

# Unexpected isolation, and structural characterization, of a $\beta$ -hydrogen-containing $\sigma$ -alkylpalladium halide complex in the course of an intramolecular Heck reaction. Synthesis of polycyclic isoquinoline derivatives†

Blandine Clique, Charles-Henry Fabritius, Cédric Couturier, Nuno Monteiro\* and Geneviève Balme\*  
Laboratoire de Chimie Organique 1, CNRS UMR 5622, Université Claude Bernard, Lyon 1, CPE. 43, Bd du 11 Novembre 1918, 69622 Villeurbanne, France. E-mail: balme@univ-lyon1.fr

Received (in Cambridge, UK) 28th November 2002, Accepted 6th December 2002

First published as an Advance Article on the web 19th December 2002

The isolation of a stable  $\beta$ -hydrogen-containing R-PdL<sub>n</sub>-X complex (R = alkyl; X = halide) issued from a Heck reaction is reported together with some aspects of its reactivity.

Transition metal-catalyzed carbocyclizations of unsaturated compounds constitute powerful tools to build up complex polycyclic structures in a minimum number of steps.<sup>1</sup> Intramolecular versions of the Pd-catalyzed arylation of alkenes are among the highest performing transformations available in this field as they may be involved in cascade processes or be integrated in sequential reactions.<sup>2</sup> In recent papers we have demonstrated the synthetic utility of a new Pd-(or Cu)-promoted anionic [3 + 2] cycloaddition reaction involving propargylic amines and electron-deficient olefins, which gives direct access to five-membered heterocycles containing useful functionalities for further synthetic transformations.<sup>3</sup> By building on our expertise in this area, we recently explored the feasibility of combining this type of cycloaddition with a subsequent intramolecular Heck reaction as it should enable the development of versatile routes toward polycyclic isoquinoline derivatives and particularly the pyrrolo[2,1,a]isoquinolines (**4**). These structures are of interest as components of plant alkaloids<sup>4</sup> and biologically active compounds.<sup>5</sup> The strategy relies on the assembly of a *N*-propargyl allylic amine **2** and a arylidene malonate **1** via one carbon–nitrogen and two carbon–carbon linkages (Fig. 1).

We report herein our preliminary results toward this goal which will emphasize the unexpected and unprecedented isolation and characterization of a stable amine-stabilized  $\sigma$ -alkylpalladium halide bearing  $\beta$ -hydrogens in the course of a Heck reaction.

For preliminary studies, we chose dimethyl 2-iodobenzylidene malonate (**1a**), which is readily available by Knoevenagel condensation, as a substrate, and carried out the Cu-catalyzed cycloaddition reaction with *N*-allylpropargylamine (**2a**) under the conditions previously reported (10 mol% *n*-BuLi, 3 mol% CuI(PPh<sub>3</sub>)<sub>3</sub>, THF, rt).<sup>3</sup> The desired 4-*exo*-methylene pyrrolidine **3a** was indeed obtained in good yield (79%). In parallel, we also examined the reaction of dimethyl 1-iodonaphthalen-2-yl-

methylene malonate (**1b**) which, in case of success, would open access to interesting steroid-like polycycles. When subjected to identical reaction conditions, **1b** proved less reactive than its homologue **1a** thus allowing for unidentified side reactions to take place. Clean conversion was nevertheless achieved in 81% yield by simply increasing the quantities of both base (20 mol%) and copper complex (15 mol%). With pyrrolidines **3a,b** in hand, we then turned our attention to the Pd-catalyzed annelation reaction. After examining several catalyst systems we found that PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (20 mol%), in the presence of an excess of PPh<sub>3</sub> (120 mol%), effectively induced the cyclization of **3a** to furnish the targeted pyrrolo[2,1,c]pyrrolidine **4a** in 81% isolated yield. However, when applying the same conditions to **3b**, we observed that most starting material remained unreacted even after prolonged reaction times. After workup and chromatography on silica gel, we were nevertheless able to isolate small quantities of a new compound. Early NMR (<sup>1</sup>H, <sup>13</sup>C, HMBC, and COSY) experiments indicated that a tetracyclic fragment had been obtained. However, to our surprise, it soon appeared that we had in fact intercepted the palladium-containing intermediate **5** (Scheme 1).

Indeed, <sup>1</sup>H NMR showed the presence of 15 hydrogen atoms around  $\delta$  7.0 ppm which suggested that one molecule of PPh<sub>3</sub> had been incorporated into the product. This was confirmed by <sup>31</sup>P{<sup>1</sup>H}NMR analysis which showed one singlet at  $\delta$  39.3 ppm. <sup>13</sup>C{<sup>1</sup>H}NMR showed a doublet at  $\delta$  50.6 ppm (*J*<sub>C,P</sub> 2 Hz) which was in agreement with the expected value for a carbon linked to the metal in sp<sup>3</sup>-hybridized alkylpalladium complexes.<sup>6,7</sup> Further evidence was provided by low resolution mass spectrometry (positive ion) which gave M<sup>+</sup> = 732.3 corresponding to the cationic phosphine-coordinated species [(C<sub>22</sub>H<sub>22</sub>NO<sub>4</sub>)Pd(PPh<sub>3</sub>)]<sup>+</sup> and exhibiting isotopic patterns indicative of the presence of the metal. We then repeated the reaction in the presence of 100 mol% PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and were pleased to obtain after 3 h palladium complex **5** in 62% isolated yield. Remarkably, despite the presence of a hydrogen atom  $\beta$  to the metal, the complex showed unexpected stability towards thermal decomposition (205–210 °C), and proved stable to air and moisture, withstanding shelf storage without noticeable decomposition. While a few stable alkyl-PdL<sub>n</sub>-X complexes (X = halide) which could suffer  $\beta$ -H-elimination have been isolated in the course of Wacker-type reactions,<sup>6,8</sup> to the best of our knowledge, such an event is unprecedented in the field of Heck reactions.<sup>9</sup> Fortunately, the alleged molecular structure of **5** was unambiguously confirmed by X-ray diffraction analysis.

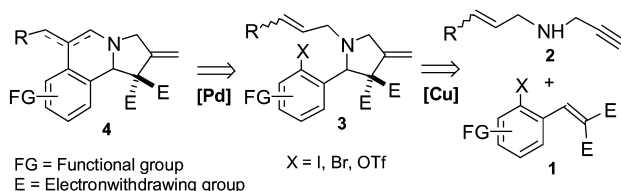
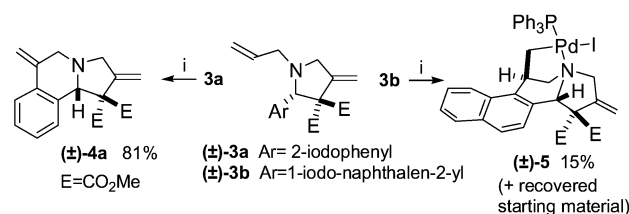
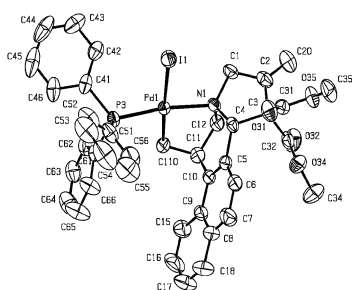


Fig. 1



**Scheme 1** Reagents and conditions: (i) 20 mol% PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>; 120 mol% PPh<sub>3</sub>; K<sub>2</sub>CO<sub>3</sub>, DMF, 90 °C, 20 h.

† Electronic supplementary information (ESI) available: Experimental information for compounds 1–7. Crystal data for **5**. Fig. SI 1 (possible conformations for the Heck insertion step). See <http://www.rsc.org/suppdata/cc/b2/b211856b>

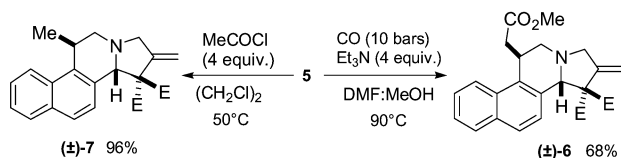


**Fig. 2** ORTEP view of complex **5**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Pd–C(110) 2.061, Pd–N 2.187, Pd–P 2.236, Pd–I 2.721.

An ORTEP representation of the structure is shown in Fig. 2.<sup>10</sup>

The structure shows a phosphine-coordinated  $\sigma$ -alkyl palladium iodo complex stabilized through chelation by the nitrogen atom contained in the carbon ligand backbone. The clear interaction between the metal and the nitrogen atom is reflected in the palladium–nitrogen distance of 2.187 Å which can be regarded as a dative bonding. The metal is thus conformationally locked in a five-membered metallacycle and cannot easily adopt the cisoid conformation needed toward the  $\beta$ -hydrogen which may account for the stability of the complex. However, at this time, the question why switching from the phenyl to the naphthyl nucleus influenced the stability of the intermediates so dramatically remains unanswered. Other factors of steric and/or stereoelectronic nature must be providing further stabilization to the naphthyl-containing alkylpalladium complex **5**. Investigations in this direction are currently underway.<sup>8</sup>

Inhibition of competitive  $\beta$ -hydride eliminations of alkyl-Pd-X intermediates remains a great challenge in the development of palladium-catalyzed coupling processes. Recent successes in this area have mentioned a beneficial stabilization of the intermediate complexes through coordination of the metal with an adjacent heteroatom.<sup>11</sup> The availability of complex **5** therefore offers a remarkable opportunity to investigate its reactivity against carbon-carbon bond forming reactions that would elaborate this intermediate further and preserve the new stereogenic center. To this end, preliminary experiments have been directed toward the synthesis of carbonylated compounds. Gratifyingly, **5** inserted carbon monoxide efficiently. Carbonylative esterification yielded isoquinoline ester **6**<sup>12</sup> in 68% isolated yield. Surprisingly, however, reaction of **5** with an excess of acetyl chloride furnished the hydrogenolyzed compound **7**<sup>12</sup> in almost quantitative yield in place of the expected acetylated compound.<sup>13,14</sup> Under identical conditions benzoyl chloride did not produce any carbonylated compound either (Scheme 2).



**Scheme 2**

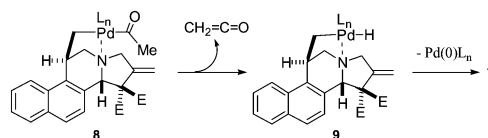
Other coupling reactions involving unsaturated reagents (*i.e.* Suzuki, Stille couplings) are also currently being investigated. The ultimate goal would be to devise catalytic pathways combining the carbocyclization process with a suitable terminating coupling reaction. The results of these studies will be reported in due course.

We acknowledge the financial assistance by the E.U. TMR program. We thank Dr C. Bavoux for the X-ray crystallographic

analysis, Dr D. Bouchu for mass spectrometric analyses, and Dr C. Copéret for his interest in this work.

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- The presence of single sets of signals in the crude <sup>1</sup>H and <sup>13</sup>C NMR spectra indicated that the palladium-containing compound was obtained as a single diastereomer. The stereochemistry of the newly created stereogenic center as depicted in Scheme 1 could be predicted by the reported preference for intramolecular Heck insertions to occur *via* eclipsed orientations of the metal–carbon  $\sigma$  and the alkene  $\pi$  bond (Fig. S1†). See M. M. Abelman, L. E. Overman and V. D. Tran, *J. Am. Chem. Soc.*, 1990, **112**, 6959.
- For interesting discussions on the factors governing the thermal stability of alkylpalladium complexes bearing  $\beta$ -hydrogens see: L. Zhang and K. Zetterberg, *Organometallics*, 1991, **10**, 3806 and references therein.
- Another stable  $\beta$ -hydrogen-containing  $\sigma$ -alkylpalladium complex issued from an intramolecular Heck reaction has been reported recently: M. Oestreich, P. R. Dennison, J. J. Kodanko and L. E. Overman, *Angew. Chem., Int. Ed.*, 2001, **40**, 1439. This complex of a different nature resulted of the intramolecular trapping of an intermediate cationic species [alkyl-PdL<sub>n</sub>]<sup>+</sup>OTf<sup>–</sup> by an internal nitrogen atom to form a stable alkyl-PdL<sub>n</sub>-N palladacycle. It should be noted that in our case triflate derivatives (*i.e.* **3a** with X = OTf) proved essentially unreactive.
- The crystal data have been deposited in the Cambridge Crystallographic Data Center as CCDC 1267/701 (see <http://www.rsc.org/suppdata/cc/b2/b211856b/> for crystallographic files in CIF or other electronic format). C. Bavoux, C.-H. Fabritius, B. Clique, N. Monteiro and G. Balme, *Z. Kristallogr.*, 2001, **216**, 633–634.
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- Compounds **6** and **7** have both been obtained as approximately 1.5:1 mixtures of isomers as indicated by their <sup>1</sup>H and <sup>13</sup>C NMR spectra. We believe that these are conformational isomers having restricted pyramidal nitrogen inversion and further experiments will be carried out to confirm this hypothesis.
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- We may suggest that the putative acyl palladium complex **8** undergoes  $\beta$ -hydrogen elimination of the acyl ligand with elimination of ketene faster than reductive elimination of the ketone. The resulting palladium hydride **9** would then undergo reductive elimination to give **7**.



A similar hypothesis has been considered in reactions of acyl chlorides with ruthenium complexes leading to stable metal hydrides. S. I. Hommeltoft and M. C. Baird, *J. Am. Chem. Soc.*, 1985, **107**, 2548. Further work will be needed so as to understand this behavior more fully.