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Transition Metal Promoted Higher-Order Cycloaddition Reactions in Organic Synthesis

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Cycloaddition has long held a prominent position as one of the most powerful and versatile methods available for ring construction in organic synthesis. The well-known Diels–Alder reaction, for example, involves the combination of a diene (a 4π component) with a dienophile (a 2π component) to afford a six-membered-ring product. Other common cycloaddition combinations involve the union of two 2π partners to make four-membered rings and various 1,3-dipolar cycloadditions that yield five-membered-ring systems. Indeed, the vast majority of cycloaddition processes are characterized by the interaction of relatively simple π-arrays to construct small ring products.[1]

When two more extensively conjugated π-systems participate in a ring-formng reaction, the process is often referred to as a higher-order cycloaddition. Typical examples are depicted in generalized form in Figure 1 and include [$4\pi + 4\pi$], [$6\pi + 2\pi$], and [$6\pi + 4\pi$] combinations.[2] It is particularly noteworthy that these transformations can, in principle, provide rapid access to medium-sized ring systems, which are otherwise quite difficult to prepare. As a class, these cycloadditions exhibit many of the features that have made the Diels–Alder reaction so important in contemporary organic synthesis. Both are characterized by (1) a high level of convergency, (2) the ability to accommodate extensive functionalization in both reaction partners, and (3) a very high degree of stereoselectivity. Unlike the Diels–Alder reaction, however, most higher-order cycloadditions proceed with modest to poor chemical efficiency. The extended π-systems that are involved in these reactions are frequently prone to participating in multiple, competitive pericyclic processes that result in low chemical yields of products. Typically, these cycloadditions afford a plethora of adducts with none predominating.[3] This phenomenon has, in the past, relegated higher order cycloadditions to the status of mere laboratory curiosities.

We first became interested in higher-order cycloadditions in connection with studies on the total synthesis of the tumor-promoting diterpene, ingenol.[4] Scheme I depicts our basic strategy, which featured a thermally allowed [$6\pi + 4\pi$] cycloaddition between a substituted tropone and a functionalized diene.[5,6] Higher-order cycloaddition was regarded as offering an ideal solution to the problem of constructing the unusual bicyclo[4.4.1]undecanone system comprising rings B and C of the target molecule.

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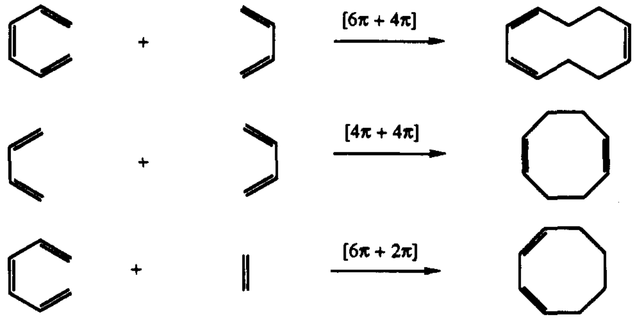

Figure 1. Generalized examples of typical higher-order cycloaddition reactions.

Although this transformation is one of the more efficient higher-order cycloaddition combinations, minor structural variations in either addend were found to completely suppress the [6 + 4] pathway. For example, reactions involving 2-substituted tropone addends (R = alkyl) afforded none of the bicyclo[4.4.1]-undecanone products. It quickly became evident that this class of reactions was too capricious and limited in scope to serve as the starting point for a synthesis of a molecule as complex as ingenol.

Recognizing the great potential that higher-order cycloaddition could have in organic synthesis if a convenient method for improving reaction efficiency could be identified, we embarked on a program to explore the utility of transition metals as possible templates for promoting these and related transformations. It was reasoned that an appropriate metal could intervene in the normal cycloaddition event by precomplexing with both reactants, rendering the process temporarily intramolecular in nature (Scheme II). The concept of exploiting a metal-templating effect for promoting higher-order cycloaddition reactions has been around for some time. Pettit was among the first to recognize its potential, although early results were of limited success.[7] More recently, Wender and associates have demonstrated the considerable utility of

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(1) For recent reviews of [4 + 2], [3 + 2], and [2 + 2] cycloaddition reactions, consult the following: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5.

(2) For a general overview of higher-order cycloaddition reactions, see: Rigby, J. H.; In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, Chapter 5.2, pp 617–43.

(3) Houk, K. N.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4143.

(4) For an overview of synthetic approaches to tumor-promoting diterpenes, see: Rigby, J. H. In *Studies in Natural Products Chemistry*; Rahman, A.-u., Ed.; Elsevier: Amsterdam, 1993; Vol. 12 (Part H), pp 233–74.

(5) For typical examples of the tropone–diene [6 + 4] cycloaddition, see: (a) Fujise, Y.; Saito, H.; Ito, S. *Tetrahedron Lett.* **1976**, 1117. (b) Garst, M. E.; Roberts, V. A.; Prussin, C. *Tetrahedron* **1983**, *39*, 581. (c) Garst, M. E.; Roberts, V. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 3882.

(6) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2398.

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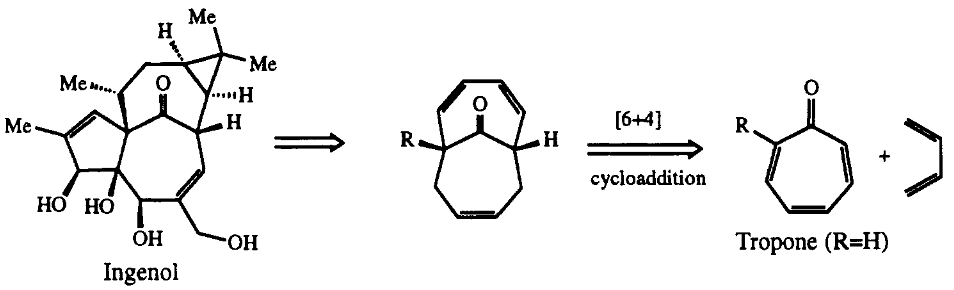
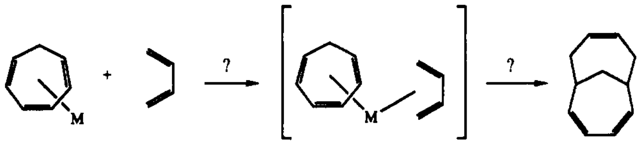
Scheme I



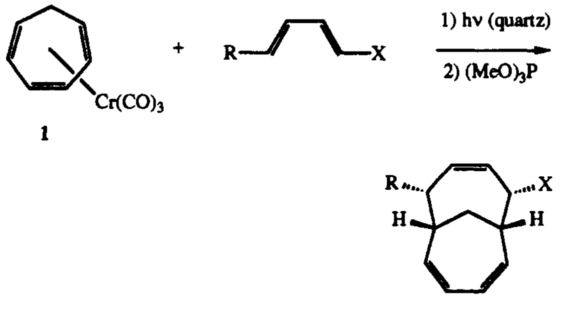
Scheme II



Ni(0)-mediated intramolecular [$4\pi + 4\pi$] cycloadditions in natural products synthesis.[8] This methodology is exceptionally well-suited for assembling targets exhibiting eight-membered carbocycles. In a development of particular pertinence to our problem, Kreiter and his collaborators had demonstrated, in a series of intriguing papers, that various chromium(0) complexes of cyclic trienes could participate in a photoinitiated [6 + 4] cycloaddition of modest efficiency with simple dienes.[9] With this precedent in hand, a detailed examination of the cycloaddition chemistry of (cycloheptatriene)tricarbonylchromium complex and its derivatives from a synthetic perspective was initiated in our laboratory.

The Chromium(0)-Promoted [$6\pi + 4\pi$] Cycloaddition Reaction

Readily available (η^6-1,3,5-cycloheptatriene)tricarbonylchromium(0) (1)[10] was the focal point of our initial investigations. It was found that irradiation (450-W Canrad-Hanovia medium-pressure Hg vapor lamp, quartz filter) of 1 in the presence of a small excess of a given diene for several hours followed by treatment of the resultant reaction mixture with excess trimethyl phosphite provided modest yields of the desired bicyclo[4.4.1]undecane cycloadducts. Several early results of this endeavor are depicted in eq 1.[11] The production



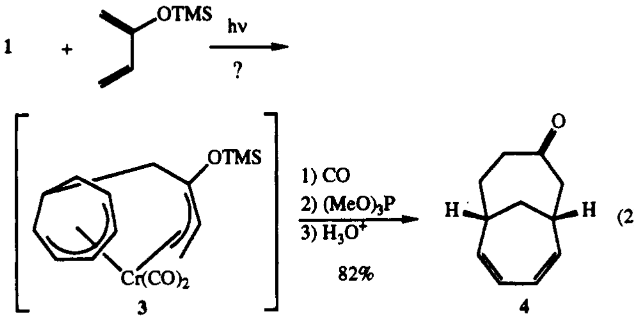
1

(1)

2a, R=H, X=OTMS (56%)
2b, R=Me, X=CO_2Me (49%)

of only the endo diastereomer is a notable feature of these cycloadditions, which can be contrasted with the exclusive formation of the exo isomer prevalent in many other higher-order cycloaddition reactions.[2] Remarkably, the electronic nature of the diene partner in the metal-mediated process appears to be of little consequence for influencing reaction efficiency. This observation can be distinguished from the Diels–Alder reaction wherein the use of properly matched participants is a prerequisite for effective bond formation.

A particularly revealing cycloaddition conducted early in our investigations employed 2-[(trimethylsilyl)oxy]butadiene as the 4π participant (eq 2). In contrast



1

3

4

(2)

to previous results, all attempts to effect this cycloaddition failed. Instead of yielding the expected adduct, a structurally ill defined and labile species exhibiting only two carbonyl ligands bound to the metal center appeared to be involved. Structure 3 was tentatively assigned to this intermediate on the basis of what little spectral data we could accumulate at the time. Kreiter had made some related observations during his investigations of (heptafulvene)tricarbonylchromium.[9c] Significantly, this intermediate was observed to collapse rapidly to the expected cycloadduct metal complex on exposure to carbon monoxide. Subsequent demetalation and silyl enol ether hydrolysis afforded adduct 4 in 82% yield. At the time, this was the highest yield of any adduct obtained in our laboratory.

All evidence collected to that time indicated that these reactions were stepwise in nature, and the developments depicted in eq 2 further suggested that a mechanism

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(7) (a) Davis, R. E.; Dodds, T. A.; Hseu, T.-H.; Wagnon, J. C.; Devon, T.; Tancrede, J.; McKennis, J. S.; Pettit, R. *J. Am. Chem. Soc.* **1974**, *96*, 7562. (b) Ward, J. S.; Pettit, R. *J. Am. Chem. Soc.* **1971**, *93*, 262.

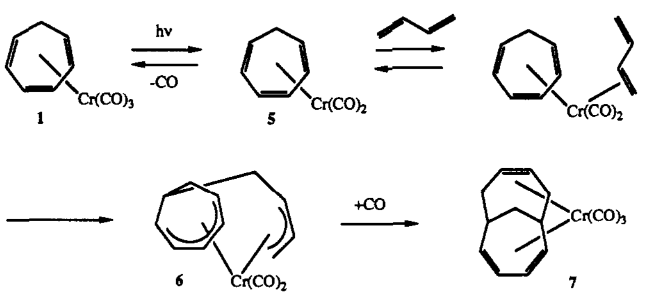
(8) (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (c) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904.

(9) (a) Özkar, S.; Kurz, H.; Neugebauer, D.; Kreiter, C. G. *J. Organomet. Chem.* **1978**, *160*, 115. (b) Kreiter, C. G.; Kurz, H. *Chem. Ber.* **1983**, *116*, 1494. (c) Michels, E.; Sheldrick, W. S.; Kreiter, C. G. *Chem. Ber* **1985**, *118*, 964. (d) Kreiter, C. G. *Adv. Organomet. Chem.* **1986**, *26*, 297.

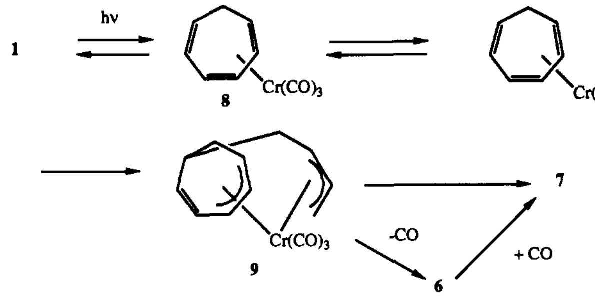
(10) (a) Abel, E. W.; Bennett, M. A.; Burton, R.; Wilkinson, G. *J. Chem. Soc.* **1958**, 4559. (b) Tate, D. P.; Knipple, W. R.; Augl, J. M. *Inorg. Chem.* **1962**, *1*, 433.

(11) (a) Rigby, J. H.; Ateeq, H. S. *J. Am. Chem. Soc.* **1990**, *112*, 6442. (b) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382.

Scheme III



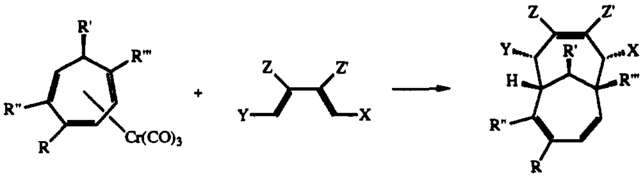
Scheme IV



may be operating that involves an initial light-induced loss of a CO ligand to produce a coordinatively unsaturated species. The basic features of this mechanism are depicted in Scheme III. The 16e metal center in **5** could then engage the diene and lead, via bond reorganization, to an intermediate **6**, which would capture carbon monoxide and collapse to the observed product. This pathway is fully consistent with the results in eq 2 and also finds support from recent investigations on related reactions reported by the Stufkens laboratory.[12] In our view, a crucial feature of this scenario appeared to be the obligatory recapture of the lost carbon monoxide ligand by species **6** to trigger the final bond formation to afford the observed cycloadduct complex **7**. We reasoned that the inefficiencies of this step could account for the typically modest yields obtained in these reactions. The observation that supplying these transformations with additional CO results in yield enhancement supports this contention. To probe this point further, two parallel cycloaddition reactions were performed: one under normal conditions and one in which a continuous purge of argon was employed throughout the photolysis process. This latter technique was used to prevent carbon monoxide recapture by removing the ejected gas from the reaction mixture as it was formed. The yield of adduct under these circumstances would be expected to decrease dramatically.[13] Surprisingly, the yield of the reaction employing the purge modification was 74% while the reaction run under "normal" conditions was only 49%.[14]

In light of these observations an alternative pathway, first suggested by Kreiter,[9c] can be considered (Scheme IV). The first step in this process would be a hapticity change (η^6 to η^4) to give the coordinatively unsaturated species **8**. Diene complexation and bond reorganization to give the bis-allyl intermediate **9**, followed by collapse to the observed cycloadduct metal complex **7**, would complete the sequence. Retention of all three CO ligands throughout the reaction is the crucial feature of this mechanism. To accommodate our observations in eq 2, species **9** could, under certain circumstances, lose a molecule of CO to produce an intermediate such as **6**, which could then be shuttled to product by the introduction of excess carbon monoxide.[11]

Table I. Representative Cr(0)-Promoted [6π + 4π] Cycloaddition Reactions



entry	substituents[a]	conditns[b]	yield (%)[c]
1	X, Y = Me	A	86
2	X, Y = CO_2Me	B	89
3	Y = CO_2Me	C	83
4	X, Y = Me; R = OMe	A	90
5	X, Y = Me, R = CO_2Me	B	90
6	X, Y = Me; R'' = CO_2Me	C	74
7	R = OMe; Z, Z' = Me	A	93
8	X, R' = Me; Y = CO_2Me	C	97
9	R''' = OMe; Z = OTBDMS	A	52

[a] Only non-hydrogen substituents are specifically identified in the table. [b] Reaction conditions: (A) Pyrex filter, N_2 purge, CO, $(MeO)_3P$; (B) Pyrex filter, Ar purge, $(MeO)_3P$; (C) uranium glass filter, Ar purge, $(MeO)_3P$. [c] Isolated yields of a single diastereomer in each case.

While the intricacies of the possible mechanistic pathways for these cycloadditions remain unresolved, consideration of these issues afforded a bounty of synthetically significant innovations, not the least of which was the systematic optimization of reaction conditions. The notion that efficiency could be augmented by providing excess carbon monoxide to the reaction mixture was examined for a range of examples, and it was noted that only those cycloadditions involving electron rich dienes benefited from this treatment. In contrast, the yields for all reactions examined to date were improved by employing the inert gas purging technique. Furthermore, irradiation through Pyrex or uranium glass filters rather than quartz also enhanced reaction efficiency. These observations and techniques were then combined to develop a set of useful reaction conditions that when applied appropriately resulted in excellent cycloadduct yields. A number of representative examples of the metal-promoted [6 + 4] cycloaddition reaction illustrating the benefits of these optimized conditions are compiled in Table I. It is quite evident from the data that a wide variety of substitution patterns can be tolerated by the reaction, and considerable stereochemical information is created during these cycloadditions; as many as five contiguous stereogenic centers can arise when 7-substituted cycloheptatriene ligands are employed as 6π partners (entry 8). One of the more striking features of the Cr(0)-mediated [6 + 4] reaction is the capacity for accommodating substituents at the bond-forming centers in the triene moiety (entry 9). As mentioned previously, similarly substituted tropone species failed to provide

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(12) Van Houwelingen, T.; Stufkens, D. J.; Oskam, A. *Organometallics* **1992**, *11*, 1146.

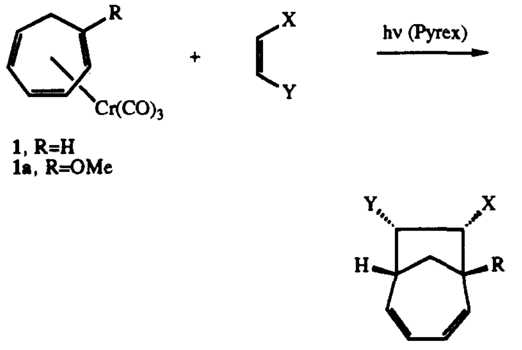
(13) Indeed, Stufkens noted that if the evolved CO was allowed to escape from his reaction mixtures, no cycloaddition products were observed; see ref 12.

(14) Removal of adventitious oxygen gas from the reaction mixture may account for the observed yield enhancement in this case: Cotton, F. A.; McCleverty, J. A.; White, J. E. *Inorg. Synth.* **1967**, *9*, 121.

any higher-order cycloadducts in the thermal, metal-free version of this reaction. This capability dramatically extends the potential synthetic utility of this cycloaddition process and provides a possible solution for one of the major tactical difficulties that confronted the application of higher-order cycloaddition technology to the ingenol problem.

The Chromium(0)-Promoted [6π + 2π] Cycloaddition Reaction

From our perspective, an important implication of the mechanisms outlined in Schemes III and IV is the possibility of implementing other types of higher-order cycloaddition reactions using metal mediation by modifying the trienophile addends. For example, when (cycloheptatriene)tricarbonylchromium(0) (1) was irradiated in the presence of ethyl acrylate, a high yield of the corresponding [6π + 2π] cycloaddition product was obtained as a single endo diastereomer. Several representative examples of this transformation are shown in equation 3.[15]



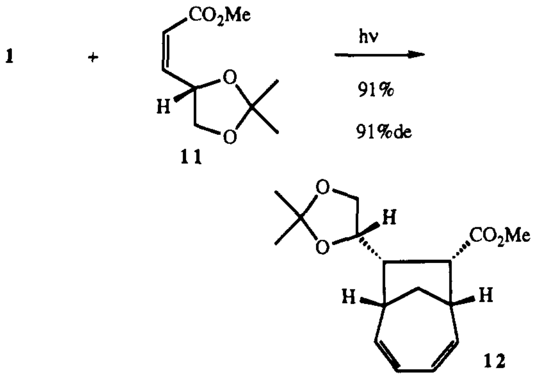
1, R=H
1a, R=OMe

(3)

10a, X=CO$_2$Et, R=H (92%)
10b, X=COMe, R=H (97%)
10c, X, Y=CO$_2$Et, R=H (80%)
10d, X=CO$_2$Et, R=OMe (81%)

In accord with the [6π + 4π] process, the metal-promoted [6 + 2] combination affords high yields of diastereomerically homogeneous products. Employing complexes with substituents at the bond-forming centers in the triene ligand also gives rise to good yields of products with virtually complete control of regiochemistry (eq 3). In stark contrast to the [6 + 4] reactions, however, electron-rich partners do not participate in the metal-promoted [6 + 2] cycloaddition. For example, butyl vinyl ether afforded none of the expected bicyclo[4.2.1]nonadiene product when reacted with complex 1.

The construction of the bicyclo[4.2.1]nonane carbon skeleton via cycloaddition is, in general, a very difficult conversion to accomplish,[16] and a few metal-mediated examples have appeared, but they have been of limited scope.[17] Subsequent to our initial disclosure of the Cr(0)-promoted [6π + 2π] reaction, two alkyne–(cycloheptatriene)tricarbonyl chromium(0) based [6 + 2] reactions were reported.[18] Among the more notable achievements in the realm of [6 + 2] chemistry has been the development of the photoinitiated, intramolecular cycloadditions of protonated tropones by Feldman and his co-workers that promises considerable synthetic utility.[19]



11

12

(4)

An important contemporary issue in organic synthesis is the ability to create carbon–carbon bonds with control of absolute stereochemistry, and several instances of quite remarkable levels of stereoinduction have been observed during metal-mediated cycloaddition. For example, commercially available ester 11 combines effectively with complex 1 to afford an excellent yield of the corresponding adduct 12 exhibiting a 91% diastereomeric excess (eq 4).

Synthetic Applications of Metal-Promoted Higher-Order Cycloaddition Reactions

As implied in the introductory paragraphs of this Account, higher-order cycloaddition reactions offer unique opportunities for accessing medium-ring carbocycles. With a few notable exceptions, simple eight- and 10-membered rings have not been prepared via cycloaddition.[8,20] In light of the obvious advantages of ring formation via this strategy, it would be desirable to design variants of the metal-promoted [6 + 2] and [6 + 4] reactions that would be amenable to simple medium-sized-ring construction. An intriguing solution to this problem would employ heterocyclic triene complexes that would give rise to heterobicyclic adducts from which the heteroatom could be excised to reveal the carbocyclic framework (Scheme V). Candidate heterocycles would have to be readily prepared, be amenable to complexation with the metal, and contain a heteroatom that could be subsequently extruded with facility. Azepine and thiepin derivatives appeared to meet these criteria, and they became the subjects of our initial inquiries in this area.[21]

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(15) Rigby, J. H.; Henshilwood, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5122.

(16) Jenner, G.; Papadopoulos, M. *J. Org. Chem.* **1986**, *51*, 585.

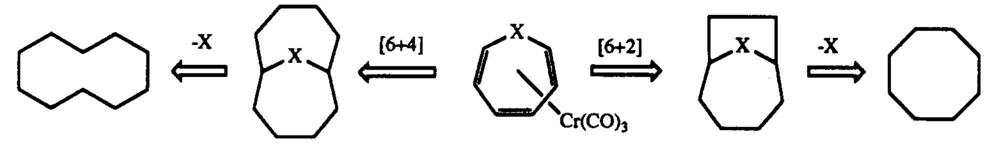
(17) (a) Green, M.; Heathcock, S.; Wood, D. C. *J. Chem. Soc., Dalton Trans.* **1973**, 1564. (b) Chopra, S. K.; Moran, G.; McArdle, P. *J. Organomet. Chem.* **1981**, *214*, C36. (c) Kreiter, C. G.; Michels, E.; Kurz, H. *J. Organomet. Chem.* **1982**, *232*, 249. (d) Mach, K.; Antropiusova, H.; Petrusova, L.; Hanus, V.; Turecek, F. *Tetrahedron* **1984**, *40*, 3295. (e) Bourner, D. G.; Brammer, L.; Green, M.; Moran, G.; Orpen, A. G.; Reeve, C.; Schaverien, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1409. (f) Klein, R.; Sedmera, P.; Cejka, J.; Mach, K. *J. Organomet. Chem.* **1992**, *436*, 143.

(18) (a) Fischler, I.; Grevels, F.-W.; Leitich, J.; Özkar, S. *Chem. Ber.* **1991**, *124*, 2857. (b) Chaffee, K.; Sheridan, J. B.; Aistars, A. *Organometallics* **1992**, *11*, 18.

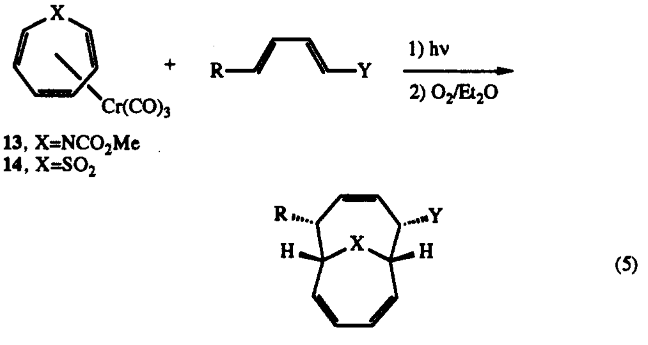
(19) (a) Feldman, K. S.; Come, J. H.; Freyer, A. J.; Kosminder, B. J.; Smith, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 1327. (b) Feldman, K. S.; Come, J. H.; Fegley, G. J.; Smith, B. D.; Parvez, M. *Tetrahedron Lett.* **1987**, *28*, 607. (c) Feldman, K. S.; Come, J. H.; Kosminder, B. J.; Smith, P. M.; Rotella, D. P.; Wu, M.-J. *J. Org. Chem.* **1989**, *54*, 592. (d) Feldman, K. S.; Wu, M.-J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 8490.

(20) (a) Sieburth, S. M.; Chen, J.-L. *J. Am. Chem. Soc.* **1991**, *113*, 8163. (b) For a review of eight-membered-ring synthesis, see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

Scheme V



The requisite *N*-(methoxycarbonyl)azepine complex 13 had been prepared previously,[22] and the heretofore unknown thiepin-1,1-dioxide complex 14 was easily accessible from the readily available heterocycle.[23,24] Both complexes were shown to be admirable participants in the photoinduced [$6\pi + 4\pi$] cycloaddition reaction (eq 5).

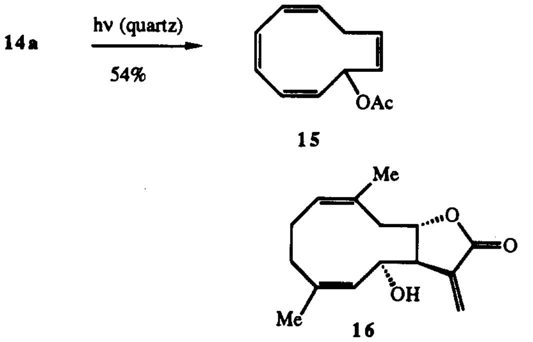


13, X=NCO_2Me
14, X=SO_2

(5)

13a, X=NCO_2Me, R=Me, Y=CO_2Me (83%)
14a, X=SO_2, R=H, Y=OAc (78%)

The adducts derived from complex 14 proved to be particularly well suited to subsequent conversion into the corresponding 10-membered carbocycles. For example, adduct 14a could be further irradiated (quartz filter) to induce a smooth cheletropic extrusion of sulfur dioxide to afford the (*all-Z*)-tetraene 15.[23c] The relationship between these extrusion products and certain cytotoxic germacranolide sesquiterpene lactones, such as 16, is noteworthy. To the best of our knowledge, this is one of the few examples of a successful cycloadditive entry into simple 10-membered rings.[25]

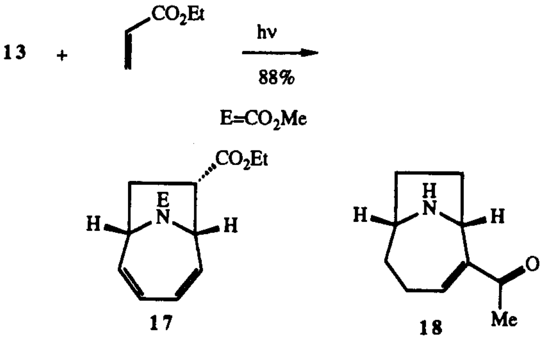


15

16

(6)

The [6 + 2] cycloaddition chemistry of the azepine complex afforded some interesting results as well. Irradiation of a mixture of complex 13 and ethyl acrylate provided the azabicyclo[4.2.1]nonane 17 in 88% yield (eq 7). While this methodology can be carried on to highly substituted eight-membered rings by cleaving either one or two carbon–nitrogen bonds,[21] it also affords a particularly efficient entry into the interesting homotropane ring system. A synthetic approach to the important neurotoxin anatoxin-a (18)[26] via a modification of this technology is currently underway in our laboratory.

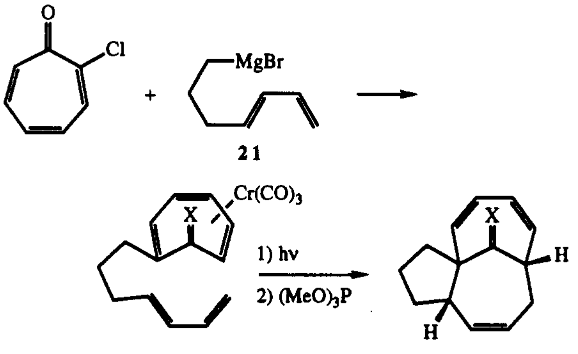


17

18

(7)

Obviously, one of the most important synthetic applications of this methodology is for the assembly of the highly substituted bicyclo[4.4.1]undecanone substructure contained within the ingenol carbon framework. An attractive strategy for convergent entry into the tricyclic framework of the natural product would feature an intramolecular version of the [6 + 4] cycloaddition process.



21

(8)

19a, X=O
19b, X=H_2

20a, X=O (52%)
20b, X=H_2 (85%)

Facile coupling of 2-chlorotropone with Grignard reagent 21 provided the requisite substrate, which when exposed to $(MeCN)_3Cr(CO)_3$ underwent selective complexation at the triene moiety to give 19a. Irradiation and demetalation afforded the ingenane tricycle 20a as a single (endo) diastereomer in modest but serviceable yield (eq 8).[27] In contrast, cycloaddition occurred with much greater facility with the corresponding cyclo-

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(21) Rigby, J. H.; Ateeq, H. S.; Krueger, A. C. *Tetrahedron Lett.* **1992**, *33*, 5873.

(22) Kreiter, C. G.; Özkar, S. *Z. Naturforsch.* **1977**, *32B*, 408.

(23) (a) Mock, W. L. *J. Am. Chem. Soc.* **1967**, *89*, 1281. (b) Mock, W. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1254. (c) For an informative overview of cheletropic extrusion reactions, see: Mock, W. L. In *Pericyclic Reactions* Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. II, pp 141–79.

(24) Recently, the corresponding iron(0) tricarbonyl complex of this heterocycle has been described: Nishino, K.; Takagi, M.; Kawata, T.; Murata, I.; Inanaga, J.; Nakasuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 5059.

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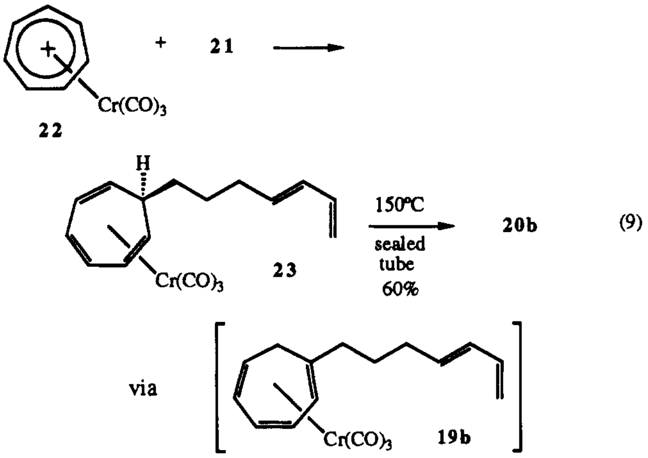
(26) For other approaches into this ring system, see: (a) Malpass, J. R.; Smith, C. *Tetrahedron Lett.* **1992**, *33*, 273. (b) Javier Sardina, F.; Howard, M. H.; Morningstar, M.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5025 and references cited therein.

(27) Rigby, J. H.; Sandanayaka, V. P. *Tetrahedron Lett.* **1993**, *34*, 935.

heptatriene-derived complex **19b**. This difference in behavior is most certainly associated with the greater lability of the tropone–metal complex.[11b,28] Unfortunately, complex **19b** is not as readily accessible as **19a**,[29] a fact which prompted a fundamental reevaluation of how the *intramolecular* metal-promoted reactions were conducted.

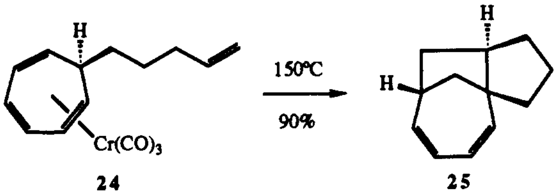
We had previously noted that both [6 + 4] and [6 + 2] cycloaddition could be effected with (cycloheptatriene)tricarbonylchromium complexes under thermal activation conditions to afford adducts that were identical in all respects with the corresponding photochemically derived products.[11b] Furthermore, it is well-known that cycloheptatriene–group 6 metal complexes undergo facile, thermally induced 1,5-hydrogen migrations within the cyclic triene moiety.[30] Combining these two processes in tandem could afford a potential *one-pot* method for effecting intramolecular cycloaddition in this series. A crucial aspect of this analysis was the assumption that only the 1-substituted cycloheptatriene isomer would readily undergo cycloaddition. To test this concept, Grignard reagent **21** was added to tropylium ion complex **22** to afford the key 7-exo-substituted substrate **23**.[31] Heating **23** in a sealed tube at 150 °C indeed provided the anticipated adduct **20b**, which was found to be identical in all respects to the photochemically derived material. It is presumed that this transformation occurred via the intermediacy of the 1-substituted complex **19b**, which was formed in equilibrium with other isomers through metal-promoted 1,5-hydrogen migration.



(9)

An even more remarkable example of the one-pot isomerization–cycloaddition protocol was realized with the readily available complex **24** (eq 10). This transformation served as a useful extension of the corresponding thermally activated intermolecular [6 + 2] process.[27,32]

In all cases examined to date, the thermal versions of these cycloaddition reactions provided products that



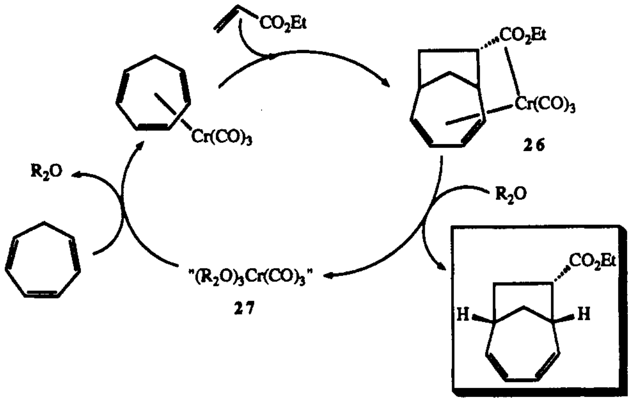
(10)

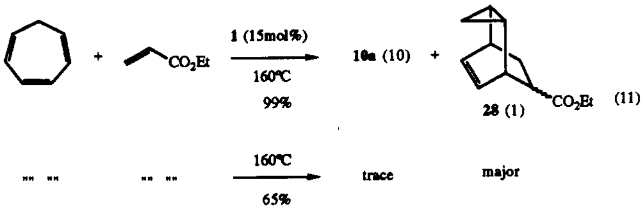
were indistinguishable from those obtained photochemically. One of the more revealing examples of this equivalency is the thermal cycloaddition of the chiral 2π partner **11**, which provided adduct **12** with the same sense and level of asymmetric induction observed in the corresponding photochemical reaction (see eq 4).

Catalytic Metal-Promoted Higher-Order Cycloaddition Reactions

An important criterion that transition metal mediated transformations, in general, must satisfy to achieve widespread acceptance by the synthetic community is the capability of being effected catalytically. Observations made in conjunction with the thermal versions of our metal-mediated cycloadditions suggested that these transformations could be rendered catalytic in chromium(0) with only a minor modification of the reaction conditions. A catalytic cycle such as depicted in Scheme VI for the [6 + 2] reaction could be envisioned in which substoichiometric quantities of metal–triene complex were employed. To facilitate catalyst turnover, an interactive solvent such as an ether would serve to rapidly demetalate the cycloadduct–metal complex **26** as it was formed and in so doing produce a very reactive "$Cr(CO)_3$" transfer species, **27**, which could engage additional triene to perpetuate the cycle. Intermediates related to **27** have been invoked as active catalysts in other chromium(0)-mediated reactions.[33]

Scheme VI





(11)

In the event, heating a mixture of cycloheptatriene and excess ethyl acrylate in the presence of (cycloheptatriene)tricarbonylchromium(0) (**1**) (15 mol %) (160 °C, n-Bu_2O) afforded a 99% yield of a mixture of [6 +

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[28] Pauson, P. L.; Todd, K. H. *J. Chem. Soc. C* **1970**, 2315.

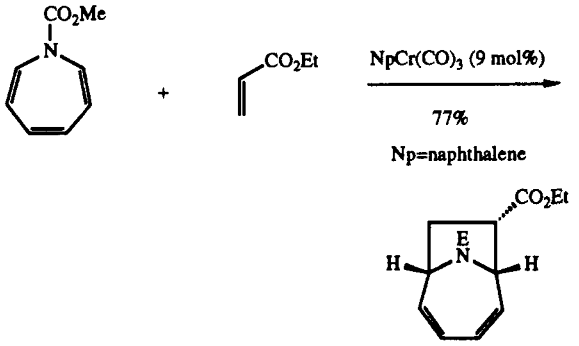
[29] 1-Substituted cycloheptatriene complexes are prepared from the readily available 7-exo-isomer, followed by thermal isomerization and a tedious separation: (a) Pauson, P. L.; Smith, G. H.; Valentine, J. H. *J. Chem. Soc. C* **1967**, *1057*, 1061. (b) Munro, J. D.; Pauson, P. L. *J. Chem. Soc.* **1961**, 3475.

[30] (a) Roth, W. R.; Grimme, W. *Tetrahedron Lett.* **1966**, 2347. (b) Foreman, M. I.; Knox, G. R.; Pauson, P. L.; Todd, K. H.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 1141.

[31] Pauson, P. L.; Munro, J. D. *J. Chem. Soc.* **1961**, 3479, 3484.

[32] Rigby, J. H.; Short, K. M.; Ateeq, H. S.; Henshilwood, J. A. *J. Org. Chem.* **1992**, *57*, 5290.

2] adduct **10a** along with cycloadduct **28** in a ratio of 10:1, respectively. The minor component of this reaction is the normal product of the metal-free cycloaddition between cycloheptatriene and ethyl acrylate.[34] It is noteworthy that when the same reaction was carried out in the absence of the metal catalyst, only a trace of **10a** could be isolated (eq 11). These and related transformations can also be effectively carried out using (naphthalene)tricarbonylchromium(0)[35] as the catalyst as illustrated in the cycloaddition of *N*-(methoxycarbonyl)azepine[36] shown in eq 12.



(12)

17

Unfortunately, to date, the corresponding [6 + 4] reactions employing substoichiometric amounts of a "$Cr(CO)_3$" source have remained somewhat less efficient. It is currently believed that the more robust (cycloadduct)tricarbonylchromium(0) complexes involved in the [6 + 4] reactions are demetalated inefficiently under these reaction conditions, thus inhibiting catalyst turnover. Work is currently underway to address this issue.

Conclusions and Future Prospects

The intervention of transition metals in the higher-order cycloaddition process has been demonstrated to greatly facilitate reactions that are otherwise difficult or even impossible to carry out. The high level of reaction efficiency that is now attainable under these conditions, when combined with the other attributes of higher-order cycloadditions, makes these transformations powerful additions to the armory of synthetically useful operations.

The versatility and generality of these metal-mediated cycloadditions will permit the future targeting of structurally elaborate and stereochemically rich natural products. The extensive stereocontrol characteristic of these transformations renders them particularly well suited for constructing systems that exhibit an array of multiple, contiguous stereogenic centers. Possible target molecules of this type would include the ansa bridge moieties of various ansamycin antibiotics. Work in this direction is currently under active investigation in our laboratory.

I wish to express my sincerest gratitude to all of my coworkers at Wayne State University who are cited throughout the reference section. Their enthusiasm and diligence have been instrumental in the development of the chemistry described in this Account. I would also like to thank the National Institutes of Health for their generous support of this research.

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(34) (a) Bellus, D.; Helferich, G.; Weis, C. D. *Helv. Chim. Acta* **1971**, 54, 463. (b) Rigby, J. H.; Denis, J.-P. *Synth. Commun.* **1986**, *16*, 1789.

(35) Desobry, V.; Kündig, E. P. *Helv. Chim. Acta* **1981**, *64*, 1288.

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