

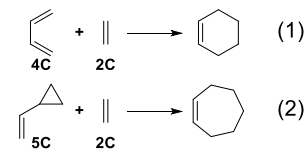
# SELECTIVITY IN [5+2] CYCLOADDITIONS WITH VINYL CYCLOPROPANES

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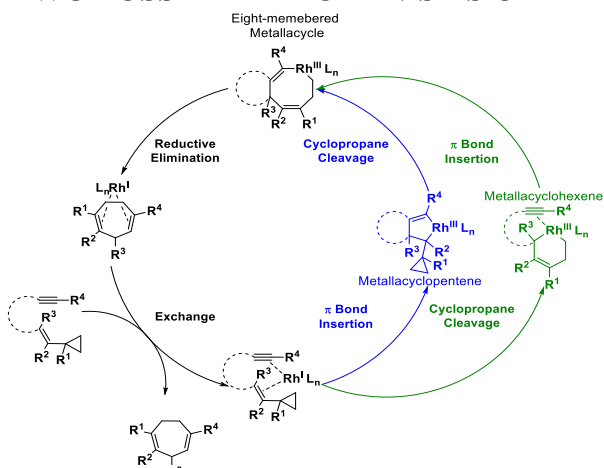
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## INTRODUCTION

Cycloaddition reactions, which allow for the formation of multiple carbon-carbon bonds in a single step with high regioselectivity, represent a powerful method for the synthesis of four-, five- and six-membered ring compounds. Despite the discovery of many bioactive natural products like ingenol<sup>1</sup> and guanacastepene A<sup>2</sup> with seven-membered rings, cycloadditions that form this larger ring are less well studied compared to their smaller counterparts. In 1995, Wender and co-workers reported a homologous Diels-Alder cycloaddition (Eq. 1) for seven-membered rings (Eq. 2); the first intramolecular rhodium-catalyzed [5+2] cycloaddition of vinylcyclopropanes (VCPs) with alkynes using Wilkinson's catalyst.<sup>3</sup>



## TWO POSSIBLE MECHANISMS OF THE [5+2] CYCLOADDITION WITH VCP



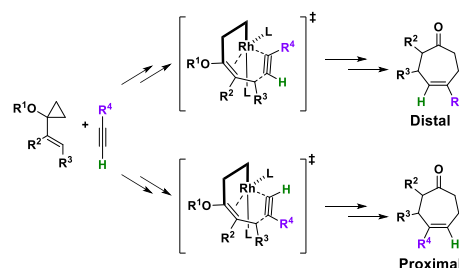
Scheme 1. [5+2] Cycloadditions with VCPs: Two Mechanisms

Since the introduction of [5+2] cycloadditions with VCP, the reaction mechanism has been widely debated. Two divergent mechanistic hypotheses have been postulated differing only in the order of cyclopropane cleavage and  $\pi$ -bond insertion (Scheme 1).<sup>4</sup> Although mechanistic understanding is still incomplete, the identity of the metal and the molecularity of the reaction have been suggested to affect the mechanism.<sup>4</sup> The regio-, diastereo- and periselectivity of these cycloadditions can be better understood through careful examination of each step.

## UNDERSTANDING THE SELECTIVITY OF THE [5+2] CYCLOADDITION WITH VCP

### $\pi$ -Bond Insertion

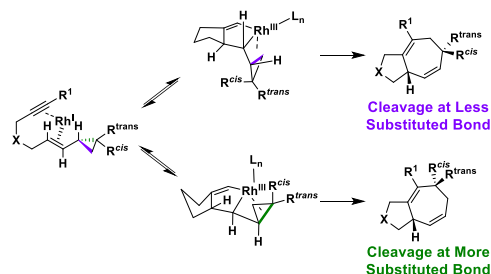
If the mechanism proceeds through the metallacyclohexene intermediate, the  $\pi$ -bond insertion is the regioselectivity determining step as all previous steps are reversible. In the intermolecular case, this step leads to the production of constitutional isomers depending on the identity of the alkyne substituents and the ligands (Scheme 2).<sup>5</sup> In the intramolecular case,  $\pi$ -bond insertion controls the diastereoselectivity of the reaction.



Scheme 2.  $\pi$  Bond Insertion Regioselectivity

## Cyclopropane Cleavage

In the alternative metallacyclopentene mechanism, cyclopropane cleavage determines regioselectivity where the 1,2-disubstituted cyclopropane substituent and the catalyst ligand determine which bond of the cyclopropane is cleaved (Scheme 3).<sup>6</sup> Electron withdrawing groups located at  $R_{cis}$  or  $R_{trans}$  weaken the more substituted C-C bond activating it for cleavage. This electronic preference predominates unless the ligands enforce a significant steric influence.



Scheme 3. Regioselectivity in Cyclopropane Cleavage

## Reductive Elimination

With the addition of carbon monoxide to the reaction conditions, a CO insertion precedes reductive elimination resulting in a cyclooctenone product. The use of alkenes as the  $2\pi$  component helps to bias the  $[(5+2)+1]$  reaction as the addition of CO produces a more favorable reductive elimination.<sup>7</sup>

## APPLICATION IN NATURAL PRODUCT SYNTHESIS

These principles have been applied to the synthesis of a wide variety of natural products. In the total synthesis of (+)-frondosin A, Trost and co-workers control the diastereoselectivity of the key  $[5+2]$  cycloaddition with VCP (Eq. 3) by combining the principles of the cyclopropane cleavage and  $\pi$ -bond insertion steps.<sup>8</sup> By utilizing a methyl group the cyclopropane breakage occurs preferentially at the less substituted C-C bond. In the total synthesis of ( $\pm$ )-hirsutene, Yu and coworkers carried out the  $[(5+2)+1]$  cycloaddition/aldol addition preferentially through the incorporation of an alkene coupling partner to give the desired hirsutene scaffold (Scheme 5).<sup>7</sup>

## FUTURE DIRECTIONS

For widespread application of the  $[5+2]$  cycloaddition with VCP, necessary mechanistic studies on the role of the metal, ligands, and the molecularity of the reaction need to be pursued. Such studies would allow for the accurate prediction of the regio- and diastereo- and periselectivity and thus a more efficient application of the Diels-Alder homologue.

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