(η^3-Pyranyl)TpMo(CO)$_2$ Complexes as Chiral Scaffolds for the Enantiocontrolled Construction of 2,3,6-Trisubstituted Dihydropyrans (Tp = Trispyrazolylborate)

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TpMo(CO)$_2$(3-oxopyranyl), **1**, is a potent chiral synthetic scaffold (Figure 1). As described previously, conversion of **1** into the η^3-pyranylmolybdenum complex **2** sets the stage for an efficient and enantiocontrolled [5 + 2] cycloaddition leading to oxabicyclo[3.2.1]octenes of high enantiopurity.[1] Herein is demonstrated a second example of the synthetic power of chiral scaffold **1**—the efficient and enantiocontrolled construction of 2,3,6-trisubstituted dihydropyrans proceeding through a novel, stepwise functionalization of **2**. 2,3,6-Trisubstituted dihydropyran rings are found in a large number of important natural products.[2] Despite the many efforts directed toward the synthesis of dihydropyrans, very few *general* methods to synthesize 2,3,6-trisubstituted derivatives are known.[3]

Racemic 3-oxopyranyl complex **(±)-1** is easily prepared on large scale from 6-acetoxydihydropyran-3-one, and the separate antipodes of **1** are readily available in multigram quantity and high ee[1] from the easily resolved diastereomeric (*R*)-pantolactone-substituted-*2H*-pyran-3(*6H*)-ones.[4] Regiocontrolled functionalization of **1** began with the high yield conversion of the (+)-antipode into the η^3-pyranyl complexes **(−)-2a,b** by the addition of a Grignard reagent (MeMgBr: −78 to 0 °C; PhMgBr: −40 to 0 °C) to the carbonyl group of **1** (Scheme 1). A direct quench of the MeMgBr reaction mixture with trifluoroacetic anhydride/triethylamine gave **2a** in 82% overall yield and 95% ee (from a 95% ee sample of **(+)-1**). For the PhMgBr system, it proved expeditious to isolate the 3° alcohol resulting from addition of the Grignard to **1** (83% yield) and then treat it with trifluoroacetic anhydride/triethylamine to produce **2b** in 90% yield and 97% ee (from a 97% ee sample of **(+)-1**).

Treatment of **(±)-2a** with Br_2 at −78 °C generated a reactive, uncharacterized dibromo adduct. Addition of 2.5 equiv of MeMgBr to dibromo-**2a** produced a quantitative yield of 2,3,6-trimethyl-dihydropyranylmolybdenum complex **(±)-3**. Extending this chemistry to the sequential and selective addition of two different Grignard reagents was not successful. However, treatment of **2a** and **2b** with 1.1 equiv of Br_2 at −78 °C followed by a methoxide quench (40% NaOMe in MeOH) gave the stable and isolable 3-substituted-2,6-dimethoxydihydropyranylmolybdenum complexes **4a** and **4b** in high yield (98 and 94%, respectively). These compounds proved to be excellent precursors to a variety of trisubstituted pyrans, which can be generated in high enantiopurity.

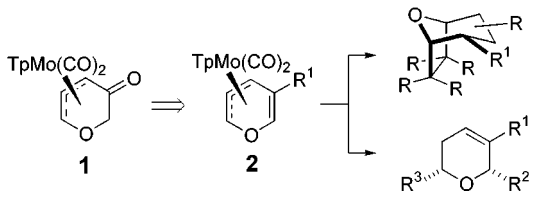
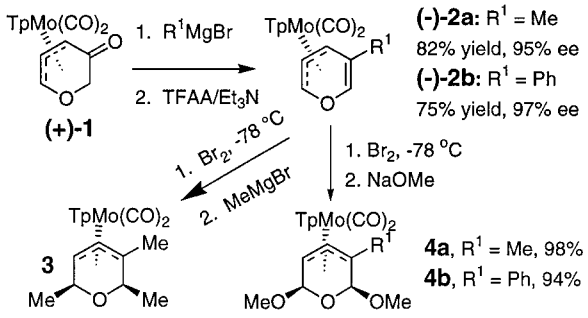


Figure 1.

Scheme 1. Activation of **1** for Sequential Functionalization



Racemic and chiral non-racemic variants of the 2,6-dimethoxy-3-substituted pyranylmolybdenum complexes **4a,b** were useful for the controlled, stepwise introduction of substituents to the pyran ring (Table 1). Unusually selective abstraction of the methoxy group adjacent to the 3-substituent of **4a** (>84 to 1) and **4b** (100:0) was achieved upon addition of 1.0 equiv of Ph_3CPF_6 to a solution of **4a** or **4b** in dichloromethane at −78 °C then warming to 0 °C over 5 min. The resulting cationic dienes **5a,b** were precipitated with methyl *tert*-butyl ether (MTBE), washed, and redissolved in THF prior to subsequent functionalization. Cationic diene complex **5a** (R^1 = Me) rapidly decomposed upon isolation, so it was made and freshly used every time.

The very high selectivity for abstraction of the 2-methoxy group of complexes **4a/b** might be a function of ground-state energy steric acceleration of abstraction of the more hindered leaving group. It can also be rationalized using the frontier molecular orbital arguments proposed earlier by Eisenstein, Butler, and Pearson[5] to explain selective formation of cyclohexadienyliron complexes by hydride abstraction. Compared to abstraction of the 6-methoxy group, abstraction of the 2-methoxy group leads to a diene ligand whose HOMO/LUMO orbital pair provides a stronger bonding interaction with the complementary LUMO/HOMO d-orbitals of the metal.[6] These interactions are presumably reflected in the transition structures for methoxy abstraction.

The cationic dienes **5a,b** were treated with R^2M to give intermediates **6**. Complexes **6** were sensitive to work up and purification, and were either used directly for the next step, or were only subjected to a brief work up to remove inorganic salts and volatile byproducts. Nevertheless, intermediate **6i** (R^2 = Et) was fully characterized. Methoxy abstraction from **6** was accomplished with HBF_4, which, unlike Ph_3CPF_6, could be used in an excess amount with THF or dichloromethane and MTBE as solvents and be readily removed after reaction. Subsequent treatment of the cationic dienes derived from **6** with nucleophiles R^3M led to 2,3,6-trisubstituted complexes **7**, which were obtained in moderate to high overall yields in four simple steps. Therefore, using the sequential methoxy abstraction protocol, a large variety of different functional groups can be introduced in a controlled fashion at the 2- and 6-positions of either **4a** or **4b** (Table 1).

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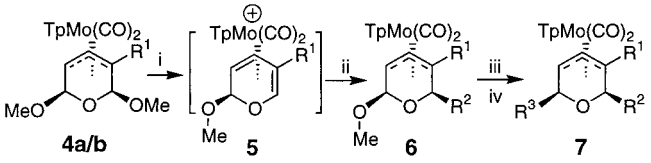
Table 1. Regio- and Stereocontrolled Synthesis of 2,3,6-Trisubstituted Pyranylmolybdenum Complexes[a]



i. Ph_3CPF_6 (1.00 equiv), -78 °C to 0 °C, CH_2Cl_2; ii. R^2M, THF, -78 °C, 15 min iii. HBF_4, (THF)-MTBE, 0 °C, 5 min; iv. R^3M, -78 °C, THF.

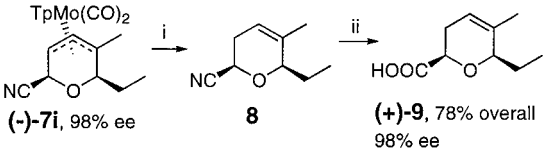
Entry	4	R^2M, R^3M	7, Yld(%),[b] ee(%)
1[c]	4a	MeMgBr, EtMgBr	7a, 82, --
2[c]	"	MeMgBr, VinylMgBr	7b, 70, 98[e]
3[c]	"	VinylMgBr, MeMgBr	7c, 74, --
4[d]	"	PhMgBr, VinylMgBr	7d, 73, --
5[d]	"	MeO_2CCH_2Li, PhMgBr	7e, 72, --
6[d]	"	PhC≡CLi, $PhCOCH_2Li$	7f, 37, --
7[d]	"	PhC≡CLi, $MeOOCCH_2Li$	7g, 43, --
8[d]	"	PhC≡CLi, MeMgBr	7h, 80, --
9[d]	"	EtMgBr, $N{\equiv}CNBu_4$	7i, 85, 98[f]
10[d]	"	EtMgBr, *sec*-ButylMgCl	7j, 90, --
11[d]	"	$MeOOCCH_2Li$, $PhCOCH_2Li$	7k, 65, --
12[d]	4b	EtMgBr, VinylMgBr	7l, 63, 97[g]
13[d]	"	VinylMgBr, EtMgBr	7m, 63, --

[a] For enolates, 3.0 equiv were used; for others, 1.1−1.5 equiv were used; [b] Overall yield from **4a/b**; [c] Method A: **6** was used directly for the next step without isolation; [d] Method B: the reaction mixture of **6** was passed through a pad of silica gel (treated with 5% Et_3N/hexane) with ether, concentrated, and used for the next step; [e] Starting from **4a** that was synthesized from **(+)-2a** in 98% ee; [f] Starting from **4a** that was synthesized from **(−)-2a** of 98% ee. [g] Starting from **4b** that was synthesized from **(−)-2b** of 97% ee.

The generality of this method is demonstrated by the wide range of functional groups introduced using these highly selective methoxy abstractions with Ph_3CPF_6 or HBF_4, and the high yield additions of readily available nucleophiles such as Grignard reagents, lithium reagents, enolates, and cyanide. More importantly, **(+)-2a** led to **(+)-7b** in 98% ee (>99.9% ee after one recrystallization), and **(−)-2a** gave **(−)-7i** in 98% ee (>99.9% ee after one recrystallization), and **(+)-2b** led to **(−)-7l** in 97% ee (entries 2, 9, 12).

Various stereo- and regiocontrolled demetalations of $TpMo(CO)_2$(allyl) complexes have been described elsewhere.[1−7] Therefore, this general and efficient enantiocontrolled synthesis of 2,3,6-trisubstituted hydropyranyl molybdenum complexes should provide 2,3,6-trisubstituted hydropyrans of high enantiopurity upon demetalation. The potential of this current methodology was demonstrated by the synthesis of **(+)-9**, a key intermediate that was used in the total synthesis of natural (+)-ambruticin by Kende et al. (Scheme 2).[8] A 10 mM solution of pyranylmolybdenum complex **(−)-7i** (98% ee) and 2.0 equiv of HOAc in CH_2Cl_2 was irradiated and gave the protodemetalation product **8** in 78% yield (8% of the less substituted alkene protodemetalation product was also formed, but not separated).[9] Hydrolysis of the cyano group of **8** gave **(+)-9** in 78% yield over two steps in 98% ee. Its spectroscopic data are consistent with those reported in the literature ($[\alpha]_D$ = +168 °, *c* 0.18 EtOH, 98% ee; lit. $[\alpha]_D$ = +169.4 °, *c* 0.85 EtOH, >98% ee).

Scheme 2. Enantiospecific Synthesis of the Ambruticin Intermediate, **(+)-9**



i. HOAc (2.0 equiv), hv, CH_2Cl_2, 10 mM, 24 h, 78%.

ii. 30% H_2O_2, 3 N NaOH, EtOH, 60 °C, 2 d, 100%.

Although some chiral, non-racemic η^3-pyranylmolybdenum complexes exhibit racemization,[1] no racemization was observed for those complexes studied herein. Racemization was previously explained via an η^3-to-η^1 slippage of the η^3-pyranylmolybdenum followed by Lewis acid induced or thermal opening of the η^1-2H-pyran complex.[1] Although a firm understanding of the process is not yet in hand, the ease of racemization appears to be a function of the substitution pattern on the pyranyl complex, which affects the ease with which η^3-to-η^1 slippage and subsequent η^1-2H-pyran complex ring opening can occur.

In conclusion, a novel method for elaboration of 2,3,6-trisubstituted dihydropyrans from chiral, non-racemic $TpMo(CO)_2$-(3-oxopyranyl) complexes has been disclosed. The latter functions as a chiral scaffold, and could be amenable to diversity-based synthesis if practical extensions to solid-state chemistry can be developed.

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Supporting Information Available: A complete description of the synthesis and characterization of all compounds prepared in this study (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The first general description of synthetically useful transformations of $TpMo(CO)_2(\eta^3$-allyl) and $TpMo(CO)_2(\eta^4$-diene) complexes is documented within the Supporting Information for Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 897−898; Pearson, A. J.; Douglas, A. R. *Organometallics* **1998**, *17*, 1446−1448; Moretto, A.; Liebeskind, L. S. *J. Org. Chem.* **2000**, in press.

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(9) Treatment of a dilute solution of complexes **7** in CH_3CN with 10 equiv of conc HCl produces the less substituted protodemetalation product with delivery of the proton from the $TpMo(CO)_2$ face, while irradiation in CH_2Cl_2 with 1.1 equiv of HOAc produces the more substituted protodemetalation product. Details will be provided in a future publication.