

Diazonium Salts as Substrates in Palladium-Catalyzed Carbonylative Coupling Reactions

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Introduction:-

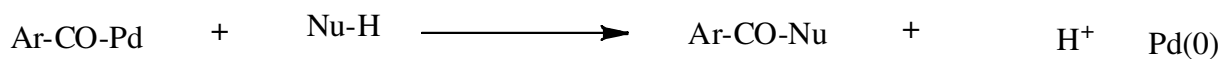
Aromatic diazonium salts have been prepared and extensively used for years. They are prepared by reaction of anilines with a source of nitrite. When the reaction is performed in water, sodium nitrite and a strong acid is the combination of choice according to the stoichiometry.

The general reactivity of diazonium aromatic cations is conditioned by the low stability of arene cations, the result of nitrogen elimination. The salts featuring low nucleophilic counteranions (tetrafluoroborate, hexafluorophosphate, among others) can be isolated and manipulated even though they contain an excellent leaving group such as nitrogen. Thermal elimination of nitrogen is possible and underlies preparation of fluoroaromatics (the Balz-Schiemann reaction) when BF_4 of iodoaromatics in the presence of potassium iodide. Heating in aqueous sulfuric acid gives phenols in a particular case of solvolysis. Certain reducing agents promote the formal transfer of hydride to the cation in a method to eliminate the NH_2 function.

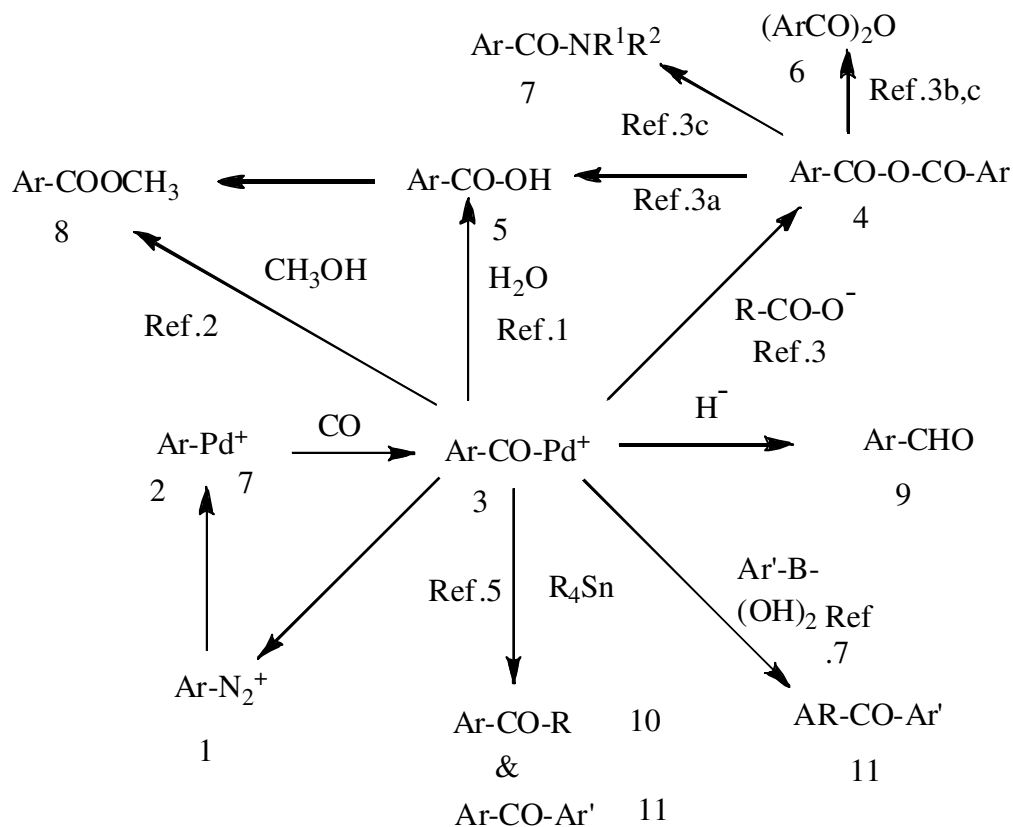
Carbonylative Coupling:-

Arylpalladium complexes 2 of whatever origin react with carbon monoxide to give electrophilic aroylpalladium complexes 3, which can be trapped by a wide variety of nucleophiles with simultaneous recovery of the catalytic $\text{Pd}(0)$, thus permitting preparation of different final products. Scheme 1 shows the formation and reactivity of these cationic aroylpalladium complexes.

Scheme 1



3



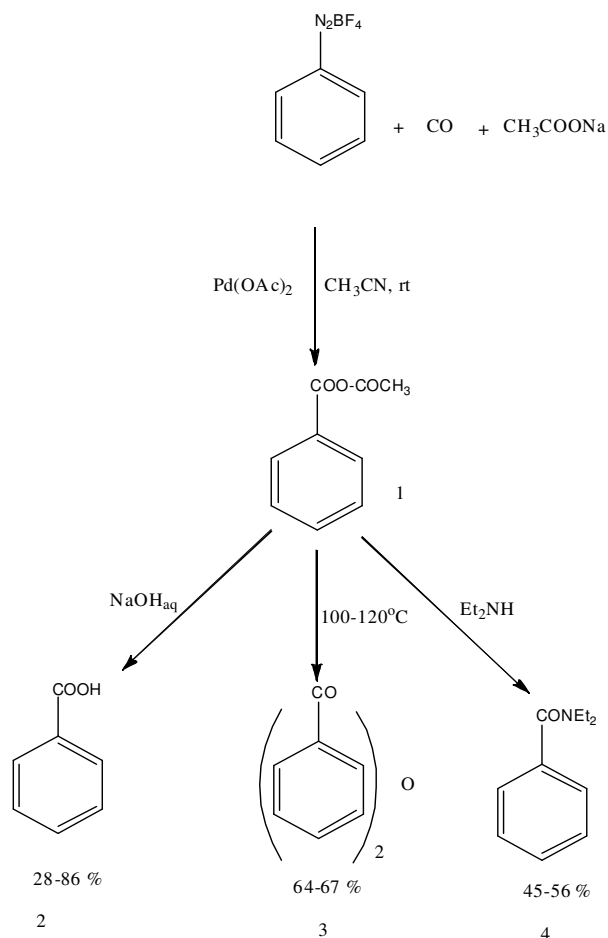
Pd(II) acetate or other Pd(II) species are frequently introduced as precatalysts. It is assumed that CO reduces Pd(II) to Pd(0) in situ (eq 1).



1

Kikukawa, Matsuda et al.³ pioneered the use of diazonium salts in carbonylation reactions. They first reported the Pd catalyzed reaction of arenediazonium tetrafluoroborates with CO in the presence of sodium acetate, or other sodium carboxylates, in acetonitrile. The acetate anion was the trapping nucleophile, providing mixed anhydrides 1 which gave (a) arenecarboxylic acids 2^{3a} upon hydrolysis, (b) arenecarboxylic anhydrides 3^{3b,c} upon heating, and (c) arenecarboxamides 4 upon addition of an amine^{3c} (Scheme 2).

Scheme 2

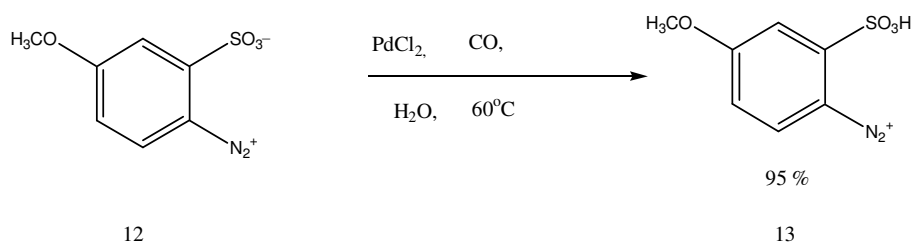


It is noteworthy that this preparation of anhydrides 1 tolerated both electron-withdrawing (4-NO_2) and electron donating (4-OMe) substituents. More important is the fact that iododiazonium tetrafluoroborates reacted with palladium exclusively at the diazonium group. As commented on with regard to the above cross-coupling reactions, this is a general trend: oxidative addition of palladium in the C-N_2 bond is faster than in any C-halogen bond. Attempts by these authors to prepare esters by trapping intermediates 3 with methanol or ethanol failed as these alcohols had the effect of reducing the intermediate to Ar-H .

Further improvements and simplifications have been reported. Thus, direct carbonylation in water of diazoniumsulfonate 12 directly gave carboxylic acid 13 (Scheme 3) in the herbicide CGA 308 956 preparation step.¹ It should be noted that the distribution of substituent's in

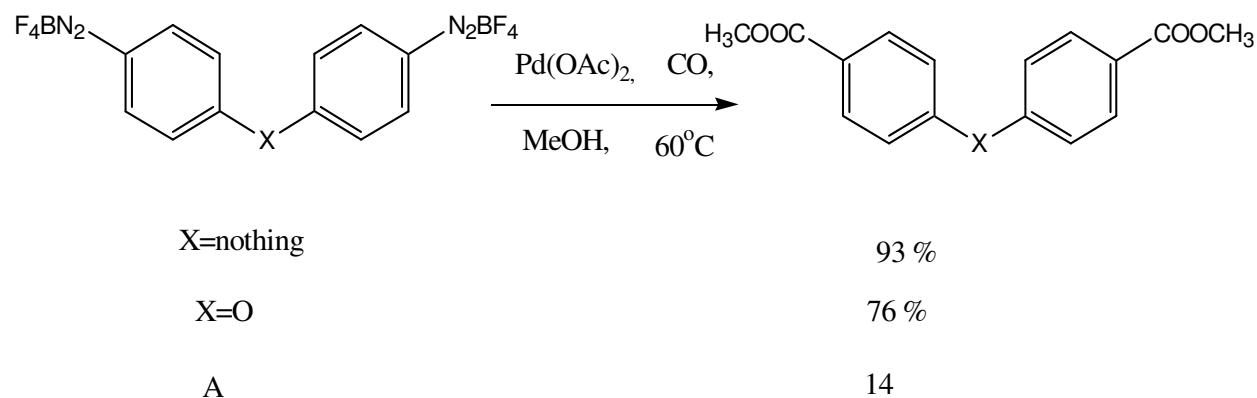
benzene makes more classical routes based on electrophilic substitution and the rules of orientation difficult.

Scheme 3



Later, direct preparation of esters 14 was achieved by carbonylation of bisdiazonium salts A in methanol² (Scheme 4).

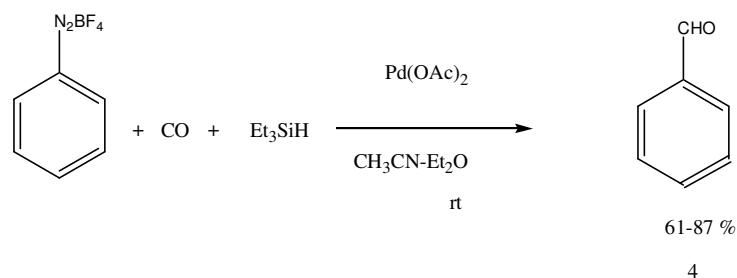
Scheme 4



Therefore, it is seen that careful selection of experimental conditions including the solvent water or alcohol permitted direct preparation of acids and esters, avoiding formation of mixed anhydrides. No general solution has been reported for esterification with solid or highly valuable alcohols for which one equivalent would be required.

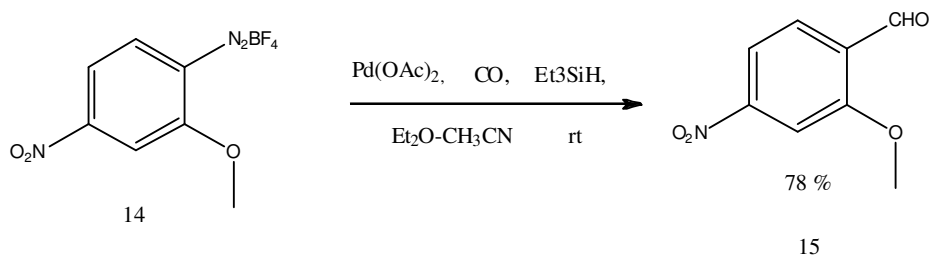
Kikukawa et al.⁴ described the use of triethylsilane (HSiEt_3) and polymethylhydrosiloxane (PMHS) as sources of hydride ion in the preparation of aromatic aldehydes 4 by trapping the aroylpalladium intermediate formed from several diazonium tetrafluoroborates (Scheme 5). This process provided one more example of the greater reactivity of diazonium leaving group with respect to halide (Cl, Br, and I) since 4-halobenzenediazonium tetrafluoroborate gave 4-halobenzaldehyde upon reductive carbonylation.

Scheme 5



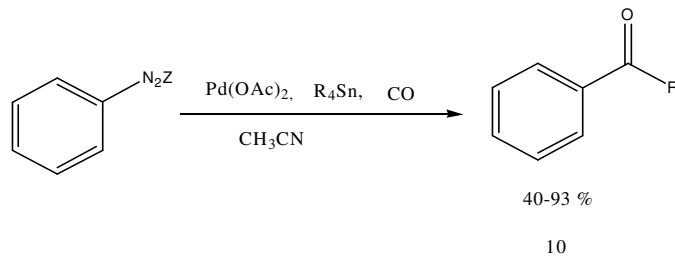
This formylation process has been successfully applied in the preparation of aldehyde 15 from the arenediazonium tetrafluoroborate 14 (Scheme 6), a key step in the synthesis of the hepatitis C drug candidate VX-497 (merimepobid) 13 in a multigram scale (see Scheme 3).

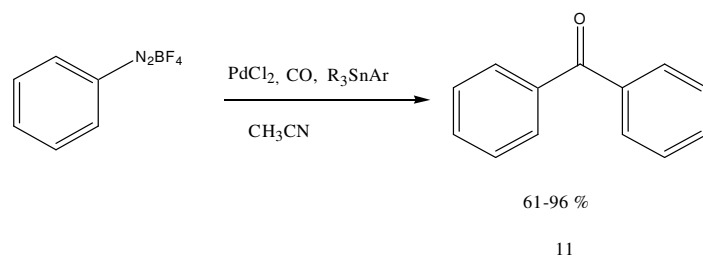
Scheme 6



Reaction with carbon nucleophiles after carbonylation or, in other words, interception of the intermediate 3 with carbon nucleophiles gives ketones. Kikukawa, Matsuda et al.⁹⁹ were again the pioneers in the Pd-catalyzed carbonylation of arenediazonium salts in the presence of tin compounds, and their first communication appeared in 1982,^{5a} the same year that arylboronic acids were described for the first time⁶ (Scheme 7). The reaction of tetraalkyltins and aryltrialkyltins with diazonium cations in an atmosphere of CO and in the presence of catalytic quantities of palladium acetate gave alkyl aryl ketones 95 and diaryl ketones 11 in 30 min.

Scheme 7

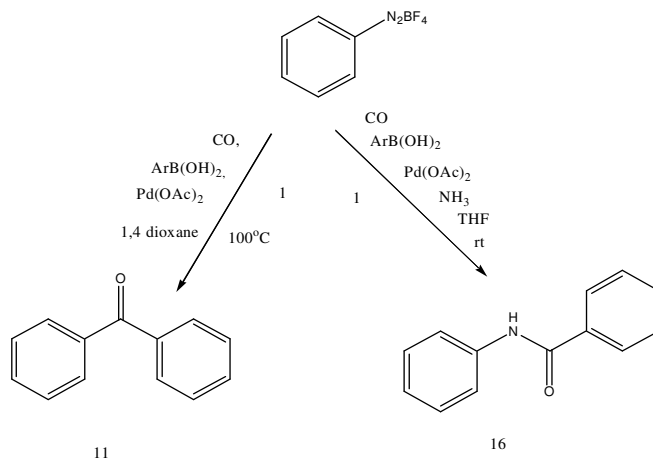




The other product of the reaction was probably F-SnR₃. In the synthesis of diaryl ketones 11 the reaction was very selective: no products containing any alkyl group from Ar'SnR₃ were observed. Furthermore, neither symmetrical ketones (ArCOAr or Ar'COAr') nor biaryls were formed.

Since their introduction, arylboronic acids have gained importance with respect to tin compounds. Andrus et al.⁷ described the carbonylative coupling of arenediazonium salts with arylboronic acids to produce diaryl ketones 11 when the reaction was catalyzed by a combination of Pd(OAc)₂ and N,N-bis-(2,6-diisopropylphenyl)dihydroimidazolium chloride in dioxane at 100 °C in 5 h (Scheme 8). This same palladium-ligand combination has been shown to efficiently catalyze both Matsuda-Heck and Suzuki-Miyaura reactions.

Scheme 8



The same group of Andrus reported four-component sequential reactions of diazonium tetrafluoroborates with ammonia, CO, and boronic acids and other boron compounds.⁸ The reaction gave amides 16 in which the amine portion came from the diazonium counterpart and the acid part came from the boron compounds. The outcome depended on the relative rates of the individual steps involved. The results led them to conclude that insertion of ammonia into the arenepalladium complex (from the arenediazonium) is faster than insertion of CO, and therefore, CO is inserted when the key NH-Ph-X structure is already formed.

References:-

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