

A New Reaction Sequence Involving Palladium-Catalyzed Unsymmetrical Aryl Coupling

Fiorenza Faccini, Elena Motti, and Marta Catellani*

Dipartimento di Chimica Organica e Industriale dell'Università, Università di Parma, Parco Area delle Scienze, 17/A, 43100 Parma, Italy

Received October 14, 2003; E-mail: marta.catellani@unipr.it

We report that biphenyls, **4**, with two different substituents, R₁ and R₂, are selectively formed by palladium-catalyzed sequential coupling of an aryl iodide bearing an ortho electron-donating group (**1**) with an aryl bromide containing an electron-withdrawing substituent (**2**, Y = Br) and a terminal olefin (eq 1). The reaction is promoted by palladium acetate and norbornene in the presence of potassium carbonate in DMF and leads only to compound **4** of the possible aryl coupling products (Figure 1).

We have previously reported the synthesis of biphenyl derivatives **5** by palladium and norbornene-catalyzed reaction of ortho-substituted aryl iodides **1** with terminal olefins.¹ The reaction, which provides a new entry into the wide field of coupling reactions,² implies a symmetrical aryl coupling via palladacycles promoted by the presence of an ortho substituent.^{1,3}

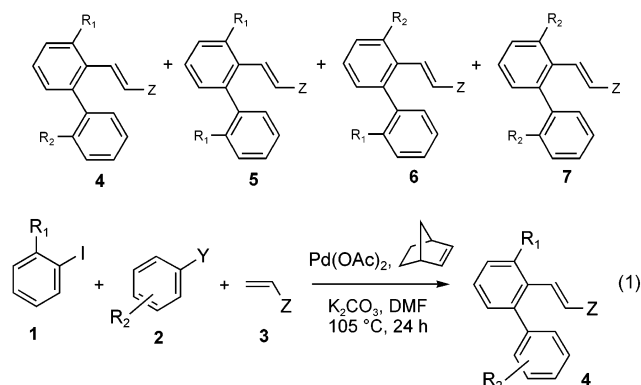


Figure 1. Possible aryl coupling products from ortho-substituted aromatic halides **1** and **2**.

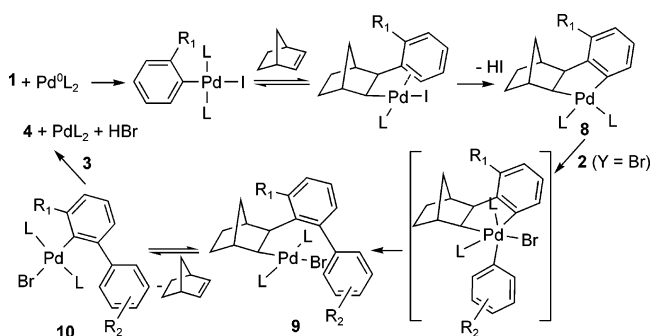
Our first attempts to effect an unsymmetrical coupling selectively were unsuccessful. Thus, the reaction of *o*-iodotoluene (**1**, R₁ = Me) and *o*-iodoethylbenzene (**2**, R₂ = *o*-Et, Y = I) in 1:1 molar ratio with methyl acrylate (**3**, Z = CO₂Me) under the conditions of eq 1 afforded a mixture of all four compounds **4–7** in 13, 46, 13, and 23% yield, respectively (based on the reacted aryl iodide). Replacement of *o*-iodoethylbenzene with an aryl iodide bearing an *o*-electron-withdrawing group such as methyl *o*-iodobenzoate (**2**, R₂ = *o*-CO₂Me, Y = I) gave only one unsymmetrically substituted compound (**4**, R₁ = Me, R₂ = CO₂Me) together with the two symmetrically substituted ones (**5**, R₁ = Me, and **7**, R₂ = CO₂Me) in 30, 18, and 56% yield, respectively (based on the reacted aryl iodide). The predominant formation of **7** (R₂ = CO₂Me), which results from the reaction of only **2** (R₂ = *o*-CO₂Me, Y = I), indicated that an aryl iodide bearing an electron-withdrawing substituent reacted both as **1** and **2** (eq 1). However, we found that when we used the less reactive methyl *o*-bromobenzoate as reactant **2** (R₂ = *o*-CO₂Me, Y = Br) while keeping electron-releasing substituents in iodide **1**, the reaction path dramatically changed. Thus, by heating an ortho-substituted aryl iodide (**1**, 0.56 mmol), methyl *o*-bromobenzoate (**2**, R₂ = CO₂Me, Y = Br; 0.56 mmol),

Table 1. Reaction of an *o*-Substituted Aryl Iodide, Methyl *o*-Bromobenzoate, and Methyl Acrylate in the Presence of Pd(OAc)₂ and Norbornene as Catalysts^a

run	R ₁	4 yield (%) ^b	run	R ₁	4 yield (%) ^b
1	Me	80	4	Ph	73
2	<i>i</i> -Pr	74	5	OMe	83
3	<i>t</i> -Bu	37 ^c	6	NMe ₂	82

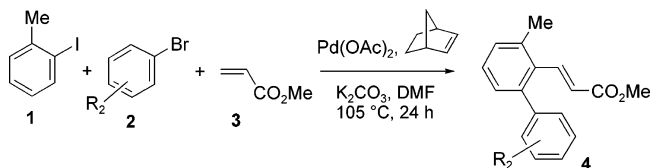
^a Reaction conditions: Pd(OAc)₂ (0.011 mmol), aryl iodide (0.56 mmol), methyl *o*-bromobenzoate (0.56 mmol), methyl acrylate (0.90 mmol), K₂CO₃ (1.34 mmol), norbornene (0.56 mmol) in DMF (5 mL) at 105 °C for 24 h. ^b Isolated yield based on the aryl iodide. ^c The main product (42%) was 5-*tert*-butyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene.^{3b}

Scheme 1



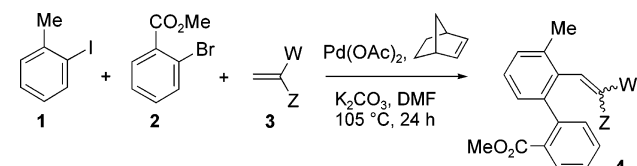
methyl acrylate (**3**, Z = CO₂Me; 0.90 mmol), Pd(OAc)₂ (0.011 mmol), norbornene (0.56 mmol), and potassium carbonate (1.34 mmol) in DMF (5 mL) for 24 h at 105 °C under nitrogen, the desired single compound **4** was isolated in good yields (Table 1).

The reaction of Table 1 can be interpreted, in a more general form, by Scheme 1 (L = solvent, coordinating reagents). The sequence is initiated by the *o*-substituted iododerivative **1**, which reacts faster than methyl *o*-bromobenzoate **2** with the palladium(0) species. Stereoselective insertion of norbornene into the resulting aryl-palladium bond⁴ followed by electrophilic aromatic substitution⁵ leads to the *cis*,*exo* palladium(II) metallacycle **8**.⁶ At this stage, both the aryl iodide **1** and methyl *o*-bromobenzoate **2** would be able to react with **8** to give aryl coupling likely through a palladium(IV) intermediate (shown in brackets).⁷ Compound **2** (R₂ = *o*-CO₂Me, Y = Br) must react preferentially, however. This also indicates that **2** is more reactive to palladium(II) than to palladium(0), just the opposite of what happens with **1**. This unexpected behavior is under investigation. Complex **9**, resulting from selective attack of **2** (R₂ = *o*-CO₂Me, Y = Br) to the aromatic site of palladacycle **8**,^{3b} undergoes norbornene deinsertion⁸ to afford **10**; the catalytic cycle is then completed by acrylate insertion. The

Table 2. Reaction of *o*-iodotoluene, an Aryl Bromide and Methyl Acrylate in the Presence of Pd(OAc)₂ and Norbornene as Catalysts^a

run	R ₂	4 yield (%) ^b	run	R ₂	4 yield (%) ^b
1	<i>o</i> -CF ₃	^c	7	<i>o</i> -CN	13
2	<i>m</i> -CF ₃	71	8	<i>m</i> -CN	62
3	<i>p</i> -CF ₃	80	9	<i>p</i> -CN	79
4	<i>o</i> -CO ₂ Me	80	10	<i>o</i> -F	24
5	<i>m</i> -CO ₂ Me	37	11	<i>p</i> -F	24
6	<i>p</i> -CO ₂ Me	71	12	<i>o</i> -OH	61 ^d

^a Reaction conditions as in Table 1. ^b Isolated yield based on aryl iodide. ^c Only traces, if any. ^d The product was isolated as the 6*H*-dibenzopyran.⁹

Table 3. Variation of the Olefin in the Reaction of *o*-Iodotoluene with *o*-Bromobenzoate^a

run	Z	W	4 yield (%)
1	Ph	H	71
2	Hex	H	74 ^b
3	<i>O</i> - <i>n</i> -Bu	H	75 (branched ^c /linear) ^b
4	CO ₂ Me	Me	73 ^b

^a Reaction conditions as in Table 1. ^b After hydrogenation with H₂ on Pd/C. ^c Not in the title equation. From attack on the internal vinyl carbon.

proposed pathway is based on the isolation of the relevant species formulated in Scheme 1 and from the study of stoichiometric reactions.^{3b,4d,5,6a,c,8a,b} As anticipated, the selective aryl–aryl coupling to afford complex **9** is caused by the presence of the ortho R₁ substituent in palladacycle **8**.^{3b} It follows that the sequence leading to aromatic arylation is feasible only if initiated by ortho-substituted aryl iodide **1**, which gives alkylaromatic palladacycles containing an ortho substituent as in complex **8**. Since this requirement does not apply to compound **2**, we carried out the reaction of *o*-iodotoluene with aryl bromides **2** bearing electron-withdrawing substituents in ortho, meta, and para positions (Table 2).

The data reported in Tables 1 and 2 show that the reaction is strongly influenced by the substituents present on both the aryl halides. A variety of ortho-substituted aryl iodides **1** can be used (Table 1) with good results, a lower yield being obtained only with the bulky *t*-Bu (Table 1, run 3). Functional groups such as methoxy and dimethylamino are well tolerated but hydroxy, monomethylamino, or amino substituents hinder the reaction sequence.¹ The use of aryl iodides bearing electron-releasing rather than electron-withdrawing substituents is dictated by the need to prevent a reaction of the same iodide with palladacycle **8** faster than with the bromoderivatives **2** (Scheme 1). Variation of R₂ in **2** (Table 2) led to satisfactory results with *o*-, *p*-CO₂Me, *m*-, *p*-CF₃, and *m*-, *p*-CN.¹⁰ *o*-Bromophenol (Table 2, run 12) reacts normally, despite the presence of an electron-releasing substituent, which should make it much less reactive with palladacycle **8** than *o*-iodotoluene. This is attributable to a positive chelation effect since *p*-bromophenol did not react at all.

Variation of the terminal olefin leads to results similar to those previously observed for the symmetrical coupling reaction (Table

3).¹ Styrene forms only the *E*-compound while 1-octene leads to a mixture of three isomers (1-*cis*, 1-*trans*, and 2-*trans* in ca. 1:10:1 molar ratio), which gives only one linear species after hydrogenation.¹ The electron-rich *n*-butyl vinyl ether gives one branched and two linear isomers (*cis,trans*) in ca. 1:1:1.5 molar ratio which were isolated and characterized after hydrogenation. Despite the steric hindrance methyl methacrylate gave three isomers with internal (*cis,trans*) and external (vinylidene) bond in ca. 1:1:4 molar ratio (73% total yield after hydrogenation), while 1,2-disubstituted olefins such as methyl 2-butenate did not react.

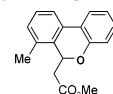
In conclusion, unsymmetrical aryl coupling has been obtained selectively on the basis of a novel conceptual advance: the different reactivity of certain bromo- and iododerivatives with palladium(0) and palladium(II) complexes.

Acknowledgment. We thank Professor P. Maitlis, University of Sheffield, for helpful discussion.

Supporting Information Available: General experimental procedure and spectroscopic characterization of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Motti, E.; Ippomei, G.; Deledda, S.; Catellani, M. *Synthesis*, in press.
- (a) *Metal-Catalyzed Cross-Coupling Reactions*; Dietrich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (b) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: Chichester, U.K., 2000. (c) Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley: New York, 2002; Vol. 1, p 215. (d) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506.
- (a) Catellani, M. *Synlett* **2003**, 298. (b) Catellani, M.; Motti, E. *New J. Chem.* **1998**, 759. (c) Catellani, M.; Motti, E.; Baratta, S. *Org. Lett.* **2001**, *3*, 3611. (d) Motti, E.; Mignozzi, A.; Catellani, M. *J. Mol. Catal., A* **2003**, *204–205C*, 115.
- (a) Horino, H.; Arai, M.; Inoue, M. *Tetrahedron Lett.* **1974**, 647. (b) Li, C.-S.; Cheng, C.-H.; Liao, F.-L.; Wang, F.-L. *Chem. Commun.* **1991**, 710. (c) Portnoy, M.; Ben-David, Y.; Rouso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465. (d) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Careno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336.
- Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *425*, 151.
- (a) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1988**, *346*, C27. (b) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *437*, 369. (c) Liu, C.-H.; Li, C.-S.; Cheng, C.-H. *Organometallics* **1994**, *13*, 18. (d) Cámpora, J.; Palma, P.; Carmona, E. *Coord. Chem. Rev.* **1999**, *193–195*, 207. (e) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. C. *Principles and Applications of Organotransition Metal Chemistry*; University Science: Mill Valley, CA, 1987.
- The intermediacy of this species is suggested by analogy with the isolation of palladium(IV) complexes from reaction of **8** with alkyl halides. See: (a) Catellani, M.; Mann, B. E. *J. Organomet. Chem.* **1990**, *390*, 251. (b) Bocelli, G.; Catellani, M.; Ghelli, S. *J. Organomet. Chem.* **1993**, *458*, C12. For other references on palladium(IV) chemistry see: (c) Cauty, A. *J. Acc. Chem. Res.* **1992**, *25*, 83 and references therein.
- (a) Catellani, M.; Fagnola, M. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (c) Lautens, M.; Piguol, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045. (d) Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147. (e) Hosokawa, T.; Maitlis, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 3238. For examples of C–C bond-breaking processes of different types, see: (f) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (g) Edelbach, B. L.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 2843 and references therein. (h) Alper, H.; Saldana-Maldonado, M. *Organometallics* **1989**, *8*, 1124. (i) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.
- The reaction leading to the structure below offers a new entry to condensed polycycles which is currently investigated.



- The *o*-CF₃ and *o*-F groups, and to a lower extent the *o*-CN group, prevent the formation of **4** (R₁ = Me, R₂ = *o*-CF₃, *o*-F, *o*-CN, Z = CO₂Me; runs 1, 7, and 10, Table 2), and only **5** was found (R₁ = Me, Z = CO₂Me, Figure 1; 72, 71, and 25%, respectively). This suggests an inhibiting interaction with complex **8** of Scheme 1. The low yield with *m*-CO₂Me and *p*-F might be related to their σ Hammett constants.

JA039043G