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Synthesis and Properties of π-Complexes of Morphine Alkaloids with Palladium

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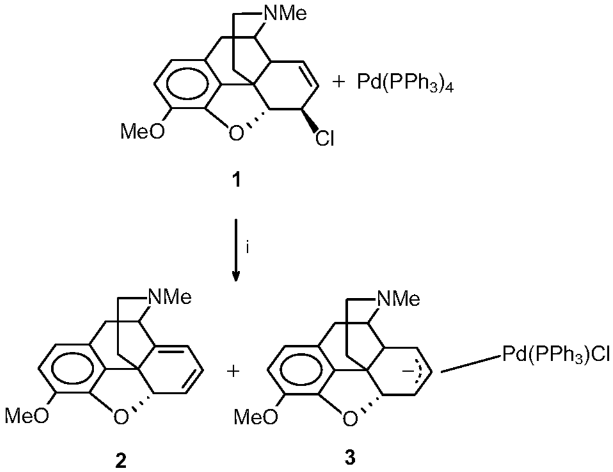
Treatment of 6β-chloro-6-deoxycodeine **1** with $Pd(PPh_3)_4$ yields 6-demethoxythebaine **2** and the π-allylic palladium complex **3**, which further reacts with RZnX to give the cross-coupling product of the allylic ligand and R (compounds **5** and **6**, respectively). The same products are formed upon reaction of 6β-chloro-6-deoxycodeine **1** with RZnX in the presence of catalytic amounts of $Pd(PPh_3)_4$.

Reactions of transition metal complexes with morphine alkaloids are useful for the stereocontrolled introduction of substituents into the morphinan skeleton and for protection of ring C against further modification of the morphine alkaloids.[1–4]

It has been found previously that codeine and morphine react with aryl iodides in the presence of catalytic amounts of palladium(II) salts to give 8β-aryldihydrocodeinones and -morphinones.[5,6] Reactions of 6α-xanthate-6-deoxycodeine and 8α-dithiocarbonate-8-deoxypseudocodeine with $Pd(PPh_3)_4$ leads to elimination of the corresponding thioacids to give 6-demethoxythebaine.[7] It is known that heating of 3-acetoxy-cyclohex-1-ene in the presence of a palladium catalyst results in elimination of acetic acid and formation of cyclohexadiene.

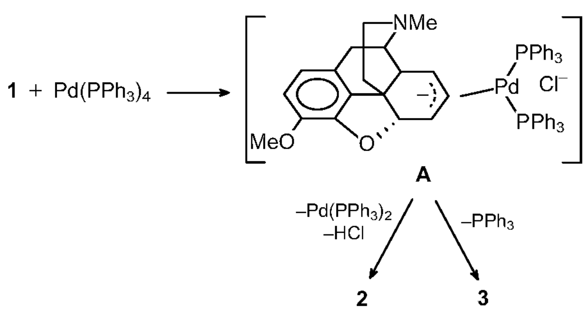
For example, treatment of 3-acetoxy-5-carbomethoxycyclohex-1-ene with 5% $Pd(PPh_3)_4$ afforded 5-carbomethoxycyclohexa-1,3-diene.[8]

We have found that 6β-chloro-6-deoxycodeine **1** reacts with $Pd(PPh_3)_4$ to give two products: 6-demethoxythebaine **2**[9] and the π-allylic palladium complex **3** (Scheme 1).



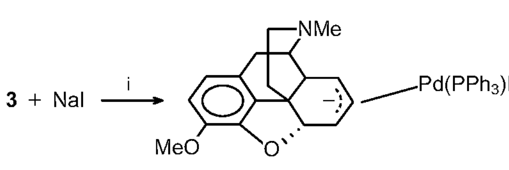
Scheme 1 *Reagents and conditions*: i, THF, 0 °C, 4 h.

One may suggest that oxidative addition of $Pd(PPh_3)_4$ occurs during this reaction and that π-allylic intermediate **A** is formed followed by its reductive elimination to give **2** and **3** (Scheme 2).



Scheme 2

We have found that reaction of **3** with NaI results only in the exchange of the halogen atom to give complex **4** (Scheme 3).

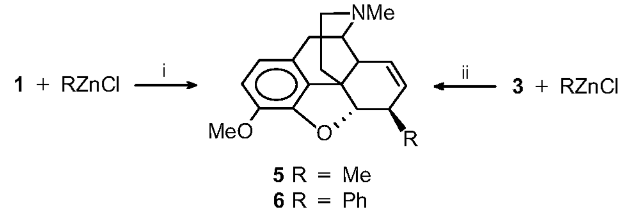


Scheme 3 *Reagents and conditions*: i, THF, 0 °C, 0.5 h.

Reaction of **3** with RZnCl leads to 6β-substituted derivatives of 6-deoxycodeine (compounds **5** and **6**, respectively), which were identical with authentic samples.[10,11] The same products (**5** and **6**) were obtained by reaction of **1** with RZnCl in the presence of catalytic amounts of $Pd(PPh_3)_4$ (Scheme 4).

Since compound **1** does not react with RZnCl alone, one may assume that the reaction proceeds *via* complex **3**.

These are the first examples of π-complexes of morphine alkaloids with palladium. The proposed reaction presents significant potential for the introduction of different substituents into ring C of morphine alkaloids *via* palladium-catalysed cross-coupling reactions.



Scheme 4 *Reagents and conditions*: i, THF, −20 °C, 10% $Pd(PPh_3)_4$, 1 h; **5**: yield 28%; **6**: yield 40%; ii, THF, −20 °C, 1 h; **5**: yield 33%; **6**: yield 42%.

All new complexes gave satisfactory analytical and spectroscopic data.†

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† **3**: yield 31%, m.p. 119–120 °C (decomp.); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.38 (s, 3H, MeN), 3.77 (s, 3H, MeO), 3.85 (m, 1H, H-6), 3.90 (d, 1H, *J* 2.6 Hz, H-5), 5.14–5.90 (m, 2H, H-7, H-8), 6.55 and 6.65 (2d, *J* 8.2, 8.2 Hz, H-1, H-2), 7.19–7.82 (m, 15 arom. H).
4: yield 68%; m.p. 125–126 °C (decomp.); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H, MeN), 3.72 (s, 3H, MeO), 3.79 (m, 1H, H-6), 4.25 (d, 1H, *J* 2.7 Hz, H-5), 5.10–5.76 (m, 2H, H-7, H-8), 6.50 and 6.60 (2d, *J* 8.2, 8.2 Hz, H-1, H-2), 7.36–7.65 (m, 15 arom. H).