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Review

Pd-Catalyzed Intermolecular Dehydrogenative Heck Reactions of Five-Membered Heteroarenes

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Abstract: The Pd-mediated cross-coupling of (hetero)arenes with alkenes may be an effective method for the formation of a C–C bond from two C–H bonds. Discovered by Fujiwara and co-workers in 1967, this reaction led to a number of reports that we firstly highlighted in 2011 (review with references till June 2010) and for which, we retained the name “dehydrogenative Heck reaction”. The topic, especially the reactions of five-membered heteroarenes, has been the subject of intensive research over the last ten years. The present review is limited to these dehydrogenative Heck reactions published since 2010, underlining the progress of the procedures.

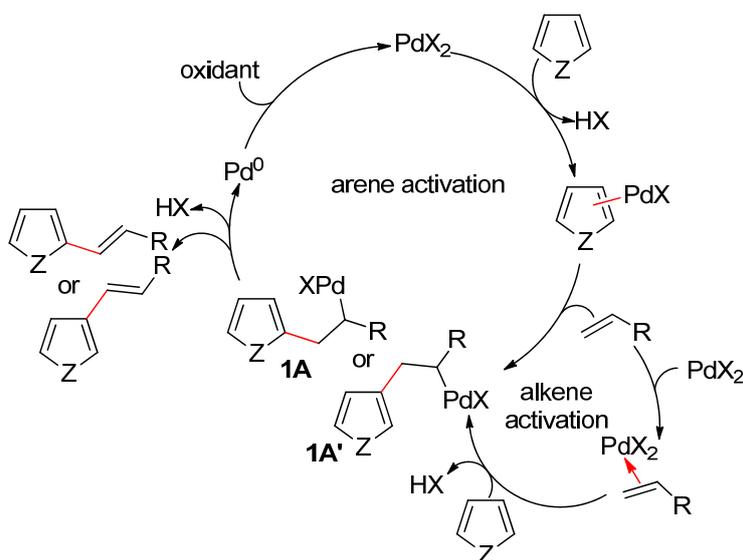
Keywords: palladium; heteroarenes; dehydrogenative cross-couplings; C–H activation

1. Introduction

Palladium-catalyzed C–H functionalization has been at the forefront of organic synthesis over the last half-century [1–4]. Through the multitude of reactions, the coupling leading to a C–C bond from two C–H bonds is an atom-economical process because any prefunctionalization is required. In the late sixties, Fujiwara’s team disclosed the Pd^{II}-mediated synthesis of stilbene from the cross-coupling of styrene with benzene [5,6]. This synthesis contrasts with the usual Pd-catalyzed method independently discovered by the teams of Mizoroki [7], Julia [8], and Heck [9] (The Mizoroki publication, submitted on 20, October, 1970, was cited by Heck’s team which submitted their report on 13, January, 1972. On 12, January, 1971, Julia’s team deposited a “Pli cacheté”, i.e., a sealed envelope, to the Société Chimique de France, which was open on 5, May, 1973.), which requires phenyl halide instead of benzene. Although the above Fujiwara cross-coupling initially occurred with a very low palladium turnover [6], such dehydrogenation reactions, which could be named “Dehydrogenative Heck Reactions” (DHRs), have been the subject of intensive research over the last half century leading to efficient catalytic procedures. We previously reviewed the corresponding literature with references until sep 2010 [10]. Through the DHRs, those of the five-membered heteroarenes have especially retained our attention, and are the subject of the present review which is limited to reports of the last ten years (For more general reviews containing some examples, see [11–15].) The reactions of fused bicyclic heteroarenes that do not involve the C–H bond of the small hetero ring (See examples in [16–18]) will be discarded. For convenience, the framework of the text depends on the nature of the aromatic substrate.

The simplified mechanism of DHRs usually admitted implicates the activation of a C–H bond of the arene by Pd^{II} species leading to an arylpalladium intermediate which adds to the alkene to provide **1A** or **1A'** (Scheme 1, arene activation). Subsequent β -H elimination delivers the cross-coupling product and Pd⁰. The active Pd^{II} species are regenerated with an oxidant. Another mechanism involving the coordination of the alkene to afford a η^2 -palladium complex susceptible to nucleophilic attack by the arene has been hypothesized (Scheme 1 alkene activation) [19]. Such a reaction would also afford intermediate **1A** or **1A'**. Both catalytic cycles describe dehydrogenative cross-coupling reactions, but a

reaction via the alkene complex cannot be named DHR. Broggini's team proposed the term "alkene activation" for the corresponding catalytic cycle [19]. In fact, coordination of the alkene to palladium decreased the electron density of the double bond, leading to its activation towards nucleophilic attack, that is, a Friedel–Crafts reaction. Electrospray ionization mass spectrometry (ESI-MS) [20–26] and nuclear magnetic resonance (NMR) [27] studies would favor the arene activation process for the majority of the dehydrogenative cross-coupling reactions.



Scheme 1. Catalytic cycles of the dehydrogenative cross-coupling reactions.

The site selectivity of the heteroarene is governed by the "innate" or "guided" C–H bond activation [13]. The former relies on the electronic properties of the heterocycle induced by the heteroatom [28], whereas the latter is relevant to either a directing group or a specific additive.

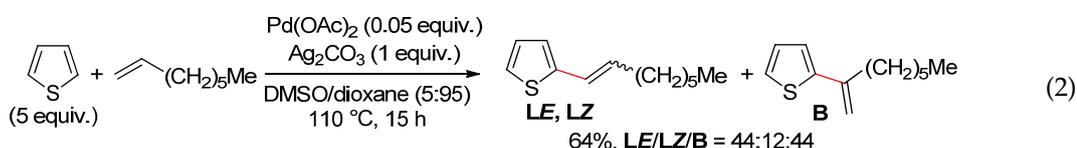
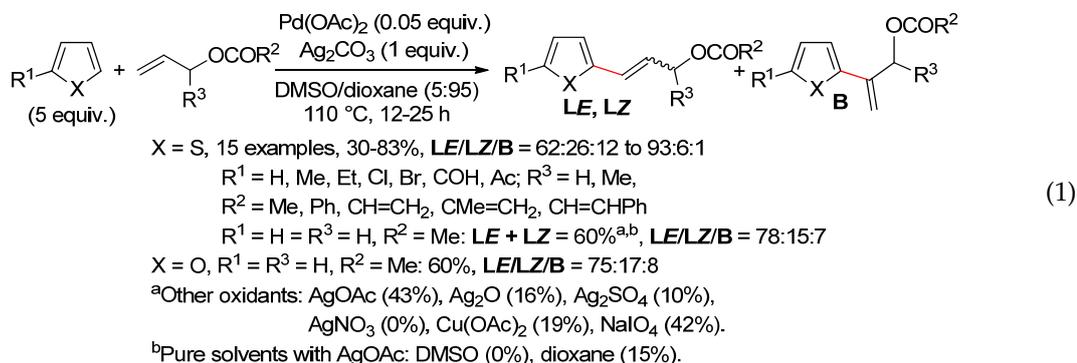
2. S-Arenes

2.1. Thiophenes

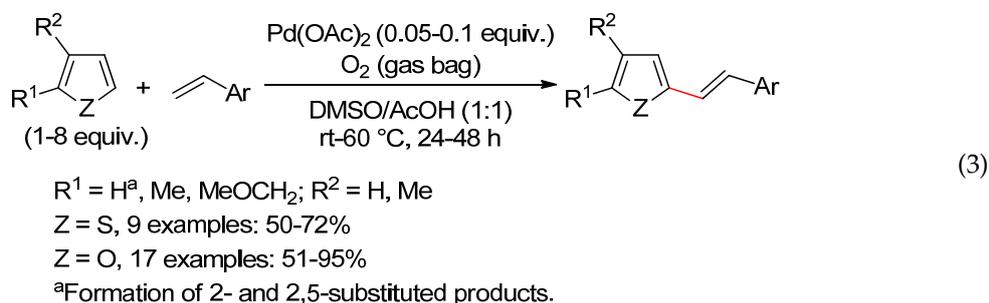
Subsequently to the report by Fujiwara's team on the cross-coupling of thiophene with styrene mediated by stoichiometric amounts of $\text{Pd}(\text{OAc})_2$ in refluxing AcOH /dioxane [29], Kozhevnikov disclosed catalytic conditions with $\text{Cu}(\text{OAc})_2$ to regenerate active Pd species and CaCl_2 as additive in DMF [30]. The catalyst turnover was low and other reoxidation methods, namely, $\text{Cu}(\text{OAc})_2/\text{air}$ [31,32], $\text{H}_6\text{PMo}_9\text{V}_3\text{O}_{40}$ [33], $\text{HPMo}_{11}\text{V}/\text{air}$ [34], and AgOAc [35], have been then proposed with various additives and solvents [10]. A number of procedures have been published since 2010.

Liu's team carried out the cross-coupling with allyl esters using $\text{Pd}(\text{OAc})_2/\text{Ag}_2\text{CO}_3$ in DMSO/dioxane leading to a 88:12-99:1 mixture of linear and branched compounds via β -H elimination rather than β - OCOR^2 elimination (For such competitions, see [36]) (Equation (1)) [37]. Other oxidants and use of pure solvents greatly depreciated the yields. The reaction also occurred with allyl phenyl

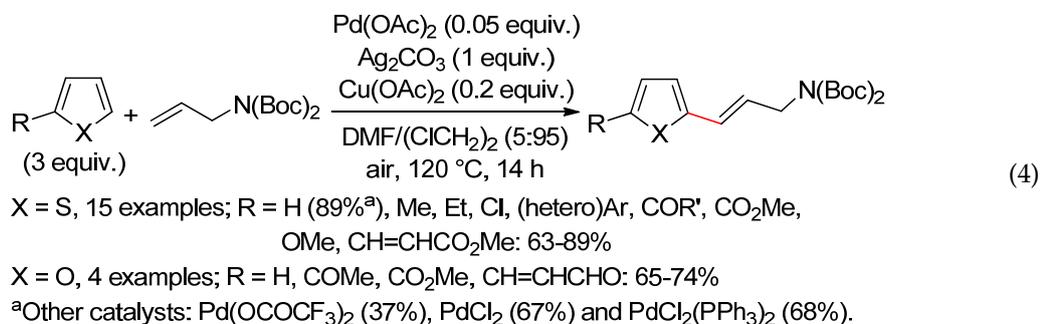
ether and 1-octene (Equation (2)). The formation of linear/branched products from 1-octene will be discussed in Sub-chapter 6.3.

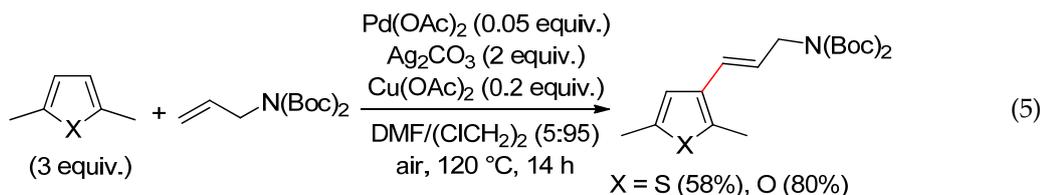


In DMSO/AcOH, thiophenes underwent efficient Pd(OAc)₂-catalyzed aerobic DHRs with styrenes (Equation (3)) [22]. Under these conditions, we observed that addition of metallic co-oxidants, such as AgOAc, Cu(OAc)₂, Mn(OAc)_n (*n* = 2 or 3), or MnO₂, disfavored the yields. (For the power of DMSO/O₂ to regenerate active Pd^{II} species, see [38,39].)

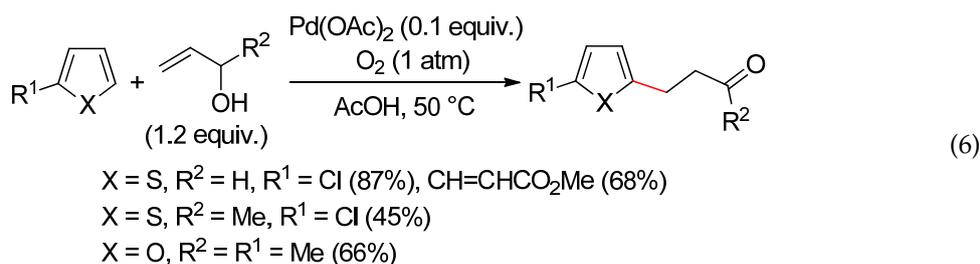


Xu and co-workers reported the Pd(OAc)₂-catalyzed C2-substitution of thiophenes with allylamines using Ag₂CO₃/Cu(OAc)₂/air as reoxidant (Equation (4)) [40]. Yields diminished with other Pd catalysts. The method led to C3-substitution from 2,5-dimethylthiophene (Equation (5)).

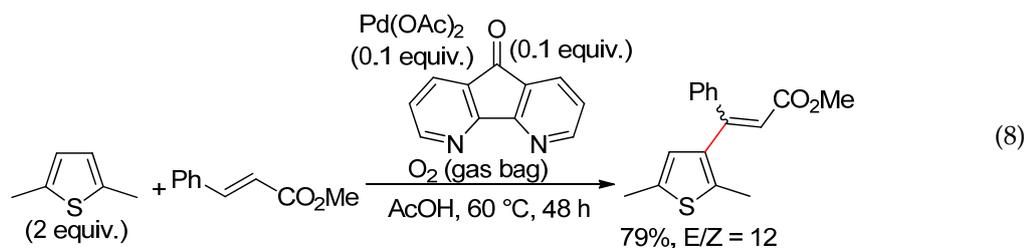
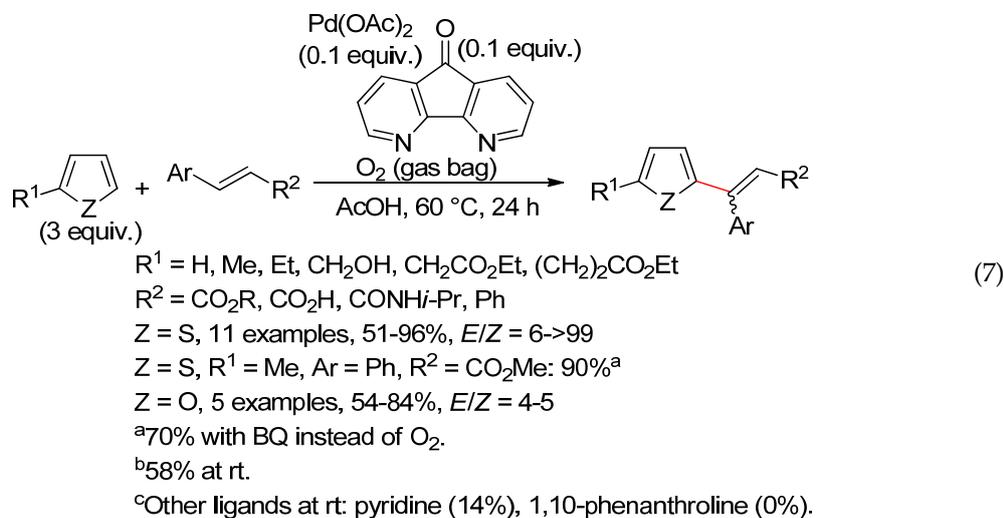


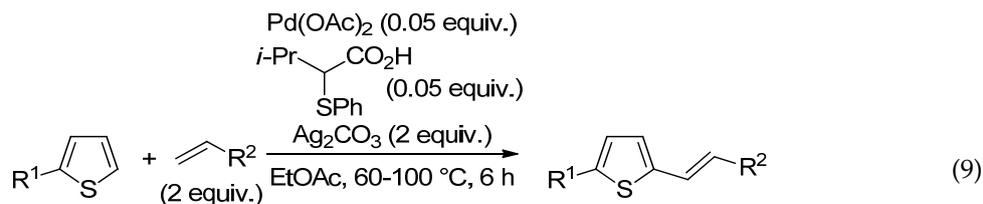


The aerobic DHR with allylic alcohols disclosed by Jiang's team (In contrast to the captions of the publication tables [41], oxygen was the sole oxidant. Personal communication from H. Jiang, 24, April, 2020.), led to aldehydes or ketones (Equation (6)) through hydrogen migration [41] as that occurs from the Heck reaction of such substrates [42].

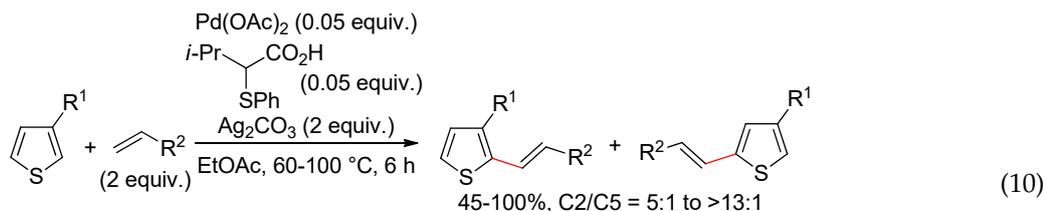


Procedures using palladium associated to various ligands have been reported for olefination with acrylates, enones, acrylamides, styrenes, vinyl phosphonates, or sulfones (Equations (7) and (8) [24], Equations (9) and (10) [43], Equations (11) and (12) [44], Equation (13) [45], and Equation (14), respectively [46]).



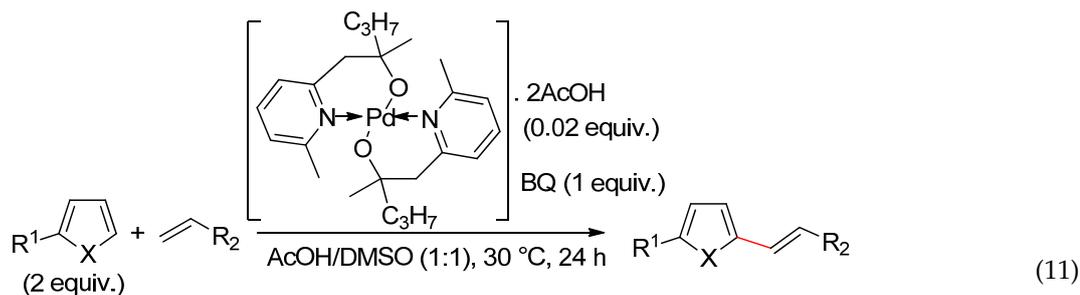


16 examples 40-97%; R¹ = H, Me, OMe, Ph, Br, Cl, CO₂Me, CN
 R² = CO₂R, COMe, CONMe₂, PO(OMe)₂, SO₂Ph
 R¹ = H, R² = CO₂Bu: 48% plus 13% of the diolefinated product.



14 examples; R¹ = Me, Et, Ar, Cl, CO₂Me; R² = CO₂R, COMe, CONMe₂, PO(OMe)₂, SO₂Ph
 R¹ = Me, R² = CO₂Bu: 69%, C2/C5 = 9:1^a
 R¹ = CO₂Me, R² = CO₂Bu: 41%, C2/C5 = 1:3

^aWithout ligand: 11%, C2/C5 = 2.4:1.



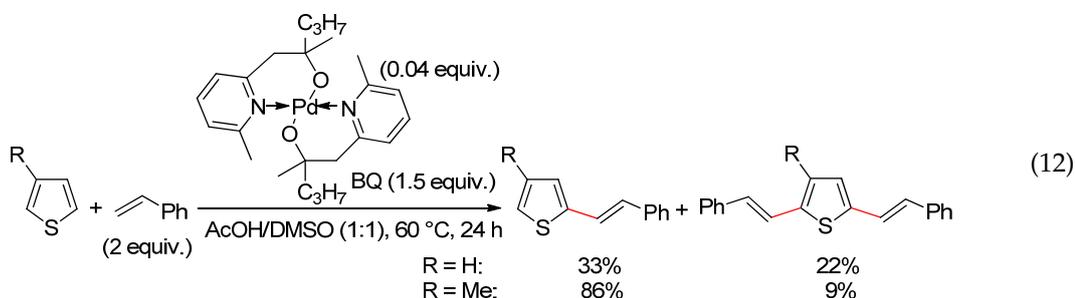
X = S, 20 examples, R¹ = Me, R² = Ph (95%)^{a,b,c}, *m*-ClC₆H₄ (80%), CH=CHCO₂Et (98%)
 R¹ = Br, R² = Ph (70%), *m*-ClC₆H₄ (83%), CH=CHCO₂Et (80%)

X = O, 4 examples, R¹ = Et, R² = Ph (81%), CH=CHCO₂*t*-Bu (70%)

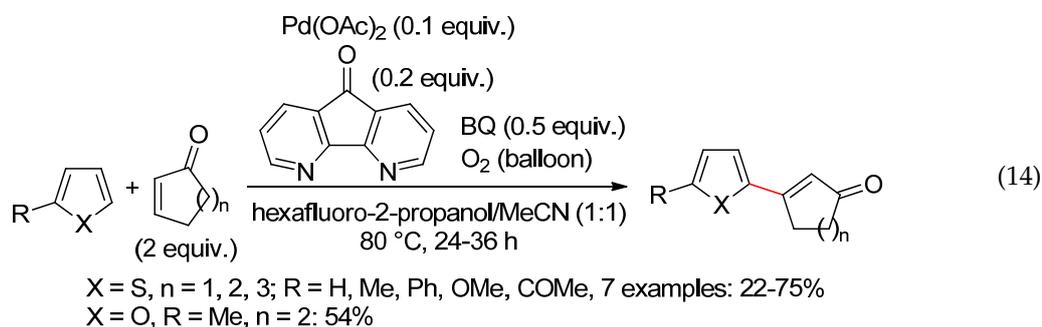
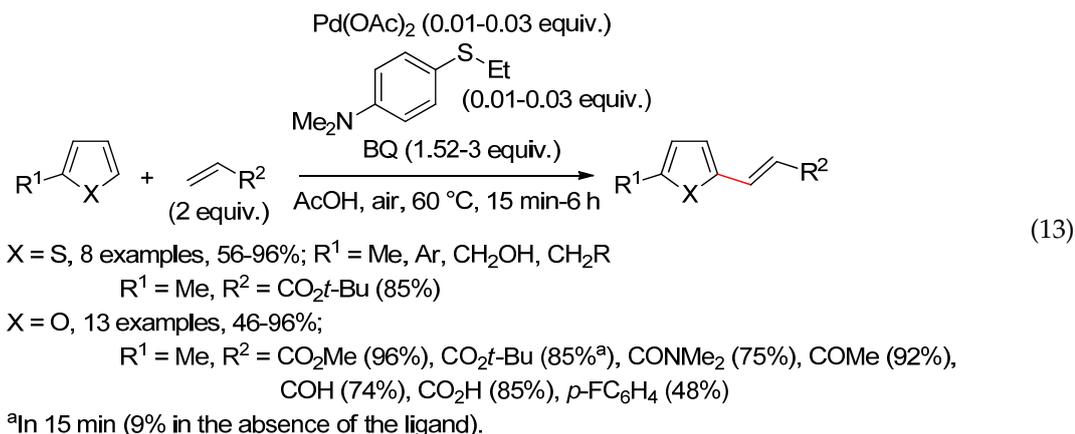
^aOther oxidants: Ag₂CO₃ (40%), Cu(OAc)₂ (trace), K₂S₂O₈ (trace).

^bPure solvents: AcOH (59%), DMSO (trace).

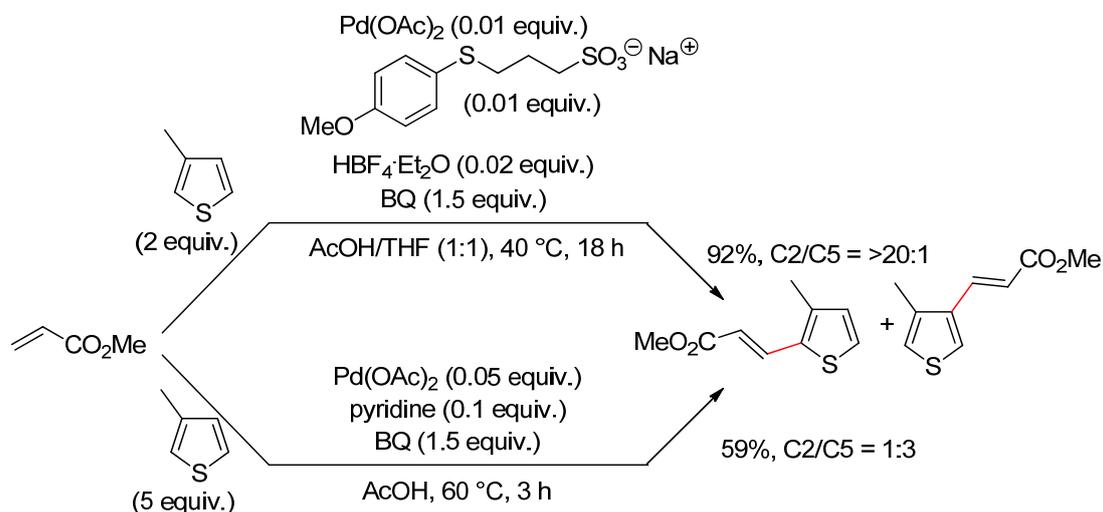
^cCatalyst with CMePh instead of CMeC₃H₇: 44%.



R = H: 33% 22%
 R = Me: 86% 9%

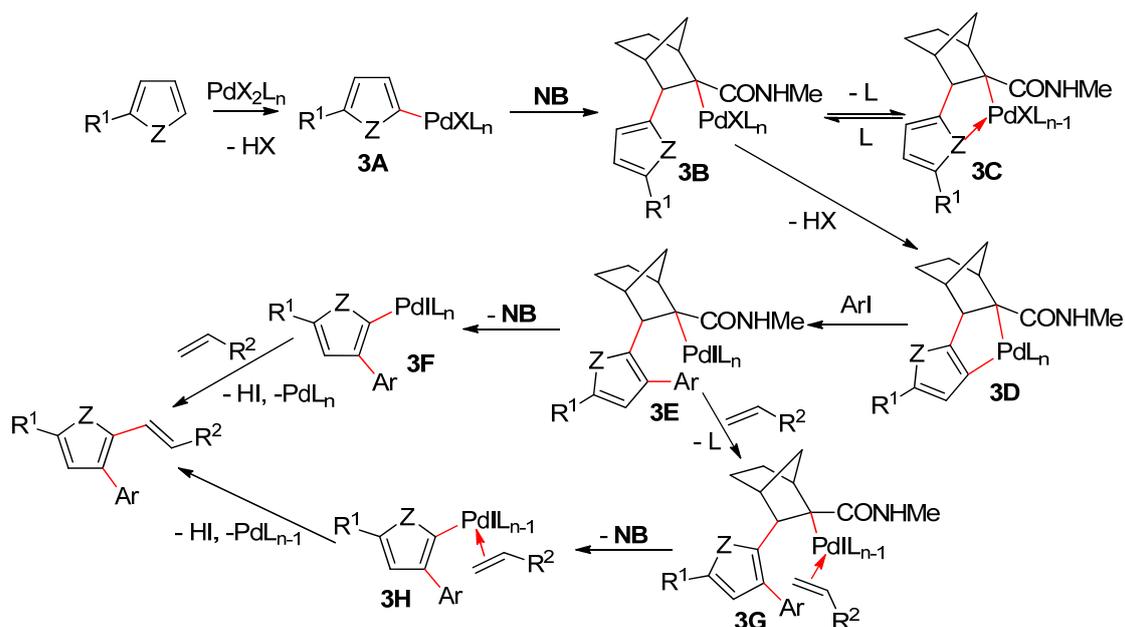


The selected ligands, especially 4,5-diazafluorenone [24], sodium 3-((4-methoxyphenyl)thio)propane-1-sulfonate, and 4-(ethylthio)-*N,N*-dimethylaniline [45], improve the stability of the catalyst and, consequently, the yields (Equations (7) and (13)), and also the selectivity (Scheme 2) [45].

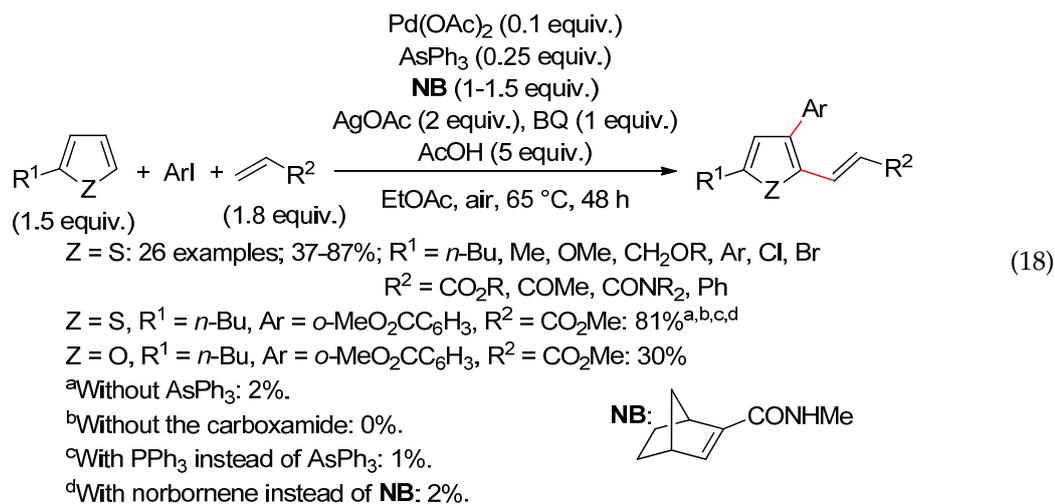


Scheme 2. Carrow's regiodivergent Dehydrogenative Heck Reactions (DHRs).

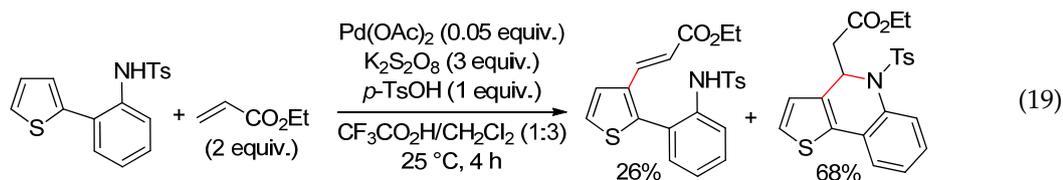
Jia, Xi, and coworkers prepared a heterogeneous catalyst from deposition of PdCl₂ onto the surface of MoS₂ nanosheets [47]. Small amounts of this catalyst mediated the effective C5 alkenylation of 3-ethylthiophene in DMF with Cu(OAc)₂ as oxidant (Equation (15)). The authors did not comment on the catalyst recyclability. Recently, De Vos' team prepared a palladium–organic framework (noted Pd@MOF-808-L1) from Pd(OAc)₂ and a metal–organic framework (noted MOF-808-L1) containing S,O-moieties, the latter increasing the catalytic activity of Pd^{II} [48]. DHR of 2,6-dimethylanisole with *n*-butyl acrylate showed that the catalytic power of Pd@MOF-808-L1 was superior to Pd(OAc)₂ (63% instead of 22%) and similar to a mixture of Pd(OAc)₂ and MOF-808-L1 added separately. Consequently,



Scheme 3. Plausible pathways of vicinal difunctionalizations.

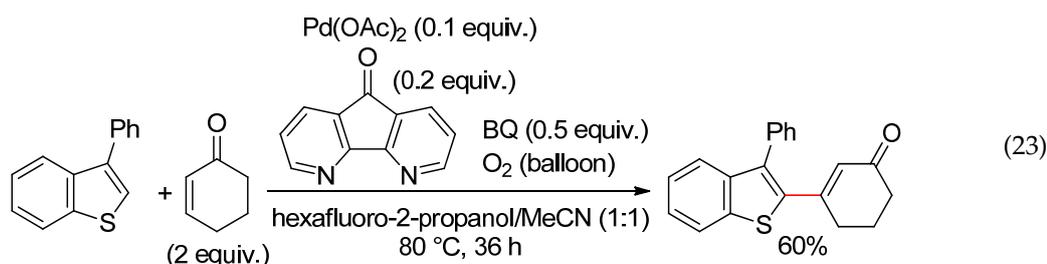
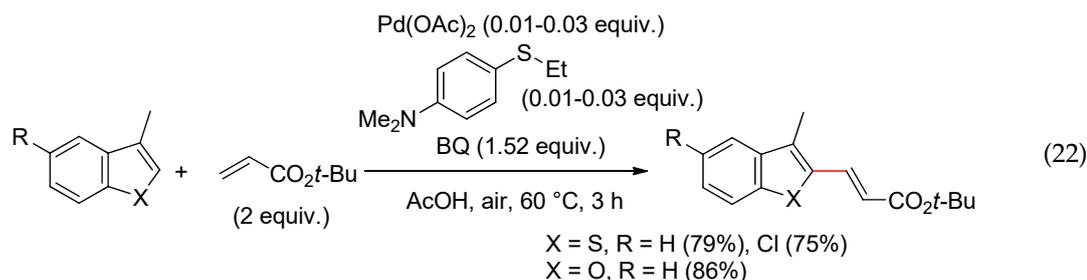
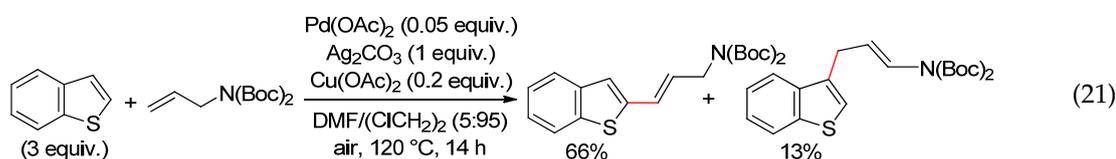
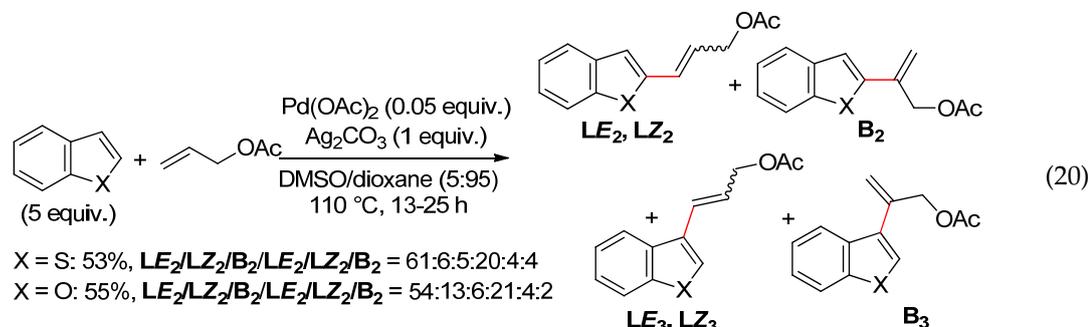


2-Thienyl-*N*-tosylaniline undergoes regioselective DHR with ethyl acrylate leading to the C3 substituted thiophene and a fused heterocycle due, according to Youn and co-workers, to subsequent cyclization of the C3 substituted thiophene (Equation (19)) [55]. We will come back in Sub-chapter 4.1. to the mechanism and catalytic cycle of substrates with a directing group (Scheme 9).



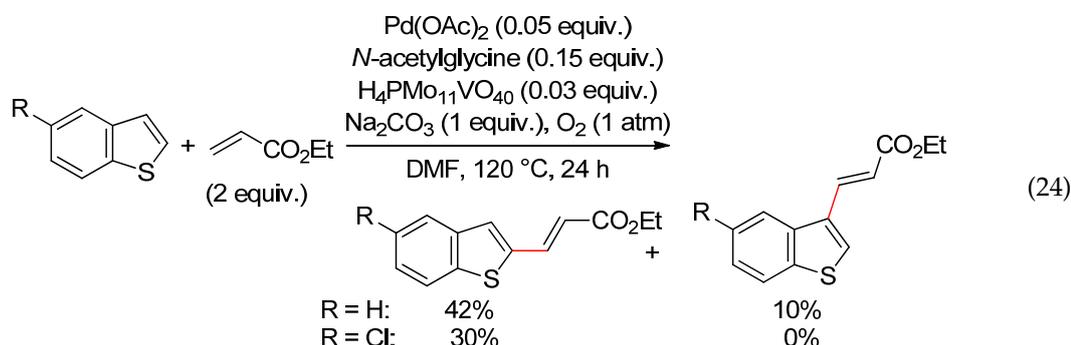
2.2. Benzothiophenes

Some of the above procedures have been used for DHRs of benzothiophenes (Equations (20) [37], (21) [40], (22) [45], and (23) [46]). A mixture of C-2 and C-3 cross-coupling products was obtained with allyl acetate and allyl amines, the 2 position being the most reactive (Equations (20) and (21)).

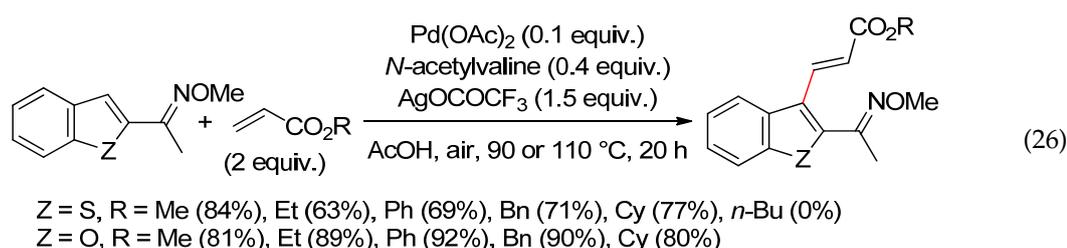
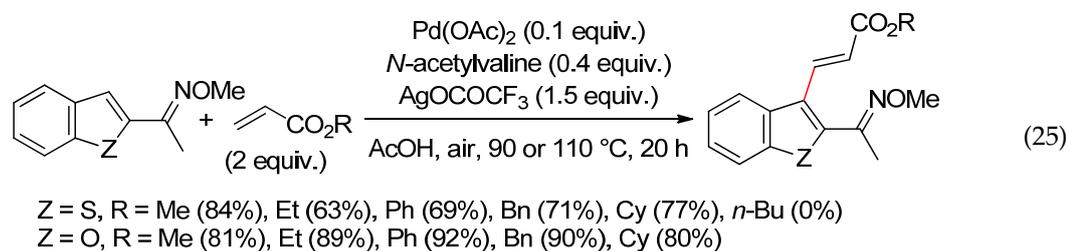


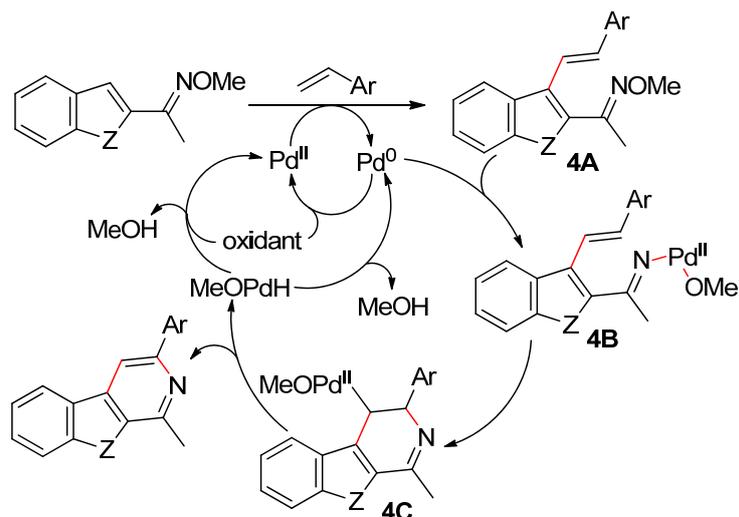
Yu's team disclosed the promotion of DHR's by monoprotected amino acids [56,57]. Such an additive led however to modest yields for the cross-coupling of benzothiophenes with ethyl acrylate, as reported by Huang, Lin, and co-workers, using Pd(OAc)₂ combined with 11-molybdovanadophosphoric acid and *N*-acetylglycine under oxygen [58]. The regioselectivity

depended on the substituents of the six-membered ring (Equation (24)). The procedure was nevertheless effective for benzofurans (see Equation (32)).



In contrast to the above example, the presence of *N*-acetylvaline allowed high yields of the Pd(OAc)_2 -catalyzed DHR of 1-(benzo[*b*]thiophen-2-yl)ethanone *O*-methyl oxime with acrylates (except butyl acrylate) using $\text{AgOCOCF}_3/\text{air}$ as oxidant (Equation (25)) [59]. Under these conditions, the cross-coupling with styrenes led to domino reactions giving annulation products, in improved yields with pyridine instead of *N*-acetylvaline (Equation (26)). According to Xia, Ji, and co-workers, the DHR product **4A** undergoes reaction with the simultaneously formed Pd^0 , giving **4B** via oxidative addition to N-O bond [60,61] (Scheme 4). Subsequent amino-Heck reaction provides **4C**, which endures β -H elimination, affording the annulation product and MeOPdH . Under the reaction conditions, the latter leads to Pd^{II} via, possibly, Pd^0 .

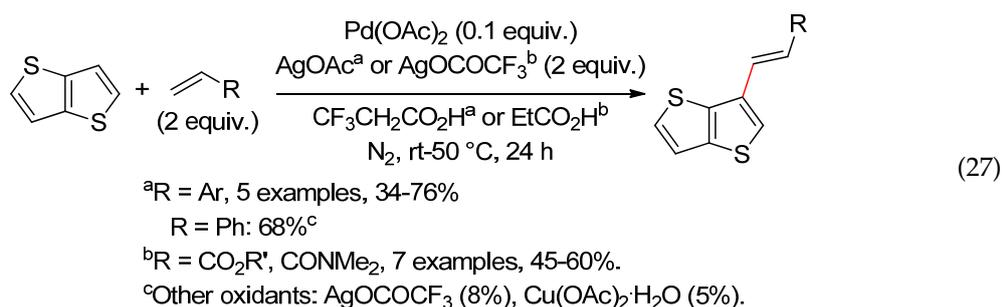




Scheme 4. Annulation via a Pd^{II}/Pd⁰ domino reaction.

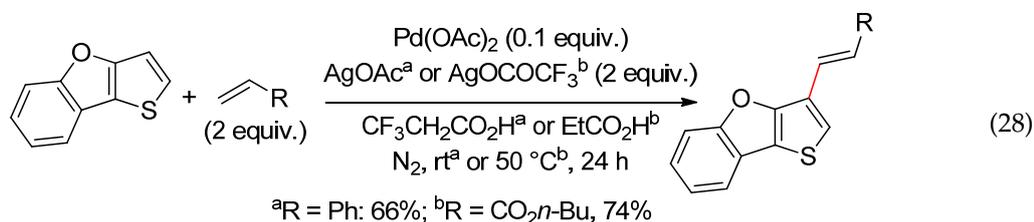
2.3. Thieno[3,2-*b*]thiophene

The best results of the Pd(OAc)₂-catalyzed DHR of thienothiophene with styrenes were obtained with AgOAc in CF₃CH₂CO₂H, while the coupling with acrylates and *N,N*-dimethylacrylamide was best carried out with AgOCOCF₃ in EtCO₂H (Equation (27)) [62].



2.4. Thieno[3,2-*b*]furan

Effective DHR of thieno[3,2-*b*]benzofuran with styrene and butyl acrylate (Equation (28)) was carried out under conditions of Equation (27) [62].



2.5. Sub-Conclusion

The 2-position of thiophenes and benzothiophenes is the most reactive towards the DHR. Regiodivergent reaction of thiophenes occurs when the 2- and 5-positions are already substituted or in the presence of a directing substituent. Regioselectivity may also depend on the ligand.

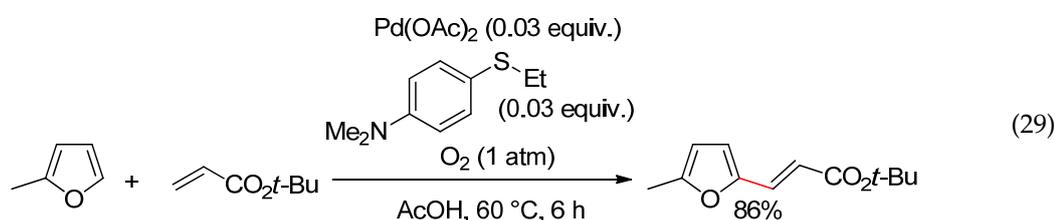
In contrast to thiophenes and benzothiophenes, thienothiophene and thienofuran react in the 3-position.

3. O-Arenes

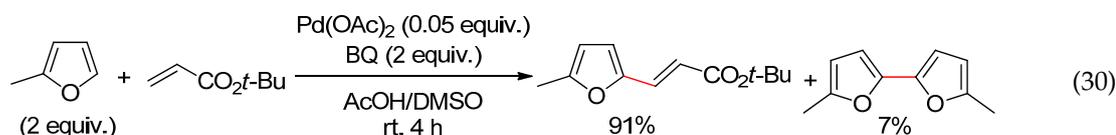
3.1. Furans

Subsequently to the reports by Kasahara's and Fujiwara's teams on the cross-coupling of furans with activated alkenes mediated by stoichiometric amounts of Pd(OAc)₂ in refluxing AcOH [63] or AcOH/dioxane [29], Kozhevnikov disclosed catalytic conditions with Cu(OAc)₂ to regenerate active Pd species [30]. Increased catalyst turnovers were subsequently reported with Cu(OAc)₂/O₂ [31,64], Cu(OAc)₂/air [32], benzoquinone (BQ), Cu(OAc)₂/BQ/O₂ [65], H₆PMo₉V₃O₄₀/air [33], HPMo₁₁V/air [34], BQ/*t*-BuOOH [66], AgOAc [35], or PhCO₃*t*-Bu [67] as oxidants with various additives and solvents [10].

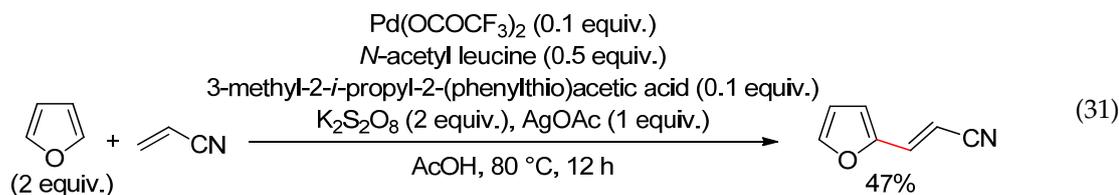
Most of the above DHR methods of thiophenes were also used for the reaction of furans (Equation (1) [37], Equation (3) [22], Equations (4) and (5) [40], Equation (6) [41], Equation (7) [24], Equation (12) [44], Equation (13) [45], Equation (14) [46], Equation (15) [47], Equation (16) [48], Equation (17) [49], and Equation (29) [46]). The difunctionalization of 2-butylfuran was also carried out (Equation (18)) [53].



We efficiently carried out the above DHR using BQ as oxidant, at room temperature, in AcOH/DMSO (Equation (30)) [21]. Slight homo-coupling of the furan was concomitantly observed.



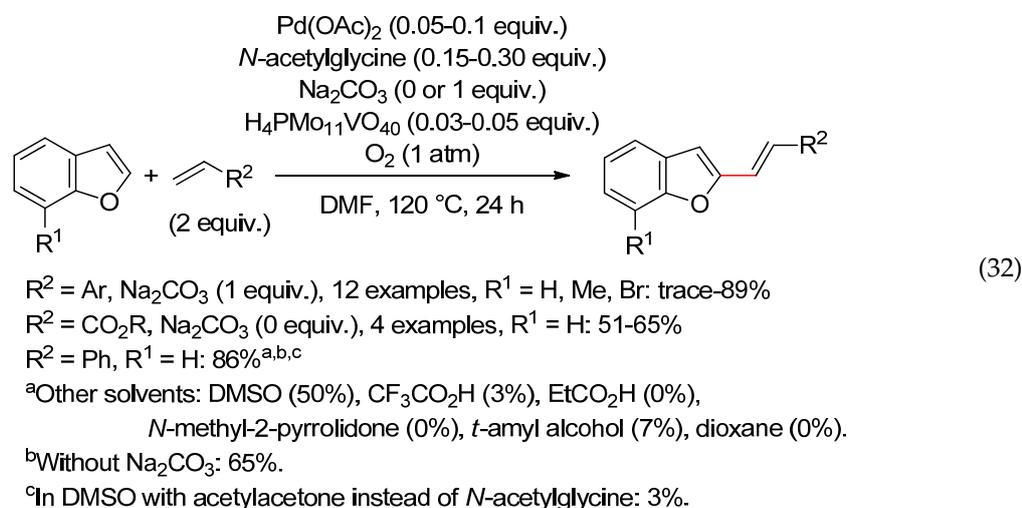
Recently, Zhu's team disclosed an efficient dual ligand-promoted DHR of aryl ethers, and applied their method to the dehydrogenative cross-coupling of furan with acrylonitrile [68]. The modest yield (Equation (31)) indicates that the sophisticated experimental conditions of the method are not adequate for such a substrate.



3.2. Benzofurans

In most cases, reports of the DHRs of benzothiophenes also provided DHRs of benzofurans (Equation (20) [37], Equation (22) [45], Equation (25), and Equation (26) [59]). Although *N*-acetylglycine

was not effective for the DHR of benzothiophenes using Pd(OAc)₂/H₄PMo₁₁VO₄₀/O₂ (Equation (24)), this additive may mediate fair to high yields from benzofurans (Equation (32)) [58].



3.3. Sub-Conclusion

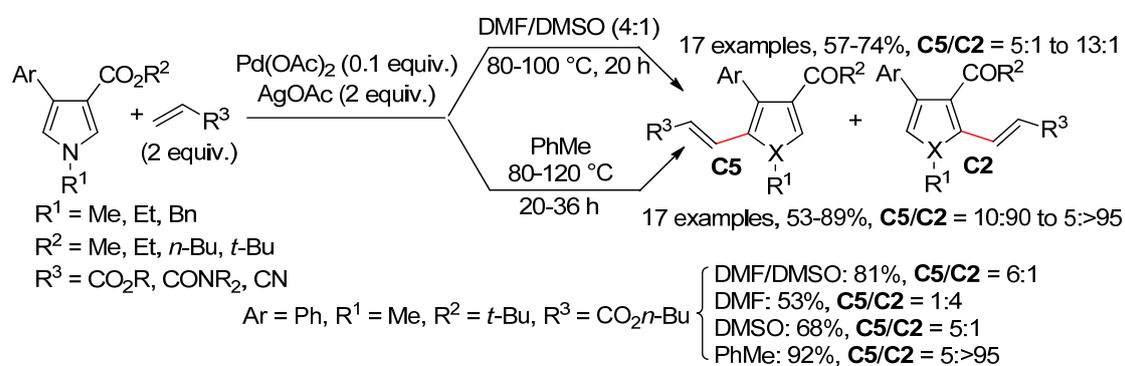
The exchange of the S atom for the O atom has no effect on the DHR regioselectivity of the five-membered heterocycle, the 2-position of furans and benzofurans being the most reactive in the absence of particular substituents.

4. N-Arenes

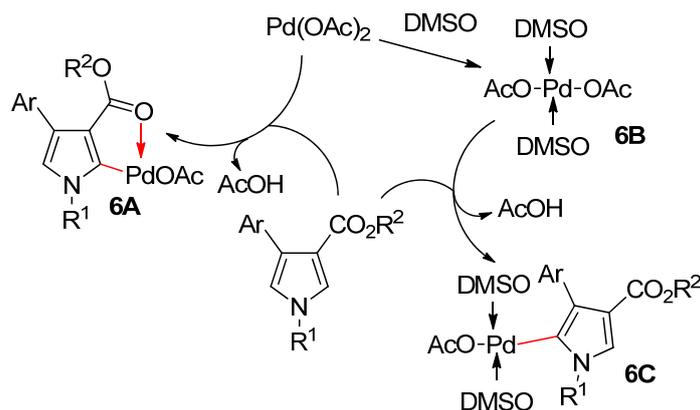
4.1. Pyrroles

In 1973, Fujiwara's team disclosed the synthesis of 2- and 3-styryl-*N*-methylpyrroles from stoichiometric amounts of *N*-methylpyrrole, styrene, and Pd(OAc)₂ in refluxing AcOH/dioxane [29]. Various catalytic conditions are related in our 2011 review [10].

The regioselectivity of the alkenylation of 4-aryl-1*H*-pyrrole-3-carboxylates is highly dependent on the solvent (Scheme 5) [69,70]. In benzene, assisted chelation by the carboxylate would favor the formation of **6A** (Scheme 6). DMSO which is a strong coordinating solvent would add to Pd(OAc)₂ to afford **6B** [71]. That overrides the chelation with the carboxylate and promotes the palladation at C5 position giving **6C** as intermediate. Subsequent reaction of **6A** and **6C** with the alkenylating agent affords the two DHR products (Scheme 1).

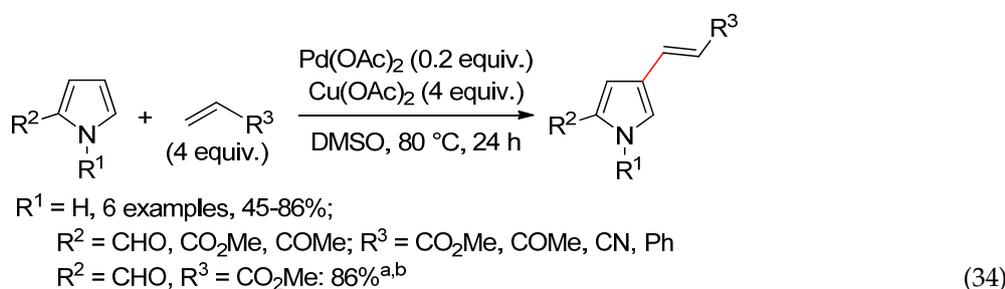
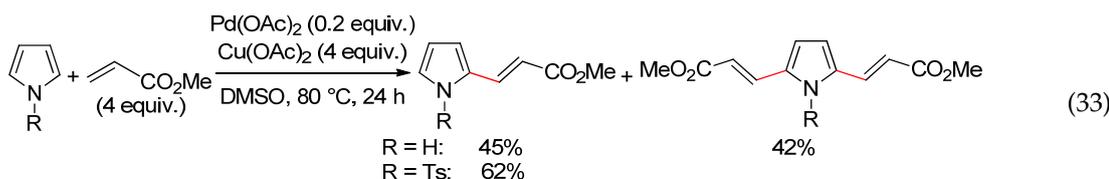


Scheme 5. Lin and Yao's regiodivergent DHRs.



Scheme 6. Regioselectivity depending on intra- or inter-coordination.

The DHR with Pd(OAc)₂/Cu(OAc)₂ in DMSO of free (NH)-pyrrole occurred in C2 and C5 positions, while *N*-tosylpyrrole afforded the mono-adduct (Equation (33)) [72]. In contrast, free (NH)-pyrrole with an electron-withdrawing C2 substituent led to alkenylation in C4 position (Equation (34)). The same regioselectivity was observed from *N*-methyl, *N*-benzyl, and *N*-tosylpyrroles, the latter reacting under different conditions (Equation (34)). Subjected the cross-coupling products to a second DHR led to C5 substitution with, in the case of the tosylpyrrole, a domino reaction leading to an indole (Scheme 7).



R¹ = H, 6 examples, 45–86%;

R² = CHO, CO₂Me, COMe; R³ = CO₂Me, COMe, CN, Ph

R² = CHO, R³ = CO₂Me: 86%^{a,b}

R¹ = Me, R² = COMe, R³ = CO₂Me: 56%

R¹ = PhCHMe, R² = R³ = CO₂Me: 53%

R¹ = Ts, R² = CHO, R³ = CO₂Me: 42%^c

^aWith Pd(OAc)₂ (0.1 equiv.) and Cu(OAc)₂ (2 equiv.): 53%.

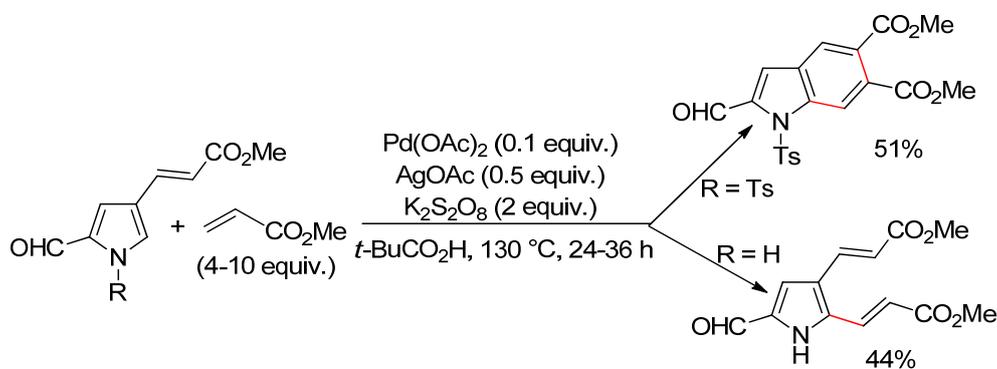
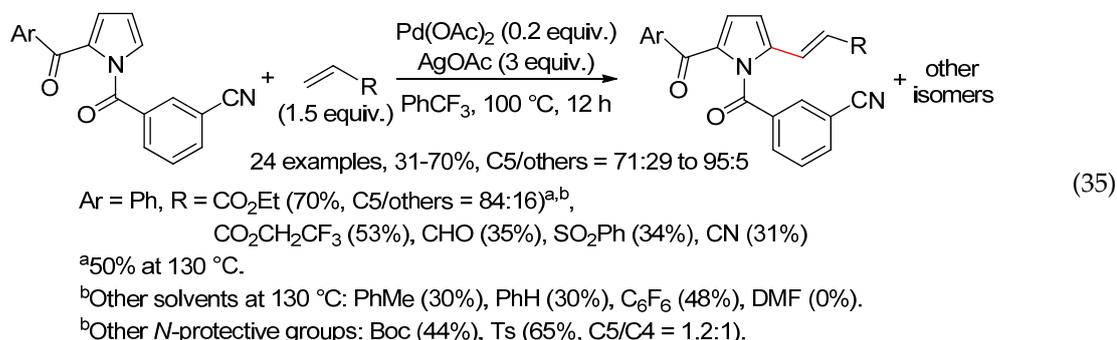
^bOther oxidants (2 equiv.) with Pd(OAc)₂ (0.1 equiv.):

AgOAc (31%), K₂S₂O₈ (0%).

^cUsing Pd(OAc)₂ (0.1 equiv.), AgNO₃ (3 equiv.) in MeCN at 80°C for 24 h.

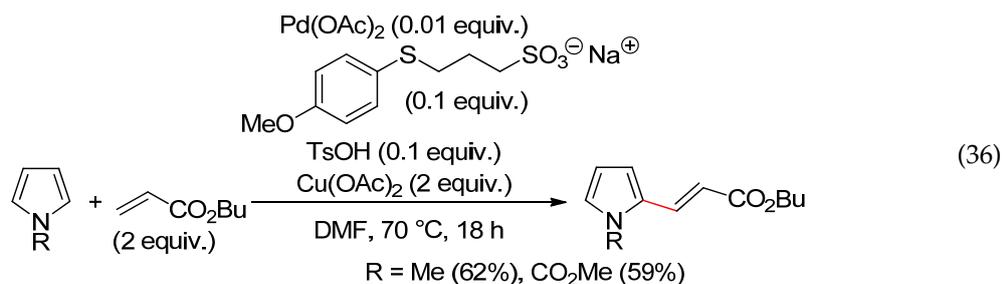
In contrast to the above, the DHR of *N*-(*p*-NCC₆H₄CO)-2-acylpyrroles mainly occurred at the C5 position (Equation (35)) [73]. According to Sun and co-workers, the carbonyl of the protecting group

could have a directing effect but “should not be dominant for this C5-alkenylation”. We suspect a C5 selectivity favored by coordination of the nitrile moiety to Pd-intermediates.



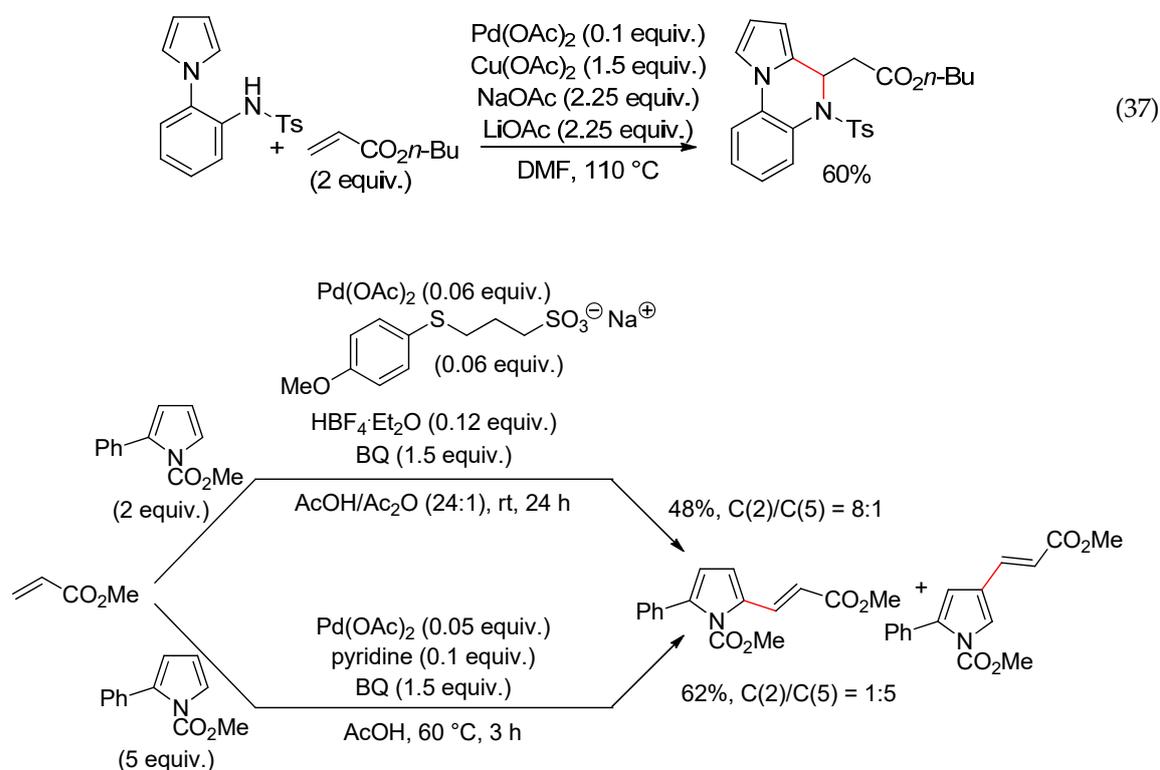
Scheme 7. Domino reaction or not depending on N substitution.

The thioether previously used as additive (Scheme 2) also participated in the DHR of *N*-protected pyrroles (Equation (36)), directing the reaction to the 5-position of 2-phenyl-pyrroles (Scheme 8) [45].

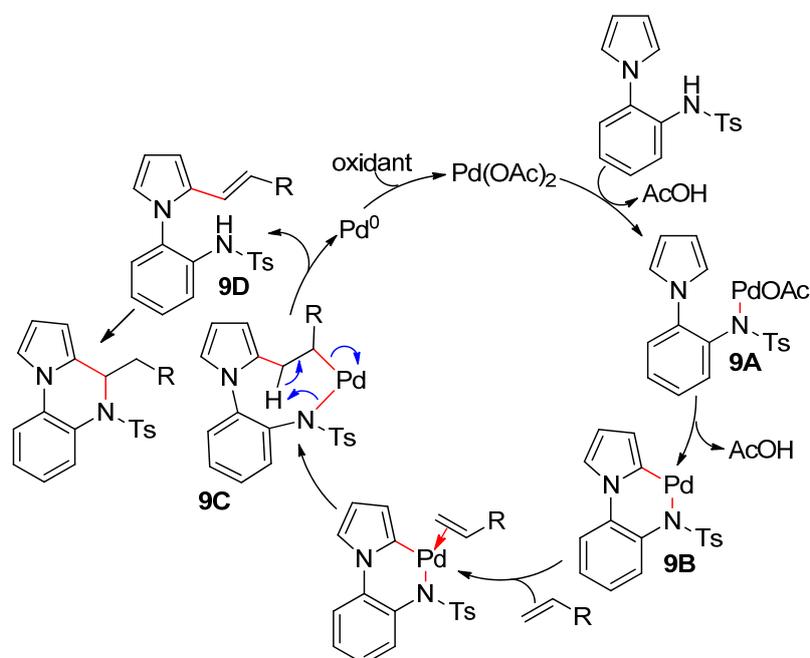


Reaction of *N*-(2-(1*H*-pyrrol-1-yl)phenyl)-4-methylbenzenesulfonamide with butyl acrylate provided a quinoxaline derivative (Equation (37)) [74]. According to Xiao, Wang, and co-workers, the reaction pathway begins with the palladation of the secondary nitrogen giving **9A** (Scheme 9, this scheme differs from that proposed by the authors [74], and also by Youn’s team [55]). Selective activation of the α-C–H bond of the pyrrole provides palladacycle **9B**. Coordination of the alkenating

agent followed by insertion into the C-Pd bond affords **9C**. Nitrogen-assisted β -hydrogen elimination leads to **9D**. Subsequent hydroamination gives the product.

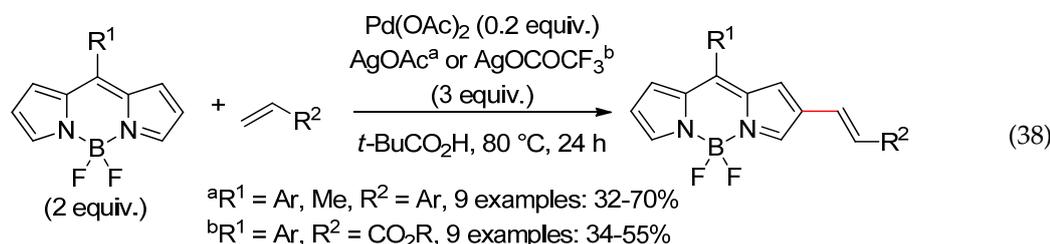


Scheme 8. Carrow's regiodivergent DHRs.



Scheme 9. Annulation of *N*-(2-(1*H*-pyrrol-1-yl)phenyl)-4-methylbenzenesulfonamide.

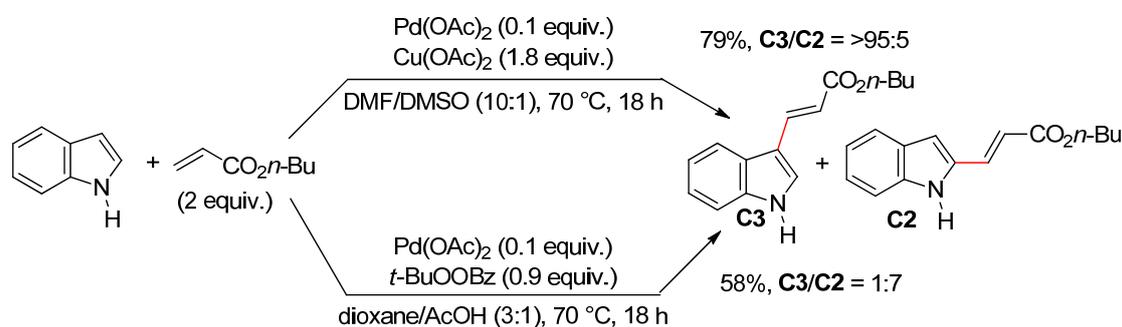
Pd^{II}-catalyzed DHRs of boron dipyrromethene derivatives were carried out with either styrenes and AgOAc [75] or acrylates and AgOCOCF₃ (Equation (38)) [76], affording dyes with improved properties.



4.2. Indoles

Our 2011 review [10] contains a great number of DHRs of indoles. The topic continued to retain the attention of researchers resulting into papers with different N-protecting groups and experimental conditions. Reviews not limited to palladium catalysis and DHR have been published [77–79]. As pointed in the introduction chapter, we will limit the examples to the DHRs of the heterocycle (For reactions at C4, C5, C6, and C7 positions of the benzenoid ring, see [18]).

Before presenting the results of the ten last years, it is necessary to remember the important communication of Gaunt and co-workers who, in 2005, disclosed the selective 2- or 3-alkenylation of free (NH) indoles, depending on the experimental conditions, especially the solvent (Scheme 10) [80]. The optimum conditions also allowed the selective 3-alkenylation of *N*-methyl indole but were ineffective for the C2. According to the authors, the reaction starts with palladation at C3. Acidic conditions would allow migration of the C3-Pd bond leading to C2-Pd bond, hence the observed results.

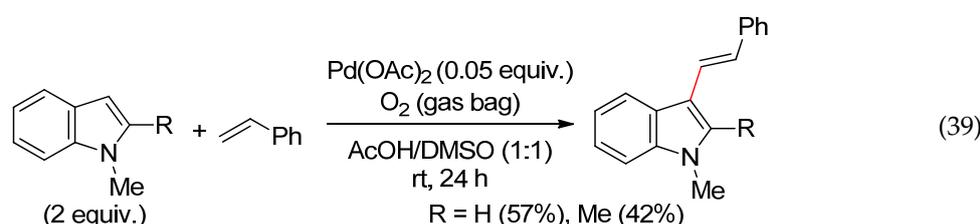


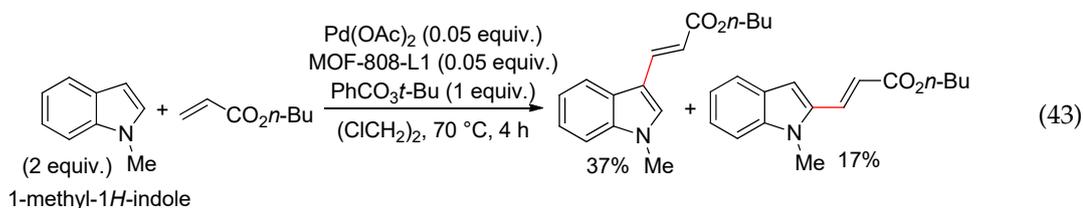
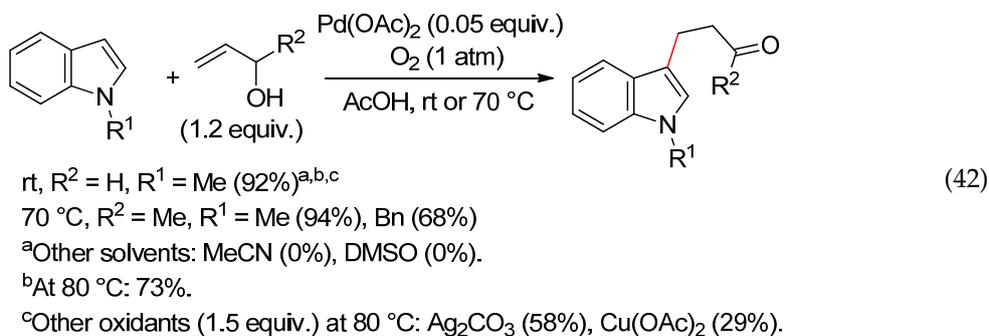
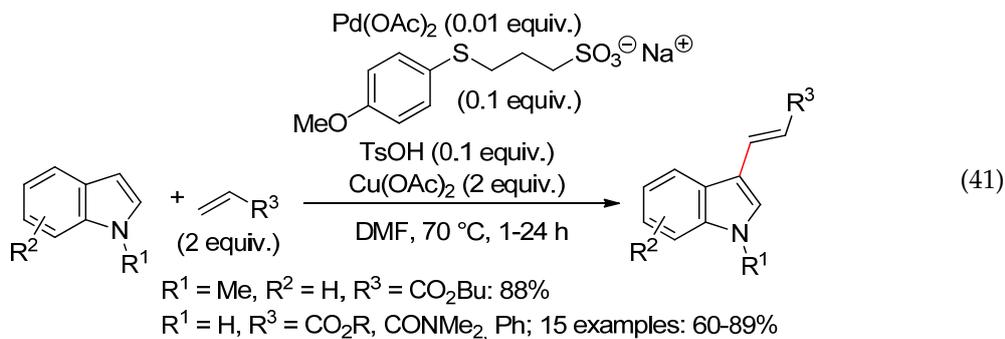
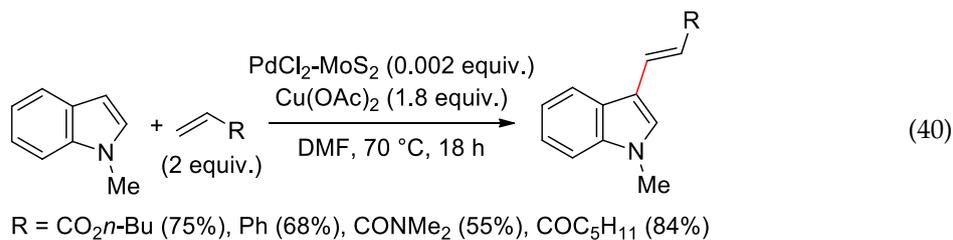
Scheme 10. Gaunt's divergent DHRs.

This chapter is divided in three parts corresponding to reactions in C3, C2, or both C2 and C3 positions.

4.2.1. C3 Alkenylations

Some of the above procedures have been used (Equations (39) [22], (40) [47], (41) [45], and (42) [41]). Surprisingly, the addition of metallic co-oxidants may have a negative effect on the aerobic DHR [22]. The Pd(OAc)₂/MOF-808-L1/PhCO₃*t*-Bu procedure (Equation (16)) mainly led to C3 alkenylation of 1-methyl-1*H*-indole (Equation (43)) [48]

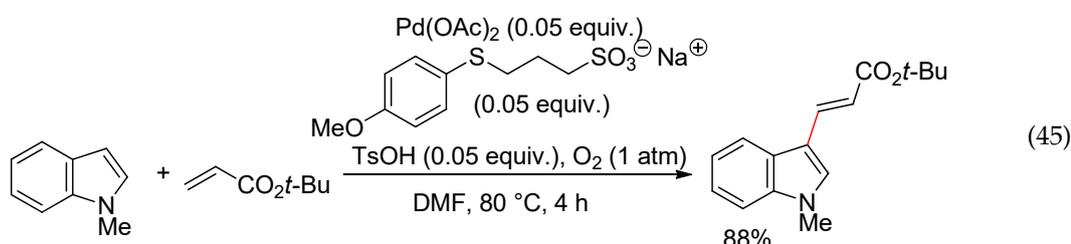
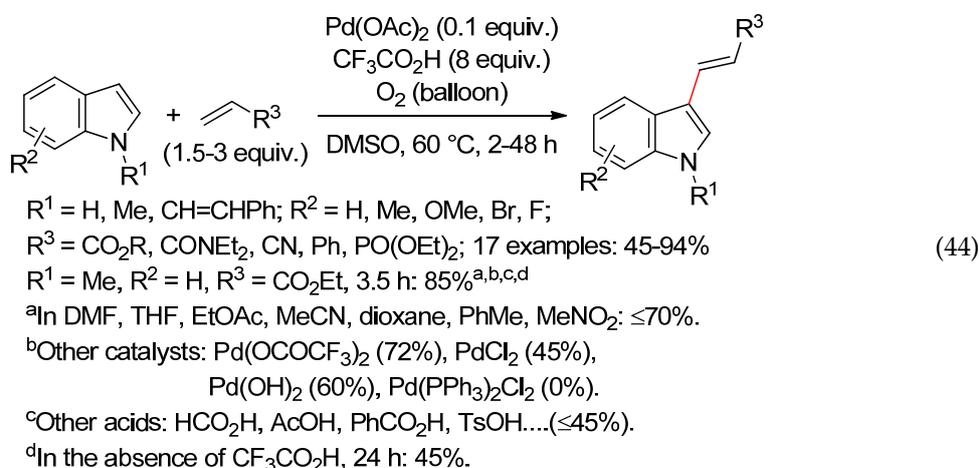




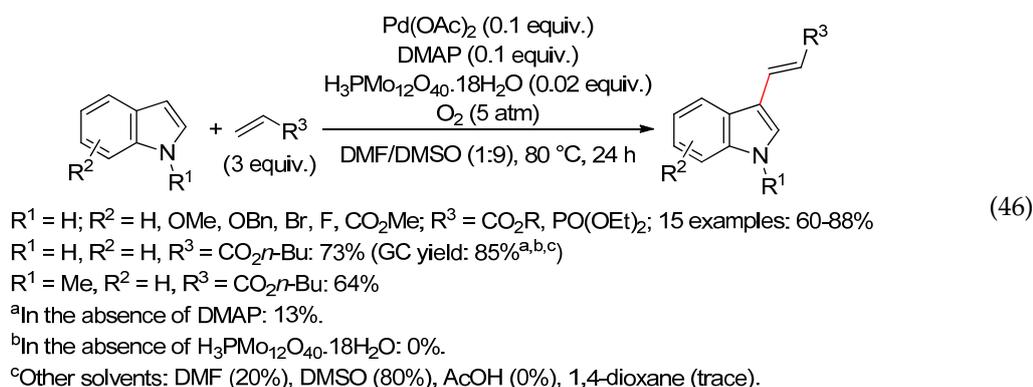
Other aerobic procedures have been proposed.

The PdX₂/acid/DMSO method is very sensitive to the nature of X and the acid, Pd(OAc)₂/CF₃CO₂H being the optimum (Equation (44)) [81]. The cross-coupling occurred with lower yields in other solvents. In fact, the Pd coordination ability of DMSO could prevent the precipitation of Pd⁰ [80,82]. Although

TsOH was ineffective for the PdX₂/acid/DMSO method (Equation (44)), this acid was retained for the DHR in the presence of a thioether ligand (Equation (45)) [45].

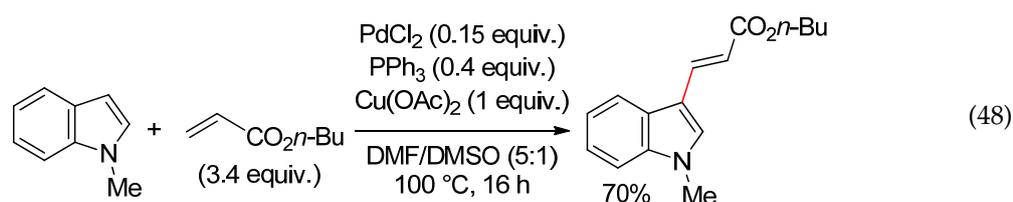
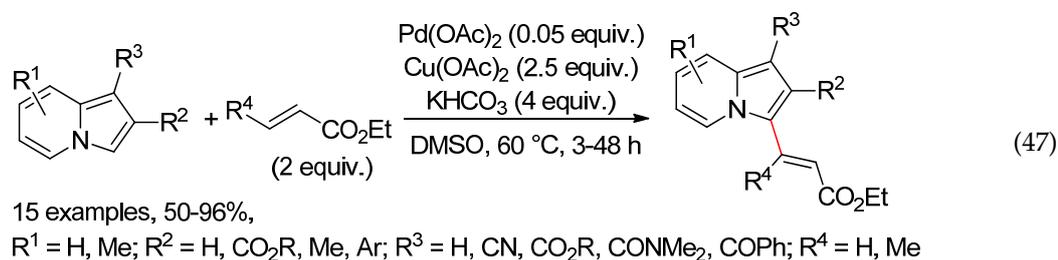


Catalytic amounts of Pd(OAc)₂ and a molybdophosphoric acid with 4-dimethylaminopyridine under oxygen pressure in DMF/DMSO led to DHRs of various indoles. All components and solvents have a decisive role on the yields (Equation (46)) [83].

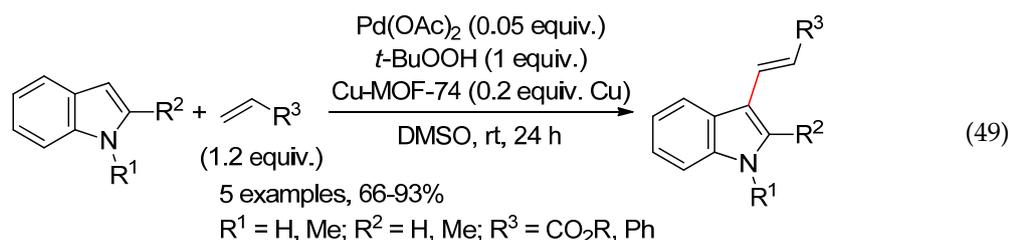


DMF/DMSO was also the solvent mixture for the catalytic DHR of free (NH) indoles with maleimides (Equation (47)) [84]. The DHR of *N*-methylindole with butyl acrylate arose in fair yield using PdCl₂/PPh₃/Cu(OAc)₂ in the solvent mixture (Equation (48)) (Under these conditions, free (NH)

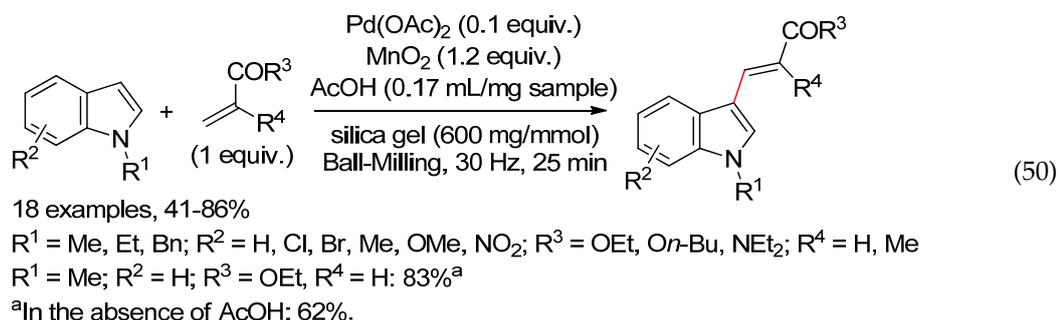
indoles led mainly to annulation products, like those of Equation (61)) [85]. Note that yields may depend on the DMF/DMSO ratio [85].



t-Butylhydroperoxide associated to catalytic amounts of a heterogeneous copper catalyst has been proposed as reoxidant for the Pd(OAc)₂-catalyzed DHR of free (NH) and *N*-methylindoles in DMSO (Equation (49)) [86].

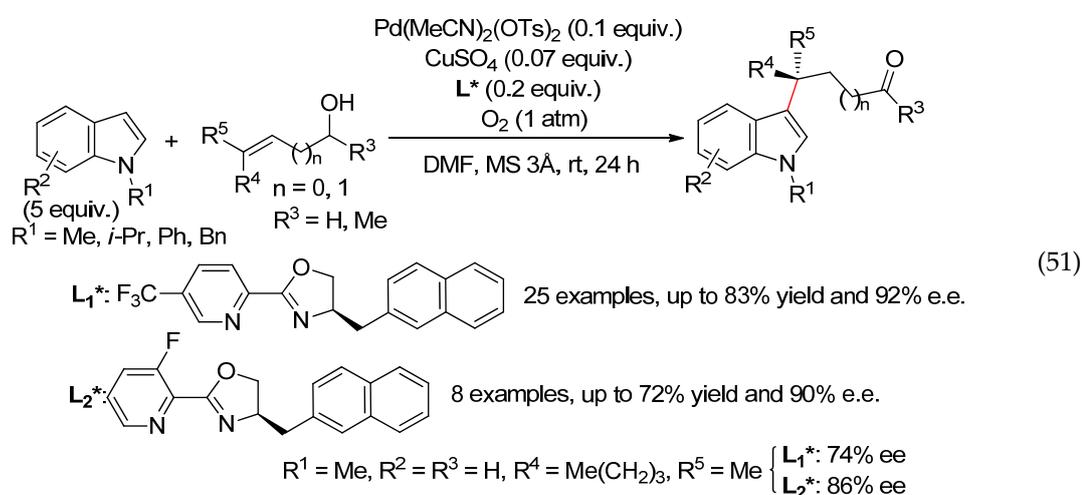


Bolm's team introduced the mechanochemical activation for solventless Rh-catalyzed DHRs [87]. Su and co-workers used this high-speed ball-milling process for the fast Pd-catalyzed C3 alkenylation of indoles with MnO₂ as oxidant (Equation (50)) [25].



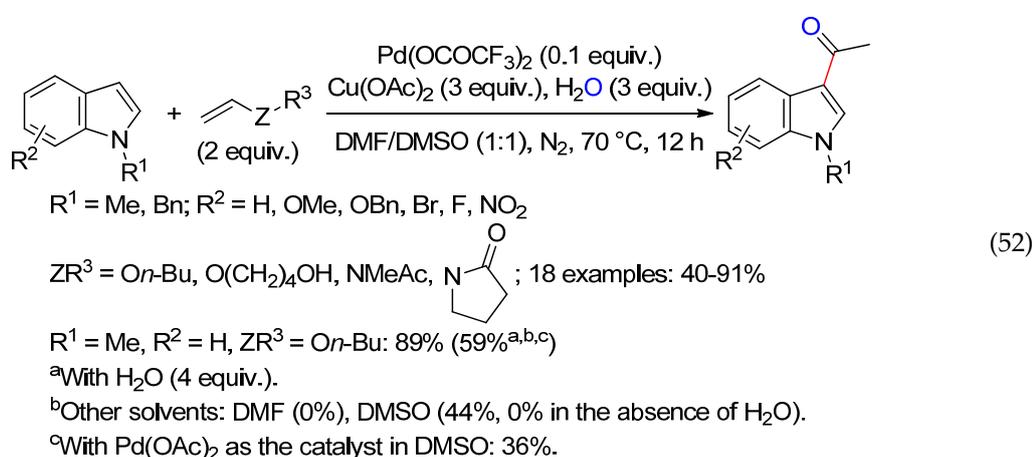
On the basis of their previous studies [88,89], Sigman and co-workers used chiral pyridine oxazoline ligands to perform the enantioselective DHR of indoles with prochiral unsaturated alcohols [90]. Yields and enantioselectivities greatly depended on the substitution of the ligand. Ligands with a naphthyl

group such as L_1^* and L_2^* were particularly effective providing aldehydes and ketones in good yields with e.e. up to 92% (Equation (51)).

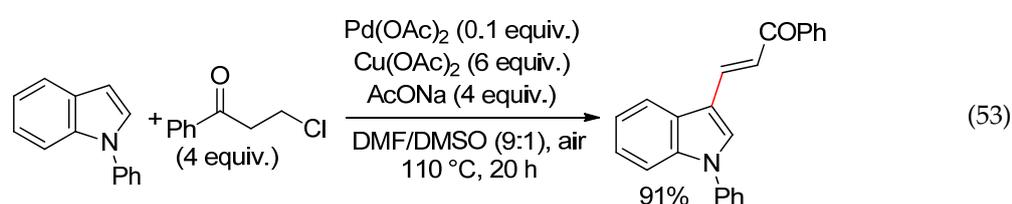


The domino C3 styrenation/annulation with the benzothiophene with an *O*-methylketoxime group depicted in Chapter 2.2 also occurred with the corresponding indoles (Equation (26)) [59].

Using $\text{Pd}(\text{OCOFC}_3)_2/\text{Cu}(\text{OAc})_2/\text{H}_2\text{O}$ in DMF/DMSO, enol ethers, and enamides underwent reaction with indoles at their α -position to afford the branched adduct, which, under the reaction conditions, led to 3-acylindoles (Equation (52)) [91]. The team of Li and Xiao proposed a mechanism involving alkene activation as depicted in Scheme 1. Nevertheless, a DHR mechanism cannot be discarded, since the Heck reaction of acyclic enol ethers and enamides could also occur at the α -position [92–94].

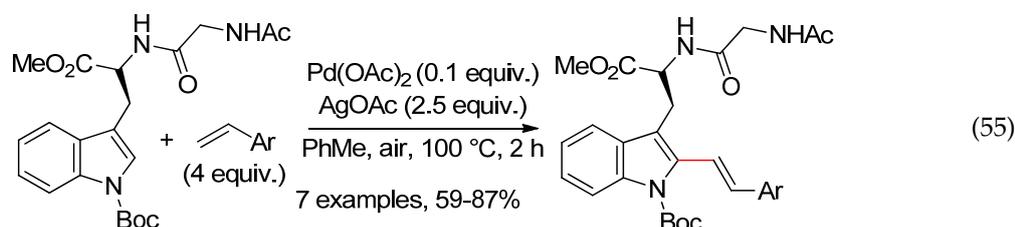
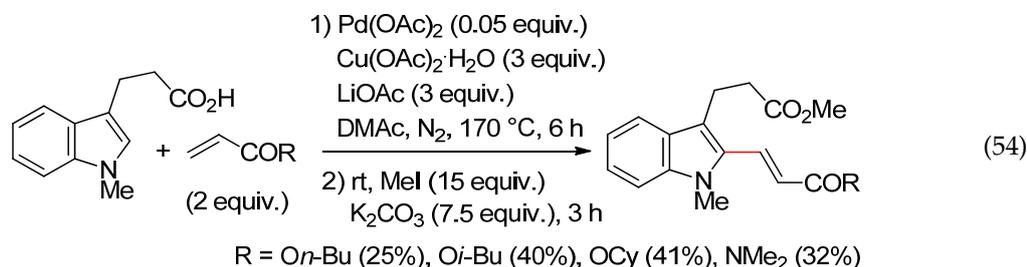


Reaction of *N*-phenylindole with 3-chloro-1-phenylpropan-1-one provided high yield of the C3 alkenylation, via in situ generation of the enone from the β -chloro ketone (Equation (53)) [95]. (Under these conditions, *N*-alkyl, *N*-benzyl, and *N*-allylindoles led mainly to annulation products, like those of Equation (61).)

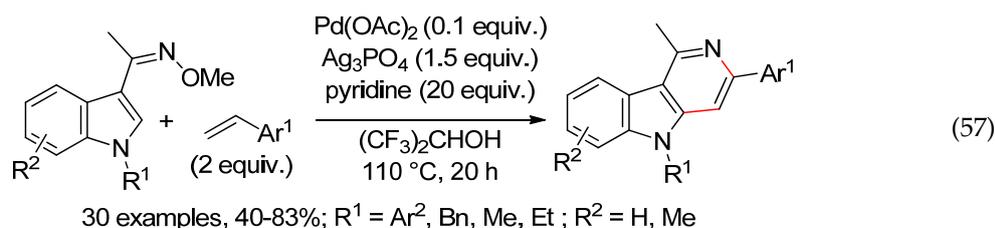
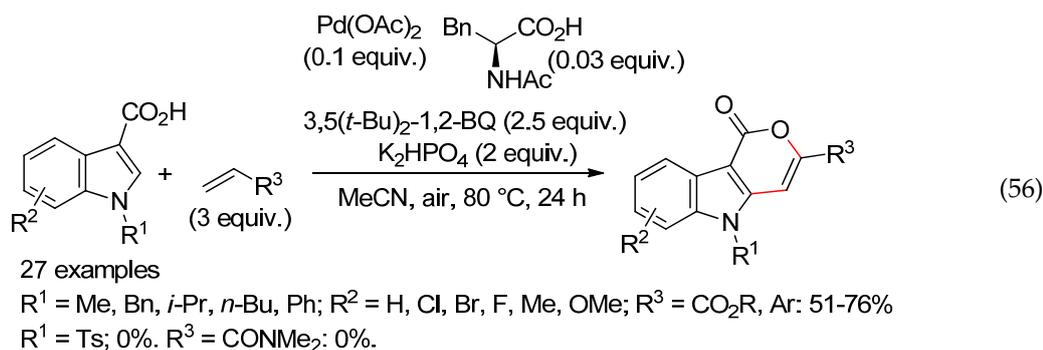


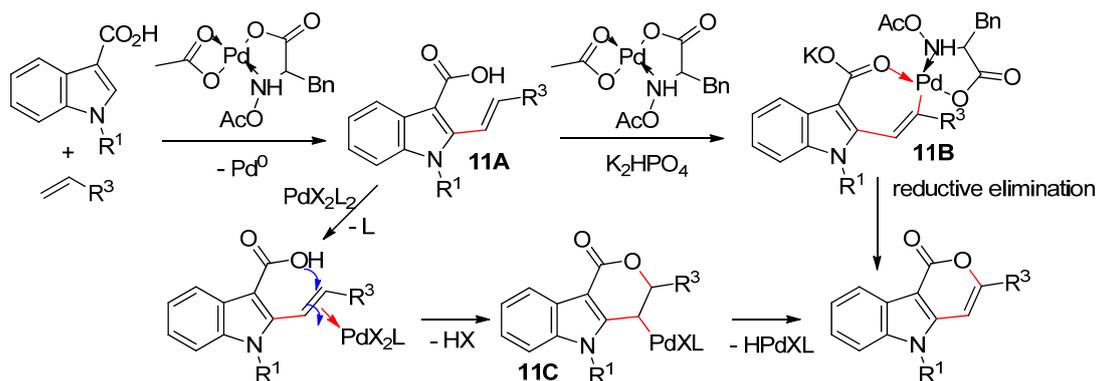
4.2.2. C2 Alkenylations

Most reports of selective C2 alkenylations are due to substrates already C3 substituted, as exemplified with Equation (54) [96], Equation (55) [97], Equation (56) [98], and Equation (57) [99].

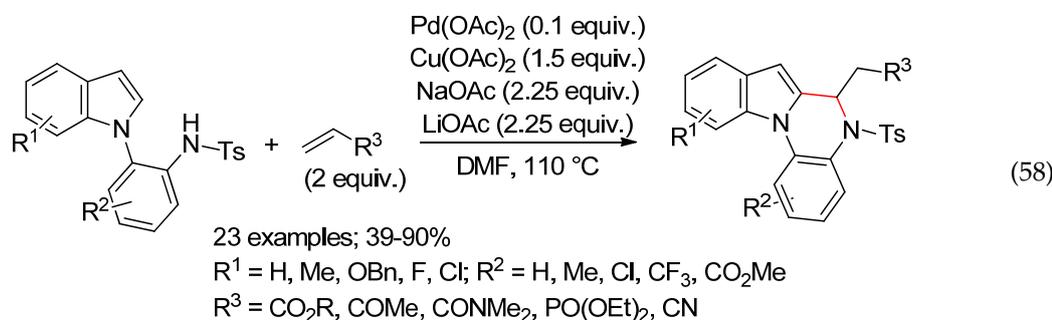


C2 alkenylation may be followed by annulation with the C3 substituent (Equations (56) [98] and (57) [99]). The lactonization depended on the N-substituent of the indole and did not occur with *N,N*-dimethylacrylamide as the alkenylating reagent (Equation (56)). The aza-heterocycle (Equation (57)) would be formed as depicted in Scheme 4. Regarding the lactone (Equation (56)), Liu, Zeng, and co-workers proposed the activation of an olefinic C–H bond of the DHR product **11A**, leading to the seven-membered palladacycle intermediate **11B** (Scheme 11). Subsequent reductive elimination gives the lactone. We rather suspect a Wacker-type reaction [100]: activation of the double bond by coordination to Pd^{II} mediating the nucleophilic addition leading to **11C**. The latter would endure β-H elimination affording the lactone.

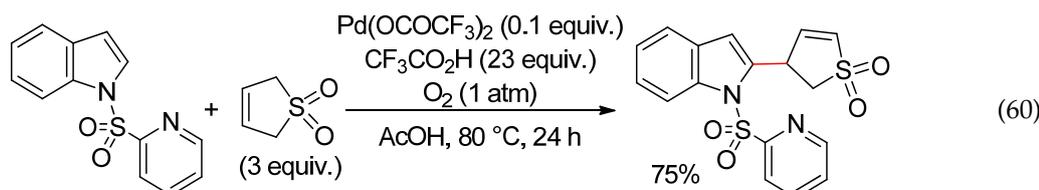
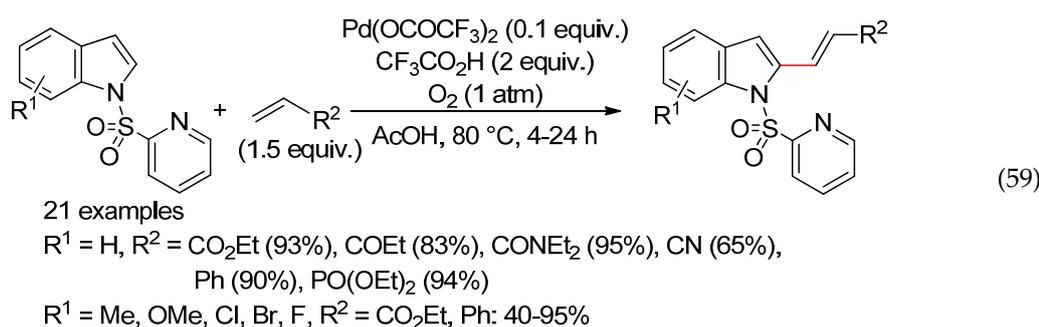




The C2 alkenylation/annulation of *N*-(2-(1*H*-pyrrol-1-yl)phenyl)-4-methylbenzenesulfonamide (Equation (37)) also arose from corresponding indoles (Equation (58)) [74].



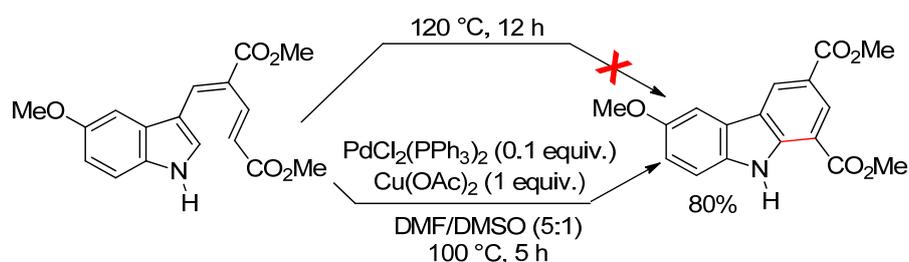
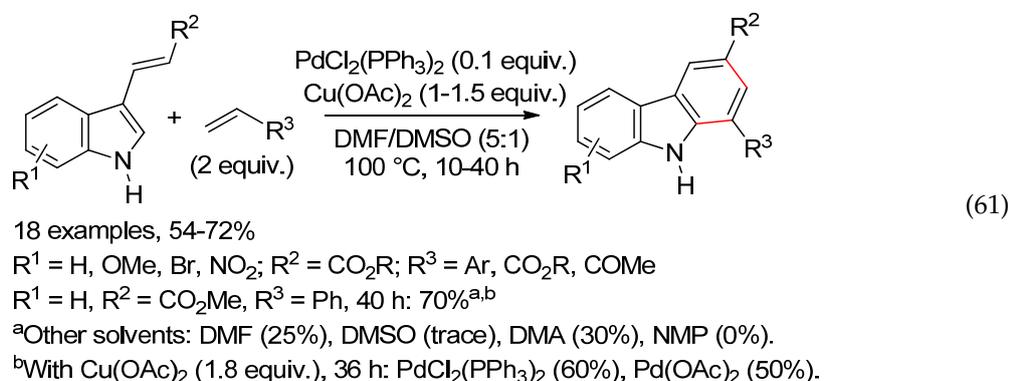
Wang's team effectively carried out various 2-alkenylation of *N*-(2-pyridyl)sulfonylindoles (Equation (59)) [101]. The cross-coupling with 2,5-dihydrothiophene 1,1-dioxide was followed by migration of the C=C bond (Equation (60)). Comparison of the rate of alkenylation of *N*-(2-pyridyl)sulfonylindoles bearing either a C2 or C3 methyl group indicated that the protecting group activates the 2-alkenylation.



4.2.3. Domino Reactions

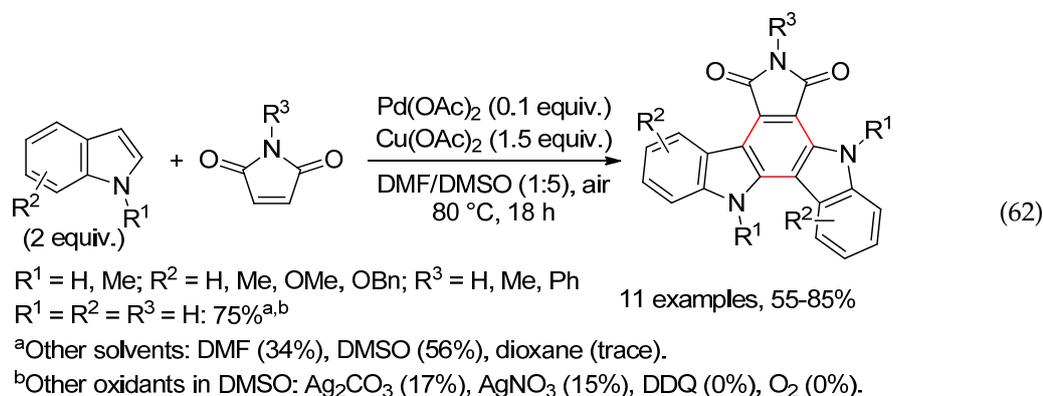
Domino reactions involving DHRs in 2-position have been above documented (Equations (56)–(58)).

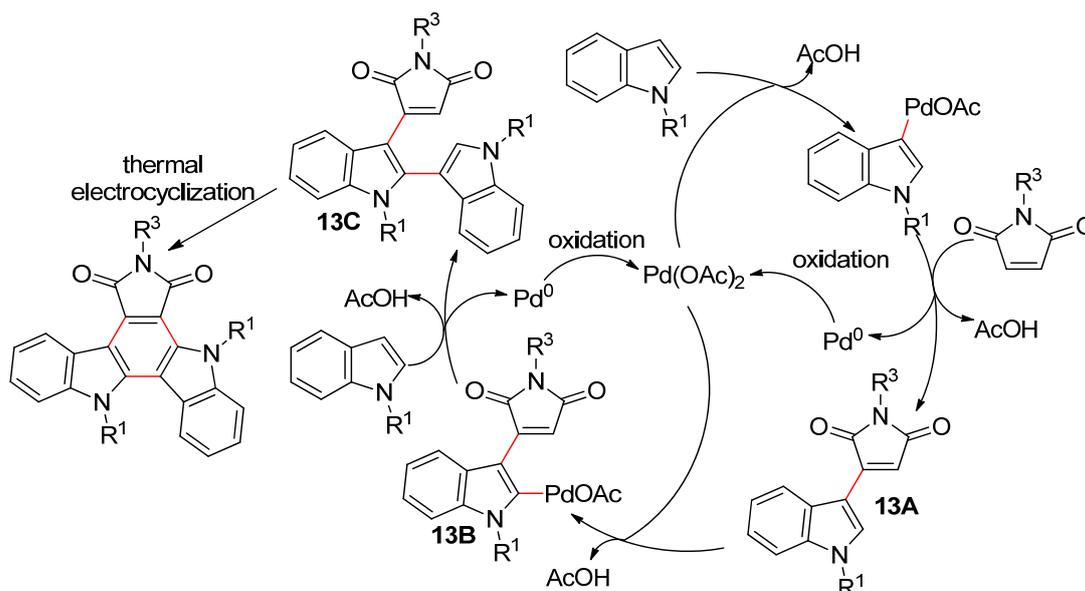
The annulation depicted in Equation (61) [102] differs from those of Equations (56) and (57). Indeed, the reaction of the exocyclic C=C bond with the unsaturated reagent was one of the key intermediates. Plausible intermediates were proposed by Verma's team. According to Scheme 12, the cyclization step is Pd-catalyzed. Similar annulations were reported [85,95,103], but, differing from the DHRs, they will not be more commented.



Scheme 12. Cyclization via Pd-catalysis versus thermal conditions.

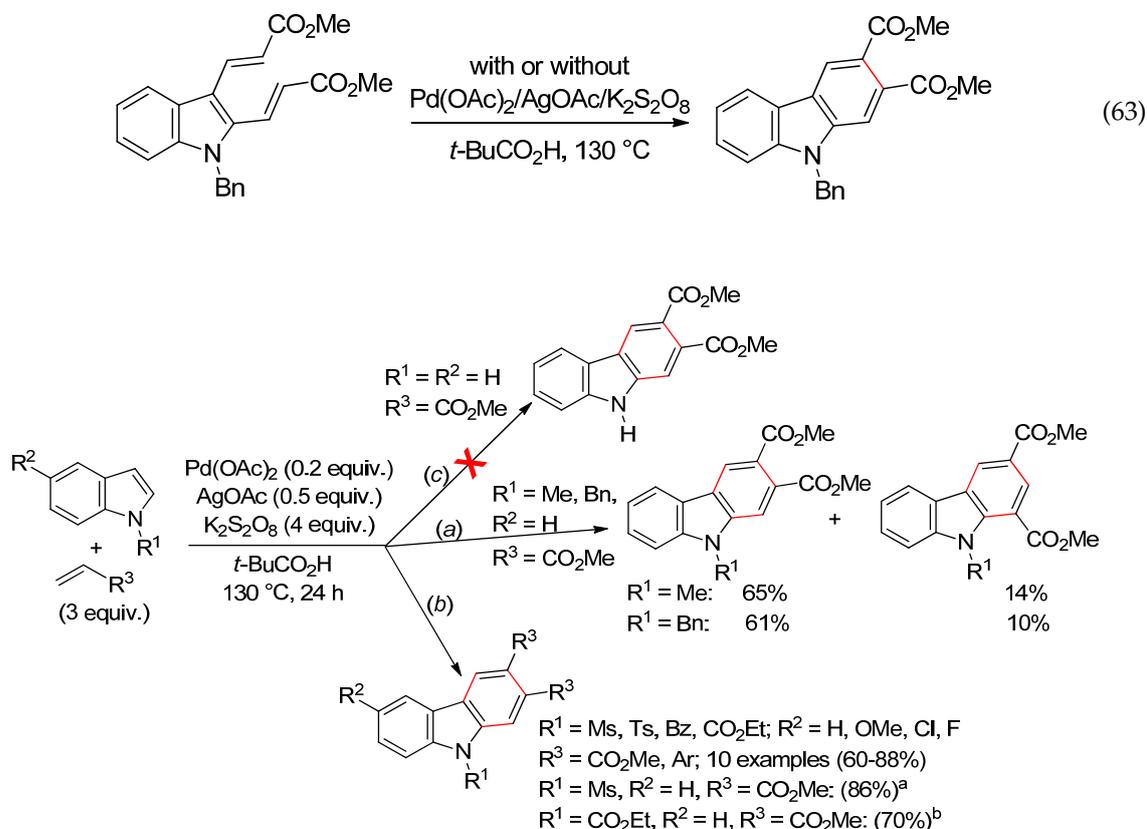
Increasing the indole/maleimide ratio provided indolopyrrolocarbazoles (Equation (62)) under experimental conditions previously used in Equation (47) [84]. The mechanism proposed by Zhao and co-workers involves the DHR leading to C3 alkenylation product **13A** (Scheme 13). Activation of the C2-H bond of **13A** affords **13B** which reacts with indole to afford **13C**. Subsequent thermal electrocyclization gives the product. In agreement with this proposal, the carbazole was also obtained from the reaction of C3 alkenylation product with maleimide.





Scheme 13. Domino reaction of maleimide with indole.

The cross-coupling of *N*-methyl and *N*-benzylindoles with methyl acrylate afforded a mixture of two isomeric carbazoles (Scheme 14, path *a*) [104]. The process became selective with others *N*-substituents, (path *b*) arising from a double DHR reaction followed, according to Equation (63), thermal electrocyclization. The annulation was not observed from free (NH) indole (path *c*).



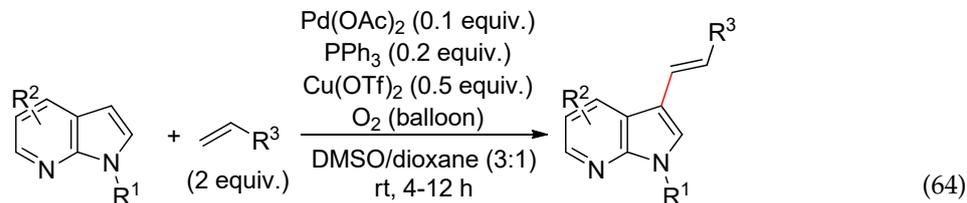
^aOxidants with Pd(OAc)₂ (0.15 equiv.) and *t*-BuCO₂Cs (0.3 equiv.) as additive:
 AgOAc/K₂S₂O₈ (80%), AgOAc (68%), Ag₂O (69%), K₂S₂O₈ (58%), BQ (0%).

^bPlus the *N*-deacylation product (13%).

Scheme 14. Reactivity depending on the N substituent.

4.3. 7-Azaindoles

7-Azaindoles underwent aerobic C-3 alkenylation at room temperature using catalytic amounts of Pd(OAc)₂, PPh₃, and Cu(OTf)₂ (Equation (64)) [105]. The yields were very sensitive to the solvent and oxidant.



49 examples, 30-85%

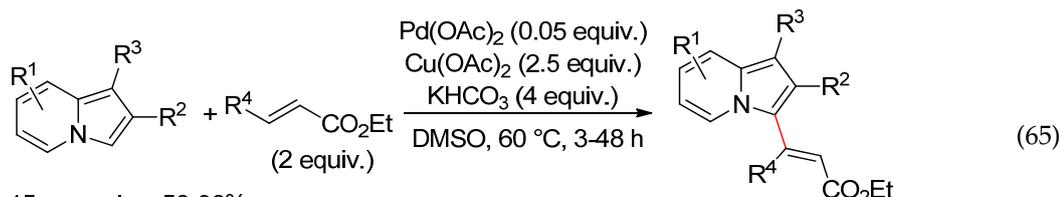
R¹ = PMB, Bn, Ph; R² = H, Cl, Br, Ar, OMe; R³ = CO₂R, CN, Ar

R¹ = PMB, R² = H, R³ = CO₂*n*-Bu: 80%^a

^aOther oxidants: O₂, BQ, PhI(OAc)₂, K₂S₂O₈ (10-20%).

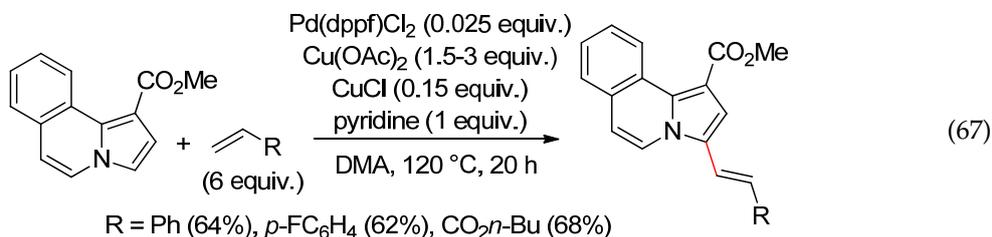
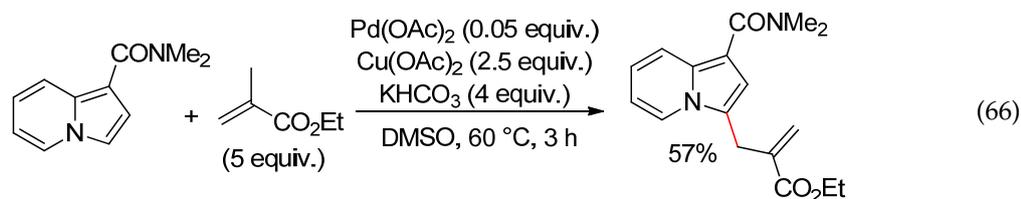
4.4. Indolizines

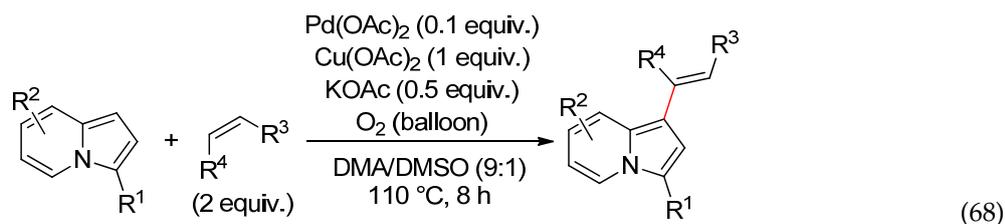
The DHR of indolizines preferentially occurred at the 3-position (Equations (65) and (66)) [27] and Equation (67) [106]. When the 3-position was already occupied, the cross-coupling arose in C1 position (Equation (68)) [107].



15 examples, 50-96%,

R¹ = H, Me; R² = H, CO₂R, Me, Ar; R³ = H, CN, CO₂R, CONMe₂, COPh; R⁴ = H, Me





26 examples, 42-95%

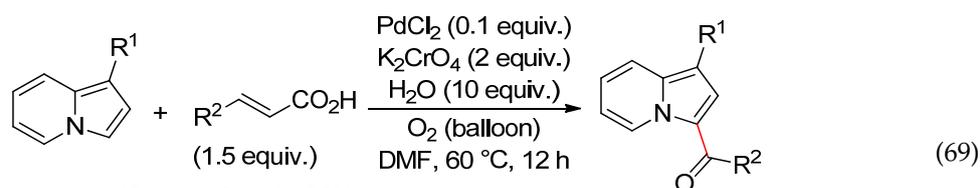
$R^1 = \text{COAr}, \text{CO}_2\text{R}, \text{Ph}; R^2 = \text{H}, \text{CO}_2\text{R}; R^3 = \text{CO}_2\text{R}, \text{CONMe}_2, \text{PO(OMe)}_2, \text{Ar};$

$R^4 = \text{H}, \text{CO}_2\text{Me}, p\text{-MeC}_6\text{H}_4$ (E/Z = 1.3:1)

$R^1 = \text{COPh}, R^2 = R^4 = \text{H}, R^3 = \text{CO}_2\text{Bu}; 88\%^a$

^aIn the absence of Cu(OAc)_2 : 79%.

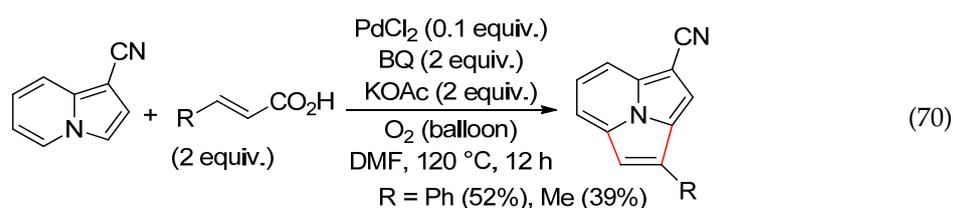
Using $\text{PdCl}_2/\text{K}_2\text{CrO}_4/\text{H}_2\text{O}/\text{O}_2$ in DMF, C1-substituted indolizines underwent cross-coupling with α,β -unsaturated carboxylic acids to produce C3 acylated compounds (Equation (69)) [108]. Traces of annulation products were identified; they were selectively formed under modified experimental conditions (Equation (70)). According to Zhang and co-workers, the first steps of the acylation are those of the DHR leading to **15A** (Scheme 15). Oxidation of the activated tertiary hydrogen bond of **15A** with K_2CrO_4 provides **15B**. Subsequent hydrolysis of the C-Pd bond affords **15C** that is oxidized with K_2CrO_4 giving the acylated compound. The annulation product would arise from **15A** via β -H elimination leading to **15D**. Subsequent oxidation with BQ/ K_2CrO_4 affords **15E**. Activation of C-H bond in 5 position gives the palladacycle **15F**, which delivers the product via reductive elimination and decarboxylation.



16 examples, 41-66%

$R^1 = \text{CO}_2\text{R}, \text{CN}; R^2 = \text{Ar}, \text{Me}, n\text{-Pr}$

$R^1 = \text{CO}_2\text{Me}, R^2 = \text{Ph}$ (58%), Me (41%)

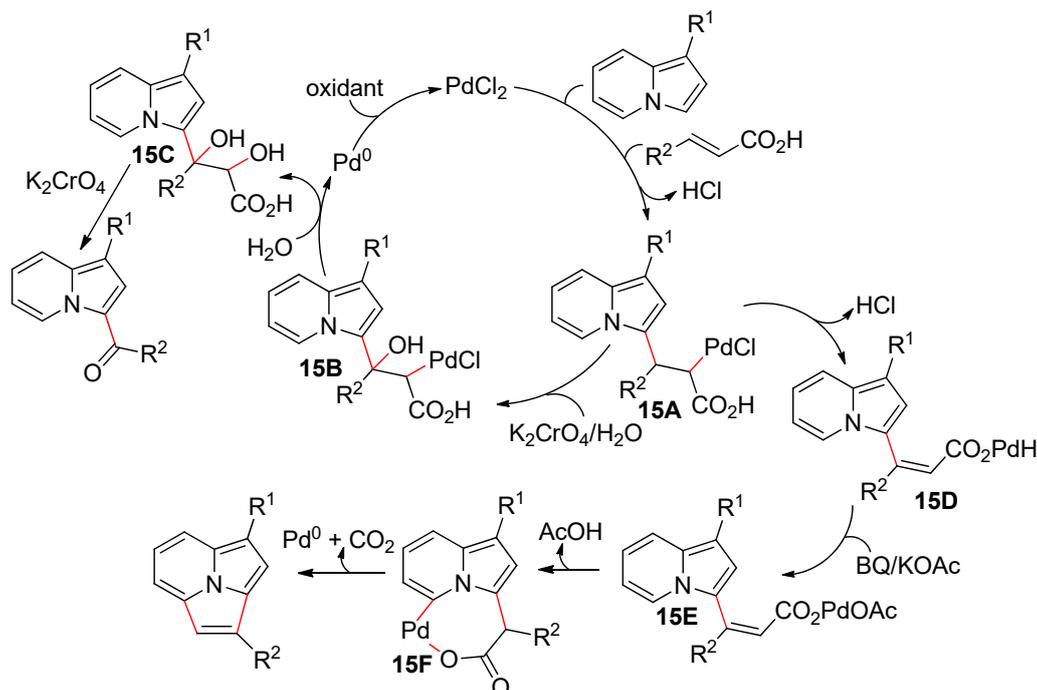


$R = \text{Ph}$ (52%), Me (39%)

4.5. Sub-Conclusion

The regioselectivity of the DHR of pyrroles depends on solvent, N protective group, and, if present, electron-withdrawing substituents. Indoles react in 3 position in the absence of directing substituent.

Under DHR conditions, the C3 position of 7-azaindoles and indolizines is the more reactive. It seems however necessary to note that the C3 position relative to the N atom is β for the former and α for the latter.



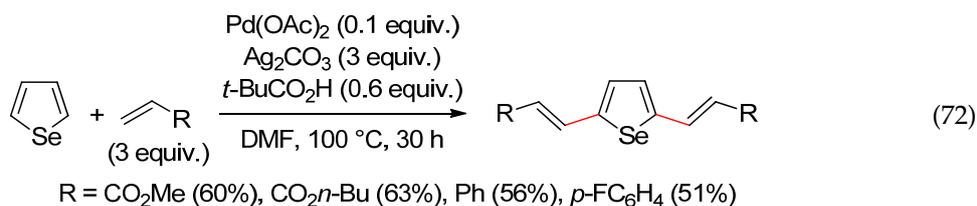
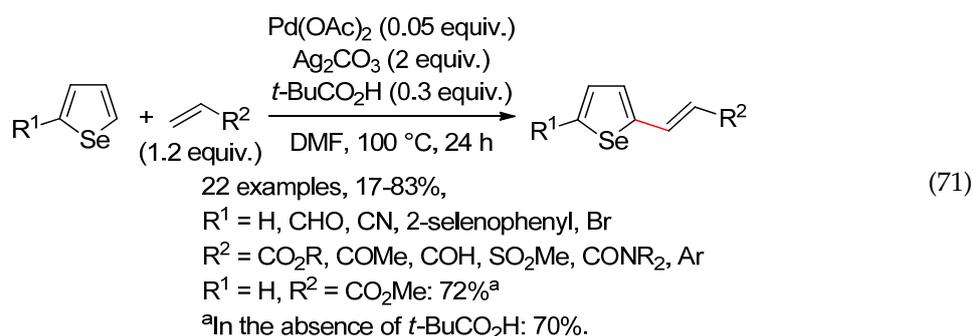
Scheme 15. DHRs with α,β -unsaturated carboxylic acids: acylation versus annulation.

5. Se-Arenes

Although Fujiwara's team disclosed, in 1973, the synthesis of 2-styrylselenophene and 2,5-distyrylselenophene from stoichiometric amounts of selenophene, styrene, and $\text{Pd}(\text{OAc})_2$ in refluxing AcOH /dioxane [29], the DHRs of Se-arenes under catalytic conditions have been seldom reported.

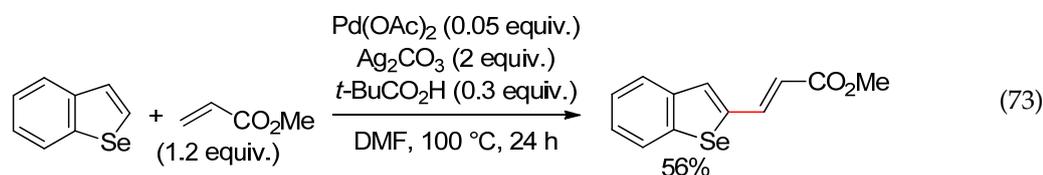
5.1. Selenophenes

$\text{Pd}(\text{OAc})_2$ -catalyzed DHR of selenophenes with Ag_2CO_3 as oxidant in the presence of $t\text{-BuCO}_2\text{H}$ provided the α -mono or α,α' -diolefination products depending on the olefinating agent/selenophene ratio (Equations (71) and (72)) [109].



5.2. Benzoselenophene

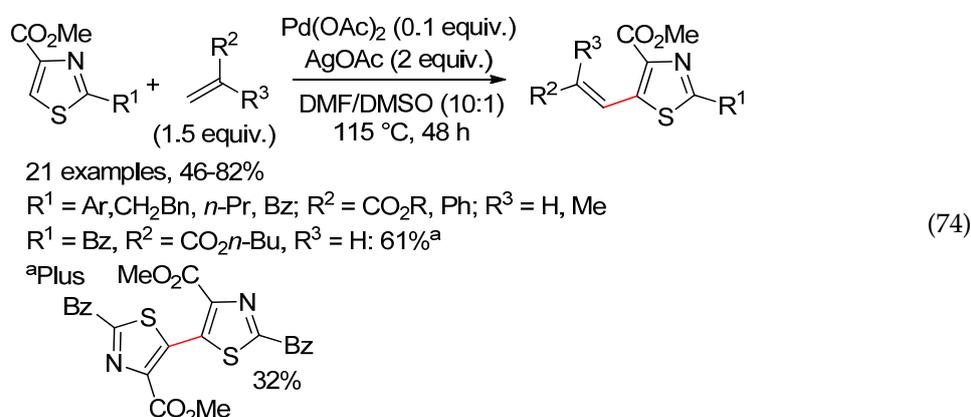
Benzoselenophene reacted under conditions of selenophene to yield the C2 substituted product (Equation (73)) [109].



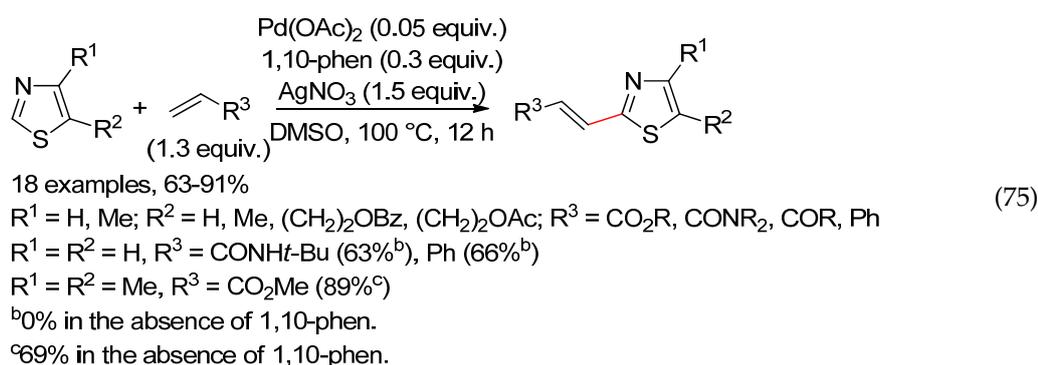
6. S,N-Arenes

6.1. Thiazoles

Homocoupling competed with DHR from thiazoles substituted in 2 and 5 positions (Equation (74)) [110].

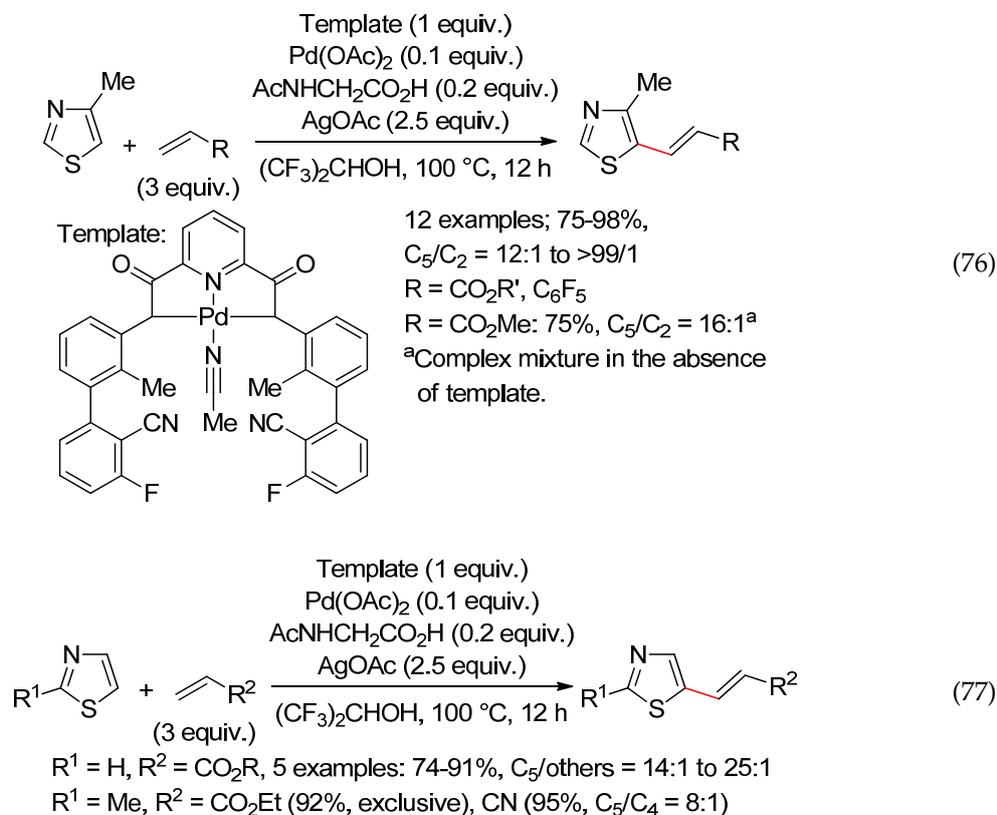


Unsubstituted thiazole and thiazoles substituted in 4 or/and 5 position underwent C-2 selective olefination using Pd(OAc)₂/1,10-phenanthroline/AgNO₃ in DMSO (Equation (75)) [111]. The presence of 1,10-phenanthroline was essential for this DHR.

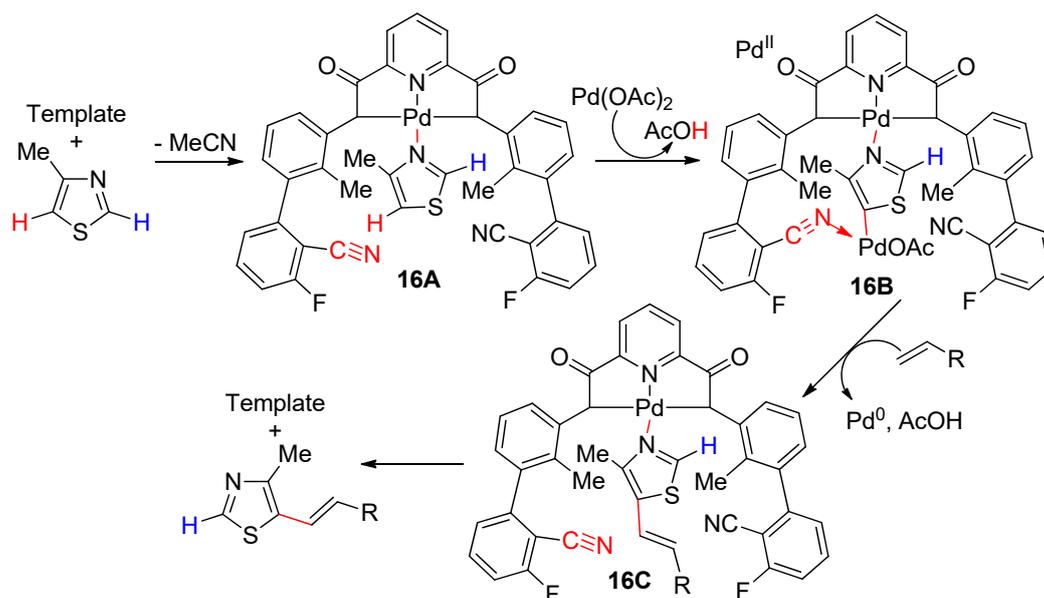


Maiti's team studied the olefination of 4-methylthiazole [112]. With Pd(OAc)₂/AgOAc in trifluoroethanol containing catalytic amounts of *N*-acetylglycine, the reaction with methyl acrylate led to a complex mixture (Equation (76)). The authors examined the DHR in the presence of tricoordinating templates to direct the metal catalyst to the desired C5–H bond. They founded an effective recyclable

template for the purpose (Equation (76)). Interestingly, selective C5-olefination also occurred from 4-chlorothiazole, 2-methylthiazole, and unsubstituted thiazole (Equation (77)).



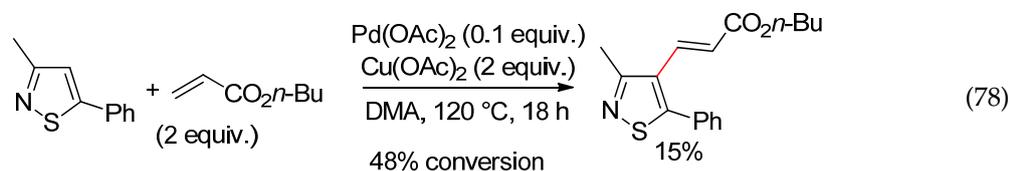
The key intermediates proposed by Maiti's team for the template reactions are depicted in Scheme 16 [112]. Exchange between acetonitrile and thiazole provides **16A**. Activation of C5-H bond due to interaction with the aromatic nitrile allowed regioselective palladation leading to **16B**, while the C2-H bond is preserved. Subsequent reaction with the olefin gives **16C**, which liberates the product and regenerates the template.



Scheme 16. Template-mediated regioselectivity.

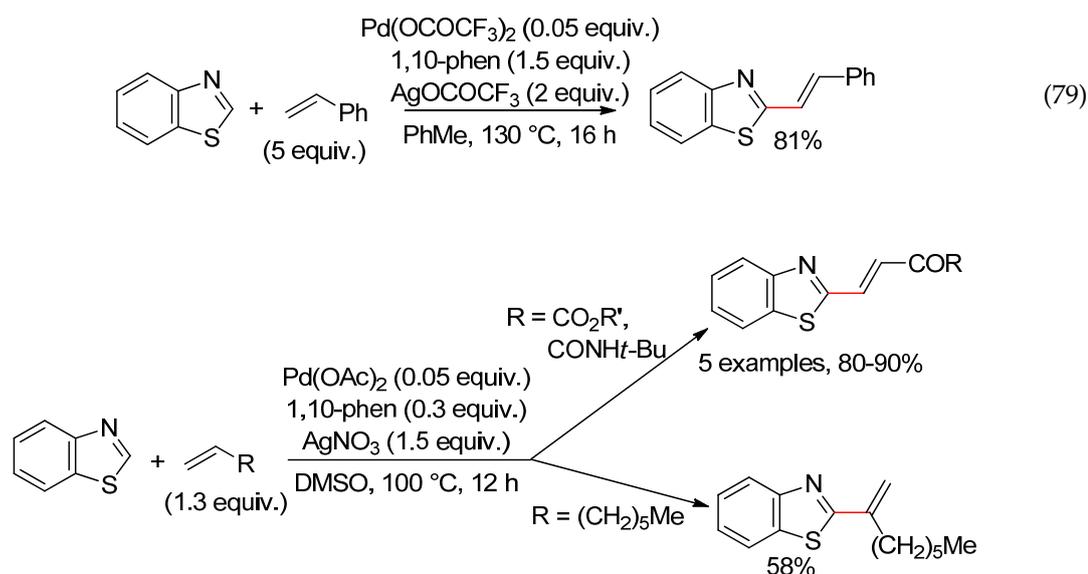
6.2. Isothiazoles

The DHR of 3-methyl-5-phenylisothiazole with butyl acrylate using Pd(OAc)₂/Cu(OAc)₂ in DMA was sluggish at 120 °C, giving the product in a low yield (Equation (78)) [113].



6.3. Benzothiazoles

The Pd(OAc)₂/1,10-phenanthroline association (Equation (75)) also led to efficient C2 substitution of benzothiazole with acrylates, *N*-methylacrylamide (Scheme 17) [111], and styrene (Equation (79)) [114]. Lower yield was obtained with 1-octene (Scheme 17). Moreover, the formation of the branched cross-coupling product led us to suspect a mechanism involving activation of the alkene (Scheme 1). Indeed, the Heck reaction of terminal alkenes preferentially occurs at the terminal carbon [115,116], while nucleophilic addition to Pd-coordinated alkenes arises rather at the internal carbon [117–119].

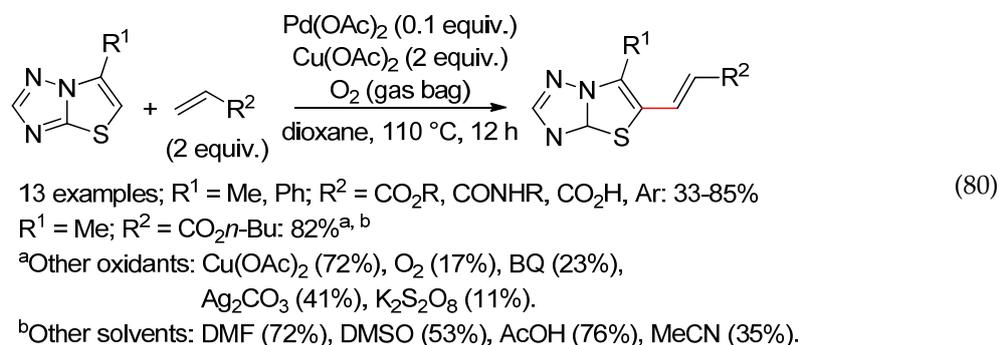


Scheme 17. Linear and branched cross-coupling products.

6.4. Thiazolotriazoles

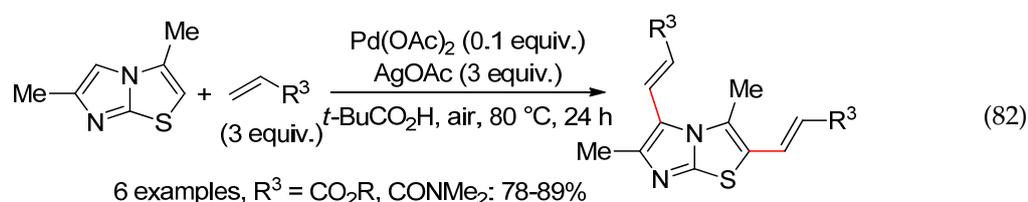
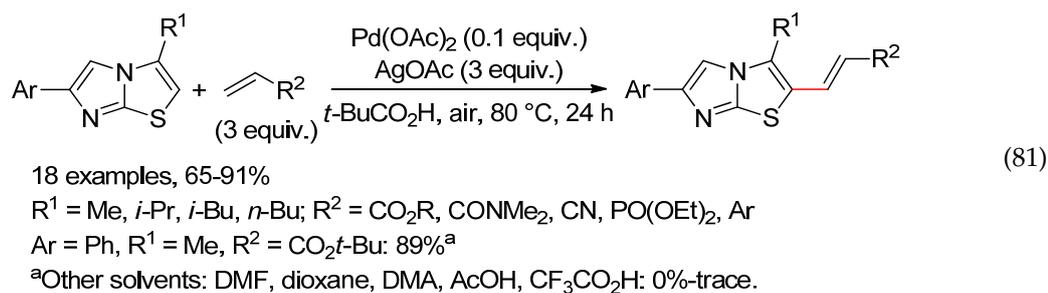
Both Cu(OAc)₂ and O₂ as the oxidation system and dioxane as the solvent were used as optimum conditions for the Pd(OAc)₂-catalyzed DHR of 6-substituted thiazolo[3,2-*b*]-1,2,4-triazoles, leading to

selective 5-alkenylation (Equation (80)) [120]. It seems necessary to point out the absence of reaction at the 2-position.



6.5. Imidazo[2,1-*b*]thiazoles

3-Substituted imidazo[2,1-*b*]thiazoles bearing an aryl group in C6 underwent selective 2-alkenylation (Equation (81)), while change of the aryl group for a methyl led to 2,5-disubstitution (Equation (82)) [121]. According to Huang, Chen, and co-workers, electronic effects played a more important role than steric effects in the reaction.

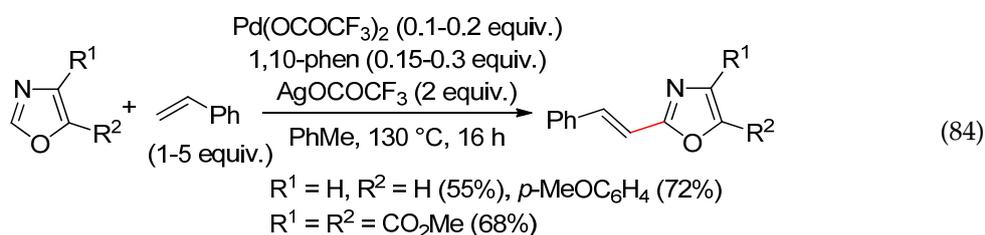
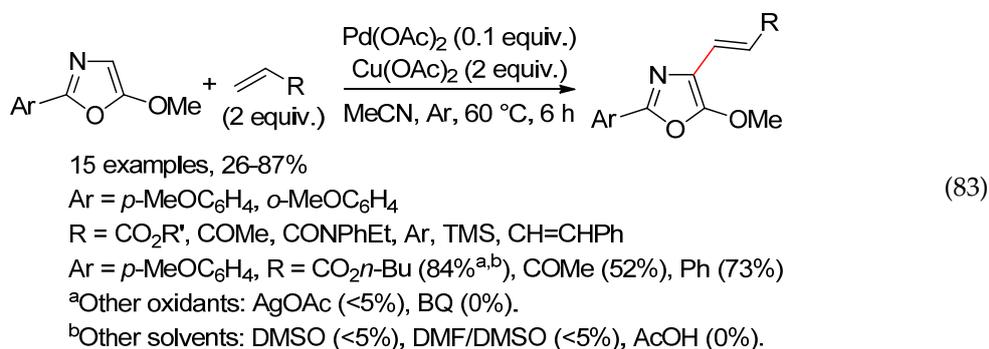


7. O,N-Arenes

7.1. Oxazoles

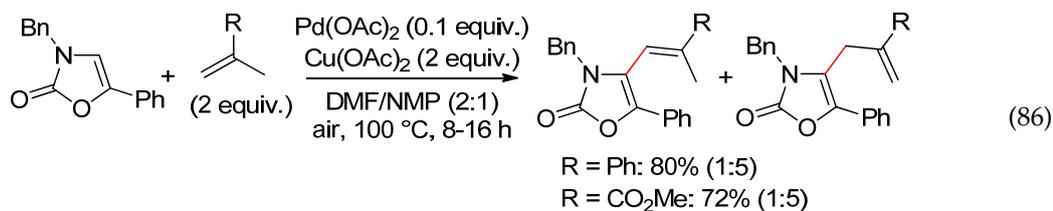
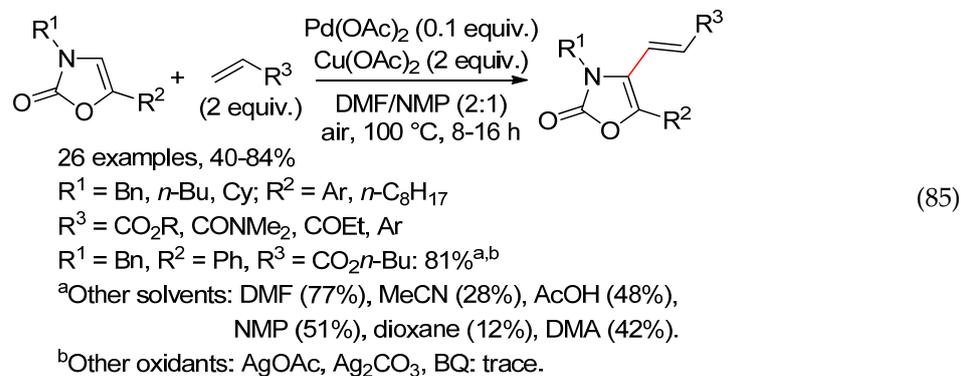
Olefination of disubstituted oxazoles in either the 4- (Equation (83)) [122] or 2-position (Equation (84)) [114], depending on the substitution of the starting material, have been reported. $\text{Pd}(\text{OAc})_2$ -catalyzed DHR of 5-methoxy-2-(4-methoxyphenyl)oxazole with *n*-butyl acrylate occurred in high yield in MeCN with $\text{Cu}(\text{OAc})_2$ as oxidant, but changing the oxidant or the solvent provided

only traces of the cross-coupling product, especially in DMF/DMSO which is often used for DHR of five-membered heteroarenes (Equation (83)).



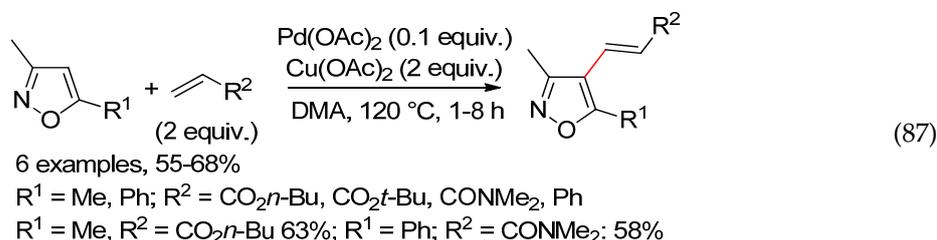
7.2. Oxazolones

4-Alkenylation of 5-substituted-2-oxazolones mediated with the Pd(OAc)₂/Cu(OAc)₂ system was very sensitive to the experimental conditions (Equation (85)) [123]. Unconjugated compounds, formed via β-H elimination involving the methyl group, were the main cross-coupling products from α-methylstyrene and methyl methacrylate (Equation (86)).



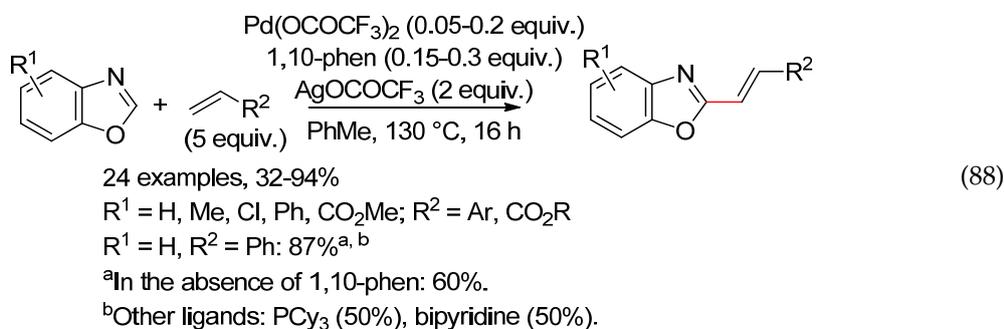
7.3. Isoxazoles

The Pd(OAc)₂/Cu(OAc)₂/DMA association which has a low efficiency for the DHR of isothiazole (Equation (78)) afforded fair yields from isoxazoles (Equation (87)) [113].



7.4. Benzoxazoles

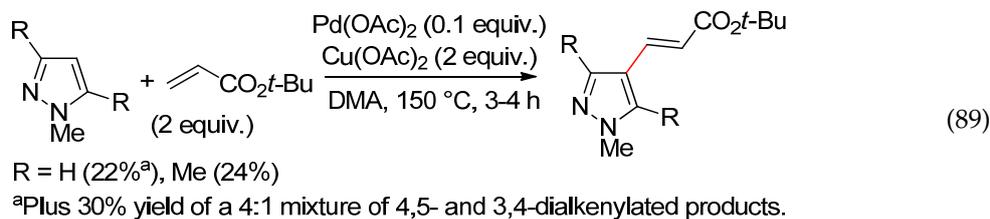
1,10-Phenanthroline would be the optimum ligand of Pd(OCOCF₃)₂ for the 2-alkenylation of benzoxazoles (Equation (88)) [114].



8. N,N-Arenes

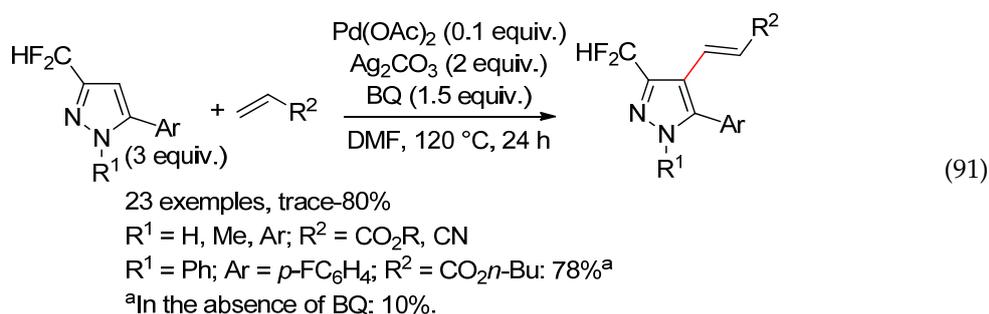
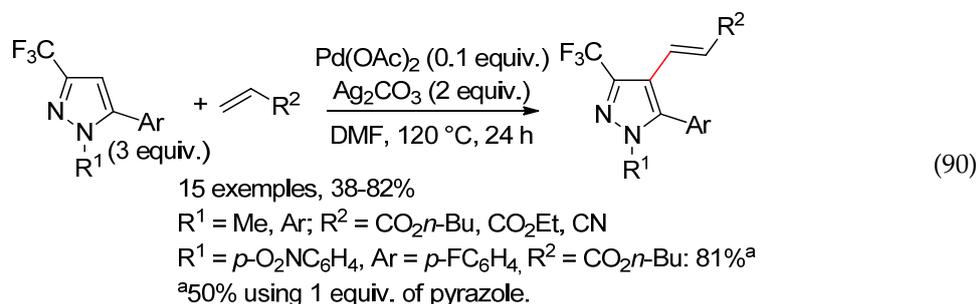
8.1. Pyrazoles

The 4-alkenylation of *N*-methylpyrazole and 3,5-dimethyl-*N*-methylpyrazole using Pd(OAc)₂/Cu(OAc)₂/DMA occurred in low yields (Equation (89)) [113]. *N*-phenylpyrazole was unreactive [113], but could react under different conditions (see Equation (91)).

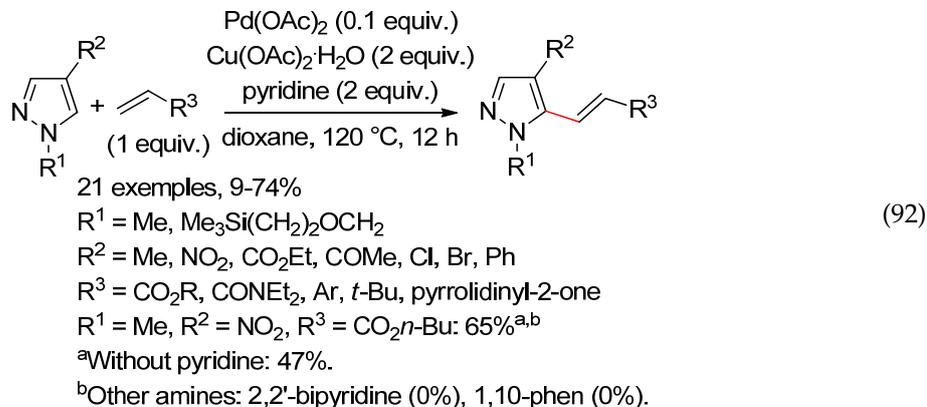


The DHR of 5-aryl-3-(trifluoromethyl)-1*H*-pyrazoles using Pd(OAc)₂/Ag₂CO₃ in DMF required an excess of the pyrazole to afford fair to good yields (Equation (90)) [124]. These conditions were

not effective for the DHR of 3-(difluoromethyl)-5-aryl-1*H*-pyrazoles: addition of BQ was required (Equation (91)).

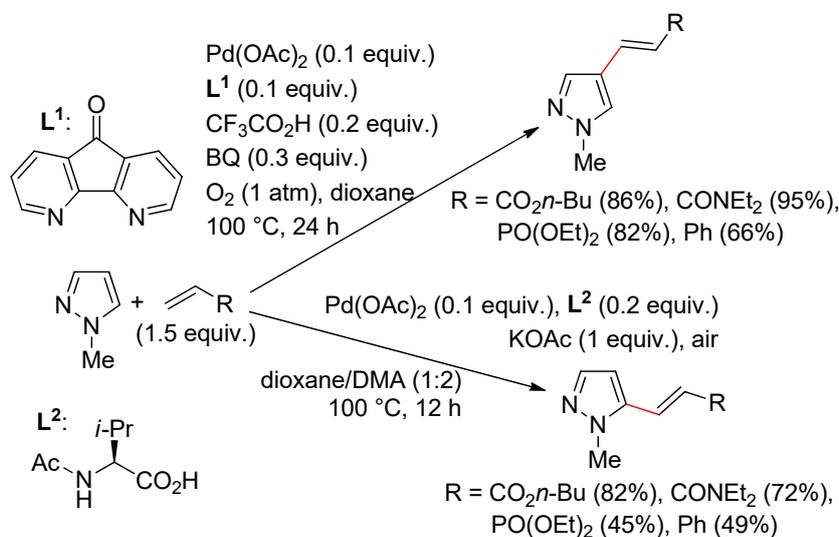
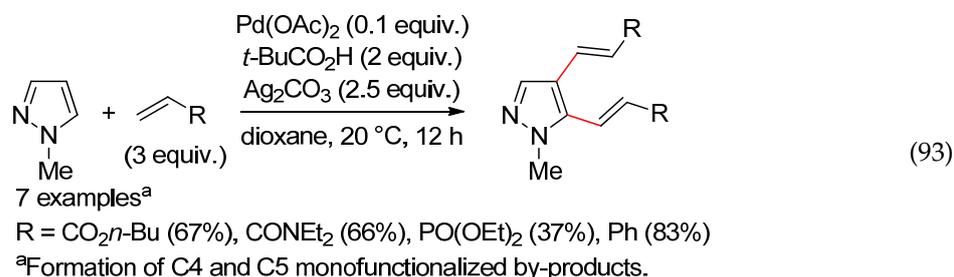


4-Substituted pyrazoles underwent C5 alkenylation using Pd(OAc)₂/Cu(OAc)₂ in dioxane, in increased yields with pyridine as additive (Equation (92)) [125].



The teams of Lim, Baik, and Joo joined their efforts to selectively obtain either C4 or C5 alkenylation of 1-methyl-1*H*-pyrazole, via a ligand-controlled regiodivergent process (Scheme 18) [126]. Besides the ligand, the experiment conditions also differed. The two methods were applied to

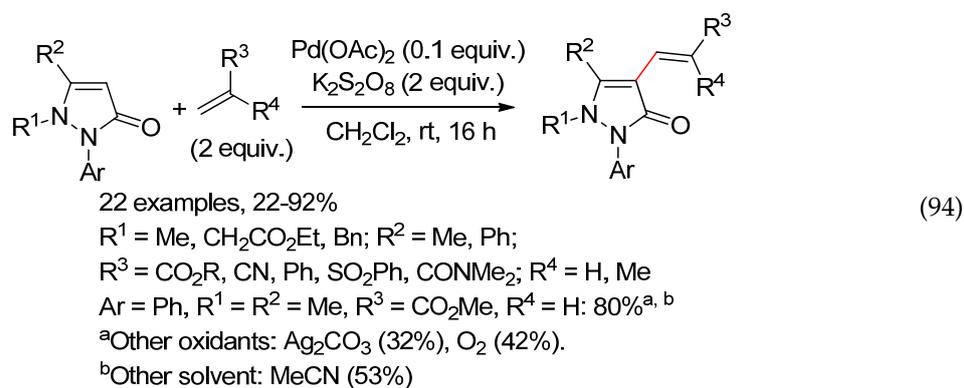
different N-substituted pyrazoles, possibly C3-substituted. A third method was optimized for the 4,5-dialkenylation (Equation (93)).



Scheme 18. Lim, Baik, and Joo's divergent DHR's.

8.2. Pyrazolones

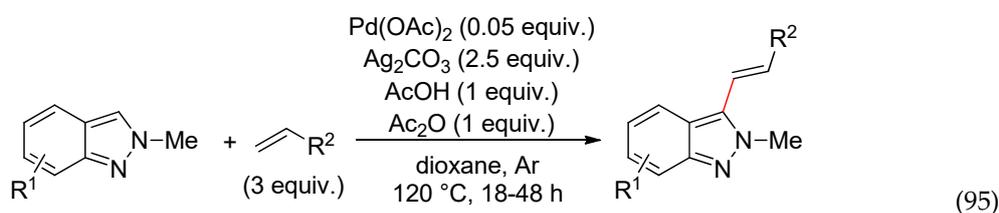
Substituted 5-pyrazolones led to various 4-alkenylated pyrazolones via DHRs sensitive to the nature of oxidant and solvent (Equation (94)) [127].



8.3. Indazoles

Guillaumet's team disclosed the Pd^{II}-catalyzed C3-alkenylation of 2-methyl-2*H*-indazoles (Equation (95)) and 1-methyl-1*H*-indazoles (Equation (96)) using Ag₂CO₃ as oxidant and stoichiometric amounts of both AcOH and Ac₂O for optimum yields [128]. The DHR arose in C7 from C3-substituted substrates. The same substrates were subsequently C3-alkenylated with butyl acrylate

and *N,N*-diethylacrylamide (42–72% yields) by Joo's team under experimental conditions they used for pyrazoles (Equation (92)) [125].



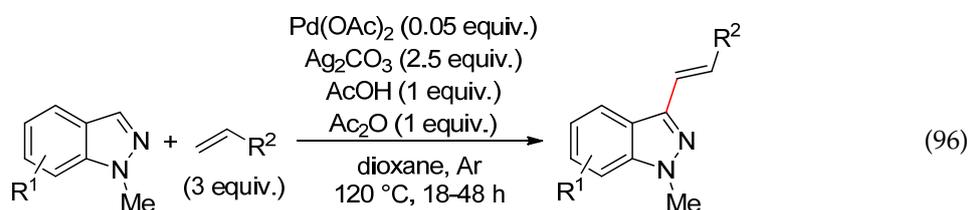
19 examples, 51–93%

$R^1 = \text{H, NO}_2, \text{CN, CF}_3, \text{F, OMe}; R^2 = \text{CO}_2\text{R, CONH}t\text{-Bu, Ar}$

$R^1 = \text{H, } R^2 = \text{CO}_2\text{Et: 87\%}^{\text{a,b}}$

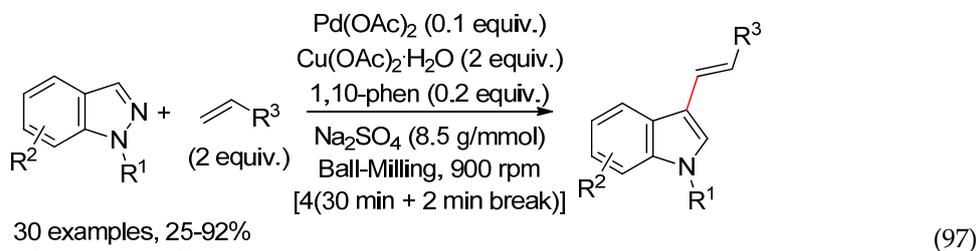
^aOther oxidants: AgOAc (69%), AgNO₃ (65%), Cu(OAc)₂ (51%).

^bInstead of AcOH/Ac₂O: AcOH (75%), Ac₂O (50%), PhCO₂H (59%).



12 examples, $R^1 = \text{H, NO}_2, \text{OMe}; R^2 = \text{CO}_2\text{R, CN, Ar (45–78\%)}$

Su's team again used the mechanochemical strategy (Equation (50)) [25], but under different conditions for the C3-alkenylation of 1-methyl(or benzyl)-1*H*-indazoles (Equation (97)) [129]. Cu(OAc)₂·H₂O and 1,10-phenanthroline were essential for good reactivity.



30 examples, 25–92%

$R^1 = \text{Me, Bn}; R^2 = \text{H, Cl, Me, OMe, CN, NO}_2$

$R^3 = \text{CO}_2\text{R, CONR}_2, \text{PO(OEt)}_2, \text{Ar}$

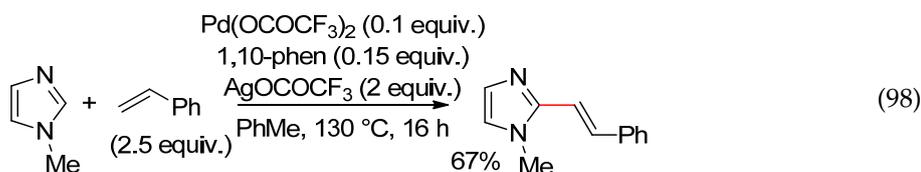
$R^1 = \text{Me, } R^2 = \text{H, } R^3 = \text{CO}_2n\text{-Bu: 64\%}^{\text{a,b}}$

^aOther oxidants: Ag₂CO₃ (41%), Ag₂O (0%).

^bUsing 0.1 equiv. of additive: 1,10 phen (42%), pyridine (23%), bipyridine (38%).

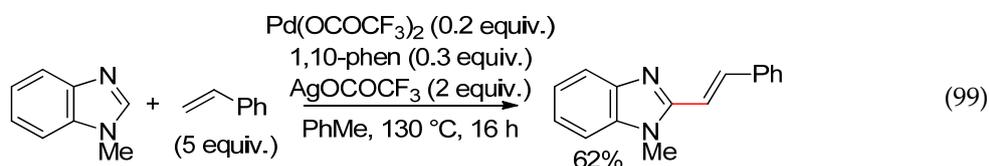
8.4. Imidazoles

The Ong procedure already used for other azoles (Equations (79), (84), and (88)) led to C2-styrenylation of 1-methyl-1*H*-imidazole (Equation (98)) [114].



8.5. Benzimidazole

C2-styrenylation of 1-methyl-1*H*-benzo[*d*]imidazole was also performed using Ong's procedure (Equation (99)) [114].

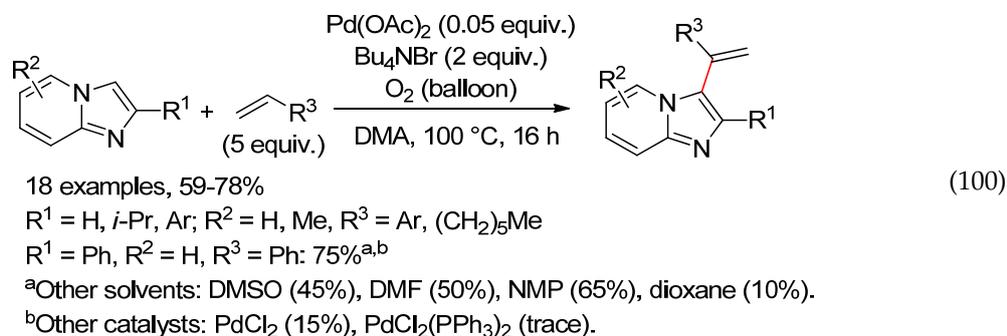


8.6. Imidazo[1,2-*a*]pyridines

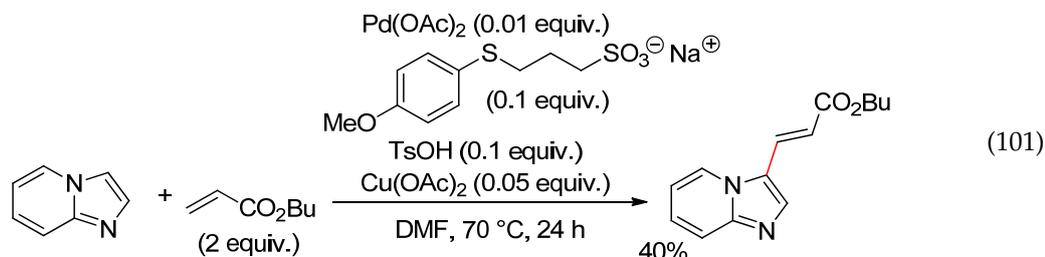
Mahdavi and co-workers have recently reviewed different C3-functionalization of imidazo[1,2-*a*]pyridines [130].

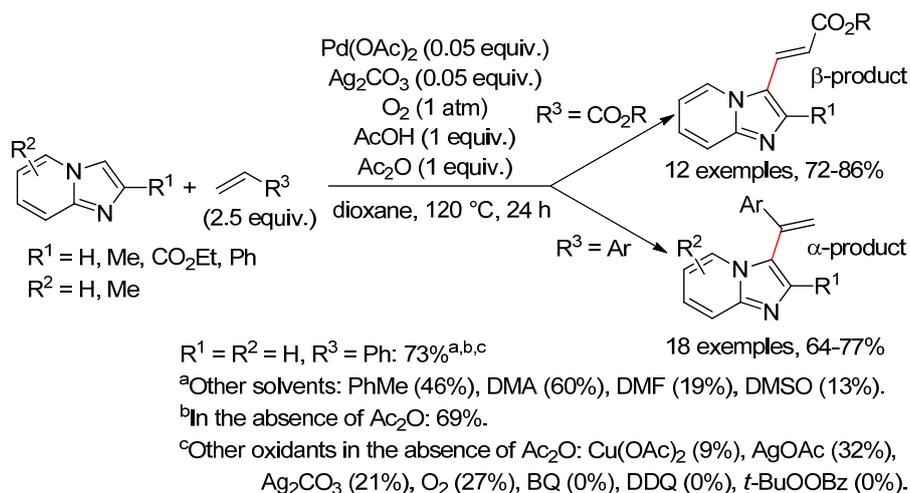
An efficient and highly regioselective Pd^{II}-catalyzed C-3 alkenylation of imidazo[1,2-*a*]pyridines with acrylates and styrenes was developed by Cao's team using oxygen as the main oxidant [131]. Catalytic amounts of Ag₂CO₃ and stoichiometric quantities of both AcOH and Ac₂O were required for optimum results. Acrylates and acrylonitrile tended to form β-products, while styrenes tended to form α-products (Scheme 19). The authors proposed two different catalytic cycles like those of Scheme 1, "arene activation" for the β-products and "alkene activation" for the α-products.

Using oxygen as the sole oxidant, Pd(OAc)₂-catalyzed 2-phenylimidazo[1,2-*a*]pyridine with styrene in DMSO provided the C3 branched adduct in low yield [132]. Changing the solvent for DMA with, especially Bu₄NBr as additive, led to a fair yield (Equation (100)). Other substituted substrates and styrenes were reacted under the same conditions. The branched product was also obtained with 1-octene. Hajra and co-workers retained the mechanism of Scheme 1, alkene activation.



Carrow's conditions used in Schemes 2 and 8 and Equations (36), (41), and (45) mediated the C3-olefination of imidazo[1,2-*a*]pyridine with butyl acrylate (Equation (101)) [45].

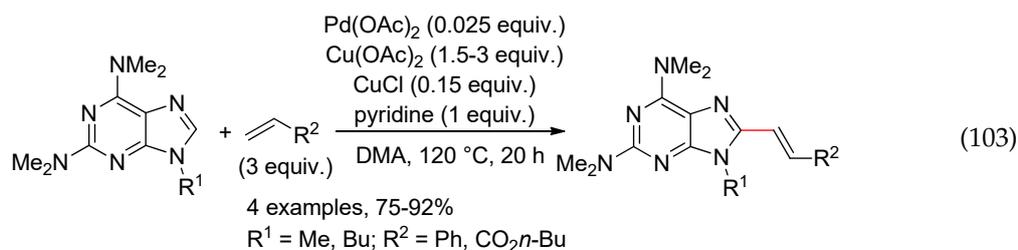
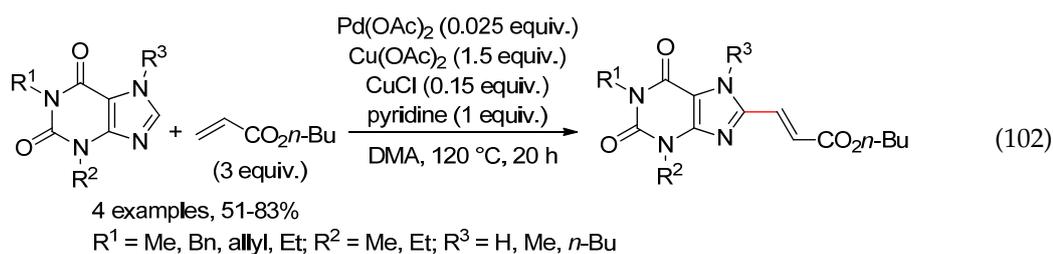




Scheme 19. Linear or branched cross-coupling product.

8.7. Purines

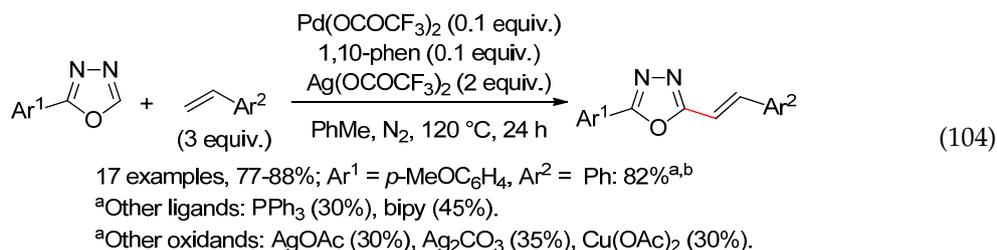
C8-olefination of biologically relevant purines occurred (Equations (102) and (103)) under experimental conditions used for DHRs of indolizines (Equation (67)), leading to fluorescent molecules with potential role in biological imaging [106].



9. O,N,N-Arenes

9.1. 1,3,4-Oxadiazoles

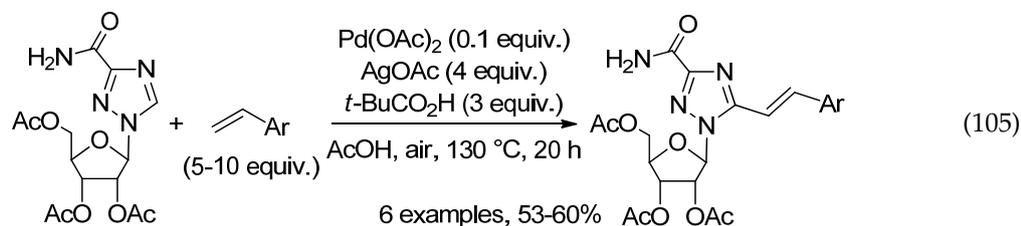
The $\text{Pd(OCOCF}_3)_2/\text{Ag(OCOCF}_3)_2/1,10$ phen would be the optimum association at 130 °C in toluene for the DHR of 2-aryl-1,3,4-oxadiazoles with vinyl(hetero)arenes (Equation (104)) [133].



10. N,N,N-Arenes

10.1. 1,2,4-Triazoles

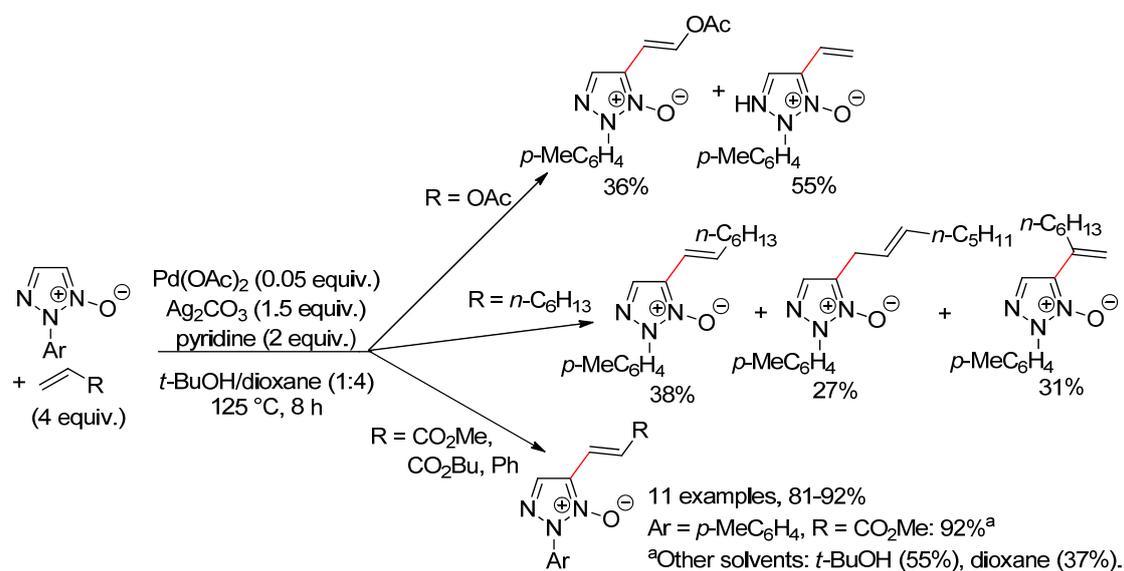
Arylvinyltriazole nucleosides have been synthesized via DHR of the triazole core with a variety of styrenes (Equation (105)) [137].



Kuang and co-workers reported the reluctance of 2-(*p*-tolyl)-2*H*-1,2,3-triazole towards the DHR with methyl acrylate under experimental conditions of Scheme 20 [138].

10.2. 1,2,3-Triazole *N*-Oxides

The Pd(OAc)₂/Ag₂CO₃/pyridine system in *t*-BuOH/dioxane led to efficient DHRs of 2-aryl-2*H*-1,2,3-triazole 1-oxides with acrylates and styrene (Scheme 22) [138]. The presence of pyridine and the 1:4 ratio of *t*-BuOH/dioxane were essential for yields. The reaction with vinyl acetate provided a mixture of the cross-coupling and corresponding deacetoxy products, while that of 1-octene led to three isomers. Kuang and co-workers proposed that the three isomers were issued from the DHR (Scheme 1, arene activation). The formation of the branched product led us to suspect the possibility of a nucleophilic attack on the octene-coordinated palladium complex (Scheme 1, alkene activation). The mixture obtained from vinyl acetate does not allow the prioritization of a catalytic cycle (see Scheme 21 and discussion of Sub-chapter 9.2).



Scheme 22. Products depending on the olefinating agents.

11. Conclusions and Remarks

Undeniably, the development of DHRs of five-membered heteroarenes has greatly progressed in the last ten years. Their exclusive properties have attracted the attention of scientists all over the world, leading to processes that would be valuable tools for academic and industrial applications.

A number of Pd(OAc)₂-catalyzed methods seem almost identical. In fact, the oxidant, required for the turnover, and the solvent often varied with the substrate. Additives, which may also be ligands, have, in most cases, a decisive role on the efficiency. As the range of oxidants, solvent mixtures, and additives is large, it is not obvious to choose the right combination for a new reaction. Complexity increases with N-heterocycles because their reactivity may depend on the N-substitution. Even if the wide published procedures give valuable indications, the chemist should try and see to reach fine results from a new DHR.

Compared to traditional Heck reactions, the DHR's have a "green" character, because prefunctionalization of the starting aromatic partner is avoided, improving step economy, and also the high atom efficiency gained by formal removal of only the molecular hydrogen. Nevertheless, the DHR's are usually performed with an excess of heteroarene or alkenating reagent, and only a few methods use solely oxygen to regenerate the Pd active species. Consequently, expensive silver salts are often required as oxidants. Leading to wastes, these conditions decrease the "green" aspect of the procedures and their compatibility with the atom economy principle [139].

In our opinion, five publications are particularly important [49,69,70,112,126] and complete the older Gaunt report [80]. One of them revealed a regioselectivity depending on the metal catalyst [49], while three others related regioselectivity mainly depending on solvent [69,70] or ligand [126]. The fifth publication disclosed a template directing the regioselectivity [112]. Another important report related regioselectivity depending on the substitution [72]. Although these reports concern DHRs of only a few substrates, they represent breakthroughs for researchers involved in the selective synthesis of regioisomers from the same starting material.

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

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