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LETTER

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# Catalytic Formation of Silyl Enol Ethers and Its Applications for Aldol-Type Condensation and Aminomethylation Reactions

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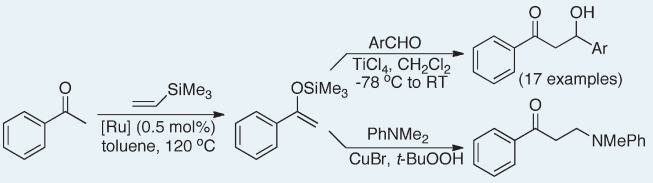
Supporting Information

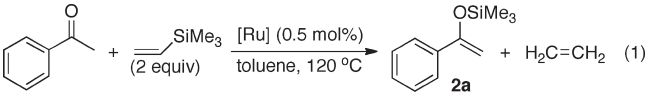
**ABSTRACT:** A new catalytic method for the synthesis of silyl enol ethers has been developed from the coupling reaction of ketones with $CH_2$=$CHSiMe_3$ by using a ruthenium hydride catalyst $(PCy_3)_2(CO)RuHCl$. The synthetic utility of silyl enol ethers was demonstrated for both Mukaiyama aldol condensation and aminomethylation reactions in forming $\beta$-hydroxyketones and $\beta$-aminoketones, respectively.




**KEYWORDS:** silyl enol ether, vinylsilane, aldol condensation, ruthenium catalyst

Silyl enol ethers are synthetically versatile substrates for a wide range of C−C and C−X bond-forming reactions, such as aldol-type condensation and Micheal-type addition,[1−3] as well as for α-C−H insertion reactions.[4,5] Because silyl enol ethers are traditionally synthesized from trapping metal enolates with $R_3SiCl$, such synthetic methods are inherently incompatible with base-sensitive functional groups and are often problematic in controlling regio- and stereoselective formation of the enol ethers.[6,7] Considerable efforts have been devoted to develop catalytic formation of enol ethers to overcome shortcomings such as requiring a strong base and generation of copious amount of byproducts associated with the stoichiometric methods.[8−14] Selected recent examples of the transition metal-catalyzed silyl enol ether formation methods include Rh-catalyzed aldehyde-to-diazosilane coupling reaction,[15,16] carbonylative silylation of alkenes by Ir catalysts,[17,18] and Cu-catalyzed silyl migration of acylsilanes.[19,20] *N*-Heterocyclic carbenes have been found to be particularly effective in mediating silyl transfer reactions.[21] Direct dehydrogenative silylation reactions of ketones and enones have also been achieved by using Rh or Pt[22−26] and Cu catalysts,[27−30] respectively. Since these catalytic methods require either reactive reagents or multiple steps leading to the products, generally applicable catalytic methods that can produce silyl enol ethers directly from readily available ketones would be highly desirable from a synthetic point of view.

We previously reported that the well-defined ruthenium hydride complex $(PCy_3)_2(CO)RuHCl$ (**1**) is an effective catalyst precursor for the oxidative silylation reactions of alkenes and alkynes.[31,32] In an effort to extend the synthetic utility of silylation reactions, we have begun to explore the activity of **1** toward silane-to-carbonyl coupling reactions. Here, we report a catalytic formation of silyl enol ethers from the intermolecular coupling reaction of ketones and vinylsilanes and its synthetic utility for Mukaiyama aldol condensation and α-functionalization reactions.




(1)

Initially, the activity of selected ruthenium catalysts was screened for the ketone silylation reaction. Thus, the treatment of acetophenone (1.0 mmol) with $CH_2$=$CHSiMe_3$ (2.0 mmol) in the presence of a ruthenium catalyst (0.5−1.0 mol %) in toluene (2 mL) at 120 °C was analyzed by GC/MS after 12 h of the reaction time (eq 1). Among selected ruthenium catalysts, complex **1** was found to exhibit uniquely high activity for the silylation reaction, giving >95% of **2a** with less than 1 mol % of the catalyst loading (Table 1). None of other screened ruthenium catalysts showed any significant activity except $(PPh_3)_3(CO)RuH_2/H^+$, which gave a modest activity of ∼20% yield under similar reaction conditions (entry 4).

The scope of the silylation reaction was explored by using the ruthenium hydride catalyst **1**. Since many of the silyl enol ether products were found to be thermally unstable and could not be isolated by column chromatography, the isolated yield of the silyl enol ether products was inferred from the subsequent Mukaiyama aldol condensation reaction (Table 2).[33−35] Both alkyl- and aryl-substituted ketones were found to react smoothly with $CH_2$=$CHSiMe_3$ to give high conversions (>90%) to the silyl enol ether products **2** by using a relatively low catalyst loading (0.5−1 mol %). Two equivalents of vinylsilane was found to give an optimum conversion of the silyl enol ethers **2** in most cases; employing less than 1.5 equiv of the silane led to substantially lower conversion of **2**. The crude silyl enol

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**Table 1. Catalyst Survey for the Silylation of Acetophenone.**[a]

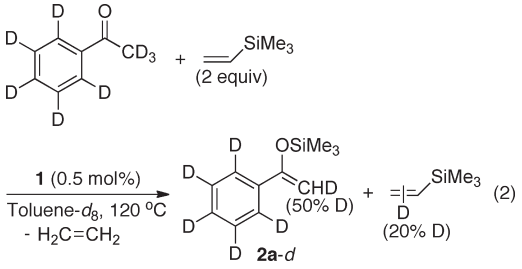
| entry | catalyst | additive | yield (%)[b] |
|---|---|---|---|
| 1 | $(PCy_3)_2(CO)RuHCl$ (**1**) | | >95 |
| 2 | $[(COD)RuCl_2]_x$ | | 0 |
| 3 | $(PPh_3)_3RuCl_2$ | | 0 |
| 4 | $(PPh_3)_3(CO)RuH_2$ | $HBF_4 \cdot OEt_2$ | 20 |
| 5 | $(PPh_3)_3RuHCl$ | | 0 |
| 6 | $RuCl_3 \cdot 3H_2O$ | | 0 |
| 7 | $Ru_3(CO)_{12}$ | $NH_4PF_6$ | 0 |
| 8[c] | $[(PCy_3)_2(CO)(S)_2RuH]^+BF_4^-$ | | <5 |
| 9 | $[(p\text{-cymene})RuCl_2]_2$ | | 0 |
| 10 | $PCy_3$ | | 0 |

[a] Reaction conditions: acetophenone (1.0 mmol), vinylsilane (2.0 mmol), catalyst (0.5−1.0 mol %), additive (1.0 equiv to Ru), toluene (2 mL), 120 °C, 12 h. [b] Determined by GC/MS. [c] S = $CH_3CN$.

ether product **2** was subsequently treated with a stoichiometric amount of $p$-$NO_2$−$C_6H_4CHO$ and $TiCl_4$, which resulted in β-hydroxyketone product **3**. Analytically pure product **3** was obtained after an aqueous workup and silica gel column chromatography. Dehydrated enone products were obtained from aliphatic ketones with benzaldehyde under similar reaction conditions (entries 12−14). A highly anti diastereoselective formation of β-hydroxyketone products **3** was resulted from the stereoselective Mukaiyama aldol condensation for cyclic ketones (entries 10, 11, 15). In a control experiment, the direct aldol condensation of acetophenone with $p$-$NO_2$−$C_6H_4CHO$ and $TiCl_4$ without first generating the silyl enol ether led to virtually no cross-coupling products under otherwise similar conditions. In all cases, synthetically useful silyl enol ethers are predictably formed from the direct coupling reaction of ketones with vinylsilane without employing any reactive agents.

The synthetic utility of silyl enol ether formation was further demonstrated by performing a number of α-functionalization reactions of ketones (Scheme 1). For example, the treatment of acetophenone (2.0 mmol) with $CH_2$=$CHSiMe_3$ (2 equiv) in the presence of the catalyst **1** (0.5 mol %) produced the enol ether product **2a**. The crude product **2a** was subsequently reacted with acetyl chloride (2.5 mmol) and $TiCl_4$ (3.0 mmol) to afford the 1,3-diketone product **4a** in 43% isolated yield.

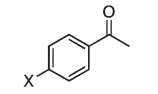
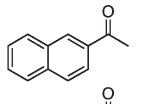
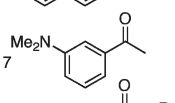
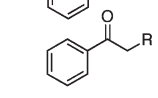
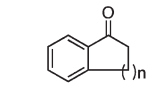
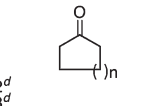
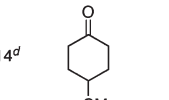
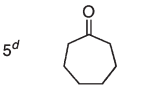
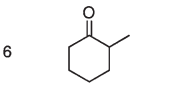
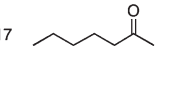
In an analogous fashion, the crude enol ether products derived from benzophenone **2a** as well as from benzocyclic ketones **2j** and **2k** were treated with Selectfluor in $CH_3CN$, which produced the α-fluoro products **5a**, **5j**, and **5k**, respectively.[36] Next, the aminomethylation reaction of the silyl enol ethers was performed by following a recently reported procedure.[37] Thus, the treatment of crude enol ether product **2a** and benzocyclic **2j** and **2k** with *N*,*N*-dimethylaniline and CuBr cleanly afforded β-aminoketone products **6a**, **6j**, and **6k** in 53−72% isolated yields. All of these α-functionalization reactions can be run conveniently in a one-pot procedure without isolating the enol ether products.



(2)

The following kinetic experiments were performed to probe mechanistic aspects of the catalytic formation of silyl enol ethers.

**Table 2. Catalytic Formation of Silyl Enol Ethers and Mukaiyama Aldol Condensation with Aldehydes.**[a]

| entry | ketone | aldol product(s) | convn (%)[b] | yield (%)[c] |
|---|---|---|---|---|
| 1 |  | **3a** (X = H)<br>**3b** (X = $CH_3$)<br>**3c** (X = OMe)<br>**3d** (X = Br)<br>**3e** (X = Cl) | 98<br>95<br>94<br>90<br>90 | 85<br>75<br>73<br>80<br>81 |
| 6 |  | **3f** | 97 | 88 |
| 7 |  | **3g** | 94 | 80 |
| 8<br>9 |  | **3h** (R = $CH_3$; syn:anti = 83:17)<br>**3i** (R = Ph; syn:anti = 70:30) | 93<br>96 | 83<br>75 |
| 10<br>11 |  | **3j** (n = 1)<br>**3k** (n = 2) | 98<br>97 | 85<br>87 |
| 12[d]<br>13[d] |  | **3l** (n = 1)<br>**3m** (n = 2) | 97<br>99 | 83<br>93 |
| 14[d] |  | **3n** | 99 | 85 |
| 15[d] |  | **3o** | 99 | 80 |
| 16 |  | **3p** (syn:anti = 75:25) | 85 | 65 |
| 17 |  | **3p** (syn:anti = 17:83) | 90 | 78 |

[a] Reaction conditions. Silylation: ketone (2.0 mmol), $CH_2$=$CHSiMe_3$ (4.0 mmol), **1** (0.5 mol %), toluene (3 mL), 120 °C, 12−15 h. Aldol condensation: (i) $p$-$NO_2$−$C_6H_4CHO$ (3.0 mmol), $TiCl_4$ (3.0 mmol), $CH_2Cl_2$ (10 mL), −78 to 20 °C, 8 h; (ii) aqueous workup. [b] The formation of silyl enol ether products was detected by both $^1H$ NMR and GC/MS in the crude reaction mixture, and their conversion was determined from GC/MS analysis. [c] Isolated yield of the aldol products based on the ketone substrate. [d] PhCHO was used for the aldol condensation.

First, the deuterium labeling experiment was performed by examining the treatment of $C_6D_5COCD_3$ (25 mg) with $CH_2$=$CHSiMe_3$ (2 equiv) and **1** (0.5 mol %) in toluene-$d_8$ (0.5 mL) at 120 °C (eq 2). The enol ether product **2a**-*d* showed ∼50% D on the vinyl positions and nearly 20% D has been incorporated to unreacted vinylsilane substrate, as determined by both $^1H$ and $^2H$ NMR (Figure S1, Supporting Information). The extensive H/D exchange on the vinyl positions of both **2a**-*d* and the vinylsilane substrate is consistent with rapid and reversible olefin insertion of $CH_2$=$CHSiMe_3$ and keto−enol tautomerization of the ketone substrate prior to the silylation.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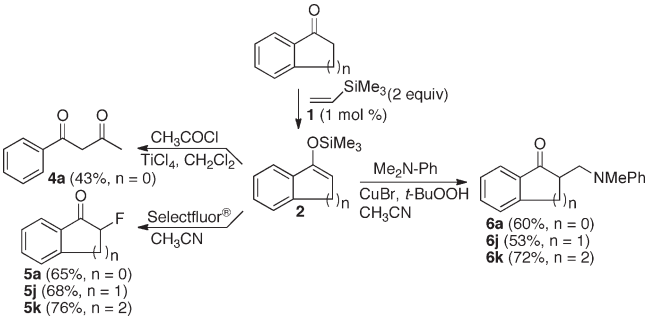
**Scheme 1**



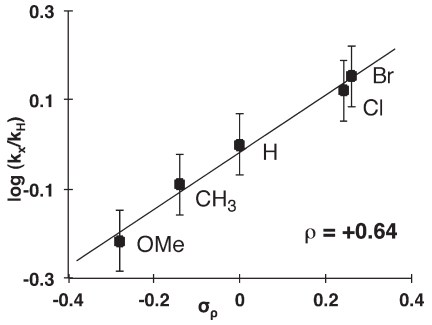




**Figure 1.** Hammett plot of the coupling reaction of para-substituted $p$-X−$C_6H_4COCH_3$ (X = OMe, $CH_3$, H, Cl, Br) with $CH_2$=$CHSiMe_3$.

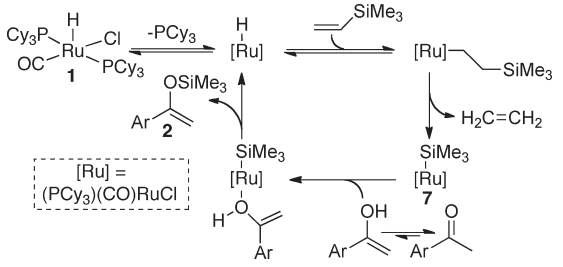
Second, the catalytic reaction was found to be strongly inhibited by a phosphine ligand. The rate of the coupling reaction of acetophenone (24 mg) with $CH_2$=$CHSiMe_3$ (40 mg, 2 equiv) and **1** (0.5 mol %) in toluene-$d_8$ (0.5 mL) was measured as a function of [$PCy_3$] (Figure S2, Supporting Information). A steady decrease in the reaction rate on added [$PCy_3$] suggests that the active Ru catalyst is generated from an initial dissociation of $PCy_3$. Similar phosphine inhibition kinetics have been commonly observed in other coupling reactions catalyzed by **1**.[38,39]

To examine the electronic influence of the ketone substrate, a Hammett plot was constructed from the correlation of relative rates with $\sigma_p$ for a series of *para*-substituted acetophenones $p$-X−$C_6H_4COCH_3$ (X = OMe, $CH_3$, H, Cl, Br) at 120 °C. The plot of $\log(k_X/k_H)$ with $\sigma_p$ resulted in a linear fit with a positive slope of $\rho = +0.64 \pm 0.1$ (Figure 1).[40] Strong promotional effect from electron-withdrawing groups suggests the O−Si bond formation rate-limiting step, in which the coordination of carbonyl oxygen to the electrophilic Ru catalyst can be envisaged as a key intermediate species.

A plausible mechanistic rationale for the silyl enol ether formation is compiled on the basis of these results (Scheme 2). We propose that the catalytically active Ru-silyl species **7** is initially formed from an alkene insertion followed by the elimination of an ethylene molecule. In support of this notion, the formation of ethylene was detected by GC in the crude reaction mixture, and a similar ethylene elimination has been known to be a driving force in other catalytic coupling reactions of vinylsilanes.[41,42]

The keto−enol tautomerization and the coordination of an enol substrate should form a Ru enolate species. Although the exact nature of the O−Si bond formation step is still unclear, one can envision a silyl migration to enol oxygen atom that is coupled

**Scheme 2**




to the oxidative addition/reductive elimination sequence of the O−H bond in yielding the silyl enol ether product **2**. A positive Hammett $\rho$ value obtained from the correlation of para-substituted arylketones suggests that the silyl migration to the oxygen atom can also be explained in terms of the formation of a metal enolate complex and its stabilization from an electron-deficient aryl group. Late transition metal enolate complexes have been commonly proposed as a key species in a number of cross-coupling reactions.[43−45] In addition, regioselective formation of sterically more demanding silyl enol ethers can also be rationalized from a thermally induced keto−enol tautomerization under equilibrium-controlled conditions.

In summary, we successfully developed an operationally simple catalytic method for silyl enol ethers from the direct coupling reaction of ketones and vinylsilane. As demonstrated from both Mukaiyama aldol condensation and aminomethylation reactions, the catalytic method should find a range of useful applications in α-functionalization reactions of ketones.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental details and characterization data of the products (36 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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## ■ ACKNOWLEDGMENT

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