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Reactions of cyclopalladated compounds and alkynes: new pathways for organic synthesis?

Michel Pfeffer

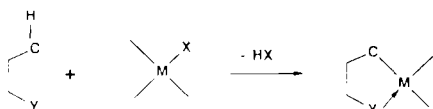
Laboratoire de Chimie de Coordination, URA 416 du NRS, 4, rue Blaise Pascal, 67000 Strasbourg, France

(Received June 6th, 1990)

Abstract. Cyclometallated compounds, obtained by direct intramolecular C–H activation of a ligand by transition metals, are fairly reactive [especially those derived from palladium(II)] towards insertion of internal alkynes into their metal–carbon bond. This reaction leads to either new organometallic compounds by inclusion of one to three alkynes into the M–C bond, or organic compounds which are either carbocyclic or heterocyclic, their nature depending upon the alkyne substituents as well as upon the cyclometallated ligand.

Introduction

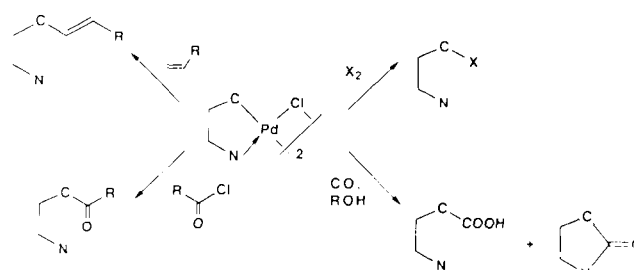
Since the initial discovery, about 25 years ago, of the intramolecular metallation of a ligand by transition metal complexes, this reaction¹, successively named orthometallation and then cyclometallation², raised a great deal of interest amongst inorganic chemists. This interest was connected, in the early times, to the more general C–H activation problem, and also to the fact that the synthesized compounds were soon recognized to be potential, powerful starting materials for organic synthesis. The general reaction leading to these compounds is schematically represented below:



Scheme 1

In this equation, Y represents a two-electron donating group or atom, such as an alkene unit, a pnictogen (N, P, As) or a chalcogen atom (O or S), M is a transition metal and X is an anionic leaving group, such as halide, alkyl, hydride, acetate, etc. Many examples of such compounds have now been described and syntheses have been extensively reviewed^{3–11}. However, only limited applications to organic synthesis have so far been described, although this is now becoming a subject of rapidly growing interest. An excellent review by Ryabov has been recently published¹², which establishes the state of the art for the most common reactions, such as carbonylation, vinylation, acylation or halogenation (see Scheme 2).

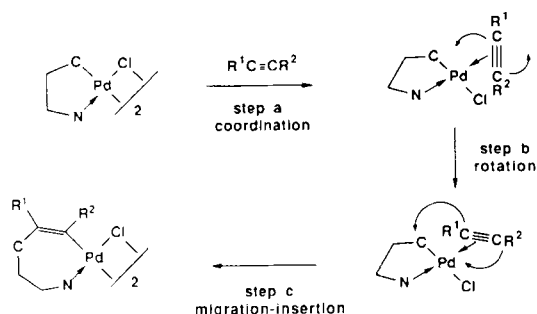
The aim of the present article is to describe how, through reactions with alkynes, cyclometallated compounds can lead to a very productive and somewhat unexpected organo-



Scheme 2

metallic and organic chemistry. Most of the work reported here concerns cyclopalladated ligands. The choice of palladium is governed by the fact that hundreds of examples of cyclopalladated compounds are now known¹¹ and Pd(II) is by far the most efficient metal for achieving intramolecular C–H activation of a great variety of ligands. Another good reason is that Pd is one of the most versatile metals for C–C- or C–Y-bond synthesis¹³. Alkynes have long been known to be very useful building blocks for organic synthesis, since they display a wide reactivity: they can be considered as electrophiles or nucleophiles, depending upon the nature of the substituents and they, therefore, lead to a large variety of reactions¹⁴. Finally, an attempt is made to define the reactivity of cyclopalladated ligands in which the Y atom (see Scheme 1) is nitrogen because numerous such N donor ligands have been cyclopalladated. Any new reaction may, therefore, be tested on a large variety of starting materials. It was soon recognized that these compounds are much more reactive than the corresponding compounds in which Y represents other heteroatoms, such as sulfur or phosphorus¹².

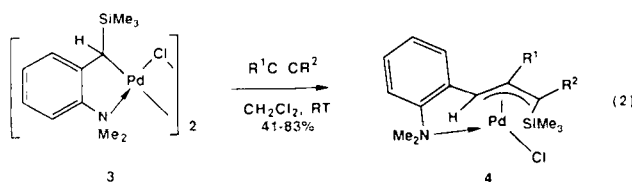
The reactions of cyclopalladated compounds with alkynes which are relevant to carbopalladation of alkynes¹⁵, will be



Scheme 4

The regioselectivity of the reaction is in accord with this suggestion, since the carbon bearing the smaller R group is always found on the metal and this reduces the steric hindrance at the palladium¹⁸. Further justification for this proposition has been found when comparing the reactivity of related palladated ligands which only differ by the nature of their Y group. In the case of NMe₂ and SMe units, a dramatic lowering of the reactivity for the thioether-containing compared to the dimethylamino ligand was observed^{34,35}. Since the *trans* effect of a thio group is much larger than that of the corresponding amino group, it can be predicted that an alkyne coordinated to the metal *trans* to the former group will be more destabilized than when it is *trans* to the latter. The insertion should be, therefore, more difficult to achieve with S-containing ligands; this is in fact observed.

The presence of bulky groups at the palladated carbon atoms has a dramatic effect on the structure of the compounds resulting from the reactions with alkynes. Thus, for benzylic carbon atoms substituted by a SiMe₃ group^{24,27}, the puckering of the resulting seven-membered ring does not allow the SiMe₃ unit to stay on the same carbon atom:



The SiMe₃ unit, therefore, experiences a 1,3 sigmatropic shift which leads to the formation of a novel η^3 -allylic ligand, for which, however, the coordination of the NMe₂ group to the Pd atom has not been unambiguously established²⁷.

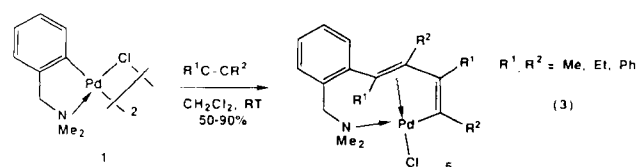
The regioselectivity of the insertion reaction with asymmetrical alkynes is quite high and, in most cases when using, for instance, alkyl 3-phenylpropynoate, only one regioisomer is found, in which the phenyl group is invariably located at the carbon atom σ -bonded to Pd²⁰. This selectivity is most likely governed by steric factors since, with diarylacetylenes substituted by two different aryl groups, no selectivity is observed. According to *Mailis'* observations¹⁸, the smallest group should be located on the palladated carbon centre. Recently, the opposite trend has been established by *Liebeskind*³⁶ for aryl ketones cyclometallated by manganese, which also leads to C–C-bond formation upon reaction with alkynes: it was found that, with alkynes substituted by two groups of different sizes, the less hindered C atom has a marked tendency to stay away from the metal during the insertion process. A hypothesis to explain this different regioselectivity is that the alkyne is activated in an axial position with respect to the plane containing the cyclo-

manganated unit. Some kind of interaction between the alkyne substituents (such as an alkoxycarbonyl group) and Mn might occur prior to insertion, to direct the manner of the addition.

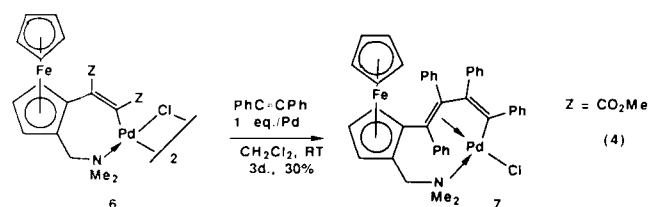
Reactions with mono-substituted alkynes or acetylene itself are not clean and lead to untractable polymeric materials^{29,39}. This is in marked contrast to the results reported for Mn complexes, for which the reactions with HC≡CR are possible, leading, however, directly to the organic products (see below)³⁶.

1.2. Insertion of two alkynes. Synthesis of palladocyclic compounds having 8 or 9 atoms within the organometallic ring

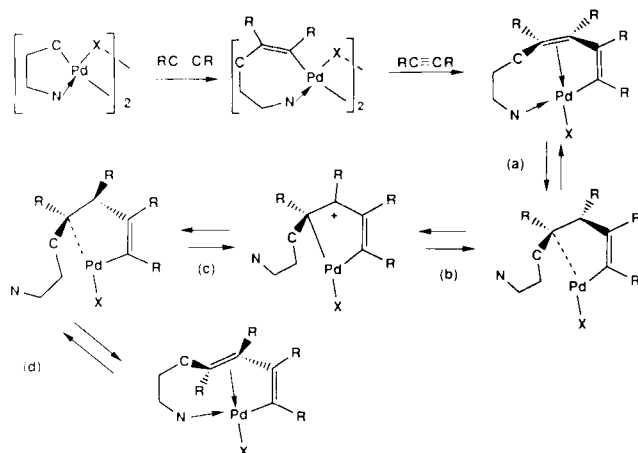
The reactivity of the Pd–C bond of some cyclopalladated compounds towards alkyne insertion is sometimes far too high to allow the isolation of the monoinserted products described in the previous chapter and a compound resulting from bisinsertion of the alkyne is obtained directly^{19,32}. This occurs more readily with electron-rich acetylenes, such as 3-hexyne⁴⁰, or diphenylacetylene¹⁹.



In these cases, attempts to trap the mono-insertion intermediate by adjusting the stoichiometry led only to mixtures of the starting material and the di-inserted products²⁰. It appears, therefore, that the reactivity of the Pd–C bond of the mono-insertion compounds **2** obtained with these electron-rich alkynes is much higher than that of the starting dimer **1**. The compounds formed via reaction **1** usually lead to insertion of a second alkyne, the structure of the resulting compound being obviously analogous to that observed in the direct double-insertion reaction **3**²⁰. There are cases, however, where this latter reaction is not possible because the resulting compound contains only the second type of alkyne. This suggests that insertion of the first alkyne (as in reaction (4)), might be reversible affording the starting material which then reacts preferentially with the second alkyne to lead to a bisinsertion reaction⁴¹:



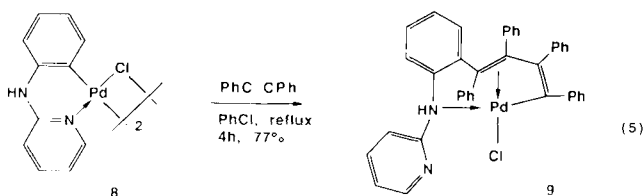
The structures of these compounds containing nine-membered rings invariably show the same feature: the butadiene C₄ chain which links the previously palladated carbon atom and the palladium atom has a "*trans + cis*" type structure, as shown in several compounds fully characterized by X-ray diffraction studies^{19,40,42,43,44}. Thus, the vinyl group that is immediately adjacent to the palladium atom has a *cis* configuration, whereas the second vinyl group has *trans* geometry. Isomerisation from *cis* to *trans* of the latter vinyl group could be rationalized via a metallo-cyclic flip, analogous to that proposed by *Mailis* in related systems⁴⁵:



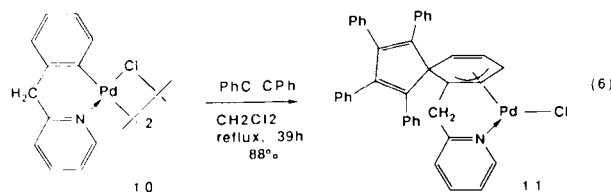
Scheme 5

According to *Maitlis*, isomerisation around the C=C bond should be induced by slight steric repulsion between the R substituents at step c of Scheme 5. This is, however, not completely satisfactory since very often the "C" group and the two R groups have similar steric requirements (they may all be phenyl units). The driving force for the process could, thus, be found in the conformation of the initially formed nine-membered ring with the four R groups *cis* to each other. Molecular models of this *cis* arrangement suggest that the C=C unit (that should be η^2 -bonded to Pd) is not ideally located with respect to the metal, so that it does not allow good overlap of the π orbitals of the olefin with the $d\pi$ orbitals of the palladium atom. The stabilisation of the palladium is, therefore, smaller than for the isomer having the "trans-*cis*" conformation. This driving force is, however, not sufficiently strong to prevent this process being reversible, as will be seen later for some depalladation reactions of compounds having two alkynes inserted into the Pd-C bond (see Section 2.2).

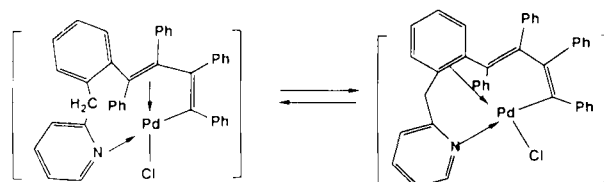
With starting materials having an extra heteroatom within the palladocyclic unit, this heteroatom is often coordinated to the metal after insertion of two alkynes. This has mainly been encountered with starting materials in which the palladocyclic unit contains a six-membered ring [see ligands (j), (k), (l) or (p) of Table I]³²:



It appears from this latter example that there is some tendency to avoid the formation of ten-membered rings. This behaviour was further illustrated through other related six-membered cyclopalladated compounds lacking a second coordinating group within the metalocyclic unit, such as the 2-benzylpyridine ligand³⁰:

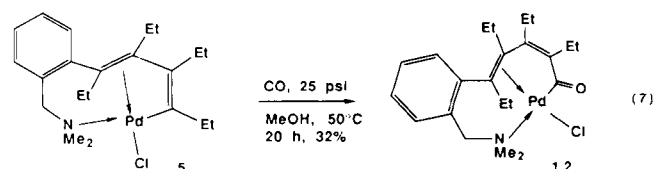


In this reaction, the two alkynes that have been added to the starting material have undergone ring contraction, leading to a spirocyclic junction between the formerly palladated aryl ring and the new cyclopentadiene ring. This can be explained by the geometry within the hypothetical ten-membered ring that would have resulted from double insertion of the alkynes in the Pd-C bond of the palladated benzylpyridine compound if the stabilisation of the Pd atom does occur through η^2 coordination to the metal of a C=C bond, as for the related nine-membered rings shown in compounds **5**, **7a** or **9**. Molecular models show that interaction between the C=C bond adjacent to the benzyl ring and the Pd atom is almost impossible, but that an interaction between one C=C bond of the aryl ring and the palladium atom is more likely to occur, as depicted below:



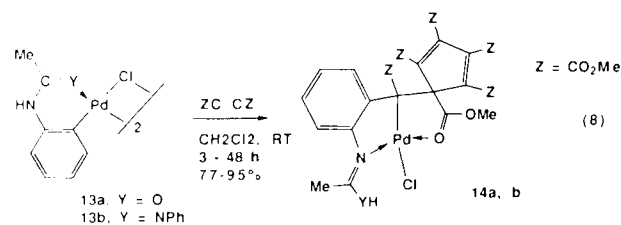
Rearrangement could then take place through nucleophilic attack of the palladated carbon on the aryl ring, that has now become electrophilic through its interaction with the Pd atom. This then leads to formation of the spirocyclic unit of the final product³⁰.

The reactivity of the novel organometallic units which were obtained by insertion of two alkynes will be discussed later. However, the reaction with CO of a related dimethylbenzylamine derivative **5** that led to a stable acyl ligand is another illustration of some kind of strain that also exists within the butadienyl unit η^3 -bonded to Pd⁴⁰:

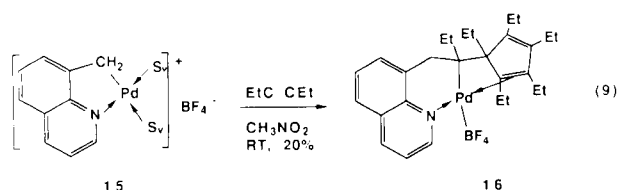


1.3. Insertion of three alkynes. Synthesis of cyclopentadienyl units by ring contraction

The reactions of electron-poor alkynes, such as dimethyl acetylenedicarboxylate, very often lead to the insertion of three alkynes into the Pd-C bond³⁰. The structure of the resulting compounds invariably contains the same C₅ cyclopentadienyl unit, as shown in the following example³²:



Coordination around the palladium atom may be completed either by one of the substituents of the alkyne (as above, where one oxygen atom of the ester groups also coordinates to Pd) or by one C=C bond of the C₅ ring unit, as for the compound obtained with 3-hexyne⁴⁶:



The geometry of these compounds is akin to that found earlier by *Mailis* when studying the oligomerization of alkynes with Pd–Cl- or Pd–aryl-containing complexes¹⁸. The likely reaction path for the formation of these species also involves, as for the synthesis of the spirocyclic compound seen in the previous section, nucleophilic rearrangement of the triply inserted alkyne, leading to ring contraction of the new organopalladium compound.

No further insertion has been observed at the new Pd–C bond thus formed, probably because the coordination site *cis* to this palladated carbon atom is no longer available for coordination of an alkyne. However, it has been mentioned several times that polymerization of alkynes can occur in these reactions, usually leading to untractable polymeric material²⁹.

2. Demetallation of the organopalladium compounds resulting from alkyne insertion into the Pd–C bond of cyclo-palladated compounds

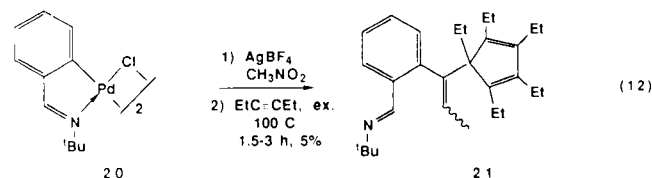
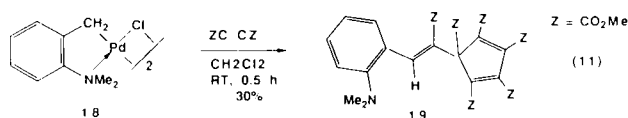
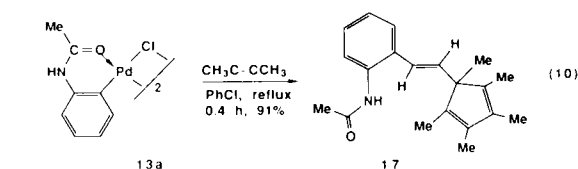
Most of the compounds described in the previous sections are quite stable, especially towards thermal decomposition. It was shown, however, that the reactivity of the organopalladium compounds can be dramatically increased by using their cationic derivatives instead of the chloride-substituted compounds. The results of this simple change in the coordination sphere of the metal are two-fold: (i) it enhances the reactivity of the Pd–C bond towards any kind of insertion and (ii) it significantly lowers the thermal stability of the new compounds. In the present study, the abstraction of the halide by a silver salt allowed the observation of several types of rearrangements of organopalladium compounds.

Another efficient way of activating palladium compounds is to use their iodide complexes. However, in this case, the substitution of iodide often has a side effect since depalladation of the organopalladium compounds occurs with some decomposition of the resulting organic moiety.

2.1. Formation of alkenes

In some cases, the above reactions do not give rise to the formation of organopalladium compounds that can be isolated. Examples of such cases are given below, where this occurs after tri-insertion of the alkyne^{32,47,48}.

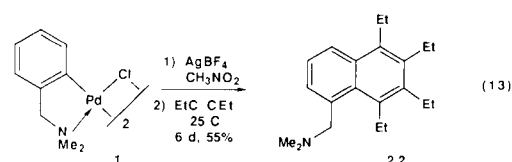
This type of reaction takes place when β elimination is possible after insertion of the alkyne. This occurs either with alkynes substituted by alkyl groups or with cyclopalladated



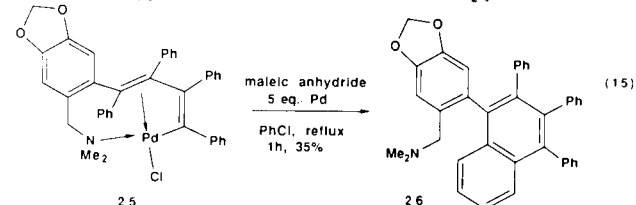
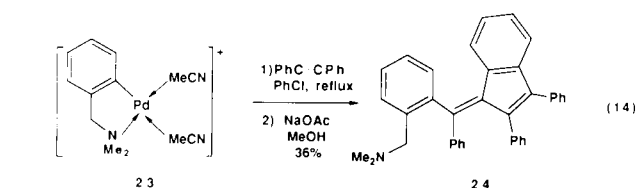
ligands in which the palladated carbon atom bears hydrogens. These are, however, marginal cases that are not often encountered. An easy way to circumvent this should be to adjust the Pd–alkyne stoichiometry so that no multiple insertion can take place, although we have seen previously that this is not always an efficient method to prevent polyinsertion of alkynes.

2.2. Formation of carbocyclic compounds. Annulation of aryl rings

One rearrangement pathway for compounds obtained by polyinsertion of alkynes leads to an important class of compounds (after depalladation) in which an aryl ring has been annulated, thus forming a new carbocyclic unit. This reaction can take place either at the palladated aryl ring⁴⁸ (Eqn. 13) or at an aryl substituent of the alkyne that has



been used to form the new organometallic species. Two different cases have been found for diphenylacetylene^{40,43,47} (see Eqns. 14 and 15).

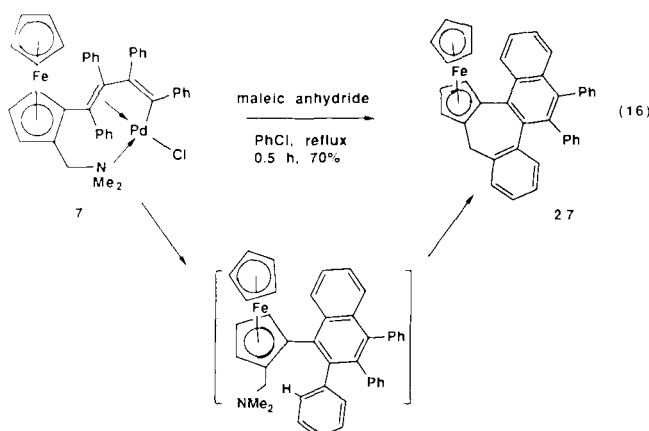


Thus, either a fulvene **24** or a naphthalene unit **26** has been formed, depending upon whether annulation has taken place at the *ortho* position of the phenyl group of the C₄Ph₄ unit located at the carbon α or β to the benzylamine ligand, respectively. These two latter compounds obviously arise from the same doubly inserted intermediate, *i.e.*, in which the new C₄ chain already has its "*trans + cis*" structure, as depicted in reaction 3. More surprisingly, the annulated compound obtained with 3-hexyne can also be formed via the same isomeric species that was isolated and converted to the cation; nevertheless, the yield of the resulting annulated compound is then significantly lower (*ca.* 20%) than for the direct reaction with the cationic non-inserted palladium material⁴⁰. This result strongly suggests, however, that isomerisation of the doubly inserted product from

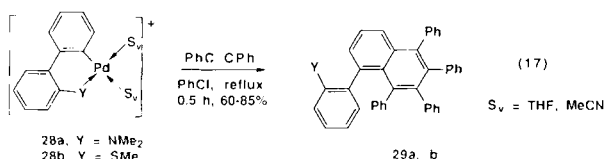
the "cis + cis" to the "trans + cis" situation must be reversible, since it is only the first isomer that leads to the annulated product.

The role of maleic anhydride as an activating ligand in reaction 15 is not yet fully understood. It might play the role of an electrophilic ligand which could displace the NMe_2 as well as the $\text{C}=\text{C}$ bond coordinated to the metal in such a way that the geometry of the palladated ligand is completely disturbed compared to that in the cationic complex. Therefore, the de-palladation reactions follow different routes leading to either a naphthalene or a fulvene unit via the annulation of two different aryl rings.

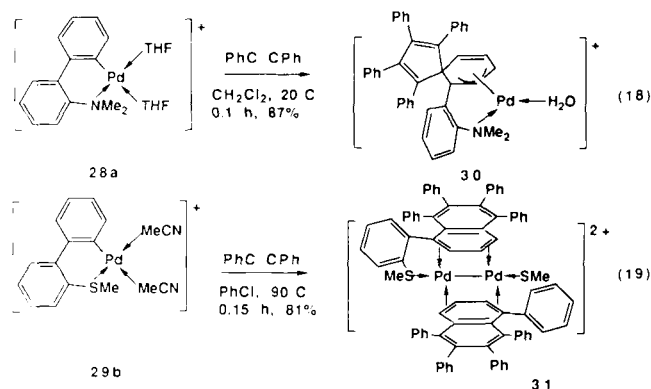
Double annulation of aryl rings has also been observed with cyclopalladated ferrocene upon reaction with diphenylacetylene⁴³:



In the final product, the NMe_2 group has been displaced by another *ortho* C–H unit of a second aromatic ring, leading unexpectedly to the formation of a seven-membered carbocyclic ring. A likely intermediate has been drawn in which only the phenyl α -positioned to the Cp ring has been annulated. The lability of the dimethylamino moiety might well be related to the well established weakening of C–Y bonds α to a ferrocene unit in the presence of protons⁴⁹, which in fact are probably produced in the first annulation reaction. *Ortho*-palladated biphenyl compounds **28** stabilized by intramolecular coordination of a NMe_2 or a SMe unit lead to related reactions with diphenylacetylene when carried out at relatively high temperature³³:



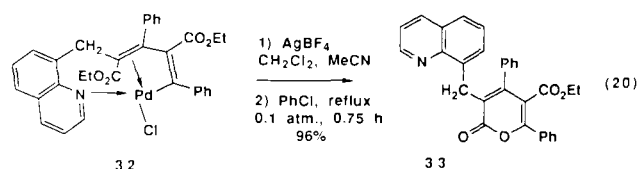
If the reactions are performed under milder conditions (*i.e.*, at room temperature in CH_2Cl_2 or at *ca.* 70°C for the NMe_2 and the SMe substituted derivatives **28**, respectively), two basically different organometallic compounds can be synthesized. These are a spirocyclic compound **30** in the case of the nitrogen-containing complex and a dimeric ($\text{Pd}(\text{I})$) species **31** in the case of the palladated thioether. Both compounds were obtained almost quantitatively and they both led to organic annulated compounds upon thermal rearrangement. It is, thus, tempting to assume that the spirocyclic compound **30** might be a kind of "Wheland-type" intermediate, which could then evolve to the annulated species via a concerted one-electron-transfer mechanism, the palladium being eliminated as $\text{Pd}(\text{I})$, which could



then be trapped by the thioether ligand and then dimerize to form the dicationic complex.

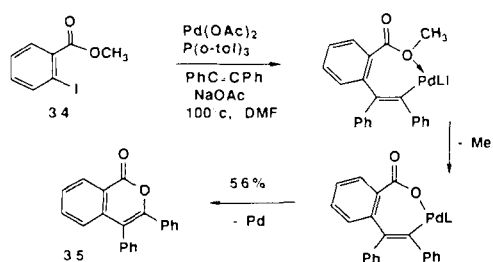
2.3. Formation of α -pyrones

Alkoxycarbonyl-containing compounds **32** led to the cleavage of an O–R bond when heated above 100°C ⁴⁷:



Better yields of the resulting pyrone **33** have been obtained by treating the cationic, cyclopalladated 8-methylquinoline compounds in the presence of two equivalents of ethyl 3-phenylpropynoate. It was also shown that, in the presence of excess pyridine at room temperature, the chloride compound produces the pyrone instantaneously and quantitatively (as far as NMR is concerned). Unfortunately, this is not an efficient way to produce the pyrone in high yields because, upon work-up of the reaction mixture, substantial decomposition occurred, most probably because of the presence of palladium(0) in the reaction mixture.

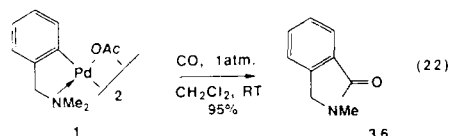
The mechanism through which the O–alkyl bond is broken is not yet clearly defined. A related result was found recently by Heck⁴⁰ when investigating the reaction between methyl 2-iodobenzoate **34** and diphenylacetylene in the presence of catalytic amounts of palladium acetate. This reaction gave good yields of 3,4-diphenyl-2,1-benzopyrone **35**, which is probably formed via a seven-membered palladacyclic ring:



2.4. Synthesis of heterocyclic compounds

It has long been recognised that the most interesting way to functionalize cyclometallated compounds is to design reactions in which the carbon–metal as well as the heteroatom–metal bonds are involved. This can be realized if the reaction leads to an heterocyclic compound as, for instance, in the carbonylation reactions of cyclopalladated

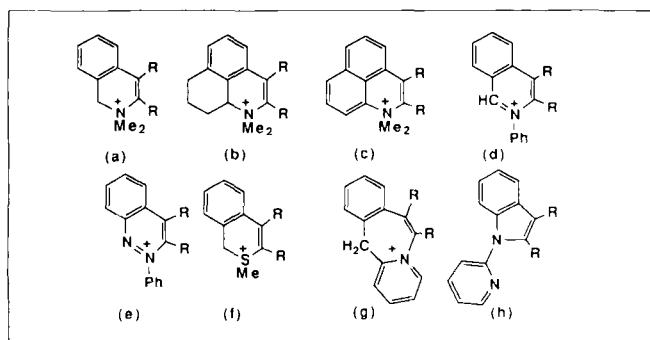
compounds that have been shown to lead *inter alia* to five-membered heterocycles, such as isoindolinones **36**^{12,50}:



Similar reactions can be performed with alkynes, one or two alkynes per metallated ligand being found in the heterocyclic compound.

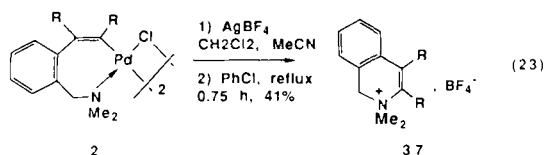
2.4.1. Heterocycles containing one alkyne per palladated ligand. Under thermal conditions, the palladium atom can be reductively eliminated from the mono-inserted cationic complexes derived from the neutral compounds discussed in the Section 1.1.

Table II Some heterocyclic compounds obtained from corresponding palladated ligands (see Table I).



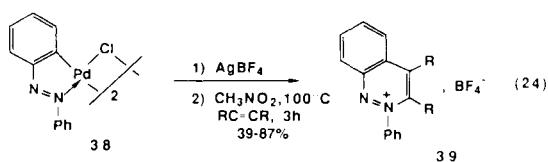
References: (a): 20; (b): 23; (c): 20; (d): 28; (e): 29; (f): 34; (g): 30; (h): 31.

Several examples of the resulting compounds are shown in Table II. For compounds (a), (b), (f) and (g), the mono-inserted complexes were first isolated and then activated by abstraction of chloride ion by a silver salt, prior to treatment in refluxing chlorobenzene, as depicted in the following example²⁰:



This latter procedure is obviously preferred when multiple insertion can occur at higher temperatures, thus pulling the reaction away from the desired products.

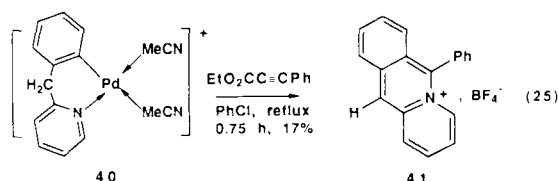
The other compounds, (c)–(e) and (h), can be made directly from the cyclopalladated cations, either made *in situ* or isolated, on which one equivalent of the alkyne per palladium atom is slowly added at temperatures around 100°C²⁹:



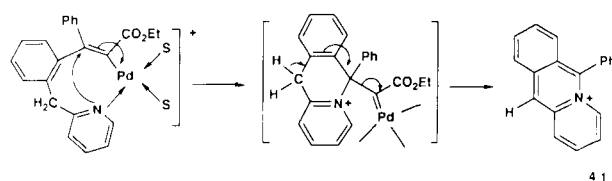
Six- or seven-membered heterocyclic rings have been synthesized by this method, depending upon whether the starting cyclopalladated unit contained five or six atoms, respectively. In the case of the 2-anilino-pyridine ligand, the product formed is a five-membered indole ring³¹. Thus, the de-palladation of the organometal-inserted compound may involve a heteroatom located within the palladocyclic unit. This reaction is obviously under thermodynamic control. In the latter case, for instance, the formation of a five-membered ring is thermodynamically favoured over that of a seven-membered ring.

Reactions with asymmetric alkynes are highly regioselective as are insertions into the Pd–C bonds described above.

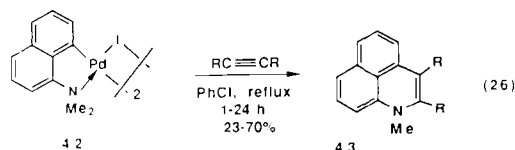
The formation of the C–N bond can be rationalized by a simple reductive elimination process⁵¹ through which the organic ligand is oxidized, while the carbon–heteroatom is produced. The higher reactivity of the cationic compounds could, therefore, be explained by increased electrophilicity of the palladium atom which is then prone to more facile reductive-elimination. However, another explanation of how these reactions proceed might be that they are akin to Michael-type additions of nucleophiles on an activated olefin. This was deduced from the reaction between the cationic palladated 2-benzylpyridine complex **40** and ethyl 3-phenylpropynoate which gave a benzo[b]quinolizinium derivative **41** in moderate yield (<20%) as the only identifiable product. No product containing an ethoxycarbonyl group could be identified⁵²:



It is clear that the depalladation reaction should proceed through de-coordination of the nitrogen atom that then is able to perform a nucleophilic attack on the palladated olefin activated by the ethoxycarbonyl group according to the following scheme:

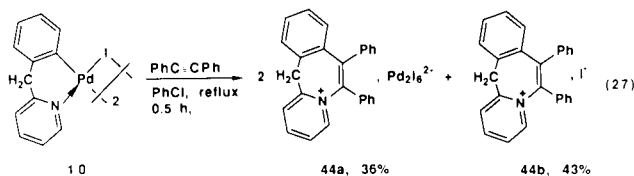


Another efficient method of synthesis of heterocyclic compounds is to use iodide derivatives, which have been shown to display thermal behaviour similar to those found for related cationic complexes. However, in this case, the formation of the product frequently occurs with some ligand rearrangement as shown below²⁰:



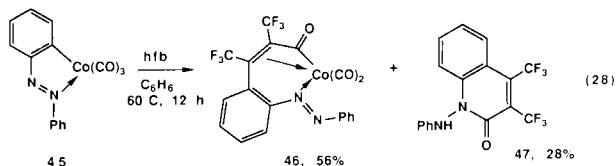
For ligands containing a NMe₂ unit, the loss of a methyl group is very often observed, taking place with formation of MeI. In other cases, some decomposition of the palladated compound occurs, leading to a cationic compound

stabilized by a $\text{Pd}_2\text{I}_6^{2-}$ unit (which most probably arises from decomposition of the starting material rather than from reoxidation of some Pd^0)^{20,30}.



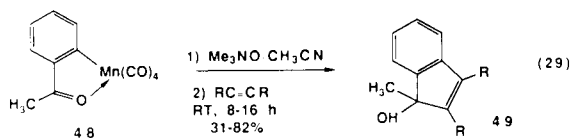
The role played by the iodide ligand in these compounds in promoting the formation of a C–N bond during depalladation of the complexes might be due to its poorer σ -donor properties compared to those of the chloride, a feature that was shown to be of crucial importance in reductive elimination processes involving palladium²⁰.

Related syntheses of heterocycles have also been performed, though less readily, with other transition metals. Thus, azobenzene, cyclometallated with cobalt carbonyl, **45**, reacts with hexafluoro-2-butyne (hfb) to give 2-quinoline derivatives **47**⁵³:

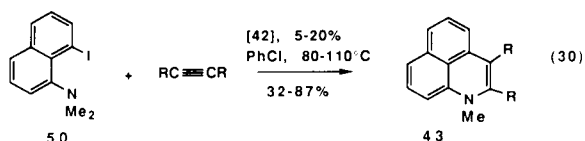


It is, however, worth mentioning that the cobalt compound **45** must be synthesized via a transmetalation reaction between cyclopalladated azobenzene and tetracarbonylcobalt anion. Moreover, this reaction is rather limited in scope since it cannot be extended to other alkynes⁵⁴.

Although they do not lead to heterocyclic compounds, cyclomanganated aryl ketones have also been shown to produce good yields of organic products upon reaction with alkynes. Like their palladium counterparts, the organometallic compounds **48** must be activated (a decarbonylating agent must be used prior to reaction with alkynes) to obtain a large series of indenols **49**³⁶:



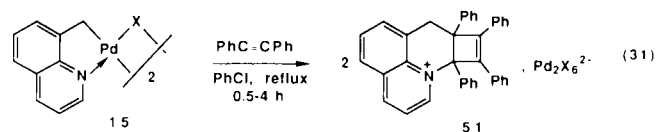
The reactions above are stoichiometric in palladium. *In-situ* reoxidation of palladium for designing catalytic procedures has not yet been successful. However, with an iodide-substituted ligand, catalytic reactions involving a large variety of alkynes are possible⁵⁵:



It is noteworthy that the only active catalyst for this reaction was found to be bis(iodo)bis[8-(dimethylamino)-1-naphthyl]dipalladium, **42**. No other classical catalyst, such as $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}[\text{PhCH}=\text{CH}-\text{CO}-\text{CH}=\text{CHPh}]_n$

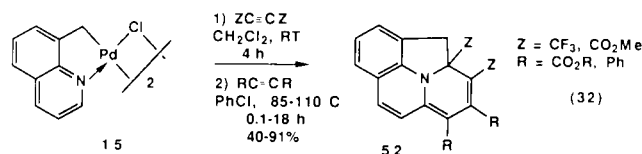
etc., could be used. This is a further illustration that any additional ligands, such as phosphine or 1,5-diphenyl-1,4-pentadien-3-one, can be detrimental for an alkyne insertion reaction into the Pd–C bond.

2.4.2. Heterocycles containing two alkynes per palladated ligand. Due to the various rearrangements observed in Section 2.2, the formation of heterocycles is less frequently observed for those compounds where two alkynes have been inserted into their Pd–C bonds. However, this has been encountered with palladated 8-alkylquinoline units where the reactions leading to two main types of products depend on the nature of the substituents of the alkynes. With diphenylacetylene, the new heterocyclic unit formed is a six-membered ring²⁰:



As in previous examples, the reaction was found to give higher yields of **51** for X = I (up to 59% based on I) than for X = Cl (<1%). Moreover, for the iodide derivative, the reaction can take place at room temperature (very slowly), whereas for the chloride derivative the reaction must take place in refluxing chlorobenzene.

Markedly different products are produced when a sequence of alkynes activated with electron-withdrawing groups and other internal alkynes were employed⁵⁶:

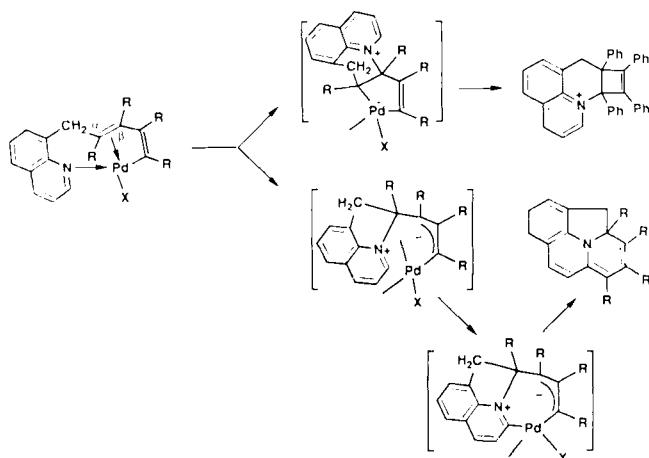


The synthesis of these [3.3.2]cyclazines (1*H*-pyrrolo-[2,1,5-*de*]quinolizines) **52** can be performed stepwise because the reaction of the chloro-bridged dimer of 8-methylquinoline with hexafluoro-2-butyne or dimethyl acetylenedicarboxylate gives high yields of the mono-inserted dimers. These dimers can then be treated with another equivalent of alkyne to give good yields of the new, polyfused heterocycles.

A similar mechanism should be operative for both reactions, assuming that they both have the same doubly inserted intermediate. A key step for determining which type of compound will then result from the elimination of palladium is the orientation of the nucleophilic attack of the pyridine nitrogen atom, which should take into account the electrophilicity of the R groups. It can take place either at the β carbon to the CH_2 group, thus leading to a six-membered ring or at the α carbon to give a five-membered ring. In the first case, reductive elimination of palladium produces a cyclobutene unit, whereas another kind of annulation reaction (most likely Pd-mediated) is observed in the second case, thus leading to a fused heterocyclic unit via C–C bond formation.

Conclusions

The reactions between cyclopalladated compounds and alkynes lead to a great variety of products, the paths followed being determined by several parameters. These include the nature of the cyclometallated ligand, the substituents on the alkynes, the stoichiometry and also the



other ligands on the palladium atom. These are all of major importance for predicting which type of compound, organometallic or organic, will be obtained. The chemo-, regio- and stereoselectivity of the reactions is quite high in most cases. Clean depalladation reactions may be induced under mild conditions leading to new pathways for the synthesis of various carbo- or heterocyclic systems. However, so far no catalytic reactions involving initial C-H activation have been designed. The crucial unresolved problem is *in-situ* regeneration of the metal in an oxidation state that allows it to metallate the heteroatom-containing ligand. Despite this limitation, this procedure might be quite useful for the synthesis of organic compounds otherwise difficult or impossible to achieve. Thus, many elemental heterocyclic units such as those found in natural alkaloids (e.g., isoquinolines) may be synthesized in this way. More detailed knowledge of the reactivity (formation of carbon-carbon and/or carbon-heteroatom bonds) and the demetallation procedures of known or new cyclometallated compounds is, therefore, still required because of the apparent complexity of the reactions observed.

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