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The Use of Rhenium (VII) Oxide as a Catalyst for the Substution of Hemiacetals

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THE USE OF RHENIUM (VII) OXIDE AS A CATALYST FOR THE SUBSTITUTION OF HEMIACETALS

By

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THE USE OF RHENIUM (VII) OXIDE AS A CATALYST FOR THE SUBSTITUTION OF HEMIACETALS

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Rhenium (VII) oxides have proven to be mild and versatile catalysts in organic chemistry. They have previously been utilized to catalyze the transposition of allylic aclohols, Prins reaction, and reductive amination to name a few examples. This thesis reports the application of Re(VII) oxide in the substitution of hemi-acetals with a wide array of nucleophiles including oxo-, thio-, and peroxy-nucleophiles. These reactions proceed efficiently with rapid reaction times and high yields.

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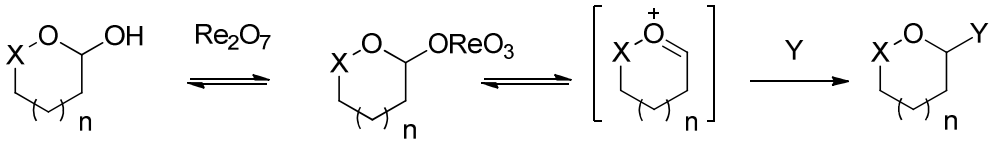
Our group has long been interested in the synthesis of alkoxydioxolanes, alkoxydioxanes, and alkoxydioxines-as will be described later. This project grew from efforts to achieve preparation of these substrates under mild conditions based upon Re(VII)-promoted etherifications. Re_2O_7 has remarkable reactivity, as it reacts with characteristics of both Bronsted and Lewis acids. This thesis describes the application of rhenium (VII) oxides to catalyze the formation of acetals from hemiacetals, including hemiacetals of cyclic peroxides, by utilizing oxygen, sulfur, nitrogen, and carbon nucleophiles. The majority of my work will focus on the substitution of hydroxyl or silyloxy groups from 5- and 6-membered lactols, and the scope of nucleophiles which can be applied in these reactions (Scheme 1). Multiple reviews on chemistry involving Re(VII) oxides have been published.[1,2]



n = 0,1
X = CH_2, O
Y = ROH, RSH, RNH_2

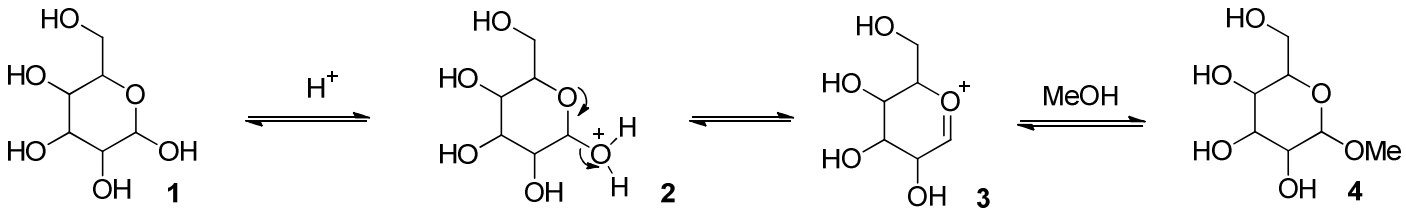
Scheme 1

Section 1

Previous Work

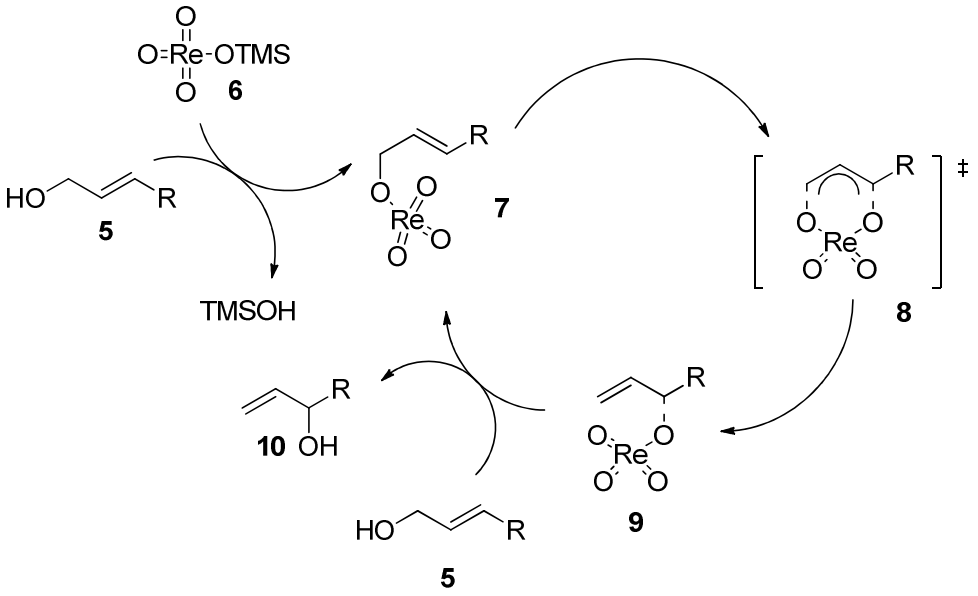
A wide variety of techniques exist for the etherification of hemiacetals. Early work focused mainly on etherification of various glycosides. Fischer[3] discovered that when glucose was heated in a sealed tube containing methanol and HCl, the corresponding methyl-glycopyranoside was produced (Scheme 2). The mechanism for this reaction starts with the protonation of the hemiacetal (**1**) by HCl. Once the alcohol is protonated, **2** loses a molecule of

water, stabilized by the formation of the oxocarbenium ion **3**. Finally, **3** is attacked by methanol to form **4**. Others improved his initial work by heating the reaction under reflux[4] and increasing the concentration of the acid.[5]



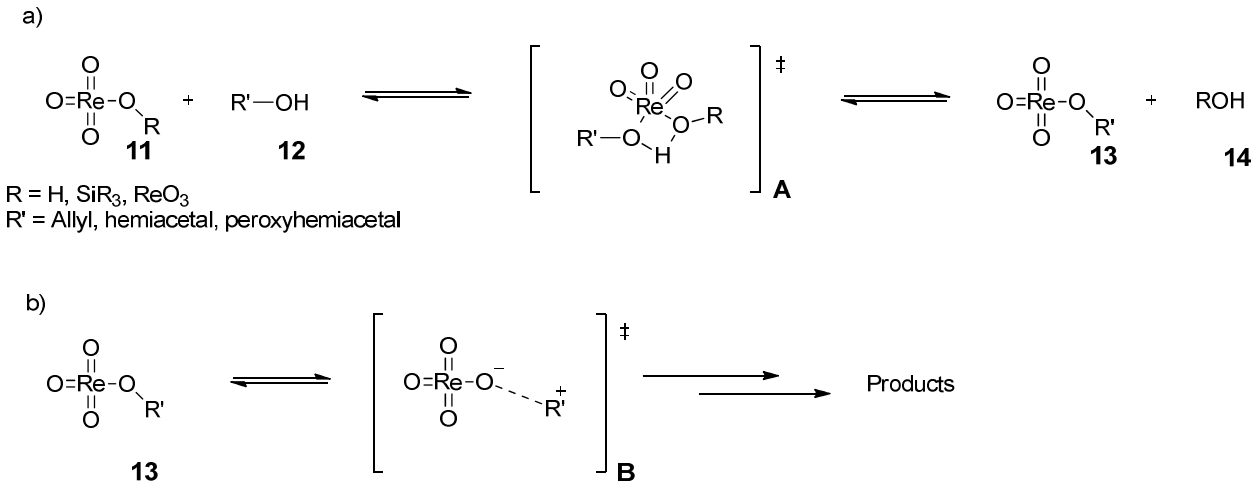
Scheme 2

Similar to the formation of the oxocarbenium ion, allylic alcohols can form a stabilized carbocation, albeit to a lesser extent. The use of rhenium to isomerize allylic alcohols was first reported by Osborn in 1997.[6] In his article he suggests that $ReO_3(OSiMe_3)$ or $ReO_3(OSiPh_3)$ can exchange onto allylic hydroxides as shown below in the mechanism proposed by his paper (Scheme 3). Osborn's mechanism starts with exchange of the Re(VII) catalyst **6** with hydroxyl of **5**, resulting in complex **7** and an equivalent of TMSOH. Complex **7** can undergo a 3-3-rearrangement similar to that of a Claisen[7] rearrangement via **8** to afford **9**.[8] Complex **9** can then continue to complex **10** or go back to compound **6** via the same transition state **8**.



Scheme 3

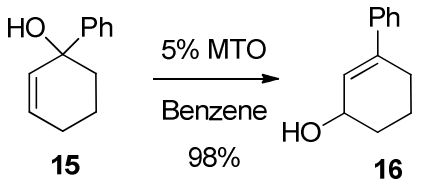
The exchange of Re(VII) with various alcohols was reported by Wilkinson.[9] His article proposed this exchange happening through a transetherification step. As shown below (Scheme 4) in step (a), the alcohol first approaches the Re(VII) catalyst (transition state **A**), followed by a transetherification to afford **13** and **14**. After the exchange, the C-O bond can polarize as shown in transition state **B**, resulting in a reactive electrophilic carbocation-like ion-pair.



Scheme 4

Osborn also shows that this isomerization is successful for silyl protected versions of alcohol **5**.[10] The mechanism proposed is the same as Scheme **3** except the first exchange of the rhenium produces an equivalent of $R_3SiOTMS$ instead of Me_3SiOH. The use of silyl ethers also resulted in a slight alteration of the regioselectivity of products. Solvent effects were also investigated in Osborn's work with the silyl ethers. Notably, the use of coordinating solvents such as THF or MeCN led to a 20-fold or 10-fold decrease in turnover rate, respectively, relative to the rate in CH_2Cl_2.

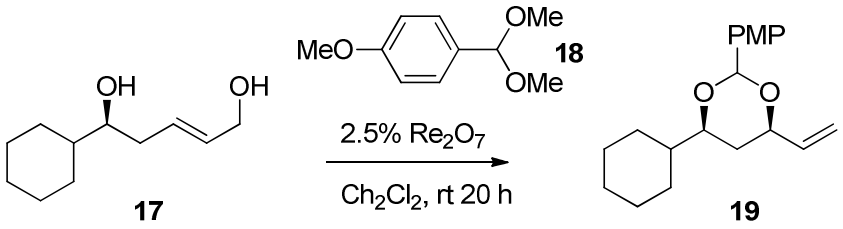
A number of methods for controlling the isomerization regioselectivity have been developed following Osborn's initial work. Gordon[11] has shown that regioselectivity can be controlled when the isomerized alkene is stabilized by conjugation. As seen in Scheme 5 the conjugated product is obtained in 98% yield using methyltrioxorhenium (MTO). Benzene was chosen as a solvent due to its ability to better stabilize the MTO during the reaction.



Scheme 5

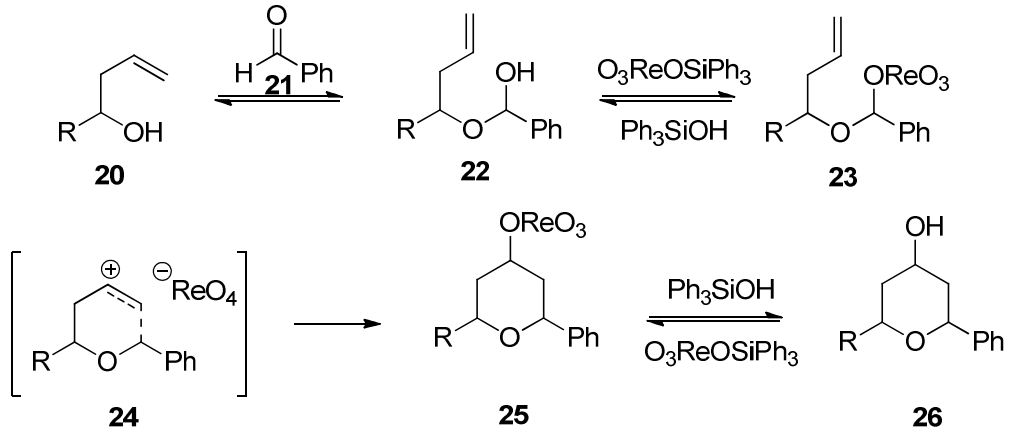
Another approach to controlling reaction regioselectivity was described by Zakarian.[12] His method involves control of the regioselectivity by selective capture of the product alcohol as part of a cyclic acetal. As seen in Scheme 6, the isomerized to a 1,3-diol product can form a 6-membered acetal by attacking the additive. Once the protected diol is formed, the reverse reaction ceases, driving the reaction towards desired product **19**. It should also be noted that a

shared theme of the Re(VII)-catalyzed reactions is that the dialkyl ethers, once formed, are stable and do not further undergo activation by Re(VII).



Scheme 6

Directly relevant to the work discussed in this thesis is the use of Re (VII) to catalyze Prins reactions. Rychnovsky has reported the use of silyl perrhenates to catalyze intramolecular Prins reactions.[13] Scheme 7 illustrates the proposed mechanism of the rhenium (VII) catalyzed Prins reaction. Initial attack on the aldehyde **21** by homoallylic alcohol **20** leads to hemiacetal **22**. Rhenium (VII) then inserts into the **C-O** bond of **22** to afford **23**, which rearranges to **25** via transition state **24**. Lastly, the alcohol is exchanged back on to afford **26** as final product.

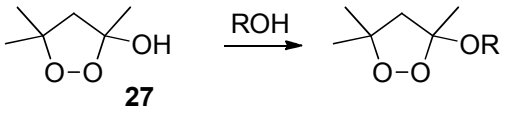


Scheme 7

Section 2

Dr. Charles Schiaffo's Work

The use of rhenium oxide as a catalyst for the etherification of 1,2-dioxolan-3-ols was initially investigated by Schiaffo during his efforts to prepare alkoxydioxolanes as potential antimalarials.[14] His work showed that rhenium (VII) outperformed simple Bronsted acids, such as *p*-toluenesulfonic acid (PTSA), in not only yield, but reaction times (Table 1). With a primary alcohol nucleophile such as 2-phenylethanol the reaction time was decreased three fold (3h to 1h) and the yield was increased by 10% when comparing PTSA to rhenium oxide. This disparity becomes larger as a more hindered alcohol such as 1-adamantanemethanol is used. The reaction time decreases by six-fold (12h to 2h) and the yield is increased by an impressive 50%. A steric limit for both catalysts is reached with 1-adamantanol as a substrate, neither reaction proceeds due to the extremely bulky tertiary alcohol.



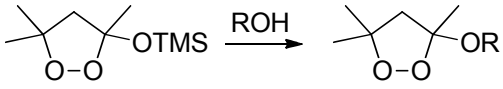
27

Alcohol	Product	PTSA (10 mol%)	Re_2O_7 (1 mol%)
2-Phenylethanol	**28a**	73% (3 h)	83% (1 h)
1-Adamantanemethanol	**28b**	28% (>12 h)	78% (2 h)
1-Adamantanol	**28c**	Failed	Failed

Table 1

Like earlier researchers, Sciaffo found that the versatility of the rhenium oxide catalyst allowed this methodology to be applied to silyl ethers (Table 2). After protecting **27** with

chlorotrimethylsilane to afford silyl ether **29**, Schiaffo was able to obtain comparable yields of **30a** and **30b**, although reaction times were increased in both cases.

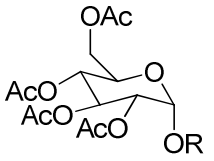


29

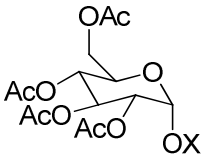
Alcohol	Product	Re_2O_7 (1 mol%)
2-Phenylethanol	**30a**	81% (2 h)
1-Adamantanemethanol	**30b**	65% (>12 h)
1-Adamantanol	**30c**	Failed

Table 2

The reactivity of rhenium oxide was also briefly explored with simple lactols (hemiacetals). Etherification (glycosylation) of sugars was an attractive target for this methodology. However, as seen in Table 3, rhenium oxide was unable to catalyze any appreciable product formation from a sugar hemiacetal (**31a**), the corresponding silyl ether (**31b**), or acetate (**31c**). The poor reactivity was attributed to the adjacent strongly electron withdrawing **C-O** linkages.



XOH
Re_2O_7 (1 mol%)



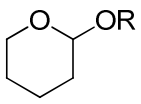
R = H (**31a**)
R = Ac (**31b**)
R = TBS (**31c**)

X = CH_2Ch_2Ph (**32a**)
X = Me (**32b**)

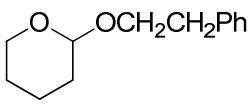
R	X	Yield
H	CH_2CH_2Ph	Failed
OAc	CH_2CH_2Ph	Failed
TBS	CH_2CH_2Ph	Failed
H	Me	4%

Table 3

Fortunately, when a simple lactol such as **33** is used as a substrate, the etherification product **35** is produced in 89% yield (Scheme 8). Without the adjacent alcohols (or their corresponding silyl ethers or acetates) Re(VII) is capable of catalyzing the etherification quite nicely. As expected, the silyl ether **34** also produced **35** in excellent yield.



2-Phenylethanol
Re_2O_7 (1 mol%)
CH_2Cl_2

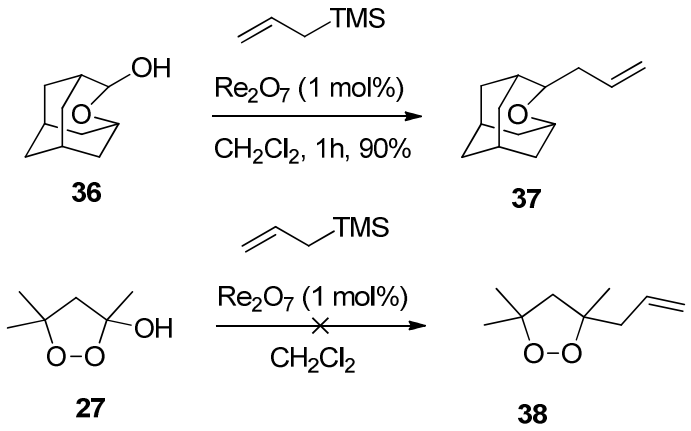


35

R = H (**33**) 89%
R = TBS (**34**) 82%

Scheme 8

Scheme 9 shows that rhenium (VII) also readily catalyzes the allylation of hemiacetals. Compound **36** is converted to homoallylic ether **37** rapidly and in high yield with addition of allyltrimethylsilane. However, the analogous reaction with **27** fails.



Scheme 9

Presumably, the lower reactivity of the dioxanol results from the peroxide being less capable of donating electron density to the carbocation intermediate. The 2nd oxygen of the peroxide may be pulling enough electron density away from the carbocation intermediate to prevent its formation (Sceme 10).

Scheme 10

Section 3

Hypothesis

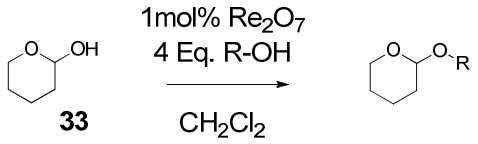
The preliminary work by Schiaffo suggested it would be worthwhile to investigate the scope of Re (VII) activity in substitution reactions involving electron rich alcohols. Re(VII) is an appealing catalyst for various reasons, including mild reaction conditions, ease of work-up/purifications of products, and a certain niche reactivity due to its apparent ability to behave similar to both Bronsted and Lewis acids. Rhenium oxide was chosen to investigate the reactivity due to its relative high stability and tolerance of water compared to other Re (VII) species (Ex. MTO, Me_3SiReO_3). Hemiacetals were chosen as substrates due to their availability and wide use in organic synthesis.

We were interested in several classes of oxygen nucleophiles (alcohols, hydroperoxides, and phenols). We are also interested in whether the Re (VII) oxides would promote reactions of lactols with amines (to form hemiaminals) or thiols (to form mixed O,S-acetals). The reaction with thiols would test the chemoselectivity of the Re (VII) species for hemiacetal exchange versus redox chemistry. Finally, we were curious whether the rhenium oxides could sufficiently activate a hemiacetal to allow reactions with an electron-rich alkene.

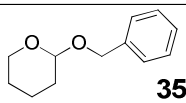
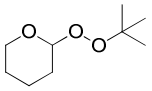
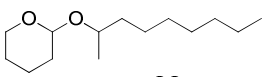
Section 4

Results

These general reaction conditions were employed for screening the rhenium catalyzed substitution of lactols: ***1% Re_2O_7, 2-4Eq. Nucleophile, CH_2Cl_2, rt***. These conditions were chosen based on the results from previous work discussed in earlier sections. Detailed reaction conditions and characterization or references for each product can be found in the experimental section.



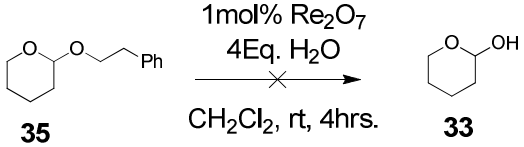
33

Nucleophile	Product	Yield (mol %)
2-phenylethanol	 **35**	89[a]
tBuOOH	 **40**	71
2-Octanol	 **39**	70

a: from Scheme 8

Table 4

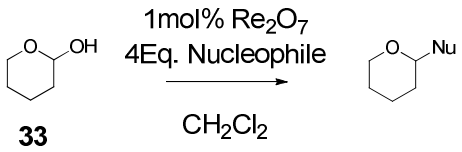
We initially investigated the acetalization of 2-tetrahydropranol (**33**) with oxygen nucleophiles, including *t*-BuOOH and 2-octanol. The starting hemiacetal was prepared from the hydrolysis of dihydro-2H-pyran. Both *t*-BuOOH, which afforded 71% of substituted product (**39**), and 2-octanol (**40**:70%) proved be competent nucleophiles. The decrease in yield of the peroxy nucleophile, compared to the primary alcohol, is likely due to the volatility of the final product and consequent loss of material during removal of solvent under reduced pressure. The lowered yield for acetalization of a secondary alcohol, presumably reflecting an increase in steric hindrance, is consistent with findings by Schiaffo who observed a similar influence of sterics in Re (VII) promoted reactions of 1,2-dioxolan-3-ols.



35 33

Scheme 11

The previous reaction was an investigation into the effects of water. The reaction described in Scheme 11 employed 4 equivalents of the nucleophile, in part because of the perception that we needed to bias an equilibrium vs. the co-product, water. In an effort to determine if the reactions were reversible, the isolated etherification product 2-phenethylacetal **35** was treated with 1% Re_2O_7 and 4 eq. of H_2O in CH_2Cl_2. As seen from the results, the equivalent "reverse" reaction using water as the nucleophile does not proceed to any extent. No formation **33** is observed, providing evidence that rhenium does not readily insert into **C-O** linkages of ethers.



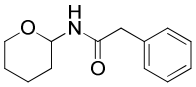
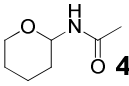
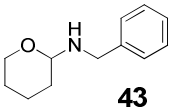
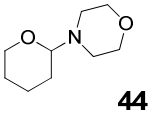
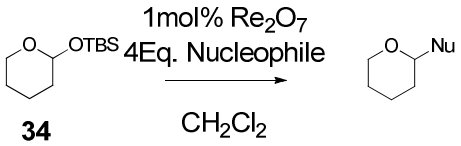
Nucleophile	Product	Yield (mol %)
Benzamide	 **41**	10
Acetamide	 **42**	Failed
Benzylamine	 **43**	Failed
Morpholine	 **44**	Failed

Table 5

We were also interested in investigating the ability of Re(VII) oxides to catalyze substitution of OH by nitrogen nucleophiles. We were unaware of any direct precedent for this

reaction. As seen from Table 5, nitrogen containing compounds proved to be poor targets for this reaction. Benzamide was the only target that formed any product (**41**), with a dismal 10%. The other amine or amide target would not react with the starting material after 4 hours of reaction time and returned only starting material.

As with other reactions involving Re(VII), water was thought to be a problem, as stoichiometric water is produced in each of the reactions for every product. Osborn noted that small amounts of water present during the Re(VII) catalyzed transposition of allylic alcohols decreased the catalytic activity of the Re(VII) catalyst.[6] Previous work by Schiaffo showed that the introduction of sieves to the reaction could increase yield of the products.[13] Despite the results with the hydrolysis of acetals, we felt water might compete with the nucleophile for reactions with hemiacetals. Table 6 reflects an attempt to remedy the possible negative influence of water by employing a sliylated hemiacetal as a substrate. Displacement of the silanol would be expected to lead to removal of a portion of the water as a bis-silyl ether.



34

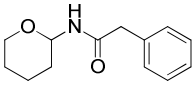
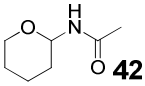
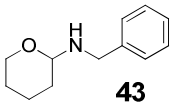
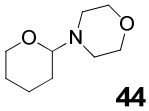
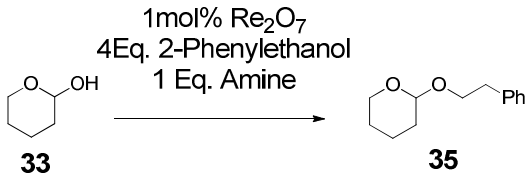
Nucleophile	Product	Yield (mol %)
Benzamide	 41	Failed
Acetamide	 42	Failed
Benzylamine	 43	Failed
Morpholine	 44	Failed

Table 6

The results from Table 6 suggest that water is not necessarily at fault in the failure of reactions with nitrogen nucleophiles. The nitrogen nucleophiles themselves may have inherent incompatibility with the Re (VII) catalyst or they may not react readily with the apparent carbocation formed by the pyranols.



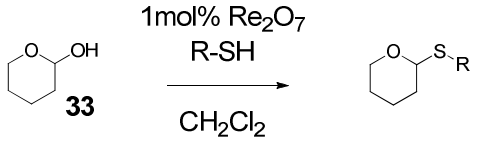
33 35

Amine	Result
Pyridine	Failed[a,b]
Morpholine	Failed[a,b]

Conditions: a: DIchlormethane, rt, 4hrs. b: Dichloroethane, reflux, 4hrs.

Table 7

To further investigate this possibility, the etherification of tetrahydropyranol by 2-phenylethanol, previously demonstrated to proceed in good yield (Table 4), was attempted in the presence of an amine. In an effort to determine whether the failure of the lactols to react with the amines results from the inactivation of the catalyst in the presence of basic nitrogen, we attempted one of the more successful acetalisation reactions in the presence of stoichiometric pyridine or morpholine. As can be seen, neither the product formed by the addition amine nor the product from the addition of the 2-phenylethanol is formed. It is believed that the basic nature of the amines is hindering the ability of the Re (VII) to efficiently catalyze the formation of the carbocation, therefore inhibiting any product formation, regardless of the nucleophile. However, successful reactions employing nitrogen nucleophiles have recently been reported. Ghorai has reported that Re(VII) will tolerate electron poor nitrogen nucleophiles in the reductive amination of amines and substitution of allylic alcohols. [15]



33

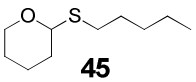
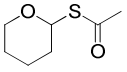
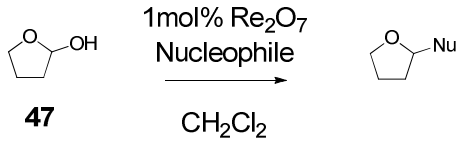
Nucleophile	Product	Yield (mol %)
Pentanethiol	 **45**	88
Thioacetic acid	 **46**	10

Table 8

Sulfur nucleophiles were investigated in the hopes of obtaining a mild method for C-S bond formation. We were not at all sure of the viability of the reaction. Thiols are easily oxidized and the rhenium catalyst is formally in the +7 oxidation state. Table 8 shows that a thiol is tolerated very nicely under the reaction conditions. Product **45** was obtained in an excellent 88% isolated yield. No ring opened dithioacetal products were ever observed. Also, the thiols, as opposed to the amine nucleophiles, do not seem to be sufficiently basic to interfere with the Re (VII)'s ability to catalyze the formation of the ion-pair carbocation intermediate.[1] Compound **46** proceeds resulted in a low 10% yield, presumably due to the adjacent carbonyl group lowering the activity of the nucleophile.

It should be noted that the reactions with the thiol and thioacetate nuclephiles may not follow the same pathways as the reactions with alchohols. It is interesting to compare the appearance of Re (VII) oxide reactions in the presence of O- v.s S-nucleophiles. For the reactions of alcohols previously described in this section, the solid Re (VII) catalyst usually dissolves fully upon addition of the reagent starting material or nucleophile and remains in solution for the duration of the reaction. However, for the reactions with the sulfur containing nucleophiles, the catalyst dissolves initially, and then a black precipitate crashes out of solution, which in turn, slowly dissolves over a few minutes. This may indicate a ligand exchange on the Re (VII) during the course of the reaction, but it does not seem to interfere with the overall ability for the rhenium to catalyze the formation of the ion-pair carbocation intermediate.[1]



47

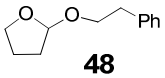
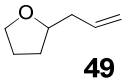
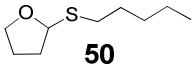
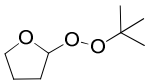
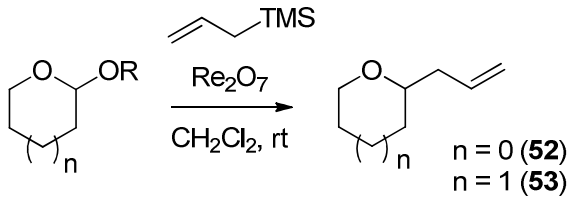
Nucleophile	Product	Yield (mol %)
2-Phenylethanol	 **48**	83
Allyltrimethylsilane	 **49**	85
Pentanethiol	 **50**	80
t-Butylhydroperoxide	 **51**	68

Table 9

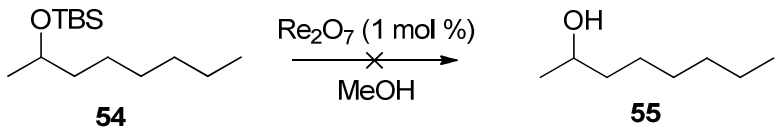
The reactivity of tetrahydrofuranols was also investigated as a substrate for the Re (VII) catalyzed substitution reactions. As seen in Table 9, furanols are excellent substrates for these types of reactions. The yields follow the same general trends as those from the pyranol series, with comparable yields in all cases.



Entry	n	R	Yield (%)
1	1	H	83
2	1	TBS	78
3	0	H	85

Table 10

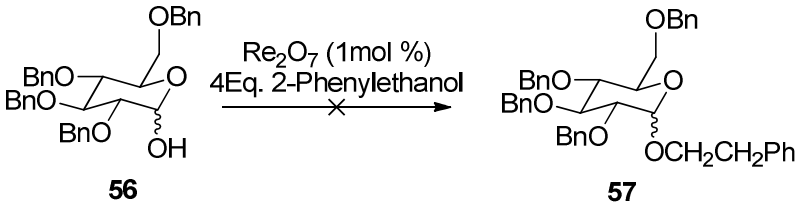
Table 10 shows the ability of Re (VII) to catalyze the allylation of tetrahydropyranol and tetrahydrofuranol. Excellent yields for both lactols (**33, 47**) and the protected silyl ether (**34**). This result is quite different than what was observed by Schiaffo for 1,2-dioxolan-3-ols, which failed to undergo any detectable allylation under comparable conditions. The results are apparently due to the more electron-donating nature of the ether oxygen in the tetrahydropyran vs. the peroxide oxygen in the dioxolane. The sensitivity of Re (VII) oxide displacements to substrate electron-density suggests there is a practical limit to the ability of Re to activate an attached oxygen.



54 **55**

Scheme 12

Re (VII) oxide's apparent ability to insert into silyl ethers of hemiacetals led us to investigate the potential use of this catalyst for the deprotection of silyl ethers. Above is an attempt at deprotecting a simple silyl protected secondary alcohol. The alcohol is unlikely to ionize to the carbocation to give any etherification products, thus avoiding any side reactions. As shown, the Re (VII) is unable to catalyze the deprotection. This reaction further exemplifies Re(VII) oxide's niche reactivity as it will not deprotect silyl ethers of unactivated alcohols. If Re(VII) was simply behaving as a Bronsted acid (as small amounts of perrhenic acid form), some deprotection should be observed, however, none were ever observed.



56 **57**

Conditions a:Dichloromethane, rt, 4hrs b: Dichloroethane, reflux, 4hrs

Scheme 13

Finally, we investigated the ability of the Re(VII) oxides to activate the hydroxyl of an ether-protected glycopyranose. The benzyl protected sugar was made due to the suspicion that the presence of strongly sigma electron withdrawing acyl groups in the glucose pentacetate derivative investigated by Schiaffo were inhibiting carbocation formation. Rhenium does not seem to interact with ether linkages, so the benzyl protected sugar was an attractive target. However, the reaction fails to produce any product. After 4 hours the only material that can be seen by TLC was the starting benzyl protected sugar. This supports Schiaffo's hypothesis that the **C-O** strongly electron withdrawing linkages adjacent to the hemiacetal of the sugar are interfering with the formation of the carbocation.

Section 5

Conclusion

The results from the previous section show the capability of Re_2O_7 to catalyze the substitution of the hydroxyl from tetrahydropyranol and tetrahydrofuranol by oxygen, sulfur, allylsilane and peroxide nucleophiles. These reactions proceed efficiently with a low catalyst loading of 1% and with reaction times less than one hour. The reaction conditions are remarkable mild and no byproducts are ever observed. The reaction either proceeded as expected, or failed to

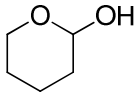
react, giving back all starting material. This is a useful trait when applying these conditions to a valuable substrate that is in the later stages of a synthesis.

Re_2O_7 has a certain niche reactivity which is highly useful. It has reactivity similar to a Bronsted acid, yet does not interfere with proton sensitive groups (such as the deprotection of trimethylsilyl alchohols). Re (VII) also shares a lot of similarities of a Lewis acid. It can catalyze the ionization of hydroxyl and silyl ethers, but it seems incapable of catalyzing the ionization of ethers. The utility Re_2O_7 is just beginning to be discovered and it has a promising future in organic chemistry.

Section 7

Experimentals

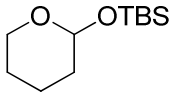
All reagents were used as received from commercial vendors, with the exception of CH_2Cl_2, which was distilled from CaH and THF distilled from sodium/benzophenone. Re(VII) oxide 99.9% was obtained from Alfa Aesar. All reactions were conducted under an atmosphere of N_2 except where noted; round bottom flasks (RBF) and 8 dram glass vials were flame-dried and used as reaction vessels. Thin layer chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates; developed plates were visualized by staining: 1% ceric sulfate and 10% ammonium molybdate in 10% H_2SO_4 (general stain, after charring); 1% N,N'-dimethyl-p-phenylenediamine solution in 1:20:100 acetic acid/water/methanol (specific for peroxides); 1% aq. $KMnO_4$ (for unsaturated compounds). Standard drying and purification procedures consist of drying of organic extracts over Na_2SO_4, removal of solvent under vacuum, and purification by flash chromatography using the indicated eluting solvent. ^1H /^{13}C NMR spectra were recorded at 300 or 400 MHz in $CDCl_3$; peaks are reported as: chemical shift (multiplicity, J couplings in Hz, number of protons).



Tetrahydro-2H-pyran-2-ol (33):

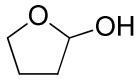
To a RBF containing 3,4-dihydro-2H-pyran (3.36 g, 40 mmol), 0.2M HCl(aq.) (8.33 mL, 1.67 mmol) was added and stirred overnight. Crude product extracted with 3X10 mL CH_2Cl_2 and the organic layer was washed with 10 mL sat. sodium bicarbonate. Solution was then subjected to standard drying and purification with 20% EA/Hex to afford **33** (1.17g, 28.8%). Rf (40%

EA/Hex): 0.40. ^{1}H NMR (400 MHz): 4.90 (m, 1H), 4.02 (m, 1H), 3.56 (m, 1H), 3.45 (d, J = 4.89, 1H), 1.93- 1.78 (2H), 1.57-1.46 (4H). The NMR spectra matched that previously reported.[16]



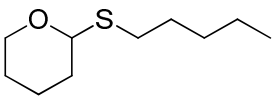
tert-Butyldimethyl((tetrahydro-2H-pyran-2-yl)oxy)silane (34):

In a flame dried RBF, imidazole (408 mg, 6.00 mmol) was dissolved in 45mL THF, followed by addition of **33** (510 mg, 5.00 mmol). TBSCl (900mg, 6.00mmol) was dissolved in 5mL THF and added to the RBF. The reaction was stirred overnight and then quenched with 30 mL H_2O and extracted with diethyl ether (3X10 mL).The resulting solution was subjected to standard drying and purification with 10% EA/ Hex to afford **34** (287mg, 13.3%). Rf (10% EA/Hex): 0.48. ^{1}HNMR (400MHz): 4.91 (m, 1H), 3.99 (m, 1H), 3.51 (m, 1H), 1.89-1.68 (6H), 0.91 (s, 9H), 0.12 (s, 3H), 0.90 (s, 3H). The NMR spectra matched that previously reported.[14]



Tetrahydrofuran-2-ol (47):

To a RBF containing 2,3-dihydrofuran (2.8 g, 40 mmol), was added aq. 0.2M HCl (8.33 mL, 1.67 mmol) and stirred 24 hrs. The crude product extracted with CH_2Cl_2 (3X10 mL) and the organic layer was washed with 10 mL sat. sodium bicarbonate. The resulting solution was subjected to standard drying and purification with 20% EA/Hex to afford **47** (880mg, 25.0%). Rf (30% EA/Hex): 0.32. ^{1}HNMR (400MHz): 4.91 (m, 1H), 4.03 (m, 1H), 3.56 (dt, J = 9.90, 6.02 Hz, 1H), 3.19 (d, J = 4.85, 1H), 1.61-1.47 (4H). The ^{1}HNMR spectra matched that previously reported. [17]



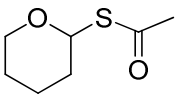
2-(Pentylthio)tetrahydro-2H-pyran (45):

Via Alcohol

To a vial containing Re_2O_7 (2.5 mg, 0.0052 mmol) in CH_2Cl_2 (3 mL), was added pentanethiol (128 mg, 1 mmol), followed immediately by **33** (51 mg, 0.5 mmol). The reaction was stirred for 1 hour, then subjected to standard drying and purification procedures with 30% EA/Hex to afford **45** (104.4mg, 88%). ^{1}HMNR (400MHz) 4.86 (m, 1H), 4.11 (m, 1H), 3.52 (m, 1H), 2.63 (m, 2H), 1.94 (m, 1H), 1.84 (m, 1H), 1.73-1.53 (6H), 1.43-1.29 (4H), 0.91 (t, J = 6.92, 3H). The ^{1}HNMR spectra matched that previously reported. [18]

Via Silyl Ether

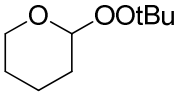
To a vial containing Re_2O_7 (2.5 mg, 0.0052 mmol) in CH_2Cl_2 (3 mL) was added pentanethiol (128 mg, 1mmol, followed immediately by **34** (108 mg, 0.5 mmol). The reaction was stirred for 1 hour, then subjected to standard drying and purification procedures with 30% EA/Hex to afford **45** (80.3 mg, 85.4%).



***S*-(tetrahydro-2*H*-pyran-2-yl) ester (46):**

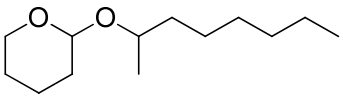
To a vial containing Re_2O_7 (2.5 mg, 0.0052 mmol) in CH_2Cl_2 (3 mL) was added thioacetic acid (76 mg, 1.0 mmol), followed immediately by **33** (65 mg, 0.64 mmol). The reaction was stirred for 1 hour, then subjected to standard drying and purification procedures with 30% EA/Hex to

afford **46** (10 mg, 9.7%) Rf (20%EA/Hex): 0.51. ^{1}HMNR (400MHz) 5.71 (m, 1H), 3.90 (m, 1H), 3.74 (m, 1H), 2.38 (s, 3H), 2.02 (m, 1H) 1.77-1.55 (5H).



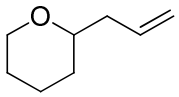
2-(tert-Butylperoxy)tetrahydro-2H-pyran (39):

To a vial containing Re_2O_7 (5.0 mg, 0.010 mmol) in CH_2Cl_2 (5 mL), 5.5M (in decane) *t*-butylhydroperoxide (0.36, 2.0 mmol) was added, followed immediately by **33** (102 mg, 1.00 mmol). The reaction was stirred for 1 hour, then the solution was washed with 5mL H_2O and the resulting mixture was extracted with CH_2Cl_2 (3X5 mL). The resulting solution was subjected to standard drying and purification procedures with 30% EA/Hex to afford **39** (124 mg, 71.2%). Rf (30% EA/Hex): 0.62. ^{1}HMNR (400 MHz): 5.07 (m, 1H), 4.05 (m, 1H), 3.63 (m, 1H), 1.83-1.71 (2H), 1.66-1.53 (4H), 1.30 (s, 9H).



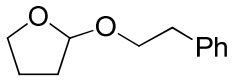
2-(Octan-2-yloxy)tetrahydro-2H-pyran (40):

To a vial containing Re_2O_7 (5.0mg, 0.010 mmol) in CH_2Cl_2 (5 mL), was added 2-Octanol (0.63 mL, 4.0 mmol), followed immediately by **33** (102 mg, 1.00 mmol). The reaction was stirred for 1 hour, then subjected to standard drying an purification procedures with 20% EA/Hex to afford **40** (150 mg, 70.0%). Rf (20% EA/Hex): 0.52. ^{1}HMNR (400 MHz): 3.89 (m, 2H), 3.70 (m, 1H), 2.02 (m, 1H), 1.88 (m, 3H), 1.58 (s, 1H), 1.46-1.56 (1H), 1.25-1.43 (10H), a pair of doublet 1.19 and 1.12 (J = 6.30 and 6.11 respectively 3H), 0.903 (t, J = 7.14 Hz, 3H). The ^{1}HNMR spectra matched that previously reported.[19]



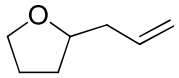
2-Allyltetrahydro-2H-pyran (52):

To a vial containing Re_2O_7 (5.0 mg, 0.0010 mmol) in CH_2Cl_2 (5mL), was added allyltrimethyl silane (1.58 mL, 5.00 mmol), followed immediately by **33** (102 mg, 1.00 mmol). The reaction was stirred for 1 hour then subjected to standard drying and purification procedures with 20% EA/Hex to afford **52** (73.1 mg, 83.1%).[1]HNMR (400 MHz): 5.85 (dqd, J = 17.2, 7.08, 3.04 Hz, 1H), 5.08 (m, 2H), 4.01 (m, 1H), 3.45, (dt, J = 11.5, 2.69 Hz, 1H), 3.34 (m, 1H), 2.34-2.15 (2H), 1.85, (m, 1H), 1.55 (m, 4H), 1.29 (m, 1H). The [1]HNMR spectra matched that previously reported.[20]



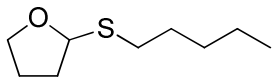
2-Phenethoxytetrahydrofuran (48):

To a vial containing Re_2O_7 (2.5 mg, 0.00050 mmol) in CH_2Cl_2 (5 mL), was added 2-Phenylethanol (244 mg, 2.00 mmol), followed immediately by **47** (44 mg, 0.50 mmol). The reaction was stirred for 1 hour then subjected to standard drying and purification procedures with 20% EA/Hex to afford **48** (73.1 mg, 83.1%).[1]HNMR (400 MHz): 7.27 (m, 5H), 5.14 (m, 1H), 3.95-3.87 (4H), 2.90 (t, J = 7.78 Hz, 2H), 2.07-1.79 (4H). The [1]HNMR spectra matched that previously reported. [21]



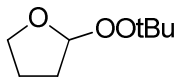
2-Allyltetrahydrofuran (49):

To a vial containing Re_2O_7 (2.5 mg, 0.00050 mmol) in CH_2Cl_2 (5mL), was added allyltrimethylsilane (0.79 mL, 2.50 mmol), followed immediately by **47** (44 mg, 0.50 mmol). The reaction was stirred for 1 hour then subjected to standard drying and purification procedures with 30% EA/Hex to afford **49** (45.1 mg, 85.1%).[1]HMNR (400MHz): 5.85 (ddt, J = 17.2, 10.2, 6.98, 1H), 5.09 (m, 2H), 3.81 (m, 2H), 3.73 (dt, J = 6.43, 6.43 1H), 2.35 (ddd, J = 14.1, 7.1, 7.1 Hz, 1H), 2.25 (ddd, J = 14.1, 7.1, 7.1 Hz, 1H), 1.51 (ddd, J = 11.8, 7.7, 7.7 Hz, 1H). The [1]HNMR spectra matched that previously reported. [17]



2-(Pentylthio)tetrahydrofuran (50):

To a vial containing Re_2O_7 (2.5 mg, 0.00050 mmol) in CH_2Cl_2 (3mL), was added pentanethiol (0.15 mL, 1.00 mmol), followed immediately by **47** (44mg, 0.50 mmol). The reaction was stirred for 1 hour then subjected to standard drying and purification procedures with 10% EA/Hex to afford **50** (69.6 mg, 80.1%).[1]HMNR (400MHz): 4.62 (m, 1H), 3.76 (m, 2H), 2.54 (m, 2H), 1.83-1.63 (6H), 1.39-1.26 (4H), 0.91 (t, J = 6.92, 3H).



2-(tert-Butylperoxy)tetrahydrofuran (51):

To a vial containing Re_2O_7 (2.5 mg, 0.0050 mmol) in CH_2Cl_2 (3 mL), was added 5.5M (in deacane) *t*-Butylhydroperoxide (0.18 mL, 1.0 mmol), followed immediately by **47** (44 mg, 0.50 mmol). The reaction was stirred for 1 hour, then washed with 5mL H_2O and extracted with 3X5 mL CH_2Cl_2. Reaction was subjected to standard drying an purification procedures with 30%

EA/Hex to afford **51** (54.4 mg, 68.0%)[1]HMNR (400MHz): 5.57 (t, J = 4.65 Hz, 1H), 3.98 (t, J = 14.2 Hz, 2H), 1.82 (m, 4H), 1.25 (s, 9H). The [1]HNMR spectra matched that previously reported.[22]

Section 7

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