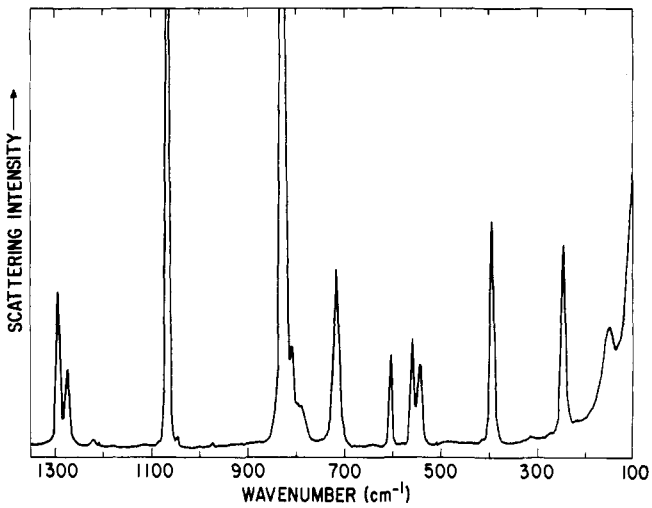


*Figure 2.* Raman spectrum of $RbSO_4F$. Excitation was with the 5145-Å line of a Coherent Radiation Model 52 argon ion laser. Measurements were made with a Spex 1401 monochromator linear in wavenumber and an RCA C31034 photomultiplier tube. Spectral slit width was approximately 5 $cm^{-1}$. The spectrum of $CsSO_4F$ is similar, except that only a single broad band is observed at 1280 $cm^{-1}$.

The fluorine-19 NMR spectra of $CsSO_4F$ and $RbSO_4F$ solutions in acetonitrile have been measured, using a Varian A-56/60 spectrometer. (Fluoroxysulfate is more stable in acetonitrile than in water.) With both salts a single line was observed at −132.3 ppm relative to $CFCl_3$. In contrast, an aqueous solution of $KSO_3F$ gave a line at −37.5 ppm. These results provide further confirmation that the fluorine in $SO_4F^-$ is bonded to oxygen rather than to sulfur, as it is in $SO_3F^-$. The isoelectronic $FClO_4$ has a resonance at −225.9 ppm.[6]

The solid salts appear to be fairly stable, although we have observed a slow loss of oxidizing power (ca. 3–5% per month). Heating to ca. 100 °C leads to a mild detonation, and mass spectrometric analysis of the gases evolved indicates $O_2$ to be the principal gaseous product, as expected for the reaction

$$MSO_4F \rightarrow MSO_3F + \tfrac{1}{2}O_2$$

Small amounts of $SO_2F_2$, $SO_2$, and $SOF_2$ are also formed. Thus an 18.9$_2$-mg sample of $RbSO_4F$ produced 0.0462 mmol of $O_2$ (calcd for $RbSO_4F$: 0.0472), along with 0.0073 mmol of $SO_2F_2$, 0.0011 mmol of $SO_2$, and 0.0002 mmol of $SOF_2$.

As Fichter reported, aqueous solutions of fluoroxysulfate are unstable. They decompose gradually, with the evolution of varying amounts of $O_2$. The acidity of the final solution is considerably lower than would result from the reaction

$$SO_4F^- + H_2O \rightarrow HSO_4^- + HF + \tfrac{1}{2}O_2$$

and it is likely that substantial quantities of $SO_3F^-$ are formed. Variable amounts of two oxidizing species remain in solution after the decomposition. One reacts rapidly with $I^-$ and is presumably peroxymonosulfate; the other reacts slowly with $I^-$ unless molybdate is present and is presumably hydrogen peroxide. At 15 °C, the initial half-life of fluoroxysulfate in acid is around 30 min, but successive half-lives are shorter, probably because of the reaction of $SO_4F^-$ with $H_2O_2$.

In alkaline solution the decomposition of fluoroxysulfate is essentially instantaneous. A transient yellow color is frequently observed, and a pungent odor is detected. Mass spectrometric analysis indicates the formation of $O_2$ mixed with small amounts of $OF_2$.

Also in agreement with Fichter's observations, aqueous solutions of fluoroxysulfate are very powerfully oxidizing. Chloride, bromide, and iodide are oxidized first to the free halogens and then to higher states. Vanadium(IV) is oxidized to vanadium(V), Ce(III) to Ce(IV), and Co(II) to Co(III). Manganous ion is oxidized first to Mn(III) and then to permanganate. $Pb^{2+}$, $Tl^+$, and $Ag^+$ are all oxidized. Surprisingly, chromium(III) is not oxidized in acidic solution, though in base chromate is formed. Fluoroxysulfate reacts vigorously with aqueous hydrazoic acid to produce a mixture of $N_2$, $N_2O$, and $N_3F$. In general, though not invariably, fluoroxysulfate is a considerably more rapid oxidant than peroxymonosulfate.

When toluene was shaken with aqueous fluoroxysulfate, the reaction products, as determined by gas chromatography–mass spectrometry, included fluorotoluenes and fluorobenzyl fluorides, cresols and fluorocresols, fluorobenzyl alcohol, and benzaldehyde. No nonaromatic products were observed.

Fluoroxysulfate is the first known example of an ionic hypofluorite. Its ionic character is of especial significance in that it permits the formation and isolation of relatively stable salts. The stability of these salts, along with their ease of preparation and unusual reactivity, may well make the fluoroxysulfates uniquely useful synthetic and analytical reagents for both inorganic and organic chemistry.

**Note Added in Proof.** Although the fluoroxysulfates do not ordinarily decompose violently, on two occasions the introduction of a spatula into a 100-mg sample of $CsSO_4F$ produced a sharp detonation. Caution is called for in the handling of larger quantities of these salts.

**Acknowledgment.** We wish to thank Dr. Randall Winans for the GC–MS measurements and for stimulating discussions concerning the possible applications of fluoroxysulfate in organic chemistry. Mrs. A. G. Engelkemeir carried out the mass spectrometric analyses of some of the gas mixtures. We are grateful to Dr. Dominic Ip for the NMR measurements.

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*Received January 18, 1979*

## The Enzymatic Conversion of Farnesyl to Nerolidyl Pyrophosphate: Role of the Pyrophosphate Moiety

*Sir:*

Since the introduction of the isoprene rule by Ruzicka in the early 1920s,[1] the acyclic sesquiterpene alcohol farnesol (**1a**) and its tertiary allylic isomer, nerolidol (**2a**), have played a prominent role in biogenetic speculations and related chemical model studies.[2] Although a great deal is now known about farnesyl pyrophosphate biosynthesis, the details of the formation and subsequent metabolism of nerolidol and its biologically activated ester, nerolidyl pyrophosphate (**2b**), remained obscure until only very recently.[3] As reported in previous communications,[4] using both intact cells and cell-free enzymes of *Gibberella fujikuroi*, we have demonstrated that the fungal sesquiterpene metabolite cyclonerodiol (**3b**) is

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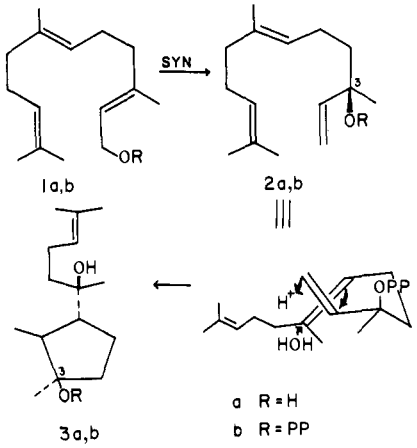
Scheme I



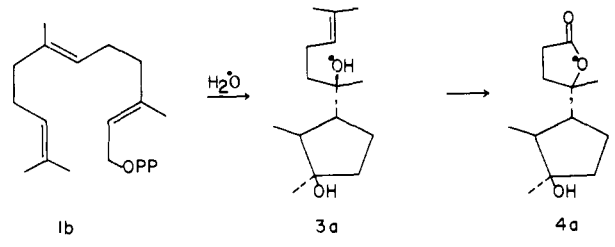

formed from nerolidyl pyrophosphate by net trans addition of water across its central and vinyl double bonds, followed by pyrophosphate ester hydrolysis. Nerolidyl pyrophosphate is itself formed by isomerization of farnesyl pyrophosphate and experiments with stereospecifically deuterated and tritiated precursors established that this allylic rearrangement takes place with suprafacial (syn) stereochemistry. This latter conclusion involved the well-precedented assumption that hydrolysis of the pyrophosphate ester bond of the presumed intermediate, cyclonerodiol pyrophosphate (**3a**), to the corresponding alcohol (**3b**) occurs with P–O bond cleavage,[5] implying that the nerolidyl pyrophosphate itself must possess the 3*R* configuration. We have now experimentally confirmed both of these latter assumptions and our results, in full accord with our previous arguments, are reported below. We then describe further $^{18}O$-labeling experiments whose results strongly suggest an ion-pair mechanism for the farnesyl–nerolidyl pyrophosphate rearrangement.

The occurrence of P–O bond cleavage during pyrophosphate ester hydrolysis was established by converting farnesyl pyrophosphate to cyclonerodiol in $^{18}O$-enriched water, using an improved preparation of the previously described cell-free system to effect the transformation.[4,6] Thus 0.144 mmol ($9.17 \times 10^4$ dpm) of [12,13-$^{14}C$]farnesyl pyrophosphate was incubated for 3 h at 26 °C with the cell-free extract obtained from 14 L of *G. fujikuroi* culture in 5.0 mL of [$^{18}O$]water (37.7 atom % excess).[7] The resulting labeled cyclonerodiol was isolated and purified as previously described[4] to give 1.08 mg of **3b** (2.9% conversion). Treatment of **3b** with osmium tetroxide–sodium periodate, followed by Jones oxidation, gave the hydroxy lactone **4a** which was purified by PLC (methylene chloride–ether, 3:1, two developments, $R_f$ 0.43) and recrystallized from chloroform.[4] Examination of the mass spectrum of the hydroxy lactone thus obtained established that only the side chain hydroxyl at C-7 of cyclonerodiol is derived from water, as required by the previously established mechanism. The parent (M), as well as M − $CH_3$, M − $H_2O$, and M − $CH_3$, $H_2O$ fragments of labeled **4a** showed an enrichment of 24.8% atom excess $^{18}O$ over the corresponding peaks of unlabeled **4a**.[8] The fact that no M + 4 peak was detected and that the isotopic enrichment was unchanged in the fragments corresponding to loss of water from the ring confirmed that hydrolysis of the pyrophosphate ester takes place with exclusive P–O bond cleavage.

If the pyrophosphate ester **3a** is cleaved at phosphorus, it is reasonable to infer that the stereochemistry at C-3 of nerolidyl pyrophosphate will not be affected by the cyclization and subsequent hydrolysis. A direct test of this assumption required a sample of optically pure [$^{14}C$]nerolidyl pyrophosphate. The requisite (3*S*)-[12,13-$^{14}C$]nerolidol was prepared from (3*S*)-nerolidol ($\alpha_D$ +15.2°) by oxidation of the distal double bond and treatment of the resulting trisnoraldehyde with [$^{14}C$]isopropylidenetriphenylphosphorane as previously described.[4] Conversion to the corresponding (3*S*)-[12,13-$^{14}C$]nerolidyl pyrophosphate was effected in the usual manner.[4] The enantiomeric purity of the (3*S*)-pyrophosphate was verified by alkaline phosphatase-catalyzed hydrolysis of a 6-mg sample and examination of the $^1H$ NMR spectrum of the derived nerolidol in the presence of 40 mol % Eu(tfc)$_3$,[9] confirming that no racemization had occurred. The $^{14}C$-labeled (3*S*)-nerolidyl pyrophosphate (0.93 μmol, $1.56 \times 10^6$ dpm) was mixed with racemic [1-$^3H$]nerolidyl pyrophosphate (1.35 μmol, $1.23 \times 10^6$ dpm), $^3H/^{14}C$ 0.77,[10] and the mixture was incubated with the cell-free extract from 0.6 L of *G. fujikuroi* for 3 h at 26 °C.[11] If only the 3*S* enantiomer of **2b** were utilized, the $^3H/^{14}C$ value of the resulting cyclonerodiol would be exactly half the $^3H/^{14}C$ ratio of the nerolidyl pyrophosphate mixture. Were both enantiomers consumed, the $^3H/^{14}C$ ratio would remain unchanged, while conversion of only the 3*R* enantiomer of **2b** will give exclusively $^3H$-labeled cyclonerodiol. In the event the isolated cyclonerodiol ($2.71 \times 10^4$ dpm $^3H$, 2.98%) was devoid of $^{14}C$ activity as was the corresponding recrystallized bis(dinitrobenzoate) ester.[4] These results unambiguously demonstrate that the absolute configuration of the nerolidyl pyrophosphate precursor is 3*R*, as had been previously assumed.

The above experiments establish that the hydroxyl oxygen at C-3 of cyclonerodiol corresponds to the C-3 pyrophosphate ester oxygen of the intermediate nerolidyl pyrophosphate. With this information in hand, it was then possible to examine the fate of the pyrophosphate moiety during the established suprafacial farnesyl to nerolidyl pyrophosphate isomerization. Four mechanisms, illustrated in Scheme III, might be advanced, a priori, to account for this allylic rearrangement: A, a concerted phospho-Claisen or ionic stepover mechanism; B, a stabilized allylic carbonium ion in which free inorganic py-

Scheme II




Scheme III

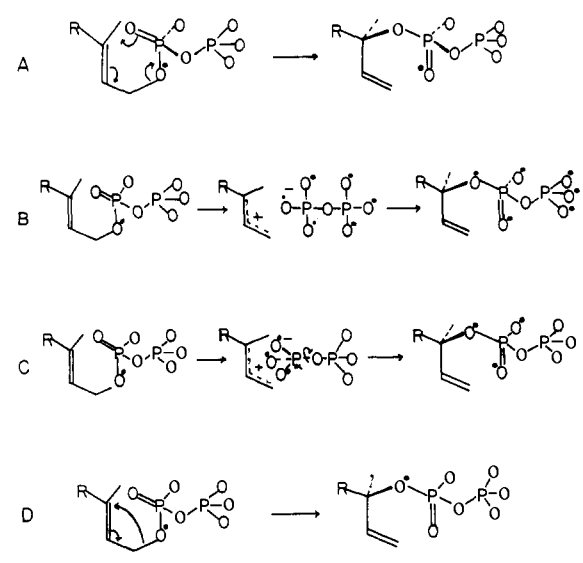
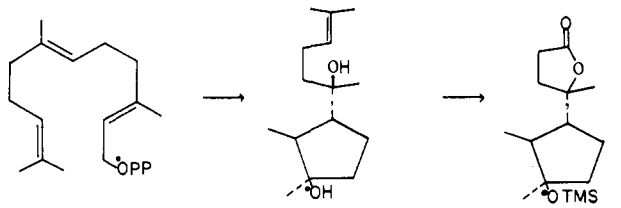


**Table I.** Conversion of [1-$^{18}$O]Farnesyl Pyrophosphate to Cyclonerodiol

| substrate | $^{14}$C, dpm/mmol | $^{18}$O, excess atom %[8] |
|---|---|---|
| [1-$^{18}$O]farnesyl-OPP | $2.85 \times 10^{6}$ [a] | 78.5 [b] |
| [1-$^{18}$O]farnesol [c] | | 76.4 [b] |
| cyclonerodiol | $2.86 \times 10^{6}$ [d] | $27.0 \pm 0.8$ [e] |

[a] Determined on crystalline farnesyl diphenylurethane obtained by alkaline phosphatase hydrolysis of FPP and treatment with diphenylcarbamoyl chloride. [b] Based on farnesyl acetate. [c] Recovered from incubation mixture. [d] Determined on crystalline bis(3,5-dinitrobenzoate). [e] Determined on trimethylsilyl ether of hydroxy lactone (**4b**), average of four determinations (Table II).

Scheme IV




1b 3a 4b

rophosphate is formed; C, an ion-pair intermediate in which there is sufficient time for rotation about the $P_\alpha$–$OP_\beta$ bond; and D, a 1,3-sigmatropic rearrangement or tight ion pair in which $P_\alpha$–$OP_\beta$ rotation is restricted. Each of these mechanisms can be distinguished experimentally by determining the relationship of the ester oxygen of the primary allylic pyrophosphate to the corresponding ester oxygen of the resulting tertiary allylic pyrophosphate, using [1-$^{18}$O]farnesyl pyrophosphate.

The requisite [1-$^{18}$O]farnesyl pyrophosphate was prepared by reacting the corresponding chloride[12] with [$^{18}O_2$]sodium acetate,[13] followed by mild base hydrolysis ($K_2CO_3$, methanol) and pyrophosphorylation in the usual manner. After mixing with a small quantity of [12,13-$^{14}$C]farnesyl pyrophosphate,[4] the $^{18}$O-enriched **1b** (0.16 mmol) was incubated for 3 h at 26 °C with the cell-free extract derived from a total of 13 L of *G. fujikuroi* culture. Extraction with ether and PLC purification (methylene chloride–ether; 3:1, two developments) gave 1.43 mg of cyclonerodiol and 16 mg of farnesol, the latter formed as a result of the phosphatase activity always found in the cell-free enzyme preparation. The mass spectrum of the derived farnesyl acetate indicated the $^{18}$O enrichment of the recovered farnesol to be unchanged from that of the precursor (Table I). A small portion of the cyclonerodiol (0.5 mg) was converted to the bis(dinitrobenzoate) ester, whose specific activity proved to be identical with that of the precursor [$^{14}$C,$^{18}$O]farnesyl pyrophosphate indicating that no dilution with endogenous substrates had occurred. Finally the remaining 0.9 mg of cyclonerodiol was converted as before to the hydroxy lactone and thence to the trimethylsilyl ether (trimethylsilylimidazole, pyridine, 4 h, 25 °C). Examination of the parent (M) and M − 15 peaks in the mass spectrum of **4b** showed the $^{18}$O enrichment at C-3 to be almost exactly one-third the $^{18}$O enrichment of the [1-$^{18}$O]farnesyl pyrophosphate precursor (Tables I and II). This result conclusively rules out mechanisms A, B, and D for the allylic pyrophosphate rearrangement and strongly supports the tightly bound ion pair of pathway C.[14]

It is instructive to compare the conclusions of the present series of experiments with the results of earlier investigations of related chemical and biological processes. In a classic series of papers,[15] Goering has examined the rearrangements of a number of allylic esters, concluding that these processes most often occur by tight ion-pair intermediates, with preferential syn stereochemistry and concurrent scrambling of the ester

**Table II.** Corrected[8] Relative Peak Intensities of [$^{18}$O]-Trimethylsilyloxylactone (**4b**)

| | *m/e* | | | |
|---|---|---|---|---|
| scan | 286 | 284 | 271 | 269 |
| run A | 27.5 | 72.5 | 27.8 | 72.2 |
| run B | 26.4 | 73.6 | 26.2 | 73.8 |

oxygens to an extent determined by the relative stability of the derived allylic cation. Thus the isomeric rearrangement of optically active *trans*-$\alpha,\gamma$-dimethylallyl *p*-nitrobenzoate in 90% aqueous acetone results in interconversion of enantiomers by way of a tight ion pair in which the rate of scrambling of the ester oxygens is 1/2.9 times that of racemization,[15b] whereas the formation of *trans*-$\alpha$-methyl-$\gamma$-phenylallyl *p*-nitrobenzoate from the *trans*-$\alpha$-phenyl-$\gamma$-methyl isomer results in almost complete randomization of the carboxyl oxygens accompanied by partial loss of optical purity.[15c] Although the reactions of allylic phosphates and pyrophosphates have been the subject of considerable investigation,[2] few mechanistic studies have been reported. In one case, Herriott found that the rearrangement of crotyl phenylphosphonate to $\alpha$-methylallyl phenyl phosphonate was subject to acid catalysis and was strongly inhibited by added bases such as pyridine, suggesting an ionic rather than a concerted mechanism.[16] Finally it is worth noting the similarity of our own conclusions regarding the rapid scrambling of phosphate oxygens with the recent results of both Rose[17] and Lowe[18] who independently observed enzyme-mediated scrambling of the terminal oxygens of transiently generated ADP during investigation of a number of ATP-dependent processes. The implication that these oxygens are free to rotate in spite of a presumably strong interaction with $Mg^{2+}$ is particularly striking.

**Acknowledgments.** This work was supported by the National Science Foundation, No. PCM 74-07924. We would like to acknowledge generous gifts of (3*S*)-nerolidol from Professor Niels Andersen of the University of Washington and Professor V. Herout of the Czechoslovak Academy of Science, Prague, Czechoslovakia.

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monium sulfate precipitate was dissolved in 10 mL of the 0.1 M phosphate, pH 7.6/glycerol/DTE/EDTA buffer and dialyzed overnight at 4 °C against four to five changes of the same buffer. The dialysate supplemented with 0.1 M $MgCl_2$ was used as the source of enzyme in the incubations at 26 °C. For the run in [$^{18}O$]water, the dialysate was first lyophilized, dissolved in 1 mL of [$^{18}O$]water, relyophilized, and then redissolved in [$^{18}O$]-water.

(7) Obtained from Mound Laboratory, Miamisburg, Ohio.
(8) Mass spectra were obtained at 50 eV using a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Regions of interest were repetitively scanned at slow speed and the areas of the resulting peaks determined by cutting and weighing. Isotope enrichments represent the average of several scans and are corrected by comparison with spectra of unlabeled substrates.
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(10) The $^3H/^{14}C$ ratio was determined by hydrolyzing a portion of the nerolidyl pyrophosphate mixture with alkaline phosphatase to free [$^3H$,$^{14}C$]nerolidol, which was converted, as previously described,[4] to the crystalline 10,11-dihydroxynerolidol (mp 72–73 °C) which was then recrystallized to constant activity.
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(14) The present experiment measures only *net* scrambling of nerolidyl pyrophosphate released from the isomerase. In the absence of purified enzyme it is not possible to determine the scrambling for a single turnover, nor the number of times FPP and NPP are interconverted at the active site prior to product release. The presence of the cyclase, which converts the NPP to cyclonerodiol pyrophosphate, while not excluding rebinding of free NPP to the isomerase, makes such an event unlikely. Reversal of pathway A would not result in the observed scrambling, since in this mechanism the oxygens attached to $P_\alpha$ remain stereochemically distinct.
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(19) Fellow of the Alfred P. Sloan Foundation, 1978–1980; National Institutes of Health Research Career Development Award, 1978–1983.

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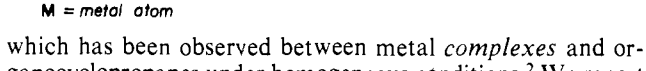
## Reactions of Organocyclopropanes and Spirocycles with Metal Atoms

*Sir:*

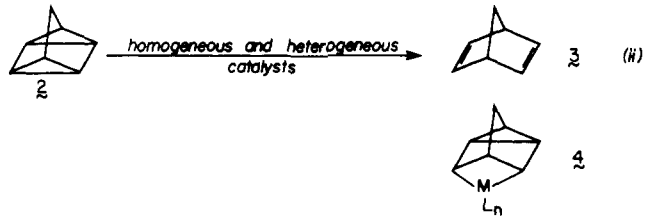
Interest in the reactions of metal *atoms* with organocyclopropanes arises from the possibility of realizing direct metallocyclobutane generation[1] (eq i) and the wealth of chemistry




M = metal atom

which has been observed between metal *complexes* and organocyclopropanes under homogeneous conditions.[2] We report in this communication an extensive study which precisely delineates the substrate features required to observe metal atom–organocyclopropane reactions. Furthermore, this investigation has also resulted in a new and potentially general metallocene synthesis: the cocondensation of iron atoms with spirocyclic precursors affords entry into a number of novel, difficultly accessible substituted ferrocenes.

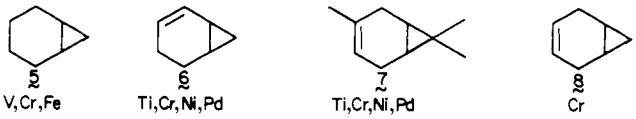
The highly strained bis(cyclopropane)quadricyclane (**2**) is thermally robust (half-life 14 h at 140 °C)[3] but is rapidly isomerized to norbornadiene (**3**) by a variety of metal catalysts (eq ii).[3,4] Metallocyclobutanes such as **4** have been postulated




as intermediates in this isomerization. We cocondensed **2** with a variety of metal atoms at 77 K over a 0.5–1.0-h period in the type of reactor employed by Skell[5] and Klabunde.[6] The matrix was allowed to warm for 1 h under static vacuum (unless noted) before product analysis. While the data, summarized in Table I, indicate the ability of **2** to undergo reaction, control experiments suggest that little if any **4** is formed.

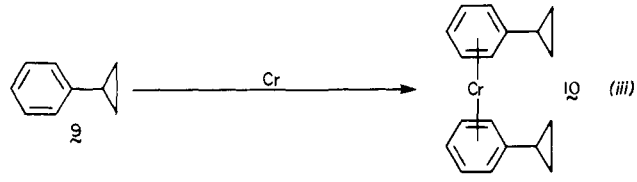
A comparison of entries 3–5 (Table I) is instructive. Cocondensation of **2** and chromium (entry 3) resulted in the efficient isomerization of **2** to **3**. When chromium alone was evaporated onto the reactor walls (77 K), followed by deposition of **2** (entry 4), little isomerization was observed. Thus chromium surfaces produced in this fashion do not efficiently isomerize **2**. However, when a cocondensation was conducted as usual but the subsequent 1-h matrix warmup eliminated (entry 5), virtually no isomerization was observed. During the warm-up period, the matrix melts and, if no stable complexes are formed, the metal aggregates. Klabunde has shown that finely dispersed metal particles which have superior catalytic properties are produced under these conditions.[7] Since entry 5 indicates the yield of **3** is dependent upon the contact time of **2** with the metallic residue from the thawed matrix, we conclude that most of the observed isomerization is heterogeneously catalyzed. Similar results were obtained in experiments with iron, in which lower ratios of **2** to metal were employed. Significantly, a preformed iron surface (entry 7) was as active as codeposited iron (entry 6).

Reactions of norcarane (**5**) and the structurally related vinylic and allylic cyclopropanes (**6–8**) with metal atoms (see formulas below) were investigated next. It has been generalized




that unless the organic reactant has nonbonding or $\pi$ electrons, metal atom aggregation will be rapid at 77 K.[6] Thus the olefinic groups in **6–8** might be expected to promote reaction by initially binding the metal. However, when reacted as described for **2, 5–8** were recovered in near-quantitative yields; no isomers could be detected by GLC or $^1H$ NMR, even in the reactor residue. Since any metallocyclobutane should give subsequent reactions (isomerization, polymerization) upon warming the matrix,[1] we conclude that no carbon–carbon bond insertion occurs.

Although a phenyl substituent might be expected to facilitate cyclopropane ring rupture, cocondensation of chromium atoms (2.3 mmol) with cyclopropylbenzene (**9**, 69 mmol) yielded only the bis(arene) complex **10** (eq iii, 1.0 mmol; 45% based upon chromium).[8] Reactions were also conducted with Ni and V and **9**. In no case was allylbenzene, methylstyrene, or styrene detected.

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