

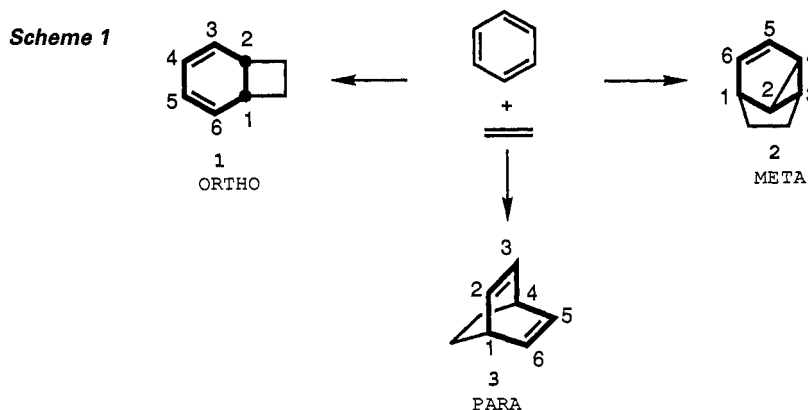
Arene–alkene cycloadditions and organic synthesis

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Abstract - Factors influencing the selectivities of the arene-alkene photo-cycloaddition have been investigated in connection with the application of this process in complex molecule synthesis. Described herein are syntheses of silphinene, subergorgic acid, retigeranic acid, and a grayanotoxin II precursor based on this process. The discovery of a new cycloaddition based on 4-pyrones is also summarized.

Arene-alkene photo-cycloadditions (Scheme 1) are among the most powerful and versatile strategy level reactions for complex molecule synthesis. Discovered over a period of a decade beginning in the late 1950's, these remarkable reactions have attracted considerable mechanistic and theoretical interest, leading in recent years to spectacular applications in synthesis.¹ This lecture is designed to provide an overview of recent advances in this field with an emphasis on the development of the arene-alkene cycloaddition as a tool for the rational synthesis of complex molecules.



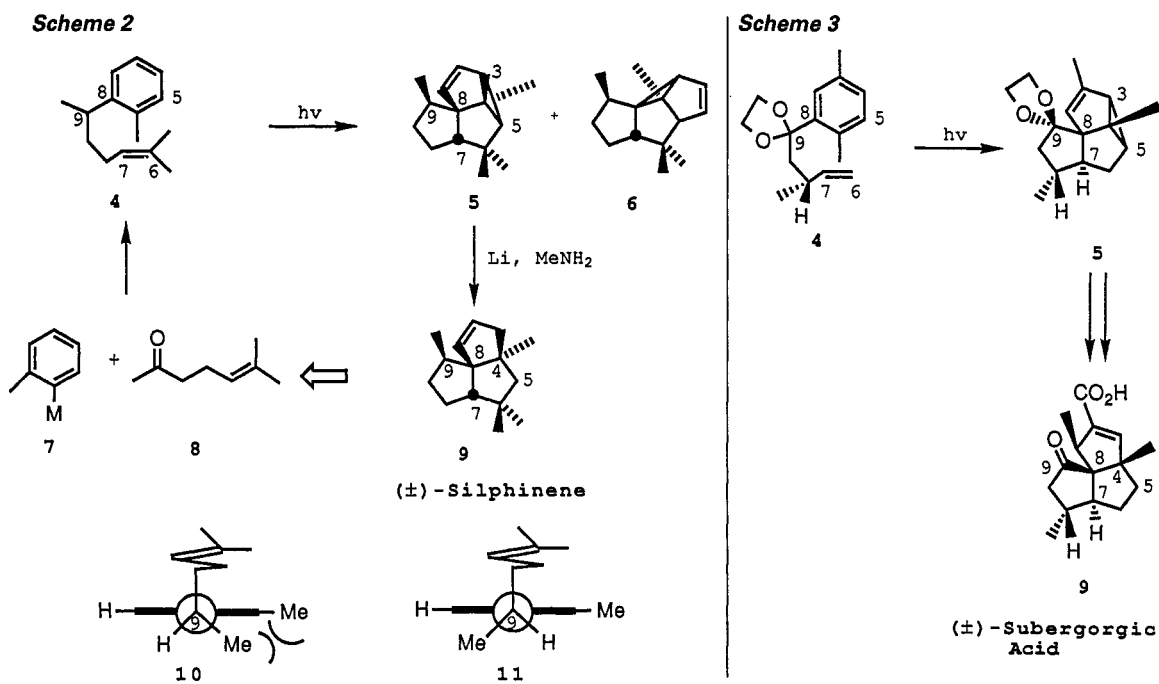
In order to establish the context for our studies, it is appropriate to consider the potential role of arene alkene cycloadditions in synthesis. Organic synthesis has evolved rapidly and impressively since its genesis in the nineteenth century with each generation defining an ever-more demanding set of goals. As empiricism gave way to mechanistic understanding, a foundation was laid for the realization of greater control over reaction selectivity and thereby for the advent of complex molecule synthesis. Indeed, the past three decades have witnessed impressive successes in the synthesis of complex structures. The problems originally posed by many synthetic targets have now been *solved* at a *practical* level. However, *for the majority of synthetic problems, solutions either do not exist or are far from being practical.* In general, few solutions approach the ideal, wherein the target is prepared from readily-available starting materials in one step that proceeds in 100% yield and is operationally safe, simple, and ecologically acceptable. Obviously, this is a rather demanding but not unrealistic objective. While it is unlikely to be commonly achieved, efforts to reach this standard of sophistication are of great importance as they are likely to lead to the fundamentally new science that will clearly have a profound impact on the ways in which total synthesis will be done in the future.

The relationship of the arene-alkene cycloadditions and other strategy level reactions of this calibre to this goal of simplifying complex molecule synthesis can be appreciated from an analysis of a typical synthesis. Generally, a total synthesis proceeds from simple starting materials to a complex target. While *simple* and *complex* are frequently intuitive or at best qualitative descriptors of molecules, it is possible to determine more quantitatively these relative attributes of structure through the use of simple graph theory.² In essence, the atoms and bonds of a molecule can be related to the points and lines of a graph. The relative complexity of a graph (molecule) is therefore a function of the number of points (atoms) in the graph (molecule) and of the nature and number of their connections (bonds). It necessarily and objectively follows from this consideration that the average complexity increase per step in a synthesis determines the total number of steps needed to produce the target (complexity level), provided that the increase is relevant to the target. From a chemical viewpoint, this is equivalent to stating that the average number of target bonds formed per step necessarily determines the number of steps needed to complete a synthesis. Consequently, the incorporation of reactions like the arene-alkene *meta*-cycloaddition, the Diels-Alder cycloaddition, or polyene cyclizations into a synthetic plan, will generally produce a greater increase in average complexity in the synthetic sequence, thereby leading to a shorter synthesis.

The conclusions drawn from the above graph theoretical analysis of the arene-alkene cycloaddition are also consistent with simple synthetic considerations. Thus, the value of the arene-alkene *meta*-cycloaddition can be seen to arise from its capacity to produce a cycloadduct with three new rings and up to six new stereocenters, an impressive feat even when compared with the highly regarded Diels-Alder cycloaddition. Moreover, the cycloadduct can be used in the synthesis of a variety of commonly encountered structural types including cyclopentanes, cycloheptanes, bicyclo[3.2.1]octanes, and bicyclo[3.3.0]octanes. While frequently overlooked in some discussions of reaction classification, the overall processes leading to cycloheptanes, bicyclo[3.2.1]octanes, and bicyclo[3.3.0]octanes are clearly classifiable as [5C + 2C], [3C + 2C], and [3C + 2C] cycloadditions, respectively.

While providing less of a complexity increase than the *meta*-cycloaddition, the *ortho*- and *para*-modes of cycloaddition nevertheless offer a significant increase, not unlike that attending the Diels-Alder reaction. In both, a new ring and up to four contiguous stereocenters are formed. From a synthetic view, the *ortho*-cycloaddition offers access to four- and six-membered rings, bicyclo[4.2.0]octanes, and eight-membered rings, the last through cleavage of the ring fusion bond. These processes are formally examples of [2C + 2C] and [6C + 2C] cycloadditions. The *para*-cycloaddition also affords access to six-membered rings as well as bicyclo[2.2.2]octanes through a [4C + 2C] connection. *Para*-cycloadditions involving dienes or a second arene additionally provide access to eight-membered rings through a [4C + 4C] cycloaddition.

The synthesis of silphinene (Scheme 2: 9),³ based on the *meta*-cycloaddition, provides an illustration of the aforementioned relationship between the complexity increase achieved in a reaction and the length of a synthesis. Silphinene is an angularly fused triquinane with four stereogenic centers, two of which are vicinal quaternary centers (C8 and C9). Its synthesis has been achieved in several laboratories in several ingenious ways, with most solutions falling in the 10-20 step range. As illustrated in Scheme 2, the complexity increase achieved in the arene-alkene *meta* cycloaddition reduces this problem to a *three step synthesis*. Thus, commercially available *o*-bromotoluene is converted to an organolithium intermediate (7: M=Li), which is condensed with 6-methyl-hept-5-en-2-one (8) and the resulting alkoxide reduce *in situ* to give arene-alkene 4 in step one. Photolysis



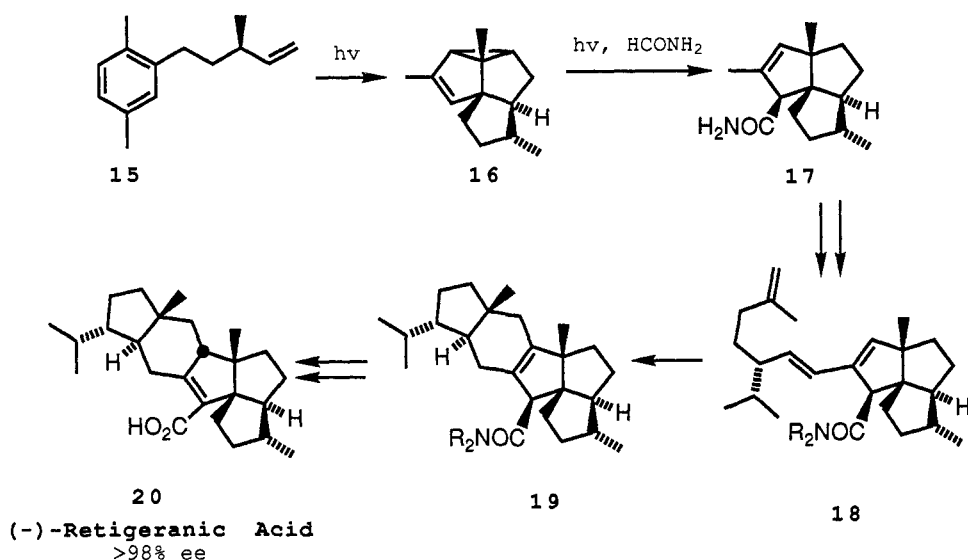
of this material leads in step two to the formation of a 1:1 mixture of *meta* cycloadducts **5** and **6**. Finally, in step three, reductive cleavage of the C3-C5 cyclopropane bond gives the tricyclic target. As a further consequence of the brevity of this synthesis, it is noteworthy that multigram quantities of the target can be produced in a period of a few days.

The spectacular simplicity of this synthesis of silphinene reflects on the developing predictive capabilities associated with the *meta*-cycloaddition. It should be noted that analyses of reaction complexity indicate that any reaction with the potential to produce a highly complex *product* also has the potential to provide a highly complex *product mixture*, if its selectivity is not controlled. Thus, in the synthesis of silphinene, over 100 photocycloadducts could be produced. The observation of only two products indicates that mode, regio-, *exo/endo*, and stereoselectivities have all been controlled. The basis for this control derives from the following considerations. Mode (*meta* vs. *ortho* vs. *para*) selectivity is determined by the electronic features of the interacting arene and alkene. In cases like **4**, the observed *meta* selectivity is consistent with there being a small difference in the free energy of electron transfer between the π -systems. Regioselectivity is regulated by donor alkyl groups on the arene, directing addition of the alkene to flanking *ortho* positions. In arene-alkene **4**, addition is preferentially directed by the methyl group as addition across the C8 alkyl group would create severe non-bonded interactions in the product determining exciplex or transition state. *Exo/endo* selectivity in intramolecular systems such as **4** is regulated by strain: orbital overlap can not be achieved without introducing strain for the *endo* complex, resulting in an *exo*-selective reaction. Finally, stereoselection by the C9 center is seen to be a consequence of the greater non-bonded interactions in complex **10** vs. its diastereoisomer **11**. All of these selectivities are thus regulated in each of the observed cycloadducts, which differ only as vinylcyclopropane isomers.

The extension of this work to subergoric acid (Scheme 3: **14**)⁴ provides a further test of the stereoselection of the key cycloaddition, in this case arising from an allylic tertiary center. Of further importance in this study is the finding that benzylic ketals can be used in the cycloaddition. This suggests the possibility of using chiral ketals to regulate the absolute stereochemistry of the cycloaddition process.

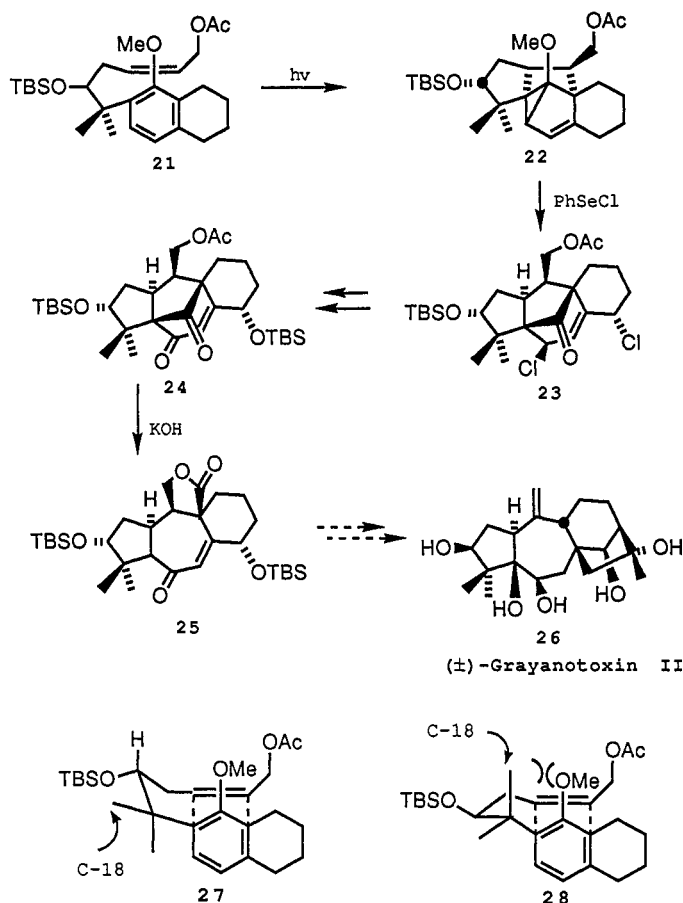
The successful elaboration of silphinene provides the basis for the general application of the arene-alkene *meta*-cycloaddition to targets incorporating an angularly-fused tricyclopentanoid ring system. A further and significant illustration of the exquisite effectiveness of this process for this structural class is seen in the asymmetric synthesis of (-)-retigeranic acid (Scheme 4: 20).⁵ Here, the *meta*-photocycloaddition of 15 provides, as expected from the above analysis, cycloadduct 16 which in a second photochemical step, involving a free radical induced opening of a vinyl cyclopropane, is converted to triquinane 17. Elaboration of this polycycle involving an intramolecular Diels-Alder cycloaddition provides the pentacyclic target.

Scheme 4



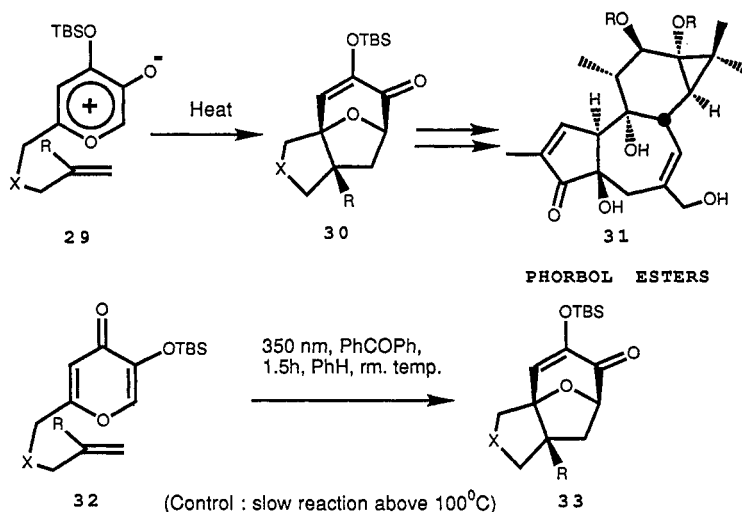
In the aforementioned studies, an arene-alkene *meta*-cycloaddition is used to establish a five-membered ring through a [3C + 2C] connection. The obvious value of this process in five-membered ring synthesis can be readily extended to a [5C + 2C] approach to the synthesis of seven-membered rings through modification of the cycloadduct cleavage procedure. A demonstration of this point is provided in the adaptation of the *meta* cycloaddition to the synthesis of grayanotoxins, such as grayanotoxin II (Scheme 5: 26).⁶ Noteworthy in this effort is the use of a bicyclic arene component, representing one of the most complex examples of this reaction studied thus far. This study also involves the first examination of stereoinduction by a homo-benzylic stereogenic center. Importantly, irradiation of arene-alkene 21 provides pentacycle 22 as the only detectable cycloadduct. Mode-, regio-, and exo-selectivity associated with this reaction are in accord with previous considerations. The observed stereoinduction can be rationalized from an examination of exciplexes 27 and 28: the latter would be expected to be destabilized by the indicated C18-methyl/methoxy interaction, thereby favoring reaction via exciplex 27. The formation of only one vinyl cyclopropane isomer is a predictable consequence of strain, which is minimized when the methoxy and C18 methyl groups are on a cyclopropane bond rather than the shorter, normal sigma bond of the isomer of 22. Overall, this transformation is a rather dramatic demonstration of the synthetic capabilities of the *meta*-cycloaddition, providing for the conversion of a simple bicyclic material (21) to a pentacyclic product (22) with seven stereogenic centers.

Scheme 5



More recently, our interests in developing [5C+2C] approaches to the synthesis of seven-membered rings has been expanded to include the ground state cycloaddition of oxidopyrylium zwitterions and alkenes (Scheme 6: **29** to **30**).⁷ In the course of these studies directed at the tumor promoting phorbol diesters (**31**),⁷ an examination was made of the photochemical behavior of 4-pyrones. In so doing, it was found that such systems (e.g., **32**) can indeed be photochemically-induced to undergo cycloaddition *at room temperature*.⁷ In striking contrast, the dark, thermal reactions of these heterocycles were found to require prolonged reaction times at high temperature. This photochemical process represents an exciting, new method for achieving a [5C+2C] cycloaddition.

Scheme 6



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