Pure Appl. Chem., Vol. 77, No. 7, pp. 1243–1248, 2005.
DOI: 10.1351/pac200577071243

New catalytic methods for the synthesis of selectively substituted aromatics through palladacycles*

Marta Catellani[1,‡], Elena Motti[1], Fiorenza Faccini[1], and Raffaella Ferraccioli[2]

[1]Dipartimento di Chimica Organica e Industriale dell'Università and CIRCC, Parco Area delle Scienze, 17/A, 43100 Parma, Italy; [2]CNR, Istituto di Scienze e Tecnologie Molecolari (ISTM), Via C. Golgi 19, 20133 Milano, Italy

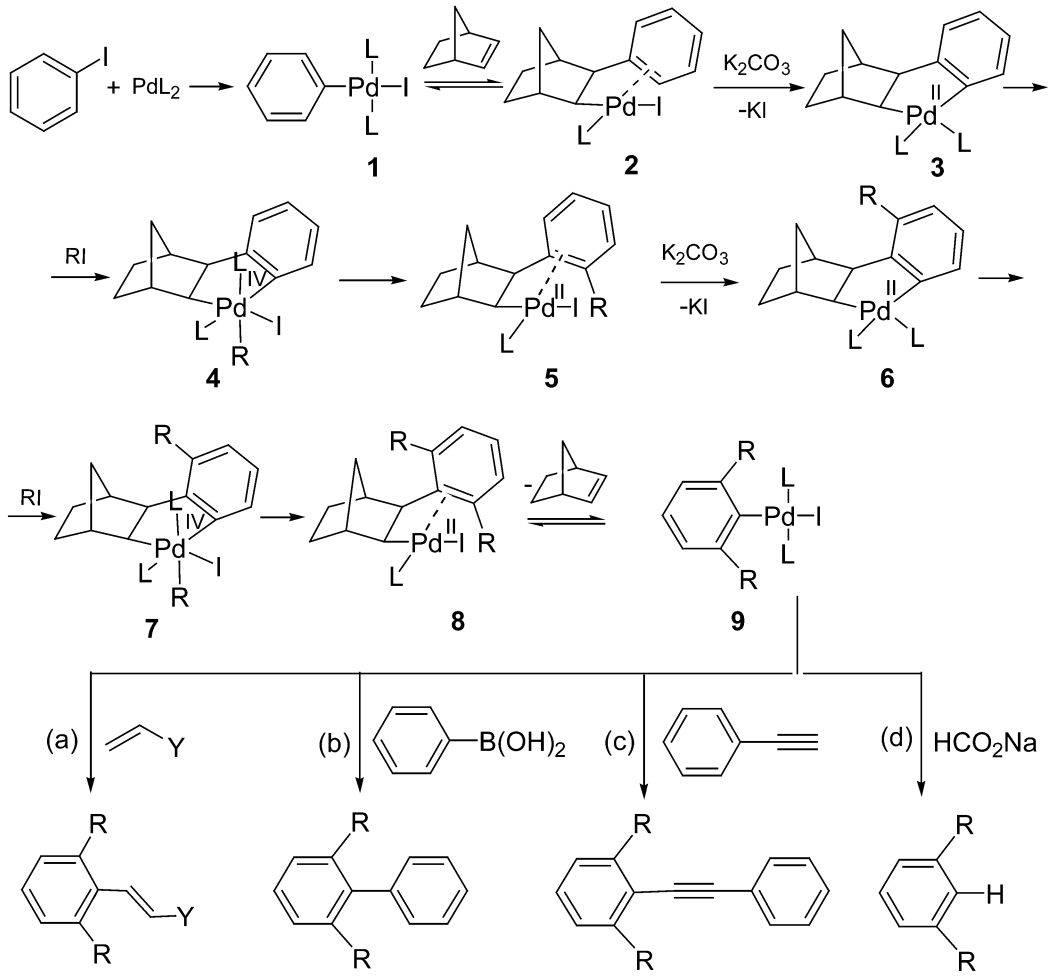
Abstract: Joint palladium and norbornene catalysis for selective aromatic functionalization via palladacycles is reported. Both alkylation and arylation of aromatics are considered after a brief outlook on the mechanism. These are multistep reactions that proceed in ordered sequences and are chemio-, regio-, and stereoselective. The study of the single steps with isolation of the organometallic species involved has allowed us to detect subtle steric and electronic effects which have been exploited to achieve catalytic reactions. Recent developments of aromatic alkylation and arylation are reported, in particular, condensed heterocyclic ring formation involving dialkylated arylpalladium complexes or both symmetrically and unsymmetrically substituted biphenylylpalladium complexes.

Keywords: Palladacycles; norbornene; aromatic functionalization; C–H activation; multicomponent reactions; homogeneous catalysis.

INTRODUCTION

Palladium-catalyzed organic reactions have rapidly been growing during the last several decades. Recent developments have been reviewed [1,2]. The present paper refers to a new methodology of selective carbon–carbon bond formation based on the joint use of two catalysts—an inorganic one, palladium, and an organic one, norbornene. Palladium(0) reacts with an organic (aromatic) halide through oxidative addition, and the resulting complex forms with norbornene a palladium(II) metallacycle which acts as a scaffold to direct the reaction, via palladium(IV), of other molecules toward the *ortho* positions of the aromatic ring. At the end of this process, the scaffold is dismantled, norbornene being spontaneously liberated, owing to steric hindrance and a new norbornene catalytic cycle starts, while palladium is cleaved from the organic product as soon as a suitable termination step is reached. Being liberated in the zero oxidation state, it begins a catalytic cycle again. Thus, the methodology we have worked out takes advantage of both the different reactivity of palladium in oxidation states 0, II, and IV and of the reversibility of norbornene insertion. As a result, we have been able to build up a variety of classes of *ortho*-substituted aromatic compounds starting from a pool of simple molecules, which can be caused to react in a sequential order in spite of the many possible combinations. Scheme 1 shows the

Pure Appl. Chem.* **77, 1087–1296. An issue of reviews and research papers based on lectures presented at the 15th International Conference on Organic Synthesis (ICOS-15), held in Nagoya, Japan, 1–6 August 2004, on the theme of organic synthesis.
‡Corresponding author



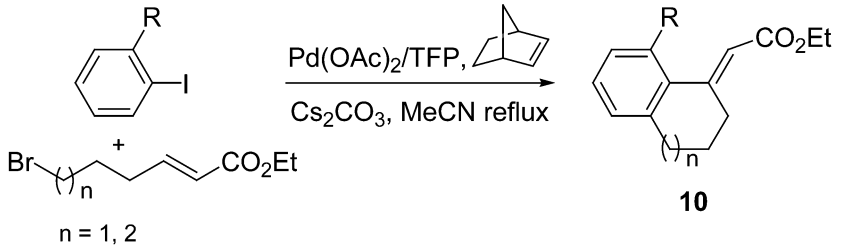
Scheme 1

various steps leading to a common arylpalladium intermediate, which in its turn is able to form selectively substituted aromatics through reaction with several reagents [3,4].

The reaction is initiated by the oxidative addition of the aryl iodide to palladium(0), formed in situ, to give **1** [5]. The subsequent norbornene insertion occurs stereoselectively and leads to species **2** containing palladium coordinated to an aromatic double bond [6–9]. Elimination of HI gives a five-membered palladacycle **3**. Oxidative addition of the alkyl iodide generates a palladium(IV) species (**4**), which reductively eliminates to palladium(II) by selective migration of the alkyl group onto the aromatic site of the palladacycle (**5**) [10]. C–H activation of the second *ortho* position of the aromatic ring and new oxidative addition of another molecule of alkyl iodide, followed by reductive elimination, leads to the species **8** which readily undergoes norbornene deinsertion with formation of an *o*,*o*'-dialkylated arylpalladium complex **9**. Norbornene deinsertion, which corresponds to a β,γ-C–C bond cleavage, is due to the steric effect generated by the two *ortho* substituents. The sequence becomes catalytic by coupling complex **9** with terminal olefins, arylboronic acids, terminal acetylenic compounds and hydrogen donors to form 2,6-dialkylated vinylarenes [11], 2,6-dialkylated 1,1'-biaryls [12], 2,6-dialkylated diarylacetylenes [13], and 1,3-dialkylated arenes [14], respectively (Scheme 1, ways a–d). The reported reaction mechanism and the role of norbornene have been discussed in our previous works [3,4].

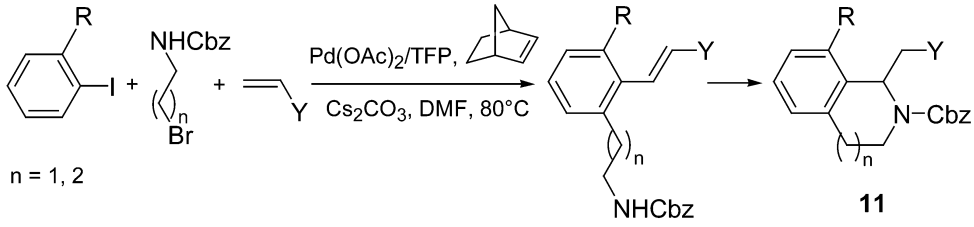
ADVANCES IN ALKYLATION METHODOLOGY

The scope of alkylation methodology could be greatly enlarged to obtain ring closure by reaction of *o*,*o'*-dialkylated arylpalladium bonds containing appropriately functionalized R groups in *ortho*. Six- and seven-membered condensed cyclic compounds were obtained by Lautens and coworkers through an intramolecular Heck reaction starting from an alkyl bromide containing the double bond (eq. 1). Compound **10** (n = 1, R = Me) was formed in 90 % isolated yield [15].



(1)

Another synthetic pathway involving intermolecular Heck reaction with an activated olefin and double bond amination was worked out (eq. 2). The synthesis of tetrahydroisoquinolines (**11**, n = 1, R = Me, Y = CO_2tBu, 68 %) and tetrahydrobenzazepines (**11**, n = 2, R = Me, Y = CO_2tBu, 43 %) was achieved using an alkyl bromide bearing a protected amine group which gave rise, after *ortho* alkylation, to a final Michael reaction on the inserted olefin [16].

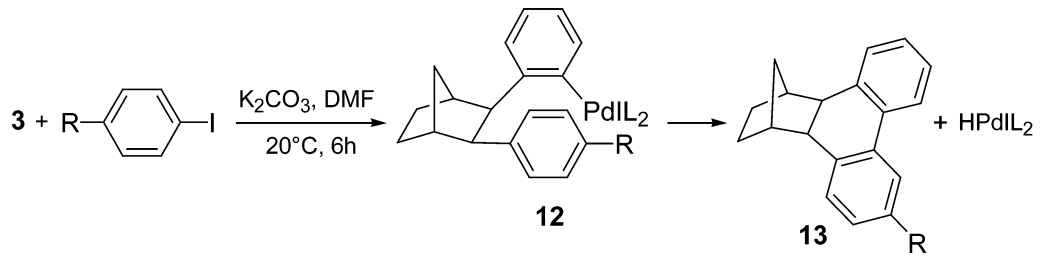


(2)

ARYLATION METHODOLOGY

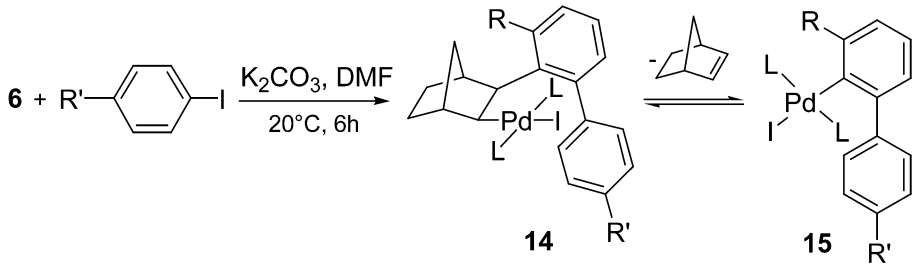
The potential of the strategy of alkylation via palladacycle could be expected to increase very much if extended to arylation of aromatic rings. The achievement of this goal was hampered, however, by the fact that alkyl and aryl halides behave in a different way. While R = alkyl reacts with palladacycle **3**, alkylating the aromatic site to give **5** according to Scheme 1, R = aryl preferentially migrates onto the norbornyl site [17].

Thus, complex **3** reacts with an aryl iodide as shown in Scheme 2, giving the arylated palladium species **12**, which spontaneously evolves toward the formation of the hexahydromethanotriphenylene derivative **13**.



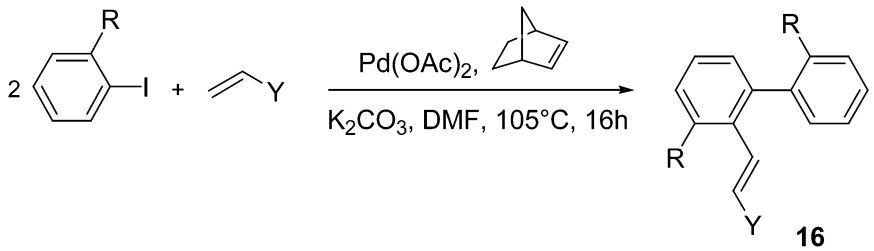
Scheme 2

The study of the substituent effect in this reaction, however, allowed us to discover that an *ortho*-alkyl group R in the palladacycle aromatic ring as in complex **6**, directed the attack of an aryl iodide on the other *ortho* position to form **14**. This fact had the important consequence of creating such a steric hindrance that norbornene spontaneously deinserted. As a result, a biphenylylpalladium complex **15** (Scheme 3), analogous to **9** (Scheme 1), was formed [17].



Scheme 3

Complex **15** could be reacted with a variety of reagents to obtain organic products containing the biaryl unit, with concomitant liberation of palladium(0). A catalytic reaction leading to the disubstituted vinylbiphenyls **16** was achieved starting from aryl iodides bearing several different *ortho* R groups such as methyl, ethyl, *n*-propyl, methoxy, and carbomethoxy and using a terminal olefin in the final step. The best results were obtained with electron-poor olefins, but also the more electron-rich ones gave satisfactory results. Yields were in the range of 73–98 % (eq. 3) [18].

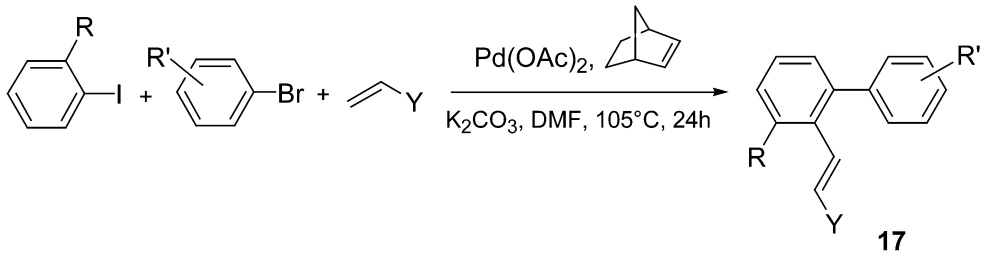


(3)

Other catalytic reactions were obtained using hydrogen donors (selectively substituted biphenyls) [19], internal aromatic alkynes (selectively substituted phenanthrenes) [20], allylic alcohols (selectively substituted biphenyls, containing a carbonyl group in an alkyl chain) [21], and arylboronic acids (selectively substituted terphenyls) [22].

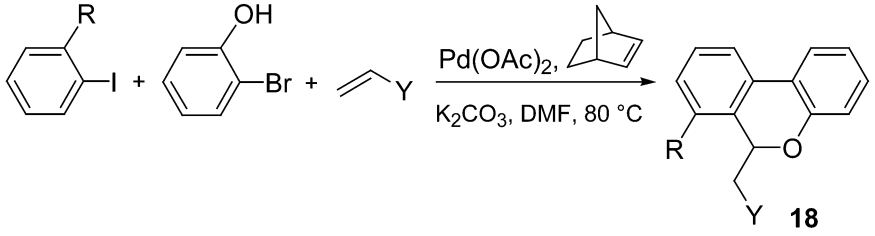
All of these reactions involved the symmetrical coupling of two identical aryl units. The task of coupling two differently substituted aryl groups turned out to be much more difficult. In fact, only a mixture of all the possible biphenyl structures was obtained by reacting differently *o*-substituted aryl iodides. It was only after a thorough study of the reaction factors that we discovered that we could take advantage of the different reactivity of palladium(0) and palladium(II) complexes with aryl iodides and bromides. While under the conditions chosen, the former reacted faster than the latter with palladium in both the oxidation states, *o*-alkyl-substituted iodides reacted much more readily with palladium(0) than with palladium(II) metallacycles, likely for steric reasons. On the contrary, aryl bromides substituted by electron-withdrawing or by certain chelating groups, preferentially reacted with palladium(II) rather than with palladium(0). These findings allowed us to achieve the unsymmetrical aryl coupling catalytically through the reaction of the resulting palladium complex with a terminal olefins to form vinylbiphenyls selectively substituted, this time, by different groups (**17**) (eq. 4). The reaction occurs with satisfactory to good yields in the presence of several R and R' and with both electron-poor and -rich

olefins. For example, with R = NMe_2, R' = *o*-CO_2Me, Y = CO_2Me compound **17** was isolated in 82 % yield [23].

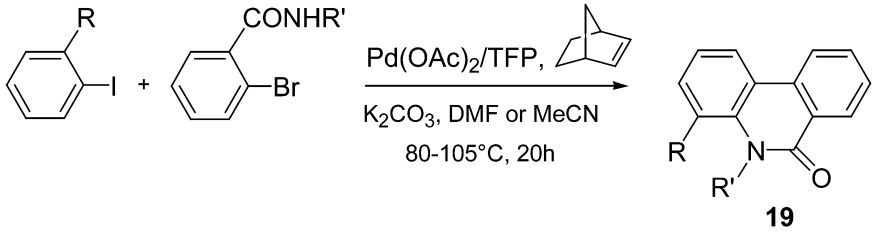


(4)

The reaction scope appears to be very wide. Not only has a series of selectively substituted molecules containing the biphenyl unit (ubiquitous in nature) become accessible, but also condensed heterocycles have been prepared by utilizing appropriately placed functional groups (eqs. 5 and 6).



(5)



(6)

In the former case, a hydroxyl function gives a Michael-type reaction on the double bond of the product deriving from the reaction with methyl acrylate to give the dibenzopyran derivative **18** (R = Me, Y = CO_2Me, 83 % yield) [24], while in the latter an amide function directly reacts with the biphenylylpalladium complex without insertion of methyl acrylate leading to the phenanthridinone derivative **19** (R, R' = Me, 87 % yield) [25].

CONCLUSION

In conclusion, the alkylation and arylation methodologies via palladacycles have made possible one-pot catalytic reactions under mild conditions, leading to a variety of organic compounds of potential interest for use as fine chemicals. The processes involve palladacycles, which are formed and demolished after they have accomplished the function of directing the process selectively. It is worth noting that this outcome would have not been achieved without the isolation and study of the reactivity of the organopalladium intermediates involved.

ACKNOWLEDGMENTS

Financial support by the University of Parma and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Cofinanziamento MIUR, project no. 2003039774) and CNR is grateful acknowledged.

REFERENCES

1. J. Tsuji. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, John Wiley, New York (2004).
2. E.-I. Negishi (Ed.). *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vols. 1, 2, John Wiley, New York (2002).
3. M. Catellani. In *Handbook of Organopalladium Chemistry for Organic Synthesis,* Vol. 1, E. I. Negishi (Ed.), p. 1479, Wiley-Interscience, New York (2002).
4. M. Catellani. *Synlett* 298 (2003).
5. P. Fitton and E. A. Rick. *J. Organomet. Chem*. **28**, 287 (1971).
6. H. Horino, M. Arai, N. Inoue. *Tetrahedron Lett*. 647 (1974).
7. C.-S. Li, C.-H. Cheng, F.-L. Liao, S.-L. Wang. *Chem. Commun*. 710 (1991).
8. M. Portnoy, Y. Ben-David, I. Rousso, D. Milstein. *Organometallics* **13**, 3465 (1994).
9. M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno, P. S. Pregosin. *J. Am. Chem. Soc*. **124**, 4336 (2002).
10. M. Catellani and M. C. Fagnola. *Angew. Chem*., *Int. Ed. Engl.* **33**, 2421 (1994).
11. M. Catellani, F. Frignani, A. Rangoni. *Angew. Chem*., *Int. Ed. Engl.* **36**, 119 (1997).
12. M. Catellani, E. Motti, M. Minari. *Chem. Commun.* 157 (2000).
13. E. Motti, M. Rossetti, G. Bocelli, M. Catellani. *J. Organomet. Chem*. **689**, 3741 (2004).
14. M. Catellani, C. Cugini. Unpublished results.
15. M. Lautens and S. Piguel. *Angew. Chem., Int. Ed. Engl*. **39**, 1045 (2000).
16. R. Ferraccioli, D. Carenzi, M. Catellani. *Tetrahedron Lett*. **45**, 6903 (2004).
17. M. Catellani and E. Motti. *New J. Chem*. **22**, 759 (1998).
18. E. Motti, G. Ippomei, S. Deledda, M. Catellani. *Synthesis* 2671 (2003).
19. S. Deledda, E. Motti, M. Catellani. *Can. J. Chem.* (2005). In press.
20. M. Catellani, E. Motti, S. Baratta. *Org. Lett.* **3**, 3611 (2001).
21. M. Catellani, S. Deledda, B. Ganchegui, F. Hénin, E. Motti, J. Muzart. *J. Organomet. Chem*. **687**, 473 (2003).
22. E. Motti, A. Mignozzi, M. Catellani. *J. Mol. Catal. A: Chem.* **204–205**, 115 (2003).
23. F. Faccini, E. Motti, M. Catellani. *J. Am. Chem. Soc*. **126**, 78 (2004).
24. M. Catellani, E. Motti, F. Ferraccioli. Unpublished results.
25. R. Ferraccioli, D. Carenzi, O. Rombolà, M. Catellani. *Org. Lett.* **6**, 4759 (2004).