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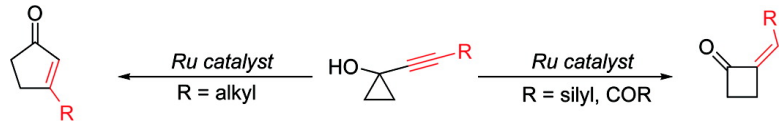

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Stereoselective, Dual-Mode Ruthenium-Catalyzed Ring Expansion of Alkynylcyclopropanols

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The fascinating chemistry of small-ring compounds stems almost invariably from the unique reactivity modes allowed by the intrinsic ring strain.[1] In particular, ring-expansion reactions have been abundantly used in organic synthesis to efficiently and expeditiously fashion functionalized molecules, and the appearance of various transition metal-catalyzed ring expansion processes has only enriched this landscape. [2,3]

There is a considerable body of work on the transition metal catalyzed ring expansion of vinyl and allenyl cycloalkanols,[4] providing useful tools for construction of various cyclic ketones. This contrasts with the scarcity of reports of transition metal promoted skeletal rearrangements of *alkynyl*cycloalkanols.[5]

Our recent interest in tapping the potential of alkynes as selective mediators in metal-catalyzed bond-forming reactions led us to speculate whether Ru catalysis would provide an interesting addition to the current arsenal of ring-expansion processes.[6] The remote analogy between the isomerization of a propargyl alcohol **1** to an unsaturated carbonyl **3** (termed the redox isomerization reaction,[7] Scheme 1) and the skeletal rearrangement of a *tertiary*, cyclopropyl carbinol **4** further spurred our interest. We report that Ru catalysis is unique in the activation of alkynyl cyclopropanols **4** as it mediates a highly selective, dual ring expansion to either four- or five-membered cyclic ketones.

Our initial forays were successful. Treatment of the TMS-substituted alkynylcyclopropanol **4a** with catalytic amounts of Ru complex **2** smoothly triggered ring expansion to alkylidene cyclobutanone **5a/6a** in essentially quantitative yield. Interestingly, the least stable (*Z*)-isomer **5a** was formed with nearly 6:1 stereoselectivity (Table 1, entry 1). Our curiosity piqued, the little precedent found for the expansion of silyl-substituted alkynyl cyclopropanols[5c] prompted us to examine further this class of substrates (results in Table 1).

The trend for the preferential formation of (*Z*)-silylalkylidene cyclobutanone products upon exposure to our conditions appears to be quite general. As the steric bulk of the silyl substituent increases, so does the *Z*/*E* ratio. The corollary of this premise is that the highly congested TIPS-substituted alkynylcyclopropanol **4f** (Table 1, entry 6) leads exclusively (based on NMR) to the (*Z*)-cyclobutanone **5f**, a most counterintuitive result!

Scheme 1. Redox Isomerization and Proposal for a Ru-Catalyzed Ring Expansion of Alkynylcyclopropanols

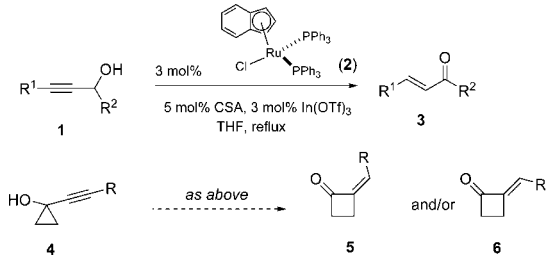
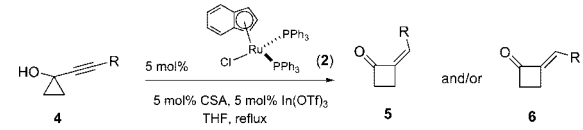


Table 1. Ru-Catalyzed Ring Expansion of Silyl-Substituted Alkynylcyclopropanols



entry	R	*Z*/*E* (**5**/**6**) ratio[a]	time (h)	yield[b]
1	TMS **4a**	5.7:1	2	98%
2	BDMS **4b**	6.0:1	4	94%
3	$SiMe_2Ph$ **4c**	6.0:1	2	96%
4	TES **4d**	10.0:1	2	97%
5	TBS **4e**	11.4:1	2	98%
6	TIPS **4f**	>20:1	2	87%[c]

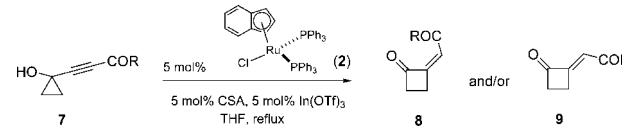
[a] Geometry was assigned by analogy to the *Z*/*E* isomers **5a/6a**: see Supporting Information (SI) for details. [b] Total yield of two isomers by ^{1}H NMR with mesitylene as internal standard. [c] Isolated yield. BDMS = benzyl(dimethyl)silyl.

Realizing that the electronic properties of silyl moieties might be playing a prominent role in this outcome, we then examined electron-withdrawing substituents (results in Table 2).

In contrast to the silyl-substituted substrates, in this case the conversion was slower, which could be ascribed to the lower electron density at the alkyne (*vide infra*). Nonetheless, good yields of alkylidene cyclobutanones **8** were obtained and this regardless of the electron-withdrawing substituent being a ketone (entry 1) or ester (entries 2−4) group. Note that the nature of the ester group (aliphatic, benzylic or nitroaromatic) also does not affect the outcome of the reaction. Importantly, and in analogy with the case of silyl-substituted alkynylcyclopropanols (cf. Table 1), a single isomer was obtained in all cases, which was assigned the (*Z*)-configuration. Note that the stereochemical outcome for these reactions is the precise *opposite* of what was reported using Au catalysis, suggesting that different mechanistic pathways may be operative in each case.[5]

Observing the ability of our catalytic system to efficiently convert silyl- and acceptor-substituted alkynylcyclopropanols to stereode-

Table 2. Ru-Catalyzed Ring Expansion of Electron-Deficient Alkynylcyclopropanols



entry	R	*Z*/*E* (**8**/**9**) ratio[a]	time (h)	yield[b]
1	Cy **7a**	>20:1	12	88%
2	OEt **7b**	>20:1	8	68%
3	OBn **7c**	>20:1	6	81%
4	O(*p*-$O_2NC_6H_4$) **7d**	>20:1	12	85%

[a] Olefin geometry assigned based on ^{1}H NMR chemical shift (see SI for details). [b] Yields refer to pure, isolated products.

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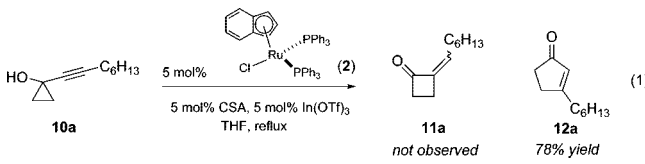
fined alkylidene cyclobutanones, we probed the stereoselectivity of the analogous process employing electron-"neutral" alkyl substituents at the alkyne.

When we exposed the hexyl-substituted alkynylcyclopropanol **10a** to our reaction conditions (eq 1), the anticipated cyclobutanone **11a** did not form but rather the unexpected β-substituted cyclopentenone **12a**.



Impressed by this complete shift in reactivity, we set out to examine the generality of this observation and briefly examined the alkyl-substituted substrates shown in Table 3.

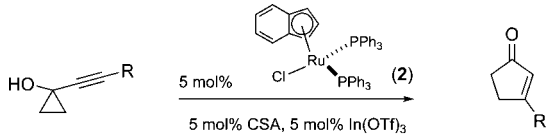
Interestingly, substrates comprising benzyl (entry 2), cycloalkyl (entry 3), or remote alkoxy (entries 4−5) and halide (entry 6) substituents underwent completely selective ring enlargement to the corresponding cyclopentenones. In all cases **12** was obtained exclusively, with only trace amounts of the analogous cyclobutanones detectable by ^{1}H NMR of the crude mixtures. To the best of our knowledge, only one example of a metal-catalyzed direct cyclopropanol−cyclopentenone rearrangement was reported prior to our findings.[5a,b]

Our mechanistic hypothesis to accommodate these results is shown in Scheme 2.[7] We believe that, in the case of silyl and electron-withdrawing substituents, the electronic properties of the system are exacerbated upon coordination to the metal catalyst. Thus, the ability of Si to stabilize a developing β-positive charge (Scheme 2, R = SiR_3) and the propensity of ynones and propiolate derivatives to undergo Michael addition (Scheme 2, R = COR) probably favor a rapid, substrate-controlled 1,2-alkyl shift. Note that the observed (*Z*)-selectivity in these cyclopropanol/cyclobutanone rearrangements suggests that internal chelation of the putative vinylmetal intermediate by the cyclobutanone carbonyl is not operative.

Yet, the electron-"neutral" substrates studied (Table 3) should be more prone to metal insertion into a C−C bond of the cyclopropane moiety (Scheme 2, R = alkyl). Such a process would provide ruthenacyclohexenone **13**, from which reductive elimination accounts for the observed products. The fact that only trace amounts of the analogous cyclobutanones are obtained implies that a net 1,2-alkyl shift is much less favored in these systems.

In summary, we have developed a novel Ru-catalyzed ring expansion of alkynylcyclopropanols. This atom-economical[8] reaction appears to proceed by two different pathways. The unique ability of

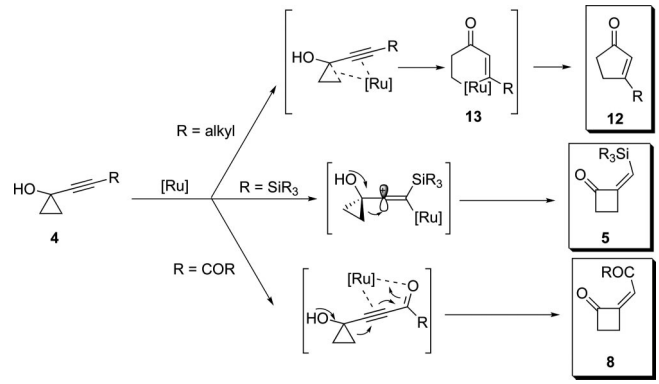
Table 3. Ru-Catalyzed Ring Expansion of Alkyl-Substituted Alkynylcyclopropanols to Cyclopentenones



entry	R	product	time (h)	yield[a]
1	n-C_6H_{13} **10a**	**12a**	4	78%
2	Bn **10b**	**12b**	6	81%
3	Cy **10c**	**12c**	4	88%
4	$(CH_2)_3OBn$ **10d**	**12d**	2	76%
5	$(CH_2)_4OBn$ **10e**	**12e**	2	68%
6	$(CH_2)_3Cl$ **10f**	**12f**	2	74%

[a] Yields refer to pure, isolated products.

Scheme 2. Mechanistic Proposal for the Dual Ring Expansions



Ru to selectively mediate either of the two pathways depending on the electronic properties of the substrate bears testament to the versatile nature of this metal in catalysis. In particular, the ability to access functionalized β-substituted cyclopentenones through a direct two-carbon homologation is appealing. Moreover, the exclusive obtention of the (*Z*)-alkylidene cyclobutanone isomers through the cyclopropanol/cyclobutanone expansion manifold is unprecedented and serves to further distinguish Ru from other, alkynophilic transition metals.

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

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