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Regio- and Stereocontrol in Rhenium-Catalyzed Transposition of Allylic Alcohols

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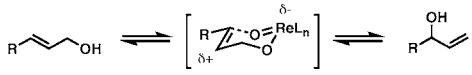
Direct catalytic transposition of allylic alcohols is a powerful approach to the synthesis of complex hydroxylated organic compounds.[1] Several transition metal catalysts have been developed for this purpose, including vanadium,[2] molybdenum,[2] and rhenium reagents.[3] Among these, rhenium(VII) oxide and triphenylsilyl perrhenate have been found to be superior in terms of reactivity and chemoselectivity, displaying high activity at low temperatures with no competitive oxidation observed with some of the other catalysts. One drawback of the reversible process (eq 1) is a general lack of regioselectivity;[4] stereoselectivity in the transposition of primary allylic alcohols is also low.



(1)

In this communication, we describe a practical method that allows for control of the regio- and stereoselectivity in the rhenium-catalyzed transposition of allylic alcohols, expanding the scope of the reaction for the stereoselective synthesis of complex molecules.[5]

In our initial experiments, rearrangement of substrate **1** in the presence of Re_2O_7 (2.5 mol %) occurred with low regio- and stereoselectivity as expected, delivering **2** with 60% conversion as a 3:2 mixture of diastereomers (Scheme 1). We hypothesized that the reaction medium must be slightly acidic due to formation of a catalytic amount of perrhenic acid ($pK_a = 1.25$)[6] upon interaction of rhenium(VII) oxide with the substrate and/or adventitious water.[7] In the presence of a catalytic acid the rearranged product can in principle be trapped as an acetal or ketal, and then the 1,3-*syn* diastereomer should be favored on thermodynamic grounds. Remarkably, upon exposure of **1** to benzaldehyde dimethyl acetal and Re_2O_7 (2.5 mol %), essentially a single product was formed in 94% yield after 20 h at room temperature. Thus, the rhenium catalyst performs a dual catalytic function as a transition metal catalyst for the hydroxyl group transposition and as an acid catalyst for acetal formation.

Screening of the reaction parameters demonstrated that although a number of solvents can be used (toluene, Et_2O, THF, CH_2Cl_2),[8] dichloromethane provides the best results in terms of reaction rate. Typically, reactions are characterized by a rapid formation of a diastereomeric mixture of rearranged diol acetals (within ~20 min at room temperature) followed by slow equilibration of the acetals to the 1,3-*syn* product (**3**).

The influence of reaction time with alternative rhenium catalysts is summarized in Table 1. With all three catalysts studied, methyltrioxorhenium (MTO), $Ph_3SiOReO_3$, and Re_2O_7, the rearrangement/acetalization was complete within 3 h at room temperature. As expected, MTO is the least reactive catalyst.[2c,9] Notably, with *all* of the three rhenium catalysts the initial acetal formation was followed by equilibration to **3**. The highest rate of equilibration was observed with Re_2O_7, generating **3** with >98% selectivity after 20 h. With $Ph_3SiOReO_3$, a high level of selectivity (96:4) was also reached after 20 h at room temperature.

Scheme 1. Re-Catalyzed Transposition of **1**

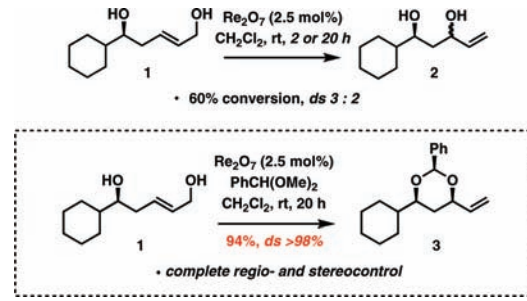
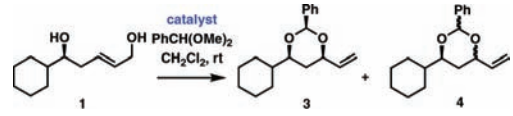


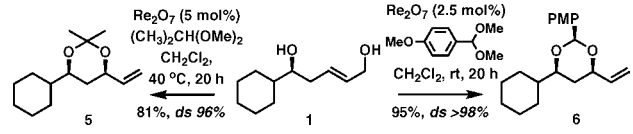
Table 1. Influence of the Catalyst and Reaction Time



entry	catalyst (mol%)	time	conversion[a]	3:4[a]
1	$MeReO_3$ (5)	40 min	~45%	36:64
2	$MeReO_3$ (5)	3 h	complete	40:60
3	$MeReO_3$ (5)	20 h	complete	63:37
4	$Ph_3SiOReO_3$ (5)	40 min	complete	65:35
5	$Ph_3SiOReO_3$ (5)	3 h	complete	87:13
6	$Ph_3SiOReO_3$ (5)	20 h	complete	**96:4**
7	Re_2O_7(2.5)	40 min	complete	80:20
8	Re_2O_7(2.5)	3 h	complete	91:9
9	Re_2O_7(2.5)	20 h	complete	>98:2

[a] Measured by 500 MHz NMR spectroscopy using a crude mixture of products.

Scheme 2. Formation of the Acetonide and PMP-Acetals

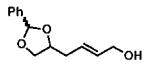
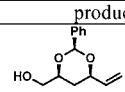
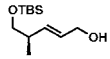
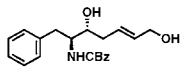
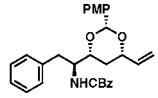
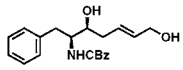
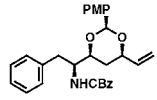
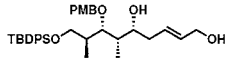
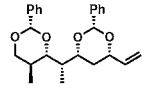
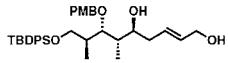
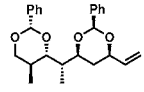
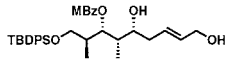
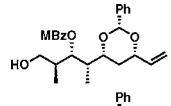
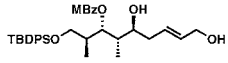
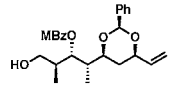
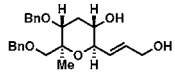
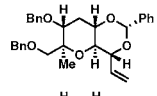
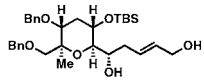
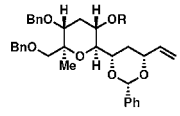
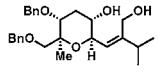
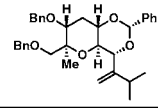


As illustrated in Scheme 2, the highly stereo- and regioselective transposition can be achieved with other commonly employed diol masking groups. Acetonide formation occurred in an 81% yield (96% ds), and the *p*-methoxyphenyl (PMP) acetal **6** was isolated in a 95% yield with greater than 98% diastereoselectivity.

The reaction scope with a range of substrates of higher complexity was explored next (Table 2). Migration of the resident benzylidene group accompanying the transposition was possible as illustrated in entry 1 (Table 2). Desilylation can be accomplished simultaneously without a need for an additional step (entry 2). A Cbz-protected primary amine is compatible with the reaction conditions, and the relative stereochemistry of the amino alcohol has no influence on the stereoselectivity of the reaction (entries 3,

10.1021/ja101673v

Table 2. Scope of the Re-Catalyzed Transposition/Acetalization with Complex Substrates[a]

entry	substrate	product (yield, dr)
1		 80%, 96:4
2		 84%, 85:15
3		 65%, >98:2
4		 71%, >98:2
5		 79%, >98:2
6		 84%, >98:2
7		 76%,[b] 10:1
8		 84%,[b] >98:2
9		 81%, 96:4
10		 82%,[c] >98:2
11		 97%, >98:2

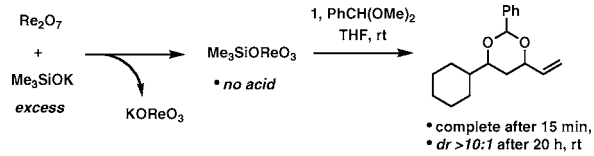
[a] Reactions were performed in CH_2Cl_2 (~0.2 M) with 2.5 mol % of Re_2O_7 and 2.0 equiv of $PhCH(OMe)_2$ or 4-MeOPhCH$(OMe)_2$; dr is determined by 500 MHz ^{1}H NMR.[b] Overall yield after treatment with TBAF.[c] R═H/R═TBS 5.3:1.

4). Upon prolonged exposure (20 h), a complete removal of acid sensitive PMB and TBDPS groups was observed, which were replaced with the benzylidene acetal (entries 5, 6). A more oxidized *p*-methoxybenzoyl (MBz) group and shorter reaction times (4 h) resulted in a much improved conservation of the original protecting groups (entries 7, 8). Functionalized tetrahydropyran substrates underwent the transposition reaction with the generally observed high regiocontrol and high stereoselectivity (entries 9, 10). Thermodynamically disfavored 1,1-disubstituted alkenes can be readily prepared in high yield (entry 11).

An intriguing aspect of the reaction is that the transposition and acetalization are typically complete in an initially nonstereoselective manner within minutes (less than 30 min), followed by relatively slow isomerization to the preferred stereoisomer. In a control experiment, when a 6:3:1 diastereomeric mixture of benzylidene acetals **4** was subjected to the standard reaction conditions (dry CH_2Cl_2, argon atmosphere, 2.5 mol % Re_2O_7, rt, 20 h), a single stereoisomer (**3**) was isolated in 90% yield. In contrast, treatment of the same mixture with *p*-TsOH (5 mol %, dry CH_2Cl_2, argon atmosphere, rt, 21 h) resulted in no change.

As was also noted by Grubbs and Rychnovsky,[4b,7] addition of 0.2 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTMP) completely

Scheme 3. Reactivity in the Absence of a Brønsted Acid



suppressed the transposition and acetalization with either Re_2O_7 or $Ph_3SiOReO_3$. Addition of Bu_4NOAc or a proton sponge also suppressed the reaction. These results may be explained either by increasing the pH of the medium or by a modification of the catalyst through irreversible complexation.[4b,7] To conclusively establish reactivity in the absence of acid or alternative ligands, we prepared the catalyst in situ using an excess of strongly basic Me_3SiOK (0.35 equiv) and Re_2O_7 (0.20 equiv) in THF.[10] As shown in Scheme 3, the system maintained full catalytic activity, indicating a possibility where the acetal formation is likely due to the Lewis acidic character of trimethylsilyl perrhenate.

In summary, we developed a method that allows the control of regio- and stereoselectivity by a neighboring hydroxyl group in the Re-catalyzed transposition of allylic alcohols with accompanying formation of acetals. Further studies aimed at a better understanding of the process are underway.

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Supporting Information Available: Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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