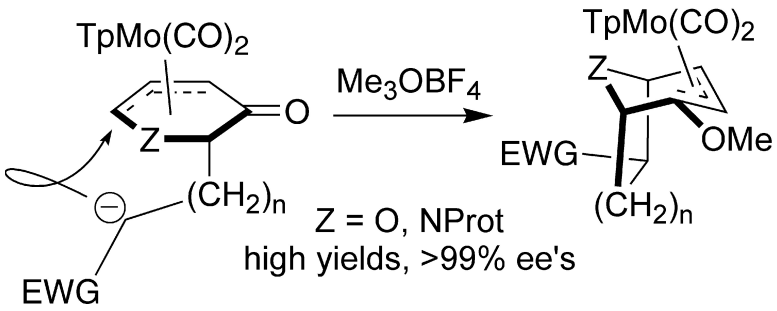
Communication

Synthesis of Substituted Oxa- and Aza[3.2.1] and [4.3.1]Bicyclics via an Unprecedented Molybdenum-Mediated 1,5-"Michael-Type" Reaction

Yongqiang Zhang, and Lanny S. Liebeskind

J. Am. Chem. Soc., **2005**, 127 (32), 11258-11259• DOI: 10.1021/ja0538132 • Publication Date (Web): 26 July 2005



More About This Article

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

- Supporting Information
- Links to the 6 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
COMMUNICATIONS

Published on Web 07/26/2005

Synthesis of Substituted Oxa- and Aza[3.2.1] and [4.3.1]Bicyclics via an Unprecedented Molybdenum-Mediated 1,5-"Michael-Type" Reaction

Yongqiang Zhang and Lanny S. Liebeskind*

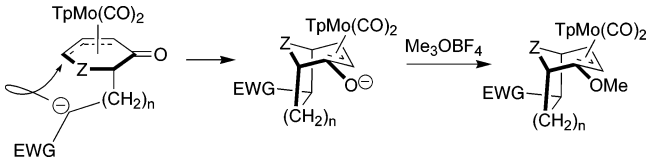
Sanford S. Atwood Chemistry Center, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322

Received June 10, 2005; E-mail: chemLL1@emory.edu

Neutral η^3-allylmolybdenum complexes bearing $CpMo(CO)_2$ and $TpMo(CO)_2$ auxiliaries (Cp = η^5-cyclopentadienyl; Tp = hydridotrispyrazolylborato) are quite robust.[1] While they do react with strong acids and electrophiles, they are stable to mild acids and electrophiles and, additionally, do not engage in direct nucleophilic functionalization of the neutral η^3-allylmolybdenumdicarbonyl. Nevertheless, these η^3-allylmolybdenum complexes are very useful in synthesis because they can be predictably activated for regio- and stereospecific *nucleophilic functionalization* by prior conversion to cationic complexes. This is achieved in one of two ways. A neutral $CpMo(CO)_2$ or $TpMo(CO)_2$ η^3-allylmolybdenum complex can be transformed into a cationic η^4-diene by abstraction of either a hydride or a heteroatom leaving group that resides on a carbon atom adjacent to the η^3-allyl moiety.[1a−c,2] Alternatively, the neutral η^3-allylmolybdenum complex can be converted to a cationic η^3-allyl complex by replacing one of the auxiliary CO ligands with a cationic NO^+ ligand.[1a,d,3] Of the two systems, the $TpMo(CO)_2$-based complexes are increasingly gaining favor because of their ease of synthesis, scalability, and broad generality.[4]

Herein is reported a new reaction profile for neutral $TpMo(CO)_2$-(η^3-allyl) complexes: the direct nucleophilic functionalization of a π-bound carbon of neutral $TpMo(CO)_2$(5-oxo-η^3-pyranyl) and $TpMo(CO)_2$(5-oxo-η^3-pyridinyl) complexes by an internal enolate (Scheme 1).[5] This unprecedented carbon−carbon bond forming

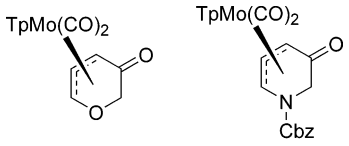
Scheme 1. "1,5-Michael-Type" Reactions of 5-Oxo-η^3-allylmolybdenum Complexes (Z = O, NProt)



reaction occurs in high yield and with excellent stereoselectivity and should allow the rapid and enantiocontrolled construction of a variety of substituted oxa- and aza-bridged bicyclics. Furthermore, it reinforces the concept that $TpMo(CO)_2$(η^3-pyranyl) and $TpMo(CO)_2$(η^3-pyridinyl) complexes represent powerful "enantiomeric scaffolds" for the asymmetric construction of a wide variety of heterocyclic systems.[4b−j]

Initial studies were conducted using racemic forms of 5-oxo-η^3-pyranyl and 5-oxo-η^3-pyridinyl molybdenum complexes **1** and **2** (Figure 1). These air-stable, solid molybdenum complexes were first transformed into silyl enol ethers using standard procedures (TBSOTf/Et_3N). The silyl enol ethers were then subjected to $TiCl_4$-induced Mukaiyama−Michael reactions with various enones to afford adducts **3**−**7** in good to excellent yields and with excellent diastereoselectivities (Table 1).[6]

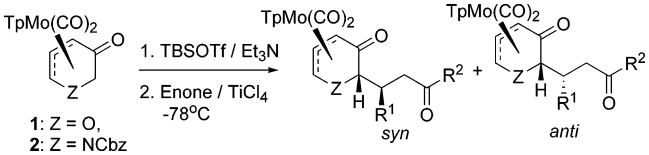
Treatment of the Mukaiyama−Michael adducts **3**−**7** with solid bases ($NaOCH_3$ or $KOSiMe_3$) suspended in CH_2Cl_2 followed by a Me_3OBF_4 quench generated "1,5-Michael" adducts in excellent yields and with excellent *exo*/*endo* selectivities.[7] As depicted in



1 **2**

Figure 1. 5-Oxopyranyl and 5-oxopyridinyl molybdenum scaffolds. Racemic and nonracemic complexes **1** were prepared by previously published procedures,[4b] and racemic 5-oxo-η^3-pyridinyl complex **2** was generated by mild acidic hydrolysis of the known $TpMo(CO)_2$(5-methoxy-dihydropyridinyl) complex.[4c]

Table 1. Synthesis of Mukaiyama−Michael Adducts of **1** and **2**



1: Z = O,
2: Z = NCbz

entry	Z	R^1	R^2	compound (yield %)	syn/anti
1	O	H	H	**3** (94)	
2	O	Ph	CH_3	**4** (71)	10:1
3	O	$-(CH_2)_3-$		**5** (91)	1:40
4	O	$-(CH_2)_2-$		**6** (70)	1:7
5	NCbz	H	H	**7** (90)	

Table 2, $KOSiMe_3$ produced, in all cases, much better yields and gave better selectivities than solid NaOMe. The bulky $TpMo(CO)_2$ group caused complete facial diastereoselectivity resulting from approach of the enone to the face of the pyranyl or pyridinyl opposite to the molybdenum. The *exo* and *endo* relationship was readily determined by comparing the coupling constants[8] between the hydrogen atoms adjacent to the bridging heteroatoms and their vicinal neighbors, previously well-established by X-ray crystallographic analysis and NMR studies.[4b]

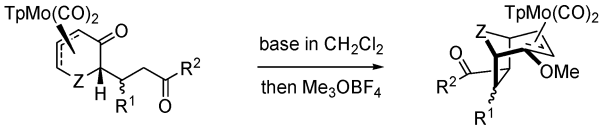
In contrast to $KOSiMe_3$, which cleanly generated variants of the bicyclo[3.2.1] ring system, the use of KO*t*-Bu as the base produced significant quantities of 1,5-Michael adducts possessing a core bicyclo[4.3.1] ring system (Table 3).[9] The composition of the [4.3.1] ring system was unequivocally established by NMR spectroscopy and was further confirmed by X-ray crystallographic analysis of (±)-**13**. The cause of the different product distributions induced by *t*-BuOK and $KOSiMe_3$ is not understood at this time.

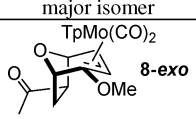
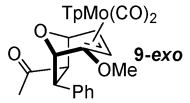
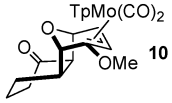
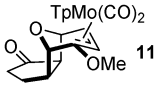
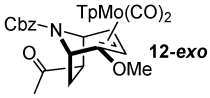
The potential of this methodology for enantiocontrolled synthesis was demonstrated by the efficient production of tricyclodiones (−)-**16** and (+)-**16** in >99% ee from 5-oxo pyranyl molybdenum complex (−)-**1** and (+)-**1**, respectively, using sequential Mukaiyama−Michael and 1,5-Michael reactions followed by cerium(IV) ammonium nitrate-mediated oxidative demetalation (Scheme 2).[10]

In conclusion, a novel Mo-mediated 1,5-Michael addition reaction is reported. The reaction proceeds in good to excellent yields and with good regio- and *exo*-selectivities and provides a new and efficient synthetic approach to oxa- and aza[3.2.1]bicyclics of high enantiomeric purity. Recent experiments also show that the intramolecular 1,5-Michael-type reaction can easily produce oxa- and

10.1021/ja0538132 CCC: $30.25

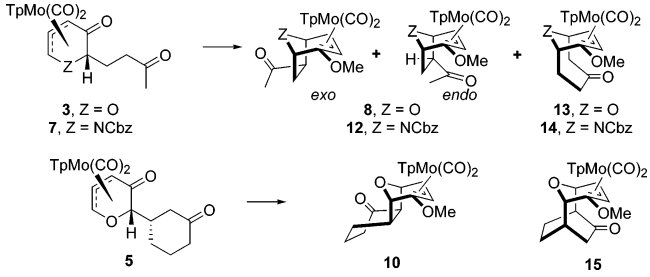
Table 2. 1,5-Michael-Type Additions Contrasting $KOSiMe_3$ and $NaOCH_3$



	reactant[a]	base	major isomer	yld, *exo:endo*
1	**3**	$KOSiMe_3$[b]	 **8-*exo***	96%, 30:1
2	**3**	NaOMe[c]		83%, 5.3:1
3	**4**	NaOMe[d]	 **9-*exo***	71%, 100:0
4	**5**	$KOSiMe_3$[e]	 **10**	97%, 100:0
5	**5**	NaOMe[f]		90%, 100:0
6	**6**	NaOMe[g]	 **11**	80%, 100:0
7	**7**	$KOSiMe_3$[h]	 **12-*exo***	97%, 40:1
8	**7**	NaOMe[i]		91%, 6.4:1

[a] The syn/anti ratios of the reactants **4**−**6** are listed in Table 1. [b] With 3.0 equiv for 1 h then 2.5 equiv of Me_3OBF_4 for 4 h. [c] With 3.0 equiv for 5 h then 3.0 equiv of Me_3OBF_4 for 4 h. [d] With 3.5 equiv for 24 h then 3.0 equiv of Me_3OBF_4 for 2 h. [e] With 3.0 equiv for 24 h then 2.5 equiv of Me_3OBF_4 for 4 h. [f] With 5.0 equiv for 20 h then 4.0 equiv of Me_3OBF_4 for 1 h. [g] With 5.0 equiv for 45 h then 4.0 equiv of Me_3OBF_4 for 1 h. [h] With 3.0 equiv for 1 h then 2.8 equiv of Me_3OBF_4 for 40 min. [i] With 6.0 equiv for 6 h then 5.0 equiv of Me_3OBF_4 for 15 h.

Table 3. Influence of the Base on 1,5-Michael-Type Reactions

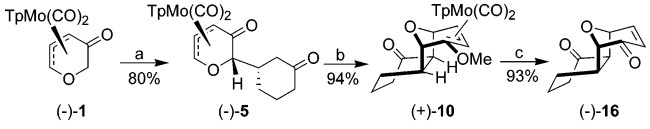


3, Z = O
7, Z = NCbz
8, Z = O
12, Z = NCbz
13, Z = O
14, Z = NCbz
5
10
15

entry	reactant	base	products[a]	ratios[b]	yield
1	**3**	*t*-BuOK	**8**-*exo*:**8**-*endo*:**13**	12:1:18	75%
2		$KOSiMe_3$		30:1:0	97%
3	**7**	*t*-BuOK	**12**-*exo*:**12**-*endo*:**14**	8:1:18	78%
4		$KOSiMe_3$		40:1:0	97%
5	**5**	*t*-BuOK	**10**:**15**	1:2	73%
6		$KOSiMe_3$		100:0	97%

[a] See ref 9. [b] Ratios determined by ^1H NMR.

Scheme 2. Enantiocontrolled Synthesis of Tricyclodiones[a,b]



(-)-**1** >99% ee
(-)-**5** 99.3% ee
(+)-**10** >99.9% ee
(-)-**16** >99.9% ee

[a] Conditions: (a) TBSOTf, Et_3N, CH_2Cl_2, 10 min, then cyclohexenone, $TiCl_4$, 15 min. (b) $KOSiMe_3$ (3.0 equiv), CH_2Cl_2, 24 h, then Me_3OBF_4 (2.5 equiv), 4 h. (c) CAN (8.0 equiv), Et_3N (1.5 equiv), H_2O/THF. [b](+)-**16** was obtained in >99.9% ee from (+)-**1** (>99% ee); enantiopurity of a 99.3% ee product of (+)-**10** was increased to >99.9% ee by recrystallization from acetonitrile.

aza[3.3.1]bicyclics using a similar approach. These studies on 1,5-Michael additions and the applications to the total synthesis of natural products will be reported in due course.

Acknowledgment. This work was supported by Grant GM522238, awarded by the National Institute of General Medical Sciences, DHHS. We acknowledge with pleasure the skilled contribution of Heilam Wong for developing the Mukaiyama−Michael reactions as well as a highly efficient synthesis of (±)-**2**. We thank colleague Dr. Kenneth Hardcastle for his skilled and efficient assistance with X-ray crystallography.

Supporting Information Available: Experimental procedures, synthesis and characterization of all new compounds, and X-ray crystallographic studies of (±)-**13** (39 pages, print/PDF); copies of ^1H and ^{13}C NMR spectra of all compounds and chiral HPLC analysis of (±)-**16**, (−)-**16**, and (+)-**16** (37 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Faller, J. W.; Rosan, A. M. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 186. (b) Faller, J. W.; Mazzieri, M. R.; Nguyen, J. T.; Parr, J.; Tokunaga, M. *Pure Appl. Chem.* **1994**, *66*, 1463. (c) Davis, R.; Kane-Maguire, L. A. P. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Elmsford, NY, 1982; Vol. 3, p 1149. (d) Pearson, A. J. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. I, p 1. (e) Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Payne, S. C.; Semones, M. A.; Liebeskind, L. S. *Organometallics* **1995**, *14*, 4132. (f) Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Liebeskind, L. S. *Organometallics* **1996**, *15*, 4201. (g) Liu, R.-S. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1998; Vol. 6, p 145. (h) Li, C.-L.; Liu, R.-S. *Chem. Rev.* **2000**, *100*, 3127.

(2) (a) Pearson, A. J.; Khan, M. N. I.; Clardy, J. C.; He, C.-H. *J. Am. Chem. Soc.* **1985**, *107*, 2748. (b) Pearson, A. J.; Khan, M. N. I. *J. Org. Chem.* **1985**, *50*, 5276−5285. (c) Hansson, S.; Miller, J. F.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 9660. (d) Rubio, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 891. (e) Ipaktschi, J.; Hartmann, A.; Boese, R. *J. Organomet. Chem.* **1992**, *434*, 303.

(3) Villanueva, L. A.; Ward, Y. D.; Lachicotte, R.; Liebeskind, L. S. *Organometallics* **1996**, *15*, 4190.

(4) Ipaktschi was the first to transform a simple $TpMo(CO)_2(\eta^3$-allyl) into a cationic diene and explore its reaction with nucleophiles.[2e] The first *general* description of synthetically useful transformations of $TpMo(CO)_2(\eta^3$-allyl) and $TpMo(CO)_2(\eta^4$-diene) complexes is documented within the Supporting Information: (a) Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 897. For additional examples, see: (b) Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 5811. (c) Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 7445. (d) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3909. (e) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083. (f) Yin, J.; Llorente, I.; Villanueva, L. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 10458. (g) Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477. (h) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 6185. (i) Alcudia, A.; Arrayás, R. G.; Liebeskind, L. S. *J. Org. Chem.* **2002**, *67*, 5773. (j) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 9026. (k) Pearson, A. J.; Douglas, A. R. *Organometallics* **1998**, *17*, 1446. (l) Pearson, A. J.; Babu, M. *Tetrahedron Lett.* **1998**, *39*, 6273.

(5) Attempted intermolecular variations of this nucleophilic addition were not successful.

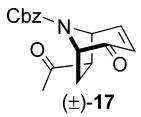
(6) *Z* Alkenes gave the *anti* isomer, while *E* alkenes formed the *syn* isomer, predominantly. These results will be described separately in a future full paper.

(7) Other bases, such as CH_3ONa in CH_3OH, NaHMDS, LiHMDS, *t*-BuLi, or $LiOCH_3$, and other solvents, such as THF or benzene, provided much poorer results. The diastereoselectivity for **12** is inversely correlated to the time of reaction after addition of the Meerwein reagent [*exo*/*endo* = 40:1 (40 min), 17:1 (4 h), 5:1 (15 h)]. In no case was an intramolecular aldol reaction at the 5-oxo group observed.

(8) The *exo* isomers show negligible coupling constants (approx 0 Hz), while the *endo* isomer coupling constants are much larger (approx 6.5 Hz).

(9) Both **13** and **15** cannot be separated from their isomers **8** and **10** by chromatography. Pure **13** and **15** were obtained by recrystallization from CH_2Cl_2 and hexanes.

(10) Oxidative demetalation of (±)-**10** with $CuCl_2$ afforded (±)-**16** in 74% yield. Oxidative demetalation of the racemic pyridinyl complex (±)-**12**-*exo* with cerium(IV) ammonium nitrate yielded (±)-**17** in 87% yield.



(±)-**17**

JA0538132