Catalytic Carbonylative Spirolactonization of Hydroxycyclopropanols

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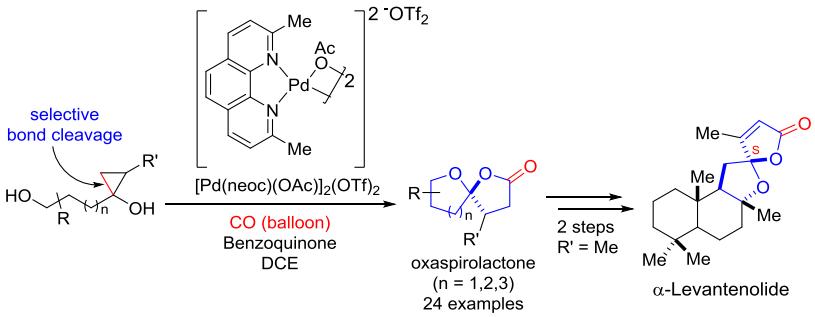

Introduction

Dioxaspiro systems, in the form of spiroketals, spiroacetals and oxaspirolactones, are a ubiquitous feature of many natural products and other bioactive molecules. [1] The oxaspirolactone moiety in particular has been discovered frequently in molecules with varied biological activity and structural complexity [2]. While many synthetic methods have been developed for the synthesis of spiroketal systems, less attention has been devoted to the synthesis of oxaspirolactones, and few general synthetic methods exist.

Our ongoing efforts to develop catalytic carbonylative methodologies for the synthesis of complex, biologically active molecules [3] inspired us to investigate the synthesis of oxaspirolactones by utilizing a combination of carbonylation and cyclopropanol ring-opening chemistry [4]. Palladium(II) catalyzed C-C bond cleavage of the strained three-membered rings of cyclopropanols lends facile access to useful metal homoenolate equivalents which we reasoned might undergo carbon monoxide migratory insertion and lactonization with an internal hemiketal. Investigation of key intermediates using high-resolution high-resolution electronspray ionization mass spectrometry [5] can give mechanistic insights and greatly facilitate the development of synthetic methodologies using novel catalytic systems.

Materials and Methods

A stirred solution of an appropriate hydroxycyclopropanol (0.1 mmol) and benzoquinone (0.2 mmol) in 1,2-dichloroethane (3 ml) was evacuated and backfilled three times using a carbon monoxide balloon. $[Pd(neoc)(OAc)]_2(OTf)_2$ (0.005 mmol) was added in one portion, and the resulting solution was stirred at 50° C for 17 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The resulting black residue was dissolved in methylene chloride and purified by flash chromatography to obtain the oxaspirolactone (50-99% yield.)

Results and Discussion

A palladium-catalyzed cascade carbonylative spirolactonization of hydroxycyclopropanols was developed for the efficient synthesis of oxaspirolactones. The reaction features mild conditions, broad substrate scope and good scalability, and was applied in the expedient total syntheses of the Turkish tobacco natural products α-levantanolide and α-levantenolide in two and four steps, respectively. The reaction was found to be efficiently catalyzed by a bimetallic, cationic palladium complex ligated by neocuprione. The hydroxycyclopropanol substrates are readily available in one step via a Kulinkovich reaction of the corresponding lactones. Mechanistic studies utilizing high-resolution high-resolution electronspray ionization mass spectrometry identified several key intermediates in the catalytic cycle, as well as those related to catalyst decomposition and competitive pathways.

Significance

The aforementioned catalytic transformation is expected to greatly facilitate the ease of synthetically accessing the oxaspirolactone, an important structural motif of many bioactive natural products. Moreover, this reaction demonstrates a catalytic pathway utilizing a class of dimeric cationic palladium catalysts and showcases their reactivity in cyclopropanol ring-opening and carbonylation chemistry. Mechanistic studies utilizing ESI-MS showcase the power of mass spectrometry in elucidation the identity of intermediates in novel catalytic cycles, as well as identifying possible side reaction and decomposition pathways.

References

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