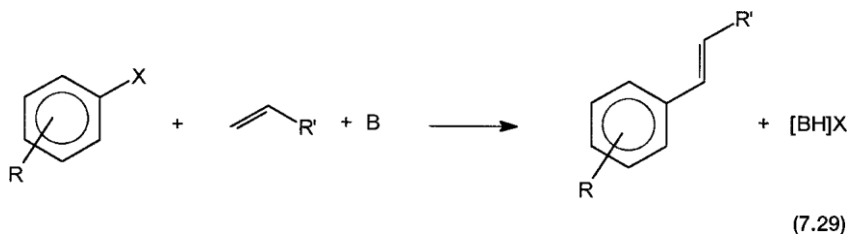
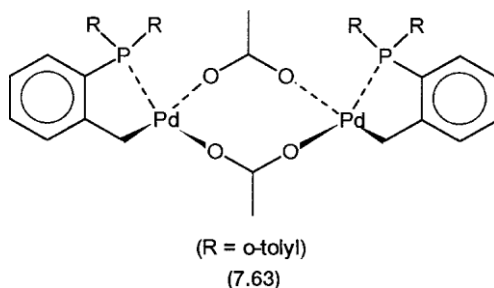
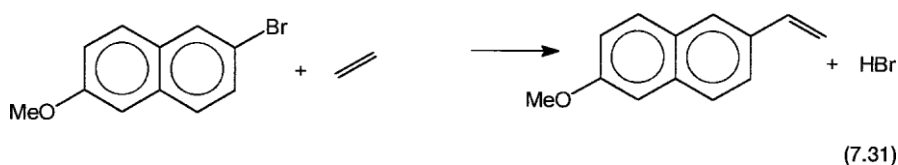


## C–C COUPLING AND CYCLOPROPANATION REACTIONS

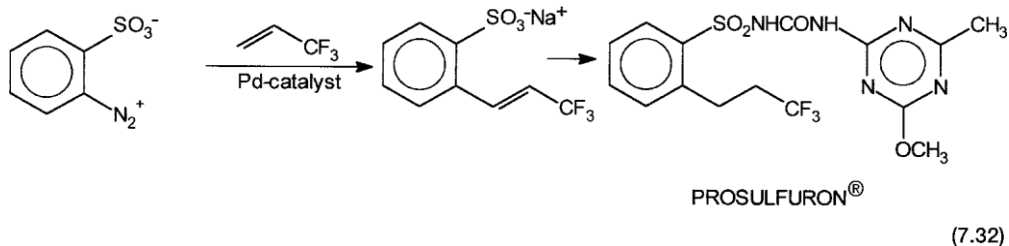
Soluble palladium complexes catalyze a large number of reactions of the type 7.29 and 7.30. These reactions are often referred to as Heck reactions. The precatalyst is usually  $\text{PdL}_4$  ( $\text{L} = \text{PPh}_3$ ) or a combination of  $\text{Pd}(\text{OAc})_2$  with  $\text{L}$ . The base  $\text{B}$  could be organic or inorganic.



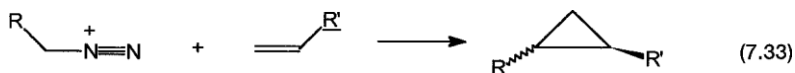
Although these reactions are highly versatile, so far they have not found significant industrial applications. The main reasons for this are relatively low thermal stabilities and turnover numbers of the catalytic systems, and the salt waste problem. However, Hoechst is trying to develop an industrial process for the manufacture of 6-methoxy 2-vinylnaphthalene by reaction 7.31. The pre-catalyst used is the dimeric phosphapallada cycle 7.63, which operates below a pressure of 20 atm and temperature of 130° C.



Another variant of this type reaction has recently been utilized by Novartis to manufacture an intermediate for Prosulfuron® (see Table 1.1). The synthetic scheme is shown by reaction 7.32. The soluble palladium-complex-catalyzed C–C coupling between a diazonium salt and a fluoro alkene gives the required intermediate. This is then converted to the final product by standard reactions of synthetic organic chemistry.



Metal-catalyzed cyclopropanation of an alkene by a diazo compound, reaction 7.33, is another reaction where new C–C bonds are formed. This reaction finds use in the industrial manufacture of synthetic pyrethroids. The precatalysts for carbene addition reactions are coordination complexes of copper or rhodium. It should be noted that reaction 7.33 gives a mixture of isomers (*syn* plus *anti*) of the cyclopropane derivative. However, with some chiral catalysts, only one optical isomer with good enantioselectivity is obtained (see Section 9.5).



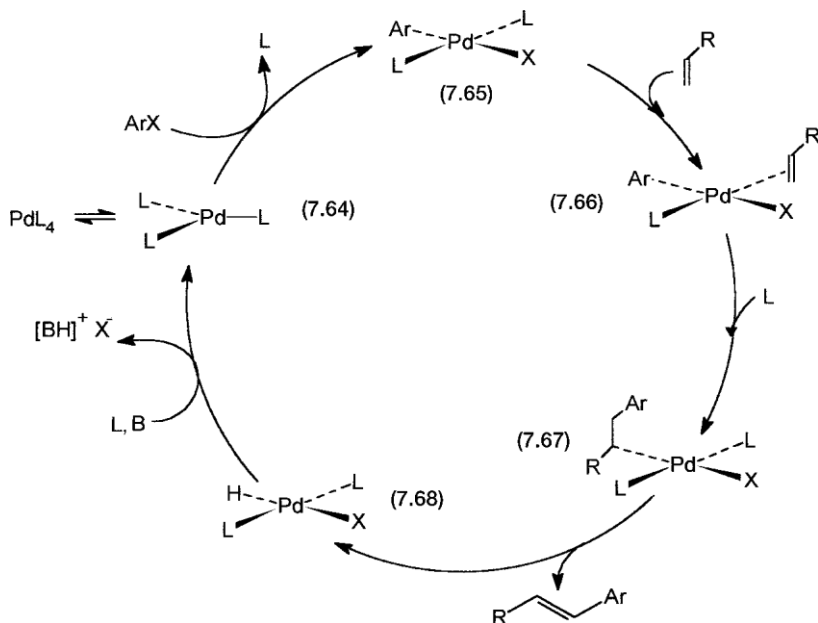
### Catalytic Cycle for the Heck Reaction

A general catalytic cycle proposed for Heck reaction is shown in Fig. 7.17. While all the steps in the catalytic cycle have precedents, the proposed reaction mechanism lacks direct evidence. The basic assumption is that under the reaction conditions, the precatalyst is converted to 7.64, a coordinatively unsaturated species with palladium in the zero oxidation state. Oxidative addition of ArX, followed by alkene coordination, leads to the formation of 7.65 and 7.66, respectively. Alkene insertion into the Pd–C bond followed by *β*-H abstraction gives 7.67 and 7.68, respectively. Reductive elimination of HX, facilitated by the presence of base B, regenerates 7.64 and completes the catalytic cycle. The C–C coupled product is formed in the 7.67 to 7.68 conversion step.

There are two main uncertainties associated with this general mechanism. First, there are a number of C–C coupling reactions where there is no direct evidence for the reduction of the Pd(II) precatalyst into a zero-valent palladium species. Second, like the hydrosilylation system, a number of these reactions may involve colloidal palladium. Also, the general catalytic cycle needs to be substantially modified to rationalize the successful use of 7.63 as a precatalyst.

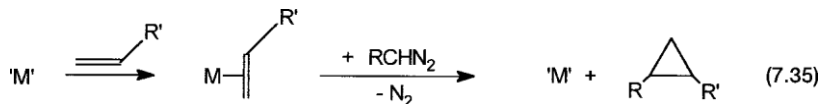
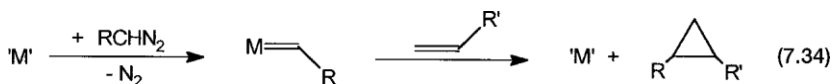
### Catalytic Cycle for Cyclopropanation

Two mechanisms have been considered for metal-assisted cyclopropanation of alkenes by diazo compounds. These are shown by reactions 7.34 and 7.35.

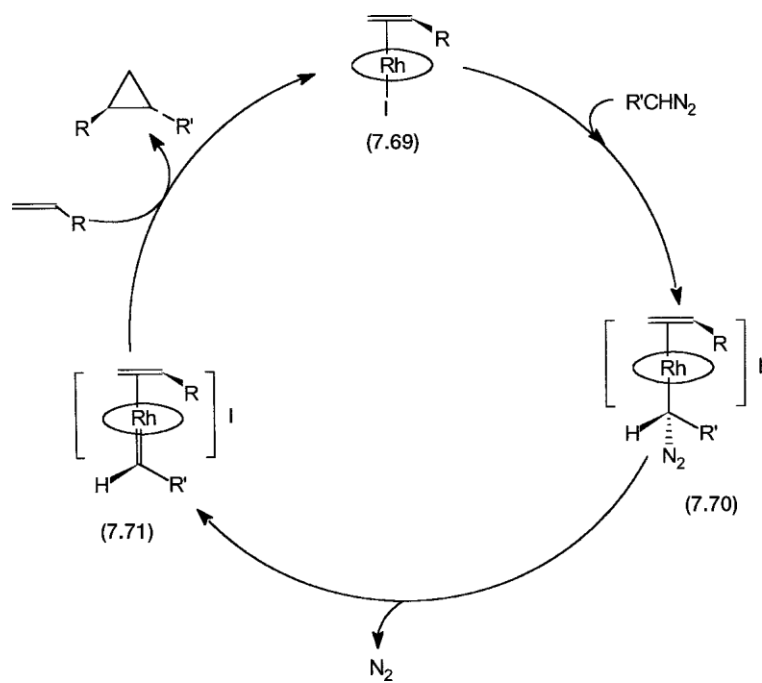


**Figure 7.17** Proposed mechanism for C–C coupling (Heck reaction). Direct evidence for the catalytic steps are lacking.

Reaction 7.34 involves a metal–carbene intermediate, while reaction 7.35 involves nucleophilic attack by the diazo compound to the coordinated alkene. With a rhodium–porphyrin catalyst direct spectroscopic evidence has been obtained for the carbene pathway (see Section 2.5.2).



The catalytic cycle proposed for the rhodium–porphyrin-based catalyst is shown in Fig. 7.18. In the presence of alkene the rhodium–porphyrin pre-catalyst is converted to 7.69. Formations of 7.70 and 7.71 are inferred on the basis of NMR and other spectroscopic data. Reaction of alkene with 7.71 gives the cyclopropanated product and regenerates 7.69. As in metathesis reactions, the last step probably involves a metallocyclobutane intermediate that collapses to give the cyclopropane ring and free rhodium–porphyrin complex. This is assumed to be the case for all metal-catalyzed diazo compound-based cyclopropanation reactions.



**Figure 7.18** Catalytic cycle for the cyclopropanation of alkene by diazo compounds