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Mechanism of Ru(II)-Catalyzed Rearrangements of Allenyl- and Alkynylcyclopropanols to Cyclopentenones

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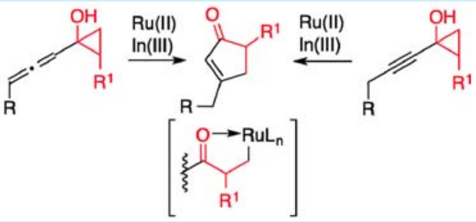
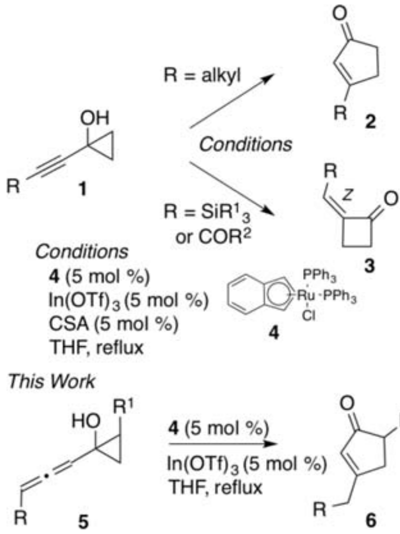
S *Supporting Information*

ABSTRACT: A comparison study of the Ru(II)-catalyzed rearrangements of allenyl- and alkynylcyclopropanols to the corresponding cyclopentenones has been undertaken with the aid of an alkyl substituent on the three-membered ring. These ring expansion reactions proceed with exceptional regioselectivity irrespective of the *cis*/*trans* stereochemistry of the substituents on the three-membered ring. β-Carbon elimination is the common feature in the absence of a chelating group at the 4′-position in the alkyne chain.



Cyclopentenones have long been utilized as versatile intermediates for the preparation of functionalized cyclopentane derivatives. The development of efficient synthetic methods for cyclopentenones has been an active area of research.[1] In addition to the frequently used Nazarov and Pauson−Khand reactions,[2,3] new approaches have recently emerged from transition-metal-catalyzed cycloisomerization.[4−7] A large body of work on one-carbon ring expansion of alkenyl-, alkynyl-, and allenylcycloalkanols has dealt with cyclobutanol derivatives, whereas related cyclopropanols have received limited attention.[7−9] One striking example is the Ru(II)-catalyzed ring expansion of alkynylcyclopropanols **1**, which gives two different products **2** or **3** depending on the alkyne substituents (Scheme 1).[6] Little detail was provided on the mechanism of the Trost cycloisomerization of alkynylcyclopropanols. We envisioned that Trost's Ru-catalyzed ring expansion of *alkynyl*cyclopropanols **1** would also be applicable to that of *allenyl*cyclopropanols **5**. As part of our continuing interest in the use of cyclopropanols as masked homoenols in C−C bond formation,[10] we report herein comparative mechanistic studies of the key ring-expansion reactions.

Scheme 1. Ring-Expansion Reactions



The first question was whether **4** is capable of catalyzing the hitherto-unknown cyclization of allenylcyclopropanols to cyclopentenones. We undertook a survey of reaction conditions with an unsubstituted allenylcyclopropanol to validate the feasibility. The rearrangement of cyclopropanol **7a** occurred by the action of **4** alone (Table 1, entry 2), which was in contrast to that of alkynylcyclopropanols.[11,12] Suitable reaction conditions were THF at reflux (entries 3−5). Addition of $In(OTf)_3$ resulted in a significant increase in rate (less than 30 min) (entry 1), and $InCl_3$ was not as effective as $In(OTf)_3$ (entry 6). Interestingly, the highest yield of **8** (76%) was obtained with TBS ether **7b** (entry 7), which presumably underwent in situ desilylation under the reaction conditions. The corresponding acetate or methyl ether (structure not shown) was recovered unchanged. A pronounced increase in reaction rate caused by $In(OTf)_3$ was also apparent for **7b** (entries 7 and 8), but its precise role was unclear.[13] The reaction proceeded slowly in the presence of base (entry 9), but its effect was smaller than in the rearrangement of alkynylcyclopropanols.[12] In the absence of catalyst **4**, no rearrangement was observed.

Along with cyclization of phenyl-substituted allenes **9a** and **9b**, the regioselectivity of the rearrangement was next examined by placing a substituent on the three-membered ring (Scheme 2). The presence of an alkyl substituent on the cyclopropane would not only broaden the scope but also serve as a useful mechanistic probe. 1,2-*trans*-Dialkyl allenylcyclopropanols **11a−d** were subjected to the aforementioned conditions and

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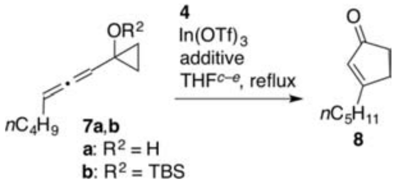
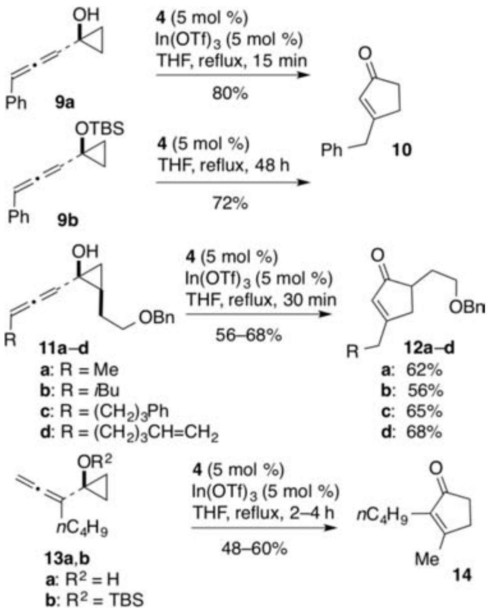
Table 1. Cyclopentenone Formation from 7a and 7b



entry	sm	conditions[a]	time (h)	yield (%)[b]
1	**7a**	**4**, In(OTf)$_3$	0.5	62
2	**7a**	**4**	6	65
3	**7a**	**4**, In(OTf)$_3$[c]	4	40
4	**7a**	**4**, In(OTf)$_3$[d]	6	35
5	**7a**	**4**, In(OTf)$_3$[e]	6	–[f]
6	**7a**	**4**, InCl$_3$[g]	4	44
7	**7b**	**4**	24	76
8	**7b**	**4**, In(OTf)$_3$	3	59
9	**7b**	**4**, In(OTf)$_3$, Cs$_2$CO$_3$[h]	6	49

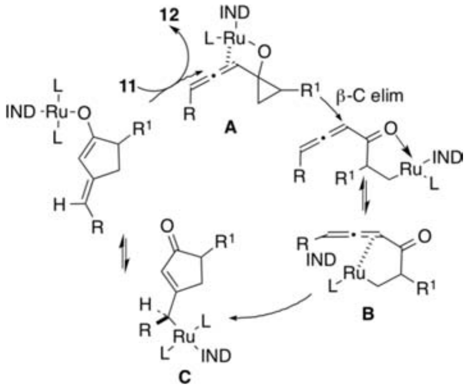
[a] The amount of each reagent was 5 mol %. [b] Isolated yields are given. [c] The reaction was carried out at 50 °C. [d] The reaction was carried out in toluene at 70 °C. [e] The reaction was carried out in MeCN at 70 °C. [f] A complex mixture was obtained. [g] 5 mol %. [h] 1.1 equiv.

Scheme 2. Cyclization of Substituted Allenylcyclopropanols

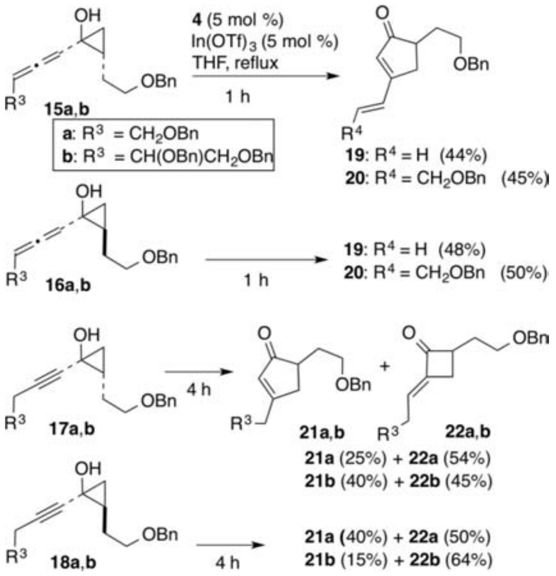


afforded cyclopentenones **12a–d** in 56–68% yield.[14] None of the alternate 4-benzyloxyethyl regioisomer was found: the observed regiochemistry was in accord with β-carbon elimination.[10,15,16] 1,1-Allenyl derivatives **13a** and **13b** also underwent the rearrangement to **14** in comparable yields. Easy access to 2,3-disubstituted cyclopentenones is an obvious advantage over the alkynylcyclopropanol route (Trost's method). Unlike cyclopropanols **7b**, **9b**, and **13b**, however, cyclization of the TBS ethers of **11a–d** was very sluggish. A plausible mechanism is shown in Scheme 3,[17a] which features β-carbon elimination of ruthenium(II) alcoholate **A** to give homoenolate **B**. Subsequent migratory insertion affords **C**. A straightforward ligand exchange completes the catalytic cycle.

Scheme 3. Plausible Mechanism for the Reaction of 11 To Give 12



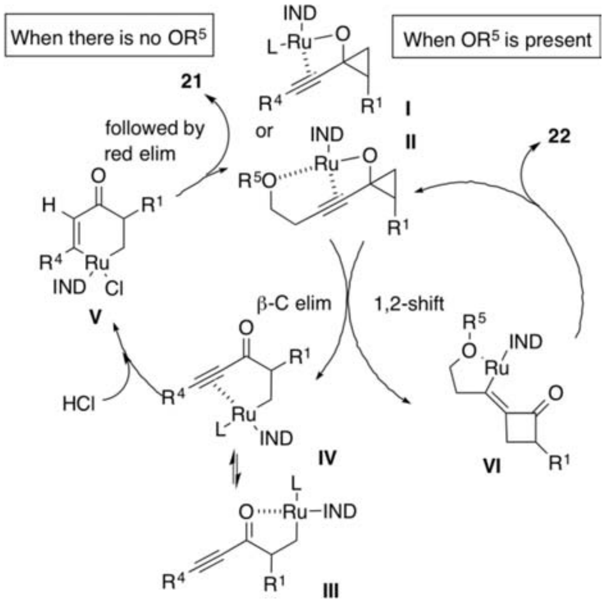
Scheme 4. Cyclization of Allenyl- and Alkynylcyclopropanols



It was tempting to speculate that the Trost cyclization of alkynylcyclopropanols might involve initial isomerization to the corresponding allenylcyclopropanols en route to cyclopentenones, as the previously reported examples possessed a propargylic proton in the alkyl side chain.[6,17b] However, little was known about transition-metal-catalyzed isomerization of alkynes to allenes.[18] We next undertook a comparison study of the key rearrangements by employing allenylcyclopropanols and the corresponding alkynyl substrates having both *cis*- and *trans*-dialkyl substituents (Scheme 4).[19] An alkoxy group was installed on the side chain to test the presumed intermediacy of **C** (Scheme 3), which would trigger elimination of the alkoxy substituent leading to 3-alkenyl-5-alkyl-2-cyclopentenones. Allenylcyclopropanols **15a**/**16a** and **15b**/**16b** indeed underwent cyclopentenone formation and concomitant elimination of the benzyloxy moiety to afford 3-alkenylcyclopentenones **19** and **20**, respectively, albeit in modest yields. There were negligible differences between the *cis* and *trans* isomers.

In contrast, the corresponding reactions of the alkynyl counterparts **17a,b** and **18a,b** gave a mixture of cyclopentenones **21a,b** and cyclobutanones **22a,b**.[20] Both the formation and the *E* configuration of the latter products were unexpected in light of Trost's original work.[6] The *E* double-bond geometry is indicative of a 1,2-alkyl shift, which is commonly observed with alkynophilic transition metals, rather than β-carbon elimination–migratory insertion. A benzyloxy substituent at the homopropargylic position in **17a,b** and **18a,b** is most likely responsible for the preponderance of four-membered ring formation in marked contrast to literature precedent.[21] The alkoxy moiety is capable of chelation to the metal, thus favoring formation of **22a,b** via a 1,2-alkyl shift (**II** → **VI**) over *β*-carbon elimination (Scheme 5). The observed regiochemistry is presumably due to steric interactions that could override the intrinsic migrating aptitude, as reported in a related Au(I)-catalyzed rearrangement that is affected by the *cis*/*trans* ring stereochemistry.[22] Most importantly, the formation of cyclopentenones **21a,b**, free from elimination (e.g., **19**/**20**), is incongruent with the intermediacy of the corresponding allenes.

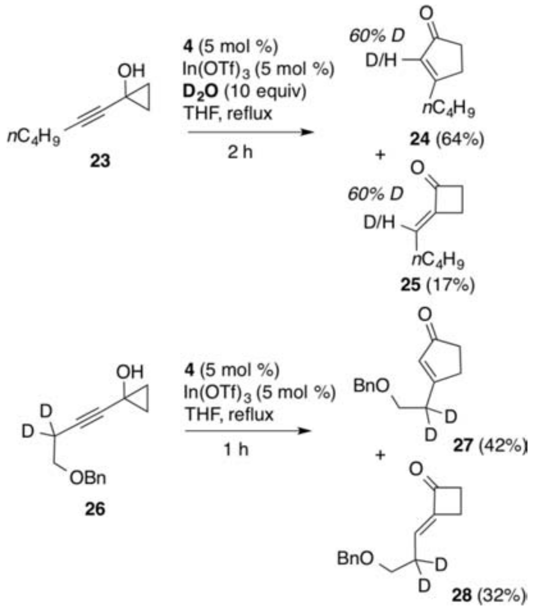
Scheme 5. Plausible Mechanism for Trost Cyclization



In the absence of a 4′-alkoxy substituent, *β*-carbon elimination (**I** → **III**/**IV**) is the predominant pathway, leading to the cyclopentenone product **21** with no elimination. A plausible mechanism for the Trost cyclization could involve addition of the alkylmetal to the alkynone functionality to give **V**, followed by reductive elimination.[23−25] Proton (generated during the formation of **I** from the cyclopropanol substrate) may be necessary for the proposed cyclization **IV** → **V**, which would account for the deleterious effects of base (Table 2 in the Supporting Information vs Table 1). Although additional studies are necessary, the proposed mechanism is consistent with preliminary deuterium-labeling experiments (Scheme 6).

In summary, a plausible mechanism is advanced for the Trost cycloisomerization of alkynylcyclopropanols to cyclopentenones. Also included are the new rearrangement of allenylcyclopropanols to cyclopentenones and a comparative mechanistic study of the rearrangements of alkynyl- and allenylcyclopropanols. Noteworthy is the Ru(II) catalyst's propensity to induce *β*-carbon elimination, in contrast to other alkynophilic transition metals. Additionally, the presence of a chelating group at the 4′-position in the alkyne chain triggers two-point complexation to the catalyst to favor a 1,2-alkyl shift over *β*-carbon elimination to yield (*E*)-alkylidenecyclobutanones as the major product.

Scheme 6. Deuterium-Labeling Experiments



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03088.

Experimental procedures and spectroscopic data for key intermediates (PDF)

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Notes

The authors declare no competing financial interest.

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(11) Unlike alkynylcyclopropanols,[5b] treatment of allenylcyclopropanols with $Co_2(CO)_8$ afforded 1,4-hydroquinones.[5a]

(12) See the Supporting Information for the screening results of the Trost cyclization.

(13) See: (a) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **1995**, *117*, 9586. (b) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 11970.

(14) The COSY spectrum of **12** clearly shows the cross-peaks (a W coupling) between the olefinic proton and the methylene protons. The C5-substituted regiochemistry was confirmed by difference NOE measurements, NOESY, HSQC, and HMBC.

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(17) (a) No β-hydride elimination of **B** (Scheme 3) was observed, which precluded a Nazarov-type reaction pathway. (b) Alkynylcyclopropanols having SiR^1_3 or COR^2 substituents (Scheme 1) are believed to rearrange via β-carbon elimination and subsequent migratory insertion, as opposed to a 1,2-alkyl shift, which accounts for the atypical *Z* geometry of the alkylidenecyclobutanone products.

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(20) The *E* geometry and regiochemistry of **22a,b** was unequivocally determined by 1D and 2D ^1H NMR spectroscopy.

(21) It is interesting to note that no cyclobutanone formation was reported for the cyclization of the one-carbon homologue, i.e., 5′-benzyloxy-1′-pentynylcyclopropanol.[6]

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(25) An alternative pathway of migratory insertion in an uncommon *trans* fashion (not shown) cannot be ruled out. A *trans* addition of Rh−H to the tethered alkyne was proposed, albeit in one-carbon homologues.[4e,f]