RECENT ADVANCES IN OXIDATIVE ALKENYLATIONl OF FIVE- AND SIX-MEMBERED HETEROCYCLIC RING SYSTEMS

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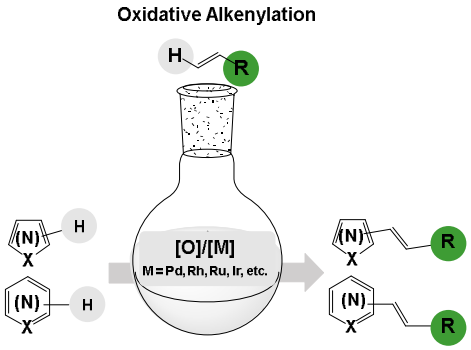
Abstract. *The transition-metal-catalyzed direct oxidative Heck-type reaction has made considerable progress in the last two decades. This review presents the recent advances in direct oxidative alkenylation of five- and six-membered heterocyclic ring systems containing nitrogen, oxygen or sulfur atom. This review focuses on the latest studies reported during the period from 2010 to early 2020 with emphasis on the reaction conditions.*

Contents

1. Introduction

The introduction of olefins groups on the heteroaryl rings can be carried out without preliminary functionalization of precursors. In modern organic synthesis, the transition-metal-catalyzed direct formation of carbon-carbon (C-C) bond *via* C-H oxidative transformation has gained more attention due to its use as alternative to the conventional approaches, which required the use of organic halides and organometallic reagents.[1-10] The pioneer initial studies on the cross-dehydrogenative C-H bond functionalizations were revealed by Fujiwara and Moritani through an oxidative palladium-catalyzed process (Scheme 1).[13,14]



Scheme 1. Oxidative alkenylation: carbon-carbon (C-C) bond formation.

This direct oxidative alkenylation, or the so-called Fujiwara-Moritani reaction, of arenes and alkenes *via* two C-H bonds cleavage has increased in popularity as a functionalization method in the field of

homogenous catalysis. This metodology is quite attractive from the point of view of sustainability and economy of atoms and steps. For these reasons, the direct oxidative reaction has realized a rapid increase in terms of molecular complexity synthesses by functionalization of various arenes and heteroarenes.[15,16]

The oxidative cross-coupling reaction requires a stoichiometric amount of organic or inorganic oxidant to transform the metal with lower oxidation state to a higher oxidation state to regenerate afterwards the active catalyst. By using this C-H/C-H oxidative alkenylation strategy, several heterocyclic systems have been olefinated,[17-25] including, the five- and six-membered ring heterocycles. In continuation of our interest in developing original methods for C-H activation,[26-32] especially, the oxidative alkylation of heteroarenes (Figure 1),[33-35] we wish to report in this review the recent advances made in this filed by focusing only on the five- and six-membered heterocyclic ring systems containing N, O, S heteroatoms.

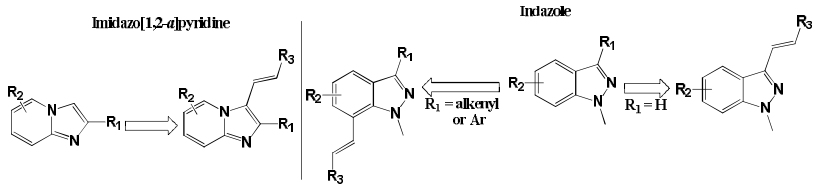


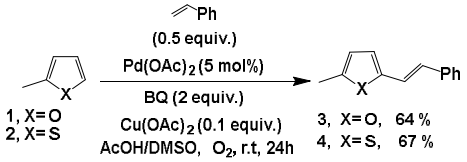
Figure 1. C3 Oxidative alkenylation of imidazo[1,2-*a*]pyridine and oxidative alkenylation on both the five-and six membered rings of indazole.

2. Alkenylation of five-membered heterocyclic ring systems

2.1. Oxidative alkenylation of thiophene and furan

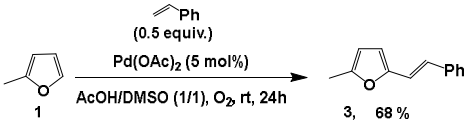
In this first section, we will fucused on the C-C bond formation *via* oxidative alkenylations of five-membered heteroarenes such as furan and thiophene.

Le Bras' group reported in 2011 the dehydrogenative coupling of thiophenes and furans under the same reaction conditions previously described [$Pd(OAc)_2$ as catalyst and BQ as oxidant in AcOH at room temperature].[36] In representative examples, **1** and **2** were treated under the optimized reaction conditions in the presence of styrene to lead to expected products **3** and **4** in 64% and 67% yields, respectively. The authors noticed that using DMSO as co-solvent was useful to achieve good reaction yield. In fact, DMSO and BQ can act as ligands to give ArPdOAc(BQ)-(DMSO) intermediate which is more susceptible to lead to olefinated products **3** and **4** (Scheme 2).



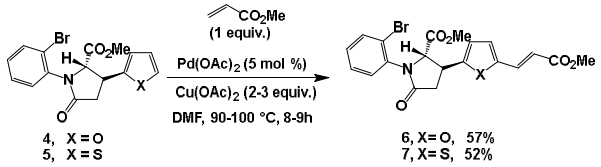
Scheme 2. Dehydrogenative coupling of furan **1** and thiophene **2** with styrene.

In 2013, the same group[37] demonstrated that the oxidative alkenylation of furan **1** with styrene was more efficient when O_2 was used as the sole oxidant in the absence of metal as co-oxidant. In this case, the reaction was achieved using $Pd(OAc)_2$ as catalyst and DMSO/AcOH as solvent at room temperature in the presence of oxygen as oxidant led to coupling product **3** in 68% isolated yield (Scheme 3). This sequence was also efficiently applied to aerobic dehydrogenative Heck coupling of thiophene and indole.



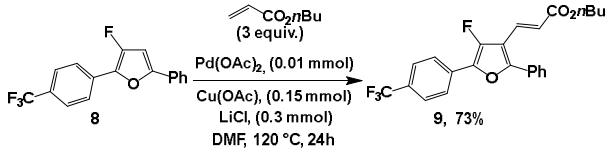
Scheme 3. Oxidative alkenylation of furan **1** with styrene.

Kar's group[38] reported the oxidative Heck reaction of methyl 1-(2-bromoaryl)-3-(2-furyl/thienyl)-5-oxopyrrolidine-2-carboxylate derivatives **4** and **5**. The treatment of **4** and **5** with methyl acrylate using $Pd(OAc)_2$ as catalyst in the presence of $Cu(OAc)_2$ as stoichiometric oxidant in DMF for 9 h led to vinylated products **6** and **7** at C2 position in moderate yield (Scheme 4). In their report, the authors observed Heck reaction at C-Br when $Pd(OAc)_2$, PPh_3, NaOAc, Bu_4NCl (cat) at 110-120 °C in DMF were used as reaction conditions.



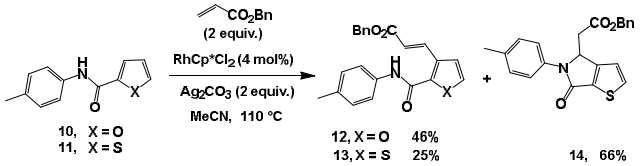
Scheme 4. Palladium-catalyzed oxidative Heck reaction of derivatives **4** and **5**.

Zhu and co-workers[39] described the vinylation of fluoro-substituted furan **8** under palladium-catalyzed oxidative coupling conditions. Thus, Heck-type product **9** was prepared using $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ as oxidant, LiCl as additive and DMF as solvent at 120 °C in good yield (Scheme 5).



Scheme 5. Oxidative alkenylation of fluoro-substituted furan **8** with *n*-butyl acrylate.

Rh(III)-catalyst was used by Li *et al.*[40] for the oxidative alkenylation reaction of five-membered aromatic heterocyclic (furan **10** and thiophene **11**) with electron-poor olefin. Thus, using Cp^*RuCl_2 as catalyst and Ag_2CO_3 as oxidant in MeCN at 110 °C, furyl-2-carboxamide **10** reacted with benzyl acrylate which led to the corresponding mono-coupling product **12** in 46% yield. In the case of thiophenyl-2-carboxamide **11**, the reaction afforded both the vinylation product **13** and intramolecular Michael reaction product **14** in 25% and 66% yields, respectively (Scheme 6).



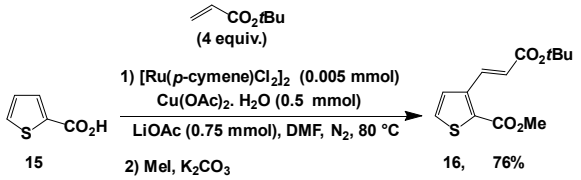
Scheme 6. Oxidative vinylation reaction of furan **10** and thiophene **11** with benzyl acrylate.

Similar work was performed by Ueyama and co-workers[41] using Rh(III)-catalyst as a tool for the alkenylation of thiophene-2-carboxylic acid **15** with different olefins. In a representative example, C3-direct alkenylation was achieved by treatment of thiophene-2-carboxylic acid **15** with *tert*-butyl acrylate in the presence of $[Ru(p\text{-cymene})Cl_2)_2$ as catalyst, $Cu(OAc)_2{\cdot}H_2O$ as oxidant, and LiOAc as additive in DMF under N_2 at 80 °C. After an esterification reaction using iodomethane and K_2CO_3, the final compound **16** was obtained in good yield (Scheme 7).

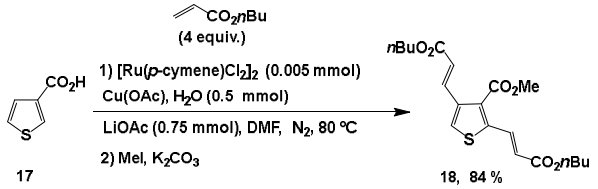
It is noteworthy that when thiophene-3-carboxylic acid **17** was treated with butyl acrylate, under similar reaction conditions, the 2,4-divinylated product **18** was obtained in 84% yield (Scheme 8).

In 2011, Miura and co-workers[42] described the Rh(III)-catalyzed oxidative C3-vinylation/decarboxylation of thiophene-2-carboxylic acid **15** with electron rich olefins. The reaction was carried out using $[Cp^*RhCl_2]$ in the presence of $Cu(OAc)_2{\cdot}H_2O$ as oxidant in DMF for 6-8 h at 140 °C.

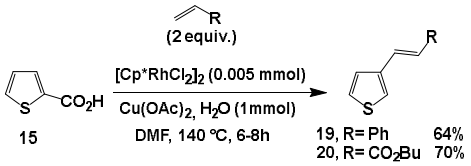
The desired products **19** and **20** were obtained in 64% and 70% yields, respectively. Notably, the directing group (the carboxylic acid group) was easily removed during the olefination reaction or post treatment (Scheme 9).



Scheme 7. Alkenylation of thiophene-2-carboxylic acid **15** with *tert*-butyl acrylate.

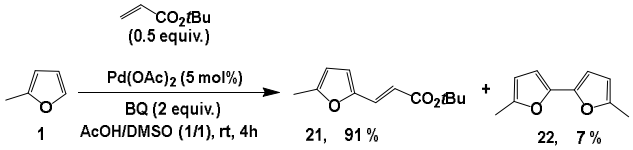


Scheme 8. Rh(III)-catalyzed oxidative dialkenylation of thiophene-3-carboxylic acid **17**.



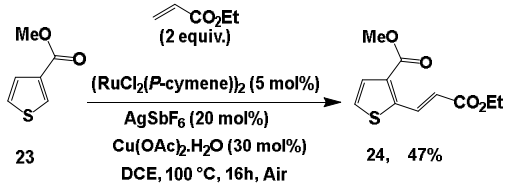
Scheme 9. Oxidative C3-vinylation/decarboxylation of thiophene-2-carboxylic acid **15** with electron rich olefins.

In another work reported by the group of Le Bras,[43] mass spectroscopy was used to study the oxidative alkenylation of furan **1** with acrylate. The coupling reaction of 2-methylfuran **1** and *tert*-butylacrylate as coupling partner in the presence of $[Pd(OAc)_2]_3$ as catalyst, BQ as oxidant in a mixture of DMSO/AcOH at room temperature for 4 h led to 5-olefinated product **21** in excellent yield. In this case, the homocoupling by-product **22** was also isolated in 7% yield. Study with electrospray ionization mass spectrometry showed that the complexation of $[Pd(OAc)_2]_3$ with DMSO afforded mono and dinuclear Pd(II) species ($[(DMSO)Pd(OAc)_2]_2$ and $(DMSO)_2{\cdot}Pd(OAc)_2$) which were involved in C-H activation mechanism (Scheme 10).



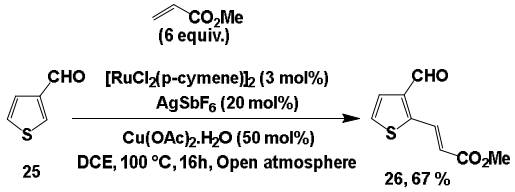
Scheme 10. Oxidative alkenylation of furan **1** with *tert*-butylacrylate.

Ackermann *et al.*[44] realized the dehydrogenative coupling of furan **23** bearing a weakly coordinating ester with ethyl acrylate, employing cationic ruthenium(II)-complex $[RuCl_2(p\text{-cymene})_2]$ as catalyst, $Cu(OAc)_2{\cdot}H_2O$ and under air as oxidants in the presence $AgSbF_6$ as additive at 100 °C in dichloroethane (dichloroethane was compared to other solvent and it was found to be the best one). Under oxidative Heck reaction, C2-alkenylated thiophene **24** was selectively isolated in moderate yield (Scheme 11).



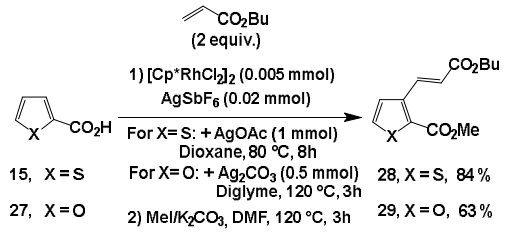
Scheme 11. C2-Oxidative vinylation of 3-formylthiophene **23**.

In 2012, Jeganmohan *et al.*[45] disclosed a method for the preparation of *O*-alkenylated-3-formylthiophene **25** through a Ru(II)-catalyzed *ortho*-olefination of 3-formylthiophene **25**. In fact, the reaction proceeded efficiently in the presence of a combination of [Ru(*p*-cymene)Cl_2]$_2$ catalyst with $Cu(OAc)_2$ as the oxidant and $AgSbF_6$ as additive in DCE at 100 °C for 16 h to give the desired product **26** in 67% yield (Scheme 12).



Scheme 12. *Ortho*-olefination of 3-formylthiophene **25** with methyl acrylate.

In 2013, the groups of Satoh and Miura[46] described the 3-vinylation/esterification of substituted thiophene-2-carboxylic acid **15** by using [Cp*$RhCl_2$]$_2$ as catalyst, $AgSbF_6$ and AgOAc as oxidant instead of $Cu(OAc)_2$ (used in the previous study), in dioxane at 80 °C to afford 3-vinylthiophene **28** in 84% isolated yield (Scheme 13). In the same report, the 3-vinylation/esterification of furan-2-carboxylic acid **27** using [Cp*$RhCl_2$]$_2$ as catalyst, $AgSbF_6$ and Ag_2CO_3 as oxidants in diglyme as solvent led to furan-2-carboxylic acid **29** in 63% yield (Scheme 13). In these two cases, the carboxylic function was efficiently used as directing group giving selectively C3-alkenylated product.

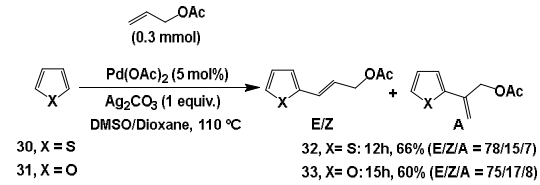


Scheme 13. C3-Oxidative vinylation/esterification of thiophene-2-carboxylic acid **15** and furan-2-carboxylic acid **27**.

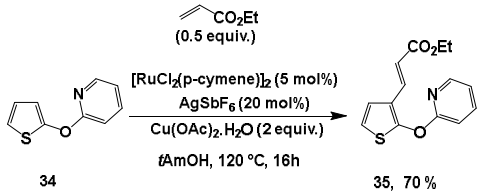
Liu and co-workers[47] designed a strategy for the synthesis of vinylated thiophene **32** with electron rich alkenes such as allyl ester and ethers by using Pd(II)-catalyzed oxidative coupling *via* highly selective *β*-H elimination process. In a representative example, the treatment of **30** by allyl acetate in the presence of $Pd(OAc)_2$ as catalyst, Ag_2CO_3 as additive in DMSO/dioxane 110 °C afforded alkenylated product **32** in 66% isolated overall yield of the *E/Z* mixture and **A** isomer (ratio of *E/Z*/**A** determined by ^{1}H NMR). In this study, authors also applied optimized reaction conditions to furan **31** (only one example was reported) which gave the desired product **33** in acceptable overall yield (Scheme 14).

Ackermann group[48] prepared the alkenylated thiophene **35** *via* oxidative C-H alkenylation using cationic ruthenium-complex. The proposed protocol enables the alkenylation of thiophene **34** bearing cleavable directing groups *O*-2-pyridyl utilizing [Ru(p-cymene)Cl_2]$_2$ as catalyst and $Cu(OAc)_2{\cdot}H_2O$ as

co-catalytic agent under an atmosphere of ambient air in *t*-AmOH (2-methylbutan-2-ol) at 120 °C. This procedure gave C3 alkenylated product **35** in good yield (Scheme 15). In this report, authors found that using $AgSbF_6$ as additive agent gave optimal results, and the use of copper acetate is essential for the reaction. The strong directing power of the *O*-2-pyridyl group was revealed by this reaction, which led to selective alkenylation at C3 position and no reaction took place at C5 position.

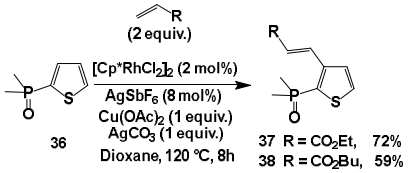


Scheme 14. Pd(II)-catalyzed oxidative alkenylation of **30** and **31**.



Scheme 15. Oxidative C-H alkenylation of thiophene **34** containing an *O*-2-pyridyl group.

Lee *et al.*[49] described in their work the oxidative coupling of dimethylthiophenephosphine oxide **36** with ethyl acrylate and *n*-butyl acrylate using $[Cp^*RhCl_2]_2$ as catalyst, Ag_2CO_3 and $Cu(OAc)_2$ as oxidant and $AgSbF_6$ as additive in dioxane for 12 h at 120 °C. This protocol afforded *ortho*-substituted furans **37** and **38** in 59% and 72% yields, respectively. (Scheme 16).

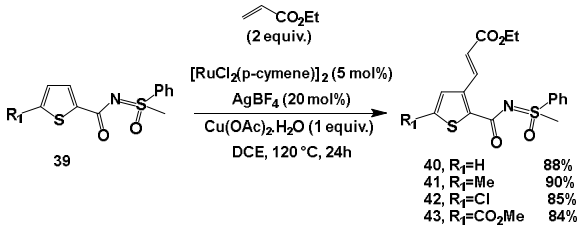


Scheme 16. Direct oxidative alkenylation of dimethylthiophenephosphine oxide **36** with ethyl acrylate and *n*-butyl acrylate.

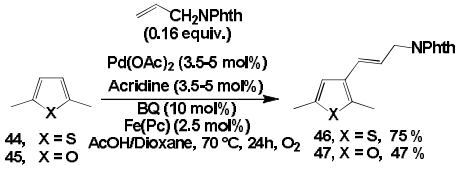
Sahoo *et al.*[50] demonstrated that using sulfoximide as directing group on C2 position of 5-substituted thienyl derivatives **39** favors the oxidative alkenylation on C3 position. The reaction was carried out using $[RuCl_2(p\text{-cymene})]_2$ as catalyst and $Cu(OAc)_2{\cdot}H_2O$ as oxidant in the presence of $AgBF_4$ as additive in DCE as solvent at 120 °C, affording the desired C3-alkenylated products **40**-**43** in good yield (Scheme 17).

In 2014, Bäckvall and collaborators[51] developed a Pd(II)-catalyzed oxidative alkelynation of thiophene **44** and furan **45**. The reaction was carried out in a mixture of AcOH/dioxane at 70 °C using either furan or thiophene derivatives as a starting material in the presence of olefin, $Pd(OAc)_2$ as catalyst, benzoquinone (BQ) and iron phtalocyanine (Fe(Pc)) as electron-transfer mediator and acridine which was found to be an efficient ligand. Under these reaction conditions, the desired products **46** and **47** were obtained in acceptable to good yields (Scheme 18).

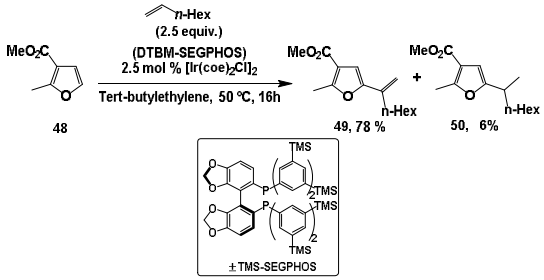
In the same year, Sevov and Hartwig[52] described an iridium-catalyzed α-stereo- and regioselective alkenylation of substituted furan **48** with unactivated 1-octene (Scheme 19). In this case, $[Ir(coe)_2Cl]_2$ was employed as catalyst, air-stable bisphosphine (±)-TMS-SEGPHOS as ligand, and *t*-butyethylene as oxidant, facilitated exclusive α-functionalization **49** and **50** as a minority. Higher yields and selectivities were recorded with furans containing electron-donating groups at C2 on the furan.



Scheme 17. Regioselective oxidative alkenylation of **39** containing directing group.

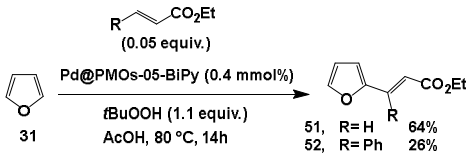


Scheme 18. Pd(II)-catalyzed oxidative alkelynation of thiophene **44** and furan **45**.



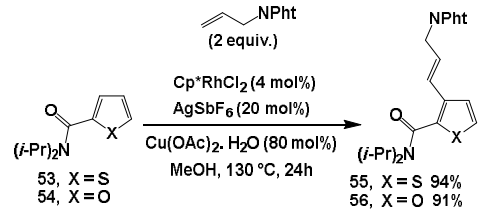
Scheme 19. Iridium-catalyzed α-stereo- and regioselective alkenylation of substituted furan **48** with unactivated 1-octene.

Recently, Zhao and Lei[53] have demonstrated that the use of Pd@PMOs-05-BiPy as heterogeneous catalyst precursor was effective for the oxidative Heck reaction of furan **31**. Thus, direct C2-olefination with ethyl acrylate in acetic acid at 80 °C in the presence of *t*-BuO_2H as oxidant led to regioselective alkenylated derivatives **51** and **52** in low to acceptable yields (Scheme 20).



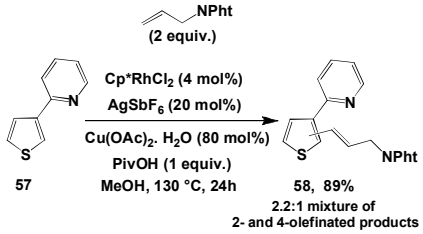
Scheme 20. Heterogeneous palladium-catalyzed oxidative Heck reaction of furan **31**.

Recently, in their investigations on the oxidative Heck reaction catalyzed by rhodium, Zhang and Xu[54] developed the direct *ortho* C-H bond olefination of furan bearing amide as directing group or thiophene bearing either amide or pyridine as directing groups. In a representative examples, starting materials, **53** and **54** were treated with aliphatic olefins using a catalytic amounts of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ as well as $AgSbF_6$ as additive in MeOH at 130 °C for 24 h. This sequence afforded the C3-vinylated products **55** and **56** with good yields and high regio- and stereo-selectivity when amide group was used as a directing group (Scheme 21).



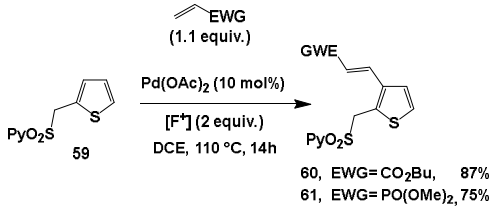
Scheme 21. C3 oxidative olefination of furan **53** and thiophene **54** containing amide as directing group.

On the other hand, in the case of 2-(thiophen-3-yl)-pyridine **57**, a mixture of 2- and 4-olefinated products **58** was observed (Scheme 22).



Scheme 22. C-H oxidative alkenylation of 2-(thiophen-3-yl)-pyridine **57**.

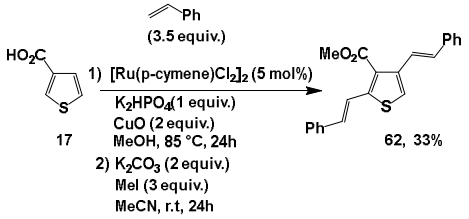
Carretero *et al.*[55] reported a highly regioselective C3-oxidative alkenylation of thiophene 2-pyridyl sulfonyl **59** with electron-deficient alkenes using *N*-fluoro-2,4,6-trimethylpyridinium triflate ([F^+]) as oxidant. The reaction was conducted using $Pd(OAc)_2$, [F^+] in DCE at 110 °C for 14 h. The desired products **60** and **61** were isolated in good yield and excellent regioselectivity. This monosubstitution selectivity was due to the chelating auxiliary (2-pyridyl)sulfonyl unit (Scheme 23).



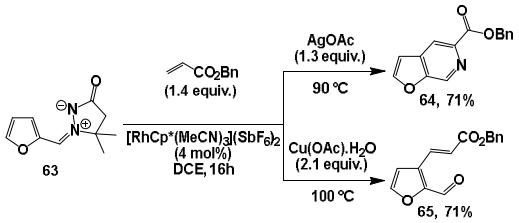
Scheme 23. Regioselective C3-oxidative alkenylation of **59** with electron-deficient alkenes.

Very recently, the Baidya research group[56] developed the synthesis of bis-olefinated thiophene-3-carboxylic acid **62** *via* oxidative Heck-type olefination followed by an esterification reaction of **17**. The target disubstituted product **62** was obtained in low yield (33%) under optimal reaction conditions involving 3.5 equiv. of styrene and [Ru(p-cymene)Cl_2] and CuO as the catalyst-oxidant pair in the presence of K_2HPO_4 as base in MeOH at 85 °C for 24 h (Scheme 24).

An oxidative C-H alkenylation of furans with olefins was developed using [RhCp*$(MeCN)_3$]$(SbF_6)_2$ as catalyst.[57] The oxidative alkenylation of azomethine compound functionalized with a 2-furanyl group **63** was reported using benzyl acrylate as alkenylating agent in DCE at 90 °C for 16 h. Under this protocol, furo[2,3-c]pyridine **64** resulting from the combination of C-H olefination and N-N cleavage was isolated in the presence of AgOAc as the oxidant, while 3-alkenylated furan aldehyde **65** generated from C-H alkenylation was accompanied by subsequent C=N bond hydrolysis when $Cu(OAc)_2 \cdot H_2O$ was used as the oxidant (Scheme 25).

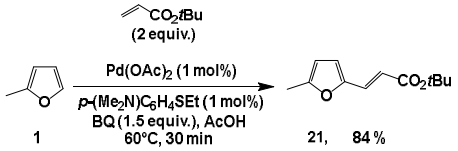


Scheme 24. Ru-catalyzed oxidative bis-alkenylation of **17** with styrene.



Scheme 25. Rh(III)-catalyzed oxidative coupling of azomethine ylides **63** with *n*-butyl acrylate.

In 2017, Carrow and co-workers[58] reported that thioether-$Pd(OAc)_2$ is a suitable catalyst precursor for the Pd(II)-catalyzed undirected C-H alkenylation of furans with acrylate. The optimized reaction conditions involved the use of catalytic amount of thioether ligands. After the screening of various conditions, authors found general conditions with the use of 2-methylfuran **1**, 2 equiv. of *t*-butyl acrylate, $Pd(OAc)_2$ (1 mol%)/ *p*-$(Me_2N)C_6H_4SEt$ (1 mol%) as catalyst and ligand and BQ as oxidant (1.5 equiv.) in acetic acid at 60 °C for 30 min. Under these conditions, the alkenylated product **21** was obtained with high yield (yield of **21** was determined by GC versus an internal standard) (Scheme 26).

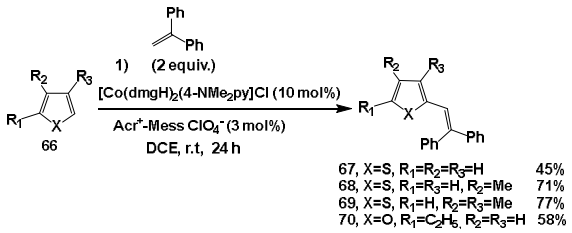


Scheme 26. C-H alkenylation of 2-methylfuran **1** using a thioether-Pd(II) catalyst.

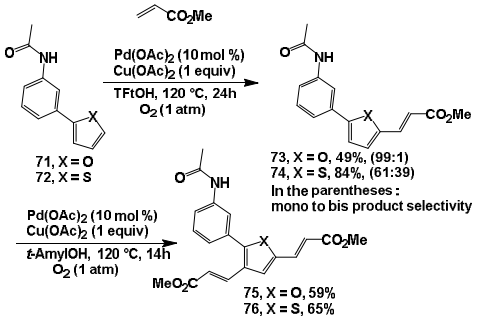
The same procedure was also applied to C-H alkenylation of other heteroarenes such as thiophene, benzofuran, benzothiophene, indole and imidazo[1,2-*a*]pyridine using acrylates.

Lei and co-workers[59] have used an efficient photo/cobaloxime dual catalytic system for oxidative C-H/C-H cross coupling of different heterocyclic systems including furan and thiophene. The reaction was achieved in dichloroethane as solvent, using Fukuzumi's acridinium as photosensitizer and cobaloxime $Co(dmgH)_2(4\text{-}NMe_2py)Cl$ as catalyst under the irradiation of blue LEDs for 24 h. In this process, the C-C bond was formed through radical cation intermediate generated *via* electron transfer between Fukuzumi's acridinium and arenes. Under the optimized conditions, various heteroarenes systems can be olifenated and can afford the alkenylated systems in good to excellent yields accompanying by release of H_2 (Scheme 27).

Recently, Chuang and co-workers[60] developed a regioselective mono- and bis-alkenylation of furan and thiophene containing *N*-acetyl-2-aminoaryl as directing group under oxidative conditions using Pd(II) as catalyst and $Cu(OAc)_2$ as oxidant. The treatment of either furan **71** or thiophene **72** by $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$, TFtOH at 120 °C for 24 h under O_2 atm led to mono alkenylated products **73** and **74** in 49% and 84% yield, respectively. It is noticed that the mono-alkenylation was very good in the case of furan while in was very poor in the case of thiophene (61:39, mono-alkenylated/bis-alkenylated products). Then, monoalkenylated products **73** and **74** were subjected again to a second alkenylation reaction (in this case, *t*-amylOH was used instead of TFEtOH) to produce bis-alkenylated product **75** and **76** in 59% and 65% isolated yield, respectively (Scheme 28).

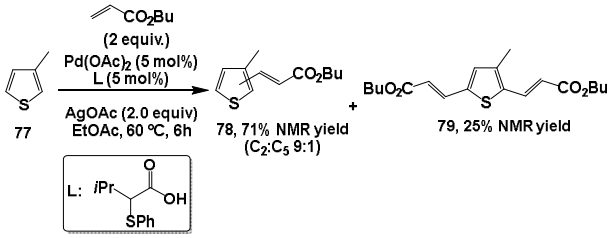


Scheme 27. Oxidative C-H/C-H cross coupling of **66** using photo/cobaloxime dual catalytic system.



Scheme 28. Mono- and bis-oxidative alkenylation of furan **71** and thiophene **72** bearing *N*-acetyl-2-aminoaryl as directing group.

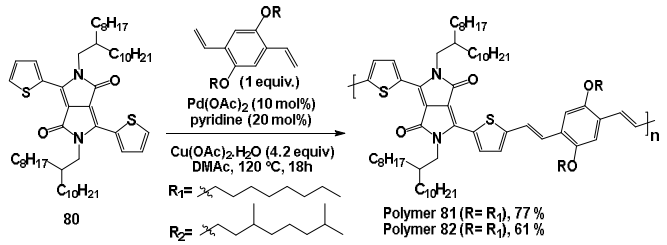
Very recently, Álvarez-Casao and Fernández-Ibáñez[61] reported the oxidative C2 alkenylation of a wide range of thiophenes bearing both electron donating and electron with drawing groups with various acrylates. In representative example, the C-H alkenylation was carried out by treatment of 3-methylthiophene **77** with 5 mol% of $Pd(OAc)_2$, 5 mol% of 3-methyl-2-(phenylthio)butanoic acid (**L**) and 2.0 equiv. of AgOAc in EtOAc at 60 °C for 6 h, providing a desired olefinated product **78** in 71% NMR yield with high C2-selectivity (9:1) (Scheme 29). In addition, they also observed the formation of the di-olefinated product **79** in 25% NMR yield. Moreover, the presence of ligand was a critical parameter for yield and regioselectivity. Indeed, the reaction without ligand provided the olefinated product in low yield (11% NMR yield) and C-2 selectivity (C-2:C-5 2.4:1) (Scheme 29).



Scheme 29. Oxidative Pd(II)-catalyzed C2 olefination of **77**.

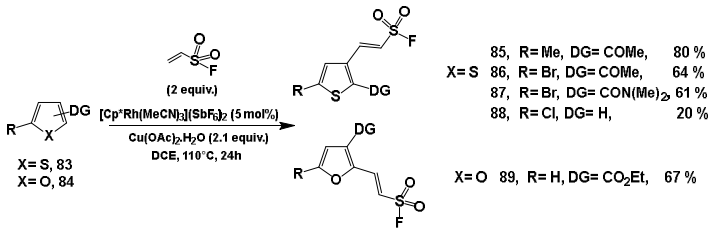
In 2019, Hwang and co-workers[62] reported the Pd(II)-catalyzed dehydrogenative direct alkenylation polycondensation to synthesis of DTPP-based conjugated polymers (π-conjugated semiconducting organic materials). 3,6-Di(thiophen-2'-yl)diketopyrrolopyrrole derivative (DTPP) **80** underwent coupling with 1,4-substituted-2,5-divinylbenzenes monomer in the presence of $Pd(OAc)_2$/pyridine as catalyst,

$Cu(OAc)_2 \cdot H_2O$ as oxidant in anhydrous DMA at 120 °C for 18 h to give a polymer **81** and **82** as a dark blue solid, respectively in 77% and 61% yield with *trans* configuration (Scheme 30).



Scheme 30. Synthetic routes of polymers **81** and **82** *via* C-H alkenylation of the C5 position of the thiophene moiety.

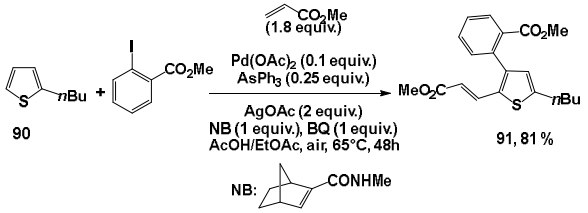
Very recently, Huestis *et al.*[63] prepared a new *β*-thiopheneethenesulfonyl fluorides and *β*-furanethenesulfonyl fluoride using directing group stategy of oxidative olefination. The C-H alkenylation of thiophenes and furan bearing differents varity of directing groups has been achieved by using the cationic (pentamethylcyclopentadienyl)Rh(III) complex $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as catalyst and Cu(II)-acetate as oxidant. The starting materials **83** and **84** were allowed to react with ethenesulfonyl fluoride using 5 mol% $[Cp^*Rh(MeCN)_3](SbF_6)_2$ and 2.1 equiv. of $Cu(OAc)_2,H_2O$ in DCE at 110 °C for 24 h. With strong directing groups such as amide and ketone in C2 position, the **83** gave the C3-vinylated products **85-87** with good yields with high regioselectivity, while without directing group, the alkenylated product **88** was obtained with weak yield. The same conditions were also used for furan **84** which has directing group in C3 position, giving the C2-vinylated compound **89** in good yield (Scheme 31).



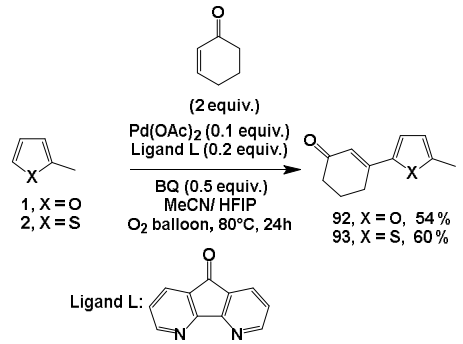
Scheme 31. C-H alkenylation of compounds **83** and **84**.

Dong and co-workers[64] reported a direct difunctionalization leading to both 5-alkenylation and 4-arylation of 1-substituted thiophenes *via* a palladium/norbornene (Pd/NBE) cooperative catalysis. This method is based on the use of 2-butylthiophene **90** and methyl acrylate/methyl 2-iodobenzoate as coupling partners in the presence of $Pd(OAc)_2$/ norbornene **NB**/$AsPh_3$ and AgOAc/BQ in a mixture of HOAc/EtOAc. The reaction mixture was heated at 65 °C for 48 h to provide the expected product **91** in 81% yield (Scheme 32). The synthetic utility has been shown in the derivatizations and the preparation of complex bioactive compounds, in addition, an open-flask gram-scale preparation has been achieved. The procedure using the optimized reaction conditions was applied to other types of difunctionalizations and other electron-rich heterocycles (besides thiophenes and furans) which led to the desired products in low to good yields.

Recently, Feng and co-workers[65] reported a $Pd(OAc)_2$-catalyzed oxidative alkenylation of thiophenes with cyclic enones using oxygen gas and BQ as oxidants. In a representative example, the treatment of **2** by cyclohex-2-enone in the presence of $Pd(OAc)_2$ as catalyst, ligand **L** and BQ in a mixture of CH_3CN/hexafluoro-2-propanol (HFIP) at 80 °C under O_2 afforded the alkenylated product **93** in 60% yield (Scheme 33). In this study, the authors also applied optimized reaction conditions to furan **1** (only one example was reported) which gave the desired product **92** in 54% yield (Scheme 33).

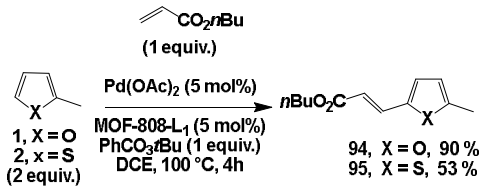


Scheme 32. Direct difunctionalization of 1-substituted thiophene **90** *via* a palladium/norbornene (Pd/NBE) cooperative catalysis.



Scheme 33. Oxidative Heck coupling between furan **1** or thiophene **2** with cyclohex-2-enone.

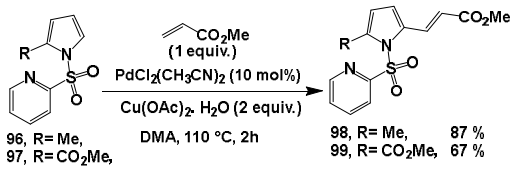
In 2020, De Vos' group[66] reported the oxidative alkenylation of 2-methylfuran and 2-methylthiophene derivatives **1** and **2** using a palladium-organic framework (noted Pd@ MOF-808-L1) obtained from $Pd(OAc)_2$ and a metal-organic framework (named MOF-808-L1) containing S,O-moieties. The treatment of **1** and **2** with *n*-butyl acrylate using Pd@MOF-808-L1 as heterogeneous catalyst in the presence of *tert*-butyl peroxybenzoate ($PhCO_3tBu$) as oxidant in DCE for 4 h led to C5 vinylated products **94** and **95** in 90% and 53% yield, respectively (Scheme 34).



Scheme 34. Pd@ MOF-808-L1 catalyzed oxidative alkenylation of furan **1** and thiophene **2**.

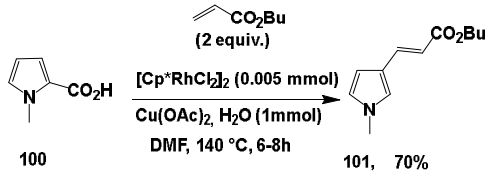
2.2. Oxidative alkenylation of pyrrole

In another interesting report, Carretero's group[67] studied the substitution of the pyrrole ring assisted by *N*-(2-pyridyl)sulfonyl group. Thus, the selective alkenylation of *N*-(2-pyridyl)sulfonylpyrrole **96** and **97** was achieved using $PdCl_2(MeCN)_2$ as catalyst, $Cu(OAc)_2$ as oxidant and methyl acrylate as model olefin. When α-methyl-substituted pyrrole was used as starting material, the expected C2-alkenylated product **98** was obtained in good yield. Also, the use of methyl 1-(pyridin-2-ylsulfonyl)-1*H*-pyrrole-α-carboxylate as starting material led to **99** in acceptable yield (Scheme 35).



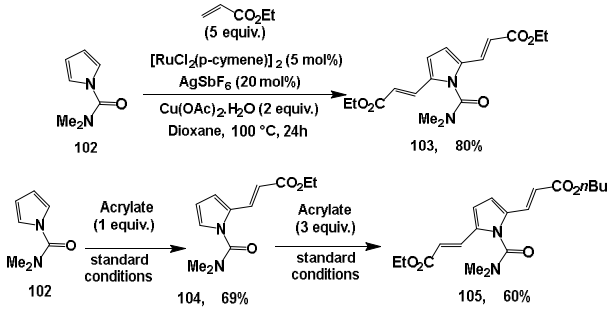
Scheme 35. A selective C2 oxidative alkenylation of pyrrole rings **96** and **97** bearing directing group.

Miura *et al.*[42] described the rhodium-catalyzed direct C3-alkenylation/decarboxylation of 1-methylpyrrole-2-carboxylic acid **100**. After a survey of reaction conditions, the coupling was carried out using butyl acrylate as coupling partner in the presence of $[Cp^*RhCl_2]$ as catalyst and $Cu(OAc)_2{\cdot}H_2O$ as oxidant in DMF at 140 °C. The desired product **101** was obtained with good yield after the remove of the carboxylic function used as directing group (Scheme 36).



Scheme 36. Rhodium-catalyzed direct C3-alkenylation/decarboxylation of **100**.

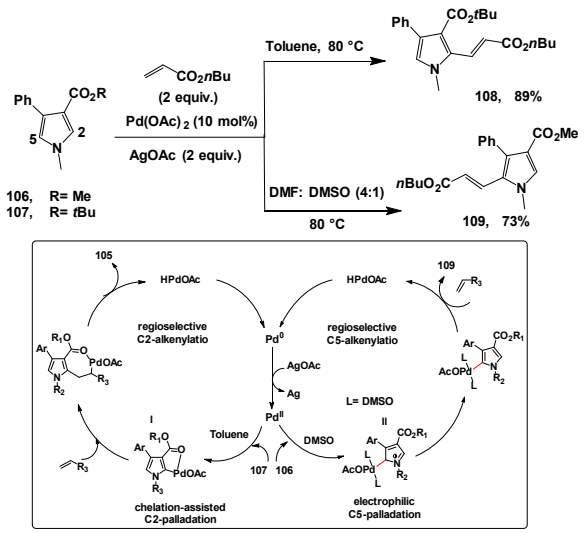
The ruthenium *p*-cymene was also used by Wang *et al.*[68] for the oxidative alkenylation of C2 position of pyrrole with different olefins. The optimal conditions were found using pyrrole which contains *N,N*-dimethylcarbamoyl as directing group **102**, $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst and $Cu(OAc)_2/AgSbF_6$ as oxidant/additive in dioxane at 100 °C for 8 h. Authors demonstrated that, using 5 equiv. of ethyl acrylate and 1 equiv. of pyrrole **102**, the reaction afforded C2,C5-double alkenylated product **103** in 80%. When 1 equiv. of ethyl acrylate with 1.5 equiv. of pyrrole **102** were used under standard conditions, C2-monoalkenylated product **104** was obtained in 69% yield and unsymmetrical C2,C5-dialkenylated product **105** was obtained in 60% yield by subsequent C5-alkenylation of **104** with 3 equiv. of *n*-butyl acrylate (Scheme 37).



Scheme 37. C2 and C2,C5 oxidative alkenylation of **102**.

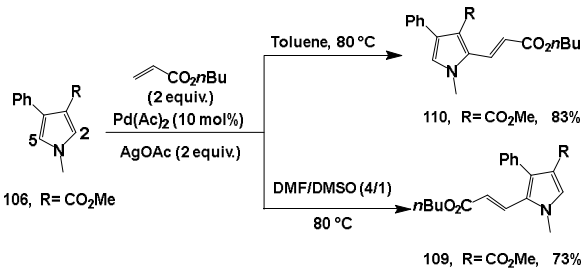
In 2014, Yao *et al.*[18] developed a solvent-controlled switchable oxidative Heck reaction of 4-phenyl-1*H*-pyrrole-3-carboxylates **106** and **107** by using $Pd(OAc)_2$ as catalyst and AgOAc as oxidant. This protocol afforded C2- or C5-alkenylated products depending on the directing group at C3 position. Toluene gave the selective C2-alkenylation **108** (C2:C5>95:5) while DMSO/DMF led to the C5-alkenylation product **109** (Scheme 38). The plausible mechanism proposed in this report started by palladation at the C2 position to form intermediate **I** in toluene or at C5 position to form intermediate **II** in DMSO. The attack at the C2 position *via* Heck-type reaction gave the alkenylation pyrrole **108**. While, in DMSO a strong coordination

solvent, promoted the palladation at C5 position, which lead to intermediate **II**. A rearomatization and then a Heck-type reaction furnished C5-alkenylated product **109**.



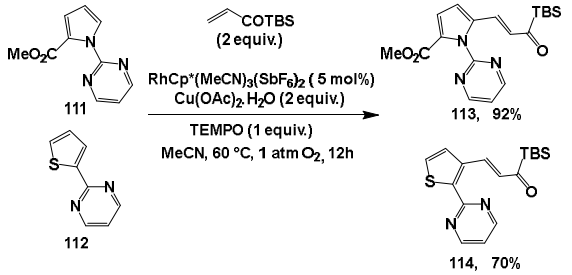
Scheme 38. A solvent-controlled switchable oxidative Heck reaction of 4-phenyl-1*H*-pyrrole-3-carboxylates **106** and **107**.

In 2015, Yao's group[69] described an interesting study of solvent-controlled C2/C5-selective alkenylation of 3,4-disubstituted pyrroles using their previous reaction conditions reported in 2014.[18] In this study, the authors highlighted the crucial effect of C3-substituents on the regio- and stereoselectivity. For example, when toluene was used as solvent, pyrrole **106** bearing a directing group at C3 position gave C2-alkenylation product **110** in 83% yield. Interestingly, the use of mixture of a DMSO/DMF as solvent system allowed C5-alkenylated product **109** in 73% (Scheme 39).



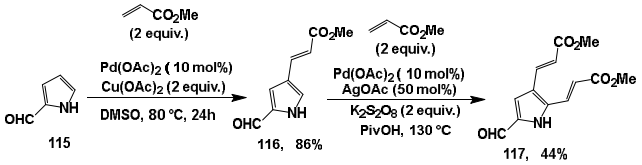
Scheme 39. A solvent-controlled C2/C5-selective alkenylation of 3,4-disubstituted pyrrole **106**.

Feng and Loh[70] described the rhodium-catalyzed direct oxidative alkenylation of pyrrole and thiophene with acryloylsilane using pyrimidyl as directing group which allow the alkenylation at the α position with respect to the pyrimidyl group attached position on pyrrole and thiophene. The protocol of this reaction was carried out using $RhCp^*(MeCN)_3(SbF_6)_2$ as catalyst, $Cu(OAc)_2{\cdot}H_2O$ as oxidant and TEMPO as additive in MeCN as solvent at 60 °C for 12 h. Pyrrole derivative **111** gave 5-olefinated pyrrole **113** in good yield of 92% and thiophene derivative **112** furnished 3-olefinated thiophene **114** in 70% yield (Scheme 40).



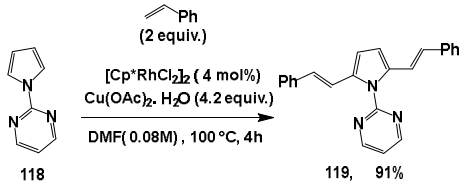
Scheme 40. Rhodium-catalysezd direct oxidative alkenylation of pyrrole **111** and thiophene **112** with acryloyl silane.

Recently, an interesting work of Laha *et al.*[71] described a regioselective oxidative C-H olefination of free (NH) pyrrole-2-carboxaldehyde **115** by methyl acrylate using $Pd(OAc)_2$ and $Cu(OAc)_2$ as catalyst and oxidant system in DMSO at 80 °C for 24 h to afford 4-olefinated pyrrole **116** in good yield 86% (Scheme 41). By using again $Pd(OAc)_2$ as catalyst, AgOAc as oxidant and $K_2S_2O_8$ as additive in PivOH at 130 °C, a second alkenylation was performed on product **116** to afford 4,5-dialkenylated product **117** in moderate yield.



Scheme 41. A regioselective oxidative C-H olefination of free (*NH*) pyrrole-2-carboxaldehyde **115**.

Very recently, Kanbara *et al.*[72] showed that 1-(2-pyrimidinyl)pyrrole **118** can be alkenylated at both C2 and C5 positions by treatment with styrene in the presence of $Cu(OAc)_2$. H_2O as oxidant and $[Cp^*RhCl_2]_2$ as catalyst in DMF at 100 °C. The desired product **119** was obtained in 91% yield (Scheme 42).



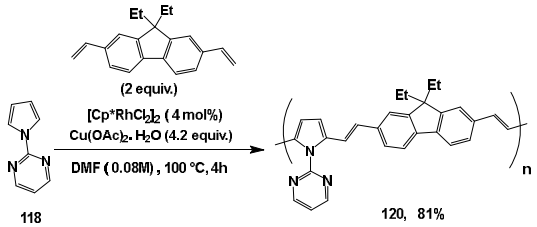
Scheme 42. Bis-oxidative alkenylation of **118** with $[Cp^*RhCl_2]_2$ at C2 and C3 positions.

This protocol was then applied to prepare pyrrole-based poly(arylenevinylene) by treatment of **118** by various diethenyl monomers. In a representative example, **118** was treated with diethenyl monomer under the optimized reaction conditions to lead to polymer **120** in 81% yield (Scheme 43).

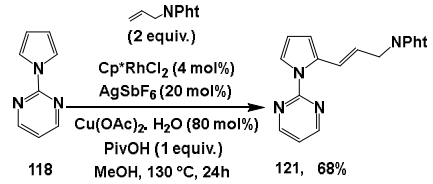
In the same year, Zhang group[53] published the Rh(III)-catalyzed oxidative Heck coupling of different heterocyclic systems. In this report, direct *ortho* C-H bond olefination of pyrrole **118** with aliphatic olefins using $(Cp^*RhCl_2)_2$ as catalyst, $Cu(OAc)_2$ as oxidant and $AgSbF_6$ as additive in MeOH at 130 °C was described. Due to the presence of pyrimidyl directing group, the coupling product **121** was achieved with high regio and stereo selectivity and isolated in acceptable yield of 68% (Scheme 44).

Very recently, Zhou and co-workers[73] reported a Pd(II)-catalyzed regioselective C5 alkenylation of 2-acylpyrroles with alkenes employing 3-nitrile benzoyl group (*N*-(3-NCC_6H_4CO-)) as an efficient *N*-protecting group (Scheme 45). For example, the alkenylation reaction between *N*-(3-CNC_6H_4CO) protected 2-acylpyrrole **122** and ethyl acrylate under optimized reaction conditions [$Pd(OAc)_2$ (20 mol%) as catalyst,

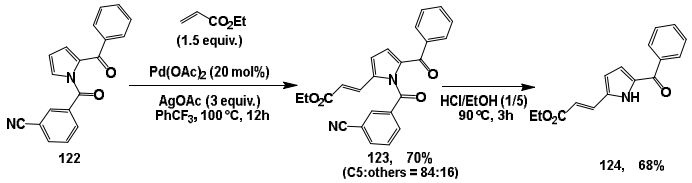
AgOAc (3 equiv.) as oxidant in trifluoromethylbenzene at 100 °C for 12 h] led to expected alkenylated product **123** in 70% isolated overall yield, (ratio of C5:others=84:16 determined by ^{1}H NMR analysis of crude). The *N*-pyrrole protecting group was removed in HCl/EtOH (1:5) for 3 h at 90 °C, yielding 68% of the (*NH*)-free product **124** (Scheme 45).



Scheme 43. Synthesis of pyrrole-based poly(arylenevinylene) **120** by oxidative C-H/C-H coupling.

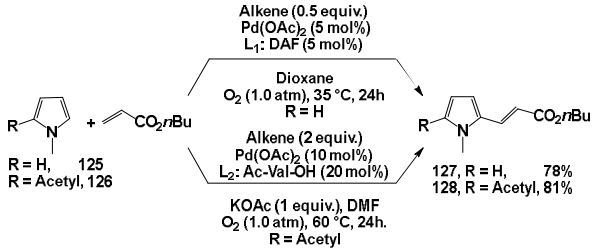


Scheme 44. Rh(III)-catalyzed direct *ortho* oxidative Heck coupling of pyrrole **118** with aliphatic olefins.



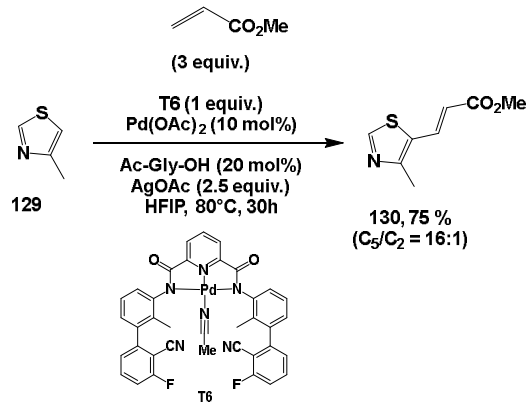
Scheme 45. Pd(II)-catalyzed regioselective C5 alkenylation of 2-acylpyrrole **122** with ethyl acrylate.

Very recently, Joo *et al.*[74] developed an undirected, aerobic strategy for the C-H alkenylation of electron-rich *N*-alkylpyrroles by ligand control. For example, the C-H alkenylation of *N*-methylpyrrole **125** with *n*-butyl acrylate in the presence of $Pd(OAc)_2$ as catalyst, 4,5-diazafluoren-9-one (DAF) as ligand **L1** in dioxane at 35 °C under 1 atm of O_2 for 24 h led to the C2-alkenylation product **127** in 78% isolated yield. Combining $Pd(OAc)_2$ with a mono-protected amino acid (Ac-Val-OH) as the ligand **L2** and KOAc as the base in DMF at 60 °C under 1 atm of O_2 for 24 h afforded the C5-alkenylation of pyrroles having electron-withdrawing groups at the C2 position **126** in 81% yield **128** (Scheme 46).



Scheme 46. Regioselective oxidative alkenylation of *N*-methylpyrroles **125** and **126** with *n*-butyl acrylate.

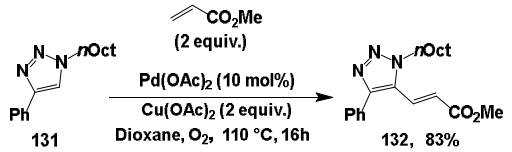
Maiti *et al.*[75] reported a selective C5 olefination of thiazoles directed by a recyclable bifunctional template **T6**. In a representatives example, the reaction was conducted using 4-methylthiazole **129** and methyl acrylate in the presence of $Pd(OAc)_2$/AgOAc and complex **T**6 in hexafluoro-2-propanol (HFIP) containing catalytic amounts of *N*-acetylglycine at 80 °C for 30 h. The desired product **130** was isolated in 75% yield and with a good C5 selectivity (C5/C2 positions=16:1) (Scheme 47). Interestingly, the selective C5-olefination also occurred when 4-chlorothiazole, 2-methylthiazole, and unsubstituted thiazole were used as starting materials.



Scheme 47. C-H alkenylation of 4-methylthiazole **129** by bimetallic catalysis.

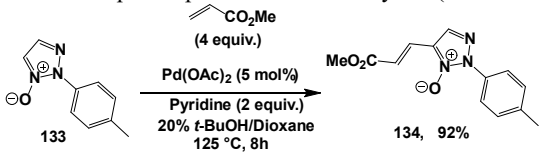
2.3. Oxidative alkenylation of azole derivatives: pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole

In 2010, Jiang and co-workers[76] reported the first example of Pd(II)-catalyzed direct alkenylation of 1,2,3-triazoles. In a representative example, starting material **131** was treated with methyl acrylate in the presence of $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ as oxidant in dioxane under 8 atm of O_2 at 110 °C to give the corresponding alkenylated product **132** in good yield (83%) and high regio- and stereoselectivities (Scheme 48).



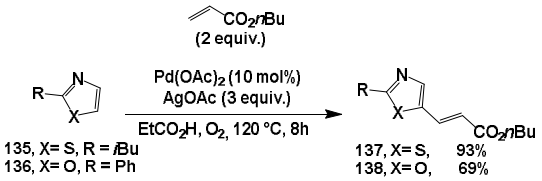
Scheme 48. Pd(II)-catalyzed direct alkenylation of 1,2,3-triazole **131** with methyl acrylate.

In 2013, Kuang and co-workers[77] developed a new method toward 1,2,3-triazole *N*-oxides olefination using 5 mol% of $Pd(OAc)_2$, Ag_2CO_3, pyridine in the presence of 20% *t*-BuOH/dioxane at 125 °C for 8 h. In a representative example, 1,2,3-triazole *N*-oxide **133** was treated by methyl acrylate under the reaction conditions cited above which led to expected product **134** in 92% yield (Scheme 49)



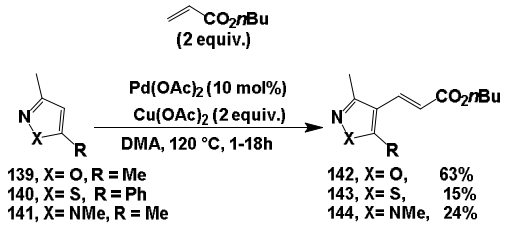
Scheme 49. Oxidative olefination of **133** with methyl acrylate.

In the same year, Miura *et al.*[78] reported the direct oxidative alkenylation of thiazole **135** using butyl acrylate in the presence of $Pd(OAc)_2$/AgOAc as catalyst and oxydant system for 8h at 120 °C in $EtCO_2H$ to afford the corresponding C5-alkenylated thiazole **137** in excellent yield (GC yield). The same reaction conditions were used to prepare C5-vinylated oxazole product **138** in good yield using oxazole **136** and *n*-butyl acrylate as coupling partners (Scheme 50).



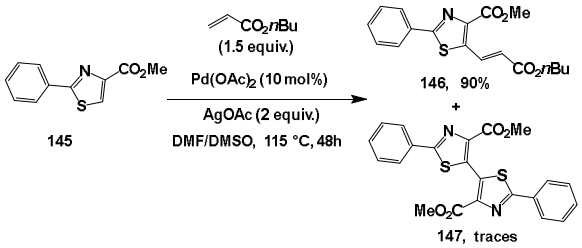
Scheme 50. Oxidative C-H/C-H coupling of **135** and **136** with *n*-butyl acrylate.

One year later, Wheeler and co-workers[79] used Miura's reaction conditions for the direct oxidative alkenylation of isoxazole **139**, isothiazole **140** and pyrazole **141**. Although the yield of C4-alkenylated isoxazole **142** was acceptable (63%), those of the oxidative alkenylation of isothiazole **143** and pyrazole **144** were very low with yields of 15 and 24%, respectively (Scheme 51).



Scheme 51. C4 oxidative alkenylation of **139-141** with *n*-butyl acrylate.

A Pd(II)-catalyzed C-H olefination of thiazole-4-carboxylate **145** with *n*-butyl acrylate was reported by Yao *et al.*[80] under mild reaction conditions (without ligand or acidic additive). The reaction was carried out using $Pd(OAc)_2$ as catalyst and AgOAc as oxidant at 115 °C in DMF/DMSO (10:1 v/v) for 48 h forming the desired product **146** in 90% yield. Notably, traces of the homocoupling product **147** was also observed (Scheme 52).

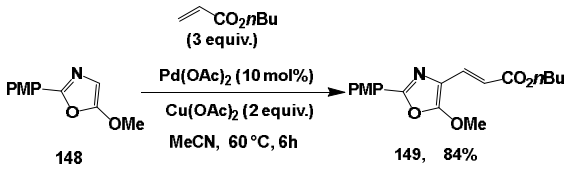


Scheme 52. Pd(II)-catalyzed oxidative coupling of thiazole-4-carboxylate **145** with *n*-butyl acrylate.

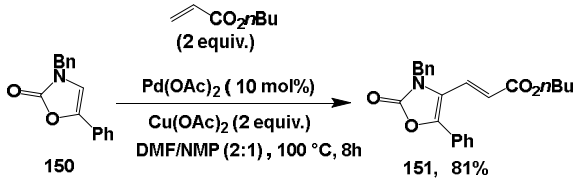
Antilla and co-workers[81] reported the oxidative Heck coupling of oxazole **148** *via* Pd(II)-catalyzed C-H bond activation. The coupling was achieved using *n*-butyl acrylate as coupling partner, $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ as oxidant in acetonitrile at 60 °C. The reaction proceeded under argon atmosphere for 12 h to give the expected product **149** in 84% yield (Scheme 53).

Under similar reaction conditions, Zhu and co-workers[82] reported the direct C-H alkenylation of 3-benzyl-5-phenyloxazolone **150** by *n*-butyl acrylate as model coupling agent. The reaction was carried out

using $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ as oxidant in a mixture of DMF and NMP as solvent at 100 °C for 8 h in air, affording 4-alkenyl-2-oxazolone **151** in good yield (81%) (Scheme 54).

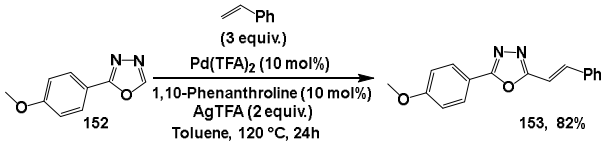


Scheme 53. Direct C-H alkenylation of oxazole **148**.



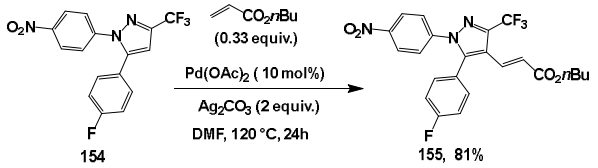
Scheme 54. Oxidative Heck coupling of 3-benzyl-5-phenyloxazolone **150** with *n*-butyl acrylate.

Recently, Salvanna and Das[83] reported a series of 2-alkenyl-1,3,4-oxadiazole *via* oxidative alkenylation reaction between 4-methoxyphenyl-1, 3, 4-oxadiazole **152** and olefins. The target product **153** was prepared in good yield (82%) without by-products by employing palladium(II)trifluoroacetate as catalyst, 1,10-phenantroline as ligand and silver trifluoroacetate as oxidant in toluene (Scheme 55).



Scheme 55. Synthesis of 2-alkenyl-1,3,4-oxadiazole **153** *via* oxidative C-H/C-H coupling reaction.

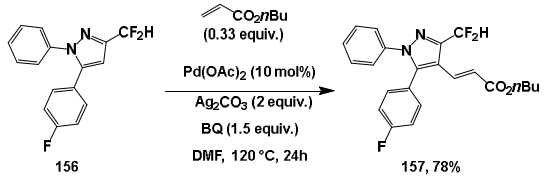
The direct C4 oxidative coupling of 3-trifluoro-pyrazole **154** were reported by Fang and Wu.[84] The coupling of 3-trifluoro-pyrazole **154** and *n*-butyl acrylate was achieved using $Pd(OAc)_2$ as catalyst and Ag_2CO_3 as oxidant in DMF at 120 °C for 24 h to afford C4-alkelynated 3-trifluoro-pyrazole **155** in good yield (Scheme 56).



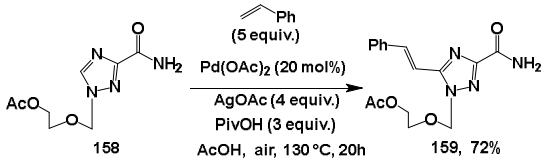
Scheme 56. C4 oxidative alkenylation of 3-trifluoro-pyrazole **154** with *n*-butyl acrylate.

Benzoquinone (BQ) was found to be a good additive for the olefination of C3-CF_2H substituted pyrazole **156** under the same reaction conditions discussed above to give C4-olefinated 3-difluoro-pyrazole **157** in good yield (Scheme 57).

An efficient Fujiwara-Moritani reaction between triazole nucleoside **158** and styrene was achieved by Peng and co-workers.[22] This reaction was carried out using $Pd(OAc)_2$/AgOAc as catalyst/oxidant system and PivOH as additive in acetic acid at 130 °C for 20 h to give the corresponding C3-alkenylated product **159** with good yield and good stereoselectivity (Scheme 58).

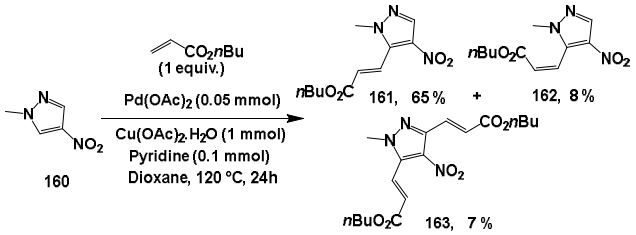


Scheme 57. Synthesis of C4-olefinated 3-difluoro-pyrazole **157** *via* dehydrogenative Heck reaction.



Scheme 58. C3 oxidative alkenylation of **158** with styrene.

Very recently, Joo et *al.*[85] reported a new method for C5-alkenylation of 1-methyl-4-nitropyrazole **160** using palladium acetate as catalyst and *n*-butyl acrylate as coupling agent. The best reaction conditions were found to be $Cu(OAc)_2$ as oxidant and pyridine as monodentate nitrogen ligand. It is noteworthy that bidentate ligands such as 2,2′-bipyridine and 1,10-phenanthroline were inefficient. Under the optimized reaction conditions [**160**, *n*-butyl acrylate, $Pd(OAc)_2$, $Cu(OAc)_2$, pyridine, dioxane, 120 °C, 24 h], the monoalkenylated products **161** and **162** were isolated as *E* and *Z* mixture in acceptable and low yields, respectively. It is noticed that the dialkenylated product **163** was also isolated in low yield (Scheme 59).



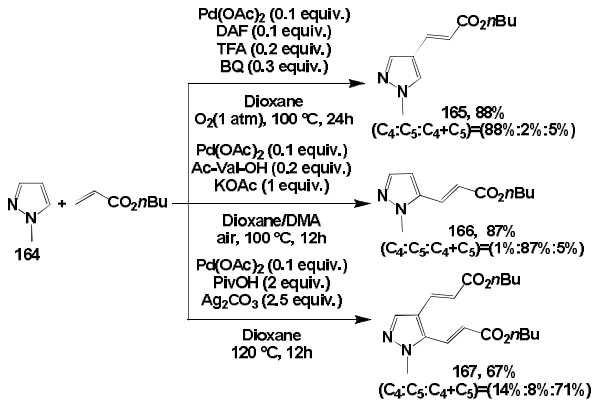
Scheme 59. Pd(II)-catalyzed C5 oxidative alkenylation of 1-methyl-4-nitropyrazole **160**.

The same procedure was successfully applied to achieve oxidative alkenylation of other heterocyclic systems such as (1*H*)- and (2*H*)-indazole derivatives.

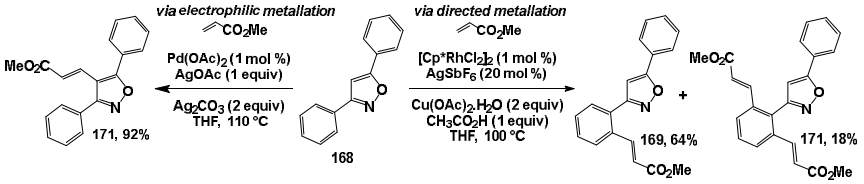
Very recently, the same group[86] developed a regioselective C4, C5, and C4,C5 di-alkenylation of pyrazoles. For example, the C-H alkenylation of *N*-methyl pyrazole **164** with *n*-butyl acrylate in the presence of $Pd(OAc)_2$ as the catalyst generated by TFA and 4,5-diazafluoren-9-one (DAF) led to C5-alkenylation product **165** in 86% isolated overall yield together with small amounts of C5 and C4,C5-di-alkenylated products [C4:C5:C4,C5=88%:2%:5% (NMR yields)]. Whereas, KOAc, mono-protected amino acid (MPAA) ligand, and Ac-Val-OH gave C5-alkenylation product **166** in 82% overall yield with C4 and C4,C5-di-alkenylated products in low yields [C4:C5:C4,C5=1%,87%,5% (NMR yields)]. Combining $Pd(OAc)_2$ with Ag_2CO_3 as the oxidant and PivOH as the additive in dioxane at 120 °C for 12 h furnished to C4, C5 dialkenylation product **167** in 67% overall yield in addition to low yields of C4 and C5 olefinated products [C4:C5: C4,C5=14%,8%,71% (NMR yields)] (Scheme 60).

Very recently, promising extensions of C-H regioselective *ortho* or C_4-H alkenylations of 3,5-diarylisoxazoles received the attention of Kumar and Kapur.[87] They described a general direct oxidative Heck reaction that exploits a novel positional-selective, catalyst-controlled C-H olefination of substituted isoxazoles. Condensation of 3,5-diphenylisoxazole **168** and methyl acrylate in the presence of $[Cp^*RhCl_2]_2$ (1 mol%), $AgSbF_6$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv.), and CH_3CO_2H (1 equiv.) in tetrahydrofuran (THF) at 100 °C, afforded the *ortho*-alkenylation of 3,5-diphenylisoxazole **169** in 64% yield (Scheme 61).

However, the yields were generally lower in these cases, presumably as the formation of the di-olefinated product **170** in 18% yield under the same reaction conditions. When the reactions were performed with methtylacrylate by using $Pd(OAc)_2$ (1 mol%) with AgOAc (1 equiv.) and Ag_2CO_3 (2 equiv.) in THF at 110 °C, the regioselectivity of the oxidative process was switched in favor of the reaction at the C4-position leading to **171** in 92% yield (Scheme 61).



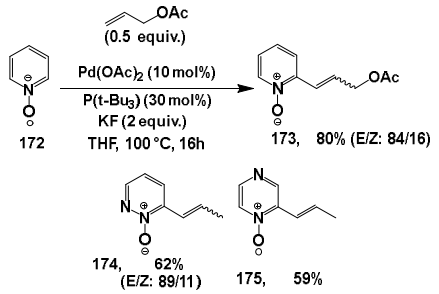
Scheme 60. Regioselective C-H/C-H alkenylation of *N*-methyl pyrazole **164** with *n*-butyl acrylate.



Scheme 61. Catalyst-controlled C-H alkenylation of 3,5-diphenylisoxazole **168**.

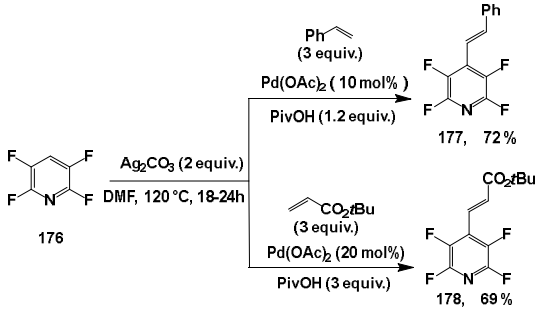
3. Alkenylation of six-membered heterocyclic ring systems: pyridine and derivatives

This year, the group of Poli and Oble[88] reported direct olefination of pyridine and azine oxides with allyl acetate using $Pd(OAc)_2$ as calayst. In a representative example, pyridine *N*-oxide **172** was treated by allyl acetate in the presence of 10 mol% of $Pd(OAc)_2$, 30 mol% of $P(t\text{-}Bu)_3{\cdot}HBF_4$, 2 equiv. of KF in THF at 100 °C for 16 h. This procedure led to expected alkenylated product **173** in 80% NMR yield. It is noticed that *E* isomer was obtained as the major (84%) while *Z* was obtained as the minor isomer 16% (based on ^1H NMR of crude product using dimethyl sulfone as internal standard) (Scheme 62). The protocol was successfully applied to direct oxidative alkenylation of various azine *N*-oxides.



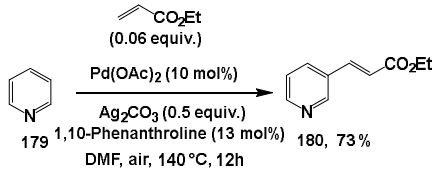
Scheme 62. Direct oxidative olefination of azine *N*-oxides.

Zhang *et al.*[89] reported a homogeneously palladium-catalyzed oxidative vinylation of a highly electron-deficient tetrafluoropyridine **176** by olefins. After a screening of various reaction conditions, the authors found that the treatment of **176** with styrene in the presence of $Pd(OAc)_2$ as catalyst, Ag_2CO_3 as oxidant and PivOH as additive in DMF at 120 °C for 24 h led to C4-vinylated product **177** in 72% yield. When *tert*-butyl acrylate was used as vinylation agent, the C4-vinylated product required 20 mol% of $Pd(OAc)_2$ and 3 equiv. of PivOH to achieve desired product **178** in 69% yield (Scheme 63).



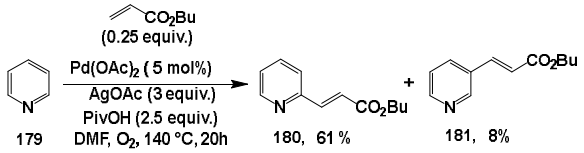
Scheme 63. Pd(II)-catalyzed oxidative vinylation of tetrafluoropyridine **176** by olefins.

In 2011, Yu *et al.*[90] reported a novel method for C3 selective C-H alkenylation of pyridine **179** based on the use of bidentate ligand as crucial tool for regioselectivity. This method afforded access to 3-alkenyl pyridine derivative **180** by using the $Pd(OAc)_2$ as catalyst, Ag_2CO_3 as oxidant and 1,10-phenantroline as ligand in DMF at 140 °C (Scheme 64).



Scheme 64. Selective C3 oxidative alkenylation of pyridine **179**.

Wen *et al.*[91] developed for the first time the selective C2 oxidative alkenylation of pyridine **179** using $Pd(OAc)_2$ as ligand, AgOAc as oxidant and PivOH as additives to afford C2-olefinated **180** as a major product with an acceptable yield (61%) and C3-olefinated product **181** as a by-product in a low yield (8%) (Scheme 65).

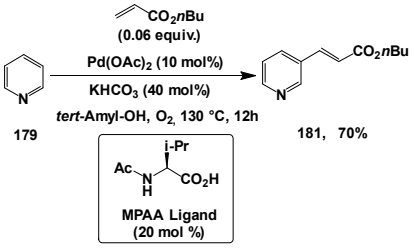


Scheme 65. C2 and C3 oxidative alkenylation of pyridine **179**.

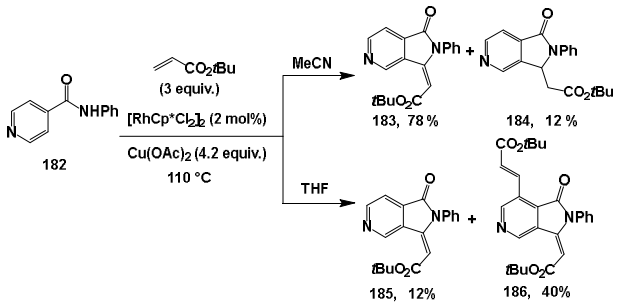
Recently, Cong *et al.*[92] developed a Pd(II)-catalyzed oxidative Heck reaction between pyridine **179** and *n*-butyl acrylate using mono-*N*-protected amino acid (MPAA) as ligand and $KHCO_3$ as base in *tert*-amyl alcohol. This reaction, carried out at 130 °C under O_2, led to C3 selective alkenylated product **181** in good yield (Scheme 66).

Rhodium(III) ($[RhCp^*Cl_2]_2$) can also catalyze the oxidative alkylenation reaction of pyridine. In fact, Wei *et al.*[93] reported a sequence of C3 oxidative alkenylation/amidation of *N*-aryl isonicotinamide **182** using $[RhCp^*Cl_2]_2$ as catalyst and $Cu(OAc)_2$ as oxidant in acetonitrile at 110 °C to give **183** as a major product in

a good yield and **184** as a by-product. Remarkably, when THF was used as solvent under the same conditions, the selectivity was lost and the major product was C3,C5-dialkenylated product **186** which was isolated with moderate yield. In this case, the monoalkenylated product **185** was obtained in very low yield (Scheme 67).



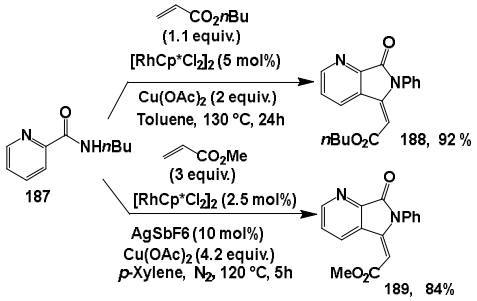
Scheme 66. Pd(II)-catalyzed oxidative Heck reaction of pyridine **179** with *n*-butyl acrylate.



Scheme 67. Rhodium(III)-catalyzed C3 oxidative alkenylation/amidation of *N*-aryl isonicotinamide **182**.

Two years later, similar cascade oxidative olefination/cyclisation of picolinamides was reported independently by two different research groups.

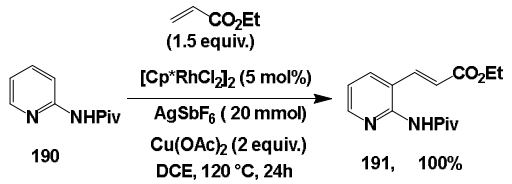
Xi *et al.*[94] used picolinamide **187** as starting material in the presence of *n*-butyl acrylate as coupling partner, $[RHCp^*Cl_2]_2$, $Cu(OAc)_2$ in toluene at 130 °C for 24 h. Under these reaction conditions, the expected product **188** was isolated in 92% yield. In the case of Carretero *et al.* report,[21] methyl acrylate was used as coupling partner instead of *n*-butyl acrylate ysed by Xi group and $AgSbF_6$ was added as additive in *p*-xylene at 120 °C which afforded the desired product **189** in 84% isolated yield (Scheme 68).



Scheme 68. The oxidative olefination/cyclisation of picolinamide **187**.

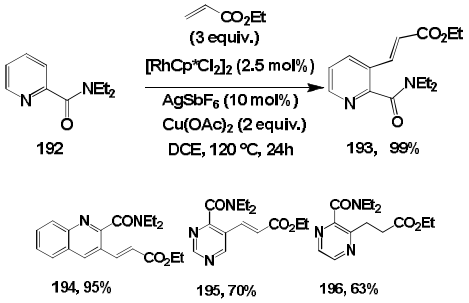
Shi *et al.*[95] reported a Rh(III)-catalyzed oxidative C-H/C-H activation of pyridine **190** containing NHPiv as a directing group at position 2. The reaction was carried out using ethyl acrylate as coupling partner in the presence of $[Cp^*RhCl_2]_2$ as catalyst, $AgSbF_6$ as oxidant and $Cu(OAc)_2$ as additive in

dichloroethane at 120 °C. This protocol afforded product **191**, alkenylated in *ortho*-position of the directing group in excellent yield. (Scheme 69).



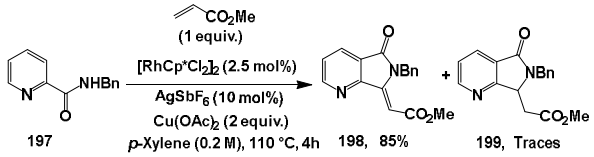
Scheme 69. Direct oxidative alkenylation at position 2 of pyridine **190** containing NHPiv as a directing group.

One year later, the same group[96] used similar reaction conditions to achieve C3 oxidative alkenylation of *N*,*N*-disubstituted picolinamide. In a representative example, C3 oxidative alkenylation of *N*,*N*-diethyl picolinamide **192** was achieved by treatment of compound**192** with ethyl acrylate in the presence of a low catalyst loading of $[Cp^*RhCl_2]_2$ to give desired product **193** in 99% yield (Scheme 70). The optimized reaction conditions were also applied to other heterocyclic systems such as quinoline and pyrimidine with ethyl acrylate leading to expected products **194** and **195** in 95% and 70% yields, respectively. However, the reaction of pyrazine with ethyl acrylate gave only the corresponding alkenylated product **196** in 63% yield.



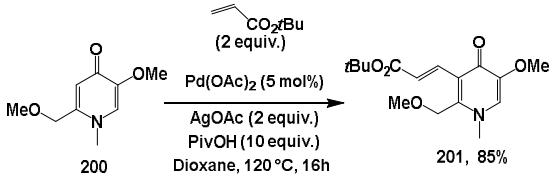
Scheme 70. Rh(III)-catalyzed C3 oxidative alkenylation of *N*,*N*-disubstituted picolinamide **192**.

Based on the reports of Shi *et al.*, Carretero's group[21] developed Rh(III)-catalyzed olefination cyclization of picolinamide **197** using similar reaction conditions by changing only the nature of the reaction solvent. In this case, the use of *p*-xylene led to desired product **198** in good yield. Traces of the reduced product **199** were also formed (Scheme 71).



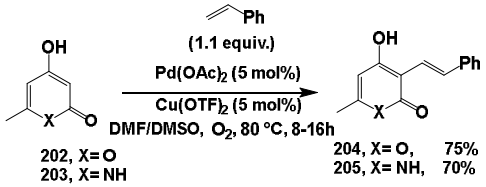
Scheme 71. Rh(III)-catalyzed olefination cyclization of picolinamide **197**.

Yao *et al.*[97] developed C3 selective oxidative alkylenation of pyridin-4(*1H*)-one **200** using palladium $Pd(OAc)_2$ as catalyzed and AgOAc as oxidant in the presence of pivalic acid as an excellent additive in dioxane at 120 °C. This method gave the C3 selective alkenylated product **201** in good yield (Scheme 72).



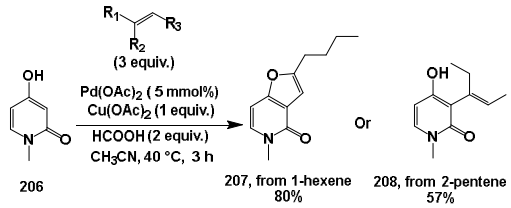
Scheme 72. Selective C3 oxidative alkylenation of pyridin-4(*1H*)-one **200**.

Yousuf *et al.*[98] reported Pd(II)-catalyzed direct alkenylation reaction of pyrones and pyridones using styrene as coupling partner. In a representative example, 4-hydroxy-6-methylpyrone **202** and 4-hydroxy-6-methylpyridone **203** were treated by styrene in the presence of $Pd(OAc)_2$ and $Cu(OTF)_2$ in mixture of DMF/DMSO at 80 °C for 8-16 h to lead regio- and chemoselective C3-alkenylated product **204** and **205** in 75% and 70% isolated yield, respectively (Scheme 73). This process was successfully applied to prepare various alkenylated pyrones and pyridones using different styrenes as olefins.



Scheme 73. Direct Pd(II)-catalyzed alkenylation reaction of pyrone **202** and pyridone **203**.

In another work, Zografos *et al.*[99] reported the first regioselctive alkenylation with unactivated alkene on the C3 position of 4-hydroxy-2-pyridone **206**. Thus, when 1-hexene was used in the presence of 4-hydroxy-2-pyridone **206**, $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ as oxidant and formic acid as additive in acetonitrile at 40 °C for 3 h, furo-cyclized product **207** was obtained in 80% yield (Scheme 74). However, when 2-pentene was used as reaction partners, it did not provide the furo-cyclized product but rather led to a regioselective addition to form C3-alkenylated product **208** in 57% yield (Scheme 74).



Scheme 74. Regioselctive C3 alkenylation of 4-hydroxy-2-pyridone **206** with unactivated alkene.

4. Conclusion and outlook

This review was focused on the advances made during the last decade on the transition-metal-catalyzed reactions for the formation of C-C bonds *via* oxidative alkenylation (also called dehalogenation reaction, C-H/C-H activation or oxidative Heck reaction and Fujiwara-Moritani reaction) between either five or six-membered ring systems and olefins. The dehalogenation reaction is a more economical and simple way to prepare original aryl-olefin, and (hetero)aryl-olefin compounds compared to conventional cross-coupling reactions. These kinds of reactions are a very attractive research topic offering alternatives to the synthesis of various products with biological and synthetic interests. This review has summarized and shown several reaction conditions developed to achieve the coupling between different olefins and five and six-membered heterocyclic ring systems. Despite the major advances made to date, the oxidative C-C activations still depend heavily on expensive and/or toxic transition metals as catalysts as well as on sacrificial oxidants, which are generally copper(II) and silver(I). The reaction suffers also from the

lack of reactivity because the regioselective functionalization of more than one C-H bond on heterocyclic systems is still very challenging. The regiogelectivity is an important issue to address using innovative approaches such as the use of directing groups or solvents controlled regioselectivity. Through this review, we hope that the present contribution will assist interested researchers to contribute new discoveries in this areas.

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