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To cite this version:

Clément Chauvier, Timothé Godou, Thibault Cantat. Silylation of O–H Bonds by Catalytic Dehydrogenative and Decarboxylative Coupling of Alcohols with Silyl Formates. Chemical Communications, 2017, 53, pp.11697-11700. 10.1039/C7CC05212J . cea-01612948

HAL Id: cea-01612948

https://cea.hal.science/cea-01612948

Submitted on 9 Oct 2017

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Silylation of O–H Bonds by Catalytic Dehydrogenative and Decarboxylative Coupling of Alcohols with Silyl Formates

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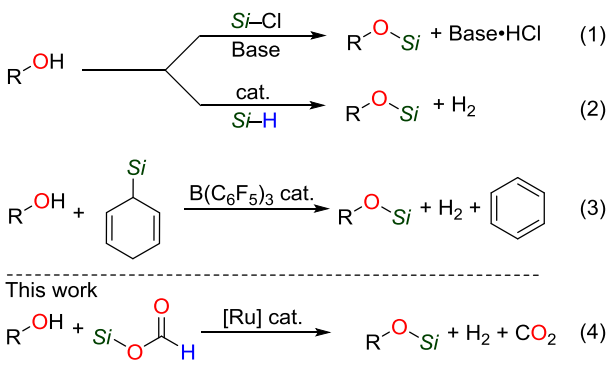
The silylation of O–H bonds is a useful methodology in organic synthesis and materials science. While this transformation is commonly achieved by reacting alcohols with reactive chlorosilanes or hydrosilanes, we show herein for the first time that silylformates HCO_2SiR_3 are efficient silylating agents for alcohols, in the presence of a ruthenium molecular catalyst.

The replacement of polar O–H bonds in alcohols and phenols with the O–Si linkage is of great importance across the chemical sciences. For example, in synthetic organic chemistry, the silyl ether functionality is frequently installed for the temporary protection of otherwise reactive hydroxyl groups.[1] In this respect, the wide availability of various silyl groups with tunable stereo-electronic properties has considerably facilitated the total synthesis of complex natural products.[2] In addition, silyl ethers generally display increased thermal stability and volatility as well as decreased polarity compared to their parent alcohols. Trimethylsilylation of the latter has thus become an invaluable tool for their derivatisation prior to GC analysis.[3]

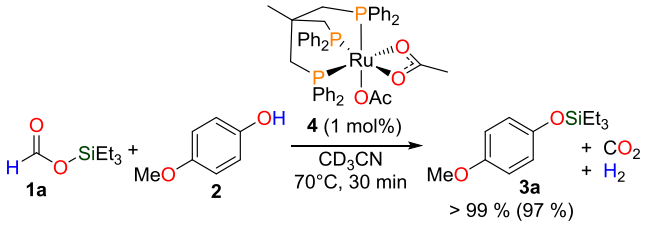
The silylation of hydroxyl groups commonly relies on the use of silyl chlorides or silyl triflates in the presence of a stoichiometric amount of a Brønsted base (Scheme 1, top).[4] While the implementation of this protocol is generally straightforward, the separation of the salt (typically an ammonium hydrochloride salt) from the product may be tedious. To circumvent this limitation, salt-free silylation methods based either on hydrosilanes or on sophisticated trimethylsilyl (TMS) group donors such as bis(trimethylsilyl)acetamide (BSA)[5] or *N*-trimethylsilylimidazole (TMSIM)[6] have been devised. Hydrosilanes are particularly attractive in this context as gaseous H_2 is the sole byproduct in the dehydrogenative Si–O coupling, and a plethora of transition metal-[7] and main-group-based[8] catalysts has been reported for this reaction (Scheme 1).



Scheme 1. Overview of the prototypical methodologies for the silylation of alcohols (Eqs. 1 and 2) and the new protocols based on silyl group transfer reagents (Eq. 3 and 4).

Nevertheless, the lightest hydrosilanes, e.g. Me_3SiH, are gaseous and/or pyrophoric reagents, and not suitable for practical organic syntheses. This issue has been tackled *via* the use of surrogates of hydrosilanes as shown by Oestreich and coworkers, with silylated cyclohexa-1,4-dienes (1,4-CHDN). In the presence of catalytic amounts of $B(C_6F_5)_3$, the authors were able to promote the transfer hydrosilylation of a variety of unsaturated functional groups[9] as well as the dehydrogenative silylation of alcohols (Scheme 1, Eq. 3).[10] Recently, we demonstrated that silylformates, HCO_2SiR_3, could serve as a new class of hydrosilane surrogates in the transfer hydrosilylation of aldehydes, by formal decarboxylation of the formate ligand in the presence of a metal catalyst.[11] This approach has the advantage of utilizing formic acid, a mild reductant derived from biomass or CO_2, as a hydride source.[12] In comparison, hydrosilanes are classically formed from chlorosilanes and $LiAlH_4$ as an energy intensive hydride donor.[13] Herein we report the successful silylation of O–H bonds by catalytic dehydrogenative and decarboxylative coupling of alcohols and phenols with silyl formates (Scheme 1, Eq. 4).

We started our study with the silylation of 4-methoxyphenol (**2**) in the presence of triethylsilyl formate ($Et_3SiOCHO$, **1a**) as a surrogate of the widely used triethylsilane (Et_3SiH). Because a catalyst is seemingly required to promote the decarboxylation of the formate moiety in **1a**, we initially selected the ruthenium-based complex [Ru(κ^1-OAc)(κ^2-OAc)(κ^3-triphos)] (triphos: 1,1,1-tris(diphenylphosphinomethyl)ethane) (**4**) (Scheme 2). This complex has indeed proven competent to generate reactive hydride-containing ruthenium complexes *via* decarboxylation of **1a** under catalytic conditions.[11]

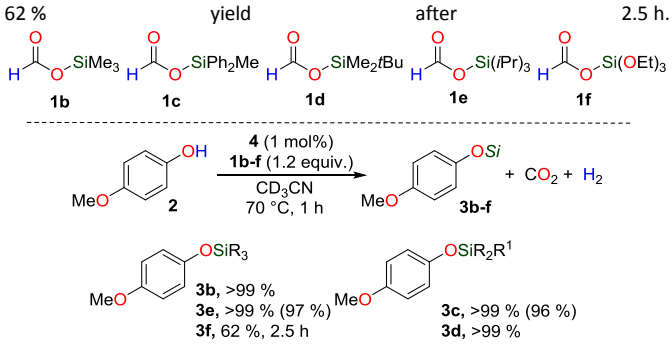


Scheme 2. Catalytic dehydrogenative and decarboxylative silylation of phenol **2**.

After optimisation of the nature of the solvent, the temperature and the catalyst loading (see ESI), we found that phenol **2** is quantitatively silylated by a slight excess of silyl formate **1a** (1.2 molar equiv.) after 40 min at 70 °C, with 1 mol% of complex **4**. While the formation of silyl ether **3a** is conveniently monitored by ^{13}C NMR spectroscopy, we also confirmed the co-generation of H_2 (δ_H = 4.57 ppm in CD_3CN) and CO_2 (δ_C = 125.9 ppm in CD_3CN) during the course of the reaction. In contrast, in the absence of catalyst, only traces amounts of **3a** were detected (<2 %) after 1.5 h at 70 °C. The

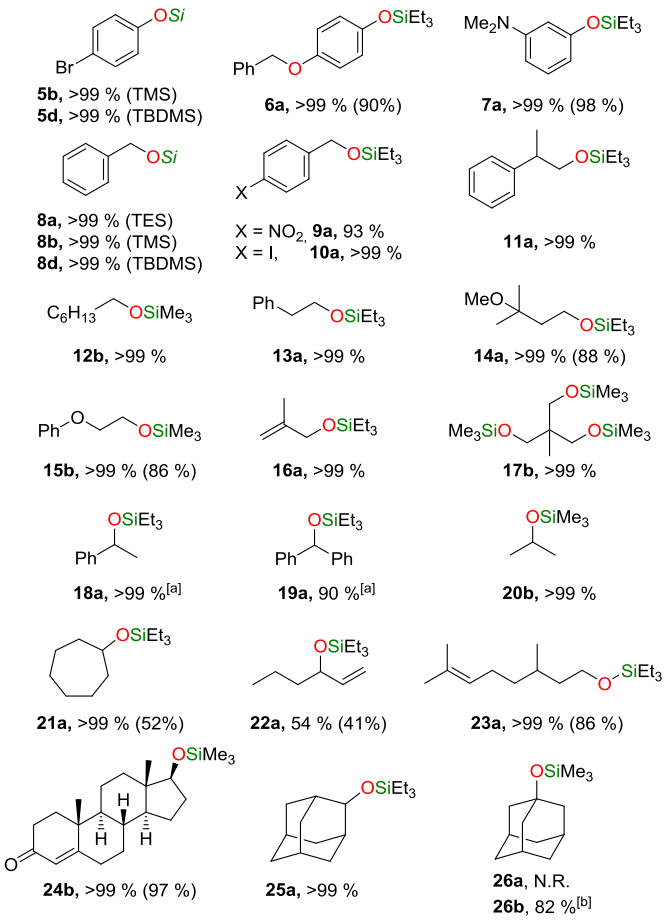
formation of **3a** from **1a** and **2** represents the first example of the utilization of a silylformate reagent for the silylation of an O–H bond.

In order to evaluate the influence of the silyl group on the reactivity, the silylation of phenol **2** was carried out with various silylformates substituted with alkyl and aryl groups (**1b-e**) (Scheme 3). Notably, the TMS group is efficiently transferred from trimethylsilyl formate (**1b**) as the silyl ether **3b** was obtained in quantitative yield after 30 min. **1b** thus behaves as a new liquid surrogate of Me_3SiH (b.p. 86 °C for **1b** *vs.* 6.7 °C for Me_3SiH) and it complements the trimethylsilylated CHDN derivative developed by the group of Oestreich. Bulky TBDMS (*tert*-butyldimethylsilyl) and TIPS (triisopropylsilyl) groups were also successfully introduced without altering the optimized conditions. Conversely, the silylation with triethoxysilyl formate **1f** is somewhat less efficient and silylether **3f** was obtained in 62 % yield after 2.5 h.



Scheme 3. Dehydrogenative silylation of phenol **2** with various silyl formates. Isolated yields in brackets

The generality of the dehydrogenative coupling was further evaluated with a variety of alcohols featuring diverse functional groups (Scheme 4 and ESI). Phenols substituted with bromo, benzyloxy, dimethylamino, amino and acetamido (ESI) groups reacted analogously to **2** and the corresponding silyl ethers (**5b-d**, **6a** and **7a**) were obtained in excellent yields. A similar outcome is seen for primary alcohols (**8**-**17**) that are fully converted into their silyl-protected analogues within 1 h at 70 °C. For example, the silylation of benzyl alcohol with the silyl formates **1a**, **1b** or bulkier **1d** yields the corresponding ethers (**8a-b** and **8d**) quantitatively. In contrast, the $B(C_6F_5)_3$-catalyzed silylation of benzyl alcohol with silylated 1,4-CHDN leads to substantial amounts of toluene *via* deoxygenation. Importantly, fragile or reducible functional groups are also well-tolerated under our reaction conditions as the nitro, iodo and C=C groups are preserved in the silyl ethers **9a**, **10a** and **16a** as well as the epoxide, imine of alkynyl functionalities.[14] The clean three-fold transfer of the TMS group from **1b** (3.5 equiv.) to 2-methylglycerol, a reaction potentially relevant to biodiesel quality assessment, was also noted and **17b** was obtained in excellent yield (> 99 %) after 3 h at 70 °C.

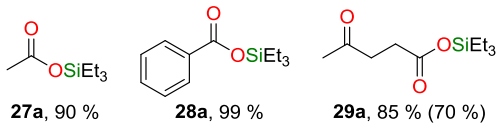


Scheme 4. Scope of the transfer dehydrogenative silylation of alcohols with silyl formates. Reaction conditions: alcohol (0.1 mmol); silyl formate (0.14 mmol); complex **4** (1 mol%); MeCN (0.4 mL; 0.2 M); 1 h at 70 °C. Yields determined by ^1H NMR analysis using mesitylene (10 µL) as an internal standard. Isolated yields from upscaled experiments (0.5 mmol scale) in brackets. [a] 2 mol% **4** used. [b] Yield determined after 5.5 h.

Secondary alcohols are likewise prone to undergo the catalytic transfer dehydrogenative coupling with either **1a** or **1b** providing the corresponding silyl ethers in high yields (> 90 % for **18-21**). For example, 1-phenylethanol (**18**) was silylated with **1a** and 2 mol% **4** affording the corresponding silyl ether **18a** in quantitative yield after 1 h. A competition experiment carried out between **18** and the related primary benzyl alcohol (**8**) revealed that the latter reacted with **1a** *ca.* 3 times faster than the secondary alcohol **18** (see ESI). The silylation of the allylic alcohol 1-hexen-3-ol (**22**) with $Et_3SiOCHO$ afforded **22a** with a moderate yield of 54 %, presumably because of the competing catalytic 1,3-hydrogen transfer yielding the saturated 3-hexanone (observed by ^1H NMR). The utility and practicality of our method was further established with naturally-occurring testosterone that was chemoselectively trimethylsilylated within 2 h at 70 °C. Owing to the gaseous nature of the byproducts, the corresponding silyl ether **24b** was isolated in 97 % yield merely after the removal of the catalyst onto a short plug of silica gel. The transfer of the TES group to bicyclic 2-adamantanol also proceeded with ease providing **25a** quantitatively, while its tertiary congener, 1-adamantanol, remained unchanged even under forcing conditions (100 °C,

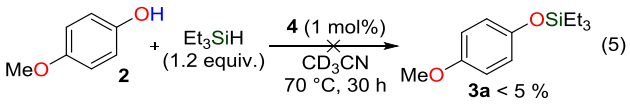
24 h). The transfer of the less hindered TMS group to 1-adamantanol was nonetheless possible and **26b** was formed in 82 % yield after 5.5 h at 70 °C.

Based on the successful results obtained with alcohols, the transfer hydrosilylation of a few carboxylic acids was attempted. While silyl esters find applications in material science and in organic synthesis,[15] their preparation by catalytic dehydrogenative coupling with hydrosilanes has only been scarcely investigated.[16] We were thus pleased to observe the clean formation of triethylsilyl acetate (**27a**) and benzoate (**28a**) in excellent yields after respectively 2.5 h and 2 h at 70 °C (Scheme 5). Additionally, levulinic acid, a biogenic carboxylic acid obtained from cellulosic materials, was chemoselectively silylated in good yield (**29a**, 85 % after 3 h at 70 °C), as the keto group remained untouched.[17] To the best of our knowledge, these examples constitute the first report of silylation of carboxylic acids with a surrogate of a hydrosilane.



Scheme 5. Silyl esters obtained by dehydrogenative silylation of carboxylic acids with **1a**.

From a mechanistic standpoint, triethysilane (Et_3SiH), which may be generated by catalytic decarboxylation of triethylsilyl formate **1a**, could not be detected in solution. In fact, phenol **2** did not react with Et_3SiH under the optimized reaction conditions, even after 30 h at 70 °C (Eq. 5), thereby ruling out its involvement as a competent intermediate. In this respect, silyl formates radically differ from silylated 1,4-CHDN that have been shown to act as precursors of hydrosilanes. The latter indeed releases the free hydrosilane upon catalysis with $B(C_6F_5)_3$ prior to the dehydrocoupling with the alcohol whose addition to the reaction mixture must therefore be delayed by at least 30 min to prevent the deactivation of the catalyst.[10]



In contrast, formic acid (FA) was the only intermediate observed by ^1H and ^{13}C NMR spectroscopy upon silylation of phenol **2** with triethylsilyl formate **1a**, in the presence of catalyst **4**. In the absence of catalyst, an equilibrium is slowly established within 110 h at 70 °C between the free phenol and the corresponding silyl ether, with concomitant release of FA (black curve in Fig. 1, $K^0_{343K} = 1.7$).[18] In contrast, no reaction occurs between the bulky triisopropylsilyl formate **1e** and phenol **2** after 7 days at 70 °C, although **1e** is able to transfer the TIPS group to phenols under catalytic conditions (see Scheme 3). According to these observations, the ruthenium complex **4** plays a dual role in the reaction (Scheme 6). At the outset, the catalyst facilitates the exchange of formate and phenolate anions at the silicon center (blue curve in Fig. 1), leading to the formation of FA. It also catalyses the irreversible decomposition of FA into H_2 and CO_2, thereby shifting the aforementioned equilibrium to the right (green curve in Fig. 1).

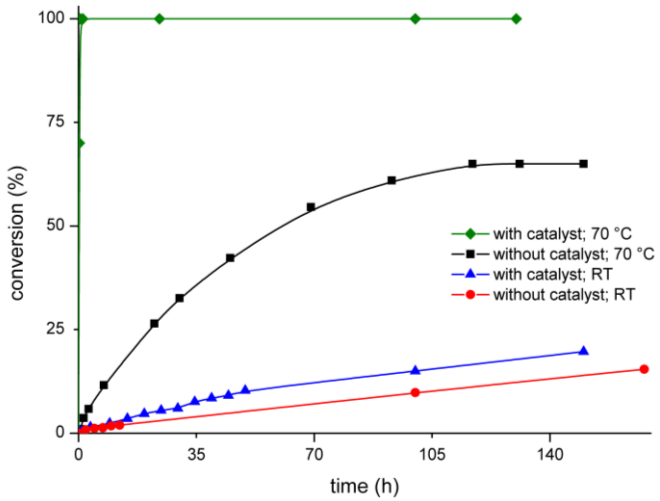
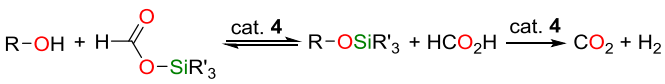
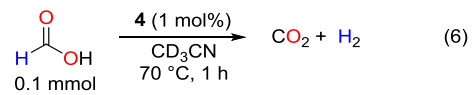


Figure 1. Silylation of phenol **2** with silyl formate **1a** in the presence (♦ at 70 °C and ▲at RT) or in the absence (■ at 70 °C and • at RT) of catalyst **4**.

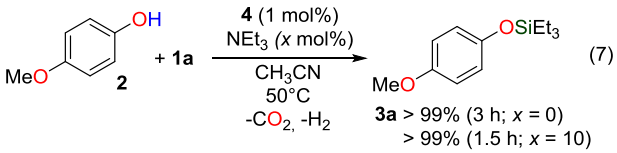


Scheme 6. Proposed mechanism for the dehydrogenative and decarboxylative silylation of alcohols with silyl formates.

The ability of ruthenium complex **4** to promote the acceptorless dehydrogenation of FA (ADH) was further assessed: an acetonitrile solution of FA was fully decomposed into CO_2 and H_2 within 1 h at 70 °C with 1 mol% of the complex **4** (Eq. 6). This result demonstrates that **4** is a competent catalyst for the base-free dehydrogenation of FA under mild conditions.[19] In line with the well-established positive influence of bases on the rate of FA decomposition,[20] we also observed a rate enhancement of our transfer dehydrocoupling protocol by the addition of a catalytic amount of triethylamine (10 mol%) (Eq. 7). This result suggests that the decarboxylation of a formate anion at the ruthenium center, which precedes the formation of H_2, is the rate determining step of the transfer dehydrocoupling of phenol **2** with triethylsilyl formate **1a**.



base-free ADH of FA



In conclusion, silyl formates have been shown to serve as salt-free silylating agents for O–H bonds, for the first time, leading to gaseous CO_2 and H_2 as the only by-products. Using the ruthenium(II) complex **4**, supported by a triphosphine ligand, a variety of silyl formates were used as surrogates of

hydrosilanes for the silylation of alcohols and carboxylic acids. The *decarboxylative* and *dehydrogenative* coupling between alcohols and silyl formates was shown to rely on a catalytic sequence based on a trans-silylation equilibrium, affording the desired silyl ether along with HCO_2H, and the subsequent irreversible base-free dehydrogenation of formic acid.

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