Heterocycles

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A Double Donor-Activated Ruthenium(VII) Catalyst: Synthesis of Enantiomerically Pure THF-Diols**

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Dedicated to Professor Hans-Ulrich Reissig on the occasion of his 60th birthday

Chiral tetrahydrofuran diols (THF-diols, Figure 1) represent a characteristic structural motif in a range of biogenetically unrelated natural product families.[1] The most prominent

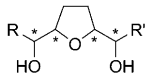
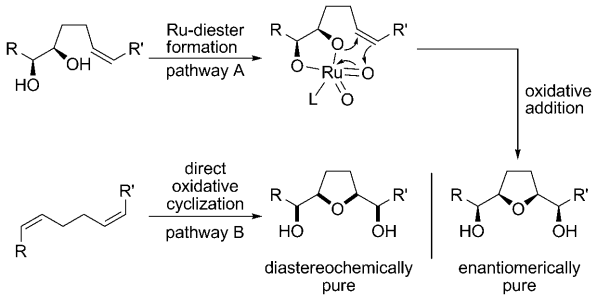


Figure 1. General structure of THF-diols—a central motif in different classes of biologically active compounds. R,R' = different substituents, the asterisks indicate stereogenic centers.

classes are the polyether ionophores, the annonaceous acetogenines, and some terpenoid metabolites.[2] In addition, 2,5-disubstituted THFs constitute the central repeating unit of certain artificial ion channels.[3] Owing to the prevalence of this structural motif in biologically active natural and non-natural compounds, a number of methods for the stereoselective synthesis of THF-diols have been developed.[4] Strategically, the stereochemistry is often established in an initial chemical transformation (e.g. by dihydroxylation or epoxidation of a suitable olefinic precursor) followed by a separate cyclization reaction. For instance, biomimetic[5] di- and polyepoxide cyclizations have been established as a powerful means for the construction of THF-diols[6] and related polyethers.[7]

We recently described the development of ruthenium tetroxide catalyzed[8] oxidative cyclization[9] reactions of 1,5-dienes[10] and related substrate classes.[11] This methodology allows for the efficient construction of THF-diols in high yields (up to 98%) and with excellent control of relative stereochemistry (generally >95:5 d.r.;[12] pathway B in Scheme 1). The aim of the present study was to investigate



Scheme 1. Envisaged ruthenium-catalyzed oxidative cyclization of 5,6-dihydroxy alkenes to furnish enantiomerically pure THF-diols (pathway A) and direct oxidative diene cyclization yielding diastereochemically pure THF-diols (pathway B). L = ligand.

a pathway to enantiomerically pure THF-diols[13] which connects the establishment of stereogenic centers with the ring-forming reaction. Thus, 5,6-dihydroxy olefins (Scheme 1, pathway A) were identified as suitable precursors for the desired enantiomerically pure heterocycles. The synthetic strategy for this investigation is outlined in Scheme 1 (pathway A) in comparison to the direct oxidative cyclization (pathway B in Scheme 1) producing diastereomerically pure THF-diols. Based on our previous investigations,[10,11] we focused on ruthenium catalysts. To our knowledge, ruthenium catalysts have not been used for the oxidative cyclization of related bishomoallylic alcohols. Other transition-metal-based oxidants are known to promote similar reactions, however, usually stoichiometric amounts of toxic oxidants have to be used. Moreover, often moderate diastereoselectivities as well as varying amounts of constitutional isomers and other unwanted side products are obtained.[4e,f,8,14] In general, a high degree of (chemo-)selectivity has to be attained for the oxidative cyclization of this type of bishomoallylic alcohols: The catalyst should neither oxidize any alcohols (mono or vicinal diols) nor react with olefins in an intermolecular fashion. On the other hand, for the envisaged heterocyclization an intramolecular oxidative addition to the C–C double bond is desired. This reaction has to occur under participation of the oxygen atom of the proximal hydroxy group and should possibly proceed stereoselectively. To meet these multilayered requirements a double-activation concept[15]—for example, by means of a ruthenium diester intermediate—was regarded as particularly suitable.

On the basis of these considerations, we tested a set of mild ruthenium-based oxidants under different reaction conditions (co-oxidant, solvent, temperature, etc.) for their

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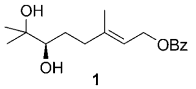
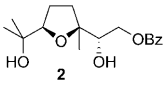
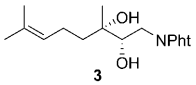
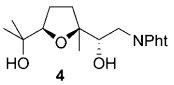
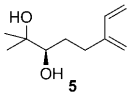
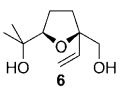
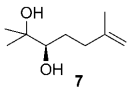
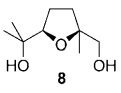
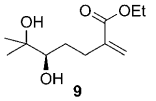
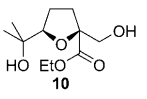
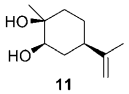
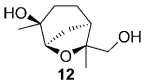
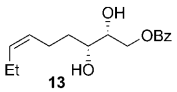
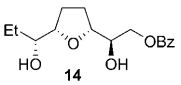
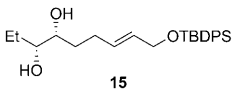
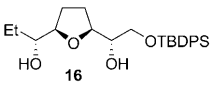
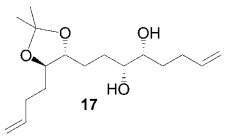
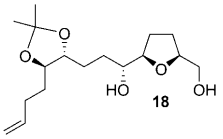
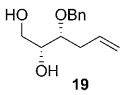
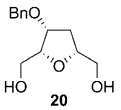
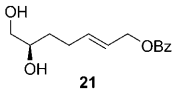
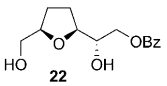
ability to promote the selective oxidative cyclization of 5,6-dihydroxy alkenes. For this investigation substrate **1** was chosen as a model substrate (Table 1, Entry 1). Intriguingly, TPAP[16] (tetrapropylammonium perruthenate) one of the mildest oxidation catalysts tested provided the desired cyclization product **2** in good yield. Importantly, the heterocyclic product was obtained with high stereoselectivity furnishing two new stereogenic centers. Thus, the enantiomerically pure alcohol **1** was converted into the desired THF-diol in enantiomerically pure form with perfect transfer of stereochemical information (>95:5 d.r., 99:1 e.r.; Table 1, Entry 1). No other stereoisomers could be detected.

TPAP is a well-established catalyst for the highly chemoselective oxidation of primary and secondary alcohols to carbonyl products. Even a number of bishomoallylic alcohols (5-hydroxy alkenes) have cleanly been converted into the corresponding carbonyl compounds without any addition or cyclization to the C–C double bond.[16] This diametric reactivity indicates that the double-activation concept appears to be operative in the observed cyclization reaction (see below). Quite remarkably, even under conditions closely resembling those of the extraordinarily mild Ley oxidation[16] using NMO (*N*-methylmorpholine-*N*-oxide) as a co-oxidant smooth ring formation took place.

We next investigated the generality of this reaction pathway and to which extent the stereoselectivity depends on the specific stereochemical arrangement and substitution pattern around the two reacting subunits (diol and olefin) (Table 1). Therefore, a range of starting materials were subjected to the optimized reaction conditions using 5 mol% TPAP in wet CH_2Cl_2, *tert*-butanol, or *tert*-amyl alcohol (see Table 1 and Supporting Information for details). Generally, the 5,6-dihydroxy olefins underwent smooth cyclization furnishing the desired THF-diols in good to high yields. Most importantly, irrespective of the starting material excellent stereoselectivities were obtained. With respect to the olefin subunit, synthetically useful results were achieved irrespective of the degree of substitution and stereochemistry of the reacting double bond. Moreover, it is worth mentioning that C–C double bonds which are not in an appropriate distance from the vicinal diol do not undergo an intramolecular oxidative cycloaddition nor any intermolecular oxidation (Table 1, Entries 3 and 9). Thus, remote olefins are compatible with the oxidative cyclization conditions described. In addition, generation of a THF-ring is apparently favored over an equally feasible formation of a six-membered heterocycle (Table 1, Entry 3).

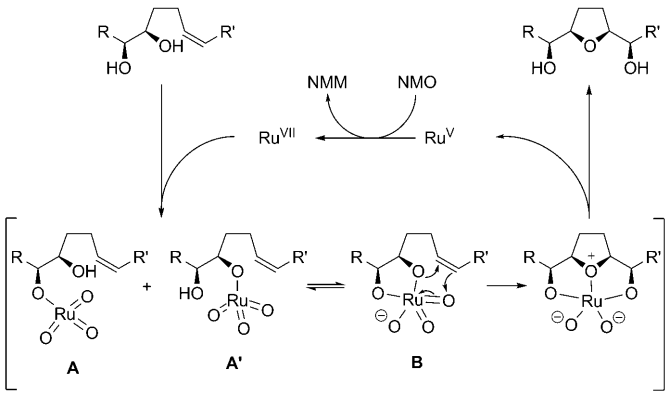
Mechanistically, we believe that the diol starting material initially undergoes formation of a ruthenium(VII) monoester similar to TPAP-catalyzed alcohol oxidations. For this first

Table 1: TPAP-catalyzed oxidative cyclization of 5,6-dihydroxyalkenes.[a]

Entry	Substrate	Product	Yield [%][b]	d.r.[c] e.r.[d]
1	 1	 2	63	>95:5 99:1
2	 3	 4	68	>95:5 88:12
3	 5	 6	52	>95:5 >99:1
4	 7	 8	72	>95:5 98:2
5	 9	 10	46	>95:5 >99:1
6	 11	 12	37	>95:5 >99:1
7	 13	 14	62	>95:5 97:3
8	 15	 16	65	>95:5 >99:1
9	 17	 18	68	>95:5 98:2
10	 19	 20	47	>95:5 >99:1
11	 21	 22	28	>95:5 85:15[e]

[a] Reaction conditions: 5 mol% TPAP, 1.2 equiv NMO, wet CH_2Cl_2, room temperature, 1–24 h. Bz = benzoyl, NPht = phthalimide, TBDPS = *tert*-butyldiphenylsilyl, Bn = benzyl. [b] Yield of isolated product after chromatographic purification. [c] Diastereomeric ratio (d.r.) determined by NMR spectroscopy of crude reaction mixtures. [d] Enantiomeric ratio (e.r.) determined by chiral HPLC with a Chiralpak AD-Column. [e] The enantiomeric ratio (e.r.) of the starting material was 85:15.

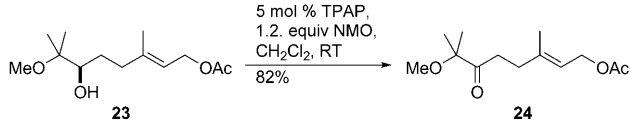
step two regioisomeric intermediates **A** and **A′** (Scheme 2) are conceivable, the ratio of which will primarily be controlled by steric factors.[16] Instead of mediating an alcohol oxidation, the high Lewis acidity of the metal center is assumed to drive



Scheme 2. Mechanistic hypothesis for the ruthenium(VII)-catalyzed oxidative cyclization of 5,6-dihydroxy alkenes. NMM = *N*-Methylmorpholine.

an intramolecular interaction with the neighboring hydroxy group. Thus, both intermediates **A** and **A′** will rapidly be converted into the same cyclic ruthenium(VII) diester **B** (Scheme 2). Within this key intermediate the doubly activated transition metal is now electrophilic and carbophilic enough to undergo a [3+2]-cycloaddition to the proximal C–C double bond. Finally, hydrolysis liberates the THF-diol product and a ruthenium(V) species which is reoxidized with NMO to the active catalyst (Scheme 2).

Our mechanistic model rests upon the assumption that only the ruthenium(VII) diester **B** (Scheme 2) exhibits an appropriate reactivity to productively interact with the C–C double bond. This hypothesis is already supported by the fact that olefins are generally compatible with TPAP-catalyzed alcohol oxidations.[16] However, to seek further experimental support to corroborate this assumption and to investigate whether a covalent dual activation is indeed essential for the oxidative cyclization, we prepared the monomethylether **23** and subjected this bishomoallylic alcohol to our standard cyclization conditions (Scheme 3). Indeed, this simple structural alteration leads to a complete switch of mechanistic pathways. Now, the secondary alcohol is oxidized cleanly to the corresponding ketone **24** leaving the double bond untouched. Therefore, this control experiment provides support in favor of our proposed reaction mechanism and the involvement of ruthenium(VII) diesters as reactive intermediates (**B** in Scheme 2). In addition, it may be speculated that a cyclic ruthenium diester—other than an acyclic monoester—leads to a highly ordered and rigid transition state which is in turn the basis for an effective transfer of stereochemical information.



Scheme 3. Control experiment: use of a monomethylether.

In summary, we have presented a new catalytic method for the stereocontrolled oxidative cyclization of 5,6-dihydroxy alkenes to yield THF-diols in high diastereo- and enantiopurity. Up to two new chiral centers are created in these cyclization reactions. Our investigation describes the first ruthenium-catalyzed oxidative cyclization of this class of substrates and uncovers an unprecedented reactivity of ruthenium(VII) catalysts. A mechanistic rationale and preliminary experiments in support of this model are also described. Thus, intramolecular donor activation changes the transition metal into a more carbophilic and, in this respect, more electrophilic species and hence allows for the unusual perruthenate-mediated dioxygenation reaction.[17]

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