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Synthesis and reactivity of a cationic palladium complex as possible intermediate in a Suzuki-Miyaura cross-coupling reaction

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Dedicated to Prof. Antonio Togni the winner of the ACS Prize in Fluorine Chemistry 2017.

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ABSTRACT

A stoichiometric reaction of a palladium fluorido complex with an aromatic boronic ester yielded a fluorinated 4-aryl phenylalanine derivative (aryl = 4-$C_6H_4SF_5$) as Suzuki-Miyaura cross-coupling product. Due to the high reactivity of the metal complex, the reaction proceeded smoothly at ambient temperature. Low-temperature NMR investigations revealed a possible role of *trans*-[Pd{BF(4-$C_6H_4SF_5$)(pin)}(Phe^{Et})($PiPr_3$)$_2$] (**5**, Phe^{Et} = bound phenylalanine derivative = 4-$C_6H_4CH_2C${NHC(O)CH_3}(CO_2Et)$_2$, pin = pinacolato = $O_2C_2Me_4$) as a potential intermediate of the transmetallation step. Compound **5** resulted from fluoride transfer from palladium to boron. The similar complex *trans*-[Pd(BF_4)(Phe^{Et})($PiPr_3$)$_2$] (**7**) was generated on treatment of the fluorido complex with $NaBF_4$. Complex **7** is not stable at room temperature. Degradation gave the phosphonium salt [$PiPr_3Phe^{Et}$][BF_4] (**4**). Interestingly, the same compound was also found in the initially mentioned cross-coupling reaction as minor product.

1. Introduction

The formation of a biaryl palladium(II) complex as intermediate in the Suzuki-Miyaura cross-coupling reaction is facilitated by a base, but its role in the transmetallation step is still a matter of discussion [1]. Two distinct reaction pathways are often assumed to be decisive for conversion of an oxidative addition product at a metal centre with a boronic acid or ester in the presence of a base [1e,f,l]. On the one hand the base could react with the boronic compound to generate a more nucleophilic boronate first, capable of reacting with the oxidative addition product. On the other hand, the base might replace the metal-bound halogen atom of the oxidative addition product. The resulting complex can be of higher reactivity towards the boronic acid or ester. Both possibilities might facilitate a proper transmetallation which yields a biaryl palladium(II) compound. Amatore, Jutand and coworkers described antagonistic effects using fluoride or hydroxide as base in the coupling [1h,i,k–n]. They revealed that the fluorido complex *trans*-[PdF(4-C_6H_4CN)(PPh_3)$_2$] is a highly reactive key intermediate in the transmetallation step whereas the boronates [$B(C_6H_5)(OH)_{3-n}(F)_n$]$^-$ (n = 1–3) have to be regarded as unreactive compounds [1h,i]. Thus, a transmetallation via a fluorido complex is clearly favored. It has been reported that the fluorido complex *trans*-[PdF(Phe^{Et})($PiPr_3$)$_2$] (**1**) revealed a remarkable high reactivity towards the boronic ester 2-$BpinC_5NF_4$ [1a]. Note that **1** was synthesized by treatment of its bromo analogue *trans*-[PdBr(Phe^{Et})($PiPr_3$)$_2$], with NMe_4F in CD_2Cl_2 at room temperature [1a]. However, the complex *trans*-[Pd{BF(2-C_5NF_4)(pin)}(Phe^{Et})($PiPr_3$)$_2$] was observed after a fluoride transfer from palladium to boron and is assumed to be an intermediate or a resting state of the coupling reaction [1e,1f,1m,1n,2]. In this contribution, we report on the reactivity of the fluorido complex *trans*-[PdF(Phe^{Et})($PiPr_3$)$_2$] (**1**) towards the boronic ester 4-$BpinC_6H_4SF_5$ and also of **1** with $NaBF_4$.

2. Results and discussion

Treatment of the fluorido complex *trans*-[PdF(Phe^{Et})($PiPr_3$)$_2$] (**1**) with equimolar amounts of the boronic ester 4-$BpinC_6H_4SF_5$ in the absence of additional base at room temperature led to the formation of the cross-coupling product (4-$C_6H_4SF_5$)Phe^{Et} (**2**) as major product within 2 h (Scheme 1). Additionally, [Pd($PiPr_3$)$_2$] (**3**), FBpin and minor amounts of the phosphonium salt [4-$PiPr_3Phe^{Et}$][BF_4] (**4**) were formed. The reaction includes a transmetallation and a reductive elimination step, which are considered to be key-steps of Suzuki-Miyaura cross-coupling reactions. **2** and **4** were characterized by their NMR spectroscopic and HR ESI/MS data. Analytical data for [Pd($PiPr_3$)$_2$] (**3**) are in accordance to literature data [1a,3]. FBpin was identified by its $^{11}B\{^1H\}$ NMR spectrum, where its signal appears as a broad singlet at δ = 22 ppm [4].

The reaction of **1** with 4-$BpinC_6H_4SF_5$ was monitored by variable-temperature NMR spectroscopy starting from −80 °C in [D_8]THF. The $^{19}F\{^1H\}$, $^{31}P\{^1H\}$ and $^{11}B\{^1H\}$ NMR spectra revealed the formation of

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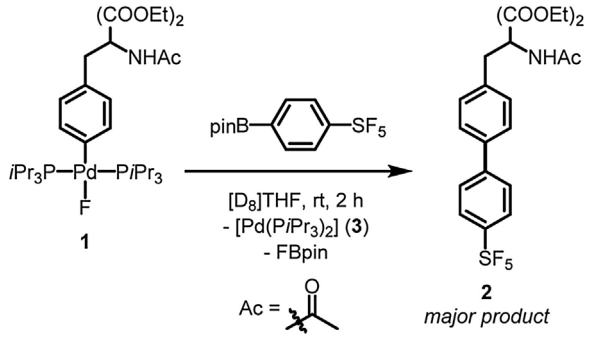
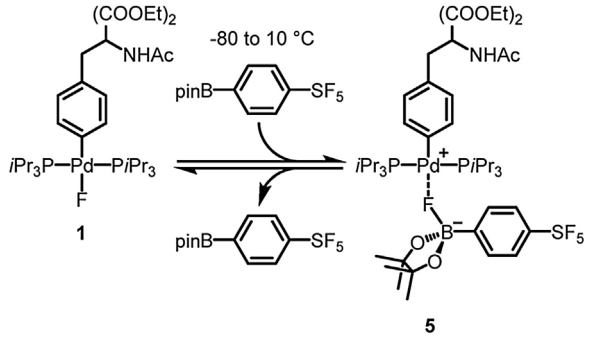


Scheme 1. Reaction of *trans*-[PdF(Phe^{Et})(P*i*Pr$_3$)$_2$] (**1**) with 4-BpinC$_6$H$_4$SF$_5$ at room temperature. [4-P*i*Pr$_3$Phe^{Et}][BF$_4$] (**4**) was formed as minor product in addition to the cross-coupling product **2** (ratio 1:8).



Scheme 2. Reversible formation of the ionic intermediate *trans*-[Pd{BF(4-C$_6$H$_4$SF$_5$)(pin)}(Phe^{Et})(P*i*Pr$_3$)$_2$] (**5**) at low temperatures.

the compound *trans*-[Pd{BF(4-C$_6$H$_4$SF$_5$)(pin)}(Phe^{Et})(P*i*Pr$_3$)$_2$] (**5**) between −80 °C to 10 °C (Scheme 2, Figs. 1 and 2). Compound **5** resulted from a fluoride transfer from the palladium atom of **1** to the boron atom of 4-BpinC$_6$H$_4$SF$_5$. Note that ionic intermediates in cross-coupling reactions were considered before [1a,1e–f,2b,2c,2e,2f,2h,2j]. Although we have no distinct experimental evidence, it is rather likely that the cation *trans*-[Pd(Phe^{Et})(P*i*Pr$_3$)$_2$]$^+$ and its anionic boronate interact with each other like it is the case for [Pd(BF$_4$)(CF=CFCF$_3$)(PCy$_3$)$_2$] [5]. Alternatively, the free coordination side at Pd could also be vacant or coordinated by [D$_8$]THF. The possibility that the transmetallation product *trans*-[Pd(Phe^{Et})(4-C$_6$H$_4$SF$_5$)(P*i*Pr$_3$)$_2$] instead of **5** is formed can be ruled out since no signal for FBpin, which should be liberated simultaneously, was observed by ^{11}B{^{1}H} NMR spectroscopy as it was the case for the room temperature attempt described above. For the cation of **5**, a singlet at δ = 30.9 ppm was obtained by ^{31}P{^{1}H} NMR spectroscopy at −50 °C. No coupling to fluorine was detected, as it is the case in the starting compound **1**. For the boronate [BF(4-C$_6$H$_4$SF$_5$)(pin)]$^-$, three resonances at δ = 88.7, 63.6 and −128.5 ppm were found by ^{19}F{^{1}H} NMR spectroscopy at the same temperature. The first two signals, a quintet and a doublet, were assigned to the SF$_5$ group of **5**, each with a $^2J_{F,F}$ coupling constant of 149 Hz [6]. The latter signal at −128.5 ppm resulted from the fluoride of the B−F unit. A broad singlet at δ = 6 ppm in the ^{11}B{^{1}H} NMR spectrum was found for the boron atom of **5** at −20 °C. The chemical shift of the signals for the anion [BF(4-C$_6$H$_4$SF$_5$)(pin)]$^-$ of **5** are in good accordance to data for [BF(4-C$_6$H$_4$SF$_5$)(pin)]$^-$ with Cs$^+$ as counter ion [1a].

However, the formation of *trans*-[Pd{BF(4-C$_6$H$_4$SF$_5$)(pin)}(Phe^{Et})(P*i*Pr$_3$)$_2$] (**5**) at low temperature was not quantitative. In fact, the fluorido complex *trans*-[PdF(Phe^{Et})(P*i*Pr$_3$)$_2$] (**1**) remained as main complex in between −80 to 10 °C (Scheme 2, Figs. 1 and 2). While the concentration of **5** compared to **1** increased from −80 to −50 °C, a reversed tendency was found by elevating the temperature further until no signal for **5** was detected at −10 °C by ^{31}P{^{1}H} NMR spectroscopy (Fig. 1). In between −10 to 10 °C, signals for both complexes possibly obscure each other, which impedes the detection of **5**. Note that signals for the corresponding boronate of **5** were observed up to 10 °C by ^{19}F{^{1}H} NMR spectroscopy (Fig. 2). According to the ^{31}P{^{1}H} NMR spectra at various temperatures, the highest concentration of **5** was obtained at −50 °C with a ratio for **1** to **5** of 3:1. The generation of **1** seems to be thermodynamically preferred at low temperature. On the other hand, the polarity of THF increases by lowering the temperature which might in turn favor the formation of ionic compound **5** [7]. These opposing effects might explain the simultaneous observation of **1** and **5** in different ratios at different temperatures.

Above −10 °C, the cross-coupling product (4-C$_6$H$_4$SF$_5$)Phe^{Et} (**2**) was liberated along with [Pd(P*i*Pr$_3$)$_2$] (**3**) and FBpin (Scheme 3, Figs. 1 and

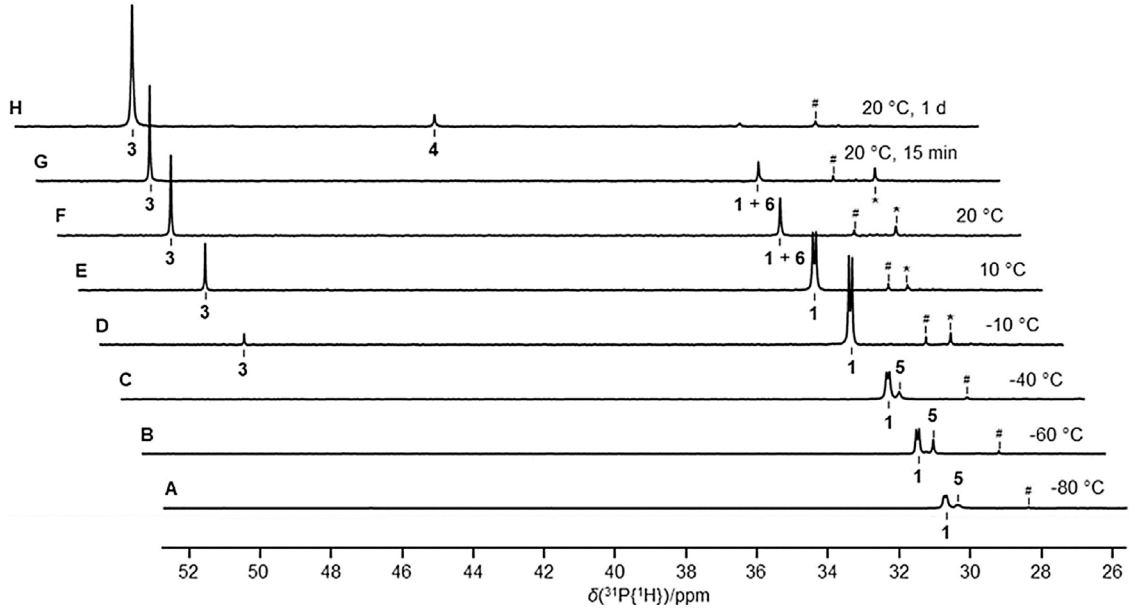


Fig. 1. ^{31}P{^{1}H} NMR spectra of the treatment of *trans*-[PdF(Phe^{Et})(P*i*Pr$_3$)$_2$] (**1**) with 4-BpinC$_6$H$_4$SF$_5$ in [D$_8$]THF at various temperatures. **A-C** Fluorido complex **1** and *trans*-[Pd{BF(4-C$_6$H$_4$SF$_5$)(pin)}(Phe^{Et})(P*i*Pr$_3$)$_2$] (**5**). **D-G** Formation of [Pd(P*i*Pr$_3$)$_2$] (**3**) (along with the cross-coupling product (4-C$_6$H$_4$SF$_5$)Phe^{Et} (**2**), FBpin) and an unknown compound *. **F-G** Formation of *trans*-[Pd(FHF)(Phe^{Et})(P*i*Pr$_3$)$_2$] (**6**) at room temperature which is at equilibrium with **1**. **H** Formation of [Pd(P*i*Pr$_3$)$_2$] (**3**) and [4-P*i*Pr$_3$Phe^{Et}][BF$_4$] (**4**) in a ratio of 5.5:1 as final phosphorus containing products. # *trans*-[PdCl(Phe^{Et})(P*i*Pr$_3$)$_2$] from the synthesis of the Pd fluorido complex **1** [1a].