

which is most plausibly derived from polyacetate as is indicated by hydration of the double bond (7).¹⁵

Vermiculine (5) has the fewest asymmetric centers of any of the macrolide antibiotics. In view of vermiculine's relative simplicity and its useful antibiotic properties, studies on the possible complexation of metal ions as well as approaches to the total synthesis are currently underway in our laboratories.

Supplementary Material Available. The fractional coordinates (Table I), important bond distances (Table II), and important bond angles (Table III) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-74-5954.

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Stereochemistry of Oxidative Addition of Benzyl- α -d Chloride to Tetrakis(triphenylphosphine)palladium(0). Direct Evidence for Configurational Inversion at Carbon via a Nonradical Mechanism

Sir:

Oxidative addition of alkyl halides to low valent group VIII transition metal complexes may involve intermediate free carbon radicals^{1,2} or occur by an

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SN₂-type transition state³⁻⁸ depending on the nature of the reactants. Recently, we reported⁹ that the reaction of tetrakis(triphenylphosphine)palladium(0) (1) with α -phenethyl bromide (2) in the presence of carbon monoxide gave the acylpalladium complex 3, PhCH(CH₃)(CO)Pd(PPh₃)₂Br, in which >90% inversion of configuration at the benzylic carbon had occurred. This stereochemistry is consistent with an initial oxidative addition of 2 to palladium, with inversion of configuration at carbon, to yield an alkylpalladium intermediate 4, PhCH(CH₃)Pd(PPh₃)₂Br, which then undergoes carbon monoxide insertion, with complete retention of configuration at carbon,¹⁰ to afford 3. However, an attempt to isolate the alkylpalladium complex 4 from the reaction of 1 with 2 afforded only dibromobis(triphenylphosphine)palladium(II).

Recently, a nonchain radical mechanism has been proposed for the oxidative addition of methyl iodide, ethyl iodide, and benzyl bromide to tris(triphenylphosphine)platinum(0) based on the observation of the derived nitroxide radical, *t*-Bu(R)NO· (R = CH₃, C₂H₅, PhCH₂), in esr using *tert*-nitrosobutane as a spin trap.¹¹ The spin trapping results together with the failure to isolate 4 suggest the possibilities that the formation of the acyl complex 3 may involve direct nucleophilic attack by a palladium-bonded carbonyl at the benzylic carbon, and the reaction of benzyl halides with 1 in the absence of carbon monoxide may occur by a radical pathway with racemization at carbon. This communication reports the stereochemistry of the oxidative addition reaction of benzyl- α -d chloride (5) with 1 to afford the benzylpalladium complex 6, PhCH(D)Pd(PPh₃)₂Cl, and spin trapping studies of the addition of benzyl halides to 1.

Optically active (*S*)(+)-5¹²⁻¹⁴ was prepared by the reaction of optically pure (*S*)(+)-benzyl- α -d alcohol (7)¹⁶ with phosgene. Treatment of (*S*)(+)-5 with 1 in degassed benzene under nitrogen afforded the benzyl complex 6 which upon carbonylation yielded the phenylacetyl palladium complex 8. Both 6 and 8 exhibited only very small optical rotation. Bromine cleavage of 8 followed by methanolysis gave (-)-methyl phenylacetate- α -d (9), and lithium aluminum hydride reduction of the levorotatory ester 9 gave the known (*R*)(-)-

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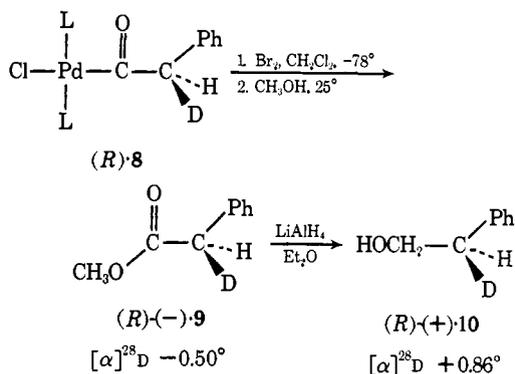
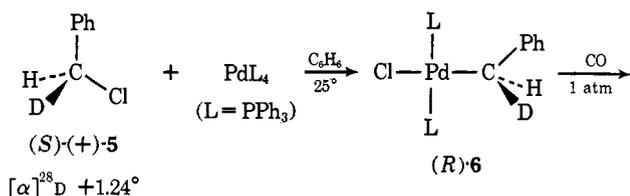
(14) A calculated optical purity of 99 ± 6% can be assigned to (*S*)(+)-5 if the reaction of chiral benzyl- α -d tosylate with chloride ion to afford chiral benzyl- α -d chloride is assumed to take place with complete inversion of configuration at carbon as the ethanolysis of benzyl- α -d tosylate does.¹⁵

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2-deuterio-2-phenylethanol (**10**) with an optical rotation approximately 50% of the highest reported value ($[\alpha]^{25}_D + 1.74^\circ$).¹⁷ Since neither the bromine cleavage of **8** nor the reduction of **9** would lead to inversion of configuration at the chiral center, both the acyl complex **8** and the ester **9** have the *R* configuration.

Consequently, the oxidative addition of **5** to **1** proceeds with inversion of configuration at the benzylic carbon since the carbonylation of palladium-carbon σ bonds occurs with 100% retention of configuration.¹⁰ The stereospecificity of the reaction sequence, however, cannot be estimated because of the lack of data for the optical purity of **10**. The addition of a chiral shift



reagent, $\text{Eu}(\text{tfac})_3$ ($\text{tfac} = 3$ -trifluoroacetyl-*d*-camphorato anion), to a deuterated chloroform solution of (*R*)-(+)-**10** did not produce any enantiomeric separation in the nmr spectrum.

The substantial loss of optical activity in (*R*)-**10** can be partially accounted for by the partial racemization of **5** under reaction conditions. The unreacted (*S*)-(+)-**5** ($[\alpha]^{25}_D + 1.12^\circ$) recovered from the oxidative addition of **5** to **1** suffered a 10% loss of its optical activity. In addition, racemization of **6** could occur *via* a reversible σ - π rearrangement¹⁸ or a nucleophilic exchange process^{8,9} between **6** and a palladium(0) species.

Spin trapping experiments for α -phenethyl bromide (**2**) and benzyl chloride (**5a**) were carried out under conditions similar to those reported for tris(triphenylphosphine)platinum.¹¹ The esr spectrum of a benzene solution containing equimolar amounts of **2** and **1** in the presence of 5–10 mole % of *tert*-nitrosobutane (**11**) showed a clean signal of *tert*-butyl α -phenethyl

nitroxide ($a^N = 14.93$, $a^{\text{H}_{\text{CH}_2}} = 3.60$)^{19–21} as a triplet of doublets. In an identical experiment for **5a**, the esr spectrum showed an overlapping triplet of triplets for benzyl *tert*-butyl nitroxide ($a^N = 15.63$, $a^{\text{H}_{\text{CH}_2}} = 7.54$)^{20,22} as well as a triplet for di-*tert*-butyl nitroxide ($a^N = 15.56$).^{23–25} The spectra for solutions of **11** and benzyl halides **2** and **5a** in the absence of **11** showed only a signal for di-*tert*-butyl nitroxide due to the decomposition of **11**. Since the observed stereochemistry for the oxidative addition of **5** to **1** is inconsistent with a radical pathway,²⁶ the formation of benzyl *tert*-butyl nitroxide radical is most likely the consequence of a spin-trap induced radical mechanism for the oxidative addition or a radical decomposition (thermal or spin-trap induced) of the oxidative addition adduct **6a**, $\text{PhCH}_2\text{Pd}(\text{PPh}_3)_2\text{Cl}$. This latter possibility was demonstrated by the fact that *benzyl tert-butyl nitroxide is indeed formed* (as observed by its esr spectrum) on mixing a benzene solution of the benzylpalladium complex **6a** and *tert*-nitrosobutane (**11**).²⁷ The formation of **6a** in the presence of **11** *via* a radical pathway cannot be discounted, however.

Inversion of configuration at the benzylic carbon during the oxidative addition of **5** to **1** suggests an $\text{S}_{\text{N}}2$ displacement of benzylic halides by palladium and is incompatible with either a chain or nonchain radical mechanism. The particular mechanism followed in a given system, however, probably depends on the nature of the reactants.^{1,2,8} A radical decomposition of the oxidative addition adduct is most likely responsible for the observation of the derived nitroxide radical during the reaction of **5** to **1**. The proposed nonchain radical mechanism for the oxidative addition of alkyl halides to tris(triphenylphosphine)platinum(0) on the basis of spin trapping experiments should therefore be considered with caution.

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