A Mechanistic Dichotomy in Ruthenium-Catalyzed Propargyl Alcohol Reactivity: A Novel Hydrative Diyne Cyclization
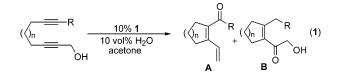
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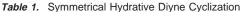Received May 29, 2003; E-mail: bmtrost@stanford.edu

The discovery of new reaction manifolds is often possible through greater understanding of mechanisms and the factors controlling various pathways. The development of new mechanistic models to explain unexpected product formation in one case can lead one to discovery of novel reactivity in related systems.
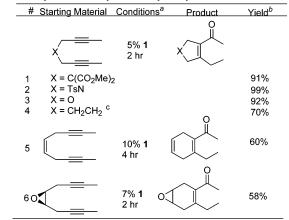
In this communication, we demonstrate the delicate balance among several mechanisms by a simple change of substrate in ruthenium-catalyzed reactions of diynes. Recently, we have developed a [CpRu(CH$_3$CN)$_3$]PF$_6$ (1) catalyzed diyne-ol cyclization to produce cyclic dienones and dienals.[1] We proposed a mechanism for this reaction based upon the known propensity of 1,6- and 1,7-diynes to form ruthenacyclopentadienes with coordinately unsaturated Ru(II).[2] Elimination of a molecule of water was then proposed to precede attack of water at the incipient carbene carbon center either through direct attack or metal-coordination and insertion. The elimination step was proposed to occur first in relation to the related intermolecular dimerization,[3] which only works with propargyl alcohols, as well as the fact that the reactivity decreases in the order tertiary > secondary > primary propargylic alcohols. Indeed, while exploring primary propargyl alcohol diynes for the synthesis of kainic acid,[4] along with the expected product **A**, we found a side product **B** resulting from addition of a water molecule to the carbon adjacent to the hydroxyl group (eq 1). A possible explanation

envisions direct attack of water on the metallacyclopentadiene in relation to Kirchner's stoichiometric work on the addition of nucleophiles to simple metallacyclopentadienes.[5] This led us to investigate whether the propargylic oxygen was required for cyclization. We now report, that simple nonterminal diynes cyclize in the presence of ruthenium catalyst **1** and water to form α,β-unsaturated ketones in good to excellent yields (eq 2, path a and Table 1).
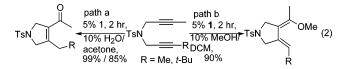
While it could be envisioned that the tertiary, secondary, and primary diyne-ols, as well as the simple diynes, operate by the same mechanism, and only result in different products because of a facile elimination pathway, our current work makes evident that these two reactions operate by distinct mechanisms, with primary propargyl alcohols bridging the gap between these two pathways. The first clue of a new mechanistic manifold was the contrasting reaction rates. The diyne-ol reactions occur rapidly with 1 mol % **1** and ~1 equiv of water;[6] however, for cyclization of simple diynes, excess water and higher catalyst loadings are required for reaction to occur at a reasonable rate. Also, diynes containing terminal alkynes did not lead to the expected products; whereas, terminal diyne-ols give dienals. Electron-deficient diynes also did not lead to expected products, while in the case of the diyne-ol reactions,

Table 1. Symmetrical Hydrative Diyne Cyclization

#	Starting Material	Conditions[a]	Product	Yield[b]
1	X = C(CO$_2$Me)$_2$	5% **1** 2 hr		91%
2	X = TsN			99%
3	X = O			92%
4	X = CH$_2$CH$_2$ [c]			70%
5		10% **1** 4 hr		60%
6		7% **1** 2 hr		58%

[a] The reactions were carried out at 0.1 M (in substrate) in 10 vol % water/acetone at 60 °C. [b] Isolated yields. [c] Run with 10% **1**.
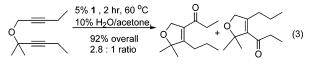
the corresponding substrate cyclizes readily.[7] One of the most mechanistically revealing experiments is the addition of methanol instead of water. Simple diynes cyclize rapidly in acetone or dichloromethane with 10 vol % MeOH to yield dienol ethers as single isomers[8] in excellent yields (eq 2, path b).

We anticipate that the isomer that is seen results through minimization of steric strain in the product. On the other hand, diyne-ols react very slowly with methanol to yield a mixture of dienones and the corresponding dimethylacetals. Our current mechanistic understanding is depicted in Scheme 1. We believe that Path A is the predominate reaction manifold for tertiary and secondary diyne-ol substrates, while Path B is followed by simple diynes, and primary diyne-ols may react by both pathways.
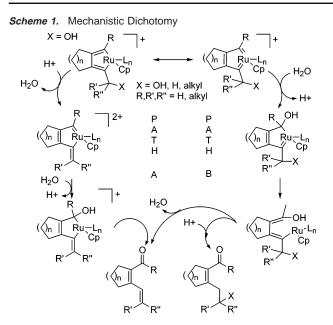
The scope of the hydrative diyne cyclization was then explored to examine the generality of this novel transformation. Both five- and six-membered rings with a range of functionality can be formed, with the five-membered cases giving higher yields with lower catalyst loadings (Table 1).

Unsymmetrical substrates were examined to explore the possibility of chemoselective addition. In fact, this reaction seems to be very sensitive to subtle steric differences. Addition of water takes
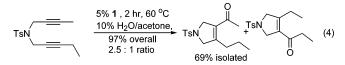
Scheme 1. Mechanistic Dichotomy

Table 2. Unsymmetrical Hydrative Diyne Cyclization

#	Starting Material	Conditions[a]	Product	Yield[b]
1	R = t-Bu	10% 1, 2-8 hr		85%
2	R = cyclopropyl			97%
3	R = Ph			90%
4	TsN ... TMS	10% 1, 2 hr		97%
5		5% 1, 24 hr		90%
6		10% 1, 30 min[c]		97%[d]
7	R = c-C$_6$H$_{11}$, R' = Me	5% 1, 4 hr		92%
8	R = C(H)(Et)(OH), R' = Et			80%
9		10% 1, 40 hr		61%

[a] The reactions were carried out at 0.1 M (in substrate) in 10 vol % water/acetone at 60 °C. [b] Isolated yields. [c] Reaction run at rt. [d] Isolated as a 9:1 ratio with the α,β,γ,δ-unsaturated ketone.
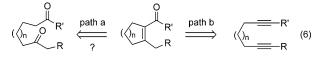
place at the more sterically accessible side in all cases studied. Higher selectivity is realized if the steric differences are on the outside of the ring being formed (eqs 3, 4).
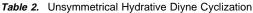

$$(4)$$

If the steric differences are made more significant, complete chemoselectivity is achieved (Table 2). While hydroxy groups β to an alkyne, behave like a branch site (entry 8), a γ hydroxyl adds in a manner similar to that of methanol to give a dienol ether as a single geometrical isomer (eq 5).
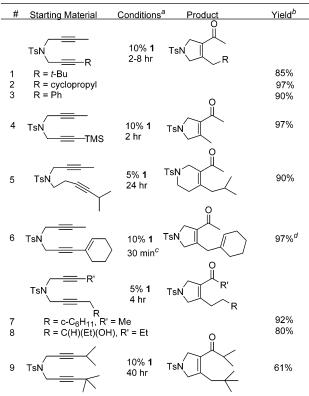

$$(5)$$

In conclusion, we have shown that simple nonterminal diynes react with water and a catalytic amount of ruthenium catalyst **1** to yield five- and six-membered enones in good to excellent yields (path b, eq 6). Along with indications that a new mechanism is involved, these products have great synthetic potential as valuable intermediates. Currently, there are few straightforward general methods for the synthesis of simple cyclic enones. While the enones can be viewed as aldol condensation products (path a, eq 6) they are not easily attainable by this method except with symmetrical ketones.[9]

$$(6)$$

The more classical method to construct enones such as these is through acylation chemistry.[10] Further development of this reaction and applications to total synthesis are currently under way in our laboratory.

Supporting Information Available: Sample experimental procedure and experimental details and characterization data for all new products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

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(6) Diyne-ols cyclize nearly instantaneously with excess water as well.
(7) Trost, B. M.; Rudd, M. T. Unpublished results. When the electron-withdrawing group is a terminal methoxycarbonyl substituent, the product is actually isolated as the isomeric pyran.
(8) The isomer depicted was confirmed though nOe difference experiments.
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JA036410F