Communications to the Editor

The Transition Metal-Catalyzed Intermolecular [5+2] Cycloaddition: The Homologous Diels−Alder Reaction

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Cycloaddition reactions are among the most frequently used processes in organic synthesis, providing practical access to complex molecules of theoretical, technological, commercial, and medical interest, often from simple starting materials.[1] In 1959, a homologue of the Diels−Alder cycloaddition was reported[2] involving the [5+2] cycloaddition of a vinylcyclopropane and maleic anhydride to form a seven-membered-ring product. Efforts to reproduce this reaction have, however, not been successful,[3,4] and its extension to other simple vinylcyclopropanes has not been reported.[5] Thus far, this reaction has been limited to a few examples of conformationally constrained, heteroatom- or strain-activated substrates and activated alkynes.[6,7] Simple vinylcyclopropanes do not react "even [with] the strongest dienophiles".[4]

In 1995, as part of our studies on [*m*+*n*] cycloadditions which in the absence of catalysts are theoretically forbidden or difficult to achieve,[8,9] we reported the first examples of a transition metal-catalyzed *intra*molecular [5+2] cycloaddition of simple vinyl-cyclopropanes and alkynes.[10] This reaction has more recently been achieved with alkenes and with asymmetric catalysis.[11] We now report the first metal-catalyzed *inter*molecular [5+2] cy-cloadditions of simple vinylcyclopropanes and alkynes, the long sought homologue of the Diels−Alder cycloaddition, and a fundamentally new and remarkably general process for the synthesis of seven-membered rings.

Our initial attempts to effect the metal-catalyzed *inter*molecular [5+2] cycloaddition failed with various vinylcyclopropanes and

Table 1. The Transition Metal-Catalyzed [5+2] Cycloadditions of 1-(*tert*-Butyldimethylsilyloxy)-1-vinylcyclopropane with Alkynes

entry	alkyne[a]	product	time/temperature[b]	yield[c]
1	E≡H		2h / 40 °C	93%
2	E≡Me		1.5h / 40 °C	92%
3	O≡H		2.5h / 40 °C	88%
4	MeO~≡H		1.5h / 40 °C	88%
5	HO~≡H		1.5h / 40 °C	74%
6	(Me)₃Si≡H		2h / 40 °C	77%
7	Ph≡H		3h / 30 °C	81%
8			3h / 40 °C	75%
9			2h / 40 °C	88%
10			2.5h / 40 °C	84%
11			7h / 40 °C	65%
12	H≡H		6h / 40 °C	79%

[a] E = CO₂Me. [b] See General Procedure in footnote 16. [c] Overall yields for cycloaddition and hydrolysis steps.

alkynes using Wilkinson's catalyst (Rh(PPh₃)₃Cl), even when conditions were employed for which the corresponding *intra*molecular reaction worked well. Either the starting materials did not react or under more forcing conditions the alkyne cyclotri-merized or the vinylcyclopropane isomerized.[12] A solution to these relative rate problems was fashioned from our previous observations that oxygen substitution of the vinylcyclopropane facilitates the *intra*molecular cycloaddition[13] and that [Rh(CO)₂-Cl]₂[14] can be used to effect intramolecular [5+2] cycloadditions of unreactive substrates. Thus, when siloxycyclopropane **1**[15] was treated with dimethyl acetylenedicarboxylate in the presence of [Rh(CO)₂Cl]₂ in CDCl₃ at 40 °C, the facile formation of a single cycloadduct **2** was observed by NMR spectroscopy. For ease of

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(5) For related studies on vinylcyclopropanes, see: Effenberger, F.; Podszun, W. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 976. Nishida, S.; Moritani, I.; Teraji, T. *J. Chem. Soc., Chem. Commun.* **1970**, 501. Sarel, S.; Felzenstein, A.; Yovell, J. *J. Chem. Soc., Chem Commun.* **1974**, 753. For a review, see: Tsuji, T.; Nishida, S. *Acc. Chem. Res.* **1984**, *17*, 56.

(6) Tanny, S. R.; Fowler, F. W. *J. Org. Chem.* **1974**, *39*, 2715. Herges, R.; Ugi, I. *Angew. Chem., Intl. Ed. Engl.* **1985**, *24*, 594.

(7) Fenton, G.; Isaacs, N. S.; Gilbert, A. *Tetrahedron Lett.* **1985**, *26*, 1597. Baldwin, J. E.; Pinschmidt, R. K., Jr. *Tetrahedron Lett.* **1971**, *14*, 935.

(8) Representative examples include [4+4] cycloadditions (Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904) and [4+2] cycloadditions (Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824).

(9) For reviews on metal-catalyzed cycloadditions, see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129. Dell, C. P. *Contemp. Org. Synth.* **1997**, *4*, 87.

(10) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. For recent applications, see: Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075. Binger, P.; Wedemann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113.

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(12) For a review on transition metal-mediated reactions of vinylcyclo-propanes, see: Khusnutdinov, R. I.; Dzhemilev, U. M. *J. Orgmet. Chem.* **1994**, *471*, 1.

characterization, **2** was hydrolyzed during workup by brief treatment of the reaction mixture with 1% HCl/EtOH to give ketone **3** in >90% yield. In the absence of catalyst, no reaction was observed even after 3 days. The reaction can be conducted in a variety of solvents (e.g., THF, toluene, and EtOH) although the use of weakly coordinating solvents (CHCl$_3$ and CH$_2$Cl$_2$) allows for shorter reaction times (ca. 1–3 h) and milder conditions (40 °C).
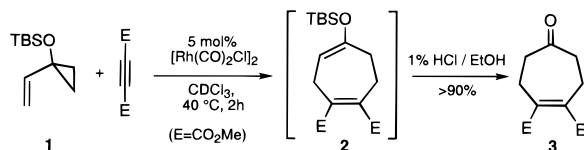
The scope of this new cycloaddition reaction was investigated with a range of alkynes, representing the types required in fine, bulk, and complex chemical synthesis. As summarized in Table 1, the reaction is remarkably general. To allow for comparisons, all reactions were conducted with 5 mol % catalyst on a 1 mM scale and 1.2–1.5 equiv of the alkyne (except in the case of acetylene, entry 12). Reactions were not individually optimized to establish the generality of the procedure. The initial cycloadduct was hydrolyzed upon workup to provide the ketone product.[16] *Electron rich, electron poor, conjugated, internal, and terminal alkynes, even acetylene itself, were found to provide cycloadducts in good to excellent yields.* Most reactions were complete in 1–3 h at 40 °C. Competition experiments showed that the relative rates of cycloadditions for different alkynes differ sufficiently to allow for chemoselective reactions. Thus, when 1 equiv of **1** was mixed with 1.1 equiv each of dimethyl acetylenedicarboxylate, phenyl acetylene, and methyl propargyl ether, only the

(13) Replacement of hydrogen by an ethoxy group results in a 5–10-fold rate acceleration in the intramolecular reaction (Heiko Rieck, unpublished results, Stanford University). For other reactions of donor-substituted cyclopropanes, see: Jun, C.-H.; Kang, J.-B.; Lim, Y.-G. *Tetrahedron Lett.* **1995**, *36*, 277. Ryu, I.; Ikura, K.; Tamura, Y.; Maenaka, J.; Ogawa, A.; Sonoda, N. *Synlett* **1994**, 941. Ryu, I.; Murai, S. In *Methods of Organic Chemistry*; de Meijere, A., Ed.; Georg Thieme Verlag: Stuttgart, 1997; Vol. E17c, p 1985. Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 1.
(14) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164.
(15) Prepared on a large scale by analogy to the methods in the following: Salaün, J.; Marguerite, J. *Org. Synth.* **1985**, *63*, 147. Wasserman, H. H.; Hearn, M. J.; Cochoy, R. E. *J. Org. Chem.* **1980**, *45*, 2874.
(16) General procedure: To an oven-dried, argon-purged Schlenk flask was added [Rh(CO)$_2$Cl]$_2$ (0.05 mmol) and anhydrous CH$_2$Cl$_2$ (10 mL) under an argon atmosphere. Argon was bubbled through the resultant yellow solution (1 min) and **1** was added (1 mmol). After an additional argon purge (1 min), the alkyne (1.1–1.5 mmol) was added. The flask was placed in an oil bath preheated to 40 °C. The reaction was monitored by TLC. Upon completion, the reaction was usually dark in color. The reaction mixture was treated with 1% HCl in EtOH (0.2 mL) and the resulting mixture was filtered through a short pad of silica gel (Et$_2$O eluant) and concentrated in vacuo. The residue was purified by flash column chromatography. This procedure was not optimized for the isolation of the silylenol ether cycloadducts. With unsymmetrical alkynes, spectroscopic studies suggest that one regioisomer is preferentially formed.

Scheme 1
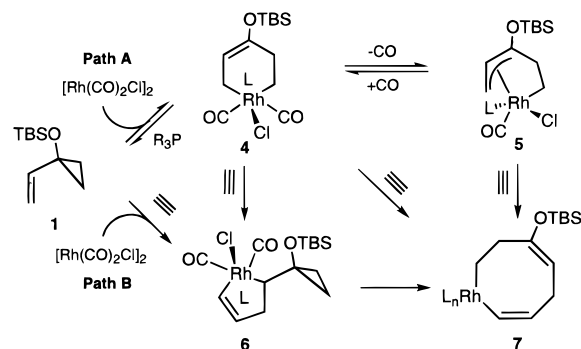
cycloadduct of the diester was obtained. The functional group tolerance of this reaction is also noteworthy as ketones, esters, ethers, and even unprotected alcohols do not inhibit catalysis.[17]

Two general mechanisms, differing by the sequence of cyclopropane cleavage, are possible for this cycloaddition (Scheme 1). While studies on these (and other) pathways are in progress, the reaction of **1** with a stoichiometric amount of [Rh(CO)$_2$Cl]$_2$ has been found to produce an equilibrium mixture of two spectroscopically observable complexes.[18] When an alkyne is added to this mixture, the expected cycloadduct is formed, indicating that these complexes might be competent intermediates in the catalytic cycle or more likely could serve as a resting state for the catalyst.

Overall, a new class of cycloaddition reactions has been developed that offers a strategically novel and practical route to an otherwise difficult-to-prepare but common ring system, based on simple vinylsiloxycyclopropanes and alkynes. The reaction works well with a broad range of alkynes. The siloxy substituent on the cyclopropane has the special synthetic advantage of providing access to silylenol ether cycloadducts and their ketone derivatives. It is of further synthetic significance that these cycloadducts possess differentiated functionality, allowing for their flexible use as building blocks for complex molecules and for combinatorial libraries. Further studies are in progress.

Supporting Information Available: Procedures and spectroscopic data for representative products (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(17) Substituted vinylsiloxycyclopropanes can also be used (Hartung, I.; Rieck, H. Unpublished results, Stanford University). For example, the use of propenylsiloxycyclopropane with HCCCOOMe gives a 92% yield of 3-methyl-5-carbomethoxycyclohept-4-en-1-one.
(18) The NMR spectrum of this mixture is consistent with the σ,η^1-allyl and σ,η^3-allyl complexes **4** and **5**.