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Application of a New Combination of Palladium and $CaCO_3$ for an Aerobic Heck Reaction using Arenediazonium-Salts

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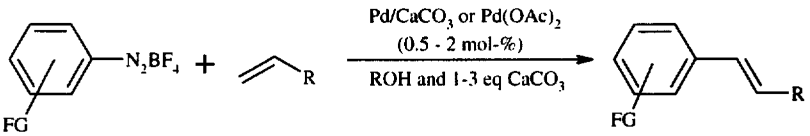
Abstract : *Efficient Heck reactions under aerobic conditions were carried out using Pd-catalyst in the presence of $CaCO_3$. Under these conditions a neat Heck Reaction using arenediazonium salts bearing functional groups including nitro functionalities can generally take place in good yields up to 95%.* © 1999 Published by Elsevier Science Ltd. All rights reserved.

Since the early seventies the Heck reaction became of greater importance in the formation of new C-C-bonds between $C(sp^2)$-centers as well in the laboratory as in industry and is characterized by a high chemoselectivity. This methodology is established in the field of the total synthesis of complex target structures and industrial relevance.[1,2] Although aryl and vinyl halides are the classical electrophiles in this reaction the use of different other substrates like benzoic anhydrides[3], aroyl chlorides (« Blaser reaction »)[4] and pseudohalides offer a broader scope in organic synthesis and catalysis.[1,5] Especially the utilization of arenediazonium salts both in the Heck reaction[6] and the Suzuki reaction[7] has generated a major stimulus.

In all these reactions it is known that the use of bases and strongly coordinating ligands in reactions with arenediazonium salts is detrimental in consequence of dediazotation and represents a limitation in alcoholic solvents.[6d,6f,8] The use in the Heck reaction of arenediazonium salts bearing nitro groups also frequently fails because of the decomposition of these substrates.[6d,6f] Furthermore the formation of acids caused by β-H-elimination can be very problematic for acid labile substrates and products. Thus Beller et al. have described, that in the Heck-reaction with arenediazonium salts and economically important acrylic esters the formed fluoroboric acid frequently causes transesterification reactions using ethanol as solvent and Pd/C as catalyst, while on the other hand they could use the phenomenon for a tandem Heck-esterification-reaction in the case of acrylic acid in methanol. Here we describe a new approach and improvements that overcome the above mentioned problems.[9] In this study we have found that by using the heterogeneous $Pd/CaCO_3$ catalyst or $Pd(OAc)_2$ as a homogeneous precatalyst with additional $CaCO_3$ as base in alcoholic solvents it is possible to avoid side reactions and enlarge the synthetic usefulness (Scheme 1). The base $CaCO_3$ distinguishes itself fom others by its attractive price and its ecological compatibility. Furthermore it can be separated from the product by a simple filtration. Our results are summarized in Table 1.



Scheme 1

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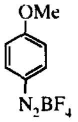
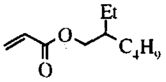
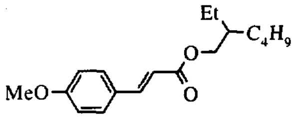
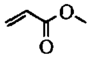
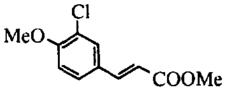
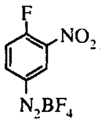
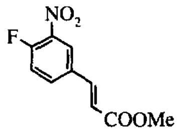
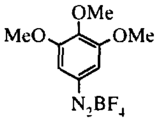
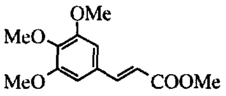
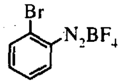
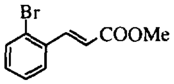
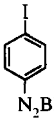
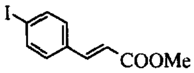
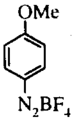
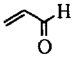
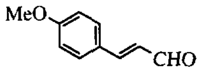
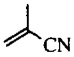
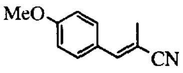
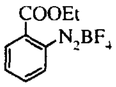
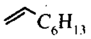
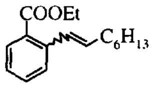
Table 1 Heck reaction using catalytic Pd/CaCO$_3$ systems (using between 0.5 – 2 mol-% Pd)$^{(a)}$

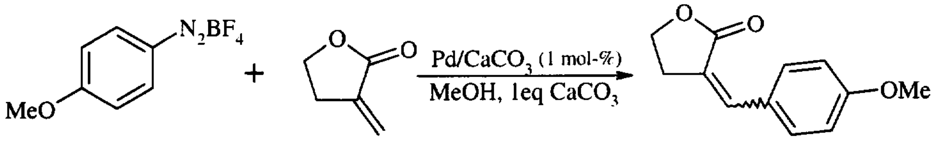
Entry	Diazonium salts	Olefin	Product	Yield$^{(b)}$ (%)
1				93
2				72
3		"		74
4		"		95
5		"		92
6		"		92
7				71
8	"			72$^{(c)}$
9				61 (E/Z = 70:30)

(a) Reaction times between 15 min and 2 hours. (b) Isolated yields. (c) Using Pd(OAc)$_2$/CaCO$_3$

It is noteworthy in the light of the results of Beller et al. that the synthesis of industrial important cinnamic acid derivatives of higher alcohols as UV absorbers, antioxidants in plastics or key intermediates and starting materials in the synthesis of a variety of pharmaceuticals, agrochemicals and flagrances[10] does not represent any problem using our heterogeneous Pd/$CaCO_3$-system neither in methanol nor in ethanol nor in the nontoxic isopropanol (Table 1, entry 1). While synthezising these products using different alcohols, no significant reduction or dependence of reactivity could be observed. A careful examination has shown an optimum of the reaction using acrylic esters at a temperature between 30°C for electron deficient and 50°C for electron rich arenediazonium salts within 15 min and 2 hours using the different alcohols as solvents and Pd/$CaCO_3$ as catalyst. With the use of $Pd(OAc)_2/CaCO_3$ the reactions can be carried out at room temperature and are finished within a few minutes.

Although aryl halides and triflates are the most common starting materials in Palladium-catalyzed cross-couplings our protocol also distinguishes itself by an excellent compatibility of these functional groups compared to previous observations of our and other groups. It has to be pointed out, that because of the insensitivity against air and moisture all these described reactions are *practical in an instant way under aerobic conditions using commercial and not degassed solvents.*[13] Beyond this simplification it must be noted that 0.5 – 2 mol-% of the heterogeneous catalyst Pd/$CaCO_3$ is sufficient for a smooth reaction. Even arenediazonium salts bearing nitro groups can be converted (Table 1, entry 3), which suffer decomposition using Kikukawa basic conditions[6d] and the conditions of Sengupta et al.[6f]

The synthetic application of this protocol is not limited to the utilization of activated olefins like acrylic esters, but can also be used for other alkenes (Table 1, entry 7 and 8). Furthermore this protocol could be applied for the synthesis of substituted α–benzylidene-γ–butyrolactones (example given in Scheme 2) in excellent yields. The latter represent an important class of bioactive molecules and interesting building blocks for the synthesis of linearly condensed heterocyclic systems.[11] To our knowledge these products were frequently prepared by direct aldol condensations, Wittig reactions and Stille couplings[11], but only a few examples using Heck reactions were reported.[12]



88% (E/Z = 54 : 46)

Scheme 2

In summary we have shown the possibility to use $CaCO_3$ as a base in the Palladium-catalyzed alkenylation in alcoholic solvents. Further investigations in the use of other olefinic substrates and applications towards natural product synthesis are currently underway in our laboratory.

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13. *Typical procedure for the synthesis of cinnamic acid esters:* In a reaction flask 1 mmol of the corresponding arenediazonium salt, 0.01 mmol of Pd/$CaCO_3$ (5% of weight) and 1 mmol $CaCO_3$ are suspended in 5 mL solvent. Subsequently 1 mmol of the acrylic acid ester is added and the mixture is warmed. After the reaction is completed the solvent is evaporated and the residue is purified by flash chromatography on silica.