Short Communication

Synthesis of a Binuclear 6-Purinylpalladium(II) Complex and Its Possible Role in Stille Couplings of 6-Chloropurines

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Pd-Catalyzed cross couplings of halopurines with organometallic reagents like organotin,[1] organozinc,[11,1n,2] organoaluminium[3] or Grignard reagents[4] are valuable reactions for C–C bond formation in purines. Similar coupling reactions of simple aryl halides are generally believed to proceed via catalytic cycles initiated by an oxidative addition of an aryl halide to Pd(0), followed by transmetallation from an organometallic reagent, isomerization and reductive elimination of the coupling product.[5] A detailed understanding of Pd-catalyzed couplings of halopurines is complicated by the fact that the exact nature of the palladium–purine complexes involved in the reactions is unknown. Complexes formed by oxidative addition of heteroaryl halides to Pd(0) species have received relatively little attention,[6] and purine derivatives are not among the heteroarenes studied. However, it is demonstrated that both mononuclear and binuclear complexes might be formed when 2-haloazines or halodiazines are allowed to react with $Pd(PPh_3)_4$.[6a,b,d-g] Among the factors governing the position of the equilibrium between the monomer and the dimer is the electron donating ability of the nitrogen atoms in the heterocyclic ligand; high basicity of the heterocycle favors formation of the dimer.[6g] To the best of our knowledge the role that this class of binuclear palladium–heterocycle complexes may play in Pd-catalyzed couplings of heteroaryl halides has never been investigated. Binuclear complexes with the general structure $(PdLXAr)_2$ have recently been reported to be involved in Pd-catalyzed amination of simple aryl halides.[7] In this communication we report the first study of complexes formed from oxidative addition of a halopurine to Pd(0), and their possible role in Pd-catalyzed couplings.

9-Benzyl-6-chloropurine 1[11] was reacted with $Pd(PPh_3)_4$ in 1,2-dichloroethane (DCE) at 70 °C for 4 h, to give a ca. 9:1 mixture of the monomer 2 and dimer 3 as judged by the NMR spectra of the crude product (Scheme 1).

The ^{31}P NMR spectrum of crude product indicated that the mononuclear complex 2 had the expected *trans* geometry. The equivalent phosphorus atoms in the compound 2 resonated as a singlet (22.8 ppm relative to H_3PO_4), whereas a doublet of doublets would be expected for the phosphorus atoms in the *cis* isomer.[6h] No attempt was made to isolate the monomer 2 owing to its susceptibility to dimerization. The crude mixture of the complexes 2 and 3 was treated with H_2O_2 in 1,2-dichloroethane in order to oxidize the free PPh_3 and shift the monomer–dimer equilibrium completely towards the dimer.[6g] After the oxidation, the binuclear complex 3 could be isolated in 70 % yield.

The dimer 3 was reacted with triphenylphosphine (2 equiv.) in DMF-d_7 or CD_2Cl_2 at ambient temperature, and the reaction was followed by ^{31}P NMR spectroscopy. The monomeric complex 2 formed slowly, and oxidation of triphenylphosphine to triphenylphosphine oxide was also observed. When all the dimer 3 and free triphenylphosphine was consumed, a slow dimerization of the monomer 2 back to the dimer 3 was observed.

Having established that both the binuclear complex 3 and the mononuclear complex 2 are formed after reaction between $Pd(PPh_3)_4$ and the 6-chloropurine 1, the reactivity of the complex 3 towards organotin reagents was examined. The complex 3 was reacted with tributyl(vinyl)tin 4a (2 equiv.) in DCE at 70 °C (Scheme 2). After 3.5 h, almost all the tin reagent was consumed, but only ca. 14 % 6-vinylpurine 5a[11] was formed as judged by the ^1H NMR spectrum. At this time, the formation of Pd(s) could be observed and ^{31}P NMR showed that Ph_3PO was formed.
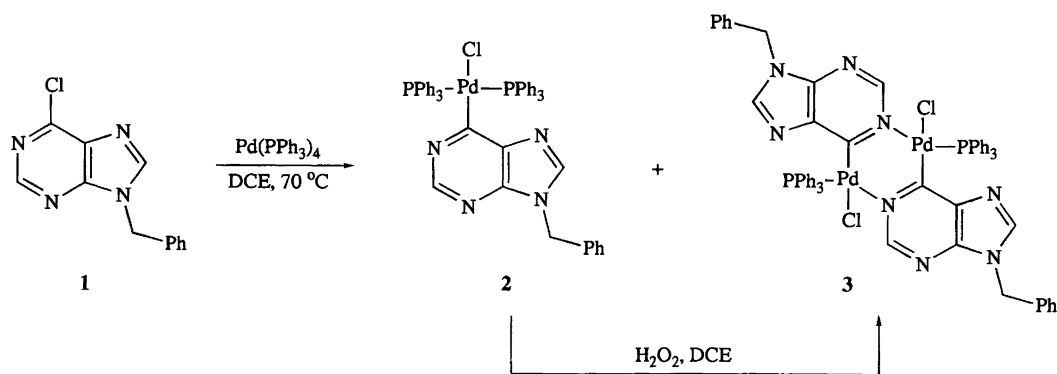
Scheme 1
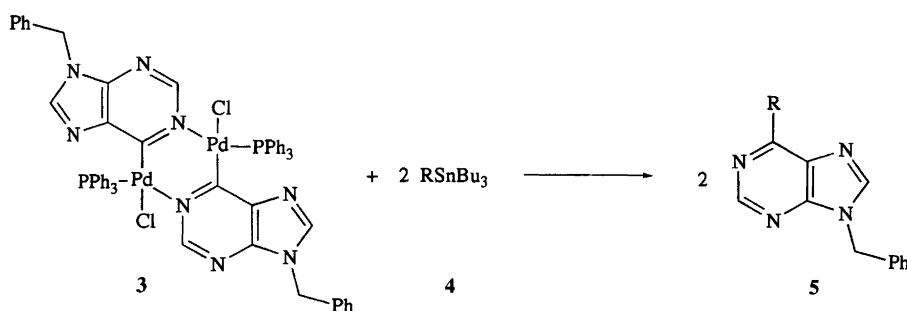
R in 4		Solvent	T /°C	t / h	Yield (%), 5[a]
CH₂=CH	4a	DCE	70	4	ca.14, 5a[b]
Ph	4b	DMF	110	17	77, 5b
2-Thienyl	4c	DMF	100	16	72, 5c

[a] Yield of isolated products. [b] From ¹H NMR of the crude product.

Scheme 2

No PPh₃ or monomer 2 could be detected. Increasing the amount of the tin reagent to 10 equiv. did not result in a significant increase in the yield of 5a, and only traces of the vinylpurine was formed when the reaction was performed in DMF at various temperatures.

The reactivity of the complex 3 towards tin reagents appears to be highly dependent on the nature of the organostannane. Almost all the complex 3 was converted to the 6-arylpurines 5b and 5c,[11] when reacted with 2 equiv. of the aryl(tributyl)tin reagents 4b and 4c in DMF overnight. The products 5b and 5c were isolated in high yields. These results show that the binuclear Pd complex 3 is capable of reacting with organotin reagents to form the compounds 5, and that both purine ligands in the dimer 3 can be converted to the coupling product. The reactions were performed without the addition of triphenylphosphine, and the complex 3 is completely stable for weeks in the solvents used. Hence it can be ruled out that the dimer 3 is in equilibrium with the monomer 2 and that the latter complex is the actual participant in the transmetallation, at least initially. To our knowledge, these are the first examples of trans-metallation reactions of this class of binuclear Pd complexes.

Finally, the ability of the binuclear Pd complex 3 to catalyze cross couplings between the 6-chloropurine 1 and organostannanes 4 was examined (Scheme 3). The coupling with tributyl(vinyl)tin 4a in the presence of 5 mol % of 3 in refluxing DCE was sluggish. After 3.5 h the organotin reagent was consumed, but only ca. 15 % of the vinylpurine 5a was formed, as judged by ¹H NMR spectroscopy. Compound 5a has previously been isolated in high yield when (Ph₃P)₂PdCl₂ was used as a catalyst under otherwise identical reaction conditions.[11] On the other hand, the coupling between the chloropurine 1 and the arylstannanes 4b and 4c proceeded essentially to completion in the presence of 5 mol % of 3, and the isolated yields of the coupling products 5b and 5c were comparable with those obtained when (Ph₃P)₂PdCl₂ was employed as catalyst.[11]

This communication constitutes the first study of complexes formed after oxidative addition of a halopurine to Pd(0), and the results described herein demonstrate that binuclear Pd complexes such as 3 undergo trans-

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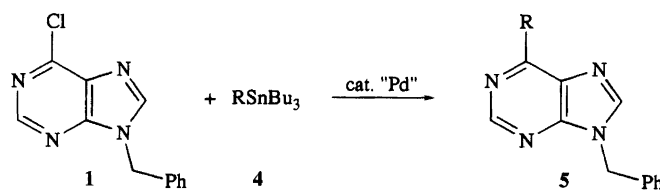
R in 4		"Pd"	Solvent	$T / °C$	t / h	Yield (%), 5[a]
CH₂=CH	4a	3	DCE	Δ	4	ca.15, 5a[b]
CH₂=CH	4a	(Ph₃P)₂PdCl₂	DCE	Δ	4	87, 5a[c]
Ph	4b	3	DMF	110	7	78, 5b
Ph	4b	(Ph₃P)₂PdCl₂	DMF	110	7	75, 5b[c]
2-Thienyl	4c	3	DMF	100	16	91, 5c
2-Thienyl	4c	(Ph₃P)₂PdCl₂	DMF	100	16	87, 5c[c]

[a] Yield of isolated products.   [b] From ¹H NMR of the crude product.   [c] From Ref. 11.

Scheme 3

metallation with organotin reagents and catalyze Stille couplings. Such binuclear complexes might be real intermediates in Pd-catalyzed coupling reactions.

Experimental

The ¹H NMR spectra were recorded at 300 MHz with a Varian XL-300, or at 200 MHz with a Varian Gemini 200 or a Bruker Avance DPX 200 instrument. The ¹³C{¹H} NMR spectra were recorded at 75 MHz or 50 MHz with the same instruments.

³¹P{¹H} NMR spectra were recorded at 121 MHz using the above mentioned Bruker instrument. 1,2-Dichloroethane was distilled from CaH₂ and DMF from BaO. 9-Benzyl-6-chloro-9*H*-purine[11] and 2-(tributylstannyl)thiophene[8] was prepared as described before. All other reagents were commercially available and used as received.

Synthesis of the binuclear complex 3. Triphenylphosphine (839 mg, 3.2 mmol) and Pd₂dba₃·CHCl₃ (414 mg, 0.4 mmol) in dry dichloroethane (50 ml) was stirred at ambient temperature under N₂ for 10 min. 9-Benzyl-6-chloro-9*H*-purine (196 mg, 0.8 mmol) was added and the reaction mixture was stirred at 70 °C for 4 h and concentrated to a small volume *in vacuo*.

The residue was washed with diethyl ether and dissolved in dichloroethane (30 ml). H₂O₂ (35 %, 1.0 ml) was added. The mixture was stirred at ambient temperature for 2 h, dried (Na₂SO₄) and concentrated to a yellow foam. The residue was washed with diethyl ether and dissolved in a minimum amount of dichloromethane. Methanol (20 ml) was added and the solution was concentrated *in vacuo* until precipitation began. The resulting mixture was kept at −4 °C overnight. The product was filtered off, washed with diethyl ether and dried *in vacuo*;

yield 344 mg (70%), powdery yellow crystals. M.p. 229–231°C (dec.). ¹H NMR (200 MHz, CD₂Cl₂): δ 4.90 (d, *J* 15 Hz, 2 H, H_A, CH₂), 5.07 (d, *J* 15 Hz, 2 H, H_B, CH₂), 7.0–7.3 (m, 28 H, Ph), 7.58 (s, 2 H, H-8), 7.8–7.9 (m, 12 H, Ph), 8.70 (s, 2 H, H-2). ¹³C{¹H} NMR (75 MHz, CD₂Cl₂): δ 47.2 (CH₂), 128–131 (Ph), 135–136 (Ph), 140.7, 142.8, 143.4, 152.3, 193.9. ³¹P{¹H} NMR (121 MHz, CD₂Cl₂): δ 28.08.

General procedure for the reaction of the dimer 3 with organotin reagents. The dimer 3 (0.17 mmol) and the organostannane 2 (0.34 mmol) was reacted as shown in Scheme 2. The reaction mixture was evaporated, and the product 5 was isolated as reported earlier.[11]

General procedure for the coupling of 9-benzyl-6-chloro-9H-purine with organotin reagents. The 6-chloropurine 1 (0.5 mmol) was reacted with organostannane 4 (0.7 mmol) in the presence of the dimer 3 (0.02 mmol) under the same conditions as reported earlier.[11]

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