Elaboration of Conjugated Alkenes Initiated by Insertion into a Vinylic C−H Bond

Barry M. Trost,* Katsuharu Imi, and Ian W. Davies

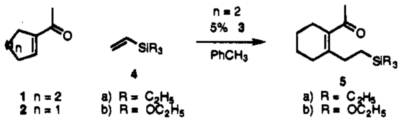
Department of Chemistry, Stanford University
Stanford, California 94305-5080

Received January 25, 1995

Increasing our repertoire of addition reactions enhances our opportunities to increase synthetic efficiency.[1] Formation of C−C bonds by additions of C−H bonds across π-unsaturation constitutes a particularly valuable strategy. The importance of alkenes in and of themselves and as building blocks for construction of complex molecules makes their availability in a geometrically controlled fashion by such processes important. One strategy involves elaboration of simple alkenes into more complex ones. With alkenes conjugated to an electron-withdrawing group, formation of new carbon−carbon bonds generally involves conjugate addition which removes the double bond[2] or alkylations via enolates.[3] Their high reactivity toward additions to themselves complicates a reaction of the type shown in eq 1 which is initiated by a metal-catalyzed C−H insertion[4−6] wherein the organometallic intermediate might simply add to its precursor. On the other hand, the prospects to develop a fully stereocontrolled alkene synthesis which is especially difficult for tri- and tetrasubstituted alkenes in such an efficient manner enticed us to examine such a process.

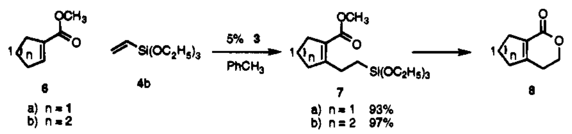
(1)

Initial work centered on 1-acetylcyclohexene (**1**) and -cyclopentene (**2**) using ruthenium complexes which have been successful in aryl systems, the most notable being the work of Murai et.al.[4] Treatment of the former (0.25 M) with 2 equiv of triethylvinylsilane (**4a**) in toluene with 5% $(Ph_3P)_3RuH_2(CO)$ (**3**) at reflux gave a 94% isolated yield of the addition product **5a**[8] (eq 2). The utility of alkoxysilanes as easy precursors of alcohols[7] led to our examination of triethoxyvinylsilane, which participated equally well, giving the adduct **5b**[8] in 76% isolated yield. Surprisingly, 1-acetylcyclopentene (**2**) returned starting material.



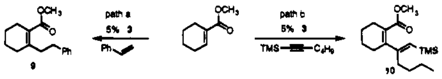
(2)

In contrast to this result, methyl 1-cyclopentenecarboxylate (**6a**) reacted efficiently with 1.2 equiv of alkene **4b** to give the desired adduct **7a**[8] (eq 3). The greater effectiveness of the ester in promoting the addition in comparison to the ketone is noted in the reaction times. The 65 h reaction time for **1** was reduced to 18 h for **6b**. More dramatically, the lack of reactivity of 1-acetylcyclopentene contrasts with a 3 h reaction time for **6a**, even faster than the six-membered-ring analogue **6b**. Basic peroxide ($KHCO_3$, H_2O_2, THF, CH_3OH, room temperature) smoothly converted the adduct **7b** to the lactone **8**[8] ($n = 2$) in 86% isolated yield. Other ruthenium complexes including Cp (COD)$RuCl_2$ (with or without silver triflate or ligands) and arene ruthenium complexes[10] gave unsatisfactory results. Replacing triphenylphosphine of **3** with the acceptor ligand trifurylphosphine[11] also proved undesirable. In contradistinction to the above, methyl benzoate failed to react under the above conditions, highlighting the differences between the vinyl and aryl systems.



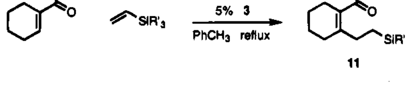
(3)

Styrene (1.2 equiv) gave similar results (eq 4, path a) albeit in a somewhat slower reaction. After 40 h, a 70% yield of adduct **9**[8] was obtained with starting material remaining (92% yield based upon recovered starting material (brsm)). A silylalkyne also proved to be a satisfactory acceptor (eq 4, path b), in which case the percent conversion increased by using 2 equiv (82% yield, 95% yield brsm) of acceptor rather than 1.2 equiv (52% yield, 99% yield brsm). Only a single geometric isomer and regioisomer tentatively assigned as **10**[8] based on 2D NMR studies was obtained.



(4)

The chemoselectivity was explored with a series of esters as summarized in eq 5 and Table 1. As expected, aromatic rings (entry 1), esters (entry 2), and silyl ethers (entry 3) have no



(5)

---

[1] Trost, B. M. *Science* **1991** *254*, 1471; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

[2] Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Vol. 4, Chapter 1.1, pp 1−68. Lee, V. J. *Idem.*; Chapter 1.2, pp 69−138; Chapter 1.3, pp 139−168. Kozlowski, J. A. *Idem.*; Chapter 1.4, pp 169−198. Schmalz, H. G. *Idem.*; Chapter 1.5, pp 199−236. Hulce, M.; Chapdelaine, M. J. *Idem.*; Chapter 1.6, pp 237−268.

[3] Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Vol. 3, Chapter 1.1, pp 21−25, 50−53.

[4] Cyclometalation of substituted aromatics is well documented; see: Newcome, G. R.; Puckett, W. E.; Gupta, V. K.; Kiefer, G. E. *Chem. Rev.* **1986**, *86*, 451. Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403. Dunina, V. V.; Zalevskaya, D. A.; Potapov, V. M. *Russ. Chem. Rev.* **1990**, *90*, 403. For a recent reference, see: Valk, J.-M.; Maassarani, F.; van der Slius, P.; Spek, A. L.; Boersma, J.; van Koten, G. *Organometallics* **1994**, *13*, 2320. For catalytic reactions involving initiation by such a process with Ru complexes, see: Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778. Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888. Murai, S.; Kakiuchi, F.; Sekimo, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

[5] Net addition of a vinylic C−H bond across a double bond not involving a metal-catalyzed C−H insertion as the initiation step is known. Misono, A.; Uchida, Y.; Hidai, M.; Inomata, I. *J. Chem. Soc. D* **1968**, 704. Bogdanovic, B.; Henc, B.; Meister, B.; Pauling, H.; Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *84*, 1070. Nugent, W. A.; Hobbs, F. W. *J. Org. Chem.* **1983**, *43*, 5364. Nugent, W. A.; McKinney, R. J. *J. Mol. Catal.* **1985**, *29*, 65. Buono, G.; Siv, C.; Peiffer, G.; Triantaphylides, C.; Denis, P.; Mortreux, A.; Petit, F. *J. Org. Chem.* **1985**, *50*, 1781. McKinney, R. J.; Colton, M. C. *Organometallics* **1986**, *5*, 1080. Brookhart, M.; Sabo-Etienne, S. *J. Am. Chem. Soc.* **1991**, *113*, 2777. Kovalev, I. P.; Strelenko, Y. A.; Ignatenko, A. V.; Vinogradov, M. G.; Nikishin, G. I. *J. Organomet. Chem.* **1991**, *420*, 125. Ohgomori, Y.; Ichikawa, S.; Sumitani, N. *Organometallics* **1994**, *13*, 3758.

[6] For oxidative addition of a ruthenium complex into a vinylic C−H bond, see: Komiya, S.; Yamamoto, A. *Chem. Lett.* **1975**, 475. Komiya, S.; Ito, T.; Cowie, M.; Yamamoto, A.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 3874.

[7] Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37. Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694.

[8] This compound has been fully characterized spectroscopically.

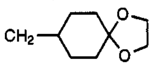
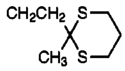
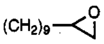
[9] Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199. For a review, see: Davies, S. G.; McNally, J. P.; Smallridge, A. J. *Adv. Organomet. Chem.* **1990**, *30*, 1.

[10] leBozec, H.; Touchard, D.; Dixneuf, P. H. *Adv. Organomet. Chem.* **1989**, *29*, 163.

[11] Allen, D. W.; Hutley, B. G; Mellor, M. T. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 63. Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 5739.

0002-7863/95/1517-5371$09.00/0

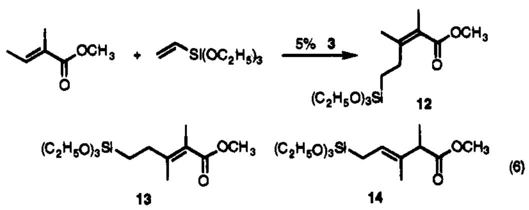
Table 1. Chemoselectivity of Ruthenium-Catalyzed Addition[a]

entry	R	R′	% yield[b]	compd no.
1	CH_2Ph	C_2H_5O	91	**11a**
2	$(CH_2)_5CH_2OAc$	C_2H_5	85 (90)	**11b**
3	$(CH_2)_5CH_2OTBDMS$	C_2H_5	91	**11c**
4		C_2H_5	73 (84)	**11d**
5		C_2H_5O	92	**11e**
6	$(CH_2)_{10}CON(CH_3)_2$	C_2H_5	93	**11f**
7		C_2H_5	73 (77)	**11g**
8	$(CH_2)_5CH_2Br$	C_2H_5O	54 (68)	**11h**
9	$(CH_2)_5CH_2CN$	C_2H_5	19 (55)	**11i**

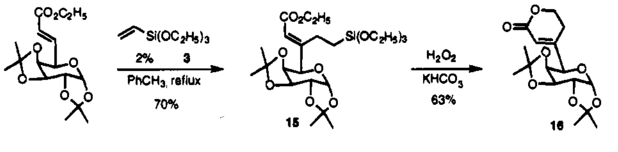
[a] All reactions were performed in toluene at reflux with 5% **3** for 20 h. [b] Yields in parentheses are based upon recovered starting material (brsm).

effect. Interestingly, both ketals (entry 4) and thioketals (entry 5) are well tolerated. The coordinating ability of an amide (entry 6) does not inhibit reaction in contrast to the case of a nitrile (entry 9) which apparently does.[12] Remarkably, alkylating agents like an epoxide (entry 7) and a bromide (entry 8) are also tolerated. Surprisingly, the (*Z*)-3-hexenyl and 3-hexynyl esters failed to react.

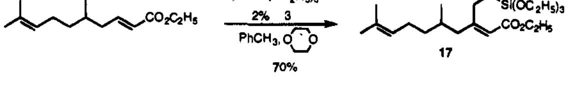
Acyclic substrates react but can lead to isomerizations of the initial products. For example, methyl tiglate gave an 88% yield of a 17:2:3 ratio of adducts **12**,[8] **13**, and **14**[8] under the usual conditions in 2 h. Use of THF as solvent inhibits the isomerization but slows reaction such that a 52% isolated yield of **12** is obtained after 65 h (eq 6). Use of 1 equiv of dioxane in toluene proves most satisfactory, giving an 86% yield of **12** in 20 h. Disubstituted alkenes were converted stereoselectively into trisubstituted ones **15** and **17** (eqs 7 and 8). The product **15** was fully characterized as the lactone **16** formed upon oxidative cleavage of the silane. Presumably, the ether oxygens in the substrate precluded the need to add exogenous ethers to inhibit product isomerization. The compatibility of the remote trisubstituted double bond in eq 8 contrasts with the incompatibility of disubstituted double bonds in eq 5 (vide supra). *N*-Methylcinnamide gave the expected adduct **18**[8] in 80% yield even in the absence of dioxane (eq 9).



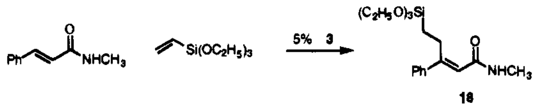
(6)



(7)

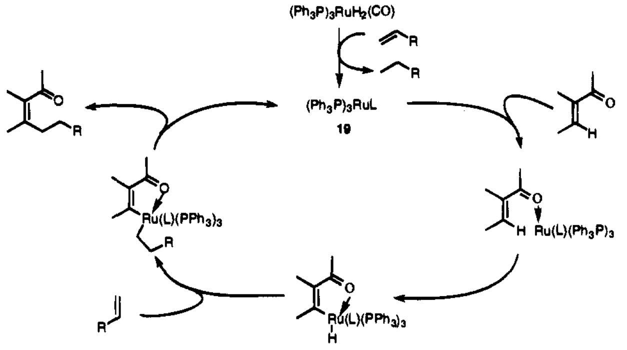


(8)



(9)

Scheme 1. Mechanism of Addition



The mechanism of this reaction can be envisioned as shown in Scheme 1. Evidence for "activation" of the catalyst by loss of hydrogen was pursued by spectral studies. Addition of the acceptor alkene triethoxyvinylsilane to complex **3** in a NMR tube shows disappearance of the signals corresponding to the ruthenium hydride at δ −6.87 and −8.82 with only a new set of aromatic signals (δ 7.25−9.00) remaining. Furthermore, the infrared spectrum shows a new CO peak at 1903 cm^{-1}. GC analysis also shows the presence of the hydrogenation product from the acceptor alkene. This resultant species is catalytically active. A reasonable conjecture for the structure of this species is a coordinatively unsaturated complex such as **19** which may be stabilized by solvent serving as a weakly coordinating ligand. Strong inhibition by performing the reaction in the presence of a CO atmosphere and modest inhibition by performing the reaction in a closed system suggest that loss of CO to yield **19** is also required. Thus, a highly coordinatively unsaturated ruthenium bearing only the three phosphine ligands stabilized by solvent serving as a weakly coordinating ligand may be the active species.[13] The retardation effect of THF as solvent and the strong influence of ether additives support this contention. Consistent with the cyclometalation as the first step is the lack of reactivity wherein the β C−H bond is *trans* to the carbonyl group.[14] The ability to elaborate activated alkenes into more substituted ones with excellent retention of alkene geometry by addition to a vinylic C−H bond should prove to be a useful methodology that enhances synthetic efficiency.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for the generous support of our programs, NATO for a fellowship for I.W.D., and the Sumitomo Chemical Co. for a fellowship for K.I. Mass spectra were generously provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the National Institute of Research Resources.

Supplementary Material Available: Characterization data for **5a,b**, **7a,b**, and **8−18** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9502536

---

(12) For a leading reference, see: Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S.; Naota, T. *Chemtracts: Org. Chem.* **1994**, *7*, 281.

(13) Highly coordinatively unsaturated ruthenium complexes bearing triphenylphosphine ligands are also known to slip to form η^6 complexes with one of the phenyl rings. Cf.: McConway, C.; Skapski, A. C.; Phillips, L.; Young, R. J.; Wilkinson, G. *J. Chem. Soc., Chem. Commun.* **1974**, 327. However, such a species would not be expected to be catalytically active in these reactions.

(14) This observation combined with the position of the double bond in the product suggests that a metallacycle intermediate involving the two alkene reactants that could be envisioned as an intermediate is unlikely. Metallacycles between alkenes and alkynes are known with this catalyst; see: Warrener, R. N.; Abbenante, G.; Kennard, C. H. L. *J. Am. Chem. Soc.* **1994**, *116*, 3645.