Stereocontrolled Oxidative Addition of Zerovalent Molybdenum to Enantiomerically Pure Allylic Acetates with Either Inversion or Retention at the Stereogenic Center

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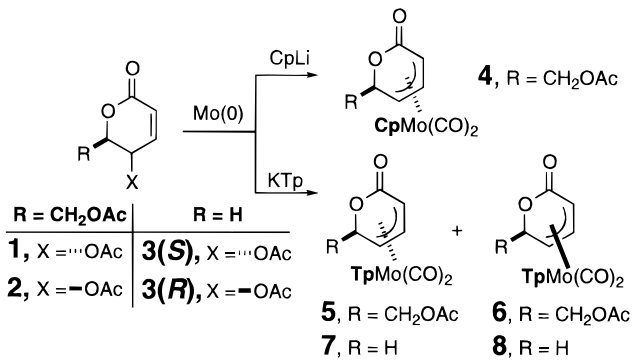
In both the catalytic and stoichiometric manifold, allylic substitutions catalyzed by transition metal complexes have contributed significantly to the library of transformations available to the synthetic organic chemist. Palladium and molybdenum appear prominently in synthetically useful, metal-mediated allylic substitutions, the former in catalytic[2−8] and the latter in both catalytic and stoichiometric modes.[9−24] Essential to the use of these processes in synthesis is control of (1) the stereochemistry of the oxidative addition of the metal to the allylic substrate and (2) the regiochemistry and stereochemistry of the nucleophilic attack. Most palladium-catalyzed reactions of allylic substrates with stabilized enolates proceed with overall retention of configuration, an outcome dictated by an *anti* oxidative addition and an *anti* nucleophilic attack on an η^3-allyl. Though not common, formation of an (η^3-allyl)palladium via *syn* oxidative addition has been demonstrated for allylic substrates bearing various leaving groups ($Ph_2PCH_2CO_2$, Cl, $OCOCF_3$).[25−27] Molybdenum-*catalyzed* allylic alkylations occur with net retention of configuration, suggesting a double-inversion mechanism similar to the palladium case. However, Kočovský and co-workers have very recently offered strong evidence implicating a double-retention pathway[28] which bears upon earlier observations by Trost and co-workers that Mo-

Scheme 1



$(CO)_6$-*catalyzed* substitutions of allylic acetates in toluene occur with overall retention of stereochemistry.[9,10] Oxidative addition with *retention* of stereochemistry has been unambiguously demonstrated in the stoichiometric reaction of $Mo(CO)_3(CH_3CN)_3$ with both acyclic[29] and cyclic[16] allylic acetates.

During a previous study, the enantiomerically pure pyranone **1**, derived from D-glucose,[30] produced the (π-allyl)molybdenum complex **4** with retention of allylic acetate stereochemistry (Scheme 1).[16] Surprisingly, the related allylic acetates **2** and **3(*S*)** derived from D-galactose[31] and D-arabinose,[31] respectively, failed to give analogous π-allyl complexes under standard conditions. However, using a recently described protocol[32] for the preparation of complexes based on the hydridotris(1-pyrazolyl)borate ligand[33,34] (Tp), this limitation was overcome and a practical construction of enantiomerically enriched (π-allyl)molybdenum complexes derived from D-glucose, D-galactose, and D- and L-arabinose was achieved. During these and ancillary studies a delicately balanced yet synthetically useful competition between retention and inversion pathways for the oxidative addition was revealed.

Treatment of the dihydropyranone **1** with 1.0 equiv of $(DMF)_3Mo(CO)_3$[35] in CH_2Cl_2 at room temperature followed by addition of potassium hydridotris(pyrazolyl)borate (K^+Tp^-) provided complex **5** in 91% yield with complete *retention* of configuration. Under identical reaction conditions the diastereomeric dihydropyranone **2** gave in 82% yield a 12:1 mixture of the complexes **5** and **6**, the result of a highly selective *inversion* of configuration. Diastereomer **6** was independently prepared in modest yield by the addition of dihydropyranone **2** to a solution of (toluene)$Mo(CO)_3$[36] in CH_2Cl_2 at 25 °C followed by the addition of K^+Tp^-. Under these conditions, the mode of oxidative addition switched and proceeded with complete *retention* of stereochemistry. The relative stereochemical relationship of the $TpMo(CO)_2$ fragment and the acetoxymethyl group in complexes **5** and **6** was deduced by the conversion of **5** into (2*S*,6*R*)-2-(acetoxymethyl)-6-methyltetrahydropyran[16] (see supporting information).

These observations underscored the ease with which the oxidative addition of zerovalent molybdenum to an allylic acetate can proceed through either a retention or an inversion mechanism in response to the Mo(0) source as well as to steric constraints imposed by the substrate. In that light, conversion of the *sterically unbiased* dihydropyranone **3(*S*)** into its corre-

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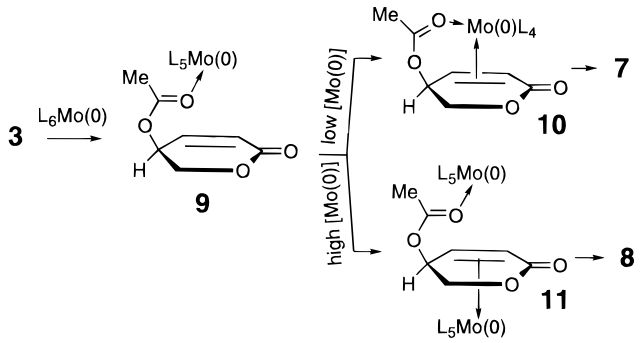
sponding (π-allyl)molybdenum complex proved instructive. Addition of **3(*S*)** to a CH_2Cl_2 solution of $(DMF)_3Mo(CO)_3$ at 22 °C followed 2 h later by the addition of K^+Tp^- provided a 34:66 mixture of enantiomers corresponding to retention product **7** and inversion product **8**, respectively, in 93% isolated yield. The selectivity for the *inversion* enantiomer **8** was improved either by lowering the reaction temperature or by using 2 equiv of $(DMF)_3Mo(CO)_3$. Addition of **3(*S*)** to a CH_2Cl_2 solution of 2 equiv of $(DMF)_3Mo(CO)_3$ at −40 °C followed by the addition of K^+Tp^- provided the *inversion* enantiomer **8** in 57% yield and 84% ee. Dramatically, a simple solvent change from CH_2Cl_2 to THF produced an excess of the *retention* enantiomer **7** (86% yield, 88% ee), which was also obtained in excellent yield and enantiomeric excess (86% yield and 94% ee) by adding a solution of $(DMF)_3Mo(CO)_3$ in CH_2Cl_2 dropwise over a 45 min period to the allylic acetate **3(*S*)** (inverse addition). The enantiopurities were determined by chiral shift reagent analysis of the ^1H NMR spectra using $Eu(hfc)_3$; the assignment of **7** and **8** is described below.

Consistent with the double-retention pathway for molybdenum-*catalyzed* allylic substitutions,[9,10,28] dihydropyranone **3(*S*)** reacted with $Mo(CO)_6$ in refluxing toluene followed by metathesis with K^+Tp^- to produce **7** with high enantiomeric excess (>90%), although the chemical yields were low and variable (18−40%). However, using (toluene)$Mo(CO)_3$[36] in CH_2Cl_2, the oxidative addition proceeded at room temperature and gave the retention product **7** in good isolated yield (60−70%) with excellent ee's (>95%). Unlike reactions with $(DMF)_3Mo(CO)_3$, the enantiomeric excess of the product generated from (toluene)-$Mo(CO)_3$ was not concentration dependent: the addition of 5.8 g of **3(*S*)** to 9.1 g of (toluene)$Mo(CO)_3$ in 30 mL of CH_2Cl_2 gave 10.4 g of **7** in 67% yield and 96% ee. The enantiomer **8** is available from **3(*S*)** and $(DMF)_3Mo(CO)_3$, as described above, in 57% yield and 84% ee, or more conveniently from dihydropyranone **3(*R*)** (prepared from L-arabinose[31]) in 63% yield and 98% ee. The enantiopurities of **7** and **8** were determined by HPLC analysis using a Chiralpak AD column. The absolute stereochemistry of the retention product, **7**, was established through X-ray crystallography[37] and by conversion of **7** through standard functionalization to (2*S*,6*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid methyl ester[38] (see supporting information).

The experiments outlined above suggested that the retention pathway was favored at low effective concentration of $(DMF)_3Mo(CO)_3$ relative to the allylic acetate (dilute solution, ≤1 equiv of Mo(0), slow addition of Mo(0) to allylic acetate), or more simply by the use of (toluene)$Mo(CO)_3$. The inversion pathway predominated at high effective concentration of $(DMF)_3Mo(CO)_3$ relative to the allylic acetate (concentrated solution, >1 equiv of Mo(0), addition of the allylic acetate to Mo(0)) and at low temperature. These observations suggest that the mechanistic pathways leading to the retention and inversion products differ in the order of the metal in the rate-determining steps and are consistent with the rationale shown in Scheme 2.[39] The pathways diverge from the intermediate, **9**, where a 16-electron Mo(0) fragment is coordinated to the allylic acetate leaving group. At low Mo(0) concentration, further ligand loss from the Mo(0) fragment of **9** could lead to the chelated intermediate **10**, which would undergo internal redox providing the retention oxidative addition product. Since

Scheme 2



this path requires facile and multiple ligand dissociation from the Mo(0) species, it should be favored by Mo(0) species capable of low coordination numbers (i.e., loss of toluene from (toluene)-$Mo(CO)_3$). At high Mo(0) concentrations, intermediate **9** could competitively combine with another 16-electron Mo(0) fragment leading to the doubly coordinated species **11**. Steric effects would dictate coordination of the second Mo(0) trans to the allylic acetate group and lead to the inversion oxidative addition product. At low temperature, entropic factors ($T\Delta S$) should increase the concentration of the doubly coordinated species **11** and lead to an increase in the inversion product, as observed.

Through the proper choice of reaction conditions a single enantiomer of the allylic acetates investigated in this study can be transformed by either a retention or inversion process into a (π-allyl)molybdenum complex in good yield and with high enantiopurity. The facility with which the mechanism of oxidative addition changes from retention to inversion clearly suggests that observations of overall retention of stereochemistry in molybdenum-*catalyzed* allylic substitutions of sterically unbiased substrates can be accounted for by either an inversion−inversion or a retention−retention pathway. These results prescribe the use of caution in predicting the stereochemical outcome of molybdenum-catalyzed allylic substitutions. The pyranose-derived (π-allyl)molybdenum complexes described in this study are readily available on large scale in high yield and high enantiopurity from inexpensive materials. The use of these complexes in enantiocontrolled organic synthesis will be described in forthcoming papers.

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Supporting Information Available: Complete description of the synthesis and characterization of all compounds in the manuscript and a listing of bond lengths and angles, non-hydrogen thermal parameters, and hydrogen fixed positional and final thermal parameters for the crystal structure determination of compound **7** (27 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(37) Crystal data for **7**: orange/red prisms (0.22 × 0.33 × 0.41) from CH_2Cl_2 ($C_{16}H_{15}BMoN_6O_4$, FW = 462.09, orthorhombic, $P2_12_12_1$, a = 12.980(4) Å, b = 13.604(3) Å, c = 20.067(5) Å, V = 3544(2) Å^3, λ(Mo Kα) = 0.710 73 Å, D_c = 1.516 g/cm^3, Z = 6, T = 173 K, $F(000)$ = 1624, μ = 6.81 cm^{-1}). Of the 13 418 data (including Friedel pairs) collected, 4336 were considered observed ($F > 4.0\,\sigma(F)$). The structure was solved by Patterson methods and refinement carried out using SHELXTL (1994). The absolute stereochemistry was determined by collecting Friedel pairs and inverting the structure to give the absolute structure parameter of 0.04-(12). Full-matrix least-squares refinement on F^2 resulted in a final R_{index} (observed data) of 5.46%, a goodness of fit of 1.073, and a data-to-parameter ratio of 9:1.

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(39) One referee suggested that dihydropyranones **3(*S*)** and **3(*R*)**, while not *sterically biased*, are *conformationally biased*. A conformational bias would be mechanistically significant only if the more abundant half-chair (pseudoequatorial OAc) and the less abundant half-chair (pseudoaxial OAc) each react selectively under different reaction conditions. To account for the observed oxidative addition stereoselectivities, oxidative addition at low Mo(0) concentration could proceed selectively *syn* to the pseudoaxial allylic acetate, in which case at high effective Mo(0) concentration oxidative addition must proceed *anti* to the pseudoequatorial OAc group, possibly through a molybdenum aggregate.