Pergamon

Tetrahedron 55 (1999) 4521–4538

TETRAHEDRON

Tetrahedron report number 488

Chromium(0)-Promoted Higher-Order Cycloaddition Reactions in Organic Synthesis

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Received 21 December 1998

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INTRODUCTION

Cycloaddition is one of the most powerful and versatile methods for the assembly of ring systems used in contemporary organic synthesis.[1,2] Six-membered carbocycles, for example, can be easily made by employing the well-known Diels-Alder reaction, which is characterized by a highly stereoselective combination of a 4π partner (the diene) and a 2π partner (the dienophile). In addition, a wide variety of five-membered ring targets can be prepared using one of the many forms of the 1,3-dipolar cycloaddition process that have been developed over the years, and four-membered systems are available from the addition of a pair of 2π reaction partners. The ring-forming event becomes somewhat more challenging in the seven-membered case. However the advent of reliable [4+3] cycloaddition methods,[3] and, more recently, the corresponding [5+2] cycloaddition processes,[4] have made cycloadditive entry into cycloheptane systems a reasonable synthetic method in a number of contexts. More difficult still is the efficient construction of 8-10-membered ring systems via cycloaddition, and relatively few methods for achieving these cyclizations currently exist.

Figure 1 depicts a series of generic examples of cycloaddition reactions that are somewhat unusual in that they are characterized by the combination of more extensively conjugated π-systems than are typically seen in the cyclizations used for smaller ring formation. These reactions are commonly referred to as higher-order

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PII: S0040-4020(99)00186-6

cycloadditions, and recent advances in metal-facilitated versions of these processes promise to make this otherwise obscure family of transformations important members of the modern synthetic repertoire. This review will discuss the most synthetically useful of these recent advances with a particular emphasis on transformations that are known to be facilitated by the presence of a chromium(0) metal center.

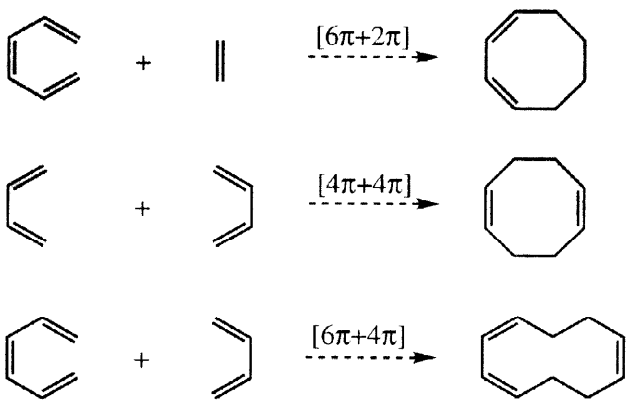
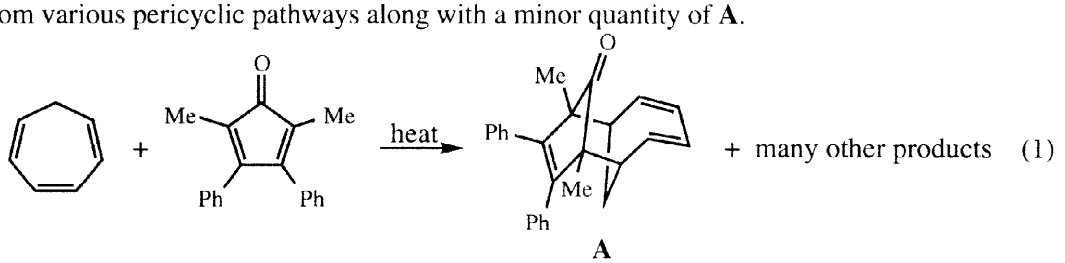


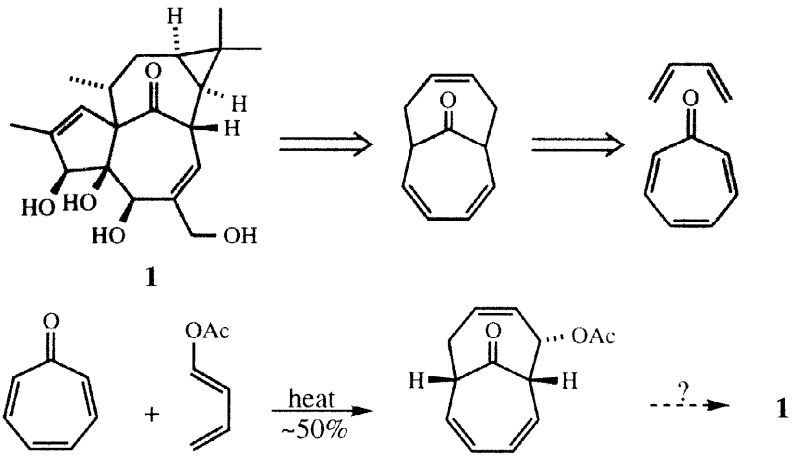
Figure 1. Generic examples of common higher-order cycloaddition reactions.

The most frequently encountered higher-order cycloadditions typically involve [4π+4π], [6π+2π] and [6π+4π] combinations,[5] which can, in principle, provide rapid access to 8- and 10-membered rings, respectively. As a class, these transformations exhibit many of the features that have made other cycloadditions, such as the Diels-Alder reaction, so central to the practice of modern organic synthesis. For example, each process is highly convergent, can accommodate substantial functionalization in both reaction partners, and proceeds with a high degree of predictable stereoselectivity. Unfortunately, higher-order reactions often provide only low chemical yields of adducts due to low periselectivity that is a consequence of the extended π systems involved. These arrays can, and frequently do, participate in multiple competitive pericyclic events. A classic example of a [6π+4π] cycloaddition that illustrates this point is shown in equation (1).[6] Although the higher-order pathway that yields [6+4] adduct **A** is thermally-allowed, the reaction actually affords numerous products derived from various pericyclic pathways along with a minor quantity of **A**.

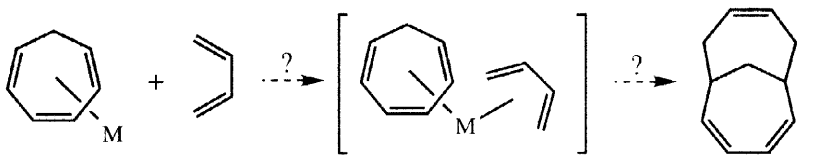


A

Until quite recently the low chemical yields associated with most higher-order cycloadditions relegated these reactions to the status of mere laboratory curiosities.[7] However, the intricate molecular structures of a number of natural product targets, including the tumor-promoting diterpene, ingenol (**1**), appeared to be ideally suited to assembly via [6+4] cycloaddition. Thus an important impetus for creating new and more efficient methods for effecting higher-order cycloadditions came to the fore, and bringing this strategy to practice by way of the well-known thermally-allowed tropone-diene [6+4] cycloaddition process has been the subject of considerable effort in recent years.[7a,b] However, the inefficiencies encountered early on with this crucial higher-order cycloaddition step prompted us to consider methods for intervening in the reaction with the objective of improving periselectivity, and hence chemical yield, without compromising the other attractive attributes of the process. An intriguing idea for achieving this goal would be to employ an appropriate transition metal as a



template that would precomplex the two π-partners prior to the ring-forming event, rendering the reaction temporarily intramolecular in nature (Scheme 1). While there was not a large body of literature in this area at the outset of our investigations, several critical antecedents pointed to the viability of the concept as applied to higher-order cycloadditions. For example, Pettit and his coworkers were early proponents of the concept of metal-facilitated cycloaddition,[8] and more recently Wender's laboratory has very nicely developed the intramolecular version of the well-known Ni(0)-butadiene cyclodimerization process into a powerful methodology for construction of eight-membered carbocyclic systems.[9]



Scheme 1

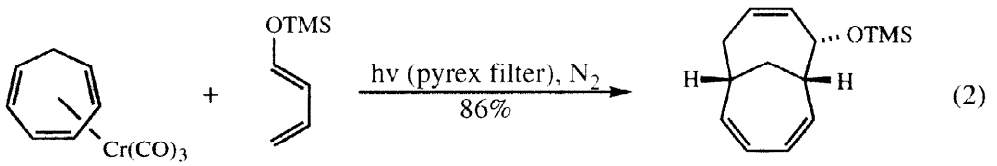
While relatively little relevant precedent was available for bringing this notion to practice in the context of [6+4] cycloaddition, a series of intriguing reports appearing from the Kreiter laboratory suggested that certain chromium(0) complexes could participate with modest efficiency in this type of process under photochemical activation conditions.[10] Recognizing the great preparative potential that higher-order cycloaddition could have if reaction efficiency could be improved, we embarked on a systematic study of transition metal-mediated cycloaddition chemistry with the goal of developing reactions that could be useful in complex natural product synthesis.

THE CHROMIUM(0)-PROMOTED [6π+4π] CYCLOADDITION REACTION

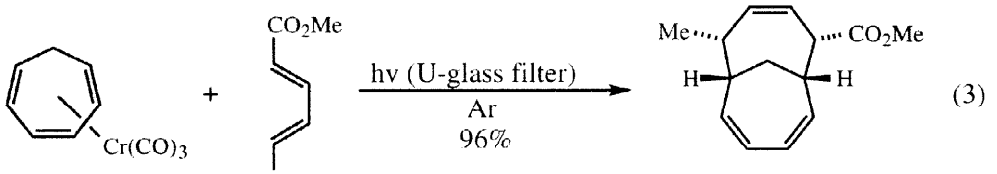
This section of the review will emphasize developments in the study of the Cr(0)-mediated [6π+4π] cycloaddition that have occurred since 1995. Furthermore, there will be particular emphasis placed on the utility of the method for natural product synthesis throughout the following discussions. Thorough accounts of the developmental phases of these investigations, as well as mechanistic treatments, have appeared elsewhere, and the interested reader should consult these sources for further information in this regard.[11]

Equations (2) – (4) present the salient characteristics of the photochemical Cr(0)-promoted [6+4] cycloaddition process as it is currently practiced. Chemical yields are uniformly high, and, in contrast to the

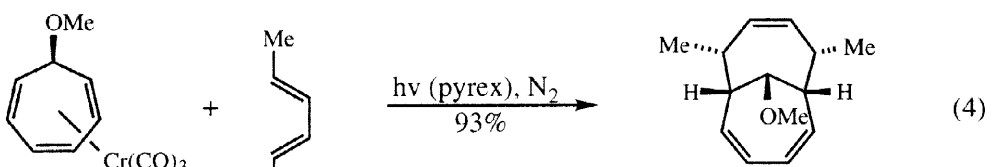
Diels-Alder reaction, wherein diene/dienophile electronics must be carefully matched, reaction efficiencies are independent of the electronic nature of the participants. The reactions feature a high level of stereoselectivity in which the isomer derived from an *endo* transition state prevails in each case. This is particularly noteworthy since the thermal, metal-free [6+4] process is known to proceed via an *exo*-transition state, rendering the two reaction pathways stereocomplementary.[5] An additional stereochemical feature of the process is revealed in the conversion of complex **5** to adduct **6**, in which the diene partner reacts with the triene complex exclusively on the face bearing the metal center. Thus, as many as five contiguous stereogenic centers can be reliably produced in one operation using this chemistry. Furthermore, the intrinsic facial bias of the bicyclo[4.4.1]undecane system ensures that additional substituents can be installed with complete control of stereogenicity.



2 **3** (2)

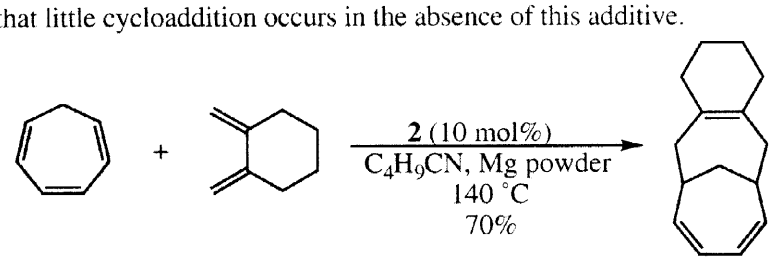


2 **4** (3)



5 **6** (4)

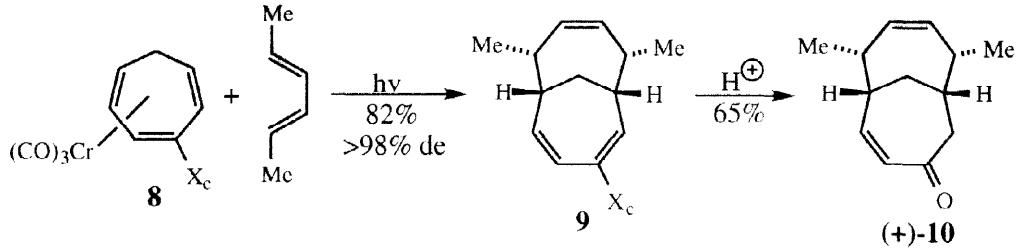
A critical advance in the development of metal-promoted [6+4] cycloaddition as a synthetically useful tool occurred with the implementation of a thermally-activated process employing only substoichiometric quantities of metal.[12] A typical example of this "catalytic" cycloaddition is depicted in equation (5). Other sources of "$Cr(CO)_3$," such as (η^6-naphthalene)tricarbonylchromium(0),[13] are also effective pre-catalysts in this reaction. A critical feature of these reaction conditions is the presence of magnesium powder, which serves to reduce oxidized chromium species that accumulate during reaction back to the catalytically active Cr(0) oxidation state. It is noteworthy that little cycloaddition occurs in the absence of this additive.



7 (5)

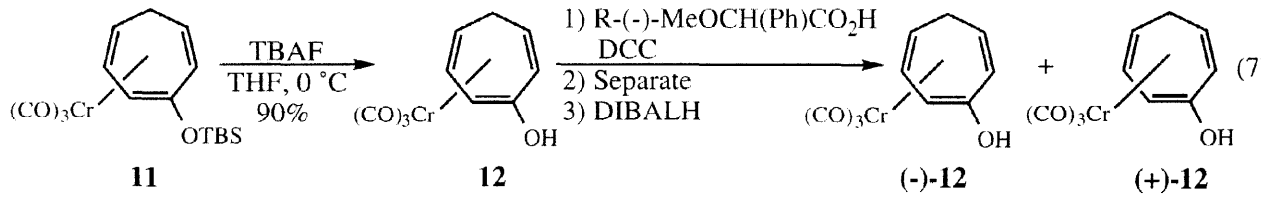
The ability, in general, to effect cycloadditions with high levels of asymmetric induction is an issue of contemporary importance, and various auxiliary-controlled methods have been found to provide higher-order

adducts exhibiting excellent enantiomeric purities. Cycloaddition of the readily available, enantiomerically pure complex **8** (X_c = (+)-camphorsultam), for example, afforded the [6+4] adduct **9** with extremely high levels of diastereoselection. Hydrolysis allowed for recovery of the auxiliary and provided the bicyclo[4.4.1]-undecenone product in enantiomerically pure form.[14] Auxiliaries located on the 4π partner can also be effective for inducing asymmetry in the corresponding cycloadducts.[15]

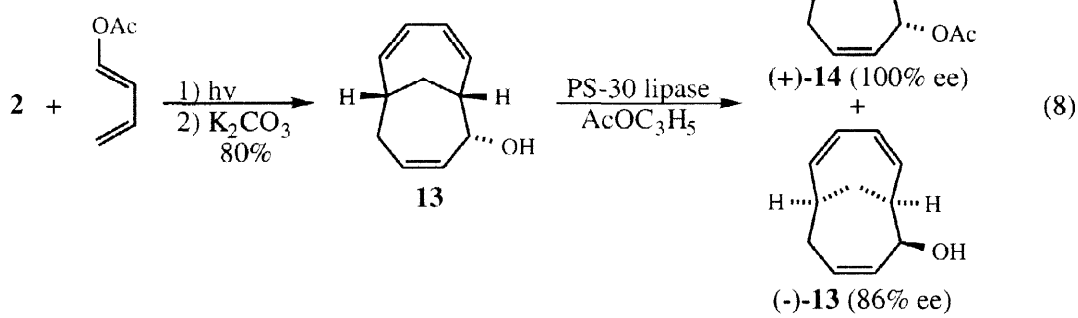


(X_c = (+)-camphorsultam)

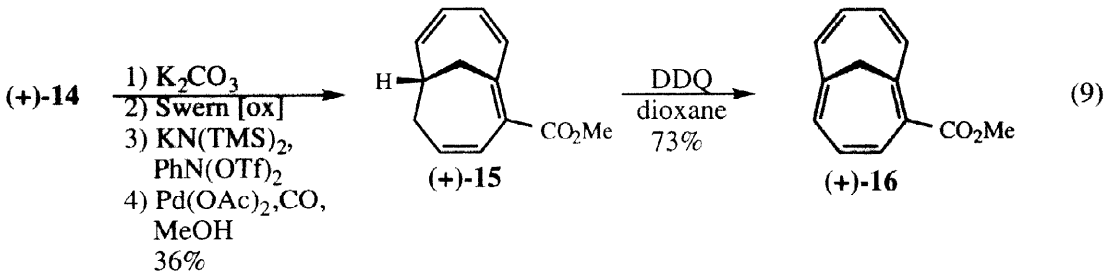
A fascinating method for accessing enantiomerically pure triene complexes has been identified that exploits the surprising stability of the enol function within the cycloheptatriene ligand framework. Thus, complex **11** can be desilylated to afford the racemic enol complex **12**. Derivatization of this stable material with (-)-α-methoxyphenylacetic acid, followed by diastereomer separation and auxiliary removal furnished both enantiomers of **12** in optically pure form.[16] These species can then be further utilized in cycloadditions of considerable synthetic importance.



Another effective route into enantiomerically-enriched cycloadducts is via enzymatic resolution of appropriately functionalized bicyclo[4.4.1]undecane intermediates. Various lipases have proven useful for delivering systems with quite good enantiomeric excesses (Eq. (8)).[17] It is noteworthy that prior to these

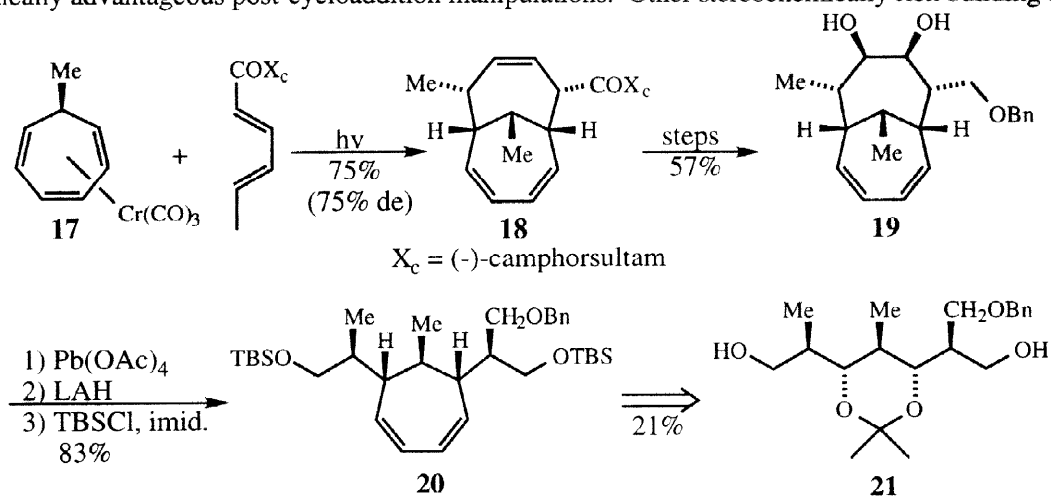


investigations, it was unclear as to whether enzymes would accept these bicyclic systems as substrates. The resultant enantiomerically-enriched adducts have been successfully carried forward in an efficient synthesis of enantiomerically-enriched, substituted 1,6-methano[10]annulene products as outlined in equation (9).[17]



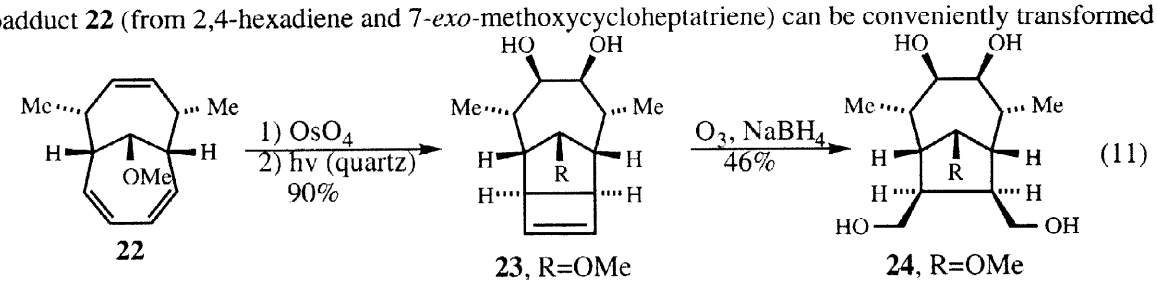
(9)

It was noted earlier that placing an appropriate chiral auxiliary on the diene partner can also afford cycloadducts with useful levels of enantiomeric enrichment. Equation (10) shows a sequence of transformations leading from enantio-enriched bicycle **18** to compound **21**. This latter material represents the C_5 through C_{11} segment of the ansa bridge of the intriguing antibiotic streptovaricin D,[19] and this set of operations nicely illustrates that the products emerging from these higher-order cycloadditions are well-suited to a range of synthetically advantageous post-cycloaddition manipulations. Other stereochemically rich building blocks can be



(10)

accessed by processing the 1,3-butadiene function that is produced during the cycloaddition event. Thus, cycloadduct **22** (from 2,4-hexadiene and 7-*exo*-methoxycycloheptatriene) can be conveniently transformed via

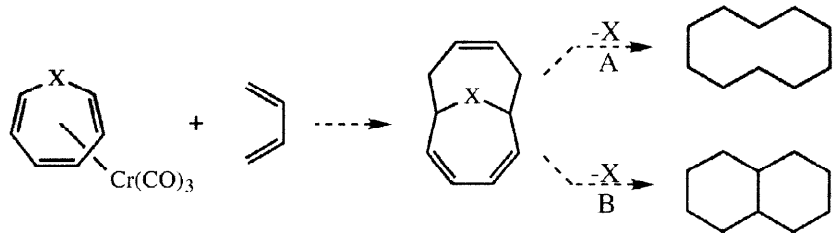


(11)

electrocyclization into tricycle **23**, which can, in turn, be cleaved oxidatively to afford a bicyclo[4.2.1]nonane derivative **24**. It is significant that every ring carbon of this compound possesses a stereogenic center.[20]

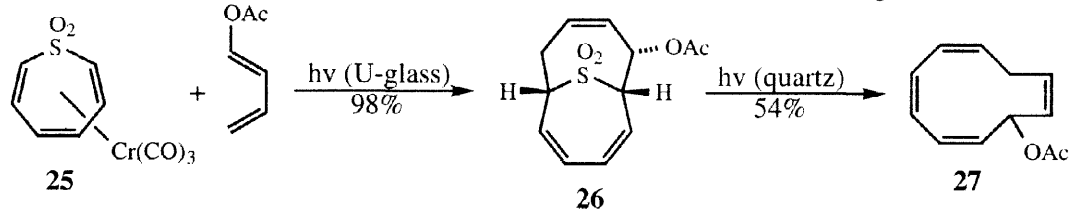
Another very appealing post-cycloaddition manipulation that is potentially available to certain functionally-modified bicyclo[4.4.1]undecane systems would feature a heteroatom extrusion step that would afford various carbocyclic products that can be difficult to make in other ways. As depicted in Scheme 2, an appropriate heterocycle-based complex could undergo conventional [6+4] cycloaddition to afford a bicyclic product with the heteroatom strategically located for convenient excision. Depending on the method of extrusion, either 10-membered carbocycles or fused bicycles could result. During the formative stages of this investigation it was

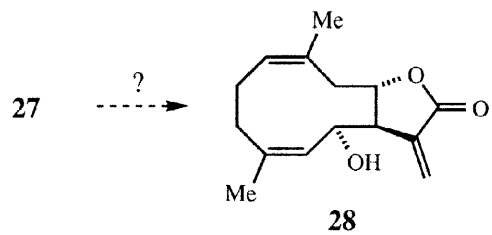
reasoned that some of the unique chemistry of the carbon-sulfur bond offered a number of possible avenues for bringing this concept to practice.



Scheme 2

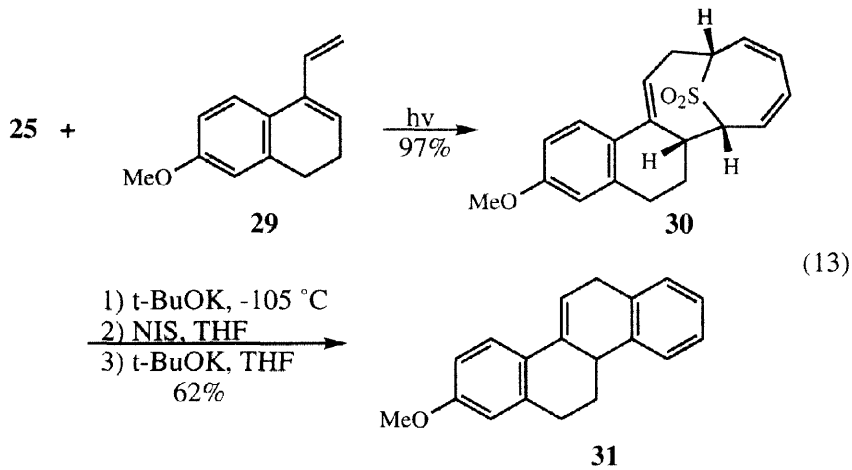
Photocyclization (uranium glass filter) between the novel thiepin dioxide complex **25**[21] and 1-acetoxybutadiene afforded the bicycle **26** as a single diastereomer, again derived from an *endo* transition state. Subsequent photochemical cheletropic extrusion (quartz filter) of sulfur dioxide afforded the all Z-cyclodecatetraene **27**. This type of intermediate is currently being used to assemble germacranolide **28**.





(12)

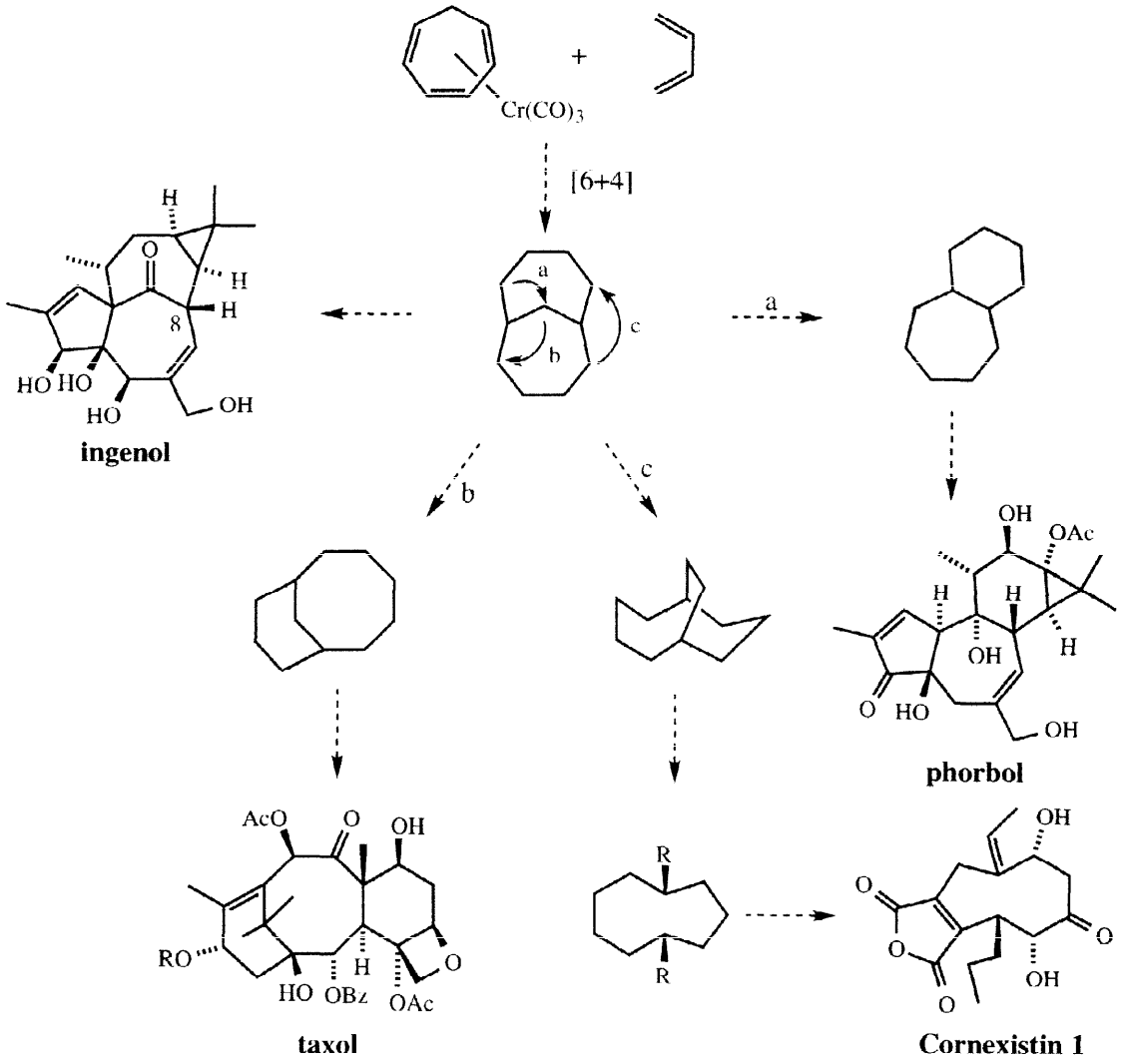
An alternative extrusion protocol can be envisioned in which the thiepin dioxide cycloadduct could be subjected to Ramberg-Bäcklund conditions to effect SO_2 excision to afford a benzo-fused adduct.



(13)

In a typical example of the concept being brought to practice, complex **25** underwent smooth photocycloaddition with the structurally elaborate diene **29** to afford tetracycle **30** as a single diastereomer in virtually quantitative yield.[22] Subsequent exposure to slightly modified Ramberg-Bäcklund conditions[23]

provided the chrysene derivative in good yield. This sequence is quite general and can be successfully applied to a number of complex target molecules.

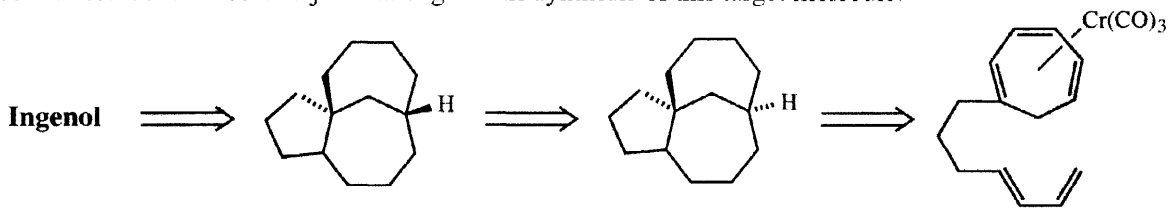


Scheme 3

The capability of producing structurally elaborate and stereochemically rich bicyclo[4.4.1]undecane systems through metal-promoted higher-order cycloaddition has clearly afforded many new synthetic opportunities that were essentially inaccessible previously due to the general inefficiencies and limited scope of the corresponding thermal, metal-free versions of these reactions. The notion that the bicyclo[4.4.1]undecane core could provide a versatile synthetic building block that could be profitably transformed into a range of target systems not necessarily structurally related to the initial cycloadduct was a direct consequence of the power and efficiency of the metal-promoted higher-order cycloaddition process. Along these lines, a "unified" entry into four distinct diterpene families was devised by considering post-cycloaddition rearrangements that could be carried out on the basic bicyclo[4.4.1]undecane core system. The salient features of this program are delineated in Scheme 3. Direct conversion of the bicyclo[4.4.1]undecane system that emerges from the Cr(0)-[6π+4π] cycloaddition into ingenol is obvious. On the other hand the bond reorganization labeled "a" leading to the isomeric bicyclo[5.4.0]undecane that comprises the BC ring sub-structure of the related diterpene phorbol is

perhaps a less obvious relationship. A range of other conversions are also possible starting from the bicyclo[4.4.1]undecane intermediate that could lead to the taxane system and to substituted nine-membered carbocycles. We have recently brought each of these "post-cycloaddition" manipulations to practice in relevant model studies.

The most obvious application of metal-mediated cycloaddition chemistry, of course, is the construction of the potent tumor-promoting diterpene, ingenol, and, indeed, it was this molecule that originally stimulated our entry into these investigations. Scheme 4 depicts the key strategic considerations for attacking this problem employing Cr(0)-mediated [6+4] cycloaddition. In addition to the highly convergent assembly of the entire ABC tricycle via intramolecular Cr(0)-mediated [6π+4π] cycloaddition,[25] the strategy addresses the installation of the crucial, highly-strained "inside, outside" or *trans*-intrabridgehead stereochemical relationship.[24] This interconversion constitutes a major challenge to the synthesis of this target molecule.



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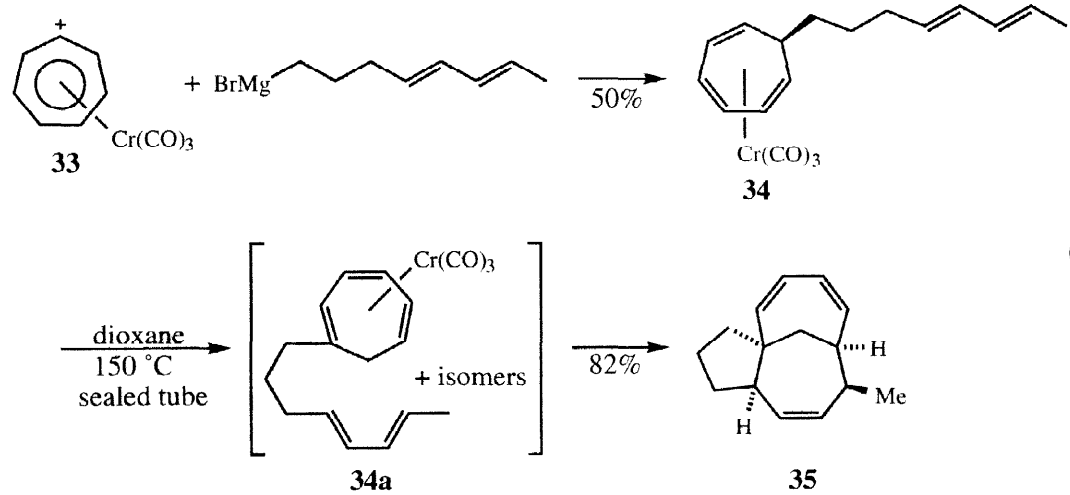
Scheme 4

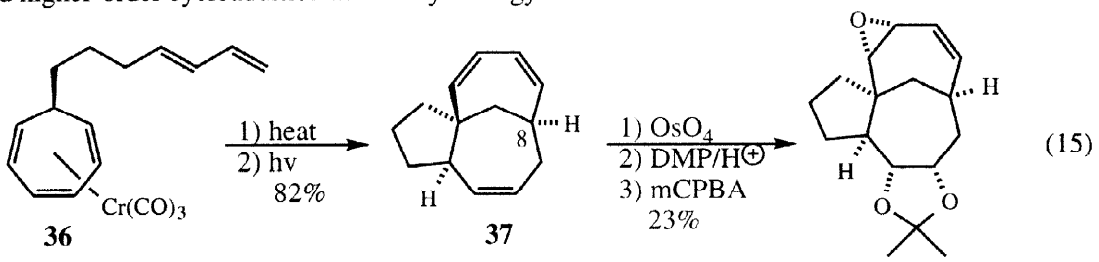
A key feature of the ingenol strategy focuses on rapid and convergent construction of the key tricyclic array via intramolecular cycloaddition. This process exploits two consecutive Cr(0)-facilitated pericyclic events to afford the final product, all carried out in one pot. First, thermal 1,5-hydrogen sigmatropy mediated by the metal center[26] equilibrates the initial triene 7-*exo*-complex into a mixture of all possible positional isomers. Of these various isomers only the 1-substituted complex (**34a**) can undergo [6+4] cycloaddition thus removing this material from the equilibrium and eventually driving the entire process to the desired product. This reaction scheme is brought to practice as illustrated in equation (14), wherein 7-*exo*-cycloheptatriene complex **34** is heated to set up the equilibrium among all possible isomers. Due to geometric constraints only the 1-substituted isomer (**34a**) can undergo effective cycloaddition, ultimately giving product **35** in excellent yield.



(14)

In a subsequent ingenol model study, complex **36** was most effectively converted to tricycle **37** in high overall yield by employing a two-step process that included a thermal rearrangement followed by a

photochemical cycloaddition.[27] Routine functional group manipulation of the adduct afforded epoxide **38** in modest yield. The low yield in this reaction is due to the lack of regioselectivity in the epoxidation step. Treating **38** with lithium diethylamide provided the key dienol **39** required for delivery of the β-oriented hydrogen at C-8 by employing the intriguing, but little used alkoxide accelerated 1,5-H sigmatropy.[28] To our delight, exposing compound **39** to KH/18-crown-6 at 0 °C afforded a good yield of the desired inside, outside-isomer **40**, the structure of which was confirmed by single crystal X-ray analysis. Thus rapid entry into a highly functionalized and highly strained in, out-ingenol ABC tricycle has been established using Cr(0)-promoted higher-order cycloaddition as the key strategy-level transformation.



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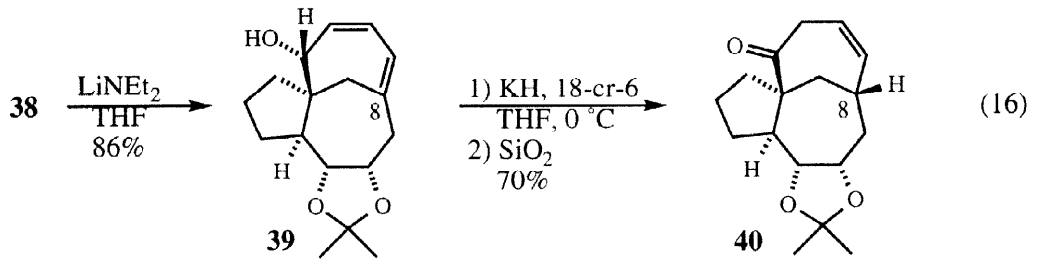
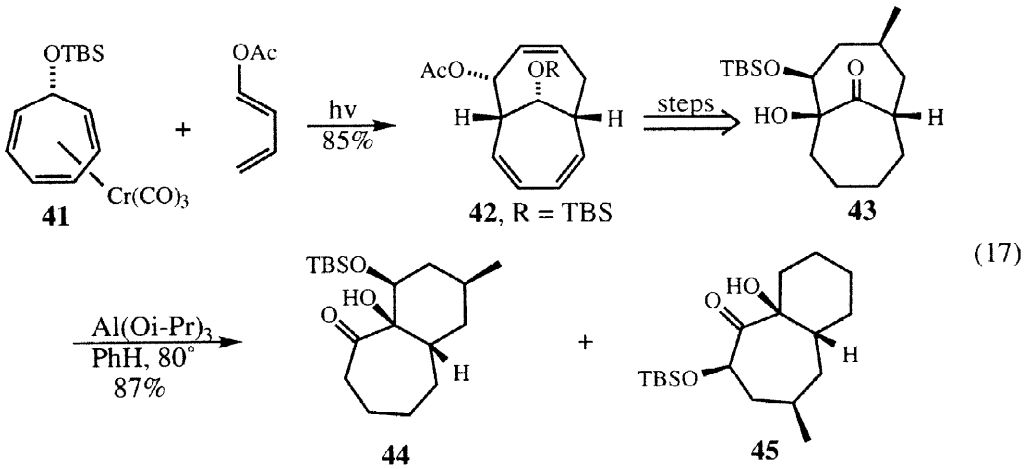


(16)

Phorbol is a diterpene that is structurally closely related to ingenol, and the BC ring moieties of the two compounds can, in principle, be interconverted by simply performing the bond migration labeled (a) in Scheme 3. Ultimately, this projected bond reorganization should be greatly facilitated by the release of the considerable strain associated with the inside, outside topography of the ingenol tricycle, and it is noteworthy that there is one report in which ingenol is, in fact, converted into a tigliane (phorbol) ring structure by this process.[29]

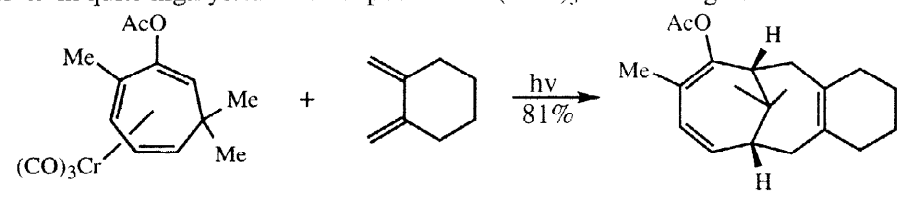
In a model study conducted to test the viability of this notion, access to the tigliane (phorbol) BC ring system was envisioned to occur through either a pinacol or α-ketol rearrangement starting from the readily available (out, out)-bicyclo[4.4.1]undecane **42** (Eq. (17)).[30] Thus, routine functional group processing from



(17)

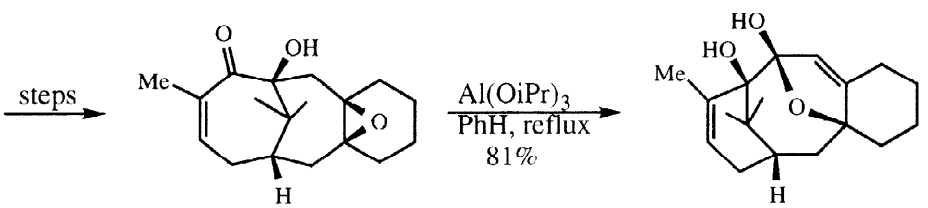
42 afforded α-ketol **43**, which underwent smooth, but not regioselective, reorganization to the two bicyclo[5.4.0]undecanes **44** and **45**. Despite the production of two products, these results confirm the utility of rearranging appropriately functionalized bicyclo[4.4.1]undecane systems into isomeric bicyclo[n.m.0]-undecane systems as a general route into phorbol as well as related diterpenes targets.

In another application of this strategy, the taxane ABC ring system can also be quickly prepared starting with Cr(0)-mediated [6π+4π] cycloaddition.[30] In the event, efficient reaction of complex **46**, derived from eucarvone, and 1,2-dimethylenecyclohexane gave adduct **47** in 81% yield. Further processing, in a manner not unlike that in the phorbol model study, furnished α-ketol **48**, which underwent smooth rearrangement to the taxane tricycle **49** in quite high yield when exposed to $Al(OiPr)_3$ in refluxing benzene.



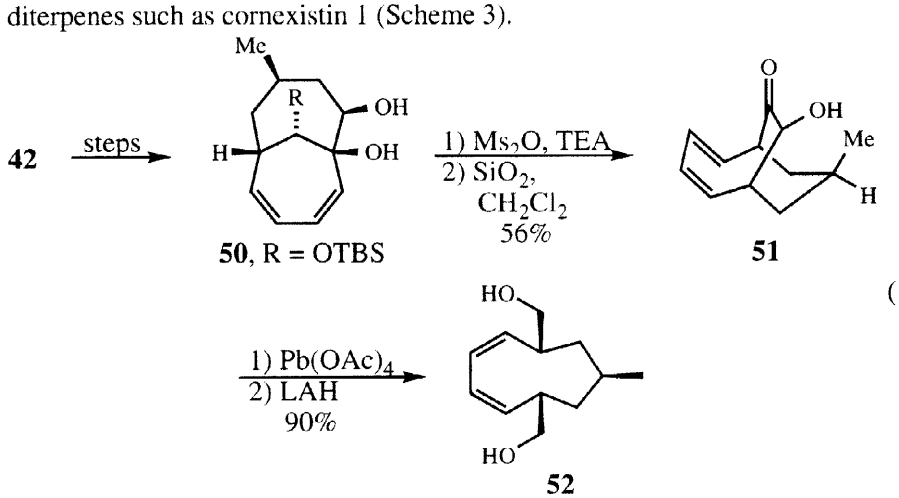
46 **47**

(18)



48 **49**

Finally, nine-membered carbocycles can also be prepared by a third rearrangement pathway. Cycloadduct **42** can be converted into diol **50** using conventional chemistry that has been well-established in the preceding studies. Subsequent mesylation of the 2° alcohol in this compound and exposure of the resultant mesylate to silica gel precipitated a bond reorganization to afford the isomeric bicyclo[4.3.2]undecane **51**. Oxidative cleavage and reduction yielded the cyclononadiene **52**. This protocol can be used to prepare a number of nine-membered ring diterpenes such as cornexistin 1 (Scheme 3).



50, R = OTBS **51**

(19)

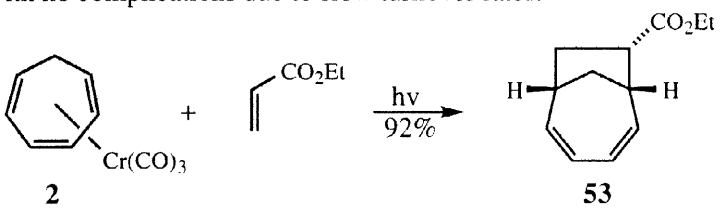
52

From the model studies described above, it is clear that functionalized bicyclo[4.4.1]undecane systems are quite versatile and powerful building blocks for complex synthesis. They have proven to be amenable to

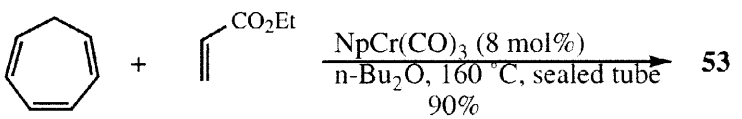
interconversions into structurally different ring systems that often bear little resemblance to the starting materials. These synthetic opportunities were made possible because of the unique characteristics of Cr(0)-promoted higher-order cycloaddition.

THE CHROMIUM(0)-PROMOTED [6π+2π] CYCLOADDITION REACTION

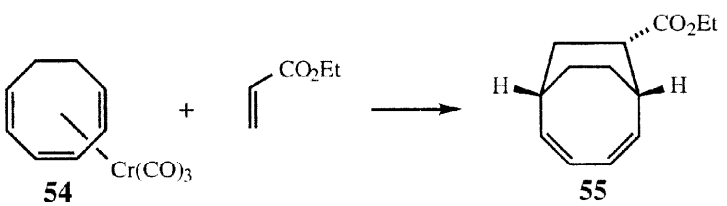
During the investigation of the Cr(0)-mediated [6+4] cycloaddition process, we had occasion to test the related [6π+2π] process, which, based on mechanistic reasoning, appeared to be a candidate for Cr(0) mediation. To our delight, the reaction proceeded with great ease to afford highly functionalized bicyclo[4.2.1]nonane adducts derived exclusively from an *endo* transition state.[32,33] The reaction also proved to be amenable to thermal activation employing a sub-stoichiometric quantity of Cr(0)-precatalyst.[34] Unlike the corresponding "catalytic" [6π+4π] cycloaddition described previously, the [6+2] process was found to be particularly facile with no complications due to slow turnover rates.



2 **53** (20)

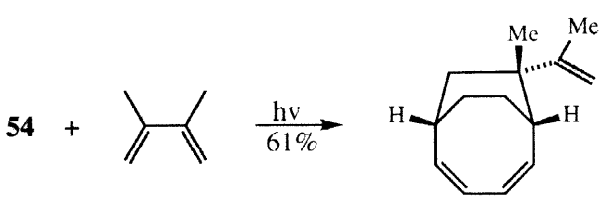


An interesting feature of the [6+2] reaction was that it could be effected using larger ring triene reaction partners, an attribute not shared by the [6+4] process. Thus, (η^6-1,3,5-cyclooctatriene)tricarbonyl-chromium(0) (**54**) underwent clean photochemical [6+2] cycloaddition with ethyl acrylate to afford compound **55**.[35] The corresponding cyclooctatetraene complex also gave [6+2] adducts in good yields. Furthermore, efforts to effect [6+4] cycloaddition of **54** with a simple diene partner failed, providing only the corresponding [6+2] adduct as a single diastereomer.

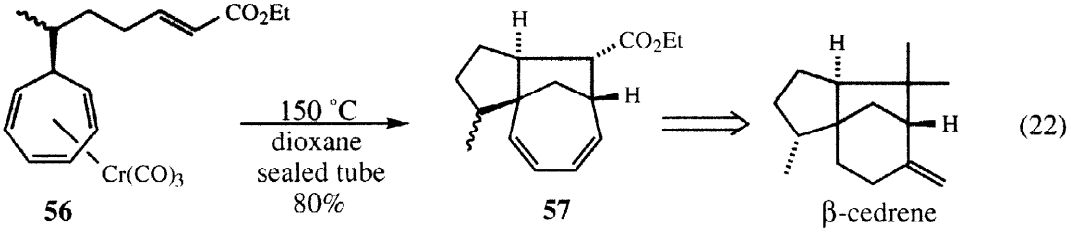


54 **55**

Conditions: hv 60%
140 °C 79% (21)

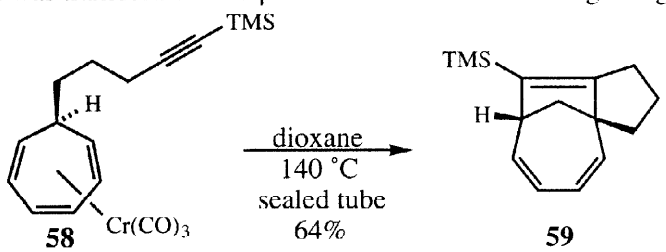


A particularly noteworthy feature of this process is that the efficiency of the corresponding thermally activated reaction was considerably greater than the photochemical version (Eq. (21)).



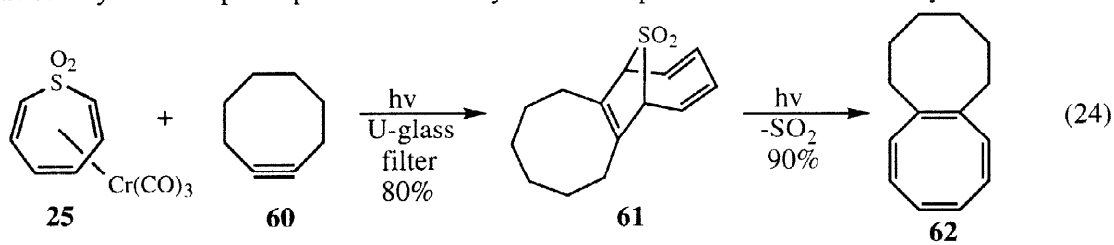
(22)

In a parallel observation, the thermally-induced intramolecular [6+2] process was found to be considerably more effective at delivering adducts than the corresponding [6+4] reaction discussed previously in this document. As before, a tandem Cr(0)-promoted 1,5-H-shift-[6π+2π] cycloaddition process was exploited for this rapid, one pot assembly of the target tricycle. Thus, readily available **56** afforded **57** in excellent yield, and the latter compound was transformed into β-cedrene in short order using straightforward chemistry.[36]



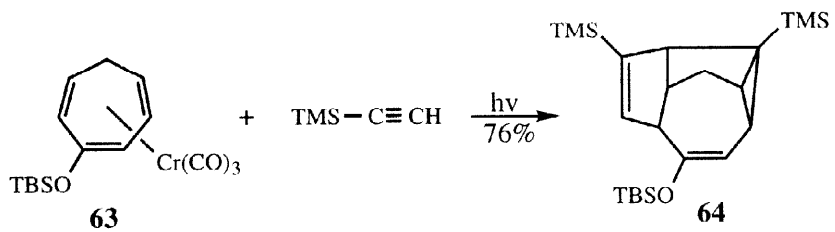
(23)

A closely related thermal cycloaddition of a tethered alkyne also proved effective for providing a range of structurally and functionally elaborate tricyclic products.[37] Indeed, alkyne-based 2π partners have been shown to be particularly versatile participants in various cycloaddition processes in our laboratory.



(24)

As an example of this versatility, alkyne cycloaddition with thiepin dioxide complex **25** allowed for rapid access to a variety of substituted cyclooctatetraene products via a [6+2] cycloaddition/photo-SO_2 extrusion sequence.[38] Unusual 2π partners such as cyclooctyne (**60**)[39] were well-behaved addends in this context (Eq. (24)).



(25)

One of the most remarkable Cr(0)-mediated transformations that has emerged from our studies in this area was an efficient, highly-selective three-component triene/alkyne cycloaddition process.[40] Equations (25) and (26) illustrate some of the key features of the reaction. The most notable characteristic of the overall process is the rapid increase in molecular complexity that accompanies the multistep cycloaddition event.[41,42] Fully four

new rings are created when the two alkynes are tethered together as in the example depicted in equation (26). Furthermore, the intermolecular examples studied to date have been shown to produce a single regioisomer in each case, thus adding to the potential synthetic utility of the method. Experimental observations made during this study suggest that a stepwise [6π+2π] cycloaddition-homo [6π+2π] cycloaddition sequence is followed in this reaction (Figure 2).

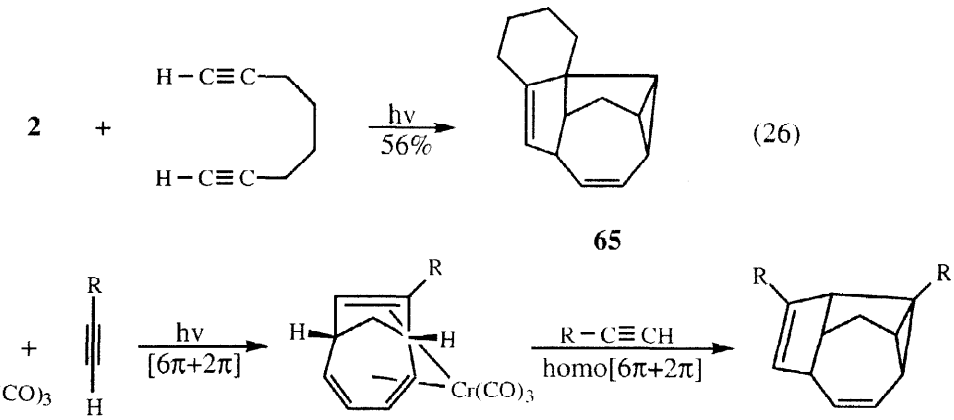
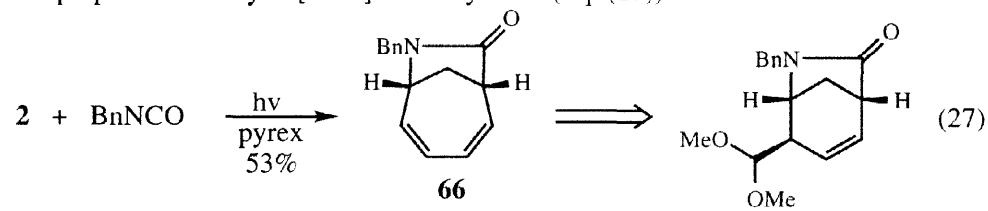
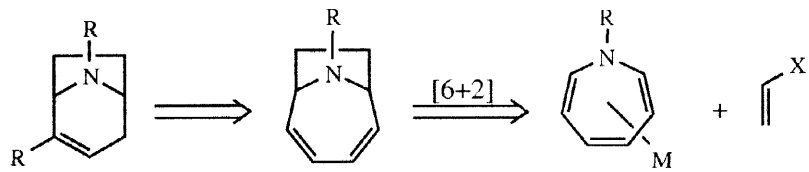


Figure 2. Putative pathway for the [6π+2π+(2π)] Cycloaddition

Nitrogen-based reaction partners have been particularly useful in applications of Cr(0)-promoted [6+2] cycloaddition to natural product synthesis. Isocyanates can be employed as novel 2π partners to afford highly-functionalized azabicyclo[4.2.1]nonane products that can be subsequently transformed into the interesting and often difficult to prepare 6-azabicyclo[3.2.1]octane systems (Eq. (27)).[43]



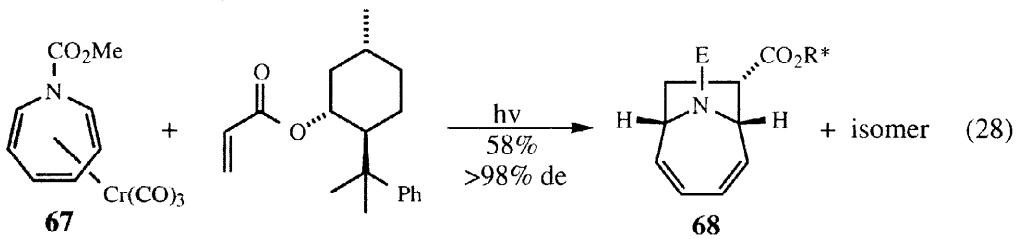
In closely related chemistry, chromium(0)-promoted [6π+2π] cycloaddition of an azepin-based complex would be expected to provide for a particularly rapid entry into functionalized homotropane ring systems[44] suitable for subsequent conversion into the tropane skeleton via ring contraction.[45] Critical to the success of this strategy is the ability to efficiently contract the homotropane system into the tropane bicycle, and while the 1,3-butadiene moiety that emerges from the cycloaddition event is ostensibly a useful function for effecting this conversion, many otherwise attractive methods failed to deliver significant quantities of the desired product. In the end, however, a novel application of the well-known Taylor-McKillop reaction succeeded admirably for this purpose.[45]

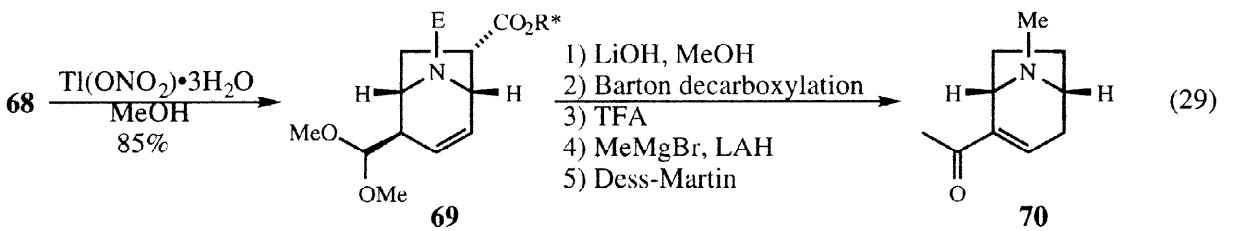


Scheme 5

In the event, auxiliary-controlled [6+2] photocyclization of azepin complex **67** with (-)-8-phenylmenthyl acrylate afforded a serviceable yield of adduct **68** with high diastereoselectivity.[46] After considerable

experimentation, a Tl(III)-mediated oxidative bond reorganization (Taylor-McKillop reaction) afforded tropane **69** in excellent yield and as a single regio- and stereoisomer. The extraordinary regiocontrol exhibited by this reaction may be due to electronic effects of the carboalkoxy group present on the two-carbon bridge. Routine functional group manipulation of **69** afforded enantiomerically pure (+)-ferruginine (**70**) (Eq. (29)). This synthesis represented the first total synthesis of this tropane alkaloid in enantiomerically pure form, and the success of this strategy for delivering these species with high stereoselectivity suggests that a range of tropane alkaloids can be assembled in quite similar fashion.





CONCLUSIONS

Once a laboratory curiosity, higher-order cycloaddition can now be included among the more powerful ring construction methods available in the contemporary synthetic repertoire. With the advent of the chromium(0)-mediated versions of these cycloadditions, many ring systems that were previously either difficult or even impossible to make using conventional methods are now readily accessible, often in enantiomerically enriched form. The capability of creating polycyclic arrays that are sufficiently functionalized for subsequent conversion into other systems is one of the chief attributes of this new chemistry. Furthermore, since metal-promoted higher-order cycloadditions proceed with concomitant high levels of predictable stereoselection, they are quite appropriate as starting points for complex natural product synthesis as is testified to by the many examples in this review.

Acknowledgement. I wish to thank the National Institutes of Health for their generous support of this research program over the years. I am also particularly grateful for the hard work and enthusiasm of the many co-workers who have made this research possible.

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