Bicyclic Cyclopentenes

DOI: 10.1002/anie.200902404

A Palladium-Catalyzed Formal (4+1) Annulation: A New Approach to Cyclopentene Construction

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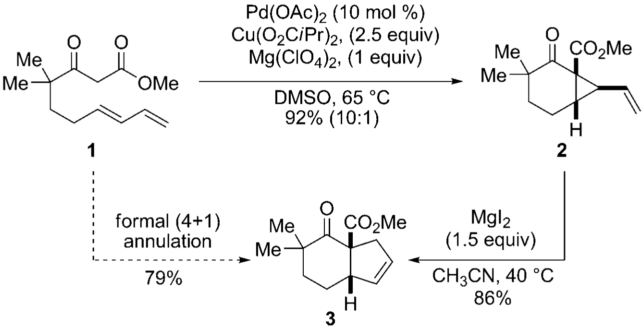
annulation · cycloaddition · cyclopentenes · homogeneous catalysis · palladium

Since Diels and Alder first reported the [4+2][1] cycloaddition of conjugated dienes with electron-deficient alkenes in 1928,[2] cycloaddition reactions have evolved into one of the cornerstones of organic synthesis. The prominence of cycloaddition reactions in the lexicon of organic synthesis is a reflection of the efficient and regio- and stereoselective manner in which these reactions generate carbo- and heterocyclic motifs that are common to many naturally occurring and biologically active molecules.[3] Transition-metal catalysis has played a significant role in the development of cycloaddition chemistry, serving both to enhance the efficiency and/or stereoselectivity of cycloaddition reactions and, more importantly, to enable transformations not feasible in the absence of a transition-metal complex.[4]

The (4+1) cycloaddition of a diene with a two-electron, one-carbon fragment is a particularly attractive transformation because of both the importance of cyclopentene units in naturally occurring molecules and the limited set of transformations available for their synthesis. Unfortunately, efficient (4+1) cycloaddition processes are extremely scarce,[5] and there has been considerable interest in alternative approaches to the synthesis of (4+1) cycloadducts. One such approach is the two-step, formal (4+1) cycloaddition of a carbenoid reagent with a 1,3-diene developed independently by the Danheiser[6] and Hudlicky[7] groups. These processes involve initial (2+1) cycloaddition to form a vinyl cyclopropane (VCP) followed by isomerization to the desired cyclopentene (CP). The utility of these processes is limited, however, by the employment of a carbenoid reagent as a coupling partner and by the rather forcing conditions required to effect the requisite VCP→CP rearrangement.

A recent report by Coscia and Lambert describes a potentially general and operationally straightforward approach to the synthesis of cyclopentenes through a formal (4+1) annulation process.[8] Although the Coscia–Lambert approach involves a diene cyclopropanation/VCP→CP rearrangement sequence analogous to that of the Danheiser–Hudlicky procedures, the requisite VCP intermediate is generated not through the (2+1) cycloaddition of a diene with a carbenoid reagent, but by the palladium-catalyzed oxidative cyclopropanation of a diene with a β-keto ester. As an example of the two-step sequence, treatment of ε-dienyl β-keto ester **1** with a catalytic amount of palladium acetate, 2.5 equivalents of copper(II) isobutyrate, and 1.0 equivalent of magnesium perchlorate in DMSO at 65 °C for 12 h led to isolation of the 7- vinylbicyclo[4.1.0]-2-heptanone derivative **2** in 92% yield as a 10:1 mixture of diastereomers (Scheme 1). Treatment of **2** with 1.5 equivalents of magnesium iodide in acetonitrile at 40 °C led to isolation of the bicyclo[4.3.0]non-7-ene-2-one derivative **3** in 86% yield (Scheme 1).



Scheme 1. Formal (4+1) annulation of **1** by Pd^{II}-catalyzed oxidative cyclopropanation followed by MgI_2-mediated VCP→CP rearrangement. DMSO: dimethylsulfoxide.

The oxidative cyclopropanation step (**1**→**2**) that is key to the Coscia–Lambert annulation protocol builds upon the work of Bäckvall and Andersson,[9] Ikegama et al.,[10] Widenhoefer et al.,[11] and Yang et al.[12] Nevertheless, this transformation is unique with respect to palladium catalysis. Oxidative cyclopropanation of **1** presumably occurs through outer-sphere attack of the Mg^{II}-stabilized enol moiety of **I** on the palladium η^2-diene moiety coupled with loss of HO_2CR and tautomerization to form palladium π-allyl intermediate **II** (Scheme 2).[11,12] Subsequent outer-sphere attack of the enol moiety at the proximal carbon atom of the π-allyl moiety of **II**[10] coupled with loss of a second molecule of HO_2CR would form **2** with concomitant reduction of Pd^{II} to Pd^0. Palladium(0) is then oxidized by the copper(II) salt to regenerate the catalytically active Pd^{II} species. Interestingly, employment of copper(II) acetate rather than copper(II) isobutyrate as the

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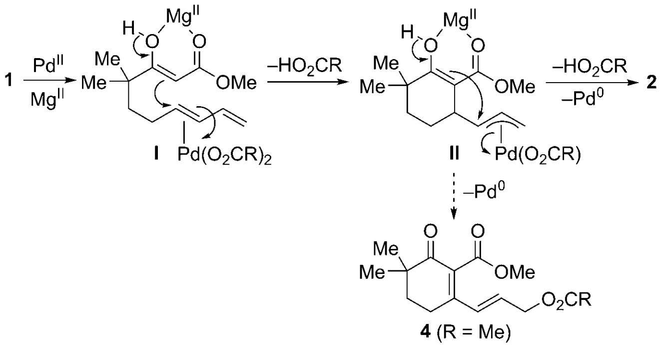
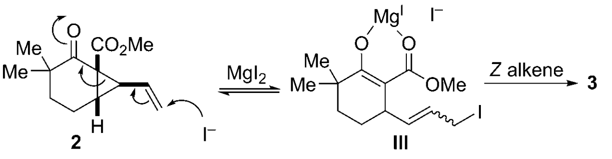


Scheme 2. Plausible mechanism of the conversion of **1** to **2** and byproduct **4**.

terminal oxidant led to formation of allyl ester **4** as a byproduct in the transformation, presumably via competitive reductive elimination from **II** with subsequent oxidation (Scheme 2).

Attack of the enol carbon at the internal carbon of the π-allyl moiety of **II** to form the vinyl cyclopropyl group of **2**, as opposed to attack at the terminal π-allyl carbon atom[9,10] to directly form the desired cyclopentene necessitates a secondary VCP→CP rearrangement to complete the formal (4+1) annulation. Although this kind of rearrangement has been realized under a variety of conditions,[13] none of the common protocols proved effective for the conversion of **2** to **3**. As a solution to this problem, Coscia and Lambert developed a magnesium iodide mediated conversion (Scheme 1). The process takes advantage of the known propensity of iodide ions to undergo homoconjugate ring-opening addition to VCPs[10] coupled with the Mg^{II} stabilization of the β-keto ester derived enolate **III** [Eq. (1)].



(1)

Although the formal (4+1) annulation protocol developed by Coscia and Lambert represents a promising approach to the synthesis of functionalized cyclopentenes, the substrate scope of the transformation is limited. In particular, oxidative cyclopropanation was demonstrated only for ε-dienyl β-keto esters that possessed geminal alkyl substituents at the γ- or ε- position. This latter substitution pattern was required to prevent Saegusa-type oxidation to form the corresponding cyclohexenone.[14] A number of questions pertaining to scope remain to be answered. Can the method be applied to the synthesis of other skeletal motifs such as bicyclo[3.3.0]oct-6-ene-2-one and bicyclo[5.3.0]dec-8-ene-2-one motifs and/or to the synthesis of monocyclic cyclopentenes through intermolecular (4+1) annulation? Will other activated methylene compounds such as β-diketones or α-aryl ketones prove effective one-carbon coupling partners for this formal (4+1) annulation? Can the deleterious Saegusa-type oxidation be curtailed through catalyst rather than substrate control?

Several technical issues are also likely to be addressed in the continued development of Pd-catalyzed formal (4+1) annulation. For example, oxidative cyclopropanation suffers from poor atom economy owing to the high catalyst loading and employment of stoichiometric quantities of both Cu^{II} and Mg^{II} salts. Worth noting, however, was that oxidative cyclopropanation of **1** utilizing a catalytic amount of $Cu(OAc)_2$ under an oxygen atmosphere provided **2** in 52% yield. Also problematic is that the formal (4+1) annulation required two separate synthetic operations owing to solvent incompatibilities between the oxidative cyclopropanation (DMSO) and the VCP→CP rearrangement (acetonitrile). As noted by the authors, however, the similarity of the two solvent systems bodes well for the identification of a solvent system compatible with both transformations and development of a one-pot (4+1) annulation process.

Building from known Pd-catalyzed π-activation chemistry, Coscia and Lambert have developed an effective method for the formal (4+1) annulation of a conjugated diene with a β-keto ester. The two-step protocol holds considerable promise as a general and efficient method for the synthesis of functionalized cyclopentenes from readily available coupling partners under mild conditions. Continued effort, however, will be required to realize the full potential of this new transformation.

Received: May 6, 2009

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[1] According to the IUPAC system for the classification of cycloaddition reactions, square and round brackets denote the number of electrons and atoms, respectively, involved in the transformation. Therefore, cycloaddition of a conjugated diene with a carbene, for example, is properly classified as a (4+1) and a [4+2] cycloaddition. P. Muller, *Pure Appl. Chem.* **1994**, *66*, 1077–1184.

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