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Rhenium(V)-Catalyzed Synthesis of 2-Deoxy-α-glycosides

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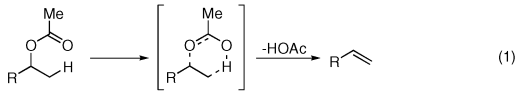
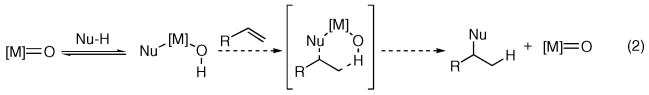
The formation of carbon−heteroatom bonds through acid-mediated electrophilic activation of an olefin has a rich history in organic chemistry.[1,2] The harsh reaction conditions often required for the acid-mediated process prompted the development of alternative strategies involving stoichiometric reagents (Hg^{2+}, I^+, $PhSe^+$) for alkene activation.[2] These methods generate carbon−heteroatom bonds from olefins under mild conditions, but suffer from the requirement for a stoichiometric activating reagent and the need for reductive removal from the substrate. A mild catalytic method that allows for addition of nucleophiles to olefins is therefore highly desirable.

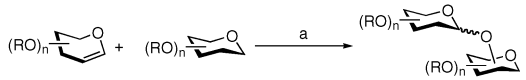


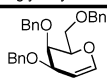
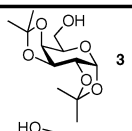
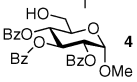
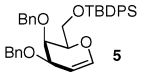
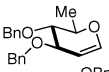
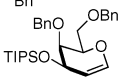
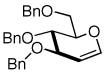
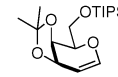
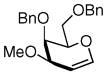
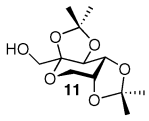
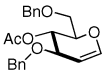
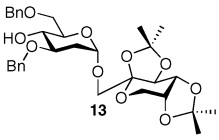


Our interest[3] in the use of high-oxidation-state metal complexes as catalysts for organic reactions led us to consider mechanisms related to the microscopic reverse of the well-studied acetate pyrolysis[4] (eq 1) as a means to add nucleophiles across a carbon−carbon multiple bond. We reasoned that a protonated metal−oxo,[5] generated by the activation of a nucleophile (Nu−H) by the metal−oxygen multiple bond, could replace the hydroxyl group of acetic acid (eq 2). This approach presents several advantages. The use of high-oxidation-state complexes as catalysts should render the reaction tolerant of air and moisture. Additionally, the mild reaction conditions of the metal−oxo-catalyzed reaction could allow for the activation of sensitive olefins, such as glycals. However, successful use of metal−oxo complexes for preparation of 2-deoxyglycosides[6] requires that the traditional behavior of these complexes as oxidizing agents of the nucleophile[7] and glycal[8] be suppressed. Furthermore, the competing Ferrier rearrangement,[9] generally mediated by Lewis acids, must be avoided.

A survey of a number of high-valent metal complexes uncovered a Re(V)−oxo complex, $[ReOCl_3(SMe_2)(Ph_3PO)]$ **1**,[10] as the catalyst of choice. We found that **1** was a competent catalyst for the glycosylation in a variety of solvents; however, nonpolar solvents proved most effacious.[11] With optimized reaction conditions in hand, the scope of the Re(V)-catalyzed glycosylation was examined. The reaction was found to be compatible with a large variety of both glycosyl donors and acceptors (Table 1). Glucal and galactal donors function well in the glycosylation, the latter preceding with high anomeric α-selectivity. The catalytic system tolerated a number of commonly employed protecting groups, including isopropylidene acetals, silyl ethers, acetates, and benzoates. Importantly, the disaccharide product (**13**) from entry 9 served as a viable donor, thus demonstrating the synthetic utility of this method for the preparation of 2-deoxyoligosaccharides (entry 10).

Table 1. Re(V)-Catalyzed *O*-Glycosylation[a]



entry	glycosyl donor	acceptor	yield[b]	α/β[c]
1	 **2**	 **3**	60	α
2	**2**	 **4**	86	α
3	 **5**	**3**	70	α
4	 **6**	**3**	70	2.7:1
5	 **7**	**3**	68	α
6	 **8**	**3**	64	3.5:1
7	 **9**	**3**	60	α
8	 **10**	 **11**	86	α
9	 **12**	**11**	56[d]	α
10	**2**	 **13**	78	α

[a] Reaction conditions: 0.4 M glycosyl acceptor in PhMe, 1.5 equiv of glycal, 1 mol % **1**, 0 °C to room temperature. [b] Isolated yield after chromatography. [c] Determined from ^1H NMR of isolated material. [d] 4-OAc was hydrolyzed to allow purification; reported yield is over two steps.

Having demonstrated the ability to efficiently generate *O*-glycosides using metal−oxo complex **1**, we chose to examine other heteroatom nucleophiles in the reaction. Toward that end, the coupling of tri-*O*-benzyl-D-galactal **2** with *p*-toluenesulfonamide proceeded efficiently, providing the desired amino-glycoside in 81% yield.[12] Catalytic addition of thiols to olefins is particularly challenging because thiols often serve as poisons for transition metal complexes and are readily oxidized to disulfides.[13] We were therefore pleased to find that complex **1** readily catalyzes the addition of thiophenol and 2,3,4-tri-*O*-benzoyl-6-thio-α-methyl-D-glucopyranoside to galactal **2** to selectively afford α-thioglycosides[14] **15** and **16** in 94% and 81% yield, respectively (eq 3).

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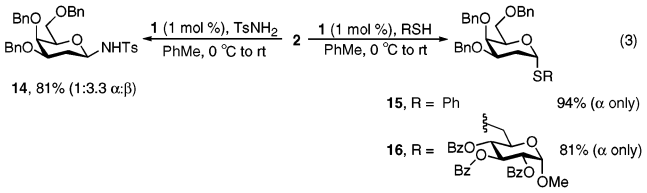
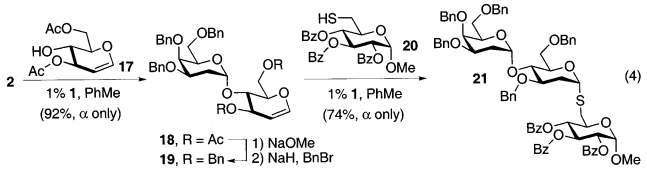


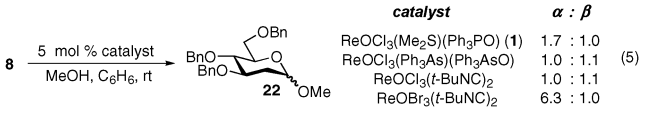
(3)

Our mild catalyst system allows the use of nucleophiles that would be unstable under the conditions traditionally employed for additions to olefins. For example, substitution of electron-withdrawing groups at C-3 renders the glycal completely unreactive[15] and provides the means to couple two glycals using the Re(V)-catalyzed method. Thus, 3,6-di-O-acetyl-D-glucal (**17**) was coupled with galactal **2**, catalyzed by 1 mol % **1**, to afford disaccharide **18** as a single anomer in 92% yield (eq 4). This disaccharide is now poised for further elaboration, through employment of either an oxidative glycosylation[8] or a second Re(V)-catalyzed reaction providing an iterative approach to the synthesis of 2-deoxyoligosaccharides. In the event, rhenium-catalyzed coupling of **19** with thiol **20** provided trisaccharide **21** in 74% yield as a single anomer.[16,17]



(4)

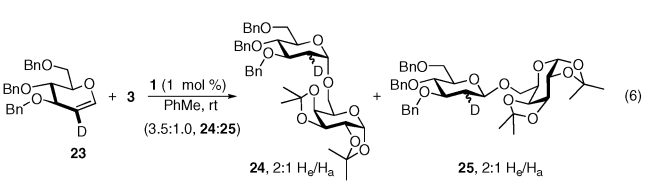
In the hopes of extending application of this method to the synthesis of β-glycosides, we examined the effect of variation of the rhenium−oxo complex on the selectivity of the glycosylation (eq 5). Variation of the neutral ligands to arsine/arsine oxide or *tert*-butylisocyanide slightly increased the amount of β-anomer formed, while changing the anionic ligands from chloride to bromide increased the selectivity for the α-anomer. Unfortunately, these variations did not deliver the desired β-selective glycosylation.



catalyst	α : β
$ReOCl_3(Me_2S)(Ph_3PO)$ (**1**)	1.7 : 1.0
$ReOCl_3(Ph_3As)(Ph_3AsO)$	1.0 : 1.1
$ReOCl_3(t\text{-BuNC})_2$	1.0 : 1.1
$ReOBr_3(t\text{-BuNC})_2$	6.3 : 1.0

(5)

To gain insight on the source of the selectivity, we examined the facial preference of C-2 protonation. Coupling of 2-*d*-3,4,6-tri-O-benzyl-D-glucal (**23**) with **3**, catalyzed by 1 mol % **1**, furnished a 3.5:1 mixture of α- and β-dissaccharides (eq 6). Furthermore, a 2:1 ratio[18] in favor of equatorial protonation was observed in both the α- and the β-anomers, suggesting that the initial olefin activation has very little directing influence on the anomeric selectivity. These results suggest that the reaction is not proceeding through concerted transfer of a proton and nucleophile from the rhenium complex. Furthermore, it appears that the selectivity is determined not in the olefin activation step, but in the transfer of the nucleophile.



(6)

In conclusion, we have demonstrated that a high-oxidation-state rhenium−oxo complex serves as an air- and moisture-tolerant catalyst for the formation of 2-deoxy-α-glycosides from glycals. The catalyst system tolerates a wide range of functional groups and allows for the use of alcohols, sulfonamides, thiols, and glycals as nucleophiles. Traditionally, these high-valent metal−oxo complexes have been associated with oxidative transformations of olefins; however, adjusting the reactivity of these systems to promote alternative reactions is of fundamental importance in expanding the repertoire of transition metal catalysis. Application of this catalytic system to other olefin addition reactions is currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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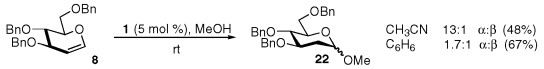

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