Highly Diastereoselective Cyclizations of Bishomoallylic Tertiary Alcohols Promoted by Rhenium(VII) Oxide. Critical Steric versus Chelation Effects in Alkoxyrhenium Intermediates

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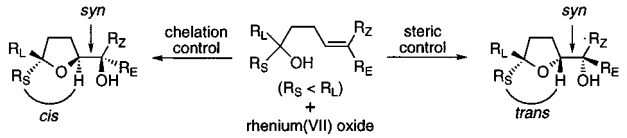
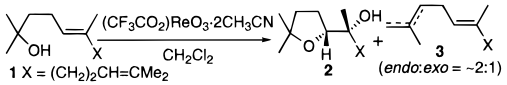
2,5-Disubstituted tetrahydrofurans (THF) have structural features commonly encountered in such natural products as polyether antibiotics[1] and acetogenins,[2] which possess a variety of important and potent biological activities. Therefore, the preparation of such THF skeletons has attracted particular attention from many synthetic organic chemists.[3] Among them, hydroxy-directed oxidative cyclizations of acyclic bishomoallylic alcohols promoted by metal oxo species are one of the most efficient synthetic methods of producing 2,5-disubstituted tetrahydrofurans. Recently, oxidation reactions employing rhenium in a high oxidation state[4] have been intensely studied in organic syntheses.[5] In this context, Kennedy[6] and McDonald[7] have pioneered diastereoselective methods for construction of these THF skeletons by means of syn oxidative cyclizations[8] of bishomoallylic alcohols by rhenium(VII) oxide,[9] though the applicable substrates were limited to primary and secondary alcohols.[10] The origin of high diastereoselectivity in the reaction has been explained by steric (nonbonding) interaction in an alkoxyrhenium intermediate.[7b] In this paper, we describe the new reaction conditions applicable to bishomoallylic tertiary alcohols and report conventional steric interaction and an unexpected but efficient chelation effect[11] as the cause of excellent diastereoselectivities (Scheme 1).

Scheme 1. The Rule for Syn Oxidative Cyclizations by Re(VII) Oxide



Scheme 2



additive	temp	time	product (yield)
2,6-lutidine	rt	3 h	**2** (trace) + **3** (18%)
2,6-lutidine	0 °C	3 h	**2** (11%) + **3** (34%)
2,6-lutidine	−78 °C	4 h	no reaction
2,6-lutidine	−45 °C	10 h	**2** (7.1%) + **1** (75%)
—	−45 °C	8 h	**2** (76%)
$(CF_3CO)_2O$	−45 °C	1.5 h	**2** (66%)

!!

First, we attempted to find the reaction conditions compatible with tertiary alcohols using $(CF_3CO_2)ReO_3 \cdot 2CH_3CN$[12] as rhenium(VII) oxide in the presence or absence of some additives in CH_2Cl_2 at various temperatures (Scheme 2). Although treatment of **1** with Re(VII) oxide in the presence of 2,6-lutidine, reported as a standard additive,[6,7] at room temperature or 0 °C afforded syn oxidative cyclization product **2** albeit in very low yields, the major product was dehydration compound **3** in contrast to primary and secondary alcohols. The reaction did not proceed at −78 °C, and although the dehydration was inhibited at −45 °C, most of the starting material **1** was recovered. Because we thought 2,6-lutidine as a base might be implicated in the dehydration of **1**, in the absence of 2,6-lutidine, the reaction was performed to give the desired **2** in reasonable yield. Furthermore, it has also been found that trifluoroacetic anhydride (TFAA)[13] accelerates the oxidative cyclization approximately five times that in the absence of TFAA, despite subtly lowering the yield.

Since the optimal reaction conditions applicable to tertiary alcohols have been developed, various substrates such as **4** and **5** (R = Me, Et, *i*-Pr)[14] were subjected to the syn oxidative cyclization promoted by Re(VII) oxide (Table 1). The reaction of olefinic regioisomers **4** and **5** (R = Me)[7b] stereospecifically proceeded to provide syn oxidative cyclization products **6** and **8** (R = Me),[15] respectively, in good yields (entries 1 and 2). To evaluate the diastereoselectivity[16] between 2- and 5-positions in the THF ring, substrates **4** and **5** (R ≠ Me) were examined next. When R = Et, trans isomers **6** and **8** were obtained as a major

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(9) Although other hydroxy-directed syn oxidative cyclizations by chromium(VI) oxide have also been reported, the products obtained were usually lactones accompanied by C−C bond cleavage except for vicinal diol substrates, wherein the desired THF products were provided only in low yields. (a) Chakraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1984**, *25*, 2895−2896. (b) Schlecht, M. F.; Kim. H.-J. *Tetrahedron Lett.* **1985**, *26*, 127−130. (c) Chakraborty, T. K.; Chandrasekaran, S. *Chem. Lett.* **1985**, 551−554. (d) McDonald, F. E.; Towne, T. B. *J. Am. Chem. Soc.* **1994**, *116*, 7921−7922. (e) Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727−730. (f) Walba, D. M.; Stoudt, G. S. *J. Org. Chem.* **1983**, *48*, 5404−5406. (g) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171−3174.

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(11) Although McDonald has already invoked a chelation effect to elucidate the minor product in Re(VII)-induced cyclization (ref 7b), this work is the first example of chelation-controlled diastereoselective cyclization. After submission of our work, however, a paper by Sinha et al. has independently appeared that reports the cis diastereoselective cyclization: Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014−12015.

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(13) McDonald has proposed that the TFAA additive traps trace amounts of perrhenic acid present in the reaction media as its effect (ref 7). We are now investigating this novel acceleration effect of TFAA.

(14) For the preparation and characterization of these substrates, see the Supporting Information.

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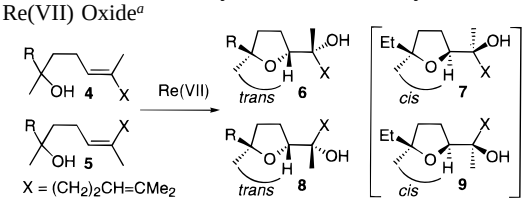
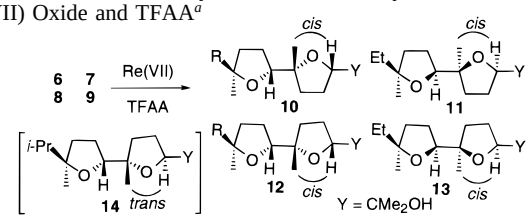
Table 1. Trans Selective Cyclizations of Tertiary Alcohols **4** and **5** by Re(VII) Oxide[a]



entry	substrate	product (% yield)[b]	ratio (trans:cis)[c]
1	**4** (R = Me)	**6** (76)	
2	**5** (R = Me)	**8** (71)	
3	**4** (R = Et)	**6** + **7** (59)[d]	4:1
4	**5** (R = Et)	**8** + **9** (64)[d]	4:1
5	**4** (R = *i*-Pr)	**6** (63)	>99:1[e]
6	**5** (R = *i*-Pr)	**8** (44)	>99:1[e]

[a] Substrates **4** or **5** were treated with $(CF_3CO_2)ReO_3 \cdot 2CH_3CN$ (4 equiv) in CH_2Cl_2 in the presence of activated molecular sieves (MS) 4A (300 wt %) at −45 °C for 8 h under N_2 atmosphere. [b] Isolated yields. [c] Ratios were determined by ^1H NMR integration of the mixture. [d] As a mixture of 4:1. [e] Cis isomer could not be detected by ^1H NMR.

Table 2. Cis Selective Cyclizations of Tertiary Alcohols **6**−**9** by Re(VII) Oxide and TFAA[a]



entry	substrate	product (% yield)[b]	ratio (cis:trans)[c]
1	**6** (R = Me)	**10** (71)	>99:1
2	**8** (R = Me)	**12** (88)	>99:1
3	**6** (R = Et) + **7**[d]	**10** + **11** (79)[d]	>99:1
4	**8** (R = Et) + **9**[d]	**12** + **13** (71)[d]	>99:1
5	**6** (R = *i*-Pr)	**10** (71)	>99:1
6	**8** (R = *i*-Pr)	**12** + **14** (70)[e]	2:1

[a] Substrates **6**−**9** were treated with $(CF_3CO_2)ReO_3 \cdot 2CH_3CN$ (4 equiv) and TFAA (4 equiv) in CH_2Cl_2 in the presence of activated MS 4A (300 wt %) at −45 °C for 4−8 h under N_2 atmosphere. [b] Isolated yields. [c] Trans isomer could not be detected by ^1H NMR except for entry 6. [d] As a mixture of 4:1. [e] As a mixture of 2:1.

product with modest diastereoselectivity of trans:cis = 4:1 (entries 3 and 4). When R = *i*-Pr, complete trans selectivity (trans:cis = >99:1) was observed (entries 5 and 6).[15b]

Monocyclized compounds **6**−**9** shown in Table 1 were further subjected to the second syn oxidative cyclization promoted by Re(VII) oxide in the presence of TFAA (Table 2). In this case, the addition of TFAA was essential to induce the reaction[13] due to no reaction at −45 °C and a complex mixture at elevated temperatures without TFAA. *Surprisingly, all of the products* ***10***−***13***,[16] *except for that in entry 6, were only cis isomers in contrast to those in Table 1 (entries 1*−*5)!!* This is the first explicit case of cis selectively controlled cyclizations promoted by Re(VII) oxide, while secondary alcohols with a THF ring neighboring the hydroxyl group merely exhibit the usual trans

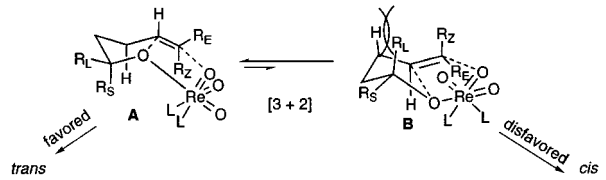


Figure 1. Steric control models for trans selective cyclizations.

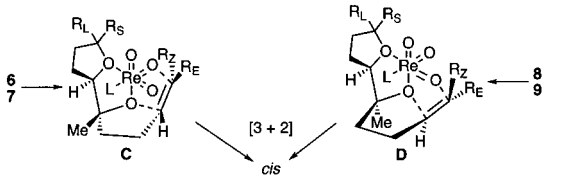


Figure 2. Chelation control models for cis selective cyclizations.

selectivity.[7,10,11] Only the diastereoselectivity of **8** (R = *i*-Pr) was low with the cis isomer predominating (entry 6).

These critical results might be rationalized as follows. The formation of trans tetrahydrofurans from rhenium(VII)-promoted oxidative cyclizations in Table 1 is consistent with a chairlike conformation of the alkoxyrhenium intermediate **A** in which the alkene and sterically large group R_L are pseudoequatorially positioned (Figure 1).[17] As exemplified by the *A*-values (kcal/mol) of the substituents R_L (Me = 1.70 < Et = 1.75 ≪ *i*-Pr = 2.15),[18] the lower trans selectivity in R_L = Et than in R_L = *i*-Pr may be attributed to deficiency in the steric bulkiness of R_L in the conformer **B** required for the exellent diastereoselectivity.

On the other hand, a reversal of the diastereoselectivity (i.e., cis selectivity) in the second Re(VII)-promoted oxidative cyclizations must be apparently relevant to the THF ring neighboring the hydroxyl group in the substrates, irrespective of the vicinal relative configuration (Table 2). The intramolecular coordination of the THF ring to rhenium[17] could form alkoxyrhenium intermediates **C** and **D** from **6**, **7** and **8**, **9**, respectively (Figure 2). Considering the [3 + 2] mechanism[19] in that chelation model, the least strained approach of the alkene toward the Re oxo moiety appears to be similar to that shown in Figure 2 (i.e., methyl and the olefinic hydrogen are cis). Because trans selectivity is observed in secondary alcohols even if the substrates have the neighboring THF ring,[7,10,11] a tertiary property in the alcoholic substrates might play an important role in forming the rigid cyclic coordinative intermediates such as **C** and **D** (cf., *gem*-dimethyl effect[20]). Although the reason for lowering the cis selectivity in entry 6 of Table 2 is not clear at present, **8** (R = *i*-Pr) appears to have difficulty in forming such a rigid chelation structure.

In summary, we have achieved steric interaction controlled trans and chelation-controlled cis highly diastereoselective cyclizations of bishomoallylic tertiary alcohols promoted by rhenium(VII) oxide. Clarification of the more detailed reaction mechanisms and application of this reaction to natural products synthesis are in progress.

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Supporting Information Available: Preparation of **4** and **5**, typical experimental procedure for oxidative cyclization, selected characterization data for **4**−**14**, and NOE data for structural evidence of **6**−**13** (10 pages). See any current masthead page for ordering and Web access instructions.

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(15) (a) All new compounds in this paper were satisfactorily characterized by ^1H and ^{13}C NMR, IR, MS, and HRMS spectra. (b) The stereochemistry of the products **6** and **8** (R = Me, *i*-Pr) was determined as follows. That is, **6** (R = Me) was identical with the net anti oxidative cyclization product from V(V)-catalyzed epoxidation of **5** (R = Me) followed by acid-catalyzed epoxide opening, and **8** (R = Me) with that from **4** (R = Me). Predictably, **6** (R = *i*-Pr) was identical with the minor trans isomer (major cis:minor trans = 8.5:1) from V(V)-catalyzed monocyclization of **5** (R = *i*-Pr) and **8** (R = *i*-Pr) with the minor trans isomer (major cis:minor trans = 5.4:1) from **4** (R = *i*-Pr). We thank the referee for suggesting this experiment on the V(V)-catalyzed monocyclization of **4** and **5** (R = *i*-Pr).

(16) (a) The relative stereochemistry between the 2- and 5-positions in the THF ring-containing products **6**−**13** was determined by the presence of NOEs observed between the oxymethine proton and the group in a relationship cis to that proton in their NOE difference spectra. See the Supporting Information. (b) Bistetrahydrofuranyl alcohols **10** and **12** (R = Me) in this reaction were identical with the authentic samples prepared from **5** and **4** (R = Me), respectively, by Towne and McDonald using vanadium methodology (ref 7b).

(17) The octahedral crystal structure of $(CF_3CO_2)ReO_3 \cdot 2CH_3CN$ by X-ray has been revealed, and also the structure of rhenium(VII) complexes possessing tetrahydrofuran as a ligand has been spectroscopically characterized (ref 12).

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(19) In Re(VII)-promoted syn oxidative cyclizations, the [3 + 2] mechanism has been preferred to [2 + 2] followed by reductive elimination (refs 6d and 7). For the controversy over [3 + 2] vs [2 + 2] mechanisms in the oxidation reaction of olefins by metal oxo species, see: Jørgensen, K. A.; Schiøtt, B. *Chem. Rev.* **1990**, *90*, 1483−1506.

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