

Note

Suzuki–Miyaura coupling in the presence of (2,2,2-triferrocenylethyl)diphenylphosphane

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Abstract

The electron rich and sterically bulky title phosphane was prepared and efficiently applied in the palladium catalyzed Suzuki–Miyaura cross-coupling reaction. With electron rich aryl chlorides and bromides the yields and reaction times were significantly improved by microwave heating.

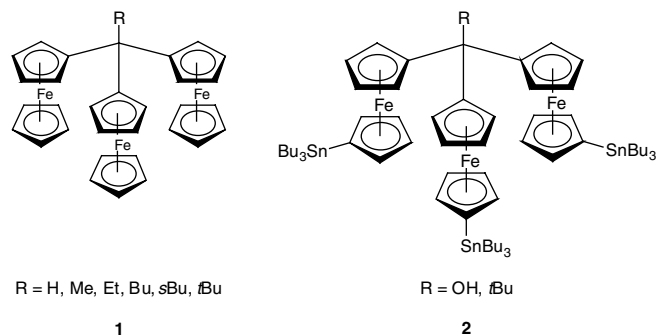
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Much attention has lately been devoted to the chemistry of ferrocene derivatives, which combine chemical versatility with high thermal stability. These, together with its exceptional electrochemical properties, make ferrocene-based complexes promising candidates for the preparation of new materials with applications in organic synthesis, catalysis and material science [1]. Although a wide range of molecular structures containing more than one ferrocene unit have been described [2–10], triferrocenylmethyl derivatives have been investigated little so far, and this is most likely because of the difficulties encountered in the synthesis of the triferrocenylmethyl scaffold. Triferrocenylmethanol has been previously synthesized by Pauson and Watts by the addition of ferrocenyllithium to diferrocenylketone. The stumbling block in this sequence actually is the availability of the starting materials rather than their conversion to triferrocenylmethanol [11].

As part of a program focussing on the syntheses and applications of triferrocenylmethane derivatives, we recently reported a general and practically useful method for the synthesis of substituted triferrocenylmethane

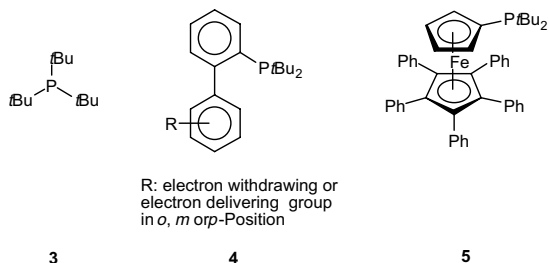
derivatives such as **1** and 1'-substituted derivatives **2** [12]. Herein we disclose results of the use of this new methodology in the synthesis of a triferrocenylmethane based phosphane ligand for the palladium catalyzed Suzuki–Miyaura cross-coupling reaction.



Electron rich and bulky monodentate phosphanes have recently been recognized as important and useful ligands in palladium(0) catalyzed processes. Most attention has recently focused on ligands such as tri-*tert*-butylphosphane (**3**), dialkyl(biphenyl)phosphanes **4** and pentaarylferrocenylphosphane (**5**), since they have been proven to be

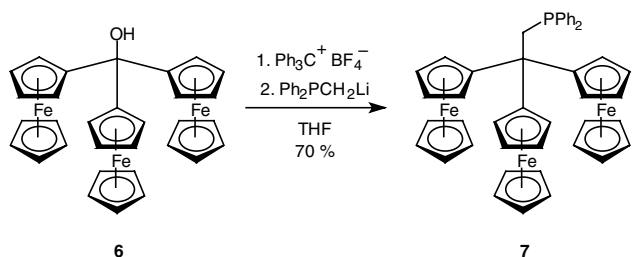
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unique, highly efficient ligands for a large number of transition metal catalyzed transformations such as C–C coupling reactions (Suzuki–Miyaura, Heck, Stille, Sonogashira, Negishi and enolate coupling) and C–O and C–N bond formation reactions [13].



The extraordinary activity of palladium catalysts formed with these electron rich and sterically bulky phosphines in coupling reactions involving aryl chlorides has been explained by an increased propensity of the more electron rich catalyst to an oxidative addition of the aryl halide and an easier decomplexation of one phosphane ligand finally resulting in the formation of the catalytically active Pd(0)L species (L = phosphane) [14]. The so far limited structural diversity of electron rich and sterically bulky monophosphanes causes major interest in the synthesis of novel bulky and electron rich monophosphanes.

In our earlier work we had developed a procedure to incorporate the sterically bulky and electron rich triferrocenylmethyl fragment by reaction of the triferrocenylmethyl carbenium ion with nucleophiles. The carbenium ion was easily generated by treatment of triferrocenylmethanol (**6**) with triphenylmethyl tetrafluoroborate [12]. According to this procedure treatment of the triferrocenylcarbenium ion with lithiated methylphenylphosphane gave phosphane **7** in 70 % yield. **7** was characterized spectroscopically.



Phosphine **7** was tested in the Suzuki–Miyaura coupling reaction of phenylboronic acid and selected electron poor and as well as electron rich aryl bromides and chlorides. Results are summarized in Table 1.

The results indicate that phosphane **7** promotes the Suzuki–Miyaura coupling of aryl bromides and chlorides. Best results were achieved with electron poor aryl halides **9–11**. More electron rich aryl halides such as bromobenzene (**8**) or 4-methylbromobenzene (**12**) give poorer yields. Higher yields and significantly shorter reaction times

became possible by microwave irradiation (250 W, 150 °C, 8 bar) [16]. In particular, the reaction of 4-methylbromobenzene (**12**) gave a fourfold higher yield than with conventional heating, and the reaction time was reduced from 24 h to 1 h. For 4-chlorobenzonitrile (**11**) the yield increased from 92% to 95% with a reduction in reaction time from 72 h to 1 h. The highest yield (97 %) was achieved by using 4-bromoacetophenone (**16**) under microwave irradiation (entry 13). Initial experiments showed Pd(dba)₂ to be a better palladium source than Pd(OAc)₂ (entries 1–3).

Suzuki–Miyaura coupling reactions were first reported in 1981 [17] and have since then been further developed by modifications in the metal catalyst, the phosphane ligand, and reaction conditions such as solvent or the introduction of microwave heating [18–22]. Some of the results shown in Table 1 compare quite well with those of other groups. For example, the reaction with 4-bromoacetophenone (**16**, entry 13) gives 97% yield, while the reaction achieved 91% in a phosphane free, microwave heated reaction. Similarly, the reaction of 4-methoxybromobenzene (**14**, entry 11, 88%) compares to 86% under such conditions [21]. Although more sophisticated diphosphine ligands give better results in some cases [19], the results obtained for 4-chlorobenzonitrile in the presence of **7** particularly with aryl chloride **11** compare very well with those obtained e.g. by Hierso with a much more complicated ferrocene-based phosphane [23] or by Buchwald with 2-(di-*tert*-butylphosphino)biphenyl [15].

In conclusion, we have presented the synthesis of (2,2,2-triferrocenylethyl)diphenylphosphane and demonstrated its suitability as a ligand in the palladium catalyzed Suzuki–Miyaura cross-coupling reaction with several aryl bromides and 4-chlorobenzonitrile. Improved yields and shorter reaction times were realized under microwave irradiation.

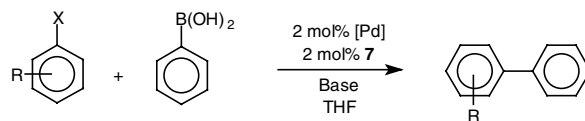
1. Experimental

1.1. (2,2,2-Triferrocenylethyl)diphenylphosphane (**7**)

At 25 °C, a well stirred suspension of triferrocenylmethanol (**6**) (0.666 g, 1.1 mmol) in 50 mL of anhydrous diethyl ether was treated with Ph₃CBF₄ (0.377 g, 1.1 mmol), and the solution was allowed to react until no starting material remained (TLC, CH₂Cl₂). The green precipitate was washed three times with 3 × 50 mL of anhydrous DEE each, dissolved in 50 mL of anhydrous THF and cooled to –78 °C. To this solution (lithiomethyl)diphenylphosphane borane complex, which was obtained from methylphenylphosphane borane complex (0.466 g, 2.1 mmol), *s*-BuLi (1.86 mL, 1.8 M in DEE, 1.0 mmol) and 9.32 mL of THF [24], was added. The reaction mixture was allowed to warm to 25 °C, and after 1 h 40 mL of Et₂NH was added. After stirring for 2 d at 25 °C the volatiles were removed at reduced pressure. The remaining solid was washed with anhydrous CH₂Cl₂ until no product remained

Table 1

Pd-catalyzed Suzuki–Miyaura cross-coupling reactions of aryl halides with phenylboronic acid



Entry	Aryl halide	[Pd]	Base	Product ^a	Reaction time [h]	Isolated yield [%]
1 ^b	C ₆ H ₅ Br (8)	Pd(OAc) ₂	CsCO ₃	17	24	30
2 ^c	C ₆ H ₅ Br (8)	Pd(OAc) ₂	KF	17	24	46
3 ^b	C ₆ H ₅ Br (8)	Pd(dba) ₂	KF	17	19	54
4 ^b	4-NCC ₆ H ₄ Br (9)	Pd(dba) ₂	KF	18	19	95.5
5 ^b	4-O ₂ NC ₆ H ₄ Br (10)	Pd(dba) ₂	KF	19	72	97
6 ^b	4-NCC ₆ H ₄ Cl (11)	Pd(dba) ₂	KF	20	72	92
7 ^b	4-MeC ₆ H ₄ Br (12)	Pd(dba) ₂	KF	21	24	13
8 ^d	4-NCC ₆ H ₄ Cl (11)	Pd(dba) ₂	KF	20	1	95
9 ^d	4-MeC ₆ H ₄ Br (12)	Pd(dba) ₂	KF	21	1	52
10 ^d	2-MeC ₆ H ₄ Br (13)	Pd(dba) ₂	KF	22	1	77
11 ^d	4-MeOC ₆ H ₄ Br (14)	Pd(dba) ₂	KF	23	1	88
12 ^d	2-Bromo-naphtalene (15)	Pd(dba) ₂	KF	24	1	62
13 ^d	4-Bromoacetophenone (16)	Pd(dba) ₂	KF	25	1	97

^a Identified spectroscopically; [15].^b 60–65 °C.^c 80 °C.^d μW: 250 W, 150 °C, 8 bar.

and the ammonium salts were removed by filtration through Celite. The solvent was removed at reduced pressure to yield an orange solid, which was washed with cold degassed methanol, resulting in pure (¹H, ¹³C NMR)**7** (0.616 g, 0.8 mmol, 70%).

¹H NMR (400 MHz, CDCl₃): δ = 3.6 (d, ³J = 4.1 Hz, 2H, CH₂), 3.98 (s, 15H, H_{Cp}), 4.12 + 4.12 (AA'BB' line system, 2 × 6H, H_{CpR}), 7.2–7.4 (m, 10H, Ph) ppm. ¹³C NMR (100 MHz, BB, HMBC, HMBC, CDCl₃): δ = 40.4 (d, ²J_{P,C} = 14.8 Hz, CF₃), 48.4 (d, ¹J_{P,C} = 18.6 Hz, CH₂), 66.3 (br s, CpR-CH), 68.6 (d, ¹J_{P,C} = 5.3 Hz, CpR-CH), 69.0 (Cp), 99.3 (d, ¹J_{P,C} = 3.8 Hz, CpR-CR), 128.1 (d, ¹J_{P,C} = 1.6 Hz, Ph), 133.1 (d, ¹J_{P,C} = 4.9 Hz, Ph), 141.1 (d, ¹J_{P,C} = 3.6 Hz, Ph), 128.0 (Ph) ppm. ³¹P NMR (121.5 MHz, CDCl₃): δ = -21.78 (PPh₂) ppm. MS (ESI, ES+): m/z = 767 [M⁺+H], 783 [M⁺+O]. HRMS (ESI) (C₄₄H₄₀Fe₃P): calc. 767.0916; found, 767.0912 [M+H].

1.2. General procedure for the synthesis of biaryls (GPI)

The palladium salt (0.02 mmol), the boronic acid (0.183 g, 1.5 mmol) and KF (0.174 g, 3.0 mmol) are added to a Schlenk tube under argon. The Schlenk tube is evacuated and then refilled with argon three times. Next the solution of **7** (2.0 mL, 0.01 M in THF, 0.02 mmol) and the arylhalide (1.0 mmol) are added, the Schlenk tube is closed with a stopper, and the reaction is stirred at the indicated temperature for the indicated amount of time. The mixture is hydrolyzed by addition of 25 mL of water, and the mixture is diluted with 25 mL of diethyl ether. The organic layer is washed with 3 × 25 mL of H₂O, dried over MgSO₄, and the solvent is removed at reduced pressure. The biaryl is isolated by column chromatography.

1.3. General procedure for the synthesis of biaryls assisted by microwave irradiation (GP2)

The palladium salt (0.02 mmol), the boronic acid (0.183 g, 1.5 mmol) and KF (0.174 g, 3.0 mmol) are added to a heavy-walled microwave vial under argon. The vial is evacuated and then refilled with argon three times. Next the solution of **7** (2 mL, 0.01 M in THF, 0.02 mmol, 2.0 mL) and the arylhalide (1.0 mmol) are added, the vial closed, and the contents of the flask is irradiated for 1 h with a power of 250 W heating until a maximum of 150 °C. The mixture is hydrolyzed by addition of 25 mL of water, and the mixture is diluted with 25 mL of diethyl ether. The organic layer is washed with 3 × 25 mL of H₂O, dried over MgSO₄, and the solvent is removed at reduced pressure. The biaryl is isolated by column chromatography.

Acknowledgements

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