Communication

-Pyranyl and -Pyridinyl Molybdenum -Complexes as Chiral Scaffolds for the Enantioselective Construction of Substituted Oxa- and Aza[3.3.1]bicyclics: First Enantio- and Regiocontrolled [5+3] Cycloaddition Reactions

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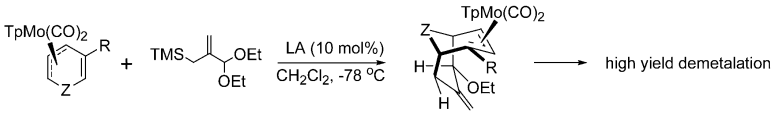

Z = O; Z = NCbz: ylds 77-84%; ee's >98%

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η^3-Pyranyl and η^3-Pyridinyl Molybdenum π-Complexes as Chiral Scaffolds for the Enantioselective Construction of Substituted Oxa- and Aza[3.3.1]bicyclics: First Enantio- and Regiocontrolled [5+3] Cycloaddition Reactions

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Readily accessible transition metal π-complexes of high enantiopurity have emerged as versatile and powerful chiral scaffolds for the construction of substituted carbo- and heterocycles.[1] Particularly useful are strategies based on stereocontrolled cycloadditions to unsaturated transition metal complexes for preparing stereochemically rich and structurally elaborate polycyclic systems.[1,2] Within this context, we have previously demonstrated that molybdenum π-complexes of unsaturated oxygen and nitrogen heterocycles such as **1** and **2** (Figure 1), both antipodes of which are readily available, can function as excellent scaffolds for the rapid assembly of bridged and fused heterocyclic ring systems through [5+2][3] and [4+2][4] cycloaddition reactions. Inspired by the work of Harmata,[5] Cha,[6] and others[7] in the use of oxyallyl cations in [4+3] cycloadditions, we show herein that the oxyallyl cation precursors[8] $Me_3SiCH_2(C{=}CH_2)CH(OEt)_2$, **3**, and 2-(triisopropylsilyloxy)acrolein, **4**, participate efficiently as three-carbon components in novel Lewis acid-catalyzed regio- and enantiocontrolled [5+3] cycloadditions with $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) scaffolds (Tp = hydridotrispyrazolylborate). This strategy leads to the rapid construction of oxa- and aza[3.3.1]-cyclooctenes of high enantiopurity through a new [5+3] cycloaddition.[9]

All molybdenum complexes used in this study are air-stable, yellow to orange solids available in multigram scale by simple benchtop techniques. The racemic and enantiomerically enriched 3-substituted pyranyl (**1b**,**c**)[3a,10] and pyridinyl (**2a**,**b**)[11] molybdenum complexes were easily prepared according to previously established protocols. The racemic unsubstituted complex **1a** and the 2-substituted complex **1d** were prepared in a similar fashion.[12]

Treatment of a CH_2Cl_2 solution of molybdenum complex **1a** and allylic acetal **3** with $Sc(OTf)_3$ (10 mol %, −78 °C to room temperature) provided a 92:8 mixture of the [5+3] and [2+3] cycloadducts, respectively, the former of which was isolated in 78% yield after an easy chromatographic purification (Scheme 1). A very similar result was obtained using 10 mol % Me_3SiOTf as the catalyst.[13]

As depicted in Scheme 1, this [5+3] cycloaddition protocol was efficient and general for all 3-substituted pyranyl and pyridinyl molybdenum complexes investigated.[14] Starting from enantioenriched complexes, cycloadducts of high enantiomeric purity (ee up to 99.5%) were obtained without racemization. In contrast to the typically poor regio- and diastereoselectivity provided by oxyallyl cations in intermolecular [4+3] cycloadditions,[6,8] only one [5+3] cycloadduct was obtained in high yield in each case investigated in this study. The bulky $TpMo(CO)_2$ group caused complete facial diastereoselectivity resulting from attack of the

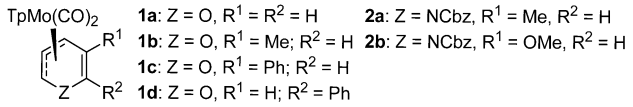
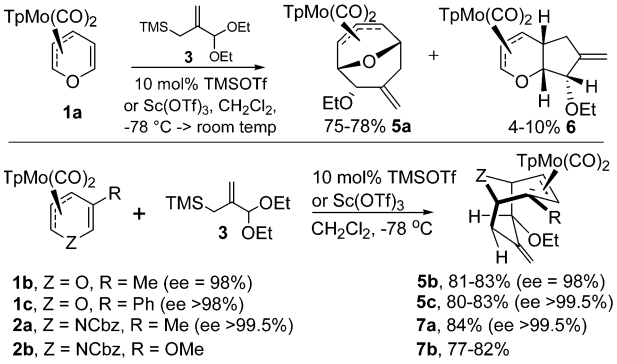


Figure 1. Pyranyl and pyridinyl enantiomeric scaffolds.

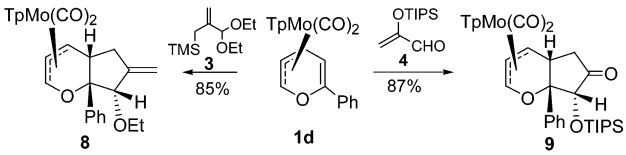
Scheme 1. [5+3] Cycloadditions of **3** to Complexes **1b**,**c** and **2a**,**b**



1b, Z = O, R = Me (ee = 98%)
1c, Z = O, R = Ph (ee >98%)
2a, Z = NCbz, R = Me (ee >99.5%)
2b, Z = NCbz, R = OMe

5b, 81-83% (ee = 98%)
5c, 80-83% (ee >99.5%)
7a, 84% (ee >99.5%)
7b, 77-82%

Scheme 2. [2+3] Cycloadditions of **3** and **4** to Complex **1d**[a]



[a] Conditions: 10 mol % $Sc(OTf)_3$, CH_2Cl_2, −78 °C, 2 h.

oxyallyl cation at the pyranyl or pyridinyl face opposite the molybdenum. In addition, complete endo-selectivity was observed in all cases. The regio- and the stereochemistry of the cycloadducts were unequivocally established by NMR, mainly using COSY and NOESY experiments. X-ray crystallographic analyses of (±)-**5b** and (±)-**7b** confirmed both the regiochemistry and the endo-approach of the oxyallyl cation anti to the molybdenum.

The course of the cycloaddition was sensitive to structural features on the heterocycle scaffold. For example, in contrast to the 3-substituted heterocycle complexes **1b**,**c** and **2a**,**b** that follow a [5+3] pathway, the C-2 substituted heterocycle complex **1d** gave [2+3] cycloadducts, exclusively, upon $Sc(OTf)_3$-catalyzed cycloadditions with both **3** and **4** (Scheme 2). Furthermore, these [2+3] cycloadducts were formed with a regiochemistry opposite to that observed for the [5+3] cycloadducts − the alkoxy group appears adjacent to the 2-phenyl substituent.[15]

A concerted mechanism cannot explain the complete change from a [5+3] to a [2+3] cycloaddition observed for the 3- versus the 2-substituted molybdenum complexes. Rather, the data are consistent with a competition between two different stepwise mechanisms shown in Scheme 3. The noncoordinated double bonds of complexes

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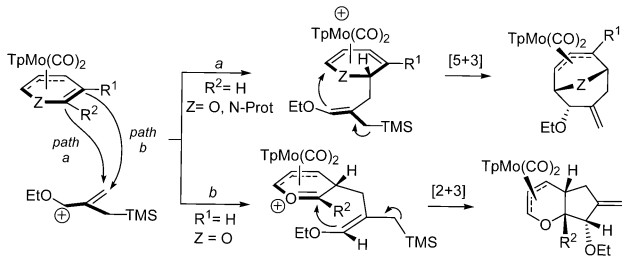
Scheme 3. Proposed Mo- and O-Promoted Stepwise Mechanisms



1 and **2** are made uniquely nucleophilic by the cation stabilizing ability of the adjacent η^3-allyl molybdenum moiety. For the 3-substituted heterocycle complexes, a Mo-promoted, stepwise mechanism (path a) leads to the [5+3] cycloadducts. The observed regio- and stereoselectivity profile is consistent with attack of the nucleophilic double bond anti to the $TpMo(CO)_2$ moiety at the less substituted terminus of the allyl cation. A preferred W configuration for the transient cationic intermediate[16] and minimization of the repulsive dipolar interactions between the C−O and C−Z dipoles might explain the exclusive endo-selectivity. For the 2-substituted complex **1d**, nonbonded steric effects from the phenyl group at C-2 retard the Mo-promoted path a and make more favorable the O-promoted, stepwise mechanism depicted as path b of Scheme 3. As shown above in Scheme 1, the absence of a substituent at C-2 or C-3 leads to a mixture of [5+3] and [2+3] adducts, the former path being favored.

The synthetic potential of these new [5+3] and [2+3] cycloadditions was probed through a variety of functionalization-demetalation protocols, which are shown in Figure 2. Protodemetalation[3a,11a] of **5c** and **7a** with strong acids (concentrated HCl or excess TFA) provided the alkenes **10** and **11**, respectively. While ceric ammonium nitrate (CAN)-mediated oxidative demetalation of the 3-methoxy substituted complex **7b**[3b,c] afforded enone **12**, oxidative decomplexation of the 3-methylated compounds **5b** and **7a** with CAN in the presence of Et_3N[3a] gave trienes **13** and **14**, respectively. Finally, demetalation of **1c** and **9** with pyridinium dichromate (PDC) in the presence of silica gel[17] (CH_2Cl_2, room temperature) allowed the regioselective introduction of a carbonyl group at an allyl terminus, providing the α,β-unsaturated ketone **15** and the lactone **16** in a single step. All three protocols gave products in good yields with functional groups poised for further manipulation.

In summary, the reported Mo-mediated cycloadditions of 3-substituted pyranyl and pyridinyl molybdenum π-complexes represent the first enantiocontrolled [5+3] cycloadditions described to date and provide a new and efficient synthetic approach to oxa- and aza[3.3.1]bicyclics of high enantiomeric purity. The reaction proceeds in good to excellent yields and with complete regio- and endo-selectivities; it diverts to a [2+3] cycloaddition pathway when 2-substituted heterocycle π-complexes are used. This methodology, coupled with a variety of general demetalation protocols, holds much promise in synthetic applications.

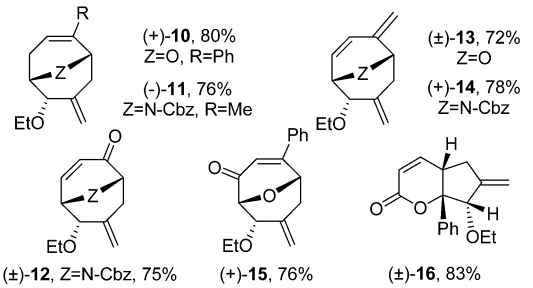


Figure 2. Demetalation products from [5+3] and [2+3] cycloadducts. Enantiomeric excess >99.5% for (+)-**10** and (+)-**15** was determined by HPLC analysis. Similar ee's are presumed for (+)-**14** and (−)-**11**.

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Supporting Information Available: Experimental procedures, characterization data of new compounds, and X-ray crystallography data of (±)-**5b** and (±)-**7b**; copies of ^1H and ^{13}C NMR spectra of all molybdenum complexes and demetalation products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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