Heterocyclic Synthesis

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Efficient Oxidative Cyclization of 1,6-Dienes: A Highly Diastereoselective Entry to Substituted Tetrahydropyrans**

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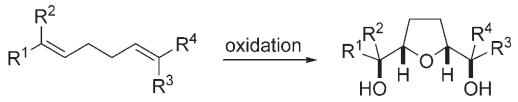
The oxidative cyclization[1] of 1,5-dienes represents a unique method for the preparation of 2,5-disubstituted tetrahydrofurans (Scheme 1).[2] For this nonclassical approach to these herterocycles stoichiometric amounts of permanganate[3] or



Scheme 1. Oxidative cyclization of 1,5-dienes.

catalytic amounts of osmium[4] or ruthenium tetroxide[5,6] have been used. This methodology has been known for some time and recent investigations have led to high-yielding procedures as well as some synthetic applications.[7]

Whereas the oxidative cyclization of 1,5-dienes thus appears to be a firmly established process, the corresponding oxidative cyclization of homologous 1,6-dienes has rarely been studied[8] and never achieved satisfactorily. In view of the relevance of tetrahydropyrans[2] as substructures in many classes of natural products, we decided to investigate this transformation in detail. Herein, we report the first general method for the oxidative cyclization of 1,6-dienes which provides access to diastereomerically pure tetrahydropyrans (THPs).

On the basis of our previous investigations in the area of oxidative cyclizations,[6] we employed ruthenium tetroxide as a catalyst and sodium periodate on wet silica[9] as the terminal oxidant. Initial experiments on 1,6-diene **1** (Table 1, entry 1), chosen as a model substrate, yielded the desired cyclization product only as a minor component among a range of other products, including stereoisomers, dihydroxylation, and C–C-bond cleavage products. Pleasingly, systematic optimization

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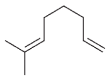
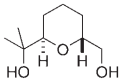
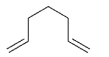
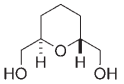
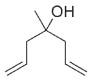
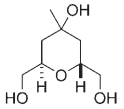
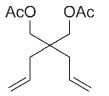
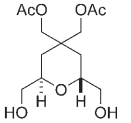
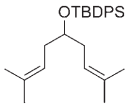
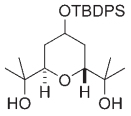
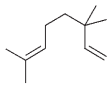
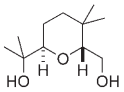
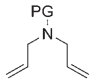
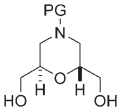
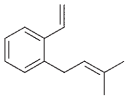
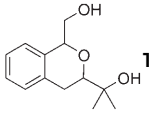
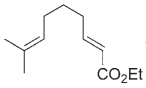
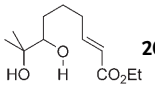
Supporting information for this article (detailed experimental procedures and representative spectroscopic data) is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Oxidative cyclization of 1,6-dienes.[a]

Entry	Substrate		Product		Yield [%][b]	d.r.[c]
1		**1**		**2**	85[d]	>95:5
2		**3**		**4**	53[e]	>95:5
3		**5**		**6**	70	>95:5
4		**7**		**8**	65[e]	>95:5
5		**9**		**10**	58	>95:5
6		**11**		**12**	48	>95:5
7		**13**[g]		**14**	60[d,e]	>95:5
8		**15**[g]		**16**	87[d,e]	>95:5
9		**17**		**18**	41	60:40
10		**19**		**20**	52(72)[f]	–

[a] Reaction conditions: 5 mol% $RuCl_3$, 4 equiv $NaIO_4$ on wet silica, EtOAc/MeCN (1:1), 0°C, 10 min. [b] Yields of isolated cyclization product after column chromatography. [c] Ratio determined by ^1H NMR spectroscopy or gas chromatography of crude reaction mixtures. [d] 1 mol% ruthenium catalyst was used. [e] A reductive work up was carried out to convert small amounts of aldehyde side product into the same diol main product (see the Supporting Information). [f] The yield in parenthesis refers to the sum of the yields of the diol and tetrol product. [g] **13**: PG = Bz (benzoyl), **15**: PG = $p$$NO_2$Bz.

of reaction parameters (solvent, temperature, concentration, and precatalyst) enabled the formation of these unwanted products to be almost completely suppressed. Both a polar solvent mixture (MeCN/EtOAc) and a dilute reaction solution (0.03 M) proved crucial for achieving good results. Under optimized reaction conditions using 5 mol% ruthenium trichloride as a precatalyst (for the in situ generation of ruthenium tetroxide) the cyclization product **2** was obtained in high yield (85%) and, more importantly, as a single diastereoisomer.

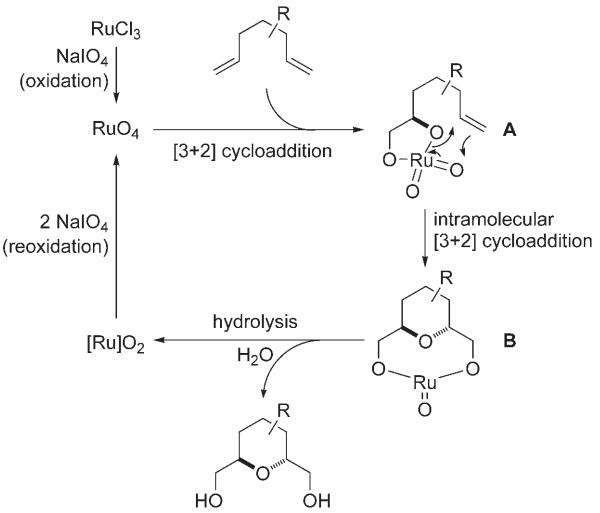
Gratifyingly, this protocol was applicable to a range of 1,6-dienes (Table 1). The cyclization product was formed rapidly (usually within 10 min at 0°C) and with high selectivity, irrespective of the starting material. Terminal alkenes, which are commonly known to result in diminished yields in the case of 1,5-dienes,[3] afforded the heterocyclic products in good yields. Even a chiral morpholine derivative was accessible in excellent yield (87%) starting from simple protected diallylamine (Table 1, entry 8). Since a solid-supported terminal oxidant[10] is used, the work-up procedure is extremely simple and requires only filtration after deactivation of the catalyst (see the Supporting Information). Thus, even hydrophilic diol and triol products can be isolated without difficulty.

In contrast to the oxidative cyclization of 1,5-dienes,[5,6] α,β-unsaturated esters did not undergo cyclization, and only dihydroxylation products[11] were observed (Table 1, entry 10). Neither the diol nor the tetrol could be forced to undergo cyclization, even when stirred for extended reaction times or under forcing reaction conditions.[12] From all the 1,6-diene substrates investigated in this study, such electron-deficient alkenes represent the only class of substrates that did not undergo oxidative cyclization.

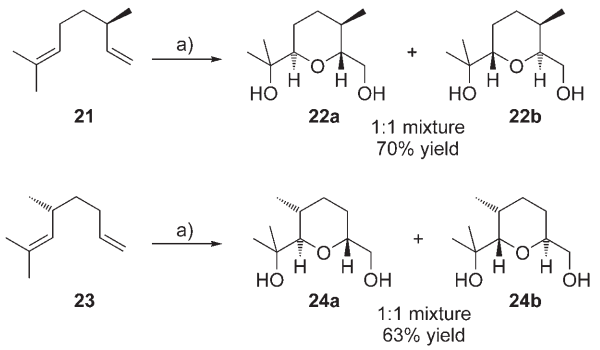
The diastereoselectivity of the cyclization was generally high, and the 2,6-*cis*-THP could usually not be detected in the crude reaction mixtures (NMR or GC). Only isochromane (**18**) was obtained as a mixture of isomers (60:40; Table 1, entry 9) presumably because of the almost planar linkage between the two reacting double bonds. The relative stereochemistry of THP products was established by spectroscopic means and was confirmed by comparison with authentic samples (for compounds **2** and **4**).[13] Interestingly, in all cases the contra-thermodynamic 2,6-*trans*-substituted THP derivatives were formed.[14] It is also worth noting that most cyclization products depicted in Table 1 are either C_2- or pseudo-C_2-symmetric (with a chiral chirotopic C atom) and methods for the desymmetrization of these compounds are conceivable.[15]

Mechanistically we presume a similar pathway[16] as was first suggested by Baldwin et al.[16a] for the related permanganate-promoted oxidative cyclization of 1,5-dienes. Thus, after conversion of the precatalyst into ruthenium tetroxide a [3+2] cycloaddition[17] to one of the double bonds occurs (Scheme 2). This step is followed by a second intramolecular [3+2] cycloaddition to the adjacent olefin. At this crucial stage the stereochemistry across the THP system is set. Finally, hydrolysis of the intermediate ruthenate ester **B** (Scheme 2) liberates the product and a low-valent ruthenium species which in turn is oxidatively converted into the active ruthenium(VIII) catalyst.

We next investigated the stereoselectivity of the process using starting materials containing a stereogenic center within the C_3 bridge. Thus, the two chiral and nonracemic substrates **21** and **23** (Scheme 3) were submitted to the optimized oxidation conditions. Disappointingly, no influence on the stereochemical course of the reaction was detectable, irrespective of the position of the stereogenic center (Scheme 3). In both cases the cyclization products were obtained as a 1:1 mixture of diastereoisomers. The lack of any stereochemical induction is most likely a result of the fact that the initial [3+2] cycloaddition occurs at the double bond remote from the branched stereogenic center.[4c] Although the diastereo-



Scheme 2. Proposed mechanism for the oxidative cyclization of 1,6-dienes.

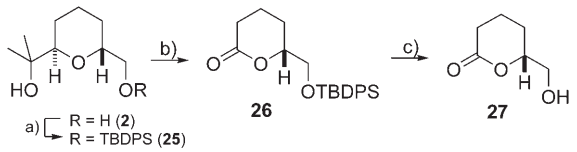


Scheme 3. Oxidative cyclization of chiral 1,6-dienes: a) 5 mol% $RuCl_3$, 4 equiv $NaIO_4$ on wet silica, EtOAc/MeCN (1:1), 0°C, 10 min, reductive work up.

selectivity of this transformation is not satifactory it should be noted that enantiomerically pure products with two new stereogenic centers are accessible after separation.

We next sought to extend the scope of this new oxidative cyclization by seeking conditions to convert the 2,6-bis(hydroxymethyl)tetrahydropyrans into δ-lactones. The primary hydroxy function of the cyclization product **2** (which could be prepared on a gram scale) was first protected (Scheme 4). Conditions for the oxidative cleavage of the tertiary hydroxy methyl group were then investigated. Pyridinium chlorochromate (PCC)[18] proved to be the most efficient reagent for this purpose, and the oxidative cleavage to δ-lactone **26** proceeded smoothly (70% yield). Fluoride-induced deprotection provided the free alcohol **27** in an overall yield of 47% (over 4 steps) starting from commercially available diene **1**. This δ-lactone has previously been used as a key intermediate in natural product synthesis.[19]

In summary, the first general and efficient procedure for the oxidative cyclization of 1,6-dienes has been presented. The cyclization products were obtained in good to high yields and excellent diastereoselectivity. 1–5 mol% ruthenium tetroxide is sufficient to accomplish complete conversion of the starting diene within minutes. The scope of this novel cyclization method has been extended by the conversion of the initial cyclization product into a synthetically useful δ-lactone. Further investigations into the mechanism and the development of an asymmetric variant of this type of oxidation reaction are currently underway.



Scheme 4. Synthesis of 6-hydroxymethyl-δ-valerolactone (**27**): a) TBDPSCl, imidazole, CH_2Cl_2, 89%; b) PCC, 4-Å MS, CH_2Cl_2, 50°C, 70%; c) TBAF, THF, 0°C, 88%. TBDPSCl = *tert*-butyldiphenylsilyl chloride, PCC = pyridinium chlorochromate, MS = molecular sieves, TBAF = tetrabutyl ammoniumfluoride.

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