Transition Metal-Catalyzed Alkyl Heck-type Reactions

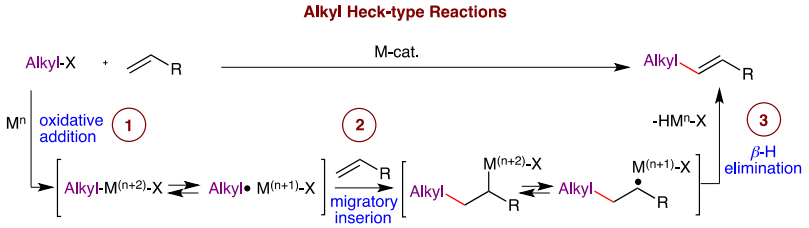
Daria Kurandina[+a]
Padon Chuentragool[+a]
Vladimir Gevorgyan[a*]

[a] University of Illinois at Chicago, 845 West Taylor Street Chicago, IL 60607-7061, USA

vlad@uic.edu

[+] These authors contributed equally

Published as part of the *50 Years SYNTHESIS – Golden Anniversary Issue*



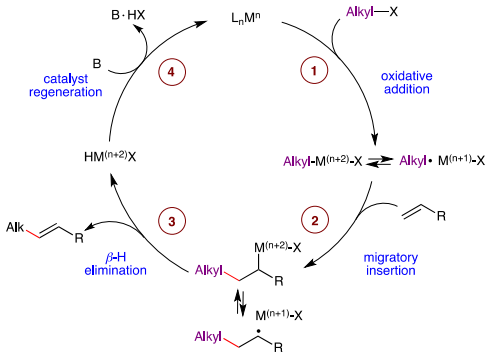
Received:
Accepted:
Published online:
DOI:

Abstract Heck reaction is one of the most reliable and useful strategies for construction of C-C bonds in organic synthesis. However, in contrast to the well-established aryl Heck reaction, the analogous reaction employing alkyl electrophiles is much less developed. A significant progress in the area was recently achieved by merging the radical- and the transition metal-catalyzed approaches. This review summarizes all the advances in the alkyl Heck-type reactions from its discovery in early 70s until end of 2018.

Key words Heck reaction, cross-coupling, alkyl halides, alkenes, transition metal catalysis

1 Introduction

Mizoroki-Heck reaction[1] is one of the most powerful approaches towards multisubstituted alkenes. This reaction represents the first example of Pd-catalyzed C–C bond forming reactions,[2] which follow a classical Pd(0)/Pd(II) catalytic cycle



Scheme 1 Mechanism of transition metal-catalyzed alkyl Heck-type reactions

enabling coupling of aryl and vinyl electrophiles with olefins. The reaction has been exhaustively employed in organic synthesis, drug discovery, electronics, and industry,[3] which led to its recognition with a Nobel Prize in 2010. The current efforts in this area are placed on the use of decreased loadings of palladium,[4] employment of low-cost transition metals,[5] and the development of asymmetric protocols.[6] Historically, aryl halides/pseudohalides were electrophiles of choice for all cross-coupling reactions, thus not surprisingly they were most extensively used in the Heck reaction as well. Throughout the years, these works were summarized in numerous excellent reviews.[7] In contrast, alkyl electrophiles were found to be more challenging coupling partners, mostly due to the competing β-H elimination process[2] and slower rates of the oxidative addition step.[8] Nonetheless, under more recently developed conditions, alkyl halides[9] were shown to be capable partners for this transformation. Yet, the number of reports on alkyl Heck reaction remains scarce compared to that for aryl substrates.

In general, alkyl Heck reactions feature the mechanism of a classical Heck reaction between aryl halides and alkenes that includes: (1) oxidative addition; (2) migratory insertion; (3) β-

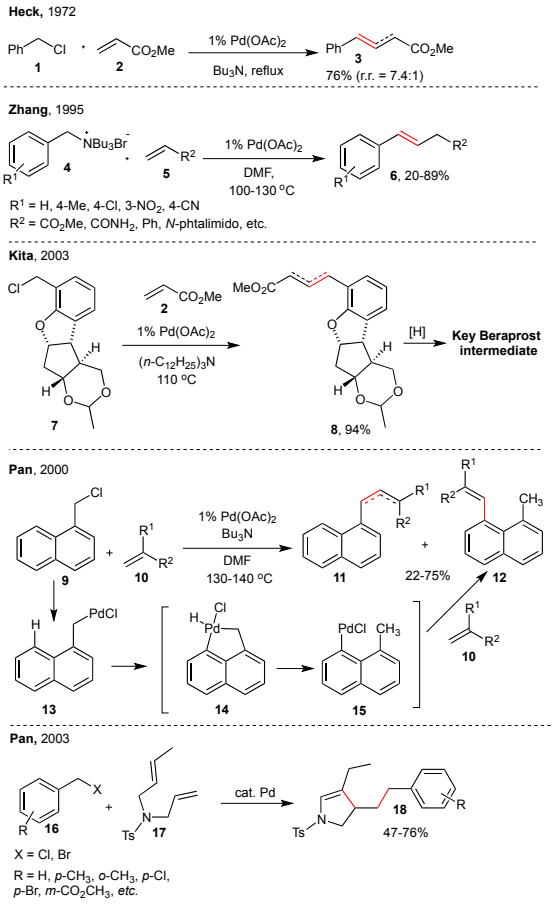
hydrogen elimination; and (4) catalyst regeneration steps (Scheme 1). However, in contrast to the aryl Heck reaction, its alkyl version often presumed to involve radical intermediates, thus operating via a hybrid organometallic–radical scenario. The mechanistic studies, such as radical trapping,[10] radical clock experiments,[11] as well as ESR studies, proved the presence of radical species in some of the alkyl Heck reactions. The mechanisms of their formation, which may depend on the nature of the alkyl component, the leaving group, and the metal catalyst, are still not completely understood. It was shown that employment of visible light allows accomplishing alkyl Heck reactions under milder conditions; and in the recent years this area has been vastly growing. Various complexes of Co, Ir/Ru, Au, Pd, and other transition metals were found to catalyze this reaction under visible light irradiation with significantly expanded scope. This review highlights the advances in the field of alkyl Heck-type reactions of alkyl electrophiles with alkenes since its discovery in the early seventies.[1d] It is systematized by the type of electrophile used, such as benzylic, activated (possessing carbonyl or its equivalents at the *β*-position), perfluorinated, and unactivated alkyl electrophiles. Related transformations, such as Heck-type reactions involving *β*-X elimination step and cascade transformations commencing with radical addition into an alkene moiety are not discussed herein.[12]

2 Pd-Catalyzed Heck-type Reactions

2.1 Benzylic Electrophiles

The first example of the coupling of alkyl halide with olefin was reported by Heck in his original seminal work in 1972 (Scheme 2).[1d] Benzyl chloride **1** reacted with methyl acrylate **2** in the presence of 1 mol % of $Pd(OAc)_2$ and Bu_3N as a base to deliver a regiomeric mixture of alkenes **3.** In 1995, Zhang and co-workers developed a base-free alkyl Heck reaction of benzyltris(*n*-butyl)ammonium bromide salts **4** toward exclusive formation of the conjugated product **6** (Scheme 2).[13] Both electron-rich and electron-deficient alkenes **5** were efficiently benzylated under these conditions. Based on the ESR studies, the authors suggested involvement of the benzyl radicals, which would form via the reductive cleavage of the benzyl quaternary ammonium salt by palladium(0) species. Later, coupling of benzyl chlorides with olefins was elegantly utilized by Kita to obtain the key intermediate **8** in the synthesis of Beraprost, a vasodilator and antiplatelet agent (Scheme 2).[14] In this work, the Heck reaction followed by hydrogenation was shown to be superior over other methods tested for installation of an alkyl chain into the benzyl position of compound **7**.

In 2000, Pan and co-workers observed an interesting Pd-catalyzed rearrangement in the vinylation reaction of α-chloromethylnaphthalene **9** (Scheme 2).[15] In the reactions with *N*-vinylimides, besides the expected Heck products **11**, a product with an olefin attached to the *peri* position of the naphthalene ring was detected. This unusual rearrangement product **12** was proposed to form via the cyclopalladation intermediate **14** where the nitrogen-containing alkene served as a stabilizing ligand for benzylpalladium species **13**. Later, Pan showed the Pd-catalyzed cascade reaction of benzyl halides with

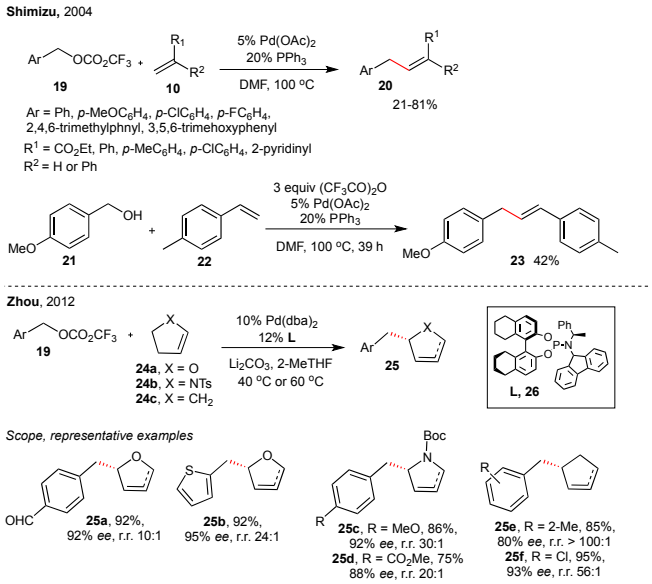


Scheme 2 Pd-catalyzed Heck reaction of benzyl halides

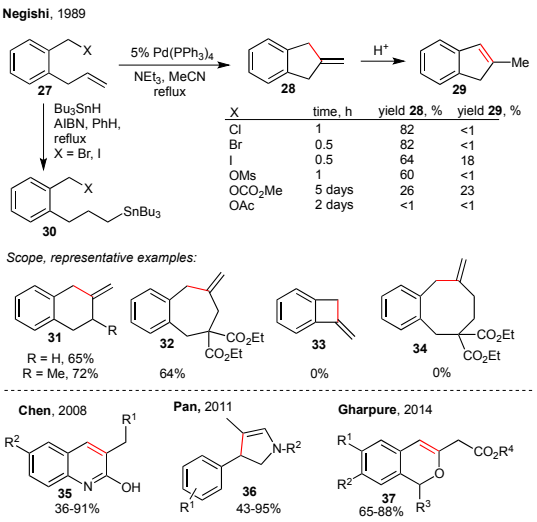
N-allyl-*N*-(2-butenyl)-*p*-toluenesulfonamide **17** to furnish dihydropyrroles **18** with excellent regioselectivity (Scheme 2).[16]

In addition to benzyl halides, benzyl trifluoroacetates were also found to be compatible coupling partners for the Heck reaction. In 1999, Yamamoto reported that mixing benzyl trifluoroacetate with phosphine-coordinate Pd(0) leads to the formation of an oxidative addition complex.[17] In 2004, Shimizu showed that the reaction of this complex with ethyl acrylate under heating produced the corresponding Heck reaction product.[18] Based on these initial discoveries, the catalytic benzylation of olefins with benzyl trifluoroacetates **19** was developed (Scheme 3).[18] Moreover, the authors were able to achieve the benzylation of *p*-methyl styrene **22** with *p*-methoxybenzyl alcohol **21** using trifluoroacetic anhydride as an additive. Later, Zhou introduced an asymmetric Heck reaction of benzyl trifluoroacetates **19** with 5-membered cyclic olefins **24**.[19] In the presence of Pd/phosphoramidite (L, **26**) catalyst, 2,3-, and 2,5-Dihydrofurans, *N*-boc-2,3-pyrroline, and cyclopentene (**24a-c**) were smoothly alkylated with electronically diverse benzyl trifluoroacetates leading to the corresponding products **25a-f** in high yields, and high degrees of regioselectivity, and enantioselectivity (Scheme 3).

The first intramolecular Heck reaction of benzyl halides was developed by Negishi to access five- to seven-membered cyclic compounds (Scheme 4).[20] The initial screening of the leaving group at *o*-allylbenzyl electrophile **27** revealed that Cl, Br, and OMs are acceptable leaving groups leading almost exclusively to the formation of 2-methyleneindan **28**. In the cases of I and



Scheme 3 Pd-catalyzed Heck reaction of benzyl fluoroacetates

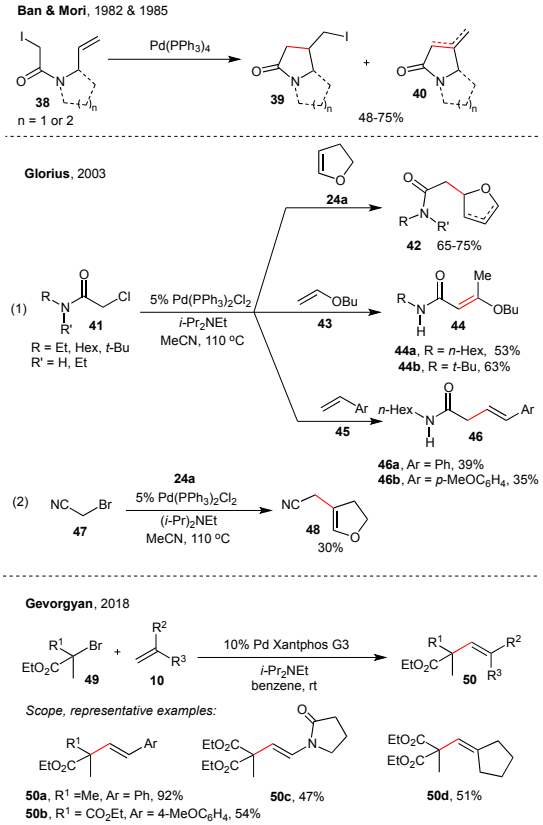


Scheme 4 Intramolecular Pd-catalyzed Heck reaction of benzyl halides

OCO_2R leaving groups, the cyclization occurred quite efficiently but with low regioselectivity, as the formation of regioisomer **29** was detected in significant amounts. Lastly, *o*-allylbenzyl acetate was practically unreactive. Interestingly, the attempts to induce this cyclization under typical radical conditions led to the hydrostannation product **30** only, thus illustrating the superiority of the Heck reaction path for this type of cyclization. The developed intramolecular Heck reaction was also able to deliver six- and seven-membered cyclic compounds **31** and **32** from the corresponding benzyl chlorides in good yields and regioselectivity. However, attempts to obtain four- and eight-membered rings using this strategy (**33** and **34**, respectively) were unsuccessful.

In 2008, Chen applied intramolecular Heck-type approach for synthesis of 3-alkyl-*1H*-quinolin-2-ones **35** via cyclization of benzyl halides with α,β-unsaturated amides.[21] In 2011, Pan introduced another regioselective intramolecular Heck-type coupling for assembly of a biologically important core, 4-aryl dihydropyrroles **36**.[22] In this case, cyclization favours products with endocyclic double bond, so that most dihydropyrroles were obtained as single regioisomers. In 2014, Gharpure disclosed a straightforward synthesis of isochromene derivatives **37** using intramolecular Heck reaction of benzyl halides and vinylogous carbonates (Scheme 4).

2.2 α-Carbonyl Alkyl Halides



Scheme 5 Pd-catalyzed Heck reaction of α-carbonyl alkyl halides

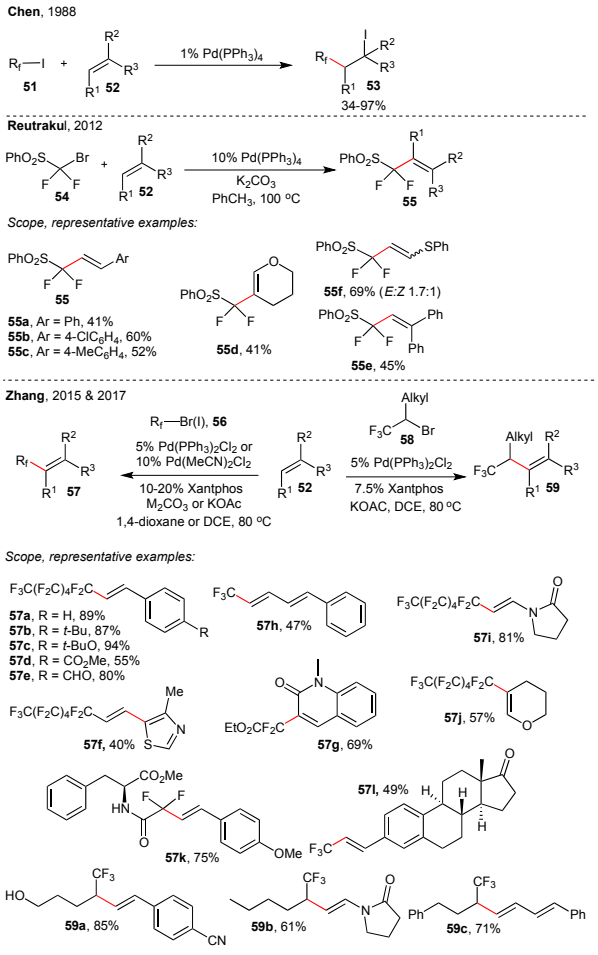
In the eighties, Ban and Mori performed the initial study on the $Pd(PPh_3)_4$-catalyzed intramolecular alkylation of olefins using α-carbonyl alkyl halides **38**.[23] The reaction proceeded with low selectivity, delivering mixtures of the Heck and atom transfer radical cyclization (ATRC) products (**39** and **40**, respectively) in moderate yields (Scheme 5). In 2003, Glorius reported an intermolecular Heck reaction of 2-chloro acetamides **41** with 2,3-dihydrofuran **24a**, butyl vinyl ether **43** and styrenes **45** (Scheme 5, eq 1).[24] Alkylation of **24a** and **43** led to the exclusive formation of α-alkylated olefins **42** and **44**, respectively, thus supporting the reaction mechanism involving palladium enolates rather than alkyl radical intermediates. Conversely, the reaction of bromo acetonitrile **47** with **24a** produced β-alkylated 2,3-dihydrofuran **48** in 30% yield as a single product (Scheme 5, eq 2). This reaction was suggested to proceed via a radical pathway.

More recently, Gevorgyan has showed that activated tertiary alkyl bromides possessing α-carbonyl moiety **49** can efficiently react with styrenes and electron-rich alkenes at room temperature (Scheme 5).[25] Catalyzed by Pd Xantphos G3 complex, the reaction furnished the Heck products **50a-d** in moderate to high yields. Radical clock experiment suggested

that the catalytic cycle might potentially involve alkyl Pd-radical hybrid species.

2.3 Fluoroalkyl Halides

In 1985, Chen reported the first Pd-catalyzed addition of perfluorinated alkyl iodides **51** to alkenes **52** leading to alkyl iodides **53**, the atom transfer radical addition (ATRA) products (Scheme 6).[26] A radical nature of this transformation was strongly supported by the mechanistic studies, which led the authors to propose an involvement of the Pd(0) complex in a radical initiation event. In 2012, Reutrakul developed the $Pd(PPh_3)_4$-catalyzed Heck reaction of (bromodifluoromethyl)-sulfones **54** with alkenes (Scheme 6).[27] The reaction proceeded smoothly in toluene at 100 °C delivering the coupling products **55a-f** in moderate yields. Later, Zhang reported the first Heck reaction of perfluorinated alkyl halides with vinyl arenes/heteroarenes (**57a-g**), dienes (**57h**), and electron-rich olefins (**57i-j**) (Scheme 6).[28] The reaction features a quite general scope leading to valuable fluoroalkylated alkenes in good to excellent yields. Moreover, this method was shown to be effective for synthesis of complex molecules possessing fluorinated fragment (**57k**, **l**). In the follow-up work, the same group demonstrated that a similar catalytic system involving Pd(II)-precatalyst and Xantphos ligand enabled a Heck-type coupling of secondary trifluoromethylated alkyl bromides (Scheme 6, products **59a-c**).[29] The performed mechanistic studies supported a hybrid Pd-radical mechanism and ruled out the possible involvement of the corresponding ATRA products (bromide-containing analogs of **53**) for both reactions.[28,29]

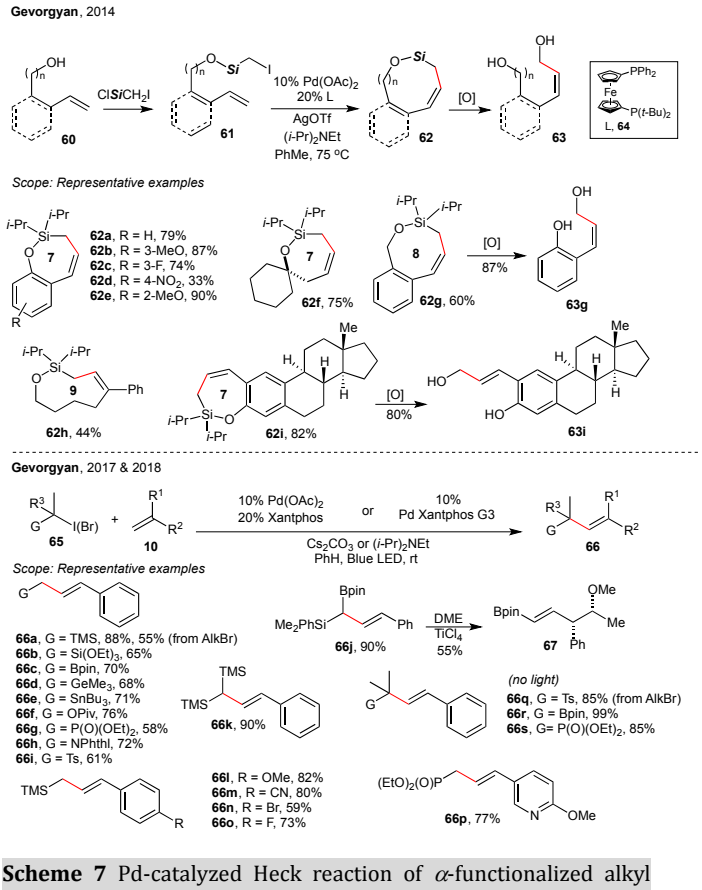


Scheme 6 Pd-catalyzed Heck reaction of ????o??alkyl halides

2.4 α-Functionalized Alkyl Halides

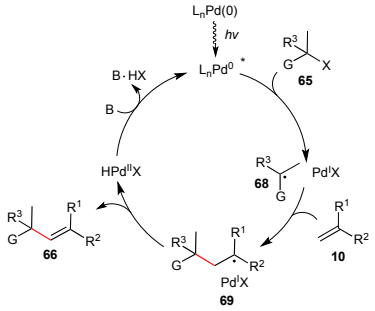
In 2014, Gevorgyan reported the Pd-catalyzed *endo*-selective Heck-type reaction of iodomethylsilyl ethers **61** employing ferrocene-derived bidentate phosphine ligand **64** (Scheme 7).[30] The reaction was able to deliver seven-, eight-, and nine-membered siloxycycles **62a-i** in good yields, which could further be converted into the corresponding allylic alcohols (see **63g, i** as examples) via oxidation. Formally, this transformation provides a tool for a selective (*Z*)-hydroxymethylation of phenols and alkenols **60**. The mechanistic studies suggested a hydrid Pd-radical mechanism for this Heck reaction. Also, the silicon atom was found to be crucial for the observed *endo*-selectivity.

In 2017, Gevorgyan group developed the first visible light-induced Pd-catalyzed Heck reaction of alkyl halides at ambient temperature and exogenous photosensitizer-free conditions to furnish valuable allylic systems of diverse electronic nature (Scheme 7).[31] Allylic silanes (**66a-b, 66k-o**), -boronates (**66c, j**), -germanes (**66d**), -stannanes (**66e**), -pivalates (**66f**), -phosphonates (**66g, p**), -phthalimides (**66h**), and -tosylates (**66i**) were easily synthesized from primary and secondary α-functionalized alkyl halides and vinyl arenes/heteroarenes. The obtained allylic systems can be further modified, for example, via Hosomi-Sakurai reaction (**66j**→**67**). Later, the same group applied these developed photoinduced conditions for the Heck reaction of α-heteroatom-substituted tertiary alkyl iodides with



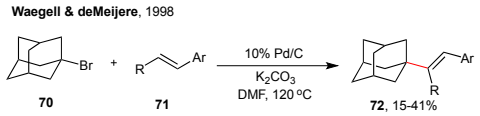
Scheme 7 Pd-catalyzed Heck reaction of α-functionalized alkyl halides

styrene (Scheme 7, products **66q-s**).[25] Notably, in this case, presumably due to the insufficiently low reduction potentials of the activated tertiary substrates, activation by light was not necessary to obtain the Heck reaction products. The performed radical clock- and radical trapping experiments, described in these reports,[25,31] support a radical-type mechanism. It was also shown that Pd(0)L_n complexes were the single light-absorbing species in this reaction. Its excited state is quenched by an alkyl halide presumably via an SET event, which was calculated to be "barrierless"[12c] to form the alkyl Pd hybrid species **68**, that adds to an alkene producing a new radical species **69** (Scheme 8). A subsequent *β*-H elimination from the latter delivers the product **66**; while the base regenerates the Pd(0)-catalyst (Scheme 8).



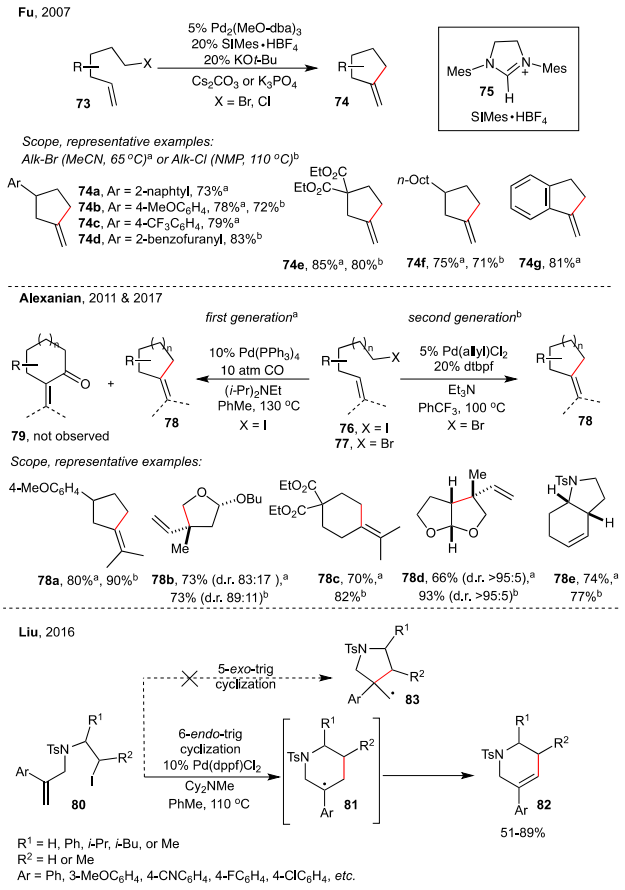
Scheme 8 Gevorgyan's mechanism of visible light-induced Pd-catalyzed Heck reaction

2.4 Unactivated Alkyl Halides

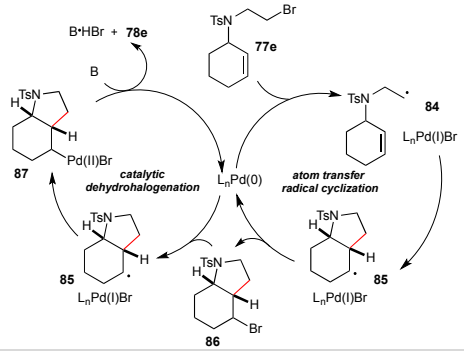


Scheme 9 Waegell & deMeijere's first Pd-catalyzed Heck reaction of unactivated alkyl halides

The first Heck reaction of unactivated alkyl halides with alkenes was reported by Waegell and deMeijere in 1998 (Scheme 9). In this report, 1-bromoadamantane **70**, a substrate which is not disposed to a *β*-hydrogen elimination, was employed. Upon this Pd/C-catalyzed reaction at 120°C, a number of substituted olefins **72** were obtained in low to moderate yield. In 2007, Fu introduced the first protocol for the Heck reaction of unactivated alkyl bromides and chlorides containing eliminable *β*-hydrogens (Scheme 10).[32] The employment of the bulky NHC-ligand **75** on the Pd catalyst was the key for the success of this transformation allowing an intramolecular insertion of alkyl-Pd species into a double bond to proceed faster than the premature *β*-hydrogen elimination. The cyclopentane derivatives possessing exo-alkene moiety **74a-g** were obtained in high yields and regioselectivity from the corresponding unsaturated alkyl bromides and even chlorides **73** at elevated temperatures. The stereochemical outcome of this transformation supports the S_N2 mechanism for the oxidative addition step, thus eliminating involvement of radical intermediates in this reaction.



Scheme 10 Pd-catalyzed intramolecular Heck reaction of unactivated alkyl halides



Scheme 11 Alexanian's mechanism of Pd-catalyzed carbocyclization of unactivated alkyl bromides via auto-tandem catalysis

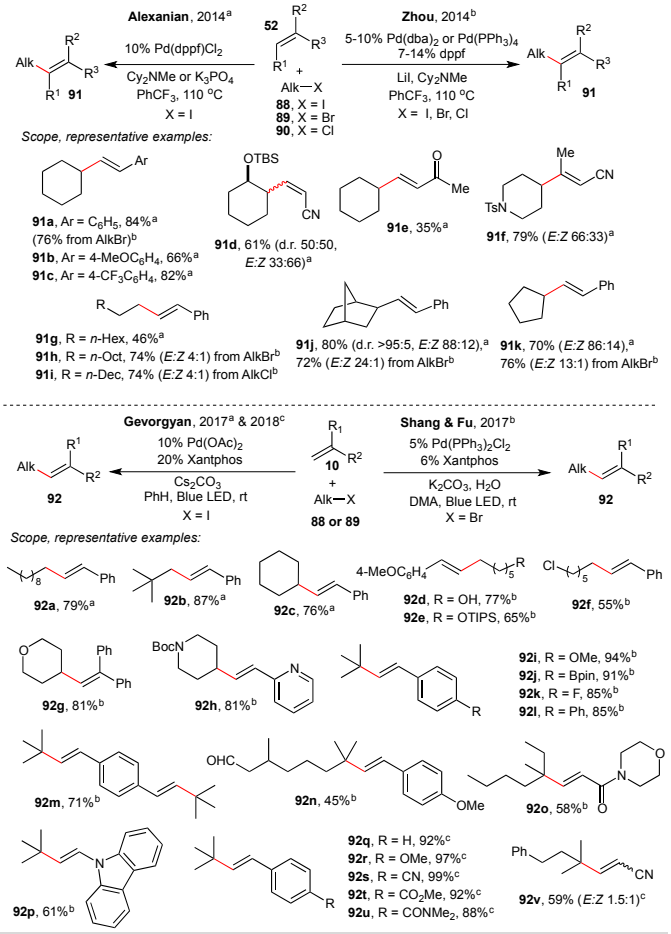
In 2011, Alexanian developed a protocol for an intramolecular alkyl-Heck reaction, which relied on a radical reactivity (Scheme 10).[33] Following his previous work on carbonylative Heck-type reaction,[34] he showed that under increased CO pressure, $Pd(PPh_3)_4$ is capable of catalyzing the 5- or 6-*exo*-trig cyclization reaction of alkenyl iodides **76**, leading to the exclusive formation of Heck reaction products **78a-e** rather than the corresponding cycloalkenones **79**. Interestingly, in the absence of CO, the reaction proceeded as well, albeit with lower efficiency and regioselectivity. In contrast to Fu's work, the mechanistic studies, including the radical trapping experiment, indicated the formation of radical species under these conditions. Accordingly, a hybrid Pd-radical mechanism

was postulated. In 2017, the same group introduced a second-generation Pd-based catalytic system for an intramolecular Heck-type reaction, thus enabling efficient carbocyclization of unsaturated alkyl bromides **77** under CO-free conditions (Scheme 10).[35] Moreover, in this work, the authors investigated the difference in the reactivity of alkyl iodides vs. alkyl bromides in this cyclization. It was hypothesized that, in a case of alkyl bromides, the cyclization proceeds via auto-tandem catalysis (Scheme 11). Initiated by Pd(0) complex, the ATRC leads to the formation of alkyl bromide **86**, which could be isolated from the reaction mixture. Subsequently, the Pd(0)-catalyzed dehydrohalogenation of **86** delivers the Heck reaction product. Alternatively, for alkyl iodides, the radical chain mechanism initiated by Pd(0)-catalyst was suggested as a more likely scenario.

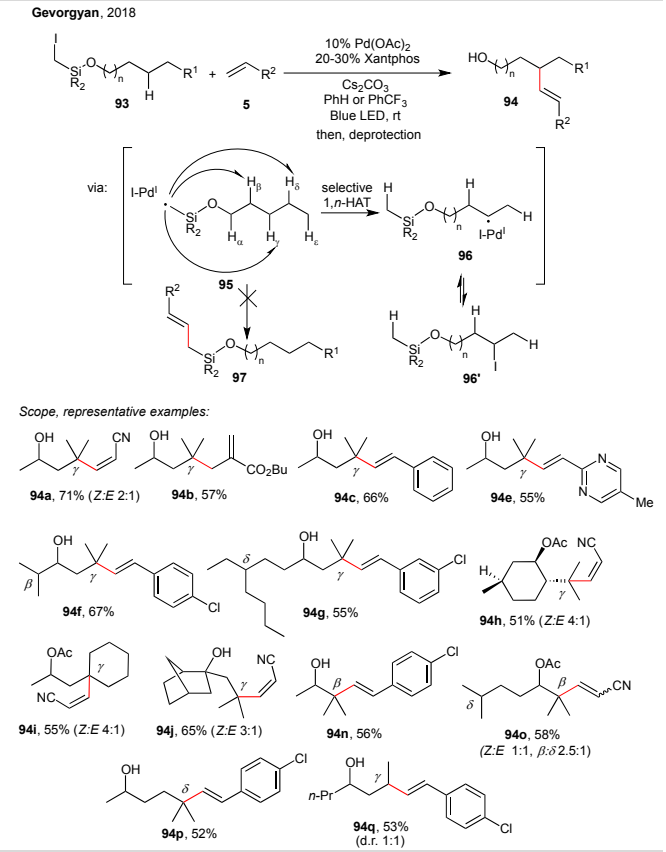
In 2016, Liu reported a related Pd-catalyzed radical Heck-type cyclization utilizing alkyl iodides **80** possessing a 1-aryl-substituted alkene moiety (Scheme 10).[36] The use of these specific substrates resulted in the exceptional *endo*-selective cyclization. This outcome is attributed to a much higher stability of the forming tertiary benzyl radical intermediate **81** vs. a non-stabilized primary radical species **83**, which would arise via an alternative 5-*exo*-trig cyclization. Thus, a number of 5-aryl-1,2,3,6-tetrahydropyridines **82**, structural motifs found in a variety of natural products and pharmaceutical compounds, were synthesized using this approach.

In 2014, Alexanian developed an intermolecular version of alkyl Heck reaction of unactivated alkyl iodides (Scheme 12).[37] By employing Pd(dppf)Cl_2-catalyst, both primary and secondary alkyl iodides **88** reacted smoothly with styrene and acrylonitrile derivatives producing alkylated olefins **91a-k** in moderate to excellent yields. Shortly after, Zhang applied a combination of Pd(0)-precatalyst and dppf ligand, which allowed to perform an intermolecular Heck reaction of styrenes with alkyl iodides **88**, bromides **89** and even chlorides **90** (Scheme 12).[38] The use of LiI additive in the reaction was crucial for achieving higher yields with halides **89** and **90** presumably due to *in situ* generation of more reactive iodide species. As a result, the corresponding Heck reaction products (**91a, h-k**) were obtained with the yields comparable to those reported by Alexanian employing alkyl iodides. Similarly to the previously reported Heck-type cyclization reactions, the mechanistic studies in both reports were consistent with a hybrid Pd-radical pathway, thus further illustrating the prominence of this pathway for overcoming premature β-hydrogen elimination process in alkyl-Heck reactions.

Until recently, all the reported methods for the Heck reaction of unactivated alkyl halides required elevated temperatures. In 2017, Gevorgyan group demonstrated the possibility of achieving a room temperature Heck reaction of unactivated primary and secondary alkyl halides under visible light-induced exogeneous photosensitizer-free conditions employing Pd(0)/Xantphos catalytic system (Scheme 12, products **92a-c**).[31] Shortly after, the groups of Shang, Fu, independently, developed a similar method for reaction of primary and secondary unactivated alkyl bromides with styrenes to provide the Heck reaction products **92d-h** in excellent yields and *E/Z* ratios.[39] Moreover, the challenging tertiary alkyl bromides were found to



Scheme 12 Pd-catalyzed intermolecular Heck reaction of unactivated alkyl halides



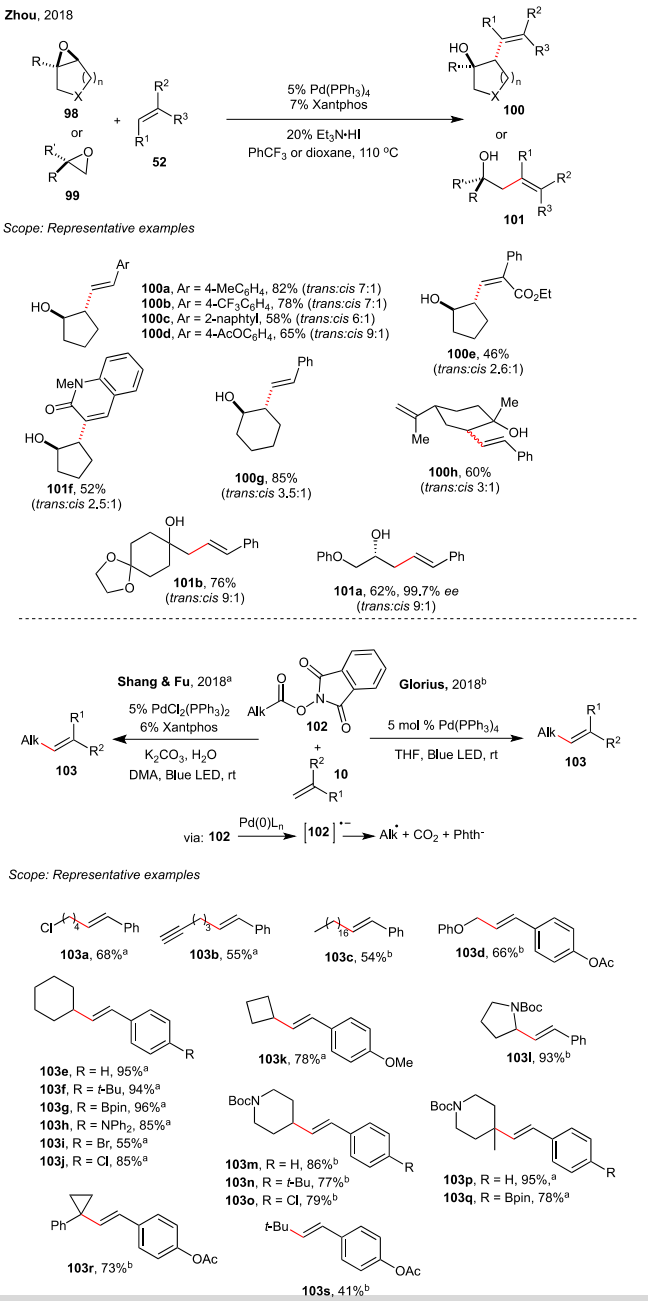
Scheme 13 Pd-catalyzed aliphatic radical relay Heck reaction at unactivated C(sp^3)-H sites of alcohols

be capable coupling partners, as well (products **92i-n**). In addition to styrenes, unactivated tertiary alkyl bromides also reacted with electron-deficient alkenes in a highly efficient manner (products **92o-p**). The mechanistic studies of this work strongly supported a radical pathway, which was initiated by an SET event from the photoexcited Pd(0) complex to an alkyl halide (see Scheme 8). Furthermore, the performed X-ray photoelectron spectroscopy studies detected palladium in three oxidation states: Pd(0), Pd(I), and Pd(II), thus demonstrating that the Pd(0)- Pd(I)-Pd(II)-catalytic cycle is a highly feasible scenario for these visible light-induced conditions. Shortly after, Gevorgyan group independently reported analogous efficient alkyl Heck reaction of unactivated tertiary alkyl iodides with styrenes and acrylonitrile (Scheme 12, products **92q-v**).[25]

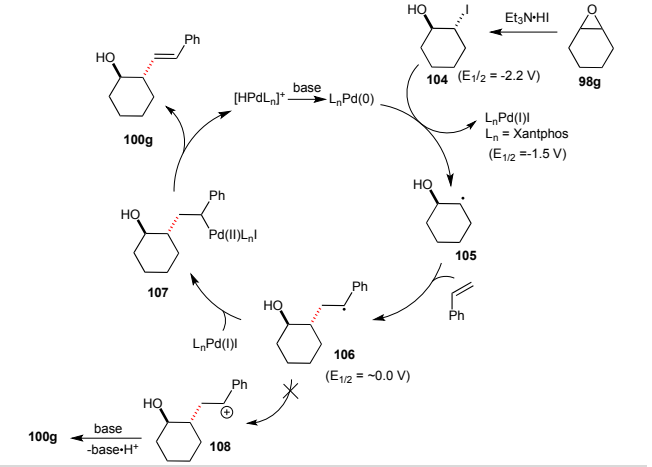
Very recently, Gevorgyan group reported a photoinduced Pd-catalyzed radical relay Heck reaction at remote unactivated C(sp^3)–H sites of aliphatic alcohols, which synergistically combines a C–H activation via hydrogen atom abstraction (HAT) process and an alkyl Heck reaction (Scheme 13).[40] The control of the β-, γ-, or δ-sites in this regioselective Heck reaction was achieved by an employment of easily installable/removable iodomethyl silyl tethers on alcohols (**93**). These tethers are known to engage in an SET process with the photoexcited Pd-complex to form the Pd-radical hybrid species **95**.[30-31] Remarkably, **95** bypasses the potential side-reaction processes, such as hydrodehalogenation or premature Heck reaction (**97**), but rather undergoes a selective 1,5-, 1,6- or 1,7-HAT to produce the translocated Pd-radical hybrid species **96**. Subsequently, the latter is able to couple with acrylonitrile, acrylate or styrene derivatives to afford the remote Heck reaction products **94a-q** in good yields. Interestingly, the iodine-atom transfer intermediate **96'** was observed during this reaction, which presumably is formed via a reversible I-atom transfer from the $Pd^{I}I$ species.

Lately, the scope of alkyl electrophiles in the Heck reaction has been expanded. Thus, in 2018, Zhou group reported a Heck-type reaction of cyclic **98** and acyclic **99** epoxides under Pd(0)-Xantphos catalytic system (Scheme 14).[41] Styrenes, conjugate dienes, and electron-deficient olefins were efficiently alkylated to give ring-opening products **100a-h**, **101a-b** with the retention of stereochemistry of the original epoxides. The authors proposed that the reaction proceeds via the *in situ* generation of β-iodohydrins **104** from the epoxide **98g** and $Et_3N{\bullet}HI$, which undergoes an SET reduction by the Pd(0) complex to form an alkyl Pd hybrid radical species **105** (Scheme 15). Subsequently, the species **105** adds to the double bond to form a new radical species **106**, which gives the reaction product via the followed recombination with Pd(I) and β-H elimination. The measured redox potentials of the reaction components are consistent with this hypothesis, thus ruling out an alternative radical polar crossover pathway involving oxidation of benzyl radical species **106** by Pd(I) into the corresponding benzyl cation **108**.

In addition to alkyl halides and epoxides, the redox active esters have also been found to undergo an efficient Heck-type reaction. In 2018, groups of Shang, Fu and Glorius independently discovered a photoinduced Pd-catalyzed Heck reaction of redox active esters, aliphatic *N*-(acyloxy)phthalimides **102**, with



Scheme 14 Pd-catalyzed intermolecular Heck reaction of epoxides and redox-active esters



Scheme 15 Zhou's mechanism of Pd-catalyzed Heck reaction of epoxides

styrenes (Scheme 14).[42] The reaction of primary, secondary and tertiary substrates proceeded smoothly at room temperature (products **103a-t**), thus providing an alternative approach towards alkylated alkenes starting from readily available carboxylic acids. Overall, the scope of these transformations was comparable with that of the visible light-induced Heck reaction of alkyl halides. Likewise, the mechanistic studies have proven the radical-type mechanism, initiated by an SET event between photoexcited Pd(0)-complex and a redox-active ester, followed by its decarboxylative fragmentation towards an alkyl hybrid Pd-radical species. The latter would be engaged in the hybrid Pd-radical catalytic cycle, ultimately generating the corresponding Heck reaction products. Furthermore, the photophysical studies revealed that the Pd-complex is the only light absorbing species in this transfromation, while *N*-(acyloxy)phthalimides **102** showed no absorption in the visible light region.

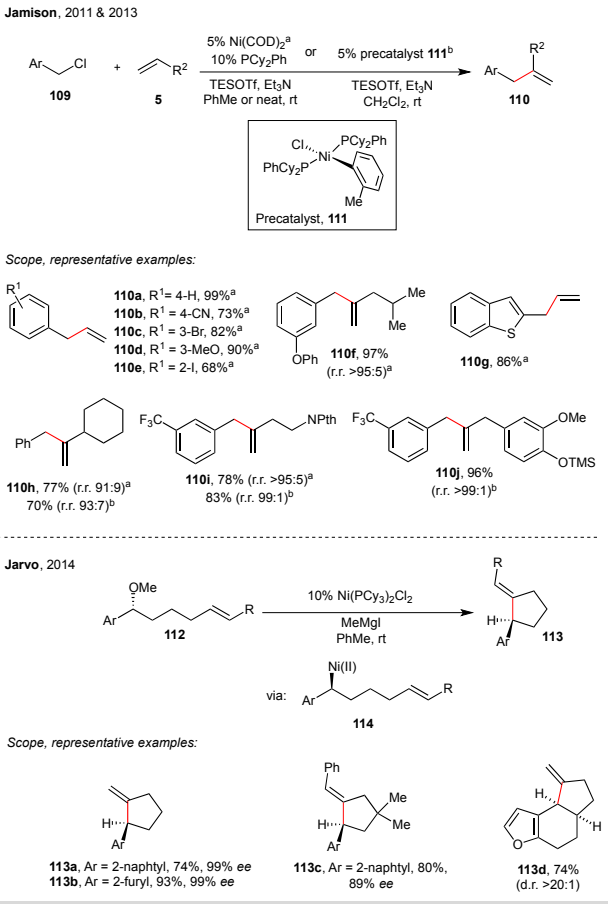
3 Ni-Catalyzed Heck-type Reactions

3.1 Benzylic Electrophiles

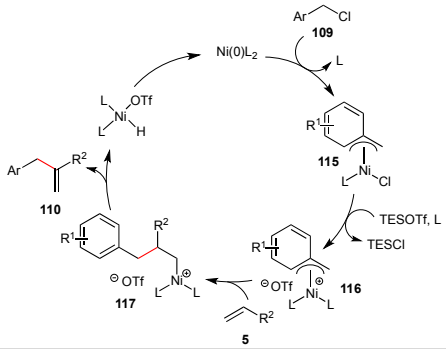
Following his work on the Ni-catalyzed allylic alkenylation,[43] in 2011, Jamison introduced a protocol for Heck coupling of benzyl chlorides with terminal aliphatic alkenes. A number of branched Heck reaction products **110** were efficiently obtained at room temperature in the presence of $Ni(COD)_2$ with the monodentate phosphine ligand PCy_2Ph and TESOTf as an additive (Scheme 16).[44] The reaction was proposed to occur via a cationic Heck reaction pathway (Scheme 17). First, the oxidative addition complex **115** undergoes a counteranion exchange with TESOTf to generate the cationic benzyl-Ni(II) species **116**, followed by an olefin coordination and sterics-controlled migratory insertion. The subsequent *β*-H elimination of the formed alkyl-Ni(II) complex **117** affords the branched Heck reaction product **110** and HNi(II)OTf species, which upon reduction to Ni(0) returns to the catalytic cycle. This protocol is unique for alkyl-Heck reactions, as it provides access to 1,1-dialkyl-substituted alkenes **110a-i** in excellent yields and regioselectivity (> 95:5 for most cases). Two years later, the same group discovered a precatalyst **111** that allows this reaction to proceed much faster and, most remarkably, to be carried out under open flask conditions, where no exclusion of air, water, or degassing of solvents and reagents is required.[45] Relying on these new conditions, a diverse range of allylbenzene derivatives **110h-j** were efficiently synthesized in comparable yields to those reported under the previous protocol (Scheme 16).

In 2014, Jarvo developed a highly efficient stereospecific Ni-catalyzed intramolecular benzylic Heck reaction of chiral methyl benzyl ethers **112** into methylenecyclopentanes **113** (Scheme 16).[46] The stereochemical outcome of this reaction arose from inversion at the oxidative addition event, thus providing a single enantiomer of the key alkyl-Ni intermediate **114**. The stereochemistry at this carbon center remained unchanged throughout the following steps.

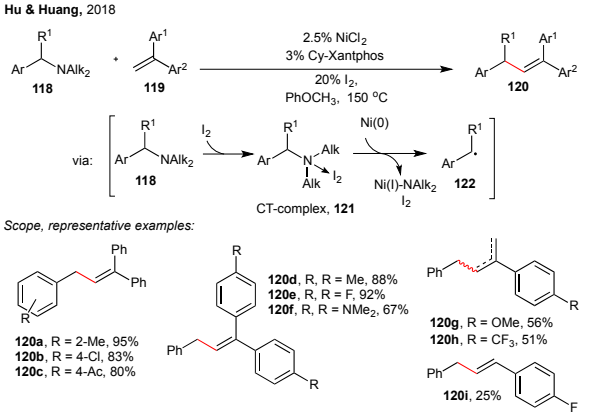
Recently, Hu and Huang reported the Ni-catalyzed Heck reaction of benzylamines **118** proceeding via a C-N bond activation (Scheme 18).[47] The reaction is believed to occur via a



Scheme 16 Ni-catalyzed Heck reaction of benzylic electrophiles



Scheme 17 Jamison's mechanism of Ni-catalyzed Heck reaction of benzylic chlorides

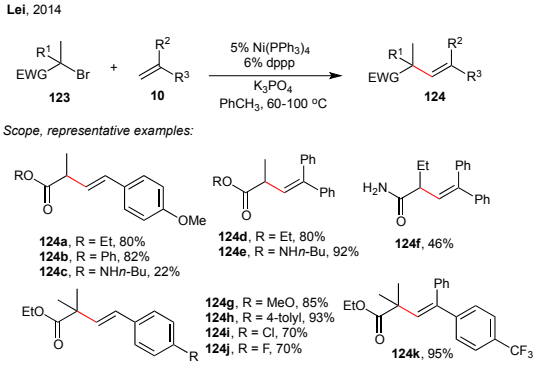


Scheme 18 Ni-catalyzed Heck reaction of benzylamines

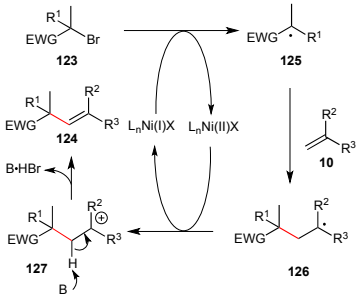
charge transfer (CT) complex **121**, which undergoes an SET with the Ni(0) catalyst to form alkyl radical species **122**. The latter can be captured with styrene derivatives to produce Heck reaction products **120a-i** in moderate to good yields.

3.2 α-Carbonyl Alkyl Halides

In 2012, Lei reported the Ni-catalyzed Heck-type reaction of α-carbonyl-substituted alkyl halides **123** with styrenes to construct α-alkenyl carbonyl derivatives **124** (Scheme 19).[48] Both amide- and ester-possessing secondary and tertiary alkyl bromides were reactive under $Ni(PPh_3)_4$/dppp-catalyzed conditions leading to the products **124a-k**. Interestingly, the authors shown that Ni(I)-complex such as $Ni(PPh_3)_4Cl$ was able to catalyze this reaction, as well. Thus, the following radical-type mechanism has been proposed (Scheme 20). Assumingly, the Ni(I) species is generated *in situ* from Ni(0)-catalyst and an alkyl bromide via an SET event. The second SET event would produce the Ni(II)-complex and alkyl radical species **125**, which undergoes radical addition to alkene to form benzylic radical **126**. A subsequent radical polar crossover process would regenerate the active Ni(I)-catalyst and produce cationic intermediate **127**, which upon base-assisted deprotonation provides the final product. The involvement of radical polar crossover pathway was supported by the presence of the lactam cyclization by-product in significant amounts in the reaction towards **124f** (Scheme 19).



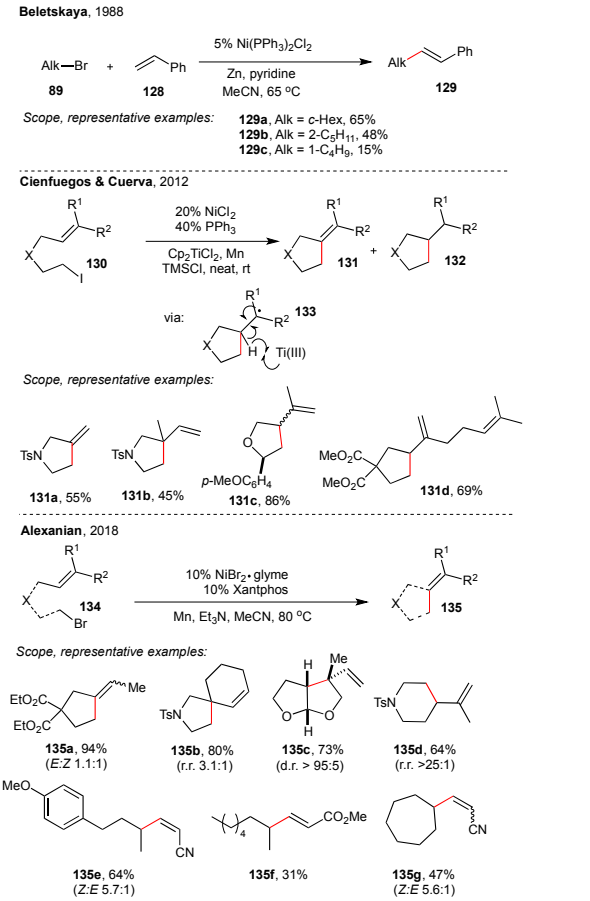
Scheme 19 Ni-catalyzed Heck reaction of α-carbonyl alkyl halides



Scheme 20 Lei's mechanism of Ni-catalyzed Heck reaction of α-carbonyl alkyl halides

3.3 Unactivated Alkyl Halides

The first example of Ni-catalyzed Heck reaction of unactivated alkyl halides was reported by Beletskaya in 1988 (Scheme 21). The $Ni(PPh_3)_4Cl_2$/Zn/pyridine system was shown



Scheme 21 Ni-catalyzed Heck reaction of unactivated alkyl halides

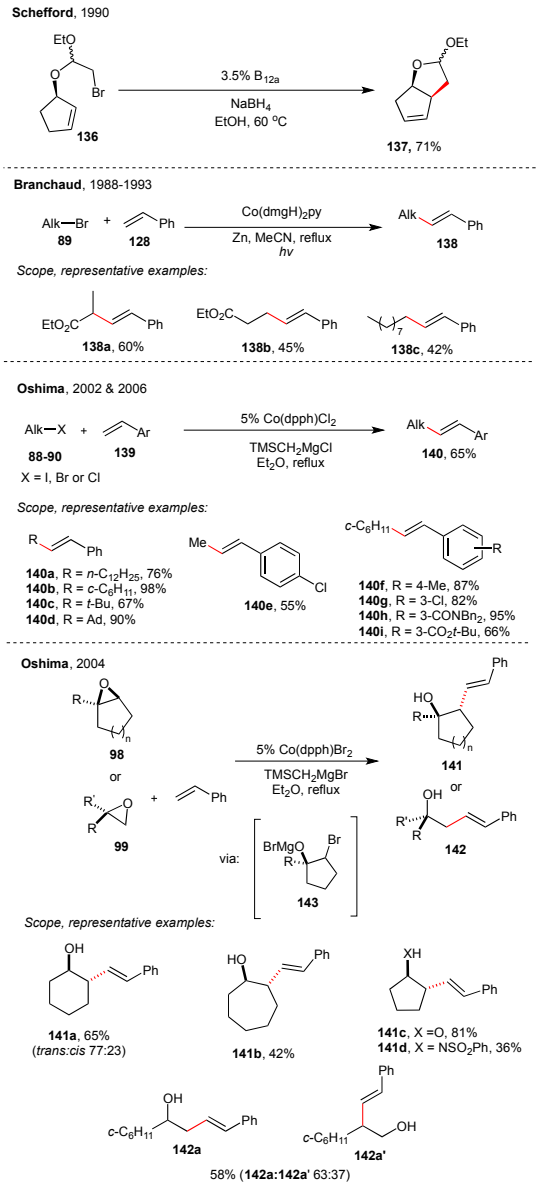
to be capable to catalyze the reaction of unactivated primary and secondary alkyl bromides with styrene toward the Heck reaction products **129a-c** in low to moderate yields.[49] In 2012, Cienfuegos and Cuerva introduced a Heck-type cyclization of alkyl iodides **130** under Ni/Ti-synergetic catalysis at room temperature (Scheme 21).[50] Interestingly, depending on the conditions, the reaction could provide either normal- or reductive Heck products (**141a-d** or **132**, respectively). In the case of standard Heck reaction conditions, the Ni(I) complex is suggested to be the active catalyst to initiate the radical-type mechanism via an SET with an alkyl iodide; whereas the role of Ti(III) is believed to execute a hydrogen atom transfer (HAT) from the intermediate **133**. The latter hypothesis seems to be consistent with the results on the more efficient production of **132** in the reactions of less hindered alkenes. This outcome is attributed to the ability of Ti(III) to irreversibly trap less bulky radical intermediates **133**, thus providing the corresponding reduced products upon acidic quenching. Recently, Alexanian developed the Ni-catalyzed intramolecular and intermolecular Heck reactions of alkyl bromides **134** (Scheme 21).[51] Employing Ni/Xantphos catalyst and Mn reductant, this reaction produced cyclized products **135a-d** in good yields and enhanced alkene regioselectivity compared to the previously developed Pd-catalyzed carbocyclizations.[35] Moreover, using these conditions, an intermolecular coupling of primary and secondary alkyl bromides with electron-deficient alkenes was accomplished, as well (products **135e-g**). Mechanistic studies suggested a radical-type scenario commenced by an SET between Ni(0) and an alkyl bromide. In contrast to the Pd-catalyzed carbocyclization of

alkyl bromides,[35] no ATRC product was observed in the course of this transformation.

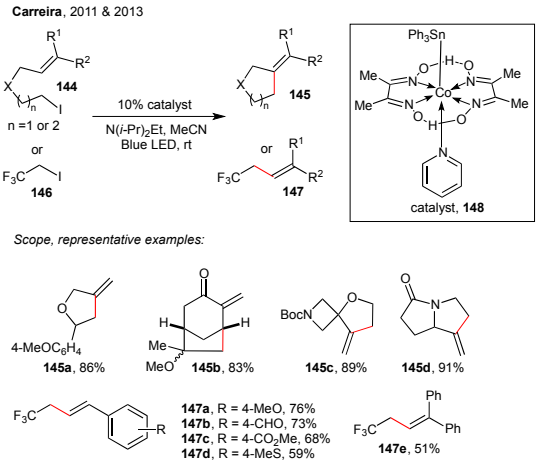
4 Co-Catalyzed Heck-type Reactions

The area of Co-catalyzed alkylation reactions has arisen after the seminal discovery by Tada on the generation of alkyl radicals from alkyl halides in the presence of cobaloxime(I)-catalyst.[52] A number of reports on Co-catalyzed Heck reaction on intramolecular fashion by Schefford[53] and others,[54] as well as on intermolecular fashion by Branchaud,[55] appeared at the early stage of its development (Scheme 22). These initial protocols usually employed strong reductive conditions, and electrochemical or photoinduced activation of cobalamin (B_{12a}) or cobaloxime complexes. In 2002, and his follow up work in 2006, Oshima reported the Co-catalyzed Heck reaction of alkyl halides in the presence of Grignard reagent, such as Me_3SiCH_2MgCl (Scheme 22).[56] Alkyl iodides, bromides, and even chlorides reacted efficiently with styrene derivatives, producing the Heck reaction products **140a-i** in good yields. Spectroscopic and crystallographic studies supported an SET process between the *in situ*-generated Co(0)-complex and an alkyl halide leading to the alkyl radical species engaged in the hybrid-radical mechanism. In 2004, the same group applied these conditions towards Heck reaction of epoxides **98-99** (Scheme 22).[57] The reaction proceeded through an *in situ* generation of 2-bromo magnesium methoxide **143** followed by the Co-catalyzed Heck reaction of alkyl bromides analogously to the prior work.[56] The reaction was fairly effective for Heck reaction of symmetrical epoxides (**141a-d**), while asymmetrical substrates yielded a mixture of regioisomers (**142a** and **142a'**).

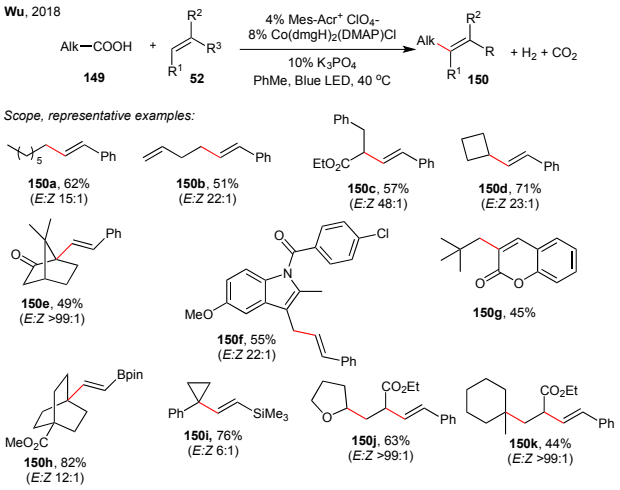
In 2011, Carreira developed a room temperature visible light-induced intramolecular Heck reaction employing a cobaloxime catalyst **148** (Scheme 23).[58] In contrast to the previously reported Co-catalyzed Heck reactions, the method relied on the Hunig's base [$N(i\text{-}Pr)_2Et$]-promoted Co(I)-catalyst turnover via the deprotonation of the Co(III)–H intermediate. Therefore, strong reductants such as RMgX or Zn were no longer required, which significantly expanded the functional group compatibility of the Co-catalyzed Heck reaction. Excitingly, the authors were able to apply this mild protocol for the late-stage cyclization step in the total synthesis of (+)-Daphmanidin.[58] Later, Carreira reported an intermolecular version of this coupling using 2,2,2-trifluoroethyl iodide **146** and styrene derivatives (Scheme 23).[59] Both intramolecular and intermolecular Heck reaction proceeded uneventfully, generating the Heck products in good to excellent yields (Scheme 23, **145a-d**, **147a-e**). Sensitive functionalities such as amides, esters, ketones, and aldehydes were well tolerated. Recently, Wu and co-workers developed a room temperature Heck reaction of widely available alkyl carboxylic acids **149** using an organo photo-redox/cobaloxime dual catalysis (Scheme 24).[60] The scope of this reaction was fairly broad as primary, secondary and tertiary alkyl radicals, generated from carboxylic acids, could be efficiently coupled with vinyl arenes/heteroarenes leading to the corresponding products **150a-g** in good to excellent yields. Vinyl boronates and vinyl silanes (products **150h** and **150i**, respectively) were also shown to be competent alkene coupling partners in this



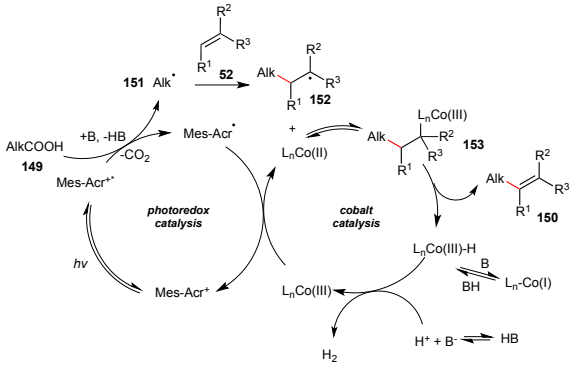
Scheme 22 Co-catalyzed Heck reactions using strong reducing reagents



Scheme 23 Carreira's Co-catalyzed Heck reaction using Hunig's base



Scheme 24 Wu's Co-catalyzed Heck reaction of carboxylic acids

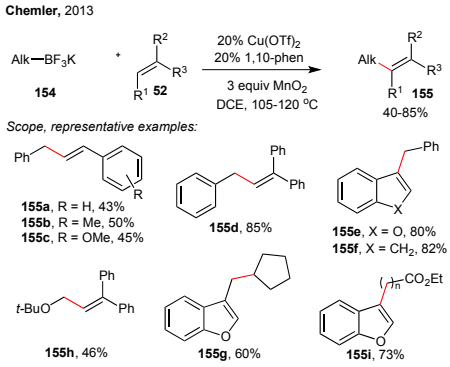


Scheme 25 Wu's mechanism of Co-catalyzed Heck reaction of carboxylic acids

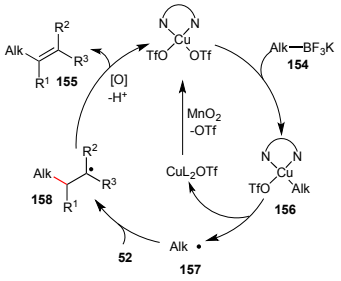
reaction, which further extended the synthetic utility of this protocol. Moreover, under the developed conditions, an unprecedented three-component coupling of alkyl carboxylic acid, acrylates, and styrenes was demonstrated to afford highly functionalized vinyl arenes in good yields as single regioisomers with exclusive *E* configuration (products **150j**, **150k**). Mechanistic studies, as well as the DFT calculations, supported a radical-type mechanism (Scheme 25). According to which, an SET process from the carboxylate to the excited Mes-Acr+* is followed by radical decarboxylation to produce an alkyl radical species **151**. A subsequent trapping of the latter by an alkene, and then by the Co(II)-catalyst leads to alkyl-Co(III)-species **153**, which undergoes a *β*-H elimination towards the Heck reaction product **151** and Co(III)-H species. Deprotonation of this species, followed by an SET with the reduced photocatalyst regenerates the both active catalysts, Co(II)L_n, and Mes-Acr$^+$. This represents the first method for the Heck reaction of unactivated alkyl carboxylic acids, with H_2 and CO_2 being the only by-products.

5 Cu-Catalyzed Heck-type Reactions

In 2013, Chemler group reported the first Cu-catalyzed alkyl Heck reaction (Scheme 26). In contrast to many alkyl-Heck reactions, this reaction employed alkyl nucleophiles, such as

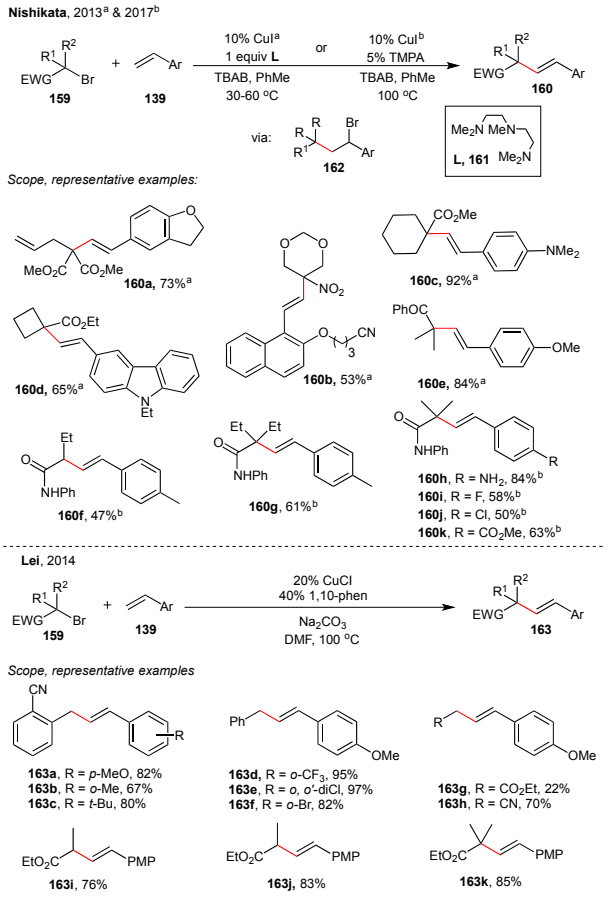


Scheme 26 Chemler's Cu-catalyzed Heck reaction of alkyl trifluoroborates

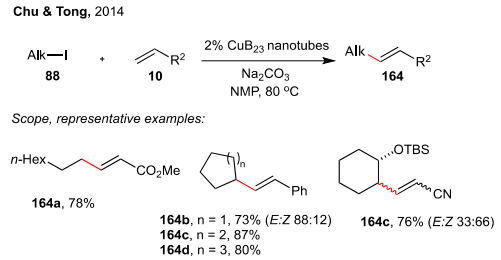


Scheme 27 Chemler's mechanism of Cu-catalyzed Heck reaction of alkyl trifluoroborates

alkyltrifluoroborates **154**, as coupling partners for alkenes.[61] The outcome of the TEMPO-trapping and radical clock experiments indicated the radical nature for this transformation. The authors proposed that, under oxidative conditions, generation of alkyl radical species **157** and Cu(I) species occurs via homolysis of the Cu-C bond in the complex **156**, which formed via transmetalation of Cu(II)-catalyst with alkyl trifluoroborate **154** (Scheme 27). Addition of **157** to an alkene, followed by a subsequent oxidation and deprotonation produces the Heck reaction product **155**. Yet, to regenerate the catalyst, Cu(I) species has to be oxidized by an external oxidant such as MnO_2. This oxidative transformation features a quite general scope with regards to the trifluoroborate salt as benzyl, primary, and secondary substrates could efficiently react with styrene derivatives to afford the Heck products **155a-i** in good yields. In the same year, Nishikata developed the Cu(I)/triamine (**161**)-catalyzed Heck reaction of activated tertiary alkyl bromides **159** with styrenes (Scheme 28).[62] Ester, nitro, or keto group-possessing tertiary alkyl bromides were demonstrated to couple with electron-rich styrenes (products **160a-e**) under mild conditions, assumingly via the formation of ATRA intermediate **162**. The TEMPO-trapping experiment confirmed the intermediacy of tertiary alkyl radical species in this reaction. Later, the same group introduced a modified Cu(I)/triamine-based catalytic system to accomplish the Heck reaction of amido-possessing alkyl bromides, unreactive in the previous conditions,[62] with both electron-rich and -deficient styrene derivatives (Scheme 28).[63] The reaction required higher temperatures and tri-(2-picolyl)amine (TMPA) as a ligand to furnish products **160f-k** in reasonable yields. In 2014, Lei developed the Cu(I)/1,10-phen-catalyzed Heck reaction of primary benzylic and activated secondary and tertiary alkyl



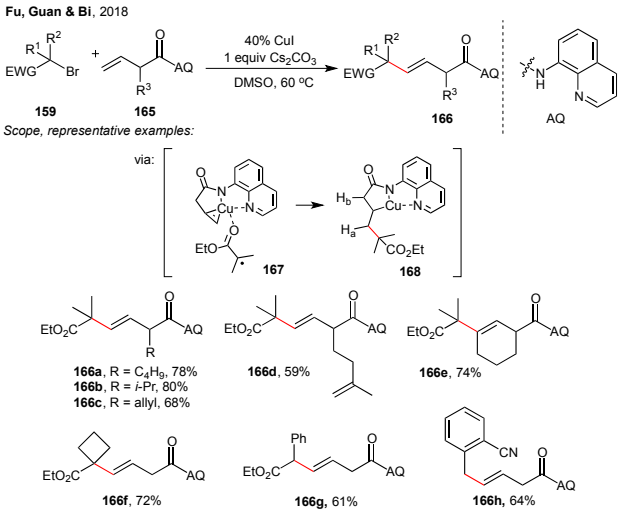
Scheme 28 Cu-catalyzed Heck reaction of activated alkyl halides



Scheme 29 Cu-catalyzed Heck reaction of unactivated alkyl halides

bromides with electron-rich styrenes (Scheme 28, products **163a-k**).[64] An EPR experiment supported the SET event between the Cu(I)-catalyst and an alkyl bromide. In 2014, Chu and Tong synthesized Cu-B alloy short nanotubes, which were found to be capable of catalyzing the Heck reaction of unactivated alkyl iodides **88** under ligand-free conditions (Scheme 29).[65] Under these conditions, primary and secondary substrates reacted smoothly, assumingly via a radical pathway (products **164a-c**). This method provided slightly superior yields compared to the Pd-catalyzed Heck reaction.[37] Moreover, the catalyst showed a great recycling performance.

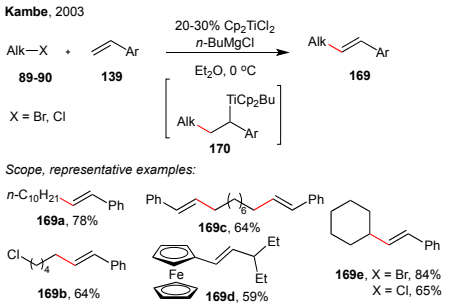
Regioselectivity has been an issue in the Heck reactions of unactivated aliphatic olefins due to the indiscriminable C–H sites for β-H elimination. Very recently, the first regioselective Heck reaction of alkyl bromides with unactivated aliphatic olefins was reported by Bi and co-workers (Scheme 30).[66] The



Scheme 30 Fu, Guan & Bi's directed Cu-catalyzed Heck reaction of unactivated olefins

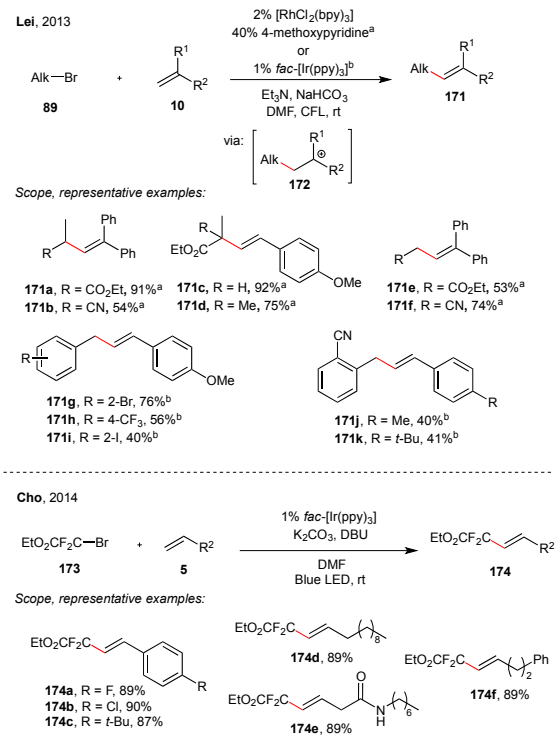
high reactivity and regioselectivity of this transformation were governed by the amino quinolone directing group (AQ) on the alkene (**165**), whose coordination to the Cu(I)-catalyst activated the double bond (**167**), as well as provided the control of the regioselectivity for the β-H elimination step (**168**). Detailed mechanistic studies and DFT calculations indicated a radical pathway involving a dimethyl sulfoxide-assisted concerted H–Br elimination event of a conformationally strained Cu(III) cyclic transition state. Activated primary, secondary, as well as tertiary alkyl bromides, were capable substrates in this reaction (products **166a-h**).

6 Other Metals in Heck-type Reactions

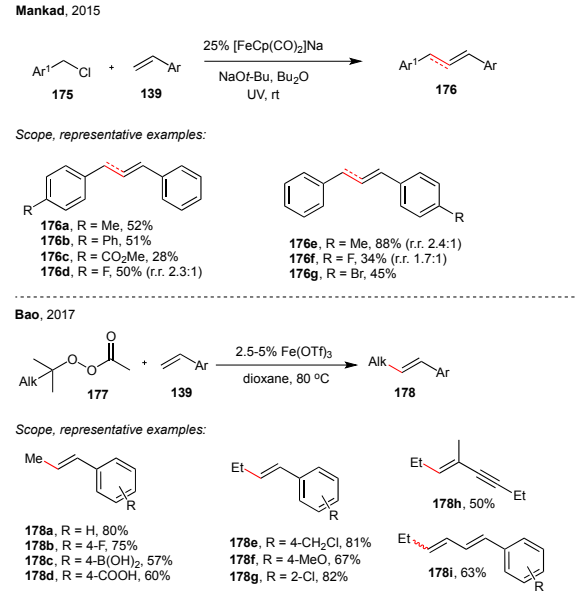


Scheme 31 Ti-catalyzed Heck reaction

In 2003, Kambe reported titanocene-catalyzed Heck-type reaction of alkyl halides with vinyl arenes (Scheme 31).[67] The reaction proceeded efficiently at 0 °C for unactivated primary and secondary alkyl bromides and even chlorides (products **169a-e**), however, considerable amounts of by-products were observed in some cases. The Ti(III)-complex formed *in situ* from Ti(IV)-catalyst and Grignard reagent is believed to generate alkyl radicals, as well as to trap the benzylic radical intermediate towards an alkyl Ti(IV) species **170**, which upon β-H elimination delivers the Heck product **169**. In 2013, Lei group

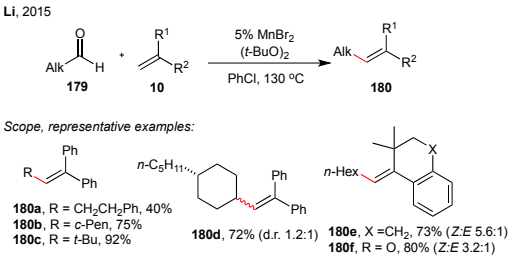


Scheme 32 Rh- and Ir-catalyzed Heck reactions

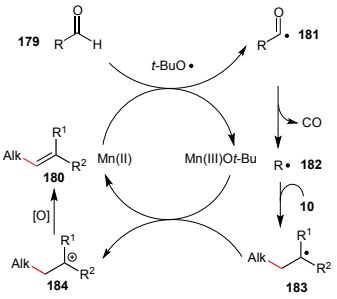


Scheme 33 Fe-catalyzed Heck reactions

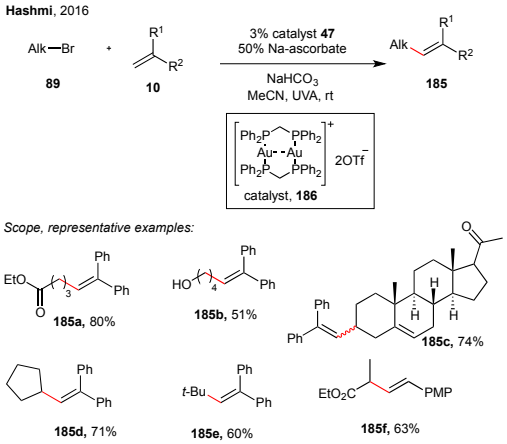
applied Rh- and Ir-photoredox catalysis for the Heck reaction of activated alkyl bromides with vinyl arenes (Scheme 32).[68] The reaction operates via a radical-polar crossover pathway, where a photoredox catalyst is involved in an SET with an alkyl bromide, and in oxidation of the benzylic radical intermediate towards the carbocation **172**. Activated tertiary and secondary alkyl bromides reacted efficiently under the Rh-catalyzed conditions (**171a-f**), whereas activated primary alkyl bromides required Ir-catalyzed conditions for the same coupling (**171g-k**). Later, Cho employed ethyldifluoroacetate (**173**) in a photoinduced Ir-catalyzed Heck reaction (Scheme 32).[69] Besides styrene derivatives (products **174a-c**), unactivated aliphatic alkenes (products **174d-f**) were also capable partners in the reactions with alkyl bromide **173**, which is quite rare for alkyl-Heck reactions. In 2015, the Fe-catalyzed Heck reaction of benzyl chlorides **175** under UV-irradiation was reported by Mankad (Scheme 33).[70] The authors favored a classical Heck reaction mechanism for this transformation, where UV irradiation promoted the CO dissociation to reveal reactive coordinatively unsaturated Fe-containing intermediates. A radical-type process was considered to be an unproductive pathway under these conditions, competing with the Heck reaction and leading to decomposition. Therefore, the reaction suffered from moderate yields and regioselectivity due to alkene isomerization (products **176a-g**). In 2017, Bao reported another Fe-catalyzed Heck reaction using peresters **177** as the source of alkyl radicals (Scheme 33). [71] This reaction was proposed to occur via radical-polar crossover mechanism initiated by the Fe(II)-catalyst. Methylated and ethylated styrene derivatives



Scheme 34 Mn-catalyzed Heck reaction



Scheme 35 Li's mechanism of Mn-catalyzed Heck reaction



Scheme 36 Au-catalyzed Heck reaction

178a-g, enynes **178h**, and dienes **178i** were obtained in reasonable yields under these conditions. In 2014, decarbonylative Heck-type reaction employing *tert*-butyl peroxide and a catalytic amount of $MnBr_2$ was reported by Li (Scheme 34).[72] Under peroxide-induced H-atom abstraction from aldehyde **179** the carbonyl radical **181** is formed, which upon releasing CO fragments into an alkyl radical **182** (Scheme 35). The subsequent radical addition of the latter at the alkene, followed by oxidation and deprotonation furnishes the Heck-type product **180**. The reaction proceeds well with primary, secondary, and tertiary aldehydes, however is limited to 1,1-disubstituted styrenes (products **180a-f**). In 2016, Hashmi group showed that dinuclear gold-complex **47** could catalyze a Heck reaction of alkyl bromides under UVA-irradiation (315-400 nm) (Scheme 36).[73] In this reaction, electron-rich vinyl arenes were efficiently alkylated with primary, secondary, and tertiary alkyl bromides to afford Heck products **185a-f** in good yields. The method was also applicable for the late-stage functionalization of complex molecule, such as pregnenolone derivative (**185c**). Mechanistic studies supported the Au-catalyzed radical polar-crossover mechanism induced by an SET from the photoexcited Au(I)-Au(I) complex to an alkyl bromide.

7 Conclusion

Although, the first alkyl-Heck reaction was reported by R. Heck in his original work, this transformation remained underdeveloped until recently, especially for unactivated hindered alkyl halides possessing eliminable β-hydrogens. However, a merge of radical- and transition metal-catalyzed approaches has significantly driven this area. Nowadays, in addition to Pd, other transition metals such as Ni, Co, Cu, Fe, and others were shown to efficiently catalyze Heck-type reaction, generally following a hybrid-organometallic radical mechanism. Unactivated alkyl electrophiles possessing eliminable β-hydrogens appeared to be non-problematic for this mechanism. Moreover, the employment of mild photoinduced conditions has further broadened the scope of alkyl-Heck reaction. Although, a significant effort has been made to expand the scope with regards to the alkyl component, the scope of the alkenes remains mostly limited to good radical acceptors such as styrenes and acrylate derivatives. Examples of alkylation of unactivated aliphatic alkenes are rare. Therefore, the future direction of this transformation may rely on the development of new systems that would enable unactivated alkenes to undergo selective and efficient Heck-type reaction. Obviously, the detailed mechanistic studies are warranted for better understanding the alkyl Heck-type reactions.

Funding Information

We thank the National Institutes of Health (GM120281) and National Science Foundation (CHE-5 1663779) for the financial support of this work.

References

(1) (a) Oestreich, M. *The Mizoroki-Heck Reaction*; Wiley: Chichester, **2009**. (b) Gharpure, S. J.; Shelke, Y. G.; Reddy, S. R. B. *RSC Advances* **2014**, *4*, 46962. (c) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707. (d) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. (e) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133. (f) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

(2) Meijere, A. d.; Bräse, S.; Oestreich, M. *Metal-Catalyzed Cross-Coupling Reactions and More*; Wiley: Weinheim, **2014**.

(3) (a) Biajoli, A. F. P.; Schwalm, C. S.; Limberger, J.; Claudino, T. S.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2014**, *25*, 2186. (b) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (c) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086. (d) Majid, M. H.; Razieh, M.; Masoumeh, M. *Curr. Org. Chem.* **2018**, *22*, 165.

(4) Roy, D.; Uozumi, Y. *Adv. Synth. Catal.* **2018**, *360*, 602.

(5) Wang, S.-S.; Yang, G.-Y. *Cat. Sci. Tech.* **2016**, *6*, 2862.

(6) Mc Cartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122.

(7) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (c) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (d) de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed.* **1995**, *33*, 2379.

(8) Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 4030.

(9) (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (b) Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070. (c) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(10) (a) Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790. (b) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588.

(11) (a) Newcomb, M.; Toy, P. H. *Acc. Chem. Res.* **2000**, *33*, 449. (b) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197.

(12) (a) Wang, C.; Lei, Y.; Guo, M.; Shang, Q.; Liu, H.; Xu, Z.; Wang, R. *Org. Lett.* **2017**, *19*, 6412. (b) Fan, J.-H.; Wei, W.-T.; Zhou, M.-B.; Song, R.-J.; Li, J.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 6650. (c) Kancherla, R.; Muralirajan, K.; Maity, B.; Zhu, C.; Krach, P. E.; Cavallo, L.; Rueping, M. *Angew. Chem., Int. Ed.* **2018**, doi: 10.1002/anie.201811439.

(13) Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synthesis* **1995**, *1995*, 245.

(14) Higuchi, K.; Sawada, K.; Nambu, H.; Shogaki, T.; Kita, Y. *Org. Lett.* **2003**, *5*, 3703.

(15) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725.

(16) Hu, Y.-m.; Zhou, J.; Long, X.-t.; Han, J.-l.; Zhu, C.-j.; Pan, Y. *Tetrahedron Lett.* **2003**, *44*, 5009.

(17) Kazuhiro, N.; Isao, S.; Akio, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 799.

(18) Hirohisa, N.; Akio, Y.; Isao, S. *Chem. Lett.* **2004**, *33*, 348.

(19) Yang, Z.; Zhou, J. *J. Am. Chem. Soc.* **2012**, *134*, 11833.

(20) Wu, G. Z.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507.

(21) Liu, Z.; Shi, C.; Chen, Y. *Synlett* **2008**, *2008*, 1734.

(22) Zhou, W.; An, G.; Zhang, G.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2011**, *9*, 5833.

(23) (a) Mori, M.; Oda, I.; Ban, Y. *Tetrahedron Lett.* **1982**, *23*, 5315. (b) Mori, M.; Kanda, N.; Oda, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 5465.

(24) Glorius, F. *Tetrahedron Lett.* **2003**, *44*, 5751.

(25) Kurandina, D.; Rivas, M.; Radzhabov, M.; Gevorgyan, V. *Org. Lett.* **2018**, *20*, 357.

(26) Chen, Q.-Y.; Yang, Z.-Y.; Zhao, C.-X.; Qiu, Z.-M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 563.

(27) Surapanich, N.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V. *Eur. J. Org. Chem.* **2012**, *2012*, 5943.

(28) Feng, Z.; Min, Q.-Q.; Zhao, H.-Y.; Gu, J.-W.; Zhang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1270.
(29) Fan, T.; Meng, W.-D.; Zhang, X. *Beilstein J. Org. Chem.* **2017**, *13*, 2610.
(30) Parasram, M.; Iaroshenko, V. O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014**, *136*, 17926.
(31) Kurandina, D.; Parasram, M.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2017**, *56*, 14212.
(32) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340.
(33) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146.
(34) Bloome, K. S.; Alexanian, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 12823.
(35) Venning, A. R. O.; Kwiatkowski, M. R.; Roque Peña, J. E.; Lainhart, B. C.; Guruparan, A. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2017**, *139*, 11595.
(36) Dong, X.; Han, Y.; Yan, F.; Liu, Q.; Wang, P.; Chen, K.; Li, Y.; Zhao, Z.; Dong, Y.; Liu, H. *Org. Lett.* **2016**, *18*, 3774.
(37) McMahon, C. M.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5974.
(38) Zou, Y. J.; Zhou, J. R. *Chem. Commun.* **2014**, *50*, 3725.
(39) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 18307.
(40) Gevorgyan, V.; Chuentragool, P.; Yadagiri, D.; Morita, T.; Sarkar, S.; Parasram, M.; Wang, Y. *Angew. Chem., Int. Ed.* **2018**, doi:10.1002/anie.201812398.
(41) Teng, S.; Tessensohn, M. E.; Webster, R. D.; Zhou, J. S. *ACS Catal.* **2018**, *8*, 7439.
(42) (a) Wang, G.-Z.; Shang, R.; Fu, Y. *Org. Lett.* **2018**, *20*, 888. (b) Koy, M.; Sandfort, F.; Tlahuext-Aca, A.; Quach, L.; Daniliuc, C. G.; Glorius, F. *Eur. J. Chem.* **2018**, *24*, 4552.
(43) Matsubara, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 6880.
(44) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020.
(45) Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585.
(46) Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825.
(47) Yu, H.; Hu, B.; Huang, H. *J. Org. Chem.* **2018**, *83*, 13922.
(48) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638.
(49) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253.
(50) Millán, A.; Álvarez de Cienfuegos, L.; Miguel, D.; Campaña, A. G.; Cuerva, J. M. *Org. Lett.* **2012**, *14*, 5984.
(51) Kwiatkowski, M. R.; Alexanian, E. J. *Angew. Chem., Int. Ed.*, *2018*, doi:10.1002/anie.201810757.
(52) Okabe, M.; Abe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 1775.
(53) Busato, S.; Tinembart, O.; Zhang, Z.-d.; Scheffold, R. *Tetrahedron* **1990**, *46*, 3155.
(54) (a) Giese, B.; Erdmann, P.; Göbel, T.; Springer, R. *Tetrahedron Lett.* **1992**, *33*, 4545. (b) Torii, S.; Inokuchi, T.; Yukawa, T. *J. Org. Chem.* **1985**, *50*, 5875. (c) Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1984**, *25*, 4317.
(55) (a) Branchaud, B. P.; Meier, M. S.; Choi, Y. *Tetrahedron Lett.* **1988**, *29*, 167. (b) Branchaud, B. P.; Yu, G. X. *Organometallics* **1993**, *12*, 4262. (c) Branchaud, B. P.; Detlefsen, W. D. *Tetrahedron Lett.* **1991**, *32*, 6273. (d) Branchaud, B. P.; Meier, M. S. *J. Org. Chem.* **1989**, *54*, 1320. (e) Branchaud, B. P.; Choi, Y. L. *Tetrahedron Lett.* **1988**, *29*, 6037. (f) Branchaud, B. P.; Meier, M. S. *Tetrahedron Lett.* **1988**, *29*, 3191.
(56) (a) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514. (b) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068.
(57) Ikeda, Y.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Adv. Synth. Catal.* **2004**, *346*, 1631.
(58) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11125.
(59) Kreis, L. M.; Krautwald, S.; Pfeiffer, N.; Martin, R. E.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 1634.
(60) Cao, H.; Jiang, H.; Feng, H.; Kwan, J. M. C.; Liu, X.; Wu, J. *J. Am. Chem. Soc.* **2018**, *140*, 16360.
(61) Liwosz, T. W.; Chemler, S. R. *Org. Lett.* **2013**, *15*, 3034.
(62) Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc.* **2013**, *135*, 16372.
(63) Nishikata, T.; Itonaga, K.; Yamaguchi, N.; Sumimoto, M. *Org. Lett.* **2017**, *19*, 2686.
(64) Zhang, X.; Yi, H.; Liao, Z.; Zhang, G.; Fan, C.; Qin, C.; Liu, J.; Lei, A. *Org. Biomol. Chem.* **2014**, *12*, 6790.
(65) (a) Yang, F.; Fu, S. Y.; Chu, W.; Li, C.; Tong, D. G. *Rsc Advances* **2014**, *4*, 45838. (b) Fu, S. Y.; Li, Y. Z.; Chu, W.; Lia, C.; Tong, D. G. *Cat. Sci. Tech.* **2015**, *5*, 1638.
(66) Tang, C.; Zhang, R.; Zhu, B.; Fu, J.; Deng, Y.; Tian, L.; Guan, W.; Bi, X. *J. Am. Chem. Soc.* **2018**, doi: 10.1021/jacs.8b10874.
(67) Jun, T.; Hiroyasu, W.; Masako, M.; Nobuaki, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2209.
(68) Liu, Q.; Yi, H.; Liu, J.; Yang, Y.; Zhang, X.; Zeng, Z.; Lei, A. *Eur. J. Chem.* **2013**, *19*, 5120.
(69) Yu, C.; Iqbal, N.; Park, S.; Cho, E. J. *Chem. Commun.* **2014**, *50*, 12884.
(70) Waldhart, G. W.; Mankad, N. P. *J. Organomet. Chem.* **2015**, *793*, 171.
(71) Zhu, N.; Zhao, J.; Bao, H. *Chem Sci* **2017**, *8*, 2081.
(72) Zong, Z.; Wang, W.; Bai, X.; Xi, H.; Li, Z. *Asian J. Org. Chem.* **2015**, *4*, 622.
(73) Xie, J.; Li, J.; Weingand, V.; Rudolph, M.; Hashmi, A. S. K. *Eur. J. Chem.* **2016**, *22*, 12646.

Biographical Sketches

Daria Kurandina received her BS from St. Petersburg State University, Russia. In 2014, she joined Gevorgyan's group at the University of Illinois at Chicago as a PhD student. Her work focuses on the development of novel transition metal-catalyzed synthetic methodologies.

Padon Chuentragool obtained his BS and MS degrees from Chulalongkorn University, Bangkok, Thailand. He received his PhD in 2018 under guidance of Prof. Gevorgyan at the University of Illinois at Chicago, where he was focusing on the development of selective methods for C(sp^3)-H functionalizations via photoexcited Pd-catalysis.

Vladimir Gevorgyan received his PhD in 1984 from the Latvian Institute of Organic Synthesis, where then he worked as a group leader. After postdoctoral research at Tohoku University with Prof. Y. Yamamoto as the JSPS- and then Ciba Geigy International Postdoctoral Fellow, in 1996 he joined the faculty position there. In 1999, he moved to UIC as an Associate Professor, and was promoted to the Full Professor in 2003. From 2012, he is a Distinguished Professor of LAS. His group is interested in the development of novel synthetic methodologies.