A facile one-step catalytic synthesis of biphenyl phosphanes by Suzuki coupling

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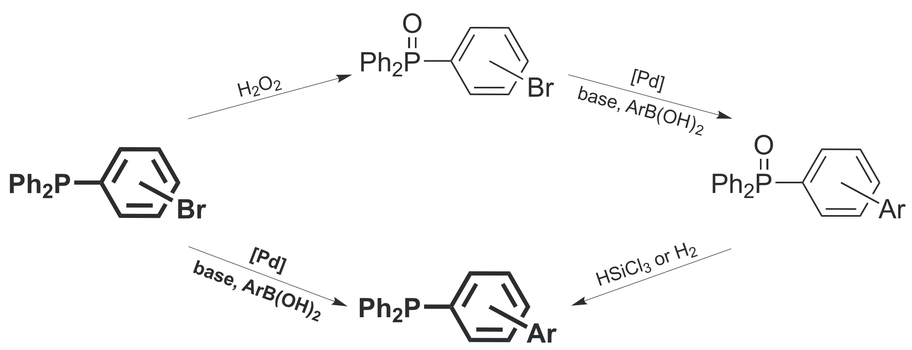
Introduction

The palladium catalysed Suzuki reaction has emerged as an extremely efficient and important carbon–carbon cross-coupling reaction. [1] It is of great importance in total synthesis [2] and is used at an industrial level for the preparation of pharmaceuticals and fine chemicals. [3] This catalytic reaction has several advantages including relative mild reaction conditions, tolerance of a broad range of functionalities, and its compatibility towards water as solvent or co-solvent. [1]

In homogeneous catalysis Lewis-base ligands including phosphanes are essential, as their electronic and steric properties allow to control, for example, the reaction rate and regio- and stereoselectivity. [1b] Recently, biphenyl-based phosphanes became attractive as auxiliary ligands in palladium catalysed carbon–carbon cross-coupling reactions. [4] For the synthesis of such phosphanes most likely classical methodologies including Grignard and lithium reagents were used, [5] while lately the Suzuki coupling reaction was applied to phosphane oxides. [6] However, the latter catalytic procedure requires a consecutive three-step reaction sequence including phosphorus oxidation, carbon–carbon cross-coupling and phosphorus reduction to obtain the corresponding biphenyl phosphanes (Figure 1). [6c–g] The most limiting aspect of this synthesis methodology is the reduction of the phosphane oxide by chlorosilanes or hydrogen significantly lowering the over-all yield.

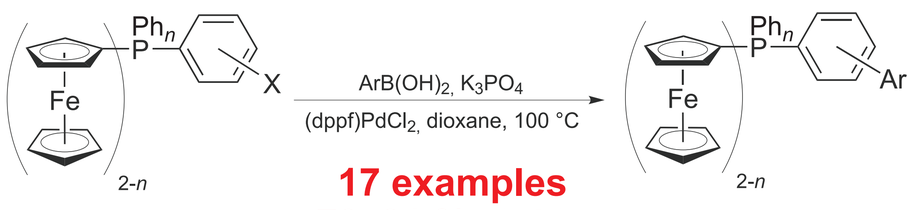
This prompted us to develop a more simple and hence, straightforward synthesis protocol for the preparation of biphenyl phosphanes avoiding phosphorus oxidation (Figure 1).



Scheme 1: Two routes for the synthesis of biphenyl phosphanes.

Results and Discussion

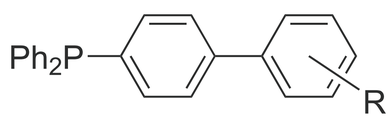
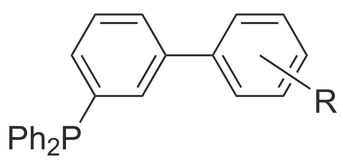
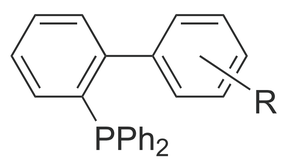
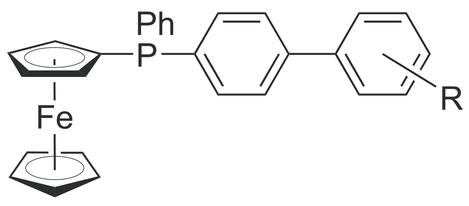
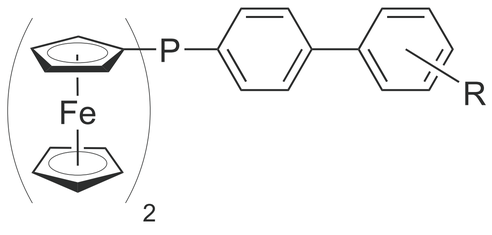
The carbon–carbon coupling reactions were carried out with compounds $Fc_{2-n}Ph_nP(C_6H_4X)$ (X = 4-Br, *n* = 2; X = 3-Br, *n* = 2; X = 2-Br, *n* = 2; X = 4-Br, *n* = 1; X = 4-Br, *n* = 0), 1.1 equiv. of the boronic acids $(HO)_2BAr$ (Ar = C_6H_5, C_6H_3-2-Cl-5-CF_3, C_6H_4-2-OMe, C_6H_4-3-NO_2, C_6H_4-4-Me, C_6H_4-4-NMe_2, C_6H_4-4-OMe), 3.3 equiv. of K_3PO_4 in 1,4-dioxane as solvent in presence of (dppf)$PdCl_2$ (loading of 0.5 mol-% Pd) under inert gas atmosphere at 100°C (Figure 2, Table 1). After appropriate work-up, the corresponding coupling products $Fc_{2-n}Ph_nP(C_6H_4Ar)$ could be isolated as colorless or orange to red solids in yields > 70 %. As expected, the homo-coupling of the appropriate boronic acids were formed as by-products and could be separated by column chromatography.



17 examples
70–91 % yields

Scheme 2: Synthesis of biphenyl phosphanes by Suzuki coupling.

Table 1: Synthesis of biphenyl phosphanes by Suzuki coupling. [a]

Product	Entry	R	Yield / % [b]
	1	H	73
	2	4-OMe	70
	3	4-NMe_2	86
	4	3-NO_2	71
	5	H	75
	6	4-OMe	83
	7	3-NO_2	74
	8	H	79
	9	4-Me	91
	10	4-NMe_2	74
	11	4-Me	71
	12	2-Cl-5-CF_3	75
	13	2-OMe	79
	14	H	77
	15	4-OMe	82
	16	4-NMe_2	78
	17	3-NO_2	72

[a] Reaction conditions: 1.1 equiv. $ArB(OH)_2$, 3.3 equiv. K_3PO_4, 0.5 mol-% (dppf)$PdCl_2$, 10 mL 1,4-dioxane, 100 °C.
[b] Based on isolated material.

Due to the presence of NMR active phosphorous in substrate and product, the Suzuki coupling can easily be monitored by $^{31}P\{^1H\}$ NMR spectroscopy (Figure 1).

The catalytic reaction also takes place when no additional phosphane is present, for example, when $Pd_2(dba)_3$ (dba = dibenzylidenacetone) is used as palladium source. However, this tactic reduces the over-all yield due to complexation of the palladium atoms – in case of (dppf)$PdCl_2$ no ligand scrabble occurs. Furthermore, a higher palladium concentration or a longer reaction time is necessary when $Pd_2(dba)_3$ is used instead of (dppf)$PdCl_2$.

Carbon–carbon bond forming reactions of Ph_2P-C_6H_4-4-$B(OH)_2$ and Fc_2P-C_6H_4-4-$B(OH)_2$, respectively, with, for example, Br-C_6H_4-4-Me in presence of catalytic amounts of a Pd source under similar reaction conditions (vide supra), however, did result in the formation of a dark brown slurry, from which the expected coupling product could not be isolated. The substitution of Br by $(HO)_2B$ has obviously significant consequences on the coupling reaction. Apparently, differences exist in the tolerance of the boron or halide component towards the corresponding functionality in case of phosphorus(III) compounds. Likely, the non-polar R_2P entity influences the nature of the boronic acid or its base adduct thus avoiding the formation of the catalytic active species or trans-metallation.

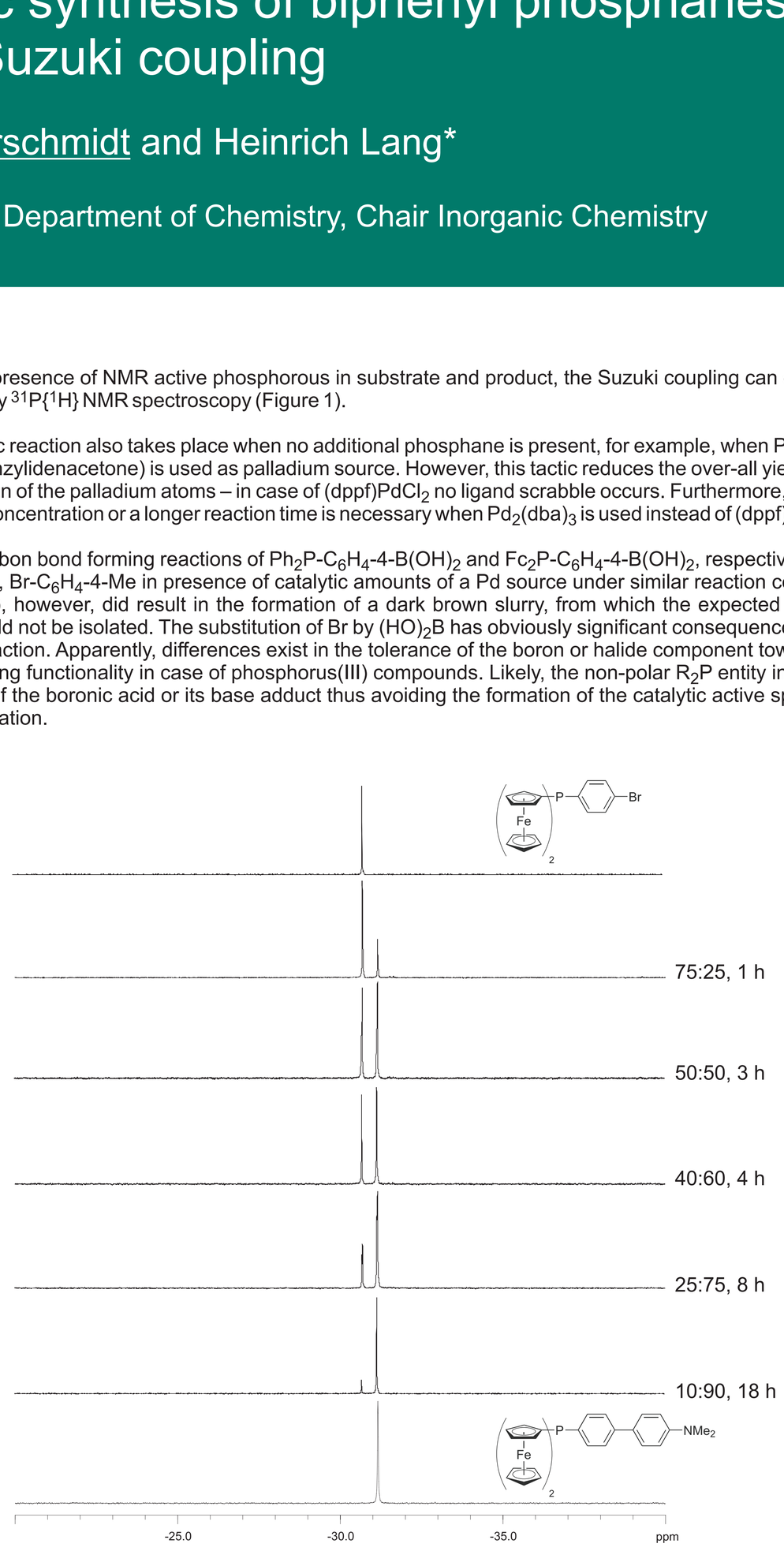


Figure 1: $^{31}P\{^1H\}$ NMR spectroscopic monitoring of the Suzuki coupling.

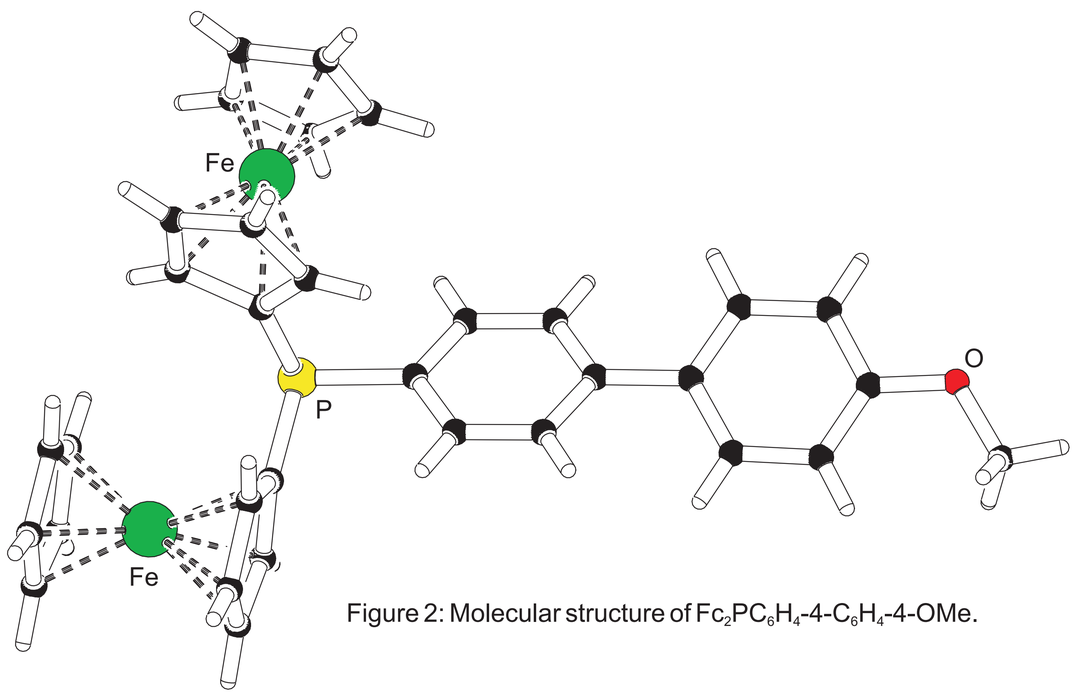


Figure 2: Molecular structure of $Fc_2PC_6H_4$-4-C_6H_4-4-OMe.

Conclusion

In summary, a facile one-step catalytic route to biphenyl phosphanes of general composition $Fc_{2-n}Ph_nP(C_6H_4Ar)$ (Ar = C_6H_5, C_6H_3-2-Cl-5-CF_3, C_6H_4-2-OMe, C_6H_4-3-NO_2, C_6H_4-4-Me, C_6H_4-4-NMe_2, C_6H_4-4-OMe; *n* = 2, 1, 0) via Suzuki coupling has been reported and it was shown that this synthesis protocol is applicable both for different phosphane substituents and boronic acid substrates without phosphorus protection; this methodology permits an efficient and hence, convenient access to biphenyl phosphanes featuring diverse electronic and steric properties.

References and Acknowledgement

[1] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) *Transition Metals for Organic Synthesis*, (Ed.: M. Beller, C. Bolm), 2nd ed., Wiley-VCH, Weinheim, **2004**.
[2] K.C. Nicolaou, P.G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[3] a) K.C. Nicolaou, C.N.C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem. Int. Ed.* **1999**, *38*, 2096; b) D.L. Boger, S. Miyazaki, S.H. Kim, J.H. Wu, S.L. Castle, O. Loiseleur, Q. Jin, *J. Am. Chem. Soc.* **1999**, *121*, 10004; c) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; e) N. Yasuda, *J. Organomet. Chem.* **2002**, *653*, 279; f) C.E. Tucker, J.G. de Vries, *Top. Catal.* **2002**, *19*, 111.
[4] See, for example: R. Martin, S.L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461 and references therein.
[5] a) H. Tomori, J.M. Fox, S.L. Buchwald, *J. Org. Chem.* **2000**, *65*, 5334; b) S. Kaye, J.M. Fox, F.A. Hicks, S.L. Buchwald, *Adv. Synth. Catal.* **2001**, *343*, 789.
[6] a) M. Czupik, N. Bankey, E. Fossum, *Synth. Commun.* **2004**, *34*, 705; b) M. Albrecht, Y. Song, *Synthesis* **2006**, 3037; c) P. Machnitzki, M. Tepper, K. Wenz, O. Stelzer, E. Herdtweck, *J. Organomet. Chem.* **2000**, *602*, 158; d) H.-B. Yu, Q.-S. Hu, L. Pu, *J. Am. Chem. Soc.* **2000**, *122*, 6500; e) C. Baillie, W. Chen, J. Xiao, *Tetrahedron Lett.* **2001**, *42*, 9085; f) W. Tang, Y. Chi, X. Zhang, *Org. Lett.* **2002**, *4*, 1695; g) C. Baillie, J. Xiao, *Tetrahedron* **2004**, *60*, 4159.

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