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The Enantiomeric Scaffold Approach to Highly Functionalized 1-Oxadecalines: Enantio- and Regiocontrolled [4 + 2] Cycloadditions of 5-Alkenyl-η^3-Pyranylmolybdenum Complexes

Ramón Gómez Arrayás,† Jingjun Yin,‡ and Lanny S. Liebeskind*

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

Received October 4, 2006; E-mail: chemLL1@emory.edu

Abstract: TpMo(CO)$_2$(5-alkenyl-η-2,3,4-pyranyl) diene complexes function as excellent chiral scaffolds for the efficient regio- and enantiocontrolled synthesis of highly functionalized 1-oxadecaline derivatives through a novel transition metal-mediated Diels−Alder reaction. Very good to excellent yields and excellent levels of *endo* selectivity are obtained, and the reaction gives products with complete retention of enantiomeric purity when carried out with chiral, nonracemic scaffolds. A subtle structural modification on the diene (replacement of an H by a *trans*-CH_3 group) leads to a complete change of regiochemistry, which is discussed from a mechanistic point of view. The role of the η^3-coordinated TpMo(CO)$_2$ moiety is also critical to the further functionalization of the [4 + 2] cycloadducts, as illustrated by the preparation of 20 variously functionalized 1-oxadecaline derivatives (>98% ee when carried out with high enantiopurity scaffolds).

Introduction

The 1-oxadecalin (or saturated chroman) skeletal framework is a key structural unit found in a diverse array of biologically interesting natural products,[1−3] including, *inter alia*, phomactin A, a selective antagonist of platelet activating factor,[4] diterpenoids such as jamesoniellide E,[5] and koninginin G, a metabolite with antifungal activity isolated from a strain of *Trichoderma aureoviride*[6] (Figure 1). Highly functionalized enantiopure 1-oxadecalin derivatives could serve as useful intermediates for the enantiocontrolled synthesis of these types of naturally occurring substances.

Although the 6,6-bicyclic ring-fused system can, in principle, be directly assembled with high regio- and stereocontrol through intermolecular Diels−Alder reaction of pyranyl-based dienophiles or dienes, convergent approaches to 1-oxadecalines have met with limited success. The preparation of 1-oxadecalines via Diels−Alder reaction of 2,3-dihydro-4*H*-pyran-4-ones with electron-rich dienes has been reported, mainly by Totah and co-workers.[7−11] Although useful levels of diastereoselectivity

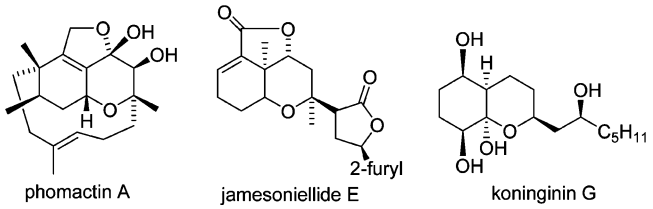

Figure 1. Examples of natural products containing the 1-oxadecalin framework.

can be achieved, the enantioselective version of this strategy has yet to be developed. Moreover, the corresponding Diels−Alder reaction of pyranyl-based dienes with electron-deficient alkenes is limited to highly electrophilic dienophiles, such as maleimides or maleic anhydride, most likely due to the poor reactivity associated with these types of dienes under thermal conditions. For example, cycloadditions of 5-vinyl-2,3-dihydro-4*H*-pyran have been described only with highly electrophilic dienophiles such as tetracyanoethylene, *N*-phenyltriazolinedione, or diethyl azodicarboxylate.[12] Despite low reactivity, high diastereoselectivity was observed in the intermolecular Diels−Alder reaction of enantiomerically pure dienes, such as those depicted in Figure 2,[13−16] and other related 1-oxapyranyl dienes.[17−20] The use of Lewis acid promoters to enhance the

† Current address: Department of Organic Chemistry, Facultad de Ciencias, Cantoblanco, 28049 Madrid, Spain. E-mail: ramon.gomez@uam.es.
‡ Current address: Merck and Co., Inc., RY800-B361, P.O. Box 2000, Rahway, NJ 07065.

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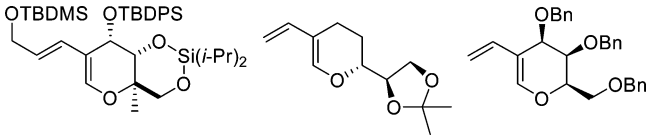

Figure 2. Examples of pyranyl-based dienes used in Diels−Alder reactions.

reactivity of dienophiles with these pyranyl dienes remains largely unexplored, most likely due to the low reactivity of the dienes and their high propensity to decompose in the presence of Lewis acids. Indeed, the reaction of pyranyl dienes with less reactive mono-activated olefins, such as acrylates, has only been achieved in an intramolecular fashion under thermal conditions.[21,22]

How else might the 1-oxadecaline ring system be constructed in an enantiocontrolled fashion? We have described an exploration of the synthetic potential of stoichiometric molybdenum π-complexes of unsaturated oxygen and nitrogen heterocycles. In this study, chiral nonracemic stoichiometric molybdenum π-complexes function as *enantiomeric scaffolds* or *organometallic chirons* for the rapid enantioselective synthesis of highly functionalized molecules of certain structural complexity.[23−58]

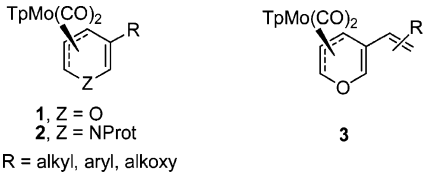

Figure 3. η^3-Pyranyl- and pyridinylmolybdenum complexes as scaffolds for enantiocontrolled synthesis.

It was demonstrated that pyranyl- and pyridinylmolybdenum scaffolds (**1** and **2**, Figure 3), both enantiomeric antipodes of which are readily available, participate in Mo-mediated, regiocontrolled, sequential functionalization at C-2 and C-6 to afford 2,3,6-trisubstituted pyran[31] and piperidine[25,28,32] derivatives. Moreover, they can lead to the rapid assembly of heteroatom-bridged bicyclic ring systems through either [5 + 2][23,33−35] or [5 + 3][26] cycloaddition processes, or via sequential Mukaiyama−Michael and subsequent 1,5-Michael-type reaction.[23] The organometallic chiron strategy is particularly useful because the molybdenum enantiomeric scaffolds undergo multiple, sequential regio- and stereocontrolled transformations that cannot be achieved using traditional synthetic organic approaches, in terms of either a unique bond construction or unique regio- and stereocontrol imparted by the metal and its auxiliary ligands. Additional attributes that enhance this concept are the use of an inexpensive metal source, the easy accessibility of both enantiomers of the metal complex in high yield and large quantity, and the air and moisture stability of the metal complexes.

In extending the synthetic toolbox available from these molybdenum-based enantiomeric scaffolds, it was envisioned that 5-alkenyl-substituted pyranylmolybdenum complexes (**3**, Figure 3) could serve as chiral, nonracemic dienes in [4 + 2] cycloadditions with electron-deficient alkenes, delivering 1-oxadecalines of high enantiopurity. The η^3-coordinated TpMo(CO)$_2$ fragment would not only control the facial selectivity of the reaction by blocking one of the two faces of the diene, but also increase the reactivity of the diene,[59] allowing its intermolecular reaction with mono-activated olefins. Additionally, the presence of a double bond conjugated to the π-allyl molybdenum moiety, together with well-established demetalation procedures, offer varied opportunities for further regio- and stereoselective functionalization of the [4 + 2] cycloadducts. Herein, we report that 5-alkenyl-substituted η^3-pyranylmolybdenum complexes

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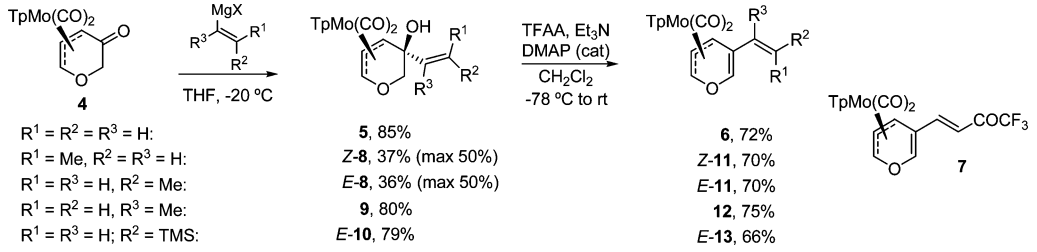
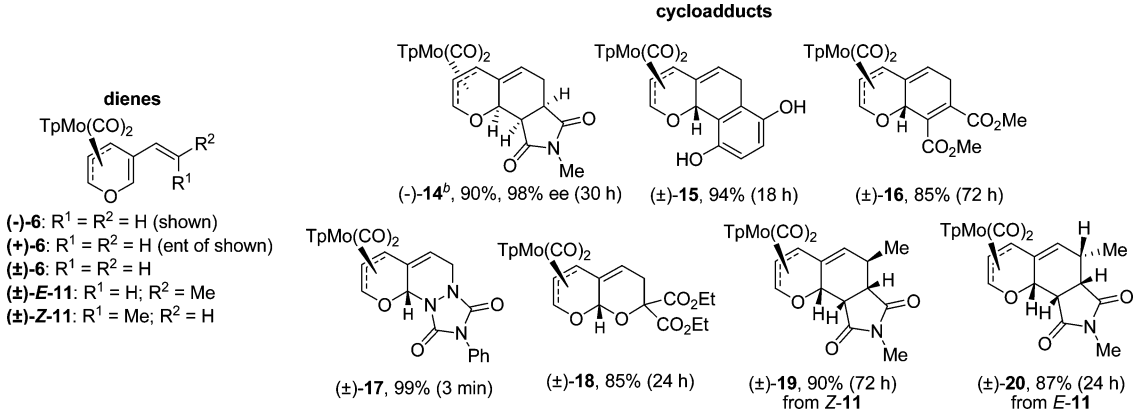
Scheme 1. Synthesis of $TpMo(CO)_2$(5-Alkenyl-η-2,3,4-pyranyl) Complexes



Scheme 2. Thermal [4 + 2] Cycloadditions of Molybdenum Dienes **6** and **11**[a]



[a] Conditions: dienophile (1.5 equiv), CH_2Cl_2, rt. [b](−)-**14** was obtained in 98% ee from (+)-**6** (of 98% ee).

function as excellent diene scaffolds for a variety of intriguing [4 + 2] cycloadditions, allowing direct access to highly functionalized 1-oxadecalines of high enantiopurity.[60]

Results and Discussion

Synthesis of 5-Alkenyl-η-2,3,4-pyranylmolybdenum π-Complexes. Racemic diene **6** was readily prepared in good yield from 5-oxopyranyl complex (±)-**4**[35] in two steps involving the addition of vinylmagnesium chloride (THF, −20 °C), followed by dehydration of the resulting allylic alcohol **5** with TFAA/Et_3N (Scheme 1). However, dehydration of **5** proved to be somewhat more difficult than anticipated, since the typical reaction conditions successfully used for the preparation of complexes **1** where R ≠ alkenyl (TFAA, Et_3N, CH_2Cl_2, room temperature, 40 h)[35] produced **6** in low yield (up to 45%) together with a significant amount of the trifluoromethyl ketone **7** (32%), which is likely formed via a Friedel−Crafts-like reaction of the electron-rich diene **6** with TFAA. Other attempts to eliminate the corresponding mesylate or triflate with Et_3N or DBU prevented the formation of **7**, but also led to extensive decomposition. Fortunately, the dehydration of **5** with TFAA/Et_3N in the presence of a catalytic amount of DMAP occurred cleanly and rapidly under mild conditions (CH_2Cl_2, 1 h, −78 to 0 °C) to give diene **6** in 72% yield. The separate antipodes of diene **6** were easily prepared in 98% ee starting from (+)-**4** or (−)-**4** (both in 98% ee)[35] using the same synthetic sequence.

As shown in Scheme 1, dienes **11**−**13** were prepared analogously to the parent vinyl system. The addition of an excess of a mixture of *E*/*Z*-1-propenylmagnesium bromides[61] to (±)-**4** led to an approximate 1:1 mixture of alcohols *Z*-**8** and *E*-**8** that could be efficiently separated by flash chromatography and transformed into the corresponding dienes *Z*-**11** and *E*-**11**, respectively, under the optimized dehydration reaction conditions. The stereochemistry of the dienes was unequivocally established by single-crystal X-ray analysis of the intermediate allylic alcohol *E*-**8** (see Supporting Information for details). Similarly, the 5-isopropenyl and 5-[*E*-(2-trimethylsilyl)vinyl] molybdenum complexes **12** and *E*-**13** (the latter being interesting for mechanistic as well as synthetic purposes as indicated in Scheme 10) were readily obtained by dehydration of the corresponding allylic carbinols **9** and **10**. Importantly, dienes **6** and **11**−**13** are easily handled, air-stable, yellow solids that can be stored at room temperature on the bench for months.

Thermal [4 + 2] Cycloaddition Reactions of Dienes 6 and *E*-11 and *Z*-11. Thermal [4 + 2] cycloadditions were performed with molybdenum scaffolds **6** and ***E*-11** and ***Z*-11** using strongly electron-deficient dienophiles and heterodienophiles (Scheme 2). Simply stirring the diene in dichloromethane or 1,2-dichloroethane at room temperature with a highly reactive olefin such as *N*-methylmaleimide, *p*-benzoquinone, or dimethyl acetylenedicarboxylate, heterodienophiles such as *N*-phenyltriazolinedione, and diethyl oxomalonate led to single diastereomeric adducts **14**−**20** in good to excellent yields (76−99%).

The bulky $TpMo(CO)_2$ moiety induces complete facial diastereoselectivity derived from attack of the dienophile at the face of the diene away from the molybdenum. The regiochemistry and the endo stereochemistry of the cycloadducts were

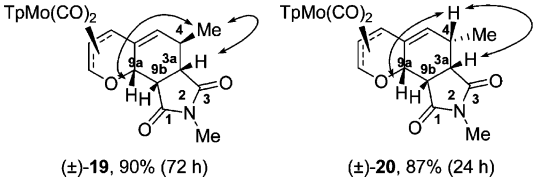
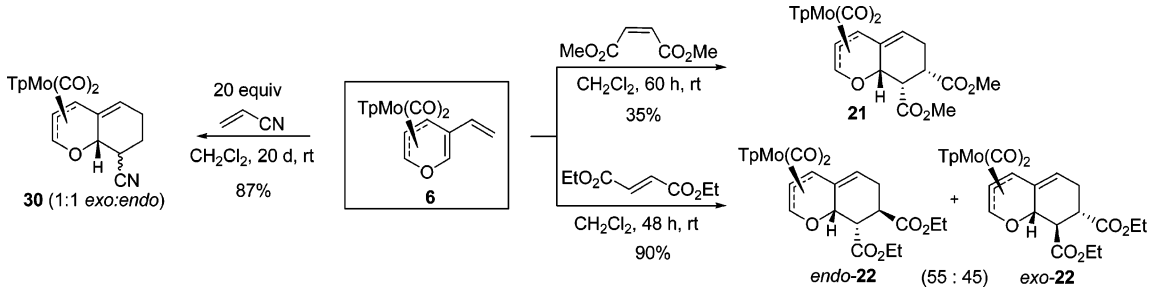


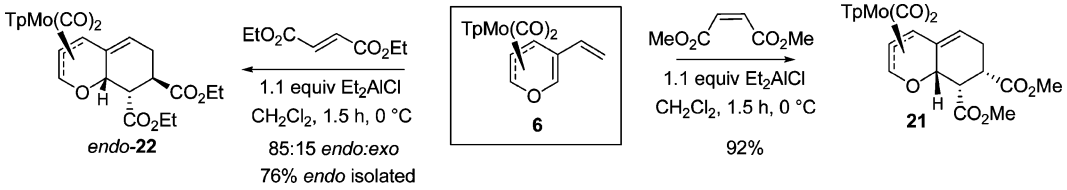
Figure 4. NOE interactions in diastereomers **19** and **20**.

(60) For a preliminary communication, see ref 30.
(61) The Grignard reagent was prepared from a commercially available 70:30 mixture of *Z*/*E*-1-bromopropene.

Scheme 3. Uncatalyzed [4 + 2] Cycloaddition of Less Reactive Dienophiles



Scheme 4. Et_2AlCl Catalyzed [4 + 2] Cycloadditions of **6** with Dimethyl Maleate and Diethyl Fumarate



unequivocally established by NMR, using COSY and NOESY experiments. As one example, the relative configuration of the cycloadducts **19** and **20** (Figure 4) derived from the Diels−Alder reaction of 1-propenyl dienes *Z*-**11** and *E*-**11** with *N*-methylmaleimide was determined by 2D NMR experiments (COSY and NOESY). In particular, for cycloadduct **19** the NOE correlations of the methyl group at C-4 with H-3a and H-9a, which were absent in compound **20**, along with observation of NOE cross-peaks of H-4 with H-3a and H-9a in **20** confirmed the structures of the cycloadducts (endo approach of the *N*-methylmaleimide dienophile to the face of the molybdenum complexes *Z*-**11** and *E*-**11** opposite to the $TpMo(CO)_2$ moiety).

In contrast to the Diels−Alder reactions described above, [4 + 2] cycloadditions with less reactive olefins were inefficient or nonselective under noncatalyzed conditions. For example, reaction of diene **6** with dimethyl maleate afforded only 35% yield of the *endo* adduct **21** after 60 h at room temperature, while the use of diethyl fumarate as the dienophile produced in 90% yield a 55:45 mixture of *endo*/*exo*-**22** (Scheme 3). Mono-activated olefins in stoichiometric quantities proved to be unsuitable dienophiles under the noncatalyzed reaction conditions: starting materials were typically recovered unaltered after 48 h.[62] Attempts to force the noncatalyzed cycloadditions at higher temperatures were unsuccessful since decomposition of the diene was observed in the reaction of **6** with several dienophiles such as acrylonitrile or methyl acrylate in toluene or dioxane at reflux.

Lewis Acid Promoted [4 + 2] Cycloaddition Reactions of Dienes 6 and 11−13. With the aim of enhancing the reaction rate and the stereoselectivity of the cycloaddition reaction, especially with mono-activated alkenes, a number of Lewis acids were surveyed as catalysts for the cycloaddition. While $ZnCl_2$, $EtAlCl_2$, $BF_3{\cdot}Et_2O$, and $Eu(fod)_3$ did not give acceptable yields of [4 + 2] cycloadducts, a full equivalent of Et_2AlCl produced a remarkable enhancement in the reaction of **6** with dimethyl maleate or diethyl fumarate (Scheme 4). In the presence of Et_2AlCl the cycloadduct **21** was obtained as a single diastereomer in 92% yield after only 1.5 h at 0 °C. In addition, the stereoselectivity of the reaction of **6** with diethyl fumarate was increased to 85:15 when promoted by Et_2AlCl, which allowed the isolation of cycloadduct *endo*-**22** in 76% yield.[63]

As depicted in Table 1, a variety of mono-activated dienophiles, including variously substituted α,β-unsaturated aldehydes, ketones, and esters, did participate in the Et_2AlCl-promoted [4 + 2] cycloaddition protocol (products **23**−**32**). The reaction was highly efficient, not only with monosubstituted electrophilic olefins, but also with α-alkyl, β-alkyl, and α,β-dialkyl-substituted olefins. Particular attention should be given to the reaction with α-butyl and α,β-dimethyl acrolein (products (−)-**27** and (±)-**28**, respectively), which allows the generation of products with quaternary stereocenters. Even the generally unreactive β,β-dimethyl-substituted unsaturated ketone mesityl oxide reacted with (±)-**6** to afford only one cycloadduct in very good yield (product (±)-**32**). Excellent regio- and stereoselectivities were attained in the reaction with aldehydes, ketones, and esters as alkene-activating substituents. Complete facial diastereoselectivity was also observed in all cases as a result of the bulky $TpMo(CO)_2$ group, which blocks one of the two faces of the diene system. Excellent endo selectivity[63] was observed for all cases reported.[64] Importantly, cycloaddition products of high enantiomeric purity (98% ee) were obtained when starting from (+)-**6** or (−)-**6** (each of 98% ee), demonstrating that this procedure takes place without erosion of the enantiopurity of the starting diene.

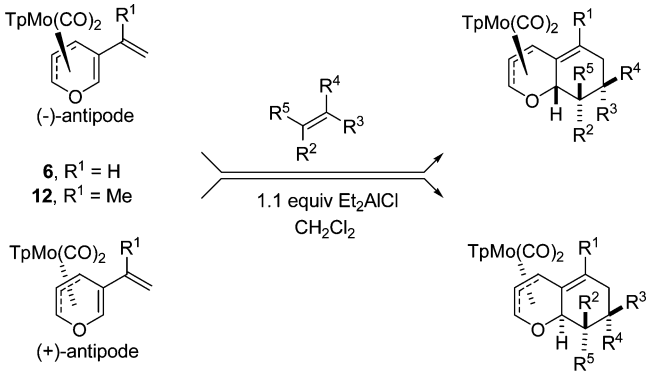
Although the Diels−Alder cycloadducts were highly stable as solids, a clean double bond isomerization was observed in solution in the presence of traces of Lewis or Brønsted acids. Thus, simple treatment of the endo products (−)-**24**, (−)-**25**,

(62) A 50:50 mixture of exo/endo cycloadducts could be obtained in good yield when diene **6** was treated with 20 equiv of acrylonitrile after 20 days in CH_2Cl_2 at room temperature.

(63) The regio- and the stereochemistry of all the Diels−Alder cycloadducts were unequivocally established by NMR. $^{13}C-^{1}H$ heteronuclear correlation and ^{1}H-COSY experiments were used for proton assignment, while the endo/exo configuration was determined based on the values of the coupling constants of key protons and 2D-NOESY experiments. For instance, values of $J_{8,8a} = 5.0-5.9$ Hz for products with cis relative configuration between H-8 and H-8a and $J_{8,8a} = 11.1-12.0$ Hz for adducts with *trans*-H-8/H-8a were of great diagnostic value. Similar differences in coupling constants stand for the cis/trans relative stereochemistry between H-7 and H-8. Also, the X-ray crystallographic analysis of (±)-**26** and (±)-**36** confirmed both the regiochemistry and the endo approach of the dienophile anti to Mo (see Supporting Information).

(64) Of all substrates studied to date, α,β-unsaturated nitriles such as acrylonitrile and benzylidene malononitrile behaved anomalously and gave endo/exo mixtures. This behavior is not fully understood and will be reported separately at a later date.

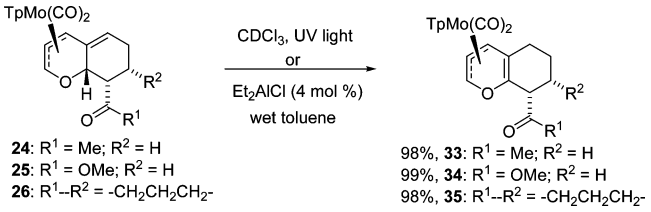
Table 1. Et_2AlCl-Promoted [4 + 2] Cycloadditions of Mo-Dienes **6** and **12**[a]



entry	diene	conditions	prod	R^1	R^2	R^3	R^4	R^5	yield (%)	ee (%)
1	(−)-**6**[b]	−78 °C, 5 min	(+)-**23**	H	CHO	H	H	H	95	98
2	(−)-**6**[b]	−78 °C, 10 min	(−)-**24**	H	COMe	H	H	H	91	98
3	(−)-**6**[b]	0 °C, 6 h	(−)-**25**	H	CO_2Me	H	H	H	90	98
4	(−)-**6**[b]	0 °C, 7 h	(−)-**26**	H	$-CO(CH_2)_3-$		H	H	86	98
5	(+)-**6**[b]	−78 °C, 15 min	(−)-**27**	H	CHO	H	H	*n*-Bu	81	98
6	(+)-**6**[b]	0 °C, 1 h	(+)-**28**	H	CHO	H	Me	Me	92	98
7	(±)-**12**	0 °C, 6 h	(±)-**29**	Me	CO_2Me	H	H	H	86	
9	(±)-**6**	0 °C, 45 min	(±)-**30**	H	CHO	H	*Z*-3-hexenyl	H	87	
10	(±)-**6**	0 °C, 10 min	(±)-**31**	H	CHO	H	Ph	H	73[c]	
11	(±)-**6**	rt, 24 h	(±)-**32**	H	COMe	Me	Me	H	88	

[a] General conditions: 1.1 equiv of Et_2AlCl, CH_2Cl_2. [b] 98% ee. [c] endo/exo = 90:10.

Scheme 5. Acid-Catalyzed Double Bond Isomerization of the Diels−Alder Cycloadducts



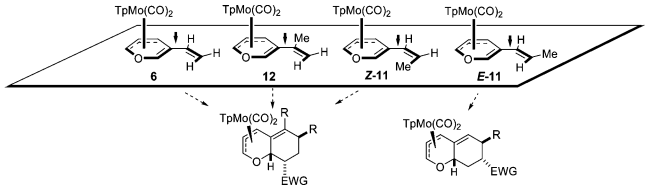


Figure 5.

and (−)-**26** with 4 mol % of Et_2AlCl in wet toluene, or upon exposure of a $CDCl_3$ solution of such products to UV light,[65] led to the corresponding isomerized complexes **33**, **34**, and **35**, respectively, in almost quantitative yields (Scheme 5). Although the mechanism of this facile isomerization has not been studied, it is of potential synthetic value since the η^3-pyranylmolybdenum complexes can participate in a variety of high-yield [5 + 2] and [5 + 3] cycloaddition reactions.[26,35]

Compared to the [4 + 2] reactions of vinyl diene **6**, which maintain a complete or very high endo selectivity and a regiochemistry typified by placement of the electron-withdrawing substituent of the dienophile adjacent to the pyran ring,[63] the subtle structural modification of replacing a terminal H of the parent diene **6** with a *trans*-CH_3 group (diene *E*-**11**) unexpectedly led to a clean reversal of the 4 + 2 regiochemistry in the Et_2AlCl-promoted [4 + 2] cycloadditions.[66] As shown in Scheme 6, not only did simple activated alkenes such as acrolein, methyl vinyl ketone, and methyl acrylate (products **36**−**38**, respectively) efficiently participate in this reaction, less reactive dienophiles such as β-alkyl and α,β-dialkyl-substituted unsaturated aldehydes also led to the corresponding adducts (**39**−**41**) in good yields (62−76%).

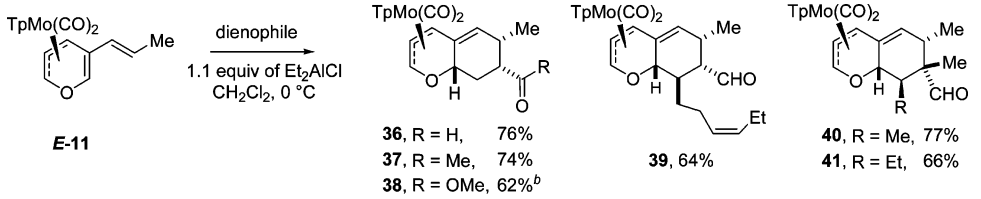
In contrast, *cis*-diene *Z*-**11** was significantly less reactive than *E*-**11** and upon treatment with acrolein gave predominantly the [4 + 2] cycloadduct **43** (62% yield) possessing the "normal" regiochemistry, along with 26% of the corresponding [5 + 2] cycloadduct *exo*-**44** (Scheme 7; the formation of the [5 + 2] product in this case is discussed below). A dramatic competition experiment highlighted the decreased reactivity of *Z*-**11**: when a 1.3:1 mixture of *E*-**11** and *Z*-**11** was treated with acrolein (1.0 equiv) in the presence of Et_2AlCl (1.1 equiv) in CH_2Cl_2 at −78 °C for 5 min, adduct **36** (44%) was obtained as the only product. Unreacted *Z*-**11** was recovered; no traces of *E*-**11** were detected in the NMR spectra of the crude reaction mixtures.

Mechanistic Proposal. Any mechanistic working model for the [4 + 2] cycloadditions of these 5-alkenyl-η^3-pyranyl complexes must accommodate the dramatic change in adduct regiochemistry observed between *Z*-**11** as well as the parent vinyl and 2-propenyl systems **6** and **12**, and *E*-**11** (compare Table 1, Schemes 6 and 7). It is doubtful that conformational issues about the central diene bond of the scaffolds play an important role, since the uncongested, unsubstituted diene **6** as well as the sterically more congested dienes 2-propenyl **12** and 1-propenyl Z-**11** provide 4 + 2 adducts possessing the same

(65) ^1H NMR monitoring of the double bond isomerization showed quantitative conversion within 2 to 3 h when a $CDCl_3$ solution of the 4 + 2 product was irradiated with a simple UV lamp (254 nm) typically used for monitoring thin layer chromatography. In the presence of Et_2AlCl and traces of moisture, the double bond isomerization takes place under ambient room light.

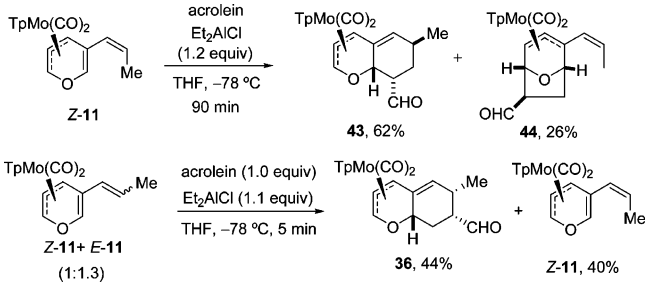
(66) A mixture of two other unidentified compounds was obtained in less than 5% yield in most cases. In the reaction of *E*-**11** with methyl acrylate (12 h, 0 °C), the regioisomer typical of the uncatalyzed reactions (COOMe adjacent to the pyran ring and endo) could be isolated in 8% yield and characterized.

Scheme 6. Et_2AlCl-Promoted [4 + 2] Cycloadditions of (±)-*E*-**11**: "Reversed" Regiochemistry[a]

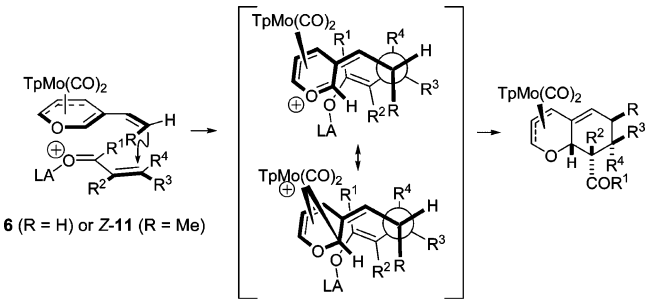


[a] General conditions: 1.1 equiv of Et_2AlCl, CH_2Cl_2, 0 °C, 10−45 min. [b]The reaction takes 12 h at 0 °C and 8% of the endo cycloadduct with the "normal" regiochemistry isolated (compound **42** with COOMe adjacent to the pyran ring can be found in the Experimental Section).

Scheme 7. Et_2AlCl-Promoted Cycloadditions of *Z*-**11** and *E*-**11** (Competition Experiment)



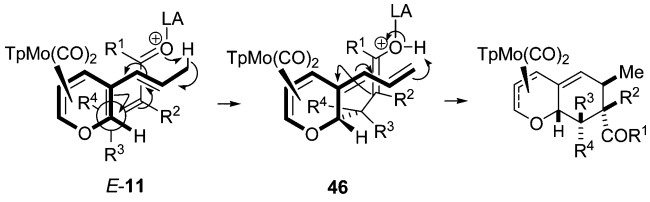
Scheme 8. endo-Selective, Stepwise Mechanism



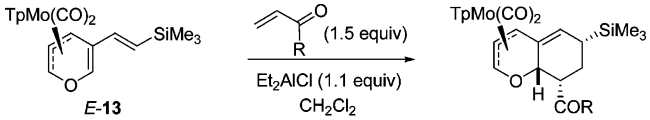
regiochemistry, while the sterically less congested 1-propenyl *E*-**11** delivers adducts of "reversed" regiochemistry (Figure 5).

A stepwise, endo-selective (dipole-stabilized) mechanism for the [4 + 2] cycloaddition of the unsubstituted vinylpyranyl complex **6** and the *cis*-propenyl diene *Z*-**11** proceeding through a Mo-stabilized cation (canonical structures **45** shown in Scheme 8) is fully consistent with the observed results.[67] Indeed, the rate of product formation is strongly retarded by the presence of substituents at the β-position of the α,β-unsaturated dienophile (compare conditions for the cycloaddition of **6** to acrolein with those for *E*-cinnamaldehyde or 2*E*,6*Z*-nonadienal in Table 1), while α-alkyl substituents do not produce any noticeable difference in reactivity (compare reaction conditions for the reaction of **6** with acrolein or α-butylacrolein, or those required for the formation of products **28** and **31** in Table 1). In accord with the stepwise mechanism depicted in Scheme 8, placement of a *cis*-CH_3 substituent on the vinylpyranyl complex (i.e., *Z*-**11**) introduces conformational and nonbonded steric effects that retard the stepwise [4 + 2] process allowing the competitive formation of the [5 + 2] cycloadduct as shown above in Scheme 7.

Scheme 9. Hypothetical 10π Ene-like Mechanism



Scheme 10. [4 + 2] Cycloadditions of Mo-Diene *E*-**13**



[a] The corresponding desilylated product (±)-**25** (Table 1) was also isolated in 14% yield.

The complete change of regiochemistry observed in the Et_2-AlCl-promoted cycloadditions of *E*-**11** compared to that of dienes **6**, *Z*-**11**, and **12** suggests that a different mechanism must operate in the former case, *specific to the presence of a trans-CH_3 substituent*. A concerted [4 + 2] cycloaddition pathway seems unlikely for this particular case alone (and not, for example, with the parent scaffold diene **6**); rather, a 10π-electron ene-like mechanism proceeding through intermediate **46** shown in Scheme 9 is suggested as a more plausible option.

In support of the 10π-electron ene-like mechanism for reactions of *E*-**11** with dienophiles, the diene *E*-**13**, in which the *trans*-trimethylsilyl substituent prevents an ene-type process, cleanly provided products (**47**−**49**) possessing the "normal" Lewis acid catalyzed regiochemistry as observed with dienes **6**, *Z*-**11**, or **12**. Diene *E*-**13** also showed high levels of reactivity similar to that of dienes **6** and **12** (Scheme 10). Except for the reaction of *E*-**13** with methyl acrylate, in which adduct **49** was accompanied by a small amount of the corresponding desilylated **25** (Table 1), only one cycloadduct was obtained in good yield in the reactions of *E*-**13**.

Mo-Promoted Functionalization of the Diels−Alder Cycloadducts. The ability of a $TpMo(CO)_2(\eta^3$-allyl) complex to stabilize a positive charge on a carbon atom adjacent to the allyl should increase the susceptibility of the noncoordinated double bond of a η^3-pentadienylmolybdenum fragment toward electrophilic attack. The cationic molybdenum complex resulting from such an electrophilic addition would be highly activated for a subsequent regio- and stereospecific nucleophilic func-

(67) An alternative mechanism suggested by one reviewer to explain the reversal of regiochemistry for the propenyl derivatives (**11**) is a Michael addition to the scaffold diene carbon atom adjacent to the ring oxygen (which creates an intermediate cationic η^4 triene complex) followed by enolate ring closure to form the six-membered ring. While more straightforward than the mechanistic proposal in the text of this article, the reviewer's mechanism does not accommodate the reaction path switch observed with *Z*-**11**, **6**, **12**, and then *E*-**11**. Phrased another way, why would the presence of a *trans*-methyl substituent in *E*-**11** perturb the system to follow a different reaction path than the simple unsubstituted scaffold diene complex **6** follows? Both **6** and *E*-**11** are relatively unencumbered about the diene chromophore, both can easily accomodate the reviewer's suggested mechanism, and yet the two complexes follow completely different reaction paths.

Scheme 11

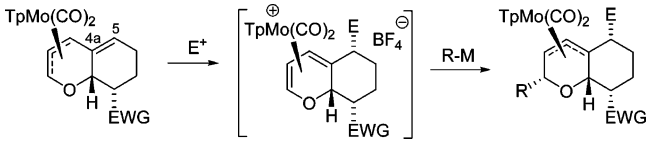
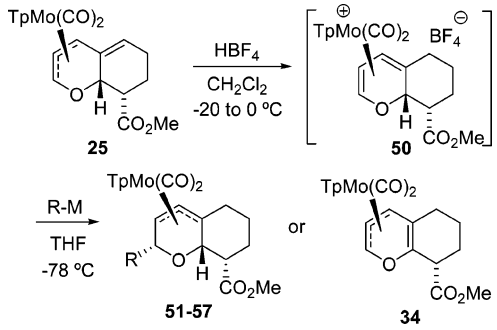


Table 2. Regio- and Stereocontrolled Nucleophilic Functionalization of **25** at C-2



entry	nucleophile (RM)	product	yield (%)[a]
1[b]	$NaBH_4$	**51**[c]	96[b]
2	MeMgBr	**52**	96
3	BnMgBr	**53**	98
4	HC≡CNa	**54**	63
5	TMS-C≡CNa	**55**	90
6	$[MeO_2CCH_2]Na$	**56**	86
7	$[(MeO_2C)_2CH]Na$	**57**	92

[a] Pure product after chromatography. [b] Reaction performed in MeOH at −40 °C. [c] Product of 98% ee (determined by HPLC), obtained from (+)-**25** of 98% ee.

tionalization. This reaction sequence, envisioned in Scheme 11 using Mo-[4 + 2] cycloadducts bearing a double bond at C4a−C5, would offer varied opportunities for the preparation of complex 1-oxadecalines.

While the reaction of [4 + 2] adduct **25** with several electrophiles such as typical alkylating agents or Michael acceptors was unsuccessful, a clean and rapid protonation of the alkene was observed in the presence of tetrafluoroboric acid (1.1 equiv) to afford quantitatively the cationic molybdenum complex **50** (Table 2). The course of the reaction, which takes 1 h from −20 to 0 °C, was easily monitored by IR spectroscopy using a React-IR spectrometer by following the ν_{CO} resonances.[68] In spite of its relative instability to air and moisture, complex **50** could be isolated as a red-orange solid.

As shown in Table 2, the intermolecular addition of a variety of organometallic nucleophiles including hydride (entry 1), primary alkyl Grignard reagents (entries 2 and 3), sodium alkynylides (entries 4 and 5), and sodium enolates (entries 6 and 7) proceeded in high yield in THF at low temperature, allowing the rapid functionalization of the 1-oxadecaline skeleton at C-2 with excellent regio- and stereoselectivity (products **51**−**57**). As a limitation of this procedure, secondary alkyl or aryl Grignard reagents induced a fast acid−base reaction to afford the pyranyl complex **34**.

A related protonation/nucleophilic functionalization sequence was explored using the isomeric η^3-pyranyl complexes that were obtained after facile isomerization of the noncoordinated double bond of the [4 + 2] adducts (shown in Scheme 5). Unfortunately, this protonation/nucleophilic functionalization strategy was not effective when the noncoordinated double bond was positioned at C4a−C8a. Thus, transformation of **34** into the corresponding cationic complex **58** by protonation was much slower, requiring 1.5 equiv of HBF_4 and more than 3 h at room temperature to reach completion according to IR monitoring. Subsequent treatment of **58** with sodium malonate in THF at −78 °C led to recovered **34** as the main product (67% yield), along with a small amount of a compound tentatively identified as complex **59**,[69] which would be the C8a ring fusion diastereomer of **57** (Scheme 12). Cationic diene complexes **50** (Table 2) and **58** (Scheme 12) are simple epimers differing only in the stereochemistry of the ring fusion hydrogen atom relative to the $TpMo(CO)_2$ moiety. The facile deprotonation of cationic complex **58** relative to that of **50** is simply a function of the greater accessibility of the acidic hydrogen in the former system.

Demetalation/Functionalization of Molybdenum-Chromenyl Scaffolds. The synthetic potential of this [4 + 2] cycloaddition was fully realized through a variety of efficient demetalation procedures. The (η-2,3,4-chromenyl)molybdenum [4 + 2] products were demetalated following two protocols (Scheme 13). Activation of the $TpMo(CO)_2$ moiety by replacing one of the auxiliary CO ligands with a cationic NO^+ ligand[28,70−77] using $NOPF_6$ produced a cationic η^3-allylmolybdenum complex that reacts with soft nucleophiles such as hydride, phenylthiolate, cyanide, and malonate to give the C-2-functionalized 1-oxadecalines **60**−**67** in a regio- and stereocontrolled fashion (Scheme 13). Alternatively, oxidative demetalation using PDC/SiO_2[27] allowed the regioselective functionalization at the same allyl terminus (C-2) by introduction of a carbonyl group and provided the corresponding tetrahydro-2*H*-2-chromenones **68**−**72** in good yields (60−83%). As expected, complete retention of enantiomeric purity was observed when any of these two demetalation protocols were applied to chiral, nonracemic cycloadducts. The preparation of (+)-**67**, (+)-**69**, and (+)-**70**, with 98% ee, or (−)-**72** with 99.8% ee highlights the potential of this methodology for enantiocontrolled synthesis of chromene derivatives.

The (η-3,4,4a-chromenyl)molybdenum cycloadducts (e.g., 51−**57**) were also suitable substrates for several general, well-established demetalation procedures, which are depicted in Scheme 14. Complex **53** was chosen to illustrate the versatility of these products toward demetalation/functionalization. Protodemetalation[38,39] of **53** with strong acids such as trifluoroacetic acid provided hexahydro-2*H*-chromene **73** in 63% yield, the alkene resulting from protonation at Mo and reductive elimination to the more substituted terminal carbon of the π-allylmolybdenum moiety. Iododemetalation[35,78,79] proceeded in good yield (84%) in the presence of excess of iodine to give diene **74**, most likely through elimination of hydrogen iodide from

(68) Starting material ν_{CO} at 1934 and 1849 cm^{-1} disappeared; product ν_{CO} at 2007 and 1938 cm^{-1} appeared.

(69) Compound **59** depicted in Scheme 12 was not fully characterized.

(70) Faller, J. W.; Rosan, A. M. *J. Am. Chem. Soc.* **1976**, *98*, 3388−3389.
(71) Faller, J. W.; Rosan, A. M. *J. Am. Chem. Soc.* **1977**, *99*, 4858−4859.
(72) Cosford, N. D. P.; Liebeskind, L. S. *Organometallics* **1994**, *13*, 1498−1503.
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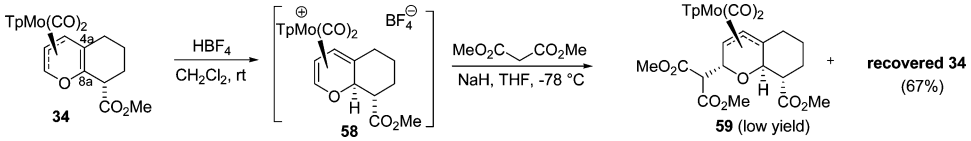
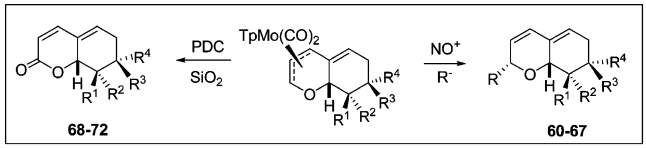
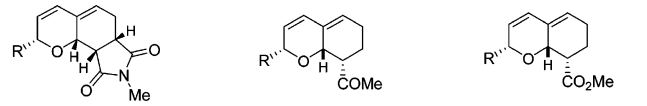
(74) Pearson, A. J.; Douglas, A. R. *Organometallics* **1998**, *17*, 1446−1448.
(75) Faller, J. W.; Chao, K.-H. *J. Am. Chem. Soc.* **1983**, *105*, 3893−3898.
(76) Faller, J. W.; Chao, K.-H. *Organometallics* **1984**, *3*, 927−932.
(77) Faller, J. W.; Chao, K. H.; Murray, H. H. *Organometallics* **1984**, *3*, 1231−1240.
(78) Pearson, A. J.; Khan, M. N. I.; Clardy, J. C.; He, C.-H. *J. Am. Chem. Soc.* **1985**, *107*, 2748−2757.
(79) Pearson, A. J.; Khan, M. N. I. *J. Org. Chem.* **1985**, *50*, 5276−5285.

Scheme 12. Attempts at Protonation/Nucleophilic Functionalization of **35**



Scheme 13. Demetalation Protocols for η-(2,3,4)-Molybdenum [4 + 2] Cycloadducts[a]

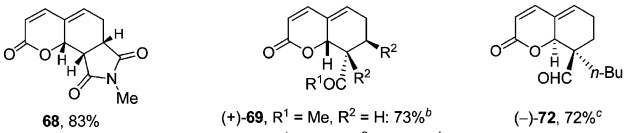




60, R = H: 73%
61, R = SPh: 60%
62, R = CN: 68%
63, R = CH(E)$_2$: 72% (E = CO_2Me)

64, R = H: 58%

65, R = H: 70%
66, R = CN: 75%
(+)-**67**, R = CH(E)$_2$: 70%[b]



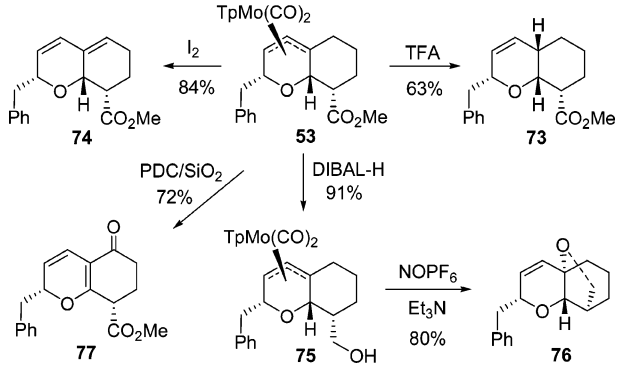
68, 83%

(+)-**69**, R^1 = Me, R^2 = H: 73%[b]
(+)-**70**, R^1 = OMe, R^2 = H: 60%[b]
71, R^1 = H, R^2 = Me: 68%

(–)-**72**, 72%[c]

[a] Conditions: Nucleophilic functionalization [$NOPF_6$ (1.2 equiv), CH_2Cl_2, 0 °C, 30 min; then, nucleophile (1.2−1.5 equiv)]. Oxidative demetalation [PDC (3 to 4 equiv)/silica gel, CH_2Cl_2, rt]. [b]98% ee. [c]Obtained in 99.8% ee from (+)-**27** (of 99.8% ee). Enantiomeric excesses were determined by HPLC.

Scheme 14. Demetalation Protocols for η-(3,4,4a)-Molybdenum [4 + 2] Cycloadducts[a]

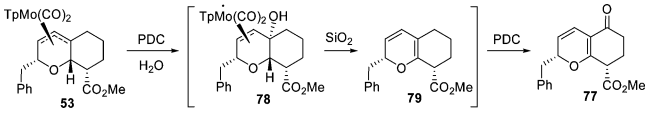


[a] Conditions: Protodemetalation [TFA (excess), CH_2Cl_2, rt, 20 min]. Iododemetalation [I_2 (3 equiv), CH_3CN, 0 °C, 30 min]. Nucleophilic functionalization [$NOPF_6$ (1.2 equiv), CH_2Cl_2, 0 °C, 30 min; then, Et_3N, CH_3CN, 0 °C to rt]. Oxidative demetalation [PDC (4 equiv)/silica gel, CH_2Cl_2, rt].

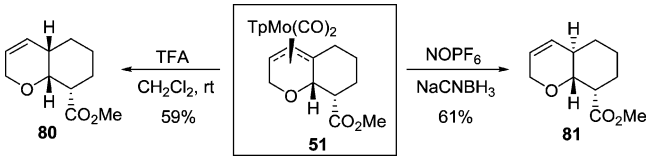
an intermediate unstable allylic iodide. Reduction of the ester group of **53** to the corresponding primary alcohol **75** was followed by activation of the TpMo(CO)$_2$(allyl) moiety with $NOPF_6$.[28,70−77] Subsequent intramolecular, Et_3N-induced nucleophilic addition of the alcohol to the cationic allylmolybdenum complex and demetalation resulted in the dioxatricyclo product **76** in very good overall yield.

Finally, oxidative demetalation of **53** with an excess of pyridinium dichromate (3.5 equiv) in the presence of silica gel gave the tetrahydro-2*H*-chromen-5-one **77** in 72% yield (Scheme 15). According to the proposed mechanism for this oxidative

Scheme 15. Mechanistic Rationalization for the Formation of Product **77**



Scheme 16. Stereodivergent Synthesis of 1-Oxadecalines with Opposite Ring-Fused Stereochemistry



demetalation procedure,[27] the formation of **77** can be rationalized by an allylic oxidation of diene **79**, which would result from the dehydration of the tertiary alcohol **78**, itself formed by oxidative demetalation of the tertiary alcohol **78**. Upon initial oxidation of **53** with PDC, alcohol **78** forms via addition of water (present in the silica gel) anti to the TpMo(CO)$_2$ moiety at the more substituted η^3-allyl terminus of the cationic radical allyl molybdenum complex.

As deduced from Schemes 13 and 14, two fundamental elements of stereocontrol are exploited in the demetalation of functionalized molybdenum scaffolds: a nucleophilic attack upon a cationic η^3-allylmolybdenum, which takes place from the face opposite to the TpMo moiety, and an electrophilic addition (typically H^+), which occurs first at the molybdenum followed by internal delivery of hydrogen to an allylic terminus syn to the metal (compare, for example, formation of products **73** and **76** in Scheme 14). To showcase the synthetic potential of these stereocontrolled transformations, the same π-allylmolybdenum complex, **51**, was used in a stereodivergent fashion to prepare either the cis-ring-fused 1-oxadecaline **80** or its ring-fused isomer, trans-ring-fused **81** (Scheme 16). Reductive demetalation using CO/NO^+ ligand exchange followed by reaction with $NaCNBH_3$ afforded the trans-fused 1-oxadecaline **81** in 61% yield with complete selectivity. Protodemetalation of **51** with trifluoroacetic acid led to cis-fused 1-oxadecaline **80** in comparable 59% yield.

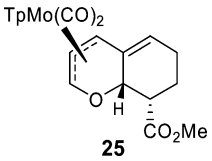
Conclusions

We have developed a novel regio- and enantiocontrolled route to highly functionalized 1-oxadecaline derivatives (i.e., chromenes) that relies on an efficient and versatile molybdenum-mediated [4 + 2] cycloaddition of TpMo(CO)$_2$(5-alkenyl-η-2,3,4-pyranyl) complexes. The reaction proceeds in good to excellent yields, with good *endo* selectivity and affords products with complete retention of enantiomeric purity when carried out with nonracemic scaffolds (98% ee). The role of the η^3-coordinated TpMo(CO)$_2$ moiety was essential not only to promote the [4 + 2] cycloaddition in a regio- and stereocontrolled fashion, but also to further functionalize the resulting cycloadducts. Four different protocols involving nucleophilic demetalation (NO^+/

nucleophilic addition), protodemetalation (TFA), iododemetalation (I_2), and oxidative demetalation (PDC/SiO_2) were developed for the efficient removal of the metal−ligand moiety from the η^3-chromenyl cycloadducts, leading to a variety of functionalized 1-oxadecaline derivatives in high yield, with high enantiopurity when starting from nonracemic adducts.

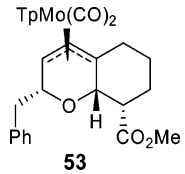
Experimental Section

A few representative examples are listed here. Full experimental details for all reactions and characterization data for all compounds can be found in the Supporting Information.



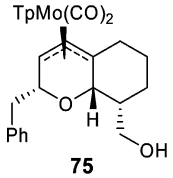
25

(−)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(2*S*,8*S*,8a*S*)-(η-2,3,4)-8-(methoxycarbonyl)-6,7,8,8a-tetrahydro-2*H*-chromen-2-yl]-molybdenum, (−)-25. To a solution of a 98% ee sample of (-)-**6** (150 mg, 0.32 mmol) in CH_2Cl_2 (3.5 mL) were successively added at 0 °C methyl acrylate (46 μL, 0.51 mmol) and a 1 M solution of Et_2AlCl (370 μL, 0.37 mmol). The solution was stirred at 0 °C for 7 h, and it was passed through a short pad of neutralized silica gel (CH_2Cl_2/EtOAc, 6:1). After evaporation, the resulting solid was triturated with ether and filtered to afford pure (−)-**25** (158 mg, 90%) in 98% ee {$[\alpha]_D$ −38.9 (*c* 0.41, CH_2Cl_2)} as a yellow solid. The racemic cycloadduct (±)-**25** was obtained in the same manner. TLC (*n*-hexanes/CH_2Cl_2, 1:3, R_f = 0.19); mp = 208−210 °C (dec). IR (cm^{-1}): 2949 (w), 2482 (w), 1934 (s), 1849 (s), 1741 (m), 1409 (m), 1305 (m), 1220 (m), 1197 (m), 1166 (m), 1123 (m), 1050 (m). ^{1}H NMR: δ 8.53 (d, *J* = 1.9 Hz, 1H), 7.77 (d, *J* = 1.9 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.57 (d, *J* = 2.2 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.09 (dd, *J* = 4.4, 2.2 Hz, 1H), 6.29 (t, *J* = 2.2 Hz, 1H), 6.20 (t, *J* = 2.2 Hz, 1H), 6.18 (t, *J* = 2.2 Hz, 1H), 5.69 (m, 1H), 4.85 (dd, *J* = 7.0, 1.9 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, *J* = 7.0, 4.4 Hz, 1H), 3.29 (m, 1H), 2.98 (q, *J* = 5.1 Hz, 1H), 2.24 (m, 2H), 2.09−2.02 (m, 1H), 1.90−1.81 (m, 1H). ^{13}C NMR: δ 226.0, 225.4, 172.4, 147.3, 141.9, 141.7, 136.0, 135.9, 134.4, 132.9, 120.7, 108.2, 106.0, 105.6, 105.3, 71.5, 70.6, 57.1, 51.5, 41.7, 24.0, 22.7. Anal. Calcd for $C_{22}H_{23}BMoN_6O_5$: C, 47.34; H, 4.15; N, 15.06. Found: C, 47.32; H, 4.16; N, 14.99.



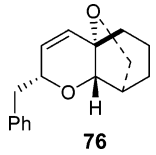
53

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(2*R*,3*S*,8*S*,8a*S*)-(η-3,4,4a)-2-benzyl-8-methoxycarbonyl-3,5,6,7,8,8a-hexahydro-2*H*-chromen-3-yl]molybdenum, (±)-53. Following the general procedure shown on page S-23 of the Supporting Information, (±)-**25** (206 mg, 0.36 mmol) was treated at −40 °C with HBF_4 (54 wt %, 55 μL, 0.40 mmol) to afford the diene cation (±)-**50**, which was dissolved in THF (5 mL) and treated at −78 °C with a 1 M solution of benzylmagnesium chloride in diethyl ether (440 μL, 0.44 mmol). After chromatographic purification (*n*-hexanes/CH_2Cl_2, 1:1.5), (±)-**53** (232 mg, 97%) was obtained as a yellow solid. TLC (*n*-hexanes/CH_2Cl_2, 1:1.5, R_f = 0.23); mp = 141−142 °C (dec). IR (cm^{-1}): 2949 (w), 2872 (w), 2482 (w), 1926 (s), 1837 (s), 1737(m), 1505 (w), 1436 (w), 1409 (m), 1305 (m), 1208 (m), 1123 (m), 1050 (s). ^{1}H NMR: δ 8.53 (d, *J* = 1.6 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.45−7.06 (m, 6H), 5.92 (t, *J* = 2.2 Hz, 1H), 5.86 (t, *J* = 2.2 Hz, 1H), 5.76 (t, *J* = 2.2 Hz, 1H), 4.86 (d, *J* = 4.4 Hz, 1H), 4.42 (dd, *J* = 7.3, 1.3 Hz, 1H), 4.32 (t, *J* = 6.6 Hz, 1H), 4.22 (d, *J* = 7.0 Hz, 1H), 3.41 (s, 3H), 3.23 (dd, *J* = 12.7, 7.3 Hz, 1H), 3.11−3.03 (m, 1H), 2.49−2.38 (m, 1H), 2.26−2.17 (m, 1H), 2.01−1.93 (m, 1H), 1.71−1.51 (m, 3H), 1.47 (m, 1H). ^{13}C NMR: δ 232.6, 229.9, 173.2, 146.9, 145.5, 139.9, 138.4, 136.6, 135.8, 134.2, 129.9, 128.1, 126.1, 105.7, 105.5, 105.2, 98.2, 80.8, 78.3, 77.6, 64.7, 51.4, 45.8, 31.2, 23.6, 17.0. Anal. Calcd for $C_{29}H_{31}BMoN_6O_5$: C, 53.56; H, 4.80; N, 12.92. Found: C, 53.79; H, 4.69; N, 13.13.



75

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato]{(3*S*,8*R*,8a*S*)-(η-3,4,4a)-8-[(hydroxy)methyl]-3,5,6,7,8,8a-hexahydro-2*H*-chromen-3-yl}molybdenum, (±)-75. To a solution of (±)-**55** (120 mg, 0.18 mmol) in CH_2Cl_2 (2 mL), cooled to −78 °C, was added a 1 M solution of DIBAL-H in hexanes (453 μL, 0.45 mmol). The mixture was allowed to reach 0 °C over 1 h, then stirred at 0 °C for 1.5 h, and it was passed through a short pad of silica gel (CH_2Cl_2/EtOAc, 9:1). After concentration, the residue was purified by flash chromatography (*n*-hexanes/CH_2Cl_2, 1:8) to afford (±)-**75** (105 mg, 91%) as a yellow solid. TLC (CH_2Cl_2, R_f = 0.16); mp = 118−120 °C (dec). IR (cm^{-1}): 3443 (br), 2957 (w), 2930 (w), 2872 (w), 2482 (w), 1926 (s), 1837 (s), 1505 (w), 1409 (m), 1305 (m), 1220 (m), 1123 (m), 1050 (m). ^{1}H NMR: δ 8.47 (d, *J* = 1.6 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.57 (s, 2H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.36−7.24 (m, 6H), 6.23 (t, *J* = 2.2 Hz, 1H), 6.15 (m, 2H), 4.35 (dd, *J* = 7.3, 1.0 Hz, 1H), 4.31 (d, *J* = 7.3 Hz, 1H), 4.02 (d, *J* = 3.8 Hz, 1H), 3.96 (t, *J* = 7.0 Hz, 1H), 3.67 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.54−3.49 (m, 1H), 3.08 (d, *J* = 7.0 Hz, 2H), 2.53 (m, 1H), 2.24−1.87 (m, 4H), 1.79 (dd, *J* = 12.7, 5.7, 1H), 1.60−1.49 (m, 2H). ^{13}C NMR: δ 232.0, 230.9, 147.0, 145.3, 140.2, 137.9, 136.5, 135.8, 134.2, 129.5, 128.5, 126.5, 105.7, 105.5, 105.1, 99.9, 81.7, 80.5, 78.4, 65.7, 65.6, 45.9, 40.4, 30.7, 24.5, 16.8.



76

(±)-(1*S*,4*R*,6*S*,7*R*)-4-Benzyl-5,11-dioxatricyclo[5.3.2.0^{1,6}]dodec-2-ene, (±)-76. To a solution of (±)-**75** (230 mg, 0.35 mmol) in degassed CH_2Cl_2 (3.5 mL), cooled to 0 °C, was added $NOPF_6$ (65 mg, 0.37 mmol) as a solid in one portion. The mixture was stirred at 0 °C for 30 min, and the orange solution was concentrated under vacuum. The resulting orange solid was dissolved in CH_3CN (3.5 mL) and stirred at 0 °C for 45 min, and then Et_3N (54 μL, 0.37 mmol) was added. The mixture was slowly (over 1 h) allowed to reach room temperature before CH_2Cl_2 (15 mL) and water (10 mL) were added. The organic layer was dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography (*n*-hexanes/EtOAc, 20:1) to afford (±)-**76** (39 mg, 80%) as a colorless oil. TLC (*n*-hexanes/EtOAc, 15:1, R_f = 0.14). ^{1}H NMR: δ 7.32−7.20 (m, 5H), 5.80 (dd, *J* = 10.2, 1.3 Hz, 1H), 5.75 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.32−4.25 (m, 2H), 3.89 (d, *J* = 7.3 Hz, 1H), 3.54 (s, 1H), 3.03 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.78 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.41 (bs, 1H), 1.83−1.69 (m, 3H), 1.58−1.51 (m, 2H), 1.41−1.33 (m, 1H). ^{13}C NMR: δ 137.8, 132.3, 129.6, 128.3, 126.9, 126.4, 83.9, 74.3, 72.0, 41.5, 41.4, 35.2, 29.3, 18.8. HRMS *m*/*z* [M^+] calcd for $C_{17}H_{20}O_2$: 256.1463. Found: 256.1456.

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Supporting Information Available: Full experimental details and characterization data for all compounds and copies of proton and carbon NMR spectra of all new compounds prepared in this study. Full X-ray crystallography data for compounds (±)-*E*-**8**, (±)-**27**, and (±)-**38** are given in the Supporting Information for the preliminary communication of this work[30] as compounds (±)-*E*-**5**, (±)-**11**, and (±)-**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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