Tandem Catalytic Asymmetric Ring-Opening Metathesis/Ring-Closing Metathesis

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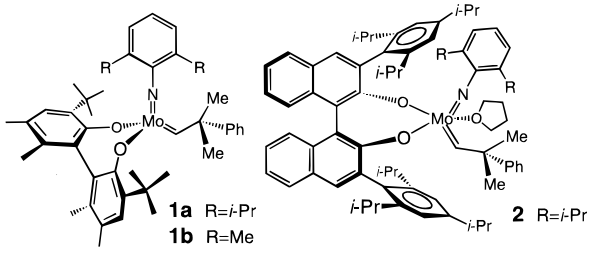
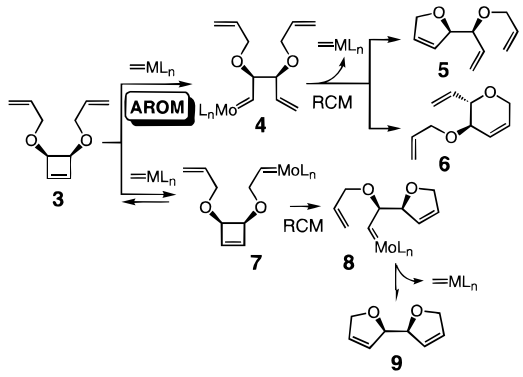
We recently reported the first examples of asymmetric ring-opening metathesis (AROM) of strained disubstituted cyclic alkenes, followed by an intermolecular cross metathesis.[1] The initial ring-opening event is effected by the Mo−alkylidene formed by the reaction of the catalyst with the terminal olefin substrate. These tandem AROM/CM reactions, catalyzed by optically pure complexes **1a**, **1b**,[2] and **2**,[3] proceed efficiently, with high alkene stereocontrol and with excellent enantioselection. However, one notable drawback is that, if the disubstituted olefin is not sterically protected (e.g., norbornene), competitive intermolecular reaction of the resulting Mo−alkylidene (AROM adduct) with another molecule of the strained olefin leads to rapid polymerization. To circumvent such shortcomings, we have examined another tandem process involving a catalytic AROM and an *intra*molecular ring-closing metathesis (RCM). *The transformations discussed here, proceed enantioselectively (>84% ee) and provide an exceptionally rapid entry to optically enriched heterocycles that are not easily accessible by any other catalytic asymmetric protocol (including other enantioselective metathesis reactions).*[4] This disclosure puts forth the first example of an asymmetric variant of this tandem catalytic process.



The general strategy used in our studies (Scheme 1, triene **3** used as example)[5] deals with several important mechanistic complexities that are distinct from the catalytic AROM/CM.[1] Similar to the AROM/CM protocol,[1] enantioselectivity should depend on the kinetic asymmetric induction in the catalytic AROM; regeneration of the starting cycloalkene (**4** → **3**) is likely disfavored due to ring strain. A critical factor for the success of this approach is that the transformation must be initiated site-selectively and irreversibly at the central alkene to generate **4**

Scheme 1



(with AROM/CM, catalyst initially reacts with the terminal olefin substrate). If the sequence commences with a catalytic RCM (**3** → **7** → **8**), substantial amounts of achiral **9** would be formed. The latter pathway involves a Mo−alkylidene intermediate (**8**) that would readily undergo a second closure to deliver **9**. Moreover, the rate of catalytic AROM (**3** → **4**) must be faster than that of the second closure (e.g., **5** → **9**). That is, the overall process will not afford optically enriched products unless RCM of **4** to **5** represents a matched[6] and rapid closure and that of **5** to **9** (or **6** to the respective bicycle) constitutes a mismatched and slow ring formation. Another potentially damaging factor is that the subsequent catalytic RCM of chiral **4** may afford dihydrofuran **5** or dihydropyran **6**. At the outset, it was unclear to us which pathway, if any, would predominate.

As illustrated in Table 1 (entry 1), when **3a** (R = H) is treated with 5 mol % **1a** for 10−15 min, **5a** is isolated in only ∼10% yield but in >98% ee; meso **9** is the major product (73%). When **3b** (R = Me) is subjected to the catalytic metathesis conditions (entry 2), **5b** is obtained within 30 min in 92% ee and 69% yield after silica gel chromatography.[7] The latter finding indicates that the ring-opened Mo−alkylidene (**4**) reacts faster with an internal disubstituted alkene than with another unreacted cyclobutene, a process that would afford oligomerization products. Furthermore, it merits mention that: (i) In the above reactions, the corresponding dihydropyran (cf. **6**) is not observed (<2%). (ii) The subsequent RCM completely inhibits adventitious polymerization, such that even high dilution conditions are not necessary.

When a similar protocol is applied to bicyclic meso triene **10a** in the presence of 5 mol % **1a** (R = H, entry 3), **11a** is obtained in 98% ee (76%). In contrast to **3a**, the derived meso bicycle is no longer the major product. Only 1 mol % **1b** (entry 4) is sufficient to initiate reaction with **10a**; these conditions deliver less meso bicycle (2% vs 20%; cf. **9**, Scheme 1), but also lower amounts of **11a** are formed with diminished enantioselectivity (84 vs 98% ee).[8] Catalytic reactions of the more substituted **10b** are promoted by 2 mol % **1b** to afford **11b** in 98% ee (84%) within 15 min (entry 5). In this instance, catalyst **1a** is less effective than **1b** (compare entries 5 and 6).[9]

Unlike the processes shown in Table 1, in the reactions presented in Table 2 formation of a meso bicycle is not feasible. The more reactive **1b** effects **12** → **13** in 72% ee (65% conv in

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(1) La, D. S.; Ford, G. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603−11604.

(2) (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.

(3) 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.

(4) For a recent review on catalytic metathesis, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(5) For related non-asymmetric transformations, see: Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640.

(6) The metal complex bears a chiral ligand, and there are stereogenic centers within the chain that undergoes cyclization. Thus, the combination of metal-center and chain chirality may prove to be mismatched (slow closure) or matched (fast closure). This was exploited in the Mo-catalyzed kinetic resolution processes (ref 2).

(7) The constitutional and stereochemical identities of **5a** and **5b** were determined by comparison to authentic materials, prepared through a 10-step enantioselective synthesis (see the Supporting Information). The stereochemical outcomes of **10a** and **10b**, involving exo face addition, are by inference.

(8) Complex **2** is typically less effective in promoting the catalytic AROM/RCM discussed here (e.g., **11a** is formed with 30% conv).

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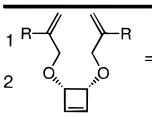
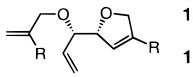
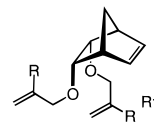
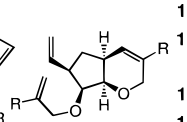
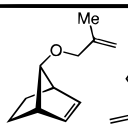
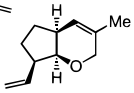
Table 1. Desymmetrication of Trienes by Tandem Asymmetric Mo-Catalyzed Ring-Opening/Ring-Closing Metathesis[a]

entry	substrate	product	catalyst; mol %	time (h)	conv (%);[b] bicycle (%)[c]	yield (%);[d] ee (%)[e]
1			**1a**; 5	0.2	83; 73	10; >98
2			**1a**; 5	0.5	>98; --	69; 92
	3a R=H **3b** R=Me	**5a** R=H **5b** R=Me				
3			**1a**; 5	0.2	***>98; 20***	***76; 98***
4			**1b**; 1	0.2	63; <2	55; 84
5			**1a**; 5	0.2	>98; 35	42; 92
6			**1b**; 2	0.2	***>98; 10***	***84; >98***
	10a R=H **10b** R=Me	**11a** R=H **11b** R=Me				

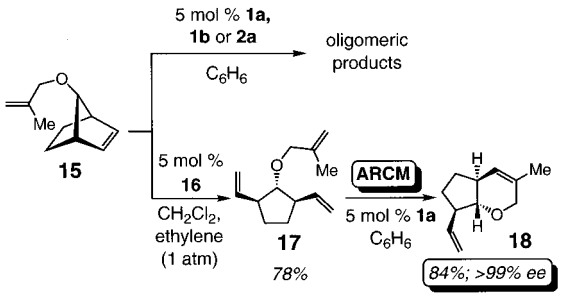
[a] Conditions: Ar atm, 22 °C. [b] By GLC (internal standard). [c] By 400 MHz ^{1}H NMR analysis. [d] Isolated yield of purified products by silica gel chromatography. [e] By chiral GLC (CD-GTA).

Table 2. Enantioselective Desymmetrization of Dienes by Tandem Mo-Catalyzed Ring-Opening/Ring-Closing Metathesis[a]

entry	substrate	product	catalyst; mol %	additive (mol %)	time (h); conv (%)[b]	yield (%);[c] ee (%)[d]
1			**1b**; 5	none	7; 65	60; 72
2			**1a**; 5	none	24; <2	--; --
3			**1a**; 5	**14** (10)	***24; 85***	***54; 92***
	12	**13**				

[a] –[c]See Table 1. [d] By chiral GLC (CD-GTA).

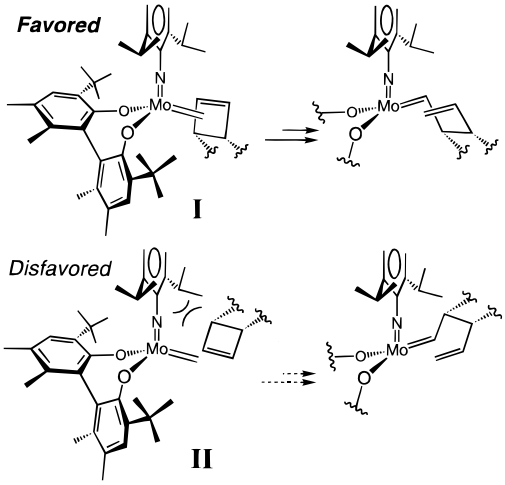
Scheme 2



7 h).[10] With the sterically more demanding catalyst **1a**, <2% product is formed (entry 2, Table 2). When the reaction is conducted in the presence of 10 mol % diallyl ether (**14**), 85% conv is observed within 24 h and **13** is isolated in 92% ee (54%). The positive influence of **14** is likely due to the initial formation of the more reactive chiral metal−methylidene complex ($L_nMo{=}CH_2$) which can readily initiate the catalytic AROM of the sterically demanding **12** (compared to the starting neophylidenes **1a** or **1b**).[11]

In contrast to diene **12**, the stereoisomeric **15** (Scheme 2), in the presence of **1a**, **1b**, or **2**, is converted to oligomeric products. The more exposed bicyclic alkene likely reacts intermolecularly

Scheme 3



with the Mo−alkylidene in preference to undergoing an intramolecular RCM. To address this complication, the ROM/ARCM sequence in Scheme 2 was devised. Treatment of **15** with the less reactive $(PCy_3)_2Cl_2Ru{=}C(H)Ph$[5] (**16**) in the presence of ethylene (1 atm) results in the formation of **17** (78%). Subjection of **17** to 4 mol % **1b** affords **18** in >99% ee (84%).[12,13] By eliminating the presence of the reactive bicyclic olefin, while the catalytic RCM takes place (preformation of **17**), oligomerization is circumvented, and the optically pure heterobicycle is obtained.

The stereochemical outcomes in the catalytic AROM processes discussed above may be due to the stereoselective approach of the reactive cyclic alkene to the chiral Mo complex (**I**, Scheme 3).[14] Association of the substrate and the chiral complex is expected to occur from the face opposite to the protruding *t*-Bu unit of the biphen group (front face of the complex, Scheme 3).[15] Approach of the alkene through mode **II** would lead to unfavorable steric interactions.[16]

The development of Mo-catalyzed asymmetric variants of other metathesis-based transformations, and their applications to target-oriented synthesis,[17] are in progress.[18]

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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(9) It is unlikely that with substrates in Table 1, reaction of the Mo−alkylidenes at the terminal olefins (reversible) leads to a productive pathway. The subsequent ARCM should prove prohibitive; not only are the cyclobutene and norbornene olefins substantially more reactive (particularly where 1,1-disubstituted alkenes are involved), but the requisite metallacyclobutanes would also be highly strained.

(10) The stereochemical identity of **13** was determined through correlation with a closely related compound, the stereochemistry of which was determined by X-ray crystallography. See the Supporting Information.

(11) (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.

(12) The stereochemical identity of **18** was established through comparison with authentic materials prepared through a seven-step independent synthesis. See the Supporting Information.

(13) Reaction of **12** in the presence of **14** (Table 2, entry 3) may partially proceed via a similar triene intermediate (ARCM rather than AROM). However, the data in entry 1 of Table 2 indicate that catalytic AROM *can* occur with enantioselection, since the formation of the purported triene intermediate (cf. **17**) requires the presence of a terminal alkene or ethylene. With **3a** and **10a**, reaction of the intermediate alkylidene (e.g., **4**, Scheme 1) with a substrate molecule may lead to the formation of the derived tetraene which could undergo ARCM. In such cases, intermolecular reaction of the alkylidene with the substrate's more reactive cyclic olefin (vs a terminal alkene) would be expected to predominate, leading to oligomerization.

(14) The first catalytic cycle is initiated by the original neophylidine complex, unless ethylene is present (or by addition of **14**). Similar arguments as in Scheme 3 can be applied to the initial neophylidenes.

(15) Schrock, R. R. *Top. Organomet. Chem.* **1998**, *1*, 1−36 and references therein.

(16) On the basis of the identity of the product enantiomer and the model presented in Scheme 3, the approach of the chiral Mo-methylidene to the cyclic alkene of **12** occurs from the bicycle's endo face. This is presumably because the exo face is sterically rendered less accessible by the bridgehead alkoxide. Detailed mechanistic studies are in progress.

(17) For a recent application of Mo-catalyzed ARCM to natural product synthesis, see: Burke, S. D.; Muller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827−1829.

(18) This research was supported by the NSF (CHE-9905806 to A.H.H.) and the NIH (GM-47480 to A.H.H.).