

Some palladium-catalyzed carbon-carbon bond formation reactions

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Abstract - Some palladium-catalyzed multistep reactions, occurring in ordered sequences, are described. The initial steps consist of either oxidative addition of aromatic halides or nucleophilic attack on unsaturated substrates. Chemo, regio and stereoselective reactions can thus be achieved. Several synthetic applications are reported.

INTRODUCTION

Catalysis by transition metal complexes to effect the synthesis of organic molecules from simple building blocks has attracted the interest of several research groups for a long time. This type of molecular architecture consists of many elementary steps and modification of any of them results in new synthetic pathways (ref. 1). As in catalytic polymerization we talk about initiation (formation of a C-Metal bond) and termination (metal elimination from the organic chain) steps. The nature of the intermediate steps is quite variable, however. Different molecules and groups can be added to the initial bond and several transformations can occur before termination takes place.

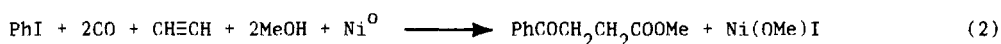
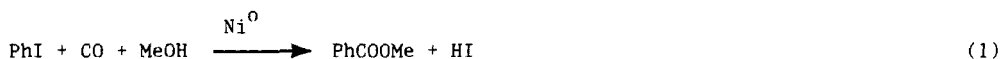
We shall focus on our recent results concerning palladium-catalyzed reaction sequences, initiated by: A) activation of aromatic compounds; B) activation of metal-coordinated unsaturated molecules.

A. ACTIVATION OF AROMATIC COMPOUNDS

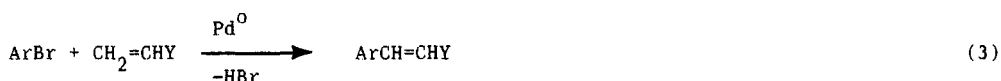
First of all we shall consider the simplified elementary step sequence: aromatic substitution (oxidative addition) / insertion(s) / reductive elimination.

Fundamentally two approaches can be distinguished in activation of aromatic compounds: 1) attack on an aryl-X bond, where X is a halide or another leaving group; 2) direct activation of an aromatic C-H bond.

Route 1 has its origin in carbonylation reactions with nickel catalysts at high pressure and temperature (ref. 2). It was not until the sixties, however, that methods working under mild conditions were reported (refs. 3, 4). Two examples are given below (eqs. 1, 2):

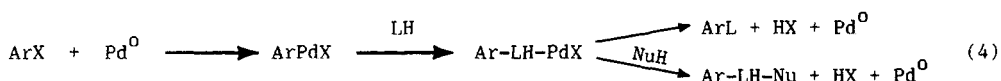


Reaction 1 was subsequently obtained with nickel catalysts also starting from the bromide (refs. 5, 6). A versatile palladium-catalyzed reaction (eq. 3), involving addition of olefins in place of carbon monoxide, was reported in 1967 (refs. 7, 8):



where Y is an electron-withdrawing group.

The reactions just shown are all based on an initial oxidative addition to palladium(0), followed by insertion and reductive elimination (eq. 4, LH = inserting molecule, NuH = nucleophile).

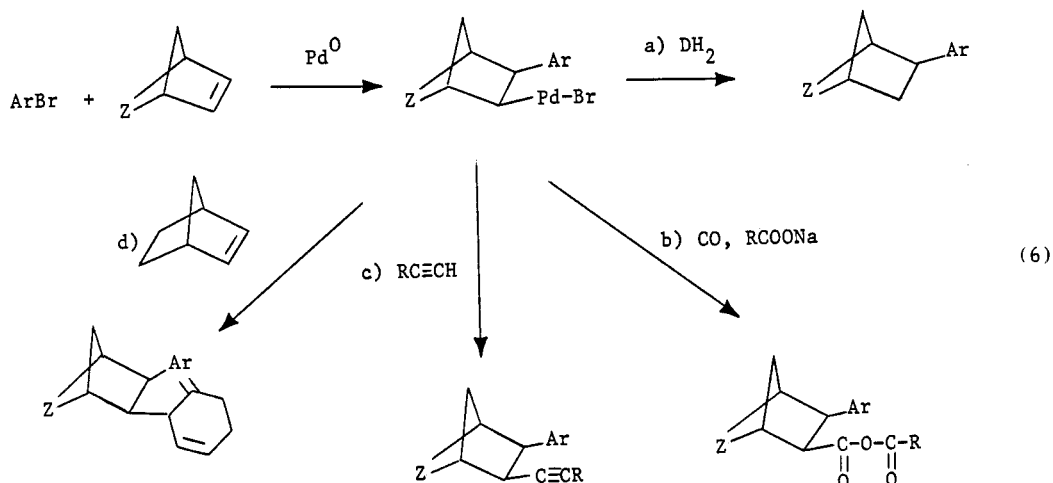


As to direct activation of an aromatic C-H bond (refs. 9, 10) in the initial step of a reaction sequence, palladium-catalysis has been reported to occur (see for example ref. 11) in the presence of reoxidants of the palladium (0) formed (eq. 5, ArH = naphthalene). The results reported here refer to catalytic C-H activation during the subsequent steps.



A1-initial attack on C-Hal bond

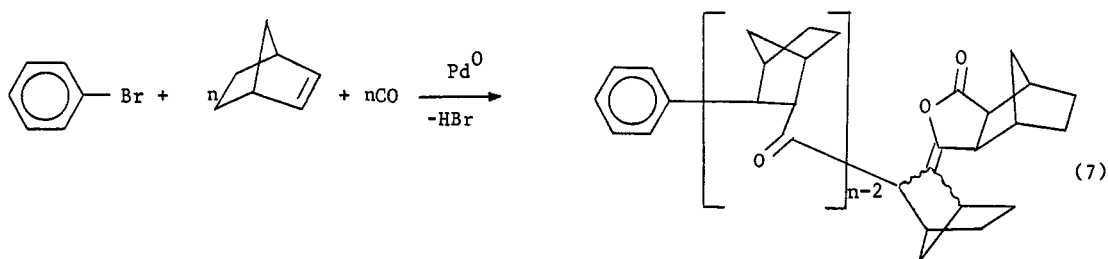
Some years ago it was observed that when reductive elimination was precluded in palladium-catalyzed reactions, the insertion process could be pushed forward until a favorable arrangement for reductive elimination was reached (ref. 12). The discovery of new elimination pathways was shown to be a major requisite to obtain new synthetic reactions. Some examples are shown below (eq. 6).



These reactions all occur under mild conditions, at ca. 80°C and are stereoselective, the *cis*, *exo* isomers only being formed.

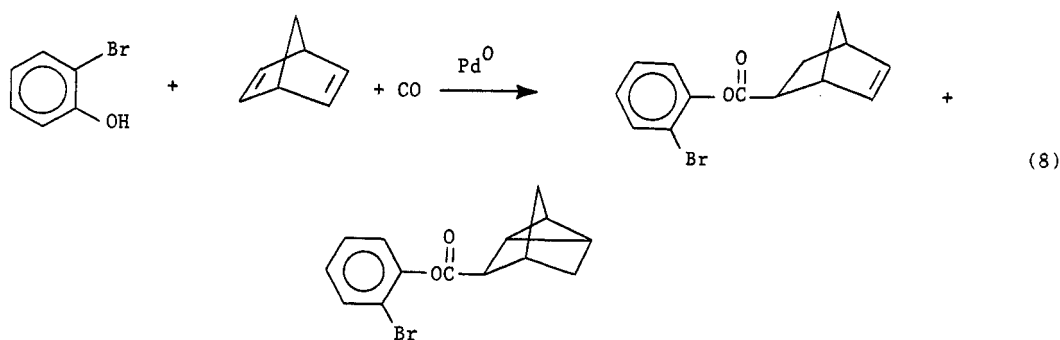
The reductive elimination steps differ from each other: in (a) a H-donor molecule DH, for example ammonium formate, cleaves the Pd-C bond, which cannot undergo hydrogen elimination (ref. 13); in (b) the acyl group, formed by further carbon monoxide insertion, is trapped by the anion of an organic acid RCOO⁻ to form an anhydride (ref. 14); in (c) the anion RC≡C⁻ replaces X in the palladium complex and then couples with the palladium-bonded organic group (ref. 15); in (d) the insertion of a norbornene molecule is followed by ring opening, which generates a palladium-carbon bond able to undergo reductive elimination (ref. 16). The reactivity of intermediates resulting from aromatic substitution and insertion can thus be finely tuned by the appropriate choice of molecules, able to lead the system to the termination step.

It is worth noting at this point that methods of the kind shown above can readily lead to polymers or copolymers. A case in point derives from way (b): carbon monoxide would react further with the olefinic double bond, were not for the efficient trapping of the acyl group by the carboxylate group (from the added salt of a carboxylic acid), which blocks the copolymerization process. The latter can be readily effected at 60–80°C and atmospheric pressure, according to *cis*, *exo* stereochemistry. A way to terminate the process (eq. 7) is provided by the formation of an exocyclic unsaturated lactone (ref. 17). This reaction liberates a proton, which can start a new copolymerization without the involvement of the aryl group.

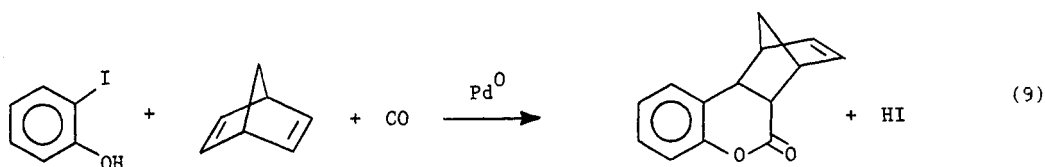


The study was carried out on oligomers in order to detect the terminal groups. Dimers could also be prepared in a similar way. Once again the discovery of a new way to effect an elementary step such as reductive elimination coincided with the achievement of a new synthetic method.

In the presence of an alcohol or of a phenol, the reaction could also be terminated at any point of the polymerization process. This suggested the possibility of turning this process into simple syntheses of cyclic compounds by introducing an *ortho* OH group in bromobenzene. The expected cyclization took place only to a limited extent, however, because of the much higher activity of the hydroxyl proton, which started a competing olefin insertion reaction. The latter was followed by carbonylation and termination by phenoxy group attack on the acylpalladium bond thus formed (ref. 18). With norbornadiene two products (bicyclic/tricyclic 5/1) were formed in 80% yield (eq. 8):

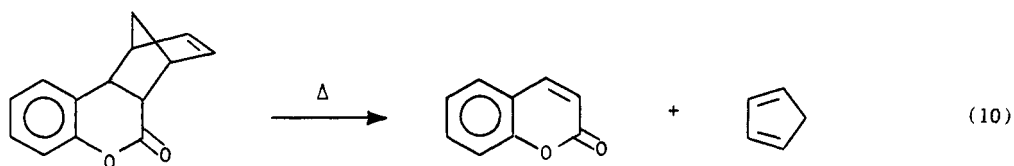


The nortricyclene formation is possibly connected with a different coordination mode of norbornadiene (bidentate vs monodentate). The desired oxidative addition of the aryl halide occurred in preference to protonation with iodophenol in place of bromophenol (60–80°C). Norbornadiene preceded carbon monoxide in the insertion sequence and the hydroxyl group completed the cyclization process (eq. 9, yield 80%) through a reductive elimination step (ref. 18).



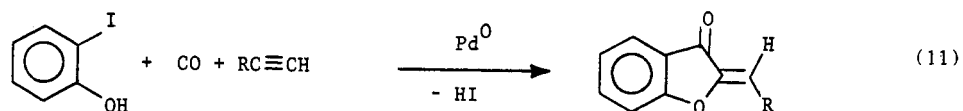
Also in this case the reaction proved to be stereoselective, *cis*, *exo* bonds only being formed.

It is noteworthy that the product formed underwent a retro-Diels Alder reaction under exceedingly mild conditions. At 150° its transformation into coumarin was complete (eq. 10).



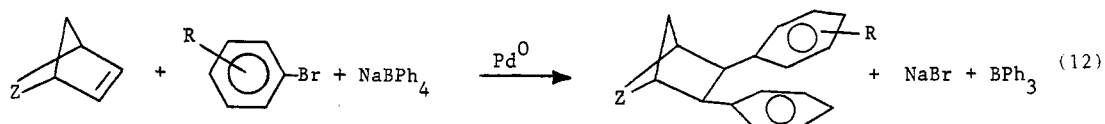
This new synthetic pathway is interesting in view of the possibility to synthesize coumarins, containing other substituents in the benzene ring. It has been shown for example that the formyl group is compatible with the reaction conditions.

The synthesis shown above essentially consists of the reaction of the phenolic ring with acetylene and carbon monoxide, the norbornadiene molecule being formally splitted into acetylene and cyclopentadiene. If, however, an alkyne is used in place of norbornadiene, the reaction takes a different course (eq. 11), this time carbon monoxide being preferred in the first insertion step (ref. 18):

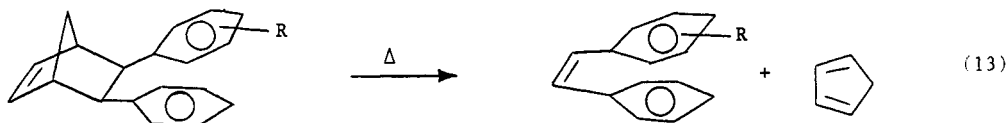


The reaction can be conveniently applied to arylacetylenes, which readily form *Z*-aurones, an interesting class of natural substances. The use of halogenophenols thus allows to obtain a wide range of products by aromatic substitution under mild conditions.

Reaction (11), as well as reaction (6, path c), involves carbon-carbon coupling with palladium-bonded alkynyl groups, formed by replacement of the halide in palladium complexes. Metathetical replacement could also be possible with other groups, provided that appropriate sources are used. The tetraphenylborate anion was found to be suitable, because it readily splits a phenyl group. In the presence of norbornene or norbornadiene a new high yield (up to 95%) synthesis of diaryl-substituted norbornanes or norbornenes (eq. 12) was thus found (ref. 19).

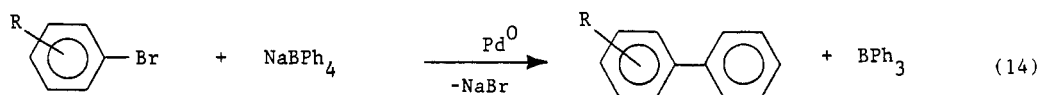


This is again a one pot stereoselective (*cis*, *exo*) reaction, which allows the introduction of two aromatic groups in adjacent positions of norbornene or norbornadiene. The reaction products with $Z = \text{CH}=\text{CH}$ can be subjected to thermolysis to give stilbene derivatives, containing different aromatic groups (eq. 13):



Although other organometallics can be used for reaction (12) (ref. 20), sodium tetraphenylborate has the advantage of being a commercial reagent and a very effective phenyl transfer agent.

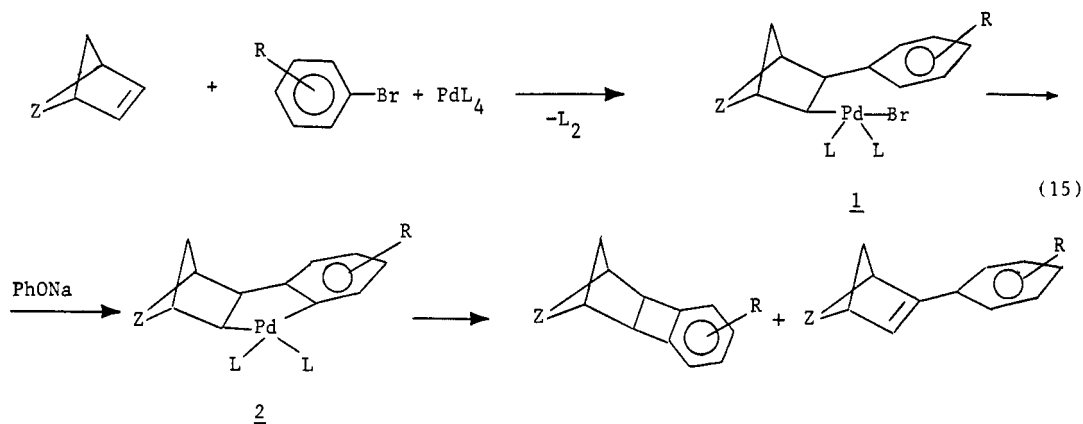
These properties can also be utilized to obtain the catalytic coupling of two aromatic moieties through aromatic substitution (oxidative addition) / reductive coupling (ref. 21). This reaction also occurs as a secondary one along with reaction (12) (eq. 14):



Triphenylborane further decomposes, however, giving homocoupling of the phenyl groups as a side reaction (ref. 21).

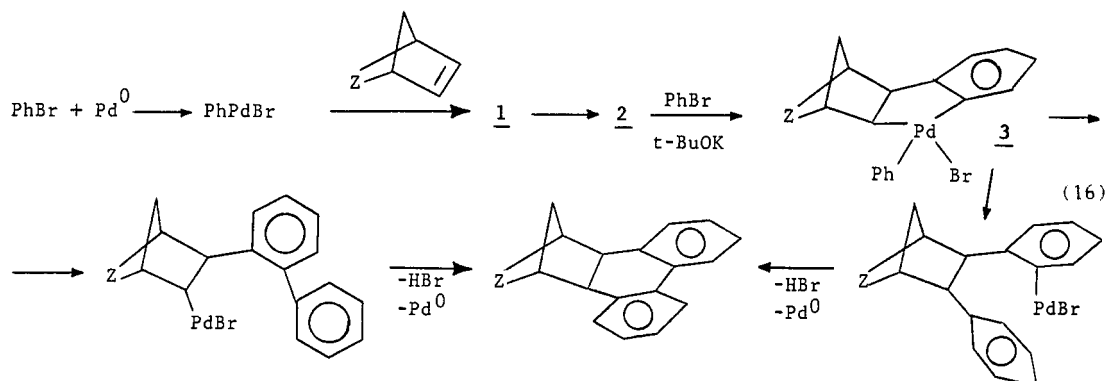
A2-activation of aromatic C-H bonds

Another reaction sequence, which not only involves aromatic substitution through activation of an aromatic C-Halogen bond but also activation of an aromatic C-H bond, is the following: aromatic substitution (C-Hal activation) / insertion / aromatic substitution (C-H activation) / reductive elimination. Although stoichiometric reactions of aromatic compounds were described several years ago (refs. 22, 23) and intramolecular stoichiometric reactions, leading to metallacycles, were also reported later (ref. 24), it was not until 1982 (ref. 25) that intramolecular carbon-carbon coupling reactions were described, occurring catalytically without the need for additional oxidants to reoxidize the metal. The simplest of these reactions (ref. 26), is shown below (eq. 15):

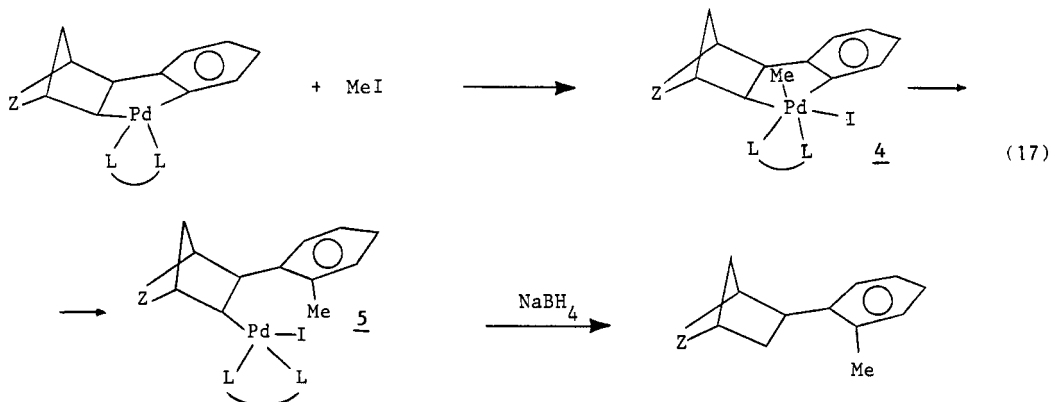


These reactions involve the intermediacy of palladacycle 2 (L = triphenylphosphine). Cyclization of 1 to 2 was shown to be an electrophilic process (ref. 27).

Beside giving the compounds of eq. (15), complex 2 is able to undergo a wide range of reactions, involving further oxidative addition to palladium (II) with formation of palladium (IV). Eq. (16) corresponds to the sequence: aromatic substitution (C-Hal) / insertion / aromatic substitution (C-H) / aromatic substitution (C-Hal) / reductive elimination / aromatic substitution (C-H) / reductive elimination (ref. 28). This also is a catalytic reaction, involving changes in the oxidation state of palladium from 0 to II to IV and then back to II and 0.



Complex 1 was recently prepared using phenanthroline as ligand and its cyclization reaction in the presence of sodium phenoxide was followed by n.m.r. (ref. 29). Complex 2 (Z = CH₂CH₂) was isolated and fully characterized. Further reaction with methyl iodide was also followed by n.m.r. and the palladium complex 4 could be isolated. Furthermore, a selective methyl migration on the aryl group was observed (eq. 17):

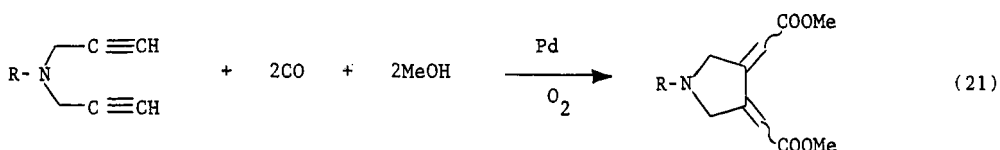


In this case the elementary step sequence is: aromatic substitution (C-Hal) / insertion / aromatic substitution (C-H) / aliphatic substitution (C-Hal) / reductive elimination / reductive elimination (the last step being obtained by borohydride addition).

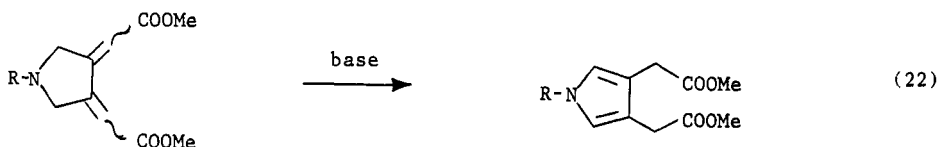
The presence of the oxazoline compound further supports the hypothesis that the amido group assists the carbonylation process, because it implies that this group was in the correct position for a chelating arrangement.

The ring closure process, observed with dialkynes, must also be an assisted one, because of the presence of two triple bonds able to chelate to the metal. In addition the ring closure and the subsequent steps help pushing the reaction to right. Other factors, favoring a suitable conformation of the diyne molecules to achieve chelation, are the presence of geminal groups in alpha to the triple bonds or the presence of bulky groups, bonded to a central nitrogen atom (amides, carbamates R-N).

Following these concepts an efficient procedure to effect bicarboxylation of diynes (yields up to more than 90 %) was recently worked out (ref. 39), based on the use of a very simple catalytic system, palladium on carbon and potassium iodide in the presence of a gaseous mixture of carbon monoxide and air. Alcohols or aqueous solutions were used as solvents at room or slightly higher temperature. The synthesis of pyrrolidine derivatives is reported here (eq. 21):

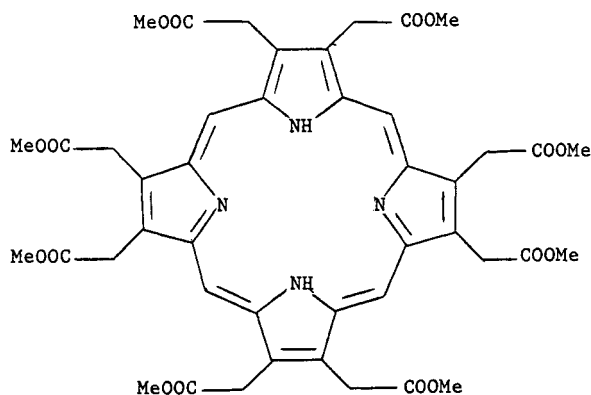


The products are obtained as E,E (predominant), E,Z and Z,Z (minor amounts) isomers. Several transformations, such as Diels-Alder-type reactions can be obtained. In particular these compounds are precursors of a to our knowledge still unknown term of the pyrrole family, pyrrole-3,4-diacetic acid. Isomerization in the presence of bases readily converts the pyrrolidine derivatives into pyrrole derivatives (eq. 22):



Isomerization can also be carried out concomitantly with saponification of either the ester or the amido group or of both.

Having positions 2 and 5 free these pyrrole derivatives lend themselves to numerous transformations, ranging from polymerization to condensation. The preparation by literature methods (ref. 40) of a porphyrin, containing eight acetic functionalities (ref. 41), which had been previously prepared by a more laborious procedure (ref. 42), is worth mentioning:



Some higher esters of porphyrinoctaacetic acid, which can be prepared directly from dipropargylamine derivatives by means of the just reported procedure, have been recently shown to display properties of discotic liquid crystals (ref. 43). It should be pointed out in this context that the emerging area of new materials will undoubtedly benefit from new methodologies which make accessible compounds with unexpected properties.

Acknowledgement

This work has been supported by Consiglio Nazionale delle Ricerche.

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