PALLADIUM CATALYSED COUPLING OF HALOBENZENES WITH ARYLBORONIC ACIDS: RÔLE OF THE TRIPHENYLPHOSPHINE LIGAND

David F. O'Keefe, Megan C. Dannock and Sebastian M. Marcuccio*

CSIRO Division of Chemicals and Polymers Private Bag 10, Clayton, Victoria, Australia 3168.

Key Words: Biaryl; palladium catalysed coupling; triphenylphosphine; arylboronic acids; ligand derived product.

Abstract: The synthesis of unsymmetrically substituted biaryls via palladium catalysed coupling of aryl halides with arylboronic acids was found to produce biaryl by-products where one aryl was derived from the triphenylphosphine ligand. The use of substituted triphenylphosphine ligands to minimise this side reaction was investigated.

Methods employing the use of metal catalysts to couple dissimilar aryls have provided efficient routes to unsymmetric biaryls. The palladium catalysed coupling of aryl boronic acids with aryl halides,¹ or triflates,² provides unsymmetrically substituted biphenyls in high yields.

We required quantities of the unsymmetrical biaryl 3 for use in further synthesis and biological testing and so considered the coupling of the appropriate arylboronic acid and arylbromide using tetrakis(triphenylphosphine)palladium[0] as catalyst.³



Reaction of 2,3,4-trimethoxyphenylboronic acid (1) with , 4-bromo-1,2-methylenedioxybenzene (2) using the conditions of Miyaura *et al.* (3 mole% Pd(Ph₃P)₄ in benzene),¹ gave 3,4-methylenedioxy-2',3',4'-trimethoxybiphenyl (3) in 54% isolated yield. However, the product was contaminated with a similar compound which was identified as 2,3,4-trimethoxybiphenyl (4) (27% yield).

The use of 1,2-dimethoxyethane (DME) as solvent gave similar results indicating that the catalyst was the only possible source of the phenyl moiety in 4. This was confirmed by repeating the reaction, omitting 2, which gave the biphenyl (4) in 29% yield, representing 76% of the phenyl moieties in the catalyst used. As Miyaura *et al.*¹ had used unsubstituted phenylboronic acid exclusively, any catalyst derived unsymmetrical biphenyl would have been impossible to detect.

In order to maximise the yield of the desired product 3 we investigated: (a) varying the amount of catalyst and (b) the use of substituted triphenylphosphine ligands. Reduction of the amount of catalyst to 1 mole% from 3 mole% proved to be the practical minimum, increasing the yield of 3 to 82% and reducing 4 to 11%. Various trisarylphosphines were tried as ligands; tris(2-methoxyphenyl)phosphine was effective in reducing the amount of by-product (3%) while maintaining a high yield of the desired product 3 (79%).

An important intermediate in this coupling reaction is formed by the addition of one of the reactants(ArX) to the catalyst to form the species 5.4 The formation of the by-product 4 can be rationalised by an aryl-aryl exchange in the intermediate palladium(II) complex (leading to either 6, 7 or 8) and subsequent coupling with the phenylboronic acid (1).



Recently a facile aryl-aryl exchange between the palladium centre and phosphine ligands in palladium(II) complexes has been reported by Kong *et al.*⁵ They established that an equilibrium existed between the species **5-8** and found that the migration from palladium to phosphorus was enhanced by electron donating substituents.⁶ Thus the tendency for the aryl group to migrate to the phosphorus atom is exacerbated, in our case, by the multiple alkoxy substituents on the reactants. Kong *et al.*⁵ also found the above equilibrium to be suppressed by the addition of a further mole of trisarylphosphine. Under the reaction conditions used in our case, additional trisarylphosphine reduced the amount of catalyst derived biphenyl. This approach, however, was not a synthetically useful way of inhibiting the formation of **4** as the reaction was slowed considerably.⁷

This work indicates that reduction of the catalyst quantity from 3 to 1 mole% appears to be the practical minimum for good catalysis, allowing workable reaction times with excellent yields and that the formation of catalyst derived biaryls can be modified to a considerable extent by the choice of the trisarylphosphine ligand.

References and Notes

- 1. Miyaura, N.; Yanagi, T.; Suzuki, A. Synth. Commun. 1981, 11, 513-9.
- 2. Fu, J.-m. Snieckus, V. Tetrahedron Lett., 1990, 31, 1665-8.
- 3. Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. New Pathways in Organic Synthesis -Practical Applications of Transition Metals; Plenum Press 1984; p 384.
- 4. Sekiya, A. Ishikawa, N. J. Organomet. Chem. 1976, 118, 349-54.
- 5. Kong, K-C.; Cheng, C-H. J. Am. Chem. Soc. 1991, 113, 6313-15.
- 6. Kong *et al.*⁵ have found that when Ar was p-tolyl, the equilibrium ratio of 7:5 was 90/10, whereas the ratio was 96/4 when Ar was p-methoxyphenyl.
- 7. This presumably occurred by the additional trisarylphosphine competing for the coordination site required by the reacting aryl moiety.

(Received in UK 10 August 1992)