Table I. $X_3SnCo(CO)_4$ ^{13}C NMR

X	Av chem shift[a,b]	T_c, °C	Axial chem shift[b]	Radial chem shift[b]	$\Delta G^{\ddagger}$, kcal/mol	e^2qQ/h, MHz
$C_6H_5CH_2$	198.8	−111	205.3	196.6	7.1	100.4
n-C_4H_9	200.6	−110	206.1	198.7	7.2	–
C_6H_5	199.0	−110	204.9	197.1	7.2	104.1[7]
CH_3	200.4	−119	205.8	198.6	6.8	96.8[6]
Cl	191.1	<−155	–	–	–	163.4[7]

[a] Fast exchange value. [b] All shifts are ±0.1 ppm, downfield from Me_4Si with $HFCCl_2$ as secondary standard (−94.2 ppm).

Below −90 °C the line broadens, and below −120 °C a pair of lines of intensity ratio 1:3 emerges.

In the slow exchange region, the lines corresponding to the axial and radial CO groups exhibit chemical shifts of −205.3 and −196.6 ppm downfield, respectively, relative to Me_4Si. The coalesence temperature for the intramolecular exchange of axial and radial CO groups is −111 °C. A preliminary analysis of line shapes at various temperatures yields values of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ for the exchange of 7.1 kcal/mol, 8.2 kcal/mol, and 7.1 cal/°K, respectively. (In making this analysis we have assumed that the scalar interaction with ^{59}Co makes no contribution to the line shape in the temperature region in which spectra were analyzed, i.e., below about −100 °C. This seems a reasonable assumption, since the line width remains 10 Hz from −60 to −80 °C.)

These results are, so far as we are aware, the first reported example of a stopped exchange in any compound of the form $XM(CO)_4^n$, possessing idealized axial symmetry at the metal. Low temperature ^{13}C NMR spectra of several compounds of this general formula, e.g., $C_5H_5NFe(CO)_4$,[9] $PF_3Fe(CO)_4$,[10] $(C_6H_5)_3PFe(CO)_4$,[11] and (olefin)$Fe(CO)_4$,[12] have been reported. With the exception of the olefin compounds, in which the olefin occupies an equatorial site, none of these systems has shown evidence of slow exchange at the lowest temperature studied. The origin of the barrier to the intramolecular rearrangement in the olefin systems is thought to lie in the necessity for the olefin group to rotate in the course of the rearrangement.[12] One previously studied system which bears some resemblance to those reported here is $CF_3Co(CO)_3PF_3$, in which cis and trans isomers have been observed.[13] The exchange between the isomeric forms, as observed in the ^{19}F NMR spectra, is slowed at −70 °C.

The barrier to intramolecular rearrangement in $Fe(CO)_5$ is thought to be very low.[10,14] On the other hand, the barriers in ML_5^n compounds (M = Co, Rh, Ir, Ni, Pd, Pt), where L is a phosphine or phosphite, are sufficiently high so that the stopped exchange region for intramolecular exchange can be observed in the ^{31}P NMR spectra.[15]

It is well known that the detailed pathway by which an $XM(CO)_4$ species undergoes axial-radial exchange cannot be determined by observation of the ^{13}C NMR spectra of any of the possible variously labeled molecules.[16-18] However, a related matter of possibly more significance, the dependence of the kinetics of axial-radial interchange on the nature of X, can be determined by systematic studies. Table I shows preliminary ^{13}C NMR data for several $X_3SnCo(CO)_4$ compounds at low temperatures. The slow exchange region is reached for all except $Cl_3SnCo(CO)_4$. The relationship of the ^{13}C NMR results to ^{59}Co quadrupole coupling constants is interesting. The four organotin compounds all possess considerably lower quadrupole coupling constants than $Cl_3SnCo(CO)_4$, which in turn possesses a quadrupole coupling constant very near the value of 156 MHz predicted[19] for the as yet unknown $Co(CO)_5^+$. By analogy with the results for isoelectronic $Fe(CO)_5$, one might expect the intramolecular exchange rate in $Co(CO)_5^+$ to be very rapid. Barring the possibility that the chemical shift difference between axial and radial CO groups in $Cl_3SnCo(CO)_4$ is small, these preliminary results suggest that the ability of the X group in $XCo(CO)_4$ compounds to act as a π-acceptor is an important factor in determining the barrier to axial-radial interchange. Detailed line shape analyses and studies of other $XCo(CO)_4$ compounds are underway.

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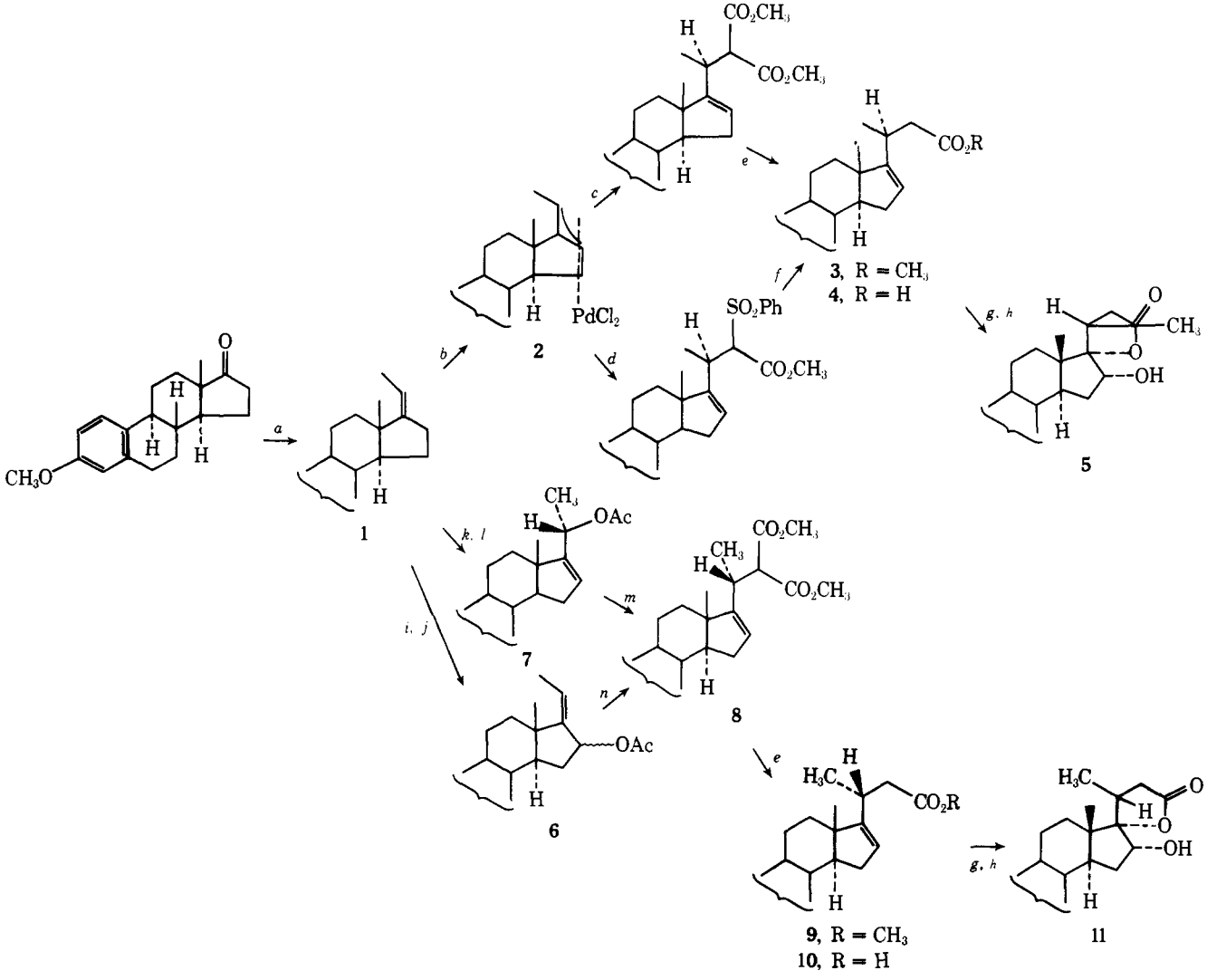
New Synthetic Reactions. Catalytic vs. Stoichiometric Allylic Alkylation. Stereocontrolled Approach to Steroid Side Chain

Sir:

Control of stereochemistry in acyclic systems remains a formidable problem in synthetic organic chemistry. A classic example is creation of stereochemistry at C-20 of steroids.[1-3] Absorption of the substrate on a transition metal to enforce conformational rigidity and thus stereochemical control is a possible approach to the problem. In this paper, we wish to report that either stereochemistry at the C-20 position of a steroid can be obtained via π-allylpalladium complexes[4-6] from the same olefin substrate. In particular, the results demonstrate a contrast between the catalytic and stoichiometric approaches to allylic alkylation utilizing organopalladium chemistry and offer insight into the mechanism of the catalytic process.[7] Furthermore, the catalytic palladium reaction allows an overall SN2 displacement with a net retention of configuration at the carbon undergoing displacement.

Scheme I. Catalytic vs. Stoichiometric Allylic Alkylation via Palladium Complexes



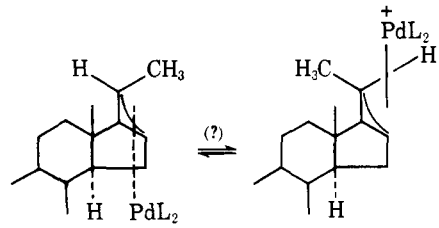
[a] $Ph_3{}^+PCH_2CH_3Br^-$, $KOC(CH_3)_3$, THF, reflux, 30 h, 81%. [b] $PdCl_2$, NaOAc, NaCl, $CuCl_2$, HOAc, Ac_2O, 70°, 60 h, 67%. [c] $NaCH(CO_2CH_3)_2$, DIPHOS, THF, 25°, 24 h, 81%. [d] $NaCH(CO_2CH_3)SO_2Ph$, DIPHOS, THF, 25°, 24 h, 82%. [e] $(CH_3)_4N^+{}^-OAc$, HMPA, 100°, 13 h, 91%. [f] Ca, NH_3, reflux, 10 min, then $PhCO_2Na$, NH_4Cl, 61%. [g] OsO_4, ether, pyridine, 25°, 14 h. [h] *p*-TsOH, PhH, reflux, 2 h, 53%. [i] SeO_2, C_2H_5OH, reflux, 8 h, 65%. [j] Ac_2O, pyridine, 25°, 79%. [k] MCPBA, $CHCl_3$, 0°, 5 h, 99%. [l] $LiN(C_2H_5)_2$, hexane, HMPA, 25°, 10 h, CH_3COCl, 74%. [m] Catalytic amount of $[Ph_3P]_4Pd$, Ph_3P, $NaCH(CO_2CH_3)_2$, THF, reflux, 20 h, 83%. [n] Catalytic amount of $[Ph_3P]_4Pd$, Ph_3P, $NaCH(CO_2CH_3)_2$, DMSO, 80–120 °C, 30 h, 36%.

3-Methoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene, mp 77.5–79.0°,[8] **1**, available from estrone methyl ether utilizing the Wittig reaction under reversible ylide generation conditions (see Scheme I), may be converted to its π-allylpalladium complex **2**, mp 161–182° dec, as outlined previously.[9] NMR suggests it is a single isomer (δ 1.00, 3 H, s; 1.26, 3 H, d, J = 8 Hz; 3.56 and 3.74, 1 H each, m). Alkylation of **2** utilizing 1,2-bisdiphenylphosphinoethane as the activating ligand gives the product of alkylation at the side chain carbon exclusively. For characterization, it was decarbomethoxylated utilizing tetramethylammonium acetate to **3** (NMR δ 0.84, 3 H, s; 1.10, 3 H, d, J = 6 Hz; 5.36, 1 H, m). The same compound is obtained by alkylation with methyl phenylsulfonylacetate followed by reductive desulfonylation as determined by spectral comparison and mixture melting points (161.0–162.5°) of the acids. Hydrolysis of **3** gave the carboxylic acid **4**, mp 161.0–162.5°; hydroxylation of **3** and lactonization of the resultant diol gave the hydroxy lactone **5**, mp 250–251°. Most interestingly, lanthanide induced shifts for **5** show that the C-18 methyl group (δ 0.82) shifts 87 Hz whereas the C-21 methyl group (δ 1.27) moves 130 Hz upon addition of 33.4 mol % $Eu(dpm)_3$ supporting the S stereochemistry (unnatural series) as assigned.

For the catalytic process, initial allylic oxidation was performed. Oxidation of **1** with selenium dioxide followed by acetylation gives **6**, whereas, epoxidation, base catalyzed ring opening, and acetylation give **7**, mp 124.5–126°. The stereochemistry of **7** derives from the known configuration of the olefin **1**[8,10] and the preference for reagents to attack the C-17–C-20 double bond on the α-face.[8,11] Treatment of acetate **7** with 0.1 to 1 mol % of tetrakis(triphenylphosphine)palladium with dimethyl sodiomalonate in the presence of additional triphenylphosphine gives a malonate **8** which was decarbomethoxylated to **9** (NMR δ 0.77, 3 H, s; 1.03, 3 H, d, J = 7.5 Hz; 5.17, 1 H, m).[12] As in the case of **3**, hydrolysis gave a carboxylic acid **10**, mp 162.5–164.0°, which suffers a sharp melting point depression upon mixing with **4** (mmp 139–155°). Hydroxylation and lactonization gave a hydroxylactone **11**, mp 202–203°. In this case, the C-18 methyl group (δ 0.96) shifts 85 Hz whereas the C-21 methyl group (δ 1.15) shifts 83 Hz upon addition of 30 mol % $Eu(dpm)_3$. Furthermore, the pro *R* hydrogen at C-22 (δ 3.19) shifts 298 Hz. These data clearly indicate the *R* con-

figuration (natural series) as assigned. Compound **6** reacts much more slowly, less cleanly, and in lower yield, under catalytic conditions to give **8**.

The stereochemistry of **3** obtained in the stoichiometric reaction is that expected from the anticipated preference for the bulky palladium to be on the less crowded α face of the steroid and the known preference for complexes to possess the syn rather than anti configuration.[4,5] We previously established that the nucleophile attacks the complex on the face opposite to palladium.[5b] On the other hand, the complementary stereochemistry obtained in the catalytic reaction is quite surprising. Firstly, the stereospecificity suggests that alkylation is faster than equilibration of the π-allyl complexes, and secondly, that the less stable diastereomeric complex **12a** or **12b**, which may be in dynamic equilibrium with each other, is probably involved. Considering the stereochemistry of **7**, this result indicates that the oxidative addition to the Pd complex is stereospecific and occurs with inversion of configuration.[13,14] Thus, the effect of the two inversions is an overall stereospecific SN2 displacement of the allylic acetate with a net retention of configuration, a result which should prove useful in organic synthesis.[15]



12a 12b

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(16) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient, 1970–1975.

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The ^{15}N Nuclear Magnetic Resonance of Friend Leukemic Cell [Gly-^{15}N] Hemoglobin. The Resolution of Noncovalent Bonding Interactions

Sir:

A number of nitrogen NMR studies of amino acids[1] and short peptides[2] have indicated that nitrogen chemical shifts may be more easily correlated to macromolecular phenomena than those of ^{1}H and ^{13}C. However, the field of nitrogen-15 NMR of macromolecules has remained completely unexplored until now, due to the poor sensitivity routinely encountered in ^{15}N NMR, which is caused by the low natural abundance and relative insensitivity of nitrogen-15 nuclei. We here report the first nitrogen-15 NMR spectrum of a selectively ^{15}N enriched protein, which was achieved by using a Friend leukemic cell (FLC) culture to prepare hemoglobin 50% ^{15}N enriched in glycyl residues. The ^{15}N NMR spectra of [Gly-^{15}N]hemoglobin demonstrates that ^{15}N NMR can be used to distinguish between glycyl residues whose N–H groups are hydrogen bonded to water and those intramolecularly hydrogen bonded to peptide carbonyl groups. These results indicate that ^{15}N NMR might be a useful tool to study N–H noncovalent bonding interactions in oligopeptides, polyamino acids, and proteins.

[Gly-^{15}N]Hemoglobin (Hb-^{15}N) was obtained from the lysate of DMSO-treated Friend leukemic cells (FLC) (Clone 707)[3] grown on a medium containing 150 mg/l. of glycine-^{15}N (90% ^{15}N). The Hb-^{15}N (10% of the lysate proteins) was purified under CO on a CM-50 Sephadex column using a phosphate buffer pH gradient and shown by pH 6–8 polyacrylamide gel isoelectric focusing to have a p*I* = 7.52 and corresponded to the major compound of mouse DBA/2 hemoglobin, and the single band of mouse C57/BL hemoglobin. The freely reacting cysteine groups were carboxymethylated to prevent hemoglobin polymerization.[4]

The ^{15}N NMR spectrum of CO-Hb-^{15}N in H_2O (Figure 1A) displays a doublet, $^{1}J_{NH}$ = 94 Hz, centered at 81.4 ppm (downfield from 4 M $^{15}NH_4Cl$ in 2 M HCl) and a partially resolved shoulder at 90.0 ppm. Exchange of the peptide hydrogens for deuterium results in the collapse of the 81.4 ppm doublet into a singlet, and allows the second resonance at 90.0 ppm to be clearly resolved, as seen in the spectrum of CO-Hb-^{15}N in D_2O (Figure 1B). The proton-noise decoupled ^{15}N NMR spectrum of a FLC hydrolysate (Figure 2) displays a single intense resonance at 6.2 ppm corresponding to the chemical shift of glycine at pH 5.1 and indicates that no transfer of ^{15}N to other amino acids occurred and corraborates the mass spectrometric ^{15}N analy-