Chapter 7
Carbonylative Heck Reactions

The "Carbonylative Heck Reaction" is not the same as those that were traditionally called "Heck carbonylations". Heck carbonylations normally include alkoxycarbonylation, aminocarbonylation and hydroxycarbonylation, while a carbonylative Heck reaction is more related to a Heck reaction. In the late 1960s, Richard Heck developed several coupling reactions of arylmercury compounds in the presence of either stoichiometric or catalytic amounts of palladium salts [1–7]. Based on this work in 1972, he described a protocol for the coupling of iodobenzene with styrene, which today is known as the "Heck reaction" [8]. In contrast to this, the catalytic insertion of olefins into acylpalladium complexes is called a "Carbonylative Heck reaction". Here the acylpalladium complexes can either by CO insertion or by the oxidative addition of benzoyl precursors [9, 10].

The first palladium-catalyzed copolymerization of carbon monoxide (CO) with olefins was described in 1982 [11], and as a consequence, carbonylative coupling reactions with alkenes were reported soon after. Notably, it was Negishi and Miller who discovered the first two examples of intramolecular carbonylative Heck reactions of 1-iodopenta-1,4-dienes by applying stoichiometric amounts of palladium [12]. 5-Methylenecyclopent-2-enones as the products were produced in moderate yields (Scheme 7.1).

However, using **1a–1e** as substrates, no desired carbonylation products were detected, although the complete conversion of starting material occurred. Presumably, the polymerization of **1a–1e** (Scheme 7.2) took place [13]. Negishi and Miller's group improved the methodology two years later [14]. In their new methodology, **1a–1e** were applied as starting materials and the corresponding products were obtained in moderate to excellent yields using catalytic amounts of palladium salts in the presence of MeOH. A possible reaction mechanism was proposed, and "CO-free" carbonylative Heck reactions were realized. 2-Methylene-2,3-dihydro-inden-1-one **1g** was produced from the corresponding acid chloride **1f** in a 50 % yield under "CO-free" conditions.

Negishi et al. continued their interest in this topic by synthesizing various quinones using *o*-iodoaryl cyclohexyl ketones as the starting materials [15]. In the presence of Pd(dba)$_2$ as a catalyst (5 mol %) and under CO pressure (41 bar), quinones were produced in good yields with 100 % regioselectivity (Scheme 7.3).

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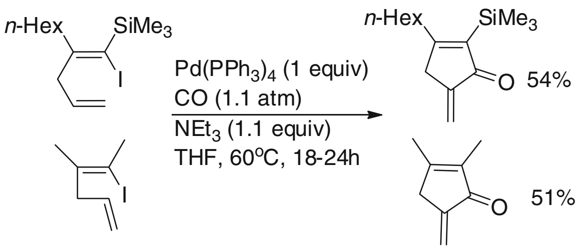
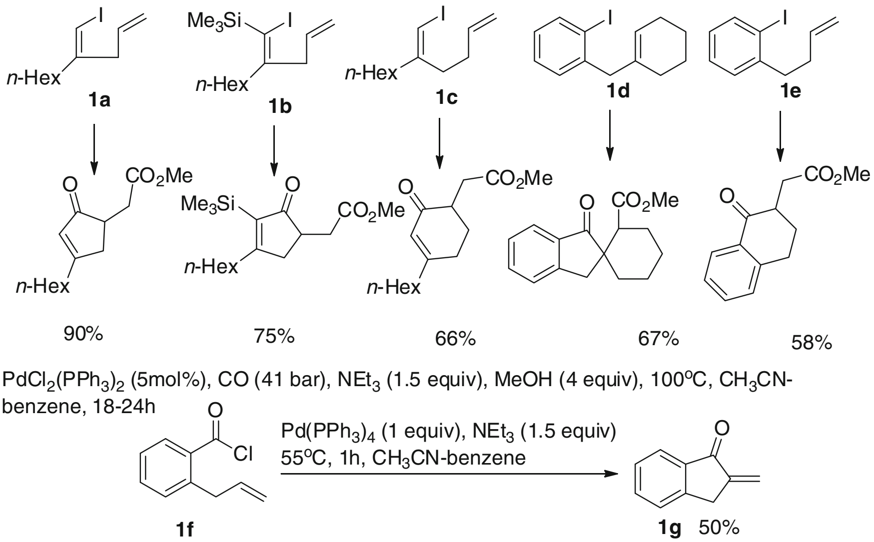


Scheme 7.1 The first examples of palladium-mediated intramolecular carbonylative Heck reactions

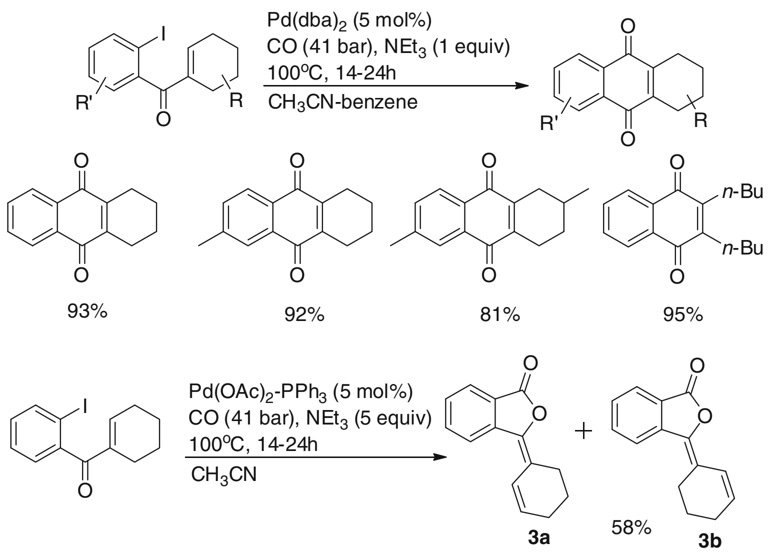


Scheme 7.2 Palladium-catalyzed intramolecular carbonylative Heck reaction

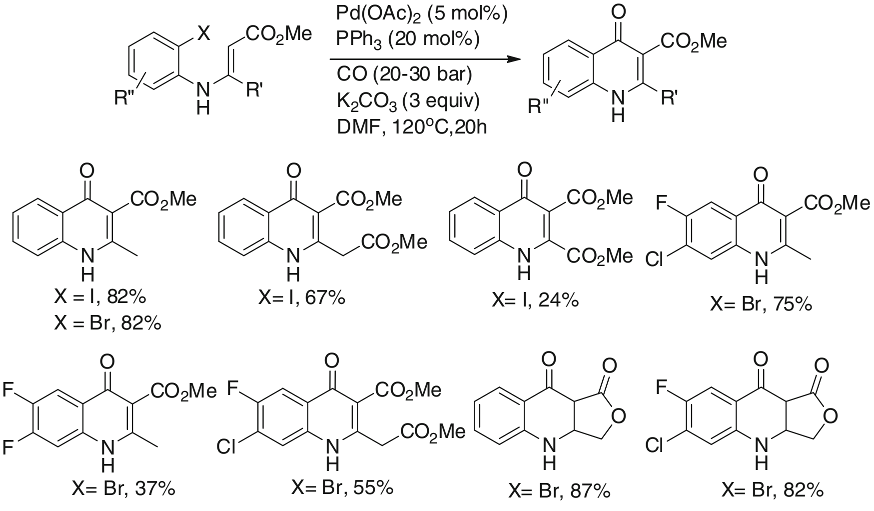
In this catalytic system, 58 % of furanones were formed instead of quinones if $Pd(OAc)_2/PPh_3$ was used. This latter work can be considered to be the first real palladium-catalyzed intramolecular carbonylative Heck reaction. In 1996, a full account using various vinyliodides was published by the same group [16–18].

In 2002 Ryu and colleagues reported on similar work that was catalyzed by Pd in the presence of light [19]. Similar products are obtained by the palladium-catalyzed carbonylative coupling of allyl acetate with benzynes [20].

Notably, Torii and colleagues reported the intramolecular carbonylative Heck coupling of 3-(2-haloarylamino)prop-2-enoates to the corresponding quinolinone derivatives [21]. In the presence of a catalytic amount of $Pd(OAc)_2$ under 20 bar of CO at 120 °C, quinolinones were synthesized in good yields (Scheme 7.4). A related carbonylative cross-coupling of aryl iodides with alkynones was reported

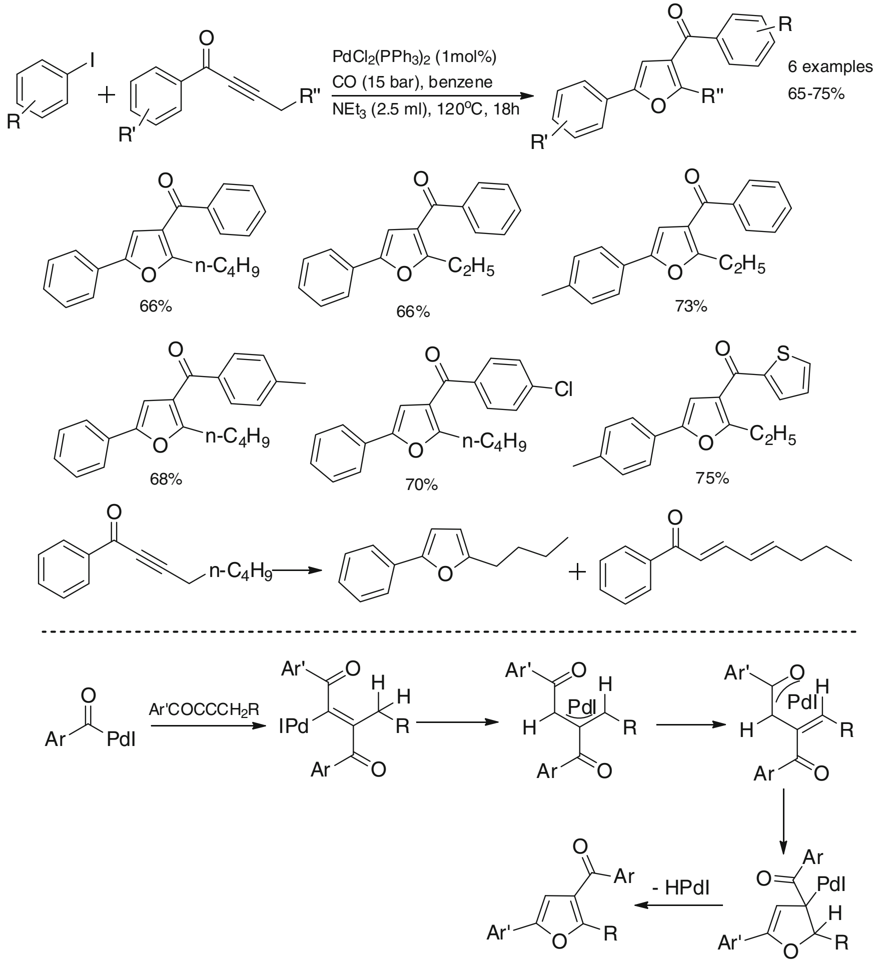


Scheme 7.3 First palladium-catalyzed intramolecular carbonylative Heck reaction



Scheme 7.4 Palladium-catalyzed carbonylative Heck reaction to quinolinones

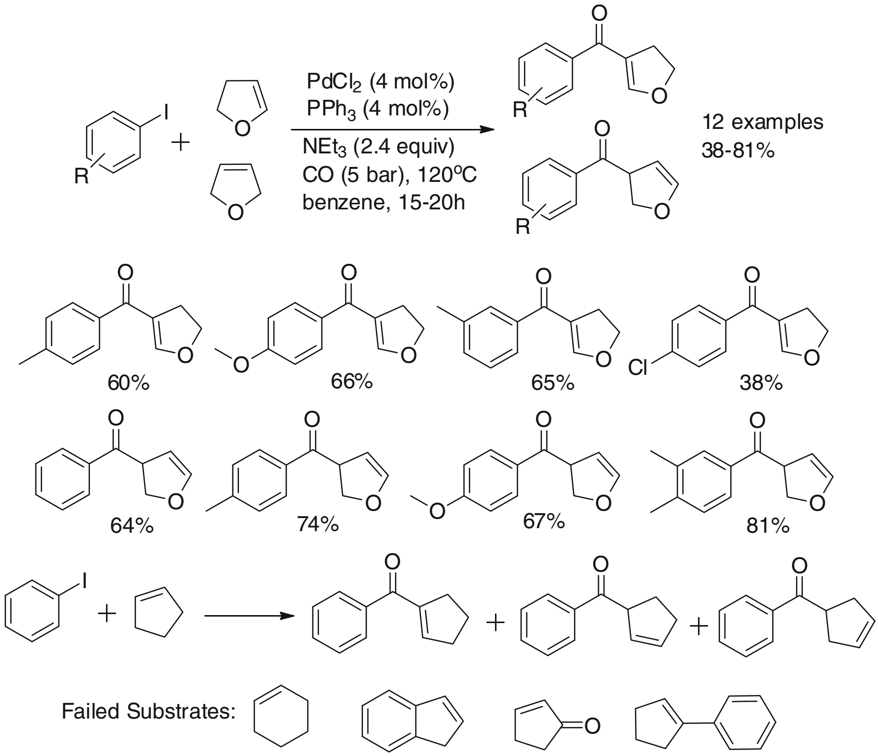
by Miura's team [22]. They showed that in the presence of CO and a palladium catalyst, various furans were produced in good yields (Scheme 7.5). Recently, Beller, Wu and colleagues succeeded in extending the reaction to aryl bromides and terminal alkynes. The reaction was believed to go through alkynone as the intermediate [23].



Scheme 7.5 Palladiumd-catalyzed carbonylative cross-coupling reactions of aryl iodides with alkynones to furans

In 1995 Miura and colleagues described a palladium-catalyzed carbonylative cross-coupling of aryl iodides with five-membered cyclic olefins [24]. This represents the first palladium-catalyzed *intermolecular* carbonylative cross-coupling of aryl iodides with olefins. Various benzoylated cyclic olefins were isolated in good yields (Scheme 7.6). Unfortunately, the reaction with cyclopentene led to a mixture of three regioisomers of benzoylcyclopentene. During their investigations, Miura‘s group found that the amount of PPh_3 added to the reaction mixture markedly influenced the product yields.

In 1997, Alper and colleagues applied allenes as a special family of alkenes in palladium-catalyzed carbonylative reactions with *o*-iodophenols [25]. Remarkably,



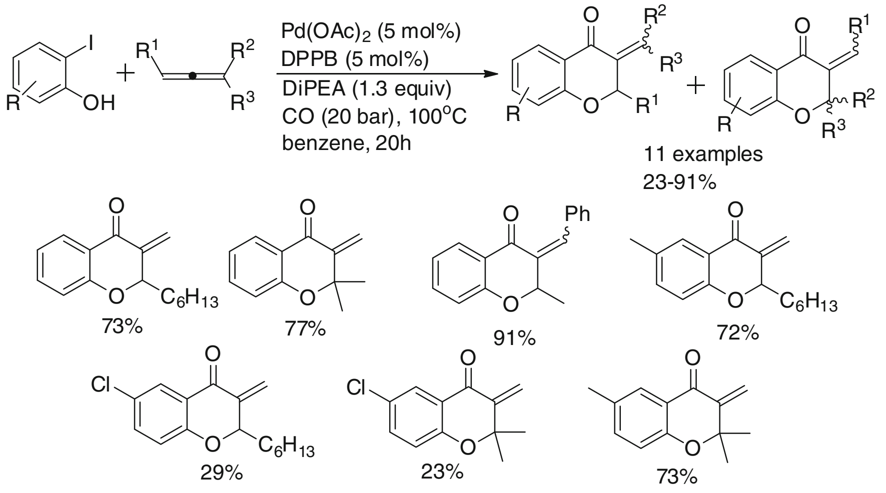
Scheme 7.6 Palladiumd-catalyzed carbonylative cross-coupling of ArI with cyclic olefins

the reaction works in a highly regioselective manner and only one single benzopyranone isomer was obtained in good yields (Scheme 7.7). That same year, Grigg and Pratt reported another carbonylative cascade reaction. Starting from 2-methallyliodobenzene, allenes were incorporated during the cascade process [26].

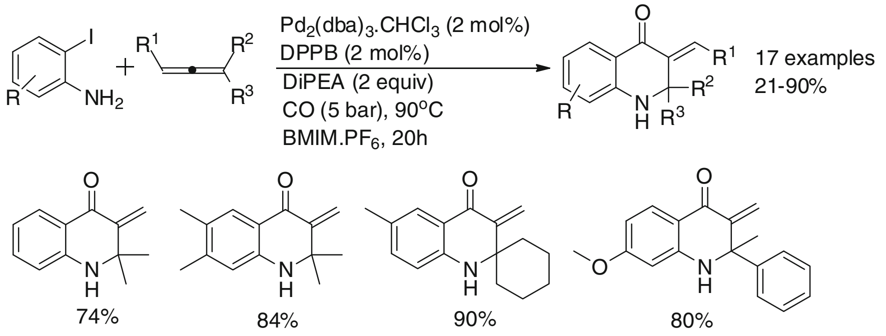
Similar to their previous work, Alper and colleagues succeeded in describing a palladium-catalyzed carbonylative coupling of *o*-iodoanilines with allenes in 2007 [27]. Quinolinones were synthesized in moderate to good yields under low CO pressure (5 bar) (Scheme 7.8). Here, an ionic liquid was used as solvent and promoter to enhance the efficacy of the cyclization protocol. Interestingly, the recyclability of the system was also demonstrated.

In 1999, Iwasawa and Satoh reported a new Heck-type coupling for the synthesis of 4,5-didehydrotropone-$Co_2(CO)_4$dppm complexes [28]. The palladium-catalyzed carbonylation was promoted by a diphenylacetylene cobalt complex **A** and gave the desired complexes in high yields (Scheme 7.9).

The same year, Hayashi and colleagues described an enantioselective palladium-catalyzed intramolecular carbonylative coupling of aryl and alkenyl triflates [29]. Enantiomerically enriched cyclopentenones were prepared in high yields



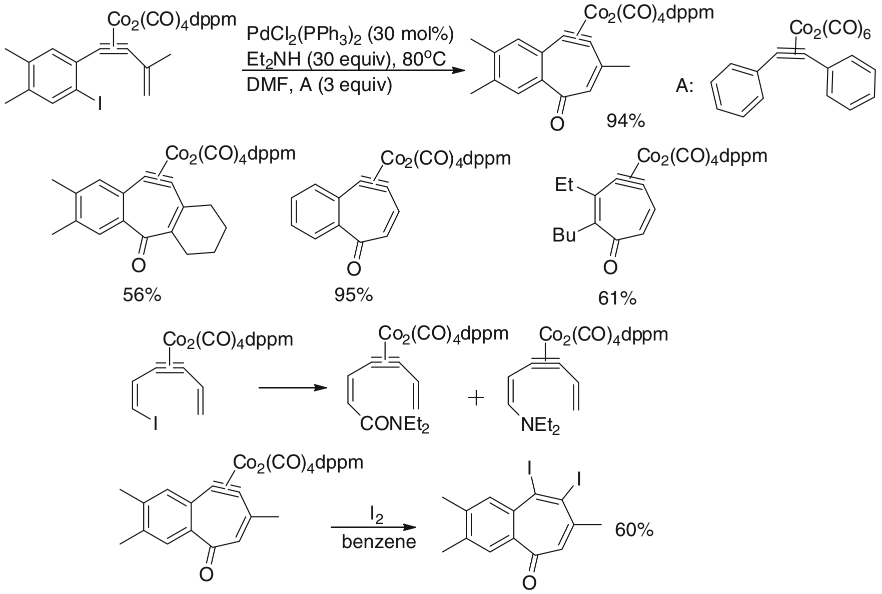
Scheme 7.7 Palladium-catalyzed carbonylative coupling of *o*-iodophenols with allenes



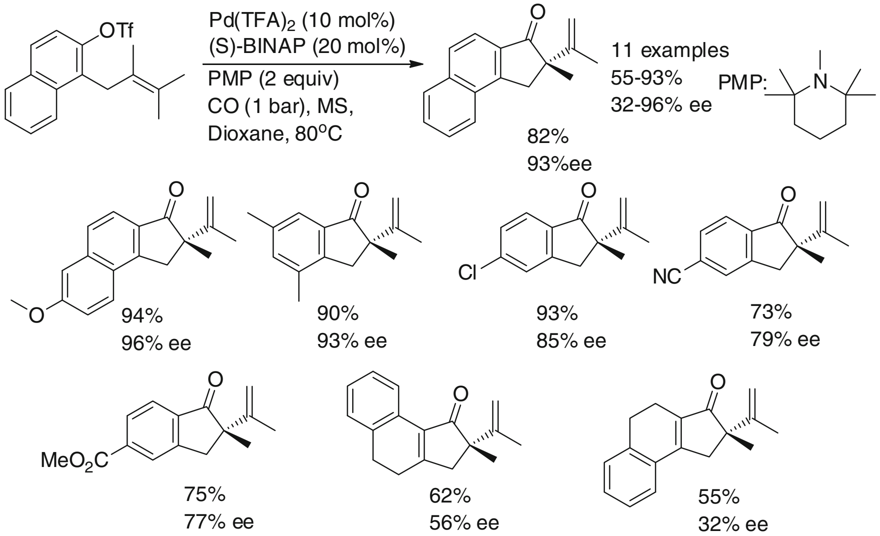
Scheme 7.8 Palladiumd-catalyzed carbonylative coupling of *o*-iodoanilines with allenes

from prochiral *o*-allylaryl triflates and 2-allylalkenyl triflates using Pd(TFA)$_2$/(*S*)-Binap as the catalyst (Scheme 7.10). In this system, PMP as a kind of special base was applied.

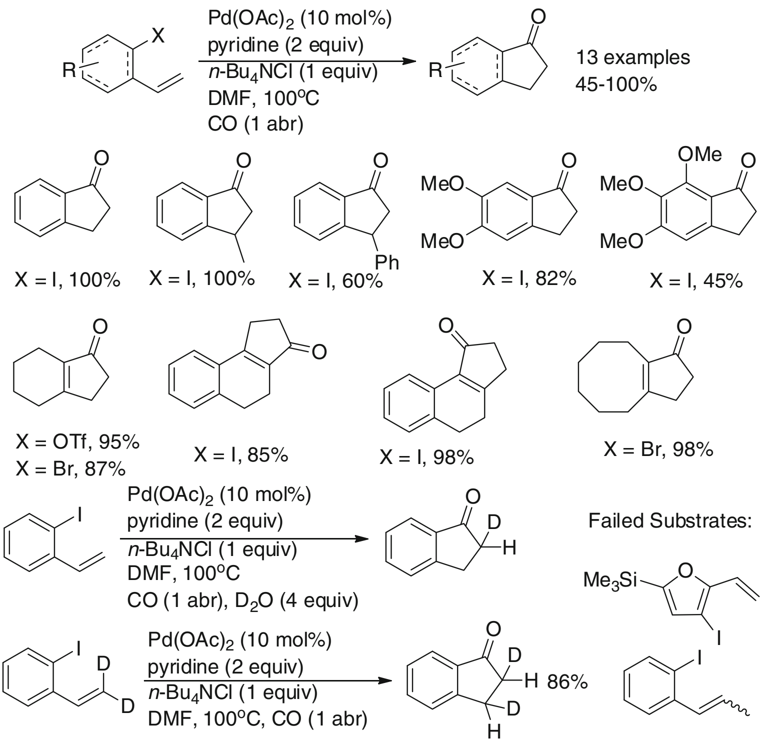
Larock and Gagnier discovered a general and efficient methodology for the synthesis of indanones and 2-cyclopentenones in 2003. Using *o*-halogen styrenes as their substrates, the desired products were prepared in good to excellent yields (Scheme 7.11) [30]. In the same way, Negishi and colleagues described the synthesis of indenones from *o*-iodostyrene. Afterwards, they extended this methodology to dienyl triflates, iodides, and bromides. All products were isolated in good yields. Regarding the mechanism, a trace of water in the solvent may serve as a proton source to favor the formation of indanone instead of indenone.



Scheme 7.9 Palladium-catalyzed cyclization of 4,5-didehydrotropone-Co$_2$(CO)$_4$.dppm complexes via carbonylative Heck reaction



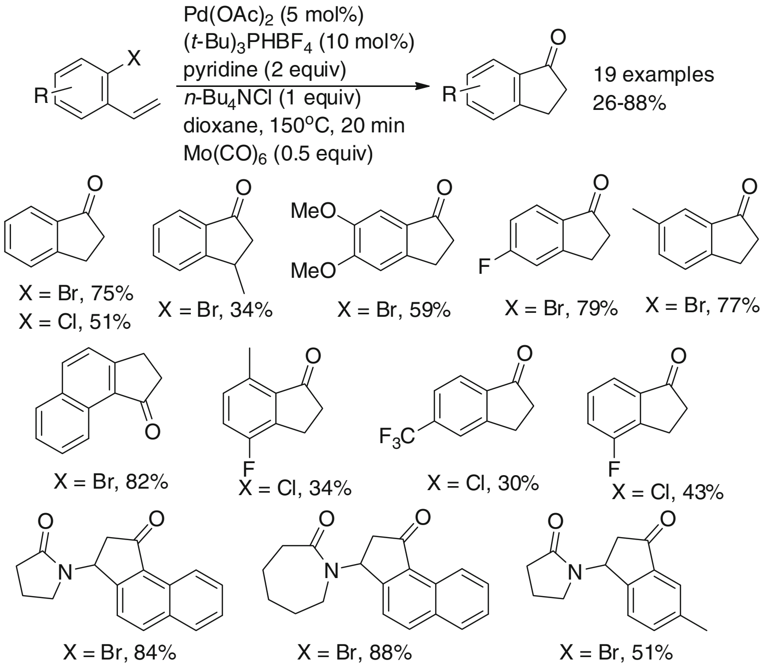
Scheme 7.10 Palladium-catalyzed intramolecular carbonylative coupling of aryl and alkenyl triflates to cyclopentenones



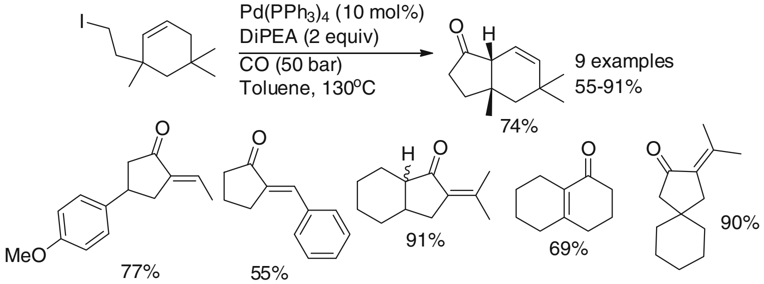
Scheme 7.11 Palladium-catalyzed carbonylative indanone synthesis

More recently, Larhed and his team developed a metal carbonyl-mediated and microwave supported intramolecular carbonylative coupling reaction of *o*-bromostyrenes [31]. Indanones and 3-acylaminoindanones were produced in good yields. In the presence of $Pd(OAc)_2/(t\text{-}Bu)_3PHBF_4$ with $Mo(CO)_6$ as a CO source, and under the irradiation of MW, indanones were achieved in 20 min from the corresponding aryl bromides and chlorides. Both electron-withdrawing and electron-donating groups are tolerated on the arene part, but electron-poor *o*-bromocinnamic acid derivatives furnished only the corresponding lactones via a hydroxycarbonylation-Michael addition sequence (Scheme 7.12).

Last year, Alexanian and Bloome described a palladium-catalyzed carbonylative Heck-type cyclization of alkyl halides [32]. The treatment of a range of primary and secondary alkyl iodides in the presence of a palladium catalyst under CO pressure yielded a variety of synthetically versatile enone products. This novel palladium-catalyzed Heck-type cyclization is a rare example where inactivated alkyl halides with β-hydrogens are involved. Various substituted alkenes were well tolerated, and mono- as well as bicyclic carbocycles are easily accessed (Scheme 7.13).

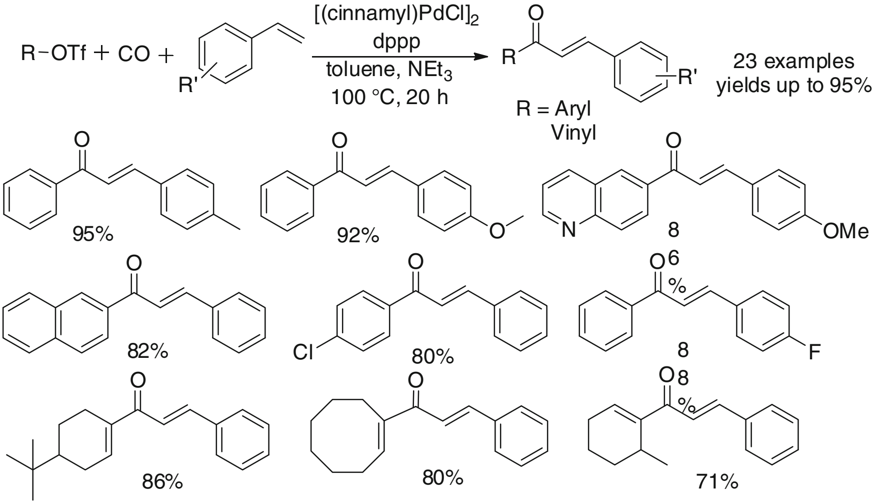


Scheme 7.12 Palladium-catalyzed carbonylative synthesis of indanones using MW



Scheme 7.13 Palladium-catalyzed carbonylative Heck-type cyclization of alkyl halides

It is clear that the main efforts in this area have so far focused on intramolecular carbonylative Heck reactions. A general intermolecular carbonylative coupling of aryl halides or triflates with terminal olefines was not known until the recent work of our group. Initially, we succeeded in carbonylative Heck couplings of aryl triflates with styrenes [33]. Starting from easily available aryl and alkenyl triflates, the corresponding unsaturated ketones are obtained in good yields (Scheme 7.14). The resulting products represent useful building blocks for the synthesis of a variety of biologically active compounds.

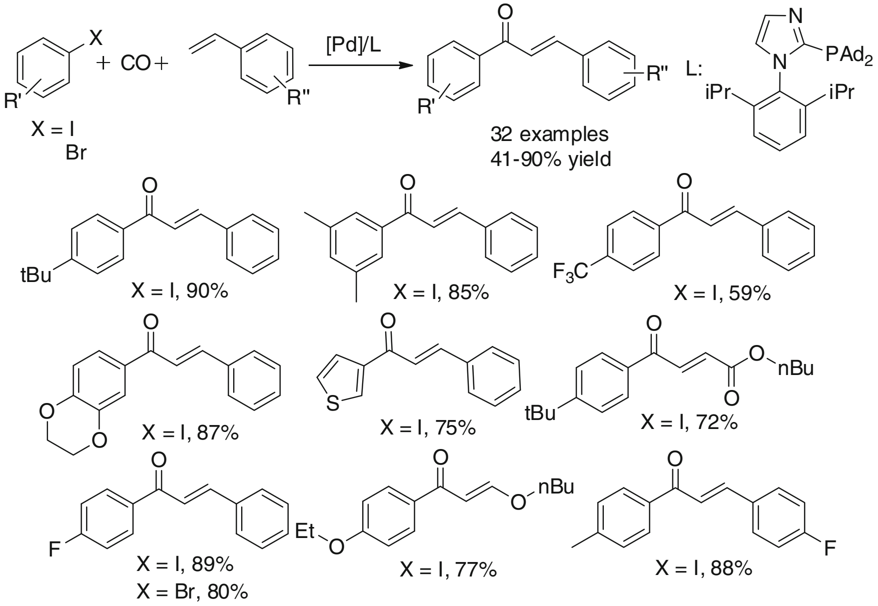


Scheme 7.14 Palladiumd-catalyzed carbonylative Heck reaction of ArOTf with styrenes

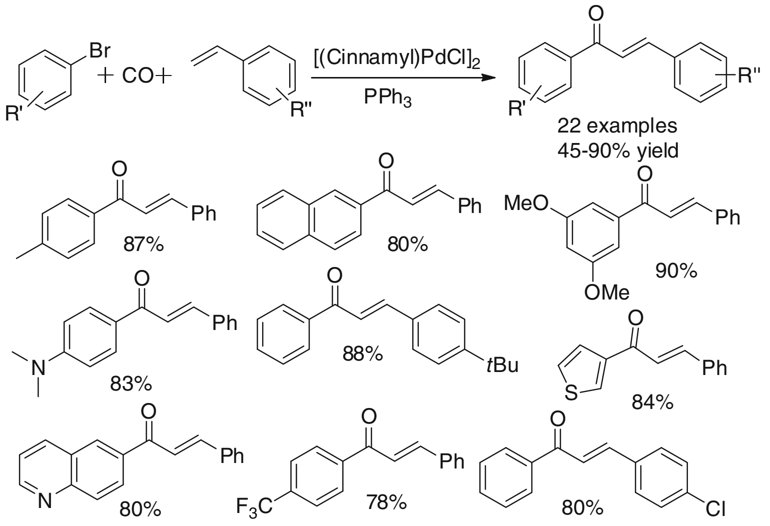
Shortly thereafter, a more general palladium-catalyzed carbonylative Heck reaction of aryl halides was able to be developed by our group [34]. For the first time, various aromatic and aliphatic alkenes were used successfully in this system, and good yields of the corresponding α,β-unsaturated ketones were obtained (41–90 %). Starting from easily available aryl iodides and bromides, interesting building blocks were obtained under mild conditions (Scheme 7.15). With respect to the reaction mechanism, the aryl palladium complex and acyl palladium complex were characterized by X-ray, and the mechanism was studied step by step. The results fit well with DFT calculations.

Most recently, the synthesis of chalcones from aryl bromides in the presence of PPh_3 as a ligand was achieved (Scheme 7.16) [35]. Later on, this group extended our methodology to vinyl ethers [36]. Based on both experimental results and DFT calculations, a proposed mechanism for this reaction is shown in Scheme 7.17. It begins with the oxidative addition of ArX to the Pd^0 center to form the corresponding aryl palladium complex. Followed by the coordination and insertion of CO, the respective acyl palladium complex is produced. After coordination, addition, and elimination processes, the desired chalcone is produced. Under the assistant of the base, Pd^0 is regenerated and starts the next reaction cycle.

The group of Skrydstrup developed a two-chamber technology for the carbonylations. Using this two-chamber technology, CO was generated ex situ. By applying near-stoichiometric amounts of the carbon monoxide precursor, an effective exploitation of the hazardous CO gas is obtained affording chalcone derivatives in good yields from the corresponding aryl iodides and styrenes and vinyl ethers [37, 38]. Application to isotope labeling, incorporating ^{13}CO, was further established.

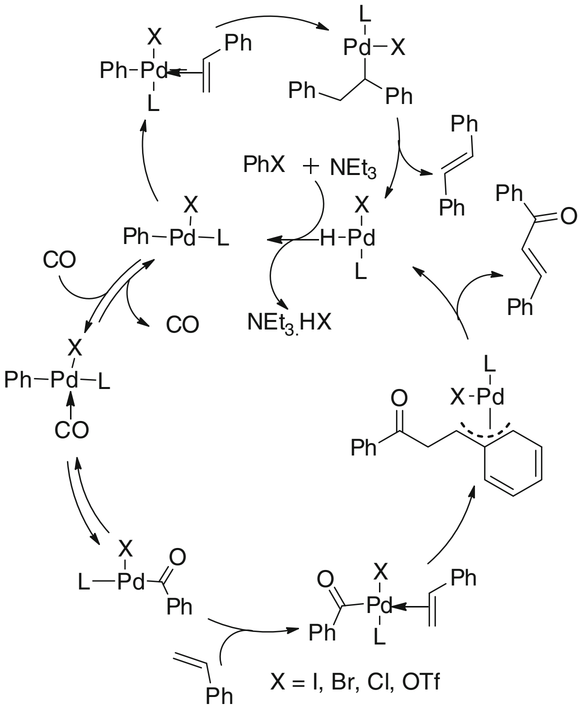


Scheme 7.15 Palladium-catalyzed carbonylative Heck reaction of aryl halides

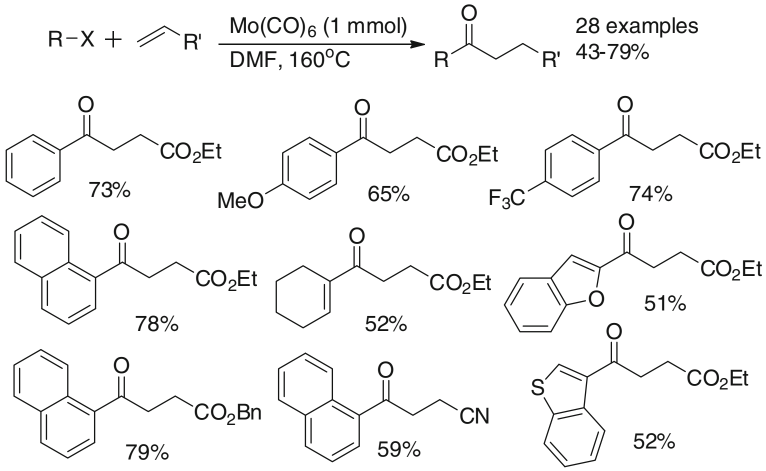


Scheme 7.16 Palladium-catalyzed carbonylative Heck reaction of aryl bromides

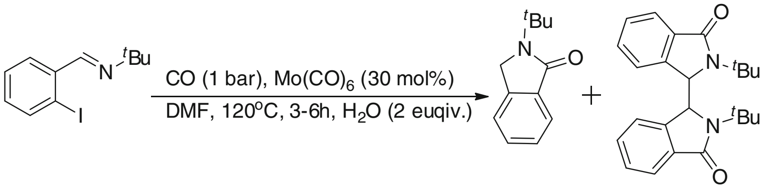
A molybdenum carbonyl complex was used as a promoter in carbonylation reactions as well [39]. Iwasawa and colleagues developed an intermolecular addition reaction of an acylmetal species generated by the oxidative addition of



Scheme 7.17 General reaction mechanism for carbonylative Heck reaction



Scheme 7.18 $Mo(CO)_6$-promoted carbonylation of alkenes



Scheme 7.19 $Mo(CO)_6$-Promoted carbonylative cyclization of *o*-haloaryl and *β*-haloalkenylimines

aryl or alkenyl halides to $Mo(CO)_6$. The reaction needed a stoichiometric amount of $Mo(CO)_6$, and a variety of substituted ketones were produced from readily available materials (Scheme 7.18).

A molybdenum carbonyl complex that promoted the carbonylative cyclization of *o*-haloaryl and *β*-haloalkenylimines was also developed by this group (Scheme 7.19) [40]. *γ*-Lactams were produced in good yields; the two kinds of products can be obtained selectively by changing the reaction conditions.

In this chapter, we discussed carbonylative Heck reactions, or the reaction of C–X with alkenes. *β*-hydride elimination is the step that distinguishes this type of carbonylation reaction from the other carbonylation reactions, from a mechanism point of view.

In the next chapter, oxidative carbonylation reactions will be summarized.

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