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Transition Metal-Catalyzed [5 + 2] Cycloadditions of 2-Substituted-1-vinylcyclopropanes: Catalyst Control and Reversal of Regioselectivity

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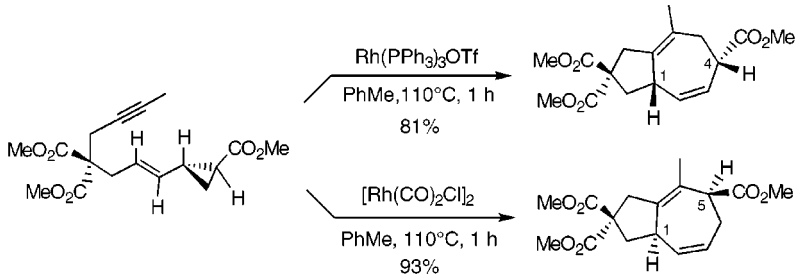
ABSTRACT



Studies on the stereo- and regioselectivity of rhodium(I)-catalyzed [5 + 2] cycloadditions of 2-substituted-1-vinylcyclopropanes are described. The relative stereochemistry of vicinal cyclopropane substituents is found to be conserved in these reactions, translating into distinct 1,4- or 1,5-stereorelationships in the cycloadducts. Exceptional regioselectivity in cyclopropane bond cleavage and even reversal of cleavage selectivity can be obtained through judicious selection of substituents and/or catalyst.

The rhodium(I)-catalyzed [5 + 2] cycloaddition of vinylcyclopropanes with a 2π component, first reported from this laboratory in 1995, serves as a robust and versatile new reaction for the formation of seven-membered rings. Initially explored with alkynes as the 2π component,[1] the intramolecular cycloaddition has now been successfully conducted with alkenes[2] as well as allenes,[3] thus providing overall access to a broad range of synthetically useful frameworks containing the bicyclo[5.3.0]decane or the bicyclo[5.4.0]-undecane systems. Additionally, the development of an attenuated catalyst system for these cycloadditions {[Rh-$(CO)_2Cl]_2$} has provided improved selectivity and rates for some otherwise problematic substrates.[4] This catalyst has also made possible for the first time a general *intermolecular* metal-catalyzed [5 + 2] cycloaddition of siloxyvinylcyclopropanes.[5]

Collectively, these reactions bring forth a variety of new questions and opportunities, including regio- and stereoselectivity issues of fundamental and applied significance.[6] For example, in the case of 1,2-disubstituted cyclopropanes, ring expansion could occur through cleavage of either of two

(1) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721.

(2) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940−1941. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203−7220.

(3) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−5349.

(4) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164−4165.

(5) (a) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−10977. (b) For an isolated example of an intermolecular [5 + 2] cycloaddition, see: Binger, P.; Wedmann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113−119.

(6) For other work related to metal-catalyzed [5 + 2] cycloadditions, see: Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075−2078.

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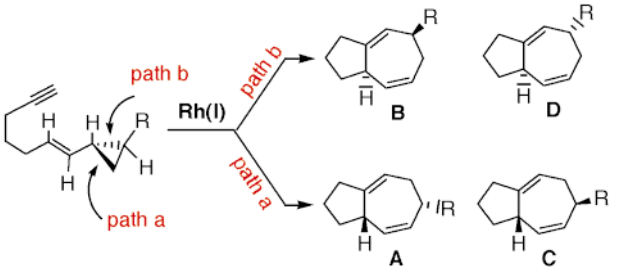
distinct bonds, leading to the possible formation of two regioisomeric cycloadducts (Scheme 1: **A**/**C** vs **B**/**D**).[7]

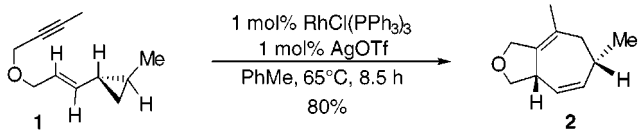
Scheme 1



Furthermore, either of these cleavages could proceed with retention or loss of configuration (Scheme 1: **A** vs **C** and **B** vs **D**). Thus, for a given cycloaddition precursor, four products could arise depending upon the regioselectivity of the ring expansion and the influence of the olefin and cyclopropyl geometries over the formation of diastereomeric products.

We previously reported that methyl substitution of the cyclopropane at the 2-position led to the formation of a single cycloadduct arising from cleavage of the less substituted cyclopropane bond (Scheme 2).[8,9] We have now examined

Scheme 2

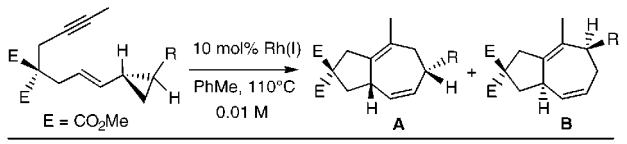


the selectivity of this reaction as a function of the nature of the R group and of the catalyst. Through judicious choice of substituent and catalyst, it is shown that one can selectively produce any one of the four possible cycloadduct types (Scheme 1: **A**, **B**, **C**, or **D**).

To explore whether the regiochemical outcome and hence the synthetic utility of this process could be influenced through modification of the substituent and/or catalyst system, a series of compounds was prepared incorporating cyclopropyl substituents with differing steric, electronic, and coordinative characteristics. The selection includes a range of functionalities commonly required for synthetic applications. These substrates were exposed to two catalytic systems possessing dissimilar steric and electronic properties which have previously exhibited differing reactivities.[4] One system was composed of Wilkinson's catalyst $[Rh(PPh_3)_3Cl]$ along with a silver triflate (AgOTf) additive, while the second catalyst was the dimeric rhodium(I) species $[Rh(CO)_2Cl]_2$. To determine the stereochemical relationship between the substrates and products, *cis*- and *trans*-cyclopropane isomers were prepared and reacted independently.

The results from the *trans*-cyclopropane series are shown in Table 1. In general, the yields are found to be good to

Table 1. *trans*-2-Substituted-1-vinylcyclopropanes



Entry	R	Catalyst[a]	Time	Product	Yield[b]	A : B : (X)[c]
1	CH_2OH (**3**)	$Rh(PPh_3)_3OTf$	1.5 h	**4**	96%	1 : 0
2	"	$[Rh(CO)_2Cl]_2$	0.5 h	**4**	86%	2.3 : 1
3	CH_2OAc (**5**)	$Rh(PPh_3)_3OTf$	2 h	**6**	92%	1 : 0
4	"	$[Rh(CO)_2Cl]_2$	1.5 h	**6**	85%	2.5 : 1
5	CH_2OTBS (**7**)	$Rh(PPh_3)_3OTf$	1 h	**8**	95%	1 : 0
6	"	$[Rh(CO)_2Cl]_2$	1 h	**8**	86%	3.5 : 1
7	CHO (**9**)	$Rh(PPh_3)_3OTf$	16 h	--	decomp.	-----
8	"	$[Rh(CO)_2Cl]_2$	0.5 h	**10**	68%	0 : 1 : (1.4)
9[d]	"	$[Rh(CO)_2Cl]_2$	8 h	**10**	98%	0 : 1
10	CO_2H (**11**)	$Rh(PPh_3)_3OTf$	2 h	**12**	69%	4 : 1 : (1)
11	"	$[Rh(CO)_2Cl]_2$	2 h	**12**	73%	1 : 22
12	CO_2Me (**13**)	$Rh(PPh_3)_3OTf$	1 h	**14**	81%	20 : 1
13	"	$[Rh(CO)_2Cl]_2$	1 h	**14**	93%	1 : 11

[a] $Rh(PPh_3)_3OTf = Rh(PPh_3)_3Cl + AgOTf$ (1:1). [b] isolated yields. [c] ratios determined by g.c. analysis, (X) refers to isomerized byproducts. [d] reaction at 55°C

excellent over the range of functional group variations. Analogous to the stereochemical result obtained with methyl substrate **1**, for each of the examples studied the initial cyclopropane configuration is translated without loss to the cycloadduct. For the free and protected hydroxymethyl substrates (Table 1: entries 1−6), the regioisomer arising from cleavage of the less substituted cyclopropane bond predominated, giving preferentially or exclusively products of type **A**. With modified Wilkinson's catalyst, the regiocontrol is complete (Table 1: entries 1, 3, and 5) while utilization of the rhodium dimer catalyst led to a mixture of regioisomers favoring type **A** cycloadducts (Table 1: entries 2, 4, and 6).

Entries 7−13 for the trans series show the effects of various electron-withdrawing substituents. Initial attempts to utilize an aldehyde substituent (**9**) met with poor results under the standard conditions. Slow decomposition of the starting material was observed with catalytic amounts of $Rh(PPh_3)_3$-OTf, while reaction with the rhodium dimer catalyst afforded regioisomer **10B** along with a secondary isomerization product (Table 1: entries 7 and 8). However, by reducing

(7) For selectivity in vinylcyclopropane bond cleavage, see: Ryu, I.; Ikura, K.; Tamura, Y.; Maenaka, J.; Ogawa, A.; Sonoda, N. *Synlett* **1994**, 941−942. Hayashi, M.; Ohmsato, T.; Meng, Y.-P.; Saigo, K. *Angew. Chem., Int. Ed.* **1998**, 837−840.

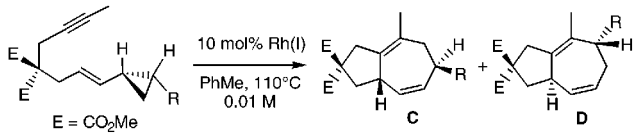
(8) (a) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A. Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442−10443. (b) The reactions of **3**, **7**, and **17** with modified Wilkinson's catalyst were previously reported in ref 8a. They are included here for ease of comparison.

(9) A racemic mixture was used in all cases. Only one enantiomer is depicted for simplicity.

the temperature to 55 °C, reaction with the dimer catalyst resulted in an excellent yield (98%) of **10B** as a single regioisomer and diastereomer with no decomposition or secondary isomerization problems. For carboxylic acid and ester substituted substrates **11** and **13**, the regiochemistry was effectively controlled and even reversed through the choice of catalyst. Reaction of ester **13** with the modified Wilkinson's catalyst selectively afforded cycloadduct **14A** (20:1). When substrate **13** was reacted with the rhodium dimer catalyst, the *regioselectivity was reversed* to favor product **14B** over **14A** in a ratio of 11:1. Importantly, the carboxylic acid functionality was well tolerated, with reaction of compound **11** displaying similar results to those of **13** in catalyst control of regioselectivity.

Cycloadditions with *cis*-cyclopropanes also occurred in good-to-excellent isolated yields (81−98%) and were found to proceed with the *formation of single diastereomers complementary to those from the trans series* (Table 2). For

Table 2. *cis*-2-Substituted-1-vinylcyclopropanes



Entry	R	Catalyst[a]	Time	Product	Yield[b]	C : D[c]
1	CH_2OH (**15**)	$Rh(PPh_3)_3OTf$	1 h	**16**	84%	3.5 : 1
2	"	$[Rh(CO)_2Cl]_2$	1 h	**16**	93%	9.0 : 1
3	CH_2OTBS (**17**)	$Rh(PPh_3)_3OTf$	2 h	**18**	81%	1 : 0
4	"	$[Rh(CO)_2Cl]_2$	1 h	**18**	96%	1 : 0
5	CHO (**19**)	$Rh(PPh_3)_3OTf$	4 h	--	decomp.	-----
6[d]	"	$[Rh(CO)_2Cl]_2$	15 h	**20**	92%	0 : 1
7	CO_2Me (**21**)	$Rh(PPh_3)_3OTf$	2 h	**22**	95%	6.4 : 1
8	"	$[Rh(CO)_2Cl]_2$	2 h	**22**	98%	1.5 : 1

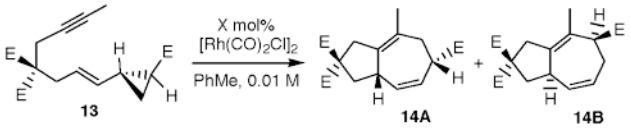
[a] $Rh(PPh_3)_3OTf$ = $Rh(PPh_3)_3Cl$ + AgOTf (1:1). [b] isolated yields. [c] ratios determined by g.c. analysis. [d] reaction at 55°C

cis-hydroxymethyl substrate **15**, ring cleavage of the less substituted cyclopropane bond predominated for both catalysts, giving preferentially product **16C**. The TBS-protected compound (**17**) reacted with complete regioselectivity in the presence of either catalyst to give only product **18C**.

Although *cis*-aldehyde **19** was unstable in the modified Wilkinson's catalyst reaction, treatment with the rhodium dimer catalyst at 55 °C led to highly regioselective cleavage of the *more substituted* bond, providing **20D** in excellent yield. In contrast to the *trans*-cyclopropane series, reaction of the *cis*-vinylcyclopropane ester **21** did not produce a reversal in regioselectivity upon variation of the catalyst. Cycloadduct **22C** was obtained with good regioselectivity with the modified Wilkinson's catalyst, while reaction with the rhodium dimer catalyst provided little selectivity, yielding a 1.5:1 mixture of regioisomers **22C** and **22D** (Table 2: entries 7 and 8). For this case, it appears that the competing steric and electronic factors influencing bond cleavage are closely balanced.

Investigations into the effect of catalyst loading and reaction temperature on the product selectivity were carried out for *trans*-ester substrate **13** (Table 3). Significantly,

Table 3. Catalyst Loading and Temperature Effects



Entry	mol%	Temp.	Time	Conversion[a]	14A : 14B[a]
1	40	80°C	2 h	98%	1 : 7.9
2	10	80°C	4 h	100%	1 : 11.1
3	1	80°C	8 h	91%	1 : 16.7

Entry	mol%	Temp.	Time	Conversion[a]	14A : 14B[a]
4	10	40°C	48 h	93%	1 : 8.4
5	10	80°C	4 h	100%	1 : 11.1
6	10	110°C	0.75 h	100%	1 : 11.3

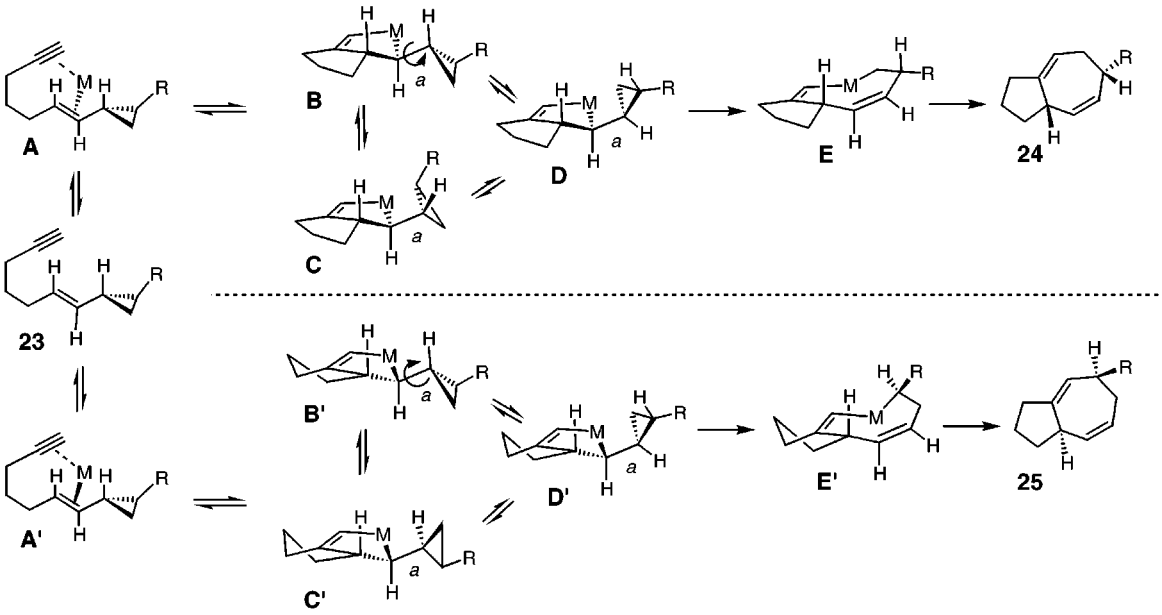
E = CO_2Me, [a] determined by g.c. analysis

progressive reduction of the catalyst loading was found to provide an increase in selectivity for product **14B**. While at 40 mol % of $[Rh(CO)_2Cl]_2$ the ratio of **14A:14B** was 1:7.9, at 1 mol % loading the selectivity reached 1:16.7. Interestingly, the selectivity was also found to *increase* with an *increase* in temperature. These combined results indicate the presence of multiple catalytic species in the reaction process.

Mechanistic analysis of the reaction of substituted cyclopropanes reveals that each regioisomeric cycloadduct correlates uniquely with a metal−π-system complex (Scheme 3: **A** and **A′**). Metal coordination to either of the two vinyl π-system faces of **23** followed by oxidative coupling leads to diastereomeric metallacyclopentenes **B** or **B′**.[10] The subsequent formation of a *cis*-olefin in **E** and **E′** requires a *syn* alignment of the protons along bond a, which is achieved through rotation around this bond to give **D** or **D′**. These conformations allow only one cyclopropyl carbon−carbon bond to properly overlap with the carbon−metal bond as required for concerted ring expansion. Each of the complexes (**D** or **D′**) aligns a different cyclopropane bond for cleavage, leading to the formation of different regioisomers **24** or **25**, respectively. As the cyclopropyl substituent (R) in **23** is spatially removed from the vinyl fragment during the initial coordination, very little π-facial selectivity would be expected in the formation of diastereomeric complexes **A** and **A′** and their downstream intermediates and products. The observed high selectivity is thus a consequence of the reversibility of

(10) For brevity, only one mechanistic possibility is presented. An alternative set of mechanistic possibilities can be formulated around the initial formation of metallacyclohexenes followed by coordination to the tethered alkyne and convergence on the advanced intermediates **E** and **E′** (see ref 5a). While differing in the timing of connections, the issues of regio- and stereoselectivty are treated similarly.

Scheme 3



the initial mechanistic steps and the influence of the substituent on a later step, putatively involving irreversible cleavage of the cyclopropane (**D** → **E** vs **D′** → **E′**).

In summary, it is shown that through selection of cyclopropyl substituents and/or catalyst modifications, excellent control over the regiochemical outcome of the [5 + 2] cycloaddition can be achieved. Additionally, the cis or trans configuration of the cyclopropyl substituents directly determines the diastereomeric nature of the cycloadducts. Significantly, in connection with synthetic applications, the cycloadditions of disubstituted cyclopropanes occur in good-to-excellent yields for a range of commonly used functionalities, and selective access to all four regioisomeric and diastereomeric cycloadduct types is readily achieved.

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Supporting Information Available: Procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org

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