Enantioselective Synthesis of Unsaturated Cyclic Tertiary Ethers By Mo-Catalyzed Olefin Metathesis

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One popular approach to the synthesis of optically pure materials involves catalytic metatheses performed on substrates that have already been accessed in the nonracemic form.[1,2] A more direct approach to enantioselective synthesis takes advantage of a unique attribute of catalytic metathesis: structural reorganization of an achiral substrate leading directly to a chiral nonracemic product.[3] Such an objective can now be realized with the advent of efficient Mo-based chiral complexes represented by **1**−**4** (Chart 1).[4] The results of our studies regarding the catalytic enantioselective synthesis of unsaturated pyrans through Mo-catalyzed alkene metathesis are reported herein. Readily available starting materials are used to obtain optically enriched unsaturated cyclic tertiary ethers that are difficult to access by alternative methods. Unlike previous cases, highly strained olefins are not required as substrates.[3]

To initiate our studies, we subjected cyclopentene **5** (Table 1) to 5 mol % chiral Mo catalysts shown in Chart 1 (22 °C, C_6H_6, 12 h). Appreciable conversion was observed in all cases (Table 1), with catalysts **3a** and **3b** exhibiting the highest levels of asymmetric induction. Whereas similar enantioselectivity is obtained at 0 °C, when **5** is treated with 5 mol % **3a** at 50 °C (4 h), **6** is generated in 96% ee and 87% isolated yield (see entry 1, Table 2). Data in Table 2 indicate that a variety of cyclopentenyl substrates undergo enantioselective Mo-catalyzed rearrangement to afford the desired pyrans in >90% ee (>70% yield). Several issues regarding results in Table 2 merit comment: (1) All transformations were carried out with 5 mol % **3a**. Lower catalyst loadings may however be employed. Treatment of **5** with 2 mol % **3a** (C_6H_6, 55 °C) leads to the formation of **6** in 92% ee and 90% yield (>98% conv, 24 h).[5] (2) All reactions may be performed at 50 °C with **3a**, except for that shown in entry 3. Dihydropyran **10** is formed in 62% ee (53% conv, 2 h) at 50 °C; at 80 °C (toluene), >98% conv is achieved and **10** is generated in 93% ee and 93% yield. (3) In all the transformations in Table 2, <2% dimeric products are detected (^{1}H NMR analysis).

The higher enantioselectivity at elevated temperatures is not due to equilibration (ring-opening/ring-closing) of the initially formed and less enantiopure dihydropyrans. Treatment of a sample of **6** (53% ee) with 5 mol % optically pure **3a** (C_6H_6, 5 mol % diallyl ether,[3] 60 °C) leads to the recovery of **6** in 55% ee. Moreover, a similar equilibration does not lead to diminution of selectivity: when an optically enriched sample of **8** (91% ee) is subjected to 5 mol % racemic catalyst (6 h, 50 °C), the unsaturated pyran is recovered in 91% ee.

Several plausible mechanistic scenarios are illustrated in Scheme 1. Asymmetric ring-opening metathesis (AROM) of cyclopentenyl substrate ***i*** could lead to the preferential formation of ***ii*** or ***iv***, which would then undergo RCM to deliver the desired pyran. Pathways (a) and (b) are more complex than previously reported reactions of cyclobutene- and norbornene-containing substrates,[3,6] where Mo-catalyzed rupture of strained alkenes is irreversible. Here, intermediates ***ii*** and ***iv*** can readily re-convert to ***i***; such a possibility renders the identity of the stereochemistry-determining step more ambiguous. Initial AROM may be enantioselective but the resulting Mo−alkylidene might revert back to the starting cyclopentene faster than conversion to the corresponding unsaturated pyran. In turn, it may be the minor product from the AROM process that rapidly undergoes RCM and thus the majority of products may be generated by such a route. A third pathway (c) involves reaction through Mo−alkylidene ***v***, which would subsequently undergo asymmetric ring-closing/ring-opening metathesis (ARCM/ROM). As in the case where AROM

Chart 1

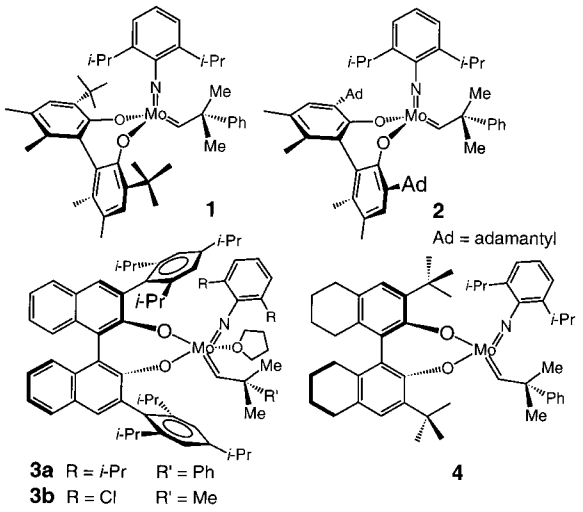
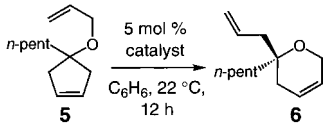


Table 1.



catalyst	conv (%)[a]	ee (%)[b]
1	86	15
2	>98	29
3a	91	68
3b	77	66
4	90	14

[a] Determined by ^{1}H NMR. [b] Determined by chiral GLC (CDGTA); major isomers in entries 1−2 are enantiomers of those in entries 3−5.

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(1) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(2) For representative examples, see: (a) Johannes, C. W.; Visser, M. S.; Weatherhead G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340−8347. (b) Furstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738−1742. (d) Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071−8072.

(3) For a previous report involving structural reorganization of strained substrates through AROM/RCM, see: Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828−1829.

(4) Complex **1**: (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. Complex **2**: (c) Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H. *Organometallics* **2000**, *19*, 3700−3715. Complex **3a**: (d) 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. (e) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553−9559. Complex **4:** (f) Aeilts, S.; Cefalo, D. R.; Bonitatbeus, Jr.; P. J.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, in press.

(5) With 1 mol % **3a**, **6** is formed in 91% ee and 79% isolated yield.

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

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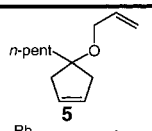
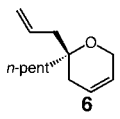
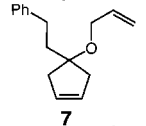
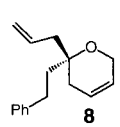
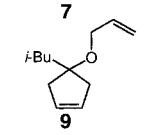
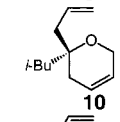
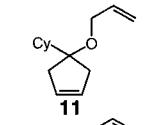
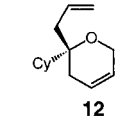
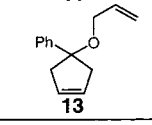
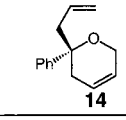
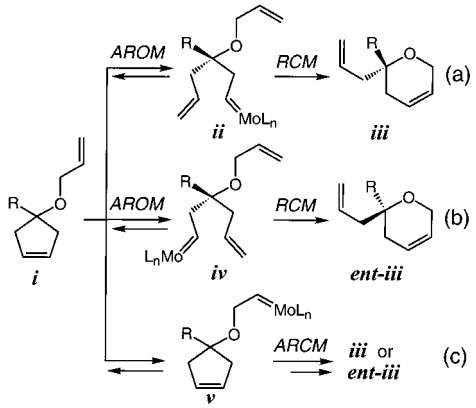
Table 2. Mo-Catalyzed Enantioselective Rearrangement of Cyclopentenes to Unsaturated Pyrans[a]

entry	substrate	product	time (h)	yield[b] (%)	ee[c] (%)
1	 **5**	 **6**	4	87	96
2	 **7**	 **8**	6	95	91
3	 **9**	 **10**	2[d]	93	93
4	 **11**	 **12**	24	73	96
5	 **13**	 **14**	2	91	74

[a] Conditions: 5 mol % **3a**, C_6H_6, 50 °C. [b] All reactions proceed to >98% conv, except for entry 4 (80% conv). Isolated yields. [c] Enantioselectivities determined by chiral GLC (β-DEX, entries 4−5 and CDGTA, entries 1, 3) and HPLC analysis (Chiralcel OJ column, entry 2). [d] Reaction carried out in toluene at 80 °C.

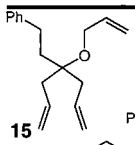
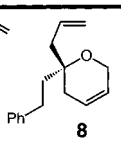
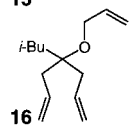
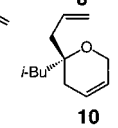
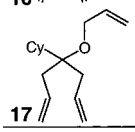
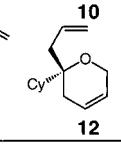
Scheme 1



is stereochemistry-determining, the involvement of the cyclic alkene is critical in establishing stereochemistry in an ARCM mechanism.

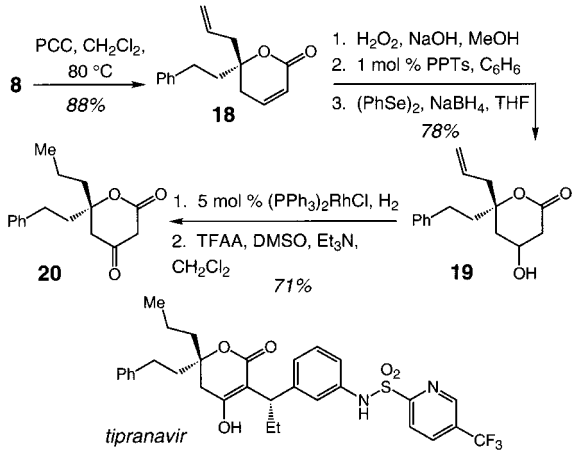
To address these issues, we studied the reactions of the derived triene substrates (see Table 3). We surmised that if the RCM processes (***ii*** → ***iii*** vs ***iv*** → ***ent-iii***) are stereochemistry-determining (vs the initial ROM or reaction via ***v***), then similar levels of selectivity should be observed with triene substrates, as intermediates ***ii*** and ***iv*** would remain equally accessible. Treatment of trienes **15**, **16**, and **17** (Table 3) with the same reaction conditions described in Table 2 leads to significantly lower enantioselectivity (35, 30, and 77% ee, respectively). These findings suggest that AROM or ARCM involving the *cyclic* cyclopentyl olefin are (at least) partially responsible for the levels of asymmetric induction shown in Table 2. Nevertheless, as depicted in Table 3, when catalytic metatheses are carried out at elevated temperatures (65−80 °C), **16** and **17** are converted to unsaturated pyrans **10** and **12** with high enantioselectivity. Although formation of **8** from **15** occurs with 74% ee, catalytic metatheses of trienes **16** and **17** deliver **10** and **12** in >99% ee and 92% ee, respectively. The rationale for dependence of enantioselectivity on temperature may

Table 3. Acyclic Trienes to Unsaturated Pyrans by Asymmetric Mo-Catalyzed Metathesis[a]

substrate	product	at 50 °C conv[c]; ee (%)[d]	at >50 °C[b] yield[e]; ee (%)[d]
 **15**	 **8**	>98; 35	93; 74
 **16**	 **10**	75; 30	90; >98
 **17**	 **12**	>98; 77	93; 92

[a] Conditions: 5 mol % **3a**, toluene, 3 h at 50 °C and 2−3 h at 80 °C. [b] Entries 1−2 at 80 °C; entry 3 at 65 °C. All reactions proceed to >98% conv. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC (Chiralcel OJ column, entry 1) and chiral GLC (CDGTA, entry 2 and β-DEX for entry 3). [e] Isolated yields.

Scheme 2



well be due to varying involvement of different pathways in Scheme 1.

In light of the scarcity of asymmetric protocols for the synthesis of tertiary ethers,[7] the present approach offers an efficient method for the enantioselective preparation of difficult-to-access nonracemic pyrans. The protocols described here should thus find applications in target-oriented synthesis: unsaturated pyran **8** is converted to the lactone moiety of the anti-HIV agent tipranavir[8] by a six-step sequence (Scheme 2). The stereochemical identity of **20** (Scheme 2) was compared to an authentic sample; this analogy establishes the absolute stereochemistry of the product of the Mo-catalyzed process.[9,10]

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

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(7) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446. (b) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061−1063.
(8) Fors, K. S.; Gage, J. R.; Heier, R. F.; Kelly, R. C.; Perrault, W. R.; Wicnienski, N. *J. Org. Chem.* **1998**, *63*, 7348−7356.
(9) The stereochemical outcome, assuming a stereochemistry-determining ROM step, is consistent with the model in ref 3.
(10) This research was supported by the NIH (GM-59426) and the NSF (CHE-9905806). Additional assistance was provided by ChiroTech, Schering-Plough and Natural Sciences and Engineering Research Council of Canada (J.Y.J.). We are grateful to Dr. V. Farina of Boehringer-Ingelheim for authentic samples of **20** and tipranavir.