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Silylative Carbocyclization of Allenyl-carbonyl Units with Et_3SiH Catalyzed by Rhodium: Cis-Stereoselective Synthesis of Homoallylic Cycloalkanols†

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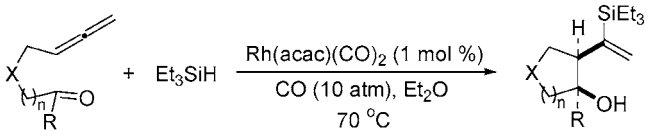
ABSTRACT



X = NTs, $C(CO_2Et)_2$, O R = H, Me, Et n = 1, 2

A new procedure for the synthesis of *cis*-2-triethylsilylvinyl-cyclopentanols and -cyclohexanols from allenyl-aldehydes and -ketones with Et_3SiH through rhodium-catalyzed silylative carbocyclization is described. The use of $Rh(acac)(CO)_2$ (1 mol %) to promote the reaction results in a mild and convenient protocol for the three-component assembly.

The availability of efficient synthetic methods in the construction of cyclic system via organotransition metal catalysts or reagents is of considerable current interest in organic chemistry. As a consequence, many advances in the cyclization mediated by transition metals have been made through a variety of synthetic strategies.[1] Of particular interest is the transition metal-catalyzed silylative carbocyclization of dienes,[2] enynes,[3] diynes,[4] and tetraenes[5] employing trialkylsilanes to find practical chemical routes in the synthesis of both carbocycles and heterocycles. For example, Ojima and co-workers developed the rhodium-catalyzed silylcarbocyclizations of 1,6-enynes, endiyne,[3b] and triynes[4c] to afford structurally unique cyclic compounds. This approach involving the use of rhodium catalyst with trialkylsilane was expanded to silylcarbocyclization[6] of 5-hexyn-1-al to produce (*Z*)-exo-triethylsilyl-methylene-1-cyclopentanol as a major product in part of the rhodium-catalyzed silylformylation.[7,8] To the best of our knowledge, rhodium-

† Dedicated to the memory of Professor Suk-Ku Kang who died suddenly on September 27, 2002.

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(4) (a) Ojima, I.; Zhu, J. Vidal, E. S.; Kass, D. F. *J. Am. Chem. Soc.* **1998**, *120*, 6690−6697. (b) Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 7325−7328. (c) Ojima, I.; Vu, A. T.; McCullagh, J. V.; Kinoshita, A. *J. Am. Chem. Soc.* **1999**, *121*, 3230−3231. Ni(0): (d) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478−6480. Pt: (e) Madine, J. W.; Wang, X.; Widenhoefer, R. A. *Org. Lett.* **2001**, *3*, 385−388.

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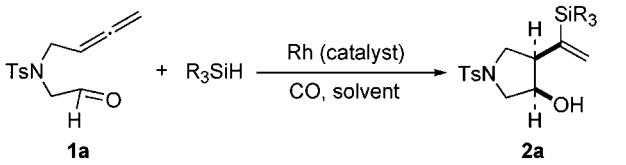
catalyzed silylative carbocyclization of allene derivatives, as well as hydrosilylation of even simple allenes, has not been described. In our continuous efforts to utilize allenyl functionalities,[9] we became quite interested in the development of a novel cyclization of allenyl-carbonyl compound **1** with trialkylsilanes in forming **2** through a rhodium-catalyzed silylcarbocyclization. We recently have disclosed the utility of tethered allenyl-aldehydes and allenyl-ketones as substrates for the transition metal-catalyzed stereoselective carbocyclization to form carbo and heterocycles.[10] The efficiency of these protocols in terms of catalytic ability and structural features has encouraged us to apply the extension of this method to more versatile systems that would expand the scope and utility of transition metal-catalyzed cyclizations. Described herein is an extension of our strategy aimed at finding new catalysts and realizing practical ways to advance new levels of transition metal catalysis.

With this issue in mind, we set out to establish the scope of the reaction for the synthesis of intramolecular allylated product **2** from **1** as outlined in Scheme 1. To find optimum

Scheme 1. Preliminary Investigations



conditions, a series of experiments was performed with allenyl-aldehyde **1a** as a model substrate. Preliminary investigations for the transformation of **1a** with trialkylsilane indicated that the conversion to the corresponding **2a** could not be satisfied under various conditions with rhodium complexes such as $RhCl(CO)(PPh_3)_2$, $[RhCl(CO)_2]_2$, and $Rh_4(CO)_{12}$ mainly due to a lack of reactivity. Fortunately, we found that $Rh(acac)(CO)_2$ was able to promote the catalytic process; this rhodium complex was generally superior and was chosen for systematic studies. After numerous conditions were surveyed, several key findings emerged. (i) The use of 1 mol % $Rh(acac)(CO)_2$ turned out to be optimal in terms of chemical yields and reaction rates. (ii) We observed that the introduction of Et_3SiH proved to be effective in comparison with other inactive silanes such as Ph_3SiH, Me_2PhSiH, and $(EtO)_3SiH$ (no reaction occurred). (iii) Use of 2 equiv of Et_3SiH is needed for optimum conditions, whereas the reaction with 1.2 equiv of Et_3SiH resulted in seriously diminished chemical yield (46%). (iv) *It is critical to run the reaction under an atmosphere of CO, presumably due to the facile regeneration of catalyst.* Under 1 atm of CO, the reaction did not proceed. Reactions performed at 10 atm of CO pressure proved to be better than those at 5 or 20 atm. (v) Reaction performed at 70 °C in Et_2O resulted in optimal chemical yields in comparison with other solvents such as toluene, THF, CH_3CN, CH_2Cl_2, and THF. (vi) Only cis-isomer **2a** was formed as determined by the analysis of 500 MHz ^1H NMR spectra of crude products.

Under optimal conditions, the silylative carbocyclization of **1a** was carried out as follows. A stainless steel autoclave was charged with **1a** (1 equiv), triethylsilane (2 equiv), and $Rh(acac)(CO)_2$ (1 mol %) in anhydrous diethyl ether. The system was flushed three times with CO (10 atm); the autoclave was pressurized to 10 atm, and the mixture was stirred at 70 °C for 8 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo to give crude products, which were subjected to silica gel column chromatography (EtOAc/hexanes 1:2, $R_f = 0.51$) to afford the cyclized product **2a** in 74% yield. The cis stereochemistry was deduced by NOESY experiments. With the notion that this approach might lead to a general and efficient method for diastereoselective synthesis of **2**, we set out to determine the scope of reaction with various substrates **1** to produce carbo- and heterocycles as summarized in Table 1.

Indeed, the method is successful with allenyl-aldehydes **1a** and **1b**, affording five-membered products **2a** and **2d** in diastereomerically pure form as shown in Table 1. This silylative carbocyclization can be extended to the synthesis of six-membered cyclohexanol derivatives, even if the transition metal-catalyzed silylative carbocyclization is often restricted to the formation of five-membered rings.[6,11] The ether-linked allenyl-aldehyde **1c** and the ϵ-allenyl-aldehyde **1d** were treated with Et_3SiH to afford *cis*-cyclohexanols **2c** and **2d** in 68 and 61% yields, respectively (entries 3 and 4). The stereochemistry of **2d** was unambiguously confirmed by NOE experiments together with the NOESY spectrum. This cyclization was also applied to allenyl-ketones. The allenyl methyl ketone **1e** was treated with Et_3SiH to afford the methyl-substituted *cis*-cyclopentanol **2e** containing quaternary homoallylic centers in 59% yield (entry 5). To the best of our knowledge, this is the first example of rhodium-catalyzed hydrosilylative carbocyclization of ketones. The cis stereochemistry of **2e** was unambiguously determined by NOE interaction between the methyl protons and the proton at the ring junction (2.80% enhancement). It is notable that the higher branched ethyl ketone **1f**, bigger than methyl

(5) Pd: (a) Takacs, J. M.; Chandramouli, S. *Organometallics* **1990**, *9*, 2877−2880. (b) Takacs, J. M.; Zhu, J.; Chandramouli, S. *J. Am. Chem. Soc.* **1992**, *114*, 773−774.

(6) Ojima, I.; Tzamarioudaki, M.; Tsai, C.-Y. *J. Am. Chem. Soc.* **1994**, *116*, 3643−3644. Ojima et al. reported the formation of the (*E*)-isomer and the simple silylformylated product and that no cyclization to form six- or seven-membered rings occurred.

(7) Ojima and co-workers explored silylformylation of alkynes: (a) Ojima, I.; Vidal, E.; Tzamarioudaki, M.; Matsuda, I. *J. Am Chem. Soc.* **1995**, *117*, 6797−6798. (b) Ojima, I.; Ingallina, P.; Donovan, R. J.; Clos, N. *Organometallics* **1991**, *10*, 38−41. (c) Ojima, I.; Kass, D. F.; Zhu, J. *Organometallics* **1996**, *15*, 5191−5195. (d) Ojima, I.; Zhu, J.; Vidal, E. S.; Kass, D. F. *J. Am. Chem. Soc.* **1998**, *120*, 6690−6697.

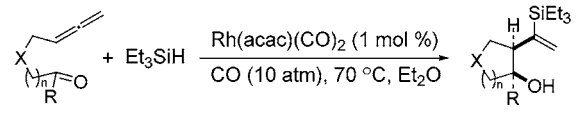
(8) For an account, see: Chatani, N.; Murai, S. *Synlett* **1996**, 414−424.

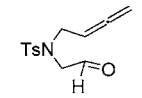
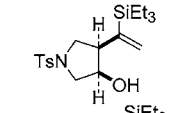
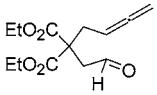
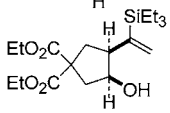
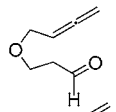
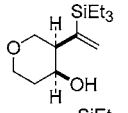
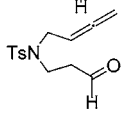
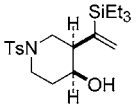
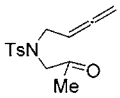
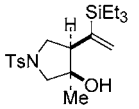
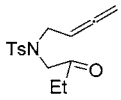
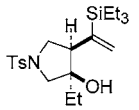
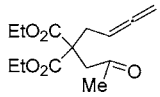
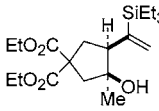
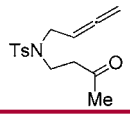
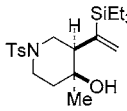
(9) (a) Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2392−2395. (b) Kang, S.-K.; Kim, Y.-M.; Ha, Y.-H.; Yu, C.-M.; Yang, H.; Lim, Y. *Tetrahedron Lett.* **2002**, *43*, 9105−9108.

(10) (a) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343−345. (b) Ha, Y..-H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143−1146. (c) Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1584−1586.

(11) Pd-catalyzed cyclization/hydrosilylation of 1,7-dienes to form six-membered carbocycles has been observed (see ref 2b), and Ni(0)-catalyzed cyclization/hydrosilylation of 1,7-diynes to form 1,2-dialkylidene cyclohexanes has also been observed (see ref 4d).

Table 1. Silylcarbocyclization of Allenyl-aldehydes and -Ketones

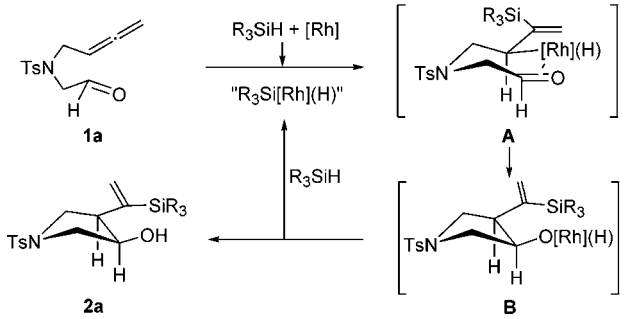


Entry	Substrate		Product		yield (%)
1		**1a**		**2a**	74
2		**1b**		**2b**	68
3		**1c**		**2c**	68
4		**1d**		**2d**	61
5		**1e**		**2e**	64
6		**1f**		**2f**	56
7		**1g**		**2g**	56
8		**1h**		**2h**	54

ketone, tolerated and reacted with Et_3SiH to give **2f** (entry 6). The ϵ-allenyl methyl ketone **1h** is readily cyclized with Et_3SiH to form **2h** (entry 8). The structure of **2h** was also deduced by NOESY experiment. It is worthy of note that the reaction produced none or only trace amounts of minor products according to the analysis of 500 MHz ^1H NMR spectra of crude products.

Although the exact mechanistic aspects of this transformation, including oxidation states and geometrical features for the active rhodium species, have not been rigorously elucidated, the following pathway could be a probable regio- and stereochemical route on the basis of product formation, as illustrated in Scheme 2. Addition of active $Et_3Si[Rh](H)$ generated from [Rh] with Et_3SiH to the internal double bond of the allene moiety results in the formation of thermodynamically favorable allylic rhodium **A**. Subsequent cyclization of **A** to **B** followed by reductive elimination of the intermediate **B** could afford the cyclopentanol **2a** with the regeneration of Rh complex. Thus, we believe that the origin of regiochemical and cis geometry outcomes for this transformation might be a subtle geometrical preference for

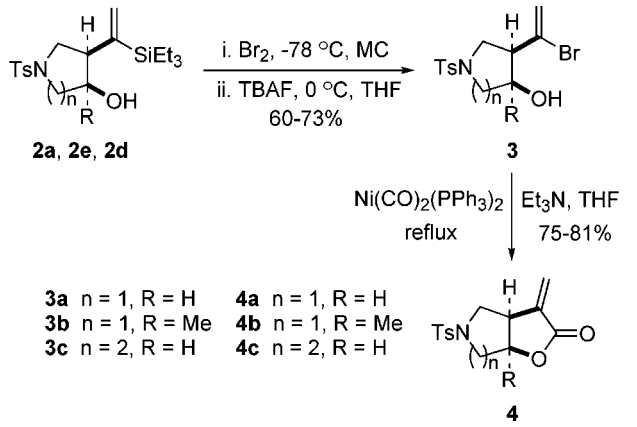
Scheme 2



orientation in the transition states offered by catalytic system with substrate.

Products **2** are readily amenable for further conversion to useful synthetic intermediates by the functional group transformations of vinylsilane.[12] For this purpose, we decided to undertake synthesis of bicyclic *cis*-α-methylene-γ-butyrolactones **4**, which was accomplished in our laboratory,[10c] not only to show synthetic applicability but also to prove stereochemical relationships as demonstrated in Scheme 3.

Scheme 3



Bromovinylic alcohol **3** was obtained by the treatment of **2** with bromine followed by Bu_4NF to cleave silyl ether in 60−73% yield.[13] Synthesis of the α-methylene-γ-butyrolactones **4** was accomplished by carbonylative cyclization of **3** with $Ni(CO)_2(PPh_3)_2$ in the presence of Et_3N under reflux conditions for 40 min in THF in 75−81% yields.[14] Thus, the stereochemical outcome for **2** from **1** was also ascertained by this study.

In summary, the rhodium-catalyzed intramolecular silylative carbocyclization of allenyl-aldehydes and -ketones with Et_3SiH to form *cis*-homoallylic cycloalkanols has been

(12) For discussions, see: Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192.
(13) Bjorkling, F.; Norin, T.; Unelius, C. R.; Miller, R. B. *J. Org. Chem.* **1987**, *52*, 292−294.
(14) Semmelhack, M. F.; Brickner, S. J. *J. Org. Chem.* **1981**, *46*, 6, 1723−1725.

accomplished in a general and efficient way that promises to be widely useful. Further studies, including synthetic applications and extension of this method into enantiomeric pathways, are in progress.

Acknowledgment. Generous financial support by grants from the Ministry of Science and Technology through the National Research Laboratory (NRL) program and the Center for Molecular Design and Synthesis (CMDS: KOSEF SRC) at KAIST is gratefully acknowledged.

Supporting Information Available: Spectroscopic and analytical data for **2a**−**h**, **3a**−**c**, and **4a**−**c** and NOESY and NOE experiments for **2a**, **2d**, **2e**, and **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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