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Digest paper

Palladium-catalyzed sp^3 C-H oxidation using oxime as directing group – applications in total synthesis

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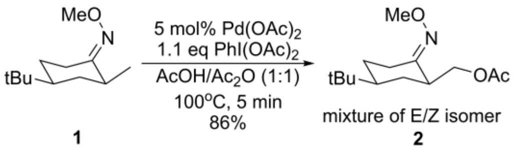
ABSTRACT

Palladium-catalyzed sp3 C-H bond activation using various directing group has been a hot research topic in last decade. Recently, palladium-catalyzed sp3 C-H acetoxylation using oxime as directing group, which was developed by Sanford and co-workers in 2004, has been utilized successfully in total synthesis of several biologically active natural products. In this digest paper, we describe these efforts and highlight the critical role of this impressive method in improving efficiency of natural product synthesis.

Introduction

Palladium-catalyzed sp^3 C-H bond activation using various directing group has been a hot research topic in last decade.[1-10] Due to the inertness nat. of sp^3 C-H bond against activation upon palladium catalysis, directing groups, either monodentate or bidentate, is usually adopted to achieve sp^3 C-H bond functionalization and have been applied in unnatural amino acids synthesis [11, 12] and total synthesis of natural products.[13-18] In 2004, palladium-catalyzed sp^3 C-H acetoxylation using oxime as directing group has been developed by Sanford and co-workers.[19] (Scheme 1) Despite this method has been found for a decade, no application in total synthesis was reported until 2014. With the pioneering application of this palladium-catalyzed sp^3 C-H acetoxylation in Sorensen's jiadifenolide synthesis[20], several biologically active targets were completed by other research groups with this fascinating chemistry.[21-24] (Figure 1) As we have been interested in applying novel methods to synthesize biologically important molecules, it drives us to explore potential methodology, particularly C-H activations for our current syntheses. In this digest, we aimed to provide a concise summary on the recent total synthesis utilized Sanford's methodology with an emphasis of key steps toward the completion of synthesis.

Two-decades before the report of Sanford's investigation, Baldwin and co-workers demonstrated the idea of using cyclo-palladium complex, which was an initial report by Shaw and coworkers earlier in 1978,[25, 26] to facilitate inert sp^3 C-H bond activation with oxime as directing group in 1985.[27] (**Scheme 2**) According to Shaw's report, stoichiometric palladium complex was synthesized by reaction between oxime 6**a** and Na_2PdCl_4 to give 6**b** in the form of dimer complex, which can be converted to monomer form 6**c** via treatment with ligand. (**Scheme 2a**) After preparation of cyclo-palladium complexes, Baldwin demonstrated that both the dimer complex 6**b** and monomer **6c** can be functionalized by chlorination and oxidation to give product 6**d**. (**Scheme 2b**)



Scheme 1. Palladium-catalyzed sp3 C-H acetoxylation reported by Sanford and coworkers in 2004.

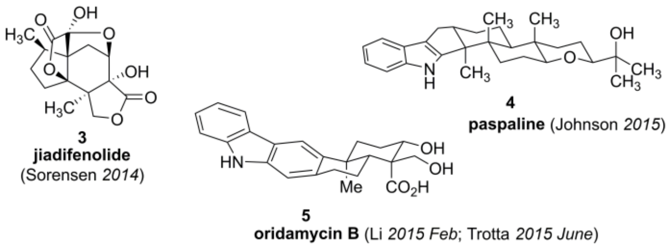


Figure 1. Recent synthetic targets demonstrated Palladium-catalyzed sp^3 C-H acetoxylation.