



## Digest paper

## Recent topics in application of selective Rh(II)-catalyzed C–H functionalization toward natural product synthesis



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## SUMMARY

Direct C–H bond functionalization reactions promise to be among the most efficient methods for the synthesis of organic molecules. This review focuses on recent syntheses of natural products via chemo-, regio-, and stereoselective Rh-catalyzed C–H insertion reactions.

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## Introduction

Carbon-hydrogen (C–H) bonds have low reactivity, and unactivated C–H bonds do not participate in reactions. Recently, direct transformation reactions of C–H bonds have been discovered and developed and promise to be among the most efficient methods for the synthesis of organic molecules. A typical class of C–H functionalization reaction comprises the activation of C–H bonds by metals. In this type of reaction, a transition metal activates a C–H bond to produce a reactive species, which can now react with other

functional groups. In many such reactions, a directing group is used to select the desired C–H bond and promotes the transformation. An alternative class of C–H functionalization reaction comprises the insertion of a carbene or nitrene into a C–H bond.<sup>1,2</sup> Carbenes contain a neutral, divalent C atom with a lone electron pair and an empty orbital, whereas nitrenes are the corresponding N-containing compounds. These molecules are so reactive that it is often difficult to control the reaction. A transition metal complex such as a rhodium (II) salt promotes the production of a carbenoid or nitrenoid, which are stabilized by the transition metal and react in the same way as free carbenes and nitrenes. Both carbenes (carbenoids) and nitrenes (nitrenoids) can be inserted into an unreactive C–H bond to form a new C–C bond and a new C–N bond, respectively. Because some

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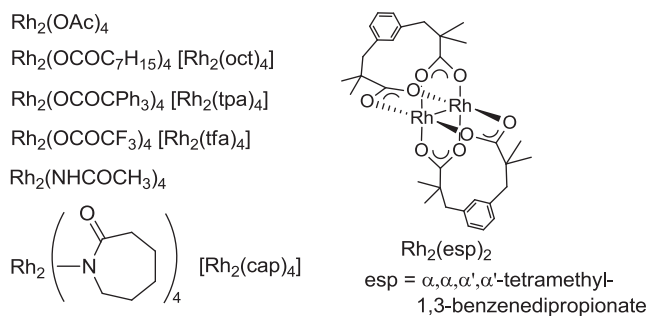


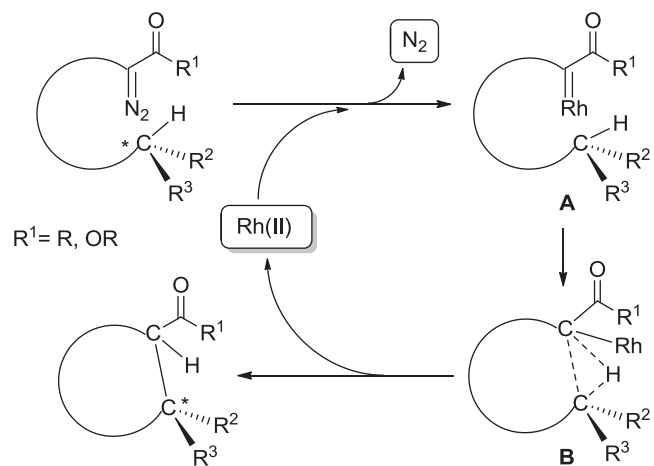
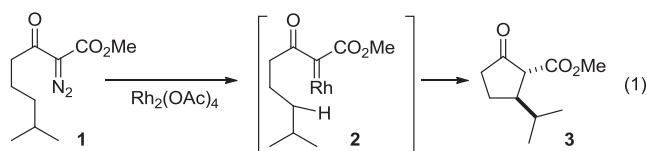
Fig. 1. Representative Rh(II) catalysts.

excellent reviews of metal-catalyzed C–H amination reactions have recently been reported,<sup>3</sup> in this review we intend to focus on recent applications of selective Rh-catalyzed C–H insertion reactions for the synthesis of natural products.<sup>4</sup>

### Rh(II)-catalyzed CH insertion

#### Generation of rhodium carbenoid and mechanism

A typical C–H insertion reaction using a rhodium carbenoid is illustrated in Eq. (1).<sup>5</sup> The rhodium carbenoid **2** is generated by the reaction of the diazo compound **1** with a catalytic amount of dirhodium tetraacetate ( $\text{Rh}_2(\text{OAc})_4$ ) to produce the cyclopentanone **3**.  $\alpha$ -Diazocarbonyl and  $\alpha$ -diazo- $\beta$ -ketocarbonyl compounds are usually used as precursors of the carbenoids. Although diazo compounds are chemically unstable, potentially explosive, and toxic, an electron-withdrawing group such as a carbonyl group stabilizes them and facilitates their handling and can be readily introduced by reactions such as the acylation of diazoalkanes or diazo transfer reactions of carbonyl compounds. The treatment of a diazocarbonyl compound with a rhodium(II) salt (Fig. 1) such as dirhodium tetraacetate ( $\text{Rh}_2(\text{OAc})_4$ , a dimer of rhodium diacetate) generates the corresponding rhodium carbenoid. Rhodium carbenoids contain an Rh=C double bond and undergo reactions that are typical of singlet carbenes, such as reaction with a C–H bond and insertion into a C–H  $\sigma$ -bond to form a new C–C  $\sigma$ -bond. This reaction is most useful when it takes place intramolecularly, in which case insertion into a  $\delta$  C–H bond occurs preferentially to produce a five-membered compound.

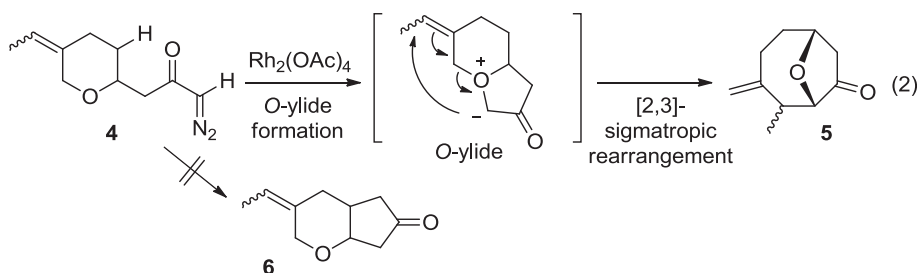


Scheme 1.

The mechanism of C–H insertion reactions using rhodium carbenoids is believed to proceed through a three-centered transition state (TS), although it remains elusive (Scheme 1).<sup>1,6</sup> A rhodium(II) salt promotes the decomposition of a diazo compound to generate the rhodium carbenoid **A** with the loss of a nitrogen molecule. The resulting rhodium carbenoid attacks the desired C–H  $\sigma$ -bond to form the three-centered TS **B**. The simultaneous formation of new two  $\sigma$ -bonds (C–C and C–H) and the breaking of the C–H  $\sigma$ -bond produce a C–H insertion product and regenerate the catalytically active rhodium(II) salt, which completes the catalytic cycle. In the case of the reaction of a stereogenic C–H bond, the reaction proceeds with retention of configuration.

#### Chemo-, regio- and stereoselectivity

A rhodium carbenoid can react with heteroatoms such as oxygen, sulfur, and nitrogen, carbon–carbon multiple bonds, and heteroatom–hydrogen bonds, as well as C–H bonds. Because rhodium carbenoids are electrophilic, C–H bonds are the least reactive of these functional groups. It is usually difficult to perform chemoselective reactions with C–H bonds in preference to the other functional groups. For example, the Rh(II)-catalyzed reaction of the diazoketone **4** takes place at the ring oxygen atom to generate the furanone **5** selectively via the formation of an oxonium ylide and subsequent [2,3]-sigmatropic rearrangement with no C–H insertion products such as **6** (Eq. (2)).<sup>7</sup>



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