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GROUP VIII METAL-CATALYZED C–C BOND-FORMING SEQUENCES

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Introduction

This review is devoted to work on catalysis of C–C bond formation carried out since 1975, when I began my research activity at the University of Parma. This was after many years spent in basic research in industry and in teaching activities.

Working in industry I had become aware of the problems raised by linking research to economic objectives. This demands that a scientist be ready to leave his research topics if the latter are not considered to be conducive to the economic objective chosen. Solving scientific problems, however, always demands a methodological approach based solely on the logic of research, and this process may come into conflict with the need to attain economic objectives. There is no question, however, that a background in fundamental research enables industrial scientists to solve their problems in the best way even in applied research. To overcome this contrast one has to choose a broad research topic which is of permanent interest to industry and cannot be prematurely terminated.

Training people in Universities for industrial posts should also be based on such broad topics. One of these is certainly catalysis of organic syntheses. If one recalls that in a few decades chemistry has succeeded in developing catalytic processes which in some cases compete in efficiency with those involving enzymes, and that the instruments to gain insight into mechanism have improved greatly, an exponential growth of industrial catalytic processes can be expected.

Thus when I came to the University of Parma I felt that catalysis of organic reactions should be the central theme for the group working in industrial organic chemistry. This paper is intended to give an overview of the way research lines were conceived and developed over the years as a result of conceptual and experimental interplay. It will be seen that this research has been rewarding both from the scientific and the industrial point of view. Detailed examination of single reactions is beyond the scope of this review.

The starting point, was based on my previous experience [1], which made me aware of the importance of carrying out organic syntheses by stepwise additions of molecules and groups under the control of a metal center. High yields and catalytic efficiency under mild conditions on the one hand, and precise control of chemo-, regio-, stereo- and enantio-selectivity on the other, could be achieved. The know-

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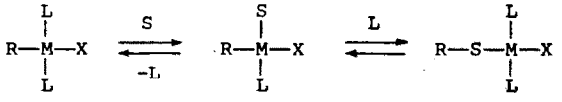
ledge acquired from this activity could have many types of industrial application. I felt that the best approach would be to study factors involved in promotion of C–C bond formation in Group VIII metal-catalyzed, homogeneous phase reactions (assistance effects). This knowledge would form the basis for achieving multistep reactions and the synthesis of complex molecules.

Our work has since developed along the lines: "Assisted C–C bond formation" and "Multiple additions in sequence".

Assisted C–C bond formation

New processes involving insertion (eq. 1, R = organic group, L = ligand, X = anion, S = substrate) [2] or nucleophilic attack (eq. 2) [3] were found, and investi-



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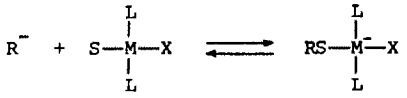

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gated with a view to increasing the yield and catalytic efficiency and to controlling chemo-, regio-, stereo- and enantio-selectivity. In particular, in addition to ligand effects we studied the behaviour of chelating or metallacycle-forming substrates and of various terminating agents (i.e. agents favoring metal elimination after formation of the new bond). The scope of these factors encompasses coordination, formation and stabilization of the initial R–M bond, insertion or nucleophilic attack, stabilization of the new group formed and metal elimination, and it is not easy to dissect the separate effects involved in each step. In most cases our knowledge in these areas is still in its infancy. Any progress in understanding catalytic steps, however, will always have important consequences for synthesis.

Carboxylate anion-promoted insertion

A case in point is offered by the carboxylate group as anionic ligand in Ni- or Pd-catalyzed insertions involving unsaturated substrates. As a bidentate ligand the carboxylate group can occupy the coordination site left free by a migrating group, giving rise to monomeric or dimeric complexes, but it can also help olefin coordination as a consequence of its high electron-withdrawing power, and finally it can pick up a proton from the metal-coordinated group in the reductive elimination step.

We described [4–6] new reactions of this kind (eq. 3–6 show some examples) which were promoted by nickel(0), palladium(0) or rhodium(I) complexes at mild temperature (R = organic group):

$$RCHO + CH_2{=}CHCH_2OAc \xrightarrow[2.\ H_3O^+]{1.\ Ni^0} RCHOHCH_2CH{=}CH_2 + Ni(OH)OAc \quad (3)$$

$$RR'C{=}NNHPh + CH_2{=}CHCH_2OAc \xrightarrow[-AcOH]{Ni\ cat} CH_2{=}CHCH_2CRR'{-}N{=}N{-}Ph \quad (4)$$

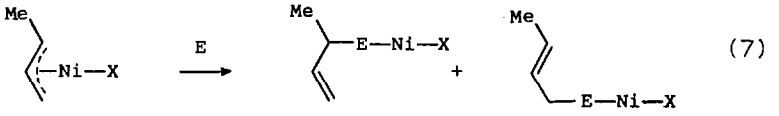
$$RC{\equiv}CH + CH_2{=}CHCH_2OAc \xrightarrow[-AcOH]{Ni^0 \text{ or } Pd^0 \text{ cat}} RC{\equiv}CCH_2CH{=}CH_2 \quad (5)$$

$$CH_2{=}CHCH_2COOCH_2CH{=}CH_2 \xrightarrow{Ni^0 \text{ or } Rh^I \text{ cat}}$$

$$CH_2{=}CHCH_2CH_2CH{=}CHCOOH + CH_2{=}CHCH_2CH{=}CHCH_2COOH \quad (6)$$

Study of each reaction in its turn revealed interesting selectivity aspects and offered new synthetic potentialities.

For example, reaction 3 is the transition metal analogue of a Grignard reaction, with the differences that it can be performed in protic solvents and is selective for aromatic aldehydes at room temperature (benzaldehyde gives a 70% yield in methanol), whereas ketones require higher temperature (ca. 70°C). Selectivity in its various aspects is a constant feature of transition metal-promoted reactions. This is a case of chemoselectivity but regioselectivity also can be obtained. With allylic esters having terminal alkyl groups, the preferential reaction at the substituted end in the presence of a nickel(0) catalyst, other factors being equal, is a function of substrate electronegativity. Mostly linear products (eq. 7) are formed with olefins, and almost entirely branched products with aldehydes, ketones, phenylhydrazones. Alkynes occupy an intermediate position (E = electrophile) [7].



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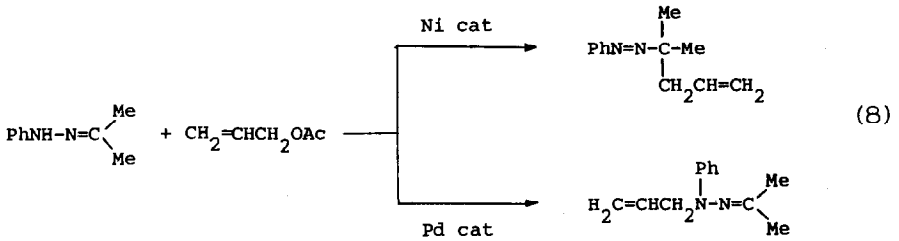
The metal also plays an important role in promoting regioselective attack. For example an allyl group attacks phenylhydrazones on carbon with Ni and on nitrogen with Pd (eq. 8) [8].



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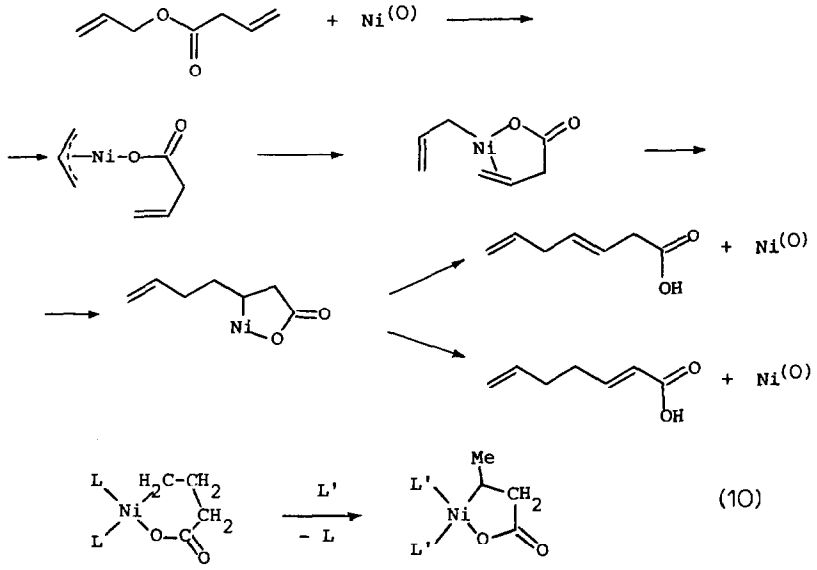
The use of trialkyl phosphites, particularly triisopropyl phosphite, as Ni ligands in reaction 8 to improve catalytic efficiency is worthy of mention, since it is one of the many cases in which the catalyst is inactivated by accumulation of the reaction product. Addition of phosphites in large excess (up to 40 mol) helps to protect the catalyst, and increases the number of catalytic cycles (from 10 to 50 in tetrahydrofuran (THF)).

The reaction of allyl compounds with alkynes (eq. 5) is also favored by the carboxylate anion, and can give synthetically interesting compounds (for example pheromones). With phenylacetylene and allyl acetate at 75°C in THF, $Ni[P(O\text{-}i\text{-}Pr)_3]_4$ or $Pd(PPh_3)_4$ gave the product in 84 and 72% yields, respectively.

Insertion promoted by chelating or metallacycle-forming substrates

Olefins are not readily inserted into certain carbon–metal bonds such as allyl nickel bonds. It is necessary to provide some facile elimination step after insertion and/or to promote insertion step by bringing about formation of energetically favorable intermediates. An example is provided (eq. 6) by the attack of the allyl group, formed by oxidative addition of allyl 3-butenoate to nickel(0), on the terminal carbon atom of the 3-butenoic chain of the same molecule [6]. The driving force of this reaction must lie in the formation of a metallacycle (eq. 9).



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(10)

Allyl esters were also formed as by-products. In THF at 75°C with $Ni[P(OiPr)_3]_4$ as catalyst a 90% yield of acids and their allyl esters (2,6/3,6 = 1/2) was obtained (200 mol per mol of catalyst).

The terminal position is preferred because the five-membered metallacycle is favored, as shown by the ready transformation of the six-membered metallacycle, obtained from nickel(0) and 3-butenoic acid, into the five-membered metallacycle on addition of sterically-demanding ligands [9] (eq. 10). Accordingly, only 3-butenoic esters are reactive in our case.

Another Group VIII metal complex, $RhCl(PPh_3)_3$ or its cationic analogues, proved to be much more selective in this synthesis (90% of the 3,6 acid under the same conditions). It is noteworthy that while with Ni the main product has the newly formed double bond conjugated with the carboxyl group, the product with Rh has the double bond in internal position. This means that Ni has more affinity for acidic hydrogen than Rh.

As to the site of attack of the allyl moiety bearing one terminal methyl substituent, it is largely at the unsubstituted end of the allylic system (ca. 85% with Rh and 82% with Ni). In the presence of rhodium(I), non-chelating olefins also react with allyl derivatives, but attack on the internal position of the butenoic double bond predominates.

Generation of an allylic group is also possible by protonation of dienes. Thus the features described above for allylic butenoates were also observed in the reaction of

butadiene with butenoic acid (eq. 11) [10].

$$CH_2{=}CHCH{=}CH_2 + CH_2{=}CHCH_2COOH \xrightarrow{cat}$$

$$CH_3CH{=}CHCH_2CH{=}CHCH_2COOH + CH_3\underset{\displaystyle CH{=}CH_2}{\underset{|}{C}}HCH{=}CHCH_2COOH \qquad (11)$$

Comparison with the previously reported [11] reaction of butadiene with olefins shows that, in contrast to our case, the olefin chain gives rise mainly to branched products, thus confirming the importance of chelation and metallacycle-formation for obtaining high regioselectivity.

A remarkable result was obtained as far as catalytic efficiency was concerned. More than 22000 cycles were reached per mol of catalyst using $RhCl(PPh_3)_3$ at 120°C without solvent. A cationic complex $Rh(COD)(PPh_3)_2PF_6$ (COD = 1,5-cyclooctadiene) gave 4500 cycles under the same conditions, but the product was more than 93% linear (ca. 89% with $RhCl(PPh_3)_3$).

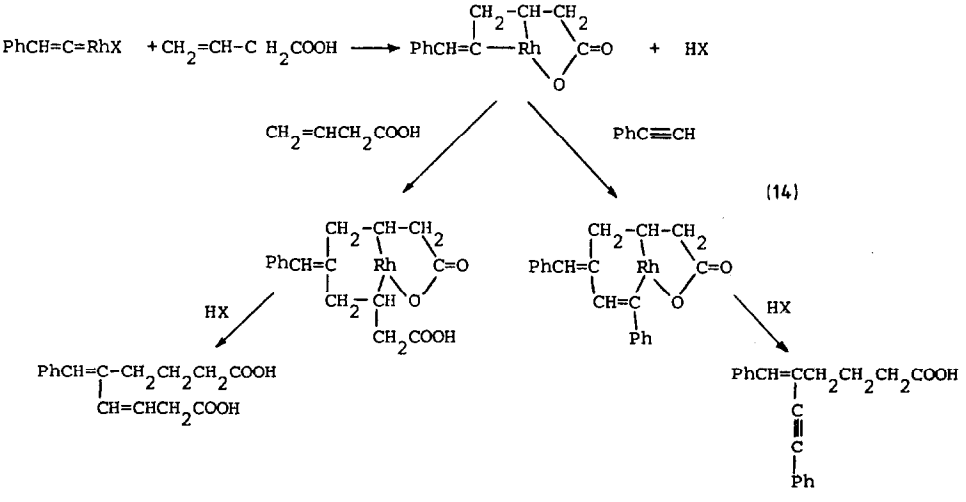
The reaction of vinyl halides with butenoic acids showed interesting aspects. From *E*-β-bromostyrene two isomers were formed (3-*E*-5-*E* and 3-*Z*-5-*E*) in 1/1 ratio at 85°C in ethanol (yield 65%) (eq. 12) [12]:

$$PhCH{=}CHBr + CH_2{=}CHCH_2COOK \xrightarrow{Rh\ cat} PhCH{=}CHCH{=}CHCH_2COOH + KBr \qquad (12)$$

When a similar reaction was carried out with phenylacetylene (eq. 13) in place

$$PhC{\equiv}CH + CH_2{=}CHCH_2COOH \xrightarrow[base]{Rh\ cat} PhCH{=}CHCH{=}CHCH_2COOH \qquad (13)$$

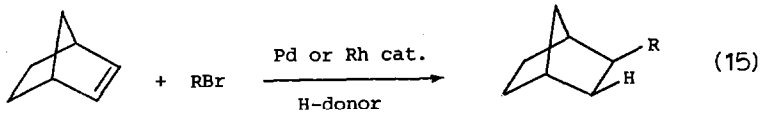
of styryl bromide all the four possible stereoisomers were obtained (3-*E*-5-*Z*/3-*Z*-5-*Z*/3-*Z*-5-*E*/3-*E*-5-*E* = 32/22/15/31). This may be taken to indicate that styryl metal bonds are not involved, and that a vinylidenerhodium complex of the type PhCH=C=Rh–, formed by isomerization of phenylacetylene [13], is the intermediate. This is also in accord with the fact that some by-products were obtained, corresponding to further insertion of either butenoic acid or phenylacetylene, which could be accounted for by assuming metallacycle intermediates formed by carbene-olefin coupling (eq. 14) for example (X = Cl or anion):



The hypothetical sequence shown in eq. 14 nicely fits the proposal [14] that in some cases C–C coupling does not proceed via the classical insertion reaction but via carbene intermediates. These results prompted us to investigate further the problem of metallacyclobutane formation, and work on this subject is still in progress.

Coupling C–C bond formation with reduction or oxidation processes

Olefin insertion is relatively easy when a β-H-elimination can occur [15] but when the olefin gives rise by insertion to a metal–carbon bond not able to, or reluctant to, undergo elimination, another termination step must be provided. We utilized a hydride source to couple an insertion process with hydrogenation. An example is the reaction of organic bromides RBr with bicycloheptene (eq. 15) [16]. Curiously, in some cases the hydrogenation process could also be delayed until a new bond was formed (eq. 16).



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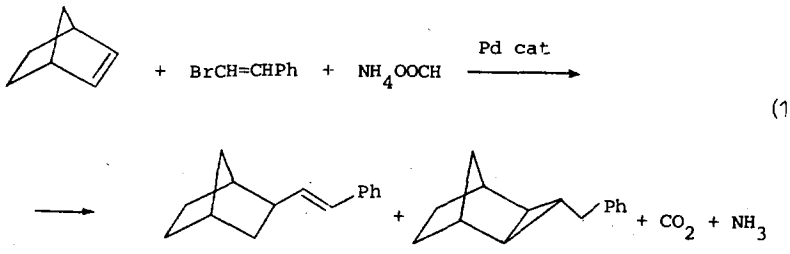
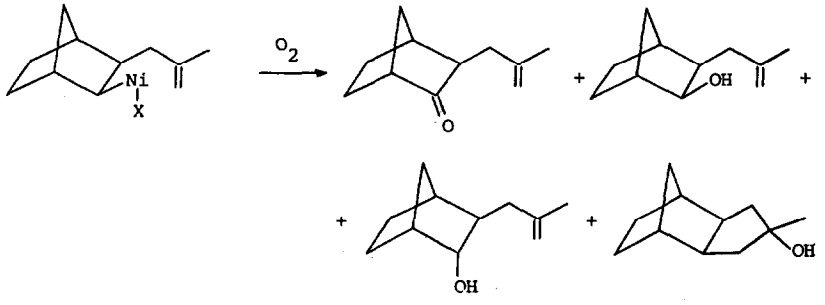


(16)

Thus a 51% yield of the condensed cyclopropane and a 20% yield of the styryl derivative were obtained with $Pd(PPh_3)_4$ at 80°C. This observation gave us a hint which led to the development of the multiple insertion processes described in the next section.

Another coupled process consisting of insertion + oxidation at room temperature was worked out starting from a Ni complex (eq. 17) [17].

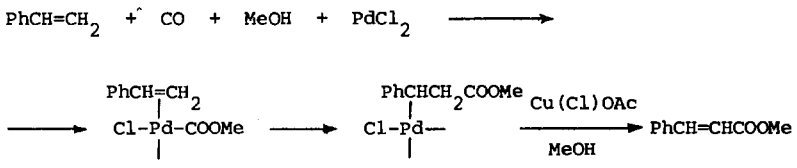


(17)

The reaction is not catalytic but it provides useful information about the possibility of inducing insertion with oxidants [18]. Furthermore the last compound of eq. 17

corresponds to a "delayed oxidation", which is parallel to the "delayed reduction" mentioned above. The process shows radical character.

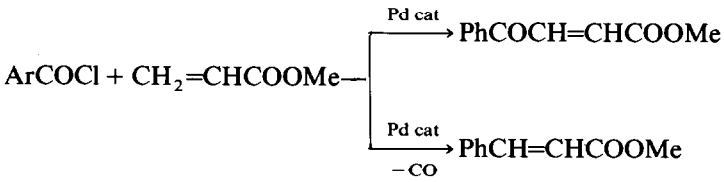
An insertion process coupled with oxidation is the well known oxidative carbonylation [19]. We were interested in carbonylation of styrene to give cinnamic esters. Carbonylation of styrene to phenylsuccinic esters had been previously reported, but only extremely poor results had been obtained on trying to direct the synthesis towards cinnamic esters. We employed a Pd catalyst in a concentrated solution of $CuCl_2$/NaOAc in methanol, with the aim of keeping the CO concentration low (the partial pressure of CO was also reduced by using a CO/N_2 20/80 mixture) and of preventing further CO coordination and insertion. The reaction went very well at 28°C giving yields of the order of 80% of methyl cinnamate (100 mol per mol of catalyst) (eq. 18) [20].



(18)

Insertion and β-hydrogen elimination

This is a well known method of inducing olefin insertion [15] into alkyl– or aryl–metal bonds. We succeeded in bringing about a catalytic reaction starting from aromatic acyl halides and activated olefins in the presence of phosphine-palladium(0) complexes and of tertiary amines as H-acceptors. During this study we observed an interesting side-reaction consisting of Pd-catalyzed decarbonylation, followed by attack of the resulting phenyl group on the olefin [21]. This result revealed a remarkable synthetic potential because it meant that instead of working with ArCl compounds, which are unreactive or poorly reactive under the mild conditions used, it was possible to use the corresponding ArCOCl compounds; for example, methyl cinnamate could be obtained, together with methyl benzoylacrylate, from benzoyl chloride and methyl acrylate (eq. 19):



(19)

This reaction was not optimized, but later work at Ciba Geigy [22], based on the use of nitrogen ligands in place of phosphines, led to very high catalytic activities.

The reactivity of nickel (0) was also compared with that of palladium(0), and once again it was observed that, owing to the reluctance of Ni to undergo reductive elimination, the reaction was only very weakly catalytic.

Carbon monoxide insertion, and nucleophilic attack on the acyl group thus formed

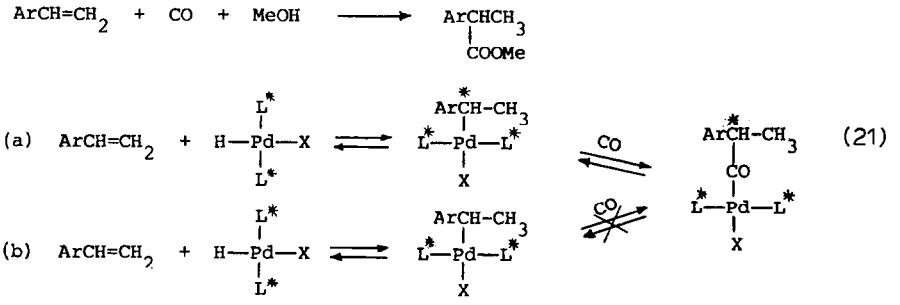
Reactions of olefins with carbon monoxide and alcohols or water were described by several groups including ours [23], but with palladium(0) as catalyst and vinyl-

aromatics as substrates the results were not satisfactory in terms of the use of mild conditions and of high regioselectivity. We achieved the synthesis of arylpropionic esters very simply using trifluoroacetic acid and the vinylaromatic in methanol at room temperature with a palladium(0) complex with neomenthyldiphenylphosphine as catalyst [24]. Under these conditions, for example, more than 96% regioselectivity towards the internal carbon atom of the styrene double bond was obtained (eq. 20).

$$PhCH{=}CH_2 + CO + MeOH \xrightarrow{\text{Pd cat}} PhCH(Me)COOMe \qquad (20)$$

Since arylpropionic esters are important antiinflammatory agents the synthesis was extended to many other substrates of pharmaceutical interest. Moreover with the same asymmetric phosphine it was possible for the first time to obtain satisfactory asymmetric induction, which reached 52% e.e. with styrene.

We later established indirectly that asymmetric induction takes places at an earlier stage, probably that of hydride transfer to styrene [25] and not as kinetic resolution at the stage of CO insertion (eq. 21). This was shown by causing partial

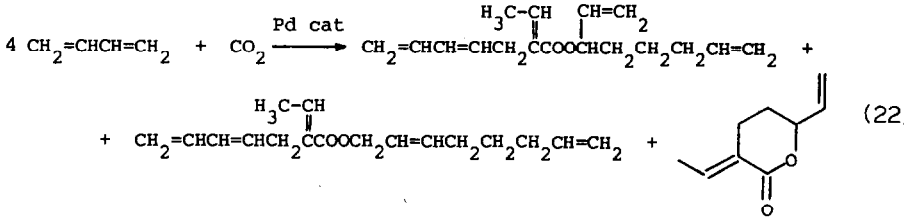


(21)

decarbonylation of the inactive α-phenylpropionyl group (the inverse reaction) in the presence of the optically active ligand without observing optical activity in the remaining acyl group (after hydrolysis to ester) [24]. The reason why this system is able to lead to an unprecedented extent of asymmetric induction is still obscure, and research aimed at elucidating this point is continuing.

Insertion followed by C–C coupling or H transfer

This approach was attempted for reactions of dienes with unsaturated compounds. Reactions of carbon dioxide with carbanions had been the subject of our research in earlier years [26], and we set out to bring about a catalytic reaction with butadiene using palladium(0) as catalyst. In the meantime a Japanese group showed that this reaction could be effected, although in poor yield [27]. Under our conditions a catalytic reaction took place, at 80°C under CO_2 pressure, leading mainly to esters (a lactone was also isolated) (eq. 22).



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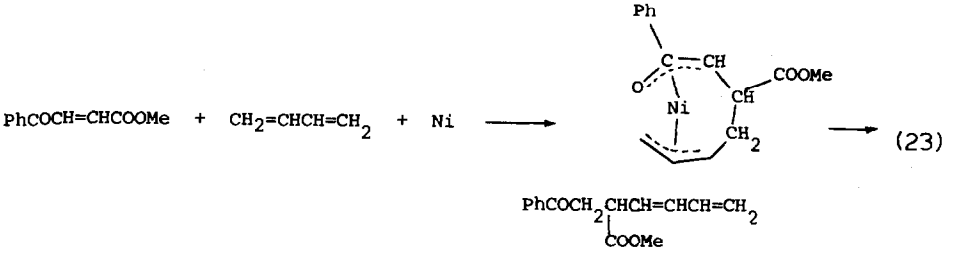
What renders this reaction catalytic is the final coupling to give either a lactone or an ester. Formation of the latter also requires a hydrogen transfer from the butadiene-derived acylic chain of the ester to the alkylic one. Whether this occurs within a dimeric Pd complex has not yet been established. This work was carried out independently by two Italian groups and patented jointly [28]. Further work on allyl palladium complexes confirmed that C–C coupling in the elimination step is an effective way of favouring CO_2 insertion [28].

We also achieved C–C coupling between butadiene and an activated olefin, methyl benzoylacrylate, by utilizing an intramolecular H-transfer in the elimination step [29] (eq. 23). The reaction gave a 79% yield at room temperature.



It is noteworthy that nickel(0) forms an open-chain adduct under conditions, which normally would lead to a Diels–Alder reaction.

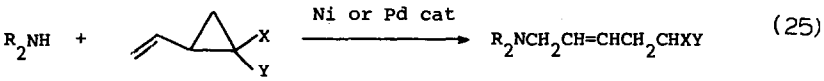
Nucleophilic attack

Nucleophilic addition to double bonds was also studied as a general method of achieving C–C or C–N bond formation. We were interested in the analogy between Michael-type addition and nucleophilic attack on Pd-coordinated olefin, and were able to show that carbanions were generally reactive, irrespective of their soft or hard character, provided that they were kinetically stable [30]. Thus alkyl monoester carbanions readily undergo β-hydrogen elimination or Claisen condensation and, for example, the addition of the lithium salt of methyl propionate to Pd-coordinated ethylene gave only a 2% yield, but with methyl isobutyrate the yield was much higher, at 90% (eq. 24, L = Et_3N).

$$Me_2C(Li)COOMe + (CH_2{=}CH_2)PdCl_2L \rightarrow$$
$$Me_2C(COOMe)CH{=}CH_2 + Me_2C(COOMe)CH_2CH_3 \qquad (24)$$

This reaction is not catalytic because the proton is used up in hydrogenolysis of the Pd–alkyl bond.

A successful approach to catalytic nucleophilic additions was based on attack of an amine on the double bond of a vinylcyclopropane [31]. This reaction was highly regioselective and led to formation of a linear chain by cyclopropane ring opening (eq. 25, R = alkyl; X,Y = electron-withdrawing substituents). Both nickel(0) and palladium(0) were effective catalysts. Yields of the order of 95–98% were obtained both with $Ni[P(O\text{-}i\text{-}Pr)_3]_4$ and $Pd(PPh_3)_4$, but the latter gave much longer catalytic cycles (ca. 2000) than the former (50–100):



Further addition of butadiene to the products in the presence of palladium(0) according to a well-known process [32], gave long chain amines [33] (eq. 26) with high yield (90%) and catalytic efficiency (1000 cycles at room temperature).

$$R_2NCH_2CH{=}CHCH_2CHXY + 2CH_2{=}CHCH{=}CH_2 \xrightarrow{\text{Pd cat}}$$

$$\rightarrow R_2NCH_2CH{=}CHCH_2CH(X)(Y)CH_2CH{=}CHCH_2CH_2CH_2CH{=}CH_2 \qquad (26)$$

It is interesting to note even when all the reagents were introduced together the addition order amine → vinylcyclopropane → two molecules of butadiene did not change. These ordered sequences form the subject of the following section.

Multiple additions in sequence

The reactions described in the preceding section pointed the way towards complex multiple step reactions. Thus metal elimination can be delayed in order to permit further addition of molecules or groups.

Basically two methods could be envisaged: the first involves the use of substrates bearing more than one reactive function able to interact with the metal, so that many bonds can be formed before metal elimination; in the second elimination is made more difficult by appropriate choice of the substrates, and further insertion of new molecules or groups is favoured until conditions for ready elimination are met. The two approaches can in practice be used together.

Substrates with more than one reactive function

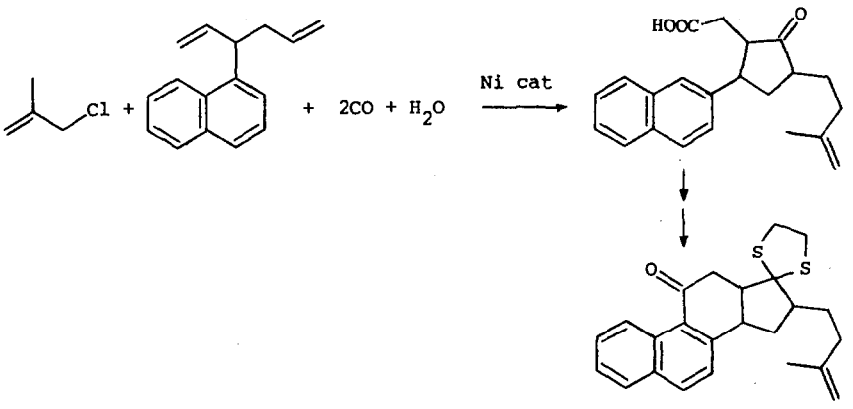
An early example involved the use of 1,5-chelating olefins for insertion into an allyl–nickel bond followed by carbonylation. With the 1,5,9,13-tetradecatetraene system the following reaction occurred with CO and methallyl chloride in the presence of nickel(0) as catalyst at 25°C (eq. 27) [34].

$$CH_2{=}\overset{\overset{Me}{|}}{C}CH_2Cl + CH_2{=}CHCH_2CH_2CH{=}CHCH_2CH_2CH{=}CHCH_2CH_2CH{=}CH_2 + 4CO + H_2O \longrightarrow \qquad (27)$$

$$\xrightarrow{\text{Ni cat}} CH_2{=}\overset{\overset{Me}{|}}{C}CH_2CH_2\text{–}(C_5H_6O_3)\text{–}CH_2COOH$$

An interesting feature is that not only does the reaction occur regio- and stereo-selectively, but the three cyclopentanone units are arranged with their C–O–C planes tilted as in an incipient helicoidal structure. This reaction can, in fact, be regarded as the beginning of a stereospecific polymerization. All-*trans* 1,5-dienes are required.

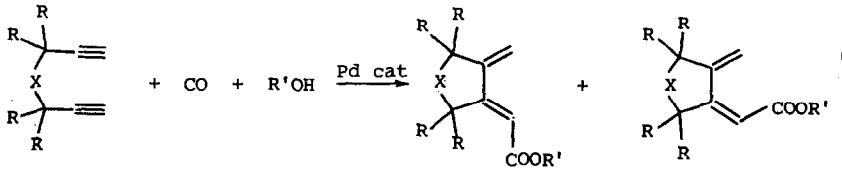
The possibility of obtaining regio- and stereo-selective reactions prompted us to examine the behaviour of more complex molecules. Use of a 2-hexadienylnaphthalene with methallyl chloride in the presence of nickel(0) at 50°C resulted in the ring closure of a cyclopentanone unit; further cyclization gave rise to a steroid analogue with the cyclopentanone ring formally corresponding to ring D (eq. 28) [35]. Other



(28)

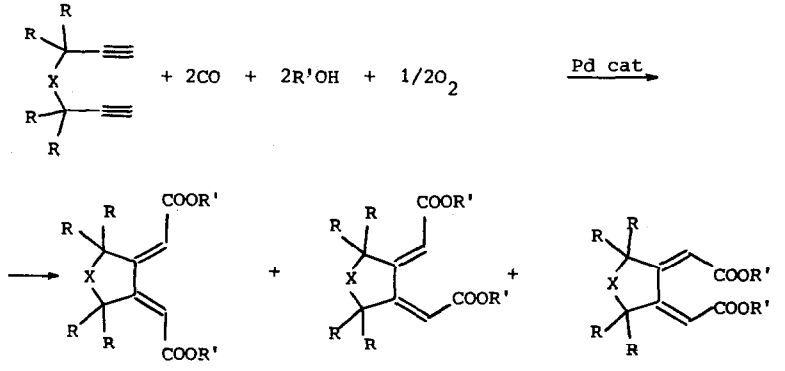
reactions of this kind were studied and a short review appeared [36].

Among other chelating systems 1,6-diacetylenic species were extensively used by us in a series of reaction with or without carbon monoxide. For reactions with CO we used the $PdCl_2$/thiourea method, which had proved to be very effective with acetylene [37]. We observed that the diynes $HC{\equiv}CCR_2XCR_2C{\equiv}CH$ (X = CH_2, NH; R = H, alkyl) could be cyclized, without CO incorporation in the ring, at room temperature and atmospheric pressure. A 65% yield of two isomers (*syn*/*anti* 2/1) was obtained in methanol (eq. 29) [38].



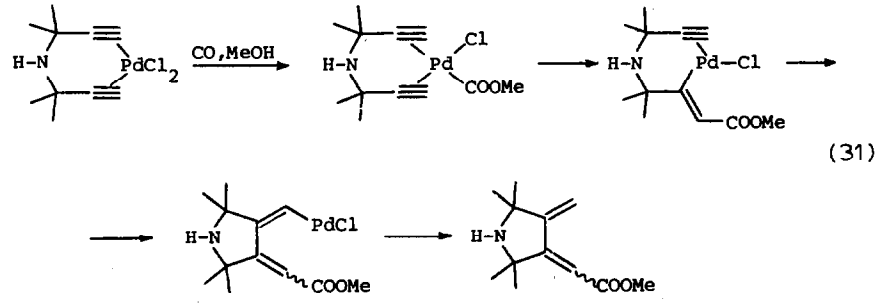
(29)

The most effective substrates were substituted dialkynes, particularly, α,α'-tetra-substituted amines. Conformational and steric effects [39] played an important role in determining efficiency and selectivity of this reaction. It is noteworthy that when alkyl substituents were present on the carbon atoms α to X the major products resulted from additive carbonylation, uptake of a second CO molecule being prevented by steric effects due to the alkyl substituents and to the thiourea ligand. Without such substituents or thiourea there was an increase in the yields of oxidative carbonylation products (eq. 30). Similar behaviour was observed with monoalkynes.



(30)

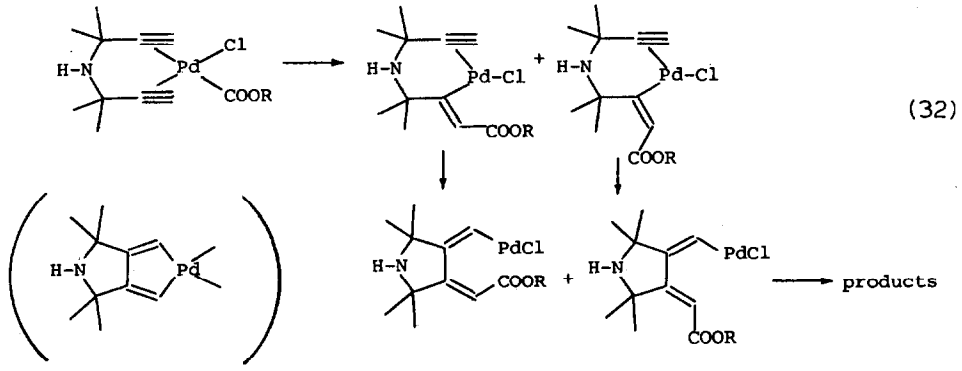
The two types of carbonylation thus appear to have a common first step, namely formation of a Pd-bonded COOH (with water) or COOAlk (with alcohols) group able to attack the triple bond (eq. 31). This aspect had been previously pointed out for a stoichiometric reaction with preformed Pd-$COOCH_2CH_2C{\equiv}CH$, but in this case no pathway was available other than ring closure and final protonation [40].



(31)

As mentioned above, catalytic oxidative and additive carbonylation processes are consistent with an initial attack on the triple bond by the carboxyl group. The latter should give rise to a stereoselective reaction, but mixtures of *syn* and *anti* isomers are found. This behaviour could conceivably be attributed to isomerization, but this proved to be very slow under the conditions used.

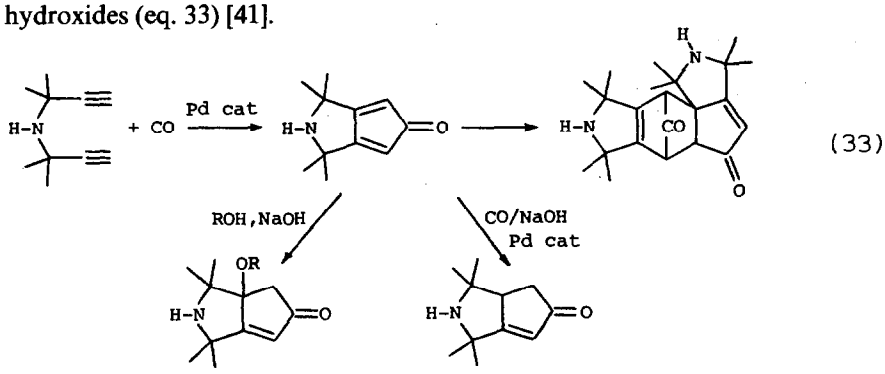
Isomerization at the last stage before final elimination also has to be considered in the light of the results obtained in the presence of deuteromethanol, which gave deuteration of the *anti* proton of the methylene group of the *syn* product, as expected, and deuterium scrambling among the three unsaturated carbons in the case of the *anti* compound. Had isomerization occurred at the last stage the *syn* and *anti* compounds should have given the same result. The possibility is left that *syn* and *anti* intermediates are formed at an earlier stage (by direct attack or by isomerization, see for example eq. 32, R = H, alk), and that after ring closure only the Pd-bonded *anti* intermediate is able to exchange deuterium with all the three positions available. From these observations we also argue that a palladacyclopentadiene (in parentheses) should not be the intermediate because its rigid structure would favour a stereoselective attack.



(32)

The latter complex, however, is likely to be the intermediate in another series of reactions performed in the absence of thiourea with palladium(0) complexes and also

with Pd/C under CO at atmospheric pressure. A cyclopentadienone is formed, which has a strong tendency to dimerize. The example refers to the tetramethyl derivative (TMDPA) which gave a yield of the ketonic dimer of more than 90%. It was possible to intercept cyclopentadienones in presence of metal alkoxides or alkali hydroxides (eq. 33) [41].



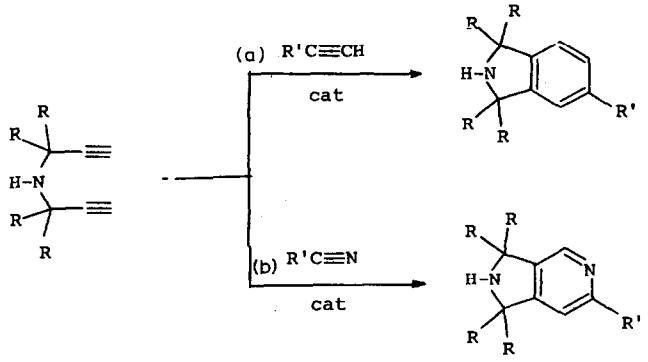
(33)

Whereas alkoxide attack corresponds to a Michael-type reaction, hydrogenation originates from the Pd-catalyzed transformation of CO into CO_2 and H_2 in NaOH solution. Combining two processes on a metal catalysts is a general problem in catalysis. We had previously observed hydrogen evolution coupled with oxidation of a benzylic alcohol to the corresponding sodium benzoate in a Pd-catalyzed reaction in NaOH solution (80% yield with benzyl alcohol) (eq. 34) [42] and certainly many other reactions based on similar concepts are possible.

$$PhCH_2OH + NaOH \rightarrow PhCOONa + 2H_2 \quad (34)$$

Going back to the palladacyclopentadiene, which can be postulated as the intermediate in reaction 33, we examined other reactions, which might involve analogous nickel or cobalt complexes. TMDPA was the substrate of choice because of its coordinating properties.

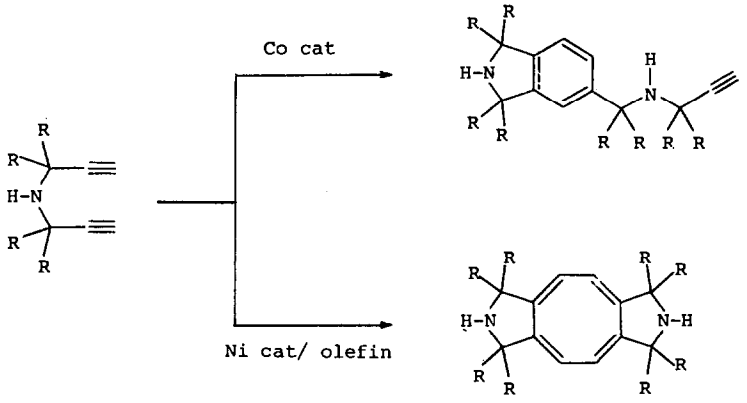
In the presence of nickel(0) we observed a chemoselective reaction of substituted dipropargylamines with monoalkynes. In spite of the many possible combinations, the main product was derived from 1/1 addition of the dialkyne to the monoalkyne, for example (eq. 35, way a, R = alkyl, R′ = alkyl, aryl) [43]. Yields ranged from 60 to 80%. Again this was due to the substituent effect mentioned before, and accordingly, low selectivity was obtained with 1,6-heptadiyne. The same substituent effect [39] enabled us to incorporate the nitrile triple bond, although to a limited extent (eq. 35, way b). A 15% yield was obtained with succinonitrile by incorporation of one CN group.



(35)

Since the reaction between alkynes and nitriles had previously been reported to occur with cobalt(I) complexes [44], we also tried cobalt(I) catalysts, but with poor results. By contrast, the reaction at 80°C with a catalyst prepared by reduction of $CoCl_2$ with Mn or Zn powder gave excellent results both in term of yield (98% yield with MeCN) and catalytic efficiency (30 cycles) [45]. This was unexpected in view of the fact that these systems are not effective with monoalkynes. We suggested that cobalt(0) is involved [46] and that the latter is much more sensitive to steric and conformational effects than cobalt(I). Thus *N*-methyldipropargylamine or 1,6-heptadiyne with cobalt(0) gives codimerization, even in the presence of acetonitrile as solvent, but the tetralkyl-substituted diacetylenic amine mainly gives nitrile incorporation. Varying the oxidation states of the same metal to obtain different chemoselectivities appears to offer promising research possibilities. As mentioned before nickel(0) and cobalt(I) also differ markedly in their behaviour towards alkynes and nitriles.

A further observation on nickel(0) deserves mention. When the dimerization reaction of sterically hindered diacetylenic amines is carried out in the presence of an olefin such as methyl acrylate or styrene as solvent the main product is no longer that resulting from trimerization of the triple bond but instead is a cyclooctatetraene compound, for example (eq. 36) [47] (68% yield with $Ni[PhP(O\text{-}i\text{-}Pr)_2]_4$. In the light

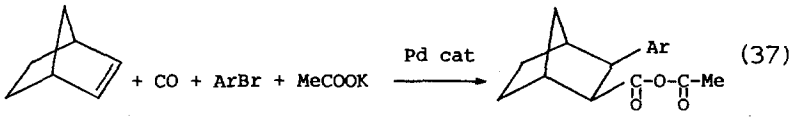


(36)

of previous work, showing that ligand addition shifted alkyne tetramerization towards trimerization [48], this result was unexpected. It seems to confirm the hypothesis that cyclooctatetraene formation involves dimerization of two coordinated molecules [49].

Substrates leading to C–metal bonds reluctant to β-H elimination

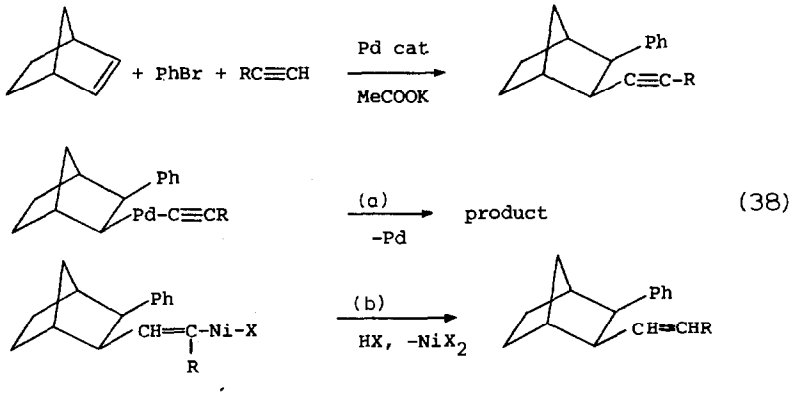
In the preceding section bicycloheptene (BCH) and its derivatives were mentioned as examples of molecules which undergo metal-catalyzed insertion with formation of a metal–carbon bond stable towards β-H elimination. Taking advantage of this we caused aromatic and vinylic halides to react at 80°C with BCH and CO in anisole or butanol in the presence of a palladium(0) catalyst and potassium acetate. Elimination following the BCH insertion having been prevented, BCH and CO insertion took place in sequence, followed by nucleophilic attack of the acetate anion on the acyl–palladium bond thus formed, to give mixed anhydrides (eq. 37) [50] (45–65% yields). These gave rise to the respective simple anhydrides or were hydrolyzed by



(37)

alcohols to acids and esters. The sequence observed is of interest in view of the fact that a different sequence: Ar → ArCO → ArCO-olefin is preferred in other cases [51]. The carboxylate anion seems to be responsible for the preferential coordination and insertion of the olefin relative to that of CO.

The same concept was also applied to another sequential process, involving the same 3-substituted bicycloheptylpalladium complex. Aromatic, vinylic or allylic bromides give rise to a catalytic cycle by reacting with bicycloheptene and alkynes RC≡CH. Yields vary from 46 to 86%. The termination process probably consists of a coupling reaction in which an alkynyl group attacks the Pd-bonded bicycloheptyl group (eq. 38, path a) [52].

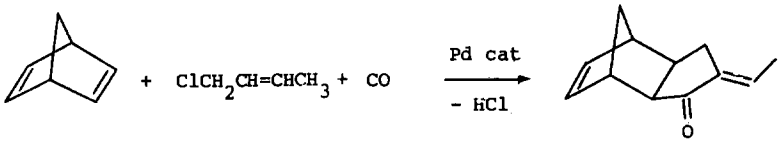


(38)

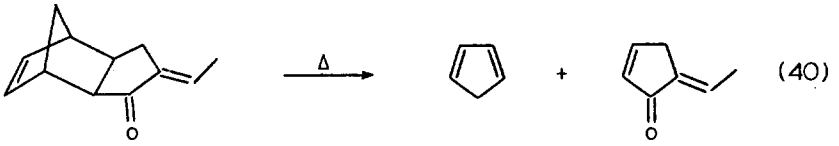
That an insertion reaction is not likely is indicated by the ready reaction of the arylbicycloheptylpalladium complex with sodium acetylides [53] and, indirectly, by the behaviour of the same reagents with nickel. The latter gave a stoichiometric insertion reaction, involving protonation of the final complex and formation of a double bond (eq. 38, way b) [52]. This may be taken to indicate that, when insertion occurs, H-uptake rather than H-elimination is preferred. This is not the only difference between the two metals. In fact their abilities to stabilize different types of C–metal bonds and to undergo reductive elimination differ markedly; for example, aryl and vinyl halides give satisfactory results with Pd and poor results with Ni, while the opposite is true with allyl halides.

Another instance of the differing behaviour is offered by the carbonylation of allyl halides. While this reaction had been previously shown to occur quite easily with Ni [1], the use of Pd requires special conditions (protic solvents, salts of carboxylic acids, 80°C) and final products are different [54]. An example involving bicycloheptadiene is shown (eq. 39). The product can also be used as a source of a versatile cyclopentenone, which is obtained from a retro-Diels–Alder-type reaction (eq. 40).

A remarkable aspect of reaction 40 is that it also occurs at 80°C in the presence of the same Pd catalyst. The yield was particularly good in butanol, where reactions 39 + 40 gave a combined yield of 89% (34% from reaction 40), and 45 mol of



(39)

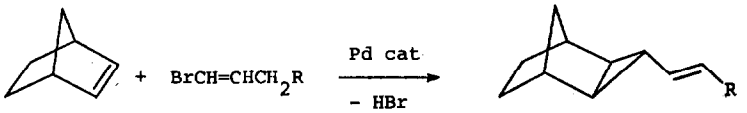


(40)

product per mol of catalyst were formed.

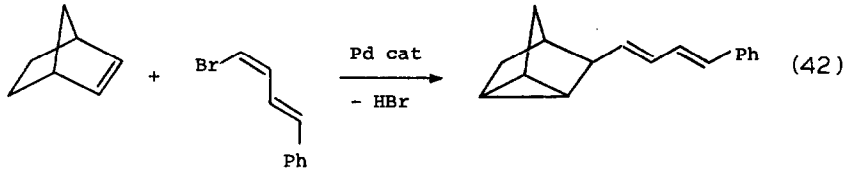
If CO is not used, the reaction with BCH or other strained olefins is generally more complex and offers a variety of patterns, depending markedly on the termination processes which are allowed by the different substrates used. Some representative reactions with BCH at 80°C in anisole are shown below. They are catalytic, although few catalytic cycles are generally observed. Potassium acetate is used in stoichiometric ratio to the bromide.

Vinyl bromides. Insertion of two double bonds with formation of a condensed cyclopropane followed by H-elimination (eq. 41, R = alkyl group) [55,56] (ca. 30% yield).



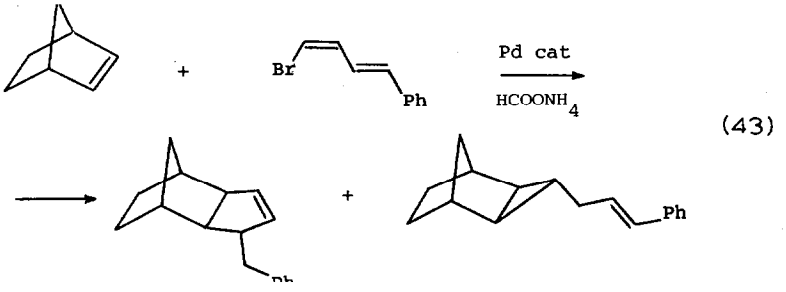
(41)

Conjugated dienyl bromides. Insertion of one double bond and tricyclene formation [55,56], probably via a solvolytic mechanism (eq. 42) [57] involving activation of a BCH saturated CH_2 (ca. 32% yield).



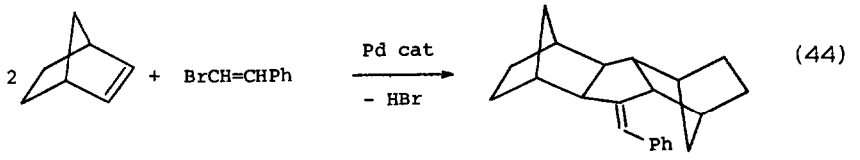
(42)

The initially *Z,E* double bonds become *E,E*, isomerization being faster than tricyclene ring formation. If, however, a reaction faster than isomerization, such as H-transfer from ammonium formate, is caused to occur, ring closure takes place (eq. 43) (ca. 49% yield and 24% of a condensed cyclopropane).



(43)

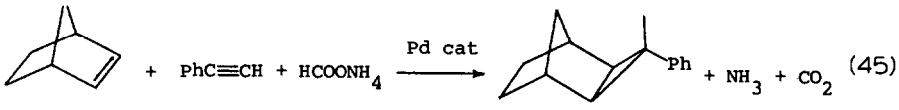
Styryl bromide. The tendency to form a cyclopropane ring is strongly reduced and a second molecule of BCH inserts, thus creating the correct arrangement for cyclopentane ring closure. At this point β-H elimination occurs readily (eq. 44) [58] (66% yield).



(44)

It is worth noting that this reaction is highly stereoselective both in relation to the *cis-exo* stereochemistry at the bicycloheptane junction and to the *syn* position of the phenyl group with respect to the methylene bridge.

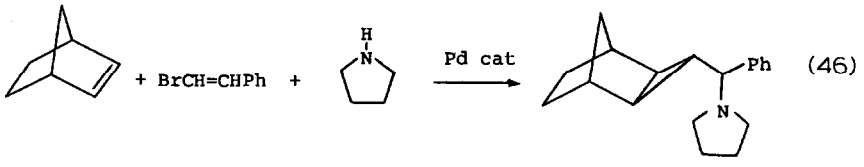
Phenylacetylene or terminal alkynes can also give rise to a styryl group: a hydrogen transfer source (ammonium formate) initiates the process, forming an α-substituted vinylpalladium bond, which in its turn inserts BCH. Cyclopropane ring formation follows, and a final H-transfer terminates the process. An example with PhC≡CH (77% yield based on converted BCH) is reported (eq. 45) [59].



(45)

This is an useful reaction because it allows cyclopropanation starting from acetylenic compounds.

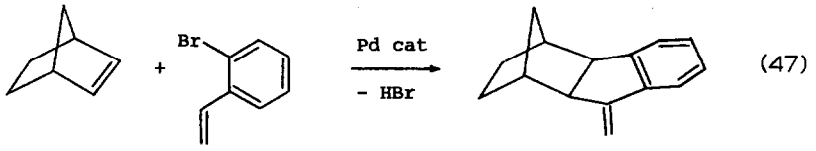
Styryl bromide and amines. Sequential insertion of the BCH and styryl double bonds to form a condensed cyclopropane occurs readily because of the N–C coupling reaction which terminates the process. Yields are satisfactory with secondary amines such as pyrrolidine (eq. 46) [60] (76% yield).



(46)

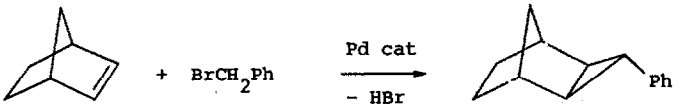
Even among secondary amines specificity is observed, yields varying from 76% with pyrrolidine to 0% with diethylamine. The amine reactivity series parallels that of the enthalpies of formation of their adducts with BH_3 [61], showing that steric effects play a determining role.

Aromatic halides bearing an ortho vinyl group. Ring closure occurs at the vinyl double bond after BCH insertion (eq. 47) [58] (75% yield).



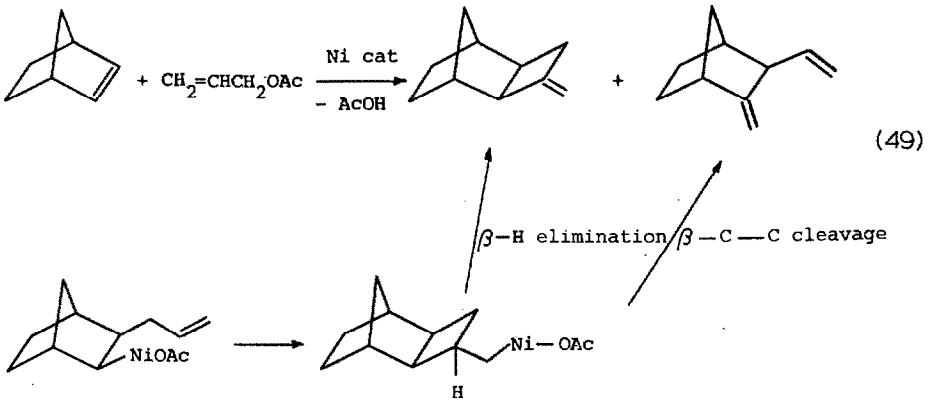
(47)

Benzyl halides. Cyclopropane ring formation occurs by activation of the benzylic CH_2 (eq. 48) [55]. This is a slow reaction, giving 52% selectivity at 20% conversion of the bromide.



(48)

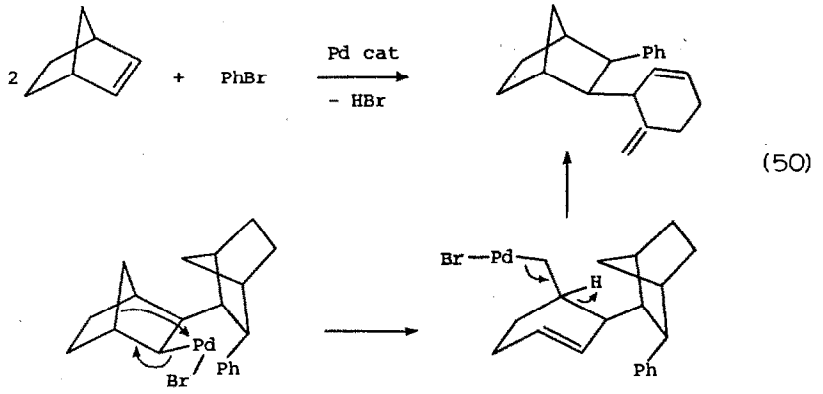
Allyl halides. Cyclobutane ring formation is the result of two sequential double bond insertions. We studied this reaction using Ni, but similar products could be obtained with Pd. Another interesting path is also available, however, that leading to β-C–C cleavage (eq. 49) [62,53].



(49)

A condensed methylenecyclobutane and a diene are formed in a 3 to 7 ratio (80% yield).

The β,γ-C–C bond cleavage deserves some comment. The literature on this subject is rather scanty, and gives the impression that it represents very unusual behaviour. In the course of our studies on systems in which β-H elimination is not possible we observed other cases, however. For example, BCH and bromobenzene, at 105°C in the presence of orthoformate as HBr acceptor give rise to the following sequence (eq. 50) [63] (33%).



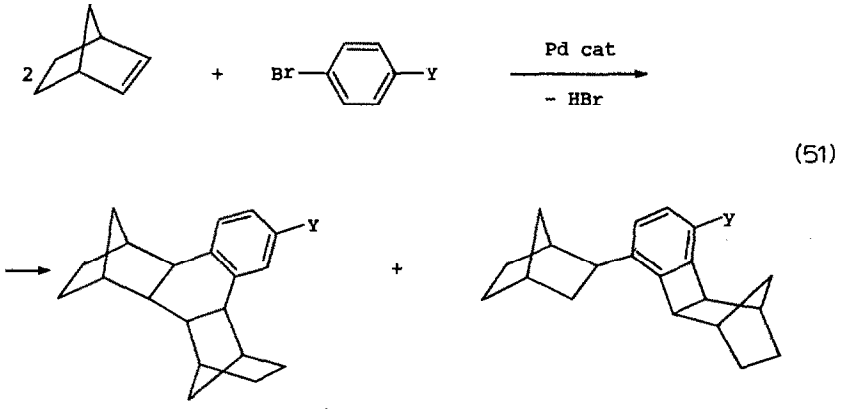
(50)

These results, together with observations [64] from other laboratories, lead us to regard β-C–C bond cleavage as a general feature of all cases when β-H elimination is not favored. This is a synthetically important key for gaining access to many compounds not otherwise readily obtainable.

So far I have listed a series of reactions with BCH or strained olefins which involve different termination steps, encompassing β-H elimination, C–C or C–N coupling, and intra- or inter-molecular H-transfer from aliphatic carbon chains. A number of variations now appear to be possible if appropriate molecules are used.

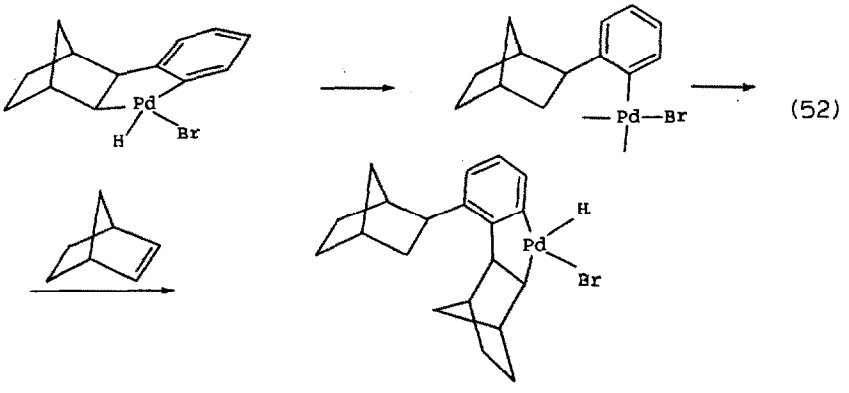
Aromatic compounds can also be involved in the termination step. They react in quite different ways, however, depending on slight modifications of the reaction conditions, particularly on the type of base used.

In the presence of carboxylate anions at 80–110°C two main products are formed, with one predominating depending on the type of substituent Y, for example (eq. 51) [65].



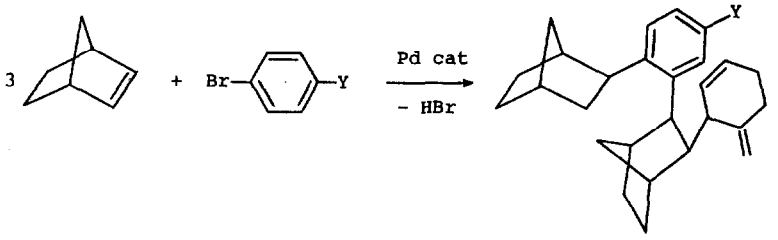
(51)

Electron-withdrawing substituents in the aromatic ring favour the latter compound (22% yield and 11% of the former with $Y = NO_2$), whereas the electron-releasing ones help formation of the former (70% yield with Y = OMe). While the effect of electron-releasing substituents is consistent with an electrophilic substitution, the methanobiphenylene derivative can only be explained in terms of the intermediate formation of a palladacyclopentene, which transfers Pd from the bicycloheptyl to the aromatic group (eq. 52) [66].



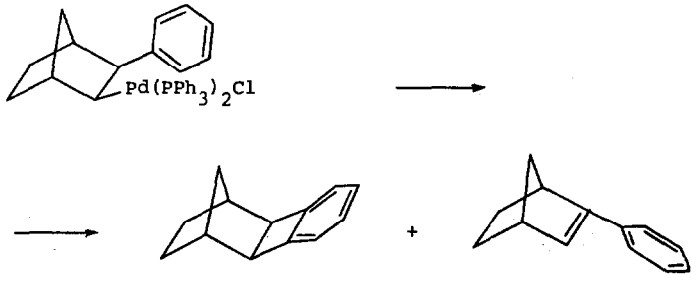
(52)

In accord with this interpretation, at 105°C and with *p*-Br as the substituent, it was possible to isolate the product resulting from further BCH insertion and ring opening (eq. 53) [67]. This is a type of initial BCH polymerization, involving chain transfer to the aromatic ring.



(53)

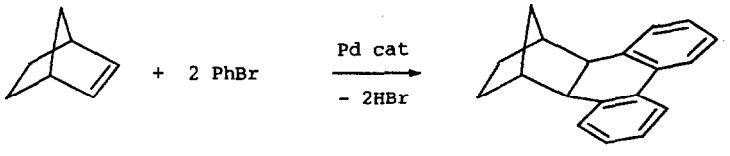
Cyclobutene ring closure apparently requires special conditions. When electron-withdrawing substituents are present on the aromatic nucleus only small amounts of the hexahydromethanobiphenylenes, resulting from ring closure at the level of the first complex of eq. 52, are formed. Starting from arylbicycloheptylpalladium complexes with triphenylphosphine, however, ring closure can be achieved by heating in the presence of potassium acetate. Hexahydromethanobiphenylene is formed from the corresponding complex, together with phenylbicycloheptene (eq. 54) [66,67].



(54)

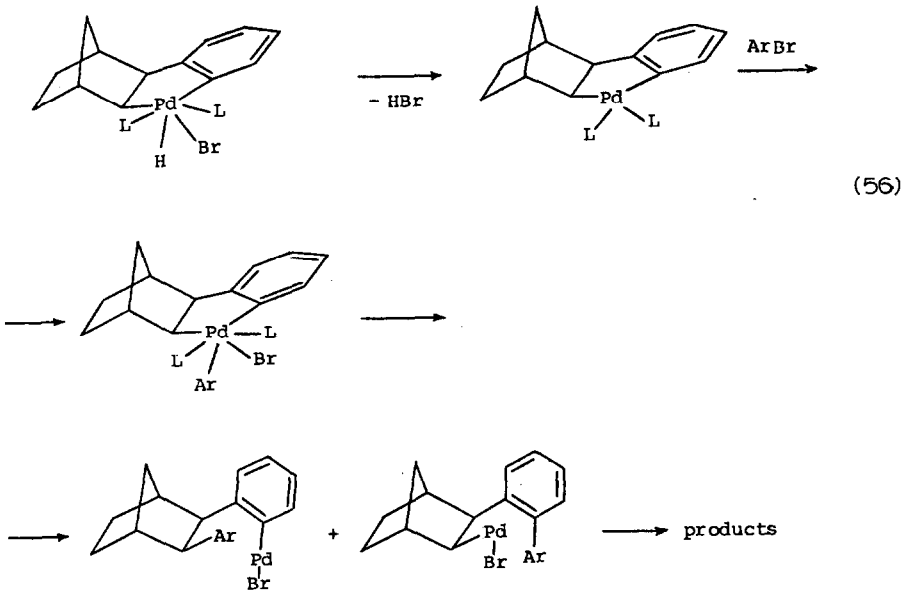
Recent work on this subject has led us to a catalytic synthesis of hexahydromethanobiphenylene derivatives. Phenoxides are the bases of choice. High selectivities are attained with hindered phenoxides [68].

If alkoxydes such as t-butoxide are used in place of alkali carboxylates the reaction takes another course (eq. 55) [69] leading to a methanotriphenylene derivative (65% yield).



(55)

In this case the reaction should still involve the same palladacycle, but for reasons which are not yet completely clear the metallacycle persists after HBr elimination, and is susceptible to a new oxidative addition of another molecule of PhBr. Formation of a new palladium(IV) complex should then give rise to C–C and Pd–C bonds, as depicted in eq. 56, and to ring closure.



(56)

The course shown (eq. 56) was proved by placing a substituent *para* to the bromine on the aromatic ring, two isomers deriving from the two proposed ring-opening pathways being isolated. Since this is a catalytic reaction, it shows how a catalytic C–C coupling can be brought about by taking advantage of different oxidation states of the same metal.

It is apparent from the experiments with aromatic bromides that coupling insertion of strained olefins with aromatic substitution is a versatile technique, slight variation in the type of base used leading to completely different products. The crucial point, which remains unclear is the way by which the intermediate palladacycle forms and undergoes further reaction.

Conclusion

Many new organometallic pathways have been detected and synthetic applications demonstrated.

Our research is now developing along the lines which have emerged from testing working hypotheses experimentally. In particular C–C bond formation via catalytic C–H activation and syntheses involving chelated or metallacyclic structures are being actively investigated. Many problems remain to be solved, however, in particular those related to mechanism, selectivity control, and catalyst deactivation.

On the other hand, as always happens when general methodologies are studied, several practical applications emerged. It is only a matter of being informed about industrial needs. Thus we were able to patent or file patent applications on pheromones (eq. 5), fatty acids (eq. 11), cinnamic acids (eq. 18), antiinflammatory agents (eq. 20), auxiliary textile agents (eq. 26), antioxidants (eq. 29, 30, 33, 35, 36), cyclopentanoids, prostaglandins and their analogues (eq. 37–40) and there are prospects of several other applications.

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