Zr-Catalyzed Kinetic Resolution of Aliphatic Cyclic Allylic Ethers. Carbocycles to Heterocycles by Ru- and Mo-Catalyzed Ring-Opening and Ring-Closing Metathesis

Jeffrey A. Adams, J. Gair Ford, Paul J. Stamatos, and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

Received August 19, 1999

The Zr-catalyzed kinetic resolution of aliphatic allylic ethers derived from five-, six-, seven-, and eight-membered ring allylic alcohols is reported. The level of resolution efficiency varies as a function of ring size and substitution pattern of the pendant alkene. The metal-catalyzed transformation of the above unsaturated ethers to dihydrofurans is also disclosed. Seven- and eight-membered ring substrates are readily converted to furans in the presence of 10 mol % Ru catalyst **16**. In contrast, the less reactive cyclopentenol systems demand the more potent Mo-based metathesis catalyst **3**. The selectivity and reactivity patterns in the Zr-catalyzed process and the Ru- or Mo-catalyzed reactions differ from the previously reported reactions of the related styrenyl ethers.

Introduction

Recent disclosures from these laboratories have outlined catalytic procedures that lead to the enantioselective formation of 2-substituted chromenes.[1] As the example in Scheme 1 indicates, we have demonstrated that functionalized unsaturated carbocycles can be efficiently resolved by Zr-catalyzed asymmetric ethylmagnesation;[2] the resulting optically pure dienes, may then be converted to 2-substituted chromenes by a Mo-catalyzed tandem ring-opening/ring-closing metathesis[3] sequence (ROM/RCM). We have utilized the Zr- and Mo-catalyzed process en route to the first enantioselective total synthesis of the antihypertensive agent (*S*,*R*,*R*,*R*)-nebivolol (Scheme 1).[4]

As illustrated in Scheme 2, we became interested in synthesizing chiral dihydrofurans in the optically pure form by utilizing the tandem Zr-catalyzed resolution[5]/Ru- or Mo-catalyzed metathesis process on cycloalkenes bearing *aliphatic* ether units. Our interest was based on the fact that, unlike chiral dihydropyrans[6] and as a result of well-established mechanistic principles, Zr-catalyzed enantioselective alkylation cannot be used in the catalytic kinetic resolution of dihydrofurans.[7]

Initially, it was not clear to us how readily aliphatic ethers would undergo intramolecular metathesis as compared with styrenyl substrates (e.g., **1**). The main reason that we investigated the chemistry of styrenyl ethers was due to the groundbreaking investigation of Crowe on the ease of Mo-catalyzed cross-metathesis between aliphatic and aryl alkenes (vs two aliphatic olefins).[8] With an all-aliphatic system, especially with substrates that bear terminal alkenes, potential lack of site- or chemoselectivity could lead to no reaction or substrate oligomerization (see below).

The results described herein illustrate that allylic ethers of the type shown in Scheme 2 do readily undergo metathesis reactions and that these processes, which are inherently reversible, are governed by subtle structural attributes of the substrate and the product. In addition, we illustrate that some, but not all, of the diene precursors can be resolved by Zr-catalyzed alkylation; these processes are also strongly influenced by structural variations.

Results and Discussion

Zr-Catalyzed Kinetic Resolution of Cycloalkenyl Ethers. To initiate our studies, we examined the Zr-catalyzed kinetic resolution of various allylic ethers derived from several cycloalkenols. As illustrated in entry 1 of Table 1, cyclopentenyl substrate **6** is resolved with only modest levels of selectivity ($k_{rel} = 3.7$). This observation is consistent with our previous findings regarding the relative lack of efficiency in catalytic resolutions of the corresponding cyclopentenyl styrenyl ether derivatives (cf. **1** in Scheme 1).[4] However, whereas in the catalytic alkylation of the derived styrenyl ethers noticeable background reaction is observed, with **6**, <5% conversion is detected in the absence of the chiral metallocene catalyst. The k_{rel} value[9] for cyclohexenyl

(1) (a) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488−1489. (b) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S. *J. Am. Chem. Soc.* **1998**, *120*, 2343−2351.

(2) (a) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6697−6698. (b) Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097−7104. (c) For a recent reviews, see: Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262−1284. (d) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535−544.

(3) For recent reviews of catalytic 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**, *107*, 1833−1836. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.

(4) Johannes, C. W.; Visser, M. S.; Weatherhead G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340−8347.

(5) For a recent comprehensive review on metal-catalyzed kinetic resolution, see: Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 489−526.

(6) Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383−4394.

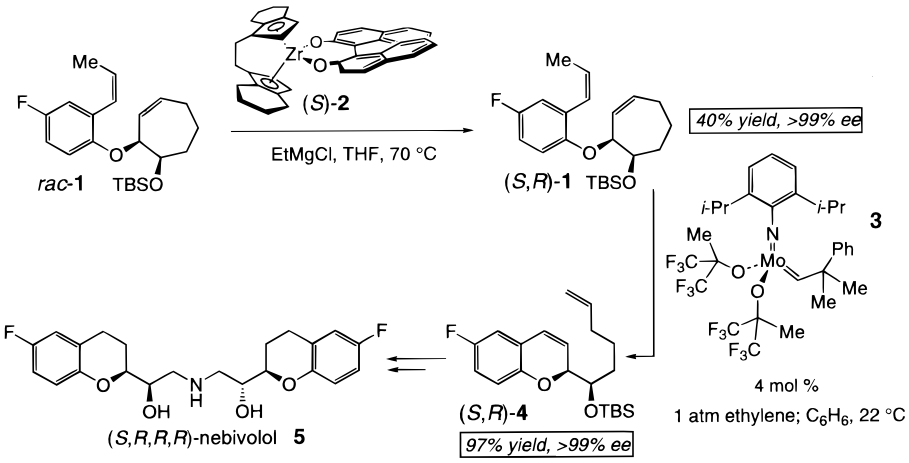
(7) (a) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123−3124. (b) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291−4298.

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

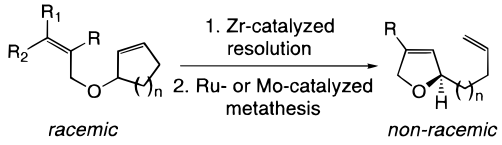
(9) Relative rates are calculated on the basis of the equation reported by Kagan. See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

10.1021/jo991323k CCC: $18.00
Published on Web 12/24/1999

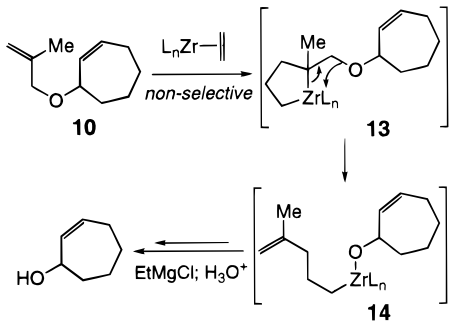
Scheme 1



Scheme 2



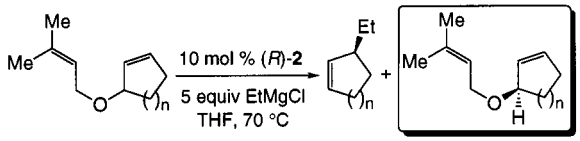
Scheme 3



substrate **7** was somewhat surprising, since we had previously found that the derived *n*-butyl ether can be resolved under similar reaction conditions with better levels of enantioselection ($k_{rel} = 6$; see below for the effect of acyclic olefin on resolution efficiency).[10] Thus, it appeared that the nature of the pendant alkoxy substituent can exert an influence on the efficiency of the kinetic resolution.

The data shown in entries 3−5 of Table 1 further indicate that a subtle structural modification within the substrate can significantly alter the efficiency of the Zr-catalyzed kinetic resolution. *In contrast to cyclohexenyl* ***7*** *(entry 2), the derived cycloheptenyl system* ***8*** *can be effectively resolved with excellent efficiency ($k_{rel} > 25$); similar excellent levels of selectivity are detected with the isomeric* ***9***. However, catalytic resolution of **10**, which structurally differs with **9** in that substrate **10** bears a less substituted pendant alkene, is less efficient ($k_{rel} = 2.8$). Two critical observations regarding the reaction of 1,1-disubstituted olefin **10** merit mention: (i) Similar to substrates for entries 1−4, **10** undergoes <5% alkylation in the absence of the chiral metallocene catalyst (results are due to Zr-catalyzed alkylation). (ii) Unlike reactions depicted in entries 1−4 of Table 1, in the catalytic resolution of **10** the parent cycloheptenol is obtained as a side product (31% after silica gel chromatography). These findings suggest that competitive formation of

Table 1. Zr-Catalyzed Kinetic Resolution of Cycloalkenyl Allylic Ethers[a]



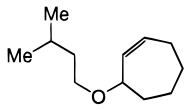
entry	substrate	conv (%);[b] time (h)	k_{rel}[c]
1	**6**	57; 3	3.7
2	**7**	52; 5	1.9
3	**8**	***53; 6***	***>25***
4	**9**	***48; 5***	***>25***
5	**10**	84; 4	2.8
6	**11**	39; 7	2.2
7	**12**	73; 6	3.2

[a] Reaction conditions: 10 mol % (*R*)-**2**, 5 equiv EtMgBr, THF, 70 °C, 4−6 h. [b] Conversion determined by GLC with internal standard (entries 1−6) or by 400 MHz ^{1}H NMR. [c] Value for ee determined by GLC (ALPHADEX 120 chiral column by SUPELCO, entries 1, 3−6) or by GLC (CHIRALDEX, CDGTA) of the derived bisepoxides (entry 2) or analysis of the 400 MHz ^{19}F NMR spectrum of the derived (*R*)-MPTA esters in comparison with authentic and racemic materials (entry 7).

(10) Visser, M. S.; Harrity, J. P. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 3779−3780.

zirconacyclopentane **13** (Scheme 3) occurs in the presence of the disubstituted olefin. Because reaction at the acyclic alkene is not likely to be enantiodifferentiating (too remote from the stereogenic center), kinetic resolution suffers in efficiency.

To gain further insight regarding the above processes, we examined the Zr-catalyzed resolution of allylic ether **15**, which differs from diene **8** in that it lacks the less



15 (k_{rel} = 5.5)

reactive acyclic trisubstituted alkene. Remarkably, *in the absence of the trisubstituted olefin, the catalytic resolution proves to be significantly less discriminating* (k_{rel} = 5.5 for **15** vs >25 for **8**).[11] These data clearly indicate that in certain cases, a "spectator alkene" may well be involved in the enantioselective alkylation; the exact nature of this participation, however, is unclear at the present time.

The catalytic resolution in entries 6 and 7 of Table 1 show that the positive influence of the trisubstituted alkene does not carry over to cyclooctenol derivatives or to the more substituted cycloheptenol systems. In connection to the catalytic resolution of silyl ether **12**, it is worth mentioning that the corresponding anti isomer of styrenyl ether **1** (Scheme 1) is resolved with k_{rel} >25. These data further underline the strong dependence of the asymmetric alkylation on substrate substituents.

Despite the aforementioned limitations in the Zr-catalyzed resolution, we began to investigate the conversion of this class of compounds to substituted dihydrofurans (Scheme 2). We judged that, because there exists a number of available methods for the enantioselective synthesis of cyclic allylic alcohols,[12] with the availability of an efficient catalytic metathesis method, the derived optically pure dihydrofurans would also be rendered readily accessible.

Ru-Catalyzed Metathesis Reactions of Cycloheptenyl and Cyclooctenyl Ethers. First, we investigated the possibility of converting various allylic ethers derived from cycloheptenol and cyclooctenol to the corresponsing heterocycles. For reasons that will be discussed below, these substrates are expected to undergo reaction more readily than their cyclopentenyl or cyclohexenyl counterparts. As depicted in Table 2, allylic ethers of varied substitution patterns are readily converted to the derived dihydrofurans in the presence of 10 mol % $(PCy_3)_2Cl_2$-Ru=C(H)Ph[13] (**16**) in 55−95% yield within 24 h at 22 °C. Thus, heterocycles bearing di- or trisubstituted olefins can be readily synthesized through this catalytic protocol.

Table 2. Ru-Catalyzed Conversion of Medium-Ring Carbocycles to Dihydrofurans[a]

entry	substrate	product	yield (%)[b]
1	**17** n =1	**19** n =1	89
2	**18** n = 2	**20** n = 2	89
3	**8** n =1		89
4	**11** n = 2		55
5	**10** n =1	**22** n =1	88
6	**21** n = 2	**23** n = 2	93
7	**9** n =1		75
8	**24** n = 2		79
9	**25**	**26**	95
10	**27**	**28**	76

[a] Conditions: 10 mol % **16**, CH_2Cl_2, ethylene (1 atm), 22 °C, 24 h. [b] Yields of purified products after silica gel chromatography.

Three important points in relation to the reactions in Table 2 merit discussion: (i) With substrates that contain a terminal olefin (e.g., **17**) transformation is likely initiated through the formation of a terminal metal-carbene, followed by reaction with the cyclic alkene via the derived metallacyclobutane. With starting materials that contain more highly substituted olefins (e.g., **8**−**10**) the transformation likely commences by ring-opening metathesis (ROM) at the cycloalkenyl π system and subsequent ring closure by reaction with the pendant acyclic alkene.[14] This mechanistic scenario is based on the expected reactivity of a disubstituted cycloalkene vs that of an acyclic trisubstituted or 1,1-disubstituted

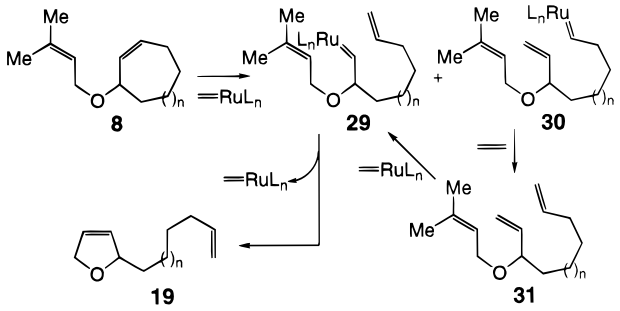
(11) For an example of a catalytic reaction where a pendant acyclic π cloud directs the addition of the metal complex to a cyclic alkene to significantly facilitate the rate of the reaction, see: Trost, B. M.; Tasker, A. S.; Ruther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670−672.

(12) (a) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708−710. (b) Faller, J. W.; Tokunaga, M. *Tetrahedron Lett.* **1993**, *34*, 7359−7362. (c) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547−5550. (d) Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **1997**, *36*, 6425−6428. (d) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831−1834. (e) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945−2948. (f) Andrus, M. B.; Asgari, D.; Sclafani, J. A. *J. Org. Chem.* **1997**, *62*, 9365−9368. (g) DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 2633−2636. (h) Sodergren, M. J.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 7577−7580. (i) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337−6350. For Pd-catalyzed enantioselective synthesis of cyclic allylic esters, see: (j) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320−10321.

(13) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.

(14) For Mo-catalyzed ROM reactions, involving five-membered ring olefins, see: (a) Sita, L. R.; Lyon, S. R. *J. Am. Chem. Soc.* **1993**, *115*, 10374−10375. For related Ru-catalyzed ROM/RCM reactions, see: (b) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640 and references therein. For representative recent reports on Ru-catalyzed ROM, see: (c) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478−1479. (d) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257−259.

Scheme 4

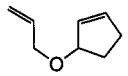
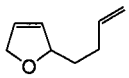
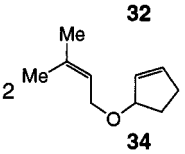
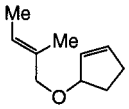
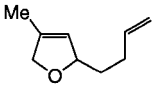
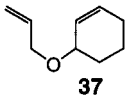
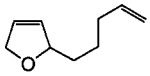
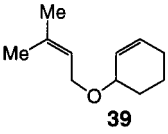
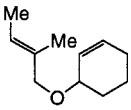
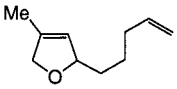


olefin; this paradigm is also consistent with the results of extensive mechanistic studies on the related styrenyl systems (cf. **1**, Scheme 1).[1b] (ii) The Ru-catalyzed transformations must be carried out under an atmosphere of ethylene; otherwise, reactions are either far less efficient (~10% conversion) and/or afford substantial amounts of product dimer.[15] The reasons for the positive influence of ethylene may be summarized as follows: (a) Under ethylene atmosphere the more reactive (less sterically demanding) $L_nRu{=}CH_2$ serves as the active catalyst. (b) The Ru-carbene derived from the terminal alkene of the product reacts more rapidly with ethylene than with another molecule of the product (minimum dimerization). (c) Catalytic ROM of cycloalkenes (e.g., **8** or **11**) are likely nonregioselective (**29** and **30**, Scheme 4). Thus, in the absence of ethylene, the undesired carbene **30** may either reclose to **8** (presumably a slow process, especially in the case of cyclooctenes) or it might oligomerize. In the presence of ethylene, Ru-carbene **30** quickly reacts with ethylene to afford **31**. As shown in Scheme 4, further reaction with the active Ru-methylidene at the alternative alkene site affords the desired metal-carbene **29**, leading to the formation of **19**; the formation of **19** is thermodynamically irreversible. (iii) The reactions in Table 2 are under thermodynamic control, where heterocyclic products should be able to revert back to the cycloalkenyl substrates. The reason for the favorable equilibrium likely lies with the formation of the less strained five-membered ring heterocycles.[16] In addition, where the heterocyclic product contains a trisubstituted cyclic olefin, reversal is discouraged as a result of the lack of reactivity of the product alkene.

Ru- and Mo-Catalyzed Metathesis Reactions of Cyclopentenyl and Cyclohexenyl Ethers. Next, we turned our attention to the reaction of smaller cycloalkenes. As depicted in entry 1 of Table 3, when cyclopentenyl substrate **32** is treated with 10 mol % Ru catalyst **16** (CH_2Cl_2, 22 °C), dihydrofuran **33** is obtained in 75% yield after silica gel chromatography. However, under identical conditions, but with diene **34** as the starting material (entry 2), the reaction proceeds only to 33% conversion after 24 h. With the more reactive Mo-based Schrock complex[17] 72% conversion is attained (→ **33**). An even larger reactivity difference is observed in reactions of diene **35** (entry 3); whereas with Ru catalyst **16** only 21% conversion to **36** is detected, with Mo complex **3**, reaction proceeds to completion and **36** is isolated in 93% yield after silica gel chromatography. The reactions with cyclohexenyl substrates (entries 4−6) are inefficient or do not proceed at all even in the presence of the more potent Mo complex **3**. The latter findings are in contrast to the reactions of the corresponding styrene ethers; in such cases, although the Ru catalyst **16** proves ineffective, reactions with **3** proceed smoothly.[1b]

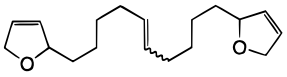
The inefficiency of **37** → **38** is partly due to the lack of the reactivity of the relatively strain-free cyclohexene moiety (slow reaction with the neighboring terminal metal-carbene or -alkylidene). In addition, control experiments indicate that **38** readily reverts back to **37** under the reaction conditions by a similar sequence of transformations: treatment of **38** with 5 mol % **3** (22 °C, 37 h) leads to the formation of a ~2:1 mixture of **37**/**38** (as judged by 400 MHz ^{1}H NMR). A similar equilibrium does not exist between **33** and **32** (reaction of **32** proceeds to completion). It is plausible that, whereas there is little

Table 3. Ru- and Mo-Catalyzed Conversion of Small Carbocycles to Dihydrofurans[a]

entry	substrate	product	yield (%) Ru cat.	yield (%) Mo cat.
1	 **32**	 **33**	75[b]	--
2	 **34**		(33)[c]	(72)
3	 **35**	 **36**	(21)	93[b]
4	 **37**	 **38**	(24)	(36)
5	 **39**		NR	(15)
6	 **40**	 **41**	NR	NR

[a] Conditions: See Table 2 for Ru-catalyzed reactions. 5 mol % **3**, C_6H_6, ethylene (1 atm), 22 °C, 20 h. [b] Yields of purified products. [c] Numbers in parentheses refer to conversions (by 400 MHz ^{1}H NMR).

(15) The dimer we observe is the cross-metathesis product from reaction of the Ru-carbene (or Mo-alkylidene) derived from the terminal olefin of one product molecule with another product molecule through its terminal alkene. The example shown below is illustrative (dimer of **19**).

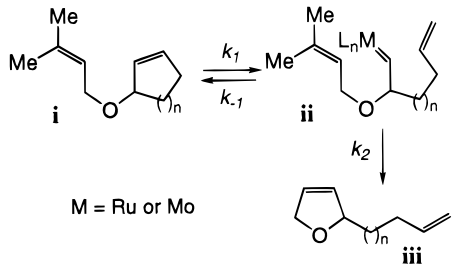


"dimer" derived from **19**

(16) Calculations carried out at the BP/DN**//PM3 level indicate that whereas dihydrofurans derived from cyclopentenyl, cycloheptenyl, and cyclooctenyl ethers are thermodynamically lower in energy, products from cyclohexenyl substrates are higher in energy and the reaction is thus thermodynamically disfavored.

(17) (a) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287−2289. (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.

Scheme 5

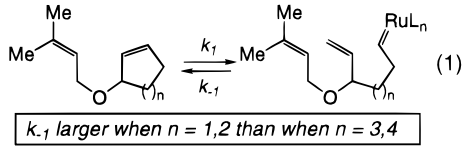


k_{-1} larger when n = 1,2 than when n = 3,4
k_2 >> k_{-1} when n = 3,4 than when n = 1,2
k_2 larger when M = Mo than when M = Ru

or no energetic difference between the carbocycle in **37** and the heterocycle in **38**, the furan ring in **33** bears less strain than the cyclopentenyl unit of **32**. Indeed, molecular mechanics calculations support this contention.[16] Cyclohexenyl substrates **39** and **40** are unreactive, or slow to react, in the presence of the less potent catalyst **16**, likely because of the relative inertness of the cyclohexenyl olefins toward catalytic ROM. With the more reactive Mo catalyst **3**, as illustrated in Scheme 5 (n = 2), the ring-opened product(s) (e.g., **ii**) likely revert back to the starting cyclohexene before reaction of the metal-alkylidene with the trisubstituted olefins. This paradigm accounts for the higher level of reactivity of styrenyl ethers of cyclohexenol; the Mo-alkylidene from the catalytic ROM reacts more readily with an electronically matched styrenyl alkene than an aliphatic olefin.[8]

Variations in Reactivity as a Function of Size of Carbocyclic Ring. Similar arguments can be made for the difference in the efficiency of the reactions of cyclopentenyl substrate **34** and its larger ring analogues **8** and **11** (entries 3−4, Table 2); the same applies for reactions of **35** vs that of **9** and **24** (entries 7−8, Table 2). The Ru-carbene intermediate (ROM product **ii**, Scheme 5) more readily reverts back to a five-membered (n = 1, Scheme 5) than a seven- or an eight-membered ring (n = 3 or 4). That is, in reactions shown in Table 2, reversal to the starting material (**ii** → **i**, when n = 3, 4) is more sluggish than, or at least kinetically competitive with, RCM with the neighboring alkene to afford the desired product.

Another reason for the lower reactivity of cyclopentenyl substrates, compared to the reactions in Table 2, is in relation to the reaction of ethylene with the ROM products. As mentioned before, both regioisomeric Ru-carbenes or Mo-alkylidenes derived from catalytic ROM of the larger rings may react with ethylene to afford a triene, which can then be converted to the desired product (e.g., **30** → **31** → **29** → **19** in Scheme 4). As was discussed above, such capping of the unwanted Ru-carbene or Mo-alkylidene results in a more efficient formation of the desired heterocycle. Trapping of the undesired alkylidene or carbene regioisomer is less competitive with cyclopentenyl substrates, as reclosure is more facile for entropic reasons (eq 1). The higher conversion with the more



(1)

k_{-1} larger when n = 1,2 than when n = 3,4

reactive Mo catalyst **3** in reactions of **34** and **35** is likely because a larger fraction of Mo-alkylidene (vs the less potent Ru-carbene) obtained from ROM undergoes RCM with the more substituted olefin (k_2 larger for M = Mo than M = Ru in Scheme 5).

Conclusion

We report, for the first time, the Zr-catalyzed kinetic resolution of allylic ethers of carbocyclic allylic alcohols. Although certain cycloheptenyl substrates resolve with excellent efficiency, the related five-, six-, and eight-membered ring substrates are resolved with moderate levels of selectivity. Such levels of efficiency in the Zr-catalyzed resolution differ from those observed for the styrenyl ethers of similar cycloalkenols. In addition, we disclose the metal-catalyzed conversion of the aforementioned allylic ethers to 2-substituted dihydrofurans. These catalytic transformations can be readily effected through Ru- or Mo-catalyzed metathesis; in cases where higher levels of olefin substitution are involved, the Mo-based catalyst **3** proves to be significantly more efficient. In these metathesis processes, reactivity trends differ from those of the styrenyl substrates as well. Notable is the facility with which styrenyl ethers of cyclohexenols, unlike the related allylic ethers (Table 3, entries 4−6), are readily converted to the derived heterocycles; this reactivity difference may well be linked to the better electronic compatibility of styrenyl and aliphatic alkenes (vs two aliphatic olefins).

Research toward effecting catalytic and enantioselective conversion of allylic ethers to heterocycles through chiral metathesis catalysts[18] by either resolution or desymmetrization reactions is in progress.

Experimental Section

Enantiomeric ratios were determined by GLC with either a CHIRALDEX G-TA (30 mm × 0.25 mm) chiral column by Astec or an ALPHA-DEX GTA (20 mm × 0.25 mm) chiral column by Alltech Assoc. Microanalyses were performed by Robertson Microlit Laboratories (Madison, NJ). High-resolution mass spectra were obtained at the Mass Spectrometry Facility of the University of Illinois (Urbana−Champaign, Illinois).

All reactions were conducted in oven- (135 °C) and flame-dried glassware under an inert atmosphere of dry argon. Tetrahydrofuran and benzene were distilled from sodium metal/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Ethylmagnesium chloride was prepared from ethyl chloride from Aldrich and Mg turnings from Strem that were washed with 20% HCl/ethanol prior to use. (*R*)-(ebthi)-Zr-binol was prepared by published methods.[19] Nonracemic (ebthi)$ZrCl_2$ and (ebthi)Zr-binol were stored under argon in a glovebox. $(PCy_3)_2Cl_2Ru{=}CHCPh$ (**16**) was prepared by the method of Grubbs.[13] $Mo(CHCMe_2Ph)(N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))OCMe(CF_3)_2)_2$ (**3**) was prepared by the method of Schrock.[17] The requisite allylic alcohols were prepared according to published procedures;[10] subsequent alkylation of these unsaturated

(18) (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.; 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) La, D. S.; Ford, J. G.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, in press.

(19) (a) Wild, F. R. W. P.; Waiucionek, M.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1985**, *288*, 63−67. (b) Diamond, G. M.; Rodewald, S.; Jordan, R. F. *Organometallics* **1995**, *14*, 5−7 and references therein.

alcohols afforded the desired allylic ethers. Allylic ethers **12**, **25**, and **27** were synthesized through protocols reported previously.[4]

Representative Procedure for Zr-Catalyzed Kinetic Resolution. Allylic ether **8** (0.562 mmol) was weighed into a 5 mL flame-dried round-bottom flask along with 50 mg of dodecane as an internal standard. After addition of THF (0.30 mL), freshly prepared EtMgCl was added (1.54 mL of a 1.83 M solution in THF, 2.81 mmol). A t_0 aliquot was removed, quenched with wet diethyl ether, and diluted with water, and the resulting mixture was washed twice with diethyl ether. The combined ether layers were passed through a silica plug to give a solution suitable for GLC analysis. At this point, (*R*)-(ebthi)Zr-binol (35.8 mg, 0.056 mmol) was added to the reaction mixture, and a flame-dried reflux condenser was quickly fitted onto the reaction vessel. The flask was lowered into a preheated 70 °C oil bath, and the reaction mixture was stirred at this temperature for 6 h, at which time GLC analysis of an aliquot, treated as above, showed that the reaction had proceeded to 58% conversion. The reaction mixture was cooled to 0 °C in an ice bath, and excess EtMgCl was quenched by the dropwise addition of 1 mL of a 1.0 M aqueous solution of HCl. The mixture was diluted with distilled water (10.0 mL) and washed with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to yield a clear yellow oil. Silica gel chromatography with 100:1 pentane/Et_2O afforded the recovered starting material (0.212 mmol, 92% yield based on 58% conversion).

Representative Procedure for Ru-Catalyzed Reactions. Allylic ether **8** (0.26 mmol) was weighed into a 10 mL flame-dried round-bottom flask and dissolved in CH_2Cl_2 (2.60 mL). Ru complex **16** (23.6 mg, 0.028 mmol) was added in two equal portions (second portion added after 12 h). The reaction vessel was carefully evacuated under vacuum and refilled with ethylene three times; it was then kept under an atmosphere of ethylene (balloon). The reaction was allowed to stir at 22 °C for a total of 21 h. The reaction was quenched by the addition of ~200 μL of undistilled ethyl vinyl ether. After the volatiles were removed under vacuum, the unpurified reaction mixture was loaded onto a silica gel column and eluted with 50:1 pentane/Et_2O to afford the dihydrofuran **19** as a colorless oil (0.23 mmol, 89% yield).

Representative Procedure for Mo-Catalyzed Metathesis. Allylic ether **35** (0.16 mmol) was weighed into a 5 mL round-bottom flask and dissolved in degassed benzene (1.60 mL) in a glovebox. Mo complex **3** (6.3 mg, 0.008 mmol, 5 mol %) was then added to the reaction mixture. The reaction vessel was subsequently removed from the glovebox and was immediately put under an atmosphere of ethylene through a balloon fitted with a needle and another smaller bore needle to purge the flask. The reaction mixture was allowed to stir at 22 °C for 20 h. After the reaction was quenched by the addition of 500 μL of MeOH, the unpurified mixture was filtered through a plug of silica gel (packed with pentane); elution with 10% Et_2O in pentane gave the desired furan **35** (0.15 mmol, 93% yield).

2-(3-Methyl-2-butenoxy)-cycloheptene (8). IR (NaCl): 2926 (s), 2854 (s), 1684 (m), 1671 (m), 1082 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82−5.72 (m, 2H), 5.36 (m, 1H), 4.01−3.88 (m, 3H), 2.19−2.09 (m, 1H), 2.02−1.83 (m, 3H), 1.71 (s, 3H), 1.65 (s, 3H), 1.66−1.46 (m, 3H), 1.35−1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 137.7, 131.5, 122.5, 79.7, 66.0, 34.1, 29.6, 28.7, 27.7, 26.9, 19.1. MS *m*/*z* (EI) 180 (M^+, 2%), 111 (M − C_5H_9, 30), 95 (M − C_5H_9O, 52), 69 (M − $C_7H_{11}O$, 100). HRMS Calcd for $C_{12}H_{20}O$: 180.1514. Found: 180.1512.

2-(*trans*-2-Methyl-2-butenoxy)-cycloheptene (9). IR (NaCl): 2924 (s), 2855 (s), 1652 (m), 1080 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82−5.71 (m, 2H), 5.47 (m, 1H), 3.95 (br d, 1H, J = 7.5 Hz), 3.86 (d, 1H, J = 11.0 Hz), 3.81 (d, 1H, J = 11.0 Hz), 2.20−2.09 (m, 1H), 2.05−1.82 (m, 3H), 1.63 (s, 3H), 1.60 (d, 3H, J = 7.0 Hz), 1.70−1.46 (m, 3H), 1.37−1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 134.3, 131.4, 123.1, 79.3, 75.6, 34.0, 29.6, 28.6, 27.8, 14.8, 14.3. MS *m*/*z* (EI) 180 (M^+, 1%), 111 (M − C_5H_9, 54), 95 (M − C_5H_9O, 78), 69 (M − $C_7H_{11}O$, 100). HRMS Calcd for $C_{12}H_{20}O$: 180.1514. Found: 180.1516.

2-(5-Hexenyl)-2,5-dihydrofuran (19). IR (NaCl): 3079 (w), 2931 (s), 2853 (s), 1641 (m), 1461 (m), 1352 (m), 1081 (s), 911 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90−5.74 (m, 3H), 5.03−4.95 (m, 1H), 4.95−4.90 (m, 1H), 4.85−4.78 (m, 1H), 4.69−4.55 (m, 2H), 2.10−2.00 (m, 2H), 1.60−1.50 (m, 2H), 1.48−1.30 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 129.8, 126.3, 114.3, 86.0, 74.9, 35.9, 33.7, 29.0, 24.8. MS *m*/*z* (EI) 150 (M^+ − 2H, 26%), 81 (M − C_4H_7O, 100), 69 (M − C_6H_{11}, 75). HRMS Calcd for $C_{10}H_{14}O$ (M-2H): 150.1045. Found: 150.1047.

2-(6-Heptenyl)-2,5-dihydrofuran (20). IR (NaCl): 2936 (s), 2848 (s), 1073 (s), 897 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90−5.74 (m, 3H), 5.02−4.95 (m, 1H), 4.95−4.89 (m, 1H), 4.85−4.77 (m, 1H), 4.69−4.55 (m, 2H), 2.08−1.99 (m, 2H), 1.60−1.48 (m, 2H), 1.48−1.20 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 129.8, 126.3, 114.2, 86.1, 74.9, 36.0, 33.7, 29.2, 28.9, 25.1. MS *m*/*z* (EI) 164 (M^+ − 2H, 25%), 81 (M − C_5H_7O, 100), 69 (M − C_7H_{13}, 30). HRMS Calcd for $C_{11}H_{16}O$ (M-2H): 164.1201. Found: 164.1201.

2-(5-Hexenyl)-4-methyl-2,5-dihydrofuran (22). IR (NaCl): 2930 (s), 2861 (s), 1445 (m), 1055 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87−5.75 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz), 5.40−5.36 (m, 1H), 5.03−4.96 (m, 1H), 4.96−4.90 (m, 1H), 4.82−4.74 (m, 1H), 4.53−4.41 (m, 2H), 2.09−2.01 (m, 2H), 1.73 (s, 3H), 1.55−1.48 (m, 2H), 1.46−1.26 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 135.9, 123.8, 114.3, 86.7, 77.7, 36.2, 33.8, 29.0, 24.8, 12.3. MS *m*/*z* (EI) 166 (M^+, 3%), 83 (M − C_6H_{11}, 100), 55 (M − $C_7H_{11}O$, 18). HRMS Calcd for $C_{11}H_{18}O$: 166.1358. Found: 166.1357.

2-(6-Heptenyl)-4-methyl-2,5-dihydrofuran (23). IR (NaCl): 2924 (s), 2855 (s), 1640 (m), 1445 (m), 1061 (s), 910 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86−5.74 (ddt, 1H, J = 17.0, 10.5, 7.0 Hz), 5.40−5.34 (m, 1H), 5.03−4.95 (m, 1H), 4.95−4.89 (m, 1H), 4.82−4.73 (m, 1H), 4.52−4.40 (m, 2H), 2.08−1.99 (m, 2H), 1.73 (s, 3H), 1.54−1.46 (m, 2H), 1.44−1.26 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 135.9, 123.8, 114.1, 86.7, 77.6, 36.3, 33.7, 29.2, 28.9, 25.1, 12.3. MS *m*/*z* (EI) 180 (M^+, 3%), 83 (M − C_7H_{13}, 100), 55 (M − $C_9H_{13}O$, 17). HRMS Calcd for $C_{12}H_{20}O$: 180.1514. Found: 180.1510.

(±)-*syn*-2-(2-Methyl-2-propenoxy)-3-(1-*tert*-butyldimethylsilyloxy)-cycloheptene (25). IR (NaCl): 3075 (w), 3043 (s), 2930 (s), 2855 (s), 1652 (m), 1476 (m), 1476 (s), 1130 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88−5.83 (m, 1H), 5.59−5.56 (m, 1H), 4.99−4.83 (2s, 2H), 3.99−3.94 (m, 4H), 2.25−2.18 (m, 1H), 2.08−1.90 (m, 2H), 1.74 (s, 6H), 1.72−1.64 (m, 1H), 1.43−1.38 (m, 1H) 0.88 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5, 111.3, 81.1, 72.8, 71.1, 35.8, 28.2, 25.8, 21.5, 19.6, 5.0, 4.6; HRMS Calcd for $C_{10}H_{14}O$ (M + 1H): 297.2172. Found: 297.2242. Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 68.64; H, 11.04.

(±)-*anti*-2-(1-*tert*-Butyldimethylsilyloxy)-5-hexenyl-4-methyl-2,5-dihydrofuran (26). IR (NaCl): 2928 (s), 2857 (s), 1106 (s), 1078 (s), 836 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (dddd, 1H, J = 17.0, 10.5, 7.0, 6.5 Hz), 5.45−5.40 (m, 1H), 4.99 (m, 1H), 4.94 (m, 1H), 4.71−4.64 (m, 1H), 4.52−4.39 (m, 2H), 3.64−3.57 (m, 1H), 2.09−1.99 (m, 2H), 1.73 (s, 3H), 1.62−1.35 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 138.0, 122.3, 115.5, 91.0, 79.2, 75.9, 35.1, 34.4, 27.0, 25.6, 19.2, 13.4, −3.3, −3.4. MS *m*/*z* (EI) 295 (M^+ − 1, 2%), 213 (M − C_5H_7O, 46), 115 ($SiMe_2{}^tBu$, 21), 73 (M − $C_{13}H_{23}OSi$, 100).

(±)-*anti*-2-(2-Methyl-2-propenoxy)-3-(1-*tert*-butyldimethylsilyloxy)-cycloheptene (27). IR (NaCl): 2951 (w), 2928 (s), 2885 (s), 2856 (s), 1671 (m), 1462 (m), 1252 (s), 1080 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87−5.81 (m, 1H), 5.60−5.55 (m, 1H), 4.98−4.85 (m, 2H), 3.98 (s, 2H), 3.86−3.83 (m, 1H), 3.69−3.64 (dt, 1H, J = 10.0, 6.5 Hz), 2.17−1.97 (m, 3H), 1.73 (s, 6H), 1.43−1.32 (m, 2H), 0.88 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.3, 133.0 112.6, 82.5, 75.2, 73.8, 38.2, 29.3, 27.0, 24.3, 20.8, 3.4, 3.9. HRMS Calcd for $C_{10}H_{14}O$ (M − 1H): 295.2172. Found: 295.2090. Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 68.60; H, 11.00.

(±)-*syn*-2-(1-*tert*-Butyldimethylsilyloxy)-5-hexenyl-4-methyl-2,5-dihydrofuran (28). IR (NaCl): 2928 (s), 2856 (s), 1252 (s), 1108 (s), 1079 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (dddd, 1H, J = 17.0, 10.0, 7.0, 6.5 Hz), 5.37 (m, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 4.77−4.71 (m, 1H), 4.51−4.40 (m, 2H), 3.66−3.58 (m, 1H), 2.12−1.96 (m, 2H), 1.75 (s, 3H), 1.60−1.27 (m, 4H), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 138.4, 121.9, 115.4, 90.8, 79.2, 75.6, 35.0, 33.0, 27.0, 26.3, 19.2, 13.4, −3.3, −3.6. MS *m*/*z* (EI) 295 ($M^+ - 1$, 4%), 213 ($M - C_5H_7O$, 28), 115 ($SiMe_2{}^tBu$, 18), 73 ($M - C_{13}H_{23}OSi$, 100).

2-(3-Butenyl)-2,5-dihydrofuran (33). IR (NaCl): 2929 (s), 2854 (s), 1077 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91−5.75 (m, 3H), 5.03 (m, 1H), 4.95 (m, 1H), 4.89−4.81 (m, 1H), 4.69−4.56 (m, 2H), 2.22−2.06 (m, 2H), 1.72−1.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 129.5, 126.6, 114.5, 85.5, 75.0, 35.1, 29.5. MS *m*/*z* (EI), 124 (M^+, 4%), 69 ($M - C_4H_7$, 100), 55 ($M - C_4H_5O$, 19). HRMS Calcd for $C_8H_{12}O$: 124.0888. Found: 124.0866.

2-(3-Butenyl)-4-methyl-2,5-dihydrofuran (36). IR (NaCl): 3078 (w), 2919 (s), 2844 (s), 1054 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (ddt, 1H, J = 17.0, 10.0, 7.0 Hz), 5.39−5.33 (m, 1H), 5.00 (m, 1H), 4.92 (m, 1H), 4.83−4.74 (m, 1H), 4.52−4.38 (m, 2H), 2.18−2.00 (m, 2H), 1.71 (s, 3H) 1.63−1.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 137.3, 124.6, 115.5, 87.3, 78.8, 36.5, 30.6, 13.4. MS *m*/*z* (EI) 138 (M^+, 2%), 83 ($M - C_4H_7$, 100), 55 ($M - C_5H_7O$, 52). HRMS Calcd for $C_9H_{14}O$: 138.1045. Found: 138.1042.

2-(4-Pentenyl)-2,5-dihydrofuran (38). IR (NaCl): 3077 (w), 2927 (s), 2852 (s), 1646 (m), 1080 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90−5.74 (m, 3H), 5.00 (d, 1H, J = 17.0 Hz), 4.94 (d, 1H, J = 10.0 Hz), 4.87−4.79 (m, 1H), 4.69−4.56 (m, 2H), 2.07 (dt, 2H, J = 7.0, 7.0 Hz), 1.62−1.40 (m, 2H), 1.34−1.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 130.8, 127.5, 115.6, 87.0, 76.1, 36.5, 34.9, 25.6. MS *m*/*z* (EI) 138 (M^+, 1%), 95 ($M - C_2H_3O$, 14), 69 ($M - C_5H_9$, $M - C_4H_5O$, 100), 55 ($M - C_5H_7O$, 7). HRMS Calcd for $C_9H_{14}O$: 138.1045. Found: 138.1050.

Acknowledgment. This research was supported by the NIH (GM-47480) and the NSF (CHE-9905806). These studies were initiated by Dr. Joseph P. A. Harrity (University of Sheffield). We are grateful to Professor Larry T. Scott for helpful discussions.

Supporting Information Available: Characterization data for all new compounds. This material is available free of charge vis the Internet at http://pubs.acs.org.

JO991323K