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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 HCO₂Si₃ 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. 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. 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. 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). 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) or N-trimethylsilylimidazole (TMSIM) have been devised. Hydrosilanes are particularly attractive in this context as gaseous H₂ is the sole byproduct in the dehydrogenative Si–O coupling, and a plethora of transition metal- and main-group-based catalysts has been reported for this reaction (Scheme 1).

Nevertheless, the lightest hydrosilanes, e.g. Me₃SiH, 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(C₆F₅)₃, the authors were able to promote the transfer hydrosilylation of a variety of unsaturated functional groups as well as the dehydrogenative silylation of alcohols (Scheme 1, Eq. 3). Recently, we demonstrated that silylformates, HCO₂Si₃, 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. This approach has the advantage of utilizing formic acid, a mild reductant derived from biomass or CO₂, as a hydride source. In comparison, hydrosilanes are classically formed from chlorosilanes and LiAlH₄ as an energy intensive hydride donor. 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 triethylsilyleformate (Et₃SiOCHO, 1a) as a surrogate of the widely used triethylsilyl (Et₃SiH). Because a catalyst is seemingly required to promote the decarboxylation of the formate moiety in 1a, we initially selected the ruthenium-based complex [Ru(k⁺-OAc)(k²-OAc)(κ¹-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.

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 ¹³C NMR spectroscopy, we also confirmed the co-generation of H₂ (δH₂ = 4.57 ppm in CD₂CN) and CO₂ (δCO₂ = 125.9 ppm in CD₂CN) 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

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

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).
formation of 3a from 1a and 2 represents the first example of the utilization of a silylfomate 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 silylates 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 Me3SiH (b.p. 86 °C for 1b vs. 6.7 °C for Me3SiH) 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.

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 bulker 1d yields the corresponding ethers (8a–b and 8d) quantitatively. In contrast, the B(C6H3)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 alkenyl 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 70 °C.

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 co. 3 times faster than the secondary alcohol 18 (see ESI). The silylation of the allylic alcohol 1-hexen-3-ol (22) with Et3SiOCHO 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 1-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, their preparation by catalytic dehydrogenative coupling with hydrosilanes has only been scarcely investigated. 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. 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](image)

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

From a mechanistic standpoint, triethysilane (Et₃SiH), which may be generated by catalytic decarboxylation of triethysilyl formate 1a, could not be detected in solution. In fact, phenol 2 did not react with Et₃SiH 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(C₆F₅)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.

![Scheme 6](image)

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

In contrast, formic acid (FA) was the only intermediate observed by ¹H and ¹³C NMR spectroscopy upon silylation of phenol 2 with triethysilyl 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°θ553K = 1.7). In contrast, no reaction occurs between the bulky triisopropylosilyl 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 H₂ and CO₂, thereby shifting the aforementioned equilibrium to the right (green curve in Fig. 1).

![Figure 1](image)

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.

R−OH + HCO2 • cat 4 → R−OSiR3 + CO₂ • cat 4

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 CO₂ and H₂ 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. In line with the well-established positive influence of bases on the rate of FA decomposition, 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 H₂, is the rate determining step of the transfer dehydrocoupling of phenol 2 with triethysilyl formate 1a.

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 CO₂ and H₂ 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
For recent total syntheses involving at least one silyl ether protecting group, see: (a) T. Maehara, K. Motoyama, T. Toma, S. Yokoshima and T. Fukuyama, 
*Angew. Chem. Int. Ed.*, 2017, 56, 1549-1552; (b) A. W. Schuppe and T. R. Newhouse, 

For further illustrations of the functional group tolerance of our transfer dehydrogenative silylation protocol, see the ESI.

For examples of base-free dehydrogenation of FA, see: (a) B. Bodden, D. Meilmann, F. Gärnter, R. Jackstell, H. Junge, P. J. Dyson, G. Laurency, R. Ludwing and M. Beller, 
*Science*, 2011, 333, 1733; (b) S. Oldenhof, B. de Bruin, M. Lutz, M. A. Siegler, F. W. Patureau, J. L. van der Vlugt and J. N. H. Reek, 

Nevertheless, prolonged heating of the crude reaction mixture after completion of the reaction lead to some reduction of the keto group, presumably by hydrogenation with H₂ generated by the dehydrogenative coupling.

Equilibria between carboxylic acids and acyloxysilanes are known, see: S. Kozuka, T. Kitamura, N. Kobayashi and K. Ogino, 

For further illustrations of the functional group tolerance of our transfer dehydrogenative silylation protocol, see the ESI.