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Beneficial Effect of Cesium Salts on Pd-Catalyzed Hydroxycarbonylation

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Abstract—A Pd(0)-catalyzed hydroxycarbonylation of the aryl bromide was effectively carried out in the presence of some Cs salts such as cesium carbonate, cesium bicarbonate, and cesium acetate in wet DMF solution. For the understanding of their function, an oxy-coordinated intermediate arising from a Cs–oxygen–Pd interaction has been postulated, which is likely to be responsible for related Cs assisted catalytic processes. © 2000 Elsevier Science Ltd. All rights reserved.

As a result of their widespread and diverse utility, Pd-catalyzed transformations are an essential tool for modern synthesis.[1] In addition to the reported (original) protocols which have been found to be widely applicable, further modifications in reagent composition have also been devised to attain the optimum efficiency.[2] Among the beneficial additives employed in various Pd-catalyzed processes, some cesium salts played an important role in attaining regioselectivity and stereoselectivity, as well as rate enhancement.[3] Most of these reactions were carried out by the utilization of Cs_2CO_3 in strictly anhydrous conditions.

We have shown that a certain cesium assisted catalytic amination (Buchwald amination) was accelerated in the presence of a catalytic Crown ether.[4] This finding along with some related observations indicated to us the possibility that a Cs–oxygen–Pd interaction might be important in such catalytic processes. Buchwald also indicated a facile Pd–N bond formation from the initial Pd–X intermediate in these catalytic aminations by the presence of some Crown ethers.[5]

We were interested in the utilization and function of some Cs salts as co-catalysts in the Pd-catalyzed carbonylation reaction in the presence of H_2O as an oxygen source. We now wish to describe herein some rate-accelerating effects of wet Cs salt in such catalytic processes, which indicated to us a key interaction between Pd and Cs.

Our study of catalytic carbonylation was focused on the benzamide (**1**). Before this study, we carried out some preliminary searches with other substrates (e.g., **4** and **5**),[6] which indicated to us the use of the standard Heck carbonylation protocol: $Pd(OAc)_2$–PPh_3 in DMF–Bu_3N–H_2O. These conditions have turned out to be useful for the substrates bearing polar nitrogen substituents such as **1**.

In the pilot study (Table 1) a satisfactory result was obtained with more than 2.5 mol% Pd under 6 h reflux period. Few reports have described a successful Pd catalyzed reaction with a free NH containing substrate. In such substrate (**1**) that bears an amide NH substituent and sterically demanding *ortho*-methyl group, directed *ortho*-palladation could be a preferable reaction course with Pd(II).[3a] This pathway would interfere with the desirable reaction at the *para*-position. In fact, the conventional Heck protocol did not work well at the low Pd catalyst loading of less than 1 mol%. It was then found that addition of K_2CO_3 was somewhat effective as shown in the experiment of run 3 (Table 1), providing an improved result with 85% crystalline product with 98% purity. However, upon further decreasing the amount of Pd catalyst, the effect of K_2CO_3 diminished or could not be reproduced as in the example of Table 2. In the unsuccessful reactions, a formation of the debrominated byproduct (**3**) was often observed. Obviously, further improvements were required in order to carry out the reaction with reasonably less catalyst and suppress the unwanted side products.

We thus started our own investigation on the additive effects, with the aim of understanding the functions of

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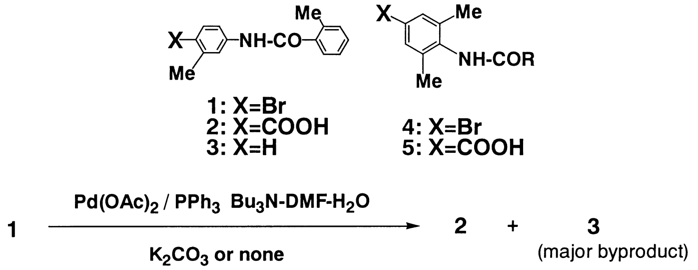
some inorganic carbonates in catalytic carbonylation.[7] A brief survey using various kinds of carbonate salts (Na_2CO_3, $CuCO_3$, K_2CO_3, Cs_2CO_3) indicated that beneficial effects of the salts were observed when these salts formed homogenized solution. Among the carbonate salts, Cs_2CO_3 dissolved well in wet DMF–Bu_3N (TBA) and always showed beneficial effects, while K_2CO_3 did in some occasions. These observations were interpreted in the following way: (1) K_2CO_3 worked well as a trap of some acid contaminants (AcOH, HBr) present in the bromide starting material. (2) Cs_2CO_3 showed beneficial effects especially in the presence of H_2O. Thus, Cs_2CO_3 formed a clear yellow mixture with the substrate in wet DMF to work as both base (HX trap) and promoter for catalytic cycle.

Further experiments showed that variable amounts of Cs_2CO_3 (0.5–0.3 equiv) worked well in the same manner. Other cesium salts ($CsHCO_3$, CsOAc) worked in the same way as summarized in Table 2. From the results obtained, a mechanistic proposal for Cs-assisted hyroxycarbonylation is shown, in which proper coordination by hard OH ligand stabilized the Pd(II) intermediate of this catalytic carbonylation. Precipitation of the insoluble CsBr after carbonylation was also observed as the reaction proceeded. The best result was obtained by the use of CsOAc in a concentrated solution with 2 equiv of H_2O and 1.5 equiv of Bu_3N as shown in Table 2 (run 10). The experimental simplicity and swift reaction course are the merits of the present protocol.

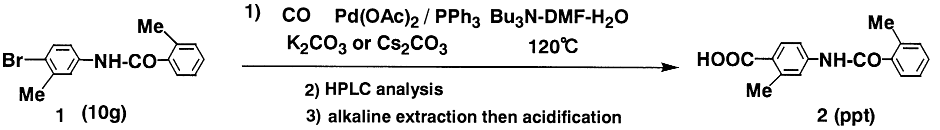
In summary, we found that some cesium salts could assist the catalytic carbonylation as summarized above. We assumed that (hydrated) Cs salt could interact with Pd(II) intermediate by offering OH ligand to facilitate

Table 1. Initial study



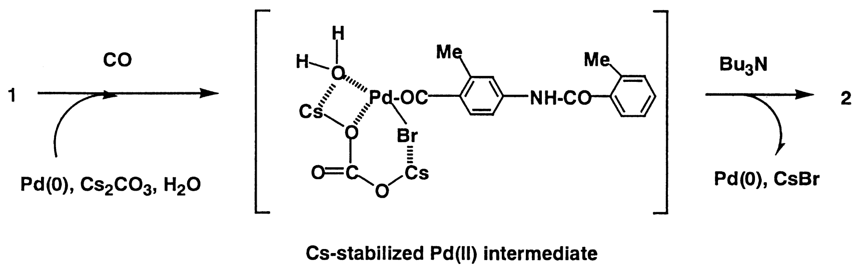
Run	M_2CO_3	Pd–PPh_3	Solvent (ratio)	Heating	**2** (Isolated yield)
1	None	2.5–20 mol%	DMF:TBA:H_2O (20:3:4)	6 h	60%
2	None	1.6–15 mol%	DMF:TBA:H_2O (30:8:4)	6 h	53% + tarry gum
3	K_2CO_3	2.5–15 mol%	DMF:TBA:H_2O (20:4:2)	6 h	85%

Table 2. Pd-catalyzed carbonylation of **1** (1.6 to 0.4 mol% Pd)



Run	M_2CO_3	Pd–PPh_3 (mol%)	Solvent (mL)	Time (h)	HPLC ratio and **2** (% yield as isolated cryst)
4	None	0.8–10	DMF:TBA:H_2O (30:10:1.5)	6	ca. 20% conversion
5	K_2CO_3 (1 equiv)	1.6–15	DMF:TBA:H_2O (30:8:4)	6	45%
6	Cs_2CO_3 (0.5 equiv)	1.6–15	DMF:TBA:H_2O (30:8:4)	6	80–83%
7	Cs_2CO_3 (0.3 equiv)	0.8–10	DMF:TBA:H_2O (30:10:1.5)	6	HPLC: 2/1 = 60/8 81%
8	$CsHCO_3$ (1 equiv)	0.8–10	DMF:TBA:H_2O (30:10:1.5)	6	HPLC: 2/1 = 72/1 85%
9	Cs_2CO_3 (0.3 equiv)	0.4–5	DMF:TBA:H_2O (30:10:1.5)	6	HPLC: 2/1 = 65/15 60%
10	CsOAc (1 equiv)	0.8–10	DMF:TBA:H_2O (26:12:2)	3	> HPLC: 2/1 = 80/10 81% (after recrystallization)

Mechanisitic proposal for Cs-Assested hydroxycarbonylation



the Pd–CO intermediate formation as well as assisting a rate-determining step (product forming step).[8]

Additionally, removing HBr as a form of CsBr is another beneficial aspect. Further exploration with other substrates and assessment of the true function of the salt effect on the related Pd-catalyzed reaction including amidocarbonylation and alkoxycarbonylation are in progress.

Experimental

A stirred suspension of the bromide (**1**, 10.0g) and CsOAc (5.00 g) in DMF (26 mL)–H_2O (2.0 mL)–Bu_3N (12.0 mL) was charged with CO, before the quick addition of Ph_3P and $Pd(OAc)_2$. The mixture was tightly kept in a CO atmosphere and heated at around 120 °C for ca. 3 h. HPLC analysis at 3 h indicated ca. 10% of SM remained. After cooling, the mixture was directly diluted with toluene (100 mL)–NaOH aq (1 N, 150 mL) and stirred at rt for 0.5 h. The aqueous layer was separated and acidified by 5 N HCl to form a white precipitate at $pH = 1$. The precipitate was cooled in an ice–water bath, which was collected by filtration and washed with cold H_2O to leave a crude crystalline acid. Further recrystallization afforded purified product (81%) with 99.1% purity.

Acknowledgements

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