Synthesis of chiral β-aminoalcohol palladium complexes exhibiting cytotoxic properties†

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Original palladium complexes involving (−)-ephedrine, (−)-norephedrine, L-prolinol, L-valinol and L-isoleucinol have been rapidly prepared in neutral or basic medium and simply purified. They have been fully characterized by classical analytical methods and four of them were characterized by X-Ray analysis. In parallel with the experimental work, HF-DFT(B3LYP/PCM) computations were performed to obtain additional structural information. Their antiproliferative properties have been evaluated and some complexes showed small activities especially towards HT29 human cancer cells.

Introduction

Chiral aminoalcohols play an important role in modern chemistry, in medicinal chemistry or as chiral ligands and auxiliaries in organic chemistry. Syntheses of 1,2 aminoalcohols and their derivatives as chiral moieties have already been largely reported. In medicinal chemistry, they revealed particular interests in cardiovascular diseases, in intracellular mechanisms and also as antidepressive agents.

Most applications in catalysis focused particularly on asymmetric transfer hydrogenation of ketones associated to Zn, Ni, Ru or Ir, and Rh salts or complexes. Some V or Ti complexes were also used for asymmetric sulfoxidation or Strecker reactions. Recently, the implication of 1,3-aminoalcohols and their derivatives associated to transition metals (Pd, Rh, Ti and Cu) in asymmetric organic synthesis was also reviewed.

In the field of materials, aminoalcohates are good ligands for metals such as Cd or Ta in LPCVD or MOCVD processes. As many complexes of transition metals have been reported, a large contribution of Cu, Sn or Pt ones is noticed in the field of biology as DNA cleavers or cytotoxic agents.

In fact, since three decades, a considerable amount of interest has been also devoted to the chemistry of Pd and Pt complexes, mostly focusing on their structural diversities and activities. Concerning antitumor agents, Pt chemistry has been largely developed since the discovery of the cytotoxic activity of cisplatin by Rosenberg in 1969. Most of the time, ligands associated to Pt are amines, diamines or N-containing heterocycles and di- or poly-nuclear complexes which revealed to be generally more active. Other ligands such as thiosemicarbazones, thiourea, aminoalcohols or aminosugars are also employed.

In this field of application, palladium complexes have been also developed but received less attention. Until the 1980s, the Pd-complexes similar to the Pt ones showed low cytotoxic activity. In 1984, Gill et al. described some amine containing Pd-complexes which showed similar activity compared to the activity of cisplatin. Since then, many Pd-complexes containing amines or amino acids revealed some interesting antitumor and antiviral properties.

In the course of our studies in Pd-catalyzed enantioselective hydrogenation of enones, we described the formation of palladium complexes involving (−)-ephedrine as chiral aminoalcohol (Scheme 1). Since preliminary biological evaluation of complexes 1b and 2 (see Table 3 later) was promising, we decided to extend this study to other aminoalcohol ligands. Herein, we report:

(a) the synthesis of new palladium complexes (PdCl₂L₂, Pd(OAc)₂L₂ and PdL₂),
(b) the unusual behaviour in solution of Pd(OAc)₂L₂ complexes, that exhibit different conformations in solution,
(c) the evaluation of the cytotoxicity of these new palladium complexes.

Results and discussion

Aminoalcohols with primary amine function were used to see the influence of the substitution of the nitrogen atom on complexation or biological properties.