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Recent Advances on Palladium Radical Involved Reactions

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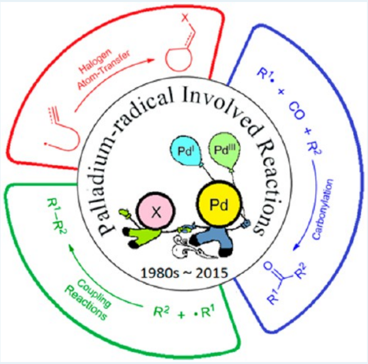
ABSTRACT: Transformations involving Pd(I) and Pd(III) have received growing attention over the past few years, providing various methodologies for the construction of numerous carbocyclic and heterocyclic ring systems. Compared with Pd(0)/(II)/(IV) chemistry, Pd(I)/(III)-mediated reactions are generally conducted through a single electron transfer process, leading to so-called palladium radical involved reactions. This review gives an up-to-date overview of catalytic methodologies involving palladium radical intermediates, which are sorted into two categories: (i) Pd(I) involved reactions and (ii) Pd(III) involved reactions. For most of these transformations, plausible mechanisms are demonstrated in detail. Clarification of these issues is the key point for understanding the palladium radical involved reactions and developing new high-performance methodologies.



KEYWORDS: *Pd-catalyzed, radical, atom transfer, carbonylation, coupling reactions*

1. INTRODUCTION

Pd-catalyzed transformations have become some of the most versatile and widely used synthetic tools in modern academic and industrial research in the past few decades.[1] Numerous applications of palladium catalysts have been developed for the preparation of fine chemicals, pharmaceutically active compounds, agrochemicals[2] and advanced materials as well as in natural product synthesis.[3] The significance of palladium catalysis was emphasized by the 2010 Nobel Price to R. Heck, A. Suzuki, and E. Negishi for their pioneering work in this field.[4] Palladium exhibits not only versatility and high functional-group tolerance but also facile interconversion between diverse oxidation states, which is responsible for the broad utility of palladium in organic chemistry.

Generally, palladium appears in three oxidation states: Pd(0), Pd(II), and Pd(IV). The catalytic Pd(0)/Pd(II) cycles are quite universal to various coupling reactions such as Heck, Stille, Suzuki, Sonogashira, and Buchwald−Hartwig coupling, Wacker oxidation, and allylic acetoxylation. In addition, Pd(II)/Pd(IV) cycles are well-established, in which many strong oxidants such as $PhI(OAc)_2$, $PhI(TFA)_2$, $PhICl_2$, Oxone, H_2O_2, and Selectfluor® have been applied.[5] It is well-known that both the Pd(0)/Pd(II) and Pd(II)/ Pd(IV) catalytic cycles are achieved through a double electron transfer process and that the final bond-formation step occurs through reductive elimination from a high-valent metal catalyst.[6] Recently, single electron transfer (SET) processes involving Pd(I) and Pd(III) intermediates, leading to so-called Pd radical involved reactions, have caught more and more attention.[7] In 2014, Studer and Curran contributed a review named "The electron is a catalyst", which modernized and simplified concepts of redox catalysis of radical reactions in organic synthesis.[8] A variety of transition metals, such as nickel, iron, copper, ruthenium, and iridium, can readily induce radical processes,[9] but Pd-mediated radical reactions are not quite as well exploited. Nevertheless, there has recently been a dramatic rise in the development of SET processes in palladium catalysis. The development of these new methodologies is significantly expanding the scope of Pd-catalyzed processes. In 2012, the Ritter group presented an elegant account of Pd(III) chemistry,[10] but there has been no comprehensive summary of Pd radical involved chemistry. This review summarizes the main achievements in this area. It is organized with respect to Pd(I) and Pd(III) involved reactions, and most of the reaction mechanisms are highlighted.

2. PD(I) INVOLVED REACTIONS

To date, Pd(I) complexes have normally shown two forms (Figure 1): monomers (I and II) and dimers (III, IV, and V).

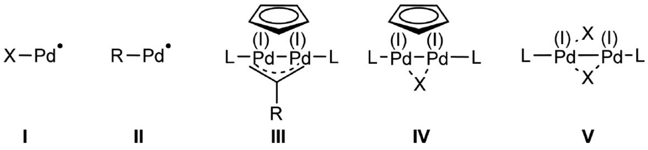


Figure 1. Pd(I) complexes.

Generally, Pd(I) monomers can be formed via single-electron oxidation of Pd(0)[11] and subsequently participate in radical-chain or hybrid organometallic−radical pathways. A number of

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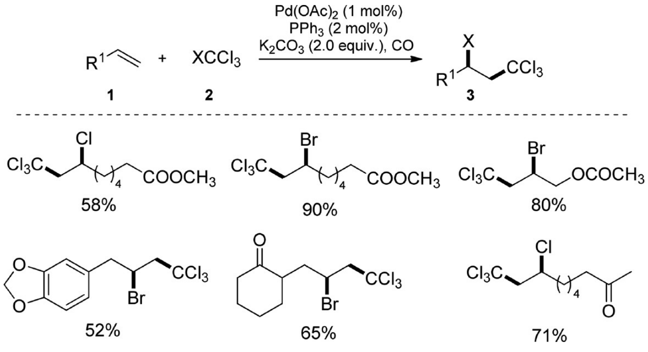
Pd(I) dimer species featuring distinct Pd−Pd bonds have been synthesized[12] or partially detected or isolated from catalytic transformations.[13] This section will present examples of Pd(I)-catalyzed reactions and mechanisms, organized in terms of halogen-atom transfer reactions, carbonylation reactions, and coupling reactions. Hence, publications focusing primarily on Pd(I) complex characterization are not discussed here.

2.1. Halogen-Atom-Transfer Reactions. Pd-catalyzed carbohalogenation of terminal alkenes was achieved by the Tsuji group via homolytic cleavage of the C−Cl/Br bonds of CCl_4 and $BrCCl_3$ (Scheme 1).[14] CO atmosphere could accelerate the reaction speed, and bases such as NaOAc and K_2CO_3 could improve the yield. Olefins bearing an ester, ketone, or ether group afforded the desired products in good yields (Scheme 1). When high-pressure carbon monoxide was applied, esters could be obtained besides the addition products.[15] In 2002, the Oshima group performed the Pd(0)-catalyzed reaction of terminal alkenes with bromotrichloromethane in a heterogeneous aqueous system within 2 h at room temperature.[16] They found that surfactants lowered the efficiency of the reaction, indicating that the heterogeneous aqueous system could be an excellent medium for substrates insoluble in water.

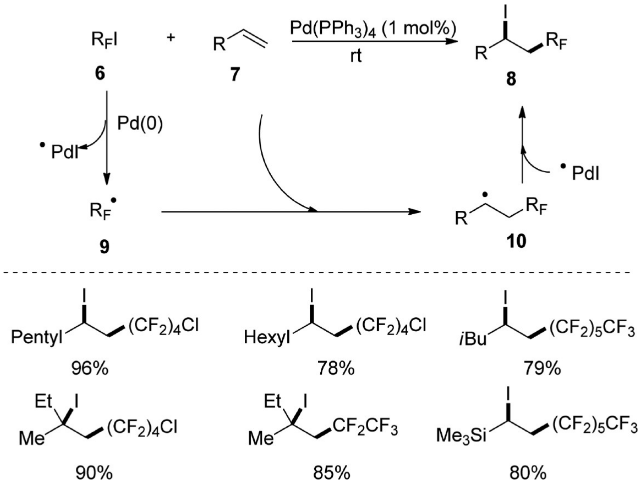
Scheme 1. Tsuji's Pd-Catalyzed Carbohalogenation of Terminal Alkenes with CCl_4 and $BrCCl_3$



A plausible single electron transfer mechanism is depicted in Scheme 2. Homolytic cleavage of the C−Cl bond of polyhaloalkanes afforded trichloromethyl radical **4** in the presence of Pd(0). Subsequently, the radical addition to alkene **1** formed the new radical **5**, which abstracted halide from either the polyhaloalkane or PdX to generate the product **3**.

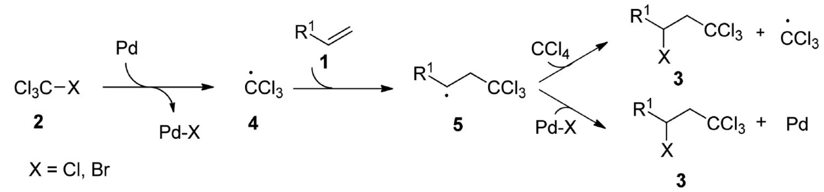
Chen et al.[17] reported $Pd(PPh_3)_4$-initiated addition of fluoroalkyl iodides to alkenes, including a detailed mechanistic study of the single electron transfer process. The reaction occurred at room temperature without any solvent and gave the corresponding adducts in excellent yields. The palladium complex $C_2F_5PdI(PPh_3)_2$, generated from Pd(0) and C_2F_5I via traditional oxidative addition, was isolated and characterized by X-ray crystallography. However, it could not react with the alkene, suggesting that $C_2F_5PdI(PPh_3)_2$ was not the intermediate, thus excluding the oxidative addition pathway. On the other hand, electron paramagnetic resonance (EPR) experiments on the reaction of $Cl(CF_2)_4I$ with Pd(0) showed an apparent signal in the presence of the radical trapping reagent *N-tert*-butyl-α-phenylnitrone, confirming the existence of the R_F radical. A Pd(0)-mediated radical-chain process was proposed in this reaction, as shown in Scheme 3. The formation of radical **9** was initiated by Pd(0), followed by the addition of **9** to the alkene to afford the secondary radical **10**. Then Pd(I)I complex rejoined intermediate **10** to produce the carboiodination product **8**. Alkenes bearing electron-donating groups exhibited better reactivity than those with electron-withdrawing groups. In addition, nonterminal alkenes resulted in lower conversion, and fluoroalkyl bromides did not give the desired product. In 1995, Burton and co-workers applied iododifluoromethylphosphonate and iododifluoromethyl ketones in a similar carboiodination of terminal alkenes (Scheme 4).[18] Variety of α,α-difluoro functionalized Phosphonates and ketones were obtained in high yields with good functional group tolerance.

Scheme 3. Chen's Pd(0)-Initiated Addition of Fluoroalkyl Iodides to Alkenes

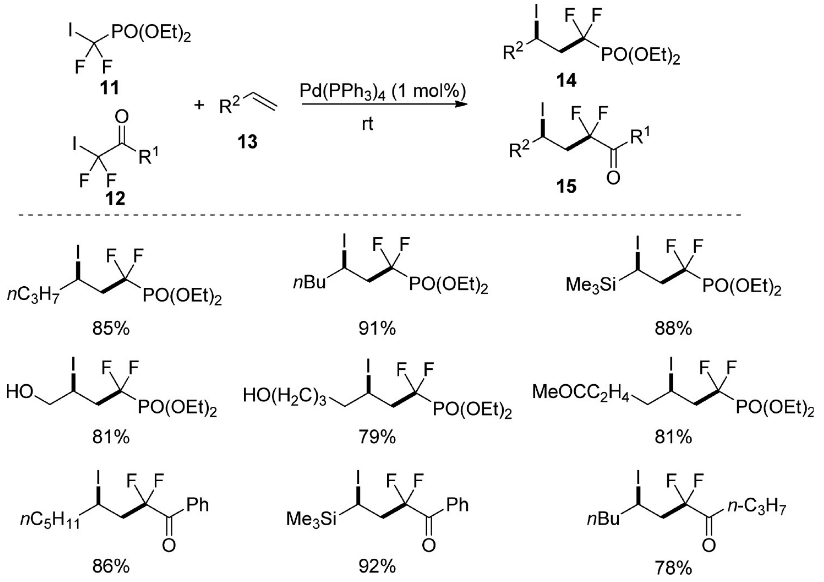


In the 1980s, Mori, Ban, and co-workers developed a Pd(0)-catalyzed ene-halogenocyclization of unsaturated α-iodocarbonyls into a powerful synthetic tool, but the reaction mechanism was not well investigated.[19] In 1990, Curran and Chang[20] studied the mechanism of halogenocyclization by comparing the cyclization of α-iodocarbonyls to that of γ-iodocarbonyls using catalytic quantities of either hexabutylditin or Pd(0) (Scheme 5). Iodo ester **16** produced a mixture of *cis*/*trans*-**17** and *cis*/*trans*-**18** in excellent overall yield (Scheme 5, eq 1). The ^{1}H NMR spectra of the two crude reaction mixtures were virtually identical and the same ratio and yields were obtained, indicating that the Pd(0) catalyst did not serve as Pd(0) performed in an organometallic

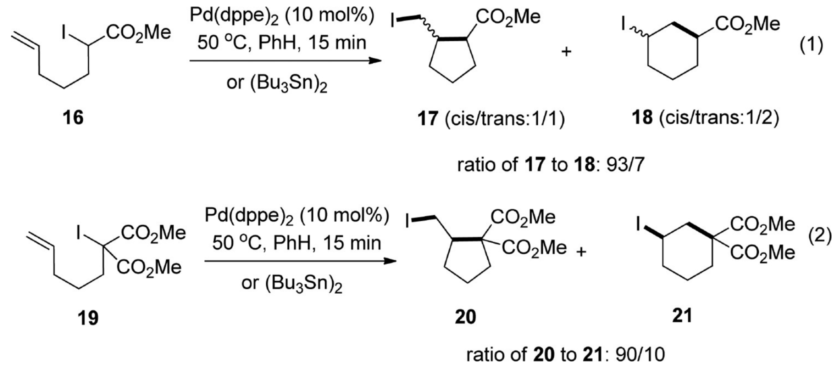
Scheme 2. Mechanism for Pd-Catalyzed Carbohalogenation of Terminal Alkenes



Scheme 4. Burton's Pd(0)-Catalyzed Addition of Iododifluoromethylphosphonate and Iododifluoromethyl Ketones to Alkenes



Scheme 5. Curran's Pd(0)-Catalyzed Isomerization Reactions of Unsaturated α-Iodocarbonyls

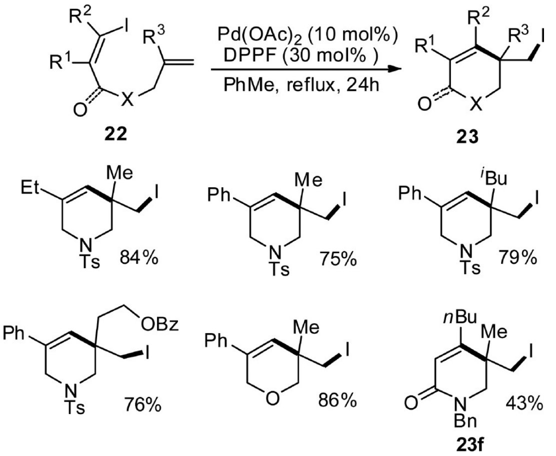


reaction but rather as a promoter of a free radical chain. The ratio of products generated from iodomalonate **19** was identical whether the isomerization was conducted using $(Bu_3Sn)_2$ or Pd(0). In contrast, allylic iodides showed no tendency to go through a radical process.

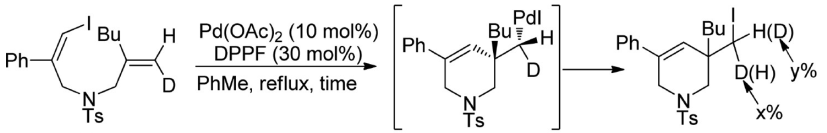
In the past few years, the groups of Lautens,[21] Doyle,[22] and Tong[23] separately reported various Pd-catalyzed carbohalogenation reactions of alkenes via halogen atom transfer processes that proceeded through a traditional Pd(0)/Pd(II) pathway. Among these reports, the Tong group described a Pd-catalyzed iodine atom transfer cycloisomerization of (*Z*)-1-iodo-1,6-diene, affording a facile method to construct six-memebered heterocycles bearing an alkyl iodide group (Scheme 6).[24] The combination of 30 mol % 1,1′-bis(diphenylphosphino)ferrocene (dppf) and 10 mol % $Pd(OAc)_2$ proved not only to be the optimal choice for the cycloisomerization but also to promote a radical transfer process of the product that was responsible for scrambling the stereochemistry of the alkyl iodide. A wide range of (*Z*)-1-iodo-1,6-dienes presenting a nitrogen or oxygen linkage delivered alkyl iodide derivatives **23** in moderate to good yields. An R^1 group was well-tolerated with both alkyl and aryl substituents, but an R^2 group led to lower reactivity of the transformation (**23f**, Scheme 6).

To study the reaction mechanism, deuterium scrambling experiments were performed at different reaction times (Scheme 7). Within 2 h, **26a** was isolated in 60% yield without deuterium scrambling. With increasing reaction time, the corresponding products were isolated in higher yields with increased deuterium scrambling. When the reaction time was prolonged to 24 h, the deuterium scrambling reached 35% and 40%, disclosing that the deuterium scrambling happened after the formation of the alkyl iodide via a radical pathway. However, in the presence of 2 equiv of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as a radical

Scheme 6. Tong's Pd-Catalyzed Iodine Atom Transfer Cycloisomerization of (*Z*)-1-Iodo-1,6-dienes



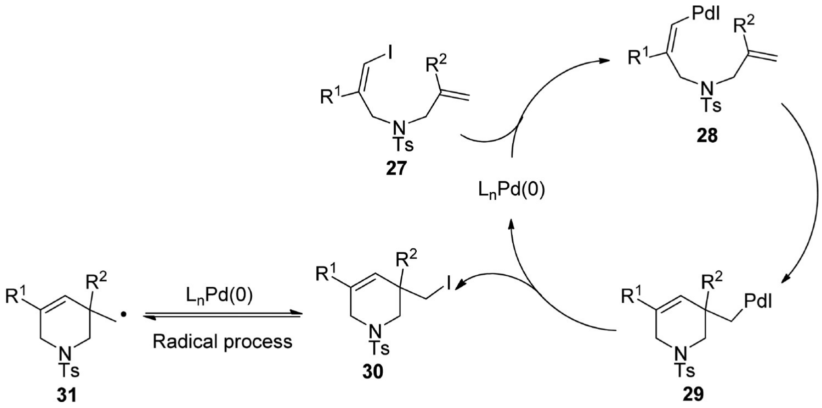
Scheme 7. Deuterium Scrambling Experiments



24 (75% D) 25 26 a-e

entry	time	24 recovery	product	isolated yield
1	2 hr	33%	**a** (x = 75, y = 0)	60%
2	6 hr	20%	**b** (x = 73, y = 2)	64%
3	10 hr	5%	**c** (x = 71, y = 4)	75%
4	16 hr	0%	**d** (x = 58, y = 17)	79%
5	24 hr	0%	**e** (x = 40, y = 35)	72%

Scheme 8. Proposed Mechanism for Pd-Catalyzed Carbon−Halide Bond Formation

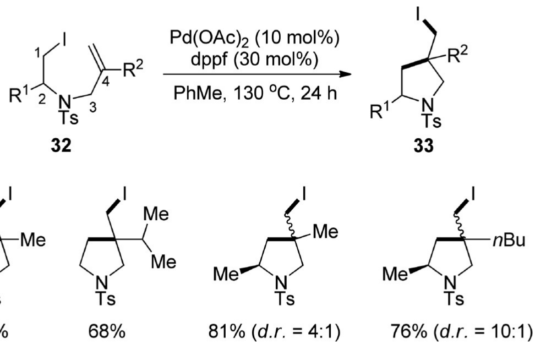


scavenger, the deuterium scrambling was shut down, indicating that the radical pathway was inhibited.[25]

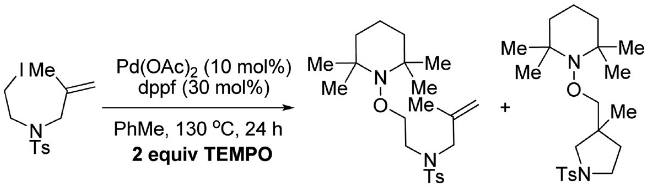
A proposed mechanism is shown in Scheme 8. The iodine atom transfer cycloisomerization was initiated by oxidative addition of Pd(0) to the vinyl iodide, which was followed by alkene insertion and C(sp^3)−I bond reductive elimination to produce the desired product **30**. In the presence of $Pd(OAc)_2$/dppf, alkyl iodide **30** underwent a reversible radical process. This work presented a detailed mechanistic investigation of the C(sp^3)−I bond formation that was helpful for the further development of Pd-catalyzed carbon−halide bond construction.

In 2012, Jiang and co-workers applied the same conditions as Tong to an atom transfer radical cyclization of unactivated alkyl iodides (Scheme 9).[26] Various 5-hexenyl iodides **32** afforded the corresponding alkyl iodide derivatives **33** in moderate to good yields. Substitutions at C2 and C4 were well-tolerated. However, six- and seven-membered rings could not be formed through this procedure. To probe the mechanism, the radical scavenger TEMPO was used in this system. The TEMPO adducts **35** (8% yield) and **36** (3% yield) were isolated, indicating that a radical process was involved (Scheme 10).

Scheme 9. Jiang's Pd-Catalyzed Atom Transfer Radical Cyclization of Inactivated Alkyl Iodides



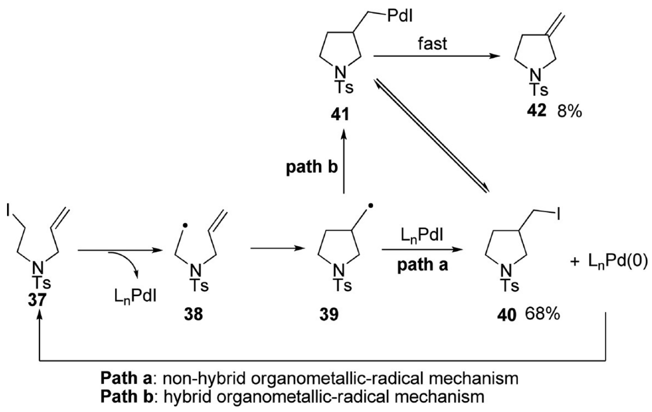
Scheme 10. TEMPO Testing Experiments



34 75% of **34** was recovered **35** 8% yield **36** 3% yield

A nonhybrid organometallic−radical mechanism was proposed (Scheme 11, path a). In the presence of the Pd(0) catalyst, substrate **37** produced an L_nPdI species and carbon-centered free radical **38** via a single electron transfer process. Intramolecular radical addition of intermediate **38** could form a second carbon-centered free radical, **39**, and subsequent iodide abstraction from the L_nPdI species would deliver the iodide atom transfer cyclization product **40** with concomitant regeneration of the catalyst. On the other hand, the hybrid organometallic−radical mechanism (path b) could also be responsible for product **40**. Since alkylpalladium intermediate **41** underwent β-H elimination rapidly, it barely had a chance to generate alkyl iodide product **40** via reductive elimination, indicating that the hybrid

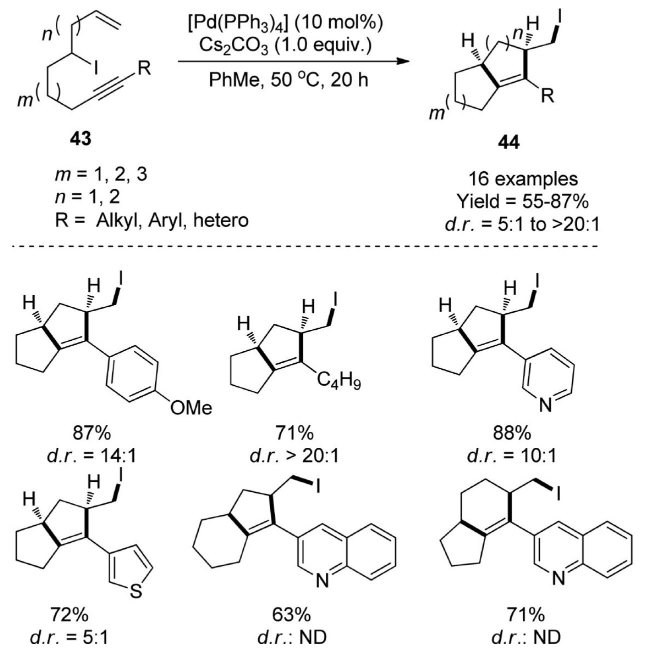
Scheme 11. Proposed Mechanism for Atom Transfer Radical Cyclization of Inactivated Alkyl Iodides



organometallic−radical mechanism was not so reasonable.[20] This explanation provided a complementary understanding of the hybrid organometallic−radical mechanism of palladium radical chemistry.

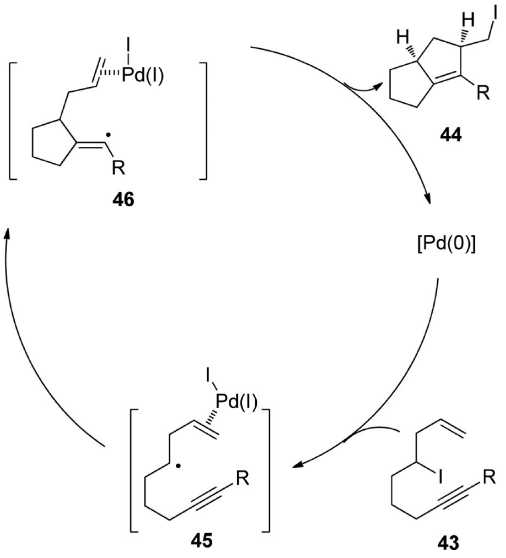
Atom transfer radical cyclization was also performed in alkyne-containing substrates. In 2013, Monks and Cook[27] demonstrated a Pd-catalyzed iodine transfer reaction delivering primary iodides from acyclic secondary iodides with concomitant creation of a bicyclic ring bearing stereo- and regiodefined tetrasubstituted olefins (Scheme 12). The reaction was performed in the presence of $[Pd(PPh_3)_4]$ and Cs_2CO_3 in PhMe at 50 °C for 20 h. The substituents on the alkynes exhibited good tolerance to a variety of alkyl, aryl, and heterocycles. Cs_2CO_3 played an important role in the reduction of Pd(II) species to inhibit precipitation of $[Pd(PPh_3)_2I_2]$. On the other hand, superstoichiometric amounts of iodine additive could shut down the reaction completely. In preliminary mechanistic studies, the poorly stereoselective, reversible, two-electron oxidative addition was not responsible for the formation of racemic product from enantioenriched secondary iodide, which ruled out the S_N2 oxidative addition. At the same time, phosphine ligands could impact the conversion and diastereomeric ratio (d.r.) of the transformation, arguing against a purely free radical process.

Scheme 12. Cook's Pd-Catalyzed Iodine Transfer Reaction of Alkyne-Containing Substrates



On the basis of the experimental results, a possible mechanistic pathway was proposed (Scheme 13). Palladium(0) played the role of a radical initiator to generate radical intermediate **45** by abstraction of an iodide radical from **43**. Intermolecular radical addition and cyclization then formed intermediate **46**, which subsequently furnished the bicyclic ring bearing a primary alkyl iodide in the presence of Pd(I)I.

Scheme 13. Proposed Catalytic Cycle for the Pd-Catalyzed Iodine Transfer Reaction



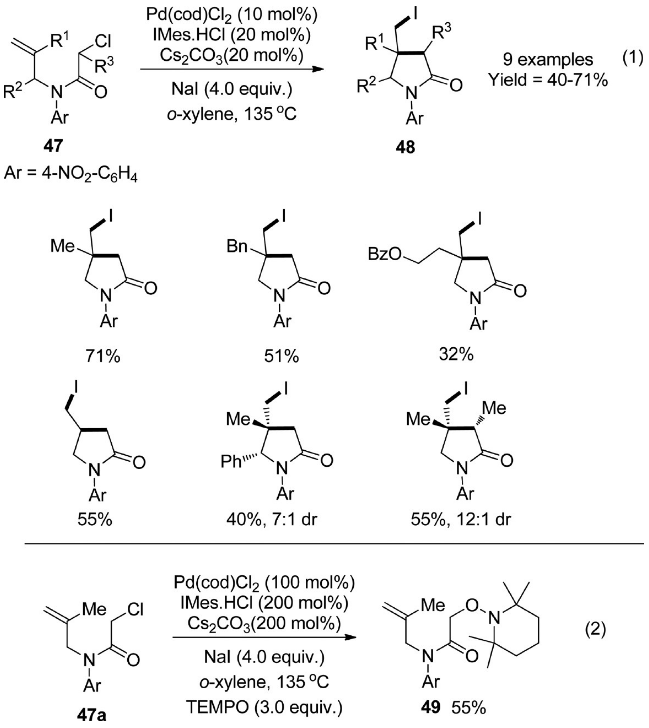
Very recently, the Tong group demonstrated an atom transfer radical cyclization of *N*-allyl-*α*-chloroamides in the presence of $Pd(cod)Cl_2$/IMes (cod = 1,5-cyclooctadiene; IMes = 1,3-dimesitylimidazolium chloride). which provided a facile way to synthesize *β*-iodomethyl-*γ*-lactams (Scheme 14).[28] When 3.0 equiv of TEMPO was introduced under the standard conditions, the transformation was completely suppressed. However, when a stoichiometric amount of the palladium catalyst was used, the TEMPO adduct **49** was obtained in 55% yield (Scheme 14, eq 2). Both of these control experiments indicated that the reaction proceeded via a radical mechanism.

2.2. Carbonylation.

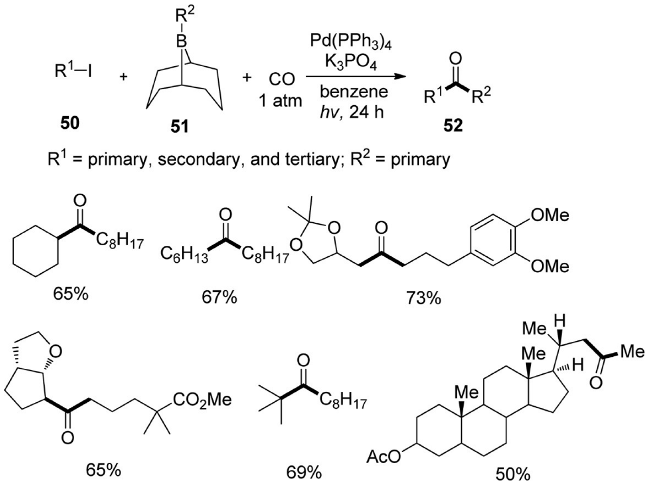
A palladium-catalyzed carbonylative cross-coupling reaction of iodoalkanes with 9-alkyl-9-borabicyclo[3.3.1]nonyl (9-alkyl-9-BBN) derivatives was achieved by the Suzuki group in 1991 (Scheme 15).[29] The 9-alkyl-9-BBN derivatives were generated in situ from terminal alkenes. The alkyl iodides could be primary, secondary, and tertiary. The reaction was extremely accelerated by irradiation with 100 W unsmoked tungsten light, suggesting that a free radical process was involved in the oxidative addition of the iodoalkane to the Pd(0) complex.

In 1995, Miyaura and co-workers reported a Pd-catalyzed intramolecular cyclization and carbonylative coupling reaction for the synthesis of unsymmetrical ketones from 6-iodo-1-hexene derivatives (Scheme 16).[30] The cyclization of unsaturated iodides always produced five-membered rings instead of six-membered ones in moderate to high yields. The radical oxidative addition of the iodoalkene to Pd(0) allowed the intramolecular

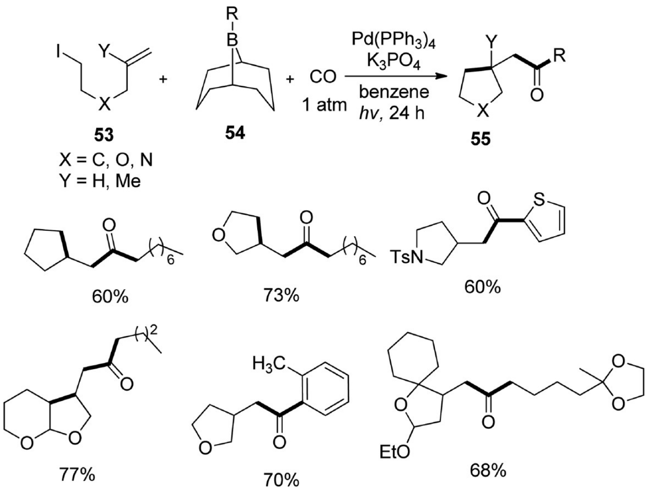
Scheme 14. Tong's Pd(0)-Catalyzed Atom Transfer Radical Cyclization of *N*-Allyl-*α*-chloroamides



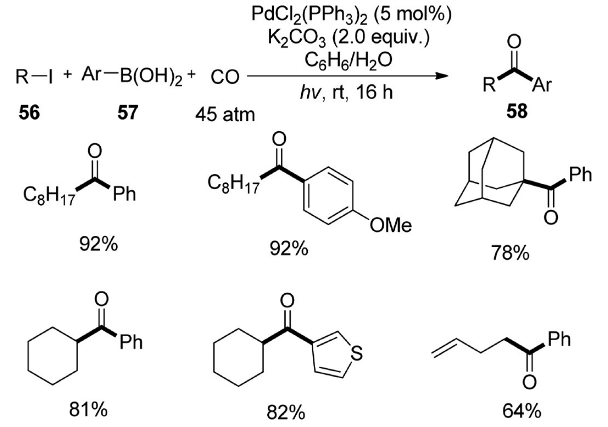
Scheme 15. Suzuki's Pd-Catalyzed Carbonylative Cross-Coupling Reaction of Iodoalkanes with 9-Alkyl-9-BBN Derivatives



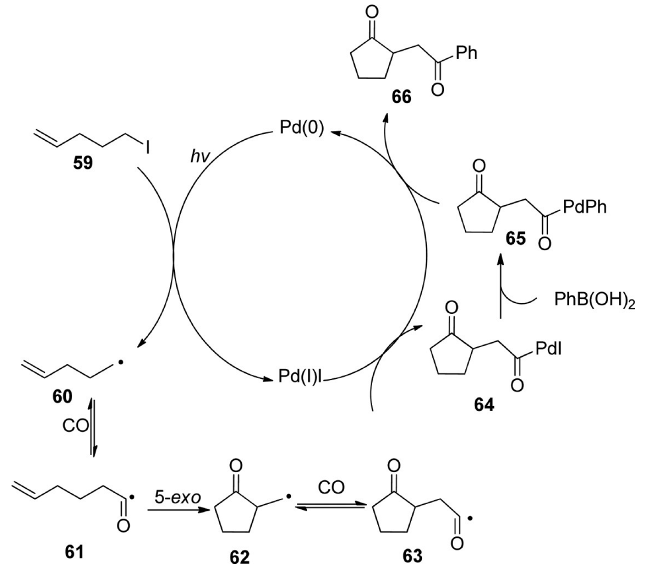
Scheme 16. Miyaura's Pd-Catalyzed Carbonylative Cross-Coupling of Iodoalkenes, CO, and 9-BBN Derivatives



Scheme 17. Ryu's Pd-Catalyzed Carbonylation for Alkyl Aryl Ketone Synthesis



Scheme 18. Proposed Mechanism for Pd-Catalyzed Carbonylation

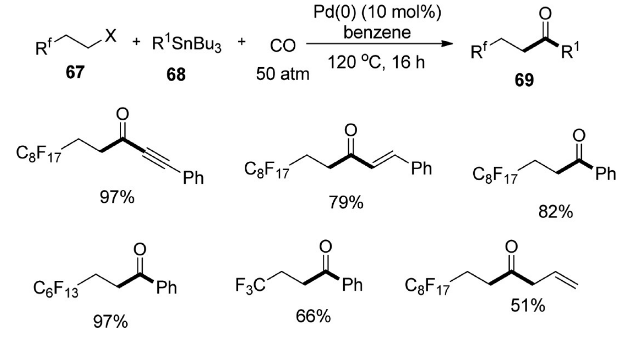


cyclization of the iodoalkene to form the five-membered ring prior to the couplings with CO and the boron reagent.

The Ryu group made a big contribution to palladium-catalyzed carbonylation of alkyl iodides, and an elegant review was recently reported.[31] Compared with the work of Suzuki, Ryu and coworkers applied readily available and easily handled arylboronic acids to the carbonylative coupling reaction of alkyl iodides to give good yields of alkyl aryl ketones (Scheme 17).[32] Both the alkyl iodides and arylboronic acids exhibited excellent compatibility. The tertiary iodide gave the coupling product in 78% yield, and the homoallylic iodide afforded the ketone in 64% yield. The proposed mechanism is depicted in Scheme 18. First, Pd(0) abstracted the iodine atom from alkyl iodide **59** to afford alkyl radical **60** and Pd(I)I under irradiation conditions. Subsequently, the acyl radical **61** was generated via the addition of CO, followed by 5-exo cyclization to give alkyl radical **62**. Then a second molecule of CO added to alkyl radical **62** to form acyl radical **63**, which could couple with Pd(I)I to form acylpalladium intermediate **64**. In the end, transmetalation and reductive elimination afforded the product **66** with accompanying liberation of Pd(0).

The carbonylative coupling reaction of β-perfluoroalkyl-substituted alkyl halides and organostannanes was achieved in the presence of a Pd(0) complex to afford the corresponding fluorine-containing ketones in good yields (Scheme 19).[33] Allyl-, vinyl-, phenyl-, and alkynyl-substituted stannanes could be converted to the corresponding fluorine-containing ketones efficiently.

Scheme 19. Fuchikami's Carbonylative Coupling Reaction of β-(Perfluorooctyl)ethyl Halides with Organostannanes

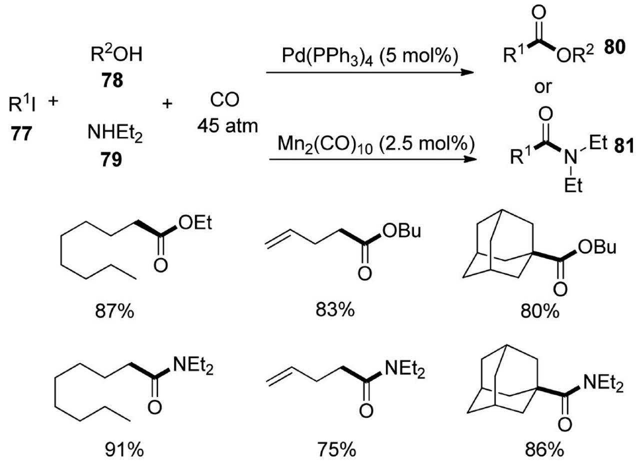


In 2002, Ryu, Komatsu, and co-workers developed a Pd/light-catalyzed multiple carbonylation and cyclization of 4-alkenyl iodides through a hybrid radical/Pd pathway (Scheme 20).[34]

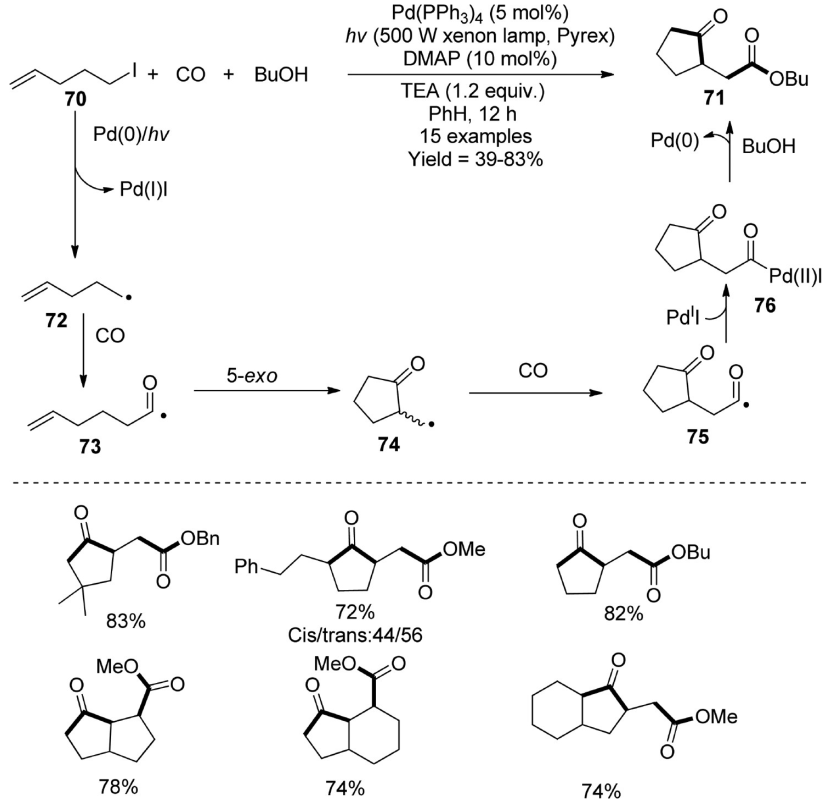
Generally, primary alkyl iodides resulted in moderate to good yields. When secondary iodides were used, the products were stereoisomers, indicating that a radical process was involved. The proposed mechanism is shown in Scheme 20. Palladium(0) combined with $h\nu$ generated radical **72**, which subsequently underwent CO addition, 5-exo-trig acyl radical cyclization and a second CO addition to afford acyl radical **75**. Then the combination of **75** with Pd(I)I formed acylpalladium intermediate **76**, leading to the final product in the presence of BuOH.

Without a double bond on the alkyl iodide, the carbonylation could also work very well. Both esters and amides were synthesized by Ryu in the presence of Pd(PPh$_3$)$_4$ or Mn$_2$(CO)$_{10}$ under photoirradiation conditions (Scheme 21).[35]

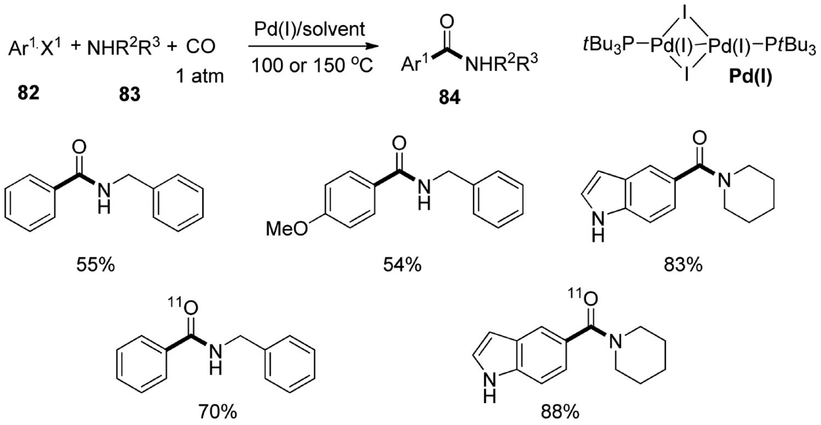
Scheme 21. Ryu's Pd-Catalyzed Carbonylation of Iodoalkanes with Diethylamine



Scheme 20. Pd/Light-Induced Cyclizative Carbonylation Reactions of 4-Alkenyl Iodides



Scheme 22. Vilar's Aminocarbonylation Reactions of Aryl Halides Catalyzed by Pd(I) Dimers

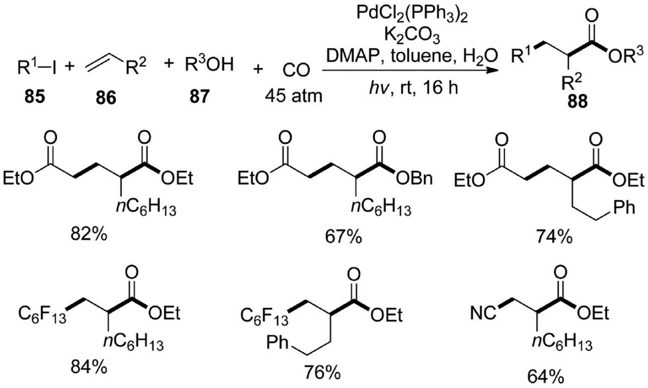


Primary, secondary, and tertiary iodides were all suitable for esterfication and amidation systems. Notably, when amines were used as coupling reagents, palladium catalysis gave keto amides via double carbonylation, whereas $Mn_2(CO)_{10}$ could selectively deliver single-carbonylation amides with diethylamine. It is worth mentioning that the atom transfer carbonylation leading to esters could also proceed in the absence of the Pd(0) and $Mn_2(CO)_{10}$ catalysts, but the catalysts accelerated and improved this transformation.[36]

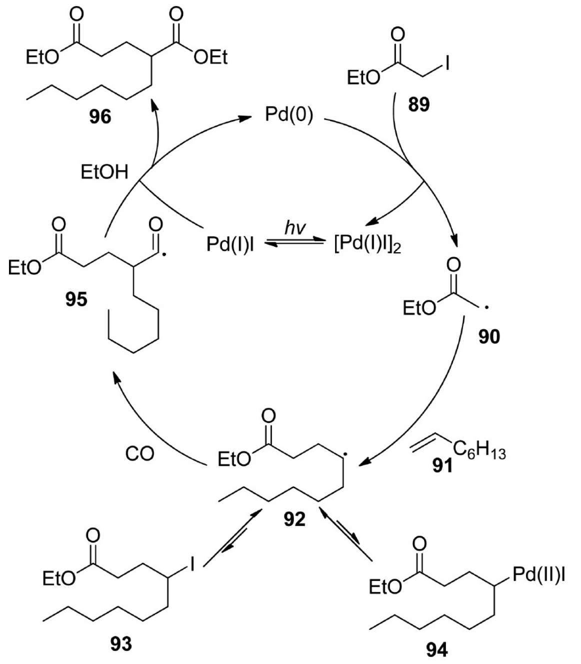
In 2011, Vilar and co-workers reported a Pd(I) dimer-mediated aminocarbonylation of aryl halides to give amides in high yields (Scheme 22).[37] The reaction could be finished within 10 min, allowing this methodology to be applied in the synthesis of radiolabeled amides for positron emission tomography imaging using ^{11}CO gas.

In 2011, the Ryu group described a four-component coupling reaction leading to functionalized esters using α-substituted iodoalkanes, alkenes, CO, and alcohols under combined Pd/light conditions (Scheme 23).[38] It is worth mentioning that the alkyl iodides were activated ones that were substituted by electron-withdrawing groups. A possible mechanism is shown in Scheme 24. The alkyl radical **90** was generated through single electron transfer from the photoirrariated Pd(0) complex, which added to the alkene to form the new alkyl radical **92**. Then **92** was trapped by carbon monoxide and alcohol subsequently to generate the product **96**. Alternatively, radical species **92** could also trap Pd(I) to afford Pd(II) intermediate **94** or abstract an iodine atom from **89** to give iodoalkane **93**. However, no β-elimination products were observed, indicating these two processes scarcely contributed in this system.

Scheme 23. Ryu's Four-Component Coupling Reactions Leading to Esters



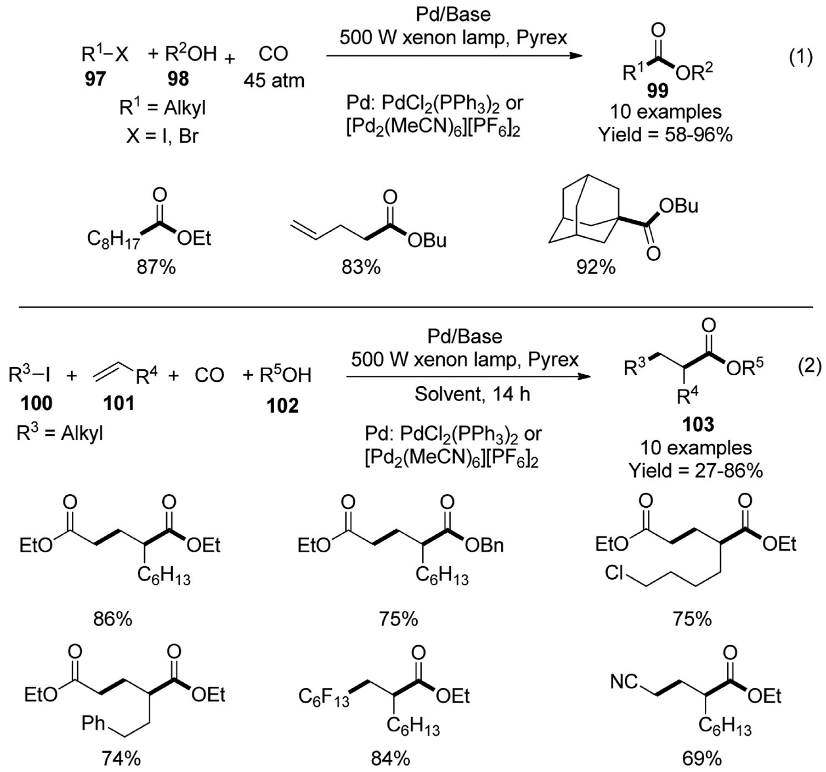
Scheme 24. Proposed Mechanism for the Four-Component Coupling Reaction



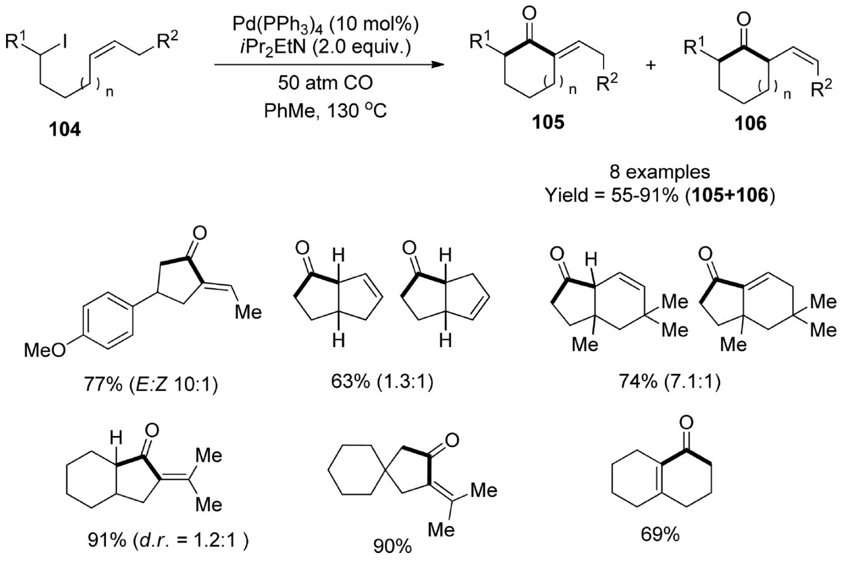
The same strategy was applied in the atom transfer carbonylation of alkyl iodides by the Ryu group in 2012 (Scheme 25).[39] Both three- and four-component coupling reactions proceeded smoothly to produce a wide range of carboxylic acid esters in good to excellent yields. The Pd dimer complex $[Pd_2(MeCN)_6][PF_6]_2$[40] could undergo homolysis under photoirradiation conditions to produce a pair of Pd radicals, which induced both three- and four-component coupling reactions very well. This protocol provided a general synthetic approach for the synthesis of carboxylic acid derivatives via useful cascade sequences.

In 2010, Bloome and Alexanian[41] developed a Pd-catalyzed carbonylative Heck-type cyclization of unactivated alkyl iodides (Scheme 26). Both primary and secondary alkyl iodides worked smoothly to provide a variety of synthetically versatile enone products. To explore the reaction pathway, TEMPO (1.0 equiv) was added to the reaction of alkyl iodide **107** (Scheme 27). Besides the products **108** and **109**, which were isolated in 65%

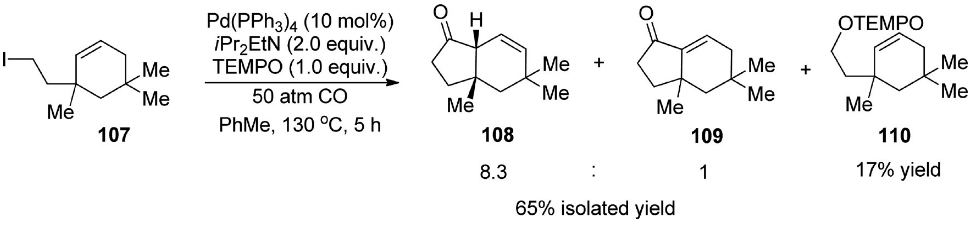
Scheme 25. Ryu's Pd-Catalyzed Carbonylation of Alkyl Halides



Scheme 26. Alexanian's Pd-Catalyzed Carbonylative Cyclization of Alkyl Iodides



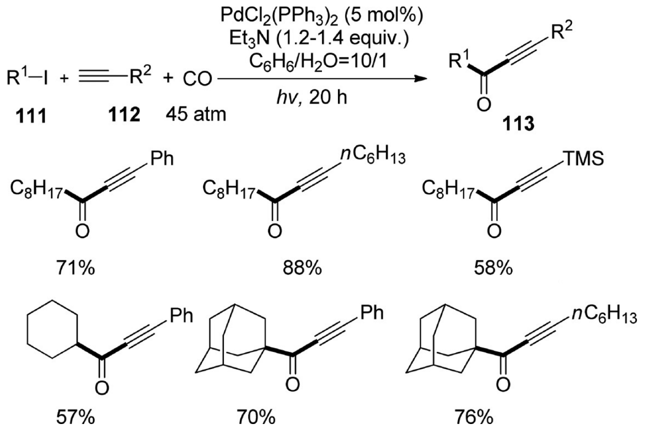
Scheme 27. Carbonylative Cyclization of Alkyl Iodide 107 in the Presence of TEMPO



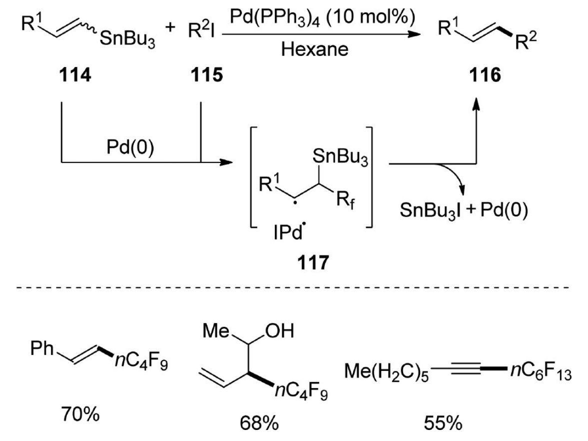
yield, the TEMPO adduct **110** was also observed in 17% yield by ^{1}H NMR spectroscopy, indicating the potential involvement of carbon-centered radicals in this transformation.

In 2010, Ryu and co-workers demonstrated Pd/light-induced three-component coupling reactions of iodoalkanes, CO, and 1-alkynes to deliver alkynyl ketones in good yields (Scheme 28).[42]

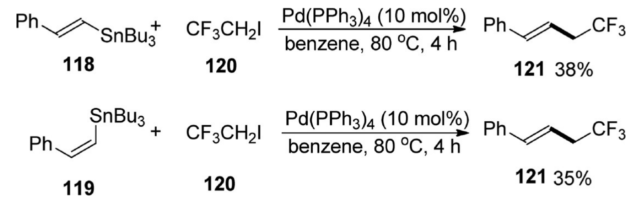
Scheme 28. Ryu's Carbonylative Sonogashira Coupling Reaction Leading to Alkynyl Ketones



Scheme 29. Matsubara's Pd-catalyzed Cross-Coupling of Perfluoroalkyl Iodides with Organotin Compounds



Scheme 30. Examination of the Stereospecificity with l-Iodo-2,2,2-trifluoroethane



Primary, secondary, and tertiary alkyl iodides were all well-tolerated. Both phenyl and alkyl alkynes provided the corresponding products efficiently. The use of readily available alkyl iodides and terminal alkynes made it a promising procedure for alkynyl ketone synthesis.

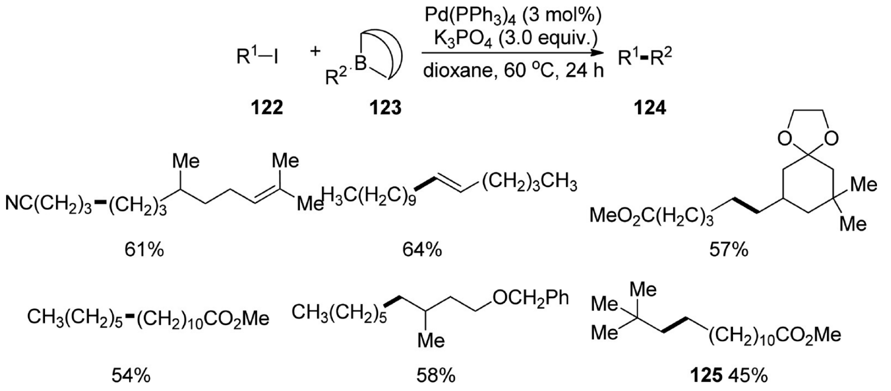
2.3. Coupling Reactions. Pd-catalyzed cross-coupling reactions have been developed for about half a century, among which Pd(0)/(II)-mediated reactions have been investigated extensively in both academia and industry. Recently, Pd(I)-involved cross-coupling reactions have attracted more and more attention, and some elegant coupling methodologies have been achieved, such as the Suzuki, Heck, Negishi, and Stille couplings, among others.

2.3.1. Coupling with Organometallic Reagents. Matsubara et al.[43] realized a Pd-catalyzed Stille coupling of perfluoroalkyl iodides with alkenyl-, allyl-, and alkynylstannanes to deliver alkenes and alkynes bearing a perfluoroalkyl group (Scheme 29). To explore the stereospecificity of the reaction, (*E*)- and (*Z*)-stannanes were separately examined with iodide **120**. The two reactions provided the same *E* coupling product **121**, indicating that the reaction might involve a radical process (Scheme 30). In the presence of Pd(0), the perfluoroalkyl radical could be generated and subsequently add to the alkenylstannane to afford radical intermediate **117**. Then elimination of iodotributylstannane could yield the corresponding product **116**.

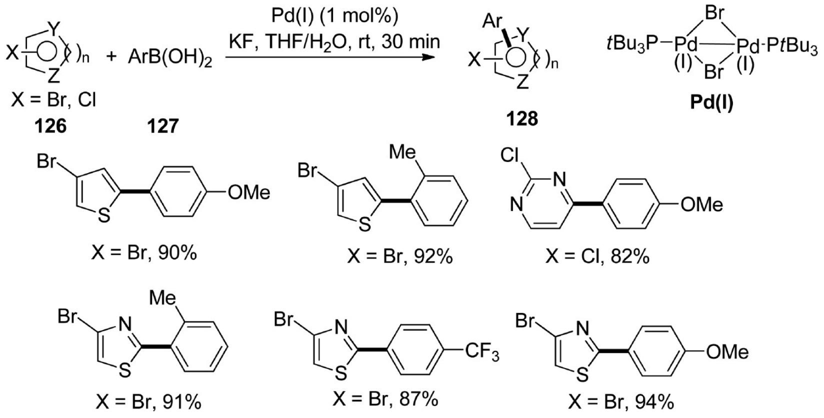
In 1992, Suzuki and co-workers described a $Pd(PPh_3)_4$-catalyzed cross-coupling reaction using 9-alkyl-9-BBN derivatives and alkyl iodides to deliver coupling products in fairly good yields (Scheme 31).[44] It is worth noting that neopentyl iodide worked very well (**125**, Scheme 31), while secondary iodides and secondary bromides did not provide the corresponding products. The reaction exhibited quite good tolerance of functionalized boronates containing cyano, ester, and acetal groups, among others.

The reactivity and stability of the dinuclear Pd(I)−Pd(I) complex $[Pd(PtBu_3)Br]_2$ was investigated through experimental, computational, and spectroscopic techniques by the Schoenebeck group (Scheme 32).[45] $[Pd(PtBu_3)Br]_2$ as a precatalyst exhibited excellent catalytic activity in Suzuki cross-coupling, which provided high regio- and chemoselectivities in short reaction times at room temperature. Dibrominated thiophenes underwent the Suzuki coupling at the 2-position with high selectivity. 2,4-Dichloropyrimidine and 2,4-dibromothiazole also gave the selective coupling products under identical conditions (Scheme 32). Both ^{31}P NMR and density functional theory (DFT) studies indicated that the real catalyst was not the dimer

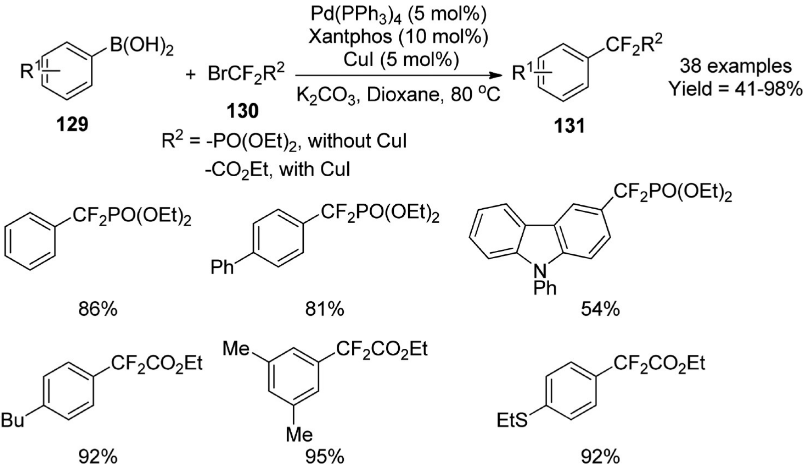
Scheme 31. Suzuki's Pd-Catalyzed Cross-Coupling of Alkyl Iodides with 9-Alkyl-9-BBN Derivatives



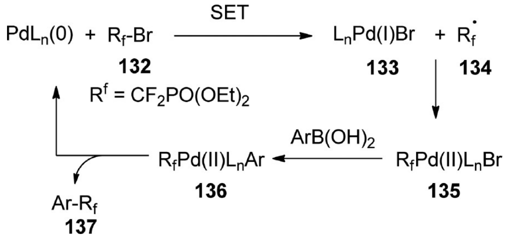
Scheme 32. Schoenebeck's Regioselective Suzuki Couplings of Halogenated Heterocycles via Pd(I) Dimer



Scheme 33. Zhang's Palladium-Catalyzed Difluoroalkylation of Arylboronic Acids



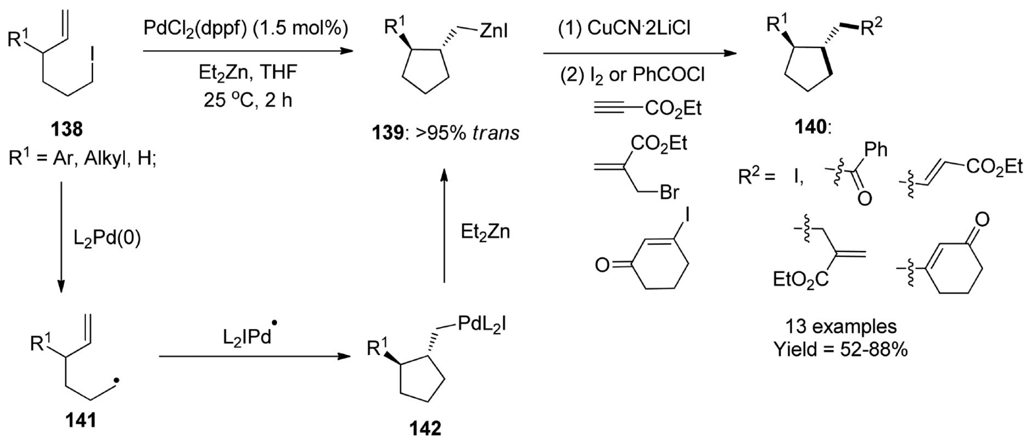
Scheme 34. Proposed Mechanism for Palladium-Catalyzed Difluoroalkylation



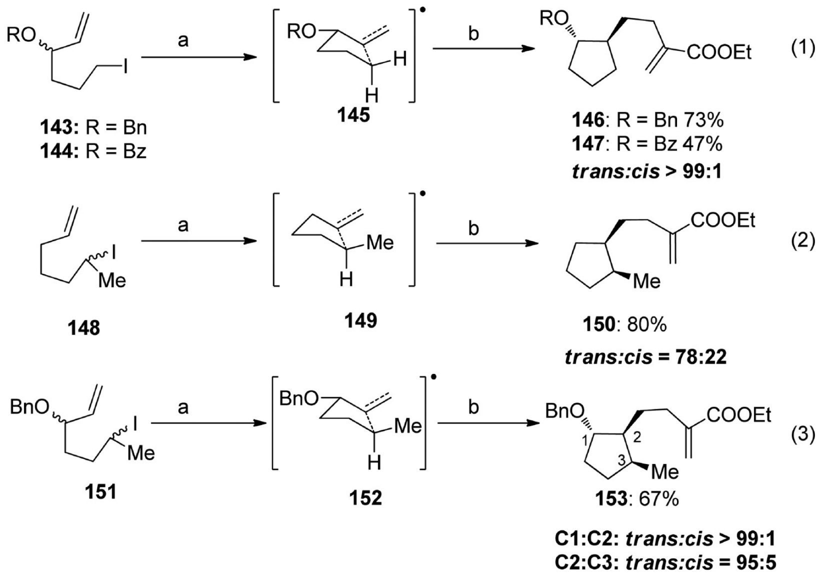
but rather the Pd(I)L monomer, which was generated through reduction of the $[\mathrm{Pd}(\mathrm{P}t\mathrm{Bu}_3)\mathrm{Br}]_2$ precatalyst.

In 2014, Zhang and co-workers disclosed a palladium-catalyzed difluoroalkylation of arylboronic acids affording a series of functionalized difluoromethylated arenes (Scheme 33).[46] The bidentate ligand Xantphos was shown to be important to the reaction efficiency. Mild reaction conditions, broad substrate scope, high efficiency, and excellent functional group compatibility enabled this methodology to be promising in further applications. A proposed $\mathrm{PdL}_n(0)$-promoted single electron transfer pathway

Scheme 35. Knochel's Pd/Zn-Catalyzed Ring-Closure Reaction of Alkenyl Iodides

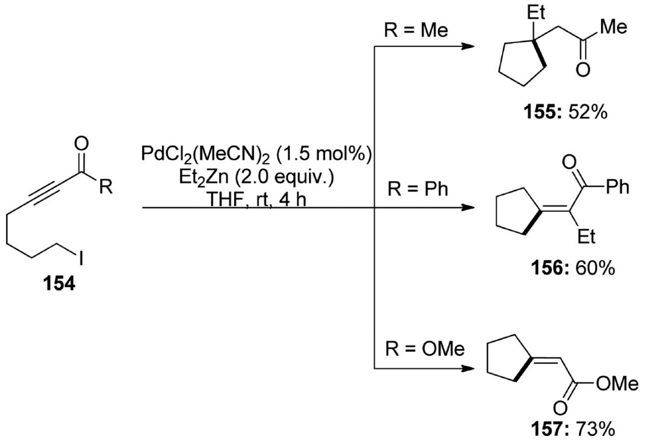


Scheme 36. Examination of the Stereochemistry[a]

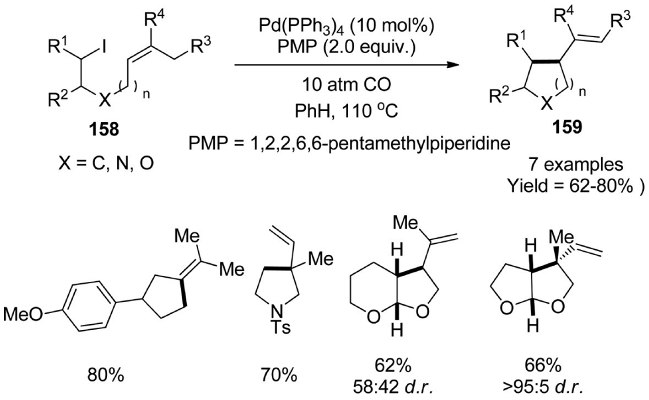


[a]Conditions: (a) PdCl$_2$(dppf) (2.5 mol %), Et$_2$Zn (2.0 equiv), THF, rt, 2 h; (b) CuCN·2LiCl, BrCH$_2$C(CH$_2$)CO$_2$Et, −78 °C to rt.

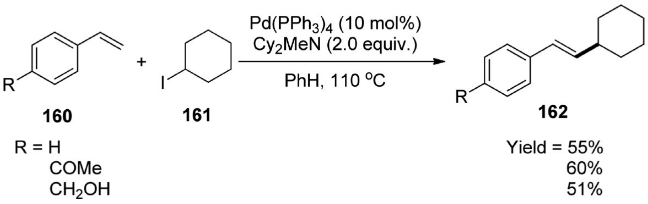
Scheme 37. Pd/Zn-Catalyzed Cyclization of Acetylenic Esters or Ketones



Scheme 38. Alexanian's Pd-Catalyzed Intramolecular Heck-Type Reaction of Unactivated Alkyl Iodides



Scheme 39. Intermolecular Heck-Type Reaction of Unactivated Alkyl Iodides

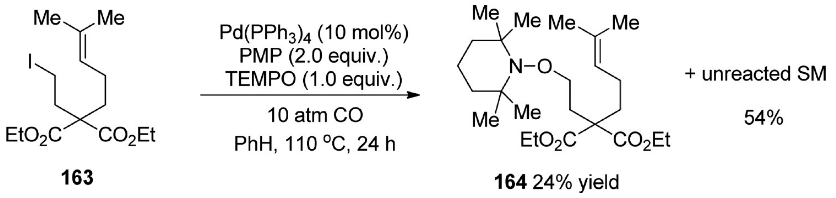


is shown in Scheme 34. Difluoroalkyl radical **134** was generated via a SET pathway from PdL$_n$(0). Then the radical **134** was supposed to combine with Pd(I) complex **133** to give Pd(II) complex **135**. Subsequent transmetalation and reductive elimination afforded the product **137**. In this proposed mechanism, only the initial step was thought to proceed via a radical process.

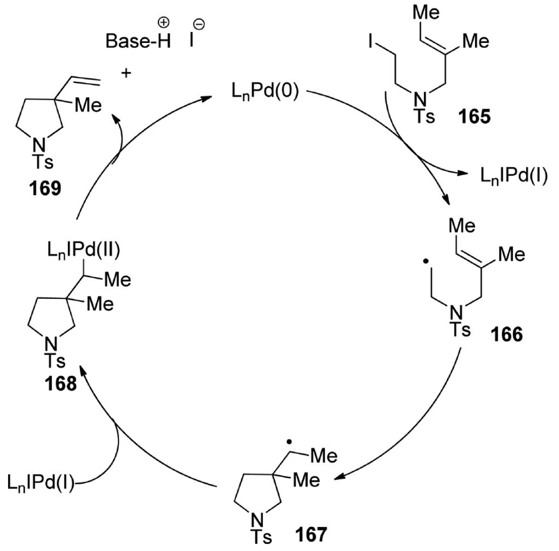
Knochel and co-workers described a Pd-catalyzed radical cyclization affording di- and trisubstituted cyclopentylmethylzinc iodides with excellent stereoselectivity (Scheme 35).[47] The organozinc species could react with a wide range of electrophiles to furnish the corresponding products in good yields. The generation of organozinc intermediate **139** was assumed to occur through a Pd-catalyzed radical process, as shown in Scheme 35. Three control experiments were carried out to demonstrate the stereochemistry of this transformation (Scheme 36). The stereoconvergence of the cyclizations could be explained by the radical transition states **145**, **149**, and **152**. Additionally, the cyclization of acetylenic esters and ketones also proceeded very well, as shown in Scheme 37. However, different substitutions could lead to different products, which indicated that the electronic properties of the substituents on the alkyne were critical to this transformation.

2.3.2. Heck-Type Reactions. Alexanian and co-workers described a Pd-catalyzed Heck-type reaction of unactivated alkyl iodides in 2011.[48] Both intra- and intermolecular Heck-type reactions were achieved in this system (Schemes 38 and 39). To investigate the potential carbon-centered radical intermediate, the radical scavenger TEMPO was added to the reaction of substrate **163**. The TEMPO adduct **164** was obtained in 24% yield, but no alkyl-Heck-type products were observed (Scheme 40). On the basis of these results, the hybrid organometallic−radical

Scheme 40. Pd-Catalyzed Heck-Type Reaction of Alkyl Halides in the Presence of TEMPO



Scheme 41. Possible Mechanism for the Carbocyclization via an Organometallic−Radical Process

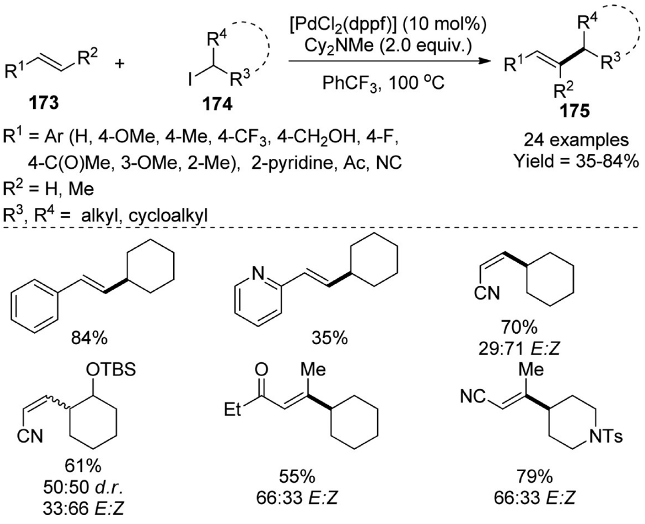


mechanistic hypothesis shown in Scheme 41 was proposed. Carbon-centered free radical **166** was generated via single electron transfer from Pd(0) and then delivered a second carbon-centered radical, **167**. Interception of radical species **167** by a putative Pd(I) species formed alkylpalladium(II) complex **168**, which yielded the product **169** and regenerated Pd(0) through reductive elimination.

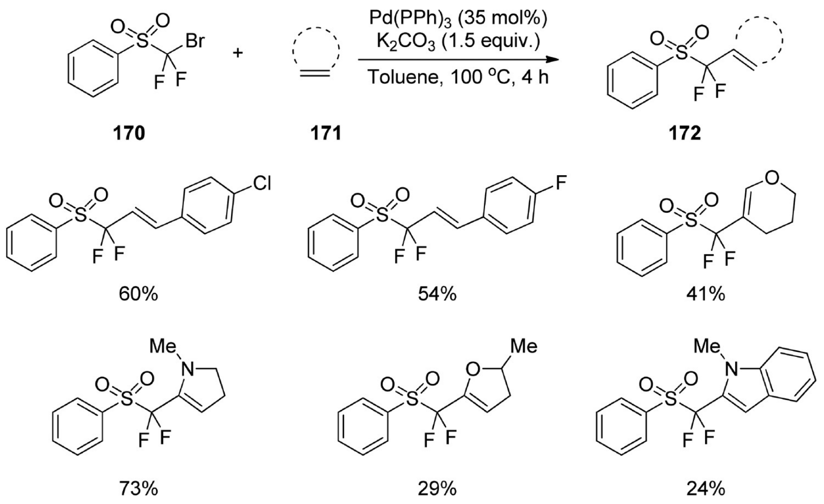
In 2012, Reutrakul and co-workers described a palladium-catalyzed Heck-type reaction of [(bromodifluoromethyl)-sulfonyl]benzene affording *α*-alkenyl- and *α*-heteroaryl-substituted *α*,*α*-difluoromethyl phenyl sulfones in moderate yields (Scheme 42).[49] It was a quite good procedure for introducing a (phenylsulfonyl)difluoromethylene group onto olefins, but the reaction efficiency needed to be improved.

As a continuation of their earlier work, the Alexanian group described a Pd-catalyzed intermolecular Heck-type coupling of alkyl iodides and alkenes in 2013 (Scheme 43).[50] Both primary and secondary unactivated alkyl iodides proceeded smoothly, including substrates bearing *β*-hydrogens. The non-styrenyl substrates were first used in alkyl-Heck cross-couplings. The cross-coupling reaction mechanism was proposed to be a hybrid organometallic−radical pathway (Scheme 44). Single-electron

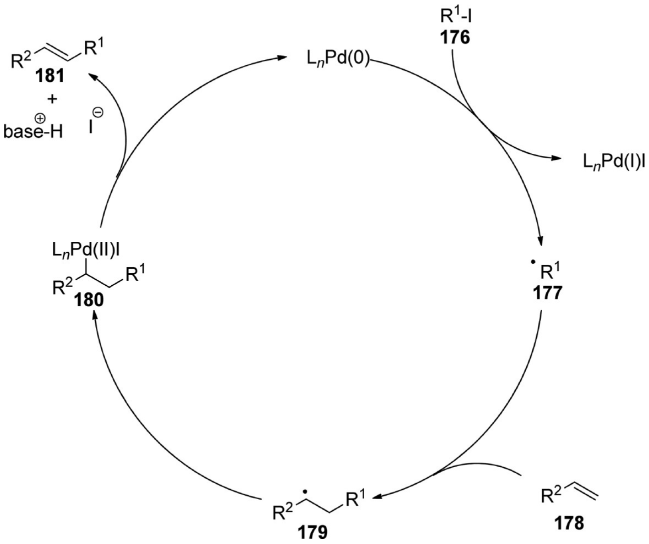
Scheme 43. Alexanian's Pd-Catalyzed Intermolecular Alkyl-Heck-Type Cross-Coupling



Scheme 42. Reutrakul's Palladium-Catalyzed Heck-Type Reaction of [(Bromodifluoromethyl)sulfonyl]benzene

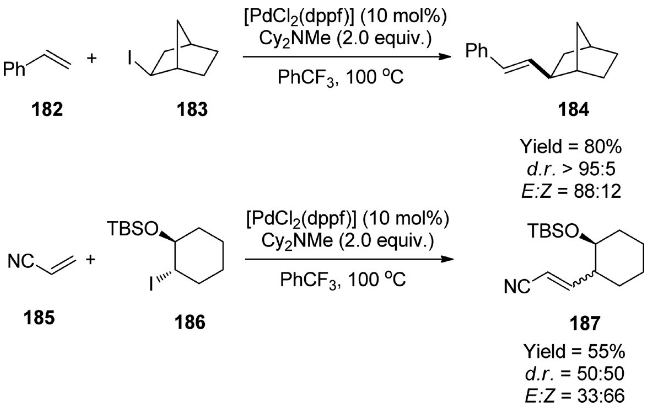


Scheme 44. Proposed Pathway for the Pd-Catalyzed Alkyl-Heck-Type Cross-Coupling



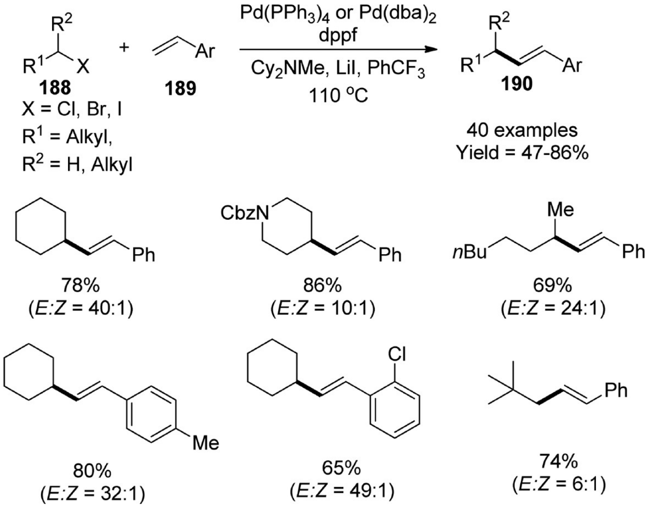
oxidative addition of the alkyl iodide substrate could generate carbon-centered radical intermediate **177**, followed by alkene addition to give secondary carbon-centered radical **179**. Finally, the alkylpalladium(II) species **180** was formed, which subsequently underwent β-hydride elimination to deliver the cross-coupling product **181**. The evidence obtained from both the exclusive formation of the exo-substituted product **184** with *exo*-2-norbornyl iodide (**183**) and the stereoablation in diastereomerically pure cyclic substrate **186** supported a single-electron pathway (Scheme 45).

Scheme 45. Investigation of the Stereochemistry

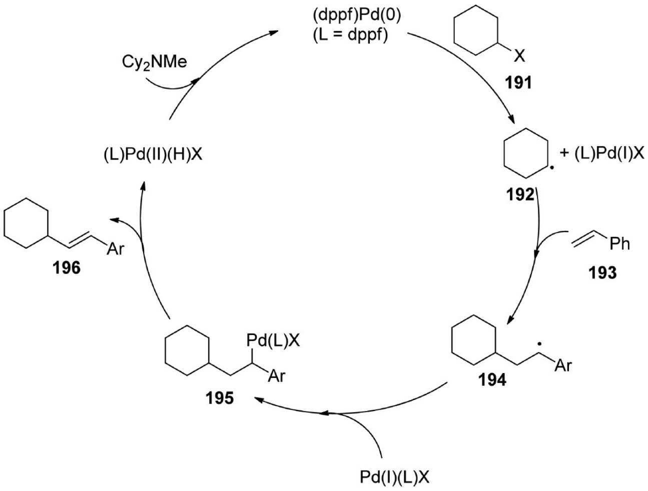


In 2014, Zou and Zhou[51] disclosed a Pd-catalyzed intermolecular Heck reaction of alkyl halides and styrenes (Scheme 46). Both primary and secondary alkyl halides smoothly delivered the corresponding cross-coupling products. The reaction started with single electron transfer from (dppf)Pd(0) to the alkyl halide, yielding alkyl radical **192**, which subsequently added to styrene (**193**) (Scheme 47). The formed benzylic radical **194** and (dppf)XPd(I) furnished (alkyl)PdX **195**, which underwent Pd-assisted β-hydride elimination to give the Heck product **196**. Use of the radical scavenger TEMPO shut down the cross-coupling reaction and gave the TEMPO−alkyl adduct as the only product, indicating that a radical process might involved. Additionally, a competitive reaction of benzylic iodide **198** and cyclohexyl iodide (**197**) was conducted with styrene (Scheme 48). If the transformation underwent a sequence of atom transfer radical addition to form the benzylic iodide followed by base-assisted elimination to form the Heck product, the model “intermediate” benzylic iodide **198** should be converted to **200** easily. However, only a 41% yield of the expected elimination product **200** was obtained, which indicated that the benzylic iodide was not the intermediate and excluded the two-step route.

Scheme 46. Zhou’s Pd-Catalyzed Intermolecular Heck Reaction of Alkyl Halides and Styrenes

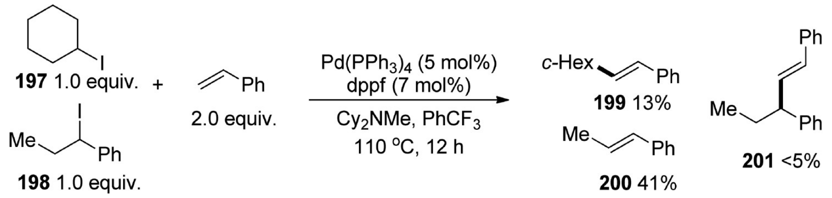


Scheme 47. Possible Mechanism for the Heck Reaction of Alkyl Halides

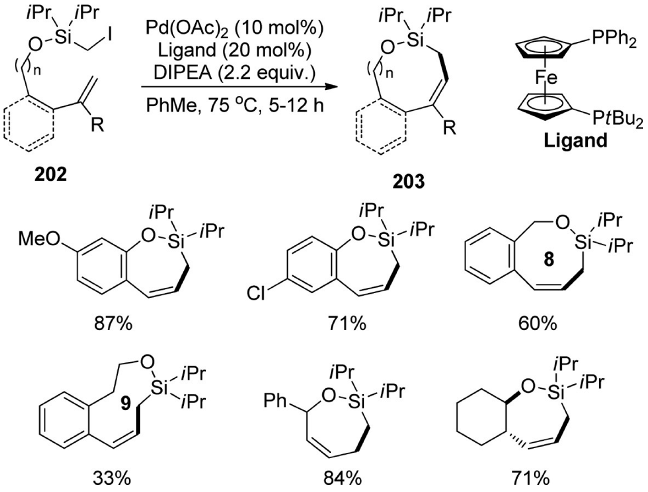


In 2014, Gevorgyan and co-workers realized an endo-selective alkyl-Heck reaction of phenols and aliphatic alkenols with iodomethylsilyl ethers (Scheme 49).[52] Varieties of silyl-tethered vinylphenols and aliphatic alkenols were smoothly cyclized into the corresponding products with delightfully high endo selectivity. This methodology furnished not only rings via 7-endo cyclization but also medium-sized rings via 8-endo and 9-endo cyclization in reasonable yields. However, olefins bearing substitution at the β-position reversed the regioselectivity trend, affording exo-trig cyclization products. The proposed mechanism is shown in Scheme 50. Pd-mediated homolysis of substrate **204** generated radical **205**. If the alkene possessed a substituent

Scheme 48. Competitive Reaction of a Benzylic Iodide and Cyclohexyl Iodide



Scheme 49. Gevorgyan's Pd-Catalyzed Endo-Selective Alkyl-Heck Reaction Using Iodomethylsilyl Ethers



at the *β*-position, it underwent 6-exo-trig cyclization to give product **210**. Otherwise, selective endo-trig cyclization occurred to produce cyclic alkyl radical **206**, which recombined with Pd(I) to form alkylpalladium species **207**. Elimination of the two alternative hydrogens, H_h and H_a, led to homoallylic silanes **208** and allylic silanes **209**, respectively.

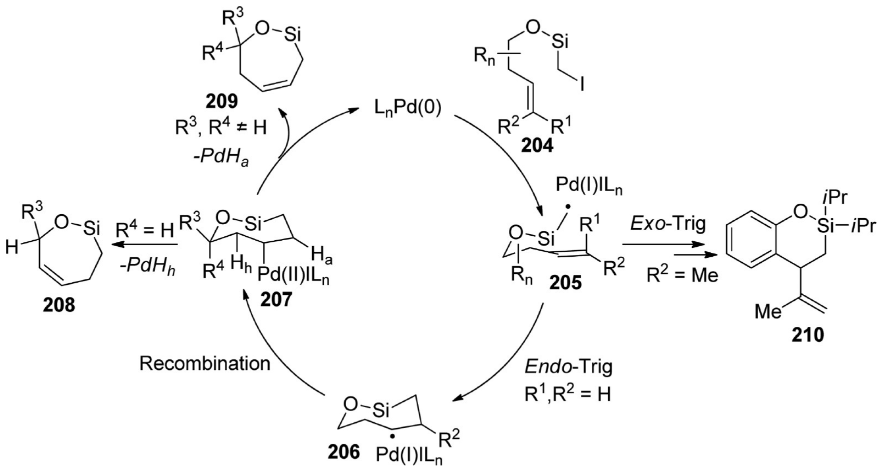
In 2015, Zhang and co-workers demonstrated a palladium-catalyzed Heck-type fluoroalkylation of alkenes with fluoroalkyl bromides (Scheme 51).[53] This protocol showed wide substrate scope and high efficiency. Moreover, the late-stage fluoroalkylation of bioactive compounds was achieved in good yields (**214** and **215** in Scheme 51). Some tentative experiments, including a radical clock reaction, were performed to obtain insight into the reaction mechanism. The results indicated that this transformation might involve free fluoroalkyl radicals generated from the Pd/Xantphos complex.

2.3.3. Coupling with C–H Bonds. In 2013, the Fu group reported a C–H activation/C–C cross-coupling reaction of pyridine *N*-oxides with nonactivated secondary and tertiary alkyl bromides (Scheme 52).[54] The good compatibility with many synthetically relevant functional groups made this reaction a practical tool for the synthesis of alkylpyridine derivatives. The chiral secondary alkyl bromides **219** (axial) and **220** (equatorial) were subjected to the standard conditions to probe the stereochemistry of the C–H bond alkylation process (Scheme 53, eq I). The results showed that the two chiral substrates provided mixtures of two diastereomers in ratios of 1.0:2.6 and 1.0:1.9, respectively. On the other hand, the cross-coupling reaction of **222** with *exo*-2-bromonorbornane (**223**) gave the single equatorial product **224** (Scheme 53, eq II). These observations indicated that C–Br bond cleavage proceeded through a hybrid organometallic–radical mechanism.

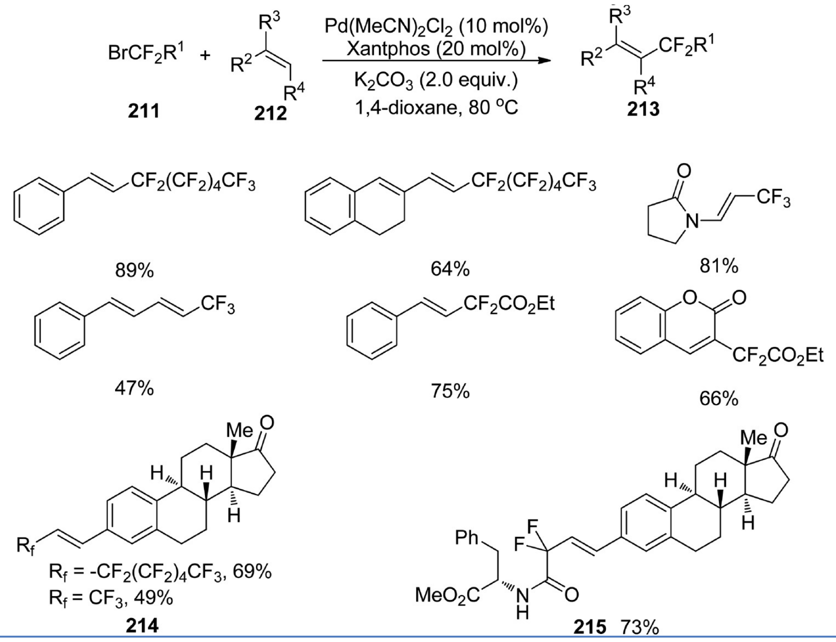
Zhou and co-workers described a general alkylation of heterocycles through Pd-catalyzed C(sp^2)–H activation and coupling with alkyl halides (Scheme 54).[55] Most types of heterocycles, including pyridines, indoles, furans, thiophenes, and pyrroles, could couple with unactivated secondary and tertiary alkyl halides efficiently. Primary alkyl halides bearing linear aliphatic chains were unsuccessful because of the major side reaction of elimination to produce olefins. Both radical trapping experiments and DFT calculations provided support for a radical pathway (Scheme 55). The alkyl radical **229** was generated via single electron transfer from [(dppf)Pd(0)] to alkyl halide **228** and then added to the heterocycle to generate heterocyclic radical **231**. After single-electron oxidation and deprotonation, the coupling product **233** was obtained.

Very recently, the Alexanian group developed an intramolecular aromatic C–H alkylation using unactivated alkyl

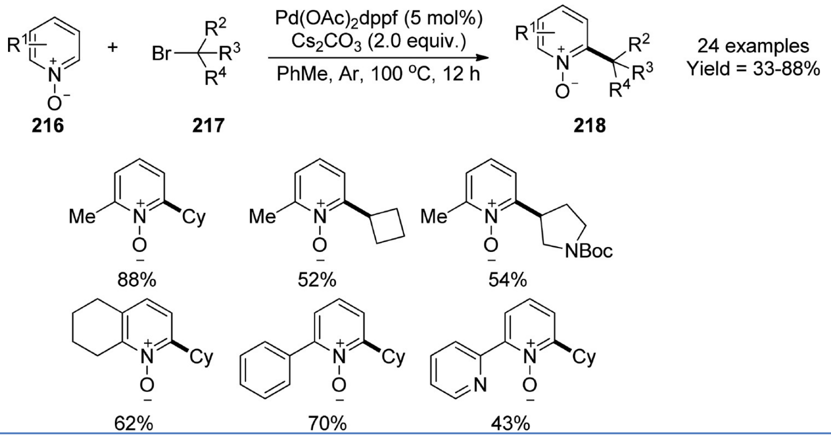
Scheme 50. Possible Mechanism for the Pd-Catalyzed Silylmethyl Heck Reaction



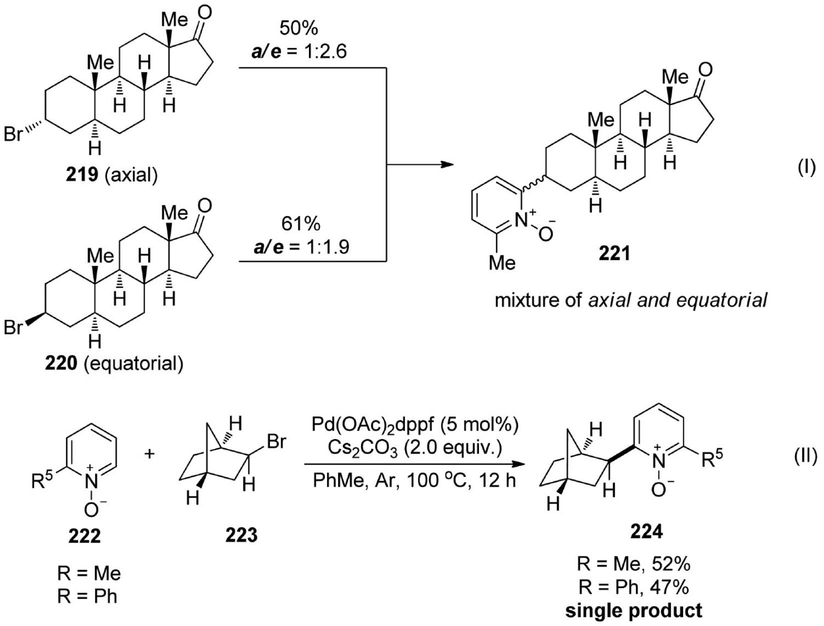
Scheme 51. Zhang's Palladium-Catalyzed Heck-Type Fluoroalkylation of Alkenes



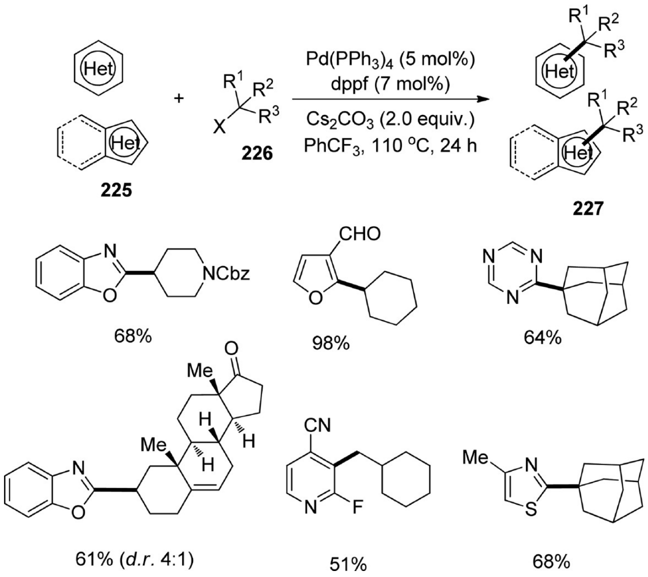
Scheme 52. Fu's Cross-Coupling of Pyridine *N*-Oxides with Nonactivated Alkyl Bromides



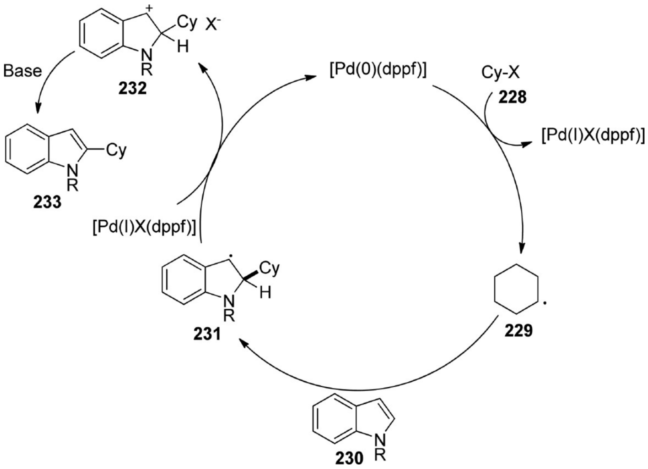
Scheme 53. Investigation of the Stereochemistry Using Chiral Substrates



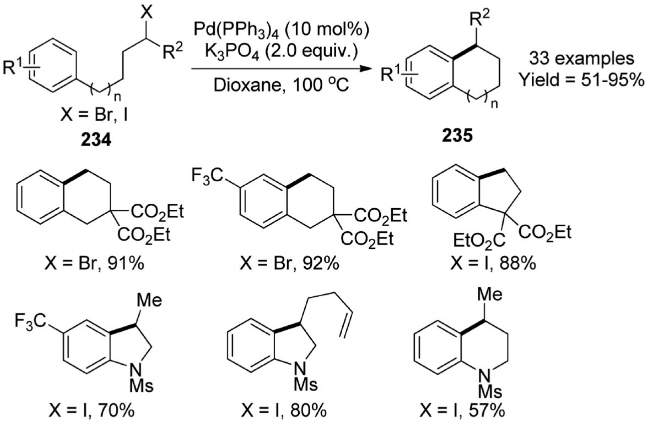
Scheme 54. Zhou's C−H Bond Alkylation of Heterocycles with Alkyl Halides



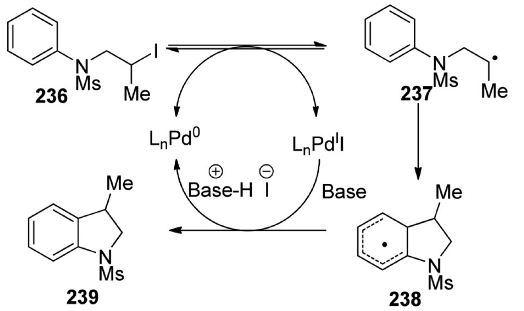
Scheme 55. Proposed Mechanism for Pd-Catalyzed C−H Bond Alkylation of Heterocycles



Scheme 56. Alexanian's Pd-Catalyzed Cyclization by C−H Alkylation with Unactivated Alkyl Halides



Scheme 57. Plausible Pathway for the Pd-Catalyzed Ring-Forming C−H Alkylation



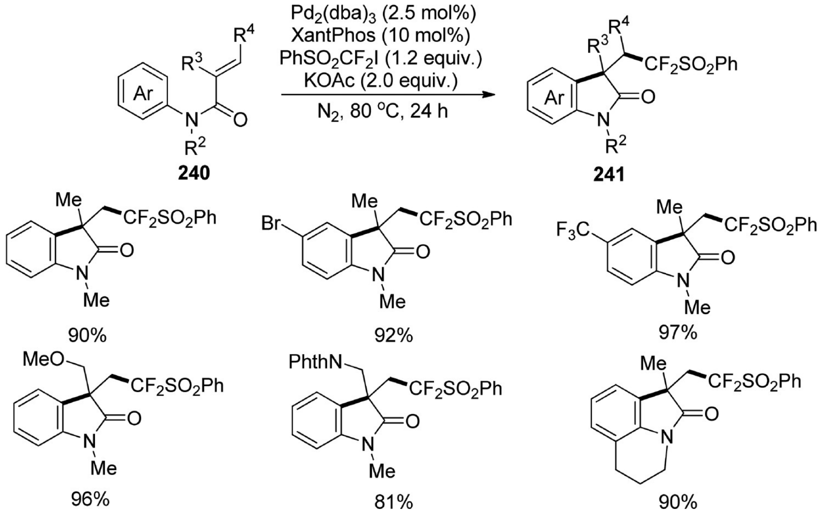
halides (Scheme 56).[56] Both primary and secondary alkyl iodides and bromides furnished the corresponding carbocyclic and heterocyclic compounds efficiently. The mechanistic hypothesis for the ring-forming aromatic C−H alkylation is described in Scheme 57. Reversible single-electron oxidative addition of the alkyl halide substrate formed carbon-centered radical **237**, which added to the aromatic ring to afford cyclohexadienyl radical **238**. Finally, rearomatization via single-electron oxidation released one proton to give the product **239** and regenerate the Pd(0) catalyst.

The Wang group described a Pd(0)-catalyzed intramolecular radical aryldifluoromethylation of activated alkenes to construct various difluoromethylated oxindoles (Scheme 58).[57] A series of radical trapping experiments were performed to provide insight into the mechanism. When TEMPO was introduced into the reaction, the formation of the corresponding product was drastically inhibited, consistent with the radical pathway proposed in Scheme 59. First, radical **242** was generated from Pd(0) and the aryldifluoromethyl iodide. Then **242** added to the double bond to give the new carbon radical **244**, which was then trapped by the aryl ring to give **245**. The generated aryl radical **245** could go through two possible pathways. In path I, the Pd(I) complex was captured to afford Pd(II) intermediate **246**, which could undergo *β*-hydride elimination to produce the final product **247**. Alternatively, in path II, radical **245** was oxidized to aryl cation **248** by the Pd(I) complex, followed by base-mediated deprotonation to yield product **247**.

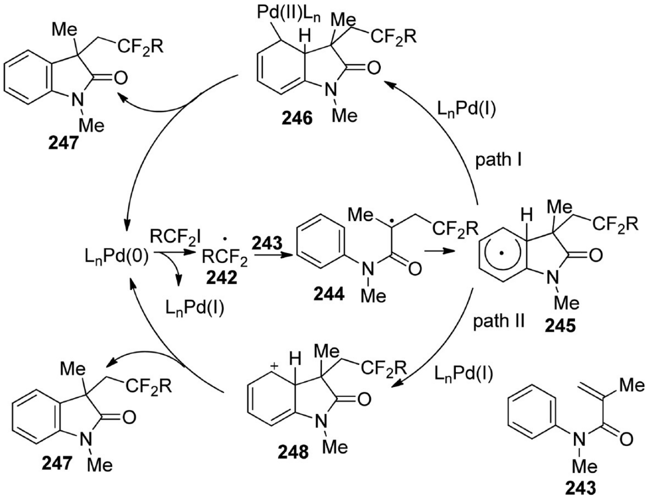
2.3.4. Other Coupling Reactions. In 2002, Hartwig and coworkers developed a C−N bond coupling reaction of various aryl chlorides or bromides and amines using the air-stable Pd(I) dimers $[\mathrm{Pd}(\mathrm{PR}t\mathrm{Bu}_2)\mathrm{Br}]_2$ as active catalysts (Scheme 60).[58] The coupling reactions were finished in few minutes at room temperature and gave excellent yields. Various aryl chlorides or bromides and amines exhibited quite good functional group tolerance in the amination reaction. The catalyst $[\mathrm{Pd}(\mathrm{PR}t\mathrm{Bu}_2)\mathrm{Br}]_2$ was also examined in Suzuki−Miyaura reactions at room temperature. Various aryl bromides, such as *p*-bromotoluene and *o*-cyano-, *o*-trifluoromethyl-, and 2-bromoanisole, produced the Suzuki coupling products in excellent yields (Scheme 61).

In the same year, Prashad et al.[59] described an efficient amination of aromatic bromides with hindered *N*-alkyl-substituted anilines catalyzed by $[\mathrm{Pd}(\mathrm{P}t\mathrm{Bu}_3)(\mu\text{-Br})]_2$ (Scheme 62). Although only secondary amines were tested with aromatic bromides containing electron-donating or electron-withdrawing groups, the yields of the coupling reactions were excellent. Generally, reactions with the Pd(I) dimer as the catalyst afforded better yields than those with the combination of $\mathrm{Pd(OAc)_2}$ and $\mathrm{P}t\mathrm{Bu}_3$. In addition, the Pd(I) dimer $[\mathrm{Pd}(\mathrm{P}t\mathrm{Bu}_3)(\mu\text{-Br})]_2$ was air-stable and easily handled.

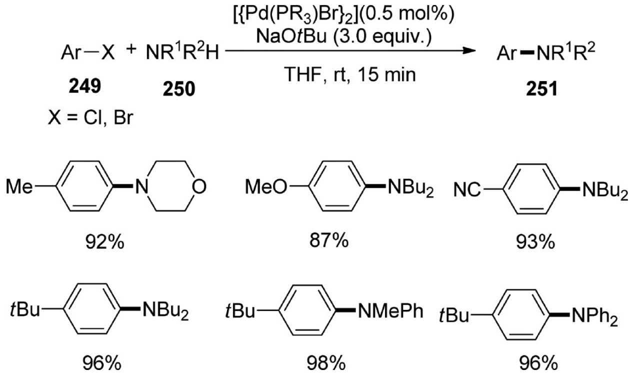
Scheme 58. Wang's Pd(0)-Catalyzed Intramolecular Radical Aryldifluoromethylation of Activated Alkenes



Scheme 59. Plausible Mechanism for Pd(0)-Catalyzed Intramolecular Radical Aryldifluoromethylation

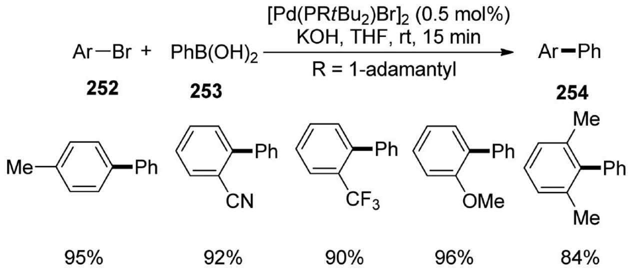


Scheme 60. Hartwig's Pd(I) Dimer-Catalyzed Amination of Aryl Halides

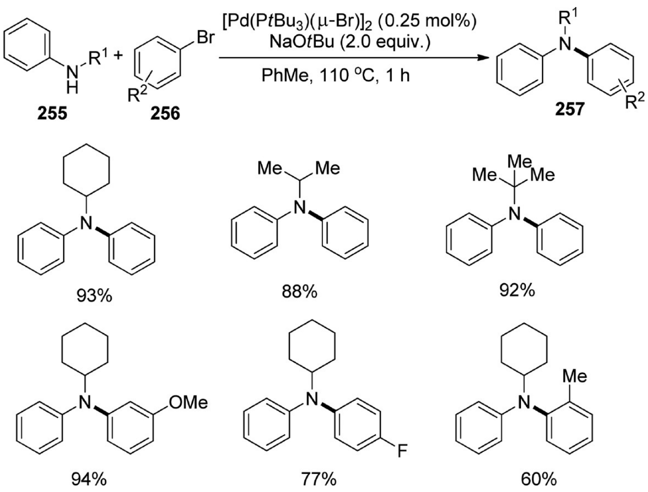


In 2008, the Hartwig group applied the dimeric Pd(I) species [Pd(PtBu$_3$)Br]$_2$ in the α-arylation of esters (Scheme 63).[60] The low catalyst loading and good functional group tolerance on the aryl halides made this protocol a quite promising methodology in α-arylation of esters. Esters such as acetates, propionates,

Scheme 61. Hartwig's Pd(I) Dimer-Catalyzed Suzuki–Miyaura Coupling



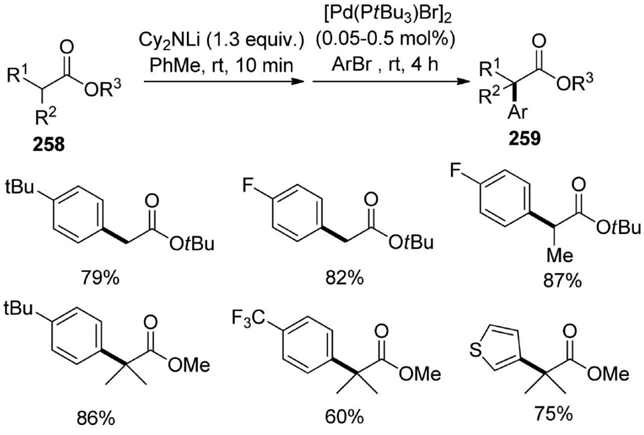
Scheme 62. Prashad's Pd(I)-Catalyzed Amination of Aromatic Bromides



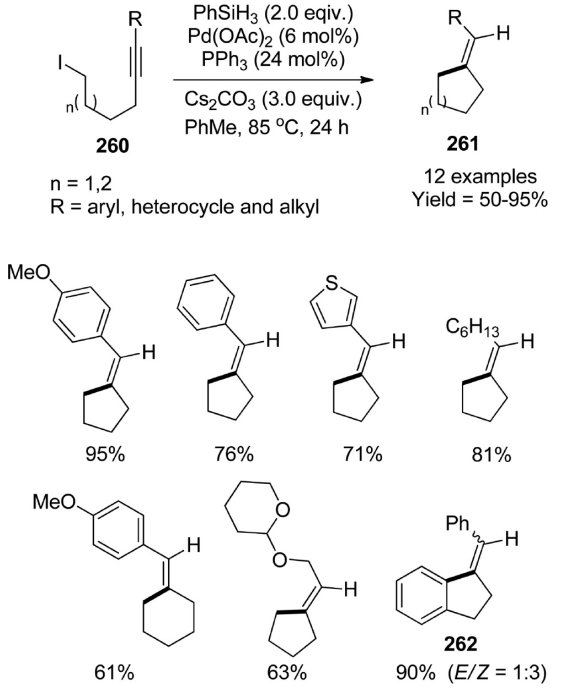
and isobutyrates could couple with a variety of bromoarenes in moderate to high yields. Notably, the arylation of *tert*-butyl propionate on a 10 g scale was achieved successfully in good yields (79–86%) in the presence of 0.05% catalyst while on a 1 mmol scale the reactant could not be totally converted to product under the same conditions, indicating that the reaction was more efficient on a larger scale than on a 1 mmol scale.

In 2013, Cook and co-workers described a Pd-catalyzed alkyne insertion/reduction reaction with unactivated alkyl

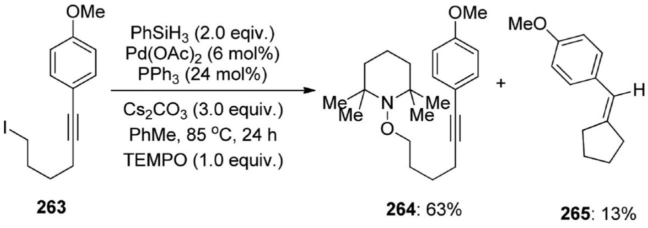
Scheme 63. Hartwig's Pd(I)-Catalyzed α-Arylation of Esters



Scheme 64. Cook's Pd-Catalyzed Alkyne Insertion/Reduction with Unactivated Alkyl Iodides

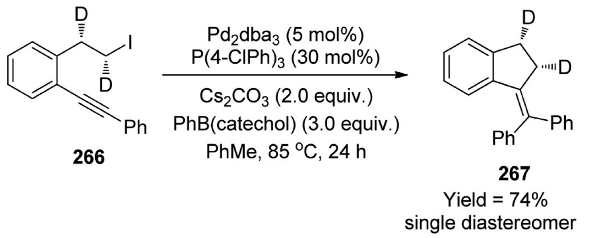


Scheme 65. Reaction in the Presence of the Radical Inhibitor TEMPO

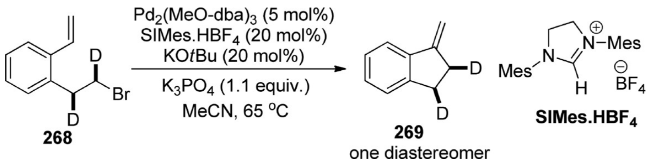


iodides to furnish trisubstituted olefins in good to excellent yields (Scheme 64).[61] When the substrate 1-(2-iodoethyl)-2-(phenylethynyl)benzene was subjected to the standard conditions, a 1:3 *E*/*Z* mixture of stereoisomers **262** was obtained. Several phosphine ligands were screened, including electron-rich and -deficient triarylphosphines and bidentate ligands, but there was no big improvement in the *E*/*Z* selectivity. In addition, the reaction involving the radical scavenger TEMPO produced the TEMPO adduct **264** in 63% yield and trisubstituted olefin **265** in 13% yield (Scheme 65). Both of these results indicated a hybrid radical−organometallic mechanism.

Scheme 66. Cook's Pd-Catalyzed Alkyne Insertion/Suzuki Reaction with a Deuterium-Labeled Substrate



Scheme 67. Fu's Pd-Catalyzed Intramolecular Heck Reaction with a Deuterium-Labeled Substrate



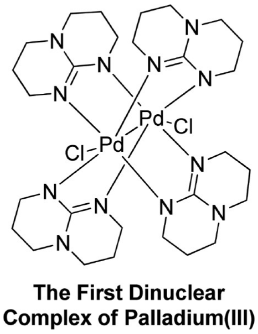
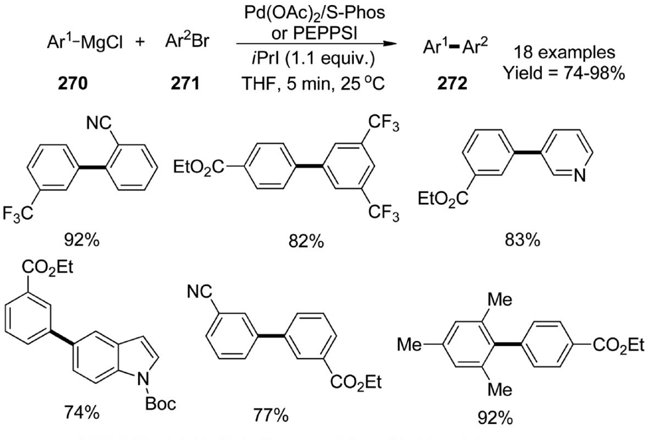


Figure 2. Cotton and Murillo's Pd(III) complex.

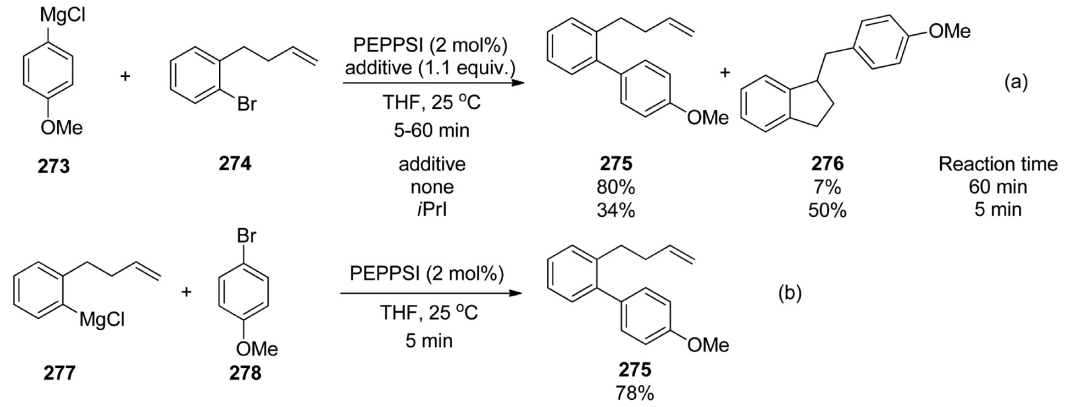
Scheme 68. Knochel's Kumada Cross-Coupling Using Functionalized Grignard Reagents



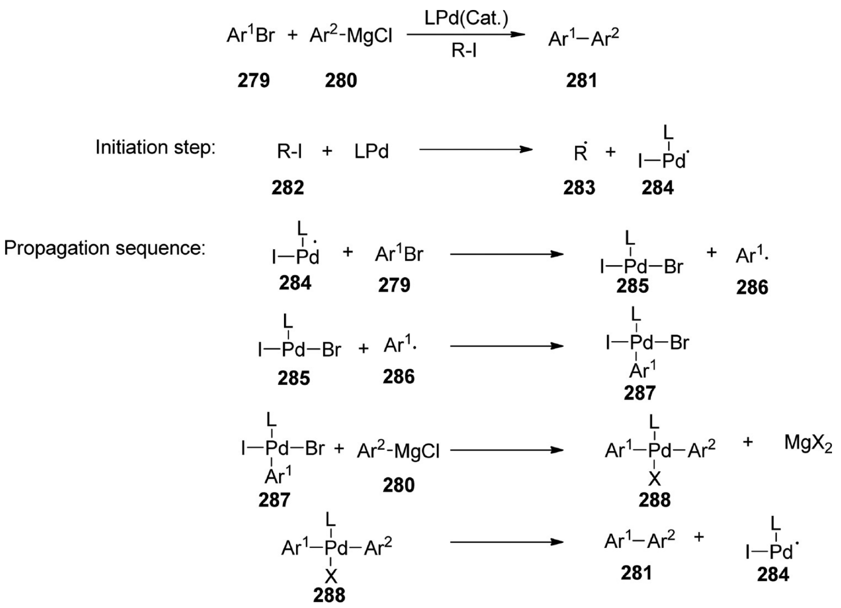
(PEPPSI= 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride)

It is worth mentioning that previous work reported by the Cook group in 2012 demonstrated a Pd-catalyzed alkyne insertion/Suzuki reaction with unactivated alkyl iodides (Scheme 66).[62] The deuterium-labeled substrate **266** afforded

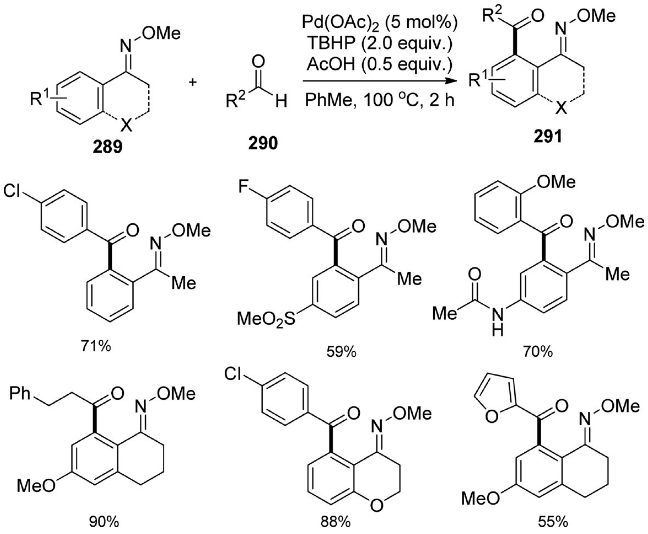
Scheme 69. Control Experiments with Substrates Bearing a Remote Double Bond



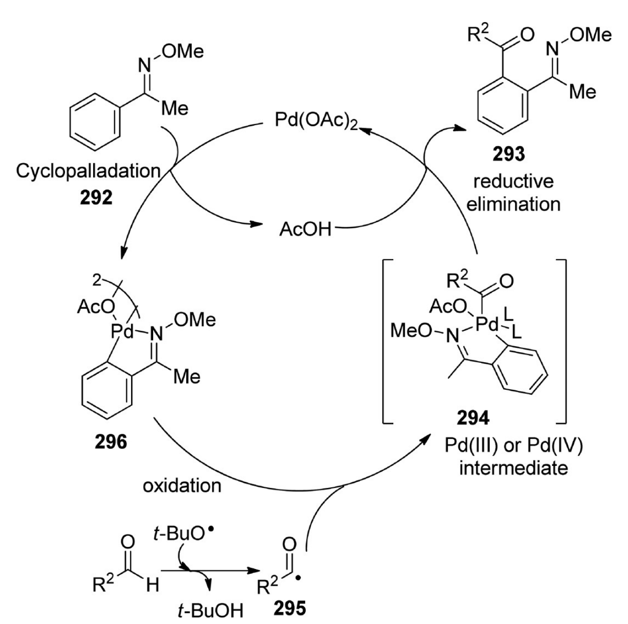
Scheme 70. Tentative Mechanism for the Kumada Cross-Coupling via a Radical Process



Scheme 71. Yu's Pd-Catalyzed Oxidative C–H Bond Coupling of Aromatic Oximes with Aldehydes

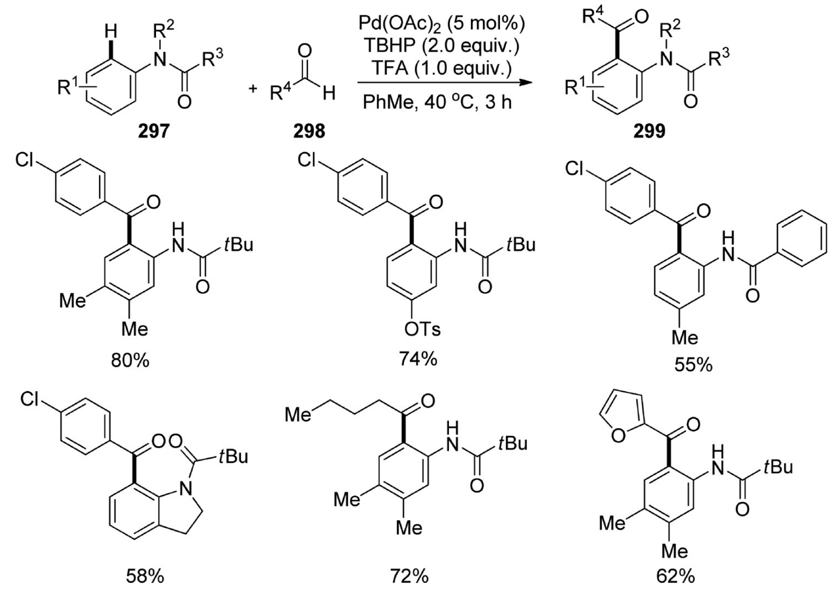


Scheme 72. Possible Mechanism for the Pd-Catalyzed C–H Bond Coupling

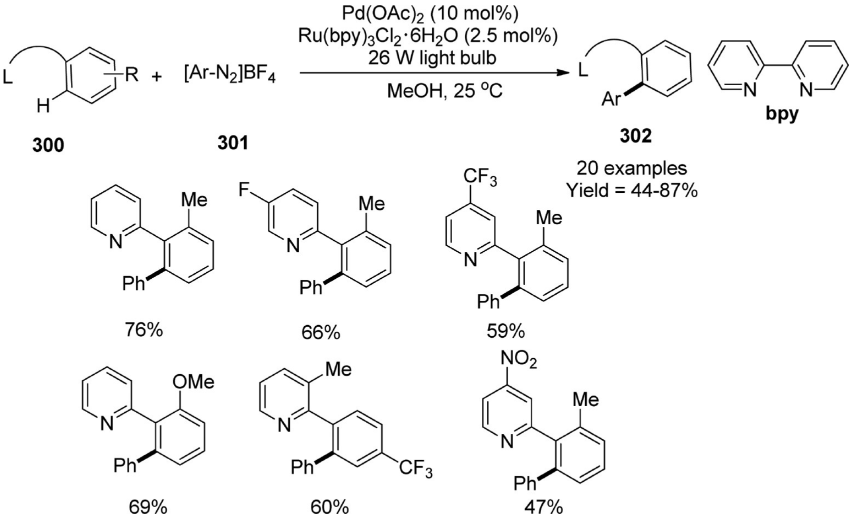


a single syn diastereomer in 74% yield under the standard reaction conditions, suggesting an S_N2 oxidative addition of

Scheme 73. Yu's Pd-Catalyzed Ortho C−H Acylation of Anilides with Aldehydes



Scheme 74. Pd/Ru-Catalyzed C−H Arylation



Pd(0) for this reaction rather than a radical process. Similar results had already been reported by the Fu group in their work on the intramolecular Heck reactions of unactivated alkyl bromides and chlorides in 2007 (Scheme 67).[63] The deuterium-labeled substrate **268** produced a single diastereomer in the presence of Pd/SIMes, the stereochemistry of which was consistent with an S_N2 oxidative addition mechanism.

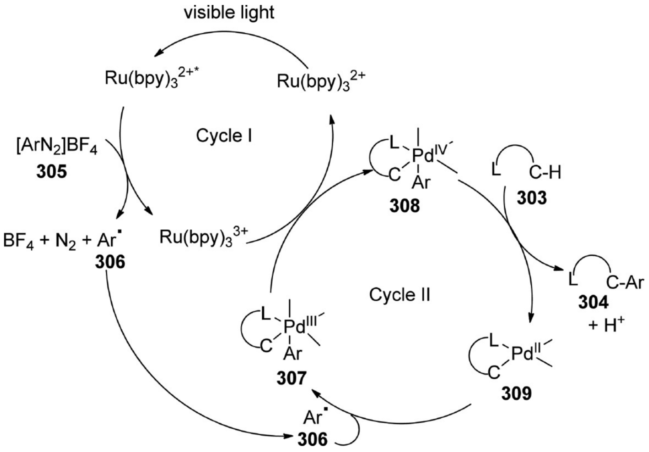
3. PD(III) INVOLVED REACTIONS

In 1987, Cotton, Murillo, and co-workers first oxidized a binuclear Pd(II) complex to give the Pd(III) complex, which was isolated and characterized in 1998 (Figure 2).[64] However, the stability of the Pd(III) compound was relatively poor compared with that of Pd(I) complexes. During the last decades, many beautiful works have contributed to the synthesis, isolation, characterization, and transformation of Pd(III) complexes.[65] Here we will focus on the catalytic reactions involving Pd(III) complexes.

In 2009, Manolikakes and Knochel[66] realized a Pd-catalyzed Kumada cross-coupling using aryl bromides and functionalized aryl- and hetero-Grignard reagents via a radical process (Scheme 68). The reaction performed at room temperature reached completion within a few minutes and gave excellent yields. The alkyl iodide *i*PrI showed an accelerating effect on the Kumada coupling reaction. Control experiments were performed to investigate the reaction mechanism (Scheme 69). Substrate **274** bearing a remote double bond was examined, as shown in Scheme 69a. The reaction led to a mixture of the cyclized product **276** (50% yield) and the noncyclized product **275** (34% yield), which supported a radical intermediate. However, the use of Grignard reagent **277** bearing a remote double bond did not produce cyclization product but gave only the cross-coupling product biphenyl **275** in 78% yield, as shown in Scheme 69b. On the basis of these results, the radical-involved mechanism shown in Scheme 70 was proposed. Initially, the Pd(0) catalyst could react with alkyl iodide (RI) to generate alkyl radical R· (**283**) and Pd(I) intermediate **284**, which could furnish aryl radical Ar^1· (**286**) by reaction with an aryl bromide. Ring closure might happen in the presence of a remote double bond, as shown in Scheme 69a. Trapping of aryl radical **286** with [$LPdX_2$] led to the

Pd(III) intermediate [Ar^{1}PdL(I)(Br)] (**287**), which provided diaryl Pd(III) halide **288** via ligand exchange with Ar^{2}MgBr. Reductive elimination of **288** yielded the cross-coupling product Ar^1−Ar^2 (**281**) and regenerated the PdI radical chain carrier **284**. This methodology provided a rapid coupling of functionalized aryl- and heteroarylmagnesium reagents with aryl bromides.

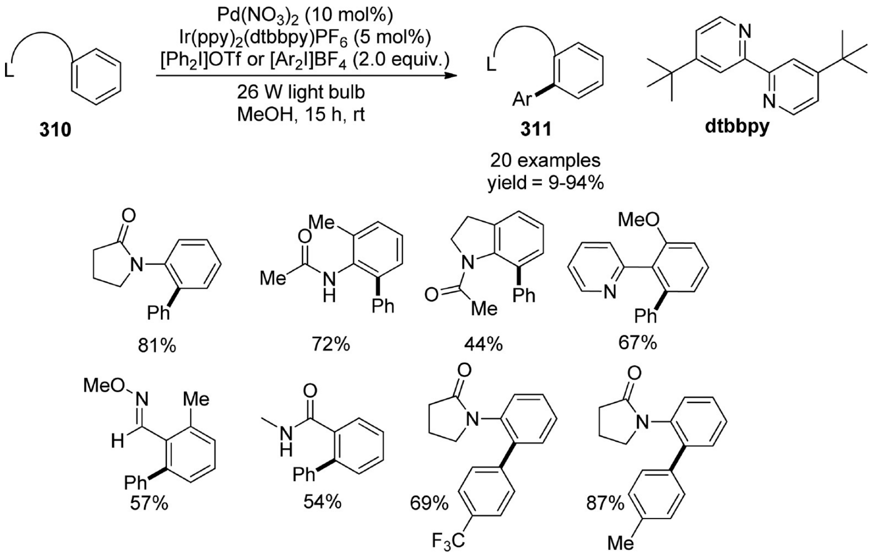
Scheme 75. Proposed Mechanism for the Pd/Ru-Catalyzed C−H Arylation



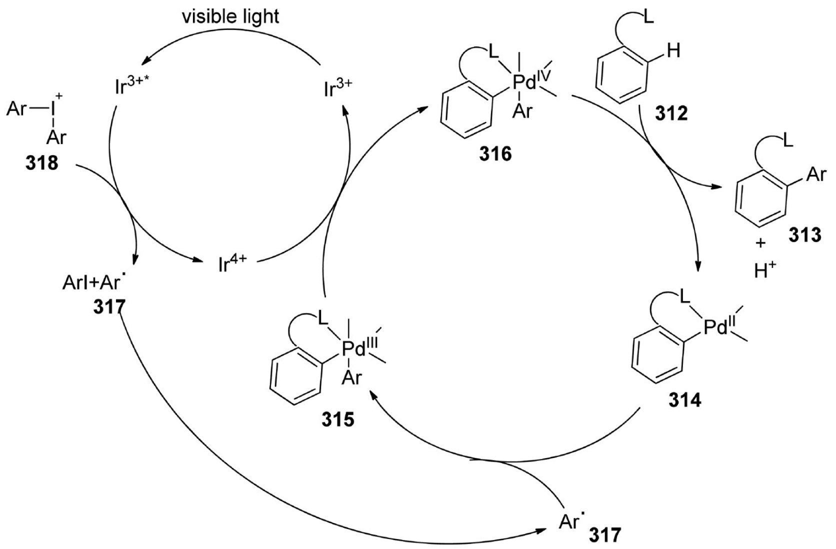
In 2010, Yu and co-workers reported a Pd-catalyzed ortho-selective C−H acylation reaction of aromatic oximes with aldehydes using *tert*-butyl hydroperoxide (TBHP) as the oxidant, providing a diverse library of diaryl ketone derivatives (Scheme 71).[67] The acylation reaction exhibited remarkable regioselectivity depending on the oxime group. It also presented excellent functional group tolerance for both aliphatic and heteroaromatic aldehydes. A plausible mechanism is shown in Scheme 72. First, the oxime-assisted ortho-selective cyclopalladation produced palladacycle **296**, which reacted with the in situ-generated acyl radical **295** to afford the product diaryl ketone **293** via reductive elimination of either reactive Pd(IV) or dimeric Pd(III) intermediate **294**.

A very similar strategy was applied by the Yu group in the direct ortho C−H acylation of anilides through Pd-catalyzed cross-coupling (Scheme 73).[68] Various 2-aminobenzophenone derivatives were efficiently synthesized under very mild conditions.

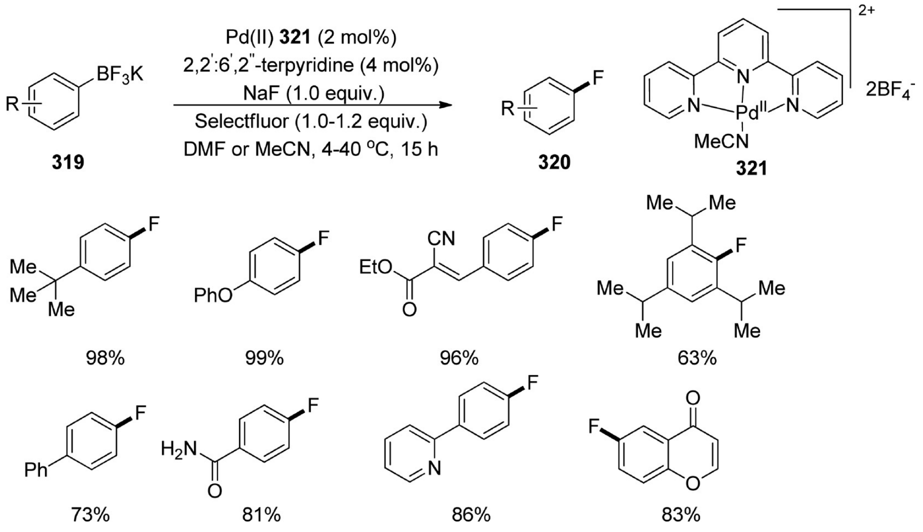
Scheme 76. Sanford's Pd/Ir-Catalyzed C−H Arylation Reaction with Diaryliodonium Reagents



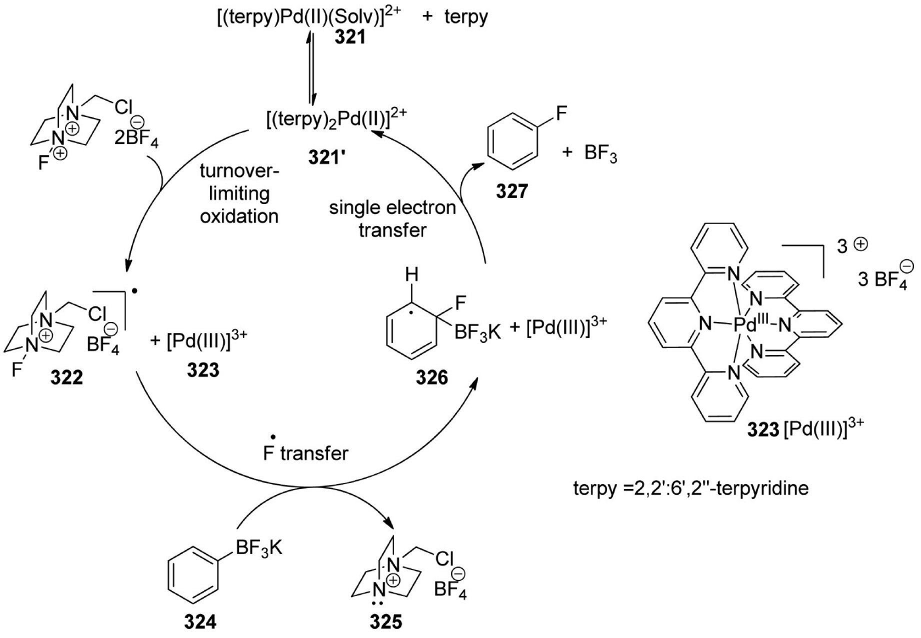
Scheme 77. Plausible Mechanism for the Pd/Ir-Catalyzed C−H Arylation



Scheme 78. Ritter's Pd(III)-Catalyzed Fluorination of Aryltrifluoroborates



Scheme 79. Proposed Mechanism for the Pd(III)-Catalyzed Fluorination of Aryltrifluoroborates

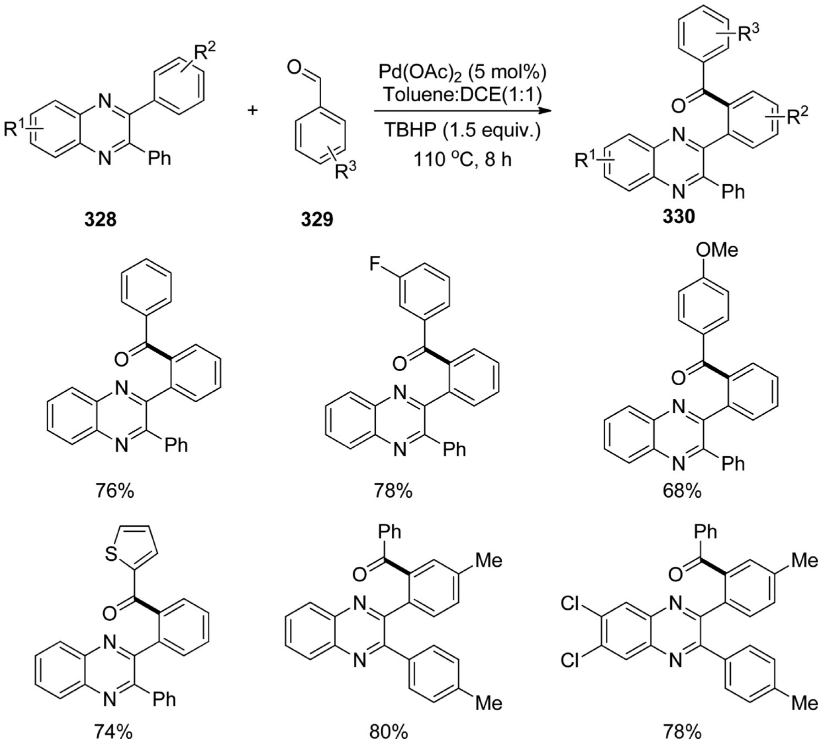


Only the anilides with electron-neutral and electron-donating groups on the aryl ring were favorable for this transformation. The reactive Pd(IV) and dimeric Pd(III) complexes were also considered to be key intermediates, as in Scheme 72.

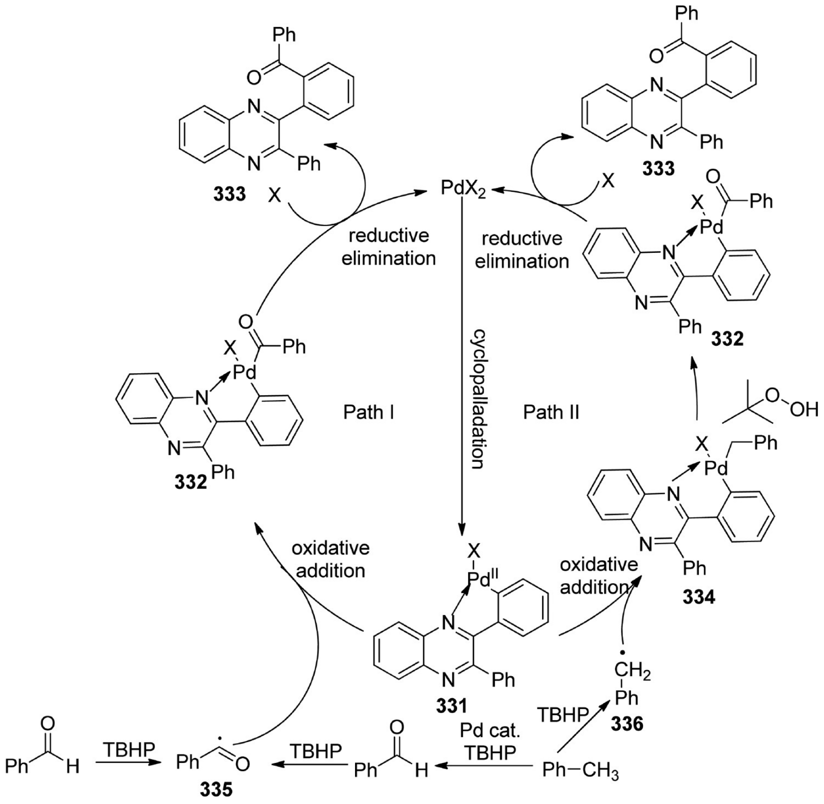
In 2011, Sanford and co-workers developed a ligand-directed C−H arylation reaction using aryldiazonium salts by the merger of Pd-catalyzed C−H functionalization and visible-light photoredox catalysis at room temperature (Scheme 74).[69] A range of functional groups, directing ligands, and aryldiazonium salts were compatible in this system. Two catalytic cycles are shown in Scheme 75. In cycle I, photoexcitation of the Ru catalyst generated $Ru(bpy)_3^{2+*}$, and this was followed by reduction of the aryldiazonium salt to give aryl radical **306** and concomitant oxidation of the Ru center to form $Ru(bpy)_3^{3+}$. In cycle II, Pd(II) intermediate **309** was generated by C−H activation of **303**. It then reacted with aryl radical **306** to give Pd(III) intermediate **307**, which was oxidized to Pd(IV) complex **308** via one-electron oxidation by $Ru(bpy)_3^{3+}$. Finally, reductive elimination of Pd(IV) complex **308** released the arylated product **304** and regenerated the Pd(II) catalyst.

In 2012, Neufeldt and Sanford[70] reported a photoredox-based palladium/iridium-catalyzed C−H arylation with diaryliodonium reagents through a radical-mediated transformation at room temperature (Scheme 76). A variety of directing groups, such as carbonyl, amide, pyridyl, and oxime, smoothly afforded the coupling products in moderate to high yields. Both the addition of the radical scavenger TEMPO (which decreased the yield from 79% to 6%) and the use of light with a photocatalyst were consistent with a radical mechanism. A reaction pathway that merges Pd(II)/(IV) and Ir(III)/(IV) catalytic cycles was proposed, as shown in Scheme 77. The Ir^{3+*} complex generated from ground-state Ir^{3+} through photoexcitation by visible light reduced Ar_2I^+ to aryl radical **317**, ArI, and Ir^{4+}. Aryl radical **317** oxidized cyclopalladated complex **314** to Pd(III) intermediate **315**, which was further oxidized to Pd(IV) complex **316** by Ir^{4+}, regenerating Ir^{3+}. Finally, reductive elimination from

Scheme 80. Pd-Catalyzed Ortho Aroylation of 2,3-Diphenylquinoxaline with Aromatic Aldehydes



Scheme 81. Proposed Mechanism for Pd-Catalyzed Ortho Aroylation of 2,3-Diphenylquinoxaline



Pd(IV) intermediate **316** afforded product **313** and regenerated Pd(II).

In 2013, Ritter and co-workers reported the first metal-catalyzed fluorination of arylboronic acid derivatives using a Pd(III) complex (Scheme 78).[71] This strategy was tolerant toward air and moisture and was amenable to functionalized aryl fluorides on a multigram scale, providing a level of practicality and operational simplicity. However, heterocycles could not be fluorinated using this method. Mechanistic studies showed that the well-defined Pd(III) intermediate **323** was involved in these transformations, and its structure was confirmed by X-ray crystallography (Scheme 79). In addition, EPR spectroscopy, magnetic susceptibility measurements, UV−vis−NIR spectroscopy, and DFT calculations supported a d^7 configuration at Pd with an unpaired electron rather than a ligand-centered radical. The proposed mechanism is depicted in Scheme 79. Pd(III) intermediate **323** and Selectfluor® radical cation **322** were generated via turnover-limiting oxidation in the presence of bis(terpyridyl) Pd(II) complex **321′**. Subsequently, a fluorine radical was transferred from Selectfluor® radical cation **322** to the aryltrifluoroborate to afford delocalized radical **326** with the formation of a C−F bond. The final single electron transfer provided the product **327** with the release of BF_3.

In 2014, Patel et al.[72] described a 2,3-diarylquinoxaline-directed ortho monoaroylation employing aromatic aldehydes or alkylbenzenes as aroyl precursors in the presence of Pd/TBHP (Scheme 80). Varieties of functional groups present in the 2,3-diarylquinoxalines, aromatic aldehydes, and alkylbenzenes were well-tolerated. A mechanism involving Pd(III) intermediates **332** and **334** was proposed, as shown in Scheme 81. In path I, cyclopalladation of 2,3-diphenylquinoxaline led to palladium complex **331**, which was oxidized to Pd(III) intermediate **332** by aroyl radical **335** obtained from the aryl aldehyde. Then reductive elimination of **332** delivered the ortho-aroylated product **333**. In path II, the benzyl radical **336** generated from toluene and TBHP oxidized Pd(II) complex to Pd(III) intermediate **334**, which was further transformed to Pd(III) intermediate **332**. The final reductive elimination provided the desired product **333**.

4. CONCLUSIONS

This review has summarized the recent advances in Pd radical involved reactions. To make the reader understand this field easily and deeply, most of the reaction mechanisms have been discussed in detail. It is worth noting that most of the transformations include alkyl halides, which might be favorable for radical transformations. Various Pd(I) and Pd(III) involved reactions have been well-established, such as carbohalogenation, C−H bond activation, Heck reactions, Suzuki coupling, and Negishi coupling, which are employed in the synthesis of very important medicinally active carbocyclic and heterocyclic ring systems. Compared with Pd(0)/(II) chemistry, Pd(I)/(III) chemistry has been less explored and used, perhaps because of the difficulty of controlling radical reactions. However, no expensive and toxic radical initiator is used in the triggering of the radical process, providing this strategy quite promising prospects for application. Thus, we can expect to see many more developments of new methodologies soon.

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Notes

The authors declare no competing financial interest.

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