714 *J. Am. Chem. Soc.* **2000,** *122,* 714−715

Ruthenium-Catalyzed Cycloisomerizations of 1,6- and 1,7-Enynes

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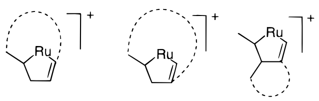
Received September 20, 1999

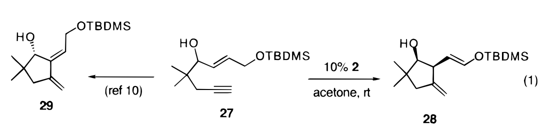
Transition metal catalysis offers the unique means by which to achieve synthetic efficiency not normally accessible by traditional methods.[1] One example of this is the ene-type reaction between an alkene and an alkyne (as the enophile). A variety of transition metal catalysts have been reported to catalyze the intramolecular coupling of alkenes and alkynes to produce cyclic 1,4-dienes.[2,3] A few years ago, we reported that the intermolecular version of this reaction can be catalyzed by cyclopentadienyl (1,5-cyclooctadiene) ruthenium chloride complex.[4] Our initial attempts to develop the intramolecular version of the ruthenium-catalyzed Alder-ene were thwarted by the fact that, with CpRu(COD)Cl as a catalyst, only monosubstituted olefins participated in the reaction. The requirement for the alkene substituent to be on the carbon attached to ruthenium (to allow for β-hydride elimination) demands that the postulated metallacyclopentene intermediate have a 1,3-bridging as in **1a** or **1b**—a type of bridging that cannot be accommodated by short tethers. Our recent discovery that the use of the cationic ruthenium catalyst $CpRu(CH_3CN)_3^+ PF_6^-$ **2** allowed for the participation of 1,2-disubstituted alkenes[5] should now permit cyclizations to normal ring sizes via a ruthenacycle such as **1c** in a process that may complement the selectivity observed with Pd-catalyzed cycloisomerizations, enhancing the scope of such reactions, and provide mechanistic insight into these reactions.



1a **1b** **1c**

We initially examined the reaction of the 1,5-enyne **3** (Table 1, entry 1). Subjecting it to 10% **2** and 30% camphorsulfonic acid (CSA) in 2-butanone at 60 °C led to the 1,4-diene **4** which was isolated in 68% yield. Further experimentation revealed that the acid cocatalyst could be omitted and the temperature lowered to room temperature. Under these latter conditions, the 1,4-diene **4** was isolated in 80% yield (Table 1, entry 2). Use of an electron-deficient alkyne has no deleterious effect on the course of the reaction (entries 3, 11, and 12). Unlike the intermolecular version, the reaction proceeds in the presence of branching at the allylic carbon (entries 4 and 5). The formation of the ene-type product in such a case contrasts to the regioselectivity observed with Pd catalysis. When employing a trisubstituted olefin **9** from which a new quaternary center is generated in the product, solvent choice proved critical and had to be switched from the less polar acetone (entry 6) to the more polar DMF (entry 7). In contrast to the titanium-catalyzed reaction,[3b] the Ru-catalyzed reaction is stereoselective with respect to the formation of a new 1,2-disubstituted olefin (entry 8). Furthermore, the Ru-catalyzed reaction is not impeded by either ether (entries 9−12 and 14) or amide (entries 13 and 17) functionalites.[7] 1,7-Enynes also readily participate in our ruthenuim-catalyzed cycloisomerization reaction to produce six-membered carbocyclic rings (entries 15 and 16)[8] and a piperidine (entry 17). The reaction shows modest to good 1,3-diastereoselectivity (entries 9−12 and 14). Ruthenium-catalyzed cycloisomerization of enyne **13** affords 83−86% of only the 1,4-diene with a 1.4:1 diastereoselectivity (entries 9 and 10) in contrast to the Pd-catalyzed reaction[9] wherein mixtures of the 1,3- and 1,4-dienes are obtained. Most notably, isomerization of enyne **7** gave only 1,4-diene **8** (entries 4 and 5), whereas, the palladium process gave only the 1,3-diene.

We also examined the regio- and diastereoselectivity utilizing enyne **27**. This substrate has been previously employed in the Pd-catalyzed Alder-ene reaction to afford the 1,3-diene **29**, an intermediate in the synthesis of sterepolide.[10] In contrast, the Ru-catalyzed reaction affords the silyl enol ether **28** in 72% yield as a single diastereomer (eq 1). The ability to form an enol silyl ether in the presence of a free hydroxyl group is, to our knowledge, unprecedented. Furthermore, the fact that a silyl enol ether is stable, even in the presence of a free hydroxyl group, is a testament to the mildness of the conditions for the Ru-catalyzed ene-type reaction.



When unsymmetrically trisubstituted olefins, such as **30**, are subjected to the Pd-catalyzed ene-type reaction, products of the type **33** are obtained.[11] In stark contrast to this selectivity, Ru-catalyzed cycloisomerization of geranyl based **30** affords selectively (8:1) the more substituted 1,4-diene **31** (eq 2). Switching to the neryl-based enyne **32** completely reverses the selectivity to afford **33** with a 17:1 selectivity. This is the first example in which regioselectivity is dependent on the geometry of the starting olefin. Examination of the proposed ruthenacycle intermediates provides a possible explanation for this phenomenon. Much like in the titanacycles,[3b] the substituent situated in a pseudoequatorial position as in **34** and **35** places a hydrogen proximal to the metal

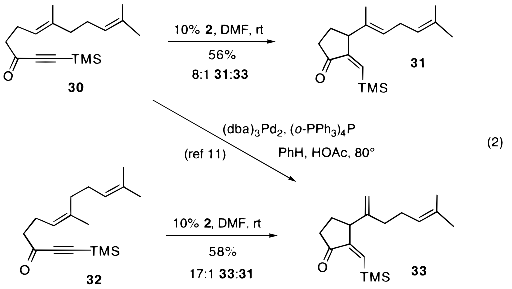


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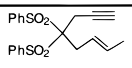
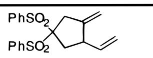
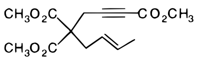
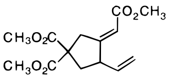
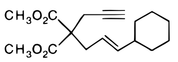
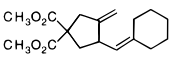
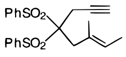
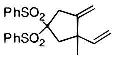
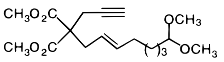
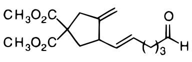
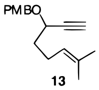
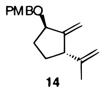
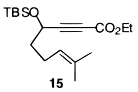
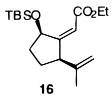
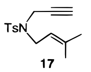
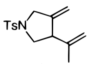
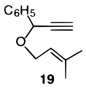
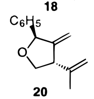
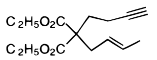
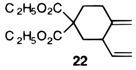
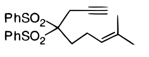
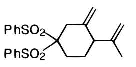
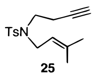
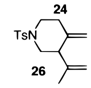
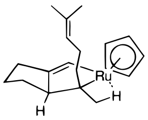
Table 1. Ru-Catalyzed Cycloisomerization of 1,6- and 1,7-Enynes

Entry	Substrate	Product	Conditions[a] (time)	Yield (dr)[b]
1	 **3**	 **4**	**D** (2h)	68
2			**A** (2h)	80
3	 **5**	 **6**	**A** (2h)	71[c]
4	 **7**	 **8**	**A** (6h)	74[d]
5			**B** (1h)	82
6	 **9**	 **10**	**A** (8h)	NR
7			**B** (4h)	69
8	 **11**	 **12**	**A** (8h)	58
9	 **13**	 **14**	**A** (1h)	83 (1.4:1)
10			**B** (2h)	86 (1.4:1)
11	 **15**	 **16**	**A** (6h)	46 (3.0:1)
12			**B** (6h)	54 (1.1:1)
13	 **17**	 **18**	**A** (2h)	80
14	 **19**	 **20**	**A** (2h)	62 (8:1)
15	 **21**	 **22**	**C** (10h)	67
16	 **23**	 **24**	**A** (2h)	72
17	 **25**	 **26**	**A** (2h)	75

[a] (**A**) 10% **1**, 0.2 M acetone, rt. (**B**) 10% **2**, 0.2 M DMF, rt. (**C**) 10% **2**, 0.2 M 2-butanone, 60 °C. (**D**) 10% **2**, 30% CSA, 0.2 M 2-butanone, 60 °C. [b] Diastereomeric ratios determined by ^{1}H NMR. Relative stereochemistry of determined by nOe experiments. [c] 11% of the β-ketoester resulting from hydration of the alkyne was also isolated. [d] Isolated as a 1:1 mixture of the 1,4- and the isomerized 1,5-dienes.

center, in a position which allows for the necessary overlap for β-hydride elimination.



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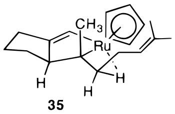

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We have previously proposed two possible mechanisms for the intermolecular ene-type reactions.[4] We favored the mechanism involving a ruthenacyclopentene; however, the possibility remained that the reaction proceeded via a ruthenium π-allyl generated by CH activation. The second possibility becomes especially attractive when the more substituted olefins are used. However, we have recently demonstrated that CH activation occurs selectively at the *cis* substituent.[6a] Therefore, even with the more substituent olefins, it appears that the intramolecular ene-type reaction occurs through a metallacyclopentene.

This reaction also sheds some light on the Pd-catalyzed reaction which has been suggested to proceed via a similar metallacycle and/or a hydropalladation pathway. The striking differences observed between Pd and Ru catalysis appears to be best compatible with the hydrometalation route being the predominant (if not exclusive) one operative for the Pd-catalyzed reactions.

In conclusion, we have demonstrated that the cationic ruthenium catalyst **2** tolerates the use of 1,2-di- and trisubstituted olefins in the intramolecular ene-type reaction, therefore allowing for the formation of five- and six-membered rings. A wide range of functional groups and of alkene and alkyne substitution has little effect on the course of the reaction. A striking example of the extreme mildness of the ruthenium catalyst system is the formation of silyl enol ethers. In a number of the examples, the ruthenium reaction is complementary to the Pd-catalyzed reaction, selectively forming the 1,4-diene in place of the 1,3-diene. Finally, we have reported the first example of a cycloisomerization in which the selective formation of the product 1,4-diene can be accomplished by choosing the geometry of the starting enyne.

Acknowledgment. We thank the National Science Foundation and the National Institute of Health, General Medical Sciences, for their generous support of our programs. Mass Spectra were provided by the Mass Spectroscopy Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Sample procedure and characterization data for **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **26**, **28**, **31**, and **33** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA993401R