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Enantioselective Synthesis of Cyclic Amides and Amines through Mo-Catalyzed Asymmetric Ring-Closing Metathesis

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Abstract: First, an efficient method for the synthesis of optically enriched N-fused bicyclic structures is reported. Through Mo-catalyzed desymmetrization of readily available achiral polyene substrates, 5,6-, 5,7-, and 5,8-bicyclic amides can be synthesized in up to >98% ee. The effects of catalyst structure, olefin substitution, positioning of Lewis basic functional groups and ring size are examined and discussed in detail. In the second phase of investigations, a catalytic asymmetric method for highly enantioselective (up to 97% ee) synthesis of small- and medium-ring unsaturated cyclic amines is reported; optically enriched products bear a secondary amine or a readily removable Cbz or acetamide unit. Regio- and diastereoselective functionalizations of olefins within the optically enriched amine products have been carried out. Both catalytic asymmetric methods include transformations that lead to the formation of trisubstituted as well as disubstituted cyclic alkenes. The protocols outlined herein afford various cyclic amines of high optical purity; such products are not easily accessed by alternative protocols and can be used in enantioselective total syntheses of biologically active molecules.

Introduction

Cyclic and acyclic chiral amines are important building blocks required for the synthesis of a variety of biologically active organic molecules. Design and development of catalytic methods that lead to enantioselective formation of N-containing compounds therefore define an important area of research in organic synthesis.[1] Within this context, several programs in these laboratories have been focused on the discovery and utility of various chiral catalysts that promote efficient enantioselective synthesis of a range of acyclic[2] and cyclic amines[3] with high levels of optical purity.

One area of investigation is in connection with the development of a class of chiral Mo-based alkylidenes (see Chart 1)[4] that may be used to prepare optically enriched cyclic amines[5] through catalytic asymmetric ring-closing metathesis (ARCM).[6,7] As summarized in Scheme 1, we have recently disclosed that in the presence of chiral Mo complexes, a number of achiral N-containing trienes can be efficiently desymmetrized to afford the derived unsaturated amines in up to >98% ee.[8] These investigations established for the first time that enantioselective olefin metathesis can be used to obtain enantioenriched unsat-

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(1) For reviews regarding enantioselective synthesis of amines, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. For representative recent reports, see: (d) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875−5878. (e) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056. (f) Dahmen, S.; Brase, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940−5941. (g) Hermanns, N.; Dahmen, S.; Bolm, C.; Brase, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694. (h) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (i) Boezio, A. A.; Charrette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692−1693. (j) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686−5687. (l) Keith, J. M.; Jacobsen, E. N. *Org. Lett.* **2004**, *6*, 153−155. (l) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167−169.

(2) For example, see: (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985. (b) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. (c) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244−4247. (d) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734−3735. (e) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829−2832. (f) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584−4585.

(3) For example, see: Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018−4019.

(4) For a review on Mo-catalyzed enantioselective olefin metathesis, see: Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633.

(5) For a review on synthesis of N-containing compounds through catalytic olefin metathesis, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. For a review on catalytic RCM in alkaloid synthesis, see: (b) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712.

(6) For Mo-catalyzed ARCM, see: (a) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041−4142. (b) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720−9721. (c) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553−9559. (d) Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139−3140. (e) Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868−2869. (f) Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779−10784.

(7) For Ru-catalyzed ARCM, see: (a) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225−3228. (b) VanVeldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502−12508.

(8) (a) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991−6997. (b) Dolman, S. J.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2003**, *5*, 4899−4902.

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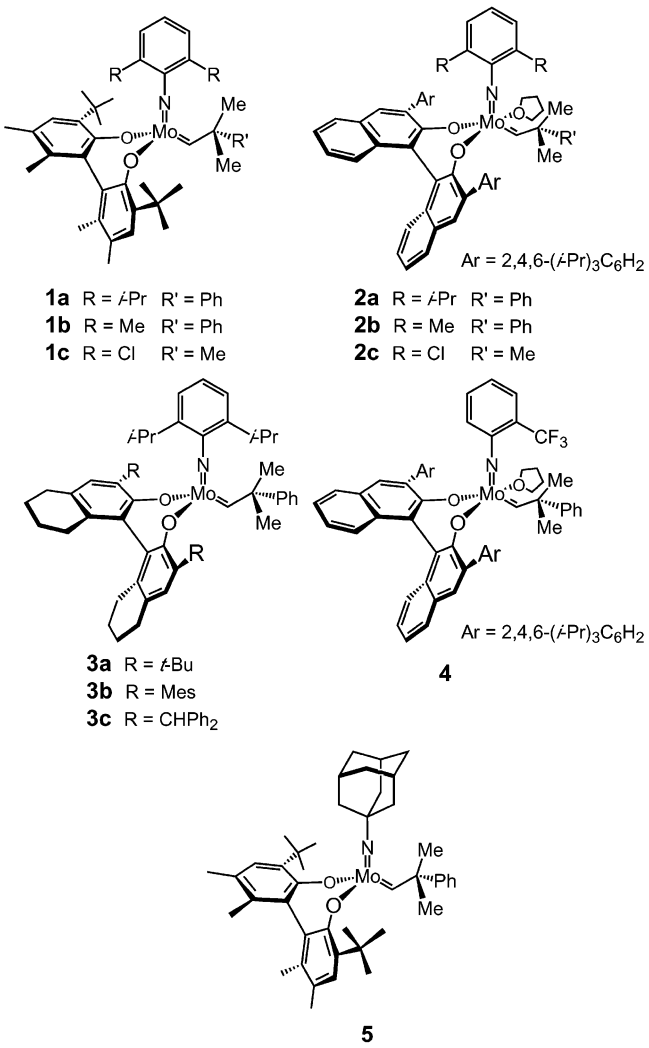
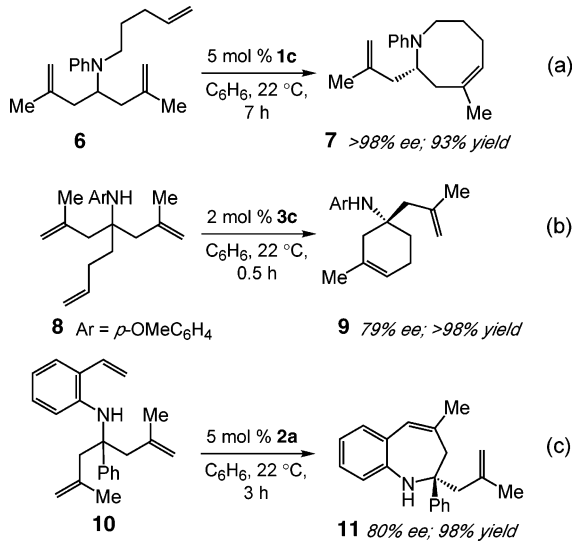
Chart 1. Representative Chiral Mo Catalysts for Olefin Metathesis



Scheme 1. Mo-Catalyzed ARCM of Unsaturated Arylamines



urated hetero- and carbocyclic amines (cf. Scheme 1), products that are more difficult to synthesize by alternative approaches. Another notable feature of the methods summarized in Scheme 1 is the efficiency of catalytic ARCM reactions that deliver medium ring structures, even under conditions that exclude the use of solvent (<2% undesired homodimeric products isolated). As an example, conversion of **6** (Scheme 1, eq a) can be performed neat in the presence of 4 mol % of **1c** at 22 °C to afford eight-membered ring amine **7** in 97% ee and >98% isolated yield.

Despite the abovementioned advances, several critical questions remained unanswered. One noteworthy issue is whether chiral Mo-based complexes can be used to initiate olefin metathesis reactions of amine substrates where the heteroatom does not bear an aryl substituent. As illustrated in Scheme 1, so far, our studies have been limited to reactions of various unsaturated *aryl*amines. The decision to focus the first phase of our investigations on reactions of sterically hindered arylamines was based on the supposition that interaction of a Lewis acidic Mo center with a Lewis basic nitrogen could lead to catalyst deactivation. In addition, since conversion of arylamines such as **7** and **9** to the derived unprotected dialkylamines ($ArNR_2 \rightarrow HNR_2$) remains an inefficient procedure, development of synthesis methods that afford optically enriched secondary amines (HNR_2) emerges as a critical objective.

Herein, we disclose the results of our investigations illustrating that Mo-based chiral alkylidenes (Chart 1) can be used to promote ARCM of unsaturated amines that do not bear an N-aryl group. We demonstrate that a variety of N-fused bicyclic structures can be accessed in high optical purity through efficient Mo-catalyzed ARCM processes. Furthermore, we put forth catalytic protocols for enantioselective synthesis of a variety of unsaturated 2-substituted N-containing heterocycles that contain either *unprotected secondary amines* or bear an easily removable amine protecting group (e.g., NCbz). Finally, we report the first instances of metal-catalyzed ARCM used in the enantioselective synthesis of cyclic amines that bear a disubstituted endocyclic olefin (vs a trisubstituted alkene from reaction of an acyclic 1,1-disubstituted olefin); representative examples of regio- and diastereoselective alkene functionalization of the optically enriched amine products are provided.

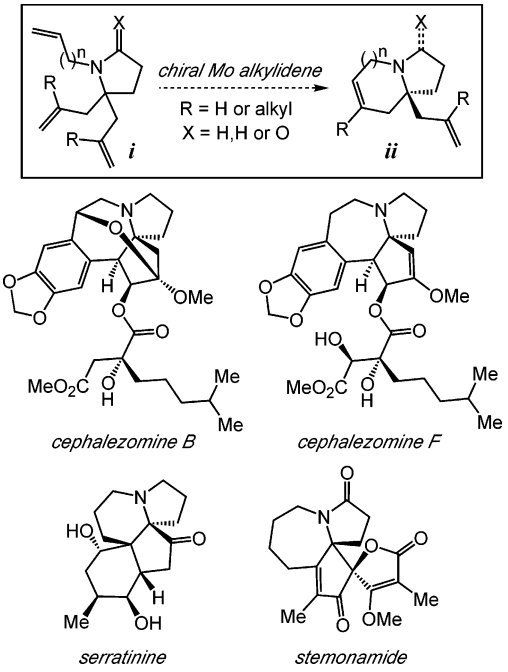
Results and Discussion

1. Mo-Catalyzed Enantioselective Synthesis of N-Fused Bicyclic Amides. The first phase of our investigations involved examination of Mo-catalyzed ARCM reactions that would lead to the formation of optically enriched N-fused bicyclic structures,[9] represented by conversion of achiral triene **i** to diene **ii** in Scheme 2. The initiative to develop this class of catalytic asymmetric transformations was inspired by the presence of these structural units in a number of biologically significant molecules such as cytotoxic alkaloids cephalezomines B and F,[10] serratinine,[11] and stemonamide,[12] an alkaloid isolated from the root of a Chinese medicinal plant (Scheme 2).

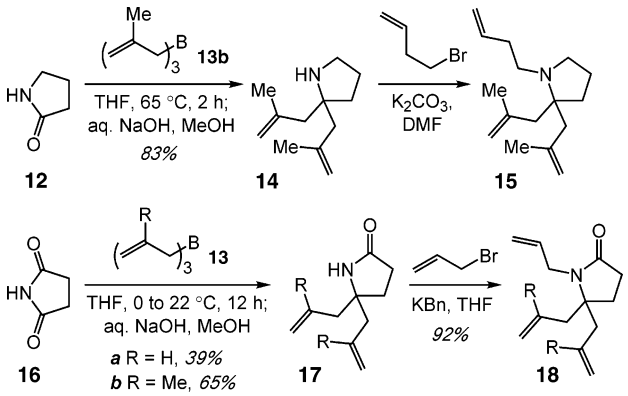
a. Synthesis of Substrates. Triene substrates were synthesized as depicted by the representative cases shown in Scheme

(9) For initial key reports on the use of Mo-catalyzed RCM to synthesize N-containing cyclic structures, see: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 4324−7325. (b) Houri, A. F.; Xu, Z. M.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943−2944. (c) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251−7264.
(10) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 2929−2934.
(11) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 6241−6245.
(12) Ye, Y.; Qin, G.-W.; Xu, R.-S. *J. Nat. Prod.* **1994**, *57*, 665−669.

Scheme 2



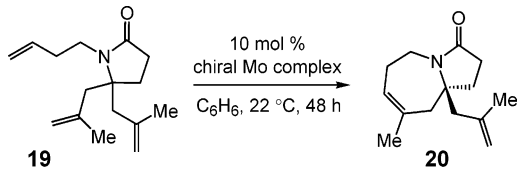
Scheme 3. Synthesis of Substrates for Mo-Catalyzed Enantioselective Synthesis of N-Fused Bicyclic Structures



3. Thus, according to a procedure reported by Bubnov[13] and co-workers, treatment of cyclic amide **12** with triallylborane **13b** (R = Me)[14] led to smooth formation of amine **14** in 83% isolated yield. Subjection of **14** to the appropriate unsaturated alkyl halide (e.g., allyl bromide) afforded the desired ARCM substrate. The derived amides **17a**,**b** and **18a**,**b**, shown in Scheme 3, were prepared by a similar procedure (see the Supporting Information for details).

b. Screening of Chiral Catalysts. With various triene substrates in hand, we began the first segment of our investigation by studying the ability of various chiral Mo-based alkylidenes to promote enantioselective synthesis of N-fused bicycles. The results of a representative screening study, involving the asymmetric formation of 5,7-bicyclic amide **20**, are summarized in Table 1. As indicated, subtle variations in the structure of the chiral catalyst can lead to significant alteration in reaction efficiency and/or enantioselectivity.[15] For example, whereas binaphthol-based chiral complexes **2a** (entry 4, Table 1) and

Table 1. Initial Catalyst Screening for Mo-Catalyzed ARCM of **19**



entry	Mo complex	conv (%)[a]	ee (%)[b]	entry	Mo complex	conv (%)[a]	ee (%)[b]
1	**1a**	51	63	6	**3a**	53	50
2	**1b**	43	75	7	**3c**	>98	33
3	**1c**	31	77	8	**4**	38	50
4	**2a**	90	<10	9	**5**	95	85
5	**2c**	44	<10				

[a] Conversion to the desired product; measured by analysis of 400 MHz ^{1}H NMR spectrum of the unpurified mixture; homodimers derived from reaction of terminal olefins observed in several classes. [b] Determined by chiral GLC analysis (CDGTA column).

3c (entry 7) provide high conversion to the desired bicyclic amide, the optical purity of **20** is low and not at a synthetically useful level (<10% and 33% ee, respectively). Alternatively, biphenyl-based complexes **1a** and **1b** (entries 1 and 2, Table 1) give rise to higher asymmetric induction but at substantially lower conversion. It is chiral Mo complex **5**, bearing an alkylimido unit (entry 9), that gives rise to the most efficient (95% conversion) and selective ARCM of **19** to afford **20**. Thus, as illustrated in entry 1 of Table 2, in the presence of 15 mol % of **5** (to ensure reliably high levels of conversion), **20** may be obtained in 84% yield and 85% ee after silica gel chromatography.

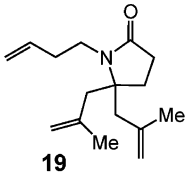
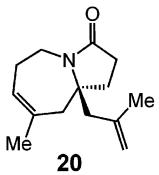
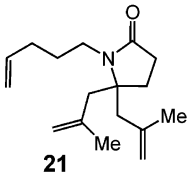
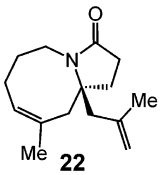
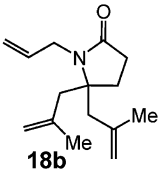
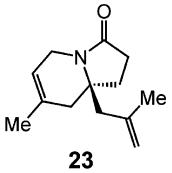
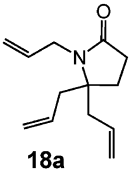
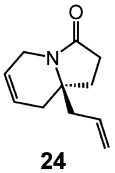
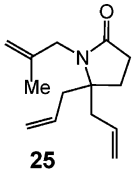
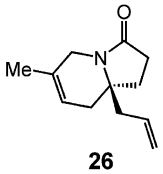
c. Scope and Limitations of the Mo-Catalyzed ARCM Method. On the basis of the positive outcome of our studies regarding enantioselective synthesis of bicyclic amide **20** (Table 1), we investigated the Mo-catalyzed ARCM of a range of related substrates. The results of some of these studies are summarized in entries 2−5 of Table 2 and Scheme 4.

As depicted in entry 2 of Table 2, formation of the 5,8-bicyclic amide **22** is best effected in the presence of 15 mol % of Mo complex **3c** at 22 °C for 48 h; the desired compound is isolated in 90% ee and 94% yield. Catalytic asymmetric synthesis of 5,6-bicyclic amide **23** also requires 48 h but proceeds to >98% conversion with 10 mol % catalyst loading; in this instance, screening studies point to binaphthol-based Mo complex **2a** as the most effective chiral catalyst, affording **23** in 91% isolated yield and >98% ee.

As may be expected, triene **18a**, bearing three terminal olefins, undergoes ARCM at a faster rate (>98% conversion with 5 mol % of **2a** after 12 h). However, the efficient (92% isolated yield) and enantioselective (88% ee) formation of **24**, an N-fused bicyclic amide that contains a *di*substituted cyclic alkene, is noteworthy for several reasons.[16] In Mo-catalyzed ARCM reactions depicted in entries 1−3 of Table 2, the catalytic cycle is likely initiated through reaction with the terminal olefin to afford a monosubstituted Mo alkylidene, which subsequently reacts with one of the diastereotopic neighboring 1,1-disubsti-

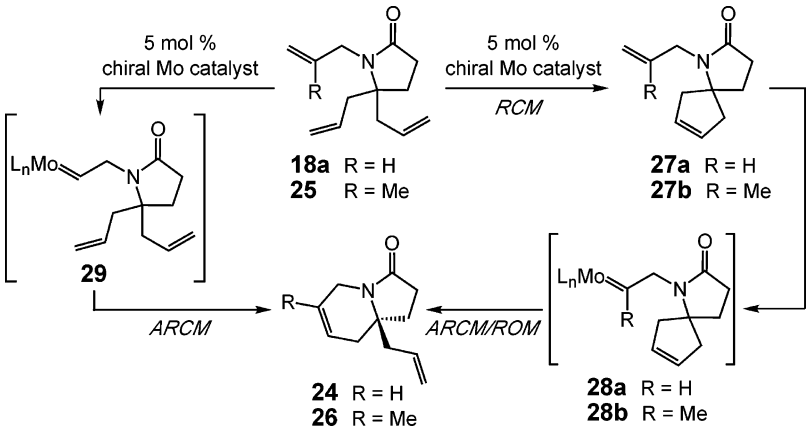
(13) Bubnov, Y. N.; Pastukhov, F. V.; Yampolsky, I. V.; Ignatenko, A. V. *Eur. J. Org. Chem.* **2000**, 1503−1505.
(14) Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1986**, *51*, 427−432.
(15) For a discussion of catalyst generality as a function of substrate structure, see: Hoveyda, A. H. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; pp 991−1016.
(16) For an alternative approach to enantioselective synthesis of this class of bicyclic amides, see: Groaning, M. D.; Meyers, A. I. *Chem. Commun.* **2000**, 1027−1028.

Table 2. Enantioselective Synthesis of Bicyclic Lactams through Mo-Catalyzed ARCM[a]

entry	substrate	product	catalyst; (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1	 **19**	 **20**	**5**; 15	48	84	85
2	 **21**	 **22**	**3c**; 15	48	94	90
3	 **18b**	 **23**	**2a**; 10	48	91	>98
4	 **18a**	 **24**	**2a**; 5	12	92	88
5	 **25**	 **26**	**2a**; 5	30	30[d]	90

[a] Reactions carried out in C_6H_6 or toluene at 22 °C. See the Supporting Information for additional experimental details. [b] Conversion >90% in all cases, measured by analysis of the 400 MHz ^{1}H NMR spectrum of the unpurified mixture; isolated yields of purified materials are reported. [c] Determined by chiral GLC analysis (see Supporting Information for details). [d] >98% conversion to **26** (30%) and the derived achiral spirocycle **27b** (70%).

Scheme 4



tuted olefins. In contrast, with substrates such as **18a**, initiation may occur at *any* of the three terminal olefins. Such a possibility can lead to alternative reaction pathways that can lead to low efficiency and/or enantioselectivity. As an example, achiral spirocycle **27a** (Scheme 4) can lead to the generation of Mo alkylidene **28a** (R = H), which might undergo asymmetric ring-closing metathesis/ring-opening metathesis (ARCM/ROM) to afford **24**. The above reaction route finds support in the catalytic asymmetric conversion of triene **25** to **26** (entry 5, Table 2). The desired bicyclic amide **26** is cleanly generated in 90% ee but only constitutes 30% of the product mixture, 70% of which is achiral spirocycle **27b** (R = Me, Scheme 4). Formation of 1,1-disubstituted Mo alkylidene **28b** is likely unfavorable and, if generated, it would be significantly less reactive than a

terminal alkylidene such as **28a**.[17] Accordingly, **27b** cannot be readily converted to the bicyclic final product **26**. In the context of such mechanistic complexities, it should be noted that the enantioselectivity (88% ee) observed for the formation of **24** (R = H) may arise from at least two different pathways: (1) through a catalytic ARCM (**18a→24**) that involves Mo−alkylidene **29** (Scheme 4) as the key intermediate and (2) by a sequence that proceeds through **18a→27a→28a→24**. To what extent these two routes contribute to the eventual generation of the desired product is difficult to establish rigorously at the present time.

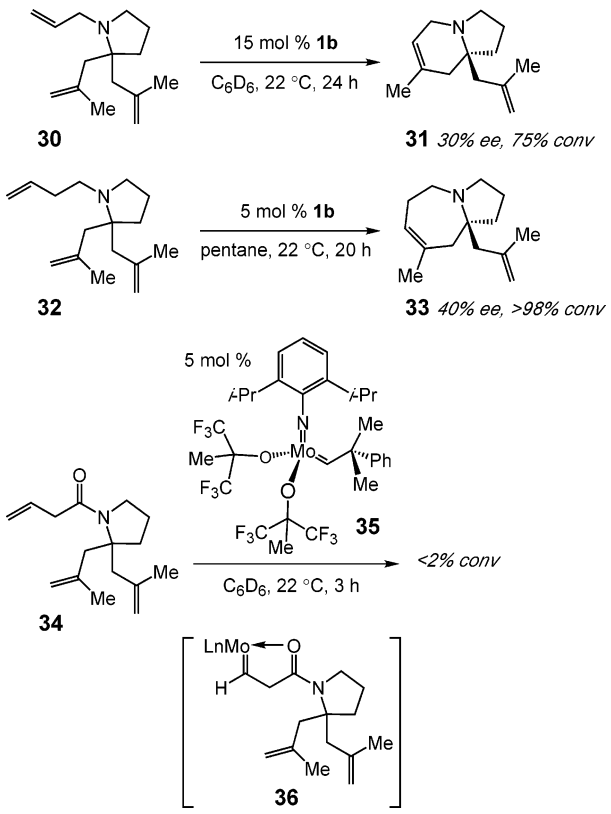
Several additional points regarding this phase of our studies merit mention.

(a) As indicated by the data in Tables 1 and 2, the identity of the optimal Mo-based catalyst can change, depending on the particular reaction at hand. For example, in studies regarding catalytic ARCM of triene **21**, leading to the formation of 5,8-bicycle **22**, all chiral alkylidenes examined, with the exception of **3c**, give rise to near exclusive formation of homodimers derived from reactions of the terminal olefin.[18] As mentioned previously, subtle alterations in the structure of a substrate can lead to significant differences in reactivity and selectivity. As a result, the availability of a *class* of chiral catalysts (Chart 1) offers a notable advantage; the possibility that a highly effective chiral catalyst may be found for a particular application is more likely when several catalyst candidates are available.

(b) As illustrated by the representative cases shown in Scheme 5 (**30** → **31** and **32** → **33**), Mo-catalyzed ARCM of the corresponding amines is significantly less enantioselective. The higher catalyst loading required for the reaction of allylic amine **30** (relative to **32**) may be due, among other factors, to the increased proximity of the electron-withdrawing heteroatom, leading to stabilization and lower activity of the derived Mo alkylidene.[19]

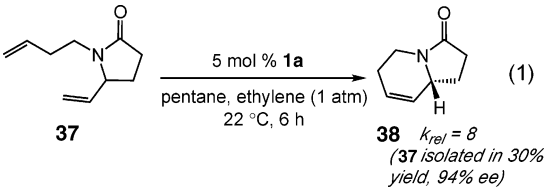
(c) Amide substrates, where the carbonyl group is positioned on the side chain moiety, do not undergo efficient RCM reactions. As depicted in Scheme 5, even in the presence of highly reactive achiral **35**, <2% conversion is observed in attempts to induce amide **34** to undergo ring closure. To gain insight into the aforementioned lack of reactivity, a mixture of achiral complex **35** and triene **34** was monitored by ^{1}H NMR spectroscopy. The resulting spectrum contains a triplet (J = 4.7 Hz) at δ 11.97 ppm, corresponding to the formation of a new Mo alkylidene. This observation suggests the formation of chelated alkylidene complex **36**, illustrated in Scheme 5; the purported complex **36** would be expected to exhibit significantly reduced levels of reactivity toward reaction with a neighboring olefin. The lower reactivity of **36** is supported by the finding that the above-mentioned triplet signal persists for several hours, even when the sample is heated to 60 °C.[20] It is therefore

Scheme 5. Mo-Catalyzed ARCM of Amines and Isomeric Amides



plausible that such modes of catalyst sequestration and deactivation are less likely with substrates such as those shown in Table 2, because of the increased distance between the terminal alkene and the Lewis basic amide.

(d) As the example in eq 1 indicates (**37** → **38**), this class of



Mo-catalyzed ARCM can be used to effect kinetic resolution[21] of the corresponding chiral diene substrates with appreciable enantioselectivity. When the reaction is not carried out under an atmosphere of ethylene, lower enantioselectivity is observed. This is likely because formation of the initial Mo alkylidene occurs at a similar rate for both enantiomers of **37**. If ring closure proceeds prior to the release of the metal alkylidene from the slower reacting isomer, the efficiency of kinetic resolution suffers. Ethylene reacts with the Mo alkylidene that undergoes ring closure at a slower rate (mismatched substrate enantiomer), thus giving rise to higher optical purity of the recovered starting material.

2. Mo-Catalyzed Enantioselective Synthesis of N-Containing Heterocycles That Do Not Bear a Protecting Group or Contain One That Is Readily Removable. a. Introduction. The second phase of our studies focused on Mo-catalyzed

(17) For isolation and characterization of a disubstituted Mo-based alkylidene complex, see: Schrock, R. R.; DePue, R.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423−1435.

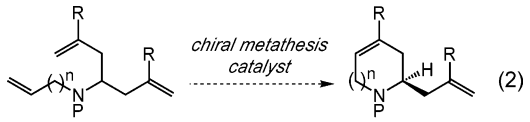
(18) Typically, homodimer formation is detected in all cases. However, in the more desirable instances, the chiral catalyst converts such compounds to the ARCM products (homodimers detected if reaction mixture is spectroscopically monitored).

(19) For another study where electron-deficient Mo alkylidenes exhibit lower reactivity than their more electron-rich counterparts, see: La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767−7778.

(20) For instances where similar Mo-based internal chelates have been proposed, see: (a) Fox, H. H.; Lee, J.-K.; Park, L. Y.; Schrock, R. R. *Organometallics* **1993**, *12*, 759−768. (b) ref 9a.

(21) For recent reviews of metal-catalyzed kinetic resolutions, see: (a) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 537−574. (b) Cook, G. R. *Curr. Org. Chem.* **2000**, *4*, 869−885. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *1*, 5−26.

desymmetrization reactions that deliver heterocyclic amines where the N atom is either unprotected (R_2NH) or bears a protecting group that can be removed with relative ease (eq 2).



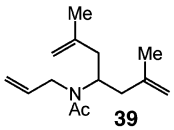
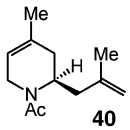
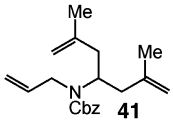
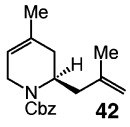
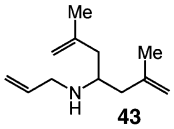
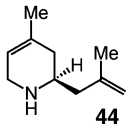
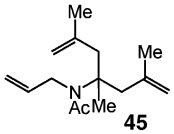
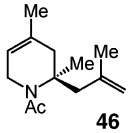
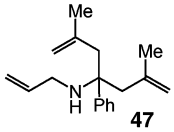
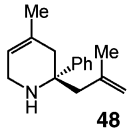
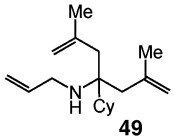
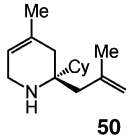
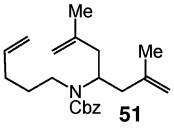
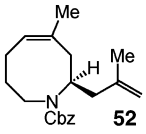
The ability of achiral Mo complexes to promote olefin metathesis reactions of tertiary amines (e.g., **30** → **31**, Scheme 5) lends credence to the possibility that Mo-based complexes can be used effectively to convert readily accessible achiral substrates to synthetically versatile N-containing cyclic structures that are otherwise difficult to synthesize.

b. Scope and Limitations of the Mo-Catalyzed ARCM Method. The ability of various chiral Mo complexes (Chart 1) to effect ARCM of acetamide **39** was screened, leading us to determine that adamantylimido complex **5** (5 mol %) promotes the formation of **40** in 96% ee and 90% yield after purification (entry 1, Table 3). This finding, in addition with the studies outlined above, further indicated that highly enantioselective Mo-catalyzed ARCM is feasible with substrates that do not bear an N-aryl unit. We subsequently discovered that when triene **41**, bearing the readily removable Cbz group, is subjected to the same reaction conditions, unsaturated piperidine **42** is isolated in 95% ee and 98% yield.

Next, we investigated the possibility of catalytic ARCM with unprotected secondary amine **43** (entry 3, Table 3). Although appreciable conversion is observed with the more reactive achiral Mo complex **35** (5 mol %; 75% conversion after 12 h at 22 °C), with the available chiral alkylidenes there is <2% reaction. We surmised that such lack of reactivity is likely the result of internal chelation between the Lewis basic amine and the Lewis acidic Mo center. To address this reactivity issue, as illustrated in Scheme 6, we subjected **43** to 1 equiv of catecholborane at 22 °C (Et_2O, 12 h), leading to clean formation of azaboronate **53**. Treatment of **53** (without purification) to 10 mol % of **1a** (identified as optimal by examining various Mo complexes) gives rise to formation of **44** in 87% ee and 50% overall yield (boronate removed by aqueous NaOH workup; see the Supporting Information for details).[22]

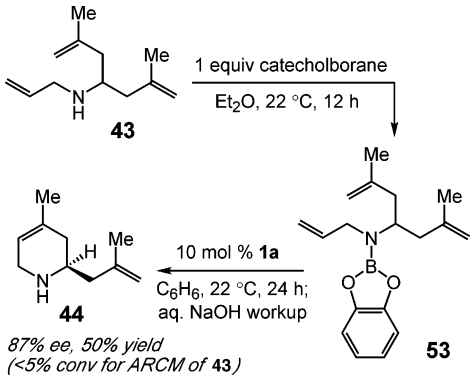
The Mo-catalyzed ARCM in entry 4 of Table 3, leading to the formation of an N-substituted quaternary carbon stereogenic center, affords unsaturated piperidine **46** in 75% ee and 63% isolated yield. Comparison of catalytic ARCM of **45** with cyclic amide **18b** (see entry 3, Table 2) is noteworthy. These closely related substrates, in the presence of the same optimal chiral Mo complex (**2a**), undergo ring closure with significantly different levels of asymmetric induction (75% vs >98% ee). In contrast to amine **43** (entry 3), unprotected amine **47** readily undergoes catalytic ARCM in the presence of 5 mol % of **1c** to generate the desired product **48** in 71% ee and 95% isolated yield. As illustrated in entry 6 of Table 3, triene **49** is less reactive and undergoes Mo-catalyzed ARCM with significantly lower enantioselectivity (33% ee). The difference in reactivity between unprotected amine **43** (entry 3) and **47** or **49** (entries 5 and 6) may be because with sterically hindered amines internal coordination of the Lewis acidic Mo with the Lewis basic

Table 3. Enantioselective Synthesis of Cyclic Amines through Mo-Catalyzed ARCM[a]

entry	substrate	product	catalyst	yield (%)[b]	ee (%)[c]
1	 **39**	 **40**	**5**	90	96
2	 **41**	 **42**	**5**	98	95
3[d]	 **43**	 **44**	**1a**	50	87
4	 **45**	 **46**	**2a**	63	75
5	 **47**	 **48**	**1c**	95	71
6	 **49**	 **50**	**1b**	56	33
7	 **51**	 **52**	**1b**	94	97

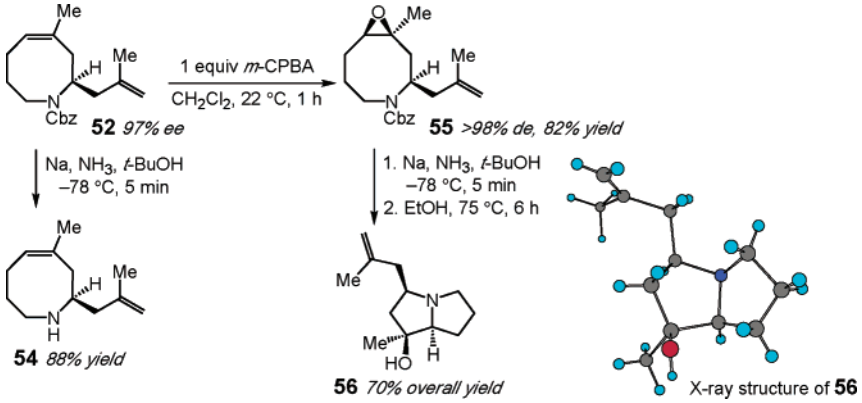
[a] Conditions: 5 mol % of catalyst, N_2 atm., C_6H_6, 22 °C, 24 h. See the Supporting Information for additional experimental details. [b] Conversion >98% in all cases, except 75% conversion for entry 3, 70% conversion for entry 4, and 60% conversion for entry 6; measured by analysis of the 400 MHz ^{1}H NMR spectrum of the unpurified mixture. Isolated yields of purified materials are reported. [c] Determined by chiral HPLC or GLC of the derived acetamides (entries 3 and 5−7) analysis (see Supporting Information for details). [d] Reaction via the derived catecholate (see the text).

Scheme 6. Synthesis and Mo-Catalyzed ARCM of Catechol-Protected Amines

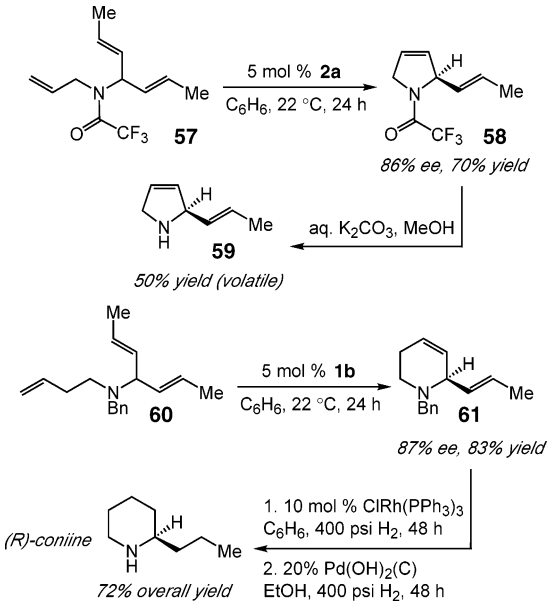


(22) For use of borane-protected phosphines in catalytic RCM, see: Slinn, C. A.; Redgrave, A. J.; Hind, S. L.; Edlin, C.; Nolan, S. P.; Gouvernour, V. *Org. Biomol. Chem.* **2003**, *1*, 3820−3825.

Scheme 7. Deprotection of Optically Enriched Cyclic Amines and Subsequent Functionalization



Scheme 8. Enantioselective Synthesis of Cyclic Amines Bearing Disubstituted Olefins



heteroatom is less favored. Finally, as depicted in entry 7 of Table 3, catalytic ARCM of unsaturated amine **51** leads to the formation of the eight-membered ring amine **52** in 94% yield and with exceptional enantioselectivity (97% ee).

c. Functionalizations and Application of the Catalytic Asymmetric Method. The Mo-catalyzed asymmetric protocol allows access to a variety of synthetically useful cyclic amines in the optically enriched form. For example, as illustrated in Scheme 7, Cbz-protected **52** (97% ee) may be readily converted to the derived secondary amine **54** (88% yield). Alternatively, a highly diastereo- (>98% de) and regioselective (>98%) oxidation in the presence of 1 equiv of *m*-CPBA gives rise to the formation of epoxyamine **55** in 82% yield after silica gel chromatography. In two straightforward operations, **55** can be converted to bicyclic amine **56** in 70% overall yield; the stereochemical identity of **56** was established through X-ray structure analysis (Scheme 7; see the Supporting Information for details).

The functionalizations illustrated in Scheme 8 demonstrate a critical aspect of the Mo-catalyzed ARCM protocol: substrates bearing disubstituted olefins can be effectively utilized to obtain the desired product with high selectivity. Thus, trifluoroacetamide **57** and benzylamine **60**, in the presence of an appropriate chiral Mo complex (identified by screening) are transformed to cyclic amines **58** and **61** in 86% ee (70% yield) and 87% ee (83% yield), respectively. (*R*)-Coniine is obtained in 72% yield from optically enriched **61** in two simple reductive steps.[23]

Conclusions

We disclose two separate but related methods for enantioselective synthesis of N-containing unsaturated heterocycles through Mo-catalyzed ARCM. In the first segment of our studies we illustrate how various chiral Mo alkylidenes can be utilized to access optically enriched (85 to >98% ee) N-fused bicyclic structures of various sizes (5,6-, 5,7-, and 5,8-bicyclic amides). Requisite substrates are readily prepared by reductive bisalkylation of succinimide, followed by alkylation of the N atom with an appropriate unsaturated acyclic side chain. In the second phase of our investigations, we were able to develop Mo-catalyzed ARCM reactions that deliver unsaturated small- and medium-ring cyclic amines in 71−97% ee. Importantly, in several cases the substrate contains an unprotected amine and in some instances the heteroatom is protected by the readily removable Cbz unit.

A key feature of the studies described herein is that, unlike previous reports, catalytic ARCM does not involve N-aryl substrates. Furthermore, cyclic structures bearing trisubstituted as well as disubstituted cyclic alkenes can be accessed by both catalytic asymmetric protocols outlined in this study.[24] We demonstrate that olefins in the optically enriched amine products can be site and diastereoselectively functionalized. The N-containing unsaturated heterocycles obtained through the present approach cannot be easily accessed by alternative protocols and should prove to be of notable utility in the synthesis of biologically important molecules.

Design of new chiral catalysts for olefin metathesis, development of additional catalytic asymmetric olefin metathesis reactions, related mechanistic studies as well as applications to target-oriented organic synthesis continue in these laboratories.

(23) Olefin hydrogenation in the presence of Wilkinson's catalyst is required before Pd-catalyzed debenzylation, since the latter conditions give rise to substantial amounts of C−N bond cleavage.

(24) Since the majority of the substrates used in this study are solids or semisolids, Mo-catalyzed ARCM reactions cannot be carried out easily in the absence of solvent. In one representative case, the reaction mixture had to be heated to achieve dissolution of the catalyst sample, leading to significant lowering of product optical purity (reaction of **18b** without solvent at 80 °C afforded **24** in 75% ee and 62% isolated yield vs 98% ee and 88% yield at 22 °C in benzene).

Acknowledgment. This research was funded by the NIH (GM-59426 to A. H. H. and R. R. S.). Additional support was provided by the American Chemical Society and Wyeth Research (2003-4 graduate fellowship to E.S.S.) and Pfizer and NIH (predoctoral fellowships to G.A.C.). We thank Dr. Richard Staples and Mr. Keith Griswold for obtaining the X-ray structure of **56**.

Supporting Information Available: Experimental procedures and spectral data for substrates and products (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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