Reactions of Palladium(II) Chloride with Aziridine Rings. Catalytic Rearrangement of *N*-Carbethoxy-8-azabicyclo[5.1.0]oct-3-ene to *N*-Carbethoxynortropidine[1]

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Abstract: Reaction of *N*-carbethoxy-8-azabicyclo[5.1.0]oct-3-ene (**3a**) with dichlorobis(benzonitrile)palladium(II) results in essentially quantitative rearrangement of the aziridine **3a** to *N*-carbethoxynortropidine. The rearrangement is catalytic, but the conditions were not optimized. On the basis of ^{1}H NMR results and product isolation studies, the reaction is believed to proceed in four steps: (1) formation of the palladium-π olefin complex with **3a;** (2) attack of chloride on the aziridine ring to cleave one C–N bond regioselectively; (3) regioselective intramolecular attack of $^-NCO_2R$ on the olefin coordinated to palladium; and (4) 1,3 Pd–Cl elimination or 1,2 Pd–H elimination/addition followed by 1,2 Pd–Cl elimination. An intermediate with a palladium–carbon σ bond was detected by borohydride reduction of the reaction mixture to yield *N*-carbethoxy-4-chloro-8-azabicyclo[3.2.1]oct-2-ene. The same intermediate was quenched both by carbonylation of the reaction mixture to yield *N*-carbethoxy-2-carbomethoxy-4-chloro-9-azabicyclo[3.2.1]oct-2-ene, and by reaction with 1,2-bis(diphenylphosphino)-ethane (diphos), which resulted in isolation of the unusually stable diphos adduct of the palladium alkyl. *N*-Carbomethoxy-8-azabicyclo[5.1.0]octane was also found to react with dichlorobis(benzonitrile)palladium(II). After hydrolysis, the isolated product in this case was 1-(carbomethoxy)amino]-2-chlorocycloheptane. The reactions reported here are among the first reports of aziridine transition metal reactions, and represent a potentially versatile new approach to the 8-azabicyclo[3.2.1]octene (nortropidine) skeleton. This ring system is the backbone of the tropane alkaloids, which include cocaine, atropine, and scopolamine, among other physiologically active compounds.

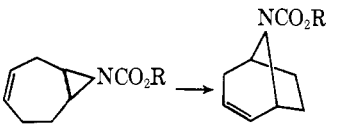
Introduction

The study of the reactions of palladium(II) halides with three-membered rings is an area of continuing interest in our laboratory. Previously, we have reported on the organopalladium chemistry of bicyclo[6.1.0]non-4-ene[2] (**1**) and bicyclo[5.1.0]oct-3-ene[3] (**2**). Compounds **1** and **2,** upon reaction with dichlorobis(benzonitrile)palladium(II) ($PdCl_2(PhCN)_2$) in low polarity media, undergo facile chloropalladation of the internal cyclopropane carbon–carbon bond to yield palladium(II) σ,π chelates. Both σ,π chelates undergo a subsequent rearrangement. Thus **1** finally yielded dichloro(1,2:5,6-η-*cis,cis*-cyclononadiene)palladium(II), while **2** gave the π-allylic di-μ-chloro-bis(1-3-η-5-chlorocyclooctenyl)palladium(II).

The results obtained with **1** and **2** have prompted us to expand our area of study to include three-membered heterocycles. We were particularly interested in comparing our previous cyclopropane work with the palladium-induced reactions of heteroatom analogues of **1** and **2.** Of particular interest was the possibility of carbon–carbon bond cleavage, as opposed to the carbon–heteroatom bond cleavage normally observed in reactions of three-membered heterocycles.[4]

The literature pertaining to reactions of transition metals with cyclopropane rings is extensive. However, this is not the case with three-membered heterocycles. Grigg and co-workers reported the reaction of catalytic amounts of di-μ-chloro-tetracarbonyldirhodium(I) with norbornadiene *exo*-epoxide and hexamethyl(Dewar benzene) epoxide,[5] vinylic epoxides and oxetanes,[6] and cyclooctatetraene epoxide.[7] There have been reports of epoxide deoxygenation by transition metals in the presence of reducing agents (such as *n*-butyllithium) to give olefinic products,[8,9] and Aumann and Averbeck[10a] found that cyclooctatetraene epoxide rearranges to 2,3,4,5-η:7,8-η-9-oxabicyclo[4.2.1]nona-2,4,7-triene·$Fe(CO)_3$·$Fe(CO)_4$ on photolysis in the presence of excess $Fe(CO)_5$. We are aware of only one report of transition metal–aziridine reactions. Aumann, Fröhlich, and Ring have recently reported on the photochemical reaction of $Fe(CO)_5$ with *N*-carbomethoxy-2-vinylaziridine, in which C–N cleavage is observed.[10b]

In the present communication we report the reactions of *N*-carbethoxy- (or methoxy-) 8-azabicyclo[5.1.0]oct-3-ene (**3a** and **3b**) with dichlorobis(benzonitrile)palladium(II). Spectroscopic and chemical studies of this reaction lead to the conclusion that four distinct steps are involved, beginning with coordination of **3** to Pd(II) through the double bond, followed by regioselective metal-promoted chloride displacement of an aziridine carbon–nitrogen bond, and terminating with Pd–Cl elimination to yield *N*-carbethoxy- (or methoxy-) nortropidine **4a** and **4b,** as uncomplexed molecules. The rearrangements proceed in high overall yields.



(1)

3 **4**

a, R = CH_2CH_3
b, R = CH_3

The **3a** → **4a** rearrangement has also been found to be catalytic and represents a new route to the 8-azabicyclo[3.2.1]-octene skeleton. This ring system is of considerable importance due to its relatively widespread natural occurrence and due to the fact that it is the backbone of the tropane alkaloids, including such drugs as cocaine, atropine, and scopolamine.[11,12]

Results

N-Carbethoxy-8-azabicyclo[5.1.0]oct-3-ene (**3a**) is readily synthesized via the photolytic reaction of ethyl azidoformate and 1,4-cycloheptadiene. *N*-Carbomethoxy-8-azabicyclo[5.1.0]oct-3-ene (**3b**) was similarly prepared using methyl azidoformate.

Aziridine **3a** reacts instantaneously with $PdCl_2(PhCN)_2$ at room temperature in CH_2Cl_2, $CHCl_3$, or C_6H_6. A typical reaction in CH_2Cl_2 yields after 49 h an 83% isolated yield of the

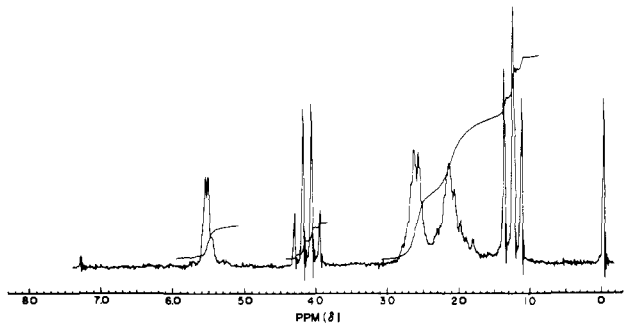


Figure 1. The 60-MHz ^1H NMR spectrum of *N*-carbethoxy-8-azabicyclo[5.1.0]oct-3-ene (**3a**).

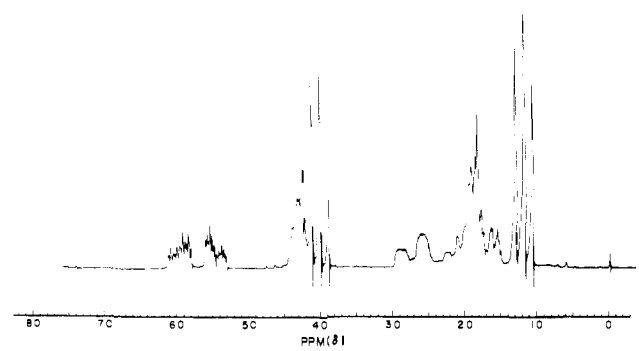


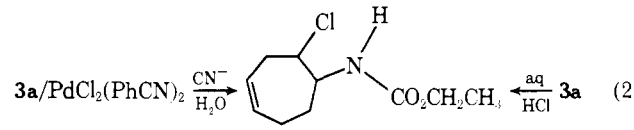
Figure 2. The 60-MHz ^1H NMR spectrum of *N*-carbethoxy-8-azabicyclo[3.2.1]oct-2-ene (**4a**).

known *N*-carbethoxy-8-azabicyclo[3.2.1]oct-2-ene (**4a**). Similarly, the reaction of **3a** with $PdCl_2(PhCN)_2$ in benzene gave a 71% isolated yield of **4a** after 60 h (spectroscopic yield > 85%). In either reaction mixture, **4a** is present as an uncomplexed molecule. The palladium either completely precipitates as $PdCl_2$ (in benzene solution) or remains partially dissolved, presumably as $[PdCl_2(PhCN)]_2$[13] (in CH_2Cl_2 or $CHCl_3$), and is recovered nearly quantitatively. The ^1H NMR spectra of **3a** and **4a** are shown in Figures 1 and 2. *N*-Carbethoxy-8-azabicyclo[3.2.1]oct-2-ene (**4a**) has been reported previously by two groups.[14,15] Our ^1H NMR spectrum of **4a** is identical with that of an authentic sample.[16] Pure **4a** gives no indication (^1H NMR) of interaction with $PdCl_2(PhCN)_2$ in $CDCl_3$ solution over a period of 24 h.

The **3** → **4** rearrangement has been monitored extensively by ^1H NMR. An ^1H NMR of a solution of equimolar quantities (~1.3 M concn) of **3a** and $PdCl_2(PhCN)_2$ in $CDCl_3$ taken at ambient probe temperature (~35 °C) within 1 min of mixing shows no apparent olefinic resonances. At least two different quartets arising from the ethyl-CH_2 group are apparent, indicating the presence of more than one $-CO_2CH_2CH_3$ environment. After 10 min the initially clear yellow solution begins to darken and the olefinic and several higher field resonances of **4a** begin to appear. These resonances continue to grow in intensity until after 12 h the spectrum is essentially that of pure **4a.**

When the reaction of **3a** with $PdCl_2(PhCN)_2$ is monitored by ^1H NMR in $CDCl_3$ at −20 °C, the disappearance of the olefinic resonance requires ca. 10 min. However, even at this low temperature, no evidence of a Pd(II)-π-olefin complex was obtained. Monitoring the analogous **3b** → **4b** reaction in $CDCl_3$ at ambient probe temperature by ^1H NMR yields additional data. At t = 5 min, the ^1H NMR show no evidence of olefinic absorption, only one carbomethoxy resonance at δ 3.67, and new resonances at δ 4.35 (1 H, linewidth at half-height $\omega_{1/2} \cong 13$ Hz) and 4.08 (1 H, linewidth at half-height $\omega_{1/2} \cong 12$ Hz). Analogues of these latter two resonances are obscured by the $-CH_2-$ quartet in the **3a** → **4a** reaction. Also at 5 min there is a broad 1 H resonance which is centered near δ 4.0. Beyond 5 min, the δ 4.35 resonance increases in intensity with respect to those at 4.08 and 4.0. after 10 h the δ 4.08 and 4.0 resonances are absent and the spectrum is essentially that of pure **4b.** Early in the reaction, the δ 4.35, 4.08, and 4.0 resonances are assigned to an intermediate (a palladium σ-alkyl-see Discussion). Later the absorption at δ 4.35 arises mainly from the bridgehead hydrogens in product **4b.**

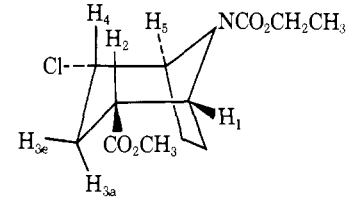
Aqueous cyanide treatment of aliquots of the **3a**/$PdCl_2(PhCN)_2$ reaction mixtures in either $CDCl_3$ or C_6H_6 during the first hour of reaction results in detection and isolation (by GLC) of compound **5,** $C_{10}H_{16}ClNO_2$. After 30 min reaction in $CDCl_3$, the concentration of **5** maximizes, the mole fractions of **5, 3a,** and **4a** being 0.25, 0.00, and 0.75, respectively. After 90 min only **4a,** benzonitrile, and solvent were detected. In benzene **5** reaches a maximum concentration after 12 min (0.37 mole fraction), with the mole fractions of **3a** and **4a** being 0.07 and 0.56, respectively. Treatment of the **3a**/$PdCl_2(PhCN)_2$ reaction mixture in benzene after 15 min with aqueous cyanide and extraction of the organic products yields **5** in 30% spectroscopic yield. Compound **5** has also been obtained from the reaction of **3a** with HCl (57% isolated yield). The ir spectrum of **5** clearly shows bands due to an N-H group at 3415 (sharp) and 3310 cm^{-1} (broad, hydrogen bonded). The ^1H NMR spectrum of **5** is shown in Figure 3. Although the spectra do not allow an unambiguous assignment of the structure of **5,** we favor the structure shown below, which results from cleavage of the C(1)-N bond in **3a.** This cleavage is regiospecific at the homallylic carbon.



(2)

5

When **3a** reacts with $PdCl_2(PhCN)_2$ in a CH_2Cl_2 solution which is saturated with carbon monoxide, there is no apparent decomposition after 20 min. If the solution is then treated with KOH/CH_3OH, palladium metal precipitates and analysis by gas-liquid chromatography shows, in addition to **4a** and **5,** a new peak of very long retention time. Purification by GLC yields compound **6** ($C_{12}H_{18}NO_4Cl$) in 20% isolated yield. The approximate ratios of **4a:5:6** by GLC analysis are 2:1:1. The yield of **6** (by ^1H NMR) was determined to be ca. 30%.



6

The infrared spectrum of **6** shows no N-H absorption, but does show two separate $\nu_{C=O}$ bands at 1740 (CO_2CH_3) and 1705 cm^{-1} ($NCO_2CH_2CH_3$). The ^1H NMR of **6** has been obtained at 60, 100, and 300 MHz (Figure 4). At 300 MHz the following resonances are apparent: broad resonances at δ 4.5 (1 H, H_1), 4.35 (1 H, H_5), 4.07 (1 H, H_4), and 2.84 (1 H, H_2); a three-proton singlet at δ 3.68 (CO_2CH_3), and a double triplet at δ 2.34 (Figure 4, inset A) (1 H, H_{3e}, $J_{3e,3a}$ = 14 Hz, $J_{3e,2} = J_{3e,4}$ = 5 Hz). At 60 MHz the δ 2.84 resonance is resolved into eight lines (Figure 4, inset B) resulting from a 12.5 Hz coupling ($J_{3a,2}$), a 3 Hz coupling ($J_{2,1}$), and a 5 Hz coupling ($J_{2,3e}$). The H_1 and H_5 assignments are consistent with the bridgehead proton assignments in **4a** which are found at δ 4.32 (in **4a,** H_1 and H_5 are not resolved even at 300 MHz).

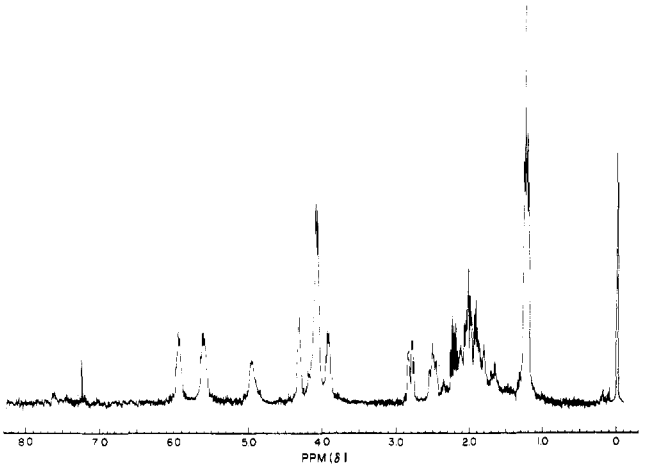


Figure 3. The 60-MHz ^1H NMR spectrum of 1[(carbethoxy)amino]-2-chlorocyclohept-4-ene (**5**).

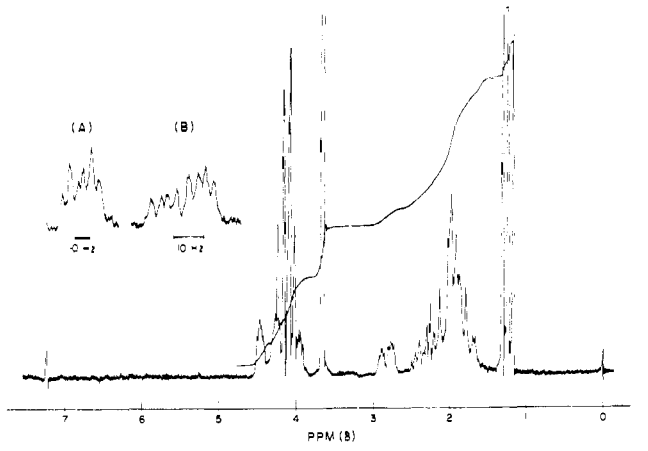
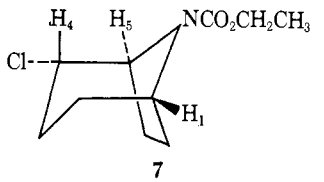


Figure 4. The 100-MHz NMR spectrum of *N*-carbethoxy-2-carbomethoxy-4-chloro-8-azabicyclo[3.2.1]octane (**6**). Inset A: the δ 2.34 multiplet at 300 MHz. Inset B; the δ 2.84 multiplet at 60 MHz.

The downfield position of H_1 relative to H_5 results from deshielding of H_1 by the carbomethoxy group and is consistent with results from similar systems.[17] The positions of H_4 and H_2 are in the ranges expected from methine protons α to chlorine and carbomethoxy, respectively.[18] The assignment of the δ 2.34 resonance as H_{3e} is based on the expected lower field resonance position of the equatorial hydrogen and on the size of its couplings to H_4 and H_2.[18] Although the H_4 resonance partially overlaps the $-CH_2-$ quartet, we have been able to determine its structure by irradiation of the ethoxy methyl to narrow the $-CH_2-$ absorption. This leads to the conclusion that the H_4 resonance is nearly identical with that of H_2, consisting of eight lines arising from one large coupling (ca. 12 Hz) and two smaller couplings (ca. 2 and 5 Hz).

If after 15 min reaction time the **3a** + $PdCl_2(PhCN)_2$ reaction mixture is treated with $NaBH_4$ under conditions which are known to selectively reduce palladium–carbon bonds,[19] compound **7** ($C_{10}H_{16}NO_2Cl$) is isolated in 30% yield. GLC



7

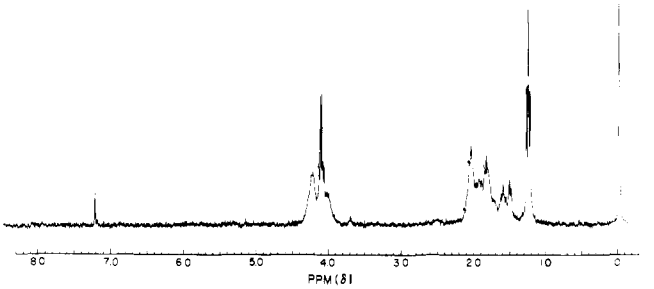
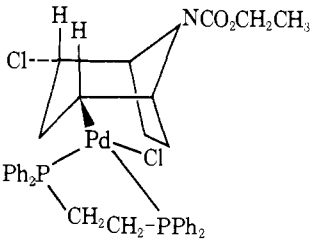


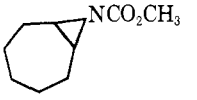
Figure 5. The 300-MHz NMR spectrum of *N*-carbethoxy-4-chloro-8-azabicyclo[3.2.1]octane (**7**).

analysis of the crude reaction shows the presence of **3a, 5,** and **7** in the approximate ratio 1:1:2. The ir spectrum of **7** has $\nu_{C=O}$ at 1705 cm^{-1} and no absorption due to an N–H group. The ^1H NMR spectrum of **7** is shown in Figure 5. Treatment of the **3a**/$PdCl_2(PhCN)_2$ reaction mixture in benzene after 15 min with an equivalent of bis(1,2-diphenylphosphino)ethane (diphos) results in the isolation of a yellow-white solid (**8**). Elemental analyses and solution molecular weight are consistent with the formulation (diphos)$PdCl_2(C_{10}H_{15}NO_2)$. The ^1H NMR of **8** shows no olefinic absorption and the integrated intensity of the diphos aromatic signal in comparison to the rest of the spectrum also shows the 1:1 ratio of diphos to $C_{10}H_{15}NO_2$. Reaction of **8** with CO/CH_3O^- yields only **6** in 75% yield. The ^1H NMR of a solution of **8** is unchanged after several weeks at room temperature or after treatment with aqueous cyanide. We have tentatively assigned **8** the structure shown.

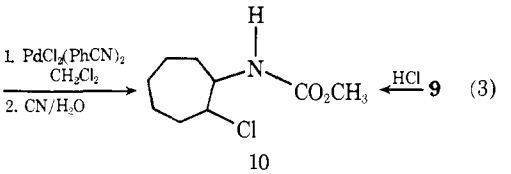


8

When a solution of equimolar quantities of *N*-carbomethoxy-8-azabicyclo[5.1.0]octane (**9**) and $PdCl_2(PhCN)_2$ in CH_2Cl_2 is stirred for 1 h and then treated with aqueous cyanide, **10** is obtained in 50% yield, along with 50% unreacted **9**. **10** is also obtained when **9** reacts with HCl. In a separate experiment **9** was shown to be stable to aqueous cyanide.



9



(3)

10

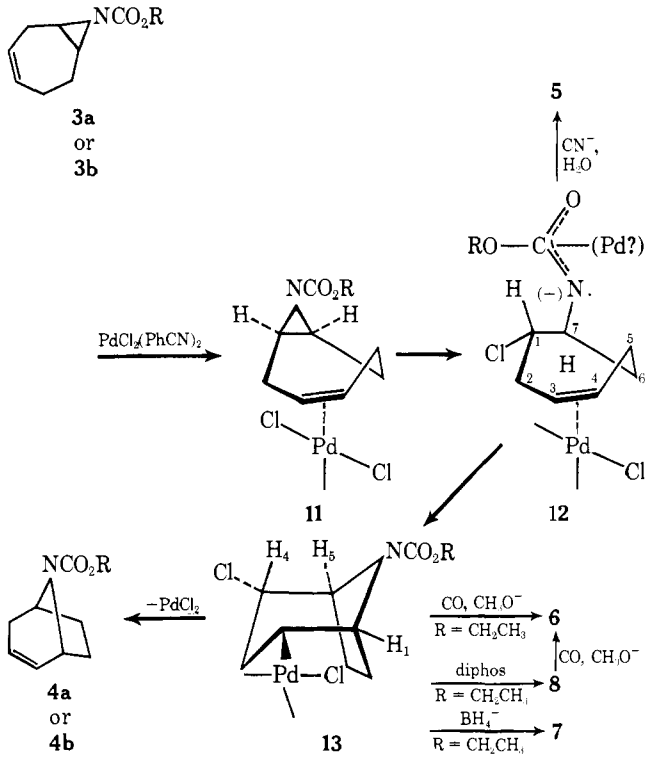
The **3a** → **4a** rearrangement has also been run catalytically. Thus, equimolar quantities of **3a** and $PdCl_2(PhCN)_2$ were stirred at room temperature in CH_2Cl_2 for 15 min, after which an aliquot of **3a** equal to the starting quantity was added. This addition was repeated after an additional 30 min and then after an additional 3 h (a total of 1.43 mmol of **3a** was added). The reaction was then stirred for 18 h. Analysis of the products

after treatment with CN^-/H_2O, followed by extraction, showed no **3a**, 0.98 mmol of **4a**, and 0.26 mmol of **5**. We could not account for the remaining 0.18 mmoles. The 0.98 mmol of **4a** produced represents approximately a 2.5-fold turnover with respect to starting palladium(II). We did not attempt to optimize the turnover in this reaction.

Discussion

The transformation of *N*-carbethoxy-8-azabicyclo[5.1.0]-oct-3-ene to *N*-carbethoxy-8-azabicyclo[3.2.1]oct-2-ene is a considerable structural rearrangement. To account for this novel reaction we propose the mechanism shown in Scheme I (heavy arrows).

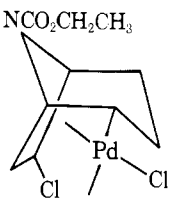
Scheme I



In previous work with bicyclo[6.1.0]non-4-ene (**1**) and bicyclo[5.1.0]oct-3-ene (**2**), initial Pd(II)–π-olefin complexes were detected. In the case of **1**, this complex was isolated and characterized, while the analogous complex arising from **2** was only detected by low temperature ^{1}H NMR. At −20 °C, the ^{1}H NMR of the π-olefin complex of **2** was unchanged after 45 min. In the present study of the reaction of **3a** with $PdCl_2(PhCN)_2$, we have been unable to detect a similar π-olefin complex even at reduced temperatures. Additionally, at −20 °C the resonance due to the double bond in **3a** disappears in only ca. 10 min. These observations indicate the much higher reactivity of **3a** in comparison to **1** and **2**.

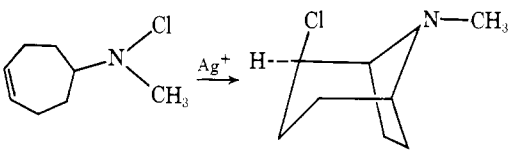
Although definitive evidence for the π-olefin complex **11** is lacking, there is ample precedent for the expectation that the olefin complex would be formed instantaneously from **3a** and $PdCl_2(PhCN)_2$. The observation that *N*-carbethoxy-8-azabicyclo[5.1.0]octane (**9**) ring-opens sluggishly to **10** on reaction with $PdCl_2(PhCN)_2$ also points to the involvement of the olefinic bond of **3** in promoting instantaneous ring opening to **12**. We favor initial olefin complexation by the metal trans to the aziridine ring as shown in **11**. This is followed rapidly by regioselective attack by chloride at the homoallylic carbon (C(1)). This reaction is postulated to occur cis to the palladium and with inversion of the homoallylic carbon. Since carboxylated aziridines are activated toward ring opening reactions,[4b] we propose that the inability to detect **11** is due to the rapidity of ring opening. This is not surprising since in our work with the trans-halopallladation reaction of 7-methylene bicyclo[2.2.1]heptene[20] we were unable to detect an initial palladium–π-olefin complex, even at −40 °C. Intermediate **12** has escaped spectroscopic detection, but **12** is implicated by the isolation of **5** on treatment of reaction mixtures of **3a** and $PdCl_2(PhCN)_2$ with aqueous cyanide. We observe here that ring opening of **3a** via C(7)–N cleavage could not lead to final product **4** or to the derivatives of intermediate **13.** For this reason we prefer the structure assigned above to **5,** which arises from cleavage at C(1). Intermediate **12** is somewhat unattractive owing to the formally negatively charged nitrogen. We feel that in order for **12** to reach sufficient concentrations to allow the isolation of **5, 12** must be stabilized both by delocalization through the carboxyl group and coordination to an additional Pd(II). It should be noted that the isolation of **10** from the reaction of **9** with $PdCl_2(PhCN)_2$ clearly indicates that aziridine rings can be chloropalladated. The likely intermediate in the **9** → **10** reaction is a complex analogous to **12.** The isolation of a 50% yield of **10** after 1 h is indicative of the stability of an intermediate such as **12** in the absence of further potential reaction, such as **12** → **13** ring closure.

The third step in the reaction sequence is an unusual *intramolecular* nucleophilic attack on the coordinated double bond, occurring regioselectively at C(4). The ability of palladium to promote intermolecular nucleophilic attack on coordinated olefinic carbon atoms by a wide varety of nucleophiles, including amines, is well established.[21a,b] However, we know of no established instances of such an intramolecular process. The new C–N bond must form at C(4), as formation of a bond between the nitrogen and C(3) would yield **14** with the chlorine and palladium on different rings. Complex **14** could not sensibly decompose to **4.**



14

The **12** → **13** ring closure has some precedent. Hobson and Riddell[22] reported the reaction of the *N*-chloramine **15** with silver ion to give **16** (eq 3). This reaction is not however, believed to be mechanistically similar to the **12** → **13** ring closure.



(4)

15 16

Both NMR and chemical evidence support the intermediacy of **13.** The area one resonances at δ 4.35, 4.08, and 4.0 which were previously mentioned as being present in the ^{1}H NMR spectrum of the reaction of **3b** with $PdCl_2(PhCN)_2$ are assigned to H_5, H_1, and H_4, respectively, in intermediate **13.** Rapid formation of **13** also accounts for the early disappearance of olefinic absorption in the NMR. Intermediate **13** reacts with BH_4^- to yield *N*-carbethoxy-4-chloro-8-azabicyclo[3.2.1]octane (**7**) and with CO/CH_3O^- to yield *N*-carbethoxy-2-carbemethoxy-4-chloro-8-azabicyclo[3.2.1]-octane (**6**). Both reactions are diagnostic of the palladium–carbon σ bond. In addition, **13** is trapped by reaction with di-

phos to give the stable complex **8,** and **8** also carbonylates to give **6.**

The ^{1}H NMR spectrum of ester **6** is particularly informative with respect to several reaction stereochemistries. The H_2 resonance in **6** has one large coupling, 12.5 Hz, consistent only with a trans axial-axial coupling.[18] Thus, H_2 is axially oriented with $J_{2,3a}$ = 12.5 Hz, and the carbomethoxy group is therefore equatorial and trans to the bridging nitrogen. Since it is established that the carbonylation of palladium-carbon σ bonds occurs with retention of configuration at carbon,[21b,23] the palladium is equatorial and trans to the nitrogen in **13.** The orientation of the chlorine in **6** is also easily ascertained. Since the H_4 multiplet pattern is nearly identical with that of H_2, the two hydrogens are both oriented axially. We therefore conclude that the chlorine is also equatorial in **6** and trans to the nitrogen bridge. The equatorial orientations of chlorine and palladium are also presumed in **7** and **8,** both of which are derived from **13.**

Palladium alkyls are normally unstable toward eliminations to give olefins.[21] Thus, it is not surprising that **13** undergoes Pd-Cl elimination to give **4.** This reaction is likely to occur by one of two paths: 1) by a 1,2-Pd/H interchange (reversed β-hydrogen elimination) followed by a 1,2 Pd-Cl elimination; or 2) by 1,3 Pd-Cl elimination accompanied by a hydrogen migration. The latter alternative has been observed[2] in the reaction of bicyclo[6.1.0]non-4-ene with $PdCl_2(PhCN)_2$ to give dichloro(1,2:5,6-η-*cis*-*cis*-cyclononadiene)palladium(II). In the present case, we have concluded that Pd and Cl are 1,3-diequatorial in **13.** Activation of **13** to a "boat" conformation with Pd and Cl in a 1,3 diaxial relationship could initiate the 1,3 Pd-Cl elimination. It is also possible that a 1,2-Pd/H interchange occurs followed by a fast β-chloride elimination to give **4.** A fast β-chloride elimination following the 1,2-Pd/H interchange would also account for lack of scrambling of $-CO_2CH_3$ between positions 2 and 3 in the **13**/CO/CH_3O^- reaction product (**6**).

The diphos derivative of **13,** complex **8,** is an unusually stable palladium(II) alkyl, as it does have two β-hydrogens in the 3 position and a γ chlorine capable of elimination. The ^{1}H NMR of solutions of **8** were unchanged after several weeks at room temperature, or after treatment with aqueous cyanide. The stability of **8** probably results from the lack of an open coordination position on the metal to permit initiation of Pd-H or Pd-Cl elimination, or from steric hindrance by coordinated diphos. A second contributing factor could be the ca. 60° dihedral angle imposed between Pd-C and either C-H_{3a} or C-H_{3e}. Whitesides and co-workers have emphasized the importance of a 0° dihedral angle in facile β-hydrogen eliminations.[24a,b]

The final rearrangement product **4** is formed as an uncomplexed molecule. This is most likely due to (1) the crowded nature of **4,** which prevents palladium(II) binding to the olefin, and to (2) the nitrogen lone pair delocalization in the *N*-carbalkoxy group, which greatly reduces the basicity of the nitrogen. The lack of complexation of **4a** by palladium(II) is believed to be crucial in permitting the **3a** → **4a** rearrangement to occur catalytically.

The palladium(II)-catalyzed multistep rearrangement of *N*-carbethoxy-8-azabicyclo[5.1.0]oct-3-ene to *N*-carbethoxynortropidine is an intriguing and a potentially synthetically useful reaction. Several of the reaction steps, namely chloride attack on the aziridine ring, intramolecular attack on the coordinated double bond, and overall 1,3 Pd-Cl elimination to yield olefin have little or no precedent in organopalladium chemistry. There is an additional important aspect of the reactions reported here. Each reaction step is highly regioselective. The controlling aspect in each step of the **3b** → **4b** reaction is undoubtedly the presence of the palladium. The fact that each step occurs with such high selectivity is a remarkable illustration of the ability of a transition metal to control the reaction pathway.

Experimental Section

Microanalysis for C, H, N, and Cl was performed by Chemalytics, Inc., Tempe, Ariz. Melting points are uncorrected. Ir spectra were obtained on a Perkin-Elmer 621 grating spectrophotometer. ^{1}H NMR spectra were obtained in $CDCl_3$ solutions using Varian spectrometers. The 300 MHz ^{1}H NMR spectra were obtained using a Varian HR-300. Chemical shifts (δ) were referenced to Me_4Si. Mass spectra were obtained using a Perkin-Elmer/Hitachi RMU-9D double focusing instrument. Molecular weights were measured using a Mechrolab Osmometer, Model 301A, operating at 25°. Gas-liquid chromatography (GLC) was done using an Aerograph Model 90P instrument with a 2 ft × ¼ in. 30% Apiezon L on a dichlorodimethylsilane-treated Chromosorb W column.

Cyclohepta-1,4-diene.[25] Freshly chopped sodium metal (100 g) was dissolved in 3000 ml of NH_3 at −65 °C. The resulting deep blue solution was stirred for 10 min and then 180 g of 1,3,5-cycloheptatriene was cooled to −78 °C and added in 5-ml aliquots of 30-s intervals. Addition of the cycloheptatriene at too rapid a rate resulted in the boiling off of the NH_3. The temperature was monitored continually and maintained at −65 to −70 °C. When the addition was complete, the solution was stirred for 20 min, at which time it was bright red. Solid NH_4Cl (250 g) was then added and the reaction decolorized in <1 min. after the mixture was stirred for an additional 10 min at −70 °C, the cooling bath was removed, 1 l. of pentane was added to the solution, and the ammonia was allowed to evaporate overnight. Water (1500 ml) was then added and the pentane layer was removed. The aqueous layer was extracted with pentane (1 × 500 ml) and the combined pentane extracts were washed with water (1 × 500 ml) and dried over $MgSO_4$. Distillation (760 Torr) of the crude product was followed by heating over maleic anhydride for ca. 3 h at 80° to remove cycloheptatriene and 1,3-cycloheptadiene. Finally atmospheric pressure fractional distillation yielded 85 g of 1,4-cycloheptadiene (bp 112–116 °C collected), which by ^{1}H NMR and GLC had a purity of not less than 95%.

***N*-Carbethoxy-8-azabicyclo[5.1.0]oct-3-ene (3a).** Cyclohepta-1,4-diene (20 g) and 21 ml of ethyl azidoformate were combined in a quartz tube which had been flushed with N_2. The mixture was photolyzed using a Hg lamp until the ir spectrum of an aliquot was free of azide absorption at 2210 and 2140 cm^{-1} (~48 h). Vacuum distillation up a short fractionating column yielded 8.5 g of **3a** (64–66 °C at 0.2 mmHg).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.30; H, 8.29; N, 7.73; mol wt, 181. Found: C, 66.85; H, 8.47; N, 7.88. Molecular ion in the mass spectrum at *m/e* 181; ^{1}H NMR (Figure 1); ir $\nu_{C=O}$ 1710 cm^{-1} (vs).

***N*-Carbomethoxy-8-azabicyclo[5.1.0]oct-3-ene (3b).** **3b** was prepared in 35% yield by a procedure similar to that used for **3a,** using methyl azidoformate.

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.67; H, 7.78; N, 8.38; mol wt 167. Found: C, 64.63; H, 7.72; N, 8.33. Molecular ion in the mass spectrum at *m/e* 167; ^{1}H NMR 5.6 (2 H, m), 3.75 (3 H, s), 3.0–1.3 (8 H,broad).

***N*-Carbethoxy-8-azabicyclo[3.2.1]oct-2-ene (4a).** Dichlorobis(benzonitrile)palladium(II) (1.1 g) was added to a rapidly stirred solution of 500 mg of **3a** in 25 ml of benzene. The initially clear solution was stirred at room temperature for 60 h during which time it gradually darkened. After 60 h, there was a considerable amount of solid, which was separated by filtration. Concentration of the filtrate to 15 ml yielded more solid, which was also removed by filtration. The solids were combined and were converted to Pd metal by ignition, which yielded 295 mg of palladium (97% of that expected from 1.1 g of $PdCl_2(PhCN)_2$. The filtrate was concentrated to remove solvents and analysis by GLC showed only benzonitrile and an additional compound (**4a**). Purification by GLC (130°) yielded 350 mg of **4a** (71%). Comparison of the spectral properties of **4a** with published data[14-16] identified **4a** as *N*-carbethoxy-8-azabicyclo[3.2.1]oct-2-ene (^{1}H NMR, Figure 2). Similarly, the reaction of **3a** with $PdCl_2(PhCN)_2$ in CH_2Cl_2 resulted in an 84% isolated (by GLC) yield of **4a** after 49 h. Spectroscopic yields of **4a** from the reaction of **3a** with $PdCl_2(PhCN)_2$ were generally 85–95%.

1-[(Carbethoxy)amino]-2-chlorocyclohept-4-ene (5). A mixture of 500 mg of **3a** and 1.05 g of $PdCl_2(PhCN)_2$ in 25 ml of benzene was stirred for 15 min and was then treated with 25 ml of a saturated solution of NaCN in H_2O. The mixture was then extracted with ether

(100 ml). The extract was dried over $MgSO_4$ and was concentrated. Only peaks due to **4a** and **5** (at much longer retention time) were detected by GLC. Compound **5** was purified by GLC (130°), yielding 160 mg of white solid (27%, mp 68–70 °C). Analysis of a different reaction by ^1H NMR indicated a yield of **5** of 30%.

Anal. Calcd for $C_{10}H_{16}NO_2Cl$: C, 55.18; H, 7.36; mol wt, 217.5. Found: C, 54.73; H, 7.38; molecular ions in the mass spectrum at *m/e* 219 and 217 (^{37}Cl and ^{35}Cl). ^1H NMR (Figure 3) δ 5.95 (1 H, m, olefin), 5.61 (1 H, m, olefin), 4.93 (1 H, broad, NH), 4.31 (1 H, ClCH or NCH), 4.1 (2 H, q, J = 7 Hz), 3.92 (1 H, m, NCH or ClCH), 2.9–1.5 (6 H), 1.22 (3 H, 5, J = 7 Hz).

Compound **5** was also obtained as follows: aziridine **3a** (300 mg) was dissolved in 2 ml of low-boiling petroleum ether. Concentrated aqueous HCl (150 μl) was added, followed by vigorous shaking for 1 min. The mixture was agitated for 1 h, followed by addition of 2 ml of H_2O and 2 ml of diethyl ether, shaking, and separation of the ether layer. The ether layer was dried with $MgSO_4$, filtered, and concentrated. Compound **5** was collected by GLC (130°, same retention time as above). A colorless oil (203 mg, 57%) was obtained. This oil is believed to be a mixture of **5,** and the isomeric compound from C(7)–N cleavage. The ^1H NMR and ir spectra of the oil clearly show the presence of both **5** and a second structurally very similar molecule. Absorptions of the second molecule are totally absent in the sample of **5** from the $PdCl_2(PhCN)_2$ route above.

***N*-Carbethoxy-2-carbomethoxy-4-chloro-8-azabicyclo[3.2.1]octane, (6).** To a solution of 1.0 g of **3a** in 15 ml of CH_2Cl_2 which had been saturated with CO and through which CO was slowly bubbling were added 2.2 g of $PdCl_2(PhCN)_2$. The solution was stirred at room temperature for 20 min, at which time it was light orange. Anhydrous CH_3OH (10 ml) containing 0.4 g of KOH were then added. The solution immediately blackened and was stirred for an additional 10 min with CO bubbling through it. The mixture was then filtered, extracted with H_2O (2 × 10 ml), dried over $MgSO_4$, and concentrated. Peaks due to compounds **4a, 5,** and an additional long retention time peak for **6** were detected by GLC. Isolation of **6** by GLC (170°) gave 300 mg (20%). Analysis of a different reaction mixture by ^1H nmr indicated a yield of **6** of 27%.

Anal. Calcd for $C_{12}H_{18}NO_4Cl$: C, 52.28; H, 6.53; mol wt 275.5. Found: C, 52.89; H, 6.77; molecular ions in the mass spectrum of *m/e* 275 and 277. (^{37}Cl and ^{35}Cl). The ^1H NMR is shown in Figure 4.

***N*-Carbethoxy-4-chloro-8-azabicyclo[3.2.1]octane (7).** Cyclohexane (1 ml) and 50 mg of $NaBH_4$ were dissolved in 10 ml of 1,2-dimethoxyethane. The solution was cooled to −40 °C under a nitrogen atmosphere. In a separate flask 210 mg of **3a** and 330 mg of $PdCl_2(CH_3CN)_2$ in 5 ml of glyme were allowed to react for 15 min. This solution was then poured into the cooled $NaBH_4$ solution. There was an immediate black color. The mixture was stirred at or below −35 °C for 1 h. Water (20 ml) was added and the solution was extracted with 25 ml of ether. The ether extract was washed with 20 ml of H_2O, dried over $MgSO_4$, and then concentrated. Analysis by GLC showed the presence of **4a** and a new long retention time peak for **7.** Isolation by GLC (130°) yielded 75 mg of **7** (30%).

Anal. Calcd for $C_{10}H_{16}NO_2Cl$: C, 55.18; H, 7.36; mol wt, 217.5. Found C, 55.07; H, 7.40; molecular ions in the mass spectrum at *m/e* 217 and 219 (^{37}Cl and ^{35}Cl). ^1H NMR (Figure 5) δ 4.32 (2 H, m, H_1 and H_5), 4.21 (2 H, q, J = 7 Hz), 4.1 (1 H, broad, H_4), 2.4–1.4 (8 H), 1.3 (3 H, t, J = 7 Hz).

Chloro[1,2-bis(diphenylphosphino)ethane](2-η^1-*N*-carbethoxy-4-chlorobicyclo[3.2.1]octyl)palladium(II) (8). Dichlorobis(benzonitrile)palladium(II) (670 mg) was added to a solution of 330 mg of **3a** in 20 ml benzene. The solution was stirred at room temperature for 15 min, after which time 720 mg of diphos was added. The stirring was continued for 5 min and 750 mg of pale red solid was filtered off. The solid was redissolved in 20 ml of CH_2Cl_2, filtered, and combined with the original benzene filtrate. The resultant solution was concentrated to 15 ml, at which point 350 mg of $PdCl_2$(diphos) precipitated. Filtration and concentration to ca. 5 ml, followed by addition of 15 ml of diethyl ether yielded 300 mg of pale brown solid. This was filtered off and then 30 ml of low-boiling petroleum ether were added to the filtrate. The yield was 155 mg of pale yellow solid. The initial brown precipitate was recrystallized from CH_2Cl_2 to yield an additional 250 mg of **8.** The total yield was 405 mg (mp 75–80 °C).

Anal. Calcd for $C_{36}H_{39}NO_2P_2Cl_2Pd$: C, 57.15; H, 5.36; Pd, 14.1; mol wt, 756. Found: C, 57.78; H, 5.36; Pd, 14.9; mol wt in CH_2Cl_2 was 721 g/mol. ^1H NMR δ 7.48 (20 H, broad), 4.5–0.9 (19 H, broad, unresolved).

Carbonylation of Complex 8. Carbon monoxide was bubbled slowly through a solution of 45 mg of KOH in 4 ml of CH_3OH for 5 min. Complex **8** (240 mg) was then added as the solid. The solution gradually darkened and CO bubbling was continued for an additional 60 min. The solution was filtered and 10 ml of H_2O was added. The solution was then extracted with diethyl ether (1 × 10 ml). After concentration, analysis by GLC and ^1H NMR showed that only **6** was present. The yield was 75% (by ^1H NMR).

***N*-Carbomethoxy-8-azabicyclo[5.1.0]octane (9).** Aziridine **9** was synthesized in 25% yield by a procedure analogous to that used in the preparation of **3a** and **3b.** The boiling point was 62–70 °C, at 0.15 mmHg.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.95; H, 8.87; mol wt, 169. Found: C, 63.95; H, 8.96; molecular ion in mass spectrum at *m/e* 169. ^1H NMR δ 3.7 (3 H, s), 2.65 (2 H, m), 2.2–1.3 (10 H, broad).

1-[(Carbomethoxy)amino]-2-chlorocycloheptane (10). Aziridine **9** (280 mg) was dissolved in 5 ml of CH_2Cl_2 and then 650 mg of $PdCl_2(PhCN)_2$ was added. The deep red homogeneous solution stood at room temperature for 1 h and was then treated with 5 ml of $NaCN/H_2O$. The CH_2Cl_2 layer was separated, washed with H_2O (2 × 5 ml), dried over $MgSO_4$, and then concentrated. GLC analysis showed ca. 1:1 ratio of **9** and **10.** Compound **10** was collected, yielding 185 mg of white solid (55%, mp 82–85 °C).

Anal. Calcd for $C_9H_{16}NO_2Cl$: C, 52.57; H, 7.79; mol wt, 205.4. Found: C, 52.61; H, 7.58; molecular ions in the mass spectrum at *m/e* 205 and 207 (^{35}Cl and ^{37}Cl). ^1H NMR δ 5.2–4.6 (1 H, broad), 4.2–3.5 (2 H, broad), 3.7 (3 H, s), 2.4–1.3 (10 H, broad). Compound **10** was also obtained in 72% isolated yield when aziridine **9** reacted with an equivalent of concentrated aqueous HCl, using a procedure similar to that for **3a** + HCl → **5.** The melting point of **10** in the case was 83–86 °C, and there was no depression of melting point in a mixture of the two samples of **10.**

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References and Notes

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Trifluoroethylamine-Catalyzed Isomerization of β,γ-Unsaturated Ketones. Nucleophilic Catalysis via Schiff Base Formation

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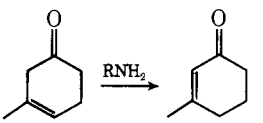
Abstract: The isomerizations of 3-methyl-3-cyclohexenone (**1**) to 3-methyl-2-cyclohexenone (**2**), and 1-acetyl-2-cyclohexene (**5**) to 1-acetyl-1-cyclohexene (**6**) are efficiently catalyzed by trifluorethylamine (TFEA). In the case of **1** → **2**, the reaction proceeds via the intermediate formation of trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (**3**), the Schiff base of TFEA and **2**. Formation of **3** is rapid under the conditions employed (pH 4.85–6.90, TFEA buffers) with hydrolysis of **3** to **2** occurring as a subsequent slow reaction. The formation of **3** was investigated in detail. The rate of this reaction is predominantly dependent on a second-order term in TFEA ($k^{AB}[RNH_2][RNH_3^+]$) with small first-order terms in free amine ($k^B[RNH_2]$) and protonated amine ($k^A[RNH_3^+]$). A mechanism is proposed which involves preequilibrium formation of the β,γ-unsaturated Schiff base from **1** (**8**) followed by isomerization through a dienamine (**9**) to the α,β-unsaturated Schiff base (**3**). Examination of solvent isotope effects on this reaction shows that protonation of **9** occurs with approximately equal facility to give **3** and to regenerate **8**. In contrast to **1**, the TFEA-catalyzed isomerization of **5** proceeds directly to **6** with no detectable accumulation of intermediate. These reactions are discussed as possible models for enzymatic interconversions of α,β-unsaturated ketones and their β,γ isomers.

The interconversion of β,γ-unsaturated ketones and their α,β-unsaturated isomers has been shown to be catalyzed by both acids[1-5] and bases.[3,6-8] The acid-catalyzed reaction involves the formation of a dienol intermediate, followed by protonation at the α or γ carbon to give β,γ or α,β product, respectively,[1,2] and an analogous pathway through an enolate ion intermediate has been proposed[3] for the base-catalyzed process. In addition, several enzymes are known which carry out this type of isomerization.[9-11] The only enzyme of this type which has been studied in detail is the Δ^5-3-keto steroid isomerase from *P. testosteroni*,[9] although the mechanism for this reaction has yet to be fully elucidated.

In a preliminary communication[12] we reported that primary amines are capable of catalyzing the isomerization of β,γ-unsaturated ketones to their α,β-unsaturated isomers through the formation of a dienamine intermediate, analogous to the dienol in the corresponding acid-catalyzed rearrangement. Furthermore, the amine-catalyzed reaction is much more efficient than either the acid- or base-catalyzed reactions at neutral pH, and may represent a model for some of the corresponding enzymatic isomerizations. Benisek and Jacobson[13] have also reported that this type of isomerization is subject to amine catalysis and have advanced essentially the same mechanism to account for their results. In this report, we present a full account of our investigation into the kinetics and mechanism of the trifluoroethylamine catalysis of the isomerization of 3-methyl-3-cyclohexenone and 1-acetyl-2-cyclohexene.

Results

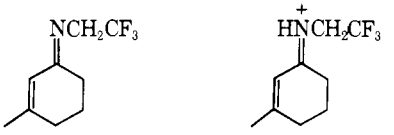
3-Methyl-3-cyclohexenone. The isomerization of 3-methyl-3-cyclohexenone (**1**) to the conjugated isomer, 3-methyl-2-cyclohexenone (**2**), was found to be efficiently catalyzed by primary amines. Our investigation of this reaction



1 **2**

with 2,2,2-trifluoroethylamine (TFEA) buffers showed that, although **2** was the sole final product ($\lambda_{max}^{H_2O}$ 240), another uv-absorbing species was produced during the reaction. During the initial phases of the reaction, an intermediate was formed with an absorption maximum at approximately 268 nm. Addition of **1** to TFEA produced a rapid rise in absorbance at 268 nm followed by a slower decay, suggesting that this species is involved in the overall catalytic process. When the appearance of **2** was monitored at 240 nm, an induction period was observed, providing further evidence for the existence of an intermediate on the reaction pathway.

In order to isolate and identify this intermediate, **1** was allowed to react with TFEA in carbon tetrachloride, using molecular sieves to remove the water produced to prevent hydrolysis of the intermediate to **2**. Purification of the product



3 **4**

by GLC yielded a colorless oil which was shown to be the α,β-unsaturated Schiff base **3**, based on elemental analysis and spectral data.

The NMR spectrum of **3** showed a singlet at δ 5.75 assigned to the olefinic proton, a quartet at δ 3.58 with J = 10 Hz (incorrectly given as δ 5.58, J = 16 Hz in our preliminary com-