

Intermolecular Dehydrogenative Heck Reactions

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1. INTRODUCTION

The Pd-catalyzed reaction of an aryl halide with an alkene affords, in most cases, the corresponding arylalkene. It is usually considered that this reaction, which is called the Heck reaction or the Mizoroki–Heck reaction, was discovered by the teams of Mizoroki and Heck, independently. However, in their original report,¹ Heck and Nolley cited the publication signed by Mizoroki, Mori, and Osaki.² The papers from Mizoroki and Heck teams were submitted on October, 20, 1970, and January, 13, 1972, respectively, but on January 12, 1971, M. Julia and M. Duteil deposited to the Société Chimique de France, a “Pli cacheté”, that is, a sealed envelope, disclosing the same reaction. This “Pli cacheté”, opened on May 5, 1973, and then published,³ is not mentioned in most subsequent reports and reviews. This type of reaction, which could be named the Mizoroki–Julia–Heck reaction, led to a plethora of papers and, recently, to a book.⁴

Before finding the catalytic conditions leading to the insertion of palladium into the Ar–X bond, Heck performed, at the end of the 60s, the *in situ* synthesis of ArPdX complexes from

the reaction between palladium salts and aryl–mercury, -lead, or -tin compounds.⁵ Over the past few years, this trans-metalation has been revisited and, carried out using catalytic amounts of palladium, has been named oxidative Heck reaction,⁶ Mizoroki–Heck-type reaction,⁷ or Heck cross-coupling reaction.⁸

The Mizoroki–Heck reaction occurs with a Pd(0) catalyst and affords HX as side-product which is trapped by a base (Scheme 1). The oxidative Heck reaction implies catalysis with Pd(II), requires a reoxidant to regenerate the active catalytic species, and affords more side-products (Scheme 2). Another condition to prepare arylalkenes is the Pd-catalyzed coupling of ArH with alkenes. As the above oxidative Heck reaction, this process requires a Pd(II) catalyst and a reoxidant. Although it is sometimes also called oxidative Heck reaction^{9,10} or oxidative Heck-type reaction,^{11,12} its mechanism is strongly different since it involves a C–H activation of ArH instead of a trans-metalation (Scheme 3). Fujiwara’s team having, in 1967, disclosed the synthesis of stilbene from the reaction of the styrene–PdCl₂ complex with benzene¹³ and, in 1968, the oxidative coupling between styrene and benzene with two turnovers of palladium,¹⁴ these Pd-catalyzed reactions are, sometimes, named Fujiwara,^{15,16} Fujiwara–Moritani,^{9,17–21} or Fujiwara–Moritani oxidative Heck²² reactions. However, Fujiwara and Kitamura used, in 2005, the term Fujiwara reaction for the Pd-catalyzed hydroarylations of alkenes and alkynes.²³ Consequently, we propose the term dehydrogenative Heck reaction (DHR) for the Pd-catalyzed oxidative couplings of arenes and heteroarenes with alkenes; this suitable name has been, at least once, already used.²⁴

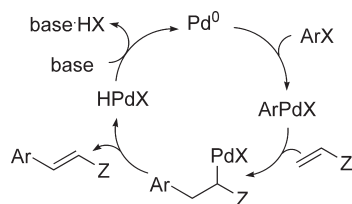
Among the above three synthetic methods of arylalkenes, and if we consider only the substrates, the atom economy principle²⁵ is the most respected with the last one, since the result of the DHR is the formation of a C–C bond from two C–H bonds. Given this observation, it is not surprising that active research in this area of intermolecular couplings, which obviate the complications associated with preparing aryl halides that can minimize the waste, has been documented in recent years. The aim of the present review is to highlight this subject and, in particular, the progress of the procedures.^{26,27} The synthetic interest of the DHRs is limited to couplings promoted with catalytic amounts of palladium, but its historical interest leads us to first introduce a section devoted to early stoichiometric conditions. For convenience, the framework of the text depends on the nature of the aromatic substrate, and

Special Issue: 2011 Frontiers in Transition Metal Catalyzed Reactions

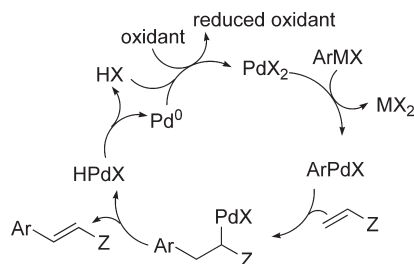
Received: July 7, 2010

Published: March 09, 2011

Scheme 1



Scheme 2

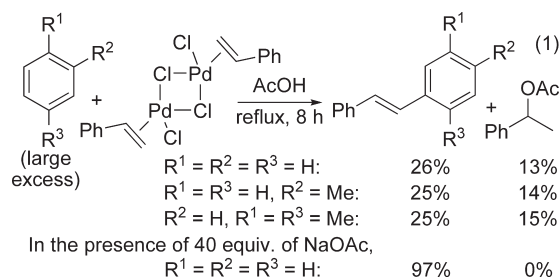


the comparison of the different catalytic systems is mainly presented in general tables.

2. STOICHIOMETRIC PALLADIUM-MEDIATED ARYLATIONS

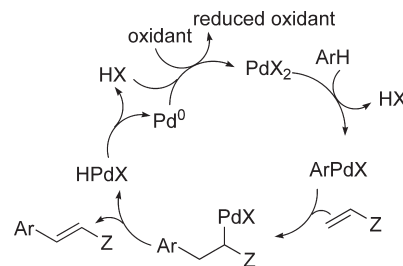
2.1. Arenes

2.1.1. Results. In 1967, Moritani and Fujiwara disclosed a new synthetic procedure for the preparation of stilbene derivatives, by heating at reflux an AcOH solution of an aromatic compound and a dimeric styrene–PdCl₂ complex (eq 1).¹³ This coupling reaction, which was accompanied by the formation of 1-phenylethyl acetate, was relatively sensitive to steric hindrance since no stilbene derivative was obtained with mesitylene as the aromatic compound.²⁸ The absence of coupling without AcOH showed its key role, possibly in dissolving the complex.²⁸ The acetate anion can also favor the reaction since the (*E*)-stilbene yield was greatly improved in the presence of sodium acetate (eq 1).²⁹

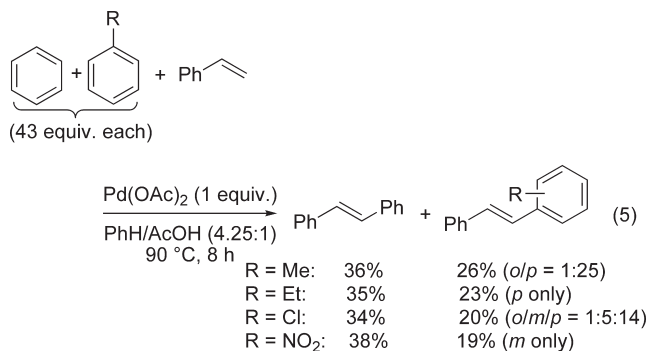
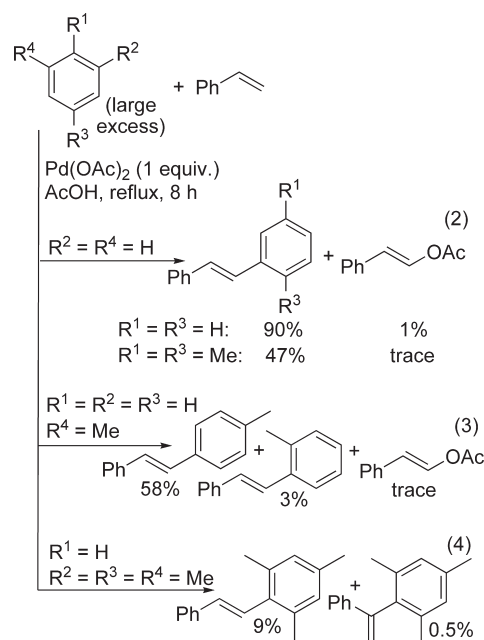


In 1968, the Japanese team revealed the DHR of styrene with benzene in high yield using a stoichiometric amount of Pd(OAc)₂ in refluxing AcOH.²⁹ Under these conditions, β -acetoxystyrene was obtained as a side-product (eq 2). With alkylbenzenes, the DHR efficiency decreased with the steric hindrance as shown in eqs 2–4;^{29–31} this was also exemplified from competitive reactions of benzene and monosubstituted benzenes toward styrene (eq 5).^{30,32} These oxidative couplings have also been mediated with PdCl₂

Scheme 3

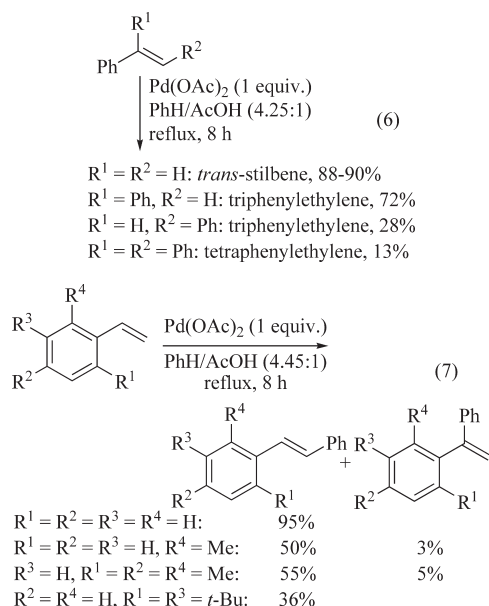


and an excess of NaOAc or KOAc, but in lower yields; metathesis leading to coordination of the acetate anion to palladium was thus suspected.^{29,30,33} Use of palladium powder with 2 equiv of silver acetate afforded also stilbene from the reaction of styrene with benzene, but in no more than 21% yield.¹⁴

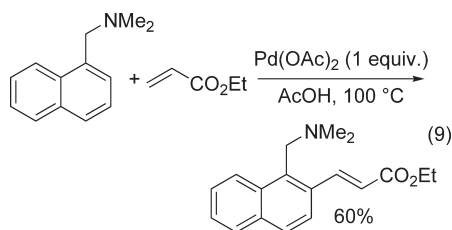
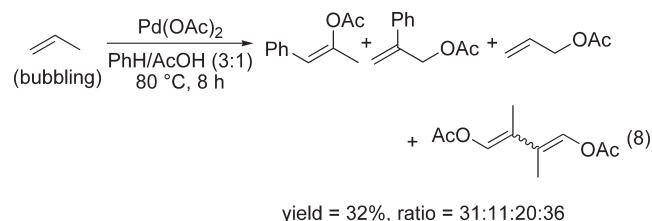


The efficiency of the oxidative coupling and the regioselectivity depend not only on the arylating agent (eqs 2–5), but also on the substitution of the styrene-type compound as exemplified in eqs 6 and 7.^{31,33–35} It is worth mentioning that the same compounds, that is, triphenylethylene in one case (eq 6; 28% and 72% yields) and 1,3,5-trimethyl-2-styrylbenzene in another case (eqs 4 and 7; 9% and 55%

yields), are synthesized in yields depending highly on the starting units.

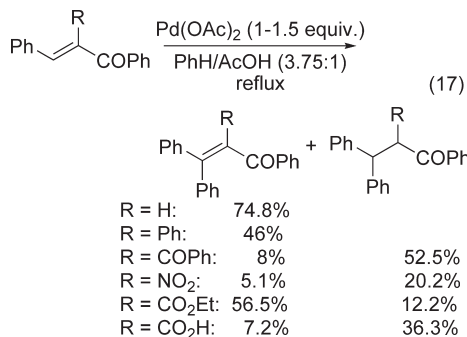
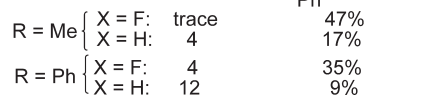
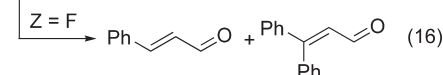
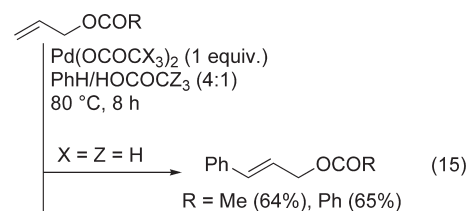
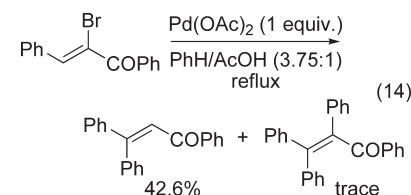
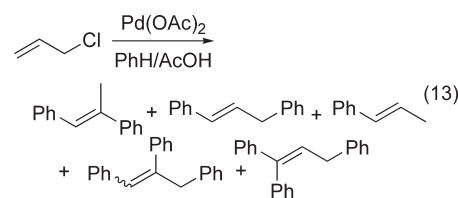
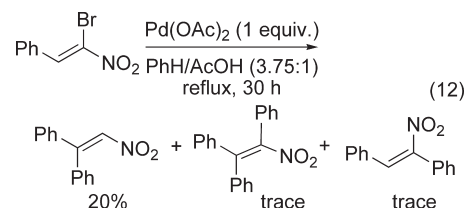
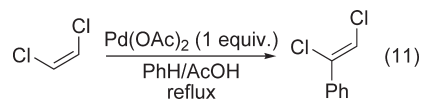
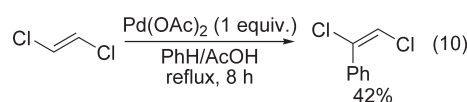


The stoichiometric arylating procedure has been extended, using ethylene, terminal alkenes such as 1-propene, 1-butene, 1,3-butadiene, internal alkenes such as (*E*)- and (*Z*)-2-butenes,^{34,36,37} and olefins containing a polar group such as acrylonitrile, vinyl acetate, ethyl vinyl ether,^{34,38} but in most cases, mixtures and low yields were obtained as depicted in eq 8 for the reaction of propene with benzene. M. Julia and co-workers used the Fujiwara procedure³⁴ for the effective and regioselective oxidative coupling of 1-dimethylnomethylnaphthalene with ethyl acrylate (eq 9).³⁹



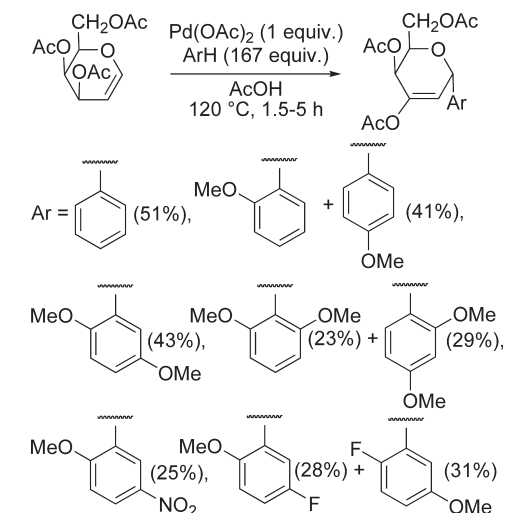
Vinyl and allyl halides, as well as allyl esters, have also been reacted with benzene. While (*E*)- and (*Z*)-1,2-dichloroethylenes led to the expected substitutions with retention of the configuration of the olefin (eqs 10 and 11),⁴⁰ β -bromo- β -nitrostyrene afforded a mixture of compounds which have lost the bromide atom (eq 12).³⁵ The halide atom was also eliminated in the course of the reaction of allyl chloride⁴¹ or α -bromochalcone⁴² with benzene (eqs 13 and 14). The reaction of allyl esters is greatly dependent on the experimental conditions: at 80 °C, the use of Pd(OAc)_2 in PhH/AcOH led to the usual phenylation (eq 15), whereas a mixture of cinnamaldehyde

and 3,3-diphenylacrylaldehyde was produced with Pd(OAc)_2 or $\text{Pd(OCOCF}_3)_2$ in $\text{PhH/CF}_3\text{CO}_2\text{H}$ (eq 16).^{41,43}

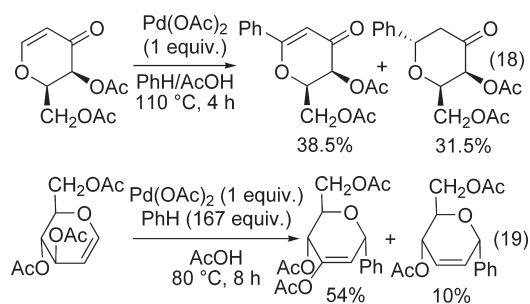


Yamamura revealed that the DHR selectivity of α -substituted chalcones depends greatly on the nature of the α -substituent, those with a α -COPh, α -NO₂, or α -CO₂H leading to the

Scheme 4

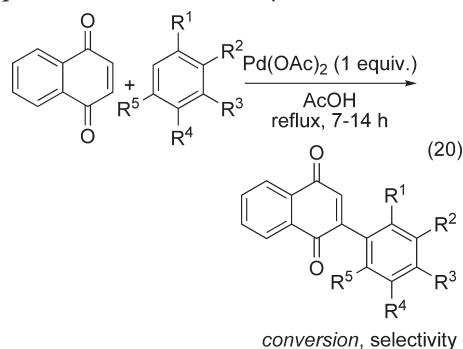


hydrophenylation adduct as the main product (eq 17).⁴² Mixtures of benzylated enones and benzylated ketones have been also obtained by Czernecki et al. from the reaction of PhH with acetylated enones derived from glycals (eq 18).⁴⁴ A substrate-dependent selectivity has been observed for the arylation of peracetylated glycals as shown in eq 19 and Scheme 4.^{45,46}



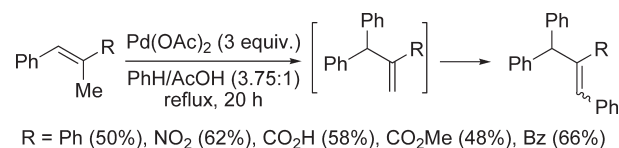
A series of 2-substituted-1,3,3-triphenylpropenes have been synthesized from β -substituted- β -methylstyrenes and benzene via a stepwise reaction with, likely, 2-substituted-3,3-diphenylpropenes as intermediates (Scheme 5).⁴⁷

The oxidative coupling of various arenes with 1,4-benzoquinone, 2-phenyl-1,4-benzoquinone, 1,4-naphthoquinone (eq 20), and 1,2-naphthoquinone has been achieved by Itahara.^{48,49}

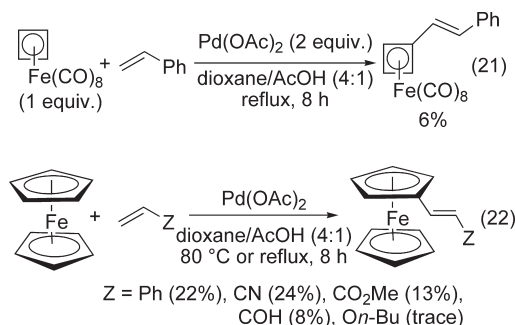


$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$, 14 h: 100%, 85%
 $\text{R}^2 = \text{R}^3 = \text{R}^5 = \text{H}$, $\text{R}^1 = \text{R}^4 = \text{Me}$, 14 h: 100%, 78%
 $\text{R}^2 = \text{R}^3 = \text{R}^5 = \text{H}$, $\text{R}^1 = \text{R}^4 = \text{Cl}$, 14 h: 100%, 70%
 $\text{R}^2 = \text{R}^3 = \text{R}^5 = \text{H}$, $\text{R}^1 = \text{R}^4 = \text{F}$, 7 h: 40%, 76%
 $\text{R}^2 = \text{R}^4 = \text{H}$, $\text{R}^1 = \text{R}^3 = \text{R}^5 = \text{Me}$, 7 h: 37%, 69%
 $\text{R}^5 = \text{H}$, $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{Me}$, 7 h: 89%, 86%

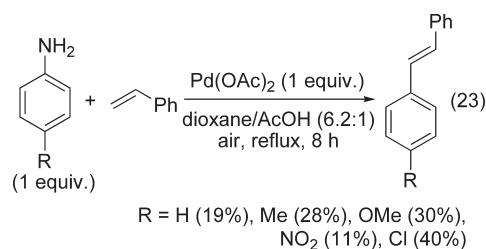
Scheme 5



Reaction of tricarbonyl(η^4 -cyclobutadiene) iron with styrene provided a low yield of the DHR adduct (eq 21).³² Another arene iron complex, ferrocene, reacted with various vinylic compounds, leading to the corresponding alkenylation products in no more than 24% yield (eq 22).^{50,51}

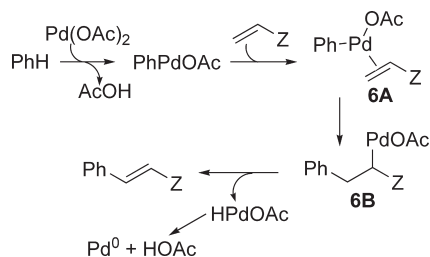


According to the above examples, the substitution of a vinylic $\text{C}-\text{H}$ by an Ar group can occur without reaction of functional groups such as vinylic Cl , Br , NO_2 , CO_2R , COR , and OR , or aryl Cl , Br , F , and NO_2 . In contrast, the $\text{Pd}(\text{OAc})_2$ -mediated reaction of styrene with anilines involved the cleavage of the $\text{C}-\text{N}$ bond (eq 23).⁵²

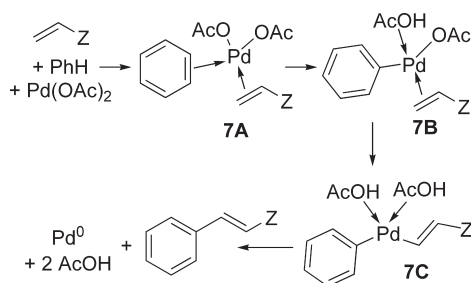


2.1.2. Mechanism. In their seminal 1967 report, Moritani and Fujiwara excluded a cascade reaction involving the hydrophenylation of the $\text{C}=\text{C}$ bond of the styrene– PdCl_2 complex and then dehydrogenation to explain the formation of stilbene depicted in eq 1.¹³ The first mechanism proposal, suggested on April 15, 1969, by Fujiwara's team for reactions proceeding as shown, for example, in eqs 2–5, is related to the Mizoroki–Heck reaction. Indeed, it successively involves ArPdOAc , coordination to the alkene leading to **6A**, insertion of the $\text{C}=\text{C}$ bond into the $\text{Ar}-\text{Pd}$ bond to afford **6B**, and β -H elimination (Scheme 6).³⁴ However, on May 19, 1969, the same team disclosed a different proposal which considers the doubly coordinated π -complex **7A** (Scheme 7).³⁸ This complex would evolve to the σ,π -complex **7B** and then, the doubly coordinated σ -complex **7C** via the successive insertions of palladium into an aromatic and a vinylic $\text{C}-\text{H}$ bond, reductive elimination of palladium from **7C** delivering the substituted olefin.³⁸ In another paper submitted also on May 19, 1969, Fujiwara et al. disclosed that the reactivity of monosubstituted benzenes with styrene is not influenced by the substituent.³⁰ This led them to conclude that “the reaction may

Scheme 6

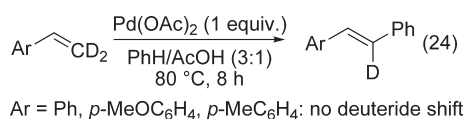


Scheme 7



proceed through a *sigma* bonded benzene-palladium complex”, and that “the rate determining step cannot be the formation of a *sigma* bond between benzene and palladium” but may be the step “where a *sigma*-bond develops between palladium and olefin”.³⁰

According to the authors, the phenylation of $\text{ArCH}=\text{CD}_2$ without deuteride shift (eq 24) contrasts with a Wacker-type mechanism,^{53,54} and supports a 7C-type intermediate.⁵⁴ Shue also suspected such an intermediate, but the comparison of the Pd(II)-catalyzed reactivity of PhH toward $\text{PhCH}=\text{CD}_2$ and $\text{PhCH}=\text{CH}_2$ led him to suggest “that the cleavage of the styrene- β -hydrogen bond is not involved in the rate-determining step of olefin arylation”.⁵⁵ Moreover, experiments using C_6H_6 , C_6D_6 , $\text{PhCH}=\text{CH}_2$, and $\text{Pd}(\text{OAc})_2$ led Shue to assume that “palladium-aryl bond formation is a slow, irreversible step in olefin arylation”.⁵⁵ It seems, however, necessary to remark that no deuteride would be shifted from a reaction of PhH with $\text{ArCH}=\text{CD}_2$ occurring via a Heck-type mechanism, except if a readdition/elimination of DPdOAc could arise.

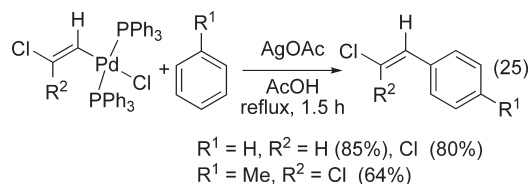


The DHR of benzene with ethylene led to a mixture of styrene and (*E*)-stilbene. Fujiwara proposed that stilbene is issued from the arylation of styrene,^{26b,34} while Kozhevnikov and Matveev assumed a formation of styrene and stilbene from a shared intermediate, possibly a Pd(I) complex.⁵⁶ These latter authors suggested that the reaction pathways could, however, depend on the relative concentrations of the reactants.

Reacting the *trans*-chloro and dichloro-vinylpalladium complexes shown in eq 25 with benzene in the presence of AgOAc , Fujiwara et al. isolated *trans*- β -chlorostyrene and β,β -dichlorostyrene, respectively.⁵⁷ *trans*- β -Chlorostyrene was also obtained from *cis*-chlorovinylpalladium complex (82% yield); in this case,

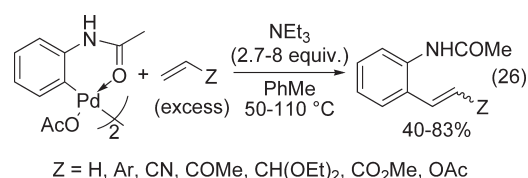
the isomerization of the initially formed *cis*- β -chlorostyrene into the *trans*-isomer under the reaction conditions was proposed.^{58,59}

The formation of β,β -dichloro-4-methylstyrene when using toluene instead of benzene (eq 25) demonstrated that, in the other examples, the phenyl group does not come from PPh_3 . According to the authors, these reactions prove the mechanism depicted in Scheme 7, AgOAc abstracting the chloride ligand of the Pd complex enabling the coordination of benzene to the vinylpalladium. Since the experimental conditions differ strongly from those used for the Pd(II)-mediated DHRs, these reactions are, in our opinion, not really a proof. In contrast, the preservation of the C=C bond geometry in the course of the phenylation of (*E*)- and (*Z*)-dichloroethylenes (eqs 10 and 11) agrees with an intermediate such as 7C.⁴⁰



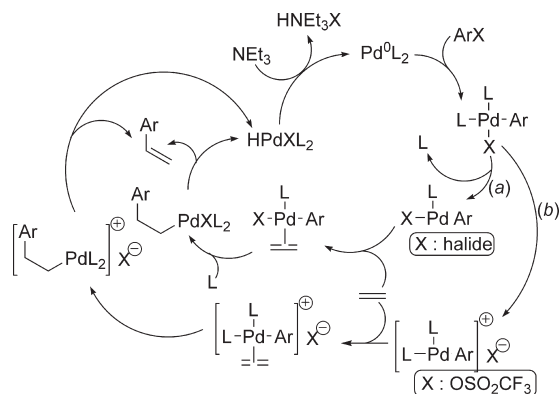
Given the relative reactivity of benzene and monosubstituted benzenes toward styrene in the presence of $\text{Pd}(\text{OAc})_2$, Fujiwara et al. suggested on November 13, 1975, that “the reaction involves an electrophilic attack of Pd(II) on the aromatic ring to form an aromatic palladium σ complex”.³¹ This agreed with the Heck-type mechanism proposed by Yamamura, one year before (manuscripts submitted on October 4, and November 13, 1974)^{35,47} to schematize the DHR of olefins with benzene, this proposal being retained in a subsequent report published in 1978.⁴²

According to the above literature data, it appears that the in situ formation of $\text{ArPd}(\text{II})$ species from the $\text{CH}_2=\text{CHZ}/\text{ArH}/\text{Pd}(\text{OAc})_2$ mixtures is accepted. Moreover, the possible arylation of olefins by aromatic palladium σ -complexes was exemplified by earlier studies from the teams of M. Julia^{39,60} and Horino (eq 26).^{61,62}

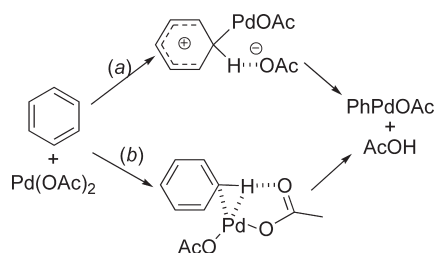


For the Mizoroki–Heck reactions, it is often assumed that the reactive $\text{ArPd}(\text{II})$ species formed from $\text{Pd}(0)\text{L}_n$ and aryl halides or triflates are neutral or cationic, respectively, this leading to neutral (path *a*) or cationic (path *b*) processes as outlined in Scheme 8.⁶³ Moreover, Åkermarck and co-workers have revealed that the ionic processes are favored in dissociating solvents.⁶⁴ As the stoichiometric DHRs have been carried out in AcOH or in solvent mixtures containing AcOH , we suspect that AcOH could act as an ionizing agent protonating off an acetate ligand²⁴ to afford $[\text{ArPd}(\text{II})]^+$ species. Thus, these DHRs would occur through cationic mechanisms. It is, nevertheless, worth mentioning that the $\text{ArPd}(\text{II})$ intermediates formed under Mizoroki–Heck and dehydrogenative Heck conditions differ, in most cases, in their coordination sphere, because the Mizoroki–Heck reactions are, in contrast to the DHRs, usually performed in the presence of added ligands such as phosphines.

Scheme 8



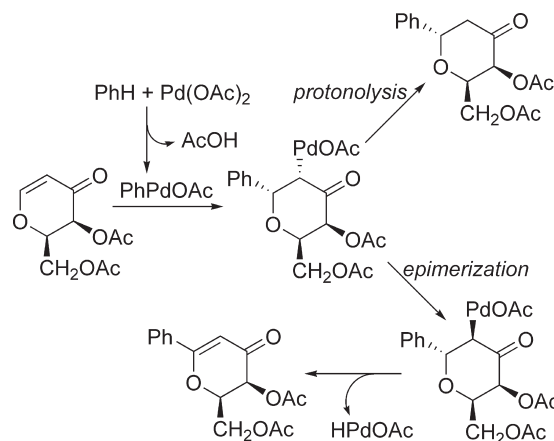
Scheme 9



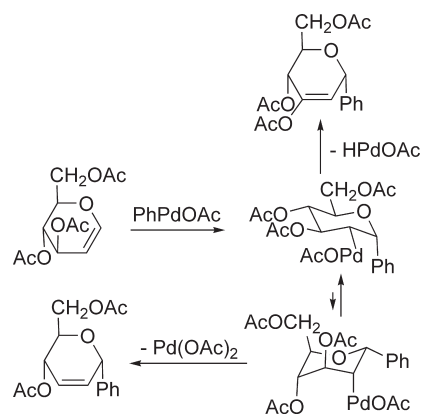
But, how is ArPd(II) from ArH and Pd(OAc)_2 produced? In 1978, Kozhevnikov et al. proposed the palladium cyclohexadienyl intermediate depicted in Scheme 9, path *a*, because the promotion of the DHRs by the acetate ion could be due to its assistance to the removing of H^+ .⁶⁵ Another proposal is contained in the recent review of Davies and Macgregor's teams who summarize literature computational studies of metal-induced C–H bond activation.⁶⁶ They pointed out the report of Sakaki et al.,⁶⁷ which leads them to assume an assistance by the acetate ligand (Scheme 9, path *b*),⁶⁶ Davies and Macgregor suggesting the term “ambiphilic metal ligand activation” to describe such reactions.

Different mechanistic proposals lie also in the reaction of ArPd(II) with the olefin, this occurring through either the insertion of the $\text{C}=\text{C}$ bond into the Ar-Pd bond (Scheme 6), or the activation of a vinylic C–H bond (Scheme 7). Retaining Scheme 6 to explain the reactions of (*E*)- and (*Z*)-1,2-dichloroethylenes (eqs 10 and 11) imply that the corresponding eliminations of HPdOAc occur through unusual *trans*-processes.⁶⁸ Scheme 6 is nevertheless usually admitted for DHRs. Moreover, a common intermediate, obtained from *cis*-addition of PhPdOAc to the $\text{C}=\text{C}$ bond, has been postulated when mixtures of substitution and hydroarylation products have been isolated as depicted in eqs 17–19 and Schemes 10 and 11. It seems worth mentioning that Czernecki et al. proposed (i) an epimerization step rather than a *trans* β -H elimination to form the arylated ketone shown in eq 18, this epimerization being promoted by the adjacent carbonyl group (Scheme 10)⁴⁴ and (ii) an *anti*-elimination of Pd(OAc)_2 after a conformational change to explain the formation of the minor compound depicted in eq 19 (Scheme 11).^{46,69} Thus, for the reaction of 1,2-dichloroethylenes (eqs 10 and 11), we suspect that the vinylic chloride atoms favor

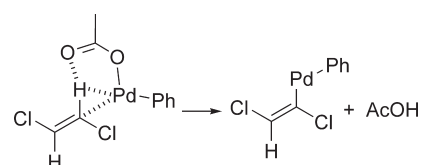
Scheme 10



Scheme 11



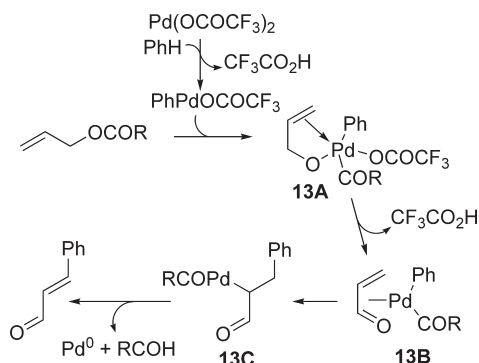
Scheme 12



7C-type intermediates via a vinylic C–H activation similar to that admitted from Ph-H (Scheme 12), some coordination of the proximal Cl to Pd being also plausible.

The mechanism of formation of α,β -unsaturated aldehydes from allyl esters (reaction depicted in eq 16) is unclear. Indeed, allyl trifluoroacetate and cinnamyl trifluoroacetate in PhH/AcOH led also to these two aldehydes in the presence of Pd(OAc)_2 .⁴³ Hydrolysis of the ester to allyl alcohol followed by its oxidation and phenylation was discarded as a plausible mechanism because allyl alcohol, under the reaction conditions (i.e., in $\text{CF}_3\text{CO}_2\text{H}$), afforded only 3% cinnamaldehyde without production of 3,3-diphenylacrylaldehyde. This observation led Fujiwara et al. to suggest a reaction via the insertion of Pd(0) into the acyl-O bond of the ester to afford allylOPdCOCF_3 as intermediate, but no information concerning a possible pathway leading to the products from this intermediate was provided. Since this report (1982), the literature contains a number of examples of Pd(IV) complexes or intermediates,⁷⁰ with in

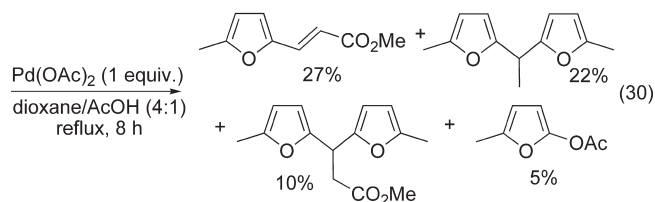
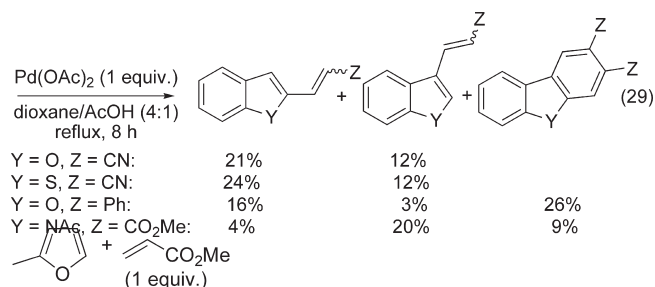
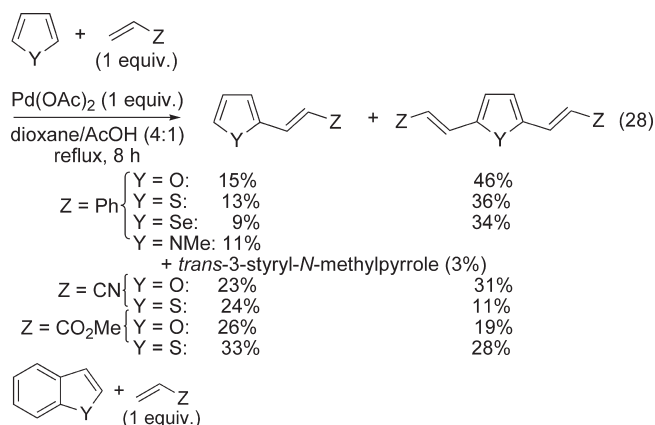
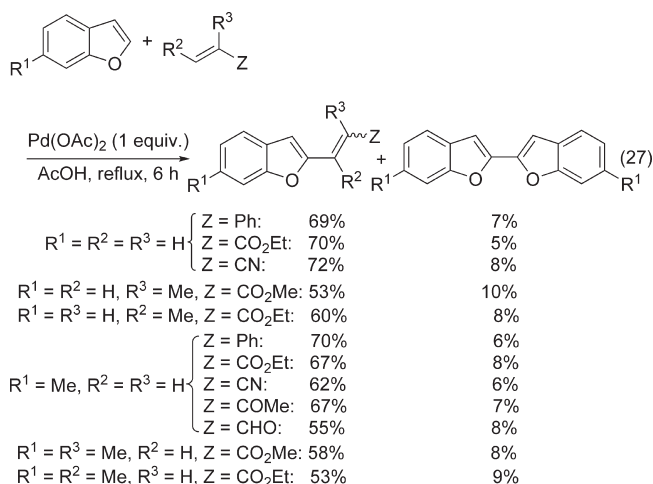
Scheme 13



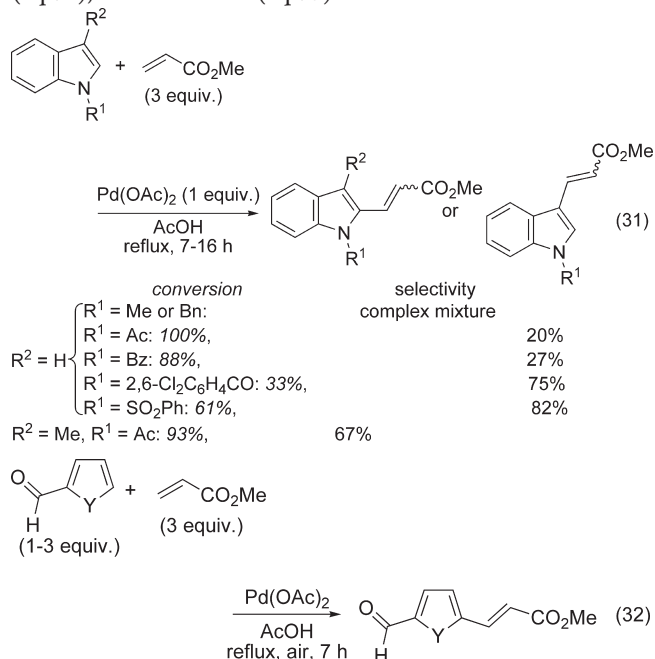
particular, trifluoroacetate as ligand.⁷¹ This led us to envisage the formation of Pd(IV) intermediate **13A** from the insertion of Pd(II) rather than Pd(0) into the acyl-O bond (Scheme 13). From **13A**, β -H elimination would afford $\text{CF}_3\text{CO}_2\text{H}$ and **13B**. Insertion of the $\text{C}=\text{C}$ bond of the coordinated acrylaldehyde into the Ph-Pd bond would provide **13C**, which evolves toward cinnamaldehyde.

2.2. Heteroarenes

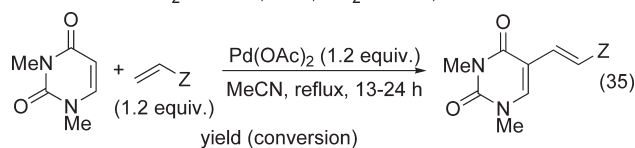
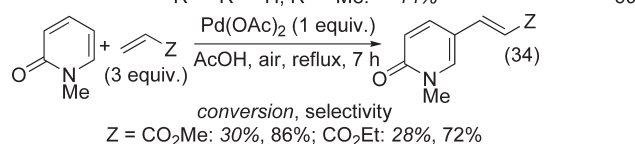
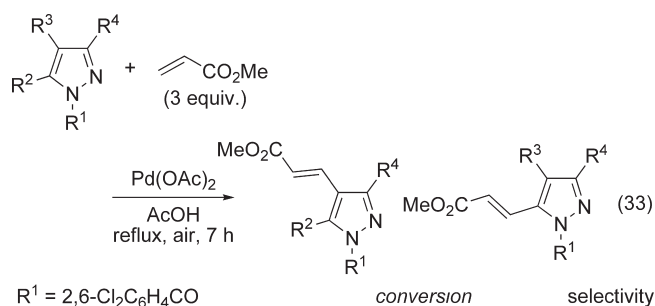
2.2.1. Results. In 1972, the teams of Kasahara and Fujiwara submitted independently, and almost simultaneously (June 8 and July 27, respectively), the $\text{Pd}(\text{OAc})_2$ -mediated reaction of heteroarenes with olefins.^{72–74} Kasahara et al. used benzofurans with a variety of olefins (eq 27),⁷² while Fujiwara et al. used various heteroarenes with styrene (eq 28).⁷³ In 1976, Kozhevnikov reported the selective α -vinylation of furan, thiophene, and furfural under similar conditions. Besides the 2-vinyl derivatives, traces of the 3-vinyl derivatives were observed and, in the case of thiophene, a small amount of (Z)-1,2-dithienylethylene.⁷⁵ Subsequently, Fujiwara's team extended their substitution process to acrylonitrile and methyl acrylate (eq 28), and revealed that, in contrast to Kasahara's results (eq 27), the alkenylation of benzofuran proceeded at 2- and 3-positions, this being also observed using benzothiophene and N-acetylindole as substrates (eq 29).^{76,76} Moreover, some disubstitution of benzofuran and N-acetylindole occurred, leading to an aromatic ring under the experimental conditions (eq 29).⁷⁶ With 2-methylfuran as substrate, the reaction with methyl acrylate provided unexpected adducts as shown in eq 30.⁷⁸



Between 1983 and 1987, Itahara and co-workers reported the direct $\text{Pd}(\text{OAc})_2$ -mediated alkenylation of various substituted indoles (eq 31),^{48,49,79,80} furans, thiophenes, pyrroles (eq 32),^{48,49,81,82} pyrazoles (eq 33),^{49,82} 1-methyl-2-pyridone (eq 34),^{49,81} and uracils (eq 35).⁸³

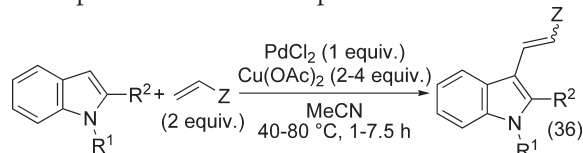


$\text{Y} = \text{O}$: 56% yield; $\text{Y} = \text{S}$: 34% yield
 $\text{Y} = (2,6\text{-Cl}_2\text{C}_6\text{H}_4\text{CO})\text{N}$: 34% conversion, 87% selectivity



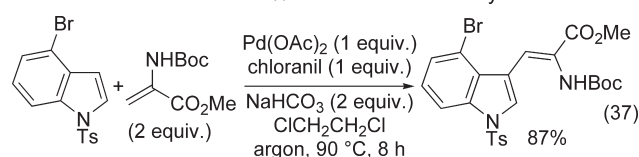
$Z = \text{CO}_2\text{Me}$: 92%, CN : 73% (91%), COMe : 74% (85%), Ph : 86%

Murakami's team, also, carried out the DHR of indoles with olefins but, mainly, with PdCl_2 in MeCN. Despite the use of a stoichiometric quantity of palladium, the addition of 2–4 equiv of $\text{Cu}(\text{OAc})_2$ was required to obtain satisfactory yields (eq 36), the $\text{PdCl}_2/\text{Cu}(\text{OAc})_2$ becoming slightly more efficient than $\text{Pd}(\text{OAc})_2$. Switching from $\text{PdCl}_2/4 \text{ Cu}(\text{OAc})_2$ in MeCN at 80 °C to $\text{PdCl}_2/4 \text{ NaOAc}$ in AcOH at 100 °C gave similar results.⁸⁴ To synthesize clavicipitic acid, Murakami et al. reacted 4-bromo-1-tosylindole with *N*-(*t*-butoxycarbonyl)dehydroalanine methyl ester and $\text{Pd}(\text{OAc})_2$ in AcOH. Literature conditions were not suitable, but the use of an aprotic solvent in the presence of sodium bicarbonate and chloranil (2,3,5,6-tetrachlorobenzoquinone) afforded a high yield of the required protected 4-bromodehydrotryptophan (eq 37).⁸⁵ Subsequently, the team reported that the DHR of 4-bromo-1-tosylindole with ethyl acrylate using stoichiometric amounts of $\text{Pd}(\text{OAc})_2$, in 1,2-dichloroethane, 1,2,4-trichlorobenzene, or AcOH was also improved with chloranil as additive.⁸⁶ Given these observations, it appears that, despite the use of stoichiometric quantities of $\text{Pd}(\text{II})$, these DHRs require the presence of an oxidant ($\text{Cu}(\text{OAc})_2$ or a quinone) or acetate ions to be effective; these species could stabilize the palladium intermediates.

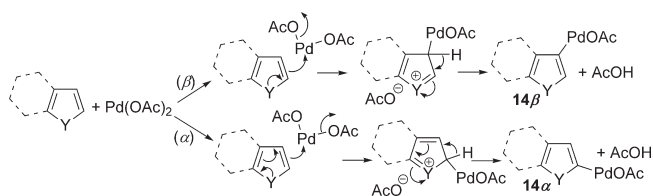


$R^1 = \text{H}, R^2 = \text{CO}_2\text{Et}, Z = \text{CO}_2\text{Et}$ (50%), COMe (53%), Ph (44%^a)
 $R^1 = \text{Bn}, R^2 = \text{CO}_2\text{Et}, Z = \text{CO}_2\text{Et}$ (72%), CO_2Me (84%^b),
 COMe (69%), Ph (69%^c), CN (73%)
 $R^1 = \text{Bn}, R^2 = \text{H}, Z = \text{CO}_2\text{Et}$ (60%), COMe (56%)

^a+ 19% of the α -substituted styrene
^b2% yield in the absence of $\text{Cu}(\text{OAc})_2$
^c+ 5% of the α -substituted styrene



Scheme 14



2.2.2. Mechanism. When a mechanism scheme is provided, all above reports suggest the formation of $(\text{YAr})\text{PdOAc}$ from $(\text{YAr})\text{H}$ and $\text{Pd}(\text{OAc})_2$ as the first reactive intermediate.^{48,72,75,76,78–80,82} From competitive reactions of ArH and $(\text{OAr})\text{H}$ toward styrene, Fujiwara's team estimated the following order of reactivity: benzene (1) < naphthalene (4) < ferrocene (100) < furan (1000) with the approximate relative rates showed in brackets.³² The authors have noted that this sequence “is similar to but its magnitude is greatly different from that of the usual electrophilic substitution”. Using benzofuran deuterated in C2 position or $\text{PhCH}=\text{CD}_2$ to carry out the DHR depicted in eq 27, Kasahara et al. demonstrated the absence of hydride shift.⁷²

According to the literature, the stoichiometric $\text{Pd}(\text{II})$ -mediated alkenylation of heteroarenes follows reactive pathways similar to those proposed from arenes. We, however, suspect the assistance by the heteroatom of the formation of $(\text{YAr})\text{PdOAc}$ (Scheme 14), but which factors determine the regioselectivity? According to eqs 27–30 and 32, furan, thiophene, selenophene, 1-substituted pyrroles, and benzofuran are palladated at C2 position leading to 14α as intermediate complex, while 1-substituted indoles gave the complex 14β (eqs 29, 31, 36 and 37). In the section devoted to the catalytic reactions of heteroarenes, we will see that the regioselectivity can depend on the experimental conditions and the substrate substitution.

3. CATALYTIC PALLADIUM CONDITIONS

The seminal discovery by Moritani and Fujiwara, at the end of the 60s, of the intermolecular coupling of benzene with styrene²⁹ has been the starting point of an intensive research activity on the Pd -catalyzed C–H activation. The present chapter, which covers the catalytic oxidative coupling of arenes and heteroarenes with olefins, will be partitioned following the nature of the aromatic substrate. Since the proposed organopalladium intermediates leading to the compounds are similar to those suspected in sections 2.1.2 and 2.2.2, a section devoted specially to mechanisms will not be here included. New or particular mechanism information will be provided when necessary.

3.1. Arenes

3.1.1. Benzene. One year after the report of the oxidative coupling of benzene with styrene in the presence of stoichiometric amounts of $\text{Pd}(\text{II})$, Fujiwara's team reported the first catalytic conditions. The procedure, which used $\text{Pd}(\text{OAc})_2$ as the catalyst and AgOAc as the reoxidant in AcOH for the DHR of ethylene and styrene with benzene, led however to a turnover number (TON) not higher than 2 (Table 1, Entry 1; Table 2, Entry 1).^{14,87} In the course of this work, it was observed that $\text{Pd}(\text{OAc})_2$ can be obtained from palladium powder and AgOAc

Table 1. Pd(OAc)₂-Catalyzed Reaction of Benzene with Ethylene
$$\text{PhH} + \text{H}_2\text{C}=\text{CH}_2 \longrightarrow \text{Ph}-\text{CH}=\text{CH}_2 \quad \text{Sy} \quad \text{Ph}-\text{CH}=\text{CH}-\text{Ph} \quad \text{Sb}$$

entry	PhH equiv	Pd equiv	oxidant, additive (equiv)	solvent (ratio)	<i>t</i> °C; time, h	yield % (TON)
1 ¹⁴	<i>a</i>	<i>b</i>	AgOAc (10/Pd) ^c	PhH/AcOH (4:1)	Rx; 8	Sy: (0.59) Sb: (0.75)
2 ⁸⁸	33	0.013	O ₂ (20 bar)	PhH	80; 5.5	Sy: (6.48) Sb: (0.39)
3 ⁶⁵	<i>b</i>	0.083	H ₃ PMo ₇ V ₂ O ₄₀ (0.42) LiOAc (5), air (1 bar)	PhH/DMF (7:3)	96; 3	Sy: 14 (1.7)
4 ⁸⁹	≈60	0.005	BzCH ₂ Bz (0.06) H ₃ PMo ₁₂ O ₄₀ ·30H ₂ O (0.0034) NaOAc (0.016), air (1.6 bar)	EtCO ₂ H	120; 8	Sy: (100) Sb: (67)

^a Ethylene bubbling in Ph. ^b Not indicated. ^c According to a subsequent paper,³³ it seems that the reaction was performed with continuous bubbling of air.

Table 2. Pd(OAc)₂-Catalyzed Reaction of Benzene with Styrenes and Vinylcyclohexane
$$\text{PhH} + \text{CH}_2=\text{CH}-\text{Z} \longrightarrow \text{Ph}-\text{CH}=\text{CH}-\text{Z}$$

entry	Z	PhH equiv	Pd equiv	oxidant, additive (equiv)	solvent (ratio)	<i>t</i> °C; time, h	yield % (TON)
1 ¹⁴	Ph	45	0.4	AgOAc (2)	PhH/AcOH (4:1)	Rx; 8	(1.38)
2 ³⁴	Ph	45	0.1	AgOAc (0.1) O ₂ (50 bar)	PhH/AcOH (4:1)	80; 8	25
3 ³⁴	Ph	45	0.1	Cu(OAc) ₂ (0.1) O ₂ (50 bar)	PhH/AcOH (4:1)	80; 8	44
4 ⁸⁸	Ph	4.5	0.011	O ₂ (20 bar)	PhH	100; 5	(11)
5 ⁹⁰	Ph	173	0.1	P(<i>p</i> -Tol) ₃ (0.67) O ₂ (3.5 bar)	PhH	55; 20	(6.1) ^a
6 ⁹¹	Ph	173	0.1 ^b	P(<i>p</i> -Tol) ₃ (0.67) O ₂ (3.5 bar)	PhH	55; 20	(1.2) ^c
7 ⁹²	Ph	5	0.01	BQ (0.1) AgOBz (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	25
8 ⁹³	Ph	20	0.07	AcCH ₂ Ac (0.07) HPMo ₁₁ V (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	90; 12	31
9 ⁸⁸	<i>p</i> -ClC ₆ H ₄	45	0.1	O ₂ (20 bar)	PhH	80; 2.5	(2.14)
10 ⁸⁸	Cy	48	0.1	O ₂ (20 bar)	PhH	80; 2.5	(1.77)

^a Plus traces of PhCH=CH(*p*-Tol) and (PhCH=CH)₂. ^b Pd(NO₃)₂ was used as catalyst. ^c Plus PhCH=CH(*p*-Tol) (TON = 0.6).

in AcOH.¹⁴ Improvement of the catalysis efficiency was achieved in 1969 in performing the reaction under oxygen pressure with catalytic quantities of either AgOAc or, better, Cu(OAc)₂ (Table 2, Entries 2 and 3).³⁴ Subsequently, Shue carried out the coupling of various olefins with benzene, using only oxygen (3.5–20 bar) as reoxidant (Table 1, Entry 2; Table 2, Entries 4, 9 and 10).^{88,94–96} This catalytic process, which was disclosed in 1971, could be the first using solely oxygen to regenerate active Pd(II) species.⁹⁷ Shue's reactions were carried out in the absence of AcOH; this has the advantage to preclude the formation of byproduct such as vinylic acetates. Decreasing the amount of catalyst but increasing the reaction time, Jacobs team has, under 8 bar of oxygen, efficiently phenylated butyl acrylate with time-dependent selectivity (Table 3, Entries 1 and 2).¹⁵ The same pressure of oxygen has been used with manganese

triacetate as cocatalyst to effect the highly efficient DHR of benzene with 4-phenylbut-3-en-2-one (Table 4, Entry 1).¹⁵ Lower oxygen pressure (3.5 bar) with Pd(OAc)₂ or Pd-(NO₃)₂ associated to various phosphines or diphenylsulfide, has been used by Park and co-workers for the DHR of styrene with benzene. No other solvent than benzene was used, but the efficiency of these procedures was low and some stilbene-type compounds were formed from the reaction between styrene and the arylated phosphines (Table 2, Entries 5 and 6).^{90,91}

The above catalytic oxygen procedures suffer from the use of oxygen pressures higher than 1 bar. Thus, Czernecki and Dechavanne have, in 1982, only used copper acetate as reoxidant to carry out the phenylation of a peracetylated glycol (eq 38),⁴⁵ while Itahara in 1982,⁹⁸ then Tsuji and Nagashima in 1983,⁹⁹ tested peroxides as stoichiometric

Table 3. Pd(OAc)₂-Catalyzed Reaction of Benzene with α,β -Unsaturated Esters, Methyl Vinyl Ketone, and Acrylaldehyde

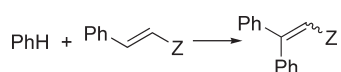
$$\text{PhH} + \text{CH}_2=\text{CH}-\text{Z} \longrightarrow \text{Ph}-\text{CH}=\text{CH}-\text{Z} \quad \text{M} \quad \text{Ph}-\text{CH}=\text{CH}-\text{Z} \quad \text{D}_\alpha \quad \text{Ph}-\text{CH}=\text{CH}-\text{Z} \quad \text{D}_\beta \quad \text{Ph}-\text{CH}=\text{CH}-\text{Z} \quad \text{T}$$

entry	Z	PhH equiv	Pd equiv	oxidant, additive (equiv)	solvent (ratio)	<i>t</i> °C; time, h	yield % (TON)
1 ¹⁵	CO ₂ <i>n</i> -Bu	12–15	0.01	O ₂ (8 bar)	PhH	90; 47	M: 87 D _β : 11
2 ¹⁵	CO ₂ <i>n</i> -Bu	12–15	0.01	O ₂ (8 bar)	PhH	90; 165	M: 7 D _β : 18 T: 73
3 ⁹³	CO ₂ <i>n</i> -Bu	20	0.07	AcCH ₂ Ac (0.07) HPMo ₁₁ V (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	90; 2.5	M: 70 D _β : 11
4 ⁹⁸	CO ₂ Me	56	0.025	Na ₂ S ₂ O ₈ (0.5) air	PhH/AcOH (1:1)	Rx; 8	M: 18 (732)
5 ⁹⁹	CO ₂ Me	11	0.05 ^a	PhCO ₃ <i>t</i> -Bu (2)	PhH/AcOH	100; 3	D _β : 70
6 ⁹³	CO ₂ Me	20	0.07	AcCH ₂ Ac (0.07) HPMo ₁₁ V (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	90; 2.5	M: 68 D _β : 16
7 ¹¹	CO ₂ Me	19	0.05	PhI(OAc) ₂ (2) air	PhH/DMF	153; 1	M: 85
8 ⁹²	CO ₂ Et	5	0.03	BQ (0.1) 80% <i>t</i> -BuOOH (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	M: 31
9 ¹⁰⁰	CO ₂ Et	10	0.07	AcCH ₂ Ac (0.07) H ₄ PMo ₁₁ VO ₄₀ (0.013) NaOAc (0.05) O ₂ (balloon)	AcOH	90; 6	M: 63 D _β : 15 ^b
10 ⁹³	CO ₂ Et	20	0.07	AcCH ₂ Ac (0.07) HPMo ₁₁ V (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	90; 2.5	M: 74 D _β : 13
11 ¹⁶	CO ₂ Et	20–30	0.1	2,6-bis(2-ethylhexyl)-pyridine (0.2) Ac ₂ O (1), O ₂ (balloon)	PhH	90; 24	M: 77
12 ⁹²	COMe	5	0.03	BQ (0.1) 80% <i>t</i> -BuOOH (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	M: 26
13 ¹⁰¹	CHO	20	0.07	BzCH ₂ Bz (0.07) H ₄ PMo ₁₁ VO ₄₀ ·26H ₂ O (0.013) Na ₂ CO ₃ (0.03) O ₂ (balloon)	EtCO ₂ H	90; 1.5	M: 59 D _β : 5
14 ¹⁰¹	CHO	20	0.07	BzCH ₂ Bz (0.07) H ₄ PMo ₁₁ VO ₄₀ ·26H ₂ O (0.013) Na ₂ CO ₃ (0.03) O ₂ (balloon)	EtCO ₂ H	90; 3	M: 17 D _β : 40

^a Pd(OBz)₂ was used as catalyst. ^b Plus AcOCH=CHCO₂Et (10%).

reoxidants. While H₂O₂, *t*-BuOOH, *t*-BuOO*t*-Bu were ineffective, a little activity was observed with BzOOBz, and fair results were achieved with Na₂S₂O₈ (Table 3, Entry 4)⁹⁸ and PhCO₃*t*-Bu (Table 3, Entry 5)⁹⁹ for the DHR of PhH with α,β -unsaturated carbonyl compounds, even those β -substituted (Table 4, Entries 2, 6 and 9, eq 39). Itahara disclosed also the phenylation of 1,4-naphthoquinone and 1,4-benzoquinone (BQ) using various inorganic reoxidants in air, the best one being sodium peroxydisulfate (eqs 41 and 42).^{48,98,102} This author considered that the reoxidation of palladium is mediated by the quinone, and that the hydroquinone thus

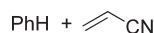
obtained is reoxidized into quinone as shown in Scheme 15.⁴⁸ Concerning BQ as the reoxidant, Fujiwara, also in 1982, reported that the stoichiometric reaction depicted in eq 16 acquires a catalytic character (TON < 4) when effected in the presence of this compound.⁴³ With PhCO₃*t*-Bu as the oxidant and Pd(OCOPh)₂ as the starting catalyst, Tsuji and Nagashima suggested a regeneration of active catalytic species from either Pd⁰ via its insertion into the O–O bond of the perester leading to Pd(OCOPh)(Ot-Bu), or HPdOCOPh via the six-membered cyclic transition state depicted in Scheme 16.⁹⁹

Table 4. Pd(OAc)₂-Catalyzed Reaction of Benzene with β -Substituted Styrenes

entry	Z	PhH equiv	Pd equiv	oxidant, additive (equiv)	solvent (ratio)	<i>t</i> °C; time, h	yield ^a %
1 ¹⁵	COMe	12–15	0.01	Mn(OAc) ₃ (0.04) O ₂ (8 bar)	PhH	90; 77	99
2 ^{99,b}	COMe	11	0.05	PhCO ₃ <i>t</i> -Bu (1)	AcOH	100; 3	65
3 ⁹²	COMe	5	0.01	BQ (0.1) 80% <i>t</i> -BuOOH (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	74
4 ⁹²	COMe	20	0.07	AcCH ₂ Ac (0.07) H ₇ PMo ₈ V ₄ O ₄₀ (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	90; 3	70
5 ⁹³	COMe	20	0.07	AcCH ₂ Ac (0.07) HPMo ₁₁ V (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	2.5	93
6 ^{99,b}	CHO	11	0.05	PhCO ₃ <i>t</i> -Bu (1)	AcOH	100; 3	64
7 ⁹²	CHO	5	0.03	BQ (0.1) 80% <i>t</i> -BuOOH (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	36 ^c
8 ⁸⁹	CHO	13	0.07	BzCH ₂ Bz (0.07) H ₄ PMo ₁₁ VO ₄₀ (0.013) Na ₂ CO ₃ (0.03) O ₂ (balloon)	EtCO ₂ H	90; 2	61
9 ^{99,b}	CO ₂ Me	11	0.05	PhCO ₃ <i>t</i> -Bu (1)	AcOH	100; 3	56
10 ¹⁰¹	CO ₂ Me	20	0.07	AcCH ₂ Ac (0.07) H ₇ PMo ₈ V ₄ O ₄₀ (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	90; 3	84
11 ⁹²	CO ₂ Et	5	0.01	AgOAc or AgOBz (1.3)	AcOH	90; 12	(51–53)
12 ⁹²	CO ₂ Et	5	0.01	BQ (0.05) MnO ₂ (1.3)	AcOH	90; 12	(46)
13 ⁹²	CO ₂ Et	5	0.01	BQ (0.05) 30% H ₂ O ₂ (1.3)	AcOH	90; 12	(35)
14 ⁹²	CO ₂ Et	5	0.01	80% <i>t</i> -BuOOH (1.3)	AcOH	90; 12	(60)
15 ⁹²	CO ₂ Et	5	0.01	BQ (0.1) 80% <i>t</i> -BuOOH (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	72
16 ⁹²	CO ₂ Et	5	0.01	Cu(OAc) ₂ (0.05) 80% <i>t</i> -BuOOH (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	(25)
17 ⁹³	CO ₂ Et	20	0.07	AcCH ₂ Ac (0.07) HPMo ₁₁ V (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	90; 2.5	88
18 ⁹²	CO ₂ H	5	0.03	BQ (0.1) 80% <i>t</i> -BuOOH (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	(25)
19 ⁹²	CN	5	0.03	BQ (0.1) 80% <i>t</i> -BuOOH (1.3)	AcOH/Ac ₂ O (3:1)	90; 12	15
20 ⁹³	Ph	20	0.07	AcCH ₂ Ac (0.07) HPMo ₁₁ V (0.013) NaOAc (0.05) O ₂ (balloon)	EtCO ₂ H	90; 2.5	76

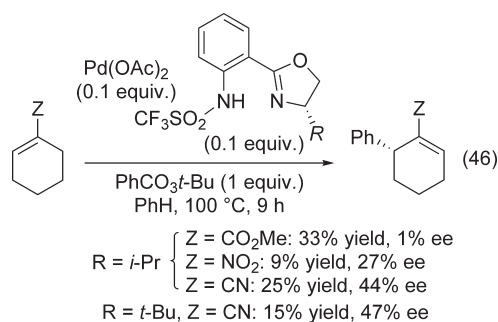
^a Isolated yield, GC yield is in brackets. ^b Pd(OBz)₂ was used as catalyst. ^c Formation also of PhCH=CHCO₂H (10%) and Ph₂C=CCO₂H (40%).

of oxygen. The Ishii coupling was primitively carried out using ethyl acrylate in AcOH, with acetylacetone and NaOAc as additives for an optimum efficiency, but acetylation of the olefin was a concurrent pathway (Table 3, Entry 9).¹⁰⁰ In contrast, the use of propionic acid instead of acetic acid led to a clean process with, moreover, a decrease of the reaction time (Table 3, Entry 10).^{93,100} The method was effective for the phenylation of ethylene (Table 1, Entry 4),⁸⁹ stilbene (Table 4, Entry 20),⁹³ α - β -unsaturated ketones, esters, and aldehydes (Table 3, Entries 3, 6, 13, 14; Table 4, Entries 4, 5, 8, 10 and 17),^{89,92,93,100,101} lower yields being obtained from styrene (Table 2, Entry 8).^{93,100} As documented in these reports, the efficiency of these reactions depends highly on the structure of the heteropoly acid (for an example, compare Entries 4 and 5 of Table 4). The DHR of benzene with acrylonitrile is moreover sensitive to their ratio, a large excess of benzene being required to achieve good yields (eq 45).^{93,104} According to the authors, the use of less amounts of benzene could favor the coordination of acetonitrile rather than benzene to palladium.¹⁰⁴



using $\text{H}_4\text{PMo}_{11}\text{VO}_{40} \cdot 22\text{H}_2\text{O}$ with $\begin{cases} 20 \text{ equiv. of PhH: } 12\% \\ 40 \text{ equiv. of PhH: } 66\% \\ 60 \text{ equiv. of PhH: } 78\% \end{cases}$
 using $\text{H}_6\text{PMo}_9\text{V}_3\text{O}_{40} \cdot 20\text{H}_2\text{O}$ with 40 equiv. of PhH: 35%

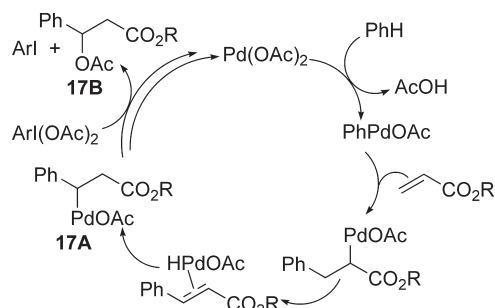
Mikami et al. have used the Tsuji catalytic procedure⁹⁹ in the presence of chiral ligands for the phenylation of prochiral olefins with, however, moderate chemical yields and enantiomeric excesses (eq 46).¹⁷ Although this interesting reaction was published in 1999, it seems that no further report on this topic has appeared in the literature.¹⁰⁵



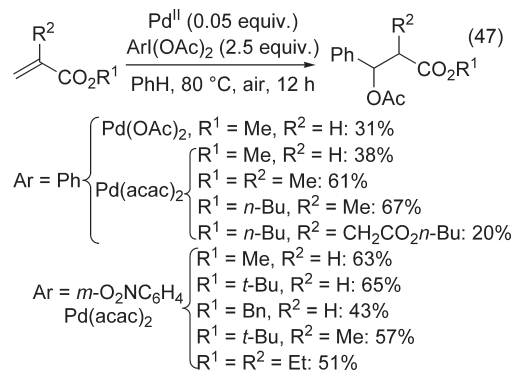
Over the last 10 years, the direct reoxidation of Pd(0) by oxygen has made great progress, and nowadays, can be very efficient when pyridyl-type ligands of palladium are used.^{97,106} This has led J.-Q. Yu and co-workers to disclose, in 2009, the phenylation of ethyl acrylate in 77% yield, using only 1 bar of oxygen as reoxidant, thanks to 2,6-bis(2-ethylhexyl)pyridine as ligand (Table 3, Entry 11).¹⁶

Recently, Rodriguez and Moran have used iodobenzene diacetate as the reoxidant.¹¹ Running the reaction of methyl acrylate in a PhH/DMF mixture, at 153 $^\circ\text{C}$, with Pd(OAc)_2 as the catalyst provided 85% methyl cinnamate (Table 3, Entry 7) while, in refluxing PhH, a three-component coupling reaction was achieved in a yield improved with Pd(acac)_2 as the catalyst and $m\text{-NO}_2\text{C}_6\text{H}_4\text{I(OAc)}_2$ as the reoxidant (eq 47).¹⁰⁷ The

Scheme 17

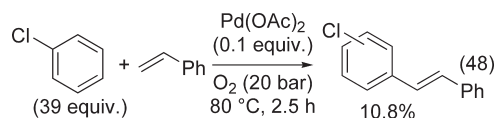


proposed mechanism (Scheme 17) proceeds through the addition of PhPdOAc to the $\text{C}=\text{C}$ bond followed by the usual β -H elimination and then, the fast readdition of the resulting HPdOAc species to afford the σ -complex **17A**. Product **17B** would be obtained from **17A** from either reductive elimination or oxidation into a Pd(IV) complex¹⁰⁸ followed by displacement with acetate.¹¹

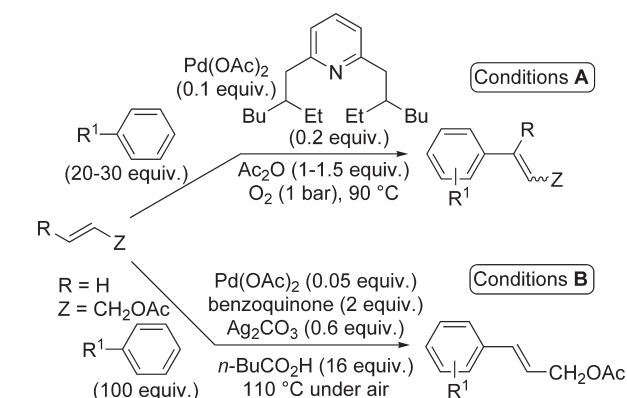


3.1.2. Substituted Benzenes. The DHRs of substituted benzenes afford usually mixtures of isomers, except when a substituent provides a directing effect via its electronic properties, or as transitional ligand of palladium. This led us to split up this section into two parts, which correspond to reactions without or with coordination of a substituent.

3.1.2.1. Without Substituent Coordination. Shue reacted toluene, aniline, and chlorobenzene with ethylene, styrene, and cyclohexene under oxygen pressure using palladium carboxylates as catalysts,^{88,94–96} the reaction of chlorobenzene with styrene leading to a mixture of *o*-, *m*-, and *p*-chloro-stilbenes in a low yield (eq 48).



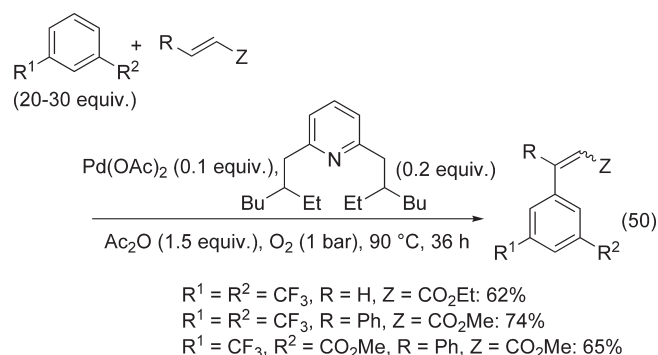
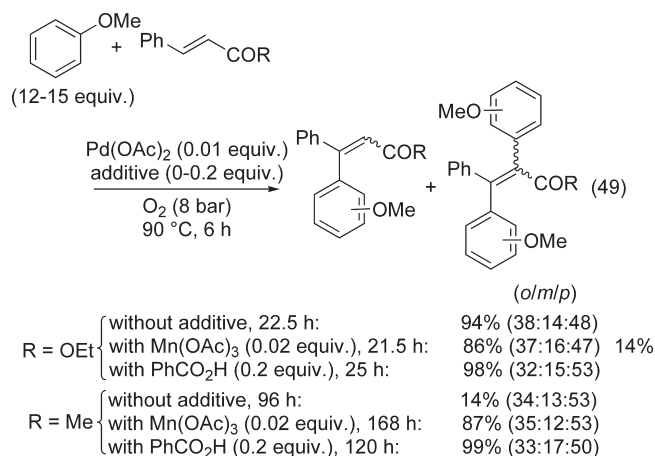
For the DHR of anisole with α,β -unsaturated esters and ketones, Jacobs et al. also used oxygen to regenerate active Pd species. Under 8 bar of oxygen, the efficiency was improved in the presence of manganese acetate or benzoic acid (eq 49).¹⁵ Optimization of the reaction parameters led to TON up to 780 and TOF = 183/h.¹⁰⁹ The authors showed the decisive role of the counterion of palladium. PdCl_2 and PdI_2 were totally ineffective because the strong coordination of halide

Table 5. Olefination of Electron-Deficient Arenes^{16,22}

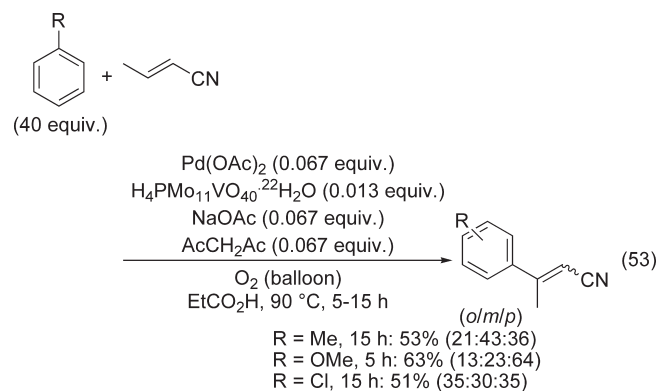
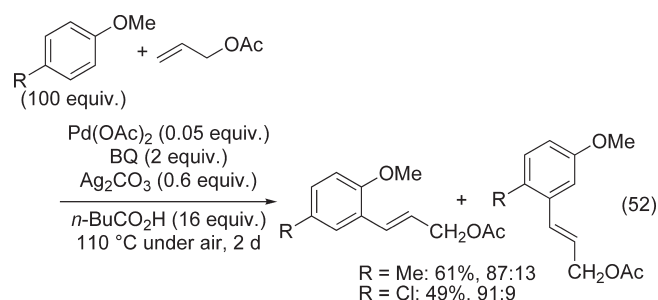
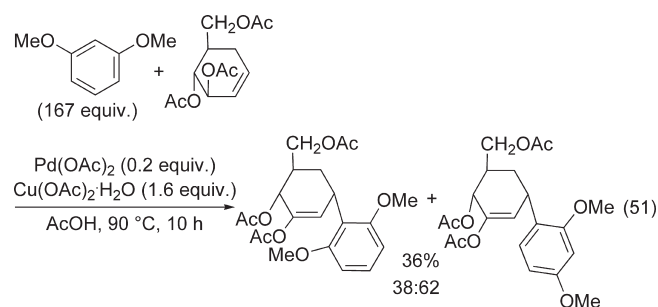
entry	conditions	R^1	R	Z	time (h)	yield %	<i>o/m/p</i> ratio
1 ¹⁶	A	CO_2Et	H	CO_2Et	2	70	0:80:20
2 ²²	B	CO_2Me	H	CH_2OAc	48	46	15:64:21
3 ¹⁶	A	CF_3	H	CO_2Et	20	72	0:78:22
4 ¹⁶	A	CF_3	H	$\text{CO}_2\text{t-Bu}$	5	71	0:83:17
5 ¹⁶	A	CF_3	H	$\text{PO}(\text{OEt})_2$	56	70	0:78:22
6 ²²	B ^a	CF_3	H	CH_2OAc	48	37	>95:?:?
7 ¹⁶	A	CO_2Et	Ph	CO_2Me	24	81	0:79:21
8 ¹⁶	A	COMe	Ph	CO_2Me	60	65	0:83:17
9 ²²	B	COMe	H	CH_2OAc	48	34	15:66:19
10 ¹⁶	A	NO_2	Ph	CO_2Me	16	73	0:84:16
11 ²²	B	NO_2	H	CH_2OAc	48	39	18:61:21
12 ²²	B	Cl	H	CH_2OAc	48	52	34:36:30

^a Reaction performed at 100 °C.

ions to Pd. It has been proposed that $\text{Pd}(\text{OAc})_2$ reacts with BzOH to afford $\text{Pd}(\text{OBz})_2$ and that ArH suffers an electrophilic aromatic substitution by the ionic species $[\text{PdOBz}]^+$.¹⁰⁹ Heterogeneous Pd catalysts were also used to carry out such reactions but with lower efficiency.¹¹⁰ Recently, J.-Q. Yu and co-workers have used a lower pressure of oxygen, but with a higher catalyst loading, a Pd ligand and a solvent (Ac_2O), to perform the olefination of various substituted benzenes (Table 5, Entries 1, 3–5, 7, 8 and 10), 1,3-bis(trifluoromethyl)benzene affording selectively the corresponding 1,3,5-trisubstituted benzenes (eq 50).¹⁶

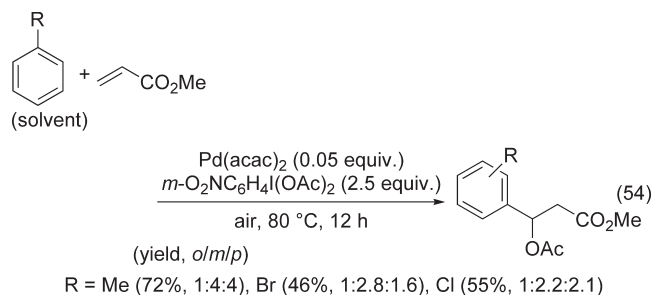


The reaction of 1,3-dimethoxybenzene with the tri-*O*-acetyl-D-galactal, carried out with $\text{Cu}(\text{OAc})_2$ as the reoxidant, provided a mixture of the corresponding 1,2,3- and 1,3,4-trisubstituted benzenes (eq 51).⁴⁵ In 2010, M. Yu, N. Jiao, and co-workers used the procedure disclosed in eq 44 for the DHR of various arenes with allyl acetate (Table 5, Entries 2, 6, 9, 11, and 12; eq 52),²² whereas Ishii et al. used the one depicted in Tables 2 (Entry 8), 3 (Entries 3, 6, and 10), 4 (Entries 4, 5, 10, 17, and 20) and eq 45 for the coupling with acrylonitrile and crotononitrile (eq 53).¹⁰⁴

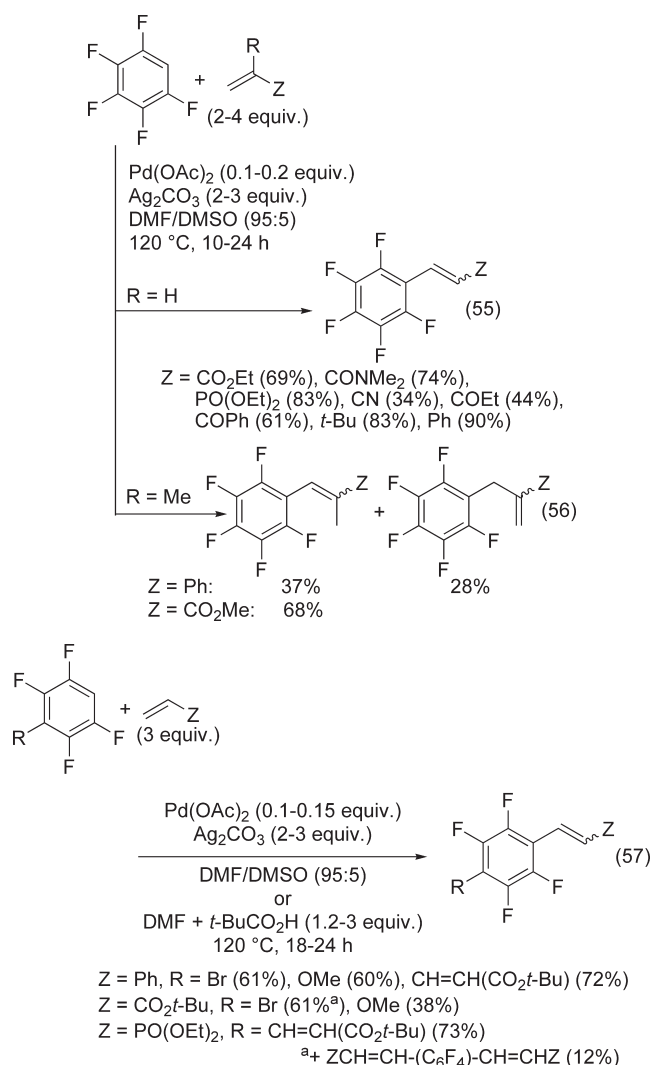


The three-component coupling process of Rodriguez and Moran (eq 47) has been used with substituted benzenes.

Toluene, chloro- and bromobenzenes reacted with methyl acrylate in fair yields (eq 54), while *p*-xylene gave only 25% of the 1,2,4-trisubstituted benzene.¹¹

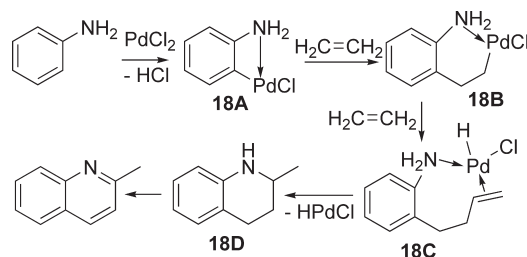


Recently, Zhang and co-workers disclosed the Pd(OAc)₂-catalyzed alkenylation of electron-deficient fluoroarenes using either 95:5 DMF/DMSO or DMF containing pivalic acid as solvent,¹¹¹ and Ag₂CO₃ as the reoxidant.^{112,113} As exemplified from eqs 55–57, these conditions are efficient and compatible with activated and nonactivated olefins, as well as different arene substituents, even a bromide one.

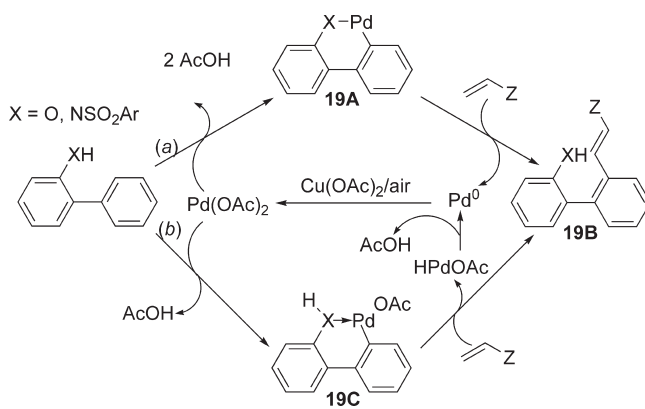


3.1.2.2. With Substituent Coordination. In 1979, Diamond and co-workers reported the formation of both 2-methylquinoline

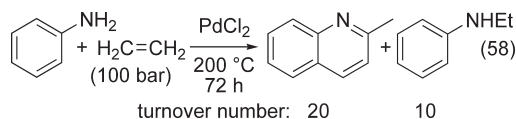
Scheme 18



Scheme 19

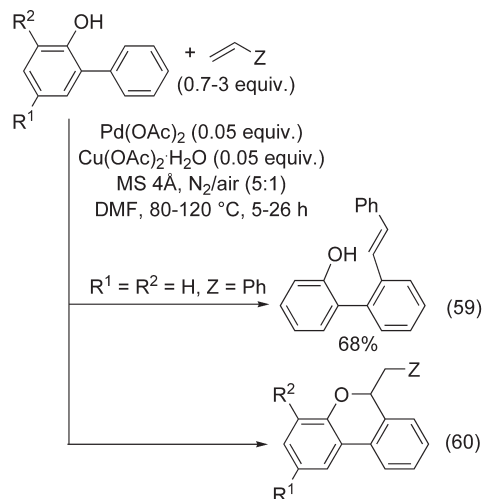


and *N*-ethylaniline from the PdCl₂-catalyzed reaction of aniline with ethylene at 200 °C (eq 58).¹¹⁴ This synthesis of 2-methylquinoline would involve the reaction of the *o*-palladated aniline **18A** with ethylene leading to **18B** (Scheme 18). A subsequent Heck-type reaction with a second molecule of ethylene could afford **18C**. The hydroamination of the C=C bond of **18C** would give the tetrahydroquinoline **18D**, which would suffer aromatization under the reaction conditions. The weakness of this mechanism concerns mainly the pathway leading to the regeneration of the catalyst. In contrast to the above reaction, the Pd(OAc)₂-catalyzed oxidative coupling between 3,5-dimethoxyaniline and *n*-butyl acrylate in AcOH did not occur, the reaction being however carried out at a lower temperature (80 °C).¹¹⁵ Moreover, we have above documented the instability of anilines in the presence of Pd(OAc)₂ (eq 23).⁵²

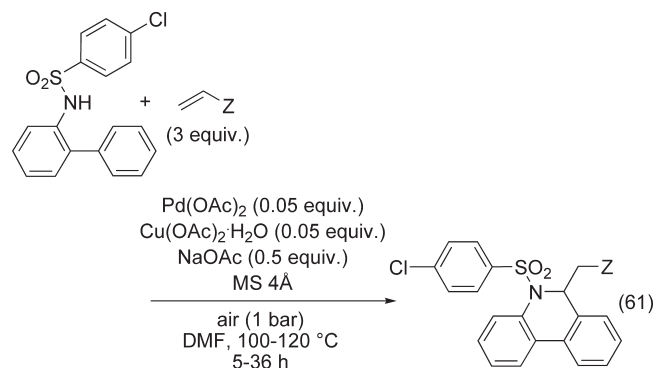


Miura et al. studied the Pd(OAc)₂-catalyzed alkenylation of *o*-heterosubstituted arylbenzenes shown in eqs 59, 60,¹¹⁶ and 61.¹¹⁷ The authors proposed that the OH and ArSO₂NH substituents direct the palladation of the benzene ring in the *o*-position to afford the heteropalladacycle **19A** and its subsequent intermolecular reaction with the C=C bond leading to **19B** (Scheme 19, path *a*).¹¹⁷ Instead of such a reactive pathway, we suggest the formation of complex **19C** which would evolve to **19B** via a Heck-type reaction (Scheme 19, path *b*). Whatever the correct mechanism, the acidic nature of the NH and OH protons of the substrates are crucial factors, since the catalytic

oxidative coupling did not proceed with 2-phenylaniline and *N*-benzylideneaniline as substrates. After alkenylation, an oxa-Michael-type reaction occurs if the starting C=C bond is substituted by an electron-withdrawing group (eqs 60 and 61). For these reactions, the absence of molecular sieves caused a strong decrease of the yields (eq 60), while the absence of the copper salt was less dramatic (eq 61).



$\text{R}^1 = \text{R}^2 = \text{H}$, $Z = \text{CO}_2i\text{-Bu}$ (79%), CO_2Et (80%), CO_2Cy (72%), CONMe_2 (48%)
 $Z = \text{CO}_2n\text{-Bu}$ $\left\{ \begin{array}{l} \text{R}^2 = \text{H}, \text{R}^1 = \text{Cl} \text{ (27\%, } t\text{-Bu (60\%))} \\ \text{R}^1 = \text{H}, \text{R}^2 = \text{Ph (52\%)} \\ \text{R}^1 = \text{R}^2 = \text{H (69\%)} \\ \text{R}^1 = \text{R}^2 = \text{H in the absence of MS (17\%)} \end{array} \right.$

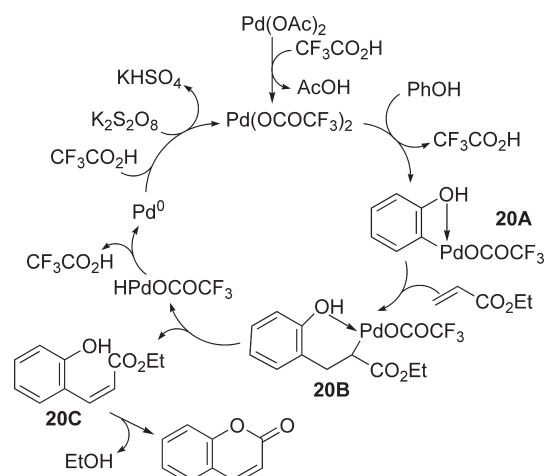


$Z = \text{CO}_2\text{Et}$ (91%), $\text{CO}_2n\text{-Bu}$ (97%), $\text{CO}_2i\text{-Bu}$ (92%), $\text{CO}_2t\text{-Bu}$ (95%), CONMe_2 (76%), CN (38%)

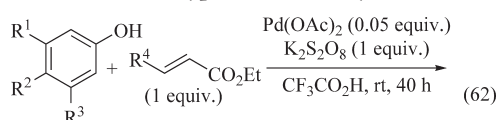
$Z = \text{CO}_2\text{Et}$ in the absence of copper salt: 57%

The synthesis of coumarins from the DHR of phenols with ethyl acrylates, at room temperature in $\text{CF}_3\text{CO}_2\text{H}$ (eq 62), has been reported by Kitamura et al., who observed the superior efficiency of $\text{K}_2\text{S}_2\text{O}_8$ compared to $\text{Cu}(\text{OAc})_2$ and oxone for the regeneration of active Pd species.¹¹⁸ According to the authors, the mildness of the reaction conditions is attributable to the in situ formation of a catalyst with an increased reactivity, namely, $\text{Pd}(\text{OCOCF}_3)_2$, from $\text{Pd}(\text{OAc})_2$ and $\text{CF}_3\text{CO}_2\text{H}$.^{119,120} The mechanism proposed for the formation of coumarin involves the addition of *o*-palladated phenol **20A** with ethyl acrylate to afford **20B** (Scheme 20). Elimination of HPdOCOCF_3 from **20B** gives **20C**, which undergoes cyclization into the coumarin. As for HPdOCOCF_3 , it evolves to Pd^0 , which is oxidized into $\text{Pd}(\text{OCOCF}_3)_2$ with the $\text{K}_2\text{S}_2\text{O}_8$ /

Scheme 20

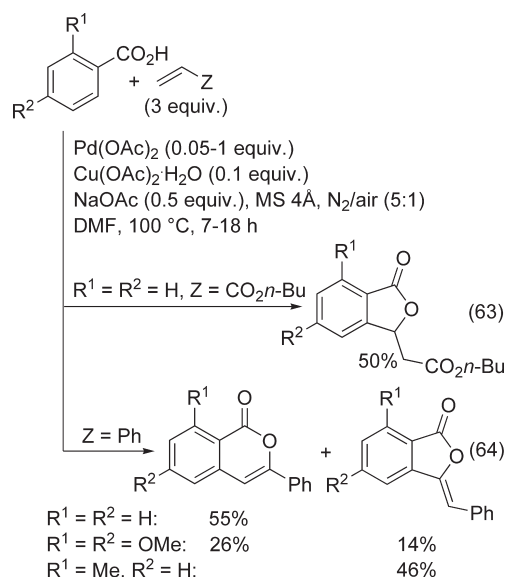


$\text{CF}_3\text{CO}_2\text{H}$ association. It is worth mentioning that when the acrylate is β -substituted, the cyclization requires the *E* to *Z* isomerization of the C=C bond of the intermediate corresponding to **20C** if the corresponding **20A** \rightarrow **20B** and **20B** \rightarrow HPdOCOCF_3 steps occur via the usual *cis*-addition and *syn*-elimination, respectively. This point led us to envisage another mechanism which involves dihydrocoumarin as intermediate and its subsequent Pd(II)-catalyzed dehydrogenation.¹²¹ Indeed, the teams of Kitamura¹²² and Tunge¹²³ have disclosed the room temperature $\text{CF}_3\text{CO}_2\text{H}$ -mediated synthesis of dihydrocoumarins from phenols and cinnamic acids or esters; this occurs via either formation of the Ar–C bond by coupling of the two substrates followed by intramolecular transesterification^{122,123} or intermolecular transesterification¹²⁴ and subsequent intramolecular formation of the Ar–C bond.^{123,125} Such a mechanism has, however, to be treated with caution because Kitamura et al. assumed that “no products were formed in the absence of $\text{Pd}(\text{OAc})_2$ ” from a $\text{CF}_3\text{CO}_2\text{H}$ mixture of 3,5-dimethoxyphenol and ethyl cinnamate.¹¹⁸

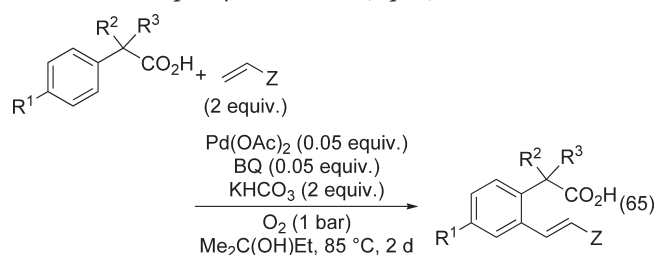


$\text{R}^1 = \text{R}^3 = \text{OMe}, \text{R}^2 = \text{H}$: 46%
 $\text{R}^1 = \text{R}^3 = \text{Me}, \text{R}^2 = \text{H}$: 46%
 $\text{R}^1 = \text{OMe}, \text{R}^2 = \text{R}^3 = \text{H}$: 75%
 $\text{R}^1 = \text{Me}, \text{R}^2 = \text{R}^3 = \text{H}$: 46%
 $\text{R}^1 = \text{R}^2 = \text{Me}, \text{R}^3 = \text{H}$: 11%
 $\text{R}^1 = \text{R}^3 = \text{OMe}, \text{R}^2 = \text{H}$: 25%
 $\text{R}^1 = \text{OMe}, \text{R}^2 = \text{R}^3 = \text{H}$: 32%
 $\text{R}^4 = \text{H}, \text{R}^1 = \text{R}^3 = \text{OMe}, \text{R}^2 = \text{H}$: 40%

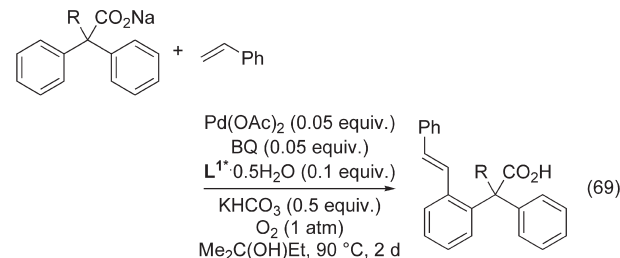
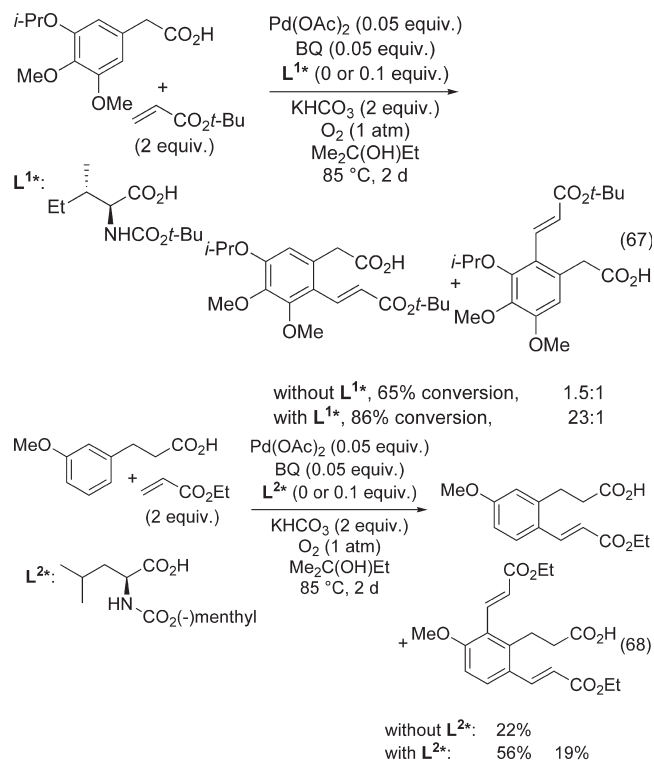
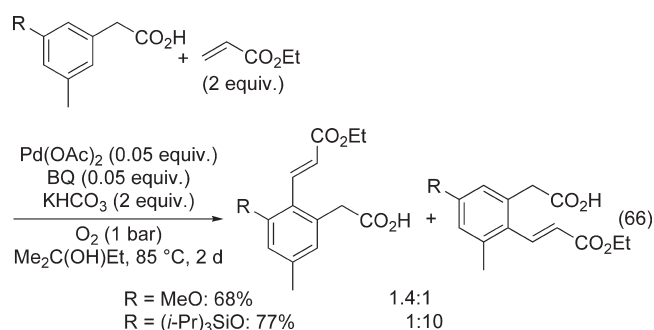
DHRs of benzoic acids with C=C bonds have also been achieved by Miura's team.¹¹⁷ These reactions afford phthalides when the C=C bond belongs to butyl acrylate (eq 63), while isocoumarins and/or benzylidenephthalides are obtained using styrene as the alkenylating agent (eq 64). The synthesis of these lactones proceeds via ortho-vinylation of the benzoic acid followed by either nucleophilic cyclization or Wacker-type reaction.¹²⁶



In 2009, J.-Q. Yu and co-workers disclosed DHRs of phenylacetic acids (eqs 65–67) and 3-phenylpropionic acids (eq 68) instead of benzoic acids as substrates.¹²⁷ The reactions were carried out under basic conditions, at 85°C in *t*-amyl alcohol, with regeneration of the active Pd species by oxygen associated to catalytic amounts of BQ. These conditions are compatible with the presence of chloride on the aromatic ring, and the cyclization of the obtained mono- or dialkenylated adducts did not occur (eqs 65–67). For unregioselective reactions, the steric properties of the metal center have been modified using mono-*N*-protected amino acids to induce selectivity (eq 67). This ligand-controlling selectivity can be accompanied by a yield increase (eq 68). This process has been used for the enantioselective olefination of diphenylacetic acids (eq 69).¹²⁸



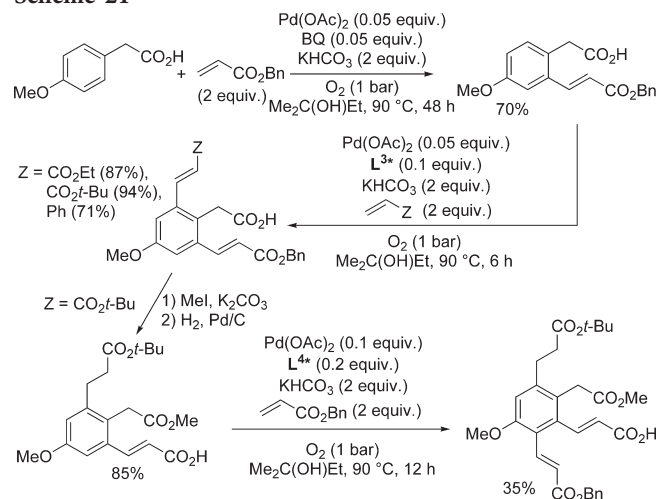
$\text{R}^1 = \text{MeO}$, $\text{R}^2 = \text{R}^3 = \text{H}$, $\text{Z} = \text{CO}_2\text{Et}$ (96%), $\text{CO}_2t\text{-Bu}$ (96%), COMe (46%), Ph (68%)
 $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$, $\text{Z} = \text{CO}_2\text{Et}$ (92%)
 $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{Me}$, $\text{Z} = \text{CO}_2\text{Et}$ (96%)
 $\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{R}^3 = \text{Me}$, $\text{Z} = \text{CO}_2\text{Et}$ (97%)
 $\text{R}^1 = \text{F}$, $\text{R}^2\text{-R}^3 = (\text{CH}_2)_4$, $\text{Z} = \text{CO}_2\text{Et}$ (93%)
 $\text{R}^1 = \text{Me}$, $\text{R}^2\text{-R}^3 = (\text{CH}_2)_2$, $\text{Z} = \text{CO}_2\text{Et}$ (92%)



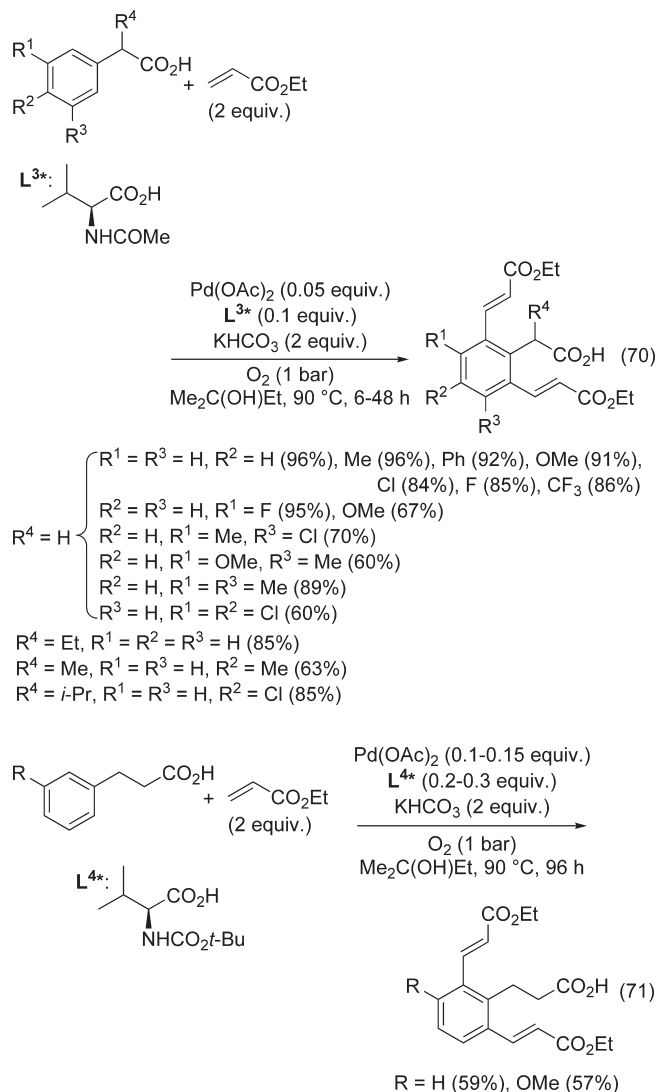
$\text{R} = \text{Me}$ (73% yield, 97% ee), Et (61% yield, 72% ee), H (69% yield, 58% ee)

In 2010, J.-Q. Yu's team performed the diolefination of phenylacetic acids (eq 70) or hydrocinnamic acids (eq 71).¹²⁹ With these latter substrates, higher catalyst loadings and extended reaction times were required to obtain efficient disubstitutions. In contrast to the above monoolefinations, these diolefinations occurred in the absence of benzoquinone, this

Scheme 21

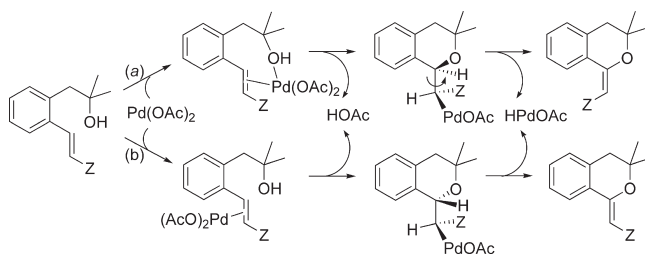


latter decreasing the reaction rate. Of note, the sequential C–H olefination of phenylacetic acids and, even, an iterative reaction were carried out, as shown in Scheme 21.

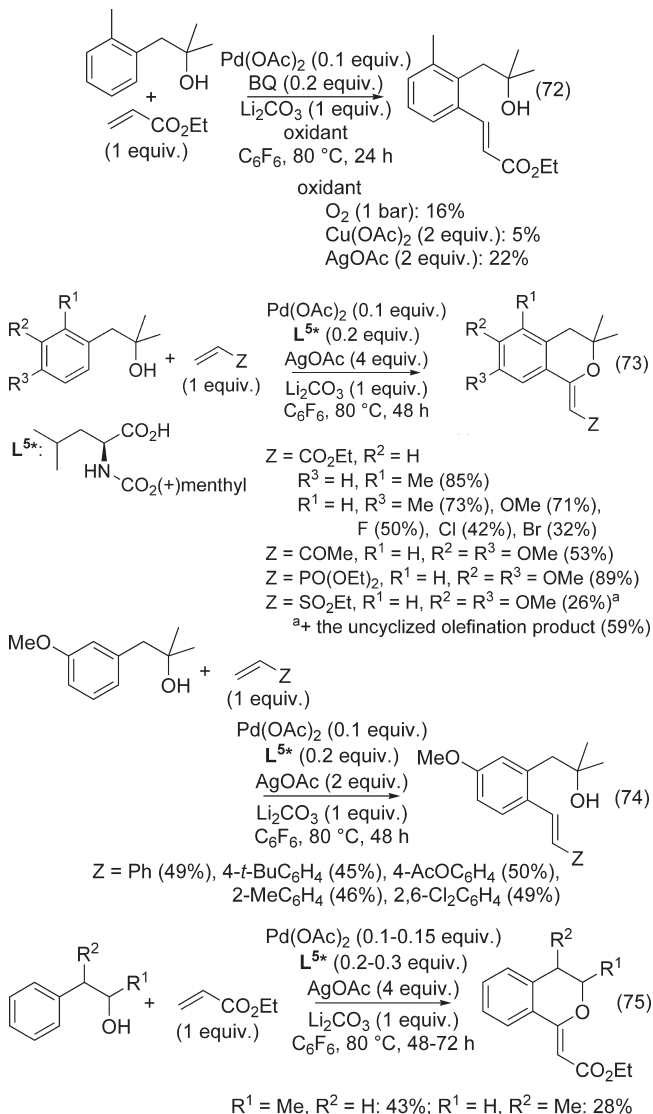


J.-Q. Yu's team also reported the use of homobenzylic hydroxyl groups to direct the olefination of arenes.¹³⁰ The reactions were first carried out with tertiary alcohols, that is, substrates which are prone to decomposition under Pd(II) catalysis.¹³¹ Extensive screening of solvents and bases led the authors to choose Li_2CO_3 as base and C_6F_6 as solvent but, initially, with moderate results (eq 72). The efficiency was greatly improved using, as above, mono-*N*-protected amino acids as ligands. Under these conditions, electron-deficient alkenes underwent, in most cases, a cascade reaction leading to pyrans (eq 73), whereas electron-neutral alkenes afforded the uncyclized coupling products (eq 74). The procedure has then been applied to primary and secondary alcohols (eq 75). Although such alcohols are sensitive to oxidation under Pd(II) catalysis,¹³² only low amounts of aldehyde or ketone were detected. As depicted in eq 73, this DHR procedure is compatible with halogenated arenes but afforded moderate yields. The authors pointed out that “it remains unclear whether the alcohol directing group coordinates as a neutral ligand or as an anionic ligand during the C–H activation”. The oxidative cyclization of the initial olefination product could arise via either *syn*- or *anti*-addition of the hydroxy

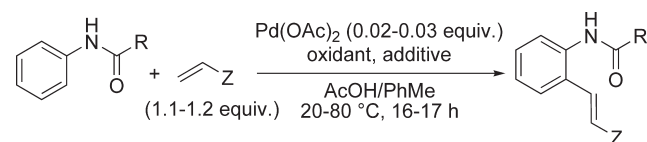
Scheme 22



as outlined in Scheme 22 (paths *a* and *b*, respectively). Since the elimination of HPdOAc occurs usually via a *syn*-process, the *Z*-geometry of the cyclized product indicates an antialkoxypalladation of the C=C bond (path *b*).¹³⁰



The *ortho*-selective oxidative coupling of anilides with olefins was performed in 2002–2010 by, successively, the teams of de Vries/van Leeuwen,¹¹⁵ Prasad,¹³³ Amatore/Jutand,¹³⁴ Liu/Guo,¹³⁵ Brown⁹ (Tables 6 and 7), and Lipshutz (eq 76, Table 8).²¹ All teams, except the last one, used $\text{Pd}(\text{OAc})_2$ as the catalyst in acidic organic solvents, changing $\text{Pd}(\text{OAc})_2$ for PdCl_2 , $\text{PdCl}_2(\text{PPh}_3)_2$, or Pd/C resulting in less than 10% conversion.¹¹⁵

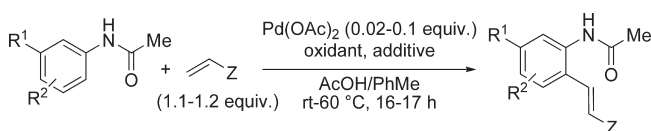
Table 6. Alkenylation of *N*-Phenylamides in AcOH/PhMe

entry	R	Pd equiv	oxidant, additive (equiv)	t °C	yield ^a %
Z = CO ₂ <i>n</i> -Bu					
1 ^{115,b}	Me	0.02	BQ (1)	20	54
2 ¹¹⁵	Me	0.02	BQ (1), TsOH (0.5)	20	72
3 ¹³⁵	Me	0.02	Cu(OAc) ₂ (0.05), TsOH (0.5) O ₂ (balloon)	80	(81)
4 ¹³⁵	Me	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	82
5 ¹¹⁵	Me	0.02	H ₂ O ₂ , TsOH (0.5)	20	29
6 ¹³⁵	Me	0.02	TsOH (0.5), O ₂ (balloon)	80	(49)
7 ¹³⁵	Et	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	(71)
8 ¹¹⁵	Ph	0.02	BQ (1), TsOH (0.5)	20	55
9 ¹³⁵	Ph	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	79
10 ¹¹⁵	H	0.02	BQ (1), TsOH (0.5)	20	(26)
Z = CO ₂ Me					
11 ¹³⁵	Me	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	57
Z = Ph					
12 ¹³⁵	Me	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	26

^a Isolated yield; GC, HPLC and ¹H NMR yields are in brackets.

^b Without PhMe as cosolvent.

The processes differ on the reoxidation method and the nature of additives. Stoichiometric amounts of BQ were at room temperature by de Vries, van Leeuwen, Prasad, Brown, and co-workers. It was noted that the used presence of TsOH increased the efficiency (Table 6, compare Entries 1 and 2). The de Vries/van Leeuwen team used 0.5 equiv of this additive (Table 6, Entries 2, 8 and 10; Table 7, Entries 1, 3, 4, 6 and 20), while the teams of Prasad and Brown increased its amount to 1 equiv (Table 7, Entries 7, 11–19, 23 and 24). Amatore/Jutand's team did not use TsOH and decreased the amount of BQ to 0.1 equiv but at the expense of the quantity of Pd(OAc)₂, BQ being electrochemically regenerated (Table 7, Entries 21 and 25). In fact, active Pd species can be regenerated, under suitable electrochemical conditions, even in the absence of BQ, with, however, a low efficiency (Table 7, Entry 22). Liu, Guo and co-workers used TsOH as an additive, with catalytic amounts of Cu(OAc)₂ and oxygen atmosphere instead of BQ, and a higher reaction temperature (Table 6, Entries 3, 4, 7, 9, 11, and 12; Table 7, Entries 2, 5 and 8–10). H₂O₂ as reoxidant is less efficient than BQ (Table 6, Entry 5 vs Entry 2). O₂/TsOH¹³⁵ and Cu(OAc)₂/TsOH¹¹⁵ were much less effective than the Cu(OAc)₂/O₂/TsOH association.¹³⁵ It was proposed¹¹⁵ that BQ has a dual role: reoxidant of Pd(0) and ligand stabilizing the different Pd species.¹³⁶ De Vries and van Leeuwen suspect that the beneficial effect of TsOH is due to the electrophilicity

Table 7. Alkenylation of *N*-Arylacetamides in AcOH/PhMe

entry	R ¹	R ²	Pd equiv	oxidant, additive (equiv)	t °C	yield ^a %
Z = CO ₂ <i>n</i> -Bu						
1 ¹¹⁵	H	<i>p</i> -Me	0.02	BQ (1), TsOH (0.5)	20	85
2 ¹³⁵	H	<i>p</i> -Me	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	91
3 ¹¹⁵	H	<i>o</i> -Me	0.02	BQ (1), TsOH (0.5)	20	(38)
4 ¹¹⁵	H	<i>p</i> -OMe	0.02	BQ (1), TsOH (0.5)	20	62
5 ¹³⁵	H	<i>p</i> -OMe	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	89
6 ¹¹⁵	H	<i>p</i> -CF ₃	0.02	BQ (1), TsOH (0.5)	20	(29)
7 ¹³⁵	H	<i>p</i> -Cl	0.05	BQ (1), TsOH·H ₂ O (1)	22	(25)
8 ¹³⁵	H	<i>p</i> -Cl	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	(11)
9 ¹³⁵	H	<i>p</i> -Br	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	14
10 ¹³⁵	H	<i>p</i> -NO ₂	0.03	Cu(OAc) ₂ (0.03), TsOH (0.33) O ₂ (balloon)	60	0
11 ¹³³	<i>m</i> -Cl	H	0.05	BQ (1), TsOH·H ₂ O (1)	22	(48)
12 ¹³³	<i>m</i> -Cl	<i>o</i> -Me	0.05	BQ (1), TsOH·H ₂ O (1)	22	(28)
13 ¹³³	<i>m</i> -Cl	<i>p</i> -Me	0.05	BQ (1), TsOH·H ₂ O (1)	22	(70)
14 ¹³³	<i>m</i> -Cl	<i>p</i> -OMe	0.05	BQ (1), TsOH·H ₂ O (1)	22	(82)
15 ¹³³	<i>m</i> -F	<i>p</i> -OMe	0.05	BQ (1), TsOH·H ₂ O (1)	22	(100)
16 ^{9,b}	F	H	0.03	BQ (1), TsOH (1)	rt	83
17 ¹³³	F	<i>p</i> -Me	0.05	BQ (1), TsOH·H ₂ O (1)	22	(95)
18 ^{9,b}	F	<i>p</i> -F	0.05	BQ (1), TsOH (1)	rt	60
19 ¹³³	Br	<i>p</i> -Me	0.05	BQ (1), TsOH·H ₂ O (1)	22	(67)
20 ¹¹⁵	Me	H	0.02	BQ (1), TsOH (0.5)	20	91
21 ^{134,c}	Me	H	0.1	BQ (0.1), <i>n</i> -Bu ₄ NBF ₄ C anode	rt	(82)
22 ^{134,c}	Me	H	0.1	<i>n</i> -Bu ₄ NBF ₄ , C anode	rt	(30)
23 ¹³³	Me	<i>p</i> -I	0.05	BQ (1), TsOH·H ₂ O (1)	22	(54)
Z = CO ₂ H						
24 ¹³³	Cl	<i>p</i> -OMe	0.05	BQ (1.3), TsOH·H ₂ O (1)	rt	70
Z = Ph						
25 ^{134,c}	Me	H	0.1	BQ (0.1), <i>n</i> -Bu ₄ NBF ₄ C anode	rt	(36)

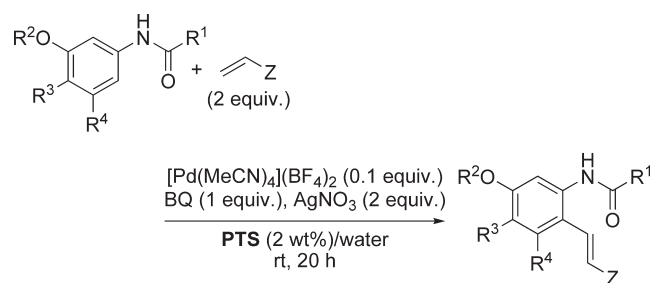
^a Isolated yield; GC, HPLC, and ¹H NMR yields are in brackets.

^b Reaction in 24 h. ^c Reaction in 4 h without PhMe as cosolvent.

increase of Pd(II) in its presence, resulting in faster metalation of ArH.¹¹⁵ Liu and Guo agree with this proposal and suggest the replacement of AcO[−] by TsO[−];¹³⁵ this could lead to cationic [PdOAc]⁺.¹¹⁵

Liu and Guo claimed that their procedure affords higher yields than the de Vries/van Leeuwen method, but this assertion is valid only for a few cases.¹³⁵ Indeed, they did not make comparison with results published by Prasad et al., who used experimental conditions similar to those of de Vries/van Leeuwen. Besides, Liu and Guo reported the absence of oxidative coupling using *N*-methyl-*N*-phenylacetamide as a substrate, an observation disclosed five years earlier by de Vries/van Leeuwen's team. This unreactivity agrees with the absence of *ortho*-palladation with PdCl₂¹³⁷ and Pd(OAc)₂⁶² of this compound, noticed as early as 1975 and 1981, respectively. This suggests the formation of

PhN(Pd⁺)COMe or as the intermediate leading to *o*-(AcOPd)C₆H₄NHCOMe from PhNHCOMe. *N*-(4-Nitrophenyl)acetamide was also reluctant to give the expected product

Table 8. Alkenylation of *m*-Alkoxy-functionalized Anilides and Ureas in Water²¹

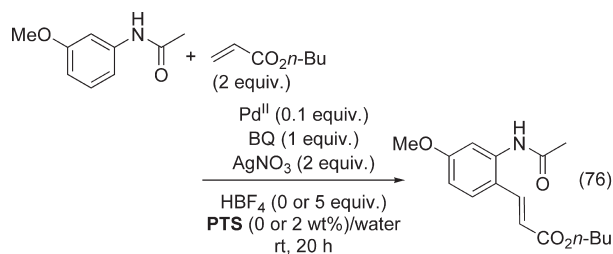
entry	R ¹	R ²	R ³	R ⁴	Z	yield %
1	Me	Me	H	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	76
2	Me	<i>n</i> -Pr	H	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	96
3	Me	<i>i</i> -Pr	H	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	90
4	Me	<i>i</i> -Pr	H	H	CO ₂ (CH ₂) ₁₁ Me	70
5	<i>n</i> -Pr	Me	H	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	80
6	<i>i</i> -Pr	Me	H	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	91
7	<i>i</i> -Pr	Me	H	H	CO ₂ (CH ₂) ₂ Cy	77
8	<i>i</i> -Pr	Me	H	H	CO ₂ (CH ₂) ₁₁ Me	80
9 ^a	<i>i</i> -Pr	Me	MeO	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	89
10 ^a	<i>i</i> -Pr	Me	MeO	H	CO ₂ CHMe(CH ₂) ₅ Me	80
11	<i>i</i> -Pr	Me	Me	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	72
12	<i>i</i> -Pr	Me	Me	H	CO ₂ (CH ₂) ₂ CHMe(CH ₂) ₃ <i>i</i> -Pr	81
13	<i>t</i> -Bu	Me	H	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	43
14	<i>i</i> -Pr	Me	H	OMe	CO ₂ (CH ₂) ₂ CHMe(CH ₂) ₃ <i>i</i> -Pr	80
15	NMe ₂	Me	H	H	CO ₂ CH ₂ CHEt(CH ₂) ₃ Me	74
16	NMe ₂	Me	H	H	CO ₂ CHMe(CH ₂) ₅ Me	76

^a Reaction time: 48 h.

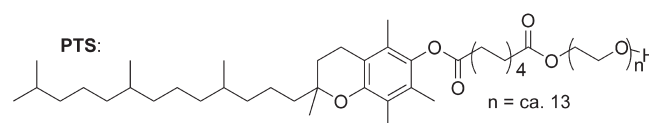
(Table 7, Entry 10); this contrasts with the reactivity of nitrobenzene shown in Table 5, Entries 10 and 11.

Over the past few years, the Lipshutz team reported a variety of Pd-catalyzed reactions in water containing the designer surfactant polyoxyethanyl α -tocopheryl sebacate (PTS).¹³⁸ Very recently, this team has used such a medium to perform the DHR, at room temperature, of *m*-alkoxy-functionalized anilides with α,β -unsaturated esters.²¹ As exemplified in eq 76, the cross-coupling occurs selectively at the *ortho*' position and without external acid, when the cationic complex Pd(MeCN)₄(BF₄)₂ is used as the catalyst with a mixture of benzoquinone and silver nitrate as oxidant. In the absence of PTS, that is, on water,¹³⁹ the yield is depressed. A range of DHRs has been carried out under the optimum conditions (Table 8), the coupling being limited to anilides with a *m*-alkoxy substituent, no reaction occurring from isomeric *p*-alkoxy analogues. Interestingly, an anilide with methoxy substituents in *meta* and *meta*' positions has been functionalized in a single position (Table 8, Entry 14). The efficiency of this Lipshutz external acid-free procedure is due to the use of a cationic palladium catalyst. It is necessary to point out an uncited paper, published two years earlier by Lloyd-Jones, Booker-Milburn, and co-workers, who disclosed DHRs using Pd(MeCN)₄(OTf)₂ as the catalyst in the absence of added acid (see below eq 82).¹⁴⁰ No recycling of the catalyst was mentioned in the Lipshutz report, and ethyl acetate was used to extract the cross-coupling adducts. These two points

lead to the decrease of the competitiveness of the procedure, since the main advantage of the use of water as solvent for homogeneous metal-catalyzed reactions requiring a workup with an organic solvent is the recycling of the catalyst.¹⁴¹

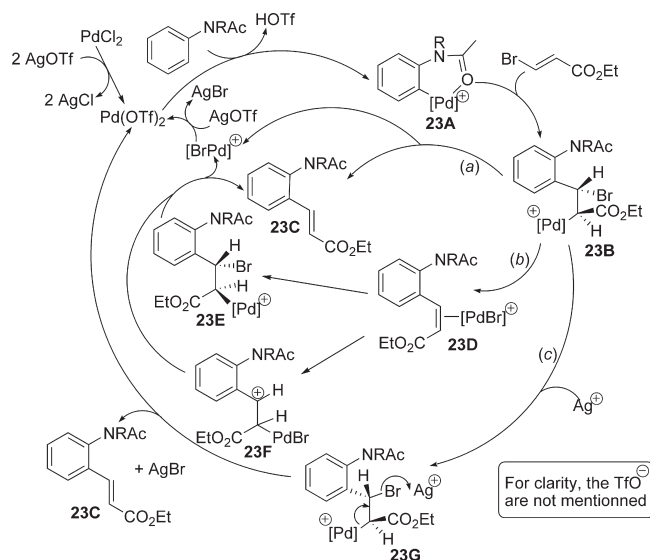


without PTS { Pd(OAc)₂ with HBF₄: 72%
Pd(OAc)₂ without HBF₄: trace
[Pd(MeCN)₄](BF₄)₂ without HBF₄: 66%
with PTS { Pd(OAc)₂ with HBF₄: 95%
[Pd(MeCN)₄](BF₄)₂ without HBF₄: 85%

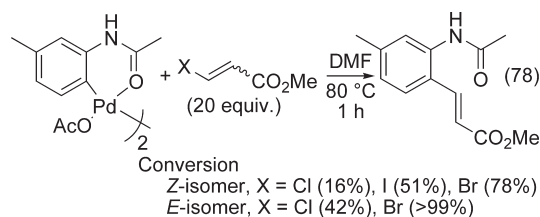
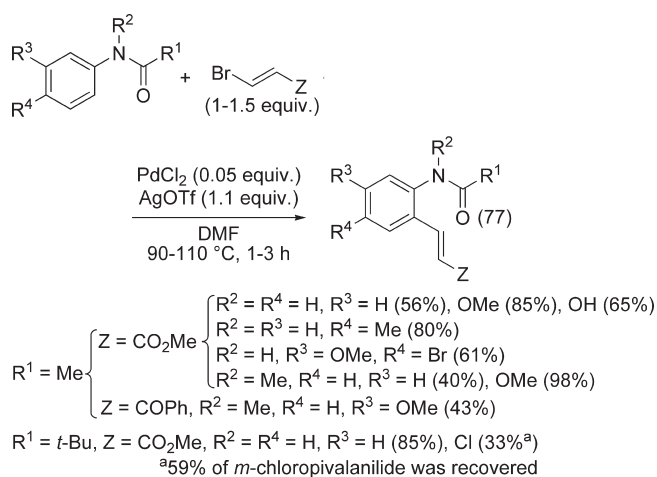


The *ortho*-selective oxidative alkenylation of *N*-acylated anilines has also been reported by Zaitsev and Daugulis, but using methyl (*E*)-2-bromopropenoate as olefin, and PdCl₂ as the catalyst in the presence of a stoichiometric amount of AgOTf, at 90–110 °C in DMF.¹⁴² As shown in eq 77, this method is rather functional group tolerant and led also to the *o*-alkenylation of *N*-methyl-*N*-arylacetamides. The authors proposed (i) an exchange between AgOTf and PdCl₂ leading to a Pd catalyst with a less coordinating anion, (ii) on the basis of kinetic isotope effects, a turnover-limiting step depending of C–H bond cleavage, (iii) a catalytic cycle similar to that of the usual DHRs except for the step leading to the isolated compound, which would be a β -Br elimination instead of a β -H elimination, and (iv) an exchange of anion between the resulting PdBr species and AgOTf, silver being recovered as AgBr in yield higher than 90%. Having observed the inhibition of the reaction by addition of the coupling product, the authors suggested that this could explain the moderate conversion of the less reactive substrates, as depicted in eq 77 for the DHR of *m*-chloropivalanilide. We suspect that this is due to trapping of AgOTf by this additive. On the basis of the authors' remarks and literature reports, we tentatively construct a scheme describing the mechanism of this oxidative coupling process, which would preserve the initial oxidation state of palladium all along the catalytic cycle (Scheme 23). The reaction of PdCl₂ with excess AgOTf leads to Pd(OTf)₂,¹⁴³ this species being plausibly under a cationic form,¹⁴⁴ especially in a dissociating solvent such as DMF.¹⁴⁵ Pd(II)-mediated activation of the *ortho* C–H bond of the anilide gives **23A**, which affords **23B** through the insertion of the C=C bond of the bromoolefin into its C–Pd bond. The stereochemistry of the C=C bond of the isolated coupling product being *E*, it is now necessary to examine the plausible ways leading to this isomer, that is, **23C**. An anti- β -Br elimination from **23B** can be first considered (path *a*). The stereochemistry of the elimination of PdCl species from PdC–CCl systems has been studied: nonstereospecific eliminations have been documented by Henry,¹⁴⁶ whereas Lu and co-workers have exemplified anti- β -Br eliminations,¹⁴⁷ but both teams performed their reactions in

Scheme 23

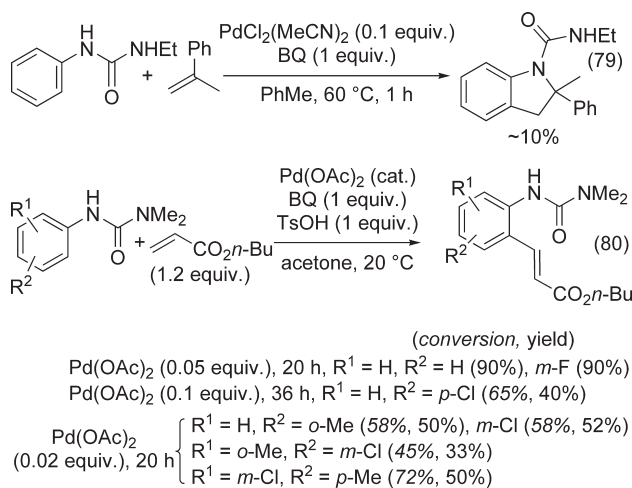


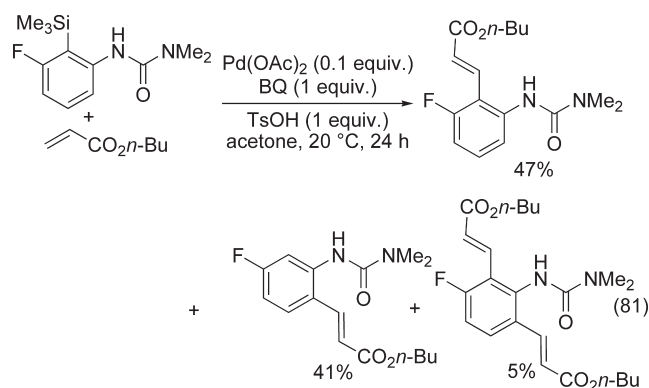
AcOH in the presence of overstoichiometric amounts of LiCl. The excess of halide ions can make the Pd coordinatively saturated and, thus, could preclude the syn- β -Br eliminations. Under the experimental conditions of Zaitsev and Daugulis, no halide ions were added. Moreover, the authors have also obtained the *E* product from the reaction of a **23A**-type complex with methyl (*E* or *Z*)-2-halopropenoates, the reactivity of the haloolefin being $E > Z$ and $\text{Br} > \text{I} > \text{Cl}$ (eq 78).¹⁴⁸ Given these remarks, other reactive pathways occurring from **23B** have to be considered. A syn- β -Br elimination would lead to the *Z* product, but this compound could remain coordinated to palladium, giving **23D** (path *b*). Spencer et al. have proposed that the PdCl_2 -catalyzed *Z* to *E* isomerization of alkenes which do not have available hydrogen in the allylic position occurs either through trans addition of the catalyst to the $\text{C}=\text{C}$ bond followed by rotation and syn- β -elimination of PdCl_2 , or via a carbocation.¹⁴⁹ Such a proposal applied to **23D** would lead to **23C** through the formation of **23E** or **23F**, respectively. We suspect another mechanism which involves the interaction of **23B** with AgOTf as depicted with **23G** to directly afford **23C**, AgBr and $\text{Pd}(\text{OTf})_2$ (path *c*).



It is worth stressing the difference of reactivity between the procedures which use anilides and either olefins or bromoolefins. *N*-Methyl-*N*-phenylacetamide did not react with *n*-butyl propenoate,^{115,135} but the reaction succeeded with methyl (*E*)-2-bromopropenoate, such coupling occurring also with *N*-(3-methoxyphenyl)-*N*-methylacetamide and (*E*)-1-phenyl-3-bromo-2-propenone (eq 77).¹⁴² This difference could be ascribed to the dissimilar experimental conditions. The absence of *ortho*-palladation of *N*-methyl-*N*-phenylacetamide with PdCl_2 ¹³⁷ and $\text{Pd}(\text{OAc})_2$ ⁶² has been previously mentioned. Given the above remarks, it could be of interest to investigate the use of $\text{PdCl}_2/\text{AgOTf}$ for the *ortho*-palladation of *N*-methyl-*N*-phenylacetamide and its catalytic DHR with *n*-butyl propenoate.

In 2008, Lloyd-Jones, Booker-Milburn, and co-workers reported the reaction of *N*-ethyl-*N*'-phenyl urea with α -methylstyrene in PhMe, using 0.1 equiv of $\text{PdCl}_2(\text{MeCN})_2$ as the catalyst (eq 79). This led to the unexpected depicted indoline, with no more than ~10% yield, despite the presence of a stoichiometric amount of BQ.¹⁴⁰ In contrast, Brown et al. obtained the usual DHR compounds from various *N*-dimethyl-*N*'-aryl ureas and butyl acrylate using, in acetone, the above $\text{Pd}(\text{OAc})_2/\text{BQ}/\text{TsOH}$ method (eq 80).⁹ In the presence of an aryl SiMe_3 substituent, some cleavage and substitution of this group were observed (eq 81).^{9,19,150} From quantitative comparisons between the DHRs of anilides and aryl ureas, Brown's team showed the higher reactivity of the latter. They also noted that palladacycles are formed faster from aryl ureas than from anilides. According to the authors,⁹ this is significant information because the turnover-limiting step is the formation of the palladacycle.¹¹⁵ Nevertheless, we have to point out that the comparisons were made in acetone, whereas the oxidative substitutions of anilides were performed in AcOH or AcOH/PhMe (Tables 6 and 7); thus, the involved palladium intermediates could be different.





The external acid-free aqueous procedure recently disclosed by Nishikata and Lipshutz for DHRs of anilides (eq 76; Table 8, Entries 1–14) is also effective for the DHR of *N*-dimethyl-*N'*-(3-methoxyphenyl) urea (Table 8, Entries 15 and 16).²¹

Lloyd-Jones, Booker-Milburn, and co-workers suspected that the indoline shown in eq 79 is produced “via an interrupted Heck-type process”,¹⁴⁰ in other words an interrupted DHR, because of the intramolecular reaction of a palladium intermediate with NH instead of its usual evolution via the β -H elimination.¹⁵¹ This urges them to improve such a cyclization pathway in studying the coupling of 1,1-dimethyl-3-phenylurea with (*E*)-ethyl penta-2,4-dienoate using the de Vries/van Leeuwen procedure at 50 °C.¹⁴⁰ Using the usual AcOH/PhMe mixture, the expected indoline was obtained in no more than 37% yield in 24 h, but in THF containing either 3 Å MS or Ac₂O, the yield in 4 h increased to 80–82%, Ac₂O and 3 Å MS acting as drying agents. After testing a range of acids, in lieu of TsOH, and solvents, a variety of *N*-aryl ureas have been reacted with electron-deficient dienes under conditions shown in the equation of Table 9. Fair to high yields were obtained except when the aryl unit was substituted with a CF₃ or *o*-Me group (Entries 4, 7 and 8). A domino reaction leading to a tricyclic compound occurred from the reaction of *N*-ethyl-*N'*-phenyl urea with (*E*)-ethyl penta-2,4-dienoate (Entry 15). An indoline was also isolated from acetanilidine but with a poor yield (Entry 16), highlighting the activating effect of the urea unit. The requirement of TsOH in the reaction medium led the authors to perform reactions catalyzed by Pd(MeCN)₂(OTs)₂ in the absence of TsOH. Under these conditions, the indoline was again effectively obtained in THF containing either Ac₂O or 3 Å MS, while the absence of additive or the use of 1 equiv of AcOH as additive was detrimental to the yield (eq 82). These results demonstrated that Ar–H activation can occur under mild conditions, that is, relatively non acidic conditions and 50 °C for 2–4 h, when highly electrophilic Pd(II) species are used as catalysts.

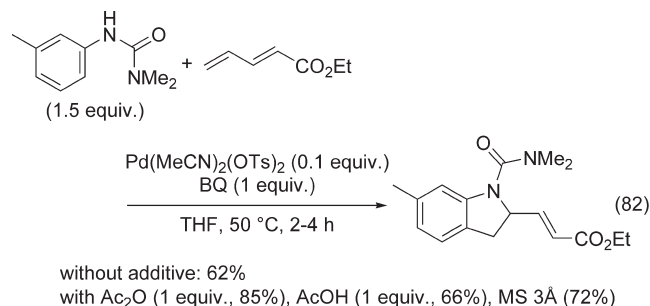
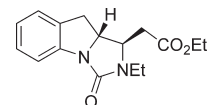


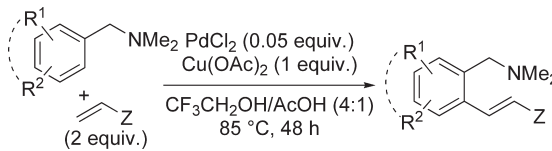
Table 9. Indoline Formation under Lloyd-Jones/Booker-Milburn's Conditions¹⁴⁰

entry	R ¹	R ²	Z	yield %
1	NMe ₂	H	CO ₂ Et	82
2	NMe ₂	<i>m</i> -Me	CO ₂ Et	90 ^a
3	NMe ₂	<i>m</i> -OMe	CO ₂ Et	53 ^a
4	NMe ₂	<i>m</i> -CF ₃	CO ₂ Et	0
5	NMe ₂	<i>p</i> -Me	CO ₂ Et	62
6	NMe ₂	<i>p</i> -OMe	CO ₂ Et	52
7	NMe ₂	<i>p</i> -CF ₃	CO ₂ Et	25
8	NMe ₂	<i>o</i> -Me	CO ₂ Et	0
9	NMe ₂	H	SO ₂ Ph	45
10	NMe ₂	H	CN	70
11	NMe ₂	H	NO ₂	70
12	NMe ₂	H	COMe	48
13	NMe ₂	H	Ph	45
14		H	CO ₂ Et	72
15	NHEt	H	CO ₂ Et	^b
16	Me			15

^a Substitution in *ortho*' position. ^b Formation (43% yield) of



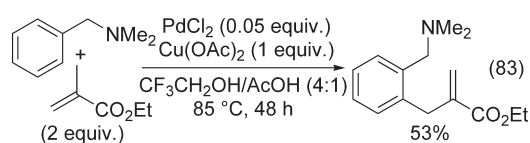
The *ortho*-palladation of *N,N*-dimethylbenzylamine was reported in 1966 by Cope and Friedrich,¹⁵² the reaction of the corresponding complex with styrene being disclosed, without experimental details, in 1969 by Tsuji.¹⁵³ To our knowledge, it took six years for the appearance of another report on this subject, M. Julia et al. reporting the reaction of a similar complex with ethyl acrylate,^{39,154} and more than a quarter of a century for the publication of a catalytic procedure, this being proposed by Shi's team.¹⁵⁵ From the exploration of various Pd(0) reoxidants including Cu(II) salts, O₂, BQ, PhI(OAc)₂, and solvents, it appeared that the use, at 85 °C, of 1 equiv of Cu(OAc)₂ and 16 equiv of AcOH in CF₃CH₂OH afforded the optimum results. These conditions have been applied to a set of olefins with an efficiency sensitive to their substitution (Table 10). Indeed, styrene led, at the best, to traces of the expected product (Entry 7), (*E*)-ethyl but-2-enoate gave no more than 10% of the product, and ethyl methacrylate afforded ethyl 2-(2-((dimethylamino)methyl)benzyl)acrylate (eq 83) instead of the more conjugated isomer. This oxidative coupling method is however compatible with esters and amides functions as well as various substituents on the aryl ring, even in *o*-position (Entries 8 and 11) or an acetal (Entry 17). The olefination of different *N*-substituted benzylamines has been

Table 10. Olefination of *N,N*-Dimethylbenzylamines under Shi's Conditions¹⁵⁵


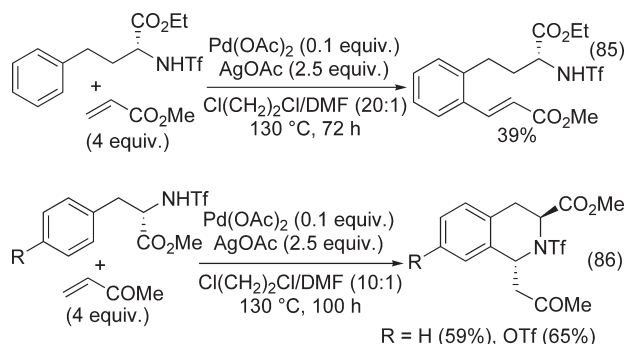
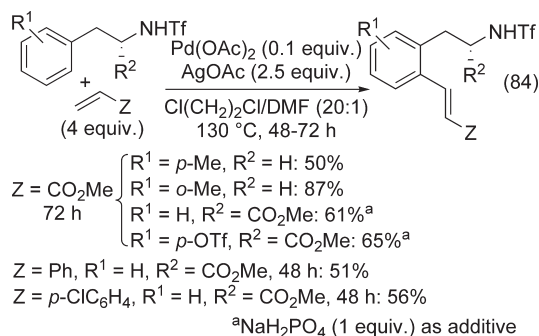
entry	R ¹	R ²	Z	yield %
1	H	H	CO ₂ <i>n</i> -Bu	86
2	H	H	CO ₂ Et	85
3	H	H	CO ₂ Me	66
4	H	H	CO ₂ Bn	86
5	H	H	CO ₂ NH ₂	82
6	H	H	CON(CH ₂) ₄	54
7	H	H	Ph	<5
8	<i>o</i> -Me	H	CO ₂ <i>n</i> -Bu	75
9	<i>m</i> -Me	H	CO ₂ <i>n</i> -Bu	75 ^a
10	<i>p</i> -Me	H	CO ₂ <i>n</i> -Bu	70
11	<i>o</i> -OMe	H	CO ₂ <i>n</i> -Bu	75
12	<i>p</i> -OMe	H	CO ₂ <i>n</i> -Bu	76
13	<i>m</i> -F	H	CO ₂ <i>n</i> -Bu	86 ^a
14 ^b	<i>p</i> -F	H	CO ₂ <i>n</i> -Bu	76
15 ^b	<i>p</i> -Cl	H	CO ₂ <i>n</i> -Bu	85
16 ^b	<i>p</i> -CF ₃	H	CO ₂ <i>n</i> -Bu	74
17	<i>m,p</i> -O(CH ₂) ₂ O	H	CO ₂ <i>n</i> -Bu	80 ^a
18	<i>m,p</i> -(CH) ₄	H	CO ₂ <i>n</i> -Bu	85 ^a

^a Mixture of *m,o*- and *m,o'*-isomers, main substitution occurring in the less hindered position (*o'*-position). ^b Using 0.1 equiv of PdCl₂.

explored, but all of them afforded lower yields. The requirement of AcOH under the above experimental conditions urged the authors to test a cationic catalyst, Pd(MeCN)₄(BF₄)₂, in the absence of AcOH. For the reaction corresponding to Table 10, Entry 1, the yield with this system was only 34%, but increased to 82% for a reaction in the presence of AcOH. Consequently, it has been proposed that "the role of the AcOH is most likely to tune the concentration of the free amine moiety so that the amine promotes directed Pd-catalyzed C–H cleavage to realize this transformation".¹⁵⁵ Studies using a deuteriated *N,N*-dimethylbenzylamine have indicated that the cleavage of the Ar–H bond is involved in the rate-determining step.¹⁵⁵



Recently, J.-Q. Yu and co-workers, using AgOAc as reoxidant in a DMF/ClCH₂CH₂Cl mixture, have performed the *ortho*-alkenylation of arenes substituted by a C₂ or C₃ alkyl tether terminated by a NHTf group (eqs 84 and 85).¹⁵⁶ Dialkenylated products were formed in some cases, their amount decreasing in the presence of NaH₂PO₄. Vinyl ketones provided tetrahydroisoquinolines via alkenylation and subsequent aza-Michael addition (eq 86).



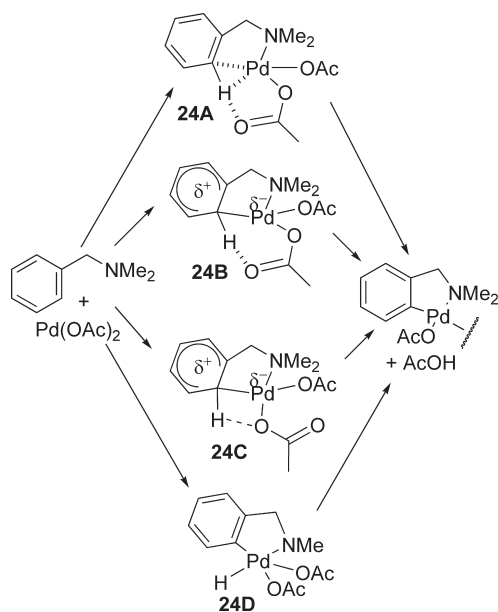
Given the above examples, it seems that no example of olefination of aryl acetate is reported in the literature. In fact, Cameron and Kilner revealed that the *ortho*-metalation of such compounds using PdCl₂ or K₂PdCl₄ did not occur.¹³⁷

Before the end of this section, it is worthwhile to briefly comment on the mechanism of the *ortho*-palladation. Indeed, the metalation of the substrate, which involves the coordination of the exocyclic heteroatom to palladium, leads to the key intermediate which determines the regioselectivity. In Scheme 9, we show two proposals for the insertion of Pd(OAc)₂ into a C–H bond of benzene. These proposals were retained, among others, as plausible for the palladation of substrates bearing a coordinating substituent.⁶⁶ Distinguishing between the possibilities by experiments being virtually impossible, Davies and Macgregor's teams performed DFT calculations to determine the role of acetate and the pathways leading to the metalation of *N,N*-dimethylbenzylamine with Pd(OAc)₂.¹⁵⁷ According to them, this reaction involves an agostic interaction of Pd with the C–H bond in *ortho* position as depicted in **24A**, rather than the Wheland-type intermediate **24B**¹⁵⁸ (Scheme 24). **24A** exhibits also a H-bonding interaction between the *ortho*-H and an acetate; this makes easier the deprotonation which releases AcOH and the *ortho*-palladated species. Much higher energy are required for other intermediates¹⁵⁷ such as **24C**¹⁵⁹ which involves a deprotonation via a four-membered transition state instead of the above six-membered transition state, or **24D**¹⁶⁰ which is a Pd(IV) species. A Wheland-type intermediate is, nevertheless, speculated for the *ortho*-palladation of anilides²¹ and aryl ureas.¹⁶¹

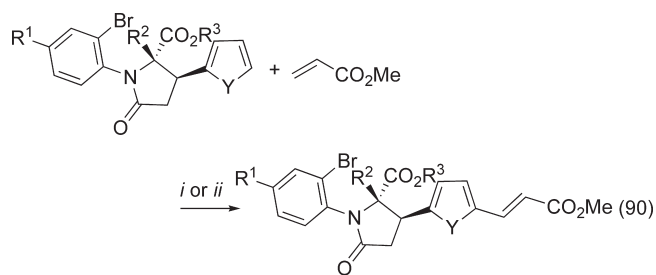
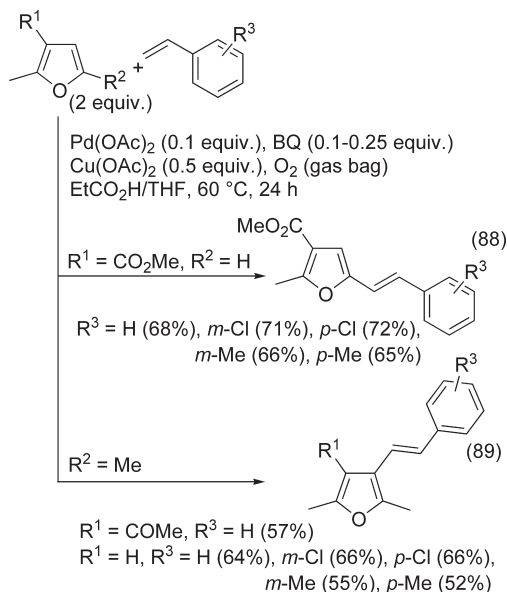
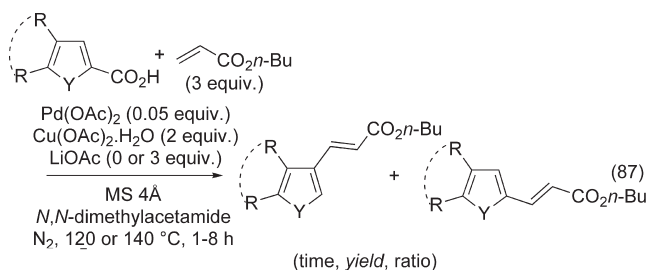
3.2. Heteroarenes

3.2.1. O-Arenes. In 1976, Kozhevnikov disclosed the Pd(OAc)₂-catalyzed oxidative coupling of furan with ethylene in low yields, using DMF as the solvent, Cu(OAc)₂ as the reoxidant and CaCl₂ as additive (Table 11, Entry 1).⁷⁵ Subsequently, DHRs

Scheme 24



have been carried out with olefins substituted with various electron-withdrawing groups (Table 11), and with substituted furans (Tables 12 and 13). Various $\text{Cu}(\text{OAc})_2/\text{O}_2$ combinations in dioxane/AcOH (Table 11, Entries 4, 5, 12, and 13)^{76,162} or DMF (Table 12, Entries 9 and 10)¹⁶⁵ have been tested by the teams of Fujiwara and Miura, but were ineffective when using a low quantity of the copper salt. The last team observed that alkenylation of furan- and benzofuran-2-carboxylic acids was accompanied by decarboxylation (eq 87);¹⁶⁶ this contrasts with the reactivity of benzoic acids (eqs 63 and 64). Experiments in DMF were sometimes performed with LiOAc as additive. According to Miura et al., one of the plausible roles of LiOAc is to provide AcO^- as a ligand to stabilize the $\text{Pd}(0)$ intermediates.¹⁶⁵ Note that Kozhevnikov who, 30 years before, observed the promotion of the oxidative couplings by AcO^- , suspected its participation in the formation of ArPdOAc from ArH (Scheme 9, path a).⁶⁵ In 2009, we disclosed an efficient procedure for the DHR of furans with styrenes, which uses the $\text{BQ}/\text{Cu}(\text{OAc})_2/\text{O}_2$ system as reoxidant in $\text{Et}_2\text{O}/\text{EtCO}_2\text{H}$ or $\text{THF}/\text{EtCO}_2\text{H}$, and is compatible with various functions (Table 11, Entries 14 and 15; Table 13, Entries 3–18; eqs 88 and 89), EtCO_2H as cosolvent leading to higher yields than AcOH.¹⁶⁴ $\text{Cu}(\text{OAc})_2$ in DMF and air atmosphere has been recently used by Kar and co-workers to perform, under Pd-catalyzed conditions, the DHRs shown in eq 90 (*i* conditions).^{167,168} With substrates having $\text{R}^2 = \text{CO}_2\text{Et}$ and $\text{R}^3 = \text{Et}$, the reaction occurred even in the absence of any oxidant (eq 90, *ii* conditions). These last conditions led however to the usual Heck reaction, that is, coupling at the level of the ArBr unit when $\text{R}^2 = \text{H}$ and $\text{R}^3 = \text{Me}$. According to the authors, the absence of the Heck coupling when $\text{R}^2 = \text{CO}_2\text{Et}$ and $\text{R}^3 = \text{Et}$ is due to the steric hindrance caused by the two esters.¹⁶⁷ No explanation was provided by the authors concerning their DHRs in the absence of added reoxidant. The yields were however moderate (no more than 55%), and recovery of starting substrate was not mentioned. Therefore, we suspect some regeneration of active Pd species via the participation of the arylbromide unit.¹⁶⁹



i: $\text{Pd}(\text{OAc})_2$ (0.05 equiv.), $\text{Cu}(\text{OAc})_2$ (2–3 equiv.), DMF, air atmosphere, 90–100 °C, 8–9 h

$\text{Y} = \text{O}$ $\begin{cases} \text{R}^1 = \text{H} \begin{cases} \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}: 57\% \\ \text{R}^2 = \text{CO}_2\text{Et}, \text{R}^3 = \text{Et}: 59\% \end{cases} \\ \text{R}^1 = \text{Me} \begin{cases} \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}: 52\% \\ \text{R}^2 = \text{CO}_2\text{Et}, \text{R}^3 = \text{Et}: 59\% \end{cases} \end{cases}$

$\text{Y} = \text{S}$ $\begin{cases} \text{R}^1 = \text{H} \begin{cases} \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}: 52\% \\ \text{R}^2 = \text{CO}_2\text{Et}, \text{R}^3 = \text{Et}: 53\% \end{cases} \\ \text{R}^1 = \text{Me} \begin{cases} \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}: 54\% \\ \text{R}^2 = \text{CO}_2\text{Et}, \text{R}^3 = \text{Et}: 57\% \end{cases} \end{cases}$

ii: $\text{Pd}(\text{OAc})_2$ (0.05 equiv.), PPh_3 , $n\text{-Bu}_4\text{NCl}$ (cat.), NaOAc, DMF, argon atmosphere, 110–120 °C, 8–12 h

$\text{R}^2 = \text{CO}_2\text{Et}, \text{R}^3 = \text{Et}$

$\text{Y} = \text{O}$ $\begin{cases} \text{R}^1 = \text{H}: 36\% \\ \text{R}^1 = \text{Me}: 55\% \end{cases}$

$\text{Y} = \text{S}$ $\begin{cases} \text{R}^1 = \text{H}: 35\% \\ \text{R}^1 = \text{Me}: 42\% \end{cases}$

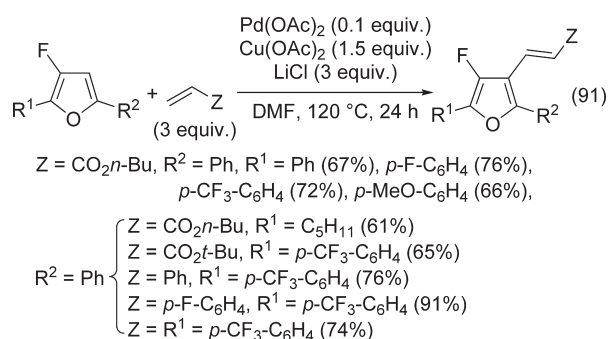
Zhao, Zhu, and their co-workers also used DMF as the solvent and $\text{Cu}(\text{OAc})_2$ as the oxidant but with LiCl as the additive rather

Table 11. Alkenylations of Furan

entry	Z	furan equiv	Pd equiv	oxidant, additive (equiv)	solvent (ratio)	<i>t</i> °C; time, h	yield % ^a
1 ⁷⁵	H	4.5	0.033	Cu(OAc) ₂ (1.67) CaCl ₂ (0.67)	DMF ^b	96; 2	M (13)
2 ⁶⁵	H	5	0.025	H ₆ PMo ₉ V ₃ O ₄₀ (0.125) LiOAc (1.5), air (1 bar)	DMF	96; 3	M (3.3) ^c
3 ⁶⁵	H	5	0.025	H ₆ PMo ₉ V ₃ O ₄₀ (0.125) LiOAc (1.5), air (1 bar)	DMF/AcOH (1:1)	96; 3	M (4)
4 ^{76,162}	CO ₂ Me	1	0.02	Cu(OAc) ₂ (0.1) O ₂ (1 bar)	dioxane/AcOH (4:1)	100; 8	M (7) D (1)
5 ^{76,162}	CO ₂ Me	1	0.02	Cu(OAc) ₂ (2.05) O ₂ (1 bar)	dioxane/AcOH (4:1)	100; 8	M (20) D (9)
6 ¹⁰⁰	CO ₂ Et	2	0.07	H ₇ PMo ₈ V ₄ O ₄₀ (0.013) O ₂ (balloon) AcCH ₂ Ac (0.07) NaOAc (0.05)	AcOH	30; 12	M 62 D 10
7 ⁹²	CO ₂ Et	1	0.005	<i>t</i> -BuOOH (1.3) BQ (0.05)	Ac ₂ O/AcOH (1:3)	50; 12	M 56 D 10
8 ⁹⁹	CO ₂ Et	1	0.05 ^d	PhCO ₃ <i>t</i> -Bu (1)	AcOH	100; 3	M 53
9 ¹⁶³	CO ₂ <i>n</i> -Bu	4	0.1	AgOAc (2) pyridine (4)	DMF	120; 12	M 76
10 ¹⁶³	CONMe ₂	4	0.1	AgOAc (2) pyridine (4)	DMF	120; 12	M 64
11 ⁹²	COMe	1	0.005	<i>t</i> -BuOOH (1.3) BQ (0.05)	Ac ₂ O/ AcOH (1:3)	50; 12	M 72
12 ^{76,162}	CN	1	0.02	Cu(OAc) ₂ (0.5) O ₂ (1 bar)	dioxane/ AcOH (4:1)	100; 8	M (21) D (13)
13 ^{76,162}	CN	1	0.02	Cu(OAc) ₂ (2) air (1 bar)	dioxane/ AcOH (4:1)	100; 8	M (39) D (21)
14 ¹⁶⁴	Ph	0.45	0.1	Cu(OAc) ₂ (0.5) BQ (0.1), O ₂ (gas bag)	EtCO ₂ H/Et ₂ O (1:1)	40; 24	D 50
15 ¹⁶⁴	4- <i>t</i> -BuC ₆ H ₄	0.45	0.1	Cu(OAc) ₂ (0.5) BQ (0.1), O ₂ (gas bag)	EtCO ₂ H/Et ₂ O (1:1)	40; 24	D 60

^a Isolated yield; GC, HPLC, and ¹H NMR yields are in brackets. ^b In the original report, the solvent was named DMFA without meaning of this abbreviation, but, according to a subsequent report from the team, DMFA was for dimethylformamide. ^c Plus 3-vinylfuran (0.6%). ^d Pd(OBz)₂ was used as the catalyst.

than LiOAc, for the alkenylation of trisubstituted furans having a fluor at C3 position (eq 91).¹⁷⁰



In 1978, Kozhevnikov et al. used H₆PMo₉V₃O₄₀ with LiOAc instead of their previous Cu(OAc)₂/CaCl₂ system; a low

efficiency of the vinylation of furan was again observed (Table 11, Entries 2 and 3).⁶⁵ These authors mentioned that the procedure could be carried out with catalytic amounts of the heteropoly acid, seeing that oxygen is provided in the mixture. This has been fulfilled, 25 years later, by Ishii's team, a mixture of mono- and diaddition products being obtained in fair yields, under an atmospheric pressure of oxygen and in the presence of catalytic amounts of both acetylacetone and sodium acetate as additives (Table 11, Entry 6).¹⁰⁰

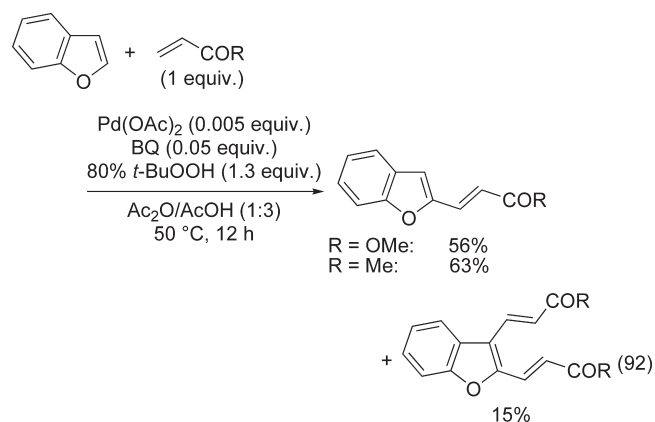
Peroxidic species have also been used as oxidants, first by Tsuji and Nagashima who performed the reaction in AcOH with a perester (Table 11, Entry 8; Table 12, Entries 1 and 8),⁹⁹ and second by Fujiwara and co-workers, who used *t*-BuOOH in association with a catalytic amount of benzoquinone (Table 11, Entries 7 and 11; Table 12, Entries 2, 5–7; eq 92).⁹² In fact, BQ in an acidic medium¹⁷¹ can be also used

Table 12. Alkenylations of 2-Substituted Furans with α,β -Unsaturated Esters, *N,N*-Dimethylacrylamide Methyl Vinyl Ketone, Acrylaldehyde, and Acrylonitrile

entry	Z	furan equiv	Pd equiv	oxidant (equiv), additive (equiv)	solvent (ratio)	<i>t</i> °C; time, h	yield % ^a
R = Me							
1 ^{99,b}	CO ₂ Et	1	0.05	PhCO ₃ <i>t</i> -Bu (1)	AcOH	100; 3	67
2 ⁹²	CO ₂ Et	1	0.005	<i>t</i> -BuOOH (1.3) BQ (0.05)	Ac ₂ O/AcOH (1:3)	50; 12	75
3 ¹⁶³	CO ₂ <i>n</i> -Bu	4	0.1	AgOAc (2) pyridine (4)	DMF	120; 12	90
4 ¹⁶³	CONMe ₂	4	0.1	AgOAc (2) pyridine (4)	DMF	120; 12	76
5 ⁹²	COMe	1	0.005	<i>t</i> -BuOOH (1.3) BQ (0.05)	Ac ₂ O/AcOH (1:3)	50; 12	73
6 ⁹²	CHO	1	0.005	<i>t</i> -BuOOH (1.3) BQ (0.05)	Ac ₂ O/AcOH (1:3)	50; 12	20
7 ⁹²	CN	1	0.005	<i>t</i> -BuOOH (1.3) BQ (0.05)	Ac ₂ O/AcOH (1:3)	50; 12	23
R = CHO							
8 ^{99,b}	CO ₂ Me	1	0.05	PhCO ₃ <i>t</i> -Bu (1)	AcOH	100; 3	34
R = <i>t</i> -Bu							
9 ¹⁶⁵	CO ₂ <i>n</i> -Bu	0.33	0.05	Cu(OAc) ₂ ^c (2) LiOAc (3) air (1 bar)	DMF	120; 2	57 (67)
R = 1,3-dioxolan-2-yl							
10 ¹⁶⁵	CO ₂ <i>n</i> -Bu	0.33	0.05	Cu(OAc) ₂ ^c (2) LiOAc (3) air (1 bar)	DMF	120; 8	40 (53)

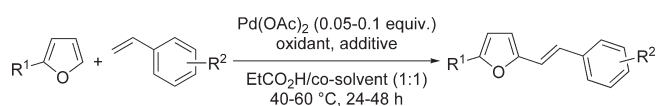
^a Isolated yield; GC, HPLC, and ¹H NMR yields are in brackets. ^b Pd(OBz)₂ was used as the catalyst. ^c Cu(OAc)₂·H₂O was used.

as the sole oxidant (Table 13, Entries 1 and 2).¹⁶⁴ Recently, AgOAc as oxidant with pyridine as additive allowed, in DMF, effective Pd-catalyzed oxidative couplings of furans with α,β -unsaturated esters and amides (Table 11, Entries 9 and 10; Table 12, Entries 3 and 4).¹⁶³



With BQ as the sole reoxidant, we noticed a drastic effect of the solvent mixture.¹⁷² While both Pd(OAc)₂- and

Pd(OCOCF₃)₂-catalyzed reactions of 2-methylfuran with styrene in Et₂O/AcOH afforded 2-methyl-5-styrylfuran (Table 13, Entries 1 and 2), the use of Pd(OCOCF₃)₂ in MeCN/AcOH gave a 85:15 mixture of 2-phenylbis-(5-methyl-2-furyl)ethane and phenylbis(5-methyl-2-furyl)-ethane in 60% yield (Table 14, Entry 1). As shown with the examples depicted in Table 14, the method is compatible with various substituted olefins. With styrenes and α,β -unsaturated esters, the main reaction occurred at the β -position (Table 14, Entries 1–9, 13–17, and 19), while allylarenes provided the 2-difuryl products as the main compounds (Table 14, Entries 10–12 and 20). In fact, the formation of the products did not involve a DHR followed by a hydrofurylation, since the reaction of 2-methyl-5-styrylfuran did not afford such compounds (Table 14, Entry 18). The selectivity toward the formation of the difurylalkanes was dependent on the nature of the catalyst (eq 93).¹⁷² Indeed, the Pd(OAc)₂-catalyzed coupling of 2-methylfuran gave (i) with allylbenzene, a 1:1 mixture of the two adducts, (ii) with styrene, the usual DHR compound as a third adduct, and (iii) with *t*-butyl acrylate, the usual DHR compound as the main product. These results, associated with experiments using styrene-*d*₈, AcOD and mass spectroscopy techniques, led us to propose the

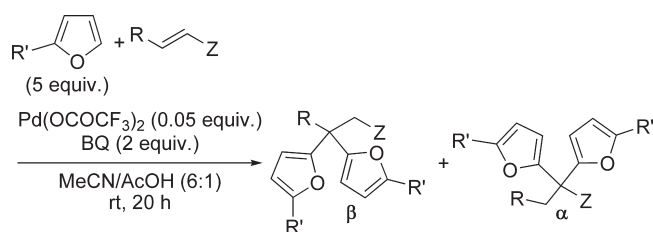
Table 13. Alkenylations of 2-Substituted Furans with Styrenes¹⁶⁴

entry	R ²	furan equiv	Pd equiv	oxidant (equiv), additive (equiv)	cosolvent	<i>t</i> °C; time, h	yield % ^a
R ¹ = Me							
1 ^b	H	1.1	0.05	BQ (2)	Et ₂ O	40; 24	55
2 ^{b,c}	H	1.1	0.05	BQ (2)	Et ₂ O	40; 24	51
3	H	1.1	0.05	Cu(OAc) ₂ (0.5)	Et ₂ O	40; 24	65
4	<i>p</i> -Me	2	0.05	BQ (0.1), O ₂ (gas bag)	Et ₂ O	40; 24	71
5	<i>o</i> -Me	2	0.05	Cu(OAc) ₂ (0.5)	Et ₂ O	40; 24	63
6	<i>p</i> -F	1.1	0.05	BQ (0.1), O ₂ (gas bag)	Et ₂ O	40; 24	64
7	<i>p</i> -OAc	1.1	0.05	Cu(OAc) ₂ (0.5)	Et ₂ O	40; 24	62
8	<i>p</i> -(<i>t</i> -Bu)	1.1	0.05	BQ (0.1), O ₂ (gas bag)	Et ₂ O	40; 24	56
9	<i>m</i> -Cl	1.1	0.05	Cu(OAc) ₂ (0.5), dba (0.2)	Et ₂ O	40; 48	64
R ¹ = Et							
10	<i>p</i> -Me	2	0.05	BQ (0.1), O ₂ (gas bag)	THF	60; 24	64
11	<i>p</i> -F	2	0.1	Cu(OAc) ₂ (0.5)	THF	60; 24	78
12	<i>p</i> -OAc	2	0.1	BQ (0.1), O ₂ (gas bag)	THF	60; 24	60
13	<i>p</i> -(<i>t</i> -Bu)	1.1	0.05	Cu(OAc) ₂ (0.5)	Et ₂ O	40; 24	63
R ¹ = CH ₂ OAc							
14	H	2	0.1	BQ (0.25), O ₂ (gas bag)	THF	60; 24	50
15	<i>p</i> -OAc	2	0.1	Cu(OAc) ₂ (0.5)	THF	60; 24	53
R ¹ = CH=CHCO ₂ Me							
16	H	2	0.1	BQ (0.25), O ₂ (gas bag)	THF	60; 24	60
17	<i>m</i> -Cl	2	0.1	Cu(OAc) ₂ (0.5)	THF	60; 24	62
18	<i>p</i> -Cl	2	0.1	BQ (0.25), O ₂ (gas bag)	THF	60; 24	64

^a Isolated yield. ^b Using AcOH instead of EtCO₂H. ^c Pd(OCOCF₃)₂ was used as the catalyst.

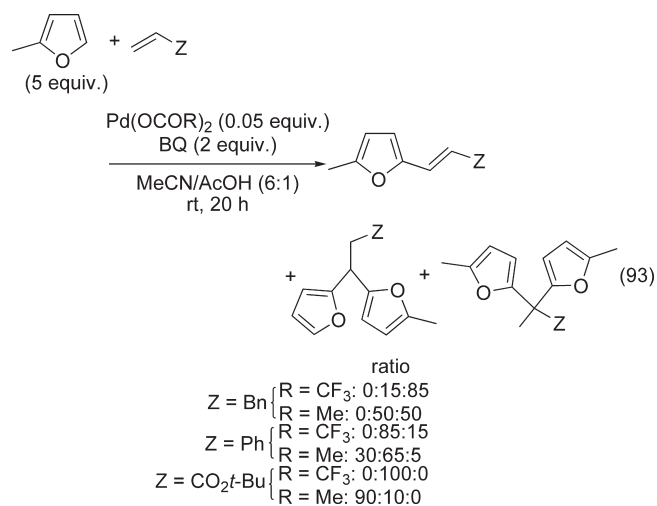
mechanism depicted in Scheme 25. The insertion of Pd(II) into the OC-H bond of the furan leading to **25A** is the only step corresponding to the DHR mechanism. This is followed by the C-H activation of a second molecule of the furan to afford **25B**, the reaction of which with the alkene giving **25C**. The β-H elimination leads to the

hydridopalladium complex **25D**. The addition of the HPd unit of **25D** to the coordinated exocyclic double bond provides the five-membered palladacycle **25E**.¹⁷³ Reductive elimination from **25E** delivers the isolated adduct and Pd(0) species, these latter being oxidized via their reaction with the BQ/HX association.

Table 14. Synthesis of Difurylalkanes¹⁷²

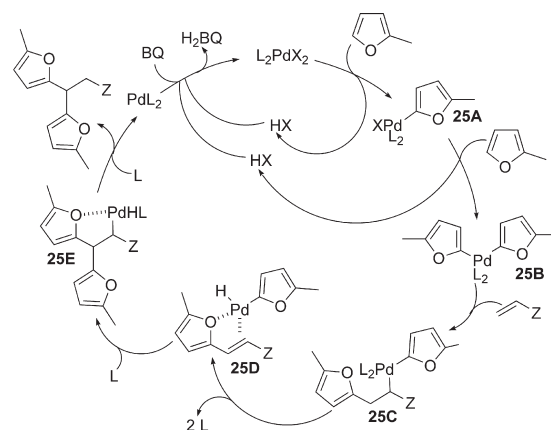
entry	R'	R	Z	yield %	β/α ratio
1	Me	H	Ph	60	85:15
2	Me	H	4-MeC ₆ H ₄	50	75:25
3	Me	H	4-ClC ₆ H ₄	62	83:17
4	Me	H	4-BrC ₆ H ₄	60	87:13
5	Me	H	3-ClC ₆ H ₄	62	89:11
6	Me	H	2-naphthyl	30	84:16
7	Me	H	C ₆ F ₅	76	75:25
8	Me	H	CO ₂ Et	57	100:0
9	Me	H	CO ₂ <i>t</i> -Bu	71	100:0
10	Me	H	Bn	94	15:85
11	Me	H	4-MeOC ₆ H ₄ CH ₂	52	40:60
12	Me	H	3,4-(MeO) ₂ C ₆ H ₃ CH ₂	62	40:60
13	Me	Me	Ph	70	100:0
14	Me	Me	4-MeOC ₆ H ₄	74	85:15
15	Me	Me	2-MeOC ₆ H ₄	75	83:17
16	Me	Me	2-BnOC ₆ H ₄	41	80:20
17	Me	Et	Ph	65	100:0
18 ^a	Me		Ph	0	<i>b</i>
19	Et	H	Ph	51	90:10
20	Et	H	Bn	60	25:75

^a A E/Z mixture of the alkene was used (33:67). ^b Only traces of bis(5-methyl-2-furyl)styrene, i.e. the DHR-type adduct, were detected.



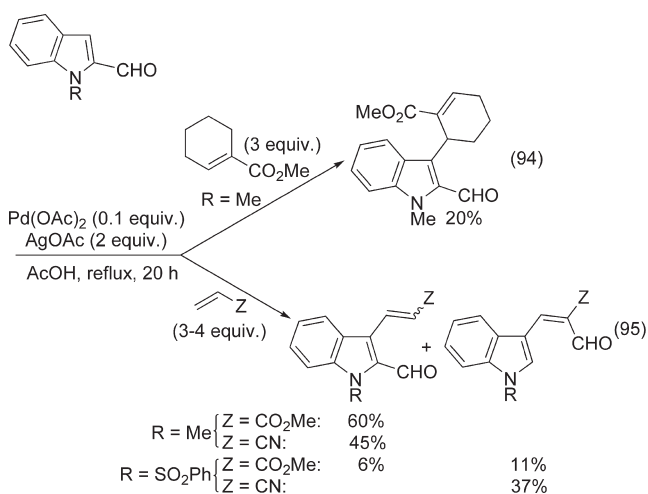
3.2.2. N-Arenes. The large amount of studies devoted to the oxidative coupling, under Pd catalysis, of *N*-arenes with

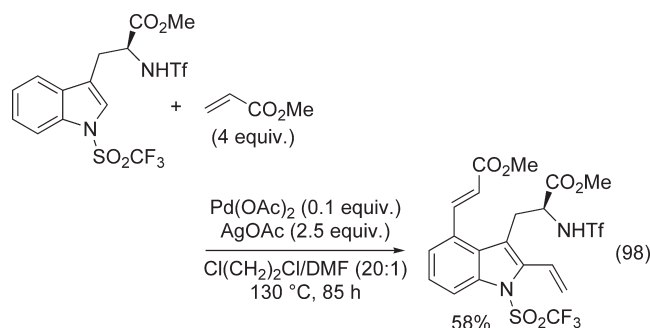
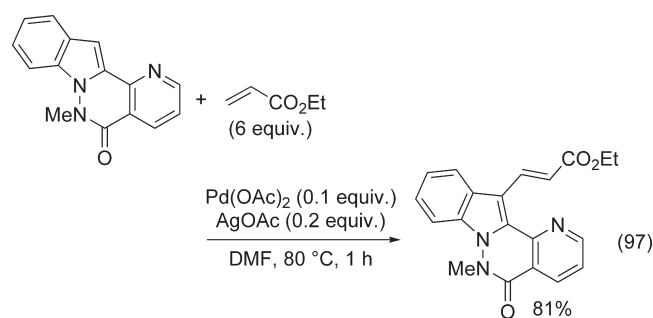
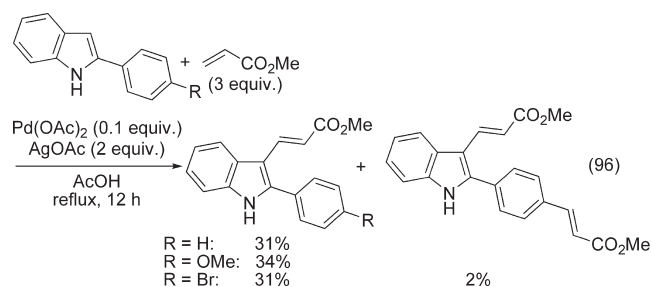
Scheme 25



alkenes urged us to divide the corresponding literature into four parts.

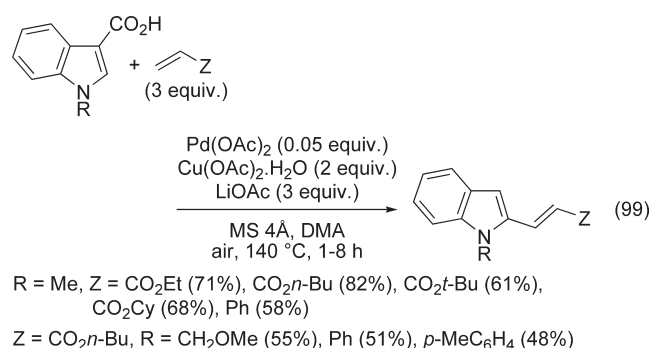
3.2.2.1. Indoles. The first report concerning the Pd-catalyzed DHR of *N*-arenes is from Itahara and co-workers, who, in 1983, disclosed the alkenylation of 1-(2,6-dichlorobenzoyl)indole with methyl acrylate.⁷⁹ Pd(OAc)₂ as the catalyst with AgOAc, Cu(OAc)₂, Na₂S₂O₈, or NaNO₂ as the reoxidant under air atmosphere in refluxing AcOH, led to the 3-substituted adduct but with a low conversion, the best result being obtained with AgOAc (Table 15, Entry 1). Switching to 1-benzenesulfonylindole as the substrate increased the efficiency with yields up to 42% (Entries 2–4).⁸⁰ The procedure was used with indoles bearing at C2 position an aldehyde or aryl group (eqs 94–96).¹⁷⁸ An unexpected product corresponding to the 1,4-migration of the aldehyde was observed in one case (eq 95), while traces of the Heck-type compound were isolated from 2-(*p*-bromophenyl)indole (eq 96). The 81% yield reported for the DHR depicted in eq 97 is surprising since the reaction was performed under argon atmosphere with only 0.2 equiv of AgOAc as reoxidant.¹⁷⁹ Recently, J.-Q. Yu et al. have used an excess of AgOAc to couple, under Pd(II) catalysis, the 3-substituted-1-(trifluoromethylsulfonyl)indole shown in eq 98 with methyl acrylate, this leading to alkenylation of both C2 and C4 positions.¹⁵⁶



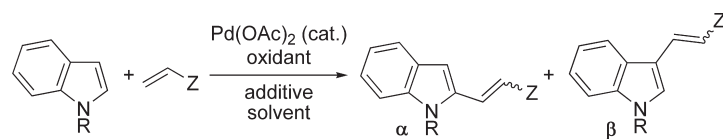


In 2005, Gaunt et al. reported the evaluation of various reactive media to optimize the $\text{Pd(OAc)}_2/\text{Cu(OAc)}_2$ procedure for the alkenylation of indole, which can afford 2- and 3-substituted adducts.¹⁷⁴ The DHR of this substrate with *n*-butyl acrylate in DMF or DMSO gave the β -adduct (Table 16, Entries 1 and 2), while a 1:1 mixture of the two adducts was obtained by addition of AcOH as cosolvent of DMF (Table 16, Entry 3).¹⁸¹ Surprisingly, DMSO as cosolvent of DMF improved the yield (Table 16, Entry 4). These conditions have been efficiently used to achieve the C3-functionalization of (i) indole with electron-deficient alkenes (Table 16, Entries 10, 14, 16, and 17) including α -methylene- γ -butyrolactone, or nonactivated alkenes such as styrene (Table 16, Entry 19) and cyclohexene, and (ii) 1-methylindole (Table 15, Entry 5), 5-bromoindole and 5-nitroindole with *n*-butyl acrylate.¹⁷⁴ Simultaneously to Gaunt, Brown, and co-workers used also Cu(OAc)_2 as reoxidant, but with PdCl_2 as the catalyst and MeCN as the solvent, to functionalize 1-benzylindole with methyl acrylate (Table 15, Entry 8).¹⁷⁵ With 1-(pyridin-2-yl)methylindole and methyl acrylate, 1-(vinylsulfonyl)benzene or acrylonitrile, the DHRs provided the corresponding 2-substituted compounds, highlighting an interesting directing group participation (Table 15, Entry 9).¹⁷⁵ These reactions led to 99% conversion of the substrate, but the yields are not specified, and according to a footnote, the system $\text{Pd(OAc)}_2/\text{Cu(OAc)}_2/\text{AcOH}/\text{dioxane}$ at 70 °C afforded improved results. The use of this system was recently

reported for the alkenylation of indoles *N*-substituted with a methylene bearing a bicyclic or tricyclic aza-aromatic group (Table 15, Entries 16–18).¹⁷⁷ The C2-functionalization, in yields depending on the *N*-substituent, can be accompanied by a subsequent functionalization at the 7-position. In 2007, Djakovitch and Rouge disclosed the alkenylation of free NH-indoles in DMF/DMSO, using air bubbling with only catalytic amounts of either Cu(OAc)_2 or CuCl_2 to regenerate Pd(II) species. The dependence of the efficiency and regioselectivity on the nature of the copper anion was noted (Table 16, Entries 5 and 6).¹⁸⁰ The $\text{Pd(OAc)}_2/\text{Cu(OAc)}_2/\text{O}_2$ procedure yielded also selectively the C3-alkenylated product from 2-methyl and 2-phenylindoles, but led to a mixture of 1- and 3-alkenylated products from methyl indole-2-carboxylate. Miura et al. have performed the DHR of 1-methylindole with butyl acrylate using lower amounts of palladium in the presence of air and overstoichiometric quantities of both $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ and LiOAc . The reaction, carried out in DMF at 120 °C, occurred more rapidly than under Gaunt's conditions, but gave a lower yield (Table 15, Entry 6).¹⁶⁶ The use of this procedure in DMA for the alkenylation of indole-2 (or 3)-carboxylic acids proceeds with decarboxylation as shown in eqs 87 and 99.¹⁶⁶ The authors proposed that the reaction of the 3-carboxylic acids occurs via the palladium carboxylates **26A** and the palladacycles **26B**. The insertion of the alkene into the C–Pd bond of **26B** followed by a β -H elimination would afford **26C**, decarboxylation of **26C** giving the 2-alkenylated compounds and Pd(0) (Scheme 26).

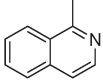
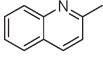
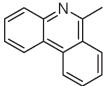


In 2009, Carretero and co-workers exemplified the effect of the *N*-substitution of indoles on the efficiency and regioselectivity of the $\text{PdCl}_2(\text{MeCN})_2$ -catalyzed reaction with methyl acrylate in DMA using $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ as the reoxidant; some results are collected in Table 15, Entries 11–15 and Table 16, Entry 12.¹⁷⁶ While the previous methods led, in most cases, mainly to the substitution at C3 position, these authors have discovered that *N*-(2-pyridyl)sulfonylindole reacted at C2 position with more than 98% selectivity (Table 15, Entry 15). This urged them to perform the alkenylation of such substituted indoles with a range of alkenes (eqs 100 and 101). In a subsequent publication, the team reported that blocking the C2 position of the substrate with a methyl group results in alkenylation at C3 position, albeit in lower yield (eq 102).¹⁸² Mechanistic work using indoles having different electronic characters and pyrroles (see section 3.2.2.2) led the authors to suggest a chelation-assisted electrophilic aromatic substitution palladation mechanism.¹⁸²

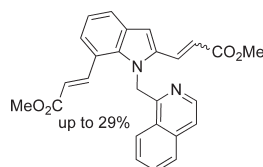
Table 15. Alkenylations of *N*-Substituted Indoles

Entry	Pd equiv.	R	Z (equiv.)	Oxidant, additive (equiv.)	Solvent (ratio)	t °C; time, h	Yield % (conv. %)
1 ⁷⁹	0.02		CO ₂ Me (3)	AgOAc (1), air	AcOH	Rx; 16	β : 18 (23)
2 ⁸⁰	0.1	PhSO ₂	CO ₂ Et (3)	AgOAc (2), air	AcOH	Rx; 18	β : 31 (32)
3 ⁸⁰	0.1	PhSO ₂	CO ₂ Et (3)	Cu(OAc) ₂ (2), air	AcOH	Rx; 18	β : 41 (69)
4 ⁸⁰	0.1	PhSO ₂	CO ₂ Et (3)	Na ₂ S ₂ O ₈ (2), air	AcOH	Rx; 18	β : 42 (100)
5 ¹⁷⁴	0.1	Me	CO ₂ <i>n</i> -Bu (2)	Cu(OAc) ₂ (1.8)	DMF/DMSO (9:1)	70; 20	β : 75
6 ¹⁶⁶	0.05	Me	CO ₂ <i>n</i> -Bu (3)	Cu(OAc) ₂ ^a (2), air, LiOAc (3)	DMF	120; 2	β : 53
7 ¹⁷⁴	0.2	Me	CO ₂ <i>n</i> -Bu (2)	PhCO ₃ <i>t</i> -Bu (0.9)	dioxane /AcOH (3:1)	70; 18	no reaction
8 ^{175,b}	0.1	Bn	CO ₂ Me ^c	Cu(OAc) ₂ (2)	MeCN	60; 14	β : 95
9 ^{175,b}	0.1		SO ₂ Ph, CN or CO ₂ Me ^c	Cu(OAc) ₂ (2)	MeCN	60; 14	α : (95)
10 ^{175,d}	0.1	CONMe ₂	CO ₂ Me ^c	BQ ^c	THF/DMF	80; 18	β : 54
11 ^{176,d}	0.1	<i>t</i> -BuO ₂ C	CO ₂ Me (2)	Cu(OAc) ₂ ^a (1)	DMA	110; 8	β/α = 32:68 (10)
12 ^{176,d}	0.1	Ts	CO ₂ Me (2)	Cu(OAc) ₂ ^a (1)	DMA	110; 8	β/α = 13:87 30 (45)
13 ^{176,d}	0.1		CO ₂ Me (2)	Cu(OAc) ₂ ^a (1)	DMA	110; 8	β/α = 50:50 (18)
14 ^{176,d}	0.1		CO ₂ Me (2)	Cu(OAc) ₂ ^a (1)	DMA	110; 8	β/α = 24:76 (27)
15 ^{176,d}	0.1		CO ₂ Me (2)	Cu(OAc) ₂ ^a (1)	DMA	110; 8	β/α = <2:>98 75 (100)

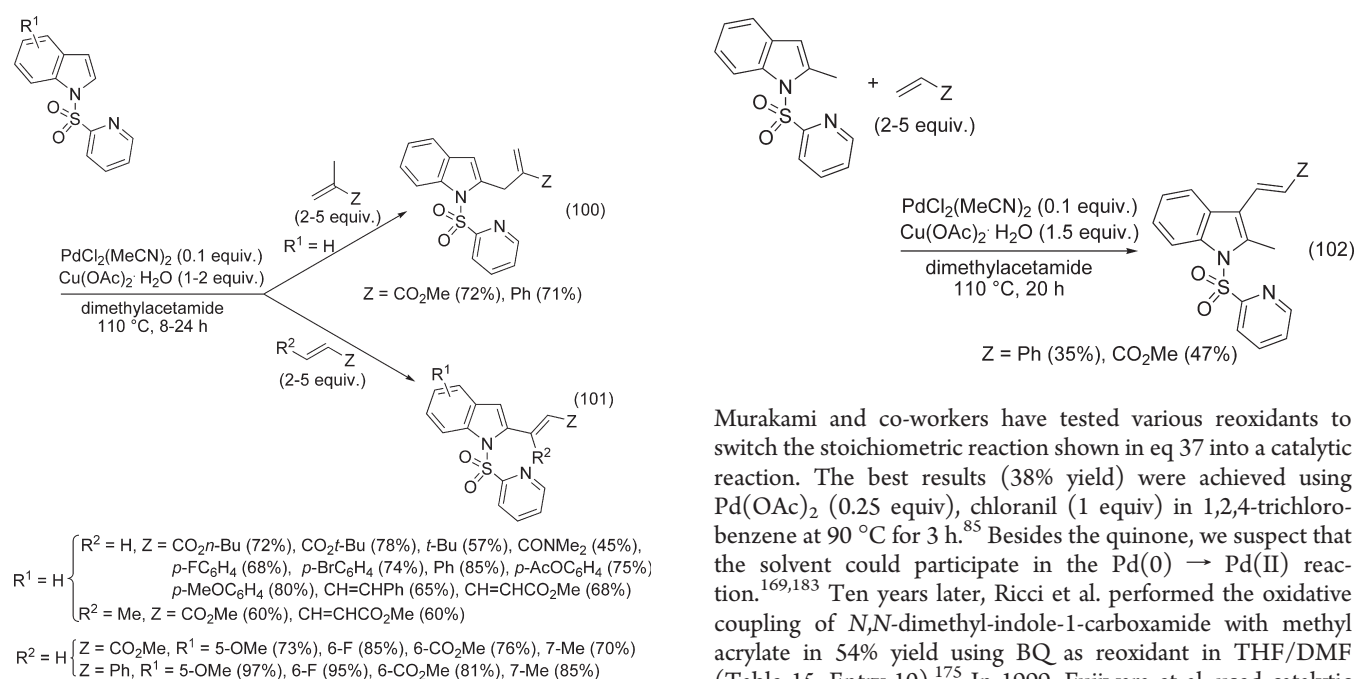
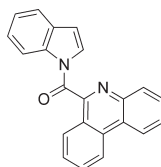
Table 15. Continued

Entry	Pd equiv.	R	Z (equiv.)	Oxidant, additive (equiv.)	Solvent (ratio)	t °C; time, h	Yield % (conv. %)
16 ¹⁷⁷	0.1		CO ₂ Me ^c	Cu(OAc) ₂ ^c	dioxane /AcOH	70; ^e	α : 44 ^f
17 ¹⁷⁷	0.1		CO ₂ Me (4)	Cu(OAc) ₂ (4)	dioxane /AcOH	70; 72	α : 53
18 ¹⁷⁷	0.1		CO ₂ Me ^c	Cu(OAc) ₂ ^c	dioxane /AcOH	70; ^e	α : 16 ^g

^a Cu(OAc)₂·H₂O was used. ^b PdCl₂ was used as catalyst. ^c Amount not indicated. ^d PdCl₂(MeCN)₂ was used as catalyst. ^e Time not indicated. ^f Formation also of



^g Formation of several products including



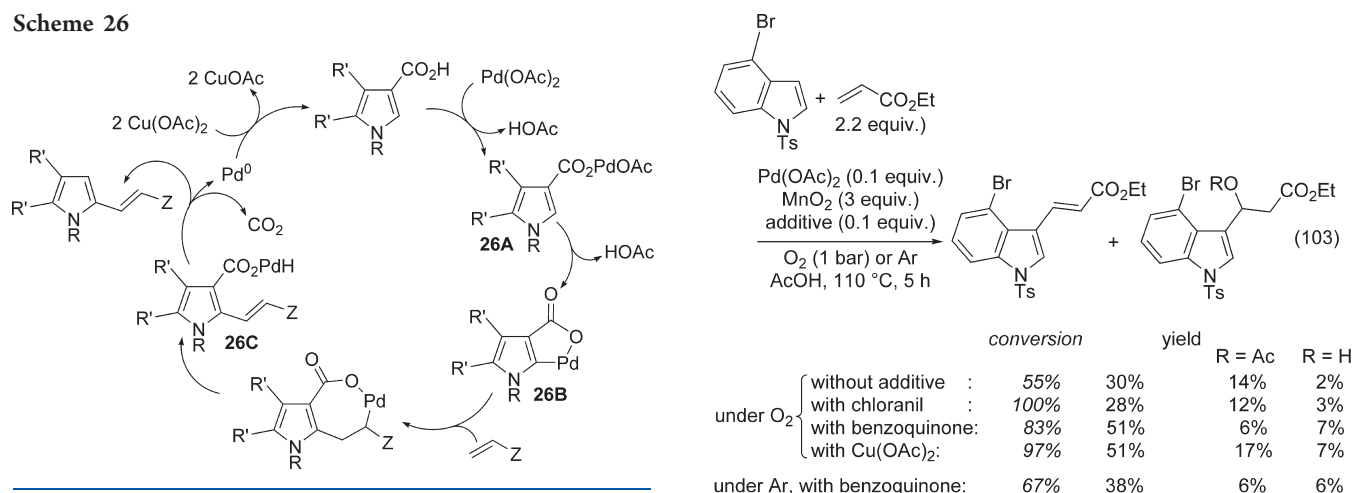
Murakami and co-workers have tested various reoxidants to switch the stoichiometric reaction shown in eq 37 into a catalytic reaction. The best results (38% yield) were achieved using Pd(OAc)₂ (0.25 equiv), chloranil (1 equiv) in 1,2,4-trichlorobenzene at 90 °C for 3 h.⁸⁵ Besides the quinone, we suspect that the solvent could participate in the Pd(0) → Pd(II) reaction.^{169,183} Ten years later, Ricci et al. performed the oxidative coupling of *N,N*-dimethyl-indole-1-carboxamide with methyl acrylate in 54% yield using BQ as reoxidant in THF/DMF (Table 15, Entry 10).¹⁷⁵ In 1999, Fujiwara et al. used catalytic

Table 16. Alkenylations of Indole

entry	Pd equiv	Z (equiv)	oxidant, additive (equiv)	solvent (ratio)	<i>t</i> °C; time, h	yield % (conv %)
1 ¹⁷⁴	0.1	CO ₂ <i>n</i> -Bu (2)	Cu(OAc) ₂ (1.8)	DMSO	70; 18	66 β/α = >95:<5
2 ¹⁷⁴	0.1	CO ₂ <i>n</i> -Bu (2)	Cu(OAc) ₂ (1.8)	DMF	70; 18	54 β/α = >95:<5
3 ¹⁷⁴	0.1	CO ₂ <i>n</i> -Bu (2)	Cu(OAc) ₂ (1.8)	DMF/AcOH (3:1)	70; 18	54 β/α = 1:1
4 ¹⁷⁴	0.1	CO ₂ <i>n</i> -Bu (2)	Cu(OAc) ₂ (1.8)	DMF/DMSO (10:1)	70; 18	79 β/α = >95:<5
5 ¹⁸⁰	0.1	CO ₂ <i>n</i> -Bu (2)	Cu(OAc) ₂ (0.1), air bubbling	DMF/DMSO (10:1)	70; 20	β/α = 100:0 (52)
6 ^{180,a}	0.1	CO ₂ <i>n</i> -Bu (2)	CuCl ₂ (0.1), air bubbling	DMF/DMSO (10:1)	70; 20	β/α = 67:33 (30)
7 ¹⁷⁴	0.1	CO ₂ <i>n</i> -Bu (2)	PhCO ₃ <i>t</i> -Bu (0.9)	MeCN/AcOH (3:1)	70; 18	65 β/α = >95:<5
8 ¹⁷⁴	0.1	CO ₂ <i>n</i> -Bu (2)	PhCO ₃ <i>t</i> -Bu (0.9)	dioxane	70; 18	48 β/α = 1:2
9 ¹⁷⁴	0.2	CO ₂ <i>n</i> -Bu (2)	PhCO ₃ <i>t</i> -Bu (0.9)	dioxane/AcOH (3:1)	70; 18	58 β/α = 1:7
10 ¹⁷⁴	0.1	CO ₂ <i>t</i> -Bu (2)	Cu(OAc) ₂ (1.8)	DMF/DMSO (9:1)	70; 20	β : 91
11 ¹⁷⁴	0.2	CO ₂ <i>t</i> -Bu (2)	PhCO ₃ <i>t</i> -Bu (0.9)	dioxane/AcOH (3:1)	70; 18	α : 57
12 ^{176,b}	0.1	CO ₂ Me (2)	Cu(OAc) ₂ ^c (1)	DMA	110; 8	β/α = >98:<266 (75)
13 ⁹²	0.005	CO ₂ Me (1)	BQ (0.05) <i>t</i> -BuOOH (1.3)	Ac ₂ O/AcOH (1:3)	50; 12	β : 52
14 ¹⁷⁴	0.1	CONMe ₂ (2)	Cu(OAc) ₂ (1.8)	DMF/DMSO (9:1)	70; 20	β : 70
15 ¹⁷⁴	0.2	CONMe ₂ (2)	PhCO ₃ <i>t</i> -Bu (0.9)	dioxane/AcOH (3:1)	70; 18	α : 34
16 ¹⁷⁴	0.1	CON-C ₃ H ₁₁ (2)	Cu(OAc) ₂ (1.8)	DMF/DMSO (9:1)	70; 20	β : 68
17 ¹⁷⁴	0.1	PO(OEt) ₂ (5)	Cu(OAc) ₂ (1.8)	DMF/DMSO (9:1)	70; 20	β : 70
18 ¹⁷⁴	0.2	PO(OEt) ₂ (2)	PhCO ₃ <i>t</i> -Bu (0.9)	dioxane/AcOH (3:1)	70; 18	α : 51
19 ¹⁷⁴	0.1	Ph (0.5)	Cu(OAc) ₂ (1.8)	DMF/DMSO (9:1)	70; 20	β : 62

^a PdCl₂ was used as catalyst. ^b PdCl₂(MeCN)₂ was used as catalyst. ^c Cu(OAc)₂·H₂O was used.

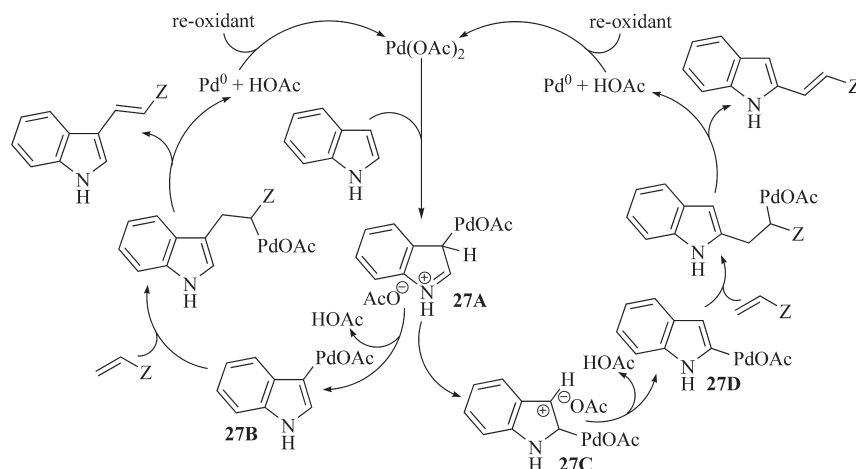
Scheme 26



amounts of both Pd(OAc)₂ and BQ in conjunction with *t*-BuOOH for the DHR of indole with methyl acrylate (Table 16, Entry 13); the formation of the 3-substituted indole contrasts with the regioselectivity from benzofuran, which reacted mainly at C2 position under the same experimental conditions.⁹² In 2002, Murakami's team studied the Pd(OAc)₂-catalyzed DHR of 4-bromo-1-tosyl indole with ethyl acrylate using overstoichiometric MnO₂ associated with other oxidants (eq 103).⁸⁶ The best yields were obtained in AcOH under oxygen with catalytic amounts of BQ or Cu(OAc)₂ as co-oxidants of MnO₂. Small amounts of Michael-type compounds due to the addition of the solvent and residual water were isolated as side-products. Use of DMF, MeCN, 1,2-dichloroethane, or 1,2,4-trichlorobenzene as solvent led to a very low efficiency of the transformation.

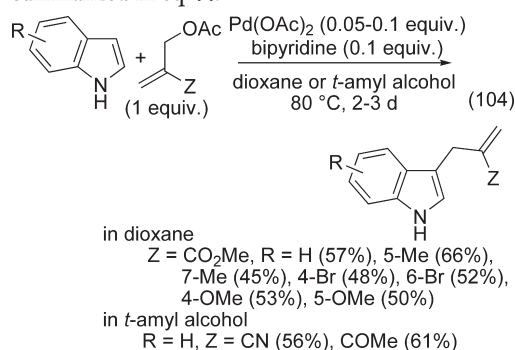
In their 2005 paper on the DHR of indole with *n*-butyl acrylate, Gaunt et al. reported different yields and selectivities when using PhCO₃*t*-Bu as the reoxidant instead of Cu(OAc)₂.¹⁷⁴ In dioxane, the DHR, which did not occur with Cu(OAc)₂, gave a 1/2 mixture of β - and α -adducts with PhCO₃*t*-Bu (Table 16, Entry 8). While AcOH as cosolvent was, with Cu(OAc)₂, detrimental to the selectivity (Table 16, Entry 3), the use of MeCN/AcOH with PhCO₃*t*-Bu afforded the β -adduct with more than 95% regioselectivity (Table 16, Entry 7). The solvent-dependent regioselectivity was exemplified with the dioxane/AcOH mixture which led to the α -adduct with 87% regioselectivity (Table 16, Entry 9). These last conditions were used for the synthesis of various 2-substituted indoles (Table 16, Entries 11, 15, and 18) but were

Scheme 27



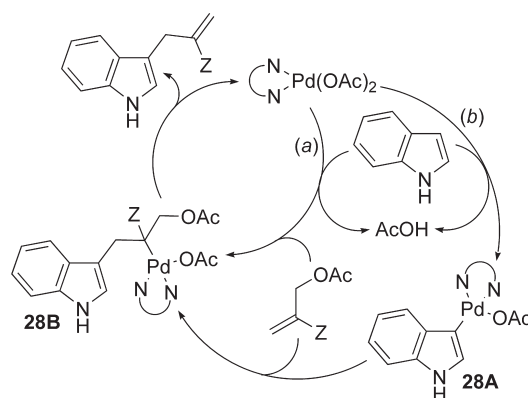
ineffective for the coupling of 1-methylindole with *n*-butyl acrylate (Table 15, Entry 7). According to the authors, the acid, AcOH or PhCO₂H produced from PhCO₃*t*-Bu, has a predominant role toward the switch in regioselectivity. Plausible pathways leading to the two regioisomers, which start similarly to Scheme 14, path β , with the production of the intermediate **27A**, have been proposed (Scheme 27).¹⁸⁴ Aromatization of **27A**, via removing of a proton by the acetate ion, led to **27B** which reacts with the alkene to afford the β -adduct. Under acidic conditions, the above deprotonation would be slower, this allowing the migration of PdOAc to give **27C**. Rearomatization leads to **27D**, which evolves to the α -adduct via its reaction with the alkene.¹⁸⁵ The effect of the cosolvent is, however, important since the use of a strongly coordinating solvent such as MeCN “override any effect that the presence of acid may have, thus leading to C3 selectivity”¹⁷⁴ (Table 16, Entry 7).

S. Ma and S. Yu have performed the effective Pd(OAc)₂/bipyridine-catalyzed reaction of indoles with 2-acetoxymethyl substituted electron-deficient alkenes, in either dioxane or *t*-amyl alcohol under external-oxidant-free conditions (eq 104).¹⁸⁶ No reaction occurred under Pd(PPh₃)₄ catalysis, or with allyl acetate, or in changing bipyridine to pyridine. The authors envisaged the regeneration of the catalyst and the formation of the adduct from **28B** via the β -OAc elimination¹⁸⁷ depicted in Scheme 28, **28B** being obtained either directly (path *a*) or via **28A**. This reaction, published in 2004 and which involves regeneration of the Pd(II) catalyst via the cleavage of the C–OAc bond, contrasts with the 2010 report summarized in eq 44.¹⁸⁸

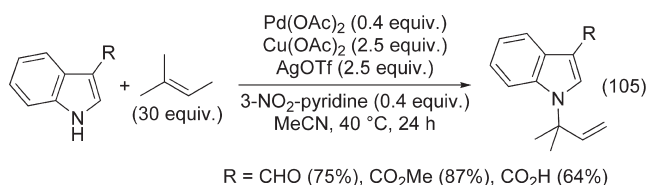


Even if they do not involve dehydrogenative Heck reactions, it is worthwhile to include in this section two recent reports,

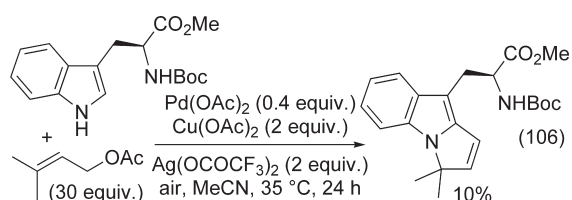
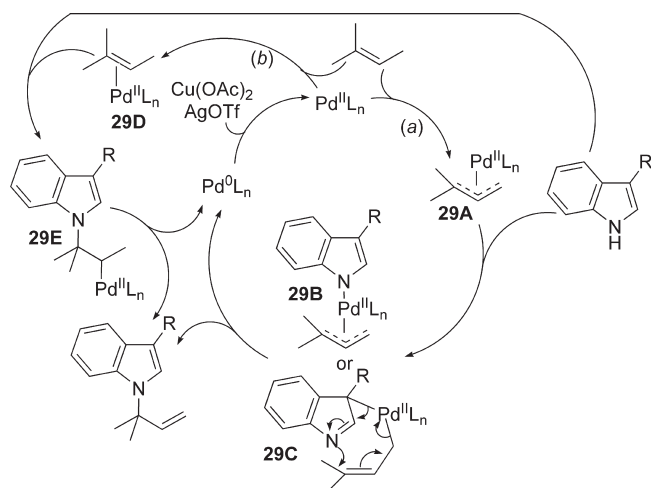
Scheme 28



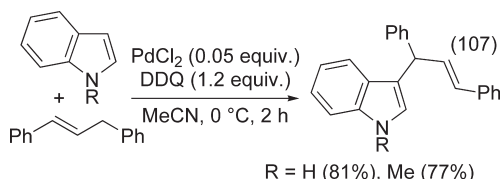
which disclose Pd(II)-catalyzed oxidative coupling reactions between indoles and alkenes.^{189,190} In contrast to the formation of the C–C bonds from unprotected indoles shown in Table 16 and eqs 96 and 104, Baran et al. obtained the chemoselective *N*-*tert*-prenylation of various indoles using 2-methyl-2-butene and various additives to regenerate Pd(II) species (eq 105).¹⁸⁹ This oxidative reaction could involve a Tsuji–Trost or Wacker-type reaction (Scheme 29, *a* and *b*, respectively). Coordination of 2-methyl-2-butene to the catalyst would afford η^3 (**29A**) or η^2 (**29D**) complex. Coupling of indole with **29A** would proceed via either *N*-coordination to palladium (**29B**) or through a metallo-Claisen rearrangement (**29C**).¹⁹¹ As for **29D**, its reaction with indole would give **29E**, which would suffer β -H elimination leading to the product. Use of prenyl acetate instead of 2-methyl-2-butene provided a low yield of a cyclized compound, a tentative assignment of its structure is shown in eq 106.¹⁸⁹ Such a compound could be formed from a Pd(II)-mediated cascade reaction leading first to the C–C bond as depicted in Scheme 28, and then to the N–C bond via a Wacker-type reaction.



Scheme 29

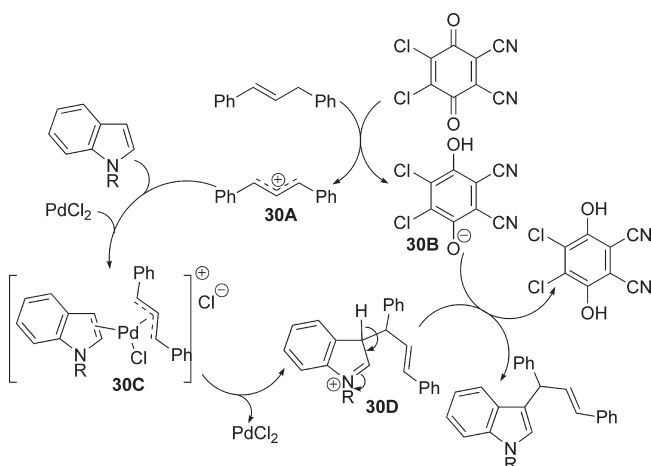


The second report, from Bao and Mo, concerns the efficient PdCl_2 -catalyzed coupling of indoles with 1,3-diarylpropenes, at 0 °C in the presence of 2,3-dichloro-5,6-dicyanoquinone (eq 107).¹⁹⁰ This oxidative cross-coupling process is neither a dehydrogenative Heck reaction nor a Tsuji-Trost reaction. The mechanism proposed by the authors (Scheme 30) involves hydride abstraction from the diarylpropene by DDQ to form ion pair **30A**, **30B**. Carbometallation of **30A** with PdCl_2 and indole led to η^3 -allylpalladium **30C**. Elimination of PdCl_2 from **30C** affords **30D**. Abstraction of a proton of **30D** by **30B** gives the allylated indole and dihydro-DDQ.



3.2.2.2. Pyrroles. In 1985, Itahara and co-workers revealed the DHR of methyl acrylate with 1-(2,6-dichlorobenzoyl) pyrrole.⁸² Using $\text{Pd}(\text{OAc})_2$ as the catalyst with AgOAc , $\text{Cu}(\text{OAc})_2$, $\text{Na}_2\text{S}_2\text{O}_8$ or NaNO_2 as the reoxidant under air atmosphere in refluxing AcOH , a mixture of the mono- and disubstituted products was isolated in fair yields (eq 108). Further studies on such reactions of pyrroles were published more than 20 years later by Gaunt et al., who highlighted the crucial influence of the *N*-substituent on both efficiency and regioselectivity of the oxidative coupling (Table 17, Entries 1–6; eqs 109–111).^{192,193} Using benzyl acrylate with *t*-butyl perbenzoate as the reoxidant, this team observed that pyrroles with a *N*-Boc-, *N*-Ac-, or *N*-Ts form the 2-alkenylated products (Entries 3–5; eqs 109 and 111), while

Scheme 30



1-(tri-isopropylsilyl)-pyrroles afford the 3-alkenylated products (Entry 6, eqs 110 and 111), pyrroles with a *N*-Bn or *N*- $\text{CH}_2\text{O}(\text{CH}_2)_2\text{SiMe}_3$ leading to a mixture of the two adducts (Entries 1 and 2). The switch from α - to β -selectivity has been attributed to “the sterically demanding nature of the TIPS group that shields the C2 position from reaction with the palladium catalyst, forcing the reactive pyrrole to palladate at C3”.^{192,194} Various alkenes, even β -substituted α,β -unsaturated carbonyl compounds, underwent the DHR with high regioselectivity (Entries 7–21). Interestingly, the reaction occurred also using oxygen instead of the perester (Entries 5–14). The presence of a substituent in C3 position of the starting *N*-Boc pyrrole induced a steric hindrance, favoring the alkenylation at the C5 rather than at the C2 position (eq 111).¹⁹³

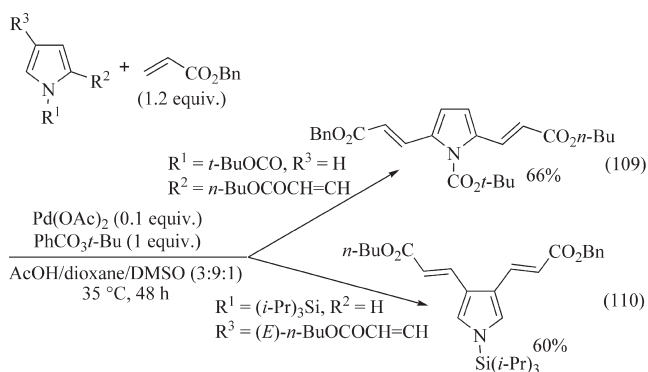
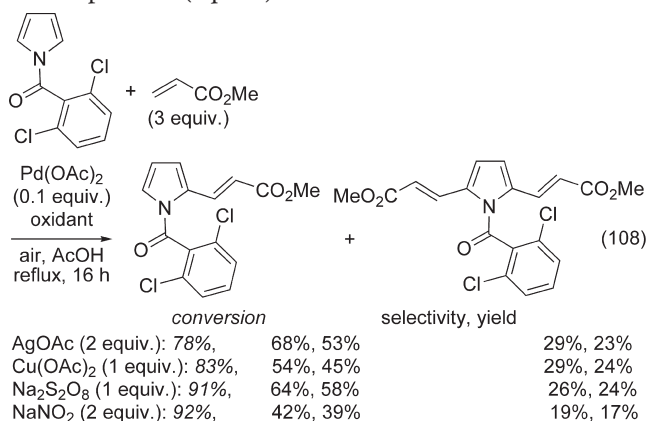
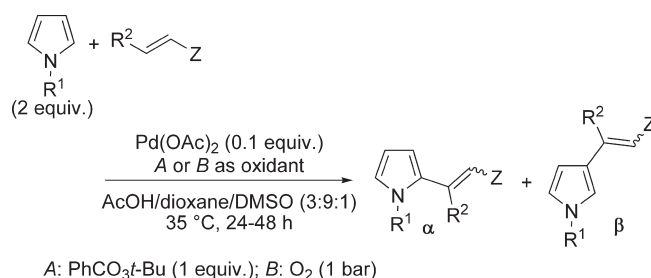
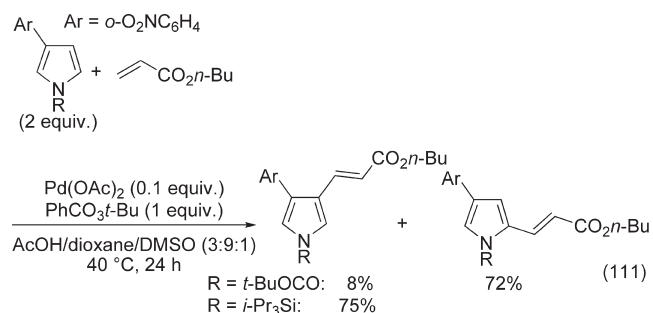


Table 17. Alkenylation of Pyrroles under Gaunt's Conditions¹⁹²

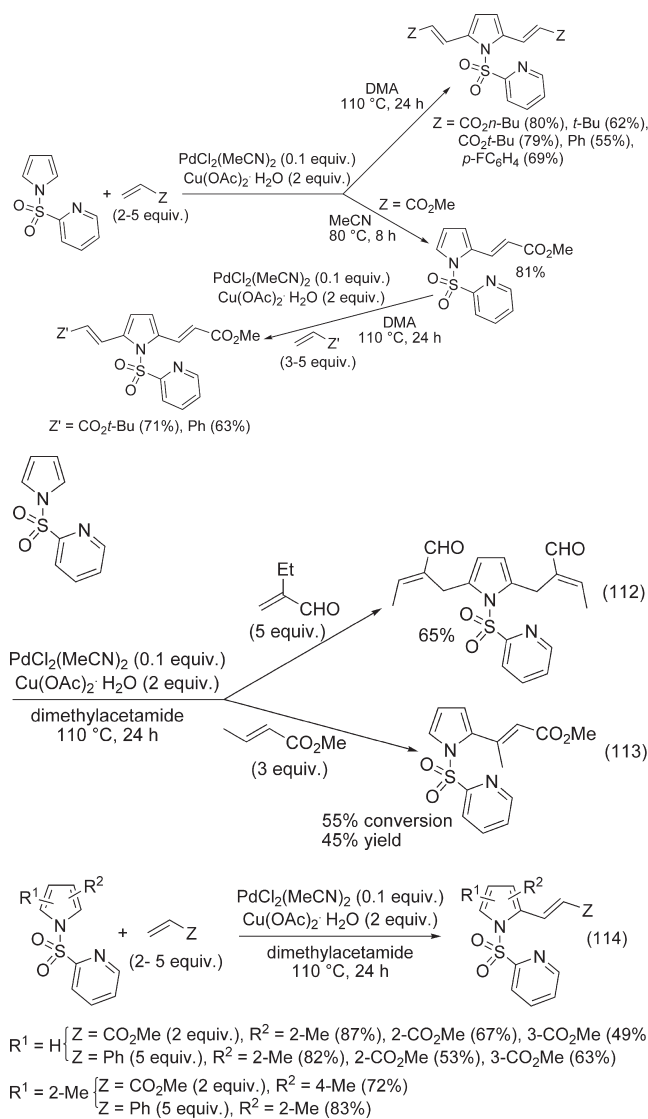
entry	R ¹	Z	α, yield % using		β, yield % using	
			A	B	A	B
R ² = H						
1	Bn	CO ₂ Bn	48		23	
2	Me ₃ Si(CH ₂) ₂ OCH ₂	CO ₂ Bn	48		21	
3	Ac	CO ₂ Bn	65			
4	Ts	CO ₂ Bn	70			
5	<i>t</i> -BuOCO	CO ₂ Bn	73	73		
6	(<i>i</i> -Pr) ₃ Si	CO ₂ Bn			78	75
7	<i>t</i> -BuOCO	CO ₂ <i>n</i> -Bu	75	73		
8	(<i>i</i> -Pr) ₃ Si	CO ₂ <i>n</i> -Bu			81	73
9	<i>t</i> -BuOCO	COR	R = Et: 69	R = <i>n</i> -Pr: 71		
10	(<i>i</i> -Pr) ₃ Si	COR			R = Et: 69	R = <i>n</i> -Pr: 76
11	<i>t</i> -BuOCO	<i>p</i> -(MeO ₂ C)C ₆ H ₄	60	53		
12	(<i>i</i> -Pr) ₃ Si	<i>p</i> -(MeO ₂ C)C ₆ H ₄			63	58
13	<i>t</i> -BuOCO	SO ₂ Me	69	38		
14	(<i>i</i> -Pr) ₃ Si	SO ₂ Me			71	45
15	<i>t</i> -BuOCO	PO(OEt) ₂	60			
16	(<i>i</i> -Pr) ₃ Si	PO(OEt) ₂			70	
17	<i>t</i> -BuOCO	CN	63			
18	(<i>i</i> -Pr) ₃ Si	CN			60	
R ² = Me						
19	<i>t</i> -BuOCO	CO ₂ Et	40			
20	(<i>i</i> -Pr) ₃ Si	CO ₂ Et			70	
R ² CH=CHZ = 2-cyclohexenone						
21	(<i>i</i> -Pr) ₃ Si				72	



Using their $\text{PdCl}_2(\text{MeCN})_2/\text{Cu}(\text{OAc})_2$ procedure of alkenylation of N -(2-pyridyl)sulfonylindoles (eqs 100 and 101), Carretero and co-workers observed a selectivity toward the mono- and disubstitution of N -(2-pyridyl)sulfonyl pyrrole depending on the reaction conditions: the alkenylation

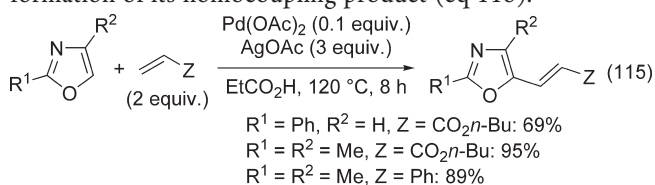
occurred at C2 position in MeCN at 80 °C, and at both C2 and C5 positions in DMA at 110 °C. This provided access to unsymmetrical 2,5-disubstituted pyrroles by sequential double alkenylation (Scheme 31).¹⁷⁶ Reaction with α -ethylacrolein afforded the double bond isomerized alkenylation product (eq 112), whereas a relative low conversion was obtained with styrene¹⁷⁶ or a 1,2 disubstituted alkene such as (*E*)-methylcrotonate (eq 113).¹⁸² Regioselective DHRs occurred with fair to high yields from substituted N -(2-pyridyl)sulfonyl pyrroles (eq 114).¹⁸² Competitive kinetic studies from electron-rich and electron-poor substrates ($k_{\text{Me}/\text{CO}_2\text{Me}} = 14.3$ for C2 substitution), as well as the study of the kinetic isotope effect in a C2 monodeuterated substrate ($k_{\text{H}/\text{D}} = 1.4$) agree with an electrophilic aromatic-type substitution rather than a direct C–H activation process.^{182,195}

Scheme 31

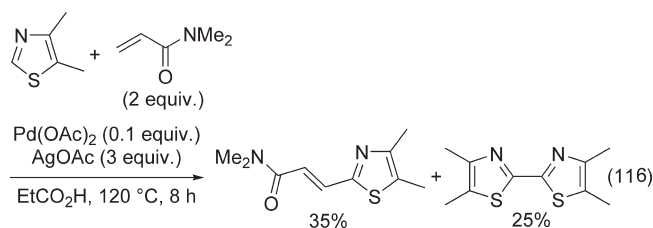


As expected from the reaction of *O*-arenecarboxylic acids, the alkenylation of 1-methylpyrrole-2-carboxylic acid is accompanied by decarboxylation (eq 87).¹⁶⁶

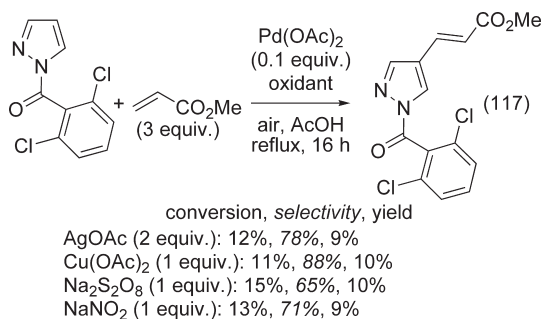
3.2.2.3. Thiazoles and Oxazoles. Miura's team which, as depicted above, reported the alkenylation of furans (Table 12, Entries 9 and 10)¹⁶⁵ and indoles (Table 15, Entry 6),¹⁶⁶ recently has disclosed the DHR of thiazoles and oxazoles.¹⁹⁶ The optimum reaction conditions, AgOAc as the reoxidant and EtCO₂H as the solvent, differ from those previously used. Thiazoles and oxazoles substituted in C2 react selectively in C5 (Table 18, Entries 1–9; eq 115). Fair yields were also obtained from those substituted in C2 and C4 (Table 18, Entries 10 and 11; eq 115). In contrast, the alkenylation of 4,5-dimethylthiazole proceeded in a low yield, because of the formation of its homocoupling product (eq 116).

Table 18. Alkenylation of 2-Substituted Thiazoles and 2,4-Disubstituted Thiazoles¹⁹⁶

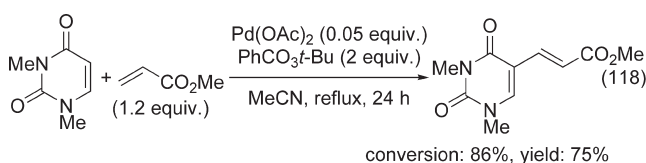
entry	R ¹	R ²	Z	yield %
1	<i>i</i> -Bu	H	CO ₂ Ph	81
2	<i>i</i> -Bu	H	CONMe ₂	85
3	<i>i</i> -Bu	H	Ph	78
4	<i>i</i> -Bu	H	<i>p</i> -MeOC ₆ H ₅	69
5	<i>i</i> -Bu	H	<i>p</i> -CF ₃ C ₆ H ₅	64
6	MeO	H	CO ₂ <i>n</i> -Bu	56
7	MeS	H	CO ₂ <i>n</i> -Bu	40
8	Ac(<i>n</i> -Bu)N	H	CO ₂ <i>n</i> -Bu	73
9	(<i>n</i> -Bu) ₂ C(OH)	H	CO ₂ <i>n</i> -Bu	73
10	Ph	Me	CO ₂ <i>n</i> -Bu	63
11	Me	Me	CO ₂ <i>n</i> -Bu	75



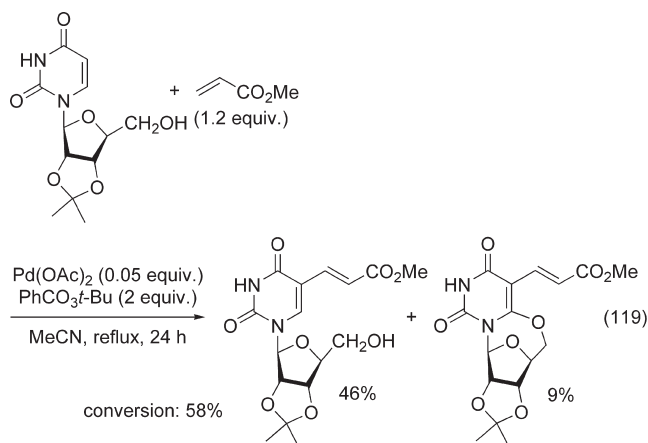
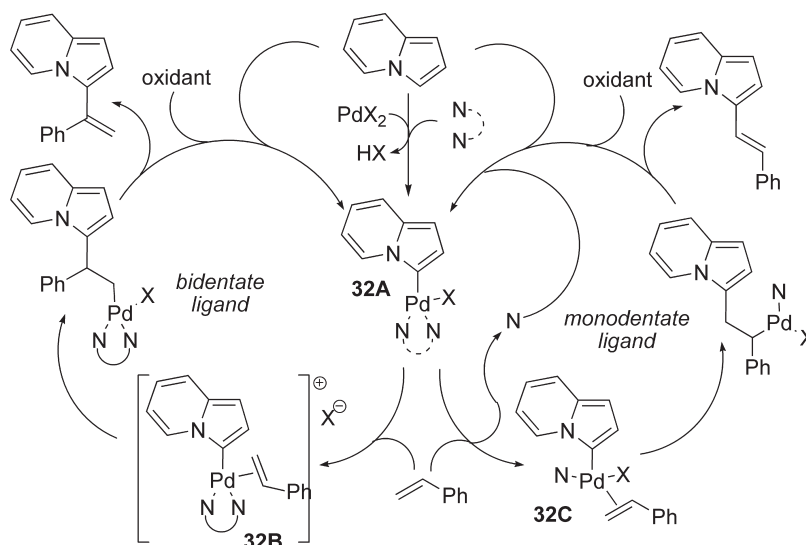
3.2.2.4. Others. In contrast to 1-(2,6-dichlorobenzoyl)pyrrole (eq 108), 1-(2,6-dichlorobenzoyl)pyrazole is reluctant to react under catalytic alkenylation conditions employing various salts as reoxidants, fair selectivity was obtained but with low conversion (eq 117).⁸²



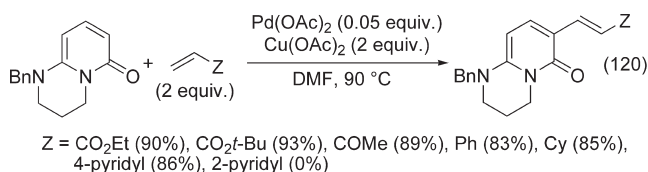
Catalytic oxidative coupling of 1,3-dimethyluracil with methyl acrylate in the presence of *t*-butyl perbenzoate afforded selectively the corresponding 5-substituted compound (eq 118).⁸³ An unexpected Wacker-type intramolecular reaction can accompany this DHR if the uracil bears a suitable hydroxy tether (eq 119).



Scheme 32

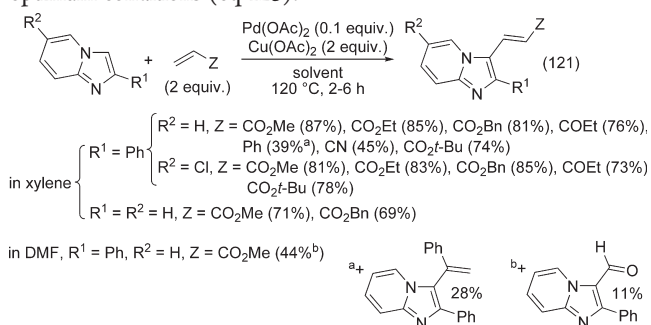


The regioselective $\text{Pd}(\text{OAc})_2$ -catalyzed alkenylation of a bicyclic pyridine was disclosed in 2009 by Cheng and Gallagher using $\text{Cu}(\text{OAc})_2$ as the reoxidant. Reactive media containing AcOH were inefficient, while yields up to 93% were obtained in DMF (eq 120). Monitoring by ^1H NMR the interaction of the substrate with $\text{Pd}(\text{OAc})_2$, the authors characterized the $(\text{NAr})\text{PdOAc}$ intermediate.¹⁹⁷ The absence of the coupling of the pyridone with 2-vinylpyridine was attributed to the coordination of this latter, via its pyridine lone pair and its adjacent $\text{C}=\text{C}$ unit, to $(\text{NAr})\text{PdOAc}$ leading to a stable chelate.

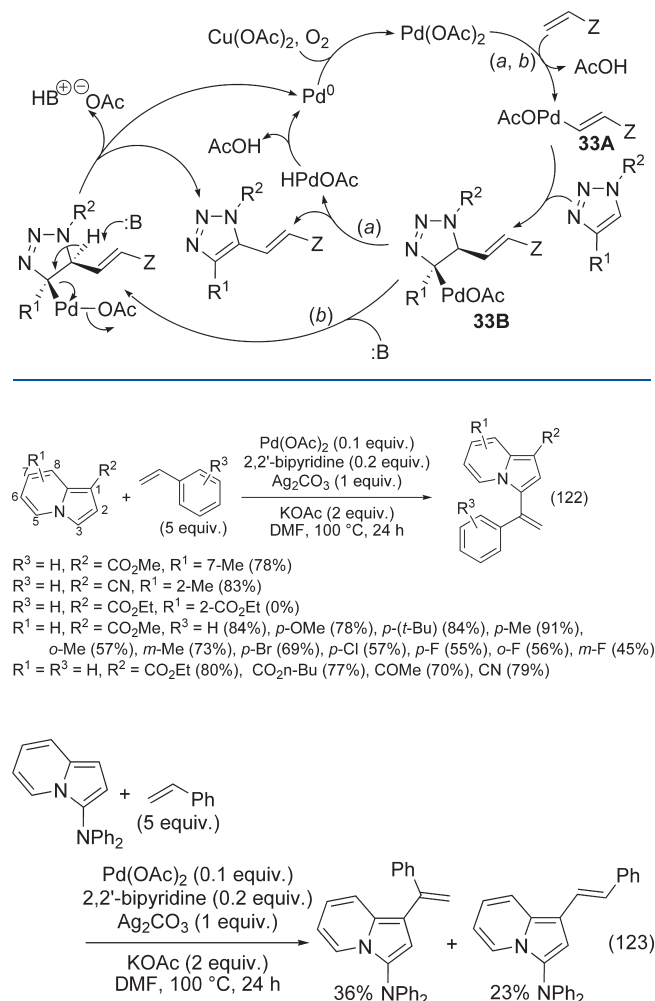


Berteina-Raboin and co-workers, also in 2009, reported the Pd-catalyzed alkenylation of imidazo[1,2-*a*]pyridines. Through the various catalyst, reoxidant, additive and solvent combinations which have been tested, the optimum conditions were achieved in xylene or toluene, under argon, with $\text{Cu}(\text{OAc})_2$ and a Pd(II) catalyst, in particular, $\text{Pd}(\text{OAc})_2$ (eq 121).¹⁹⁸

The use of DMF as the solvent led to a formylated byproduct (eq 121).^{145,198} A few months later, the DHR of indolizines with vinylarenes, occurring effectively in DMF, was nevertheless reported (eq 122).¹⁹⁹ Zhang et al. showed that a Pd(II) catalyst, preferably $\text{Pd}(\text{OAc})_2$, was required, and that the regioselectivity depended on the ligand. With Ag_2CO_3 as reoxidant, the coupling of methyl indolizine-1-carboxylate occurred at its C3-position with the α -C and β -C of styrene in the absence of ligand or with PPh_3 or pyridine, and with selectively the α -C of styrene in the presence of 2,22-bipyridine. These last conditions have been used to perform the regioselective DHR of various indolizines with a range of styrenes (eq 122), diethyl indolizine-1,2 dicarboxylate being however inactive.^{199,200} The inactivity of this heterocycle would be due to the electron deficiency caused by its two electron-withdrawing substituents, hence its reluctant electrophilic palladation. The differences of regioselectivity toward styrene would be in part related to the nature of the intermediates which, themselves, would depend on the ligands. According to the Heck literature, monodentate ligands lead rather to neutral intermediates favoring linear olefins, while ionic pathways resulting in branched olefins dominate with bidentate ligands.^{63,201,202} Given these remarks, the authors proposed the reactive pathways shown in Scheme 32. Palladation of indolizine would afford **32A** which reacts with styrene to give either the ionic complex **32B** or the neutral intermediate **32C**, depending on the nature of the ligand. These complexes evolve toward the branched and the linear olefins, respectively. A detailed mechanism remains however to elucidate because *N,N*-diphenylindolizine-3-amine gave a mixture of α - and β -substituted vinylation products under the above optimum conditions (eq 123).¹⁹⁹

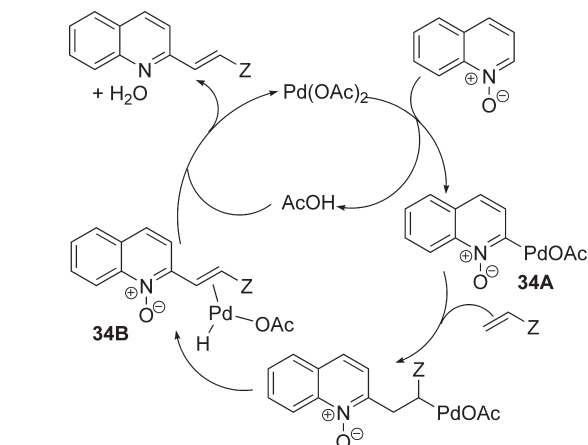


Scheme 33

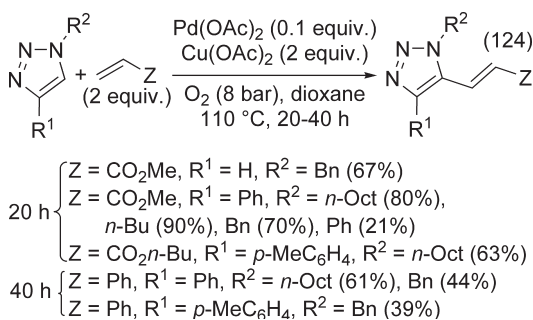


Recently, Jiang and co-workers have disclosed the alkenylation of 1,2,3-triazoles with terminal conjugated alkenes.²⁰³ The reaction occurred at 110 °C in dioxane, under pressure of oxygen, with Pd(OAc)_2 as the catalyst and an overstoichiometric amount of Cu(OAc)_2 (eq 124). Other Pd catalysts or reoxidation systems were much less efficient. The authors proposed the usual DHR mechanism, that is, activation of the (NAr)-H bond of the triazole as the first step, or the mechanism shown in Scheme 33, path *a*. This latter mechanism would involve the formation of vinyl palladium complex **33A** from the reaction of the catalyst with the alkene. Then, insertion of the triazole into the vinyl-Pd bond gives complex **33B**, which evolves via β -H elimination to the product and HPdOAc. The published scheme did not indicate the relationship between the AcOPd and $\text{CH}=\text{CHZ}$ substituents. In contrast, Scheme 33 is drawn with a *syn*-relationship between these two groups, because of the usual stereochemistry of the insertion of $\text{C}=\text{C}$ bonds into the $\text{C}-\text{Pd}$ bonds.^{201,204} Thus, the elimination of HPdOAc would be an *anti*-process,⁶⁸ instead of the usual *syn*-process which is developed from an agostic interaction.²⁰⁵ Nevertheless, the formation of the $\text{C}=\text{C}$ bond could occur from an intermediate such as **33B**, particularly in the presence of a base which would abstract the hydrogen, but this led to Pd(0) instead of HPdOAc (Scheme 33, path *b*).²⁰⁶ However, Jiang's team has noted that the addition of base to the reactive mixture has a deleterious effect on their reaction.²⁰³

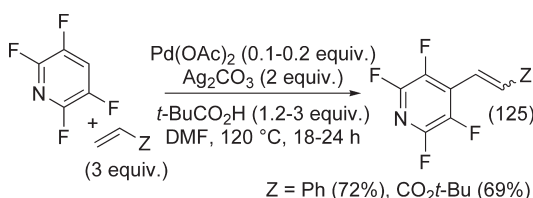
Scheme 34



Given these remarks, we favor the usual DHR mechanism to interpret this Jiang reaction.

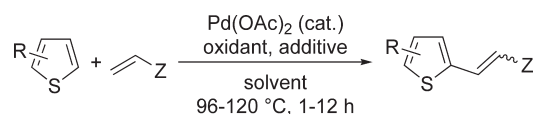


Zhang and co-workers used their procedure of alkenylation of fluororenes (eqs 55–57) for the DHR of 2,3,5,6-tetrafluoropyridine with styrene and *t*-butyl acrylate (eq 125).¹¹²



In the course of the last two years two papers appeared devoted to the Pd(OAc)_2 -catalyzed DHR of aromatic *N*-oxides with alkenes.^{207,208} Under the optimum conditions of the first report, that is, pyridine as additive, Ag_2CO_3 as reoxidant, and dioxane as solvent, Chang et al. obtained the regioselective alkenylation at the 2-position (eqs 126 and 127).²⁰⁷ These authors noted that the complex $\text{C}_5\text{H}_5\text{NOPdCl}_2(\text{PPh}_3)_3$, synthesized from pyridine *N*-oxide and $\text{PdCl}_2(\text{PPh}_3)_2$, did not afford the alkenylated product under the reaction conditions. One of the roots of the studies disclosed by Wu and co-workers in the second report²⁰⁸ was the property of *N*-oxides, in particular, pyridine *N*-oxide, to be prototypical oxygen atom transfer reagents.²⁰⁹ These authors synthesized substituted quinolines, isoquinolines, and quinazolines from the corresponding heteroaryl *N*-oxides under external-oxidant-free conditions (eqs 128 and 129). Surprisingly, no product was

Table 19. Alkenylation of Thiophenes

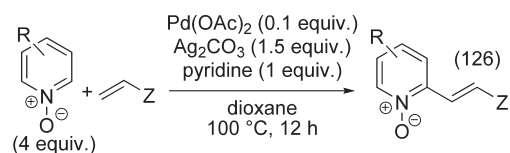


entry	ratio ^a	R	Z	oxidant (equiv), additive (equiv)	solvent (ratio)	<i>t</i> °C; time, h	yield % ^b
1 ⁷⁵	8.3:1:0.033	H	H	Cu(OAc) ₂ (1.67) CaCl ₂ (0.67)	DMF	96; 2	5
2 ⁶⁵	12.5:1:0.025	H	H	H ₆ PMo ₉ V ₃ O ₄₀ (0.125) LiOAc (1.5)	HOAc	96; 3	(5.8)
3 ^{76,162}	1:1: 0.02	H	CO ₂ Me	Cu(OAc) ₂ (2) air (1 atm)	dioxane/AcOH (4:1)	100; 8	(3)
4 ^{76,162}	1:1:0.02	H	CN	Cu(OAc) ₂ (2) air (1 atm)	dioxane/AcOH (4:1)	100; 8	(7) ^c
5 ¹⁶³	4:1:0.1	H	CO ₂ <i>n</i> -Bu	AgOAc (2) pyridine (4)	DMF	120, 12	83
6 ¹⁶³	4:1:0.1	H	CO ₂ <i>t</i> -Bu	AgOAc (2) pyridine (4)	DMF	120, 12	90
7 ¹⁶³	4:1:0.1	H	CONMe ₂	AgOAc (2) pyridine (4)	DMF	120, 12	85
8 ^{93,d}	2:1:0.07	2-Me	CO ₂ Et	HPMo ₁₁ V (0.013) O ₂ (balloon) NaOAc (0.05)	EtCO ₂ H	60; 2.5	86
9 ¹⁶³	4:1:0.1	2-Me	CO ₂ <i>n</i> -Bu	AgOAc (2) pyridine (4)	DMF	120, 12	87
10 ¹⁶³	4:1:0.1	2-Me	CONMe ₂	AgOAc (2) pyridine (4)	DMF	120, 12	90
11 ¹⁶³	1:1:0.1	2-Me	CN	AgOAc (2) pyridine (4)	DMF	120, 12	38
12 ¹⁶³	4:1:0.1	2-MeO	CO ₂ <i>n</i> -Bu	AgOAc (2) pyridine (4)	DMF	120, 12	62
13 ¹⁶³	4:1:0.1	2-MeO	CONMe ₂	AgOAc (2) pyridine (4)	DMF	120, 12	70
14 ¹⁶³	4:1:0.1	2-MeO	CN	AgOAc (2) pyridine (4)	DMF	120, 12	46
15 ¹⁶³	1:4:0.1	2-Ar	CO ₂ <i>n</i> -Bu	AgOAc (2) pyridine (4)	DMF	120, 12	75–87 ^e
16 ¹⁶⁵	1:3:0.05	2-C(OH)Ph ₂	CO ₂ Et	Cu(OAc) ₂ ^f (2), air (1 atm), LiOAc (3)	DMF	120, 4	(63) 55
17 ¹⁶⁵	1:3:0.05	2-C(OH)Ph ₂	Ph	Cu(OAc) ₂ ^f (2), air (1 atm), LiOAc (3)	DMF	120, 1	(30)
18 ¹⁶⁵	4:1:0.1	3-Me	CO ₂ <i>n</i> -Bu	AgOAc (2) pyridine (4)	DMF	120, 12	89 ^g
19 ¹⁶⁵	4:1:0.1	2,3-(CH) ₄	CO ₂ <i>n</i> -Bu	AgOAc (2) pyridine (4)	DMF	120, 12	84

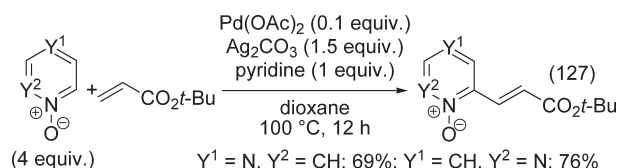
^a Thiophene/alkene/catalyst ratio. ^b Isolated yield; GC, HPLC and ¹H NMR yields are in brackets. ^c Also 0.3% of the 2,5-disubstituted compound. ^d Pd(OAc)₂/C was used as catalyst. ^e Ar = Ph (80%), *p*-MeOC₆H₄ (87%), *m*-OCHC₆H₄ (75%), *p*-FC₆H₄ (76%), 1-naphthyl (80%). ^f Cu(OAc)₂·H₂O was used. ^g Mixture of the two regioisomers (~ 4:5).

obtained from monocyclic substrates such as *N*-oxides derived from pyridine, pyrazine, pyrimidine, and 1-methylimidazole. According to mechanism studies, alkenylated quinoline-*N*-oxide, but not quinoline-*N*-oxide, can be reduced by Pd(0). This led the authors to assume a regeneration of active Pd species from the interaction of the alkenylated quinoline-*N*-oxide with HPdOAc. They suspected that the regioselective

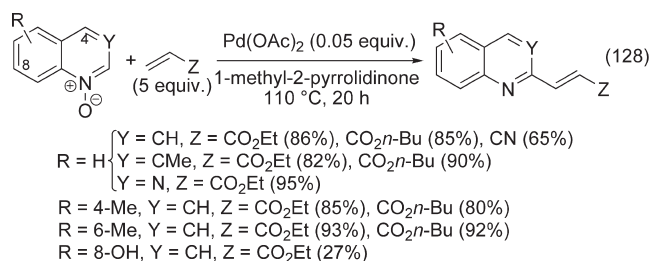
palladation at C2 position of quinoline-*N*-oxide occurs via the coordination of the palladium atom to the *N*-oxide; this leads to **34A** (Scheme 34). The mechanism depicted in Scheme 34 differs slightly from the authors proposal, since we suggest a catalyst regeneration occurring from an intramolecular reaction at the level of the palladium hydride complex **34B**, which is obtained from **34A** via alkene insertion followed by β-H elimination.



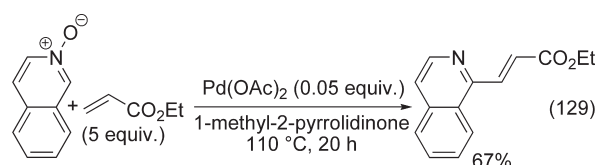
R = H, Z = CO₂t-Bu (91%), COMe (62%), Ph^a (64 %),
 PO(OEt)₂ (70%), t-Bu (53%), CONMe₂ (87%)
 Z = CO₂t-Bu, R = *p*-Ph (68%), *m*-Ph (88%), *o*-Ph (73%)
^aat 120 °C for 16 h



Y¹ = N, Y² = CH: 69%; Y¹ = CH, Y² = N: 76%



[Y = CH, Z = CO₂Et (86%), CO₂*n*-Bu (85%), CN (65%)
 R = H; Y = CMe, Z = CO₂Et (82%), CO₂*n*-Bu (90%)
 Y = N, Z = CO₂Et (95%)
 R = 4-Me, Y = CH, Z = CO₂Et (85%), CO₂*n*-Bu (80%)
 R = 6-Me, Y = CH, Z = CO₂Et (93%), CO₂*n*-Bu (92%)
 R = 8-OH, Y = CH, Z = CO₂Et (27%)



3.2.3. S-Arenes. The alkenylation of S-arenes has benefited from the range of studies performed with arenes and other heteroarenes. Most of the results are included in reports concerning the O- and N-arenes; they are summarized in Table 18 and eq 116 for thioazoles, in eq 87 for a thiophene and a benzothiophene substituted with a carboxylic group, eq 90 for polyfunctionalized γ -lactams bearing a thiophenyl unit as well as Table 19 for thiophenes. To our knowledge, the only paper mainly devoted to thiophenes is from Zhang et al. who have shown that under their conditions (Table 19, Entries 5–7, 9–15, 18 and 19), Cu(OAc)₂ instead of AgOAc, AcOH instead of DMF, or another base (DABCO except) instead of pyridine, dropped the yield.¹⁶³

4. CONCLUSIONS

The foregoing sections have clearly demonstrated the impressive progress made in the area of palladium-based formation of C–C bonds from the intermolecular coupling of C–H bonds. Whereas these reactions were first carried out using stoichiometric quantities of palladium, efficient catalytic methods are now available. Most catalytic DHRs use, however, an excess of either the arene or the alkene with, often, a relatively high Pd load, and require a terminal oxidant other than molecular oxygen, this terminal oxidant being sometimes expensive. These conditions, which could be a problem for applications on large scales, decrease, presently, the “green” aspect of these procedures and their compatibility with the atom economy principle. Moreover, a wide variety of C–C bond-forming reactions via C–H bond cleavages, as well as methods to control or improve the regioselectivity, which would be useful in organic synthesis, remain to be achieved.

The area of the dehydrogenative Heck reactions is still in its infancy. Given the growing number of papers related to this challenging subject and published over the past few years, many breakthroughs will be, undoubtedly, presented in the near future, leading to sustainable processes, which would be valuable tools for diverse academic and industrial applications.

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Jacques Muzart was born in 1946, in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at the Université de Reims Champagne-Ardenne and received his degrees (Doctorat de 3^{ème} cycle in 1972, Doctorat d'Etat in 1976) for his work with J.-P. Pète on photochemical rearrangements of α,β -epoxy ketones and β -diketones. He was appointed at the Centre National de la Recherche Scientifique (CNRS) in 1971 and spent 15 months (1977–1978) as a postdoctoral fellow of National Science Foundation working with E. J. Corey at Harvard University on natural product synthesis. In 1988, he was promoted to Directeur de Recherche CNRS. His research interests concentrate on transition metal-catalysis with particular emphasis on oxidations, asymmetric reactions, C–H activations and mechanisms. He is also involved in the valorization of agricultural byproduct and in the use of water and molten salts as solvents for organic synthesis.



Jean Le Bras was born in Brest and obtained his Engineering Diploma from ENSCP-Paris and his MSc. degree (DEA) from Université Pierre et Marie Curie. In 1996, he joined the group of Dr. Hani Amouri where he studied iridium mediated phenols functionalization and obtained his Ph.D in 1998. He then joined the group of Professor John A. Gladysz as a postdoctoral fellow in Salt Lake City (USA) and in Erlangen (Germany) and has worked on the synthesis of organometallic complexes with 17 valence electrons and polyyne diyl chains. In 2000, he became a CNRS fellow at Université de Reims Champagne Ardenne. His current interests are concentrated on transition metal-catalysis with particular emphasis on oxidations, C–H activation, and valorization of agricultural byproduct.

ACKNOWLEDGMENT

We thank Prof. Kitamura for correspondence. We are greatly indebted to co-workers, whose names are shown in the references, for their outstanding contributions.

LIST OF ABBREVIATIONS

ArH	arene
Boc	CO ₂ t-Bu
BQ	1,4-benzoquinone
Bz	benzoyl
Cy	cyclohexyl
DDQ	2,3-dichloro-5,6-dicyanoquinone
DHR	dehydrogenative Heck reaction
DMA	dimethylacetamide
MS	molecular sieves
Rx	reflux
TIPS	Si(i-Pr) ₃
Tf	SO ₂ CF ₃
p-Tol	p-MeC ₆ H ₄
TON	turnover number
X	halide, OTf
(YAr)H	heteroarene (Y = O, N, S).

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