The Heck Reaction as a Sharpening Stone of Palladium Catalysis

Irina P. Beletskaya* and Andrei V. Cheprakov

Department of Chemistry, Moscow State University, 119899 Moscow, Russia

Contents

I. Introduction

Palladium catalysis has achieved the status of an indispensable tool for both common and state-of-the-art organic synthesis. Among basic types of palladium-catalyzed transformations, the Heck reaction and related chemistry occupy a special place. Though in specific areas other palladium-catalyzed transformations such as, e.g., allylic substitution of cross-coupling may seem to be more advanced, none can match Heck chemistry in resourceful versatility, the overwhelming ability to spawn new, hitherto unexpected applications, and resolving challenges. The task to comprehensively review Heck chemistry is now a hopeless adventure and would require a multivolume set. To find all instances of its applications, the literature must be manually browsed, article by article, page by page. More and more often researchers do not bother to mention in the titles, abstracts, or keywords if they used Heck-type chemistry in their syntheses, because it became one of basic tools of organic preparations, a natural way to assemble molecules.

There are a number of masterful reviews covering different aspects of Heck chemistry.[1–15] The goal of this review is to try to cover Heck chemistry from a different angle. We shall consistently try to elucidate and discuss everything what makes Heck chemistry so intriguingly flexible, expandable, adaptable, and unpredictable. Indeed, most organic reactions, particularly catalytic ones, are well defined and specific to require some particular reagents and catalysts, to operate within a confined domain, the definition of which includes a more or less limited scope and optimal conditions, solvents, ligands, etc. Several general procedures cover almost all conceivable applications. Yields for similar substrates can be extrapolated.

Nothing like that is true for Heck chemistry. The limits of scope are blurred, the substrates which yesterday had been considered as *unheckable* are being cracked on need with yet another improvement. The catalyst is often anything containing palladium, even in homeopathic doses, and other metals can perform the task in the absence of palladium. As far as the solvent type, almost any media seems to have been already tried and none has been altogether discarded. On the other hand, often a small variation of substrate structure, nature of base, ligands, temperature, pressure, etc., leads to unpredictable results. Trends in reactivity and selectivity are uneven and often break when nobody would expect. Brand-name precious ligands which worked miracles for some sophisticated transformations often fail in the simplest cases. An obvious question of what is the

Irina Beletskaya received her Diploma degree in 1955, her Ph.D. degree in 1958, and her Doctor of Chemistry degree in 1963 from Moscow State University. The subject for the latter was Electrophilic Substitution at Saturated Carbon. She became a Full Professor in 1970 and in 1974 a Corresponding Member of the Academy of Sciences (USSR) of which she became a full member (Academician) in 1992. She is currently Head of the Laboratory of Organoelement Compounds, Department of Chemistry, Moscow State University. Irina Beletskaya is Chief Editor of the Russian Journal of Organic Chemistry. She was President of the Organic Chemistry Division of IUPAC from 1989 to 1991. She was the recipient of the Lomonosov Prize (1979), the Mendeleev Prize (1982), and the Nesmeyanov Prize (1991). She is the author of over 500 articles and 4 monographs. Her current scientific interests are focussed on (i) transition-metal catalysis in organic synthesis; (ii) organic derivatives of lanthanides; and (iii) carbanions and nucleophilic aromatic substitution.

Andrei V. Cheprakov graduated from the Department of Chemistry of Moscow State University in 1983 and joined Professor I. Beletskaya's Laboratory of Organoelement compounds. His Ph.D. theses were devoted to the oxidative halogenation of aromatic compounds and were defended in 1989. Currently he is a docent at the Chair of Organic Chemistry of Moscow University. His research interests include the palladium-catalyzed reactions in aqueous and microheterogeneous media, catalytic activity of nanoparticles, and the chemistry and synthesis of extended porphyrins.

best catalyst and procedure remains unanswered even for the simplest cases, though studied in hundreds of works. Heck chemistry continues to be a fascinating puzzle. It is multidimensional and along each of its dimensions intersects with the domains of other palladium-catalyzed processes with common steps, ideas, techniques. Tuning Heck chemistry reciprocates in palladium catalysis as a whole.

The Heck-type reactivity, one of the basic types of reactivity in palladium-driven catalytic cycles, comes from the ability of Pd(0) species to undergo oxidative addition to various C–X bonds and the addition of thus formed RPdX intermediates to unsaturated bonds. The term Heck chemistry is associated in the first place with the catalytic arylation and alkenylation of olefins, that is the original Heck or Mizoroki–Heck reaction, discovered independently by Mizoroki[16] and Heck[17] and developed by Heck in a number of fundamental papers into a general method of organic chemistry.

The reaction presents one of the simplest ways to obtain variously substituted olefins, dienes, and other unsaturated compounds, many of which are useful as dyes, UV screens, pharmaceuticals, etc. The reaction is also useful in polymerization chemistry, giving access to conjugated polymers applicable, e.g., as new materials for optoelectronic devices.

The reaction can be catalyzed by palladium complexes with or without phosphine ligands (phosphine-assisted vs phosphine-free catalysis). A primary role of phosphine ligands is to support palladium in its zero oxidation state in the form of stable PdL_4 or PdL_3 species. The phosphine-assisted method may be regarded as conservative, as it relies not on *a priori* unknown reactivity of palladium catalyst in a given catalytic cycle, but rather on ligands which can sustain the catalytically active species even outside of the catalytic cycle. The phosphine-assisted approach is the classical and well-established method which gives excellent results in a majority of cases. Then why seek anything else?

The reasons are both economical and chemical. Phosphine ligands are expensive, toxic, and unrecoverable. In large-scale applications on industrial and semi-industrial scale, the phosphines might be a more serious economical burden than even palladium itself, which can be recovered at any stage of production or from wastes. The chemical reason is lower reactivity of fully ligated complexes of palladium, the main result of which is the need for higher loads of catalyst to achieve appropriate rates of reaction and therefore further aggravation of procedure cost.

Both underligated and phosphine-free catalysis are opposite to the phosphine-assisted conservative methodology. It relies not on the intrinsic stability of properly ligated isolable complexes, but rather on making zerovalent palladium species run for life within the Heck catalytic cycle or die as inactive black sediments. Underligated Pd(0) species (the term underligated means that a given palladium complex bears less strongly bonded ligands than is required to form a stable complex) are intrinsically unstable to survive outside of the cycle but are likely to have higher reactivity; therefore, their stationary concentration in a catalytic system is much lower. Unlike phosphine-assisted systems which are based on thoughtful design and knowledge of intimate details of coordination chemistry, phosphine-free systems are illegitimate children of circumstance. Nevertheless, there is a hope that on gathering more data on such reactions, some helpful trends could be evaluated and used to refine the procedures. The award is huge catalytic efficiency and economical feasibility of processes.

II. The Heck Catalytic Engine

Scheme 1 gives a simplified scheme introducing the major steps of the Heck catalytic cycle. The scheme

Scheme 1
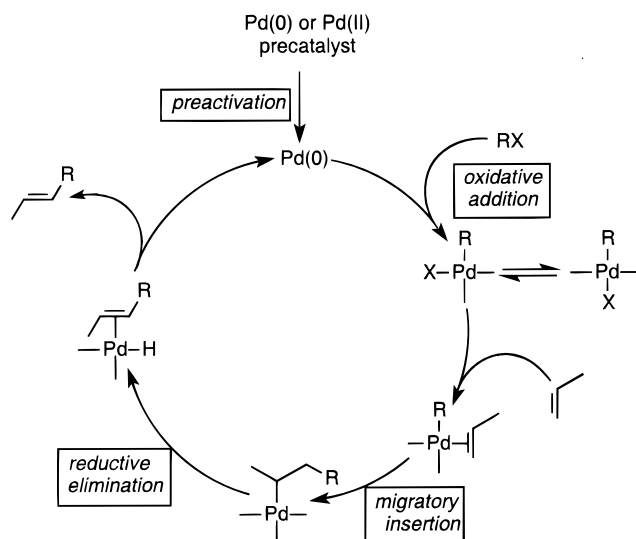
is intended as a very rough approximation because a single scheme, disregarding however detailed it is, cannot reflect all relevant variants of Heck chemistry.

A. Preactivation Step

The entry into the catalytic cycle includes the reduction of Pd(II) complexes to Pd(0) and the generation of active species through multiple ligand exchange equilibria. In kinetic measurements, this stage is revealed by a latent (inductive) period. Due to the labile character of Pd(0) complexes, in most cases there must be a manifold of more and less reactive species with varying coordination shells. The preactivation has been extensively studied by Amatore and Jutand et al.[18,19] for phosphine-assisted reactions.

The primary reduction of Pd(II) to Pd(0) is most likely accomplished by phosphine in the phosphine-assisted catalytic cycles.[20-22] The reduction is assisted by hard nucleophiles, of which the most common are hydroxide[23-25] and alkoxide ions,[26] water,[27] and water and acetate ion,[21] though in special cases even fluoride in the presence of water can play the role.[28,29] Most probably the nucleophile either attacks the coordinated phosphine in a way that can be simplistically viewed as a nucleophilic substitution at phosphorus atom. An inner-shell mechanism involving the reductive elimination of phosphonium species is also possible. The liberated phosphonium intermediate is transformed into phosphine oxide in one or another way (Scheme 2).

Contrary to a common-sense belief that donor phosphines are more susceptible for oxidation, in this

Scheme 2
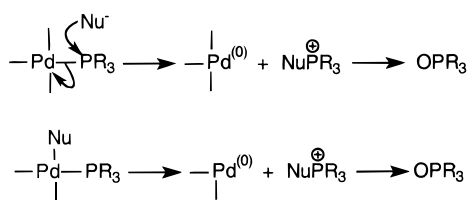
process electron-withdrawing groups in phosphine increase the rate of reaction,[22] possibly because the nucleophilic attack at more electrophilic phosphorus atom is facilitated. The role of water in phosphine-mediated reduction is not clear, as there is both evidence on the catalytic effect[21] and opposite evidence on the absence of effect of water on the reduction rate.[22] Nevertheless, the final form of phosphine oxidation, phosphine oxide, is most likely formed due to the action of either stray or deliberately added water.

In phosphine-free systems, the primary reduction of Pd(II) can be effected by amines, if these are used as base, or olefin. It is interesting to note that neither Et$_3$N nor olefin have any detectable influence on the reduction rate in the presence of phosphine.[22] Still, it is well-known that in the absence of phosphine, olefins are oxidized by Pd(II) via the first turn of a Waker-type catalytic cycle. This process may be a serious yield-decreasing factor in the reactions with high initial loads of palladium salts in phosphine-free systems if the olefin is taken in an equimolar amount with respect to the electrophilic substrate (that is the by-default case in the intramolecular Heck cyclizations).

Indirect evidence tells that Pd(II) → Pd(0) reduction can also be effected by quaternary ammonium and phosphonium salts (cf., e.g., refs 30 and 31), possibly initiated by oxidative addition to C−P or C−N bonds. Thus, Herrmann reported that the addition of TBABr eliminated the induction period in the reaction catalyzed by Pd carbene complex.[32]

To enter the catalytic cycle through the oxidative addition, palladium(0) species must have a proper coordination shell. No more than two strongly bound ligands are allowed. This requirement places a serious restriction on the choice of ligands and their concentration in the reaction mixture.

The most important problem of monodentate phosphine-mediated catalysis is the very low concentration of reactive dicoordinated Pd(0) complex due to very low equilibrium constants for the respective equilibrium.[33]

$$PdL_4 \rightleftharpoons PdL_3 + L \qquad K_1 \gg 1 \text{ M} \qquad (1)$$

$$PdL_3 \rightleftharpoons PdL_2 + L \qquad K_2 \ll 1 \text{ M}$$
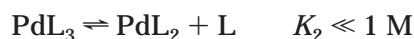
In the presence of excess ligand, the concentration of active species is strongly decreased, which leads to the inhibition of catalytic process. However, if we take exactly 2 equiv of the ligand, the disproportionation of the dicoordinated complex to a stable tricoordinate complex and unstable low-ligated complexes occurs, which undergo a fast aggregation to clusters and further to give off inactive metallic particles:

$$PdL_2 \rightleftharpoons PdL_3 + PdL \rightarrow Pd_nL_m \rightarrow \text{Pd-black} \quad (2)$$
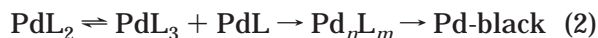
This problem arises in all methods of the generation of catalytically active Pd complexes, either by reduction of PdL$_2$X$_2$ by means of chemical reductants[34] or in an electrochemical cell,[35] or by a reaction of Pd(OAc)$_2$ with 3 equiv of phosphine[20]
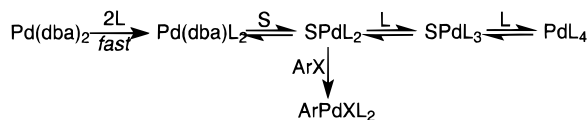
$$Pd(OAc)_2 + 3PPh_3 \rightarrow Pd(PPh_3)_2 + Ph_3PO \quad (3)$$

or by a displacement of dba ligand

$$Pd(dba)_2 + 2L \rightarrow PdL_2 + 2dba \quad (4)$$

This latter process is further complicated by incomplete deligation of dba, which happens to be a ligand comparable to or better than monodentate phosphines (Scheme 3).[33,36,37]

Scheme 3

Full displacement of dba takes much more than 4 equiv of phosphine; thus, the catalyst based on Pd-$(dba)_2$ plus several equivalents of phospine might happen to be inferior in reactivity than preformed PdL_4 complex. The presence of dba can have a strong negative effect on the rate of oxidative addition to less reactive electrophiles, e.g., aryl triflates.[38]

Even more complex is the behavior of *para*-substituted triarylphosphines.[36] The less electron-rich the phosphine, the higher the concentration of species directly involved in the catalytic process through the deligation of PAr_3 ligand. However, the rate of the oxidative addition decreases with the decrease of donor character. Thus, higher concentrations of reactive species are formed in the presence of less donating phosphines, though their reactivity is lower.

B. Oxidative Addition

The oxidative addition of low-valent transition-metal complexes to C–X bonds is among one of the basic processes of organometallic chemistry. The oxidative addition proceeds as a concerted process in which C–X bond rupture is more or less perfectly synchronized with the formation of M–C and M–X bonds. Unlike stepwise addition–elimination mechanisms of nucleophilic aromatic or vinylic substitution[39,40] in which the addition to the unsaturated system is the primary and often rate-limiting stage while the rupture of C–X bond is fast, the oxidative addition is much less sensitive to the substituents in the unsaturated system but much more sensitive to the nature of nucleofuge and the strength of C–X and M–X bonds. The order of reactivity I ≫ OTf > Br ≫ Cl,[41] common to oxidative addition, has no precedence in nucleophilic substitution at sp^2-C, in which a roughly opposite order of leaving-group effect is normal.

In phosphine-assisted catalysis, C–P bonds of phosphine ligand can compete for Pd(0) with less reactive substrates, leading both to the scrambling of substituents in product and to the depletion and deactivation of catalyst.[42]

In most cases except for the complexes with chelating ligands, the isolable product of the oxidative addition possesses *trans*-geometry, though it is obvious that *cis*-complex must be formed first. Moreover,

it is *cis*-complex which enters the next stage of the catalytic cycle. Recent studies explicitly revealed both the formation of *cis*-adduct and *cis*–*trans* isomerization.[43] The latter process can proceed by several independent routes, both through dissociation–isomerization–addition and through association–pseudorotation–dissociation. The availability of the latter route involving five-coordinate complexes is of prime importance for complexes with strongly bonded undissociating ligands, which otherwise would be unable to participate in the Heck reaction.

C. Migratory Insertion

Migratory insertion is the product-forming step of the Heck cycle, in which a new C–C bond is formed. It is this step which is most likely responsible for regio- and stereodiscrimination as well as substrate selectivity. Therefore, the understanding of how this step is realized is of prime importance. Three raw possibilities exist.

(1) RPdX intermediate behaves, similar to organometallic derivatives of nontransition and early transition metals, as a carbanion, and the insertion is a nucleophilic addition similar to that found in vinylic nucleophilic substitution mechanism.[39] A well-known high reactivity of typical Michael donors (acrylates, acrylonitrile, etc.) in the Heck reaction is practically the only evidence in favor of this mechanism while all other data refute it.

(2) RPdX and particularly RPd^+ intermediates are metal-centered electrophiles attacking the double bond in a sort of classical electrophilic addition process. This mechanism is much more solidly justified by experimental evidence and, at least in some cases, is relevant.

(3) RPdX and RPd^+ intermediates add to the double bond in a concerted process. The variable transition state of this mechanism is adaptable to the electronic demands of the involved species in a flexible way well-known, e.g., for the classical concerted mechanism—S_N2—and other concerted mechanisms of common organic chemistry. The adaptability of concerted mechanisms to electronic factors puts forward steric factors as a main source of all types of selectivity.

The reaction of the product of oxidative addition with olefin requires that palladium gets rid of one of the strongly bonded ligands to free a coordination site for alkene. Two different routes have been proposed and proven for this process for phosphine-assisted reactions: the nonpolar route initiated by the deligation of neutral ligand (phosphine in most cases) and the cationic (we prefer the name *polar* for this route to eliminate misleading allusions connected with the word *cationic*) route initiated by the deligation of anionic ligand.[44–46] It must be emphasized that it is the nature of the detached ligand that is most essential for the definition of route while the formal charge on palladium is of lesser importance.

For monodentate phosphine complexes, both routes can be realized (Scheme 4).

For bidentate phosphine complexes, the realization of a nonpolar route appeared to be doubtful, though it cannot be altogether neglected, particularly for large bite-angle diphosphines in which phosphine

Scheme 4
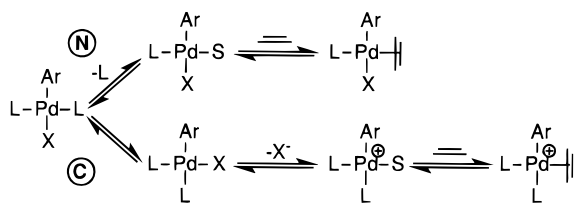
residues are connected with more flexible spacers, and the angle P−Pd−P is essentially larger that 90° required by the square-planar cofiguration (see, e.g., ref 47; Scheme 5).

Scheme 5
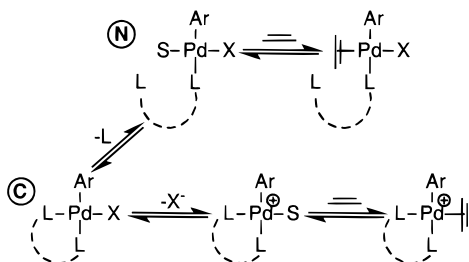
In enantioselective intramolecular Heck reactions, the binding of alkene is often thought to be a main discriminating step[48] and the correct stereochemistry can be explained by regarding the molecular models for the intermediate η^2-alkene complex.

Though no experimental data is available, we may argue that in phosphine-free systems the nonpolar route is hardly conceivable. This may explain why the overwhelming majority of phosphine-free reactions are realized in polar media or in the presence of additives, which assist in exchange of anionic ligands.

The data gathered so far on the reactivity and selectivity of the migratory insertion step show that the electrophilicity of arylpalladium species has nothing or at least little to do with positive charge, and both ArPd$^+$ and ArPdX may behave as a tacit electrophile with donor olefins or a tacit nucleophile with acceptor olefins. The insertion is a concerted process with a variable reaction path which can adapt itself to the electronic properties of the engaged fragments, as well as steric factors and auxiliary interactions (e.g., agostic bonds, allylic or benzylic η^3-bonding, other types of stabilization or assistance). Though there is a temptation to regard the chemistry of cationic and neutral arylpalladium intermediates as a reincarnation of S$_N$1/S$_N$2 paradigm, ArPd$^+$ complex is not by default an electrophile neither it is necessarily more electrophilic than the respective neutral ArPdX species. The data are scattered and obscure but quite indicative of this uncertain status. Amatore has shown that PhPd(PPh$_3$)$_2^+$ complex reacts with styrene, a very reactive olefin in the electrophilic addition processes, much slower than the corresponding neutral complex PhPd(PPh$_3$)$_2$(OAc).[49] The theoretical computations by the quantum chemical density functional method of the insertion stage of the model cationic carbene complex PhPd{C(NH$_2$)$_2$}$_2^+$ showed that the degree of charge

transfer from Pd to olefin is very small and nowhere on the reaction coordinate occurs anything resembling a carbocation (nor a carbanion). Moreover, the addition of proximate counterion to the cationic complex brings a negligible disturbance to the state of reacting species (Scheme 6).[50]
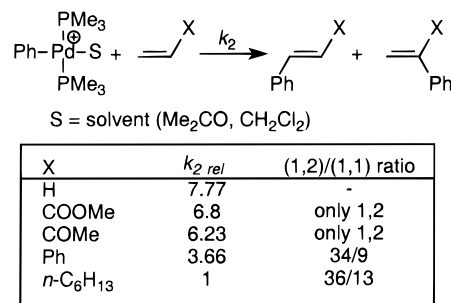
Scheme 6
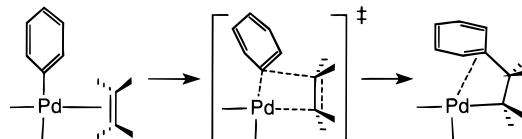
There are several degrees of freedom in the structure of the transition state of a given insertion act. According to the commonly adopted model based on theoretical studies,[51] π-complexed alkene rotates to an in-plane position before the insertion process starts and thus adapts itself by turning either of the ends to go to two different transition states and follow the route with a lower barrier (or both if the barriers are comparable). In the transition state, either C$_{aryl}$−C$_{alkene}$ bond formation can be faster than Pd−C$_{alkene}$ bond formation or vice versa, the latter bond can be formed faster. The computational evidence[50] on the insertion of ethylene into cationic carbene complex reveals the latter case very clearly, as in the transition state the length of Pd−C bond is almost equal to the equilibrium length of this bond in the insertion complex (2.16 vs 2.11 Å) while the formation of new C−C bond significantly lags behind (2.11 vs 1.54 Å).

The measurement of kinetics of the addition of cationic Pd complex to olefins in a solvent mixture of low polarity revealed that electronic effects of substituents are indeed too small for true electrophilic addition with subsequent migration of aryl group. Steric reasons must be much more influential as ethylene was found to be the best olefin for insertion (Scheme 7).[52]

Scheme 7

S = solvent (Me$_2$CO, CH$_2$Cl$_2$)

X	$k_{2\ rel}$	(1,2)/(1,1) ratio
H	7.77	-
COOMe	6.8	only 1,2
COMe	6.23	only 1,2
Ph	3.66	34/9
n-C$_6$H$_{13}$	1	36/13

The insertion of cationic palladium intermediate into alkene is sometimes viewed as an electrophilic addition to a double bond, which allows the regioselectivity of insertion to be regarded as resulting from the reasoning based on the stability of carbocations. The migratory insertion is split into a two-step process starting from the electrophilic addition of cationic palladium complex to the double bond followed by 1,3-shift of aryl group (the second substage is particularly questionable since 1,3-sigmatropic shift has no certain precedence while the reductive

elimination seems to be a more probable pathway, as is indeed the case in Heck-type arylation of enolates or electron-rich arenes).
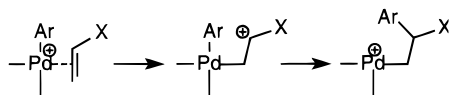

We have to note that such an approach, if applied systematically, may lead to contradictory results. Indeed, in the computational data[50] on the insertion transition state, the degree of charge transfer and formal charges on carbon atoms is rather small. In the transition state in which Pd–C bond formation develops faster than C–aryl bond formation, a moderate positive charge does appear at the carbon atom which is being bonded to aryl, so that electronic effects favoring the carbocation at this atom must work, though not as strongly as in a true carbocation.

The charge on Pd atom in cationic complexes is formal, as the deligation of either neutral phosphine ligand or negative ion (both ligands are σ-donors) leads to the same electronic state of Pd atom. The properties of the remaining Pd complex are defined not by the ligand which departed, but by the ligands which stay bonded. And indeed, in those cases where the data is available, a pure carbocationic route is not unambiguously seen.

Thus, the regiochemistry of carbopalladation by arylpalladium complexes with bidentate phosphines was studied in an attempt to elucidate the main factors governing the direction of attack of cationic arylpalladium complex.[53] A number of complexes (L–L)Pd(Ph)X (where L–L = dppp, dppe, etc.; X = I, OTf, OAc, PF$_6$, BF$_4$) were obtained by the exchange of (tmeda)Pd(Ph)I first with bidentate phosphine and second with AgX salts. The complexes undergo a facile addition to styrene and propene at 0 °C in a stoichiometric reaction to give both 1- and 2-arylation products (Scheme 8).

Scheme 8
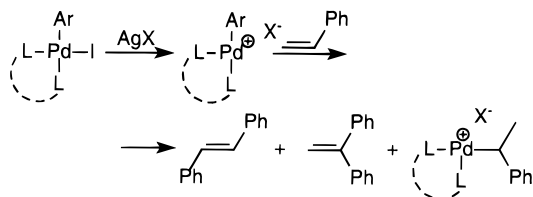
The regiochemistry of the addition to styrene is strongly dependent on the nature of the anionic ligand and solvent. The greater the contribution of truly cationic form of palladium complex, that is the higher the solvent polarity and the poorer the coordination ability of ligand, the higher the relative yield of 1,1-diphenylethylene, the product which must form if the addition were an electrophilic reaction. Thus, e.g., the same regioselectivity is obtained either for X = PF$_6$, BF$_4$ in DMF or for X = OTf in DMF–water (9:1), as in both systems up to 42−43% of 1,1-isomer is formed. However, this ideal picture is observed only if dppp is the ligand—with all other ligands (all have smaller bite angle than dppp) the yield of 1,1-isomer does not exceed 10−15%.

The arylation of the small olefin propene in a stoichiometric reaction, on the other hand, leads predominantly to the formation of 1′-methylstyrene irrespective of whatever complex, neutral or cationic, or solvent is taken.[53] Moreover, the results of the stoichiometric reaction are in contrast to a catalytic reaction, in which propene formed only a nonbranched olefin (Scheme 9).[54]

Scheme 9

A: Pd(OAc)$_2$, KHCO$_3$, LiCl, NBu$_4$Br, 100°C
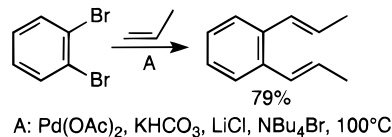
Thus, even with this next to the simplest of olefins, we cannot make any predictions about the regiochemistry of arylation. More data needs to be accumulated and analyzed, and temptations to find simple rules should be discarded.

Thus, steric reasons dominate in regioselection of the addition of a phosphine-free complex (C$_6$F$_5$)PdBr-(MeCN)$_2$ to a series of dienes.[55] The site of attachment of the aryl group is shown by an arrow to reveal a precise discrimination between similar positions in favor of a less hindered one (Scheme 10).

Scheme 10
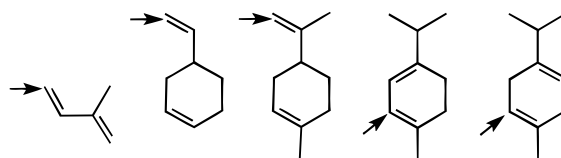
In the pivotal works by Cabri,[6,56−60] the regioselectivity and substrate selectivity of Heck arylation of various electron-rich olefins has been used to discriminate between nonpolar and cationic (polar) routes. Internal arylation products were shown to be formed in reactions of aryl triflates catalyzed by palladium complexes with chelating ligands: diphosphines or phenanthrolines. The most precise regiodiscrimination has been achieved with complexes of palladium with 2,9-dimethylphenanthroline. In the competitive tests with electron-rich and Michael-type olefins, it was shown that the trends in regioselectivity are supported by an unusual substrate selectivity pattern (Scheme 11).

Scheme 11

A: Pd(OAc)$_2$, L, Et$_3$N, DMF, 80°C
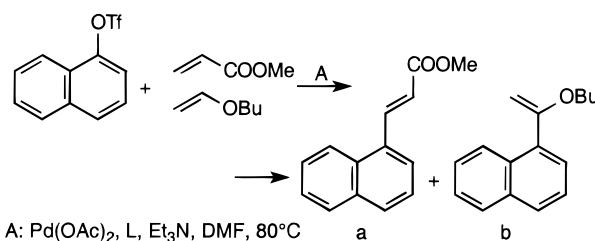
L	a/b
Ph$_3$P	75/21
dppp	28/72
phen	8/92
2,9-Me$_2$phen	1/99

Thus, bidentate ligands show negative substrate selectivity toward electron-deficient olefins and with 2,9-dimethylphenanthroline not only regiodiscrimation but also substrate discrimination is absolute. Positive substrate selectivity toward alkenes bearing carbocation-stabilizing substituents has been also noted by Hallberg et al. in the internal arylation of allylsilanes by aryl triflates in the presence of dppf complex of palladium.[61]

Though an obvious explanation of these facts can be sought in the electrophilic mechanism of the attack by cationic palladium complex, the reasoning based on steric factors is also conceivable. Indeed, unlike monodentate phosphines, both wide bite-angle diphosphines and phenanthrolines possess a special type of steric bulk, leaving the space below and above the coordination plane relatively or absolutely free but bulging out of the area confined within the 90° sector normally occupied by monodentate ligands on the coordination plane. Strongly bonded chelating ligands thus may partially or totally block the motions of ligands engaged in elementary steps of the catalytic reaction. The planar bulk is particularly important for the migratory insertion step, in which olefin first rotates from out-of-plane to an in-plane position. The motions of both aryl and olefin require ample space to be available in the coordination plane. 2,9-Dimethylphenanthroline is obviously the most bulky ligand in the series, as it leaves a sort of narrow pocket for other two ligands—aryl and olefin—to fit in. In Scheme 12 it is obvious that in the case

Scheme 12
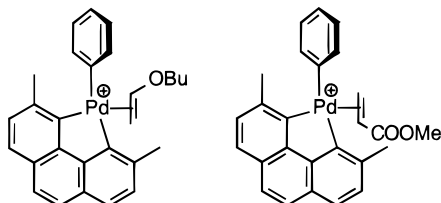
of Michael-type olefin (and more generally for the formation of terminal arylation product), proper alignment of the double bond for migratory insertion is hindered by methyl groups.

The importance of planar bulk is well seen for diphoshine complexes of palladium. Wherever the data are available, dppp and dppf ligands give the best regioselection toward internal arylation (see above). The ligands with smaller chelate cycles, as well as the ligands with larger chelate cycles, lose the ability to cleanly discriminate between the ends of the double bond. For example, the arylation of vinyl ether of *N,N*-dimethylaminoethanol by phenyl triflate in the presence of palladium complexes with chelating phosphines shows this trend quite clearly (Scheme 13).[62]

Phosphine-free conditions and monophoshine ligand exclusively give a terminal product. In this case, entropic factor (additional coordination of olefin through nitrogen atom) overrides electronic effects favoring internal arylation. In the case of chelating phosphines, this factor cannot interfere. Indeed, dppp and dppf ligands show paradigmatic behavior ideally

Scheme 13

| L	i/t
none	1/99
Ph$_3$P	1/99
dppm	1/99
dppe	83/17
dppp	99/1
dppb	77/23
dppf	99/1
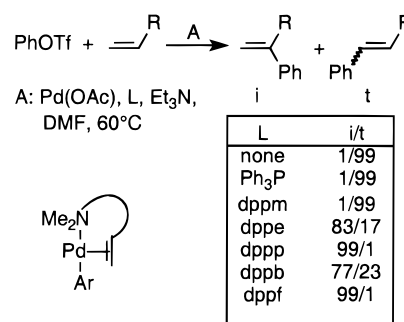
fitting into the concept of electrophilic attack. The ligands dppm and dppb fail because these ligands may dechelate during the reaction due to too small or too wide a chelate ring. But why is strongly chelating dppe again not as effective as dppp? The answer is likely to be associated with lower planar bulk of this ligand as compared to dppp and particularly dppf. In the case of diphosphines, the estimate of planar bulk can be done by comparing bite angles (dppe, 85°; dppp, 90°; dppf, 99°).

Therefore, we have to admit that the data published so far on the regioselectivity of arylation with both neutral and cationic arylpalladium complexes show that (i) in reactions with electron-rich olefins, both neutral and cationic arylpalladium intermediates attack the double bond so that palladium prefers to bind to the atom with higher electron density; (ii) this preference is much weaker than might be expected if the attack resembled the canonical electrophilic addition; (iii) thus, electronic preferences are easily overridden by entropic (steric) factors, which are indeed the most important discriminating force in intermolecular Heck chemistry.

In the intramolecular reactions, entropic factors become an absolute dominant. In the majority of studied cases, this reaction proceeds in the *exo-trig* mode, as this way is by far less sterically demanding. Five-membered cycle formation is preferred, though smaller three- and four-membered cycles can also be formed.[63−68] The *endo-trig* mode requires that the olefinic bond is moved inside the loop in the intermediate π-complex, which requires a much more flexible tether between it and the aromatic ring to be able to freely bend into the proper conformation (Scheme 14).

Scheme 14
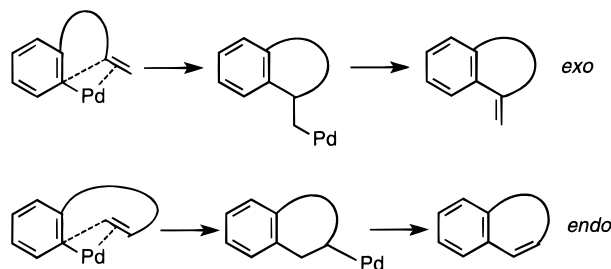
In those cases when 6-*endo* cyclization does take place, a bypass mechanism has been put forward to explain how it may be realized, as the direct process is highly improbable due to geometric reasons.[69−71]

The normal 5-*exo* process is followed by 3-*exo* cycliza-tion with subsequent attack of palladium at a strained bicyclohexane intermediate (Scheme 15).
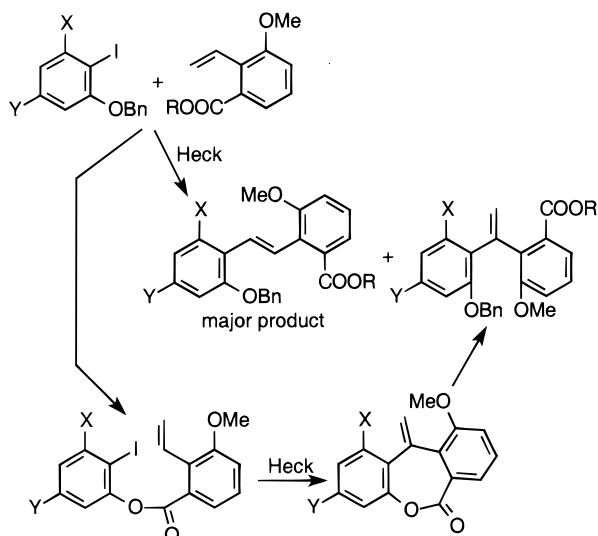
Scheme 15
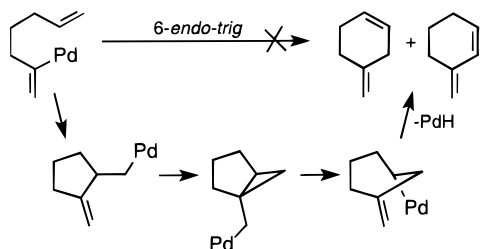
In those cases when the *endo* mode is favored for electronic reasons (e.g., if the substrate going into the cyclization contains a Michael-type olefinic fragment), the reaction can lead to larger cycles. The need for a more flexible chain is likely to explain why the yield of the *endo*-cyclization product steadily grows with longer chain length—a behavior not common in the cyclization chemistry[72] (cf. ref 73; Scheme 16).

Scheme 16

A: Pd(OAc)$_2$ (2.5 mol%), NaHCO$_3$, MS 3A, Bu$_4$NCl, 105-110°C, 16 *h*

| n	Yield, %
1	41
2	63
3	89
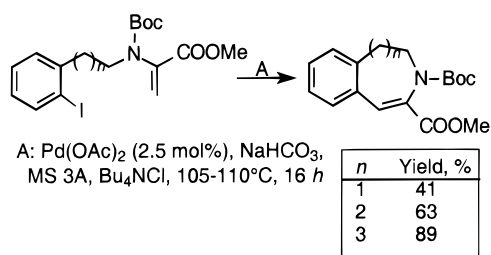
The different regioselectivity of the intra- and intermolecular Heck reactions can be made to work in complex synthetic tasks. Indeed, whatever the catalyst, internal arylation of the styrene double bond remains a minor reaction pathway. An ingenious way to overcome normal regioselectivity has been recently proposed to utilize *exo* cyclization with subsequent cleavage of temporary cycle (Scheme 17).[74]

Scheme 17

Long-range interactions can help the insertion to tie together distant units. An interesting case of macrocyclization by the Heck reaction was recently reported (Scheme 18).[75]

Scheme 18

A: Pd$_2$(dba)$_3$ (10 mol%), Ag$_3$PO$_4$, THF, reflux, 11 *h*

R = H   66%
R = Me   2%
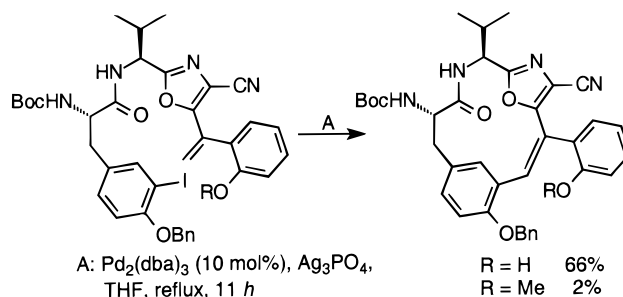
The process obviously operates through a pal-ladium phenoxide complex, which ties together two ends of the molecule to be cyclized. Weak coordina-tion with an alkoxide group is not enough to make the macrocyclization efficient. It should be noted that here phosphine-free conditions are crucial, as at least three coordination sites must be available for this otherwise unfavorable process to occur (Scheme 19).

Scheme 19
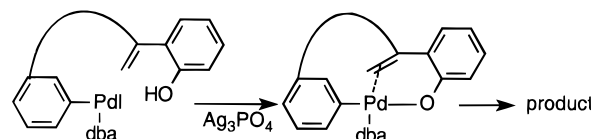
In another notable example, the stacking of por-phyrin rings enables an effective double Heck reac-tion leading to the formation of bis-porphyrin com-plex. The best yield is achieved for the length of spacer matching an optimal distance between stacked porphyrin rings (Scheme 20).[76]

Scheme 20
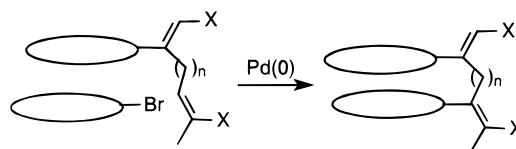
The problem of possible involvement of five-coordinate intermediates at the migratory insertion step has been raised. In most studied cases of enantioselective intramolecular Heck reactions cata-lyzed by Pd complexes with chiral bidentate ligands, the process follows the cationic mechanism (a re-view[48] and references therein). However, at least in a special case discovered and thoroughly studied by Overman, enantioselective Heck reaction proceeds via the neutral pathway and five-coordinate com-plexes of palladium are involved (Scheme 21).[77,78]

Enantioselective reaction can proceed in high yields and ee in the absence of halide scavengers in the presence of amine base equally well in solvents of high and low polarity. Actually this mechanism states that there exists a sort of *hidden gate* between neutral and cationic manifolds, and alkene itself can lend assistance for the transition between the mech-
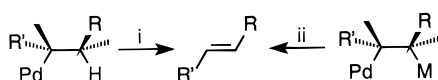
Scheme 21

pseudorotation
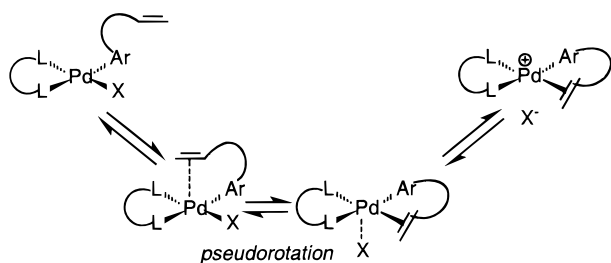
anisms. The importance of Overman's mechanism might be much wider than just the explanation of a specific stereoselection case.

D. Termination

After the migratory insertion comes the step in which palladium(0) is released and launches the next turn of the Heck cycle. There are several possibilities briefly delineated below. (i) Palladium hydride is eliminated to release the double bond (path i in Scheme 22). This is the most common termination

Scheme 22

of the canonical Heck–Mizoroki reaction. (ii) Elimination of other Pd-M complex occurs with the same outcome (path ii in Scheme 22). The best known alternative to PdH is the elimination of Pd–SiX$_3$.[79–82] (iii) Palladotropic shift may occur giving a new intermediate with its own chemistry. There is evidence that such a process can occur, e.g., in the arylation of enones, which gives the product of Michael addition instead of Heck arylation (path iii in Scheme 23). (iv) PdH elimination cannot occur by

Scheme 23
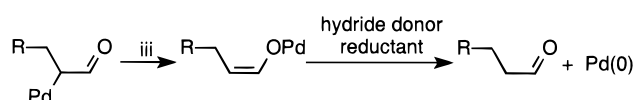
stereochemical reasons or is slow. The termination occurs by nucleophilic attack at Pd, which either by nucleophilic substitution or by reductive elimination of coordinated nucleophile leads to the release of Pd-(0). The product formed may be formally viewed as a *syn*-adduct of R–Nu to the starting olefin. (v) As in iv but the alkylpalladium intermediate goes into a subordinate catalytic process—a *cascade* of Pd-catalyzed transformations is thus initiated realizing the *atom economy* principle.[83,84] Almost any of the known catalytic cycles can inherit from the primary Heck cycle (1) allylic substitution, (2) cross-coupling, (3) electrophilic palladation leading to palladacycles and their subsequent transformations, (4) carbonylation, and (5) another Heck-type reaction possibly leading to the next cascaded cycle. In addition, somewhere down the cycle even some other transition-metal-catalyzed process may take over. This is a sort of molecular chess game, with an overwhelming variety of scenarios, seemingly never to be

exhausted, limited only by fantasy and God's will and played by the grandmasters (Scheme 24).[4,5,85,86,87,88]

Scheme 24
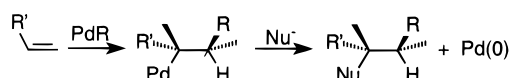
E. Palladium Hydride Elimination

After elimination, PdH is coordinated to alkene. If PdH is not scavenged fast by base, the readdition to the double bond may occur. As PdH is smaller than hydrocarbylpalladium, it adds to either end of the double bond, giving a new intermediate which can pass Pd further along the chain (Scheme 25).

Scheme 25
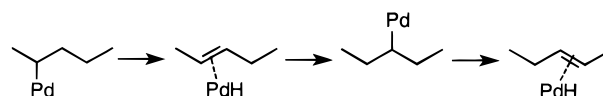
PdH can also be scavenged by starting alkene, which is always more reactive than the Heck product due to its smaller size. This process is well-known as it leads to the isomerization of alkenes, which results in the formation of isomeric Heck products with the wrong stereochemistry (Scheme 26).[89]

Scheme 26
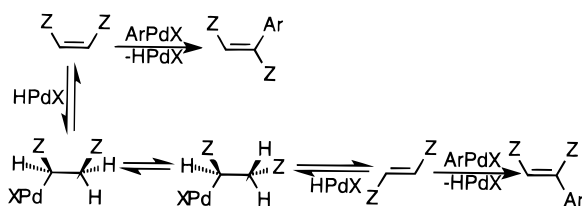
Trapping of PdH by starting alkene is also well documented in stoichiometric modeling of the Heck reaction (Scheme 27).[53,90]

Scheme 27
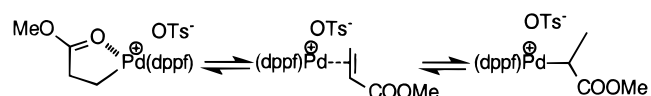
There is a question of how does the PdH elimination occur? A vast majority of data on the selectivity of the Heck reaction can be explained by a concerted *syn*-elimination of PdH. This process is opposite to the addition of PdH to the double bond. The theoretical computations[50,91] reveal such a process with a high degree of certainty. The elimination goes through a rather strong agostic interaction (so strong that in a minimum corresponding to the agostic complex C–H bond to be ruptured is significantly elongated and the β-carbon atom is drawn toward Pd so that the Pd–C$_\alpha$–C$_\beta$ angle becomes acute) of palladium with hydrogen atom and thus proceeds as a concerted *syn*-process without the involvement of the base.

syn-Elimination defines the stereoselectivity of the Heck reaction. In the great majority of cases, the elimination obeys the well-known Curtin–Hammett kinetic control principle[92] and the ratio of *E*- and *Z*-isomers reflects the relative energy of the respec-

tive transition states. Unless R is very small (CN is the best known example), *E*-isomer is predominant and the reaction is highly stereospecific even for very simple models, which is one of the major advantages of the Heck protocol over such classical methods of olefination as the Wittig–Horner reaction (Scheme 28).
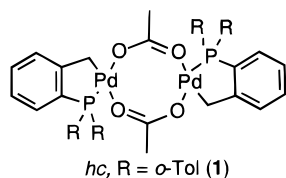
Scheme 28
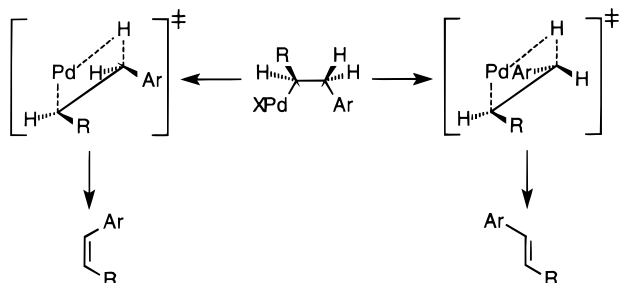
The cases in which a non-Curtin–Hammett distribution of isomers is formed present a special interest. Besides, PdH-induced isomerizaion of starting alkene, the wrong *E/Z* ratio may come from (i) postreaction isomerization of products, leading to thermodynamically controlled mixture of isomers; (ii) isomerization of product–PdH complex before the deprotonation takes place; (iii) a different mechanism of PdH elimination.

The last case is particularly intriguing, as base-catalyzed β-elimination via the E2-like mechanism cannot be completely ruled out. This problem has been recently revisited in an investigation of the arylation of disubstituted olefins.[93] The arylation of disubstituted olefins has been investigated in the presence of Herrmann's palladacycle catalyst *hc* (**1**; Scheme 29).

Scheme 29

hc, R = *o*-Tol (**1**)

The process leads to a mixture of internal and terminal olefins with a ratio depending on the nature of the base (Scheme 30).

Scheme 30
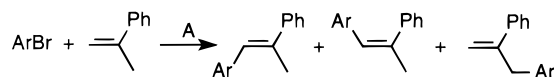
A: *hc* (0.1 mol%), base, DMA, 140°C
Ar = *p*-ClC$_6$H$_4$

| base	internal/terminal	internal *E/Z*
NaOAc	39/61	17
(*i*Pr)$_2$NEt	95/5	2.5

The reaction in the presence of inorganic bases such as NaOAc gave the mixture of internal and terminal olefins with a ratio apparently equal to the ratio of the number of protons at the respective sites,

which has been interpreted as a result of conventional base-independent *syn*-elimination. The reaction in the presence of amine base yielded almost exclusively the internal product. The latter finding indeed might have revealed that stronger base can switch the process to base-catalyzed elimination, giving a more stable internal olefin.

This conclusion is very important, as if base-catalyzed elimination can indeed occur, it would have a strong influence both on the reactivity and stereochemistry of Heck reactions. Therefore, we have to draw attention to a more conservative explanation, additionally revealing some interesting details about the hydride elimination process. First of all, the ratio 2/3 is actually not statistical as it may seem from the formal count of hydrogen atoms at the respective carbons (due to predominant formation of *E*-product from less sterically hindered conformer, statistical weights of two routes of elimination are not equal as the one leading to *Z*-diastereomer can be neglected). Moreover, the elimination of terminal hydrogen and internal hydrogen also have different probabilities. As soon as the actual product ratio is about 2/3, the elimination leading to the internal olefin is twice as probable as the elimination of each of three identical terminal hydrogens. This is not surprising because we must also take into consideration that in the complex preceding the elimination Pd is known to be additionally bonded to benzene ring by an η^2-bond. This interaction partially interferes with elimination from the terminal site. Besides, the internal benzylic hydrogen atom may be more easily available through stronger agostic interaction, than less acidic terminal H atoms.

The results obtained in the reaction in the presence of bulky amine can have a different interpretation, which stays within a classical base-independent mechanism of concerted *syn*-elimination. From the data published it is evident that in this case not only the internal/terminal product ratio, but also the *E/Z* ratio of internal olefin undergoes a significant change, thus revealing a strong contribution of the isomerization route. The data on insignificant isomerization by separately exposing the products to palladium catalyst under the conditions (temperature, solvent) of the arylation experiment cannot rule out the isomerization pathway, because the latter is triggered by the transient Pd hydride complex formed by elimination and staying bonded with olefin in the real arylation experiment. The mechanism of isomerization may look like the one shown in Scheme 31.

Scheme 31
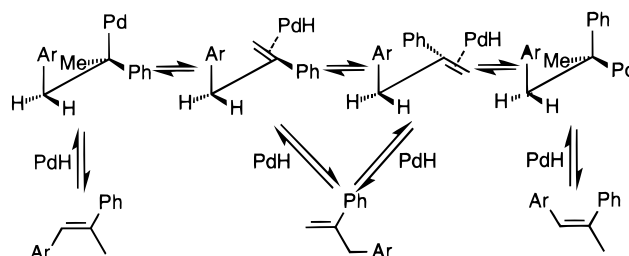
Both internal and terminal olefins equilibrate through reversible addition and elimination of PdH,

which stays bonded with olefin. The preferred conformation of the terminal olefin complex is likely to be the one with the double bond bearing a bulky palladium pendant turned off the aryl. Readdition from this complex leads to the σ-Pd complexes with configurations ready for elimination to give the Z-isomer of the internal olefin. Thus, such equilibration would lead to the redistribution of olefins in favor of more stable internal olefin though with an abnormally increased Z/E ratio, that is exactly what is observed.

Stoichiometric experiments[47,52,53,90,94] on the reaction of arylpalladium complexes with olefins never revealed observable PdH complexes, showing that the lifetime of such complexes is very short (this is valid for Heck reaction conditions, as otherwise hydrido complexes of palladium with proper ancillary ligands are well-known).[95] Thus, it either undergoes the reverse addition to the double bond or encounters with the base. Bulky amine probably is less efficient in the abstraction of proton from PdH, thus giving the addition−elimination reactions more time to settle down to the equilibrium.

Threfore, the question of the involvement of base-assisted β-elimination in the Heck reaction is still open, though the probability of such processes is, in our opinion, rather low. Still, if such processes can be realized, it would give a key to the normal Heck reaction with olefins lacking hydrogens in proper positions for syn-elimination (norbornene, indene etc.). As far as we know, this has hitherto never been observed.

III. The Chase for the Highest Activity

A. Phosphine-Assisted Catalysis

The phosphine-assisted Heck process,[96,97] besides the apparent drawbacks discussed above, has a good potential for development. A pioneering effort in the elucidation of possibilities to boost the catalytic activity and productivity in the Heck reaction was made in the early 1980s by Spencer,[98] who showed that the arylation of olefins with activated aryl bromides can be run with low loads of catalyst and be a high TON process, if carried out in polar aprotic solvents such as DMF, HMPA, DMA, NMP, in the presence of NaOAc, and phosphine ligands, preferably P(o-Tol)$_3$ (Scheme 32).

Scheme 32

A: Pd(OAc)$_2$ (0.001%), 4P(o-Tol)$_3$,
NaOAc, DMF, 130°C

79% yield
TON 79000
TOF 3300 h^{-1}
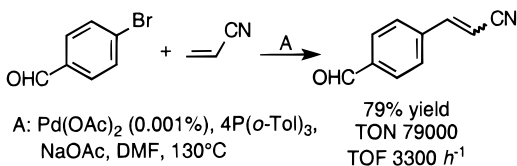
The unique potential of P(o-Tol)$_3$, which had been introduced in the classical works by Heck,[2] made it a ligand of choice for common phosphine-assisted Heck arylation. It is interesting to note that, as can be deduced from the description of experiments, besides the mixture Pd(OAc)$_2$−P(o-Tol)$_3$, Spencer also apparently used a complex which much later has

been rediscovered by Herrmann as a now famous palladacycle catalyst *hc*, though no specific advantages were then noted.

The results of Spencer set the initial point for assessing further improvements in developing Heck reaction protocols. Spencer's modification of the phosphine-assisted reaction became a basic technique successfully used until today for all kinds of reactions belonging to Heck chemistry with bromo- and iododerivatives. Spencer's protocol has been tried for the reactions with chloroarenes, though only those bearing electron-withdrawing groups. The best but still modest yields and TONs were obtained with PPh$_3$ and P(p-Tol)$_3$, while other ligands including P(o-Tol)$_3$, chelate biphosphines, and PPh$_2$tBu were much less effective (Scheme 33).[99]

Scheme 33

A: Pd(OAc)$_2$ (1mol%), 4P(o-Tol)$_3$,
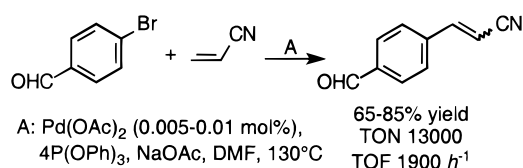NaOAc, DMF, 150°C

34% yield
TON 34
TOF 5.7 h^{-1}
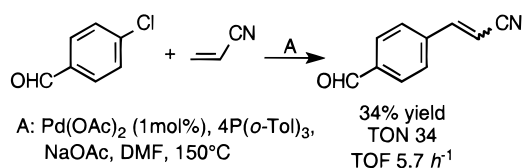
Further studies for better phosphine-assisted reactions were targeted at increasing the activity of catalytic system with the goals (i) to find systems suitable for the processing of aryl chlorides, (ii) to obtain higher activity of the catalystic system allowing one to minimize the load of palladium and ligand, and (iii) to find cheaper ligands.

It should be noted that the development of new phosphine ligands rarely leads to really good new ligands for the Heck reaction. For instance, among the most recent results, no advantages were discovered for new phosphine ligands bearing one, two, or three 2-pyrimidyl residues (Ph$_2$P(2-C$_4$H$_3$N$_2$), PhP(2-C$_4$H$_3$N$_2$)$_2$, P(2-C$_4$H$_3$N$_2$)$_3$). Only the first was able to catalyze a standard reaction of PhBr with styrene with efficiency comparable to that of trivial Ph$_3$P ligand. The yield drops for bis-pyrimidyl ligand and goes to a negligible 3% for tris-pyrimidyl ligand, thus giving additional evidence on the detrimental influence of electron-withdrawing groups in phosphine on the rate of the Heck reaction with less reactive substrates for which the oxidative addition is the rate-limiting step.[100]

Reactions of aryl chlorides and less reactive aryl bromides are thought to be dependent on the ability of a given catalytic system to undergo oxidative addition to C−Cl and C−Br bonds, which requires highly donating phosphine ligands. However, such ligands have an adverse influence on the rate of further stages of the Heck catalytic cycle and are very sensitive to air, which makes the whole catalytic system quite inconvenient, particularly for possible large-scale applications. Two recent independent publications demonstrated that electron-rich phosphines are not the only solution for the design of highly reactive catalytic systems. Cheap and readily available phosphites can be used to replace phoshines. The application of P(OPh)$_3$ was described as early as in 1983 (Scheme 34).[98]

Scheme 34

A: Pd(OAc)$_2$ (0.005-0.01 mol%),
4P(OPh)$_3$, NaOAc, DMF, 130°C

65-85% yield
TON 13000
TOF 1900 h^{-1}

These results were comparable to those obtained with classical phosphines PPh$_3$ and P(o-Tol)$_3$. However, due to weak binding, phosphites make rather unstable catalysts. Fast deactivation of catalyst can be overcome if phosphites are taken either in large excess or as a preformed orthopalladated complex and the reactions are run at high temperatures.

Activated chloroarenes (3- or 4-CF$_3$, 2-Me-4-NO$_2$-chlorobenzenes) react with standard Heck olefins (styrene, n-butylcrylate, dimethylacrylamide) in the presence of trialkyl phosphite (Alk = Et of i-Pr) or triaryl phosphite (Ar = Ph or tris(2,4-di-tert-butylphenyl) taken in 10−100 fold excess with respect to Pd giving moderate to good yields of the arylation products.[101] Chloroarenes require the addition of n-Bu$_4$NBr (20 mol %). The method was applied for a single-step synthesis of a nonsteroid antiinflammatory drug *nabumethone* (Scheme 35).

Scheme 35

A: Pd(OAc)$_2$, 10 P(OC$_6$H$_3$Bu$^t_2$-2,4)$_3$, Na$_2$CO$_3$, DMA, 160°C
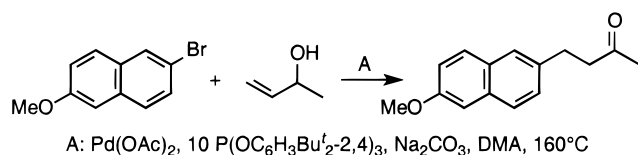
The features of phosphite-catalyzed reactions make them belong to both ligand-assisted and phosphine-free manifolds. Among other weakly coordinating ligands, AsPh$_3$ (**2**) should be mentioned. In some special cases the application of this ligand proved to be advantageous. Thus, it proved to be a better ligand for the arylation of norbornene and related bicyclic structures in the presence of formate hydride donor for reductive trapping of organopalladium intermediate. The procedure was applied to the synthesis of the alkaloid *epibatidine* in 92% yield (Scheme 36).[102]

Scheme 36

A: Pd(OAc)$_2$, Ph$_3$As, NEt$_3$, HCOOH, DMSO
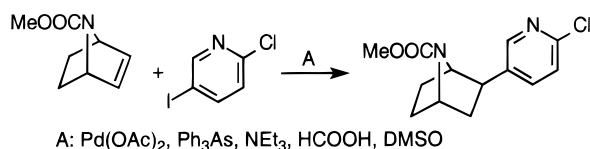
Diisopropylphosphinoferrocene (**3a**, **4a**, R = iPr) ligands were shown to be more efficient than the respective diphenylphosphinoferrocene (**3b**, **4b** (dppf), R = Ph) ligands (Scheme 37).[103]
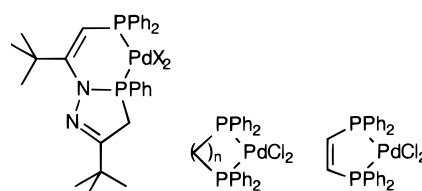
Scheme 37

3a, b   **4a, b**   **5**
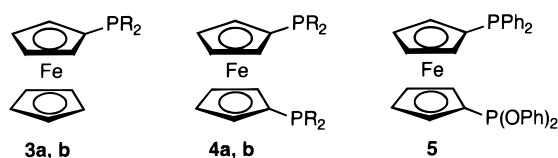
Though the reaction chosen for testing these expensive ligands is too simple to serve as a really severe probe (arylation of PhI or 1-iodoferrocene by methyl acrylate, NEt$_3$, MeCN, reflux 24 h, 1 mol % Pd catalyst) while the experimental procedure is rather unusual (cuprous iodide is added as a promoter to the palladium complex and preheated in the presence of base prior to the addition of olefin and aryl iodide to give a black solution which may possibly be a palladium sol), some important conclusions can be made. In the case of R = Ph, monodentate ligand **3b** is better than the well-known bidentate dppf (**4b**) ligand, the complex of which fails under such conditions. Meanwhile, the performance of both monodentate **3a** and bidentate **4a** ligands was good and almost identical. A mixed phosphine−phosphite ligand built over ferrocene scaffold **5** has been later introduced to show the activity to be slightly inferior to bis-phosphine ligand **4a**.[104]

Chelating biphosphines were from the beginning considered as poor ligands for Heck reactions with aryl halides. Later it was shown that switching to the cationic route can make bidentate phoshines work and reactions proceed at a reasonable rate. As a result, chelating phosphines play a major role in the processes in which an intimate control of the coordination sphere is vital, in the first place in enantioselective catalysis.[48] The necessity to apply special tricks, such as the use of triflates in place of halides, the addition of halide scavengers−salts of silver and thallium−made chelating phosphines a poor choice for simple arylation and vinylation reactions. However, the findings made in the last few years revealed that diphosphines actually *can* make good catalysts for simple Heck reactions in the absence of expensive and toxic additives. Besides a mere satisfaction that chelating ligands can be forced to serve, bidentate phosphines have several important advantages: (i) no need for an excess of ligand to make stable complexes of Pd(0), the ratio of 1:1 leading to (L−L)Pd complex is enough; (ii) more stable complexes result in longer life of catalyst and thus in higher TONs; (iii) higher stability of catalyst is a must for designing recyclable (supported, biphasic, etc.) catalyst systems. So why are the ligands earlier used almost exclusively in delicate enantioselective synthesis being allowed to return to basic Heck chemistry? We can only suppose that it might be the *Overman's hidden gate* from neutral to cationic manifolds (see above) which is being inadvertently opened. So far, no one seems to know where (in which combination of conditions and reagents) lies the key.

Scheme 38

Indeed, Shaw[105] demonstrated that preformed complexes of palladium(II) with chelating phosphines

shown in Scheme 38 ($n = 1-4$) as well as dppf are efficient catalysts for Heck reactions of standard aryl halides (PhI, p-BrC$_6$H$_4$Ac, p-BrC$_6$H$_4$CN) with styrene and methylacrylate (DMF, 50−150 °C, 12 h to 12 days, Bu$_3$N as base) in excellent yields and exemplary TONs reaching 224 700 and mean TOF 3100 h^{-1}, as exemplified for the reaction shown in Scheme 39.

Scheme 39
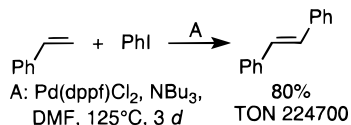
It is evident that the reactions are run under classical conditions for the neutral pathway. The use of preformed complexes was stated to be a crucial factor. Poor performance of chelating phosphines reported by earlier workers has been ascribed to the easy and quantitative formation of very stable bis-diphosphine complexes, which cannot form any catalytically active species as $K_2 \gg K_1$ due to the very high *trans*-effect of a phosphine ligand greatly facilitating the exchange of halide ligands in (L−L)PdX$_2$ complex (Scheme 40).

Scheme 40
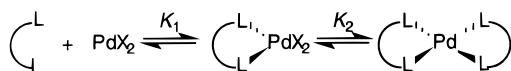
Though the author himself suspects a Pd^{II}−Pd^{IV} mechanism for these processes, we would suggest that a conventional Pd(0)−Pd(II) cycle operates with the transition from the neutral to cationic path assisted by the olefin (Scheme 41).

Scheme 41

pseudorotation
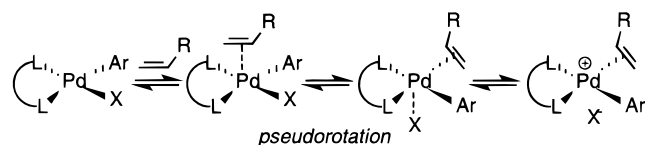
Highly basic bidentate ligands with diisopropylphosphine groups were developed to solve the task of making chloroarenes react under standard palladium-catalyzed reactions. Several ligands of the series were prepared to show an interesting dual reactivity pattern.[106]

The ligand 1,3-bis(diisopropylphosphino)propane (dippp) is inefficient as a ligand for the Heck reaction under basic conditions. The palladium complex with two ligands bears one ligand in a chelated and one in a monodentate form. A highly reactive monochelated Pd(0) species, formed by a de-ligation of monodentate ligand, does undergo an oxidative addition with PhCl, and the resulting complex enters the migratory insertion step via the cationic route, which is revealed by a huge acceleration by polar solvents, a common ion effect, and other typical criteria. The cationic route in this case is definitely accounted for by easier de-ligation of chloride, as compared to bromide and particularly iodide. A huge *trans*-effect of a strong ligand makes the reductive

elimination of alkene very fast, leading to the formation of considerable amounts of less favorable *Z*-olefin.[107] The hydride complex formed due to the same *trans*-effect happens to be an acid, apparently stronger than HCl, as the deprotonation is effected by chloride ion to give catalytically active Pd(0) complex. The other molecule of PdH complex is protonated to give dichloride complex (Scheme 42).

Scheme 42
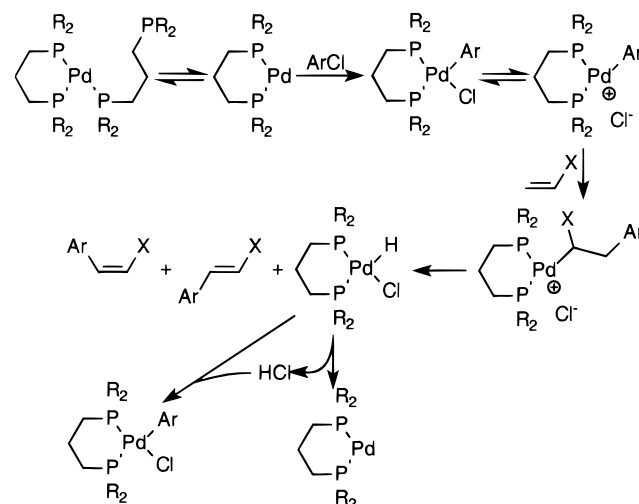
Interestingly enough, the addition of base, which might have scavenged HCl liberated possibly to suppress protolysis, has no effect on this process. The mechanism of disproportionation of two molecules of (L−L)PdHCl to (L−L)Pd and (L−L)PdCl$_2$ may thus be intramolecular, occurring via a binuclear complex of palladium.

The dichloride complex cannot be transformed into catalytically active species by base, though the addition of an appropriate reductant such as zinc or copper metal opens an unusual reductive pathway of the Heck reaction.[106] Heck arylation under reductive conditions occurs with aryl chlorides, while aryl bromides give biphenyls as byproducts (Scheme 43).

Scheme 43
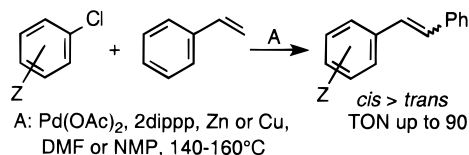
Interestingly, besides dippp, only 1,2-bis(diisopropylphosphino)ethane was able to catalyze the eductive Heck process, while 1,4-bis(diisopropylphosphino)-butane (dippb), which is very efficient under conventional basic conditions, proved to be totally inactive. The latter ligand catalyzes the reaction with aryl chlorides via a nonpolar mechanism. The seven-membered chelate is rather weak and undergoes the cleavage of chelate ring to generate in situ very reactive single-phosphine complex (Scheme 44).[47,108]

A further increase of the steric bulk in the phosphine (iPr$_2$CH)$_2$P(CH$_2$)$_4$P(iPr$_2$CH)$_2$ structurally analogous to dippb gave the infinitely stable palladium(0)

Scheme 44
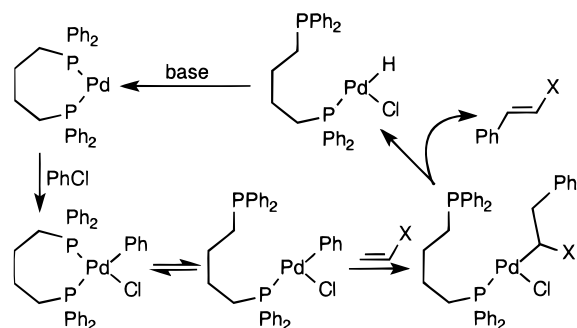
complex totally inactive in the Heck reaction even with bromobenzene.[109]

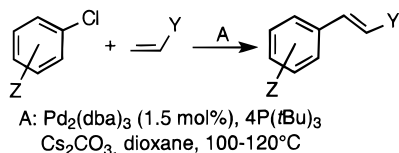Quite recently, tris(*tert*-butyl)phosphine has been shown to be a good catalyst for the Heck reaction with aryl chlorides, including not only activated ones, but also chlorobenzene itself and even deactivated *p*-methoxychlorobenzene and *o*-chlorotoluene (Scheme 45).[110]

Scheme 45

A: Pd$_2$(dba)$_3$ (1.5 mol%), 4P(tBu)$_3$
Cs$_2$CO$_3$, dioxane, 100-120°C

Under these conditions, all other phosphines, among which are PPh$_3$, P(*o*-Tol)$_3$, BINAP, dppf, P(*n*-Bu)$_3$, PCy$_3$, Cy$_2$PCH$_2$CH$_2$PCy$_2$, and tris(2,4,6-trimethoxyphenyl)phosphine, failed to catalyze the process to a measurable extent, which reveals that the donor character or cone angle is not a good predictor in the search for better ligands. Indeed, as it is evident now, a lot of phosphines are capable of oxidative addition to the C–Cl bond, but only a few of them can drive more than a single turn of the Heck cycle. Too strongly donating ligands may disable the regeneration of Pd(0) by making hydride complex too unstable to survive until it can be attacked by base, and too bulky ligands hinder the coordination of olefin, etc. A good effective catalytic cycle can be regarded as a perfect synchronization of all major and minor factors influencing the individual rate constants of reactions constituting a given catalytic cycle (Amatore put forward a similar idea that individual rate constants of a good catalytic cycle must be comparable, while the case when some constant is much higher than the others may be as bad as an opposite case of some elementary process(es) being a bottleneck[18]). So far, in all catalytic systems proposed for Heck reactions with chloroarenes, at least some of steps are off-sync. As the individual rate constants cannot be predicted, the only practical solution for searching for a good catalytic system is a randomized search,[111] and as long as our intimate knowledge on what is really going on in a given Heck reaction is minimal, this search must rely on high-throughput procedures. The first and indeed pioneering effort in this direction was recently undertaken by Hartwig,[112] who used the combinatorial chemistry approach by designing a model process with resin-bound aryl halide and olefin

bearing a fluorescent dye probe. Highly reactive systems were readily diagnosed by strong fluorescence of resin beads after reaction (Scheme 46).

Scheme 46

A: Pd(dba)$_2$, L, NaOAc
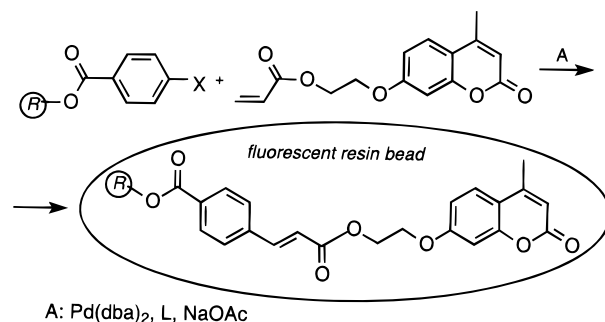
A comprehensive set of 45 ligands, both published and prepared for the first time, was tested in this system.

The only two bidentate phosphines which showed any reasonable activity at 100 °C were two structurally similar molecules, though both lost their activity at lower temperatures, being inferior to monodentate phosphines (Scheme 47).[113]

Scheme 47
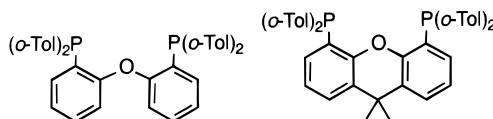
In the monodentate series, more molecules showed a considerable activity. All of them were electron-rich and bulky, so we might consider that we have reached a conclusion that a combination of these properties is necessary, but unfortunately the same study tells that this is not sufficient. The comparison of, for example, the following pairs shows that there is something we cannot understand at this moment but that makes some ligands shine and a closely similar ligand fail. Both ligands marked as *good* made catalysts which were capable of processing reactive bromoarenes even at as low as 50 °C (Scheme 48).

Scheme 48
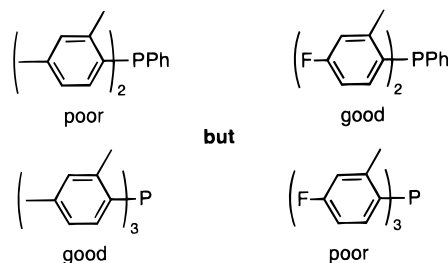
The screening revealed two outstanding ligands: tris(*tert*-butyl)phosphine (tBu$_3$P), independently and simultaneously described in ref 110, and a new one bis(*tert*-butyl)phosphinoferrocene (tBu$_2$PFc). These ligands gave inferior results compared to Herrmann's palladacycle *hc* in reactions with activated bromoarene both in net catalytic activity and in the stability of catalytic systems in long runs, which

imposes a serious limit on the load of catalyst sufficient to achieve high conversions (Scheme 49).

Scheme 49
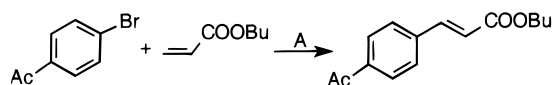
A: Pd cat (10^{-4} mol%), NaOAc, DMA, 100°C

Pd catalyst	TON after 16 h	TON after 90 h
hc	144000	256000
Pd(dba)$_2$/2(tBu)$_2$PFc	113000	151000
Pd(dba)$_2$/2(tBu)$_3$P	54000	53000

However, both Hermann's palladacycle and P(o-Tol)$_3$ are much less effective in the reactions with donor-substituted bromoarenes, as well as chloro-arenes, than monophosphines with a tBu$_2$P group. The latter gave excellent results with such sub-strates, though these reactions required a high load of catalyst. Prime importance of fine-tuning of ligand structure and properties is emphasized as three similar ligands differed a lot in activity and stability of the catalyst (Table 1).

This study gives us a valuable clue to the distinc-tions between catalytic systems. The oxidative addi-tion step is likely to work as a main differentiating factor. As we commented earlier, in any palladium-catalyzed systems there is a manifold of catalytically active species capable of driving the Heck cycle. It is the rate of oxidative addition that is likely to set the upper limit of the turnover frequency. If the oxidative addition is fast, many catalytic species shall pass through it and the system shall choose which are the best at next steps, first of all for the migratory insertion, which in its turn (due to high steric demand) prefers the species with the least loaded coordination spheres. Underligated catalysts (phos-phine-free systems as well as single-phosphine sys-tems like Herrmann's palladacycle and possibly other palladacycles, etc.) do shine in reactions with such substrates. Going down in catalyst load becomes possible, and even welcome, because higher concen-trations of unstable underligated palladium com-plexes lead to faster deactivation (vide infra). Tle lower limit for catalyst load is defined only by practical reasons and parasite processes killing the active species at very low concentrations. This type of catalytic cycle is common for iodoarenes and activated bromoarenes.

On the other hand, if the oxidative addition is slow, this step is the bottleneck to be passed only by catalysts with high intrinsic activity, defined by properly selected ligands. Good ligands are bulky donor phosphines, which at the same time are not

Table 1. Comparison of Phosphine Ligands in Reactions of Bromo- and Chloroarenes with n-butylacrylate (2.5 mol % Pd(dba)$_2$, 2L, NaOAc, DMF)[112]

		ligand			
substrate	conditions	P(o-Tol)$_3$	tBu$_2$PFc	tBu$_2$PPh	tBu$_3$P
p-BrC$_6$H$_4$COOMe	2 h, 75 °C	97%	92%	n/a	94%
p-BrC$_6$H$_4$Me	2 h, 75 °C	31%	100%	n/a	100%
p-ClC$_6$H$_4$COOMe	4 h, 110 °C	0%	97%	77%	96%
p-ClC$_6$H$_4$Me	22 h, 110 °C	0%	67%	16%	51%

very good for the migratory insertion step; however, this is of no concern here since all efforts are paid only to push such substrates through the bottleneck. Still, the unusual behavior of Milstein−Portnoy ligands[47,106] shows that there are limits for increasing the donor character of ligand, as this changes the chemistry of the reductive elimination steps. This type of Heck cycle is serviced by phosphine-assisted catalysis. Therefore, a high concentration of catalyst is required to keep the rate at a reasonable level, mostly because the actual concentration of catalyti-cally active species in the phosphine-assisted process is low (see above). Due to slow oxidative addition, a high steady-state concentration of Pd(0) species is being accumulated, and therefore, a generous load of ligands must be applied to keep the catalyst in stable fully ligated form. This picture, though simpli-fied but looking quite close to reality, prompts a pessimistic conclusion that the challenge of involving cheaper chloroarenes in large-scale Heck reactions in place of expensive iodo- and bromoarenes might be doomed. The economy on substrates is by far outweighed by the cost of expensive nonrecoverable ligands and increased load of palladium.

Possibly the solution must be sought in bimetallic catalysis, in which in a reliable palladium-catalyzed Heck cycle a cocatalyst gives a bypass to the slow oxidative addition step. So far not much effort has been devoted to such bimetallic catalysis. The first solution found for solving the problem of the pos-sibility to use chloroarenes in the Heck reaction was actually a palliative, as chloroarenes were trans-formed in situ to iodoarenes by a well-known nickel-catalyzed halogen exchange (Scheme 50).[114]

Scheme 50
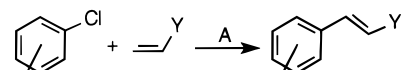
A: Pd$_2$(dba)$_3$ (0.5-2 mol%), NiBr$_2$ (20 mol%),
(o-Tol)$_3$P, NaI, Et$_3$N, DMF, 140°C, 14-16 h
X = H, COOMe, Ac, OMe, Me, CN;
Y = COOEt, CN

Still the method is quite efficient, though it re-quires an 80-fold (with respect to Pd) amount of supporting phosphine to fill the coordination spheres of both metals.

As the other variant of a bimetallic system, the activation of chloroarenes by complexing with electron-acceptor organometallic residues such as Cr(CO)$_3$ appears as rather unpractical for simple cases,[115,116] because the cheapness of chloroarenes in comparison with bromo- and iodoarenes is by far outweighed by the necessity of prior modification of chloroarenes through expensive, hazardous, tedious, low-yield introduction of an activating organometallic residue, which is irrevocably destroyed by oxidation after it serves its rather limited function. This method is justified for more complex tasks, e.g., for intramo-lecular cyclizations, in which tricarbonylchromium pendant introduces planar chirality and defines the preferential route for insertion as in the following Heck reaction terminated by methoxycarbonylation (Scheme 51).[117]

Scheme 51
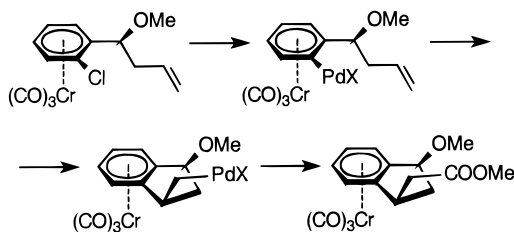
Still this method could be made more economical if chromotricarbonyl residue can migrate from the products to uncomplexed chloroarene, thus making the process catalytic with respect to the primary Cr-$(CO)_3$ carrier. Such a process was indeed realized, though again for the intramolecular Heck reaction (Scheme 52).[118]

Scheme 52
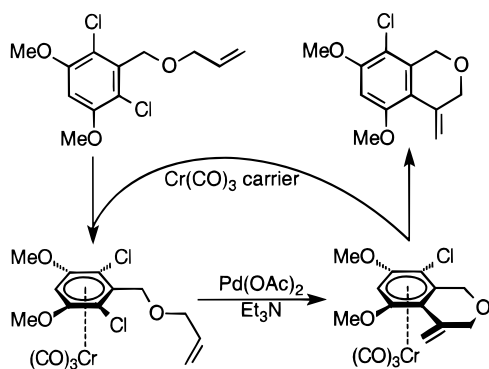

The cyclization can be accomplished in a stoichiometric mode with a specially prepared $Cr(CO)_3$ complex of the starting chloroarene. However, the reaction can be made to proceed also in the presence of catalytic amounts of either $Cr(CO)_6$ or a chromotricarbonyl complex of naphthalene with a TON of up to 5.4 with respect to chromium. This is possible because for some reason the $Cr(CO)_3$ complex of the product is less stable than the complex of the starting chloroarene, which leads to in situ transmetalation. Certainly, as this trick depends on a fortunate interplay of stability constants, it can hardly be developed into a general method, but even in this and possibly some other cases yet to be discovered, it shows that the hitherto latent potential of chromotricarbonyl activation of inactive chloroaromatics can indeed be realized in a practical way.

A synergistic effect of Wilkinson's catalyst $(PPh_3)_3$-RhCl on the rate and selectivity of an intramolecular Heck reaction has been recently noted.[119] The nature of this effect is unknown, which makes it impossible to guess how general it might be for other Heck reactions.

B. Palladacycles

The discovery by Herrmann and Beller et al. of the unique catalytic activity of a well-known dimeric complex $Pd_2(P(o\text{-Tol})_3)_2(\mu\text{-OAc})_2$, as is now obvious, has set a milestone in palladium catalysis.[120] This and similar complexes derived from tris(mesityl)-phosphine and $o\text{-TolPR}_2$ ligands are obtained by reacting the respective phosphines with $Pd(OAc)_2$ in

high yield using simple procedures applicable both on a micro- and macroscale. All are stable to air and moisture. The parental structure, which is now often referred to as Herrmann's catalyst (**1**, *hc*) is definitely one of the most convenient forms of palladium complexes applied in homogeneous catalysis. Even if the palladacycle would have no specific properties but was equivalent to the mixture of palladium salt and phosphine, as is indeed the case in, e.g., catalytic amination,[121] it still would deserve a place in the first row of catalysts due to exceptional ease of handling (Scheme 53).
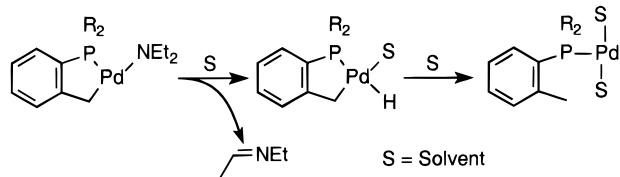
Scheme 53
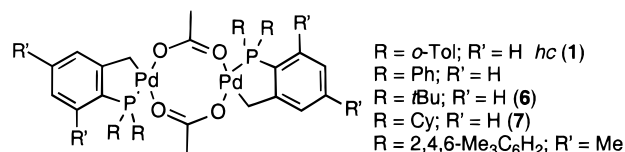
The palladacycle *hc* is not only a convenient precursor and a truly beautiful structure, but also an ingenious catalyst which breeds a new generation of catalytic systems—the *underligated single-phosphine catalysts*. As noted in the Introduction, it is impossible to generate palladium complexes with a single phosphine ligand in traceable concentration starting from either a mixture of palladium precursor plus added phosphine or from a stable multiphosphine complex of palladium. Now at least two ways to generate such species are known: (i) decomposition or reduction of palladacycles and (ii) oxidative addition of phosphine-free palladium to Ar_4P^+ salts. Besides, the behavior of chelate ligand dippb of Portnoy and Milstein (vide infra), which has been proven to undergo dechelation during the process to leave a single monodentate phosphine ligand on Pd, also looks like the same type of system.

Single-phosphine catalysts are highly reactive due to an almost free coordination shell but are still much more stable than phosphine-free complexes, due to the presence of stabilizing ligand. Thus, while phosphine-free systems are capable of huge catalytic activity for activated haloaromatics but are not stable enough to survive longer reaction times with less reactive substrates, palladacycles and similar catalyst precursors are suitable for setting both TON (stability + activity) and TOF (activity) records.

Herrmann's palladacycle is the best studied catalyst of this type. It has been shown to be a highly effective catalyst for the Heck reaction with aryl bromides (conditions: NaOAc, DMF, 100–140 °C), particularly those with electron-withdrawing groups (CN, CHO, COMe) for which TON values up to 10^6 were observed. It has been proven that the palladacycle serves as a source of Pd(0) species of unidentifiable nature. Under Heck reaction conditions, the preactivation was proven not to be effected by olefin in a Wacker-type process, not by the reductive elimination from a palladium hydride precursor similar to the process proven by Hartwig for amination (Schemes 54 and 55).[121]

There are data against these mechanisms of preactivation. Wacker-type products are not observed in

Scheme 54

S = Solvent

Scheme 55

hc
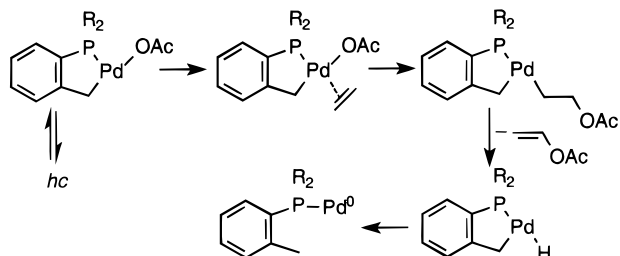
reaction mixtures. The addition of deuterated styrene does not lead to the incorporation of D into the methyl group of P(*o*-Tol)$_3$ ligand.[122] Therefore, the actual mechanism of the preactivation remains an enigma, though it may happen that the complex generated from the palladacycle is so active that only a small fraction of *hc* is transformed into it; thus, any token byproducts are formed in amounts below detection limits. Nevertheless, as the heating of palladacycle with μ-acetato ligands in the absence of substrate to temperatures above 120 °C leads to the formation of metallic palladium deposits, the reduction of palladium to the Pd(0) state does happen. Reactions using *hc* do display an inductive period which may be shortened or eliminated by the addition of appropriate reductants. Unstable underligated single-phosphine Pd(0) species are likely to be trapped via fast oxidative addition by activated bromoarenes. Beller et al. have shown that an independently prepared complex (ArPd(P(*o*-Tol)$_3$)Br)$_2$ catalyzes the arylation of α-methylstyrene under the same conditions as the palladacycle, though without an induction period and leading to an almost identical product distribution.[93]

Bromide- or chloride-exchanged complexes are more stable and start to decompose at higher temperatures. Moreover, the effect of halides (*n*-Bu$_4$NBr, LiBr, or other such salts used in huge excess over

the catalyst) in the reactions with underligated palladium complexes is to prolong the lifetime of the reactive species due to the formation of anionic complexes. The deactivation occurs via the collisions of underligated Pd(0) species, and charged particles have to overcome an extra Coulombic barrier to collide and stick together (Scheme 56). Thus, $k_{ArBr} > k_d > k_{ArCl}$ but $K'_{ArCl} > K'_d$.

Scheme 56
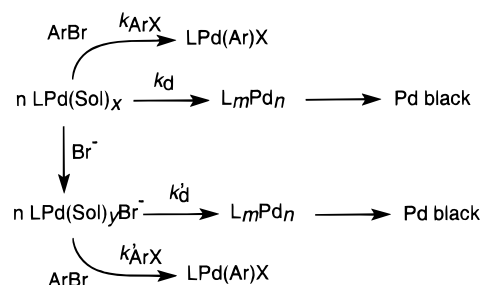
Thus, $k_{ArBr} > k_d > k_{ArCl}$, but $k'_{ArCl} > k'_d$.

Thus, unactivated bromoarenes and chloroarenes can be processed in the presence of NBu$_4$Br or PPh$_4$-Cl (with the latter salt Reetz's activation mode[30] is also possible, which is evidenced by the formation of scrambled byproducts) at 130−160 °C. A huge TON of 40 000 and enviable TOF values were recorded for the reaction of *p*-chloroacetophenone with butyl acrylate, which has a potential industrial value. Interesting to note is that the palladacycle is less reactive for iodoarenes (this was the reason *hc*, isolated and characterized for the first time by Heck, had been rejected as a useless side product and abandoned until its rediscovery, cf. ref 123), which gives another clue for the hypothesis that the system preactivation involves the cleavage of palladacycle, since the liberated iodide blocks the coordination sites through the exchange of labile acetato ligands. Also, Herrmann palladacycle is of no use if the reaction is to be conducted at lower temperatures (roughly below 110−115 °C, though there are examples in which the reactions with more reactive iodoarenes can be run at temperatures below 100 °C), in which cases the classical mixture of Pd(OAc)$_2$ + P(*o*-Tol)$_3$ works much better (see, e.g., Table 2).

Another type of PC-palladacycles is formed from tris(α-naphthyl)phosphine (PNph$_3$; **8**).[126] Several com-

Table 2. Palladacycles as Highly Reactive Catalysts for Heck Reaction

| palladacycle (mol %)	ArX/alkene	conditions	conversion	TON (TOF, h^{-1})	ref
hc (0.001)	4-BrC$_6$H$_4$CHO/CH$_2$=CHCO$_2$Bu	NaOAc, DMA, 135 °C, 12 h	100	100 000 (8300)	120
hc (0.0001)	4-BrC$_6$H$_4$CHO/CH$_2$=CHCO$_2$Bu	NaOAc, Bu$_4$NBr, DMA, 130 °C, 24 h	100	1 000 000 (42 000)	120
hc (0.001)	4-ClC$_6$H$_4$Ac/CH$_2$=CHCO$_2$Me	NaOAc, Bu$_4$NBr, DMA, 130 °C, 72 h	40	40 000 (550)	120
hc (0.2)	4-ClC$_6$H$_4$CHO/CH$_2$=CHCO$_2$Me	NaOAc, Bu$_4$NBr, DMA, 130 °C, 24 h	81	405 (17)	120
9b (0.0007)	PhBr/CH$_2$=CHCO$_2$Me	Na$_2$CO$_3$, NMP, 140 °C, 63 h	93	132 900 (2100)	125
9b (0.0007)	4-BrC$_6$H$_4$CHO/CH$_2$=CHCO$_2$Me	Na$_2$CO$_3$, NMP, 140 °C, 63 h	79	113 300 (1800)	125
9b (0.0007)	PhI/CH$_2$=CHPh	Na$_2$CO$_3$, NMP, 140 °C, 60 h	93	133 000 (2200)	125
9a (0.000175)	PhI/CH$_2$=CHCO$_2$Me	Na$_2$CO$_3$, NMP, 140 °C, 350 h	91	520 500 (1490)	125
8 (0.5)	4-BrC$_6$H$_4$Ac/CH$_2$=CHPh	Bu$_3$N, DMF, 125 °C, 7 h	94	180 (26)	126
8 (0.1)	PhBr/CH$_2$=CHPh	Bu$_3$N, DMF, 115 °C, 30 h	77	770 (26)	126
8 (0.0001)	PhI/CH$_2$=CHPh	Bu$_3$N, DMF, 120 °C, 120 h	65	650 000 (5400)	126
8 (0.00005)	PhI/CH$_2$=CHCO$_2$Me	Bu$_3$N, DMF, 95 °C, 312 h	56	1 120 000 (3600)	126
11a (0.0001)	4-BrC$_6$H$_4$Ac/CH$_2$=CHCO$_2$Me	NaOAc, DMA, 160 °C, 6 h	100	1 000 000 (170 000)	127
11a (0.0001)	4-BrC$_6$H$_4$Ac/CH$_2$=CHPh	NaOAc, DMA, 160 °C, 69 h	58	5 750 000 (83 000)	127
12 (0.00001)	PhI/CH$_2$=CHCO$_2$Bu	Na$_2$CO$_3$, NMP, 180 °C, 22 h	89	8 900 000 (400 000)	128

plexes of this series, both dimeric and monomeric diketonates, were prepared and tested in Heck reactions with iodo- and bromoarenes to give the reactivity pattern complementary to that of Herrmann's palladocycle. The activity and productivity of this catalyst with bromoarenes is rather low, either due to the negative influence of PNph₃ ligand or due to deactivation through competitive oxidative addition to the C–P bond. With iodoarenes the activity is higher, though still being inferior to many systems described in the present review, while the stability is outstanding, among the best values achievable for millimole scale experiments (Scheme 57).

Scheme 57
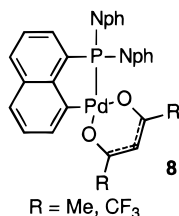
Bis-chelate complexes **9a**–**c** were found to be excellent catalysts for arylation of standard olefins (methyl acrylate and styrene) by iodo- and bromobenzenes but not chlorobenzenes (Scheme 58).[125]

Scheme 58
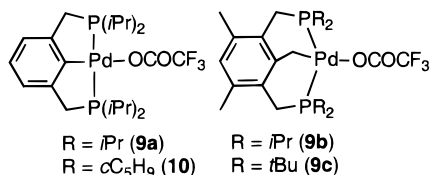
All three complexes show an exceptional thermal stability and robustness to oxygen that enables Heck reactions to be carried out under aerobic conditions. Near to quantitative conversions, huge TON values, and high, though not record-making, TOF values were observed.

These complexes were stated not to be able to operate in the usual Pd(0)–Pd(II) cycle due to very high persistence of the dual chelate, as it was shown that the complex is recovered unchanged (except that the labile ligand CF₃COO is exchanged for halogen) after the completion of reactions which are carried out for several days at 140–160 °C. Thus, the only possibility purportedly left is some version of the elusive Pd(II)–Pd(IV) cycle (cf. ref 129). However, we have to note that the conventional Pd(0)–Pd(II) cycle cannot be given up in this case without further evidence against it, as at this time there is no unambiguous evidence in favor of a Pd(II)–Pd(IV) mechanism while the evidence *against* the conservative Pd(0)–Pd(II) mechanism is relevant but not flawless.

First of all, the sensitivity of bulky trialkyl-substituted phosphines to air is often overestimated. Such compounds are indeed pyrophoric when exposed to air as pure liquids thinly distributed over such combustible materials as cotton. However, in solutions the oxidation of such phopshines by air is neither too fast nor quantitative. Furthermore, Herrmann's palladacycle was also found to be recovered from reaction mixtures,[122] though all evidence gained so far shows that it operates through a conventional Pd(0)–Pd(II) cycle.

It may be argued that the persistence of the palladacycles might mean only that these robust molecules are restored after the depletion of the reagents after the last molecule is processed. It may well operate through the dechelation of one arm giving a monopalladacycle bearing a certain structural similarity (in what concerns the geometry of palladacycle, bulkiness and strain) to Herrmann's palladacycles, particularly to those such as **6** or **7**. Since the temperature of operation of PCP catalysts is higher than that used for Herrmann's palladacycles, further dechelation of monopalladacycle with the reduction of palladium to its zerovalent state is inevitable. Herrmann has shown that monopalladacycles (**6**, **7**) formed from dialkyl-*o*-tolylphosphine similar to the substructure of PCP catalyst are less reactive than basic palladacycle *hc*, and indeed Milstein's PCP catalysts showed lower activity in reactions with bromoarenes and altogether failed in reactions with chloroarenes.

The dechelation of the first phosphine arm is not so improbable, as the PCP complexes actually possess an essentially distorted configuration, quite far from square planar. As according to X-ray data of complex **9c** the angle P–Pd–P is as small as 152°, this fragment bears an essential strain. The strain can be relieved by the dechelation, which therefore seems rather probable at least at high temperatures. Thus, we may tentatively assume that PCP catalysts may be activated through thermally induced disassembly of the bis-palladacycle structure, which is reassembled after the reaction is complete. It is interesting to notice that it is air which may help to restore the initial palladacycle, as Pd(0) leaving the catalytic cycle must be reoxidized to the Pd(II) state to enable palladacycle formation.[130]

The disassembled ligand resembles the dippb ligand proposed by the same authors but with an even larger bite angle. Therefore, in our opinion, PCP ligands represent another subset of underligated single-phosphine systems. However, as PCP complexes are stronger than monopalladacycles, the postrun reassembly of PCP structure may be near to quantitative, which reveals an indisputable value of these catalysts for designing recyclable palladacycle-catalyzed processes. In comparison with PCP palladacycles, the recovery (reassembly) of monopalladacycles is far from quantitative (70% was reported for *hc*), so no recyclable process can be built around such complexes.

Pincer-type systems conaining several palladacycle moieties per molecule have been synthesised and successfully applied as precatalysts for the Heck reactions (Scheme 59).[131]

The possibility of either the Pd(II)–Pd(IV) mechanism or any other hitherto unidentified route cannot be altogether rejected. Indeed, there are several (though still a few) indications that palladacycles may display specific reactivity or selectivity features

Scheme 59
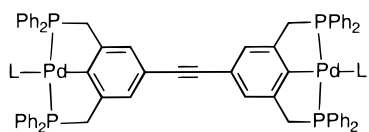
as compared to conventional phosphine-assisted systems. Thus, in a recent paper[132] it has been shown that a full structural analogue **10** of Milstein's palladacycle **9a** is effectively poisoned by 1,4-dienes. The presence of 1,4-diene moiety in the substrate or deliberate addition of a 1,4-diene to reaction mixtures catalyzed by **10** suppressed both the intra- and intermolecular Heck reactions while a convenional Pd(OAc)$_2$/PPh$_3$ system was absolutely insensitive to such additives (Scheme 60).

Scheme 60
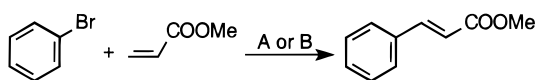
A: **10** (0.5 mol%), Na$_2$CO$_3$, NMP, 135°C
B: Pd(OAc)$_2$ (2 mol%), 3Ph$_3$P, Na$_2$CO$_3$, NMP, 135°C

	half-life, h
A	4.5
A + diene	150
B	4.5
B + diene	3.5

Phosphites were shown to serve as ligands for the formation of palladacycles both of PC and pincer PCP types, possessing an outstanding robustness and activity in the Heck reaction. The dimeric orthopalladated complex **11a** obtained from commercially available cheap tris(2,4-di-*tert*-butylphenyl)phosphite turned out to be a highly efficient catalyst for the reaction of bromoarenes with styrene or butyl acrylate (0.00001–0.2 mol % catalyst, NaOAc or K$_2$CO$_3$ as base, DMA, 140–160 °C, 1–65 h; Scheme 61).[127]

Scheme 61
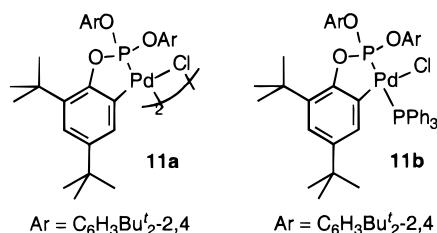
Record values of TONs were observed for the reaction of 4-bromoacetophenone with butyl acrylate (up to 1 000 000, TOF = 166 667 with 100% conversion) and styrene (up to 5 750 000 but with lower TOF = 83 333 and lower conversion 57.5% and selectivity, as substantial amounts of styrene are oligomerized). Deactivation of catalyst due to palladium black deposition can be avoided by the addition of an extra amount of ligand tris(2,4-di-*tert*-butylphenyl)phosphite (5-fold relative to palladium complex), thus giving a system formally similar (in what concerns the constituents and their relative content) to that described in.[101] The system is robust to air. The monomeric phosphite–phosphine complex

11b proved to be considerably less active, most likely due to the deactivating influence of PPh$_3$. The application of cyclopalladated complexes to the reactions with aryl chlorides was not described.

Pincer-type phosphite-based palladacycle has been developed by Shibasaki.[128] The study of Shibasaki's palladacycle in the Heck reaction revealed an unusual substrate selectivity trend which can be interpreted in favor of a possible Pd(II)–Pd(IV) mechanism. Indeed, as shown in Scheme 62, electron-rich

Scheme 62
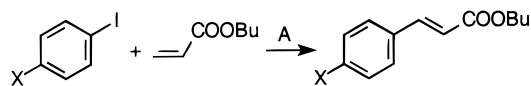
A: **12** (0.0001 mol%), Na$_2$CO$_3$, NMP, 140°C, 40-72 h

|	H	OMe
Yield, %	68	98
TON	680000	980000
TOF, h^{-1}	17000	14000

R = p-C$_6$H$_4$OMe (**12**)

aryl iodide gives apparently better net results (conversion and cumulative TON) than PhI, though in what concerns the measure of catalytic activity (TOF), the difference is less obvious. The preference for electron-rich substrate is unprecedented in the Heck reactions catalyzed by conventional phosphine-assisted or phosphine-free systems, and thus it may reveal the participation of a Pd(II)–Pd(IV) route as the oxidative addition to Pd(II) is well-known to be facilitated by electron-donating substituents. Still more kinetic data obtained by either competitive experiments or direct measurements of rate constants is required to support or disprove this interesting selectivity trend.

As soon as palladacycles are likely to be unassembled at the preactivation stage, expensive phosphorus-containing structures may not be required at all. The palladacycles generated from nonphosphine ligands, hundreds of which are published, may be tried as a source of palladium for phosphine-free catalysis.

Nitrogen-, oxygen-, and sulfur-containing palladacycles were demonstrated to serve as excellent precatalysts in the Heck reactions. A successful application of a palladacycle obtained by cyclopalladation of benzylamine has been mentioned.[127] Milstein prepared a number of oxazoline-basing palladacycles **13** and showed that such compounds can be used in the Heck reaction of iodoarenes with simple olefins to show huge TON values.[133] Beletskaya et al. have shown that a wide range of five- and six-membered palladacycles including CN and CO types (structures **14–18** present a subset of palladacycles tested), many of which are produced from "junk compounds", the cost of which is negligible so that the palladacycle-forming ligand serves as a disposable wrapper for palladium, can serve as catalyst precursors in the arylation of olefins by iodoarenes. High TON values were obtained showing that this class of complexes is far from being exhausted for the search for other

good precatalysts for effective processes.[134] It is now obvious that a stock of compounds capable of generating catalytically active palladacycles is practically endless (Scheme 63).

Scheme 63
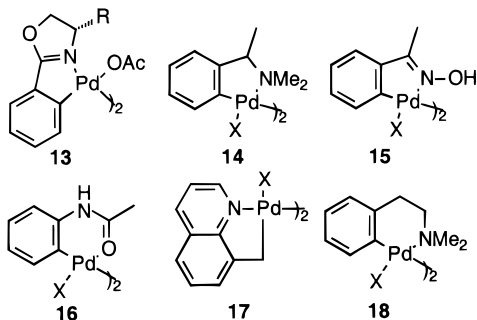
Sulfur-containing palladacycles were also prepared and showed an outstanding activity. SCS palladacycles, similar in structure to Milstein's PCP catalysts, were obtained and tested in the Heck reaction. 4-Acetamidosubstituted compound turned out to be the most stable and efficient, though only for the reactions with iodoarenes.[135] The reactions are insensitive toward oxygen and unpurified solvents. In the reaction of PhI with methyl acrylate, a TON of 70 000 (TOF 1167 h^{-1}) was achieved, which is high but clearly inferior to many other systems, including much cheaper ones (Scheme 64).
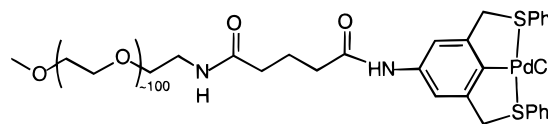
Scheme 64
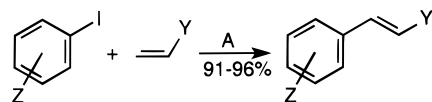
A: **19** (0.1mol%), Na$_2$CO$_3$, DMF, 110°C, 6 *h*
Y = COOMe, COO*t*Bu, CN, Ph, 4-pyridyl
Z = H, *p*-NHAc, Ome, COOH
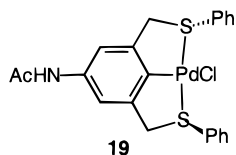
These catalysts really shine when it comes to ease of modification. As an example, the catalyst modified with the poly(ethylene glycol) (PEG-5000, which is roughly equivalent to about 100 oxyethylene units) residue was obtained. This catalyst is as modest in requirements to atmosphere and solvent purity as its parent and is easily recyclable, e.g., by reprecipitation by ether. No loss of activity was noted in three reuses. Further modifications of this molecule, e.g., by the introduction of C$_2$-chirality due to pyramidal configuration of sulfur atoms, has been announced and could be expected to bring a new dimension to this area, though if this catalyst works through a dechelation of the sulfur arms, which is a very likely option, the chirality would be unstable (Scheme 65).
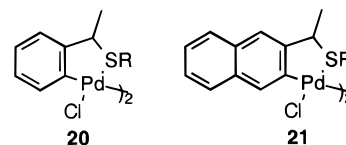
Simpler SC palladacycles **20**, **21** were recently proved as some of the most active precatalysts known so far. TON values of up to 1 850 000 were recorded. The SC palladacycles are able to catalyze the reac-

Scheme 65

tions with a wide selection of iodo-, bromo-, and even some chloroarenes as well as vinyl halides (Scheme 66).[136]

Scheme 66

Apart from model Heck reactions, the application of palladacycles for more complex synthetic purposes has been so far limited to Herrmann's palladacycle *hc*, which is used in those cases where high reactivity and/or smaller steric demands are in need. The arylation of disubstituted olefins present a certain challenge because of low reactivity and poor regioselectivity. Still, the reaction of bromoarenes with *n*-butyl methacrylate in the presence of Herrmann's palladacycle and stronger base Bu$_3$N, which effectively captures intermediate Pd hydride and thus interferes with isomerization of primary product, gave good yields of 2-aryl methacrylates. High TON (up to 8300) and TOF (up to 1000 h^{-1}) were recorded (Scheme 67).[137] The dependence of regioselectivity for

Scheme 67
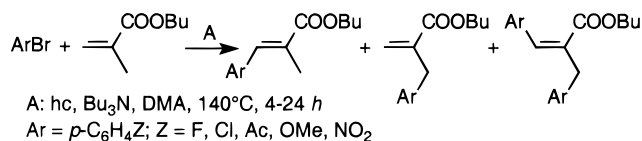
A: hc, Bu$_3$N, DMA, 140°C, 4-24 *h*
Ar = *p*-C$_6$H$_4$Z; Z = F, Cl, Ac, OMe, NO$_2$

the arylation of α-methylstyrene catalyzed by Herrmann's palladacycle has been discussed above.[93]

Herrmann's palladacycle has been successfully applied in the synthesis of several complex molecules.[138,139] Thus, an exemplary case of intramolecular *exo* cyclization was provided in ref 140. This sterically very demanding process failed in the presence of overligated [Pd(PPh$_3$)]$_4$ catalyst. The palladacycle, on the other hand, catalyzed the formation of a seven-membered cycle condensed with a *spiro*-system in high yield and stereoselectivity. The reaction took place in a homogeneous aqueous system with soluble acetate base (Scheme 68).

Scheme 68
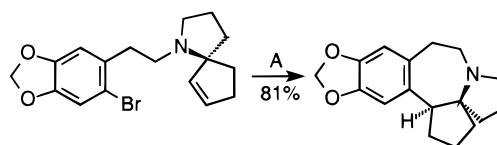
A: hc (4 mol%), Bu$_4$NOAc, DMF/MeCN/H$_2$O, 110-120°C

The palladacycle showed spectacular efficiency for the enantioselective synthesis of estrone by intramolecular cyclization. The reaction in aqueous solvent

was very fast and gave a quantitative yield of the desired estrone precursor. Other catalysts such as Pd(OAc)$_2$/PPh$_3$ gave yields not exceeding 63–85% after a 15 times longer reaction time. The reaction catalyzed by the palladacycle can be conducted even in domino fashion, though with much lower yield (Scheme 69).[141]

Scheme 69
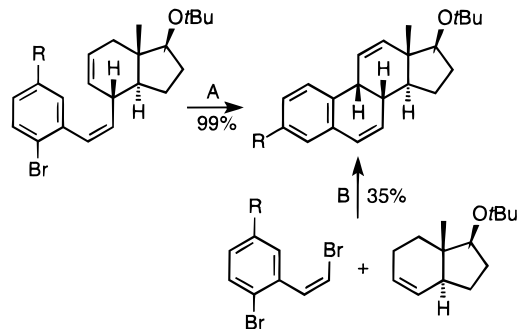
A: hc (2,5 mol%), Bu$_4$NOAc, DMF/MeCN/H$_2$O, 115°C, 4.5 h
B: hc (2,5 mol%), Bu$_4$NOAc, DMF/MeCN/H$_2$O, 60°C, 168 h

Due to the requirement of preactivation which needs higher temperatures, Herrmann's catalyst may happen to be inferior to the mixture Pd(OAc)$_2$ and P(o-Tol)$_3$ for reactions at low temperatures. Such a case has been, e.g., reported by Overman for the intramolecular cyclization at 50 °C in the cardenolide synthesis.[124]

The industrial application of *hc* for the production of *naproxen* antiinflammatory drug via the Heck arylation of ethylene by 2-bromo-6-methoxynaphthalene is being developed.[122]

C. Carbene Complexes

A new principle for designing catalysts for palladium-catalyzed reactions has been proposed by Herrmann et al.[32] Stable heterocyclic carbenes, the derivatives of imidazole and 1,2,4-triazole, turned out to be excellent ligands forming a wide range of complexes (cf., e.g., refs 142–144 and references therein). Carbene ligands (for ab initio computations on the structure, cf. ref 145) are strong σ-donors which lack any appreciable ability for π-acceptor back-bonding, and in this respect these ligands resemble donor phosphines, though with somewhat lower steric bulk.[146] As in the complexes with both monocarbenes and chelating bis-carbenes the heterocyclic rings are turned out of the plane formed by the square-planar coordination shell of palladium, steric hindrance at the migratory insertion step of the Heck cycle should be low. Bis-carbene complexes are capable of *cis–trans*-isomerism, the process required for some steps of catalytic cycle.[147]

Bis-carbene complexes are obtained either by electrophilic palladation of imidazolium salts[142,143,148,149] (dmiy = 1,3-dimethylimidazol-2-ylidene (**22**); tmiy = 1,3,4,5-tetramethylimidazol-2-ylidene (**23**); dmmdiy = 3,3′dimethyl-1,1′-methylenediimidazol-2,2′-diylidene (**24**)), Scheme 70, or by various ligand exchange equilibria with the involvement of free carbenes

Scheme 70
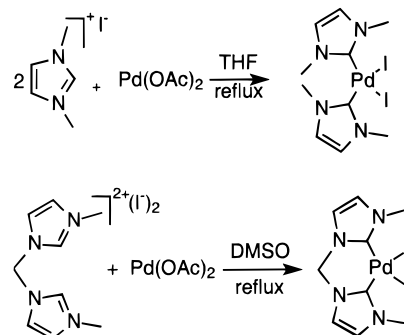
which are stable in solution and thus can be used as regular ligands.[148,150,151]

Mixed carbene–phosphine complexes are also available and have been tested in Heck and other palladium-catalyzed reactions.[149,152] The ligand exchange of Pd(dba)$_2$ with carbenes gives uncharacterized Pd-(0) carbene complexes which undergo an oxidative addition, though only on reflux in THF–toluene mixture (Scheme 71).[148]

Scheme 71
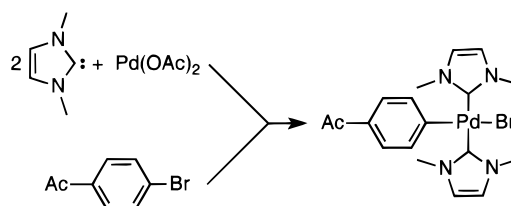
Modest reactivity of carbene complexes toward the oxidative addition was further corroborated. A fully characterized (tmiy)$_2$Pd(0) complex reacted with iodobenzene only at temperatures above 60 °C[151] to give the *trans*-product, which readily decomposed to form Pd black, an imidazolium salt, biphenyl, and *cis*-PdL$_2$I$_2$ carbene complex (Scheme 72).

Scheme 72
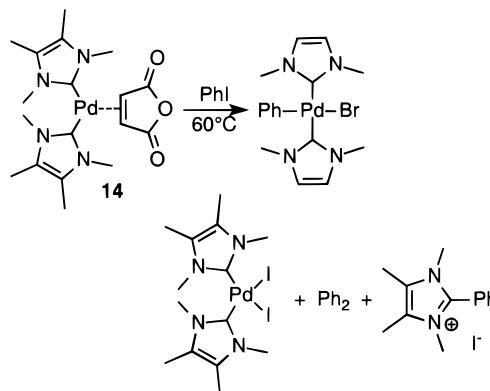
Stoichiometric experiments on modeling the Heck reaction by reactions of ArPdXL$_2$ (L = carbene) complexes with olefins showed that the intermediate complexes are unstable toward the decomposition to give imidazolium salts, biaryls, and Pd black. Nevertheless, under catalytic conditions, mono-, bis-, and chelated carbene complexes showed excellent stability and reaction rates (Table 3), which enabled the use of tiny loads of these catalysts (of 10^{-4} mol %

Table 3. Performance of Carbene Palladium Complexes in the Reaction of *p*-bromoacetophenone with *n*-butylacrylate (NaOAc, DMA, 120−125 °C)

complex (mol %)[a]	time (h)/conversion (%)	TON	mean TOF (TOF$_0$), h^{-1}	ref
cis-(dmiy)$_2$PdI$_2$ (0.5)	10/99	200	20 (n/a)	148
(dmmdiy)PdI$_2$ (0.5)	10/99	200	20 (n/a)	148
(dmiy)$_2$Pd[b] (2×10^{-4})	96/66	330 000	3440 (n/a)	148
cis-(tmiy)$_2$Pd(TCE) (2.1×10^3)	n/a	50 000	n/a	151
trans-(tmiy)$_2$Pd(p−O$_2$NC$_6$H$_4$)I (2.1×10^3)	n/a	50 000	n/a	151
(dmiy)Pd(Me)(acac) (4.0×10^4)	7.5/29	74 500	10 000 (24 000)	150
(dmiy)Pd(Me)(hfacac) (4.6×10^4)	11.7/50	109 000	9300 (10 400)	150
trans-(dmiy)$_2$Pd(Me)Cl (4.6×10^4)	8.5/40	100 500	12 000 (24 000)	150

[a] TCE = tetracyanoethylene, acac = acetylacetone, hfacac = hexafluoroacetylacetone. [b] Generated in situ, see text.

order of magnitude) to achieve high TON values (100−300 thousands and more). Very high initial TOF values (up to 24 000 h^{-1}) were noted both for bis-monocarbene and for chelating carbene complexes. If taken in small quantities, the catalysts showed excellent stability over time. In the case of monocarbene complex (dmiy)Pd(Me)(hfacac), the initial TOF was found to be almost equal to the mean TOF measured over the period of 12 h. Interesting to note is that this complex is the most unstable of the series studied, and in higher loads (0.5 mol %) the catalyst is rapidly decomposed giving Pd black after a short initial period of high activity.

Carbene complexes of Pd(II) of the type L$_2$PdX$_2$ or (L−L)PdX$_2$ need to be prereduced in order to enter the catalytic cycle, which can be done either by external reducing agents such as hydrazine or formates or by tetraalkylammonium salts,[32] while the respective hydrocarbyl complexes L$_2$Pd(Me)X and the complexes of Pd(0) enter the reaction without the induction period.

It is generally accepted that carbene deligation is highly improbable, though at the temperatures used for carrying out Heck reactions with such complexes (140 °C and higher) this cannot be altogether neglected. Therefore, the reactions are usually supposed to proceed via a cationic pathway by deligation of halide, though some doubt was expressed because cationic complexes with carbene ligands were noted to be less stable than neutral ones.[150,151] We can only add that the instability of carbene complexes in stoichiometric tests, the need to perform the reations at high temperature, as well as a very characteristic behavior to display top activity at low concentrations brings these systems very close to phosphine-free catalysis. Thus, as an alternative, the catalysis may proceed through a primary decomposition of carbene complex to liberate underligated palladium. Therefore, chiral carbene complexes can hardly be expected to have a coordination shell stable enough to catalyze enantioselective reactions. The first example of such a chiral complex has been recently introduced, though no indication on the use of this sophisticated molecule for the Heck reaction other than a simple standard process has been made (Scheme 73).[153]

D. Underligated and Phosphine-Free Systems

As it is evident by now, none of the steps in the general Heck cycle requires the presence of a phosphine ligand nor any other strongly bound ligand in the coordination shell of palladium. The oxidative

Scheme 73
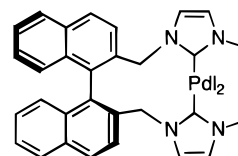
addition, migratory insertion, and hydride elimination do not require the assistance of specific ancillary ligands. The inherent reactivity of nonligated palladium is sufficient for oxidative addition to most kinds of C−X bonds. On the other hand, phosphine-free processes could lead to huge catalytic activity and the possibility of performing catalytic transformations in the cases of high steric demands.

The most serious drawback of phosphine-free systems is the inherent instability of catalytic cycles driven by palladium complexes with an undefined coordination shell. Mismatch of reaction rates of individual stages leading to the deactivation of catalyst can be caused by many factors including temperature, variation of concentration, change of the composition of reaction mixture in the course of reaction, etc. Phosphine-free systems thus ought to be specifically and separately tailored to each reaction. Often success is a matter of chance. Nevertheless, more and more data are being gained which reveal the potential of such systems.

Due to the lack of strongly bound neutral ligands, phosphine-free systems are bound to proceed via the cationic route via the de-ligation of anionic ligands. Therefore, phosphine-free systems are realized in polar solvents (DMF and the like), particularly in aqueous media.

In the seminal work by Spencer,[98] a phosphine-free system has been shown to be quite suitable for the reactions with activated bromoarenes showing almost identical TONs, TOFs, and yields to the system supported by 4 equiv of PPh$_3$ ligand, though inferior to the P(*o*-Tol)$_3$-assisted system. Further development of the phosphine-free protocol is associated with the introduction of phase-transfer agents, halide salt promoters, and aqueous systems.[7]

E. Phase-Transfer Agents in Heck Chemistry

As in any reaction requiring basic catalysis, the Heck reaction is responsive to phase-transfer phenomena. The beneficial effect of quaternary ammonium salts was first noted by Jeffery,[154−156] and in further literature the Heck reaction in the pres-

ence of quaternary ammonium salts has been referred to as Jeffery's conditions or Jeffery's protocol.

The protocol gained in popularity after Larock advanced it from simple model reactions to intramolecular cyclization and revealed the potential of this method for complex organic synthesis.[157]

Despite a unifying feature of the presence of quaternary ammonium salts, there is actually not a single but several distinct protocols in which quaternary salt may play the following roles. (i) It can act as a solid−liquid phase-transfer agent in the reactions catalyzed by solid salts such as sodium or potassium acetates, carbonates, hydrocarbonates, phosphates, etc., are practically insoluble in the solvents used in Heck chemistry.; (ii) It can serve as a liquid−liquid phase-transfer agent, e.g., in the reactions in aqueous solvents, in which the base is soluble while the substrate is not. Phase-transfer methods are useful for all sorts of phosphine-assisted, underligated, and phosphine-free catalytic systems. (iii) Halide, acetate, and possibly other anions can serve as promoters to increase the rates of some steps of the catalytic cycle, as, for instance, of the oxidative addition due to the increase of electron density on Pd atom due to the formation of more electron-rich anionic Pd(0) species. This effect has been unveiled in fundamental studies of Amatore and Jutand et al.[18] Not only tetraalkylammonium, but also other soluble halide salts, e.g., LiCl, can be even more effective.[158] (iv) It can act as a stabilizing additive to increase the lifetime of underligated Pd(0) species to match slower oxidative addition rates with less reactive substrates. This effect is exerted by chloride and bromide ions, which are likely to enter the coordination shell of underligated palladium and form either more stable neutral or even anionic complexes to impose a Coulombic barrier for collisions and formation of clusters further growing into metal particles. The stabilization of catalytic systems by halide salts has been demonstrated by extending the lifetime of the Herrmann's palladacycle.[120] This effect is very important for phosphine-free and underligated systems. (v) It can act as an ion exchanger that is particularly important for the reactions with iodides. The exchange of iodide for chloride in the coordination shell of, e.g., arylpalladium intermediate may lead to switching from the neutral to cationic mechanism (Scheme 74).

Scheme 74
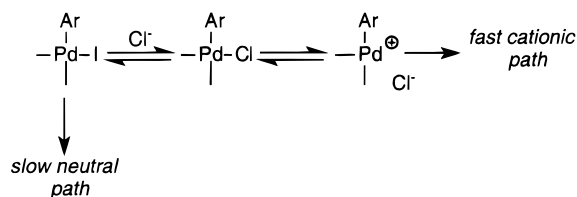
Indeed, despite some contradictory evidence (cf. data on binding constants for cationic palladium complex given in ref 18), chloride must be a weaker ligand for Pd(II) than iodide. Milstein and Portnoy et al. have unambiguously proven the cationic mechanism to be realized for chloride complex (dippp)Pd-(Ph)Cl in polar solvents[106] in the absence of any

halide scavengers. The exchange of iodide for acetate leads to a huge increase of the migratory insertion rate.[49]

In most cases the exact nature of the influence of quaternary salts on the rate and selectivity of a given reaction cannot be traced down to a single effect but rather is a superposition of several. This is not surprising as the influence of phase-transfer agents is altogether difficult to explain and predict even in much simpler organic reactions.[159] Phase-transfer phenomena often include mass-transfer processes as rate-determining processes and require the knowledge of how ions and molecules are transported across liquid−liquid interfaces or from crystal to liquid. These processes depend on dispersity, crystal structure, interphase tension, and other interfacial phenomena, a method of reasoning not quite familiar to organic chemists. Therefore, we have to rely on simple model studies bearing in mind that their conclusions must be treated with care.

The most detailed study by Jeffery[160−162] describes the influence of tetrabutylammonium salts on the model reaction of PhI with methyl acrylate both in anhydrous and aqueous media, in the presence of PPh_3, and in phosphine-free mode. The choice of this highly reactive system obviously hides any specific effects associated with the activation of palladium catalyst but instead spotlights the effects of phase transfer and stabilization of Pd(0) in phosphine-free modes.

Under all conditions studied, tetrabutylammonium salts exerted a dramatic positive influence. The best results obtained during this study are summarized in Table 4. The salts with three different counterions Cl, Br, and HSO_4 showed comparable performance with some rather subtle variations depending on the nature of base, solvent, and catalytic mode, though the chloride salt n-Bu$_4$NCl invariably is among the best, which is particularly true for phosphine-free conditions under which chloride may additionally act as a supporting ligand for Pd(0) species.[18] An interesting observation is that the choice of base is determined by the presence or absence of water in the reaction media. Weaker bases, such as acetates and hydrocarbonates, performed well only under anhydrous conditions, additionally enforced by the addition of powdered molecular sieves (though we cannot completely rule out that the sieves are not just a dehydrating agent but can more actively participate in the catalysis, cf., e.g., ref 163). Stronger bases, alkali metal carbonates, on the other hand, require the addition of at least 10 vol % water to the solvent and can be used for reactions in neat water. As far as it can be deduced from the description of experiments and data on the solubility of the involved salts, all of these reactions are run in heterogeneous systems in which the inorganic base is either a poorly soluble solid or is contained in an aqueous solution. Thus, all reactions involved either solid−liquid or liquid−liquid phase transfer.

On the other hand, amines as bases do not require phase transfer. Still, all three salts exerted a positive influence on the rate, though in general the reactions in the presence of Et$_3$N showed inferior performance,

Table 4. Best Results Achieved in the Reaction of PhI with Methyl Acrylate (5 mol % Pd(OAc)$_2$, 10 mol % Ligand, Base, QX, Solvent)

base	ligand	solvents	QX	yield	T (°C)/time (h)
NaHCO$_3$	PPh$_3$	MeCN DMF	n-Bu$_4$NCl n-Bu$_4$NHSO$_4$	98−99	60/3.5
NaHCO$_3$	No	MeCN	n-Bu$_4$NCl	90	60/3.5
NaHCO$_3$	No	DMF	n-Bu$_4$NCl n-Bu$_4$NHSO$_4$	99	60/3.5
KOAc	PPh$_3$	MeCN	n-Bu$_4$NCl n-Bu$_4$NBr	92−95	50/2
KOAc	PPh$_3$	DMF	n-Bu$_4$NCl n-Bu$_4$NHSO$_4$	92−94	50/2
n-Bu$_4$NOAc	PPh$_3$	DMF	No	98	50/2
KOAc	No	DMF	n-Bu$_4$NCl n-Bu$_4$NBr	99	50/2
K$_2$CO$_3$	PPh$_3$	MeCN−H$_2$O DMF−H$_2$O (10:1)	n-Bu$_4$NCl n-Bu$_4$NBr n-Bu$_4$NHSO$_4$	96−99	50/2
K$_2$CO$_3$ or Na$_2$CO$_3$	PPh$_3$	H$_2$O	n-Bu$_4$NCl n-Bu$_4$NBr n-Bu$_4$NHSO$_4$	95−98	50/2
K$_2$CO$_3$	PPh$_3$	H$_2$O	n-Bu$_4$NCl n-Bu$_4$NHSO$_4$	98	25/24
K$_2$CO$_3$	No	DMF−H$_2$O (10:1)	n-Bu$_4$NCl n-Bu$_4$NBr	98	50/2
K$_2$CO$_3$	No	H$_2$O	n-Bu$_4$NCl n-Bu$_4$NBr	92	50/2
Et$_3$N	No	MeCN	n-Bu$_4$NCl n-Bu$_4$NBr n-Bu$_4$NHSO$_4$	70−79	50/2

possibly due to a well-known ability to block coordination sites of palladium catalyst, which is particularly important because the reactions studied were run at rather low temperatures at which ligation−de-ligation equilibria are more strongly shifted toward species with filled coordination shells. The positive influence of salts may be associated with the displacement of amine or iodide from the coordination shell of palladium. At least in the case of n-Bu$_4$-NHSO$_4$, this explanation seems to be the only realistic factor.

One of the most important advantages of the Jeffery−Larock protocol is the possibility to perform reactions under mild conditions at temperatures below 100 °C, at least for the reactions with iodides, which in selected cases can be run even at room temperature.[154] As a result, the addition of promoter salts became a very popular technique in Heck chemistry ranging from simple reactions to enantioselective processes, intramolecular cyclizations, and cascades. Variation of the nature of the phase-transfer ion and promoter additives can lead to spectacular trends in selectivity.

A subtle difference in basicity can have a dramatic effect on the selectivity of arylation, which was demonstrated for the reaction of dihydrofuran with aryl iodides in the phosphine-free mode in the presence of quaternary ammonium salts.[164] The primary product of arylation, 2,5-dihydrofuran, is formed in the presence of either silver carbonate or n-Bu$_4$NOAc, while the product of double-bond migration is formed in the presence of separately added base and phase-transfer agent, the results provoking an idea that the difference is accounted for by the concentration of base in the reaction mixture. The soluble salt n-Bu$_4$-NOAc can furnish higher basicity to immediately trap palladium hydride than a combination of solid KOAc assisted by solid−liquid phase-transfer agent n-Bu$_4$-NCl. The system n-Bu$_4$NCl−KOAc at room temperature leaves Pd hydride free to accomplish near to quantitative transformation of primary product to a more thermodynamically stable 2,3-dihydrofuran. The same system at higher temperatures provides higher basicity that results in the formation of a mixture of primary and rearranged product. In a full accordance with this simple hypothesis, n-Bu$_4$NBr is even less efficient as an extractor of acetate ions from the solid phase, thus giving even better selectivity toward rearranged product, though at an expense of net reactivity (Scheme 75).

Scheme 75
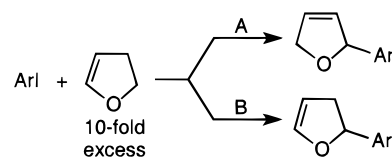
A: Pd(OAc)$_2$ (5 mol%), Bu$_4$NOAc, DMF, 4A MS, r.t., 10 h
B: Pd(OAc)$_2$ (5 mol%), Bu$_4$NCl, KOAc, DMF, 4A MS, r.t., 10 h
Ar = Ph, p-MeOC$_6$H$_4$, p-AcC$_6$H$_4$, 1-naphthyl

Mild reaction conditions assisted by tetrabutylammonium salts in phosphine-free mode helped to realize a highly chemoselective processes of the arylation of vinyltrimethylsilane.[82] The use of tetrabutylammonium acetate in polar solvent enables a selective formation of β-trimethylsilylstyrenes, while the use of potassium fluoride assisted by tetrabutylammonium chloride leads to an introduction of vinyl group. The method seems very convenient for the preparation of sophisticated styrenes, even though it requires a 3−4-fold excess of vinyltrimethylsilane. Both reactions are rare examples of

Heck arylation run at room temperature (Scheme 76).
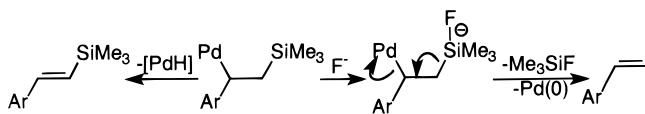
Scheme 76
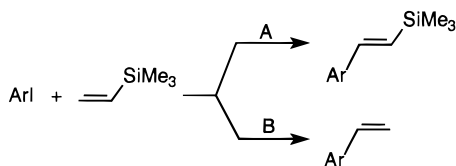
A: Pd(OAc)$_2$ (3-5 mol%), Bu$_4$NOAc, DMF, r.t.
B: Pd$_2$(dba)$_3$ (3-5 mol%), KF, Bu$_4$NCl, PhMe, r.t.
Ar = Ph, *p*-MeOC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-AcC$_6$H$_4$, 1-naphthyl.

Obviously fluoride assists in desilylation of the carbopalladated intermediate, thus making this route the main pathway of the catalytic cycle (Scheme 77).

Scheme 77

A spectacular application of phase-transfer phosphine-free catalysis toward Heck vinylation with substrate bearing a thermolabile peroxide group shows that the limits of tolerance of this mild protocol are very wide. The reaction is run at room temperature (Scheme 78).[165]

Scheme 78
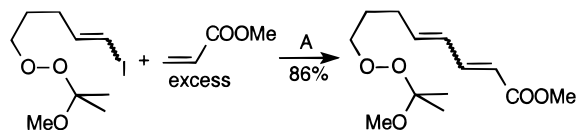
A: Pd(OAc)$_2$ (10-15 mol%), K$_2$CO$_3$, Bu$_4$NBr, no solvent, r.t.

Phase-transfer conditions are beneficial if the substrate can bind palladium as a monodentate or chelate complex and thus additionally steal a site or two from the coordination shell of palladium. If the shell is already burdened by phosphine ligands, the catalytic process is inhibited. This situation is common for reactions with nitrogen-containing substrates. One of the most recent examples involves the reaction of aminoquinoxalines, which are good chelating agents. As a result, the reaction under standard phosphine-assisted conditions was very slow and gave marginal yields of target products. Phase-transfer phosphine-free conditions gave good to high yields of pyrroloquinoxalines and were very fast requiring only 2 h even when X = Cl[166] (Scheme 79).

Scheme 79
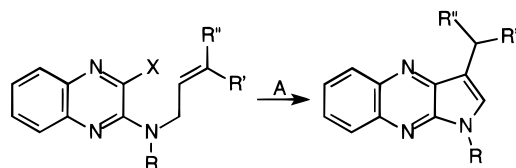
A: Pd(OAc)$_2$ (10 mol%), Bu$_4$NBr, K$_2$CO$_3$, DMF, 80-100°C

Phosphine-free systems can be adjusted for arylation of disubstituted olefins, e.g., cinnamonitriles,[167] cinnamates,[168,169] and methacrylates.[169] The reactions

can be run in the presence of quaternary ammonium salts and either inorganic bases (phase-transfer conditions) or bulky tertiary amines (Scheme 80).

Scheme 80
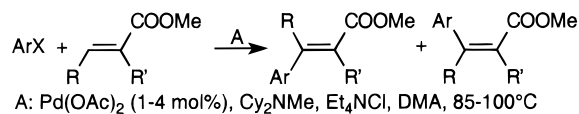
A: Pd(OAc)$_2$ (1-4 mol%), Cy$_2$NMe, Et$_4$NCl, DMA, 85-100°C

An unprecedented regioselectivity pattern has been established for the reaction carried out in the presence of bulky amines, as in all cases the diastereomer with an *E*-configuration of incoming aryl and carbomethoxy group was formed, irrespective of the configuration of the starting alkene. Moreover, in the reaction with deuterated bromobenzene, an equimolar mixture of diastereomers was formed. The latter experiment completely rules out any possibility that the stereochemistry can be accounted for by any process involved in the Heck cycle (Scheme 81).

Scheme 81
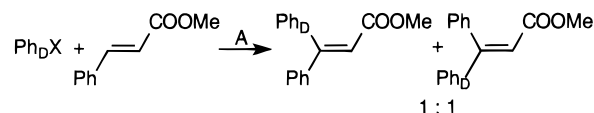
Therefore, the stereochemistry of this reaction is likely to be defined by the isomerization of products leading to the accumulation of the more thermodynamically favorable isomer. This is not surprising as the olefins with such a substitution pattern must indeed be susceptible to base-catalyzed *E/Z*-isomerization.

The phosphine-free phase-transfer method was found to be advantageous for combinatorial chemistry application of the Heck reaction[170] with resin-bound *m*-iodobenzyl alcohol and a wide range of olefins (Scheme 82).

Scheme 82
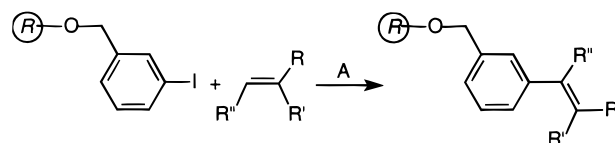
A: Pd(OAc)$_2$ (25 mol%), NaOAc, Bu$_4$NCl, DMA, 100°C

Heck reactions under phase-transfer conditions were applied to the construction of large highly conjugated molecules, e.g., the derivatives of para-cyclophane[171,172] or benzocyclobutenoacenaphthylene (Scheme 83).[173]

Scheme 83
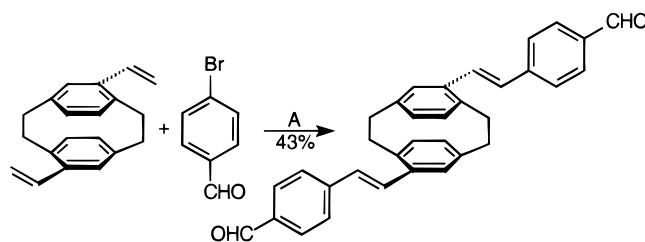
A: Pd(OAc)$_2$ (3 mol%), K$_2$CO$_3$, Bu$_4$NBr, DMA, 105°C, 2 *d*

In the multiple Heck reaction given in Scheme 84

Scheme 84
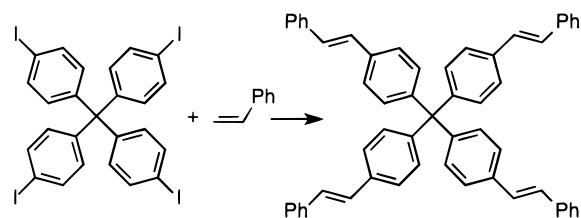
the phase-transfer phosphine-free procedure was found to be vastly superior to a standard phosphine-mediated technique. In the same reaction, Herrmann's catalyst gave a yield of 72% while the mixture of Pd(OAc)$_2$ and P(o-Tol)$_3$ failed.[174]

Besides tetrabutylammonium salts, other phase-transfer agents have been rarely tried, despite the possibility that the variation of such agents may bring interesting findings. For instance, in a report[175] on the arylation of PEG-bound cinnamic acids, it was found that the PEG residues can serve as phase-transfer agents and no quaternary ammonium salt is needed. Moreover, the effect of the PEG tails accounting for very high stereoselectivity of arylation as Z-isomer was almost exclusively formed, as compared to the arylation of the same cinnamic acids esterified not by PEG but by simple alcohols (Scheme 85).

Scheme 85

Ar = 2-MeOC$_6$H$_4$; Ar' = 4-MeC$_6$H$_4$;
A: Pd(OAc)$_2$ (10 mol%), NaHCO$_3$, Bu$_4$NBr, DMF, 145°C
B: Pd(OAc)$_2$ (10 mol%), NaHCO$_3$, DMF, 145°C

A good choice of stabilizing ligands may have a strong effect on the stability of the catalytic system. In this respect, the importance of discovery of Reetz et al. on the activation of a phosphine-free catalytic system by N,N-dimethylglycine (DMG)[176] cannot be overestimated. Turnover numbers of up to 106 700 were achieved for the reaction of bromobenzene with styrene catalyzed by 0.0009 mol % of PdCl$_2$(PhCN)$_2$ in the presence of a 20-fold (with respect to palladium) amount of DMG (NMP, NaOAc, 130 °C, 96 h; Table 5).

Actually DMG exerts a noticeable effect only for high initial loads of palladium catalyst, while at
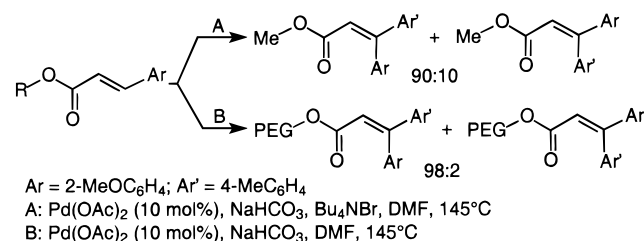
Table 5. Influence of *N,N*-Dimethylglycine (DMG) on Phosphine-Free Heck Reaction

| | Pd(OAc)$_2$ | | | | PdCl$_2$(PhCN)$_2$ + 20 DMG | |
| | conversion | | | conversion | | |
[Pd]$_0$	(%)	TON	TOF	(%)	TON	TOF
1.5	51	33	1.1	98	65	6.5
0.1	n/a	n/a	n/a	96	960	96
0.01	77	8 600	360	98	9 800	408
0.0009	85	94000	980	96	106 700	1 100

lower palladium concentrations the effect of DMG is very small. Moreover, two important conclusions can be inferred from these data. The performance of a simple phosphine-free system for the reactions of nonactivated aryl bromides can be huge, so huge that the system described was announced as "one of the most reactive and selective catalyst systems for the Heck reaction of aryl bromides with olefins known to date" at least under the conditions described. This invites a careful reinvestigation of the preparative potential of such systems. The second conclusion is no less paradoxical: the lower the concentration of palladium, the higher the rate of the catalytic process estimated by mean TOF values. The increase is huge, eliminating any doubts on the validity of this conclusion which may arise because TOF values averaged over the duration of reaction are too rough an estimate of the true rate of catalytic process. In our opinion, the reciprocal dependence of TOF on initial palladium concentration is a trend of common relevance for underligated and phosphine-free systems. As we noted earlier, the catalytic cycle is unstable due to competition of oxidative addition triggering the Heck process and the clustering of Pd(0) species leading to deactivation. By decreasing the concentration of palladium, the rate of aggregation (second or higher order in Pd) is much more strongly decreased than the rate of oxidative addition (first order in Pd). Thus, at lower concentrations, catalytically active Pd-(0) species (both monomolecular and small clusters) should have longer lifetimes to effectively participate in reaction with even such unreactive halides as PhBr. The role of DMG is likely to extend either the lifetime or the activity of catalyst. The finding that the effect of DMG fades away for smaller concentrations of palladium tells that the influence on the lifetime is predominant. DMG under the conditions described is a betaine which is likely to have an effect similar to acetate ion but stronger because of a more favorable chelation mode (Scheme 86).

Scheme 86
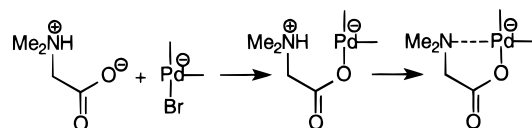
Chelated DMG can have the additional function of effecting intramolecular deprotonation of the PdH intermediate. Thus, it would be interesting to study the influence of this and other such chelating additives on the regioselectivity of arylation in the cases when the double bond undergoes PdH-induced migration.

The method has been applied for arylation of styrene by both electron-rich and electron-deficient bromides to give the respective stilbenes in good to high yields and excellent *trans*-stereoselectivity (Scheme 87).

The increase of catalytic efficiency on the addition of weak ligands applied in huge excess with respect to palladium may be a general phenomenon. For example, there is an evidence[177] that pyridine can

Scheme 87
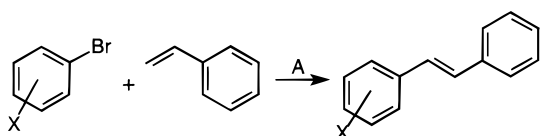
A: PdCl$_2$(PhCN)$_2$ (1.5 mol%), DMG (30 mol%),
   NaOAc, NMP, 130°C, 10 h
X = p-NO$_2$ (100% conversion), p-CF$_3$ (96%), p-CN (100%),
   p-Ac (100%), p-OMe (89%), m-OMe (60%), p-NMe$_2$ (60%)

serve as a relatively effective supporting ligand (TON = 1520, TOF = 21 h^{-1}; Scheme 88).

Scheme 88
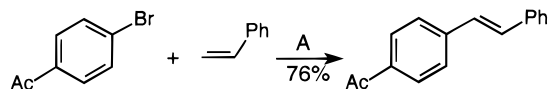
A: Pd(OAc)$_2$ (0.05 mol%), py (50 mol%), Bu$_3$N,
   PhMe, 140°C, 3 d

The effect of DMF and other aprotic bipolar solvents, as well as water, capable of weak complexation with palladium could be at least partially ascribed to this phenomenon.

The addition of tetraarylphosphonium salts has been discovered by Reetz et al. to lead to a huge increase of catalyst activity. The catalytic system thus obtained is among the most reactive described so far. Chlorobenzene reacts with styrene in high conversions (up to 96%). Considerable amounts of 1,1-diphenylethylene are formed (Scheme 89).

Scheme 89
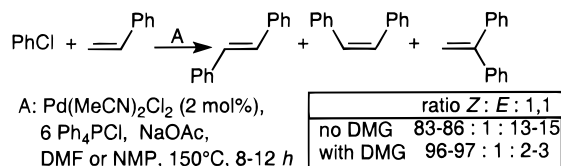
A: Pd(MeCN)$_2$Cl$_2$ (2 mol%),
   6 Ph$_4$PCl, NaOAc,
   DMF or NMP, 150°C, 8-12 h

	ratio Z : E : 1,1
no DMG	83-86 : 1 : 13-15
with DMG	96-97 : 1 : 2-3

Further activation of catalyst is done by the addition of DMG. Besides the increase in conversion, higher regioselectivity is observed, as the yield of 1,1-byproduct is markedly decreased. The formation of considerable amounts of 1,1-diphenylethylene is characteristic for the cationic pathway (see above). The influence of DMG clearly shows that this molecule is bound to palladium at least in the migratory insertion step and serves as a temporary site holder by switching from monodentate to bidentate mode and back. The role of phosphonium salt has been proven to supply a single phosphine molecule through an oxidative addition to the C−P bond. This process has been proven by reacting Pd(OAc)$_2$ with Ph$_4$PCl in the presence of ethanol as a reducing agent. The resulting ins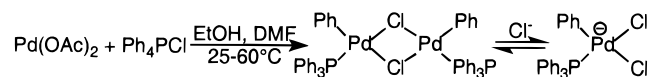oluble dimeric or polymeric complex is dissolved in DMF in the presence of chloride ions, probably giving anionic complexes (Scheme 90).

Scheme 90

This complex has been proven to catalyze the reaction of chlorobenzene with styrene, though in the absence of Ph$_4$PCl the lifetime of such a catalytic system is short giving only about 15% conversion, which definitely happens because of degradation of phosphine ligand at high temperature of reaction.[42] In the presence of 6 equiv of phosphonium salt, the conversion is near to quantitative. Thus, Ph$_4$PCl indeed serves as a renewable source of *single-phosphine palladium complex*, which endures 6−10 turns of the catalytic cycle before the phosphine ligand it bears gets cleaved.

The participation of phenyls from phosphonium salt leads to aryl scrambling in the reactions of substituted chlorobenzenes. This unwanted side process can be minimized by decreasing the load of catalyst and phosphonium salt, though naturally this is possible only for activated chloroarenes and bromoarenes. In this way, a TON value of 950 has been obtained for the reaction of styrene with p-chlorobenzaldehyde catalyzed by as low as 0.1 mol % of palladium in the presence of 0.6 mol % of Ph$_4$PCl.

F. Palladium Nanoparticles and the Problem of Catalyst Deactivation

In phosphine-free and underligated systems, the deactivation of palladium occurs mainly through the formation of inactive sediments consisting of particles of metallic palladium referred to by the nickname *black*. The understanding of the mechanism of this deactivation requires an intimate knowledge of factors controlling the nucleation and growth of metallic particles passing through the stages of small clusters, nanometer-scale particles, crystals, etc.[178] The physical chemistry of such phenomena is extremely complex, and relevant data are still lacking. Yet some important questions can be addressed and solved.

Several recent papers describe the catalytic activity of palladium nanoparticles obtained by different methods in Heck and some other catalytic processes. Palladium is known not to readily afford stable reproducible sols in the absence of stabilizing amphiphiles or polymers. Therefore, in reaction mixtures the formation of metallic particles, if started, swiftly goes to full sedimentation of palladium metal sediments of unknown morphology. The growth of particles cannot stop at monodispersed sols.

Several methods of palladium sol stabilization have been published. The data on the conditions of sol formation and the catalytic activity are summarized in Table 6.

In most of the methods palladium salts are reduced in the presence of either surfactants or polymers, the molecules of which form protective layers on the surface of metallic nanoparticles preventing their further growth. Surfactants are absorbed at the surface of palladium particle by the interaction of headgroups with metal. Thus, the nanoparticles are exposed to the solvent by hydrocarbon tails making such *liosols* dispersible in organic solvents but not in water. Palladium colloids can be obtained and stored in dry form and redispersed when needed in the appropriate solvent.

**Table 6. Heck Reaction in the Presence of Palladium Sols of Different Origin**

Pd sol (reductant/ stabilizing agent)	reaction conditions	(conversion/TON/TOF)	ref
polymethylhydrosiloxane/ polymethylhydrosiloxane	PhI + styrene (n/a)	0	179
LiBEt$_3$H/polystyrene-b-poly-4-vinylpyridine	4-BrC$_6$H$_4$COMe + styrene (Bu$_3$N, PhMe, 140 °C)	68/57 000/475	177
cathode/propylene carbonate	PhCl + styrene (Na$_2$CO$_3$, propylene carbonate, 155 °C)	55/16/0.25	180
cathode/propylene carbonate	4-BrC$_6$H$_4$COMe + styrene (Et$_3$N, propylene carbonate, 130 °C)	70/20/1	180
R$_4$NBEt$_3$H/R$_4$NCl	4-BrC$_6$H$_4$COMe + butyl acrylate (NaOAc, DMA, 140 °C)	97/1 940/24 000	181
cathode/R$_4$NCl	PhI + butyl acrylate (NaHCO$_3$, DMF, 30 °C)	ca. 100/100/<10	182
H$_2$/poly(vinylpyrrolidone)	4-BrC$_6$H$_4$CHO + butyl acrylate (NaOAc, DMA, 140 °C)	99/100 000/80 000	183
ArI + styrene/microemulsion	PhI + styrene	90/50 000/10 000	184

Several of such colloids were produced by the fast reduction of palladium salts by superhydride MBEt$_3$H or in an electrochemical cell in the presence of various anionic, cationic, or zwitterionic surfactants. The sols are obtained under anaerobic conditions and consist of large clusters of palladium with highly reactive palladium atoms at the surface. Such colloids are more or less efficient catalysts of Heck reactions suitable even for aryl chlorides, thus corroborating the conclusion that the intrinsic reactivity of palladium is sufficient for activation of even C−Cl bonds. A rule of thumb is that the weaker and thinner the protective shell, the higher the activity of the sol. However, such sols are not very stable. The protective shell is stripped under the conditions of Heck arylation, which leads to deactivation of the catalyst due to the redistribution of palladium between unprotected nanoparticles and formation of polydispersed palladium blacks.

More persistent sols are protected by polymers, the layers of which better withstand fierce perturabtion during the reaction but at the cost of lower catalytic activity. A sol protected by nonpolar siloxane polymer has been found to be totally inactive, possibly because such a dense coat disallows the effective diffusion of components needed for the Heck reaction or, even more likely, it does not let out the liberated salt, which chokes the surface of nanoparticle after several turns of catalytic cycle. Much better results are achieved with polar polymers, such as poly(vinylpyrrolidone), the coat of which may work like a layer of polar solvent NMP often used for Heck reactions. Such a layer lets in and out the reagents, products and liberated salt.

In what concerns sols, the most important question is whether the nanoparticle works as is through metal atoms which stay bonded to the surface or the atoms are being chipped off the surface in the oxidative addition and palladium goes into solution to fulfill the catalytic duty as soluble phosphine-free catalyst. In the latter case, the sol cannot survive because either the rate of oxidative addition is high and nanoparticles are fully dissolved or, if oxidative addition is slow and reprecipitation of metal occurs, the entropy commands that initially monodispersed sol will be transformed to polydispersed sediment with redistribution of metal to bigger inactive particles.

At least in one case and for a limited time the nanoparticles were shown to operate as a whole through reactive palladium atoms located at the edges of the cluster.[183] Using a very simplistic model schematically shown in Scheme 91, it has been

Scheme 91
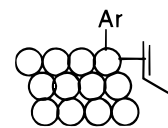
argued that only palladium atoms located at the edges, vertexes, and other defects of the crystal lattice can provide enough coordination sites required for the catalytic action. A correlation between the rate of the Heck reaction catalyzed by Pd nanoparticles and the estimated relative number of such atoms has been observed and regarded as evidence in favor of the mechanism in which an intact nanoparticle takes part in the catalytic process.

However, it is more likely that in the majority of cases this static mechanism cannot be the sole one operating. Chipping does occur, and the beautiful nanoparticle structure is eventually ruined.

The experiments with nanoparticles may be regarded as models for testing the reactivity of metallic palladium. As soon as these tests are positive, further studies should be devoted to increasing the stability of reactive forms of palladium by designing supporting systems which prevent chipping resulting in the fatal growth of polydispersity.

A more stable palladium sol, which functions as a true continuous-flow nanoreactor which is loaded with reagents and unloaded from products through mass transfer between the interior and the bulk environment, was described quite recently.[177] The sol is generated in the core of micelles of amphiphilic block copolymer, such as polystyrene-b-poly-4-vinylpyridine (Scheme 92).

Scheme 92
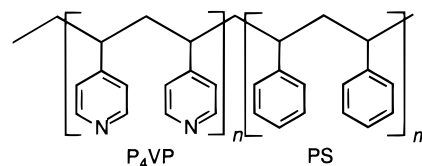
The idea is to obtain a microstructure partially resembling an inverted micelle but much more persistent as the block copolymer folds in a way that the polar part composed of vinylpyridine residues forms a micelle core while polystyrene tails grow outward, thus rendering the micelles soluble in nonpolar solvents. The polar core solubilizes palladium salts, and reduction with fresh superhydride LiBEt$_3$H gives a fine sol encapsulated in polymeric micelles. The sol turned out to be quite efficient in Heck arylation of styrene with reactive aryl bromides, provided that the hydrophobic base NBu$_3$, capable of diffusion to the core where the reagents are located, is used:

So, here, the reaction is forced to occur in a nanoreactor built by a copolymer micelle, as, indeed, the compartmentalization of all participating species is unambiguous. The encapsulated catalyst has an outstanding stability and fully retains the activity after 50 000 catalytic cycles (in fact much more as interior atoms of palladium cluster cannot take part in the reaction and turnover number is estimated given the net amount of palladium in a sol at 140 °C in a fairly aggressive environment and taking into account that the reaction leads to the formation of NBu$_3$HBr). It is noteworthy that the pyridine residues in the micelle cores themselves may and indeed should act as the base required by the Heck reaction mechanism, though the accumulation of bound protons and bromide counterions in the nanoreactors may destroy the internal structure. Thus, tributylamine in this system acts as a pseudophase-transfer agent to carry away the liberated HBr.

The important role of sols in the phosphine-free Heck reaction was established by running the process in aqueous microemulsions, which have been shown to behave as a universal aqueous (in a sense that the main component of the media is water) media to carry out the reactions between water-insoluble reagents.[184] The reactions in both cationic or anionic microemulsions turned out to actually run through a fast formation of stable palladium sols. Once formed, the sol shows no signs of further evolution during the reaction. Moreover, the performance of the catalytic system changed in parallel with the ability of the media to assist the formation of colloid and sustain it. The reactions showed high turnover numbers (up to 50 000), which is not surprising as only a fraction of palladium atoms located at the surface of the cluster actually react; thus, lowering the initial concentration of palladium leads only to the formation of smaller particles having fewer inactive palladium atoms in the interiors of nanoparticles. The microphase of the solubilized system acts as a self-sustained nanoreactor, the role of which is performed by the interfacial layers and surfactant-stabilized Pd clusters. Aqueous and oil phases act as feedstocks of hydrophilic (base) and hydrophobic (aryl iodide, olefin) reagents. Chipping of palladium does occur, but it does not lead to redistribution of metal and formation of large inactive particles of *black,* possibly because the microheterogeneous environment limits the mobility of species within interfacial layers in which the reaction takes place (Scheme 93).

Scheme 93
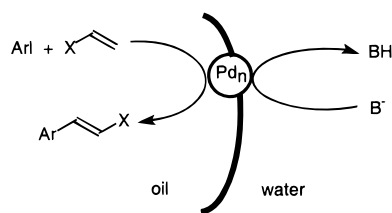
Moreover, the study of Heck and Suzuki reactions in the balanced microemulsions afforded experimental evidence in favor of the hypothesis that phosphine-free palladium catalysis is accounted for by the formation of palladium clusters. The factors which help to stabilize reactive clusters and prevent further aggregation leading to unreactive blacks (which are likely to consist of relatively large crystalline particles with rather small surface area) act in favor of phosphine-free reactions. Thus, tetraalkylammonium salts, which are ubiquitous in phosphine-free methods, may have yet another function of absorbing at the surface of the emerging nanoparticles and forming a supporting shell for them.

The important role of palladium nanoparticles in phosphine-free Heck reactions has been recently corroborated.[185]

IV. Extensions of Common Heck Chemistry

A. Less Usual Means of Activation

1. Effects of Pressure and Microwave Heating

Additional improvement of Heck procedures can be sought in ultrafast heating and pressure effects.

Very fast heating by means of microwaves leads to shortening of the reaction time, while the yields and selectivity do not greatly differ from the same reactions carried out using conventional heating.[186] The effect can be observed for simple arylation reactions of both Michael-type and donor olefins by aryl iodides, bromides, and triflates in phosphine-assisted or phosphine-free processes.

No specific effects belonging to any particular type of reaction were noted. Most probably the influence of microwave heating is associated with direct and uniform input of energy to the reaction media. Heck reactions are very well-known to run better at higher temperatures, naturally if reagents, products, and catalyst can survive such a harsh treatment. In conventional heating the energy is transferred by heat transfer through the walls of the reaction vessel and further on through convection causing nonuniform distribution of heat. Local overheating at the walls leads to decomposition of catalyst. Uniform deployment of heat directly to the reacting molecules by means of absorption of microwave energy by a polar solvent effectively affords higher temperatures than those achievable through conventional heating.

High pressure can also have a beneficial effect on Heck reactions. The key steps of the Heck cycle—oxidative addition and migratory insertion—have a negative activation volume and thus are likely to be accelerated by pressure.[5] On the other hand, PdH
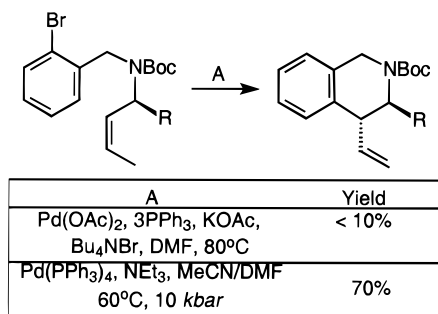
elimination can be retarded by high pressure, which may lead to a change of the product distribution.[187]

Pressure extends the lifetime of palladium catalyst. Two orders of magnitude increase of TON has been noted for phenylation of 2,3-dihydrofuran and similar alkenes. A huge increase in catalyst stability has been accounted for by the inhibition of deligation of palladium catalyst, so that lower amounts of ligand can sustain the Pd(0) state. High pressure is also likely to favor association−dissociation ligand exchange mechanisms involving five-coordinate intermediates.[188]

The increase of oxidative addition with pressure rate makes it possible to perform reactions with substrates, practically unreactive under normal pressure, e.g., to perform differential Heck reaction by substituting a better leaving group (nonaflate) at normal pressure and poorer leaving group (chlorine) at high pressure[189] as well as to use bromoderivatives in place of iododerivatives (Scheme 94).[190,191]

Scheme 94

A	Yield
Pd(OAc)$_2$, 3PPh$_3$, KOAc, Bu$_4$NBr, DMF, 80°C	< 10%
Pd(PPh$_3$)$_4$, NEt$_3$, MeCN/DMF 60°C, 10 *kbar*	70%

B. Less Usual Media

Though virtually all solvents seem to have been used for Heck reactions, the most useful are polar aprotic solvents having an ability to additionally support palladium complexes by weak coordination, such as MeCN, DMF, DMA, NMP, etc., suitable for all kinds of reactions. The search for alternative media for Heck chemistry is targeted at the development of highly productive, environmentally safe, recyclable techniques which can be promoted to large-scale applications.

1. Aqueous Heck Chemistry

Palladium-catalyzed processes including the Heck reaction, Suzuki and Stille cross-coupling, Sonogashira reaction, carbonylation, hydrogenation, hydrogenolysis, and Wacker-type oxidation can be run in the presence of water or in mainly aqueous environments.[192] The use of aqueous solvents pursues such utilitarian goals as the development of environmentally and technologically safe processes but also brings a new dimension into the chemistry of palladium-catalyzed reactions.

Water is one of the most polar solvents known. As such it must have an accelerating influence on the Heck reaction as it promotes the migratory insertion to follow the cationic mechanism. Therefore, the effect of water must be more pronounced for underligated

and phosphine-free systems. However, we have to admit that nothing is known so far about the influence of water on the oxidative addition reaction. This influence may even be negative. The processes in which oxidative addition is TOF-limiting stage, e.g., the reactions of aryl chlorides and unactivated aryl bromides, have not been hitherto seen to benefit from aqueous techniques.

Water is a good ligand for palladium—strongly bonded but kinetically labile. Brown has estimated a stability constant for the hydration equilibrium as 500 M^{-1}.[90] Water is thus a good placeholder ligand, particularly effective in phosphine-free reactions. Due to the high concentration in aqueous solvents (water is often added in 5−10 vol % amounts, which corresponds to 3−6 M concentrations giving a huge excess over the palladium catalyst), water is able to displace other labile ligands from the coordination shell of palladium, particularly iodide which poisons the catalyst and blocks the cationic path. Water literally washes iodide and other interfering ligands out of the coordination shell. Again, this is not always good as water equally well washes off some helpful ligands, for example, acetate. Jeffery noted a negative influence of water on the reactions in which acetates of hydrocarbonates were used as bases.[162]

Moreover, the aqueous environment has an effect similar to the effect of high pressure discussed above, as hydrophobic interactions make more compact transition states more favorable. Therefore, highly aqueous media must exert an influence on the rates and regioselectivities of Heck reactions, particularly intramolecular cyclizations, in a way similar to a well-known effect of water on Diels−Alder reactions, Claisen rearrangement, etc.[192] Indeed, a positive effect of water on the intramolecular Heck reaction has been noticed and exploited (the examples can be found throughout this review), though so far such examples are rare and, as far as we know, no rationale for the effect of water has been given.

Still, water has been allowed to enter Heck chemistry only relatively recently. The traditional technique for carrying out the Heck reaction has been to use anhydrous polar solvents (DMF and MeCN are most frequently used) and tertiary amines as bases.

First, it was shown that the Heck reaction can be accomplished under PTC conditions[154] with inorganic carbonates as bases under very mild conditions even at room temperature. The reactions were carried out in a liquid−liquid system. As the reaction in such systems actually runs in the nonaqueous phase formed by organic reagents, this case cannot be regarded as a true aqueous Heck process.

Water and aqueous organic solvents can be successfully used for carrying out the Heck reaction in the aqueous phase catalyzed by simple palladium salts in the presence of inorganic bases K$_2$CO$_3$, Na$_2$CO$_3$, NaHCO$_3$, or KOH.[193] The reaction of water-soluble acrylic acid with aryl iodides and bromides with both electron-donating and electron-withdrawing substituents can be easily carried out in DMF−H$_2$O or HMPA−H$_2$O mixtures with a water content

from 10% to 80% (v/v) at 70−100 °C in the presence of Pd(OAc)$_2$ as catalyst precursor and K$_2$CO$_3$ as base. Aryl bromides required the addition of P(o-Tol)$_3$ (Scheme 95).

Scheme 95
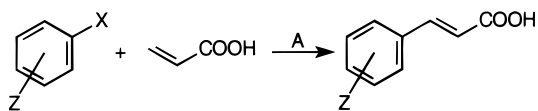
A: PdCl$_2$, Na$_2$CO$_3$, DMF-H$_2$O, HMPA-H$_2$O or H$_2$O, 100°C
X = I, Br;
Z = H, p-Cl, p-MeO, p-Me, p-Ac, p-NO2, p-CHO, p-OH, m-COOH

Arylation of acrylonitrile can be carried out in phosphine-free mode either in aqueous HMPA for water-insoluble aryl iodides or neat water for water-soluble iodobenzoate and iodophenolate.[194]

The presence of water in the solvent has a definite positive influence on the reaction rate and eficiency of the catalytic system. Thus, the reaction of bromobenzene with acrylic acid catalyzed by Pd(OAc)$_2$ in the presence of P(o-Tol)$_3$ and K$_2$CO$_3$ gave only 12% of cinnamic acid in DMF while on addition of 10% (v/v) or more of water the yield increased to nearly quantitative. The beneficial effect of water on the rate of phosphine-free Heck reaction of PhI with methyl acrylate in N-methylpyrrolidone solvent has been noticed.[195] The addition of water has been found to promote the formation of palladium nanoparticles, which evidently served as a precatalyst, similar to that observed for the reactions in microemulsions (cf. above).

The reaction with water-soluble iodoarenes, such as o-iodobenzoic acid, showed record making turnover numbers. As low as 0.0005 mol % Pd(OAc)$_2$ was sufficient to achieve full conversion, which is equivalent to 200 000 catalytic cycles.

The arylation of styrene can be achieved in a biphasic system with an aqueous solution of K$_2$CO$_3$ forming one phase and styrene plus aryl halide forming another phase, in the presence of either 10 mol % of Bu$_3$N or 5 mol % Bu$_4$NBr. A broad range of aromatic and heteroaromatic bromides and iodides can be thus transformed into the corresponding stilbenes. The reaction with less reactive aryl bromides bearing electron-donating substituents, such as o-bromoaniline or 5-bromo-2-aminopyridine, gave better results if carried out in aqueous DMF with a high content of water in the presence of inorganic base such as K$_2$CO$_3$ (Scheme 96).

Scheme 96
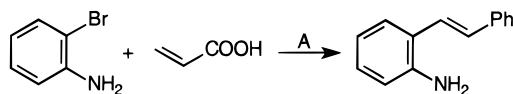
A: PdCl$_2$, 4(o-Tol)$_3$P, K$_2$CO$_3$, DMF-H$_2$O (2:5, v/v), 100°C

The arylation of allyl and vinylphosphonates can be performed in aqueous DMF with sodium hydroxide or carbonate as base. This approach allows not only the lowering of the reaction temperature from 100 to 70−80 °C and an increase of the yield of

products, but also a marked shortening of the time of reaction, as high yields are typically achieved in 1 h as compared with 12−16 h needed for the conventional procedure. The reaction is stereospecific to give E-isomers:[196] The arylation of allylphosphonates in aqueous DMF in the presence of NaOH at 75−80 °C leads exclusively to γ-arylallylphosphonates. The aqueous phosphine-free procedure is milder and more selective than phosphine-assisted reaction in anhydrous solvent.[196]

A marked positive effect of water was observed in Heck reactions of 2,3-dihydrofuran with iodo- and bromoderivatives of pyrimidines and other nitrogen-containing heterocycles.[197] In several cases the reactions which could not be achieved under conventional conditions (DMF, Et$_3$N + NaOAc as base) and took place in aqueous ethanol (1:1, v/v) with NaHCO$_3$−Et$_3$N mixture in the presence of Bu$_4$NCl. Another notable feature of the reactions in aqueous solvent was a partial or full suppression of double-bond migration. This procedure has been applied to a protected glycal giving an approach to C-nucleosides (Scheme 97).

Scheme 97
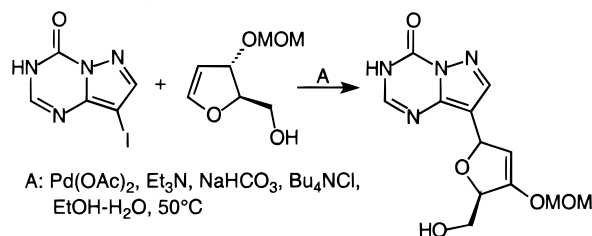
A: Pd(OAc)$_2$, Et$_3$N, NaHCO$_3$, Bu$_4$NCl,
   EtOH-H$_2$O, 50°C

This example represents another field of application of aqueous procedures—the synthesis and modification of naturally ocurring molecules. Indeed, compounds such as carbohydrates, nucleosides, amino acids, etc., are strongly hydrophilic. To perform reactions in organic solvents, such compounds must be first modified and hydrophobized. It would be desirable to have methods allowing the processing of such compounds under near-to-native conditions, e.g., in aqueous media where no heavy protection by large hydrophobic groups is required. In a further example, the modification of 2-bromo-D-glucal has been realized in aqueous solvents (Scheme 98).[198]

Scheme 98
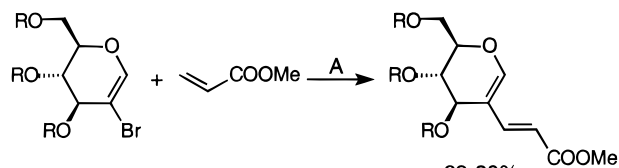
R = H or Ac
A: Pd$_2$(dba)$_3$ (1-5 mol%), 2P(o-Tol)$_3$, Et$_3$N or K$_2$CO$_3$/Bu$_4$NHSO$_4$,
   MeCN-H$_2$O or DMF-H$_2$O, 80°C, 21-30 h
62-90%

The intramolecular Heck reaction on a carbohydrate template carried out in aqueous solvent has been shown to lead to a bicyclic derivative to provide a unique case of Heck cycle termination through the elimination of alkoxy group (Scheme 99).[199,200]

Methyl acrylate reacts with 5-iodo-2,4-dimethoxypyrimidine under aqueous phase-transfer conditions

Scheme 99
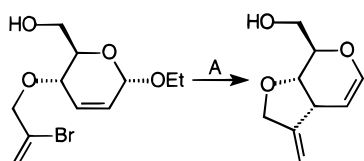
A: Pd(OAc)$_2$ (5 mol%), 2PPh$_3$, Et$_3$N,
Bu$_4$NHSO$_4$, MeCN-H$_2$O, 80°C

at room temperature, giving high yields of product on a multigram scale (Scheme 100).[201]

Scheme 100
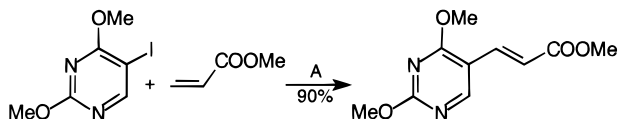
A: Pd(OAc)$_2$ (7 mol%), 2PPh$_3$, K$_2$CO$_3$, Bu$_4$NHSO$_4$, H$_2$O, r.t.

The aqueous protocol has been applied to Heck reactions with immobilized iodoarenes used to build combinatorial chemistry libraries.[202] There is contradictory evidence on the influence of water on the reactions with immobilized reagents. A detrimental effect of water, reported for instance in ref 170, can be accounted for by folding of the polymeric support to limit diffusion of soluble reagents, and thus, it must be dependent on the content of water.

Reactions in highly aqueous environments are restricted to water-soluble reagents or are run in heterogeneous phase-transfer-assisted systems. In search of a general approach to process all sorts of substrates—hydrophilic and hydrophobic—in aqueous media with high water content, the application of aqueous solubilized systems (microemulsions, swollen micelles, Winsor systems) has been proposed.[184] Kinetic measurements with a model Heck reaction of 4-vinylpyridine with 4-N,N-dimethylaminoiodobenzene showed that microemulsions are roughly equivalent to aqueous DMF concerning the media effect on the rate. Similar performances have been noted for systems built with anionic or cationic surfactants.

Phosphine-assisted catalysis in highly aqueous systems requires water-soluble (hydrophilized) ligands. Lots of such ligands have been developed (see for instance ref 192 and references therein). Sulfonated phosphines constitute the largest subset,[203−219] of which TPPMS (Ph$_2$PC$_6$H$_4$-m-SO$_3$Na), and particularly the extremely hydrophilic TPPTS (P(C$_6$H$_4$-m-SO$_3$Na)$_3$) are considered as the basic choice.

Heck reactions have been conducted in homogeneous aqueous systems in the presence of water-soluble phosphines TPPMS[212] and TPPTS. Reactions of iodoarenes and iodoalkenes in aqueous MeCN can be conducted under very mild conditions at temperatures not exceeding 40 °C (Pd(OAc)$_2$ (2.5 mol %), 2TPPTS, Et$_3$N, MeCN−H$_2$O (15:1), 25−40 °C). Notable is the ease and high regioselectivity of reaction with cycloalkenes, giving exclusively 3-arylcycloalkene (Scheme 101).[220]

Moreover, the use of an aqueous catalytic system leads to the dramatic change of the regioselectivity

Scheme 101
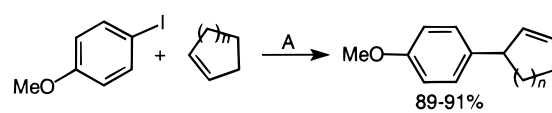
A: Pd(OAc)$_2$ (2.5mol%), 2TPPTS, NEt$_3$, MeCN-H$_2$O, 25-37°C

of ring closure. While a standard method of Heck-type cyclization (anhydrous solvent, Ag$_2$CO$_3$ as the base) is well-known to give the product of *exo* cyclization, the aqueous method gave predominantly the *endo* product (Scheme 102).[221]

Scheme 102
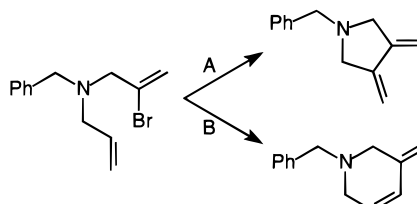
A: Pd(OAc)$_2$, Ph$_3$P, Ag$_2$CO$_3$, (i-Pr)$_2$NEt, MeCN, 90°C
B: PdCl$_2$, TPPTS, (i-Pr)$_2$NEt, MeCN-H$_2$O, 70°C

This interesting trend, which is not simple to explain, has been confirmed in a study of the cyclization of a series of N-ω-alkenyl-N-methyl-o-iodoanilines.[222] While the reaction using either the standard phosphine-assisted method or the phosphine-free phase-transfer method gave exclusively the products of *exo-trig* cyclization, the reaction in an aqueous system in the presence of TPPTS gave ample amounts of the *endo* product (Scheme 103).

Scheme 103
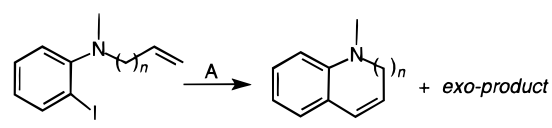
n = 1, 2, 3   17-28%   72-83%
A: PdCl$_2$ (10 mol%), 2TPPTS, (i-Pr)$_2$NEt, MeCN-water, reflux

The search for other hydrophilic ligands useful for the Heck reaction has not, so far, brought spectacular improvements (cf., e.g., ref 219). Thus, a series of water-soluble sulfonated dibenzofuranylphosphine ligands was prepared with a goal to develop a reliable set of water-soluble ligands[223] which can be easily prepared in high yields avoiding usual problems encountered with other sulfonated phosphines, usually prepared by sulfonation under harsh conditions giving modest yields. The dibenzofurane residue is selectively sulfonated at the free position *para* to oxygen atom under very mild conditions, as the sulfonato group enters the ring which is not deactivated by protonation of phosphorus (Scheme 104).

Scheme 104
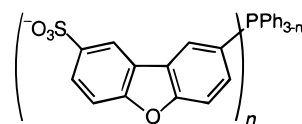
The ligands were employed in monophasic aqueous Heck arylations in MeCN−water mixture and in neat water to show results which are inferior to those obtained under similar conditions with TPPTS ligand. High water content was needed because the ligands are practically insoluble in organic solvents, which could potentially be used for easy recycling of catalyst, though this has not been reported. Two intramolecular and two intermolecular reactions were described, with one example shown in Scheme 105.

Scheme 105

A: Pd(OAc)$_2$, 3L, MeCN-H$_2$O (1:1), Et$_3$N
or H$_2$O, Na$_2$CO$_3$, 95°C
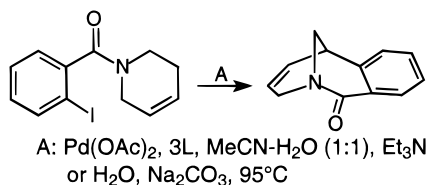
2. Molten Salts

The use of molten salts as media (the so-called nonaqueous ionic liquids[224]) allows for both easy recycling of catalytic system (e.g., due to temperature-dependent miscibility with nonpolar solvents and water[31]) and possible activation of catalyst.[225,226] Molten salts are highly polar, thus facilitating the cationic mechanism of Heck reactions, and can contribute to the stabilization of underligated Pd(0) species by forming anionic complexes with halide ions. The following molten salts were used: n-Bu$_4$-NBr, Ph$_3$MePCl, Ph$_3$MePBr, n-Bu$_3$-n-C$_{16}$H$_{33}$NBr, and 1-methyl-3-propylimidazolium bromide. The simplest salt of the series n-Bu$_4$NBr performed the best and thus was recommended as a basic choice for such media.[226] Better stability of underligated palladium complexes is revealed by enhanced reactivity of PhCl. Chlorobenzene reacts in a melt with styrene (NaOAc as base, 130 °C, 14−24 h) in the presence of 0.5 mol % of the Herrmann's palladacycle catalyst hc giving arylation products (1,1-diphenylethylene, Z- and E-stilbenes in 3−15:0−3:85−96 ratio, depending on conditions). Moreover, molten n-Bu$_4$NBr made possible the first sensible example of the Heck reaction of chlorobenzene in a phosphine-free system to yield 28% conversion of PhCl on 16 h heating in the presence of 1 mol % Pd(OAc)$_2$. Even better results with twice as high yields were obtained on further optimization of reaction conditions.[227] This finding may be actually the most important result of this work, as it shows that chloroarenes can react under reasonable conditions without any expensive and nonrecoverable additives, which would completely eliminate any economical advantages gained by the replacement of bromo- and iodoarenes. The best TONs and yields are nevertheless obtained if Herrmann's palladacycle catalyst is helped by Ph$_4$PCl or especially Ph$_4$AsCl additives in 6−20 mol % amounts. Activated chloroarenes (p-NO$_2$, p-Ac, p-CF$_3$) react under these conditions giving quantitative conversions requiring the promoter phosphonium or arsonium salts in only an equimolar amount with respect to the catalyst. A record making TON of about 10 00 (higher than any TON value ever observed for a chloroarene) was obtained in the reaction of p-chloroacetophenone in the presence of Ph$_4$AsCl. No promoters are required for achieving quantitative conversions for the reactions of bromoarenes bearing either donor or acceptor substituents with styrene. The recycling is achieved by evaporation of organic materials from the reaction mixture, and thus all inorganic byproducts and tars are retained in the media, thus limiting its lifetime. Still, the activity was shown to be retained almost fully after eight cycles in which 3 g of ionic melt of Bu$_4$NBr was used to process a total amount of ca. 3 g of PhBr with a total TON roughly equal to a very decent value of 1520, thus making the whole process economically viable.

The results obtained in Bu$_4$NBr melt were consistently higher than results obtained with the same catalytic system under the same conditions but in DMF solvent. The catalytic system is generally more stable in the melts than in conventional homogeneous media.[227]

Further development of the ionic melt protocol involves the use of salts which are liquid even at room temperature and immiscible both with water and hydrocarbons: 1-butyl-3-methyl-imidazolium (bmim), 1-pentyl-3-methylimidazolium (pmim), and 1-hexyl-pyridinium (C$_6$py) cations and chloride, BF$_4$, or PF$_6$ as counteranions.[228] Though the procedure is announced as multiphasic, the reaction itself is carried out in a single phase of molten salt. The reaction of iodobenzene with ethyl acrylate proceeds smoothly in phosphine-free mode in chloride-containing melts of C$_6$pyCl salt and give quantitative yields of ethyl cinnamate even at 40 °C with either Et$_3$N or NaHCO$_3$ as base (2 mol % Pd(OAc)$_2$). The addition of Ph$_3$P retards the reaction this system. Imidazolium salts were inefficient in the absence of phosphine ligands at temperatures below 100 °C, possibly due to the formation of carbene complexes, which release catalytically active palladium only at higher temperatures (vide supra). However, in the presence of Ph$_3$P, the system based on (bmim)PF$_6$ salt and Et$_3$N as base gave quantitative yields at 100 °C. The system is easily rejuvenated after reaction by extraction of triethylammonium iodide with water and the product with cyclohexane. After this procedure, the system is charged with fresh reagents and base and the catalytic process is restarted without a loss of activity. As many as six of such cycles were repeated to give a total TON of about 300 (average TOF = 50 h^{-1}). Certainly, this parameter is easily outperformed by a lot of more simple systems in one run, but otherwise the ionic liquid process appears as one of the cleanest recyclable procedures so far described for the Heck reaction, because the catalyst-holding phase is declared to be purged from all products and byproducts. If this is true, then the lifetime of catalyst with due care may be practically unlimited. Besides this, the system possesses an impressive capacity which cannot be rivaled by any conventional solvent, as 5 g of the molten salt is used to process 2 g of PhI in one run (or 12 g or more than twice as the amount of melt in six runs).
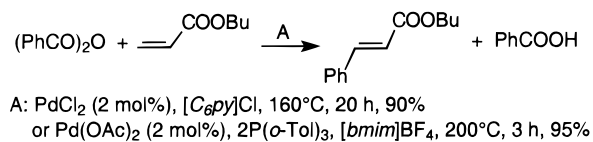
Unfortunately, imidazolium salt melts were independently shown by several researchers to be inef-

fective for processing chloroarenes. Still, ionic melts of imidazolium salts can be positioned as one of the best recyclable systems for processing bromoarenes, even as unreactive as 4-bromoanisole. At 140 °C the conversion reaches 94% (TOF = 2.6 h^{-1}) in (bmim)-PF$_6$ in the presence of Et$_3$N. The yield may be slightly improved by the addition of such ligands as Ph$_3$P, o-Tol$_3$P, dppf, and Ph$_3$As, though (PhO)$_3$P, dppe, and Ph$_3$Sb gave poor results. As the system operates at 140 °C, the respective carbene complex can form and take part in the process by maintaining the pool of palladium precatalyst, at least in the absence of other ligands. At 100 °C, the reaction gave good yields only in the presence of Ph$_3$P and o-Tol$_3$P ligands.

Indeed, the formation of carbene complexes in imidazolium salt melts has been recently proven. Moreover, it has been shown that only bromide salt melt (bmim)Br gives rise to carbene complexes, while no such complexes were detected on heating palladium salts in tetrafluoroborate salt melt (bmim)-BF$_4$. In parallel with this finding, it has been shown that (bmim)Br melt is much more efficient as a media for the Heck reaction, particularly with less reactive substrates, than (bmim)BF$_4$ melt.[229] Thus, it may be argued that carbene complex serves as a temporary storage for palladium, keeping it from deactivation through reduction to Pd(0) and nucleation of inactive metal particles.

Benzoic anhydride can be used as a substrate in molten salts in a base-free Heck reaction (Scheme 106).[228] Here, the revitalization of the catalytic

Scheme 106

(PhCO)$_2$O + ⟋COOBu →[A] ⟋COOBu (Ph) + PhCOOH

A: PdCl$_2$ (2 mol%), [C_6py]Cl, 160°C, 20 h, 90%
or Pd(OAc)$_2$ (2 mol%), 2P(o-Tol)$_3$, [$bmim$]BF$_4$, 200°C, 3 h, 95%

system is achieved by extraction of both the product and the byproduct PhCOOH with ether. The reaction is done in phosphine-free mode in chloride-containing melt, while the imidazolium salts with nonnucleophilic counterions require the presence of phosphine and are run at extreme temperatures.

3. Supercritical and Subcritical Fluids

Supercritical fluids draw considerable attention as promising media for organic reactions.[230] Supercritical CO$_2$ is considered as one of the most perfect environmentally friendly solvents. Though CO$_2$ itself is an environmentally unwanted greenhouse gas, it can be more easily and quantitatively recycled than any other liquid used as solvent to allow the design of a true waste-free technology. Therefore, the attempts to use it as solvent for such an important process as the Heck reaction cannot be overlooked.

Liquid CO$_2$ is a good solvent for organic compounds but very poor solvent for inorganic salts and complexes. Solvent properties of CO$_2$ resemble those of fluorinated liquids (so-called fluorous systems, vide infra). An increase in solubility is achieved by attaching fluorinated ligands, though the degree of fluorination sufficient for solubilization of a given compound in CO$_2$ is less than that in true fluorous

systems requiring sophisticated perfluorinated molecules with 60% or more fluorine content. Phosphines, bearing fluorine-containing groups, even as simple as tris(trifluoromethyl)phosphine were found to assist in the Heck reaction in supercritical CO$_2$.[231,232]

Later it was shown that the solubilization of palladium catalyst can be more simply achieved by using a fluorine-containing precatalyst.[233] Quite surprisingly, the best choice of catalyst precursor turns out to be Pd(OCOCF$_3$)$_2$, which is never used in more conventional media as it is known to be a rather strong electrophile and oxidant. Both this salt and palladium hexafluoroacetylacetonate (also a nontrivial choice because the metal in this complex is strongly chelated and could be assumed not to open the coordination shell for catalytic transformations under relatively mild conditions) in conjunction with all types of phosphine ligands (PPh$_3$, P(o-Tol)$_3$, P(2-furyl)$_3$ but also tributyl and tricyclohexylphosphine) catalyze the phenylation of methyl acrylate by PhI (80 °C, 1600 psi, EtN(i-Pr)$_2$ as base, 15−24 h) in excellent yields, though still rather low efficiency. A phosphine-free process can also be realized though it requires as much as 6 mol % of rather expensive Pd(OCOCF$_3$)$_2$ to achieve high yields and conversions. The original Hermann's palladacycles are poor catalysts, but a similar palladacycle obtained by cyclopalladation of tris(o-tolyl)phosphine by Pd(OCOCF$_3$)$_2$ is a good catalyst. Notable is that this sort of palladacycle seems to be activated at lower temperatures than **7**, so probably it is worth trying in other Heck reactions to overcome a well-known drawback of palladacycles operating only at temperatures above 100 °C.

The use of palladium on charcoal allowed avoidance of the problems associated with solubilizing palladium catalysts in scCO$_2$. The method is applicable to aryl iodides and gives moderate to good yields after prolonged exposure. (Scheme 107).[234]

Scheme 107

ArI + ⟋Z →[A] ⟋Z (Ar)

A: Pd/C, Et$_3$N, scCO$_2$, 80°C, 100 bar, 60 h
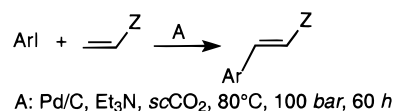
Besides CO$_2$, water is an appealing choice for building environmentally friendly technologies. Reactions in overheated water have little to do with the aqueous chemistry discussed above. Near the critical point (373 °C, 221 bar), water loses its famous structure and turns into a nonpolar liquid with ϵ close to 6, which leads to a dramatic increase of the solubility of organic compounds and makes it a good solvent even for reactions with hydrophobic substrates.[235] Even at much lower temperatures, above 200 °C the polarity of water is greatly diminished to match that of aliphatic alcohols. Several reports on the use of overheated water for Heck arylations have been published.[236,237] The reactions can be run in both overheated water (260 °C) and supercritical water (400 °C), though with the latter solvent all kinds of side reactions (hydrogenation, hydrogenolysis, etc.) occurred. Olefins can be generated in situ from the corresponding bromoderivatives by elimination of

HBr but not from chlorides, alcohols, or esters with the only exclusion of β-phenylethanol, which behaved as a source of styrene. All kinds of palladium derivatives, either with or without phosphine ligands, catalyze the reactions. Aryl iodides, bromides, chlorides, and triflates as well as vinyl halides are all reactive, and the scope of olefins which take part in the reaction is also quite broad and included styrene, methacrylic acid and esters, allyl halides, etc., though under such harsh conditions the initial products of arylation underwent a partial destruction, e.g., by ester hydrolysis and decarboxylation (Scheme 108).

Scheme 108

A: Pd(OAc)$_2$, NaHCO$_3$, H$_2$O, 260°C
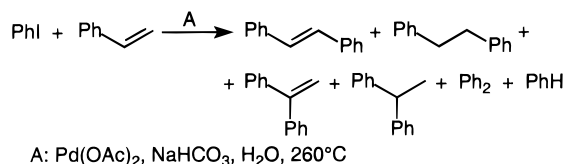
The formation of considerable amounts of 1,1-diphenylethylene can be regarded as a token of the involvement of a cationic palladium intermediate, though the realization of the cationic route in such a nonpolar media is doubtful. Simple alkenes and iodoar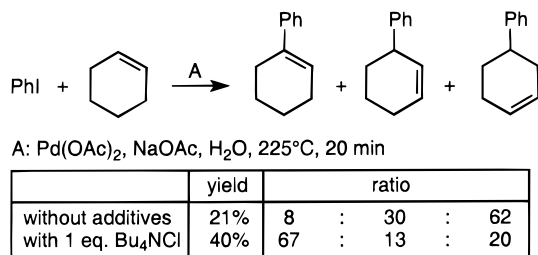enes with donor groups did not react. Later this was ascribed to design flaws of the reactors used, as incomplete loading of reactor with water might have resulted in the formation of gaseous-phase overcompressed liquid water and thus volatile organics might have escaped the reaction mixture. In the latest effort,[238] the temperature of water was diminished even more to 225 °C but the reactor was completely filled with water to exclude gaseous pockets. Under such conditions, arylation went smooth and very fast to involve all sorts of iodoarenes and cycloalkenes, which sluggishly react under conventional conditions. The main problem of high-temperature water reactions is the degradation of products on longer exposure; thus, conversions have to be kept low (20−50%). Interestingly enough, the addition of tetrabutylammonium chloride has a strong influence on the yield and regioselectivity resulting in the predominate formation of the most stable conjugated olefin (Scheme 109).
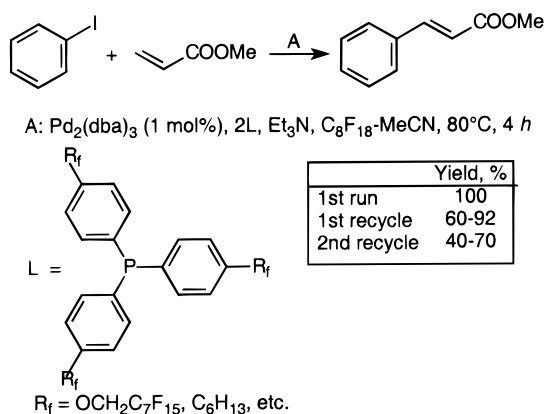
Scheme 109

A: Pd(OAc)$_2$, NaOAc, H$_2$O, 225°C, 20 min

	yield	ratio				
without additives	21%	8	:	30	:	62
with 1 eq. Bu$_4$NCl	40%	67	:	13	:	20

4. Fluorous Systems

The success of aqueous biphasic catalysis brought about several imitations, of which the most famous and ambitious is the so-called *fluorous* (a hybrid of words *fluorine* + *aqueous*) catalysis employing a specific affinity of fluorinated compounds for perfluorinated solvents. The solubilization of the catalyst requires the use of fluorinated ligands with high fluorine content. Such solvents are not miscible with most organic solvents, which allows the design of biphasic systems in which the product is extracted from a reusable catalytically active fluorous phase. This protocol has been applied to a number of catalytic processes with a variable degree of success.[239,240] The Heck reaction in a fluorous system has been reported very recently[241] to involve palladium complex with triphenylphosphines modified by long fluorinated tails in a biphasic system fluorocarbon−MeCN (Scheme 110).

Scheme 110

A: Pd$_2$(dba)$_3$ (1 mol%), 2L, Et$_3$N, C$_8$F$_{18}$-MeCN, 80°C, 4 *h*

	Yield, %
1st run	100
1st recycle	60-92
2nd recycle	40-70

R$_f$ = OCH$_2$C$_7$F$_{15}$, C$_6$H$_{13}$, etc.

As can be seen, the first attempt to assemble a fluorous Heck system shows that though the catalyst has a good activity in the first run, the system is subject to considerable loss of activity in each recycle either because of partial deactivation of catalyst due to formation of Pd black or because of partitioning of palladium species into MeCN. It could not even be excluded that the reaction itself proceeds not only in fluorous, but also in the common organic phase. The attempt to bind the catalyst to fluorous phase more strongly with addition of 4 equiv of fluorous phosphine resulted in a full suppression of the catalytic process, which might be regarded as extra evidence in favor of reaction in nonfluorous phase as an inhibition of the Heck catalytic cycle by excess phosphine is never so dramatic in conventional systems.

C. Recyclable (Phase-Separation) Catalysis

The increase of catalytic activity is not the sole solution of the task to increase the productivity of a given catalytic system per unit load of precious catalyst. The other solution is to build a recyclable system[242] in which the catalyst can be easily separated from the products and recycled through a separate rejuvenation procedure. In the best cases the catalyst can be reused several times as is before being rejuvenated.
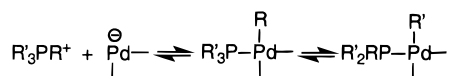
Heck reactions are a tough challenge for designing recyclable systems. First of all, as we noted earlier, the catalytic cycle is unstable, very responsive to various factors. The reaction needs at least three reagents (electrophile, unsaturated substrate, base) besides additional promoter additives and the catalyst itself and breeds, besides the product, the

conjugate acid of base and the leaving group, which yield a salt. The salt is accumulated in the reaction media and in one way or another leads to the degradation of the catalytic system (poison the catalyst, increase the ionic strength of media changing the solubility parameters, form a precipitate which captures the catalyst, etc.). If we view the Heck cycle as a sophisticated engine, the wastes it produces cause it to wear in time, be choked. Indeed, in all cases where TOF has been measured as a function of time, this parameter steadily decreases after a short period of the peak activity. Any engine works well only in a stationary environment. Due to the change of reaction mixture composition, the Heck process always works in a varying environment. In this respect processes such as hydrogenation or hydroformylation, in which no salt-like side products are formed, are much more suitable for designing recyclable systems, and indeed, the most famous examples of such were realized for these reactions.

The wear of the Heck engine is also associated with the depletion of catalyst. In the case of phopshine-assisted systems, a serious problem comes from the participation of phopshine ligand in such reactions as the exchange of hydrocarbyls between palladium and phosphine[42,243,244] or the reductive elimination of phopshonium cation (Scheme 111).

Scheme 111

$$R'_3PR^+ + \overset{\ominus}{\underset{|}{Pd}}- \rightleftharpoons R'_3P-\overset{R}{\underset{|}{Pd}}- \rightleftharpoons R'_2RP-\overset{R'}{\underset{|}{Pd}}-$$

Nevertheless, due to the industrial importance of the Heck reaction, work on designing recyclable systems is continuing, and already lots of approaches have been tested and brought encouraging results. Perhaps, the main idea of all is to heterogenize the reaction system so that products and catalysts can be tied to different phases (the phase-separation catalysis). The phase-separation approach has one additional advantage—it might be possible to find systems which can, due to thermodynamic reasons, sustain a stationary state of the reaction in a subsystem (e.g., one of the phases or microscopic domains which function as self-sustained micro- or even nanoreactors). In this case, the system itself may correct the inborn flaw of the Heck catalytic engine being choked by its own wastes, and the task to build a highly efficient recyclable wearless process may not be so hopeless.

Recyclable systems may be built in solid–liquid and liquid–liquid modes.

1. Liquid–Liquid Systems

In biphasic liquid–liquid system, the reagents and products are held in the organic phase while the catalyst is held in a different nonmiscible phase like water or other hydroxylic solvents, of which ethylene glycol is the most popular.[245] The prototypes of these systems are well-known profitable industrial processes—the hydroformylation of propylene[246] and Shell Higher Olefin Process (SHOP).

The catalyst can be bound to aqueous or similar polar hydroxylic phase by the hydrophilic ligands discussed above in the section devoted to aqueous catalysis.

The reaction in a biphasic system may be thought to proceed at the interface, but this is hardly so because of too severe mass-transfer restrictions. As the interfacial tension between water and low-polar organic liquids is very high, the area of the interface is small even with vigorous stirring. Actually, the reaction proceeds in the polar phase and the rate depends on the solubility of organic reagents in this phase. Therefore, separation and catalytic efficiency come to a contradiction.

A biphasic toluene-ethylene glycol system based on the TPPTS ligand has been reported for the standard Heck reaction of PhI with acrylates and styrene.[247] Four equivalents of TPPTS was needed to make the system stable and suppress leaching of palladium into organic phase. The catalytically active ethylene glycol layer can be reused no less than three times without loss of activity. As soon as this layer accommodates liberated KI, the number of reuses of the catalytic broth ought to be limited. The activity of this system is quite meager (TON 100, TOF less than 10), being most likely limited by mass-transfer. In the same system the complexes of other metals were tested, and those of Ni, Ru, Co, and Pt were found to be capable of driving Heck transformation (cf. below). Though all showed inferior activity in comparison with Pd, Ni(OAc)$_2$ and RuCl$_3$ showed comparable activity only twice as low as that of the Pd system. Moreover, nickel-catalyzed system required only 2 equiv of expensive TPPTS. The sparing use of the ligand is particularly important in this case, since nickel is much cheaper than the sulfonated phosphine.

Liquid CO$_2$ at pressures both below and above the critical point has been used to form the second nonpolar phase in biphasic catalysis with TPPTS as ligand and water or ethylene glycol as the catalyst-containing phase for reaction of PhI with n-butyl acrylate (5 mol % Pd(OAc)$_2$, 4TPPTS, Et$_3$N, 60 °C, 1–140 bar, 17 h).[248] The results clearly show that CO$_2$ actually inhibits the reaction as the best conversion (68%) and TONs (135) were obtained at 1 bar, at which pressure the occurrence of liquid CO$_2$ in a closed reactor is very unlikely, and thus, the second phase is formed just by liquid organic reagents. The conversions fall to 36–45% at pressures above the critical pressure, possibly because liquid supercritical CO$_2$ is a very poor solvent for polar molecules and the solubility of catalyst in such liquid is negligible. Therefore, the reaction falls victim to the well-known paradox of biphasic reactions—the better the separation of reagents and catalyst in different phases, the lower the rate of reaction. However, from a technological point of view, it is the poor solubility of catalyst in the organic phase that is the raison-d'être of biphasic catalysis, as it limits the leak of catalyst and enables an efficient near-quantitative recycling. Thus, though the first results obtained with Heck

reactions under biphasic catalysis conditions with scCO$_2$ are rather poor, the idea itself may be fruitful.

The increase of productivity of biphasic systems may be sought in two ways: (i) designing systems in which phase-separation can be controlled by, e.g., temperature, and (ii) increasing the area of contact between phases.

Controllable phase-separation is achieved (i) by selecting solvents with temperature-dependent miscibility (those which exhibit the so-called *miscibility gap*) and (ii) by designing thermomorphic ligands with temperature-dependent solubility (cf. ref 249 and references therein).

The latter principle mimics nature—the behavior of carbohydrates or their technical ersatz poly-(ethylene glycol)s which are strongly hydrophilic at ambient temperature but lose hydration water and become increasingly hydrophobic on heating. Therefore, the reactions catalyzed by such catalysts at elevated temperatures are likely to proceed not in aqueous (polar) layer, but rather in nonpolar phase, which should have a large positive effect on the rate.

The use of triphenylphosphine attached to the residues of three natural carbohydrates—D-glucose, D-galactose, D-*N*-acetylglucosamine—were tested in a biphasic system xylene—ethylene glycol. Compared with the performance of TPPTS ligand under the same conditions, the productivity increased by about an order of magnitude because at the temperature of the experiment the ligands became less hydrophilic and were partitioned between xylene and ethylene glycol phases. The catalytic reaction runs in the nonpolar phase, while on cooling the catalyst returns to the polar phase for easy recycling (Scheme 112).[250]

Scheme 112

|	TON
TPPTS	78
*Gal*OPDPP	880
AcNH*Glu*OPDPP	850
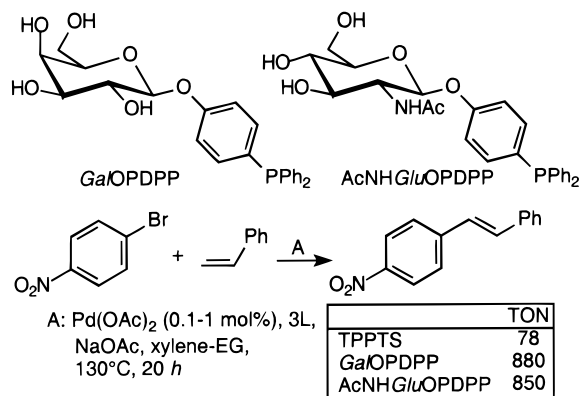
Increasing the area of contact between immiscible phases can be achieved through the distribution of one of the phases over a solid support with a huge surface area in a way similar to that common in chromatography with liquid stationary phases (such as GLC). The result is referred to as supported liquid-phase catalysis (SLPC).[251] The catalyst is dissolved in the supported liquid phase, and otherwise the system works as common biphasic liquid—liquid catalysis. The application of such an approach to the Heck reaction has been described.[252] Special sorts of mesoporous silica with a narrow distribution of pore size (the so-called controlled porosity glasses) are usually applied as supports. The support is impreg-

nated with a solution of PdCl$_2$ or Pd(OAc)$_2$ and TPPTS or TPPMS ligands in ethylene glycol. The resulting catalyst has a modest activity in reactions of iodoarenes with methyl acrylate (1—5 mol % Pd, Et$_3$N, hexanes—Et$_2$O as bulk solvent, reflux, 1—2 days) and displayed a very low level (<1 ppm) of Pd leach. Unfortunately, reused catalyst showed a strongly degraded performance, likely due to solubilization of Et$_3$NHI in the supported phase.

A further development of the supported liquid phase concept utilizes derivatized silica supports widely used in high-performance liquid chomatography. Various residues (ranging from simple hydrocarbon tails to complex molecules capable of specific binding to a certain class of molecules) are bonded to silica surface onto residual silanol groups via a silane link. The bonded phase resembles, to a certain degree, a physically absorbed liquid film, and thus, this approach can be categorized as a kind of SLPC.

The silica derivatized with octyltrimethoxysilane (such sorbents are named C$_8$-silica in chromatography applications) was used for obtaining the Heck reaction.[253] This coat is hydrophobic enough to hold organic molecules as if they were dissolved in a thin unimolecular layer of nonpolar hydrocarbon, and at the same time it is thin enough for the polar surface of silica to be "seen" through it to provide interactions necessary for absorption of polar molecules, even from polar hydroxylic solvents such as water or water—organic mixtures. Stronger binding with background silica is very likely to hold the palladium complexes, thus minimizing the leach of catalyst into the liquid reaction media, which would be inevitable if the catalyst were held only by a nonpolar layer (Scheme 113).

Scheme 113
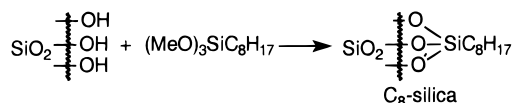
Such a support was simply impregnated by a solution of Pd(OAc)$_2$ and PPh$_3$ or P(*o*-Tol)$_3$ to give catalysts showing good activity in Heck reactions with both water-soluble and water-insoluble substrates (1—2 mol % Pd, K$_2$CO$_3$ or Et$_3$N as bases, 100 °C). The catalysts are air stable and can be reused without a noticeable decrease in activity. The leaching per run usually is less than 0.1%, which is roughly equal to 0.001—0.002 mol % Pd going into solution. It should be noted that this amount of phosphine-free Pd is well-known to be able to catalyze Heck reactions with aryl iodides and even aryl bromides, so at least part of catalytic activity might be due to leached catalyst (Scheme 114).
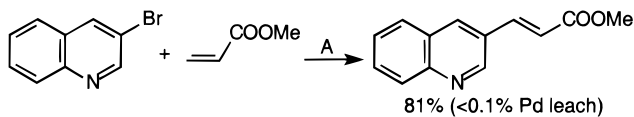
Scheme 114

90% (0.18% Pd leach)

A: [Pd(OAc)$_2$ (2 mol%), 4Ph$_3$P] on C$_8$-silica, K$_2$CO$_3$, water, 100°C, 2 *h*
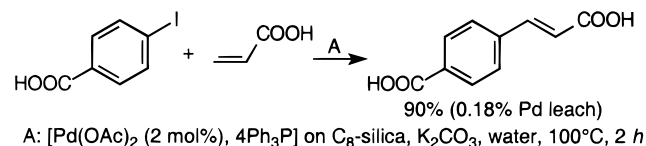
The catalyst proved to be particularly effective for arylation of bromoderivatives of nitrogen-containing

heterocycles, which are well-known to bind to palladium, which could have lead to increased leaching and decreased activity (Scheme 115).

Scheme 115

81% (<0.1% Pd leach)

A: [Pd(OAc)$_2$ (1 mol%), 4(*o*-Tol)$_3$P] on C$_8$-silica, Et$_3$N, no solvent, 100°C, 17 *h*

2. Solid–Liquid Systems

In solid−liquid phase-separation catalysis, the catalyst is held by solid support. For simplicity, we discuss in this section the approaches in which macromolecules are used as support. The most essential difference between liquid−liquid and liquid−solid phase-separation modes is, in our opinion, the degree of mobility of the catalyst. In liquid−liquid systems, the catalyst is held by liquid phase and thus retains diffusional mobility within this phase. In solid−liquid systems (including macromolecular supports), the catalyst is bonded to the support and thus has no mobility of its own. As a result, solid−liquid systems are usually more persistent and allow for more recycles. On the other hand, limited mobility imposes a severe mass-transfer limitation on the net rate of the catalytic process.

(a) Polymeric Supports. The application of polymeric supports for the Heck reaction has not been very successful, though several interesting examples have been published. We cannot expect much from this approach. Palladium must be strongly bonded to the resin if we expect to obtain recyclable catalyst with low leach. Such bonding can be done via phosphine anchor groups, preferably through chelating phosphines, as monophophsine anchors cannot be expected to form sufficiently strong complexes. Polymer-bound phosphine complexes of palladium are applicable only to the reactions with highly reactive iodoarenes and monosubstituted alkenes. We can hardly expect to ever see a polymer-bound catalyst with activity suitable for large-scale processing bromo- or chloroarenes and not compromising on leaching and recyclability, which are the main driving force of developing such catalysts. It should also be noted here that combinatorial chemistry employs a complementary approach by bonding the reagents to the support while the catalyst and auxiliary reagents are administered as solutions. The separation of product from catalyst is thus easily achieved. Several successful applications of combinatorial chemistry methods to Heck reactions have already been published.[170,202,254−258]

An early report of palladium catalyst based on triphenylphosphine-bonded polystyrene resin describes the arylation of olefins by iodoarenes. The catalyst showed better activity than soluble palladium catalysts, both phosphine-assisted and phosphine-free. Careful examination of the catalyst beads showed that palladium nanoparticles are actually formed and are the true catalyst. Thus, the resin is likely to serve only as a supporting colloid for

palladium sol.[259] In a more recent study, polymer-supported 1,2-bis(diisopropylphosphino)benzene has been used for preparing a catalyst for standard reaction of PhI with methyl acrylate. Higher TON values were noted for supported catalyst in comparison with soluble complexes of palladium both with 1,2-bis(diisopropylphosphino)benzene and PPh$_3$ as the supported catalyst is more stable toward the formation of Pd black and thus has a longer lifetime.[260] Another type of solid-supported palladium catalyst was developed[261] to utilize a new method of phosphine modification. Readily available phosphine−borane complexes are deprotonated at the α-carbon to give anions, which can be reacted with any S$_N$2-capable linker, for instance, Scheme 116.

Scheme 116
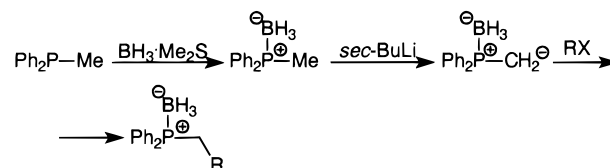
Using this method, the phoshine−borane moiety has been tethered to polypyrrole (Scheme 117).
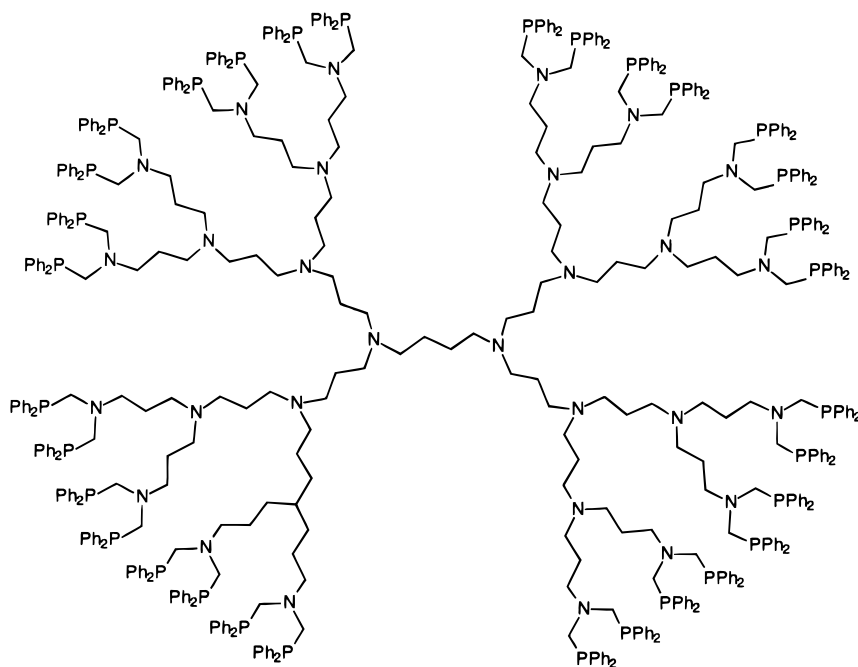
Scheme 117
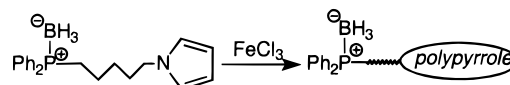
The phosphine−borane can either be exchanged with amine to obtain the free phosphine or used as is for the reduction of Pd(II) salts giving the supported Pd(0)−phosphine complex ready for catalysis. This catalyst has been found to be moderately active in the reactions of PhI with acrylic acid (3 mol % Pd, Et$_3$N, THF, 65 °C, 3 h, 72%) and cyclohexanone (DMF, 60 °C, 24 h, 50% 3-phenylcyclohexan-2-one) under unhydrous conditions as well as of *p*-methoxyiodobenzene with cyclohexene under aqueous conditions without double-bond migration (DMF−water, 70 °C, 60 h, 64% 3-arylcyclohexene). The support can be recycled, though it must be recharged with Pd(0) using Pd(dba)$_2$ in the next run. The fate of palladium is not disclosed.

A further step forward takes advantage of a new class of macromolecules, the dendrimers. Dendrimers can be better supports than linear or irregularly branched macromolecules because of several distinctions. First of all, as dendrimers are individual well-characterized compounds, the catalysts formed with such ligands have definite structures. Therefore, the design of dendrimeric catalysts is based not on stochastic, but on rigorous structural considerations. A very strong advantage of dendrimeric support over other kinds of organic polymers is a full exposure of catalytic centers to the environment. As the whole macromolecule is inside the particle, diffusion limitations are not relevant. On the other hand, linear or cross-linked polymeric supports undergo folding in solutions to partially hide catalytic centers. Commercially available dendrimer based on 1,4-diaminobutane bearing peripheral amino groups was de-

Scheme 118

rivatized with diphenylphosphine residues to give a macromolecule with 16 chelating diphosphine units DAB-*dendr*-[N(CH$_2$PPh$_2$)$_2$]$_{16}$, which can bind transition metals, e.g., palladium, nickel, and rhodium to give complexes (Scheme 118).[262]

Like other macromolecules, dendrimers can be precipitated from solutions by the addition of weakly interacting solvents, which makes them useful for recycling purposes. Dendrimeric catalyst DAB-*dendr*-[N(CH$_2$PPh$_2$)$_2$PdMe$_2$]$_{16}$ showed about three times higher catalytic activity than the parent complex *n*-PrN(CH$_2$PPh$_2$)$_2$PdMe$_2$ in the Heck arylation of stilbene with bromobenzene carried out in DMF at 130 °C in the presence of NaOAc as base, due to the higher stability of the former. Indeed, the deactivation of the palladium catalyst in catalytic reactions is due to the formation of large metallic particles, a process which is initiated by encounters of Pd(0) species. It is evident that the encounter rate is much higher for small molecules than for macromolecules, due to both diffusional and entropic considerations. The recycling of dendritic catalysts is effected by a simple precipitation by ether, and the recovered catalyst retains the activity.

(b) Inorganic Supports. The use of commercial hydrogenation catalysts (Pd/C, Pd/SiO$_2$, Pd/Al$_2$O$_3$, etc.) in Heck reactions has been occasionally described (ref 263 and references therein). Early results by Julia et al. showed that commercial Pd/C catalyst is active in the arylation of styrene by chloroarenes.[264] Low turnover numbers (22−28) were obtained. The reaction was run in hydroxylic solvents at high temperature (150 °C) in a closed vessel. The addition of Ph$_3$P resulted in the suppression of reaction. Since then, Pd/C has been occasionally used for Heck reactions but has shown no outstanding results (cf., e.g., ref 265).

*(1) Inorganic Supports with Bonded Ligands.* Silica or other supports can be used for derivatization with phosphine ligands. This approach is roughly the same as that for the use of macromolecular supports as it suffers from the same problems: the irreversible wear of supported catalyst due to degradation of phosphines and the compromise between leaching and activity.

Modification of nucleosides has been achieved in the presence of palladium catalyst immobilized on silica derivatized with mercaptopropyltriethoxysilane.[266] Palladium is thus bonded to a sulfur-containing group. The catalyst is used after prereduction by hydrazine. Unfortunately, no information on the state of palladium in this catalyst is provided, since it would be very interesting to understand how the zerovalent Pd could be supported in an active but stable form by a sulfur ligand. In the absence of such data, silica-supported palladium nanoparticles seem to be the most likely hypothesis. This recyclable catalyst is active in the reaction of protected 5-iodo-2′-deoxyuridine with a range of olefins giving the respective products in high yields under rather mild conditions. No double-bond migration is reported (Scheme 119).

The product is stated to be free of Pd impurities, which present a serious problem in biochemical applications. The catalyst is reported to fail in the reactions of olefins "containing protected and unprotected carboxylic groups". If this means that the catalyst failed with acrylic acid and its derivatives, which are, undoubtedly, among the most reliable olefins in Heck chemistry, then it possesses unique chemoselectivity features which can be matched only by the phenanthroline complexes discussed above.[56]

(2) Microporous Zeolites. Palladium complexes entrapped in zeolite NaY were tested as catalyst for Heck arylation.[267] Zeolite pores are rather narrow (7.4 Å), which sets serious limitations on the dimensions of the involved species. Of the four complexes of palladium, the smallest (Pd(NH$_3$)$_4$Cl$_2$) gave the

Scheme 119

A: (Si-S-Pd)-catalyst, iPr_2NEt, p-xylene, 100°C
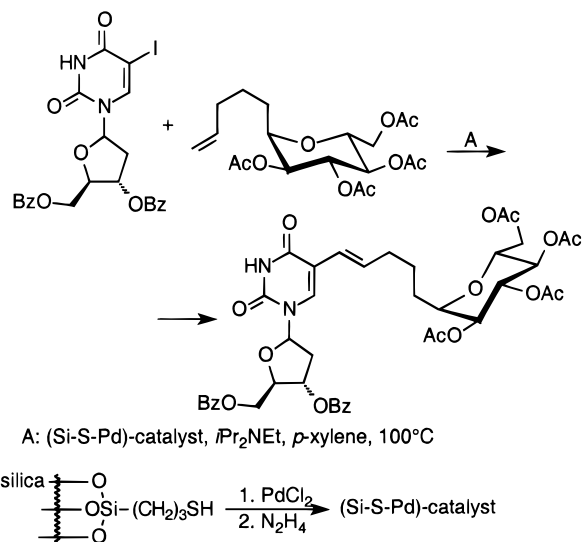
most active supported catalyst. $Pd(OAc)_2$ and [Pd-$(C3H5)Cl]_2$ were moderately active, while Herrmann palladacycle **7** apparently choked the zeolite pores to show only marginal activity. Thus, zeolite supports can be used only in phosphine-free catalysis (with a possible exclusion of smallest trialkylphosphines which can fit the cavities). A zeolite-supported Pd-$(NH_3)_4Cl_2$ complex showed considerable activity in the reactions of bromoarenes with styrene and methyl acrylate comparable to that of the same catalyst in the homogeneous reaction:[268]
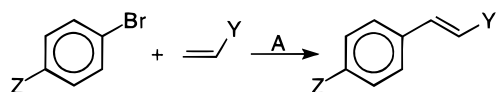
A: $Pd(NH_3)_4Cl_2$/NaY (0.1 mol%), NaOAc, DMA, 100-140°C, 20 h
Y = Ph, COOMe
Z (yield) = H (85%), F (93%), NO_2 (95%), MeO (81%)

Kinetic measurements showed that the reaction with p-bromofluorobenzene taken as a model exhibited a short latent period (<5 min) and then proceeded to completion at an amazing pace within 20 min, which corresponds to TOF equal to about 3000 h^{-1}, putting this catalytic system among the most efficient known. Given that the diffusion in zeolite pores is limited, this means that the actual activity of entrapped catalyst may be huge. The catalyst can be reused, either directly if it was exploited at 140 °C or after revitalization by heating at this temperature if the reaction had been conducted at lower temperature. The leaching of catalyst into the homogeneous phase was negligible.

All data show that the entrapped catalyst behaves almost exactly as the same catalyst in homogeneous solution but is more stable. It is interesting that the catalyst prepared by the calcination of $Pd(NH_3)_4Cl_2$-modified zeolite, both in Pd(II) or Pd(0) (prereduced by hydrogen), showed poorer activity and increased leaching than the original complex.[269] Thus, it is indeed the entrapped complex and not any forms of palladium deposited on zeolite surface which are the most active catalysts. The pore of zeolite with the entrapped complex behaves as a fully functioning

nanoreactor. Narrow zeolite pores impose limits for mobility of entrapped species, which may have a strong positive effect because catalytically active low-ligated palladium species cannot meet often to grow into large clusters. Thus, the ordinary microporous zeolite controls the activity of palladium catalyst much better than the advanced mesoporous MCM-41 material, the pores of which are 1–2 orders of magnitude larger, and cannot preclude the nucleation and growth of large Pd particles, which choke the channels and crush the fine structure (see below).

(3) Mesoporous Zeolites and Other Mesoporous Supports. Mesoporous supports[163] possess pores large enough for free movement of larger molecules. On the other hand, binding of catalysts to such supports cannot be based on physical absorption (trapping) but require chemical bonding or the deposition of active metal.

Mesoporous molecular sieves MCM-41 are an ingenious combination of microstructures formed by surfactants and silicate frameworks. Silicate ions are gathered from the solution by microstructures formed by surfactants from simple micelles to hexagonal phases (dense assemblies of rodlike micelles), which serve as templates for the construction of inorganic framework. After calcination, the remaining polysilicate material is a postmortem mask of the microstructured template, a regular porous material with wide pores (20–100 Å) and enormous surface area (up to 1200 m^2/g; Scheme 120).

Scheme 120


= SiO_4 structural unit
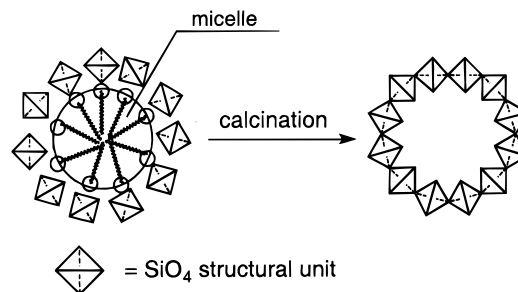
The first report on the use of this material grafted with palladium for Heck arylation was recently published.[270,271] Palladium metal was deposited onto the hexagonal mesoporous zeolite MCM-41 by vacuum deposition of the volatile complex $(\eta^3\text{-}C_3H_5)(C_5H_5)Pd$ with subsequent reduction by hydrogen. In the resulting catalyst, palladium metal is uniformly dispersed over the pores (26 Å diameter) of mesoporous material, forming no observable crystalline particles. Thus, Pd is either monatomic or clustered into very small amorphous particles formed by several atoms and thus must be and really is very active. This was established for the arylation of butylacrylate by bromoarenes (0.02–0.1 mol % Pd, Et_3N as base, DMA, 120–170 °C) or even chlorobenzene (at 170 °C, TON 64). For the standard reaction of p-bromoacetophenone, maximum TON and TOF values achieved were equal to 5000 and 5000 h^{-1}, respectively. The TOF is very high, which reveals a very high activity of this form of palladium metal, resembling that of freshly prepared Pd sols (see

above). The catalyst can be reused up to three times but apparently no more as its marvelous structure appears to be fragile. Indeed, as in the case of sols, palladium chipping is likely to occur, which leads to the redistribution of metal on the surface. The underligated Pd(0) species are unstable and cannot be kept in the catalytic process due to limited feed of reagents because of diffusion limitations in narrow tubular pores. Clusters grow larger into big multi-atom nanoparticles which possess a much lower activity. The leach of Pd in a single run is negligible, but after several reuses, it reaches several percent. Still, such catalysts can have good perspectives because in comparison to other supports mesoporous materials allow for very high loads of palladium (30% and even higher). The consumption of unrecoverable support in a process with a TON of several thousands is relatively low and economically feasible.

Meanwhile, diffusion limitations have a puzzling positive consequence of insensitivity of the catalyst to air. Given that a trivial freshly reduced palladium black is pyrophoric in air, it is really hard to believe that monatomic or amorphous palladium can be stable toward oxygen. Apparently, this trick is due to very limited supply of O_2 molecules into the nanoreactors filled with liquid, particularly at high temperature of reaction, since the solubility of oxygen and of any other gas decreases with temperature.

An interesting family of regular layered porous materials has been generated based on zirconia forming layered networks built of ZrO_6 octahedra. The zirconium hydroxide structure can be doped with phosphites, phosphates, or organic phosphonates, allowing simultaneously imparting regular porous structure and attaching ligands to the walls of the pores. A phosphine-modified zirconium phosphite system has been reported as a heterogeneous catalyst for the Heck reaction (Scheme 121).[272]

Scheme 121
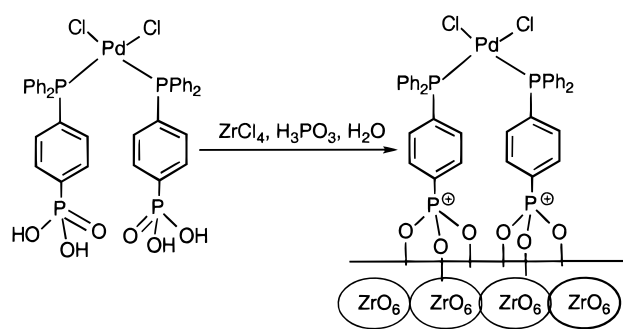
This catalyst, prereduced with Et_3SiH, showed a high activity in Heck reaction of iodoarenes with methyl acrylate (Et_3N, TolH, reflux). Though it is extremely sensitive to oxidation, the catalyst fully retains the initial activity after several reuses provided that all manipulations are carried out in an inert atmosphere, which demonstrates a high stability of the structure of inorganic polymer. Even more interesting is the finding that the reactions with this catalyst reveal a small but recognizable selectivity toward the size of substrates, very similar to that typical for reactions with the participation of host–guest complexes with, e.g., cyclodextrins. The devel-

opment of inorganic materials capable of molecular recognition but much less expensive and more easily recoverable than the organic counterparts may have a strong impact on the development of recyclable catalysts.

Yet another catalyst has been obtained with Pd-$(NH_3)_4Cl_2$ deposited on porous glass (the section on SLPC glass, cf. above) and prereduced by $NaBH_4$. The catalyst thus obtained was used in the arylation of styrene by 4-bromoacetophenone giving quantitative conversions (catalyst 0.02–1 mol %, NaOAc, DMA, 140–180 °C, TON values up to 4000) under aerobic conditions both with conventional and microwave heating. The catalyst is recyclable. Unfortunately, the paper is silent on the pore size of the support used.[273]

(4) Clays. Montmorillonite clays are widely used as supports for various reactions.[274,275] The Heck reaction is no exception. Early results were obtained with clay chemically modified with phosphine ligands.[276] Such an approach is subject to the usual problems due to irreversible degradation of the anchored phosphine. A simpler and more practical solution has been suggested. As montmorillonite K10 clay is an ion exchanger; it can be charged with Pd-(II) and other metal cations. Such catalysts proved to be active in a reaction of iodoarenes with methyl acrylate as well as iodo- and bromoarenes with styrene (catalyst 0.06 mol % Pd, K_2CO_3, DMF, 150 °C, 2 h).[277] The most interesting finding of this study is that an unambiguous synergistic effect was noted as clay exchanged with both Pd and Cu salts in a roughly equal ratio gave better yields than clay charged with only Pd. In a phosphine-free system, Pd–Cu–K10 catalyst has been found to be active enough for the reaction with PhBr (TON near to 900). The catalyst can be recycled by simple filtration and reused at least three times without the loss of activity. The clay is a soft Lewis acid, which can promote the Heck reaction by assistance in the de-ligation of halide in the cationic mechanism. The same role can be played by copper. Alternatively, the synergystic effect of Cu and Pd can be explained by the formation of transient organocopper intermedi-ates, which then undergo transmetalation with Pd-(II) and enter the Heck cycle. At the end of each turn, Pd(0) is reoxidized by Cu(II). Such hypothetical bimetallic Cu(I)/Cu(II)/Pd(0)/Pd(II) catalysis might be an interesting alternative to the regular Heck ca-talysis. Moreover, copper-exchanged clay has been found to give 30–50% yields of arylation products in the reaction of iodoarenes with methyl acrylate, very close to the results obtained with similarly prepared palladium-exchanged clay (cf. section on other met-als).

The promoter action of tetraphenylphosphonium salts described by Reetz[30] inspired an attempt to prepare a supported palladium catalyst doped with this reagent. Montmorillonite K10 clay was impreg-nated by $Pd(OAc)_2$ and Ph_4PBr to give a catalyst capable of driving a standard Heck reaction of iodoarenes and activated bromoarenes with styrene (NaOAc, DMF, reflux, 1.5–25 h).[278] No scrambling of aryl and phenyl was observed for these substrates. However, a single attempt to involve an activated

chloroarene *p*-chlorobenzaldehyde lead exclusively to the formation of unsubstituted stilbene, which is likely to come from the arylation by intercalated Ph_4-PBr, although the amount of this salt reported to be contained in the catalyst is too low to account for the reported yield (Scheme 122).

Scheme 122
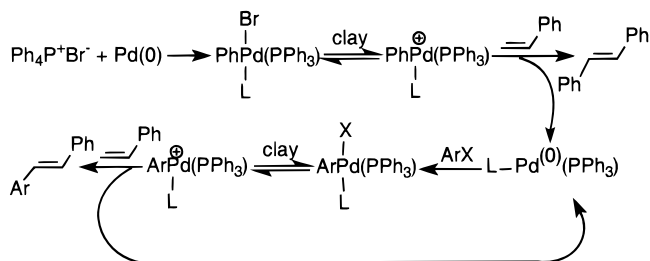
From the given scheme, it is also seen that the first cycle which triggers the catalysis must yield unsubstituted stilbene, and the fact that it was not detected means that actually only a small fraction of the palladium loaded on the clay is catalytically active. Still, the catalyst is very stable and allows for several recyclings without the loss of activity. The catalyst was also tried in the reaction in neat water conducted with microwave heating to give results identical to those observed in DMF with conventional heating.

D. Less Usual Leaving Groups

Besides halides and triflates, other electrophiles have been tested for Heck-type reactions. The search for alternative leaving groups is targeted on finding more reactive substrates and milder procedures.

Though nonaflates (nonafluorobutanesulfonates)[189] may be regarded as a trivial extension of triflate-based chemistry, convenient handling of the respective fluoroanhydride makes possible interesting transformations, such as, e.g., one-pot processing of silyl enol ethers (Scheme 123).[279]

Scheme 123
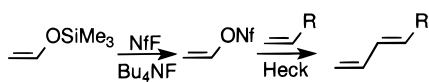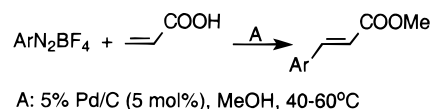

1. Diazonium Salts

Diazonium salts were the first alternative tried,[280,281] and since then this has been developed into a valuable method of synthesis. The reaction does not require the presence of base and phosphines, the addition of which leads to uncontrolled decomposition of diazonium salt. Arenediazonium tetrafluoroborates are commonly used, though several other counterions (such as perchlorate or fluoride) have also been tested.[282] It is not easy to understand how the reaction with diazonium salt can run in the absence of base and how PdH intermediate is transformed into Pd(0). In the absence of strong ligands (phosphines, amines, halides, etc.), PdH intermediate is likely to possess higher acidity to get rid of a proton more easily. The most common protocol uses alcohols as solvents, the basicity of which may be enough for the deprotonation (an inner-sphere variant is pos-

sible), which may lead to the transesterification of esters or esterification of carboxylic acids (Scheme 124).[283]
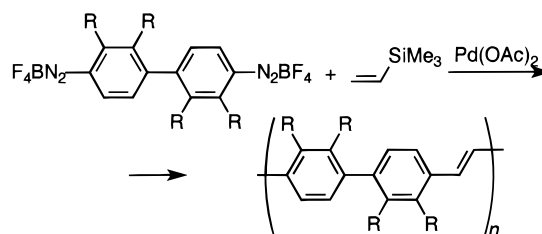
Scheme 124

A: 5% Pd/C (5 mol%), MeOH, 40-60°C

The Heck reaction with diazonium salts is mild and fast but rather inefficient as the loadings of palladium precatalyst required are usually no less than 1−2 mol %. Most probably this is associated with inefficient preactivation of the catalyst. In the absence of phosphines, amines, and other nucleophilic reducing agents, primary reduction to Pd(0) most likely occurs due to partial decomposition of diazonium salt via a free-radical mechanism.

Still, the arylation with diazonium salts is a welcome addition to Heck-type arylation procedures, particularly in those cases where mild conditions are needed. Diazonium salts were extensively studied for the arylation of vinylsilanes. In the absence of base, desilylation is the most frequent outcome of these reactions.[284] In the reaction of diazonium salts with disubstituted vinylsilanes, desilylation products were also predominantly formed,[285,286] in contrast with the regular Heck reaction in the presence of acetate ion which leads to β-arylvinylsilanes via the acetate-assisted deprotonation pathway.[287,288] It is interesting to note that unlike the elimination of PdH which, as we noted earlier always occurs as a *syn*-process, the desilylation is often not stereospecific, as it may proceed not only as *syn*-elimination of $PdSiR_3$, but also by nucleophile-assisted E2 elimination as well as electrophlic protodesilylation of the vinylsilane. However, the possibility to displace both hydrogen and a SiR_3 group affords dual arylation, which can be used, for instance, for the preparation of polyconjugate polymers (Scheme 125).[289]
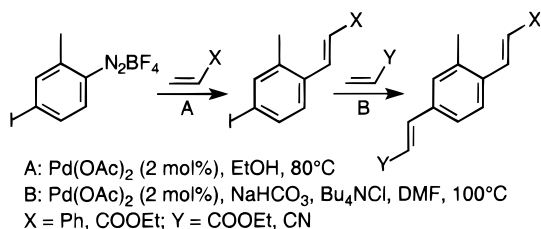
Scheme 125

The arylation by bisdiazonium salts has been applied to the synthesis of polyconjugated molecules (Scheme 126).[290,291]

Scheme 126

A: Pd(OAc)$_2$ (2 mol%), EtOH, reflux
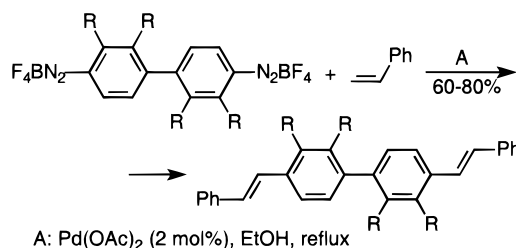
The different reactivity of iodine and diazonium groups enables stepwise assembly of complex molecules[292] (cf. the differential Heck reactions of bromoiodoarenes;[293−295] Scheme 127).

Scheme 127

A: Pd(OAc)$_2$ (2 mol%), EtOH, 80°C
B: Pd(OAc)$_2$ (2 mol%), NaHCO$_3$, Bu$_4$NCl, DMF, 100°C
X = Ph, COOEt; Y = COOEt, CN

An aqueous version of Heck arylation with diazonium salts has been proposed,[296] in which diazotization of anilines and subsequent Heck reaction can be performed as a one-pot procedure. The aqueous protocol has been applied to the synthesis of tetrapods (Scheme 128).[297]

Scheme 128

A: Pd(OAc)$_2$ (5 mol%), EtOH-H$_2$O, 80°C, 1 h
Z = Ph (yield 80%), COOEt (75%), SO$_2$Ph (20%)
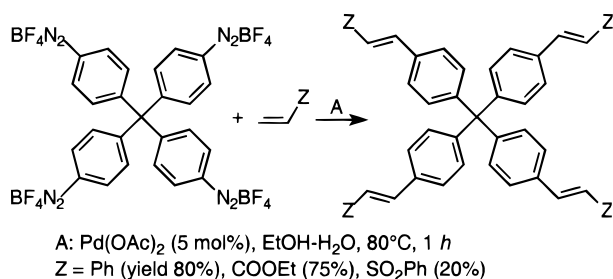
Diazonium salts do not need to be introduced to the reaction in a pure form. Diazotization by alkyl nitrite and the Heck reaction can be performed in a tandem mode,[298] as for instance in a one-pot procedure to convert anilines into styrenes.[299]

Among the other precursors of diazonium salts used for palladium-catalyzed arylation are arylhydrazines,[280] *N*-aryl-*N*-nitrosoacetamides ArN(NO)-Ac,[300] aryltriazenes,[301] arylazoaryl sulfones ArN$_2$SO$_2$-Ar′,[302] and arylazoxyaryl sulfones ArN(O)NSO$_2$-Ar′.[303,304]

Due to mild conditions and high reactivity, diazonium salts are a valuable arylating reagent for cyclic olefins, such as, e.g., camphene,[305] 2,5-dihydrofuran,[306] and sulfolene.[307] The low temperature of reaction in the latter case is necessary as sulfolenes undergo the extrusion of SO$_2$ above 100 °C. This reaction can be regarded as an indirect method of the Heck arylation of butadiene with the aryl group being attached to the internal carbon. Thus, this method is complementary to the direct arylation of dienes, which gives terminal substitution products (Scheme 129).[308]
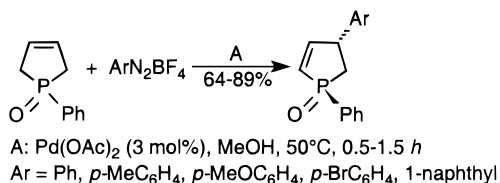
Scheme 129
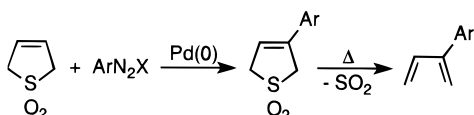
1-Phenylphosphol-3-en-1-oxide gives good yields of arylation products only with diazonium salts. The reaction is fully stereospecific and involves the attack of arylpalladium intermediate at the less hindered face of phosphole (Scheme 130).[309]

Scheme 130

A: Pd(OAc)$_2$ (3 mol%), MeOH, 50°C, 0.5-1.5 h
Ar = Ph, *p*-MeC$_6$H$_4$, *p*-MeOC$_6$H$_4$, *p*-BrC$_6$H$_4$, 1-naphthyl

The potential of diazonium salts as arylating agents can be further illustrated by a recent synthesis of the alkaloid codonopsine. A key step is the arylation of 2,3-dihydropyrrole. While all of attempts to perform a Heck reaction with the respective iodide or triflate failed (besides a low yield and miserable rate, these reactions require expensive ligands and a huge excess of valuable olefinic substrate prepared via multistep enantioselective procedure), the stereospecific arylation with simple diazonium salt gave high yields of target product in a fast phosphine-free procedure with only 50−100% excess of 2,3-dihydropyrrole. The addition of base is required here to suppress side reactions (Scheme 131).[310]

Scheme 131

A: Pd(OAc)$_2$ (10 mol%), 2,6-*t*-Bu$_2$Py, EtOH, 55°C, 15 min
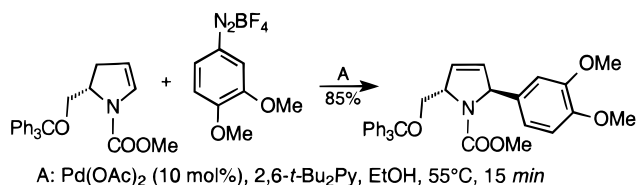
Pd(OAc)$_2$ is used as a catalyst precursor in most of the described protocols. Several commercial heterogeneous catalysts Pd/C, Pd/BaSO$_4$, Pd/Al$_2$O$_3$, and Pd/SiO$_2$ were also tried and gave good results for the arylation of acrylates using the base-free procedure in alcohols. Unfortunately, the catalysts cannot be effectively recycled and were found to lose the activity after recovery from reaction mixtures.[283]

The base-free conditions of the Kikukawa−Sengupta protocols lead to acidification of the reaction mixture, overuse of reagents wasted in side-reactions, and other disadvantages limiting the use of diazonium salts in more complex syntheses. The development of a base-assisted arylation procedure is the contribution which can move the application of these arylating agents to new levels. Indeed, an excellent procedure utilizing another commercial heterogeneous catalyst Pd/CaCO$_3$ has been eventually put forward for Heck reaction with diazonium salts.[311] The key is a precise choice of the very mild heterogeneous base CaCO$_3$, which minimizes undesirable spontaneous degradation of diazonium salts and serves the goal of assisting in trapping the PdH intermediate. The procedure is exceptionally mild and gives excellent yields of Heck products, and even with terminal normal alkene, no migration of the double bond has been noted. Moreover, if the substrate contains both iodine atom and diazonium group, only the latter is transformed, thus leaving

the iodine atom for subsequent reactions (e.g., another Heck reaction (Scheme 132).

Scheme 132
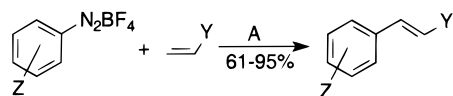
A = Pd/CaCO$_3$ (0.5-2 mol%), CaCO$_3$, ROH (R = Me, Et, i-Pr),
     30-50°C, 15 min - 2 h.
Z = 4-OMe, 3-Cl-4-OMe, 3-NO$_2$-4-F, 3,4,5-(OMe)$_3$, 2-Br, 4-I, 2-COOEt
Y = COOMe, COOCH$_2$CH(n-Bu)Et, CHO, C$_6$H$_{13}$

The procedure uses palladium deposited on CaCO$_3$, a commercially available hydrogenation catalyst, though Pd(OAc)$_2$ can also be used in some cases, e.g., for the arylation of methacrylonitrile. It was particularly emphasized that the procedure is very robust and tolerates aerobic conditions and technical-grade solvents without prior purification and thus is a good candidate for implementation on a larger scale in industry. It only deserves a remark that low sensitivity to air and quality of solvents is actually a common feature of many Heck reactions of iodoarenes under phosphine-free conditions. Oxygen is known not to be a good reoxidizer of Pd(0) to Pd(II). Sensitivity to oxygen and impurities is indeed a problem of phosphine-mediated catalysis, as phosphine ligands are scavenged by oxygen both themselves (there are indications that this process can be catalyzed by palladium) and in the form of Pd(0) complexes.

A good example of the application of the new Genet's procedure is the arylation of exomethylene-γ-butyrolactone without the migration of the double bond (Scheme 133).

Scheme 133
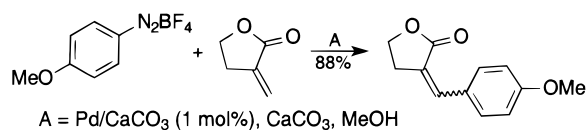
A = Pd/CaCO$_3$ (1 mol%), CaCO$_3$, MeOH

2. Iodonium Salts

Iodonium salts show a similar behavior as diazonium salts, though with better tolerance to conditions and particularly to bases. Low temperatures of reaction and very high rates make this method particularly suitable for complex cases which cannot endure the harsh reaction conditions of the conventional Heck reaction. However, iodonium salts are not as easily available as diazonium salts, and their preparation requires in most cases the respective iododerivatives. Therefore, the application of iodonium salts for simple arylations is not justified.

Due to the availability of vinyliodonium salts, vinylation under mild conditions can be achieved[312] to give conjugated dienes. The Heck reaction with acrylic acid can be carried out at room temperature if diaryliodonium salts are taken as arylating agents in neat water.[313] At room temperature, only one aryl group of iodonium salt is transferred to the product, while at 100 °C, both aryl groups are utilized (Scheme 134).

Scheme 134
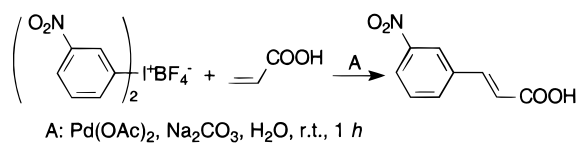
A: Pd(OAc)$_2$, Na$_2$CO$_3$, H$_2$O, r.t., 1 h

However, under mild conditions, iodonium salts transfer only one group. This would have been a waste of valuable organic residue, but in many cases unsymmetrical iodonium salts with one junk residue (usually Ph) can be used. In alkenylphenyliodonium salts, the alkenyl residue is the one transferred. Unsymmetrical arylphenyliodonium salts present an interesting deviation from a common reactivity pattern of oxidative addition. Unlike the well-known trend in the oxidative addition of haloarenes, in iodonium salts, Pd(0) selectively adds to the C−I bond with more electron-donating aryl group.

Alkenylphenyliodonium salts were studied in enantioselective Heck reactions giving ee up to 78%.[314]

Arylation of allenic alcohols gives in high yields the products of cascaded intramolecular allylic substitution leading to epoxides or carbonates[315] as well as 5−10-membered heterocycles.[316] Allylic carbonates are arylated and alkenylated by iodonium salts without cleavage of carbonate under both aqueous and nonaqueous conditions.[317] Iodonium salts are mild arylating agents for allylic alcohols under phosphine-free aqueous or an anhydrous conditions giving the arylallylic alcohols without the concomitant formation of ketones or aldehydes (Scheme 135).[318]

Scheme 135
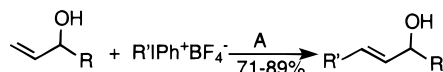
A: Pd(OAc)$_2$ (2 mol%), NaHCO$_3$, DMF or MeCN/H$_2$O (5:1), r.t.
R = H, n-C$_5$H$_{11}$, CH(OH)CH$_2$OBn
R' = Ph, PhCH=CH$_2$

Reactions in aqueous solvent were faster, requiring only 30 min for completion.

The use of iodonium tetrafluoroborates under phosphine-free conditions allows the generation of practically unshielded cationic palladium intermediate. A very interesting hypothesis that the elimination of α-H is suppressed due to the formation of four-membered chelate has been confirmed by the formation of aldehydes when the counterion of iodonium salt was changed to bromide (Scheme 136).
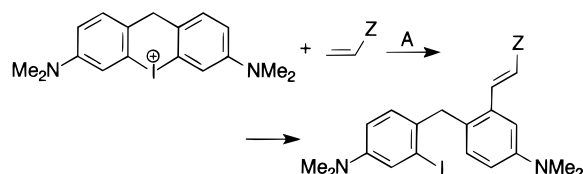
Scheme 136
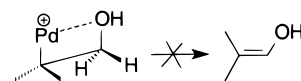
Selective arylation of allylic alcohols and diols without the rearrangement to aldehydes or ketones is otherwise a serious challenge requiring unusual ligands or the protection of the hydroxy-group.[319,320]

The reaction with cyclic iodonium salt has been described[321] (Scheme 137).

Scheme 137

A: Pd(OAc)$_2$ (2 mol%), Na$_2$CO$_3$, DMF, r.t., 4 h
Z = COMe, CHO, COOH, COOMe, CN

3. Thallium(III) and Lead(IV) Derivatives

Organometallic derivatives of the main group elements cannot react with Pd(0) and thus are not suitable for catalytic Heck process. We do not discuss here the reactions initiated by transmetalation with Pd(II), as such processes are noncatalytic in the absence of oxidants and belong to a different type of catalytic cycle than those discussed here. Nevertheless, some main group metal derivatives in higher oxidation states, such as arylmetal carboxylates (metal = Pb(IV) or Tl(III)) can take part in a classical Pd(0)/Pd(II) catalytic Heck cycle showing similar reactivity to iodonium salts. The examples are scarce but unambiguous.

Organolead(IV) tricarboxylates, easily prepared by electrophilic plumbylation of reactive arenes by Pb-(IV) salts or by transmetalation, undergo a Heck-type reaction under very mild conditions. As a result, no double-bond migration was reported for this reaction, neither in the classical test for this process in the arylation of 2,3-dihydrofuran nor in more complex cases (Scheme 138).[322]

Scheme 138
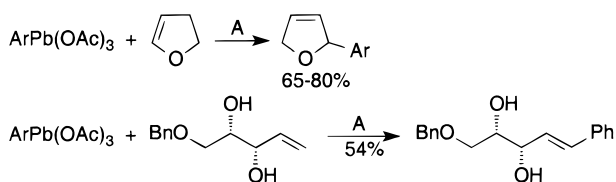
A: Pd$_2$(dba)$_3$ (5 mol%), NaOMe, MeOH/MeCN, r.t., 3 h

Organothallium(III) dicarboxylates are known to have similar reactivity to organolead(IV) tricarboxylates in reactions with nucleophiles and thus may behave similarly in the oxidative addition to Pd(0) allowing them to take part in the Heck catalytic cycle. As such organothallium carboxylates are easily produced by electrophilic thallation,[323] regiospecifically directed to ortho-position by any substituent capable of coordination, the thallation followed by the Heck reaction can be used for annulations.[324,325]

4. Acid Chlorides and Anhydrides

Acid chlorides were among the earliest discovered alternative substrates for the Heck reaction.[99,326,327] The process (a rare Blaser reaction) involves a decarbonylation with further evolution exactly following the canonical Heck cycle with aryl chloride. Thus, Blaser reaction gives an opportunity to model the Heck reaction with aryl chlorides after the oxidative addition step is bypassed. The process is facile and does not require the presence of any specific ligands (Scheme 139).

Scheme 139
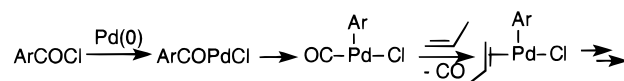
The decarbonylation is the most demanding step of the whole procedure, and indeed it defines the conditions as it requires three available coordination sites for CO migration. Any good ligand which can bind to palladium at this step makes this reversible process run in an opposite direction and thus suppresses the catalytic cycle. Thus, the process is best run in nonpolar solvents (as polar solvents such as DMF are proven ligands) in the presence of bulky weakly coordinating amines (BnNMe$_2$ and the like) in the phosphine-free mode. Two equivalents of Ph$_3$P inhibit the reaction almost completely. Otherwise, the reaction is quite remarkable in catalytic efficiency (it can be run in the presence of as low as 0.005 mol % Pd(OAc)$_2$ giving TONs up to 10 000 and TOF up to 135 h^{-1} (though the rate of reaction decreases with time possibly due to poisoning by CO), tolerance to functional groups on the acid chloride, and good yields of arylation products even with poorly reactive disubstituted alkenes. Moreover, as aryl bromides are unreactive under the very mild conditions of the Blaser reaction, a differential Blaser–Heck process can be realized (Scheme 140).[328]

Scheme 140
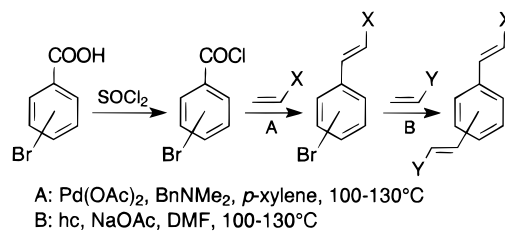
A: Pd(OAc)$_2$, BnNMe$_2$, p-xylene, 100-130°C
B: hc, NaOAc, DMF, 100-130°C

Despite indisputable merits, the Blaser reaction has been rarely used since its discovery. Among the few examples are the preparation of conjugated trienes from fumaryl chloride[329] and the arylation of vinyl ethers in which a simple variation of conditions can lead both to aryl- and aroyl-substituted products[265,330] (see also ref 331).

Arylation by arylsulfonyl chlorides with the extrusion of SO$_2$ has been discovered by Miura et al.[332,333] Similar to the Blaser reaction, this process runs under phosphine-free conditions.

The use of acid anhydrides has been recently described.[162,334] At first glance, this process seems to be an obvious variant of Blaser reaction but its true value is more significant. This reaction is unique because it does not require the addition of base (not like the reactions with iodonium or diazonium salts which for some obscure reasons *can* run in the absence of base), since the leaving group is in this case the carboxylate, which itself can assist in deprotonation of PdH intermediate. This process can occur in the coordination sphere of palladium (the hypothesis of the inner-sphere deprotonation of PdH inter-

mediate has been proposed[169] to account for specific acceleration effect of bases on the rate of the Heck reaction). The base-free protocol is a true gem when simplification of the composition of reaction mixture is desired, as is indeed the case in recyclable systems in which any extra component brings in new problems (Scheme 141).

Scheme 141
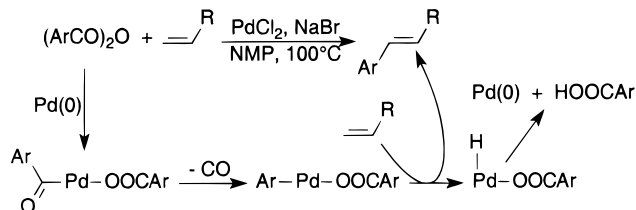
E. Other Metals as Catalysts

Heck-type reactions can be catalyzed by a number of other metals. Though none of them can rival palladium in synthetic versatility, some features may complement Heck chemistry to provide either cheaper catalysts or catalysts capable of effective processing of some specific substrates.

Copper salts are well-known for their ability to promote substitution processes, though the actual mechanism of such processes is obscure and seems to involve transient organocopper intermediates. Therefore, it is not surprising that cuprous salts were shown to enable the arylation of olefins by aryl iodides (PhI, p-ClC$_6$H$_4$I, o-ClC$_6$H$_4$I, p-MeOC$_6$H$_4$I, p-O$_2$NC$_6$H$_4$I) either in catalytic or equimolar amounts (K$_2$CO$_3$, NMP, 150 °C, 24 h) in the absence of any extra ligands.[335] Though this system has a very poor catalytic efficiency (the best TONs are less than 10), it may present a certain interest due to low cost of copper salts, of which both CuI and CuBr show similar reactivity. Besides aryl iodides, this reaction can be applied to β-styryl bromide. The reaction is stereospecific to give only *E*-olefins in all studied cases. A single example of intramolecular *endo-trig* arylation was also reported (Scheme 142).

Scheme 142

A: CuI, K$_2$CO$_3$, NMP, 150°C
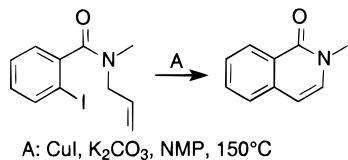
Similar to numerous other copper(I)-mediated substitution reactions, the mechanism of arylation is unknown, which certainly hampers any further progress in the elaboration of this potentially very interesting method.

A close relative of palladium, nickel is a most appealing candidate for possible replacement of expensive Pd catalysts in the Heck reaction. Earlier attempts to use NiCl$_2$(PPh$_3$)$_2$ complex showed that the Ni-catalyzed arylation is indeed possible but requires stoichiometric amounts of a reductant such as Zn dust to ensure a catalytic effect, which means that Ni(0) species are not effectively regenerated by

the mechanism common to palladium-catalyzed Heck reaction through deprotonation of hydride complex by base).[336,337] Instead, the regeneration is enabled by a reductive pathway, possibly similar to that recently discovered by Milstein et al. for palladium-catalyzed Heck reaction.[106] The more persistent character of the nickel hydride complex is evidenced by the formation of considerable amounts of hydrodimerization product from styrene (Scheme 143).

Scheme 143
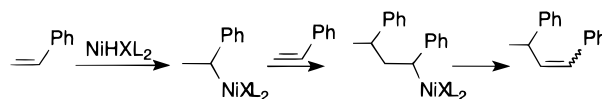
The nickel-catalyzed Heck reaction nevertheless has one distinct advantage over the classic Pd-catalyzed reaction as it allows for the use of aliphatic halides (cyclohexyl bromide, secondary alkyl bromides) in addition to aryl and vinyl halides, e.g., Scheme 144.

Scheme 144

A: NiCl$_2$(PPh$_3$)$_2$ (5 mol%), Zn, py, MeCN, 65°C, 4 h
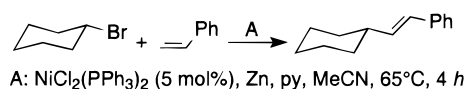
The mild conditions of the reductive nickel-catalyzed Heck process are also worth noting. Moreover, chlorobenzene was shown to be reactive and give a result very close to that obtained with bromobenzene, under very mild conditions and without any specific efforts of optimization. The arylation of acrylate esters in the presence of nickel catalysts gives not cinnamates but β-arylpropionates as major products. The proton was proven to come from stray or deliberately added water. Thus, the attack of arylnickel at the olefin bearing the electron-accepting substituent can be viewed as a regular Michael addition (Scheme 145).

Scheme 145
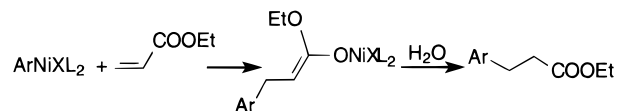
Arylation and vinylation of electron-acceptor-substituted alkenes in a reductive mode has been realized in an electrochemical cell using a sacrificial iron cathode.[338,339] The vinylation proceeds with complete retention of configuration of the vinyl halide. This method was successfully applied to a simple synthesis of the pheromone of *Damaliscus dorcas dorcas* (Scheme 146).

Scheme 146

A: NiBr$_2$·3H$_2$O, Fe-cathode, DMF/MeCN (1:1), 60-80°C
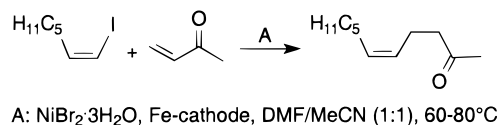
The nickel-catalyzed Heck reaction with nonreductive basic regeneration of Ni(0) is nevertheless possible, though requires a different catalyst and harsh

conditions.[340] Recently, stable phosphite complexes of nickel(0) Ni[P(OR)3]$_4$ (R = Et, Ph) were shown to smoothly catalyze the reaction of olefins with aryl iodides and vinyl bromides (10 mol % of catalyst, K$_2$CO$_3$ as base, NMP, 150 °C, 12−24 h) in good to high yields and excellent *trans*-stereoselectivity. The data on regioselectivity is contradictory, as while the reaction of *p*-methoxyiodobenzene with styrene gave as much as 15% of 1,1-diarylethylene byproduct, the arylation of cyclooctene with the same iodide gave only 1-arylcyclooctene; thus, no migration of the double bond, which is a true plague in Pd-catalyzed arylation, was noticed. At least this feature, if a wider scope can be experimentally proven for it, can make nickel-catalyzed arylation a very valuable addition to preparative Heck chemistry (Scheme 147).

Scheme 147

A: Ni(OPh)$_3$, K$_2$CO$_3$, NMP, 150°C, 24 h
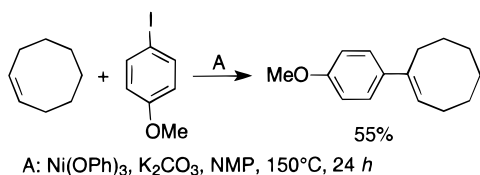
The reductive nickel-catalyzed Heck-type chemistry was used for the construction of cyclopentadienes and α-pyrones from (*Z*)-3-halopropenoates and acetylenes.[341] It is interesting that in the pathway leading to cyclopentadienes the halopropenoate molecule plays the roles of both halide and the olefin as it virtually vinylates itself through an extension formed through two consecutive insertions of acetylene (Scheme 148).

Scheme 148
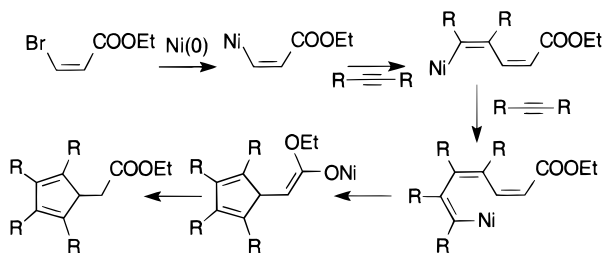
Thus, we may argue that nickel is very likely to have a huge but still largely hidden, due to scarce efforts given hitherto to this metal, potential for Heck chemistry, as it can participate in the Heck catalytic cycle, though with a different balance of individual steps and varied behavior of key intermediates, which account for the different reactivity and selectivity features. Nickel catalysts are definitely more reactive than the corresponding palladium catalysts.

The third member of the nickel triad, Pt also was found to be able to participate in Heck-type chemistry. Platinum complex Pt(COD)Cl$_2$ catalyzes the arylation of simple olefins (methyl acrylate, methyl methacrylate, styrene) by aryl iodides (PhI, *p*-ClC$_6$H$_4$I, *o*-ClC$_6$H$_4$I, *p*-MeOC$_6$H$_4$I) at 130 °C in NMP in the presence of sodium carbonate as base and 2 equiv of triphenylphosphine.[342] Low TONs (in most cases lower than 50), very low TOF (<3 h^{-1}), and inferior selectivity, as even in the best cases 5−10% of the

reductive dehalogenation product are formed, make this expensive catalyst hardly worth further studies. It should be noted that the apparent inability of platinum complexes to effectively catalyze Heck reactions raises more doubts about the feasibility of the Pd(II)−Pd(IV) mechanism. If such a mechanism were general in palladium-catalyzed chemistry, platinum should be able to behave in a similar fashion, as higher oxidation states are more stable in the third triad.

The complexes of cobalt and its relatives Rh and Ir (CoCl(PPh$_3$)$_3$, RhCl(PPh$_3$)$_3$, IrCl(CO)(PPh$_3$)$_2$),which are known to undergo facile oxidative addition reactions, were chosen for another study of Heck chemistry extensions.[343] All three complexes gave high yields of arylation products in reactions of aryl iodides (PhI, *p*-ClC$_6$H$_4$I, *o*-ClC$_6$H$_4$I, *p*-MeOC$_6$H$_4$I, *p*-O$_2$NC$_6$H$_4$I, *p*-MeC$_6$H$_4$I, *o*-MeC$_6$H$_4$I) with methyl acrylate or styrene under rather harsh conditions (5 mol % of catalyst, K$_2$CO$_3$, NMP, 110 or 150 °C, 24 h) giving arylation products in high yields. Co and Rh complexes showed similar performance, though only the latter was able to catalyze the reaction with *ortho*-substituted iodoarenes. Iridium complexes required higher temperatures and gave lower yields. Both chloro- and bromoarenes were unreactive.

Several ruthenium complexes including Ru(COD)-(COT) and {RuCl$_2$(C$_6$Me$_6$)}$_2$ as well as simple salt RuCl$_3$•nH$_2$O were found to catalyze the vinylation of activated olefins (acrylates, acrylamide, methyvinyl ketone, methyl methacrylate) by vinyl bromides and chlorides in the presence of triethylamine (Scheme 149).[344]

Scheme 149

A: Ru-cat (2-5 mol%), NEt$_3$, no solvent, 100°C, 4-22 h
X = Cl (26-45%); X = Br (57-68%)
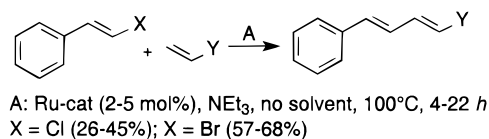
The addition of tris(*p*-fluorophenyl)phosphine results in a small increase of yields. The mechanism proposed for this reaction is a copy of the classical mechanism of palladium-catalyzed Heck reaction. Though the scope of the Ru-catalyzed process is obviously inferior, the readiness of the involvement of chloroderivatives deserves further study.

F. Less Usual Substrates and Heck-Like Reactions

Besides C(sp^2)−X electrophiles, there are unique examples of the involvement of C(sp^3)−X and C(sp)−X bonds.

The adamantylation of olefins catalyzed by Pd/C recently discovered by de Meijere[345] formally looks like a regular Heck reaction (Scheme 150).

Scheme 150

10% Pd/C (5 mol%), K$_2$CO$_3$, DMF, 100-120°C, 12 h
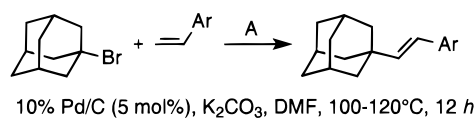
However, the mechanism must be different as (i) it is not catalyzed by palladium salts or complexes; (ii) in the reaction with *trans*-2'-deuteriostyrene it gives a 1:1 mixture of deuterated and nondeuterated stilbenes, while the latter cannot form by reductive elimination of palladium hydride due to stereochemical reasons; and (iii) under the same conditions the adamantilation of arenes, including electron-poor haloarenes, occurred. All these observations point to some sort of an electrophilic mechanism.
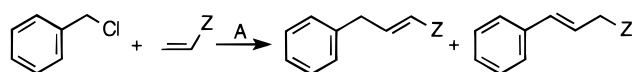
The use of benzyl halides for Heck reaction has been described[346,347] to give both the regular Heck-type product and the isomeric olefin resulting from double-bond migration (Scheme 151).

Scheme 151

A: Pd(OAc)$_2$ (1 mol%), Bu$_3$N, DMF, reflux

Besides benzyl halides, quaternary ammonium salts with benzyl group can serve as substrates. Thus, due care should be exercized when using benzyl-substituted phase-transfer agents for the Heck reaction.[348]

A single example of the Heck-type reaction with 1-chloro-2-phenylacetylene has been reported to give moderate yields of expected products.[349]

Many more possibilities are opened by the variation of unsaturated substrate.

1. Involvement of Palladium Enolates

Among the reactions leading to the participation of α-palladated ketones or aldehydes are the Heck reactions with α,β-unsaturated carbonyl compounds as well as a newly discovered α-arylation of ketones.

Conjugate addition may compete with regular Heck arylation. Conjugate addition is usually observed for arylation of α,β-unsaturated enones and enals in the presence of Et$_3$N as base,[350] while inorganic bases favor regular arylation. Recently this technique was refined as it was shown that the reaction can be very finely controlled by a choice of base, preferably with palladium complex with bidentate dppp as a catalyst. Heck arylation is achieved by the use of NaHCO$_3$ and LiBr as promotor, while conjugate addition is favored by Et$_3$N.[351,352] Bromide ions (either liberated from substrate or deliberately added) inhibited the conjugate addition (Scheme 152).

Scheme 152
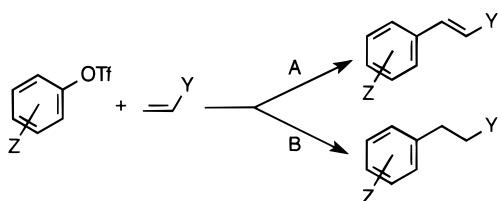
A: PdCl$_2$(PPh$_3$)$_2$ (5 mol%), dppp, NaHCO$_3$, LiBr, DMF, 150°C, 6.5 *h*
B: PdCl$_2$(PPh$_3$)$_2$ (5 mol%), dppp, Et$_3$N, DMF, 150°C, 6 *h*
Y = COMe, COEt, COOMe, CN
Z = 4-Cl; 4-MeO; 3,4-(OCH$_2$O); 2,3,5-Me$_3$, 2,3,6-Me$_3$, 2,4,5-Me$_3$, *etc.*

It can be argued that the α-palladated ketone can rearrange into the respective *O*-enolate, particularly if the harder cationic palladium complex is involved. The enolate cannot eliminate Pd hydride, and the catalytic effect must be furnished by an external reductant, the role of which can be played by Et$_3$N (cf. ref 353; Scheme 153).

Scheme 153
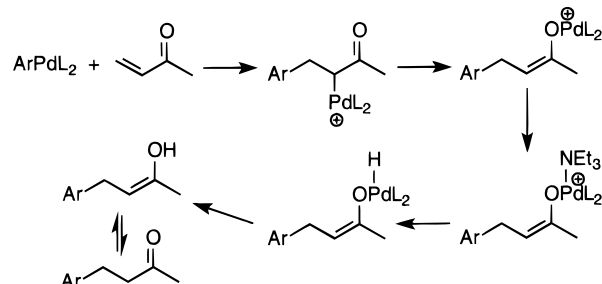
Bromide-ions scavenge cationic palladium intermediates to form neutral complexes with softer palladium centers, which are unlikely to migrate onto oxygen via a metallotropic rearrangement, and thus can suppress the formation of enolate complexes. It should also be noted that conjugate addition becomes a normal pathway for nickel-catalyzed Heck-type processes, possibly due to a higher affinity of nickel toward oxygen.

The involvement of *O*-enolates of palladium is a subject of dispute (cf., e.g., ref 354). Though such forms were rarely suggested to play a significant role, (cf., e.g., ref 355), there are data which can be interpreted through the formation of such complexes. Though palladium prefers to form *C*-enolates, η^3-oxoallyl bonding is also known.[356,357] The latter can be regarded as an intermediate form between the more stable *C*-enolate and the less stable *O*-enolate (Scheme 154). *O*-Enolate has been detected in the

Scheme 154
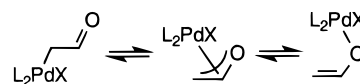
stoichiometric reaction of (DPPF)PdAr(Br) with isobutyrophenone enolate.[358]

The involvement of either η^3-oxoallyl or *O*-enolates can account for the formation of the regular Heck product in the arylation of 2-cyclohexenone,[220] Scheme 155, as well as in the arylation of 1,2-cyclohexanedi-

Scheme 155

2 : 3
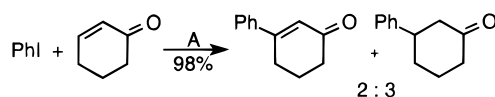
one and ethyl ether of its monoenol,[359] which can be realized in aqueous DMF to give 3-aryl derivatives in moderate to good yields (Scheme 156).

In both cases the primary arylpalladated intermediate cannot eliminate PdH directly. In the case of 2-cyclohexenone, the stereochemistry of the organo-

Scheme 156
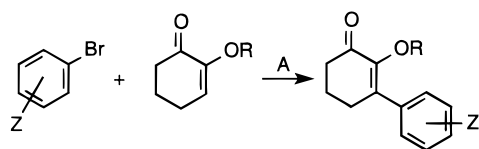
A: Pd(OAc)$_2$ (5 mol%), 2L, iPr$_2$NEt, DMF-H$_2$O (85:15, v/v),
    100°C, 16-96 h or microwave oven, 10 min
Z = H, o-, m-, p-Me, m-MeO, p-Et, m-, p-Ac, p-CF$_3$, o-, m-, p-Cl
R = H, L = PPh$_3$
R = Et, L = P(o-Tol)$_3$

palladium intermediate can be inverted through enolization (Scheme 157).

Scheme 157
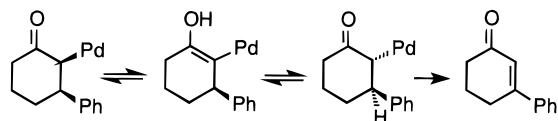
However, in the second case the enolization is not possible and the only way leading to elimination and continuation of the catalytic cycle is a hop to the other side of the ring via Pd enolate, as shown in, e.g., Scheme 158.

Scheme 158
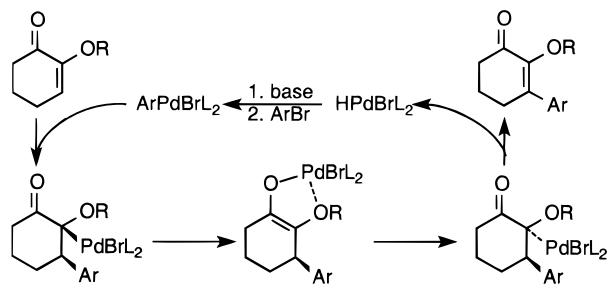
In both cases it is notable that the reactions are run in aqueous media, since water may lend assistance in such equilibria. In latter case, the formation of the palladium enolate is likely to occur due to additional chelate stabilization.

The arylation of Baylis−Hillman adducts was achieved under phosphine-free phase-transfer conditions in high yields and selectivity toward the rearranged product.[360] Exclusive formation of the rearranged product is likely to be accounted for by a succession of palladotropic and prototropic shifts and is further evidence in favor of formation of a chelated Pd enolate (Scheme 159).

Scheme 159

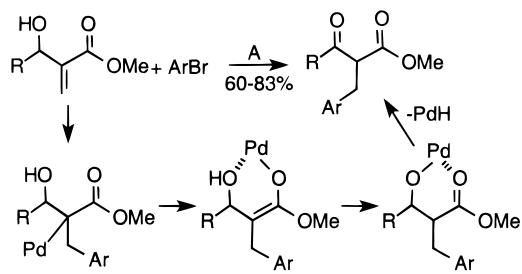A: Pd(OAc)$_2$ (2 mol%), NaHCO$_3$, Bu$_4$NBr, THF, reflux, 7-18 h

Arylation of ketones is likely to proceed as a Heck-type attack of arylpalladium intermediates on enols or enolates. We do not discuss here the reactions with covalent-bonded enolates (Si, Sn, etc., enol ethers) which can be used in similar arylation reactions, because formally such reactions occur through trans-metalation and thus belong to cross-coupling chemistry (cf., e.g., refs 361−365)

Several versions of direct arylation of ketones and other CH-acids were published. The phenylation of benzyl ketones by iodobenzene in a phosphine-free system has been reported (Scheme 160).[366]

Scheme 160
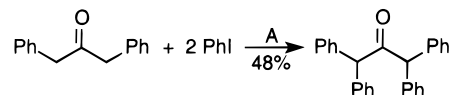
A: PdCl$_2$ (5 mol%), Cs$_2$CO$_3$, LiCl, DMF, 100°C, 5 h

Intramolecular arylation of ketones leading to 7-hydroxyquinolines[367] and benzocycloalkanones has been reported.[368]

Simultaneously two general wide-scope procedures for ketone arylation have been proposed. Buchwald et al.[369] utilized the system Pd$_2$(dba)$_3$/BINAP or, better, TolBINAP in the presence of tBuONa in THF. The reaction in the presence of chiral ligands can be run in an enantioselective mode.[370] The reaction is exceptionally regioselective due to high sensitivity to steric factors, as in the case of unsymmetrical ketones only the less hindered product is formed from the less substituted enolate (Scheme 161).

Scheme 161
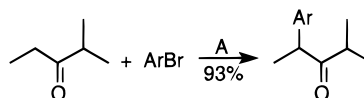
A: Pd$_2$(dba)$_3$ (1.5 mol%), 2TolBINAP, tBuONa, THF, 70°C
Ar = p-PhC$_6$H$_4$

Hartwig et al.[371] proposed a similar procedure using Pd$_2$(dba)$_3$/DPPF in the presence of a stronger base KN(SiMe$_3$)$_2$ in THF. Again, a more hindered analogue of DPPF, 1,1′-bis[bis(2-methylphenyl)phosphino]ferrocene (DTPF), gave better results. The procedure is particularly selective toward monoarylation. Later Hartwig has shown that more reactive arylation system can be built with sterically hindered di- and monophosphines DtBPF (1,1-bis-(di-$tert$-butylphosphino)ferrocene), PPF-tBu$_2$ (1-diphenylphosphino-2-(di-$tert$-butylphosphino)ethylferrocene), PCy$_3$, and PtBu$_3$.[358] Aryl bromides and aryl chlorides showed similar reactivity and gave high yields of monoarylated ketones under mild conditions. The system can be applied to the arylation of malonates (Scheme 162).

PPF-tBu$_2$ was particularly effective for arylation with aryl triflates. A very important result of this study is the demonstration of a high activity of an underligated system. The best results were obtained for the ratio Pd/L = 1 for monophosphines and Pd/L

Scheme 162
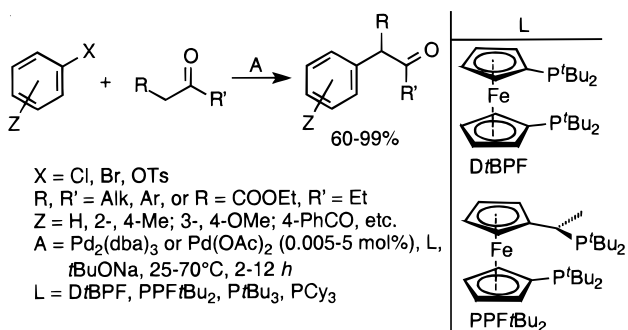
= 2 for diphosphines. In the study of the stoichiometric reaction it was shown that DtBPF ligand forms η^1-enolate complex, which gives the arylation product on annealing. The competition of β-hydride elimination is inessential, and chelation control plays no role in suppressing this route (Scheme 163).

Scheme 163
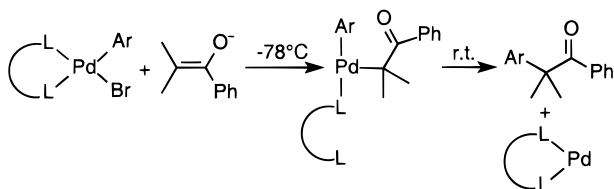
Thus, the mechanism of the catalytic cycle involves an electrophilic attack of neutral (L–L)PdAr(X) intermediate at electron-rich alkene (enolate), most likely occurring via a five-coordinate complex or complexes.

Vinylogous arylation of α,β-unsaturated aldehydes and ketones at the γ-position has been described. An unusual reaction of substrates, which are at least formally capable of the regular Heck reaction, occurs in the presence of a relatively strong base Cs$_2$CO$_3$ in good to high yields (Scheme 164).[372]

Scheme 164
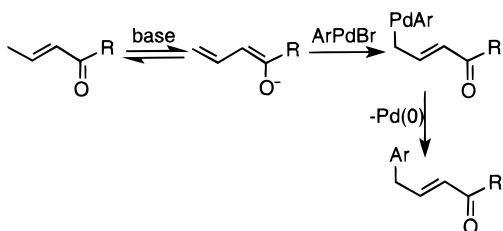
as shown in, e.g., Scheme 165. A tandem aldol–arylation reaction has been realized (Scheme 166).

Scheme 165

A: Pd(OAc)$_2$ (5 mol%), 2PPh$_3$, Cs$_2$CO$_3$, DMF, 60°C, 6 h
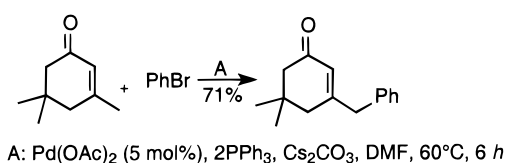
Besides enolates, other resonance-stabilized carbanions can supply substrates for the Heck reaction. There are still only a few examples of this reaction,[373−377] but progress in understanding the trends

Scheme 166

A: Pd(OAc)$_2$ (5 mol%), 2PPh$_3$, Cs$_2$CO$_3$, DMF, 60°C, 46 h
R = n-C$_6$H$_{13}$, Ar = p-PhC$_6$H$_4$
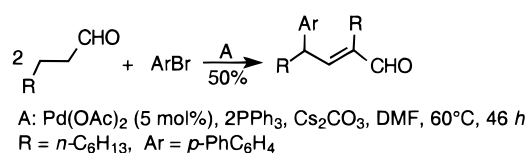
and real scope of the Heck cycle shall undoubtedly very soon multiply the applications in an avalanche manner. So far, we may site the arylation of alkylnitrobenzenes and alkylazines (Scheme 167).[378]

Scheme 167

A: Pd(OAc)$_2$ (5 mol%), 4PPh$_3$, Cs$_2$CO$_3$, DMF, 140°C
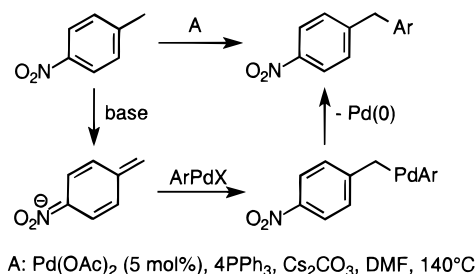
2. Heck-Like Reactions with Aromatic Substrates

Aromatic compounds also take part in Heck-type reactions, as electrophilic aryl- or vinylpalladium can attack aromatic rings. In most cases, this reaction is limited to strongly electron-donating aromatics, such as phenols, in which case the analogy with enols is obvious.

The arylation of phenols (or rather phenolates, as the reaction runs in the presence of base) is formally similar to the arylation of enolates. The intermolecular version[366,377] can be applied to o-phenylphenols and naphthols. Mono- or bis-arylation can be selectively achieved using an equimolar phenol:iodoarene ratio or large excess of iodoarene, respectively, Scheme 168.

Scheme 168

A: Pd(OAc)$_2$ (5 mol%), Cs$_2$CO$_3$, DMF, 100°C, 22-44 h
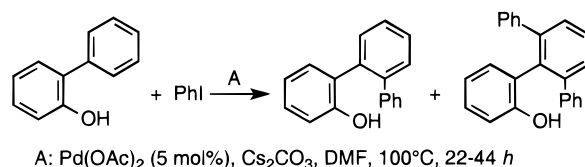
The directing effect of the phenolate group is the key factor of this reaction (Scheme 169).

Scheme 169
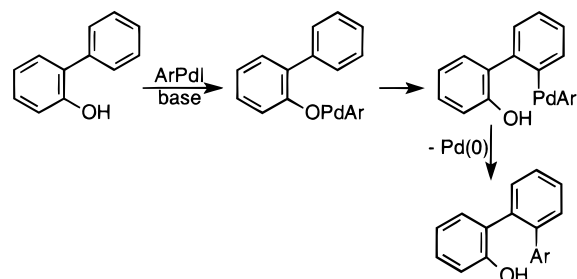
$ortho$-Directed self-arylation may run until steric reasons command it to stop. Curious structures can

be built this way in considerable yields from very simple precursors (Scheme 170).[379]

Scheme 170

A: Pd(OAc)$_2$ (5 mol%), 4PPh$_3$,Cs$_2$CO$_3$, xylene, reflux
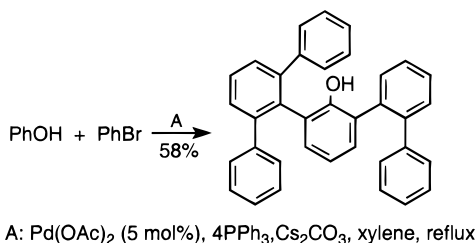
However, when the *ortho*-positions are occupied as in 2,6-di(*tert*-butyl)phenol, the arylation is directed to the *para*-position,[380] and when there are no free *ortho/para*-sites, benzylic arylation occurs.[379]

An intramolecular version of this reaction has been realized using Pd(OAc)$_2$,[381,382] Pd(PPh$_3$)$_4$, or Herrmann's palladacycle *hc* as the catalyst.[383,384] The latter can be replaced by an equimolar mixture of Pd-(OAc)$_2$ and P(*o*-Tol)$_3$, while the addition of second equivalent of P(*o*-Tol)$_3$ retards the reaction significantly. A phenolic hydroxyl is required to enable the process—methyl ethers are practically unreactive under the conditions described (Scheme 171).

Scheme 171

A: *hc* (5 mol%), Cs$_2$CO$_3$, DMA, 80-115°C, 24-60 *h*
X = Br, I; Y = CH$_2$, O, N(COOMe)
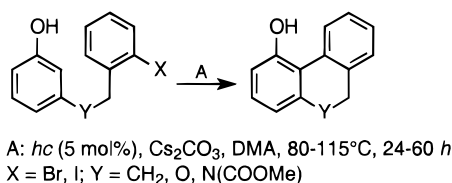
Electron-rich heterocycles can be arylated by aryl halides in a Heck-type reaction. Furan, thiophene, pyrrole, azoles, and their respective benzo derivatives were arylated by aryl bromides or some reactive heteroaryl chlorides in the presence of Pd(PPh$_3$)$_4$ or Pd(OAc)$_2$ and PPh$_3$[385−388] under rather harsh conditions (5−10 mol % Pd catalyst, K$_2$CO$_3$ or Cs$_2$CO$_3$, DMF, 140 °C, 1−3 days).

Thiophenes substituted by electron-withdrawing groups can be subject to arylation in an aqueous system in the presence of a phase-transfer agent under milder conditions to give high yields of 2- or 5-arylthiophenes (Scheme 172).[389]

Scheme 172

A: Pd(OAc)$_2$ (5 mol%), K$_2$CO$_3$, Bu$_4$NBr,
   MeCN/H$_2$O, 80°C, 3-54 *h*
Z = 2-CHO, 3-CHO, 2-NO$_2$, 2-CN, 3-CN
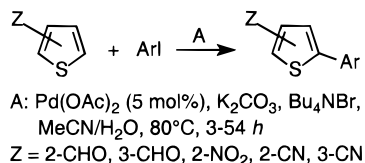
Other examples of the arylation of thiophene include the reaction with 5-halo-2,4-dimethoxypyrimidine[201] and the polymerization of iodothiophenes.[390]

Going back to the arylation of aromatic molecules, it should be noted that while only electron-rich phenols or heterocycles were, so far, involved in the intermolecular version, intramolecular arylation is a well-known process, examples of which are numer-

ous though random. Thus, the intramolecular reaction of *cis-o*-bromostilbenes under phase-transfer phosphine-free conditions has been found to lead to phenanthrenes in good yield.[391]

In contrast, the reaction of *trans-o*-bromostilbenes leads exclusively to a product of intermolecular double Heck reaction (Scheme 173).[391]

Scheme 173

A: Pd(OAc)$_2$ (10 mol%), K$_2$CO$_3$, LiCl, Bu$_4$NBr, DMF, 110°C
Ar = Ph, 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-O$_2$NeC$_6$H$_4$,
   2-pyridyl, 2-furyl, 4-MeOOCC$_6$H$_4$, 3,5-*t*-Bu$_2$C$_6$H$_3$,
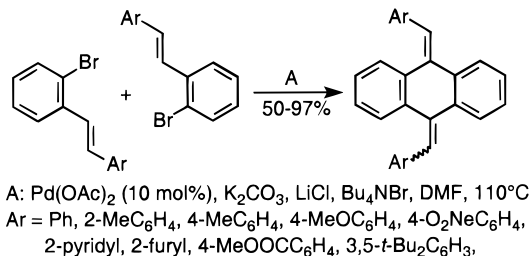
The same product (Ar = Ph) is formed from the reaction of *o*-dibromobenzene with styrene. The annulation occurs only under phase-transfer phosphine-free conditions, while a standard Heck procedure (Pd(OAc)$_2$−PPh$_3$−Et$_3$N) leads exclusively to debromination products.

3. Other Types of Unsaturated Substrates

Besides double and triple carbon−carbon bonds, multiple carbon−heteroatom bonds also can take part in Heck-like processes. Intermolecular versions of such reactions are so far unknown, but intramolecular reactions involving such steps have been described.

The intramolecular arylation or vinylation of a C=O double bond occurs in several interesting reactions. One of the examples is the arylation of salycilic aldehydes (Scheme 174).[392]

Scheme 174
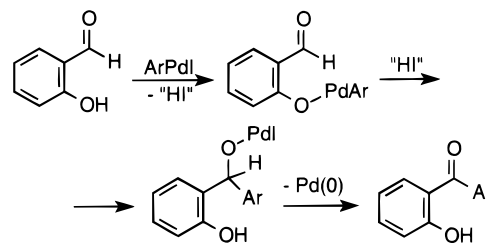
The so-called Heck−Larock annulation also can be cited as a similar process (Scheme 175).[393,394,395]

Scheme 175

A: Pd(OAc)$_2$ (5 mol%), Na$_2$CO$_3$, Bu$_4$NCl, DMA, 100°C
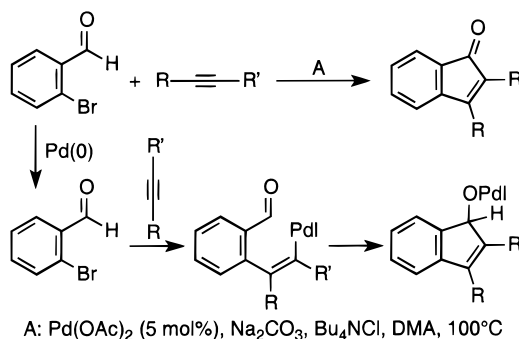
In the presence of a proton donor, the O−Pd intermediate can be trapped to give indenols in good yields.[396,397] Indenols can be transformed into indenones by heating with Pd(OAc)$_2$, which confirms that the mechanism for Heck−Larock cyclization indeed involves the addition of vinylpalladium intermediate to C=O bond (Scheme 176). The noncatalytic sto-

Scheme 176

A: Pd(OAc)$_2$ (5 mol%), KOAc, EtOH, DMF, 60°C
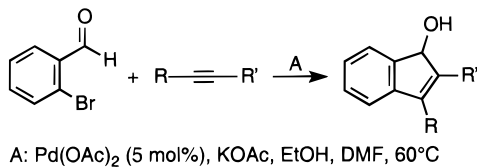
ichiometric version of this reaction has been described earlier.[398,399]

The intramolecular vinylation of C≡N and C=N bond runs in a similar fashion giving various annulation products,[400−402] though this reaction may be complicated by the cascade arylation of phenyl ring.[403]

Scheme 177

A: Pd(OAc)$_2$ (5 mol%), Na$_2$CO$_3$, LiCl, DMF, 100°C
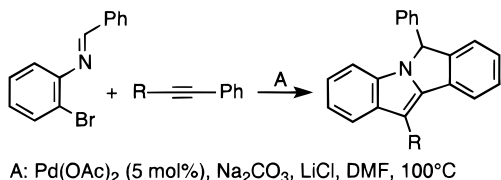
Besides multiple bonds three- and four-membered cycles can undergo an insertion of arylpalladium intermediates. Thus, an interesting Heck-type transformation occurs with α-substituted cyclobutanols under Heck arylation conditions.[404] The reaction re-

Scheme 178

A: Pd$_2$(dba)$_3$ (1 mol%), 2 BINAP, K$_2$CO$_3$, dioxane, 100°C
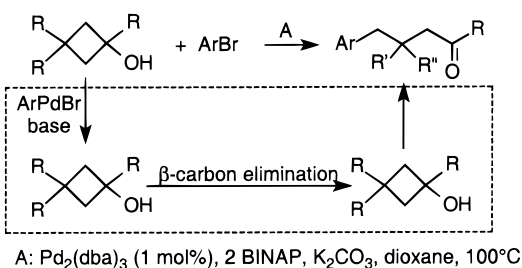
quires chelate phosphine ligands (dppe and dppf were efficient while dppp and dppb were much less so). The process is formally equivalent to the Heck reaction, though not with a π-bond but rather with a strained σ-bond rupture (Scheme 177).

Scheme 179
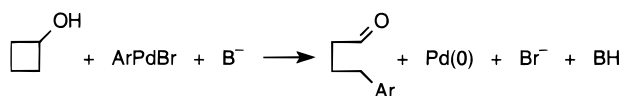
Similar ring-opening arylation has been described for silyloxycyclopropanes.[405]

4. Conjugation of Pd(IV)/Pd(II) Processes with Pd(II)/Pd(0) Catalysis

A number of interesting extensions of the Heck reaction comes from manipulations with olefins

which give migratory insertion intermediates that are not able to undergo *syn*-PdH elimination.

It is well-known that the arylpalladium intermediate can be involved in an intramolecular attack at aromatic rings or other groups activated for electrophilic attack giving rise to palladacycles and thus switching to Pd(IV)−Pd(II) chemistry.[406] We have purposefully avoided the discussion of the Pd(IV)−Pd(II) alternative for regular Heck chemistry[129] as we believe that all of the known experimental data on the Heck reactions can be rationalized in terms of a canonical Heck cycle based on Pd(II)−Pd(0) and do not require alternative chemistry to be involved. Still, the processes driven by the Pd(IV)−Pd(II) mechanism are well-known and adequately proven, e.g., for complexes containing C(sp^3)−Pd bonds. This chemistry is not a twin of Pd(II)−Pd(0) but has its own well-recognizable features and uses.[5,407,408]

Among the interesting examples of the involvement of neighboring groups via Pd(IV)−Pd(II)−Pd(0) cycle, notable is the formation of benzofurans in the arylation of bromoolefins by *o*-methoxyiodoarenes, discovered by Dyker (Scheme 180).[409]

Scheme 180

A: Pd(OAc)$_2$ (10 mol%), K$_2$CO$_3$, Bu$_4$NBr, DMF, 100°C, 3 d
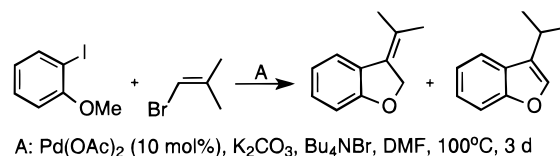
Among several plausible mechanisms the one shown in Scheme 181 involving the oxidative addition

Scheme 181
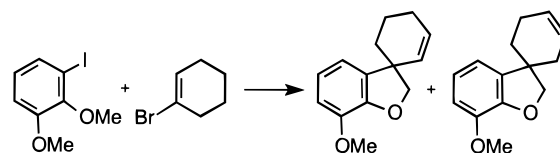
of vinyl bromide to a Pd(II) palladacycle fits the experimental data best, as an alternative mechanism involving only Pd(II)/Pd(0) steps fails to explain the reaction with 1-bromocyclohexene).
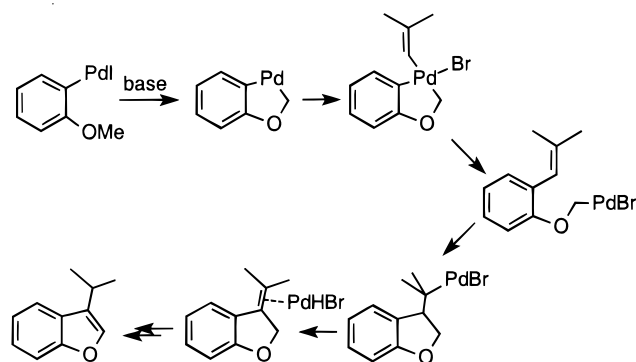
Similar transformations account for the formation of self-arylation products on exposure of *o*-iodoanisole to palladium catalysts, e.g., Herrmann's palladacycle *hc*,[410,411] see ref 412. A *tert*-butyl group can also be

involved in the palladacycle-mediated homocoupling of *o-tert*-butyliodobenzene.[413]

Several beautiful tricks were developed by Catellani and Chiusoli et al. based on a sort of *retro*-Heck process. Some σ-hydrocarbyl complexes of palladium can undergo the extrusion of arylpalladium intermediate. This transformation is a reverse reaction to migratory insertion. The reversibility of migratory insertion in a normal Heck process is not a well studied subject, though it might have an influence on, for instance, the scrambling of aryls via Scheme 182.

Scheme 182
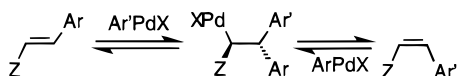
The extrusion of the ArPdX intermediate can occur from a heavily hindered σ-hydrocarbyl intermediate with favorable geometry. Such complexes can be readily generated by reactions of norbornene and other alkenes which cannot give regular Heck products because *syn*-PdH elimination from the intermediates formed by migratory insertion is not possible.

A beautiful extension of the Heck reaction enabling easy preparation of *o,o*-disubstituted cinnamates was developed by Catellani.[414,415] The net reaction can be written as shown in Scheme 183.

Scheme 183
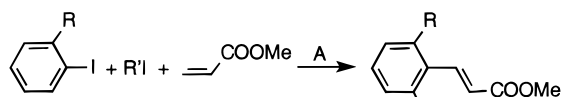
A: Pd(OAc)$_2$, norbornene, K$_2$CO$_3$, AcOK, DMF, 55°C

Starting from unsubstituted iodobenzene, symmetrical *o,o*-dialkylcinnamates can be formed in a one-step procedure. The mechanism of this reaction employs the reversibility of insertion of arylpalladium complex to the double bond of norbornene, the formation of palladacycle, and a Pd(II)/Pd(IV) catalytic process (Scheme 184).

Scheme 184
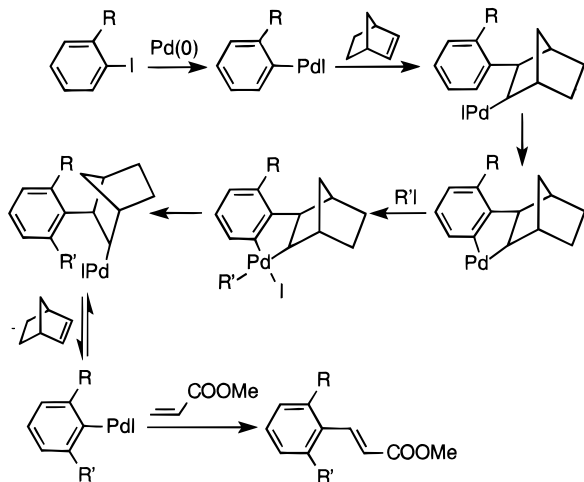
Vinylmethyl ketone and acrylonitrile can be used in place of methyl acrylate with relative success. The whole process has a very low catalytic efficiency (TON 3.5−3.8) and is very slow, but the result achieved here in one step must otherwise be pursued in a multistep procedure with uncertain outcome.

The reaction of norbornene-based palladacycles with aryl halides can follow two different routes depending on the substituents.[416−418] The upper route leads through a spontaneous extrusion to di- and terphenyls with rare substitution patterns (Scheme 185).[419]

Scheme 185
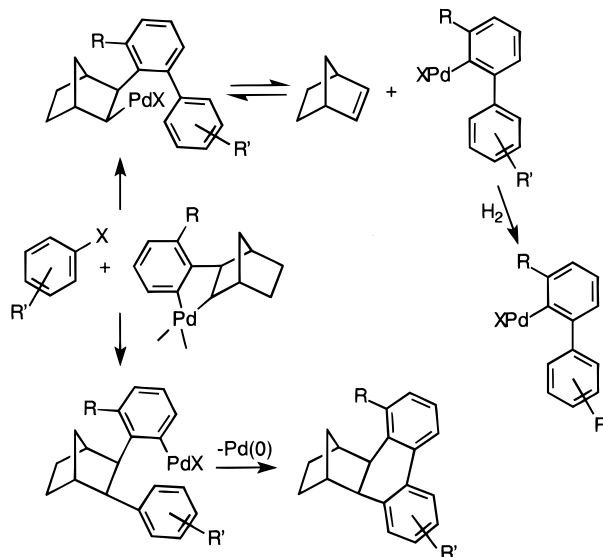
The reaction of 1-naphthylmethyl chloride with olefins under Heck reaction conditions leads to the formation of an interesting byproduct via a process in which the reactive organopalladium center is pruned from the initial site and grafted onto the adjacent position of the naphthalene ring, likely through the formation of a palladacycle (Scheme 186).[347]

Scheme 186
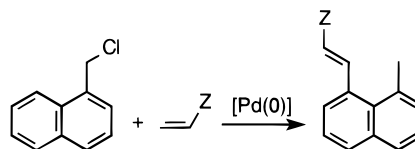
References

(1) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4.
(2) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345.
(3) Daves, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.
(4) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *33*, 2379.
(5) De Meijere, A.; Braese, S. In *Transition Metal Catalyzed Reactions*; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999.
(6) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
(7) Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; Jai Press Inc: Greenwich, CT, 1996; Vol. 5.
(8) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.
(9) Brase, S.; deMeijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.
(10) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.
(11) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.

(12) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.
(13) Link, J. T.; Overman, L. E. *Chemtech* **1998**, *28*, 19.
(14) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447.
(15) Reetz, M. T. In *Transition Metal Catalyzed Reactions*; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Sci.: Oxford, 1999.
(16) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
(17) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *14*, 2320.
(18) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254.
(19) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
(20) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009.
(21) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, *11*, 2177.
(22) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. *Organometallics* **1995**, *14*, 1818.
(23) Ioele, M.; Ortaggi, G.; Scarsella, M.; Sleiter, G. *Polyhedron* **1991**, *10*, 2475.
(24) Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 1890.
(25) Grushin, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5831.
(26) Roffia, P.; Gregorio, G.; Conti, F.; Pregaglia, G. F. *J. Mol. Catal.* **1977**, *2*, 191.
(27) Amatore, C.; Jutand, A.; Medeiros, M. J. *New J. Chem.* **1996**, *20*, 1143.
(28) Mason, M. R.; Verkade, J. G. *Organometallics* **1992**, *11*, 2212.
(29) McLaughlin, P. A.; Verkade, J. G. *Organometallics* **1998**, *17*, 5937.
(30) Reetz, M. T.; Löhmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 481.
(31) Dullius, J. E. L.; Suarez, P. A. Z.; Einloft, S.; de Souza, R. F.; Dupont, J.; Fischer, J.; De Cian, A. *Organometallics* **1998**, *17*, 815.
(32) Herrmann, W. A.; Elison, M.; Fischer, J.; Koecher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371.
(33) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168.
(34) Negishi, E.-i.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, *17*, 1338.
(35) Amatore, C.; Azzabi, M.; Calas, P.; Jutand, A.; Lefrou, C.; Rollin, Y. *J. Electroanal. Chem.* **1990**, *288*, 45.
(36) Amatore, C.; Jutand, A.; Meyer, G. *Inorg. Chim. Acta* **1998**, *273*, 76.
(37) Amatore, C.; Jutand, A.; Meyer, G.; Atmani, H.; Khalil, F.; Chahdi F. O *Organometallics* **1998**, *17*, 2958.
(38) Tschoerner, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 670.
(39) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7.
(40) Crampton, M. R. In *Organic Reaction Mechanisms 1995*; Knipe, A. C., Watts, W. E., Eds.; John Wiley & Sons Ltd.: New York, 1997.
(41) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810.
(42) Herrmann, W. A.; Brossmer, C.; Oefele, K.; Beller, M.; Fischer, H. *J. Organomet. Chem.* **1995**, *491*, C1.
(43) Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954.
(44) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.
(45) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* **1991**, *56*, 5796.
(46) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, *10*, 1953.
(47) Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465.
(48) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1.
(49) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M.; Meyer, G. *Organometallics* **1995**, *14*, 5605.
(50) Albert, K.; Gisdakis, P.; Roesch, N. *Organometallics* **1998**, *17*, 1608.
(51) Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2029.
(52) Kawataka, F.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 654.
(53) Ludwig, M.; Strömberg, S.; Svensson, M.; Åkermark, B. *Organometallics* **1999**, *18*, 970.
(54) Bräse, S.; Rümper, J.; Voigt, K.; Albecq, S.; Thurau, G.; Villard, R.; Waegell, B.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, *671*, 1.
(55) Albéniz, A. C.; Espinet, P.; Lin, Y.-S. *Organometallics* **1995**, *14*, 2977.
(56) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1993**, *58*, 7421.
(57) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3654.
(58) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Tetrahedron Lett.* **1991**, *32*, 1753.
(59) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558.
(60) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481.
(61) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 5076.

(62) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285.
(63) Grigg, R.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *32*, 3855.
(64) Meyer, F. E.; Parsons, P. J.; Meijere, A. d. *J. Org. Chem.* **1991**, *56*, 6487.
(65) Grigg, R.; Dorrity, M. J.; Malone John F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett* **1990**, *31*, 1343.
(66) Zhang, Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1989**, *111*, 3454.
(67) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.
(68) Liu, C. H.; Cheng, C. H.; Cheng, M. C.; Peng, S. M. *Organometallics* **1994**, *13*, 1832.
(69) Rawal, V. H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583.
(70) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E.-i. *J. Am. Chem. Soc.* **1992**, *114*, 10091.
(71) Albeniz, A. C.; Espinet, P.; Lin, Y.-S. *J. Am. Chem. Soc.* **1996**, *118*, 7145.
(72) Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans 1* **1997**, 447.
(73) Gibson, S. E.; Guillo, N.; Tozer, M. J. *J. Chem. Soc., Chem. Commun.* **1997**, 637.
(74) Denieul, M.-P.; Skrydstrup, T. *Tetrahedron Lett.* **1999**, *40*, 4901.
(75) Jeong, S.; Chen, X.; P. G., H. *J. Org. Chem.* **1998**, *63*, 8640.
(76) Risch, N.; Gauler, R.; Keuper, R. *Tetrahedron Lett.* **1999**, *40*, 2925.
(77) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.
(78) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477.
(79) Tietze, L. F.; Schimpf, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1089.
(80) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896.
(81) Karabelas, K.; Hallberg, A. *Acta Chem. Scand.* **1990**, *44*, 257.
(82) Jeffery, T. *Tetrahedron Lett.* **1999**, *40*, 1673.
(83) Trost, B. M. *Science* **1991**, *254*, 1471.
(84) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
(85) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813.
(86) Grigg, R.; Sridharan, V. *Pure Appl. Chem.* **1998**, *70*, 1047.
(87) Negishi, E. I.; Coperet, C.; Ma, S. M.; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.
(88) Trost, B. M. *Pure Appl. Chem.* **1994**, *66*, 2007.
(89) Spencer, A. *J. Organomet. Chem.* **1982**, *240*, 209.
(90) Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 984.
(91) Deeth, R. J.; Smith, A.; Hii, K. K.; Brown, J. M. *Tetrahedron Lett.* **1998**, *39*, 3229.
(92) Hammett, L. P. *Physical organic chemistry; reaction rates, equilibria, and mechanisms*, 2nd ed.; McGraw-Hill: New York, 1970.
(93) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29.
(94) Brown, J. M.; Hii, K. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 657.
(95) Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011.
(96) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.
(97) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083.
(98) Spencer, A. *J. Organomet. Chem.* **1983**, *258*, 101.
(99) Spencer, A. *J. Organomet. Chem.* **1984**, *270*, 115.
(100) Reetz, M. T.; Demuth, R.; Goddard, R. *Tetrahedron Lett.* **1998**, *39*, 7089.
(101) Beller, M.; Zapf, A. *Synlett* **1998**, *7*, 792.
(102) Namyslo, J. C.; Kaufmann, D. E. *Synlett* **1999**, *1*, 114.
(103) Boyes, A. L.; Butler, I. R.; Quayle, S. C. *Tetrahedron Lett.* **1998**, *39*, 7763.
(104) Laly, M.; Broussier, R.; Gautheron, B. *Tetrahedron Lett.* **2000**, *41*, 1183.
(105) Shaw, B. L.; Perera, S. D. *Chem. Commun* **1998**, 1863.
(106) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734.
(107) *Z*-Olefins resulting from the less favorable conformer are not sole *kinetic control* products. The formation of such products along with regular *E*-olefins in some reactions is likely to be accounted for by the rate of reductive elimination being fast on the time scale of internal rotation around the C−C bond (the anti-Curtin−Hammett kinetics).
(108) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995.
(109) Graf, C.-D.; Malan, C.; Harms, K.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 5581.
(110) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.
(111) Cooper, A. C.; McAlexander, L. H.; Lee, D.-H.; Torres, M. T.; Crabtree, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 9971.
(112) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123.
(113) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694.
(114) Bozell, J. J.; Voght, C. E. *J. Am. Chem. Soc.* **1988**, *110*, 2655.

(115) Scott, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1755.
(116) Kiji, J.; Okano, T.; Ooue, A. *J. Mol. Catal. (A)* **1999**, *147*, 3.
(117) Crousse, B.; Xu, L. H.; Bernardinelli, G.; Kuendig, E. P. *Synlett* **1998**, *6*, 658.
(118) Bräse, S. *Tetrahedron Lett* **1999**, *40*, 6757.
(119) Bankston, D.; Fang, F.; Huie, E.; Xie, S. *J. Org. Chem.* **1999**, *64*, 3461.
(120) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.
(121) Louie, J.; Hartwig, J. F. *Angew. Chem.* **1996**, *108*, 2531.
(122) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23.
(123) Mitsudo, T.-a.; Fischetti, W.; Heck, R. F. *J. Org. Chem.* **1984**, *49*, 1640.
(124) Overman, L. E.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4643.
(125) Ohff, M.; Ohff, A.; Boom, M. E. v. d.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687.
(126) Shaw, B. L.; Perera, S. D.; Staley, E. A. *Chem. Commun.* **1998**, 1361.
(127) Albisson, D. A.; Bedford, R. B.; Scully, P. N. *Tetrahedron Lett.* **1998**, *39*, 9793.
(128) Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 7379.
(129) Shaw, B. L. *New J. Chem.* **1998**, 77.
(130) As soon as postrun catalyst recovery experiments are likely to be done for reactions with reasonable loads of catalyst, and the activity of catalytic species generated is very high, it also may be argued that only a tiny fraction of palladacycle precursor underwent the cleavage into catalytically active species while the major part of it has not participated in the reaction.
(131) Beletskaya, I. P.; Chuchurjukin, A. V.; Dijkstra, H. P.; van Klink, G. P. M.; van Koten, G. *Tetrahedron Lett.* **2000**, *41*, 1075.
(132) Kiewel, K.; Liu, Y.; Bergbreiter, D. E.; Sulikowski, G. A. *Tetrahedron Lett.* **1999**, *40*, 8945.
(133) Ohff, M.; Ohff, A.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1999**, 357.
(134) Beletskaya, I. P.; Kashin, A. N.; Karstedt, N. B.; Chuchurjukin, A. V. OMCOS 10, Varsailles, France, 1999; p SL.
(135) Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. *J. Am. Chem. Soc.* **1999**, *121*, 9531.
(136) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287.
(137) Beller, M.; Riermeier, T. H. *Tetrahedron Lett.* **1996**, *37*, 6535.
(138) Tietze, L. F.; Schirok, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1124.
(139) Tietze, L. F.; Noebel, T.; Spescha, M. *Angew. Chem.* **1996**, *108*, 2385.
(140) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.
(141) Tietze, L. F.; Noebel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971.
(142) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93.
(143) Herrmann, W. A.; Schwarz, J.; Gardiner, M. G.; Spiegler, M. *J. Organomet. Chem.* **1999**, *575*, 80.
(144) Gardiner, M. G.; Herrmann, W. A.; Reisinger, C.-P.; Schwarz, J.; Spiegler, M. *J. Organomet. Chem.* **1999**, *572*, 239.
(145) Heinemann, C.; Muller, T.; Apeloig, Y.; Schwarz, H. *J. Am. Chem. Soc.* **1996**, *118*, 2023.
(146) Froehlich, N.; Pidun, U.; Stahl, M.; Frenking, G. *Organometallics* **1997**, *16*, 442.
(147) Herrmann, W. A.; Fischer, J.; Oefele, K.; Artus, G. R. J. *J. Organomet. Chem.* **1997**, *530*, 259.
(148) Herrmann, W. A.; Elison, M.; Fischer, J.; Koecher, C.; Artus, G. R. J. *Angew. Chem.* **1995**, *107*, 2602.
(149) Enders, D.; Gielen, H.; Raabe, G.; Runsink, J.; Teles, J. H. *Chem. Ber.* **1996**, *129*, 1483.
(150) McGuinness, D. S. G.; Melinda J.; Cavell, Kingsley J.; Skelton, Brian W.; White, Allan H. *J. Organomet. Chem.* **1998**, *565*, 165.
(151) McGuinness, D. S. G.; Melinda J.; Cavell, Kingsley J.; Skelton, Brian W.; White, Allan H. *Organometallics* **1999**, *18*, 1596.
(152) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348.
(153) Clyne, D. S.; Jin, J.; Genest, E.; Gallucci, J. C.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 1125.
(154) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, *19*, 1287.
(155) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
(156) Jeffery, T. *Synthesis* **1987**, *1*, 70.
(157) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.
(158) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
(159) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis,* 3rd ed.; VCH: New York, 1993.
(160) Jeffery, T.; Galland, J.-C. *Tetrahedron Lett.* **1994**, *35*, 4103.
(161) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051.
(162) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.
(163) Corma, A. *Chem. Rev.* **1997**, *97*, 2373.
(164) Jeffery, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751.
(165) Dussault, P. H.; Eary, C. T. *J. Am. Chem. Soc.* **1998**, *120*, 7133.
(166) Li, J. J. *J. Org. Chem.* **1999**, *64*, 8425.
(167) Moreno-Manas, M.; Pleixats, R.; Roglans, A. *Synlett* **1997**, *10*, 1157.
(168) Moreno-Manas, M.; Perez, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449.
(169) Guertler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107.
(170) Berteina, S.; Wendeborn, S.; Brill, W. K. D.; Mesmaeker, A. D. *Synlett* **1998**, *6*, 676.
(171) Koenig, B.; Knieriem, B.; Meijere, A. d. *Chem. Ber.* **1993**, *126*, 1643.
(172) Bazan, G. C.; Oldham, W. J.; Lachicotte, R. J.; Tretiak, S.; Chernyak, V.; Mukamel, S. *J. Am. Chem. Soc.* **1998**, *120*, 9188.
(173) Buchacher, P.; Helgeson, R.; Wudl, F. *J. Org. Chem.* **1998**, *63*, 9698.
(174) Oldham, W. J.; Lachicotte, R. J.; Bazan, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 2987.
(175) Blettner, C. G.; Koenig, W. A.; Stenzel, W.; Schotten, T. *Tetrahedron Lett.* **1999**, *40*, 2101.
(176) Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449.
(177) Klingelhofer, S.; Heitz, W.; Greiner, A.; Oestreich, S.; Forster, S.; Antonietti, M. *J. Am. Chem. Soc.* **1997**, *119*, 10116.
(178) Schmid, G. *Clusters and Colloids*; VCH: Weinheim, 1994.
(179) Fowley, L. A.; Michos, D.; Luo, X.-L.; Crabtree, R. H. *Tetrahedron Lett.* **1993**, *34*, 3075.
(180) Reetz, M. T.; Lohmer, G. *J. Chem. Soc., Chem. Commun.* **1996**, *16*, 1921.
(181) Beller, M.; Fischer, H.; Kuehlein, K.; Reisinger, C. P.; Hermann, W. A. J. *J. Organomet. Chem.* **1996**, *520*, 257.
(182) Reetz, M. T.; Breinbauer, R.; Wanninger, K. *Tetrahedron Lett.* **1996**, *37*, 4499.
(183) Le Bars, J.; Sprecht, U.; Bradley, J. S.; Blackmond, D. G. *Langmuir* **1999**, *15*, 7621.
(184) Cheprakov, A. V.; Lomakina, M. A.; Tsarkova, L. A.; Beletskaya, I. P. Manuscript in preparation.
(185) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 165.
(186) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582.
(187) Sugihara, T.; Takebayashi, M.; Kaneko, C. *Tetrahedron Lett.* **1995**, *36*, 5547.
(188) Hillers, S.; Sartori, S.; Reiser, O. *J. Am. Chem. Soc.* **1996**, *118*, 2087.
(189) Voigt, K.; Schick, U.; Meyer, F. E.; de Meijere, A. *SYNLETT* **1994**, 189.
(190) Tietze, L. F.; Burkhardt, O.; Henrich, M. *Liebigs Ann., Recl.* **1997**, *5*, 887.
(191) Tietze, L. F.; Burkhardt, O.; Henrich, M. *Liebigs Ann., Recl.* **1997**, *7*, 1407.
(192) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie: London, 1998.
(193) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem.* **1989**, *371*, 397.
(194) Bumagin, N. A.; Andryukhova, N. P.; Beletskaya, I. P. *Dokl. Chem. (Engl. Transl.)* **1990**, *313*, 183.
(195) Zhao, F.; Shirai, M.; Arai, M. *J. Mol. Catal. (A)* **2000**, *154*, 39.
(196) Demik, N. N.; Kabachnik, M. M.; Novikova, Z. S.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1995**, *31*, 57.
(197) Zhang, H. C.; Daves, G. D. *Organometallics* **1993**, *12*, 1499.
(198) Hayashi, M.; Amano, K.; Tsukada, K.; Lamberth, C. *J. Chem. Soc., Perkin Trans 1* **1999**, 239.
(199) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 6827.
(200) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 1341.
(201) Basnak, I.; Takatori, S.; Walker, R. T. *Tetrahedron Lett.* **1997**, *38*, 4869.
(202) Hiroshige, M.; Hauske, J. R.; Zhou, P. *Tetrahedron Lett.* **1995**, *36*, 4567.
(203) Sinou, D. *Bull. Soc. Chim. Fr.* **1987**, *3*, 480.
(204) Bartik, T.; Bunn, B. B.; Bartik, B.; Hanson, B. E. *Inorg. Chem.* **1994**, *33*, 164.
(205) Fell, B.; Papadogianakis, G. *J. Prakt. Chem./Chem. Zeit.* **1994**, *336*, 591.
(206) Bartik, T.; Bartik, B.; Hanson, B. E.; Guo, I.; Toth, I. *Organometallics* **1993**, *12*, 164.
(207) Bartik, T.; Ding, H.; Bartik, B.; Hanson, B. E. *J. Mol. Catal. A: Chem.* **1995**, *98*, 117.
(208) Herrmann, W. A.; Kohlpaintner, C. W.; Bahrmann, H.; Konkol, W. *J. Mol. Catal.* **1992**, *73*, 191.
(209) Herrmann, W. A.; Kohlpaintner, C. W.; Manetsberger, R. B.; Bahrmann, H.; Kottmann, H. *J. Mol. Catal. A: Chem.* **1995**, *97*, 65.
(210) Bianchini, C.; Frediani, P.; Sernau, V. *Organometallics* **1995**, *14*, 5458.
(211) Heeschewagner, K.; Mitchell, T. N. *J. Organomet. Chem.* **1994**, *468*, 99.
(212) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324.

(213) Gulyas, H.; Arva, P.; Bakos, J. *J. Chem. Soc., Chem. Commun.* **1997**, *24*, 2385.
(214) Herd, O.; Hessler, A.; Langhans, K. P.; Stelzer, O.; Sheldrick, W. S.; Weferling, N. *J. Organomet. Chem.* **1994**, *475*, 99.
(215) Herrmann, W. A.; Albanese, G. P.; Manetsberger, R. B.; Lappe, P.; Bahrmann, H. *Angew. Chem.* **1995**, *107*, 893.
(216) Wan, K.-t.; Davis, M. E. *J. Chem. Soc., Chem. Commun.* **1993**, *16*, 1262.
(217) Herrmann, W. A.; Kulpe, J. A.; Kellner, J.; Riepl, H.; Bahrmann, H.; Konkol, W. *Angew. Chem.* **1990**, *102*, 408.
(218) Lensink, C.; Vries, J. G. d. *Tetrahedron: Asymmetry* **1992**, *3*, 235.
(219) Dibowski, H.; Schmidtchen, F. P. *Tetrahedron* **1995**, *51*, 2325.
(220) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715.
(221) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 2003.
(222) Ha, H.-J.; Ahn, Y.-G.; Woo, J.-S. *Bull. Korean Chem. Soc.* **1998**, *19*, 818.
(223) Gelpke, A. E. S.; Veerman, J. J. N.; Goedheijt, M. S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Hiemstra, H. *T* **1999**, *55*, 6657.
(224) Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem.* **1995**, *107*, 2941.
(225) Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, *11*, 1091.
(226) Herrmann, W. A.; Boehm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141.
(227) Boehm, V. P. W.; Herrmann, W. A. *Eur. J. Chem.* **2000**, *6*, 1017.
(228) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997.
(229) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123.
(230) Dinjus, E.; Fornika, R.; Scholz, M. In *Chemistry Under Extreme or Non-Classical Conditions*; Eldik, R. V., Hubbard, C. D., Eds.; John Wiley & Sons Inc: New York, 1997.
(231) Morita, D. K.; Pesiri, D. R.; David, S. A.; Glaze, W. H.; Tumas, W. *J. Chem. Soc., Chem. Commun.* **1998**, *13*, 1397.
(232) Carroll, M. A.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1998**, *13*, 1395.
(233) Shezad, N.; Oakes, R. S.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **1999**, *40*, 2221.
(234) Cacchi, S.; Fabrizi, G.; Gasparrini, F.; Villani, C. *Synlett* **1999**, 345.
(235) Broell, D.; Kaul, C.; Kraemer, A.; Krammer, P.; Richter, T.; Jung, M.; Vogel, H.; Zehner, P. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2998.
(236) Reardon, P.; Metts, S.; Crittendon, C.; Daugherity, P.; Parsons, E. J. *Organometallics* **1995**, *14*, 3810.
(237) Diminnie, J.; Metts, S.; Parsons, E. J. *Organometallics* **1995**, *14*, 4023.
(238) Gron, L. U.; Tinsley, A. S. *Tetrahedron Lett.* **1999**, *40*, 227.
(239) Horvàth, I. T.; Ràbai, J. *Science* **1994**, *266*, 72.
(240) Horvàth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641.
(241) Moineau, J.; Pozzi, G.; Quici, S.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 7683.
(242) Herrmann, W. A.; Cornils, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1049.
(243) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576.
(244) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441.
(245) Cornils, B. *J. Mol. Catal. A: Chem.* **1999**, *143*, 1.
(246) Kuntz, E. G. *CHEMTECH* **1987**, *17*, 570.
(247) Bhanage, B. M.; Zhao, F. G.; Shirai, M.; Arai, M. *Tetrahedron Lett.* **1998**, *39*, 9509.
(248) Bhanage, B. M.; Ikushima, Y.; Shirai, M.; Arai, M. *Tetrahedron Lett.* **1999**, *40*, 6427.
(249) Bergbreiter, D. E.; Liu, Y.-S.; Osburn, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 4250.
(250) Beller, M.; Krauter, J. G. E.; Zapf, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 772.
(251) Davis, M. E. *CHEMTECH* **1992**, 498.
(252) Tonks, L.; Anson, M. S.; Hellgardt, K.; Mirza, A. R.; Thompson, D. F.; Williams, J. M. J. *Tetrahedron Lett.* **1997**, *38*, 4319.
(253) Anson, M. S.; Mirza, A. R.; Tonks, L.; Williams, J. M. J. *Tetrahedron Lett.* **1999**, *40*, 7147.
(254) Yu, K.-L.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1994**, *35*, 8919.
(255) Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189.
(256) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5748.
(257) Kulkarni, B. A.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 373.
(258) Bolton, G. L.; Hodges, J. C. *J. Comb. Chem.* **1999**, *1*, 130.
(259) Andersson, C.-M.; Karabelas, K.; Hallberg, A.; Andersson, C. *J. Org. Chem.* **1985**, *50*, 3891.
(260) Wang, P.-W.; Fox, M. A. *J. Org. Chem.* **1994**, *59*, 5358.
(261) Riegel, N.; Darcel, C.; Stephan, O.; Juge, S. *J. Organomet. Chem.* **1998**, *567*, 219.
(262) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1526.
(263) Wall, V. M.; Eisenstadt, A.; Ager, D. J.; Laneman, S. A. *Platinum Met. Rev.* **1999**, *43*, 138.

(264) Julia, M.; Duteil, M.; Grard, C.; Kuntz, E. *Bull. Soc. Chim. Fr.* **1973**, 2791.
(265) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 235.
(266) Khan, S. I.; Grinstaff, M. W. *J. Org. Chem.* **1999**, *64*, 1077.
(267) Djakovitch, L.; Heise, H.; Koehler, K. *J. Organomet. Chem.* **1999**, *584*, 16.
(268) The latter finding is no less interesting than the main theme of the work under discussion, as it means that a trivial complex Pd(NH$_3$)$_4$Cl$_2$ is an excellent catalyst for reactions even with nonactivated aryl bromides in a phosphine-free mode.
(269) Djakovitch, L.; Koehler, K. *J. Mol. Catal. A: Chem.* **1999**, *142*, 275.
(270) Mehnert, C. P.; Ying, J. Y. *J. Chem. Soc., Chem. Commun.* **1997**, *22*, 2215.
(271) Mehnert, C. P.; Weaver, D. W.; Ying, J. Y. *J. Am. Chem. Soc.* **1998**, *120*, 12289.
(272) Villemin, D.; Jaffres, P.-A.; Nechab, B.; Courivaud, F. *Tetrahedron Lett.* **1997**, *38*, 6581.
(273) Li, J.; Mau, A. W. H.; Strauss, C. R. *J. Chem. Soc., Chem. Commun.* **1997**, *14*, 1275.
(274) Balogh, M.; Laszlo, P. *Organic Chemistry Using Clays*; Springer: Berlin, 1993.
(275) Cornelis, A.; Laszlo, P. *Synlett* **1994**, 155.
(276) Choudary, B. M.; Sarma, R. M.; Rao, K. K. *Tetrahedron* **1992**, *48*, 719.
(277) Ramchandani, R. K.; Uphade, B. S.; Vinod, M. P.; Wakharkar, R. D.; Choudhary, V. R.; Sudalai, A. *J. Chem. Soc., Chem. Commun.* **1997**, *21*, 2071.
(278) Varma, R. S.; Naicker, K. P.; Liesen, P. J. *Tetrahedron Lett.* **1999**, *40*, 2075.
(279) Webel, M.; Reissig, H.-U. *Synlett* **1997**, *10*, 1141.
(280) Akiyama, F.; Miyazaki, H.; Kaneda, K.; Teranishi, S.; Fujiwara, Y.; et al. *J. Org. Chem.* **1980**, *45*, 2359.
(281) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31.
(282) Sengupta, S.; Sadhukhan, S. K.; Bhattacharyya, S. *Tetrahedron* **1997**, *53*, 2213.
(283) Beller, M.; Kuehlein, K. *Synlett* **1995**, 441.
(284) Kikukawa, K.; Ikenaga, K.; Kono, K.; Toritani, K.; Wada, F.; Matsuda, T. *J. Organomet. Chem.* **1984**, *270*, 277.
(285) Ikenaga, K.; Kikukawa, K.; Matsuda, T. *J. Chem. Soc., Perkin Trans 1* **1986**, *1959*.
(286) Ikenaga, K.; Matsumoto, S.; Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1988**, *5* 873−876.
(287) Kikukawa, K.; Ikenaga, K.; Wada, F.; Matsuda, T. *Tetrahedron Lett.* **1984**, *25*, 5789.
(288) Ikenaga, K.; Kikukawa, K.; Matsuda, T. *J. Org. Chem.* **1987**, *52*, 1276.
(289) Sengupta, S.; Sadhukhan S. K *J. Chem. Soc., Perkin Trans 1* **1999**, 2235.
(290) Sengupta, S.; Bhattacharyya, S.; Sadhukhan, S. K. *J. Chem. Soc., Perkin Trans 1* **1998**, 275.
(291) Sengupta, S.; Sadhukhan, S. K.; Bhattacharyya, S.; Guha, J. *J. Chem. Soc., Perkin Trans 1* **1998**, 407.
(292) Sengupta, S.; Sadhukhan, S. K. *Tetrahedron Lett* **1998**, *39*, 715.
(293) Carlstrom, A. S.; Freijd, T. *J. Org. Chem.* **1991**, *56*, 1289.
(294) Tao, W.; Nesbitt, S.; Heck, R. F. *J. Org. Chem.* **1990**, *55*, 63.
(295) Plevyak, J. E.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 4078.
(296) Sengupta, S.; Bhattacharya, S. *J. Chem. Soc., Perkin Trans 1* **1993**, 1943.
(297) Sengupta, S.; Sadhukhan, S. K. *Tetrahedron Lett.* **1998**, *39*, 1237.
(298) Kikukawa, K.; Maemura, K.; Kiseki, Y.; Wada, F.; Matsuda, T.; Giam, C. S. *J. Org. Chem.* **1981**, *46*, 4885.
(299) Beller, M.; Fischer, H.; Kuehlein, K. *Tetrahedron Lett.* **1994**, *35*, 8773.
(300) Kikukawa, K.; Naritomi, M.; He, G.-X.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1985**, *50*, 299.
(301) Bhattacharya, S.; Majee, S.; Mukherjee, R.; Sengupta, S. *Synth. Commun.* **1995**, *25*, 651.
(302) Kamigata, N.; Satoh, A.; Kondoh, T.; Kameyama, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3575.
(303) Kamigata, N.; Satoh, M.; Fukushima, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2118.
(304) Kamigata, N.; Satoh, M.; Yoshida, M. *J. Organomet. Chem.* **1991**, *401*, C26.
(305) Yong, W.; Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synthesis* **1991**, *11*, 967.
(306) Mehta, G.; Sengupta, S. *Tetrahedron Lett.* **1996**, *37*, 8625.
(307) Sengupta, S.; Bhattacharyya, S. *Synth. Commun.* **1996**, *26*, 231.
(308) Jeffery, T. *Tetrahedron Lett.* **1992**, *33*, 1989.
(309) Desmazeau, P.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1998**, *39*, 6707.
(310) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083.
(311) Brunner, H.; Le Cousturier de Courcy, N.; Genet, J. P. *Tetrahedron Lett.* **1999**, *40*, 4815.
(312) Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. *J. Am. Chem. Soc.* **1991**, *113*, 3, 6315.

(313) Bumagin, N. A.; Sukhomlinova, L. I.; Banchikov, A. N.; Tolstaya, T. P.; Beletskaya, I. P. *Bull. Russ. Acad. Sci. Div. Chem. Sci. (Engl. Transl.)* **1992**, *41*, 2130.

(314) Kurihara, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Pharm. Bull.* **1994**, *42*, 2357.

(315) Kang, S.-K.; Yamaguchi, T.; Pyun, S.-J.; Lee, Y.-T.; Baik, T.-G. *Tetrahedron Lett.* **1998**, *39*, d(0).

(316) Kang, S. K.; Baik, T. G.; Hur, Y. *Tetrahedron* **1999**, *55*, 6863.

(317) Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Jang, S.-B. *Tetrahedron Lett.* **1995**, *36*, 8047.

(318) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1996**, *61*, 2604.

(319) Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkong, E.-Y.; Kim, T.-H. *Tetrahedron Lett.* **1995**, *36*, 6287.

(320) Nokami, J.; Furukawa, A.; Okuda, Y.; Hazato, A.; Kurozumi, S. *Tetrahedron Lett.* **1998**, *39*, 1005.

(321) Liang, Y.; Jing, H.; Liu, C.; Wu, X.; Yongxiang, M. *Tetrahedron Lett.* **1998**, *39*, 7143.

(322) Kang, S.-K.; Choi, S.-C.; Ryu, H.-C.; Yamaguchi, T. *J. Org. Chem.* **1998**, *63*, 5748.

(323) McKillop, A. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E., Eds.; Pergamon: Oxford, 1982; Vol. 7.

(324) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274.

(325) Larock, R. C.; Liu, C. L.; Lau, H. H.; Varaprath, S. *Tetrahedron Lett.* **1984**, *25*, 4459.

(326) Blaser, H.-U.; Spencer, A. *J. Organomet. Chem.* **1982**, *233*, 267.

(327) Spencer, A. *J. Organomet. Chem.* **1983**, *247*, 117.

(328) Spencer, A. *J. Organomet. Chem.* **1984**, *265*, 323.

(329) Kasahara, A.; Izumi, T.; Kudou, N. *Synthesis* **1988**, *9*, 704.

(330) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4257.

(331) Luzikova, E. V.; Bumagin, N. A.; Beletskaya, I. P. *Russ. Chem. Bull.* **1993**, *42*, 586.

(332) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *Tetrahedron Lett.* **1989**, *30*, 975.

(333) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *J. Chem. Soc., Perkin Trans 1* **1990**, 2207.

(334) Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 662.

(335) Iyer, S.; Ramesh, C.; Sarkar, A.; Wadgaonkar, P. P. *Tetrahedron Lett.* **1997**, *38*, 8113.

(336) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Ronchi, A. U. *J. Organomet. Chem.* **1986**, *301*, C62.

(337) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253.

(338) Condon-Gueugnot, S.; Dupre, D.; Nedelec, J.-Y.; Perichon, J. *Synthesis* **1997**, *12*, 1457.

(339) Condon-Gueugnot, S.; Leonel, E.; Nedelec, J.-Y.; Perichon, J. *J. Org. Chem.* **1995**, *60*, 7684.

(340) Iyer, S.; Ramesh, C.; Ramani, A. *Tetrahedron Lett.* **1997**, *38*, 8533.

(341) Kotora, T.; Kong, K. C.; Cheng C.-H *Organometallics* **1992**, *11*, 1972.

(342) Kelkar, A. A. *Tetrahedron Lett.* **1996**, *37*, 8917.

(343) Iyer, S. *J. Organomet. Chem.* **1995**, *490*, C27.

(344) Mitsudo, T.-A.; Takagi, M.; Zhang, S.-W.; Watanabe, Y. *J. Organomet. Chem.* **1992**, *423*, 405.

(345) Braese, S.; Waegell, B.; Meijere, A. d. *Synthesis* **1998**, *2*, 148.

(346) Pan, Y.; Zhang, Z.; Hu, H. *Synth. Commun.* **1992**, *22*, 2019.

(347) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725.

(348) Pan, Y.; Zhang, Z.; Hu, H. *Synthesis* **1995**, 245.

(349) Weigelt, M.; Becher, D.; Stroehl, D.; Bruhn, C.; Poetsch, E.; Steinborn, D. *Monatsh. Chem.* **1998**, *129*, 1329.

(350) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S. *Tetrahedron* **1989**, *45*, 813.

(351) Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179.

(352) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196.

(353) Murahashi, S. I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429.

(354) Albeniz, A. C.; Catalina, N. M.; Espinet, P.; Redon, R. *Organometallics* **1999**, *18*, 5571.

(355) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, *5*, 463.

(356) Lemke, F. R.; Kubiak, C. P. *J. Organomet. Chem.* **1989**, *373*, 391.

(357) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648.

(358) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(359) Garg, N.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 4158.

(360) Basavaiah, D.; Muthukumaran, K. *Tetrahedron* **1998**, *54*, 4943.

(361) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 241.

(362) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R.; Fiorani, T. *J. Org. Chem.* **1991**, *56*, 261.

(363) Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; et al. *Chem. Lett.* **1982**, 939.

(364) Shibata, I.; Baba, A. *Org. Prep. Proc. Int.* **1994**, *26*, 85.

(365) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831.

(366) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740.

(367) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577.

(368) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581.

(369) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

(370) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.

(371) Hamann, B. C.; Hartwjg, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

(372) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203.

(373) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, *14*, 932.

(374) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149.

(375) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171.

(376) Fournet, G.; Balme, G.; Hemelryck, B. v.; Gore, J. *Tetrahedron Lett.* **1990**, *31*, 5147.

(377) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.

(378) Inoh, J.-I.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673.

(379) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961.

(380) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1998**, 931.

(381) Ames, D. E.; Opalko, A. *Synthesis* **1983**, *3*, 234.

(382) Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, **1919**.

(383) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *Tetrahedron Lett.* **1997**, *38*, 6379.

(384) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.

(385) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; et al. *Heterocycles* **1990**, *31*, 1951.

(386) Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477.

(387) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kanoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257.

(388) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

(389) Gozzi, C.; Lavenot, L.; Ilg, K.; Penalva, V.; Lemaire, M. *Tetrahedron Lett.* **1997**, *38*, 8867.

(390) Sévignon, M.; Papillon, J.; Schulz, E.; Lemaire, M. *Tetrahedron Lett.* **1999**, *40*, 5873.

(391) de Meijere, A.; Song, Z. Z.; Lansky, A.; Hyuda, S.; Rauch, K.; Noltemeyer, M.; Koenig, B.; Knieriem, B. *Eur. J. Org. Chem.* **1998**, *2289*, 9.

(392) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, *9*, 823.

(393) Tao, W.; Silverberg, L. J.; R. F., H. *Organometallics* **1989**, *8*, 2550.

(394) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.

(395) Harrowven, D. C.; Newman, N. A.; Knight, C. A. *Tetrahedron Lett.* **1998**, *39*, 6757.

(396) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089.

(397) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545.

(398) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *J. Organomet. Chem.* **1992**, *436*, C9.

(399) Vicente, J.; Abad, J. A.; Gil-Rubio, J. *Organometallics* **1996**, *15*, 3509.

(400) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.

(401) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111.

(402) Wei, L.-M.; Lin, C.-F.; Wu, M. J. *Tetrahedron Lett.* **2000**, *41*, 1215.

(403) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551.

(404) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010.

(405) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296.

(406) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83.

(407) Catellani, M.; Chiusoli, G. P.; Costa, M. *J. Organomet. Chem.* **1995**, *500*, 69.

(408) Dyker, G. *Chem. Ber./Recl.* **1997**, *130*, 1567.

(409) Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426.

(410) Dyker, G. *Angew. Chem.* **1992**, *104*, 1079.

(411) Dyker, G.; Kellner, A. *J. Organomet. Chem.* **1998**, *555*, 141.

(412) Mateo, C.; Cárdenas, D. J.; Fernández-Rivas, C.; Echavarren, A. M. *Chem. Eur. J.* **1996**, *2*, 1596.

(413) Dyker, G. *Angew. Chem.* **1994**, *106*, 117.

(414) Catellani, M.; Cugini, F. *T* **1999**, *55*, 6595.

(415) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119.

(416) Catellani, M.; Chiusoli, G. P.; Ricotti, S. *J. Organomet. Chem.* **1985**, *296*, C11.

(417) Bocelli, G.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *279*, 225.

(418) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *286*, C13.

(419) Catellani, M.; Motti, E. *New J. Chem.* **1998**, 759.