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# Tetraalkylammonium Salts in Heck-type Reactions Using an Alkali Metal Hydrogen carbonate or an Alkali Metal Acetate as the Base.

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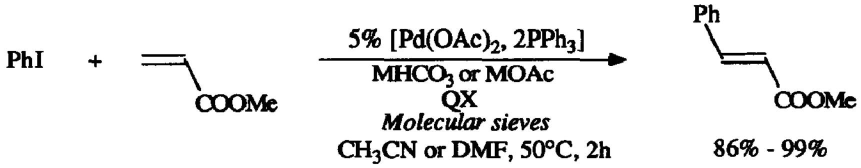
**Abstract:** When used in combination with an alkali metal hydrogen carbonate or an alkali metal acetate, various tetraalkylammonium salts can greatly promote Heck-type reactions, independently of the nature of their anion, provided that the reactions are performed in the presence of molecular sieves. In particular, tetra-n-butylammonium hydrogen sulfate is just as effective as tetra-n-butylammonium chloride under these conditions.

Tetraalkylammonium chloride and bromide have been highly useful for increasing the yield and selectivity of Heck-type reactions,[1] in contrast to tetraalkylammonium hydrogen sulfate.[2] This could suggest that the beneficial effect of quaternary ammonium salt (QX) is more due to its anion $X^-$ than to its cation $Q^+$, especially since chloride anions can be ligands for zerovalent palladium complexes, even in the presence of triphenylphosphine.[3-6]

We have recently shown[7] that tetra-n-butylammonium hydrogen sulfate, in combination with an alkali metal carbonate, can very efficiently promote Heck-type reactions, provided that the latter are performed in the presence of water.

We wish to report herein (i) that $n\text{-Bu}_4\text{NHSO}_4$ can also be effective when used in conjunction with an alkali metal hydrogen carbonate or an alkali metal acetate but (ii) that, in net contrast with the preceding results,[7] strictly anhydrous reaction conditions are required for the quaternary ammonium salt to provoke the greatest acceleration, whatever the nature of its anion. Indeed, when performed in the presence of molecular sieves, palladium-catalysed arylation of methyl acrylate has been efficiently realised under mild conditions, using a combination of $MHCO_3$ or MOAc and a tetraalkylammonium salt, whether the latter was a hydrogen sulfate, a bromide or a chloride (scheme 1).



M= Na or K
QX= $n\text{-Bu}_4\text{NHSO}_4$, $n\text{-Bu}_4\text{NBr}$ or $n\text{-Bu}_4\text{NCl}$

**Scheme 1**

As shown in the Table, the reaction can be improved upon addition of hydrated tetra-n-butylammonium chloride,[8] in the absence of molecular sieves (entry 2 compared to 1 or entry 13 compared to 12). However, the reaction yield increase is much more important when using non hydrated tetra-n-butylammonium chloride[8] and when performing the reaction in the presence of 4Å molecular sieves, whether the solvent was acetonitrile (entries 4 and 14) or N,N-dimethylformamide (entries 8 and 18). Under these strictly anhydrous conditions, n-$Bu_4NHSO_4$ proved as efficient as non hydrated n-$Bu_4NCl$, whether the inorganic base was $MHCO_3$ (entries 5, 6, 9 and 10) or MOAc (entries 16 and 19). The beneficial effect of molecular sieves has also been confirmed when using commercially available tetra-n-butylammonium acetate as the inorganic base (entries 20 and 21).

In summary, when an alkali metal hydrogen carbonate or an alkali metal acetate is used as inorganic base, addition of various tetraalkylammonium salts can greatly enhance the reaction yield, whatever the nature of their anion, provided that the reactions are performed under strictly anhydrous conditions (e.g. in the presence of molecular sieves). In particular, tetraalkylammonium hydrogen sulfate can then be just as effective as tetraalkylammonium chloride or bromide, strongly suggesting that the beneficial effect of the tetraalkylammonium salt in Heck-type reactions is mainly dependent upon the presence of its quaternary ammonium cation.

The role of a tetraalkylammonium salt in Heck-type reactions can, a priori, be multiple as the catalytic cycle of these reactions involves several elementary steps.[1] However, our previous results[7] and the observations described herein, - which clearly show a determining influence of the quaternary onium cation,- lend strong support for the involvement of a phase transfer catalysis for facilitating the regeneration of the zerovalent palladium catalyst. Indeed, the dissociation of the hydridopalladium halide complex (scheme 2)[1] should be more efficiently effected by a phase transfer catalysis when an inorganic base is involved.

$$HPd^{II}L_2X \quad + \quad Base \quad \rightleftharpoons \quad Pd^{0}L_2 \quad + \quad Base\,H^{+}X^{-}$$

**Scheme 2**

The different effect of water observed when using the catalyst systems $[Pd/M_2CO_3/QX]$[7] and $[Pd/MHCO_3/QX]$[14] or $[Pd/MOAc/QX]$[14] might be rationalised by different PTC mechanisms. Indeed, the versatile influence of water, which can be beneficial or detrimental in the so-called solid-liquid phase transfer catalysis, has been well evidenced in organic processes.[15-19] By analogy, when an alkali metal carbonate is used as inorganic base,[7] an interphase deprotonation of $HPdL_2X$ might be envisaged, with a necessary step of the alkali metal carbonate dissolution in an aqueous phase.[17] In contrast, when the reaction is performed in the presence of an alkali metal hydrogen carbonate (or an alkali metal acetate) as the base,[14] the results are more consistent with a solid-liquid phase transfer catalysis involving a decomplexing process[19] (scheme 3) for which the driest conditions are by far the most effective.[18,19]

$$[QX]_{org} \quad + \quad MY_{solid} \quad \rightleftharpoons \quad [QY]_{org} \quad + \quad MX_{solid}$$

**Scheme 3**

**Table: Influence of tetraalkylammonium salts and molecular sieves in palladium-catalysed arylation of methyl acrylate using an alkali metal hydrogen carbonate or acetate as the inorganic base.**[9]

| Entry | Inorganic base | Solvent [10] | QX | Molecular sieves | Yield[11] (%) |
|---|---|---|---|---|---|
| 1 | $NaHCO_3$ | $CH_3CN$ | none | no | 10 |
| 2 | " | " | $n\text{-}Bu_4NCl.xH_2O$ [12] | " | 57 |
| 3 | " | " | $n\text{-}Bu_4NCl$ [13] | " | 70 |
| 4 | " | " | " | yes | 99 |
| 5 | " | " | $n\text{-}Bu_4NHSO_4$ | " | 98 |
| 6 | $KHCO_3$ | " | " | " | 99 |
| 7 | $NaHCO_3$ | DMF | none | " | 16 |
| 8 | " | " | $n\text{-}Bu_4NCl$ [13] | " | 99 |
| 9 | " | " | $n\text{-}Bu_4NHSO_4$ | " | 99 |
| 10 | $KHCO_3$ | " | " | " | 93 |
| 11 | " | " | $n\text{-}Bu_4NBr$ | " | 80 |
| 12 | KOAc | $CH_3CN$ | none | no | 10 |
| 13 | " | " | $n\text{-}Bu_4NCl.xH_2O$ [12] | " | 48 |
| 14 | " | " | $n\text{-}Bu_4NCl$ [13] | yes | 92 |
| 15 | " | " | $n\text{-}Bu_4NBr$ | " | 95 |
| 16 | " | " | $n\text{-}Bu_4NHSO_4$ | " | 86 |
| 17 | KOAc | DMF | none | " | 15 |
| 18 | " | " | $n\text{-}Bu_4NCl$ [13] | " | 94 |
| 19 | " | " | $n\text{-}Bu_4NHSO_4$ | " | 92 |
| 20 | $n\text{-}Bu_4NOAc$ | $CH_3CN$ | none | no | 60 |
| 21 | " | " | " | yes | 98 |

Besides the mechanistic interest, the reported results[7,14] may have a synthetic importance by further enhancing the performance of tetraalkylammonium salts in Heck-type reactions.

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8. Both hydrated and non hydrated tetra-n-butylammonium chloride are now commercially available.
9. $Pd(OAc)_2$ (0.05 equiv.) is added to a well-stirred mixture, in $CH_3CN$ or DMF (1 ml/1 mmol of PhI), of phenyl iodide (1 equiv.), methyl acrylate (2 equiv.), $PPh_3$ (0.1 equiv.), molecular sieves (when indicated), inorganic base (2.5 equiv.) and tetraalkylammonium salt (1 equiv.) when indicated. The slurry was heated at 60°C for 3.5 h (when $MHCO_3$ is involved) or at 50°C for 2.5 h (when MOAc is used)..
10. Commercially available HPLC grade solvents were used as dry solvents.
11. GLC yields.
12. Tetrabutylammonium chloride hydrate 98% from Aldrich.
13. Tetrabutylammonium chloride 98% from Lancaster.
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