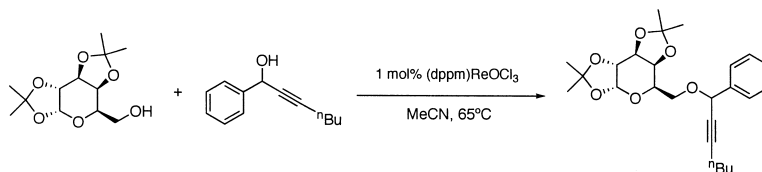Communication

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# A Mild C−O Bond Formation Catalyzed by a Rhenium-Oxo Complex

Benjamin D. Sherry, Alexander T. Radosevich, and F. Dean Toste*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720

Received January 23, 2003; E-mail: fdtoste@uclink.berkeley.edu

Simple alcohols are generally not viable nucleophiles or electrophiles for the formation of carbon−oxygen bonds. Ether formation requires deprotonation of the alcohol nucleophile and a reactive electrophile, such as a halide or pseudohalide.[1,2] For example, formation of sp³-C−O bonds by transition-metal-catalyzed allylic etherification requires the generation of copper[3a,b] or zinc[3c] alkoxides as nucleophiles and allylic esters or carbonates as electrophiles. The flexibility of the alkyne functional group makes transition-metal-catalyzed propargylic etherification an attractive alternative for the preparation of sp³-C−O bonds.[4] Very recently, a ruthenium-catalyzed propargylic etherification[5a] has been reported; however, this reaction is limited to terminal propargyl alcohols.[5b] Herein, we describe the development and application of a rhenium(V)-oxo catalyst for the formation of sp³-C−O bonds by the coupling of simple alcohols and propargyl alcohols.

As compared to the low oxidation state metal complexes[1,3] traditionally used for the formation of ethers, high oxidation state metal-oxo complexes are relatively unexplored. Our efforts toward developing this class of complexes as catalysts for organic reactions[6] led us to consider them as catalysts for propargyl etherification. On the basis of reports that metal-oxo complexes effect the rearrangement of propargyl alcohols to enones,[7] we postulated that an allenolate intermediate[8] (**1**) could undergo S$_N$2′ addition of a nucleophile[9] (eq 1).

(1)
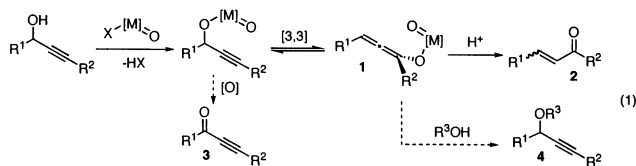
With this hypothesis in mind, we examined a variety of metal-oxo complexes for the selective conversion of propargyl alcohol **5** to propargyl ether **6** (Table 1). A vanadium-oxo complex primarily resulted in oxidation to the ketone,[10] although a small amount of propargyl substitution was observed (entry 1). On the other hand, MoO$_2$(acac)$_2$ was found to be an effective catalyst for the substitution reaction with a 1° alcohol nucleophile (entry 3), but conversion to the enone[7a] dominated when the nucleophile became more hindered. A rhenium(V)-oxo complex bearing a bidentate phosphine ligand (dppm = diphenylphosphinomethane) proved to be the most effective catalyst for the desired transformation. In solvents of high dielectric constant, this catalyst almost completely suppressed the competing oxidation and rearrangement reactions (entry 5).[11] Furthermore, substitution proceeded smoothly without exclusion of moisture or air from the reaction mixture. Further optimization led to the discovery that the catalyst loading could be decreased to 1 mol % without a significant impact on yield or reaction time. In some cases, loadings as low as 0.1 mol % could be employed, although slightly longer reaction times were required (compare entries 12 and 13, Table 2).

Table 1. Selectivity of Metal-Oxo Catalysts for Propargyl Etherification[a]

entry	catalyst	% **2**	% **3**	% **6**
1	V(O)(acac)$_2$	0	29	19
2	[Mo$_2$O$_7$(BINOL)$_2$](NBu$_4$)$_2$	0	10	15
3	MoO$_2$(acac)$_2$	20	trace	77
4	(catechol)ReOCl$_3$	75	0	25
5	(dppm)ReOCl$_3$	trace	trace	96

[a] Reaction conditions: 5 mol % catalyst, 3.0 equiv of alcohol, 1 M (substrate) in MeCN. Conversions were determined by ¹H NMR of the crude reaction mixture.

With optimized conditions for propargylic etherification in hand, we sought to investigate the substrate and nucleophile scope of the reaction. Substitution occurred with a wide variety of propargyl alcohol substrates ranging from simple phenyl substituted (Table 2, entries 1−6) to hetereoaromatic (entries 7, 8), electron-rich aromatics (entries 9−13), and sterically encumbered *ortho*-disubstituted aryl groups (entry 14). Substitution was carried out in the presence of an aryl−bromine bond (entry 17), which is prone to oxidative addition with late transition metal catalysts. Furthermore, pendant alkenyl groups (entries 9, 10) on the substrate were readily carried through the reaction, allowing for subsequent elaboration of the substrate after the etherification event. Notably, acid-labile groups, such as acetals (entry 15), ketals (entry 5), and *t*-butylcarbamates (entries 7, 8), were not cleaved under the reaction conditions.

(2)

a R¹=R²=Me,R³=Ph (69%)
b R¹=R²=Ph,R³=Me (0%)
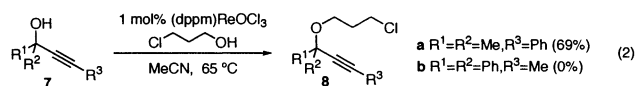
The reaction is not limited to benzylic substrates. For example, tertiary alcohol **7a** readily undergoes propargylic etherification to afford tertiary ether **8a** in 69% yield (eq 2). Conversely, 1,1-diphenylbut-2-yn-1-ol (**7b**) did not undergo substitution, but exclusively underwent rearrangement to the enone, illustrating a steric component to the reaction. Variation in the alkyne substituent from an alkyl to an aryl, trimethylsilyl, or ester moiety is well tolerated, although slightly increased temperatures (compare entry 1 to entries 2, 3) or longer reaction times (entry 11) were required. Remarkably, substitution of the propargyl alcohol occurred preferentially over conjugate addition to the alkynyl ester (entry 11) and was favored over displacement of other leaving groups on the nucleophile, such as primary alkyl halides (entries 1−3, 11). Primary and secondary alcohols (entries 7, 10) participate as nucleophiles in the reaction without a noticeable difference. On the other hand, tertiary alcohols (*tert*-butyl alcohol) produce only moderate yields (<30%) of the ether adduct. In all examples, the reaction regioselectively affords the propargyl adduct, even when competing

Table 2. Re-Oxo-Catalyzed Etherification of Propargyl Alcohols

entry	R¹	R²	R³	time (hr)	yield[a]
1	(benzyl)	n-Bu	(chloroalkyl chain)	8	78
2[b]		C₆H₅	(pentenyl chain)	14	76
3[b]		SiMe₃	(chloroalkyl chain)	8	74
4[b]		SiMe₃	(pentenyl chain)	8	88
5[e]		n-Bu	(diacetonide galactose)	10	60[d]
6[e]		–(CH₂)₃OH	Me–	20	53
7	(N-Boc indolyl)	n-Bu	(PhCH(CH₃)CH₂)	5	79[c]
8		Me	(MeO₂C chain)	7	85[d]
9	(3,4-dimethoxy, vinyl benzyl)	Me	(MeO chain)	2	86
10		Me	(isopropyl)	2	69
11[e]	(4-MeO benzyl)	CO₂Et	(chloroalkyl chain)	10	69
12		Me	Me–	4	82
13[f]		Me	Me–	8	77
14	(mesityl)	Me	(pentenyl chain)	5	79
15	(methylenedioxyphenyl)	Me	(pentenyl chain)	2	85
16	(2,6-dimethoxyphenyl)	Me	(MeO chain)	7	78
17[e]	(4-Br phenyl)	Me	(pentenyl chain)	10	60

[a] Reaction conditions: 1 M propargyl alchohol in MeCN, 3.0 equiv of R³OH. Isolated yield after chromatography. [b] Carried out at 80 °C. [c] Obtained as a 1:1.6 mixture of diastereomers. [d] Obtained as a 1:1 mixture of diastereomers. [e] Run with 5 mol % catalyst. [f] Run with 0.1 mol % catalyst.

intramolecular addition of a pendant alcohol would produce the allene (entry 6).

On the basis of our proposed mechanism (eq 1), which proceeds through a chiral allene intermediate, we anticipated that the propargylic etherification could be stereospecific. However, starting from enantiomerically enriched propargyl alcohol **5**, our rhenium-catalyzed reaction afforded racemic methyl ether **9** (eq 3). These results do not exclude our original mechanistic hypothesis[12] (eq 1); however, an alternative mechanism of ionization to produce an achiral propargyl cation,[13] possibly induced by rhenium complexation of the alkyne,[14] can also be envisioned. A more definitive answer awaits further mechanistic studies.

$$(3)$$
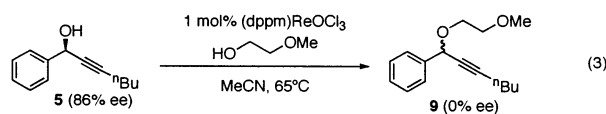
In summary, we have developed an air- and moisture-tolerant etherification of propargyl alcohols using a readily available[15] rhenium-oxo complex as the catalyst. A broad range of functional groups is tolerated, including aryl halides, alkenes, α,β-unsaturated esters, and acetals. The transformation is highly regioselective with

no competing allenic products observed. Activation of the electrophilic alcohol as an ester or sulfonate and deprotonation of the nucleophilic alcohol are not necessary; therefore, water is the only stoichiometric byproduct. Furthermore, displacement of the propargylic alcohol occurs preferentially even in the presence of reactive electrophiles such as primary alkyl halides and conjugated esters. As such, a catalytic single-step activation, ionization, and substitution is realized, as opposed to a four-step alternative that relies on the stoichiometric use of a transition metal species.[4] The broad scope, mild reaction conditions, and experimental ease of this transformation should make it a valuable alternative to classic sp³-carbon−oxygen bond forming methods. Further studies on the mechanism and new applications, including the enantioselective version of this reaction, are ongoing in our laboratories.

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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