid phase transfer can, in some cases, be in fact, a liquid-liquid phase transfer catalysis.[11] By analogy with solid-liquid phase transfer catalysed organic processes,[11] several possible mechanisms could be envisaged for the regeneration of the zerovalent palladium catalyst. An extraction mechanism, as outlined in scheme 1, would involve an exchange process between the phase transfer agent (QX) and the inorganic salt (MY), prior to deprotonation of hydridopalladium halide by QY in the organic phase, which regenerates the Pd(0) catalyst.

$$Q^+X^- + M^+Y^- \longrightarrow Q^+Y^- + M^+X^-$$

$$Q^+Y^- + [\mathrm{H\text{-}Pd\text{-}X'}] \longrightarrow YH + QX' + [Pd^0]$$

Scheme 1

An interfacial mechanism (scheme 2) would imply a deprotonation of hydridopalladium halide at the interphase, followed by extraction by QX and regeneration of Pd(0) catalyst in the organic phase.

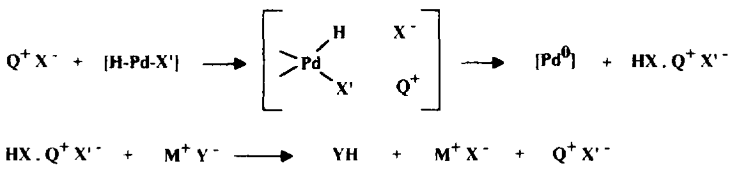
$$M^+Y^- + [\mathrm{H\text{-}Pd\text{-}X'}] \longrightarrow YH + [PdX']^-\,M^+$$

$$[PdX']^-\,M^+ + Q^+X^- \longrightarrow [PdX']^-\,Q^+ + M^+X^-$$

$$[PdX']^-\,Q^+ \longrightarrow [Pd^0] + Q^+X'^-$$

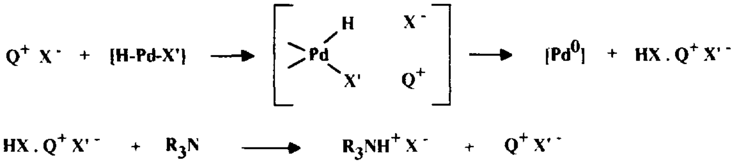
Scheme 2

A nucleophilic catalysis mechanism (scheme 3) could also be involved, implying a direct interaction through hydrogen bonding between hydridopalladium halide and tetraalkylammonim halide for promoting the regeneration of Pd(0) catalyst, with formation of HX.QX' adduct which is neutralized at the interphase by the inorganic base.



Scheme 3

When an organic base (amine) is used, "phase transfer" catalysis can not be invoked, but the accelerating effect of tetraalkylammonium salt can still be interpreted as an assistance of QX in the decomposition of the hydride palladium species into the zerovalent palladium catalyst. A nucleophilic catalysis mechanism, as depicted in scheme 4 might still occur, involving a direct interaction through hydrogen bonding between hydridopalladium halide and tetraalkylammonim halide for promoting the regeneration of Pd(0) catalyst with formation of a HX.QX' adduct which would react with trialkylamine.



Scheme 4

CONCLUSION

Several useful conclusions can be drawn from this study. Appropriate conditions are necessary for obtaining the maximum effect of tetraalkylammonium salts in Heck-type reactions, whatever the nature of their anion. Under suitable conditions, tetraalkylammonium hydrogensulfate can be just as efficient as tetraalkylammonium chloride or bromide for facilitating this type of reactions, indicating that the accelerating effect of tetraalkylammonium salts is mainly dependent upon their quaternary ammonium cation. Water can have a detrimental or beneficial effect on the efficiency of QX, depending on the nature of the base employed. And last, but not least, appropriate selection of the [Pd / Base / QX] catalyst system can allow Heck-type reactions to be efficiently realised at will (according to specific needs or practical convenience), in a strictly anhydrous medium, in a water-organic solvent mixture or in water alone, without organic solvent.

The above results should enhance the usefulness of tetraalkylammonium salts in further extending the application of Heck-type reactions in organic synthesis.

EXPERIMENTAL SECTION

General methods. All reactions were routinely carried out under an inert (nitrogen or argon) atmosphere, in a Schlenk tube or a three-necked flask fitted with a rubber septum, equipped with magnetic stirring and a nitrogen inlet. Gas chromatographic analyses were carried out on a GIRDEL DELSI 330 equipped with a capillary column OV 101, using hydrogen flame ionisation detection. Peak areas were measured by using the internal integration with tridecane as the standard and were corrected to accomodate different detector response factors.

Materials. Palladium acetate, triphenylphosphine, methyl acrylate, phenyl iodide, tetra-n-butylammonium chloride hydrate, tetra-n-butylammonium bromide and tetra-n-butylammonium hydrogen sulfate were purchased from Aldrich and anhydrous tetraalkylammonium chloride was bought from Lancaster. N,N-Dimethylformamide or acetonitrile of HPLC or ACS grade were obtained from Aldrich and used without further purification.

General procedure.

Method I: Reactions performed in the presence of alkali metal hydrogencarbonate or acetate. A suspension, in the solvent indicated (1 mL / 1 mmol of PhI), of alkali metal hydrogencarbonate or acetate (2.5 equivalent), tetraalkylammonium salt (1 equivalent when indicated) and crushed 4Å molecular sieves (0.4 g / 1 mmol of PhI when indicated) was stirred for 15 min. Triphenylphosphine (0.10 equivalent when indicated), iodobenzene (1 equivalent) and methyl acrylate (2 equivalents) were then successively added and the suspension stirred for another 15 min before addition of $Pd(OAc)_2$ (0.05 equivalent). The mixture was then maintained at the required temperature for the time indicated in Tables. After cooling to room temperature, tridecane (GLC internal standard), water and ether were then added. Yields were determined by GLC analysis of the ethereal phase.

Method II: Reactions performed in the presence of alkali metal carbonate. A suspension, in acetonitrile or N,N-dimethylformamide (1 mL / 1 mmol of PhI) and water (in the proportion indicated), of potassium or sodium carbonate (2.5 equivalents) and additives (tetraalkylammonium or alkali metal salt, 1 equivalent) was well stirred for about 20 min. Triphenylphosphine (0.10 equivalent when indicated), iodobenzene (1 equivalent), methyl acrylate (2 equivalents) were then added and the suspension stirred for another 15 min before addition of $Pd(OAc)_2$ (0.05 equivalent). The mixture was heated at 50 °C for 2h, then cooled to room temperature and tridecane (GLC internal standard), water and ether were added. Yields were determined by GLC analysis of the ethereal phase.

Method III: Reactions in water. A mixture of iodobenzene (1 equivalent), methyl acrylate (2 equivalents) and triphenylphosphine (0.10 equivalent) was well stirred for about 15 min before addition of $Pd(OAc)_2$ (0.05 equivalent). After another 15 min of stirring, water (1 mL / 1mmol of PhI), potassium carbonate (2.5 equivalents) and tetraalkylammonium salt (1 equivalent when indicated) were successively added. Stirring was continued at the required temperature for the time indicated in Table 6. The mixture was then cooled to room temperature before addition of tridecane (GLC internal standard), water and ether. Yields were determined by GLC analysis of the ethereal phase.

Method IV: Reactions performed in the presence of triethylamine. A mixture, in acetonitrile or N,N-dimethylformamide (1 mL / 1 mmol of PhI) and water (when indicated), of iodobenzene (1 equivalent), methyl acrylate (2 equivalents), triphenylphosphine (0.10 equivalent when indicated), triethylamine (2.5 equivalents), and additives (tetraalkylammonium salt and/or alkali metal salt; 1 equivalent when indicated) was well stirred for about 10 min before addition of $Pd(OAc)_2$ (0.05 equivalent). The mixture was stirred for 2h at 50 °C, then cooled to room temperature and tridecane (GLC internal standard), water and ether were added. Yields were determined by GLC analysis of the ethereal phase.

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