doi:10.1246/cl.2012.229
Published on the web February 18, 2012

Selective Reduction of Carboxylic Acids to Aldehydes by a Ruthenium-catalyzed Reaction with 1,2-Bis(dimethylsilyl)benzene

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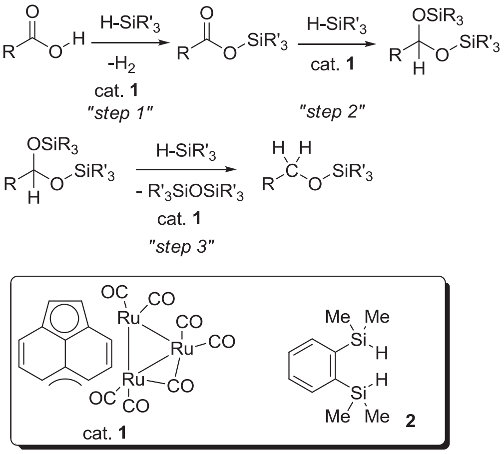
Novel transformation of carboxylic acids to aldehydes is achieved by a one-pot procedure consisting of a ruthenium-catalyzed hydrosilane reduction with 1,2-bis(dimethylsilyl)benzene (**2**) followed by hydrolysis of the resulting cyclic disilylacetals **4**.



Scheme 1.

Although reduction of carboxylic acids to aldehydes is a synthetic protocol frequently required in organic synthesis, selective and direct transformation by alumino- or borohydride reduction is difficult due to higher reactivity of aldehydes than carboxylic acids leading to facile formation of alcohols.[1] Thus, the transformation is usually performed by a two-step procedure. One of the general procedures is hydride reduction of carboxylic acid to alcohols, and subsequent oxidation of the resulting alcohols gives aldehydes.[2] Another well-established procedure is conversion of carboxylic acids to more reactive acyl chlorides,[1a,3a] acid anhydrides,[3b] and activated esters,[1a,3c] which is followed by catalytic hydrogenation or hydride reduction to aldehydes. Development of direct methods to achieve conversion of carboxylic acids to aldehydes or their equivalents has attracted attention of organic chemists; several successful examples were achieved by discovery of novel reducing reagents. Reduction of carboxylic acids with thexylborane gives the corresponding boryl esters in the first step. Further reaction of thexylborane provides diborylacetals, which hardly undergo further reduction to the corresponding alkoxy borane. Aqueous work-up of the diborylacetal gives the aldehyde.[4] The reduction with alane derivatives[5] and in situ prepared magnesium hydrides by titanocene-catalyzed reaction with *i*-BuMgBr[6] proceed in similar fashion to achieve selective transformation of carboxylic acids to aldehydes. A unique reduction of carboxylic acids was reported by Corriu and co-workers who prepared certain pentacoordinated silyl carboxylates, from which intramolecular hydride migration afforded aldehydes.[7] Although these direct methods are attractive for preparation of aldehydes from carboxylic acids, handling of the reducing reagent is not easy in the reactions with boranes, alanes, and in situ formed magnesium hydrides,[4–6] whereas harsh conditions (100–180 °C) are required for the Corriu's reaction.[7] In this context, it is desirable to develop a new method for the preparation of aldehydes from carboxylic acids using a reducing reagent, which can be handled with ease and proceeding under mild conditions. Hydrosilanes, especially tertiary silanes, are attractive from this viewpoint, however, they are essentially stable, and new catalysts which enable the reduction of carboxylic acids to aldehydes are required.[8]

In our continuous efforts to develop transition-metal-catalyzed reactions of hydrosilanes useful in organic synthesis,[8,9] we have reported that hydrosilane reduction of carboxylic acids is facilely achieved by catalysis of (μ_3, η^2, η^3, η^5-acenaphthylene)$Ru_3(CO)_7$ (**1**); the reduction of carboxylic acids to silyl ethers is achieved with monofunctional tertiary silanes such as $PhMe_2SiH$ and $EtMe_2SiH$ under mild conditions.[9b] As shown in Scheme 1, the reduction of carboxylic acids consists of three steps, dehydrogenative silylation leading to formation of silyl esters (step 1), Si–H addition of C=O bond of the silyl esters to disilylacetals (step 2), and reductive cleavage of a C–O bond in the disilylacetals to give silyl ethers (step 3). Hydrolysis of the resulting silyl ethers gave alcohols in good yields. Of interest is a possibility of selective formation of the disilylacetals, which can be achieved by making the reaction rate of step 3 slow enough to produce the disilylacetals without contamination of the silyl ethers. Acceleration of step 2 would help the selective formation of the disilylacetals. In this paper, we wish to report that a bifunctional organosilane, 1,2-bis(dimethylsilyl)-benzene (**2**) is a suitable reducing reagent for this purpose, providing a new synthetic protocol for aldehydes from carboxylic acids.

In a typical example, the reaction of 4-methoxybenzoic acid (**3a**) was carried out as follows: the catalyst **1** (1 mol % to the carboxylic acid **3a**) is dissolved in minimum amounts of tetrahydropyran (THP) and treated with **2** (1.2–2.0 equiv to **3a**) at room temperature for 30 min. Then, **3a** and THP (2 mL) are added, and the mixture is kept at 25 or 40 °C. Hexamethylbenzene is added as an internal standard to determine conversion of **3a** and yield of the products by ^{1}H NMR. After removal of the volatiles, NMR spectra of the mixture show a singlet appearing

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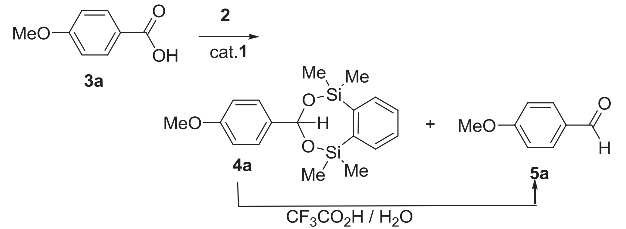
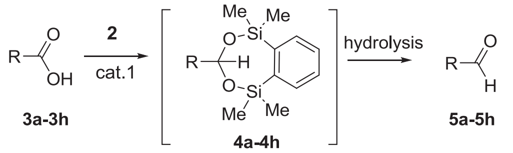
Table 1. Optimization of the reaction conditions[10]

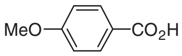
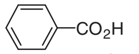
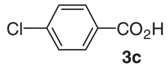
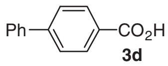
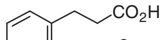
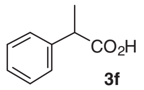
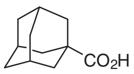
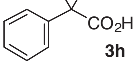


Entry	**2** /equiv	Temp /°C	Solvent for activation	Solvent for reaction	Additive /equiv	Time /h	Yield of **4a** + **5a** /%
1	1	25	THP (0.2 mL)	THP (2 mL)	none	24	52
2	2	25	THP (0.2 mL)	THP (2 mL)	none	24	64
3	2	25	none	THP (2.2 mL)	none	24	69
4	2	40	none	THP (2.2 mL)	none	5	90
5	1	25	none	THP (2 mL)	Et_3N (0.2)	1	90
6	1	25	none	THP (2 mL)	Et_3N (1)	3	64
7	1	25	none	THP (2 mL)	pyridine (0.2)	1	5

[a] All reactions were carried out with **3a** (1 mmol) and **1** (1 mol %).

Table 2. Reduction of various carboxylic acids



Entry	Carboxylic acid **3**	Temp /°C	Time /h	Hydro-lysis[b]	Product **5**	Isolated yield/%
1	 **3a**	40 25	5 1	**A** **A**	**5a**	90 90[c]
2	 **3b**	40	24	**A**	**5b**	90
3	 **3c**	50	24	**A**	**5c**	69
4	 **3d**	50	24	**A**	**5d**	90
5	 **3e**	40 40	18 18	**B** **B**	**5e**	90 20[c]
6	 **3f**	40 40	18 18	**C** **C**	**5f**	59 90[c]
7	 **3g**	50	18	**C**	**5g**	58
8	 **3h**	70	18	**C**	**5h**	71

[a] All reactions were carried out in a similar manner as that descried in Entry 4, Table 1. [b] Hydrolysis is by **A**: CF_3CO_2H/H_2O, **B**: HCl/H_2O, **C**: TBAF/H_2O. Details are described in the Supporting Information.[16] [c] Addition of Et_3N (0.2 equiv to the carboxylic acid).

at δ 6.3 which indicates formation of a disilylacetal **4a**. ^{1}H NMR peaks due to 4-methoxybenzaldehyde (**5a**) are also observed. Formation of the disilylacetal is supported by experiments of acid-promoted hydrolysis of the mixture of **4a** and **5a**, which result in quantitative conversion of **4a** to **5a**. Optimized reaction conditions are shown in Table 1. As shown in Entry 1, disilylacetal **4a** was obtained in 52% when the reaction was performed with 1 equiv of **2** at room temperature for 24 h. In increasing the amount of **2** to 2.0 equiv, the yield of **4a** was increased to 64% (Entry 2). The reaction with no solvent gave **4a** in 69%. A better yield (90%) was obtained when the reaction was carried out at 40 °C for 5 h. As reported earlier, addition of amine causes functional group selective poisoning of the catalyst **1**.[9d] Addition of Et_3N accelerated the reaction (Entries 5 and 6), while presence of pyridine inhibited the catalysis of **1** (Entry 7).[11] In the presence of Et_3N (0.2 equiv to **3a**), the yield of the products exceeded 90% even at room temperature within 1 h.

Reduction of carboxylic acids followed by hydrolysis of the resulting disilylacetals can be done by one-pot process. In Table 2 are shown several examples of reduction of carboxylic acids to aldehydes under the conditions shown in Entry 4, Table 1. Three procedures were used for the hydrolysis step, treatment of the intermediary disilylacetals with CF_3CO_2H(aq) (Entries 1–4), HCl(aq) (Entry 5), or TBAF(aq) (Entries 6–8). Reactions of substituted benzoic acids are listed in Entries 1–4.

Anisaldehyde, benzaldehyde, and *p*-phenylbenzaldehyde were obtained in over 90% isolated yields. Electron-donating substituents tend to increase the reaction rate. Benzoic acid having electron-withdrawing Cl group was slow, giving the corresponding aldehyde in lower yield. Aliphatic carboxylic acids also underwent the selective reduction to give the corresponding aldehydes. The reaction rate and the yield of the product were dependent on steric circumstances around the carbonyl group of the carboxylic acid. For example, 3-phenylpropanal (**5e**) was obtained from 3-phenylpropanoic acid (**3e**) in 90% (Entry 5), whereas slower reaction of 2-phenyl analogue **3f** gave the aldehyde **5f** in 59% isolated yield (Entry 6).[12] Two aldehydes, 1-adamantanecarbaldehyde (**5g**) and 2-phenylisobutylaldehyde (**5h**) were obtained in 58% and 71% respectively from the corresponding carboxylic acids as shown in Entries 7 and 8. As described above, addition of a small amount of Et_3N contributed to increase the yield of a mixture of the silylacetal **4a** and the aldehyde **5a** in the reduction of **3a** with **2** under milder conditions. Addition of Et_3N is also effective in the one-pot conversion of **3a** to **5a**. We expected similar additive effects in the reduction of other carboxylic acids, too; however, the results were dependent on the structure of the carboxylic acid. For example, addition of Et_3N improved the isolated yield of 2-phenylpropanal (**5f**) from 2-phenylpropanoic acid (**3f**), whereas the reduction of 3-phenylpropanoic acid (**3e**) in the presence of Et_3N made the reaction slower to result in decrease of the yield of **5e**.

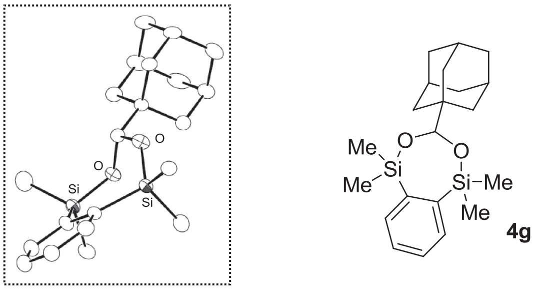


Figure 1. The ORTEP drawing of **4g**. The crystallographic data are listed in the Supporting Information.[16]

In all cases listed in Table 2, intermediary disilylacetals were unstable toward moisture leading to facile hydrolysis to aldehydes; however, careful manipulations made the isolation of the disilylacetal possible in several cases.[10] For example, the reaction of **3a** under the conditions described in Table 1, Entry 3 gave a mixture of **4a** and unreacted **2**. Purification by chromatography with florisil, followed by removal of the silicon by-products in vacuum, afforded **4a** containing a small amount of a cyclic siloxane **6**, which was produced by hydrolysis of **2** and **4a**. The data of ^{1}H, ^{13}C, and mass spectrometry are in accord with the structure of **4a** (see, the Supporting Information[16]). Similarly, a disilylacetal **4g** prepared from 1-adamantanoic acid (**3g**) was isolated, and identified by spectroscopy.[13] Although many of the silylacetals are liquid, **4g** gave a single crystal of which X-ray structure determination provided unequivocal evidence for the formation of disilylacetals. The ORTEP drawing of **4g** is depicted in Figure 1.

In summary, the present ruthenium-catalyzed reduction of carboxylic acids with bifunctional hydrosilane **2** followed by hydrolysis of the resulting disilylacetals is demonstrated to be a new method to synthesize aldehydes from carboxylic acids under mild conditions. Both the catalyst **1** and reducing reagent **2** are stable toward air and moisture, and manipulations are very easy. Suppression of step 3 in Scheme 1 is a key to achieve this new transformation, which is due to the fact that the seven-membered ring of the intermediary disilylacetal is rigid, and four methyl groups on the silicon atoms effectively protect the acetal function from further attack of Si–H in step 3. It is also worthwhile to point out that earlier studies showed proximate effect of two SiH groups accelerates the hydrosilylation,[14] which is likely to take part in accelerating the step 2 in the present reduction. These results add a new aspect in recent progress of transition-metal-catalyzed hydrosilane reductions in the point that use of the bifunctional hydrosilanes **2** plays an essential role in accelerating the reaction and in raising the selectivity of aldehydes in the reduction of carboxylic acids.[15]

This study was partially supported by the Global COE program, "New Carbon Resource Sciences" and Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology. Experimental assistance by Dr. Hironori Tsutsumi and Mr. Taisuke Matsumoto is acknowledged. The author (H.N.) is thankful for a JST-CREST program (Creation of Innovative Functions of Intelligent Materials on the Basis of the Element Strategy) to complete this work.

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10 The catalyst **1** (6.7 mg, 0.01 mmol) was pretreated with hydrosilane **2** (0.44 mL, 2 mmol) at room temperature for 30 min. Then, *p*-methoxybenzoic acid (**3a**) (152 mg, 1 mmol) suspended in THP (2.2 mL) was added, and the mixture was heated at 40 °C for 5 h. Unreacted **2** was quenched by adding diethyl ether saturated by water, and the mixture was concentrated in vacuo. The crude mixture consisiting of a mixture of **4a** and **5a** was dissolved in ether (5 mL) and treated with CH_3CO_2H and water at room temperature for 3 h. From the organic phase, **5a** was obtained, of which purification by silica gel column gave **5a** in pure form in 90% yield.

11 In the ruthenium-catalyzed hydrosilane reduction of carbonyl compounds, addition of pyridine generally inhibits the reaction presumably due to deactivation of the catalyst. In contrast, inhibition by Et_3N is also observed for the reduction of ketones and esters, but not for that of amides.[9d] Since acceleration of the disilylacetal formation by Et_3N presented in this paper is observed only for a limited number of the carboxylic acids, it is difficult to explain the mechanism at present.

12 Careful manipulation is necessary for reduction of optically active carboxylic acids. Treatment of (*R*)-2-phenylpropanoic acid, (*R*)-**3f** (>99% ee), with **2** gave the corresponding disilylacetal **4f**. For checking the possible racemization during the reduction, the reaction mixture was treated with DIBAL to afford (*R*)-2-phenylpropanol (**7f**) in 75% yield. Chiral GC analysis of the resulting **7f** showed its optical purity to be 97% ee. As noted earlier, disilylacetals is often unstable to moisture to give aldehydes as a by-product. At present, we consider that the loss of optical purity should be ascribed to the formation of a small amount of aldehyde at the work-up process of the reduction of (*R*)-**3f** with **2**. Contamination of the racemized aldehyde in the DIBAL reduction caused the loss of optical purity.

13 The compound **4g**: colorless crystals (Mp 102–107 °C), ^{1}H NMR (270.1 MHz, C_6D_6): δ 7.4 (dd, $J = 5.3, 3.3$ Hz, 2H), 7.2 (dd, $J = 5.3, 3.3$ Hz, 2H), 4.7 (s, 1H), 2.0 (m, 3H), 1.7 (m, 6H), 1.7 (m, 6H), 0.4 (s, 6H), 0.4 (s, 6H). ^{13}C NMR (67.8 MHz, C_6D_6): δ 142.6, 131.2, 126.5, 97.0, 36.1, 35.2, 34.5, 26.2, 0.0, −3.5. ^{29}Si NMR (119.2 MHz, C_6D_6): δ 9.1. MS (m/z): M^+ 372, 373, 374. HRMS (m/z): M^+ calcd for $C_{21}H_{32}O_2Si_2$, 372.1941; found, 372.1937.

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16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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