

## Tandem Catalytic Asymmetric Ring-Opening Metathesis/Cross Metathesis

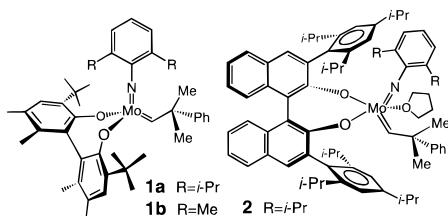
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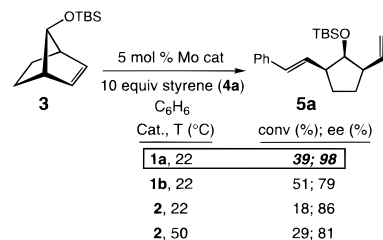
Metal-catalyzed metathesis is a powerful method in chemical synthesis.<sup>1</sup> Different versions of this important transformation include catalytic ring-closing, ring-opening,<sup>2</sup> and cross metathesis,<sup>3</sup> several approaches have been devised that employ these processes in combination.<sup>4</sup> With the availability of chiral complexes **1a**, **1b**,<sup>5</sup> and **2**,<sup>6</sup> which promote efficient asymmetric ring-closing



metathesis (ARCM), we wish to develop other catalytic asymmetric metathesis reactions. A major aspect of our program thus relates to the design of enantioselective protocols that involve the tandem occurrence of different metathesis-based processes. Herein, we report the results of our initial studies on tandem Mo-catalyzed asymmetric ring-opening/cross metathesis reactions (catalytic AROM/CM). The present method allows access to unsaturated carbocycles, which are formed in high yield, as single olefin isomers and in excellent enantiopurity. To the best of our knowledge, this disclosure documents the first examples of a catalytic AROM.

We initiated our studies by examining the possibility of effecting catalytic AROM/CM with norbornene and styrene in the presence of **1a**, **1b**, and **2**. All attempts resulted in the formation of substantial amounts of poly(norbornene), even in the presence of excess styrene. Accordingly, to discourage polymerization, we decided to use the sterically more encumbered

## Scheme 1



**Table 1.** Tandem Mo-Catalyzed Asymmetric Ring-Opening/Cross Metatheses<sup>a</sup>

entry	substrate	terminal alkene	product	time (h)	total conv (%) <sup>b</sup>	conv to product (%) <sup>b</sup>	trans (%) <sup>c</sup>	yield (%) <sup>d</sup>	ee (%) <sup>e</sup>
1	<b>3</b>	<b>4</b> a R = H	<b>5</b>	7	77	61	>98	57	96
2	<b>3</b>	<b>4</b> b R = OMe	<b>5</b>	7	90	75	>98	64	91
3	<b>3</b>	<b>4</b> c R = CF <sub>3</sub>	<b>5</b>	20	<10		>98	—	—
4	<b>6</b>	<b>4</b> a R = H	<b>7</b>	1	>98	97	>98	85	>98
5	<b>6</b>	<b>4</b> b R = OMe	<b>7</b>	1	98	98	>98	84	>98
6	<b>6</b>	<b>4</b> c R = CF <sub>3</sub>	<b>7</b>	4.5	67	54	>98	48	>97
7	<b>8</b>	<b>4</b> a R = H	<b>9</b>	0.3	>98	96	>98	96	>98
8	<b>8</b>	<b>4</b> b R = OMe	<b>9</b>	0.1	>98	95	>98	88	>98
9	<b>8</b>	<b>4</b> c R = CF <sub>3</sub>	<b>9</b>	0.4	>98	80	>98	80	>98

<sup>a</sup> Conditions: 5 mol % **1a**, 2 equiv of **4**, Ar atm, 22 °C, C<sub>6</sub>H<sub>6</sub>.

<sup>b</sup> Percent product determined by 400 MHz <sup>1</sup>H NMR analysis. <sup>c</sup> Determined by 400 MHz <sup>1</sup>H NMR analysis. <sup>d</sup> Isolated yield of purified products by silica gel chromatography. <sup>e</sup> Determined by HPLC (Chiralcel OD for entries 1, 2, 4–7 and AD chiralpak for entries 8–9), in comparison with authentic racemic materials. Analysis of products in entries 1, 4, 6, and 7 were performed on the derived acetates.

silyl ether **3**,<sup>7</sup> which was prepared and treated with styrene (**4a**) in the presence of 5 mol % **1a**, **1b**, and **2**. The biphen-based complex **1a** proves to be superior (Scheme 1); catalytic AROM/CM proceeds in the presence of 10 equiv of styrene and 5 mol % **1a** to 39% conversion (22 °C, C<sub>6</sub>H<sub>6</sub>). Importantly, the desired product (**5a**) is obtained in >98% ee and as a single olefin isomer (GLC and <sup>1</sup>H NMR analysis, respectively).

Subsequent studies indicated that lower concentrations of styrene result in higher conversions.<sup>8</sup> Thus, with **1a** as the catalyst and with 5 equiv of styrene, 52% conversion is observed; with 2 equiv of styrene, >77% conversion is attained. As shown in entry 1 of Table 1, treatment of **3** with 2 equiv of styrene (**4a**) in the presence of 5 mol % **1a** at 22 °C for 7 h affords **5a** in 57% isolated yield and 96% ee (>98% trans). The stereochemical identity of the catalytic AROM/CM product **5b** was established through determination of the crystal structure of the corresponding camphor sulfonate derivative (see the Supporting Information).

The results of our studies involving the Mo-catalyzed AROM/CM of various norbornene and styrene derivatives are summarized in Table 1. Regardless of the electronic properties of the styrene partner (**4a**, **4b**, or **4c**), reactions can be designed to proceed in high conversion to afford **5**, **7**, and **9** with complete control of olefin stereochemistry (>98% trans), in good yield and high optical purity (>91% ee).<sup>9</sup> A number of related issues are worthy of note: (1) Catalytic AROM/CM reactions can be carried out with catalyst loadings lower than 5 mol %; for example, with 1

(7) Gerteisen, T. J.; Kleinfelter, D. C. *J. Org. Chem.* **1971**, *36*, 3255–3259.

(8) The reason for this observation is unclear at the present time.

(9) The stereochemical identity of all products in Table 1 and Scheme 2 is consistent with the assignment made based on the X-ray structure (cf. Figure 1). Selected products from all substrates were converted to common intermediates (derived acetates in place of silyl or MOM ethers) and compared by chiral HPLC.

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(1) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.  
(2) For representative recent reports on Ru-catalyzed ROM, see: (a) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478–1479. (b) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257–259.

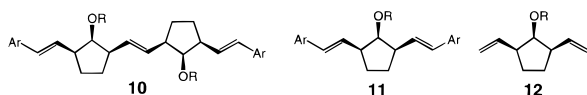
(3) (a) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162–5163. (b) For a recent review of catalytic CM, see: (b) Gibson, S. E. In *Alkene Metathesis in Organic Synthesis*; Furstner, A., Ed.; Springer, Berlin 1998; pp 155–180.

(4) For examples of non-asymmetric tandem catalytic ROM/RCM, see: (a) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343–2351. (b) Johannes, C. W.; Visser, M. S.; Weatherhead G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340–8347. For examples of nonasymmetric tandem catalytic ROM/CM, see: (c) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610–9611. (d) Reference 2b.

(5) (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.

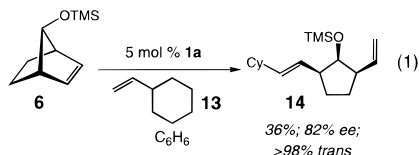
(6) Zhu, S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251–8259.

mol % **1a**, **7b** is formed in >98% ee and 92% yield (>98% trans, 5 h). (2) Toluene may be used as solvent; the reaction in entry 7 proceeds in toluene to afford **9a** in 86% isolated yield and >99% ee (0.3 h). (3) In general, catalytic AROM/CM are faster with more electron-rich styrenes. Thus, as shown in entries 1–3 of Table 1, transformations with **4a** and **4b** proceed to >75% conv within 7 h, whereas reaction with **4c** proves to be prohibitively slow. Nevertheless, as the alkene unit of the norbornene substrate becomes more sterically accessible, catalytic AROM/CM of the slower reacting and electron-deficient **4c** reaches synthetically useful levels of efficiency (entries 6 and 9). (4) With the exception of the reaction shown in entry 5, varying amounts of **10**, **11**, and **12** are isolated as minor byproducts.<sup>10</sup> If transformations are



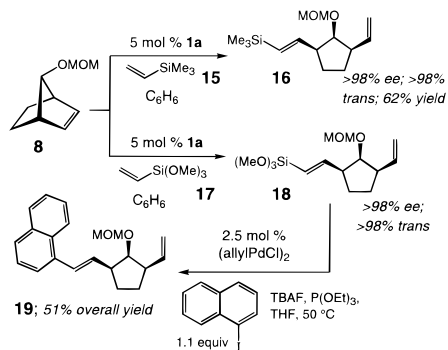
allowed to proceed for extended times (see Table 1), more of **10** (CM between product molecules) and **11** (CM between **4** and product) are formed.

Our attempts to use aliphatic olefin substrates in catalytic AROM/CM reactions have been promising but less successful. When vinyl cyclohexane **13** is employed with silyl ether **6** (eq 1), diene **14** is formed with diminished efficiency and enantiose-



lectivity (36% isolated yield, 82% ee);<sup>10</sup> <sup>1</sup>H NMR analysis of the unpurified reaction mixture indicates 30% of byproducts related to **11** and **12** and 34% recovered **6**. However, as illustrated in Scheme 2, catalytic processes with vinylsilanes afford optically pure materials in an efficient manner. Treatment of **8** with 5 mol % **1a** and one equiv of **15** (50 °C, 85% conversion, 24 h) leads to the formation of vinylsilane **16** in >98% ee and 62% purified yield (>98% trans by 400 MHz <sup>1</sup>H NMR). When trialkoxysilane **17** is utilized, catalytic AROM/CM is more efficient (>98% conversion, 22 °C, 24 h). The resulting vinylsilane **18** (>98% ee) undergoes Pd-catalyzed cross coupling with various aryl iodides to afford a wider range of optically pure adducts.<sup>11</sup> The example shown in Scheme 2 is illustrative (**8**→**19**; 51% overall).

### Scheme 2

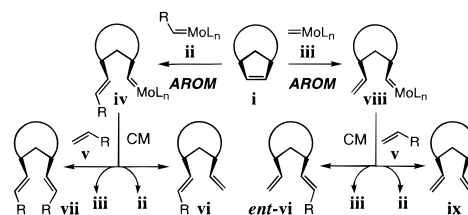


A general pathway for the catalytic AROM/CM is proposed (Scheme 3). Several intricate issues regarding the suggested mechanism merit mention: (1) The initial Mo-neophylidene (e.g., **1a**) may react with the terminal alkene (**v**) to generate  $L_nMo=$

(10) The difference between total conversion and conversion to product constitutes the percent byproduct formation.

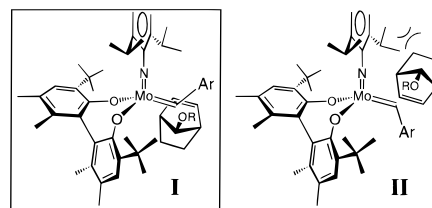
(11) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, 30, 6051–6054.

### Scheme 3



CHR (**ii**) or the less substituted  $L_nMo=CH_2$  (**iii**); each of these two complexes may then promote catalytic AROM. Initiation with **ii** generates **iv**, which can undergo catalytic CM to afford **vi**. Alternatively, reaction through Mo-alkylidene **iii** would generate *ent*-**vi** via alkylidene **viii**. If AROM occurs with the same sense of stereocontrol with **ii** and **iii**, then reaction with **ii** would afford **vi**, whereas that with **iii** would yield *ent*-**vi**. (2) One olefinic substrate (**i**, Scheme 3) must be more reactive, so that AROM occurs efficiently and effectively competes with homo-metathesis of the other alkene (**v**). (3) Terminal alkene substrates need to be sterically and electronically<sup>12</sup> compatible; if not, competitive catalytic CM might occur to reduce overall efficiency (e.g., homo-metathesis of **v** or CM of **iv** + **vi**). (4) The terminal alkene substrate (**v**) should be selected so that its reaction with **iv** or **viii** proceeds with the appropriate regiocontrol during metallacyclobutane formation; otherwise, the undesired achiral meso adducts **vii** or **ix** will form.

### Scheme 4



Mode of addition **I**, presented in Scheme 4, may be suggested as one plausible working model for the formation of the major enantiomer. In the alternative **II**, leading to the minor enantiomer, there is significant unfavorable steric strain between the substrate and the imido ligand of the chiral catalyst. The lower selectivity observed in reactions catalyzed by **1b** is consistent with this proposal: with the smaller Me groups on the imido ligand (vs *i*-Pr), reaction pathway through **II** is less disfavored. The suggestion that  $L_nMo=C(H)Ph$ , and not the corresponding  $L_nMo=CH_2$ , is the active catalyst is based on the fact that treatment of **1a** with 40 equiv of styrene<sup>13</sup> leads to <2% stilbene formation and the immediate generation of  $L_nMo=C(H)Ph$ , as judged by the appearance of new alkylidene resonances at 11.50 and 13.05 ppm (3:1, syn and anti isomers,<sup>6</sup> respectively; 400 MHz,  $C_6D_6$ ). Detailed mechanistic investigation is in progress; in addition to the above issues, these studies aim to determine whether the bridgehead alkoxide is involved in chelation with the Lewis acidic Mo.<sup>14</sup>

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

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(12) Crowe, W. E.; Zhang, Z. *J. Am. Chem. Soc.* **1993**, 115, 10998–10999.

(13) The ratio of **1a**: styrene (**4a**) was selected so as to mimic the conditions in Table 1.

(14) This research was generously supported by the NSF (CHE-9905806 to A. H. H.; CHE-9700736 to R. R. S.) and the NIH (GM-47480 to A.H.H.). D. S. L. is grateful for a graduate fellowship by the American Chemical Society (sponsored by Boehringer-Ingelheim).