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On the Regioselectivity of the Ru-Catalyzed Intramolecular [5 + 2] Cycloaddition

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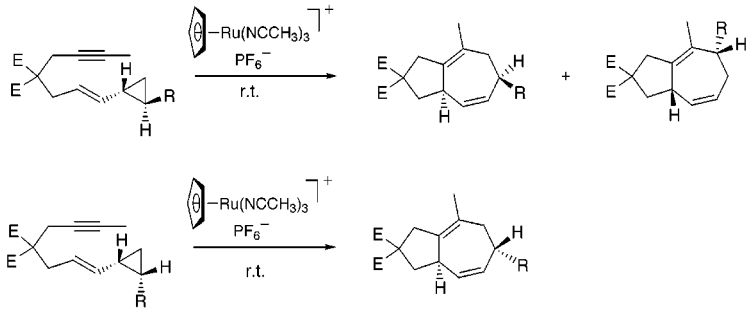
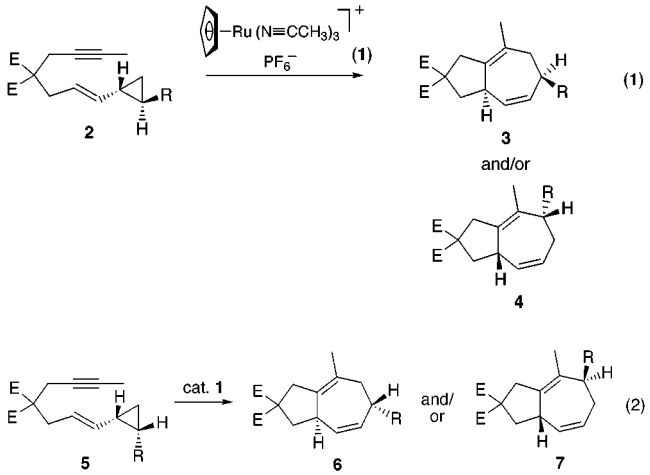
ABSTRACT



The influence of substituents on which cyclopropyl bond cleaves in the cycloisomerization of cyclopropylenynes catalyzed by $CpRu(N{\equiv}CCH_3)_3^+PF_6^-$ is compared to the corresponding Rh-catalyzed reaction. With the *trans* cyclopropyl substrates, the bond energy of the cleaving bond appears to be an important factor. With *cis* cyclopropyl substrates, steric effects appear to dominate.

The success of the rhodium-catalyzed [5 + 2] cycloaddition pioneered by the Wender group[1,2] stimulates the development of alternative catalysts that can complement this reaction. As part of our program to develop atom economical reactions involving the ruthenium complex **1**,[3,4] we discovered its ability to catalyze the intramolecular [5 + 2] cycloaddition of cyclopropyl enynes at room temperature.[5] A good probe to understand the relationship between the Rh- and Ru-catalyzed processes is to use regioselectivity with unsymmetrically substituted cyclopropane systems according to eqs 1 and 2, a system already explored by the Wender group with Rh catalysis,[1c] as a fingerprint.



(1) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164. (c) Wender, P. A.; Dyckman, A. J. *Org. Lett.* **1999**, *1*, 2089. (d) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442. (e) Also see: Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075.

(2) Also see: Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940. Wender, P. A.; Glorius, 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. Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976. Also see: Binger, P.; Wedemann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, *113*.

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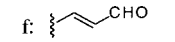
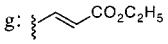
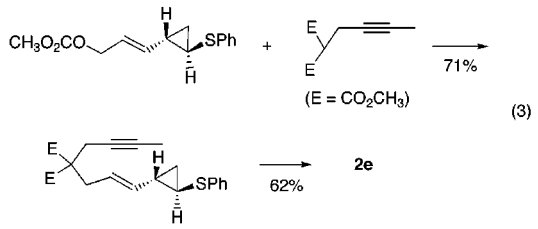
Table 1. Regioselectivity of Cycloaddition of *trans* Substrates **2**[a] (eq 1)

entry	R	additive	time	ratio[d,e] **3**:**4**	% isolated yield
1[c]	a: CHO	none	0.5 h	1:12[f]	83%
2	a: CHO	10 mol% $In(OSO_2CF_3)$	2 h	1:15[f]	83%
3	b: CO_2CH_3	none	2 h	1:2[f]	90%
4[b]	b: CO_2CH_3	none	2 h	1:2.5[f]	88%
5	b: CO_2CH_3	10 mol% $In(OSO_2CF_3)_3$	2 h	1:2.3[f]	80%
6	c: $COCH_3$	none	3 h	1.5:1	83%
7	c: $COCH_3$	15 mol% $In(OSO_2CF_3)_3$	3 h	1:1.2	88%
8	d: CN	none	2 h	1:1.9	87%
9	e: SO_2Ph	none	2 h	1:1	78%
10	f: 	none	0.5 h	1:1.6	82%
11	g: 	none	1 h	1:1.6	87%
12	h: C≡CH	none	2 h	1:2.5	85%
13	i: $CH_2OTBDMS$	none	2 h	1:1[f]	90%
14[c]	j: CH_2OTIPS	none	2 h	3:1	81%
15[b]	j: CH_2OTIPS	none	2 h	2:1	88%

(a) All reactions performed with 10 mol% **1** using 0.2 M substrate in acetone at ambient temperature unless otherwise noted. (b) Reaction performed in DMF as solvent. (c) Taken from ref. 5. (d) Ratios determined by ^{1}H nmr spectroscopy. (e) All new compounds have been fully characterized spectroscopically and elemental composition established by high resolution mas spectrometry and/or combustion analysis. (f) Cf. Ref. 1c.

Syntheses of the requisite substrates **2** and **5** took advantage of the Pd-catalyzed allylic alkylation[6] as shown in eq 3 for the preparation of the sulfone [5 mol % $(dba)_3Pd_2$·



$CHCl_3$, 30 mol % Ph_3P, $(C_2H_5)_3N$, CH_2Cl_2, room temperature]. This case exemplifies the compatibility of divalent sulfur with these homogeneous catalytic reactions. Chemoselective oxidation to the sulfone **2e** employed tetra-*n*-butylammonium oxone (CH_2Cl_2, room temperature).[7]

Table 1 summarizes the data. As previously noted,[5] the aldehyde substrate **2a** shows a strong bias to cleave the more substituted cyclopropyl bond (entry 1), a propensity that is slightly enhanced by the addition of indium triflate as a cocatalyst (entry 2). On the other hand, other electron-withdrawing substituents, specifically ester (entry 3), cyano (entry 8), and sulfone (entry 9), show a small to almost no bias in preferring migration of the more substituted cyclopropyl carbon despite the large differences in steric size of the substituent. A methyl ketone can lead to a small bias in either direction depending upon the presence of an indium cocatalyst (entries 6 and 7). Switching from acetone to the more coordinating DMF as solvent also showed only a small effect (entry 4). A vinylogous aldehyde substrate **2f** shows a sharply diminished bias for migration of the more substituted cyclopropyl carbon (entry 10) compared to the aldehyde and exhibits the same preference as for the vinylogous ester **2g** (entry 11). On the other hand, this bias increased in the case of a simple ethynyl substituent not bearing an electron withdrawing group (entry 12). We previously noted that a simple siloxymethyl substituent tips the balance in the opposite direction (entry 14), which does show a small solvent effect (entry 15). Switching from TBDMS to the more bulky TIPS led to an enhancement of the regioselectivity from 1:1 to 3:1 favoring migration of the less substituted cyclopropyl carbon (entry 13).

The *cis* substrates showed dramatically different behavior as summarized in Table 2. Remarkably, the *cis* aldehyde substrate **5a** gave a single produc, which was identical to that obtained from the *trans* substrate **2a** (entry 1). The methyl ketone does not show this behavior since the regioisomer **7b** is different from that obtained from substrate **2c** (i.e., **4c**). Furthermore, the major product now derives

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(7) Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532.

Table 2. Regioselectivity of Cycloaddition of *cis* Substrates **5** (eq 2)[a]

entry	R	time	ratio[b,d] **6**:**7**	% isolation yield
1	a: CHO	0.5 h	see text	80
2[c]	b: CO_2CH_3	3 h	2:1	93
3	c: $COCH_3$	2 h	>20:1[e]	87
4[c]	d: CN	2 h	>20:1	81
5	e: CH_2OTIPS	2 h	>20:1	85
6[c]	f: CH_3	5 h	>20:1	87

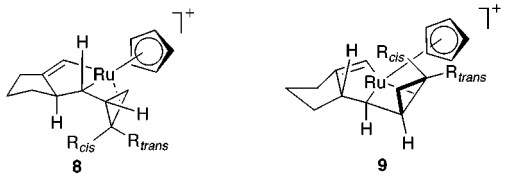
[a] All reactions performed with 10 mol % **1** using 0.2 M substrate in acetone at ambient temperature unless noted otherwise. [b] Ratios determined by ^{1}H NMR spectroscopy. [c] Reaction run at 0.1 M in substrate. [d] All new compounds have been fully characterized spectroscopically, and elemental compositions have been established by high-resolution mass spectrometry and/or combustion analysis. [e] Compare ref 1c.

from migration of the less substituted cyclopropyl carbon (entry 2). With all other substituents, even methoxycarbonyl (entry 3) and cyano (entry 4), only migration of the less substituted carbon was observed.

There are several notable aspects of these observations. First, the aldehyde substrate is different than all the others, perhaps deriving from the right combination of both steric and electronic effects. Second, cyclopropyl bond strength appears to be a significant factor in the *trans* series since all substituents show significant migration of the more substituted cyclopropyl carbon. There are clearly steric effects but these appear to be quite variable. For example, they appear to play a more significant role in entries 13 and 14 compared to entries 3 and 8. Third, the *cis* substrates, except for the carboxaldehyde and acetyl ones, show complete regioselectivity for migration of the less substituted carbon. This observation suggests the dominance of steric effects in this series.

The comparison to the Rh system illustrates several significant differences. First, the aldehyde substrates **2a** and **5a** do not lead to the same cycloaddition product with Rh catalysis. Second, siloxy substrate **2i** shows the contrasting regioselectivity with the two different catalytic systems, leading with Wilkinson's catalyst to exclusive formation of **3i**, whereas the Ru complex **1** leads to an equimolar mixture of **3i** and **4i**. Third, the conjugating ester substituent does not effect regioselectivity in the *cis* series (i.e., **5c**) with the Ru catalyst but does influence the regioselectivity in the Rh reaction.

Wender et al. have proposed two mechanisms for the Rh-catalyzed [5 + 2] cycloaddition, one involving a metallacyclopentene by interaction with the enyne portion and one involving a metallacyclohexene involving initiation of cycloaddition by interaction with the vinylcyclopropane.[2] Our extensive program on the development of Ru-catalyzed reactions has been based upon the importance of a ruthenacyclopentene intermediate[3,4] and ultimately led to our examination of the feasibility of the [5 + 2] cycloaddition.[5] We therefore, favor intermediates such as **8** and **9** for the



Ru-catalyzed reactions. These intermediates also nicely accommodate our observations, especially the relative inaccessibility of metallacycle **9** with most R_{cis} substituents and the previously observed competitive formation of the Alder ene type process with a substrate having a trisubstituted alkene bearing a methyl group.[5] Differences between the Rh and the Ru catalytic systems appear to stem more from the different ligand environments than the change in metal. The fact that the Wender group finds dramatic differences in regioselectivity by changing the Rh complex employed for catalysis[1b,c] supports this contention. Thus, variation of the Ru catalyst will be an interesting area for future work.

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Supporting Information Available: Characterization data for **3c**−**h**, **4a**, **4c**−**h**, **6b**, **6d**, **6f**, and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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