

Selective organometallic syntheses from molecular pools*

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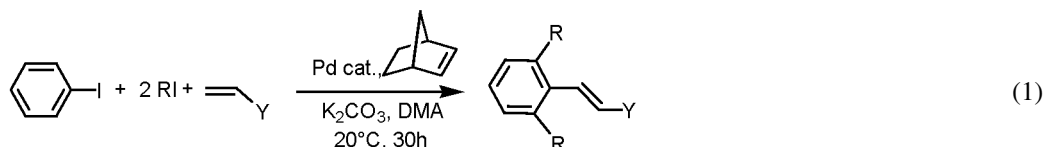
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Abstract: A new methodology is described, consisting of the use of molecular pools in palladium-catalyzed sequential processes occurring under mild conditions with high selectivity. These reactions involve palladacycle formation from aryl iodide, palladium, and norbornene, the latter behaving as a second catalyst that is first incorporated into the metallacycle and expelled at the end of the process. Selective alkylation or arylation of the arene nucleus occurring by oxidative addition/reductive elimination of palladacycles are coupled, after norbornene expulsion, with C–H or C–C bond-forming reactions such as hydrogenolysis, olefin insertion, arylboronic coupling, etc. The variety of possible combinations offers a powerful tool for the selective synthesis of unusual and not readily accessible aromatics.

During the last decades, organic chemistry has immensely benefited from the possibility to coordinate organic molecules and groups specifically to metal complexes and to obtain highly chemo-, regio-, and stereoselective reactions in sequence starting from complex mixtures. We have studied new ways to react these molecular pools by means of palladacycles, which can be formed and dismantled in catalytic processes occurring selectively under mild conditions.

SELECTIVE ALKYLATION OF AROMATICS COUPLED WITH OLEFIN INSERTION

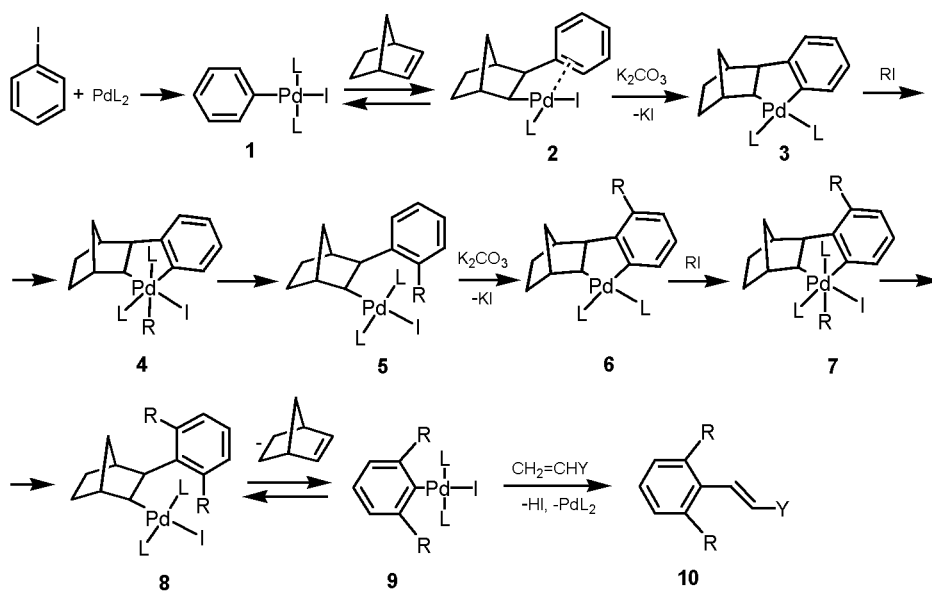
Our starting point was the following reaction (eq. 1).



Aromatic and aliphatic iodides react at room temperature with a terminal olefin in the presence of two catalysts, palladium(0) and norbornene, to give an aromatic compound selectively substituted at the 1, 2, and 3 positions. The reaction allows the preparation of a wide spectrum of 1,2,3-trisubstituted arenes not easily accessible by conventional methods.

Scheme 1 shows the course of the catalytic reaction as proved by isolating most of the relevant species involved and by studying the single steps through stoichiometric reactions. The reader is referred to our previous papers for a detailed interpretation [1,2].

*Lecture presented at the 11th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-11), Taipei, Taiwan, 22–26 July 2001. Other presentations are presented in this issue, pp. 1–186.



Scheme 1

It has to be observed that the initial norbornene insertion into **1** and the consequent palladacycle **3** formation play the role of making the selective *ortho* alkylation possible (steps **3–5** and **6–8**). Being liberated in the following deinsertion step (from **8** to **9**) norbornene thus acts as a catalyst, although an excess is necessary to push the reaction toward the desired species.

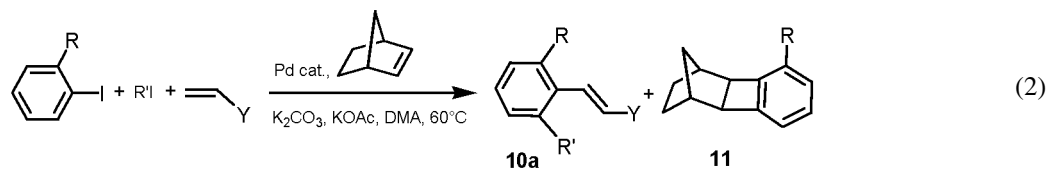
The resulting complex **9** is able to insert a terminal olefin in a Heck-type reaction, which affords the final product **10** along with the palladium(0) catalyst.

The most important features of the entire catalytic cycle can be summarized as follows: (a) alkyl groups are found exclusively in the *ortho* position shown, and they do not undergo any skeletal isomerisation as in the case of the conventional electrophilic aromatic substitution promoted by Lewis acids; (b) no β -hydrogen elimination occurs from the palladium(IV)-bonded alkyl group; this fact is probably due to an unfavorable geometry; (c) the type of organic halide undergoing oxidative addition is controlled by palladium oxidation states; under the conditions adopted only the aryl iodide reacts with palladium(0) while, on the contrary, only the alkyl iodide reacts with palladium(II); (d) olefin insertion is controlled by steric effects: norbornene selectively inserts into the unsubstituted arylpalladium bond but only the terminal olefin is able to insert into the *o,o'*-disubstituted arylpalladium bond.

We wondered whether this reaction could be extended to the selective introduction of different alkyl groups in the *ortho* positions of an aromatic ring. Using two different aliphatic iodides, we were not able to achieve this goal, however, because the system was not able to discriminate between the two aliphatic halides efficiently. We thus used an *ortho*-substituted aryl iodide as the starting material. No reaction occurred, however, under the conditions previously utilized because the first step, consisting of the oxidative addition of the aryl iodide to palladium(0), and the subsequent norbornene insertion are, at room temperature, much slower than the corresponding ones with unsubstituted aryl iodides.

To favor these two steps, we increased the temperature and added potassium acetate, which is known to assist the insertion reaction. We were pleased to observe that under the conditions chosen the reaction proceeded to form the expected palladacycle. The latter, however, readily underwent reductive elimination to *exo*-hexahydromethanobiphenylene, which is favored by the increased temperature. To contrast this undesired reaction, we added a large excess of the alkyl iodide, which attacks the metallacyclic palladium to form a palladium(IV) complex. In this way, we succeeded in obtaining a satisfac-

tory reaction: compound **10a** (eq. 2; R = Et, R' = *n*-Pr, Y = CO₂Me) was obtained in 71% yield with almost complete suppression of compound **11** (R = Et) [3].

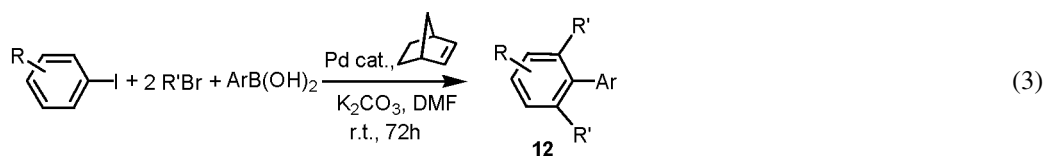


An interesting extension of reaction 2 to the formation of a condensed ring was recently reported by Lautens [4].

SELECTIVE ALKYLATION OF AROMATICS COUPLED WITH SUZUKI REACTION

Beside olefins, many other organic, inorganic, and organometallic species are able to react with the aryl-palladium complex **9** and to liberate palladium in its oxidation state zero, thus giving rise to a catalytic process.

We found an efficient way to terminate the stoichiometric sequence using arylboronic acids that undergo a Suzuki-type aryl-aryl coupling (eq. 3). The reaction leads to the formation of 2,6-dialkylated biaryls and proceeds even better than the previously described double alkylation terminated by Heck insertion. Compound **12** (R = H, R' = *n*-Pr, Ar = Ph) is obtained with 90% isolated yield.

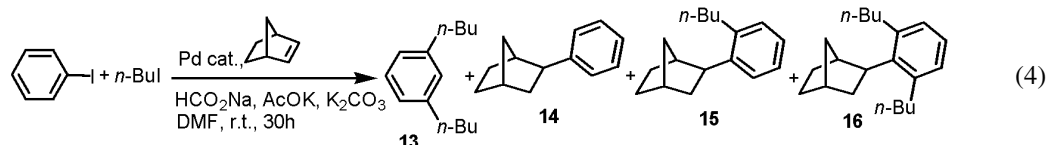


In fact, the aryl-aryl coupling has the great advantage, over the previously described termination by olefin insertion, of proceeding at room temperature even starting from *o*-substituted aryl iodides, thus leading to both symmetrical and unsymmetrical 2,6-biaryls. Although the reaction becomes slow and longer reaction times are required, selectivity remains high. Good results are also obtained in the presence of secondary alkyl groups on the aryl iodide and using a secondary alkyl halide such as the isopropyl one [5].

SELECTIVE ALKYLATION OF AROMATICS COUPLED WITH HYDROGENOLYSIS

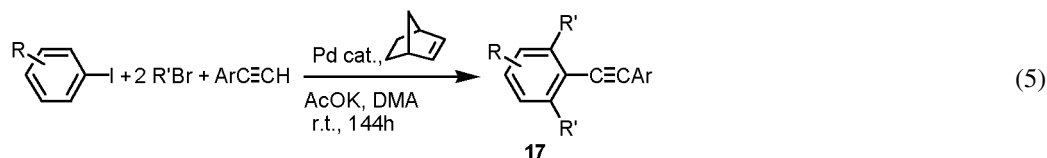
On attempting to couple the alkylation of aromatics with hydrogenolysis, we met a difficulty which is quite general in this type of chemistry. The termination step does not occur exclusively at the end of the sequence leading to the *o,o'*-disubstituted arylpalladium species **9**. Most of the intermediates necessary to build up the *o,o'*-disubstituted arylpalladium species are able to react with the terminating agent and sometimes even better than complex **9**.

Moreover, if norbornene, which acts as an organic catalyst, is incorporated into an unreactive organic molecule, it is subtracted to the molecular pool and the target reaction becomes worse and worse owing to catalyst depletion. Hydrogenolysis with sodium formate occurred on most of the intermediates involved. Only through a laborious optimization work, aimed at keeping low the concentration of the easily hydrolyzable intermediates, it was possible to reach satisfactory results. Thus, compound **13** was obtained in 76% yield together with **14** (4%), **15** (<1%), and **16** (5%) (eq. 4) [6].

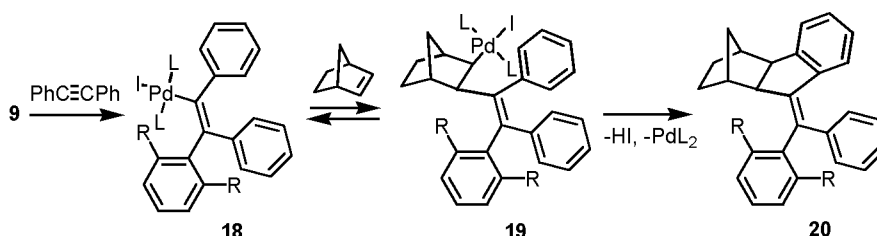


SELECTIVE ALKYLATION OF AROMATICS COUPLED WITH TRIPLE BOND ARYLATION

We could also achieve the synthesis of *o,o'*-dialkylated diphenylacetylenic compounds by terminating the stoichiometric sequence with phenylacetylene or its derivatives (eq. 5) [7].



Controlling the reactivity of this system offered some difficulties because our molecular pool became rich of a noninnocent component, diphenylacetylene, able to interfere and modify the expected reaction pathway, giving rise to a new product (**20**) according to the following Scheme 2.



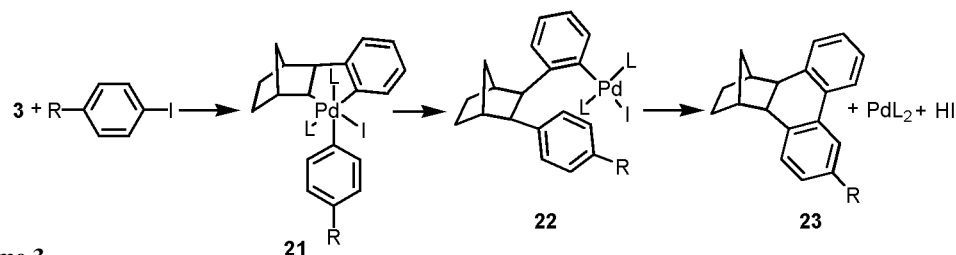
Scheme 2

It is worth noting that in the overall reaction starting from iodobenzene norbornene inserts, deinserts, and reinserts depending on steric reasons.

Product **20** (R = Me; 87%) can be obtained starting from 2,6-dimethyl iodobenzene, which directly gives **9** (R = Me) by oxidative addition to palladium(0) [8].

SELECTIVE ARYLATION OF AROMATICS COUPLED WITH SUZUKI REACTION

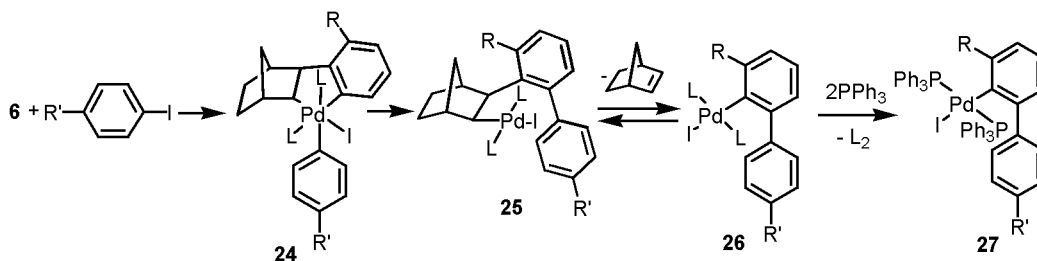
We have seen that it is possible to activate usually inert aromatic C–H bonds toward alkylation. We wondered whether arylation could be obtained in a similar way, but our experiments were unsuccessful [9,10]. To clarify this point, we carried out stoichiometric reactions starting from the dimeric arylnorbornenylpalladium chlorides, precursors of the palladacycles, and exclusively observed the formation of hexahydromethanotriphenylene derivatives according to the following Scheme 3.



Scheme 3

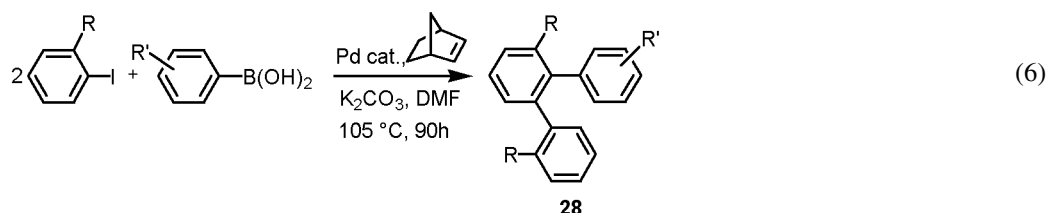
The aryl iodide reacts with the palladacycle **3**, likely through an oxidative addition process leading to an intermediate palladium(IV) complex (**21**); then the aryl group migrates towards the aliphatic part of the metallacycle leaving palladium on the aromatic ring (**22**). Finally, ring closure gives **23**. Analogous results were obtained with palladacycles of type **3** containing a *para* or *meta* substituent.

To our surprise, however, palladacycles containing a substituent in the *ortho* position led to a completely different reaction with formation of a biphenylpalladium complex **26** (isolated as complex **27**) (Scheme 4). This also helped us to explain a puzzling arylation [10,11].



Scheme 4

We have transformed this remarkable sequence into an efficient catalytic process (eq. 6). The latter is exceptionally selective.



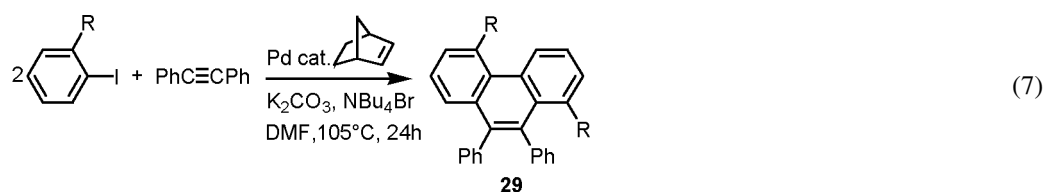
The reaction course is analogous to that shown in Scheme 4 for complex **6**. An intermediate corresponding to **26** is formed, which reacts with an arylboronic acid affording **28** catalytically.

The yield is strongly influenced by the *ortho* substituent R. Aryl iodides with both primary and secondary *ortho* alkyl groups give good-to-excellent results, while the presence of a *t*-butyl substituent prevents the formation of the corresponding terphenyl derivative. Surprisingly, the expected negative influence of the *ortho* substituent is exerted only with a tertiary group. When R = *i*-Pr, R' = H the reaction is very efficient and gives the corresponding terphenyl **28** in 93% yield [12].

SELECTIVE ARYLATION OF AROMATICS COUPLED WITH TRIPLE BOND INSERTION

From *ortho*-substituted aryl iodides and diphenylacetylene we could also obtain a palladium-catalyzed synthesis of phenanthrene derivatives. The selective *ortho* arylation process was made catalytic by combining the stoichiometric process leading to a biphenylpalladium derivative with the annulation of diphenylacetylene.

Addition of tetrabutylammonium bromide was required to increase the yield.



Also, in this case, the best results were obtained in the presence of the *iso*-propyl group (yield of **29**, R = *i*-Pr, 93%). The reaction becomes less efficient when R is a methoxy or methoxymethylene group and leads to poor results when R is a methoxycarbonyl group [13].

CONCLUSIONS

In conclusion, we have been able to assemble several molecules present in an initial pool in a definite order, thus controlling a sort of chemical evolution, which proceeds in one direction selectively, out of many possible. The tool we have worked out appears to be extremely effective and has led us to a number of applications, many of which are in progress. We are confident that this new type of chemistry occurring under mild conditions will be of increasing usefulness for the chemical community.

ACKNOWLEDGMENTS

This work was supported by Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST, project n. MM03027791), and Consiglio Nazionale delle Ricerche (CNR, Roma).

REFERENCES

1. M. Catellani, F. Frignani, A. Rangoni. *Angew. Chem., Int. Ed. Engl.* **36**, 119 (1997).
2. M. Catellani and M. C. Fagnola. *Angew. Chem., Int. Ed. Engl.* **33**, 2421 (1994).
3. M. Catellani and F. Cugini. *Tetrahedron* **55**, 6595 (1999).
4. M. Lautens and S. Piguel. *Angew. Chem., Int. Ed. Engl.* **39**, 1045 (2000).
5. M. Catellani, E. Motti, M. Minari. *J. Chem. Soc., Chem. Commun.* 157 (2000).
6. M. Catellani, E. Motti, C. Cugini. Manuscript in preparation.
7. M. Catellani, M. Rossetti, E. Motti. Manuscript in preparation.
8. E. Motti and M. Catellani. Manuscript in preparation.
9. M. Catellani and G. P. Chiusoli, *J. Organomet. Chem.* **286**, C13 (1985).
10. K. Albrecht, O. Reiser, M. Weber, B. Knieriem, A. de Meijere. *Tetrahedron* **50**, 383 (1994).
11. M. Catellani and E. Motti. *New J. Chem.* 759 (1998).
12. E. Motti, A. Mignozzi, M. Catellani. Manuscript in preparation.
13. M. Catellani, E. Motti, S. Baratta. *Org. Lett.* **3**, 3611 (2001).