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Intramolecular Hydroalkoxylation of Unactivated Alkenes Using Silane–Iodine Catalytic System

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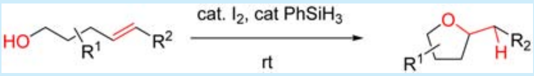
Supporting Information

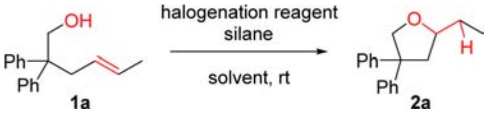
ABSTRACT: A novel catalytic system using I_2 and $PhSiH_3$ for the intramolecular hydroalkoxylation of unactivated alkenes is described. NMR study indicated that in situ generated $PhSiH_2I$ is a possible active catalytic species. This catalytic system allows an efficient intramolecular hydroalkoxylation of phenyl-, trialkyl-, and 1,1-dialkyl-substituted alkenes as well as a variety of unactivated monoalkyl- and 1,2-dialkyl-substituted alkenes at room temperature. Mechanistic consideration based on significant experimental observations is also discussed.



The intramolecular hydroalkoxylation of unactivated alkenes is an attractive strategy for constructing oxygen-containing heterocycles, because it enables the construction of cyclic ethers from the corresponding acyclic hydroxy alkenes with 100% atom efficiency.[1] Cyclic ethers are important structural motifs of biologically active natural products such as marine natural products,[2] acetogenins,[3] and sphingosines.[4] Despite the potential utilities, the intramolecular hydroalkoxylation of monoalkyl- and 1,2-dialkyl-substituted alkenes is a formidable challenge owing to the difficulty of the electrophilic activation compared with phenyl-, trialkyl-, and 1,1-dialkyl-substituted alkenes. In 2004, Widenhoefer and co-workers developed the first catalytic intramolecular hydroalkoxylation of the unactivated alkenes using the platinum(II) complexes.[5] In the same year, Coulombel and Duñach also reported the TfOH-catalyzed intramolecular hydroalkoxylation.[6] After these two seminal reports, several catalytic intramolecular hydroalkoxylation methods have been developed.[7] However, even expensive transition-metal-catalyzed methods mostly require heat and a long reaction time, and most of the reported monoalkyl- and 1,2-dialkyl-substituted alkenes have a quarternary carbon to assist the cyclization by the *gem*-dialkyl effect.[8] The reports on the substrates not having a quarternary carbon are quite limited. In this context, we turned to develop a new catalytic system for an intramolecular hydroalkoxylation. Herein, we report on a unique silicon-based system for the intramolecular hydroalkoxylation of alkenes.[9] This novel catalytic system efficiently causes the desired reaction of monoalkyl- and 1,2-dialkyl-substituted alkenes without an elevated temperature.

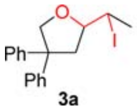
We initially paid attention to the high affinity of iodine to alkenes[10] and attempted to develop an iodine-based catalytic system in the presence of a hydrogen source (Table 1). During the investigation using silanes as a hydrogen source, we found that the desired intramolecular hydroalkoxylation reaction of the γ-hydroxy alkene **1a** was caused by 10 mol % I_2 and 150 mol % $PhSiH_3$ in toluene at room temperature, although a long reaction time was required (entry 1). Note that while most of the reported intramolecular hydroalkoxylations of 1,2-disubstituted alkenes afford the products as a mixture of five- and six-membered cyclic ethers, five-membered cyclic ether **2a** was afforded with high selectivity (>100:1) (see Table S1 in the Supporting Information).[5–7] As a result of solvent screening (Table S2), it was found that the reaction proceeded with significantly higher efficiency in CH_2Cl_2 than in toluene and was completed within 1 h (entry 2). To our delight, a catalytic amount of $PhSiH_3$ sufficiently promoted the desired reaction (entries 3 and 4). These results indicated that a new

Table 1. Optimization of Intramolecular Hydroalkoxylation

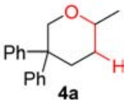


entry	halogenation reagent (mol %)	silane (mol %)	solvent	time (h)	yield (%)[a]
1	I_2 (10)	$PhSiH_3$ (150)	toluene	30	89
2	I_2 (10)	$PhSiH_3$ (150)	CH_2Cl_2	1	87
3	**I_2 (10)**	**$PhSiH_3$ (10)**	**CH_2Cl_2**	**1**	**95**
4	**I_2 (10)**	**$PhSiH_3$ (20)**	**CH_2Cl_2**	**1**	**95**
5	NIS (10)	$PhSiH_3$ (10)	CH_2Cl_2	1.5	91
6	NBS (10)	$PhSiH_3$ (10)	CH_2Cl_2	24	77[b]
7	NCS (10)	$PhSiH_3$ (10)	CH_2Cl_2	24	0
8	I_2 (10)	Ph_2SiH_2 (20)	CH_2Cl_2	2	84
9	I_2 (10)	Ph_3SiH (20)	CH_2Cl_2	24	71[c]
10	—	TMSI (10)	CH_2Cl_2	1	95

[a] Isolated yield. [b] 16% recovered starting material **1a**. [c] 14% iodoether **3a** and 5% tetrahydropyran **4a** were obtained.



3a



4a

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catalytically active species in situ generated from I_2 and $PhSiH_3$ promoted the desired reaction. 10 mol % of NIS and 10 mol % of $PhSiH_3$ also caused the desired reaction with similar efficiency (entry 5), which indicates the generation of active species identical to that from I_2 and $PhSiH_3$. The use of NBS instead of NIS prolonged the reaction time, and the use of NCS resulted in no reaction (entries 6 and 7). In the subsequent evaluation of the substituents on the silanes, several silanes efficiently catalyzed the reaction in the presence of I_2 similarly to $PhSiH_3$ (Table S3). Triaryl- and trialkyl-substituted silanes also promoted the desired hydroalkoxylation reaction, although the bulkier silanes showed lower reaction rates (entries 8–10). When Ph_3SiH was used, a small amount of the tetrahydropyran **4a** was produced along with the tetrahydrofuran **2a** and the iodoether **3a** (entry 9).

To identify the active species, ^1H NMR of the 1:2 mixture of I_2 and $PhSiH_3$ in CD_2Cl_2 was recorded (Figure 1a). The new peaks were assigned to $PhSiH_2I$ (δ_H = 4.76 ppm), $ISiH_3$ (δ_H = 3.55 ppm), and benzene (δ_H = 7.38 ppm), which are consistent with Keinan's report.[11] $PhSiH_2I$ was also observed from the NMR analysis of the mixture of NIS and $PhSiH_3$, while $ISiH_3$ and benzene were not detected (Figure 1b). These observations indicate that $PhSiH_2I$ is the possible active species of this reaction. Although the preparation of $PhSiH_2I$ is known, there are no reports on its reactivity to the best of our knowledge.[11,12] The optimization studies in Table 1 indicate that the silyl iodide (Si–I) moiety of $PhSiH_2I$ is important for its catalytic activity (entries 5–7), although the Si–H moiety is not necessary (entries 9 and 10). Because the reaction of 1 equiv each of I_2 and $PhSiH_3$ generates 1 equiv of HI together with $PhSiH_2I$, and an additional 1 equiv of $PhSiH_3$ reacts with HI to provide $ISiH_3$ and PhH, 10 mol % of I_2 and 20 mol % of $PhSiH_3$ in CH_2Cl_2 (entry 4) were selected as the optimal conditions, which includes 10 mol % of $PhSiH_3$ to quench in situ generated HI from the reaction of I_2 and $PhSiH_3$.[11]

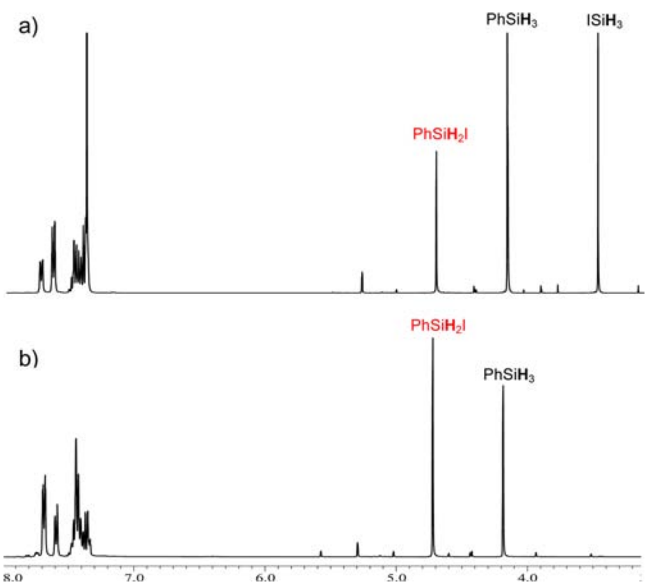
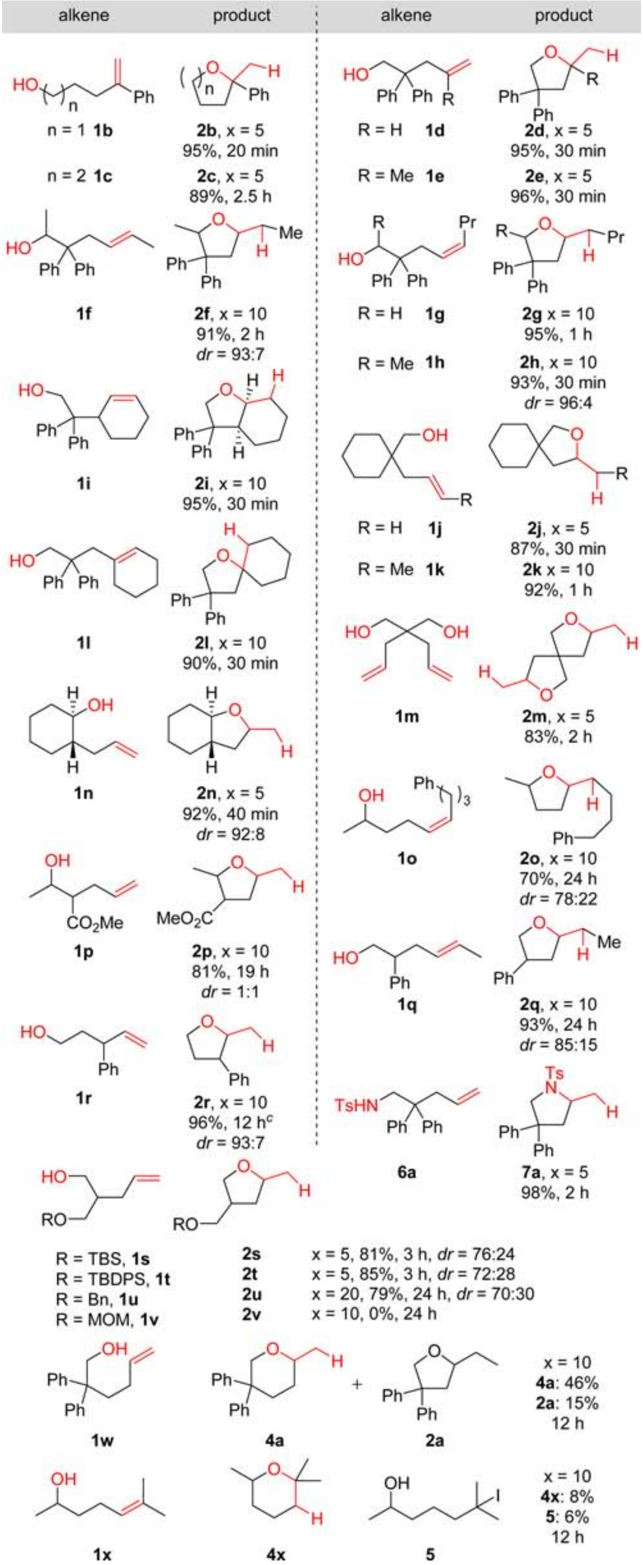


Figure 1. ^1H NMR spectra of the 1:2 mixture of I_2 and $PhSiH_3$ (a) and the 1:1 mixture of NIS and $PhSiH_3$ (b).

Table 2. Substrate Scope[a,b]

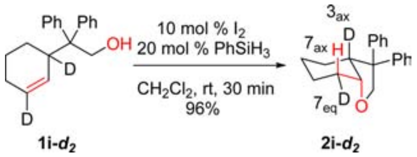


[a] Reaction condition: x mol % I_2, 2x mol % $PhSiH_3$, CH_2Cl_2, rt. [b] Yields are those of isolated products. [c] The reaction mixture was treated with 1.0 equiv of TBAF after 12 h and stirred for additional 30 min at rt.

Under the optimal reaction conditions, the substrate scope was investigated (Table 2).[13] The intramolecular hydroalkoxylations of the phenyl-substituted alkenes **1b** and **1c** were smoothly completed to give the corresponding cyclic ethers **2b** and **2c** in high yields. The mono-, 1,1-di-, 1,2-*cis*-di-, 1,2-*trans*-di-, and trisubstituted alkenes **1d–u** afforded the corresponding products **2d–u** in high yields. As with the case of **1a**, the 1,2-disubstituted alkenes **1f–h**, **1k**, **1o**, and **1q** provided the corresponding five-membered cyclic ethers **2f–h**, **2k**, **2o**, and **2q** with almost complete selectivity (>100:1). The secondary alcohols **1f**, **1h**, and **1n–p** also smoothly underwent the hydroalkoxylation. The dihydroxydiene **1m** was converted to the spirocyclic ether **2m** via double hydroalkoxylation. In the case of **1r**, although a small amount of 5-iodo-3-phenylpentan-2-ol was produced as a byproduct, the treatment with TBAF after the disappearance of **1r** promoted the recyclization of 5-iodo-3-phenylpentan-2-ol to give **2r** in high yield. Notably, the formations of the tetrahydrofuran **2o–r**, which were not enhanced by the *gem*-dialkyl effect, efficiently occurred at room temperature.[8] $PhSiH_2I$-catalyzed hydroalkoxylations of the silyl and benzyl ethers **1s–u** provided the desired products **2s–u** in high yields along with less than 10% yield of the desilylation and the debenzylation products, which exhibit good compatibilities with acid-labile protecting groups, although the MOM ether **1v** did not afford **2v**. The reaction of the δ-hydroxy alkene **1w** provided the tetrahydropyran **4a** in 46% yield, together with the 15% tetrahydrofuran **2a**. The reaction of 6-methylhept-5-en-2-ol (**1x**) gave small amounts of the desired product **4x** and the HI adduct **5**. The formations of six-membered rings are relatively slow compared with those of five-membered rings and cause the side reactions such as isomerization and HI addition. Intramolecular hydroamination of **6a** also efficiently proceeded to give **7a** in high yield.

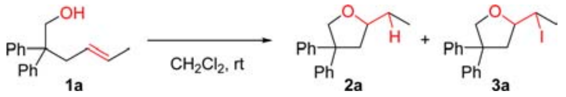
To evaluate the stereoselectivity of O–H addition toward alkenes, the deuterium-labeled γ-hydroxy alkene **1i-*d*$_2$** was subjected to the $PhSiH_2I$-catalyzed intramolecular hydroalkoxylation (Scheme 1).[14] The ^1H NMR spectroscopic analysis revealed that the obtained product is the 3_{ax} and 7_{eq} deuterated **2i-*d*$_2$**, which indicates that the O–H addition to alkenes selectively proceeds in an *anti*-fashion similar to the TfOH-catalyzed hydroalkoxylation[14] instead of the *syn*-fashion proposed for the $Al(OTf)_3$-catalyzed hydroalkoxylation.[15]

Scheme 1. Intramolecular Hydroalkoxylation of Deuterium Labelled γ-Hydroxy Alkene 1i-*d*$_2$



To investigate the reaction mechanism, several control experiments were carried out (Table 3). To evaluate the possibility of an in situ generated Brønsted acid, **1a** was treated with 10 mol % of hydroiodic acid (57% HI).[16] The reaction was stopped at a moderate conversion along with the production of the iodoether **3a** (entry 1). The iodoether **3a** was presumably formed via the iodoetherification of **1a**, which indicates the generation of iodine by aerobic oxidation of an iodide ion. Note that iodoethers were not observed under $PhSiH_2I$-catalyzed conditions. To suppress the oxidation, **1a** was treated with hydroiodic acid under degassed and dark conditions, and **2a** was produced in good yield, although an obviously longer reaction time was required than that for the $PhSiH_2I$-catalyzed method (entry 2). Although **1a** was treated with anhydrous HI prepared by Koreeda's procedure to exclude the effect of H_2O, the result was similar to the reaction with hydroiodic acid (entry 3).[17] We also examined the catalytic activities of TfOH and TMSOTf to estimate the effect of the silyl group. As the result, **2a** was obtained in only 5% yield under TfOH-catalyzed conditions after 24 h, together with 95% of the starting material **1a** whereas cyclic ethers were obtained in 50% yield (43% **2a** + 7% **4a**) under TMSOTf-catalyzed conditions.[16,18] These results support the notion that the silyl group of $PhSiH_2I$ not only suppresses the aerobic oxidation of iodide ion but also contributes to the acceleration of the reaction.[19] Very recently, Sarpong and co-workers have reported a TMSI/H_2O method for hydroamination.[9] In striking contrast to the $PhSiH_2I$-catalyzed reaction, they concluded that anhydrous HI is an active species in their catalytic system, and they did not observe any acceleration by the silyl group. To rule out the effect of adventitious water, we examined the hydroalkoxylation of **1a** on gram scale under strictly anhydrous conditions [in glovebox, dry CH_2Cl_2 (water <10 ppm)]. The reaction completed within 1 h to provide **2a** in high yield.

Table 3. Mechanistic Experiments

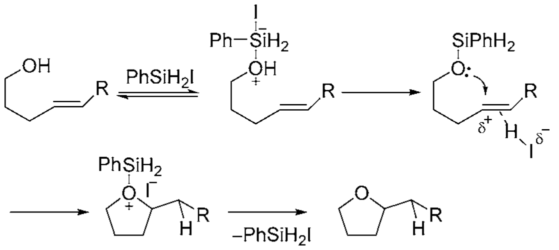


entry	conditions	time	yield (%) 2a	3a	1a
	10 mol % I_2, 20 mol % $PhSiH_3$[a]	**1 h**	95[b]	0	0
1[c]	10 mol % 57% HI	24 h	31	10	57
2[c]	10 mol % 57% HI, degass, dark	24 h	91	<1	<1
3[c]	10 mol % I_2, 20 mol % AcSH, degass, dark	24 h	75[d]	10	5
4[c]	10 mol %TfOH	24 h	5	0	95
5[c]	10 mol %TMSOTf	24 h	43[e]	0	24

[a] Standard conditions. [b] Isolated yield. [c] Determined by NMR using *n*-octyl ether as an internal standard. [d] 3% tetrahydropyran **4a** was obtained. [e] 7% tetrahydropyran **4a** was obtained.

On the basis of the above experimental observations, we propose a plausible mechanism in Scheme 2. In situ generated $PhSiH_2I$ from I_2 and $PhSiH_3$ reacts with the hydroxy group of a γ-hydroxy alkene to generate HI and the γ-silyloxy alkene. The electrophilic activation of the double bond of the γ-silyloxy alkene by HI causes the intramolecular hydroalkoxylation to provide a cyclic ether. Although γ-hydroxy alkenes can be activated by HI to afford the corresponding cyclic ethers, the hydroalkoxylation of γ-silyloxy alkenes is presumably predominant, which is suggested by the fact that a $PhSiH_2I$-catalyzed hydroalkoxylation is substantially superior to a HI-catalyzed hydroalkoxylation.

Scheme 2. Proposed Reaction Pathway



In conclusion, we have developed a novel catalytic system using I_2 and $PhSiH_3$ for intramolecular hydroalkoxylation. $PhSiH_2I$ was observed as the possible active catalytic species by NMR spectroscopic analysis. Phenyl-, trialkyl-, and 1,1-dialkyl-substituted alkenes as well as a variety of monoalkyl- and 1,2-dialkyl-substituted alkenes smoothly afforded the corresponding cyclic ethers without a need for elevated temperature. Mechanistic experiments indicate that a cooperative effect of electrophilic activation of the double bonds by HI and the acceleration by the silyl groups enables the efficient hydroalkoxylation. We expect that the present work will expand the potential of hydrofunctionalization of C−C unsaturated bonds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01797.

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Notes

The authors declare no competing financial interest.

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(9) While this manuscript was in the final stage of preparation, Sarpong and co-workers reported the efficient hydroamination of alkenes using catalytic amounts of TMSI and H_2O, with limited examples of hydroalkoxylation of olefins. They concluded that anhydrous HI is an active species of the hydroamination under their conditions and also reported the similar hydroamination under silicon-free conditions (NaI and TfOH). On the other hand, we observed that the combination of TfOH and NaI required a long reaction time similar to the case of hydroiodic acid (57% HI); see: Leger, P. R.; Murphy, R. A.; Pushkarskaya, E.; Sarpong, R. *Chem. - Eur. J.* **2015**, *21*, 4377−4383.

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(13) We observed that the use of rubber septa quenched the reaction. The reaction was carried out in a glass flask with a plastic cap. The details are provided in the Supporting Information.

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(18) The treatment of **1a** with 1 mol % TfOH resulted in the almost quantitative recovery of **1a**, together with a trace amount of **2a**.

(19) We also investigated the reaction rates for the cyclization of 4-penten-1-ol and the corresponding TMS ether by treatment with 1 equiv of TfOH. It was observed that the cyclization of the TMS ether proceeded substantially faster than that of 4-penten-1-ol. The details are provided in the Supporting Information.