

Transition-Metal-Catalyzed Alkyl Heck-Type Reactions

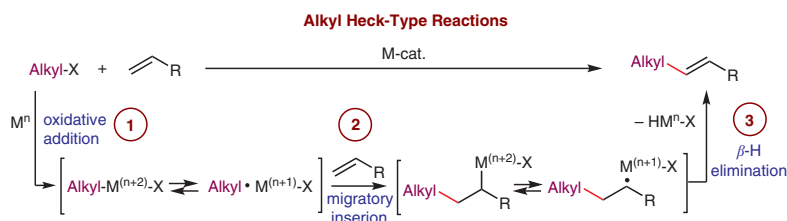
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Abstract The Heck reaction is one of the most reliable and useful strategies for the construction of C–C bonds in organic synthesis. However, in contrast to the well-established aryl Heck reaction, the analogous reaction employing alkyl electrophiles is much less developed. Significant progress in this area was recently achieved by merging radical-mediated and transition-metal-catalyzed approaches. This review summarizes the advances in alkyl Heck-type reactions from its discovery early in the 1970s up until the end of 2018.

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

1 Introduction

The Mizoroki–Heck reaction¹ 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 enabling coupling of aryl and vinyl electrophiles with olefins.

The Heck reaction has been exhaustively employed in organic synthesis, drug discovery, electronics, and in industry,³ which has led to its recognition with a Nobel Prize in 2010. Current research in this area is directed towards the use of decreased loadings of palladium,⁴ the employment of low-cost transition metals,⁵ and the development of asymmetric protocols.⁶ Historically, aryl halides/pseudohalides were the electrophiles of choice for all cross-coupling reactions, thus, not surprisingly, they were also extensively used in Heck reactions. Throughout years, this research has been summarized in many excellent reviews.⁷ In contrast, alkyl electrophiles were found to be more challenging coupling partners, mostly due to the competing β -H elimination process² and the slower rates of the oxidative addition step.⁸ Nonetheless, under more recently developed conditions, alkyl halides⁹ were shown to be suitable partners for this transformation. However, the number of reports on alkyl Heck reactions remains scarce compared to those employing aryl substrates.

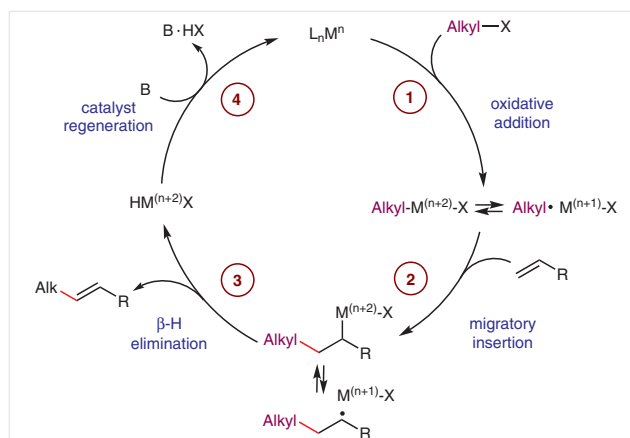
In general, alkyl Heck reactions feature the same mechanism as the classical Heck reaction between aryl halides and alkenes, involving: (1) oxidative addition, (2) migratory insertion, (3) β -hydrogen elimination, and (4) catalyst regeneration steps (Scheme 1). However, in contrast to the aryl Heck reaction, its alkyl version is often presumed to involve radical intermediates, thus operating via a hybrid organometallic–radical scenario. Mechanistic studies, such as radical trapping,¹⁰ radical clock experiments,¹¹ as well as ESR studies, have proved the presence of radical species in some 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 alkyl Heck reactions to be accomplished under milder conditions; over recent years this area of research has grown significantly. 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 organized by the type of electrophile used, such as benzylic, activated (possessing a carbonyl or equivalents at the β -position), perfluorinated, and unactivated alkyl electrophiles. Related transformations, such as Heck-type reactions involving a β -X elimination step and cascade transformations commencing with radical addition to 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 an alkyl halide with an 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 Bu₃N as the base to deliver a regiomer mixture of alkenes **3**. In 1995, Zhuangyu and co-workers developed a base-free alkyl Heck reaction of benzyltris(*n*-butyl)ammo-



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

nium bromide salts **4** toward exclusive formation of the conjugated products **6** (Scheme 2).¹³ Both electron-rich and electron-deficient alkenes **5** were efficiently benzylated under these conditions. Based on ESR studies, the authors suggested the involvement of benzyl radicals, which would form via the reductive cleavage of the benzyl quaternary ammonium salt in the presence of the palladium(0) species. Later, the coupling of benzyl chlorides with olefins was ele-

Biographical Sketches



Daria Kurandina received her BS degree from St. Petersburg State University, Russia. In 2014, she joined Prof. 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.

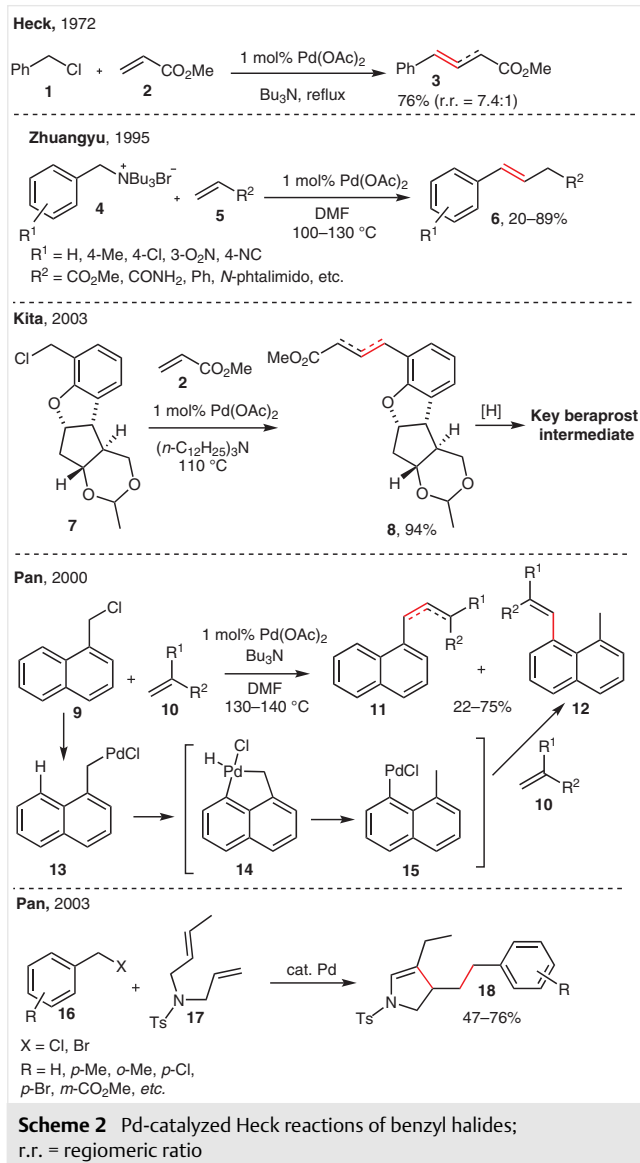
Padon Chuentragool obtained his BS and MS degrees from Chulalongkorn University, Bangkok, Thailand. He received his PhD in

2018 under the guidance of Prof. Gevorgyan at the University of Illinois at Chicago, where his work focused on the development of selective methods for C(sp³)-H functionalizations via photoexcited Pd catalysis.

Vladimir Gevorgyan received his PhD in 1984 from the Latvian Institute of Organic Synthesis, where he then worked as a group leader. After postdoctoral research at Tohoku University with Prof. Y. Yamamoto as a

JSPS Postdoctoral Fellow and then as a Ciba-Geigy International Postdoctoral Fellow, he joined the faculty at the same institute in 1996. In 1999, he moved to the University of Illinois at Chicago (UIC) as an associate professor and was promoted to full professor in 2003. In 2012, he received the LAS Distinguished Professor Award. His group is interested in the development of novel synthetic methodologies.

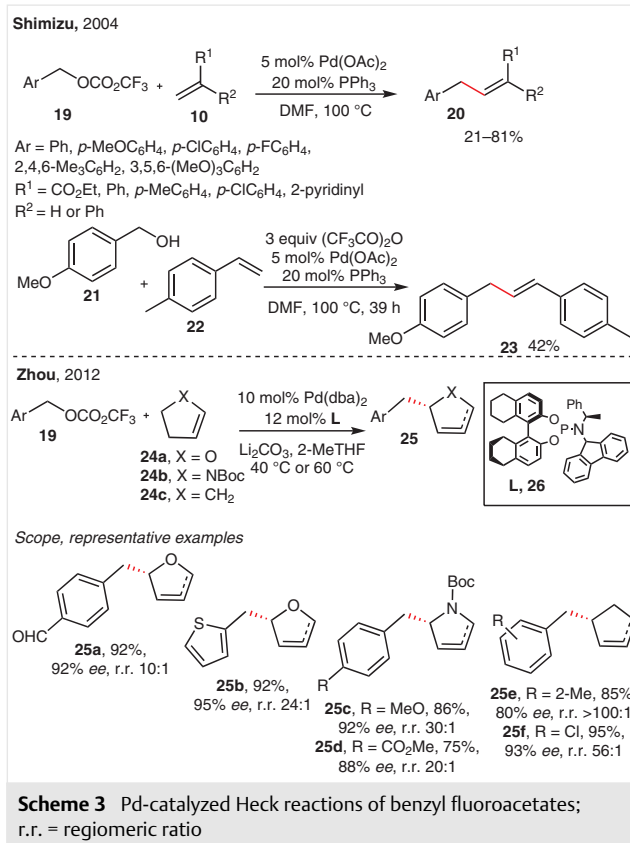
gantly utilized by Kita to obtain the key intermediate **8** in the synthesis of beraprost, a vasodilator and antiplatelet agent (Scheme 2).¹⁴ In this work, the Heck reaction followed by hydrogenation was shown to be superior over other methods tested for installation of an alkyl chain at the benzylic position of compound **7**.



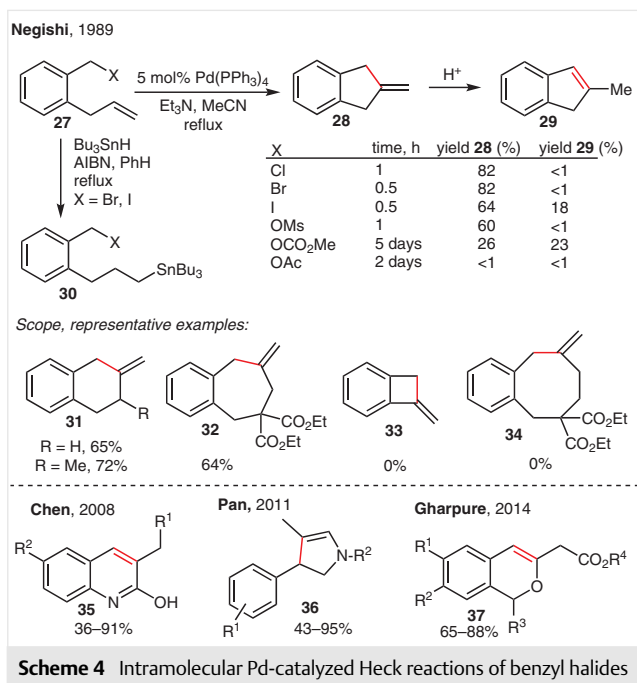
In 2000, Pan and co-workers observed an interesting Pd-catalyzed rearrangement in the vinylation reaction of α -chloromethylnaphthalene (**9**) (Scheme 2).¹⁵ In reactions with *N*-vinylimides, besides the expected Heck products **11**, a product with an olefin attached at the *peri* position of the naphthalene ring was detected. This unusual rearrangement product **12** was proposed to form via the cyclopalladation intermediate **14**, when the nitrogen-containing

alkene served as a stabilizing ligand for benzylpalladium species **13**. Later, Pan described the Pd-catalyzed cascade reaction of benzyl halides with *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-coordinated Pd(0) led 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*-methylstyrene (**22**) with *p*-methoxybenzyl alcohol (**21**) using trifluoroacetic anhydride as an additive. Later, Zhou introduced an asymmetric Heck reaction of benzyl trifluoroacetates **19** with five-membered cyclic olefins **24**.¹⁹ In the presence of Pd/phosphoramidite ligand **26**, 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 with 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 on the *o*-allylbenzyl electrophile **27** revealed that Cl, Br, and OMes were acceptable leaving groups, leading almost exclusively to the formation of 2-methyleneindane (**28**). In the cases of I and OCO₂Me leaving groups, the cyclization occurred quite efficiently but with low regioselectivity, as the formation of regioisomer **29** was detected in significant amounts.



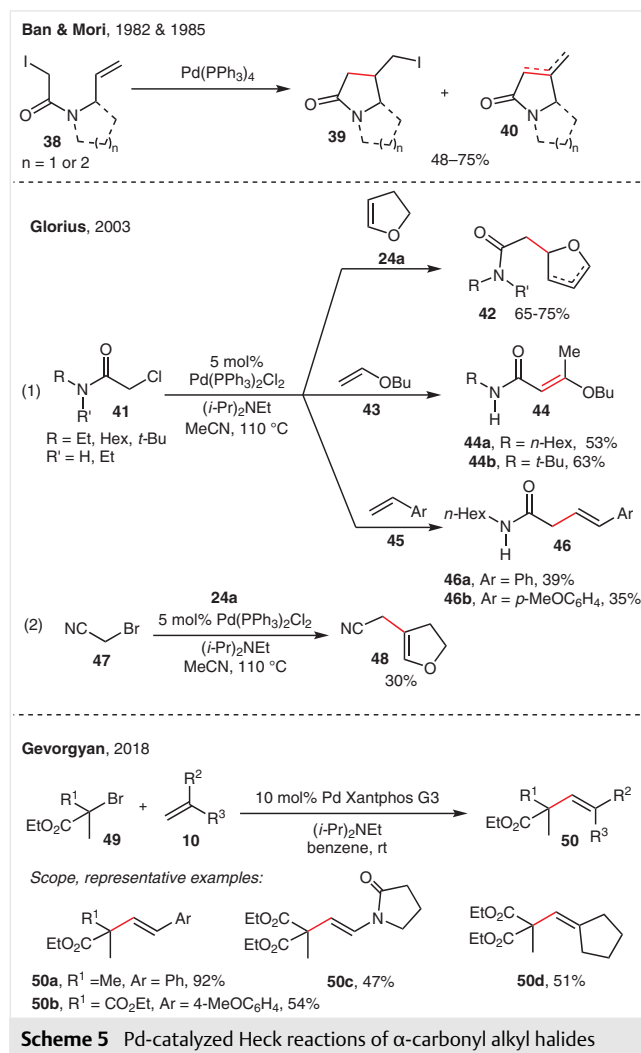
Lastly, *o*-allylbenzyl acetate was practically unreactive. Interestingly, attempts to induce this cyclization under typical radical conditions led to the hydrostannation product **30** only, thus illustrating the superiority of the Heck reaction pathway for this type of cyclization. The developed intramolecular 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 (Scheme 4).

In 2008, Chen applied an intramolecular Heck-type approach for the synthesis of 3-alkyl-1*H*-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 the assembly of a biologically important core compounds, i.e., 4-aryldihydropyrroles **36**.²² In this case, cyclization favored products with an endocyclic double bond, so that most of these dihydropyrroles were obtained as single regioisomers. In 2014, Gharpure

disclosed a straightforward synthesis of isochromene derivatives **37** via the intramolecular Heck reaction of benzyl halides and vinylogous carbonates (Scheme 4).^{1b}

2.2 α -Carbonyl Alkyl Halides

In the 1980s, Ban and Mori performed the initial study on the Pd(PPh₃)₄-catalyzed intramolecular alkylation of olefins using α -carbonyl alkyl halides **38**.²³ The reaction proceeded with low selectivity, delivering mixtures of atom transfer radical cyclization (ATRC) and Heck products (**39** and **40**, respectively) in moderate yields (Scheme 5). In 2003, Glorius reported an intermolecular Heck reaction of 2-chloroacetamides **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



bromoacetonitrile (**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.

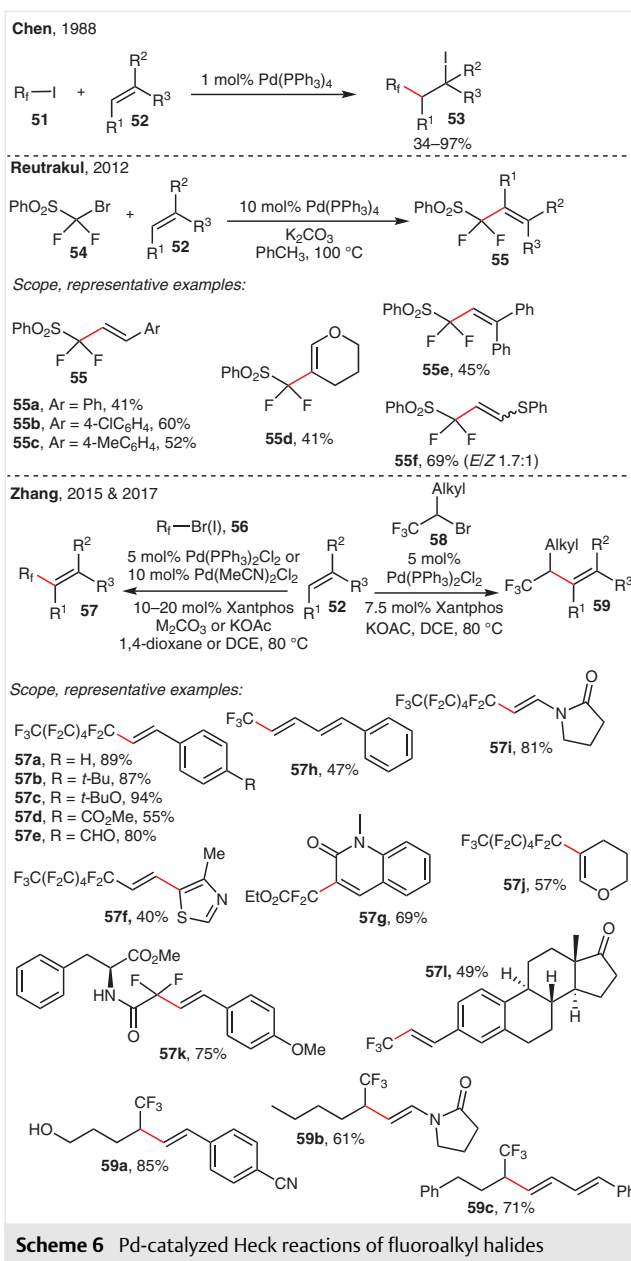
More recently, Gevorgyan showed that activated tertiary alkyl bromides possessing an α -carbonyl moiety **49** can efficiently react with styrenes and electron-rich alkenes at room temperature (Scheme 5).²⁵ Catalyzed by a Pd Xantphos G3 complex, the reaction furnished the Heck products **50a–d** in moderate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

2.3 Fluoroalkyl Halides

In 1988, Chen reported the first Pd-catalyzed addition of perfluorinated alkyl iodides **51** to alkenes **52** leading to alkyl iodides **53**, i.e., the atom transfer radical addition (ATRA) products (Scheme 6).²⁶ The radical nature of this transformation was strongly supported by the mechanistic studies, which led the authors to propose the involvement of a Pd(0) complex in a radical initiation event. In 2012, Reutrakul developed the Pd(PPh₃)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**), diene (**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 the synthesis of complex molecules possessing fluorinated fragments (**57k,l**). In follow-up work, the same group demonstrated that a similar catalytic system involving a Pd(II)-precatalyst and Xantphos as the 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 analogues of **53**) for both reactions.^{28,29}

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 the selective (Z)-hydroxymethylation of phenols and alkenols **60**. The

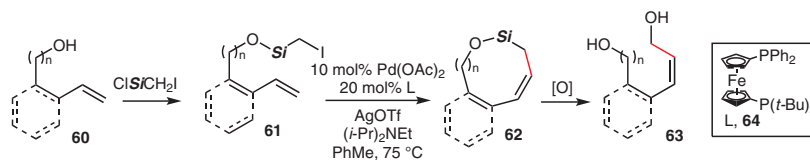


Scheme 6 Pd-catalyzed Heck reactions of fluoroalkyl halides

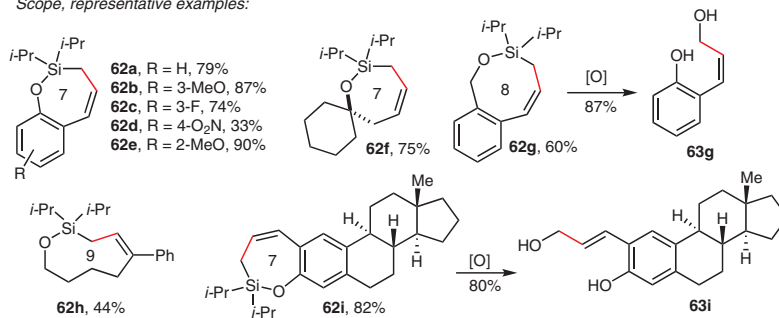
mechanistic studies suggested a hybrid Pd-radical mechanism for this Heck reaction. Also, the silicon atom was found to be crucial for the observed *endo* selectivity.

In 2017, Gevorgyan's group developed the first visible-light-induced Pd-catalyzed Heck reaction of alkyl halides at ambient temperature under exogenous photosensitizer-free conditions to furnish valuable allylic systems of diverse electronic nature (Scheme 7).³¹ Allylic silanes (**66a,b,k–o**), boronates (**66c,j**), germane (**66d**), stannane (**66e**), pivalate (**66f**), phosphonates (**66g,p**), phthalimide (**66h**), and tosylate (**66i**) derivatives were easily synthesized from primary and secondary α -functionalized alkyl halides and vinyl

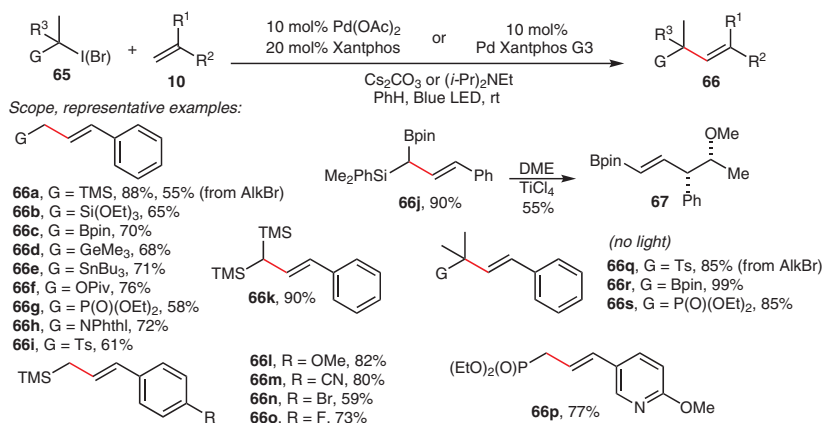
Gevorgyan, 2014



Scope, representative examples:



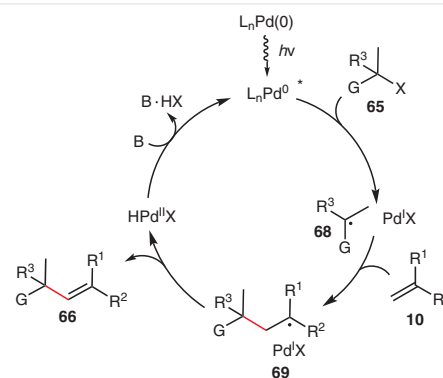
Gevorgyan, 2017 & 2018

**Scheme 7** Pd-catalyzed Heck reactions of α -functionalized alkyl halides

arenes/heteroarenes. The obtained allylic systems can be further modified, for example, via a Hosomi–Sakurai reaction (**66j** \rightarrow **67**). Later, the same group applied these photo-induced conditions for the Heck reactions of α -heteroatom-substituted tertiary alkyl iodides with 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)_n complexes were the single light-absorbing species in this reaction. The excited state is quenched by an alkyl halide, presumably via a SET event, which was calculated to be ‘barrierless’,^{12c} to form the alkyl Pd hybrid species **68** that adds to an alkene producing the new radical

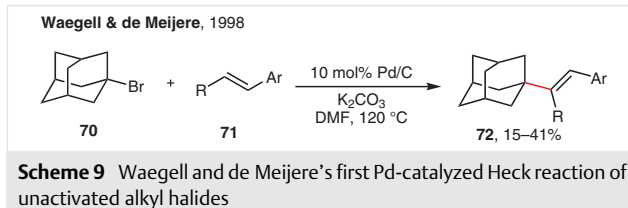
species **69** (Scheme 8). Subsequent β -H elimination from the latter delivers the product **66**, while the base regenerates the Pd(0) catalyst.

**Scheme 8** Gevorgyan's mechanism for the visible-light-induced Pd-catalyzed Heck reaction

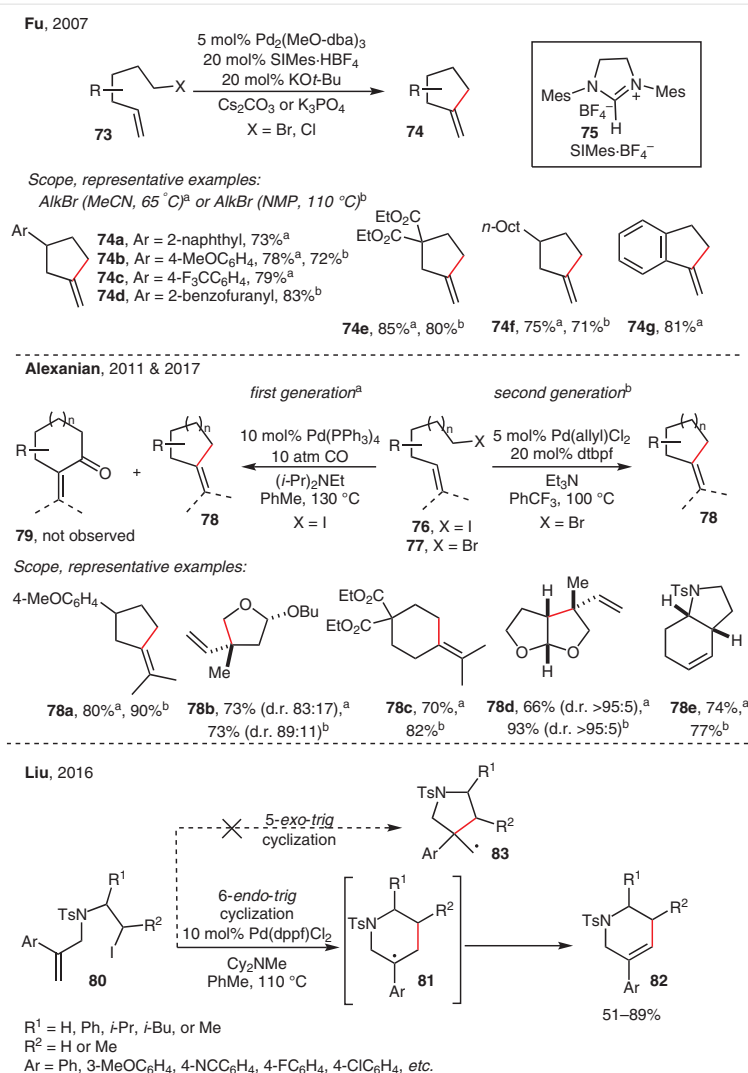
2.5 Unactivated Alkyl Electrophiles

The first Heck reaction of unactivated alkyl halides with alkenes was reported by Waegell and de Meijere in 1998 (Scheme 9).^{32a} In this report, 1-bromoadamantane (**70**), a substrate which is not disposed to 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 yields. In 2007, Fu introduced the first protocol for the Heck reaction of unactivated alkyl bromides and chlorides containing eliminable β -hydrogens (Scheme 10).^{32b} 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 the alkyl-Pd species into a double bond to proceed faster than the premature β -hydrogen elimination. Cyclopentane derivatives possessing an *exo*-alkene moiety **74a–g** were obtained in

high yields and regioselectivities 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.



In 2011, Alexanian developed a protocol for an intramolecular alkyl-Heck reaction, which relied on radical reactivity (Scheme 10).³³ Following his previous work on the car-

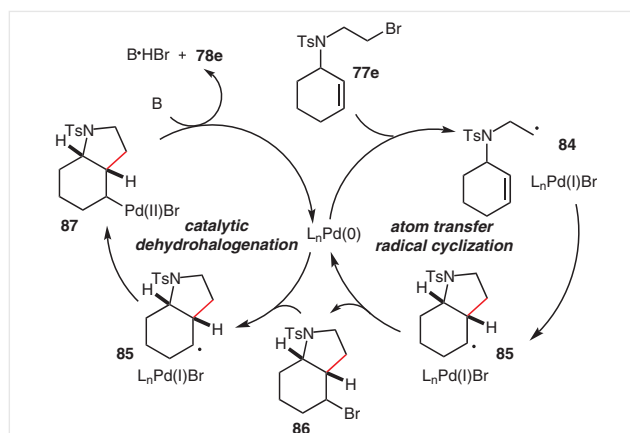


Scheme 10 Pd-catalyzed intramolecular Heck reactions of unactivated alkyl halides; d.r. = diastereomeric ratio

bonylative Heck-type reaction,³⁴ he showed that under increased CO pressure, Pd(PPh₃)₄ was 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,^{32b} mechanistic studies, including a 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 versus alkyl bromides in this cyclization. It was hypothesized that, in the case of alkyl bromides, the cyclization proceeds via auto-tandem catalysis (Scheme 11). Initiated by the Pd(0) complex, 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 the 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** versus 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**, which are 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)Cl₂ as a 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, Zhou applied a combination of a Pd(0) precatalyst and dppf as a ligand, which allowed intermolecular Heck reactions of styrenes to proceed with alkyl iodides **88**, bromides **89** and even chlorides **90** (Scheme 12).³⁸ The use of LiI as an 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 in yields comparable to those reported by Alexanian employing alkyl iodides. Similar to the previously described Heck-



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

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 in alkyl Heck reactions.

Until recently, all the reported methods for the Heck reaction of unactivated alkyl halides required elevated temperatures. In 2017, Gevorgyan's group demonstrated the possibility of achieving a room temperature Heck reaction of unactivated primary and secondary alkyl halides under visible-light-induced exogenous photosensitizer-free conditions employing a Pd(0)/Xantphos catalytic system (Scheme 12, products **92a–c**).³¹ Shortly after, the groups of Shang and Fu independently developed a similar method for the reactions 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

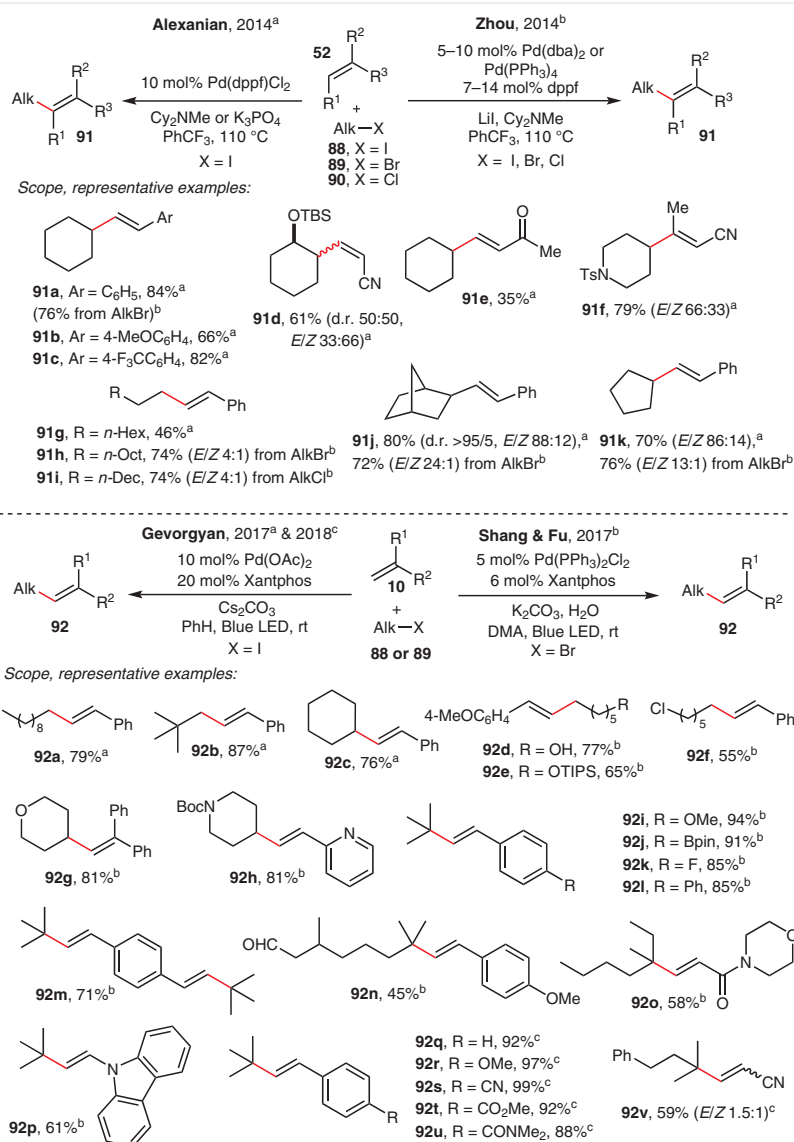
Moreover, challenging tertiary alkyl bromides were also found to be capable coupling partners (products **92i–n**). In addition to styrenes, unactivated tertiary alkyl bromides reacted with electron-deficient alkenes in a highly efficient manner (products **92o, p**). The mechanistic studies of this work strongly supported a radical pathway, which was initiated by a 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 independently reported analogous efficient alkyl Heck reactions of unactivated tertiary alkyl iodides with styrenes and acrylonitrile (Scheme 12, products **92q–v**).²⁵

Very recently, Gevorgyan's group reported a photoinduced, Pd-catalyzed radical relay Heck reaction at remote unactivated C(sp³)–H sites of aliphatic alcohols, which synergistically combines a C–H activation via a 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 the employment of easily installable/removable iodomethyl silyl tethers on alcohols **93**. These tethers are known to engage in a 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–m** in good yields. Interestingly, the iodine-

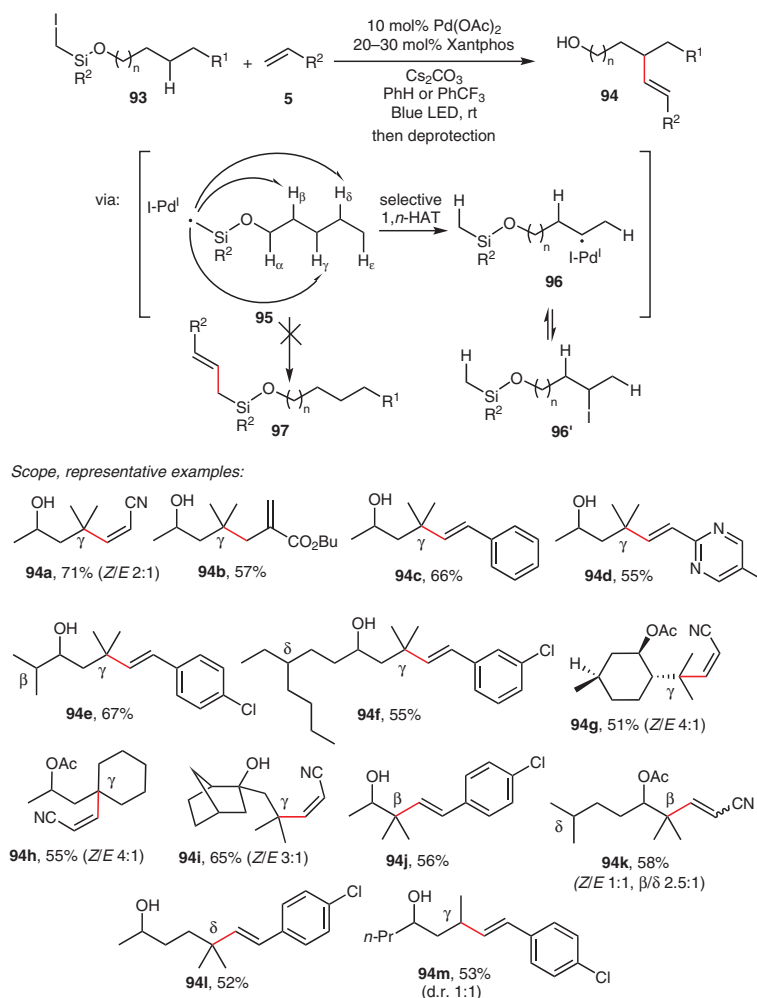
atom transfer intermediate **96'** was observed during this reaction, which presumably is formed via a reversible I-atom transfer from the Pd(I) species.

Lately, the scope of alkyl electrophiles in the Heck reaction has been expanded. Thus, in 2018, Zhou's group reported a Heck-type reaction of cyclic (**98**) and acyclic (**99**) epoxides using a Pd(0)-Xantphos catalytic system (Scheme 14).⁴¹ Styrenes, conjugated dienes, and electron-deficient olefins were efficiently alkylated to give ring-opening products **100a–h** and **101a,b** with retention of the 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 Et₃N·HI, which undergoes a SET reduction by the Pd(0) complex to form the



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

Gevorgyan, 2018

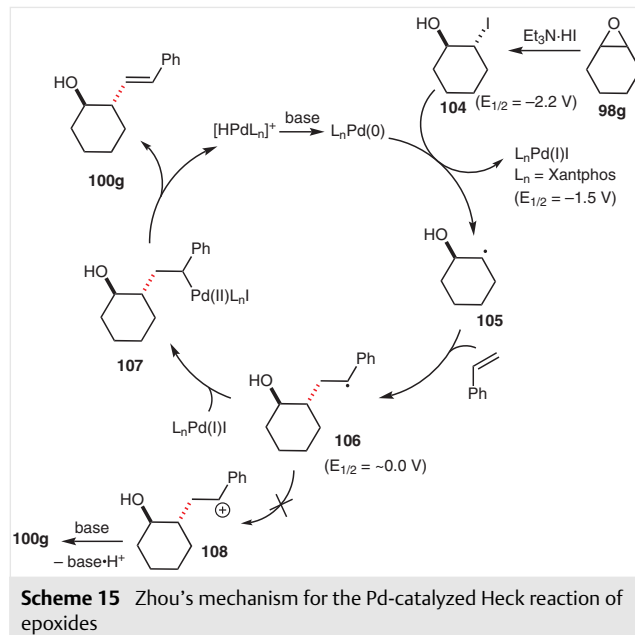
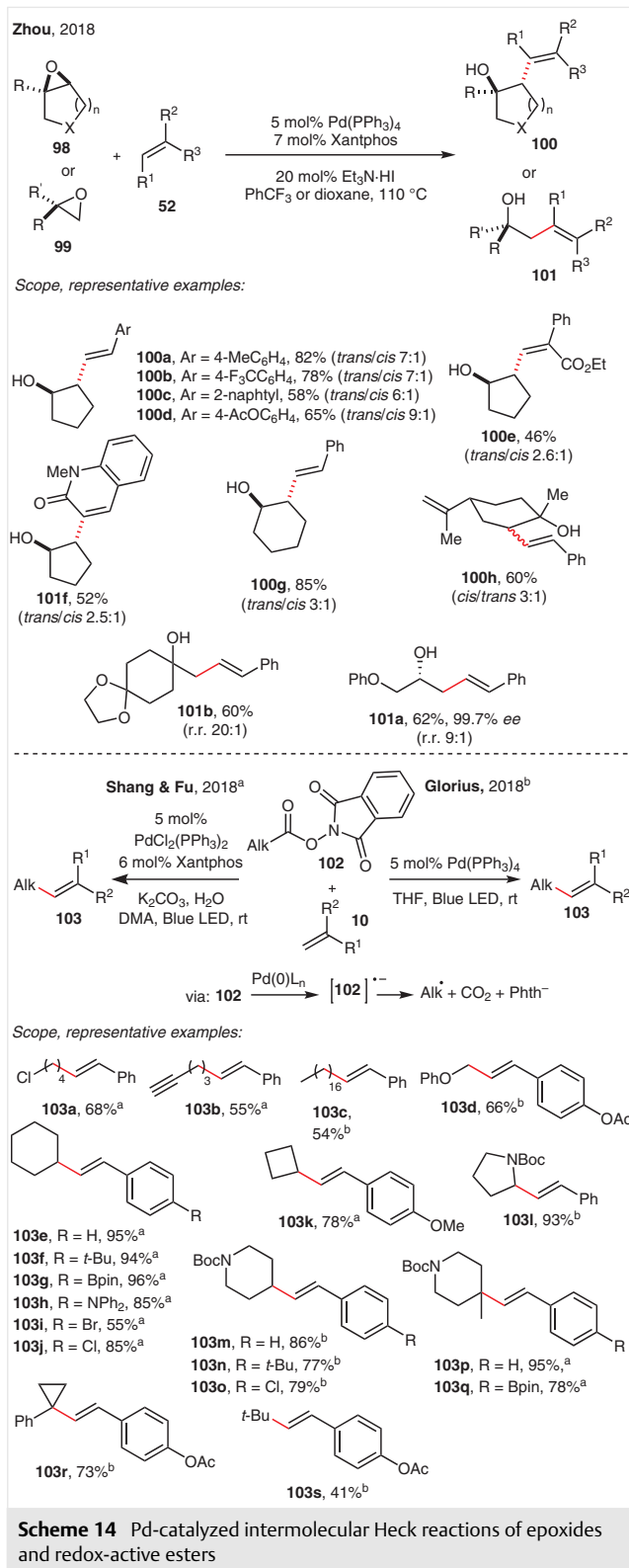


Scheme 13 Pd-catalyzed aliphatic radical relay Heck reaction at unactivated C(sp³)-H sites of alcohols

alkyl Pd-hybrid radical species **105** (Scheme 15). Subsequently, this species adds to the double bond of alkene to form a new radical species **106**, which gives the reaction product via recombination with Pd(I) and subsequent 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, the groups of Shang, Fu and Glorius independently discovered a photoinduced Pd-catalyzed Heck reaction of redox active esters, aliphatic *N*-(acyloxy)phthalimides **102**, with styrenes (Scheme 14).⁴²

The reactions of primary, secondary and tertiary substrates proceeded smoothly at room temperature (products **103a–s**), 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 reactions of alkyl halides. Likewise, mechanistic studies have proven a radical-type mechanism initiated by a SET event between a 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, photophysical studies revealed that the Pd complex is the only light-absorbing species in this transformation, while *N*-(acyloxy)phthalimides **102** showed no absorption in the visible light region.

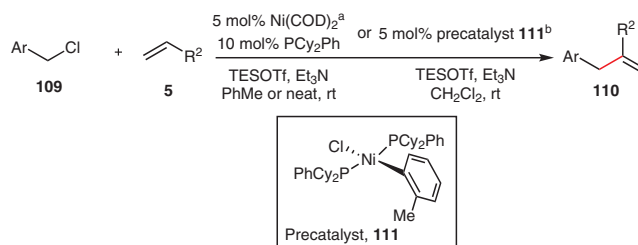


3 Ni-Catalyzed Heck-Type Reactions

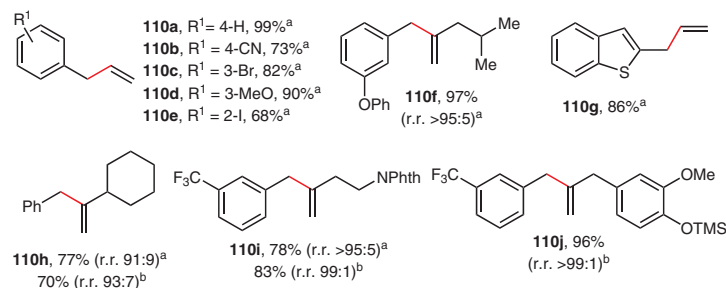
3.1 Benzylic Electrophiles

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, the monodentate phosphine ligand PCy₂Ph 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 counteranion exchange with TESOTf to generate the cationic benzyl-Ni(II) species **116**, followed by an olefin coordination and sterics-controlled migratory insertion. Subsequent β-H elimination of the formed alkyl-Ni(II) complex **117** affords the branched Heck reaction product **110** and HNi(II)OTf, 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 regioselectivities (>95:5 for most cases). Two years later, the same group discovered the 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

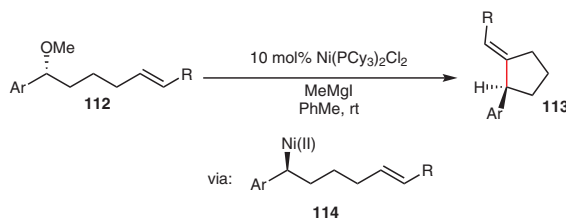
Jamison, 2011 & 2013



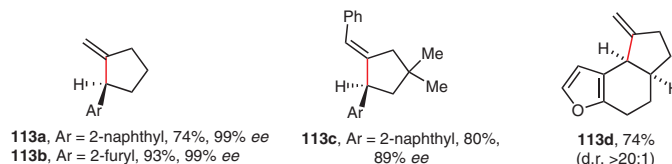
Scope, representative examples:



Jarvo, 2014



Scope, representative examples:

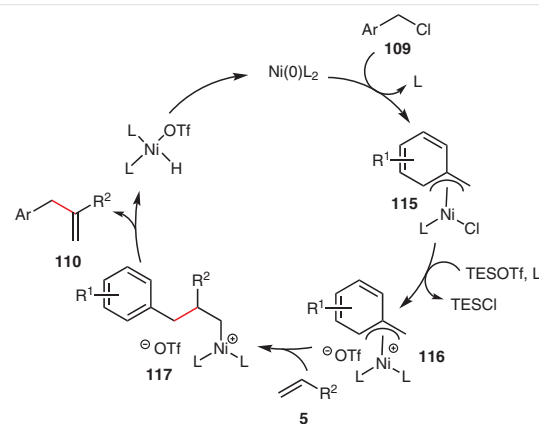


Scheme 16 Ni-catalyzed Heck reactions of benzylic electrophiles

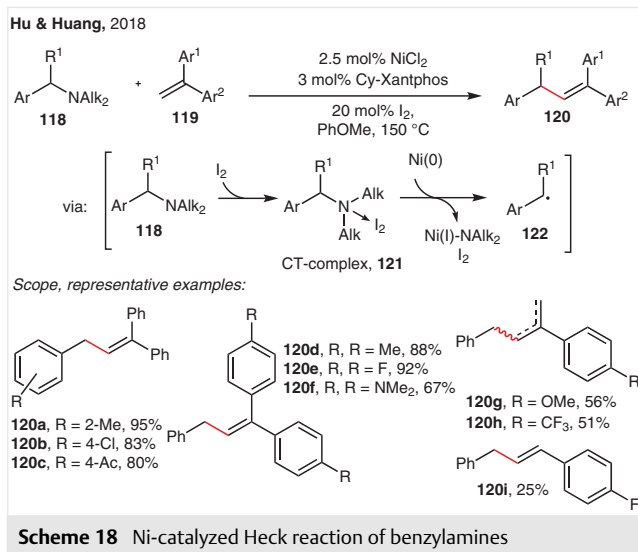
derivatives **110h–j** was efficiently synthesized in comparable yields to those reported under the previous protocol conditions (Scheme 16).

In 2014, Jarvo developed a highly efficient, stereospecific, Ni-catalyzed intramolecular Heck reaction of chiral methyl benzyl ethers **112** to give methylenecyclopentanes **113** (Scheme 16).⁴⁶ The stereochemical outcome of this reaction arose from inversion during 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



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



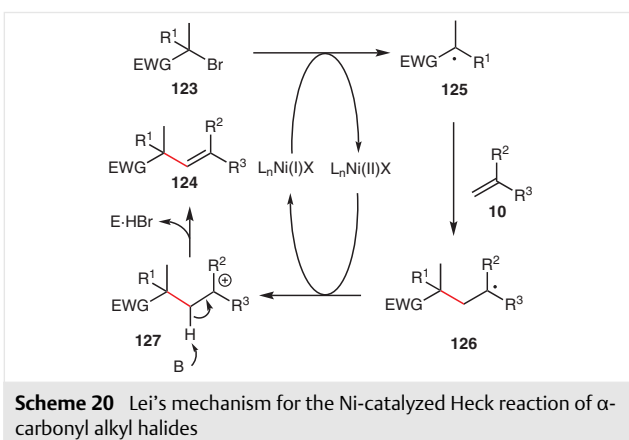
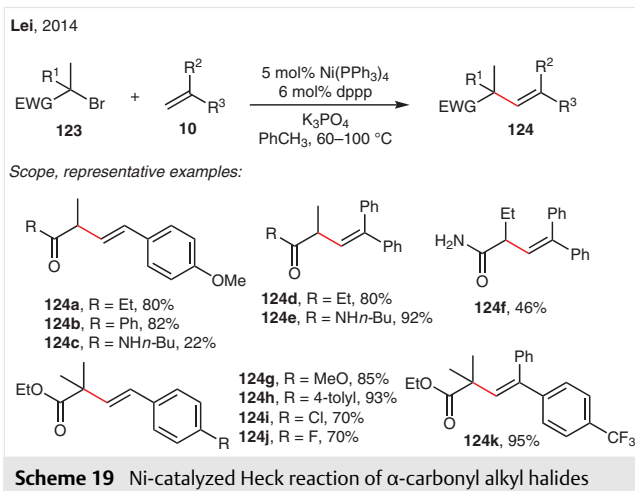
The reaction is believed to occur via a charge transfer (CT) complex **121**, which undergoes an SET with the Ni(0) catalyst to form alkyl radical species **122**. The latter can be captured with styrene derivatives to produce Heck reaction products **120a–i** in moderate to good yields.

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(PPh₃)₄/dppp-catalyzed conditions leading to the products **124a–k**. Interestingly, the authors showed that a Ni(I)-complex such as Ni(PPh₃)₄Cl was able to catalyze this reaction, as well. Thus, the following radical-type mechanism has been proposed (Scheme 20). Presumably, the Ni(I) species is generated in situ from the Ni(0)-catalyst and an alkyl bromide via a SET event. The second SET event would produce the Ni(II)-complex and alkyl radical species **125**, which undergoes radical addition to the 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 a 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).

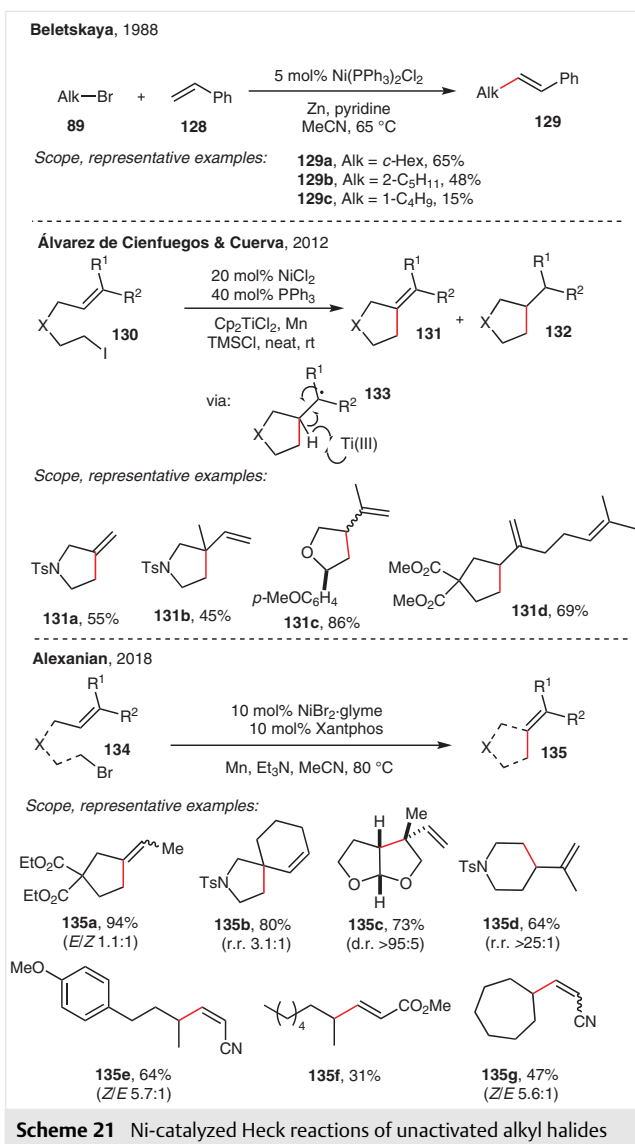
3.3 Unactivated Alkyl Halides

The first example of Ni-catalyzed Heck reactions of unactivated alkyl halides was reported by Beletskaya in 1988 (Scheme 21). The Ni(PPh₃)₄Cl₂/Zn/pyridine system was



shown to be capable of catalyzing 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, Álvarez de Cienfuegos and Cuerva introduced a Heck-type cyclization of alkyl iodides **130** under Ni/Ti-synergistic catalysis at room temperature (Scheme 21).⁵⁰ Interestingly, depending on the conditions, the reaction could provide either normal or reductive Heck products (**131a–d** or **132**, respectively). In the case of standard Heck reaction conditions, the Ni(I) complex is suggested to be the active catalyst that initiates the radical-type mechanism via 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 intermolec-

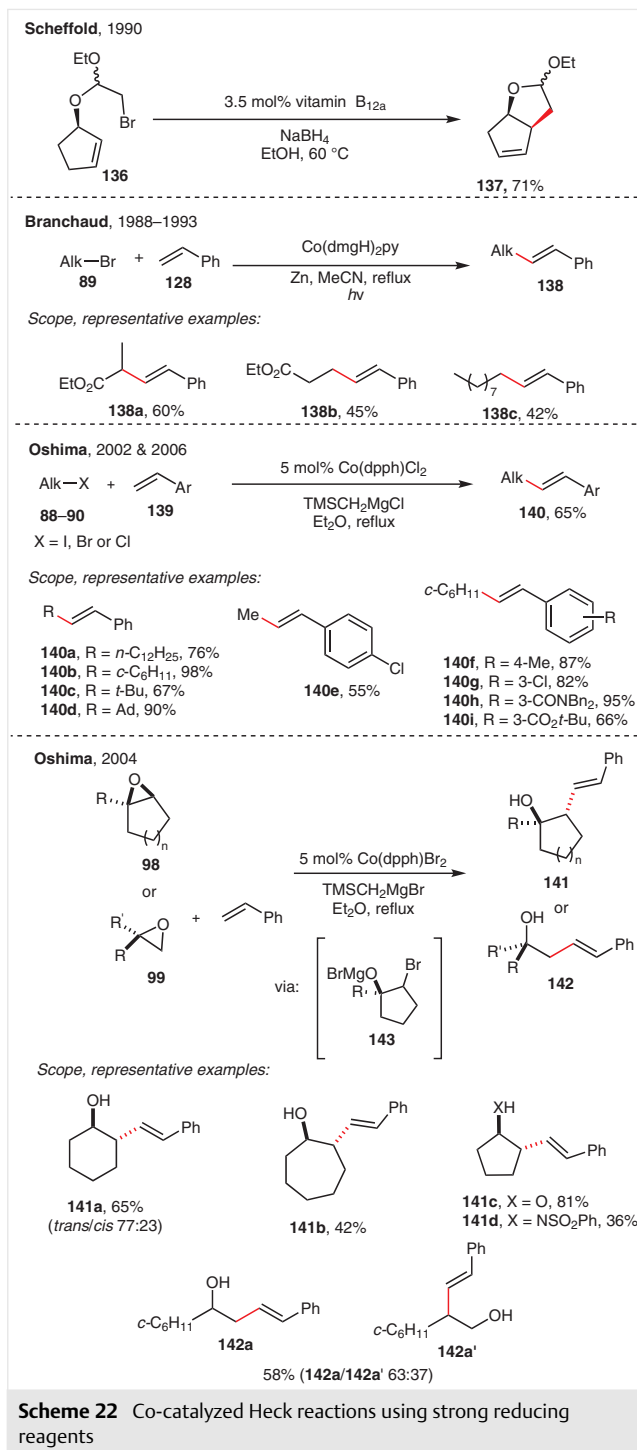


ular Heck reactions of alkyl bromides **134** (Scheme 21).⁵¹ Employing a Ni/Xantphos catalyst and Mn reductant, this reaction produced cyclized products **135a–d** in good yields and enhanced alkene regioselectivity compared to the previously developed Pd-catalyzed carbocyclizations.³⁵ Moreover, using these conditions, an intermolecular coupling of primary and secondary alkyl bromides with electron-deficient alkenes was accomplished (products **135e–g**). Mechanistic studies suggested a radical-type scenario commenced by 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.

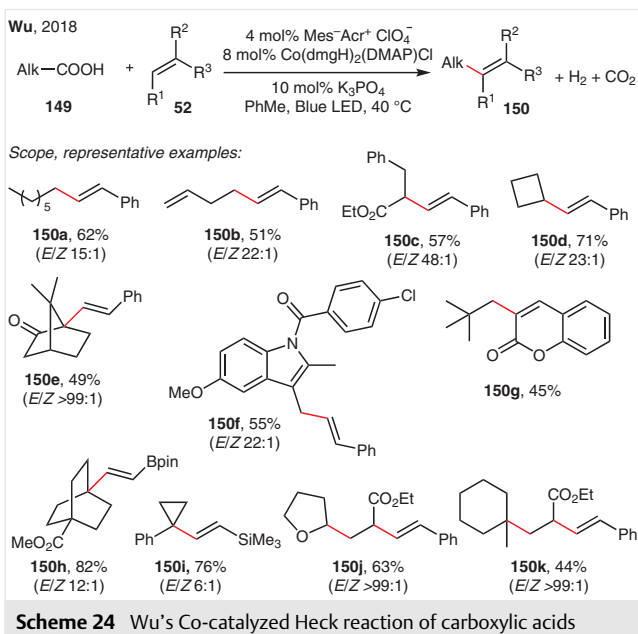
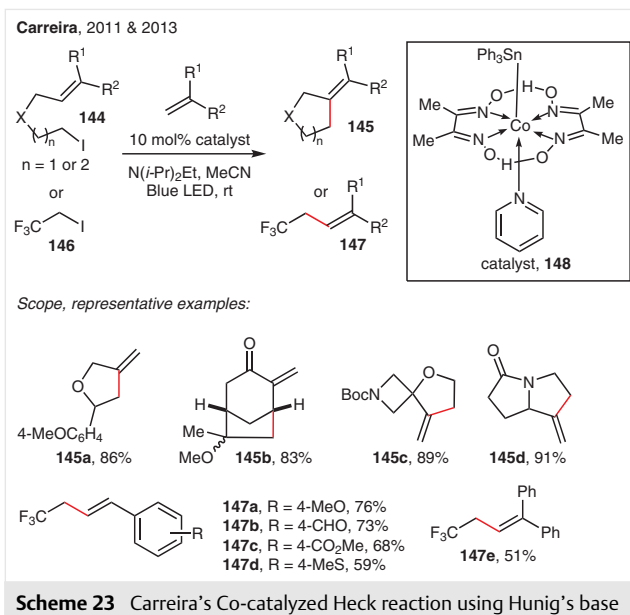
4 Co-Catalyzed Heck-Type Reactions

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) as the catalyst.⁵² A number of reports on intramolecular Co-catalyzed Heck reactions by Scheffold⁵³ and others,⁵⁴ as well as on the intermolecular version 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 hydroxocobalamin (vitamin 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 reagents such as TMSCH₂MgCl (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 a 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 reactions of epoxides **98** and **99** (Scheme 22).⁵⁷ The reaction proceeded through in situ generation of 2-bromomagnesium methoxide **143** followed by the Co-catalyzed Heck reaction of alkyl bromides analogous to the prior work.⁵⁶ The reaction was fairly effective for Heck reactions 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*-Pr)₂Et]-promoted Co(I)-catalyst turnover via 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 The intramolecular and intermolecular Heck reactions proceeded uneventfully, generating the Heck products **145a–d** and **147a–e** in good to excellent yields. 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 organo photoredox/cobaloxime dual catalysis (Scheme 24).⁶⁰ The scope of this reaction was fairly broad as primary, secondary and tertiary alkyl radi-

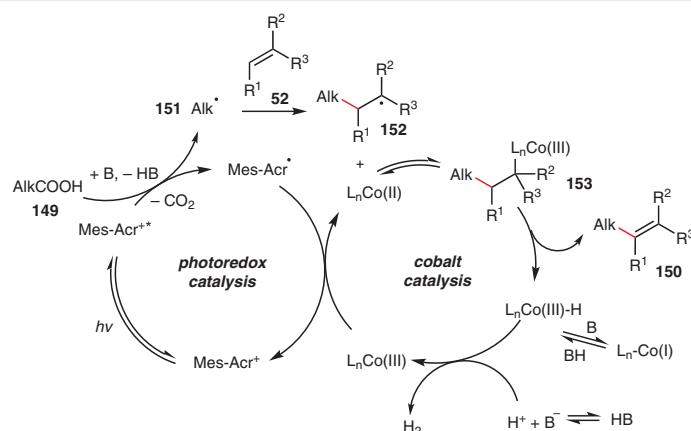


cals, generated from carboxylic acids, could be efficiently coupled with vinyl arenes/heteroarenes leading to the corresponding products **150a–g** in good to excellent yields. Vinyl boronates and vinyl silanes (products **150h** and **150i**, respectively) were also shown to be competent alkene cou-



pling partners in this 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 and as single regioisomers with exclusive *E* configuration (products **150j** and **150k**). Mechanistic studies, as well as DFT calculations, supported a radical-type mechanism (Scheme 25). According to which, a SET process from the carboxylate to the excited Mes-Acr⁺⁺ species is followed by radical decarboxyl-

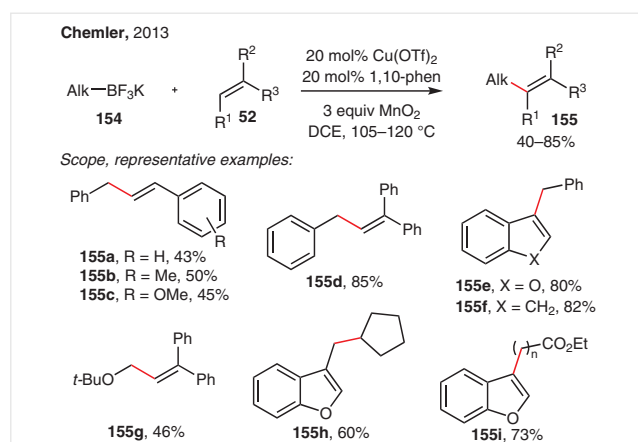


Scheme 25 Wu's mechanism for the Co-catalyzed Heck reaction of carboxylic acids

ation to produce the alkyl radical species **151**. Subsequent trapping of the latter by an alkene, and then by the Co(II)-catalyst, leads to alkyl-Co(III) species **153**, which undergoes β -H elimination towards the Heck reaction product **150** and a Co(III)-H species. Deprotonation of this species, followed by an SET with the reduced photocatalyst regenerates 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 H₂ and CO₂ being the only by-products.

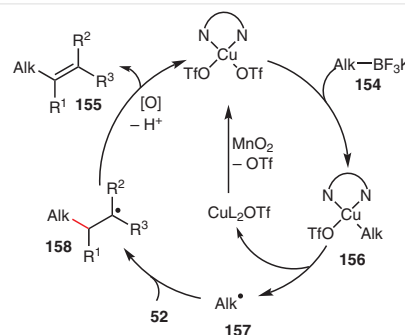
5 Cu-Catalyzed Heck-Type Reactions

In 2013, Chemler reported the first Cu-catalyzed alkyl Heck reaction (Scheme 26). In contrast to many alkyl Heck reactions, this reaction employed alkyl nucleophiles, such as alkyltrifluoroborates **154**, as coupling partners for the alkenes.⁶¹



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

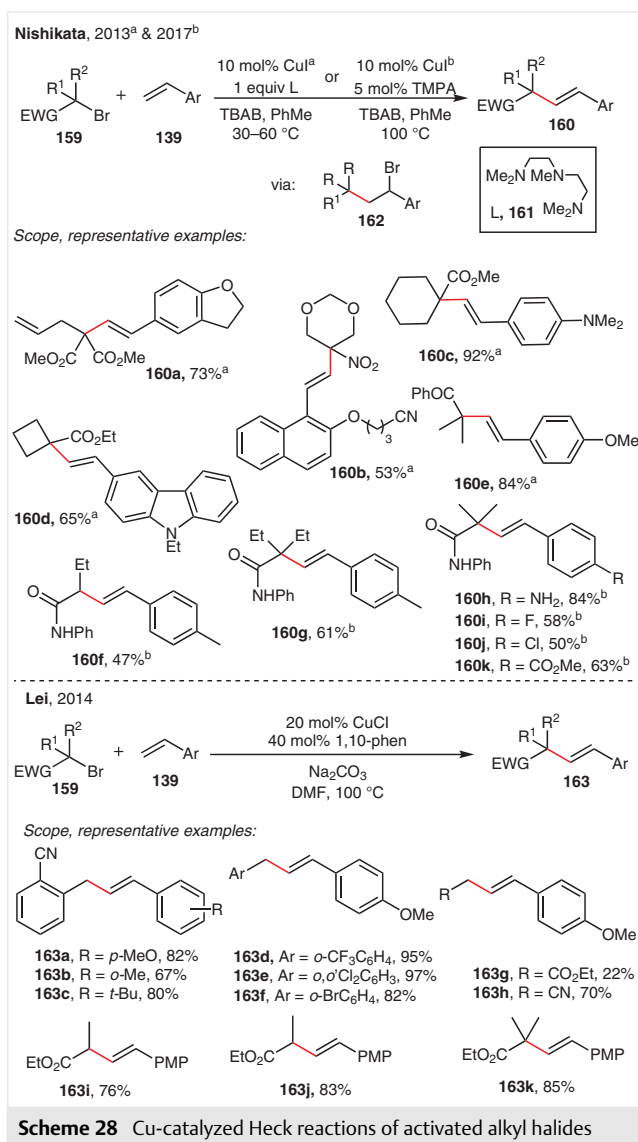
The outcome of TEMPO-trapping and radical clock experiments indicated the radical nature of this transformation. The authors proposed that, under oxidative conditions, generation of alkyl radical species **157** and a Cu(I) species occurred via homolysis of the Cu-C bond in the complex **156**, which formed via transmetalation of the Cu(II) catalyst with alkyl trifluoroborate **154** (Scheme 27). Addition of **157** to an alkene, followed by subsequent oxidation and deprotonation produced the Heck reaction product **155**. Yet, to regenerate the catalyst, the Cu(I) species had to be oxidized by an external oxidant such as MnO₂. This oxidative transformation features a quite general scope with regards to the trifluoroborate salt, as benzylic, unactivated primary, and secondary alkyl substrates could efficiently react with styrene derivatives to afford the Heck products **155a-i** in good yields.



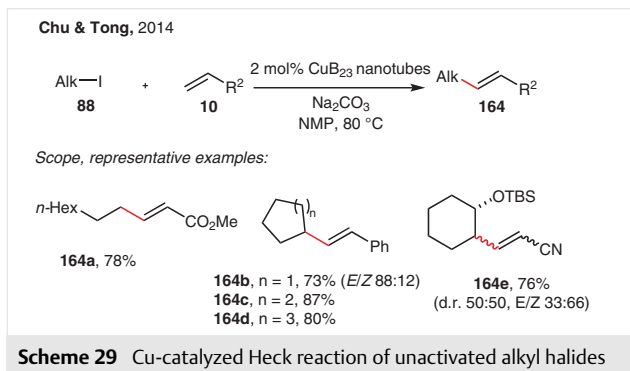
Scheme 27 Chemler's mechanism for the Cu-catalyzed Heck reaction of alkyl trifluoroborates

In the same year, Nishikata developed the Cu(I)/tri-amine (**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, presumably via the formation of ATRA intermediate **162**. A TEMPO-trapping

experiment confirmed the intermediacy of a 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, which were unreactive under the previous conditions,⁶² with both electron-rich and electron-deficient styrene derivatives (Scheme 28).⁶³ The reaction required higher temperatures and tri-(2-picoly)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 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 CuB₂₃ 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, unactivated primary and secondary substrates reacted smoothly, presumably via a radical pathway (products **164a–e**). This method provided slightly superior yields compared to the Pd-catalyzed Heck reaction.³⁷ Moreover, the catalyst showed a great recycling performance.

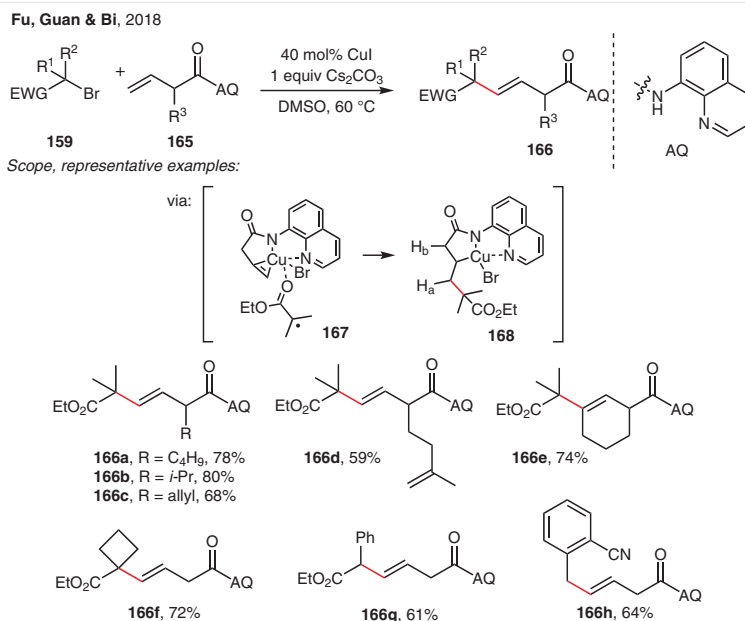


Regioselectivity has been an issue in the Heck reactions of unactivated aliphatic olefins due to the undifferentiated C–H sites for β -H elimination. Very recently, the first regioselective Heck reaction of alkyl bromides with unactivated aliphatic olefins was reported by Bi and co-workers (Scheme 30).⁶⁶

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

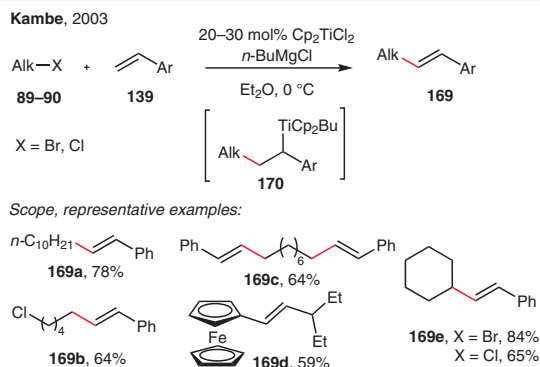
6 Other Metals in Heck-Type Reactions

In 2003, Kambe reported the 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 the Ti(IV)-catalyst and the Grignard reagent is believed to generate alkyl radicals,



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

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**.



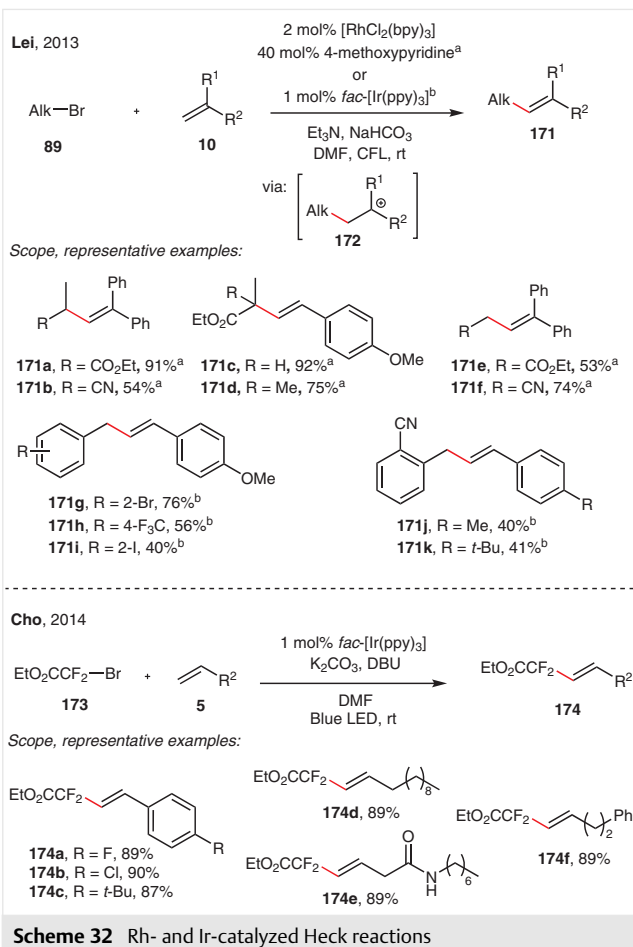
Scheme 31 Ti-catalyzed Heck reaction

In 2013, Lei's group 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 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 ethyl 2-bromo-2,2-difluoroacetate (**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 suitable partners in 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 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 a radical-polar crossover mechanism initiated by the Fe(II)-catalyst. Methylated and ethylated styrene derivatives **178a-g**, enyne **178h**, and diene **178i** were obtained in reasonable yields under these conditions.

In 2014, decarbonylative Heck-type reactions employing *tert*-butyl peroxide and a catalytic amount of MnBr₂ were reported by Li (Scheme 34).⁷² Peroxide-induced H-atom abstraction from aldehyde **179** gives the carbonyl radical **181**, which upon releasing CO fragments into an alkyl radical **182** (Scheme 35). Subsequent radical addition of the latter to the alkene, followed by oxidation and deprotonation furnishes the Heck-type product **180**. The reaction

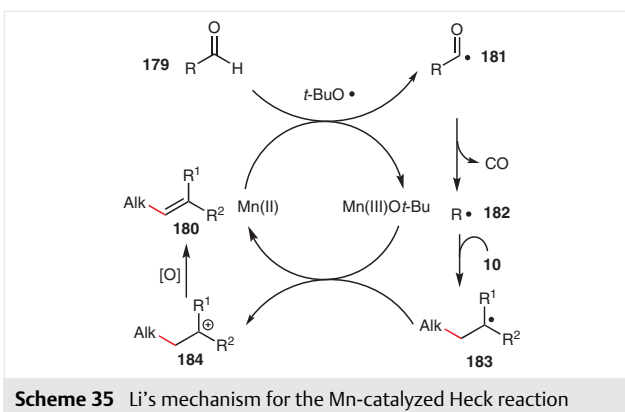
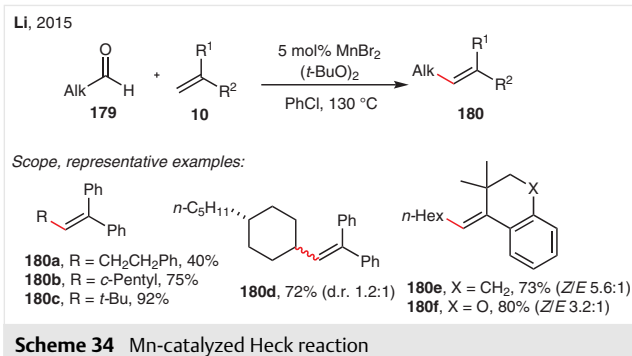
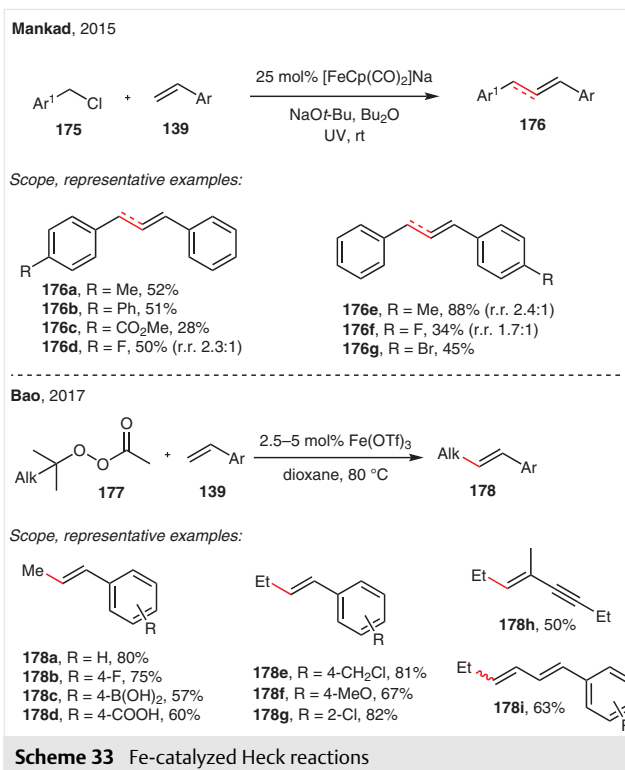


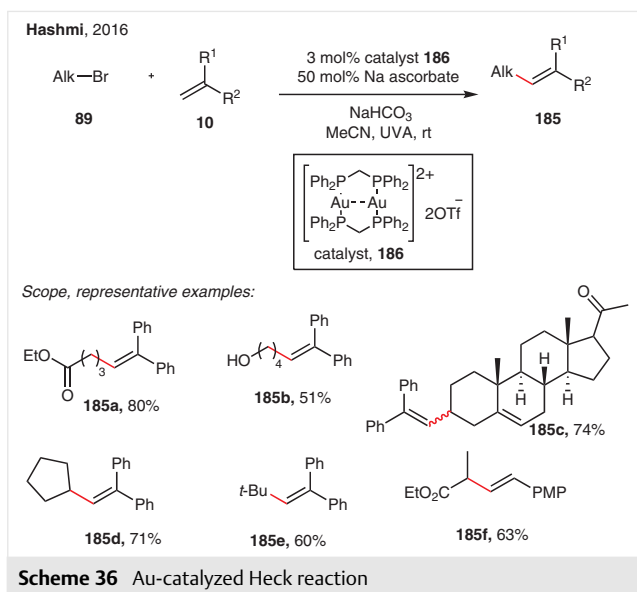
proceeds well with primary, secondary, and tertiary aldehydes, however, it is limited to 1,1-disubstituted styrenes (products **180a–f**).

In 2016, Hashmi's group showed that dinuclear gold complex **186** could catalyze the 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 a complex molecule, e.g., pregnenolone derivative **185c**. Mechanistic studies supported an Au-catalyzed radical polar-crossover mechanism induced by SET from the photoexcited Au(I)–Au(I) complex to an alkyl bromide.

7 Conclusion

Although the first alkyl Heck reaction was reported by Richard Heck in his original work,^{1d} this transformation has remained underdeveloped until recently, especially for un-





activated hindered alkyl halides possessing eliminable β -hydrogens. However, a merger 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 have been shown to efficiently catalyze Heck-type reactions, 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 the alkyl Heck reaction. Although, 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 the alkylation of unactivated aliphatic alkenes are rare. Therefore, the future direction of this transformation may rely on the development of new systems that enable unactivated alkenes to undergo selective and efficient Heck-type reactions. Obviously, detailed mechanistic studies are warranted for better understanding of alkyl Heck-type reactions.

Funding Information

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