Ru-, Rh-, and Pd-Catalyzed C−C Bond Formation Involving C−H Activation and Addition on Unsaturated Substrates: Reactions and Mechanistic Aspects

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I. Introduction

For a long time synthetic chemists have been interested in the elaboration of the cheapest and cleanest routes for the synthesis of organic molecules. However, over the last few decades the quest for the most economic ways to the formation of C−C bonds has become a matter of increasing importance among both industrial and academic research units. Thus, for instance, the concept of atom economy[1] has frequently been used to emphasize the minimal number of reactants. Another way to achieve clean and economically interesting processes is the selection of "low-energy" starting materials as substrates. Among these, substrates which contain a reactive C−H bond rather than a C−X bond would provide very interesting alternatives for synthetic purposes,[2] provided that these reactions are achievable under acceptable thermodynamic conditions such as mild temperatures and low pressures.

The aim of this review is indeed to document the various reactions known for forming C−C bonds starting with the least activated substrates. We have, thus, chosen to select those reactions which lead to the formation of one C−C bond starting from an unactivated C−H bond. In addition, to fulfill the atom economy requirement, we have only selected the reactions for which the C−H unit is added onto unsaturated substrates such as olefins, alkynes, and carbonyls. However, one important exception to this rule was the occurrence of some interesting Heck-type reactions[3] whereby the hydrogen atom is formally lost in the last β-elimination step of the process (see section II.A).

We only report procedures catalyzed by the Ru, Rh, Pd triad. Indeed, these metals are by far the most used from the periodic table in catalysis,[4] and thus, they allow a somewhat complete coverage of the various possibilities offered in this area of research.

Recent reviews[4b,c] have appeared on a topic related to the one of this paper. However, as well as other differences, these works did not analyze the coupling processes from a mechanistic point of view. In opposition, we have chosen to focus on the mechanistic aspect of the various reactions studied as it is well-known that an understanding of the mechanism of a given reaction can lead to better opportunities for improving the successful reactions and open up the possibility of discovering novel reactions.

II. Functionalization of Aromatic or Acetylenic C−H Bonds by Coupling Reactions with Multiple C−C Bonds

A. Arylation of C−C Double Bonds

Derivatives from aromatic compounds such as alkylbenzenes, phenol, aniline, and naphthalene are large-quantity chemicals manufactured by the chemical industry. Styrene is the most prevalent member of the benzene family. Since the current industrial

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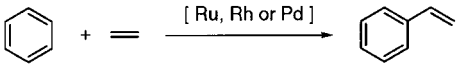
Vincent Ritleng was born in Strasbourg, France, in 1974. He received his Diplome d'Etudes Approfondies in Transition Metal Chemistry and Molecular Engineering (1997) and his Ph.D. degree (2001) from the Universite Louis Pasteur (Strasbourg) under the supervision of Dr. Michel Pfeffer. His work involved the study of ruthenium-mediated C–H bond activation and C–C bond formation under mild conditions. He recently joined the Massachusetts Institute of Technology (Cambridge, MA), where he is a postdoctoral associate of Professor Richard R. Schrock. His current research interests involve the reduction of dinitrogen using molybdenum and tungsten complexes.

Claude Sirlin performed his Ph. D. work (1982) on Supramolecular Catalysis under the supervision of Professor Jean-Marie Lehn at ULP (Strasbourg-France). After a postdoctoral stay, he obtained a position of Assistant (85-88) in the Inorganic Chemistry laboratory, directed by Professor Jacques Simon, at ESPCI in Paris. His research area was that of Molecular Materials for Electronics. In 1988, he was appointed Maître de Conférences at ULP. Up to 94, he worked on Synthetic Agents for Genic Therapy at the Faculty of Pharmacy. In 1995 he joined Dr. Michel Pfeffer's Laboratory of Metal-Induced Chemistry at the Faculty of Chemistry. His currents research interests are the molecular recognition by metalloreceptors, the construction of molecular libraries of pharmacological interest, and the green chemistry of ruthenium.



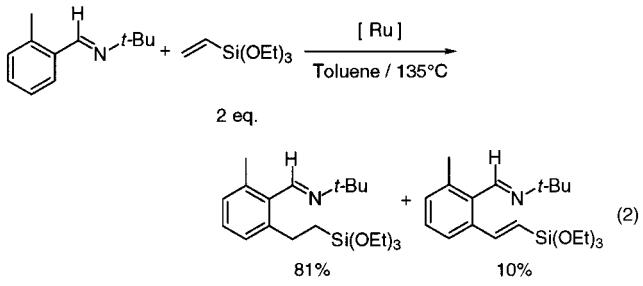
(1)

process to produce styrene consists of two steps, the alkylation of benzene with ethylene to form ethylbenzene and the dehydrogenation of ethylbenzene to afford styrene,[5] the attempt on directly forming styrene from benzene and ethylene through a C−H bond activation process is a highly desirable goal, notably from an industrial point of view. Indeed, such a reaction, which is clean from an atom economy point of view, may have advantages over other methods for the preparation of aromatic alkenes, such as the well-known Heck reaction for the vinylation of aryl halides.

Michel Pfeffer was educated at the University of Strasbourg where he received his Ph.D. degree in 1975 in the laboratory of Coordination Chemistry under the supervision of Professor Jean Dehand. He then spent one year as a postdoctoral student with Professor F. G. A. Stone at the University of Bristol (U.K.). Since 1973 he has held a position in the CNRS at the Université Louis Pasteur in Strasbourg, where he became Directeur de Recherche in 1985. His current research interests lie at the interface of inorganic, organometallic, and organic chemistry, with an emphasis on metal-mediated functionalizations of C–H bonds through reactions aimed at producing new carbon–carbon and carbon–heteroatom bond.

1. Chelation-Assisted Reactions

Examples of chelation-assisted arylation of C−C double bonds are very rare and usually arise as accidents. Thus, the first example was described in 1996 in a continuation of the work focusing on the efficient ruthenium-catalyzed hydroarylation of C−C multiple bonds, which had been discovered a few years earlier (see section II.B). Addition of aromatic imines at the ortho C−H bond to olefins, catalyzed by a ruthenium complex, led to byproducts arising from dehydrogenative coupling (eq 2).[6]

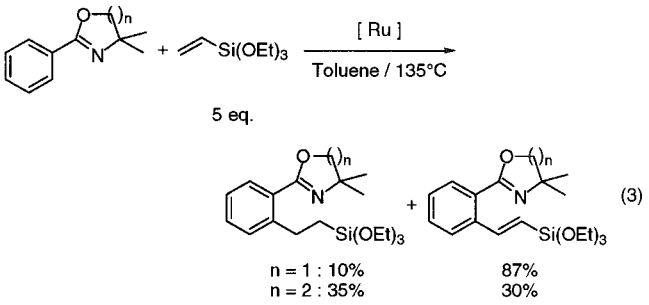


(2)

[Ru] : $Ru_3(CO)_{12}$, 2 mol%

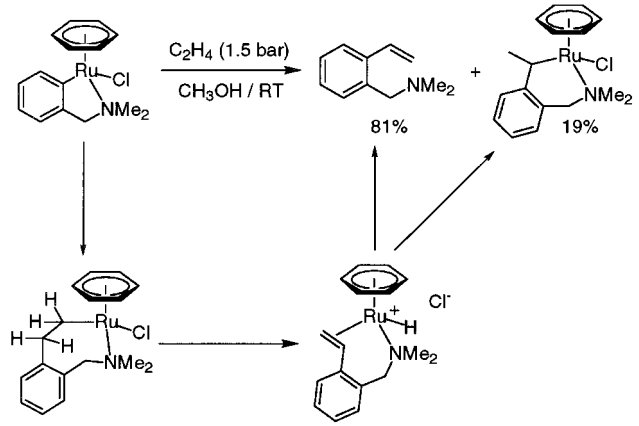
A related reaction with imidates instead of imines as the directing group also gave the olefinic analogue of the addition coupling compound.[7] In this case, it was sometimes obtained as the major product. The $Ru_3(CO)_{12}$-catalyzed reaction of 4,4-dimethyl-2-(2-methylphenyl)-4,5-dihydro-1,3-oxazole with triethoxyvinylsilane gave 87% of the dehydrogenative product (eq 3).

A control experiment demonstrated that the unsaturated compound was not formed by a secondary reaction of the addition coupling compound.[6] It is believed that this type of compound is formed by β-hydride elimination from a carbometalation intermediate resulting from olefin insertion into the Ru−C bond formed by oxidative addition of the C−H bond.[7] This hypothesis has been partially confirmed by a stoichiometric reaction between a cycloruthenated



N,*N*-dimethylbenzylamine derivative and ethylene, which afforded 2-vinyl-*N*,*N*-dimethylbenzylamine and an organometallic ruthenium derivative resulting from the overall insertion of one carbon atom in the Ru−C bond of the starting material.[8] Indeed, formation of these products is rationalized by ethylene insertion into the C−Ru bond followed by a β-hydride elimination, which leads to an olefin−hydride complex. The latter gives either the metal-free substituted olefin by demetalation or the one-carbon-atom insertion complex by Markovnikov hydrometalation of the olefinic unit (Scheme 1).

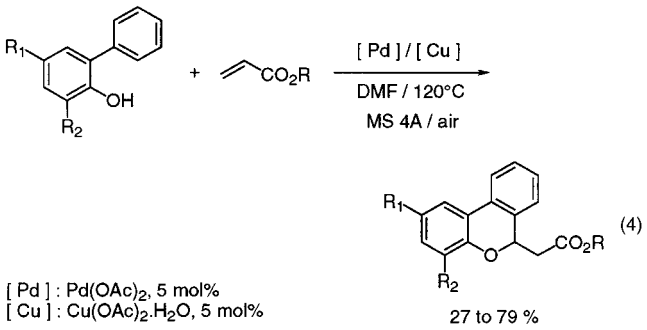
Scheme 1



Carbometalation intermediates appear to be formed only when the directing group is a nitrogen atom but not oxygen. The ruthenium-catalyzed coupling of aromatic ketones with olefins never gives rise to unsaturated byproducts (see section II.B). The ease of carbometalation could be attributed to the stabilization of the seven-membered ruthenacycle by the strong coordination of nitrogen, whereas coordination by a carbonyl oxygen would not be sufficiently strong to stabilize the similar seven-membered ruthenacycle.

Functional-group-assisted ortho-vinylation of aromatics has been applied to the synthesis of heterocycles with a palladium−copper catalyst system in air.[9] It has been found that 2-phenylphenols could catalytically react with olefins under these conditions to give 6-substituted-6*H*-dibenzo[*b*,*d*]pyran derivatives (eq 4).

This process has also been applied to *N*-(arylsulfonyl)-2-phenylaniline and even more remarkably to aromatic carboxylic acids.[9b] In all cases substitution was regiospecific. This outlines the important role

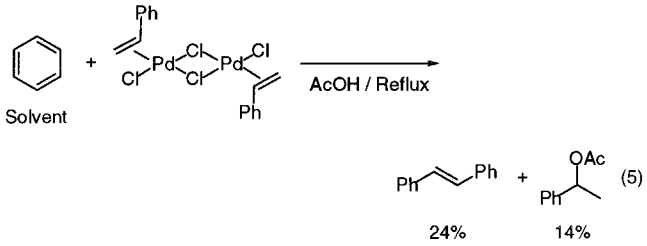


played by the anchor ligand in the initial C−H bond cleavage, i.e., cyclopalladation. As depicted in Scheme 2 for aromatic carboxylic acids, subsequent coupling with the olefin would give Pd(0) species and the corresponding vinyl derivative which would then undergo intramolecular cyclization. The role of Cu(OAc)$_2$ is purported to be reoxidation of the Pd(0) species formed in the oxidative coupling, in a manner similar to how it has generally been considered to be involved in Wacker-type reactions. Nevertheless, an alternative mechanism where the formal oxidation state of Pd(II) would remain constant during the reaction cannot be excluded.

These last examples actually constitute functional-group-assisted applications of the well-known palladium-catalyzed oxidative coupling of arenes with alkenes which do not involve chelation assistance, the so-called Fujiwara−Moritani reaction.[10−18,20]

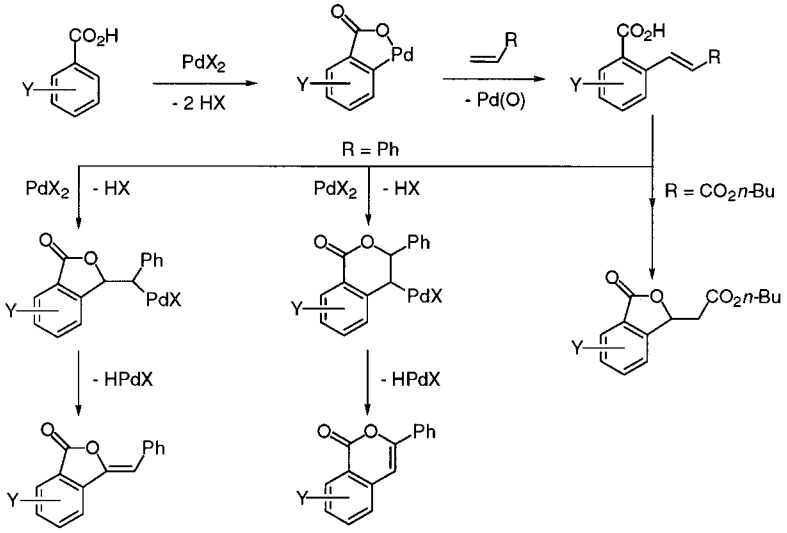
2. Nonchelation-Assisted Reactions

Although stoichiometric and with very low yields, the first example of oxidative coupling of arenes with olefins was described in 1967.[10] In a solution of dry benzene and acetic acid, a styrene−palladium chloride dimer reacted with benzene to give 24% yield (based on styrene) of *trans*-stilbene along with 14% of phenylmethylcarbinol acetate as a byproduct (eq 5).



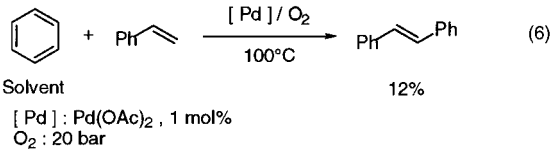
In the absence of acetic acid, styrene was recovered quantitatively. Similarly, no stilbene was obtained in the presence of hydrogen chloride instead of acetic acid. This indicated that acetic acid played an important role in this reaction. Furthermore, palladium acetate was found to be the most reactive complex. The aromatic substitution of olefins in homogeneous solutions of palladium acetate, aromatic compound (large excess), and acetic acid gave 10−90% yields of arylated products with reduced metallic palladium.[11] Note that substituted benzenes preferentially induced ortho/para orientation with electron-donating groups and meta orientation with electron-withdrawing groups. The order of reactivity found with benzene, naphthalene, ferrocene, and furan were similar

Scheme 2



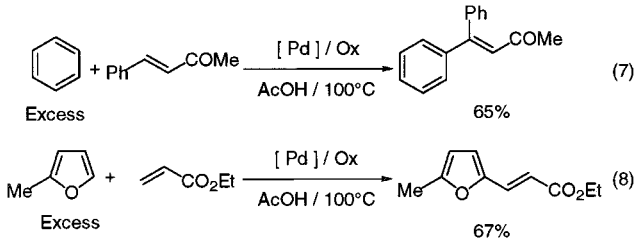
to that of the electrophilic aromatic substitution. Even if the reactivity was not influenced as much as in a typical aromatic substitution reaction, this tended to show electrophilic metalation as the first step.[12] Hence, it was proposed that the reaction involves formation of a σ-arylpalladium(II) complex followed by its addition to the olefin and β-hydride-elimination. The isolation, 20 years later, of diphenyltripalladium(II) complexes obtained by the C−H activation reaction of benzene with palladium acetate dialkylsulfide systems partially confirmed this hypothesis.[13]

A key problem in developing catalytic reactions was the reoxidation of the catalyst. After initial attempts using AgOAc or $Cu(OAc)_2$ under an oxygen atmosphere as the oxidant, for which a maximum turnover number of 2 was reached,[14] interesting results were obtained in neat benzene with oxygen as the oxidant.[15] Although the yields were still low (maximum TON = 11, eq 6), this appeared to be one of the first demonstrations of the ability to use oxygen and appropriate solvents alone to perform certain reactions catalytically, which usually reduce palladium(II) to the metallic palladium.



(6)

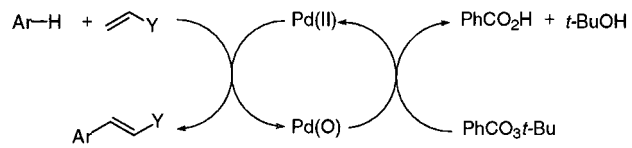
Much effort has been made to find efficient reoxidation systems to regenerate Pd(II) in situ from Pd(0). Even if relatively higher turnovers (over 20) were obtained in the reactions of furans with acrylates in the presence of the $Pd(OAc)_2$−$Cu(OAc)_2$ catalyst system,[16] no real breakthrough was made until *tert*-butyl perbenzoate was used as oxidant.[17] Indeed, heating an acetic acid solution of olefin and excess benzene or furan at 100 °C in the presence of *tert*-butyl perbenzoate afforded the corresponding vinyl derivatives with turnover numbers varying between 10 and 14 or 34 and 67, respectively (eqs 7 and 8). It is of note that in the case of furans the olefinic double



bond was exclusively anti in all cases. In the reaction of 2-substituted furans bearing either an electron-withdrawing or electron-donating group, the coupling took place at the 5-position. Monosubstituted benzenes gave mixtures of regioisomers. Olefins not bearing electron-withdrawing substituents were rarely coupled.

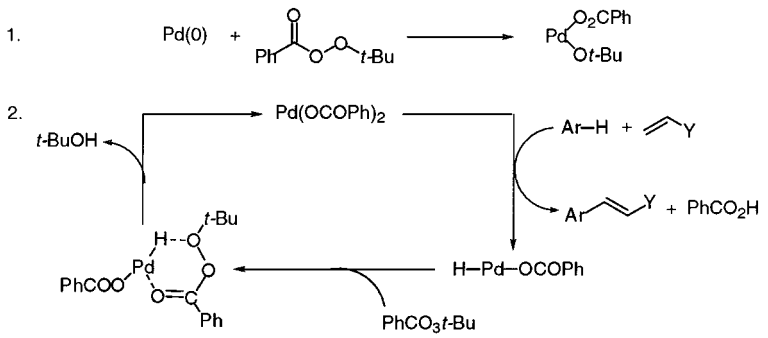
The perester was converted to equimolar amounts of benzoic acid and *tert*-butyl alcohol. This showed that the perester acted as an hydrogen acceptor in the reaction. Since the oxidative coupling of aromatic compounds with olefins is a characteristic reaction of Pd(II) and since control experiments excluded the participation of radical species, it seems reasonable that the perester reoxidizes Pd(0) as depicted in Scheme 3.

Scheme 3



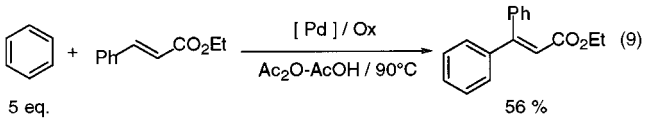
The mechanism of reoxidation itself was not clear, and two plausible explanations were proposed. One was oxidative addition of the perester to Pd(0) involving O−O bond cleavage (Scheme 4.1). The other was the direct oxidation of the palladium hydride species resulting from β-hydride elimination with the perester via a six-membered cyclic transition state as shown in Scheme 4.2. In this case also, the O−O bond cleavage is essential. In both cases, a Pd(II)

Scheme 4



carboxylate species is regenerated from the reduced Pd(0) species. Thus, the key feature of this system would be to allow the easy regeneration of the Pd(II) carboxylate species, which is believed to be the catalytically active species since the early discovery that $Pd(OAc)_2$ was the best complex.[11]

To date, the best results in terms of turnovers were obtained with a related system using peroxide as hydrogen acceptor. In the presence of palladium acetate and benzoquinone (BQ) with *tert*-butyl hydroperoxide as the oxidant, the oxidative coupling of benzene and ethyl (*E*)-cinnamate can be achieved in up to 280 turnovers (eq 9).[18] The catalytic system is



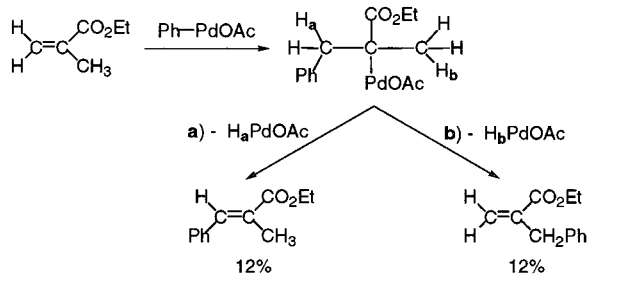
[Pd] : $Pd(OAc)_2$, 0.2 mol% / BQ, 3 mol%
Ox : *t*-BuOOH, 200 mol%

especially active for the coupling of heterocycles such as furans and indole with activated olefins, i.e., olefins bearing an electron-withdrawing group. The reaction of olefins bearing a substituent at the α-carbon is highly regio- and stereoselective, giving *β*-aryl-*anti*-olefins selectively.

The observed reactivity of aromatics and heteroaromatics as well as the observed selectivity with monosubstituted benzenes are the same as those described above. This indicates that the reaction depends on the nucleophilic nature of the arenes used in the catalytic system. Thus, the formation of the *σ*-aryl−Pd(II) complexes via electrophilic metalation is believed to be the rate-determining step. The reaction of benzene with ethyl methylacrylate gave a mixture of isomers in equal proportions, which could result from two possible palladium *β*-hydride elimination routes (routes a and b in Scheme 5) from an arylpalladation intermediate.

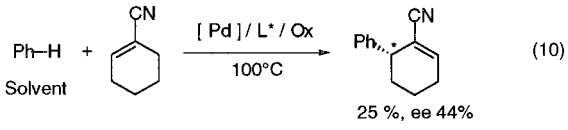
Therefore, the proposed mechanism is the following. Electrophilic substitution of an aromatic C−H bond gives a *σ*-aryl−Pd(II) complex, which undergoes *syn*-addition to an olefin. *β*-Hydride elimination then gives aryl alkenes and Pd−H or Pd(0) species. The in situ formation of BQ−Pd(0) or BQ−Pd−H complexes prevents the Pd(0) species from aggregation to Pd black and leads to the subsequent transformation of these species to Pd(II).[19] The hydroquinone, which is produced at the same time, is oxidized back to BQ by either *tert*-butyl hydroperoxide or *tert*-butyl

Scheme 5

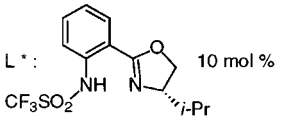


peracetate, which act as hydrogen acceptors. Acetic anhydride is presumed to remove water from the peroxide and to facilitate the formation of *tert*-butyl peracetate. Direct reoxidation of the Pd(0) or Pd−H species by *tert*-butyl hydroperoxide or *tert*-butyl peracetate can, however, not be excluded.

The first asymmetric example of this reaction was reported very recently using $Pd(OAc)_2$ with a chiral sulfonylamino-oxazoline ligand and *tert*-butyl perbenzoate as oxidant.[20] This was achieved by reacting benzene with cyclic olefins in which *β*-hydride elimination from the opposite side to the entering phenyl group is possible (eq 10). The enantiomeric excesses ranged from 1% to 49% depending on the nature of the withdrawing group present on the olefin.



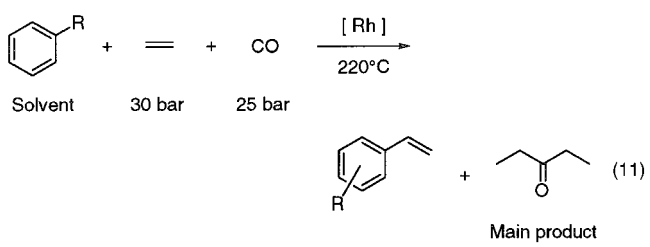
[Pd] : $Pd(OAc)_2$,10 mol%
Ox : $PhCO_3t$-Bu, 100 mol%



Despite the efforts that were made, the turnover number is still not high enough for possible industrial application. Moreover, the use of peroxide oxidants and acetic acid solvent in these systems is problematic from the industrial point of view. Therefore, it is still very desirable to find new, general, and efficient systems for the olefin arylation reaction. In this perspective there are a small number of rhodium- or ruthenium-based systems that have been developed with varying degrees of success that merit coverage.

Under a carbon monoxide pressure (20−25 bar), the $Rh_4(CO)_{12}$- or $Rh_6(CO)_{16}$-catalyzed reaction of

ethylene (30 bar) with benzene at 200−250 °C gave styrene together with pentan-3-one as the main byproduct.[21] Propiophenone, 1-phenylpent-1-en-3-one, and 1-phenylpentan-3-one were also produced in small amounts as the result of the cleavage of a C−H bond of benzene. The reaction of ethylene with monosubstituted benzenes gave monosubstituted styrenes consisting of three positional isomers, whose distributions are different from those observed in ordinary electrophilic aromatic substitution and in palladium-catalyzed arylations of olefins (eq 11).[12] Monosubstituted olefins bearing an electron-withdrawing substituent are susceptible to the reaction giving β-aryl-*anti*-olefins selectively. Disubstituted olefins bearing such electron-withdrawing substituents gave significantly lower yields.[21b]

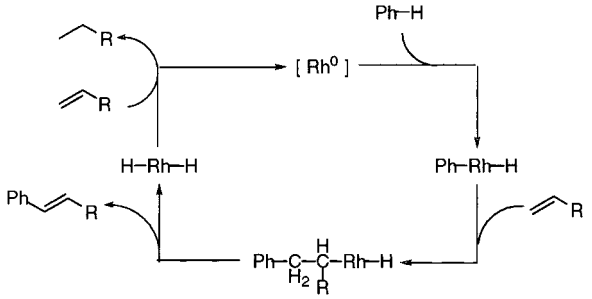


(11)

[Rh] : $Rh_4(CO)_{12}$
R : H, Me, OMe, F; TON (o/m/p) = 367, 251 (14/57/29), 433 (67/23/10), 333 (78/15/5)

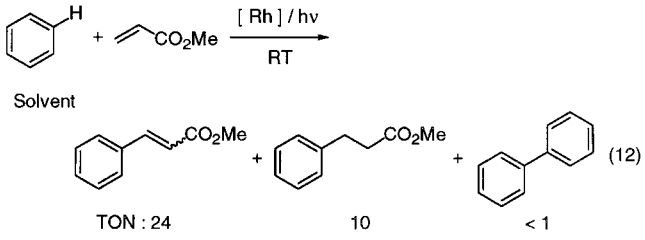
This system has, however, two main drawbacks: (i) the harsh conditions which appear to be necessary to sustain the catalytic activity, the CO pressure preventing catalyst decomposition, and the high temperature increasing the yields of styrene, and (ii) the use of aromatics as solvents, which, despite the relatively high turnover numbers, gives low yields of styrene derivatives. Its principal advantage, as compared with the Pd-catalyzed system, is that it does not require a reoxidant. Consequently the formation of the phenylated olefins has been rationalized in terms of the following steps: (i) oxidative addition of an aromatic C−H bond to the rhodium catalyst, (ii) insertion of the olefin in the resulting C−Rh bond, and (iii) subsequent β-hydride elimination, giving the styrene derivative and a rhodium dihydride complex (Scheme 6). The latter is thought

Scheme 6



to supply the hydrogen atoms for the hydrogenation and hydrocarbonylation of the starting olefin. However, this mechanism is at best a simplification which does not account for the formation of the byproducts.

Low catalytic activity was reported for the RhCl(CO)PMe_3-catalyzed photochemical coupling of benzene with methylacrylate, in which concomitant hydrogenation of the formed alkene took place and biphenyl was formed as a byproduct (eq 12).[22] We can note that the regioselectivity in the reaction of toluene, which gives meta-substituted isomers as major products, is very similar to that observed with $Rh_4(CO)_{12}$.

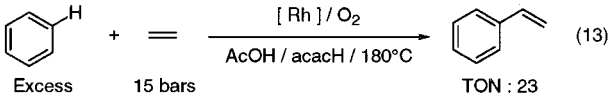


(12)

[Rh] : $RhCl(CO)(PMe_3)_2$, 0.7 mM

This catalytic system has been extensively studied for carbonylation reactions under CO pressure (see section III.A) and does not require any further comment at this stage.

Very recently, two catalytic systems, in which the C−H bond activation is assumed to occur through an electrophilic pathway and in which O_2 can be directly used as the oxidant, have been described.[23] In the first one, the oxidative arylation of ethylene to produce styrene, is catalyzed by $Rh(acac)(CO)_2$ in the presence of acetylacetone (acacH) and oxygen pressure.[23a] No reaction is observed in the absence of acacH. Despite the coexistence of acetic acid in the reaction medium, no formation of vinyl acetate was observed and styrene was obtained selectively, albeit in low yield (TON = 23, TOF = 188×10^{-4} s^{-1}) (eq 13). Other rhodium complexes, $Rh(acac)(\eta^2\text{-}C_2H_4)_2$, $[Rh(cod)Cl]_2$, and Wilkinson's catalyst $RhCl(PPh_3)_3$, which were introduced as derivatives bearing the Rh(I) oxidation state at the beginning of the reaction, showed almost the same activities. On the other hand, the rates with Rh(III) complexes were almost 1 order of magnitude slower than those with their Rh(I) congeners.



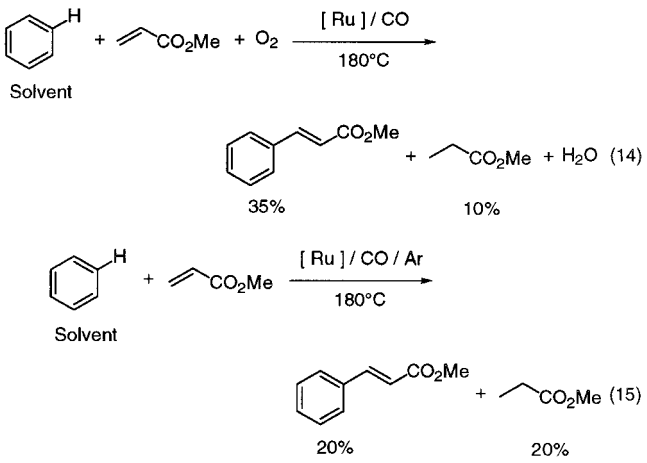
(13)

[Rh] : $Rh(acac)(CO)_2$, 1.0 mM
O_2 : 20 bar

The reaction is proposed to occur in the five following steps: (i) electrophilic aromatic C−H bond activation by a Rh(III) center (possibly formed by in situ oxidation) to produce a Rh−phenyl intermediate, (ii) olefin insertion to produce a Rh−alkyl species, (iii) product loss from the metal center by β-hydride elimination, (iv) proton release by reductive elimination, and (v) reoxidation of the reduced metal center. We can note that the C−H bond activation of benzene by the Rh/acacH/O_2 catalytic system has been demonstrated by an H−D exchange experiment with CH_3-COOD.

In the second system, the reaction is catalyzed by ruthenium complexes and requires a CO atmosphere, probably to stabilize the electrophilic species.[23b] The

complexes $RuCl_3 \cdot H_2O$, $[Ru(CO)_3Cl_2]_2$, $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$, $Ru(NO)Cl_3 \cdot 5H_2O$, and $Ru(CF_3COCHCOCF_3)_3$ show essentially the same activity. Notably, the dehydrogenative coupling proceeds under O_2 (eq 14) or in an inert atmosphere (eq 15). In the absence of O_2, the olefin itself serves as an oxidant, and a 1/1 ratio of cinnamate/propionate is obtained in the reaction of benzene and methylacrylate. In comparison, under an oxygen atmosphere, the cinnamate yield is doubled and a 3/1 ratio of cinnamate/propionate is obtained. When ethylene is used instead of methylacrylate, the reaction occurs less readily.



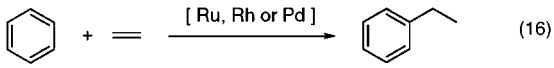
[Ru] : $RuCl_3.3H_2O$, 0.4 mol%
CO : 6 bar
O_2 or Ar : 2 bar

While the mechanism of the reaction is unclear at this stage, the following steps have been proposed: (i) electrophilic attack of the metal on a C−H bond to give an arylruthenium species (electrophilic metalation is suggested by a kinetic isotope effect of $k_H/k_D = 2$ measured in the reaction of C_6D_6 with methylacrylate and by a proton release step, by reaction inhibition in the presence of a noncoordinating base such as lutidine), (ii) olefin insertion in the resulting metal−aryl bond, (iii) β-hydride elimination to yield the aromatic alkene and a ruthenium hydride, and (iv) regeneration of the electrophilic species by olefin insertion into the Ru−H bond followed by protonation of the metal−alkyl complex and alkane elimination when an inert atmosphere is used or by oxidation when oxygen is present. The authors suggested that the C−H activation does not proceed via a simple electrophilic aromatic substitution pathway involving the arene π-system but via a mechanism involving deprotonation of an agostic arene C−H bond.

Several important results emerge from this first section. High turnover numbers have been obtained in the coupling reaction of benzene with ethyl cinnamate to produce ethyl 2,2-diphenylacrylate. This reaction was achieved with $Pd(OAc)_2$ as catalyst and benzoquinone as cocatalyst, but it required the use of a stoichiometric amount of *tert*-butyl hydroperoxide as an oxidant.[18] A second outstanding result concerns the arylation of ethene performed with a tetrarhodiumdodecacarbonyl catalyst. However, the regioselective synthesis of monosubstituted styrenes required the use of neat reactants and high pressures of carbon monoxide and ethene.[21] Less efficient dehydrogenative coupling of benzene with methyl acrylate was catalyzed by various Ru(III) or Ru(II) complexes. The notable difference is to be found in the use of molecular oxygen as the oxidant.[23b] Finally, the regiospecific olefin arylation based on chelation-assisted reactions[7] represents a process that is undoubtedly worth developing in the future.

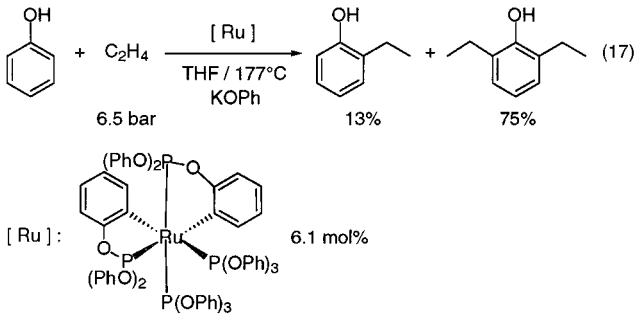
B. Hydroarylation of C–C Double Bonds

With catalysts of the Ru−Rh−Pd triad, this reaction is essentially known in its chelation-assisted version. In conventional organic synthesis, the alkylation of aromatic compounds with olefins essentially refers to the largely used Friedel−Crafts alkylation reaction.[24]

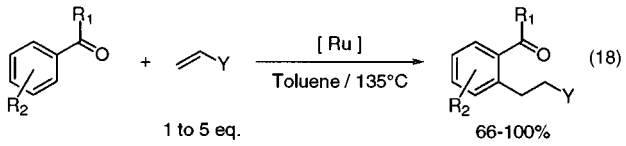


1. Chelation-Assisted Reactions

Initial success was achieved with the regioselective mono and double ortho-alkylations of phenol with ethylene by using a cyclometalated ruthenium phosphite complex (eq 17).[25] In the absence of phenol, the reaction gave free ortho-alkylated phosphites. The mechanism of this latter reaction has been studied in detail and was proposed to involve phosphite substitution by ethylene, insertion of ethylene into the Ru−C bond, orthometalation of another phosphite ligand, reductive elimination, etc. This was the first time that the principle of using orthometalated complexes for catalytic C−C bond formation had been demonstrated. Unfortunately the reaction appeared to be limited to ethylene.

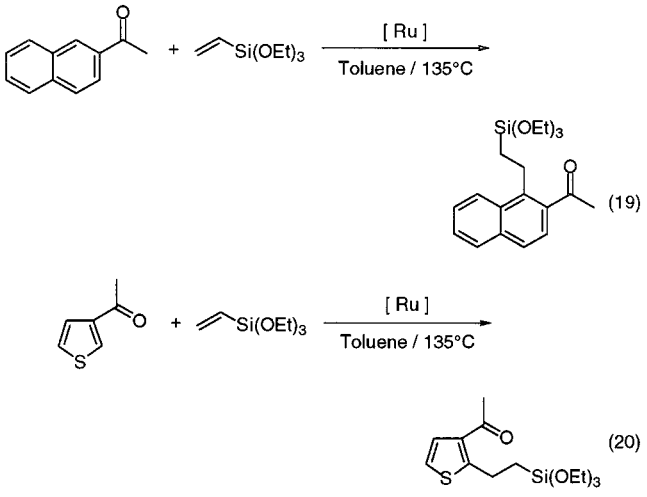


A decisive breakthrough was achieved with the ruthenium-catalyzed addition of the C−H bond at the ortho position of aromatic and heteroaromatic ketones to olefins (eq 18).[26] The complexes $RuH_2(CO)(PPh_3)_3$ and $Ru(CO)_2(PPh_3)_3$ were found to be equally effective. A remarkable feature of this reaction was its efficiency, especially in terms of the high yields of the C−H bond/olefin coupling products. In many cases, almost quantitative yields of products based on both starting materials were obtained. Such an efficiency was unprecedented at that time. In previous reactions, it was necessary to use one of the starting materials in excess (often as solvent) in order to obtain higher yields.



[Ru] : $RuH_2(CO)(PPh_3)_3$, 2 mol%
Y : H, *t*-Bu,$Si(OEt)_3$, CH_2SiMe_3, Ar

Another remarkable feature was the regioselectivity of the coupling process. When two different reaction sites are available in aromatic ketones and olefins, the regioselectivity of the catalytic process is virtually 100%, both for aromatics and olefins, producing one of the four possible regioisomers. The aryl group is added to the less hindered side of the olefin, presumably because of steric effects that keep the Y group away from the crowded center during the olefin insertion. Additionally, when two inequivalent ortho C−H bonds are present, virtual total selectivity for one of the regioisomers is observed (eqs 19 and 20).[27]

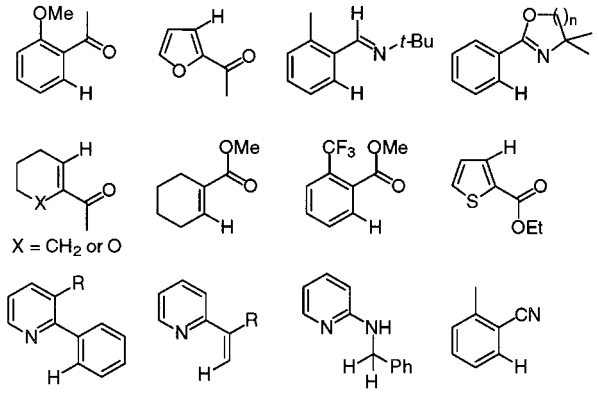


[Ru] : $RuH_2(CO)(PPh_3)_3$, 2 mol%

A key feature of the system seemed to be the involvement of chelation assistance which brings the metal closer to the ortho C−H bond.

After these encouraging initial results, the obvious challenge was to test the scope of these reactions with regard to functional-group tolerance and to the type of olefins which could insert in the C−H bond. Since this early paper, much work has been done and the field of the reaction has been extended to a series of substrates (Scheme 7).[28] Thus, it has been found that, in addition to heteroaromatic acetophenones[26] such as hydroxy-, dimethylamino-, or fluoroacetophenones can also be ortho-alkylated with various olefins.[29] Since electron-withdrawing and -donating substituents can be used, this demonstrates the high functionality tolerance of the reaction. Ortho-alkylation of aromatics bearing nitrogen directing groups such as aromatic imines and imidates is realized concomitantly with dehydrogenative coupling in the presence of catalytic amounts of $Ru_3(CO)_{12}$ (see section II.A).[6,7] The catalytic addition of olefinic C−H bonds to olefins was found possible for cyclic[30] α,β-unsaturated ketones[31a] and esters,[31b] the latter substrates being more reactive than the former. In comparison, reactions with aromatic esters were found to be difficult, and only heteroaromatic esters and those bearing strong electron-withdrawing substituents were found to be reactive.[32] This highlights the differences between the vinyl and aryl systems. The 2-pyridyl group has been used as a directing group to achieve the rhodium-catalyzed addition of aromatic and vinylic C−H bonds to alkenes.[33a,b] The $Ru_3(CO)_{12}$-catalyzed functionalization of an activated benzylic sp^3 C−H bond has also been achieved with this anchor ligand.[33c] This reaction is remarkable since many chelation-assisted alkylations are centered on the sp^2 C−H bond and not on the sp^3 C−H bond, probably due to better thermodynamic stability of the metal−sp^3 carbon bond. Finally, the reaction of aromatic nitriles with triethoxyvinylsilane proceeded in the presence of the $RuH_2(CO)(PPh_3)$-catalyst to give the corresponding C−H/olefin coupling products in high yields (Scheme 7).[34] Thus, the nitrile group is also capable of directing the ruthenium to the ortho C−H bond via a π-bonding mode.

Scheme 7

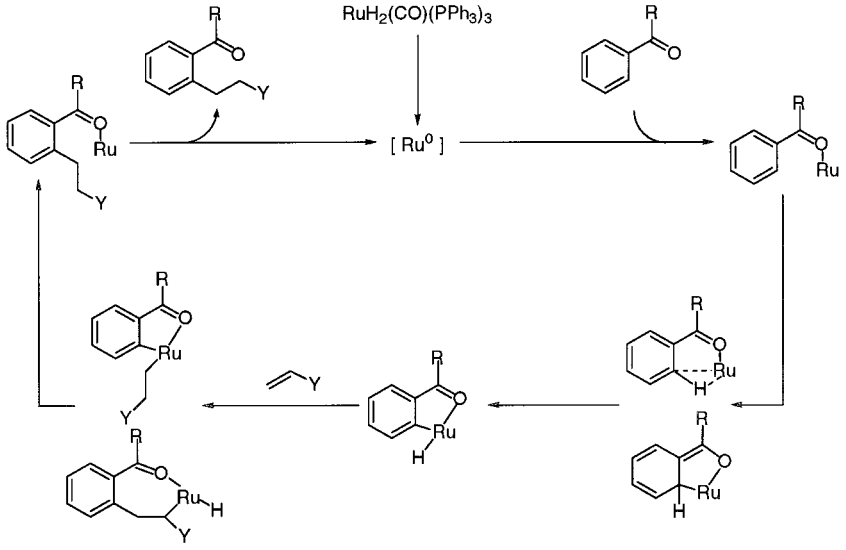


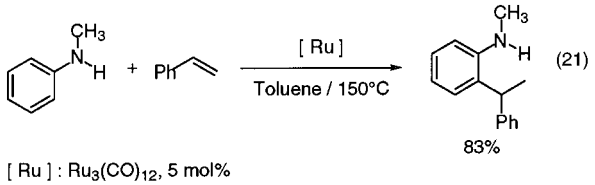
The variety of alkenes that can be inserted into the C−H bonds strongly depends on the nature of the substrate to be alkylated, but it is generally much more limited. However, the wide repertoire of substrates that can be alkylated renders this reaction the synthetically most useful process that has ever been developed for functionalizing C−H bonds via the transition-metal-catalyzed C−H activation.

Except for the coupling of acetophenone and orthomethylacetophenone with styrene which gave a mixture of regioisomers, [28a] all these reactions led selectively to straight-chain alkylarenes or alkylalkenes, i.e., to *anti*-Markovnikov coupling products. This selectivity is remarkable. Indeed, the conventional Friedel−Crafts alkylation of aromatic compounds with olefins, catalyzed by Lewis and Brönsted acid activation of the olefin, follow Markovnikov's rule, producing branched alkylbenzenes in nearly 100% selectivity.[35] However, the $Ru_3(CO)_{12}$-catalyzed hydroarylation of styrene with *N*-methylaniline gave exclusively the Markovnikov coupling product (eq 21).[36]

This atypical transition-metal-catalyzed insertion reaction, whose selectivity is poorly understood, is also the first successful example of the use of an amine as a directing group. Unfortunately no other olefins have been tested, and we do not know how general this reaction is. Note that alkynes also

Scheme 8

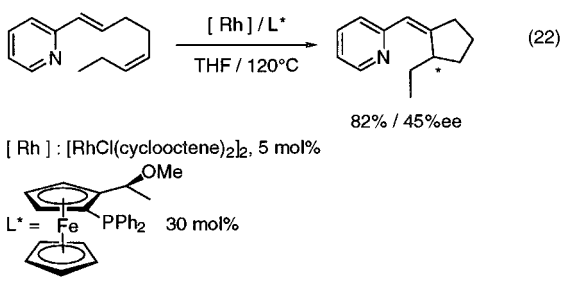




(21)

undergo Markovnikov hydroamination with this system.

An intramolecular version of this reaction has also been described.[37] 1-(2-Pyridyl)-1,5- and 1,6-dienes undergo ruthenium- and rhodium-catalyzed selective intramolecular cyclizations to give the corresponding five- or six-membered ring products. Wilkinson's catalyst showed the highest catalytic activity. Although terminal olefins tend to isomerize to internal ones in the presence of transition-metal complexes, such isomerization did not occur in the present case and internal olefins could cyclize. This opened the possibility of developing this cyclization into an asymmetric reaction. Various chiral ligands were examined, and the monodentate ligand (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylmethyl ether was found to be suitable for the rhodium-catalyzed asymmetric cyclization of 1,5-dienes.[37b] With pyridyl dienes the obtained enantiomeric excesses were low-to-moderate (eq 22). Nevertheless, cyclization of an imidazolyl diene gave significantly higher optical yields, i.e., 77−87% ee depending on the reaction temperature.



(22)

Possibilities for the mechanism of ortho-alkylation of acetophenones are suggested as follows. The course of the catalytic reaction is outlined in Scheme 8 with important alternative routes and with simplified structures. The reaction could begin with the coordination of the carbonyl group to the Ru atom of the active species, bringing the Ru atom close to the ortho C−H bond. By direct interaction of the Ru atom with the C−H bond or by 1,4-addition of the Ru species followed by a 1,2-H shift, a cyclometalated intermediate could be formed.[38] After coordination of an olefin to the latter, insertion of the former could occur either into the Ru−H bond to give a hydrometalated intermediate or into the Ru−C bond to give a carbometalated intermediate. Subsequent reductive elimination would lead to a coordination complex of the alkylated ketone, from which decomplexation of the coupling product would regenerate the catalyst. Note that the chelating group can also dissociate before the reductive elimination. Similar catalytic cycles have been postulated for rhodium- and ruthenium-catalyzed hydroarylation reactions involving substrates with a nitrogen-containing directing group.[33]

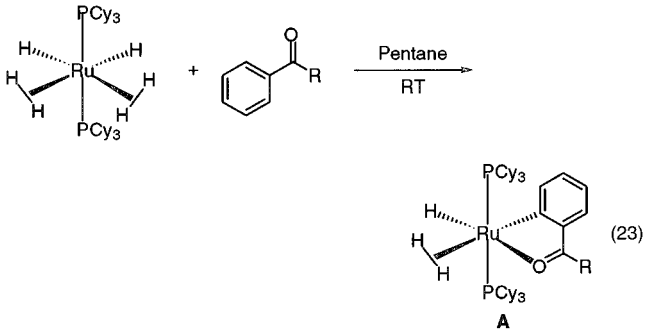
This mechanism will be the basis of the following discussion which considers each particular step on the basis of the different mechanistic studies that have been published to date.

The first question that it raises relates to the active species. The nature of the catalyst precursors that can be used suggests that neither H nor CO is the necessary ligand and that a zerovalent ruthenium, having at least two PPh_3, constitutes the essential part of the catalyst. Evidence for activation of the catalyst by loss of hydrogen was pursued by spectral studies in two independent studies.[31b,38] A priori there are three possibilities for the dehydrogenation at the initial step: (i) reductive elimination of dihydrogen, (ii) reduction of the ketone, and (iii) hydrogenation of the olefin. Control experiments showed that neither of the first two propositions was occurring.[38] Addition of the acceptor alkene to $RuH_2(CO)(PPh_3)_3$ in a NMR tube showed disappearance of the signals corresponding to the ruthenium hydride with only a new set of aromatic signals remaining. The hydrogens were completely transferred to the olefin. The structure of the resultant ruthenium complex has not

been established, but it is catalytically active.[31b,38] Strong inhibition by performing the reaction in the presence of a CO atmosphere and modest inhibition by performing the reaction in a closed system suggest that loss of CO to yield the active species is also required.[31b] Thus, a reasonable conjecture for the structure of this species is a coordinatively unsaturated complex such as $Ru(Ph_3P)_3L$ which may be stabilized by solvent serving as a weakly coordinating ligand. The retardation effect of THF as solvent and the strong influence of ether additives support this contention.[31b]

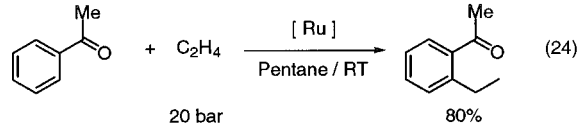
Coordination of the carbonyl oxygen to direct the metalation on the ortho carbon atom has been demonstrated by competitive reactions run with acetophenone and *o*-methylacetophenone.[39] Indeed, the proportion of the dialkylated product of acetophenone is much higher than that of the monoalkylated product of *o*-methylacetophenone, and the major portion of the product of dialkylation was suggested to be formed from the initial nonalkylated substrate without decomplexation of the carbonyl group of the monoalkylated product throughout the reaction. Consequently, this implies the intermediacy of a cyclometalated complex.

This has been partially confirmed by the synthesis of a series of hydrido orthometalated dihydrogen complexes showing catalytic activity for the coupling of ethylene to functional arenes (eq 23).[40]



R : Me or Ph

Indeed, catalytic insertion of ethylene (20 bar) is achieved at room temperature with both acetophenone and benzophenone using $RuH_2(H_2)_2(PCy_3)_2$ or $RuH(H_2)(PCy_3)_2$[2-(COMe-κO)-C_6H_4-κC^1] as the catalyst precursor (eq 24), thus confirming that orthometalated complexes such as $RuH(H_2)(PCy_3)_2$[2-(COMe-κO)-C_6H_4- κC^1] are true catalytic intermediates in the postulated catalytic cycle. Note that complexes analogous to the latter where the H_2 ligand had been substituted by CO did not show any stoichiometric or catalytic activity, substantiating the suggestion that CO must be excluded from the complex during the reaction.

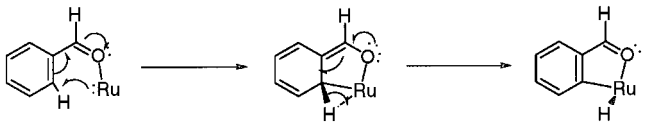


[Ru] : $RuH(H_2)(PCy_3)_2$[2-(COMe-κO)-C_6H_4-κC^1], 10 mol%

Also consistent with the cyclometalation as the first step is the lack of reactivity reported in the case of alkylation of vinylic C−H bonds for acceptor olefins wherein the β-C−H bond is trans to the carbonyl group.[31b]

Concerning the mechanism of C−H activation itself, the existence of an alternative pathway involving a 1,2-hydrogen shift mechanism has been suggested in addition to the usual oxidative addition mechanism (Scheme 8).[38] Theoretical calculations of the model catalytic cycle of benzaldehyde and ethylene with model active species $Ru(CO)(PH_3)_n$ (n = 2 or 3)[41] have shown that among the various possible paths for the oxidative addition of the C−H bond to $Ru(CO)(PH_3)_n$ the most favorable one implies first the coordination of the formyl oxygen of benzaldehyde to the Ru atom. Subsequent cleavage of the closest ortho-C−H bond occurs in two steps through an unusual d^6 five-coordinated intermediate with an agostic interaction, the stability of which gives rise to low activation barriers. This mechanism is completely different from the conventional oxidative addition proceeding in a single step. Before the C−H bond breaks, the Ru−C bond is formed, being driven by the change in π-bonds of the conjugated system. This leads to a five-coordinated metallacycle intermediate having the Ru−C bond and a C−H agostic interaction. The hydrogen of the agostic C−H is subsequently transferred to the Ru atom (Scheme 9).

Scheme 9

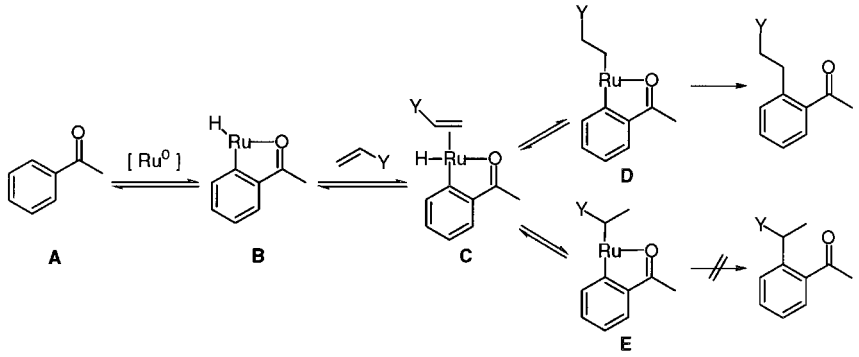


Two possibilities exist for the insertion of olefins. The first is a hydrometalation mechanism and the second a carbometalation one. The former is usually preferred.[31b,33,38] One of the given reasons for this preference is that formation of the carbometalated intermediate should give the dehydrogenative coupling product by β-hydride elimination as it is observed for aromatic imines and imidates (section II.A).[6,7] Theoretical calculations confirmed that the most favorable path adopts the ethylene insertion into the Ru−H bond.[41b]

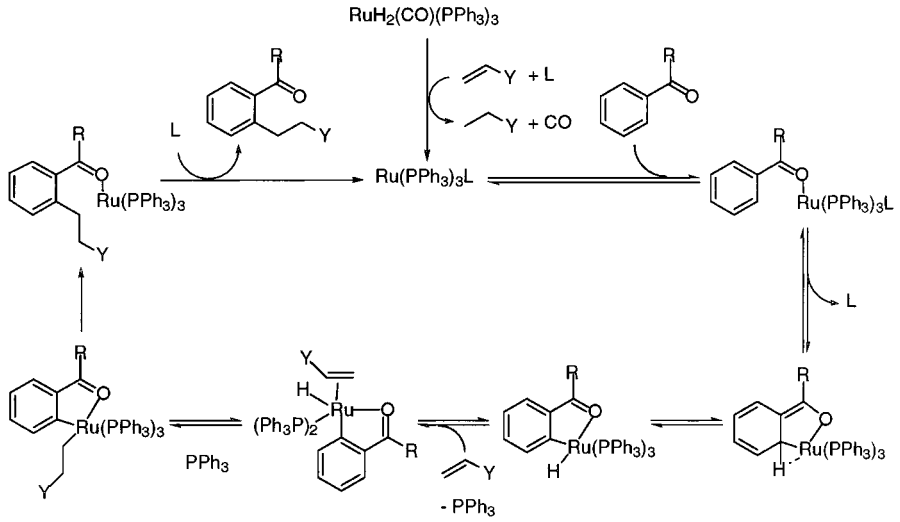
Rapid equilibria among the intermediates involved in the steps from acetophenone to the hydrometalated intermediate complex have been demonstrated by deuterium-labeling experiments. The catalytic reactions of acetophenone-d_5 with triethoxyvinylsilane at 135 °C for 10 min (57% conversion) and at 50 °C for 15 h (0% conversion) showed deuterium scrambling of the two deuterium atoms at the ortho position of the ketone over five positions, i.e., the two ortho and the three olefinic positions (eq 25).

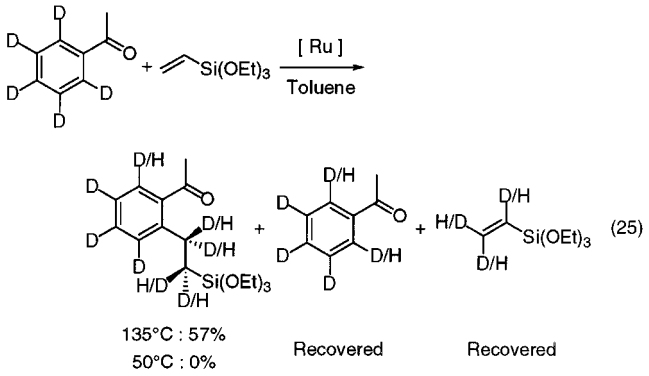
This observed H/D scrambling, even under conditions where the reaction does not afford any product, implies (i) the existence of an equilibrium between **A**, **B**, **C**, **D**, and **E** (Scheme 10) and (ii) that these processes are faster than the product-forming step. This is significant. Contrary to the widespread idea that C−H bond cleavage is difficult, it can be said

Scheme 10



Scheme 11





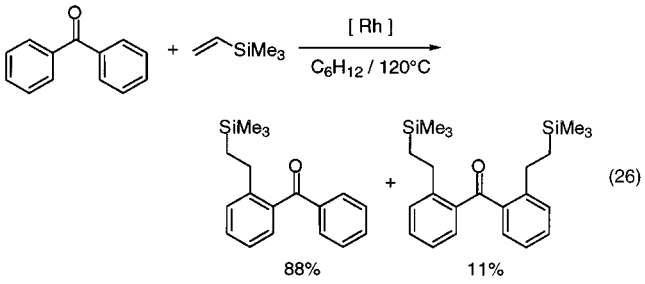
[Ru] : $RuH_2(CO)(PPh_3)_3$, 2 mol%

that it is facile compared with the product-forming step or catalyst regeneration step, i.e., C−H bond cleavage is not the rate-determining step in the present catalytic reaction. Indeed, theoretical calculations showed that the C−C bond formation requires an activation energy of 27 kcal·mol^{-1} and is, thus, rate-determining.[41b]

In fine the mechanism depicted in Scheme 11 can be proposed. Hydrogenation of an olefin and probably loss of CO generates the active catalyst $Ru(PPh_3)_3L$, which may be stabilized by solvent serving as a weakly coordinating ligand. Coordination of the carbonyl group to the Ru atom of the active species brings the Ru atom close to the ortho C−H bond. Subsequent cleavage of the C−H bond occurs in two steps through a d^6 five-coordinated intermediate with an agostic interaction to give a cyclometalated complex. After coordination of an olefin to the latter, insertion of the olefin occurs into the Ru−H bond to give a hydrometalated intermediate. Subsequent reductive elimination leads to a coordination complex of the alkylated ketone, from which decomplexation of the coupling product regenerates the active species.

The use of a half-sandwich rhodium complex as a catalyst for the addition of olefins to aromatic ketones to selectively generate ortho-alkylated aromatic ketones is noteworthy, both for its efficiency which is similar to that of $RuH_2(CO)(PPh_3)_3$ and for mechanistic aspects which markedly differ from the latter system.[42] The addition of vinyltrimethylsilane to benzophenone employing $Rh(\eta^5\text{-}C_5Me_5)(\eta^2\text{-}C_2H_3SiMe_3)_2$ as the catalyst gave mono- and dialkylated products in 88% and 11% yields respectively (eq 26). As in the case of the ruthenium-catalyzed system, only alkylation at the ortho position was observed and only the β-silyl addition product was formed (*anti*-Markovnikov addition).

The only rhodium species observed during catalysis in cyclohexane-d_{12} was $Rh(\eta^5\text{-}C_5Me_5)(C_2H_3SiMe_3)_2$, indicating that this species is the catalyst resting state. Nevertheless, as in the case of the ruthenium-catalyzed system, the active species seems to be generated by loss of a ligand. Indeed, the reaction rate decreases in the presence of excess olefin and increases with added ketone. This behavior suggests that the turnover frequency is first order in ketone

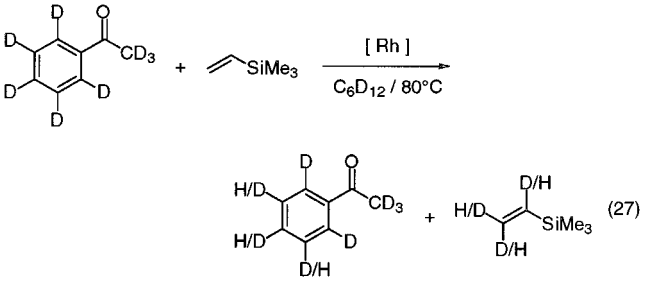


(26)

[Rh] : Rh(η^5-C_5Me_5)(η^2-$C_2H_3SiMe_3$)$_2$, 5 mol%

and inverse order in olefin, which is consistent with the proposal of reversible olefin loss from the catalyst resting state followed by reaction of Rh(η^5-C_5Me_5)-(η^2-$C_2H_3SiMe_3$) with ketone.

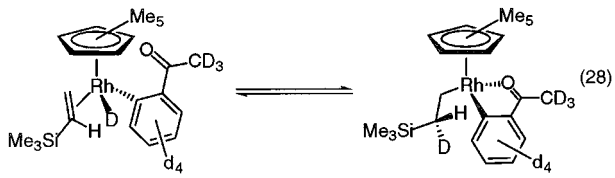
Mechanistic information was obtained from the results of the reaction of acetophenone-d_8 with trimethylvinylsilane at 80 °C, conditions under which the product formation was not observed (eq 27). The residual resonance for the ortho sites did *not* change over the 35 h during which this reaction was followed by ^{1}H NMR spectroscopy. In contrast, the resonances for the meta and para sites indicated 30% incorporation of proton label into these sites. All ^{1}H vinylic sites were reduced in intensity on the same time scale to generate *per*-deuteriovinyltrimethylsilane.



(27)

[Rh] : Rh(η^5-C_5Me_5)(η^2-$C_2H_3SiMe_3$)$_2$, 5 mol%

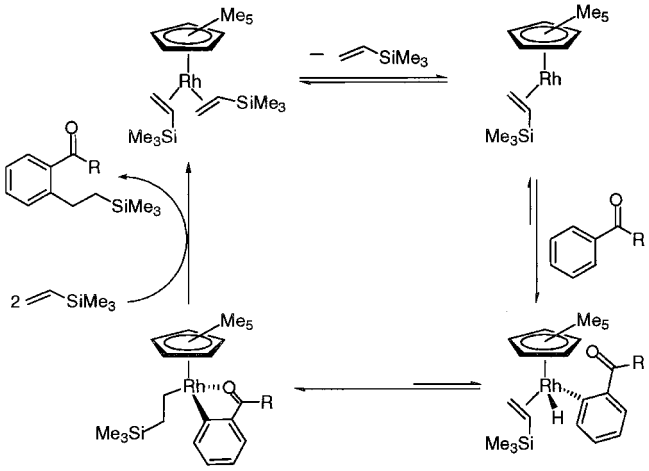
These results show that activation of the meta and para C−H bonds followed by olefin insertion is reversible and results in H/D exchange. In contrast, no H/D exchange is observed in the ortho position yet this is the sole site of alkylation. A plausible explanation, illustrated in eq 28, is that oxidative addition/migratory insertion occurs reversibly but a chelate interaction in the alkyl aryl Rh(III) intermediate renders the methylene hydrogens (in this case −CHD−) diastereotopic, and therefore, the deuterium which migrates to the olefin must, by microscopic reversibility, also return to the rhodium in the reverse β-elimination step. Thus, even though the C−H oxidative addition/migratory insertion process is reversible, no H/D exchange occurs. If this explanation is correct, it suggests that reductive elimination from the alkyl aryl intermediate is the rate-determining step and that it is assisted by chelation.



(28)

On the basis of these results, the mechanism depicted in Scheme 12 has been proposed. The

Scheme 12



increase in turnover frequency with increase in ketone concentration and suppression of the turnover frequency with added olefin suggests a reversible loss of olefin to produce an unsaturated intermediate that is trapped by the ketone to generate an oxidative addition adduct. Olefin insertion generates an alkyl aryl complex in which chelation provides an 18-electron intermediate. The barrier to reductive elimination is apparently reduced by this chelate interaction which results in exclusive ortho-alkylation.

Several significant differences are apparent in a comparison of the ruthenium- and the rhodium-based systems. The reaction conditions for both catalytic systems are similar. While optimization of the catalytic process in the ruthenium system has resulted in generally good turnover numbers, the rhodium system investigated here shows interesting potential for further development in this area. Both systems show, in general, high regioselectivity for addition to the olefin to generate the *anti*-Markovnikov product. Olefin isomerization is observed in situ with both systems, but aromatic alkylation generates only the linear products. The catalyst activation procedure in the ruthenium system is believed to be an initial olefin hydrogenation step that generates a Ru(0) olefin complex. In the rhodium system, the initial rhodium−bis-olefin complexes are believed to lose one olefin.

The key difference, however, is that in the ruthenium-catalyzed process carbonyl-coordination is presumed to be the first step, which directs the C−H bond activation to the ortho-position of the aromatic substrate, with the para and meta C−H bonds not being activated. The rhodium system, on the other hand, is not discriminating in the C−H bond activation step and activation of all sites of the substrate is observed. It has been established that C−H bond activation is fast and reversible in the Ru system and that the reductive elimination is the turnover limiting step. The same feature is believed to apply for the rhodium system. In both systems, chelation of the carbonyl group to the metal center is believed to

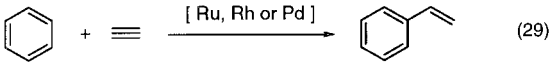
lower the barrier for reductive elimination to afford the product.

2. Nonchelation-Assisted Reactions

The Rh-catalyzed photochemical system presented in section II.A produces alkylbenzene derivatives as byproducts.[22] Hydroarylation of activated olefines has also been achieved using $Pd(OAc)_2$ in trifluoroacetic acid,[47,50] a system extensively studied for the hydroarylation of alkynes (section II.C). Finally, although not catalyzed by a metal of the Ru−Ru−Pd triad, the *anti*-Markovnikov hydroarylation of unactivated olefins with unactivated arenes which produces straight-chain alkylarenes with good selectivities and fairly good turnover numbers by means of an iridium complex need to be reported.[43] The mechanism appears to involve phenyl C−H bond activation by iridium to form an aryliridium species.

C. Hydroarylation of C–C Triple Bonds

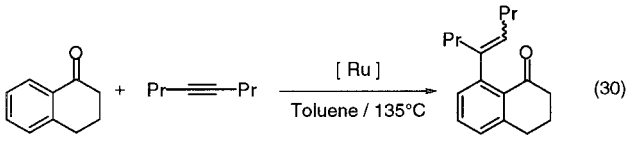
Acetylenes are known to react with transition-metal complexes in various ways. Terminal acetylenes undergo oxidative addition by their C−H bonds or form vinylidene complexes with migration of hydrogen (section II.D). Proceeding via acetylene π-complexes, the formation of metallacyclopentadienes and the trimerization of acetylenes are also known. Therefore, it is interesting to see whether the hydroarylation of C−C triple bonds can compete successfully with these known reactions.



(29)

1. Chelation-Assisted Reactions

Numerous stoichiometric examples of alkyne insertions into the M−C bond of orthometalated transition-metal complexes leading either to new complexes or to organic-coupling compounds, notably to heterocycles, are known.[44] The discovery of a chelation-assisted catalytic process for the hydroarylation of C−C double bonds[26] has opened up a wide range of opportunities in synthetic organic chemistry. Therefore, it was natural to see whether acetylenes instead of olefins could participate in this catalytic reaction. The reaction of α-tetralone and heteroaromatic ketones has been examined with various internal acetylenes (eqs 30 and 31).[45]



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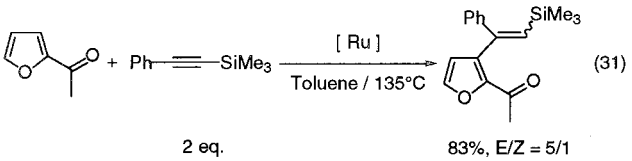
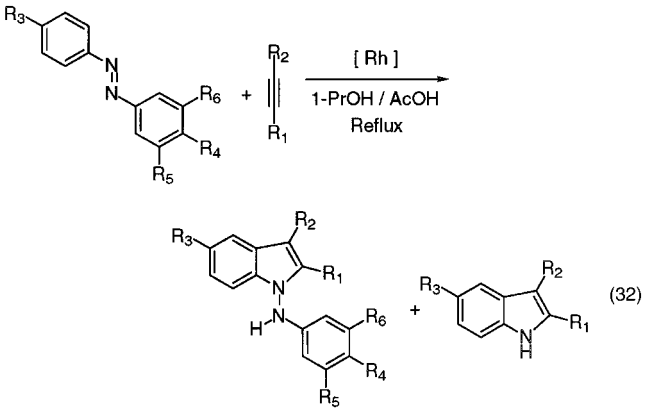


(31)

[Ru] : $RuH_2(CO)(PPh_3)_3$, 6 mol%

Symmetrically substituted dialkyl- or diarylacetylenes gave the two possible stereoisomers in good yields, the *cis*-product being predominant (eq 30). This is in marked contrast to the case of internal olefins which did not react or reacted only sluggishly.[38] Arylalkylacetylenes gave all four possible regio- and stereoisomers. In contrast, in the case of trimethylsilylacetylenes, although mixtures of stereoisomers were obtained, the regioselectivities were exclusive, the trimethylsilyl group being always β to the new C−C bond (eq 31). A similar selectivity was observed in the $Ru_3(CO)_{12}$-catalyzed reaction of an aromatic imine with 1-trimethylsilylpropyne.[27] As could be expected, terminal acetylenes did not react.

Addition of 1,2-diarylazenes to aliphatic or aromatic internal alkynes in the presence of catalytic amounts of Wilkinson's catalyst afforded *N*-(arylamino)indole derivatives.[46] Isolated yields were in the range of 55−85% for symmetrically substituted alkynes with electron-donating substituents. Unsymmetrically substituted alkynes with alkyl substituents and all alkynes with electron-withdrawing substituents gave yields in the range of 6−30% (eq 32). With unsymmetrically substituted alkynes, the reaction is regioselective. Regioselectivity originates in steric effects and is also slightly sensitive to electronic factors. Thus, bulky and electron-donating substituents are preferred in the 2-position of the product, whereas electron-withdrawing substituents preferentially stay in the 3-position.

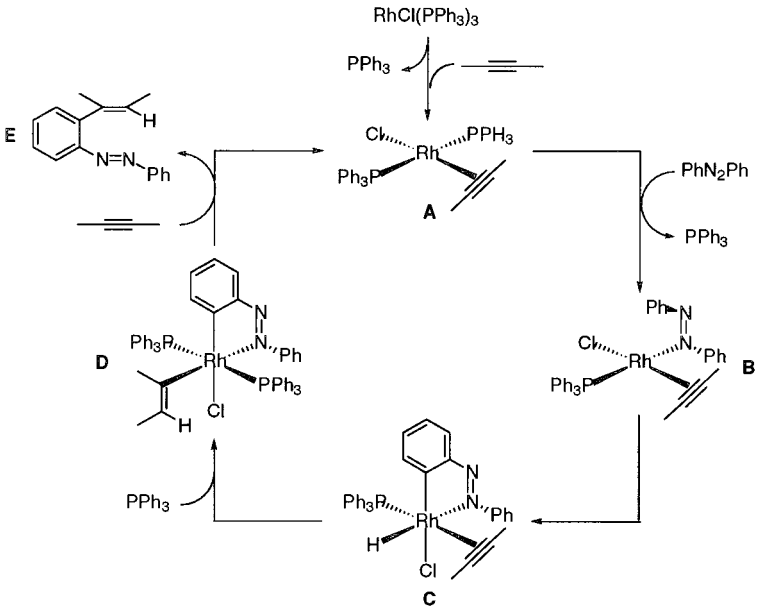


(32)

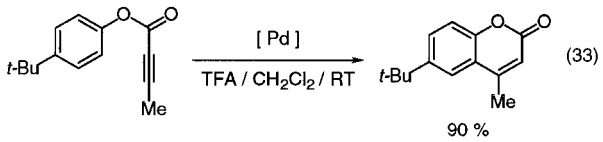
[Rh] : $RhCl(PPh_3)_3$, 2.5 mol%
R_1, R_2 : electron-donating, 55 to 85%
R_1, R_2 : elctron-withdrawing, 6 to 30%

The mechanism is believed to be essentially the same as that for olefin hydroarylation. Thus, in the latter case, the key steps are orthometalation of the diazene followed by insertion of the alkyne into a Rh−H bond and reductive elimination to afford a 1-(2-ethynylphenyl)-2-phenylazene intermediate **E**, which is converted to the *N*-(arylamino)indole derivative in an acid-catalyzed step (Scheme 13). This mechanism is substantiated by ^1H NMR experiments. Note that in this particular case, at least, kinetic measurements tended to show that the rate-determining step is the formation of the cyclometalated complex **C** instead of the usual reductive elimination step.

Scheme 13



An efficient intramolecular hydroarylation process involving C−C triple bonds has recently been reported by using an in-situ-generated highly electrophilic Pd(II) or Pt(II) cationic species in trifluoroacetic acid (TFA).[47] Aryl alkanoates prepared from the corresponding phenols and alkynoic acids underwent fast regio- and stereospecific intramolecular cyclization in the presence of $Pd(OAc)_2$/TFA, affording heterocycles, i.e., coumarins, in good to excellent yields (eq 33).



(33)

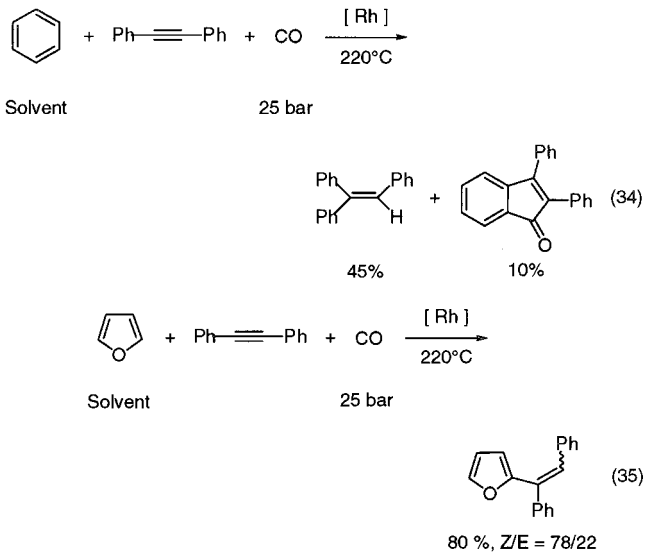
[Pd] : $Pd(OAc)_2$, 1 mol%

In this reaction the electrophilic metalation of aromatic C−H bonds by Pd(II) cationic species is believed to be assisted by ethynyl coordination. In fact, this very rare example of the combination of chelation-assistance and electrophilic metalation is a particular case of a general intermolecular hydroarylation process of acetylenes, which is presented in detail in the following section.

It seems there are no other examples of catalytic chelation-assisted insertion reactions of acetylenes into C−H bonds without the need to sacrifice any extra functional groups. Surprisingly there are more examples of nonchelation-assisted hydroarylations of C−C triple bonds.

2. Nonchelation-Assisted Reactions

The first example was reported in 1979 with the $Rh_4(CO)_{12}$/CO catalytic system,[48] which also catalyzes the dehydrogenative coupling of benzene with ethylene, albeit in very low yields (section II.A).[21] The reaction of benzene with diphenylacetylene in the presence of catalytic amounts of the rhodium catalyst under a carbon monoxide pressure gave triphenylethylene and 2,3-diphenylindenone as a remarkable byproduct resulting from the cleavage of two C−H bonds and the formation of three C−C bonds (eq 34).[48a] As for the production of styrene from benzene and ethylene, severe conditions were necessary to obtain acceptable yields of products. Decreasing the carbon monoxide pressure induced the trimerization of diphenylacetylene. The reaction was further extended to five-membered heterocyclic compounds such as furans, thiophenes, and *N*-methylpyrroles, which were also activated by $Rh_4(CO)_{12}$ and added to acetylenes to give selectively the corresponding vinyl-substituted aromatic heterocyclic compounds in good yields (eq 35).[48b]



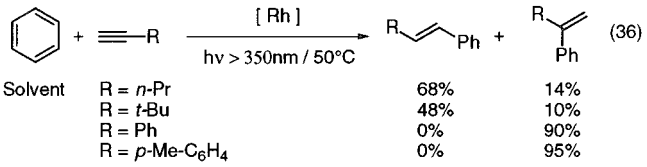
[Rh] : $Rh_4(CO)_{12}$, 1 mol% (34) and 0.5 mol% (35)

When benzene was allowed to react with other internal acetylenes, the reaction yielded coupling-products resulting from *syn*-hydroarylation selectively. The same trends have been reported for the

ruthenium- and rhodium-catalyzed chelation-assisted reactions mentioned above. In contrast, the addition of furans to acetylenes afforded mixtures of stereoisomers where the coupling product resulting from the *anti*-hydroarylation was predominant. The same trend has been reported for the palladium-catalyzed chelation-assisted hydroarylation of alkynes cited above. With unsymmetrically substituted acetylenes such as 1-phenylpropyne, the reaction was regioselective, giving alkenes with the methyl and the aromatic or heteroaromatic group in the α-position as the major coupling product. Monosubstituted benzenes such as toluene, anisole, and fluorobenzene also reacted with diphenylacetylene. The distribution of the positional isomers of the resulting olefins was similar to that observed for the dehydrogenative coupling of monosubstituted benzenes with ethylene[21] and, thus, different from that observed in ordinary electrophilic aromatic substitution or in palladium-catalyzed arylations of olefins.[12] We can note that the addition of furan or 2-substituted furans to acetylenes occurs regioselectively at the α-position of the ring, indicating that the α-C−H bond is more reactive than the β-C−H. Nevertheless, if both α-positions are occupied by substituents, the reaction can take place at the β-position. One of the most interesting features of these reactions is the much higher reactivity of furan compared with benzene, which enables one to carry out the reaction in benzene and, thus, considerably increases the yield of the coupling product based on the amount of furan.[48b]

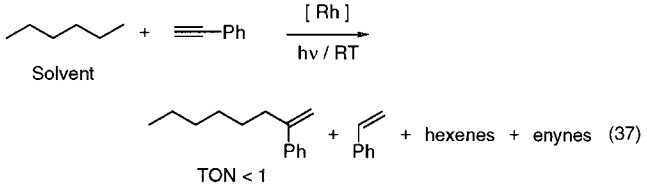
From a mechanistic point of view, the formation of the olefins has been explained in terms of the oxidative addition of benzene to the rhodium catalyst, insertion of the alkyne into the resulting arylrhodahydride intermediate, and reductive elimination of the coupling product, although this is without experimental evidence.[48a]

The insertion of terminal alkynes into aromatic C−H bonds catalyzed by $RhCl(CO)(PMe_3)_3$ under irradiation has been reported in two independent papers.[49] The reaction of benzene with phenylacetylene, in the presence of the rhodium catalyst under photolytic conditions with a high-pressure mercury lamp, gave a small quantity of 1,1-diphenylethylene along with biphenyl and dimers and trimers of phenylacetylene.[49a] These results arise from the competition between the oxidative addition of C−H bonds of benzene and that of alkynes to the metal (section II.D). An important factor dictating the selectivity to the heterocoupling product was the irradiation wavelength. Indeed, it was possible to prevent the formation of both types of homocoupling products by cutting off short wavelength radiation below 350 nm. Under these conditions the chemical yields (58−95% based on the alkyne) and turnover numbers (TON > 200) were fairly good, although the quantum efficiency was low ($Ø = 3.6 \times 10^{-3}$ in the best case). The orientation of the addition is dependent upon the nature of the alkyne substituent; for aryl substituents, exclusively 1,1-disubstituted olefins were produced, while for alkyl substituents, a mixture of 1,1- and 1,2-disubstituted olefins was formed (eq 36).[49b] The reactivities of internal alkynes were notably very low.[49a]



[Rh] : $RhCl(CO)(PMe_3)_2$, 2 mol%

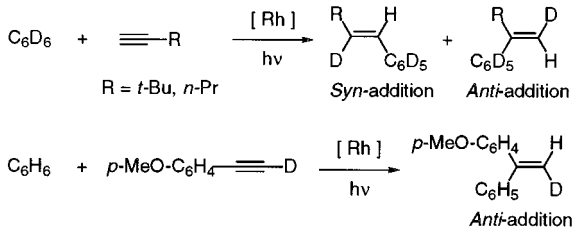
Remarkably this catalytic system was also found to effect alkyne insertion into aliphatic C−H bonds.[49a] Thus, cyclohexane, *n*-hexane, and diethyl ether reacted with phenylacetylene to give the respective adducts, i.e., α-substituted styrenes. However, the yield was very low and other products, such as styrene, alkenes resulting from alkane dehydrogenation, and enynes, were also formed (reactions run without wavelength filter). It is noteworthy that the reaction of *n*-hexane was terminal-selective (eq 37). To date, there is no other example of alkyne hydroalkylation.



[Rh] : $RhCl(CO)(PMe_3)_2$, 0.7 mM

In the reactions of benzene with terminal acetylenes, the linear olefins resulted from *syn*-addition of the aromatic C−H bond across the triple bond whereas the branched olefins resulted from *anti*-addition as shown by deuterium-labeling experiments (Scheme 14).[49b]

Scheme 14



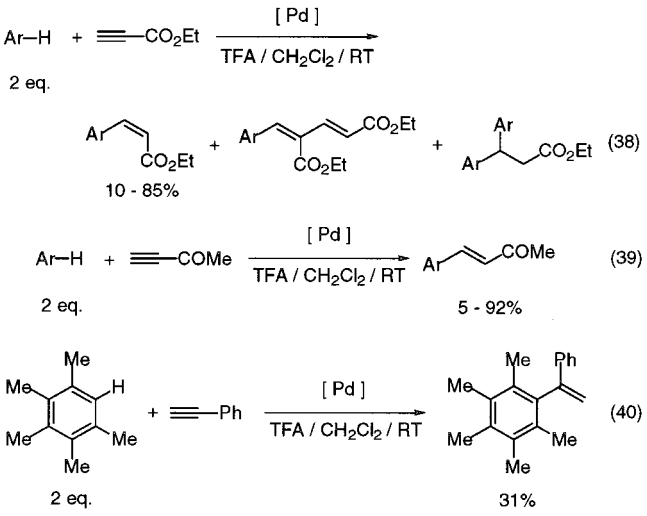
Moreover, crossover experiments revealed that both the hydrogen atom and the phenyl group that are added to a triple bond are derived from the same molecule of benzene. Thus, there is no formation of a crossover product. These observations led the authors to propose different mechanisms for the formation of the linear and branched olefins. Concerted insertions of olefins into M−H bonds generally result in *syn*-addition. Therefore, it was suggested that the 1,2-disubstituted olefins were formed by concerted insertion into a Rh−H bond resulting from the oxidative addition of benzene to the metal center and subsequent reductive elimination. On the basis

of steric considerations, such a mechanism also accounts for the observed regioselectivity. Indeed, insertion into the Rh−H bond should favor formation of the less crowded 1,2-rhodaalkylethene. The stereochemistry observed for the formation of the 1,1-disubstituted olefins (resulting from *anti*-addition) was rather enigmatic. In this context, higher kinetic isotope effects were found for the formation of the linear olefins than for the branched ones. One possible explanation was that alkyne insertion into the Rh−H bond, or a subsequent step, was rate-determining for the formation of the 1,2-disubstituted products, whereas C−H bond formation would occur after the rate-determining step in the formation of the 1,1-disubstituted olefins. Therefore, a mechanism involving rate-determining *anti*-insertion into the Rh−Ph bond followed by vinyl-H reductive elimination was suggested. On steric grounds this would be expected to yield the observed 1,1-disubstituted olefins. The exact nature of the active species and of the intermediates are not known. As for the whole reaction mechanism, it was suggested to be a one-photon mechanism with the catalytic cycle, itself, being nonphotochemical. We will see in the paragraph devoted to the $RhCl(CO)(PMe_3)_2/h\nu$-catalyzed carbonylation of benzene that this is not true (section III.A).

An efficient Pd(II)- or Pt(II)-catalyzed *anti*-hydroarylation of alkynes by simple arenes, whose intramolecular version has been briefly presented in the previous section,[47] has recently been reported.[50] This reaction was developed in order to extend the coupling reaction of arenes with olefins (section II.A),[18] but addition products were obtained instead of the expected dehydrogenative coupling products. The addition of arenes to terminal and internal alkynes was realized regio- and stereoselectively at room temperature in the presence of the Pd(II) or Pt(II) catalysts and a mixed solvent containing trifluoroacetic acid (TFA). The formation of arene/alkyne 1/2 or 2/1 adducts as side products is observed in some cases and can sometimes be suppressed by changing the catalyst, the catalyst concentration, and the reaction time. The Pt(II) system, $PtCl_2$/2AgOAc/TFA, exhibited a lower catalytic activity than $Pd(OAc)_2$/TFA but a higher selectivity, giving higher yields of 1/1 adducts at the same conversion. Of note is that no oxidant was required for the Pd(II) system.

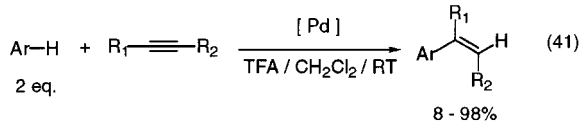
The regio- and stereoselectivity observed with terminal acetylenes was very much dependent upon the nature of the employed alkyne. Thus, the addition of arenes to ethyl propiolate gave *syn*-adducts (resulting from *anti*-addition) predominantly in most cases. Arene/alkyne 1/2 and 2/1 adducts were observed in some cases (eq 38). In contrast, reactions with 3-butyn-2-one afforded *anti*-adducts as the only products in most cases (eq 39). The reaction of pentamethylbenzene with phenylacetylene gave a 1,1-disubstituted olefin (Markovnikov-type adduct) as the only isolated product (eq 40).

The reactions with internal alkynes were slower than those with terminal alkynes. *syn*-Arylalkenes arising from *anti*-hydroarylation were obtained as the



[Pd] : $Pd(OAc)_2$, 1 mol% (38), 0.02 to 1 mol% (39), 5 mol% (40)

major products in most cases (eq 41). The Pt(II) catalytic system gave especially good yields.



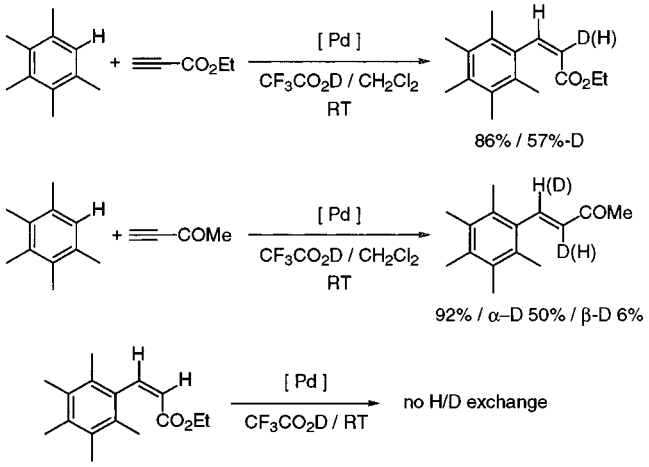
[Pd] : $Pd(OAc)_2$, 5 mol%
R_1 : Ph, Me, *n*-C_3H_7, CO_2Et
R_2 : Ph, Me, *n*-C_3H_7, CO_2Et, CO_2H, CHO, COMe

The reaction exhibited very good chemoselectivity with unprotected OH, Br, CHO, and vinyl groups on arenes, all proving to be compatible. The yields increased with an increasing number of electron-donating substituents of arenes, showing characteristics of electrophilic substitution. Interestingly, electron-rich arenes could overcome steric hindrance, and the reactions of pentamethylbenzene gave good yields of crowded molecules with all acetylenes. This is in marked contrast to other palladium-catalyzed reactions such as the Heck reaction in which steric hindrance is a big obstacle.[51] The present reaction is dictated by electronic effects of the arene substituents rather than steric effects. The C−C triple bonds conjugated to electron-withdrawing groups such as CO_nR (n = 1 or 2, R = H or alkyl) generally serve as good acceptors of aryl nucleophiles.

The fact that this hydroarylation reaction failed in solvents other than TFA, such as acetic acid, tends to indicate that the reaction requires a highly electrophilic Pd(II) species such as $[Pd(O_2CCF_3)]^+$ [52] to facilitate the formation of a σ-aryl−Pd intermediate which would undergo subsequent alkyne insertion into the thus-obtained Pd−C bond. The resulting vinyl−Pd intermediate would then undergo protonolysis by TFA. σ-Aryl−Pd(II) complexes are known as intermediates in the coupling of arenes with olefins and arenes with arenes.[13] Moreover, the formation of such complexes was partially confirmed by ^1H NMR with the disappearance of the aryl hydrogen of pentamethylbenzene during the reaction with 1 equiv of $Pd(OAc)_2$ in TFA within a few minutes at room temperature.

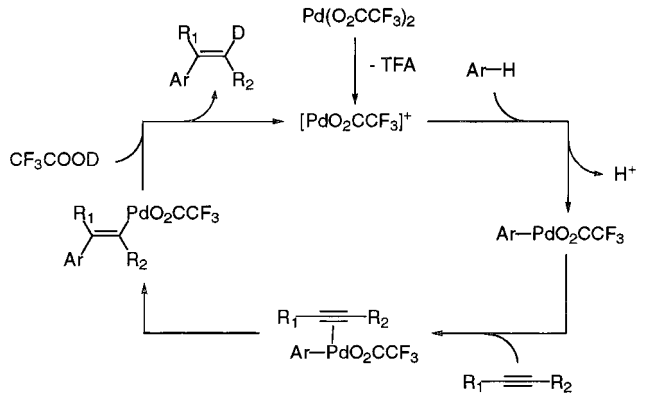
The reactions of pentamethylbenzene with two alkynes carried out in CF_3CO_2D revealed that deuterium atoms had been incorporated into adducts as vinyl atoms predominantly at the α-position (Scheme 15). The near absence of deuteration at the *β*-position[53] excluded the involvement of a Pd(II) insertion into the C−H bond of terminal alkynes as well as the involvement of vinylidene complexes.[50] Moreover, as vinyl H/D exchange between the olefin and CF_3CO_2D in the presence of the catalyst was excluded by a control experiment (last equation in Scheme 15), the observed deuteration at the α-position presumably resulted from the protonation of a vinyl−Pd(II) complex by the deuterated solvent.

Scheme 15



All these results strongly militate for a reaction pathway similar to that depicted in Scheme 16, where all the intermediates are Pd(II) species. Note that the *anti*-insertion of the coordinated alkyne into the *σ*-aryl−Pd bond is not well understood.[50]

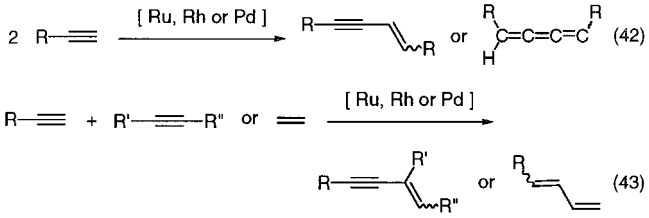
Scheme 16



In summary, this latter process offers to date the most general and efficient method for the one-step hydroarylation of internal and terminal alkynes by simple arenes.[50] The absence of competition between the activation of aromatic C−H bonds and that of an alkynic C−H bond in the reaction of arenes with terminal acetylenes is remarkable. Indeed, as discussed in the following section dealing with the hydroacetylation and hydroolefination of C−C triple bonds, the activation of the terminal C−H bond of monoaryl- or monoalkylacetylenes is relatively easy to carry out.

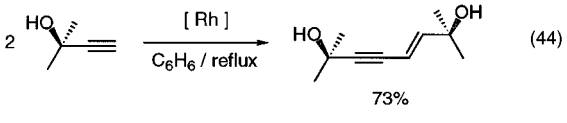
D. Homo- and Heterocoupling of Terminal Alkynes

The dimerization of terminal acetylenes to 1,3-enynes or to 1,4-disubstituted butatrienes and the cross-coupling of terminal alkynes with internal alkynes or with olefins, catalyzed by transition-metal complexes, provide highly attractive routes to C4 units containing unsaturation, which are useful for further structural elaboration. Important efforts have been made in seeking simple synthetic routes to these compounds. Among the more attractive are those allowing these couplings in an atom economical manner. Although such processes have long failed to be synthetically useful due to the lack of control, there are now a number of interesting reactions that need to be presented in this review. A rapid overview is given.



1. Terminal Alkyne Dimerization and Cross-Coupling with Internal Alkynes

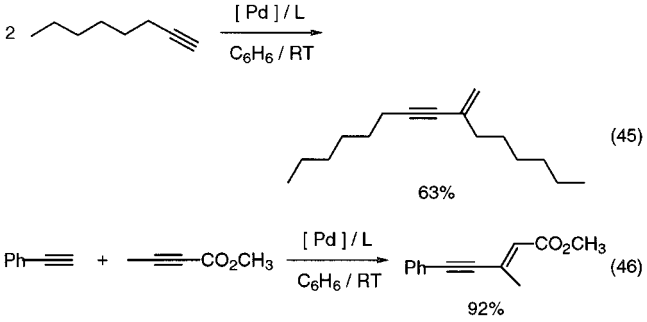
The C−H bond activation of 1-alkynes by a transition-metal catalyst constitutes one of the most important methods of preparing enynes, which can be used as precursors for the synthesis of natural products. Since the Glaser[54a] coupling of terminal acetylenes under copper catalysis and oxidation to give butadiynes and its nonoxidative variant the Strauss[54b] coupling, which gives (*Z*)- and (*E*)-1,4-disubstituted-1,3-enynes by head-to-head coupling, many papers dealing with the transition-metal-catalyzed dimerization of terminal alkynes have been reported. The first example, in which a complex of the Ru−Rh−Pd triad had been used, seems to be the dimerization of monosubstituted α-hydroxyacetylenes by Wilkinson's catalyst.[55] Indeed, 3-methylbut-1-yn-3-ol underwent head-to-head dimerization in the presence of catalytic amounts of $RhCl(PPh_3)_3$ to give (*E*)-2,7-dimethyloct-3-en-5-yne-2,5-diol selectively with yields up to 77% (eq 44).



Unfortunately no evidence for dimerization could be obtained for acetylenes which did not carry a α-hydroxy group, and it was concluded that the latter may be involved in the dimerization mechanism. In a further more detailed study, traces of head-to-tail dimer were noted,[56a] and in a third paper, the same

catalyst was reported to give mixtures of the two dimers with β-hydroxy terminal acetylenes.[56b] However, another group showed that terminal alkynes, which did not carry a hydroxy group at C-3 or C-4, such as oct-1-yne, hept-1-yne, and hex-1-yne, could be catalytically dimerized by $RhCl(PPh_3)_3$ to give predominantly the corresponding branched enynes in high yields.[57] These findings demonstrated that a hydroxy group was not essential for the dimerization of terminal acetylenes with $RhCl(PPh_3)_3$. However, α-hydroxyalkynes appeared to dimerize much more rapidly and selectively than unsubstituted alkynes,[58] probably due to the favorable orientation of the substrates and the greater stability of the organometallic intermediates. This was further demonstrated by the selective head-to-tail dimerization of α-hydroxy terminal acetylenes in the presence of a palladium(II) catalyst containing phosphonite ligands and copper(I) iodide which was assumed to reduce the divalent palladium to the zerovalent state in order to allow oxidative addition of the alkynic C−H bond onto the Pd center.[59] Note that cross-dimerization of α-hydroxy terminal alkynes with unsubstituted 1-alkynes was also studied and that the four possible head-to-tail dimers were always obtained. Nevertheless, in each case, the major cross-dimer was that obtained by addition of the nonhydroxylated acetylene across the triple bond of the hydroxylated acetylene. This tended to show preferential coordination of the hydroxylated acetylene on the σ-alkynyl hydride palladium(II) intermediate.

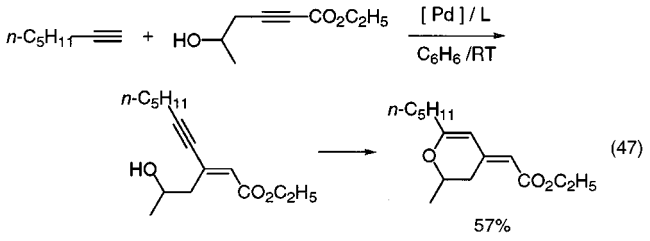
It was only in the late 1980s that a decisive breakthrough was achieved using a palladium template, which allowed the homo- and cross-coupling of various acetylenes in high yields.[60] The use of 2−5 mol % of $Pd(OAc)_2$ and tris(2,6-dimethoxyphenyl)-phosphine provided exclusively head-to-tail dimers of various alkynes in yields varying from 63% to 89% (eq 45). Even more remarkably, the incorporation of an equivalent amount of an electron-deficient internal acetylene for the reaction of a terminal acetylene with 2 mol % of $Pd(OAc)_2$ and $P[2,6\text{-}(MeO)\text{-}C_6H_3]_3$ led to cross-coupling products as single geometric isomers (eq 46). Note that the reaction proved to be compatible with esters, sulfones, and hydroxyl groups.



[Pd] : $Pd(OAc)_2$, 2 mol%

L : $P[2,6\text{-}(MeO)_2\text{-}C_6H_3]_3$, 2 mol%

The reaction was further extended to the cycloisomerization of α,ω-diynes to macrocyclic acetylenes,[61a] to the two-step preparation of dienylstannanes via alkyne cross-coupling and *syn*-addition of a tin hydride to the acetylenic function of the resulting conjugated enyne,[61b] and to atom economical syntheses of oxygen heterocycles via tandem-catalyzed reactions of terminal alkynes with hydroxyalkynoates (eq 47).[61c,d]

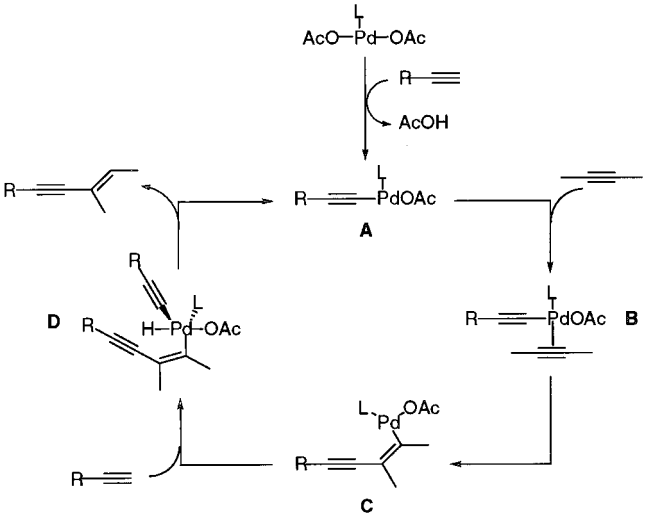


[Pd] : $Pd(OAc)_2$, 10 mol%

L : $P[2,6\text{-}(MeO)_2\text{-}C_6H_3]_3$, 4 mol%

The intimate mechanism of this efficient catalytic reaction is not completely understood. Although it is clear that it consists of the three following phases, (i) the activation of the C−H bond of the terminal alkyne, (ii) the addition of the π-system of the acceptor alkyne, and (iii) the protonation of the resulting vinylpalladium intermediate, the question of how these phases occur has not been addressed. In addition, the question of the palladium species responsible for the actual catalytic cycle is not necessarily obvious. Thus, three plausible mechanisms have been proposed.[62] The third one, which is an hybrid rationale of the two others, is outlined in Scheme 17. In this mechanism the active species **A**

Scheme 17



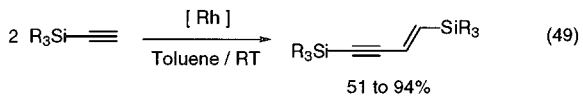
is proposed to be an alkynylpalladium acetate complex which could result from the insertion of palladium into the C−H bond of a terminal alkyne that will have become kinetically accessible by coordination of the triple bond to Pd(II). This would generate a Pd(IV) intermediate species that is not expected to be stable relative to the loss of acetic acid. The active species **A** could also be generated via direct protonation of the coordinated terminal alkyne to ligated palladium acetate or alternatively via a series of equilibria. However, such mechanisms normally involve base-catalyzed reactions and except for the phosphine, which is present in a 1/1 ratio to the palladium and is supposed to be tied up as a ligand,

no base is present. Therefore, the proposition of a Pd(IV) intermediate is preferred. Subsequent coordination of an acceptor alkyne to **A** and migratory insertion would then afford the vinylpalladium species **C**. The occurrence of 1/2 adducts in some cases[62] suggested a competition between protonation of the vinylpalladium intermediate and its reaction with another molecule of acceptor alkyne. However, such a competition did not respond to an increase in the concentration of protons, even to the extent of using a protic solvent. Therefore, it was suggested that complex **C** may react with another acceptor alkyne to form a 1/2 adduct or another terminal alkyne to give the Pd(IV) complex **D**. Subsequent reductive elimination of the conjugated enyne and the hydride would complete the catalytic cycle (Scheme 17).

However, the way this route accommodates for the selectivity observed for cross-coupling is not obvious. If the selectivity derives from alkyne coordination of **A**, a Pd(II) species bearing an electronegative group such as acetate would preferentially coordinate an electron-deficient alkyne over an electron-rich alkyne to preclude any homocoupling, a requirement that does not appear very likely. Therefore, an alternative whereby the "dummy" ligand would be a second acetylide has also been suggested. The ability of electron-deficient alkynes to compete successfully with the terminal alkyne even at a 1/1 ratio would nicely be accommodated by a species bearing strong donor acetylide ligands. However, invoking a dialkynylpalladium species, which can be formed from both Pd(0) and Pd(II) precursors, as the catalyst resting state also has its drawbacks. Indeed, suggesting its intermediacy does not attribute any difference on the oxidation state of the catalyst precursor whereas there is one.[62] At present, due to the lack of any experimental data, unambiguous differentiation among these possibilities cannot be made.

The regiochemistry of the carbometalation of the acceptor alkyne suggests both steric and electronic effects. Thus, the dimerization preferentially involves placing the palladium at the less-substituted carbon rather than the reverse, both to minimize steric hindrance and to provide the most stable C−Pd bond. The latter presumably dominates in the cross-coupling.

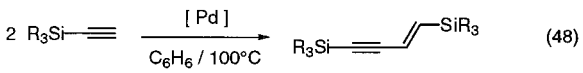
Except for the rhodium-catalyzed reaction of 1-alkynes bearing a 3-hydroxy group,[55,56] most papers focusing on rhodium- and palladium-catalyzed reactions are concerned with head-to-tail couplings.[63] Head-to-head dimerization of ethynylsilanes by Pd(0) or Rh(I) complexes has, however, been reported.[64] Treatment of ethynyl-substituted mono- and disilanes with a catalytic amount of $Pd(PPh_3)_4$ or $RhCl(PPh_3)_3$, respectively, in benzene at 100 °C or in toluene at room temperature afforded exclusively (*E*)-1,4-disubstituted enynes (eqs 48 and 49).



51 to 94% (49)

[Rh] : $RhCl(PPh_3)_3$, 5-10 mol%

In contrast to the palladium-catalyzed dimerization reaction in which the introduction of at least one

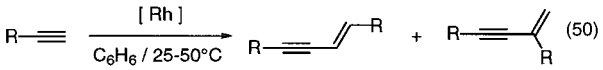


50 to 65% (48)

[Pd] : $Pd(PPh_3)_4$, 7 mol%

SiR_3 : $SiPh_nR_{3-n}$, n = 1 or 2

phenyl group onto the ethynylsilicon atom was necessary to obtain the enynes in high yields, the rhodium-catalyzed reaction gave the enynes in high yields with ethynylsilanes bearing no phenyl group. Though without any experimental proof, similar mechanisms have been proposed for both reactions.[64a,b] It is assumed to involve the insertion of a Pd(0) or Rh(I) complex into an acetylenic C−H bond to give an ethynyl−palladium(II) or −rhodium(III) complex. This would be followed by the regiospecific addition of the metal−hydride across the triple bond of a coordinated ethynylsilane and final reductive elimination. The head-to-head coupling was ascribed to the steric requirement of the bulky silyl groups.[64b] This hypothesis was partially confirmed by the exclusive formation of the head-to-tail dimer when hex-1-yne was treated with $RhCl(PPh_3)_3$.[64b] The same trend was observed in another rhodium-catalyzed alkyne dimerization.[49b] Terminal acetylenes substituted by a bulky substituent such as a *tert*-butyl group underwent head-to-head coupling to afford exclusively (*E*)-1,4-disubstituted enynes, whereas other terminal alkynes gave mixtures of dimers or exclusively head-to-tail coupling products (eq 50).



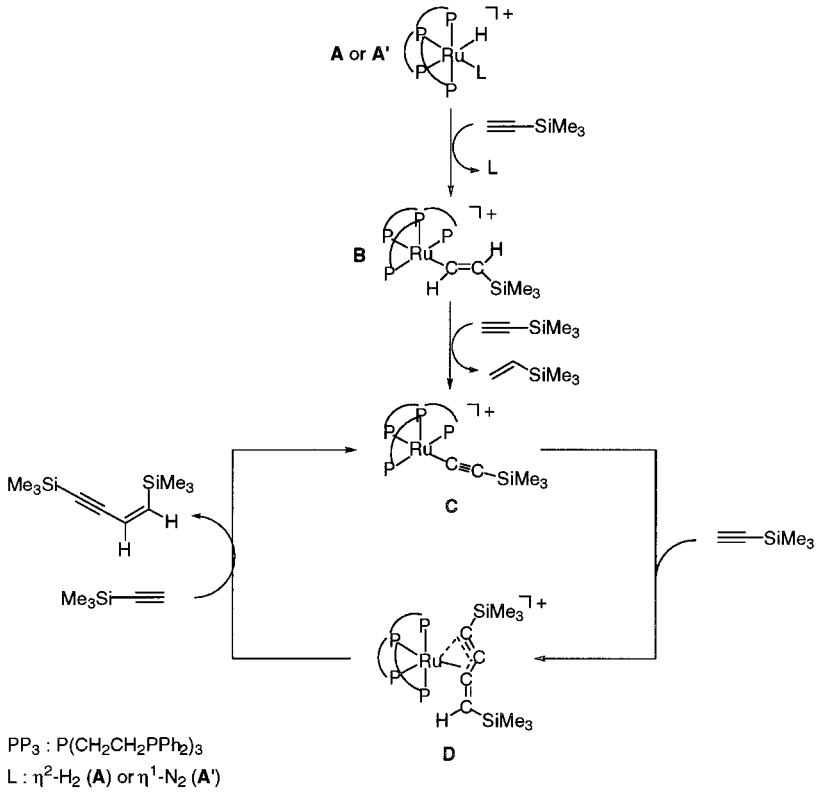
(50)

R : *n*-Pr	37%	63%
R : *t*-Bu	100%	0%
R : Ph	0%	100%
R : *p*-Me-C_6H_4	0%	100%

[Rh] : $[Rh(PMe_3)_2Cl]_2$, 2 mM

Ruthenium-catalyzed alkyne dimerizations usually give (*E*)- and/or (*Z*)-1,4-disubstituted enynes, i.e., head-to-head coupling products as sole products.[65] The reactions proceed via an intermediate containing a η^3-enynyl ligand as elegantly described in a detailed mechanistic study, leading to (*Z*)-1,4-bis(trimethylsilyl)but-3-en-1-yne, using the Ru(II) η^2-H_2 complex $[Ru(PP_3)RuH(H_2)]^+BF_4^-$ **A** or its η^1-N_2 derivative $[Ru(PP_3)H(N_2)]^+BF_4^-$ **A′** (PP_3 = $P(CH_2CH_2PPh_2)_3$).[65a] Such intermediates have also been suggested in a study where neutral analogues of these complexes, $RuL_4H(C_6H_5)$ with L_4 = $P(CH_2CH_2CH_2PMe_2)_3$, $N(CH_2CH_2PPh_2)_3$, and $MeSi(CH_2PMe_2)_3/PMe_3$, have been used.[65b] The reactions of **A** or **A′** with 3 equiv of trimethylsilylacetylene led to the formation of the enynyl Ru(II) complex **D**, which was characterized by ^1H and $^{31}P\{^1H\}$ NMR and X-ray crystallography together with 1 equiv of trimethylsilylethylene (Scheme 18). Moreover, monitoring the reaction between **A′** and variable amounts of trimethylsilylacetylene by NMR showed that the enynyl complex **D** was formed by the addition of 1 equiv of alkyne to the σ-alkynyl complex **C**, isolable in the solid state as a solvate. The σ-alkenyl complex **B** could not be isolated in pure form because its reaction with the

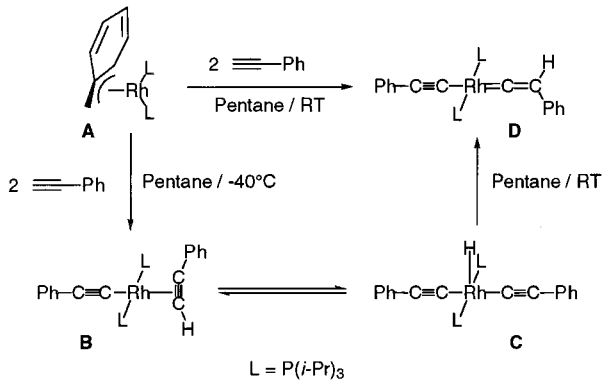
Scheme 18



alkyne was much faster than that of the alkyne with **A′**. Complexes **A**, **A′**, and **D** could be used indifferently for the catalytic dimerization of trimethylsilylacetylene or phenylacetylene. Similar catalytic activities were observed. For both 1-alkynes, the η^3-enynyl complexes were the only species observable during the course of the catalysis, which suggested that such complexes might be involved in the rate-determining step. All of these observations allowed the authors to propose the mechanism outlined in Scheme 18. Note that the transformation of the σ-alkynyl complex **C** to the η^3-enynyl complex **D** has been suggested to occur as follows: the alkyne can coordinate to **C** and rearrange into a vinylidene via a 1,2-hydrogen shift. [66] Subsequent C−C bond formation between the α-carbons of the *syn*-vinylidene and alkynyl ligands would then lead to **D**.

Complementary evidence for these latter steps, i.e., η^2-alkyne complex rearrangement to vinylidene and alkynyl−vinylidene coupling to the enynyl complex, was obtained in an elegant stoichiometric study dealing with the rhodium-mediated dimerization of phenylacetylene.[67] Using an alkynyl(vinylidene) rhodium complex, the authors were able to prepare η^2-enyne and η^1-enynyl complexes, which reacted with HX to give predominantly either (*Z*)-1,4-diphenylenyne or (*Z*)-1,4-diphenylbutatriene, depending on the reaction conditions.[68] The room-temperature reaction of the η^3-benzylrhodium(I) compound **A** with 2 equiv of phenylacetylene gave the alkynyl(vinylidene) rhodium complex **D** (Scheme 19). If the reaction was carried out at − 40 °C, the alkyne-(alkynyl)rhodium(I) intermediate **B** could be isolated. In solution, an equilibrium between **B** and the hydride(dialkynyl)rhodium(III) complex **C**, which

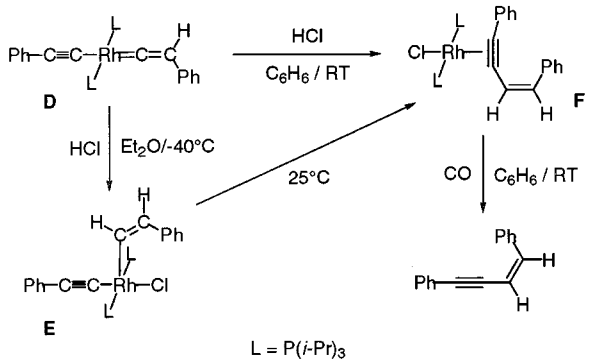
Scheme 19



rearranged quantitatively to **D**, could be observed (Scheme 19). This proved that the 1,2-hydrogen shift of the coordinated η^2-alkyne to the vinylidene complex occurs via a hydride(dialkynyl)rhodium(III) complex resulting from first oxidative addition of the alkyne.

The reaction of the alkynyl(vinylidene) complex **D** with HCl at room temperature gave the η^2-enyne complex **F**, which liberated (*Z*)-1,4-diphenylenyne on treatment with CO (Scheme 20). When the reaction was carried out at − 40 °C, the alkynyl(vinyl) compound **E** was formed quantitatively. The latter rearranged quantitatively to the η^2-enyne complex **F** when the solution was allowed to warm to room temperature. Presumably, **E** was formed via the initial oxidative addition of HCl to the metal center followed by migration of the hydride ligand to the α-carbon of the vinylidene unit.[67] This demonstrated that formation of an enyne mediated by a vinylidene transition-metal complex could result either from direct alkynyl−vinylidene coupling followed by pro-

Scheme 20



tonation of the resulting enynyl ligand or from alkynyl−vinyl coupling whereby the vinyl unit would result from protonation of the vinylidene ligand. In a catalytic reaction the protonation of the vinylidene or the enynyl ligand could result from treatment with an additional molecule of the 1-alkyne.

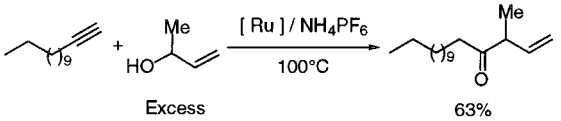
This latter assumption was partially confirmed by another reaction of the alkynyl(vinylidene) compound **D** in which the sequence of the addition of HX and CO was reversed. Indeed, reaction of **D** with CO in pentane at − 40 °C gave the η^1-enynyl complex **G**, presumably via coordination of CO to the metal and subsequent migration of the alkynyl ligand to the α-carbon of the vinylidene unit.[67] However, further protonation of **G** by trifluoroacetic acid did not afford the expected enyne but (*Z*)-1,4-diphenylbutatriene (Scheme 21). Butatriene derivative formation may seem surprising since the butatriene skeleton is thermodynamically much less stable than the enyne form, according to ab initio MO calculations.[68] Its preferential formation in the $RuH_2(CO)(PPh_3)_3$-catalyzed dimerization of *tert*-butylacetylene to (*Z*)-1,4-di-*tert*-butylbutatriene has been attributed to be the result of an equilibrium between an enynyl complex and a σ-butatrienylmetal species, the latter being preferentially attacked by an additional molecule of 1-alkyne for steric reasons.[68] This explanation cannot, however, account for the predominant butatriene formation in the case of the rhodium-mediated study.

To conclude this section, several remarks can be made. The addition of the C−H bond of terminal alkynes across the unsaturated part of an internal or a terminal alkyne creates a valuable and versatile product, a conjugated enyne. While these reactions have been observed with Ru, Rh, and Pd, they frequently produce mixtures arising from the reactivity of the initial adducts toward further additions. To date, the most synthetically useful catalytic system is the $Pd(OAc)_2/P[2,6\text{-}(MeO)_2\text{-}C_6H_3]_3$ system which can achieve homo- and cross-coupling very efficiently. Indeed, the reactions with rhodium (in some cases) and ruthenium involve a mechanism, i.e., vinylidene intermediates, that restricts the reaction to terminal alkynes. However, the ability of ruthenium complexes to form vinylidene complexes by reaction with terminal acetylenes has opened up the possibility of realizing a wide variety of atom economical reactions, especially with activated alkenes.

2. Cross-Coupling of Terminal Alkynes with Alkenes

Over the past decade the use of ruthenium catalysts for organic synthesis[4a,c] has led to the discovery of a wide range of selective transformations of alkynes[69] and C−C bond-forming processes.[70] Representative examples of the latter deal with the dimerization of alkynes to enynes or butatrienes (see previous section), with cycloaddition or cycloisomerization reactions,[71] and with the carbonylation of diynes to give phenols.[72] They also deal with the coupling of allylic alcohols with terminal alkynes via an Alder−ene-type reaction mechanism to afford γ,δ-unsaturated ketones, acetals, or aldehydes[73] or via ruthenium−vinylidene[74] or ruthenium−allenylidene[75] intermediates to afford β,γ-unsaturated ketones. We can also cite the codimerizations of alkynes with olefins via ruthenacyclopentene intermediates (i.e., Alder−ene-type reactions) which produce selectively butenes,[76] dienes,[77] and butenolides[78] or via ruthenium−vinylidene intermediates to afford dienes.[79] Most of these reactions are simple additions, and only those involving ruthenium−vinylidene[74,79] or ruthenium−allenylidene[75] intermediates involve C−H bond activation of the relatively acidic terminal bond prior to C−C bond formation. This feature outlines very well the synthetic importance of these compounds and the reason we focus on these systems.

The ability of vinylidene complexes to form spontaneously from terminal alkynes and coordinatively unsaturated metal species by a metal-promoted C−H insertion followed by tautomerization, combined with the increased susceptibility of the α-carbon of the vinylidene ligand toward nucleophilic attack, has led to the development of a condensation of allyl alcohols with terminal acetylenes to β,γ-unsaturated ketones with $[Ru(\eta^5\text{-}C_5H_5)Cl(PPh_3)_2]$ as catalyst.[74] Reaction of prop-2-en-1-ol with phenylacetylene led to the corresponding β,γ-unsaturated ketone and its isomer wherein the double bond had migrated to form the conjugated α,β-unsaturated ketone. With a branched allyl alcohol such as methylallyl alcohol, the reaction revealed a surprising regioselectivity. The new C−C bond was formed preferentially with the carbon bearing the hydroxy group. Furthermore, the β,γ-unsaturated ketone was isolated without impurities, presumably because the rate of double-bond migration was lowered considerably by the presence of the methyl substituent at the α-position (eq 51). Note that substituents on the double bond are not tolerated.

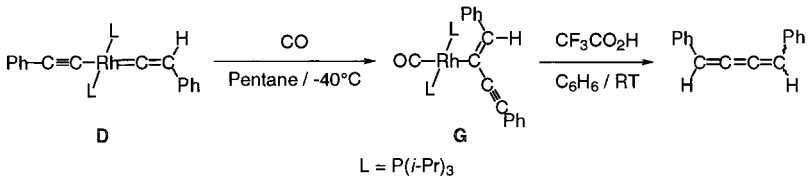


(51)

[Ru] : $[Ru(\eta^5\text{-}C_5H_5)(PPh_3)_2Cl]$, 10 mol%
NH_4PF_6 : 20 mol%

The first step is assumed to be the formation of a vinylidene−ruthenium complex by the reaction of $[Ru(\eta^5\text{-}C_5H_5)Cl(PPh_3)_2]$ and phenylacetylene. Support for this initial step was provided by control experiments in which both $[Ru(\eta^5\text{-}C_5H_5)Cl(PPh_3)_2]$ and the

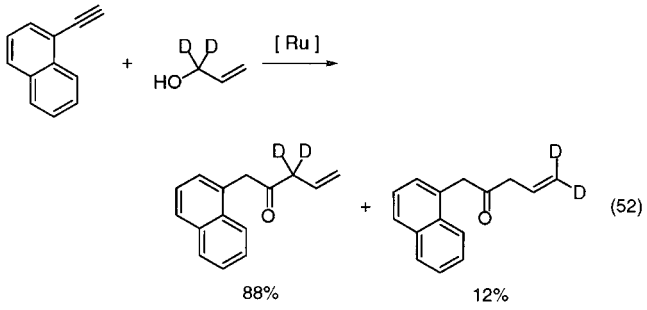
Scheme 21

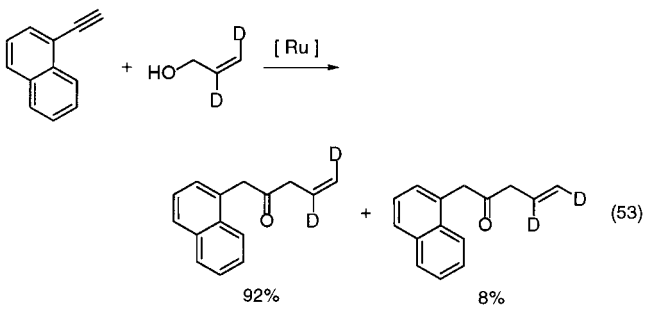


preformed vinylidene complex [(Ru=C=CHPh)(η^5-C_5H_5)(PPh_3)$_2$] were tested as catalysts for the condensation of phenylacetylene with prop-2-en-1-ol. In both cases, the rate of reactions and yields of enones were identical.[80] This strongly suggested the intermediacy of a vinylidene complex in the catalytic cycle. Furthermore, the absence of an induction period in the reaction with [Ru(η^5-C_5H_5)Cl(PPh_3)$_2$] indicated that vinylidene complex formation is not the turnover limiting step.

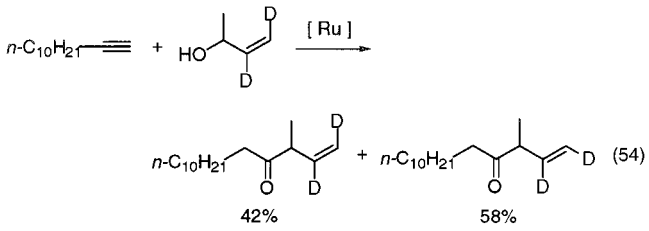
The next step of the reaction must involve the addition of the allylic alcohol to the vinylidene complex. Inhibition of the reaction in the presence of excess triphenylphosphine and the low reactivity of the vinyildene complex [(Ru=C=CHPh)(η^5-C_5H_5)-(PPh_3)$_2$] toward the addition of nucleophiles suggested that this step occurs via loss of triphenylphosphine and precoordination of the olefinic moiety of the allylic alcohol to the ruthenium.[80]

Following the addition of the allylic alcohol to the α-carbon of the vinyidene ligand, rupture of the C−O bond was suggested to occur to generate an intermediate species containing two ruthenium-bound fragments, one of which would be an allyl unit. In this respect, mechanistic insight was revealed by deuterium-labeling experiments.[80] The first indicated that in the case of an unsubstituted allylic alcohol the carbon bearing the hydroxy group also formed preferentially the new C−C bond to the terminal alkyne carbon (eq 52). The second indicated that the alkene geometry was largely retained (eq 53).





These results supported the intervention of a π-allyl species wherein rotation around the ruthenium−allyl axis is slow relative to the rate of reductive elimination. However, a third labeling experiment revealed a dramatic difference with allylic alcohols bearing a substituent on the carbinol carbon since alkene geometry was totally scrambled (eq 54).



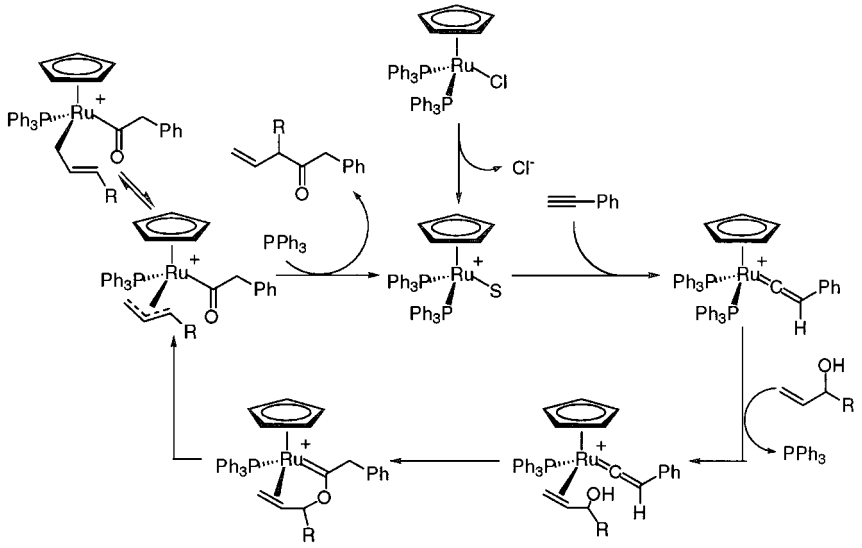
Thus, placing an alkyl group on the π-allyl carbon that participates in the new C−C bond formation sufficiently slowed the reductive elimination in the proposed π-allyl intermediate to allow competition between this latter step and η^3- to η^1-isomerization of the allyl unit. This competition also accounts for the slight isotopic scrambling observed in eq 53. Therefore, the enone may arise from rapid reductive elimination from an allylruthenium intermediate in which the hapticity of the ligand depends on its substitution: predominantly η^3 for an unsubstituted allyl, resulting in predominant retention of olefin geometry, but interconversion between η^3 and η^1 for the methyl-substituted allyl, resulting in scrambled olefin geometry.

The combined results allowed the authors to propose the mechanism outlined in Scheme 22.

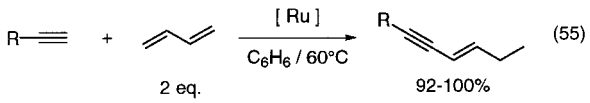
Further developments of this reaction led to the synthesis of a steroid side chain[74b] as well as to a facile furan synthesis.[74c] The use of propargyl alcohols bearing a terminal alkyne led to the development of a tandem process involving successively allenylidene− and vinylidene−ruthenium intermediates, the former resulting from C−H activation of the propargyl alcohol and subsequent dehydration.[75]

In these latter reactions and in most of the other ruthenium-catalyzed processes cited above, which allow cross-coupling of an olefin and an alkyne without C−H bond activation, the reacting organic substrates must contain functionalities such as carbonyl and hydroxyl groups. Transition-metal-catalyzed reactions that do not require the presence of functional groups are highly desirable. Such reactions are rare, but a few notable exceptions exist. Thus, a ruthenium-catalyzed Alder−ene reaction allowed the addition of unactivated alkenes to unactivated alkynes to give nonconjugated dienes.[77b,c] In terms of cross-coupling reactions involving C−H activation, the selective linear codimerization of unactivated terminal acetylenes and unactivated 1,3-dienes catalyzed by ruthenium hydride complexes was reported some time ago.[81] Terminal aliphatic acetylenes readily

Scheme 22



reacted with 1,3-butadiene in the presence of a catalytic amount of $RuH_2(P\textit{n}\text{-}Bu_3)_4$ to give regio- and stereoselectively the (*E*)-isomers of the corresponding linear conjugated enynes in high yields (eq 55). Note that dienes such as cyclohexa-1,3-diene, (*E*)-1-phenylbuta-1,3-diene, methyl (*E*)-penta-2,4-dienoate, and (*E*)-hexa-2,4-dienoate were also reactive but gave different selectivities.

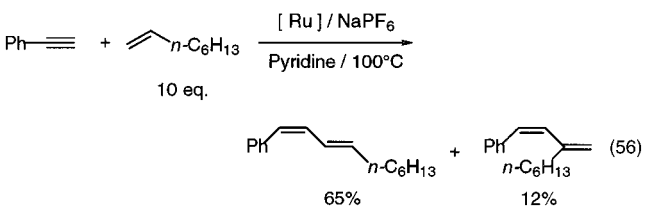


2 eq. 92-100% (55)

[Ru] : $RuH_2(P\textit{n}\text{-}Bu_3)_4$, 1 mol%
R : *n*-Pr, *n*-Bu, *t*-Bu and *n*-hexyl

Although deuterium-labeling experiments carried out with *tert*-butylacetylene-1-*d* and various dienes showed complete deuterium incorporation in the corresponding coupling products, the mechanism has not been elucidated.

More recently, a ruthenium-catalyzed addition of unactivated olefins to unactivated terminal alkynes was reported to afford 1,3-dienes.[82] When a pyridine solution of phenylacetylene and oct-1-ene was heated in the presence of $[Ru(\eta^5\text{-}C_5H_5)Cl(PPh_3)_2]$ and $NaPF_6$, linear and branched conjugated dienes were obtained in 65% and 12% yields, respectively (eq 56). Whereas C−C bond formation occurred regioselectively at the terminal position of the alkyne component, addition of both C−H linkages of the terminal olefin was observed, with terminal addition predominating. Note that disubstituted olefins also added to phenylacetylene, albeit less efficiently.



10 eq. 65% 12% (56)

[Ru] : $[Ru(\eta^5\text{-}C_5H_5)(PPh_3)_2Cl]$, 5 mol%
$NaPF_6$: 6 mol%

The key of this system as compared to the related $[Ru(\eta^5\text{-}C_5H_5)Cl(PPh_3)_2]$-catalyzed condensation of acetylenes and allyl alcohols[74] seems to be the use of pyridine as solvent. Indeed, the reaction failed in all other solvents.

On the basis of a stoichiometric reaction of a ruthenium complex that coupled a ligand olefin to a terminal alkyne and led to η^3-butadienyl and η^2-butadiene complexes,[83] the mechanism outlined in Scheme 23 has been proposed. Support for the intermediacy of the vinylidene complex has been given by the stoichiometric reaction of complex $[Ru(=C=CHPh)(\eta^5\text{-}C_5H_5)(PPh_3)_2]$ with oct-1-ene, which gave both dienes in the same proportion. Steric interactions between the phenyl group and the proximate PPh_3 ligand have been proposed to lead to the loss of this ligand, thus providing a coordination site for oct-1-ene.[82] Subsequent formation of the metallacyclobutane complex via [2 + 2] cycloaddition followed by β-hydride elimination would give the η^3-butadienyl complex.[83] Furthermore, the intermediary of such a complex was suggested by the formation of an allene in the reaction of phenylacetylene with ethylene.[82] Final reductive elimination would then give the conjugated diene and regenerate the active starting cationic complex (Scheme 23). Note that in the production of the metallacyclobutane, formation of the longer metal−carbon bond between ruthenium and the more hindered end of oct-1-ene was proposed to be favored on steric grounds.[82]

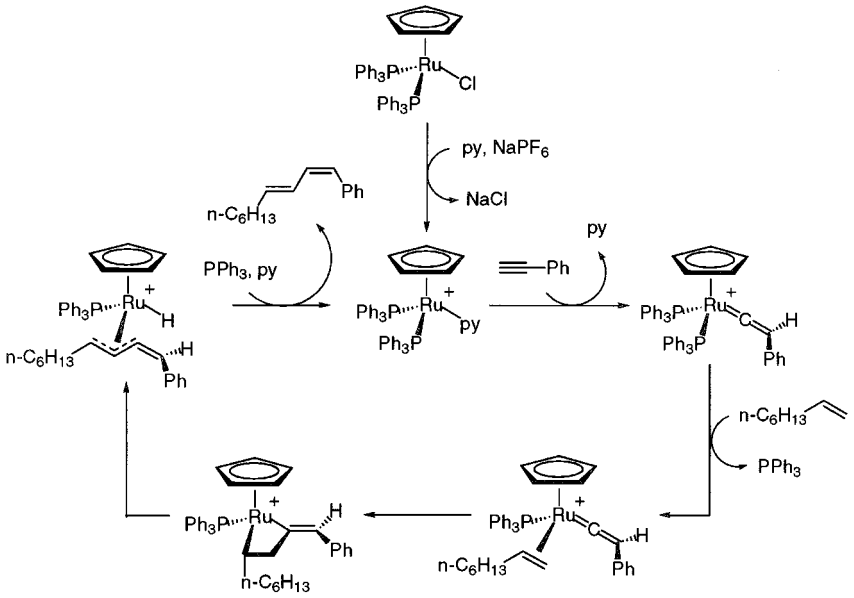
As compared to the condensation of acetylenes and allyl alcohols,[74] the principal mechanistic difference in this system lies in the fact that the C−C bond is formed before reductive elimination of the coupling product.

III. Functionalization of Aromatic or Aliphatic C–H Bonds by Coupling Reactions with Carbon Monoxide

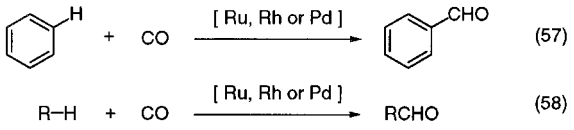
A. Carbonylation of Arenes and Alkanes

In 1983, Eisenberg et al. reported the preparation of the complex $IrH_3(CO)(dppe)$ (dppe = 1,2-bis-

Scheme 23



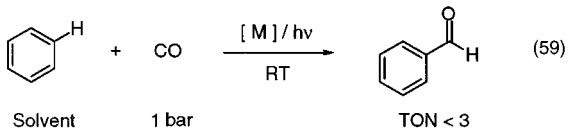
(diphenylphosphino)ethane) and its photochemical behavior.[84] Irradiation of a benzene solution of IrH_3-



(57)

(58)

(CO)(dppe) under CO produced a small amount of benzaldehyde. Despite the fact that the reaction was not catalytic, the authors had stumbled on a system that not only activated arene C−H bonds but also inserted CO to give a functionalized product. These results were followed by studies among which only complexes of Rh(I) and Ir(I) containing the ligand PPh_3 such as $RhCl(CO)(PPh_3)_3$, $RhH(CO)(PPh_3)_3$, and $IrCl(CO)(PPh_3)_3$ promoted catalytic arene carbonylation photochemically (eq 59).[85]

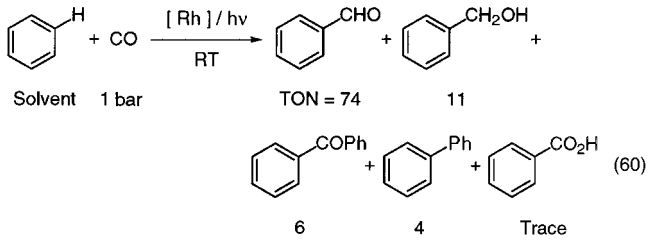


(59)

[M] : $RhCl(CO)(PPh_3)_3$, $RhH(CO)(PPh_3)_3$ and $IrCl(CO)(PPh_3)_2$; 0.7 mM

The low yields of benzaldehyde produced (TON < 3) were attributed to the unfavorable thermodynamics of benzene carbonylation ($\Delta G° = +1.7$ kcal mol^{-1}). Indeed these complexes also catalyzed the reverse benzaldehyde decarbonylation.

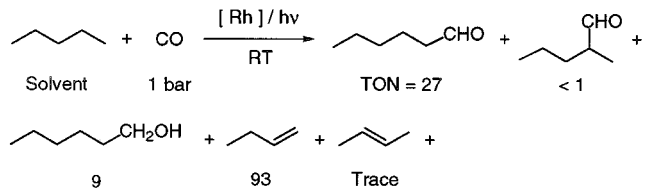
However, use of a closely related rhodium(I) complex bearing a stronger electron-donating ligand such as PMe_3 gave better yields.[86] In addition to the expected benzaldehyde, small amounts of byproducts such as biphenyl, benzyl alcohol, benzophenone, and benzoic acid[87] were also formed (eq 60). These compounds are presumably secondary products formed from benzaldehyde. Only biphenyl seems to be a primary product because it is formed catalytically even under nitrogen.[88]



(60)

[Rh] : $RhCl(CO)(PMe_3)_2$, 0.7 mM , 18h

The most exciting feature of this work is an extension of this photochemically promoted functionalization to alkane substrates including *n*-pentane and cyclohexane.[86b,89,90] Even more remarkable is the high regioselectivity observed with linear alkanes toward primary C−H bonds (eq 61). Indeed, conventional functionalization methods available for alkanes via cationic or radical reactions such as acid-catalyzed carbonylation,[91] halogenation with reagents,[92] and biomimetic hydroxylation catalyzed by metalloporphyrins[93] do not display this selectivity. This higher reactivity of primary C−H bonds is probably due to steric reasons because their bond energy is larger than that of the secondary ones. In this case, products such as alcohols or carboxylic acids[94] arising from secondary reactions are also formed. Butenes and acetaldehyde are secondary products formed via Norrish Type II photoreaction of hexanal.



(61)

[Rh] : $RhCl(CO)(PMe_3)_2$, 0.7 mM , 16.5h

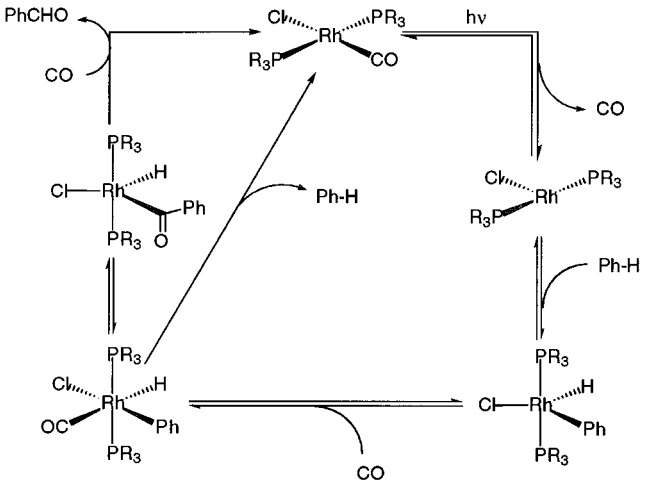
According to Tanaka et al., the restricted yield observed for benzaldehyde is not simply due to

thermodynamic limitations[85] but to two other factors. The first one arises from secondary photoreactions of benzaldehyde; the second one arises from the decomposition of the catalyst.[86b]

Other transition-metal complexes including some ruthenium complexes such as $RuCl(NO)(PPh_3)_2$, $Ru(CO)_3(PPh_3)_2$, and $Ru(CO)_4(PPh_3)$ are all less efficient.[86b,95] Application of the $RhCl(CO)(PR_3)_2/h\nu$ systems to substituted benzenes such as toluene, anisole, or chlorobenzene exclusively gave meta- and para-substituted products in a 2/1 statistical ratio. The absence of ortho-substituted products may arise from relatively severe steric congestion in the ortho-intermediate.[85b,86b]

On the basis that light was necessary to promote catalysis, the generally accepted mechanism was the following: (i) initial photodissociation of CO to generate the highly unsaturated 14-electron complex $RhCl(PR_3)_2$,[85b,86b] whose formation by flash photolysis of $RhCl(CO)(PR_3)_2$ had been demonstrated independently,[96] (ii) reversible oxidative addition of a C−H bond of the substrate, (iii) reversible CO insertion in the resulting Rh−C bond, and (iv) irreversible reductive elimination of the reaction product (Scheme 24).

Scheme 24

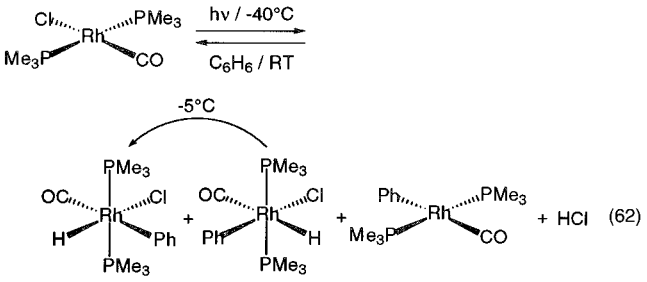


Since no net chemistry was observed in these flash photolysis experiments another photochemical process, which is much less efficient as PPh_3 dissociation, was also proposed.[85b]

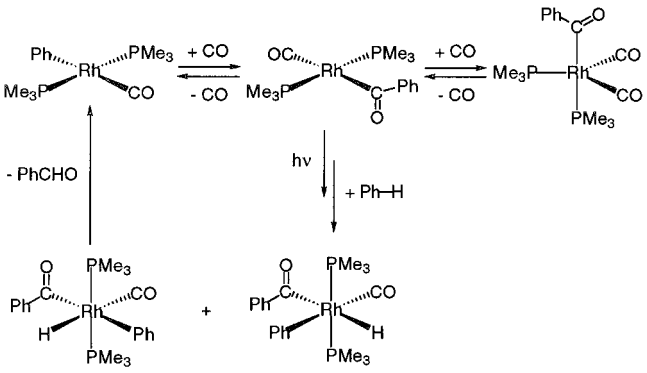
As published in 1994,[97] the above mechanism is at best a simplification because formation of the reaction byproducts cannot easily be rationalized by this pathway. Thus, it was shown that irradiation of *trans*-$RhCl(CO)(PMe_3)_3$ in a mixture of benzene/THF (1/3) at −40 °C in the absence of CO led to three new complexes, $Rh(PMe_3)_2(CO)Cl(Ph)H$ (two stereoisomers) and *trans*-$Rh(CO)(Ph)(PMe_3)_2$, that reform the starting complex on warming the reaction mixture to room temperature (eq 62).[97a]

This result strongly militates in favor of the oxidative addition of a benzene C−H bond without the prior photodissociation of a ligand from the starting complex.

It was also demonstrated that the addition of CO to a THF solution of *trans*-$Rh(CO)(Ph)(PMe_3)_2$ at −33 °C leads to the five-coordinate benzoylrhodium complex $Rh(PMe_3)_2(CO)_2(COPh)$ and that irradiation of a benzene solution of *trans*-$Rh(CO)(Ph)(PMe_3)_2$ under an atmosphere of CO gives benzaldehyde, biphenyl, and benzophenone (Scheme 25).[97a]

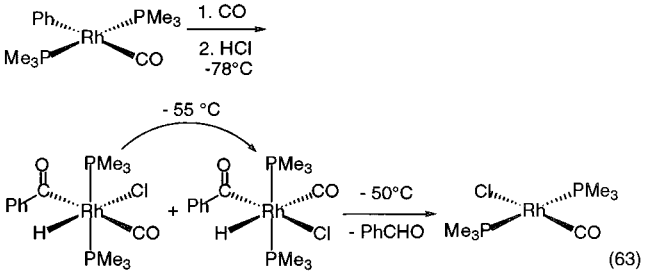


Scheme 25



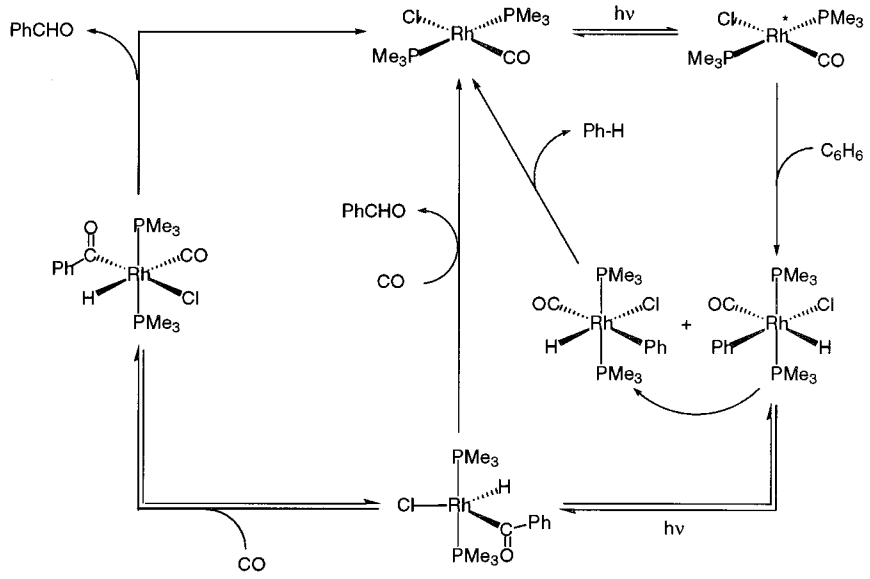
Nevertheless, the amount of benzaldehyde generated by irradiation of *trans*-$Rh(CO)(Ph)(PMe_3)_2$ under CO in benzene is significantly less than that produced by irradiation of $RhCl(CO)(PMe_3)_3$ under the same conditions.[97b] *trans*-$Rh(CO)(Ph)(PMe_3)_2$ is thus not the catalytically active species, but it still can account for the formation of the byproducts.

Moreover, when HCl was added at −78 °C to an acetone-d_8 solution of the five-coordinate benzoylrhodium complex $Rh(PMe_3)_2(CO)_2(COPh)$, formed by addition of CO to *trans*-$Rh(CO)(Ph)(PMe_3)_2$, two other six-coordinate hydridobenzoylrhodium complexes $Rh(PMe_3)_2(CO)Cl(COPh)H$ were observed by ^1H, ^{13}C, and ^{31}P NMR (eq 63).[97b]



All these results, in combination with the dependence of the reaction rate on CO pressure, wavelength, and irradiation intensity,[97b] have enabled the proposition of a mechanism of the full catalytic cycle of the *trans*-$RhCl(CO)(PMe_3)_3$-catalyzed photochemical carbonylation of benzene at short wavelengths. The most unusual aspect of this cycle is that the primary photoprocess does not involve ligand loss and, therefore, that the C−H addition step proceeds predominantly via an unrelated associated process.

Scheme 26

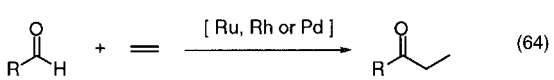


Another striking aspect of the proposed mechanism is that in addition to the primary photoprocess leading to a reactive state of the starting complex, a second photoprocess, favored by short wavelengths, is in operation (Scheme 26).

These studies show that the activation of C−H bonds by $RhCl(CO)(PMe_3)_2$ is not a simple process. Once the reaction is initiated, there are a number of secondary organometallic species produced which themselves are capable of C−H activation. The production of benzaldehyde and byproducts is the result of a complex process composed of numerous elementary steps that are often reversible. Thus, rather than any particular ability of $RhCl(CO)(PMe_3)_2$ to react with C−H bonds, the key aspect of the system seems to be the combination of the following features: (i) the ability of rhodium to shuttle between the 1+ and 3+ oxidation states, (ii) the formation of six- and five-coordinate Rh(III) aryl, alkyl, and/or benzoyl intermediates, and (iii) the ability of a 16-electron square planar precursor to remain unsaturated, even in the presence of CO.

B. Intermolecular Hydroacylation

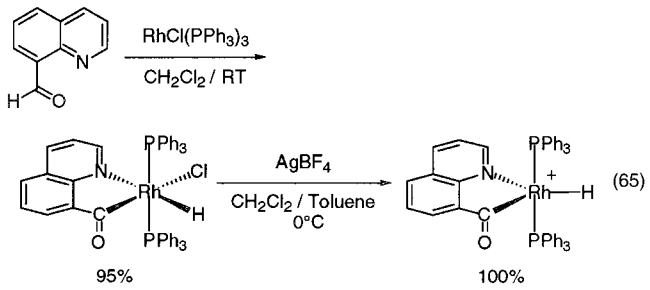
The requirement of a free-radical initiator such as a peroxide or UV light and the frequent formation of polymers as side products[98] outlines the evident synthetic interest of the transition-metal-catalyzed version of this class of reaction.



(64)

1. Chelation-Assisted Reactions

The mechanism proposed for hydroacylation reactions involves oxidative addition of the aldehyde to give an acylrhodium(III) hydride, olefin insertion to give an acylrhodium(III) alkyl, and reductive elimination to form the ketone. This was partially confirmed by the isolation of the first stable acylrhodium(III) hydride intermediate formed during an hydroacylation reaction.[99] The latter was obtained by reacting 8-quinolinecarboxaldehyde with Wilkinson's catalyst (eq 65).

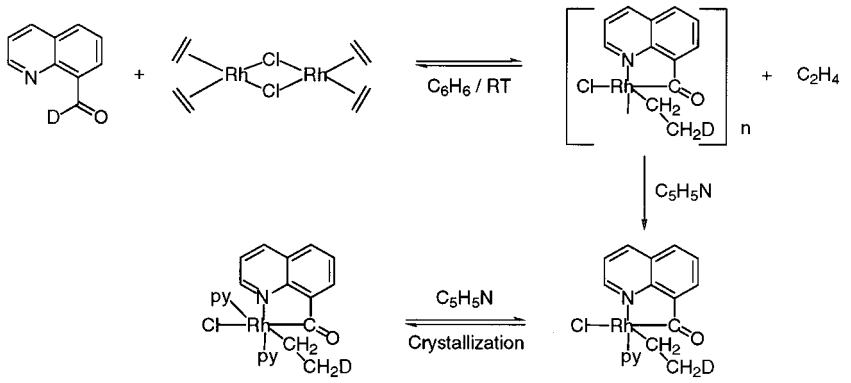


(65)

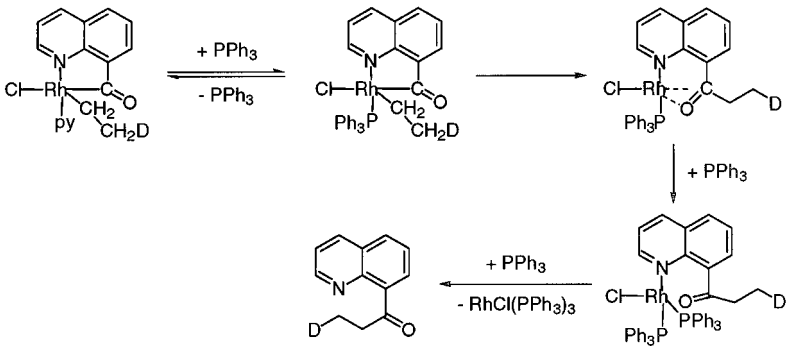
Treatment of a THF solution of the cationic hydride complex with excess oct-1-ene and 8-quinolinecarboxaldehyde at 50 °C gave a 55% yield (based on the complex) of 8-quinolinyl-*n*-octyl ketone. This confirmed that acylrhodium(III) hydrides are intermediates for the hydroacylation of terminal olefins. The isolation of the supposed second intermediate of the reaction was reported a few years later with a related system.[100] The synthesis and structure of stable acylrhodium(III) ethyl complexes derived from 8-quinolinecarboxaldehyde and $[Rh(\eta^2\text{-}C_2H_4)_2Cl]_2$ were described (Scheme 27).

A plausible mechanism for the formation of the acyl alkyl intermediate involves displacing ethylene or splitting the chlorine bridge in $[Rh(\eta^2\text{-}C_2H_4)_2Cl]_2$ followed by oxidative addition to the rhodium center. The remaining ethylene would then insert into the Rh−H bond. In agreement with this mechanism, a deuterated aldehyde reacted with $[Rh(\eta^2\text{-}C_2H_4)_2Cl]_2$ to give the deuterated complex in which all the molecules contain one deuterium in the methyl group. Substitution of the pyridine ligand by an excess of PPh_3 induced reductive elimination of 8-quinolinyl ethyl ketone and the formation of $RhCl(PPh_3)_3$. Using ^1H, ^{13}C, and ^{31}P NMR spectroscopy, the authors were able to follow the course of this ligand-promoted reductive elimination at −40 °C and identify the intermediates shown in Scheme 28.

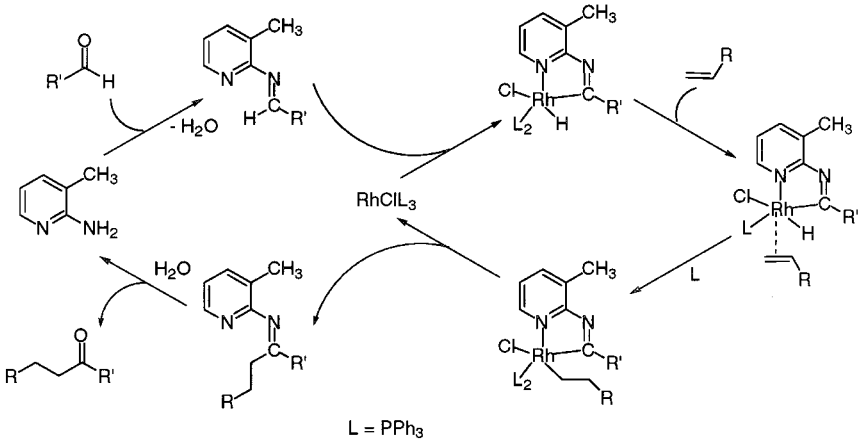
Scheme 27



Scheme 28

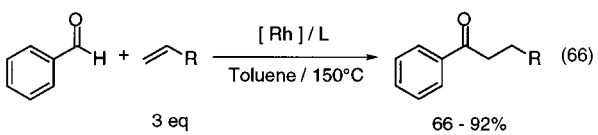


Scheme 29



Formation of an η^2-ketone complex as an intermediate in the reductive elimination of an acylmetal alkyl is noteworthy. Indeed, according to the authors, the appearance of such a complex is probably a specific example of a more general behavior of reductive elimination reactions with groups containing π-bonds or lone pairs. Unless special steric or conformational factors intervene, there should be no reason, whenever reductive elimination generates a potential ligand, the ligand should not remain coordinated to the reduced metal fragment.

Cyclometalation has been used as a directing strategy for the catalytic hydroacylation of aldehydes that are able to be converted to derivatives, i.e., carboxaldimines, in which a 1,5-relationship exists between a coordinating group and the aldehyde C−H bond.[101] Indeed, the carboxaldimines are converted by catalytic reaction with 1-alkenes into carboxyketimines which are then hydrolyzed under acid conditions to produce ketones. This indirect method consisting of a few steps has recently been reexamined, and a one-step synthesis of ketones from aldehydes with the cocatalyst system of a transition-metal complex and 2-amino-3-picoline has been developed (eq 66).[102]



(66)

3 eq 66 - 92%

[Rh] = $RhCl(PPh_3)_3$, 5 mol%

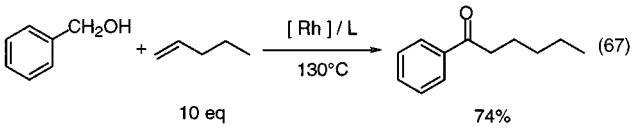
L = 2-amino-3-picoline, 20 mol%

R = H, *n*-alkyl, $PhCH_2$, 2-cyclohexene, C_6F_5

This hydroacylation process is believed to proceed as illustrated in Scheme 29.

This process was further extended to the hydroacylation of 1-alkenes with heteroaromatic aldehydes

by Rh(I) and 2-amino-3-picoline and Cp_2ZrCl_2 as additives.[103] Even more interestingly, it has been extended to a direct ketone synthesis from a primary alcohol and an 1-alkene (eq 67).[104]

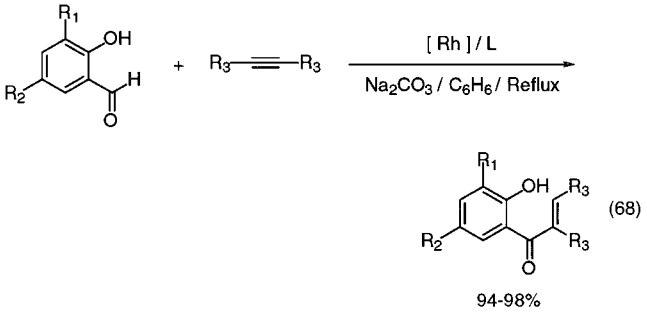


(67)

[Rh] = $RhCl(PPh_3)_3$, 10 mol%
L = 2-amino-3-picoline, 100 mol%

In this last reaction, oxidation of primary alcohols by transition-metal-mediated hydrogen transfer and hydroacylation of the resulting aldehyde occur consecutively with the aid of identical catalyst and olefin.

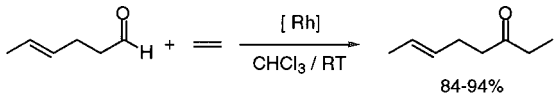
Intermolecular chelation-assisted hydroacylation of internal and terminal alkynes with salicylaldehyde has recently been reported.[105] This was achieved by using a rhodium-based catalyst system (eq 68). In contrast to other catalytic C−H/alkyne coupling reactions,[45,46] terminal alkynes reacted smoothly to give pairs of regioisomers in comparable amounts. The principal difference between this system and those presented above is that the aldehyde substrates already contain their anchor site. Thus, the present reaction may involve initial coordination of the aldehyde to a chlororhodium(I) species complexed by dppf (1,1′-bis(diphenylphosphino)ferrocene) to form a 2-formyl phenolate complex accompanied by liberation of HCl and then oxidative addition of the aldehyde C−H bond to the metal. It should be noted that 4-hydroxybenzaldehyde and 2-methoxybenzaldehyde as well as benzaldehyde itself could not be used, supporting the above consideration that previous coordination of the phenolic oxygen to the metal center plays a significant role in the reaction.



(68)

[Rh] : $[RhCl(cod)]_2$, 0.5 mol%
L = 1,1'-*bis*-(diphenylphosphino)ferrocene, 1 mol%
R_1, R_2 = H, OMe, Cl. R_3 = H, Pr, Ph, *n*-C_6H_{13}, CRR'OH, CHROAc

Finally, the pent-4-enal or hex-4-enal couplings with ethylene achieved in the presence of a rhodium(I) catalyst can also be considered as chelation-assisted intermolecular hydroacylation reactions (eq 69).[106] As it will be seen in the section concerning the intramolecular hydroacylation of pent-4-enal and hex-4-enal derivatives, the double bond may be viewed as an anchor site that brings the aldehyde C−H bond in the proximity of the metal center. Support of this proposal is given by the fact that no reaction is observed with hexanal.



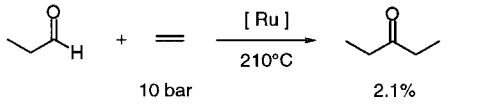
(69)

[Rh] : $Rh(CH_3COCH_2COCH_3)_2(\eta^2\text{-}C_2H_4)_2$, 8 to 13.3 mol%
C_2H_4 : saturated solution

2. Nonchelation-Assisted Reactions

Intermolecular hydroacylation reactions via the free-radical addition of aldehydes to olefins induced by photoirradiation or radical initiators have been well studied, but the efficiency is rather low. Neutral and cationic rhodium complex-catalyzed intramolecular hydroacylations of ω-unsaturated aldehydes have also been studied in detail. However, there are only a few available methods for transition-metal complex-catalyzed intermolecular hydroacylations. Furthermore, each example has severe limitations.

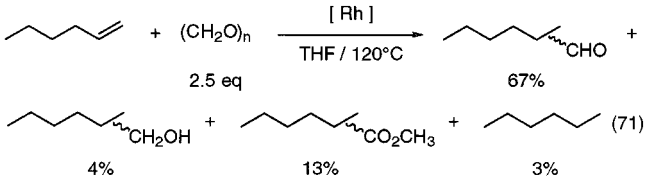
Apart from a brief mention of the synthesis of nonan-2-ones from acetaldehyde and hept-1-ene in the presence of $RhCl(PPh_3)_3$ or $Pt(PPh_3)_4$,[107] the first report of intermolecular hydroacylation, albeit in low yield, was reported in 1982 (eq 70).[108] The major side reactions consisted of aldehyde Cannizzaro- and Tishchenko-type reactions as well as aldolizations.



(70)

[Ru] : $RuCl_2(PPh_3)_3$, 0.05 mol%

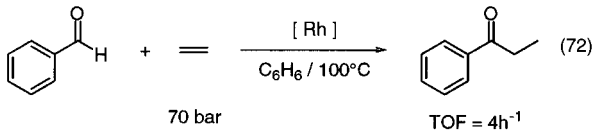
Around the same time an example of transition-metal-catalyzed hydroformylation of olefins with paraformaldehyde was also published.[109] This reaction was not selective and gave, in addition to the coupling product, small quantities of alcohols and carboxylates that are secondary products of the initial aldehyde (eq 71).



(71)

[Rh] : $RhH_2(O_2CHO)[P(i\text{-}Pr)_3]_2$, 0.25 mol%

The first general and clean method for hydroacylation reaction of ethylene by means of a rhodium indenyl complex $[Rh(\eta^5\text{-}C_9H_7)(\eta^2\text{-}C_2H_4)_2]$ was reported in 1988 (eq 72).[110]

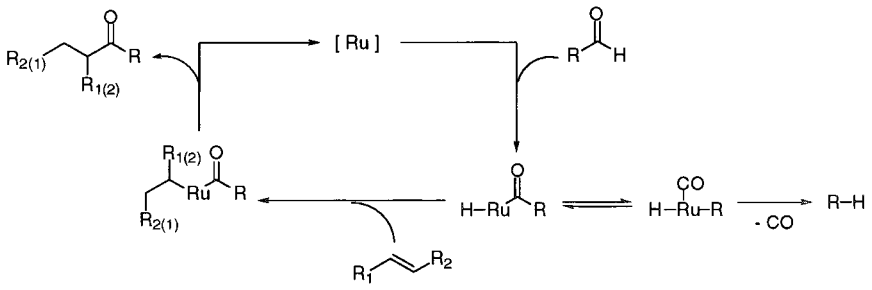


(72)

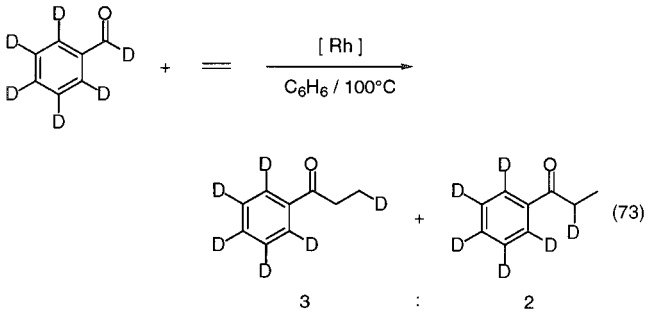
[Rh] : $[Rh(\eta^5\text{-}C_9H_7)(\eta^2\text{-}C_2H_4)_2]$, 3.6 mol%

Other aldehydes or formates also undergo clean reactions with ethylene. When using $C_6H_5{}^{13}CHO$, only $C_6H_5{}^{13}CHO$ and $C_6H_5{}^{13}COC_2H_5$ were detected. This is consistent with the absence of any significant

Scheme 30



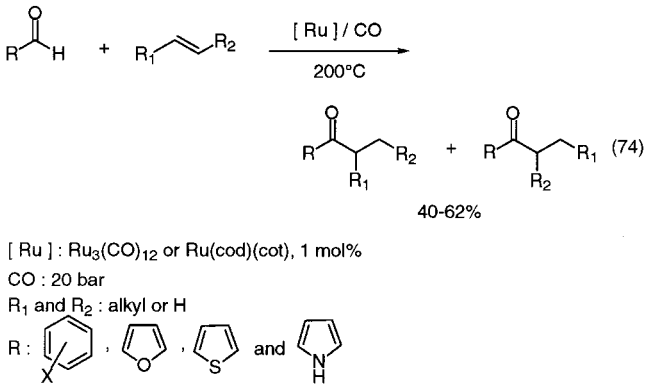
quantities of side products. Deuterium-labeling experiments with C_6D_5CDO showed that all the propiophenone produced contained exactly one deuterium atom in the ethyl group, statistically scrambled between methyl and methylene sites (eq 73).



(73)

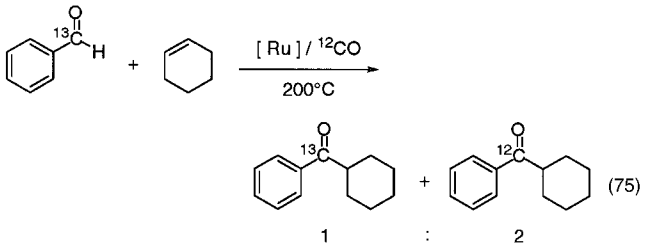
In addition, the recovered aldehyde showed only a small loss of deuterium, and unreacted ethylene did not show deuterium incorporation. Therefore, the insertion of ethylene into the Rh−D bond must take place rapidly and reversibly, and this equilibrium must be established significantly faster than either aldehyde reductive elimination or product formation.

An even more general method involves low-valent ruthenium complexes such as $Ru_3(CO)_{12}$, Ru(cod)(cot), and $Ru(\eta^5\text{-}C_5H_5)_2$. Indeed, the latter show high catalytic activity for the intramolecular hydroacylation of internal or terminal olefins with various aromatic and heteroaromatic aldehydes and CO (eq 74).[111,112]



(74)

As shown by a ^{13}C-labeling experiment, under these conditions (the presence of CO is necessary to prevent the catalyst from decomposition), decarbonylation is a competing reaction[111] in contrast to earlier results.[110] Indeed, the reaction of $C_6H_5{}^{13}CHO$ with cyclohexene demonstrated that scrambling can occur since some ^{12}CO was also incorporated in the carbonyl group of the product (eq 75).[111]



(75)

On the basis of these results, the catalytic cycle in Scheme 30 was proposed.[111]

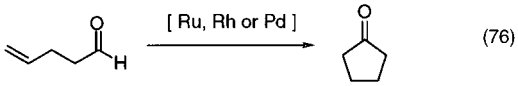
It strongly contrasts with the one proposed by others[110] where no decarbonylation occurs and where the olefin hydrometalation was proposed to occur reversibly. Note that in the latter case no deuterium-labeling experiment had been undertaken.[111] Therefore, although not proposed, reversible hydrometalation cannot be excluded.

These last two studies show that not much is known about the intimate mechanism of intermolecular hydroacylations and that the few that are known depend on the catalytic system that is used.

It will be seen in the following section that much more is known about the intramolecular hydroacylation reaction and that what really happens is much more complicated than the latter reaction path suggests.

C. Intramolecular Hydroacylation

This reaction has been studied more extensively than its intermolecular counterpart. Thus, the first

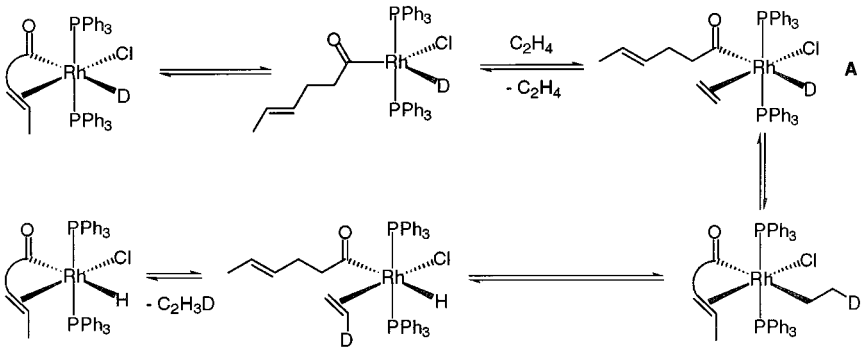


(76)

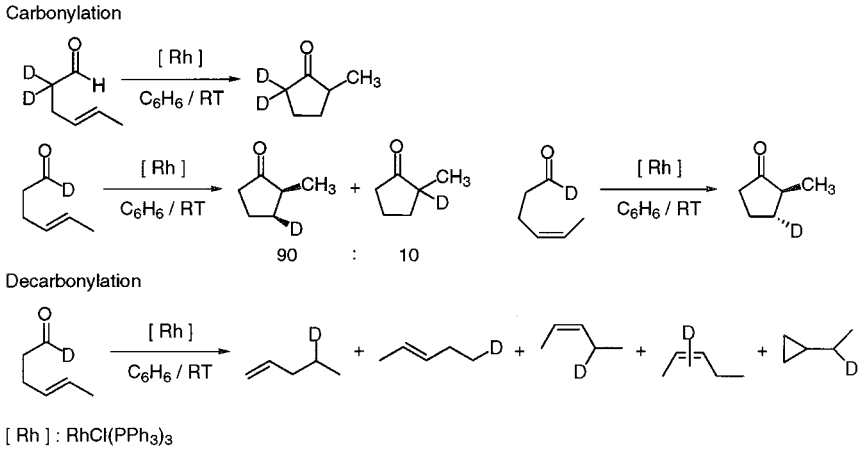
example of intramolecular hydroacylation mediated by a transition-metal complex, although not catalytic, was described in 1972 (eq 77).[113] In addition to the formation of cyclopentanone derivatives, unexpected cylopropane derivatives resulting from decarbonylation were also produced.

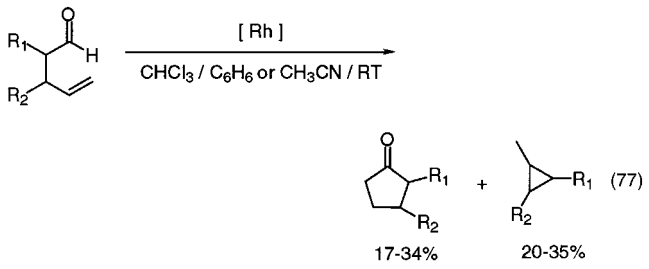
The first catalytic example was reported a few years later.[106a] As the same solvent and catalyst as

Scheme 31

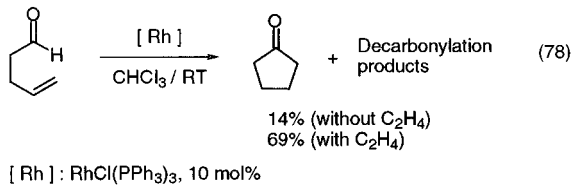


Scheme 32



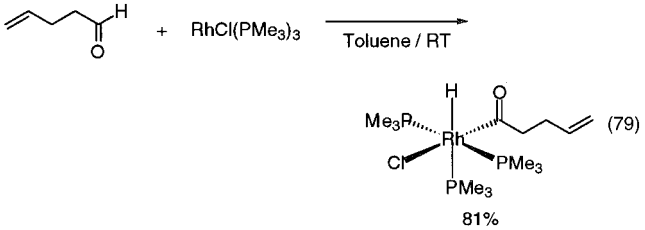


compared to the stoichiometric results[113] were used, the key feature of this system seemed to be the introduction of ethylene into the reaction mixture.[114] Indeed, higher yields of cyclopentanone derivative were obtained when ethylene-saturated chloroform was employed (eq 78).

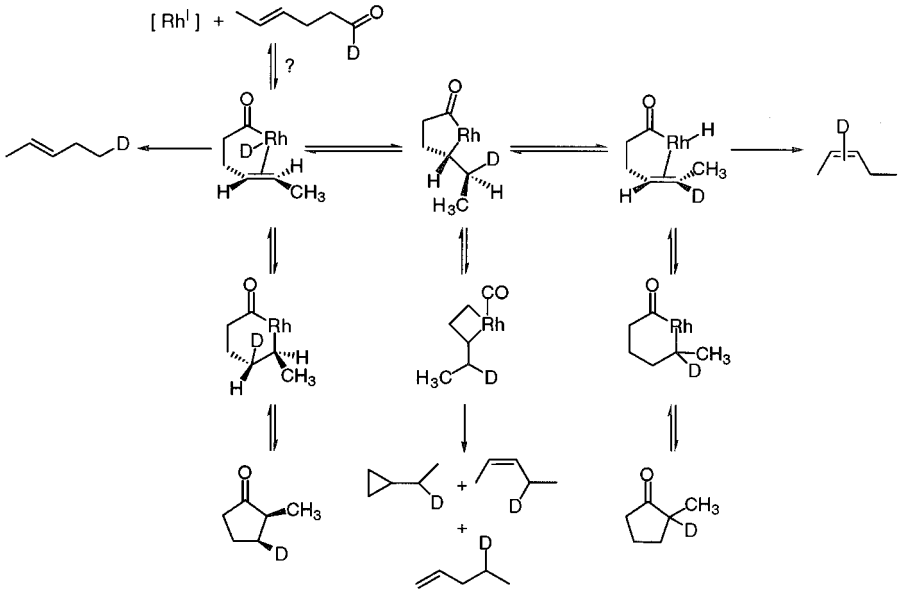


This enhanced efficiency in the presence of ethylene was not really understood. The authors assumed that alkene unsaturation preempted a metal coordination site that was required for the decarbonylation process.[106a] This was partially confirmed by an elegant mechanistic study that they published a few years later.[115] Indeed, when hex-4-enal-1-*d* was reacted with $RhCl(PPh_3)_3$ in the presence of ethylene, a substantial amount of deuterium loss via transfer to ethylene occurred. This accounts for ethylene coordination and therefore supports their early proposal that creation of a coordinatively saturated complex such as **A** obstructs decarbonylation (Scheme 31). Concerning the isomerization mechanism itself and the competing decarbonylation, the following results were obtained from deuterium-labeling experiments (Scheme 32). On this basis, a tentative mechanism has been proposed, which accounts for the stereospecific intramolecular hydrogen transfer from the aldehyde functional group to the C2 and C3 carbons in the cyclopentanone and for the fates of the hex-4-enal-1-*d* label in the competing decarbonylation reactions (if the two processes are to be considered mechanistically related) (Scheme 33).[115]

Formation of an intermediate *cis*-hydridopent-4-enoylrhodium(III) complex has been confirmed by the isolation of such an intermediate by reaction of pent-4-enal and $RhCl(PMe_3)_3$ (eq 79) and by the direct observation of its decomposition resulting in intramolecular hydroacylation and in a migratory elimination process (decarbonylation).[116]



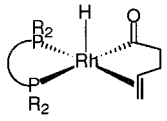
Scheme 33



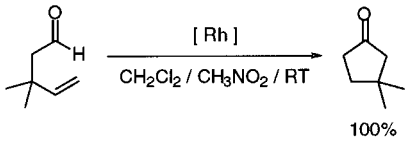
Concerning the intramolecular cyclization observed at 40 °C, it is noteworthy that the PMe_3 ligand which dissociates is the one trans to the hydride whereas the PMe_3 ligand cis to the hydride does not dissociate, probably because of a relatively large *trans*-effect exerted by the hydride ligand. This latter observation gives valuable information concerning the stereochemistry of the complex and ligand orientation when the catalyst is of the type $RhCl(PR_3)_3$.

Interesting results in terms of turnover rate and turnover numbers have been obtained by means of a strategy that relied on increasing the rates of the hydroacylation steps over the rates of the competing steps that led to side products.[117] To achieve this goal cationic rhodium(I) complexes bearing one chelating diphosphine ligand have been used. It was argued that the characteristics which favored this latter system over the neutral complexes derived from Wilkinson's catalyst were the following. First, provided that the solvent molecules are weakly bound in the $[Rh(diphosphine)(solvent)_2]^+$ catalysts, the six-coordinate rhodium(III) species that is formed after the oxidative addition of the acyl−hydrogen bond will have two coordination positions available, thus allowing coordination of the olefin as illustrated in Scheme 34.

Scheme 34



The presence of virtual coordination unsaturation in both the rhodium(I) and rhodium(III) states was expected to accelerate catalysis since slow ligand dissociation will not impede the catalytic steps as shown earlier.[116] Second, because of the positive charge and the presence of *cis*-disposed phosphines, carbonyl complexes of the type $[Rh(diphosphine)(CO)_n]^+$ were expected to be much less stable than the neutral, *trans*-disposed diphosphine complexes that are derived from Wilkinson's-type catalyst. Indeed, for the diphos−(1,2-bis(diphenylphosphino)-ethane) catalyst, between 100 and 800 rapid turnovers (maximum TOF = 2.7×10^{-1} s^{-1}) could be achieved depending on the substrate before decarbonylation, which could significantly reduce the turnover rate (eq 80).

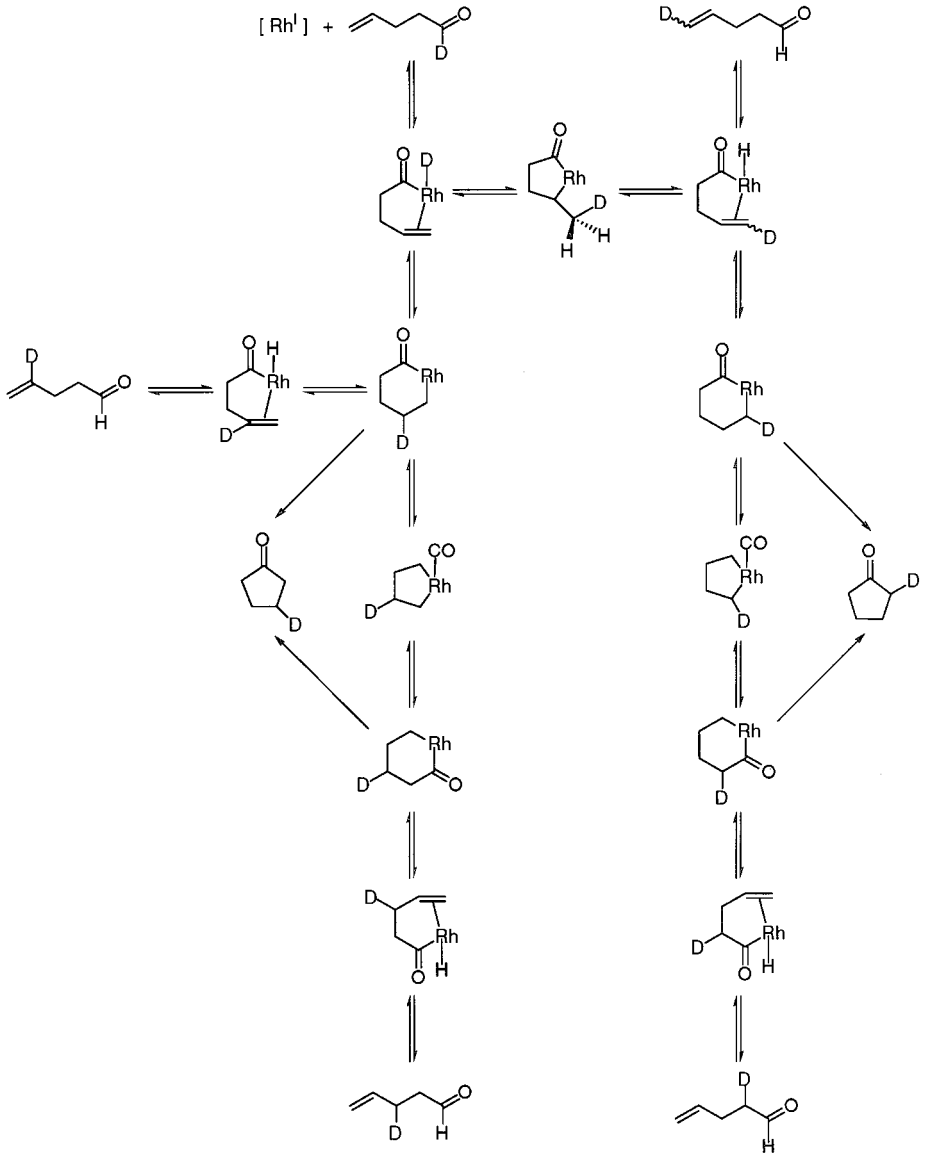


(80)

[Rh] : $[Rh(dppe)]_2(ClO_4)_2$, 1 mol%

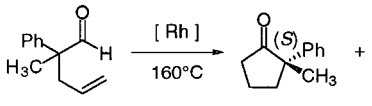
These results were presented with an incisive mechanistic study whose starting point was based on the proposal shown in Scheme 33 for the $RhCl(PPh_3)_3$ complex.[118] Numerous rapidly equilibrating catalyst−substrate adducts were observed. Most of these species are probably catalytically inactive, but they do affect both the turnover rate and the turnover number. The higher the ratio of substrate to catalyst, the slower the turnover rate but the higher the turnover number. This substrate inhibition of rate appears to be related to the catalyst being tied up as catalytically unproductive adducts. The extension of turnover number seems to be related to the suppression of decarbonylation by substrate interaction. Unfortunately no catalytic intermediates were identified, and a new mechanistic proposal was inferred from deuterium-labeling studies which showed that the cyclopentanone products contained deuterium both in the α- and β-position and remarkably that deuterium appears and disappears at every carbon of 4-pentenal during the course of catalysis. The implications of this deuterium scrambling, which is believed to be directly related to the hydroacylation mechanism, are summarized in Scheme 35.

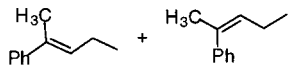
Scheme 35



Except the final reductive elimination step from a metallacyclohexanone to produce cyclopentanone, which is the turnover limiting step, all the others—C−H activation, hydride transfer to the double bond, carbonyl deinsertion—are fast and reversible. This extraordinary complexity illustrates what we pointed out in the previous section, that is, intuitive mechanisms based on well-established steps are often very far from what really happens. Indeed, aside from the catalytic cycle itself, which may be extraordinarily fast, many unproductive equilibria may be operating. Thus, it is necessary for the initial step to occur many times before the material passes from unproductive intermediates to a productive event.

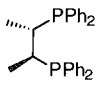
Further developments of intramolecular hydroacylation essentially focused on the asymmetric cyclization of substituted pent-4-enals by rhodium complexes bearing a chiral diphosphine ligand.[119,120] In the first reported example, [Rh(*S*,*S*-chiraphos)$_2$]-Cl was used for the kinetic resolution of neat racemic mixtures of chiral 2,2-disubstituted-pent-4-enals. Fairly good enantioselectivities were observed despite the elevated temperature employed (eq 81).[119a]



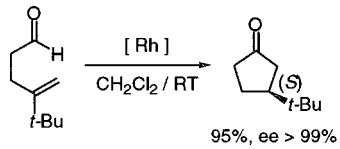


35% (81)

[Rh] : [Rh(*S*,*S*-chiraphos)$_2$]Cl, 0.17 mol%

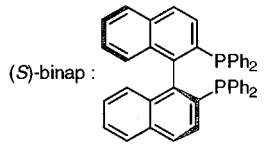
S,*S*-chiraphos: 

Later, good enantioselectivities were reported with [Rh((+)-DIPMC)]Cl ((+)-DIPMC: (1*S*,2*S*)-(+)-1,2-bis-(diphenylphosphinomethyl)cyclohexane) formed in situ for the conversion of prochiral 4-substituted-4-pentenals to chiral cyclopentanones.[119c] Recent studies gave even better results. Indeed, [Rh(*S*-binap)]-(ClO_4) and [Rh(*S*,*S*-Me-duphos)](PF_6) complexes rapidly and efficiently convert 4-substituted-pent-4-enals, bearing tertiary substituents or ester groups

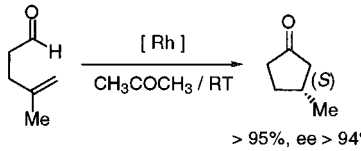


(82)

[Rh] : [Rh(*S*-binap)(CH_2Cl_2)](ClO_4), 4 mol%

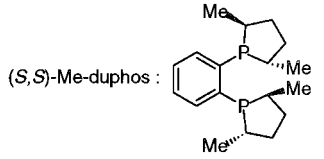


and primary or secondary substituents, respectively, to the corresponding cyclopentanones with 87–99% ee (eqs 82 and 83).[119d,f]



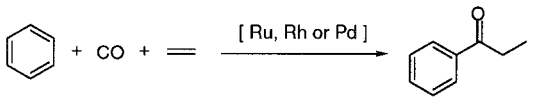
(83)

[Rh] : [Rh(*S,S*-Me-duphos)(CH_3COCH_3)$_2$](PF_6), 5 mol%



D. Aryl Acylation by Carbon Monoxide and Olefins

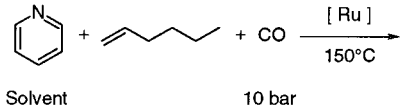
The most important method for the preparation of aryl ketones is the well-known Friedel–Crafts acylation reaction.[121] However, it does not allow the direct coupling of an aromatic compound, carbon monoxide, and an olefin as the transition-metal-catalyzed processes presented here do.



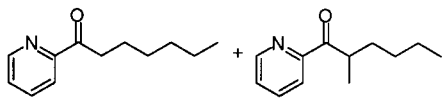
(84)

1. Chelation-Assisted Reactions

The first example of a direct method for acylation of heterocycles with CO and olefins was described in 1992 by using $Ru_3(CO)_{12}$ as catalyst.[122] Although the reaction exhibited a high regioselectivity and high turnover frequencies (TOF up to 300 h^{-1}), pyridine or pyridine derivatives were used as solvent and therefore the yields based on pyridine were not high (eq 85).



Solvent 10 bar

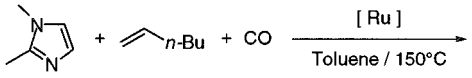


(85)

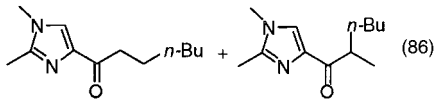
69%

[Ru] = $Ru_3(CO)_{12}$, 1.3 mol%

Further developments of direct acylation essentially concerned the reaction of benzene rings and aza-heterocycles and were described in the continuation of the discovery of efficient alkylations of aromatics by Ru-catalyzed coupling with olefins.[123] Thus, the first example of heteroaromatic C–H/CO/olefin coupling that did not require a large excess of one of the substrates concerned the regioselective acylation of 1,2-disubstituted imidazoles. Mixtures of linear and branched isomers were obtained (eq 86).[123a]



4 eq. 20 bar



94 : 6

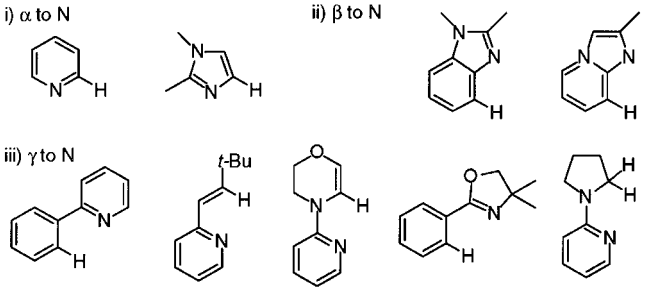
68%

(86)

[Ru] : $Ru_3(CO)_{12}$, 4 mol%

On the basis of reports to date, the catalytic carbonylation at a C–H bond can be classified into three types, depending on the position where the C–H bond is carbonylated: (i) α to N,[123a,b] (ii) β to N,[123c] and (iii) γ to N (Scheme 36).[123d–g] In all cases,

Scheme 36

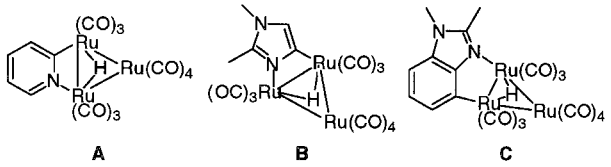


the coordination of the nitrogen to the Ru or Rh complex is essential for the site-selective cleavage of the C–H bond. Carbonylation β to N is particularly remarkable because the β-position is electronically a difficult system compared to the conjugated α- and γ-positions.[123c] Note that the products obtained upon carbonylation of these substrates are difficult to prepare using the conventional methods reported so far. Indeed, the Friedel–Crafts acylation cannot be applied because of the deactivation that occurs upon complexation of the substrate with the Lewis acid.[124]

The mechanism is believed to occur as follows. Coordination of the nitrogen to the ruthenium complex brings the metal in close proximity to a C–H bond which can then be cleaved by oxidative addition. This cleavage gives a hydride–ruthenium complex. Insertion of ethylene into the Ru–H bond gives an ethyl complex that undergoes CO insertion. Reductive elimination gives then the final product. The issue of whether the insertion of CO occurs into the alkyl–ruthenium or aryl–ruthenium bond is not known.

The structure of the catalytically active species is poorly understood. To date, characterization or isolation of the active species have been unsuccessful. As catalysts are always $Ru_3(CO)_{12}$ and/or $Rh_4(CO)_{12}$, the molecularity of the true catalytic species, intact clusters (trinuclear ruthenium species), or fragment catalytic species (dinuclear or mononuclear ruthenium species) is a recurrent question. On the basis of stoichiometric studies conducted with related substrates and complexes, its proposed nature depends on where the C−H bond is carbonylated. $Ru_3(CO)_{12}$ is reported to selectively activate the ortho positions in pyridine to form the trinuclear orthometalated complex **A**.[125] Similarly, stoichiometric reactions of the related complex $Os_3(CO)_{10}(CH_3CN)_2$ with imidazoles[126] and benzimidazoles[126a] gave (μ-H) triosmium carbonyl clusters with the C−H bond cleaved α and β to N, respectively. Thus, when carbonylation occurs α and β to N, (μ-H) trinuclear intermediates such as **A**, **B**, or **C** are generally proposed (Scheme 37).[122,123a−c] Note that in the particular case of pyridine the occurrence of such an intermediate has been partially confirmed. Indeed, the pyridyl-hydride compound **A** has been found to be catalytically active, but control experiments in the absence of olefin establish that it decomposes to $Ru_3(CO)_{12}$ and pyridine under the conditions of the acylation reaction.[122]

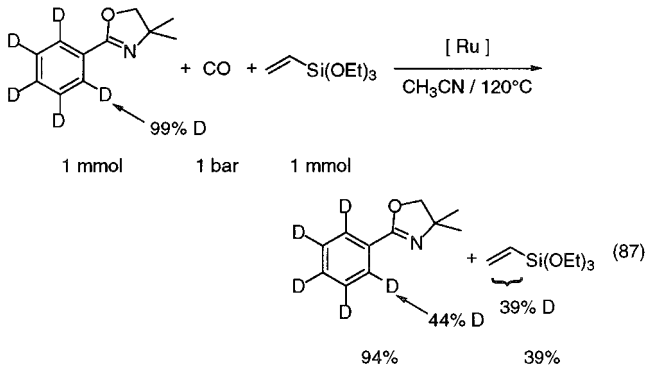
Scheme 37



A **B** **C**

When carbonylation occurs γ to N, mononuclear intermediates are generally expected to play a key role for the formation of the propionylated product. While no report of a stoichiometric reaction of 2-phenylpyridine with $Ru_3(CO)_{12}$ has yet appeared, the related cyclometalated mononuclear ruthenium complexes were isolated as a result of reactions of a benzaldehyde imine[127] or a benzo[*h*]quinoline[128] with $Ru_3(CO)_{12}$. Similarly, although the stoichiometric reaction of $Ru_3(CO)_{12}$ with pyridylolefins is not known, it was reported that $Os_3(CO)_{10}(CH_3CN)_2$ reacts with 2-pyridylethylene to give a mononuclear five-membered metallacyclic complex.[129] Moreover, in a recent study, Laine's kinetic criterion[130] was followed to determine the molecularity of the true catalytic species in the carbonylation of 2-phenyloxazoline.[123e] Using this criterion the turnover frequency decreased with increasing catalyst concentration. This tends to confirm that fragmented catalytic species ($Ru(CO)_n$ where $n = 4$ or 5) are responsible for the catalytic carbonylation of C−H bonds γ to N.

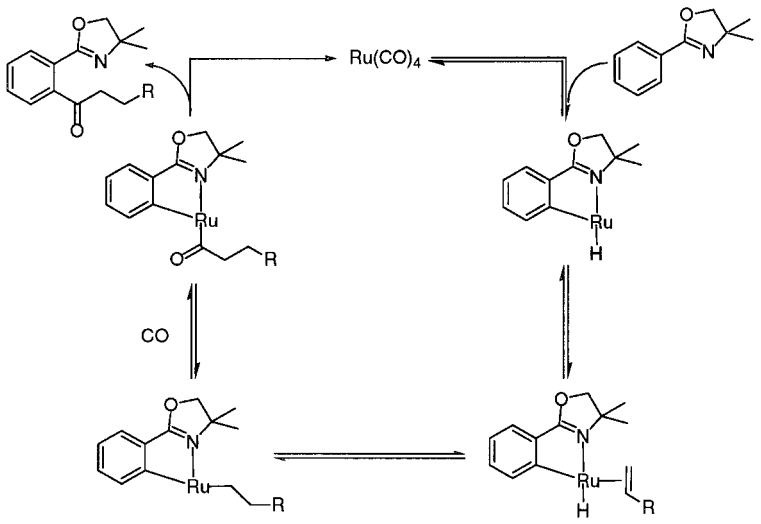
Concerning the rest of the reaction mechanism, interesting findings were obtained from a deuterium-labeling experiment.[123e] The reaction of 2-phenyloxazoline-d_5 with CO and triethoxyvinylsilane in acetonitrile (which is the solvent of choice for the carbonylation of 2-phenyloxazoline) at 120 °C gave no carbonylation product. Ninety four percent of 2-phenyloxazoline-d_5 and 39% of triethoxyvinylsilane were recovered. They showed, respectively, 55% incorporation of proton label at the ortho positions and 39% deuterium label incorporation at all three vinyl positions (eq 87). Thus, H/D exchange occurred between the C−H bonds at the ortho position in the benzene ring and the vinylic protons in the olefin. Because a complete scramble was observed at these positions, the cleavage of a C−H bond is reversible and olefin insertion/β-hydride elimination occurs faster than conversion to products. Therefore, the cleavage of a C−H bond is not the rate-determining step in this reaction and a rapid equilibrium between the substrate and the ethyl complex exists. Note that the reversibility of pyridine orthometalation under the conditions of the acylation reaction has also been established by deuterium-labeling experiments.[122]



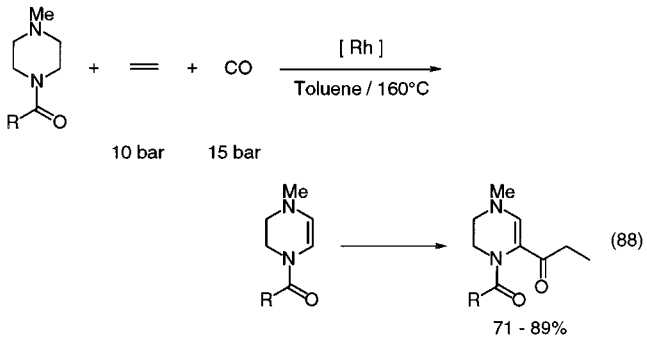
The issue of whether CO insertion occurs into an alky−Ru bond or a phenyl−Ru bond is not presently known. However, it has been recently reported on the decarbonylative cleavage of C−C bonds in alkyl phenyl ketones, which is the reverse reaction of the present carbonylation.[131] An investigation of the reaction pathway revealed that the reverse reaction is likely to proceed by way of an ethylacyl complex as an intermediate. Thus, by microscopic reversibility, the intermediacy of such a complex is currently favored in the Ru carbonylation. Therefore, the mechanism is believed to occur as shown in Scheme 38.

In terms of synthetic chemistry, a directing group should be introduced and removed or functionalized readily. In this context, except oxazoline rings which are readily available from carboxylic acids and readily converted to carboxylic acids, esters, and aldehydes, the directing groups that we have listed, in particular the pyridyl group, are not suitable for further useful transformations. A directing group that is more practical regarding its ability to promote the cleavage of a C−H bond and for ease of removal is an *N*-acyl group. It was recently found to promote the carbonylation of piperazines with $Rh_4(CO)_{12}$ as catalyst.[132] This reaction is interesting from two points of view. First, it is the only example of carbonylation at a C−H bond that is directed by a functional group other than a C=N moiety. Second, the reaction involves two successive sequences: (i) dehydrogena-

Scheme 38



tion of the piperazine ring and (ii) carbonylation at a C−H bond in the resulting olefin. Thus, the reaction proceeds via two cleavages of a C−H bond, first at an activated sp^3 C−H bond[123g] and then at a sp^2 C−H bond (eq 88).[133]

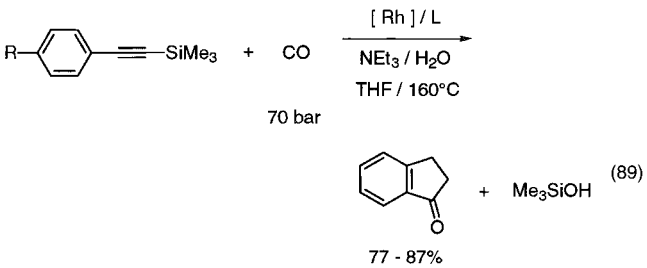


[Rh] : $Rh_4(CO)_{12}$, 4 mol%

R : Me, Ph, 4-(Me_2N)-C_6H_4, 2-pyridyl, CF_3

Another directing group that fulfills all the requirements of practical organic synthesis is an imino group, which is readily prepared from an aldehyde functionality and readily deprotected to the original aldehyde. However, the reaction of benzaldehyde imines with CO and ethylene in the presence of $Ru_3(CO)_{12}$ did not stop at the carbonylation stage and resulted in cyclocarbonylation. Thus, indenone derivatives were formed in situ via intramolecular aldol-type cyclization of the expected propionylation products.[134] Acetylenes can also be used as directing groups for cyclocarbonylation reactions. Indeed, the rhodium-catalyzed reaction of 1-aryl-2-(trimethylsilyl)acetylene with CO gives 2,3-dihydro-1-*H*-indenones under water gas shift conditions (eq 89).[135] The reaction is initiated by π-complexation of the acetylene to the rhodium which induces oxidative addition of the ortho aromatic C−H bond (Scheme 39).

As demonstrated with these last cases, chelation-assisted carbonylations are limited in terms of practical organic synthesis by the nature of the anchor ligand. The realization of this reaction without the need of a coordinating group should be ideal.



[Rh] : $[Rh(cod)Cl]_2$, 1 mol%

L : PPh_3, 40 mol%

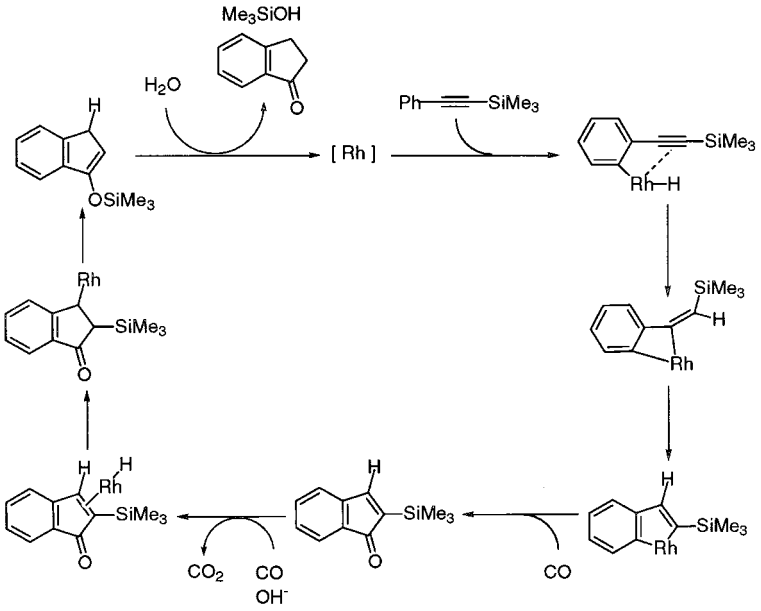
R : Me, MeO, Cl, EtO_2C, Ac and NC

2. Nonchelation-Assisted Reactions

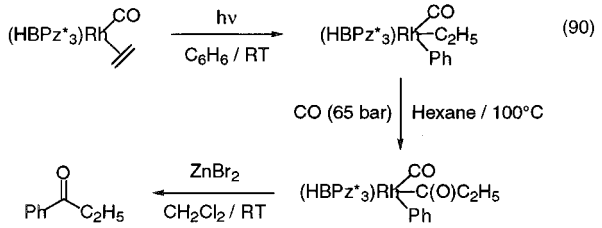
Catalytic examples of nonchelation-assisted carbonylation are very rare, and reactions are unselective. The first example was described with $Rh_4(CO)_{12}$ as the catalyst. Indeed, a small amount of propiophenone, along with styrene and pentan-3-one as the major products, was obtained in the reaction of benzene with ethylene under a CO pressure (see section II.A).[21] Drastic conditions were used (220 °C, 30 and 25 bar of ethylene and CO, respectively), and not much is known about the reaction mechanism. More recently ethylene, benzene, and CO have been combined under mild conditions with photochemical assistance to selectively produce propiophenone in three successive steps. Although stoichiometric, these reactions are of interest because the phenylalkyl− and phenylacyl−rhodium intermediates have been isolated and characterized (eq 90).[136] Isolation of $(HBPz^*_3)Rh(CO)(COC_2H_5)(Ph)$ ($HBPz^*_3$ = 3,5-dimethylpyrazol-1-yl) tends to confirm that CO insertion preferentially occurs in rhodium−alkyl bonds rather than in rhodium−phenyl bonds as proposed for the carbonylation of 2-phenyloxazoline derivatives.

Finally, as mentioned in the section concerning the coupling of alkynes with C−H bonds (section II.C), the reaction of benzene with diphenylacetylene catalyzed by $Rh_4(CO)_{12}$ under CO (25 bar) gives 2,3-diphenylindenone as a byproduct (see eq 34).[48a] This is the only example of nonchelation-assisted cyclocarbonylation. Note that the reaction has been ex-

Scheme 39



[Rh] : [Rh(cod)Cl]$_2$, 1 mol%



tended to other alkynes such as 1-phenylpropyne and bis(*p*-tolyl)acetylene. When toluene, anisole, and fluorobenzene are used instead of benzene, four positional isomers are detected. This outlines once again the absence of selectivity usually observed in the absence of a coordinating group that directs the reaction. On the basis of stoichiometric studies conducted with titanium compounds, the occurrence of phenylene−rhodium and benzorhodacyclopentadiene intermediates were suggested for the formation of the indenone derivatives.

IV. Conclusion

This review clearly shows that many C−H activation and addition reactions on unsaturated substrates have been performed and analyzed. Outstanding results have been obtained in the field of olefin arylation.[18,21] However, at this stage, these processes require reaction conditions that are environmentally not friendly. Hydroarylation of alkynes was achieved as well[48,50] but with less efficiency and under rather important carbon monoxide pressure or in trifluoroacetic acid medium. These reactions involving nonchelation-assisted couplings have been the most extensively studied for a long while. Chelation-assisted reactions have only attracted some attention more recently, with most of the references related to this work being published over the last 10 years. Reactions such as olefin arylation[7] or hydroarylation[26] and aryl acylation[123] have been performed with substrates bearing directing groups. From analyzing the results of both kind of processes, it obviously appears that the reactions involving a directing group lead more selectively to products. One could well anticipate that soon these reactions should be those leading to the more interesting results as far as selectivity is concerned. With respect to the nonchelation-assisted C−H activation and addition reactions, it appears that employing oversimplified catalyst precursors cannot be an interesting alternative for an increase in selectivity for the C−C formation, as these catalysts will not be able to selectively distinguish a given C−H bond among others. Solutions to this latter point will no doubt be the subject of intense research efforts in the future.

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