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Selected applications to organic synthesis of intramolecular C-H activation reactions by transition metals

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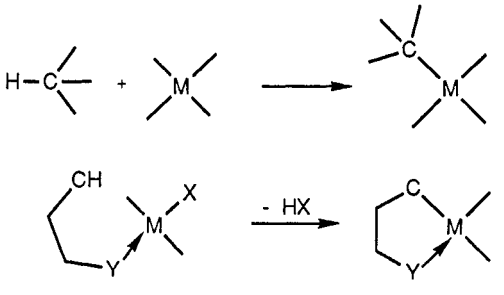
Abstract: Cyclometallated compounds obtained via the well-known intramolecular C-H activation by transition metals of N- or S- containing ligands may lead to organic heterocycles through reaction with alkynes. The mechanistic implications of the formation of both C-C and C-Y bonds are discussed. A reaction pathway involving insertion of the alkyne into the metal-carbon bond of the starting material followed by intramolecular addition of the Y atom to the resulting metallated-vinyl unit is proposed based on both the regioselectivity of the insertion and the existence of genuine isolated intermediates for the formation of the heterocyclic compounds.

INTRODUCTION

Transition metal complexes have been known to activate hydrocarbon C-H bonds for many decades and this aspect of their chemistry, whereby metal-carbon σ bonds can be formed from a C-H bond, has been thoroughly investigated. The C-H activation reaction between an organic substrate and a transition metal complex can occur either inter- (ref. 1) or intra-molecularly (ref. 2) as represented in the following scheme:

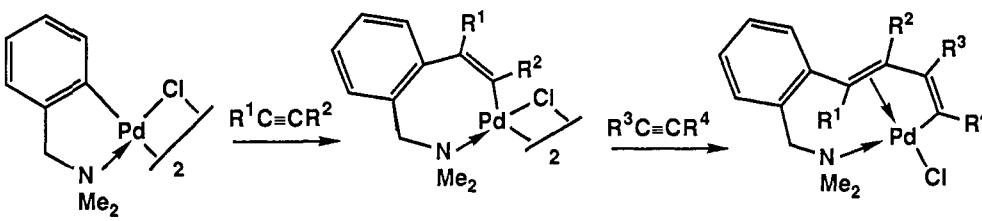
Scheme 1



The intramolecular process, also known as the cyclometallation reaction, would appear to be attracting less attention nowadays despite the fact that it was initially recognised as a major advance for the functionnalisation of unactivated C-H bonds that might be useful for organic synthesis. However, until recently no clearcut break-through has been achieved in this direction. One may however mention several interesting stoicheiometric reactions (carbonylation, vinylation, ...) of such compounds derived from the palladation of nitrogen containing ligands which have been reviewed recently (ref. 3a).

Our contribution to this field concerns the reactions of cyclopalladated compounds derived mainly from the palladation of nitrogen containing ligands. Since the latter are by far the most common ligands, any new reaction that is discovered can be tested on a large selection of starting materials.

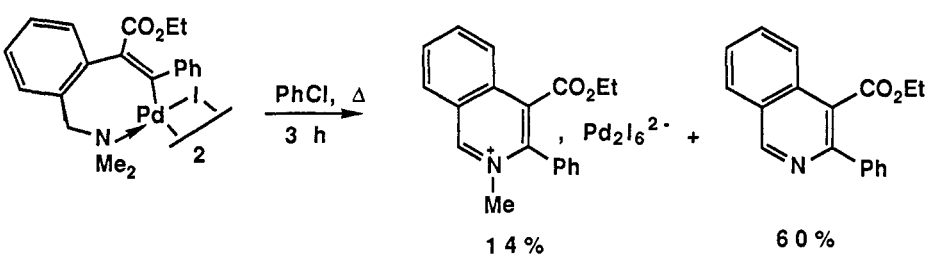
These cyclometallated compounds afford new organopalladium compounds in several instances when they are reacted with internal alkynes (ref. 4a-f). One or more equivalents of the alkyne may insert into the Pd-C bond, as illustrated in eqn. (1):



Eqn. (1)

Both types of compounds obtained in this way show interesting synthetic potentiality upon removal of the palladium centre. In this review we shall, however, only focus our attention on the reactions that might be observed when one equivalent of alkyne has reacted with the cyclometallated compounds. A more complete review has appeared recently dealing with all aspects of the reactivity of these cyclopalladated compounds with up to three alkynes per Pd atom (ref. 3b).

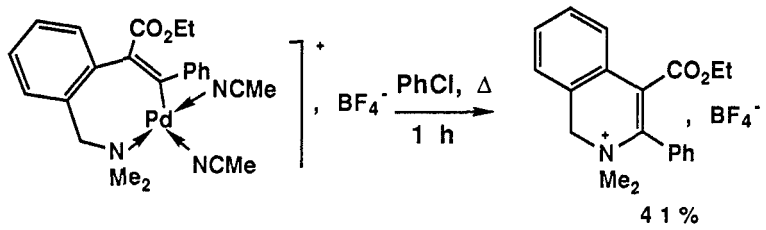
Originally these inserted compounds showed an unexpected thermal stability so that any reaction performed to recover the modified palladium-free ligand did not lead to any clean products. We found recently that the stability of these compounds is very much dependant upon the nature of the other ligands on the Pd atom. Thus we discovered that changing the chloride for an iodide, as in eqn.(2), led to a dramatic decrease in the thermal stability of the cyclopalladated compounds (ref. 4d,i). Thus, it was possible to selectively recover the modified ligands upon treatment in refluxing chlorobenzene:



Eqn. (2)

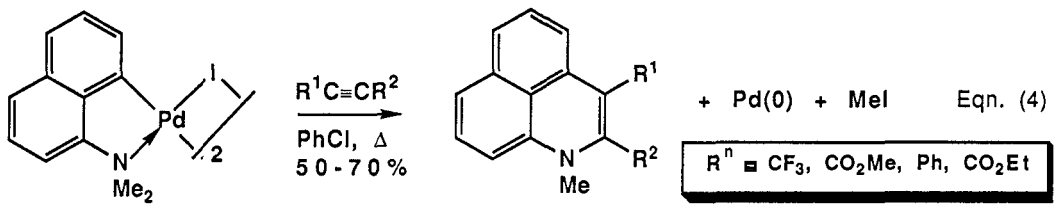
In this latter reaction partial or total dealkylation of the NMe_2 group occurs. In a related reaction it was possible to detect the presence of MeI together with amounts of CH_4 (ref. 4i). Whereas the former compound can be rationnalised by a S_N2 type of addition of I^- onto a NMe unit of an organic heterocycle, the production of methane is much more puzzling and no rational explanation for its formation has yet been found.

Another efficient way to activate the organopalladium compounds towards easy demetallation is to perform the reaction with cationic compounds (ref. 4d, f-i) so as to increase the electrophilicity of the palladium centre as shown in eq. (3). In the latter case no side reaction occurs on the NMe_2 unit, probably due the non-nucleophilicity of the BF_4 counteranion (ref. 4d). However, the scope of the reactions described in eqn.(2) and (3), *i.e.* when the cyclopalladated ligand is the N,Ndimethylbenzylamine, is rather limited. Indeed, with alkynes that are more nucleophilic than ethyl 3-phenylpropynaote (and especially with those alkynes that are substituted with electron donating groups) it is often impossible to isolate the organopalladium compound that results from the insertion of one equivalent of alkyne, the reaction leading immediately to the doubly inserted species (see eqn. (1)).



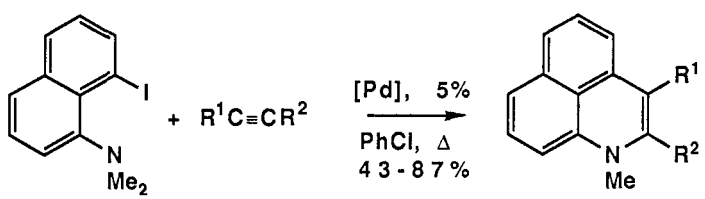
Eqn. (3)

This phenomenon does not take place with a number of other cyclopalladated compounds because they lead directly to the heterocyclic compounds, provided that the cyclopalladated starting compounds have been activated as previously mentioned (ref. 4d).



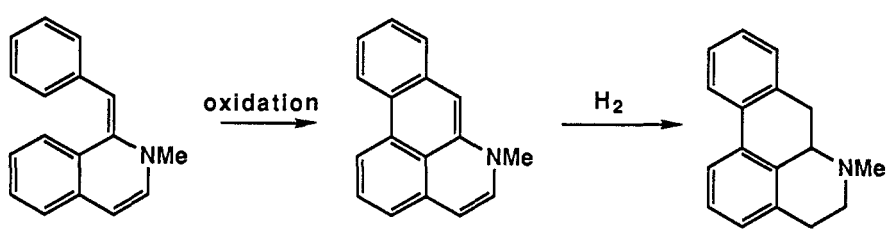
Eqn. (4)

With halide-bridged cyclopalladated compounds derived from the dimethylaminonaphthalene ligand it was very difficult to isolate an organometallic intermediate resulting from alkyne insertion into the Pd-C bond, whatever the stoicheiometry of the reaction or the alkyne used for the reaction (this occured however once with one particuliar organopalladium complex (ref.4c)). With this ligand we could perform the synthesis of N-Me benzo(d,e)quinolines using catalytic amounts of palladium. However, this was only made possible when using an iodide substituted naphthylamino ligand that reoxidises *in situ* the Pd(0) that is produced (ref. 5).

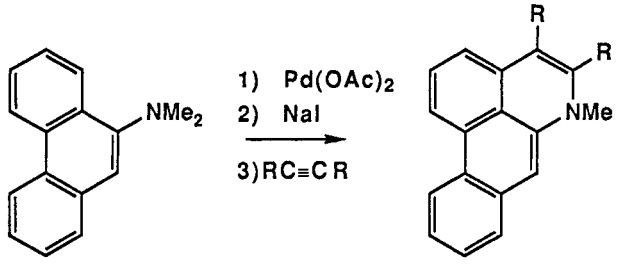


Eqn. (5)

A large variety of *internal* electrophilic or nucleophilic alkynes were found to react although the latter gave poorer yields of the quinolines. Noteworthy of mention is the fact that the only palladium catalyst that is efficient is the cyclopalladated derivative of the dimethylaminonaphthalene ligand itself. Thus the reation depicted in eqn.(5) is rather clean since no side products are formed. The structure of the quinolines produced in the previous reaction is akin to that of aporphines such as glaucine. The classical way of synthesis of these natural products involves an oxidative coupling of aromatic rings of an isoquinoline unit (ref. 6):

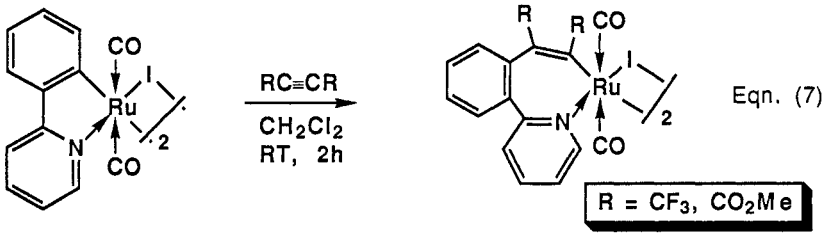


We believe that our results might provide an interesting alternative method for producing aporphine-like compounds substituted at the 2- and 3-positions by a number of functionnal groups. Recently we have found that a first step in this direction could be achieved starting with the 9-dimethylaminophenanthrene ligand (ref. 7):



Eqn. (6)

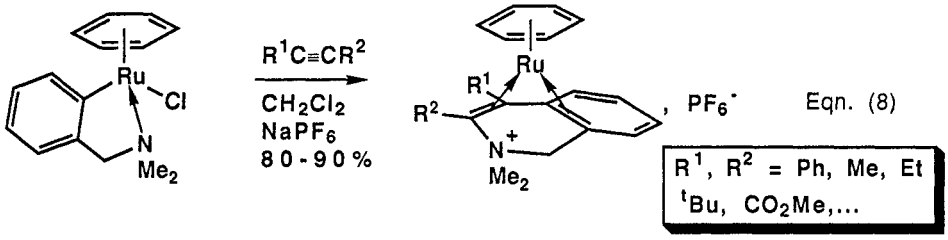
Insertion of alkynes into Ru-C bonds can also take place starting with cycloruthenated compounds. Interestingly, here too, the organoruthenium complex needs to be activated as for its palladium analogue. For example no reaction takes place between the chloride bridged cycloruthenated compound of 2-phenylpyridine with either hexafluorobut-2-yne or dimethylacetylenedicarboxylate, whereas these alkynes readily insert into the Ru-C bond of the corresponding iodide derivative (ref. 8):



Eqn. (7)

Unfortunately it has not yet been possible to demetallate the product thus obtained.

Very recently, however, we have found that related ruthenium compounds having no carbonyl present may be rather interesting alternatives to their cyclopalladated counterparts since they may lead directly to the formation of C-C and C-N bonds upon reaction with internal alkynes (ref. 9). Contrary to what was observed for palladium it is not necessary here to abstract the chloride ion from the cyclometallated species to observe heterocycle formation. As in the Pd case the ruthenium atom is reduced from Ru(II) to Ru(0), although here, the organic product remains coordinated to the metal and its recovery will probably necessitate a reoxidation of the ruthenium.



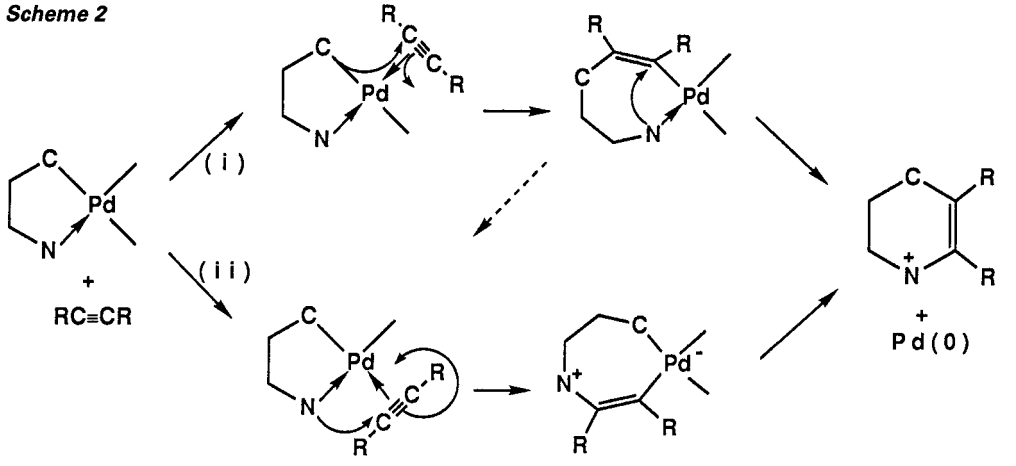
Eqn. (8)

The reaction depicted in eqn. (8) is interesting in that it establishes that ruthenium can behave in a complementary fashion to palladium. Note that with the 2-dimethylaminomethylphenyl cyclopalladated ligand the obtention of the corresponding heterocycle was rather difficult to acheive and moreover it was only possible with one given alkyne, *i.e.* ethyl 3-phenylpropynoate.

MECHANISTIC CONSIDERATIONS

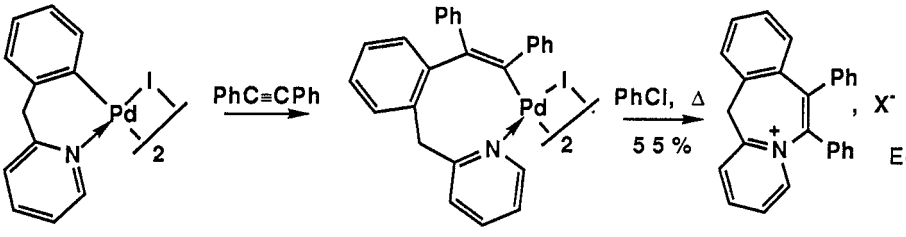
The mechanism through which the heterocycles are formed from the cyclometallated compounds can be rationalised by two reaction pathways. One may reasonably envisage that the interaction of the alkyne with the cyclopalladated compound results in its insertion into the Pd-C bond possibly followed by a reductive elimination of the metal concomitant with the formation of the carbon-nitrogen bond (route (i), scheme 2). Another plausible route involves a nucleophilic addition of the nitrogen atom onto an alkyne that is activated through coordination to the Pd centre leading to a zwitterionic organometallic species from which the reductive elimination would be more likely to occur than in the previous hypothesis (route (ii)).

Scheme 2



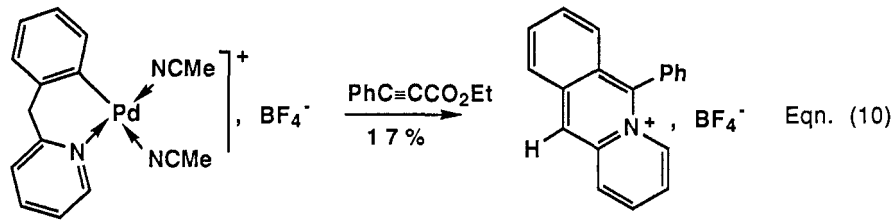
The second reaction pathway seems *a priori* less straightforward than the previous one for which we have experimental evidence for the alkyne insertion into the Pd-C bond. However, we also have some evidence that this step can be reversible (ref. 9) and thus the choice between the two pathways is less obvious than expected at first sight.

Several additional results, that shed some light upon this novel way of synthesis of heterocyclic compounds, are available. They allow us to state with more confidence that the first pathway is probably the one that is operative. Seven-membered heterocyclic rings can be formed starting with cyclopalladated compounds in which the metallocyclic unit is part of a six-membered ring. This was indeed the case with ortho-palladated 2-benzylpyridine (ref. 4e):



The dibenzazepinium derivative formed is a mixture of salts in a 4:1 ratio associated with I^- and $Pd_2I_6^{2-}$ respectively. The monoinserted organopalladium compound here must also be isolated in order to observe any formation of the heterocycle, polyinsertion of the alkyne occuring otherwise. If the corresponding cationic compound is treated with ethyl 3-phenylpropynoate under depalladation conditions (i.e. in refluxing

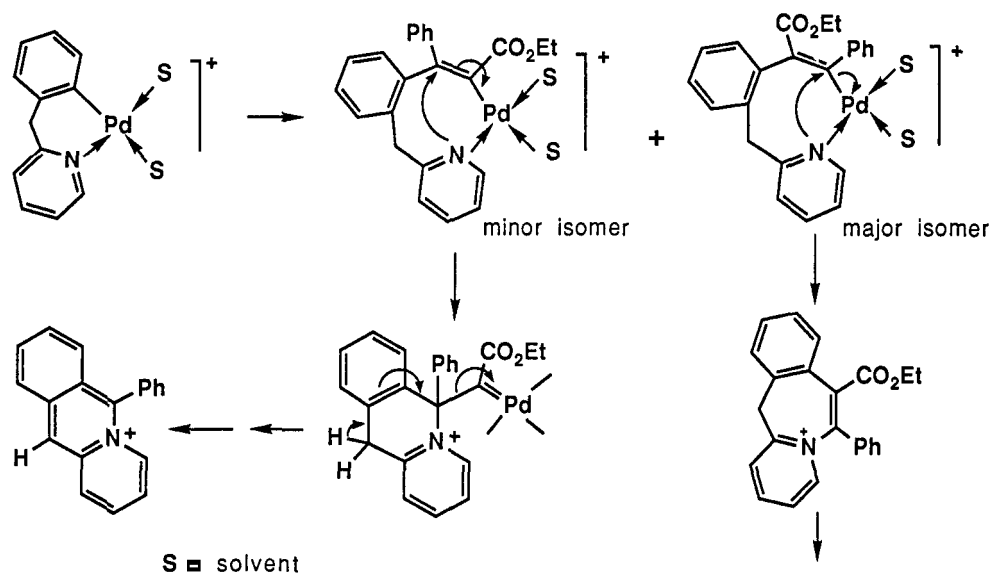
chlorobenzene) a peculiar reaction is observed, affording low yields of an heterocycle, in which no carboethoxy group is found, as the only identifiable product (ref. 10):



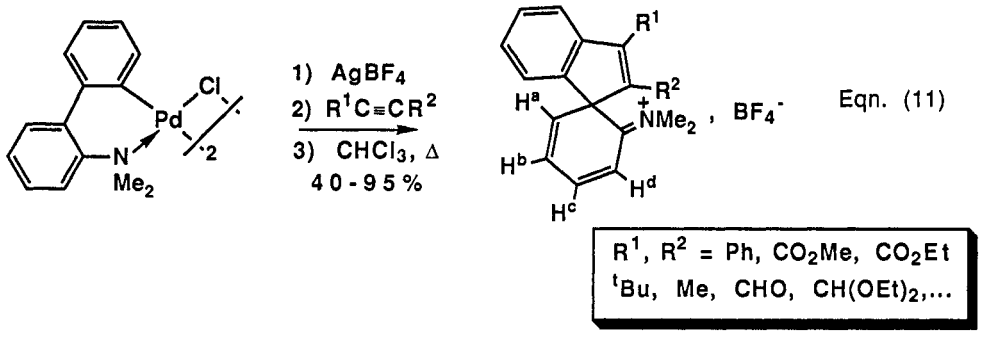
Eqn. (10)

It seems therefore that a reaction analogous to an alkyne metathesis has occured. Analysing however the yield of the benzo[b]quinolizinium salt it appears that the course of this reaction should parrallel that of the insertion of this unsymmetrical alkyne into the Pd-C bond of the cyclopalladated starting material (ref. 4e). Indeed we have shown that with this particular alkyne two regioisomers were formed through insertion, the one having the phenyl group in a remote position from the Pd centre being the less abundant. We therefore propose that the key step of the reaction is the nucleophilic addition of the nitrogen atom of the pyridine on the palladated vinyl group, the selectivity of the addition being related to that found for classical Michael-type addition of nucleophiles on activated alkenes.The formation of the C-N bond is obviously favoured because it occurs intramolecularly. The last step of the process to form the six-membered ring is somewhat unclear. We believe that it could involve the departure of a proton concomitant with the decomposition of an anionic pallacarbene whose existence has not yet been supported with experimental evidence (ref. 10). Under the reaction conditions used the seven-membered heterocycle that should be formed accordingly from the major organometallic isomer is not stable and it completely decomposes.

Scheme 3

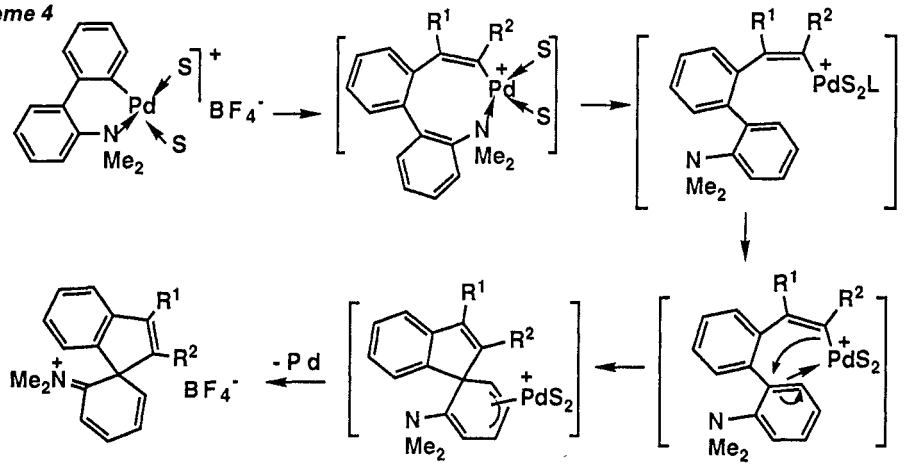


A further confirmation for the nucleophilic addition of the heteroatom onto a palladated vinyl group has been obtained from the study of two closely related compounds which only differ from each other by the nature of the coordinating group. Thus with the cyclopalladated 2-dimethylaminobiphenyl we observed the formation of a carbocyclic unit rather than an heterocycle (ref. 11) according to eqn.(11):

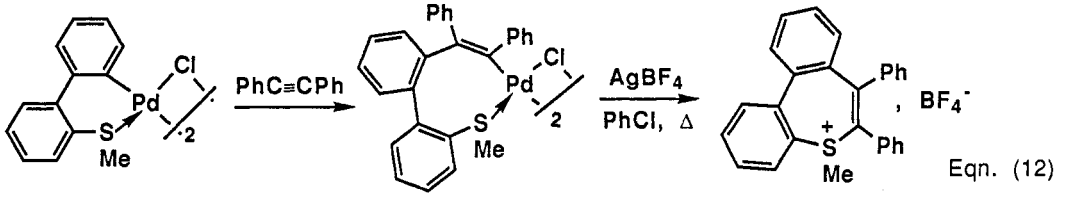


In fact this reaction provides some type of "*a contrario* "evidence for the mechanism of formation of the C-N bonds since it is clear that the NMe_2 group has a relatively poor nucleophilicity here, so that its addition onto the palladated vinyl unit is no longer possible. In marked contrast to the other reactions studied in this paper we observe now a nucleophilic addition of the palladated carbon atom on an aromatic ring which provides the spirocyclic junction. A likely reaction path is presented in scheme 4. We can prove that the decoordination of the NMe_2 unit from the Pd is easy to achieve since the monoinserted complex formed with dimethylacetylene dicarboxylate afforded with pyridine a bis ligand adduct in which the NMe_2 was no longer coordinated to Pd (ref. 11). From this observation it can be envisaged that an activation of the aryl ring occurs through interaction of one of its C=C bonds with the Pd atom. A nucleophilic addition of the carbanion on the activated aryl ring can then take place to form the spiro junction.

Scheme 4



The closely related six-membered palladocyclic ring having a thioether group in place of the dimethylamino displayed a different behaviour upon reaction with diphenylacetylene. (ref. 12)



Here the higher nucleophilicity of the SMe unit allows the formation of a C-S bond through addition on the vinyl moeity in a way similar to that observed throughout this work.

CONCLUSION

It has been shown that cyclometallated compounds display an interesting reactivity that may indeed be useful for organic synthesis. This behaviour should renew the curiosity of both the organic and inorganic synthetic chemists into this class of compounds. One has however to be aware that major problems still need to be solved such as the design of reaction systems where the metal is used as a catalyst. In this respect the regeneration of the metal in an oxidation state which will allow it to be efficient for a new intramolecular C-H activation will probably remain the main task for the near future.

Acknowledgements

I am greatly indebted to the dedicated and talented former and present students or post-doctoral fellows whose names appear in the references cited in this paper for their valuable contributions to this research. The C.N.R.S. and the E.E.C. (contracts ST2J 0090-1-F(CD) and SC1-0319-C (GDF)) are greatly acknowledged for their financial support.

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