

## Design and Stereoselective Preparation of a New Class of Chiral Olefin Metathesis Catalysts and Application to Enantioselective Synthesis of Quebrachamine: Catalyst Development Inspired by Natural Product Synthesis

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**Abstract:** A total synthesis of the *Aspidosperma* alkaloid quebrachamine in racemic form is first described. A key catalytic ring-closing metathesis of an achiral triene is used to establish the all-carbon quaternary stereogenic center and the tetracyclic structure of the natural product; the catalytic transformation proceeds with reasonable efficiency through the use of existing achiral Ru or Mo catalysts. Ru- or Mo-based chiral olefin metathesis catalysts have proven to be inefficient and entirely nonselective in cases where the desired product is observed. In the present study, the synthesis route thus serves as a platform for the discovery of new olefin metathesis catalysts that allow for efficient completion of an enantioselective synthesis of quebrachamine. Accordingly, on the basis of mechanistic principles, stereogenic-at-Mo complexes bearing only monodentate ligands have been designed. The new catalysts provide significantly higher levels of activity than observed with the previously reported Ru- or Mo-based complexes. Enantiomerically enriched chiral alkylidenes are generated through diastereoselective reactions involving achiral Mo-based bispyrrolides and enantiomerically pure silyl-protected binaphthols. Such chiral catalysts initiate the key enantioselective ring-closing metathesis step in the total synthesis of quebrachamine efficiently (1 mol % loading, 22 °C, 1 h, >98% conversion, 84% yield) and with high selectivity (98:2 er, 96% ee).

### Introduction

Herein, we first outline a scheme for a total synthesis of the *Aspidosperma* alkaloid quebrachamine, conceived specifically to challenge the state-of-the-art in catalytic olefin metathesis,<sup>1</sup> with particular emphasis on enantioselective transformations.<sup>2</sup> We detail a concise synthesis of racemic quebrachamine<sup>3,4</sup> by a route that underscores the need for substantially more efficient and selective olefin metathesis catalysts. In the second section, we illustrate how, guided by mechanistic principles and inspired by recent theoretical investigations,<sup>5</sup> we have been able to

design, synthesize, and develop an exceptionally effective new class of stereogenic-at-Mo olefin metathesis catalysts that readily promote a highly enantioselective synthesis of the target alkaloid.<sup>6</sup>

Several aspects of the investigations described in this account are noteworthy: (1) Synthesis of the chiral catalysts, which bear a stereogenic metal center, is accomplished through an unprecedented diastereoselective desymmetrization of Mo-based bispyrrolides, carried out by selective protonation of one of the two Mo–N bonds. (2) The stereogenic-at-Mo complexes developed are, to the best of our knowledge, the first effective chiral catalysts that bear a stereogenic metal center and contain only monodentate ligands. (3) The new catalysts represent a rare case

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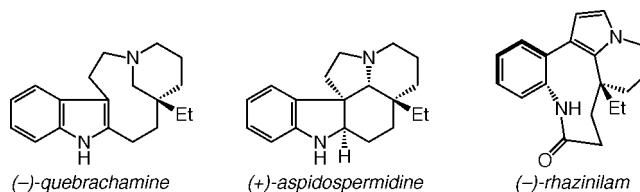
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of the successful use of a monodentate O-based chiral ligand in enantioselective catalysis [i.e., >95:5 enantiomer ratio (er) obtained].

Enantioselective preparation of a complex molecule provides an invaluable framework for the design of new methods and catalysts for efficient and selective chemical synthesis. It is often in the course of a total synthesis that shortcomings in the existing repertoire of protocols and/or catalysts become evident. Target-molecule synthesis offers the means to illustrate the advantages and limitations of a catalytic protocol, but more importantly, it can furnish a springboard for avenues of research that would otherwise remain unexplored.<sup>7</sup> As part of our program directed toward discovery and development of catalysts that promote a range of enantioselective C–C bond formation reactions, we have adopted the general strategy of designing synthesis routes that challenge the effectiveness of the existing catalysts and methods; synthesis plans that require catalyst innovation to achieve a successful enantioselective synthesis are thus favored.

Our interest in the development of more effective chiral catalysts for enantioselective olefin metathesis spans more than

**Scheme 1.** Representative Members of the *Aspidosperma* Group of Alkaloid Natural Products

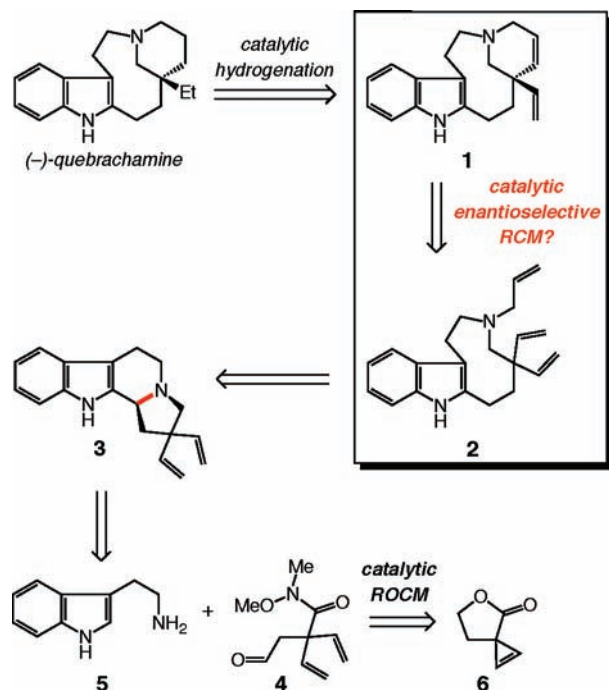


a decade of investigations, during which time we have introduced a number of chiral Mo- and Ru-based complexes that promote highly enantioselective ring-closing<sup>8,9</sup> as well as ring-opening metathesis reactions.<sup>10</sup> Such transformations offer unique opportunities for enantioselective synthesis of small organic molecules that would not be accessible by alternative approaches, such as those involving the use of achiral olefin metathesis catalysts and enantiomerically pure or highly enriched substrates secured through alternative protocols. Nonetheless, application of catalytic enantioselective olefin metathesis to natural product synthesis remains relatively uncommon, particularly in comparison with the myriad complex-molecule syntheses achieved through utilization of the corresponding achiral catalysts.<sup>11</sup> One rationale for the aforementioned paucity is that target molecules traditionally are selected subsequent to method development; as a result, a protocol may not provide an ideal solution for application to any particular total synthesis problem. In our judgment, it would be more expedient to first secure the most direct synthesis route that benefits from catalytic enantioselective processes. The effectiveness of the existing chiral complexes would then be evaluated, and if necessary, any attendant shortcomings would be addressed by new catalyst design.

Our decision to focus on the adrenergic blocking agent quebrachamine (Scheme 1),<sup>12,3,4</sup> a tetracycle from the *Aspidosperma* group of alkaloids,<sup>13</sup> two other members of which are also illustrated in Scheme 1, was based on several factors. First, a catalytic olefin metathesis reaction would have to be designed that allows for an effective transformation, likely involving sterically congested alkenes.<sup>14</sup> Second, the optimal chiral catalyst must allow for control of the absolute stereochemistry of an all-carbon quaternary stereogenic center, which represents a difficult and important challenge in modern chemical synthesis.<sup>15</sup> Third, an effective catalyst would have to remain operative in the presence of the Lewis basic amine, a functional unit that has been shown to cause deactivation of Mo alkylidenes<sup>8c</sup> as well as Ru-based carbenes.<sup>16</sup>

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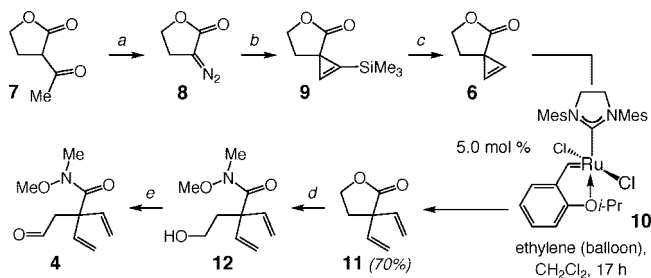
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**Scheme 2.** Retrosynthesis Analysis for Enantioselective Preparation of Quebrachamine

## Results and Discussion

**I. Total Synthesis of *rac*-Quebrachamine. 1. Retrosynthesis Plan.** The retrosynthesis plan adopted in this investigation is outlined in Scheme 2. We envisioned that formation of the tetracyclic moiety of the target alkaloid could be effected through enantioselective ring-closing metathesis (RCM) of triene **2**, concomitant with control of the all-carbon quaternary stereogenic center. Catalytic hydrogenation of the resulting diene **1** would deliver enantiomerically enriched quebrachamine.

To prepare the relatively strained nine-membered ring of the target, we took inspiration from a report by Calverley<sup>17</sup> and planned to access the requisite medium ring by reductive cleavage of the C–N bond (shown in red) of indole-based tertiary amine **3**.<sup>18</sup> The tetracycle required for the Calverley-type ring expansion would be synthesized through condensation of divinyl aldehyde **4** with commercially available and inexpensive tryptamine (**5**). We surmised that catalytic ring opening/cross metathesis (ROCM) of spirocyclic lactone **6** in the presence of ethylene would present a concise method for the preparation of **4**, an early intermediate that seemed simple but was nontrivial because of the lack of protocols for efficient synthesis of *gem*-divinyl functionality at an all-carbon quaternary center.<sup>19</sup> Successful application of catalytic ROCM would allow for direct synthesis of the requisite carbon framework through a relatively unusual cyclopropanation.

**Scheme 3.** Synthesis of Divinylamide Fragment **4** through Ru-Catalyzed ROCM<sup>a</sup>

<sup>a</sup> (a) 4.0 equiv of  $\text{NaN}_3$ , 2.0 equiv of  $\text{TiF}_2\text{O}$ , 1.0 mol % TBAB, 2.0 M NaOH, petroleum ether/MeCN, 0 °C, 30 min; 66% yield. (b) 1.0 mol %  $\text{Rh}_2(\text{OAc})_4$ ,  $\text{HCCSiMe}_3$ , 55 °C, 20 h; 64% yield. (c) 3.7 mol % KOH, EtOH, 0 °C, 5 min; 93% yield. (d) 1.3 equiv of  $\text{HCl}\cdot\text{HNMe}(\text{OMe})$ , 2.6 equiv of *i*-PrMgCl, THF, 0 °C  $\rightarrow$  22 °C, 30 min; pH 7 buffer. (e) 2.3 equiv of DMSO, 2.0 equiv of  $(\text{COCl})_2$ ,  $\text{CH}_2\text{Cl}_2$ , 7.4 equiv of  $\text{Et}_3\text{N}$ , -78 °C  $\rightarrow$  22 °C; 86% overall yield for two steps.

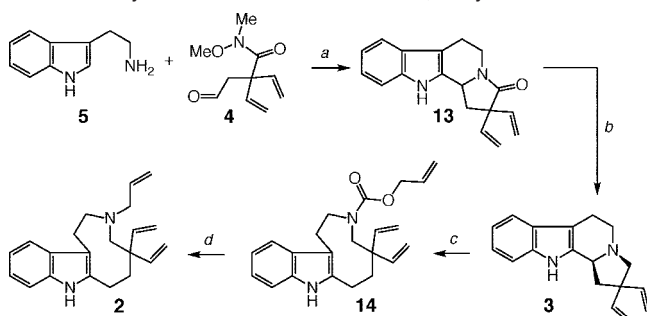
The brevity of the initial synthesis plan notwithstanding, we considered the route shown in Scheme 2 attractive for an additional and important reason: the tetracyclic diene **1**, accessed through catalytic enantioselective RCM, does more than serve as a precursor to the naturally occurring quebrachamine; because of its two differentiable alkenes, **1** might be utilized to access derivatives of this class of biologically active alkaloids.<sup>13</sup>

**2. Synthesis of Triene **2** (Substrate for Catalytic Ring-Closing Metathesis).** **a. Preparation of Divinylamide Fragment **4**.** Synthesis of divinylamide fragment **4** began with treatment of commercially available  $\alpha$ -acetylbutyrolactone **7** with  $\text{NaN}_3$ ,  $\text{TiF}_2\text{O}$ , and 1.0 mol % tetrabutylammonium bromide (TBAB) (0 °C, 30 min) to afford lactone **8** in 66% yield after deacylative Regitz diazo transfer (Scheme 3).<sup>20</sup> The *in situ* generation of the diazo transfer agent under phase-transfer conditions obviated the need for preparation and handling of trifluoromethanesulfonyl azide; gram-scale synthesis of **8** could therefore be safely performed. It should be noted that cyclopropanations of diazo compounds bearing  $\alpha$ -hydrogens are scarce since such processes typically suffer from adventitious elimination and dimerization pathways.<sup>21</sup> Efficient synthesis of Si-substituted cyclopropene **9**, however, was readily achieved by slow addition of **8** to a solution of  $\text{Rh}_2(\text{OAc})_4$  in trimethylsilylacetylene (recovered and used as the solvent for multiple transformations),<sup>22</sup> allowing us to secure the desired product in 64% yield after purification. Subjecting of vinylsilane **9** to 3.7 mol % KOH in EtOH for 5 min at 0 °C furnished spirocyclic cyclopropene **6**. Catalytic ROCM involving **6** and ethylene in the presence of 5.0 mol % of Ru carbene **10**<sup>23</sup> led to the formation of divinyl lactone **11** in 70% yield. The four-step procedure beginning with **7** constitutes a straightforward route for the preparation of lactone **11**, which contains the critical quaternary carbon center, in 27% overall yield.

Attempts to carry out a saponification/oxidation sequence were complicated by a relatively facile reconversion of deriva-

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(20) The procedure used to prepare diazo lactone **8** is based on previously reported protocols. See: Brown, R. C. D.; Bataille, C. J. R.; Brunton, G.; Hinks, J. D.; Swain, N. A. *J. Org. Chem.* **2001**, *66*, 6719–6728. (21) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22–23. (22) See the Supporting Information for complete experimental details. (23) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179. For an overview of Ru-based carbenes bearing bidentate styrene ether ligands, see: (b) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8–23.

**Scheme 4.** Synthesis of the RCM Precursor, Tricyclic Triene **2**<sup>a</sup>

<sup>a</sup> (a) HOAc, toluene, 80 °C, 2 h; 79% yield (1.5 equiv of **5** used). (b) 5.0 equiv of LAH, THF, 0 °C → 65 °C, 1 h; 97% yield. (c) 10 equiv of allyl chloroformate, THF, -78 °C, 1 h; 7.0 equiv of NaCNBH<sub>3</sub>, THF, -78 °C, 2 h; warm to 0 °C; 94% yield. (d) 2.0 mol % Pd(PPh<sub>3</sub>)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 22 °C, 20 min; 88% yield.

tives of **12** to cyclic lactone **11**. We established, however, that treatment of **11** with the magnesium amide of *N*-methoxy-*N*-methylamine,<sup>24</sup> followed by quenching with a pH 7 buffer solution, furnished the desired alcohol **12**. Immediate oxidation of **12** provided aldehyde **4** in 86% overall yield.

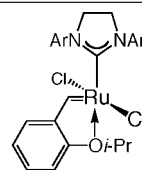
**b. Preparation of Tricyclic Triene **2** through Reductive C–N Bond Cleavage and Pd-Catalyzed Decarboxylation of an Allylcarbamate.** As illustrated in Scheme 4, synthesis of triene **2** began with Pictet–Spengler condensation of **4** with commercially available tryptamine **5** in the presence of HOAc at 80 °C, affording tetracyclic amide **13** in 79% yield after silica gel chromatography. Amine **3** was subsequently obtained in 97% yield by subsection of **13** to lithium aluminum hydride. Reductive cleavage of the C–N bond in **3** required initial activation through formation of the corresponding quaternary carbamate. The tertiary carbamate obtained as a result of the reductive C–N bond rupture would then be converted to afford the derived secondary amine, which could be alkylated to afford the desired allylamine **2**. Although the Calverley protocol<sup>17</sup> calls for use of ethyl chloroformate, we surmised that activation of the amine unit in **3** in the form of an allylcarbamate, followed by reductive C–N cleavage to afford **14**, would be more efficient. We considered the possibility that a Pd-catalyzed protocol based on recent studies by Tunge and co-workers<sup>25</sup> might afford allyl amine **2** directly, without the need to resort to carbamate deprotection. The above scenario, as depicted in Scheme 4, is viable, affording a direct route to **2**. Thus, treatment of **3** with allyl chloroformate (-78 °C, 1 h) followed by addition of purified NaCNBH<sub>3</sub> resulted in the generation of nine-membered ring **14** in 94% yield after purification. Allyl carbamate **14** is susceptible to decomposition upon storage for reasons that are unclear at the present time; accordingly, direct subsection of the allyl carbamate to 2.0 mol % Pd(PPh<sub>3</sub>)<sub>4</sub> at 22 °C for 20 min was used to secure **2** in 88% yield.

**II. Evaluation of Existing Achiral and Chiral Catalysts in Effecting a Total Synthesis of Quebrachamine. 1. Examination of Existing Catalysts to Promote Ring-Closing Metathesis of Triene **2**.** Having established an efficient route for gram-scale synthesis of tricyclic triene **2**, we began to evaluate the ability of achiral and chiral Ru- and Mo-based complexes to promote its transformation to tetracyclic diene **1**.

**a. Catalytic RCM of Triene **2** with Achiral Catalysts.** The results of studies regarding catalytic RCM reactions of tricyclic

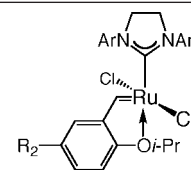
**Table 1.** Screening of Achiral Ru- and Mo-based Catalysts for Conversion of **2** to **1** through RCM<sup>a</sup>

entry	complex	mol %	time (h)	conv (%) <sup>b</sup>	yield (%) <sup>c</sup>
1	<b>10</b>	5	6	75	61 <sup>d</sup>
2	<b>10</b>	7.5	6	94	83
3	<b>15</b>	5	6	46	36 <sup>d</sup>
4	<b>16</b>	5	6	91	49 <sup>d</sup>
5	<b>17</b>	5	6	>98	65
6	<b>18</b>	5	6	67	57 <sup>d</sup>
7	<b>19</b>	30	2	>98	59



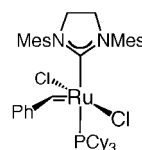
**10** Ar = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub> (Mes)

**15** Ar = 2-MeC<sub>6</sub>H<sub>4</sub>

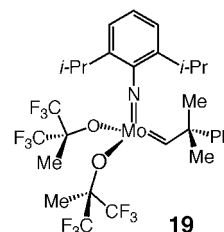


**16** R<sub>1</sub> = Ph, R<sub>2</sub> = H

**17** R<sub>1</sub> = H, R<sub>2</sub> = NO<sub>2</sub>



**18**



**19**

<sup>a</sup> Reactions were performed under N<sub>2</sub> atmosphere; see the Supporting Information for experimental details. <sup>b</sup> All conversions >98% (based on the amounts of unreacted substrate and product formed), as determined through analysis of 400 MHz <sup>1</sup>H NMR spectra of the unpurified mixtures. <sup>c</sup> Yields of purified products. <sup>d</sup> Yields were estimated from purified mixtures of **1** and **2**, which are inseparable by silica gel chromatography.

triene **2** with various achiral complexes are summarized in Table 1. In the case of Ru complex **10** (entry 1, Table 1), with 5 mol % catalyst loading (22 °C), there was 75% conversion after 6 h, and the desired product was obtained in 61% yield after purification; extended reaction time (9 h) did not lead to further conversion, an observation suggesting that in the presence of tertiary amine **2**, the typically robust **10** undergoes decomposition after several hours. Therefore, to achieve complete substrate consumption, 7.5 mol % of **10** was required (entry 2, Table 1). With the modified Ru carbene **15**<sup>26</sup> bearing less-substituted *N*-heterocyclic carbene aryl substituents (entry 3, Table 1), significantly less reaction was achieved in the same amount of time (5 mol %, 6 h, 46% conv, 36% yield); the lower level of conversion to **1** exhibited by **15** is likely a result of a faster rate of decomposition of this more sterically exposed Ru carbene. Thus, as summarized in entries 4 and 5 of Table 1, with sterically modified derivative **16**<sup>27</sup> and electronically altered

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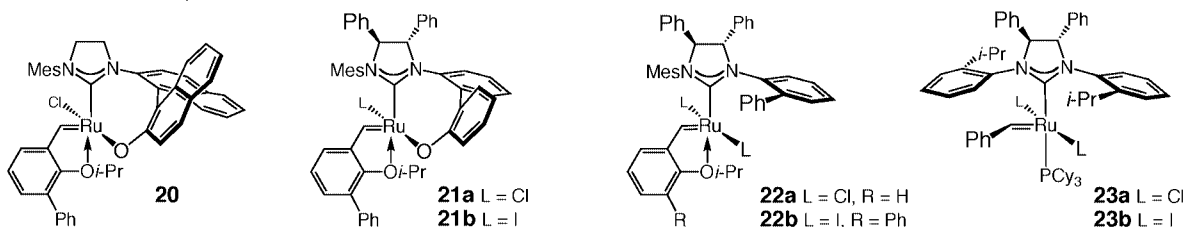
(26) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.

(27) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403–2405.

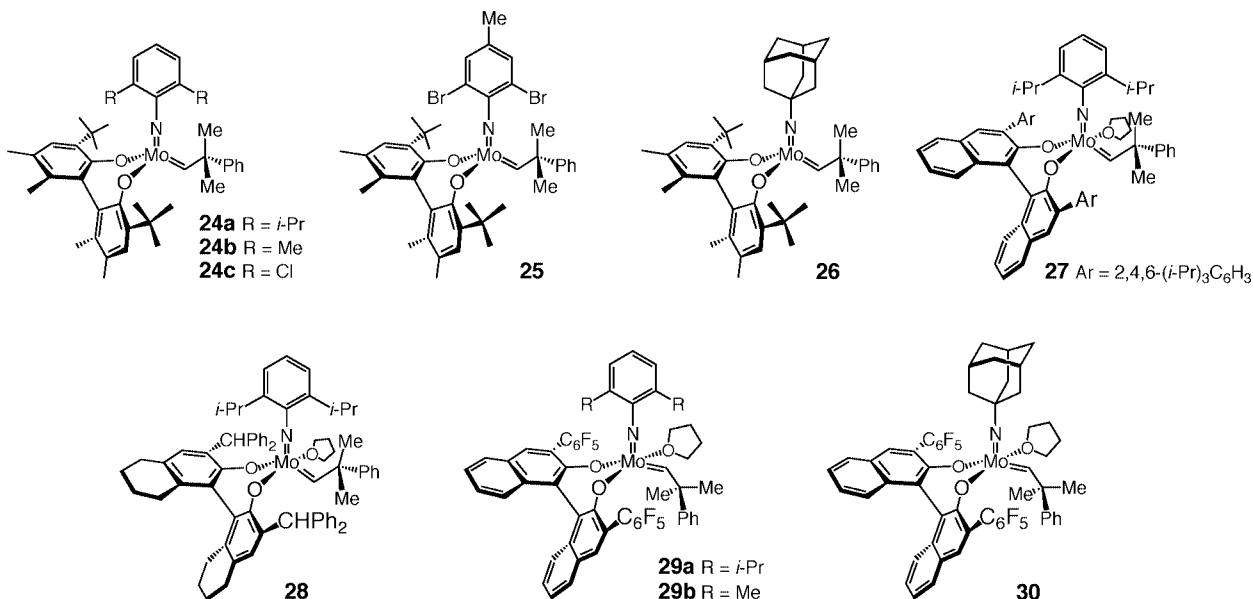
(24) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

Scheme 5. Ru- and Mo-based Chiral Catalysts Examined for RCM of Triene **2** to Afford Diene **1**

## ■ Chiral Ru-based Complexes:



## ■ Chiral Mo-based Complexes:



carbene **17**,<sup>28</sup> both of which are complexes that initiate faster than the parent complex **10**, higher conversion was obtained (91% and >98% conv, respectively); in the case of complex **17** (entry 5, Table 1), reduced reaction times (i.e., <6 h) translated to substantial amounts of recovered substrate. The phosphine-containing Ru complex **18**<sup>29</sup> (entry 6, Table 1) showed nearly the same activity and level of efficiency as **10** (entry 1, Table 1).

Larger amounts (30 mol %) of the Mo-based alkylidene **19**<sup>2</sup> were required to achieve >98% conversion of the substrate (entry 7, Table 1); the high catalyst loading is likely linked to the faster (vs Ru carbenes) rate of decomposition of **19**. It should be noted that in many of the cases shown in Table 1, and particularly with Ru complexes **16** and **17** and Mo complex **19** (entries 4, 5, and 7, Table 1), there is a significant difference between the percent conversion and the percent yield of isolated product; this discrepancy is due to formation of byproducts that we have not as yet been able to identify.

**b. Enantioselective RCM.** The chiral Ru-based (**20–23**) and Mo-based (**24–30**) complexes examined for catalytic enantioselective RCM of **2** to afford enantiomerically enriched **1** are illustrated in Scheme 5; the corresponding data are summarized in Table 2.

When chiral Ru catalysts bearing bidentate<sup>9a,30</sup> or monodentate chiral *N*-heterocyclic carbenes<sup>9b</sup> (NHCs) were used (entries

1–7, Table 2), regardless of whether these were the typically more active chlorides or the less effective but more discriminating iodides, low enantioselectivity was observed (<10% ee). The Ru chlorides bearing bidentate carbenes (i.e., **20** and **21a**) were more active than their corresponding iodide salts (e.g., **21b**); nonetheless, chloride complexes **20** and **21a** (entries 1 and 2, Table 2) required elevated temperatures (80 °C) to promote >98% conversion to **1** after 12 h. Reactions with Ru complexes bearing a dissymmetric (**22a** and **22b**;<sup>31</sup> entries 4 and 5, Table 2) or C<sub>2</sub>-symmetric (**23a** and **23b**;<sup>9b</sup> entries 6 and 7, Table 2) monodentate chiral NHC also furnished nearly racemic **1** (≤10% ee).

Mo-based diolates **24–30**<sup>2</sup> (Scheme 5), as evident from the data summarized in Table 2, were entirely ineffective in promoting the conversion of **2** to **1**. Regardless of whether we resorted to high catalyst loadings (e.g., entries 8–10 and 12–13 in Table 2) or elevated reaction temperatures (e.g., entries 8–10 and 12–17, Table 2), none of the desired ring-closed tetracyclic product (**1**) could be observed.

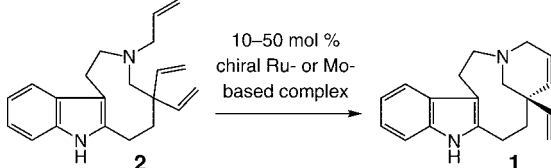
The above investigations, involving the entire range of available chiral olefin metathesis catalysts, clearly indicated that a new and significantly more effective catalyst system would be required if an efficient and enantioselective synthesis of **1** through catalytic enantioselective RCM of **2** were to be realized. The studies outlined below describe the realization of this goal.

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(29) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(30) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

(31) Zhugralin, A. R.; Hoveyda, A. H., unpublished results.

**Table 2.** Screening of Chiral Ru- and Mo-Based Catalysts for Conversion of **2** to **1** through Enantioselective RCM<sup>a</sup>


entry	catalyst	mol %	temp (°C)	time (h)	conv (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>20</b>	15	80	12	>98 <sup>d</sup>	<5
2	<b>21a</b>	15	80	12	>98 <sup>e</sup>	<5
3	<b>21b</b>	16	80	18	50	<10
4	<b>22a</b>	10	22	12	50	<5
5	<b>22b</b>	10	22	24	<10	nd
6	<b>23a</b>	15	22	12	50	10
7	<b>23b</b>	15	35	16	17	nd
8	<b>24a</b>	50	80	12	<5	—
9	<b>24b</b>	50	80	12	<5	—
10	<b>24c</b>	50	80	12	<5	—
11	<b>25</b>	10	22	12	<5	—
12	<b>26</b>	50	80	12	<5	—
13	<b>27</b>	50	80	18	<5	—
14	<b>28</b>	10	80	18	<5	—
15	<b>29a</b>	10	80	18	<5	—
16	<b>29b</b>	10	80	18	<5	—
17	<b>30</b>	10	80	18	<5	—

<sup>a</sup> Reactions were performed under N<sub>2</sub> atmosphere; see the Supporting Information for experimental details. nd = not determined.

<sup>b</sup> Conversions (based on the amounts of unreacted substrate and product formed) were determined through analysis of 400 MHz <sup>1</sup>H NMR spectra of the unpurified mixtures. <sup>c</sup> Enantioselectivities (ee) were determined by HPLC analysis; see the Supporting Information for details. <sup>d</sup> Product isolated in 54% yield. <sup>e</sup> Product isolated in 51% yield.

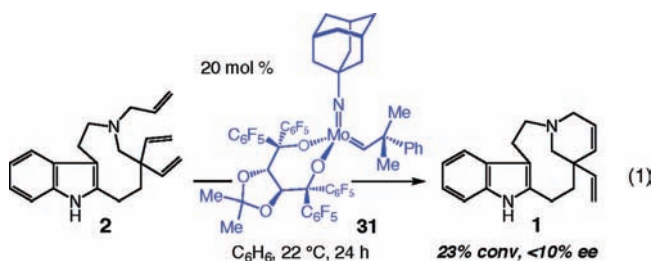
### III. Design of New Chiral Stereogenic-at-Mo Catalysts for Olefin Metathesis. 1. Mechanistic Considerations and Design Criteria.

As the first step toward designing and/or identifying a chiral catalyst that would convert tricyclic triene **2** to tetracyclic diene **1** efficiently as well as enantioselectively, we considered the structural aspects of the existing catalysts that required alteration. Since Mo-based complexes have thus far generally proven to be more effective than Ru-based carbenes in catalyzing enantioselective RCM reactions<sup>8,9</sup> (vs enantioselective ring-opening metathesis processes),<sup>10</sup> we decided to focus our attention on this class of complexes.

**a. Reducing the Strain of Metallacyclobutanes.** We began by considering the reason for the higher activity of achiral Mo alkylidene **19** (Table 1), which bears two monodentate hexafluoro-*t*-butoxide ligands, versus complexes **24–30** (Scheme 5), which contain various bidentate ligands (i.e., biphenoxides in **24–26**, binaphtholates in **27**, **29**, and **30**, or a tetrahydrobinaphtholate in **28**). We noted that the difference in reactivity is not likely due to the higher Lewis acidity of Mo in diolates [for aryl alcohol and hexafluoro-*t*-butanol, pK<sub>a</sub> ≈ 9–10 (measured in H<sub>2</sub>O)].<sup>32</sup> We reasoned that the significantly higher (albeit less than desired) activity of the achiral Mo-based complex **19** compared with the chiral variants might originate from the structural rigidity of diolates **24–30**. That is, we surmised that the strain existing within the initiating alkylidenes that carry a bidentate bisaryloxoide (vs the relatively flexible alkoxides in **19**) might be exacerbated by the formation of the spiro metallacyclobutane intermediates (i.e., **I** and **II** vs **III** and **IV** in Figure 1), causing a rise in the activation barrier for a key step of the

catalytic cycle and, as a result, a diminution in the rate of the RCM. The variation of the O–Mo–O angle in alkylidene **24a** (O–Mo–O = 127°)<sup>33</sup> from that in a closely related tungstacyclobutane analogous to **IV** (O–W–O = 98°)<sup>34</sup> indicates the potentially significant structural change involved in such transformations.

The proposal that a structurally more flexible Mo diolate might generate a higher level of catalytic activity led us to prepare complex **31**, which bears a chiral taddolate.<sup>35</sup> We predicted that the seven-membered-ring bisalkoxide in **31**, which is built from sp<sup>3</sup>-hybridized atoms, could more readily transform into the required metallacyclobutane than could complexes **24–30** (Scheme 5), each of which contains a seven-membered ring diolate with four sp<sup>2</sup>-hybridized carbon atoms. Thus, as illustrated in eq 1, we found that in the presence of 20 mol % chiral complex **31**, there was 23% conversion of triene **2** to tetracyclic **1**, albeit with minimal enantioselectivity; under identical conditions, the chiral Mo diolates shown in Scheme 5 delivered <2% of the desired product. It should be noted that the increase in catalytic activity manifested by **31** occurs in spite of the lower Lewis acidity of its Mo center, which is due to a less electron-withdrawing diolate ligand (vs the bisaryloxides in **24–30**).

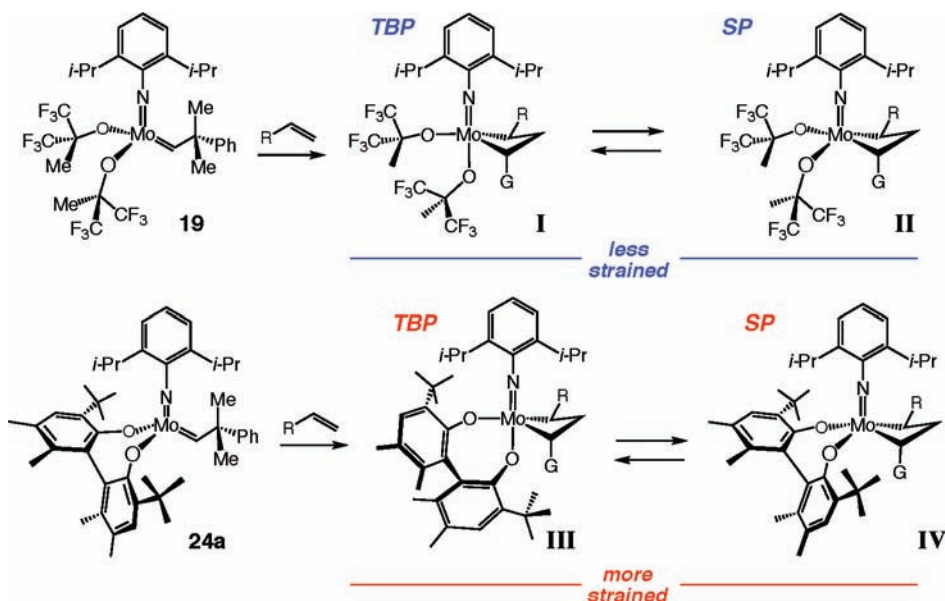


The above analysis led us to consider that Mo-based catalysts bearing monodentate ligands, either both chiral (same enantiomer, nonstereogenic-at-Mo) or one achiral and one chiral (stereogenic-at-Mo), would be more effective as chiral catalysts for olefin metathesis. Additional considerations, as detailed below, pointed to the significantly less explored alternative: a stereogenic-at-Mo complex.<sup>36,37</sup>

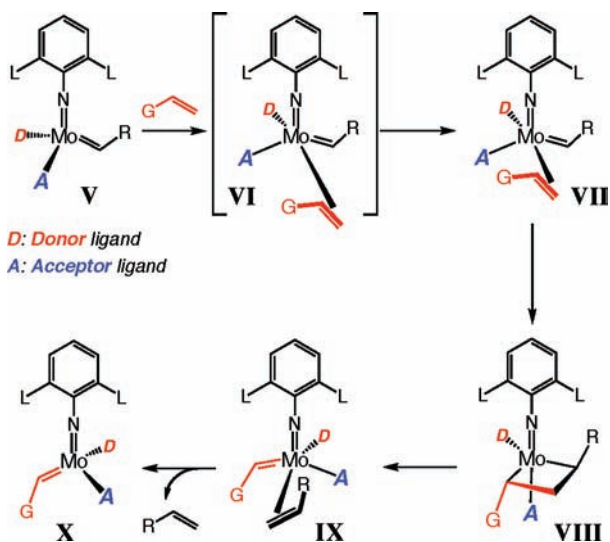
### b. Incorporation of Stereoelectronic Effects at the Metal Center: Nonstereogenic-at-Mo or Stereogenic-at-Mo? Recent

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- (34) Tsang, W. C. P.; Hultzs, K. C.; Alexander, J. B.; Bonitatebus, P. J., Jr.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2652–2666.
- (35) For a previous example of a chiral Mo-based taddolate complex, see: McConville, D. H.; Wolf, J. R.; Schrock, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 4413–4414.
- (36) For overviews regarding stereogenic-at-metal complexes, see: (a) Brunner, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1194–1208. (b) Fontecave, M.; Hamelin, O.; Ménage, S. *Top. Organomet. Chem.* **2005**, *15*, 271–288.
- (37) For enantiomerically pure stereogenic-at-Ru catalysts used in enantioselective olefin metathesis that bear a bidentate chiral ligand, see: (a) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. (b) See ref 9a. (c) See ref 10d. (d) See ref 7a. (e) Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824–3825. For stereogenic-at-Ru olefin metathesis catalysts that have been used in olefin metathesis but only in the racemic form, see: (f) Fürstner, A.; Liebl, M.; Lehmann, C. W.; Picquet, M.; Kunz, R.; Bruneau, C.; Touchard, D.; Dixneuf, P. H. *Chem.—Eur. J.* **2000**, *6*, 1847–1857. (g) Bornand, M.; Chen, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7909–7911. (h) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882–11883. (i) Bornand, M.; Torker, S.; Chen, P. *Organometallics* **2007**, *26*, 3585–3596.

(32) Filler, R.; Schure, R. M. *J. Org. Chem.* **1967**, *32*, 1217–1219.



**Figure 1.** The relatively rigid diolate ligands in Mo-based complexes translate to high-energy metallacyclobutane intermediates. Abbreviations: G = C(Ph)Me<sub>2</sub>; TBP = trigonal bipyramidal; SP = square pyramidal.



**Figure 2.** Electronic dissymmetry at the metal facilitates olefin coordination and metallacyclobutane collapse.

theoretical studies by Eisenstein and co-workers<sup>5</sup> present the case that high-oxidation-state complexes that bear a stereogenic metal center would be exceptionally effective olefin metathesis catalysts (Figure 2). First, their theoretical investigations suggest that the presence of one acceptor ligand (A in **V**, Figure 2) is required in order to ensure that the metal center possesses sufficient Lewis acidity to provide effective binding to olefins. Furthermore, and more importantly, the presence of a donor ligand (D in **V**, Figure 2) is favorable as it causes the geometrically distorted **VI** to be energetically more accessible. In contrast to tetrahedral **V**, which cannot directly coordinate with an alkene (structural distortion is required), transition complex **VI** easily provides a ligation site for an olefin. A critical aspect of the proposed scenario is that there is maximum stabilization of distorted **VI** (Figure 2) when the donor ligand D is associated with the energetically most favorable metal orbital, namely, the one that generates minimal electronic repulsion (*trans* effect). Accordingly, ligand D should occupy

an apical site in **VI** (Figure 2) with the alkylidene, acceptor, and imido ligands constituting the equatorial plane. Consequently, the weakly coordinated olefin preferably approaches the metal center *trans* to D. The suggested coordination of the substrate olefin *trans* to the donor ligand suggests that in the design of an enantiomerically enriched stereogenic-at-Mo complex, it might be preferable that the acceptor ligand A be chiral rather than the donor ligand D, since the substrate most likely approaches the catalyst *syn* to the former, leading to higher enantioselectivity.

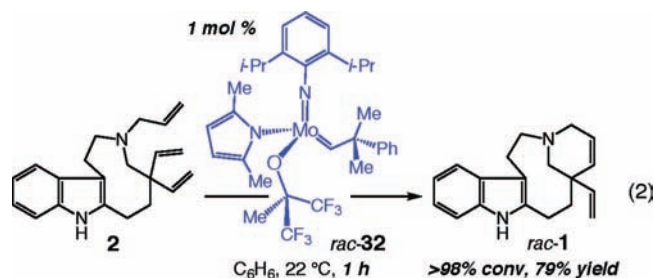
Another consequence of the above stereoelectronic principles might be that the resulting trigonal bipyramidal complex **VIII** (Figure 2) can undergo facile degradation to afford **IX**, since the carbons constituting the releasing olefin are situated *trans* to ligand D. Thus, the electronic effects caused by the presence of a donor and an acceptor ligand (a stereogenic-at-Mo complex) further facilitate catalytic turnover by elevating the energy (*trans* effect) of the metallacyclobutane complex **VIII** (thereby lowering the activation barrier for metallacyclobutane decomposition to afford **IX**).

The abovementioned hypotheses regarding the higher catalytic activity of a Mo-based catalyst that bears a donor and an acceptor ligand (vs two donor or two acceptor ligands) finds support in the remarkably facile reaction shown in eq 2: 1 mol % *rac*-**32**<sup>38</sup> promotes formation of racemic **1** within only 1 h. This level of activity is in stark contrast to that of achiral Mo complex **19** (see Table 1), a complex with two hexafluoro-*tert*-butoxide ligands. It merits mention that although RCM of **2** with complex **32** is more efficient than with the achiral Ru and Mo complexes shown in Table 1, there is still ~20% yield of unidentified byproducts generated in the transformation illustrated in eq 2.

## 2. Stereoselective Synthesis of Stereogenic-at-Mo Complexes.

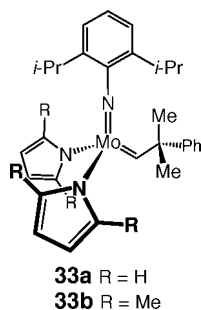
The investigations and mechanistic considerations discussed above point to structurally fluxional stereogenic-at-Mo complexes bearing appropriate donor and acceptor ligands as the

(38) Singh, R.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 12654–12655.



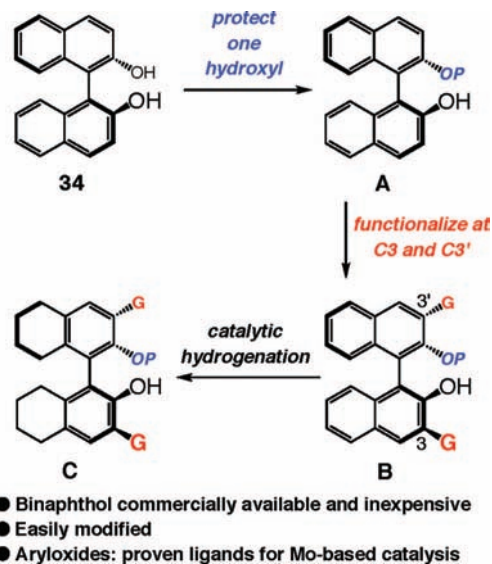
preferred class of chiral olefin metathesis catalysts. That is, to achieve an enantioselective synthesis of quebrachamine, we were required to identify an effective, enantiomerically enriched version of complex **32** (see eq 2). To achieve this goal, one possible strategy would be to use the same class of Mo alkylidene precursors that deliver monopyrrolide **32** (see below). The challenging task of identifying an appropriate set of chiral monodentate alcohol ligands that would allow for efficient and diastereoselective synthesis of stereogenic-at-Mo alkylidenes, however, remained to be accomplished.

**a. A Suitable Mo Alkylidene Precursor.** Recently, in connection with a program directed toward the development of practical methods for synthesis of chiral Mo diolate catalysts, we prepared complexes **33a** and **33b**.<sup>39</sup> These complexes, which are easily accessed from the reaction of a Mo bistriflate with an appropriate lithium pyrrolide, are converted to the desired diolates (e.g., complexes in Scheme 5) upon exposure to chiral biphenols or binaphthols; the resulting diolates can be used without isolation or purification to promote enantioselective olefin metathesis reactions with efficiencies and selectivities similar to those observed with purified catalysts.<sup>40</sup> The above investigations indicated that pyrrole molecules generated via protonation by the chiral diols do not cause diminution of catalyst activity or reaction selectivity. We thus surmised that one approach toward preparation of stereogenic-at-Mo catalysts would involve diastereoselective reaction of **33a** and **33b** with 1 equiv of a chiral enantiomerically pure alcohol. An attractive feature of such an approach would be that chiral catalysts might be generated and used *in situ* to promote olefin metathesis reactions.



**b. Identification of a Suitable Class of Enantiomerically Pure Chiral Alcohols to Serve As Chiral Monodentate O-Based Ligands.** Although a variety of diols have been utilized as ligands in enantioselective catalysis,<sup>41</sup> and whereas monodentate phosphines<sup>42</sup> or *N*-heterocyclic carbenes<sup>43</sup> can be found in the structures of chiral catalysts, monodentate O-based ligands

**Scheme 6.** Monoprotected Binaphthols: A Versatile Class of Chiral Monodentate Ligands



have scarcely been used in this context.<sup>44</sup> As the first step toward identification of an effective class of chiral monodentate alcohols, we adopted the simple strategy that such chiral ligands could simply be derived from protection of one of the hydroxyl units of a chiral diol. As such, we would be able to select from a readily available class of ligands (i.e., chiral diols). The above considerations led us to identify binaphthol-derived alcohols as the most desirable. As illustrated in Scheme 6, monoprotected binaphthols benefit from a number of attributes that are critical to chiral catalyst development: (a) ease and low cost of synthesis through protection of commercially available and inexpensive binaphthol (e.g., **34** → **A** in Scheme 6) and (b) the facility of ligand modification for fine-tuning the steric and electronic attributes of the stereogenic-at-Mo catalysts, as represented by functionalization at C3 and C3' sites and partial hydrogenation of the aromatic rings<sup>45</sup> (as illustrated by **A** → **C** in Scheme 6.) Since bisaryloxides have proven to be effective ligands for Mo-based olefin metathesis catalysis, we judged monoaryloxides should prove to be effective catalysts as well.

(41) For reviews regarding the use of binaphthol and its derivatives as chiral ligands, see: (a) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3212. (b) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–898. For an overview of taddol-type chiral ligands in stereoselective synthesis, see: (c) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92–138. (d) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490. For a review that includes diols as chiral Brønsted acids, see: (e) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758.

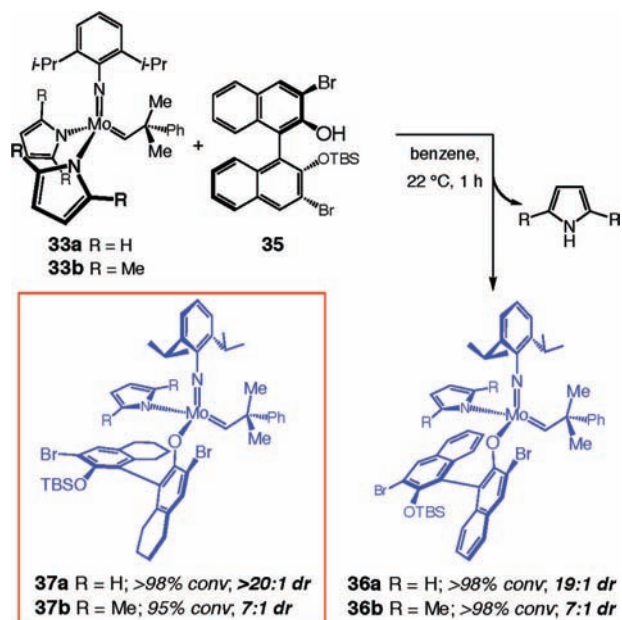
(42) For use of monodentate phosphoramidites as ligands in enantioselective catalysis, see: (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353. (b) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506–15514. (c) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267–1277.

(43) For monodentate chiral NHCs used as ligands in enantioselective catalysis, see: (a) César, V.; Bellemin-Lapponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619–636. (b) Gade, L. H.; Bellemin-Lapponnaz, S. *Top. Organomet. Chem.* **2007**, *21*, 117–157. (c) Douthwaite, R. E. *Coord. Chem. Rev.* **2007**, *251*, 702–717.

(44) We are aware of only two examples where a chiral O-based monodentate ligand was systematically used in enantioselective catalysis. In both cases, low enantioselectivity (up to 72% ee, based on optical rotation values) was observed. See: (a) Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437–438. (b) Tayama, E.; Saito, A.; Ooi, T.; Maruoka, K. *Tetrahedron* **2002**, *58*, 8307–8312.

(39) (a) Hock, A. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 16373–16375. (b) Singh, R.; Czekelius, C.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *Organometallics* **2007**, *26*, 2528–2539. (40) Pilyugina, T.; Schrock, R. R.; Hoveyda, A. H., unpublished results.



**Scheme 7.** Diastereoselective Synthesis of Stereogenic-at-Mo Complexes


**c. Preparation of Stereogenic-at-Mo Complexes through Diastereoselective Protonation of Mo Bispyrrolides.** Having identified Mo-based precursors and a readily available class of chiral monodentate alcohols, we turned our attention to stereoselective synthesis of stereogenic-at-Mo complexes. We initiated our studies by examining the reactions of bispyrrolides **33a** and **33b** with several monoprotected diols derived from commercially available enantiomerically pure binaphthol **34**. These investigations led us to establish that, as illustrated in Scheme 7, treatment of **33a** with 1 equiv of enantiomerically pure bisbromide monoprotected binaphthol **35** leads to the formation of **36a** with 19:1 diastereoselectivity. When complex **33b** bearing 2,5-dimethylpyrrolide ligands is used, **36b** is generated with lower selectivity as a 7:1 mixture (Scheme 7).

Our previous studies involving Mo diolates indicated that complexes bearing a tetrahydrobinaphtholate ligand (e.g., **28** in Scheme 5) might exhibit different and at times superior reactivity and selectivity levels in comparison with binaphtholates (e.g., **27**, **29**, and **30** in Scheme 5) or biphenolates (e.g., **24–26** in Scheme 5).<sup>46</sup> Structurally, tetrahydrobinaphtholates contain features of both Mo biphenolates (tetraalkyl-substituted biphenyl) and the corresponding binaphtholates. The observed differences in the activities and enantioselectivities of catalysts bearing the partially reduced ligands<sup>47</sup> may be attributed to differences in the dihedral angle of the two aromatic planes.

(45) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930–1946.

(46) For examples of tetrahydrobinaphthol-based chiral Mo diolate complexes, see: (a) Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J., Jr.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452–1456. (b) Schrock, R. R.; Jamieson, J. Y.; Dolman, S. J.; Miller, S. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *Organometallics* **2002**, *21*, 409–417. For a review regarding the differences between binaphthol and its hydrogenated derivatives, see: (c) Au-Yeung, T. T.-L.; Chan, S.-S.; Chan, A. S. C. *Adv. Synth. Catal.* **2003**, *345*, 537–555.

(47) For examples where tetrahydrobinaphthol-based Mo-diolate complexes outperform other olefin metathesis catalysts, see refs 8a–c.

**Table 3.** Catalytic Enantioselective RCM of Triene **2** Promoted by Stereogenic-at-Mo Complexes<sup>a</sup>

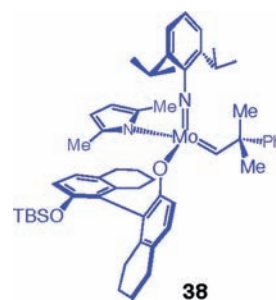
entry	chiral complex; mol %	conv (%), <sup>b</sup> yield (%) <sup>c</sup>	er <sup>d</sup>	ee (%) <sup>d</sup>
1	<b>36a</b> ; 1	<10; nd	nd	nd
2	<b>36b</b> ; 1	24; nd	nd	nd
3	<b>36b</b> ; 5	>98; 60	83.5:16.5	67
4	<b>37a</b> ; 1	<5; nd	—	—
5	<b>37b</b> ; 1	>98; 83	97.5:2.5	95
6	<b>38</b> ; 1	19; nd	nd	nd

<sup>a</sup> Reactions were performed under N<sub>2</sub> atmosphere; see the Supporting Information for experimental details. nd = not determined.

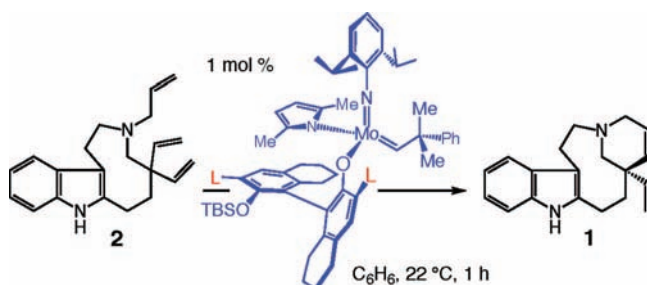
<sup>b</sup> Conversions (based on the amounts of unreacted substrate and product formed) were determined through analysis of 400 MHz <sup>1</sup>H NMR spectra of the unpurified mixtures. <sup>c</sup> Yield of **1** after purification. <sup>d</sup> Enantiomer ratios (er) and enantioselectivities (ee) were determined by HPLC analysis; see the Supporting Information for details.

Chiral Mo aryloxides **37a** and **37b** were prepared by the same procedures as described above, with nearly identical results (Scheme 7). We established the identity of the major diastereomer of **37b** through X-ray crystallography.<sup>6</sup> The diastereoselective desymmetrizations depicted in Scheme 7 are highly efficient: the reactions proceed to >95% conversion at 22 °C within 1 h.

The presence of the bromide substituents at the C3 and C3' positions of the chiral ligand are necessary for clean generation of the desired monoaryloxides. Attempts to prepare stereogenic-at-Mo complexes derived from reactions of unsubstituted monosilyl-protected binaphthol under conditions used to access **36a**, **36b**, **37a**, and **37b** (with 1 equiv of alcohol) gave rise to a mixture containing a substantial amount of the bisaryloxide. When 1 equiv of monosilyl-protected tetrahydrobinaphthol is used instead of the corresponding binaphthol, however, the desired monoaryloxide (**38**) can be obtained selectively.


**IV. Total Synthesis of Quebrachamine through Efficient**

**Enantioselective RCM of Triene 2.** With several stereogenic-at-Mo complexes available (Scheme 7), we began to examine the ability of these systems to promote enantioselective RCM of **2**. For ease of operation, the *in situ*-prepared complexes were used in the initial studies. That is, in all cases, reactions were performed in the presence of diastereomeric mixtures of stereogenic-at-Mo complexes. Catalytic enantioselective RCM in the presence of 1 mol % **36a**, as shown in entry 1 of Table 3, gave rise to <10% conversion of **2** to the desired tetracycle **1** in 1 h; longer reaction times (e.g., 6 h) did not lead to further transformation. Higher reaction efficiency (24% conversion to **1**) was observed with the 2,5-dimethylpyrrolide complex **36b**

**Table 4.** Effect of Halogen Substituents of the Monodentate Chiral Ligand on Catalytic Enantioselective RCM of Triene **2**<sup>a</sup>


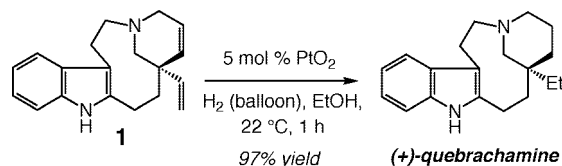
entry	chiral complex; L	conv (%); <sup>b</sup> yield (%) <sup>c</sup>	er <sup>d</sup>	ee (%) <sup>d</sup>
1	<b>39</b> ; F	>98; 80	92:8	84
2	<b>40</b> ; Cl	>98; 84	98:2	96
3	<b>37b</b> ; Br	>98; 83	97.5:2.5	95
4	<b>41</b> ; I	>98; 93	96.5:3.5	93

<sup>a</sup> Reactions were performed under N<sub>2</sub> atmosphere; see the Supporting Information for experimental details. <sup>b</sup> Conversions (based on the amounts of unreacted substrate and product formed) were determined through analysis of 400 MHz <sup>1</sup>H NMR spectra of the unpurified mixtures. <sup>c</sup> Yield of **1** after purification. <sup>d</sup> Enantiomer ratios (er) and enantioselectivities (ee) were determined by HPLC analysis; see the Supporting Information for details.

under identical conditions (entry 2, Table 3). When 5 mol % **36b** was used (entry 3, Table 3), RCM proceeded to complete conversion, affording **2** as an 83.5:16.5 mixture of enantiomers (67% ee). As in the case of complex **36a**, the presence of 1 mol % unsubstituted monopyrrolide **37a** did not lead to formation of the desired product after 1 h (entry 4, Table 3). As shown in entry 5 of Table 3, however, with 1 mol % 2,5-dimethylpyrrolide complex **37b**, RCM of triene **2** was complete (>98% conv) within 1 h, affording diene **1** in 95% ee (97.5:2.5 er) in 83% yield after purification. As illustrated in entry 6 of Table 3, with monoaryloxide **38**, a complex that lacks the bromide substituents at the C3 and C3' positions, <20% conversion to **1** was observed. It is also important to note that the bisaryloxides derived from reactions of pyrrolide complex **33a** with (mono-*t*-BuMe<sub>2</sub>Si)binaphthol or the derived tetrahydrobinaphthol were not effective in catalyzing the conversion of **2** to **1** (~5% conv at 5 mol % loading, 1 h, 22 °C).

A mechanistically critical aspect of the highly enantioselective process promoted by chiral complex **37b** prepared and used *in situ* as a 7:1 mixture of diastereomers relates to the relative activity of each catalyst isomer. Initial studies (analysis by 400 MHz <sup>1</sup>H NMR spectroscopy) indicate that <5% of the minor complex diastereomer is initiated, allowing only the major isomer to perform the enantioselective RCM reaction. Furthermore, when a sample of diastereomerically pure **37b** prepared after a single recrystallization was utilized to promote conversion of triene **2** to tetracycle **1**, nearly identical levels of reactivity and enantioselectivity were observed as when the 7:1 mixture was used directly. Additional details will be provided in separate accounts along with the results of mechanistic investigations.

Next, we investigated the effect of the halide substituents of the chiral monodentate ligand on the enantioselective RCM of **2**; the results of these studies are summarized in Table 4. Reaction in the presence of bisfluoride complex **39** was equally efficient as that with **37b** (entry 3) but delivered **1** with lower selectivity (92:8 er, 84% ee vs 97.5:2.5 er, 95% ee). Dichloride **40** (entry 2, Table 4) and diiodide **41** (entry 4, Table 4) promoted efficient reactions (>98% conv, 1 mol %, 1 h, 22 °C), and furnished **1** with high enantioselectivities (96 and 93% ee,

**Scheme 8.** Completion of the Enantioselective Total Synthesis of Quebrachamine

respectively), with the former complex delivering a slightly higher level of enantiodifferentiation (compare entries 2 and 4, Table 4). It is also noteworthy that the yields of isolated **1** in Table 4 are in some instances significantly higher than those obtained with achiral catalysts or *rac*-**32** (see Table 1 and eq 2, respectively); smaller amounts of the aforementioned unidentified products are generated in the transformations promoted by enantiomerically pure chiral Mo monoaryloxides.

With an efficient catalytic enantioselective RCM of **2** in hand, we turned our attention to the completion of the total synthesis of (+)-quebrachamine. As illustrated in Scheme 8, catalytic hydrogenation in the presence of 5 mol % PtO<sub>2</sub> under H<sub>2</sub> atmosphere (balloon) afforded the desired target molecule in 97% yield after purification. This final step thus completes a total synthesis of the natural alkaloid in 12% overall yield through a scheme containing two separate six-step linear sequences.

## Conclusions and Future Research

The stereogenic-at-metal complexes designed, synthesized, and examined in the course of this study represent a new approach to the development of catalysts for efficient and stereoselective olefin metathesis.<sup>48</sup> Specific electronic factors incorporated within the structure of the chiral catalysts as a result of previous theoretical studies are largely responsible for the exceptional levels of reactivity and selectivity observed. Stereoelectronic and conformational mobility considerations, together with the tetrahedral structure of high-oxidation-state alkylidenes, led us to consider designing chiral complexes that bear a stereogenic metal center and only monodentate ligands.

Development of stereogenic-at-metal catalysts presents complications that must be addressed if such complexes are to be employed effectively in promoting catalytic enantioselective transformations. First, stereoselective synthesis of the catalyst and control of metal stereogenicity might be required. We have addressed this problem by a diastereoselective process through the use of a readily available enantiomerically pure monoprotected binaphthol-based ligand. The mechanistic details of stereoselective reactions of Mo-based bispyrrolides with various chiral aryloxides and the rationale for the lower rate of initiation of the minor Mo alkylidene diastereomer are subjects of ongoing investigations.

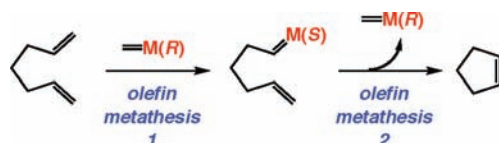
Second, the stereogenic-at-Mo complex must avoid uncontrolled stereomutation in the course of a catalytic process. Otherwise, low enantioselectivity is likely to result if both diastereomers are reasonably reactive or do not easily isomerize; in the case that the minor chiral complex diastereomer is unreactive, there would be reduced activity unless higher catalyst loadings are used. Such considerations bring forth a notable advantage of this class of high-oxidation-state complexes for the design of stereogenic-at-metal catalysts: the absence of

(48) Stereogenic-at-metal Ru-based catalysts for enantioselective olefin metathesis have been developed in these laboratories; such complexes, however, bear a bidentate chiral ligand. See refs 37a–e.

coordinatively labile ligands (e.g., phosphines) minimizes the possibility of complex planarization and loss of stereochemical integrity.<sup>49</sup> An important attribute of an olefin metathesis reaction, one that becomes crucial in cases where stereogenic-at-metal complexes are involved, is that the catalyst's metal center undergoes inversion with each olefin metathesis event (see Figure 2 and related discussions).<sup>5,37g</sup> A ring-closing process involves *two* olefin metathesis events, however, so the original isomer of a chiral complex should emerge after completion of each catalytic cycle (double inversion).<sup>50</sup> Stereomutation through degenerate olefin metathesis can therefore be a possible pitfall in the use of conformationally flexible stereogenic-at-metal complexes. On the other hand, if one diastereomer is lower in energy and catalytic activity, degenerate processes can furnish a "correcting mechanism" and thus prove to be beneficial. Studies that clarify the above mechanistic subtleties are in progress.

(49) For a stereogenic-at-Fe complex that undergoes racemization faster than it promotes ketone hydrosilylation, see: Brunner, H.; Fisch, K. *Angew. Chem., Int. Ed.* **1990**, *29*, 1131–1132.

(50) As illustrated in the hypothetical case below, each catalytic RCM process involves two distinct olefin metathesis reactions, one involving formation of the substrate-bound Mo alkylidene (or Ru carbene) and the other the ring closure:



Thus, in the case of a stereogenic-at-metal complex in the absence of alternative stereomutation mechanisms (e.g., by a degenerate olefin metathesis reaction), each catalytic cycle regenerates the original catalyst isomer. Further discussions will be provided in the full account of the mechanistic aspects of the new class of stereogenic-at-Mo complexes.

The stereogenic-at-Mo complexes presented herein offer fresh opportunities for addressing a significant number of unresolved problems in catalytic olefin metathesis; such complexes are expected to serve not only as uniquely effective catalysts for enantioselective synthesis but also as highly efficient complexes that provide unprecedented activity (see eq 2). Investigations along these lines and applications of the new chiral catalysts to additional enantioselective RCM processes as well as other types of olefin metathesis reactions will be the focus of our future studies. As was the case in the studies presented herein, we will continue to be guided by the demands presented to us in the course of our efforts in complex molecule total synthesis.

**Acknowledgment.** Financial support was generously provided by the NIH (Grant GM-59426 to A.H.H. and R.R.S.) and the NSF (CHE-0715138 to A.H.H.). We are grateful to Mr. A. Zhugralin (Boston College) for numerous invaluable discussions regarding theoretical and mechanistic issues as well as synthesis and characterization of the chiral Ru-based complexes **22a** and **22b** and to Dr. A. Hock, Dr. T. Pilyugina, and Dr. R. Singh (MIT) for helpful experimental suggestions. We are grateful to Dr. B. Bailey and Mr. K. Wampler (MIT) for assistance in obtaining the X-ray structure of the major diastereomer of Mo complex **37b**. Mass spectrometry facilities at Boston College are supported by the NSF (DBI-0619576).

**Supporting Information Available:** Experimental procedures and spectral data for substrates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA8084934