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Review

Pd-Catalyzed Mizoroki-Heck Reactions Using Fluorine-Containing Agents as the Cross-Coupling Partners

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Received: 27 December 2017; Accepted: 10 January 2018; Published: 14 January 2018

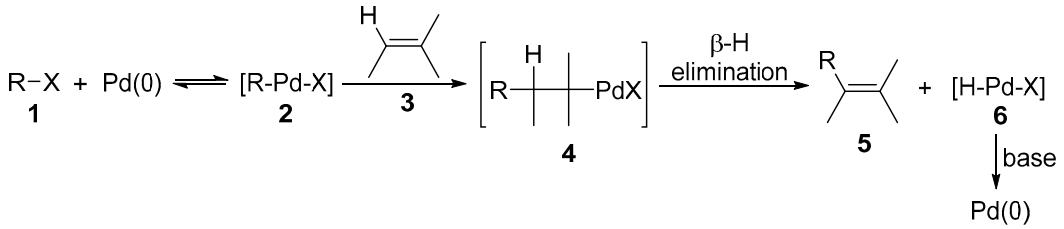
Abstract: The Mizoroki-Heck reaction represents one of the most convenient methods for carbon-carbon double bond formation in the synthesis of small organic molecules, natural products, pharmaceuticals, agrochemicals, and functional materials. Fluorine-containing organic compounds have found wide applications in the research areas of materials and life sciences over the past several decades. The incorporation of fluorine-containing segments into the target molecules by the Mizoroki-Heck reactions is highly attractive, as these reactions efficiently construct carbon-carbon double bonds bearing fluorinated functional groups by simple procedures. This review summarizes the palladium-catalyzed Mizoroki-Heck reactions using various fluorine-containing reagents as the cross-coupling partners. The first part of the review describes the Pd-catalyzed Mizoroki-Heck reactions of aryl halides or pseudo-halides with the fluorinated alkenes, and the second part discusses the Pd-catalyzed Mizoroki-Heck reactions of the fluorinated halides or pseudo-halides with alkenes. Variants of the Pd-catalyzed Mizoroki-Heck reactions with fluorine-containing reagents are also briefly depicted. This work supplies an overview, as well as a guide, to both younger and more established researchers in order to attract more attention and contributions in the realm of Mizoroki-Heck reactions with fluorine-containing participants.

Keywords: Mizoroki-Heck reaction; Pd-catalyzed; fluorine; cross-coupling; alkenes; halides

1. Introduction

The palladium-catalyzed carbon-carbon cross-coupling of an aryl or vinyl halide and an alkene in the presence of a base is referred as the "Mizoroki-Heck reaction" [1–6]. The reaction was discovered independently by Heck and Mizoroki more than 45 years ago. Heck first reported the Li_2PdCl_4-mediated reactions of organomercury compounds with olefins in acetonitrile or methanol at room temperature [7]. Then, Mizoroki and co-workers disclosed the first cross-couplings of aryl iodide with alkenes catalyzed by $PdCl_2$ in methanol in the presence of potassium acetate at 120 °C [8]. In 1972, Heck and co-worker proposed a possible mechanism for the reactions of aryl, benzyl, or styryl halides (R–X) with alkenes and a catalytic amount of $Pd(OAc)_2$ under milder conditions (Scheme 1) [9]. In these conversions, an oxidative addition occurs between Pd(0) (formed in situ from reduction of $Pd(OAc)_2$ by olefin) and R–X (**1**), presumably generating a very reactive solvated organopalladium(II) halide ([R–Pd–X], **2**), which is probably the same intermediate produced previously in the exchange reactions between palladium halides and organomercury compounds [7]. [R–Pd–X] undergoes an addition reaction with olefin (**3**) to yield a palladium adduct (**4**),

which decomposes by elimination of a hydridopalladium halide ([H–Pd–X], **6**) to form the substituted olefinic compound (**5**). Reductive elimination of HX from [H–Pd–X] in the presence of a certain base regenerates the Pd(0) species, maintaining the catalytic cycle. Formally speaking, the vinylic hydrogen atom of alkene is substituted by the organic residue (R) of R–X in the reactions (Scheme 1).



Scheme 1. A possible mechanism for the Mizoroki-Heck reactions.

Due to its high efficiency, easy operation, and good chemo- and stereoselectivity, the Mizoroki-Heck reaction has been extensively used for functionalization of various organic scaffolds since its discovery. Currently, the Mizoroki-Heck reaction has become one of the most important tools for the formation of carbon-carbon double bonds [1–6]. To manifest the importance of the Mizoroki-Heck reaction, Richard F. Heck, together with Ei-ichi Negishi and Akira Suzuki, was honored with the 2010 Nobel Prize in Chemistry for their great contribution in the development of Pd-catalyzed cross-coupling reactions in organic synthesis. The Mizoroki-Heck reactions have exhibited good functional group tolerance with a wide range of substrates under mild conditions. At present, not only aryl, vinyl, benzyl, and alkyl halides [1–6], but also the corresponding pseudo halides such as sulfonates [10–12], sulfonyl chlorides [13–15], carboxylic acid derivatives [16–18], diazonium salts [19–21], iodonium salts [22,23], phosphonium salts [24], and sulfonium salts [25], have been successfully employed as electrophiles in Heck-type cross-couplings. Both electron-poor and -rich alkenes (such as acrylic esters, enolethers, and ethylene) have proved to be viable cross-coupling partners in the reactions [1–6]. The Mizoroki-Heck reactions are originally catalyzed by palladium [1–6]. Other transition metals, such as nickel, cobalt, copper, gold, and iron, are also active catalysts for Heck-type reactions [26–33]. The visible light-induced Pd-catalyzed Mizoroki-Heck reactions between sterically hindered alkyl halides and vinyl arenes have been accomplished, as well [34,35].

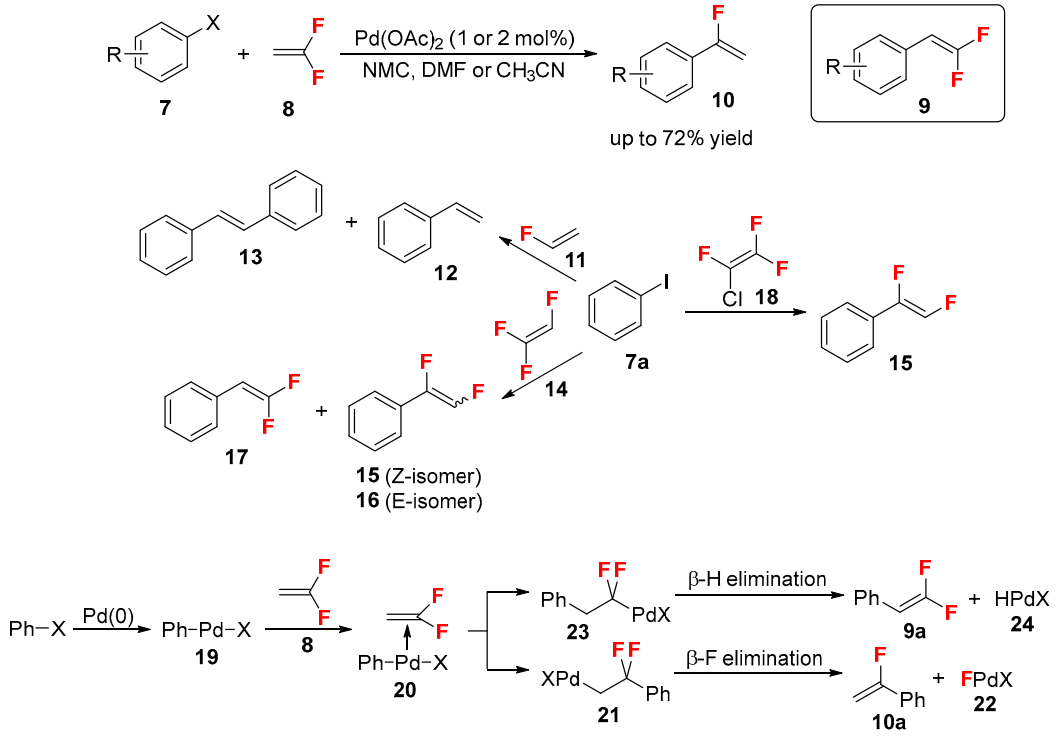
On the other hand, fluorine is a very intriguing atom for its unique properties. Introduction of fluorine atom(s) into organic molecules usually brings about a dramatic impact on the physicochemical and biological properties of the molecules [36–38]. Fluorine-containing organic compounds have found wide application in the areas of chemistry, biology, and materials science over the past several decades [39–45]. There have been as many as 25% of pharmaceuticals and 30–40% of agrochemicals on the market containing at least a single fluorine atom [41]. Because only a few naturally-occurring organofluorides have been discovered, most of the fluorinated organic compounds have to be manually synthesized [36–51]. It is undoubted that the development of efficient methods to construct fluorine-containing molecules is of great importance [46–51]. In general, the fluorinated compounds can be synthesized by direct fluorination or fluoroalkylation, or through reactions with the fluorine-containing building blocks [39–51]. The incorporation of fluorine-containing fragments into organic frameworks by Pd-catalyzed Mizoroki-Heck reactions has proved to be the simplest and most convenient pathway to build diverse alkenes bearing fluorinated functionalities. This strategy includes the Pd-catalyzed cross-couplings of fluorinated alkenes with aryl halides or pseudo halides, and Pd-catalyzed reactions of alkenes with the fluorinated aryl or alkyl halides or pseudo halides. Fluorine-containing alkenes are versatile building blocks in the synthesis of bioactive molecules for drug discovery and advanced materials for specific applications (see Sections 2–4). The concise, straightforward, selective, and highly efficient preparation of the fluorinated alkenes by the Mizoroki-Heck reactions has made these compounds easy to access and diversify.

To our knowledge, there has been no review article systematically summarizing the Pd-catalyzed Mizoroki-Heck reactions using fluorine-containing agents as the cross-coupling partners. To fill the gap in this area, we present an overview of the recent advances in the Pd-catalyzed Mizoroki-Heck reactions with the fluorinated cross-coupling participants including the fluorinated alkenes and/or the fluorinated aryl or alkyl halides. This review offers as a guide to both younger and more established researchers, and is intended to attract more attention to and contributions in the development of the Mizoroki-Heck reactions with fluorine-containing cross-coupling reagents.

2. Mizoroki-Heck Reactions of Aryl Halides or Pseudo-Halides with Fluorine-Containing Alkenes

2.1. Fluoroalkenes as Cross-Coupling Participants

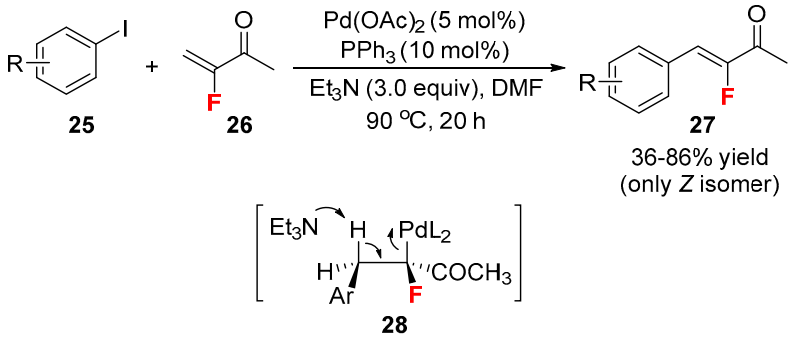
The Mizoroki-Heck reaction provides a convenient method for the arylation of olefins [1–6]. In most cases, the vinylic hydrogen atom is formally substituted by the organic residue of an organic halide under the Heck-type reaction conditions. High regioselectivities of the arylation at the less substituted site of the carbon-carbon double bond of the unsymmetrically substituted olefins are usually observed, which may be attributed to the steric factors [1–6]. One of the key steps of the reaction is β-hydride elimination. However, when aryl bromide or iodide (**7**) reacted with vinylidene difluoride (**8**) in the presence of $Pd(OAc)_2$, the expected β-H elimination product, β,β-difluorostyrene (**9**), was formed only in a very small amount (Scheme 2) [45,52]. The major product of the reaction was α-fluorostyrene (**10**). Moreover, the reaction of vinyl fluoride (**11**) with **7a** gave styrene (**12**) and stilbene (**13**), the ratio of which strongly depended on the reaction conditions. Treatment of **7a** with trifluoroethylene (**14**) produced an isomeric mixture of **15**, **16** and **17** (45%), with **15** being predominant (86% by GC). Unexpectedly, **15** again was the product when chlorotrifluoroethylene (**18**) was treated with **7a**. These results suggested the substitution of a vinylic fluorine atom in all cases, which were distinct from the known Heck-type reactions with non-fluorinated olefins [1–6]. The transformations represented the first examples of charge-controlled Heck-type reaction, which was only significant in the presence of fluoroolefins [52].



Scheme 2. Pd-catalyzed reactions of aromatic halides with fluoroolefins.

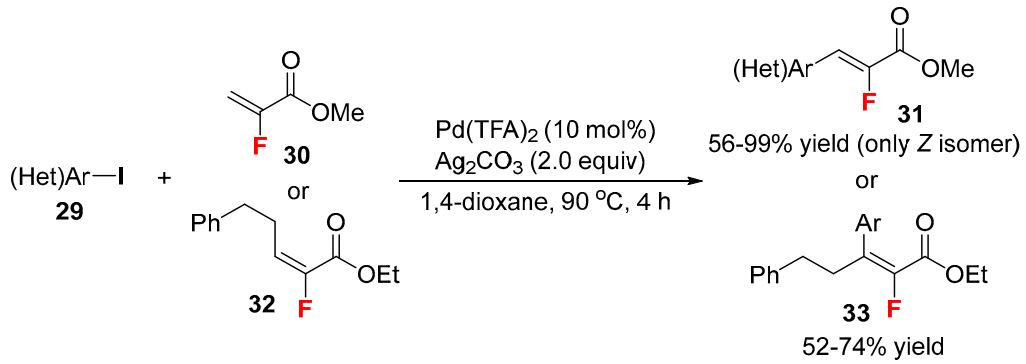
Mechanistically, the reaction starts with the formation of a palladium adduct (**19**) by the oxidative addition of the in situ generated Pd(0) species with **7a**, which undergoes olefin coordination to produce complex **20** (Scheme 2) [52]. Then, the phenyl group in **20** transfers from the Pd center to the CF_2 site of **8**, affording **21**. A β-fluorine elimination of **21** yields α-fluorostyrene (**10a**) as the final product. Compound **23** would be an intermediate, if the steric aspects were relevant, and a subsequent β-hydride elimination of **23** could form **9a**. However, the formation of **23** must be of low probability, as only trace amounts of **9a** were detected. The favorable formation of **21** in the reaction of **8** could be explained by the charge-controlled mechanism, which was verified by the MNDO-calculations [52]. Furthermore, the reactions of **7a** with **11** and **14** obeyed a mechanism similar to that of **7a** with **8**, and the reaction of **7a** with **18** underwent both the olefinic fluorine substitution and the C–Cl bond reduction. The β-fluorine elimination seemed to be the preferred type of elimination, even though the competitive β-hydride elimination was a possible pathway [45,52]. This procedure constituted a convenient method for the preparation of α-fluorostyrenes.

More than fifteen years later, Patrick and co-workers found that 3-fluoro-3-buten-2-one (**26**) reacted smoothly with aryl iodides (**25**) under the Heck-type cross-coupling conditions to give 3-fluorobenzalacetones (**27**) in good yields with only *Z*-stereoselectivity (Scheme 3) [53]. The reaction used $Pd(OAc)_2$ as a catalyst, triphenylphosphine as a ligand, and triethylamine as a base in DMF. The conjugate addition products and the fluoride elimination products were not observed. The preferable *trans* relationship between the aryl and acyl groups during the reaction was maintained in the configuration of the final product (**27**). The required *syn*-elimination of $HPdL_2$ in intermediate **28** sustained very small steric repulsion between the aryl group and the fluorine atom.



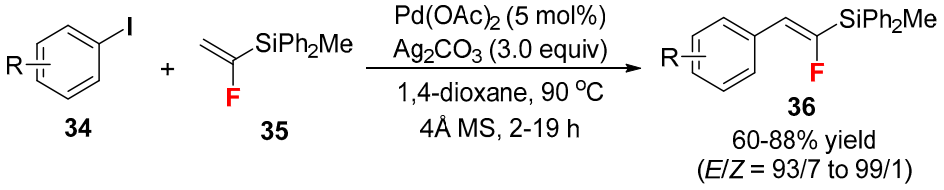
Scheme 3. Pd-catalyzed Mizoroki-Heck reactions of aryl iodides with 3-fluoro-3-buten-2-one.

In 2016, Couve-Bonnaire and co-workers reported the ligand-free palladium-catalyzed Mizoroki-Heck reactions of methyl α-fluoroacrylate (**30**) with aryl or heteroaryl iodides (**29**), leading to a cheap, efficient, and stereoselective synthesis of fluoroacrylate derivatives (**31**) in good to quantitative yields (Scheme 4) [54]. The transformation had good functional group tolerance and could be extended to more steric hindered trisubstituted alkenes, which were previously the reluctant substrates in the Mizoroki-Heck reactions. The reactions of trisubstituted (*E*)-3-alkyl-2-fluoroacrylate (**32**) with **29** under the standard conditions gave the corresponding tetrasubstituted fluoroacrylates (**33**) in fair to good yields [54]. These results constituted the first examples for the synthesis of tetrasubstituted alkenes by using the Mizoroki-Heck reaction. This methodology was also applicable to the preparation of a fluorinated analogue of a therapeutic agent against inflammation and cancers.



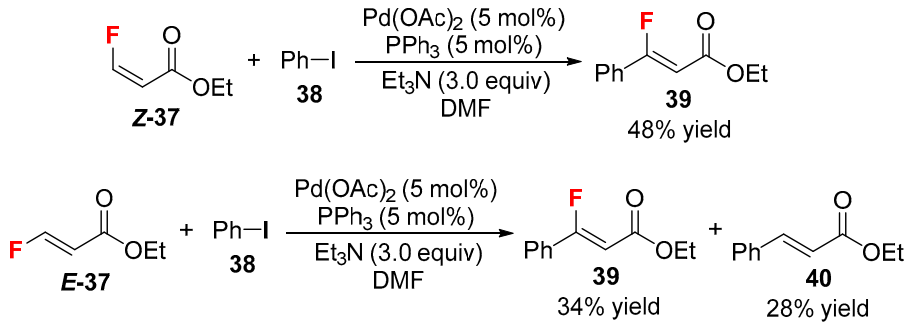
Scheme 4. Pd-catalyzed Mizoroki-Heck reactions of methyl *α*-fluoroacrylates with aryl or heteroaryl iodides.

Similarly, Hanamoto and co-worker disclosed the Mizoroki-Heck reactions of (1-fluorovinyl)methyldiphenylsilane (**35**) with aryl iodides (**34**) catalyzed by $Pd(OAc)_2$ (5 mol%) in the presence of Ag_2CO_3 (3 equiv) and 4 Å MS in 1,4-dioxane (Scheme 5) [55]. The reactions supplied a series of (*E*)-*β*-aryl-(*α*-fluorovinyl)methyldiphenylsilanes (**36**) in good yields with excellent stereoselectivity. Desilylation/protonation of the product gave the corresponding (*E*)-*β*-fluorostyrene derivative with complete retention of the configuration of the double bond, which illustrated the synthetic scope of this method.



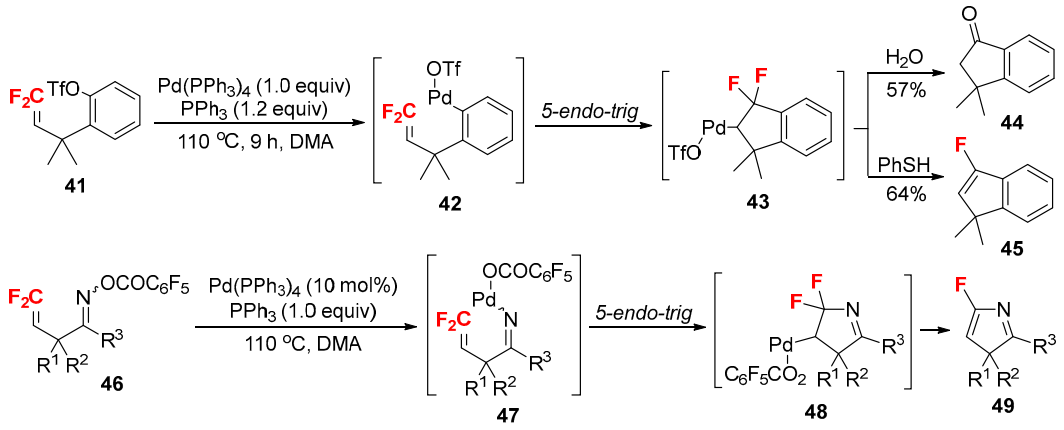
Scheme 5. Pd-catalyzed Mizoroki-Heck reactions of (1-fluorovinyl)methyldiphenylsilane with aryl iodides.

Moreover, the Mizoroki-Heck reaction of ethyl (*Z*)-3-fluoropropenoate (***Z*-37**) or ethyl (*E*)-3-fluoropropenoate (***E*-37**) with iodobenzene in the presence of $Pd(OAc)_2$ (5 mol%) produced ethyl 3-fluoropropenoate (***Z*-39**) as a sole product (Scheme 6) [56]. The reaction proceeded smoothly at the *β*-position with specific stereoselectivity. The stereochemistry of ***E*-37** was completely inverted and only ***Z*-39** was produced. Meanwhile, compound **40** was formed as a side product via loss of a fluorine atom. It was possible that the catalyst system caused the isomerization. However, the exact mechanism for the high stereoselectivity of the reaction remained unclear.



Scheme 6. Pd-catalyzed Mizoroki-Heck reactions of ethyl (*E*)- and (*Z*)-3-fluoropropenoate with iodobenzene.

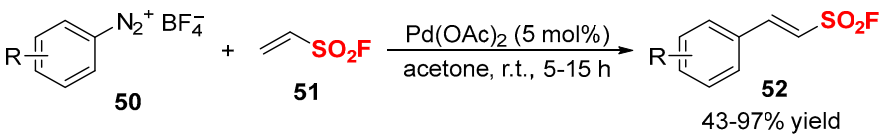
Pd-Catalyzed intramolecular cyclization of *O*-(3,3-difluoroallyl)phenyl triflate (**41**) and 3,3-difluoroallyl ketone oximes (**46**) by the Mizoroki-Heck reactions of the polarized carbon-carbon double bonds of the 1,1-difluoro-1-alkene moieties was accomplished (Scheme 7) [45,57,58]. In the first step of the reactions, an arylpalladium or aminopalladium intermediate (**42** or **47**) bearing a 2,2-difluorovinyl group is formed from **41** or **46**, respectively. Then, intermediate **42** or **47** undergoes a 5-endo-trig alkene insertion and subsequent *β*-fluorine elimination to afford ring-fluorinated indene (**45**) or 3*H*-pyrroles (**49**). In both cases, the CF_2 unit was very essential for the cyclization as the corresponding monofluoroalkene, fluorine-free alkene, dichloroalkene, and dibromoalkene didn't give the cyclized products under the same reaction conditions [57,58].



Scheme 7. Heck-type 5-endo-trig cyclization promoted by vinylic fluorines.

2.2. Fluorine-Containing Vinyl Sulfur Compounds as the Cross-Coupling Participants

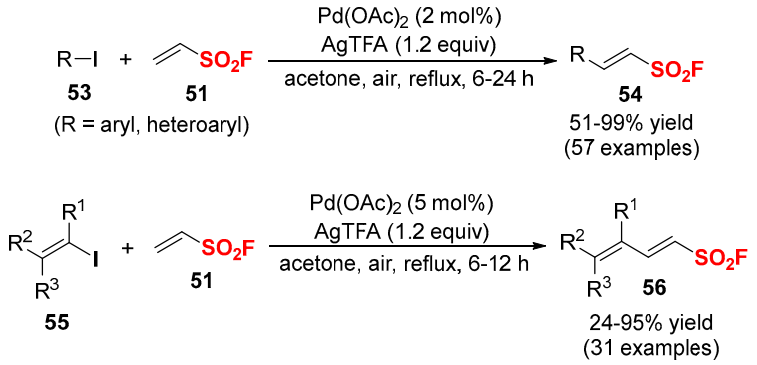
Ethenesulfonyl fluoride (ESF) is a highly reactive and versatile reagent in the synthesis of a wide variety of organosulfur compounds, which behaves as a strong Michael acceptor or a Diels-Alder dienophile to conveniently introduce an SO_2F group [59]. In 2016, Wu and Sharpless described a Pd-catalyzed Heck-Matsuda process for the synthesis of the otherwise difficult to access *β*-arylethenesulfonyl fluorides (Scheme 8) [60]. In this reaction, ethenesulfonyl fluoride (**51**) underwent *β*-arylation with the stable and readily prepared arenediazonium tetrafluoroborates (**50**) in the presence of catalytic palladium(II) acetate to afford the *E*-isomer sulfonyl analogues of cinnamoyl fluoride (**52**) in 43–97% yield. The products **52** proved to be selectively addressable bis-electrophiles for sulfur(VI) fluoride exchange (SuFEx) click chemistry, in which either the alkenyl moiety or the sulfonyl fluoride group could be exclusively attacked by nucleophiles under defined conditions, making these simple cores attractive for covalent drug discovery [60].



Scheme 8. Heck-Matsuda reactions of ethenesulfonyl fluoride (ESF) with aryldiazonium salts.

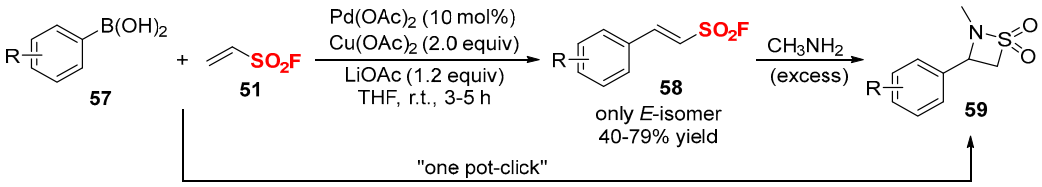
Later, Qin and Sharpless employed a similar strategy for the synthesis of 2-(hetero)arylethenesulfonylfluorides (**54**) and 1,3-dienylsulfonyl fluorides (**56**) (Scheme 9) [61]. They found that a combination of catalytic $Pd(OAc)_2$ with a stoichiometric amount of silver(I) trifluoroacetate enabled the coupling process between either an (hetero)aryl or alkenyl iodide (**53** or **55**) and ethenesulfonyl fluoride (ESF, **51**). The reaction was demonstrated in the successful synthesis of eighty-eight compounds in up to 99% yields, including the unprecedented 2-heteroarylethenesulfonyl

fluorides and 1,3-dienylsulfonyl fluorides [61]. These substituted ethenesulfonyl fluorides are useful building blocks for consequent synthetic transformations [61].



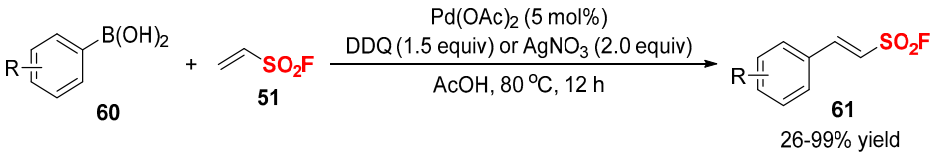
Scheme 9. Palladium-catalyzed fluorosulfonylvinylation of organic iodides.

Furthermore, the oxidative Heck cross-coupling reactions have become attractive for modern organic synthesis due to advantages such as efficiency, mild reaction conditions, good functional group tolerance, and widespread applications [62–64]. In 2017, Arvidsson and co-workers reported an operationally simple method for ligand- and additive-free oxidative Heck couplings of aryl boronic acids (**57**) with ESF (**51**) (Scheme 10) [65]. The reactions proceeded at room temperature with good chemoselectivity and *E*-selectivity and offered facile access to a wide range of *β*-aryl/heteroaryl ethenesulfonyl fluorides (**58**) from the commercially available boronic acids (**57**). The products (**58**) have a "dual warhead" with two electrophilic sites that have been used as covalent enzyme inhibitors and as synthetic reagents [65]. The authors also demonstrated that aryl-substituted *β*-sultams could be prepared through a one-pot procedure in which an excess of primary amine was added to the reaction mixture before workup [65].



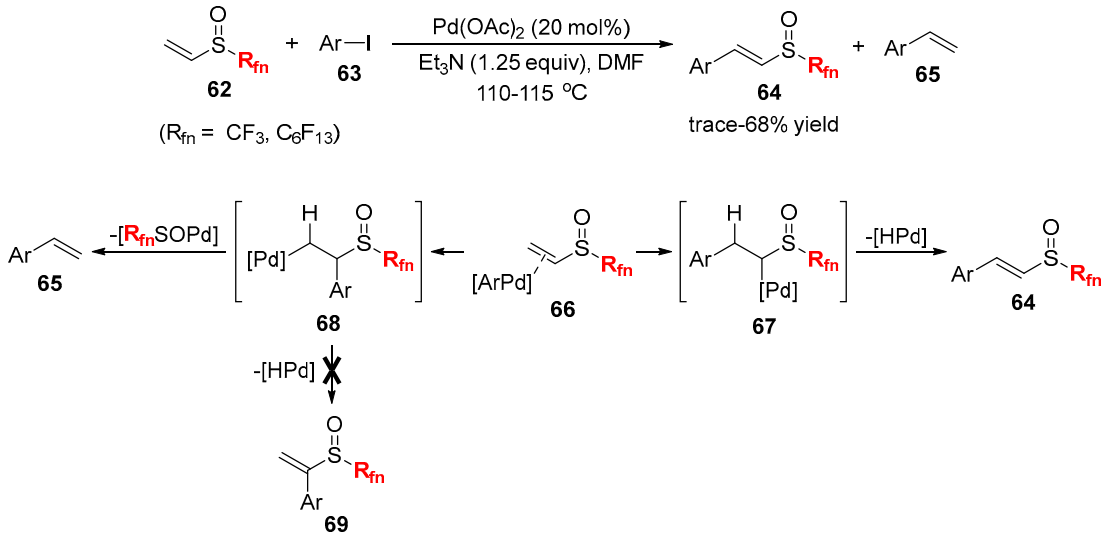
Scheme 10. The oxidative Heck couplings of boronic acids with ethenesulfonyl fluoride.

Likewise, Qin and co-workers disclosed the base-free palladium-catalyzed fluorosulfonylvinylation of (hetero)arylboronic acids (**60**) with ESF (**51**) under oxidative conditions (Scheme 11) [66]. Aryl- and heteroaryl-boronic acids (**60**) reacted with ESF in the presence of a catalytic amount of $Pd(OAc)_2$ and excess 2,3-dichloro-5,6-dicyano-p-benzoqui-none (DDQ) or $AgNO_3$ in AcOH to stereoselectively afford the corresponding *E*-isomer of *β*-arylethenesulfonyl fluoride products (**61**) in up to 99% yield. The utility of the reactions was exemplified by an expanded scope of 47 examples including *N*-, *O*-, and *S*-containing heteroaromatics, demonstrating chemoselectivity over aryl iodides [66].



Scheme 11. The oxidative Heck reactions of arylboronic acids with ethenesulfonyl fluoride.

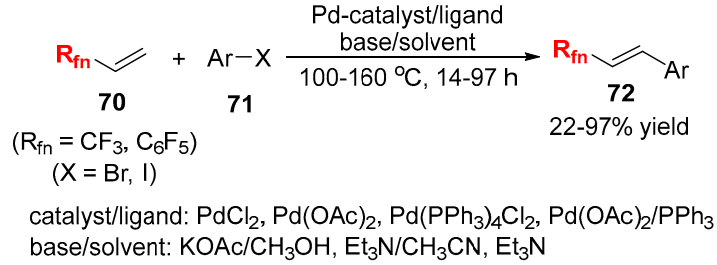
It should be noted that the sulfur-containing olefins (e.g., vinyl sulfides, sulfoxides) are the least investigated substrates in the Mizoroki-Heck reactions, as these substrates may poison the Pd-catalysts to form stable metal-sulfur complexes [67]. To date, only a handful of successful Heck cross-coupling reactions based on sulfoxides have been reported, even though these moieties have potential for many synthetic applications. Among this type of molecule, perfluoroalkyl vinyl sulfoxides possess a strongly polarized double bond and is highly reactive, which makes them interesting for investigation. In 2015, Sokolenko and co-workers explored the Heck-type reactions of trifluoromethyl or tridecafluorohexyl vinyl sulfoxides (**62**) with aryl iodides (**63**) (Scheme 12) [67]. Palladium(II) acetate was found to be the most suitable catalyst for the reactions. By this method, a series of *E*-1-aryl-2-perfluoroalkylsulfinylethylenes (**64**) were synthesized. Styrenes (**65**) without a perfluoroalkylsulfinyl group were also formed (as byproducts) in these cases. The perfluoroalkyl vinyl sulfoxides (**62**) may undergo both terminal and internal additions of the aryl group (Scheme 12). In the former case, *β*-elimination of the palladium species and hydride from **67** yields **64**. In the latter case, *β*-elimination of the palladium species and perfluoroalkylsulfinyl group from **68** leads to **65**. The formation of stable Pd–S bonds might facilitate the latter process.



Scheme 12. The Mizoroki-Heck reactions of perfluoroalkyl vinyl sulfoxides with aryl iodides.

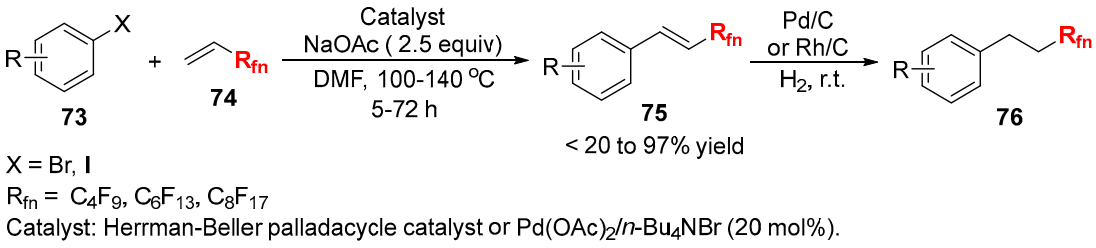
2.3. Fluoroalkylated Alkenes as the Cross-Coupling Partners

Perfluoroalkylated alkenes are important feedstocks for the synthesis of useful fluorine-containing molecules. In 1981, Ojima and co-workers reported the Pd-catalyzed Mizoroki-Heck reactions of 3,3,3-trifluoropropene or pentafluorostyrene (**70**) with aromatic halides (**71**) (Scheme 13) [68]. The cross-couplings proceeded smoothly by simply heating the mixtures of aryl iodides or bromides, trifluoropropene or pentafluorostyrene, a Pd-catalyst (1 mol%), and a base (such as Et_3N or KOAc), which gave a variety of *trans*-*β*-trifluoromethylstyrenes or *trans*-*β*-pentafluorophenylstyrenes (**72**) in good to high yields via a one-step procedure. The arylation was not sensitive to the electronic nature of the substituents on the aryl halides but was rather sensitive to the steric hindrance. However, aryl chlorides such as chlorobenzene and chlorotoluene were unreactive under the same reaction conditions.



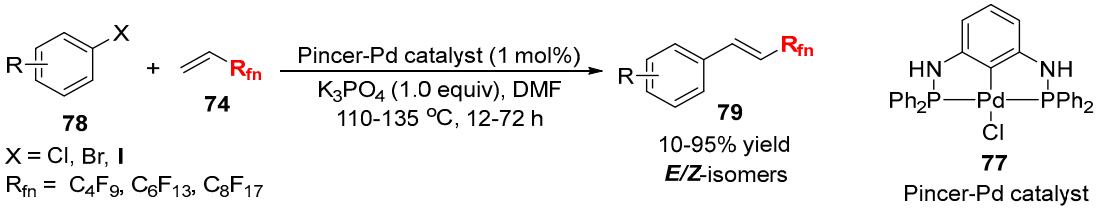
Scheme 13. The Heck-type reactions of aryl halides with 3,3,3-trifluoropropene or pentafluorostyrene.

In 2001, Xiao and co-workers found that Pd-catalyzed olefination of aryl halides (**73**) with 1*H*,1*H*,2*H*-perfluoro-1-alkenes (**74**) provided *trans*-fluorous ponytail-substituted aryl compounds (**75**) in good to excellent yields (Scheme 14) [69]. Typically, the reactions of **73** with **74** in the presence of NaOAc and the Herrmann-Beller palladacycle catalyst (0.5–1 mol%) in DMF supplied the *trans* olefins **75** in more than 90% isolated yields in most cases without optimization. Purification of **75** by flash chromatography allowed easy reduction of the C=C double bonds of **75** under the standard Pd/C- or Rh/C-catalyzed hydrogenation conditions [69]. This method was successfully applied to the synthesis of binaphthols bearing fluorinated ponytails, which are potential ligands for catalysis in $scCO_2$ and fluorous solvents [69,70]. The application of these ligands in the ruthenium-catalyzed hydrogenation of dimethyl itaconate revealed that the fluorous ponytails on the ligands imposed significant effects on the hydrogenation activity, but not on the enantioselectivity [70].



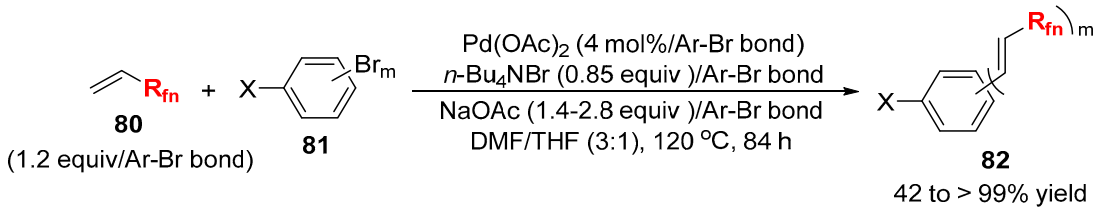
Scheme 14. The Mizoroki-Heck reactions between perfluoroalkyl alkenes and aryl halides.

Later, Cai and co-worker developed a PCP Pincer-Pd catalyst (**77**), which was favorably used in Mizoroki-Heck cross-couplings between perfluoroalkyl alkenes (**74**) and aryl halides (**78**) for the preparation of perfluoroalkenylated aryl compounds (**79**) (Scheme 15) [71]. Due to the unique tridentate coordination architecture, the Pincer complex was stable, selective, and highly reactive, and it permitted low catalyst loadings and gave the possibility of fine-tuning the catalytic properties of the metal center. Catalyst **77** showed high catalytic activity in this reaction and the corresponding arylated products were obtained in moderate to excellent yields. Moreover, **77** could be easily separated by F-SPE (Fluorous solid phase extraction) technique and reused three times without significant loss of activity.



Scheme 15. The Mizoroki-Heck cross-couplings of aryl halides with perfluoroalkyl-substituted alkenes.

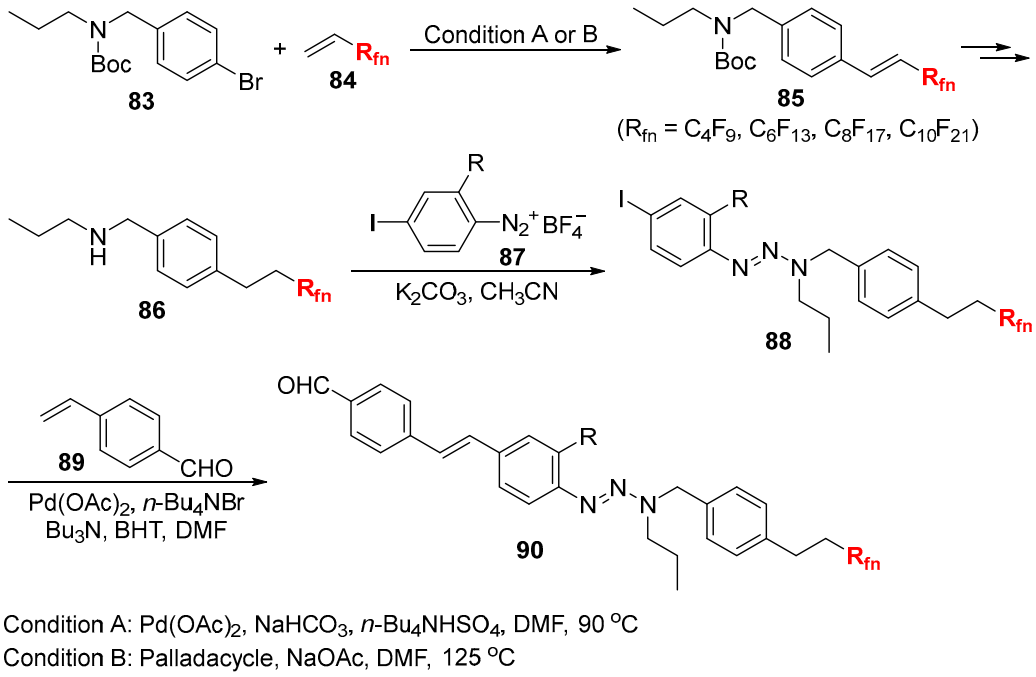
Gladysz and co-workers reported a convenient and scalable procedure for the cross-couplings of fluorous alkenes (**80**) with aryl bromides (**81**) using a modified Jeffery version of the Mizoroki-Heck reaction (Scheme 16) [72]. Fluorous alkenes (**80**) reacted with aryl monobromides and polybromides (**81**), such as 1,3- and 1,4-$C_6H_4Br_2$, 1,3,5-$C_6H_3Br_3$, 1,3,5-$C_6H_3Br_2Cl$, 1,4-XC_6H_4Br (X = CF_3, C_8F_{17}, $COCH_3$, CN, 1,4-OC_6H_4Br), 1,2-$O_2NC_6H_4Br$, 5-bromo-isoquinoline, 5-bromopyrimidine, 3-bromo-5-methoxypyridine, and 3,5-dibromopyridine, under the modified Mizoroki-Heck coupling conditions to afford the corresponding fluorophilic adducts (**82**) in good to high yields. Typically, 1.2–2.4 equiv. of alkene were employed per Ar-Br bond, together with $Pd(OAc)_2$ (4–5 mol%/Ar-Br bond), *n*-Bu_4NBr (0.8–1.0 equiv/Ar-Br bond), NaOAc (1.2–2.4 equiv/Ar-Br bond), and DMF/THF (3:1 *w*/*w*) as solvent (120 °C). It was not necessary to exclude air or moisture, and the reactions could be conducted on >10 g scales. Only *E*-isomers of the products **82** were detected. Hydrogenation of thirteen representative products with Pd/C and balloon pressure H_2 gave $Ar(CH_2CH_2R_{fn})_m$ in 92% average isolated yield.



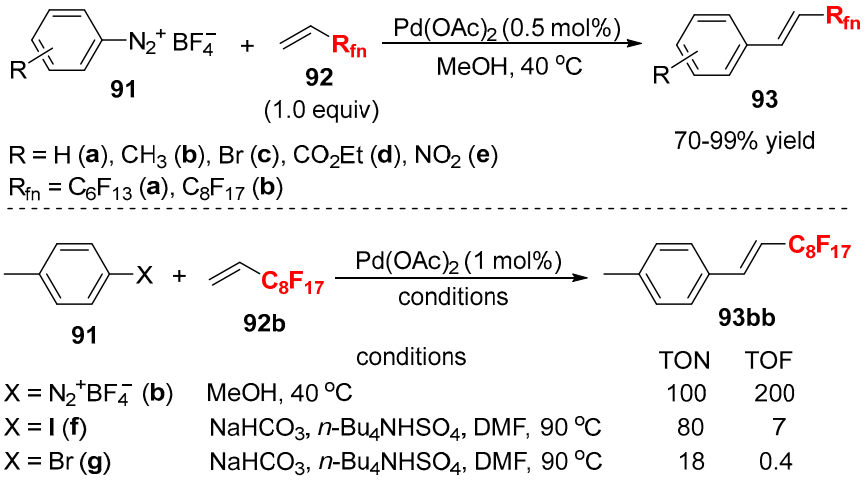
Scheme 16. The Mizoroki-Heck reactions of aromatic bromides and polybromides with fluorous alkenes.

In addition, a family of diazonium-functionalized oligo(phenylene vinylene)s (OPVs) tetramers were synthesized by alternating the Mizoroki-Heck cross-coupling and the Horner-Wadswoth-Emmons (HWE) reaction using fluorous mixture synthesis (FMS) technology (Scheme 17) [73]. The FMS technology was found to be superior to the solid-phase organic synthesis (SPOS) techniques. The Mizoroki-Heck couplings of bromide **83** with 1*H*,1*H*,2*H*-perfluoroalkenes (**84**) employed a palladacycle catalyst which proved to be a better catalyst than $Pd(OAc)_2$. Hydrogenation of the coupled alkenes (**85**) followed by removal of the Boc groups gave secondary amines as fluorous tags for diazonium-substituted aryl iodides (**87**). The final stage of OPV tetramer growth was a Heck-type reaction with an end-capping styrene derivative (**89**). At the end, the tagged products were detagged by cleaving the triazene linkage and generating a series of aryl diazonium compounds. The fluorous tags could be reused. The aryl diazonium functionalities in the products allowed them to be used as surface-grafting moieties in hybrid silicon/molecule assemblies [73].

Genêt and co-workers described the palladium-catalyzed Mizoroki-Heck reactions between aryldiazonium salts (**91**) and perfluoroalkyl alkenes (**92**) (Scheme 18) [74]. The reactions carried out in methanol at 40 °C in the presence of 0.5 mol% of $Pd(OAc)_2$ afforded a series of long-chain perfluoroalkyl-substituted aromatic compounds (**93**) in good to excellent yields. However, coupling of 4-iodotoluene (**91f**) under the same reaction conditions failed to give the desired product (**93bb**; R = CH_3, R_{fn} = C_8F_{17}). Coupling of aryl iodide in the presence of $Pd(PPh_3)_4$ and triethylamine in toluene didn't form the expected product neither. Interestingly, under Jeffery's conditions ($Pd(OAc)_2$, DMF, $NaHCO_3$, *n*-Bu_4NHSO_4), the reaction of 4-iodotoluene (**91f**) with **92b** (R_{fn} = C_8F_{17}) afforded **93bb** in 80% yield, but 4-bromotoluene (**91g**) remained much less reactive. Thanks to the difference in the reactivity of these functionalities, the Heck-type reaction of **92b** with 4-bromobenzenediazonium tetrafluoroborate (**91c**) produced **93cb** (R = Br, R_{fn} = C_8F_{17}) exclusively, showing good chemoselectivity. Hydrogenation of the carbon-carbon double bond of **93** afforded the fluorous aromatic compounds. Perfluoroalkyl-substituted aryl bromides and anilines were also accessed by this method. This protocol represented one of the most efficient methods to install a perfluoroalkyl chain onto an aromatic ring. The simple purification and the high purities of products allowed an easy scale up of this procedure.

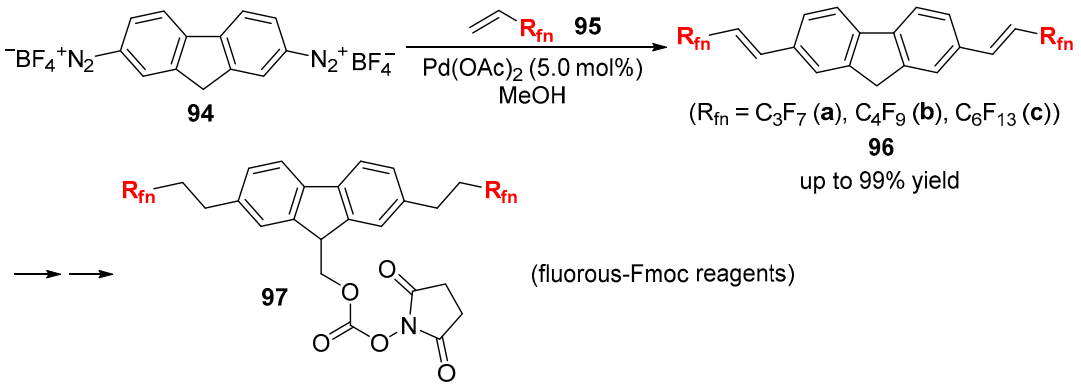


Scheme 17. Preparation of diazonium-functionalized oligo(phenylenevinylene)s by FMS technology.



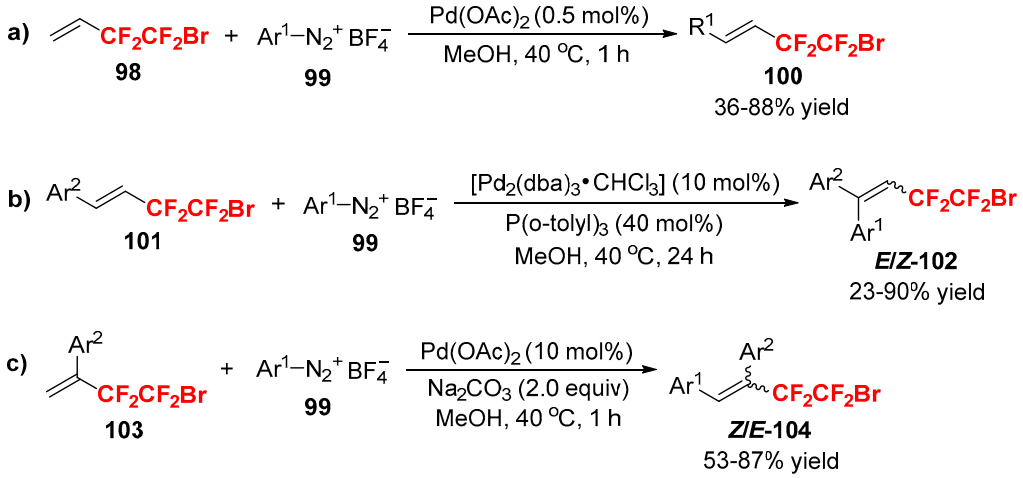
Scheme 18. The Heck-type reactions between perfluoroalkyl alkenes and aryldiazonium salts.

In 2015, Matsugi and co-workers synthesized f-Fmoc reagents (**97**) bearing C_3F_7, C_4F_9, or C_6F_{13} chains by the $Pd(OAc)_2$-catalyzed Mizoroki-Heck reaction of **94** with **95a**, **95b**, or **95c**, followed by hydroxymethylation and introduction of the *N*-hydroxysuccinimide group (Scheme 19) [75]. The method applied on a multi-gram scale after eight steps gave the desired products **97a**, **97b**, and **97c** with overall yields of 73%, 60%, and 90%, respectively. The Pd-catalyzed doubly tagging Heck reaction of **94** with a mixture of the fluorous alkenes (**95**) was also studied, leading to an encoded mixture synthesis of f-Fmoc reagents. Addition of **95** in an order of **95c**, **95b**, **95a** to the reaction mixture was found to be an effective condition in the mixed tagging Heck reaction. The target f-Fmoc reagents with C_3F_7, C_4F_9, and C_6F_{13} groups could be separated owing to the different fluorine content of the molecules. This method provided a reasonable solution to obtain various f-Fmoc reagents in a one-pot procedure. These f-Fmoc reagents would be useful protecting groups for the effective synthesis of peptide isomer libraries.



Scheme 19. Multi-gram scale and divergent preparation of fluorous-Fmoc reagents via the Mizoroki-Heck reactions.

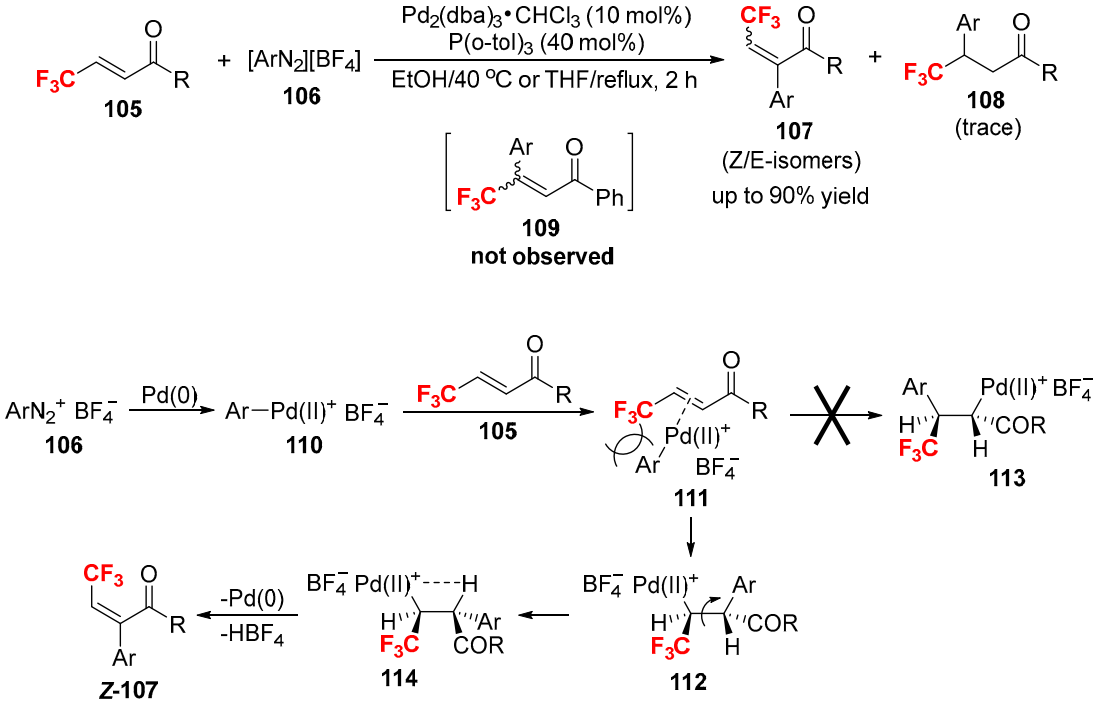
In 2017, Konno and co-workers investigated the Pd-catalyzed Mizoroki-Heck reactions of aryldiazonium tetrafluoroborates with different types of CF_2CF_2-containing alkenes (Scheme 20) [76]. A survey of the optimized reaction conditions revealed that the reactions of 4-bromo-3,3,4,4-tetrafluoro-1-butene (**98**) with aryldiazonium salts (**99**) in the presence of 0.5 mol% $Pd(OAc)_2$ in MeOH at 40 °C for 1 h gave the best yields of the products. The *E*-configured products (**100**) were exclusively obtained, and no *Z*-isomers were detected. In the cases of 4-bromo-3,3,4,4-tetrafluoro-1-aryl-1-butenes (**101**), a bulky P(*o*-tolyl)$_3$-coordinated palladium catalyst was found to be a good catalytic system, leading to an increased yield of the product (**102**). High stereoselectivity of the reaction was achieved if **102** containing an electron-deficient aromatic ring, whereas a slight decrease in the stereoselectivity was observed if **102** bearing an electron-donating substituent on the aromatic ring. In the reactions of 4-bromo-3,3,4,4-tetrafluoro-2-aryl-1-butenes (**103**) with **99**, the geometry of the major isomers of **104** was determined as *E*-configuration on the basis of a proposed reaction mechanism [76]. This protocol provided a convenient and highly stereoselective method for the preparation of multi-substituted alkenes (**100**, **102**, and **104**) bearing a tetrafluoroethylene fragment, which are promising building blocks for the synthesis of novel CF_2CF_2-containing organic molecules [76].



Scheme 20. The Mizoroki-Heck reactions of CF_2CF_2-containing alkenes with aryldiazonium tetrafluoroborates.

In a similar manner, Konno and co-workers examined the palladium-catalyzed Heck reactions of (*E*)-4,4,4-trifluoro-1-phenyl-2-buten-1-one (**105a**) with the readily available aryldiazonium salts

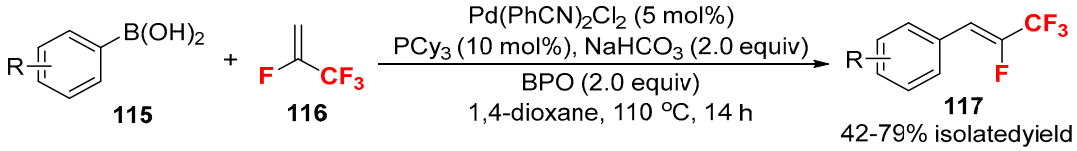
(**106**) (Scheme 21) [77]. The reactions allowed for easy and regio- and stereoselective access to a variety of 4,4,4-trifluoro-2-aryl-1-phenyl-2-buten-1-ones (**107**) in good yields. Aryldiazonium salts bearing electron-donating groups or halogens on the phenyl rings reacted nicely under the Heck-type cross-coupling conditions, preferentially forming the *Z*-isomers of the products (***Z*-107**). However, substrates with electron-withdrawing groups or bulky groups on the aryldiazonium moieties didn't give the satisfactory results. The Michael addition adducts (**108**) were formed as byproducts in most cases [77]. Later, the same research group extended the scope of the heck reaction to other types of fluorine-containing electron-deficient olefins (Scheme 21) [78]. They found that the electron-withdrawing group (EWG) on alkenes had a big influence on the efficacy of the reaction. α,β-Unsaturated ester reacted with phenyldiazonium salt to provide the corresponding adduct in very low yield. Vinylphosphonate and vinylsulfone were found to be unreactive, with only the starting materials being recovered. In the case of nitroalkene, neither the starting material nor the desired Heck adduct was detected, and the reaction became very complicated. Additionally, changing the fluoroalkyl group from CF_3 to CF_2H group caused a significant decrease in the chemical yield, although the relatively high regioselectivity was obtained. A plausible reaction mechanism was suggested in Scheme 21 [78]. The reaction presumably proceeded via (1) oxidative addition of aryldiazonium salt (**106**) to Pd(0), leading to an arylpalladium complex (**110**), (2) coordination of the electron-deficient olefin (**105**) to the metal center of **110** and subsequent insertion into the Ar-Pd bond to generate **112** other than **113**, (3) carbon-carbon bond rotation of **112** to produce intermediate **114**, and (4) reductive elimination of $[HPd]BF_4$ from **114** to finally afford tri-substituted alkene (**107**) and to regenerate the Pd(0) catalyst.



Scheme 21. The Heck-type reactions of fluorine-containing electron-deficient olefins with aryldiazonium salts.

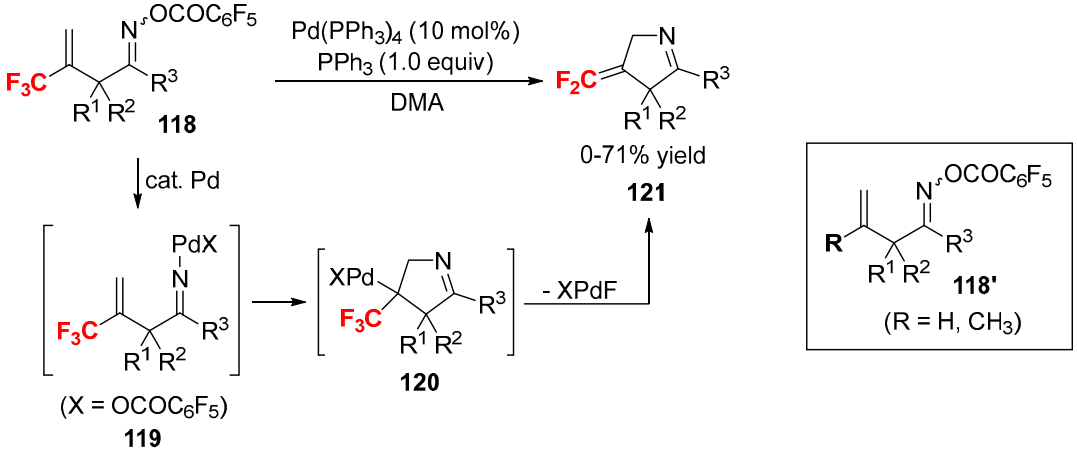
Arylboronic acids are an important class of compounds for coupling reactions, which are stable in air and to moisture, and they are compatible with a broad range of common functional groups [62–64]. In 2015, Lu and co-workers presented the first oxidative Heck-type reactions of arylboronic acids with fluoroalkylated olefin [79]. The Pd-catalyzed cross-couplings of the commercially available 2,3,3,3-tetrafluoroprop-1-ene (**116**) with diverse arylboronic acids (**115**) provided a variety of

(*Z*)-*β*-fluoro-*β*-(trifluoromethyl)styrene derivatives (**117**) in good yields (Scheme 22) [79]. The wide range of substrates and the good functional group tolerance made this strategy facile and practical for the streamlined synthesis of functional styrenes.



Scheme 22. The oxidative Heck reactions of fluorinated olefins with arylboronic acids by palladium catalysis.

Furthermore, Pd-catalyzed Heck-type cyclization of 2-trifluoromethyl-1-alkenes (**118**) bearing an *O*-acyloxime moiety was accomplished (Scheme 23) [45,80]. The reaction represented a rare example of 5-endo mode alkene insertion into transition-metal species via oxidative addition of the N–O bond (**119**). Although there were two possible pathways, namely *β*-fluorine elimination and *β*-hydrogen elimination of **120** after ring formation, the former exclusively took place to form an exo-difluoromethylene unit. This catalytic process provided facile access to 4-difluoromethylene-1-pyrrolines (**121**). To elucidate the role of the CF_3 group, the reaction of analogues (**118′**) bearing a hydrogen atom or a methyl group instead of the CF_3 functionality on the alkene fragment was examined. When **118′** was subjected to the reaction conditions similar to those for **118**, no cyclized product was obtained. The results indicated that the CF_3 group played a crucial role in the 5-endo Heck-type cyclization, wherein the trifluoromethyl substituent seemed to activate the vinylic terminal carbon in **118** and stabilize the cyclized palladium intermediate **120**.

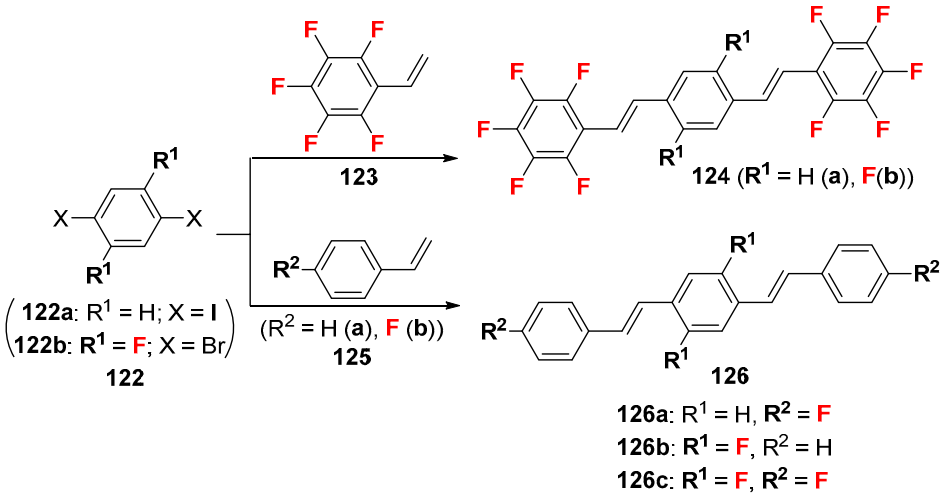


Scheme 23. Pd-catalyzed Heck-type cyclization of 2-(trifluoromethyl)allyl ketone oximes.

2.4. Other Fluorine-Containing Alkenes as the Cross-Coupling Reagents

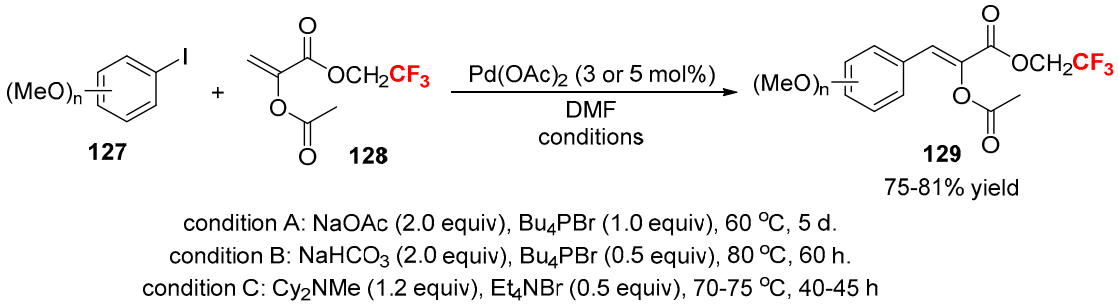
A series of fluorinated distyrylbenzene (DSB) derivatives (**124** and **126**) were synthesized by Pd-catalyzed Mizoroki-Heck cross-couplings (Scheme 24) [81]. The reaction of 1,4-diiodobenzene (**122a**) with pentafluorostyrene (**123**) or 4-fluorostyrene (**125b**) in the presence of $Pd(OAc)_2$ gave *trans-trans*-1,4-bis(pentafluorostyryl)benzene (**124a**) or *trans-trans*-bis(4-fluorostyryl)benzene (**126a**). The coupling of 1,4-dibromo-2,5-difluorobenzene (**122b**) with styrene (**125a**), 4-fluorostyrene (**125b**), or pentafluorostyrene (**123**) using $Pd(OAc)_2$ provided 1,4-bis(styryl)-2,5-difluorobenzene (**126b**), 1,4-bis(4-fluorostyryl)-2,5-difluorobenzene (**126c**), and 1,4-bis-(pentafluorostyryl)-2,5-difluorobenzene (**124b**), respectively. The products were employed to probe the effect of fluorine substitution on the molecular properties and on the arrangement of molecules in the solid state [81]. The absorption

spectroscopy showed that **124** and **126** had a λ_{max} at approximately 350 nm, and addition of dimethylaniline to the hexane solutions led to exciplex emission with λ_{max} ranging from 458 to 514 nm, depending on the positions of fluorine substitution. Moreover, the X-ray diffraction experiments for the lattice properties of **124a**, **124b**, **126b**, and **126c** indicated two possible structural motifs. One is to stack the DSB framework cofacially to form vertical "columns" within the crystal. The other is the alignment of these "columns" to maximize C–H···F electrostatic registry.



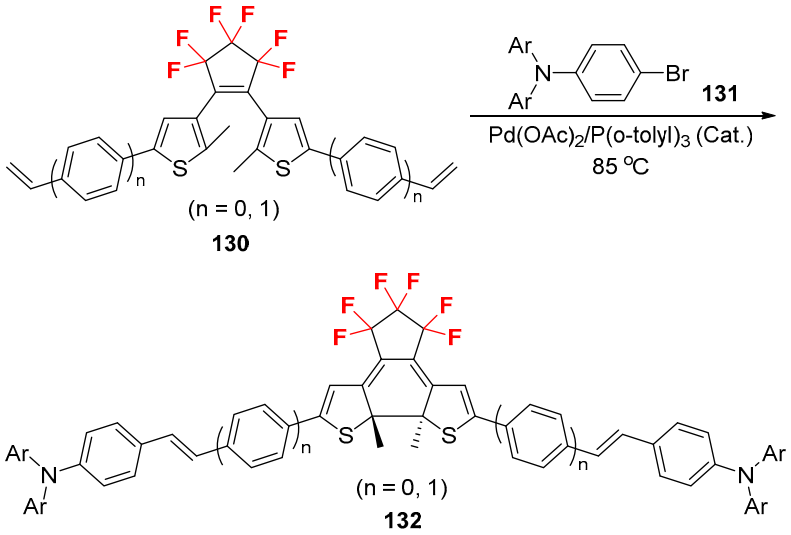
Scheme 24. Synthesis of fluorinated distyrylbenzene chromophores by Heck-type reactions.

In addition, ligand-free Pd-catalyzed Mizoroki-Heck alkenylation of iodoarenes (**127**) with trifluoroethyl 2-acetoxyacrylate (**128**) was explored, which stereoselectively produced trifluoroethyl (*Z*)-2-acetoxycinnamates (**129**) in good yields (Scheme 25) [82]. Compounds **129** underwent deacetylation followed by acylation to yield isomerically pure trifluoro-ethyl (*Z*)-2-(arylacetoxy)cinnamates. *t*-BuOK-Mediated Dieckmann condensations of these products furnished a variety of pulvinone derivatives.



Scheme 25. Pd-catalyzed Mizoroki-Heck reactions of iodoarenes with trifluoroethyl 2-acetoxyacrylate.

The D-A-D-type chromophores (**132**) with a hexafluorocyclopentene thiophene "core" flanked by triphenylamine units were synthesized by facile procedures, including the Pd-catalyzed Mizoroki-Heck reactions (Scheme 26) [83]. The triphenylamine group caused the open-ring isomer of hexafluorocylopentene thiophene to close, which resulted in intramolecular *p*-conjugation extension, thus broadening the absorption spectra ranging from 200 to 850 nm with high optical densities.

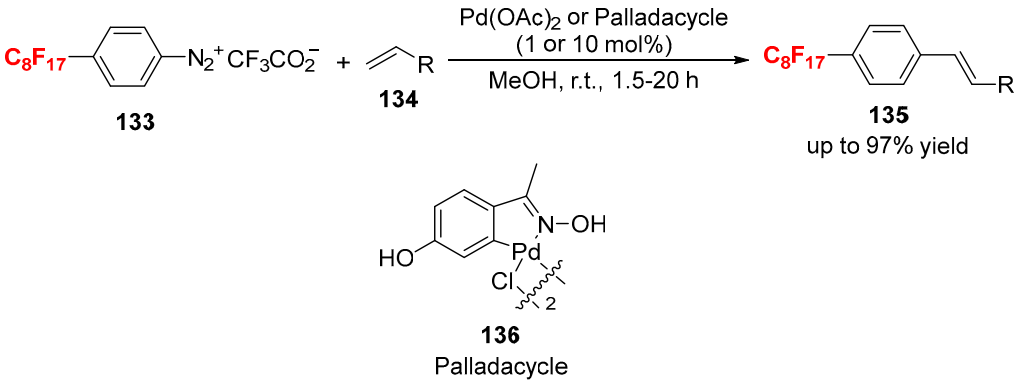


Scheme 26. Synthesis of triphenylamine derivatives with a hexafluorocyclopentene unit via the Pd-catalyzed Mizoroki-Heck cross-couplings.

3. Mizoroki-Heck Reactions of Fluorinated Halides or Pseudo-Halides with Alkenes

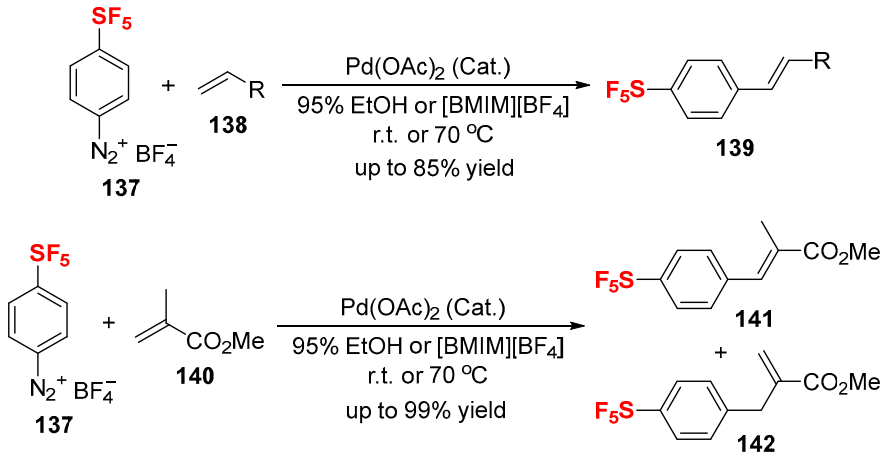
3.1. Fluorinated Aryl Halides or Pseudo-Halides as the Coupling Agents

In 2011, Vallribera and co-workers reported the Pd-catalyzed arylation of both electron-rich and -poor olefins (**134**) with 4-(perfluorooctyl)benzenediazonium trifluoroacetate (**133**) (Scheme 27) [84]. This Heck-type reaction supplied a variety of perfluoroalkylated aromatic compounds (**135**) by using $Pd(OAc)_2$ or 4-hydroxyacetophenone oxime-derived palladacycle (**136**) as an efficient source of Pd nanoparticles. Ligand-free $Pd(OAc)_2$ appeared to be a more general catalyst than palladacycle (**136**) for the reaction. The activity of **136** depended greatly on the nature of the alkene used. No external base was necessary for the conversion, and the reactions could be carried out at room temperature in the presence of 1 mol% of Pd(II) catalyst. Some intermediates derived from the oxidative addition of **133** to the catalyst were identified by ESI-MS experiments. The Pd(IV) species detected by this technique when **136** was used, did not seem to act as intermediates of the reaction. The TEM images of the reaction solutions showed, for the first time, the formation of nanoparticles with both catalysts under the Matsuda-Heck conditions. These Pd(0) nanoparticles might act as a reservoir of Pd(0) atoms involved in the reaction, which avoided the precipitation of black palladium and thus probably extended the lifetime of the catalyst.



Scheme 27. The Heck-type reactions of alkenes with arenediazonium trifluoroacetate.

A series of SF_5-bearing alkenes (**139**, **141**, and **142**) were synthesized by employing the Matsuda-Heck reactions of 4-(pentafluorosulfanyl)benzenediazonium tetrafluoroborate (**137**) with alkenes (**138** and **140**) (Scheme 28) [85]. Compound **137** was readily synthesized and isolated as a stable salt for a wide assortment of transformations. The cross-couplings of **137** with styrene and 4-substituted styrenes in the presence of catalytic $Pd(OAc)_2$ in ethanol gave the corresponding 4′-substituted 4-(pentafluorosulfan-yl)stilbenes in good yields. The reaction run in ionic liquid [BMIM][BF_4] instead of EtOH resulted in lower isolated yield due to the increased formation of homo-coupling product. Reaction of **137** with methyl acrylate in the presence of Pd(OAc)2 in 95% EtOH afforded methyl *trans*-3-[4-(pentafluorosulfanyl)phenyl]prop-2-enoate in 85% yield without *cis*-isomer. However, coupling of 137 with methyl methacrylate (140) in 95% EtOH or [BMIM][BF4] gave a mixture of methyl 2-methyl-3-[4-(pentafluorosulfanyl)phenyl]prop-2-enoate (141) and methyl 2-{[4-(pentafluorosulfanyl)phenyl]methyl}prop-2-enoate (**142**) in up to 99% yield. Furthermore, **137** enabled couplings with fluorous olefins to form the corresponding fluorinated adducts in good yields [85]. Unfortunately, the Matsuda-Heck reaction of **137** with ethyl cinnamate or norbornene in EtOH, MeOH, or [BMIM][BF_4] at room temperature or 70 °C failed to give the desired product [85].

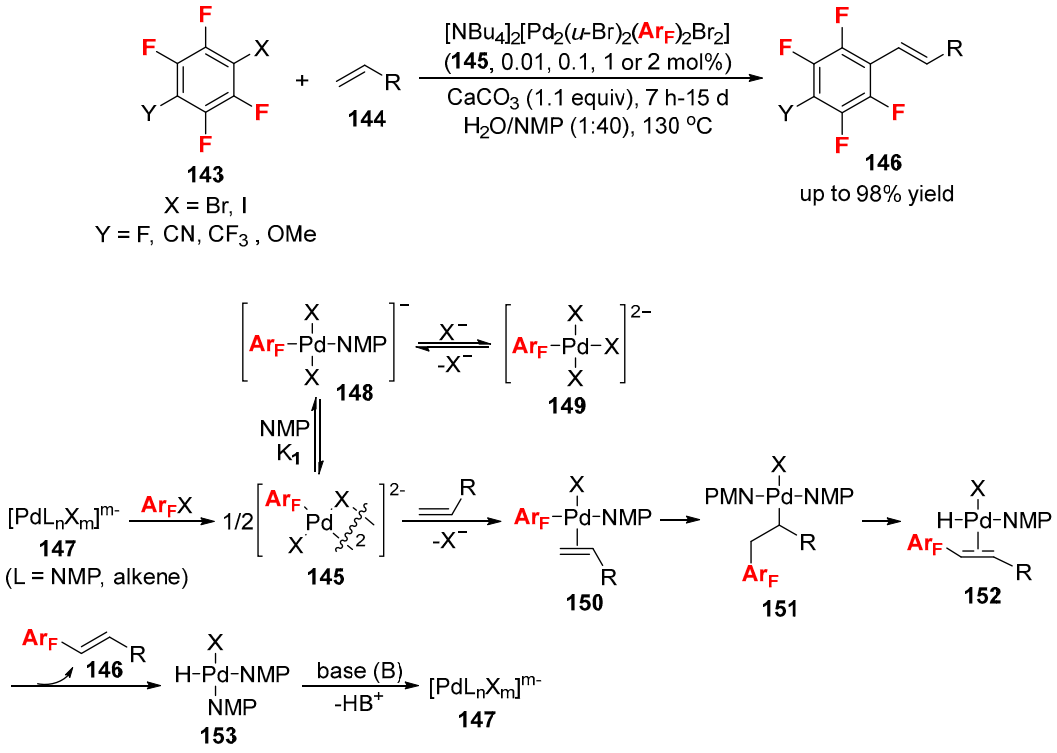


Scheme 28. The Heck-type reactions of 4-(pentafluorosulfanyl)benzenediazonium tetrafluoroborate.

An efficient catalytic system for the Mizoroki-Heck reactions of fluoroaryl halides (**143**) with alkenes (**144**) was developed (Scheme 29) [86]. Complex **145** (1 mol%) catalyzed the reaction of C_6F_5Br and styrene at 130 °C to give regioselectively *trans*-PhCH=CHAr$_F$ (**146a**, Ar$_F$ = C_6F_5) in almost quantitative yield. The studies indicated that $CaCO_3$, KF, and Na_2CO_3 were the suitable bases, and that NMP was the best solvent for the reaction. [$Pd(PPh_3)_4$] failed to initiate the reaction of styrene with C_6F_5Br. If C_6F_5I was employed as a substrate under the optimized conditions, much lower yield of *trans*-PhCH=CHAr$_F$ was obtained. C_6F_5Cl didn't react with styrene under the same conditions. The reaction was also efficient for other fluorinated aryl bromides such as *p*-XC_6F_4Br (X = CN, CF_3, OMe) and *p*-FC_6H_4Br [86]. For an activated alkene, such as methyl acrylate, the reaction proceeded fast even at 100 °C, and in this case, use of KF as a base led to higher conversion. 1-Hexene and α-methylstyrene could also be functionalized. Electron-rich alkenes such as butylvinyl ether and 2,3-dihydrofuran gave very low yields of the desired products. The reaction with styrene was not affected by oxygen or galvinoxyl, which excluded a radical addition pathway [86].

Moreover, complex **145** in $CDCl_3$ afforded immediately a 1:1.6 mixture of two isomers corresponding to the *cis* and *trans* arrangements of the two C_6F_5 groups in the dimer [86]. If **145** was dissolved in NMP at room temperature and at low concentrations, **148** was observed as the main species, determined by ^{19}F NMR spectroscopy. Upon addition of Br^- anion to **148**, **149** was also detected. The equilibrium constants between **145**, **148**, and **149** in NMP at room temperature could be measured. At higher temperatures (e.g., 120 °C), the equilibria became fast, and the signals of

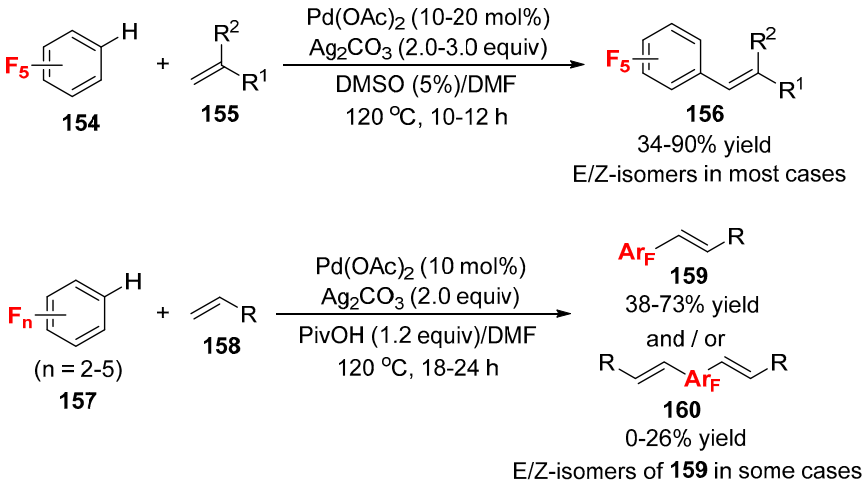
these complexes collapsed. When the reaction of C_6F_5Br and styrene was monitored by ^{19}F NMR at 120 °C under catalytic conditions, only one set of Ar_F-Pd signals was observed. Based on these studies, a possible reaction mechanism was suggested in Scheme 29 [86]. The first step of the catalytic cycle is the coordination and insertion of the alkene by **145**, generating **151**. This step is likely to be rate-determining, which is supported by the observation of the signals of the complexes preceding this step and by the fact that the reaction rate of C_6F_5Br and styrene was simply dependent upon the concentration of styrene. Then, β-H elimination of **151** followed by reductive elimination of HX from **153** provides **146** and regenerates Pd(0) species (**147**), which is stabilized by bromide anions. The reaction outside the catalytic cycle showed that the insertion of styrene into the Pd-C_6F_5 bond of **148** was retarded by addition of NBu_4Br. If the catalytic reaction was carried out under bromide-free conditions, only 3% of **146a** was obtained and the catalyst extensively decomposed. In addition to stabilizing the Pd(0) intermediate, the bromides might increase the rate of oxidative addition. Excess styrene increased the reaction rate by facilitating the coordination-insertion process, but a large excess of styrene stopped the reaction. Addition of NBu_4Br to the latter reaction mixture could reactivate the process. It seemed that displacement of bromides on Pd(0) by alkene at high concentration severely slowed the oxidative addition, which became rate-determining instead of the coordination-insertion step [86,87]. Thus, the success of this catalysis required a compromise between the optimal conditions for the oxidative addition and the coordination-insertion.



Scheme 29. The Mizoroki-Heck reactions of fluoroaryl halides with alkenes.

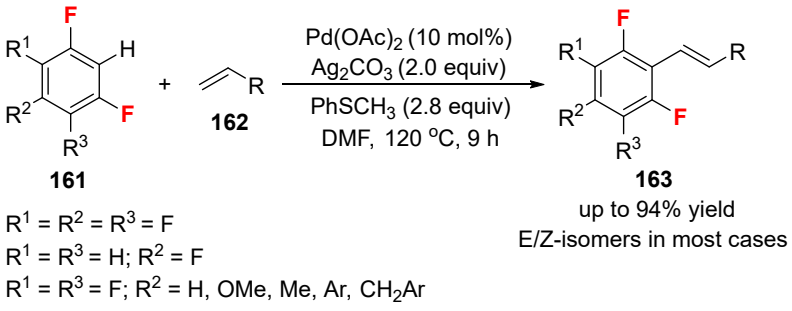
In 2010, Zhang and co-workers reported the first $Pd(OAc)_2$-catalyzed oxidative Heck-type reactions of the electron-deficient pentafluoroarene (**154**) with a broad range of alkenes (**155**) (Scheme 30) [88]. The reactions provided a great variety of pentafluorophenyl substituted alkenes (**156**) in moderate to high yields and with moderate to high stereo- and regioselectivities. A survey of reaction conditions indicated that the solvent, oxidants, and Pd-catalysts were critical for the reaction efficiency. A mixed solvent system of 5% DMSO in DMF was found to be the optimum reaction medium. The reaction using Ag_2CO_3 as both the base and oxidant in the presence of $Pd(OAc)_2$ (10 mol%) at 120 °C gave the best yield of the desired product. Electron-deficient olefins bearing

ester, amide, phosphonate, or ketone groups worked well to give moderate to excellent yields and high stereoselectivities. Notably, nonactivated aliphatic olefins and electron-rich alkenes underwent smooth reactions in good yields, which were in sharp contrast to previous results [86,87]. In the case of polyfluoroarenes (**157**), the reactions using PivOH (1.2 equiv) instead of DMSO (5%) afforded alkenylated products (**159**) in moderate yields with moderate to good regioselectivities. In general, the reactions with electron-rich alkenes afforded higher yields than those with electron-deficient ones. The most acidic C–H bonds located between two fluorine atoms were the primary reaction sites, which provided mostly the monoalkenylated products in higher yields. It was also possible to further derivatize the polyfluoroarylated alkenes through C–H functionalization. This strategy allowed the selective installation of substituents at different positions and provided a convenient access to highly functionalized fluoroarenes by catalytic methods.



Scheme 30. $Pd(OAc)_2$-catalyzed oxidative olefination of highly electron-deficient fluoroarenes with alkenes.

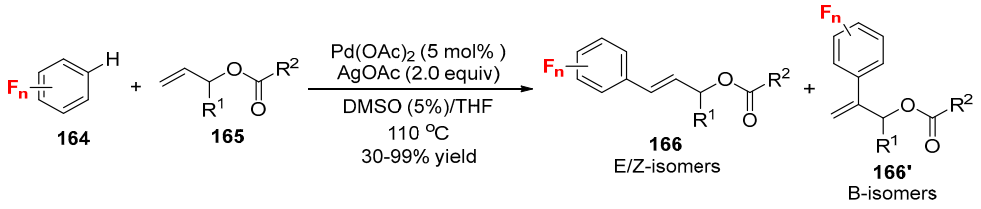
Later, Zhang's research group again disclosed the thioether-promoted direct olefination of polyfluoroarenes (**161**) with alkenes (**162**) catalyzed by $Pd(OAc)_2$ (Scheme 31) [89]. Remarkably, the "inert" substrates, such as 3-substituted tetrafluorobenzenes, which previously furnished their corresponding products in low yields, afforded the alkenylated products (**163**) in high yields and with excellent stereoselectivities using only 1.0 equiv of alkene in this reaction. The results demonstrated the power of the thioether ligand PhSMe in the Pd-catalyzed reactions of polyfluoroarenes, offering a new choice to discover more efficient catalytic systems. Furthermore, a competitive reaction between electron-deficient and electron-rich alkenes with pentafluorobenzene was conducted, which provided their corresponding products in an almost 1:1 ratio, suggesting that the direct olefination of polyfluoroarenes has no bias on the nature of alkenes under these reaction conditions [89].



Scheme 31. Thioether-promoted direct olefination of polyfluoroarenes catalyzed by palladium.

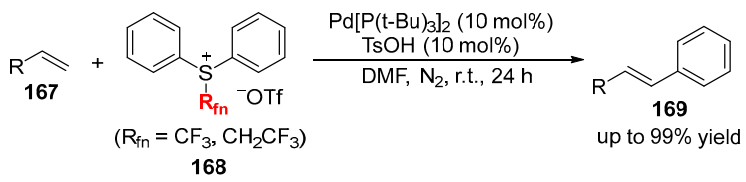
By a similar strategy, a series of olefin-containing fluorinated benzothiadiazoles were synthesized from fluorinated benzothiadiazoles in the presence of 2.5 mol% $Pd(TFA)_2$, 3.0 equiv AgOAc, 2.5 equiv $PhCO_2H$, and 0.1 equiv benzoquinone [90]. The reactions proceeded under mild conditions and showed good functional group compatibility. The products found important applications in optoelectronic materials. Significantly, the Pd-catalyzed aerobic direct olefination of polyfluoroarenes was also explored [91]. The procedure made use of molecular O_2 as the terminal oxidant instead of silver(I) salt, providing a cost-efficient and environment-benign access to polyfluoroarene-alkenes. The silver species and the thioether ligand played important roles in the reactions, but the mechanisms remained unclear.

In addition, Liu and co-workers investigated the Pd(II)-catalyzed direct olefination of electron-deficient fluoroarenes (**164**) with allylic esters and ethers (**165**) (Scheme 32) [92]. In this transformation, various γ-substituted allylic esters (mixtures of *E*/*Z*- and *B*-isomers (**166** and **166′**)) were prepared in good to excellent yields by oxidative Heck reactions via β-H elimination, rather than β-OAc elimination. Typically, the desired products were obtained in good yields under conditions composed of $Pd(OAc)_2$ (5 mol%), AgOAc (2.0 equiv), DMSO (5%)/THF, 110 °C, and 12 h. A variety of fluorinated arenes proved to be very efficient substrates under the typical conditions, and the olefination generally took place at the more sterically accessible position. This selectivity might be attributed to the acidity of C–H bonds of the fluorinated arenes even though it was located at a more sterically hindered position. Tetrafluorobenzene and fluorinated arenes bearing an electron-donating methoxy group could also give the desired products. Yields of the products decreased with the decrease in the number of fluorine atoms substituted on the aromatic rings. Significantly, allyl acrylate and allyl methacrylate afforded the corresponding products in moderate to good yields. The oxidative olefination occurred at the allylic rather than the acrylic carbon–carbon double bond. This selectivity might be ascribed to the stability of the alkyl-Pd intermediate via chelation of Pd center by the carbonyl *O*-atom. This chelation effect could also result in the high regioselectivity as the (Pd)C–C(O) bond cannot rotate freely.



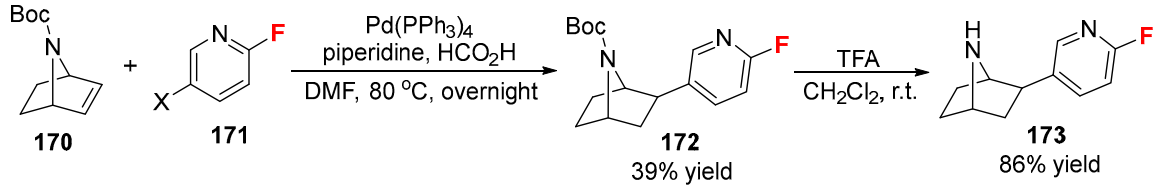
Scheme 32. The Pd-catalyzed oxidative olefination of fluoroarenes with allyl esters.

S-fluoroalkyl diphenylsulfonium triflates $[Ph_2SR_{fn}][OTf]$ (**168**, R_{fn} = CF_3, CH_2CF_3) were effective cross-coupling partners in the Pd-catalyzed Mizoroki-Heck-type reactions with alkenes (Scheme 33) [93]. The functionalization of various conjugated and unconjugated alkenes (**167**) by **168** in the presence of 10 mol% $Pd[P(t\text{-}Bu)_3]_2$ and TsOH at room temperature provided the corresponding phenylation products (**169**) in good to high yields. The bases that benefited the traditional Mizoroki-Heck reactions severely inhibited this transformation, whereas the acids significantly improved the reaction. This protocol demonstrated a new class of cross-coupling participants for Heck-type reactions [93].



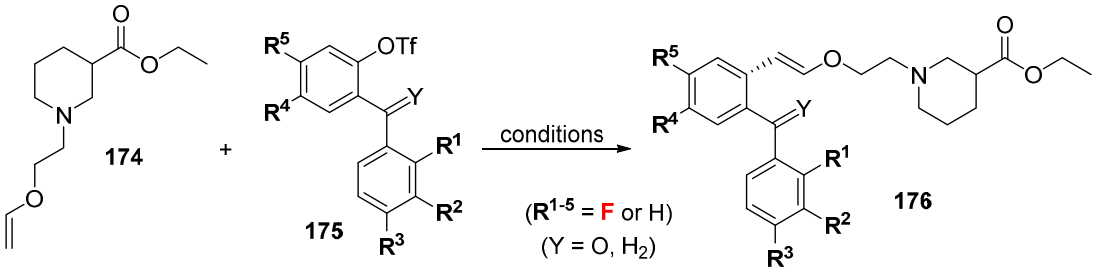
Scheme 33. Pd-catalyzed Mizoroki-Heck reactions of $[Ph_2SR_{fn}][OTf]$ with alkenes.

Epibatidine (exo-2-(2′-chloro-5′-pyridyl)-7-azabicyclo[2.2.1]heptane), a natural compound isolated from the skin of the Ecuadorian poison frog Epipedobates tricolor, is a potent nicotinic acetylcholine receptor (nAChR) agonist [94]. In order to visualize and quantify these receptors in the human brain using positron emission tomography (PET) technique, exo-2-(2′-[^{18}F]fluoro-5′-pyridyl)-7-azabicyclo[2.2.1]heptane, a fluorine-18 ($t_{1/2}$ = 110 min) radiolabeled derivative of epibatidine, was synthesized from the nucleophilic aromatic substitution of the corresponding 2′-bromo-, 2′-iodo- or 2′-nitro exo-2-(5′-pyridyl)-7-azabicy-clo[2.2.1]heptane analogue with [^{18}F]FK-K_{222} [94]. In this work, norchlorofluoroepibatidine (**173**) was employed as a reference compound, which was synthesized by reductive and stereoselective Pd-catalyzed Heck-type cross-coupling of **170** and **171** (Scheme 34) [94].



Scheme 34. Synthesis of a fluorinated derivative of epibatidine via the Mizoroki-Heck reaction.

The *β*-selective, chelation-controlled Heck-type reaction was found to be a convenient and versatile method to synthesize a series of new lipophilic *N*-alkylated nipecotic acid derivatives (**176**) bearing a vinyl ether unit embedded in the spacer and an unsymmetrical bis-aromatic residue at the terminal position of the spacer (Scheme 35) [95]. Most of the compounds displayed reasonable to good potencies and selectivities for mGAT1 (subtype of GABA transporter originating from murine cells). The influence of the presence and the position of fluorine substituents in the bis-aromatic residue concerning potency and selectivity of the compounds was defined. In general, all *Z*-isomers of the synthesized compounds were more potent than their corresponding *E*-isomers. The influence of fluorine substituents on the GAT1 uptake inhibition was generally more severe for the compounds with two aromatic rings being linked by a methanone bridge (Y = O). Substitution with fluorine in the 4-position of one aryl ring (R^4 = F) and an additional fluorine substituent at the *para*-position of the other aryl ring (R^3 = F) was the most beneficial combination, leading to one of the most potent compounds of the whole series.

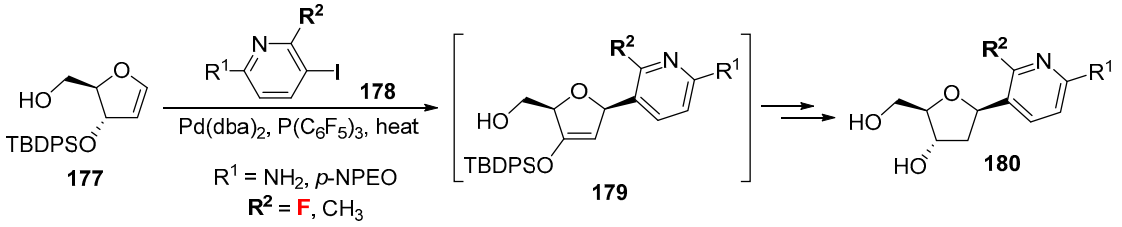


condition A: $Pd(OAc)_2/NEt_3$, DMF, 80 °C, 20 h, 39-78%
condition B: $Pd(OAc)_2/PPh_3/NEt_3$, DMF, 80 °C, 20 h, 19-55%
condition C: $Pd(OAc)_2$/LiCl/NaOAc/K_2CO_3, DMF/H_2O (v/v = 10:1), 80 °C, 20 h, 65-83%

Scheme 35. Synthesis of fluorine-containing *N*-substituted nipecotic acid derivatives by the Mizoroki-Heck reactions.

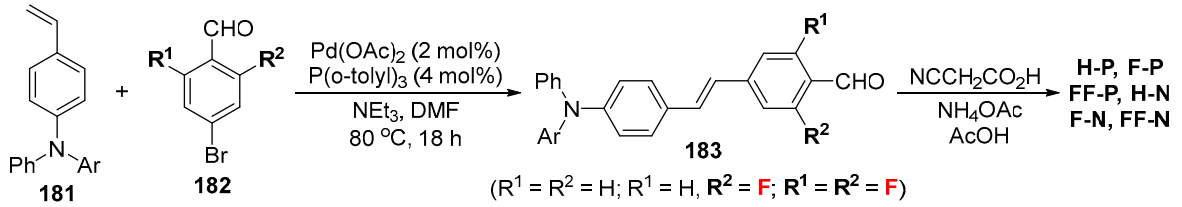
Additionally, four pyrimidine *C*-nucleosides (**180**) were built as mimics of 2′-deoxycytidine (dC) and 2′-deoxyuridine (dU). The key carbon-carbon bond formation between the readily available 2,6-substituted pyridines (**178**) and the glycal (**177**) employed palladium-catalyzed Heck-type reactions

(Scheme 36) [96]. The minor groove functional group in each derivative was replaced by a fluorine or a methyl group. Each coupling reaction yielded only the β-anomer, in part because the bulky silyl protecting group at the 3′-hydroxyl moiety precluded addition of the heterocycle from the "lower" face of the sugar. Without separating the initial coupling products (**179**) from the starting glycal (**177**), the silyl group was removed from **179** and the corresponding ketones were easily purified. Stereospecific reduction of the ketones, followed by removal of the *p*-NPE protecting group if necessary, resulted in the target compounds (**180**) (Scheme 35).



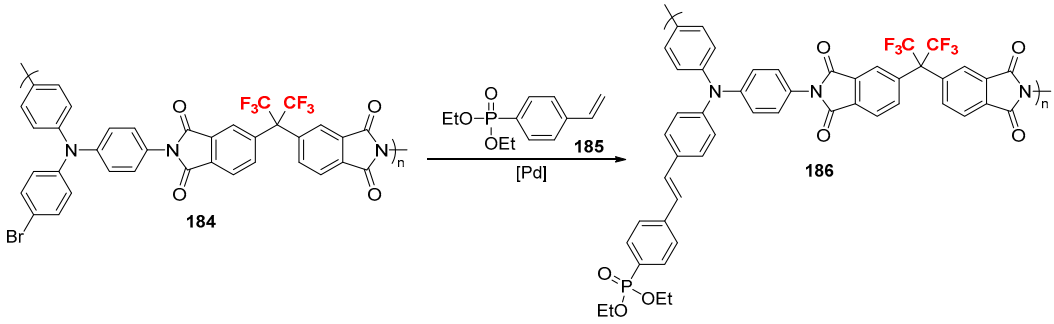
Scheme 36. Synthesis of fluorine-containing pyridine *C*-nucleosides via the Mizoroki-Heck reactions.

Two sets of organic dyes containing a stilbene backbone with fluorine substituents were constructed for a study on the quantum efficiency of dye-sensitized solar cells (DSSCs) (Scheme 37) [97]. Compound **181** was coupled with the commercially available 4-bromobenzaldehyde (**182a**), 4-bromo-2-fluorobenzaldehyde (**182b**), and 4-bromo-2,6-difluorobenzaldehyde (**182c**), respectively, by the Heck-type reactions to yield **183**, which were condensed with cyanoacetic acid via Knöevenagel reactions to afford the final products (H-P, H-N, F-P, FF-P, F-N, and FF-N). The results revealed that a fluorine substituent on the phenyl group *ortho* to the cyanoacrylate could enhance the light-harvesting performance in comparison with the unsubstituted one. The monofluorinated dyes showed larger short-circuit photocurrent density (Jsc) values than the non-substituted ones, due to the extension of the conjugation. However, the difluorinated dyes exhibited a lower performance because of a twisted geometry between the difluorophenyl group and the cyanoacrylate moieties, which reduced the efficiency of π-conjugation and thus decreased the Jsc value.



Scheme 37. Synthesis of fluorine-containing organic dyes by the Mizoroki-Heck cross-couplings.

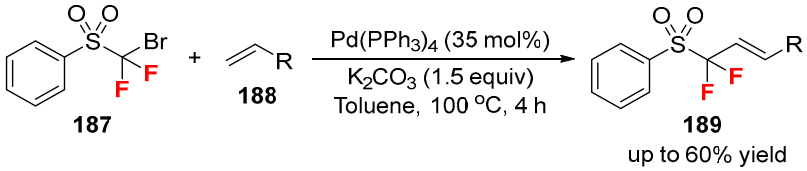
The well-defined polyimides bearing a charge transporting (CT) and nonlinear optical (NLO) functionality in each repeat unit were prepared via two methods [98,99]. One of these methods was the Heck-type cross-coupling of a CF_3-containing brominated polyimide derivative (**184**) with styrene phosphonate **185** (Scheme 38) [98,99]. Polyimide **186** exhibited high thermal stabilities, and the electron-withdrawing phosphonate group was readily incorporated into the NLO moieties.



Scheme 38. Synthesis of multifunctional polymers for photorefractive applications by the Mizoroki-Heck reactions.

3.2. RCF_2X and $R_{fn}X$ as the Cross-Coupling Reagents

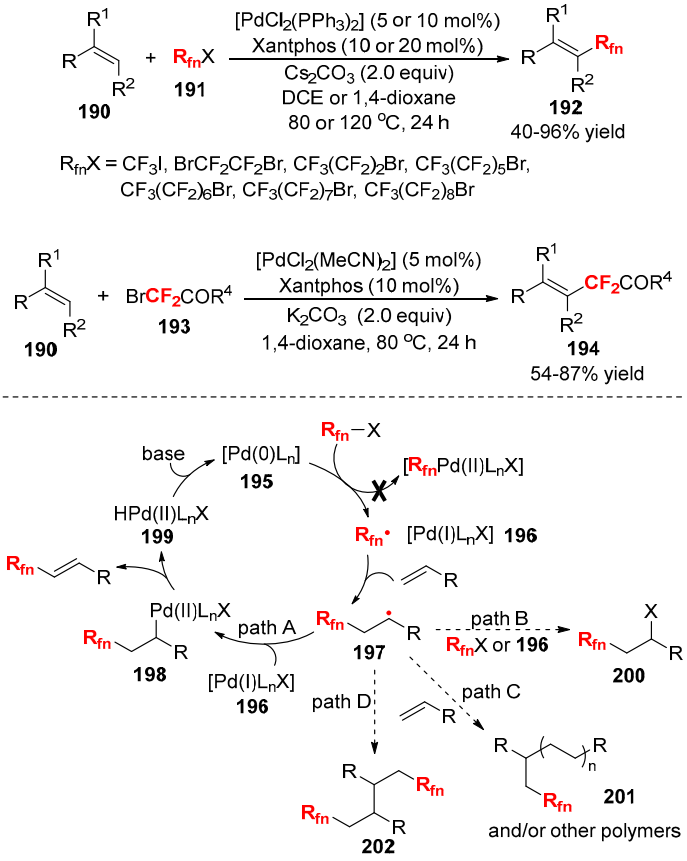
Since the fluoroalkyl groups (CF_2R and R_{fn}) have found wide applications in the areas of medicinal chemistry and/or materials science, significant efforts have been devoted to the development of efficient catalytic systems and to the design of versatile reagents for mild, convenient, and direct fluoroalkylation [39–45]. In 2012, Reutrakul and co-workers described the palladium-catalyzed Heck-type reactions of [(bromodifluoromethyl)sulfonyl]benzene (**187**) with styrenes and vinyl ethers (**188**), furnishing α-alkenyl-substituted α,α-difluoromethyl phenyl sulfones (**189**) in moderate yields (Scheme 39) [100]. Although the efficiency of the reactions was ordinary, they provided an easy procedure for installation of (phenylsulfonyl)difluoromethylene group to olefins. The $PhSO_2CF_2$-containing compounds could be readily transformed. Reductive desulfonylation of the $PhSO_2CF_2$-bearing adduct (**189**) using Mg/HOAc/NaOAc afforded the corresponding CF_2H-substituted product [100]. Furthermore, addition of 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT, 1.0 equiv) to a standard reaction mixture led to a slightly lower yield of the product, implying that the mechanistic pathway of the reaction might not proceed through a radical mechanism. This conversion represented the first report of Pd-catalyzed addition of a (phenylsulfonyl)difluoromethylene group to alkenes [100].



Scheme 39. Pd-catalyzed Heck-type reactions of [(bromodifluoromethyl)-sulfonyl]benzene with alkenes.

Later, Zhang and co-workers reported a general method for palladium-catalyzed Mizoroki-Heck-type cross-couplings of alkenes (**190**) with perfluoroalkyl bromides (**191**) (Scheme 40) [101]. The reactions proceeded under mild conditions with high efficiency and broad substrate scope, and provided a variety of fluoroalkylated alkenes (**192**) in good to high yields. The optimized reaction conditions included use of 1,2-dichloroethane (DCE) as a solvent, $[PdCl_2(PPh_3)_2]$ as a catalyst, and Cs_2CO_3 as a base. The bidentate ligand Xantphos was essential for the transformation as there was no reaction occurring when other phosphine ligands were used. The reaction could be extended to trifluoromethyl iodide, and other functional difluoromethyl bromides (**193**). The late-stage fluoroalkylation of bioactive compounds was also achieved in good yields, which supplied an efficient and straightforward route for application in drug discovery and development [101]. Mechanistic studies including a radical-clock experiment suggested that the free fluoroalkyl radicals ($R_{fn}\bullet$), initiated by Pd(0)/Xantphos complex through a single electron transfer

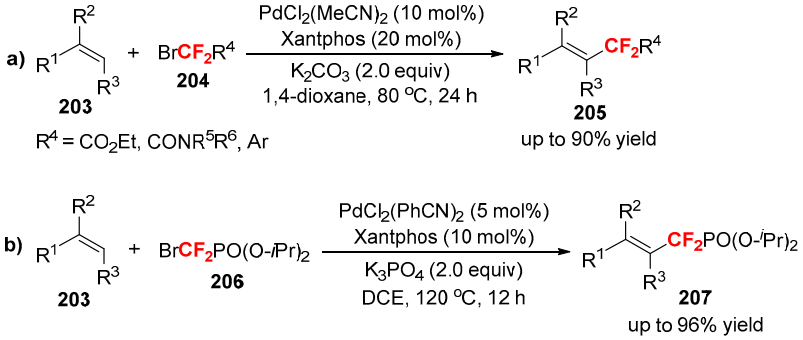
(SET) process, might be involved in the Heck-type catalytic cycle (path A, Scheme 40). The formation of fluoroalkylated alkenes (**192** and **194**) by a bromine atom transfer from $R_{fn}Br$ or **196** to alkene (path B, Scheme 40), followed by base-assisted elimination of the resulting benzyl bromides (**200**), could be ruled out, as the reaction of styrene with $C_6F_{13}Br$ in the presence of $[Pd(PPh_3)_4]$ and Xantphos without base failed to form benzyl bromide (**200**). Nevertheless, Chen and co-workers had disclosed that fluoroalkyl iodides reacted with alkyl alkenes in the presence of catalytic amounts of $Pd(PPh_3)_4$ to give the corresponding adducts (**200**) in high yields [102]. The reaction involved a radical-chain mechanism initiated by a single electron transfer (SET) from the Pd(0) species [102]. Furthermore, other competitive side reactions, such as oligomerization of **197** with alkene (path C, Scheme 40) and dimerization of **197** (path D, Scheme 40), were also reasonable pathways, for which the corresponding byproducts (**201** and **202**) were observed in the conversions [101].



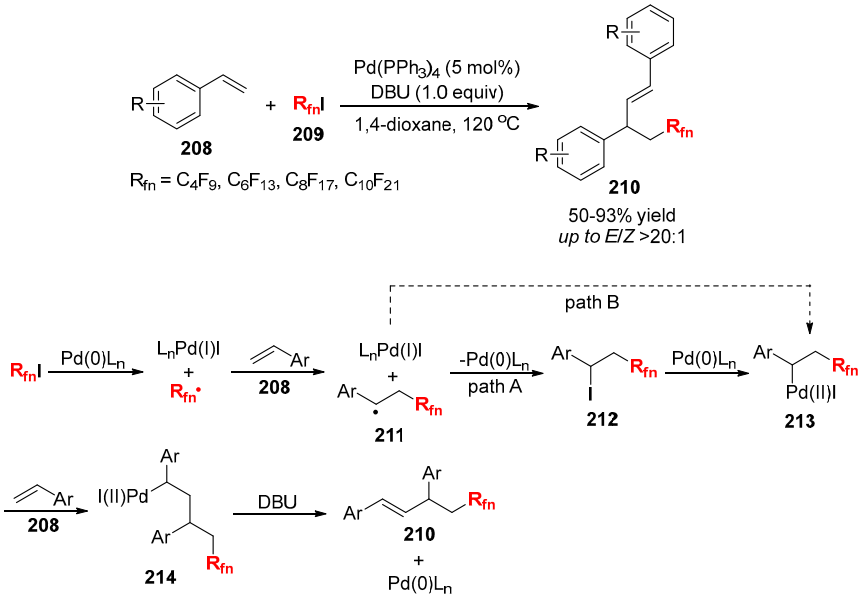
Scheme 40. Palladium-catalyzed Heck-type fluoroalkylation of alkenes.

Again, other functionalized difluoromethyl bromides (**204** and **206**) were employed as cross-coupling reagents in the Pd-catalyzed Mizoroki-Heck reactions by Zhang's research group (Scheme 41) [103,104]. With an analogous catalytic system mentioned above, a variety of difluoroalkylated alkenes (**205**) were synthesized from **203** and **204** under mild reaction conditions, showing excellent functional group compatibility (Scheme 41a) [103]. The mechanistic studies revealed again that free fluoroalkyl radicals initiated by $[Pd(0)L_n]$ complexes via a SET pathway were involved in the catalytic cycle, and that the bidentate ligand Xantphos was essential for the transformation. This strategy was also successfully applied to the preparation of phosphonyldifluoromethylated alkenes (**207**) through Pd-catalyzed Heck-type reactions with bromodifluoromethylphosphonate (**206**) (Scheme 41b) [104]. The steric effect of diisopropyl (bromodifluoromethyl)phosphonate was critical for the efficiency of the reaction. Advantage of the protocol was the synthetic simplicity, providing a facile access to biologically interesting molecules.

$Pd(PPh_3)_4$-catalyzed Mizoroki-Heck reactions of in situ-generated benzylic iodides with styrenes (**208**) were reported by Wu and co-workers (Scheme 42) [105]. Under standard reaction conditions, a mass of perfluoroalkylated alkenes (**210**) were synthesized in moderate to excellent yields with good regio- and stereoselectivity. The transformation was totally inhibited when two equivalents of TEMPO were added, suggesting a radical mechanism (Scheme 42). Presumably, perfluoroalkyl radical (R_{fn}•) and $L_nPd(I)I$ species are first generated from $R_{fn}I$ and $Pd(0)L_n$ in the reaction. Then, the R_{fn}• radical adds to alkene (**208**) to afford an alkyl radical (**211**), which reacts with $L_nPd(I)I$ to give a benzylic iodide (**212**) (path A). Reaction of **212** with $Pd(0)L_n$ forms the key intermediate **213**, which might also be obtained from the direct combination of **211** with $L_nPd(I)I$ (path B). Subsequently, a Heck-type reaction of styrene with **213** generates a Pd(II) intermediate (**214**). Finally, reductive elimination of **214** produces **210** and regenerates the $Pd(0)L_n$ species under the assistant of DBU. Nonetheless, a pathway via radical addition of **211** to another molecule of styrene in which the resulting benzyl radical couples with $L_nPd(I)I$ to form **214** cannot be excluded.



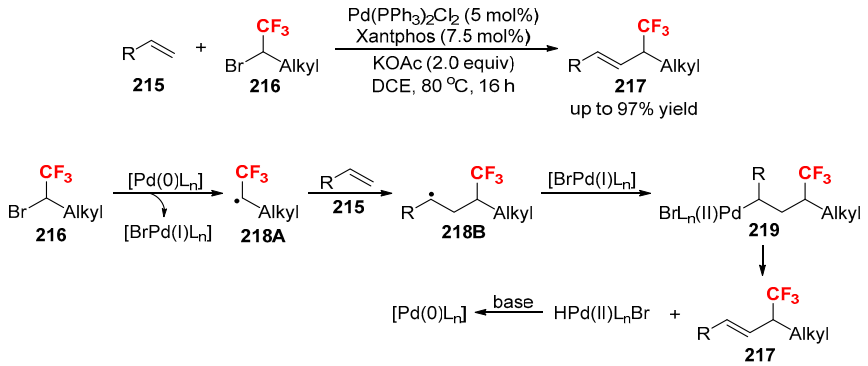
Scheme 41. Pd-catalyzed Heck-type difluoroalkylation of alkenes with functionalized difluoromethyl bromides.



Scheme 42. Palladium-catalyzed Mizoroki-Heck reactions of perfluoroalkyl iodides and styrenes.

The Pd-catalyzed Heck-type reaction of secondary fluoroalkylated alkyl halide with alkene remains a challenge due to the sluggish oxidative addition of alkyl halide to palladium and the facile β-hydride elimination of alkylpalladium species [106]. Encouragingly, Zhang and co-workers described a convenient method for palladium-catalyzed Mizoroki-Heck-type couplings of secondary

trifluoromethylated alkyl bromides (**216**) with alkenes (**215**), providing a variety of aliphatic alkenes bearing branched trifluoromethyl groups (**217**) (Scheme 43) [106]. The reactions proceeded under mild conditions and showed good functional group tolerance and high efficiency, even towards substrates bearing the sensitive hydroxy, formyl, and phthalimide groups. The reaction could also be extended to secondary difluoroalkylated alkyl iodide. The optimal reaction conditions were identified to use an assembly of $PdCl_2(PPh_3)_2$ (5 mol%), Xantphos (7.5 mol%), and KOAc (2.0 equiv) in DCE at 80 °C for 16 h. The control experiments using 1,4-dinitrobenzene as an electron transfer scavenger and the catalytic hydroquinone as a radical inhibitor suggested that a secondary trifluoromethylated alkyl radical (**218A**) via a SET pathway was likely involved in the reaction. This hypothesis was also supported by the radical clock experiment. Based on these, a plausible reaction mechanism was proposed in Scheme 43 [106]. Initially, reaction of $[Pd(0)L_n]$ with **216** via a SET process generates an alkyl radical (**218A**), which adds to the carbon-carbon double bond of alkene to produce intermediate **218B**. Then, **218B** combines with $[L_nPd(I)Br]$ to give an alkylpalladium(II) complex (**219**), which undergoes β-hydride elimination to form **217** and regenerate $[Pd(0)L_n]$ in the presence of a base.



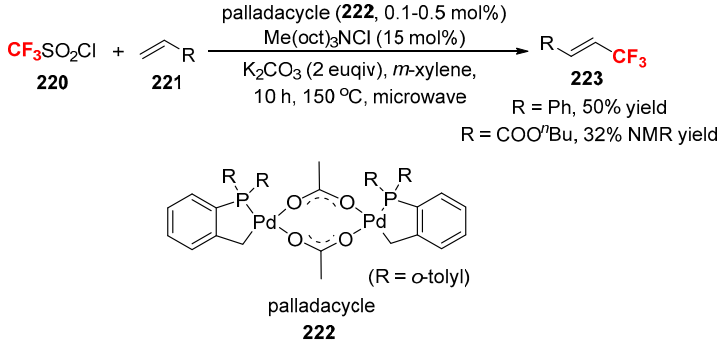
Scheme 43. Pd-catalyzed Heck-type reactions of secondary trifluoromethylated alkyl bromides with alkenes.

3.3. Fluoroalkylation Reagents as the Precursors of the Cross-Coupling Participants

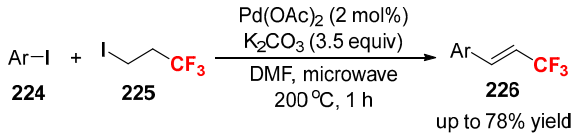
In 2005, Vogel and co-worker reported the palladium-catalyzed Heck-type reactions between terminal alkenes and sulfonyl chlorides [107]. Herrmann's palladacycle (**222**) was found to be an excellent catalyst for the Mizoroki-Heck-type reactions of mono- and disubstituted olefins with arenesulfonyl chlorides. The reactions were not inhibited by radical scavenging agents. Trifluoromethanesulfonyl chloride (**220**) reacted with an excess of styrene (**221a**) in a sealed tube or microwave oven at 150 °C under similar conditions gave the desired desulfitative Mizoroki-Heck coupling product ((*E*)-3,3,3-trifluoro-1-phenylprop-1ene) (**223a**) in 50% yield (Scheme 44) [107]. The same reaction with butyl acrylate (**221b**) produced butyl (*E*)-4,4,4-trifluorobut-2-enoate (**223b**) in 32% yield.

The 3,3,3-trifluoropropenyl ($CF_3CH=CH$-) group has found important implications in medicine and material fields [108]. Conjugated aromatic systems with trifluoromethyl groups (e.g., β-trifluoromethylstyrenes) have been widely utilized in organic light emitting diodes (OLEDs) and other materials. In 2012, Prakash and co-workers described a simple and efficient elimination/Heck domino reaction sequence for the synthesis of β-trifluoromethylstyrene derivatives (**226**) (Scheme 45) [108]. The procedure involved a ligand-free palladium-catalyzed Heck reaction between aryl halides (**224**) and 3,3,3-trifluoropropene, which was generated in situ from the commercially accessible 1-iodo-3,3,3-trifluoropropane (**225**) under basic conditions, providing interesting and previously unknown β-trifluoromethylstyrenes in moderate to good yields. The reactions avoided the use of a gaseous 1,1,1-trifluoropropene reagent as one of

the reactants and showed a broader substrate scope than the previously reported methods. Mechanistically, 1-iodo-3,3,3-trifluoropropane (**225**) may first undergo dehydrohalogenation to in situ form 3,3,3-trifluoropropene, which then reacts with **224** in the presence of a catalytic amount of $Pd(OAc)_2$ to yield the final products (**226**).



Scheme 44. Pd-catalyzed desulfitative Mizoroki-Heck type reactions of trifluoromethanesulfonyl chlorides with terminal alkenes.



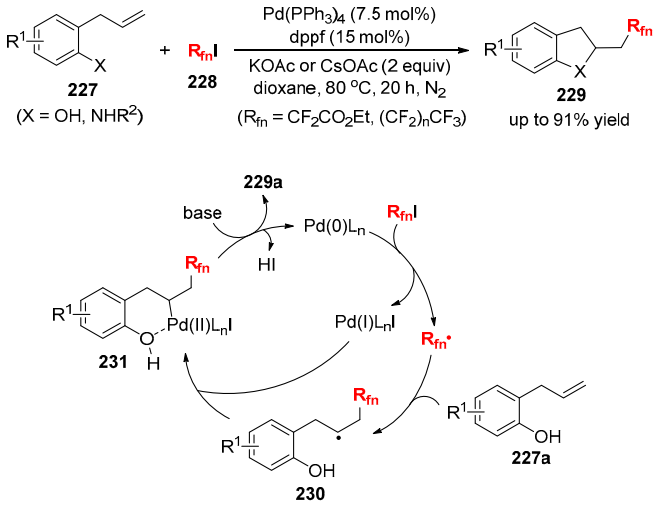
Scheme 45. The Heck-type cross-couplings of iodoarenes with 1-iodo-3,3,3- trifluoropropane.

4. Variants of the Mizoroki-Heck Reactions with the Fluorine-Containing Reagents

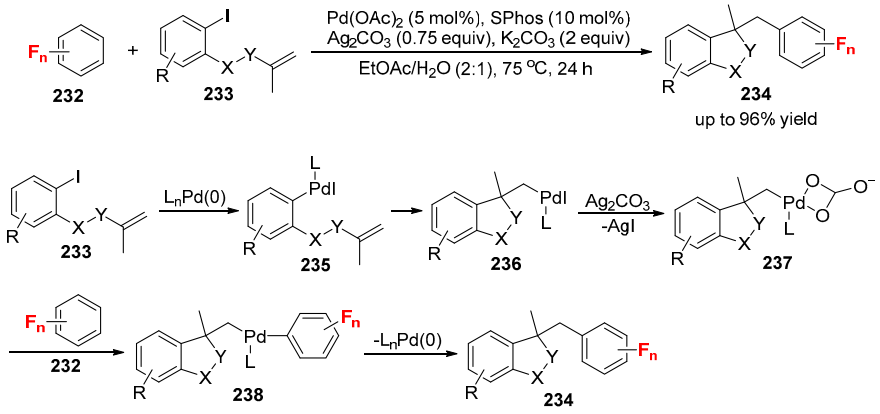
Bifunctionalization of alkenes triggered by the Mizoroki-Heck reactions has attracted great attention in organic synthesis. Jiang and co-workers reported the palladium-catalyzed fluoroalkylative cyclization of olefins (**227**) with $R_{fn}I$ (**228**), which offered an efficient method for the construction of $C_{sp}{}^3$-R_{fn} and C–O/N bonds in one step, affording the corresponding fluoroalkylated 2,3-dihydrobenzofuran and indolin derivatives (**229**) in moderate to excellent yields (Scheme 46) [109]. When the reaction of 2-allylphenol (**227aa**) with ICF_2CO_2Et was performed in the presence of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO), the formation of **229aa** (R^1 = H, R_{fn} = CF_2CO_2Et) was totally inhibited and the adduct TEMPO-CF_2CO_2Et was produced in 30% yield. If 1,1-diphenylethylene was used as a radical scavenger in the same reaction, 10% of **229aa** and 51% of ethyl 2,2-difluoro-4,4-diphenylbut-3-enoate were obtained. These preliminary experiments indicated that a free •CF_2CO_2Et radical might be involved in the reaction. Thus, a plausible mechanism was suggested for the cyclization (Scheme 46) [109]. At the beginning, fluoroalkyl radical (R_{fn}•) and $Pd(I)L_nI$ complex are formed from the interaction of Pd(0) and $R_{fn}I$ via a single electron transfer process. Subsequent electrophilic radical addition of R_{fn}• to the C=C bond of olefin (**227a**) provides an alkyl radical (**230**). Reaction of **230** with $Pd(I)L_nI$ yields an *O*-coordinated Pd(II) complex (**231**), which undergoes reductive elimination to afford **229a** (X = O) and regenerate the Pd(0) species. However, an alternative pathway using Pd(0) as a radical initiator followed by an intramolecular S_N2 substitution couldn't be excluded [109]. 2-Allylanilines could also undergo a similar mechanism.

Liang and co-workers described an efficient procedure for Pd-catalyzed domino Heck reactions/alkylation of electron-deficient polyfluoroarenes (**232**), which gave the corresponding alkylated polyfluoroarene products (**234**) in moderate to excellent yields under mild conditions (Scheme 47) [110]. The method represented a convenient, operationally simple, and useful protocol for the preparation of alkyl substituted polyfluoroarene derivatives. It was also the first example of installation of a polyfluoroarene structure involving an alkylpalladium(II) intermediate. A catalytic

cycle for the conversion was proposed in Scheme 47 [110]. Initially, the in situ generated Pd(0)L_n species undergoes oxidative addition of the C–I bond of **233** to form intermediate **235**, which is converted through an intramolecular Heck-type reaction to yield alkylpalladium intermediate **236**. Then, the silver salt abstracts iodide from **236**, producing a palladium intermediate (**237**). Subsequently, **237** goes through a concerted metalation/deprotonation process to provide **238**, which undergoes reductive elimination to produce **234** and regenerate the Pd(0)L_n species for the next catalytic cycle.



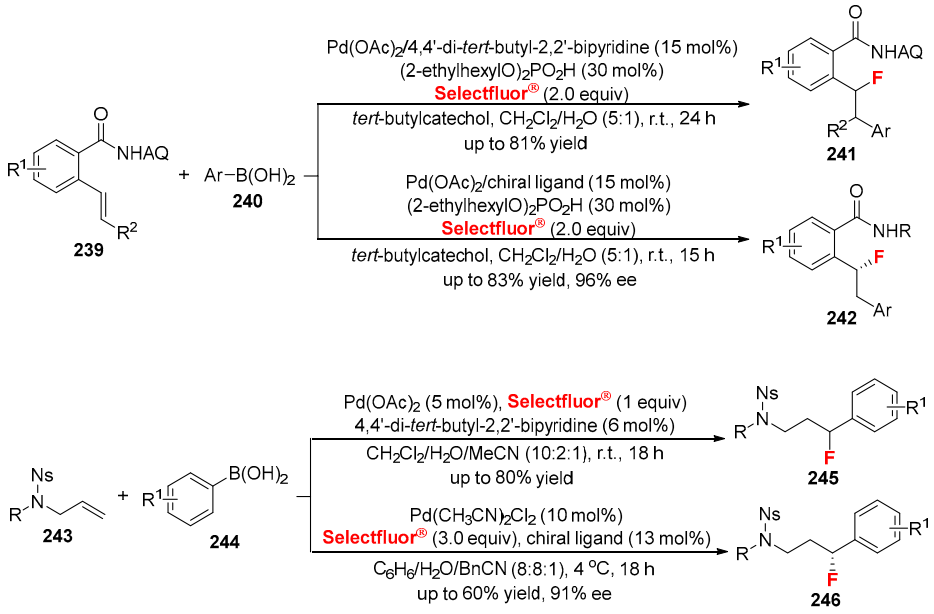
Scheme 46. Pd-catalyzed fluoroalkylative cyclization of olefins.



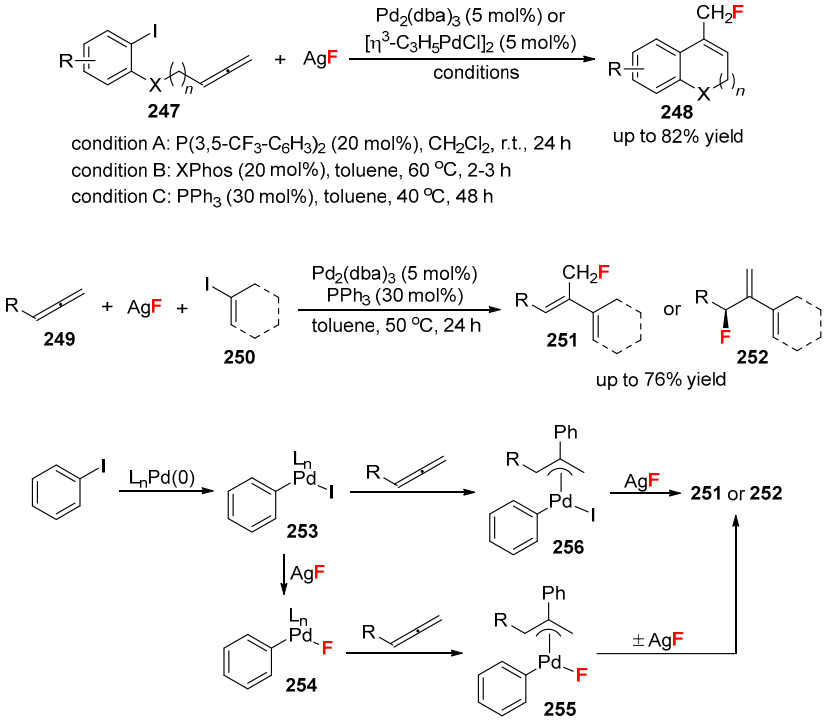
Scheme 47. Pd-catalyzed Heck/intermolecular C–H bond functionalization for the synthesis of alkylated polyfluoroarene derivatives.

Toste and co-workers disclosed the Pd-catalyzed 1,2-fluoroarylation of styrenes (**239**) with arylboronic acids (**240**) and Selectfluor® using amides (e.g., 8-aminoquinoline (AQ)) as the directing groups (Scheme 48) [111]. This strategy was also successfully used for the asymmetric 1,2-fluoroarylation of styrenes, furnishing chiral monofluorinated compounds (**242**) in good yields and with high enantioselectivies. Later, palladium-catalyzed 1,1-fluoroarylation of amino-alkenes (**243**) using arylboronic acids (**244**) as an arene source and Selectfluor® as a fluorine source was developed by the same research group (Scheme 48) [112]. The transformation likely proceeded through an oxidative Heck mechanism to afford 1,1-difunctionalized alkenes (**245**) in one pot [112], which was different from the pathway proposed for the 1,2-fluoroarylation [111]. The 1,1-fluoroarylation could also be extended to an asymmetric transformation, generating chiral benzylic fluorides (**246**) in good to excellent enantioselectivies [112]. These reactions promised powerful strategies for the difunctionalization of alkenes to chiral fluorinated molecules.

Palladium-catalyzed tandem C–C and C–F bond formation for bifunctionalization of allenes (**247**) was explored by Doyle and co-workers (Scheme 49) [113]. The intramolecular Heck/fluorination cascade provided monofluoromethylated heteroarenes (**248**), while the intermolecular variant for the three-component couplings of allenes (**249**), aryl iodides (**250**), and AgF gave the corresponding linear or branched monofluoromethyl isomers (**251** or **252**). The regioselectivity of the latter case was dramatically dependent upon the structure of allene. The mechanistic studies indicated that a palladium fluoride, generated from the halide exchange with AgF, was the key intermediate in the reaction (Scheme 49). Nevertheless, the exact mechanism of the reaction remained unclear [113].



Scheme 48. Pd-catalyzed enantioselective fluoroarylation of alkenes.



Scheme 49. Pd-catalyzed cascade carbofluorination of allenes.

5. Conclusions

In summary, the Mizoroki-Heck reaction has become a very powerful tool for building complex molecules [1–6]. The straightforward incorporation of fluorine-containing moieties by Mizoroki-Heck reactions has proved to be attractive and advantageous, as these reactions efficiently construct the carbon-carbon double bonds bearing fluorinated functionalities by simple procedures. The key to the high efficiency of the reactions is the choice of suitable fluorine-containing reagents and catalytic systems. Furthermore, the fluorinated compounds have been extensively used in the areas of materials and life sciences due to the significant impacts of fluorine substitution on the physiochemical and biological properties of the molecules. Since most fluorinated organic compounds have to be manually synthesized, the development of general and selective fluorination/fluoroalkylation methods with broad functional group tolerance that enable mild and late-stage functionalization of complex molecules is a perpetual topic in the realm of synthetic organic chemistry. Mizoroki-Heck cross-coupling has been evidenced as one of the most convenient methods for the preparation of fluorine-substituted alkenes or variants under mild conditions, which are very useful building blocks in the synthesis of functional molecules. This review highlights the palladium-catalyzed Mizoroki-Heck reactions using fluorine-containing reagents as the coupling participants. The variants of the reactions with fluorine-containing reagents catalyzed by palladium catalysts are also briefly introduced. It is undoubted that new Mizoroki-Heck reactions using fluorine-containing coupling partners will be continuously and prosperously developed. Challenging unrealized programs, such as the incorporation of elusive fluorinated functionalities (e.g., SeR_{fn}, SR_{fn}, and OR_{fn} groups) into the organic frameworks, the facile bifunctionalization of alkenes with rigid fluorine-containing reagents, and the asymmetric synthesis of complex fluorinated molecules via the Mizoroki-Heck cross-coupling reactions, will draw more attention in the future.

Acknowledgments: We thank the Army Medical University, the National Natural Science Foundation of China (21602165), the "Hundred Talent" Program of Hubei Province, and the Wuhan Youth Chen-Guang Project (2016070204010113) for financial support.

Author Contributions: Jing Yang, Hua-Wen Zhao, Jian He and Cheng-Pan Zhang analyzed the data and wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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