cessibility of water-dependent denaturation intermediates. As such, minimal added water in these systems can lead to rapid loss of activity, unlike CLCs which are stable at all water concentrations. Proteolysis resistance of CLCs is explained by the exclusion of exogenous protease, due to the size of the solvent channels defined by the crystal lattice. Large substrate/product molecules (e.g., proteins, polynucleotides, etc.) will also be restricted, of course, though most smaller substrates can be accommodated.

Conventional immobilized enzymes are principally used to facilitate catalyst recovery,[18] but they can also provide modest stability enhancements.[19] Formulated as beads or particles, however, these systems consist mostly of inert carrier material. CLCs provide their own support, and so achieve enzyme concentrations close to the theoretical packing limit—in excess of even highly concentrated enzyme solutions. As such, CLCs are particularly attractive in biosensor applications, where the largest possible signal per unit volume is often critical. We have formulated cross-linked enzyme crystals of jack-bean urease for use in clinical biosensor applications to measure urea levels in the circulation as an early indicator of renal disease.[20]

Manufacturing applications can be particularly difficult for enzyme catalysts. The artificial sweetener aspartame (L-aspartate-L-phenylalanine methyl ester), for example, can be readily obtained by deprotection of a precursor species that is formed by the thermolysin-catalyzed regio- and stereoselective condensation of (benzyloxycarbonyl)-L-aspartic acid and DL-phenylalanine methyl ester in a nonaqueous solvent.[1,2,21] Thermolysin was found, by trial and error, to be a suitable, readily available enzyme for use in this process.[1] Chemical synthesis,[22] however, has proven more viable for the large-scale manufacture of aspartame, due in part to unsatisfactory enzyme stability over the long term. We have adapted the enzymatic process[21] to take advantage of the enhanced solvent and temperature stability described above for thermolysin CLCs and have been able to produce the aspartame precursor in buffer-saturated ethyl acetate at 55 °C over a period of 18 days without significant loss of enzyme stability. Under these conditions, free thermolysin was found to be inactive on the fourth day.[20]

Temperature and protease resistance also make CLCs useful in therapeutics. Suitably implanted or orally administered CLCs may provide an alternative to gene replacement therapy for the correction of some inherited enzyme deficiencies. Finally, diffraction-quality FAB fragment crystals are known for many classes of antibodies.[23] Catalytic antibody[24] CLCs might enable practical chemical synthesis using these molecules, accelerating the benefits promised by this technology.

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**Registry No.** Aspartame, 22839-47-0; *N*-[*N*-[(phenylmethoxy)carbonyl]-L-α-aspartyl]-DL-phenylalanine methyl ester, 110220-25-2.

**Supplementary Material Available:** Experimental details for the thermolysin CLCs and plots of the absorbance and activity of CLCs and free enzyme (11 pages). Ordering information is given on any current masthead page.

## β-Hydride Elimination for an Amine Ligand and the Microscopic Reverse: The First Report of a *cis*-Iminium Hydride in Equilibrium with Its Amine Precursor

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β-Hydride elimination of metal alkyl complexes and the reverse process of olefin insertion into a metal–hydride bond are fundamental transformations in organometallic chemistry.[1] In particular, the transfer of a β-hydrogen atom from an alkyl ligand to the metal through a four-center transition state is the primary mechanism for metal alkyl decomposition. Ubiquitous in coordination complexes, aliphatic amine ligands are isoelectronic to alkyl ligands and would be expected to undergo the analogous reaction under appropriate conditions. Although β-hydride elimination is commonly invoked as the mechanism for the decomposition of amide complexes to metal hydrides,[2] the direct transformation of a coordinated amine to an iminium hydride species has never been observed. We wish to report such a transformation on Os(II), along with the observation of the microscopic reverse: iminium insertion into a metal–hydride bond.

Using a modified procedure originally outlined by Magnuson et al. for the synthesis of (dinitrogen)tetraammineosmium(II) complexes,[3] the compound *cis*-$[Os(NH_3)_4(NH_2Pr)(N_2)](OTf)_2$ (**1**, Pr = propyl, OTf = $CF_3SO_3^-$) was obtained from $[Os(NH_3)_4(N_2)_2](OTf)_2$ by refluxing the latter in a 1,2-dimethoxyethane (DME) solution of propylamine.[4,5] The dinitrogen ligand of **1** was then removed by metal oxidation in a triflic acid/bromine solution to produce $[Os(NH_3)_4(NH_2Pr)(OTf)](OTf)_2$ (**2**).[5]

† Camille and Henry Dreyfus Teacher-Scholar, 1992.

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(4) All operations are carried out under $N_2$ atmosphere unless otherwise noted.
(5) Synthesis and characterization of **1**: *N*-propylamine (1.1 g, 18.5 mmol) was added to a DME/DMA (8 mL/0.3 g; DMA = *N*,*N*-dimethylacetamide) solution containing $[Os(NH_3)_4(N_2)_2](OTf)_2$ (0.378 g, 0.617 mmol). After 2.5 h at reflux, the reaction mixture (20 °C) was treated with $CH_2Cl_2$ (20 mL) and then with $OEt_2$ (20 mL), and the yellow precipitate was collected, washed, and dried. Yield of **1**: 0.302 g, 76%. Data for **1**: $^1H$ NMR (acetone-$d_6$) δ 4.61 (br, 2 H), 4.00 (br, 12 H), 2.80 (m, 2 H), 1.60 (m, 2 H), 0.90 (t, 3 H); IR (KBr) 2037 $cm^{-1}$ (s, $\nu(N_2)$); CV ($CH_3CN$/TBAH), 100 mV/s) $E_{1/2}$ = + 0.83 V (NHE). Anal. ($OsC_5H_{21}N_7O_6S_2F_6$) C, H, N. Synthesis of **2**: Compound **1** (0.570 g, 0.7 mmol) was dissolved in neat triflic acid (6 mL), treated with $Br_2$ (60 mg, 0.4 mmol), and heated in open air (65 °C, 1 h) with periodic swirling. The reaction solution was cooled (−10 °C), and cold (0 °C) $OEt_2$ was slowly added. (EXOTHERMIC!) The resulting off-white solid was collected, washed ($OEt_2$), and dried. Yield of **2**: 0.625 g, 92%. Data for **2**: CV ($CH_3CN$ (TBAH), 100 mV/s) $E_{p,a}$ = −0.51 V (NHE). Anal. ($OsC_6H_{21}N_5O_9S_3F_9$) C, H, N.

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(23) Davies, D. R.; Padlan, E. A.; Sheriff, S. *Annu. Rev. Biochem.* **1990**, *59*, 439–473.
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Subsequent reduction of **2** ($Zn^0/Hg^0$ in methanol)[6] generated an Os(II) species, $[\mathbf{3}]^{2+}$, with an alkylamine adjacent to a labile solvent molecule, and this species isomerized over time to *cis*-$[Os(NH_3)_4(H)(\eta^2\text{-}NH_2{=}CHEt)](OTf)_2$ (**4**) (vide infra).

$^1H$ NMR data (acetone-$d_6$) for **4** reveal four $NH_3$ resonances, a hydridic signal at −10.1 ppm, and signals and couplings corresponding to a methine hydrogen adjacent to an ethyl group. Additionally, two NH resonances appear at 5.7 and 5.6 ppm, values similar to those reported for other $\eta^2$-iminium species.[7] The $^{13}C$ spectrum of **4** indicates a methyl, methylene, and methine carbon, and the latter resonance (42.7 ppm) is similar to that reported for several titanium $\eta^2$-imine complexes.[8] The absence of a strong hydride–carbon coupling ($J_{CH} < 40$ Hz) suggests that the hydride in **4** is not agostic.[9] However, a weak coupling is observed between the hydride and both the methine (2.5 Hz) and a methylene proton (1.2 Hz), which suggests that such an interaction should not be ruled out.

Infrared data for the hydride complex, **4**, reveal a weak absorption at 2095 $cm^{-1}$, and a cyclic voltammogram ($CH_3CN$/100 mV/s) shows one broad, irreversible oxidation wave at +1.02 V (NHE), similar to those reported for $[Os(NH_3)_5(\eta^2\text{-}((CH_3)_2CO)]^{2+}$[10] and $[Os(NH_3)_5(\eta^2\text{-}CH_3CH{=}NH_2)]^{3+}$.[7b] Upon reversing the sweep, a single reversible couple appears at $E_{1/2}$ = −0.05 V, a value consistent with the formation of $[Os(NH_3)_4(NH_2Pr)(CD_3CN)](OTf)_2$.[11] The synthesis of **4** may be carried out in $D_2O$ or DME[12] in place of methanol with identical results. When a sample of $[Os(ND_3)_4(ND_2Pr)(OTf)](OTf)_2$ (**2**-$d_{14}$) is reduced in $CD_3OD$,[13] an $^1H$ NMR spectrum of the reaction mixture shows the hydride resonance at full intensity, an observation which confirms that *the hydride proton originates from the alkyl group of the propylamine ligand.* Taken together, these data support the hypothesis of an alkylamine ligand undergoing $\beta$-hydride elimination on Os(II) to yield a stable *cis*-$\eta^2$-iminium hydride complex, the isoelectronic nitrogen analog to $\beta$-hydride elimination of a metal alkyl.

At fast scan rates ($\nu > 100$ mV/s), cyclic voltammograms of $[\mathbf{2}]^{2+}$ in methanol are reversible ($E_{1/2}$ = −0.48 V) and indicate that the solvated reduction product, $[\mathbf{3}]^{2+}$ assumed to be $[Os(NH_3)_4(NH_2Pr)(CH_3OH)]^{2+}$, is moderately stable.[14] Utilizing the method of Nicholson and Shain,[15] the conversion of $[\mathbf{3}]^{2+}$ to $[\mathbf{4}]^{2+}$ was found to have a specific rate of $k_1 = 6 \times 10^{-2}$ $s^{-1}$ at 25 ± 1 °C.

When a sample of the iminium hydride **4** is allowed to stand in $CD_3CN$ for several days, $^1H$ NMR spectra indicate its complete conversion to a new complex, **9**, with a specific rate of $k_2 = 2 \times 10^{-6}$ $s^{-1}$ (25 ± 1 °C). $^1H$ NMR and electrochemical data for **9** are consistent with the formation of $[Os(NH_3)_4(NH_2Pr)(CH_3CN)](OTf)_2$.[16] Repeating this reaction with 0.38 and 2.5 M $CD_3CN$ in $CD_3OD$ solvent leads to specific rates of $8 \times 10^{-6}$ and $6 \times 10^{-6}$ $s^{-1}$ at 25 °C, respectively, and demonstrates the independence of acetonitrile in the rate-determining step, which we presume to be insertion of the iminium into the metal–hydride bond. Thus, by taking the value of $k_{-1}$, the specific rate of hydride insertion, as being equal to that of $k_2$ and combining it with that of the forward process, $k_1$, a value for the equilibrium constant (Figure 1) is estimated as $K_{eq} = [\mathbf{4}]^{2+}/[\mathbf{3}]^{2+} = 1 \times 10^4$ at 25 ± 1 °C in methanol.[17]

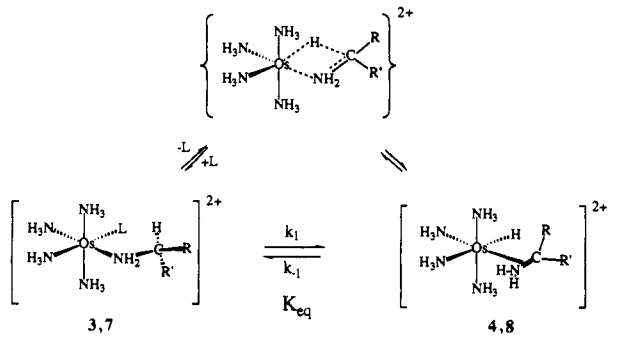


**Figure 1.** $\beta$-Hydride elimination of an alkylamine (**3**; **7**) to form an iminium hydride (**4**; **8**) and the microscopic reverse. For compounds **3** and **4**: R = H, R′ = $CH_2CH_3$, L = $CH_3OH$. For compounds **7** and **8**: R = $CH(CH_3)_2$, (R′ + L) = $CH_2OCH_3$.

As the impetus for this work came from a need to synthesize chiral pentaamineosmium(II) complexes which could be utilized in organic synthesis,[18] analogs to **1** and **2** were sought where the aliphatic amine contained a chiral carbon. Thus $[Os(NH_3)_4((+)ValOMe)(N_2)](OTf)_2$ (**5**) and $[Os(NH_3)_4(\eta^2\text{-}(+)ValOMe)](OTf)_3$ (**6**) were prepared from the methyl ether of (+)-valinol[19] ((+)ValOMe).[20] In contrast to the propylamine analog, when $[\mathbf{6}]^{3+}$ is reduced in methanol, the direct one-electron reduction product, $[Os(NH_3)_4(\eta^2\text{-}NH_2CH(CH_2OMe)(i\text{-}Pr))]^{2+}$ ($[\mathbf{7}]^{2+}$), is stable for extended periods of time,[21] an observation which suggests that the organic ligand is coordinated through both the amino and ether groups. Over a period of 24 h in $CD_3OD$, however, $[\mathbf{7}]^{2+}$ reaches a measurable equilibrium with its corresponding iminium hydride,[22] $[Os(NH_3)_4(H)(\eta^2\text{-}NH_2{=}C(CH_2OMe)(i\text{-}Pr))]^{2+}$ ($[\mathbf{8}]^{2+}$), where in methanol, $K_{eq} = [\mathbf{8}]^{2+}/[\mathbf{7}]^{2+} = 5$. From $^1H$ NMR spectra, $k_1$ and $k_{-1}$ are calculated as

(6) Synthesis of **4**: Compound **2** (0.483 g, 0.632 mmol) was dissolved in MeOH (3 mL) and treated with Zn/Hg powder (1.45 g). The reaction mixture was stirred (1.2 h) and filtered, and the filtrate was added to $OEt_2$ (120 mL). The resulting solid was collected, washed, and dried. Yield of **4**: 0.361 g, 93%. Data for **4**: $^1H$ NMR (acetone-$d_6$) $\delta$ 5.7, 5.6 (br, 2 H), 4.82 (dd, 1 H, $J$ = 6.6, 2.5 Hz), 4.8 (br, 3 H), 4.4 (br, 3 H), 2.8 (br, 3 H), 2.8 (b, 3 H), 1.85 (m, 1 H, $J$ = 7, 1.2 Hz), 1.67 (m, 1 H, $J$ = 7.2 Hz), 1.20 (dd, 3 H, $J$ = 7 Hz), −10.1 (m, 1 H, $J$ = 2.5, 1.2 Hz); $^{13}C$ NMR ($CD_3OD$) $\delta$ 42.7 (dm, $J_{CH}$ = 184 Hz, $J_{CH} < 40$ Hz (hydride)), 28.7 (t, $J_{CH}$ = 126 Hz), 14.2 (d, $J_{CH}$ = 124 Hz); CV ($CH_3CN$/TBAH, 100 mV/s) $E_{p,a}$ = +1.02 V; IR (KBr) 2095 $cm^{-1}$, $\nu$(M–H). Anal. ($OsC_5H_{21}N_5O_6S_2F_6$), C, H, N.

(7) (a) Matsumoto, M.; Nakatsu, K.; Tani, K.; Nakamura, A.; Otsuka, S. *J. Am. Chem. Soc.* **1974**, *96*, 6777. (b) Hasegawa, T.; Kwan, K. S.; Taube, H. *Inorg. Chem.* **1992**, *31*, 1598.

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(11) The compound $[Os(NH_3)_4(NH_2Pr)(CD_3CN)](OTf)_2$ (**9**) was synthesized from the reduction of **2** in $CD_3CN$ and assigned by comparison of NMR and electrochemical data with $[Os(NH_3)_5(CH_3CN)]^{2+}$: Sekine, M.; Harman, W. D.; Taube, H. *Inorg. Chem.* **1988**, *27*, 3604.

(12) Reduction is carried out in DME with *N,N*-dimethylacetamide (4:1 v/v) with $Mg^0$ powder.

(13) Prepared from **2** by precipitation from a basic solution of $CD_3OD$.

(14) For comparison, the complex $[Os(NH_3)_5(OH_2)]^{2+}$ in $H_2O$ has $E_{1/2}$ = −0.72 V. Gulens, J.; Page, J. A. *J. Electroanal. Chem. Interfacial Electrochem.* **1974**, *55*, 239.

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(17) This calculation should be regarded as approximate as it neglects any rate differences in methanol and acetonitrile.

(18) See, for example: Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1990**, *112*, 2682. Cordone, R.; Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1989**, *111*, 5969. Kopach, M. E.; Gonzalez, J.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 8972.

(19) Meyers, A. I.; Poindexter, G. S.; Birch, Z. *J. Org. Chem.* **1978**, *43*, 892.

(20) The synthesis of **5** and **6** was analogous to that of **1** and **2**, respectively. $[\mathbf{5}]^{2+}$: 76%; $^1H$ NMR (acetone-$d_6$) $\delta$ 4.74 (br mult, 1 H), 4.62 (br mult, 1 H), 4.00 (br s, 12 H), 3.60 (dd, 1 H), 3.45 (dd, 1 H), 3.40 (s, 3 H), 2.86 (mult, 1 H), 1.96 (mult, 1 H), 1.02 (d, 3 H), 0.97 (d, 3 H); IR (KBr) $\nu(N_2)$ = 2038 $cm^{-1}$. Anal. ($OsC_8H_{27}N_7O_7S_2F_6$) H, N, C (calcd 13.69, found 13.08). $[\mathbf{6}]^{3+}$: 84%; CV ($CH_3CN$ (TBAH), 100 mV/s) $E_{1/2}$ = −0.32 V (NHE). Anal. ($OsC_9H_{27}N_5O_{10}S_3F_9$) H, N. C (calcd 13.14, found 12.64).

(21) Characterization of **7**: $^1H$ NMR ($CD_3OD$) $\delta$ 3.92 (br, 3 H), 3.77 (s, 3 H), 3.65 (dd, 1 H), 3.60 (br, 3 H), 3.03 (dd, 1 H), 2.68 (br, 3 H), 2.58 (br, 3 H), 2.30 (m, 1 H), 1.77 (m, 1 H), 1.12 (d, 3 H), 1.03 (d, 3 H).

(22) Synthesis and characterization of **8**: Analogous to **4** except the filtrate was stirred overnight before it was added to the $OEt_2$, 89%. Final solid contained approximately 15% of **7**: $^1H$ NMR (acetone-$d_6$) $\delta$ 6.00 (br, 2 H), 4.75 (br 3 H), 4.32 (br, 3 H), 4.27 (dd, 1 H, $J$ = 11, 1.6 Hz), 3.78 (d, $J$ = 11 Hz, 1 H), 3.31 (s, 3 H), 2.95 (br, 3 H), 2.84 (br, 3 H), 1.36 (m, 1 H), 1.30 (d, 3 H), 1.19 (d, 3 H), −9.39 (s, 1 H); $^{13}C\{^1H\}$ NMR ($CD_3OD$) $\delta$ 75.6, 57.5, 49.3, 35.8, 20.0, 18.2; IR (KBr) 2092 $cm^{-1}$, (w, $\nu$(M–H)); CV ($CH_3CN$/TBAH), 100 mV/s) $E_{p,a}$ = +0.97 V (NHE). Anal. ($OsC_8H_{27}N_5O_7S_2F_6$) H, N, C (calcd 14.26, found 13.54).

$2 \times 10^{-4}$ and $4 \times 10^{-5}$ s$^{-1}$, respectively, where $k_{-1}$ is derived from $K_{eq}$ and $k_1$. In a separate experiment, the rate of iminium insertion is determined by treating the equilibrium mixture of $[7]^{2+}$ and $[8]^{2+}$ with 10 equiv of $CD_3CN$ in $CD_3OD$ and measuring the rate of formation of $[Os(NH_3)_4((+)ValOMe)(CD_3CN)](OTf)_2$. By this procedure, a specific rate is measured as $k_2 = 3 \times 10^{-5}$ s$^{-1}$, a value in good agreement with that for $k_{-1}$ calculated directly from $K_{eq}$.[23]

A detailed investigation of the stereochemical, kinetic, and thermodynamic aspects of the ValOMe system is currently in progress as are efforts to establish the generality of this reaction as a synthetic route to $\eta^2$-iminium complexes.

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(23) A rate of insertion, $k_{-1} = 7.5 \times 10^{-5}$ s$^{-1}$, was determined by cyclic voltammetry in $CH_3CN$. The concentration of $[Os(NH_3)_4(ValOMe)(CH_3CN)](OTf)_2$ was monitored through comparison with an internal standard ($CoCp_2^+$).

## Stereochemical Course of Direct Ring Closures of Complex Homoallylic Alcohols to Substituted Tetrahydrofurans†

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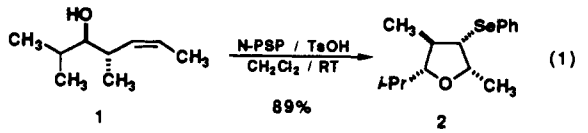
The stereoselective synthesis of highly substituted tetrahydrofurans from homoallylic alcohol precursors has only recently been reported. We have employed a three-step procedure that utilized epoxy alcohol intermediates.[1] Kang and co-workers found that simple homoallylic alcohols containing a trans double bond could be cyclized to either 2,5-syn- or 2,5-anti-substituted tetrahydrofurans with good to excellent stereochemical control.[2] These conversions have been mediated by organoselenium reagents in reactions whose stereochemical outcome has been quite solvent dependent. We sought to expand the synthetic potential of these conversions by investigating, in a systematic manner, the direct closure of homoallylic alcohols to tetrasubstituted tetrahydrofurans. This report accurately characterizes, for the first time, the stereochemical outcome of these very efficient and synthetically useful reactions.

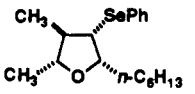
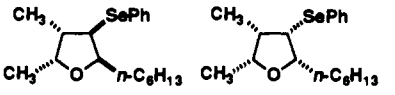
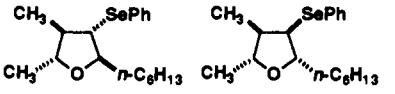
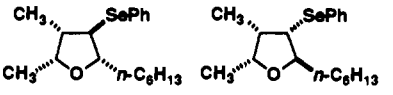
Use of the *N*-(phenylseleno)phthalimide (N-PSP) reagent introduced by Nicolaou[3] with substrate **1** resulted in the rapid and stereoselective production of tetrahydrofuran **2** (eq 1). While

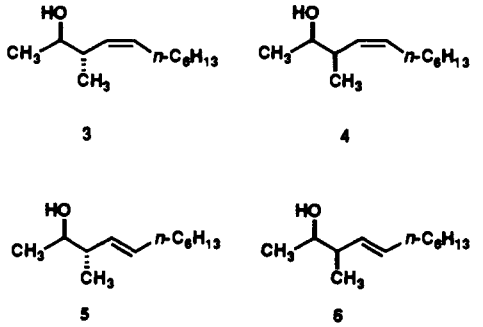



1 2 (1)

this is the same product previously made by the three-step sequence,[1] the improved yield and the simplicity of this direct conversion prompted us to survey the generality of this chemistry with substrates **3**–**6**. The results are shown in Table I.[4,5] In all cases high yields of ring-closed products were obtained within 3 h under the N-PSP conditions. Both anti and syn *Z*-olefins (**3** and **4**) gave essentially single products whose stereochemical assignments were consistent with earlier observations.[1] Anti, *E*-olefin **5** was less selective, providing a 4:1 ratio of **10**:**11**. Syn, *E*-olefin **6** gave a very slight excess of isomer **12** over its reaction partner **13**. All products (**7**–**13**) were reduced with tributyltin hydride (AIBN, PhH, reflux) to give trialkylated tetrahydrofurans **14**–**17**.

Table I. Ring Closure of Homoallylic Alcohols by Organoselenium Reagents

| Olefin | Reagent | Yield (%) | Products |
|---|---|---|---|
| 3 | N-PSP | 92 |  **7** |
| 4 | N-PSP | 84 |  **8** 97 : 3 **9** |
| 5 | N-PSP | 90 |  **10** 81 : 19 **11** |
| 5 | PhSeCl $CH_3CN$ | 90 | **10** 93 : 7 **11** |
| 6 | N-PSP | 85 |  **12** 54 : 46 **13** |
| 6 | PhSeCl $CH_3CN$ | 88 | **12** 83 : 17 **13** |




Stereochemistry can be accurately assessed in these systems by the chemical shift method described by Williams et al.[6,9] The diastereotopic hydrogens of the ring methylene for stereoisomers **14** and **15** are separated by less than 0.3 ppm due to their similar magnetic environment. For the same methylene group in the 3,5-syn isomers **16** and **17** the two protons show a 1 ppm shift

† Dedicated to Professor A. I. Meyers on the occasion of his 60th birthday.

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(4) All yields refer to isolated, chromatographed, and spectroscopically pure materials.

(5) Elemental analyses were obtained on these compounds.

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(9) The stereochemical assignments of these authors were supported by crystal structure determinations.

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