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Metal Promoted Higher-Order Cycloaddition Reactions. A Facile Entry Into Substituted Eight- and Ten-Membered Carbocycles.

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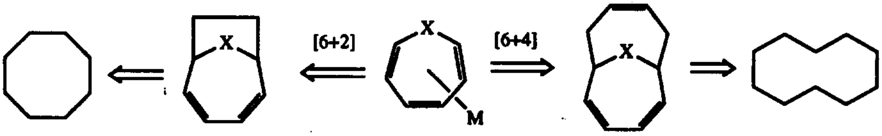
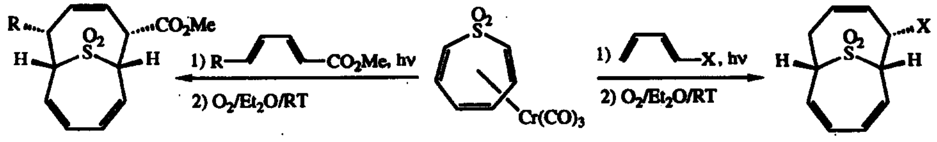
Summary: Substituted eight- and ten-membered carbocycles can be accessed by employing a metal promoted higher-order cycloaddition of heterocyclic trienes followed by heteroatom extrusion.

Higher-order cycloaddition reactions (i.e., 6π + 4π, 4π + 4π, and 6π + 2π combinations) typically display extremely high levels of stereoselectivity and low chemical efficiency.[1] The advent of effective photochemically initiated, metal-promoted versions of these transformations has provided convenient access to a range of highly-substituted bicyclo[4.4.1]undecane and bicyclo[4.2.1]nonane carbocyclic systems in diastereomerically pure form.[2,3]



Scheme I

An attractive extension of this methodology would employ heteroatom substituted cyclic triene metal complexes as potential precursors to a variety of eight- and ten-membered carbocycles via a tandem higher-order cycloaddition-heteroatom excision process (**Scheme I**). We now wish to report that this strategy has been brought to practice with the readily available (η^6-thiepin-1,1-dioxide)tricarbonylchromium(0) (1)[4] and (η^6-N-carbomethoxyazepine)tricarbonylchromium(0) (2)[5] complexes serving as the 6π cycloaddition partners.



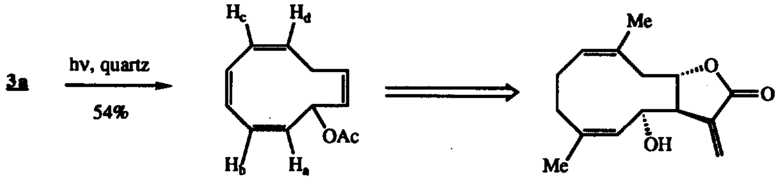
(1)

4a, R=H, 38%
4b, R=Me, 21%

1

3a, X=OAc, 78%
3b, X=OTMS, 65%

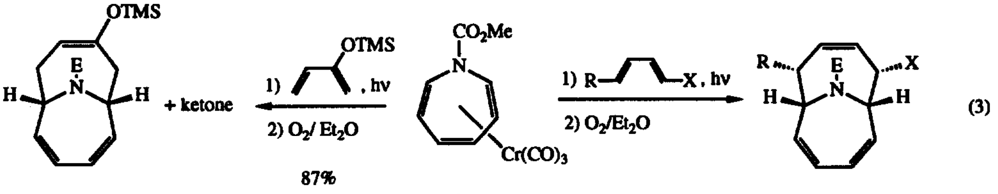
Complex 1 was available in 86% yield by exposing thiepin-1,1-dioxide[6] to trisacetonitriletricarbonylchromium(0) (THF, RT, 12h). Room temperature irradiation (450-W Canrad-Hanovia medium-pressure Hg vapor lamp, uranium glass filter) of a solution of complex 1[7] (1:1 methylene chloride/hexanes) in the presence of excess diene (10 equiv.) for 1h, followed by metal decomplexation with oxygen provided cycloadducts 3a,b[7] and 4a,b[7] as single diastereomers in each case. The relative stereochemistries assigned to these materials were based on analogy to previous results from our laboratory in which products derived from an endo transition state were obtained exclusively.[2b] Further support for the structures of these materials was available from an x-ray structure of an azepine cycloadduct (*vida infra*). Unlike previous observations in the all carbon cases, lower yields were observed in reactions involving electron deficient diene partners relative to their electron rich counterparts.[2b] No cycloaddition products were isolated when a solution of thiepin-1,1-dioxide and 1-trimethylsilyloxybutadiene was irradiated in the absence of the metal.



5 6

(2)

Photolysis (quartz filter, 1:1 methylene chloride/hexanes, 15 min, R.T.) of decomplexed cycloadduct 3a provided the all Z-cyclodecatetraene 5[7] (54%) via cheletropic extrusion of sulfur dioxide.[8] The Z geometry of the newly created unsaturation in the extrusion product was confirmed by decoupling experiments (J_{ab} = 11.0 Hz, J_{cd} = 11.1 Hz).[9] The structure assigned to 5 was further substantiated by conversion into cyclodecanol. The relationship of compound 5 to Z, Z-sesquiterpene lactones such as 6[10] is noteworthy. To date, the corresponding thermal extrusion has not been successful.



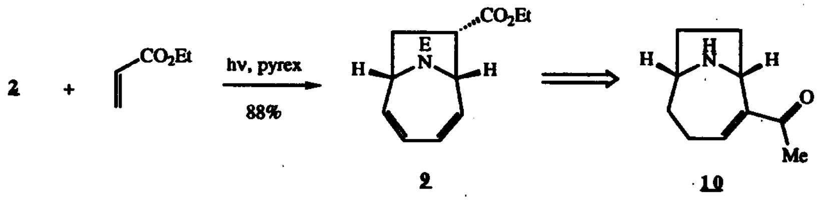
8 2

(3)

7a, R=H, X=OAc, 75%
7b, R=H, X=OTMS, 79%
7c, R=Me, X=CO_2Me, 83%

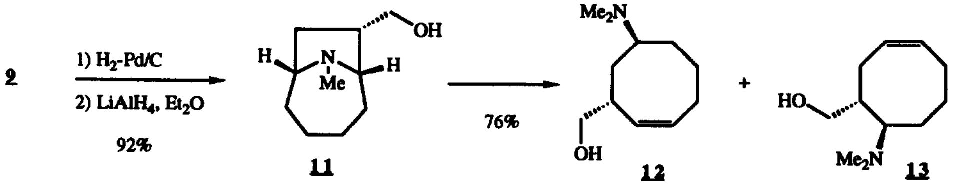
The N-carboalkoxyazepine complex 2 was also shown to efficiently give higher-order cycloadducts under standard photochemical conditions. In contrast, Paquette and co-workers have demonstrated that uncomplexed N-substituted azepines tend to participate as either 4π or 2π partners in cycloaddition reactions.[11]

In a typical experiment, irradiation (pyrex filter) of complex 2 (hexanes) in the presence of a slight excess (1.2 - 1.5 equiv.) of diene provided azabicyclo[4.4.1]undecane adducts 7a-c[7,12] and 8[7] in very good yields. In concurrence with the all carbon series reported earlier,[2b] the electronic nature of the diene partner appears to have little influence on cycloaddition efficiency in the azepine series.



(4)

An attractive extension of this chemistry that could be applicable for assembly of substituted eight-membered rings would exploit a metal-promoted [6π + 2π] cycloaddition[2a] between complex 2 and appropriate 2π partners.[13] Standard irradiation of a 1:1.5 mixture of 2 and ethyl acrylate (hexanes) respectively, provided adduct 9[7] (88%) as a single diastereomer that was assigned the endo stereochemistry based on analogy to the all carbon series.[2a] Cycloaddition reactions of this general type appear to offer a pathway for rapid entry into the interesting and important homotropane system of which the powerful nerve depolarizing agent, anatoxin (10) is a typical example.[14]



(5)

Substituted cyclooctenes can be easily accessed from adduct 9 by the following sequence of transformations. Saturation of the diene system followed by reduction of the carbamate to the requisite N-methyl derivative 11,[7,15] set the stage for exhaustive methylation which proceeded smoothly. Subsequent Hofmann elimination (Ag_2O, H_2O, KOH, 325° C, sealed tube)[16] gave a 1:1 mixture of cyclooctenes 12[7] and 13[7] in 76% overall yield. Although the regioselectivity in this relatively simple example was somewhat disappointing, it is clear from these results that this protocol is particularly well suited for rapid, stereocontrolled synthesis of highly substituted cyclooctene targets.

Work on these and related problems are currently underway in our laboratory.

Acknowledgment

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