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Propargyl Alcohols as β-Oxocarbenoid Precursors for the Ruthenium-Catalyzed Cyclopropanation of Unactivated Olefins by Redox Isomerization

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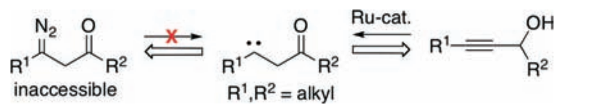
Supporting Information

ABSTRACT: An atom-economical method for the direct synthesis of [3.1.0]- and [4.1.0]-bicyclic frameworks via Ru-catalyzed redox bicycloisomerization of enynols is reported. The presented results highlight the unique reactivity profile of propargyl alcohols, which function as β-oxocarbene precursors, in the presence of a ruthenium(II) complex. Furthermore, a rare case of a formal vinylic C−H insertion reaction is described.

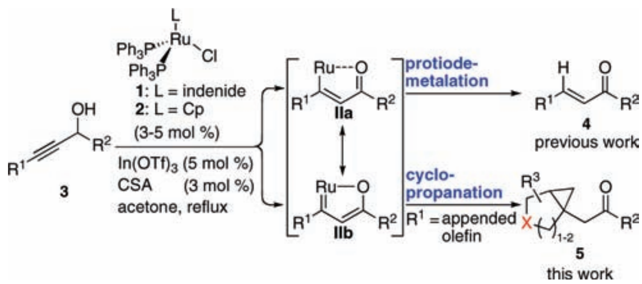
Transition-metal carbenes play a fundamental role as reactive intermediates in modern synthetic chemistry.[1] Common transformations include C−H insertion reactions and heteroatom−hydrogen bond functionalization as well as olefin cyclopropanations.[1] In view of their synthetic utility, significant efforts have been devoted to the development of novel procedures for the generation and use of transition-metal carbenes. Among other applications, metal carbenes have proven to be particularly useful in the construction of complex molecular frameworks.[2] A prevalent method for accessing these reactive intermediates is the metal-catalyzed fragmentation of diazo compounds.[3] In particular, α-diazo carbonyl compounds have found multifarious application in carbene chemistry.[2] In stark contrast to the well-studied α-oxo metal carbenes, the corresponding β-homologues with acidic α-protons have, to the best of our knowledge, not been the subject of investigations regarding catalytic transformations.[4] This substantial lack of preparative applications is in part due to the fact that methods for the synthesis of the corresponding β-diazo carbonyl precursors are absent (Scheme 1).[5] As a viable solution, we herein report the ruthenium-catalyzed redox bicycloisomerization of enynol derivatives, which presumably proceeds via a β-oxo ruthenium carbenoid intermediate.

In the course of our research program on the redox isomerization of propargyl alcohols to α,β-unsaturated carbonyl compounds,[6] we became interested in the question of whether transiently formed ruthenium carbenoid species **IIb** could react with a pendant olefin to provide an annulated cyclopropane ring system (Scheme 2).[7] Such a process bears significant advantages over traditional methods: (1) The formation of bicyclic ketones and aldehydes of type **4** proceeds in an isohypsic (overall redox-neutral) manner, which efficiently circumvents the need for separate redox manipulation steps (e.g., diazotization). (2) This protocol provides a nondissipative,[8] atom-economical,[9] and

Scheme 1. Synthetic Concept



Scheme 2. Access to β-Oxo Ruthenium Carbenoids via Redox Isomerization of Propargyl Alcohols



versatile avenue to a large variety of carbo- and heterocyclic frameworks possessing an intricate architecture. The cyclopropane entity can easily be subjected to further manipulation (e.g., hydrogenolysis), allowing for facile construction of quaternary stereogenic centers in five- and six-membered-ring systems.[10] (3) Under optimized conditions, the ruthenium carbenoid displays high selectivity for cyclopropanation over C−H insertion, which is in diametrical contrast to some cases of rhodium-based carbenes.[2b]

In order to test our hypothesis, enynol **3a** was initially reacted with 3 mol % $IndRu(PPh_3)_2Cl$ (**1**; Ind = indenyl anion) in the presence of indium triflate (3 mol %) and CSA (5 mol %) in tetrahydrofuran (THF) (0.05 M) at 66 °C (Table 1).[11] Over the course of 6 h under these conditions, an inseparable mixture of three compounds in a 1:1:1 ratio was isolated (30% yield; entry 1).[12] By means of ^1H NMR analysis, the products were identified to be the desired bicyclic ketone **5a** along with enone **6a** and unexpected cyclohexane **7a**. Use of sterically less demanding $CpRu(PPh_3)_2Cl$ (**2**) as the precatalyst and extension of the reaction time to 18 h resulted in an increase in the overall yield to 78% (entry 2). More importantly, under these conditions, cycloadduct **5a** was the major product. A screening for solvents revealed that the use of acetone (0.25 M) further increased the

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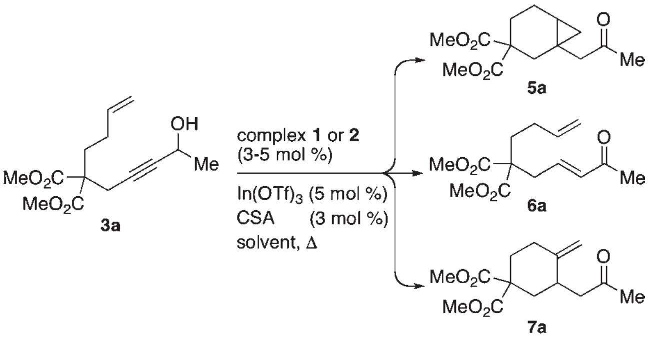
Table 1. Optimization of the Redox Bicycloisomerization Reaction[a]



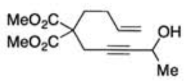
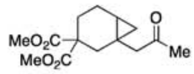
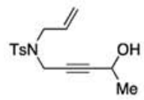
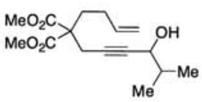
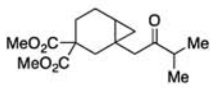
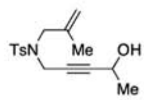
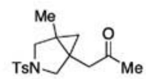
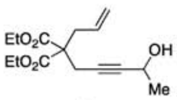
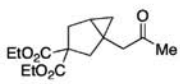
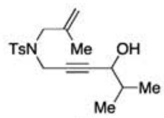
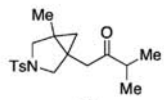
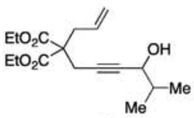
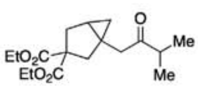
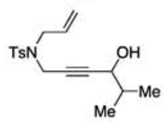
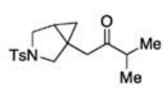
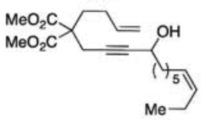
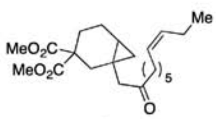
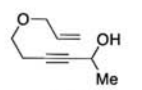
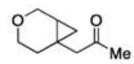
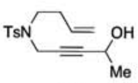
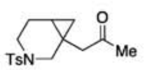
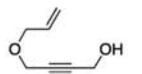
entry	complex	solvent/conc.	yield [%][b] 5a	6a	7a
1	**1**	THF/0.05 M	10	10	10
2	**2**	THF/0.05 M	53	2	23
3[c]	**2**	toluene/0.25 M	41	17	0
4	**2**	acetone/0.25 M	74	0	9
5	**2**	acetone/1 M	72	0	8

[a] Conditions: enynol (0.19 mmol) was heated to 56 °C (acetone) or 66 °C (THF, toluene). [b] Yields of the various isomers were determined by ^{1}H NMR analysis. [c] 42% of **3a** was recovered.

isomer selectivity in favor of compound **5a** (74% yield; entry 4). Under these conditions, the formation of the corresponding enone **6a** was completely suppressed. Increasing the concentration to 1 M (entry 5) did not significantly affect either the overall yield or the product selectivity. However, when the reaction was carried out in toluene, diminished product selectivity was observed (**5a**:**6a** = 2.8:1; entry 3). It is important to note that other transition-metal complexes containing platinum, palladium, and chromium have been reported to catalyze enyne cycloisomerization reactions, but in contrast to our observations, formation of [4.1.0]-bicyclic structures has been reported to be generally either impossible or low-yielding.[13]

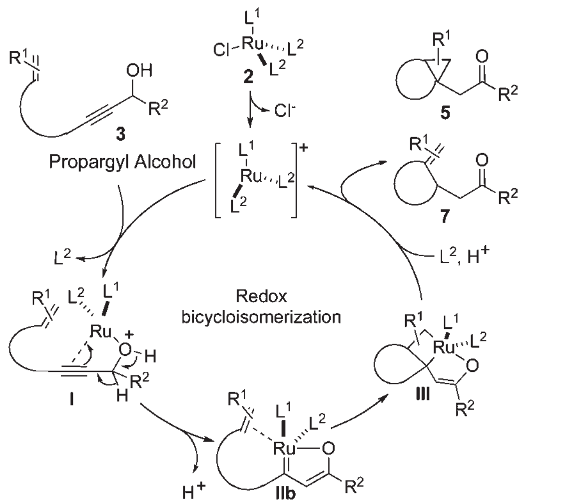
With an efficient set of conditions in hand, we next analyzed the scope of this process. For this purpose, a variety of functionalized enynols was prepared and tested in the redox bicycloisomerization (Table 2). In general, both the [3.1.0]- and [4.1.0]-bicyclic ring systems were obtained in reasonable to very good yields ranging from 52 to 88%. Furthermore, functional groups such as ethers, esters, sulfonamides, and olefins were all tolerated under the operating reaction conditions. Of particular importance is the observation that additional alkenes distal to the propargyl alcohol entity (entry 5) are well-tolerated in this transformation. This finding underscores the pronounced degree of chemoselectivity inherent in this method. As indicated in Table 1, the isomer selectivity was strongly dependent on the nature of the precatalyst and the solvent. This impact was

Table 2. Scope of the Redox Bicycloisomerization Reaction[a]

entry	enynol	product	yield [%][c]	entry	enynol	product	yield [%][c]
1[b]	 **3a**	 **5a**	74	7	 **3g**	 **5g**	84
2[b]	 **3b**	 **5b**	52	8	 **3h**	 **5h**	85
3	 **3c**	 **5c**	75	9	 **3i**	 **5i**	71
4	 **3d**	 **5d**	85	10	 **3j**	 **5j**	82
5	 **3e**	 **5e**	65	11[b]	 **3k**	 **5k**	70
6	 **3f**	 **5f**	84	12[d]	 **3l**	 **5l**	88

[a] Conditions: enynol (0.19–0.25 mmol), CpRu(PPh$_3$)$_2$Cl (5 mol %), CSA (3 mol %), and In(OTf)$_3$ (5 mol %) were heated to reflux in freshly distilled acetone (0.25 M) for 2–21 h. [b] Isomer **7** was also formed during this experiment (for more details, see the Supporting Information). [c] Yields refer to the depicted isomer **5**. [d] For this experiment, the conditions described in entry 1 of Table 1 were applied.

Scheme 3. Proposed Catalytic Cycle



particularly evident in the case of substrate **3d**. While the use of precatalyst **1** in THF (Table 1, entry 1) afforded isomers **5d** and **7d** in 26 and 52% isolated yield, respectively (not shown), the formation of isomer **7d** was completely suppressed when precatalyst **2** in acetone was employed (Table 2, entry 4).

It is noteworthy that this protocol displays tolerance toward substitution at the alkene moiety that undergoes the cyclopropanation reaction (entries 8 and 9). Of particular relevance are substrates **3h** and **3i** (entries 8 and 9), since their high-yielding conversion to pyrrolidine derivatives **5h** and **5i** exemplifies a synthetically challenging diastereoselective construction of two vicinal quaternary carbon centers.

On the basis of mechanistic investigations previously reported by our group,[6a] we propose the following catalytic cycle (Scheme 3). Upon bidentate coordination of propargyl alcohol **3** to the catalyst (structure **I**) followed by 1,2-hydride migration, the resulting ruthenium carbenoid species **IIb** presumably undergoes a [2 + 2] cycloaddition to give metallacyclobutane intermediate **III**. The latter can in turn either proceed through a sequence consisting of reductive elimination and protiodemetalation to give compound **5** or undergo β-hydride elimination followed by reductive elimination to afford isomer **7**.

In summary, we have developed a novel protocol for accessing β-oxo carbenoid species for the efficient cyclopropanation of unactivated olefins. Both [3.1.0]- and [4.1.0]-bicyclic ring systems were synthesized in generally good to very good yields with excellent chemoselectivity. The use of simple propargyl alcohols as starting materials for the generation of reactive carbenoid intermediates not only emphasizes the high degree of atom economy inherent in this method (no separate carbene precursor formation) but also highlights the synthetic value of propargyl alcohols in the construction of molecules with intricate architectures. In addition, we have demonstrated that the title transformation is inert toward various functional groups, which further underscores its synthetic utility and versatile applicability.

ASSOCIATED CONTENT

Supporting Information. Experimental details and spectroscopic data (IR, NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) An initial report of this reaction using catalyst **1** was retracted because many of the reported examples were subsequently found to be questionable. This unfortunate circumstance led us to a total re-examination and the discovery of a much improved, verified, and reliable procedure, which is the topic of this paper.

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(11) In subsequent experiments (Table 1, entries 3-5), the use of 5 mol % ruthenium catalyst **2**, 3 mol % camphorsulfonic acid (CSA), and 5 mol % of $In(OTf)_3$ was found to provide the most reliable results.

(12) The reaction described in entry 1 of Table 1 proceeded with ~30% conversion. The remaining isolated material was compound **3a**. Changing to catalyst **2** (entry 2) led to the formation of an unidentified byproduct.

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