

# Enantioselective Synthesis of Cyclic Secondary Amines through Mo-Catalyzed Asymmetric Ring-Closing Metathesis (ARCM)

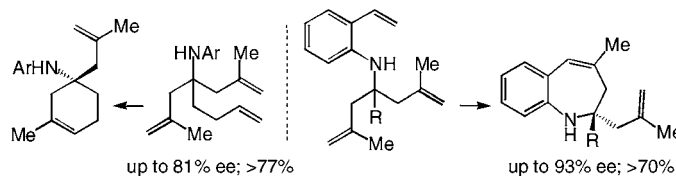
Sarah J. Dolman,<sup>†</sup> Richard R. Schrock,<sup>\*,†</sup> and Amir H. Hoveyda<sup>\*,†</sup>

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, and Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

rrs@mit.edu; amir.hoveyda@bc.edu

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## ABSTRACT



Carbocyclic amines are synthesized efficiently in up to 93% ee by asymmetric ring-closing metathesis (ARCM) with 2–5 mol % chiral Mo complexes. An example is provided where the catalyst is prepared in situ (catalyst isolation not needed) to afford secondary amines that cannot be prepared by alternative methods.

During the past several years, research in these laboratories has focused on the design and synthesis of new chiral Mo- and W-based catalysts for enantioselective olefin metathesis.<sup>1</sup> These investigations are concerned with the preparation of molecules that cannot be easily synthesized in the nonracemic form by alternative methods or through catalytic metathesis of optically pure olefin-containing substrates promoted by achiral metathesis catalysts.<sup>2</sup> Our efforts have so far led to the introduction of protocols through which, by catalytic

asymmetric ring-closing (ARCM)<sup>3</sup> or ring-opening (AROM)<sup>4</sup> metathesis, a range of optically enriched or pure organic molecules can be accessed.

One class of compounds that is of particular significance, due to their relevance to the synthesis of biologically active molecules and the paucity of effective related asymmetric methods, are acyclic and cyclic amines.<sup>5</sup> Within this context, we recently disclosed an efficient and highly enantioselective

<sup>†</sup> Massachusetts Institute of Technology.

<sup>‡</sup> Boston College.

(1) For reviews of catalytic asymmetric olefin metathesis, see: (a) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945–950. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633.

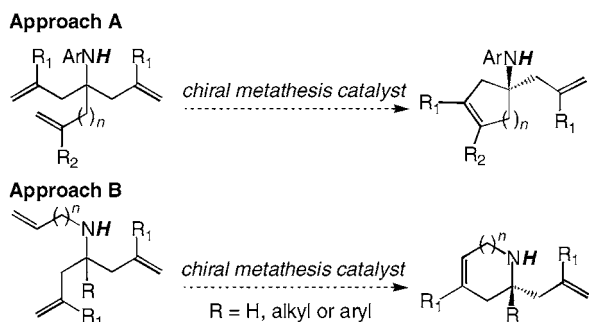
(2) For selected reviews on catalytic olefin metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833–1836. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036–2056. (d) *Alkene Metathesis in Organic Synthesis*; Furstner, A., Ed.; Springer: Berlin, 1998. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. I* **1998**, 371–388. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (g) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (h) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (i) Ref 1b.

(3) For examples of 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*, 4041–4042. (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) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251–8259. (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) Keily, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868–2869.

(4) For examples of Mo-catalyzed AROM, see: (a) La, D. S.; Ford, J. G.; Sattely, E. S.; Bonitatebus, J. P.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603–11604. (b) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828–1829. (c) La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767–7778. (d) Tsang, W. C. P.; Jernelius, J. A.; Cortez, A. G.; Weatherhead, G. W.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2652–2666.

approach, involving Mo-catalyzed ARCM, toward the synthesis of acyclic and cyclic unsaturated amines;<sup>6</sup> all compounds in the latter study were tertiary amines. A related area of interest involves the development of protocols for the enantioselective synthesis of secondary amines (e.g., R<sub>1</sub>R<sub>2</sub>NH; see Scheme 1). This class of compounds are of

**Scheme 1.** Enantioselective Synthesis of Secondary Amines by Mo-Catalyzed ARCM



notable utility, since the NH group can be functionalized and the resulting compounds may be manipulated in a variety of ways. However, metathesis-based approaches toward the enantioselective preparation of secondary amines are challenging, since (i) the sterically more accessible secondary amines (vs tertiary amines) might lead to deactivation of metal complexes through heteroatom–metal chelation and (ii) there is the potential for rupture of M–O bonds and removal of alkoxide ligands within metathesis catalysts (in the case of Mo- and W-based complexes) through protonation by an NH.<sup>7</sup>

Herein we report the results of our initial studies involving the use of Mo-catalyzed ARCM in the desymmetrization of achiral secondary amines. Two classes of Mo-catalyzed enantioselective desymmetrizations, summarized in Scheme 1 (approaches A and B), have been investigated, leading to the development of protocols for the synthesis of easily functionalizable unsaturated carbocyclic secondary amines in an efficient and enantioselective manner (up to 93% ee). *The catalytic asymmetric methods outlined herein do not require isolation and prior purification of Mo complexes*; an in situ method of preparation, involving a commercially available metal triflate, can be utilized to afford results nearly identical to those obtained from the carefully purified chiral catalysts.

We began our studies by examining the ability of unsaturated secondary anilines<sup>8</sup> (Table 1) to undergo enantioselective desymmetrization (approach A, Scheme 1). Initial catalyst screening indicated that Mo-based complex **3**,<sup>9</sup> bearing a

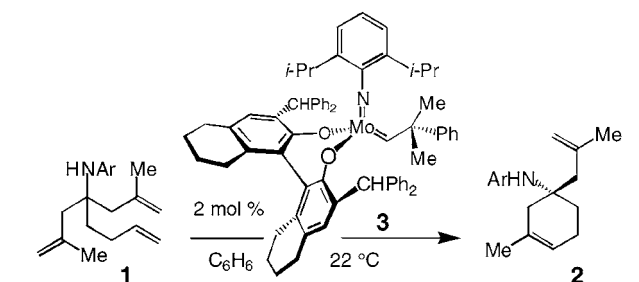
(5) (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.

(6) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991–6997.

(7) For reviews regarding the utility of catalytic olefin metathesis in the synthesis of N-containing compounds, see: (a) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75–90. (b) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, 959, 9–968.

(8) See Supporting Information for the preparation of starting amines used in this study.

**Table 1.** Enantioselective Synthesis of Secondary Amines through Mo-Catalyzed ARCM



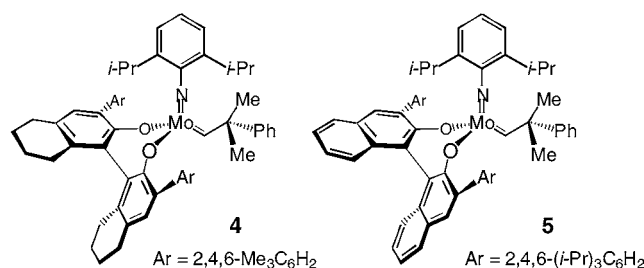
entry	Ar	time (h); conversion (%) <sup>a</sup>	yield (%) <sup>b</sup> ee (%) <sup>c</sup>
1	<b>a</b> <i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	0.5; >98	81; 64
2	<b>b</b> <i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	0.5; >98	78; 67
3	<b>c</b> <i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	0.5; >98	>98; 79
4	<b>d</b> <i>o</i> -BC <sub>6</sub> H <sub>4</sub>	0.5; >98	91; 81
5	<b>e</b> <i>m</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	0.5; >98	85; 64
6	<b>f</b> CH <sub>2</sub> Ph <sup>d</sup>	22; 87	75; 65

<sup>a</sup> Conversions determined by analysis of 500 MHz <sup>1</sup>H NMR spectrum of the unpurified reaction mixture. <sup>b</sup> Isolated yields after silica gel chromatography. <sup>c</sup> Determined by chiral HPLC analysis (Chiralpak AS column for entries 1 and 2; Chiral OD column for entries 3–5). Enantioselectivity for entry 6 was determined by analysis of the derived (*S*)-MTPA ester. <sup>d</sup> Chiral catalyst **4** was used.

benzhydryl-substituted diolate ligand, delivers the highest levels of enantioselectivity. Data from catalytic ARCM of trienes **1a–e** are summarized in Table 1. All transformations proceed readily to >98% conversion (as judged by <sup>1</sup>H NMR spectra of the unpurified products) within 30 min at 22 °C in the presence of 2 mol % **3** in C<sub>6</sub>H<sub>6</sub>. In all cases, <2% homodimerization through cross metathesis between the terminal olefin of **1** is observed. Reactions of less hindered amines **1a,b** (entries 1–2, Table 1) and **1e** (entry 5) and arylamines **1c,d** (entries 3–4) bearing an α aryl substituent proceed at nearly identical rates. There is no notable variation in reaction rate between electron-rich arylamine **1a** (bearing a *p*-OMeC<sub>6</sub>H<sub>4</sub>N group) and its electron-deficient derivative **1b** (bearing a *m*-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>N group). These findings suggest that internal chelation between the Mo-alkylidene derived from the more reactive terminal olefin in **1** and the neighboring Lewis basic heteroatom (six-membered chelate) is not operative to a significant extent in these instances.<sup>10</sup> Nonetheless, catalytic ARCM of **1c,d** occurs with higher levels of enantiodifferentiation (79–81% ee) than **1a,b** and **1e** (64–67% ee), underlining the value of local sterics in determining the degree of enantioselectivity. As illustrated in entry 6 of Table 1, the more Lewis basic benzyl ether **1f** also undergoes ARCM to afford the derived cyclic amine in 65% ee; however, in this instance, it is Mo complex **4** that delivers the highest enantioselectivity (>98% conversion in 0.5 h and 59% ee when **3** is used).

(9) Schrock, R. R.; Jamieson, J. Y.; Dolman, S. J.; Miller, S. A.; Davis, W. M.; Hoveyda, A. H. *Organometallics* **2002**, *21*, 409–417.

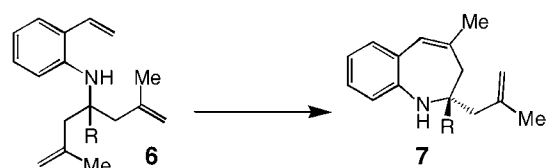
(10) For an example of olefin metathesis rate retardation as a result of (proposed) metal–heteroatom chelation, see: Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.



**Figure 1.**

Next, we investigated the possibility of enantioselective synthesis of polycyclic secondary amines through Mo-catalyzed desymmetrizations (approach B, Scheme 1). Toward this end, we prepared trienes **6a–c**,<sup>7</sup> illustrated in Table 2, and screened a range of chiral Mo complexes in order to

**Table 2.** Enantioselective Synthesis of Tertiary Bicyclic Amines through Mo-Catalyzed ARCM<sup>a</sup>

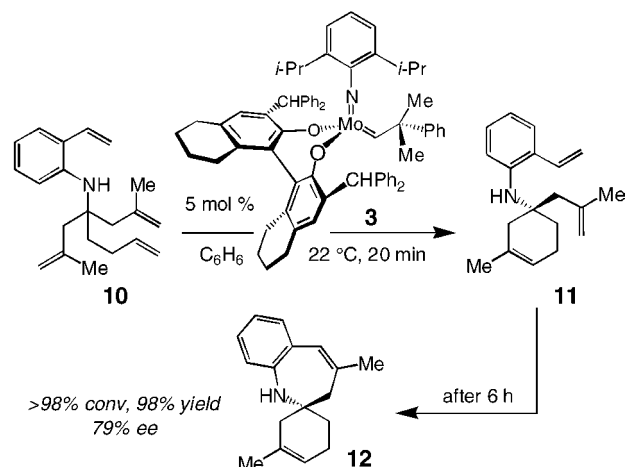


entry	R	catalyst	time (h); conversion (%) <sup>b</sup>	yield (%) <sup>c</sup> ; ee (%) <sup>d</sup>
1	<b>a</b> H	4	3; >98	75; 93
2		5	3; >87	80; 93
3	<b>b</b> Et	4	24; 90	71; 24
4		5	24; 20	nd; 22
5	<b>c</b> Ph	4	3; >98	98; 80
6		5	30; 20	nd; nd

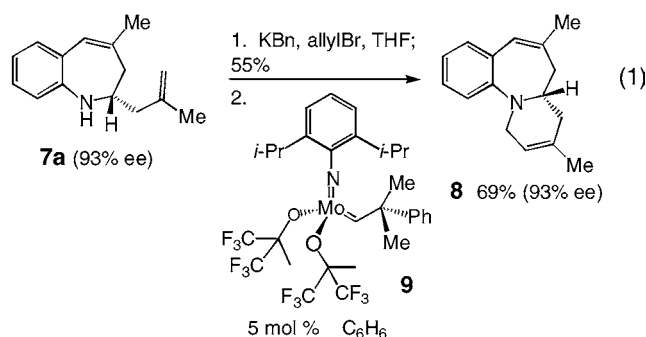
<sup>a</sup> Conditions: 5 mol % catalyst, C<sub>6</sub>H<sub>6</sub>, 55 °C, N<sub>2</sub> atmosphere. <sup>b</sup> Conversions determined by analysis of 500 MHz <sup>1</sup>H NMR spectrum of the unpurified reaction mixture. <sup>c</sup> Isolated yields after silica gel chromatography. <sup>d</sup> Determined by chiral HPLC analysis (Chiralcel OJ column).

examine their ability in promoting the enantioselective formation of **7a–c**. These studies indicate that alkylidenes **4**<sup>8</sup> and **5**<sup>3c</sup> give rise to the most efficient and enantioselective desymmetrizations. As the data in entries 1 and 2 of Table 2 indicate, catalysts **4** and **5** can be used to convert triene **6a** (R = H) efficiently (>98% conversion in 3 h) to unsaturated azepine **7a** in 93% ee. However, when **6b** is used as the substrate (entries 3 and 4), ring closures become significantly slower, particularly with catalyst **5** (entry 4), and the desired **7b** is formed in only 22–24% ee. Chiral complex **5** is equally ineffective in transformation of **6c** (entry 6, Table 2) to bicyclic amine **7c** (30% conversion after 20 h). In stark contrast, however, as depicted in entry 5 of Table 2, chiral catalyst **4** promotes the formation of **7c** efficiently (>98% conversion in 3 h) to deliver the desired amine in quantitative yield and 80% ee. It should be noted

**Scheme 2.** Enantioselective Synthesis of Polycyclic Amines through Tandem Mo-Catalyzed ARCM/RCM



that reactions in Table 2, are significantly slower when carried out at 22 °C. As an example, ARCM of **6a** with 5 mol % **4** and **5** proceeds to 55 and 53% conversion after 24 h at 22 °C, respectively (93% ee in both cases); longer reaction times did not result in additional conversion.



Several critical issues regarding the Mo-catalyzed desymmetrizations disclosed herein merit additional discussion:

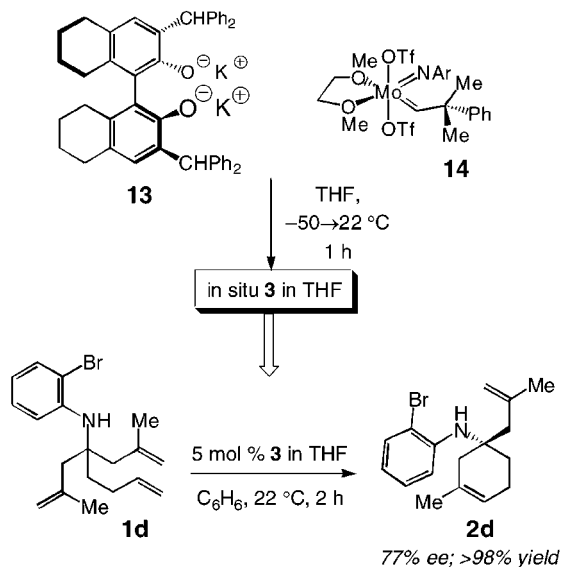
(1) The nonracemic cyclic secondary amines obtained by the Mo-catalyzed asymmetric method can be functionalized and converted to a variety of polycyclic structures. A representative example is illustrated in eq 1. Subjection of optically enriched **7a** (93% ee) with allylbromide and benzylpotassium, followed by treatment of the derived allylamine with 5 mol % achiral complex **9**,<sup>11</sup> leads to the formation of tricyclic amine **8** (93% ee).

(2) An alternative approach toward the synthesis of polycyclic amines involves reactions of tetraenes<sup>12</sup> that can undergo tandem RCM. The example shown in Scheme 2, combining the strategies outlined in Scheme 1 (see Tables

(11) (a) Murdzek, J. S.; Schrock, R. R. *Organometallics* **1987**, *6*, 1373–1374. (b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

(12) For previous examples of enantioselective desymmetrizations of tetraenes through Mo-catalyzed ARCM, see: Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553–9559.

**Scheme 3.** In Situ-Prepared Chiral Mo Catalyst Used in Enantioselective Synthesis of Amines



**1** and **2**), is illustrative. Treatment of tetraene **10** with 5 mol % **3** leads to the formation of cyclohexenylamine **11** within 20 min; prolonged reaction time leads to formation of **12** in quantitative yield and 79% ee.

(3) Chiral Mo catalysts are more reactive than their Ru-based counterparts.<sup>13</sup> On the other hand, these high-oxidation-state complexes are sensitive toward air and moisture, and their isolation and purification requires anhydrous and inert atmosphere conditions.<sup>1b</sup> As reported previously for two other Mo catalysts,<sup>14</sup> and as the example in Scheme 3 demonstrates, *chiral complex 3 can be easily prepared and used in situ, without isolation and purification, to promote efficient asymmetric metathesis with levels of enantioselectivity analogous to those obtained with the isolated and purified catalysts* (compare data in Scheme 3 with entry 4, Table 1). It is important to note that bis(alkoxide) **13** is prepared readily

by treatment of the parent diol with potassium hydride (or any other suitable base) and triflate **14** is commercially available (Strem Chemicals, Inc.; Newburyport, MA).

In summary, we disclose a method for enantioselective synthesis of cyclic unsaturated amines by Mo-catalyzed ARCM of achiral polyenes. The optically enriched products obtained cannot be readily accessed by any previously reported approaches.<sup>15</sup> Catalytic desymmetrizations are effected with secondary amine substrates, indicating the stability of chiral Mo alkylidenes to NH groups. Since optically enriched amines are critical to synthesis of biologically active molecules, improvements in the efficiency and enantioselectivity of this class of asymmetric transformations will be the subject of future investigations.<sup>16</sup>

**Acknowledgment.** This paper is fondly dedicated to the memory of the late Professor Satoru Masamune. Financial support was provided by the NIH (GM-59426). We are grateful to Elizabeth S. Sattely for helpful discussions.

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

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(13) (a) VanVeldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. (b) VanVeldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508. (c) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228.

(14) (a) Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452–1456. (b) Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779–10784.

(15) For example, with second-generation achiral Ru catalysts (Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041; Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179), the RCM illustrated in Table 1 proceed to >90% conversion at 55 °C in 1 h (vs 30 min at 22 °C with Mo catalysts). For ARCM of **1d** (Table 1, entry 4), we find that one chiral Ru catalyst (ref 13b), affords **2d** in 14% ee (33% conversion at 55 °C after 24 h).

(16) For example, the compound analogous to triene **1d** (Table 1, entry 4) but bearing terminal olefins undergoes ARCM with 5 mol % **3** to afford the desired cyclic disubstituted (vs trisubstituted) olefin in 5–10% ee (>98% conversion,  $C_6H_6$ , 22 °C, 30 min).