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Conformational Requirements of a Stereospecific Three- to Five-Carbon Ring Expansion Reaction

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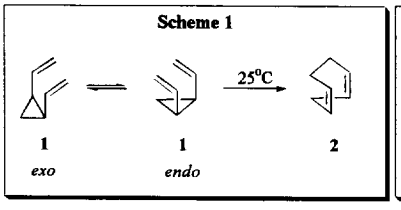
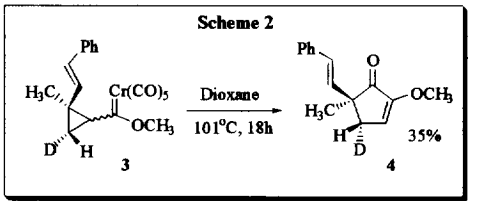
Abstract: Synthesis of conformationally-restricted 2-alkenylcyclopropylcarbene-chromium complexes has been accomplished, and subsequent thermal ring-expansion reactions examined. Thermolysis of conformationally-restricted carbene complexes yielded products that suggest this unique ring-expansion reaction is very dependent upon conformational effects.

The Cope rearrangement of divinylcyclopropane has proven to be an excellent reaction for the formation of seven-membered rings (Scheme 1).[1] The rate of the ring expansion reaction is much greater for the *cis* divinylcyclopropane than for the *trans* isomer.[2] Analysis of substituted and conformationally-restricted divinylcyclopropanes suggest that both vinyl groups must be in an *endo* configuration for the ring expansion to occur.[3]

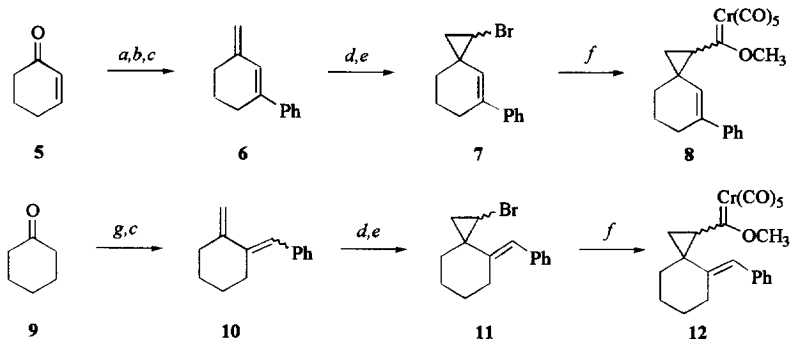




A similar process is thought to be important in the ring expansion reaction of structurally related 2-alkenylcyclopropylcarbene-chromium complexes to 5-alkenyl-2-cyclopentenones (Scheme 2),[4] which proceeds with retention of configuration.[5] Carbon-carbon bond cleavage during the ring expansion has been proposed to occur by a mechanism analogous to the divinylcyclopropane rearrangement. If similar conformational effects are operating, this would imply that the alkene and carbene carbon must be *cis* and situated above the cyclopropane ring (*endo*). To more fully understand the conformational requirements of the ring expansion reaction, 2-alkenylcyclopropylcarbene-chromium complexes **8** and **12** were synthesized (Scheme 3). In carbene complex **12**, the alkene substituent is locked into the *endo* configuration, while in carbene complex **8**, the alkene is locked into the *exo* configuration. Carbene complexes **8** and **12** were synthesized as 2:1 mixtures of *cis*:*trans* diastereomers respectively (the terms *cis* and *trans* refer to the relative stereochemistry of alkene and carbene complex substituents). Although the phenyl-substituted alkenes undergo the ring expansion less efficiently than alkyl-substituted alkenes,

the presence of the phenyl ring was necessary to direct the diene cyclopropanation reaction in the synthesis of carbene complexes **8** and **12**.

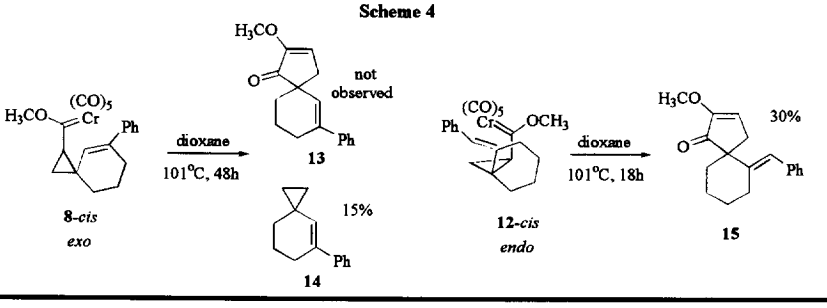
Scheme 3



a. PhLi; H_2O. *b*. PCC/CH_2Cl_2. *c*. methyltriphenylphosphonium bromide, PhLi. *d*. $CHBr_3$, KO-t-Bu. *e*. Zn/HOAc. *f*. t-BuLi, then $Cr(CO)_6$, then methyl triflate. *g*. NaOH/benzaldehyde.

Thermolysis of *exo* carbene complex **8** at 101°C resulted in none of the expected ring expanded product **13**, but instead yielded cyclopropane derivative **14** as the major organic product in 15% yield (Scheme 4). This thermolysis reaction required a considerably longer time for completion (48 h vs. 18 h) than for typical vinylcyclopropylcarbene thermolysis reactions. Cyclopropane derivative **14** may have resulted from a previously unobserved mechanistic pathway that involves demethylation of the carbene complex followed by subsequent decarbonylation and protonation. Conversely, thermolysis of *endo* carbene complex **12** led to the predicted cyclopentenone **15** in 30% yield (Scheme 4).[6] Reaction time for completion (18 h) of the rearrangement of **12** was similar to that required for other successful ring expansion reactions.[4]

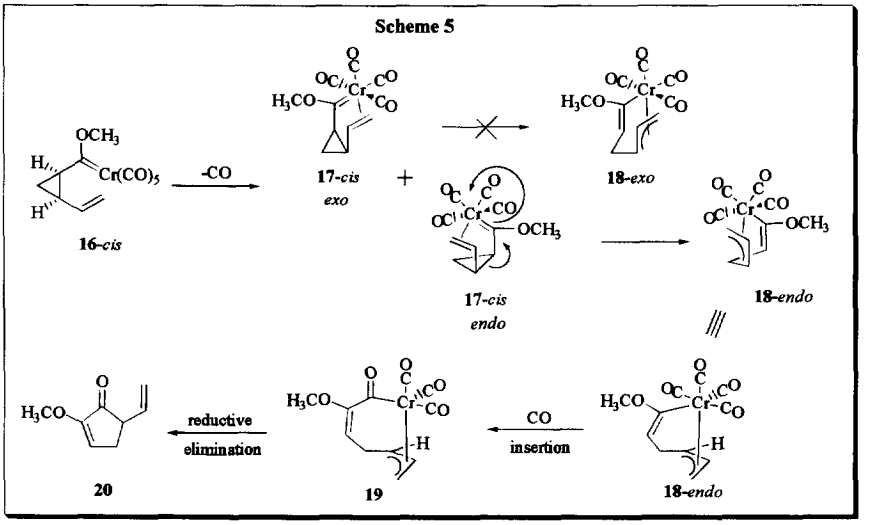
Scheme 4



This evidence suggests that a specific alkene conformation is essential for the ring expansion of 2-alkenylcyclopropylcarbene chromium complexes. The alkene must achieve an *endo* configuration for conversion to the expected cyclopentenone product. This requirement also suggests that the *trans* diastereomer can not undergo conversion to the cyclopentenone product without prior *cis-trans* isomerization. It has been previously shown that the *cis* and *trans* isomers in a similar compound can equilibrate under these reaction conditions.[4]

With these revelations, a definitive mechanism for the ring expansion can now be hypothesized (Scheme 5). The initial step seems to involve loss of carbon monoxide followed by alkene complexation to form *endo* and *exo* **17**-*cis*. Although *exo* **17**-*cis* appears less sterically congested than *endo* **17**-*cis*, the *exo* conformer is incapable of generating the observed product, since formation of the highly-strained *exo* allyl complex **18** would ultimately result in the *trans*-cyclopentenone. Isomerization between the *exo* and *endo* conformers of **17**-*cis* is especially likely based upon the lability of alkenes ligated to Fischer carbene complexes.[7] This first step is the rate limiting step, since the reaction is substantially slower when conducted in a carbon monoxide atmosphere.[4] Once alkene-complexation in the *endo* conformation is achieved, the cyclopropane opens to form the (η^3-allyl)vinylchromium complex **18**-*endo*, in a process analogous to the Cope rearrangement.[7a,8] This ring opening process must occur in the coordination sphere of chromium to account for the observed retention of stereochemistry for the ring expansion reaction.[5] Next, CO is inserted preferentially[9] into the vinyl substiuent to form (η^3-allyl)acylchromium complex **19**, and reductive elimination yields the observed cyclopentenone product **20**.

Scheme 5



In summary, we have shown that 2-alkenylcyclopropylcarbene-chromium complexes are converted to 5-alkenyl-2-cyclopentenones through a mechanism that is intrinsically similar to the divinylcyclopropane rearrangement in its conformational requirements. Alkene and carbene substituents must be cis and able to adopt an endo configuration to obtain the expected products.

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6. **15**: ^{1}H NMR ($CDCl_3$): 7.45-7.10 (m, 5H), 6.35 (t, 1H, J=1.0 Hz), 6.10 (s, 1H), 3.75 (s, 3H), 2.65 (br s, 2H), 2.10-1.45 (m, 8H). ^{13}C NMR ($CDCl_3$): 215.9; 156.5; 142.3; 137.6; 129.0; 127.9; 126.1; 123.9; 122.8; 56.8; 53.6; 37.5; 35.8; 27.1; 26.5; 22.8. IR (neat): 3060(m), 3013(m), 2931(s), 2848(s), 1707(s), 1631(s), 1448(s), 1131(s). HRMS *m/z* 268.1457 (calcd. for $C_{18}H_{20}O_2$, *m/z* 268.1463).
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