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Preliminary communication

An interesting chloride ion effect in the Heck reaction

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Abstract

Addition of chloride ion is found to enhance the yields of cross-couplings between aryl iodides and selected olefin acceptors.

The Heck palladium-catalyzed cross-coupling of unsaturated halides and olefins has proven to be a valuable vinylation methodology [1–4]. Much effort has been expended towards optimizing the reaction conditions and several reaction protocols have resulted. These include the use of soluble palladium salts ($Pd(OAc)_2$, $PdCl_2$) and amine (Et_3N, Bu_3N) or carbonate ($NaHCO_3$, K_2CO_3) bases with or without solvent (MeCN, DMF) and ligands (PPh_3, $P(o\text{-}Tol)_3$) at high temperatures [5–7] or moderate temperatures with added silver salts ($AgNO_3$, $AgCO_3$) [8,9]; the use of palladium on carbon with solvent (MeCN, DMF) and base (Et_3N, K_2CO_3) and high temperatures [10–12]; or the use of palladium salts, base ($NaHCO_3$, K_2CO_3, KOAc) and phase transfer reagent (Bu_4NCl) in DMF at room temperature [13–15]. We report herein an effect of chloride ion on Heck vinylation reactions catalyzed by palladium on carbon.

As part of a synthesis of Teleocidin A, we required the vinylation of indole **1**. After extensive screening of reaction conditions, the optimal procedure (4 mol eq olefin, 1.4 mol eq K_2CO_3, 10 mol % Pd/C (5%), DMF, 100 °C) provided product **2** in only a 40% yield. Although the mechanism of the palladium on carbon catalyzed reaction is not clear, we were curious to see if addition of chloride ion might promote the reaction either by helping to solubilize surface-bound palladium or by transmetallating with the arylpalladium iodide to generate a more electrophilic arylpalladium chloride intermediate. In the event, performing the reaction under the usual conditions, but with the addition of two mole equivalents of lithium chloride, resulted in almost doubling the yield to 77%. While this solved an important

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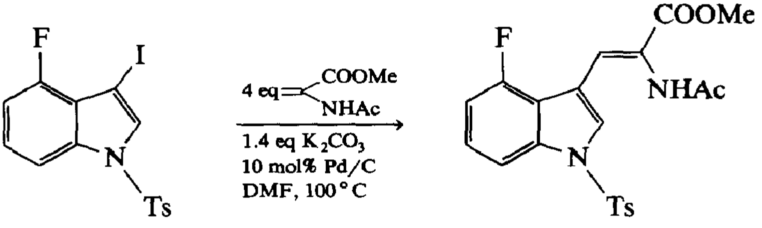
bottle-neck in our synthetic plan, we were intrigued to see if addition of alkali metal chloride salts enhanced the yields in other couplings reactions.



(1) (2)

The results of our screening reactions are given in Table 1 [16*]. Lithium chloride was used initially as the additive, but as the lithium counterion was not important (entry 2), the less hygroscopic potassium chloride is preferred. For solubility reasons, potassium chloride is also preferred over sodium chloride. It is clear that in some instances the addition of chloride is beneficial, yet in others there is no effect. Comparing entries 3 and 5 to 7 and 6 illustrates that the effect of chloride ion on the reaction is independent of the aryl iodide. In contrast, the chloride ion effect is strongly dependent on the olefin component of the reaction (entries 5 and 6). Overall, only reactions employing olefin components containing an amide function are affected by chloride ion. More specifically, the amide function must contain an NH group.

The mechanistic implications of these results are not immediately obvious, but some interpretations are possible. Without specifying the exact nature of the palladium atoms in the palladium on carbon catalyzed reaction, the generally accepted mechanism for the homogeneous reaction can be used as a working model (Scheme 1). Of the four major reactions in the catalytic cycle, only the last three are expected to be affected by chloride ion. This is supported experimentally by the independence of the effect to aryl iodide. Step II (carbopalladation) could be influenced by generation of a more electrophilic arylpalladium chloride intermediate. In fact, it has been proposed that chloride ions promote cross-coupling reactions of aryl [17,18] and vinyl [19–21] triflates using *homogeneous* palladium catalysts via generation of more reactive RPdCl intermediates. Steps III and IV (β-elimination and reductive elimination) may proceed at different rates upon changing the X group from iodide to chloride. However, a general explanation is not compatable with the specific nature (RCONHR′ sensitive) of the experimental results reported herein. Therefore, we would like to propose that amide groups coordinate to palladium intermediates to inhibit reaction and that chloride ions act as competitive ligands to overcome this problem. The requirement for unsubstituted amides may be steric. Entries 7c and 10 c were designed to test these ideas by looking for an inhibitory effect of acetamide. As no effect was observed, the inhibitory effect of amides may only occur intramolecularly, possibly in the carbopalladation step. This would be analogous to the palladium-assisted cyclization of 2-allylaniline which requires addition of triethylamine as a promoter to displace the amine nitrogen from palladium and allow reaction at the olefin [22]. Further

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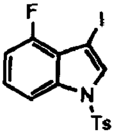
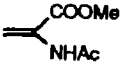
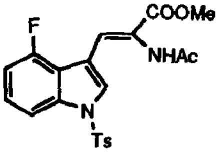
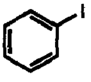
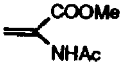
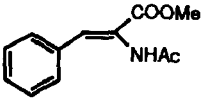
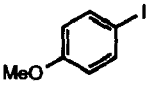
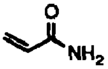
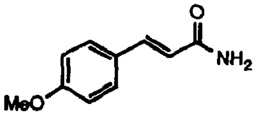
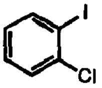
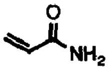
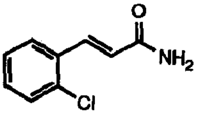
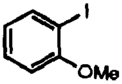
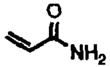
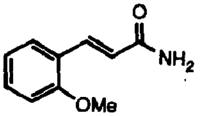
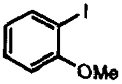
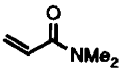
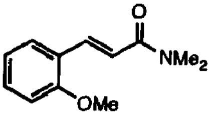
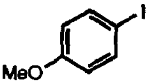
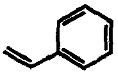
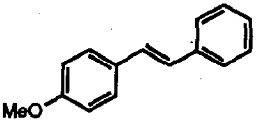
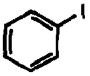
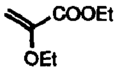
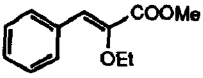
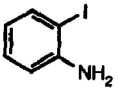
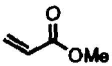
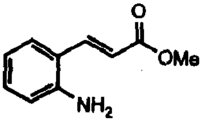
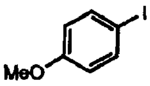
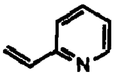
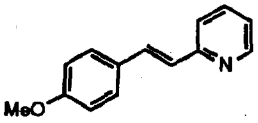
* Reference number with asterisk indicates a note in the list of references.

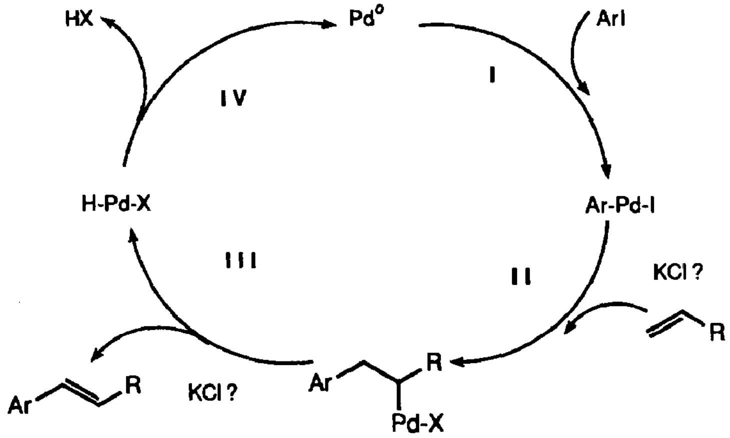
Table 1

Palladium-catalyzed vinylation of aryl iodides

Entry	Aryl iodide	Olefin	Reaction conditions [a]	Product	% Yield [b]
1		 4 eq	a) - - - b) 2 eq LiCl		40 77
2		 1.7 eq	a) - - - b) 1 eq LiCl c) 1 eq NaCl d) 1 eq KCl		55 74 71 75
3		 1.3 eq	a) - - - b) 1 eq LiCl		69 80
4		 1.5 eq	a) - - - b) 1.5 eq KCl		62 69
5		 1.5 eq	a) - - - b) 1.5 eq KCl		48 62
6		 1.5 eq	a) - - - b) 1.5 eq KCl		72 74
7		 2 eq	a) - - - b) 1.5 eq KCl c) 1.5 eq $MeCONH_2$		89 87 88
8		 1.5 eq	a) - - - b) 1.5 eq KCl		45 40
9		 1.5 eq	a) - - - b) 1.5 eq KCl		86 87
10		 1.6 eq	a) - - - b) 1.5 eq KCl c) 1.5 eq $MeCONH_2$		44 43 42

[a] 3.5 mol% Pd/C (5%), 1.5 eq K_2CO_3, DMF (0.5 *M*), 100 °C, 15–24 h.

[b] All yields refer to isolated and purified compounds.



Scheme 1

experimentation is required to develop a clearer picture of the effects of amides and chloride ions on the Heck vinylation reaction.

Although it is not a general solution to problems of low yields in Heck cross-coupling reactions, we have demonstrated that addition of alkali metal chloride salts can in some instances markedly increase the yields of coupling products in *heterogeneous* palladium-catalyzed reactions.

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