Synthetic Methods

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Heterocycle Synthesis Based on Allylic Alcohol Transposition Using Traceless Trapping Groups**

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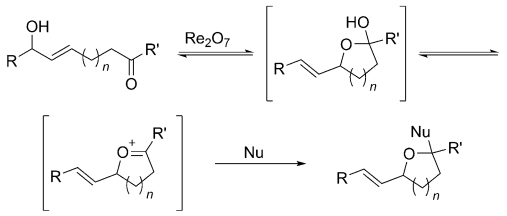
Abstract: *Allylic alcohols undergo transposition reactions in the presence of Re_2O_7 whereby the equilibrium can be dictated by trapping one isomer with a pendent electrophile. Additional ionization can occur when the trapping group is an aldehyde or ketone, thus leading to cyclic oxocarbenium ion formation. Terminating the process through bimolecular nucleophilic addition into the intermediate provides a versatile method for the synthesis of diverse oxygen-containing heterocycles. Understanding the relative rates of the steps in the sequence leads to the design of reactions which create multiple stereocenters with good to excellent levels of control.*

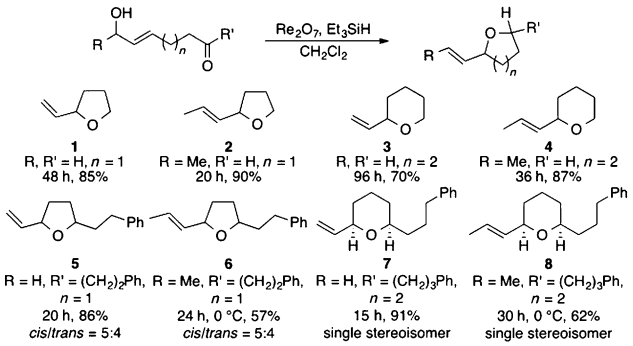
This manuscript describes the synthesis of oxygen-containing heterocycles through a sequence of allylic alcohol transposition, intramolecular trapping, oxocarbenium ion formation, and intermolecular nucleophilic addition. We[1] and others[2] have been exploring the use of allylic alcohol transposition and trapping reactions for stereocontrolled heterocycle syntheses. Our efforts have employed Re_2O_7[3] as a catalyst to initiate reversible allylic alcohol isomerization[4] and promote ring formation through nucleophilic addition of the hydroxy group of one isomeric alcohol to a proximal electrophile. A range of electrophiles are suitable for trapping the hydroxy group, and thermodynamically controlled stereoselectivity can be achieved if the reactions that lead to the final product are reversible. This stereochemical editing strategy can facilitate synthesis by minimizing reliance upon reagent-based stereoselective protocols.

The products in our initial studies generally contain a vestige of the electrophile. Increased versatility for this process could be achieved by employing a traceless trapping group. This approach can be realized through adding the allylic alcohol to a carbonyl group and ionizing the product to form an oxocarbenium ion[5] which can be trapped by an additional nucleophile to terminate the sequence (Scheme 1). The sequence described herein significantly expands the range of products that can be directly accessed through the method by eliminating the remnant of the original trapping group and by utilizing different nucleophiles in the termination step. Exploiting rate differences between the individual steps in the sequence allows the design of unique diastereoselective reactions.



Scheme 1. Transposition, trapping, ionization, and nucleophilic termination. R,R′ = H or alkyl, Nu = nucleophile.

The feasibility of this plan was demonstrated by using Et_3SiH as the terminating reagent. Several examples are shown in Scheme 2.[6] The reactions were conducted with 3 mol% Re_2O_7 and two equivalents of Et_3SiH at room temperature. Many reactions proceed in excellent yield but require somewhat prolonged exposure for completion because the initial products arise from alcohol addition to the intermediate oxocarbenium ion, and is consistent with a recent report from the group of Dussault.[7] The final products form through the ionization of the intermediate acetal products with subsequent oxocarbenium ion reduction.



Scheme 2. Reactivity in tetrahydrofuran and tetrahydropyran formation.

Many factors can influence the rates of these reactions. However several trends become apparent upon analyzing the results in Scheme 2. Secondary allylic alcohol substrates yield products more rapidly than primary allylic alcohol substrates (**2** and **4** versus **1** and **3**). We postulate that this results from increased access to the oxocarbenium ion since steric interactions in the intermediate mixed acetal should promote ionization and, subsequently, reduction. Tetrahydrofurans form more quickly than tetrahydropyrans with similar

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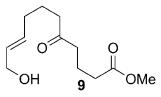
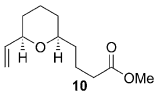
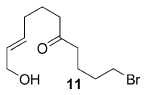
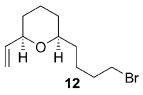
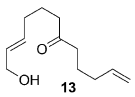
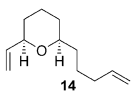
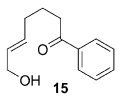
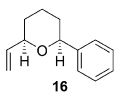
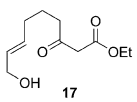
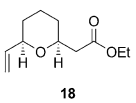
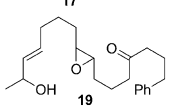
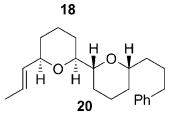
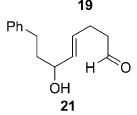
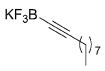
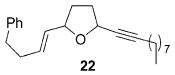
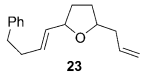
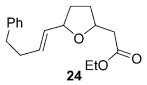
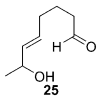
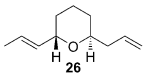
substitution patterns (**1**, **2**, **5**, and **6** versus **3**, **4**, **7**, and **8**). Again this arises from increased access to the oxocarbenium ion intermediate since tetrahydrofuranyl ethers ionize more rapidly than tetrahydropyranyl ethers.[8] Ketone trapping groups promote faster reactions than the corresponding aldehydes (**5**, **6**, **7**, and **8** versus **1**, **2**, **3**, and **4**). However, dehydration becomes a competitive side reaction for ketone substrates which contain secondary allylic alcohols. We postulate that the relative stability of ketone-derived oxocarbenium ions reduces the rate of trapping, and increased substitution augments the potential for allylic cation formation, thereby enhancing opportunities for decomposition through an E1 pathway. Acceptable yields can be achieved for these reactions simply by lowering the temperature. Stereocontrol was excellent for tetrahydropyran formation from ketone-containing substrates, but was poor for tetrahydrofuran formation. This outcome corresponds to established models for nucleophilic additions to cyclic oxocarbenium ions.[9]

Structural diversity in these reactions can be accessed by variations in the substrate, through the use of different ketones as trapping groups, or through the use of different nucleophiles. Examples of these strategies are shown in Table 1.

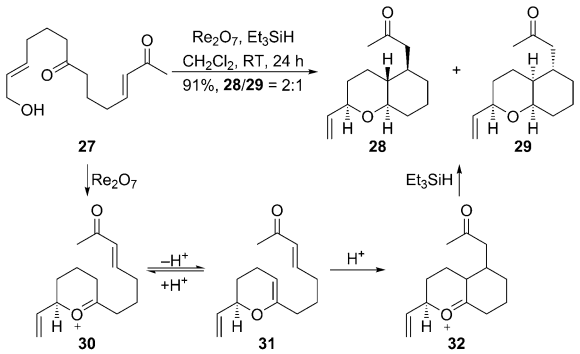
The method is tolerant of numerous functional groups, including moieties which stabilize the carbonyl trapping group through conjugation. Utilizing an epoxide as the trapping group provides opportunities for cascade cyclizations[10] in which stereochemical information from the epoxide is transferred to distal ends of the product. A limited number of nucleophiles was studied to determine the suitability of the protocol for fragment coupling reactions. Potassium alkynyltrifluoroborates,[11] allylsilanes,[7] and silyl ketene acetals add into tetrahydrofuranyl oxocarbenium ions. Stereocontrol was not observed in these reactions, and is consistent with the reductive oxocarbenium ion quenching experiments. Allyl trimethylsilane does not add into tetrahydropyranyl oxocarbenium ions, presumably because these reaction conditions do not induce a sufficient level of ionization to promote reactions with weak π nucleophiles. This problem was circumvented by adding the anion-binding sulfamide cocatalyst $[3,5\text{-}(CF_3)_2C_6H_3NH]_2SO_2$[12] to the reaction to provide **26**. Literature precedent[13] suggests that the cocatalyst enhances reactivity by binding to the perrhenate anion, thereby enhancing the acidity of Re_2O_7 or $HReO_4$. This result is significant because it demonstrates that thrmodynamically disfavored isomers can be accessed and that reductive and alkylative oxocarbenium ion quenching provide complementary 2,6-stereochemical relationships in the products.

An interesting limitation arises from the incorporation of π electrophiles, as shown in the conversion of **27** into **28** and **29** (Scheme 3). The intermediate oxocarbenium ion **30** exists in equilibrium with the enol ether **31**. Intramolecular addition of the enol ether into the enone is faster than the reduction, thus generating the oxocarbenium ion **32**. Reduction of **32** yields **28** and **29**. This pathway suggests new opportunities for reaction development which utilize the trapping group first as an electrophile and then as a nucleophile.

Table 1: Scope expansion.[a]

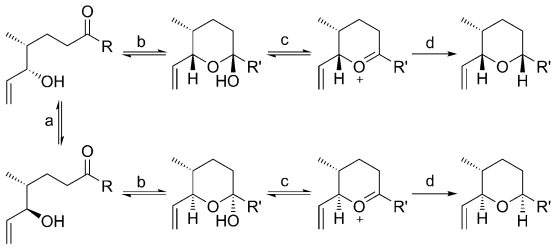
Entry	Substrate	Nucleophile	Product	Yield [%][b]
1		Et_3SiH		81
2		Et_3SiH		92
3		Et_3SiH		90
4		Et_3SiH		92
5		Et_3SiH		85
6		Et_3SiH		68
7				80[c]
8	**21**			86[c]
9	**21**			46[c]
10				83[d]

[a] See the Supporting Information for detailed procedures, substrate syntheses, and stereochemical determination. [b] Isolated as a single stereoisomer unless otherwise noted. [c] Isolated as a nearly 1:1 diastereomeric mixture. [d] Run in the presence of $[3,5\text{-}(CF_3)_2C_6H_3NH]_2SO_2$. See text for details. TBS = *tert*-butyldimethylsilyl.



Scheme 3. Reaction in the presence of a π electrophile.

These results led us to study the impact of a pre-existing chiral center on the stereochemical outcome of the reaction.[2b] Success in this endeavor requires a proper balance between the rates of equilibration with the rates of oxocar-



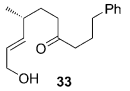
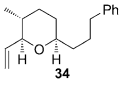
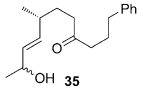
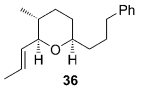
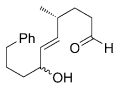
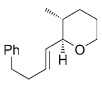
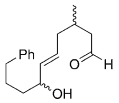
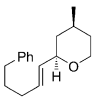
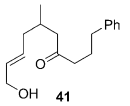
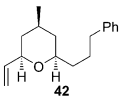
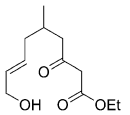
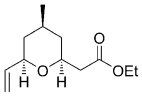
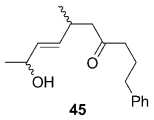
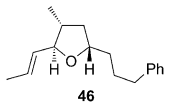
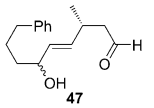
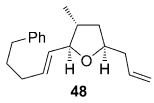
Scheme 4. An analysis of competitive processes for relative diastereocontrol. a = isomerization, b = cyclization, c = ionization, d = termination.

benium ion formation and trapping, as illustrated in Scheme 4. High levels of stereocontrol should be achieved if the stereochemical equilibration step is rapid, if the equilibrium between the hydroxy carbonyl compound and the cyclic hemiacetal does not strongly favor the cyclic hemiacetal, if the ionization step is readily reversible, and if the nucleophilic trapping step is slow. This protocol also requires that the energetic difference between the equilibrating lactols be sufficient to favor one isomer and that the stereocontrol in the trapping step be high.

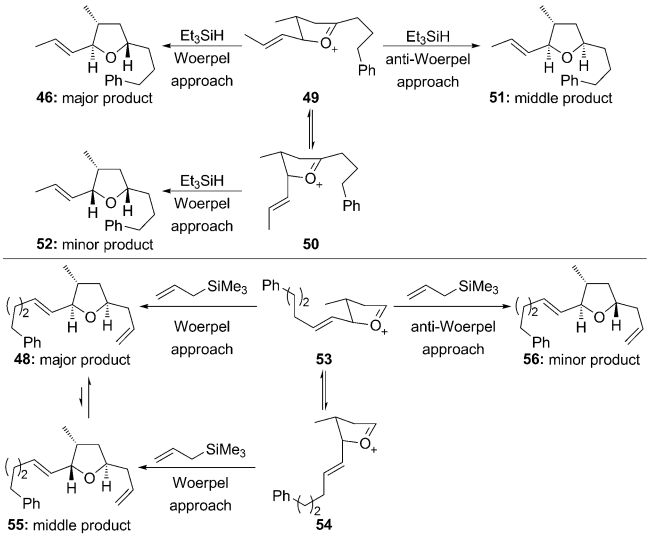
Examples are shown in Table 2. These studies show the relationship between allylic alcohol structure, trapping group, product substitution pattern, and termination agent on reaction diastereocontrol. All tetrahydropyran-forming reactions provided a 2,6-*cis*-stereochemical relationship. A comparison of entries 1 and 2 shows that the termination agent can influence the 2,3-stereochemical relationship, with Ph_3SiH providing a greater degree of stereocontrol, relative to the more reactive Et_3SiH.[14] This outcome is consistent with ionization being reversible and the less reactive trapping agent allowing greater opportunities for stereochemical equilibration. Substrates with secondary allylic alcohols show higher selectivity than similarly substituted primary alcohol substrates. This difference results from the higher rate of stereochemical equilibration through a cationic intermediate. The equilibrium of the cyclization step influences stereocontrol. Aldehydes are more prone to exist in the lactol form than ketones, thus limiting the concentration of stereochemically labile allylic alcohol and leading to diminished levels of 2,3-stereocontrol (entry 4 versus entry 3). Stereocontrol is enhanced for reactions that establish a 2,4-stereochemical relationship in the product (entries 5, 6, and 7). A significant steric clash between an axially oriented substituent and the silane is present in the termination step that leads to the minor product in these reactions. This slows reduction, allows equilibration to the more reactive precursor which leads to the major product.

Stereocontrol in tetrahydrofuran formation was lower than it was for tetrahydropyran formation, but interesting trends were noted. The ketone **45** underwent reductive cyclization to form three isomers in a 5:3:1 ratio, with the isomer **46** being the major product. This reaction proceeds through the oxocarbenium ions **49** and **50** (Scheme 5), with the 2,3-*trans*-isomer **49** dominating, as expected, to avoid eclipsing interactions in the ionization step.[15] Modest selectivity was observed for the approach of the silane from the

Table 2: Relative stereocontrol.[a]

Entry	Substrate	Nucleophile	Product	Yield [%][b] (d.r.)
1	 **33**	Et_3SiH	 **34**	96 (3:1)
2	**33**	Ph_3SiH	**34**	82 (9:1)
3	 **35**	Et_3SiH	 **36**	77 (11:1)
4	 **37**	Et_3SiH	 **38**	83 (3:1)
5	 **39**	Et_3SiH	 **40**	87 (4.6:1)
6	 **41**	Et_3SiH	 **42**	88 (30:1)
7	 **43**	Et_3SiH	 **44**	82 (1:0)
8	 **45**	Et_3SiH	 **46**	75[c] (56:33:11)
9	 **47**		 **48**	95[c] (65:22:13)[d]

[a] See the Supporting Information for detailed procedures, substrate syntheses, and stereochemical determination. [b] Yield of the isolated product. The d.r. values were determined by ^1H NMR spectroscopy. [c] Isolated as a diastereomeric mixture. [d] 79:9:12 upon re-exposure to Re_2O_7.



Scheme 5. Stereocontrol in tetrahydofuran formation.

concave face, opposite to the methyl group, and is in accord with the model proposed by Woerpel and co-workers.[9c] The aldehyde **47** also formed three stereoisomers upon allylative cyclization, with **48** as the major product. Thus stereochemical complementarity is observed for the major products of two tetrahydrofuran-producing reactions. The stereochemical preference for **53** over **54** is diminished relative to the preference of **49** over **50**, as was seen in the tetrahydropyran series. However Woerpel selectivity in the termination step was higher in this process, presumably because of the lower reactivity of the nucleophile, thus leading to a 58% yield of the major product. Resubjecting the product mixture to the reaction conditions at reflux increases the selectivity for the formation of **48**, with the ratio of **48**/**55**/**56** changing to 79:9:12 by ionization of **55** to form the allylic cation intermediate with subsequent closure to form the more stable 2,3-*trans* isomer.

We have demonstrated that heterocycles can be prepared through a sequence of allylic alcohol transposition, intramolecular trapping, ionization, and intermolecular termination. This protocol renders the initial trapping group traceless, thereby conferring significant scope to the process. Primary and secondary allylic alcohols can be used as substrates, ketones and aldehydes are suitable trapping groups, and silanes, π nucleophiles, and alcohols serve as terminating agents in the formation of tetrahydrofurans and tetrahydropyrans. Reactivity is controlled by the concentration of the intermediate oxocarbenium ion and the nucleophilicity of the trapping agent. Therefore the substitution pattern of the allylic alcohol, the trapping group, and the nucleophile influence the rate of the process. Relative stereocontrol can be achieved by rational manipulations of the transposition and termination rates, and complementary stereoisomers can be accessed through reductive and alkylative quenching processes. High stereocontrol can be achieved when the rate of transposition is high and the rate of termination is low. The capacity to couple ring formation with equilibrating stereocenter generation provides a useful alternative to reagent-based stereocontrol for the synthesis of stereochemically rich cyclic structures.

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