Transition Metal-Catalyzed [5+2] Cycloadditions with Substituted Cyclopropanes: First Studies of Regio- and Stereoselectivity

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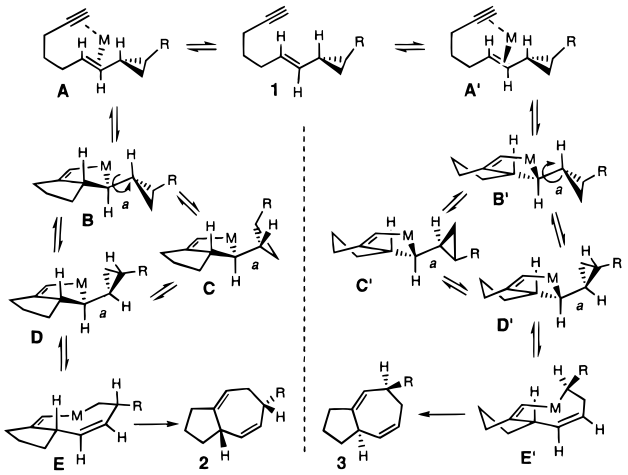
Received July 21, 1999

A continuing focus of our research involves the catalysis of reactions which in the absence of catalysts are forbidden or require forcing conditions.[1,2] As part of this program, we recently reported a new cycloaddition reaction (Scheme 1: **1** ⟹ **2** + **3**, R = H) in which the five carbons of a vinylcyclopropane are added across a two-carbon π-system.[3] We have shown thus far that this [5+2] cycloaddition occurs efficiently with alkynes,[3] alkenes,[4] and allenes,[5] and that it can be conducted *inter*molecularly.[6] An especially interesting aspect of this process relative to most cycloadditions is that it proceeds with addition across a single bond of a cyclopropane,[7] raising previously unexplored issues of mechanistic, stereochemical, and synthetic consequence. We describe herein the first studies of the stereoselectivity and regioselectivity of [5+2] cycloadditions involving substituted cyclopropanes.

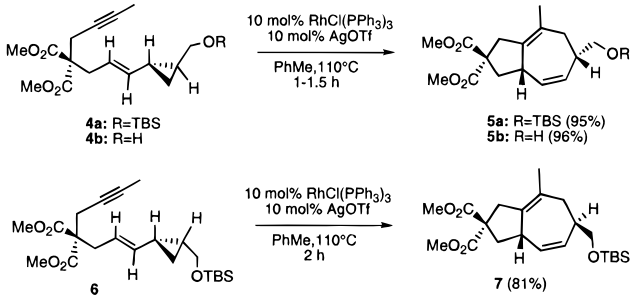
The introduction of a second cyclopropane substituent in the [5+2] cycloaddition results in a bifurcation of the reaction pathway, potentially leading to a diastereomeric mixture of regioisomers and a total of four possible products. As exemplified in Scheme 1 for *trans*-1,2-disubstituted cyclopropanes (**1**), catalyst coordination to the alkene would produce a diastereomeric mixture of complexes (**A**/**A′**) from which the diastereomeric metallacycles **B** and **B′** would be derived.[8] Subsequent cyclopropane cleavage is possible only after rotation around bond *a* which serves both to align the carbon−metal and cyclopropane C−C bonds for cleavage and to position the remaining groups in the geometry required for the formation of the *cis*-alkene intermediates **E** and **E′**. Reductive elimination would give regioisomers **2** and **3** (and related diastereomers). As the *trans*-cyclopropane substituent R in **1** is spatially removed from the alkene during the course of catalyst coordination, a nearly statistical mixture of complexes

Scheme 1



A and **A′** and subsequent intermediates would be produced. However, if the process were reversible, the product-determining step would arise at a later stage in the sequence at which point the cyclopropyl substituent could exert a greater influence over cleavage and product selectivity.

Our investigation of these mechanistic and selectivity issues began with the *trans*-disubstituted cyclopropane **4a**.[9] In the presence of a catalyst system derived from 10 mol % tris(triphenylphosphine)rhodium (I) chloride (Wilkinson's catalyst) and 10 mol % AgOTf (silver triflate), *substrate **4a** afforded after 1 h at 110°C cycloadduct **5a** as a single regio- and diastereoisomer in 95% isolated yield*.[10] This product arises from cleavage of the less substituted cyclopropane bond of **4a**. It is synthetically significant to note that the trans-stereochemistry of starting material **4a** is translated without loss in this process into a single 1,4-stereorelationship in the cycloadduct. Importantly, when the corresponding *cis*-1,2-disubstituted cyclopropane **6** is treated under similar conditions, only a single regio- and diastereoisomer (**7**) is again formed in high yield (81%) but with stereochemistry complementary to that present in **5a**.



A range of substituents is tolerated in this process without erosion of regio- or diastereoselectivity. For example, the unprotected alcohol **4b** gives cycloadduct **5b** as a single isomer

(1) Representative examples. [4+4]: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678−4679. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089−1094. [4+2]: Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432−6434. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824−825. Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255−1275.

(2) For reviews and related work see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4130−4135. Jolly, R. S.; Luedtke. G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965−4966. O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443−445. Gilbertson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077−10080.

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

(4) 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.

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

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

(7) Most cycloadditions (e.g., the Diels−Alder cycloaddition) whether concerted or stepwise are based on the reaction of two π-components (e.g., diene and dienophile).

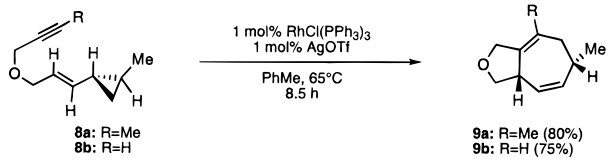
(8) For brevity, only one mechanistic possibility is presented. An alternative set of mechanistic possibilities can be formulated around the initial formation of metallacyclohexenes followed then by coordination to the tethered alkyne and convergence on the advanced intermediates **E** and **E′** (see ref 6a). While differing in the timing of connections, the issues of regio- and stereoselectivity are treated similarly.

(9) A racemic mixture was used in all cases. Only one enantiomer is depicted for simplicity. For preparation of this and other compounds, see Supporting Information.

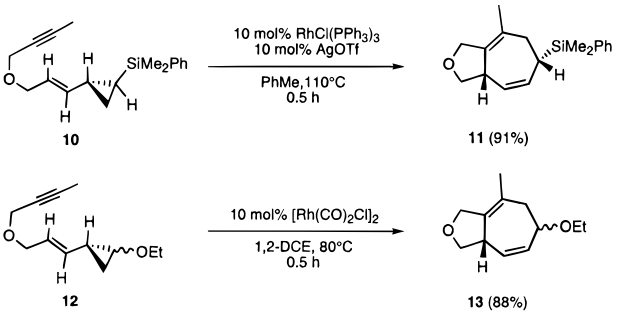
(10) In a representative procedure, to a base-washed, oven-dried Schlenk flask under an argon atmosphere is added tris(triphenylphosphine)rhodium(I) chloride (10 mol %), silver triflate (10 mol %), and distilled, argon-purged PhMe (6 mL). The solution is stirred for 5 min at room temperature, after which yne-vinylcyclopropane **4a** (24.1 mg, 0.082 mmol in 2 mL of PhMe) is added and the solution is heated to 110 °C for 1 h. After cooling, the reaction mixture is filtered through a plug of alumina and concentrated. Flash column chromatography (silica gel, EtOAc/hexane) gives cycloadduct **5a** in 95% yield as a colorless oil.

10.1021/ja992580+ CCC: $18.00
Published on Web 10/21/1999

in 96% yield. As illustrated for substrates **8a** and **8b**, replacement of the silyloxymethyl or hydroxymethyl group with a noncoordinating methyl group does not alter the high regio- and stereoselectivity observed in the cycloaddition. A secondary point of interest in these cases is that the reaction works well with an ether in the tether in place of geminal diester substituents.



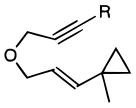
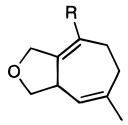
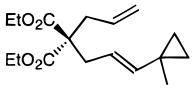
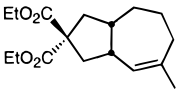
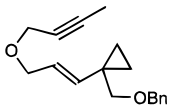
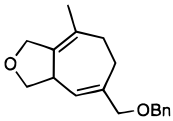
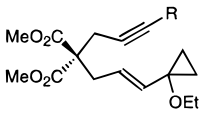
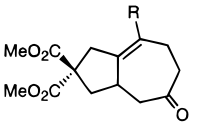
The influence of non-carbon substituents on the selectivity of the cycloaddition was first explored with the silicon-substituted cyclopropane **10**. While differing sterically and electronically from the carbon-substituted systems (**4a**, **4b**, **6**, **8a,** and **8b**) a similar regio- and stereoselectivity was observed (**10** ⟹ **11**). Oxygen-substituted cyclopropanes also reacted selectively (**12** ⟹ **13**) and with identical regiosense. While the individual isomers of **12** could not be cleanly separated, a 2:1 mixture of trans and cis **12** afforded a 2:1 mixture of diastereomeric cycloadducts (**13**) in 88% yield.



In addition to 1,2-disubstituted cyclopropanes, we also examined the effect of 1,1-disubstitution on the efficiency of the [5+2] cycloaddition. Beginning with a substrate bearing methyl substitution, in the presence of 0.5 mol % Wilkinson's/silver triflate catalyst, 1-methyl-1-vinylcyclopropane **14a** afforded cycloadduct **15a** in 83% yield after 6 h at 65 °C (Table 1, entry 1).[11] Substitution of the alkyne terminus with electron withdrawing or aromatic functionality had little effect on the reaction, with substrates **14b** and **14c** affording cycloadducts in good yields at similarly low catalyst loads (Table 1, entries 2 and 3). Likewise, utilization of an alkene as the 2 carbon component (**16**) resulted in the formation of the single cycloadduct **17**. Cyclopropane substitution with a benzyloxymethyl group (**18**) leads efficiently to cycloadducts such as **19** which are well suited for further synthetic functionalization.

Alkoxy substitution at the 1-position of vinylcyclopropanes has been shown to significantly accelerate their rearrangements, in both thermal and metal-mediated reactions.[12] A similar effect has been noted in the [5+2] cycloaddition, with 1-ethoxy-1-vinylcyclopropanes **20a** and **20b** reacting under mild conditions (Table 1, entries 6 and 7). In the presence of 5 mol % $[Rh(CO)_2Cl]_2$,

Table 1. 1-Substituted 1-Vinylcyclopropanes

Entry	Substrate	Conditions	Cycloadduct, Isolated Yield
		0.5 mol% $RhCl(PPh_3)_3$ 0.5 mol% AgOTf Solvent, Temp., Time	
1.	**14a**: R=H	THF, 65°C, 6h	**15a**: 83%
2.	**14b**: R=CO_2Me	PhMe, 110°C, 1h	**15b**: 80%
3.	**14c**: R=Ph	PhMe, 110°C, 2h	**15c**: 77%
		1 mol% $RhCl(PPh_3)_3$ 1 mol% AgOTf PhMe, 110°C, 10h	
4.	**16**		**17**: 90%
		5 mol% $RhCl(PPh_3)_3$ 5 mol% AgOTf PhMe, 110°C, 1h	
5.	**18**		**19**: 90%
		i. $[Rh(CO)_2Cl]_2$ Solvent, Temp., Time ii. HCl/MeOH	
6.	**20a**: R=H	5 mol%, $CDCl_3$, 30°C, 40h	**21a**: 81%
7.	**20b**: R=Me	0.5 mol%, CH_2Cl_2, r.t., 30h	**21b**: 73%

substrate **20a** was fully consumed after 40 h at 30 °C, revealing ketone **21a** in 81% yield upon hydrolysis of the initially formed enol ether. Likewise, **20b** reacted with 0.5 mol % $[Rh(CO)_2Cl]_2$, providing after 30 h at *room temperature* **21b** in 73% yield following hydrolysis. Utilization of the dimeric rhodium(I) catalyst, in combination with alkoxy substitution of the cyclopropane, provided a dramatic increase in the rates of these cycloadditions.

In summary, this study provides the first analysis of the effects of cyclopropane substitution on the stereoselectivity, regioselectivity, and efficiency of the [5+2] cycloaddition. 1,1-Disubstituted cyclopropanes react efficiently in all examples studied thus far, with heteroatom substitution at this position leading to significant rate enhancements. For 1,2-disubstituted systems, while two regioisomers are possible only one isomer is observed and is derived from cleavage of the less substituted bond. Additionally, for these substrates the 1,2-substituted cyclopropyl stereochemistry is retained through the cycloaddition, translating into a 1,4-stereorelationship in the product.

Acknowledgment. This research was supported by a grant (CHE-9800445) from the National Science Foundation. Fellowship support by the National Science Foundation (A.J.D.), ACS Division of Organic Chemistry, sponsored by Eli Lilly (J.A.L.) and Organic Syntheses (A.J.D.), Pharmacia-Upjohn and Boehringer-Ingelheim (C.O.H.), Eli Lilly (J.A.L.), and Deutsche Forschungsgemeinschaft (H.R.) is gratefully acknowledged.

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

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(11) THF can been used for more volatile substrates while chlorinated solvents often provide increased reactivities when utilizing $[Rh(CO)_2Cl]_2$.

(12) McGaffin, G.; de Meijere, A.; Walsh, R. *Chem. Ber.* **1991**, 939−945. Ryu, I.; Ikura, K.; Tamura, Y.; Maenaka, J.; Ogawa, A.; Sonoda, N. *Synlett* **1994**, 941−942.