



# Carbene cascades for the formation of bridged polycyclic rings



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## ABSTRACT

A general strategy to synthesize bridged polycyclic molecules is presented. The synthesis is accomplished via a cascade reaction initiated by rhodium carbene formation. Subsequent intramolecular reaction with an alkyne is then followed by a transannular C–H bond insertion. A rationale for prediction of the major structural isomer that is formed is described and applied to a wide variety of substrates. This rationale is based on conformational and stereoelectronic considerations for the ring system in the substrate.

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## 1. Introduction and background

Examples abound of polycyclic natural products where a bridged bicyclic core is fused with additional rings (Fig. 1). These compounds routinely possess important biological activities that are applicable to the study of biochemical pathways and the development of new disease treatments. Many of these natural

products are isolable in only scarce quantities from natural sources. Thus, a practical synthetic approach is needed to furnish the material to investigate the properties of these compounds. There has been a significant effort to develop methods for the synthesis of bridged bicycles. The variety of strategies developed to synthesize different bridged rings includes ring formation via radical intermediates,<sup>1</sup> enolate additions,<sup>2</sup> pericyclic cycloadditions,<sup>3</sup> and Michael reaction cascades.<sup>4</sup> However, each of these methods typically targets only one unique size and connectivity for the bridged ring system. For example, the bicyclo[2.2.2]octane cores of tashironin A (**1**) and maoecrystal V have been targeted with an intramolecular Diels–Alder reaction.<sup>5</sup> However, adenanthin (**5**) would require a completely different strategy. A rapid, generalized approach to generate different bridged polycycles from common starting points would increase synthetic utility, flexibility, and efficiency.

We recently disclosed a generalized strategy to synthesize bridged polycycles like **9** (Scheme 1).<sup>6</sup> By altering the ring in **6**, a variety of bridged ring sizes may be formed with differing points of connection. This cascade reaction approach to bridged polycycles is initiated through catalytic diazo decomposition<sup>7</sup> of an  $\alpha$ -diazo carbonyl<sup>8</sup> like **6** and terminates in a C–H bond insertion.<sup>9</sup> Importantly, the C–H bond insertion allows for new C–C bond formation without prefunctionalization of the carbocycle, allowing for greater synthetic efficiency.<sup>10</sup> The carbene cascade reaction proposed herein forms multiple C–C bonds in a single reaction to further increase efficiency. While bridged ring systems contain 17–23 kcal/mol of ring strain relative to cyclohexane,<sup>11</sup> the high reactivity of the carbene intermediates allow the reaction to proceed.

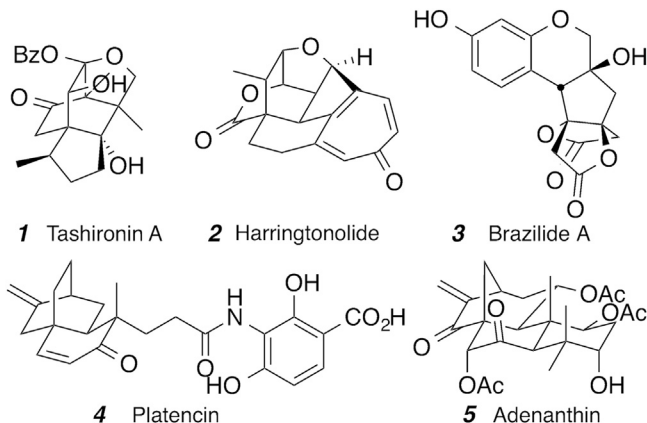
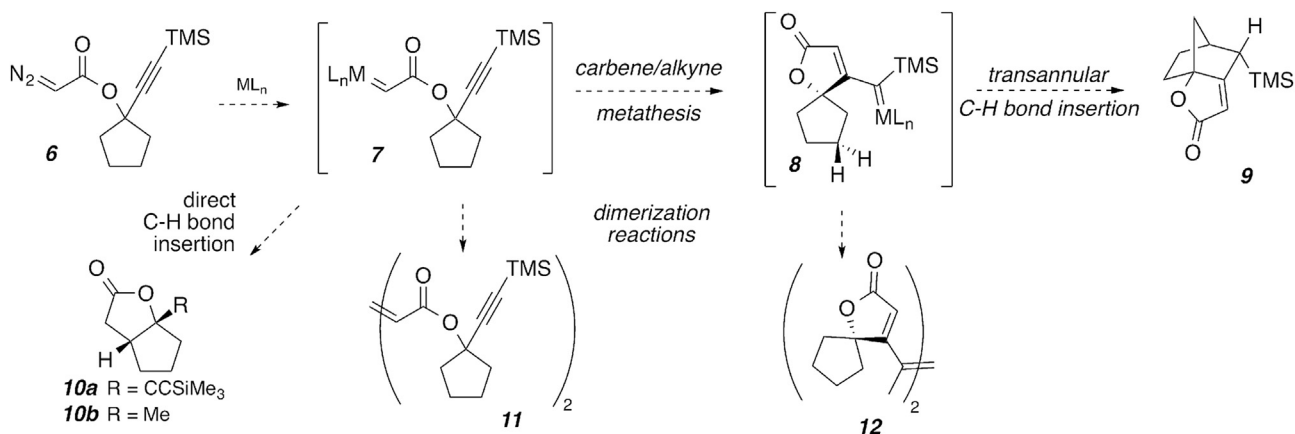


Fig. 1. Bridged polycyclic natural products.

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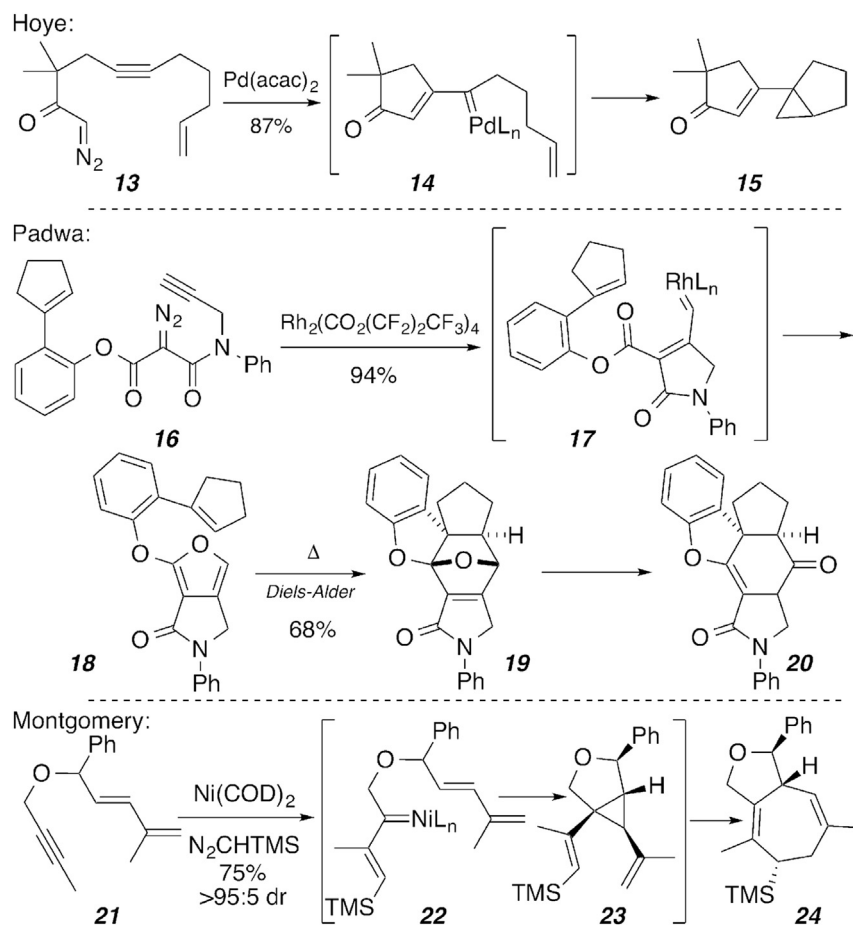


Scheme 1. The carbene cascade and potential side reactions.

Also central to the cascade strategy is the intramolecular insertion of a nearby alkyne to form a putative spirocyclic intermediate like **8**. Such a process has precedent in work by Padwa,<sup>12</sup> Hoye,<sup>13</sup> and others<sup>14</sup> (Scheme 2). In those examples, a carbene is generated from a diazo compound, usually in the presence of a transition metal catalyst that controls the carbene reactivity. This initial carbene rapidly reacts with a nearby alkynyl group intramolecularly to form a new carbene intermediate such as **14** or **17**. This new carbene can then proceed through additional reactions. An intermolecular example has even been shown by Montgomery with a Ni complex. However, little work had been reported on

a cascade reaction that terminates in C–H bond insertion to form bridged polycycles.

The allylic metal carbenes **14** and **17**, which would result from a ‘carbene alkyne metathesis’<sup>12e</sup> from the initially formed carbene, are useful hypothetical intermediates to consider and understand these reactions. However, the actual mechanistic intermediates are likely more complex. Hoye demonstrated this complexity with an elegant study that compared diazoketone **25** and diazo enone **26** (Scheme 3).<sup>15</sup> If the cascade sequence from **25** proceeded purely through a metathesis reaction to form intermediate **29**, both **25** and **26** would be expected to give the same product distribution. As can



Scheme 2. A few examples of carbene/alkyne cascade sequences.

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