Hessisches Kompetenzzentrum
für Hochleistungsrechnen

Investigation of the Diastereodivergent Asymmetric Allylic Alkylation of Cyclobutenes

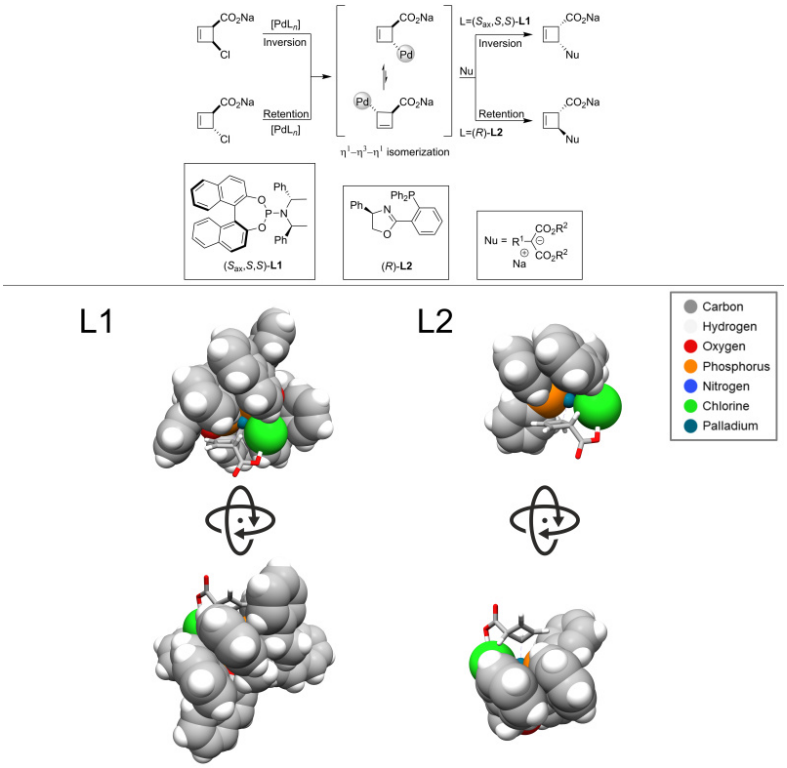


Figure 1: Reaction scheme of the allylic alkylation of cyclobutene's using ligand L1 or L2 (upper) and computed structures for the cyclobutene palladium complexes with ligands L1 or L2 (lower).

Introduction

The Pd-catalyzed asymmetric allylic alkylation of cyclobutenes is known to proceed in a deracemizing, de-epimerizing and diastereodivergent fashion, with the choice of ligand (L1 or L2) controlling the absolute and relative configuration of the product (Figure 1, upper). The reasons for this behavior are unknown. We aim at elucidating the reaction mechanism with a combination of experimental methods and quantum chemical calculations. Since the ligands used for this reaction as well as the resulting metal complexes are too large to be calculated on a personal computer, High Performance Computing (HPC) is an essential part of this project.

Methods

The computational investigation of structural details of the palladium complexes was performed initially using semi

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Clusters
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Software
ORCA

Institute
Organic Structure Analysis

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empirical Tight-Binding Quantum Chemical Methods. By employing state of the art metadynamics simulation-based screening procedures, ensembles of conformers were generated. The obtained geometries were further refined using Density Functional Theory (DFT). Chemical shifts were calculated using gauge-independent atomic orbital (GIAO)-DFT.

Results

Experimental screening of the oxidative oxidation revealed on the one hand the importance of the carboxyl group of the substrates for their discrimination with L2. While on the other hand the deprotonation of the carboxylic acid moiety of the substrates was found to be important for the energetic discrimination using L1. After the oxidative addition only the anti-configured complexes are reactive towards nucleophiles as a result of internal Palladium-oxygen chelation for the other substrates. Electrospray Ionization High Resolution Mass Spectrometry (ESI-HRMS) and ^{31}P-Nuclear Magnetic Resonance (NMR) analysis of reaction mixtures showed the formation of syn-configured alkylated cyclobutenes with L1 and anti-configured products with L2. To possibly gain insight into these intriguing reactivities, a high number of conformers for the different palladium cyclobutene complexes was generated. The DFT optimized structures and their calculated chemical shifts could be correlated with experimentally measured chemical shifts. Furthermore, the DFT calculations on the structures provided indications for the steric and electronic nature of the differences between the ligands and the reactivity of their complexes (Figure 1, lower).

Discussion

The findings in this study allow for a proposal of a reaction mechanism (Figure 1, upper) for the allylic alkylation of cyclobutenes using palladium catalysis. The observed stereochemical dichotomy in oxidative addition and nucleophilic attack based on the ligand chosen, is to the best of our knowledge unprecedented in allylic alkylation chemistry. No definitive answer in respect to the hapticity of the attacked intermediate palladium complexes could be made. For this, the prediction of ground state geometries of the transition metal containing complexes is a first step towards predicting their reactivities, especially since flexible ligands can adopt different conformations which either hinder or allow different reaction trajectories. With further validation of the palladium ligand complexes we hope to pave the path for future investigations into the full reaction mechanism.

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Publications

Primozic, J. J.; Ilgen, J.; Maibach, P.; Brauser, M.; Kind, J.; Thiele, C. M.: "Pd-Catalyzed Asymmetric Allylic Alkylation of Cyclobutenes: From Double Inversion to Double Retention", Journal of the American Chemical Society Article, 2023 https://doi.org/10.1021/jacs.3c03590

Primozic, J.J.; Ilgen, J.; Maibach, P.; Thiele, C.M.: "Diastereodivergent Asymmetric Allylic Alkylation of Cyclobutenes: A Challenging Mechanistic Puzzle", Balticum Organicum Syntheticum, Vilnius/Lithuania, 07/22

Reference

Primozic, J. J.; Thiele, C.M.: "Diastereodivergent Asymmetric Allylic Alkylation of Cyclobutenes: Kinetics and HPLC-MS Studies" International Symposium on Synthesis and Catalysis 2021, Évora/Portugal, 09/21.

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