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Fischer Carbene Catalysis of Alkynol Cycloisomerization: Application to the Synthesis of the Altromycin B Disaccharide

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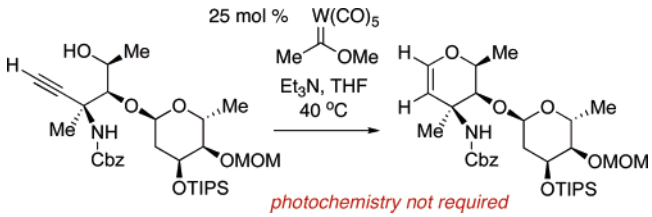
ABSTRACT



The tungsten-catalyzed cycloisomerization of alkynyl alcohols can be conducted without using photochemistry, using a stable tungsten Fischer carbene as the precatalyst for this transformation. A variety of alkynyl alcohols undergo cycloisomerization under these conditions to provide endocyclic enol ethers of five-, six-, and seven-membered ring sizes. The utility of this method is further demonstrated in the stereoselective synthesis of the disaccharide substructure of altromycin B.

The importance of cyclic enol ethers in synthetic organic chemistry has been demonstrated in several contexts, including the efficient synthesis of a variety of biologically important carbohydrate- and oligosaccharide-containing natural products, in which carbohydrate-derived cyclic enol ethers (glycals) are valuable electrophilic partners for a variety of glycoside synthesis processes.[1] Our laboratory has developed group VI transition-metal-catalyzed processes for the synthesis of structurally diverse carbohydrates arising from non-carbohydrate-derived alkynyl alcohols, which has greatly expanded the scope of available substrates for glycal-based approaches to glycoconjugate synthesis.[2] The various methods reported by our laboratory for catalytic cycloisomerization have utilized photochemical activation of molybdenum or tungsten carbonyl in the presence of a tertiary amine, with molybdenum catalysis preferred for the formation of five-membered rings[3] and tungsten catalysis proving more effective for the synthesis of six-[4] and seven-membered ring cyclic enol ethers[5] (Figure 1). However, we are aware that the requirement for photochemical activation has limited the exploration and application of this methodology to laboratories that have specialized photochemical equipment. Thus, we describe herein a new catalytic system which does not require photochemical activation, based on (methoxymethylcarbene)pentacarbonyl tungsten (**3**)[6] as a stable and easily

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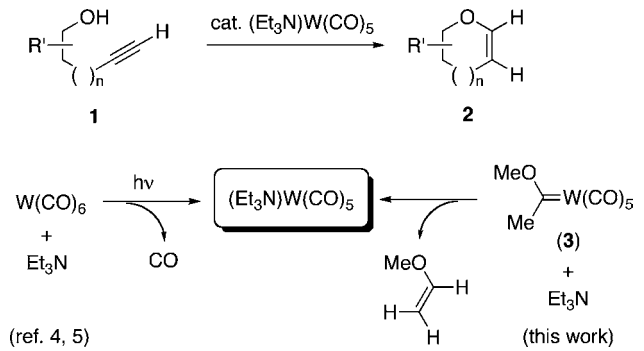
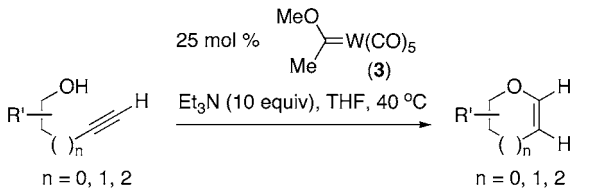


Figure 1. General concepts for generation of $(Et_3N)W(CO)_5$ as a catalyst for alkynyl alcohol cycloisomerization.

prepared precatalyst for the cycloisomerization of various alkynyl alcohols. Our design of the nonphotochemical system is predicated on the reactivity of alkyl-substituted Fischer carbenes to undergo deprotonation and in some cases demetalation to vinylic ethers, with amine−metal carbonyl complexes as the byproduct of base-promoted demetalation reactions.[7]

Optimization of conditions was initially conducted primarily with the simple aminoalkynol substrate **4**,[8] for conversion into the cycloisomeric enol ether **5**. Optimal results were obtained with 25 mol % of tungsten oxacarbene **3** in the presence of 10 equiv of triethylamine and warming to 40 °C in THF solvent for 12 h (Table 1, entry 1), at which time substrate **4** was completely consumed and **5** was produced in 92% isolated yield. The choice of triethylamine as base was critically important to the success of this transformation, as the use of 1,4-diazabicyclo[2.2.2]octane (DABCO)[9] resulted in low conversion of substrate under nonphotochemical conditions. Similar results were obtained with the diastereomeric substrate **6** as well as with several other more complex substrates **8**, **10**, and **12**,[10] with products **9**, **11**, and **13** corresponding to protected glycals of D-acosamine,[11] L-vancosamine,[12] and D-saccharosamine,[13] respectively. Substrate **14**, which differs from **8** only in the protective group pattern of the two oxygen substituents, underwent cycloisomerization under the same conditions to provide the five-membered ring enol ether **15**. With slight

Table 1. Representative Examples of Alkynyl Alcohol Cycloisomerizations Catalyzed by **3**



entry	alkynyl alcohol	enol ether	time	% yield
1	**4**	**5**	12 h	92
2	**6**	**7**	12 h	95
3	**8**	**9**	12 h	95
4	**10**	**11**	12 h	84
5	**12**	**13**	12 h	94
6	**14**	**15**	12 h	77
7	**16**	**17**	24 h (60 °C)	82[a,b]
8	**18**	**19**	24 h (60 °C)	82[b]

[a] With 40 mol % **3**. [b] After treatment with Ac_2O, Et_3N, and cat. DMAP.

increases in temperature and reaction time as well as catalytic loading in some cases, high-yield cycloisomerizations of alkynyldiols **16** and **18** to the seven-membered ring glycals **17** and **19** (corresponding to septanose glycals of D-glucal and D-galactal, respectively)[5,14] were achieved.

Fischer carbene-catalyzed cycloisomerizations of alkynyl alcohols **20** with C3- and C4-oxygen substituents[9b] required additional optimization relative to the photochemical procedure (Table 2), as substantial amounts of the exocyclic glycal were produced from substrate **20b**. As reported by others,[15] sterically bulky propargylic substituents are required for high *endo*-regioselectivity, but we observed that reduced

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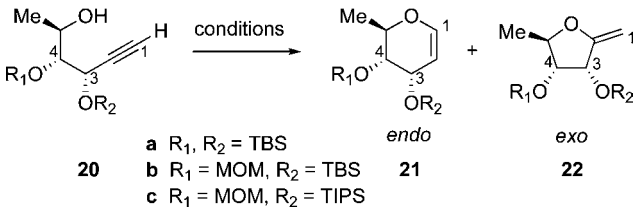
Table 2. Comparison of Nonphotochemical Procedure Catalyzed by **3** vs Photochemical Procedures



20 **a** R_1, R_2 = TBS; **b** R_1 = MOM, R_2 = TBS; **c** R_1 = MOM, R_2 = TIPS — **21** — **22**

entry	substrate	conditions[a]	% yield **21**	% yield **22**
1	**20a**	A	53[b]	0[b]
2	**20a**	B	92	0
3	**20b**	A	53	35
4	**20b**	B	65	20
5	**20b**	C	75	15
6	**20c**	A	85	9
7	**20c**	B	88	7
8	**20c**	C	88	6

[a] A: 40 mol % **3**, 10 equiv of Et_3N, THF, 60 °C, 24 h. B: 25 mol % of $W(CO)_6$, 10 equiv of Et_3N, THF, hν (350 nm), 60 °C, 6 h. C: 25 mol % of $W(CO)_6$, 2 equiv of DABCO, THF, hν (350 nm), 60 °C, 6 h. [b] 30% of **20a** was recovered.

steric bulk in the O4 methoxymethyl (MOM) protective group required increasing the steric bulk at O3 to the triisopropylsilyl ether **20c** to obtain good *endo*-regioselectivity. The formation of exocyclic glycal **22b** from substrate **20b** was rationalized as the action of tungsten pentacarbonyl as a Lewis acid to promote cyclization to **25** (Figure 2), but

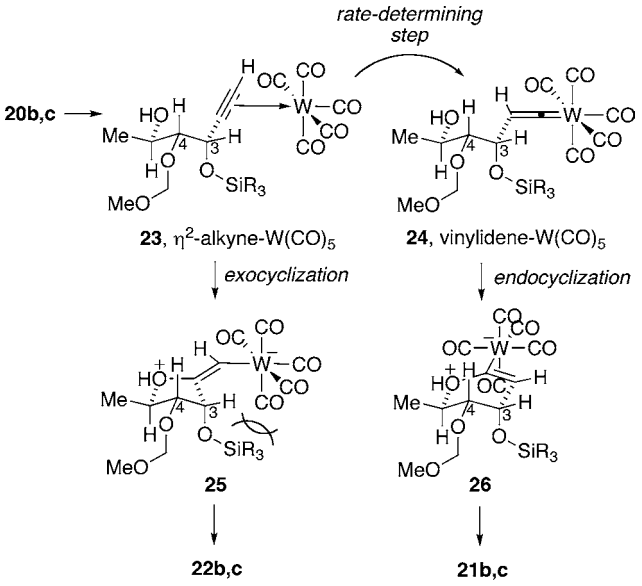
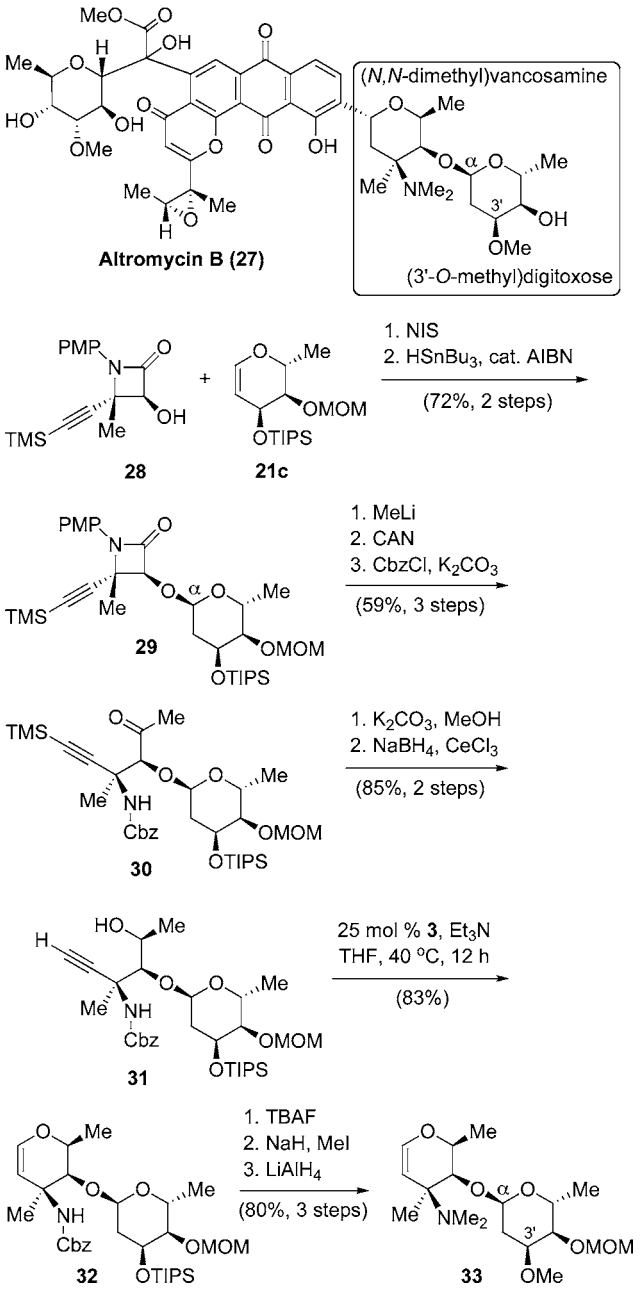


Figure 2. Proposal for substituent effects on regioselectivity.

increasing the steric bulk at O3 in substrate **20c** would increase the steric interaction between η^2-alkyne-tungsten pentacarbonyl and the O3-protective group, thus disfavoring

Scheme 1. Synthesis of the Altromycin Disaccharide



exo-mode cyclization to **25** relative to rearrangement to the vinylidene intermediate **24**, resulting in the formation of glycal **21c** via endocyclic intermediate **26**.[16]

The utility of the nonphotochemical conditions for tungsten-catalyzed alkynyl alcohol cycloisomerization is highlighted in the synthesis of the (*N*,*N*-dimethyl)vancosamine-α-(3′-*O*-methyl)digitoxose disaccharide substructure of altromycin B (**27**, Scheme 1), a glycoconjugate natural product exhibiting in vivo activities against P388 leukemia as well as colon,

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lung, and ovarian tumors.[17,18] Our synthetic strategy for the altromycin disaccharide relies mainly on iterative application of tungsten-catalyzed alkynol cycloisomerization for each of the carbohydrate moieties.[2,9,19] The synthesis commenced with NIS-mediated stereoselective *trans*-diaxial glycosylation[20] of glycal **21c** with the hydroxy β-lactam **28**,[10,21] followed by radical deiodination to produce *O*-glycoside **29**. The sequence of lactam opening to methyl ketone and exchange of N-protective groups to the less basic carbamate of **30**, followed by alkyne desilylation and Felkin−Anh-controlled reduction under Luche conditions,[10] resulted in stereoselective synthesis of alkynyl alcohol substrate **31**. Cycloisomerization of **31** under the standard conditions developed for the simpler examples in Table 1 provided the disaccharide glycal **32** in excellent yield, which was further converted into the *N*,*N*-dimethylamino-*O*-methyl ether **33**.

Although each of the transformations described herein also proceeds by the photochemical method (in some cases with lower catalytic loading), these new conditions now mean that photochemical equipment is no longer required for tungsten-catalyzed cycloisomerization of alkynyl alcohols. In addition, our alkynol cycloisomerization procedure requires neither expensive transition metals nor specialized ligands and is compatible with a broad range of functional groups.

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Supporting Information Available: Experimental procedures and characterization and spectral data on new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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