Cascade Reactions

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Cascade Approach to Stereoselective Polycyclic Ether Formation: Epoxides as Trapping Agents in the Transposition of Allylic Alcohols**

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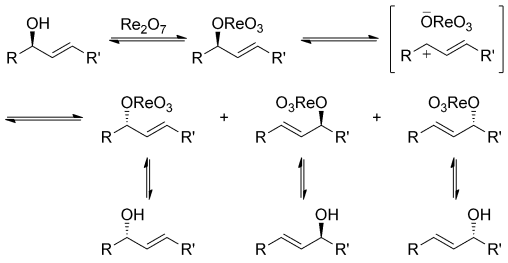
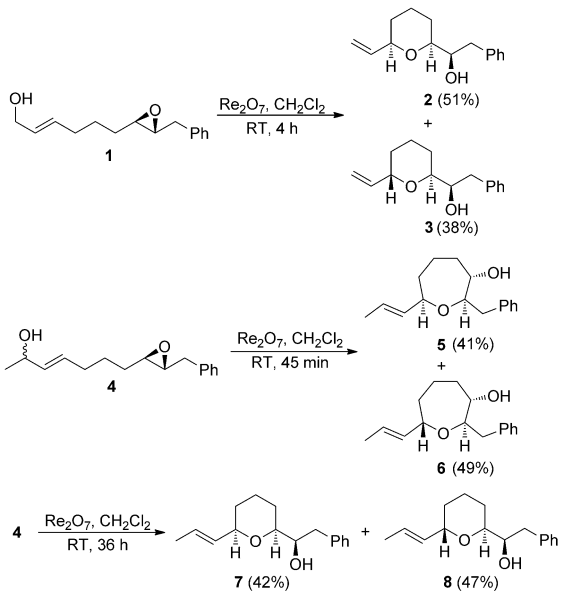
Cascade reactions[1] facilitate complex molecule synthesis through their capacity to generate multiple target-relevant[2] bonds and stereocenters in a single operation.[3] The use of thermodynamic control to dictate product formation further streamlines molecular synthesis by minimizing the need to set multiple stereocenters in the substrates. Rhenium oxide mediated allylic alcohol transpositions[4] are useful in the design of thermodynamically controlled reactions because regiochemistry[5] and stereochemistry[6] are influenced by structural changes. Thus, they are being used increasingly in complex molecule synthesis.[7] A schematic of the process that is consistent with experimental observations and computational studies[8] is shown in Scheme 1.



Scheme 1. Rhenium oxide mediated allylic alcohol transposition.

We have begun a program in which Re_2O_7-catalyzed allylic alcohol transposition reactions[5c] initiate stereoselective ring-forming processes that proceed through trapping the hydroxyl group with a pendent electrophile followed by thermodynamically controlled equilibration. Initial studies employed achiral acetal electrophiles, thereby a stereogenic center in the tether between the nucleophile and the electrophile was required to control the stereochemical outcome. The trapping of transposing alcohols with chiral electrophiles, however, offers significant advantages for the preparation of enantiomerically pure materials through this sequence. The use of epoxides in these reactions is particularly attractive because of their versatile reactivity patterns, whereby they can act as electrophiles to liberate nucleophilic hydroxy groups upon ring opening[9] or as nucleophiles to create electrophilic epoxonium ions upon reacting with a cation.[10] Moreover, several methods are commonly employed to prepare epoxides in enantiomerically pure form.[11] These attributes have led to the development of numerous epoxide-opening cascade reactions.[12] Herein, we report that epoxides can be used as trapping agents for allylic alcohols in rhenium oxide mediated transposition reactions. These reactions are used as the basis for a number of cascade processes in which several electrophiles can be used as trapping agents. Ketones are shown to be effective stereochemical conduits, that allow remote stereoinduction and bidirectional stereogenesis in the synthesis of polycyclic structures. Stereocenters are generated by functionalizing prochiral centers, in contrast to standard epoxide cascade reactions in which an equivalent number of stereocenters are present in the substrates and products. Additionally we show that Re_2O_7 can be adsorbed on silica gel to provide an easily handled and measured source of the catalyst.

The capacity of epoxides to act as trapping agents was demonstrated (Scheme 2) by treating **1** with Re_2O_7 (5 mol%) to produce tetrahydropyrans **2** and **3** in 51% and 38% yields, respectively, after 4 h at room temperature. Resubjection of the isomers to the reaction conditions resulted in no reaction, thereby establishing that this result arises from kinetic control rather than thermodynamic equilibration. The reaction of



Scheme 2. Epoxides as trapping agents in alcohol transposition reactions.

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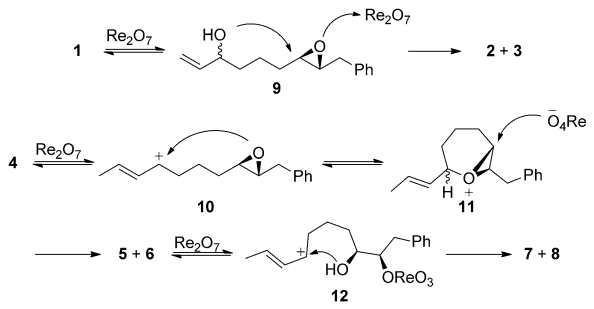
secondary alcohol **4** proved to be more complex. After 45 min the reaction produced a mixture of oxepanes **5** and **6** in a nearly 1:1 ratio. Prolonged exposure in the presence of higher catalyst loading (15 mol%) resulted in the formation of tetrahydropyrans **7** and **8**, again in a nearly 1:1 ratio. Resubjecting **5** to the reaction conditions predominantly provides **7** and resubjecting **6** to the reaction conditions predominantly provides **8**, and **7** and **8** interconvert extremely slowly when resubjected to Re_2O_7.

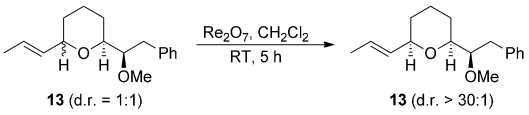
These studies showed that primary and secondary allylic alcohols react through divergent pathways in these processes (Scheme 3). Primary allylic alcohol **1** undergoes transposition to form a mixture of diastereomeric secondary alcohols **9**. The



Scheme 3. Mechanistic details.

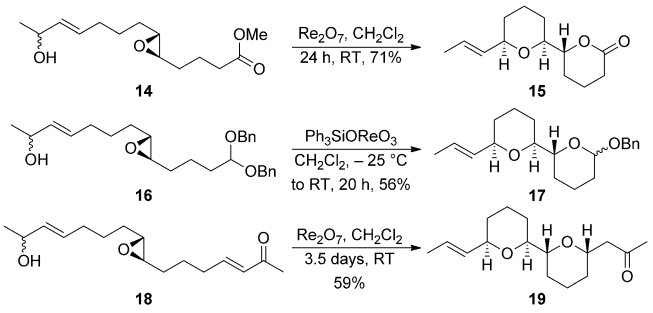
Re_2O_7 or the $HOReO_3$ that forms upon reaction with the hydroxy group, activates the epoxide group toward nucleophilic attack, thus providing the tetrahydropyran products. Secondary alcohol **4**, however, reacts with Re_2O_7 to form allyl cation **10** as the result of stabilization by the additional alkyl group. The epoxide then adds to the cation to form epoxonium ion **11**, which reacts with the perrhenate through a kinetically preferred[10e] *endo* pathway to give an oxepanyl perrhenate ester that decomposes to yield the observed oxepanyl alcohols **5** and **6** as the initial products. Crystallographic[13] and Mosher ester[14] analyses of the products from enantiomerically enriched substrates provided evidence for this pathway by showing that the absolute stereochemistry at the distal carbon of the epoxide (with respect to the allylic alcohol) was retained, whereas the absolute stereochemistry at the proximal carbon was inverted. Re_2O_7-mediated ionization of the oxepanes yields allyl cations **12**, which react with the free hydroxy groups, predominantly with stereochemical retention, to yield the tetrahydropyrans **7** and **8**, as thermodynamic products; these tetrahydropyrans appear to be inert toward further ionization. Racemization in these processes is minimal, thus indicating that allylic ethers undergo ionization at a faster rate than the aliphatic ethers.

The slow isomerization of **8**, in contrast to the isomerizations of **5** and **6**, led us to speculate that the exocyclic hydroxyalkyl group suppresses allyl cation formation. This hypothesis was tested (Scheme 4) by preparing methyl ether **13** as a 1:1 mixture of stereoisomers. Upon treatment of this mixture with Re_2O_7 for 5 h at room temperature, the *cis* isomer was obtained nearly exclusively, thereby confirming that hydrogen bonding suppresses ionization-based isomerization. An analogous terminal alkene showed very little isomerization (not shown), thus confirming the importance of cation stabilization in stereochemical equilibration. These studies indicated that these processes could provide stereochemically pure products if the hydroxy group that results from epoxide opening is used as a nucleophile in a cascade process.



Scheme 4. Stereochemical isomerization.

The initial set of cascade reactions proceeded through the incorporation of an electrophile or proelectrophile at the substrate terminus to trap the hydroxy group following epoxide opening (Scheme 5). Treatment of epoxy ester **14** with Re_2O_7 provided lactone **15** as a single stereoisomer in

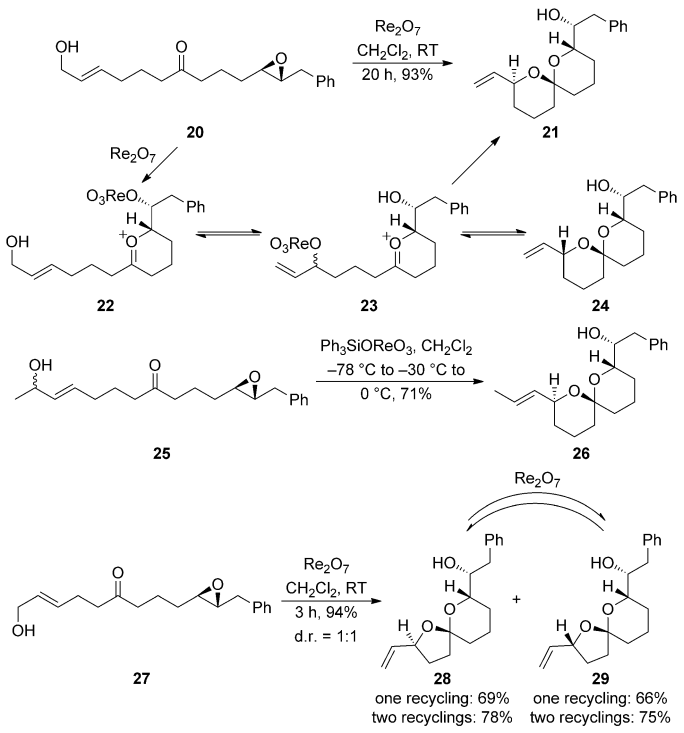


Scheme 5. Cascade reactions. Bn = benzyl.

71% yield, although the removal of MeOH proved to be essential for equilibration. Acetal **16** was prepared to study the viability of using the Lewis acidity of the rhenium oxide to promote the formation of an oxocarbenium ion[5b–c,15] as a trapping group. Treatment of **16** with Re_2O_7 at room temperature led to decomposition, whereas treatment at a lower reaction temperature provided a low yield of **17**. Switching to the more soluble catalyst $Ph_3SiOReO_3$,[16] however, allowed the initial phase of the reaction to be conducted at −25 °C. After the reaction mixture was warmed to room temperature to effect the stereochemical equilibration, **17** was isolated as a single stereoisomer with respect to the tetrahydropyran and as a 5:2 mixture at the anomeric site. This improved efficiency could be attributed to the absence of $HOReO_3$ formation when $Ph_3SiOReO_3$ is used as the catalyst. Shorter reaction times resulted in the observation of more stereoisomeric products, thus confirming that equilibration occurs after the initial cyclization. Cascade reactions with enone electrophiles provided tetrahydropyranyl ketones, as shown through the conversion of **18** into **19**. This reaction provided a bis(tetrahydropyran) within 12 h, but required 3.5 days at room temperature to provide the product as a single stereoisomer. The reaction with an enone electrophile is significant in that it demonstrates bidirectional stereogenesis, in which the introduction of new stereogeneic centers from distal prochiral units are directed by the stereogenic

centers in the epoxide group. Notably, this transformation also proceeds with perfect atom economy.[17]

The use of ketones as stereochemical conduits provides an alternate strategy to chirality transfer from the epoxide groups to remote sites. This approach uses a ketone group as a nucleophile to open the epoxide, thereby generating a chiral oxocarbenium ion[18] that acts as an electrophilic trap for the transposing alcohol. Therefore, the reaction proceeds through acetal ionization and allylic alcohol transposition rather than allylic ether ionization, thus facilitating the transfer of stereochemical information to products that contain terminal alkenes. This feature is demonstrated (Scheme 6) by the reaction of **20** with Re_2O_7, which proceeds within 20 h at room temperature to form spiroacetal **21** as a single stereoisomer in 93% yield. A plausible mechanism for this transformation proceeds through the Lewis acid mediated opening of the epoxide by the oxygen atom of the ketone to yield oxocarbenium ion **22**. The allylic alcohol reversibly transposes to form a mixture of secondary alcohols (**23**) that add to the oxocarbenium ion to form **21** and **24**. The thermodynamically less-stable **24** can revert into a single diastereomer of **23**, which undergoes stereochemical 'editing' through allylic alcohol transposition. Eventually this process leads to the thermodynamically preferred spiroacetal **21** as the sole product of this transformation. An alternative mechanism in which the transposing alcohols add to the ketone to form a mixture of hemiacetals that add to the epoxide to form **21** and **24** can also be envisioned. Secondary alcohol substrates decomposed under these reaction conditions, presumably owing to the myriad pathways that are possible upon forming an allylic cation intermediate. Success was achieved, however, by using $Ph_3SiOReO_3$ and conducting the initial phases of the reaction at −78 °C followed by slow and controlled warming. This protocol resulted in the conversion of **25** into **26** in 71% yield. A minor amount (4%) of a diastereomer was isolated, but the overall yield of **26** was compromised when the reaction was run to complete equilibration.

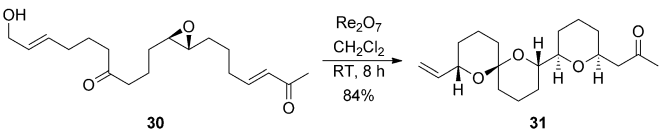


Scheme 6. Ketones as stereochemical conduits.

Lower homologues are also suitable substrates for the process, although product stereocontrol is lost in these transformations owing to the greater conformational freedom for tetrahydrofurans in comparison to tetrahydropyrans. Treatment of **27** with Re_2O_7 provided a 1:1 mixture of spirocycles **28** and **29** in 94% overall yield after 3 h. Although thermodynamic control fails to deliver a major product, either isomer is available in useful quantities through a simple recycling protocol. Thus, **28** can be obtained in 69% yield by resubjecting **29** to the reaction conditions and in 78% yield after two recyclings. Alternatively **29** can be isolated in 66% yield after subjecting **28** to one recycling and in 75% yield after two recyclings.

The use of ketones as stereochemical conduits can be combined with the inclusion of enones as terminal electrophiles to provide an impressive increase in molecular complexity through bidirectional stereogenesis. This is demonstrated (Scheme 7) by the conversion of **30** into **31**. This atom-economical transformation, in which a compound with one ring and two stereogenic centers is converted into a structure with three rings and five stereogenic centers, proceeded in 8 h at room temperature to form the product with complete stereocontrol in 84% yield.

The difficulty associated with the addition of small quantities of Re_2O_7 with precision led us to explore alternative reagent preparations. We discovered that a supported catalyst can be prepared through a convenient protocol in which a slurry of Re_2O_7 and silica gel in Et_2O is stirred for several hours followed by drying under vacuum.[19] We prepared a 10% (w/w) mixture of Re_2O_7 on SiO_2 through this protocol and showed that it is a competent catalyst for the transformations that we have previously developed. Yields and reaction times were similar when the immobilized and free catalysts were employed, with the conversion of **20** into **21** proceeding in 93% yield after 12 h and the conversion of **30** into **31** proceeding in 76% yield after 24 h, for the immobilized catalyst. Notably, the immobilized catalyst could be used for the conversion of **16** into **17** in 60% yield, thus indicating that this easily accessed material could be an alternative to the much more expensive $Ph_3SiOReO_3$. The free-flowing immobilized catalyst is easily weighed, even in humid environments, which cause Re_2O_7 to liquefy. Reactions with the immobilized catalyst do not require the induction periods that



Scheme 7. Bidirectional stereogenesis with a ketone conduit.

are often observed for the free catalyst because of superior dispersion. The catalyst could be recovered by filtration but this recovered reagent showed diminished activity, thus indicating that partial catalyst leaching occurs during the reaction. Thus this preparation primarily serves to facilitate the transformations from an operational perspective, particularly for reactions that utilize high-molecular-weight substrates.

We have demonstrated that epoxide cascade reactions can be initiated by rhenium oxide mediated allylic alcohol transposition reactions. These transformations are possible because rhenium oxide has dual roles as a transposition catalyst and as an acid that enhances the electrophilicity of the epoxide group and promotes product ionization, thereby allowing thermodynamically controlled stereochemical equilibration. The syntheses rely on the functionalization of prochiral carbons rather than the generation of stereochemically defined nucleophiles for epoxide opening. Reactions proceed either by direct addition of the transposing alcohol to the activated epoxide or by using ketones as conduits that relay the stereochemical information from the epoxide to distal regions of the molecule. Maximal increases in molecular complexity are observed when an electrophile is present to trap the hydroxy group that is liberated upon epoxide opening. Enones can be used in this capacity to provide atom-economical transformations that exhibit bidirectional stereogenesis, in which the stereogenic centers in the epoxide guide the formation of stereocenters on opposite ends of the structure.

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