Zirconium-Catalyzed Kinetic Resolution of Cyclic Allylic Ethers. An Enantioselective Route to Unsaturated Medium Ring Systems

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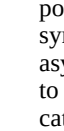
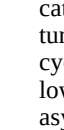
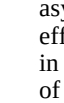
Allylic alcohols and ethers represent an important and versatile class of substrates that are often used in the preparation of a wide range of medicinally noteworthy natural products. Therefore, methods that allow the preparation of these compounds with high enantioselectivity are valuable to chemical synthesis. Within this context, the well-known Ti-catalyzed asymmetric epoxidation procedure of Sharpless[1] is often used to synthesize optically pure acyclic allylic alcohols through the catalytic kinetic resolution of easily accessible racemic mixtures.[2] However, when the catalytic epoxidation is applied to cyclic allylic substrates, reaction rates are retarded and notably lower levels of enantioselectivity are observed. Ru-catalyzed asymmetric hydrogenation has been employed by Noyori to effect resolution of five- and six-membered allylic carbinols;[3] in this instance, as with the Ti-catalyzed procedure, the presence of an unprotected hydroxyl function is required. Herein, we report the results of our initial studies on the kinetic resolution[4] of a variety of cyclic allylic ethers effected by asymmetric Zr-catalyzed carbomagnesation.[5] Importantly, in addition to six-membered ethers, seven- and eight-membered ring systems can be readily resolved by this catalytic protocol.

As illustrated in Table 1, when the benzyl ether of 2-cyclopenten-1-ol (**1**) is treated with 10 mol % of (*R*)-(EBTHI)Zr-binol[6] in the presence of 5 equiv of EtMgCl (THF, 70 °C), the recovered starting material is obtained in 52% ee (65% conversion;[7] chiral GLC). When allylic MEM ether **2**, derived from cyclohexenol, is subjected to these conditions, at 63% conversion the starting material is recovered in 50% ee (chiral GLC). In contrast, the derived *n*-butyl ether **3** is resolved more efficiently (79% ee at 63% conversion). The synthetically more useful benzyl ether **4** undergoes asymmetric ethylmagnesation and is recovered with still better enantioselection than was observed with the above substrates ((*S*)-**4** is recovered in 81% ee; chiral HPLC);[8] the latter substrate reacts faster than **2** or **3** as well (compare entries 2 and 3 with 4). Importantly, as shown in entry 5, when racemic phenyl ether **5** is treated to the Zr-catalyzed resolution conditions for 2 h, (*S*)-**5** is obtained in 97% ee at 60% conversion.[9]

The resolution data depicted in entries 8−10 in Table 1 indicate the following. (i) Disubstituted allylic ethers can be resolved through the Zr-catalyzed protocol; phenyl ether **8** is obtained in 98% ee after 55% conversion. To obtain excellent levels of enantiomeric purity in the resolution with **8** as the substrate, 20 mol % of zirconocene (*vs* 10 mol %) must be used; 15 mol % of (EBTHI)Zr-binol affords the recovered starting material in 84% ee at 60% conversion ($k_{fast}/k_{slow} = 8$);[10] with 10 mol % of precatalyst the reaction does not effectively proceed

Table 1. Zr-Catalyzed Kinetic Resolution of Five- and Six-Membered Cyclic Allylic Ethers[a]

entry	substrate			time (h)	conv.[b] (%)	recovered start. material config.; ee (%)[c]	k_{fast}/k_{slow}
1		**1**		3	65	*S*; 52	2.8
2		**2**	R = OMEM	4-5	63	*S*; 50	2.8
3		**3**	R = *n*-Bu	9-10	63	*S*; 79	6.2
4		**4**	R = Bn	2.5-3	60	*S*; 81	7.8
5		**5**	R = H	2	60	*S*; 97	>20
6		**6**	R = OMe	1.5-2	60	*S*; 93	15.4
7		**7**	R = F	2	60	*S*; 95	15.6
8		**8**	*(racemic)*	4	55	1*S*,4*R*; 98	>25
9		**9**	*(racemic)*	4-5	60	1*R*,6*S*; 82	8.4
10		**10**	*(racemic)*	5	60	1*R*,6*S*; 70	5.4

[a] Reaction conditions: 10 mol % of (*R*)-(EBTHI)Zr-binol, 5.0 equiv of EtMgCl, THF, 70 °C. Reaction in entry 8 was carried out with 20 mol % of (*R*)-(EBTHI)Zr-binol. [b] Conversions determined by GLC analysis in comparison with an internal standard, by analysis of the ^{1}H NMR of the reaction mixture, and through isolation (silica gel chromatography). [c] The identity of the recovered starting materials was determined through comparison with authentic enantiomers (see supporting information for details). Enantiomeric excess was determined by chiral GLC (BETADEX 120 chiral column by Supelco, entries 1−3, 6, and 7; CHIRALDEX-GTA chiral column by Alltech, entries 8 and 9). Recovered starting materials in entries 1, 3, 6, 7, and 8 were first converted to their derived epoxides and then analyzed. Enantiomeric excess was determined by chiral HPLC: CHIRALCEL OB-H for entries 4 and 5 and with CHIRALPAK AD for entry 10. Absolute stereochemistry was directly determined for **3**, **4**, **5**, and **8**; the remaining assignments were made by inference.

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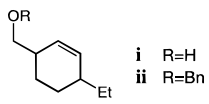
(6) (a) Wild, F. R. W. P.; Waiucionek, M.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1985**, *288*, 63−67. (b) Diamond, G. M.; Rodewald, S.; Jordan, R. F. *Organometallics* **1995**, *14*, 5−7 and references cited therein.

(7) All reactions described herein afford the expected ethylmagnesation products. In certain cases, due to substrate volatility, the alkylation product could not be isolated but was detected in the ^{1}H NMR spectrum of the unpurified mixture. In instances where volatility is not a hindrance, the product was fully characterized (*e.g.*, with **9** and **10**, **i** and **ii** were obtained, respectively). Details (including product stereocontrol) will be provided in the full account of this study.



i R=H
ii R=Bn

(8) All the catalytic resolutions described herein must be carried out with freshly prepared catalyst batches of high purity. Sluggish reactions and/or inferior enantioselectivities will be otherwise observed.

(9) The phenyl ether derived from cyclopentenol reacts with the alkylmagnesium halide in the absence of the catalyst, preempting the possibility of catalytic kinetic resolution (both at 22 and 70 °C). Nonetheless, the starting material is recovered in ∼40% ee after 60% conversion.

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Table 2. Zr-Catalyzed Kinetic Resolution of Seven- and Eight-Membered Cyclic Allylic Ethers[a]

entry	substrate			time (h)	conv.[b] (%)	recovered start. material config.; ee (%)[c]	k_{fast}/k_{slow}
1		**11**	R = Bn	9-10	60	*S*; >99	>25
2		**12**	R = Ph	3-4	56	*S*; >99	>25
3		**13**	R = *p*-MeO-Ph	15	59	*S*; 70	5.5
4		**14**	R = Ph	14-15	60	*S*; 81	8.0

[a,b] See Table 1. [c] The identity of the recovered starting materials was determined through comparison with authentic enantiomers (see supporting information for details). Enantiomeric excess was determined by chiral GLC (ALPHADEX 120 chiral column by Supelco). Absolute stereochemistry was directly determined for **11**, **13**, and **14**; the remaining assignment was made by inference.

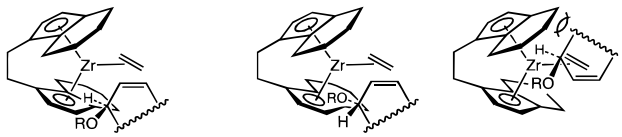
past 40% conversion. (ii) Bicyclic 1,6-disubstituted ether **9** is resolved more efficiently than the derived monocyclic substrate **10**; this outcome is notable, since we find the corresponding methoxyisopropyl ether to be an inferior substrate for the Zr-catalyzed resolution ($k_{fast}/k_{slow} = 1.5$).

As entries 1 and 2 of Table 2 illustrate, with seven-membered allylic ethers, significantly higher levels of enantioselection are achieved (in comparison to six-membered ring derivatives); **11** and **12** are resolved to afford recovered starting materials in >99% ee (chiral GLC). Data presented in entries 1 and 4 in Table 1 and entry 1 in Table 2 thus indicate that, with increasing the size of the carbocyclic ring structure, larger rate differences in the carbomagnesations of substrate enantiomers are detected ($k_{fast}/k_{slow} = 2.8$, 7.8, and >25 for **1**, **4**, and **11**). A similar trend emerges when we compare catalytic ethylmagnesations of phenyl ethers **5** and **12**. The exact reason for the dependence of the resolution efficiency on ring size must await future mechanistic studies. Although the observed selectivity patterns can be reliably extended to larger ring systems, the levels of resolution efficiency may not be. In the kinetic resolution of the phenyl ether derived from 2-cycloocten-1-ol, k_{fast}/k_{slow} is ~8 (*vs* >25 for **12**). Regardless, because of the ease of preparation of the racemic cycloheptenol and cyclooctenol derivatives and due to the paucity of available methods for the enantioselective synthesis of seven- and eight-membered ring systems, this procedure should prove useful in applications to asymmetric synthesis of natural products.

Our attempts to effect the Zr-catalyzed resolution of silyl ether derivatives of cyclohexenol were not successful; the derived TES and TBS ethers reacted sluggishly and nonselectively (k_{fast}/k_{slow} does not exceed 1.8). Parent allylic alcohols cannot be resolved through this procedure; however, allylic ethers depicted in Tables 1 and 2, which are resolved effectively by this catalytic procedure, can be deprotected to yield the parent nonracemic allylic carbinol.[11]

Results illustrated in Tables 1 and 2 indicate that simple structural changes can lead to notable differences in resolution efficiency; the reaction rate differential between phenyl ether enantiomers of **5** and benzyl ethers **4** is a case in point. In the absence of more extensive studies, it is difficult to identify the basis (steric or electronic) of the observed variations in selectivity. However, data shown in the table do imply that subtle electronic factors can be important; entries 2 and 3 suggest that electronic effects can influence the resolution efficiency (*n*-butyl and MEM groups have near identical steric requirements, unless the OMEM unit is coordinated to a Mg ion). As another example, reactions of **5** *vs* **6** or **5** *vs* **7**, or that of **13** *vs* **14**, illustrate that alteration of the electronic character of the allylic heteroatom substituent leads to detectable changes in enantioselection. Studies designed to clarify the origin of the above differences in enantioselectivity are underway.

Chart 1



Addition pathway available to the faster-reacting enantiomer

Addition pathways available to the slower-reacting enantiomer

Modes of addition shown in Chart 1 are consistent with extant mechanistic work[5b,12] and accurately predict the identity of the slower reacting enantiomer. It is noteworthy, however, that variations in the observed *levels* of selectivity as a function of the steric and electronic nature of substituents and the ring size cannot be predicted on the basis of these models alone; more subtle factors are clearly at work. In spite of such mechanistic dilemma, which will be the subject of future investigations, the metal-catalyzed resolution protocol provides an attractive option in asymmetric synthesis. This is because, although the maximum possible yield is ~40%, it requires easily accessible racemic starting materials and conversion levels can be manipulated so that truly pure samples of substrate enantiomers are obtained.[13] Further studies in the area of Zr-catalyzed asymmetric carbomagnesation and its applications to the total synthesis of natural products continue in these laboratories and will be reported shortly.

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Supporting Information Available: Experimental procedures, stereochemical proofs, and spectral and analytical data for all resolved compounds (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) Relative rates were calculated by an equation reported previously. See ref 2.

(11) For deprotection of *p*-anisyl ethers, see: Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291−6292. A benzyl ether of an allylic carbinol can be efficiently removed: Hwu, J. R.; Chua, V.; Schroeder, J. E.; Barrans, R. E.; Khoudary, K. P.; Wang, N.; Wetzel, J. M. *J. Org. Chem.* **1986**, *51*, 4733−4734.

(12) Hoveyda, A. H.; Morken, J. P. *J. Org. Chem.* **1993**, *58*, 4237−4244.

(13) Representative procedure: 3-Phenoxycyclohept-1-ene **12** (282 mg, 1.50 mmol) was dissolved in 7.5 mL of anhydrous THF, containing hexadecane (0.50 mL) as an internal standard. After addition of EtMgCl (5.2 mL, 7.50 mmol) and (*R*)-(EBTHI)Zr-binol (96 mg, 0.15 mmol), the reaction mixture was placed in an oil bath heated to 70 °C. Stirring continued at this temperature for 5 h, after which GLC analysis indicated the reaction had proceeded to 56% conversion. The reaction was quenched with 10.0 mL of H_2O; the aqueous layer was subsequently washed 3 times with 5.0 mL of Et_2O. Evaporation of the organic solvents in vacuo and purification by silica gel chromatography afforded 122 mg (0.65 mmol, 98% yield based on percent conversion) of **12** which was shown to be >99% ee by chiral GLC analysis (minor enantiomer not detected).