Enantiocontrolled [5 + 2] Cycloaddition to η^3-Pyranylmolybdenum π-Complexes. Synthesis of Substituted Oxabicyclo[3.2.1]octenes of High Enantiopurity

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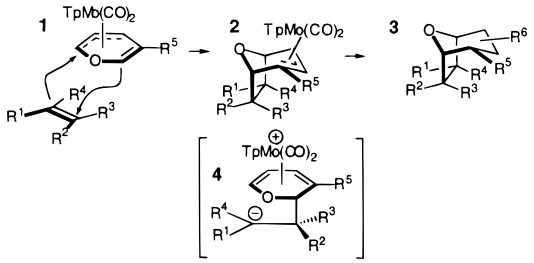
Consider the synthetic potential of *enantiomerically pure*, stoichiometric transition metal π-complexes derived from an inexpensive metal source and from readily available chiral-pool organic substrates. Assume, hypothetically, that either enantiomer of such metal π-complexes could be prepared in quantity by simple synthetic procedures and that these transition metal π-complexes were sufficiently air- and moisture-stable to allow routine handling. Furthermore, assume that a single metal and its spectator ligands could facilitate and direct *multiple and sequential regio- and stereocontrolled transformations at the* π*-ligand* (C−C, C−O, and C−N bond formation, cycloaddition, oxidation, reduction) prior to a deliberate demetalation that would deliver an enantiomerically pure organic molecule. These metal π-complexes would then represent synthetically potent *enantiomerically pure scaffolds* for the asymmetric construction of a large variety of organic molecules.

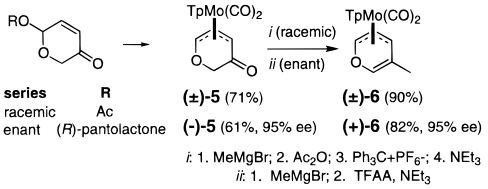
Following these principles, an enantiocontrolled synthesis of oxabicyclo[3.2.1]octanes was conceived (Scheme 1). If 3-substituted pyranyl complexes η^3-bound to a $TpMo(CO)_2$ moiety (Tp = hydridotrispyrazolylborato) could be prepared, a stepwise cycloaddition with electron-deficient alkenes would be anticipated (**1** to **2** through intermediate **4**). After a deliberate demetalation/functionalization sequence, substituted oxabicyclo[3.2.1]octanes would be obtained. If the η^3-pyranylmolybdenum complexes could be prepared in high enantiopurity, then high enantiopurity oxabicyclo[3.2.1]octanes would result. Higher-order cycloadditions to metal complexes are known.[1−4] Harman and Liu have described cycloadditions to η^2-pyrrole[5] and η^1-3-furyl complexes,[6] respectively, and reactions initiated at the noncoordinated double bond of η^3-pentadienyl and η^3-cyclohexadienyl π-complexes are known.[7−9]

The overall concept was validated through a study of the racemic η^3-3-methylpyranylmolybdenum complex (±)-**6** and the corresponding (+)-**6** antipode (97% ee). The former was easily prepared in 64% overall yield on a 12 g scale from 6-acetoxydihydropyran-3-one by way of the 3-oxopyranyl complex (±)-**5**; the latter was generated on a 5 g scale from 6-hydroxy-*2H*-pyran-3(*6H*)-one, which was resolved via the corresponding diastereomeric (*R*)-pantolactone-substituted-*2H*-pyran-3(*6H*)-one (Scheme 2).[10] For the preparation of the enantiomerically enriched sample, the separate diastereomeric pyranones were converted into the corresponding π-allylmolybdenum complexes (−)-**5** (61% yield, 95% ee) and (+)-**5** (54% yield, 95% ee) following a procedure

Scheme 1



Scheme 2. Synthesis of $TpMo(CO)_2$(3-methyl-η-4,5,6-pyranyl)



known to maximize oxidative addition with inversion of configuration.[11] Quite unexpectedly, partial racemization occurred upon conversion of (−)-**5** into the 3-methylpyranylmolybdenum complex (+)-**6**, using the conditions developed for formation of racemic (±)-**6**, shown in Scheme 2. Fortunately, a modified and simpler one-pot procedure (addition of MeMgBr, followed by a trifluoroacetic anhydride/triethylamine quench) gave (+)-**6** (95% ee) from (−)-**5** (95% ee) in very good yield and without loss of enantiopurity. Because (+)-**6** has a pronounced tendency to crystallize as a racemate, its enantiopurity was not improved by standard recrystallization; rather, the enantiopurity was increased to 97−99% ee by discarding a small amount of low ee crystals that first formed upon slow recrystallization. All neutral Mo(II) complexes described in this study are air-stable, yellow to orange solids.

A [5 + 2] cycloaddition reaction did not ensue upon simple mixing of **6** with a variety of alkenes. However, a large number of electron-deficient alkenes and an electron-deficient alkyne efficiently gave cycloadducts with **6** in the presence of $EtAlCl_2$ (Table 1, entries 1−9). For most substrates the cycloaddition reaction was rapid at room temperature in the presence of catalytic quantities of $EtAlCl_2$; however, the less reactive alkenes required larger amounts of $EtAlCl_2$. The enantiocontrolled cycloaddition of (+)-**6** with four different electron-deficient alkenes (*N*-methylmaleimide, cyclohexenone, methyl acrylate, and acrylonitrile) was also studied (Table 1, entries 3−6). Cycloaddition products of high ee were obtained for all alkenes except acrylonitrile, the least reactive of the alkenes studied. Control experiments traced the low ee for this sole alkene to an unexpected slow racemization of (+)-**6** in the presence of $EtAlCl_2$, which was eliminated or significantly minimized for the more reactive alkenes, as long as the alkene was present in greater amount than the Lewis acid. The mechanism of this unusual and unprecedented racemization will be described in detail in a future publication.[12]

X-ray crystallographic analysis of product (+)-*exo*-**7f** confirmed the anticipated overall bond construction with the depicted absolute configuration (and therefore confirmed the absolute configurations of (−)-**5** and (+)-**6**), and demonstrated that the cycloaddition occurred from the face of the η^3-pyranyl ligand opposite the $TpMo(CO)_2$ moiety (see the Supporting Information for details). It also revealed a near 90° dihedral angle between each of the C−H bonds adjacent to the bridging oxygen (H^1 and

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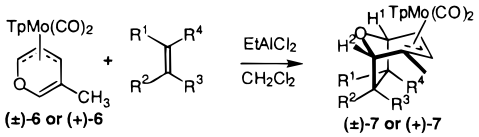
Table 1. [5 + 2] Cycloaddition of η^3-Pyranylmolybdenum Complexes



entry	alkene	cndns[a]	yld, exo:endo	prdt	R^1	R^2	R^3	R^4	%ee[b]
1	CH_2═CHCHO	20%, rt 2.5 h	87%, 10:1	*exo*-**7a**	HCO	H	H	H	
				endo-**7a**	H	H	H	CHO	
2	CH_2═CHCOMe	10%, rt 1.5 h	94%, 8.4:1	*exo*-**7b**	MeCO	H	H	H	
				endo-**7b**	H	H	H	COMe	
3	CH_2═CHCO$_2$Me	20%, rt 5 h	88%, 3.5:1	*exo*-**7c**	MeO$_2$C	H	H	H	95%
				endo-**7c**	H	H	H	CO$_2$Me	95%
4	2-cyclohexenone	20%, rt 4 h	93%, 1:0	*exo*-**7d**	−CO(CH$_2$)$_3$−		H	H	96%
				endo-**7d**	H	H	−(CH$_2$)$_3$CO−		
5	CH_2═CHCN (6 equiv)	120%, rt 4.5 h	57%, 0.64:1	*exo*-**7e**	NC	H	H	H	23%
				endo-**7e**	H	H	H	CN	23%
6	*N*-methylmaleimide	110%, rt 10 min	99%, 8:1	*exo*-**7f**	−CON(Me)CO−		H	H	97%
				endo-**7f**	H	H	−CON(Me)CO−		>90% ee[c]
7	(*E*)-2-PhCHCH(Me)CHO	20%, rt 4 h	91%, 1:1.2	*exo*-**7g**	HCO	Ph	H	Me	
				endo-**7g**	Me	Ph	H	CHO	
8	PhCH═C(CN)$_2$	20%, rt 3 h	96%, 1:0	*exo*-**7h**	NC	Ph	H	CN	
				endo-**7h**	NC	H	Ph	CN	
9	DMAD	110%, rt 10 min	43%, - - - -	**7i**	EtO$_2$C	CO$_2$Et	C−C bond		

[a] Mol % $EtAlCl_2$, temp, time. [b] Enantiomeric excess of product prepared from (+)-**6** of 97% ee. [c] Small amount of impurity precluded an accurate determination of the minor isomer ee. However, recrystallization of *endo*-**7f** gave product in >99% ee.

H^2) and their vicinal neighbors, resulting from the maleimide C−H bonds. This result was in accord with the small coupling constants observed for the two vicinal hydrogen pairs (0 and 0.8 Hz). On the other hand, the isomeric *endo*-**7f** showed much larger vicinal coupling constants (both 6.4 Hz). The exo and endo relationships for the other products shown in Table 1 were readily determined from their ^{1}H NMR spectra by analogy.[6] The regiochemistry of the cycloaddition products followed from their ^{1}H NMR spectra coupling constants and from homo-decoupling NMR experiments, which together allowed determination of the vicinal relationship of H^1 with the hydrogen substituents on the α-carbon of the electron-deficient alkene, and of H^2 with those hydrogen substituents on the alkene β-carbon.

The following facts support the stepwise mechanism presumed in Scheme 1, above. Reaction of (*E*)-2-methylcinnamaldehyde with (±)-**6** gave a 1/1.2 mixture of *exo*-**7g**/*endo*-**7g** with identically configured phenyl groups (R^2 = Ph, R^3 = H for both isomers), but with isomeric configurations at the aldehyde bearing carbon atom. Exposure of pure *endo*-**7g** to $EtAlCl_2$ (0.5 equiv) in CH_2Cl_2 for 12 h reestablished a 1/1.2 mixture of *exo*- and *endo*-**7g** (and formed traces of (±)-**6** and (*E*)-2-methylcinnamaldehyde). These data strongly indicate the initial formation of a Lewis acid-stabilized intermediate **4** (Scheme 1, above) with the bulky substituent (R^2 = phenyl) directed away from the pyranyl ring methyl substituent. Intermediate **4** then undergoes reversible ring closure from either face of the freely rotating carbanion. The existence of **4** is further supported by the formation of a small amount of a product from the reaction of benzylidene malononitrile with **6** (entry 8, Table 1), which results from internal proton transfer rather than ring closure from **4**.

The full synthetic potential of the [5 + 2] cycloaddition was realized through three general demetalation protocols, which are depicted in Figure 1 and described in the Supporting Information. Protodemetalation with strong acids (concentrated HCl or excess TFA) provided as the major product, **8**, the alkene resulting from protonation at Mo and reductive elimination to the more substituted terminal carbon of the π-allyl (alkene isomer ratios for **8**/**8′** varied from 8.1/1 to greater than 25/1). Iododemetalation proceeded in good yield in the presence of excess I_2 and gave

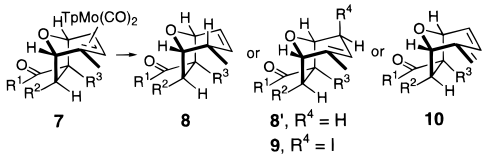


Figure 1.

the allylic iodide product **9** possessing the most substituted double bond. Finally, oxidative demetalation with ceric ammonium nitrate (CAN) in the presence of a base gave dienes **10** as products. All three protocols gave products in good to excellent yields with functional groups poised for further manipulation, if desired. To confirm the value of the enantiocontrolled cycloaddition in asymmetric synthesis, product (+)-*exo*-**7f** of 97% ee was demetalated using the three protocols mentioned above, and gave **8f**, **9f**, and **10f**, each in 97% ee. Confirmation of the relative and absolute stereochemistry shown for compound **8f** was obtained through X-ray crystallography (see Supporting Information for details).

In conclusion, a novel transition metal-mediated [5 + 2] cycloaddition reaction is reported. The reactions proceed in good to excellent yields and give products with high enantiomeric excesses, complete regioselectivities, and moderate to excellent exo/endo selectivities. A stepwise mechanism for the cycloaddition reaction was established, and three general demetalation protocols were developed to furnish a large variety of substituted oxabicyclo[3.2.1]octene rings. Since the nucleophilic addition of different Grignard or lithium reagent to **5** allows replacement of the 3-methyl group on the pyranyl ring with different substituents, it can be anticipated that a large number of substituted oxabicyclo-[3.2.1]octene ring systems can be synthesized in high enantiomeric enrichment from a common precursor, **5**. Recent experiments also confirm the use of the same cycloaddition concept for the preparation of substituted tropane derivatives. These studies will be reported in due course.

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Supporting Information Available: A complete description of the synthesis and characterization of all compounds prepared in this study and X-ray crystallographic studies of (+)-*exo*-**7f** and (+)-**8f** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) η^3 to η^1 slippage of the $TpMo(CO)_2$ fragment to the carbon atom adjacent to the pyran ring oxygen would allow reversible opening of the pyran ring to an achiral $TpMo(CO)_2$ carbene complex by molybdenum-induced cleavage of the carbon−oxygen bond (cf.: Butters, C.; Carr, N.; Deeth, R. J.; Green, M.; Green, S. M.; Mahon, M. F. *J. Chem. Soc., Dalton Trans.* **1996**, 2299.