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Practical, Scalable, High-Throughput Approaches to η^3-Pyranyl and η^3-Pyridinyl Organometallic Enantiomeric Scaffolds Using the Achmatowicz Reaction

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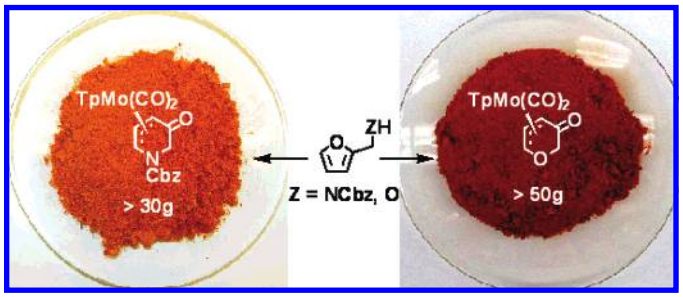

A unified strategy for the high-throughput synthesis of multigram quantities of the η^3-oxopyranyl- and η^3-oxopyridinylmolybdenum complexes $TpMo(CO)_2$(η^3-oxopyranyl) and $TpMo(CO)_2$(η^3-oxopyridinyl) is described (Tp = hydridotrispyrazolylborato). The strategy uses the oxa- and aza-Achmatowicz reaction for the preparation of these organometallic enantiomeric scaffolds, in both racemic and high enantiopurity versions.

Introduction

One of the major challenges in contemporary organic chemistry is the design and execution of concise approaches to complex molecular targets; enantiocontrolled bond construction represents a key element of this challenge. Three fundamentally different methodologies have been widely used to address the requirement for control of absolute stereochemistry: (1) syntheses that use materials originating from the "chiral pool" as "chirons",[1−3] as auxiliaries,[4,5] or for classical resolutions, (2) enzymatic transformations,[6−8] and (3) metallo-[9] or organocatalytic[10−12] asymmetric transformations. In recent decades *catalytic* approaches to enantiocontrolled bond construction have dominated the literature of new synthetic methods because of the promise of "atom economy"[13−15] and environmental sustainability.[16,17]

Enantiomeric scaffolding provides an alternative strategic and structured approach to enantiocontrolled bond construction in complex organic systems. In the scaffolding strategy, a conceptually simple core molecule of high enantiopurity that bears tactically versatile functionality is constructed. The resident functionality enables the general elaboration of the core molecule

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in ways that allow access to diverse families of important molecules. The principal examples of *organic* enantiomeric scaffolding for the enantiocontrolled synthesis of complex molecules have come from the laboratories of Comins,[18−24] Marazano,[25−29] Husson/Royer,[30−34] and Bosch,[35−44] among others (Figure 1).[45,46]

Although less well-studied, *organometallic enantiomeric scaffolding* represents another approach to enantiocontrolled synthesis.[47] Organometallic enantiomeric scaffolds are simple, readily available, *single enantiomers* of air-stable organometallic π-complexes of key unsaturated ligands from which *diverse families* of important molecular structures can be obtained in high enantiopurity. The metal and its auxiliary ligands provide a dominant regio- and stereocontrol element on the scaffold that allows the predictable introduction of new stereocenters, and that influences novel and strategic reaction pathways that are not achievable with traditional organic systems.

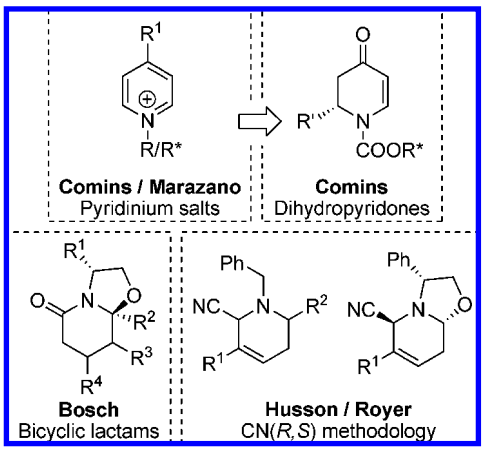

FIGURE 1. Enantiomeric scaffolds.

Organometallic enantiomeric scaffolds can be viable partners in the multistep enantiocontrolled construction of complex molecules that bear multiple stereocenters if (1) single enantiomers of the air and moisture-stable, easily handled metal complexes are readily prepared in high yield and on large scale from readily available precursors, (2) the complexation, subsequent functionalization reactions, and demetalation occur in a predictable way with maintenance of stereochemical integrity, and (3) the stoichiometric nature of the chemistry is mitigated by the use of a single metal moiety over multiple steps to impart novel reactivity and selectivity to the scaffold while, at the same time, controlling the introduction of multiple stereocenters at multiple sites around the unsaturated ligand.

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(47) In contrast to the little studied use of metal complexes as organometallic enantiomeric scaffolds, organometallic π-complexes for *non-scaffolding* approaches to stereocontrolled organic synthesis have been broadly investigated (Paley, R. S. *Chem. Rev.* **2002**, *102*, 1493−1524. Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917−2940). Many groups have been involved in the use of metal π-complexes in stereocontrolled organic synthesis dating back to the 1960's. Some of the seminal contributors are Faller (Faller, J. W.; Rosan, A. M. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 186−91), Semmelhack (Semmelhack, M. F. *Pure Appl. Chem.* **1981**, *53*, 2379−2388. Semmelhack, M. F. *J. Organomet. Chem. Libr.* **1976**, *1*, 361−395), Pearson (Pearson, A. J.; Mesaros, E. F. *Org. Lett.* **2002**, *4*, 2001−2004. Pearson, A. J.; Mesaros, E. F. *Org. Lett.* **2001**, *3*, 2665−2668. Pearson, A. J.; Neagu, I. B. *J. Org. Chem.* **1999**, *64*, 2890−2896. Pearson, A. J.; Douglas, A. R. *Organometallics* **1998**, *17*, 1446−1448. Pearson, A. J.; Neagu, I. B.; Pinkerton, A. A.; Kirschbaum, K.; Hardie, M. J. *Organometallics* **1997**, *16*, 4346−4354. Pearson, A. J. Recent Developments in the Synthetic Applications of Organoiron and Organomolybdenum Chemistry. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. I, p 1), Uemura (Uemura, M. *Top. Organomet. Chem.* **2004**, *7*, 129−156), Jaouen (Jaouen, G. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 59−78), and Stephenson (Stephenson, G. R.; Finch, H.; Owen, D. A.; Swanson, S. *Tetrahedron* **1993**, *49*, 5649−5662). More recent efforts with a focus on "dearomatization" reactions of arenes and heteroarenes have been described by Harman (Harman, W. D. *Top. Organomet. Chem.* **2004**, *7*, 95−127) and Kündig (Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917−2940. Kündig, E. P. *Pure Appl. Chem.* **1985**, *57*, 1855−1864), while Liu (Li, C.-L.; Liu, R.-S. *Chem. Rev.* **2000**, *100*, 3127−3162), Grée (Lellouche, J. P.; Gigou-Barbedette, A.; Grée, R. *Bull. Soc. Chim. Fr.* **1993**, *129*, 605−624), and Donaldson (Donaldson, W. A.; Shang, L.; Rogers, R. D. *Organometallics* **1994**, *13*, 6−7. Tao, C. L.; Donaldson, W. A. *J. Org. Chem.* **1993**, *58*, 2134−2143. Donaldson, W. A.; Jin, M. J. *Tetrahedron* **1993**, *49*, 8787−8794) have investigated lateral stereocontrol in metal complex-based synthesis.

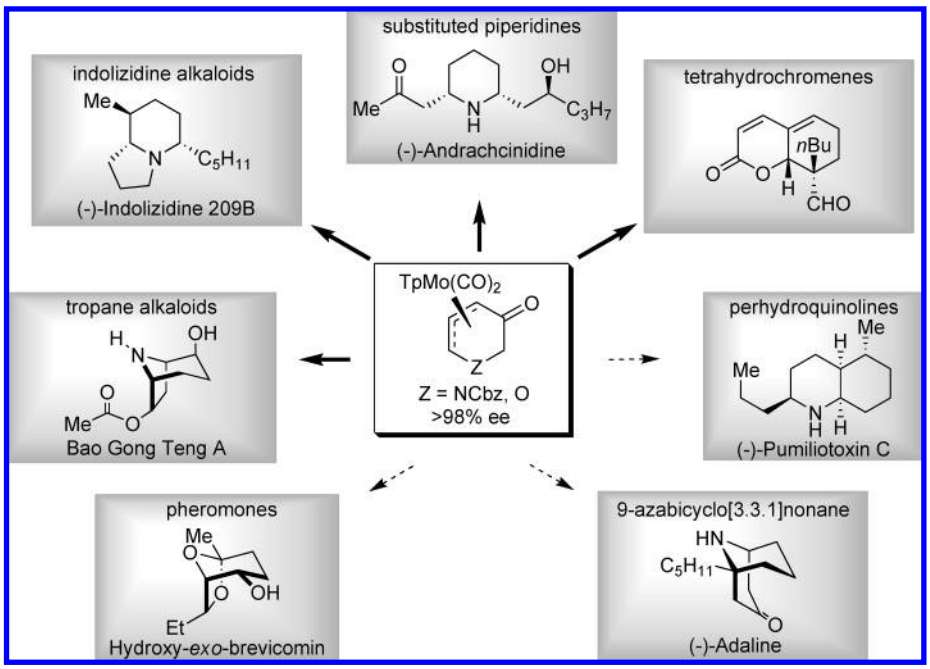
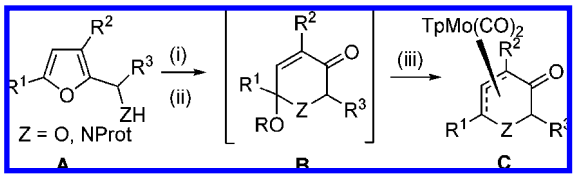


FIGURE 2. Organometallic enantiomeric scaffolding. Dashed arrows represent currently unpublished work.

High enantiopurity $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) complexes have proven to be versatile organometallic enantiomeric scaffolds.[48−66] Taking advantage of novel trends in reactivity and selectivity, single enantiomers of these air- and moisture-stable pyranyl and pyridinyl organometallic scaffolds have been used in the enantiocontrolled construction of a diverse set of heterocyclic organic systems exemplified in Figure 2. Of strategic interest in organic synthesis, the principles of organometallic enantiomeric scaffolding allow the development of parallel reaction profiles applicable to *both* pyran- and piperidine-derived systems, an option not available with traditional organic enantiomeric scaffolds.

SCHEME 1. Generalized Achmatowicz-Based Scaffold Synthesis[a]



[a] Reagents: (i) *m*-CPBA, CH_2Cl_2; (ii) Ac_2O, Et_3N, cat. DMAP; (iii) $Mo(CO)_3(DMF)_3$ then KTp.

The practical utility of these molybdenum-based scaffolds in organic synthesis warrants their simple construction on multigram scale. Herein we report a unified stategy for the practical, scalable, and high-throughput synthesis of both $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) organometallic enantiomeric complexes that is based on the oxo-[67] and aza-Achmatowicz[68−71] oxidative rearrangements. Scheme 1 highlights the generic reaction sequence whereby furfuryl alcohols and *N*-protected furfuryl amines **A** are oxidatively rearranged to hydroxypyranones and hydroxypyridinones **B**, respectively. These intermediates undergo oxidative addition to $Mo(DMF)_3(CO)_3$, either after or without acetylation of the allylic alcohol. Subsequent ligand exchange with potassium tris(pyrazolyl)-

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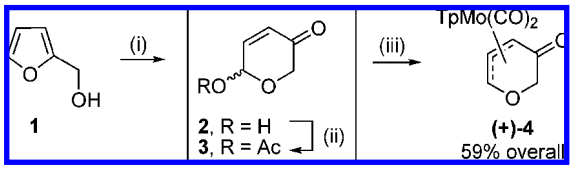
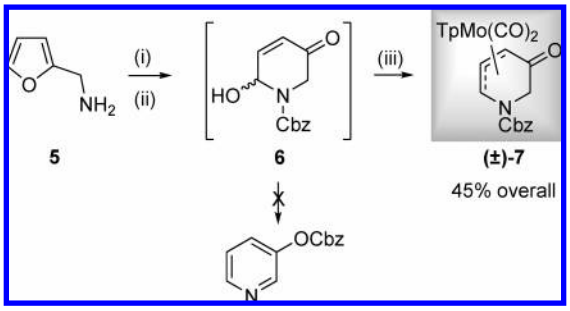
SCHEME 2. Synthesis of Racemic Oxopyranyl Scaffold[a]



[a] Reagents: (i) *m*-CPBA, CH_2Cl_2; (ii) Ac_2O, Et_3N, cat. DMAP; (iii) $Mo(CO)_3(DMF)_3$ then KTp.

SCHEME 3. Synthesis of the Racemic Oxopyridinyl Scaffold[a]



[a] Reagents: (i) NaOH, CbzCl; (ii) *m*-CPBA, CH_2Cl_2; (iii) $Mo(CO)_3(DMF)_3$ then KTp.

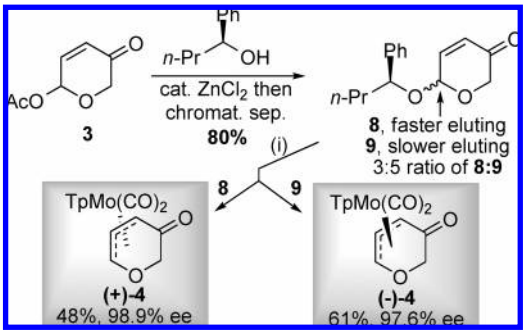
borohydride (KTp) provides the air-stable and easily handled $TpMo(CO)_2$-based 5-oxopyranyl and pyridinyl complexes **C**.

Results and Discussion

The Racemic Series Scaffolds. (a) The Oxopyranyl Scaffold. The racemic parent oxopyranyl scaffold **4** is prepared from furfuryl alcohol **1** by using a simple three-operation sequence (Scheme 2): (1) Achmatowicz reaction, (2) acetylation of the hydroxypyranone **2** to give **3**, and (3) one-pot transformation of the acetoxypyranone directly into the oxopyranyl scaffold **4**. The synthesis of (±)-**4** was described previously by using this reaction sequence, but as a three-pot transformation that required isolation and purification of intermediates.[60] In this improved version the sequence has been streamlined to permit the high-throughput preparation of racemic oxopyranyl scaffold without chromatographic purification of intermediates (i.e., 18 g of product generated with 500 mL glassware). The reaction sequence proceeds in good yield over the three operations (59%) and *requires only one aqueous wash, and only one chromatographic separation of the final product*. Attempts to shorten the reaction sequence further by direct metalation of the 6-hydroxypyranone **2** led to lower yields of the scaffold.

(b) The Oxopyridinyl Scaffold. A similar Achmatowicz approach can be used to generate the analogous racemic oxopyridinyl scaffold (±)-**7** (Scheme 3). This scaffold can be trivially prepared in only three steps from furfuryl amine **5**: (1) *N*-protection as the Cbz urethane and (2) treatment with *m*-CPBA followed by metalation with $Mo(DMF)_3(CO)_3$ and KTp. This sequence can be conducted without rigorous purification of intermediates and reproducibly provides 45% isolated yields of oxopyridinyl scaffold (±)-**7**. The key difference between the oxa- and the aza-Achmatowicz-based scaffold preparations is the direct use of the non-acetylated aza-Achmatowicz rearrangement product **6** in the oxidation addition to $Mo(DMF)_3(CO)_3$. This tactic was taken because of the tendency of the aza-Achmatowicz intermediates to rearrange to the corresponding aromatic pyridines[72−76] by transfer of the protecting group from N to O.[77] In practice, the reaction mixture

SCHEME 4. Four-Step Synthesis of Chiral, Nonracemic Oxopyranyl Scaffolds



[a] Reagents: (i) $Mo(CO)_3(DMF)_3$ then KTp.

containing the aza-Achmatowicz rearrangement product is filtered, washed, and degassed before solid $Mo(DMF)_3(CO)_3$ is added. After ligand exchange with KTp, chromatographic purification delivers the pyridinyl scaffold (±)-**7**.

The Chiral, Nonracemic Series Scaffolds. (a) The Oxopyranyl Scaffold. Both antipodes of the chiral, nonracemic oxopyranyl scaffold **4** can be accessed from racemic 6-acetoxypyranone **3** by $ZnCl_2$-mediated diastereomer formation and separation with commercially available chiral, nonracemic alcohols. In a previous report we demonstrated that diastereomerically pure (*R*)-pantolactone-derived pyranones underwent oxidative addition to $Mo(CO)_3(DMF)_3$, predominantly with inversion of configuration.[60] In the present study the use of (*S*)-1-phenylbutanol produced diastereomeric 6-alkoxypyranones **8** and **9** that consistently and reproducibly provided the oxopyranyl scaffolds in higher enantiopurities (before recrystallization) compared to the previous method with pantolactone (Scheme 4). The use of the benzyl alcohol-derived chiral auxiliary probably minimizes the coordination-induced *retention* pathway that leads to lower enantioselectivities, as is observed with the pantolactone-derived pyranone.[62] Thus, both antipodes of oxopyranyl scaffold **4** are available in high enantiopurity in four operations from commercially available furfuryl alcohol.

The stereochemistry at the acetal carbon of the 6-alkoxypyranones **8** and **9** is not known. However, the fast eluting diastereomer **8** provides (+)-**4** while the slower eluting diastereomer **9** leads to the antipodal scaffold, (−)-**4**. The absolute configurations shown for (+)-**4** and (−)-**4** are deduced from earlier studies utilizing X-ray crystallographic analysis and Flack parameters.[60]

(b) The Oxopyridinyl Scaffold. To access the chiral, nonracemic oxopyridinyl scaffold **12**, furfuryl amine was

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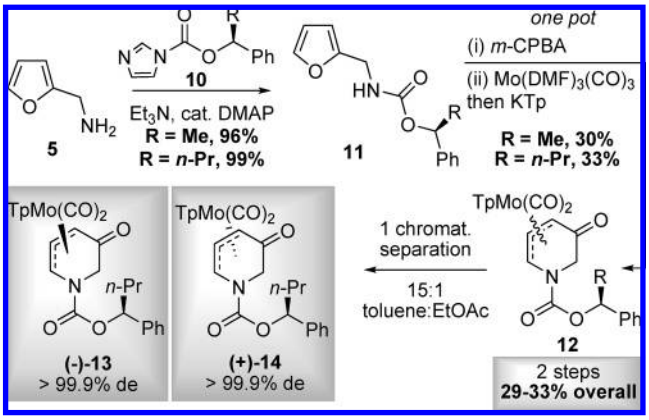
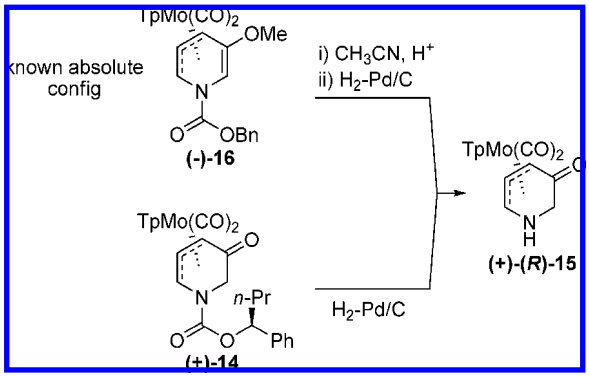
(76) Curtis, N. R.; Ball, R. G.; Kulagowski, J. J. *Tetrahedron Lett.* **2006**, *47*, 2635−2638.
(77) This undesired aromatization can be suppressed by using an electron-withdrawing *p*-toluenesulfonyl nitrogen protecting group and by exchanging the anomeric hydroxyl group for an isopropyloxy group, according to Speckamp's protocol (Hopman, J. C. P.; van den Berg, E.; Ollero, L. O.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1995**, *36*, 4315−4318). This intermediate can be metalated under standard conditions {$Mo(CO)_3$-$(DMF)_3$ then KTP} in 44% yield. Unfortunately, all attempts to remove the sulfonamide protecting group from the 5-oxopyridinyl metal complex led only to decomposition.

SCHEME 5. Two-Step Synthesis of Chiral, Nonracemic Oxopyridinyl Scaffolds



SCHEME 6. Correlation of Absolute Stereochemistry



N-protected as a $-CO_2CH(R)Ph$ urethane **11** by using the imidazolyl urethane **10**, which was derived from commercially available (*S*)-1-phenylethanol (R = Me) or (*S*)-1-phenylbutanol (R = *n*-Pr). Sequential treatment of these *N*-protected furfuryl amines in one pot without purification of intermediates with *m*-CPBA followed by metalation with $Mo(DMF)_3(CO)_3$ and KTp reproducibly provided 36−39% isolated yields of a diastereomeric mixture of *N*-protected oxopyridinyl scaffold **12** (Scheme 5). The oxopyridinyl π-facial enantiomers (−)-**13** and (+)-**14** were then easily obtained in excellent stereochemical purity on large scale by simple chromatographic separation of diastereomers on silica gel eluting with 15:1 toluene/EtOAc. Oxopyridinyl scaffolds bearing NCbz and $NCO_2CH(R)Ph$ (R = Me, *n*-Pr) urethane protecting groups display identical reaction profiles in all synthetic manipulations explored to date, thus allowing the chiral nonracemic urethanes to be retained and used as simple Cbz equivalents.

Absolute configurations of the pyridinyl metal complexes depicted in Scheme 5 were determined by preparing the free amine (+)-**15**, of known absolute configuration, from the η^3-pyridinyl complex **16**[78] by hydrolysis and hydrogenolytic removal of the Cbz protecting group (Scheme 6). The same free-base oxopyridinyl complex of identical optical rotation was obtained upon hydrogenolytic removal of the $-CO_2CH(n\text{-Pr})$-Ph urethane protecting group from (+)-**14** thus allowing assignment of the absolute stereochemistries depicted in Scheme 5.

(78) Wong, H. Design, Synthesis and Resolution of a Chiral, Non-racemic Organometallic Chiron: Asymmetric Total Syntheses of Tetrahydropyridine-based Alkaloids. Ph.D. Dissertation, Emory University, Atlanta, 2006.

SCHEME 7. Unanticipated Racemization

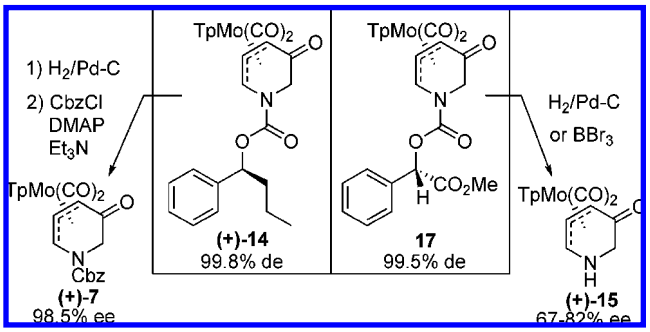
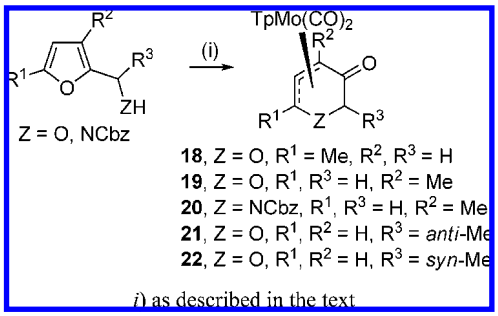


TABLE 1. Other Substitution Patterns

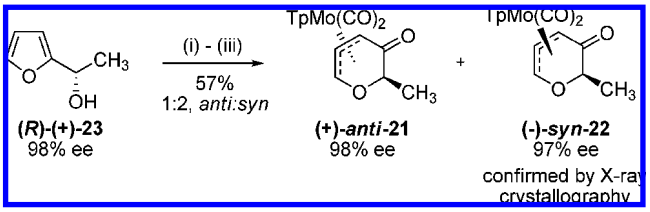


entry	Z	R^1	R^2	R^3	% overall yield
1	O	CH_3	H	H	32
2	O	H	CH_3	H	41
3	NCbz	H	CH_3	H	54
4	O	H	H	CH_3	57 (1:2, *anti*:*syn*)

Other auxiliaries were explored but were less effective than the $-CO_2CH(R)Ph$ derivatives. For example, the diastereomers resulting from the use of mandelic acid methyl ester could be easily separated (>99.5% de) by either chromatography or recrystallization, but removal of the protecting group from **17** by either Pd-catalyzed hydrogenolysis or BBr_3-mediated debenzylation resulted in degradation of enantiopurity as judged by determination of the ee of the free amine scaffold **15** (Scheme 7, 67−82% ee). In contrast, as reported above, the chiral, nonracemic auxiliary (*S*)-1-phenylbutanol provided easily separable diastereomers (>99.8% de), and Pd-catalyzed hydrogenolysis of the (*S*)-1-phenylbutanol protecting group of (+)-**14** and reprotection with CbzCl provided the desired metal complex (+)-**7** in 98.5% ee. The (*S*)-1-phenylethanol auxiliary provided similar results. The different behavior of these two auxiliary systems is not well-understood at this writing.

Other Scaffolds. The experiments depicted in Table 1 were carried out to probe the use of oxo- and aza-Achmatowicz reactions in the synthesis of $TpMo(CO)_2$ pyranyl and pyridinyl scaffolds of various substitution patterns. Methyl groups were chosen to generically represent other substituents. Entries 1−3 highlight the ease with which 2- and 4-methyl-substituted pyranyl (**18**, **19**) and 4-methyl-substituted pyridinyl (**20**) complexes may be synthesized starting from appropriately substituted furans. The synthetic protocol to prepare the methyl-substituted pyranyl scaffolds **18** and **19** shown in Table 1 is analogous to that used to prepare the unsubstituted parent oxopyranyl complex: (1) Achmatowicz oxidative rearrangement of the appropriate methyl-substituted furfuryl alcohol, (2) acetylation of the intermediate hydroxypyranone, and (3) one-pot transformation into the substituted oxopyranyl scaffold with

SCHEME 8. Synthesis of Enantiopure *syn*- and *anti*-21: Confirmation of Relative Stereochemistry[a]



[a] Reagents: (i) *m*-CPBA, CH_2Cl_2; (ii) Ac_2O, Et_3N, cat. DMAP; (iii) $Mo(CO)_3(DMF)_3$ then KTp.

$Mo(DMF)_3(CO)_3$ and KTp. The 4-methyl-substituted pyridinyl complex **20** listed in entry 3 of the table was made by analogy to the parent, unsubstituted pyridinyl complex, whereby oxidative rearrangement of the Cbz-protected furfuryl amine derivative was followed by direct metalation without acetylation of the intermediate hydroxypyridinone. In all cases, a single chromatographic purification was required at the end of the sequence to obtain the desired metal complexes in high purity.

Although not explored in this current study, the use of commercially available chiral, nonracemic alcohols to prepare and resolve diastereomeric substituted 6-alkoxypranones is expected to provide the desired substituted $TpMo(CO)_2$-(oxopyranyl) scaffolds (**18**, **19**) in high enantiopurity as observed in the asymmetric preparation of the parent, unsubstituted pyranyl scaffolds. Similarly, the use of chiral, nonracemic urethane protecting groups derived from appropriate commercially available chiral, nonracemic alcohols is expected to allow straightforward resolution of diastereomeric substituted oxopyridinyl complexes (like **20**) after metalation.

The 6-methyl-substituted scaffolds **21** and **22** shown in entry 4 of Table 1 represent a special case. The oxopyranyl scaffold is obtained as a 1:2 mixture of diastereomers (*anti:syn*), which may be separated by flash chromatography.[79] The formation of these diastereomers affords the opportunity to produce high-enantiopurity 6-methyl-substituted $TpMo(CO)_2$(oxopyranyl) scaffolds from high-enantiopurity 1-furan-2-yl-ethanol (Scheme 8), which is available via the asymmetric reduction of acetylfuran by using Noyori's protocol.[80] (*R*)-1-Furan-2-yl-ethanol (*R*)-(+)-**23** (98% ee) underwent Achmatowicz rearrangement and acetylation to produce a mixture of the diastereomeric 6-acetoxypyranones. This mixture was treated without separation with $Mo(CO)_3(DMF)_3$ followed by KTp to produce a 1:2 (*anti:syn*) mixture of the diastereomers of **21** and **22** in 98% and 97% ee, respectively. The relative and absolute configuration of the slower eluting (−)-*syn* diastereomer **22** was confirmed by X-ray crystallography. The enantiopurity of the diastereomeric scaffolds was determined by chiral HPLC by comparison to racemic mixtures.

Conclusions

Synthetically versatile oxopyranyl and oxopyridinyl organometallic enantiomeric scaffolds are easily prepared on multigram scale by using high-throughput sequences based on the oxa- and aza-Achmatowicz reactions of furfuryl alcohols and *N*-protected furfuryl amines, respectively.[81] These new protocols supersede earlier lengthier and less efficient synthetic methods for construction of molybdenum-based organometallic enantiomeric scaffolds.[57,59,60,78] It should be noted that both starting materials, KTp and $Mo(DMF)_3(CO)_3$, are easily prepared on large scale (multi-100 g lots) in one step from commercially available materials. KTp is prepared from KBH_4 and pyrazole upon heating without solvent,[82,83] while $Mo(DMF)_3(CO)_3$ is trivially generated upon heating $Mo(CO)_6$ in DMF.[84] From a synthetic perspective the $TpMo(CO)_2$ moiety functions as a non-traditional protecting group/auxiliary that can be carried through multistep sequences, and whose overall expense and scalability do not differ significantly from those of some more traditional systems. Recovery of the molybdenum complexes after demetalation, an option in large-scale operations, has not yet been investigated.

Experimental Section

Representative Experimental Procedure. (*S*)-1-Phenylbutyl 1*H*-imidazole-1-carboxylate, 10 (R = *n*-Pr): To a Schlenk flask charged with (*S*)-(−)-1-phenyl-1-butanol (98% ee, 10.7 g, 71.5 mmol, 1.00 equiv, purchased from Fluka), 1,1′-carbonyldiimidazole (12.8 g, 78.7 mmol, 1.10 equiv), and 4-(dimethylamino)pyridine (28.3 mg, 0.232 mmol, 0.3 mol %) was added CH_2Cl_2 (180 mL). The solution was stirred at room temperature for 1.75 h, washed with water (3 × 150 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 5.0 cm × 32.0 cm, hexanes:EtOAc =1:1) to afford a yellow oil **10**, R = *n*-Pr (16.9 g, 97%), which solidified at low temperature.

10 (R = *n*-Pr): TLC R_f 0.47 (50% EtOAc in hexanes). $[\alpha]^{20}_D$ +3.25 (*c* 1.23, CH_2Cl_2). IR (cm^{-1}) 2960 (w), 1752 (s), 1389 (s), 1279 (s), 1236 (s), 997 (s), 698 (s). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 7.43−7.32 (m, 6 H), 7.05 (s, 1 H), 5.90 (dd, J = 7.6, 6.5 Hz, 1 H), 2.09 (m, 1 H), 1.90 (m, 1 H), 1.38 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.9, 137.2, 130.7, 128.8, 126.7, 117.2, 80.9, 38.1, 18.8, 13.8. HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ $[M + H]^+$ 245.1290, found 245.1285.

(*S*)-1-Phenylbutyl (2-furylmethyl)carbamate, 11 (R = *n*-Pr): To a solution of (*S*)-1-phenylbutyl 1*H*-imidazole-1-carboxylate **10**, R = *n*-Pr (5.59 g, 22.9 mmol, 1.10 equiv), in CH_2Cl_2 (24 mL) were added 4-(dimethylamino)pyridine (28.3 mg, 0.232 mmol, 1.1 mol %) and Et_3N (4.36 mL, 31.2 mmol, 1.50 equiv). While monitoring the temperature inside the reaction flask, furfuryl amine **5** (1.84 mL, 20.8 mmol, 1.00 equiv) was added dropwise to the solution at 0 °C. The solution was stirred at room temperature for 20.5 h, washed with water (3 × 80 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 5.5 cm × 39.0 cm, 33% EtOAc in hexanes) to afford a yellow oil **11** (5.63 g, 99%).

11 (R = *n*-Pr): TLC R_f 0.62 (50% EtOAc in hexanes). IR (cm^{-1}) 3330 (w), 2958 (w), 1697 (s), 1506 (m), 1241 (s), 698 (s). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 6 H), 6.31 (s, 1 H), 6.19 (d, J = 3.2 Hz, 1 H), 5.69 (t, J = 7.0 Hz, 1 H), 5.18 (br s, 1 H), 4.37 (dd, J = 15.3, 6.0 Hz, 1 H), 4.28 (dd, J = 15.6, 5.5 Hz, 1 H), 1.89 (m, 1 H), 1.75 (m, 1 H), 1.33 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 151.8, 142.1, 141.3, 128.4,

(79) Examples of related transformations with substituted furfuryl amines leading to 6-substituted-5-oxopyridinyl complexes can be found in Moretto, A. F. The Utilization of Stoichiometric Molybdenum π-Complexes for the Synthesis of Substituted Piperidines. Ph.D. Dissertation, Emory University, Atlanta, 1999.

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(81) Oxopyranyl and oxopyridinyl enantiomeric scaffolds will be available from Synthonix, Ltd (www.synthonix.com).

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(83) Trofimenko, S. *J. Am. Chem. Soc.* **1967**, *89*, 3170.

(84) Pasquali, M.; Leoni, P.; Sabatino, P.; Braga, D. *Gazz. Chim. Ital.* **1992**, *122*, 275−277.

127.7, 126.5, 110.4, 107.2, 76.7, 38.7, 38.1, 18.8, 13.9. HRMS (ESI) calcd for $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.1443, found 274.1440.

(+)-Dicarbonyl[hydridotris(1-pyrazolyl)borato]{(2*R*)-(η^3-2,3,4)-5-oxo-1-[(1*S*)-phenylbutoxycarbonyl]-5,6-dihydro-2*H*-pyridin-2-yl}molybdenum, (+)-14, and (−)-Dicarbonyl[hydridotris(1-pyrazolyl)borato]{(2*S*)-(η^3-2,3,4)-5-oxo-1-[(1*S*)-phenylbutoxycarbonyl]-5,6-dihydro-2*H*-pyridin-2-yl}molybdenum, (−)-13. A solution of (*S*)-1-phenylbutyl (2-furylmethyl)carbamate **11** (R = *n*-Pr) (11.47 g, 42.0 mmol, 1.0 equiv) in CH_2Cl_2 (190 mL) was cooled to 0 °C. To the stirring solution was added *m*-CPBA (~77% purity, 14.11 g, 62.9 mmol, 1.5 equiv) portionwise, and the reaction was stirred for 5.0 h at 0 °C. The white solids were removed by vacuum filtration, and the filtrate was washed with water (2 × 100 mL). The organic phase was dried over $MgSO_4$ and filtered, and the filtrate was degassed with argon for 15 min. To the degassed solution at 0 °C was quickly added solid $Mo(DMF)_3(CO)_3$ (23.65 g, 59.2 mmol, 1.41 equiv). After stirring for 5 min at 0 °C, the reaction was warmed to room temperature and stirred for 23 h. To the reaction mixture at 0 °C was added potassium hydridotris(1-pyrazolyl)borate (KTp) (14.9 g, 59.2 mmol, 1.41 equiv). The reaction mixture was stirred at room temperature for 1.5 h, filtered through a pad of Celite, and concentrated under reduced pressure. The crude product was subjected to short filter chromatography (SiO_2, 9.0 cm × 6.0 cm, hexanes:EtOAc = 9:1 ramping gradually to 100% EtOAc). Fractions overlapping with impurities were subjected to chromatography (gravity flow, SiO_2, 7.5 cm × 35.0 cm, toluene:EtOAc = 15:1) to afford a mixture of diastereomers. Chromatography (gravity flow, SiO_2, 7.5 cm × 42.0 cm, toluene:EtOAc = 15:1) afforded (+)-**14** (4.75 g, 17.8%) and (−)-**13** (4.05 g, 15.2%) each as orange solids with complete diastereoseparation (>99.9% de for each isomer).

(+)-14: TLC R_f 0.23 (toluene:EtOAc = 15:1). $[\alpha]^{20}_D$ +566 (*c* 0.080, CH_2Cl_2). IR (cm^{-1}) 1958 (s), 1863 (s), 1702 (m), 1660 (m), 1280 (s), 1049 (s). ^1H NMR (a mixture of two rotamers—400 MHz, $CDCl_3$) δ 8.42 (d, J = 1.6 Hz, 0.8 H), 8.37 (s, 0.2 H), 8.29 (d, J = 1.6 Hz, 0.8 H), 7.73 (s, 0.2 H), 7.71 (app d, 0.8 H), 7.63 (overlapped, 0.2 H), 7.62 (d, J = 2.4 Hz, 0.8 H), 7.61 (d, J = 2.0 Hz, 0.8 H), 7.52 (d, J = 2.0 Hz, 0.8 H), 7.48 (d, J = 2.0 Hz, 0.2 H), 7.45 (s, 0.2 H), 7.43 (s, 0.2 H), 7.41−7.24 (m, 6 H), 6.30 (t, J = 2.1 Hz, 0.8 H), 6.25 (t, J = 2.1 Hz, 0.8 H), 6.23 (t, J = 2.1 Hz, 1 H), 6.12 (t, J = 2.1 Hz, 0.2 H), 6.09 (t, J = 2.1 Hz, 0.2 H), 5.75 (m, 1 H), 4.75 (dd, J = 6.2, 1.4 Hz, 1 H), 4.01 (t, J = 6.2 Hz, 0.8 H), 3.97 (t, J = 6.2 Hz, 0.2 H), 3.55 (AB quartet, J = 20.0 Hz, 0.8 H), 3.46 (AB quartet, J = 20.0 Hz, 0.2 H), 3.36 (AB quartet, J = 20.0 Hz, 0.8 H), 3.23 (AB quartet, J = 20.0 Hz, 0.2 H), 2.18 (m, 0.2 H), 1.97 (m, overlapped, 0.2 H), 1.92 (m, 0.8 H), 1.73 (m, 0.8 H), 1.44−1.20 (m, 2.0 H), 0.97 (t, J = 7.2 Hz, 0.6 H), 0.90 (t, J = 7.2 Hz, 2.4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.2, 224.7, 221.9, 193.4, 193.1, 154.2, 153.4, 147.3, 144.7, 143.4, 141.5, 141.2, 140.6, 139.8, 139.4, 136.4, 136.2, 134.8, 134.4, 128.7, 128.4, 128.2, 127.9, 127.1, 126.2, 106.2, 106.1, 106.0, 105.8, 103.5, 94.7, 92.7, 79.2, 78.5, 64.3, 63.74, 63.70, 63.0, 48.0, 47.8, 38.4, 37.7, 18.8, 18.5, 13.8, 13.6. HRMS (ESI) calcd for $C_{27}H_{29}BMoN_7O_5$ $[M + H]^+$ 640.1377, found 640.1392. HPLC: Zorbax Eclipse C8, CH_3CN:H_2O (with 0.1% CF_3CO_2H) = 55:45, 0.85 mL/min, λ = 254 nm, t_R = 25.01 min, >99.9% de.

(−)-13: TLC R_f 0.13 (toluene:EtOAc = 15:1). $[\alpha]^{20}_D$ −466 (*c* 0.190, CH_2Cl_2). IR (cm^{-1}) 1960 (s), 1865 (s), 1703 (m), 1662 (m), 1278 (s), 1049 (s). ^1H NMR (a mixture of two rotamers—400 MHz, $CDCl_3$) δ 8.49 (d, J = 2.0 Hz, 0.4 H), 8.37 (d, J = 1.9 Hz, 0.6 H), 8.21 (d, J = 2.1 Hz, 0.6 H), 8.13 (d, J = 2.0 Hz, 0.4 H), 7.80 (d, J = 2.1 Hz, 0.4 H), 7.74 (d, J = 1.7 Hz, 0.6 H), 7.70 (d, J = 2.4 Hz, 0.4 H), 7.63 (d, J = 2.4 Hz, 0.4 H), 7.61 (d, J = 2.1 Hz, 1.2 H), 7.55 (d, J = 2.1 Hz, 0.4 H), 7.49 (d, J = 1.9 Hz, 0.6 H), 7.48−7.25 (m, 6 H), 6.35 (t, J = 2.4 Hz, 0.4 H), 6.31 (t, J = 2.0 Hz, 0.4 H), 6.23 (m, 2.2 H), 5.81 (t, J = 6.8 Hz, 0.4 H), 5.75 (dd, J = 7.6, 6.0 Hz, 0.6 H), 4.76 (m, 1 H), 4.07 (t, J = 6.4 Hz, 0.6 H), 4.02 (t, J = 6.4 Hz, 0.4 H), 3.60 (AB quartet, J = 19.6 Hz, 0.6 H), 3.39 (AB quartet, J = 20.0 Hz, 0.4 H), 3.31 (AB quartet, J = 19.2 Hz, 0.6 H), 3.27 (AB quartet, J = 20.0 Hz, 0.4 H), 2.13 (m, 0.4 H), 1.94 (m, 1 H), 1.81 (m, 0.6 H), 1.35 (m, 2 H), 0.95 (t, J = 7.6 Hz, 1.2 H), 0.92 (t, J = 7.2 Hz, 1.8 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.1, 224.3, 222.8, 221.4, 193.4, 193.0, 154.1, 153.2, 147.5, 147.3, 144.5, 142.8, 141.9, 141.4, 140.3, 140.0, 136.6, 136.4, 136.3, 136.2, 134.8, 134.7, 128.6, 128.2, 127.7, 126.6, 126.1, 106.3, 106.11, 106.07, 106.0, 105.8, 105.8, 93.5, 91.6, 78.8, 78.4, 64.8, 64.2, 64.1, 63.5, 48.0, 47.8, 38.7, 38.1, 18.6, 13.8. HRMS (ESI) calcd for $C_{27}H_{29}BMoN_7O_5$ $[M + H]^+$ 640.1377, found 640.1388. HPLC: Zorbax Eclipse C8, CH_3CN:H_2O (with 0.1% CF_3CO_2H) = 55:45, 0.85 mL/min, λ = 254 nm, t_R = 23.00 min, >99.9% de.

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Supporting Information Available: Full experimental details and characterization data for all compounds and X-ray crystallography data for compound (−)-*syn*-**22** and copies of proton and carbon NMR spectra of all new compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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