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Silyl formates as hydrosilane surrogates for the transfer hydrosilylation of ketones†

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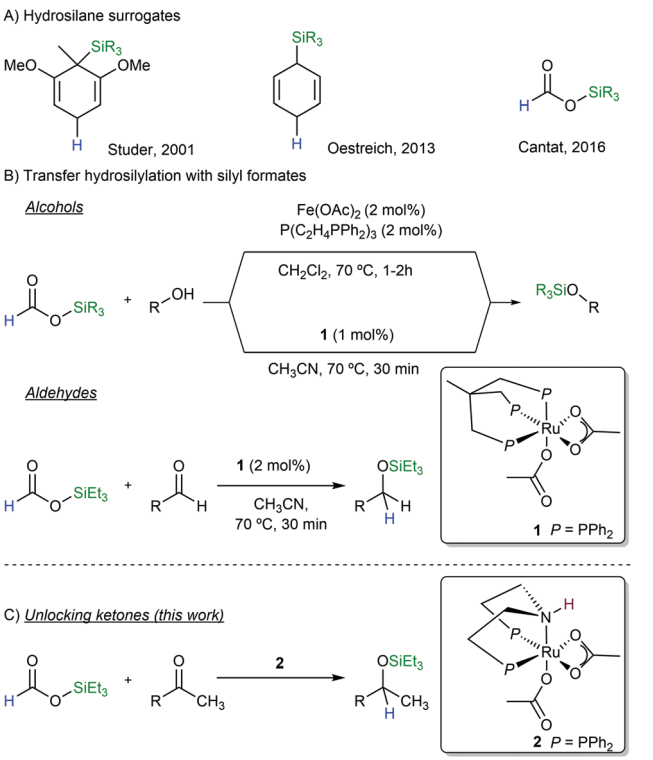
A transfer hydrosilylation of ketones employing silyl formates as hydrosilane surrogates under mild conditions is presented. A total of 24 examples of ketones have been successfully converted to their corresponding silyl ethers with 61–99% yields in the presence of a PN^{H}P-based ruthenium catalyst and silyl formate reagent. The crucial role of the ligand for the transformation is demonstrated.

Catalytic hydrosilylation is a convenient method to reduce carbonyl compounds, providing access to alcohols *via* silyl ether intermediates.[1] The latter are also an important class of protecting groups for alcohols. Their direct synthesis from the corresponding ketone is hence valuable. Transfer hydrosilylation has emerged as an alternative process for this transformation,[2] avoiding the use of difficult to handle hydrosilanes, such as the gaseous Me_3SiH. This concept was pioneered by Studer[3] and Oestreich,[4] who reported silicon-substituted cyclohexa-1,4-dienes for the transfer hydrosilylation of alkenes and carbonyl derivatives through radical and ionic processes, respectively (Scheme 1A). The formation of hydrosilylation products is accompanied by the production of quantitative arene derivatives as by-products.

We have reported an alternative using silyl formates as renewable liquid surrogates of hydrosilanes, whose only by-product is gaseous CO_2.[5] The recyclability of these reagents is ensured since they are synthesized in excellent yields from formic acid, a reagent readily available from biomass[6] or carbon dioxide.[7]

Silylformates were initially employed as hydrosilane surrogates in alcohol silylation with iron-[8] or ruthenium-based catalysts.[9] Transfer hydrosilylation of aldehydes was successfully developed using the Ru-triphos catalyst **1** (Scheme 1B).[5] During these transformations, the metal-mediated silyl formate decarboxylation generates a metal hydride species that will provide a metal–alkoxide intermediate upon reaction with the substrate. The final silylation step provides the desired product, closing the catalytic cycle. Interestingly, we could show that silyl hydride species are never formed along this process. Unfortunately, these protocols were ineffective towards the reduction of ketones. In this case, it seems that the steric hindrance around the metal–alkoxide intermediate hampers the final silylation step.[5]

In order to increase the nucleophilicity of the oxygen atom, we envisioned the possibility of weakening the ruthenium–alkoxide interaction through the action of a cooperative ligand, able to develop H-bonds. We chose the PN^{H}P–ruthenium



Scheme 1 (A) Hydrosilane surrogates. (B) Applications of silyl formates as hydrosilane surrogates. (C) Ruthenium-catalyzed transfer hydrosilylation of ketones (this work).

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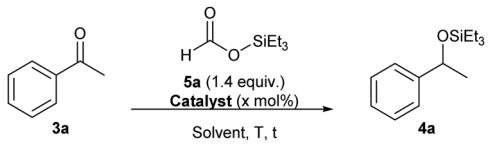
Table 1 Screening of the conditions for the transfer hydrosilylation of ketones[a]



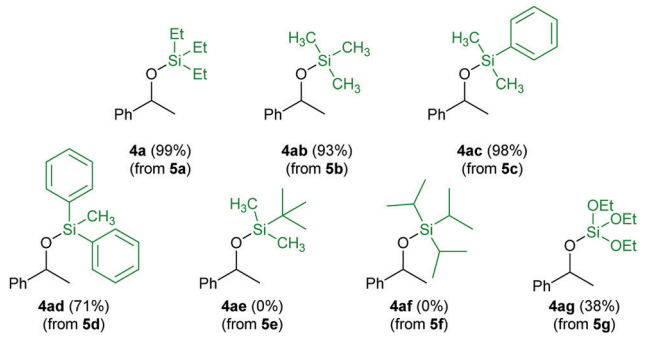
Entry	Catalyst (mol%)	Solvent	T (°C)	t (h)	Yield[b] (%)
1	**1** (3)	CD_3CN	90	24	0
2	**2** (3)	CD_3CN	90	11	78
3	**2** (3)	CD_2Cl_2	90	22	0
4	**2** (3)	d_8-THF	90	2.5	99
5	**2** (3)	d_8-Toluene	90	2.5	92
6	**2** (3)	C_6D_6	90	1.5	99
7	**2** (3)	EtOAc	90	3	97
8	**2** (3)	Anisole	90	9	77
9	**2** (1.5)	C_6D_6	90	37	79
10	**2** (3)	C_6D_6	50	36	99

[a] 0.1 mmol scale. [b] Yields are determined by ^{1}H NMR with mesitylene as an internal standard. See ESI for more details.

catalyst **2** that bears a well-known ligand for its participation in metal-catalyzed reactions through his N–H bond.[10] Major contributions on complexes bearing PN^{H}P ligands were achieved by Milstein,[11] Beller,[10b,12] Gusev,[13] and Kuriyama.[14] These species were successfully applied to the reduction of challenging substrates such as esters or amides.[10b,14,15] However, beyond hydrogenation, the use of participative PN^{H}P ligand-based catalysts in hydrosilylation is scarce,[16] and, to the best of our knowledge, it was never reported in transfer hydrosilylation reactions.

To test our hypothesis, acetophenone (**3a**) was submitted for reaction with triethylsilyl formate (**5a**) and Ru-triphos catalyst **1** in acetonitrile at 90 °C, classical conditions for the transfer hydrosilylation of aldehydes. Under these conditions, no conversion was observed (Table 1, entry 1). Changing catalyst **1** to Ru–PN^{H}P catalyst **2** provided silyl ether **4a** in 78% yield (Table 1, entry 2). While substituting CD_3CN with d_2-dichloromethane completely suppresses the reactivity (Table 1, entry 3), the use of d_8-THF, d_8-toluene or d_6-benzene increased the yields to 99%, 92% and 99%, respectively (Table 1, entries 4–6). Performing the reaction in more environment-friendly solvents such as EtOAc or anisole allowed also the obtention of the product in 97% and 77% yields, respectively (Table 1, entries 7 and 8). Among them, we finally selected d_6-benzene to rapidly evaluate the applicability of the reaction due to a lower reaction time (1.5 h). Reducing the catalyst loading from 3 mol% to 1.5 mol% results in a drop of yield to 79% (Table 1, entry 9). Decreasing the temperature to 50 °C increases the required reaction time (36 h) to obtain a comparable yield of the silylated alcohol **4a** (99%) (Table 1, entry 10).

The influence of the silicon coordination sphere on the reactivity was tested by reaction of acetophenone (**3a**) with different silylformates **5a–g** under the optimized conditions (Scheme 2). The reaction worked efficiently with triethyl-, trimethyl- or dimethylphenylsilyl formates (**5a–c**) and acetophenone (**3a**), giving compounds **4a–4ac** with yields above 93%. It is worthy to highlight that the possibility to use trimethylsilyl formate (**5b**) represents a major synthetic advantage of the use

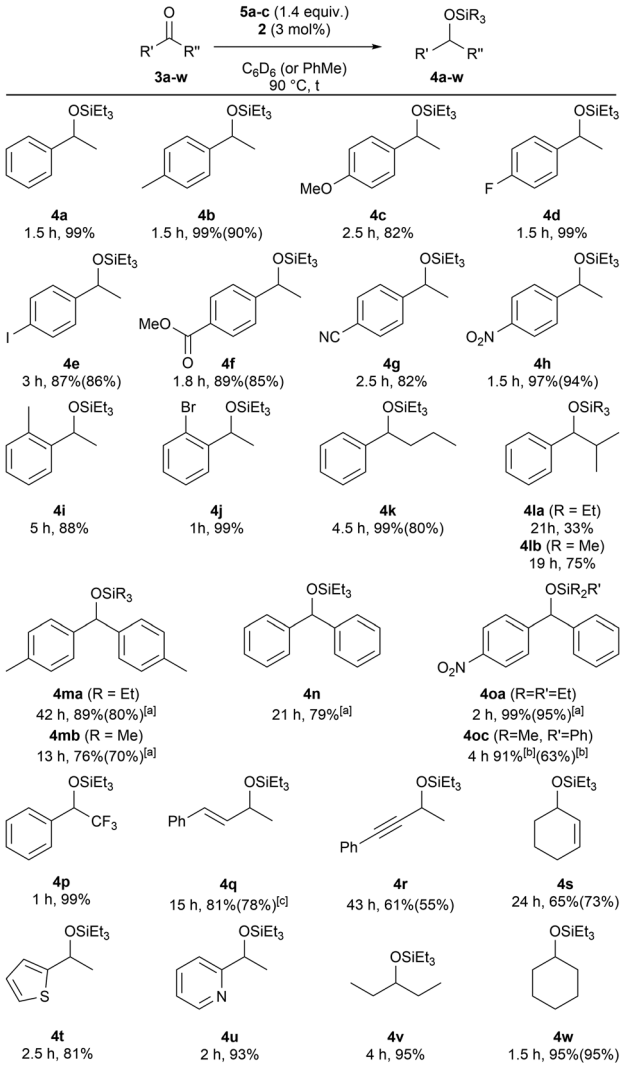


Scheme 2 Silyl formate scope for the hydrosilylation of acetophenone. 0.1 mmol scale. Yields are determined by ^{1}H NMR with mesitylene as an internal standard. See ESI† for more details.

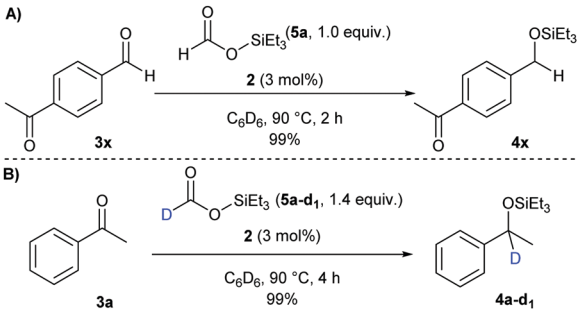
of these surrogates, because its parent hydrosilane Me_3SiH is gaseous. The increase of the bulkiness on the substituents around the silicon core implied a decrease in the yield for the transformation. While methyldiphenylsilylated alcohol **4ad** was still obtained in 71% yield, *tert*-butyldimethylsilyl and triisopropylsilyl formates (**5e** and **5f**) completely suppressed the reduction of the ketone. Finally, the use of the more acidic triethoxysilyl formate (**5g**) led to a significant drop of the yield providing the silylated alcohol **4ag** in 38% yield. This trend highlights the importance of the steric and electronic parameters of the silyl moiety on the outcome of the reaction.

A number of ketones were thereafter tested for transfer hydrosilylation with triethylsilyl or trimethylsilyl formates (**5a** and **5b**) as hydrosilane surrogates (Scheme 3). Several substituted acetophenones were successfully hydrosilylated in short reaction times. Electron-donating substituents (**4b** and **c**) or electron-withdrawing groups (**4d–h**) were well tolerated with yields above 82%. Remarkably, 4-iodoacetophenone (**3e**) reacted without any loss of the iodine core. With more challenging *ortho* substituted acetophenones, **4i** and **4j** were obtained in 88% and 99% yields, respectively. Elongating the alkyl chain (**4k**) did not affect the reactivity. However, when phenyl isopropyl ketone (**3l**) was submitted to the reaction, the yield of hydrosilylated alcohol **4la** dropped to 33% due to the higher steric hindrance present in the molecule. Hydrosilylation of this type of substrate could be carried out with higher yield if the less hindered trimethylsilyl formate (**5b**) was used, providing **4lb** in 75% yield. This proves the importance of the steric hindrance for this transformation. Another proof for the importance of this effect was obtained with 4,4′-dimethylbenzophenone (**3m**). In this case, the reaction with triethylsilyl formate (**5a**) gave silyl ether **4ma** in 89% yield, but required a longer reaction time (42 h). Reducing the bulkiness on the reagent by using trimethylsilyl formate (**5b**) afforded **4mb** with a comparable yield of 76% with a significantly reduced reaction time (13 h). Benzophenone derivatives **3n** and **3o** were also hydrosilylated in 79% and 99% yields with silyl formate **5a**, respectively. In these cases, to perform the transformation within a reasonable reaction time, the amount of silylformate reagent was increased to two equivalents.

Remarkably, compound **4oc** bearing a useful dimethylphenylsilyl protecting group was obtained in a 91% yield within 4 h



Scheme 3 Substrate scope for the transfer hydrosilylation of ketones (0.1 mmol scale). Yields were determined by ^{1}H NMR with mesitylene as an internal standard. Scaled-up reactions (0.5 mmol scale) were performed with toluene as the solvent. Yields of isolated products from scaled-up reactions are given within parentheses. [a] 2 equivalents of **5a** were used. [b] Reaction performed in anisole as the solvent. [c] Reaction performed at 60 °C.



Scheme 4 Yields were determined by ^{1}H NMR with mesitylene as an internal standard. (A) Selectivity of the PN^{H}P-based ruthenium catalyst **2** for the transfer hydrosilylation of carbonyl groups (0.1 mmol scale). (B) Deuterosilylation of ketones (0.1 mmol scale).

in anisole as the solvent. The reaction proved to be scalable to 0.5 mmol, yielding product **4oc** in 63% isolated yield. More challenging substrates, such as trifluoromethylketone **3p** and α,β-unsaturated ketones **3q–s**,[17] were successfully hydrosilylated in 61–99% yields, with a 1,2-selectivity for the latter. Among them, compound **4r** was obtained in only 61% yield due to the formation of the conjugated enolether by-product. Heteroaromatic silylated alcohols **4t** and **4u** were obtained in 81% and 93% yield, respectively. Finally, dialkyl ketones **3v** and **3w** could also react under these conditions giving a 95% yield of the hydrosilylated products in both cases. Although free alcohols, carboxylic acids, amides or amines did not shut down the reaction, they exhibited a detrimental effect on the yields (see competition reactions in the Table S4, ESI†). The selectivity between ketones and aldehydes was studied in the transfer hydrosilylation of 4-acetylbenzaldehyde (**3x**) with only one equivalent of silyl formate **5a**. Not surprisingly, the aldehyde group was fully hydrosilylated after 2 h of reaction, while the ketone moiety remained intact (Scheme 4A).

To verify the origin of the hydride, deuterated silyl formate **5a-d$_1$** was synthesized and submitted to reaction. Deuterosilylated product **4a-d$_1$** was obtained as the only product, confirming that the hydride source is indeed the formate group (Scheme 4B). In addition, the absence of the unlabeled product **4a** suggests that the N–H bond on the catalyst ligand is not cleaved during the catalysis.

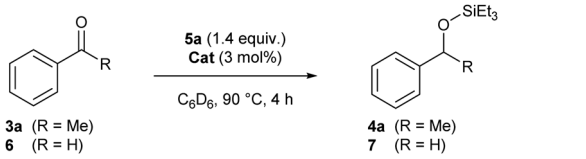
To evaluate the importance of the role of the N–H bond present in the PN^{H}P ligand on catalyst **2**, an analogous complex, where the N–H bond is methylated (**2-Me**), was synthesized. While catalyst **2** was able to reduce acetophenone (**3a**) and benzaldehyde (**6**), the parent **2-Me** catalyst could reduce aldehyde **6** but not ketone **3a** (Table 2). This observation is consistent with the requirement of the N–H motif for the reduction of ketones.

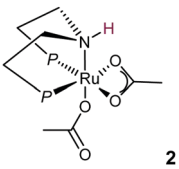
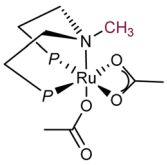
Based on these observations, a putative mechanism for this transformation is illustrated in Scheme 5. As we previously reported, an initial decarbonylation of silyl formate **5** on catalyst **2** generates the active catalyst ruthenium formate **A**, which through decarboxylation leads to the ruthenium hydride species **B**.[18] The presence of a ruthenium hydride species was confirmed by NMR analysis of the reaction mixture (see Fig. S8 and S9, ESI†).

Interaction of ketone **3** with the ruthenium–hydride complex **B** results in its reduction, presumably assisted by a hydrogen bond formed between the carbonyl group and the ligand PN^{H}P (**C**).[19] The same type of interaction in the generated intermediate **D** favours the attack of the alkoxide on the silicon center of a new molecule of silyl formate **5**, generating the final hydrosilylated product **4**, regenerating the active catalyst species **A**, and closing the catalytic cycle.

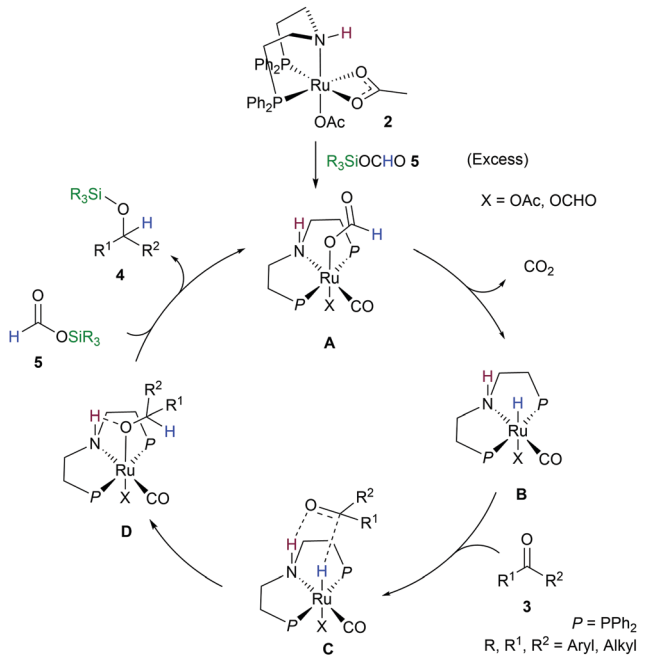
In summary, we have unlocked the possibility of using silyl formates in the transfer hydrosilylation of ketones by selecting a suitable PN^{H}P-based ruthenium catalyst 2. In addition, as shown in the control experiments, evidence of the crucial role of the N–H bond in the catalyst ligand was provided. This transformation opens the possibility of applying silyl formates

Table 2 Influence of the ligand N–H group on the transfer hydrosilylation of ketones and aldehydes[a]



Catalyst		
R	2	2-Me
H	99%[b]	99%[b]
Me	99%[b]	0%[b]

[a] 0.1 mmol scale. [b] Yields were determined by ^{1}H NMR with mesitylene as an internal standard. P = PPh_2.



Scheme 5 Putative mechanism for the transfer hydrosilylation of ketones with silyl formates.

as hydrosilane surrogates to reduce the more challenging ketones.

Conflicts of interest

There are no conflicts to declare.

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