Alkynol *endo*-Cycloisomerizations and Conceptually Related Transformations

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Abstract: A new family of *endo*-cycloisomerization transformations of terminal alkynes tethered to alcohols, and nitrogen, carbon, and sulfur nucleophiles is based on the concept of intramolecular nucleophilic addition to metal vinylidene electrophilic intermediates. Alkynol cycloisomerizations have been utilized in efficient syntheses of antiviral nucleosides, polycyclic ethers, and oligosaccharides.

Keywords: cyclizations · carbene complexes · nucleosides · oligosaccharides · synthetic methods

Introduction

The invention of new chemical transformations remains an extraordinarily fertile area of research in synthetic organic chemistry. Indeed, many conceptually simple chemical transformations can be envisioned which have not yet been reduced to practice. Additional contributions to the inventory of chemical transformations also facilitate explorations of novel strategies for efficient synthetic access to compounds of commercial and academic importance.

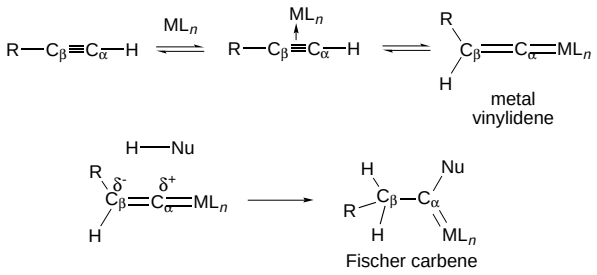
This account presents the conceptual foundation for recent discoveries of reagents and catalysts for *endo*-selective alkynol cycloisomerizations, accompanied by a brief presentation of several mechanistically related transformations as well as some synthetic applications from our laboratory.

Discussion

Background: At the outset of our studies, we believed that *endo*-cycloisomerizations of alkynyl alcohols and other alkyne-nucleophile substrates (Scheme 1) would be valuable chemical transformations, given the commercial and synthetic availability of many functionalized alkyne substrates, as well as the versatility of known methods for regio- and stereoselective manipulations of cyclic heteroatom-substituted alkenes. However, such *endo*-selective cyclization transformations were virtually unknown prior to our work in this area.[1]

Scheme 1. Alkyne nucleophile *endo*-cycloisomerization. Nu = O, N, C, S…

Examination of the organometallic literature revealed that terminal alkynes can be converted into η^2-vinylidene metal complexes by many middle and late transition metal reagents, with migration of the alkynyl hydrogen from the terminal α-carbon to the internal β-carbon atom (Scheme 2).[2] The C_α position of this metal vinylidene becomes electrophilic, and this facilitates regioselective nucleophilic addition to afford Fischer-type metal carbenes.



Scheme 2. Metal vinylidene generation and nucleophilic addition to afford Fischer carbenes.

The intramolecular reaction of simple alkynyl alcohols is a relatively general method for the generation of cyclic Fischer oxacarbenes, exemplified in Scheme 3 by the first reported five,[3] six,[4] and seven-membered[5] cyclic oxacarbenes arising from alkynol cyclizations.

We realized that this method for preparation of stoichiometric Fischer oxacarbenes[6] might be combined with deprotonation under basic conditions to provide metal carbene anions (isoelectronic with ester enolates, Scheme 4).[7] In the 1970's the laboratories of Fischer and Casey had shown that reactions of Group VI oxacarbenes with amine bases afforded conversion to metal-free vinyl ether products.[8] Thus, our

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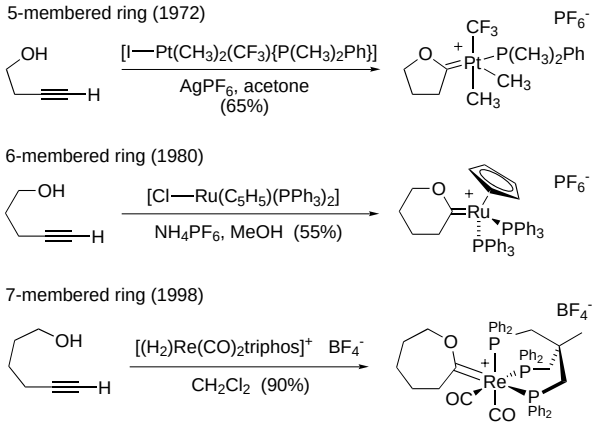
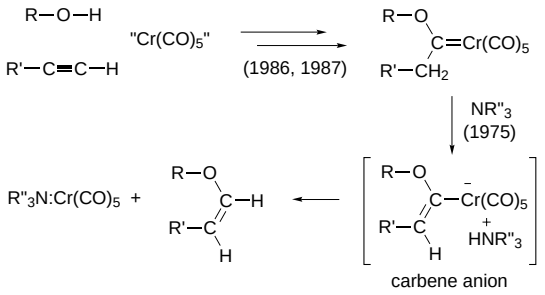


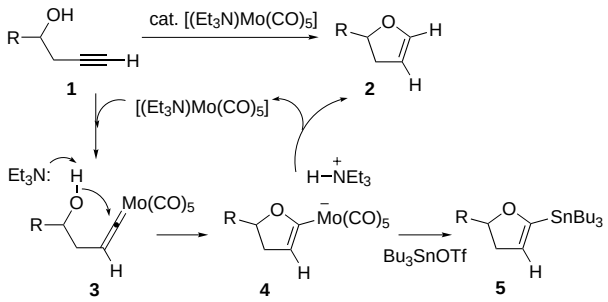
Scheme 3. Precedents for Fischer oxacarbene formation from terminal alkynyl alcohols.



Scheme 4. Multistep protocol for formation of enol ethers from alcohols and alkynes.

initial hypothesis for achieving the desired alkynol cycloisomerization transformation proposed the catalytic reaction of an alkynyl alcohol with a coordinatively unsaturated metal-ligand species in the presence of a base.

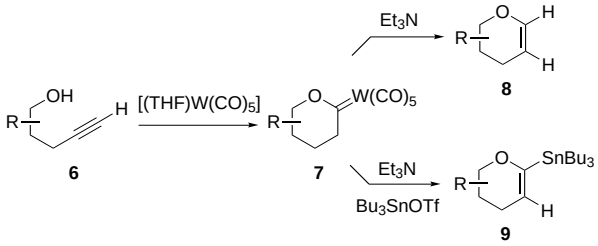
Alkynol cycloisomerizations: In the course of exploring a variety of metal carbonyl reagents and reaction conditions, we found that substituted 1-alkyn-4-ols **1** were transformed into the corresponding 2,3-dihydrofuran isomers **2** in the presence of substoichiometric amounts of trialkylamine-molybdenum pentacarbonyl (Scheme 5).[9] The important cyclic, reactive



Scheme 5. Molybdenum-catalyzed alkynol cyclizations.

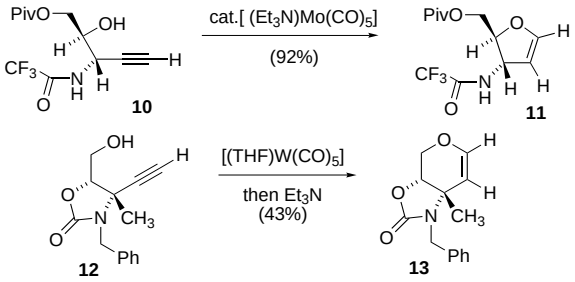
intermediate is apparently the molybdenum carbene anion **4**, which can be intercepted with a number of electrophiles. Along these lines we discovered a new and very mild method for preparing *alpha*-stannyl vinyl ethers **5** based on molybdenum-catalyzed cyclization of alkynyl alcohols **1** in the presence of tributyltin triflate.[10]

Although molybdenum-catalyzed cyclizations are largely limited to five-membered ring formation, we have discovered that tetrahydrofuran-tungsten pentacarbonyl is an effective reagent for cyclizations of 1-alkyn-5-ols **6** leading to production of six-membered rings (Scheme 6).[11] The stoichiometric



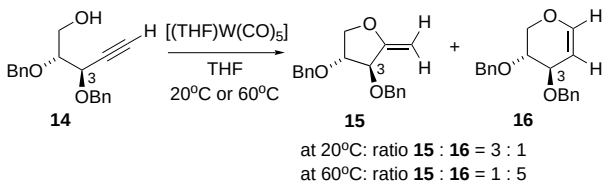
Scheme 6. Tungsten-promoted alkynol cyclizations.

tungsten oxacarbenes **7** are often but not always observed as isolable intermediates, which can be converted into metal-free dihydropyrans **8** upon reaction with triethylamine. The stannyl derivatives **9** are produced from treatment of carbene **7** with tributyltin triflate and triethylamine. The molybdenum and tungsten pentacarbonyl-promoted cyclizations are compatible with a variety of functional groups, including carboxylic esters, amides, and carbamate protective groups, as exemplified in Scheme 7.[12]



Scheme 7. Representative functional group compatibility for alkynol cyclizations.

1-Alkyn-5-ol substrates **14** bearing oxygen substituents at the propargylic position (C_3) rapidly react with the tungsten pentacarbonyl reagent, but these substrates tend to give mixtures of regioisomeric metal-free products, and favors the five-membered exocyclic enol ether **15** when the cyclization reaction is conducted at room temperature. However, the desired *endo*-selectivity for six-membered ring formation (**16**) is largely recovered when the reaction mixture is warmed (Scheme 8).[13]



Scheme 8. Temperature dependence on regioselectivity.

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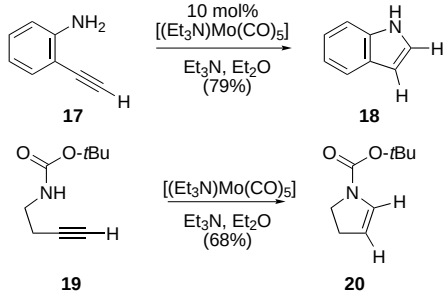
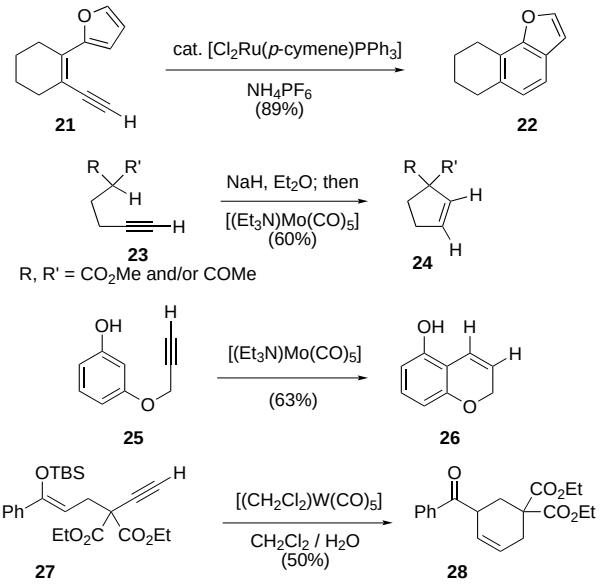
Cycloisomerizations of other nucleophiles tethered to terminal alkynes: This concept has been extended to cycloisomerization reactions with nitrogen, carbon, and sulfur nucleophiles. Although basic nitrogen substituents are incompatible with Group VI metal pentacarbonyl reagents, alkynylaniline **17** and alkynylcarbamate **19** (Scheme 9) are suitable substrates for cycloisomerization, providing the products indole **18** and cyclic enecarbamate **20**, respectively.[14]



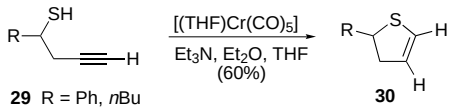
Scheme 9. Azacycloisomerizations of alkynyl-nitrogen substrates.

A variety of carbon nucleophiles also participate in vinylidene additions arising from metal-promoted rearrangements of terminal alkynes (Scheme 10). The first examples of this reaction were reported by Merlic and Pauly, who showed that diene-yne substrates such as **21** undergo cycloisomerization to the aromatic product **22** under ruthenium catalysis.[15] We have found that activated methylenes **23** also participate in cyclizations with terminal alkynes to afford cyclopentenes **24**,[16] and phenolic nucleophiles **25** undergo cycloisomerization to afford the benzopyran product **26**.[17] Maeyama and Iwasawa have recently reported mechanistically related $[W(CO)_5]$-promoted carbocyclizations of terminal alkynes tethered to silyl enol ethers **27**.[18]

We have also demonstrated the first examples of thiacycloisomerization of thiol-alkyne substrates (Scheme 11). For instance, alkynylthiol **29** undergoes molybdenum and chromium-promoted cycloisomerization to the dihydrothiophene



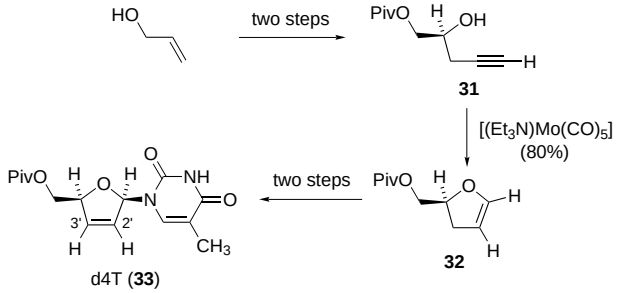
Scheme 10. Carbocycloisomerizations of alkynyl-carbon nucleophiles.



Scheme 11. Thiacycloisomerizations of alkynyl-sulfur nucleophiles.

30. The chromium-promoted procedure appears to be superior, providing a 60% isolated yield of **30** with less than 0.5 equivalents of the chromium carbonyl reagent.[19]

Synthetic applications: Not only is the alkynol cycloisomerization transformation a novel and direct method for forming dihydrofurans and dihydropyrans, but this reaction also provides an effective method for the efficient synthesis of bioactive glycoconjugates. For instance, the cycloisomerization reaction of alkynyl alcohol substrates is a key transformation in a five-step enantioselective synthesis of the HIV reverse transcriptase inhibitor d4T (**33**, Scheme 12).[20] The

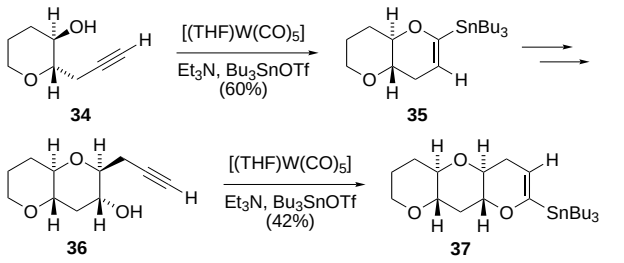


Scheme 12. A short, enantioselective synthesis of the anti-AIDS drug d4T.

alkynyl alcohol **31** arises from Sharpless–Katsuki enantioselective epoxidation of allyl alcohol followed by lithium acetylide opening of the epoxide intermediate, whereupon molybdenum-catalyzed cycloisomerization transforms the acyclic substrate **31** into a highly deoxygenated furanosyl glycal (1,2-endocyclic enol ether) **32**. This metal-free cyclization product is then stereoselectively glycosylated with thymine, and the resulting iodonucleoside undergoes regioselective elimination to place the alkene in the desired 2′,3′-position for a short and efficient synthesis of this clinically valuable anti-AIDS drug.

The alkynol *endo*-cyclization reaction coupled with the novel stannylation of the metal carbene intermediate has been utilized in an iterative synthesis of *trans*-fused polypyran substructures, as exhibited in the brevetoxin/maitotoxin natural-product family (Scheme 13).[21] Although alkynol cycloisomerization methodology is currently restricted to five- and six-membered ring products, and efficient production of the tricyclic compound **37** is hampered by a multistep reaction sequence utilized for generation of alkynol **36** from stannyl enol ether **35**, these limitations might be eventually overcome by further methodology development leading to seven-membered ring synthesis (cf. Scheme 3) coupled with other methods for alkynol generation from endocyclic enol ethers.[22]

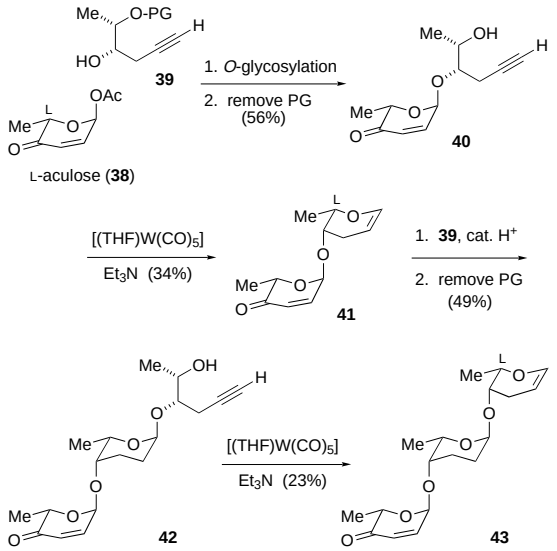
We recently disclosed a novel strategy for oligosaccharide synthesis, in which enantioselective synthesis of pyranose glycals by alkynol cycloisomerization is coupled with stereo-



Scheme 13. Iterative alkynol cyclization approach to *trans-syn-trans* polypyrans.

selective *O*-glycosylation of the alkyne-containing alcohols.[23] Such a strategy is unprecedented for oligosaccharide synthesis, which is classically conducted by coupling together two preformed carbohydrate components. Although many glycoconjugates are composed of inexpensive D-sugars (i.e., glucose, galactose, mannose), the less readily available L-sugars, as well as highly deoxygenated sugars and amino sugars, are found in some glycoconjugates that exhibit important biological activities, and the preparations of unusual monosaccharides require multistep synthetic routes prior to glycosylation.

Our new strategy for oligosaccharide construction involves iterative utilization of alkynyl alcohols **39** as the nucleophilic component (glycosyl acceptor) for glycosylation (Scheme 14). After glycosylation another hydroxyl group is then unmasked to afford alkynol **40**, which cyclizes via a tungsten oxacarbene intermediate, leading to a higher-order oligosaccharide bearing a glycal **41** at the reducing terminus. An additional cycle of this procedure provides a short synthesis of the trisaccharide moiety **43** (L-aculose-α-L-rhodinose-α-L-rhodinose) found in aquayamycin platelet aggregation inhibitors. The relatively mild conditions of the alkynyl alcohol cycloisomerization protocol are compatible with the acid-sensitive glycal and *O*-glycoside bonds, as well as the L-aculose component (arising from **38**), which is quite sensitive to basic and nucleophilic reagents. As modern methods in enantioselective synthesis can provide alkynyl alcohol building blocks with virtually all



Scheme 14. New strategy for oligosaccharide synthesis featuring iterative alkynol cycloisomerization (PG = protecting group).

possible diastereo- and enantiomeric patterns, we predict that this strategy will be applicable for the synthesis of a wide range of hexose glycals and oligosaccharide compounds.

Acknowledgments

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[24] Note in proof: A high-yield, tungsten-catalyzed cycloisomerization procedure for dihydropyran synthesis has been recently developed in our laboratory: K. S. Reddy, F. E. McDonald, unpublished results.

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