

Abstracts

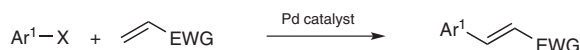
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3.1.1.1.1 Reaction with Aryl or Hetaryl Halides or Pseudohalides

C.-M. Andersson and M. Andersson

The arylation of terminal alkenes bearing mesomerically electron-withdrawing groups is the archetypal palladium(0)-catalyzed Heck reaction, also known as the Mizoroki–Heck reaction. These substrates generally provide a very high regioselectivity, with both steric and electronic factors favoring arylation at the terminal position of the alkene. Additionally, diastereoselectivity is generally very high, and products with an *E* configuration are obtained exclusively in most cases. In the wake of the pioneering studies on this reaction in which stoichiometric amounts of palladium reagents were used, iodoarenes were introduced as arylating agents in a catalytic version of the reaction; these were later supplemented by bromo- and chloroarenes. Subsequently, many other arylating agents, such as pseudohalides, aroyl chlorides, and diazonium or iodonium salts, have been introduced as electrophiles in the Mizoroki–Heck reaction. Later advances include the development of oxidative Heck arylations catalyzed by palladium(II) species.

This chapter aims to provide a general perspective on the applicability of this type of coupling chemistry, and to describe the depth and breadth of various aspects that have been researched and refined in making the Heck reaction of alkenes bearing electron-withdrawing groups a cornerstone of the art of C–C bond formation.



Ar¹ = aryl, hetaryl; X = I, Br, Cl, N₂⁺, I⁺Ar², OTf;
 EWG = COR¹, CO₂R¹, CN, CONHR¹, SOR¹, SO₂R¹, SO₂OR¹, S(O)OR¹, P(O)(OR¹)₂,
 PR¹(O)OR², NO₂, NO, CZ_nH_{3-n} (Z = halogen), aryl, hetaryl

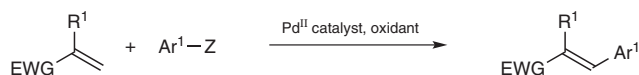
Keywords: arylation · electron-poor alkenes · catalysis · palladium · Heck reaction · Mizoroki–Heck reaction · alkenylation · aryl halides · oxidative arylation · arylboronic acids · iodonium salts · diazonium salts · aryl trifluoromethanesulfonates · ionic liquids

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3.1.1.1.2 Reaction with (Het)Arylmetals or (Het)Arenes

E. W. Werner and M. S. Sigman

The intermolecular Heck reaction, in which a vinylic C–H bond is replaced by a C–C bond under palladium catalysis, is an indispensable tool for synthetic organic chemists. The reasons for this reliance include predictable regioselectivity in the formation of the new C–C bond when electronically biased alkenes are used, and the dependable delivery of configurationally pure *E*-alkene products. When palladium(II) salts are employed as catalysts in conjunction with organometallic reagents, an external oxidant is required to render the reaction catalytic. This strategy enables the reaction to perform well under mild conditions as compared to the elevated temperatures typically required when using palladium(0) catalysts. A critical review of the reagents and conditions capable of performing such transformations upon electron-deficient alkene substrates is presented.



Ar¹ = aryl, hetaryl; Z = metal, H

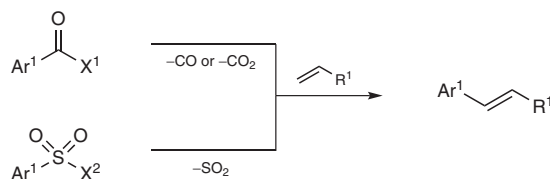
Keywords: acrylates · arenes · arylation · arylmetals · electron-deficient alkenes · hetarenes · hetarylmotals · oxidative coupling · palladium(II) catalysis · styrenes

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3.1.1.1.3 Reaction with Arene- or Hetarene-carboxylic Acids or Derivatives, or Related Compounds

M. Zhang and W. Su

This chapter presents the synthesis of aryl-substituted alkenes via transition-metal-catalyzed decarbonylative, decarboxylative, or desulfinylative Mizoroki–Heck cross-coupling reactions.



X¹ = Cl, OR², OC(O)R², OH; X² = Cl, OH

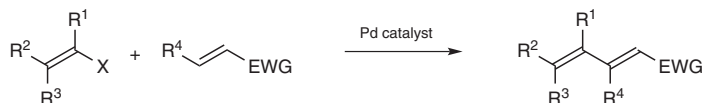
Keywords: alkenes · arylation · cross-coupling reactions · decarbonylation · decarboxylation · desulfinylation · Heck reaction · palladium catalysis · rhodium catalysis · transition-metal catalysis

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3.1.1.1.4 Reaction with Nonaromatic Halides or Sulfonates, or Related Compounds

M. Weimar and M. J. Fuchter

The Heck reaction is a widely used method in organic synthesis. This report concerns the development of methodologies to apply Heck-type chemistry to electron-poor alkenes with one or more electron-withdrawing groups and alkenyl and other nonaromatic electrophiles.



Keywords: acrylates · alkenes · alkenylation · benzylation · catalysts · C=C bonds · C–C coupling · cross-coupling reactions · dienes · enols · Heck reaction · iodonium compounds · oxidative addition · palladium catalysts · palladium complexes · phosphates · styrenes · sulfonates · vinyl compounds

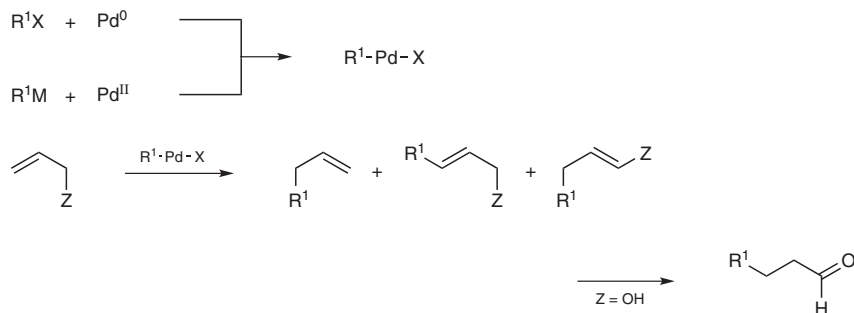
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3.1.1.2 Alkenes with Allylic Substitution and Homologues as Reaction Components

J. Le Bras and J. Muzart

The intermolecular coupling of aryl or vinyl halides (or pseudohalides) with linear alkenes having an allylic or homoallylic heteroatomic substituent occurs under palladi-

um-catalyzed conditions. The 1,2-insertion of the aryl- or vinylpalladium intermediate into the double bond is followed by the elimination of either a hydride or the heteroatomic substituent. This chapter focuses on selective procedures.



Keywords: arylation • vinylation • catalysis • regioselectivity • palladium • β -hydride elimination • β -heteroatom elimination • carbon–heteroatom cleavage • isomerization

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3.1.1.3.1 Reaction with Aryl or Hetaryl Halides or Pseudohalides

S. Liu and J. Xiao

This chapter describes the palladium-catalyzed Heck reaction of electron-rich alkenes with aryl, hetaryl, or vinyl halides or pseudohalides. The alkenes covered include vinyl ethers, enamides, and enamines generated in situ from aldehydes. The electron-neutral styrenes are also mentioned. Depending on the arylating or vinylic reagent, ligand, additive, and solvent used, the reaction can take place at either the α or β position of the alkene, and, in the past two decades or so, significant progress has been made allowing precise control of the regioselectivity.



X = I, Br, Cl, OTf, OTs, OMs; Z = O, NR²

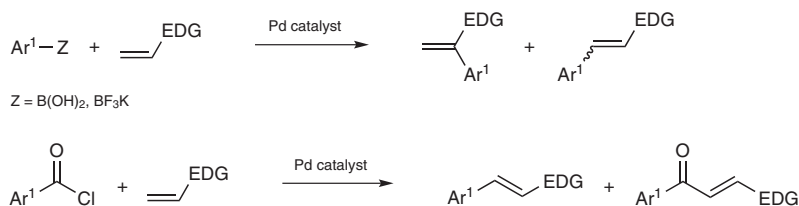
Keywords: Heck reaction • regioselectivity • electron-rich alkenes • vinyl ethers • enamides • enamines • styrenes

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3.1.1.3.2 Reaction with Arylboronic Acids or Derivatives or Aryl Halides

J. Lindh and M. Larhed

The use of electron-rich alkenes in Heck reactions was originally associated with poor regiocontrol, resulting in unwanted mixtures of regioisomers, thus severely hampering the utility of electron-rich alkenes. Today, excellent regiocontrol can be obtained by employing suitable reaction conditions. The use of electron-rich alkenes, such as enamides and vinyl ethers, in coupling reactions with arylboron compounds under cationic conditions provides easy access to the corresponding aryl ketones. Additionally, vinyl acetate can function as a convenient ethene precursor to form styrenes in coupling reactions with arylboron compounds.



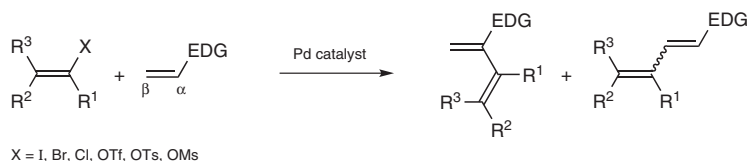
Keywords: arylation · enamides · vinyl ethers · vinyl acetate · boronic acids · trifluoroborates · aroyl chlorides · styrene · acetophenone · oxidative Heck reaction · catalysis · regioselectivity · palladium

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3.1.1.3.3 Reaction with Nonaromatic Alkenyl Halides or Alkenyl Sulfonates

P. Nilsson

The intermolecular coupling of two sp^2 -hybridized carbons is normally conveniently performed via, for example, a Suzuki or Stille reaction. However, easy access to suitably equipped starting materials, i.e. a boron or tin derivative and an aryl/vinyl halide, is not always straightforward, especially if there is an intention to couple two alkenes, thus forming conjugated dienes. In such cases the corresponding palladium(0)-catalyzed Mizoroki–Heck vinylation procedure becomes interesting since the vinyl halide (or pseudohalide) is coupled to the other alkene via a 1,2-insertion/ β -hydride elimination process and thereby offers a complementary set of coupling partners as starting materials, as well as giving good stereoselectivity. In addition, heteroatom-substituted alkenes present an opportunity for subsequent transformations on the functionalized 1,3-diene, in contrast to cross couplings where the heteroatom constitutes a part of the leaving group. This chapter summarizes developments in the field of Mizoroki–Heck vinylation of electron-rich alkenes using alkenyl–X species (X = halide, sulfonate), focusing on reactions where high yields and regioselectivities are achieved using robust protocols.



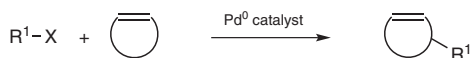
Keywords: vinylation · catalysis · regioselectivity · palladium · dienes · enol ethers · enamides

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3.1.1.4 Cyclic Alkenes as Reaction Components

V. Coeffard and P. J. Guiry

This chapter collates the relevant literature on intermolecular Mizoroki–Heck reactions of cyclic alkenes leading to the enantioselective and non-enantioselective construction of functionalized alicyclic compounds or heterocycles.

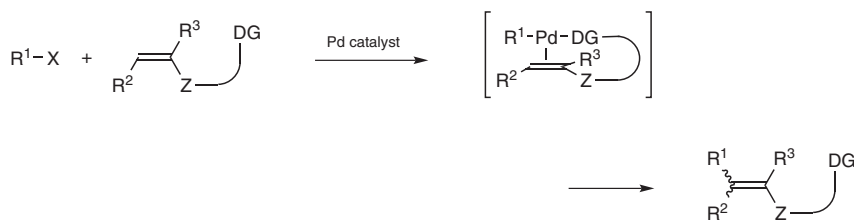


Keywords: Heck reaction · cycloalkenes · C–C coupling · palladium · regioselectivity · diastereoselectivity · enantioselectivity · oxygen and nitrogen heterocycles · chiral ligand · phosphines · dihydrooxazole ligands

3.1.1.5 Alkenes with Metal-Directing Groups as Reaction Components

A. Trejos and L. R. Odell

The use of electron-rich alkenes in Heck reactions was originally associated with poor regiocontrol, resulting in unwanted mixtures of regioisomers, thus severely hampering the utility of electron-rich alkenes. Chelation control has arisen as an attractive strategy to dictate the product outcome, as the directing effect of these substrates and the favorable formation of five- or six-membered chelates result in excellent regioselectivities. Today, excellent regiocontrol can be obtained by employing alkenes containing suitable catalyst-presenting groups. In addition, high levels of stereocontrol can also be obtained by using appropriate chiral catalyst presenting groups.



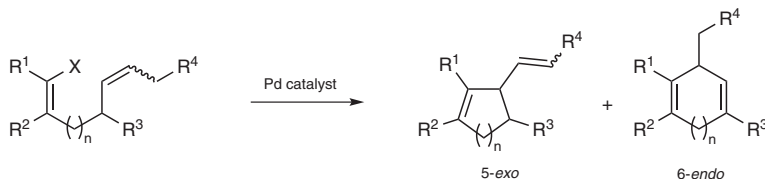
X = halide, pseudohalide; Z = CR⁴R⁵, O, S, SiR⁴R⁵; DG = directing group;
R¹ = aryl, alkenyl; R² = H, aryl, alkyl; R³ = H, aryl, alkyl

Keywords: arylation · chelation · catalysis · regioselectivity · palladium · stereoselectivity · vinyl ethers · C–H activation

3.1.2.1 Formation of Carbocycles

K. Geoghegan and P. Evans

The intramolecular Mizoroki–Heck reaction is an important method for the formation of cyclic molecules, which would often be nontrivial to assemble by alternative means. Coupling between an sp²-hybridized carbon atom and an alkene generates a C–C bond which is included within a newly formed ring. In the absence of an additional coupled process, a new alkene is also generated. A variety of ring sizes may be accessed in this class of reaction and in many instances the adducts may be isolated in excellent chemical yield. The process is typically effected under the influence of palladium catalysis and the many published examples indicate that a variety of functionalities may be tolerated without interference. Within this chapter, examples have been selected from the recent literature to illustrate the utility of this method for the construction of carbocyclic compounds.



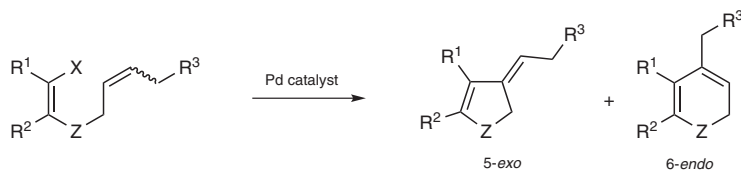
X = halide, pseudohalide

Keywords: intramolecular · Mizoroki–Heck reaction · cyclization · palladium · catalysis

3.1.2.2 Formation of Heterocycles

S. G. Stewart

The formation of heterocycles through the Heck cross-coupling reaction has been studied extensively as it allows potential efficient access to a large variety of compounds. High-yielding production of heterocyclic frameworks is of paramount importance in natural product based research as well as in medicinal chemistry programs. In particular, the intramolecular Heck reaction has been used extensively for this purpose. Cyclization methods producing the five-membered pyrrole ring contained within the indole ring system are by far the most common, possibly due to the plethora of such compounds found in nature and their corresponding biological activity. In most examples discussed in this chapter, the mechanism by which the intramolecular Heck cross coupling operates is through the standard oxidative addition, migratory insertion, C–C bond rotation, *syn*- β -hydride elimination, and reductive elimination pathway. However, sometimes this “standard” Mizoroki–Heck catalytic cycle is not always followed, and rare examples such as *anti*-elimination or oxidative Heck reaction (intramolecular Fujiwara–Moritani reaction) are further emphasized when they arise.



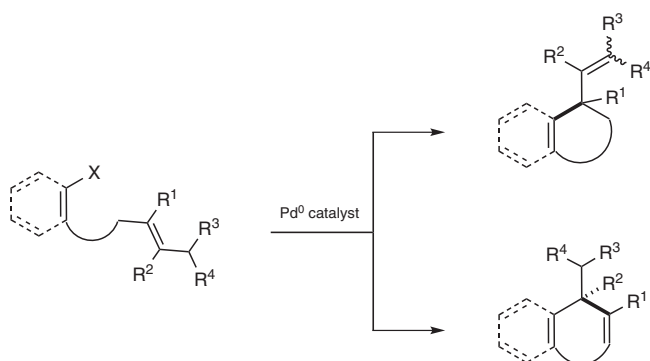
Z = NR⁴, O, S; X = halide

Keywords: Heck reaction · palladium · catalysis · intramolecular · heterocycles · cyclization

3.1.2.3 Stereoselective Formation of Tertiary and Quaternary Centers

G. Brogini, E. Borsini, and U. Piarulli

The intramolecular Heck (or Mizoroki–Heck) reaction represents a well-established methodology for the construction of isolated, fused, bridged, or spiroannulated rings of various sizes. Its asymmetric version has become a powerful tool for the synthesis of both tertiary and quaternary stereocenters. Within this chapter, intramolecular asymmetric Heck reactions are discussed in sections according to the following subdivision: (i) the substitution level of the stereocenter that is formed, i.e. the formation of tertiary stereocenters (by reaction of monosubstituted alkenyl carbon atoms) or quaternary stereocenters (by reaction of disubstituted alkenyl carbon atoms); (ii) the structure of the alkenyl substrate, i.e. acyclic or cyclic alkenes, leading to fused bi- or polycyclic products; (iii) the nature of the aryl or vinyl reagents, i.e. iodides, bromides, or trifluoromethanesulfonates; and (iv) reaction of prochiral substrates in the presence of chiral ligands, or control of the configuration of the newly formed stereocenter by existing elements of stereogenicity (use of chiral substrates).



X = I, Br, OTf

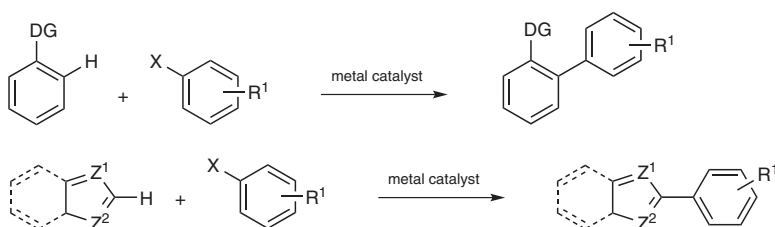
Keywords: homogeneous catalysis · asymmetric synthesis · Heck reaction · palladium · enantioselectivity · diastereoselectivity · cyclization · chiral ligands · intramolecular reactions · desymmetrization · spiro compounds · polycycles

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3.2.1 Intermolecular Coupling via C(sp²)–H Activation

A. Kantak and B. DeBoef

The synthesis of biaryl C–C bonds via the arylation of the C–H bonds of either simple arenes or heteroarenes is a rapidly expanding field. In particular, palladium, rhodium, ruthenium, iron, and copper catalysts can be used to couple a C–H carbon of one arene with a carbon bearing a reactive moiety such as a halogen, pseudohalogen, borane, or silane. Due to the ubiquity of C–H bonds in organic molecules, it is tempting to assume that these reactions will be plagued by the formation of multiple regioisomers; however, it has been repeatedly demonstrated that specific C–H bonds can be functionalized. The regioselectivity is often governed by the substrate, catalyst, or reaction conditions. This chapter describes the current state of the art in this field and guides the reader in choosing the appropriate reaction conditions for forming biaryl C–C bonds via C–H arylation. Particular focus is placed on substrates containing directing groups to achieve regioselectivity and on heteroaromatic substrates.



DG = directing group; Z¹ = NR², O, S; Z² = CH, N; X = I, Br, Cl, OTf, CO₂H, I⁺Ar¹, B(OR²)₂, SiR²₃

Keywords: arylation · heteroarenes · C–H activation · catalysis · biaryls

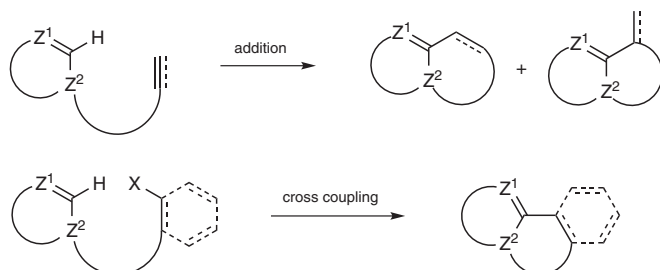
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3.2.2 Intramolecular Coupling via C(sp²)–H Activation

E. Suna and K. Shubin

This chapter focuses on transition-metal-catalyzed intramolecular C–H activation/C–C bond formation with a remote tethered carbon atom. All of the reviewed examples feature the in situ transformation of the aryl or hetaryl C–H bond into a reactive carbon–

metal bond. Palladium, rhodium, iridium, and ruthenium species are used as catalysts. Several classes of cyclization reactions are covered, including addition to multiple bonds (alkenes, alkynes, and ketones) and cross coupling with (pseudo)halides.



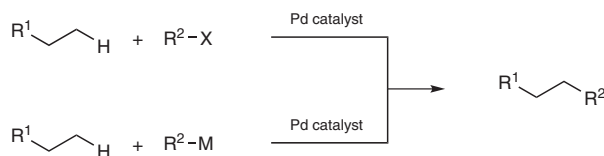
Keywords: palladium · rhodium · ruthenium · iridium · C–H activation · cross coupling · addition · cyclization · Fujiwara–Moritani · hydroarylation · intramolecular · enantioselective

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3.2.3 Coupling via C(sp³)–H Activation under Palladium Catalysis

D. Kalyani and L. V. Desai

This chapter describes the synthetic and mechanistic aspects of palladium-catalyzed arylation, carbonylation, alkenylation, and alkylation of C(sp³)–H bonds. Recent accomplishments in the enantioselective construction of C(sp³)–C bonds via C(sp³)–H activation are also detailed. Additionally, the few reported examples of the strategic application of these powerful C(sp³)–C bond forming transformations toward complex molecule synthesis are presented.



R² = aryl, alkenyl, alkyl; X = Cl, Br, I

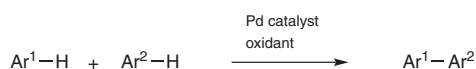
Keywords: palladium · C(sp³)–H activation · C–C bonds · asymmetric catalysis · arylation · alkenylation · carbonylation · alkylation

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3.3 C–C Cross Coupling via Double C–H Activation

C. S. Yeung, N. Borduas, and V. M. Dong

Palladium catalysts promote oxidative C–C bond formation between two arene coupling partners by twofold C–H activation. The observed regioselectivity for the biaryl products is predictable based on proximity to Lewis base functionality and inherent electronic bias.



Keywords: arylation · C–C bond formation · C–H bond activation · cross-coupling reactions · dehydrogenation · oxidation · palladium catalysis