Chiral Scaffolds for Enantiocontrolled Synthesis: Enantio- and Regiocontrolled [4 + 2] Cycloaddition to 3-Alkenyl-η^3-Pyranylmolybdenum Complexes

Ramón Gómez Arrayás and Lanny S. Liebeskind*

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

Received March 7, 2001

Enantiomerically pure stoichiometric transition metal π-complexes derived from an inexpensive metal source represent synthetically potent chiral scaffolds for asymmetric synthesis.[1] As recently described, $TpMo(CO)_2$(pyranyl) **1** and $TpMo(CO)_2$(pyridinyl) **2** (Figure 1: Tp = hydridotrispyrazolylborate), each easily prepared in high enantiopurity, are excellent chiral scaffolds for the enantiocontrolled construction of either 2,3,6-trisubstituted dihydropyrans[2] and piperidines[3] via sequential functionalization, or oxabicyclooctenes[4] and tropanes[5] via [5 + 2] cycloaddition.

The enantiocontrolled [4 + 2] cycloaddition of electrophilic olefins to alkenyl substituted heterocycle π-complexes (**1** or **2**, R^1 = alkenyl) would represent a direct access to decahydrobenzopyrans and decahydroquinolines, skeletal frameworks that are present in a number of physiologically active natural products. Although such bicyclic ring-fused systems could be assembled with high regio and stereocontrol through a Diels−Alder reaction, the synthetic utility of this approach has been mostly limited to the intramolecular version,[6] probably because of the poor reactivity of the corresponding dienes.[7] On the other hand, [4 + 2] cycloaddition to transition metal−diene complexes are known,[8] but highly electron-deficient olefins are usually the only applicable dienophiles and few examples has been described with enantiomerically enriched metal−dienes.[9]

The racemic Mo-dienes **6** and **7** were easily prepared from 3-oxopyranyl complex (±)-**3**[4] in two steps involving the addition of vinyl or propenyl[10] Grignard reagent followed by dehydration of the resulting alcohol with TFAA/Et_3N (Scheme 1). The separate antipodes of diene **6** were prepared in 98% ee starting from (+)-**3** or (−)-**3** (both in 98% ee)[11,12] using the same synthetic sequence.

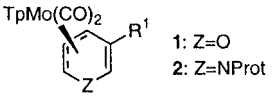
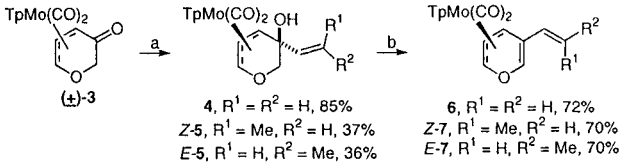


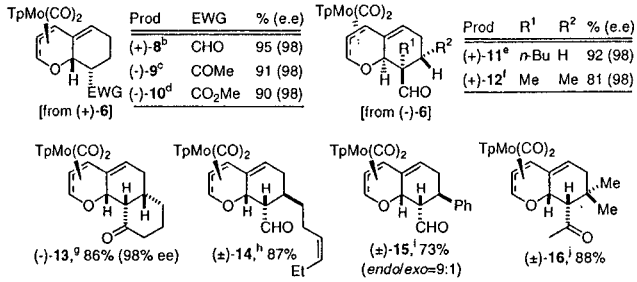
Figure 1.

Scheme 1. Synthesis of $TpMo(CO)_2$(3-alkenyl-η-4,5,6-pyranyl) Complexes



[a] VinylMgCl or propenylMgBr, THF, −20 °C. [b] TFAA, Et_3N, DMAP, CH_2Cl_2, −78 °C to rt.

Chart 1. Et_2AlCl-promoted [4 + 2] Cycloadditions of Mo-diene **6**[a]



[a] Conditions: 1.1 equiv of Et_2AlCl, CH_2Cl_2. [b] −78 °C, 5 min. [c] −78 °C, 10 min. [d] 0 °C, 6 h. [e] −78 °C, 15 min. [f] 0 °C, 1 h. [g] 0 °C, 7 h. [h] 0 °C, 45 min. [i] 0 °C, 10 min. [j] rt, 24 h.

The air-stable, solid, yellow dienes **6** and **7** participated in *thermal* [4 + 2] cycloadditions, but only with strongly electron-deficient dienophiles and heterodienophiles (to be described in a full paper). In contrast, a full equivalent of Et_2AlCl induced an efficient and very general [4 + 2] cycloaddition of **6** with a variety of dienophiles including variously substituted α,β-unsaturated aldehydes, ketones, esters and nitriles[13] (Chart 1).

The cycloaddition reaction was highly efficient, not only with monosubstituted electrophilic olefins, but also with α-alkyl and β-alkyl-substituted olefins. Even the generally unreactive β,β-dimethyl-substituted unsaturated ketone mesityloxide reacted with **6** to afford only one cycloadduct in very good yield (**16**, Chart 1). Excellent regio- and stereoselectivities were obtained in the reaction with aldehydes, ketones, and esters. The bulky $TpMo(CO)_2$ group caused complete facial diastereoselectivity derived from attack of the dienophile at the face of the diene away from the molybdenum. Excellent *endo* selectivity[14] was observed for all cases, except that with acrylonitrile.[13] Cyclo-

(1) For reviews on applications of stoichiometric transition metal complexes in asymmetric organic synthesis: (a) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1−13. (b) Stephenson, G. R. *Adv. Asymmetric Synth.* **1996**, 313−366. (c) Pearson, A. J. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, E. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, Chapter 6.3. (d) Li, C.-L.; Liu, R.-S. *Chem. Rev.* **2000**, *100*, 3127−3161.

(2) Yin, J.; Llorente, I.; Villanueva, L. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 10458−10459.

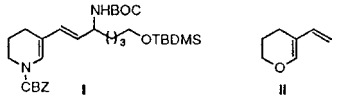
(3) Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 7445−7455.

(4) Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 5811−5812.

(5) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3909−3911.

(6) (a) Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141−145. (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205−1208. (c) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098−4103. (d) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3658.

(7) For example, racemic diene **I** (see below) was poorly reactive in Diels−Alder cycloadditions, reacting only with methyl acrylate to afford a mixture of cycloadducts inseparable by chromatography: (a) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700. Reactivity of pyranyl diene **II** has also been studied, but only [4 + 2] cycloadditions with highly electrophilic dienophiles were reported: (b) Potthoff, B.; Breitmaier, E. *Chem. Ber.* **1986**, *119*, 3204. Similar reactivity has been reported in the intermolecular Diels−Alder of other sugar-based dienes; for a review, see: (c) Giuliano, R. M. *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; ACS Symposium Series 494; American Chemical Society: Washington, DC, 1992; pp 33−49. Intermolecular [4 + 2] cycloadditions of 2-amino-1,3-dienes were recently described: Ha, J. D.; Kang, C. H.; Belmore, K. A.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 3810−3811 and Jiang, J.; DeVita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593−594.



(8) For a review of transition metal-mediated cycloadditions: Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523.

(9) (a) Richardson, B. M.; Day, C. S.; Welker, M. E. *J. Organomet. Chem.* **1999**, *577*, 120. (b) He, G.; Loh, S.-K.; Vittal, J. J.; Mok, K. F.; Leung, P.-H. *Organometallics* **1998**, *17*, 3931. (c) Kündig, E. P.; Bernardelli, G.; Leresche, J. *J. Chem. Soc., Chem. Commun.* **1991**, *1713*. (d) Kündig, E. P.; Bernardelli, G.; Leresche, J.; Romanens, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 407.

(10) The resulting 1:1 mixture of ***Z*-5** and ***E*-5** was separated by flash chromatography. The stereochemistry of ***E*-5** was unequivocally established by X-ray crystallographic analysis (see Supporting Information).

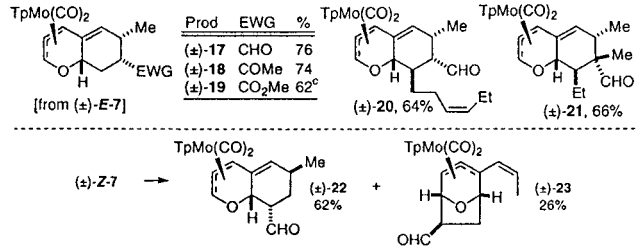
(11) Enantiopurity of a 95−97% ee sample of (+)-**3** or (−)-**3** (ref 4) was increased to 98% ee by recrystallization.

(12) Enantiomeric excesses were measured by chiral column HPLC.

(13) The reaction of (±)-**6** with acrylonitrile (0 °C, 20 min) gave a 55:45 mixture of the corresponding *endo*/*exo* cycloadducts that could not be efficiently separated by chromatographic purification.

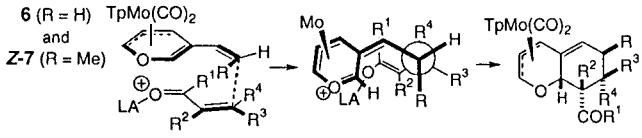
10.1021/ja010612z CCC: $20.00
Published on Web 06/02/2001

Chart 2. Et_2AlCl-Promoted [4 + 2] Cycloadditions of (±)-***E*-7**[a] and (±)-***Z*-7**[b]



[a] Conditions: 1.1 equiv of Et_2AlCl, CH_2Cl_2, 0 °C, 10−45 min. [b] 1.1 equiv of Et_2AlCl, CH_2Cl_2, −78 °C, 90 min. [c] The reaction takes 12 h at 0 °C and 8% of the *endo* cycloadduct with the opposite regiochemistry [(±)-**III**, see ref 15] was isolated.

Scheme 2. *endo*-Selective, Stepwise Mechanism



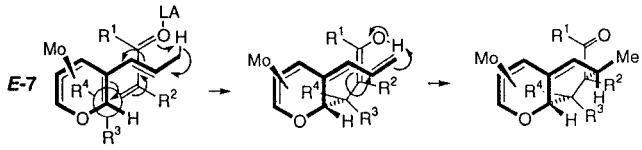
addition products of 98% ee were obtained when starting from (+)-**6** or (−)-**6** (each of 98% ee).[12]

Unexpectedly, Et_2AlCl-promoted cycloadditions of *trans*-propenyl complex ***E*-7** gave almost exclusively [4 + 2] adducts of opposite regiochemistry from the parent vinyl diene **6**,[13,15] while ***Z*-7**, which is significantly less reactive than ***E*-7**,[16] reacted with acrolein to give some of the [5 + 2] cycloadduct (±)-**23**, but predominantly the [4 + 2] adduct (±)-**22** (Chart 2).

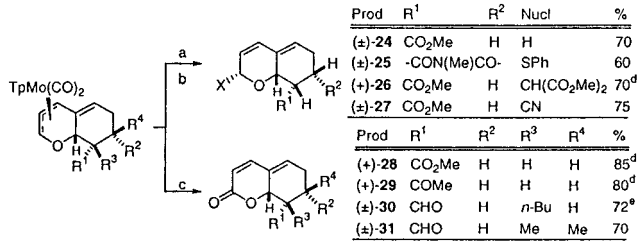
Although a concerted process is feasible, a stepwise, *endo*-selective (dipole-stabilized) mechanism for the [4 + 2] cycloaddition of the unsubstituted vinylpyranyl complex **6** and the *cis*-CH_3 substituted ***Z*-7** is suggested in Scheme 2. This is consistent with the fact that, while the rate of product formation is clearly affected by alkyl-substitution at the β-position of the dienophile (compare conditions for the cycloaddition to acrolein with those for *E*-cinnamaldehyde or 2*E*,6*Z*-nonadienal in Chart 1), **6** undergoes cycloaddition with acrolein or α-butylacrolein without a noticeable difference in reactivity (refer to reaction conditions footnoted in Chart 1). Placement of a *cis*-CH_3 substituent on the vinylpyranyl complex (i.e., ***Z*-7**) introduces conformational and nonbonded steric effects that retard the stepwise [4 + 2] process and allow competitive formation of the [5 + 2] adduct.

A mechanism specific to the presence of a *trans*-CH_3 substituent on the vinylpyranyl complex is suggested by the complete change of regiochemistry for the Et_2AlCl-promoted cycloadditions of ***E*-7**. A concerted [4 + 2] cycloaddition seems unlikely for this case alone, and while a better understanding of the mechanism must await additional experiments, a 10π-electron ene mechanism is an attractive option (Scheme 3).

Scheme 3. Hypothetical 10π Ene Mechanism



Scheme 4. Demetalation Protocols for [4 + 2] Cycloadducts



[a] $NOPF_6$ (1.2 equiv), CH_2Cl_2, 0 °C, 30 min. [b] Nucl (1.2 equiv). [c] PDC (3−4 equiv)/silica gel, CH_2Cl_2, rt. [d] 98% ee.[12] [e] (−)-**30** was obtained in 99.8% ee from (+)-**11** (of 99.8% ee).[12]

The full synthetic potential of the [4 + 2] cycloaddition was realized through two effective demetalation protocols. Activation of the $TpMo(CO)_2$ moiety (CO → NO^+) using $NOPF_6$ was followed by treatment with nucleophiles[17] such as hydride, phenylthiolate, cyanide, and malonate and gave the functionalized, demetalated 1-oxadecalines **24**−**27** (Scheme 4). Also, a new and useful oxidative demetalation protocol that allows the regioselective introduction of a carbonyl group at an allyl terminus has been found.[18] Treatment of the molybdenum [4 + 2] cycloadducts with 3−4 equivalents of pyridinium dichromate in the presence of SiO_2 (CH_2Cl_2, rt) gave the corresponding α,β-unsaturated lactones (**28**−**31**) in good yields (Scheme 4).

In conclusion, a novel, efficient, and versatile transition metal-mediated [4 + 2] cycloaddition of $TpMo(CO)_2$(3-alkenyl-η-4,5,6-pyranyl) complexes is reported. The reaction proceeds in good to excellent yields, with good regio- and *endo*-selectivities, and gives products with complete retention of enantiomeric purity when carried out with nonracemic scaffolds (98% ee). Two general demetalation protocols were developed that furnish a variety of substituted 1-oxadecalines. Related studies with *N*-containing systems are being carried out. These and other results will be reported in due course.

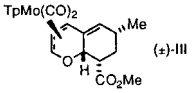
Acknowledgment. This work was supported by Grant GM43107, awarded by the National Institute of General Medical Sciences, DHHS. R.G.A. thanks NATO for a postdoctoral fellowship. We acknowledge with pleasure the skilled contribution of Dr. Jingjun Yin to the early stage of this project. We thank colleague Dr. Jiri Srogl for suggesting the ene mechanism for reaction of ***E*-7** with dienophiles.

Supporting Information Available: A complete description of the synthesis and characterization of all compounds prepared in this study, copies of proton and carbon NMR spectra of all compounds, and X-ray crystallographic studies of (±)-**11**, (±)-**17**, and ***E*-5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010612Z

(14) The regio- and the *endo*/*exo* stereochemistry of the cycloadducts were unequivocally established by NMR, mainly using COSY and NOESY experiments, respectively. Also, an X-ray crystallographic analysis of (±)-**11** and (±)-**17** confirmed both the regiochemistry and the *endo*-approach of the dienophile *anti* to Mo (see Supporting Information).

(15) A mixture of two other compounds was obtained in less than 5% yield in most cases. In the reaction of ***E*-7** with methyl acrylate (12 h, 0 °C) the regioisomer (±)-**III** could be isolated (8% yield) and characterized.



(16) In a dramatic competition experiment, when a 1:1.3 mixture of ***E*-7** and ***Z*-7** was treated with acrolein (1 equiv) and Et_2AlCl (1.1 equiv) in CH_2Cl_2, at −78 °C for 5 min, a mixture of (±)-**17** (44%) and the unreacted ***Z*-7** (40%) was obtained without traces of ***E*-7**.

(17) (a) Adams, R. D.; Chodosh, D. F.; Faller, J. W.; Rosan, A. M. *J. Am. Chem. Soc.* **1979**, *101*, 2570. (b) Pearson, A. J.; Douglas, A. R. *Organometallics* **1998**, *17*, 1446−1448. For examples of the enantioselective version of this protocol, see: (c) Faller, J. W.; Chao, K. H. *J. Am. Chem. Soc.* **1983**, *105*, 3893, and (d) Faller, J. W.; Chao, K. H. *Organometallics* **1984**, *3*, 927 and 1231.

(18) Manuscript in preparation.