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Diazonium Salts as Substrates in Palladium-Catalyzed Cross-Coupling Reactions

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Contents

Anna Roglans (left) was born in Palafrugell (Girona) in 1964. She graduated in chemistry (1988) and obtained her doctorate degree (1994) from the Autonomous University of Barcelona. Her supervisor was Professor Marcial Moreno-Mañas. After spending time at the University of Waterloo, Canada, as a postdoctoral fellow in Professor Victor Snieckus' group (1995–1996), Dr. Roglans moved back to the Autonomous University of Barcelona to work with Professor Moreno-Mañas. In 1999 she became Associate Professor at the University of Girona. Her current research focuses on organometallic chemistry, especially palladium, palladium catalysis, the recovery of catalysts, macrocyclic synthesis, and ESI-MS techniques.

Anna Pla-Quintana (right) was born in Banyoles (Girona) in 1978. She obtained both her degree in Chemistry (2000) and her doctorate degree (2004) under the supervision of Dr. Anna Roglans from the University of Girona. She did a doctoral stay in Professor Victor Snieckus' group at Queen's University, Kingston, Canada, and she is now on a postdoctoral stay in Professor Jean-Pierre Majoral's group in France, working on the synthesis of dendrimers with fluorescent properties.

Marcial Moreno-Mañas (center) (Barcelona 1941–2006) received his B.Sc (1963) and Ph.D. (1968) degrees from the University of Barcelona under the supervision of Professor Josep Pascual Vila. He spent two years as a postdoctoral student at the University of East Anglia (Norwich) with Professor Alan Katritzky, and he was a researcher at the CSIC (Barcelona) before moving in 1972 to the newly created Autonomous University of Barcelona. In 1983 he became Full Professor of Organic Chemistry at the Autonomous University of Barcelona. He coauthored more than 200 research papers and reviews. His research interests were focused on organometallic chemistry, palladium catalysis, recovery of catalysts, synthesis of unnatural amino acids and amino alcohols, enantio- and diastereoselective reactions, nanoparticles, and aerogels.

1. Introduction

Aromatic diazonium salts **1** (Scheme 1) have been prepared and extensively used for years.[1] They are prepared by reaction of anilines with a source of nitrite.[2] When the reaction is performed in water, sodium nitrite and a strong acid is the combination of choice according to the stoichiometry of eq 1. The choice of acid is of utmost importance

$$\mathrm{Ar{-}NH_2 + NaNO_2 + 2HA \rightarrow Ar{-}N{=}N^+A^- + NaA + 2H_2O} \quad (1)$$

since it defines the nature of the counteranion and the final outcome of the reaction. Generation of diazonium cations in organic solvents is possible by reaction of the

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[§] Deceased on February, 20, 2006: A.R. first met Professor Moreno in 1986 when she was a student at the Autonomous University of Barcelona. She was particularly struck by his enthusiastic personality and decided to do her Ph.D. work in his research group. During these doctoral years, Professor Moreno was always a point of reference for me, not only in the chemical research we did together, but also from a more personal point of view. We became good friends and colleagues and continued working together in our research areas up until he passed away this February. Dr. Moreno-Mañas was a person with an unusually broad range of interests and was particularly fond of history. This made it always a pleasure to converse with him about matters going well beyond what were the strict limitations of our work. Marcial, thank you for everything you have taught us.

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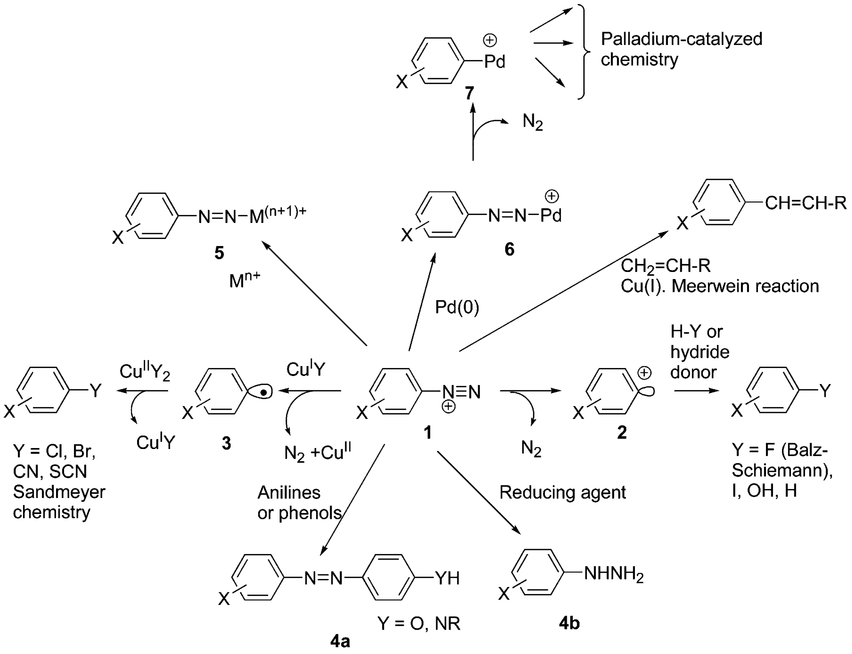
Scheme 1



aniline with an organic nitrite (eq 2).[2e]

$$Ar{-}NH_2 + RO{-}N{=}O + 2BF_3 \rightarrow Ar{-}N{\equiv}N^+BF_4^- + R{-}OH + \text{“}HOBF_2\text{”} \quad (2)$$

The general reactivity of diazonium aromatic cations shown in Scheme 1 is conditioned by the low stability of arene cations **2**, the result of nitrogen elimination from **1**.[1,3] The salts of **1** 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^- is the counteranion[2b,d] and of iodoaromatics in the presence of potassium iodide.[1,2a] Heating in aqueous sulfuric acid gives phenols in a particular case of solvolysis.[1] Certain reducing agents promote the formal transfer of hydride to the cation in a method to eliminate the NH_2 function.[1] One case of a reducing agent which is relevant to the present review is that of triphenylphosphine.[4] It has been reported that Ph_3P transfers an electron to arenediazonium tetrafluoroborates (eq 3) to afford the arene radical and the cation radical of triphenylphosphine.

$$Ar{-}N{\equiv}N^+BF_4^- + PPh_3 \rightarrow Ar\bullet + N_2 + {}^{\bullet+}PPh_3BF_4^- \quad (3)$$

The arene radical abstracts a hydrogen atom, mainly from alcoholic solvents, to generate the overall reduction products Ar−H, whereas the cation radical of triphenylphosphine is finally converted to $O{=}PPh_3$, which may explain why phosphines are not ligands of choice in palladium-catalyzed organic reactions with diazonium salts.

Elimination of dinitrogen is frequently induced by single-electron transfer (SET) from a low-valence metal, usually Cu(I).[1,5] Generation of the relatively stable arene free radical **3** induces introduction of several nucleophilic anions (chloride, bromide, cyanide, thiocyanate: Sandmeyer chemistry) probably through an aromatic radical−anion intermediate[5] with recovery of the low-valence metal that acts catalytically. Another related reaction is the so-called Meerwein reaction, arylation of olefins in which cations **1** react with olefins in a process that is synthetically, but not mechanistically, related with the Heck reaction although it has a narrower scope.[6]

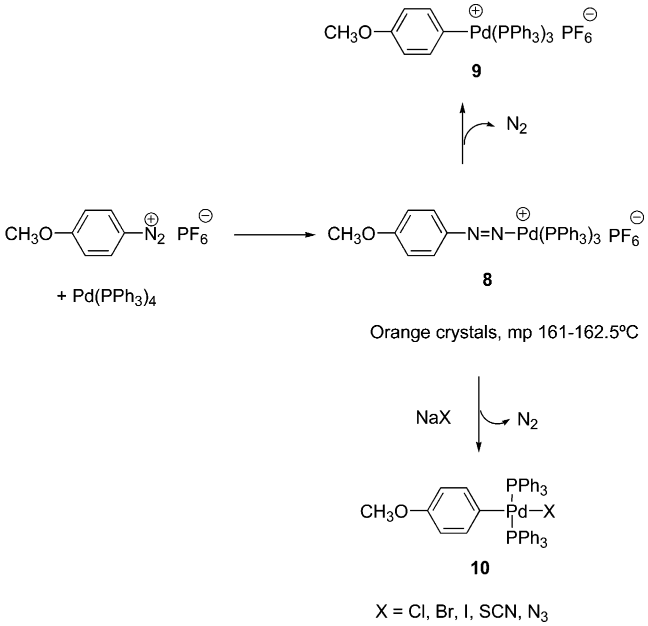
Other reactions retain both nitrogen atoms on the aromatic ring. Thus, coupling of **1** with highly nucleophilic anilines or phenolates affords diazo compounds **4a**, endowed with absorption in the visible region. They constitute the most numerous family of commercially available dyes.[7] Certain reducing agents (Na_2SO_3, $SnCl_2$/HCl, Zn/$NiCl_2$) preserve the N−N bond to afford arylhydrazines **4b**.[1]

It is less known that cations **1** can coordinate metals to give species **5** in which the metal (M) has increased its oxidation number by two units.[8] Palladium(0) gives this type of reaction producing, initially, cation **6** and, finally, arenepalladium cation **7** (Scheme 1). As a first example of this reactivity, Matsuda et al.[9] reported in 1980 isolation of salt **8** by reaction of the corresponding diazonium hexafluorophosphate with tetrakis(triphenylphosphine)palladium(0) (Scheme 2). However, attempts to isolate other related salts failed. Salts of type **8** decompose to the cationic arenepalladium complexes **9** in the absence of added nucleophilic anions, whereas in their presence, neutral complexes **10** were formed.

The work by Matsuda et al. led the way to the use of diazonium cations **1** in palladium-catalyzed organic reactions. This path has been taken by the industrial world (Scheme 3). Thus, chemists at the former Ciba Geigy AG reported an optimized preparation of Prosulfuron, an herbicide of the sulfonylurea family, by the Matsuda−Heck reaction of *o*-diazoniumsulfonate with 3,3,3-trifluoropropene. The best catalyst was $Pd_2(dba)_3$. Charcoal was added after the reaction to recover all the palladium in the form of Pd-on-charcoal, which was active in the subsequent hydrogenation step. Hence, palladium was used in two consecutive reactions and recovered by filtration.[10,11]

One example of nonreductive carbonylation has been reported in a joint paper by chemists from Solvias AG and Syngenta Crop Protection Münchweilen AG. Thus, in the

Scheme 2

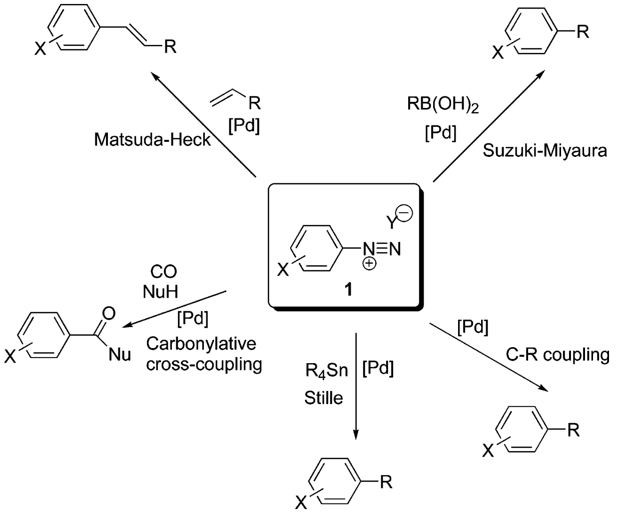


pilot-plant preparation of CGA 308 956, an herbicide of the former Ciba Geigy AG, the key intermediate 2-carboxy-5-methoxysulfonic acid was prepared by carbonylation of the diazonium inner salt in the presence of water as the nucleophile.[12]

Another industrial example is the multikilogram-scale preparation of 2-methoxy-4-nitrobenzaldehyde. This aldehyde is a key intermediate in the preparation of the hepatitis C drug candidate VX-497 (merimepobid).[13] The nucleophile that intercepts the cationic aryl−Pd intermediate is hydride from Et_3Si-H.

This review covers all typical palladium-catalyzed cross-coupling reactions in which diazonium salts have been used as electrophilic partners instead of the more usual halides or oxygen-based electrophilic components, and so Matsuda−Heck,[14] Suzuki−Miyaura,[15] carbonylative couplings,[16] Stille,[17] C−heteroatom[18] couplings, and miscellaneous reactions are included from their beginnings (Scheme 4). The authors of the present review believe that important new uses of arenediazonium salts in palladium-catalyzed reactions will be discovered soon and that their use will become more widespread for both academic and industrial applications. An attempt is made to emphasize not only the achievements but also those areas in which insufficient research has been done.

Scheme 4



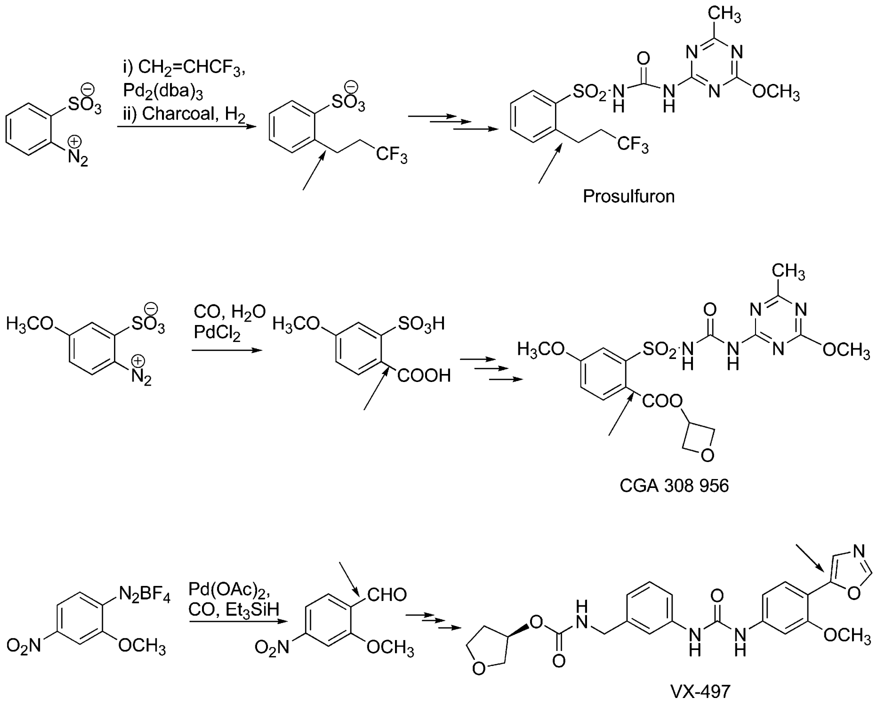
2. Palladium-Catalyzed Carbon–Carbon Coupling Reactions

2.1. Matsuda–Heck Reaction

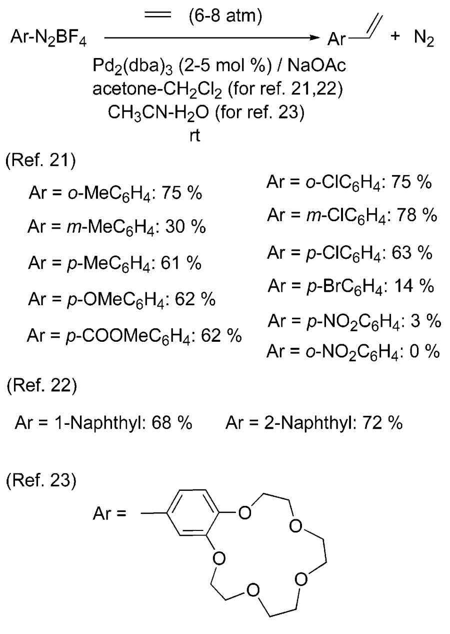
2.1.1. Olefinic Coupling Partner

Kikukawa and Matsuda were the pioneers in studying the reactivity of diazonium salts with transition metals. The first

Scheme 3



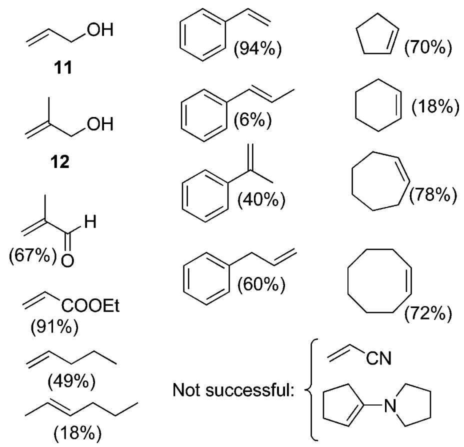
Scheme 5



published reaction of this type was in 1977,[19] when the Japanese group managed to arylate several olefins with arenediazonium salts catalyzed by zerovalent palladium. The new method emerged as a complementary strategy to the Meerwein reaction[6] for the arylation of unactivated olefins and also as an improvement on the method proposed in the early studies with aryl halides that Mizoroki and Heck separately conducted.[20] The olefins that were arylated were styrene, cyclopentene, allylic alcohols, and ethyl acrylate. The in situ reduction of LiPd(II)Cl_3 by sodium formate or $Pd_2(dba)_3$ as a source of Pd(0) in aqueous acetonitrile was used as a catalytic system. The reaction occurred at room temperature with sodium acetate as the base until production of nitrogen gas ceased. The same authors extended the methodology to the arylation of ethylene based on a comparative study of a variety of monosubstituted arenediazonium salts[21,22] (Scheme 5). Good yields of the corresponding substituted styrenes were obtained for almost all the arenediazonium salts tested. Some exceptions were *o*- and *p*-nitrobenzenediazonium salts, which only gave nitrobenzene as the main reaction product. It seems that the reaction was also sensitive to the steric effects since mesitylenediazonium salt did not produce the corresponding styrene. A specific application by the same authors was vinylation of a benzocrown ether[23] (Scheme 5).

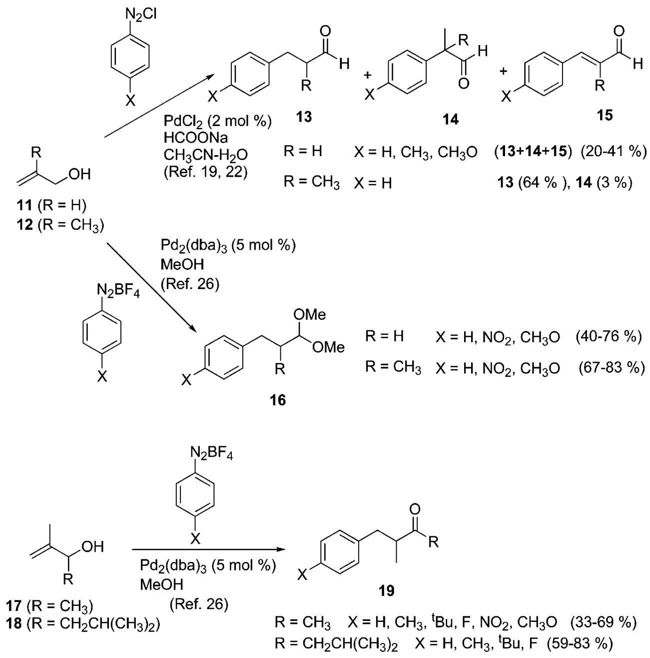
The effects of the olefinic compound and other reaction variables such as the reaction medium, catalytic systems, and additives on the arylation process were studied in detail by the same Japanese authors.[22] As a general trend, reactions took place under mild conditions, such as room temperature, over a period of just 0.5−1 h and were easy to follow given that the process ended with cessation of the production of nitrogen gas. Except for the case of nitrobenzenediazonium salts, it was found that a variety of arenediazonium salts could be used for the arylation of the studied olefins. Acetonitrile, methylene chloride, and acetone were the best solvents, whereas alcohols resulted in reduction of diazonium salts. However, later studies by other authors, which will be commented on below, have found that alcoholic solvents gave the best arylation results. $Pd_2(dba)_3$ proved to be the best catalyst, and the presence of ligands such as phosphines led to worse results being achieved since they caused decomposition of the salts.[4] Among the bases tested, NaOAc, Et_3N, Na_2CO_3, or none, NaOAc proved to be the most effective. Scheme 6 shows the different olefins that were arylated by arenediazonium salts in this study. The isolated yields of their arylation by benzenediazonium salt are given within brackets.

Scheme 6



Both electron-withdrawing and -releasing groups on the double bond gave the arylated products in moderate to good yields. An exception was acrylonitrile and 1-pyrrolidinylcyclopentene, which only gave a tarry material. The detailed study of acrylonitrile was taken up again in 2001 when Cai et al.[24] published a paper that investigated both the arylation of acrylonitrile and acrylamide with various arenediazonium tetrafluoroborates using $Pd(OAc)_2$ in EtOH at 80 °C. The corresponding (*E*)-cinnamonitrile and (*E*)-cinnamamide derivatives were obtained in yields of between 78% and 89%. Furthermore, the particular case of allylic alcohols **11** and **12** resulted in poor yields and poor regioselectivity of the corresponding arylated compounds[19,22] (Scheme 7). A careful search of the literature has revealed only two recent reports related to the Matsuda−Heck reaction (as we shall call the arylation of olefins by arenediazonium salts hereafter) of allylic alcohols with diazonium salts.[25,26] In 2001, another

Scheme 7

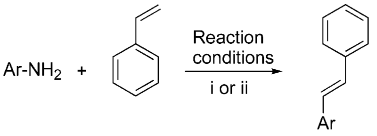


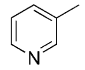
paper published by Cai et al.[25] reported yields of up to 63% for the arylation of alcohols **11** and **12** using $Pd(OAc)_2$ as the catalyst in EtOH at 60 °C. More recently, Muzart, Roglans et al.[26] achieved the arylation of several allylic alcohols with arenediazonium tetrafluoroborates with $Pd_2(dba)_3$ in MeOH, obtaining the corresponding protected aldehydes **16** from primary alcohols **11** and **12** and ketones **19** from secondary alcohols **17** and **18** (Scheme 7).

2.1.2. Nature of Arenediazonium Salts

One of the main limitations of olefin arylations by diazonium salts is the instability of some of these salts at room temperature. Studying the reaction of arylamines with styrene in the presence of palladium salts, Fujiwara et al.[27] found that addition of an equimolar amount of *tert*-butyl nitrite to the reaction mixture considerably improved the yields of the corresponding stilbenes. Inspired by Matsuda's success in obtaining aryl-substituted olefins by a Pd-catalyzed reaction of the olefin and arenediazonium salts,[19] Fujiwara described for the first time a direct domino diazotization−styrene arylation by amines in the presence of palladium salts (Scheme 8). However, in the method used by Fujiwara, stoichiometric amounts of $Pd(OAc)_2$ were required in order to obtain good yields (conditions i in Scheme 8). At the same time, Matsuda et al.[28] described the arylation of several olefins by arylamines (the examples with styrene are given in Scheme 8) using alkyl nitrite and catalytic amounts of $Pd_2(dba)_3$. In this case it was necessary to add a mixture of monochloroacetic acid and acetic acid to improve the results (conditions ii in Scheme 8).

Scheme 8



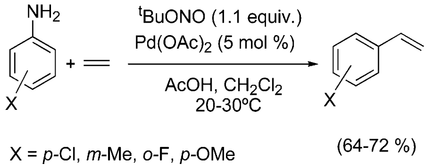
Ar	Reaction conditions[a]	yield (%)	Ref.
Ph	i	52	27
Ph	ii	97	28a,b
p-MeC_6H_4	i	74	27
p-MeC_6H_4	ii	84	28a,b
p-$OMeC_6H_4$	i	62	27
p-$OMeC_6H_4$	ii	67	28b
p-$NO_2C_6H_4$	i	51	27
p-$NO_2C_6H_4$	ii	79	28a,b
o-$NO_2C_6H_4$	ii	73	28a,b
m-MeC_6H_4	ii[b]	63	28b
o-MeC_6H_4	ii[b]	57	28b
o-$OMeC_6H_4$	ii[b]	87	28b
o-ClC_6H_4	ii[b]	58	28b
m-ClC_6H_4	ii	54	28b
p-ClC_6H_4	ii	84	28a,b
p-BrC_6H_4	ii	61	28a,b
p-IC_6H_4	ii	46	28b
1-naphthyl	i	48	27
2-naphthyl	i	38	27
	ii	49	28b

[a] Reaction conditions i) $Pd(OAc)_2$ (1 equiv.), ^tBuONO, CH_3CN, 60ºC; ii) $Pd_2(dba)_3$ (5 mol %), ^tBuONO, AcOH-$ClCH_2COOH$, 50ºC

[b] 10 mol % of $Pd_2(dba)_3$ was used

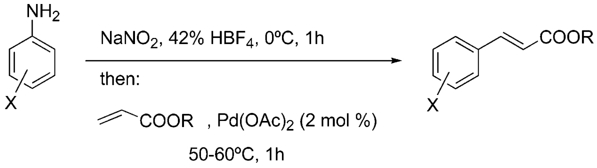
In situ generation of diazonium salts in the reaction mixture had the advantage of avoiding prior isolation of the sensitive arenediazonium salts, and the whole arylation process was run in a single step. Using this methodology, it proved possible to arylate styrene with nitro-substituted anilines, which had never been previously achieved and, additionally, arylate several olefins with 3-aminopyridine, whose diazonium salt decomposes easily at room temperature (Scheme 8). The "one-pot" diazotization−arylation reaction was also subsequently employed by other authors. Beller et al.[29] described the direct synthesis of substituted styrenes starting from several anilines and ethylene. The diazotization−arylation process took place in the presence of ^tBuONO, acetic acid, and a catalytic amount (5 mol %) of $Pd(OAc)_2$ at room temperature and with ethylene under atmospheric pressure (Scheme 9).

Scheme 9



Sengupta et al.[30] compared the arylation of several olefins starting with isolated arenediazonium tetrafluoroborates with the one-pot protocol starting directly with anilines. The yields of the corresponding arylated olefins were similar for the two methods tested. In the first methodology the authors used EtOH as a solvent and $Pd(OAc)_2$ as a catalyst. Given that the diazotization process took place in an aqueous medium, the one-pot protocol was run in water, which is advantageous from both a cost and environmental point of view (Scheme 10). In the field of the synthesis of unnatural amino acids, the same direct domino diazotization Matsuda−Heck reaction was applied by Sengupta et al.[31] to anilino−alanine derivatives to obtain good yields of the desired styrylalanines (Scheme 10). It should be noted that, as is generally found when using arenediazonium salts as electrophiles, the above-described reactions were very fast, being completed in 1 h.

Scheme 10



X	R	Yield (%)	Ref
p-OMe	Et	68	30
p-Cl	Et	80	30
o-COOH	Et	65	30
p-COOH	Et	68	30
p-$CH_2CH(CO_2Me)(NHCO_2Et)$	Me	82	31
o-OMe , m-$CH_2CH(CO_2Me)(NHCO_2Et)$	Me	80	31

With regard to functionalization of porphyrins, in situ diazotization of nickel(II) complexes of β-amino-*meso*-tetraphenylporphyrin derivatives followed by addition of several olefins (methyl acrylate, propenal, and methyl vinyl ketone) and $Pd(OAc)_2$ in THF has been reported.[32] This has permitted introduction of unsaturated substituents in the β-position of these porphyrin derivatives.

Sengupta[33] and Goeldner[34] proposed an alternative to overcome the problem of the instability of arenediazonium salts based on the study of the effect of their counteranions on the Matsuda−Heck reactions. Sengupta et al.[33] generated several arenediazonium salts in situ with different counteranions (OAc, ClO_4, F, CH_3SO_3, BF_4, CF_3CO_2) by acidolysis of 1-aryltriazenes with the corresponding acid and studied their utility in the Matsuda−Heck reaction with ethyl acrylate. With the exception of acetic acid, all acids produced clean arylation processes in high yields (73−97%). For all cases studied, the more economical diazonium perchlorates and fluorides gave better results than the corresponding isolated arenediazonium tetrafluoroborates. Goeldner et al.[34] described an efficient, mild procedure for the synthesis of arenediazonium trifluoroacetates under anhydrous conditions. The method permitted production of large quantities of an extensive series of aniline derivatives. Their application in the arylation of ethyl acrylate was studied in depth, and an interesting alternative to arenediazonium tetrafluoroborates was found.

A very recent contribution in this area is due to Barbero, Fochi et al.[35] and Dughera,[36] which use arenediazonium *o*-benzenedisulfonimides (Figure 1) as an interesting alternative to the more usual arenediazonium tetrafluoroborates. These compounds are easy to prepare and isolate and are highly stable.[37] Furthermore, benzenedisulfonimide is easily recovered for reuse at the end of the reaction. The authors use this kind of arenediazonium salt in Matsuda−Heck[35] and Stille[36] (see section 2.4.1.) coupling reactions. In the case of the Matsuda−Heck reaction, several olefins such as ethyl acrylate, acrylic acid, acrolein, styrene, and cyclopentene have been arylated efficiently using $Pd(OAc)_2$ (1 mol %) as a catalyst. The appropriate solvent and temperature are specific for each olefin. Curiously, in the particular cases of acrylic acid and acrolein, the presence of stoichiometric quantities of the base such as $CaCO_3$ are necessary to afford good yields of the corresponding cinnamic acids and aldehydes. Arenediazonium *o*-benzenedisulfonimides are highly efficient electrophiles with both electron-donating and electron-withdrawing substituents and also if they are sterically hindered.

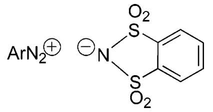
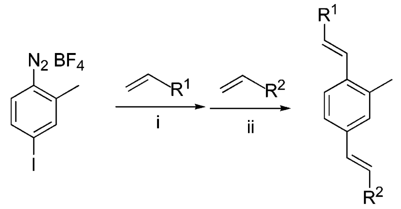


Figure 1.

2.1.3. Superior Reactivity of N_2 as the Nucleofuge

It should be noted that in most cited cases reactions with chloro-, bromo-, or iodo-substituted arenediazonium salts displayed a high degree of chemoselectivity, indicating the superior reactivity of the diazonium nucleofuge over chloride, bromide, and even iodide. This fact illustrates one of the advantages of working with arenediazonium salts as arylating reagents in Matsuda−Heck reactions and shows that the aryl−nitrogen bond is more reactive to zerovalent palladium than aryl−halogen bonds. Sengupta[38] and Xu[39] have taken advantage of the above-mentioned differential coupling of the nucleofuges. Sengupta[38] described a stepwise assembly carried out on a 4-iodo-2-methylbenzenediazonium salt to prepare unsymmetrical divinylbenzene derivatives (Scheme 11). As shown in Scheme 11, the different regioisomers were obtained by switching the order in which the olefins were added.

Scheme 11

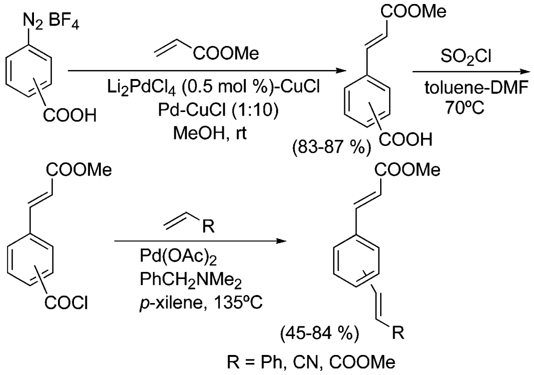


i) $Pd(OAc)_2$ (2 mol %), EtOH, 80°C
ii) $Pd(OAc)_2$ (2 mol %), $NaHCO_3$, TBAC, DMF, 100°C

R^1	R^2	Yield (%)
Ph	COOEt	55
COOEt	Ph	47
COOEt	CN	61
CN	COOMe	55

Xu et al.[39] also described the synthesis of unsymmetrical divinylbenzenes taking advantage of the superior reactivity of arenediazonium salts as compared to aroyl chlorides.[40] Several carboxybenzenediazonium salts were used to arylate methyl acrylate using Li_2PdCl_4−CuCl as a catalytic system in a methanolic solution at room temperature in 10−30 min. The corresponding alkenylated benzoic acids were transformed into their benzoyl chlorides, and this functionality was used to run a second Pd-catalyzed arylation process. Since it is known that arenediazonium salts in the presence of Cu(I) can give a Meerwein reaction, the authors ran the reaction in the absence of Li_2PdCl_4 to confirm that this reaction did not occur here. However, the authors do not explain why CuCl is required (Scheme 12).

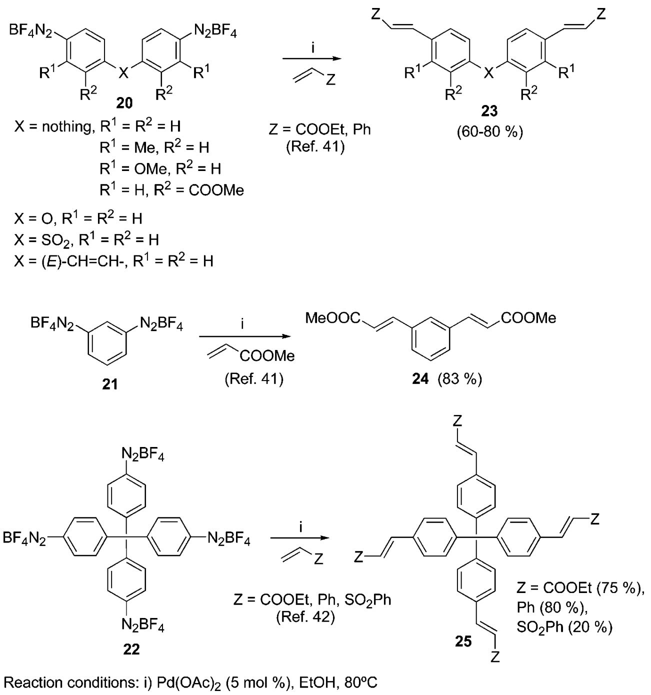
Scheme 12



Two- and 4-fold Matsuda−Heck reactions of bisdiazonium salts **20** and **21** and tetrakis-diazonium salt **22** were described by Sengupta et al.[41,42] as a further demonstration of the greater reactivity of arenediazonium salts. Matsuda−Heck adducts **23** and **24** were obtained after 1 h with 60−83% yields when $Pd(OAc)_2$ was used as a catalyst in EtOH at 80 °C. However, all attempts to synthesize unsymmetrical bisvinylated products by employing two different olefins were unsuccessful.[41] Tetravinylated products **25** were obtained in good yields from ethyl acrylate and styrene and in moderate yield from phenyl vinyl sulfone using the same reaction conditions as before. However, the Matsuda−Heck reaction of **22** with allylic alcohol failed to produce the arylated compound[42] (Scheme 13).

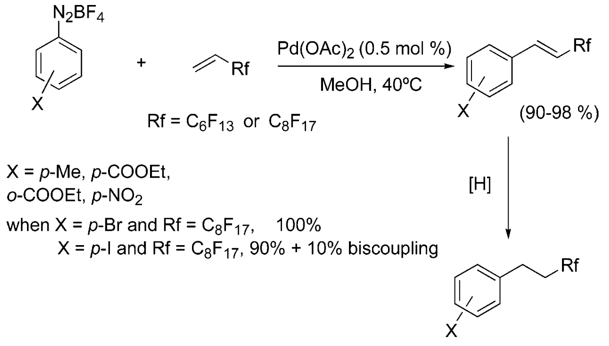
Another specific demonstration of the superior reactivity of arenediazonium salts over aryl halides as electrophiles in

Scheme 13



Matsuda−Heck reactions was given by Genêt et al.[43] on studying the arylation of perfluoroalkenes. The authors showed that only a diazonium substituent yielded an arylated product when arenediazonium tetrafluoroborates bearing a bromide substituent were coupled. In the case of the iodo substituent, 10% of a double coupling compound was also obtained. By then reducing the double bond, it was possible to prepare a large variety of perfluoroalkylated aromatic compounds (Scheme 14).

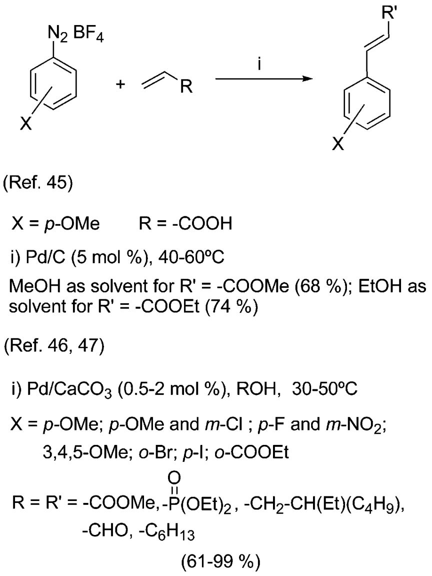
Scheme 14



2.1.4. Effect of Bases and Other Additives

Despite the work of Matsuda et al.[19,21−23] using NaOAc as a base, later studies demonstrated that not only is it normally possible to avoid bases but their use also generally gives worse results. This conclusion was also reached when phosphines were employed as an additive.[4] Both compounds were found to cause dediazoniation of the arenediazonium salts. The absence of a base in the reaction medium is another advantage of this methodology over the use of aryl halides as electrophiles. However, with the tetrafluoroborates, in the absence of base, stoichiometric quantities of fluoroboric acid are formed in the reaction medium, which could represent a significant problem for acid-labile substrates. A recent example of this in the literature was the finding that palladium-catalyzed arylation of acid-sensitive 1-alkoxy-1,3-butadiene derivatives was unsuccessful in the absence of a base.[44] However, the presence of NaOAc in the reaction medium permitted formation of Matsuda−Heck adducts although in low yields (27−37%). Moreover, generation of equimolar amounts of acid when the reaction was run in MeOH or EtOH can provoke transesterification processes in the arylation of acrylic esters. Beller et al.[45] took advantage of this to synthesize cinnamic acid esters using a tandem arylation−esterification reaction of acrylic acid (Scheme 15). In this study, Beller used a heterogeneous palladium catalyst (Pd/C) in the arylation process for the first time, but it was found that the catalyst could not be reused in subsequent reactions.

Scheme 15

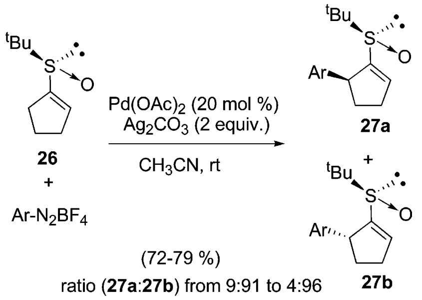


To overcome the problem of acid formation, Genêt et al.[46] improved the arylation of acrylic esters using the heterogeneous $Pd/CaCO_3$ catalytic system in alcoholic solvents at 30−50 °C. The mild heterogeneous base $CaCO_3$ helped to minimize the undesirable spontaneous degradation of arenediazonium salts. This catalyst was robust and practical since the reaction was run under aerobic conditions using nondegassed alcohols with a reaction time of less than 5 min and proved highly effective in the arylation of the problematic nitrobenzene diazonium salts. The same authors extended the method to the synthesis of arylated vinylphosphonates and used arenediazonium salts for the arylation of this kind of olefins for the first time[47] (Scheme 15).

A singular case was described by Carretero et al.[48] in the asymmetric Matsuda−Heck reaction of (*R*)-1-*tert*-butylsulfinylcyclopentene **26** with arenediazonium salts. Initial attempts to arylate the above-mentioned chiral sulfoxide derivative using aryl iodides gave a complex mixture of products due in part to the thermal instability of the alkyl sulfoxide. Since arenediazonium salts are more reactive electrophiles than iodides, allowing their use in milder reaction conditions such as lower temperatures, the authors tried to arylate the sulfoxides using these substrates. However, in the absence of a base the reaction failed, and it was necessary to use 2 equiv of Ag_2CO_3 in an acetonitrile solution (other bases such as NaOAc, K_2CO_3, $AgBF_4$, and $Tl(OAc)_2$ were tested but the conversions were in no case higher than 27%). Except for nitro- and ortho-substituted arenediazonium salts, which gave very poor results, clean reactions were obtained resulting in good yields of Matsuda−Heck adduct

27a/**27b**, and most significantly, these processes occurred in a highly stereoselective manner (Scheme 16).

Scheme 16



Ar = p-OMeC$_6$H$_4$, C$_6$H$_5$, p-MeC$_6$H$_4$, p-BrC$_6$H$_4$, m-MeC$_6$H$_4$

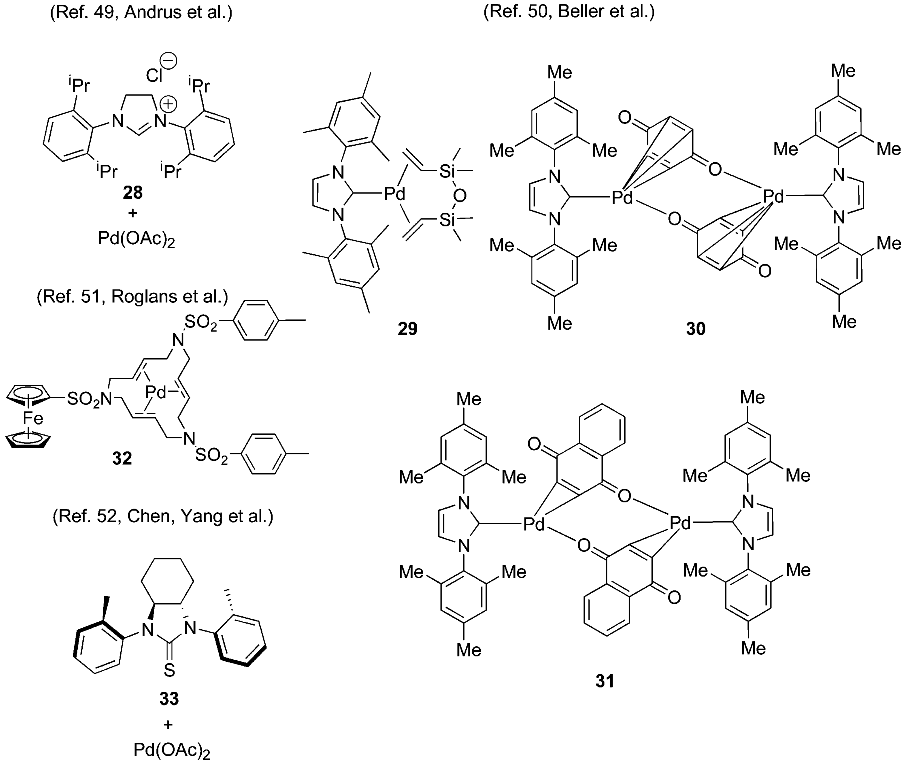
2.1.5. Improved Catalytic Systems

Since the methodology using arenediazonium salts as arylating reagents was established, progress in this field has been focused on improving the method by looking for more active and more productive catalytic systems. The most widely used palladium complexes in the Matsuda−Heck reactions in the cases commented on so far have been Pd(OAc)$_2$ as a Pd(II) source or Pd$_2$(dba)$_3$ as a Pd(0) source. Given that the presence of phosphines inhibits evolution of the reaction, use of palladium catalysts has been limited. Furthermore, a drawback of the use of arenediazonium salts compared to aryl halides is the relatively high load of palladium (2−20 mol %) required for the first substrates. One way in which this disadvantage might be overcome is to use a palladium(0) catalyst that easily generates a highly reactive 12e$^-$ or 14e$^-$ palladium complex at low temperature. Several new palladium ligands have been described which give good catalytic systems for Matsuda−Heck reactions using arenediazonium salts. Significant progress has been made over the past few years in this field. Scheme 17 shows the structure of these new and phosphine-free palladium catalysts. In 2002, Andrus at el.[49] reported the use of the in situ generation of a dihydroimidazolium (**28**) palladium complex as an efficient catalyst for Matsuda−Heck coupling between arenediazonium salts and several olefins. The reaction took place in 3−5 h at room temperature in THF without an added base and with a load of 0.1−2 mol % of catalyst. The utility of this catalytic system was further illustrated by the one-pot diazotization−arylation reaction. In situ generation of arenediazonium salt was performed at 0 °C in THF using *t*-BuONO and BF$_3$·OEt$_2$, and the mixture was warmed to room temperature after addition of the imidazolium−Pd catalyst and the corresponding olefin to the diazotizated solution.

In the same year, Beller et al.[50] described the catalytic activity of new monocarbenepalladium(0) complexes **29**−**31** in several coupling reactions of arenediazonium salts. Complex **29** gave the same good results as complexes **30** and **31**, although it was found to have the disadvantage that it decomposed to black palladium during the course of the reaction. All reactions used MeOH as the solvent with 0.5 mol % of complex **31** and were heated to 50−60 °C for 1 h. No difference in reactivity between arenediazonium salts was found even when NO$_2$ groups were present.

A novel air- and moisture-stable palladium(0) complex of a 15-membered macrocyclic triolefinic ligand **32** was described by Roglans et al.[51] as a highly active catalyst for Matsuda−Heck olefination of arenediazonium salts. It is noteworthy that the above-mentioned catalyst is the first *recoverable* system in this kind of processes. The reactions were performed under aerobic conditions at room temperature using EtOH as a solvent and 5 mol % of the Pd complex. However, since the catalyst was easily recovered by column chromatography and reused indefinitely, use of high catalyst loading was not a big drawback. The same catalyst was used

Scheme 17



in the arylation of the allylic alcohols mentioned above (see Scheme 7),[26] which demonstrated great activity in the arylation processes. However, Pd(0) complex **32** was decomplexed in the course of these experiments, making recovery of the catalyst impossible.

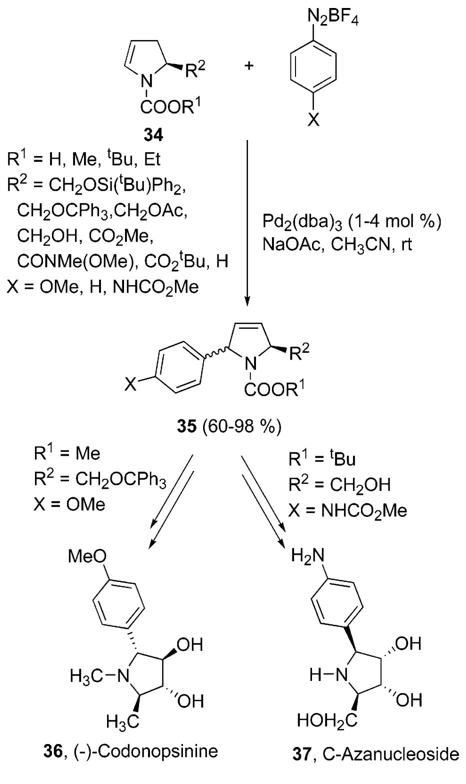
More recently, Chen, Yang et al.[52] synthesized a novel chiral thiourea-based ligand **33** as a new alternative to Matsuda−Heck olefination of styrene and methyl acrylate.

One interesting study of the recovery and recyclability of the catalytic system in these kinds of processes was described by Kabalka et al.[53] using ionic liquids as the reaction medium. For the first time, ionic liquids were used in Matsuda−Heck reactions using arenediazonium salts. Methyl acrylate and acrylonitrile were arylated using 2 mol % of $Pd(OAc)_2$ in $BmimPF_6$ as a solvent at room temperature or at 50 °C. The catalytic system was recycled four times without loss of activity. Surprisingly, when styrene was used as an olefin, no stilbene was produced but good yields of dimerization products were obtained.

2.1.6. Applications in Synthesis

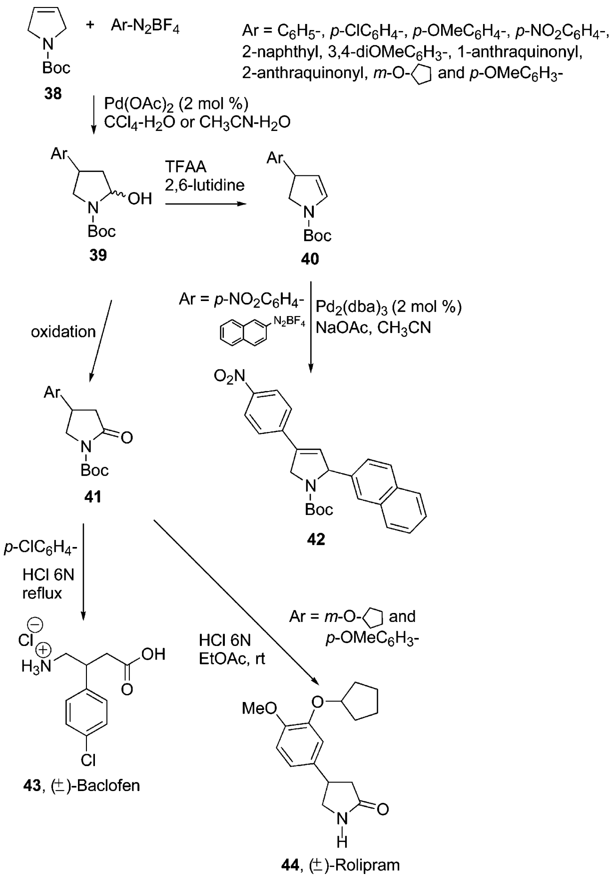
2.1.6.1. Arylation of Heterocyclic Olefins. Once the Matsuda−Heck reaction using arenediazonium salts was methodologically described, its application in the preparation of important synthetic target compounds gave further proof of its great potential. Correia et al. made a significant contribution using the reaction in the arylation of endocyclic enecarbamates[54−57] and 3-pyrrolines,[58−61] which are aryl heterocyclic frameworks present in the core structure of several natural and nonnatural compounds, some of which exhibit pharmacological activity. The authors demonstrated that arylation of several enantiomerically pure five-membered endocyclic enecarbamates **34** by arenediazonium salts was achieved using $Pd_2(dba)_3$, NaOAc as a base in CH_3CN at room temperature, and no excess of any reactants was required (Scheme 18). The initial Matsuda conditions[21,22] were found to be best for this kind of substrates, and a base was used to suppress side reactions.[55] The arylation reactions seemed to be highly regioselective without any detectable amounts of isomerized Matsuda−Heck adducts. Studies into control of diastereoselectivity for the Matsuda−Heck arylation demonstrated their dependence on the functional group R^2 at C-5 of enecarbamate **34**. Bulky and noncoordinating groups mainly gave the trans derivative, whereas coordinating groups such as CONMe(OMe) and CH_2OH gave the cis compound.[56] The trans and cis stereoselectivity were explored in the particular synthesis of the natural alkaloid (−)-codonopsinine **36** and the C-azanucleoside **37**, respectively. All attempts to arylate 2,3-dihydropyrrole derivatives with the respective iodide or triflate failed (Scheme 18).

Scheme 18

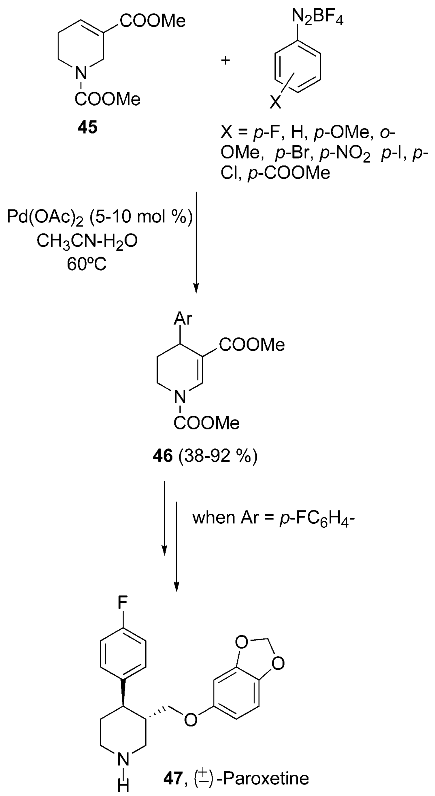


Correia et al.[58−61] also described a practical and efficient Matsuda−Heck arylation of *N*-Boc-3-pyrroline **38** with several diazonium salts using $Pd(OAc)_2$ as a catalyst with either equimolar mixtures of CCl_4-H_2O or aqueous acetonitrile as the solvent. Their protocol considerably improved on the Matsuda−Heck arylation of 3-pyrrolines using the classical aryl triflates or iodides. Since there was no base in the reaction medium, the presence of acid HBF_4 resulted in hydration of the arylated enecarbamate to give the corresponding lactamol (*N*,*O*-hemiacetal) **39**. Lactamol **39** was converted into the corresponding 4-arylenecarbamate **40** using trifluoroacetic anhydride and 2,6-lutidine or to the corresponding lactam **41** by an oxidation process. Further arylation of 4-arylenecarbamate **40** allowed the synthesis of several 2,4-diaryl-3-pyrrolines **42**. Treatment of lactam derivatives **41** with different acidic conditions permitted the synthesis of the γ-amino acid, (*rac*)-baclofen **43**, and the racemic phosphodiesterase inhibitor, (*rac*)-rolipram **44** (Scheme 19).

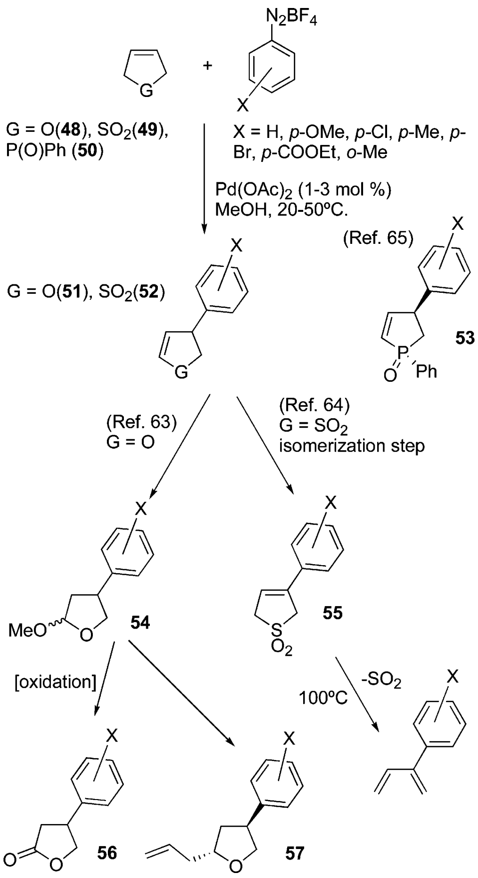
Scheme 19



Scheme 20



Scheme 21



In a very recent paper[62] the same authors described the total synthesis of (*rac*)-paroxetine **47**, an antidepressant drug, starting with the arylation of aza−endocyclic acrylate **45** with *p*-fluorophenyldiazonium tetrafluoroborate using $Pd(OAc)_2$ in acetonitrile−water at 60 °C (Scheme 20). In the present study the authors optimized the reaction conditions researching the Matsuda−Heck arylation of substituted acrylate derivatives. Since substituted olefins are more resistant to Heck arylations, this study represents an interesting contribution to this area.

Arylation of other heterocycloalkenes with arenediazonium salts has been described by other groups. Sengupta et al.[63,64] described the arylation of 2,5-dihydrofuran **48** and butadiene sulfone **49** in the presence of $Pd(OAc)_2$ in MeOH (Scheme 21). In the case of **48**, the corresponding Matsuda−Heck adduct suffered from a methanolysis process catalyzed by acid (HBF_4) to give the corresponding lactol ether **54** as was also observed in the arylation of 3-pyrrolines.[58,59,61] Derivatives **54** were oxidized to γ-butyrolactones **56** or converted to 2,4-disubstituted tetrahydrofuran derivatives **57**. Arylation of butadiene sulfone **49** gave 4-aryl-4,5-dihydrosulfolene derivatives **52**, which were isomerized to the corresponding 3-arylbutadiene sulfones **55**. Heating the arylated sulfolene **55** at 100 °C led to extrusion of SO_2, which is an indirect method of arylating butadiene in the internal carbon atom. The Matsuda−Heck reaction of **49** using aryl iodides as electrophiles was extremely slow (4−7 days) and produced low yields. Legros, Fiaud et al.[65] studied the Matsuda−Heck reaction of several 1-phenylphospholene-1-oxides **50**. Only low yields of arylated derivatives **53** were obtained employing aryl iodides after 2 days in refluxing acetonitrile. However, using several arenediazonium salts in the presence of $Pd(OAc)_2$ in MeOH at 50 °C, good yields of Matsuda−Heck adducts **53** were obtained (64−89%). The process was completely stereospecific as the arylpalladium intermediate attacked the less hindered face of phospholeneoxide **50** (Scheme 21).

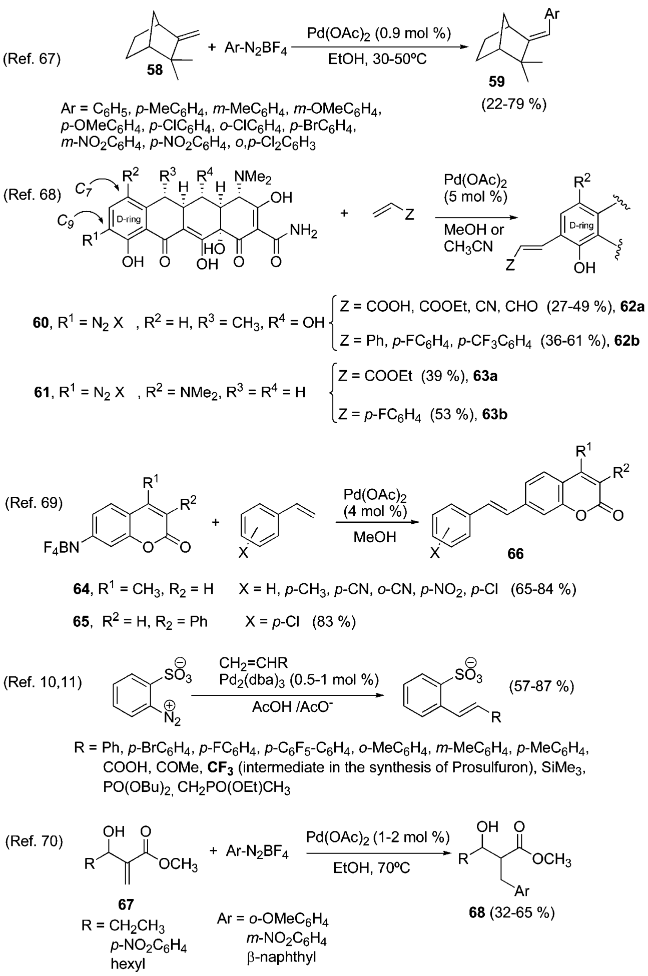
More recently, Schmidt[66] described the arylation of 4-substituted 4,5-dihydrofurans and 6-substituted dihydropyrans using the conditions described by Matsuda: $Pd_2(dba)_3$ and NaOAc in acetonitrile at room temperature. Undesired double-bond migration reactions, one of the drawbacks in intermolecular Mizoroki−Heck arylation reactions of cyclic enol ethers,[14] were not observed. Furthermore, the reactions proved to be highly diastereoselective, and the trans isomer was obtained as the main product.

2.1.6.2. Other Specific Arylation Processes.

Arenediazonium salts have also been used in the synthesis of other specific compounds (Scheme 22). Arylation of highly hindered olefin in camphene **58** was performed using a wide range of substituted arenediazonium tetrafluoroborates, a process that was unsuccessful when employing aryl halides. The reaction seemed to be sensitive to steric effects because *o*-tolyldiazonium salt could not be coupled. 8-Arylcamphenes **59** were obtained in moderate to good yields, and the reaction was stereoselective to trans configuration isomers.[67]

In the field of tetracyclines, Nelson et al.[68] introduced reactive functional groups to the D ring at positions C7 and/or C9 by palladium-mediated reactions. The nucleofuge was present in the tetracycline core in these cases since preparation of tetracycline diazonium salts and iodotetracyclines was easily achieved. As shown in Scheme 22, 9-diazoniumdoxycycline **60** and aminocycline **61** reacted with several olefins in the presence of $Pd(OAc)_2$ to yield 9-functionalized tetracycline derivatives **62** and **63**, respectively. However, the reactions, in general, suffered from low yields due in part to formation of numerous side products. Use of the corresponding iodotetracycline derivatives with palladium

Scheme 22



and phosphine ligands seemed to be more efficient than the coupling reaction with the arenediazonium salts.

The facile synthesis of coumarin diazonium salts **64** and **65** by a typical diazotization reaction of 7-aminocoumarin derivatives permitted introduction of several substituted styryl groups at position 7 by a palladium-catalyzed Matsuda−Heck reaction.[69] Excellent yields of all styrylcoumarin compounds **66** were obtained (Scheme 22).

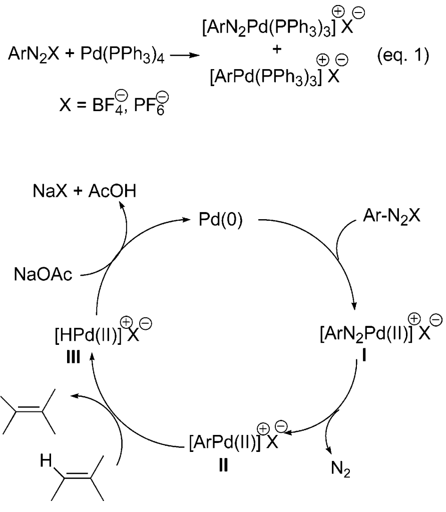
One of the most interesting cases of a Matsuda−Heck reaction is the already mentioned industrial process based on the arylation of trifluoropropene with the diazonium salt of aniline-2-sulfonic acid as a key step in the synthesis of Prosulfuron (see Scheme 3).[10,11] The optimized reaction conditions were found when the authors explored the arylation of 2-diazoniobenzenesulfonate by several olefins giving the corresponding styrenes in good yields[10a] (Scheme 22).

A very recent contribution is by Antunes et al.,[70] who describe for the first time the use of Baylis−Hillman adducts **67** as a versatile olefinic substrate for the Matsuda−Heck reaction with arenediazonium tetrafluoroborates. Moderate yields of the corresponding α-benzyl-*β*-keto esters **68** are obtained using $Pd(OAc)_2$ as a catalyst in EtOH at 70 °C. The procedure works well for arenediazonium salts with both electron-donating and electron-withdrawing substituents (Scheme 22).

2.1.7. Mechanistic Studies

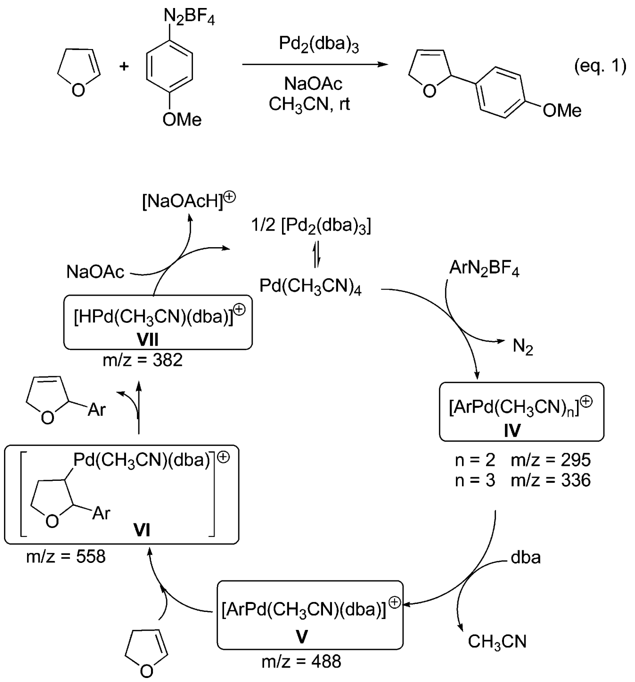
As mentioned in the Introduction, Matsuda et al.[9] isolated arylazopalladium and arylpalladium complexes by adding an equimolar amount of arenediazonium salts to $Pd(PPh_3)_4$ in acetonitrile (eq 1 in Scheme 23) leading to the proposal of the first catalytic cycle[19,22] (Scheme 23). The oxidative addition of Pd(0) to arenediazonium salt generates arylazopalladium complex **I**, which decomposes to the cationic arylpalladium complex **II** by extrusion of nitrogen gas. Insertion of the olefin to intermediate **II** and subsequent elimination of the arylated olefin give hydridopalladium(II) complex **III**. The counteranion (X) of diazonium salt is replaced by an acetate anion, and Pd(0) complex is recovered.

Scheme 23

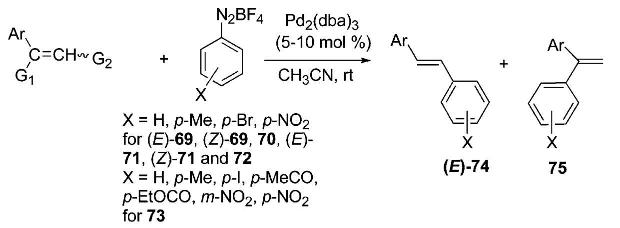


Little subsequent mention has been made about mechanistic aspects of the Matsuda−Heck reaction involving diazonium salts since its first report.[71] It has been observed that unlike the generally accepted mechanism involving aryl halides, oxidative addition of Pd(0) to diazonium salt is not the rate-determining step given that these arylation reactions are not very sensitive to the electronic nature of the substituent in the arenediazonium salts. However, it was not until 2004 that the mechanism of the Matsuda−Heck reaction with arenediazonium salts was studied in depth by Eberlin, Correia et al.[72] using electrospray ionization mass spectrometry (ESI-MS and ESI-MS/MS), a technique which has become increasingly popular as a mechanistic tool for studying short-lived reactive intermediates involved in organometallic catalytic reactions.[73] This mechanistic study was based on the arylation of 2,3-dihydrofuran with 4-methoxybenzenediazonium tetrafluoroborate using $Pd_2(dba)_3$ as a catalyst in CH_3CN at room temperature (eq 1 in Scheme 24). The proposed mechanistic cycle (Scheme 24) was based on ESI-MS detection of several cationic intermediates of the oxidative addition step (**IV** and **V**), olefin insertion step (**VI**), and *β*-elimination step (**VII**). All intermediates detected by ESI-MS were further studied by tandem mass spectrometry (MS/MS) in order to confirm their structure. The intermediates given in the boxes in Scheme 24 were those detected by ESI-MS. It should be observed that in the oxidative addition step a dynamic process with ligand equilibria between the cationic intermediates **IV** and **V** was observed with intermediate **V** being the most reactive and abundant after 90 min of reaction. Hence, adding the olefin after this period of time led to an increased yield of the arylated olefin. This ESI-MS study supported the proposed Matsuda's initial catalytic cycle (Scheme 23). The rate-determining step of the process was investigated in a parallel ESI-MS study conducted by Roglans et al.[51,74] using ethyl acrylate as the olefin and the macrocyclic palladium(0) complex **32** (Scheme

Scheme 24



Scheme 25



X = H, p-Me, p-Br, p-NO_2 for (E)-**69**, (Z)-**69**, **70**, (E)-**71**, (Z)-**71** and **72**
X = H, p-Me, p-I, p-MeCO, p-EtOCO, m-NO_2, p-NO_2 for **73**

vinyl derivative	Ar	G_1	G_2	Yields (%)	Products (ratio [(E)-**74**:**75**](%))
(E)-**69**	Ph p-MeC_6H_4 p-$NO_2C_6H_4$	H	$SiMe_3$	67-100	from 58:42 to 86:14
(Z)-**69**	Ph	H	$SiMe_3$	45-100	from 64:36 to 80:20
70	Ph	SiR_3 (R=Me, Et, Ph)	H	43-100	100:0
(E)-**71**	Ph	H	$GeMe_3$	81-87	from 52:48 to 85:15
(Z)-**71**	Ph	H	$GeMe_3$	85-95	from 64:36 to 88:12
72	Ph	$GeMe_3$	H	85-92	100:0
73	Ph	SnR_3 (R=Me, Et, Bu)	H	54-98	(Z)-**74**:(E)-**74** from 82:18 to 93:7

17). On the basis of the ESI-MS results, it can be postulated that insertion of the olefin in this specific catalytic system was the rate-determining step as the oxidative addition intermediate was generated easily and persistent in the ESI spectra until the reaction was completed.[74]

2.1.8. Related Matsuda–Heck Reactions

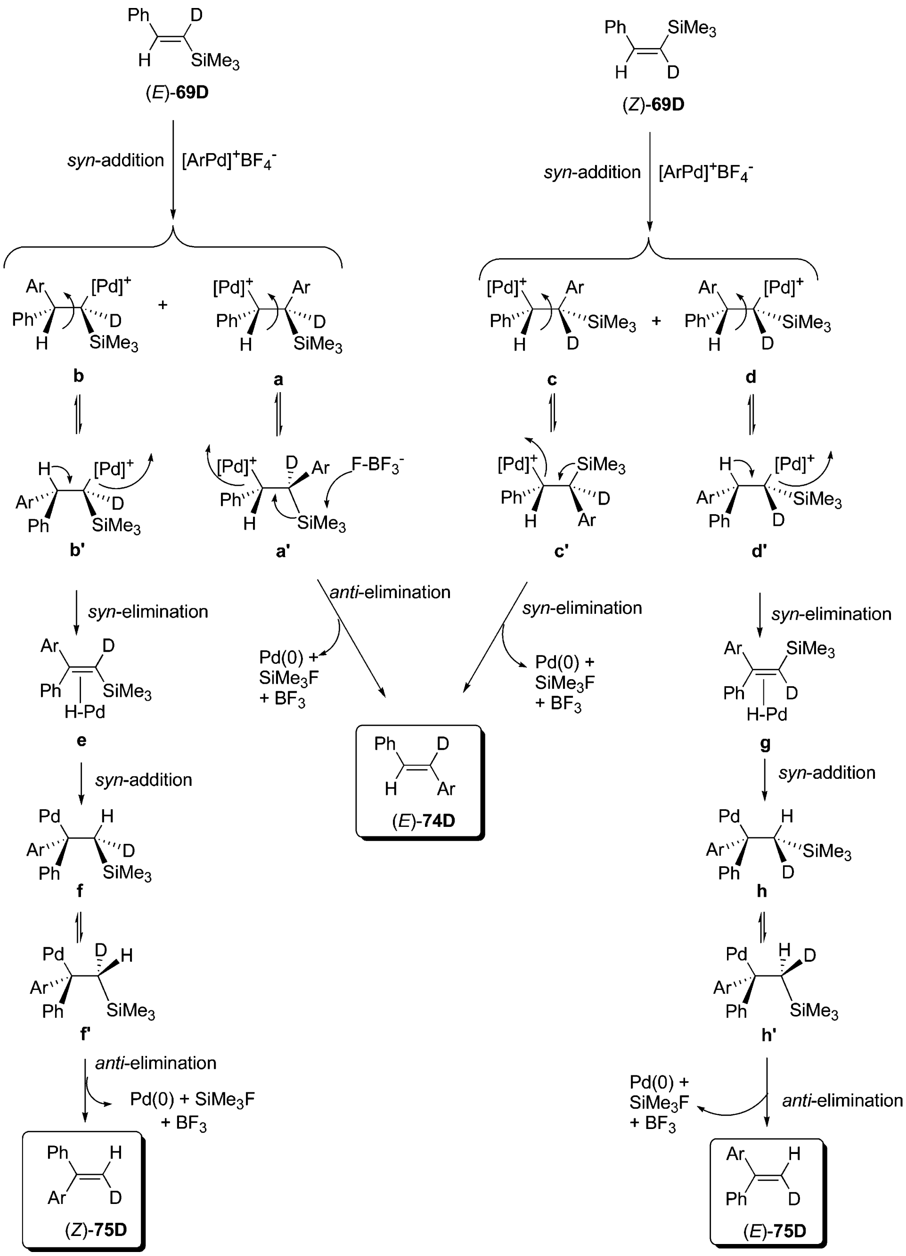
Arylation procedures which are related to the Heck type have also been described by the Japanese group of Kikukawa, Matsuda et al.[75,76] based on the aryldesilylation of α- and β-substituted vinylsilanes by arenediazonium salts to obtain stilbene derivatives (Scheme 25). These processes were one of the first examples of organosilicons with transition-metal complexes. As shown in Scheme 25, both (*E*)- and (*Z*)-β-(trimethylsilyl)styrenes (*E*)-**69** and (*Z*)-**69** were easily aryldesilylated by several arenediazonium salts in the presence of $Pd_2(dba)_3$ in acetonitrile at room temperature. Good to excellent yields of arylated styrenes were obtained (45−100%) as a mixture of (*E*)-stilbenes (*E*)-**74** and α,α-diarylated ethylenes **75** in a poor regioselective process. In no cases was the cis isomer of stilbene (*Z*)-**74** formed, not even when starting with (*Z*)-β-(trimethylsilyl)styrene (*Z*)-**69**.

Mechanistic studies were conducted using deuterium isotope labeling experiments on (*E*)- and (*Z*)-PhCH═C(D)-$SiMe_3$, (*E*)-**69D** and (*Z*)-**69D**, to understand the interesting regio- and stereoselective aryldesilylation process. Scheme 26 shows the mechanistic proposal made by the Japanese group.[75,76] Both (*E*)-**69D** and (*Z*)-**69D** gave (*E*)-**74D** as the major product, whereas (*Z*)-**75D** and (*E*)-**75D** were obtained as minor products from (*E*)-**69D** and (*Z*)-**69D**, respectively. The loss of regioselectivity in the present reactions seems to be incompatible with a transmetalation process and more in accordance with the proposed addition−elimination mechanism. The mechanism starts with syn addition of Ar−Pd species to the vinylsilane derivative to generate intermediates **a** and **b** from (*E*)-**69D** and **c** and **d** from (*Z*)-**69D**. Cleavage of the Si−C bond was postulated as being assisted by the fluoride anion present in the reaction medium as a counteranion of the arenediazonium salt. The desilylation step is often not stereospecific as there can be two possible routes that may be followed: (a) a nucleophile-assisted E_2 elimination of Pd(0) and $SiMe_3$ moieties such as **a′**, **f′**, and **h′** to give, respectively, (*E*)-**74D**, (*Z*)-**75D**, and (*E*)-**75D** or (b) syn elimination of $PdSiMe_3$ as the usual PdH syn elimination in the regular Heck reaction such as **c′** to give (*E*)-**74D**. Stereospecific formation of (*Z*)-**75D** (or (*E*)-**75D**) was postulated as following an isomerization process of intermediate **b′** (or **d′**) to **f** (or to **h**) in a syn elimination and syn addition of a H−Pd species.

In the case of α-substituted vinylsilanes **70** treated under the same reaction conditions as before, only (*E*)-stilbene derivative (*E*)-**74** was produced, and the ipso-substituted product could not be detected (Scheme 25). The new methodology was applied by the same authors to the aryldegermylation of styryltrimethylgermanes (*E*)-**71**, (*Z*)-**71**, and **72**[77] and even to the aryldestannylation of α-styrylstannanes **73**,[78] which are compounds that are highly reactive with arylpalladium species via transmetalation mechanism.[79] The same addition−elimination mechanism was postulated for the two processes. (*E*)- and (*Z*)-β-styrylgermanes (*E*)-**71** and (*Z*)-**71** had the same behavior as the equivalent (*E*)- and (*Z*)-β-(trimethylsilyl)styrenes (*E*)-**69** and (*Z*)-**69**. Furthermore, aryldegermylation of styryltrimethylgermanes **72** selectively produced the (*E*)-stilbenes derivatives (*E*)-**74** in excellent yields. Curiously, (*Z*)-stilbenes (*Z*)-**74** were selectively formed from the styrylstannanes **73**, presumably due to steric effects of aryl and R_3Sn groups on the stability of the intermediate adducts postulated (Schemes 25 and 26).

Naso et al.[80] recently adapted the same methodology as reported for α-substituted vinylsilanes **70** to the stereoselective synthesis of distyryl benzenes **76** and synthesis of conjugated polymers **77** (Scheme 27). As shown in Scheme 27, the present reactions were regio- and stereoselective and produced good yields of the final products.

Scheme 26



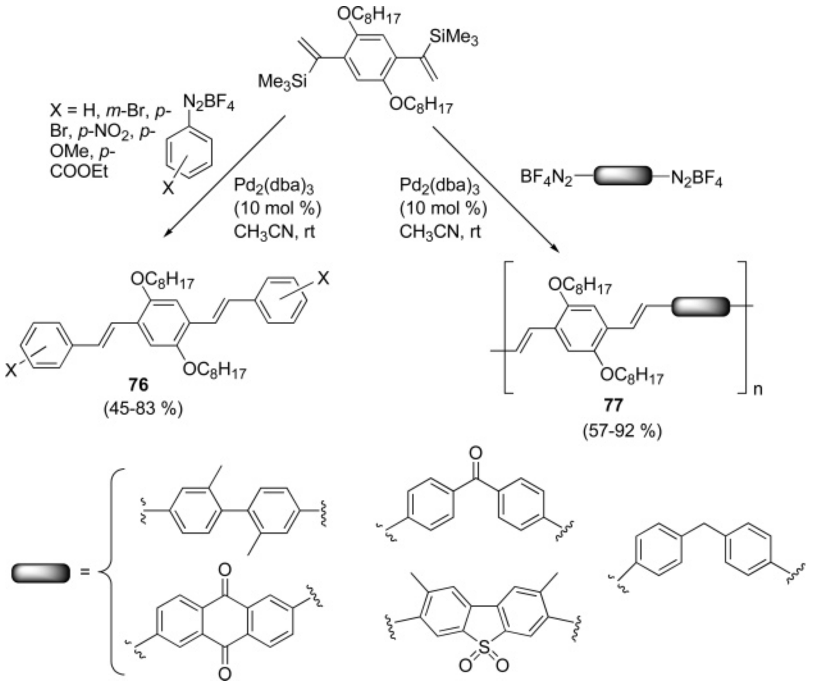
Another application of organosilanes with arenediazonium salts in the presence of palladium complexes was also described by Kikukawa et al.[81] and involved use of vinyltrimethylsilane **78** as an advantageous ethylene equivalent for the vinylation of arenediazonium salts (Scheme 28). Treatment of **78** with several arenediazonium salts using $Pd_2(dba)_3$ as a catalyst produced a mixture of styrenes, β-(trimethylsilyl)styrenes, and small amounts of α-styrylsilanes. On controlling the reaction conditions, the authors found that addition of HCl to the reaction mixture promoted protodesilylation of β-(trimethylsilyl)styrenes and gave the corresponding styrene derivatives. In addition, when an excess of vinyltrimethylsilane **78** was used, β-(trimethylsilyl)styrene was the main product. On the basis of these results, Sengupta et al.[82] reported a double Matsuda–Heck reaction with arenediazonium salts using vinyltriethoxysilane **79** as a more suitable ethylene equivalent than vinyltrimethylsilane **78**, given that **79** is cheaper and less volatile. The corresponding symmetric stilbenes were obtained in good yields.[82a] The same double Matsuda–Heck reaction starting with bisarenediazonium salts **20** allowed poly(arylenevinylene)s with high degrees of regioselectivity to be prepared[82b] (Scheme 28).

2.2. Suzuki–Miyaura Reaction

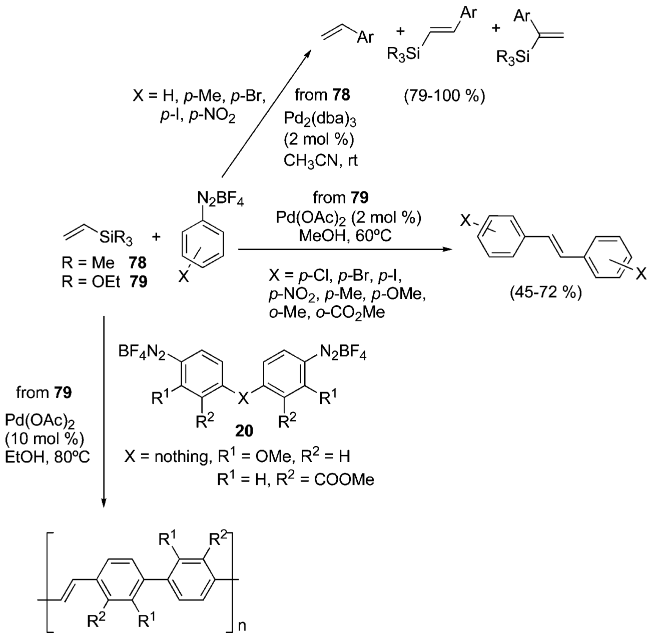
2.2.1. Early Studies

It was not until 20 years after the first utilization of the arenediazonium salts in a palladium-catalyzed reactions that these electrophiles were applied in Suzuki–Miyaura cross-couplings. This late discovery was made independently, but simultaneously, in the laboratories of Genêt et al.[83] and Sengupta at al.[84] Moderate to good yields of biaryls were obtained by coupling of arenediazonium tetrafluoroborates and arylboronic acids in the presence of catalytic amounts of $Pd(OAc)_2$ and in the absence of both an added base and ligands. The choice of both the solvent and the temperature was of great importance in the final outcome of the reaction with 1,4-dioxane at room temperature[83] or refluxing ethanol or methanol[84] being found to be the combinations which gave

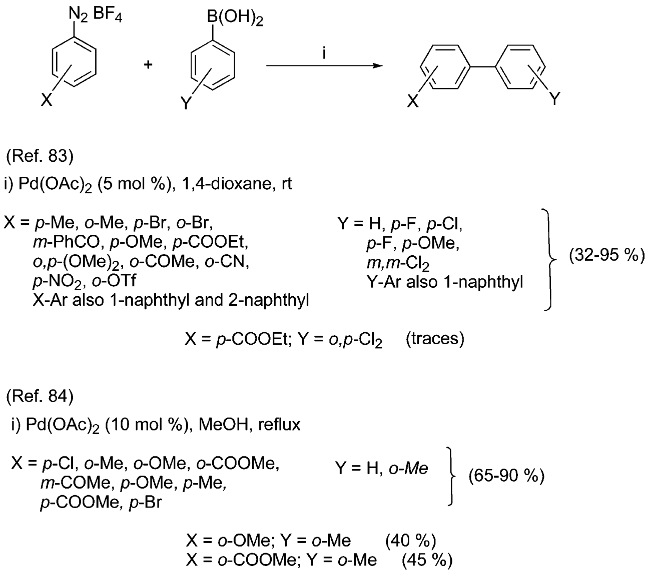
Scheme 27



Scheme 28



Scheme 29

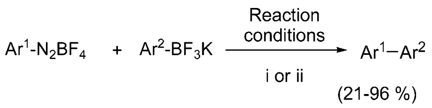


the best results (Scheme 29). A wide range of substituents could be present in both the boronic acid and the diazonium salt. Furthermore, and contrary to what is observed for Suzuki−Miyaura couplings with aryl halides, only slightly different reaction rates were observed for electron-donating and electron-withdrawing substituted arenediazonium salts: clear evidence that the oxidative addition of PdLn to the diazonium salts may not be the rate-limiting step for these reactions. As far as steric hindrance is concerned, cross-couplings were not generally affected by ortho substituents on the diazonium component, and only slightly higher yields were obtained in the para series as compared to the ortho ones. However, in the case of ortho substitution in the boronic counterpart, steric effects come into play, resulting in either only trace amounts of products being obtained using the Genêt method (even if raising the temperature up to 40 °C)[83] or moderate yields (40−45%) of ortho,ortho′ disubstituted biaryls following Sengupta's method.[84]

2.2.2. Modification of the Boronic Counterpart

After the initial discovery the Genêt group performed an intensive study to improve the reaction by modifying the boronic counterpart.[85] The search for a more nucleophilic organoborane moiety led them to test potassium aryltrifluoroborates, whose easy preparation had been previously reported by Vedejs et al.[86] in the Suzuki−Miyaura coupling. These very stable, water-resistant, and easily isolated nucleophiles were shown to be more efficient and reactive than the corresponding organoboronic acids, leading to higher product yields in shorter time periods as can be seen in the table included in Scheme 30. Even though ortho substitution of the arenediazonium salts did not hinder the coupling reaction, low yields of biaryl were obtained, together with

Scheme 30



i) $Pd(OAc)_2$ (5 mol %), 1,4-dioxane
ii) $Pd_2(\mu\text{-}OAc)_2(P(o\text{-tolyl})_3)_2$ (5 mol %), MeOH

Ar^1 = p-MeC_6H_4, p-$NO_2C_6H_4$, p-$PhCOC_6H_4$, p-$COOEtC_6H_4$, o,p-$(OMe)_2C_6H_3$, o-$CH_3COC_6H_4$, p-FC_6H_4, 4-Br-2,6-$(Me)_2C_6H_2$, p-BrC_6H_4, p-IC_6H_4, p-$OTfC_6H_4$

Ar^2 = C_6H_5, p-FC_6H_4, p-$OMeC_6H_4$, 3-thiophenyl, o,p-$(Cl)_2C_6H_3$, o-$CHOC_6H_4$, 1-naphthyl, m-$NO_2C_6H_4$, p-IC_6H_4, p-$OTfC_6H_4$

Ar^1	Ar^2	Reaction conditions	Yield (%)	Yield (%) when using $Ar^2B(OH)_2$[a]
p-MeC_6H_4	C_6H_5	i	88	87
o,p-$(OMe)_2C_6H_3$	C_6H_5	i	69	32
p-$COOEtC_6H_4$	o,p-$(Cl)_2C_6H_3$	i	26[b]	5
p-BrC_6H_4	m-$NO_2C_6H_4$,	i	60	34
p-IC_6H_4	C_6H_5	i	41	17
p-$COOEtC_6H_4$	p-$OMeC_6H_4$	i	93	57
p-$COOEtC_6H_4$	p-FC_6H_4	i	96	49
p-$COOEtC_6H_4$	o,p-$(Cl)_2C_6H_3$	ii	73	5

[a] reaction conditions: $Pd(OAc)_2$ (5 mol %), 1,4-dioxane, rt. [b] GC yield

black palladium precipitation, when ortho-substituted aryltrifluoroborates were employed. However, ortho-substituted aryltrifluoroborates could be effectively coupled using a palladacyclic palladium(II) catalyst, *trans*-di(μ-acetato)-bis-[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (Figure 2), in methanol.

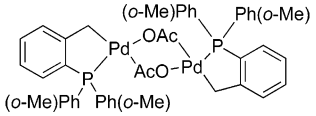


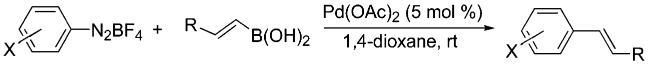
Figure 2.

Nevertheless, coupling of ortho,ortho′-disubstituted compounds could not be achieved, with one single exception when using the highly reactive naphthyltrifluoroborate, which permitted the tri-ortho-substituted 1-(4-bromo-2,6-dimethylphenyl)naphthalene to be obtained with a modest yield of 21%. It is noteworthy that heteroaromatic compounds such as potassium thiophenetrifluoroborate may also be coupled with excellent results.

Genêt et al.[83b] showed that alkenyl boronic acids could also be effectively coupled to arenediazonium tetrafluoroborates using $Pd(OAc)_2$ in 1,4-dioxane at room temperature. Stilbene and styrene derivatives were obtained in good to moderate yields (Scheme 31).

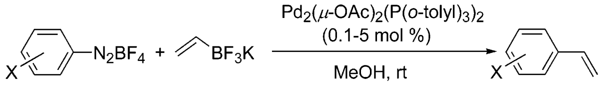
Styrene derivatives can be easily obtained by coupling vinyl bromide to an arylboronic acid[15] or coupling vinylboronic acid with an aryl halide derivative.[15,87a] However, vinylboronic acid is a relatively unstable compound,[87] and attempts carried out so far using vinylboronic ester have invariably resulted in a mixture of compounds derived from both Suzuki−Miyaura and Mizoroki−Heck coupling reactions.[88] An elegant step forward was proposed by Genêt et al.[85b,89] in describing an efficient synthesis for potassium vinyltrifluoroborate and studying its reactivity toward arenediazonium salts under palladium catalysis. Good yields of differently substituted styrenes were obtained between 5 and 120 min using 0.1−1 mol % of *trans*-di(μ-acetato)-bis-[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (Figure 2) in methanol at room temperature (Scheme 32). It must be pointed out that even acidic groups such as carboxyl were tolerated in this coupling. The same conditions were applied to the coupling of styryltrifluoroborate to arenediazonium tetrafluoroborates, giving excellent yields.

Scheme 31



X = p-OMe / R = phenyl: 75%
X = o-Br / R = phenyl: 91%
X = o-$COCH_3$ / R = phenyl: 63%
X = o-$COCH_3$ / R = butyl: 41%

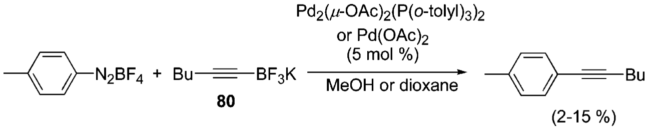
Scheme 32



X = p-OMe: 81 %
X = o-Me: 78 %
X = p-COOEt: 88 %
X = o-COOEt: 70 %
X = p-COOH: 72 %
X = m-COPh: 81 %
X = p-NO_2: 84 %
X = p-Br: 69 %
X = p-OTf: 75 %
X = m-I: 76 %

As a logical follow-up on the diversification of substrates, Genêt et al.[85b] tried to extend the diazonium−trifluoroborate coupling to formation of sp^2−sp carbon−carbon bonds. Unfortunately, only small amounts of 1-(hex-1-ynyl)-4-methylbenzene could be obtained together with decomposition products of starting materials on the coupling of the alkynyltrifluoroborate **80** with 4-methylbenzenediazonium tetrafluoroborate using either palladium(II) acetate or *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium-(II) (Figure 2) as catalyst (Scheme 33).

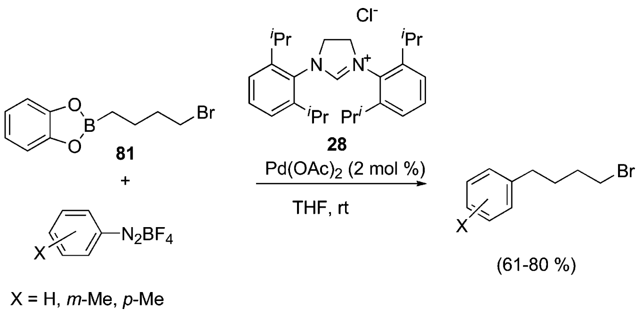
Scheme 33



The higher reactivity of the RBF_3K/RN_2BF_4 system also allowed, for the first time, the C−C coupling of weak nucleophilic compounds such as perfluorophenyl or perfluroalkenyl derivatives, as described by Frohn et al.[90] As opposed to the hydrocarbonate organoboric compounds, polyfluoroorganoboric derivatives, with the exception of 3,4,5-trifluorophenylboronic acid,[91] had never been successfully applied to cross-couplings. Indeed, $C_6F_5BF_3K$, $C_6H_{5-n}F_nBF_3K$, and $CF_2{=}CFBF_3K$ were coupled with various arenediazonium tetrafluoroborates using $Pd(PPh_3)_4$ in DME (polyfluoroaryl) or 1,4-dioxane (perfluoroalkenyl). Surprisingly, this is the only known Suzuki−Miyaura coupling of diazonium salt in which the phosphine-containing $Pd(PPh_3)_4$ catalyst renders its best performance in these reactions.

The coupling process of potassium aryl- and vinyltrifluoroborates with arenediazonium salts was adapted for use in ionic liquids by Mastrorilli et al.[92] The best performance of this reaction was achieved when using a 1:1 (v:v) mixture of $[bmim]BF_4$ and methanol, the latter acting as a scavenger for the coupling, which inhibits the BF_3 formed during the

Scheme 34



reaction. The choice of palladium source was once again of utmost importance; using Pd(OAc)$_2$ it was possible to use less catalyst than under organic solvent conditions, but the best results were achieved using the dinuclear azapalladacyclic complex (Figure 3), which reached a TOF of about 6000 h^{-1} in the coupling of arenediazonium salts with potassium vinyltrifluoroborates. Interestingly, working with a 20% excess of arenediazonium salt with respect to aryltrifluoroborate, it was possible to recycle the catalytic solution, although the yield was lower on the first run than that achieved when working with excess potassium trifluoroborate (from 93% to 72% yield) and only a moderate yield of 46% was obtained on the second catalytic run.

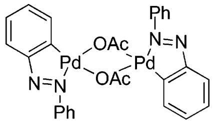


Figure 3.

2.2.3. Improved Catalytic Systems

One of the most commonly recognized drawbacks of palladium-catalyzed arenediazonium couplings is the relatively low activity of the catalysts. Some groups have tackled this by looking for more active and more productive catalysts, as already stressed in our discussion of Matsuda−Heck reactions. In fact, most of the catalysts tested in the Matsuda−Heck reaction (Scheme 17) were also tested in the Suzuki−Miyaura coupling. It should be noted that increased reactivity was especially important in the case of Suzuki−Miyaura couplings since the recyclability of the catalytic system still remains unresolved.

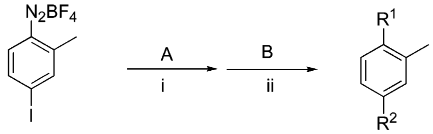
The dihydroimidazolium ligand **28** (Scheme 17) described by Andrus et al.[93] allowed catalyst loading to be reduced to 0.1 mol % in the coupling of arylboronic acids with diazonium salts in tetrahydrofuran at room temperature and using Pd(OAc)$_2$ as the palladium source. Reactions were quite fast, taking between 2 and 3.5 h, and with electron-rich diazonium salts were also successful at 0 °C. The same catalytic system was active in coupling styrylboronic acids, and coupling of arenediazonium salts with alkylboronic acid **81** was achieved for the first time (Scheme 34). The versatility of this system was further illustrated by the possibility of starting with an aniline substrate and employing an in situ diazonium formation step: a procedure widely studied in the Matsuda−Heck reaction but here applied for the first time in a Suzuki−Miyaura cross-coupling.

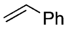
Another carbene palladium complex which has been used in the coupling of arenediazonium tetrafluoroborates with arylboronic acids was the monocarbenepalladium(0) complex **31** (Scheme 17) described by Beller et al.[50] Using MeOH as the solvent at 50 °C it was possible to decrease the amount of catalyst employed to 0.1 mol % and demonstrated that the system tolerates the one-pot procedure. Finally, Chen and Yang's C_2-symmetric thiourea ligand **33** (Scheme 17) was shown to catalyze the Suzuki−Miyaura coupling in MeOH at room temperature in 4 h when loaded with 1 mol % of catalyst.[52]

2.2.4. Superior Reactivity of N$_2$ as the Nucleofuge

In almost all of the examples of Suzuki−Miyaura coupling reactions of halide-substituted arenediazonium salts presented so far, there is a notable chemoselectivity taking place. Chemoselectivity arises both from the base-free conditions used for arenediazonium coupling unlike the case of the cross-coupling of halides and triflates where a base is required and from different Ar−X bond strengths. Sengupta et al.[38] in 1998 obtained teraryls by differential palladium-catalyzed reactions on iodoarenediazonium substrates (Scheme 35). Iodoarenediazonium salts were also subjected to sequential Suzuki−Miyaura cross-coupling and Heck olefination with the result that *p*-phenylstilbenes were obtained. Both regioisomers were obtained by prior reaction of diazonium and either boronic acid (Suzuki−Miyaura) or olefin (Matsuda−Heck).

Scheme 35

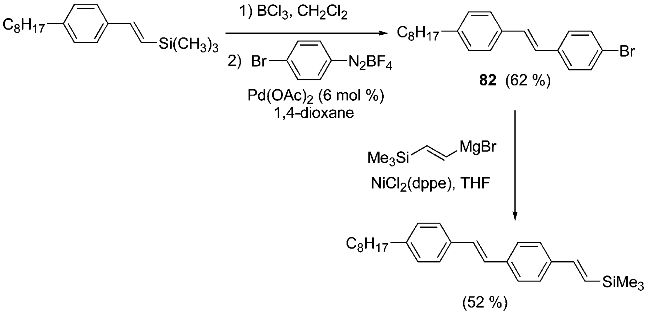


A	i	B	ii	R^1	R^2	Yield (%)
PhB(OH)$_2$	Pd(OAc)$_2$ (10 mol %) MeOH, 60°C	*o*-TolylB(OH)$_2$	Pd(OAc)$_2$ (5 mol %) Ba(OH)$_2$, EtOH, rt	Ph-	*o*-Tol-	40
PhB(OH)$_2$	Pd(OAc)$_2$ (10 mol %) MeOH, 60°C	 Ph	Pd(OAc)$_2$ (2 mol %) NaHCO$_3$, TBAC, DMF, 100°C	Ph-	PhCH=CH$_2$-	53
 Ph	Pd(OAc)$_2$ (2 mol %) EtOH, 80°C	PhB(OH)$_2$	Pd(OAc)$_2$ (5 mol %) Ba(OH)$_2$, EtOH, rt	PhCH=CH$_2$-	Ph-	60

Some groups have taken advantage of halide−diazonium chemoselectivity to construct monodisperse polymers. Pure oligomers of well-defined lengths and no chemical defects are required to better understand structure−property relationships and consider their applications as new materials. It is desirable to have bifunctional monomers with orthogonal reactivity for the synthesis of these oligomers, which can be achieved by taking advantage of the halide−diazonium chemoselectivity in the palladium-catalyzed processes.

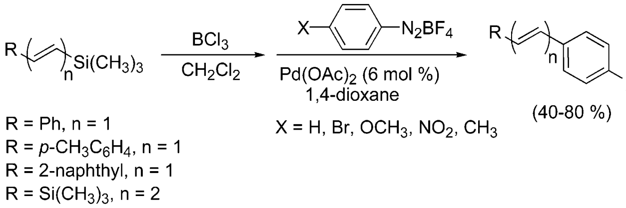
Naso et al.[80a] synthesized monodisperse poly(1,4-phenylenevinylene), PPV oligomers, using bromobenzenediazonium tetrafluoroborate as the key material in the elongation of the conjugate system (Scheme 36).

Scheme 36



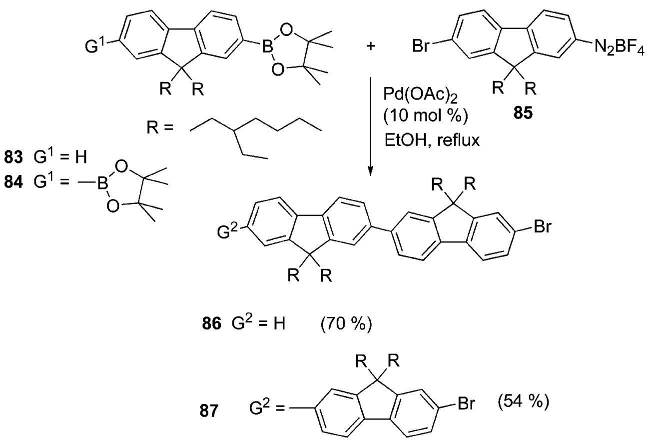
The methodology used was developed by the same group in an earlier paper in which they disclosed the formal Suzuki−Miyaura cross-coupling by a one-pot process combining ipsoborodesilylation and cross-coupling of the boron intermediates which are formed with arenediazonium tetrafluoroborates (Scheme 37).[94] The process arises as an alternative for the cross-coupling of alkenylsilanes, which until now have not proved to be reactive toward transmetalation. Unlike Kikukawa,[75] who failed to observe regio- and stereospecificity in the Matsuda−Heck-like reaction starting with β-(trimethylsilyl)styrenes **69** (as seen in Scheme 25), the authors achieved a highly regio- and stereoselective reaction starting from unsaturated silanes.

Scheme 37



Synthesis of various monodisperse oligofluorenes **86** and **87** has also been accomplished by Wegner, Yoon et al.[95] taking advantage of the superior reactivity of diazonium salts in contrast to bromide in the preparation of a key intermediate on the overall synthesis (Scheme 38). The base-free coupling was accomplished by reacting a pinacolboronic ester mono- (**83**) or diend-capped (**84**) fluorene with another fluorene unit functionalized with a bromide and one diazonium tetrafluoroborate at each side (**85**) using Pd(OAc)$_2$ in refluxing EtOH. Surprisingly, the boronic counterpart in this reaction is a boronic ester, substrates which were initially claimed not to participate in the cross-coupling with arenediazonium tetrafluoroborates[85a] and for which there is only one example described by Strongin et al.[96] In this case, moderate yields of asymmetric biaryls were obtained by the coupling of pinacolylboronic esters and arenediazonium tetrafluoroborates using a 10 mol % of palladium salt Na$_2$PdCl$_4$ in aqueous methanol at 40 °C and with added CsF (for which the authors offered no justification).

Scheme 38

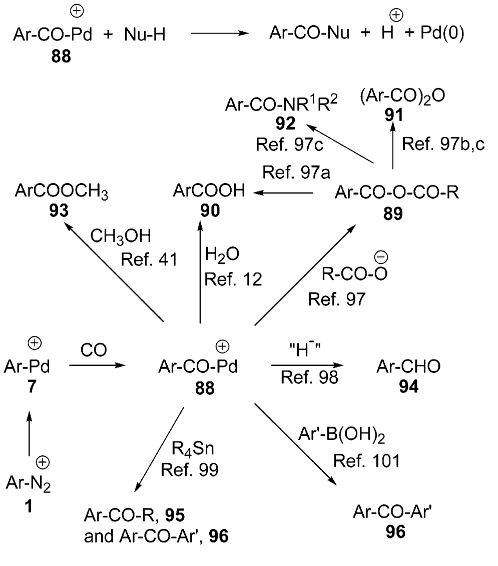


One final application of arenediazonium salts in palladium-catalyzed processes described by Nelson at al.[68] is in the synthesis of semisynthetic tetracycline derivatives. In the same study in which this group performed the already commented on Matsuda−Heck coupling shown in Scheme 22, the 9-diazoniumdoxycycline salt (chloride or tetrafluoroborate) was coupled to several arylboronic and heteroarylboronic acids in methanol or acetonitrile using Pd(OAc)$_2$ as a catalyst to afford moderate yields of C9-functionalized tetracyclines. As was also the case in the olefination reaction, use of iodotetracycline derivatives resulted in a reduction in the side products and an increase in the number of reagents that could effectively be coupled.

2.3. Carbonylative Coupling

Arylpalladium complexes **7** of whatever origin react with carbon monoxide to give electrophilic aroylpalladium complexes **88**,[16] which can be trapped by a wide variety of nucleophiles with simultaneous recovery of the catalytic Pd(0), thus permitting preparation of different final products. Scheme 39 shows the formation and reactivity of these cationic aroylpalladium complexes. Pd(II) acetate or other

Scheme 39

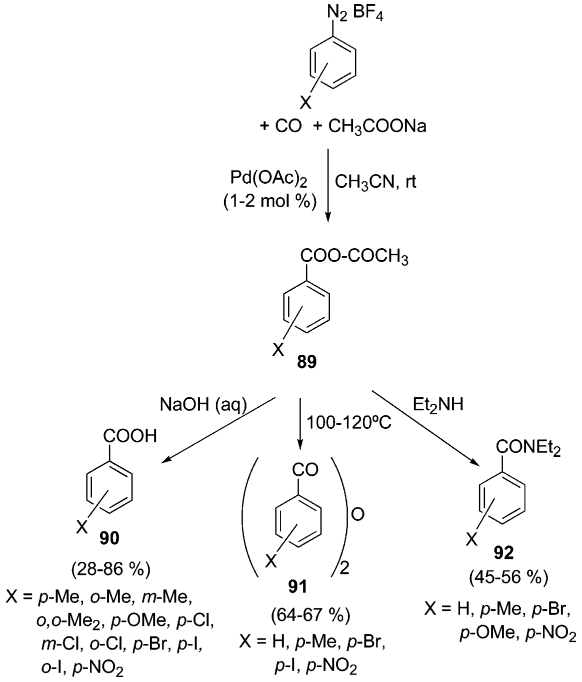


Pd(II) species are frequently introduced as precatalysts. It is assumed that CO reduces Pd(II) to Pd(0) in situ (eq 4).

$$\mathrm{Pd(OAc)_2 + CO \rightarrow Pd(0) + CO_2 + Ac_2O} \qquad (4)$$

Kikukawa, Matsuda et al.[97] 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 **89** which gave (a) arenecarboxylic acids **90**[97a] upon hydrolysis, (b) arenecarboxylic anhydrides **91**[97b,c] upon heating, and (c) arenecarboxamides **92** upon addition of an amine[97c] (Scheme 40).

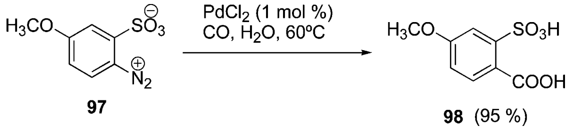
Scheme 40



It is noteworthy that this preparation of anhydrides **89** 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 **88** with methanol or ethanol failed as these alcohols had the effect of reducing the intermediate to Ar−H.

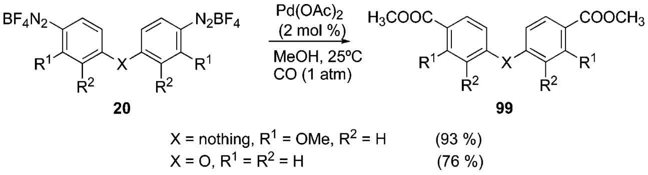
Further improvements and simplifications have been reported. Thus, direct carbonylation in water of diazoniumsulfonate **97** directly gave carboxylic acid **98** (Scheme 41) in the herbicide CGA 308 956 preparation step[12] (see Scheme 3). It should be noted that the distribution of substituents in benzene makes more classical routes based on electrophilic substitution and the rules of orientation difficult.

Scheme 41



Later, direct preparation of esters **99** was achieved by carbonylation of bisdiazonium salts **20** in methanol[41] (Scheme 42).

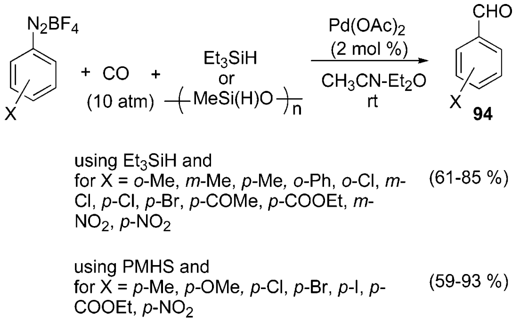
Scheme 42



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.

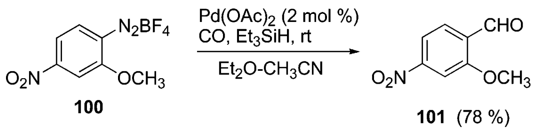
Kikukawa et al.[98] described the use of triethylsilane ($HSiEt_3$) and polymethylhydrosiloxane (PMHS) as sources of hydride ion in the preparation of aromatic aldehydes **94** by trapping the aroylpalladium intermediate formed from several diazonium tetrafluoroborates (Scheme 43). This process provided 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 43



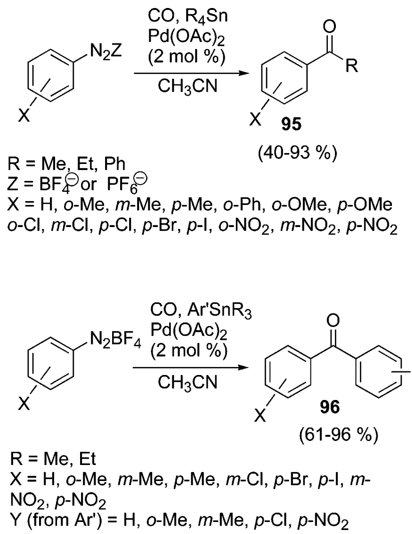
This formylation process has been successfully applied in the preparation of aldehyde **101** from the arenediazonium tetrafluoroborate **100** (Scheme 44), a key step in the synthesis of the hepatitis C drug candidate VX-497 (merimepobid)[13] in a multigram scale (see Scheme 3).

Scheme 44



Reaction with carbon nucleophiles after carbonylation or, in other words, interception of the intermediate **88** 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,[99a] the same year that arylboronic acids were described for the first time[100] (Scheme 45). The reaction of tetraalkyltins and aryltrialkyltins with diazonium cations in an atmosphere of CO and in the presence of catalytic quantities of palladium

Scheme 45



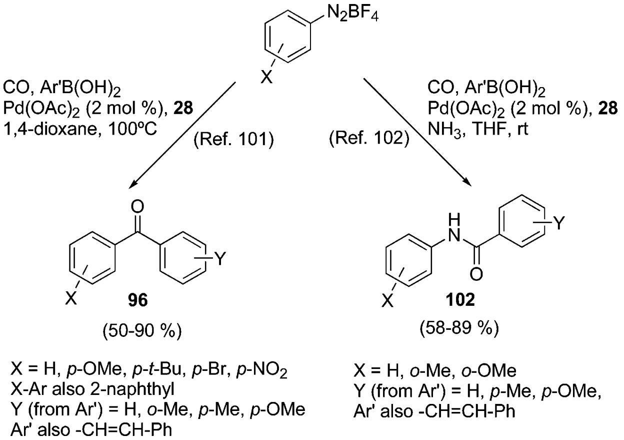
R = Me, Et, Ph
Z = $BF_4^{\ominus}$ or $PF_6^{\ominus}$
X = H, *o*-Me, *m*-Me, *p*-Me, *o*-Ph, *o*-OMe, *p*-OMe *o*-Cl, *m*-Cl, *p*-Cl, *p*-Br, *p*-I, *o*-NO_2, *m*-NO_2, *p*-NO_2

R = Me, Et
X = H, *o*-Me, *m*-Me, *p*-Me, *m*-Cl, *p*-Br, *p*-I, *m*-NO_2, *p*-NO_2
Y (from Ar') = H, *o*-Me, *m*-Me, *p*-Cl, *p*-NO_2

acetate gave alkyl aryl ketones **95** and diaryl ketones **96** in 30 min. The other product of the reaction was probably F−SnR_3. In the synthesis of diaryl ketones **96** the reaction was very selective: no products containing any alkyl group from Ar′SnR_3 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.[101] described the carbonylative coupling of arenediazonium salts with arylboronic acids to produce diaryl ketones **96** when the reaction was catalyzed by a combination of $Pd(OAc)_2$ and *N*,*N*-bis-(2,6-diisopropylphenyl)dihydroimidazolium chloride **28** in dioxane at 100 °C in 5 h (Scheme 46). This same palladium−ligand combination has been shown to efficiently catalyze both Matsuda−Heck and Suzuki−Miyaura reactions (as seen earlier in Schemes 17 and 34).

Scheme 46



X = H, *p*-OMe, *p*-*t*-Bu, *p*-Br, *p*-NO_2
X-Ar also 2-naphthyl
Y (from Ar') = H, *o*-Me, *p*-Me, *p*-OMe
Ar' also -CH=CH-Ph

X = H, *o*-Me, *o*-OMe
Y (from Ar') = H, *p*-Me, *p*-OMe,
Ar' also -CH=CH-Ph

The same group of Andrus reported four-component sequential reactions of diazonium tetrafluoroborates with ammonia, CO, and boronic acids and other boron compounds.[102] The reaction gave amides **102** 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.

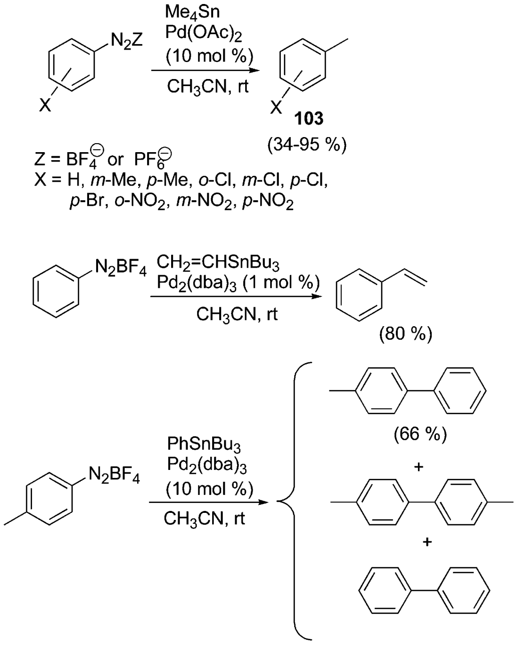
2.4. Miscellaneous

2.4.1. Stille Cross-Coupling

Conventional Stille couplings[17] with diazonium salts have attracted much less attention than both Suzuki−Miyaura cross-couplings (section 2.2) and carbonylative couplings involving organostannanes (section 2.3).

Kikukawa, Matsuda et al.[79] reported methylations with Me_4Sn to give toluenes **103**, arylations, as well as a vinylation with $CH_2{=}CH{-}SnBu_3$ that produced styrene (Scheme 47).

Scheme 47



Z = $BF_4^{\ominus}$ or $PF_6^{\ominus}$
X = H, *m*-Me, *p*-Me, *o*-Cl, *m*-Cl, *p*-Cl, *p*-Br, *o*-NO_2, *m*-NO_2, *p*-NO_2

A study into the nature of the reducing agent that converts Pd(II) into Pd(0) was undertaken for the methylations. By analyzing the gaseous products formed from the reaction carried out with or without arenediazonium salt, they observed that in the absence of the arylating agent the amount of ethane formed was significantly reduced (from 95% to 36% as methane was formed at the expense of ethane (eqs 6 and 7)). The fact that the amount of ethane formed was dependent on the presence of arenediazonium salt was taken as evidence that the electrophile reacted directly with dimethylpalladium through an electron-transfer mechanism (eq 6) instead of reacting more classically with a reduced Pd(0) catalytic species (eq 8).

$$\mathrm{SnMe_4 + Pd(OAc)_2 \longrightarrow Sn(OAc)_2 + [Me{-}Pd{-}Me]} \qquad (5)$$

$$\mathrm{[Me{-}Pd{-}Me] + ArN_2X \xrightarrow{-\,N_2} Ar{-}Pd{-}X} + \underset{(95\%)}{\mathrm{Me{-}Me}}\ \underset{(5\%)}{(+\,\mathrm{Me{-}H})} \qquad (6)$$

$$\mathrm{[Me{-}Pd{-}Me]} + \cancel{\mathrm{ArN_2X}} \longrightarrow \mathrm{Pd(0)} + \underset{(36\%)}{\mathrm{Me{-}Me}} + \underset{(57\%)}{\mathrm{Me{-}H}} + \text{ethylene} \qquad (7)$$

$$\mathrm{[Me{-}Pd{-}Me] \xrightarrow{-\,Me{-}Me} Pd(0) \xrightarrow[-\,N_2]{+\,ArN_2X} Ar{-}Pd{-}X} \qquad (8)$$

Methylation of diazonium salts, reported for the first time in this study, was carried out using arenediazonium tetrafluoroborates or hexafluorophosphates with different substituents, giving moderate to good yields of substituted toluenes **103** in 2 h (Scheme 47). The reaction did not show significant electronic or steric effects except in the case of the 2-methylbenzenediazonium salt. It has to be stressed that coupling of nitro derivatives was especially noteworthy since these highly electron-withdrawing substituents interfere with the classically used methods to functionalize aryl rings, such as Friedel−Crafts alkylations and Grignard coupling reactions.

The above-described alkylation could not be extended to other alkyl chains. The very slow reaction of benzenediazonium salt with Et_4Sn resulted in only a 7% yield of ethylbenzene formed after 1 day. Finally, no reactions succeeded when the Bu_4Sn analogue was used.

Selective vinylation of benzenediazonium tetrafluoroborate by the organotin derivative $CH_2{=}CHSnBu_3$ could only be achieved after accurate selection of both the catalyst and the mole ratio of the reactants (Scheme 47). In the first experiments a mixture of styrene, homocoupled biphenyl, and stilbene (resulting from a Matsuda−Heck reaction on the primary formed styrene) was invariably obtained. However, working with 1 mol % $Pd_2(dba)_3$ and using a 2:1 $CH_2{=}CHSnBu_3$:PhN_2BF_4 ratio, pure styrene was obtained with 80% yield.

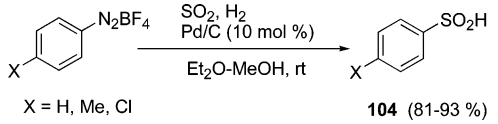
Phenylation of 4-methylbenzenediazonium tetrafluoroborate by either Ph_4Sn or $PhSnBu_3$ resulted in a mixture of the expected 4-methylbiphenyl and both homocoupled biphenyls. Formation of homocoupled products was rationalized by either a rapid interchange of the arylpalladium intermediate species or formation of a tetravalent palladium intermediate (Scheme 47). Similar results were published one decade later by a Russian group.[103]

As we mentioned in section 2.1.2 a very recent paper by Dughera[36] is based on the use of arenediazonium *o*-benzenedisulfonimides (Figure 1) as electrophiles in cross-coupling reactions with aryltin compounds. The reactions are run in the presence of $Pd(OAc)_2$ (5 mol %) in THF at room temperature or at 40 °C. Arenediazonium *o*-benzenedisulfonimides with both electron-donating and electron-withdrawing substituents are efficiently coupled with aryltin compounds with an average yield of 79%. Furthermore, the reactions are chemoselective when using diazonium salts containing a halogen atom.

2.4.2. Carbon–Heteroatom Coupling

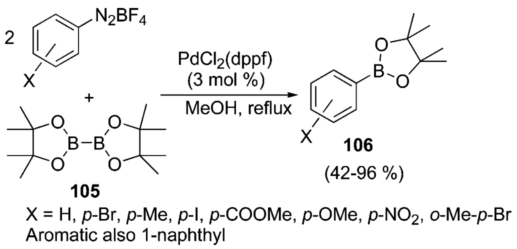
By analogy with carbonylations, Keim et al.[104] prepared sulfinic acids **104** by reaction of diazonium tetrafluoroborates in an atmosphere of SO_2 and hydrogen in the presence of 10 mol % Pd/C (Scheme 48). As a reducing agent, the authors demonstrated that hydrogen was superior to silanes, which had been used by Kikukawa et al.[98] in reductive carbonylation processes.

Scheme 48



Borylation of aromatics was achieved by Strongin et al.[105] by palladium-catalyzed carbon−boron bond formation from arenediazonium tetrafluoroborates. Thus, arenediazonium salts reacted with both halves of bis(pinacolato)diborane **105** in the presence of $PdCl_2$(dppf) in refluxing methanol to afford boronic esters **106** (Scheme 49). The range of diazonium salts was broad, from electron-withdrawing to electron-donating substituents. 4-Iodobenzenediazonium again reacted preferentially or exclusively with the diazonium group as we have repeatedly seen throughout this review.

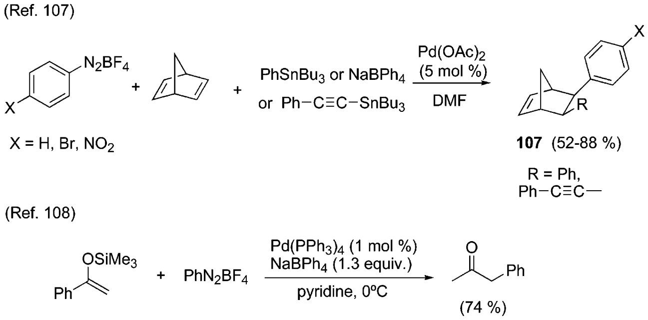
Scheme 49



Similar results were reported by Andrus at al.,[106] who prepared derivatives **106** under the catalytic action of $Pd(OAc)_2$ and dihydroimidazolium chloride **28** (see Scheme 17) in THF at room temperature.

Two processes which do not fit any of our previous headings involving arenediazonium salts in palladium cross-coupling reactions are shown in Scheme 50. A ternary coupling between norbornadiene, arenediazonium tetrafluoroborates, and tin or boron compounds as formal donors of Ph^- or $Ph{-}C{\equiv}C^-$produced norbornenes **107** in moderate to good yields.[107]

Scheme 50



The second very different case is that of the reaction of benzenediazonium tetrafluoroborate with silyl enol ethers in the presence of $Pd(PPh_3)_4$, $NaBPh_4$ using pyridine as a solvent to afford a 74% yield of α-phenyl ketone. However, the reaction was more efficient in the absence of the palladium catalyst, demonstrating that arylation proceeded via a radical mechanism promoted by pyridine.[108]

3. Concluding Remarks

In this review we have shown that arenediazonium salts are attractive partners in palladium-catalyzed cross-coupling reactions. In particular, Heck reactions involving arenediazonium salts have been extensively developed and widely used in the synthesis of natural products and other complex organic compounds. There are fewer publications involving use of these electrophiles in Suzuki−Miyaura, carbonylative, Stille, and carbon−heteroatom cross-couplings. A series of advantages of working with arenediazonium salts as electrophiles has been observed. Arenediazonium salts derive from inexpensive aromatic anilines, and the corresponding tetrafluoroborates have the additional advantage of being easily prepared in large quantities. From a processing point of view, it is important to note that (a) nondegassed and nonanhydrous solvents can be used, (b) reactions take place at room temperature or lower and are typically fast, (c) reactions can be easily monitored as they finish when nitrogen is no longer released, (d) N_2 is a good leaving group as it does not interfere with the reaction mixture, and (e) neither bases nor additives are usually required. From a synthetic point of view, use of arenediazonium salts in palladium-catalyzed reactions has made it possible to synthesize cross-coupled compounds that were not available by using classical halides or oxygen-based electrophiles. The superior reactivity of the diazonium nucleofuge over halides has also permitted the chemoselectivity of the cross-couplings, which has resulted in interesting applications being developed. Moreover, the cross-couplings do not seem to be sensitive to the electronic nature of the substituents in the arenediazonium salts, which is an important drawback when aryl halides are used.

It should also be mentioned that the protocols involving the use of arenediazonium salts have the drawbacks of the compounds being unstable when high temperatures or long reaction times are required and of needing high loads of catalysts in order to cross-couple efficiently.

Undoubtedly, there will be further applications in the future, but there are still methodological aspects to be dealt with. In the Matsuda–Heck reactions only preliminary studies on arylations of di- and trisubstituted olefins have been achieved very recently using arenediazonium salts. In the case of Suzuki–Miyaura reactions, synthesis of sterically hindered ortho,ortho′-substituted biphenyls remains unresolved as does formation of arylacetylene substrates by sp^2–sp coupling and the coupling of alkyl substrates. In addition, syntheses of challenging targets by Suzuki–Miyaura couplings of diazonium salts are scarce. It is curious to note that in the case of carbonylative cross-couplings there has been little published in academic journals about methodology and applications while two out of the three industrial processes involving arenediazonium salts in palladium-catalyzed reactions use carbonylation processes.

Further development of both diastereoselective and enantioselective procedures appears to be highly desirable. We believe that the low temperatures and short reaction times required for these reactions could be a favorable point in the development of chiral processes. Furthermore, achieving higher turnover numbers of the catalytic cycles and good catalyst recyclability should have a major impact on industry. However, to make new contributions in all the above-mentioned areas it will be essential to obtain further insights into mechanistic aspects of all these processes.

Finally, we anticipate that future studies will provide new applications to other cross-coupling reactions such as copper-free Sonogashira couplings or Buchwald–Hartwig amination reactions.

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