



Efficient coupling of heteroaryl bromides with arylboronic acids in the presence of a palladium–tetraphosphine catalyst

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Abstract—The *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/[PdCl(C₃H₅)₂] system catalyses the Suzuki cross-coupling of heteroaryl bromides with arylboronic acids with a very high substrate/catalyst ratio in good yields. Substrates such as pyridines, quinolines, thiophenes, an indole, a pyrimidine or a furane have been used successfully. © 2001 Elsevier Science Ltd. All rights reserved.

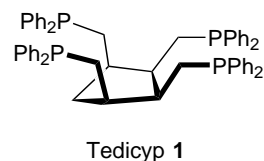
Heterobiaryls have important biological properties.¹ The palladium-catalysed cross-coupling reaction between heteroaryl halides and arylboronic acids provides a very efficient method for the preparation of heterobiaryl derivatives.^{2,3} However, this procedure suffers generally from high catalyst loading. In recent years some very efficient catalysts have been described for the Suzuki reaction.⁴ For example, bulky phosphites such as P(O-2,4-*t*Bu₂C₆H₃)₃ or P(O-*i*Pr)₃ have been successfully used.^{4f} A carbene ligand also leads to the formation of palladium catalysts that are more efficient than those of triphenylphosphine for this reaction.^{4g} A very efficient catalyst for this reaction has been prepared with the bulky ligand (*o*-biphenyl)P(*t*-Bu)₂.^{4c,e} However, most of the results described using these ligands were obtained for the coupling of simple aryl halides. Few results have been reported using heteroaromatic substrates.^{1,5} In this paper, we wish to report our results for the coupling of heteroaromatic substrates using a tetraphosphine/palladium catalyst.

The nature of the phosphine ligand in complexes has an important influence on the stability of the catalysts and on the rate of catalysed reactions. In order to find more stable and more efficient palladium catalysts, we have prepared the new tetrapodal⁶ phosphine ligand, *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp **1** (Fig. 1)⁷ in which the four

diphenylphosphinoalkyl groups are stereospecifically bound to the same face of the cyclopentane ring.

We have reported recently that the complex formed by association of **1** with [PdCl(C₃H₅)₂] is an extremely efficient catalyst⁷ for the Suzuki cross-coupling of arylbromides with arylboronic acids.⁸ Some preliminary results using 3-bromothiophene **11** and 3-bromopyridine **3** had also been described.⁸ Now, we wish to describe the results obtained with several heteroaryl bromides and arylboronic acids using **1** as the ligand.

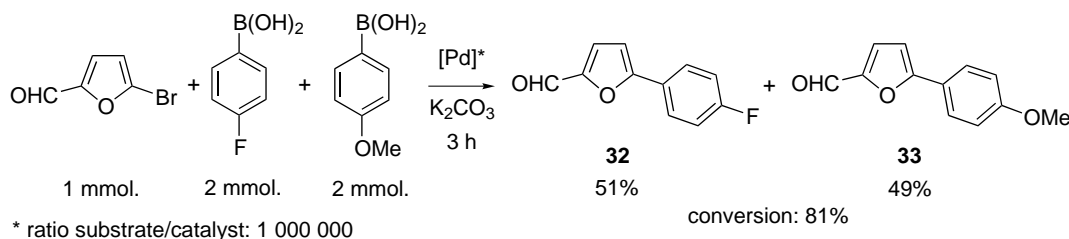
First, we studied the influence of position of the bromo substituent on pyridines on the rate of the coupling with benzeneboronic acid **13**. Due to the electronegativity of the nitrogen atom, the α - and γ -positions of halopyridines should be the most susceptible to the oxidative addition to Pd(0).¹ In fact, we observed higher TONs for the coupling with β - and γ -substituted bromopyridines **3** and **4** (2 500 000 and 810 000, respectively) than with α -substituted bromopyridine **2** (62 000) (Scheme 1, Table 1). A similar effect was observed with bromothiophenes. 3-Bromothiophene **11** led to the coupling product **30** with a very high TON of 80 000 000. On the other hand, the highest TON obtained for the reaction with 2-bromothiophene **10** was 580 000. These



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Figure 1.



Scheme 2.

Pyridines and pyrimidines are π -electron deficient heterocycles. Thiophenes and furanes are π -electron excessive.¹ Oxidative addition to palladium should be faster with π -electron deficient heterocycles; however, we observed generally higher reaction rates with π -electron excessive heterocycles. This observation suggests that the oxidative addition of the aryl bromide is not the rate-limiting step with this catalyst.

Next, we tried to evaluate the influence of the substituents on the boronic acid on the rate of this reaction; therefore, we investigated the coupling of 4-fluoro-, 4-methoxy- and 3-(trifluoromethyl)benzene boronic acids **14–16** with heteroaryl bromides. Lower reaction rates were observed with all these functionalised arylboronic acids than with simple phenylboronic acid **13**. Coupling of **14–16** with 3-bromopyridine **3** led to products **19–21** with TONs of 96 000, 120 000 and 710 000, respectively. Coupling with **12** led to adducts **32–34** with TONs of 620 000, 710 000, 880 000, respectively. In order to have a more accurate idea of the influence of the electronic factor on the rate of this reaction we performed a competitive reaction using an equimolar mixture of **14** and **15** in the presence of aryl bromide **12** (Scheme 2). We observed the formation of an almost equimolar mixture of coupling products **32** and **33**. This result seems to indicate that the lower reaction rates observed with functionalised arylboronic acids more likely comes from partial poisoning of the catalyst rather than from electronic factors.

Finally, in order to present a simple procedure using a commercially available ligand, we performed a few reactions with dppe. Palladium catalyst prepared with dppe as ligand is less active than with **1** by a factor of ten; however, dppe–Pd complex is much more stable and efficient than the popular but unstable catalyst Pd(PPh₃)₄. With dppe TONs of 82 000, 83 000 and 870 000 were obtained with substrates **3**, **7** and **12**, respectively.

In conclusion, Tedicyp–palladium complex provides a convenient catalyst for the cross-coupling of heteroaromatics with arylboronic acids. In the presence of this catalyst heteroaromatics, such as pyridines, quinolines, thiophenes, an indole or a furane, led to the coupling products in good yields. The reaction can be performed with as little as 0.00001% catalyst. This procedure represents an environmentally friendly method for the preparation of heterobiaryl compounds.

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References

- For examples of palladium cross-coupling with heteroaromatic compounds, see: Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000.
- For reviews on the cross-coupling of aryl bromides with arylboronic acids, see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, 147; (b) Suzuki, A. *Metal-catalysed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley: New York, 1998; (c) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-catalysed Organic Reactions*; Academic Press: San Diego, 1997; (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457.
- For a review on biaryl synthesis via cross-coupling, see: Stanforth, S. *Tetrahedron* **1998**, 54, 263.
- For examples of efficient catalysts for Suzuki cross-coupling, see: (a) Beller, M.; Fischer, H.; Herrmann, A.; Öfele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Eng.* **1995**, 34, 1848; (b) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095; (c) Wolfe, J.; Singer, R.; Yang, B.; Buchwald S. *J. Am. Chem. Soc.* **1999**, 121, 9550; (d) Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901; (e) Wolfe, J.; Buchwald S. *Angew. Chem., Int. Ed. Eng.* **1999**, 38, 2413; (f) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, 6, 1830; (g) McGuinness, D.; Cavell, K. *Organometallics* **2000**, 19, 741; (h) Bedford, R.; Welch, S. *Chem. Commun.* **2001**, 129.
- For recent examples of Suzuki cross-coupling with heteroaromatics, see: (a) Zhang, H.; Kwong, F. Y.; Tian, Y.; Chan, K. S. *J. Org. Chem.* **1998**, 63, 6886; (b) Sava, X.; Ricard, L.; Mathey, F.; Le Floch, P. *Organometallics* **2000**, 19, 4899; (c) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2000**, 41, 8717; (d) Cooke, G.; Augier de Cremiers, H.; Rotello, V.; Tarbit, B.; Vanderstraeten, P. *Tetrahedron*, **2001**, 57, 2787.
- For a review on the synthesis of polypodal diphenylphosphine ligands, see: Laurenti, D.; Santelli, M. *Org. Prep. Proc. Int.* **1999**, 31, 245.
- (a) Laurenti, D.; Feuerstein, M.; Pèpe, G.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, 66, 1633; (b) Feuerstein,

- M.; Laurenti, D.; Doucet, H.; Santelli, M. *Chem. Commun.* **2001**, 43; (c) Feuerstein, M.; Laurenti, D.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, 42, 2313.
8. Feuerstein, M.; Laurenti, D.; Bougeant, C.; Doucet, H.; Santelli, M. *Chem. Commun.* **2001**, 325.
9. As a typical experiment, the reaction of 3-bromoquinoline **7** (2.08 g, 10 mmol), benzenboronic acid **13** (2.44 g, 20 mmol) and K_2CO_3 (2.76 g, 20 mmol) at 130 °C during 20 h in dry xylene (10 mL) in the presence of *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/[PdCl(C₃H₅)₂] complex (0.00001 mmol) under argon affords the corresponding product **26** after evaporation and filtration on silica gel in 82% (1.68 g) isolated yield.