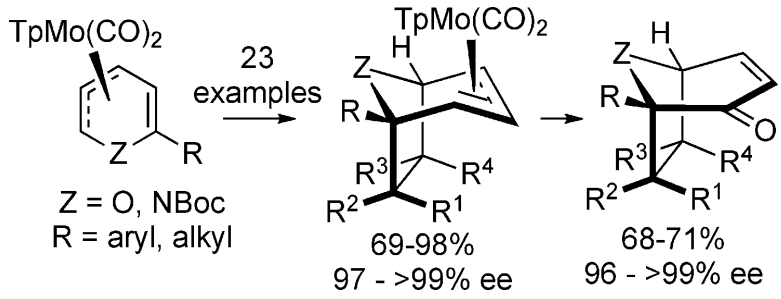
Article

Organometallic Enantiomeric Scaffolding: General Access to 2-Substituted Oxa- and Azabicyclo[3.2.1]octenes *via* a Brønsted Acid Catalyzed [5 + 2] Cycloaddition Reaction

Ethel C. Garnier, and Lanny S. Liebeskind

J. Am. Chem. Soc., **2008**, 130 (23), 7449-7458 • DOI: 10.1021/ja800664v • Publication Date (Web): 15 May 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES

Published on Web 05/15/2008

Organometallic Enantiomeric Scaffolding: General Access to 2-Substituted Oxa- and Azabicyclo[3.2.1]octenes *via* a Brønsted Acid Catalyzed [5 + 2] Cycloaddition Reaction

Ethel C. Garnier and Lanny S. Liebeskind*

Emory University, Department of Chemistry, 1515 Dickey Drive, Atlanta, Georgia 30322

Received January 31, 2008; E-mail: chemLL1@emory.edu

Abstract: 6-Substituted $TpMo(CO)_2(\eta$-2,3,4-pyranyl)- and $TpMo(CO)_2(\eta$-2,3,4-pyridinyl) scaffolds (Tp = hydridotrispyrazolylborato) function as reaction partners in an efficient regio- and stereocontrolled synthesis of functionalized oxa- and azabicyclo[3.2.1]octenes through a novel Brønsted acid catalyzed [5 + 2] cycloaddition reaction. Excellent *exo*-selectivities are obtained, and the reaction gives products with complete retention of enantiomeric purity when carried out with chiral, nonracemic scaffolds. The substituent at C-6 of the η^3-coordinated heterocyclic scaffold not only influences [5 + 2] reactivity but also plays a critical role in the demetalation step directing the reaction to only one of two possible products.

Introduction

Air-stable metal π-complexes such as the 3-oxopyranyl and 3-oxopyridinylmolybdenum complexes **1** and **2** shown in Figure 1 (Tp = hydridotrispyrazolylborato) can function as versatile organometallic enantiomeric scaffolds.[1] Short, scalable, and practicable methods of synthesis of high enantiopurity scaffolds $TpMo(CO)_2$(3-oxopyranyl) **1** and $TpMo(CO)_2$(3-oxopyridinyl) **2** have been developed,[2] and from these simple scaffolds a diverse array of biologically relevant heterocyclic core structures can be obtained in an enantiocontrolled fashion (Figure 1).[3–15] The synthetic elaboration of the 3-oxopyranyl and -pyridinyl complexes **1** and **2** often proceeds *via* the 5-substituted η^3-pyranyl and -pyridinyl scaffolds **5** and **6** shown in Figure 2.

For greatest synthetic versatility it is important to develop practical routes to pyranyl and pyridinyl organometallic scaffolds bearing additional substitution patterns about the heterocycle ring. This paper describes the high yield and high enantiopurity construction of the air-stable 2-oxo-pyranyl and -pyridinyl scaffolds **3** and **4** and their progeny, the 6-substituted η^3-pyranyl- and η^3-pyridinylmolybdenum complexes **7** and **8** (Figure 2). The latter two systems participate in versatile enantiocontrolled [5 + 2] cycloadditions taking place through an *unusual Brønsted acid assisted process* allowing access, after a *completely regioselective demetalation*, to functionalized 2-substituted oxa- and azabicyclo[3.2.1]octenes of high enantiopurity.

The oxa- and azabicyclo[3.2.1]octene skeletons are key structural units found in a large and diverse array of biologically interesting and medicinally important natural and synthetic products.[16–21] Structurally complex molecules possessing oxa- and azabicyclo[3.2.1]octane skeletons have been rapidly and efficiently generated by [5 + 2] cycloadditions of 3-oxidopyrylium[22,23] and 3-oxidopyridinium dipoles.[24] Although synthetically very powerful, these methods can be

(1) Organometallic enantiomeric scaffolds: (1) the metal/ligand auxiliary attached to the unsaturated ligand influences novel reactions, controls non-traditional selectivities, and provides a dominant regio- and stereocontrol element on the scaffold that allows the predictable introduction of new stereocenters at *multiple sites around the unsaturated ligand*, (2) a single metal/ligand auxiliary controls the introduction of multiple stereocenters over multiple steps, and (3) the organometallic nature of the scaffolding enables the use of stereodivergent tactics for the introduction of ring substituents.

(2) Coombs, T. C.; Lee IV, M. D.; Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2008**, *73*, 882–888.
(3) Shu, C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 2878–2879.
(4) Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477–12487.
(5) Yin, J.; Llorente, I.; Villanueva, L. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 10458–10459.
(6) Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 7445–7455.
(7) Rubio, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 891–901.
(8) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 9026–9027.
(9) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 6185–6186.
(10) Arrayás, R. G.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1816–1825.
(11) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465–472.
(12) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2005**, *127*, 11258–11259.
(13) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3909–3911.
(14) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083–4086.
(15) Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 5811–5812.
(16) Pollini, G. P.; Benetti, S.; Risi, C. D.; Zanirato, V. *Chem. Rev.* **2006**, *106*, 2434–2454.
(17) Lounasmaa, M.; Tamminen, T. In *Alkaloids*; Academic Press: New York, 1993; pp 1−114..
(18) Nair, V.; Treesa, P. M.; Rath, N. P.; Kunwar, A. C.; KiranKumar, K. S.; RaviSankar, A.; Vairamani, M.; Prabhakar, S. *Tetrahedron Lett.* **2002**, *58*, 7221–7231.
(19) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. *J. Am. Chem. Soc.* **2006**, *128*, 11916–11920.
(20) Han, L.; Huang, X.; Sattler, I.; Moellmann, U.; Fu, H.; Lin, W.; Grabley, S. *Planta Med.* **2005**, *71*, 160–164.
(21) Shen, Y.-H.; Li, S.-H.; Li, R.-T.; Han, Q.-B.; Zhao, Q.-S.; Liang, L.; Sun, H.-D.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 1593–1595.
(22) Wender, P. A.; Love, J. A. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford, CT, 1999; pp 1−45..
(23) Chiu, P.; Lautens, M. In *Topic in Current Chemistry*; Metz, P., Ed.; Springer-Verlag: Berlin, 1997; Vol. 190; pp 1−85..
(24) Katritzky, A. R.; Dennis, N. *Chem. Rev.* **1989**, *89*, 827–861.

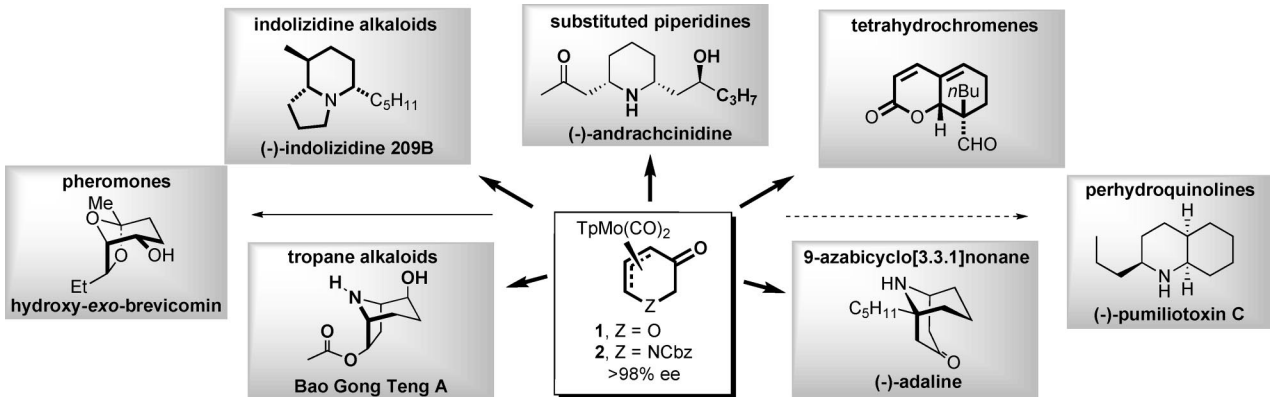


Figure 1. Organometallic enantiomeric scaffolding.

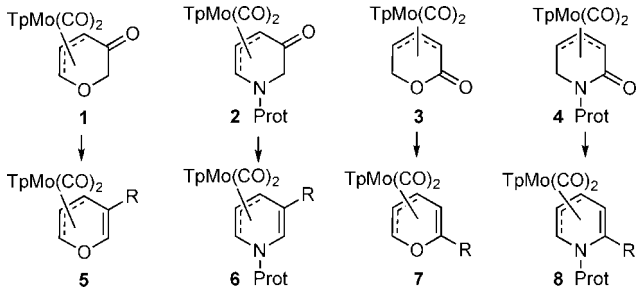
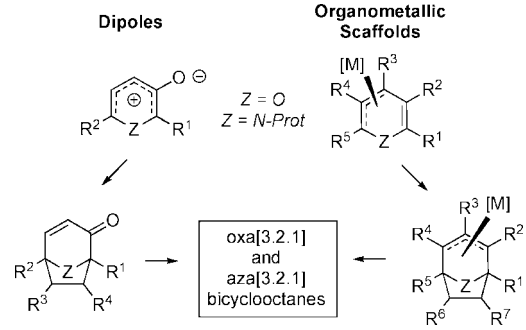


Figure 2. Core organometallic enantiomeric scaffolds.

problematic. Issues include the limited development of enantioselective versions,[25–28] the lack of control over facial selectivity[29,30] except in the case of internal directing groups,[31–37] and the regiochemistry of the cycloaddition.[38] Organometallic scaffolds of the η^3-pyranyl and η^3-pyridinyl families such as **5** through **8** shown in Figure 2 offer the opportunity for topologically similar but mechanistically distinct [5 + 2] transformations[11,13,15] as depicted comparatively in Scheme 1. While both of these [5 + 2] approaches provide controlled access to complex molecular structures, the latter organometallic protocol affords unique potential modularity because it is not dependent on the placement of dipole-generating functionality within the cycloaddition precursor.

Scheme 1. Comparative Approaches to [5 + 2] Cycloadditions

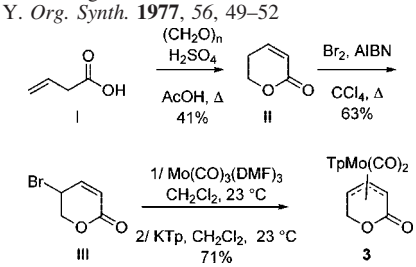


The 6-substituted η^3-pyranyl- and η^3-pyridinylmolybdenum scaffolds **7** and **8** prepared in this study serve as chiral, nonracemic substrates in [5 + 2] cycloadditions with a range of electron-deficient alkenes, delivering focused libraries of 2-substituted oxa- and azabicyclo[3.2.1]octene ring systems in high enantiopurity after demetalation (Scheme 2). This reaction allows the *installation of four stereocenters, including one quaternary carbon, in one step, with total control of the regio- and the stereochemistry* of the obtained products. Additionally, a well-established demetalation procedure[39] offers varied opportunities for further regio- and stereoselective functionalization of the [5 + 2] cycloadducts.

Results and Discussion

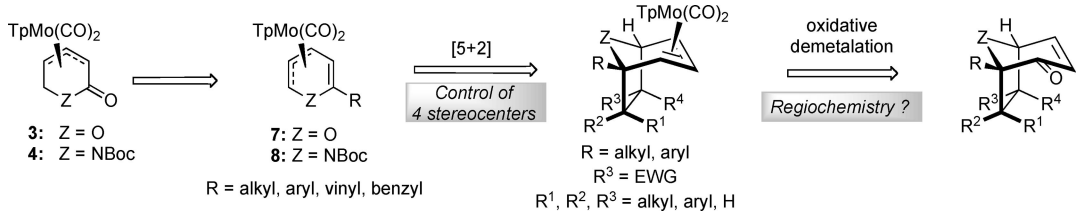
Synthesis of Lactonyl and Lactamyl Scaffolds 3 and 4. Racemic lactonyl scaffold (±)-**3** is readily available from 5-bromo-5,6-dihydro-2*H*-pyran-2-one[40] following an established procedure.[41] The previously disclosed route to the enantiomeri-

(25) Wender, P. A.; Mascareñas, J. L. *J. Org. Chem.* **1991**, *56*, 6267–6269.
(26) Krishna, U. M.; Trivedi, G. K. *Tetrahedron Lett.* **2004**, *45*, 257–259.
(27) Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J.; Adlington, R. M. *Tetrahedron Lett.* **2003**, *44*, 4543–4545.
(28) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954–8957.
(29) Furneaux, R. H.; Mason, J. M.; Miller, I. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1923–1928.
(30) Lee, H.-Y.; Sohn, J.-H.; Kim, H. Y. *Tetrahedron Lett.* **2001**, *42*, 1695–1698.
(31) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901–5904.
(32) Krishna, U. M.; Srikanth, G. S. C.; Trivedi, G. K.; Deodhar, K. D. *Synlett* **2003**, 2383–2385.
(33) Williams, D. R.; Benbow, J. W.; McNutt, J. G.; Allen, E. E. *J. Org. Chem.* **1995**, *60*, 833–843.
(34) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898.
(35) Krishna, U. M.; Deodhar, K. D.; Trivedi, G. K. *Tetrahedron* **2004**, *60*, 4829–4836.
(36) Wender, P. A.; Bi, F. C.; Buschmann, N.; Gosselin, N.; Kan, C.; Kee, J.-M.; Ohmura, H. *Org. Lett.* **2006**, *8*, 5373–5376.
(37) Prakash, K. R. C.; Trzcinska, M.; Johnson, K. M.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1443–1446.
(38) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755–767.
(39) Alcudia, A.; Arrayás, R. G.; Liebeskind, L. S. *J. Org. Chem.* **2002**, *67*, 5773–5778.
(40) Nakagawa, M.; Saegusa, J.; Tonozuka, M.; Obi, M.; Kiuchi, M.; Hino, T.; Ban, Y. *Org. Synth.* **1977**, *56*, 49–52

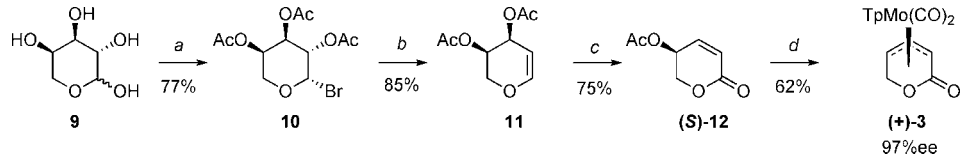


(41) Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 897–898.

Scheme 2. 6-Substituted η^3-Pyranyl and η^3-Pyridinyl Scaffolds in [5 + 2] Cycloadditions

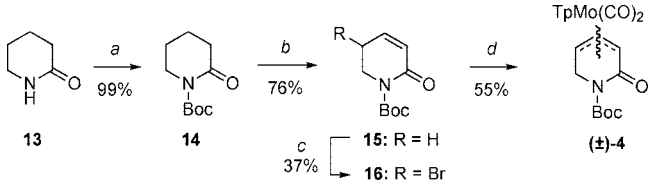


Scheme 3. Synthesis of Chiral, Nonracemic Lactonyl Scaffold (+)-**3**[a]



[a] (a) $HClO_4$, Ac_2O, P, Br_2, 23 °C; (b) Zn, $CuSO_4$, NaOAc, EtOAc, reflux; (c) 10 mol % $InCl_3$, IBX, CH_3CN/H_2O 9:1, 23 °C; (d) (toluene)$Mo(CO)_3$, then KTp, CH_2Cl_2, 23 °C.

Scheme 4. Synthesis of Racemic Lactamyl Scaffold (±)-**4**[a]



[a] (a) *n*-BuLi, THF, −78 °C then Boc_2O, THF, −78 °C; (b) LDA, THF, −78 °C then PhS(Cl)=N−*t*Bu, THF, −78 °C; (c) NBS, benzoyl peroxide, CCl_4, reflux; (d) $(DMF)_3Mo(CO)_3$ then KTp, CH_2Cl_2, 23 °C.

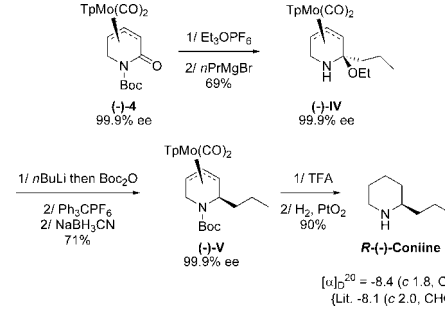
cally pure version of **3**[41] relied upon a known synthesis of allylic acetate (*S*)-**12**.[42] The preparation of (*S*)-**12** has now been significantly enhanced (Scheme 3). D-Arabinose **9** was first transformed into 3,4-di-*O*-acetyl-D-arabinal **11** by a peracetylation/bromination/elimination sequence.[43] An allylic rearrangement/oxidation of compound **11** induced by indium chloride and IBX[44] provided the enantiopure allylic acetate (*S*)-**12**[45] in 75% yield. Treatment of compound (*S*)-**12** with 1.0 equiv of (toluene)$Mo(CO)_3$[46] in dichloromethane at room temperature over 4 days, followed by the addition of potassium hydridotris(pyrazolyl)borate (K^+TP^-),[47] provided complex (+)-**3** in 62% yield with excellent enantiomeric excess (97% ee) *via* a retention of the configuration pathway.[41]

The synthesis of racemic lactamyl scaffold (±)-**4** has also been dramatically improved compared to the previously described 11-step process.[48] Racemic (±)-**4** is now available by a straightforward four-step sequence. Commercially available 2-piperidone **13** is *N*-Boc protected in quantitative yield giving **14** (Scheme 4). Dehydrogenation of compound **14** to the corresponding α,β-unsaturated carbonyl compound **15** was achieved under mild conditions[49] in 76% yield using *N-tert*-butylbenzenesulfinimidoyl chloride (PhS(Cl)=N−*t*Bu).[50] Bromination of **15** with NBS in refluxing carbon tetrachloride in the presence of benzoyl peroxide followed by metalation of the corresponding allylic bromide **16** afforded the lactamyl scaffold (±)-**4** in 15% overall yield from **13** (Scheme 4).

The separate antipodes (+)-**4** and (−)-**4**[51] are readily accessible from racemic (±)-**4** by (1) removal of the *N*-Boc protective group in slightly acidic media giving racemic (±)-**17**, (2) reprotection with a (*S*)-1-phenylbutyl-1*H*-imidazole-1-carboxylate auxiliary[52] providing the diastereomers (+)-**18** and (−)-**18′** (Scheme 5), and (3) classical resolution. Both diastereoisomers (+)-**18** and (−)-**18′** are isolable in good yield and high enantiopurity (99.9% ee) by chromatography. If desired, these compounds can be easily converted to the corresponding *N*-Boc derivatives (+)-**4** and (−)-**4** by hydrogenation of the chiral auxiliary and reprotection of the resulting secondary amine.[53]

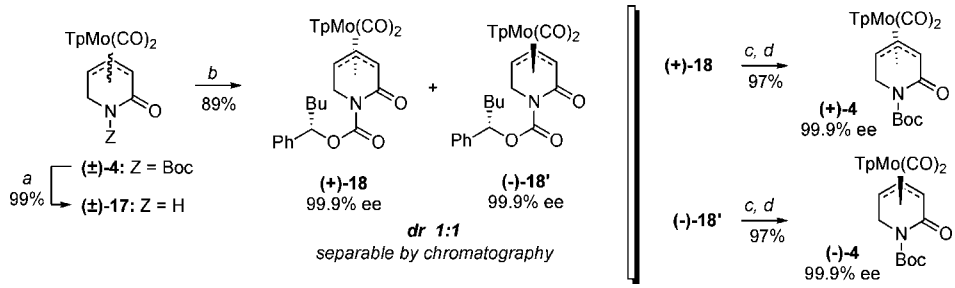
Synthesis of 6-Substituted η^3-Pyranyl- and η^3-Pyridinylmolybdenum Scaffolds. By mimicking a nucleophilic functionalization−dehydration protocol used to convert glycones into

(42) Lichtenthaler, R. W.; Rönninger, S.; Jarglis, P. *Liebigs Ann. Chem.* **1989**, 1153–1161.
(43) Areces, P.; Carrasco, E.; Mancha, A.; Plumet, J. *Synthesis* **2006**, 946–948.
(44) Yadav, J. S.; Subba Reddy, B. V.; Suresh Reddy, C. *Tetrahedron Lett.* **2004**, *45*, 4585–4585.
(45) The other antipode (*R*)-**6** would be available starting from L-arabinose following the same synthetic sequence.
(46) Nesmeyanov, A. N.; Krivykh, V. V.; Kaganovich, V. S.; Rybinskaya, M. I. *J. Organomet. Chem.* **1975**, *102*, 185–193.
(47) Trofimenko, S. *J. Am. Chem. Soc.* **1967**, *89*, 3170–3171.
(48) Arrayás, R. G.; Alcudia, A.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 3381–3383.
(49) Matsuo, J.-i.; Aizawa, Y. *Tetrahedron Lett.* **2005**, *46*, 407–410.
(50) Commercially available from Tokyo Kasei Kogyo Co., Ltd (TCI). For a reliable procedure, see: Matsuo, J.-i.; Iida, D.; Tatani, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 223–234.
(51) The absolute configuration of scaffolds (+)-**4** and (−)-**4** was determined through the synthesis of *R*-(−)-coniine starting from scaffold (−)-**4**.



(52) This reagent was obtained from condensation of (*S*)-1-phenylbutanol with CDI in the presence of catalytic DMAP in dichloromethane. For more details, see the Supporting Information.
(53) Introduction of the chiral auxiliary directly onto compound **13** was problematic, especially at the purification stage. The sequence indicated in the text proved more flexible and allowed isolation of both racemic and chiral, nonracemic scaffolds.

Scheme 5. Synthesis of Chiral, Nonracemic Scaffolds (+)-**4** and (−)-**4**[51a]



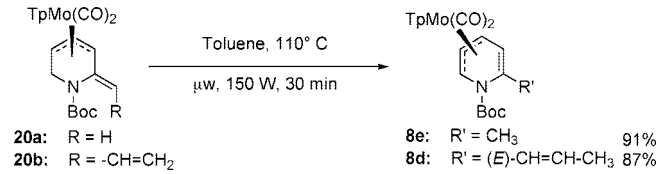
[a] (a) TFA, CH_2Cl_2, 0 °C; (b) *n*-BuLi, THF, −78 °C then (*S*)-1-phenylbutyl-1*H*-imidazole-1-carboxylate, THF, −78 °C; (c) H_2, 10 mol % Pd/C, MeOH, 23 °C; (d) *n*-BuLi, THF, −78 °C then Boc_2O, THF, −78 °C.

2-substituted glycals,[54,55] the lactonyl and lactamylmolybdenum scaffolds **3** and **4** function as precursors to the synthetically versatile 6-substituted η^3-pyranyl- and η^3-pyridinylmolybdenum scaffolds **7** and **8**. Both **3** and **4** are susceptible to nucleophilic 1,2-functionalization with Grignard reagents. By careful control of the reaction temperature and time, and by using a slight modification of Martin's conditions for the *in situ* dehydration of lactols (DMAP/TFAA),[55] the undesired ring opening of the hemiketal alkoxide intermediate can be prevented and a high-yield dehydration ensues (see Table 1).[56] The key reaction factors are maintenance of the reaction temperature for the Grignard reagent addition below −40 °C and initiation of the *in situ* dehydration with DMAP/TFAA at −78 °C. The nucleophilic addition−*in situ* dehydration is efficient in all cases studied, although the dehydration pathway diverges to two different products as depicted in Table 1.

Both (±)-**3** and (±)-**4** and their high enantiopurity versions (+)-**3**, (+)-**4**, and (−)-**4** have been studied in this chemistry. These scaffolds react with sp^2 Grignard reagents (aromatic and alkenyl) giving, after *in situ* dehydration, access to 6-substituted η^3-pyranylmolybdenum and η^3-pyridinylmolybdenum complexes **7** and **8** in good to excellent yields (Table 1, entries 1−8) and with excellent retention of enantiopurity. However, when these same scaffolds are treated with sp^3 Grignard reagents, the elimination proceeds exocyclic to the ring to generate 2-alkylidene-η-3,4,5-pyranyl- and -pyridinylmolybdenum complexes **19** and **20**, respectively, as shown in Table 1 (entries 9−14). In the specific case of the pyranylmolybdenum scaffold **3**, two of the anticipated 2-alkylidene-η-3,4,5-pyranylmolybdenum complexes, **19a** and **19c**, are apparently very electron-rich substrates and undergo an *in situ* Friedel−Crafts-like reaction with TFAA to generate the corresponding trifluoromethylketones **19b** and **19d**, respectively (Table 1, entries 9 and 10). This side reaction could not be eliminated by reducing the amount of trifluoroacetic anhydride or by reversing the order of addition of reactants. The *Z*-stereochemistry depicted for **19b** and **19d** was confirmed by an X-ray diffraction study on compound **19d** (see the Supporting Information for details). In comparison to the electron-rich and reactive alkylidene complexes generated from lactonylmolybdenum scaffold **3**, the addition of sp^3 Grignard reagents to the lactamyl scaffold **4** led to stable 2-alkylidene-η-3,4,5-pyridinylmolybdenum complexes **20a,b** (Table 1, entries 12, 13) in excellent yields. No trace of a Friedel−Crafts-like side-reaction with TFAA was observed. Interestingly, the 2-alkylidene-η-3,4,5-dihydropyridinylmolybdenum compounds **20a** and **20b** were easily isomerized to their η-2,3,4-pyridinylmolybdenum isomers **8e** and **8d**, respectively. The latter product can also be produced directly by the addition of (*E*)-$CH_3CH{=}CHMgCl$ to the lactamyl scaffold **4** (Table 1, entry 4). The isomerization was accomplished either in refluxing toluene over two days in 75% yield (Scheme 6) or more rapidly and more efficiently under microwave irradiation within 30 min (quartz reactor, 150 W, 110 °C) to give compounds **8d,e** in 91 and 87% yield, respectively. Importantly, all substrates **7**−**8** and **19**−**20** are easily handled, air-stable, orange/yellow solids that can be stored in the refrigerator for months.

η-2,3,4-Pyridinylmolybdenum complexes can therefore be generated bearing C-sp^2 and C-sp^3 substituents at the 6-position, either directly from lactamylmolybdenum complex **4** when sp^2 Grignard reagents are the reactants or indirectly *via* the 2-alkylidene-η-3,4,5-dihydropyridinylmolybdenum complexes after thermal isomerization in the case of sp^3 Grignard reagents.

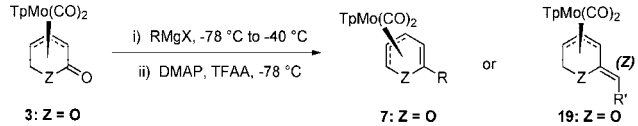
Scheme 6. Thermal Isomerization

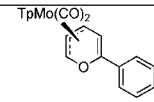
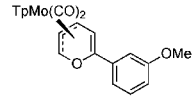
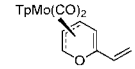
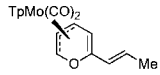
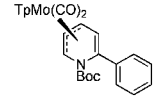
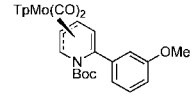
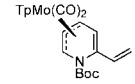
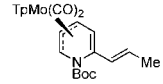
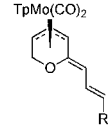
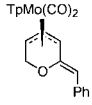
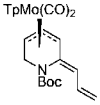
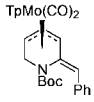


Brønsted Acid Promoted [5 + 2] Cycloaddition Reactions with Compounds 7 and 8. In earlier studies[13–15] it was shown that 5-substituted-η-2,3,4-pyranyl- and -pyridinylmolybdenum complexes were highly effective substrates in Lewis acid catalyzed [5 + 2] cycloaddition reactions with electron-deficient alkenes and alkynes. An exploration of the reactivity of 6-phenyl-η-2,3,4-pyranylmolybdenum complex **7a** with the electron-deficient alkenes methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) revealed unanticipated subtleties of the reaction system. Of the various Lewis acids initially studied ($EtAlCl_2$, Et_2AlCl, $Sc(OTf)_3$, $TiCl_4$, $BF_3{\cdot}Et_2O$), $EtAlCl_2$ was able to initiate a rapid and highly efficient [5 + 2] cycloaddition between **7a** and MVK giving the expected cycloadduct **21a** in

(54) Boyd, V. A.; Drake, B. E.; Sulikowski, G. A. *J. Org. Chem.* **1993**, *58*, 3191–3193.
(55) Li, H.; Procko, K.; Martin, S. F. *Tetrahedron Lett.* **2006**, *47*, 3485–3488.
(56) Addition of Grignard reagents at −40 °C was followed by trapping of the hemiketal at −78 °C for 1 h. The reaction mixture was then allowed to warm over 2 h.
(57) The regiochemistry and the *exo* stereochemistry of cycloadduct **21a** was established unequivocally by NMR: the regiochemistry of the reaction was determined by COSY experiment, which showed a vicinal relationship of H^6 to H^7. Moreover small coupling constants were observed for cycloadduct **21a** between H_7 and the two vicinal hydrogen pairs (0 and 1 Hz), allowing us to assume an *exo* stereochemistry. The *exo* relationships for the other examples described later in this publication were readily determined by analogy from their ^1H NMR spectra.

Table 1. Synthesis of $TpMo(CO)_2$(6-Substituted-η^3-pyranyl) and -Pyridinyl Complexes



entry	Z	RMgX	product	#	yield (%)[a]	% ee
1	O	PhMgBr		**(+)-7a**	91	97
2	O	(*m*-MeO)C_6H_4MgBr		**(+)-7b**	92	97
3	O	CH_2=CHMgCl		**(±)-7c**	72	--
4	O	CH_3CH=CHMgCl		**(±)-7d**	81	--
5	NBoc	PhMgBr		**(+)-8a** **(-)-8a** (shown)	91 90	>99 >99
6	NBoc	(*m*-MeO)C_6H_4MgBr		**(-)-8b**	90	>99
7	NBoc	CH_2=CHMgCl		**(±)-8c**	86	--
8	NBoc	CH_3CH=CHMgCl		**(±)-8d**	81	--
9	O	MeMgBr		**(±)-19a (R = H)** **(±)-19b ($R = COCF_3$)**	-- 90[b]	--
10	O	CH_2=CH-CH_2MgCl		**(±)-19c (R = H)** **(±)-19d ($R = COCF_3$)**	-- 94[b,c]	--
11	O	BnMgCl		**(±)-19e**	87	--
12	NBoc	MeMgBr		**(±)-20a**	92	--
13	NBoc	CH_2=CH-CH_2MgCl		**(±)-20b**	97	--
14	NBoc	BnMgCl		**(±)-20c**	93	--

[a] Yield of pure, isolated compound. [b] Only the *Z* isomer was observed. [c] An X-ray diffraction study conducted on compound **19d** confirmed the *Z* stereochemistry.

Scheme 7. Preliminary Observations in the [5 + 2] Cycloaddition with MVK vs EVK

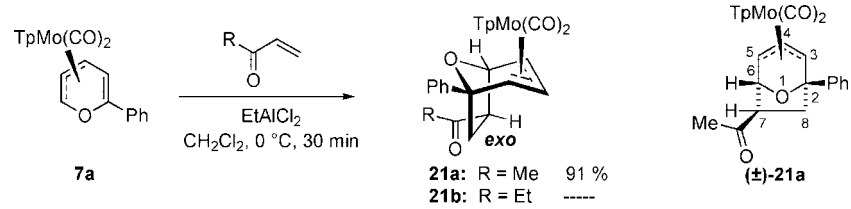
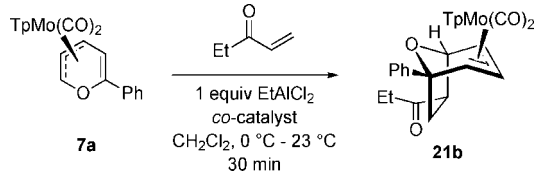


Table 2. Brønsted Lewis Acid Promoted [5 + 2] Cycloadditions



entry	Lewis acid (1 equiv)	cocatalyst (0.7 equiv)	yield (%)[a]
1	$EtAlCl_2$	---	0[b]
2	$EtAlCl_2$	AcOH	84[c]
3	---	AcOH	0[b]
4	$EtAlCl_2$	HCl	58[d]
5	$EtAlCl_2$	MeOH	79
6	$EtAlCl_2$	$Ph_3P{=}N{=}PPh_3^+Cl^-$	0[b]

[a] Yield of pure, isolated compound. [b] Starting material was entirely recovered. [c] If the ratio between $EtAlCl_2$/AcOH is <1, starting material is entirely recovered. [d] Decomposition was observed with HCl as cocatalyst.

91% yield within 30 min. Only the *exo* isomer of compound **21a** was formed (Scheme 7).[57] It was therefore totally unexpected that EVK proved to be completely unreactive toward **7a** in the presence of $EtAlCl_2$; the starting material was recovered untouched (Scheme 7 and Table 2, entry 1).

The cause of this puzzling yet reproducible observation was eventually traced to the presence of different stabilizers in commercially available MVK and EVK (Table 2). MVK is sold stabilized with 0.1% AcOH, while commercially available EVK is provided with lower levels of 2,4-di-*tert*-butyl-4-hydroxytoluene (BHT) as a stabilizer. The key role played by traces of AcOH in this chemistry was confirmed: addition of a catalytic quantity of AcOH to a mixture of 6-phenyl-η-2,3,4-pyranylmolybdenum complex **7a**, EVK, and $EtAlCl_2$ initiated a rapid reaction affording the [5 + 2] cycloadduct **21b** in 84% yield after 30 min (Table 2, entry 2). Control experiments suggested that the [5 + 2] cycloaddition is catalyzed by an *in situ* generated "super Brønsted acid" that forms upon treatment of the Lewis acidic $EtAlCl_2$ with a deficiency of AcOH.[58,59] Neither $EtAlCl_2$ nor acetic acid alone was effective in inducing a reaction, while a cocatalyst generated from a 1.0:0.7 mixture of $EtAlCl_2$ and AcOH initiated a rapid and efficient reaction (Table 2, entries 1 and 3). An effective catalyst system was also generated by replacing the AcOH with other protic acids such as HCl or MeOH (Table 2, entries 4 and 5).[60] The critical nature of the ratio between ethylaluminum dichloride and acetic acid further supports the role of a super Brønsted acid in this reaction. The reaction proceeds when the $EtAlCl_2$/AcOH ratio is >1.0, while an excess of the proton source effectively shuts down the chemistry (Table 2, entry 2, footnote c). Pairing a nonprotic coadditive with the $EtAlCl_2$ was also ineffective (Table 2, entry 6). Therefore, the 6-phenyl-η-2,3,4-pyranylmolybdenum scaffold requires the dual catalyst system $EtAlCl_2$/AcOH to engage in productive [5 + 2] cycloadditions with electron-deficient alkenes. In actual practice stoichiometric rather than catalytic quantities of ethylaluminum dichloride were used to increase the reaction rate and avoid possible racemization of the scaffolds during long reaction times.[11]

Collectively, these data are consistent with a strong Brønsted acid activation of the electron-deficient alkene leading to the formation of the cationic η^4-diene adduct **22** (Scheme 8) which is stabilized by the $TpMo(CO)_2$ moiety. The [5 + 2] cycloaddition is completed by internal quenching of the cationic complex with the pendant enol delivering the *exo* isomer exclusively. Although a potential pathway for *endo* product formation is available,[13–15] its formation was not observed. Intermediate **22** may undergo a nonreversible ring closure exclusively to the *exo* adduct, or, more likely, the *exo* isomer may be the thermodynamic cycloadduct formed under equilibrating reaction conditions.

The scope of the Brønsted acid promoted [5 + 2] cycloaddition of molybdenum scaffolds **7a** and **8a** was explored with a variety of functionalized alkenes. The results depicted in Table 3 highlight the range of electron-deficient alkenes that can participate in this transformation (alkyl or aryl substituents at the α- or β-carbons are tolerated). In each case single cycloadducts **21a**−**i**, **23a**−**i** were obtained in good to excellent yields (69−98%) simply by stirring the molybdenum complexes in dichloromethane at 0 °C in the presence of the appropriate electron-deficient alkene that was pretreated with $EtAlCl_2$/AcOH.

α,β-Unsaturated ketones (Table 3, entries 1−6), *N*-methylmaleimide (Table 3, entries 7−8), and an α,β-aldehyde (Table 3, entries 11−12) gave the expected cycloadducts in good yields from either scaffold **7a** or **8a**. The reaction also proceeded with less activated substrates like ethyl acrylate (Table 3, entries 13 and 14), acrylonitrile (Table 3, entries 15 and 16), and phenyl vinyl sulfone (Table 3, entries 17 and 18) by using longer reaction times (3−6 h) and excess quantities of the electron-deficient alkene (5 equiv). The ester and nitrile functional groups of these latter products could be used as anchors for further functionalization in potential biological applications.[61,62] Most importantly, the cycloadducts can be prepared in high enantiomeric excess (96 to >99%). Racemization, a problem recognized during earlier studies of [5 + 2] reactions of 5-substituted pyranyl and pyridinylmolybdenum scaffolds,[13–15] was insig-

(58) Garnett, J. L.; Long, M. A.; Vining, R. F. W.; Mole, T. *Tetrahedron Lett.* **1973**, 4075–4078.
(59) Magagnini, P. L.; Cesca, S.; Giusti, P.; Priola, P.; Di Maina, M. *Makromol. Chem.* **1977**, *178*, 2235–2248.
(60) 2,4-Di-*tert*-butyl-4-hydroxytoluene (BHT), the stabilizer used in commercially available ethyl vinyl ketone, could also generate a "super Brønsted acid" but is assumed to be too hindered to be effective.
(61) Huscroft, I. T.; Carlson, E. J.; Chicchi, G. G.; Kurtz, M. M.; London, C.; Raubo, P.; Wheeldom, A.; Kulagowski, J. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2008–2012.
(62) Thompson, C. G.; Carlson, E.; Chicchi, G. G.; Kulagowski, J. J.; Kurtz, M. M.; Swain, C. J.; Tsao, K.-L. C.; Wheeldom, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 811–814.

Scheme 8. Suggested Mechanism of the [5 + 2] Cycloaddition

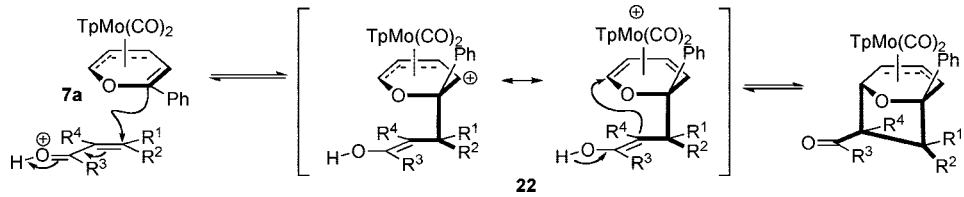
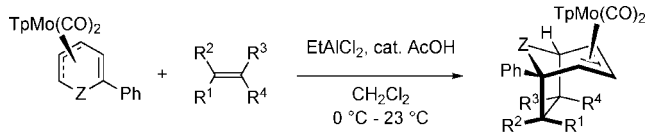


Table 3. [5 + 2] Cycloadditions of **7a** and **8a** with Electron-Deficient Various Alkenes



7a: Z = O
8a: Z = NBoc

21: Z = O
23: Z = NBoc

entry	Z	alkene	yield (%)[c]	product	R^1	R^2	R^3	R^4	% ee
1	O	CH_2=CHCOMe	98	(+)-**21a**	H	H	COMe	H	97
2	NBoc	CH_2=CHCOMe	74 [9][d]	(+)-**23a**[a]	H	H	COMe	H	>99
			73 [9][d]	(−)-**23a**[b]	H	H	COMe	H	>99
3	O	CH_2=CHCOEt	84	(±)-**21b**	H	H	COEt	H	--
4	NBoc	CH_2=CHCOEt	73 [7][d]	(±)-**23b**	H	H	COEt	H	--
5	O	2-cyclohexenone	81	(±)-**21c**	H	−$(CH_2)_3$CO−		H	--
6	NBoc	2-cyclohexenone	75 [8][d]	(+)-**23c**[a]	H	−$(CH_2)_3$CO−		H	>99
7	O	*N*-methylmaleimide	95	(±)-**21d**	H	−CON(Me)CO−		H	--
8	NBoc	*N*-methylmaleimide	72 [10][d]	(±)-**23d**	H	−CON(Me)CO−		H	--
9	O	(*E*)-PhCH=CHCOMe	73 [8][d]	(±)-**21e**	Ph	H	COMe	H	--
10	NBoc	(*E*)-PhCH=CHCOMe	70 [15][d]	(±)-**23e**	Ph	H	COMe	H	--
11	O	CH_2=C(Me)CHO[e]	88	(±)-**21f**	H	H	CHO	Me	--
12	NBoc	CH_2=C(Me)CHO[e]	72 [13][d]	(±)-**23f**	H	H	CHO	Me	--
13	O	CH_2=CHCO$_2$Et[f]	79 [9][d]	(+)-**21 g**	H	H	CO_2Et	H	96
14	NBoc	CH_2=CHCO$_2$Et[f]	78 [7][d]	(+)-**23 g**[a]	H	H	CO_2Et	H	99
15	O	CH_2=CHCN[f]	77 [9][d]	(±)-**21 h**	H	H	CN	H	
16	NBoc	CH_2=CHCN[f]	77 [7][d]	(+)-**23 h**[a]	H	H	CN	H	99
17	O	CH_2=CHSO$_2$Ph[f]	71 [20][d]	(±)-**21i**	H	H	SO_2Ph	H	--
18	NBoc	CH_2=CHSO$_2$Ph[f]	69 [23][d]	(+)-**23i**[a]	H	H	SO_2Ph	H	99

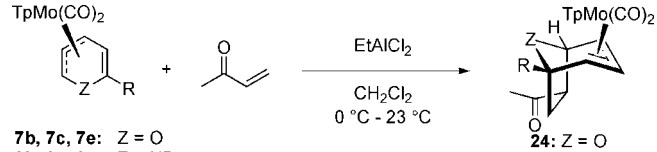
[a] From (+)-**8a**. [b] From (−)-**8a**. [c] Yield of pure, isolated compound. [d] Recovered starting material [%]. [e] NOE experiments confirmed the relative position of R^3 and R^4: NOE effects were observed between the methyl group and H^5 in (±)-**21f**. The structure of (±)-**23f** was assumed by analogy. [f] Longer time of reaction (3−6 h) or larger amounts of alkene and catalysts were required. For more details, see the Supporting Information.

nificant using these 6-substituted scaffolds (1−2%) and only noted during cycloadditions of 6-substituted scaffolds with some polar alkenes that required longer reaction times (Table 3, entry 13).

To further explore the generality of this organometallic enantiomeric scaffold-based cycloaddition, other 6-complexes were studied as substrates for [5 + 2] cycloaddition reactions using MVK (Table 4). The process appears general for 6-aryl and 6-alkyl scaffolds which reacted to give the expected products in good yields with complete retention of the enantiomeric excess. Unfortunately, the 6-vinyl-(η^3-pyranyl- and η^3-pyridinylmolybdenum) scaffolds **7c** and **8c** led to complex reaction mixtures (Table 4, entries 2 and 4) and were not further studied.

Demetalation and Access to 2-Substituted Oxa- and Aza[3.2.1]octene Derivatives. The synthetic potential of this [5 + 2] cycloaddition was realized through an efficient oxidative demetalation using PDC/SiO_2.[39] This demetalation procedure regiospecifically introduced an oxo functional group at the more hindered terminus of the allyl moiety providing the corresponding oxa- and azabicyclo[3.2.1]octenes **26**−**35** in good yields (61−71%)(Table 5). Complete retention of enantiomeric purity was observed when this demetalation protocol was applied to chiral, nonracemic cycloadducts, highlighting the potential of this methodology for enantiocontrolled synthesis of oxa- and azabicyclo[3.2.1]octane derivatives.

Table 4. Generalization of the [5 + 2] Cycloadditions to Different 6-Substituted Molybdenum Complexes in the Presence of MVK



7b, 7c, 7e: Z = O
8b, 8c, 8e: Z = NBoc

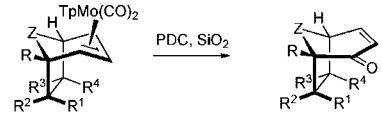
24: Z = O
25: Z = NBoc

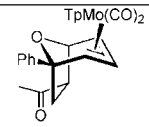
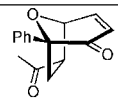
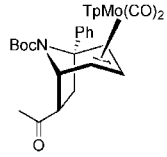
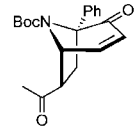
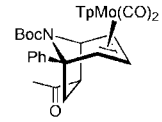
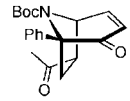
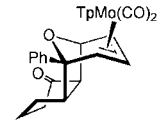
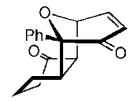
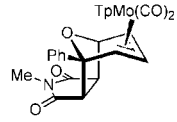
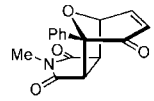
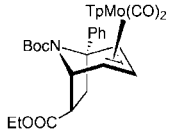
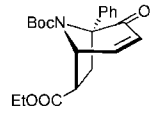
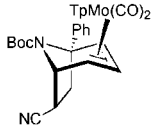
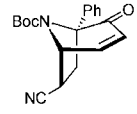
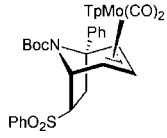
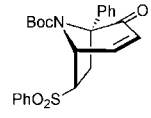
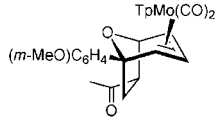
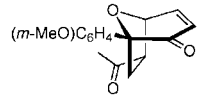
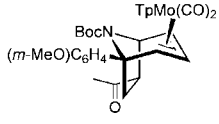
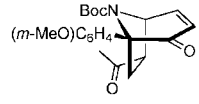
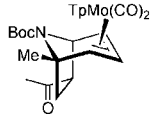
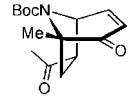
entry	compound	Z	R	product	yield (%)[a]	% ee
1	(+)-**7b**	O	−(*m*-MeO)C_6H_4	(+)-**24a**	93	97
2	(±)-**7c**	O	−CH=CH_2	(±)-**24b**	complex mixture	--
3	(±)-**7e**[c]	O	−Et	(±)-**24c**	81	--
4	(−)-**8b**	NBoc	−(*m*-MeO)C_6H_4	(−)-**25a**	88 [5][b]	>99
5	(±)-**8c**	NBoc	−CH=CH_2	(±)-**25b**	complex mixture	--
6	(±)-**8e**	NBoc	−Me	(±)-**25c**	92	--

[a] Yield of pure, isolated compound. [b] Recovered SM (%). [c] Compound **7e** is derived from compound **7c** by hydrogenation of the vinyl side chain. For more details, see Supporting Information.

The structure assigned to the product of oxidative demetalation was determined by studying the ^{1}H NMR spectrum of (+)-**26** (Figure 3). For cycloadduct **26** the enone protons H^4 and H^5 are readily apparent and assigned on the basis of chemical shifts and their coupling to each other and to the allylic

Table 5. Demetalation Protocol with PDC/SiO_2



entry	compound	#	product	#	yield (%)[a]	% ee
1		(+)-21a		(+)-26	70	96
2		(+)-23a		(-)-27	68	>99
3		(-)-23a		(+)-27	67	>99
4		(±)-21c		(±)-28	69	--
5		(±)-21d		(±)-29	68	--
6		(+)-23g		(-)-30	68	>99
7		(+)-23h		(-)-31	65	>99
8		(+)-23i		(-)-32	61	>99
9		(+)-24a		(+)-33	71	96
10		(-)-25a		(+)-34	71	>99
11		(±)-25c		(±)-35	70	--

[a] Yield of pure, isolated compound.

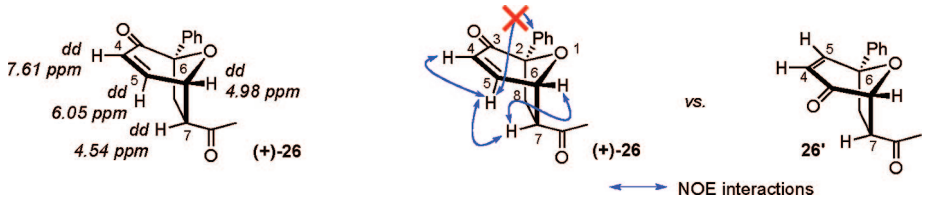
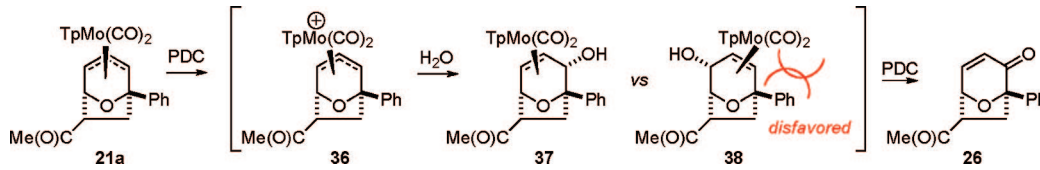


Figure 3. NOE Interactions in Cycloadduct (+)-**26**

Scheme 9. Mechanistic Proposal for the Regiospecific Oxidative Demetalation



hydrogen H^6. Consistent with earlier studies of exosubstituted oxa- and azabicyclo[3.2.1]octenes the two methine hydrogens, H^6 and H^7, do not couple to each other.[15] NOE experiments showed correlations between H^6 and H^7, but no correlation was observed between the phenyl ring hydrogens and H^5, the enone β-H. These data are fully consistent with formation of regioisomer (+)-**26** and not **26′** in the oxidative demetalation. The structures of the other oxidative demetalation products were assigned by analogy.

The formation of enone regioisomer **26** from the oxidative demetalation can be rationalized by a mechanism that begins with removal of one electron from the $TpMo(CO)_2$(allyl) complex generating the cationic allylmolybdenum species **36** (Scheme 9). An incoming water nucleophile would likely attack the cationic allyl **36** *anti* to the $TpMo(CO)_2$ moiety and at one of the two allylic termini. Although the η^3-allyl terminus adjacent to the quaternary carbon of the [5 + 2] adduct clearly presents a more hindered trajectory for attack by an incoming nucleophile, the immediate product of that nucleophilic addition of water is an η^2-alkene complexed to $TpMo(CO)_2$ (structure **38** in Scheme 9). The stability of the "product" (the η^2-alkene complex) must therefore control the regiochemical outcome of the oxidative demetalation and lead to the less sterically encumbered η^2-alkene complex **37**. This produces the allylic alcohol bearing its hydroxyl substituent adjacent to the hindered quaternary carbon; it is oxidized to the observed enone **26** by excess PDC.

Conclusions

Efficient and scalable syntheses of the molybdenum π-complex scaffolds (+)-**3**, racemic (±)-**4**, and chiral, nonracemic (+)-**4** and (−)-**4** are reported. Grignard reagents add to these substrates in excellent yields (72−97%) to provide 6-substituted $TpMo(CO)_2$(η-2,3,4-pyranyl) and $TpMo(CO)_2$(η-2,3,4-pyridinyl) complexes **7** and **8** with complete retention of enantiomeric purity. By way of a novel and versatile Brønsted acid mediated [5 + 2] cycloaddition, scaffolds **7** and **8** generate functionalized oxa- and azabicyclo[3.2.1]octenes in a regio- and enantiocontrolled fashion. The reaction proceeds in moderate to excellent yields (69−98%), with excellent *exo*-selectivity, and affords products **21/23a−i** and **24/25a−c** with complete retention of enantiomeric purity. Finally, highly functionalized 6-substituted oxa- and azabicyclo[3.2.1]octane **26−35** derivatives were generated in good yields (61−71%) and high enantiopurity (96−99% ee) by applying a very regioselective oxidative demetalation protocol. 6-Substituted-1-aryl-8-azabicyclo[3.2.1]octenes represent an important class of tropane derivatives that have been studied as CNS penetrant hNK_1 receptor antagonists.[61,62] Oxabicyclo[3.2.1]octanes have also been used as versatile building blocks in organic synthesis,[23] which has spurred the development of enantiocontrolled routes to these bicycles.[63]

Experimental Section

Representative experimental procedures are listed here. Full experimental details for all reactions and characterization data for all compounds can be found within the Supporting Information.

(−)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-(*tert*-butyloxycarbonyl)-6-phenyl-1,2-dihydropyridin-2-yl]molybdenum, (+)-8a. Under argon, at −78 °C, to a suspension of a 99.9% ee sample of the molybdenum complex (+)-**4** (0.100 g, 0.18 mmol) in dry THF (1.8 mL) was added dropwise a 0.3 M solution of phenyl magnesium bromide (650 μL, 0.20 mmol, 1.1 equiv). After 5 min, the reaction mixture was allowed to warm up at −40 °C and was stirred for 1 h. After cooling down at −78 °C, 4-dimethylaminopyridine DMAP (0.025 g, 0.20 mmol, 1.15 equiv) and trifluoroacetic anhydride TFAA (62 μL, 0.44 mmol, 2.5 equiv) were sequentially added, and the mixture was stirred for 1 h at −78 °C, then slowly warmed up at room temperature over 1 h, and stirred for further 1 h. The reaction was hydrolyzed at 0 °C by addition of ice and extracted twice with ethyl acetate and brine. The organic layers were combined, dried over magnesium sulfate, filtrated, and concentrated under vacuum. The crude product was purified by chromatography (silica gel, hexanes/EtOAc 2:1 v/v) to afford compound (+)-**8a** {91% yield and 99.7% ee, $[\alpha]_D^{20}$ +278 (*c* 0.32, CH_2Cl_2)} as a yellow powder. TLC (*n*-hexanes/CH_2Cl_2 2:1) $R_f = 0.25$; mp = 204−208 °C with decomp.; IR (cm^{-1}): 3127 (w), 3057 (w), 2980 (w), 2934 (w), 1930 (s), 1849 (s), 1702(m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.52 (d, J = 2.0 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 6.0, 2.4 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.28−7.20 (m, 3H), 7.17−7.12 (m, 2H), 6.28 (app t, J = 2.0 Hz, 1H), 6.21 (app t, J = 2.0 Hz, 1H), 6.18 (app t, J = 2.0 Hz, 1H), 5.90 (d, J = 6.0 Hz, 1H), 4.96 (td, J = 6.0, 2.4 Hz, 1H), 2.84 (dd, J = 6.0, 1.2 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 231.6, 223.8, 157.2, 153.2, 146.1, 144.9, 140.3, 139.9, 136.2, 136.0, 134.6, 131.4, 129.0, 127.7, 127.5, 127.4, 126.8, 118.0, 106.0, 105.6, 93.7, 82.6, 62.2, 53.1, 27.6 (*3); (+)-**8a**: HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $C_{27}H_{28}BMoN_7O_4$, 623.1350; found, 623.1354.

(+)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][η-(2,3,4)-(1*S*,2*R*,5*S*,6*R*)-8-aza-8-(*tert*-butyloxycarbonyl)-6-ethoxycarbonyl-1-phenylbicyclo[3.2.1]oct-3-en-2-yl]molybdenum, (+)-23g. Under argon, at 0 °C, to a solution of compound (+)-**8a** (0.125 g, 0.20 mmol) in dry dichloromethane (1.6 mL) were sequentially added ethyl acrylate (120 μL, 1.21 mmol, 6 equiv) followed by a premixed

solution of a 1.0 M solution in dichloromethane of ethylaluminum dichloride (201 μL, 0.20 mmol, 1 equiv) and glacial acetic acid (8 μL, 0.14 mmol, 0.7 equiv). After 4 h at 25 °C, the reaction mixture was hydrolyzed with ice at 0 °C and extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc 2:1 v/v) to afford after evaporation *exo*-(+)-**23g** in 78% yield and 99.6% ee {$[\alpha]_D^{20}$ +284 (*c* 0.16, CH_2Cl_2)} as an orange solid. TLC (*n*-hexanes/EtOAc 2:1) R_f = 0.25; mp = 193−194 °C with decomp.; IR (cm^{-1}): 3120 (w), 2951 (w), 1933 (s), 1847 (s), 1732 (m), 1708 (m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.42 (d, J = 1.8 Hz, 1H), 7.70 (dd, J = 1.8, 2.1 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.59 (d, J = 2.1 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.30−7.18 (m, 5H), 6.23 (app t, J = 2.4 Hz, 1H), 6.19 (app t, J = 2.1 Hz, 1H), 6.16 (app t, J = 2.1 Hz, 1H), 4.46 (d, J = 5.8 Hz, 1H), 4.39 (d, J = 6.8 Hz, 1H), 4.32 (app t, J = 6.6 Hz, 1H), 4.13 (d, J = 3.0 Hz, 1H), 3.75 (m, 1H), 3.63 (q, J = 12.0 Hz, 2H), 2.40 (m, 1H), 1.26 (t, J = 12.0 Hz, 3H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 226.4, 224.3, 173.1, 157.7, 146.3, 145.9, 139.4, 137.7, 136.6, 135.7, 134.0, 128.7 (*2), 128.2 (*2), 125.9, 105.9, 105.7, 105.2, 79.8, 76.1, 65.2, 61.9, 61.6, 50.1, 44.9, 42.4, 32.4, 28.5 (*3), 14.1; HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{32}H_{36}BMoN_7O_6$, 723.1874; found, 723.1869.

(−)-(1*S*,2*R*,5*S*,6*R*)-11-aza-11-(*tert*-butyloxycarbonyl)-6-ethyloxycarbonyl-1-phenylbicyclo[3.2.1]oct-3-ene-2-one, (−)-30. To a solution of a 99.7% ee sample of compound (+)-**23g** (0.144 g, 0.20 mmol) in dichloromethane (2 mL) was added a mixture of PDC (0.240 g, 0.64 mmol, 3.2 equiv) and silica gel (0.240 g) in one portion as a solid. The mixture was stirred at room temperature overnight. It was then passed through a short pad of Celite and eluted with dichloromethane/ethyl acetate 2:1. After concentration, the residue was purified by flash chromatography to afford (−)-**30** in 68% yield and 99.6% ee {$[\alpha]_D^{20}$ −81 (*c* 0.16, CH_2Cl_2)} as a white solid. TLC (*n*-hexanes/EtOAc 1:1) R_f = 0.27; mp = 105−106 °C with decomp.; IR (cm^{-1}): 2956 (w), 1731 (s), 1715 (s), 1202 (m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (dd, J = 9.8, 5.7 Hz, 1H), 7.31−7.22 (m, 5H), 6.77 (d, J = 9.8 Hz, 1H), 5.26 (d, J = 5.7 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.95 (dd, J = 3.5, 9.2 Hz, 1H), 2.92−2.83 (m, 1H), 2.17 (dd, J = 9.2, 14.0 Hz, 1H), 1.95 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.6, 173.1, 157.7, 147.8, 144.2, 128.6 (*2), 128.2 (*2), 128.1, 126.0, 79.8, 76.7, 61.6, 45.9, 37.0, 36.5, 28.5 (*3), 14.1; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{25}NO_5$, 371.1733; found, 371.1745.

Acknowledgment. This work was supported by Grant GM 522238, awarded by the National Institute of General Medical Sciences, Department of Health and Human Services. We are most grateful to our colleague Dr. Kenneth Hardcastle for his skilled and efficient assistance with X-Ray crystallography and to Dr. Pilar Areces of the Universidad de Extremadura, Badajoz, Spain for providing unpublished procedures and copies of spectra for compounds **10** and **11** that are mentioned in ref 43. We thank colleague Minkoo Ji for carrying out preliminary experiments confirming the thermal isomerization of exocyclic 2-alkylidene-η-3,4,5-dihydropyridinylmolybdenum complexes to their endocyclic η-2,3,4-pyridinylmolybdenum isomers.

Supporting Information Available: Full experimental details and characterization data for all compounds; copies of proton and carbon NMR spectra of all new compounds prepared in this study. Full X-ray crystallography data for compound **19d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA800664V

(63) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2000**, *2*, 1005–1007.