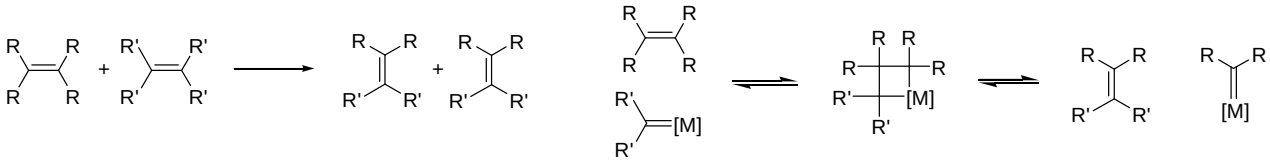
DESYMMETRIZATION THROUGH ENANTIOSELECTIVE OLEFIN METATHESIS

Min Xie November 18, 2004

INTRODUCTION

Olefin metathesis is defined as the redistribution of carbon-carbon double bonds, and is catalyzed by metal carbene complexes.[1] The generally accepted mechanism for this transformation (known as the Chauvin Mechanism) involves the reversible, formal [2+2] cycloaddition of olefins and metal alkylidenes followed by cycloreversion of the metallacyclobutane intermediates.[2]

Scheme 1



Two classes of olefin metatheis are of particular importance for synthesis. Ring-opening metathesis polymerization (ROMP) of cyclic olefins finds extensive application in the construction of macromolecules,[1] and ring-closing metathesis (RCM) is widely used for the formation of various sizes of carbo- and heterocycles.[3a] The combination of these two powerful transformations allows for unique intramolecular skeletal reorganizations of cyclic dienes or polyenes and is generally referred to as ring rearrangement metathesis (RRM).[3b]

Interesting metathesis strategy involves desymmetrization of achiral dienes and polyenes to afford enantiomerically enriched compounds.[3c] This report will highlight these desymmetrizations through catalytic enantioselective RCM (ERCM) and enantioselective RRM (ERRM).

CHIRAL MOLYBDENUM CATALYSTS FOR ASYMMETRIC OLEFIN METATHESIS

The widely applied molybdenum complex **1** (Schrock's catalyst) can be employed to catalyze the metathesis of a wide range of olefin types due to its high reactivity.[4] Two unique structural attributes of this complex offer superior opportunities for the development of chiral catalysts. First, asymmetric modification can be easily achieved by the installment of chiral alkoxide ligands. Second,

the imido as well as the alkoxide moieties allow for steric and electronic modulation to control the catalytic activity and selectivity. Based upon the parent Mo catalyst **1**, a series of chiral catalysts (represented by **2-4**) have been recently developed for enantioselective olefin metathesis.[4] Similar to the parent system **1**, these chiral molybdenum complexes are highly air and moisture sensitive.

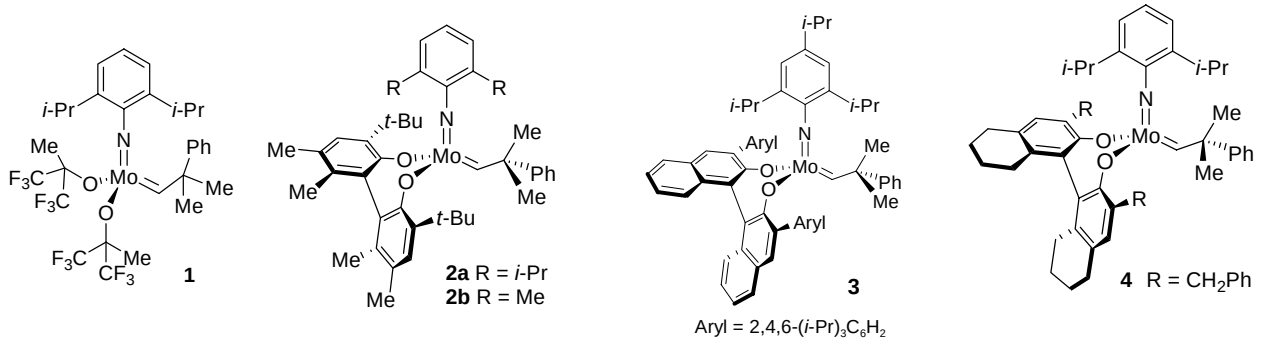


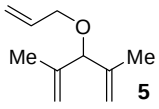
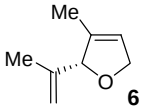
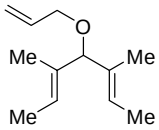
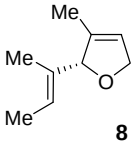
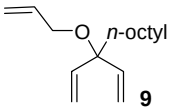
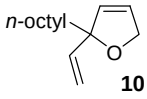
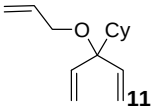
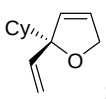
Figure 1. Achiral and Chiral Mo Catalysts for Olefin Metathesis

DESYMMETRIZATION OF POLYENES VIA ERCM

Synthesis of Cyclic Ethers and Their Functionalized Derivatives

Chiral cyclic ethers are commonly found in natural products.[3a] Consequently, their asymmetric synthesis is the subject of intense study.[3a] The first example of desymmetrization of achiral trienes to afford chiral dihydrofurans in high yield and er was achieved by Schrock and Hoveyda (Table 1).[5] Even substrates bearing sterically congested olefins produce the cyclized product in the presence of the biphenolate catalyst **2b**. Both secondary and tertiary ethers can be synthesized with this method.[5] The stereodeterming step of this reaction is likely to be the formation of the metallabicyclobutane intermediate, during which the Mo alkylidene formed initially at

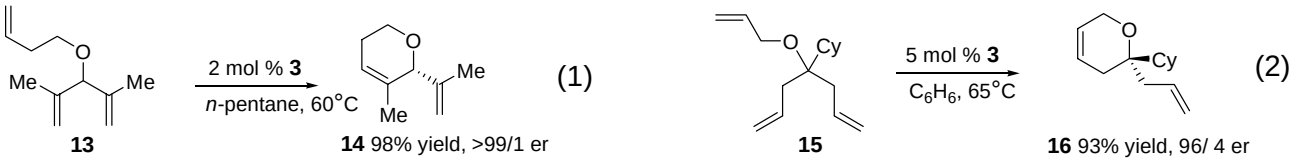
Table 1. Enantioselective Synthesis of Dihydrofurans

entry	substrate	catalyst	product	yield (%)	product er, config.
1	 **5**	5mol% **2b**	 **6**	86	96/4, *R*
2	 **7**		 **8**	83	96/4, *R*
3	 **9**		 **10**	88	55/45, ND
4	 **11**		 **12**	84	87/13, *S*

the most accessible terminal olefin reacts site-selectively with one of the olefins next to the pro-chiral center, giving rise to desymmetrization.[5] Therefore, the interaction between the substituents at the pro-stereogenic center and the chiral Mo akylidene is likely responsible for the stereochemical outcome, as the steric bulk of these substituents influences the sense and level of asymmetric induction. The diminished enantioselectivity observed in entry 3 is probably the result of competing initiation at the various terminal olefinic sites.[5]

The binaphtholate complex **3** is the optimal catalyst for the synthesis of six-memberd cyclic ethers through ERCM of trienes (Scheme 2).[6, 7] Chiral dihydropyrans with different substitution patterns can be obtained from trienes bearing variable olefinic side chains.

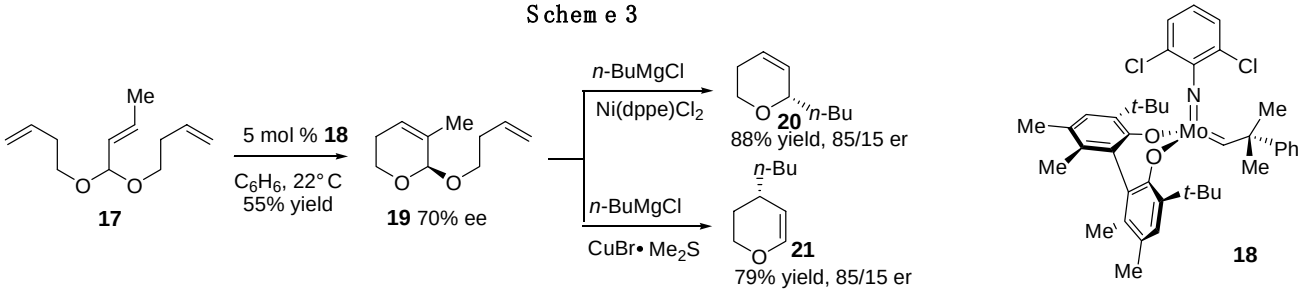
Scheme 2



13 **14** 98% yield, >99/1 er **15** **16** 93% yield, 96/ 4 er

Interestingly, the more Lewis acidic catalyst **18** emerges as the most effective catalyst for the enantioselective metathesis reaction of triene acetals (Scheme 2).[8] Although the selectivity is lower in these systems, the cyclized product allows for further functionalization to access dihydropyrans substituted at various sites. Treatment of chiral acetal **17** with Grignard reagents in the presence of different metal catalysts affords 2- or 4-substituted chiral dihydropyrans (**20**, **21**) with high regioselectivity and no loss of enantiomeric composition.

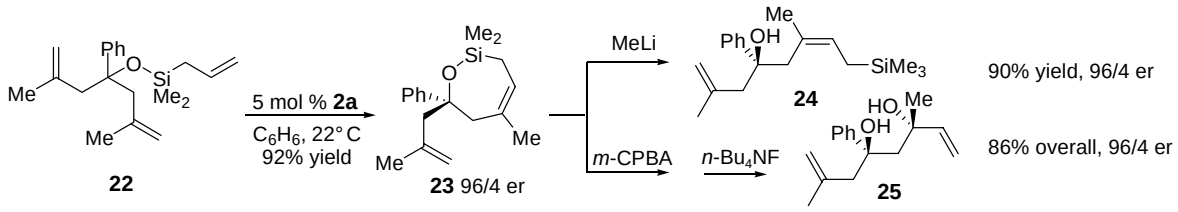
Scheme 3



17 **19** 70% ee

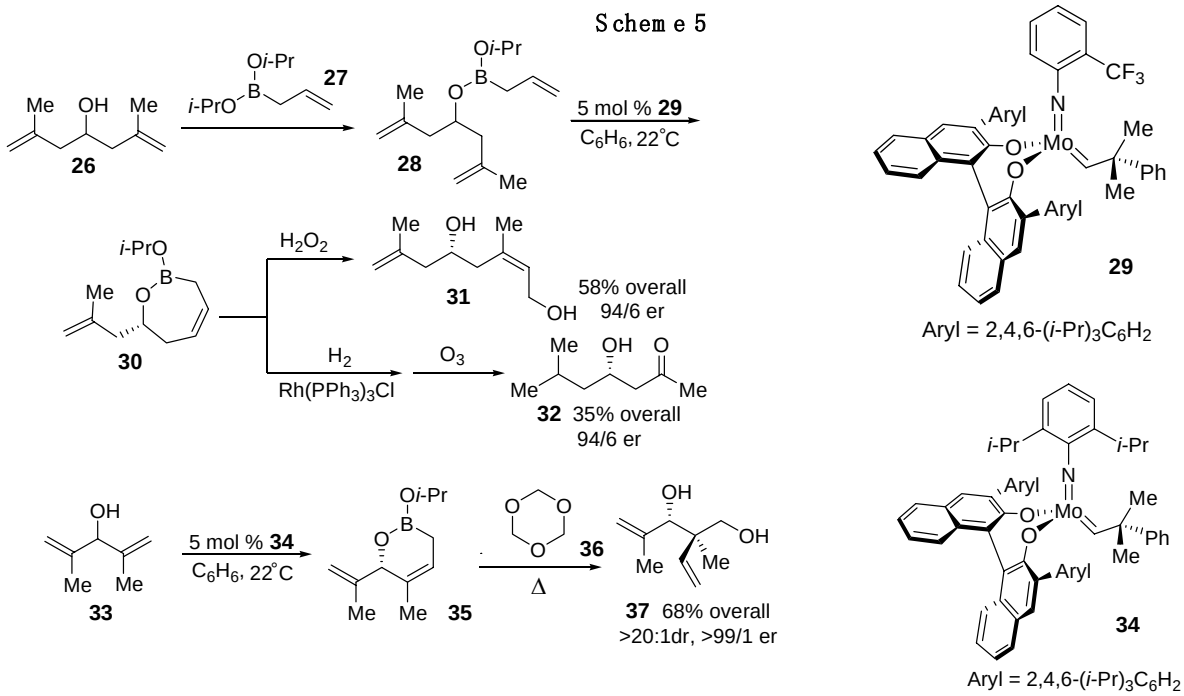
Chiral cycles bearing temporary heteroatom tethers can serve as precursors of acyclic chiral compounds. Siloxy triene substrates easily undergo ERCM to afford chiral tertiary cyclic ethers (Scheme 4).[9] Further manipulation of the enantiomerically enriched products can afford both chiral tertiary alcohols and diols, which are not easily accessible via other methods.[10]

Scheme 4



Allylboronates can also be employed as temporary tethers. Hydroxy diene **26** can be first converted to allylboronate **28**, followed by desymmetrization to afford the chiral cyclic allylboronate **30**, that can be transformed into diols and β-hydroxyl ketones (Scheme 5, **30** → **31**, **32**). [11] More interestingly, diols that bear a quaternary chiral center can be accessed by allylation of the cyclic allylboronates (**35** → **37**).

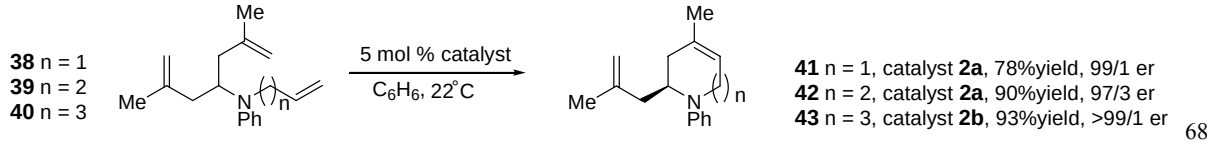
Scheme 5



Synthesis of N-Containing Cyclic Compounds

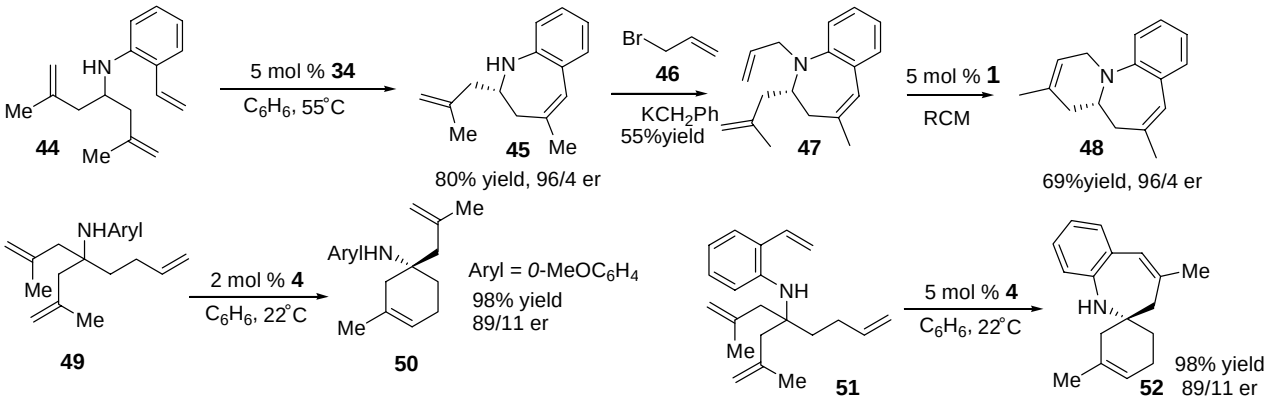
Amines are common building blocks in many biologically active agents.[12] ERCM offers a unique approach to the catalytic synthesis of chiral amines. Six-, seven- and even eight-membered cyclic aryl tertiary amines can be obtained from trienes through this method in excellent yield and er (Scheme 6).[12]

Scheme 6



Enantioselective synthesis of secondary amines is of particular interest, since they can be functionalized in a variety of ways. However, their preparation via metathesis is challenging because the secondary amine group may lead to deactivation or decomposition of the Mo catalyst. [13] Fortunately, a series of trienes bearing a secondary aryl amine group can undergo ERCM (Scheme 7) to afford the enantiomerically enriched cyclic amines (**44** → **45**, **49** → **50**). [13] Cyclic secondary amines can be easily converted to polycyclic amines (**45** → **48**). Spirocyclic amines can be obtained from corresponding achiral tetraenes (**51** → **52**). Although the enantioselectivity is not always high in these reactions, ERCM provides a method of significant importance to prepare amines, given the paucity of other effective asymmetric methods.

Scheme 7



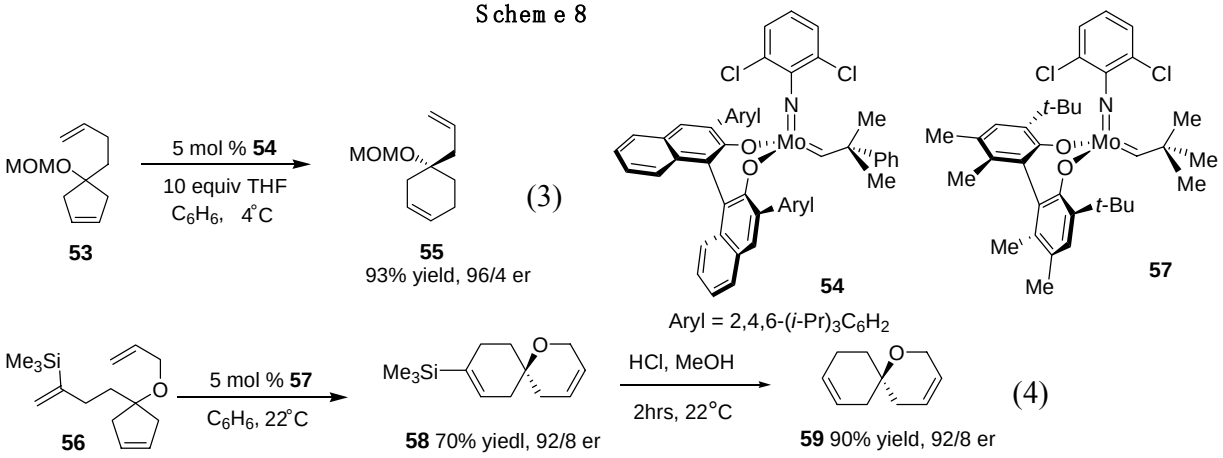
DESYMMETRIZATION OF CYCLIC DIENES AND POLYENES VIA ERRM

Strained cycloalkenes are commonly used monomers for ROMP. [14] The relief of ring strain is the thermodynamic driving force for the polymerization. [14] A cyclic olefin can undergo metathesis intramolecularly with another olefinic site in the substrate allows for the construction of a new ring with lower strain. This strain-relief ring-opening metathesis/ring-closing metathesis is collectively described as ring rearrangement metathesis (RRM). [3b] Not surprisingly, enantioselective RRM (ERRM) can give rise to desymmetrization of achiral cyclic dienes and tetraenes.

Desymmetrization of Monocycloalkenes via ERRM

As depicted in Scheme 8, chiral carbocyclic tertiary ethers can be synthezied from achiral cyclopenteneyl ethers through enantioselective RRM in high yield and er (eq 3).[15] Chiral spirocycles can also be obtained from trienes through ERRM (eq 4).[15] Similar products cannot be access through enantioselevtive RCM of polyenes, probably due to the facile reformation of cyclopentene. [15]

Scheme 8

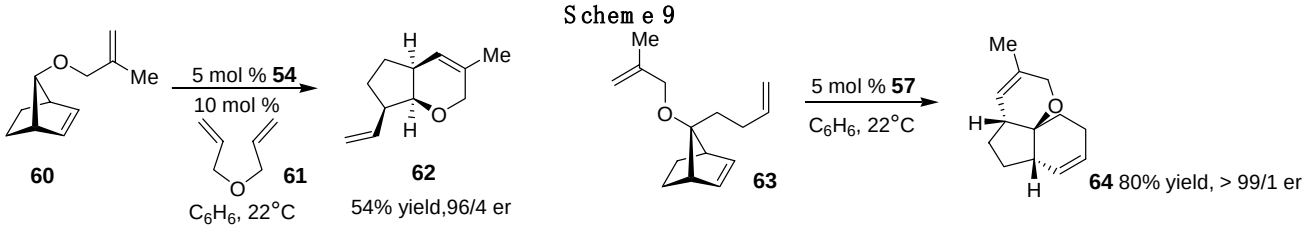


Desymmetrization of Norbornenes via ERRM

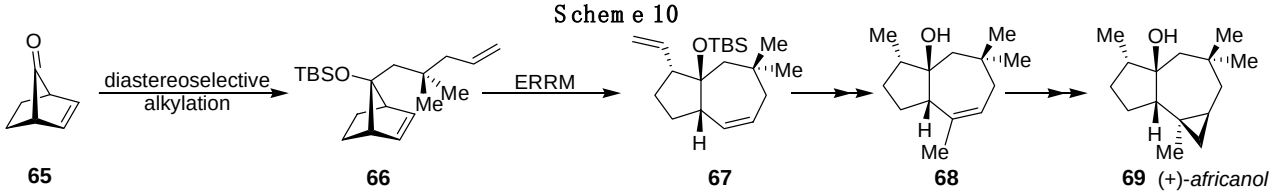
Highly strained norbornenes bearing one or more olefinic side chains can undergo RRM to afford complex polycyclic compounds. Upon treatment with chiral Mo catalysts, meso norbornene substrates undergo ERRM, rapidly affording chiral polycycles (Scheme 9).[16]

ERRM of norbornene was utilized as the key step in the recently reported formal synthesis of (+)-africanol **69** (Scheme 10)[16]. The metathesis proceeded in 97% yield and 93/7 er to provide cycloalkene **67**, a key intermediate in the synthesis, demonstrating that ERRM can offer rapid, efficient and stereoselective construction of synthetically useful molecules.

Scheme 9



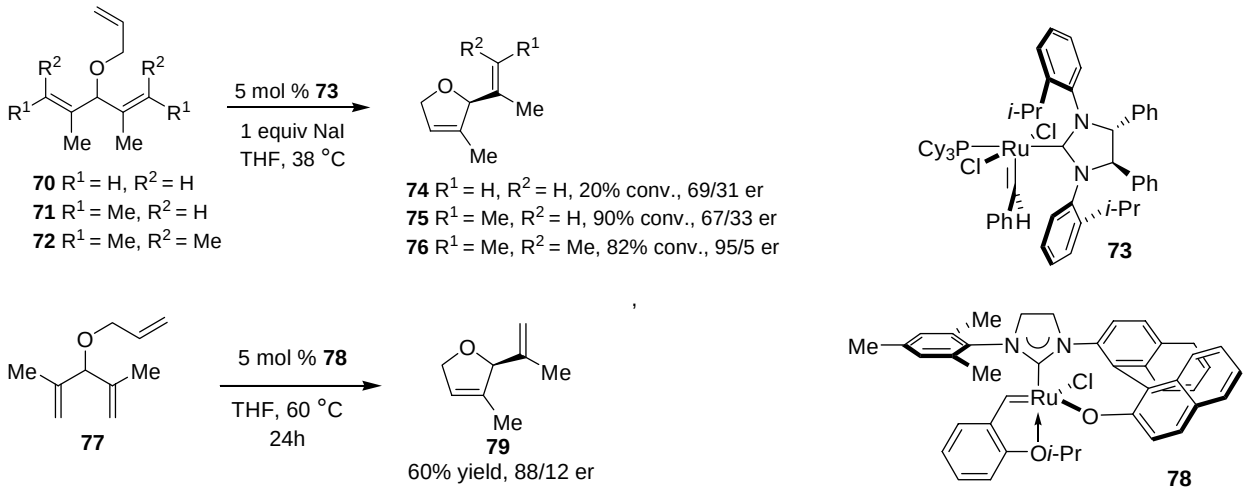
Scheme 10



RECENT DEVELOPMENT OF CHIRAL RUTHENIUM CATALYSTS

Ruthenium catalysts for olefin metathesis are much more air stable compared to molybdenum complexes and have complementary functional group tolerance.[4] Therefore, ruthenium catalysts for enatioselective olefin metathesis are expected to have tremendous potential utility. Recently, two classes of chiral ruthenium based catalysts have been developed (Scheme 11).[17, 18] Chiral N-heterocyclic carbene complexes of ruthenium (represented by **73**) exhibit high enantioselectivity (up to 95/5 er) in the desymmetrization of triene **72**.[17] Chiral bidentate imidazolinium ligand based ruthenium complexes (represented by **78**) also catalyze enantioselective RCM.[18] However, these chiral ruthenium catalysts are not generally effective.

Scheme 11



70 R^1 = H, R^2 = H
71 R^1 = Me, R^2 = H
72 R^1 = Me, R^2 = Me

74 R^1 = H, R^2 = H, 20% conv., 69/31 er
75 R^1 = Me, R^2 = H, 90% conv., 67/33 er
76 R^1 = Me, R^2 = Me, 82% conv., 95/5 er

73

77

79
60% yield, 88/12 er

78

CONCLUSION AND OUTLOOK

In the presence of chiral molybdenum catalysts, the desymmetrization of achiral dienes and polyenes via ERCM and ERRM affords products in generally high yield with high enantioselectivity. By choosing substrates judiciously, a variety of structural motifs of particular importance can be accessed. These methods allow for convenient preparation of enantiomerically enriched cyclic and polycyclic compounds that cannot be easily accessed by alternative approaches. Achieving satisfactory selectivity, recently developed chiral Ru catalysts are expected to provide complementary reactivities as well as selectivities. With an increasing number of effective catalysts and a broadened scope of substrates, enantioselective olefin metathesis will be expected to provide efficient asymmetric methods to access more versatile chiral compounds.

REFERENCES

1. Grubbs, R. H.; Chang, S. *Tetrahedron*, **1998**, *54*, 4413-4450.
2. Fürstner, A. *Angew. Chem. Int. Ed.*, **2000**, *39*, 3012-3043.
3. (a) Han, S.; Chang, S. General Ring-Closing Metathesis. In *Handbook of Metathesis*. Grubbs, R. H. Ed.; Wiley: New York, 2003. pp. (b) Randl, S.; Blechert, S. Tandem Ring-Closing Metathesis. In *Handbook of Metathesis*. Grubbs, R. H. Ed.; Wiley: New York, 2003. (c) Hoveyda, A. H. Catalytic Asymmetric Olefin Metathesis. In *Handbook of Metathesis*. Grubbs, R. H. Ed.; Wiley: New York, 2003.
4. Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592-4633.
5. 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. 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.
7. 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
8. Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553-9559.
9. Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868-2869.
10. (a) 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.
11. Lernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2004**, *60*, 7345-7351.
12. Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991-6997.
13. Dolman, S. J.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2003**, *5*, 4899-4902.
14. Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907-915.
15. Teng, X.; Cefalo, D.R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002,** *124,* 10779-10784
16. Weatherhead, G. S.; Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5805-5809.
17. Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225-3228.
18. VanVeldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502-12508.