Ruthenium-Catalyzed Intramolecular [5 + 2] Cycloadditions

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Outside of the ruthenium-catalyzed ring-closing metathesis reaction,[1] the application of ruthenium catalysts to the formation of carbon−carbon bonds is relatively unknown.[2] We have recently found the cationic ruthenium catalyst $CpRu(CH_3CN)_3PF_6$ (**1**) to be an efficient catalyst for the intermolecular ene-type coupling of alkenes and alkynes.[3] In continuation of our program directed toward the development of atom economical reactions catalyzed by ruthenium,[4] we initiated a study aimed toward developing ruthenium-catalyzed higher order cycloaddition reactions. Transition metal catalysis provides a unique means to achieve cycloadditions normally unavailable by traditional methods.[5] The recently reported catalytic [5 + 2] cycloaddition between alkynes, alkenes or allenes, and vinylcyclopropanes illustrates the concept.[6] The high temperatures and long reaction times frequently required and the high cost of rhodium compared to that of ruthenium (approximately 10-fold difference) prompted us to investigate the ability of the cationic ruthenium catalyst (**1**) to promote such a reaction via a mechanism as outlined in Scheme 1.

In an initial experiment, reaction of the 1,6-enyne **2a** with 10% **1** and 10% CSA in DMF at 60° afforded the desired [5 + 2] adduct **3a** in 87% yield (Table 1, entry 1). Further optimization showed that the reaction could be carried out with 10% **1** in the absence of acid cocatalyst in acetone at room temperature to afford **3a** in 83% yield (Table, entry 2). The tolerance of the reaction to substitution on the alkyne, alkene, and cyclopropane is illustrated by the successful [5 + 2] cycloadditions of substrates **2a**−**2d** (Table, entries 3−5). Importantly, the use of the trisubstituted olefin **2c** as a substrate proceeded cleanly at room temperature to afford the seven-membered ring diene **3c** in 87% yield without any observable trace of olefin isomerization (entry 4).[7] Reaction of the ether substrate **4a** afforded the desired tetrahydrofuran adduct **5a** in 77% yield (entry 6). The presence of a Lewis basic group, a tosylamide, in substrate **4b**, also had no deleterious effect on the reaction, and the tetrahydropyrrole adduct **5b** was obtained in 84% yield (entry 7).

Scheme 1. Proposed Catalytic Cycle for Ruthenium-Catalyzed [5 + 2] Cycloaddition

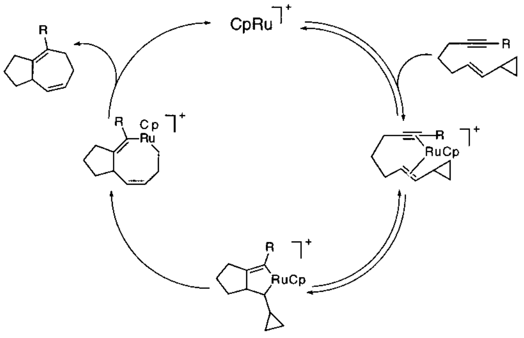
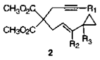
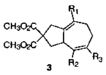
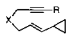
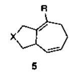
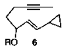
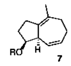
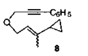
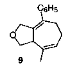
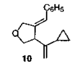
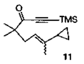
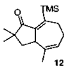
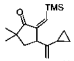


Table 1. [5 + 2] Cycloisomerization of Alkyne-Vinylcyclopropanes[a]

Entry	Substrate		Product	Yield
1[b]		**a:** R_1=H, R_2=H, R_3=H		87
2	 **2**	**a:** R_1=H, R_2=H, R_3=H	 **3**	83
3		**b:** R_1=C_6H_5, R_2=H, R_3=H		82
4		**c:** R_1=CH_3, R_2=CH_3, R_3=H (2.5:1 *E*:*Z*)		87
5[c]		**d:** R_1=CH_3, R_2=H, R_3=CH_3		75
6	 **4**	**a:** X=O, R=C_6H_5		77
7		**b:** X=NTs, R=TMS	 **5**	84
8		**a:** R=TBDMS		92 (3.1:1 dr)[e]
9[d]	 **6**	**a:** R=TBDMS	 **7**	73 (5.1:1 dr)
10[d]		**b:** R=H		70 (1.5:1 dr)
11		**a:** 2.5:1, *E*:*Z*		80 (1.7:1)[f]
12	 **8**	**b:** *Z* only	 **9**  **10**	78 (1:14)
13		**c:** *E* only		82 (6.2:1)
14	 **11**	2.0:1, *E*:*Z*	 **12**  **13**	75 (3.7:1)[g]

[a] Reactions run with 10% **1** in 0.2 M acetone at room temperature unless noted. [b] Reaction performed in DMF in the presence of CSA at 60 °C. [c] Reaction run at 60 °C. [d] Reaction run in 0.2 M DMF. [e] Ratio of diastereomers determined by ^1H NMR. Relative stereochemistry of major diastereomer **7** determined by nOe. [f] Ratio of **9**:**10** as determined by ^1H NMR. [g] Ratio of **12**:**13** determined by ^1H NMR.

Since the cationic ruthenium catalyst **1** may also act as a Lewis acid, its ability to tolerate substrates bearing an ionizable group at the allylic position was examined (cf entries 8 and 9). Under our standard conditions, the cycloaddition reaction of **6a** proceeded smoothly to afford **7a** as a 3.1:1 mixture of diastereomers and in 92% yield (entry 8). Changing the solvent from acetone to DMF improves the diastereoselectivity to 5.1:1 with only a slight decrease in yield (entry 9). To examine whether the source of the diastereoselectivity is steric or due to coordination of the allylic ether to the ruthenium, the substrate containing a free alcohol **6b** was examined. Once again the reaction proceeded cleanly in DMF to afford **7b** in 73% yield but with a diminished diastereoselectivity of 1.5:1 (entry 10)—an observation consistent with a steric effect rather than coordination. The tolerance of an unprotected allylic alcohol is noteworthy.

Unlike substrate **2c**, when a 2.5:1 mixture of the trisubstituted ether **8a** was subjected to the ruthenium-catalyzed reaction, a 1.7:1 mixture of **9:10** was obtained (entry 11). Furthermore, the ether **8a** forms a complex mixture in the presence of Wilkinson's catalyst, but forms only **9** with the rhodium dimer.[7] This contrast between the Rh- and Ru-catalyzed reactions may be an indication that the reactions are proceeding through different mechanisms.[8]

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(1) Review: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *39*, 2805.

(2) For a recent general review of ruthenium-catalyzed reactions, see: Murahashi, S.-I.; Takaya, H.; Naota, T. *Chem. Rev.* **1998**, *98*, 2599.

(3) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739. For preparation of **1**, see Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485.

(4) For examples of ruthenium-catalyzed intermolecular reactions, see: (a) Trost, B. M. Indolese, A. Muller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. (b) Trost, B. M.; Muller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888. (c) Trost, B. M.; Portnoy, M.; Kurihara, H. *J. Am. Chem. Soc.* **1997**, *119*, 836. (d) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988. (e) For a review, see: Trost, B. M. *Chem. Ber.* **1996**, *129*, 1313.

(5) For reviews of transition metal catalyzed cycloadditions see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Dell, C. P. *Contemp. Org. Synth.* **1997**, *4*, 87. (c) Wender, P. A.; Love, J. A. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford, CT, 1999; p1−49.

(6) (a) Alkynes: Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Alkenes: Wender, P. A. Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940. (c) Allenes: Wender, P. A.; Glorious, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348. Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137. d) For an intermolecular example, see: Binger, P.; Wedermann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113.

(7) In the analogous $(PPh_3)_3RhCl$-catalyzed reaction some isomerization of the double bond to a mixture of 1,3-dienes was observed.[6a] An alternative Rh catalyst was recently reported to circumvent this problem. Wender, P. A.; Sperandio, D. A. *J. Org. Chem.* **1998**, *63*, 4164.

10.1021/ja993400z CCC: $19.00

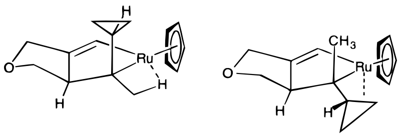
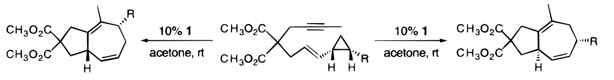


Figure 1. Proposed intermediate metallacycles derived from **8b** and **8c**.

To examine the origin of the competing β-hydrogen elimination, the geometrically pure olefin-ethers **8b** and **c** were prepared. Reaction of the *Z*-olefin **8b** with 10% **1** in acetone afforded a 78% yield of a 14:1 mixture in favor of the 1,4-diene **10** arising from β-hydrogen elimination (entry 12). Conversely, reaction of the *E*-olefin **8c** affords a 6.2:1 mixture in favor of the [5 + 2] adduct **9** (entry 13). Examining the ruthenacyclopentenes derived from **8b** and **8c**, it becomes apparent that the group that is *trans* in the starting olefin is placed in a pseudoequatorial position on the convex face of metallocycle intermediate (Figure 1). The pseudoequatorial group geometrically is better situated for interaction with the metal center, a situation similar to that recently observed in the β-hydrogen elimination in titanacyclopentenes.[9]

The advantages of the extremely mild conditions are illustrated by the excellent chemoselectivity observed with the ynone **11**, as a 2:1 mixture of *E:Z*-olefins, which reacts in the presence of 10% **1** to afford a 3.7:1 mixture of the cycloadduct **12** and the 1,4-diene **13**. Presumably in this reaction, as in the previous case, the *E*-isomer reacts selectively to produce the seven-membered ring **12**.

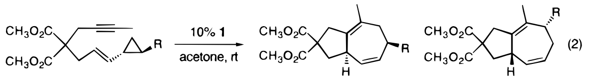
Substitution at the 2-position of the cyclopropane creates a regioselectivity issue (see eqs 1 and 2). A substrate containing a 1,2-*cis*-disubstituted cyclopropane as in **14a** under our standard condition produced exclusively the cycloadduct **15a** in 85% yield (eq 1). Significantly, the reaction is selective not only with respect to which bond is cleaved, but also with respect to the fact that only a single diastereomer is produced. Changing the electronic nature of the substituent to that of an electron-withdrawing group as in **14b** reverses the selectivity of the cycloaddition (eq 1) presumably as a result of stabilizing a C$-$Ru bond by the aldehyde. Thus, regioisomer **16b** is produced as a 10:1 ratio of diastereomer. The relative stereochemistry of **16b** is established by nOe's and correlation to **19**. On the other hand, the 1,2-*trans*-disubstituted vinylcyclopropane **17**, reacts with 10% **1** in acetone at room temperature to afford a 1.4 to 1 mixture of cycloadducts **18** and **19**, respectively. Despite this decrease in selectivity of bond cleavage, the reaction remains highly diastereoselective.



(1)

16b (80%) **14** **15a** (85%)

a R=CH$_2$OTIPS
b R=CHO



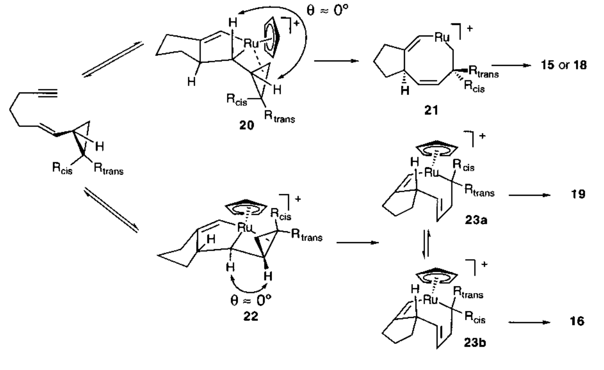
(2)

17 R=CH$_2$OTIPS **18** **19**

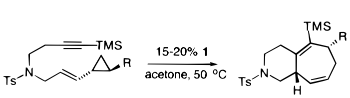
3 : 1

Scheme 2 provides a rationale where it is obvious that a *cis* substituent destabilizes **22** which leads to cleavage of the more substituted bond, relative to **20** which equates to cleavage of the less substituted one. These conformations are dictated by the requirement for formation of a *cis*-alkene in the product. The severity of the destabilizing interaction in **22** is suggested by the selectivity observed with **14b**. Even though electronic stabilization would strongly favor reaction via **22**, the selectivity deteriorates somewhat to 10:1 because of the steric stress. On the other hand, a *trans* substituent is accommodated by either conformer leading to lower regioselectivity. In the case of the aldehyde, the resultant enolate **23** (R_{cis} = CHO) allows for equilibration of stereochemistry accounting for the inversion at this center. The stereochemistry reflects a faster rate of elimination for **23b** (substituent pseudoequatorial-like and distal to Cp) compared to **23a** (substituent pseudoaxial-like and proximal to Cp).

Scheme 2. Proposed Mechanistic Rationale for the Regio- and Diastereoselectivity of Cyclopropane Ring Opening from **14** and **17**



The reaction extends to formation of [6.7] ring systems **25a,b** as shown in eq 3. The reactions are slower and require slightly elevated temperatures (50 °C). Most interestingly, the *trans*-disubstituted cyclopropane **25b** gives a single regio- and diastereomeric product in which the more substituted cyclopropane bond cleaved exclusively. This result should be contrasted to that of eq 2. The change from a 3- to a 4-atom tether apparently now disfavors the tether homologue of **20** so that the reaction proceeds via the homologue of **22**.

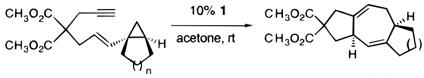


(3)

24a R = H
b R = CH$_2$OTBDMS

25a 87%
b 79%

The extraordinarily mild conditions normally required (acetone, room temperature) imparts excellent chemoselectivity as already demonstrated for an aldehyde, amide, alcohol, alkene, ketone, ether, and ester. Regioselectivity can be controlled by choice of substituents, and complete diastereoselectivity is always observed. The prospects for construction of more complicated ring systems frequently found in complex bioactive molecules is very high as demonstrated by the fact that the tricycles **27a** and **27b** (eq 4) form with complete regio- and diastereoselectivity from precursors **26a** and **26b**. In conjunction with the rhodium catalyst, [5 + 2] cycloadditions should prove to be a powerful tool for construction of seven-membered ring natural and unnatural products. Further applications of this reaction and more detailed mechanistic studies will be reported in due course.



(4)

26 a n = 1
b n = 2

27 a 85%
b 81%

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Supporting Information Available: Sample procedure and characterization data for **3a**$-$**d**, **5a**$-$**b**, **7a**, **9**, **10**, **12**, **15a**, **16b**, **18**, **19**, **25a**$-$**b**, and **27a**$-$**b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] A proposed catalytic cycle initiated by cyclopropane ring opening to form a metallocyclohexene has also been proposed by Wender.[6b]

[9] Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976.