



Conformational analysis of a TADDOL-based phosphoramidite *P,N* ligand in a palladium(II) η^3 - π -allyl complex

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ABSTRACT

The most stable conformations of a TADDOL-based phosphoramidite *P,N* ligand coordinated to a palladium(II) η^3 - π -allyl fragment have been investigated using molecular mechanical and quantum mechanical calculations. The conformational analysis initially generated 53 unique structures within 5 kcal/mol and subsequent geometry optimization narrowed the number of low-energy conformers down to 13. The two lowest energy conformers differ mainly in the conformation of the allyl group. The conformer with an endo allyl group has a slightly higher relative energy than the conformer with an exo allyl group. Comparison of the main geometric parameters around the Pd(II) metal center in the two lowest energy conformers with the available X-ray single crystal structures of Pd(II) η^3 - π -allyl complexes of *P,N* ligands shows a good agreement in both the bond lengths and angles. The lowest energy structure has a “chair” conformation of the seven-membered phospho-dioxa-cycloheptane ring and “edge-on/face-on/face-on/edge-on” arrangement of the phenyl rings. The next lowest energy conformer with an exo allyl group has a “twist” conformation of the seven-membered ring and alternating “edge-on” and “face-on” arrangement of the phenyl rings as anticipated from the Knowles “edge-on/face-on” concept. The results of this study support published hypotheses regarding the origin of the chiral induction in the enantioselective Pd(0) catalyzed intramolecular allylic alkylation reaction by the repulsive interactions between one of the phenyl groups in the seven-membered ring in the lowest energy conformer of the ligand with the substrate. As such, the results of this research can be used to guide the synthesis of new and improved variants of this important catalyst family.

1. Introduction

TetraAryl-1,3-Dioxolane-4,5-DimethanOL(TADDOL)-based phosphoramidites (Scheme 1) are exceptionally versatile chiral ligands that have found a wide range of applications in asymmetric transition-metal catalysis [1–6]. The extraordinary attractiveness of this ligand class is due to their robustness, ease of synthesis in enantiomerically pure form from inexpensive tartrate esters and their modular structure that allows for a quick assembly of a ligand library. The ketal backbone, the aryl groups and the substituents on the amine group are the three areas for introducing diversity and can be varied independently to provide diverse ligands from easily accessible starting materials. The steric and electronic characteristics of the ligand can be fine-tuned by modifying the ketal, aryl and amine substituents.

TADDOL-based phosphoramidites enable high enantioselectivities in many impactful reactions, such as Nobel prize-winning class of palladium-catalyzed cross-coupling Heck [7–9] and Suzuki [10–12] reactions; allylic alkylation [12–16], allylation [17–19], C–H

functionalization [20–26] reactions and others [27–34]. Together with Tius, we reported the enantioselective Pd(0)-catalyzed “Nazarov-type” cyclization of diketooesters using a TADDOL-based phosphoramidite ligand incorporating a pyridine ring (Scheme 2) [35]. The nitrogen atom of the pyridyl substituent in the ligand provides a second weak coordination site and improves the asymmetry transfer by limiting the degrees of rotational freedom about the Pd–P axis in the metal-ligand complex [35–37]. Recently, using density functional theory (DFT) calculations, we demonstrated that this reaction is essentially a Pd(0)-catalyzed intramolecular asymmetric allylic alkylation [38]. Our proposed mechanism contains a Pd(0)-Pd(II)-Pd(0) catalytic cycle involving a key Pd(II) η^3 - π -allyl intermediate that leads to the lowest energy pathway for the cyclization and explains the experimentally observed enantioselectivity of this reaction.

It is remarkable, given their widespread use and utility, that to date there is limited structural information available on the palladium(II) complexes of TADDOL-based phosphoramidite ligands [15]. In our previous studies [35], we based our computational model on the

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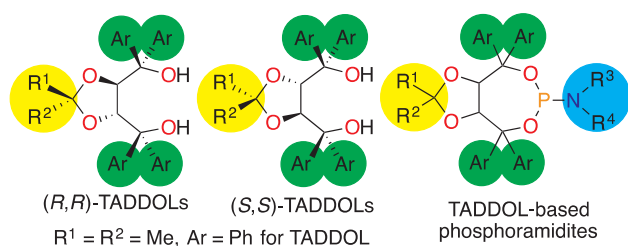
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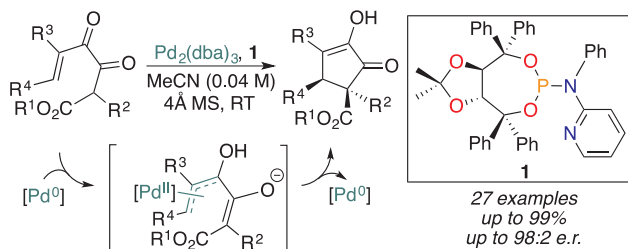
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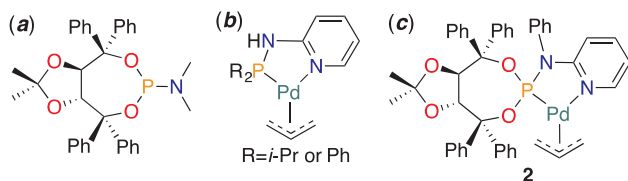
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Scheme 1. Structure of α,α,α -tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) and TADDOL-based phosphoramidites.



Scheme 2. Proposed Pd(II) η^3 - π -allyl intermediate in the Pd(0)-catalyzed intramolecular asymmetric allylic alkylation.



Scheme 3. (a) Monodentate TADDOL-based phosphoramidite ligand, (b) Pd(II) η^3 - π -allyl complexes of *P,N* ligands in reference 40, and (c) proposed structure of a Pd(II) η^3 - π -allyl complex of a TADDOL-based phosphoramidite *P,N* ligand.

available X-ray single crystal structures of a monodentate TADDOL-based phosphoramidite ligand [39] and Pd(II) η^3 - π -allyl complexes of *P,N* ligands [40,41] (Scheme 3). To address this deficiency, in this study, the conformational space of Pd(II) η^3 - π -allyl complexes of TADDOL-based phosphoramidite *P,N* ligands, **2**, is explored using molecular mechanical (MM) and quantum mechanical (QM) methods. To the best of our knowledge, no conformational data have been reported on the Pd(II) η^3 - π -allyl complexes of TADDOL-based phosphoramidite *P,N* ligands.

2. Computational details

The search for low-energy conformers of **2** was performed by first generating all of the plausible conformers using MM methods followed by geometry optimization using QM methods.

2.1. MM methods

Molecular mechanical calculations were performed using Schrödinger's MacroModel 11.8 [42]. Conformational searches were performed using the mixed Monte Carlo/Low Mode (MC/LMOD) methods [43] and the OPLS3 force field [44] as implemented in the MacroModel software. The dielectric constant (ϵ) was set at 36.64 for acetonitrile. Three independent conformational searches with a maximum number of 200,000 steps was conducted. A 100,000-step conformational search also gave similar results. All 53 non-hydrogen atoms were used for comparison when eliminating redundant conformers. The energy window for saving structures was set to 5 kcal/mol. The Truncated Newton Conjugate Gradient (TNCG) minimization method with an energy convergence threshold of 0.01 kcal/(mol Å) was used for the

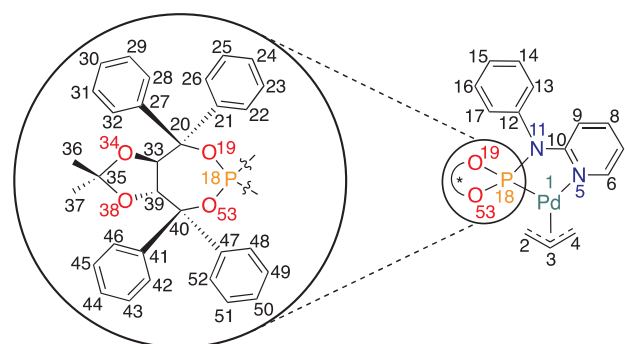


Fig. 1. Numbering of atoms in **2**.

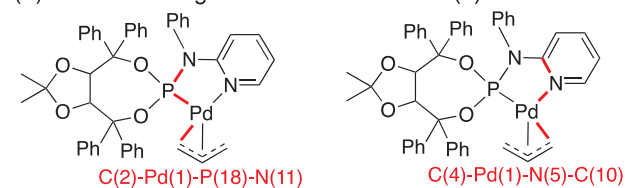
geometry optimization [45].

The structures with relative energies lower than 5 kcal/mol after 100,000 minimization iterations were further optimized by QM methods. The starting geometry of **2** was generated from the available X-ray single crystal structures of a monodentate TADDOL-based phosphoramidite ligand [39] and Pd(II) η^3 - π -allyl complexes of *P,N* ligands [40] and optimized by DFT before the conformational search. The numbering of the atoms of **2** is displayed in Fig. 1. The torsional angles C(2)-Pd(1)-P(18)-N(11) and C(4)-Pd(1)-N(5)-C(10) were constrained to preserve the square-planar coordination environment around the Pd(II) metal center. The C(5) and C(8) atoms are fixed as chiral centers. All single bonds were allowed to rotate, except the bonds involved in the ring closures (N(11)-P(18), C(20)-C(33) and C(33)-O(34)) and constrained bonds (Fig. 2).

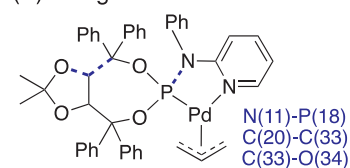
2.2. QM methods

All quantum mechanical calculations were performed using Gaussian 09 suite of programs [46]. The starting geometry of **2** and low-energy conformers found by MM methods were fully optimized in redundant internal coordinates without any symmetry constraints [47] with DFT and a wave function incorporating the hybrid functional of Truhlar and Zhao, M06 [48]. The Pd and P atoms were represented with the effective core pseudopotentials of the Stuttgart group and the associated basis sets improved with a set of *f*-polarization functions for Pd ($\alpha = 1.472$) [49] and a set of *d*-polarization functions for P ($\alpha = 0.387$) [50]. The remaining atoms (C, H, N and O) were represented with the 6-31G(d,p) basis sets [51]. The geometries were fully optimized with tight convergence criteria and with ultrafine integration grid sizes. The

(a) 2 torsional angle constraints around Pd(II) metal center:



(b) 3 ring closures:



(c) 15 rotatable bonds:

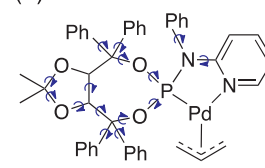


Fig. 2. Conformational search protocol for **2**. (a) The torsional angle constraints are shown in red, (b) the ring closures are shown with a dotted blue line, and (c) rotatable bonds are shown with blue arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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