The First Intermolecular Transition Metal-Catalyzed [5+2] Cycloadditions with Simple, Unactivated, Vinylcyclopropanes

Paul A. Wender,* Claudia M. Barzilay, and
Alaric J. Dyckman

Department of Chemistry, Stanford University
Stanford, California 94305

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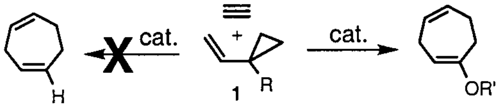
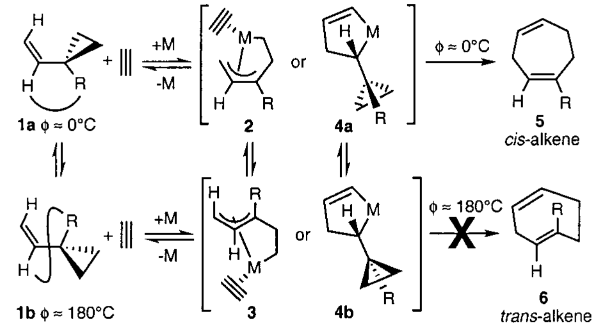
Transition metal-catalyzed reactions[1] represent powerful strategy level processes[2] for complex molecule synthesis. Of special importance and a goal of our research in this area is the development of metal-catalyzed processes that in the absence of catalyst would be difficult or impossible to achieve. The [5+2] cycloaddition of vinylcyclopropanes (VCPs) provides a dramatic illustration of this point, as simple VCPs do not cycloadd to alkenes or alkynes.[3] However, as first reported from these laboratories in 1995, in the presence of transition metal catalysts, VCPs react efficiently with a variety of π-systems.[4] For example, the intermolecular cycloadditions of 1-silyloxy-VCPs (**1**, R = OTBS) with a variety of alkynes in the presence of $[Rh(CO)_2Cl]_2$ catalyst *provide the [5+2] cycladducts in high yields and in 1−3 h at 30−40 °C.*[5,6]

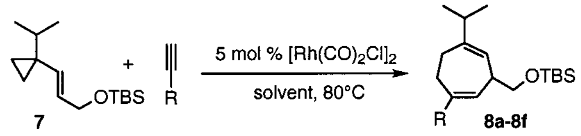


In striking contrast to the facile reactions of silyloxyVCPs, *inter*molecular cycloadditions of VCP itself (**1**, R = H) or simple substituted VCPs failed with various alkynes and catalysts.[7] While this contrasting reactivity might be attributed solely to the electronic contribution of the heteroatom substituent, it could also be a consequence of its conformational influence.[8] For example, alkyl substitution of VCPs, particularly at the 1-position, has been shown to reduce the energetic difference between the *s*-trans (**1b**) (global minimum) and *s*-cis (**1a**) (local minimum) conformations, allowing for increased population of **1a**.[9] Based on one of our proposed mechanisms for the [5+2] cycloaddtion[10] this conformational effect could favor the formation of the *Z*-allyl[11] intermediate **2** over its *E*-allyl[12] counterpart **3**. Only **2** has the appropriate dihedral angle ($\phi \approx 0$ °C) for formation of the *cis*-alkene of cycloadduct **5**. In an alternative mechanism involving initial cyclometalation,[10] a similar steric effect could manifest itself in the formation and further reaction of metallacycles **4a** and **4b**.[13,14]



A study of the cycloaddition of isopropyl-substituted VCP **7** was initiated to determine whether steric effects could be exploited to achieve the cycloaddition of simple VCPs in accord with the above analysis. Gratifyingly, reaction of **7** with various alkynes, in the presence of a rhodium(I) catalyst, readily afforded cycloheptadiene products **8a**−**8f** in excellent yields under the preferred conditions (bold, Table 1). The cycloadditions proceeded

Table 1. Cycloadditions of VCP **7** with Representative Alkynes



entry	R	solvent[a]	time	conv, %	yield, %	product
1	CO_2Me	A	2 h	100	93	**8a**
2	CO_2Me	B	1 h	100	**95**	**8a**
3	CO_2Me	C	30 min	100	85	**8a**
4	Ph	A	4 h	100	**92**	**8b**
5	Ph	B	2 h	100	81	**8b**
6	CH_2OMe	A	22 h	56	49	**8c**
7	CH_2OMe	B	5 h	>95	**90**	**8c**
8	CH_2OH	A	6 h	80	73	**8d**
9	CH_2OH	B	5 h	>95	**90**	**8d**
10	C_3H_7	A	48 h	90	79	**8e**
11	C_3H_7	B	23 h	91	**81**	**8e**
12	TMS	A	72 h		77	**8f**
13	TMS	B	23 h	>95	**90**	**8f**

[a] Solvents: A = DCE, B = 5% TFE in DCE, C = TFE.

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[1] For reviews see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. Hegedus, L. S. *Coord. Chem, Rev.* **1998**, *168*, 149−175. Haughton, L.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2645−2658.

[2] Wender, P. A.; Miller, B. A. *Org. Synth. Theory Appl.* **1993**, *2*, 27−66.

[3] Herges, R. In *Houben-Weyl Methoden der organishen Chemie*; de Meijere, A., Ed.; Georg Thieme Verlag: Stuttgart, 1997; p 2153.

[4] Alkynes: (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. (b) Wender, P. A.; Dyckman, A. J. *Org. Lett.* **1999**, *1*, 2089−2092. (c) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442−10443. Alkenes: (d) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940−1941. (e) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203−7220. (f) Allenes: Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−5349.

[5] (a) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−10977. (b) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Scanio, M. J. C. *Org. Lett.* **2000**, *2*, 1609−1611.

[6] Temperature of the NMR probe in which exploratory reactions were monitored. As found in our own work and that of others, changes in the ligands, metal, and solvent influence the facility of the reaction. For recent references from other laboratories, see: Trost, B. M.; Shen, H. *Org. Lett.* **2000**, *2*, 2523−2525 and ref 5 cited therein.

[7] Wender, P. A.; Miranda, E. Unpublished results. Over 75 reactions, combining monoalkenylcyclopropanes with a variety of dienophiles and catalysts, were investigated using previously reported conditions (refs 4a and 5a).

[8] For an isolated example of an intermolecular cycloaddition with a constrained VCP, see: Binger, P.; Wedmann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113−119.

[9] Plemenkov, V. V.; Butenko, O. Ju.; Zverev, V. V.; Ermolaeva, L. V.; Vakar, V. M.; Ignatchenko, A. V.; Bolesov, I. G. *J. Mol. Struct.* **1990**, *218*, 195−200.

[10] We have previously described two classes of possible mechanisms that differ in their timing of C−C bond formation and cyclopropane bond cleavage. See ref 5a.

[11] *E*-Allylmetallacyclohexenes from VCPs, see: Ryu, I.; Ikura, K.; Tamura, Y.; Maenaka, J.; Ogawa, A.; Sonoda, N. *Synlett* **1994**, 941−942.

[12] *Z*-Allyl meatallacyclohexenes from VCPs, see: Hanzawa, Y.; Harada, S.; Nishio, R.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 9421−9424.

[13] Preliminary calculations (MM2, **M** = PMe_3) show that the preference for **4a** increases relative to **4b** as the steric influence of the substituent increases (**R** = H, Me, ^{i}Pr, tBu).

[14] Substitution of this type has a nonnegligible electronic effect on the CP bond strength, which also is a factor in the cycloaddition.

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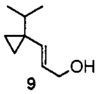
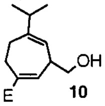
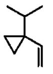
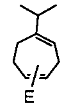
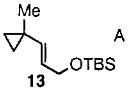
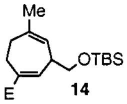
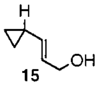
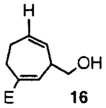
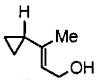
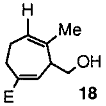
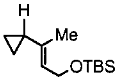
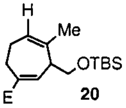
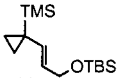
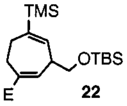
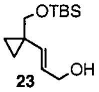
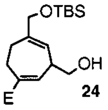
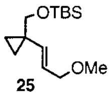
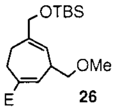
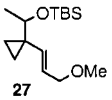
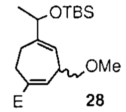
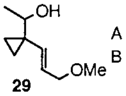
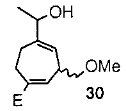
Table 2. Substituent Effects on the [5+2] Cycloadditions with Methyl Propiolate (E = CO_2Me)

Entry	VCP	Cond.[a]/ Yield	Product
1	 **9**	A 2h/ 82%	 **10**
2	 **11**	A 1.5h/ 76%	 **12**
3	 **13**	A 8h/ 81%	 **14**
4	 **15**	A 30h/ 23% B 2h/ dec.	 **16**
5	 **17**	A 72h/ 38% B 6h/ dec.	 **18**
6	 **19**	A 72h/ 64% B 45 min/ 69%	 **20**
7	 **21**	A 3h/ 53%	 **22**
8	 **23**	A 2h/ 82%	 **24**
9	 **25**	A 20h/ 75% B 3h/ 76%	 **26**
10	 **27**	A 15h/ 63% d.r. = 2:1	 **28**
11	 **29**	A >24 h/ no rxn B 21h/ 62% d.r. = 1:1	 **30**

[a] Conditions: A = 5 mol % $[Rh(CO)_2Cl]_2$, DCE, 80 °C; B = 5 mol % $[Rh(CO)_2Cl]_2$, 5% TFE in DCE, 80 °C.

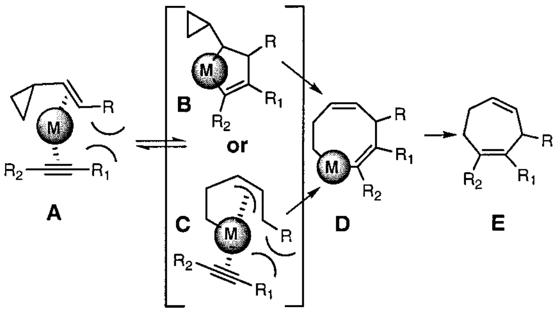
smoothly with alkynes containing alkyl, aryl, ester, hydroxyl, and silicon functionalities. Remarkably, a single regioisomer was obtained in each case.

Utilization of 5 mol % $[Rh(CO)_2Cl]_2$ in 1,2-dichloroethane (DCE) at 80 °C was found to be quite general for effecting the cycloaddition. The use of 2,2,2-trifluoroethanol (TFE) as solvent frequently led to an increase in the rate and yield of the cycloadditions, particularly for sluggish systems.[15] A similar rate enhancement was also found when TFE was employed as a cosolvent (5% TFE/95% DCE: Table 1, solvent B).

A systematic examination of cyclopropane substituent effects as well as functional group tolerance was undertaken through reaction of a range of VCPs with methyl propiolate (Table 2). Substitution of the TBS protecting group with a free hydroxyl (**7**, Table 1 vs **9**, Table 2) had little effect on the efficiency or regioselectivity of the cycloaddition. The reaction proceeded equally well for the monosubstituted VCP **11**. On the other hand, replacement of the isopropyl functionality with a methyl group (**7** vs **13**) did result in a decrease in the rate of the cycloaddition, although full conversion to **14** was still achieved in 8 h and 81% isolated yield (Table 2, entry 3). Replacement of the methyl group with a hydrogen atom (**13** vs **15**) further reduced the rate and overall yield (Table 2, entry 4). Substitution on the internal position of the vinyl moiety, also known to affect the conformational equilibrium of VCPs,[16] provided a slight yield enhancement over the unsubstituted system (**17** vs **15**). In contrast to **17**, the silyl-protected VCP **19** reacted more efficiently in DCE and significantly more rapidly in the presence of 5% TFE (Table 2, entry 6). VCPs **15** and **17** slowly decomposed in the presence of TFE.

Given the slow reactions of the H-substituted VCPs **15** and **17**, it is noteworthy that the TMS-substituted system **21**, an H–VCP surrogate, reacts in only 3 h to give **22**. Primary as well as secondary silyloxy functionalities were also tolerated in these processes (Table 2, entries 8–10), leading to cycloadducts possessing three differentiated groups symmetrically positioned on a cycloheptadiene scaffold (**24**, **26**, and **28**), a potentially useful attribute for library design. The unprotected secondary alcohol **29** was unreactive in DCE solvent, possibly due to unfavorable coordination of the metal to the hydroxyl group. However, the introduction of 5% TFE allowed for its successful conversion to **30**.

It is noteworthy that high (>10:1) if not complete regioselectivity is observed with all the above di- and trisubstituted VCPs. With monosubstituted alkynes, the substitution on the olefin terminus directs formation of a single regioisomer. The observed regioselectivity is consistent with minimization of steric effects during C–C bond formation involving either of the two general mechanistic paths.



Previous examples of intermolecular [5+2] cycloadditions required vinylcyclopropane activation by heteroatom substitution. It has now been demonstrated for the first time that *simple, unactivated vinylcyclopropanes* can be utilized to achieve intermolecular [5+2] cycloadditions. Substitution at the 1-position of the vinylcyclopropane with alkyl or silicon functionality was found to accelerate the cycloaddition, with the degree of rate enhancement correlating to the steric bulk of the substituent. The first studies on regioselectivity enabled by this advance demonstrate that a high degree of selectivity can be obtained with terminal alkynes. This cycloaddition is proving to be of broad scope in terms of its tolerance to substrate variation and of its utility in synthesis. Further studies on 5C and 2C components, catalysts, ligands, conditions, and applications are in progress.

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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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(15) For solvent effects see refs 4a and 5b and the following: Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Scanio, M. J. C. *Abstract of Papers*; 219th National Meeting of the American Chemical Society, San Francisco, CA, March 25–29, 2000; American Chemical Society: Washington, DC, 2000; ORGN 261.

(16) De Mare, G. *J. Mol. Struct. (THEOCHEM)* **1987**, *153*, 341–356.