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Pd-catalyzed intermolecular dehydrogenative Heck reactions of six membered heteroarenes

Jean Le Bras and Jacques Muzart*

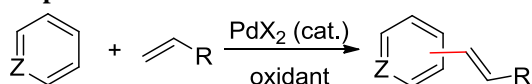
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Graphical abstract.



An update of the Pd-catalyzed cross-couplings of six-membered heteroarenes with alkenes, and the plausible mechanisms.

Abstract: The Pd^{II}-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” (DHR). The DHR of six-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 diversity of the procedures and, with personal comments, the mechanisms and intermediates that have been proposed.

Keywords: palladium; heteroarene; dehydrogenative Heck reaction; cross-coupling; C–H activation; alkenylation; catalysis.

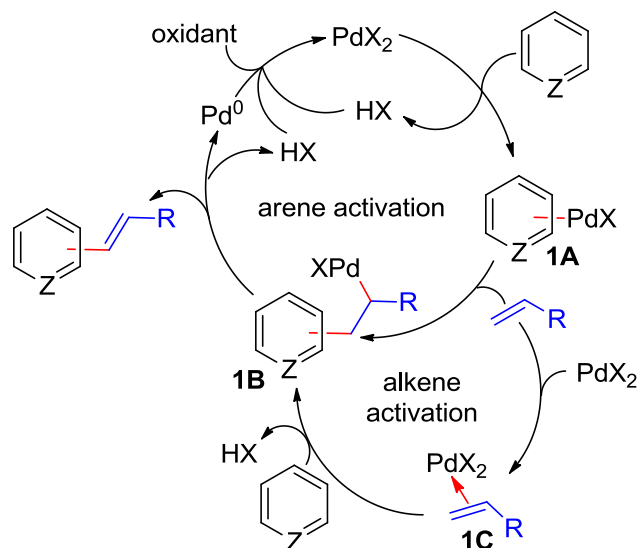
1. Introduction

Palladium-catalyzed C-H functionalization offers a broad range of transformations and has been at the forefront of organic synthesis over the last half-century [1]. In late sixties, Fujiwara’s team disclosed the Pd^{II}-mediated synthesis of stilbene from the cross-coupling of styrene with benzene [2]. This formation of a C-C bond from the coupling of two C-H bonds is a powerful alternative to the traditional Pd-catalyzed procedure independently discovered by the teams of Mizoroki, Julia and Heck [3]¹, which requires phenyl halide instead of benzene. Any prefunctionalization being required, the Fujiwara process has been the subject of intensive research leading to various efficient Pd^{II}-catalyzed couplings of (hetero)aromatic substrates with alkenes. We earlier reviewed the corresponding literature with references until June 2010 [4] using the term “Dehydrogenative Heck Reactions” (DHRs), initially proposed by Stoltz [5], to name such reactions which eliminate two H atoms and occur via an arylpalladium^{II} intermediate. Recently, we reviewed the DHRs of five membered heteroarenes reported over the last ten years [6]. We now highlight the DHRs of six membered heteroarenes published during the same period [7]. As for our recent review, the reactions of fused bicyclic arenes which do not involve the C-H bond of the hetero ring [8], as well those involving cross-coupling with another arene [9] will be discarded. The framework of the text depends on the nature of the aromatic substrate.

Pd^{II}-mediated activation of a C-H bond of the heteroarene leading to heteroaryl-palladium intermediate **1A** is usually admitted as the key step of the DHR (Scheme 1, arene activation). Addition of **1A** to the alkene gives **1B**. Subsequent β-H elimination delivers the cross-coupling product and Pd⁰, the latter being regenerated into active Pd^{II} species with an oxidant. Another mechanism involves the η²-palladium complex **1C** and its nucleophilic attack by the arene leading to **1B** (Scheme 1, alkene activation). Both catalytic cycles describe

¹ The Mizoroki publication, submitted on October, 20, 1970, was cited by Heck’s team which submitted their report on January, 13, 1972. On January 12, 1971, Julia’s team deposited a "Pli cacheté", i.e. a sealed envelope, to the Société Chimique de France, which was open on May, 5, 1973.

dehydrogenative cross-coupling reactions, but a reaction via the alkene complex cannot be named DHR. Brogini's team proposed the term "alkene activation" [10]. Actually, 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. According to ESI-MS [11], NMR [12] and kinetic isotope effect [13] studies, most dehydrogenative cross-coupling reactions would occur via the arene activation process. The site-selectivity of heteroarenes is governed by the "innate" or "guided" C-H bond activation [14]. The former relies on the electronic properties of the heterocycle induced by the heteroatom [15], whereas the latter is relevant to either a directing group or a specific additive.

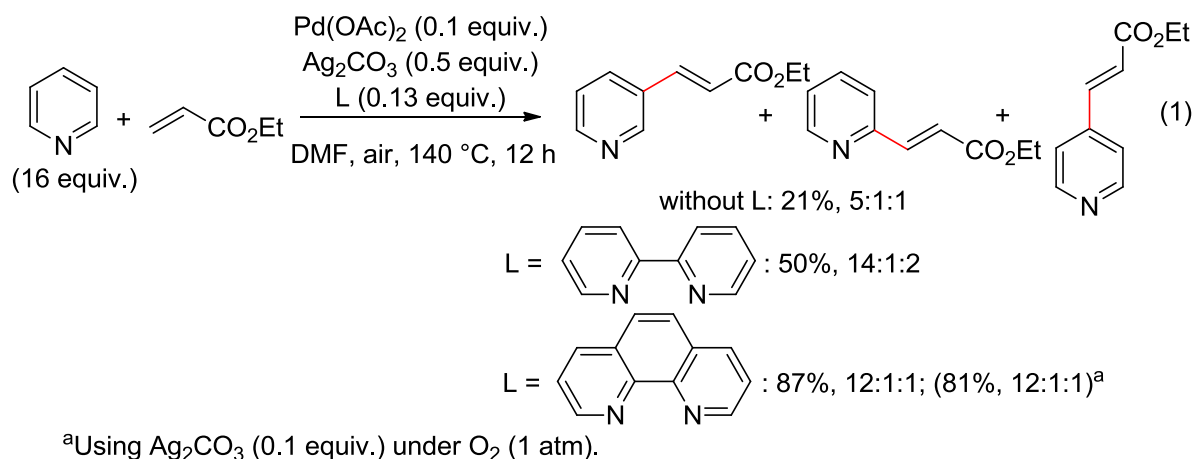


Scheme 1. Catalytic cycles of dehydrogenative cross-coupling reactions.

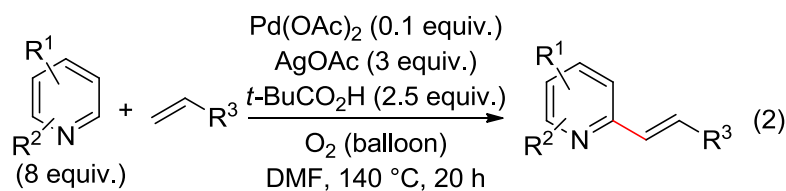
2. N-arenes

2.1. Pyridines

Pyridine (py) is often used as base [16] or ligand [17] of DHRs [4], hence the difficulty to carry out its DHR. The first report, published in 2011, is due to Yu's team [13]. Treating a 16:1 mixture of pyridine and ethyl acrylate with Pd(OAc)₂ (0.1 equiv.) and Ag₂CO₃ (0.5 equiv.) in DMF at 140 °C under air atmosphere provided 21% of ethyl pyridinylacrylates, the C3 substituted product being the main isomer (Eq. 1). The authors suspected that the low yield was due to strong coordination of the pyridine N atom to Pd^{II}, preventing interaction of the catalyst with the C-H bonds of pyridine. Thus, they presumed that use of bidentate pyridyl ligands would favor the interaction of Pd^{II} with the π-ring. As expected, the yield increased to 50% with 2,2'-bipyridine, and after extensive ligand screening, to 87% with 1,10-phenanthroline (Eq. 1). Switching to O₂ instead of air atmosphere allowed to reduce the Ag₂CO₃ amount but with slight yield decrease. The Pd(OAc)₂/Ag₂CO₃/air procedure was used for the selective 3-alkenylation (27-73% yield) of various pyridines with acrylates, *N,N*-dimethylacrylamide, styrene and 2-vinyl-1,3-dioxolane (19 examples). Lower yields (≈15%) were obtained with internal olefins. The team performed kinetic isotope effect (KIE = 4) studies and proposed a mechanism that involves the arene activation.



Selective C2 olefination was reported in 2012 by the teams of Ma and Huang using Pd(OAc)_2 catalysis, AgOAc , O_2 and pivalic acid in DMF at 140°C [18]. Yields and selectivities were tightly dependent on the pyridine:olefin: AgOAc :pivalic acid ratio, best results being with the 8:1:6:5 ratio leading in most cases to fair results (Eq. 2). Use of Ag_2CO_3 instead of AgOAc seems to be prejudicial to the selectivity but the reagents ratio was different (Eq. 2). Cross-coupling with an internal olefin such as butyl but-2-enoate did not occur. Pyridines with halogens atoms in both C3 and C5 positions afforded selective C4 olefination (Eq. 3). The authors determined a KIE identical to that observed by Yu's team ($k_{\text{H}}/k_{\text{D}} = 4$), and assumed a mechanism with Pd(OAc)_2 as the catalytic species.



$\text{R}^1, \text{R}^2 = \text{H, Me, OMe, Br, Cl, F, CN, NO}_2, \text{CO}_2\text{Me}$; $\text{R}^3 = \text{COBu, CO}_2\text{Et, CO}_2\text{Bu, CONH}_2, \text{Ph}$; 20 examples: trace-78% yield
 $\text{R}^1 = \text{R}^2 = \text{H, R}^3 = \text{CO}_2\text{Bu}$: 61%^{a,b,c,d,e}

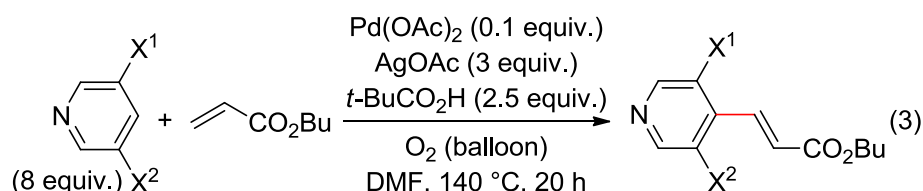
^aPlus C-3 substituted product (8%)

^b34% with AcOH instead of $t\text{-BuCO}_2\text{H}$

^cWith pyridine (4 equiv.): 43% plus C-3 substituted product (5%)

^dWith pyridine (4 equiv.) and $t\text{-BuCO}_2\text{H}$ (1 equiv.): 27% plus C-3 substituted product (9%)

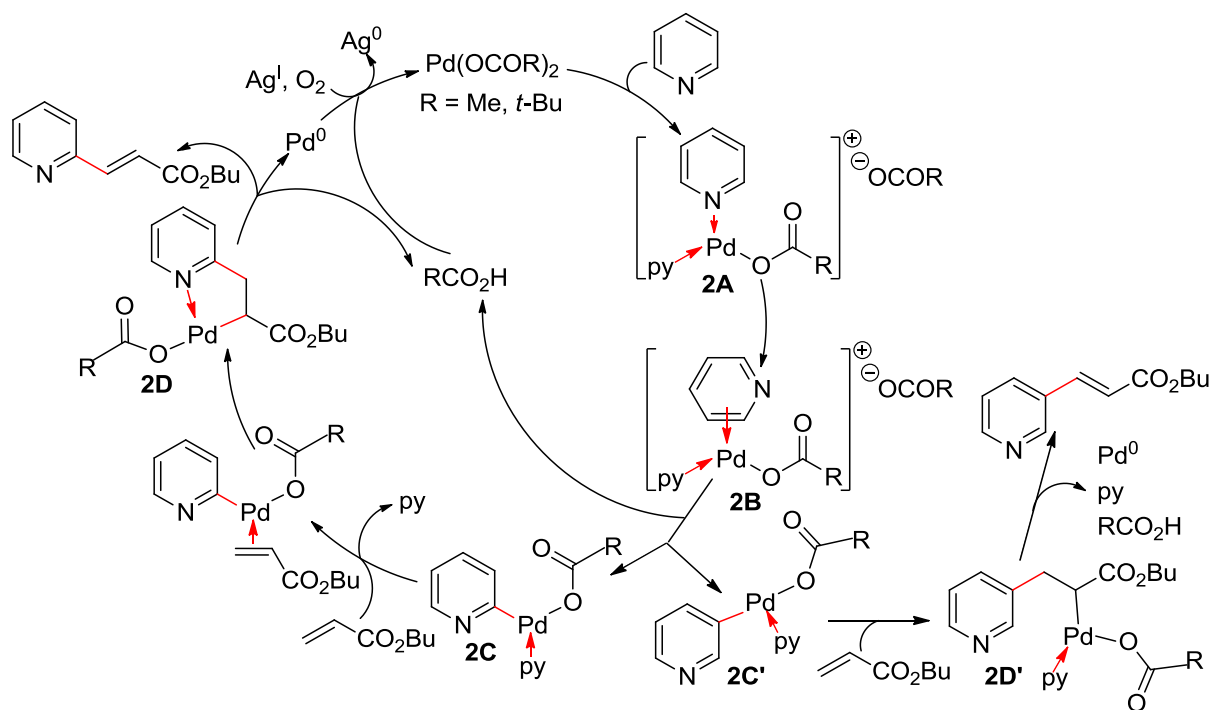
^eWith pyridine (4 equiv.), $t\text{-BuCO}_2\text{H}$ (1 equiv.) and Ag_2CO_3 (1.5 equiv.) instead of AgOAc : 17% plus C-3 substituted product (15%).



$\text{X}^1 = \text{X}^2 = \text{F}$: 70%; $\text{X}^1 = \text{X}^2 = \text{Cl}$: 68%; $\text{X}^1 = \text{Br, X}^2 = \text{F}$: 60%

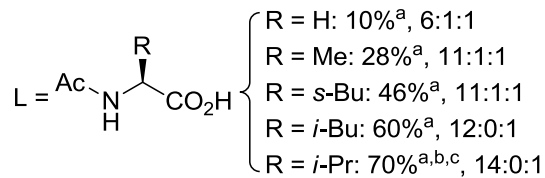
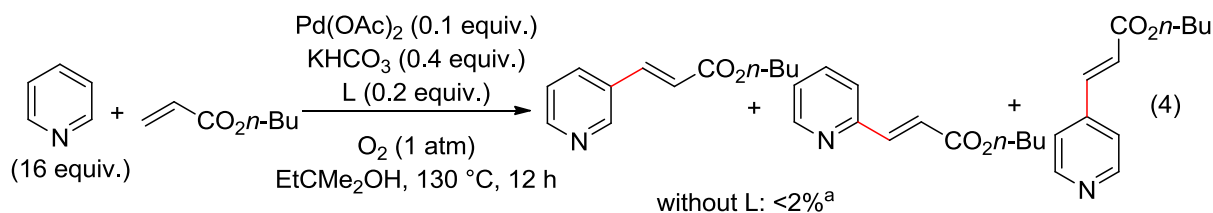
The yield decrease of the pyridine/butyl acrylate reaction using AcOH instead of $t\text{-BuCO}_2\text{H}$ and the selectivity dependence on the amount of $t\text{-BuCO}_2\text{H}$ (Eq. 2) led us to suspect the involvement of $\text{Pd(OCO}t\text{-Bu)}_2$ [19,20] or $\text{Pd(OCO}t\text{-Bu)(OAc)}$. Consequently, we retain a catalytic cycle mediated by Pd(OCOR)_2 ($\text{R} = \text{Me}$ or $t\text{-Bu}$).

Bu) (Scheme 2). N-coordination of pyridine to $\text{Pd}(\text{OCOR})_2$ provides **2A** which changes into **2B** due to a strong *trans*-effect [21] of pyridine ligand. In their above report [13], Yu's team also called upon the "*trans*-effect" for the **2A** to **2B** step and cited the same references [21], but did not really refer to such phenomena in a subsequent review [22]. Insertion of palladium into C2-H or C3-H bond of pyridine leads to **2C** and **2C'**, respectively. Ligand exchange followed by insertion of the C=C bond into the pyridinylpalladium bond affords **2D** from **2C**. Then, β -H elimination gives the C2 olefinated product. A similar pathway provides the minor product from **2C'**.



Scheme 2. Catalytic cycle adapted from [18].

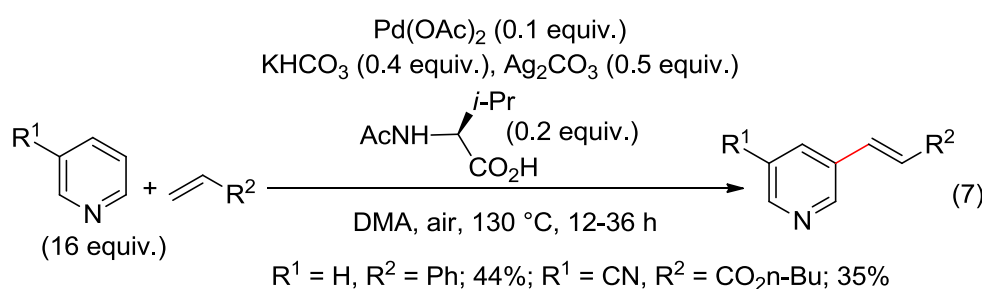
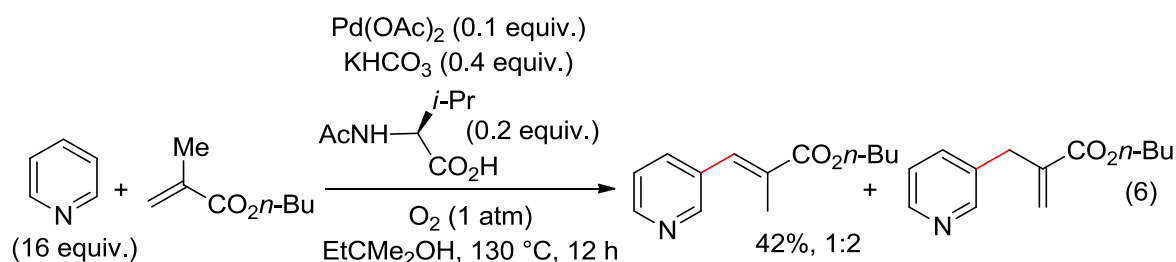
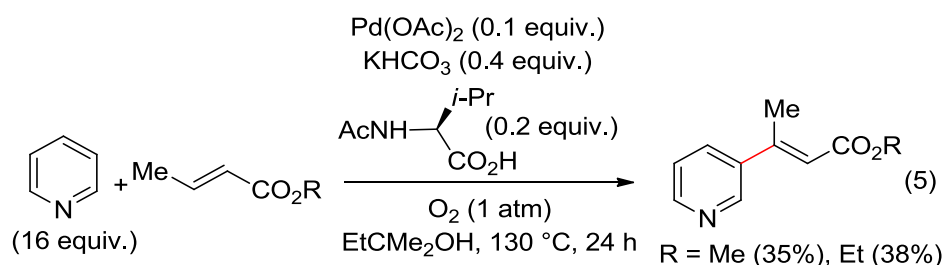
Another protocol for C3 olefination of pyridines was reported 18 months later by the team of Wu and Zeng [23]. While only traces of the C3 cross-coupling product were produced from pyridine and butyl acrylate under oxygen and $\text{Pd}(\text{OAc})_2$ catalysis at 130 °C in 2-methylbutan-2-ol containing KHCO_3 , the DHR arose in fair yields in the presence of mono-*N*-protected amino acids, especially α -isopropyl-substituted *L-N*-acetyl-valine (Ac-Val-OH) (Eq. 4). The procedure was used for the selective 3-alkenylation of various pyridines with acrylates, *N,N*-dimethylacrylamide and (hetero)styrenes (23 examples, 20-80% yield). The DHR also occurred with substituted acrylates (Eqs 5 and 6). The KIE ($k_{\text{H}}/k_{\text{D}} = 3$) lower than those obtained under the other experimental conditions [13] "is consistent with a thermodynamically unfavorable C–H activation step, and it may indicate that the Ac-Val-OH ligand enhances the electrophilic property of the palladium center in promoting the C–H bond cleavage of pyridine" [23]. In a few cases, the olefination was carried out in DMA under air with Ag_2CO_3 as additive (Eq. 7). Given a recent report from Sunoj's team [24], the silver salt could be more than a terminal oxidant, forming a Pd/Ag heterobimetallic species which would participate in the catalytic cycle.



^aIsolated yield of the C-3 cross-coupling product

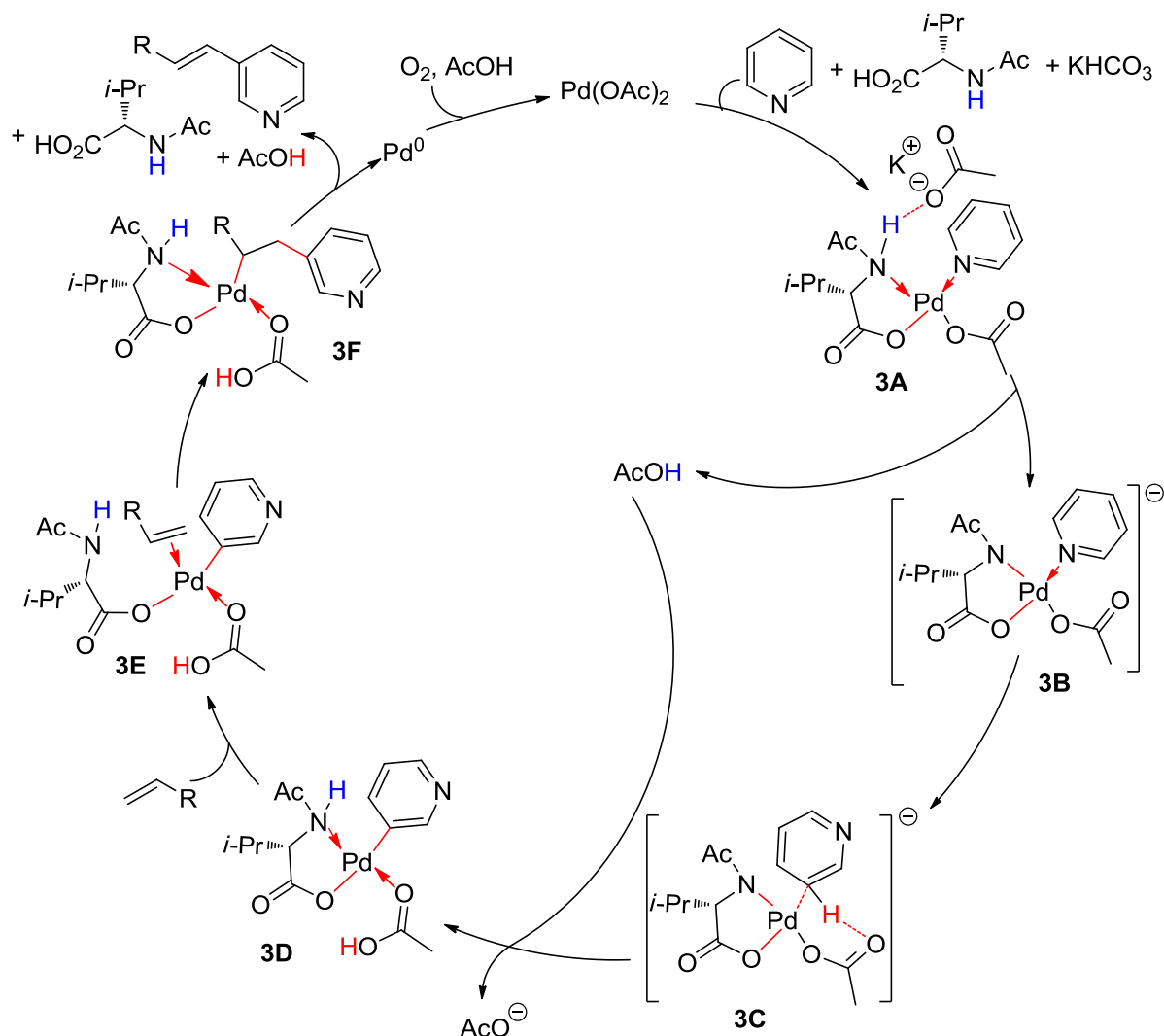
^b42% under air instead of O₂

^c40% with PdCl₂ instead of Pd(OAc)₂.



Wu, Zeng and co-workers assumed a crucial role to Ac-Val-OH becoming either one electron donor (X-type) or a two electron donor (L-type) ligand [23]. The proposed intermediates (Scheme 3) agree with extensive theoretical studies by density functional theory. From intermediate **3A**, proton abstraction transforms the LX-type bidentate ligand into a XX-type ligand giving **3B** and AcOH. Calculations indicated that the activation of C3-H is favored over C4-H and especially C2-H. That results in transition state **3C**. Intramolecular proton abstraction by the acetoxy ligand [25] and protonation of the N atom by previously liberated AcOH affords **3D**. The LX-type bidentate ligand of **3D** undergoes exchange with the alkenating agent leading to **3E**. Insertion of C=C bond into the Pd-pyridinyl bond gives **3F**. Subsequent β -H elimination liberates the C3 adduct, Ac-Val-OH and, according to the authors, Pd⁰ and AcOH. Reaction of Pd⁰ with O₂ and AcOH would regenerate Pd(OAc)₂.

The regeneration of active Pd species could also arise from reaction of PdH intermediate with O₂ [26] but such a pathway remains a matter of debate [27,28]. The role of the solvent is however ignored in this catalytic cycle. Indeed, 2-methylbutan-2-ol could cause the alcoholysis of palladium acetate leading to alkoxypalladium species as the active catalyst [29].



Scheme 3. Catalytic cycle adapted from [23].

Below, we tentatively rationalize the regioselectivity dependence of pyridine on the experimental conditions.

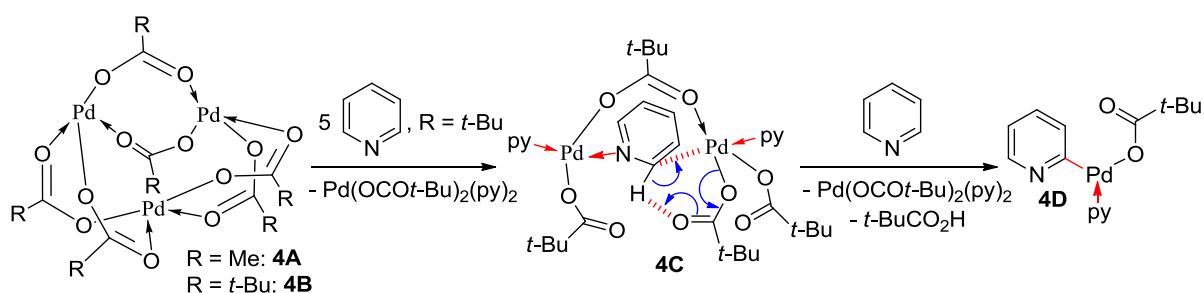
Calculations favor the C3 olefination [23,30,31]. In 2013, Yu's team nevertheless noted that "the strong preference for C-H cleavage at the C3 position is not entirely clear at this time" [22]. Computational analysis of the Pd-catalyzed arylation of pyridine [32] led Gorelsky to assume that the selectivity "is expected to switch from C3 arylation to C2 arylation" when pyridine is N-coordinated to Cu^I [31]. Thus, we suspected that the C2 selective olefination (Eq. 2) is due to a pyridine molecule N- and C2-coordinated to Pd atoms as the corresponding key intermediate.

Under the experimental conditions of Yu, Wu, Zeng and co-workers, the C3 selectivity occurred even in the absence of the bidentate ligand but the yield was lower (Eqs 1 and 4) [13,23]. Moreover, some relationship between selectivity and steric hindrance of the bidentate ligand was observed. Thus, the C2 position would be disfavored by steric effect [22]. The bidentate ligand increases the nucleophilicity of the Pd^{II} center favoring the concerted metalation/deprotonation [33] of the heteroarene ring.

The main difference between the procedures of the teams of Yu, Ma and Huang (Eqs 1 and 2) [13,18] is pivalic acid (Eq. 2), this additive reversing the selectivity. The nature of the silver salt could also have an influence, but more experiments would be required to clarify this plausible effect. Both procedures (Eqs 1 and 2)

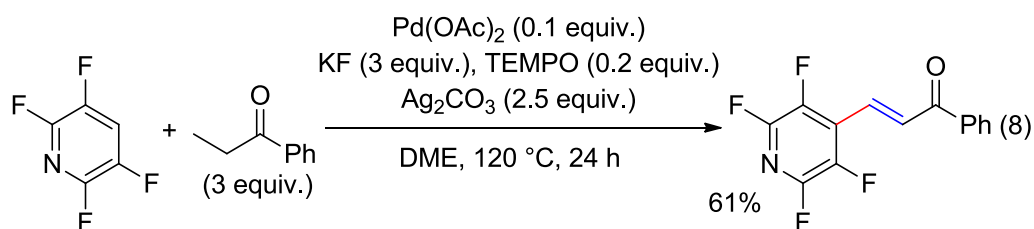
use the same coordinating solvent, DMF [34,35], at 140 °C. 2-Methylbutan-2-ol which is the solvent of the Wu and Zeng method (Eq. 4) [23] probably has coordination properties probably lower than those of DMF [35]. Consequently, the C3 versus C2 selectivity is most likely not linked to the solvent.

The complexes $\text{Pd}(\text{OAc})_2(\text{py})_2\cdot\text{H}_2\text{O}$ [36] and $\text{Pd}(\text{OAc})_2(2,6\text{-bis}(2\text{-ethylhexyl})\text{pyridine})_2$ [37] have been characterized by X-ray crystallography. In solution, the latter evolved towards $[\text{Pd}(\text{OAc})_2(2,6\text{-bis}(2\text{-ethylhexyl})\text{pyridine})_2]$ in which the $\text{Pd}(\text{OAc})_2$ units are joined by double OAc bridges [37]. Palladium acetate exists as a trimer (**4A**) in the solid state (Scheme 4) [38]. The structure is maintained in AcOH [39], EtCO₂H and EtCO₂H/THF mixture [40]. The close donating properties of THF and DMF [35] would lead to suspect that structure **4A** could be more or less [41] maintained in DMF and also be the structure for the Pd catalyst of Scheme 2 [42]. The yield dependence of the C2 olefination of pyridine (Eq. 2) with both nature and amount of the used carboxylic acid [18,43] as well as the superiority of the pivalate ligand over the acetate to abstract a proton [44-46]² led us to assume that the trimer could rather be **4B** (R = *t*-Bu). Given the above pyridine complexes and the above Gorelsky remark [31], we propose that under experimental conditions of Eq. 2, coordination of pyridine molecules to Pd atoms leads to some cleavage of bridging ligands, resulting in the formation of dimer **4C** from **4B** [33,46,47]. **4C** could also be obtained from the dimer $[\text{Pd}(\text{OCO}t\text{-Bu})_2]_2$ which would have a good stability [48]. The coordinating properties of pyridine superior to those of DMF [35a] led us to draw **4C** without ligation of DMF. H-abstraction by the pivalate ligand [49] affords **4D** from **4C**. Then, the reaction proceeds as depicted in Scheme 2. The C2 olefination being carried out in presence of a silver salt (Eq. 2), the DHR could be catalyzed by heterobimetallic species [24,50] resulting in an intermediate similar to **4C** for which the N atom is coordinated to Ag instead of Pd.



Scheme 4. A plausible transition state to rationalize the C2-H activation.

Su's team disclosed the Pd-catalyzed olefination of (hetero)arenes with saturated ketones, one example being the reaction of 2,3,5,6-tetrafluoropyridine with propiophenone which afforded (*E*)-3-(perfluoropyridin-4-yl)-1-phenylprop-2-en-1-one (Eq. 8) [51] through a domino dehydrogenation/Heck-type reaction [52]. The authors showed that the reaction arose via Pd-catalyzed dehydrogenation of the ketone into 1-phenylprop-2-en-1-one [53] followed by Pd-catalyzed DHR.

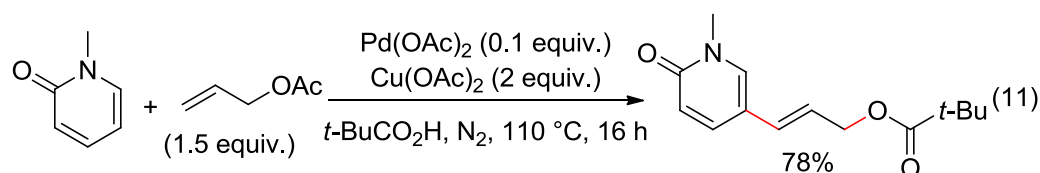
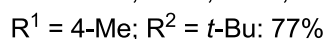
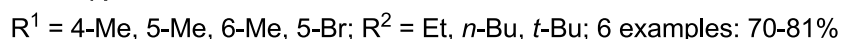
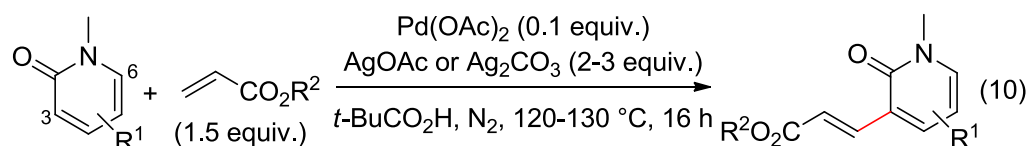
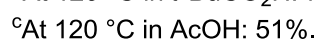
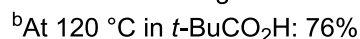
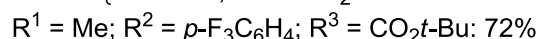
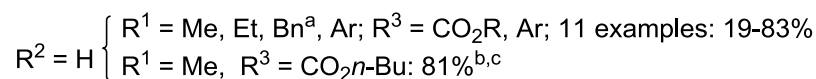
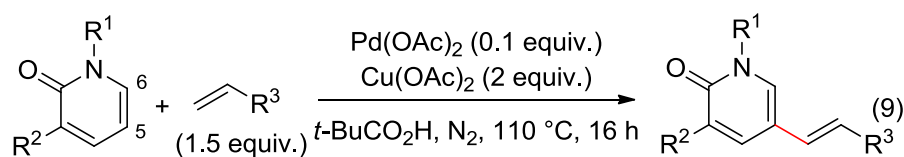


2.2. Pyridones

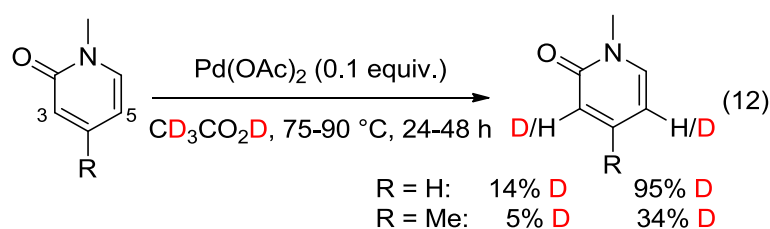
In 2012, Li's team reported the efficient $\text{Pd}(\text{OAc})_2$ -catalyzed C5 olefination of *N*-substituted pyridin-2(*1H*)-ones in pivalic acid at 110 °C with $\text{Cu}(\text{OAc})_2$ as the oxidant (Eq. 9) [54]. Lower yields were obtained in AcOH, toluene, DMF/DMSO and acetone. The DHR of 1,3-disubstituted pyridin-2(*1H*)-one arose with the same regioselectivity (Eq. 9) while *N*-methylpyridin-2(*1H*)-ones substituted in 4, 5 or 6 position were olefinated in C3

² The superiority of pivalate could be related to both its larger steric bulk and its stronger basicity [44,45c].

position (Eq.10). Olefination of both C3 and C5 positions of *N*-substituted pyridin-2(1*H*)-ones occurred via either sequential addition or one-pot in increasing the amount of acrylates. Use of allyl acetate instead of acrylates led to a DHR associated to a Tsuji-Trost reaction [55] giving C-H substitution by the allyl pivalate group (Eq. 11).

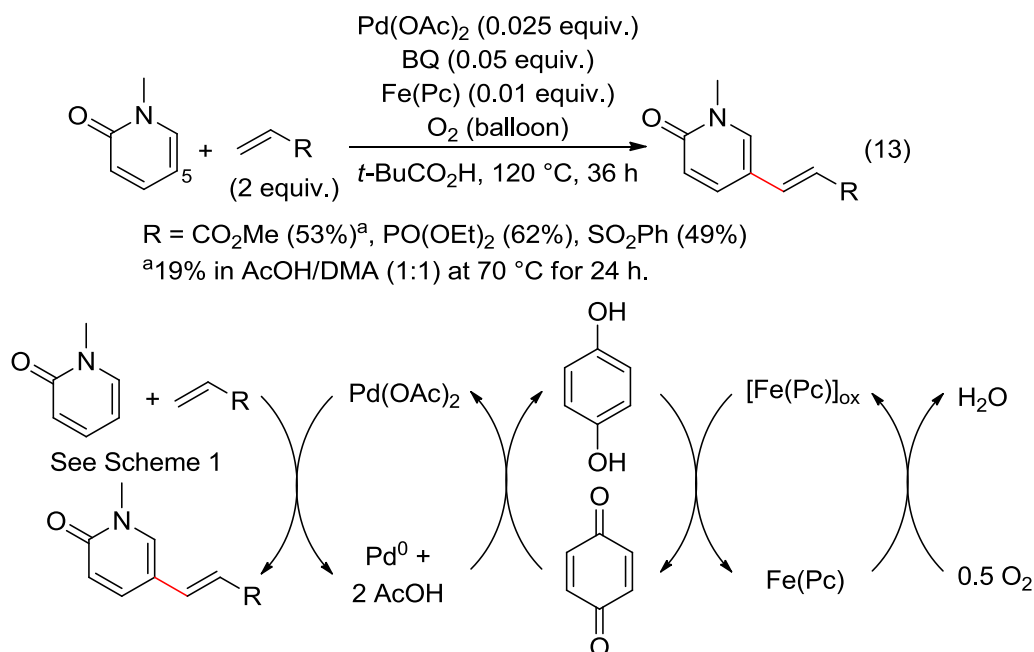


Heating 1-methylpyridin-2(1*H*)-one and 1,4-dimethylpyridin-2(1*H*)-one with catalytic Pd(OAc)₂ in CD₃CO₂D resulted in main H/D exchange in C5 position (Eq. 12) although the DHR of the disubstituted substrate selectively occurred in C3 position (Eq. 10). According to Li and co-workers, “this discrepancy can be reconciled by the inversion of relative rate of subsequent reactions when an olefin is present” and the site selectivity of the DHR “is subtly tuned by a combination of electronic and steric effects” [54].



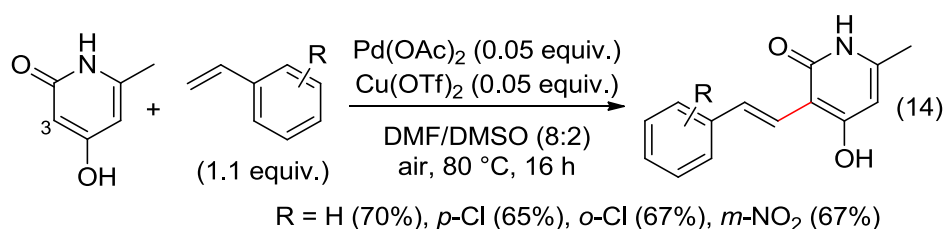
Bäckvall's team developed an aerobic oxidation system consisting of catalytic amounts of Pd(OAc)₂, benzoquinone (BQ) and an electron-transfer mediator, especially iron phthalocyanine (Fe(Pc)) [56]. The procedure has been used for the C5 olefination of *N*-methylpyridin-2(1*H*)-one in pivalic acid at 120 °C (Eq. 13) [57]. The yields dramatically decreased in a mixture of AcOH and DMA at 70 °C. The mechanism proposed by Bäckvall and co-workers for the regeneration of active catalytic species is illustrated in Scheme 5. As depicted in Scheme 1, the DHR leads to Pd⁰ and 2 AcOH. Coordination of benzoquinone to Pd⁰ form a complex which undergoes reaction with AcOH giving Pd(OAc)₂ and hydroquinone [58,59]. Oxidation of hydroquinone into

benzoquinone cannot occur with molecular oxygen but arise in the presence of the electron-transfer mediator, hence a cross-coupling reaction mediated with only catalytic amounts of Pd(OAc)₂, BQ and Fe(Pc) [56].

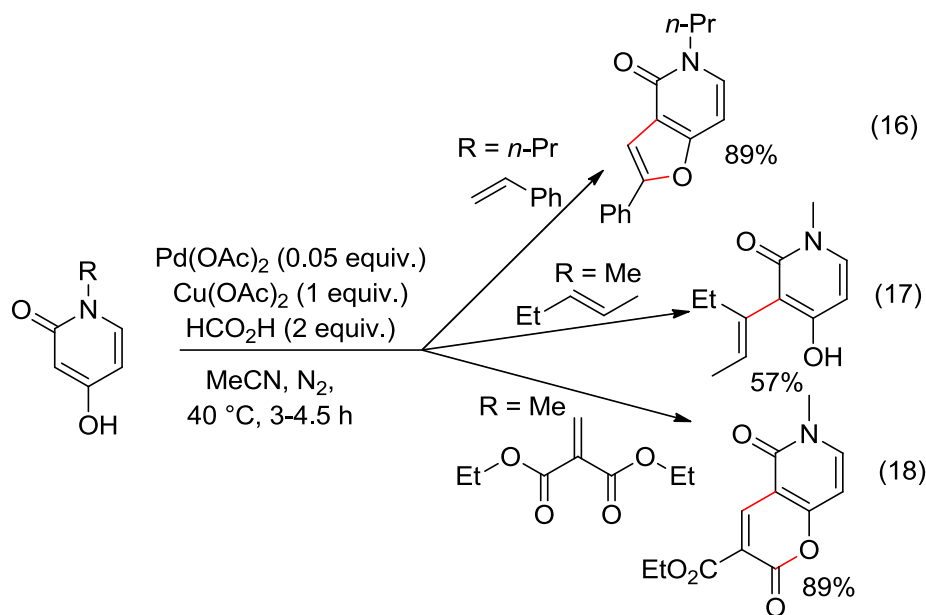
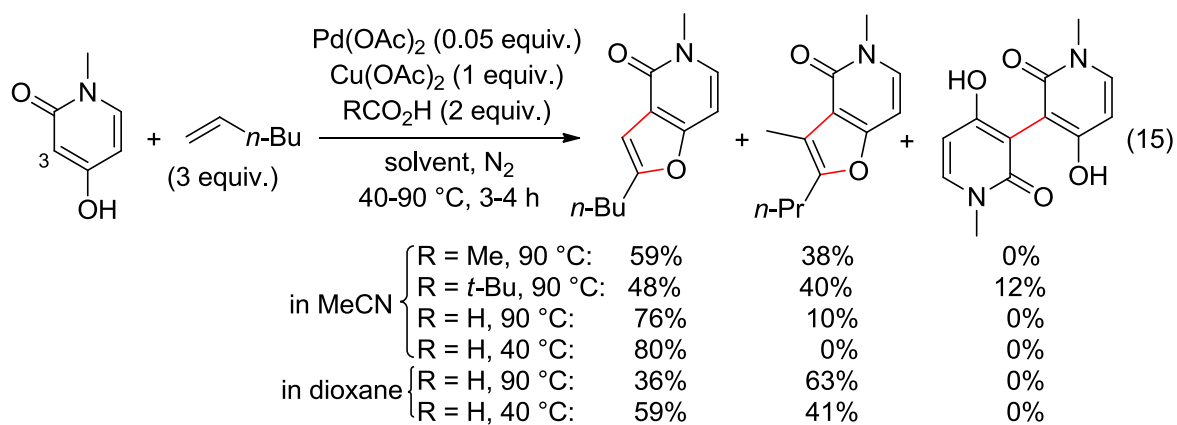


Scheme 5. Catalyst regeneration using an electron-transfer mediator.

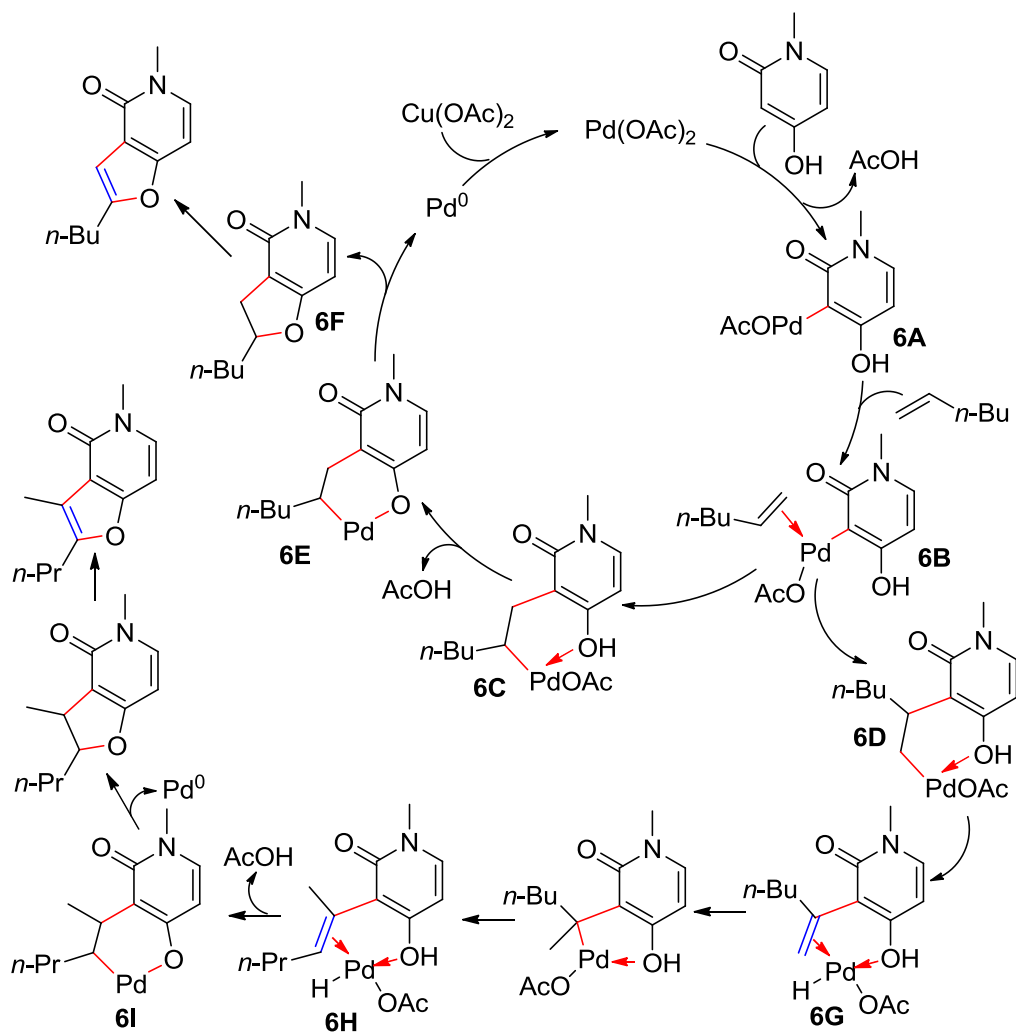
Yousuf's team carried out the selective C3 alkenylation of 4-hydroxypyridin-2(1*H*)-one with styrenes using catalytic amounts of both Pd(OAc)₂ and Cu(OTf)₂ in aerated DMF/DMSO at 80 °C (Eq. 14) [60].



A domino reaction arose from 4-hydroxy-1-methylpyridin-2(1*H*)-one and 1-hexene leading to cyclisation products (Eq. 15) [61]. Homocoupling of the aromatic substrate may be a side-product. Various Pd-catalysts, oxidants and solvents, with or without base or carboxylic acid, afforded the products. The best yield and selectivity were obtained with Pd(OAc)₂ as the catalyst, Cu(OAc)₂ as the oxidant and formic acid as the additive in MeCN. The reaction with styrene, which efficiently led to the cyclized product (Eq. 16) contrasts with that under Yousuf's conditions (Eq. 14). With shorted alkenes such as 2-pentene, the reaction stopped at the level of the alkenylation (Eq. 17). The cross-coupling cyclisation with diethyl 2-methylenemalonate led to the formation of a pyranonyl ring (Eq. 18).



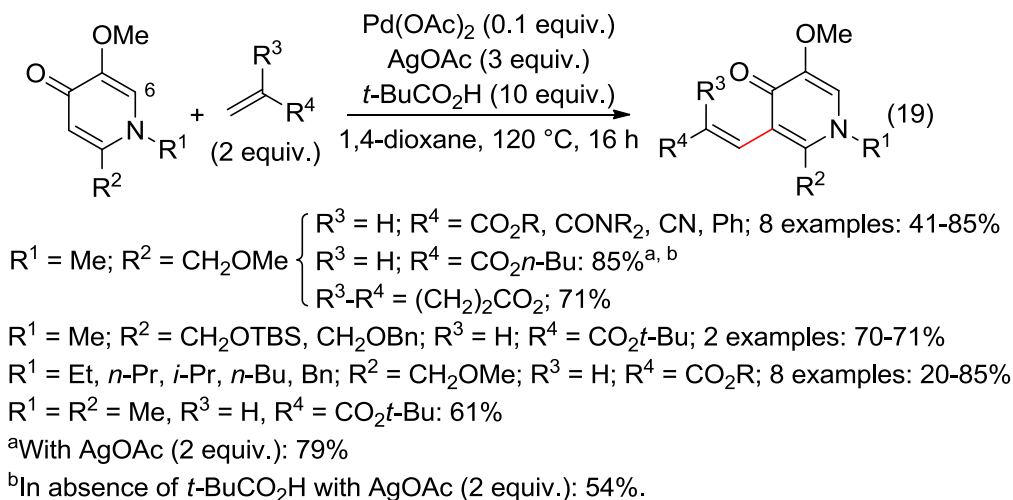
The catalytic cycle depicted in Scheme 6, which is inspired by the proposal of Zografos and co-workers [61], involves C3 palladation of the substrate giving **6A**. Coordination of 1-hexene followed by insertion into the C-Pd bond of **6B** gives **6C** and/or **6D**. Coordination of the hydroxy group to palladium atom was already assumed by Yousuf's team for the intermediate leading to cross-coupling with styrenes (Eq. 14). Intramolecular reaction of **6C** leads to palladacycle **6E**, which undergoes reductive elimination of Pd⁰ giving **6F**. Zografos team assumed that the main isolated product arises from in-situ oxidation of **6F**. The formation of the minor product is much less obvious. The authors showed the absence of isomerization of 1-hexene under the reaction conditions but were discreet on the reaction pathway. We propose a β -H elimination from **6D** leading to **6G** followed by successive addition/elimination of HPdOAc to provide **6H**. Subsequent intramolecular reaction gives **6I** which evolves as assumed for **6E**.



Scheme 6. Proposed intermediates of the cross-coupling/cyclisation reaction of 4-hydroxy-1-methylpyridin-2(1*H*)-one.

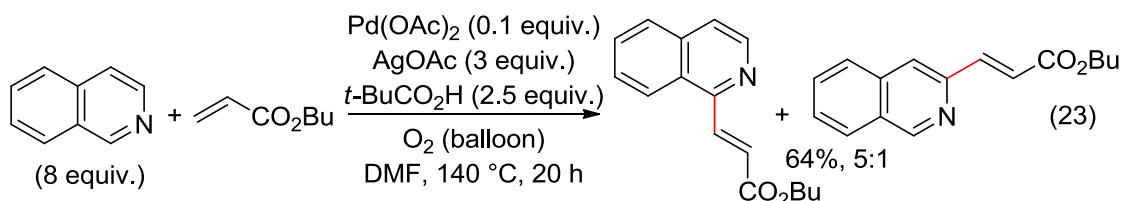
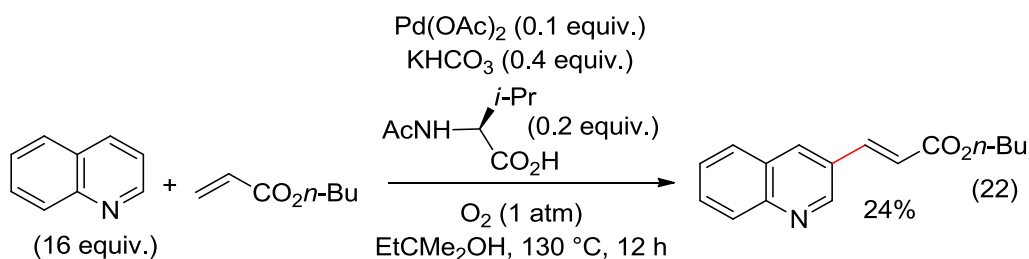
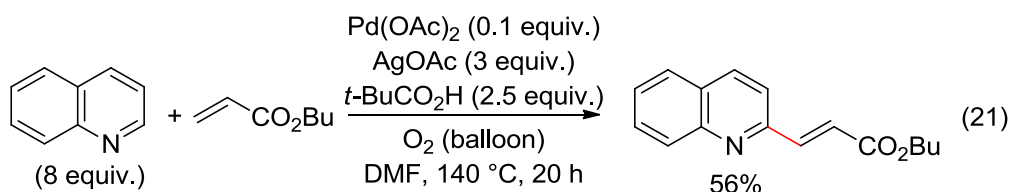
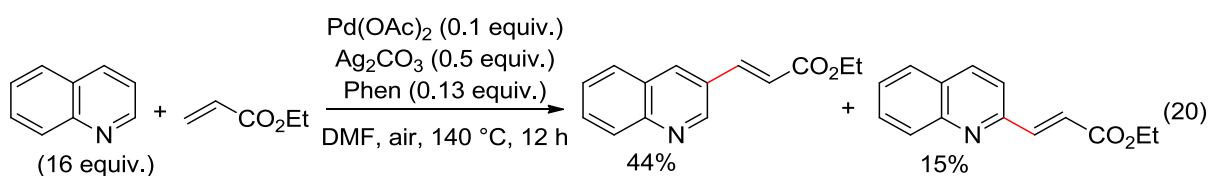
The large dependence of the reaction selectivity of 4-hydroxy-1-methylpyridin-2(1*H*)-one on the nature of both the solvent and the carboxylic acid (Eq. 15) remains undetermined. On the basis of possible change of the insertion regioselectivity of alkenes into the C-Pd bond with the nature, cationic versus neutral, of Pd intermediates [62,63], the authors proposed “neutral-type mechanism in acetonitrile which changes to cationic when reaction is conducted in dioxane” [61]. We are rather sceptic towards this hypothesis because acetonitrile and dioxane have similar coordinating properties [35]. Both solvents can be involved as co-ligand in most intermediates shown in Scheme 6, especially **6B**. Wucher and co-workers reported the influence of steric interactions on the regioselectivity of the addition of ArPd species to CH₂=CHR [64]. Consequently, we suspect that the moderate size of MeCN favors the formation of **6C** from **6B**, while the larger size of dioxane directs the insertion towards **6D**. Scheme 6 is drawn in considering a catalysis mediated by Pd(OAc)₂, as proposed in the original report [61]. In fact, exchange with the carboxylic acid (RCO₂H) used as additive could arise leading to PdOCOR-type intermediates with different steric hindrances, hence a plausible role of the size of RCO₂H on the selectivity.

An array of 2,5-disubstituted pyridin-4(1*H*)-ones underwent C3 alkenylation (Eq. 19) [65] under experimental conditions close to those of Ma and Huang (Eq. 2) [18]. Yao *et al.* showed that pivalic acid as additive was required for an effective DHR [65].



2.3. Quinoline and isoquinoline

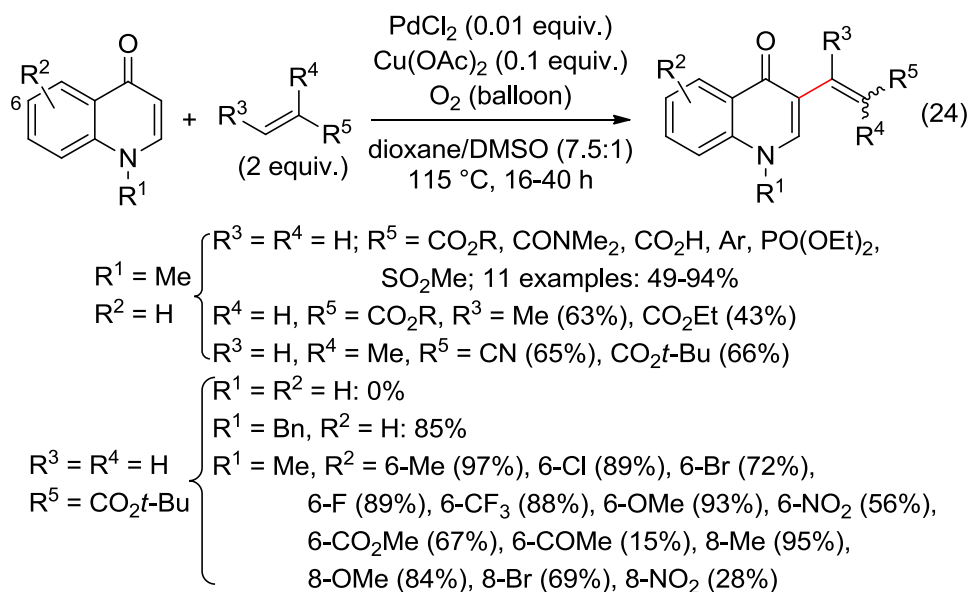
The DHRs of quinoline and isoquinoline with acrylates, carried out using the above pyridine protocols, exhibited a regioselectivity highly depending on the procedure (Eqs 20-23) [13,18,23].



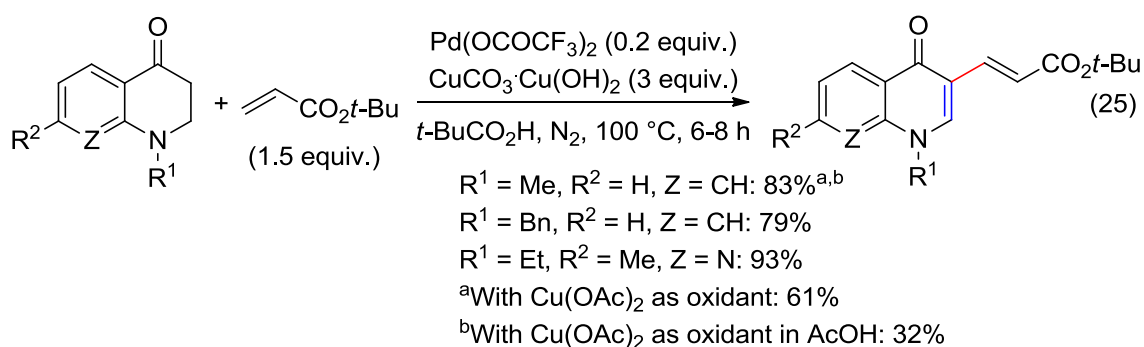
2.4. Quinolones and 1,8-naphthyridin-4(1H)-one.

An array of N-substituted quinolin-4(1H)-ones has been C3 alkenylated by Ge's team, using catalytic amounts of both PdCl_2 (0.01 equiv.) and Cu(OAc)_2 (0.1 equiv.) in dioxane/DMSO under oxygen atmosphere (Eq. 24) [66]. N-substitution was required and the DHR efficiency depended on the nature of the substituents.

The experimental conditions of the procedure ask the question of the mechanism and, consequently, on the nature of the catalytic species. The activation of the heteroaryl C-H bond involves oxidative addition, σ -bond metathesis or electrophilic substitution [46,67]³. Electrophilic substitution has been proposed for the PdCl₂-catalyzed DHR of isoquinoline and quinoline *N*-oxides (see below Eqs 29 and 30) [69]. Ge and co-workers however obtained the DHR of 1-methylquinolin-4(1*H*)-one with *t*-butyl acrylate in fair to high yields using Pd(OAc)₂ (0.1-0.2 equiv.) or Pd(OCOCF₃)₂ (0.05-0.1 equiv.) with large amounts of Cu(OAc)₂ (2 equiv.) under air atmosphere [66]. That leads us to suspect the in-situ formation of XPdOAc (X = Cl or OAc) from PdCl₂ and Cu(OAc)₂; such a species could mediate the formation of the C-Pd bond via a concerted metalation-deprotonation pathway [33,47].

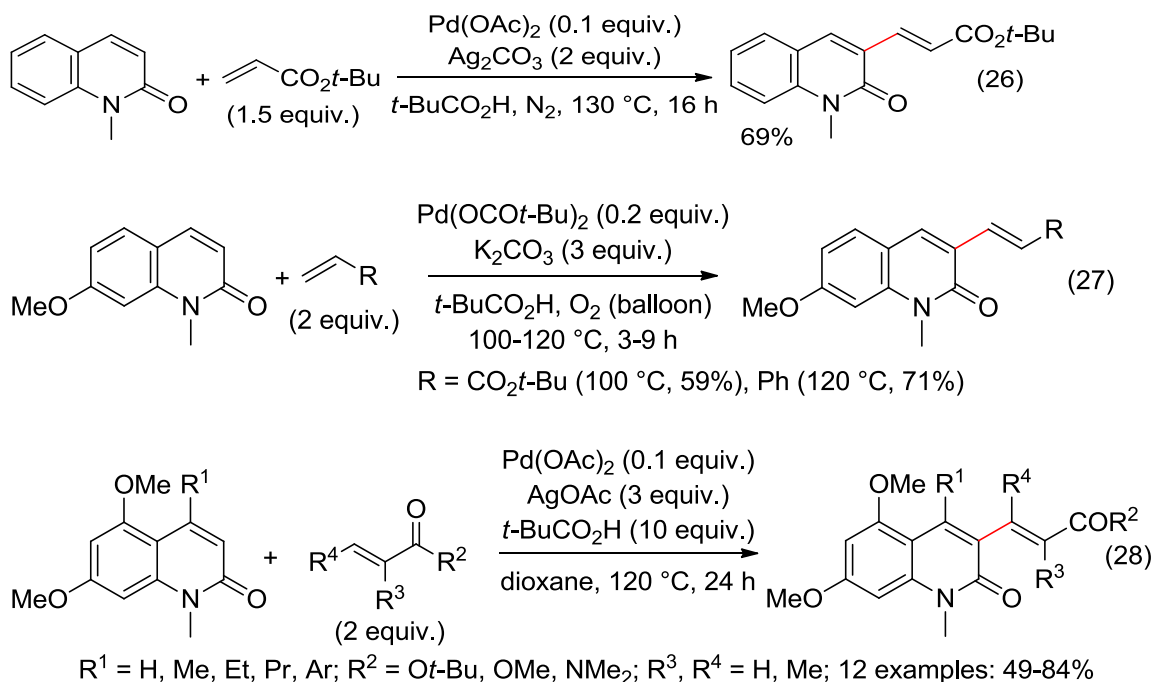


N-substituted 2,3-dihydroquinolin-4(1*H*)-ones and 1-ethyl-7-methyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one underwent a domino dehydrogenation/dehydrogenative Heck reaction [52] catalyzed by Pd(OCOCF₃)₂ [26a] leading to cross-coupling products in high yields providing that pivalic acid was the solvent (Eq. 25) [70]. It seems of interest to note the absence of DHR at the level of the pyridinyl ring of the 1,8-naphthyridin-4(1*H*)-one intermediate.



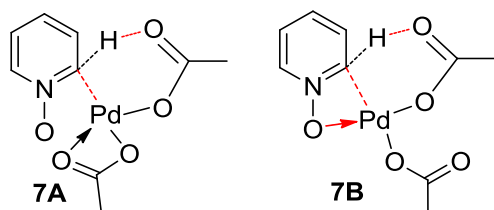
Three methods have been reported for selective C3 olefination of 1-methylquinolin-2(1*H*)-ones, all use pivalic acid either as solvent (Eqs 26 and 27) [54,71] or additive (Eq. 28) [72] and palladium acetate or pivalate as the catalyst.

³Computational studies to differentiate proton abstraction and electrophilic aromatic substitution mechanisms have been recently reported; the results were tested against literature experimental data [68].



2.5. Pyridine *N*-oxides

To the best of our knowledge, no Pd-catalyzed DHR of pyridine *N*-oxides was published since 2010 [73]⁴. The mechanism of the Pd(OAc)₂-mediated C-H activation of pyridine *N*-oxide has however been investigated by Fang and Zhang through density functional theory (DFT) calculations [75]. While coordination of the catalyst to the *N*-oxide was previously proposed as the step directing the regioselectivity of the C-Pd bond formation [76], DFT calculations indicated that the undirected mechanism is more plausible than the 4-member-directed one both thermodynamically and kinetically [75]. Consequently, the C-H activation would involve transition state **7A** rather than **7B** (Scheme 7).

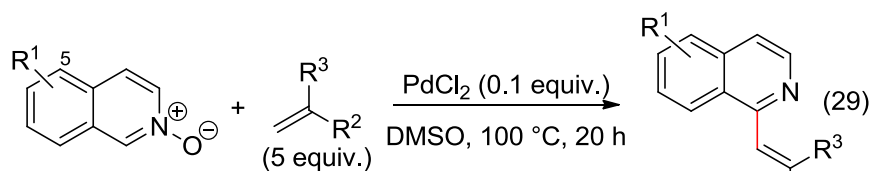


Scheme 7. Plausible transition states of the C-H activation of pyridine *N*-oxide. Adapted from [75].

2.6. Isoquinoline and quinoline *N*-oxides

Liu's team carried out the olefination of isoquinoline and quinoline *N*-oxides using catalytic PdCl₂ in DMSO [69,77]. These substrates being prototypical oxygen atom transfer reagents [78], the reactions arose under external-oxidant-free conditions leading to 1-substituted isoquinolines (Eq. 29) and 2-substituted quinolines (Eq. 30), respectively. The reaction efficiency was highly dependent on the nature of both Pd catalyst and solvent (Eq. 29).

⁴The Pd-catalyzed C2 alkenylation of pyridine *N*-oxide with allyl acetate involves a Tsuji-Trost type reaction [74].

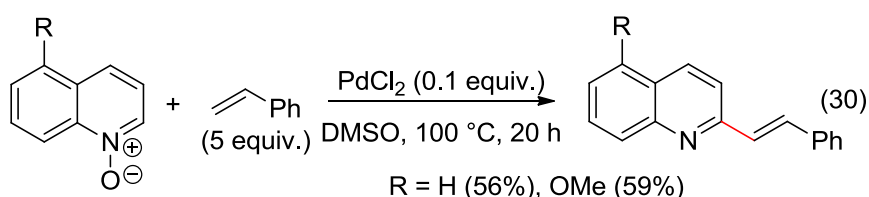


$R^1 = \text{H}, 5\text{-OMe}, 5\text{-NO}_2, 6\text{-Me}, 6\text{-F}, 9\text{-Cl}; R^3 = \text{H};$
 $R^2 = (\text{hetero})\text{Ar}, \text{CO}_2\text{Me}; 16 \text{ examples: } 31\text{-}81\%$

$R^1 = \text{H}, R^2 = \text{Ph} \begin{cases} R^3 = \text{Me: } 49\% \\ R^3 = \text{H: } 77\%^{a,b} \end{cases}$

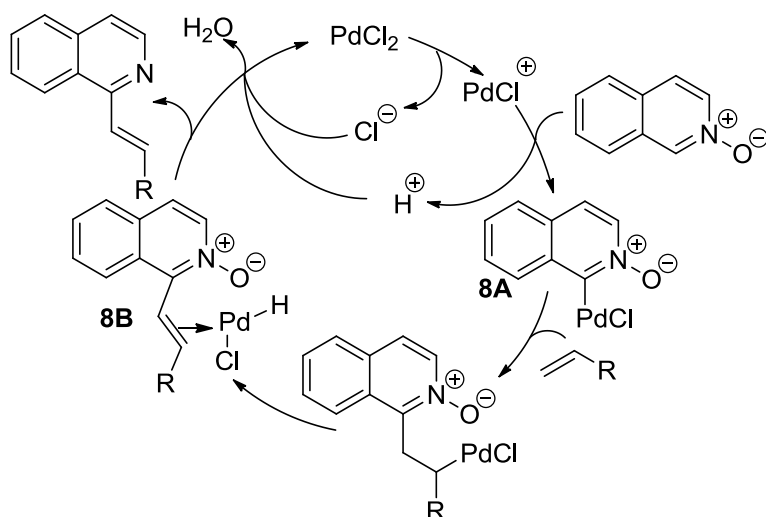
^aOther catalysts: PdBr_2 (30%), $\text{Pd}(\text{OAc})_2$ (42%),
 $\text{Pd}(\text{OCOCF}_3)_2$ (71%), PdSO_4 (trace)

^aReaction for 10 h in DMSO (50%), DMF (32%), DME (26%),
dioxane (28%), NMP (30%), xylene (trace).



$R = \text{H} (56\%), \text{OMe} (59\%)$

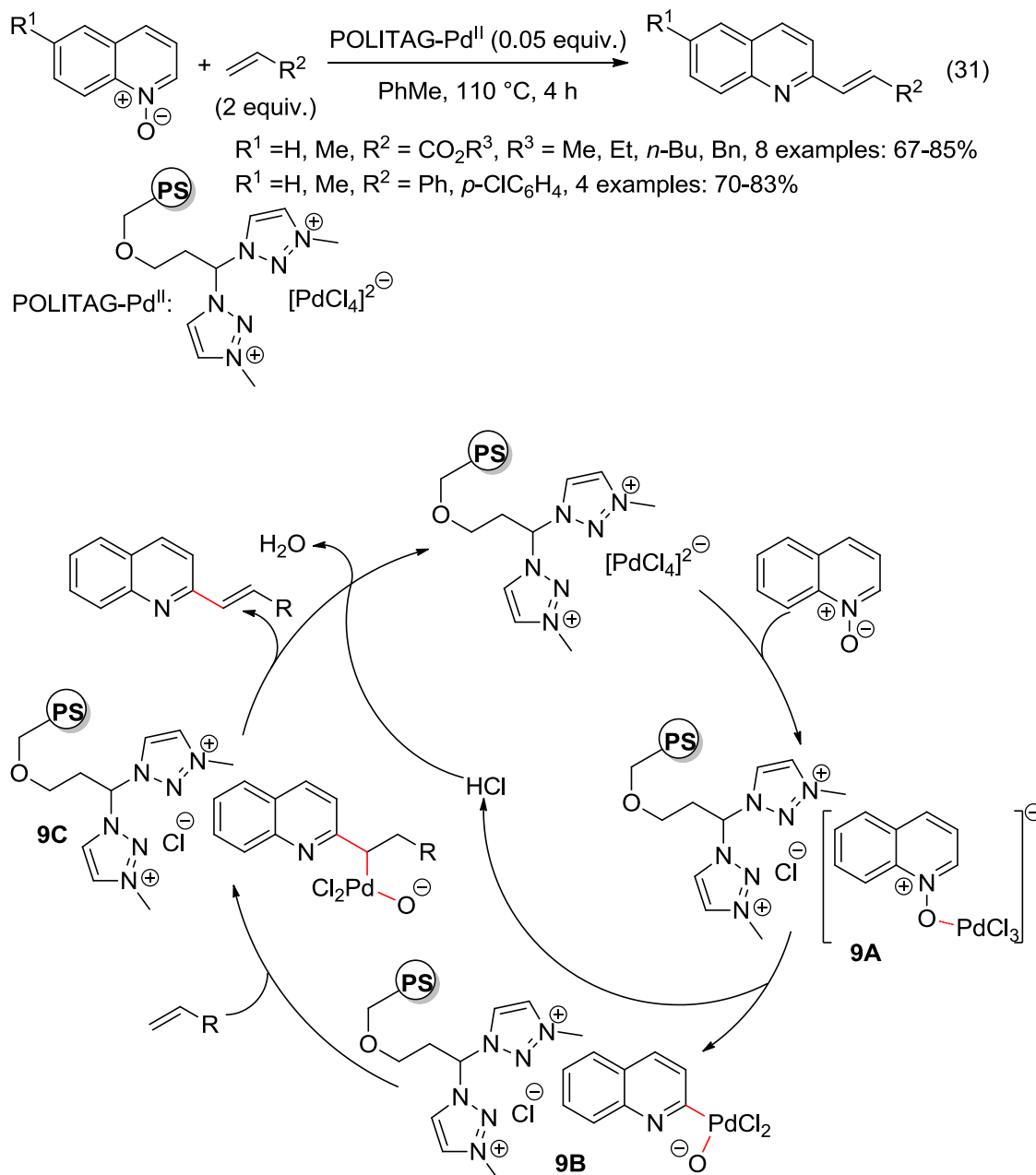
Liu's team proposed the formation of **7A** from electrophilic attack of PdCl^\oplus to the isoquinoline *N*-oxide followed by rearomatization (Scheme 8) [69]. Coordination of the olefin to the Pd atom followed by insertion and β -H elimination leads to **8B**. Subsequent intramolecular reaction delivers the product and regenerates the catalyst. Note that the teams of Cui and Wu previously disclosed the transformation of quinoline *N*-oxides under $\text{Pd}(\text{OAc})_2$ catalysis and external-oxidant-free conditions in 1-methyl-2-pyrrolidinone; they however proposed a catalytic cycle with coordination of PdOAc^\oplus to the *N*-oxide before the electrophilic attack at the 2 position [76]. Recently, Chen and co-workers carried out DFT studies of the C-H activation of quinoline *N*-oxide [79], which agree with calculations of Fang and Zhang (see Sub-chapter 2.5) [75], and led to retain the undirected pathway, that is an intermediate corresponding to **8A**. Their calculations also match with the experimental preference for C2-H activation over C8-H activation of quinoline *N*-oxide⁵.



Scheme 8. Isoquinoline *N*-oxide as both substrate and oxidant.

⁵According to DFT calculations, the reported regioselective Pd-catalyzed C8 arylation of quinoline *N*-oxide would arise *via* a cyclopalladation pathway [80].

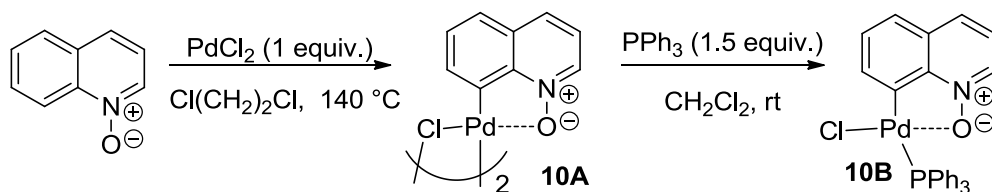
Recently, Vaccaro and co-workers proposed the use of a heterogeneous catalyst named “Polytag-Pd^{II}” obtained from Na₂PdCl₄ and an *N*-containing ligand immobilized onto a polystyrene resin, to carry out the ethylenation of quinoline *N*-oxides (Eq. 31) [81]. Recycling the catalyst showed a catalytic efficiency preserved for three consecutive runs. In contrast to intermediates of Scheme 8, the authors proposed the coordination of the oxygen of the substrate to palladium leading to **9A** followed by C-H activation and cleavage of the N-O bond to afford **9B** (Scheme 9). Subsequent insertion of the alkene into the C-Pd bond would give **9C**. According to the authors, a β-H elimination from **9C** delivers the product. We suspect the involvement of the chloride or oxygen anion of the plausible intermediate **9C** in the H elimination, leading with HCl to water and regeneration of the catalyst.



Scheme 9. Vaccaro’s mechanism of the DHR of quinoline *N*-oxides.

The C2 regioselective C-H alkylation of quinoline *N*-oxide (Eqs 30 and 31) is rather surprising since reaction of this substrate with stoichiometric PdCl₂ arose in C8 position leading to the chloride-bridged palladacycle dimer **10A** (Scheme 10) [82]. Treatment of **10A** with triphenylphosphine produced **10B**, which the structure has been confirmed by single-crystal X-ray diffraction. Moreover, Pd(OAc)₂ also led to C8-H activation of quinoline *N*-oxide [80]. The C2 attribution to the substituted position of the DHR products of quinoline *N*-oxide seems nevertheless adequate. Indeed, the ¹H and ¹³C NMR spectra and chemical shifts attributed to the quinoline *N*-

oxide/butyl acrylate cross-coupling product (Eq. 31) [81] are quasi-identical to those of (*E*)-butyl 3-(quinolin-2-yl)acrylate obtained from quinolone and butyl acrylate under Ma and Huang conditions (Eq. 21) [18].

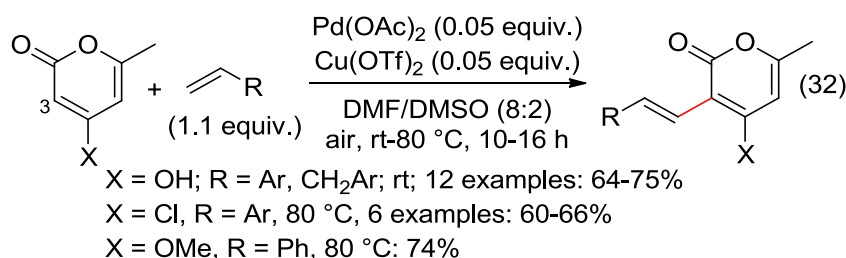


Scheme 10. Pd-mediated C8-H activation of quinoline *N*-oxide.

3. O-arenes

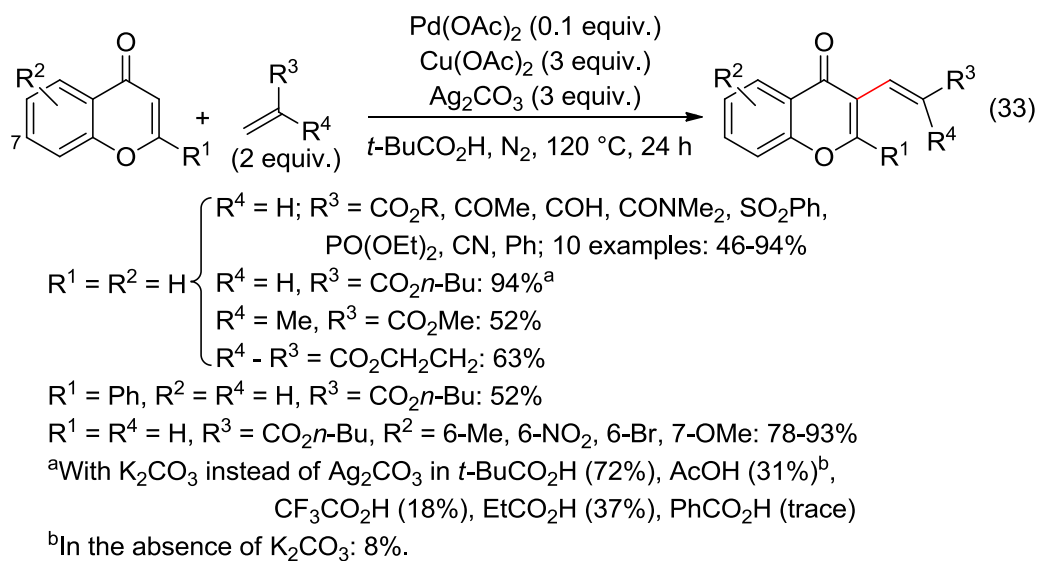
3.1. Pyrones

The C3 alkenylation procedure of 4-hydroxypyridin-2(1*H*)-one (Eq.32) was also effective for the DHR of 6-methyl-2*H*-pyran-2-ones bearing an hydroxyl, chloride or methoxy substituent in C4 position (Eq. 32) [60]. Use of DMSO as co-solvent was determinant for good yields.



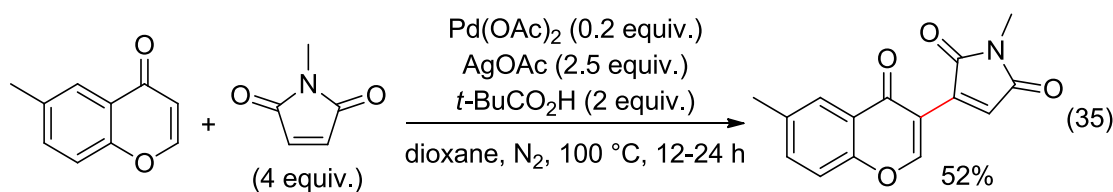
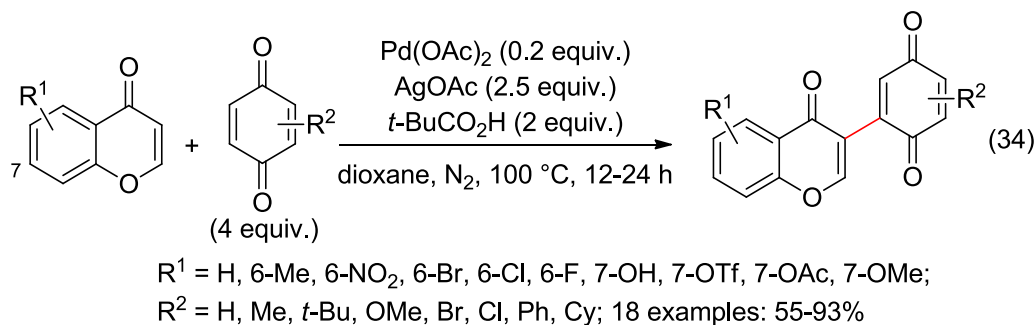
3.2. Chromen-4-ones

Pd^{II}-catalyzed alkenylation of chromen-4-ones arose in fair to high yields in pivalic acid containing Cu(OAc)₂ and Ag₂CO₃ (Eq. 33) [19]. Use of both pivalic acid and base were required for an effective procedure. According to Hong's team, the regeneration of the catalyst is essentially due to Cu(OAc)₂, while Ag₂CO₃ mainly functions as a base. Indeed, switching to K₂CO₃ led to a limited yield decrease.

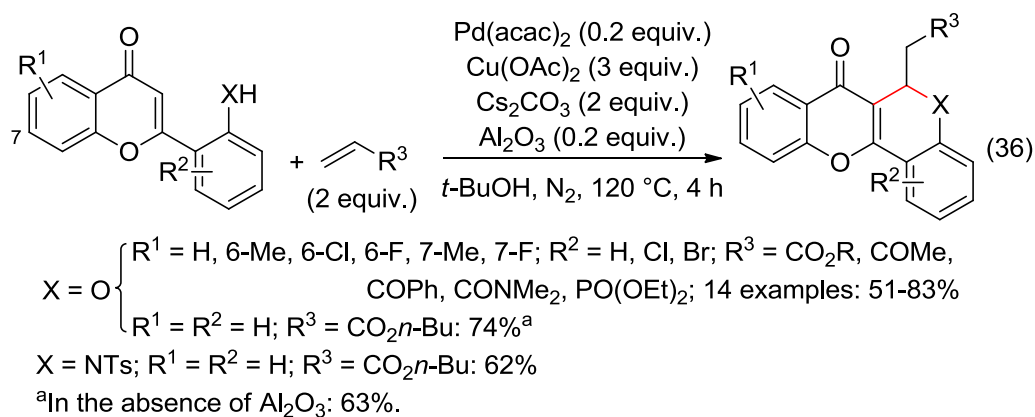


Subsequently, Hong's team carried out the DHR of chromen-4-ones with quinones (Eq. 34), *N*-methylmaleimide (Eq. 35) and 1,4-naphthoquinone using AgOAc instead of the Cu(OAc)₂/Ag₂CO₃ mixture, and pivalic acid as additive instead of solvent [83]. According to the authors, the role of AgOAc is to regenerate the

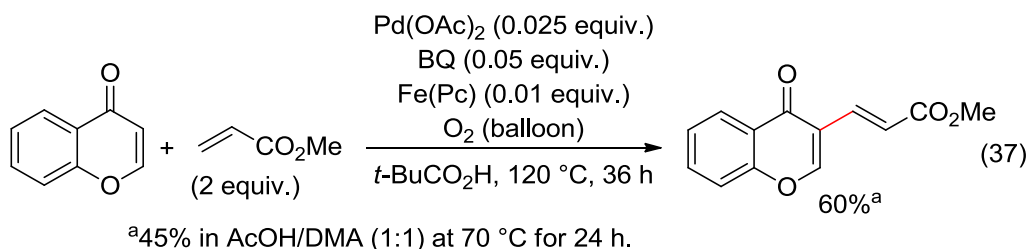
catalytic species. A large excess of the quinone being required for fair yields, we suspect its participation in the catalyst recycling [58,59].



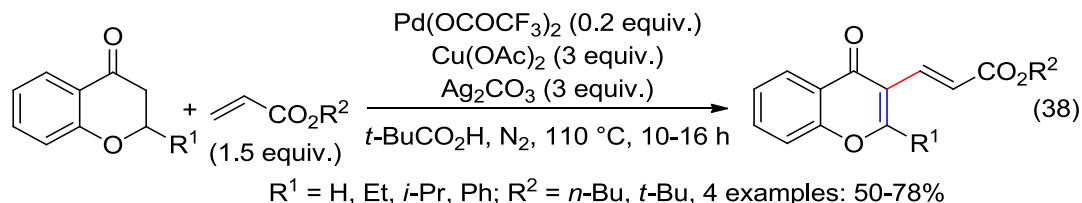
Hong's team also performed the efficient domino alkenylation/cyclization reactions depicted in Eq. 36 using catalytic amounts of $\text{Pd}(\text{acac})_2$ and Al_2O_3 in dioxane containing over-stoichiometric amounts of both $\text{Cu}(\text{OAc})_2$ and Cs_2CO_3 [84]. Yields decreased with other Pd catalysts, oxidants, bases or absence of Al_2O_3 . According to the authors, the reaction involves the C3 alkenylated intermediate which undergoes a Michael-type addition favored by Al_2O_3 .



Bäckvall's conditions used for the DHR of *N*-methylpyridin-2(1*H*)-one (Eq. 13) led to the cross-coupling of chromen-4-one with methylacrylate in a yield which also decreased when pivalic acid was exchanged for an AcOH/DMA mixture (Eq. 37) [57].

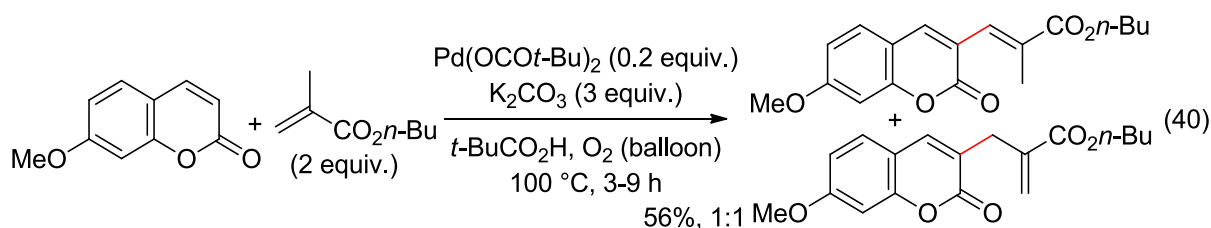
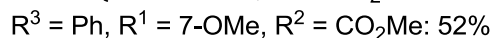
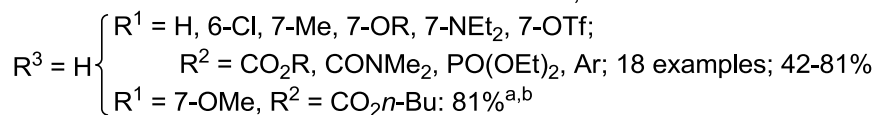
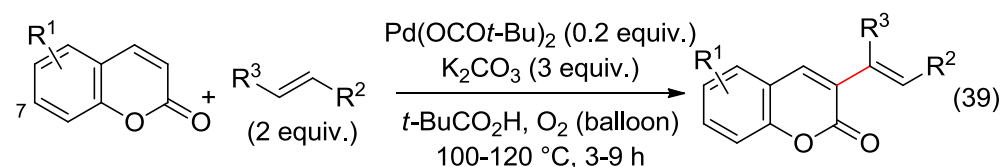


A procedure close to that used for the dehydrogenation/dehydrogenative Heck reaction of *N*-substituted 2,3-dihydroquinolin-4(1*H*)-ones (Eq. 25) has led to the corresponding domino reaction of chroman-4-ones (Eq. 38) [70].

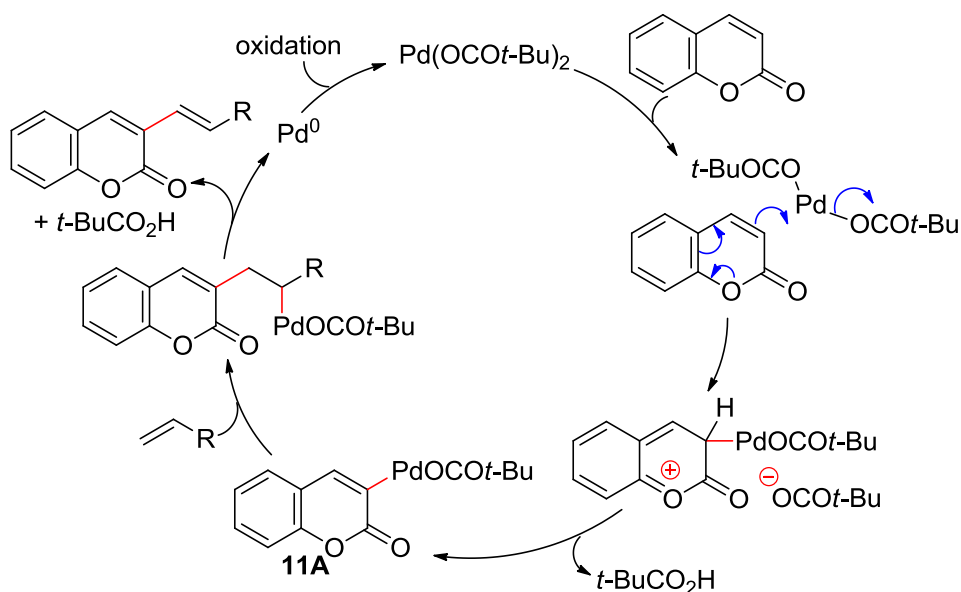


3.3. 2*H*-chromen-2-ones⁶

The $\text{Pd}(\text{OCO}t\text{-Bu})_2$ -catalyzed method used for DHRs of 7-methoxy-1-methylquinolin-2(1*H*)-one (Eq. 27) was effective for the C3 olefination of 2*H*-chromen-2-ones (Eqs 39 and 40) [71]. Regeneration of the catalyst with $\text{Cu}(\text{OAc})_2$ instead of oxygen atmosphere as well as absence of the base were detrimental to the yields (Eq. 39). Hong's team proposed the participation of the oxygen atom in the formation of the C-Pd bond to provide **11A** (Scheme 11). Subsequent insertion of the olefin followed by β -H elimination affords the product.

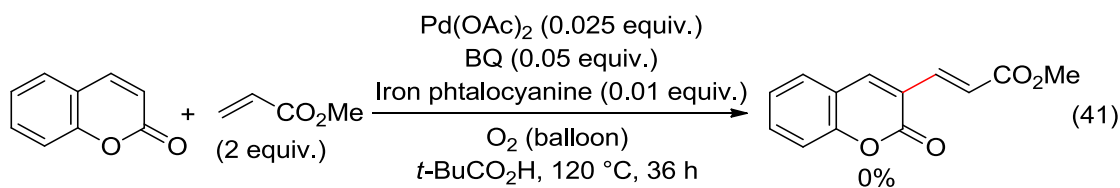


⁶ Other appellation: coumarins.

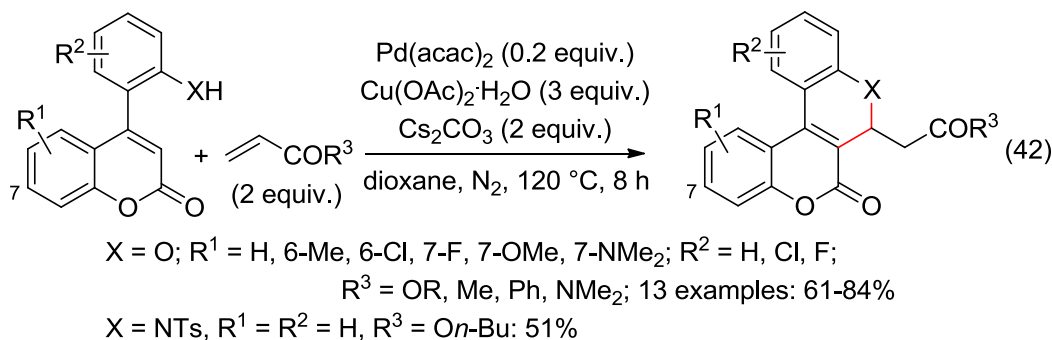


Scheme 11. The plausible participation of the oxygen ring in the DHR of *2H*-chromen-2-ones. Adapted from [70].

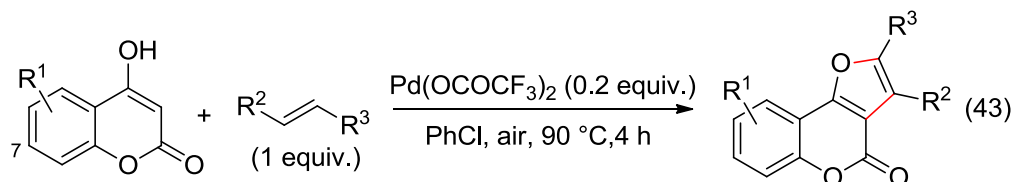
In contrast to *N*-methylpyridin-2(*1H*)-one (Eq. 13) and chromen-4-one (Eq. 37), Bäckvall's procedure did not mediate the DHR of *2H*-chromen-2-one with methylacrylate (Eq. 41) [57].



The domino alkenylation/cyclization reaction of 2-aryl-4*H*-chromen-4-ones (Eq. 36) also arose from the corresponding 4-aryl-2*H*-chromen-2-ones, but under slight modified experimental conditions for fair yields (Eq. 42) [84]. The presence of Al_2O_3 was not required for an effective cyclization step.



Domino alkenylation/cyclization reactions also occurred from 4-hydroxy-2*H*-chromen-2-ones but were limited to styrenes and stilbenes (Eq. 43) [85]. The experimental conditions were rather unusual and required catalytic $\text{Pd}(\text{OCOCF}_3)_2$ in aerated chlorobenzene for good yields. The expected adduct was not formed with 1-octene (Eq. 43), while cleavage of the C-CO₂Me bond happened with methyl methacrylate (Eq. 44).

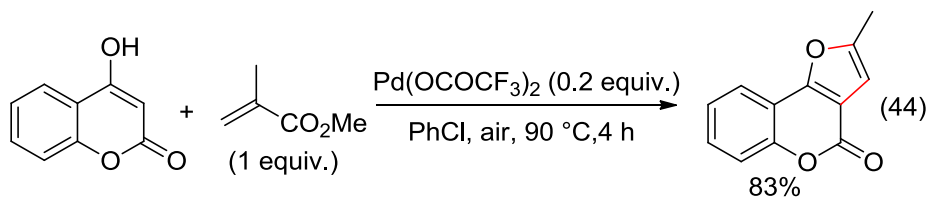


$R^1 = \text{H, 6-Me, 7-OMe}$; $R^2 = \text{H, Ar}$; $R^3 = \text{Ar}$; 11 examples: 70-84%

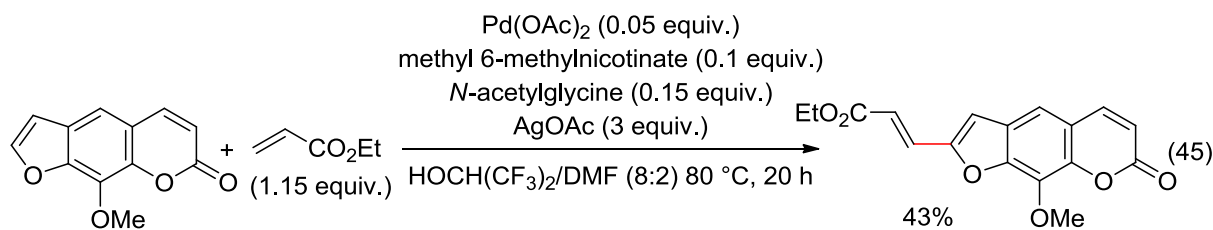
$R^1 = R^2 = \text{H}$; $R^3 = \text{Ph}$ (81%^{a,b}), $n\text{-C}_6\text{H}_{13}$ (0%)

^aOther solvents: PhMe (60%), dioxane (40%), DCE (25%), DMSO (20%), DMF (0%)

^bOther catalysts: Pd(OAc)_2 (69%), PdCl_2 (30%), $\text{Pd}_2(\text{dba})_3$ (45%).



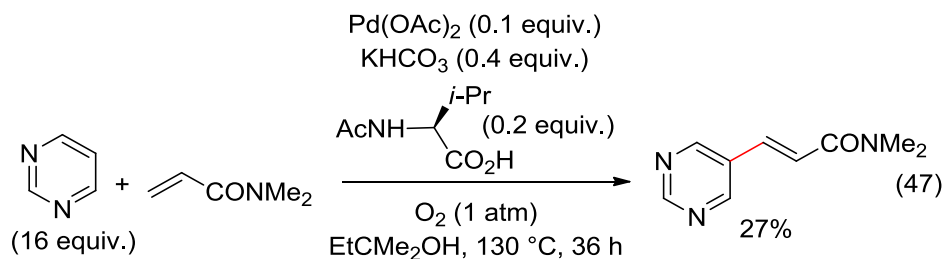
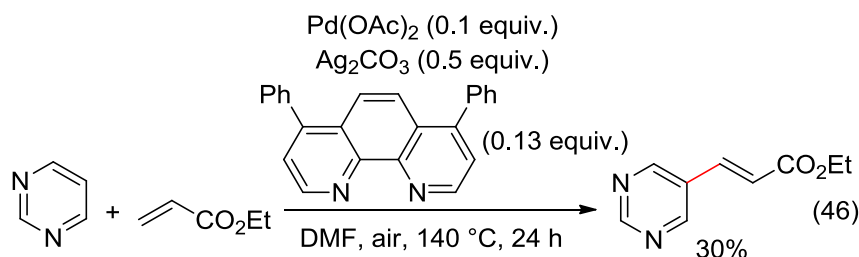
The DHR of a polycyclic substrate such as xanthoxine, which contains both five and six membered heteroaromatic rings, selectively arose at the level of the furanyl ring (Eq. 45) [86].



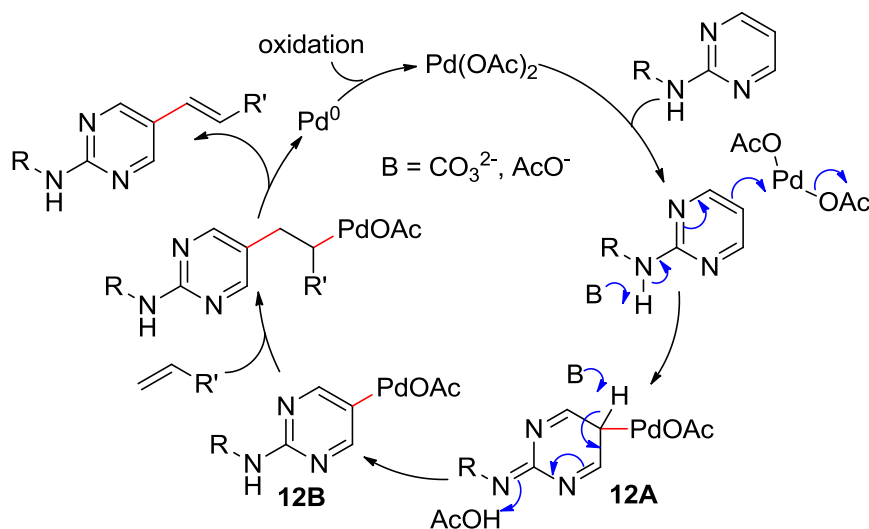
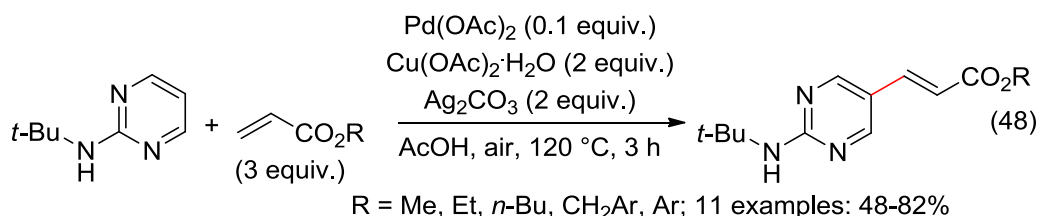
4. N,N-arenes

4.1. Pyrimidines

The experimental conditions disclosed in Eqs 1 and 4-6 for the DHRs of pyridines led to selective C5 olefination of pyrimidine (Eqs 46 [13] and 47 [23]).



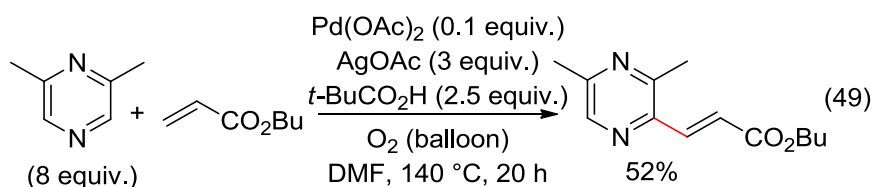
Using $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}/\text{Ag}_2\text{CO}_3$ in aerated AcOH , *N*-(*t*-butyl)pyrimidin-2-amine underwent cross-coupling with acrylates (Eq. 48) [87]. Performing the reaction in the absence of acrylates in perdeuterated acetic acid led to deuterium exchange at N and C5 positions. Moreover, arylation experiments showed the formation of only traces of cross-coupling when the NH of the substrate was protected with a methyl group. Consequently, Maji's team proposed the participation of the NH group in the mechanism of the DHR (Scheme 12). Interaction of the substrate with catalyst and base affords intermediate **12A** which, according to the authors, undergoes base-mediated H abstraction leading to **12B**. Subsequent insertion of the olefin into the C-Pd bond followed by β -H elimination gives the product.



Scheme 12. Unusual intermediate of the DHR of *N*-(*t*-butyl)pyrimidin-2-amine. Adapted from [87].

4.2. Pyrazines

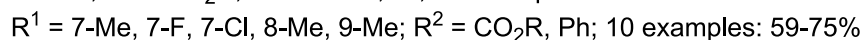
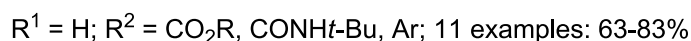
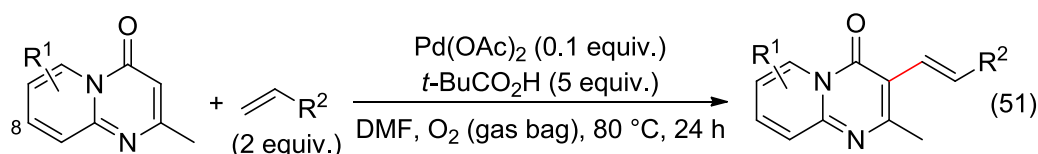
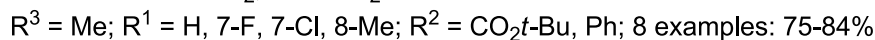
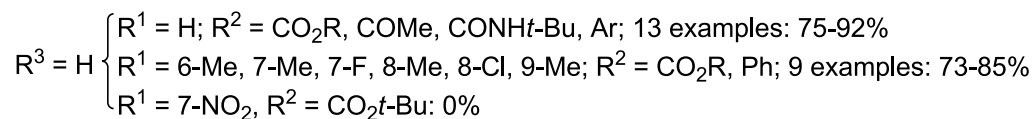
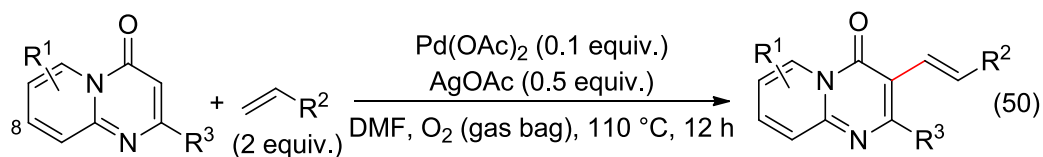
The Ma and Huang procedure of the DHR of pyridines (Eq. 2) was also used for the alkenylation of 2,6-dimethylpyrazine (Eq. 49) [18].



4.3. Pyrimidin-4-ones

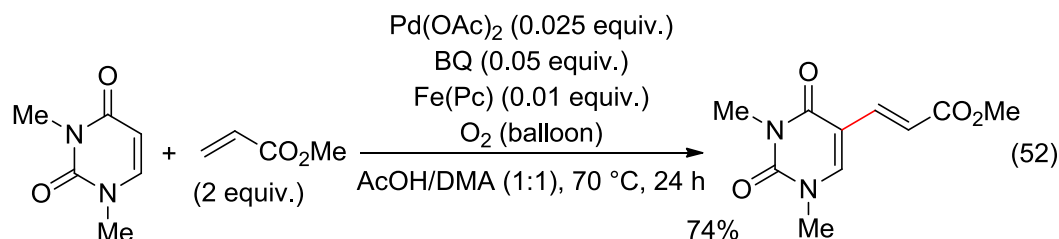
Two aerobic procedures have been reported for the DHR of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. The first one due to Wang, Cao and co-workers, used catalytic $\text{Pd}(\text{OAc})_2$ with 0.5 equiv. of AgOAc at 110 °C in DMF (Eq. 50) [88]. The yields were dramatically reduced with $\text{Cu}(\text{OAc})_2$ or only oxygen as the oxidant. Subsequently, Liang's team disclosed experimental conditions used with 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (Eq. 51) [20]. Carried out in the presence of pivalic acid, these DHRs did not require the use of AgOAc as co-oxidant.

Only one substrate was common to the two reports, leading to (*E*)-2-methyl-3-styryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 84 and 73% yields under conditions of Eqs 50 and 51, respectively.



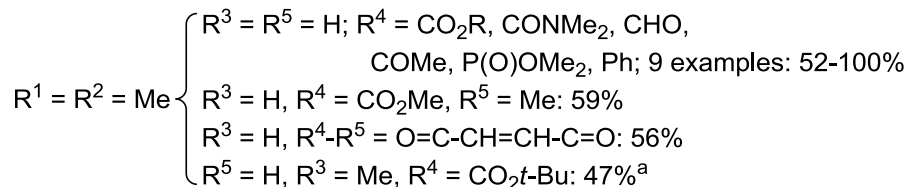
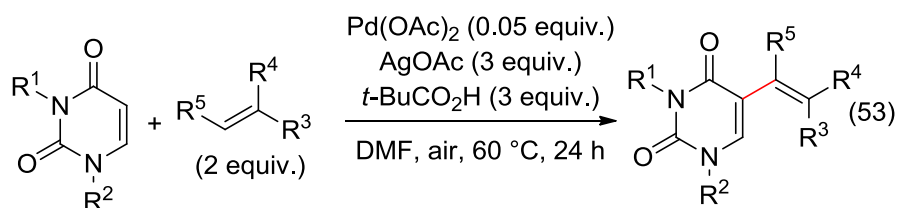
4.4. Uracils⁷

The above Bäckvall experimental conditions above used for the DHR of *N*-methylpyridin-2(1*H*)-one and chromen-4-one with methylacrylate (Eqs 13 and 37) were also effective for the regioselective C5 olefination of 1,3-dimethyluracil (Eq. 52) [57].

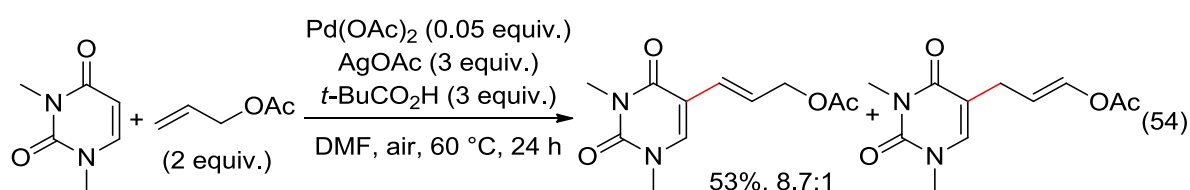
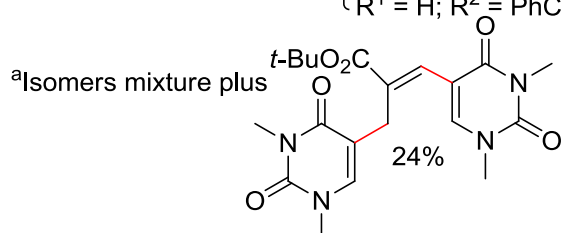
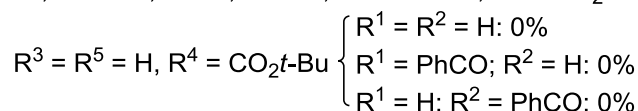


Another aerobic regioselective method, which used catalytic Pd(OAc)₂ and excesses of both AgOAc and *t*-BuCO₂H in DMF, provided fair to high yields of various C5 olefinated *N*-substituted uracils (Eq. 53) [89]. No DHR was observed when one of the two nitrogen atoms was unsubstituted. Use of α -substituted acrylates such as *t*-butyl methacrylate afforded a mixture of conjugated and deconjugated cross-coupling products as well as the cross-coupling adduct stemming from the subsequent DHR of the deconjugated product with the uracil (Eq. 53). Conjugated and deconjugated cross-coupling products were also formed from allyl acetate (Eq. 54). According to Georg and Yu, deprotonation of the uracil is assumed by pivalate as depicted for pyridine in Scheme 2 [89].

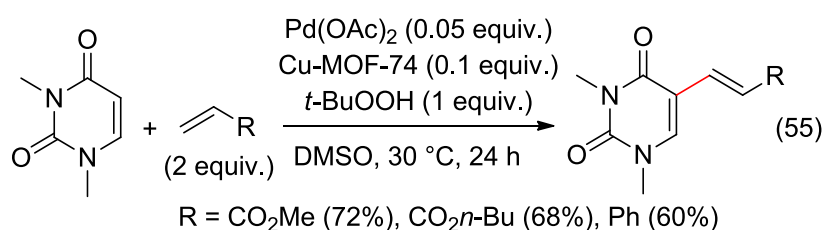
⁷Other appellation: pyrimidine-2,4(1*H*,3*H*)-diones.



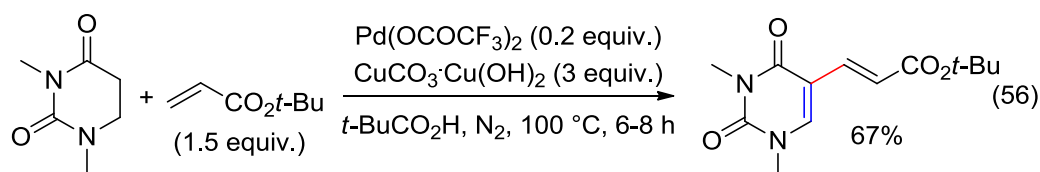
$R^1, R^2 = \text{Bn}, \text{MOM}, \text{PMB}\dots; R^3 = R^5 = \text{H}; R^4 = \text{CO}_2t\text{-Bu}; 7 \text{ examples: } 66\text{-}96\%$



A metal-organic framework, named Cu-MOF-74, has been prepared from 2,5-dihydroxyterephthalic acid and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in DMF/*i*-PrOH by Cirujano, De Vos and co-workers [90]. The authors disclosed that addition of Cu-MOF-74 to $\text{Pd}(\text{OAc})_2$ improved the lifetime of the catalyst, and used the combination for the DHR of uracil, at 30 °C in DMSO with *t*-BuOOH as the oxidant (Eq. 55).

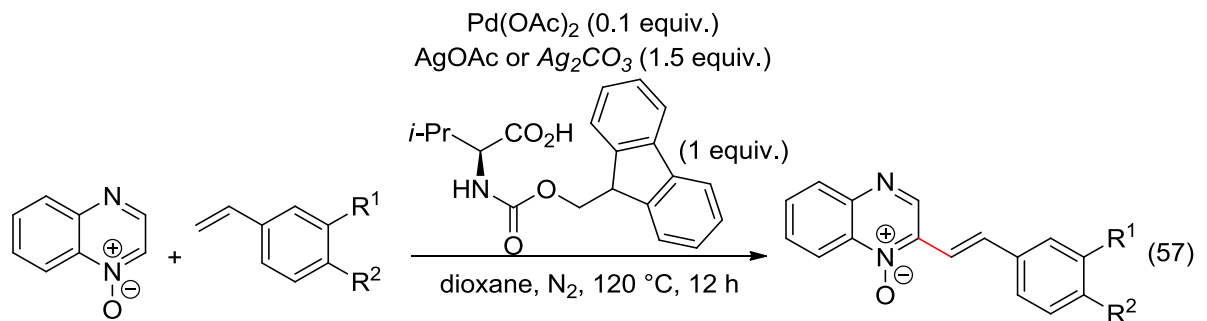


The Hong experimental conditions of above dehydrogenation/dehydrogenative Heck reactions (Eqs 25 and 38) have been used for the corresponding transformation of 1,3-dimethyldihydropyrimidine-2,4(1*H*,3*H*)-dione (Eq. 56) [70].



4.5. Quinoxaline *N*-oxide

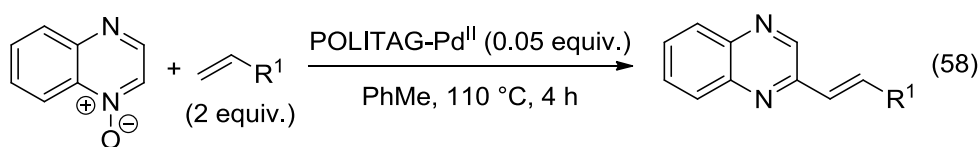
The DHR of quinoxaline N-oxide with styrene under Chang's conditions used for the cross-coupling with acrylates [91] led to the expected compound in a modest yield [92]. Emery and co-workers improved the efficiency of the procedure in using a *N*-protected amino acid (FMoc-Val-OH) and AgOAc instead of pyridine and Ag₂CO₃ (Eq. 57). Yields were however greatly dependent on the styrene substituents and the nature of silver salt. The proposed catalytic cycle was similar to that depicted in Scheme 3.



R¹ = H, R² = H (85%, 75%^a), CO₂Me (85%, 73%), OMe (42%, 84%), Br (46%, 32%), OAc (29%, 85%)
R¹ = R² = OMe (89%, 78%)

^aWith pyridine instead of FMoc-Val-OH: 64%.

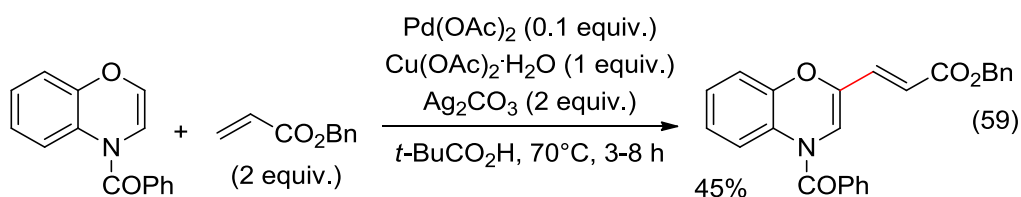
The Vaccaro procedure (Eq. 31) has also been used for the cross-coupling of quinoxaline N-oxide with acrylates and styrenes (Eq. 58) [81].



R¹ = CO₂R², R² = Me, Et, *n*-Bu, Bn, 4 examples: 62-72%
R² = Ph: 72%, R² = *p*-ClC₆H₄: 68%

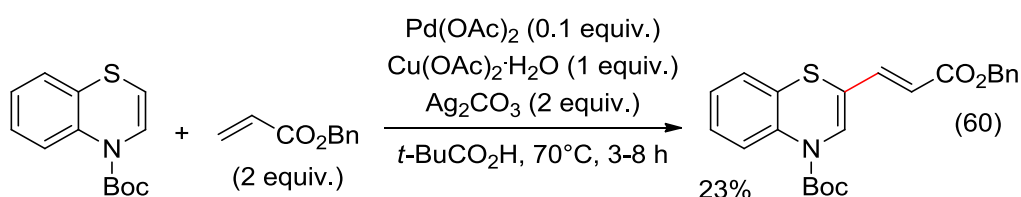
5. N,O-arene

In pivalic acid, (*4H*-benzo[*b*][1,4]oxazin-4-yl)(phenyl)methanone underwent cross-coupling with benzyl acrylate using copper acetate, silver carbonate and catalytic Pd(OAc)₂ (Eq. 59) [93].



6. N,S-arenes

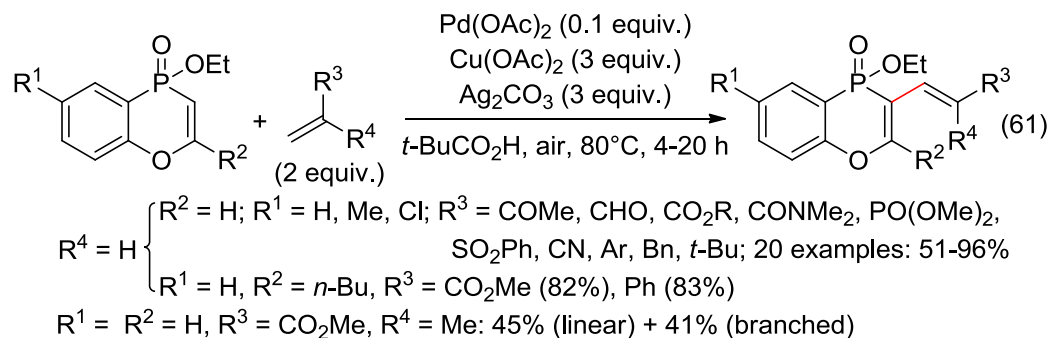
The DHR of *t*-butyl 4*H*-benzo[*b*][1,4]thiazine-4-carboxylate using the above method occurred in a low yield (Eq. 60) [93].



7. O,P-arenes

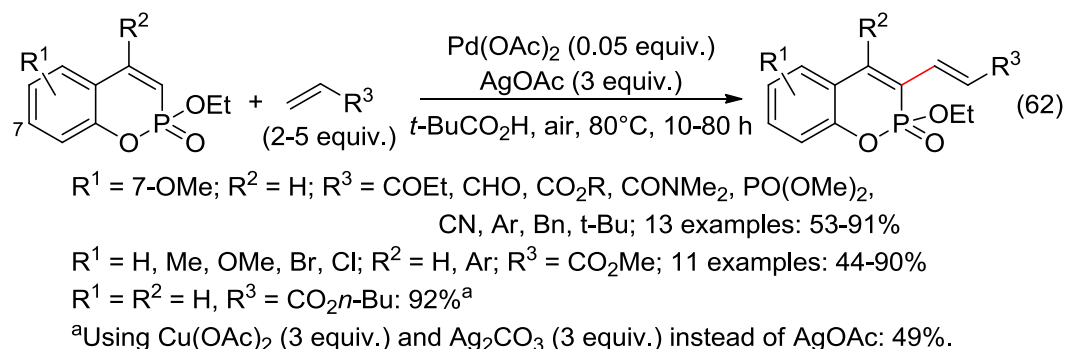
7.1. 4-Phosphachromones

C3 alkenylation of 4-ethoxy-4*H*-benzo[*b*][1,4]oxaphosphinine 4-oxides arose with a variety of activated and unactivated olefins under conditions similar to those of Eqs 59 and 60, except the use of air atmosphere (Eq. 61) [94]. Lee and co-workers showed that both copper acetate and silver carbonate were required for a successful reaction.



7.2. Phosphacoumarins

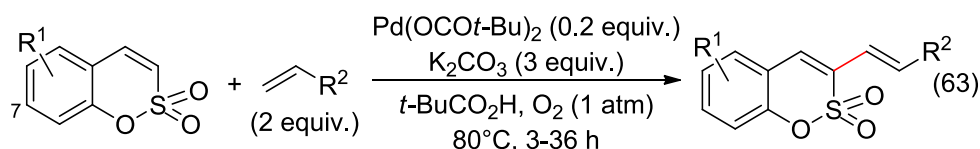
Lee's team also carried out the DHR of 2-ethoxy-2*H*-benzo[*e*][1,2]oxaphosphinine 2-oxides using AgOAc (Eq. 62) [95] instead of the $\text{Cu(OAc)}_2/\text{Ag}_2\text{CO}_3$ mixture (Eq. 61) for improved yields. The authors suggested the participation of the ring oxygen atom in the formation of the C-Pd bond as previously depicted in Scheme 11.



8. O,S-arenes

Palladium pivalate in pivalic acid catalyzed the aerobic DHR of sulfocoumarins⁸ (Eq. 63) [96]. Oxygen was superior to other oxidants. Participation of the ring oxygen atom in the formation of the C-Pd bond (Scheme 11) as above suspected [71,95] was assumed by Hong and co-workers.

⁸ Other appellation: benzo[*e*][1,2]oxathiine 2,2-dioxides.



$R^1 = \text{H}, 6\text{-NO}_2, 6\text{-}t\text{-Bu}, 7\text{-OMe}, 7\text{-OBn}, 7\text{-Cl}, 7\text{-NEt}_2, 8\text{-OMe}; R^2 = \text{CO}_2\text{R}, \text{COMe}, \text{SO}_2\text{Ph}, \text{CONMe}_2, \text{PO}(\text{OEt})_2, t\text{-Bu}, \text{Ar}; 25 \text{ examples: } 34\text{-}93\%$

$R^1 = 8\text{-OMe}, R^2 = \text{CO}_2n\text{-Bu}: 93\%$

^aOther oxidants (3 equiv.): $\text{Cu}(\text{OAc})_2$ (61%), AgNO_3 (75%).

Conclusion

As above exemplified, effective alkenylation of six membered heteroarenes may occur using the Pd^{II}-catalyzed DHR procedure. In most cases, no directing group is required to favor the initial palladation and selective transformations. The catalyst activity should be however improved since long reaction times and relatively high temperatures are usually required. In addition, some processes employ large excess of the arenes.

Most catalytic cycles proposed are very discreet on the mechanism of the C-H activation of the substrate. This formation of the C-Pd bond from the C-H bond of arenes has however been the subject of thoroughly computational studies, indicating that species coordinated to the palladium atom may have a key role.

According to the gathered above examples, the pivalate ligand favors the C-H cleavage and often increases the efficiency of the DHR. The role of pivalic acid in the Pd-catalyzed reactions is however highly dependent on the experimental conditions. Indeed, a recent report disclosed the reduction of Pd^{II} complexes by pivalate [97], that is a reaction which would be unfavorable to the Pd^{II} chemistry of the DHR process.

The presence of a silver acetate in sub- or over-stoichiometric amount is frequently required for an effective catalytic procedure. In most reports, its role is attributed to the regeneration of the catalytic species while the possibility to form an active Pd/Ag heterobimetallic catalyst is not considered.

Whatever the pathways of the C-H activation and the cross-coupling reaction, the above olefinations of six membered heteroarenes, which formally arise from the removal of only the molecular hydrogen, afford products which are commonly privileged structures in many biologically active compounds.

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